

Synthetic/Catalytic Studies Towards Construction of Macrocycles Under Batch and Continuous Flow Conditions

विद्या वाचस्पति की
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July-2024

*This Thesis is Dedicated to My
Mother, Father, & My Wife, for
Their Unwavering Love*



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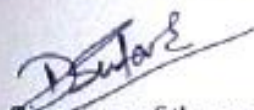
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CERTIFICATE

Certified that the work incorporated in this thesis entitled "*Synthetic/Catalytic Studies Towards Construction of Macrocycles Under Batch and Continuous Flow Conditions*" submitted by Dashrat Vishambar Sutar was carried out by the candidate, under my supervision. The work presented here or any part of it has not been included in any other thesis submitted previously for the award of any degree or diploma from any other university or institution.

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LIST OF ABBREVIATION

hr	Hours
Ac	Acetyl
AcOH	Acetic acid
CH ₃ CN	Acetonitrile
Ar	Aryl
ATR	Attenuated total reflection
Aq	Aqueous
BH	Borrowing hydrogen
Bn	Benzyl
Bs	Broad singlet
Bu	Butyl
Calcd.	Calculated
Cat.	Catalytic
CCDC	Cambridge crystallographic data centre
Conc.	Concentrated
°C	Degree Celsius
δ	Chemical shift in ppm
d	Doublet in NMR
dba	Dibenzylideneacetone
DCM	Dichloromethane
DCE	Dichloroethane

LIST OF ABBREVIATION

DEPT	Distortionless enhancement by polarization transfer
DMF	<i>N, N</i> -Dimethyl formamide
DMSO	Dimethyl sulfoxide
DMA	<i>N,N</i> -Dimethylacetamide
ee	Enantiomeric excess
EI	Electron impact
EtOAc	Ethyl acetate
equiv.	Equivalent
ESI TOF	Electrospray ionization time-of-flight
FTIR	Fourier-transform infrared spectroscopy
Gm	Grams
GC	Gas chromatography
t_R	residence time
f_R	Flow rate
BPR	Back pressure regulator
Hrs or hr	Hours
Hz	Hertz
HRMS	High-resolution mass spectroscopy
IR	Infra-red
J	Coupling constant in NMR
L	Liter
LDA	Lithium diisopropylamide
DAMPO	4-(dimethylamino)pyridine 1- oxide

LIST OF ABBREVIATION

LiAlH ₄	Lithium aluminium hydride
M	Molar (mol L ⁻¹)
m/z	Mass to charge ratio
Me	Methyl
m	Multiplet in NMR
mg	Milligram
min	Minutes
mL	Millilitre
mmol	Millimoles
MS	Mass spectroscopy
NMR	Nuclear magnetic resonance
Nu	Nucleophile
NHC	<i>N</i> -heterocyclic carbene
Pd/C	Palladium on carbon
P	Pentet in NMR
ppm	Parts per million
q	Quartet in NMR
s	Singlet in NMR
Temp	Temperature
TEMPO	(2,2,6,6-Tetramethylpiperidin-1-yl)oxyl
TMS	Tetramethylsilane
TMEDA	<i>N,N,N',N'</i> -tetramethylethylenediamine

PREFACE

Macrocycles are large, cyclic molecules composed of a sequence of atoms linked by covalent bonds, forming a cyclic structure. These fascinating compounds have garnered significant attention in various fields of chemistry due to their unique properties and potential applications. The study of macrocycles covers a broad range of disciplines, including organic chemistry, supramolecular chemistry, medicinal chemistry, and materials science. Moreover, several macrocycles are widely present in numerous natural products, musks, and drugs. The biological activity of many macrocyclic drugs often arises from the presence of a macrocyclic core. This core allows macrocycles to adopt bioactive conformations due to their inherent preorganization ability, making them essential for drug targets, particularly in protein-protein interactions. Macrocycles are also essential in supramolecular chemistry, as they can form complexes with various metals through noncovalent interactions, as seen in crown ethers. Additionally, they are involved in host-guest interactions with small drug molecules, enhancing drug efficacy. Given their importance, developing new synthetic strategies for constructing macrocycles is a highly interesting area of research.

This thesis presents the findings of research on "*Synthetic/Catalytic Studies Towards Construction of Macrocycles Under Batch and Continuous Flow Conditions*," organized into five chapters.

Chapter 1: Introduction to Macrocycles

At the outset, a brief introduction to macrocycles is described. We have discussed different classifications and applications of macrocycles. Further, we described challenges associated with macrocyclization reactions and provided selected examples of a macrocyclization reaction. In addition, we explored the catalysis and continuous flow technique for the synthesis of macrocycles including its role in enhancing reaction efficiency, selectivity, and scalability in organic synthesis. Finally, we described the aim and rationale for the thesis work.

Chapter 2: Catalytic Direct Macrocyclization using Dehydrogenative Coupling of Alcohols and Ketones and Application Towards Synthesis of Natural Product Engelhardione

In this chapter, we have demonstrated a new approach for late-stage macrocyclization through the intramolecular dehydrative coupling of alcohols and ketone, utilizing a Ru-MACHO catalyst and a KOH base. This method enables the intramolecular coupling of primary and secondary alcohol to form macrocyclic ketone. This borrowing hydrogen approach is step economic, environmentally friendly, sustainable, and generates only water as a by-product. Moreover, this process applies to a wide range of substrates, highlighting its versatility in organic chemistry. Importantly, employing higher dilution conditions is crucial in this macrocyclization strategy, as it minimizes undesired side reactions and enhances the formation of the desired macrocyclic product. Furthermore, we used this borrowing hydrogen macrocyclization approach for the synthesis of the natural product Engelhardione.

Chapter 3: Continuous Flow Inter- and Intramolecular Macrolactonization under High Dilution Conditions

In this chapter, we have described the macrolactonization reaction under a continuous flow process from seco-acid and diacid with diols. In this process, we utilized the Mukaiyama reagent (*N*-methyl-2-chloropyridinium iodide) for acid activation in the presence of 1- methyl imidazole base. This continuous flow process delivers good to high yields within a short reaction time compared to alternative methods. Using this methodology, a diverse array of compounds including macrocyclic lactones (11 compounds) from intramolecular reaction of seco-acids, dilactones (15 compounds), and tetralactone derivatives (2 compounds) from intermolecular diols and diacids spanning the ring sizes from 12 to 26 members were synthesized within a residence time as short as 35 minutes. Moreover, the continuous flow process for macrolactonization offers the distinct advantage of effectively managing high reactant dilution within a precisely confined volume of a perfluoroalkoxy alkanes (PFA) tube reactor (7 mL), demonstrating its elegance.

Chapter 4: Direct Intramolecular Coupling of Primary/Secondary Alcohols with Secondary Alcohols for Macrocyclic Alkenylation Using Ni-Zeolite Catalyst Under Continuous Flow Conditions

In this chapter, we have developed an innovative method for the synthesis of macrocyclic alkene from primary and secondary alcohols using a Ni-Zeolite catalyst in a continuous flow system. The reaction mechanism involves two key steps: first, the dehydration of secondary alcohols to form alkenes, and second, the intramolecular dehydrative coupling of these alkenes with primary alcohols. This method produces 23 macrocyclic alkenes with

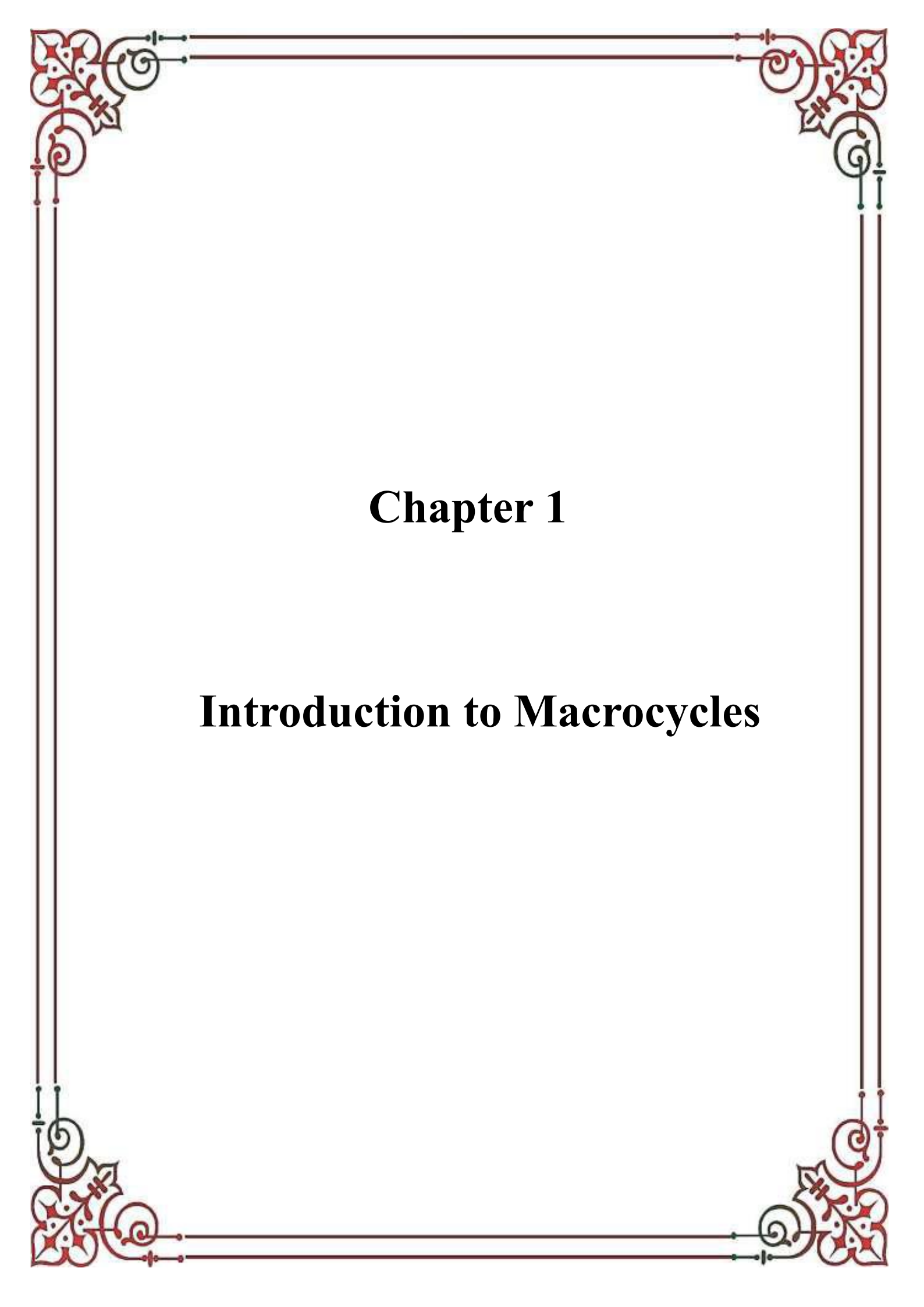
moderate yields. Additionally, this approach is applicable for intramolecular coupling of secondary-secondary alcohols and alkene-alcohols, resulting in a wide array of macrocyclic alkenes. The advantages of this method include step economy, no need for additives or pre-functionalization, and generating only water as a by-product.

Chapter 5: Intramolecular Dehydration of Diols and Seco-acids for Macrocyclic Ethers and Lactones under continuous flow

In the final chapter, we have demonstrated a straightforward, and efficient method for the intramolecular dehydrative coupling of symmetrical and unsymmetrical diols to synthesize macrocyclic ethers. This was achieved using a reusable heterogeneous Ni-Zeolite catalyst under a continuous flow system. Additionally, this method is useful for the synthesis of macrolactone from seco-acid using either Ni-Zeolite or Ru-Zeolite catalysts under a continuous flow condition. This approach produces 20 macrocyclic polyethers using one-time packed Ni-Zeolite catalyst and 11 examples of macrolactones. The advantages of this method include the generation of water as a by-product and the reusability of the heterogeneous catalysts.

LIST OF PUBLICATION

- 1) **Sutar, D. V.**; Jamdade, A. B.; Swami, G. B.; P. M. Jadhav and Gnanaprakasam, B*. Continuous-Flow Fixed-Bed Catalysis for Intramolecular Dehydration of Diols and Seco-acids for Asymmetrical Macrocyclic Ether and macrocyclic lactone using Ni/Ru-Zeolite Catalyst. *Accepted in Journal of Organic Chemistry* **2024**.
- 2) **Sutar, D. V.**; Swami, G. B.; Jamdade, A. B.; and Gnanaprakasam, B*. Direct Intramolecular Coupling of Primary/Secondary Alcohols with Secondary Alcohols for Macrocyclic Alkenylation Using Ni-Zeolite Catalyst Under Continuous-Flow Conditions. *Adv. Synth. Catal.* **2024**, *366*, 1–11.
- 3) **Sutar, D. V.**; Sarang, N. U.; Jamdade, A. B. and Gnanaprakasam, B*. Continuous Flow Inter- and Intramolecular Macrolactonization under High Dilution Conditions. *J. Org. Chem.* **2023**, *88*, 3740–3759.
- 4) Jamdade, A. B.; **Sutar, D. V.**; and Gnanaprakasam, B*. Synthesis of Macrolactams from Macrolactones Using Ru-/Ir-Catalytic System under Neutral Conditions. *Org. Lett.* **2023**, *25*, 9058–9063.
- 5) Jamdade, A. B.; **Sutar, D. V.**; and Gnanaprakasam, B*. Dehydrogenative Intramolecular Macrolactonization of Dihydroxy Compounds Using Ru-MACHO Catalyst. *Org. Lett.* **2022**, *24*, 4394–4398.
- 6) Jamdade, A. B.; **Sutar, D. V.**; Bisht, G. S.; and Gnanaprakasam, B*. Ru-MACHO-Catalyzed Direct Inter/Intramolecular Macrocyclization of Alcohols and Ketones. *Org. Lett.* **2021**, *23*, 7386–7390.
- 7) Mohanta, N.; Nair, K.; **Sutar D. V.**; and Gnanaprakasam B*. continuous-flow approach for the multi-gram scale synthesis of C2-alkyl- or β -amino functionalized 1,3-dicarbonyl derivatives and ondansetron drug using 1,3-dicarbonyls. *React. Chem. Eng.*, **2020**, *5*, 1501.
- 8) Jamdade, A. B.; Swami, G. B.; **Sutar, D. V.**; and Gnanaprakasam, B*. Ru-zeolite Catalyzed Dehydrative N-Alkylation of Amides for the Construction of Macrolactams under Continuous Flow Module. *Manuscript Submitted to E-JOC*



Chapter 1

Introduction to Macrocycles

1. Introduction to Macrocycles

1.1 Abstract

In this chapter, we described a detailed overview of macrocycles, including their classification and importance in various commercial applications. Challenges associated with macrocyclization and important strategies for synthesizing macrocycles have been briefly discussed. Importantly, we explored the effectiveness of catalysis and continuous flow technique in facilitating the synthesis of macrocycles. Moreover, the crucial role of catalysis and continuous flow technique to enhance reaction efficiency, selectivity, and scalability in organic synthesis has been thoroughly described. Finally, the aim and rationale for the thesis work has been elucidated.

1.2 Introduction to Macrocycles

Nature is a storehouse of cyclic organic compounds that are essential for our daily life.¹ It produces many cyclic compounds through selective intra or intermolecular and multimolecular transformations. Most of these naturally occurring cyclic compounds show various biological activities and act as drugs for living organisms.^{2,3} Thus, these cyclic compounds are indispensable for human beings.⁴ Traditionally, a variety of purification techniques were used to separate physiologically active molecules from natural sources like plants,⁵ microorganisms,⁶ and animals.⁷ However, these methods would produce very small amounts of the targeted molecules after consuming large amounts of natural sources with lengthy isolation procedures. Therefore, to address these drawbacks, synthetic chemists have dedicated a tremendous amount of work to synthesize targeted natural products and relative cyclic organic compounds in less number of operations *via* several bond-forming reactions. These cyclic compounds are divided into four types namely, small, normal, medium and large cycles as illustrated in Figure 1.⁸

1.2.1 Definition of Macrocycles and their Classification

Small cyclic compounds are defined as compounds bearing 3- and 4-atoms in the ring, whereas normal cyclic compounds are made up of 5- to 7-atoms.⁸ However, “*ring-shaped molecules that typically contain 12 or more than twelve-membered ring structure are called*

large cyclic or commonly known as macrocycles.” These rings can be simple or complex and may contain various functional groups in the ring system.⁹

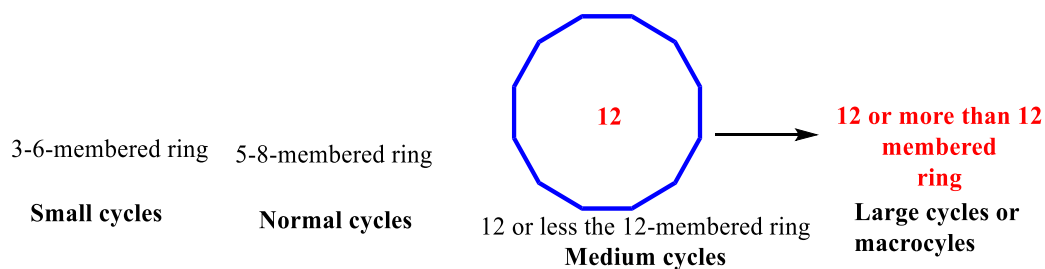


Figure 1. Classification of cyclic organic compounds

Furthermore, macrocycles can be classified according to the presence of functional groups in the macrocyclic core (Figure 2). A macrocycle that has an ester functional group is termed as macrolactone,^{8,10} while one with an amide functional group is referred to as a macrolactam.¹⁰ The large cycle that contains a ketone functional group is known as macrocyclic ketone,¹¹ and those with an ether functional group are designated as macroethers or polyethers¹² (Figure 2).

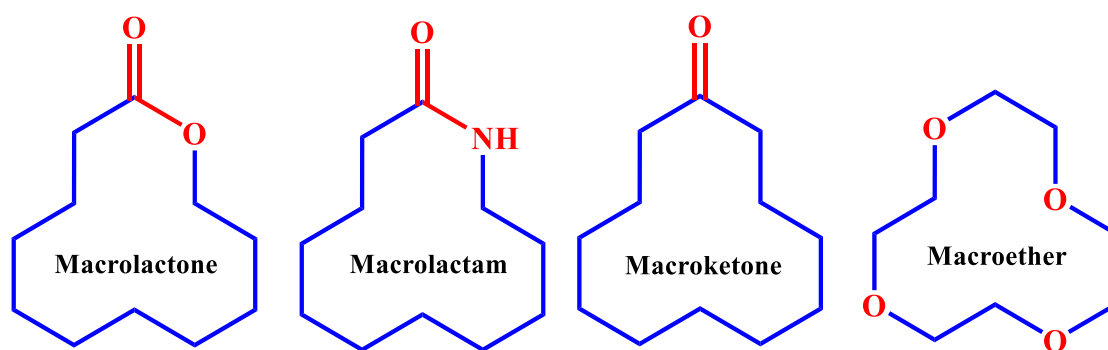


Figure 2. Classification of macrocycles based on functional group

On the other hand, structural characteristics also categorize macrocycles into three types: monocyclic¹³ which bears a single ring, bicyclic¹⁴ which contains two fused rings, and tricyclic or polycyclic,¹⁵ which possesses two or more interconnected rings (Figure 3).

Most importantly, macrocyclic compounds have a restricted number of configurations which makes them stiffer and, in most cases, more thermodynamically stable than acyclic analogues.¹⁶ Additionally, the presence of heteroatoms within the ring structure of macrocycles can significantly enhance their binding capacities toward guest molecules.¹⁷ Furthermore, the existence of multiple functional groups in macrocycles enables an extensive range of chemical properties, resulting in distinct characteristic behaviours.¹⁸

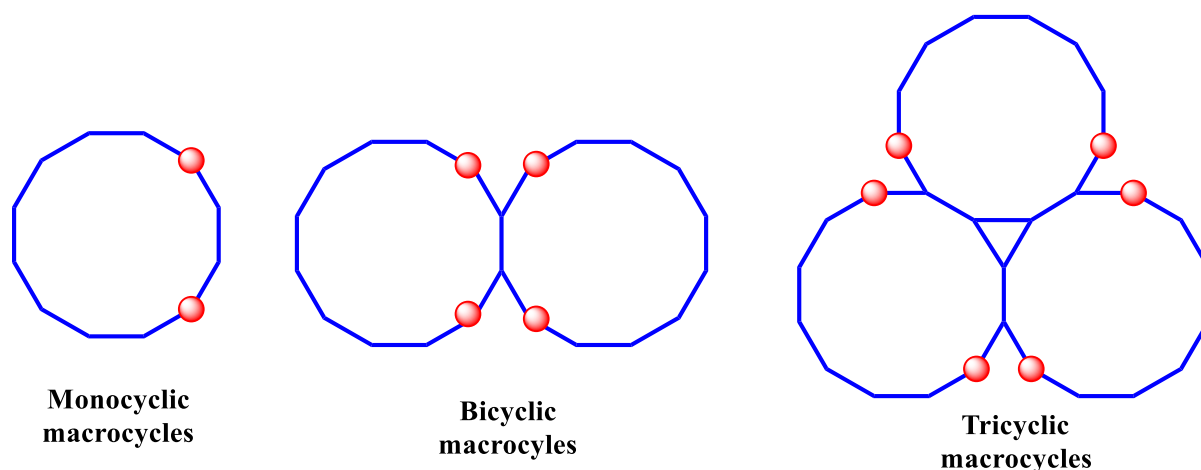


Figure 3. Classification of macrocycles based on structural framework

1.2.2 Importance of Macrocycles

Macrocyclic compounds have unique properties that make them important in various scientific fields such as industrial applications,¹⁹ drug discovery,²⁰ catalysis,²¹ supramolecular chemistry,²² materials science,²³ and sensors²⁴ (Figure 4). Their ability to form stable complexes with a wide range of guest molecules underscores their importance and versatility in modern chemistry. Notably, they have had enormous importance in drug discovery and supramolecular chemistry.

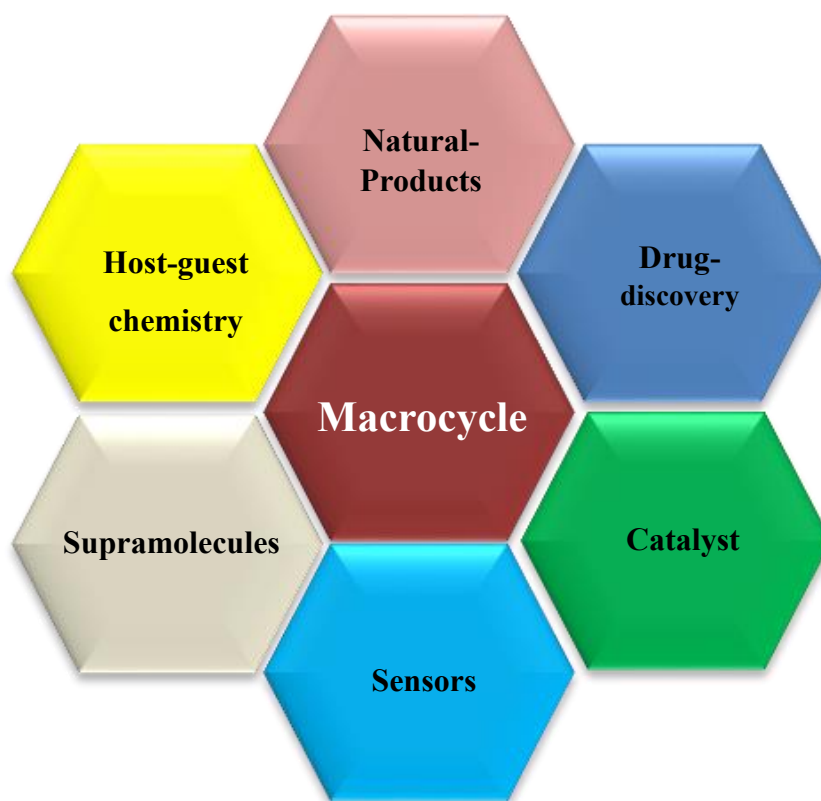


Figure 4. Important applications of macrocyclic compounds

Bioactive macrocycles, including Ovalifoliolatin B,²⁵ aza-migrastatin analogues,²⁶ acerogenins,²⁷ erythromycin,²⁸ rapamycin,²⁹ cyclosporin,³⁰ epothilone,³¹ etc. play a significant role in drug discovery due to their potent biological activities. Natural products that are composed of macrocyclic core shows biological activity. Generally, the biological activity arises due to the omnipresence of the macrocyclic core. For example, the natural product *Ovalifoliolatin B*, is isolated from *Boswellia ovalifoliolata* stem bark.²⁵ This macrocyclic compound shows biological activities that include anti-cancer,³² anti-inflammatory,³² anti-fungal,³² and anti-bacterial activities³² (Figure 5). More interestingly, aza-migrastatin analogues are synthetic derivatives of migrastatin, a naturally occurring compound isolated from *Streptomyces platensis*.³³ Migrastatin and its analogues, including aza-migrastatin, have attracted the interest of the scientific community due to their potent biological activities, particularly in the context of cancer treatment (Figure 6).³⁴

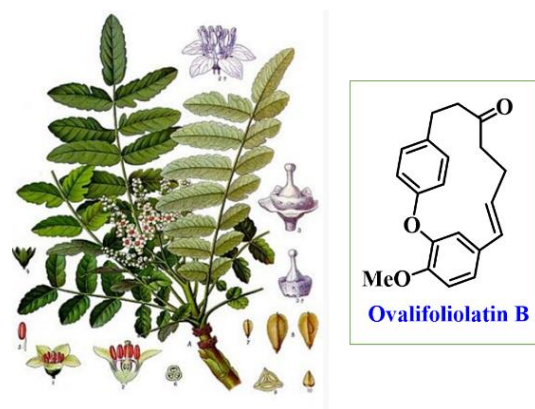


Figure 5. Macrocytic natural product Ovalifoliolatin B



Figure 6. Macrocytic drug Aza-migrastatin analogue

Intriguingly, macrocycles such as porphyrins,³⁵ cryptand,³⁶ crown ether,³⁷ cyclodextrins³⁶ and calixarenes³⁶ contribute to supramolecular chemistry by providing non-

covalent interactions with various guest molecules. Notably, these molecules are found to be effective in forming stable complexes with small drug molecules. As a result, the stability and efficiency of these small drugs increase under physiological conditions.

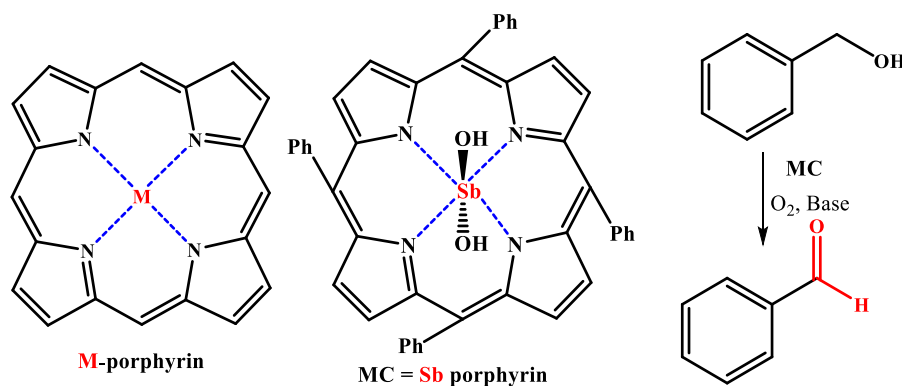


Figure 7. Macrocycles serve as catalysts (M-porphyrins)

Furthermore, macrocyclic metalloporphyrins serve as catalysts.³⁸ The porphyrin containing magnesium (Mg) is essential for photosynthesis in plants, where light energy is converted into chemical energy.³⁹ Moreover, Hajimohammadi and colleagues described the use of Sb-porphyrin as a catalyst to oxidize alcohol to aldehyde (Figure 7).⁴⁰

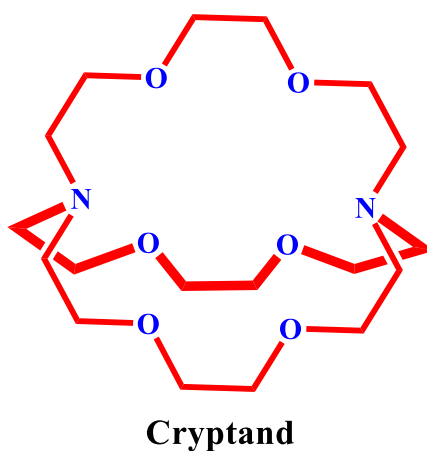


Figure 8. Cryptand as a sensor

The use of cryptands in sensor development is primarily due to their high selectivity and strong binding affinity for specific ions. Cryptand-based fluorescent sensors have been developed for the detection of calcium ions in biological samples, providing a valuable tool for studying cellular processes (Figure 8).⁴¹

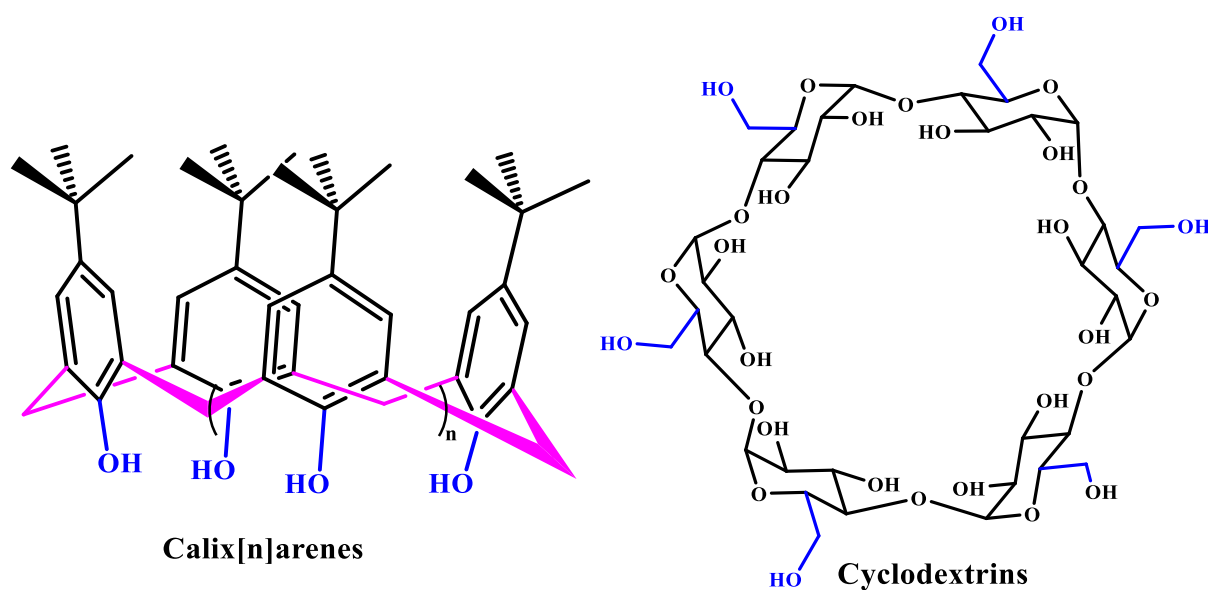


Figure 9. Calix[n]arenes and Cyclodextrins

Cyclodextrins and calixarenes play a crucial role in the field of supramolecular chemistry due to their ability to form host-guest complexes,³⁶ which are fundamental for applications in various industries, including pharmaceuticals, environmental science, and materials engineering (Figure 9).⁴²

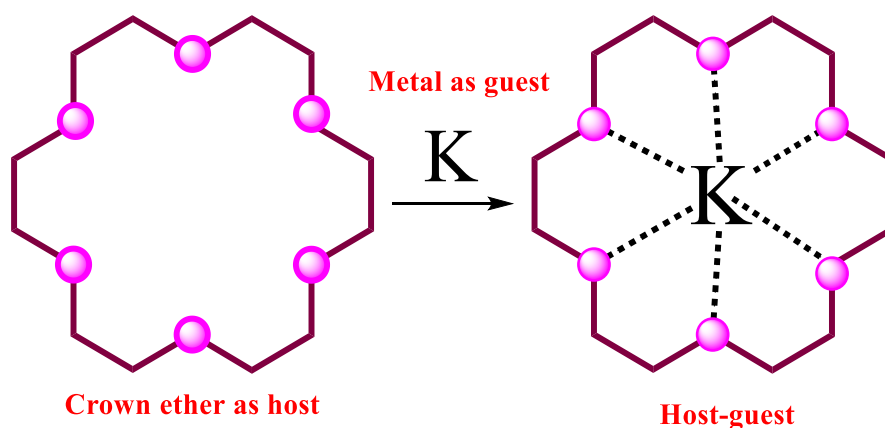


Figure 10. Crown ether as a host in host-guest chemistry

Metal-coordinated crown ether is the best example of host-guest chemistry. They serve as phase transfer catalysts, for advanced and crucial drug discovery (Figure 10).³⁷

Notably, macrocyclic compounds, with their diverse functional groups, structures, and strong binding abilities, have become essential tools in many advanced research and development fields.

1.3 Challenges Associated with Macrocyclization

Although macrocycles have extensive applications in various fields, generating novel procedures and synthesizing macrocyclic compounds are highly challenging for chemists due to a variety of complications, such as ring size,⁸ conformational isomerism,⁴³ strain effects,⁸ purification and solubility,⁴³ etc.

- **Entropic Factors:** Macrocyclic compounds typically involve the formation of large rings, which are challenging to construct due to entropic factors. The different conformational flexibility of long-chain starting material can lead to competing side reactions like dimerization, and polymerization (Figure 11).

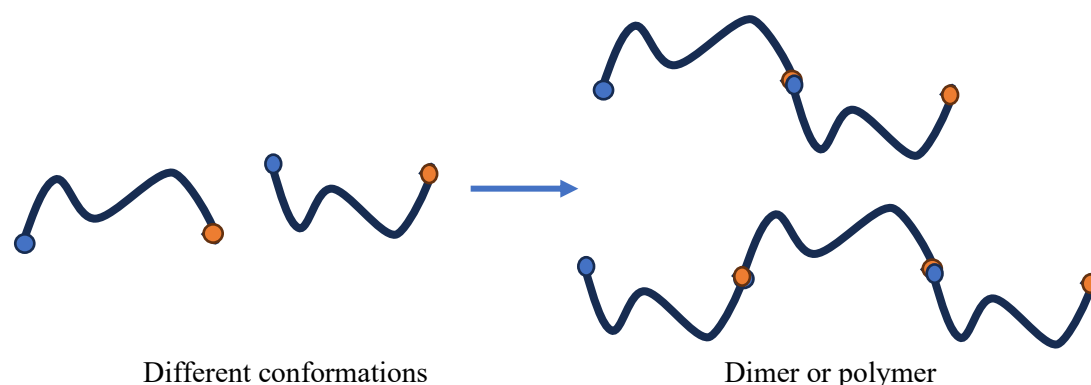


Figure 11. Conformational effect on the synthesis of macrocycles

- **Ring Size and Strain Effects:** Macrocycles often experience angle strain due to distraction from ideal bond angle of 109.5° , ring size, and torsional strain within the ring structure. (Figure 12).⁴⁴

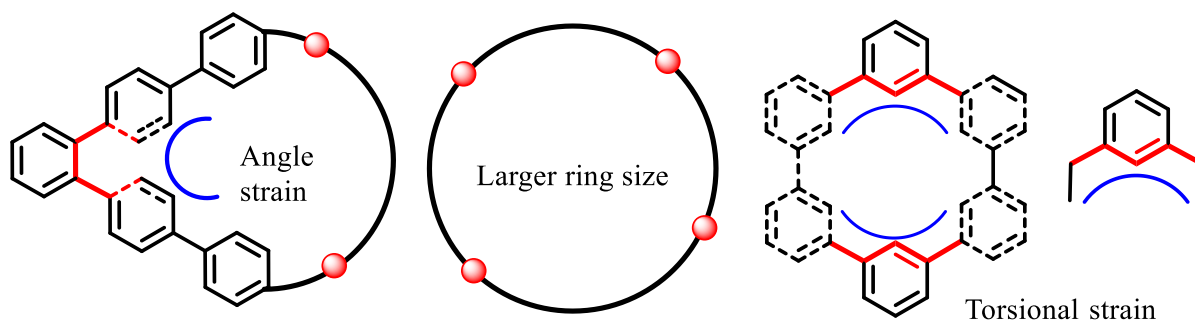


Figure 12. Effect of strain and ring size on the formation of macrocycles

- **Purification and Solubility:** Many large macrocycles usually have insufficient solubility in common organic solvents, which may cause complications in purification processes.

Despite macrocyclization being associated with challenges, researchers have developed several reactions successfully *via* both non-catalytic (stoichiometric reagents) and catalytic approaches

1.4 Overview of Macrocyclization Strategies

Macrocyclization strategies involve a variety of methods with the goal of creating large ring structures. Research endeavours have extensively reported the methods for constructing macrocycles, which involve the formation of carbon-carbon (C-C),⁴⁵ carbon-nitrogen (C-N),⁴⁶ carbon-oxygen (C-O) bonds.⁴⁷ Macrocyclization reactions can be classified into four main types: intermolecular, intramolecular, ring expansion, and multimolecular macrocyclization processes⁴⁸ (Figure 13). Each of these strategies has different challenges and benefits. For example, intramolecular reactions frequently produce more products because they have lower entropy compared to intermolecular reactions.⁴⁹ However, achieving selectivity and preventing side reactions might pose greater difficulties in intermolecular and multimolecular processes.⁹ Advancements in both stoichiometric and catalytic processes are highly desirable to improve the efficiency of macrocycle synthesis.

The aforementioned approaches can be further classified into two main categories: non-catalytic approaches and catalytic approaches, which facilitate the creation of large ring structures.

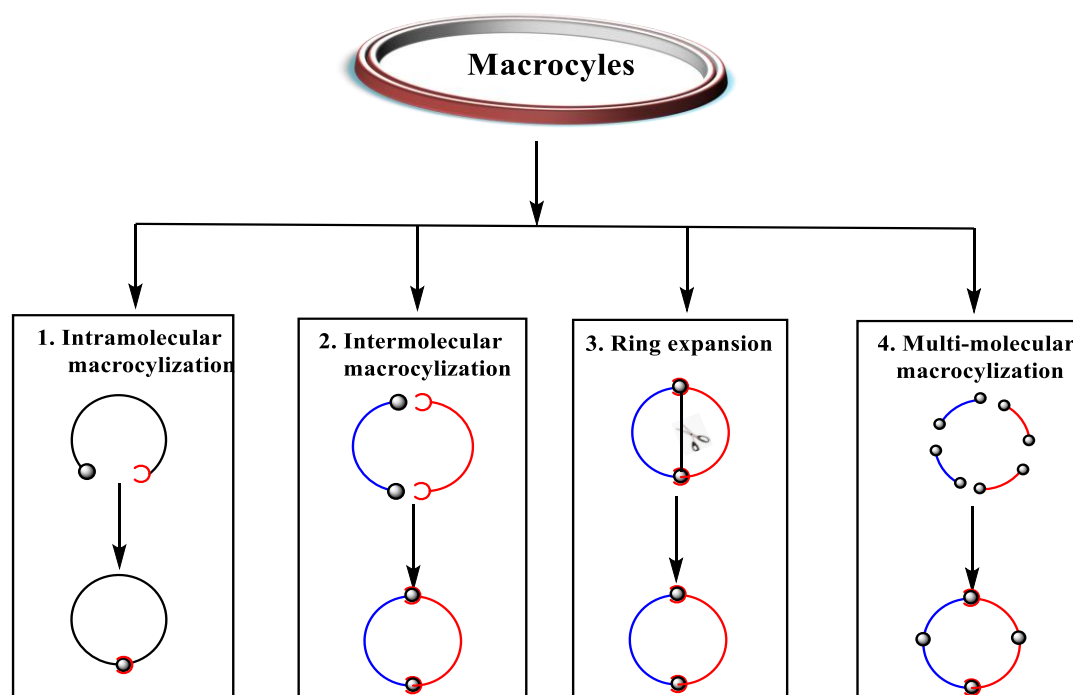


Figure 13. Different strategies for macrocyclization⁴⁸

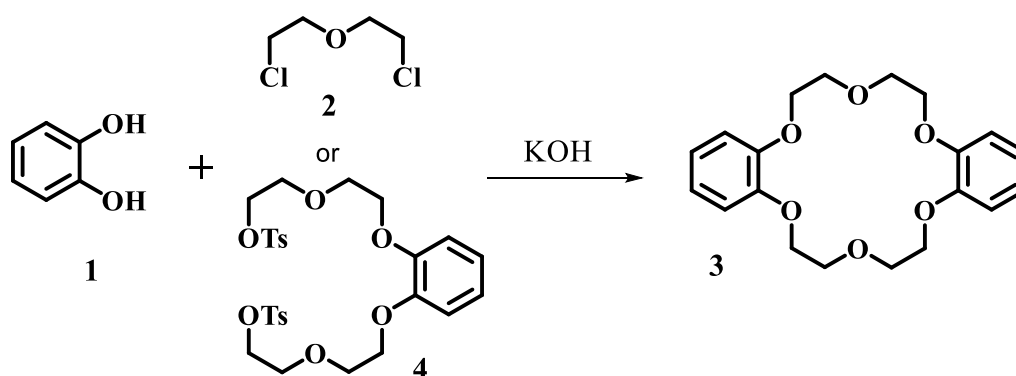
1.4.1 Non-catalytic Approach

A non-catalytic reaction is a chemical reaction that occurs without the involvement of a catalyst. In such reactions, the reactants interact directly to produce the products, eliminating the need for additional substances to accelerate the reaction.⁵⁰

In these reactions, reactants or reagents are consumed in stoichiometric amounts, meaning each reactant is used in a fixed ratio as dictated by the balanced chemical equation. These reagents are consumed during the reaction and are not regenerated or recycled.⁵¹ In addition, non-catalytic reactions may require higher activation energy compared to catalytic processes, often necessitating higher temperature or pressure to proceed at a practical rate.^{9,51} The increased activation energy and extended pathways have a direct impact on the duration required for a reaction to take place. Additionally, non-catalytic reactions play a crucial role in synthetic chemistry by providing straightforward reaction pathways to produce a wide range of organic molecules.

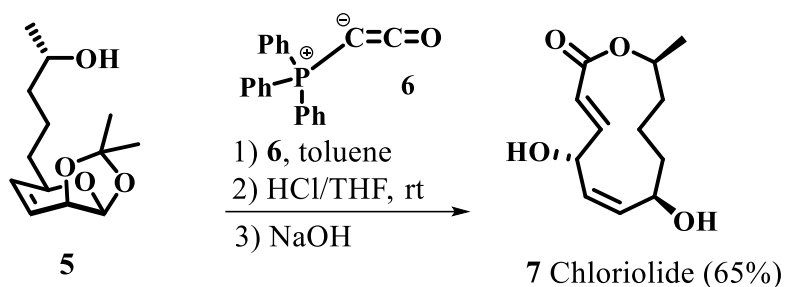
➤ Literature Overview on Non-catalytic Approaches

In this section, we provided a few representative examples of non-catalytic reactions for the synthesis of macrocycles. Williamson's etherification is a widely used classical example to synthesize macrocycles. In this reaction, an alkoxide reacts with an alkyl halide to produce an ether. Usually, the reaction occurs between a diol **1** and either a dihalide **2** or a tosylate **4**, leading to cyclization followed by the generation of macrocyclic ether **3**. (Scheme 1).⁵² This reaction generates halogenated waste and unwanted side products like oligomers.



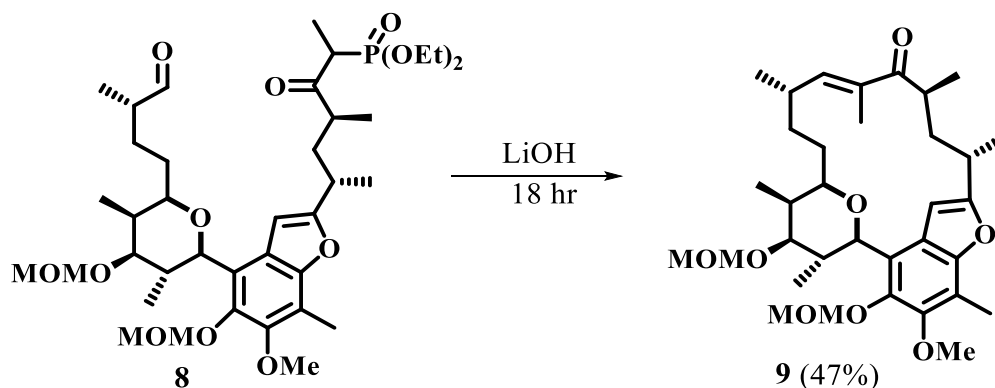
Scheme 1. An exemplary demonstration of Williamson's etherification

In 2014, Schobert and coworkers prepared chloriolide **7** by using Wittig reaction method as shown in Scheme 2. The ylide, known to be resistant to oxygen and moisture, was produced by combining alcohol **5** with Bestmann's ylide **6**. In the presence of NaOH, the ylide reacts with an aldehyde to produce the chloriolide **7** with a 65% yield (Scheme 2).⁵³



Scheme 2. Synthesis of macrocycle *via* Wittig reaction

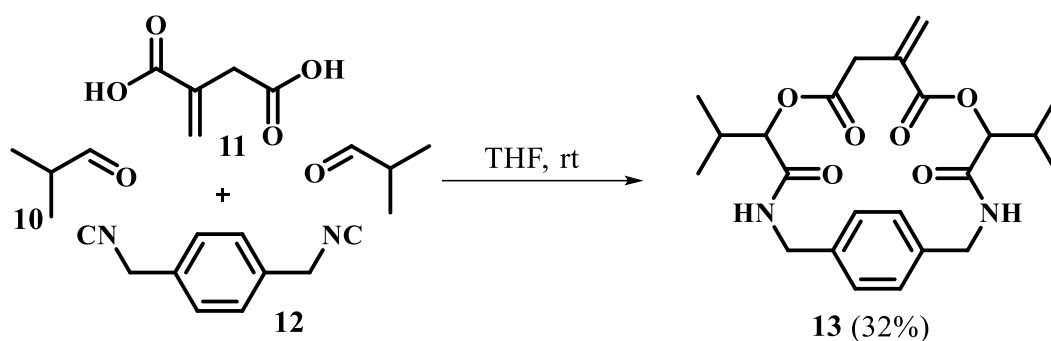
Later, Horner–Wadsworth–Emmons (HWE) intramolecular olefination was used for the total synthesis of the carbacyclic ansa antibiotic kendomycin **9**. The reaction utilizes β -keto phosphonate **8** and lithium hydroxide (LiOH) as a strong base to facilitate the transformation. After 18 hrs, this process resulted in the formation of **9** with a moderate (47%) yield (Scheme 3).⁵⁴



Scheme 3. Horner–Wadsworth–Emmons reaction for macrocyclization

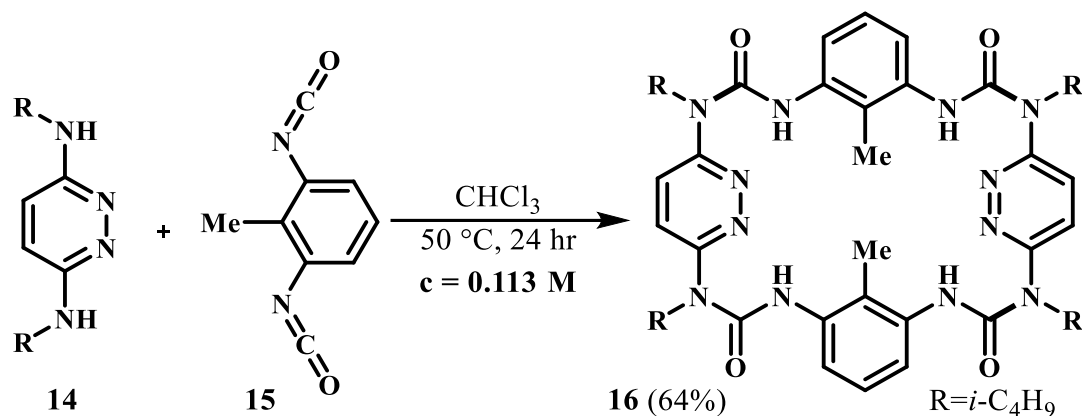
Although the HWE reaction is effective in forming carbon-carbon double bonds, it has several disadvantages. It requires the use of a strong base, which can limit substrate compatibility and lead to side reactions such as elimination or ylide decomposition, thereby reducing overall yields and tedious purification.

Next, Wessjohann and coworkers used the multicomponent Passerini reaction in 2008 to synthesize macrocycle **13** (Scheme 4). Dicarboxylic acid **11**, diisocyanide **12**, and isobutyraldehyde **10** were used in this Passerini macrocyclization to synthesize macrocycle **13** with a 32% yield. Eight new covalent bonds were formed in a single step (Scheme 4).⁵⁵ However, this reaction gives oligomers as unwanted side products.



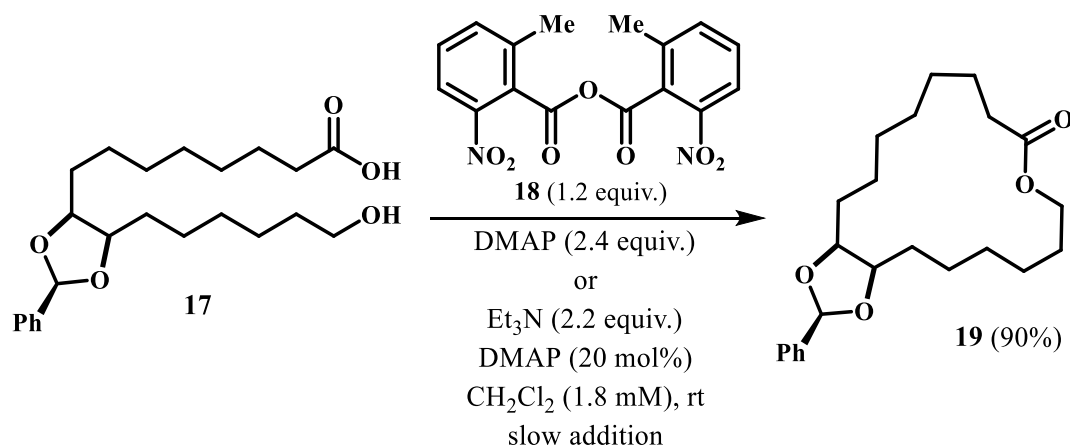
Scheme 4. Passerini reaction for macrocyclization

In another example of macrocyclization reported by Cuccia and coworkers, where diamines **14** and diisocyanates **15** reacts intermolecularly to give macrocyclic amide **16** in 64% yield at 0.113 M concentration (Scheme 5).⁵⁶



Scheme 5. Intermolecular macrolactamization reaction

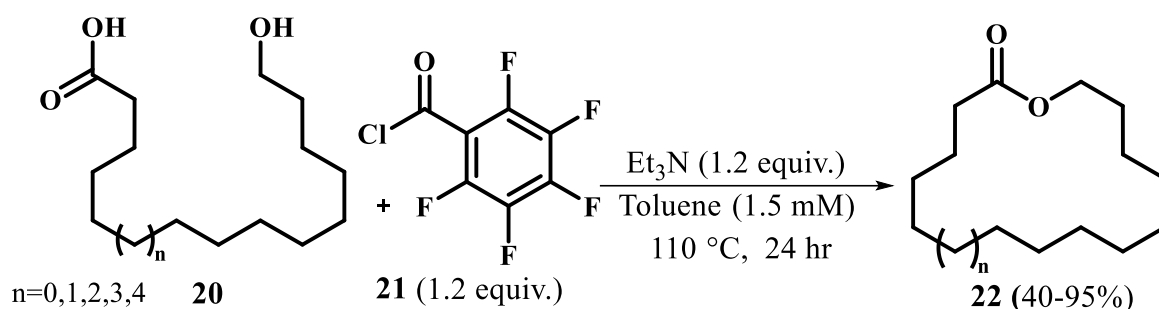
Shiina and coworkers described the intramolecular macrocyclic lactonization which utilizes 2-methyl-6-nitrobenzoic anhydride (MNBA) **18** as a stoichiometric coupling reagent, along with a base like 4-dimethylaminopyridine (DMAP) or triethylamine (Et_3N), to cyclize a



Scheme 6. Shiina macrolactonization of seco acid.

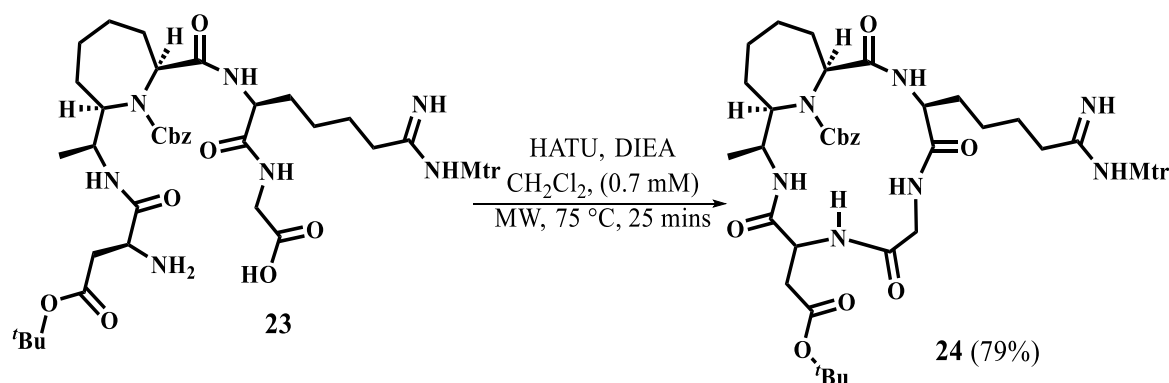
seco-acid **17** into a macrolactone **19** with a high yield of 90% (Scheme 6). However, this reaction generated stoichiometric waste. Specifically, the waste products include a derivative of the 2-methyl-6-nitrobenzoic acid, after the reaction of MNBA.⁵⁷

On the other hand, the intramolecular macrolactonization **22** was also achieved by refluxing seco-acid **20** with pentafluoro benzoyl chloride **21** in the presence of triethyl amine with 40-95% yield (Scheme 7).⁵⁸ A drawback of this reaction is that it generates an equal amount of pentafluoro benzoic acid as waste. Most importantly, slow reactant addition in a reaction mixture is always challenging stuff in large-scale reactions.



Scheme 7. Macrolactonization driven by a pentafluoro benzoyl chloride

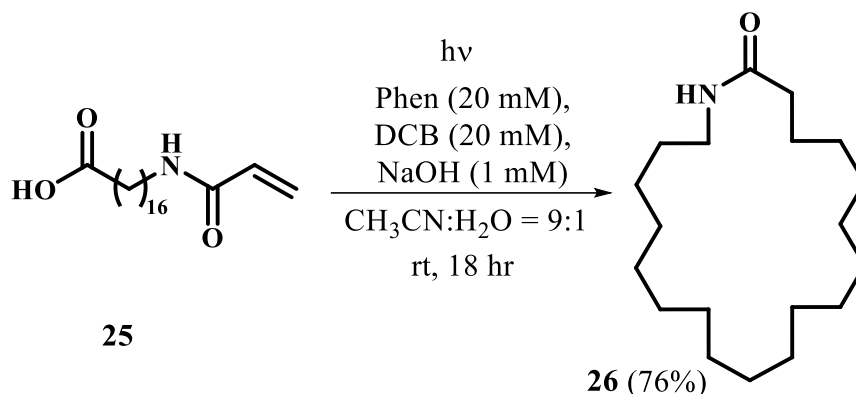
Cini et al. reported the MW-assisted synthesis of macrocyclic amide in 2012. The cyclopentapeptide analogue **24** was synthesized from a linear molecule **23** in the presence of hexafluorophosphate aza-benzotriazole tetramethyl uronium (HATU)/ *N,N*-diisopropylethylamine (DIEA) in dichloromethane (0.7 mM) at 75°C under MW irradiation for 25 min to afford **24** with 79% yield (Scheme 18).⁵⁹



Scheme 8. Synthesis of macrolactam using HATU

Next, Yoshimi and coworkers reported a photoinduced electron transfer (PET) radical photocyclization method for synthesizing a 20-membered macrocyclic lactam (**26**) from carboxylic acid acrylate amide **25**. The reaction was carried out in aqueous acetonitrile solution (9:1) with phenanthrene (phen) (20 mM), 1,4-dicyanobenzene (DCB) (20 mM), substrate **25**

(1 mM), and NaOH (1 mM) was irradiated with a 100 W high-pressure mercury lamp with a Pyrex filter ($\lambda > 280$ nm) in an argon atmosphere for 18 hours at room temperature.⁶⁰



Scheme 9. Photocyclization method for synthesizing a macrocyclic lactam

These macrocyclization reports frequently encounter common limitations listed below.

➤ **Limitations of Non-catalyzed Approach Toward Macrocycle Synthesis**⁶¹

- ✓ **Reaction time:** These reactions required longer reaction times to achieve macrocyclization, leading to decreased efficiency
- ✓ **Energy:** Higher activation energy is required
- ✓ **Reaction Efficiency:** To achieve cyclization, non-catalyzed methods require harsh reaction conditions, such as high temperatures or strong acids or bases. This can lead to lowering the yield of macrocycle
- ✓ **Scalability:** Scaling up non-catalyzed macrocycle synthesis can be challenging due to reproducibility issues. Implementing high-dilution reactions at a larger scale is particularly problematic due to handling bigger reaction apparatus
- ✓ **Environmental Impact:** Generate unwanted side products and toxic waste.

To address these limitations often requires innovative synthetic strategies or the development of new catalytic approaches to enhance efficiency, selectivity, and sustainability in macrocycle synthesis. Catalytic approaches have overcome most of the limitations associated with the non-catalytic approaches.

1.4.2 Catalytic Approaches

In general, a catalyst is a substance that facilitates a chemical reaction by lowering the activation energy of the reaction to proceed, without being consumed in the reaction itself.⁶¹ Many macrocyclization reactions are very slow due to the challenge of bringing two reactive ends closer to react.^{61,62}

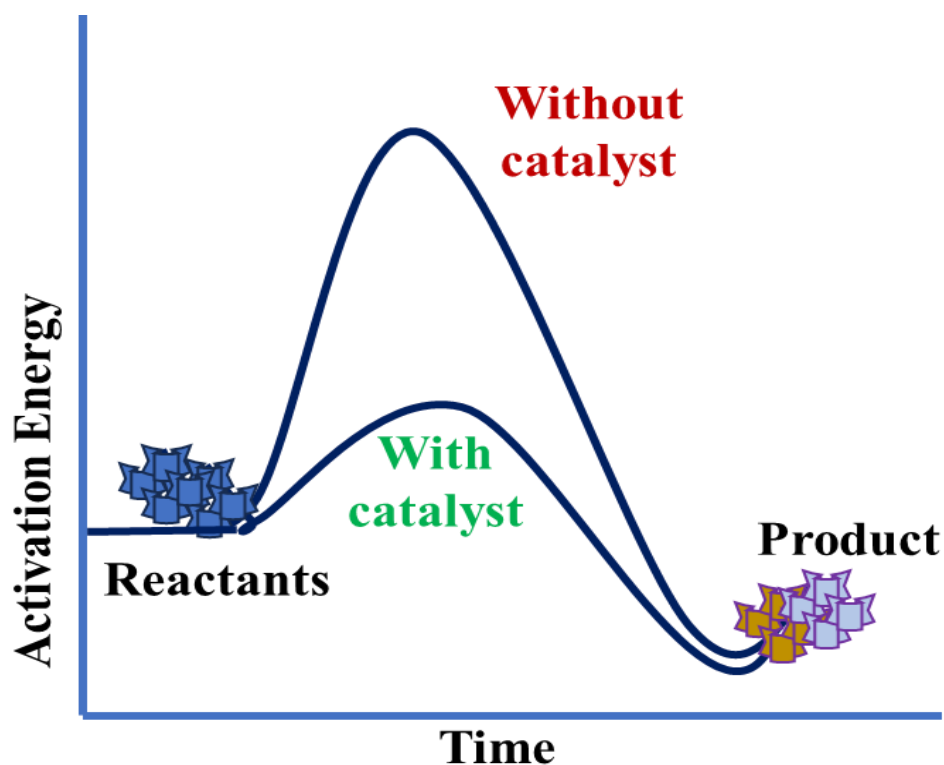


Figure 14. The energy profile diagram of a reaction with a catalyst and without a catalyst

Moreover, catalytic reactions typically operate under milder reaction conditions (e.g., lower temperatures, reduced energy consumption, and environmental impact compared to non-catalytic approaches.⁶³ The catalytic reactions offer additional benefits such as reducing process steps and improving atom economy.⁶⁴ These advantages make catalytic methods highly desirable for both research and industrial applications, which allows the synthesis of complex and diverse macrocyclic structures that are difficult to achieve through non-catalyzed reactions.

Catalysts can significantly speed up macrocyclization reactions with improved efficiency, selectivity, and yield compared to non-catalytic methods.⁶¹ Furthermore, in the process of forming macrocyclic compounds, different types of catalysts and catalytic reactions are used based up on the specific reaction conditions and the desired macrocyclic compound. For instance, the palladium-catalyzed Heck reaction,⁶⁵ copper-catalyzed click reaction,⁶⁶ and Ullmann coupling⁶⁷ can be employed. Additionally, ring-closing metathesis⁶⁸ and the use of

acid or base catalysts have also been reported (Figure 15). Therefore, these methods are commonly employed in coupling reactions to produce macrocycles. Considering all these findings and advantages, catalyst plays an essential role in green chemistry.⁶⁹

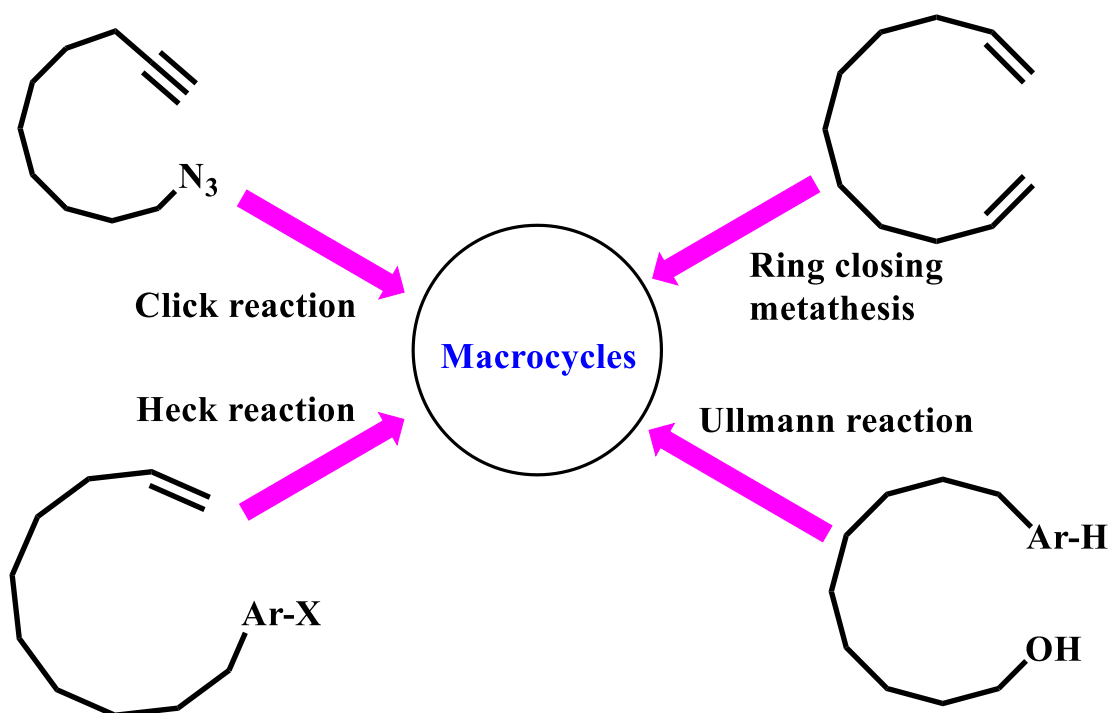


Figure 15. Illustrative examples of metal-catalyzed macrocyclization

Furthermore, catalytic processes are broadly classified into two main types: homogeneous and heterogeneous catalysis. As shown in Figure 16, this categorization is based on the uniformity of the catalyst's phase to the reactants.⁷⁰

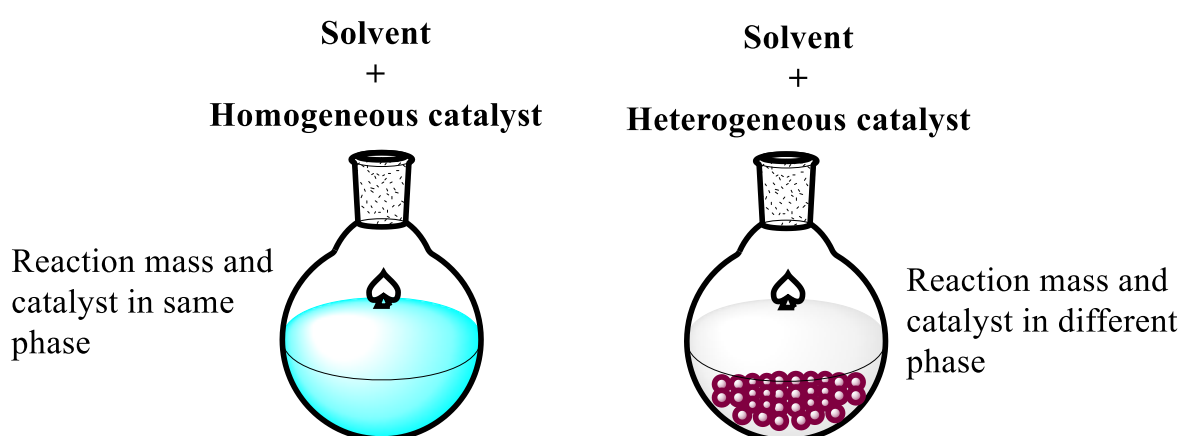
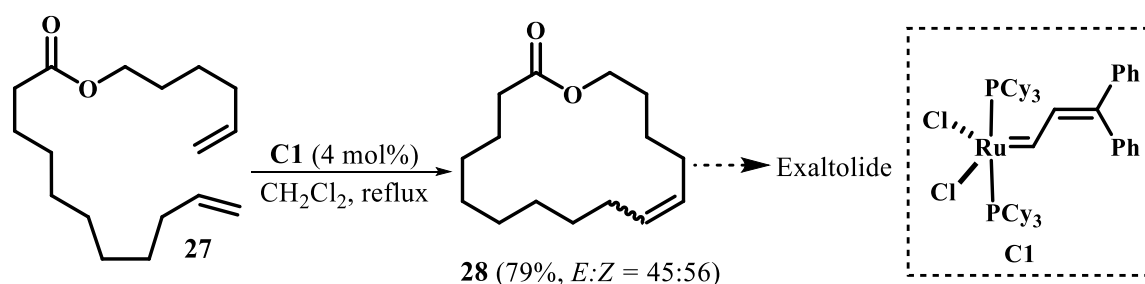


Figure 16. Homogeneous and Heterogeneous Catalysis

➤ Homogeneous catalysis

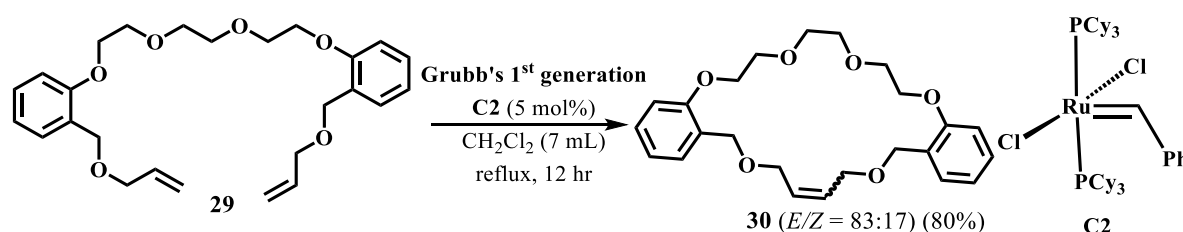
Homogeneous catalysts exist in the same phase of the reactants, usually in a liquid phase (Figure 16).⁷⁰ This allows the catalyst to interact more efficiently with the reactants, speeding up the reaction process. Additionally, catalytic cycles and mechanisms are easy to understand in homogeneous catalysis.⁷⁰ Various industrial processes and organic synthesis reactions commonly use homogeneous catalysts.

In 1997, Fürstner, and coworkers synthesized macrocycles using a ring-closing metathesis (RCM) approach. Some straightforward syntheses of macrocyclic lactones, lactams, ethers, and ketones, including the musk-smelling perfume component exaltolide are elucidated below. The dialkene **27** reacted with Ru-carbene catalyst **C1** (4 mol%) in CH₂Cl₂ and refluxing the reaction mixture afforded the 16-membered macrocyclic lactone **28** in 79% isolated yield with *E*:*Z* = 46:54 ratio (Scheme 10).⁶⁸



Scheme 10. Synthesis of macrocyclic lactone using ring-closing metathesis approach

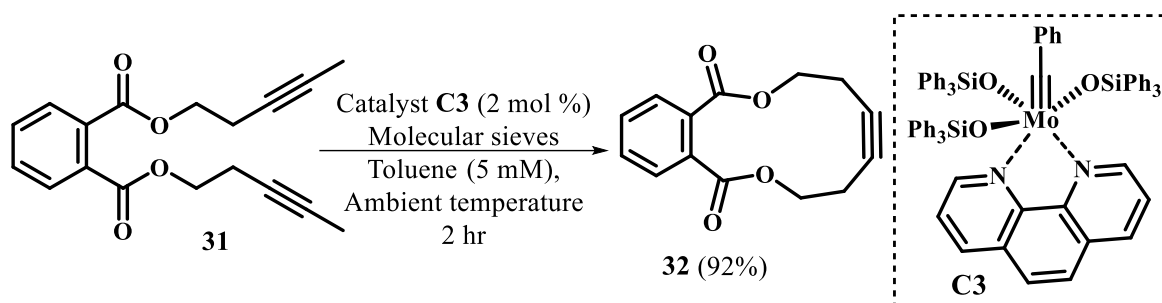
Moreover, ring-closing metathesis-based synthesis of a new class of polyether macrocyclic system was reported by the Babu group. This reaction uses Grubb's first-generation catalyst **C2** (5 mol%) and furnished the macrocyclic olefin **30** as a mixture of *E*:*Z* (83:17) with 80% yield from dialkene compound **29** (Scheme 11).⁷¹



Scheme 11. Synthesis of macrocyclic ether using RCM approach

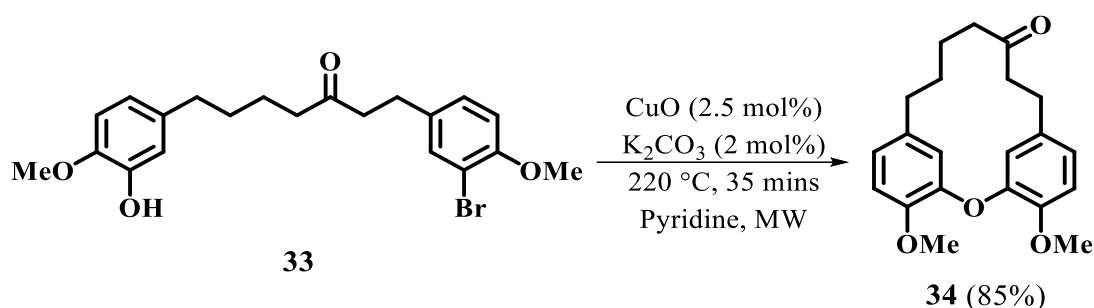
Additionally, Schrock and coworkers introduced the first alkyne metathesis catalyst in 1980. Next, Tamm and colleagues demonstrated ring-closing alkyne metathesis (RCAM) for the synthesis of medium-ring structure. In this reaction, intramolecular di-alkyne **31** reacted

with **C3** at an ambient temperature, afforded a 92% yield of macrocyclic alkyne **32** (Scheme 22).⁷²



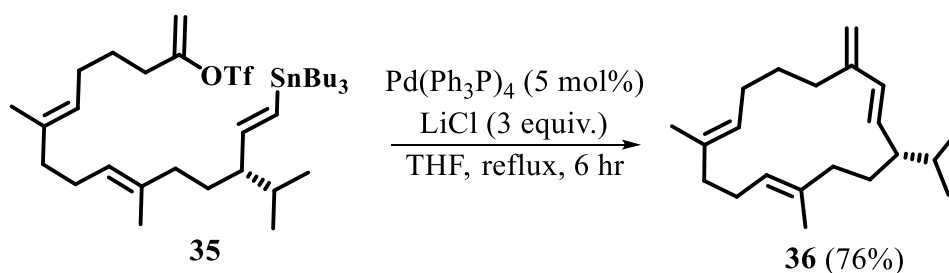
Scheme 12. Synthesis of macrocyclic lactone using RCAM approach

Next, Sun's group reported a microwave-assisted intramolecular Ullmann reaction to deliver macrocyclic diaryl ether. In this reaction, the compound **33** and 2.5 mol% of CuO and 2 mol% of potassium carbonate and pyridine as a solvent were heated at 220 °C for 35 mins in a sealed tube under microwave irradiation to afford 85% yield of the macrocyclic ether **34** (Scheme 13).⁶⁷



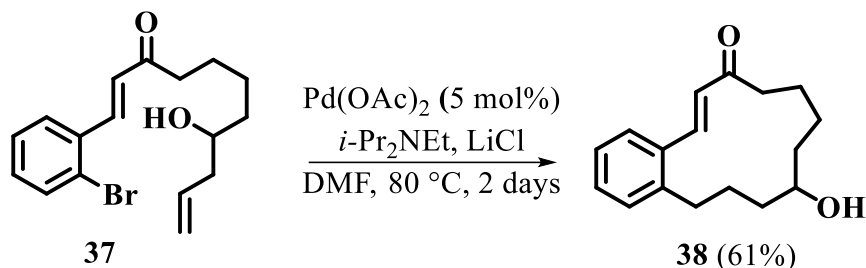
Scheme 23. Microwave-assisted intramolecular ullmann reaction

In 2003, Li and coworkers exemplified Pd-catalyzed Stille coupling for macrocyclization. Cyclization of **35** was accomplished with tetrakis(triphenylphosphine)palladium [Pd(Ph₃P)₄] (5 mol %) in the presence of lithium chloride (3 equiv.) in THF solvent under refluxing for 6 hr to afford the macrocyclic product **36** in 76% yield (Scheme 14).⁷³



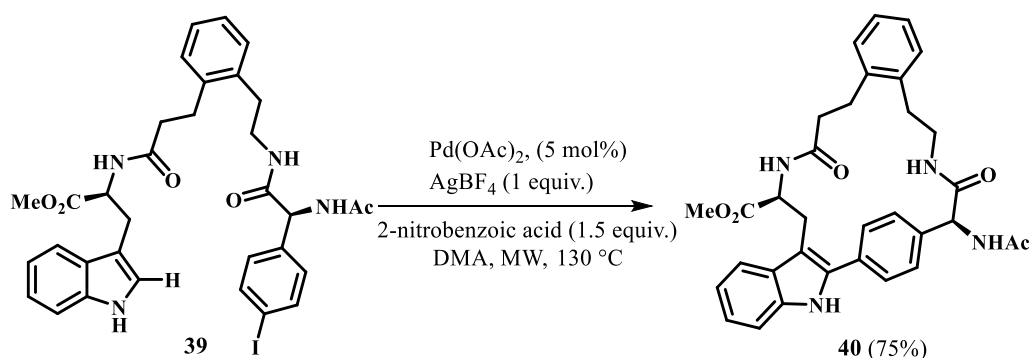
Scheme 14. Stille coupling for macrocyclization

Further, the palladium-catalyzed intramolecular coupling process leads to a functionalized macrocycle documented by Grundt and coworkers. A relatively high dilution of the **37** with 5 mol% of Pd(OAc)₂, *N*-ethyldiisopropylamine, and LiCl is crucial to obtain 61% yield of 13-membered macrocyclic compound **38** after 2 days (Scheme 15).⁶⁵



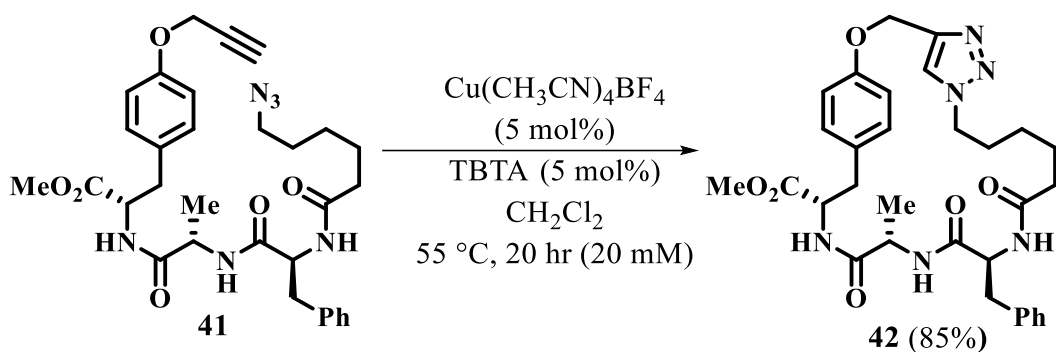
Scheme 15. Intramolecular Heck macrocyclization

Moreover, in 2012, James and coworkers reported a macrocyclization reaction *via* C-H activation. In this study, a linear compound **39** was subjected to a Pd-catalyzed intramolecular C-H arylation reaction under microwave heating, forming macrocycle **40** with a 75% yield. The reaction employed a 5 mol% of Pd(OAc)₂ as the catalyst, AgBF₄ as the additive, 2-nitrobenzoic acid as the ligand, and dimethylacetamide (DMA) as the solvent at 130 °C (Scheme 16).⁶⁶



Scheme 16. Macrocyclization *via* C-H activation

Later, same group reported macrocyclization *via* a copper-catalysed azide-alkyne cycloaddition (CuAAC) reaction from compound **41** in CH₂Cl₂ (0.02 M substrate concentration) for 20 hr using tris[(1-benzyl-1*H*-1,2,3-triazol-4-yl)methyl]amine (TBTA) (5 mol%) and tetrakis(acetonitrile)copper(I)tetrafluoroborate (Cu(CH₃CN)₄BF₄) (5 mol%) delivered 85% yield of compound **42** (Scheme 17).⁶⁷



Scheme 17. Macrocyclization using click reaction

Overall, homogeneous catalyzed reactions play a crucial role in macrocycle synthesis, yet their catalysts often lack diversity in substrates and reusability for subsequent reactions. In contrast, heterogeneous catalysts are significant in these syntheses due to their ability to be reused and recycled across several reaction cycles.

➤ Heterogeneous Catalysis

Heterogeneous catalysts are substances that accelerate chemical reactions while remaining in a different phase than the reactants.⁷⁴ Typically, these catalysts are solids, and the reactants could be solids, gases, or liquids (Figure 13). The use of heterogeneous catalysts dates back to ancient times, with early examples including solid materials in fermentation and the production of alcoholic beverages. The modern understanding of heterogeneous catalysis began to take shape in the 19th and 20th centuries, with significant advancements made by chemists such as Fritz Haber.⁷⁵

Importantly, heterogeneous catalysts are valuable tools in chemical synthesis, including the production of macrocycles and other complex molecules. These catalysts offer several advantages in chemical reactions.

➤ Advantages of Heterogeneous Catalysts⁷⁶

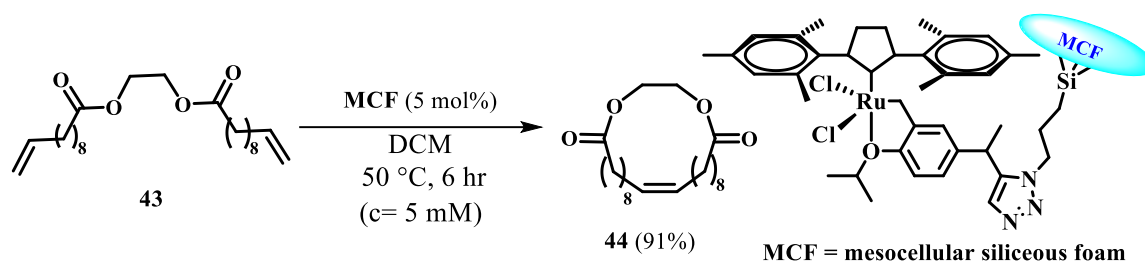
1. Easy to separate and recover the catalyst from the reaction mixture as the catalyst and reactants/products are in different phases.
2. Due to the reusability feature of heterogeneous catalysts, it increases the overall cost-effectiveness of industrial processes.
3. Heterogeneous catalysts decrease the activation energy required for the reaction, thereby increasing the reaction efficiency.
4. Typically, heterogeneous catalysts remain stable under reaction conditions, enabling repeated use without any significant loss in catalyst activity.

- Heterogeneous catalysis helps in minimizing waste and by-products, which is crucial for a sustainable synthesis and manufacturing process.

Additionally, heterogeneous catalysts are used for environmental cleanup processes and are also utilized to degrade organic pollutants in water and air, thereby contributing to a greener ecosystem. Moreover, the synthesis of macrocyclic compounds involves many heterogeneous catalysts. They facilitate the formation of macrocyclic structures through various types of chemical reactions.

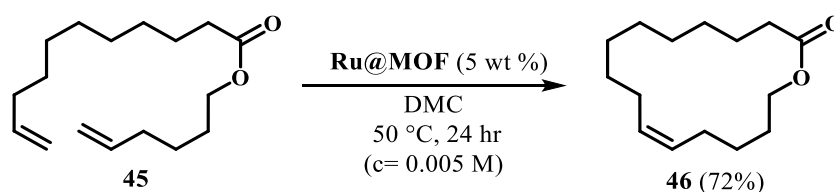
➤ Overview of Heterogeneous Catalysis for Macrocyclization

Here, we provided an overview of heterogeneous catalysis that is employed in the synthesis of macrocycles. Lee and coworkers synthesized macrocycles *via* RCM reaction using heterogeneous metathesis catalysts. Ruthenium-based metathesis catalysts immobilized on mesocellular siliceous foam (MCF) bearing large nanopores proved highly efficient and selective for macrocyclic ring-closing metathesis (RCM). In this reaction, dialkene **43** reacted with a heterogeneous Ruthenium-based catalyst in DCM solvent with high dilution conditions, delivering a 91% yield of macrocyclic dilactone **44** (Scheme 18).⁷⁷



Scheme 18. Ring-closing metathesis (RCM) by heterogeneous catalyst

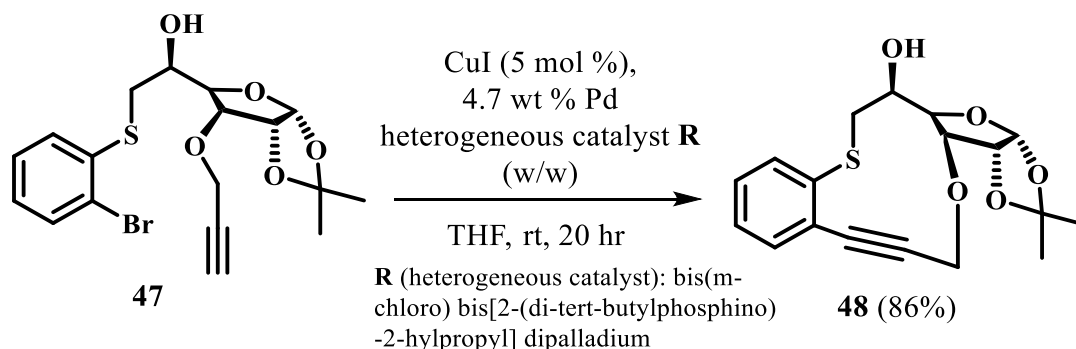
Next, Grela and coworkers synthesized a macrolactone using a heterogeneous Ru-MOF catalyst via ring-closing metathesis (RCM). In this reaction, a 5 wt% of Ru@MOF catalyst and **45** in dimethyl carbonate (DMC) solvent were heated at 50 °C to obtain 72% yield of **46** under higher dilution conditions (Scheme 19).⁷⁸



Scheme 19. RCM reaction performed by heterogeneous Ru-MOF catalyst

Next, heterogeneous Palladium-catalyzed intramolecular Sonogashira coupling was reported by Mukherjee and coworkers. In this reaction, CuI and 4.7 wt% of Pd-heterogeneous

catalyst reacted with compound **47** in THF solvent at room temperature and delivered the 13-membered macrocyclic product **48** in 86% yield (Scheme 20).⁷⁹



Scheme 20. Heterogeneous palladium-catalyzed intramolecular sonogashira reaction for macrocyclization

All non-catalytic and catalytic macrocyclization reactions were reported under conventional batch processes. Typically, macrocyclization reactions performed well under high dilution conditions with the slow addition of reactants. However, traditional batch processes have several limitations for the synthesis of macrocycles.

➤ Limitations of Batch Process for the Macrocyclization^{61,80}

- **Scalability:** Macrocycles often require high dilution and precise conditions. Consequently, the large-scale production of macrocyclic compounds is very difficult in batch process.
- **Longer reaction time:** Batch processes are time-consuming. Because of less surface area, improper mixing, and complex reaction setup
- **Yield and purity:** The formation of macrocycles often competes with linear oligomers and polymers, leading to side reactions and impurities. This results in poor yield and difficulty in the separation of the mixture
- **Reproducibility:** Reproducing the same results across different batches can be difficult
- **Multiple steps:** Conventional processes make it difficult to do multiple-step reactions
- **Increases manpower:** The need for multiple cycles of reaction and purification increases manpower and material costs
- **Control over reaction conditions:** Maintaining consistent reaction conditions can be challenging, such as temperature, pressure, and concentration can fluctuate more in batch processes

- **Safety:** Safety risks can be higher in batch processes. For example, larger volumes of hazardous or explosive reactants and products handling at one time for the large-scale reaction can increase the risk of severe accidents

To address these limitations of batch processes in chemical synthesis, continuous flow chemistry has emerged as an innovative alternative technique.

1.5 Continuous Flow Chemistry

Continuous flow chemistry involves conducting chemical reactions in a continuously flowing stream rather than in discrete batches.⁸¹ Developing a new method for macrocyclization utilizing continuous flow chemistry could address the various limitations of batch reactions, such as longer reaction times, high dilution requirements, and scale-up issues⁸⁰ Moreover, continuous flow chemistry is a well-established technique, extensively used in the

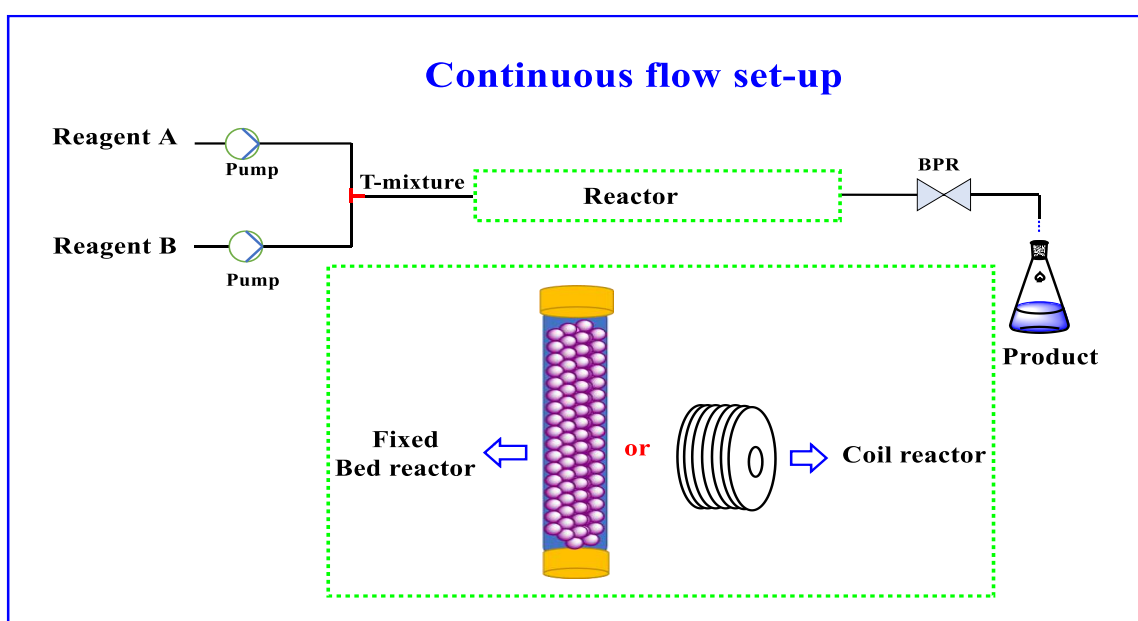


Figure 17. A representation of continuous flow set-up

large-scale production of chemical intermediates and organic compounds.⁸² Continuous flowing of the reactants through a reactor allows better control over reaction parameters like temperature, pressure, and reaction time.⁸² It also facilitates rapid optimization of reaction conditions and can lead to higher yields and purities of the desired products. By implementing continuous flow technique, the production of macrocycles could become more efficient, cost-effective, and environmentally friendly.⁸²

Notably, flow chemistry is applicable to both homogeneous and heterogeneous catalysis.⁸³ A coil reactor is used for homogeneous catalysis in which the solution flows through a coil reactor, while a fixed column bed reactor is employed in heterogeneous catalysis where

the solution passes through a stationary column bed (Figure 17). Flow chemistry has revolutionized the synthesis of organic compounds, making processes more efficient, safer, and scalable, suitable for both academic research and industrial applications.

➤ **Basic Parameters of Flow Chemistry**

- **Residence Time:** Adjusted by varying the flow rate and the reactor volume
- **Mixing:** Efficient mixing of starting materials under uniform reaction conditions, leading to better yields and selectivity
- **Pressure:** Higher pressure can increase reaction rates and solubility of gases, enabling reactions that are not feasible under ambient conditions. The pressure of the system can be controlled by a back-pressure regulator (BPR)
- **Temperature:** Temperature control is crucial for reaction rate, selectivity, and safety. Rapid heating and cooling is possible due to the high surface area-to-volume ratio in flow reactors

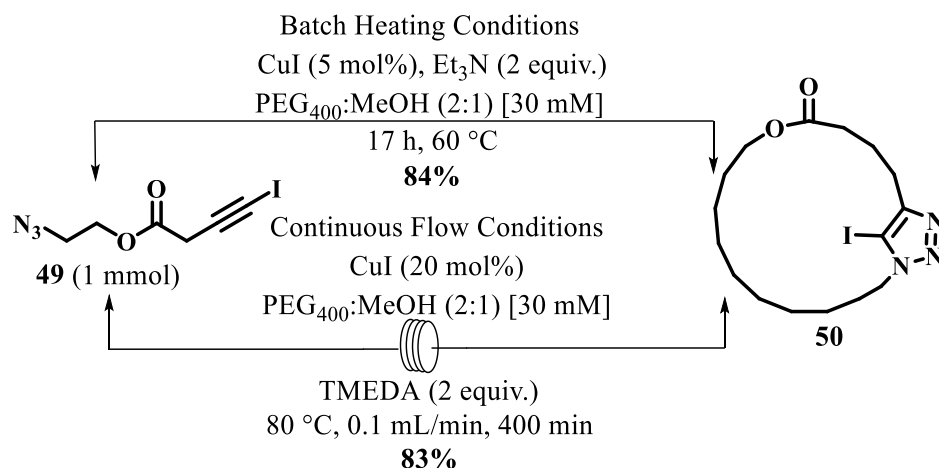
➤ **Advantages of Continuous Flow Processes**⁸⁴

- **Enhanced Safety:** Smaller reaction volumes reduce the risk of hazardous reactions
- **Better Control:** Precise control over reaction parameters leads to consistent and reproducible results
- **Scalability:** Easy to scale up by running continuous and multiple reactors in parallel
- **Efficiency:** Continuous operation can lead to high throughput and productivity
- **Easy to reuse:** Heterogeneous catalysts can be easily recovered and reused

Due to potential applications of the continuous flow technique, numerous literature reports have been developed for the synthesis of macrocycles under a continuous flow process.

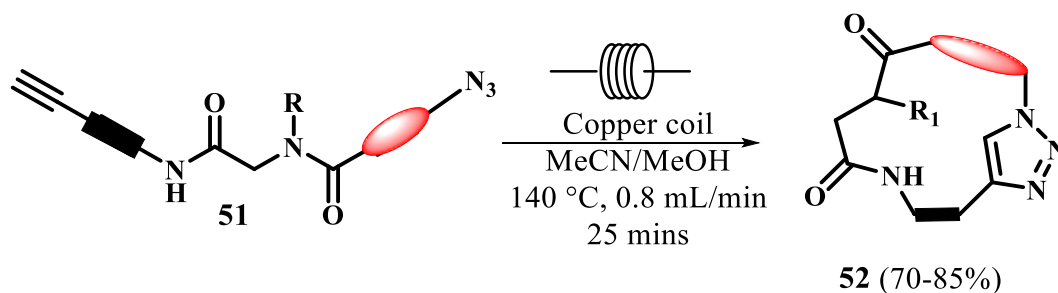
1.5.1 Literature Report on Continuous Flow Macrocyclization

In this section, we have provided a few examples of continuous flow mediated macrocyclization reactions. In 2014, Collins and coworkers demonstrated click reaction under batch and continuous flow conditions. They described Cu(I)-catalyzed azide-iodoalkyne cycloaddition (CuAiAC) for the synthesis of triazole-based macrocycle. This strategy were demonstrated on a large scale to obtain the desired triazole macrocycle **50** in 83% yield from **49** under continuous flow conditions in 400 min (6.6 h). However, batch conditions afforded 84% yield after 16 hr (Scheme 21).⁸⁵



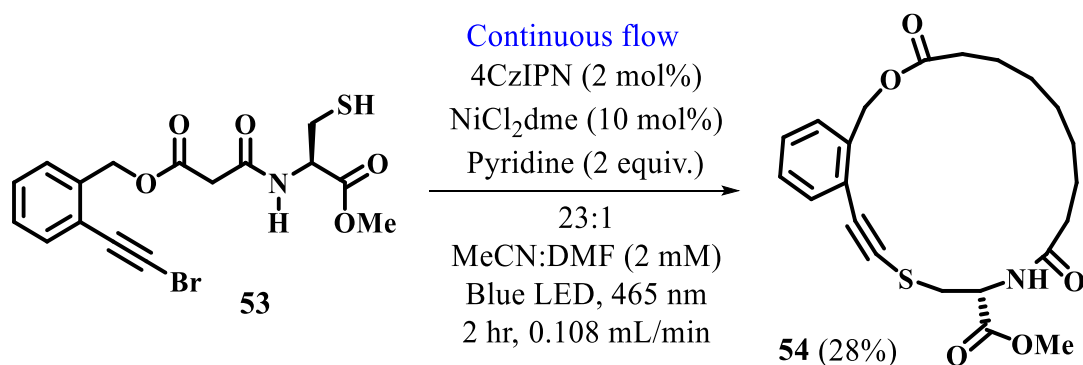
Scheme 21. Cu-catalyzed click reaction under batch and continuous flow for macrocyclization

In 2015, Oliver Kappe and coworkers reported a click reaction. In this process, linear peptides **51** in a 1:1 MeCN: MeOH mixture (2 mM) were pumped at 0.8 mL/min through a copper coil with a 20 mL internal volume, heated to 140 °C in a GC oven. This reaction yielded 70-85% of macrocycle **52** (Scheme 22).⁸⁶



Scheme 22. Intramolecular Cu-catalyzed azide-alkyne cycloaddition (CuAACs) for macrocyclization

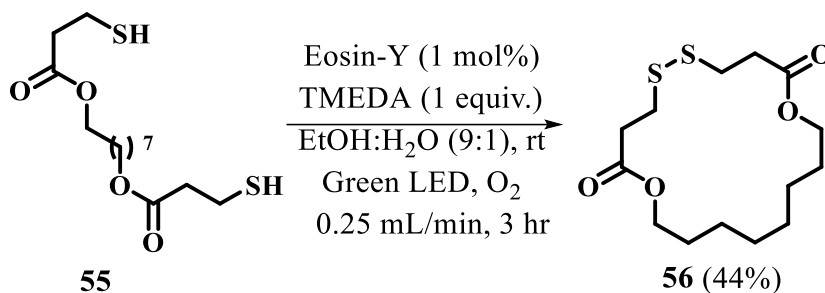
Next, the Collins group aimed to combine the benefits of photochemistry and flow chemistry for macrocyclization. They performed a reaction of **53** in the presence of a nickel complex and 2,4,5,6-Tetra(9*H*-carbazol-9-yl) (4CzIPN) as catalyst under continuous flow and



Scheme 23. Photochemical and continuous flow macrocyclization

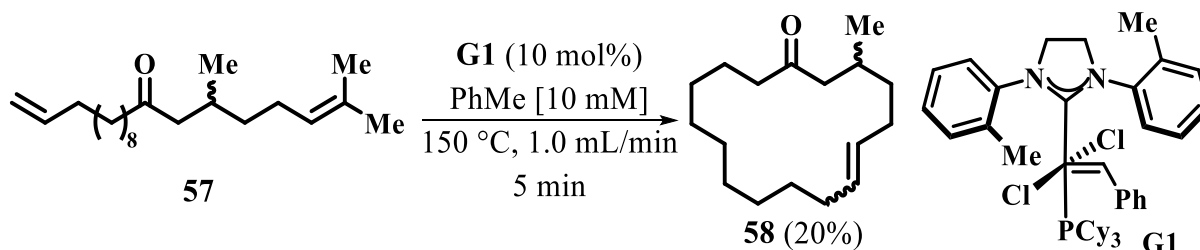
blue LED irradiation to obtain a 28% yield of the desired product **54** in 2 hr (Scheme 23).⁸⁷

After that, the same group reported intramolecular reaction of disulfide **55** under continuous flow using Eosin Y as a photocatalyst (1 mol %) and tetramethylethylenediamine (TMEDA) as a base (1 equiv.). The reaction was carried out in a 9:1 EtOH:H₂O solvent with O₂ as an oxidant. Additionally, the reaction was initiated by irradiation of green LED light to activate the photocatalyst. Under these conditions, they achieved a 44% yield of the desired macrocycle **56** (Scheme 24).⁸⁷



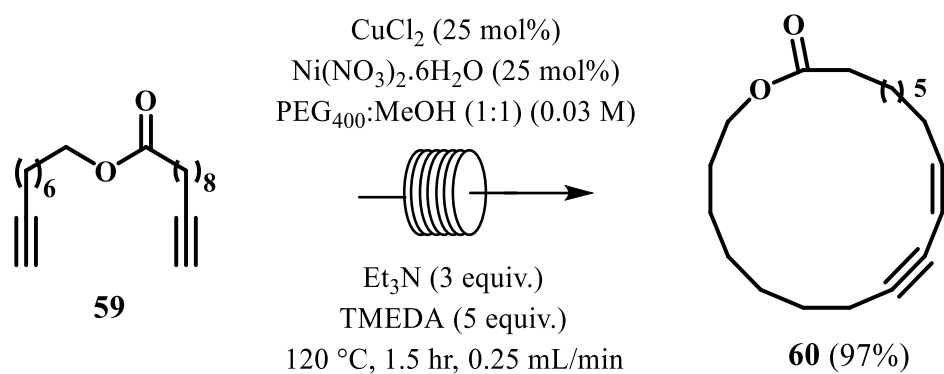
Scheme 24. Olivetylverbenyl synthesis in a continuous flow using a coil reactor

Next, Morin et al. have synthesized a macrocyclic musk using continuous flow conditions through a ring-closing metathesis reaction. In a 10 mM toluene solution of **57**, they used 10 mol% of the Ru-catalyst **G1**. The flow rate was maintained to 1.0 mL/min at 150 °C, with a residence time of 5 minutes. This process yielded a 20% conversion of alkene **57** to macrocycle **58** (Scheme 25).⁸⁸



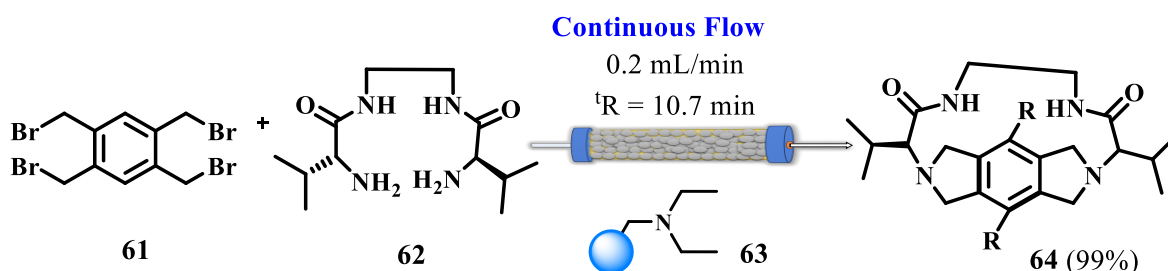
Scheme 25. Synthesis of macrocyclic musk using continuous flow conditions

Moreover, continuous flow intramolecular macrocyclization *via* coupling reaction was reported by the Collins group in high concentrations in a coil reactor. In this reaction, a solution of compound **59** with 25 mol% CuCl₂, and Ni(NO₃)₂·6H₂O, Et₃N (3 equiv.) and tetramethyl ethylene diamine [TMEDA] (5 equiv.) was added in MeOH (5 mL). This mixture was passed through a 5 mL stainless-steel coil at 0.25 mL/min at 120 °C for 1.5 h residence time afforded 97% yield of product **60** (Scheme 26).⁸⁹



Scheme 26. Macrocyclization *via* coupling reaction in a continuous flow using coil reactor

Next, García-Verdugo and coworkers reported continuous flow synthesis of constrained Pseudopeptidic macrocycles. In this reaction, the solutions of **61** and **62** in acetonitrile (4 mM) were pumped through an Omnifit column packed with 1 gm of resin-supported amine base **63** for 10.7 min of residence time by adjusting the flow rate of 0.2 mL/min afforded macrocyclic amide **64** with 99% yield (Scheme 27).⁸⁰



Scheme 27. Macrocyclic *N*-alkylation using a heterogeneous base in a continuous flow

1.6. Conclusion

In this chapter, a comprehensive overview of macrocycles, delving into their classification and highlighting their significance across various commercial applications have been provided. Further, the challenges inherent in macrocyclization, offering insights into key strategies for synthesizing macrocycles are addressed. A significant emphasis was placed on the role of catalysis and continuous flow techniques in facilitating macrocycle synthesis, illustrating how these methods can significantly enhance reaction efficiency, selectivity, and scalability in organic synthesis.

1.7. Aim and Rationale of Thesis Work

The macrocyclic framework occupies a unique segment in the chemical space and serves as a common synthetic target across various synthetic fields. Consequently, the synthesis of macrocyclic compounds remains a significant objective for research endeavours. Indeed,

developing new processes to facilitate highly scalable and faster macrocyclization is essential. Notably, traditional chemical processes often generate toxic waste and by-products, affecting the environment and human health. However, the advent of green chemistry principles presents an opportunity for developing more economically viable and safer processes. In this context, catalysis and continuous flow reactions play a crucial role in the synthesis of macrocycles, with extensive applications in natural products and their analogues. Despite these advancements, fully adhering to all green chemistry principles remains a challenging task. Thus, we propose that catalysis and continuous flow method offers a promising approach to tackle the challenges in macrocyclization reactions. Therefore, this thesis aims to develop innovative synthetic approaches for macrocyclization and design new tools for easy scale-up for handling the high dilution conditions while minimizing waste generation. This approach would contribute to advancing the field of synthetic organic chemistry and enhance efforts toward sustainability and environmental protection.

1.8 Objectives of the Thesis Work

➤ **Catalytic Direct Macrocyclization Using Dehydrogenative Coupling of Alcohols and Ketones and Application Towards Synthesis of Natural Product Engelhardione**

The objective of this work is to develop a new approach for intramolecular end-to-end cyclization toward the synthesis of macrocyclic compounds *via* the coupling of ketone-alcohol and primary/secondary alcohol using a metal catalyst. Previous reports demonstrate the use of oxidative reagents, strong bases, halogenated leaving groups, air-sensitive catalysts, and multi-step reactions, which lead to side reactions and significant waste generation. Therefore, our goal is to establish an environmentally friendly protocol that avoids these traditional methods and multi-step processes.

To achieve this, we focused on developing intramolecular macrocyclization reactions using keto-alcohol in the presence of Ru-catalyst and base. Furthermore, this method generates water as the only by-product, thereby minimizing environmental impact. Additionally, we planned to apply this approach to synthesize the natural product Engelhardione.

➤ **Handling of High Dilution Macrolactonization Reaction in Homogeneous Conditions under Continuous Flow Process**

Macrocycles containing an ester functional group are known as macrolactones, which play a crucial role in numerous natural, biologically active pharmaceuticals, agrochemicals, supramolecular chemistry, fragrance industry, and various other fields. Several classical reports

are available for the synthesis of macrolactones using seco acids through the activation of carboxylic acids or hydroxy groups. Coupling reagents such as 2,2'-dipyridyl disulfide (PyS)₂, 2-Methyl-6-nitrobenzoic anhydride, 2,4,6-trichloro benzoyl chloride (TCBC), Diisopropyl azodicarboxylate (DIAD), and the Mukaiyama reagent (2-chloro-1-methyl pyridinium iodide) are commonly employed in batch conditions.

However, batch macrolactonization is typically limited to small-scale synthesis because it requires higher dilution and slow addition of reagents, which also necessitates a larger area for synthesis. Therefore, our objective is to develop an innovative methodology for macrolactonization using seco acids and cost-effective Mukaiyama reagents under continuous flow conditions with higher dilution conditions, enabling efficient operation in smaller spaces while prioritizing scalability. This approach aims to address these challenges by establishing a scalable method for synthesizing macrolactones.

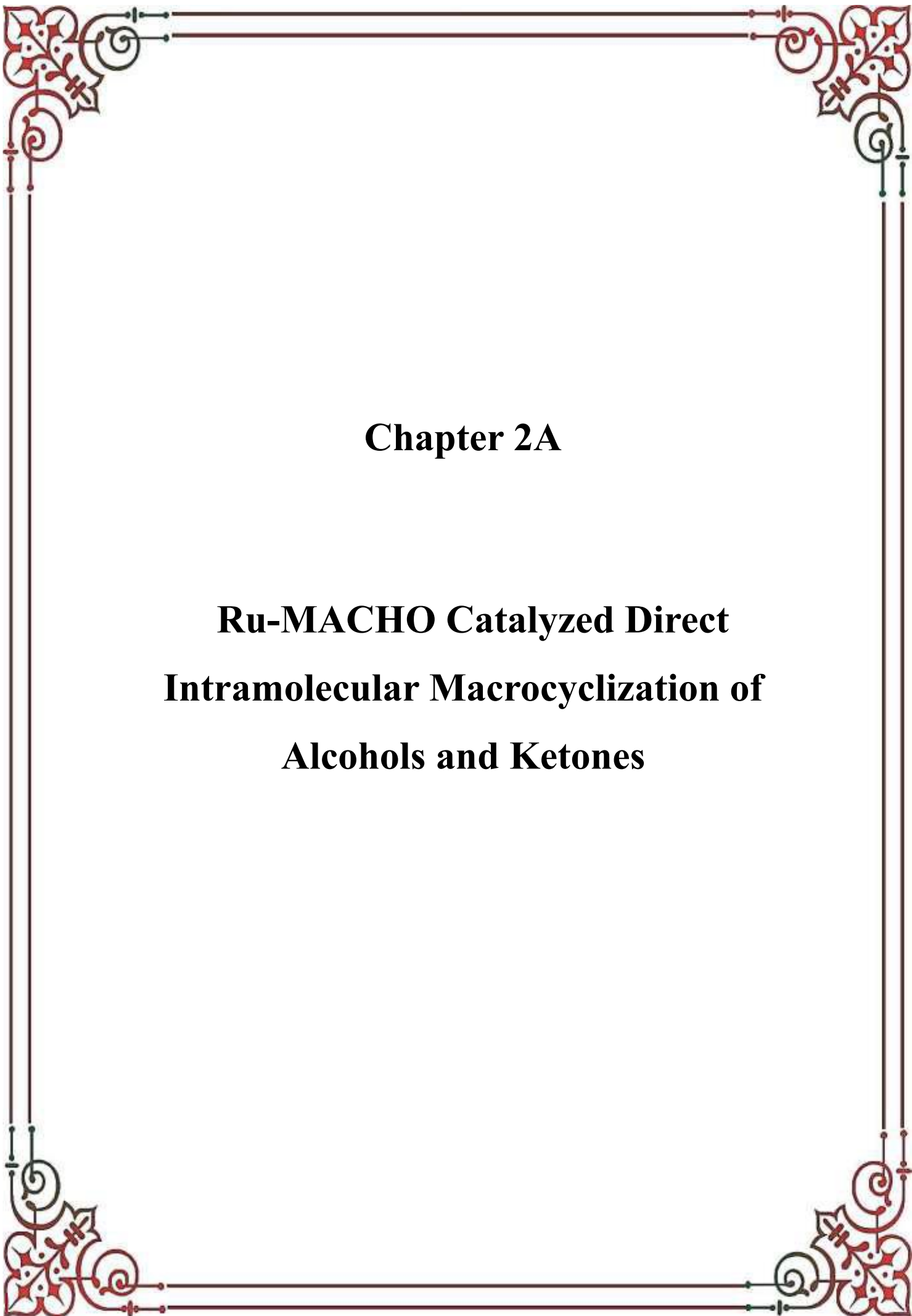
➤ **Direct Intramolecular Coupling of Primary/Secondary Alcohols with Secondary Alcohols for Macrocyclic Alkenylation Using Ni-Zeolite Catalyst Under Continuous Flow**

In continuation to macrocycle synthesis, this chapter is focused on developing a method for the dehydrative coupling of alcohol for macrocyclic alkenylation under continuous flow conditions. In literature, numerous approaches have been developed for the synthesis of macrocyclic alkenes such as ring-closing metathesis, witting reaction, C-H activation, Heck reaction, and Stille coupling. These methods require preactivated substrates and specially designed alkene precursors. Moreover, all these reactions were reported on air-sensitive, and expensive catalysts. To address this limitation, we aimed to develop an alternative approach involving a highly reusable and recyclable heterogeneous Ni-Zeolite catalyst. In this reaction, the heterogeneous catalyst is used for dehydration of alcohols followed by intramolecular coupling to deliver a high yield and higher regioselectivity of macrocyclic alkenes and generating water as the sole byproduct.

➤ **Intramolecular Dehydration of Diols and Seco-acids for Macrocyclic Ethers and Lactones under Continuous Flow**

Macrocyclic etherification and lactonization is a fascinating area of organic synthesis due to their unique binding affinity toward the metals, and variable biological properties. Our objective is to develop an innovative approach to synthesize macrocyclic ethers and macrolactones, overcoming the limitations of previous methods such as alcohol protection-deprotection chemistry, acid/ alcohol activation, use of stoichiometric reagents/bases, and

homogeneous catalysis. Hence, we aimed to develop a sustainable approach for the synthesis of macrocyclic ethers and macrolactones using a heterogeneous catalytic system under continuous flow. This simple method would utilize heterogeneous metal-supported catalysts, Ni-Zeolite and Ru-Zeolite, employed in a continuous flow to facilitate the dehydration of alcohols followed by an intramolecular reaction with alcohol/ carboxylic acid. This approach minimizes waste by producing water as a by-product and improves the sustainability profile of the synthetic process.



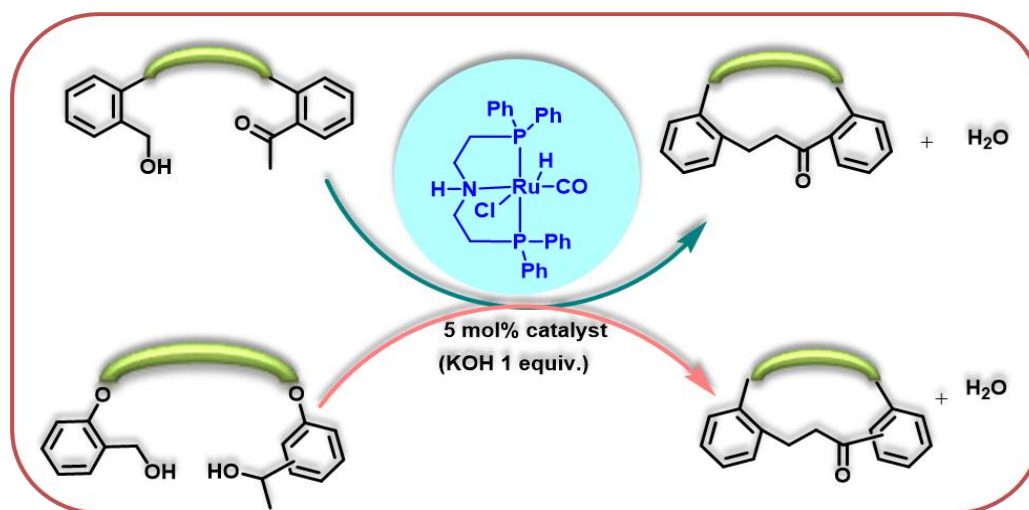
Chapter 2A

Ru-MACHO Catalyzed Direct Intramolecular Macrocyclization of Alcohols and Ketones

2A. Ru-MACHO Catalyzed Direct Intramolecular Macrocyclization of Alcohols and Ketones

2A.1 Abstract

In this chapter, we have described a new approach for ring-closing macrocyclization through the intramolecular dehydrative coupling of alcohols and ketone in the presence of a Ru-MACHO catalyst and a base. Additionally, this method demonstrates an intramolecular coupling of primary and secondary alcohol to form macrocyclic ketone. This approach is environmentally friendly, sustainable, and generates only water as a by-product. This process applies to a wide range of substrates, highlighting its versatility in synthetic chemistry. Notably, higher dilution conditions play a crucial role in the macrocyclization strategy, as they help to prevent undesired side reactions and promote the formation of the desired macrocyclic product.



2A.2 Introduction to Macrocyclic Ketone

Macrocyclic ketone constitutes a special class of chemical compounds that are fascinating in organic chemistry. This macrocyclic ketone often exhibits unique properties and can serve various functions, including drug delivery⁹⁰ and perfume industry.⁹¹ For example, Ovalifiliolatin B²⁵ and Acerogenin L²⁷ macrocyclic ketone shows biological applications like antifungal, anticancer, etc (Figure 18). Similarly, Civetone⁹² and Exaltone⁹³ show musk properties (Figure 18). Their diverse structural motifs make them a rich area of study in organic chemistry. The synthesis of macrocycles through the linear long chain is very challenging

because of several factors such as entropy, ring size, and angle strain (Figure 11, 12). Achieving selectivity during macrocyclization presents a challenge due to potential side reactions that can reduce the overall yield of the desired product. Although macrocyclization poses several challenges, numerous methods have been developed for the construction of macrocyclic ketones.^{25,27,92,93}

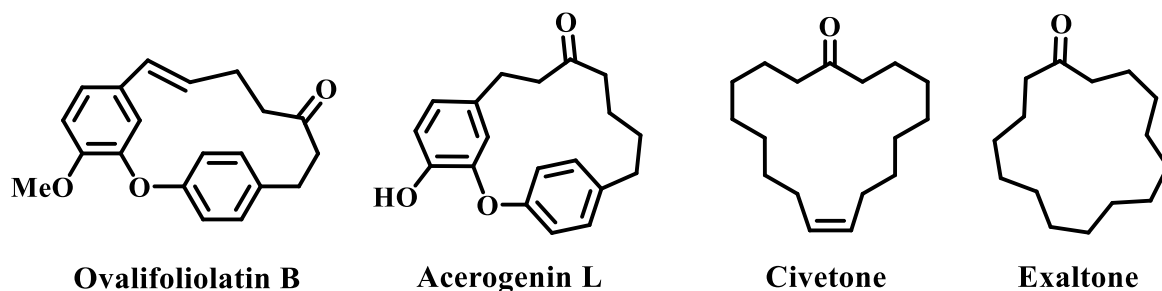
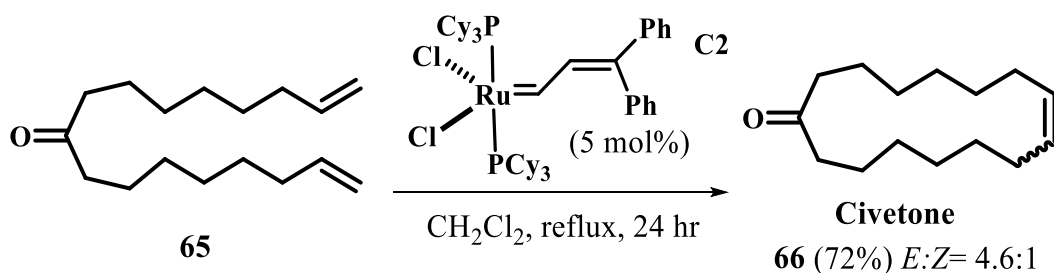


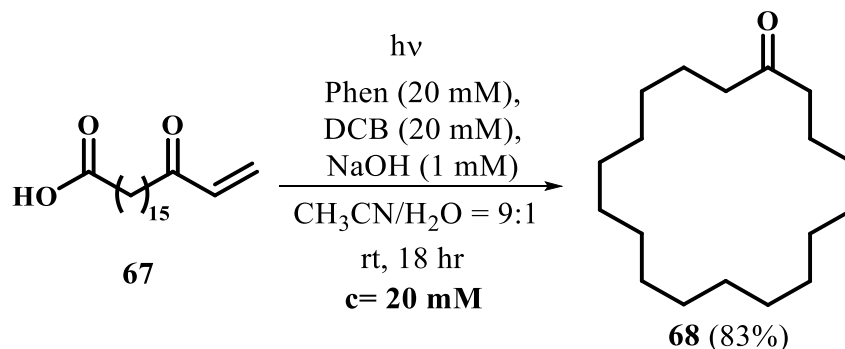
Figure 18. Example of macrocyclic ketone

2A.3 Literature Overview on the Synthesis of Macrocyclic Ketone Compounds

A few examples on the synthesis of macrocyclic ketones are illustrated below. In contemporary macrocyclization strategies, transition-metal-catalyzed reactions have been well-documented, showcasing various end-group functionalities. Civetone **66** synthesized by Fürstner from dialkene **65** in the presence of 5 mol% of Ru-catalyst **C2** and DCM solvent (Scheme 28).⁹⁴

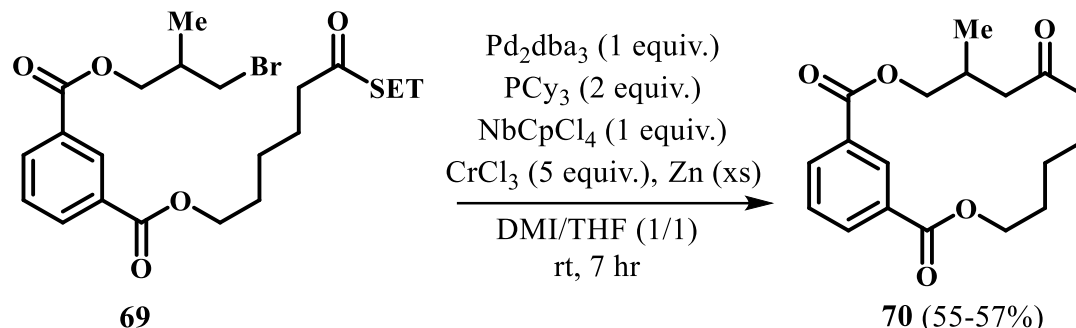


Scheme 28. Synthesis of macrocyclic ketone *via* RCM



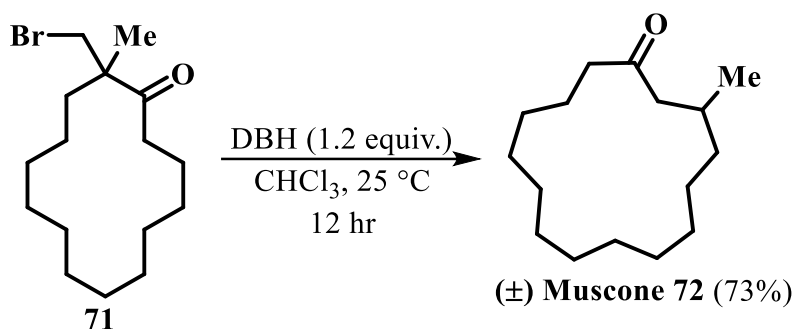
Scheme 29. Synthesis of macrocyclic ketone under light irradiation

Next, Yoshimi and coworkers synthesized macrocyclic ketone under light irradiation. In this reaction, they utilized compound **67** with phenanthrene (20 mM), 1,4-dicyanobenzene (DCB) (20 mM), and NaOH (1 mM) in aqueous acetonitrile solution ($\text{CH}_3\text{CN}/\text{H}_2\text{O} = 9:1$) afforded 18-membered macrocyclic ketone **68** with 83% yield (Scheme 29).⁹⁵



Scheme 30. Synthesis of macrocyclic ketone using Pd-catalyst

Further, Kishi and coworkers reported the Pd-catalyzed synthesis of macrocyclic ketone **70** from compound **69**. The reaction involves a tris(dibenzylideneacetone)dipalladium (Pd_2dba_3) (10 mol %) catalyst and PCy_3 (tricyclohexylphosphine) (20 mol %) as a ligand reacted with compound **69** in the presence of chromium(II) chloride (CrCl_2) (0.5 equiv.), tetrachloro(cyclopentadienyl)niobium (NbCpCl_4) (10 mol %), and lithium iodide (LiI) (1 equiv.), with an excess of zinc (Zn) to afford 55-57% yield of **70** (Scheme 30).⁹⁶

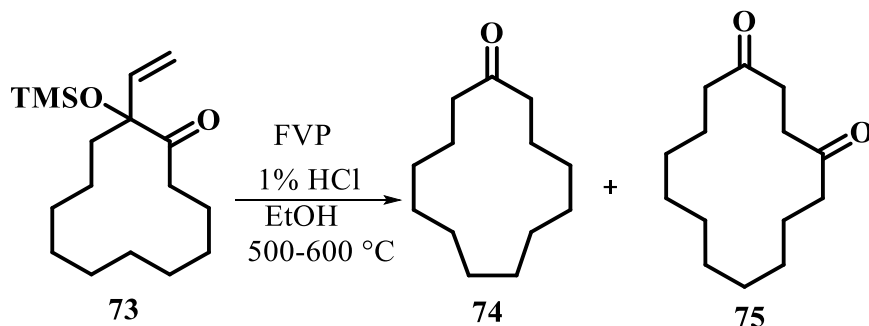


Scheme 31. Synthesis of (±) Muscone **72** via ring expansion approach

Yeung and coworkers synthesized (±) Muscone **72** using Dowd–Beckwith rearrangement. In this reaction, they synthesized **72** from 14-membered macrocyclic ketone **71** through a ring expansion approach using 1,3-dibromo-5,5-dimethylhydantoin (DBH) afforded 73% yield of (±) Muscone **72** (Scheme 31).⁹⁷

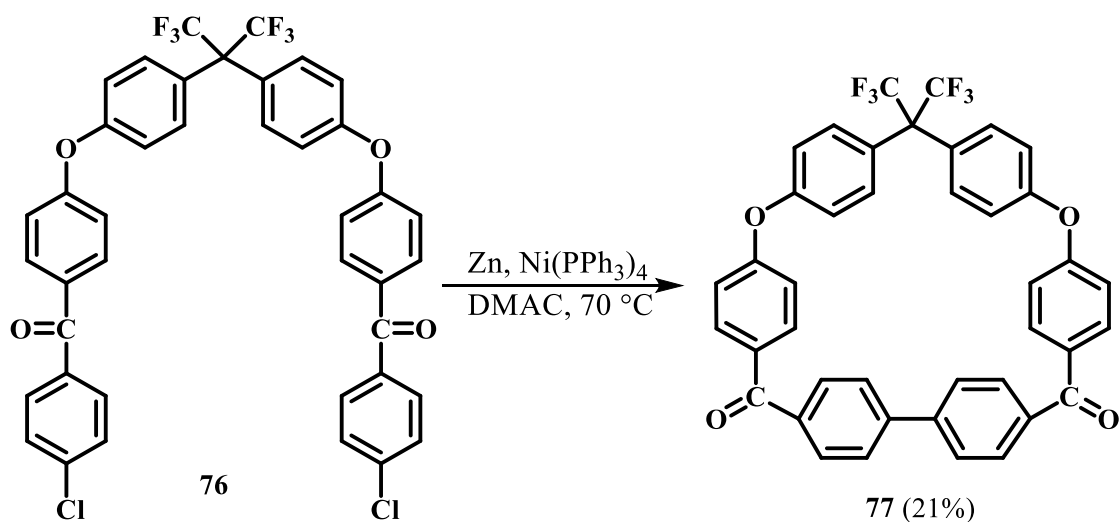
Another example of a ring expansion approach was reported by Rüedi and coworkers in 2004. They described a diradical-mediated ring expansion reaction using flash vacuum pyrolysis (FVP) at 500-600 °C in 1% HCl in EtOH, which afforded a 14-membered

macrocyclic diketone **75** *via* ring expansion. Additionally, a 13-membered macrocyclic ketone **74** was obtained by removing CO from the 12-membered ketone **75** (Scheme 32).⁹⁸

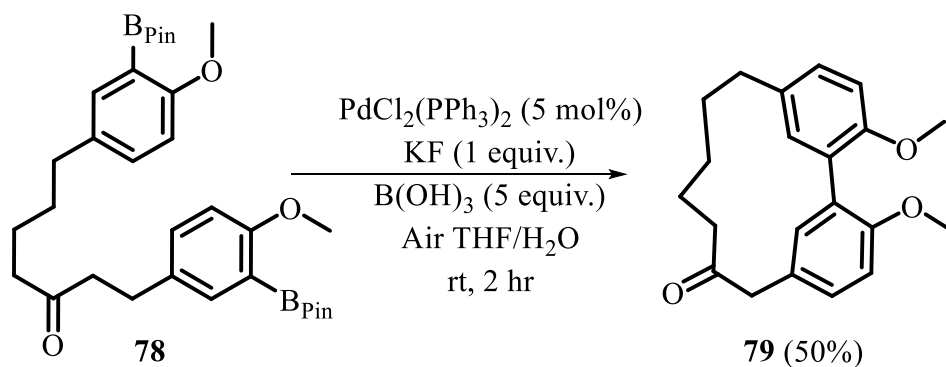


Scheme 32. Rüedi expansion approach for macrocyclic ketone

In 2001, Williams and coworkers described intramolecular nickel-catalyzed dehalogenative coupling in the presence of zinc powder in dimethylacetamide (DMAc) solvent at 70 °C to achieve macrocyclic diketone **77** with 21% yield from bis-chlorophenylene-terminated precursor **76** (Scheme 33).⁹⁹



Scheme 33. Williams's approach to macrocyclic ketone synthesis



Scheme 34. Synthesis of macrocyclic ketone *via* oxidative homocoupling of diboronic ester

Furthermore, Jasti and coworkers synthesized Acerogenin E by utilizing 5 mol% $\text{PdCl}_2(\text{PPh}_3)_2$ with $\text{B}(\text{OH})_3$ (5 equiv.) and KF (1 equiv.) at room temperature, which afforded a 50% yield of macrocyclic ketone **79** through the oxidative homocoupling of diboronic ester **78** (Scheme 34).¹⁰⁰

Although these metal-catalyzed methods are efficient and productive methods with high atom economy, they are associated with the necessity of external additives and oxidants. Moreover, early reports on such transitions have highlighted limitations due to harsh conditions such as high temperatures and air-sensitive catalysts. Indeed, developing new methods for effective macrocyclization to gain high selectivity and sustainability is highly desirable. In the 21st century, different transformations by borrowing hydrogen concept of the concept in metal-catalysis have become a more efficient approach toward C–C, C–O, and C–N bond formation.¹⁰¹

2A.4 Borrowing Hydrogen Concept (BHC)

The concept of "borrowing hydrogen" typically refers to a chemical reaction where hydrogen atoms are temporarily transferred from one molecule to another within a reaction process. This catalytic approach, also known as hydrogen auto-transfer, is widely used in organic chemistry and catalysis to facilitate diverse transformations.¹⁰²

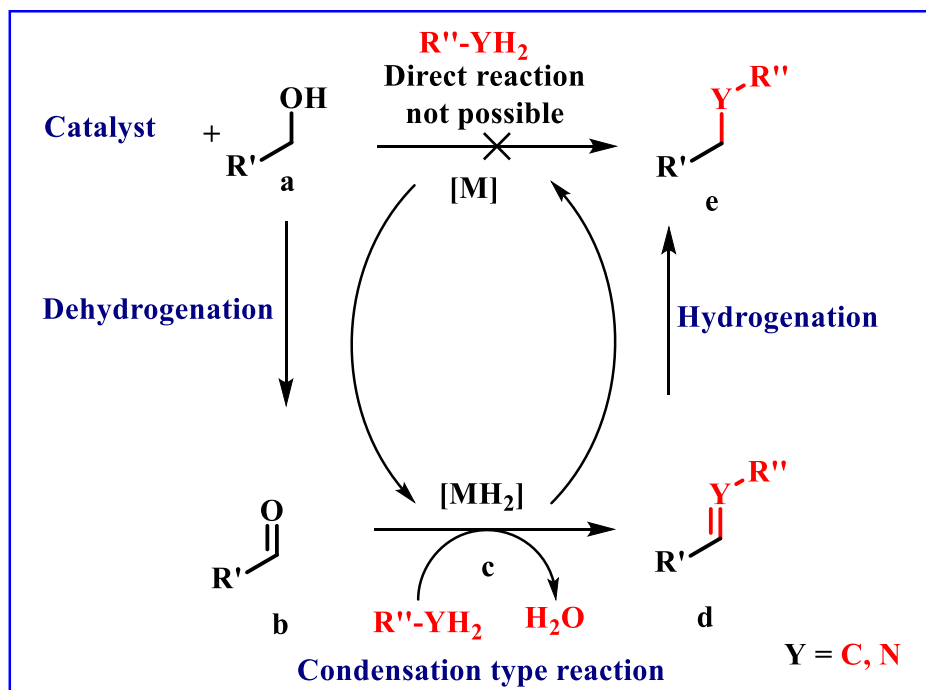


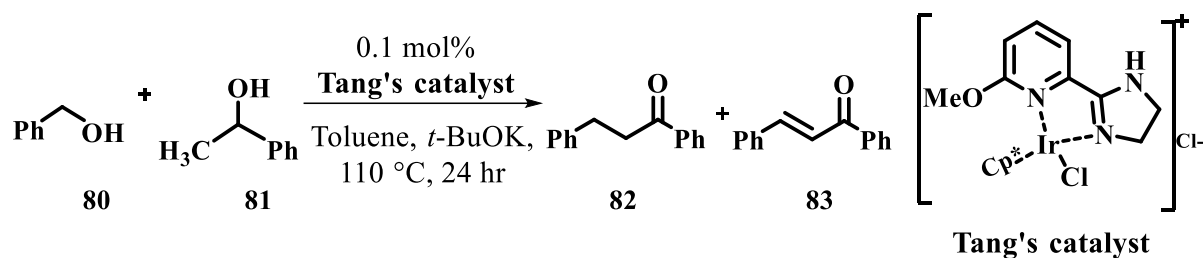
Figure 19. Borrowing hydrogen concept

The process typically involves dehydrogenation of an alcohol (**a**) to form an aldehyde (**b**), which then reacts with nucleophiles like amines or enolates to produce an unsaturated

intermediate **(c)**. In situ generated H₂, from alcohol dehydrogenation, is subsequently employed for the reduction of unsaturated compounds to yield the desired product **(d)**. Importantly, it is atom-economic and environmentally benign which generates water as the sole by-product (Figure 19). This catalytic concept exemplifies green chemistry principles, such as atom economy, minimization of hazardous substances, reduction of energy consumption, design for degradation, and use of renewable feedstocks.

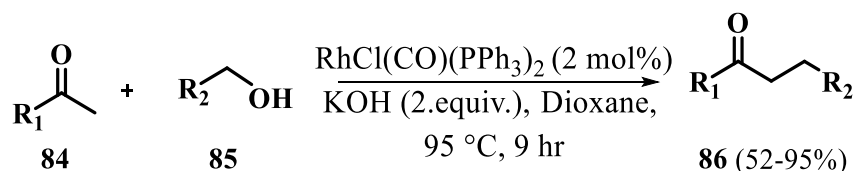
2A.4.1 Literature Report on the Borrowing Hydrogen Concept

In this section, selected examples of borrowing hydrogen catalysis are presented. Luo and colleagues conducted a study on Ir-catalyzed α -substituted C-alkylation reactions using Tang's catalyst.¹⁰³ In their experiments, benzylic alcohol **80** was reacted with secondary alcohol **81** in toluene at 110 °C. This process afforded ketone **82** with a high yield of 97% with minimal amounts of alkene compound **83** (Scheme 35).



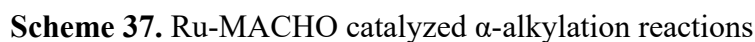
Scheme 35. Tang's catalyzed C-alkylation reactions

Moreover, Feng and coworkers described the Rh-catalyzed α -alkylation of ketones with alcohols to construct ketones *via* the borrowing hydrogen concept.⁹² They reported a C-alkylation reaction where ketones **84** were reacted with primary alcohols **85**, using RhCl(CO)(PPh₃)₂ as the catalyst, KOH as the base, and 1,4-dioxane as the solvent at 95 °C to afford **86**. The corresponding alkylated ketones **70** were obtained in yields ranging from 52% to 95% (Scheme 36).¹⁰⁴



Scheme 36. Rhodium-catalyzed α -alkylation of reactions

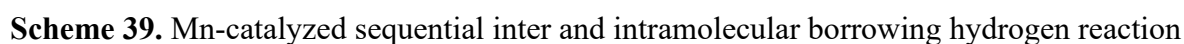
Furthermore in 2020, Gunanathan and coworkers reported an α -alkylation reaction reacting ketone **87** with secondary alcohol **88** in the presence of Ru-MACHO as a catalyst and *t*-BuOK as a base, they observed 35% to 90% yield of **89** (Scheme 37).¹⁰⁵



$\text{Ph}^*-\text{C}(=\text{O})\text{Me} + \text{91} \xrightarrow[\text{24 hr}]{\begin{array}{c} [\text{Cp}^*\text{IrCl}_2]_2 \text{ or } \text{Ru-MACHO (5 mol\%)} \\ t\text{-BuONa (2 equiv.)} \\ \text{Toluene, 120 }^\circ\text{C} \end{array}} \text{92 (21-83\%)}$

$\text{X} = \text{O, NR}$

Afterward, Maji and coworkers reported Mn-catalyzed borrowing hydrogen (BH) catalysis to synthesize 4 to 7-membered cycles from methyl ketone **93** and **94**. This reaction involved the formation of two C-C bonds *via* a sequence of intermolecular and intramolecular borrowing hydrogen catalysis, yielding product **95** in 50-85% (Scheme 39).¹⁰⁷



2A.5 Objective of the Work

The synthesis of macrocyclic ketone compounds is quite important in organic chemistry, especially considering the drug discovery and perfume industry applications. As a result, several synthetic approaches to these compounds have been reported. Most of these methods, however, suffer from major drawbacks such as air-sensitive catalysts, high catalyst

loadings, additives, activated reagents, multi-step processes, and narrow substrate scope, which reduce their efficiency.

Due to these limitations, an effective and sustainable catalytic method is needed. The borrowing hydrogen concept demonstrated tremendous catalytic activity in alcohol activation that leads to new catalytic reactions for C–C, C–O, and C–N bond formation. The literature, reports borrowing hydrogen concept used for the synthesis of 5- to 8-membered small rings. However, BHC has not yet been explored for the construction of macrocyclic compounds *via* C–C bond formation.

Hence, we aim to develop a new macrocyclization protocol based on the borrowing hydrogen concept. This approach aims to be additive-free, with less catalyst amount which provides a more effective, and sustainable method for synthesizing macrocyclic ketones, eliminating non-hazardous waste.

2A.6 Results and Discussion

To accomplish a macrocyclization reaction using BHC, we began our investigation by dehydrogenative coupling of compound 1-(2-(4-(2-(hydroxymethyl)phenoxy)butoxy)phenyl)propan-1-one **96a** as a model starting material. Initially, the reaction was performed without a catalyst or the base, no cyclic product was observed (Table 2.1, entries 1, 2). In these control experiments, we found that the catalyst and base were crucial for this transformation. Notably, heating the reaction mixture at 140 °C, which contains 1 mol% of Ru-MACHO catalyst and 1 equiv. KOH as a base, yielded macrocycles **97a** (30%), along with a minor product, (*E*)-16-methyl-6,7,8,9-tetrahydro-15*H*-dibenzo[*g,l*][1,6]dioxacyclotridecin-15-one **98a** (Table 2.1, entry 3).

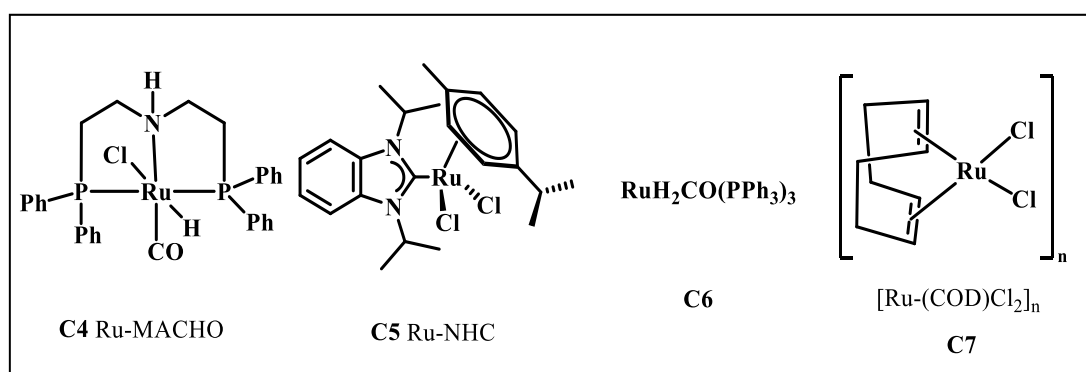
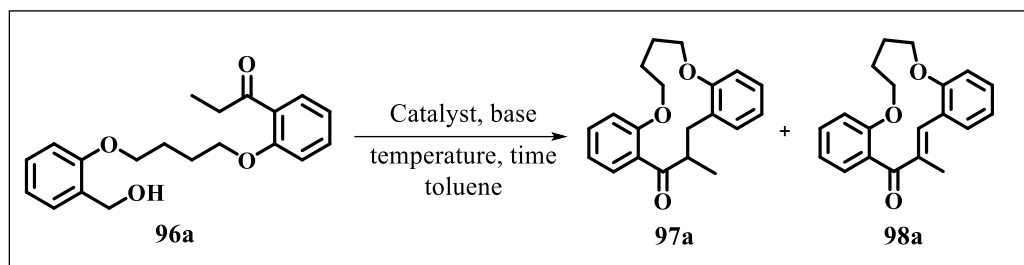


Figure 20. Various Ru-complexes used for optimization

By increasing the reaction temperatures to 160 °C and 180 °C, we observed yields of 30% and 33% yields of product **97a**, was observed (Table 2.1, entries 4, 5). Increasing the catalyst amount to 5 mol % and reducing the concentration of starting material **96a** led to 46%

yield of product **97a** at 160 °C and 54% yield at 180 °C was observed (Table 2.1, entries 6 and 7). Furthermore, the use of NaOH base resulted in a slight decrease in the product yield to

Table 2.1 Optimization table for the intramolecular macrocyclization of keto-alcohol



Entry	Catalyst	Catalyst (mol%)	Base (equiv.)	Temp. (°C)	Time (hr)	Yield of 97a/98a (%)
1	-	(1)	KOH (1)	180	24	-
2	Ru-MACHO	(1)	-	180	24	-
3	Ru-MACHO	(1)	KOH (2)	140	24	30/Traces
4	Ru-MACHO	(1)	KOH (1)	160	24	30/10
5	Ru-MACHO	(1)	KOH (1)	180	24	33/10
6	Ru-MACHO	(5)	KOH (1)	160	24	46/06
7^b	Ru-MACHO	(5)	KOH (1)	180	24	54/03
8 ^b	Ru-MACHO	(5)	NaOH (1)	180	24	42/02
9 ^b	Ru-MACHO	(5)	<i>t</i> -BuOK (1)	180	24	Trace
10 ^b	RuH ₂ CO(PPh ₃) ₃	(5)	-	180	24	Trace
11 ^b	[Ru-(COD)Cl ₂] _n	(5)	KOH (1)	180	24	Trace
12 ^b	Ru-NHC	(5)	NaOH (1)	180	24	42/02

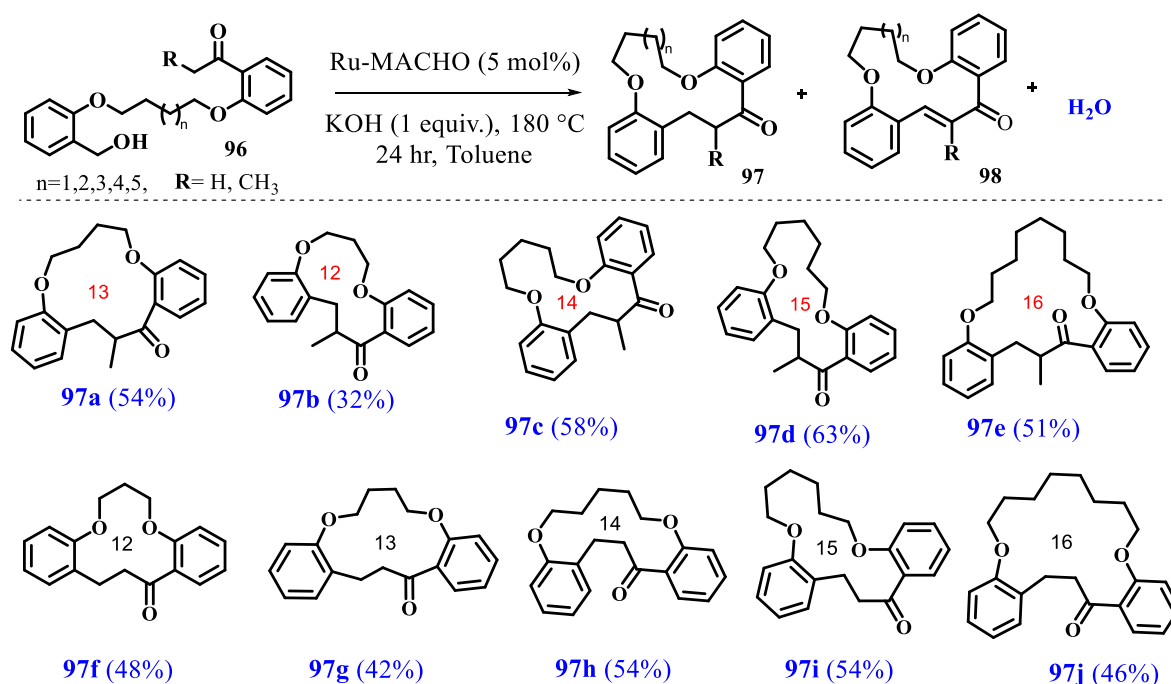
^a**Reaction Conditions:** Compound **96a** (0.075 M solution in toluene), Ru-MACHO (mol%), see table and base were added in a sealed vial and heated see table for 24 h, ^bcompound **96a** (0.01 M solution in toluene).

42% (Table 1, entry 8). Additionally, we observed a trace amount of product when *t*-BuOK was used (Table 1, entry 9). Other catalysts (Figure 20), including RuH₂CO(PPh₃)₃ without

base and $[\text{Ru}(\text{COD})\text{Cl}_2]_n$ **C7** were determined to be inefficient for macrocyclization (Table 1, entries 10 and 11). Later, the Ru-NHC catalyst with NaOH base afforded a 42% yield of macrocyclic ketone **97a** (Table 1, entry 12). The best-optimized conditions are found in Table 1, entry 7, where we utilized 5 mol% Ru-MACHO and 1 equiv. of KOH in toluene solvent at 180 °C.

2A.7. Substrate Scope for the Synthesis of Macrocyclic Ketone

Inspired by the optimized results, we investigated the substrate scope for this method with various keto–alcohol derivatives. A propyl spacer compound produced macrocycle **97b** with a 32% yield (Scheme 40). Moreover, increasing the spacer length of the ketone and expanding the ring size from 14 to 15 members led to an increase in yield from 58% to 63% for macrocycles **97c** and **97d** respectively (Scheme 40). Octyl spacer macrocycle **97e** afforded a 51% yield (Scheme 40). 12-membered macrocycle **97f** furnished a 48% yield (Scheme 40). Next, keto-alcohol containing butyl spacer **96g** delivered a 42% yield of compound **97g**



Scheme 40. Substrate scope for intramolecular macrocyclization.

Reaction conditions: keto-alcohol derivatives **96** (0.01 M solution in toluene), Ru-MACHO (5 mol %), and KOH (1 equiv.) were added in a sealed vial. The reaction mixture was heated at 180 °C in an oil pre-heated bath for 24 hr.

(Scheme 40). Interestingly, Pentyl spacer **96h** starting material afforded 54% yield of macrocycle **97h** with 3% yield of the macrocyclic alkene **98c** (Scheme 40). The compound **97h**

was confirmed by the single crystal XRD (Figure 21). More information on crystal structures can also be obtained from the Cambridge Crystallographic Data Centre (CCDC) with deposition number 2093707.

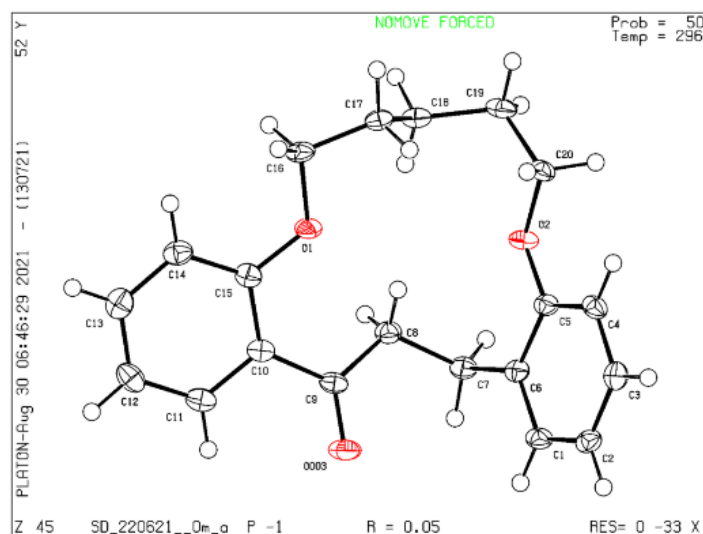
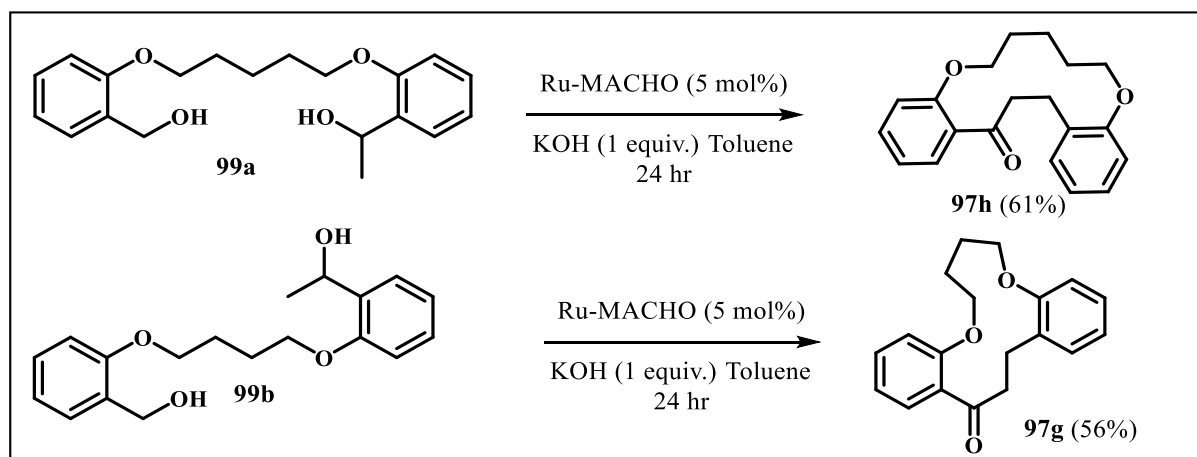


Figure 21. ORTEP drawing of **97h** showing thermal ellipsoids at the 50% probability level

However, hexyl spacer macrocyclic ketone furnished a 54% yield of compound **97i** (Scheme 50). Ketone **97j** resulted in a 46% yield of macrocycle **97i** (Scheme 40). Notably, traces of the alkene macrocycle were observed in most of these reactions.

To broaden the application scope of this strategy, we executed intramolecular macrocyclization with unsymmetrical diols. We accomplished macrocyclization by coupling **99a** bearing primary and secondary alcohols, resulting 61% yield of macrocyclic ketone **97h** (Scheme 51). This reaction was performed with another substrate having butyl spacer **99b** to obtain a 56% yield of product **97g** (Scheme 41).

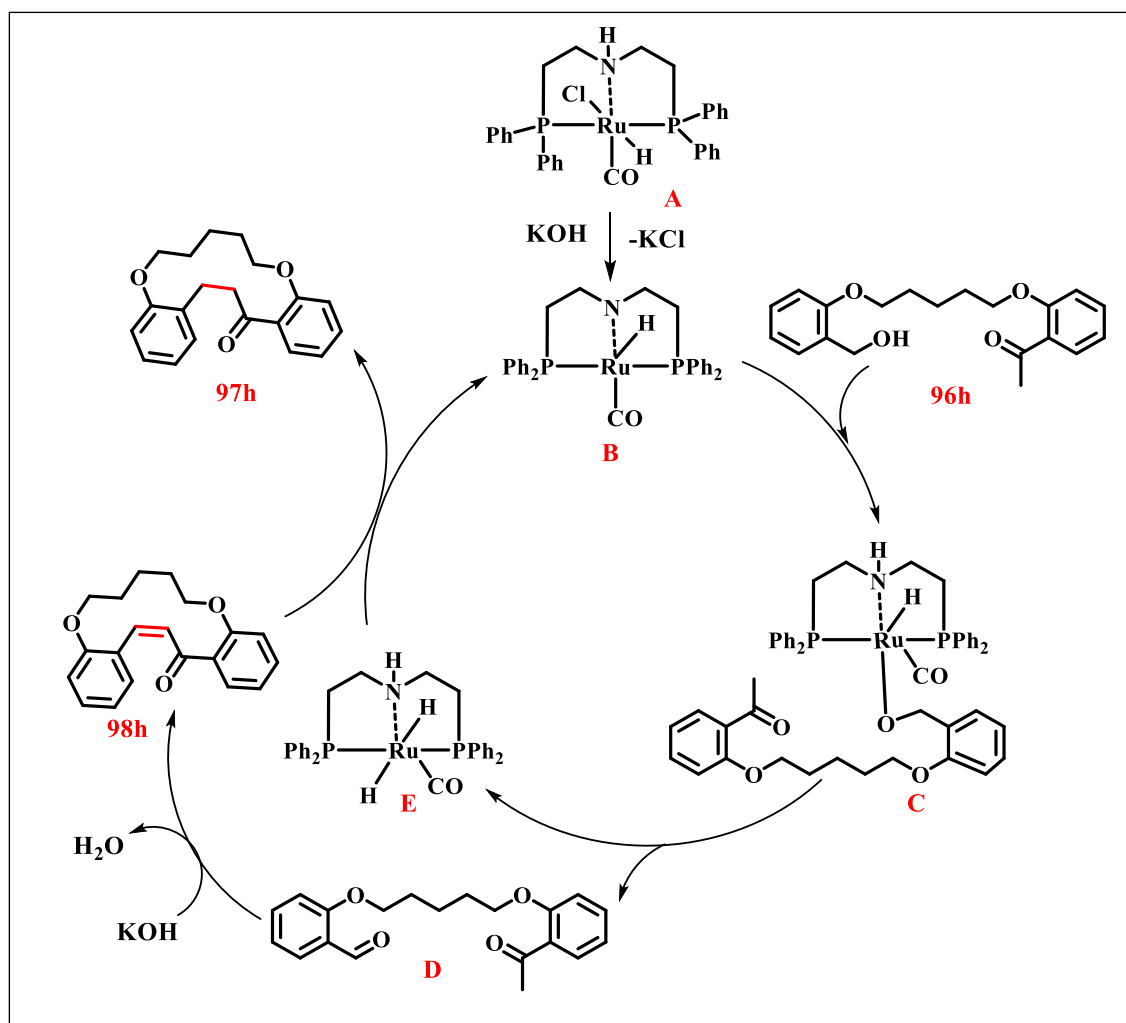


Scheme 41. Intramolecular macrocyclization using primary and secondary alcohols.

Reaction condition: Compound **99a/99b** (0.01 M solution in toluene), Ru-MACHO (5 mol %), and KOH (1 equiv.) were added in a sealed vial. The reaction mixture was heated at 180 °C in an oil bath for 24 hr.

2A.8 Plausible Mechanism for Macrocyclization

Based on literature reports,¹⁰⁵ a plausible mechanism for this transformation is depicted in Scheme 42. At the outset, KOH and Ru-MACHO catalyst **A** were used to generate active catalyst **B**. Furthermore, the active catalyst **B** effectively reacted with alcohol **96h**, resulting in the production of alkoxy-coordinated intermediate **C**. Afterward, β -hydride elimination in intermediate **C** formed aldehyde **D** and hydride intermediate **E**. Then, compound **D** underwent an intramolecular aldol condensation to generate alkene compound **98h**. At last, the hydrogenation of the alkene compound **98h** produced the desired macrocyclic ketone **97h**.



Scheme 42. Plausible mechanism for macrocyclization

2A.9 Conclusion

In conclusion, we have devised a new approach for synthesizing macrocycles through intramolecular cyclization using keto-alcohol in the presence of a Ru-MACHO catalyst and KOH as a base. This approach generates 10 macrocycles with 12 to 16-membered rings with moderate yields. This catalytic approach is highly sustainable, atom-economic, and uses easily synthesizable starting material, resulting in water as the only byproduct. This BHC involves a one-pot synthesis of macrocyclic compounds, where multiple transformations such as dehydrogenation, condensation, and hydrogenation occur sequentially without isolating intermediates. This methodology is highly desirable in organic synthesis because it reduces the number of purification steps, increases overall efficiency, and potentially leads to a higher yield of desired macrocyclic compounds.

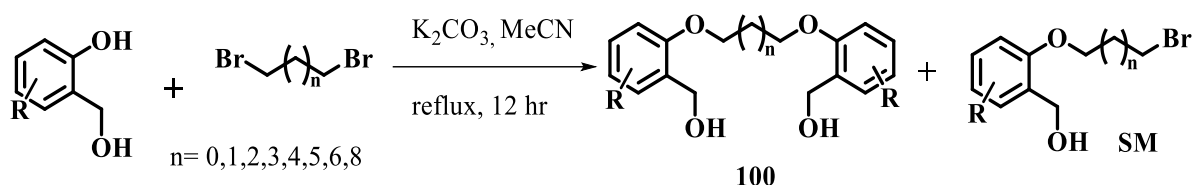
2A.10 Experimental Section and Characterization Data

2A.10.1. General Information and Data Collection

The Ru-MACHO (CAS number-1295649-40-9, SIGMA), 2-hydroxy benzyl alcohol (CAS number-90-01-7, SIGMA), 2-hydroxyacetophenone (CAS number- 118-93-4, SIGMA), 2'-hydroxypropiophenone (CAS number- 610-99-1, SIGMA), was purchased from Sigma-Aldrich. All the solvents used were dry grade. The column chromatographic separations were performed over 100-200 mesh size Silica-gel. Visualization was accomplished with UV light, PMA, and CAN stain followed by heating. ^1H and ^{13}C NMR spectra were recorded on 400 and 100 MHz respectively, using Bruker or JEOL spectrometers. Abbreviations used in the NMR follow-up experiments: b, broad; s, singlet; d, doublet; t, triplet; q, quartet; m, multiple. High-resolution mass Spectra were recorded with waters-synapt G2 using electrospray ionization (ESI-TOF). Infrared (ATIR) spectra were obtained with a Bruker Alpha-E infrared spectrometer. Single-crystal diffraction analysis data were collected at 23 °C (296 K) with a Bruker Kappa Apex III CCD single-crystal diffractometer (operated at 1500 W power: 50 kV, 30 mA) using graphite monochromatic Mo K α radiation and Cu K α radiation.

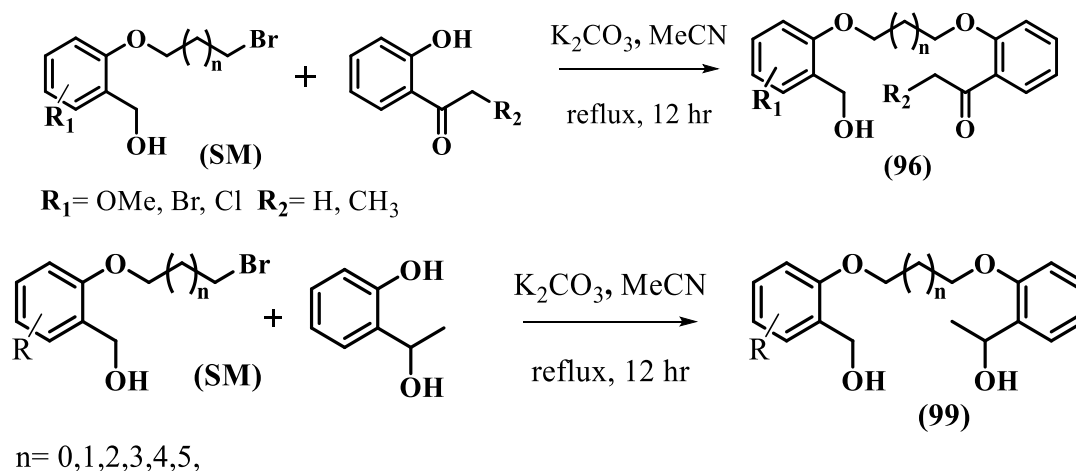
2A.10.2 Experimental Section

A) General experimental procedure for mono- and di-alkylation of 2-hydroxybenzylalcohol:¹⁰⁸



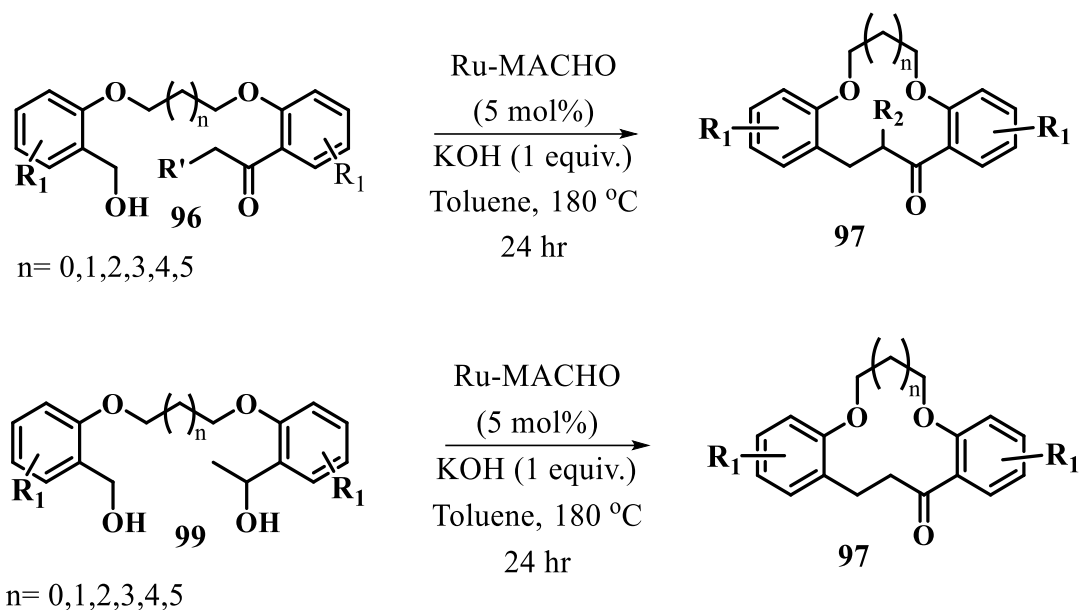
In a 100 mL round bottom flask were added 2-hydroxybenzylalcohol (745 mg, 6.0 mmol, 2 equiv.), dibromoalkanes (605 mg, 3 mmol, 1 equiv.) and potassium carbonate (K_2CO_3) (829 mg, 6.0 mmol, 2 equiv.) in acetonitrile (15 mL). The solution was refluxed at 85 °C temperature for 12 hrs. The progress of the reaction was monitored by thin layer chromatographic technique. After completion of the reaction, the mixture of products (mono- and dialkylated) was extracted in water and dichloroethane. The organic fraction was evaporated using a vacuum. The residue was directly purified by silica gel chromatography (EtOAc:*n*-hexane = 15:85 (for mono-alkylated product) **SM** and 40:60 (for di-alkylated product)) **100**.

B) General experimental procedure for alkylation of 2-hydroxy acetophenone derivatives and 2-(1-hydroxyethyl)phenol):¹⁰⁸



In a 100 mL round bottom flask were added 2-hydroxyacetophenone (517 mg, 3.8 mmol, 1 equiv.) or 2-(1-hydroxyethyl)phenol (533 mg, 3.8 mmol, 1 equiv.), and mono-alkylated 2-hydroxybenzylalcohol product **SM** (1 gm, 3.8 mmol, 1 equiv.) and potassium carbonate (K_2CO_3) (526 mg 3.8 mmol 1 equiv.) in acetonitrile (30 mL). The solution was refluxed at 85 °C temperature for 12 hr. The progress of the reaction was monitored by the thin-layer chromatography technique. After completion of the reaction, the product was extracted in water and dichloroethane. The organic fraction was evaporated using a vacuum. The residue was directly purified by silica gel chromatography (EtOAc:*n*-hexane = 25:75) to afford **96** compounds.

C) General experimental procedure for macrocyclization of keto-alcohol derivatives or unsymmetric diol (Intramolecular pathway):

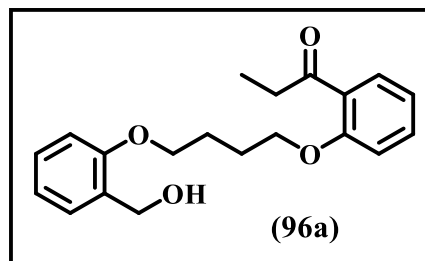


In a 50 mL Carousel tube was added Ru-MACHO (5 mol%), Ketone-alcohol compound **96** (1 equiv.), and KOH (1 equiv.) in the presence of toluene 15 mL. The tube was purged with N₂ and capped. The reaction mixture was heated at 180 °C in an oil bath or Carousel hot plate for 24 hr. After completion of the reaction, the reaction mixture was diluted with dichloromethane and methanol. Finally, a volatile component was evaporated under a vacuum. The residue was directly purified by silica gel chromatography (EtOAc:*n*-hexane = 05/95). to afford **97** compounds. The same procedure was used for the cyclization of unsymmetrical diol derivatives **99** compounds to to afford **97** compounds.

2A.10.3. Characterization Data

(1-(2-(4-(2-(hydroxymethyl)phenoxy)butoxy)phenyl)

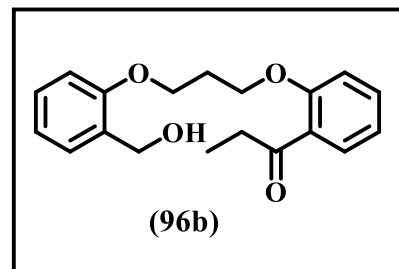
propan-1-one (96a): Prepared according to general experimental procedure 2.10.2B, using (2-(4-bromobutoxy)phenyl)methanol (500 mg, 1.93 mmol) and potassium carbonate (K₂CO₃) (266 mg, 1.93 mmol), 2-hydroxypropiophenone (287 mg, 1.93 mmol) to afford



desired product **96a** (540 mg, 1.93 mmol, 85% yield) as a white amorphous solid. ¹H NMR (400 MHz, CDCl₃) δ 7.66 (dd, *J* = 7.7, 1.7 Hz, 1H), 7.41 (dd, *J* = 8.1, 7.5 Hz, 1H), 7.34 – 7.20 (m, 2H), 7.02 – 6.89 (m, 3H), 6.87 (d, *J* = 8.1 Hz, 1H), 4.69 (s, 2H), 4.11 (dd, *J* = 6.4, 4.0 Hz,

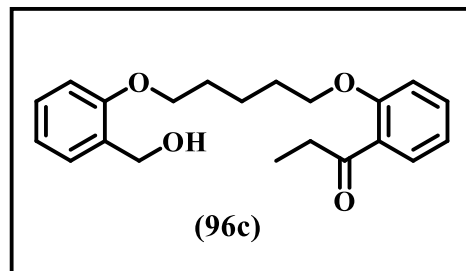
4H), 2.99 (q, $J = 7.3$ Hz, 2H), 2.49 (s, 1H) 2.03 (m, 4H), 1.16 (t, $J = 7.3$ Hz, 3H). ^{13}C NMR (100 MHz, CDCl_3) δ 203.7, 157.8, 156.6, 133.2, 130.3, 129.4, 128.9, 128.7, 120.8, 120.7, 112.3, 111.1, 68.0, 67.4, 61.8, 37.1, 26.3, 26.3, 8.6. FTIR (neat): 3451, 2935, 2874, 1669, 1595, 1236 cm^{-1} HRMS (ESI-TOF) m/z : calcd for $\text{C}_{20}\text{H}_{24}\text{O}_4\text{Na}$ $[\text{M}+\text{Na}]^+$: 351.1573, found: 351.1572.

(1-(2-(3-(2-(hydroxymethyl)phenoxy)propoxy)phenyl) propan-1-one (96b): Prepared according to general experimental procedure 2.10.2B, using (2-(3-bromopropoxy)phenyl)methanol (500 mg, 2.04 mmol), potassium carbonate (K_2CO_3) (281.9 mg, 1.22 mmol) and 2-hydroxypropiophenone (306 mg, 2.04 mmol) to afford desired product **96b** (560 mg, 2.04 mmol, 87% yield) as a white amorphous solid. ^1H NMR (400 MHz, CDCl_3) δ 7.64



(dd, $J = 7.6$, 1.8 Hz, 1H), 7.40 (dd, $J = 8.2$, 7.4 Hz, 1H), 7.27 (dd, $J = 15.7$, 8.3, 4.6 Hz, 2H), 6.96 (dd, $J = 17.0$, 11.3, 4.5 Hz, 3H), 6.87 (d, $J = 8.2$ Hz, 1H), 4.68 (s, 2H), 4.29 – 4.16 (t, 4H), 2.95 (q, $J = 7.3$ Hz, 2H), 2.54 (s, 1H), 2.38 – 2.27 (m, 2H), 1.13 (t, $J = 7.3$ Hz, 3H). ^{13}C NMR (100 MHz, CDCl_3) δ 203.5, 157.5, 156.3, 133.2, 130.2, 129.3, 128.9, 128.6, 120.9, 120.9, 112.4, 111.1, 65.1, 64.5, 61.5, 37.0, 29.3, 8.5. FTIR (neat): 3448, 2936, 2879, 1671, 1596, 1285 cm^{-1} HRMS (ESI-TOF) m/z : calcd for $\text{C}_{19}\text{H}_{22}\text{O}_4\text{Na}$ $[\text{M}+\text{Na}]^+$: 337.1416, found: 337.1415.

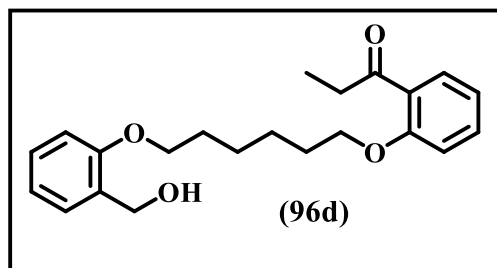
(1-(2-((5-(2-(hydroxymethyl)phenoxy)pentyl)oxy)phenyl)propan-1-one (96c): Prepared according to general experimental procedure 2.10.2B, using (2-((5-bromopentyl)oxy)phenyl)methanol (300 mg, 1.10 mmol), potassium carbonate (K_2CO_3) (151.8mg, 1.10 mmol) and 2-hydroxypropiophenone (164 mg, 1.10 mmol) to afford desired product **96c** (300 mg, 0.87mmol, 79% yield) as a white amorphous



solid. ^1H NMR (400 MHz, CDCl_3) δ 7.66 (dd, $J = 7.7$, 1.8 Hz, 1H), 7.42 (ddd, $J = 8.4$, 7.4, 1.8 Hz, 1H), 7.32 – 7.23 (m, 2H), 7.01 – 6.91 (m, 3H), 6.87 (d, $J = 8.1$ Hz, 1H), 4.69 (s, 2H), 4.11 – 4.03 (m, 4H), 3.00 (q, $J = 7.3$ Hz, 2H), 2.43 (s, 1H), 1.98 – 1.87 (m, 4H), 1.73 – 1.65 (m, 2H), 1.16 (t, $J = 7.3$ Hz, 3H). ^{13}C NMR (100 MHz, CDCl_3) δ 203.9, 157.9, 156.8, 133.2, 130.3, 129.3, 128.9, 128.7, 120.8, 120.7, 112.3, 111.1, 68.3, 67.7, 62.1, 37.2, 29.1, 29.1, 23.1, 8.7. FTIR (neat): 3439, 2939, 2872, 1670, 1596, 1238 cm^{-1} HRMS (ESI-TOF) m/z : calcd for $\text{C}_{21}\text{H}_{26}\text{O}_4\text{Na}$ $[\text{M}+\text{Na}]^+$: 365.1729, found: 365.1728.

(1-(2-((6-(2-(hydroxymethyl)phenoxy)hexyl)oxy)phenyl)propan-1-one (96d): Prepared according to general experimental procedure

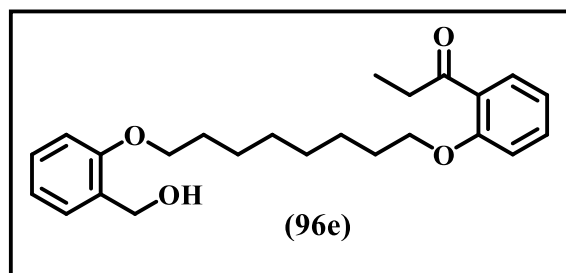
2.10.2B, using (2-((6-bromohexyl)oxy)phenyl)methanol (500 mg, 1.74 mmol), potassium carbonate (K₂CO₃) (240 mg, 1.74 mmol) and 2-hydroxypropiophenone (261 mg, 1.74 mmol) to afford desired product **96d** (495 mg,



1.39 mmol, 80% yield) as a white amorphous solid. ¹H NMR (400 MHz, CDCl₃) δ 7.67 (dd, *J* = 7.7, 1.8 Hz, 1H), 7.42 (ddd, *J* = 8.4, 7.4, 1.8 Hz, 1H), 7.30 – 7.22 (m, 2H), 7.01 – 6.92 (m, 3H), 6.87 (d, *J* = 8.1 Hz, 1H), 4.69 (s, 2H), 4.05 (dt, *J* = 8.5, 6.4 Hz, 4H), 3.00 (q, *J* = 7.3 Hz, 2H), 2.42 (s, 1H), 1.87 (tt, *J* = 13.3, 6.6 Hz, 4H), 1.61 – 1.55 (m, 4H), 1.16 (t, *J* = 7.3 Hz, 3H). ¹³C NMR (100 MHz, CDCl₃) δ 203.8, 158.0, 156.9, 133.2, 130.3, 129.2, 129.0, 128.8, 128.7, 120.7, 120.6, 112.3, 111.1, 68.4, 67.8, 62.3, 37.2, 29.3, 29.2, 26.1, 26.0, 8.7. FTIR (neat): 3453, 2938, 2868, 1671, 1596, 1239 cm⁻¹ HRMS (ESI-TOF) *m/z*: calcd for C₂₂H₂₈O₄Na [M+Na]⁺: 379.1886, found: 379.1885.

(1-(2-((8-(2-(hydroxymethyl)phenoxy)octyl)oxy)phenyl)propan-1-one (96e): Prepared according to general experimental procedure

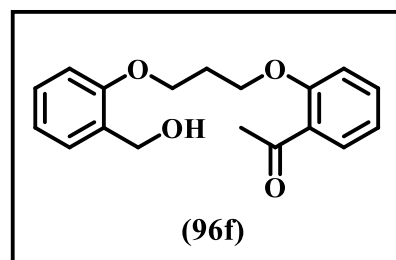
2.10.2B, using (2-((8-bromooctyl)oxy)phenyl)methanol (300 mg, 0.95 mmol), potassium carbonate (131.5mg, 0.95 mmol) and 2-hydroxypropiophenone (143 mg, 0.95 mmol) to afford desired product **96e**



(280 mg, 0.77 mmol, 76% yield) as a white amorphous solid. ¹H NMR (400 MHz, CDCl₃) δ 7.67 (dd, *J* = 7.7, 1.8 Hz, 1H), 7.41 (ddd, *J* = 8.4, 7.4, 1.8 Hz, 1H), 7.25 (dt, *J* = 7.7, 4.1 Hz, 2H), 7.00 – 6.90 (m, 3H), 6.87 (d, *J* = 8.0 Hz, 1H), 4.69 (s, 2H), 4.03 (dt, *J* = 8.5, 6.5 Hz, 4H), 3.05 – 2.96 (m, 2H), 2.46 (s, 1H), 1.89 – 1.77 (m, 4H), 1.55 – 1.45 (m, 4H), 1.41 (dd, *J* = 6.8, 3.8 Hz, 4H), 1.17 (t, *J* = 7.3 Hz, 3H). ¹³C NMR (100 MHz, CDCl₃) δ 203.9, 158.1, 157.0, 133.2, 130.3, 129.3, 128.8, 128.7, 120.7, 120.5, 112.3, 111.2, 68.5, 68.0, 62.5, 37.2, 29.4, 26.3, 26.2, 8.7. FTIR (neat): 3450, 2934, 2857, 1672, 1597, 1240 cm⁻¹ HRMS (ESI-TOF) *m/z*: calcd for C₂₄H₃₂O₄Na [M+Na]⁺: 407.2199, found: 407.2198.

(1-(2-(3-(2-(hydroxymethyl)phenoxy)propoxy)phenyl)ethan-1-one (96f): Prepared

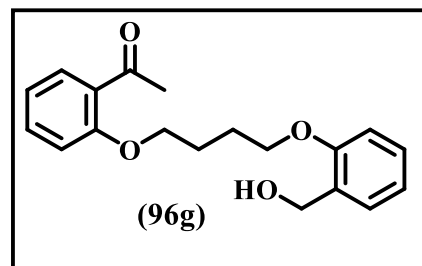
according to general experimental procedure 2.10.2B, using (2-(3-bromopropoxy)phenyl)methanol (500 mg, 2.04mmol) potassium carbonate (K_2CO_3) (281 mg, 2.04 mmol) and 2-hydroxyphenone (277 mg, 2.04 mmol) to afford desired product **96f** (480 mg, 2.04 mmol, 78% yield) as a white amorphous solid. ^1H NMR (400 MHz, $CDCl_3$) δ 7.70 (d, J =



7.7 Hz, 1H), 7.42 (dd, J = 11.7, 4.0 Hz, 1H), 7.27 (ddd, J = 15.5, 8.6, 4.7 Hz, 2H), 7.03 – 6.91 (m, 3H), 6.87 (d, J = 8.2 Hz, 1H), 4.68 (s, 2H), 4.23 (dt, J = 11.6, 5.0 Hz, 4H), 2.73 – 2.58 (m, 3H), 2.40 – 2.29 (m, 2H), OH peak exchanged with deuterium of $CDCl_3$; ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.8, 158.1, 156.3, 133.8, 130.4, 129.4, 128.9, 128.6, 128.4, 120.9, 120.8, 112.4, 111.1, 65.2, 64.5, 61.5, 32.0, 29.3. HRMS (ESI-TOF) m/z : calcd for $C_{18}H_{20}O_4Na$ $[M+Na]^+$: 323.1260, found: 323.1256.

(1-(2-(4-(2-(hydroxymethyl)phenoxy)butoxy)phenyl)ethan-1-one (96g): Prepared

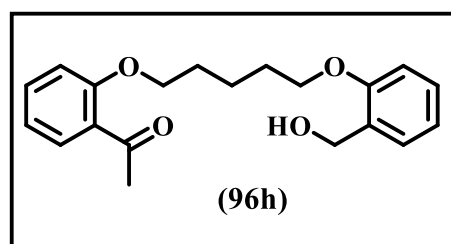
according to general experimental procedure 2.10.2B, using (2-(4-bromobutoxy)phenyl)methanol (500 mg, 1.93 mmol), potassium carbonate (K_2CO_3) (266 mg, 1.93 mmol) and 2-hydroxyphenone (262 mg, 1.93 mmol) to afford desired product **96g** (470 mg, 1.93 mmol, 77% yield) as a white amorphous solid. ^1H NMR (400 MHz,



$CDCl_3$) δ 7.73 (dd, J = 7.7, 1.8 Hz, 1H), 7.44 (td, J = 7.9, 1.0 Hz, 1H), 7.33– 7.21 (m, 2H), 7.02 – 6.90 (m, 3H), 6.87 (d, J = 8.2 Hz, 1H), 4.69 (s, 2H), 4.12 (dd, J = 12.5, 5.3 Hz, 4H), 2.62 (s, 3H), 2.40 (s, 1H), 2.05 (m, J = 2.1 Hz, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.9, 158.3, 156.6, 133.8, 130.5, 129.3, 128.9, 128.7, 128.4, 120.9, 120.7, 112.4, 111.1, 68.1, 67.4, 61.9, 32.1, 26.3, 26.2. FTIR (neat): 3403, 2941, 2874, 1668, 1596, 1237 cm^{-1} HRMS (ESI-TOF) m/z : calcd for $C_{19}H_{22}O_4Na$ $[M+Na]^+$: 337.1416, found: 337.1415.

(1-(2-((5-(2-(hydroxymethyl)phenoxy)pentyl)oxy)phenyl)ethan-1-one (96h): Prepared

according to general experimental procedure 2.10.2B, using (2-((5-bromopentyl)oxy)phenyl)methanol (300 mg, 1.10 mmol), potassium carbonate (K_2CO_3) (151 mg, 1.10 mmol) and 2-hydroxyphenone (149 mg, 1.10 mmol) to afford desired product **96h** (320 mg, 1.10

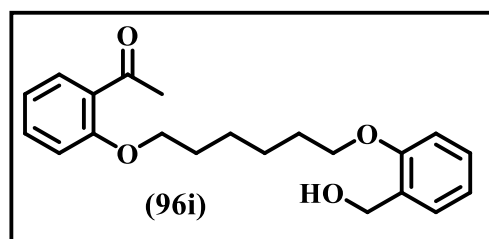


mmol, 88% yield) as a white amorphous solid. ^1H NMR (400 MHz, $CDCl_3$) δ 7.72 (dd, J =

7.7, 1.8 Hz, 1H), 7.47 – 7.36 (m, 1H), 7.29 (d, $J = 7.4$ Hz, 1H), 7.27 – 7.17 (m, 1H), 7.01 – 6.88 (m, 3H), 6.85 (d, $J = 8.2$ Hz, 1H), 4.68 (s, 2H), 4.05 (ddt, $J = 12.4, 8.1, 6.0$ Hz, 4H), 3.03 (s, 1H), 2.61 (s, 3H), 1.91 (d, $J = 5.1$ Hz, 4H), 1.69 (dd, $J = 4.6, 2.7$ Hz, 2H). ^{13}C NMR (100 MHz, CDCl_3) δ 200.1, 158.4, 156.6, 133.8, 130.4, 129.4, 128.8, 128.5, 128.3, 120.7, 120.5, 112.4, 111.0, 68.3, 67.6, 61.7, 32.1, 29.1, 29.1, 23.0. FTIR (neat): 3399, 2940, 2870, 1668, 1596, 1238 cm^{-1} HRMS (ESI-TOF) m/z : calcd for $\text{C}_{20}\text{H}_{24}\text{O}_4\text{Na}$ $[\text{M}+\text{Na}]^+$: 351.1573, found: 351.1572.

(1-(2-((6-(2-(hydroxymethyl)phenoxy)hexyl)oxy)phenyl)ethan-1-one (96i): Prepared

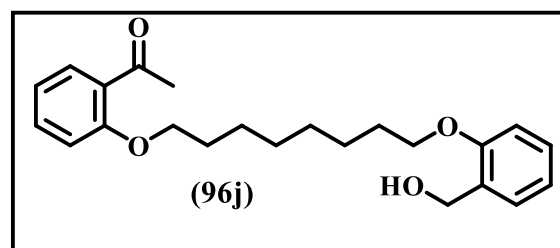
according to general experimental procedure 2.10.2B, using (2-((6-bromohexyl)oxy)phenyl)methanol (300 mg, 1.04 mmol) and potassium carbonate (K_2CO_3) (144.3 mg, 1.04 mmol) 2-hydroxyphenone (142.3 mg, 1.04



mmol) to afford desired product **96i** (310 mg, 0.90 mmol, 87% yield) as a white amorphous solid. ^1H NMR (400 MHz, CDCl_3) δ 7.72 (dd, $J = 7.7, 1.8$ Hz, 1H), 7.43 (dd, $J = 8.2, 7.4$ Hz, 1H), 7.31–7.20 (m, 2H), 7.00 – 6.89 (m, 3H), 6.86 (d, $J = 8.1$ Hz, 1H), 4.68 (s, 2H), 4.03 (ddd, $J = 9.9, 7.9, 5.5$ Hz, 4H), 2.61 (s, 3H), 2.54 (s, 1H), 1.93 – 1.81 (m, 4H), 1.57 (d, $J = 3.0$ Hz, 4H). ^{13}C NMR (100 MHz, CDCl_3) δ 200.1, 158.5, 156.8, 133.8, 130.5, 129.3, 128.9, 128.6, 128.3, 120.7, 120.5, 112.4, 111.1, 68.4, 67.8, 62.1, 32.1, 29.2, 29.2, 26.0, 26.0. FTIR (neat): 3445, 2939, 2885, 1669, 1596, 1238 cm^{-1} ; HRMS (ESI-TOF) m/z : calcd for $\text{C}_{21}\text{H}_{26}\text{O}_4\text{Na}$ $[\text{M}+\text{Na}]^+$: 365.1729, found: 365.1728.

(1-(2-((8-(2-(hydroxymethyl)phenoxy)octyl)oxy)phenyl)ethan-1-one (96j): Prepared

according to general experimental procedure 2.10.2B, using (2-((8-bromooctyl)oxy)phenyl)methanol (300 mg, 0.95 mmol), potassium carbonate (131.5 mg, 0.95mmol) to afford the desired product **96j**

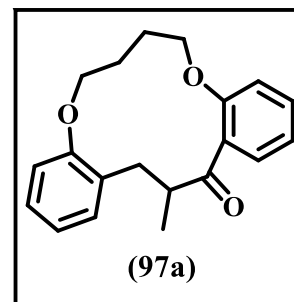


(280.51 mg, 0.75 mmol, 80% yield) as a white amorphous solid. ^1H NMR (400 MHz, CDCl_3) δ 7.73 (dd, $J = 7.7, 1.8$ Hz, 1H), 7.46 – 7.39 (m, 1H), 7.31 – 7.19 (m, 2H), 7.05 – 6.81 (m, 4H), 4.69 (s, 2H), 4.02 (ddd, $J = 14.7, 7.3, 5.3$ Hz, 4H), 2.63 (s, 3H), 2.54 s, 1H), 1.89 – 1.77 (m, 4H), 1.55 – 1.44 (m, 4H), 1.44 – 1.36 (m, 4H). ^{13}C NMR (100 MHz, CDCl_3) δ 200.1, 158.6, 156.9, 133.8, 130.4, 129.3, 128.8, 128.6, 128.3, 120.6, 120.4, 112.4, 111.1, 68.5, 67.9, 62.1,

32.1, 29.3, 26.2, 26.2. FTIR (neat): 3448, 2932, 2857, 1670, 1597, 1239 cm^{-1} ; HRMS (ESI-TOF) m/z calcd for $\text{C}_{23}\text{H}_{30}\text{O}_4\text{Na}$ $[\text{M}+\text{Na}]^+$: 393.2042, found: 393.2041.

16-methyl-6,7,8,9,16,17-hexahydro-15H-dibenzo[*g,l*][1,6]dioxacyclotridecin-15-one

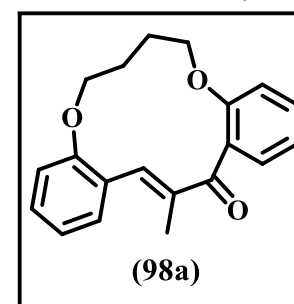
(97a): Prepared according to general experimental procedure 2.10.2D, using (1-(2-(4-(2-(hydroxymethyl)phenoxy)butoxy)phenyl)propan-1-one (50 mg, 0.15 mmol), KOH (9 mg, 0.15 mmol) and Ru-MACHO (4.6 mg, 0.0075 mmol) to afford desired product **97a** (25.4 mg, 0.082 mmol, 54% yield) as a semi



solid and 3% yield of macrocyclic alkene **98a**. ^1H NMR (400 MHz, CDCl_3) δ 7.56 (dd, $J = 7.6$, 1.8 Hz, 1H), 7.41 (ddd, $J = 8.3$, 7.3, 1.9 Hz, 1H), 7.18 (td, $J = 8.0$, 3.8 Hz, 2H), 7.01 – 6.93 (m, 2H), 6.86 (ddd, $J = 16.4$, 11.3, 4.6 Hz, 2H), 4.38 (dtt, $J = 10.5$, 7.0, 3.5 Hz, 1H), 4.20 – 4.09 (m, 3H), 4.03 – 3.97 (m, 1H), 3.42 (dd, $J = 12.9$, 3.5 Hz, 1H), 2.47 – 2.39 (m, 1H), 2.23 – 2.00 (m, 4H), 0.94 (d, $J = 7.0$ Hz, 3H). ^{13}C NMR (100 MHz, CDCl_3) δ 210.0, 157.1, 156.8, 132.5, 131.5, 130.4, 129.8, 129.4, 127.5, 120.7, 120.3, 111.4, 110.7, 67.8, 67.3, 44.8, 35.6, 28.7, 16.2. FTIR (neat): 2925, 2872, 1673, 1596, 1246 cm^{-1} . HRMS (ESI-TOF) m/z : calcd for $\text{C}_{20}\text{H}_{23}\text{O}_3$ $[\text{M}+\text{H}]^+$ 311.1647, found: 311.1654.

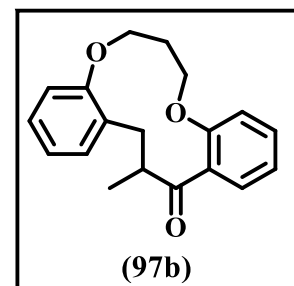
(E)-16-methyl-6,7,8,9-tetrahydro-15H-dibenzo[*g,l*][1,6]dioxacyclotridecin-15-one (98a):

^1H NMR (400 MHz, CDCl_3) δ 7.44 – 7.37 (m, 2H), 7.35 (dd, $J = 7.6$, 1.4 Hz, 2H), 7.22 – 7.17 (m, 1H), 7.01 (dd, $J = 8.5$, 6.2 Hz, 2H), 6.95 (dt, $J = 8.3$ Hz, 2H), 4.23 – 4.18 (t, 2H), 4.06 – 4.02 (t, 2H), 2.05 (s, 3H), 1.99 – 1.93 (m, 2H), 1.88 – 1.82 (m, 2H). ^{13}C NMR (100 MHz, CDCl_3) δ 200.35, 158.25, 155.56, 140.48, 138.83, 131.37, 130.04, 129.86, 129.76, 129.66, 123.09, 120.97, 120.51, 111.80, 74.50, 67.43, 27.93, 25.79, 12.91.



15-methyl-7,8,15,16-tetrahydro-6H,14H-dibenzo[*f,k*][1,5]dioxacyclododecin-14-one (97b):

Prepared according to general experimental procedure 2.10.2D, using (1-(2-(3-(2-(hydroxymethyl)phenoxy)propoxy)phenyl)ethan-1-one (50 mg, 0.15 mmol), KOH (8 mg, 0.15 mmol) and Ru-MACHO (4.6 mg, 0.0075 mmol) to afford desired product **97b** (15.2 mg, 0.051 mmol, 32% yield) as a semi solid. ^1H NMR (400 MHz, CDCl_3) δ 7.48 (dd, $J = 7.6$, 1.6 Hz, 1H), 7.43 – 7.37 (m, 1H), 7.19

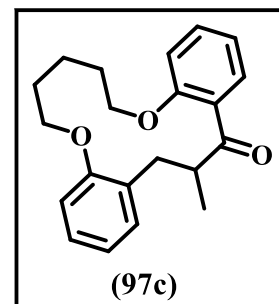


(td, $J = 7.9$, 1.4 Hz, 1H), 7.15 – 7.09 (m, 1H), 7.01 – 6.91 (m, 2H), 6.86 (t, $J = 7.5$ Hz, 1H),

6.81 (d, $J = 8.1$ Hz, 1H), 4.48 – 4.40 (m, 1H), 4.37 – 4.29 (m, 1H), 4.20 – 4.06 (m, 2H), 3.99 (dq, $J = 13.6, 6.9, 2.1$ Hz, 1H), 3.40 (dd, $J = 12.8, 1.4$ Hz, 1H), 2.50 (dt, $J = 12.5, 9.8, 2.7$ Hz, 1H), 2.27 – 2.10 (m, 2H), 0.99 (d, $J = 6.9$ Hz, 3H). ^{13}C NMR (100 MHz, CDCl_3) δ 210.0, 157.1, 156.8, 132.5, 131.4, 130.4, 129.8, 129.4, 127.5, 120.7, 120.3, 111.4, 110.7, 67.8, 67.3, 44.8, 35.6, 28.7, 16.1. FTIR (neat): 2921, 2852, 1676, 1594, 1243 cm^{-1} . HRMS (ESI-TOF) m/z calcd for $\text{C}_{19}\text{H}_{21}\text{O}_3$ $[\text{M}+\text{H}]^+$: 297.1490, found: 297.1501.

17-methyl-7,8,9,10,17,18-hexahydro-6H,16H-dibenzo[*h,m*][1,7]dioxacyclotetradecin-16-one (97c): Prepared according to general experimental procedure

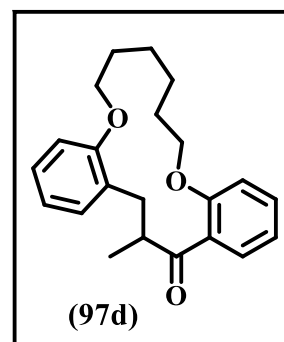
2.10.2D, using (1-(2-((5-(2-(hydroxymethyl)phenoxy)pentyl)oxy)phenyl)propan-1-one (50 mg, 0.14 mmol), KOH (8 mg, 0.14 mmol) and Ru-MACHO (4.3 mg, 0.007 mmol) to afford desired product **97c** (27.6 mg, 0.08 mmol, 58% yield) as a semi solid. ^1H NMR (400 MHz, CDCl_3) δ 7.49 (dd, $J = 7.6, 1.8$



Hz, 1H), 7.37 (ddd, $J = 8.3, 7.4, 1.8$ Hz, 1H), 7.20 – 7.11 (m, 2H), 6.96 (td, $J = 7.5, 0.9$ Hz, 1H), 6.88 – 6.79 (m, 3H), 4.26 (ddd, $J = 10.5, 7.4, 4.2$ Hz, 1H), 4.18 – 4.08 (m, 2H), 4.02 – 3.91 (m, 2H), 3.40 (dd, $J = 13.1, 4.2$ Hz, 1H), 2.49 (dd, $J = 13.1, 10.5$ Hz, 1H), 2.06 – 1.84 (m, 4H), 1.80 – 1.68 (m, 2H), 0.94 (d, $J = 7.3$ Hz, 3H). ^{13}C NMR (100 MHz, CDCl_3) δ 208.8, 157.1, 132.5, 132.4, 130.5, 129.2, 128.6, 127.4, 120.6, 119.9, 111.8, 110.4, 67.3, 64.2, 44.3, 33.7, 26.8, 26.5, 21.0, 16.9. FTIR (neat): 2925, 2869, 1675, 1594, 1241 cm^{-1} . HRMS (ESI-TOF) m/z calcd for $\text{C}_{21}\text{H}_{24}\text{O}_3\text{Na}$ $[\text{M}+\text{Na}]^+$: 347.1617, found: 347.1622.

18-methyl-6,7,8,9,10,11,18,19-octahydro-17H-dibenzo[*i,n*][1,8]dioxacyclopentadecin-17-one (97d): Prepared according to general experimental procedure

2.10.2D, using (1-(2-((6-(2-(hydroxymethyl)phenoxy)hexyl)oxy)phenyl)propan-1-one (50 mg, 0.14 mmol), KOH (9 mg, 0.14 mmol) and Ru-MACHO (4.2 mg, 0.007 mmol) to afford desired product **97d** (30 mg, 0.09 mmol, 63% yield) as a semi solid. ^1H NMR (400 MHz, CDCl_3) δ 7.67 (dd, $J = 7.7, 1.8$ Hz, 1H), 7.37 (ddd, $J = 8.4, 7.3, 1.9$ Hz, 1H), 7.21 (dd, $J =$



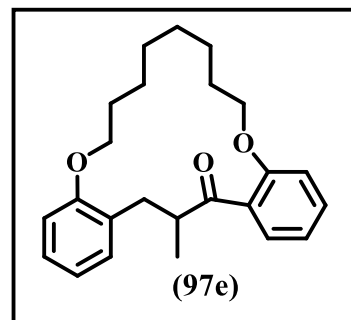
7.3, 1.7 Hz, 1H), 7.13 (td, $J = 8.0, 1.8$ Hz, 1H), 6.94 (td, $J = 7.7, 1.0$ Hz, 1H), 6.89 (d, $J = 8.3$ Hz, 1H), 6.84 – 6.78 (m, 2H), 4.16 – 4.05 (m, 4H), 4.01 – 3.96 (m, 1H), 3.26 (dd, $J = 13.0, 7.3$ Hz, 1H), 2.65 (dd, $J = 13.0, 7.3$ Hz, 1H), 1.92 (qdd, $J = 11.6, 5.6, 2.5$ Hz, 2H), 1.82 – 1.62 (m, 6H), 1.10 (d, $J = 7.2$ Hz, 3H), ^{13}C NMR (100 MHz, CDCl_3) δ 206.3, 157.7, 157.2, 133.1, 132.5, 131.1, 129.0, 128.3, 127.3, 120.6, 120.0, 112.4, 110.6, 68.2, 67.2, 45.1, 34.1, 29.8, 28.8, 27.9,

26.8, 25.5, 17.8, 14.4. FTIR (neat): 2932, 2861, 1670, 1596, 1244 cm^{-1} . HRMS (ESI-TOF) m/z calcd for $\text{C}_{22}\text{H}_{27}\text{O}_3$ $[\text{M}+\text{H}]^+$: 339.1960, found: 339.1969.

20-methyl-6,7,8,9,10,11,12,13,20,21-decahydro-19H-

dibenzo[*b,g*][1,9]dioxacycloheptadecin- 19-one (97e):

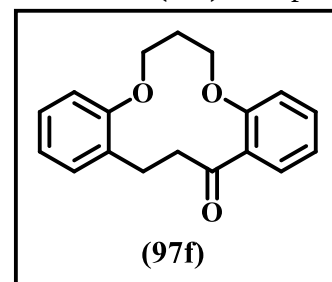
Prepared according to general experimental procedure 2.10.2D, using (1-(2-((8-(2-(hydroxymethyl)phenoxy)octyl)oxy)phenyl)propan-1-one (50 mg, 0.13 mmol) KOH (8 mg, 0.13 mmol) and Ru-MACHO (4.2 mg, 0.007 mmol) to afford desired product **97e** (24 mg,



0.062 mmol, 51% yield) as a semi solid. ^1H NMR (400 MHz, CDCl_3) δ 7.42 – 7.39 (m, 1H), 7.35 – 7.31 (m, 1H), 7.17 (dd, J = 7.5, 1.5 Hz, 1H), 7.13 – 7.07 (m, 1H), 6.90 – 6.78 (m, 3H), 6.74 (d, J = 8.0 Hz, 1H), 4.06 – 3.97 (m, 2H), 3.97 – 3.87 (m, 2H), 3.85 – 3.75 (m, 1H), 3.16 (dd, J = 13.1, 8.3 Hz, 1H), 2.79 (dd, J = 13.1, 6.4 Hz, 1H), 1.86 – 1.69 (m, 4H), 1.59 (dd, J = 12.4, 5.6 Hz, 4H), 1.48 – 1.41 (m, 4H), 1.21 (d, J = 6.9 Hz, 3H). ^{13}C NMR (100 MHz, CDCl_3) δ 207.8, 157.3, 132.5, 131.8, 130.1, 129.6, 128.9, 127.2, 120.4, 120.2, 119.9, 111.6, 110.6, 67.6, 66.3, 45.9, 34.1, 28.9, 28.6, 27.0, 26.7, 24.3, 24.1, 17.9. FTIR (neat): 2932, 2861, 1670, 1596, 1244 cm^{-1} . HRMS (ESI-TOF) m/z calcd for $\text{C}_{24}\text{H}_{31}\text{O}_3$ $[\text{M}+\text{H}]^+$: 367.2273, found: 367.2276.

7,8,15,16-tetrahydro-6H,14H-dibenzo[*f,k*][1,5]dioxacyclododecin-14-one (97f): Prepared

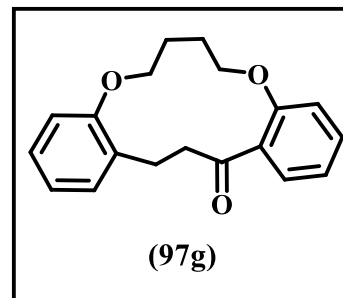
according to general experimental procedure 2.10.2D, using (1-(2-(3-(2-(hydroxymethyl)phenoxy)propoxy)phenyl)ethan-1-one (50 mg, 0.16 mmol), KOH (9 mg, 0.16 mmol) and Ru-MACHO (4.8 mg, 0.008 mmol) to afford desired product **97f** (20 mg, 0.07 mmol, 42% yield) as a semi solid. ^1H NMR (400 MHz, CDCl_3) δ



7.57 (dd, J = 7.6, 1.8 Hz, 1H), 7.43 (ddd, J = 8.3, 7.4, 1.8 Hz, 1H), 7.19 (dd, J = 12.3, 4.6 Hz, 2H), 6.98 (ddd, J = 11.3, 8.9, 4.6 Hz, 2H), 6.91 – 6.83 (m, 2H), 4.35 – 4.30 (m, 2H), 4.28 – 4.23 (m, 2H), 3.29 – 3.20 (m, 2H), 2.97 – 2.89 (m, 2H), 2.37 – 2.29 (m, 2H). ^{13}C NMR (100 MHz, CDCl_3) δ 205.3, 157.6, 157.0, 133.1, 130.6, 130.5, 130.3, 129.5, 127.6, 121.0, 120.8, 111.7, 111.6, 67.9, 67.7, 43.6, 28.9, 28.2. FTIR (neat): 2932, 2861, 1670, 1596, 1244 cm^{-1} . HRMS (ESI-TOF) m/z calcd for $\text{C}_{18}\text{H}_{19}\text{O}_3$ $[\text{M}+\text{H}]^+$: 283.1334, found: 283.1335.

6,7,8,9,16,17-hexahydro-15H-dibenzo[*g,l*][1,6]dioxacyclotridecin-15-one (97g): Prepared

according to general experimental procedure 2.10.2D, using (1-(2-(4-(2-(hydroxymethyl)phenoxy)butoxy)phenyl)ethan-1-one (50 mg, 0.15 mmol), KOH (9 mg, 0.16 mmol) and RuMACHO (4.5 mg, 0.0075 mmol) to afford desired product **97g** (20 mg, 0.067 mmol, 42% yield) as a semi solid. ¹H NMR (400 MHz, CDCl₃) δ 7.66 (dd, *J* = 7.7, 1.8 Hz, 1H), 7.44 (ddd, *J* = 8.3, 7.3,

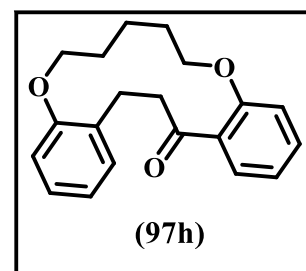


1.9 Hz, 1H), 7.25 – 7.21 (m, 1H), 7.20 – 7.16 (m, 1H), 7.02 – 6.95 (m, 2H), 6.92 – 6.83 (m, 2H), 4.21 – 4.16 (m, 2H), 4.13 – 4.08 (m, 2H), 3.37 – 3.32 (m, 2H), 3.06 – 2.99 (m, 2H), 2.19 – 2.12 (m, 2H), 2.09– 2.02 (m, 2H). ¹³C NMR (100 MHz, CDCl₃) δ 204.6, 158.5, 157.7, 133.5, 131.0, 130.7, 130.6, 129.4, 127.7, 121.0, 120.8, 112.7, 112.6, 69.5, 68.5, 43.2, 28.5, 27.5, 26.4. FTIR (neat): 2925, 2872, 1673, 1596, 1246 cm⁻¹. HRMS (ESI-TOF) *m/z* calcd for C₁₉H₂₁O₃ [M+H]⁺: 297.1490, found: 297.1501.

7,8,9,10,17,18-hexahydro-6H,16H-

dibenzo[*h,m*][1,7]dioxacyclotetradecin-16-one (97h): Prepared

according to general experimental procedure 2.10.2D, using (1-(2-((5-(2-(hydroxymethyl)phenoxy)pentyl)oxy)phenyl)ethan-1-one (50 mg, 0.15 mmol), KOH (9 mg, 0.16 mmol) and Ru-MACHO (4.5 mg, 0.0075 mmol) to afford desired product **97h** (25.6 mg, 0.082

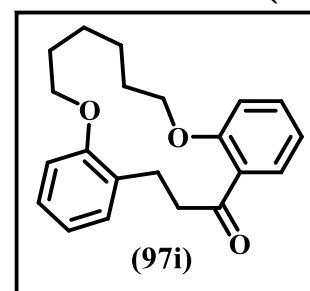


mmol, 54% yield) as a semi solid. ¹H NMR (400 MHz, CDCl₃) δ 7.56 (dd, *J* = 7.6, 1.8 Hz, 1H), 7.39 (ddd, *J* = 8.3, 7.4, 1.8 Hz, 1H), 7.23 – 7.15 (m, 2H), 6.96 (td, *J* = 7.5, 0.9 Hz, 1H), 6.89 – 6.83 (m, 3H), 4.07 (dt, *J* = 9.9, 4.9 Hz, 4H), 3.50 – 3.45 (m, 2H), 3.04 (m, *J* = 9.1, 7.1 Hz, 2H), 1.93 (m, *J* = 5.5 Hz, 4H), 1.86 (m, *J* = 10.9, 6.6 Hz, 2H). ¹³C NMR (100 MHz, CDCl₃) δ 204.2, 157.7, 157.0, 132.8, 130.8, 130.1, 129.6, 127.4, 120.6, 120.4, 111.9, 110.8, 67.5, 64.5, 44.0, 27.1, 26.8, 26.3, 21.3. FTIR (neat): 2934, 2871, 1676, 1597, 1244 cm⁻¹. HRMS (ESI-TOF) *m/z* calcd for C₂₀H₂₃O₃ [M+H]⁺: 311.1647, found: 311.1651.

6,7,8,9,10,11,18,19-octahydro-17H-dibenzo[*i,n*][1,8]dioxacyclopentadecin-17-one (97i):

Prepared according to general experimental procedure 2.10.2D, using

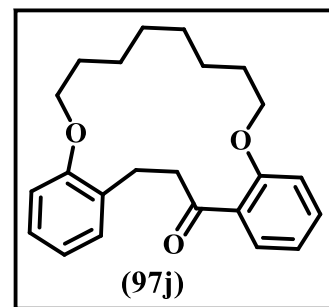
(1-(2-((6-(2-(hydroxymethyl)phenoxy)hexyl)oxy)phenyl)ethan-1-one (50 mg, 0.14 mmol), KOH (8 mg, 0.14 mmol) and Ru-MACHO (4.3 mg, 0.007 mmol) to afford desired product **97i** (24.9 mg, 0.076 mmol, 52% yield) as a semi solid. ¹H NMR (400 MHz, CDCl₃) δ 7.49 (dd,



$J = 7.6, 1.8 \text{ Hz}, 1\text{H}$), 7.38 (ddd, $J = 8.3, 7.4, 1.8 \text{ Hz}, 1\text{H}$), 7.20 – 7.13 (m, 2H), 6.96 (td, $J = 7.5, 0.9 \text{ Hz}, 1\text{H}$), 6.88 – 6.80 (m, 3H), 4.26 (dq, $J = 14.7, 7.4, 4.3 \text{ Hz}, 1\text{H}$), 4.18 – 4.09 (m, 2H), 4.03 – 3.92 (m, 2H), 3.40 (dd, $J = 13.1, 4.2 \text{ Hz}, 1\text{H}$), 2.55 – 2.45 (m, 1H), 2.04 – 1.84 (m, 4H), 1.78 – 1.69 (m, 2H), 0.94 (d, $J = 7.4 \text{ Hz}, 3\text{H}$). ^{13}C NMR (100 MHz, CDCl_3) δ 202.7, 157.9, 157.0, 133.0, 131.2, 130.5, 130.1, 129.2, 127.3, 120.7, 120.4, 112.7, 110.9, 68.4, 67.6, 44.6, 29.0, 28.1, 27.2, 26.0, 25.8, 21.8. FTIR (neat): 2922, 2855, 1669, 1596, 1242 cm^{-1} . HRMS (ESI-TOF) m/z calcd for $\text{C}_{22}\text{H}_{27}\text{O}_3$ $[\text{M}+\text{H}]^+$: 325.1803, found: 325.1811

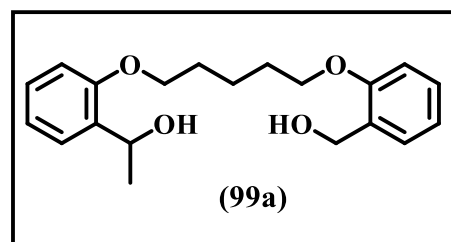
6,7,8,9,10,11,12,13,20,21-decahydro-19H-

dibenzo[*b,g*][1,9]dioxacycloheptadecin-19-one (97j): Prepared according to general experimental procedure 2.10.2D, using (1-(2-((8-(2-(hydroxymethyl)phenoxy)octyl)oxy)phenyl)ethan-1-one (50 mg, 0.13 mmol), KOH (8 mg, 0.13 mmol) and Ru-MACHO (4 mg, 0.0065 mmol) to afford desired product **97j** (21.8 mg, 0.061



mmol, 46% yield) as a semi solid. ^1H NMR (400 MHz, CDCl_3) δ 7.66 (dd, $J = 7.7, 1.8 \text{ Hz}, 1\text{H}$), 7.39 (ddd, $J = 8.4, 7.3, 1.8 \text{ Hz}, 1\text{H}$), 7.27 (dd, $J = 7.6, 1.3 \text{ Hz}, 1\text{H}$), 7.17 – 7.12 (m, 1H), 6.97 – 6.79 (m, 4H), 4.06 – 4.02 (m, 2H), 4.02 – 3.98 (m, 2H), 3.35 (t, $J = 7.2 \text{ Hz}, 2\text{H}$), 3.05 (t, $J = 7.2 \text{ Hz}, 2\text{H}$), 1.82 – 1.72 (m, 4H), 1.64 – 1.55 (m, 4H), 1.45 (dd, $J = 10.5, 3.5 \text{ Hz}, 4\text{H}$). ^{13}C NMR (100 MHz, CDCl_3) δ 202.1, 158.0, 156.9, 132.9, 131.0, 130.3, 130.0, 129.0, 127.0, 120.1, 120.0, 111.9, 110.5, 68.3, 44.5, 28.9, 28.3, 27.4, 26.6, 25.3, 24.8, 24.4. FTIR (neat): 2923, 2855, 1673, 1596, 1245 cm^{-1} . HRMS (ESI-TOF) m/z calculated for $\text{C}_{23}\text{H}_{29}\text{O}_3$ $[\text{M}+\text{H}]^+$: 353.2116, found: 353.2113.

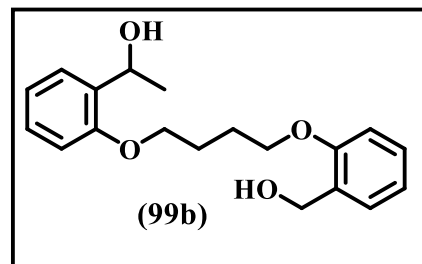
1-(2-((5-(2-(hydroxymethyl)phenoxy)pentyl)oxy)phenyl)ethan-1-ol (99a): Prepared according to general experimental procedure 2.10.2B, using (2-((5-bromopentyl)oxy)phenyl)methanol (500 mg, 1.83 mmol), potassium carbonate (K_2CO_3) (253 mg, 1.83 mmol) and 2-(1-hydroxyethyl)phenol (253 mg, 1.83 mmol) to afford desired product **99a** (500 mg,



1.51 mmol, 82% yield) as a white amorphous solid. ^1H NMR (400 MHz, CDCl_3) δ 7.36 (dd, $J = 7.5, 1.6 \text{ Hz}, 1\text{H}$), 7.32 – 7.27 (m, 1H), 7.27 – 7.18 (m, 2H), 6.95 (td, $J = 7.5, 0.8 \text{ Hz}, 2\text{H}$), 6.87 (dd, $J = 8.2, 1.2 \text{ Hz}, 2\text{H}$), 5.13 (q, $J = 6.5 \text{ Hz}, 1\text{H}$), 4.69 (s, 2H), 4.05 (t, $J = 6.2 \text{ Hz}, 4\text{H}$), 3.02 (s, 1H), 2.76 (s, 1H), 1.95 – 1.86 (m, 4H), 1.75 – 1.66 (m, 2H), 1.50 (d, $J = 6.5 \text{ Hz}, 3\text{H}$). ^{13}C NMR (100 MHz, CDCl_3) δ 156.7, 155.9, 133.6, 129.3, 128.9, 128.3, 126.2, 120.8, 120.7, 111.2, 111.1, 67.7, 67.6, 66.4, 61.8, 29.1, 29.0, 23.1. FTIR (neat): 3375, 2925, 2872, 1600,

1491, 1231 cm^{-1} . HRMS (ESI-TOF) m/z calcd for $\text{C}_{20}\text{H}_{26}\text{O}_4\text{Na}$ $[\text{M}+\text{Na}]^+$: 353.1728, found: 353.1726.

1-(2-(4-(2-(hydroxymethyl)phenoxy)butoxy)phenyl)ethan-1-ol (99b): Prepared according to general experimental procedure 2.10.2B, using (2-(4-bromobutoxy)phenyl)methanol (1 gm, 3.86 mmol), potassium carbonate (K_2CO_3) (533 mg, 3.86 mmol) and hydroxyethylphenol (533 mg, 3.86 mmol) to afford desired product **99b** (1 gm, 3.16 mmol, 81% yield) as a



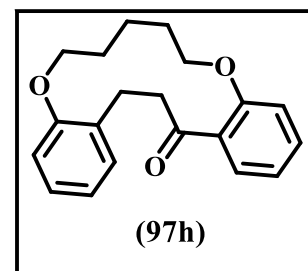
white amorphous solid. ^1H NMR (400 MHz, CDCl_3) δ 7.35 (d, J = 7.3 Hz, 1H), 7.25 (dt, J = 13.7, 7.4 Hz, 3H), 6.95 (dd, J = 14.7, 7.3 Hz, 2H), 6.86 (d, J = 6.4 Hz, 2H), 5.10 (q, J = 6.4 Hz, 1H), 4.65 (s, 2H), 4.09 (t, 4H), 2.78 (s, 1H), 2.54 (s, 1H), 2.03 (m, 4H), 1.48 (d, 3H). ^{13}C NMR (100 MHz, CDCl_3) δ 156.7, 155.8, 133.6, 129.3, 129.0, 128.9, 128.4, 126.2, 121.0, 120.8, 111.2, 111.1, 67.4, 66.4, 61.9, 33.4, 29.8, 26.3, 23.0.

FTIR (neat): 3374, 2925, 2873, 1600, 1491, 1236 cm^{-1} . HRMS (ESI-TOF) m/z calcd for $\text{C}_{19}\text{H}_{24}\text{O}_4\text{Na}$ $[\text{M}+\text{Na}]^+$: 339.1567, found: 339.1560.

7,8,9,10,17,18-hexahydro-6H,16H-dibenzo[*h,m*][1,7]dioxacyclotetradecin-16-one (97h):

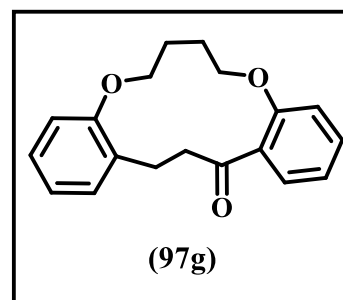
Prepared according to general experimental procedure 2.10.2D, using

1-(2-((5-(2-(hydroxymethyl)phenoxy)pentyl)oxy)phenyl)ethan-1-ol (**99a**) (50 mg, 0.15 mmol), KOH (9 mg, 0.15 mmol) and Ru-MACHO (4.5 mg, 0.0075 mmol) to afford desired product **97h** (29 mg, 0.09 mmol, 61% yield) as a semi-solid. ^1H NMR (400 MHz, CDCl_3) δ 7.56 (dd,



J = 7.6, 1.8 Hz, 1H), 7.39 (ddd, J = 8.3, 7.4, 1.8 Hz, 1H), 7.23 – 7.15 (m, 2H), 6.96 (td, J = 7.5, 0.9 Hz, 1H), 6.89 – 6.83 (m, 3H), 4.07 (dt, J = 9.9, 4.9 Hz, 4H), 3.50 – 3.45 (m, 2H), 3.04 (m, J = 9.1, 7.1 Hz, 2H), 1.93 (m, J = 5.5 Hz, 4H), 1.86 (m, J = 10.9, 6.6 Hz, 2H). ^{13}C NMR (100 MHz, CDCl_3) δ 204.2, 157.7, 157.0, 132.8, 130.8, 130.1, 129.6, 127.4, 120.6, 120.4, 111.9, 110.8, 67.5, 64.5, 44.0, 27.1, 26.8, 26.3, 21.3. FTIR (neat): 2934, 2871, 1676, 1597, 1244 cm^{-1} . HRMS (ESI-TOF) m/z calcd for $\text{C}_{20}\text{H}_{23}\text{O}_3$ $[\text{M}+\text{H}]^+$: 311.1647, found: 311.1651.

6,7,8,9,16,17-hexahydro-15*H*-dibenzo[*g,l*][1,6]dioxacyclotridecin-15-one (97g): Prepared according to general experimental procedure 2.10.2D, using 1-(2-(4-(2-(hydroxymethyl)phenoxy)butoxy)phenyl)ethan-1-ol (**99b**) (50 mg, 0.16 mmol), KOH (9 mg, 0.16 mmol) and Ru-MACHO (4.8 mg, 0.008 mmol) to afford desired product **97g** (26.3 mg, 0.088 mmol, 56% yield) as a semi-solid. ¹H NMR (400 MHz, CDCl₃) δ 7.66 (dd, *J* = 7.7, 1.8 Hz, 1H), 7.44 (ddd, *J* = 8.3, 7.3, 1.9 Hz, 1H), 7.25 – 7.21 (m, 1H), 7.20 – 7.16 (m, 1H), 7.02 – 6.95 (m, 2H), 6.92 – 6.83 (m, 2H), 4.21 – 4.16 (m, 2H), 4.13 – 4.08 (m, 2H), 3.37 – 3.32 (m, 2H), 3.06 – 2.99 (m, 2H), 2.19 – 2.12 (m, 2H), 2.09 – 2.02 (m, 2H). ¹³C NMR (100 MHz, CDCl₃) δ 204.6, 158.5, 157.7, 133.5, 131.0, 130.7, 130.6, 129.4, 127.7, 121.0, 120.8, 112.7, 112.6, 69.5, 68.5, 43.2, 28.5, 27.5, 26.4. FTIR (neat): 2925, 2872, 1673, 1596, 1246 cm⁻¹. HRMS (ESI-TOF) *m/z* calcd for C₁₉H₂₁O₃ [M+H]⁺: 297.1490, found: 297.1501.



10.5 Crystal Data:

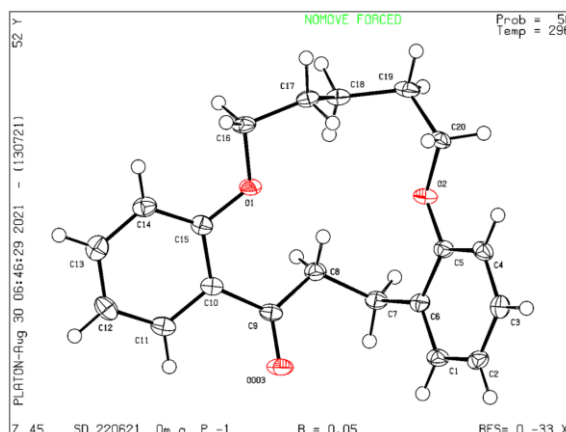
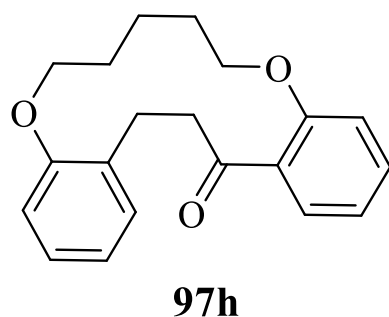


Figure 42. ORTEP drawing of **97h** showing thermal ellipsoids at the 50% probability level

Crystallographic parameters of 97h:

Parameters	97h
Emperical formula	C ₂₀ H ₂₂ O ₃
Formula Mass/g mol	310.38
Experimental crystal description	Rod
Colour	White
Dcalcd/g cm ⁻³	1.312
Crystal system	Triclinic
Space group	P -1
a/ Å	7.4537(6)
b/ Å	8.0469(7)
c/ Å	14.0332(12)
α/ deg	74.291(5)
β/ deg	79.963(5)
γ/ deg	77.790(5)
V/Å ³	785.78(12)
Z	2
T / K	296 K
Diffraction Source	CuK α
Diffraction radiation wavelength/ Å	1.54178

Diffraction reflection theta full	65.381
Reflection number total	2690
Reflection number gt	2192
μ/mm^{-1}	0.693
F(000)	332.0
$R_1, wR_2 [I > 2\sigma(I)]$	0.0546, 0.1286
$R_1, wR_2(\text{all data})$	0.0754, 0.1390
GoF	1.045

Crystal preparation: The crystals are grown by simple recrystallization method where pure compounds isolated after column chromatography are dissolved in dichloromethane and layered with hexane, kept at room temperature to get a pure crystal. More information on crystal structures can also be obtained from the Cambridge Crystallographic Data Centre (CCDC) with deposition numbers 2093707 (**197h**).

2A.11. Appendix (I): Copies of ^1H and ^{13}C NMR Spectra of Representative Compounds

Entry	Data	Figure No
96a	^1H and ^{13}C	22-23
96b	^1H and ^{13}C	24-25
66f	^1H and ^{13}C	26-27
67a	^1H and ^{13}C	28-29
97f	^1H and ^{13}C	30-31
97g	^1H and ^{13}C	32-33
97h	^1H and ^{13}C	34-35
97i	^1H and ^{13}C	36-37
97j	^1H and ^{13}C	38-39
99a	^1H and ^{13}C	40-41

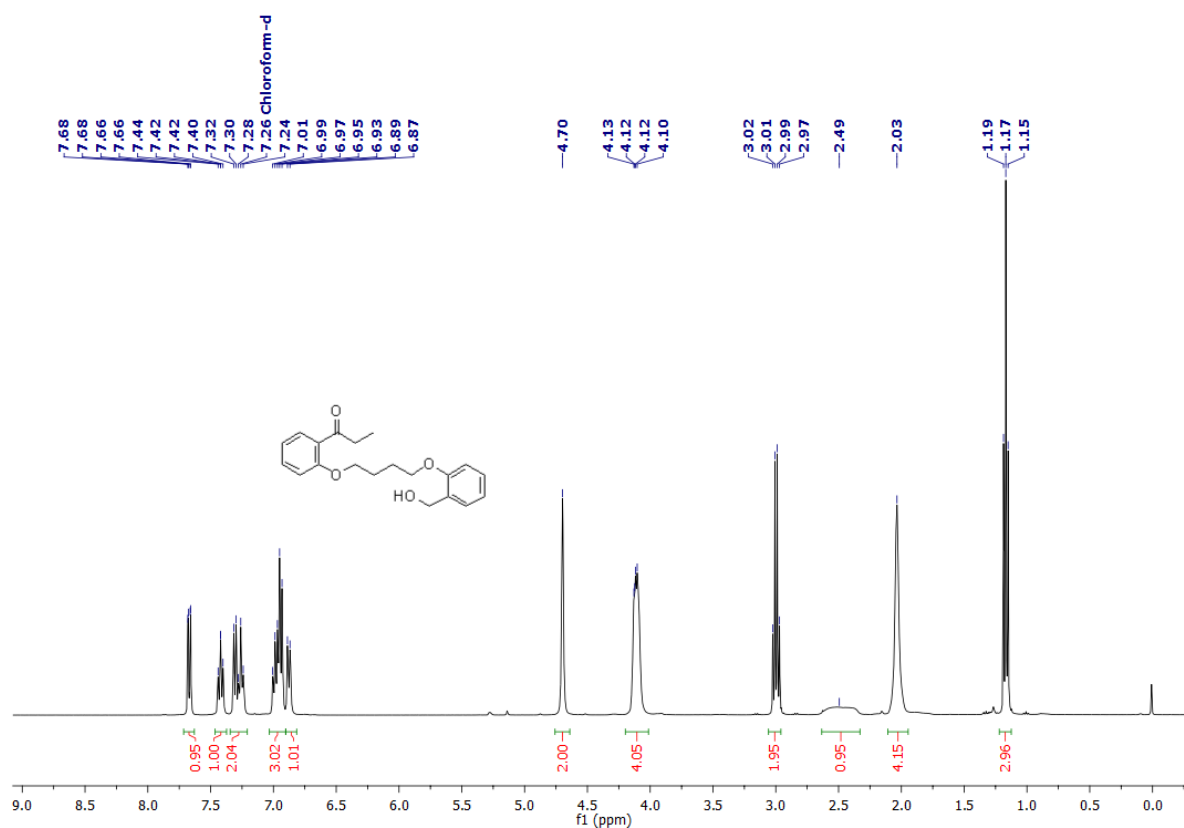


Figure 22. ¹H NMR spectra for compound **96a**, 400 MHz, CDCl₃

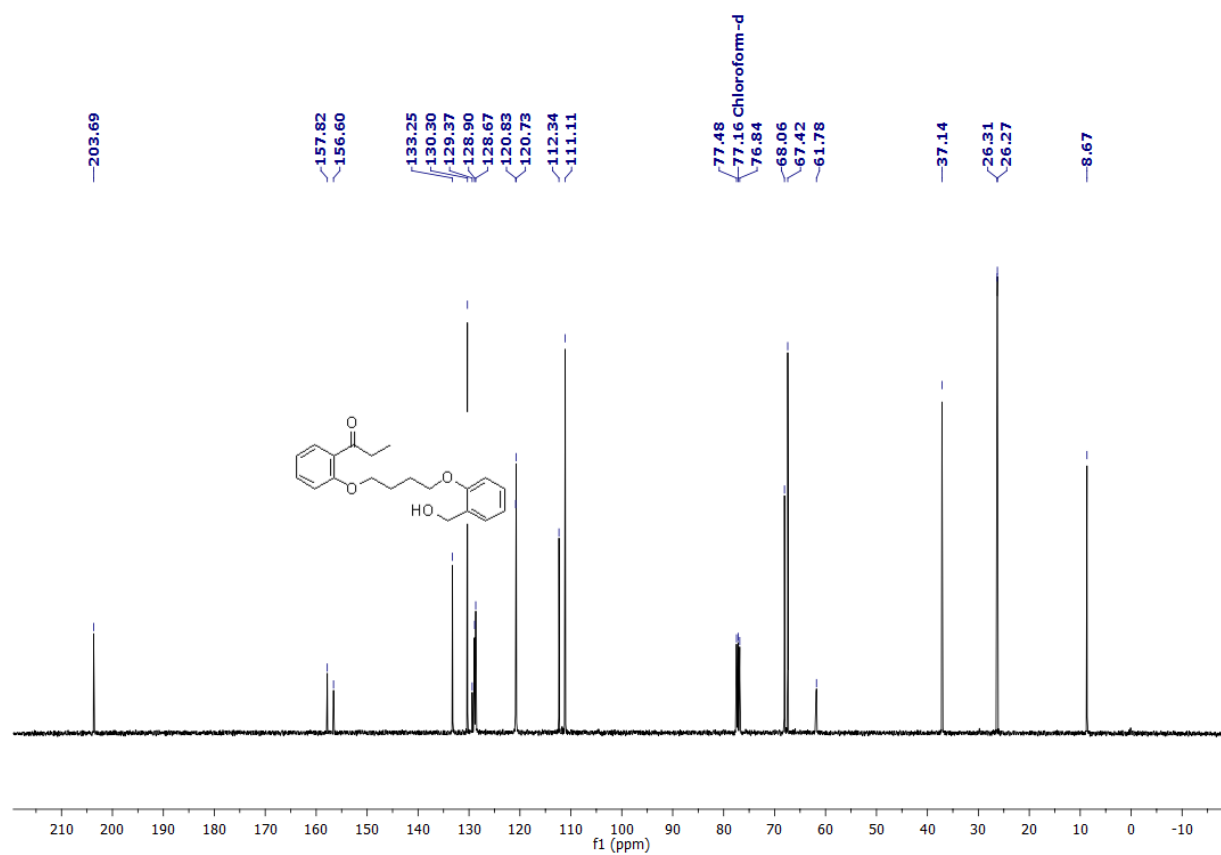


Figure 23. ¹³C NMR spectra for compound **96a**, 100 MHz, CDCl₃

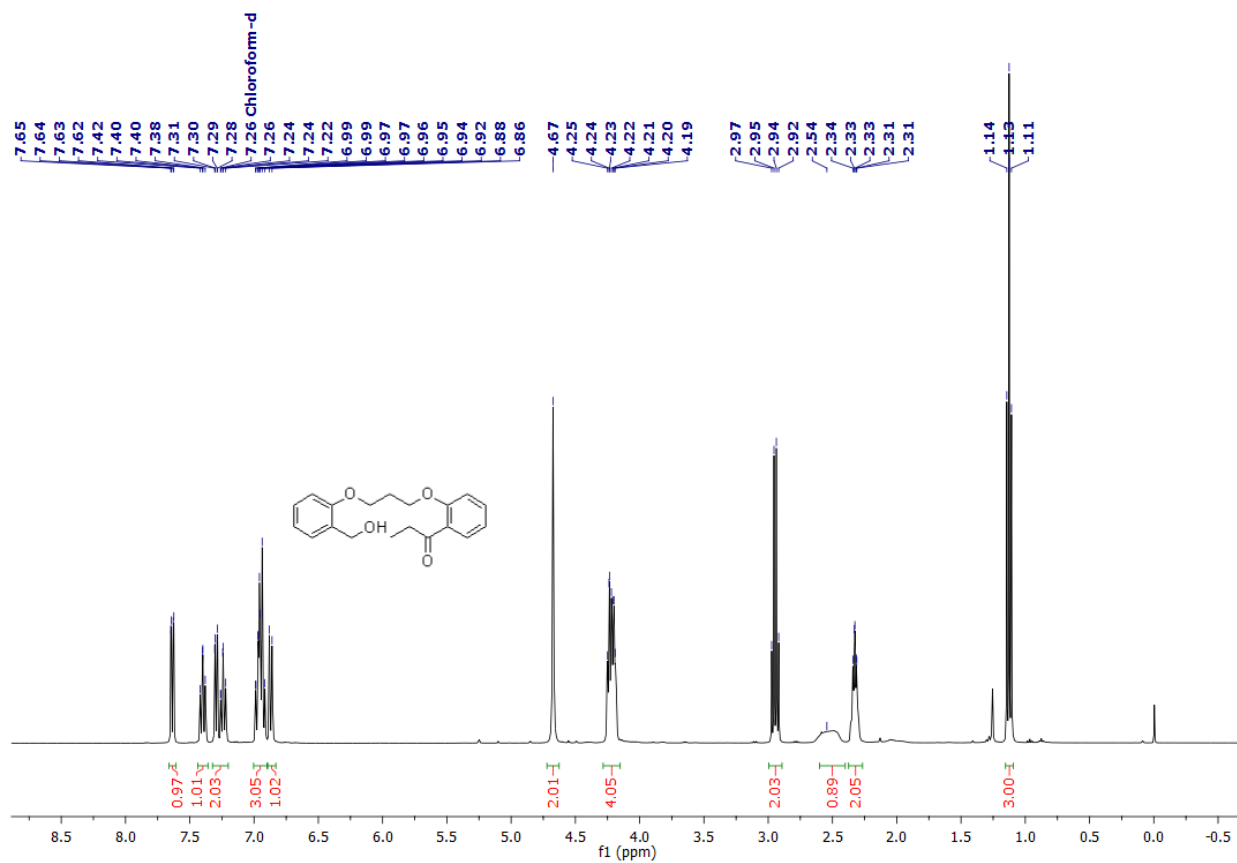


Figure 24. ¹H NMR spectra for compound **96b**, 400 MHz, CDCl₃

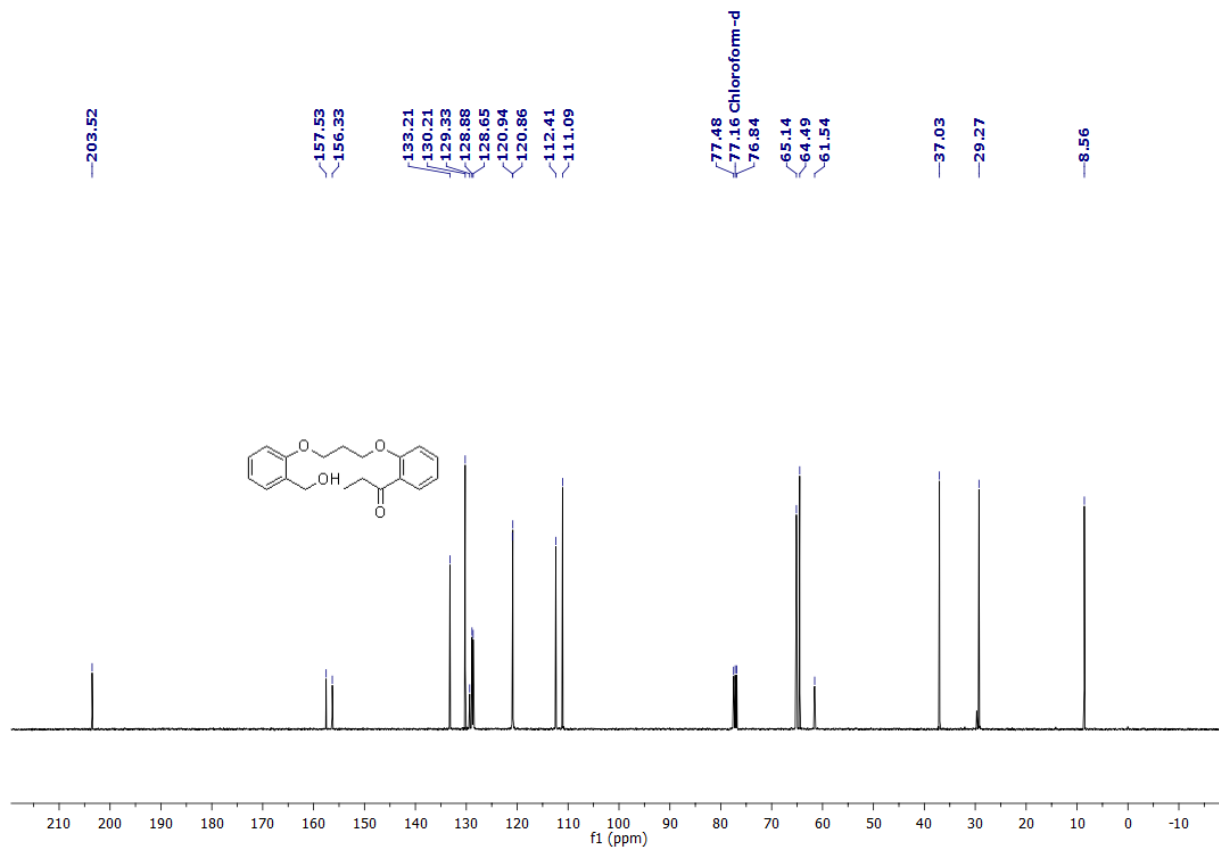


Figure 25. ¹³C NMR spectra for compound **96b**, 100 MHz, CDCl₃

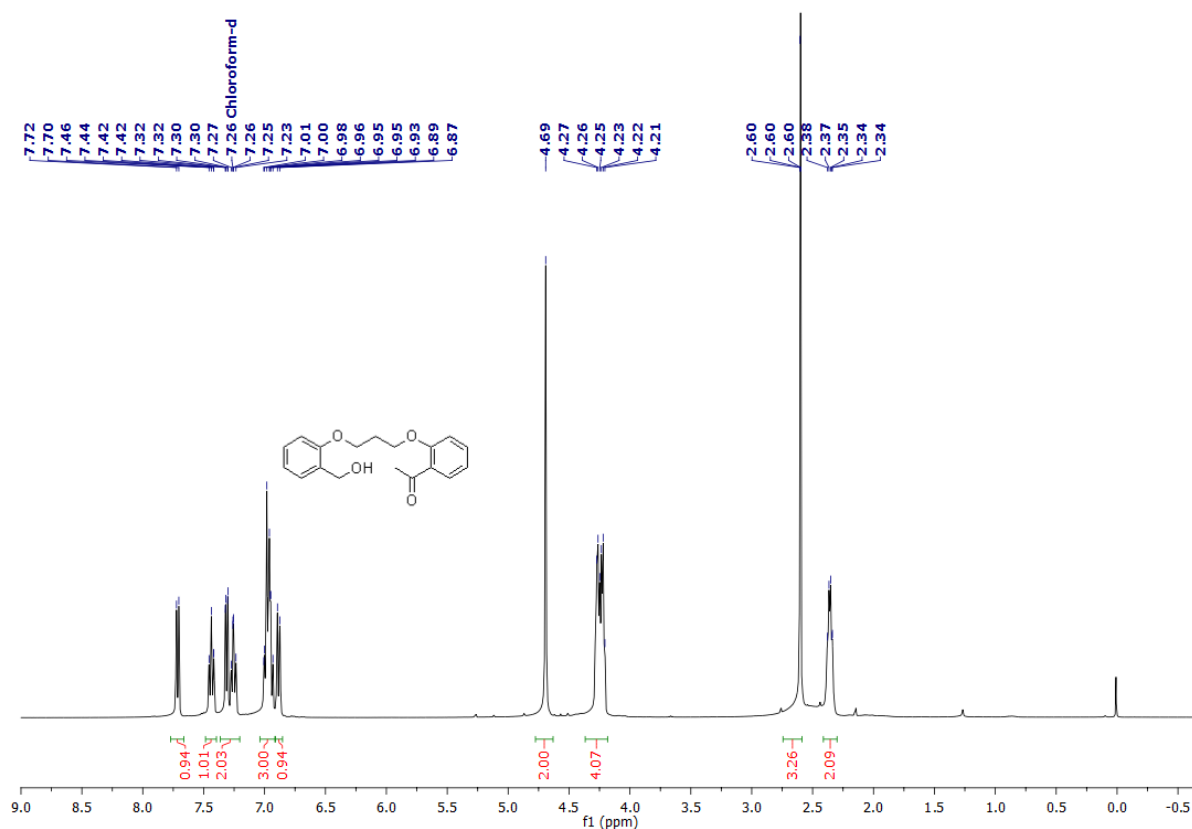


Figure 26. ¹H NMR spectra for compound **96f**, 400 MHz, CDCl₃

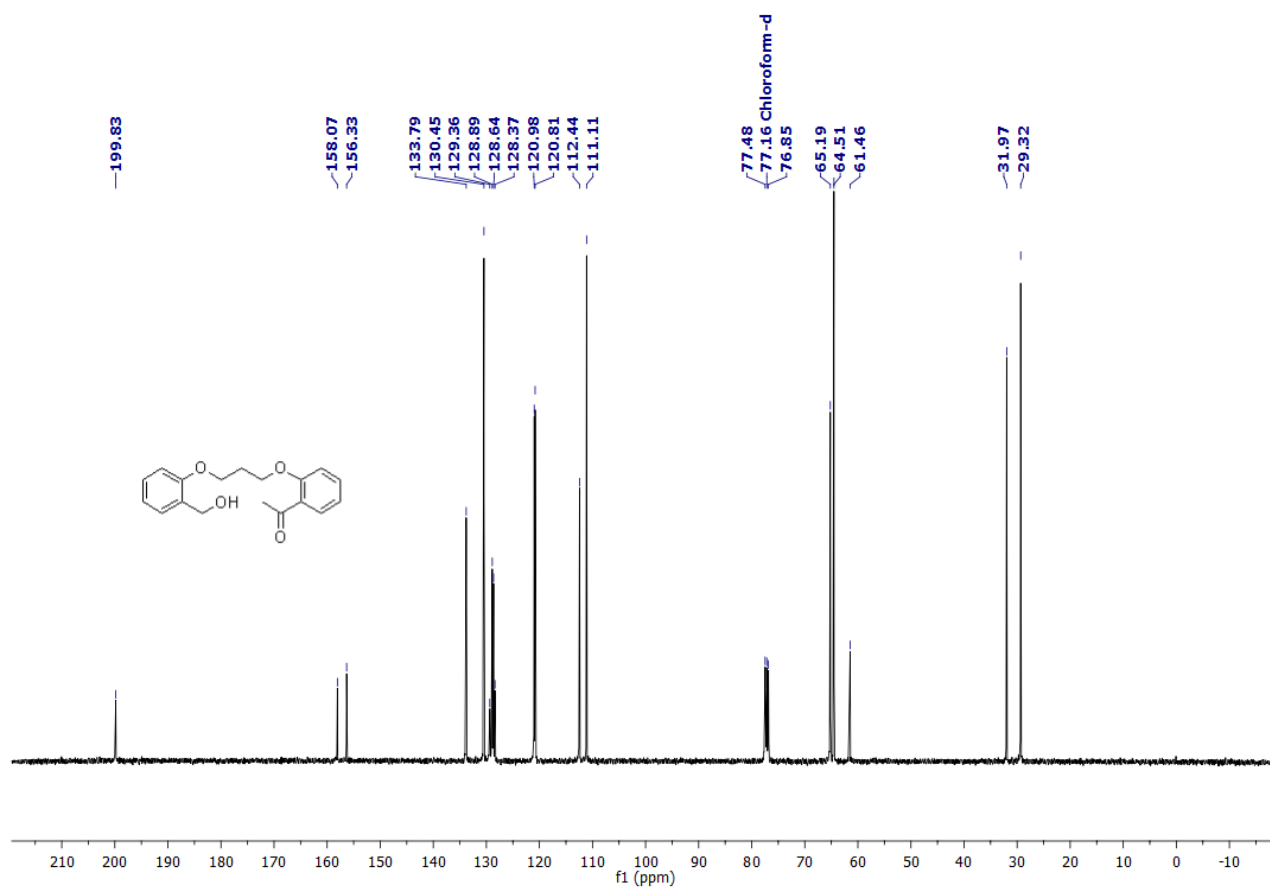


Figure 27. ¹³C NMR spectra for compound **96f**, 100 MHz, CDCl₃

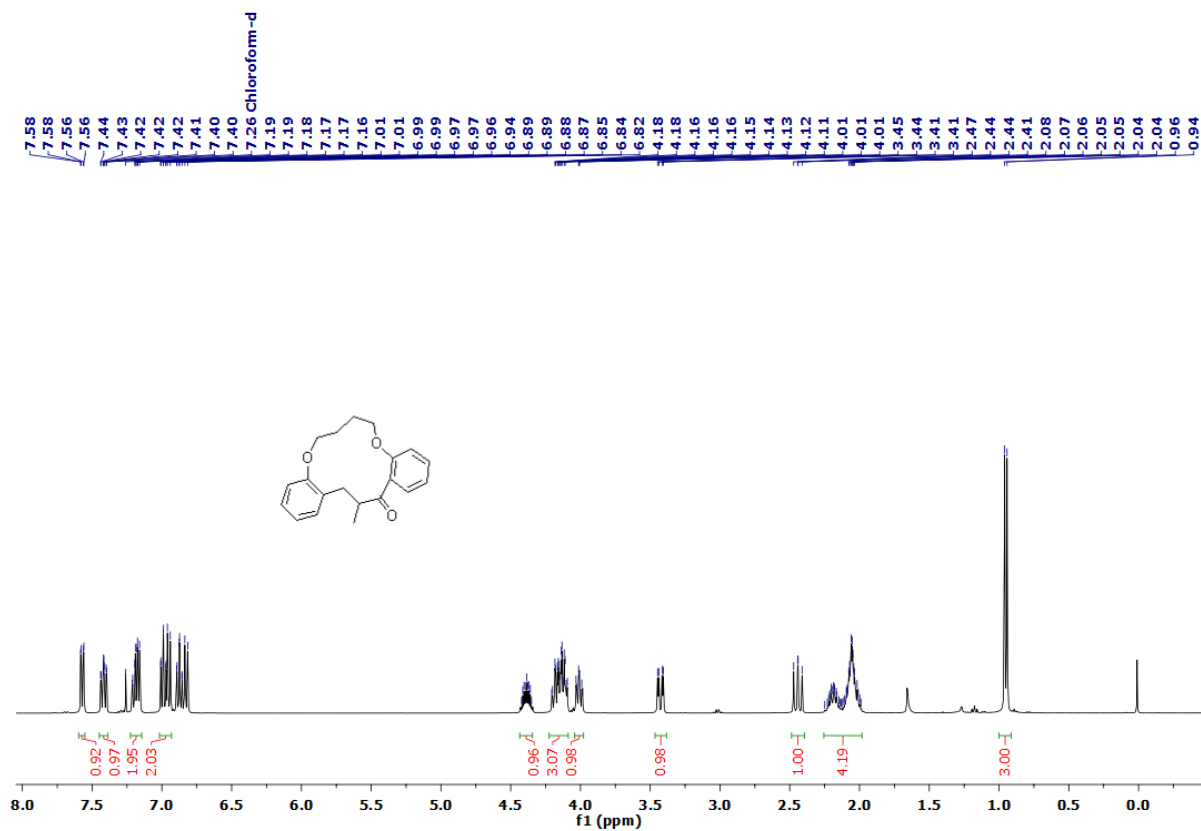


Figure 28. ¹H NMR spectra for compound **97a**, 400 MHz, CDCl₃

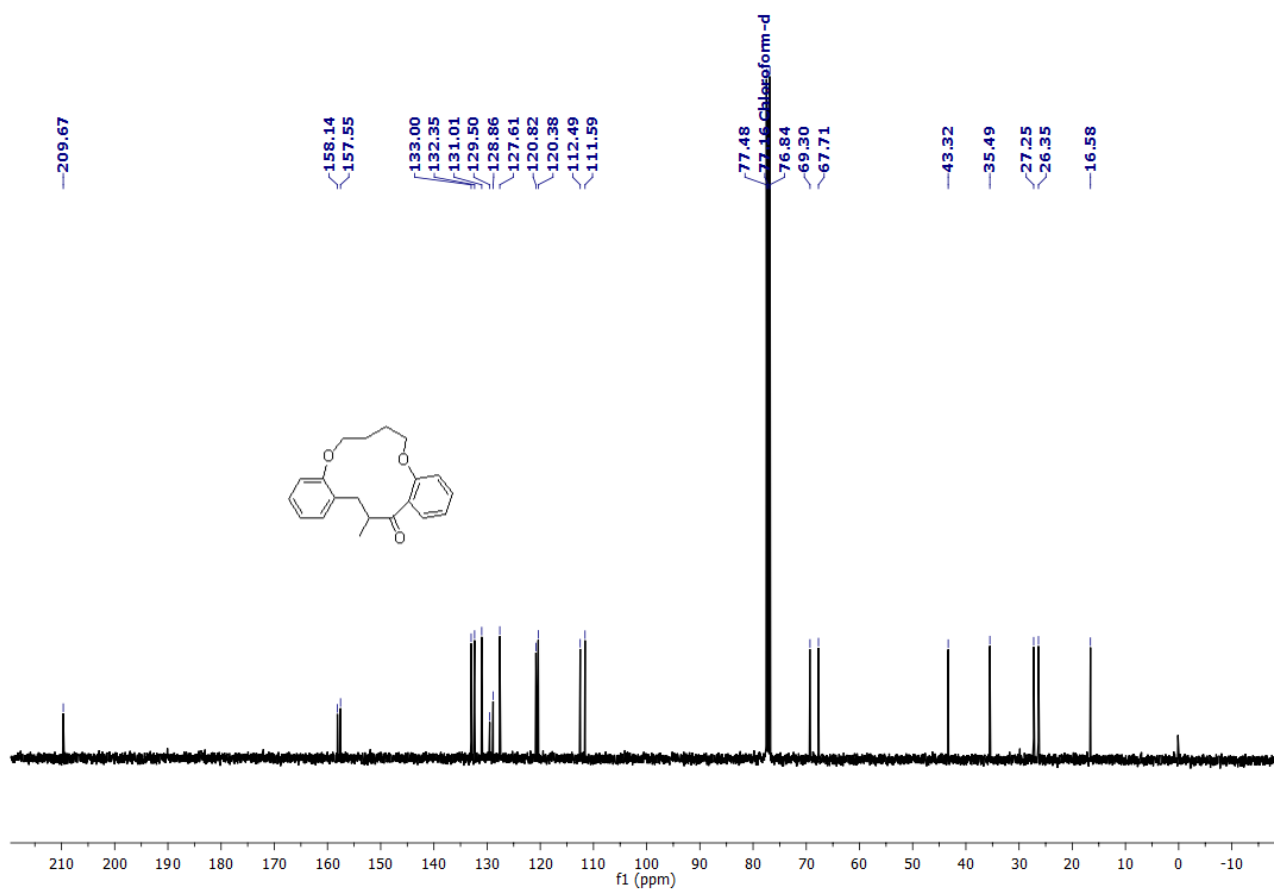


Figure 29. ¹³C NMR spectra for compound **97a**, 100 MHz, CDCl₃

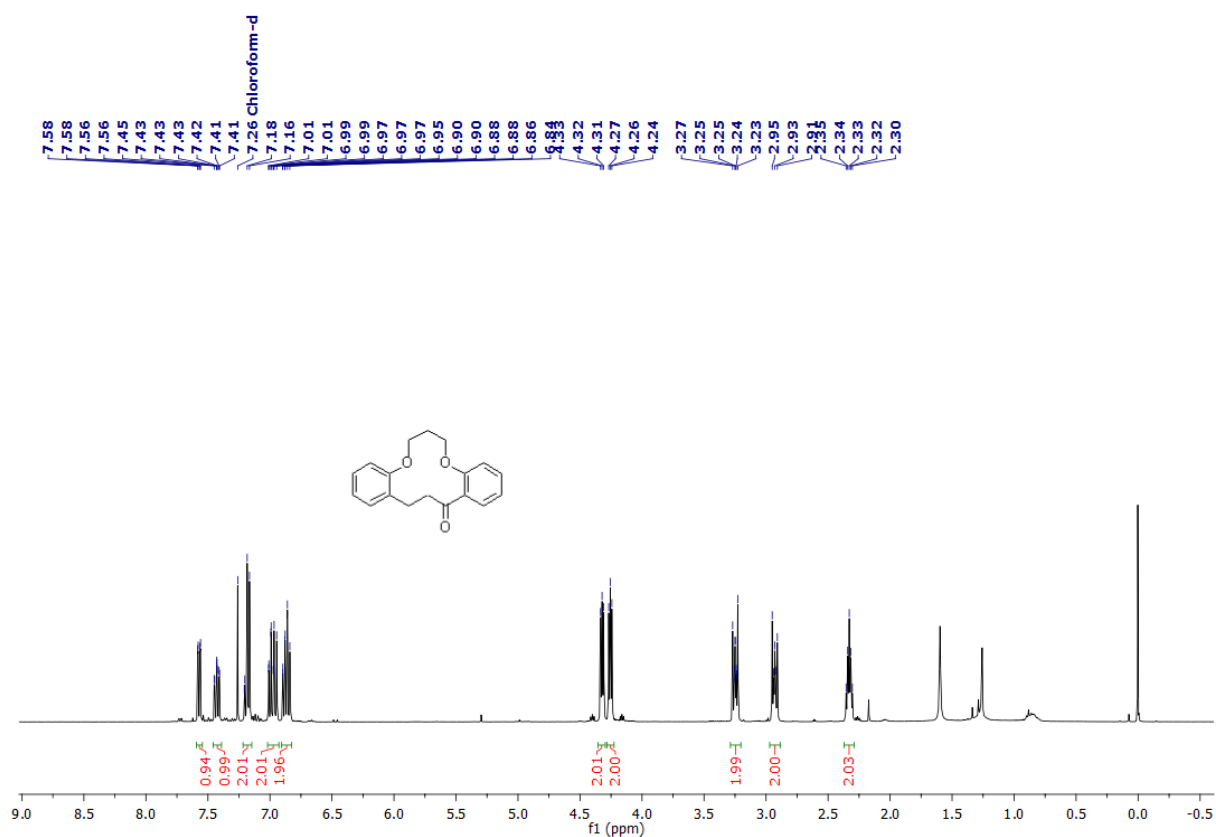


Figure 30. ¹H NMR spectra for compound 97f, 400 MHz, CDCl₃

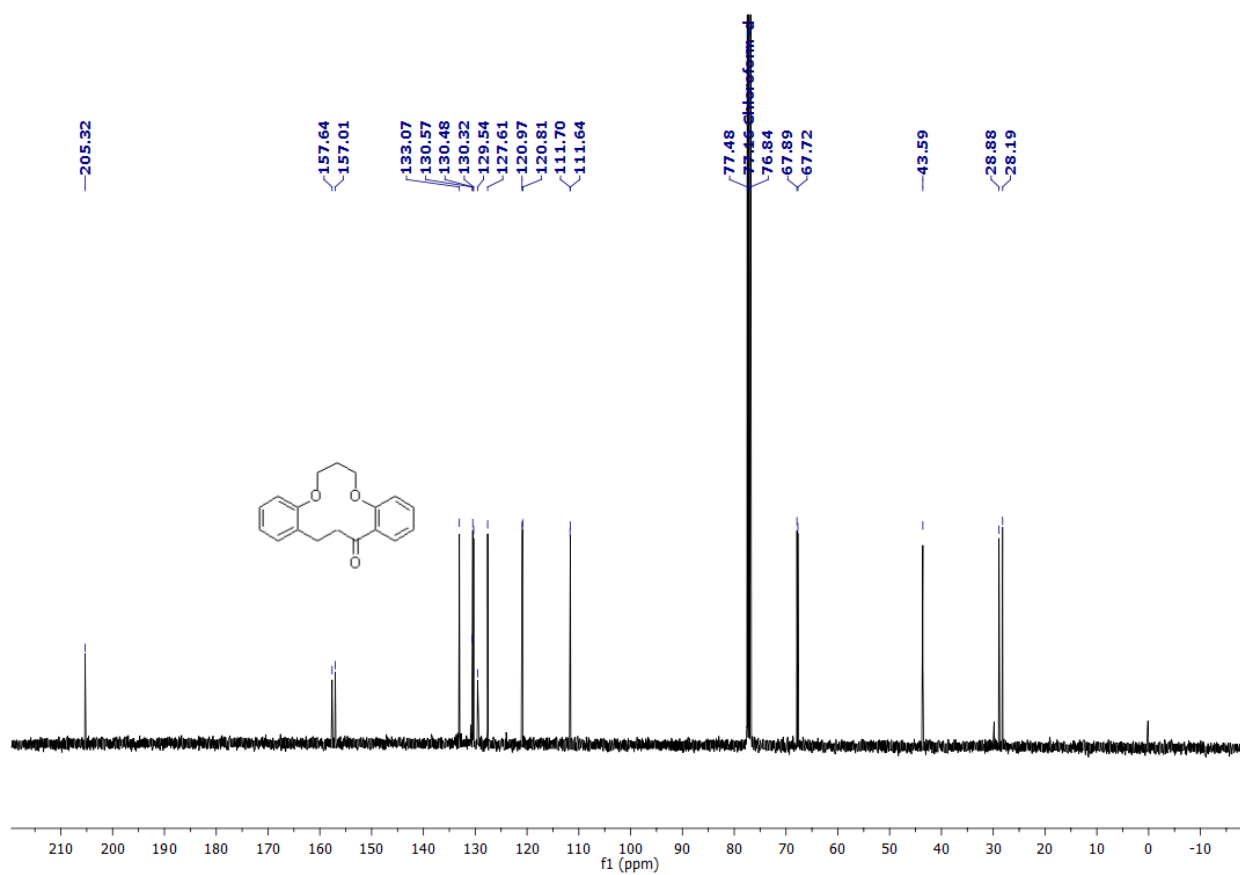


Figure 31. ¹³C NMR spectra for compound 97f, 100 MHz, CDCl₃

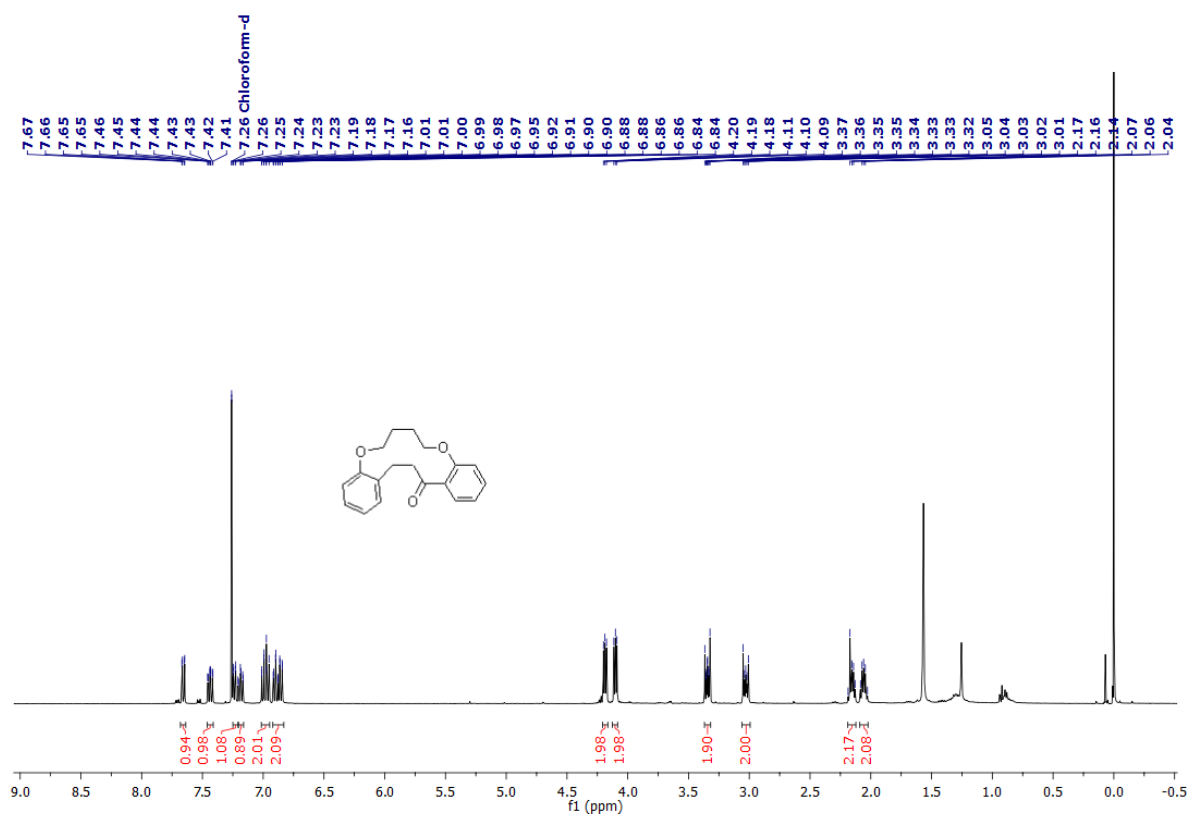


Figure 32. ^1H NMR spectra for compound **97g**, 400 MHz, CDCl_3

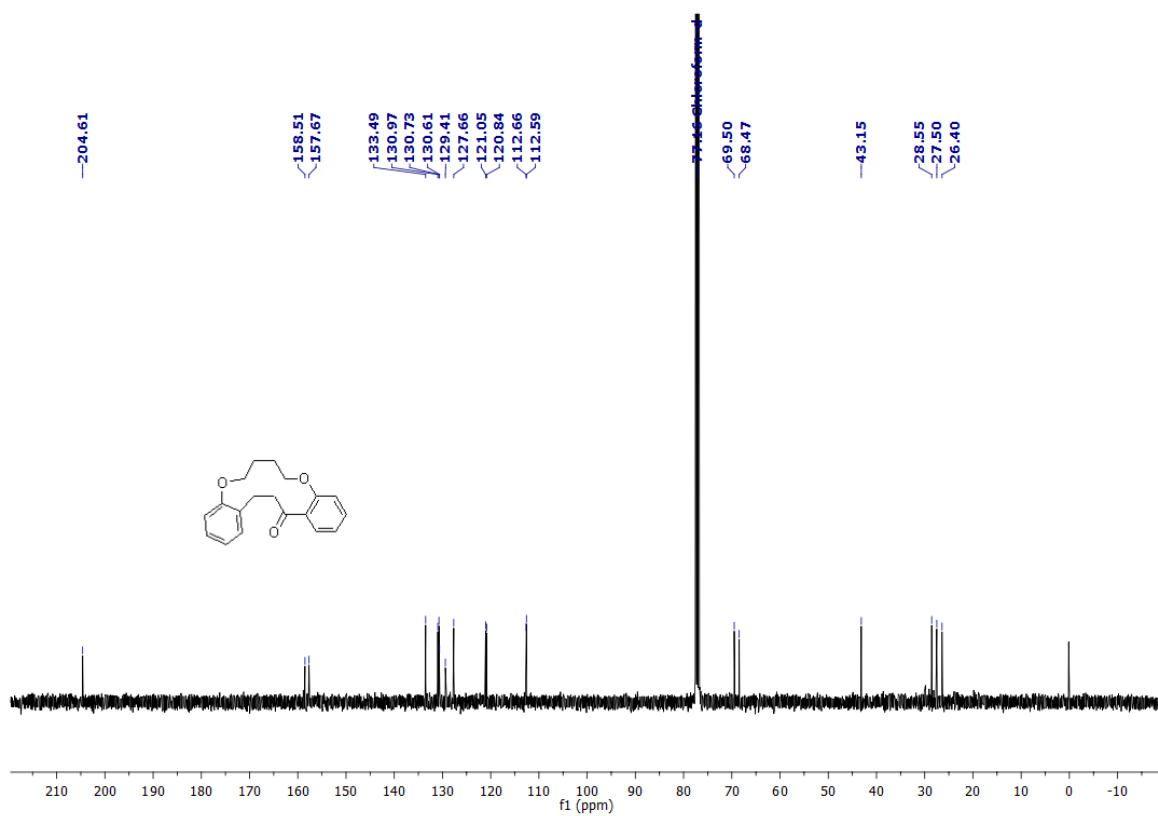


Figure 33. ^{13}C NMR spectra for compound **97g**, 100 MHz, CDCl_3

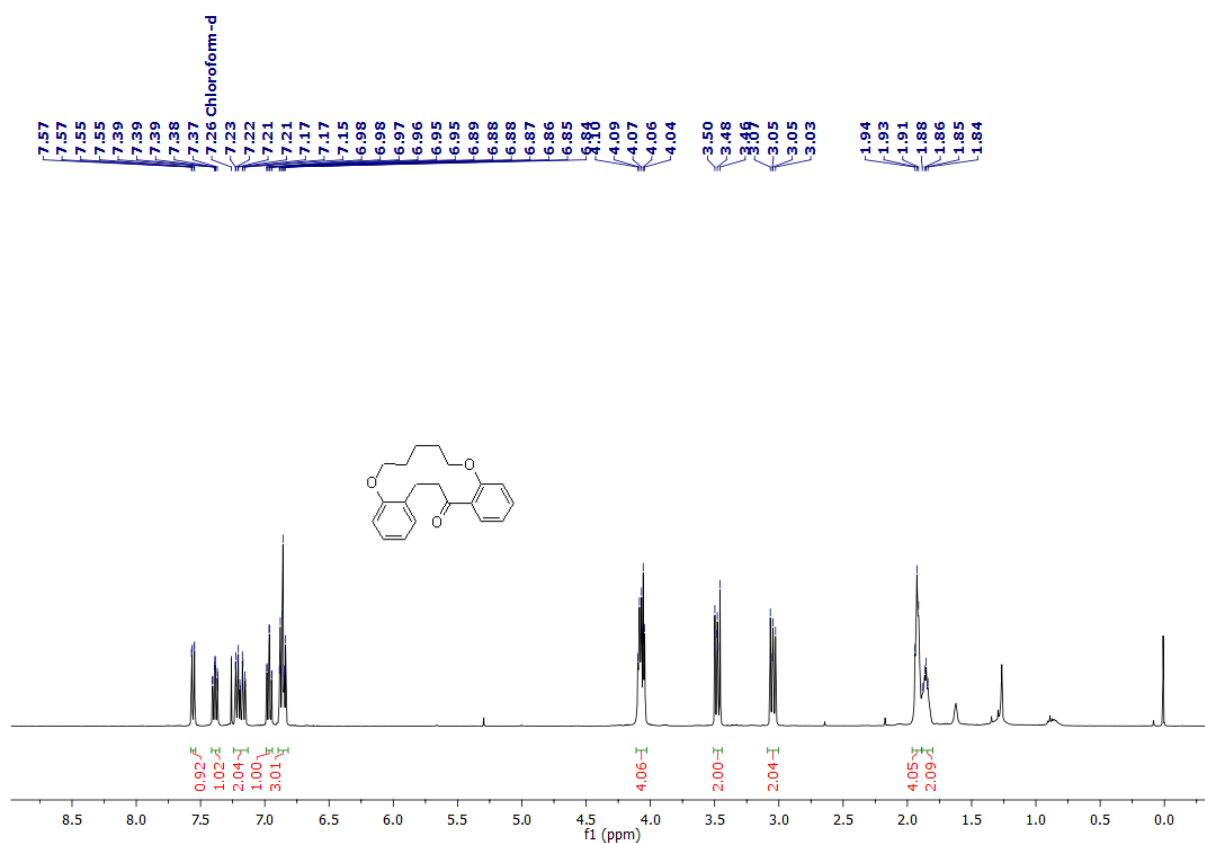


Figure 34. ¹H NMR spectra for compound **97h**, 400 MHz, CDCl₃

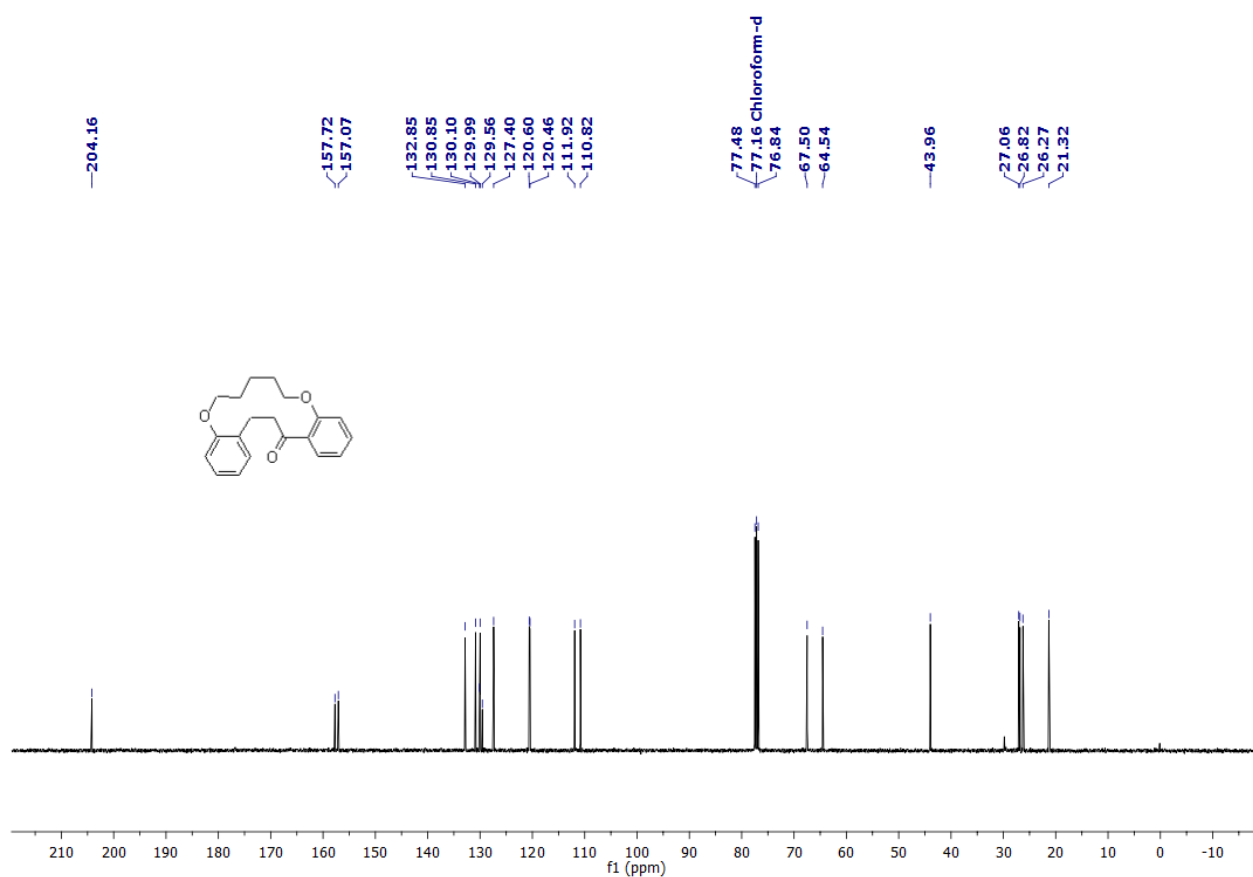


Figure 35. ¹³C NMR spectra for compound **97h**, 100 MHz, CDCl₃

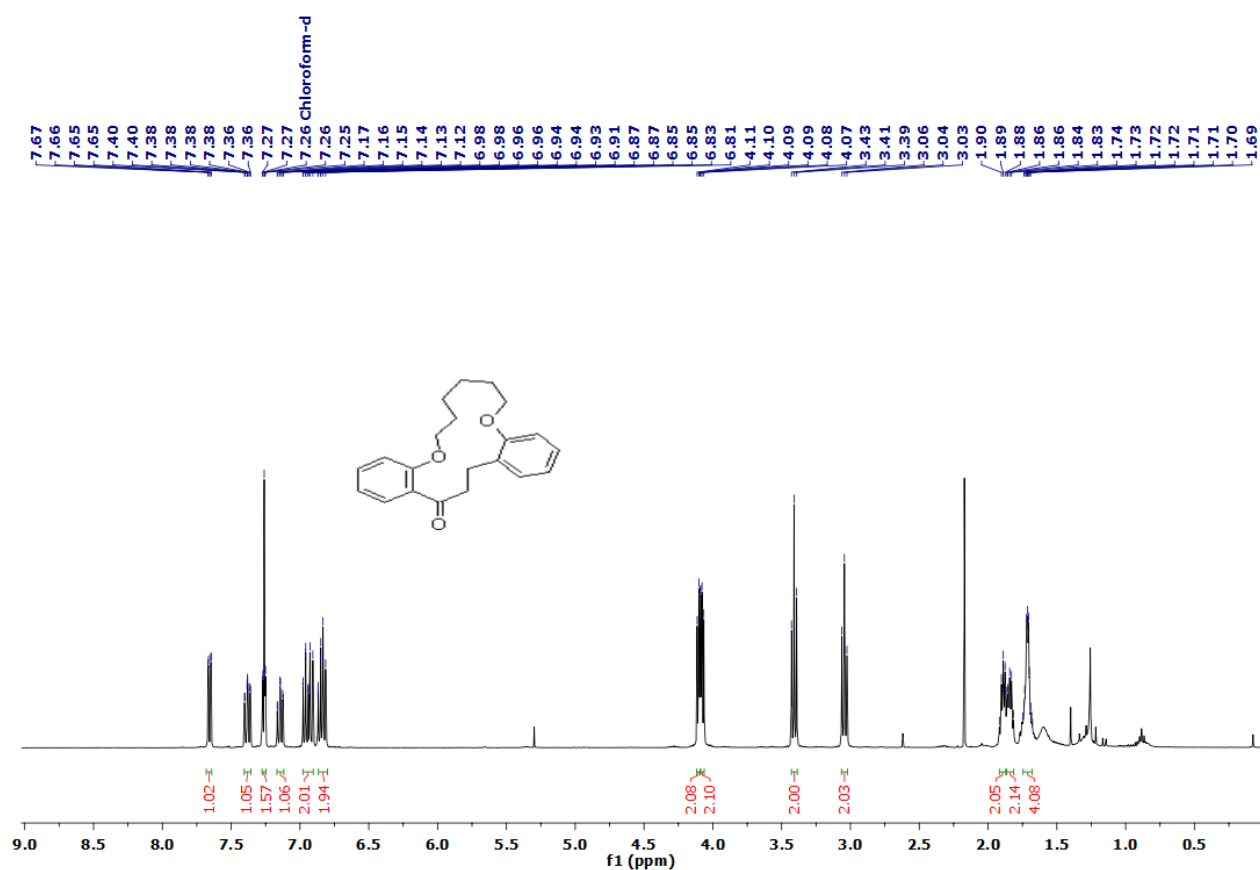


Figure 36. ¹H NMR spectra for compound **97i**, 400 MHz, CDCl₃

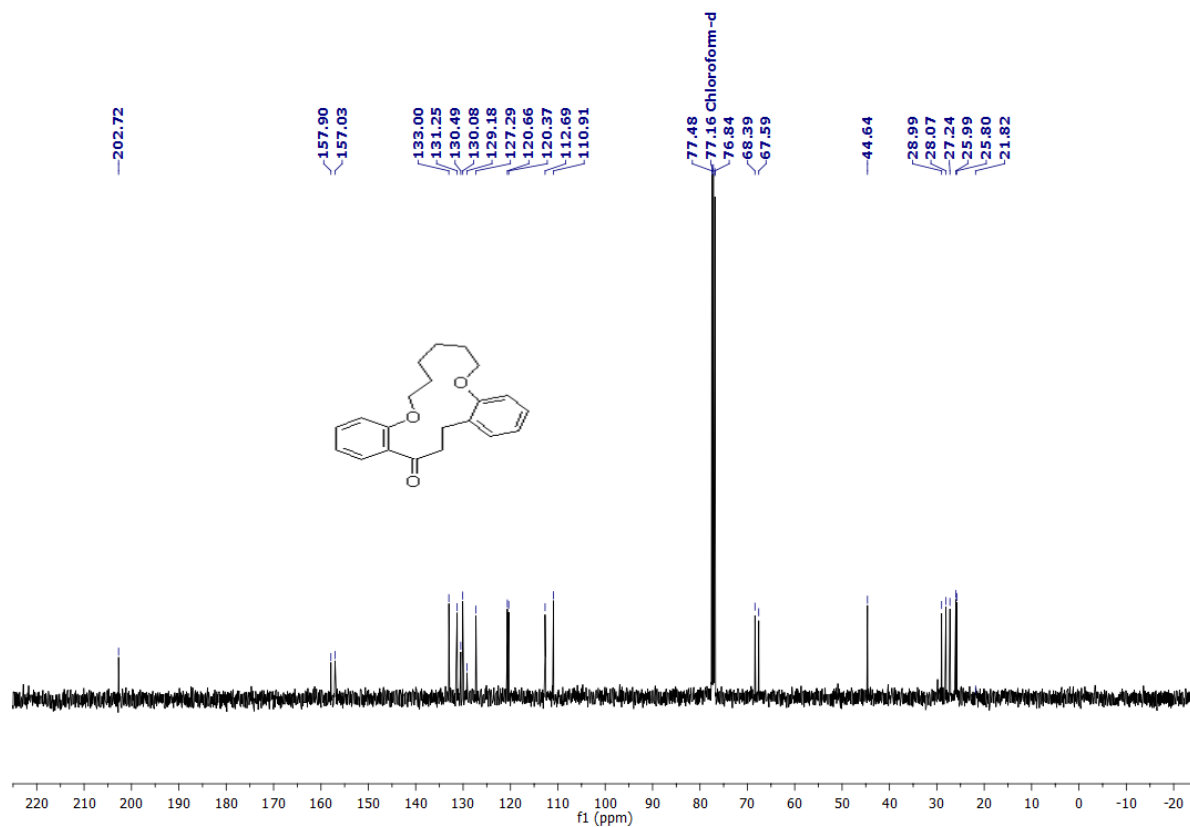


Figure 37. ¹³C NMR spectra of compound **97i**, 100 MHz, CDCl₃

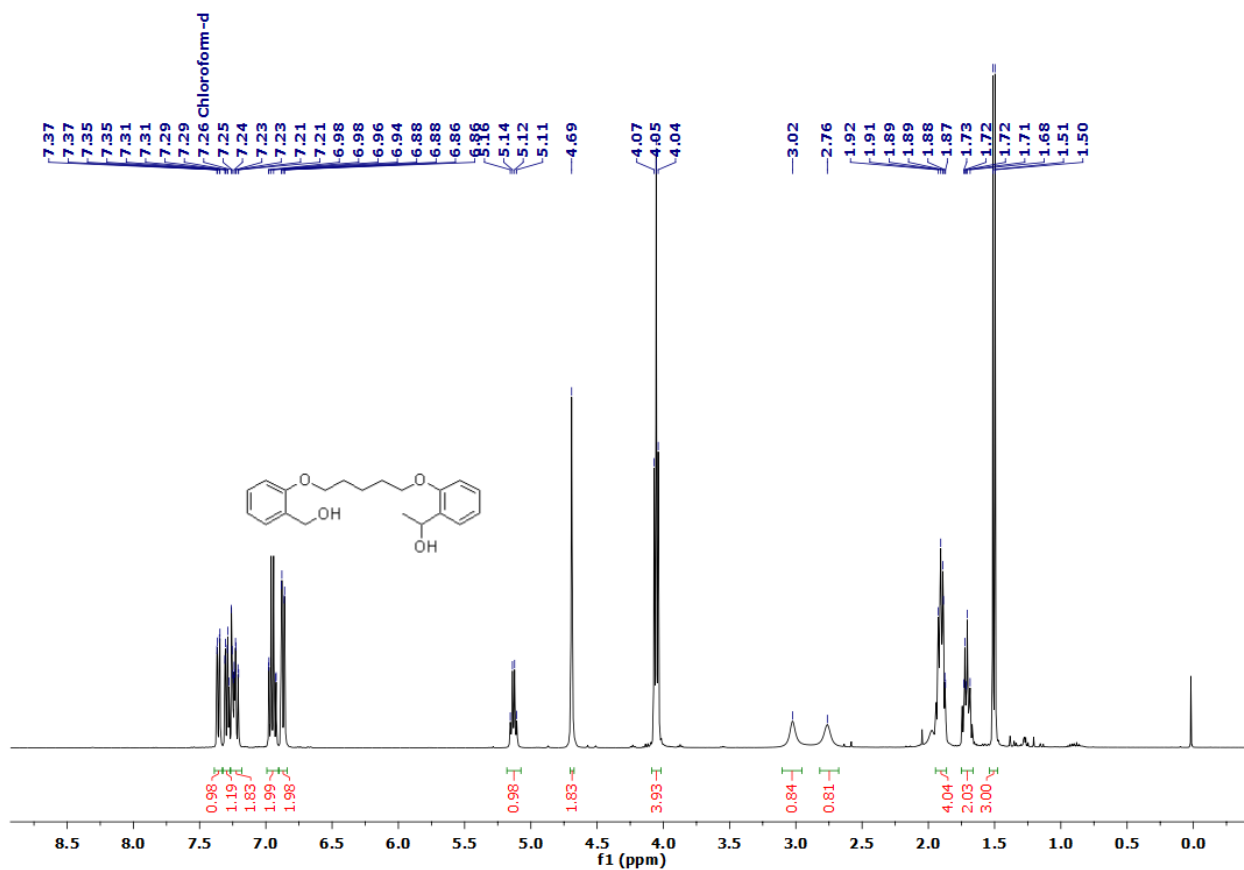


Figure 40. ¹H NMR spectra for compound **99a**, 400 MHz, CDCl₃

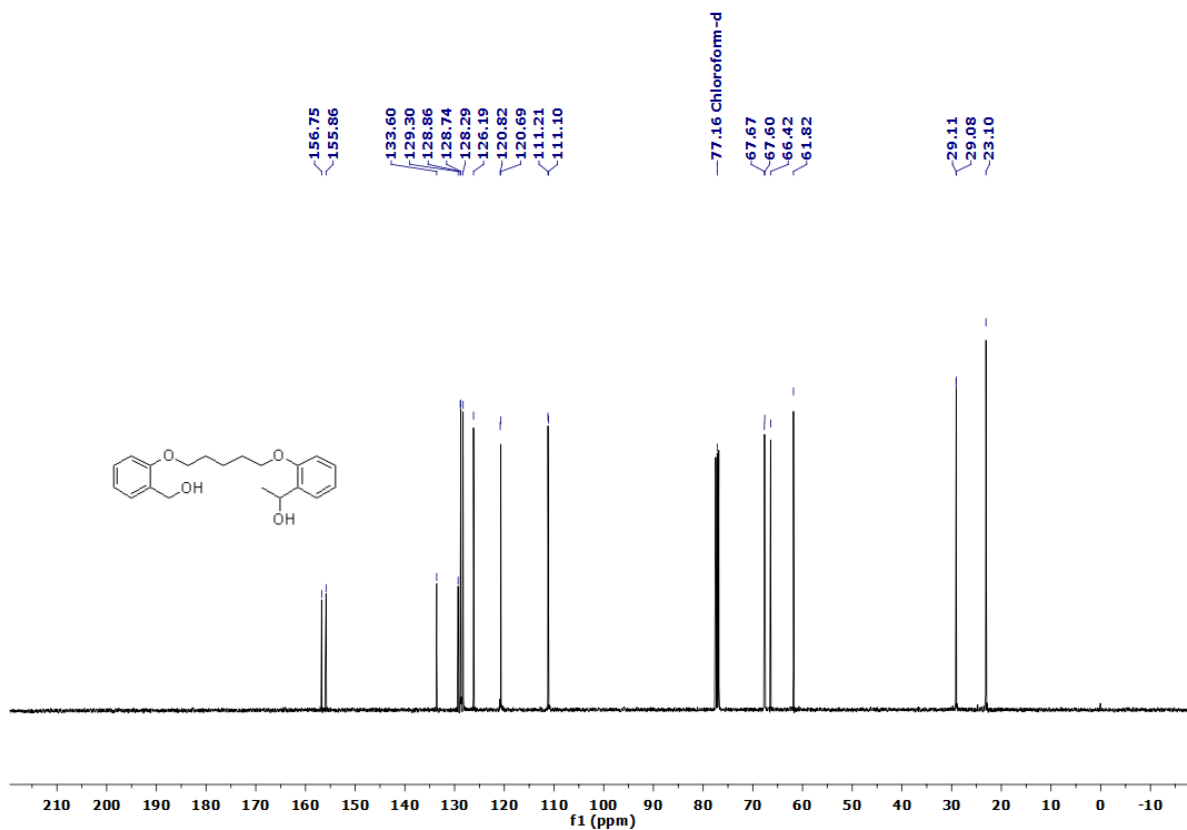
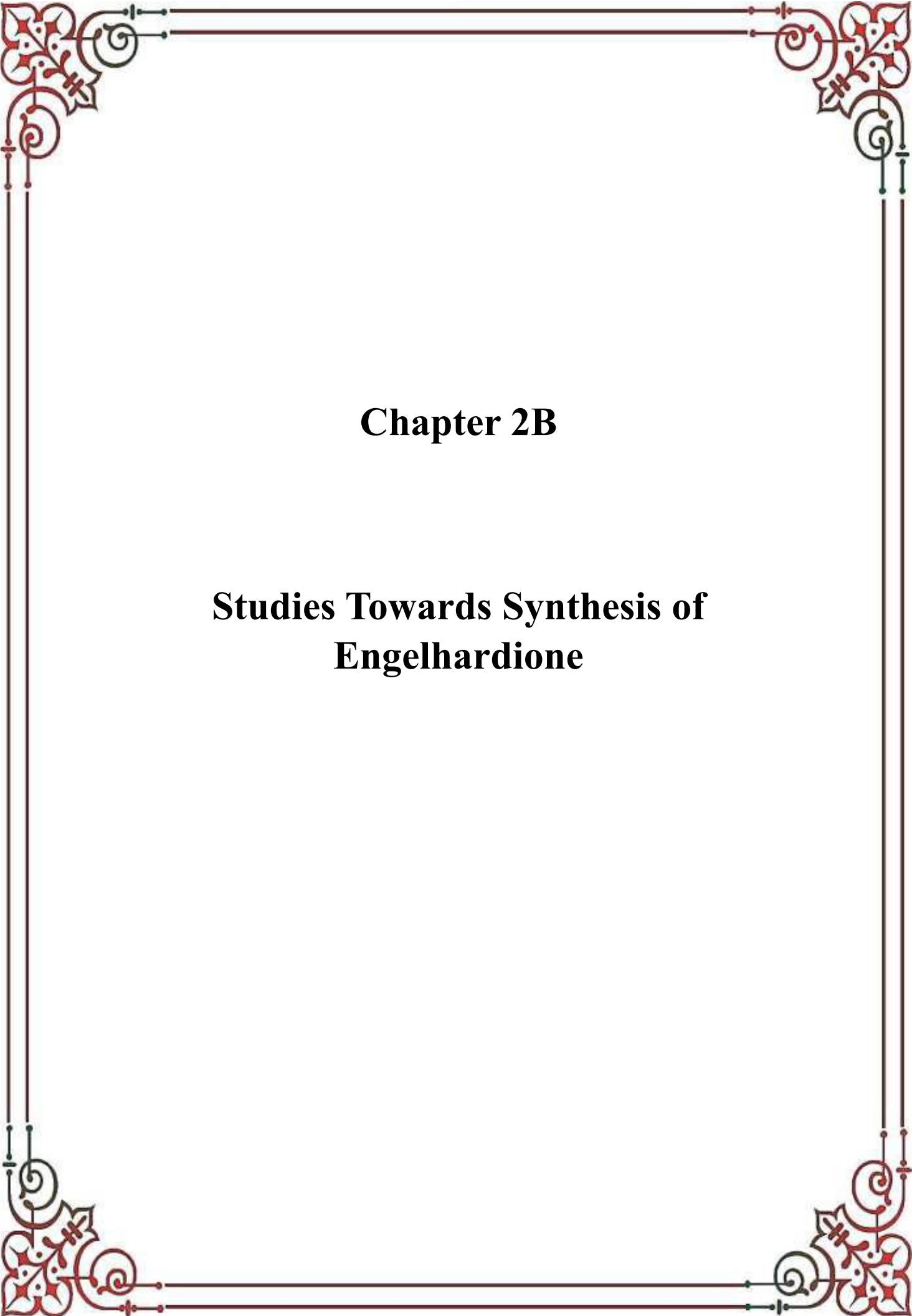


Figure 41. ¹³C NMR spectra for compound **99a**, 100 MHz, CDCl₃



Chapter 2B

Studies Towards Synthesis of Engelhardione

2B. Studies Towards Synthesis of Engelhardione

2B.1 Abstract

In this chapter, we presented a new approach for synthesizing the macrocyclic natural product engelhardione. The synthesis involves a sequence of reactions, including aldol condensation, bromination, selective hydrogenation, and Ullmann coupling reactions, to produce 4-(3-(5-(3-hydroxypropyl)-2-methoxyphenoxy)-4-methoxyphenyl)butan-2-one engelhardione **117** derivatives. This keto-alcohol **117** was followed for intramolecular borrowing hydrogen alkylation *via* C-C bond to yield macrocyclic diaryl ether analogues **116**, which upon demethylation to afford the natural product engelhardione. The key advantage of our borrowing hydrogen approach is that it generates only water as a by-product. Moreover, to the best of our knowledge, our method represents the first example of synthesizing a 14-membered macrocyclic diarylheptanoid *via* C-C bond formation.

2B.2 Introduction to Engelhardione

Natural products constitute a highly valuable source of novel bioactive molecules and chemical diversity in drug discovery.¹⁰⁹ This is attributed to their historical significance in treating and preventing human diseases.¹¹⁰ Naturally occurring macrocyclic diarylether heptanoids are important bioactive compounds found in plant materials used in folk medicine for centuries.¹¹¹ Engelhardione is a part of diarylether heptanoids that were recently isolated from the roots of *Engelhardia roxburghiana*.¹¹² They are a subset of the larger class of diarylheptanoids and are characterized by two aromatic rings linked via a seven-carbon chain and an ether bond to form the inherent macrocycle.¹¹³ Engelhardione and its diarylether heptanoid derivatives, such as acerogenins,²⁷ pterocarine, and galeon,¹¹⁴ demonstrate significant biological applications including antibacterial, and antifungal etc. properties (Figure 43).

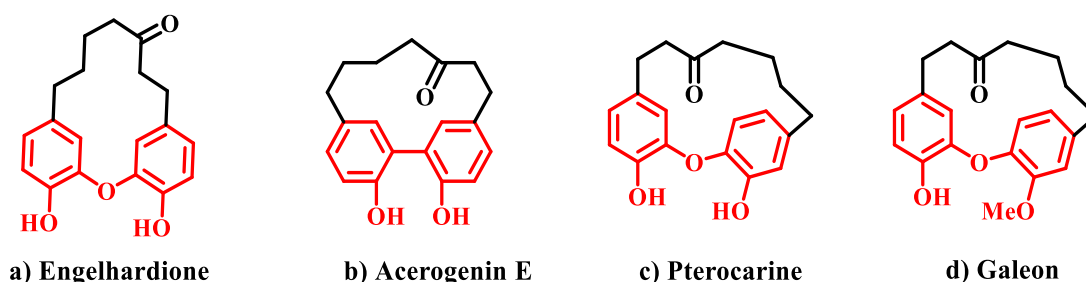


Figure 43. Selected examples of diarylether heptanoids macrocycles

2B.3 Literature Overview on Engelhardione Derivatives

The synthesis of cyclic derivatives of open-chain diarylheptanoids presents a greater challenge arising from the ring strain during the ring-closing step. The key step in forming these cyclic derivatives is the ring-closing reaction, which can be achieved by connecting either two alkyl groups or two aryl groups, forming both aryl ethers and biphenyls.¹¹⁵ Two fundamental approaches can be envisioned for crafting engelhardione as shown in Figure 44.

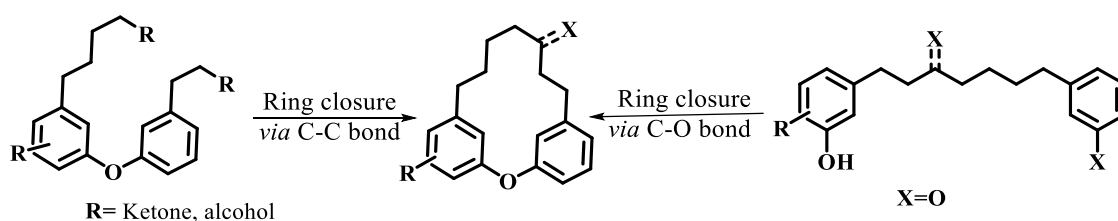
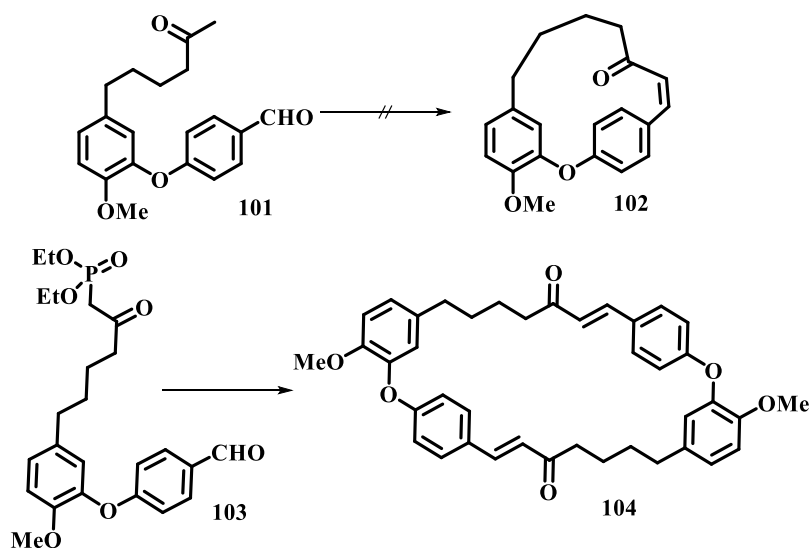


Figure 44. A general approach for the construction of engelhardione derivatives

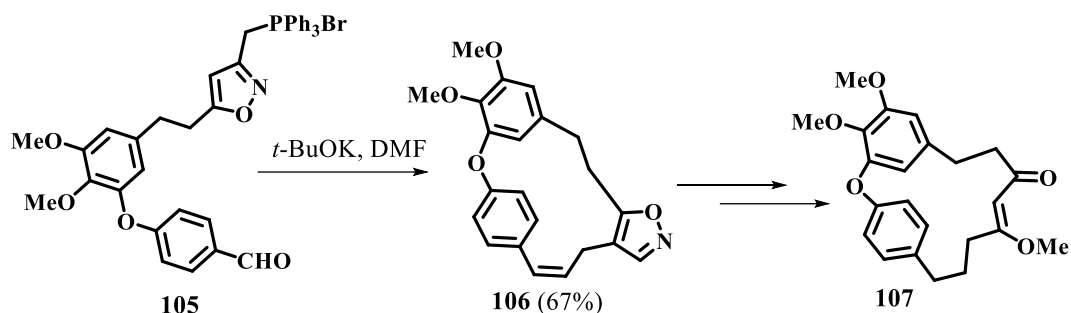
The first method involves etherification followed by ring closure, while in the second approach, late-stage etherification of linear diarylheptanes is involved. In the first strategy, challenges arise from the ring strain during the ring-closing step, resulting in an occasional failure to achieve the desired cyclic diarylheptanoids.



Scheme 43: N6grádi and Keser6's unsuccessful route for intramolecular macrocyclization

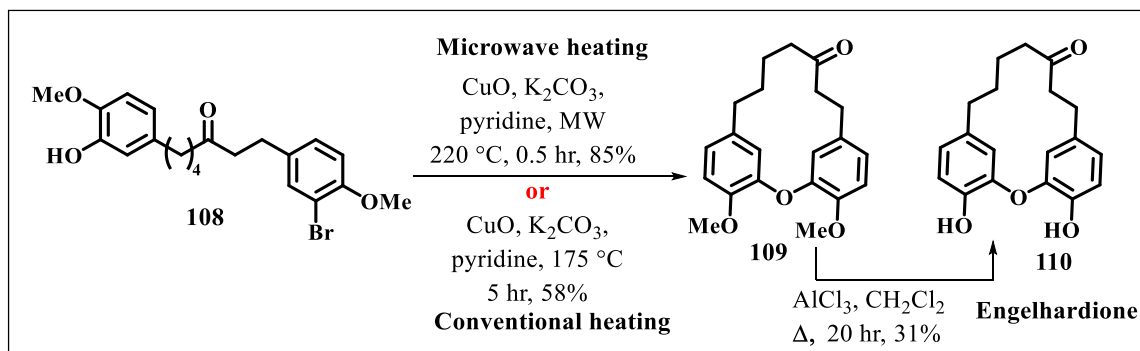
Notably, the research groups of N6grádi and Keser6 have made significant contributions to this field. In their attempts to synthesize cyclic diarylheptanoids, an intramolecular Claisen-Schmidt condensation of compound **101** failed to generate **102** (Scheme 43).¹¹⁶ Similarly, a Horner–Wadsworth–Emmons reaction (HWE) olefination of aldehyde-phosphonate **103** failed to produce a monomer, instead forming a cyclic dimer **104** (Scheme 43). An elegant alternative approach involved using isoxazole **105** to generate witting

salt in the presence of a base afforded **106** in 67% yield (Scheme 44).¹¹⁷ The isoxazole moiety facilitated molecular reorganization for the intramolecular reaction in these specific cases, but its application to other substrates was unsuccessful, highlighting the method's limited scope.



Scheme 44: Intramolecular Wittig reaction of isoxazole **105** towards cyclic diarylheptanoid derivative **106** to **107**

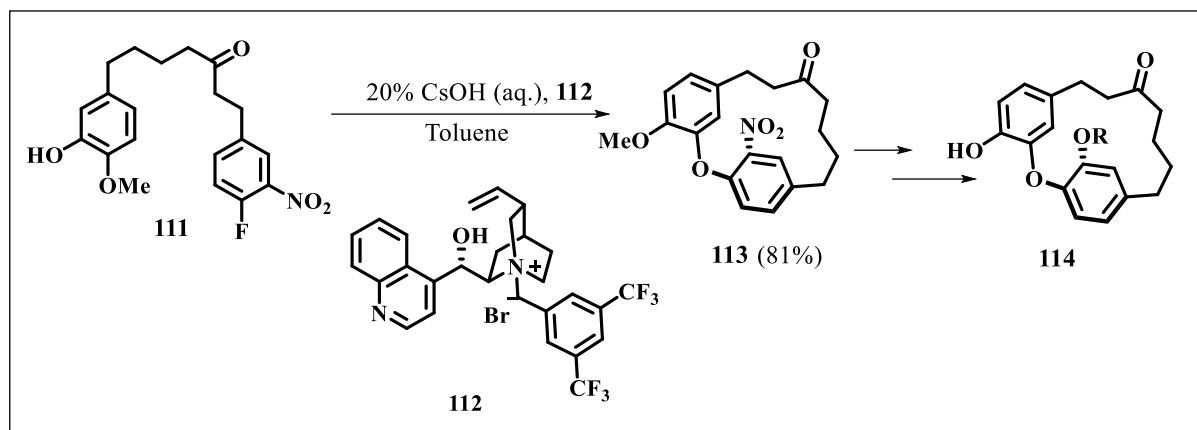
Conversely, the second strategy has shown success by utilizing aromatic nucleophilic substitution reactions. Sun and coworkers reported Ullmann's coupling reaction for the synthesis of macrocyclic diaryl ethers including diarylheptanoids in 2012. They synthesized the macrocyclic compound **109** through the intramolecular coupling of aryl bromide and phenol **108** under microwave-assisted conditions, employing CuO and K₂CO₃ in pyridine solvent, yielding 85% of product. Also, conventional conditions delivered a 58% yield of macrocyclic ketone **109**. After deprotection of the phenolic -OH deprotection of **109**, furnished engelhardione **110** (Scheme 45).¹¹⁸



Scheme 45. Synthesis of macrocyclic diaryl ethers *via* microwave-assisted Ullmann reaction

Next, an addition elimination reaction was reported by Qian Cai and coworkers. This strategy involves a chiral phase transfer catalyst **112** to form the diarylether cyclophase framework. Starting with a suitably substituted linear diarylheptanoid **111**, the cyclization reaction was conducted in the presence of a phase transfer catalyst **112** and 20% CsOH in toluene. This cyclization resulted in the formation of a chiral diarylether heptanoid macrocycle

113. The next step involves the formation of the natural product **114** by transforming the NO₂ group (Scheme 46).¹¹⁹



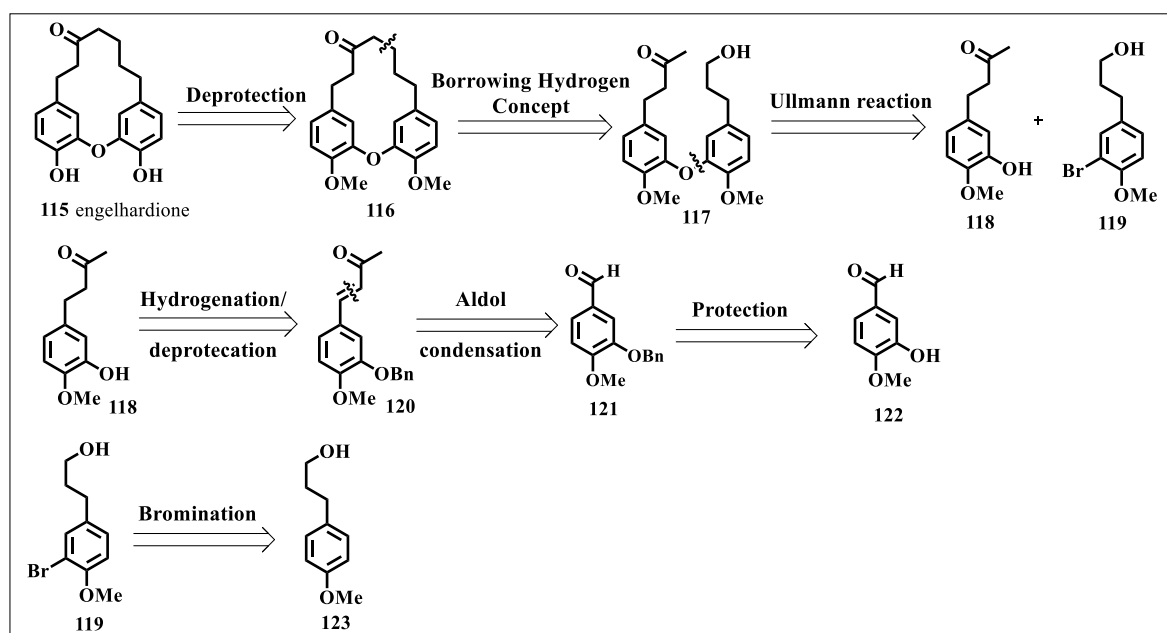
Scheme 46. Synthesis of natural diarylether heptanoids catalyzed by **114** *via* addition elimination reaction

2B.4 Objective of the Work

Macrocyclic engelhardione are important bioactive compounds usefully in drug industry. But, in the literature reports, we did not find any strategy for the total synthesis of heptanoid using borrowing alkylation. Hence, we plan to synthesize engelhardione by intramolecular reaction of a linear keto-alcohol.

2B.5 Retrosynthesis of Engelhardione

The retrosynthesis of engelhardione **115** is shown in Scheme 47. We envisioned that engelhardione **115** could be obtained by deprotection of the phenolic -OH bond in compound **116**. The macrocyclic ketone **116** could arise from our develop method of intramolecular borrowing alkylation of the linear keto-alcohol intermediate **117**. The C-O bond can be achieved through a Ullmann reaction from **118** and **119**. Precursor **118** can be synthesized by hydrogenation of a double bond and deprotecting benzyl alcohol in compound **120**. Compound **120**, in turn, can be readily accessed by condensing it with aldehyde **121**. Compound **121** can be synthesized by protecting the commercially available phenol **120**. Next, precursor **119** can be synthesized by brominating the commercially available 3-(4-methoxyphenyl)propan-1-ol.

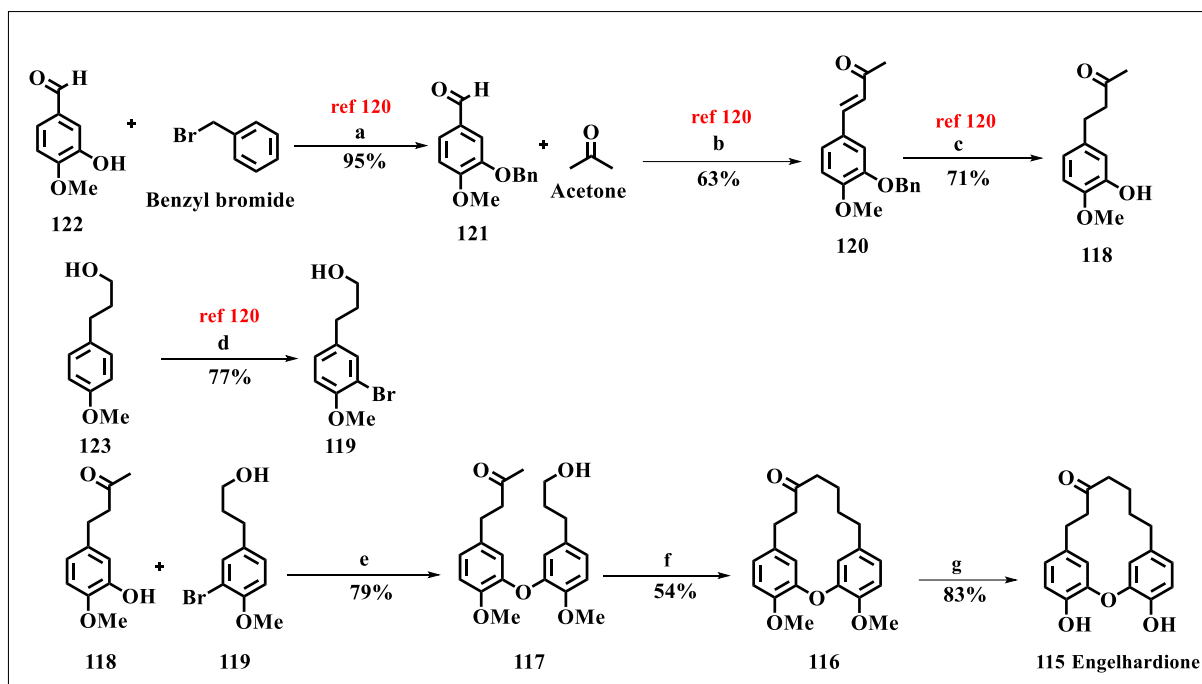


Scheme 47. Retrosynthesis of engelhardione

2B.6 Synthesis of Engelhardione

The synthesis of engelhardione **115** is depicted in Scheme 48. The commercially available 3-hydroxy-4-methoxy benzaldehyde **122** reacted with benzyl bromide in methanol in the presence of potassium carbonate afforded benzyl-protected ether **121** with a 95% yield.¹²⁰ Next, aldol condensation with acetone under microwave irradiation, delivered a 63% yield of compound **120**.¹²⁰ In this reaction, acetone serves as solvent and reactant, facilitating the formation of the desired product through a cross-aldol mechanism that generates the α , β -unsaturated ketone **120**. Subsequently, the α , β -conjugated olefin ketone **120** undergoes hydrogenation using palladium on carbon (Pd/C) as the catalyst. This process is accomplished by two key transformations: hydrogenation of the double bond and deprotection of alcohol group. The palladium catalyst facilitates the addition of hydrogen to the olefin, converting it into a saturated ketone, and also cleaving the benzyl ether to release the free hydroxyl group. This combined transformation yielded the saturated ketone intermediate **118** in 71% yield.¹²⁵

The synthesis of another precursor **119** was initiated by bromination of commercially available (3-(4-methoxyphenyl)propan-1-ol) **123** in the presence of aluminum trichloride and Br₂ in DCM solvent at room temperature, which afforded a 77% yield of the bromo compound **119**.¹²⁵ Further, synthesized precursor **118** was reacted with precursor **119** using Ullmann reaction conditions. Specifically, the reaction was conducted with 2 equiv. CuO in pyridine using 2.5 equiv. K₂CO₃ as the base, providing the alcohol-ketone product **117** in a 79% yield after 36 hr.



Scheme 48. Synthesis of Engelhardione

Reagents and conditions: (a) PhCH₂Br, K₂CO₃, MeOH, reflux, 4 hr, 95%; (b) acetone, 10% NaOH, 50 °C, MW, 15 min, 63%; (c) 10% Pd/C, H₂, MeOH, rt, 16 hr, 71%; (d) AlCl₃ (1.5 equiv.), Br₂ (1.5 equiv.), DCM, rt, 1-2 hr, 77%. (e) CuO (2 equiv.), K₂CO₃ (2.5 equiv.), pyridine, 180 °C, 36 hr, 79%; (f) Ru-MACHO (5 mol%), KOH (1 equiv.), 180 °C, 36 hr, 54% g) BBr₃ (5 equiv.), DCM, -78 °C, 4 hr, 83%.

Finally, the starting material, a diaryl compound having keto-alcohol **117**, was treated with 5 mol% of Ru-MACHO and 1 equiv. of potassium hydroxide (KOH) in toluene solvent at 180 °C. After 24 hr, this reaction yielded 35% yield of the macrocyclic ketone **116**, and a trace amount of macrocyclic alkene was observed in ¹H NMR. Extending the reaction time to 36 hr increased the yield, resulting in a 54% yield of compound **116**. Further deprotection of **116** alcohols using BBr₃ at -78 °C afforded 83% yield of **115** Engelhardione.

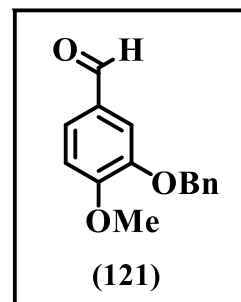
2B.7 Conclusion

We have successfully developed a new synthetic pathway for engelhardione. This method involves the formation of an intramolecular C-C bond through a borrowing hydrogen alkylation reaction. Utilizing this approach, can efficiently construct the complex molecular framework of engelhardione with improved yields and selectivity. The advantage of the borrowing hydrogen method for the synthesis of engelhardione is its ability to generate only water as a by-product. Furthermore, to the best of our knowledge, this synthesis represents the

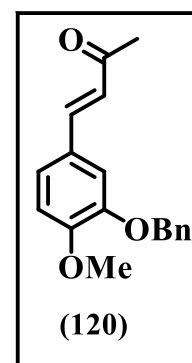
first instance of creating a 14-membered macrocyclic diarylheptanoid via C-C bond formation. This innovative technique not only enhances the overall efficiency of the synthesis but also opens up new possibilities for synthesizing other complex molecules using similar strategies.

2B.8 Experimental Section and Characterization Data

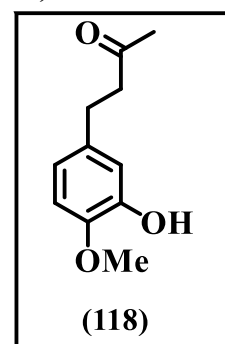
Synthesis of compound 3-(benzyloxy)-4-methoxy benzaldehyde (121)¹²⁰: A mixture of 3-hydroxy-4-methoxy benzaldehyde **122** (2 g, 13.15 mmol), benzyl bromide (2.25 g, 13.15 mmol), and potassium carbonate (2.71 g, 19.72 mmol) in methanol (20 mL) were refluxed for 4 hr. The reaction mixture was filtered, and the filtrate was evaporated under reduced pressure. Ethyl acetate (30 mL) was added to the residue, and the solution was washed with water (2 × 30 mL). Finally, the organic layer was evaporated under a vacuum. The residue was directly purified by silica gel chromatography (EtOAc: *n*-hexane = 05/95) to afford a 95% yield of compound **121**.



Synthesis of compound (E)-4-(3-(benzyloxy)-4-methoxyphenyl)but-3-en-2-one (120)¹²⁰: To a solution of benzaldehyde (500 mg, 1 equiv., 2.06 mmol), in acetone (1.5 gm, 13 equiv., 26.83 mmol) was added an aqueous solution of 10% NaOH (20 mL) in water. The mixture was stirred under microwave irradiation at 50 °C for 15 min. The product was extracted with ethyl acetate and water (3x 30 mL). The organic layer was evaporated under a vacuum. The residue was directly purified by silica gel chromatography (EtOAc: *n*-hexane = 10:90) to afford compound **120** with 95% yield. ¹H NMR (400 MHz, CDCl₃) δ 7.44 (t, *J* = 7.2 Hz, 2H), 7.38 (t, *J* = 7.4 Hz, 2H), 7.31 (t, *J* = 7.2 Hz, 1H), 7.13 (dd, *J* = 8.3, 1.8 Hz, 1H), 7.10 (d, *J* = 1.9 Hz, 1H), 6.89 (d, *J* = 8.3 Hz, 1H), 6.52 (d, *J* = 16.2 Hz, 1H), 5.16 (s, 2H), 3.91 (s, 3H), 2.34 (s, 3H).

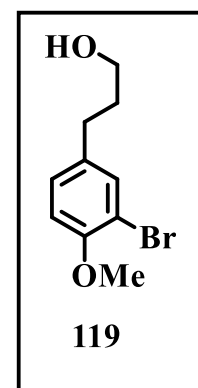


Synthesis of compound 4-(3-hydroxy-4-methoxyphenyl)butan-2-one (118)¹²⁰: A mixture of **120** (600 mg, 2.13 mmol) and 10% Pd/C (60 mg) in MeOH (10 mL) was stirred under an atmosphere of H₂ balloon at room temperature for 12 hr. The reaction mixture was filtered through a pad of celite. The solvent was removed by evaporation to give the crude product, which was further purified by flash column chromatography (EtOAc: *n*-hexane = 30:70) to give **83** as a white solid (295 mg, yield: 71%). ¹H NMR (400 MHz, CDCl₃) δ 6.78 – 6.72 (m, 2H), 6.65 (d, *J* = 8.3 Hz, 1H), 5.64 (s, 1H), 3.85 (s, 3H), 2.84 – 2.76 (m, 2H), 2.75 – 2.67 (m, 2H), 2.13 (s, 3H).

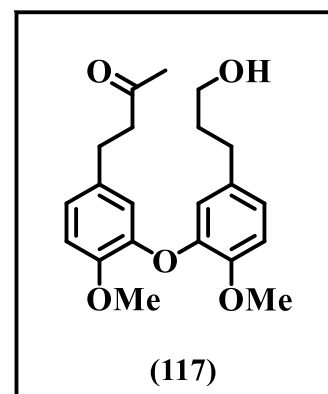


Synthesis of compound 3-(3-bromo-4-methoxyphenyl)propan-1-ol (120)¹²⁰: To a solution of 3-(4-methoxyphenyl)propan-1-ol **123** (2 gm, 12.03 mmol) in DCM solvent (60 mL) were added aluminum chloride (2.4 g, 18.04 mmol) and Bromine (2.88 gm, 18.04 mmol) dropwise at room temperature under N₂. The reaction was quenched with ice water.

The aqueous layer was extracted with DCM. The combined organic layers were washed with H₂O, saturated aqueous NaHCO₃ solution, and brine dried over Na₂SO₄, and concentrated under reduced pressure. which was further purified by flash column chromatography (EtOAc: *n*-hexane = 60:40) to give **83** as a colourless oil (2.27 gm, yield: 77%). ¹H NMR (400 MHz, CDCl₃) δ 7.38 (d, *J* = 2.1 Hz, 1H), 7.09 (dd, *J* = 8.3, 2.1 Hz, 1H), 6.81 (d, *J* = 8.4 Hz, 1H), 3.86 (s, 3H), 3.65 (t, *J* = 6.4 Hz, 2H), 2.66 – 2.59 (m, 2H), 1.88 – 1.79 (m, 2H); ¹³C NMR (100 MHz, CDCl₃) δ 154.1, 135.6, 133.2, 128.4, 112.1, 111.5, 62.01, 56.4, 34.2, 30.8.



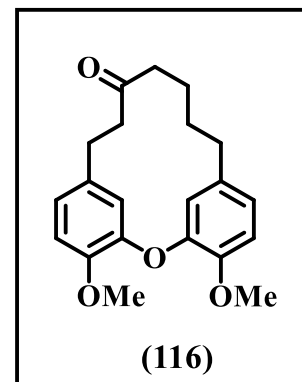
4-(3-(5-(3-hydroxypropyl)-2-methoxyphenoxy)-4-methoxyphenyl)butan-2-one (117): A mixture of **118** (70 mg, 0.36 mmol), **119** (88 mg, 0.36 mmol), Copper oxide (71.6 mg, 0.90 mmol), potassium carbonate (99 mg, 0.72 mmol), and pyridine (5 mL) in a sealed tube was heated at 180 °C for 24 hr. To cooled reaction mixture, HCl (1 M) was added and extracted in ethyl acetate and water. The organic layer was evaporated using a vacuum. The residue was directly purified by silica gel chromatography (EtOAc: *n*-hexane = 40:60 to 60:40) to give the product **117** as a white solid (102 mg, 79% yield). ¹H NMR



(400 MHz, CDCl₃) δ 6.89 (s, 2H), 6.88 – 6.83 (m, 2H), 6.66 – 6.61 (m, 2H), 3.83 (s, 3H), 3.83 (s, 3H), 3.61 (t, *J* = 6.4 Hz, 2H), 2.76 (dt, *J* = 5.3, 1.7 Hz, 2H), 2.66 (dt, *J* = 8.3, 1.7 Hz, 2H), 2.61 – 2.53 (m, 2H), 2.09 (s, 3H), 1.84 – 1.75 (m, 2H), OH peak exchanged with deuterium of CDCl₃; ¹³C NMR (100 MHz, CDCl₃) δ 208.4, 148.9, 148.8, 146.0, 145.7, 134.7, 133.7, 123.6, 123.3, 119.1, 118.8, 112.7, 112.7, 62.1, 56.2, 56.2, 45.3, 34.3, 31.3, 30.2, 29.1.

Synthesis of compound 1⁶,3⁶-dimethoxy-2-oxa-1,3(1,3)-dibenzenacyclodecaphan-6-one (116): In a 20 mL seal vial was added Ru-MACHO (5 mol%), Ketone-alcohol compound **117** (1 equiv.), and KOH (1 equiv.) in the presence of toluene 5 mL. The tube was purged with N₂ and capped. The reaction mixture was heated at 180 °C in an oil bath or Carousel hot plate for 36 hr. After completion of the reaction, the reaction mixture was diluted with dichloromethane. Finally, a volatile component was evaporated under a vacuum. The residue was directly

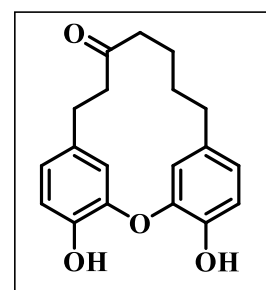
purified by silica gel chromatography (EtOAc: *n*-hexane = 20:80) to afford 23.5 mg, 54% yields of macrocyclic compound **116**. ^1H NMR (400 MHz, CDCl_3) δ 6.92 – 6.87 (m, 3H), 6.77 (dd, J = 8.2, 2.0 Hz, 1H), 6.52 (s, 1H), 6.39 (d, J = 2.0 Hz, 1H), 3.89 (s, 3H), 3.86 (s, 3H), 2.89 – 2.81 (m, 2H), 2.63 – 2.56 (m, 2H), 2.53 – 2.47 (m, 2H), 2.21 (t, J = 7.5 Hz, 2H), 1.57 – 1.52 (m, 2H), 1.32 (p, J = 7.3 Hz, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 211.1, 149.7, 148.7, 147.2, 146.5, 133.8, 133.6, 124.7, 123.2, 118.9, 118.6, 113.1, 112.9, 56.3, 56.2, 43.8, 41.7,



33.1, 29.3, 27.9, 21.5; HRMS (ESI-TOF) m/z calcd for $\text{C}_{21}\text{H}_{25}\text{O}_4$ $[\text{M}+\text{H}]^+$: 341.1753, found: 341.1755.

Synthesis of natural product engelhardione or 1⁶,3⁶-dihydroxy-2-oxa-1,3(1,3)-dibenzacyclodecaphan-6-one (117): To a solution of **116** (25

mg, 0.073 mmol) in CH_2Cl_2 (0.5 mL) cooled to $-78\text{ }^\circ\text{C}$ was added BBr_3 (1 M in CH_2Cl_2 , 1 mL). The temperature was allowed to gradually rise to $0\text{ }^\circ\text{C}$. After stirring for 4 h, saturated NaHCO_3 solution was added at $0\text{ }^\circ\text{C}$. The aqueous layer was extracted with EtOAc, dried over Na_2SO_4 , and then concentrated in vacuo.



Purification by silica gel column chromatography (hexane/EtOAc 2:1) afforded **117** (19.2 mg, 83%) as a colorless powder; ^1H NMR (400 MHz, CDCl_3) δ 6.95 (dd, J = 8.2, 1.2 Hz, 2H), 6.87 (d, J = 8.2 Hz, 1H), 6.77 (d, J = 8.1 Hz, 1H), 6.48 (s, 1H), 6.42 (s, 1H), 5.67 (s, 1H), 2.89 – 2.81 (m, 2H), 2.63 – 2.56 (m, 2H), 2.54 – 2.46 (m, 2H), 2.22 (t, J = 7.5 Hz, 2H), 1.61 – 1.53 (m, 2H), 1.34 – 1.23 (m, 2H), OH peak exchanged with deuterium of CDCl_3 ; ^{13}C NMR (101 MHz, CDCl_3) δ 211.4, 145.8, 144.9, 144.2, 143.9, 133.8, 133.6, 125.8, 124.6, 118.1, 117.1, 116.6, 43.6, 41.7, 33.1, 29.2, 27.7, 21.3.

2B.9. Appendix (II): Copies of ^1H and ^{13}C NMR Spectra of Representative Compounds

Entry	Data	Figure No
116	^1H and ^{13}C	45-46
117	^1H and ^{13}C	47-48
118	^1H	49
119	^1H	50
120	^1H	51

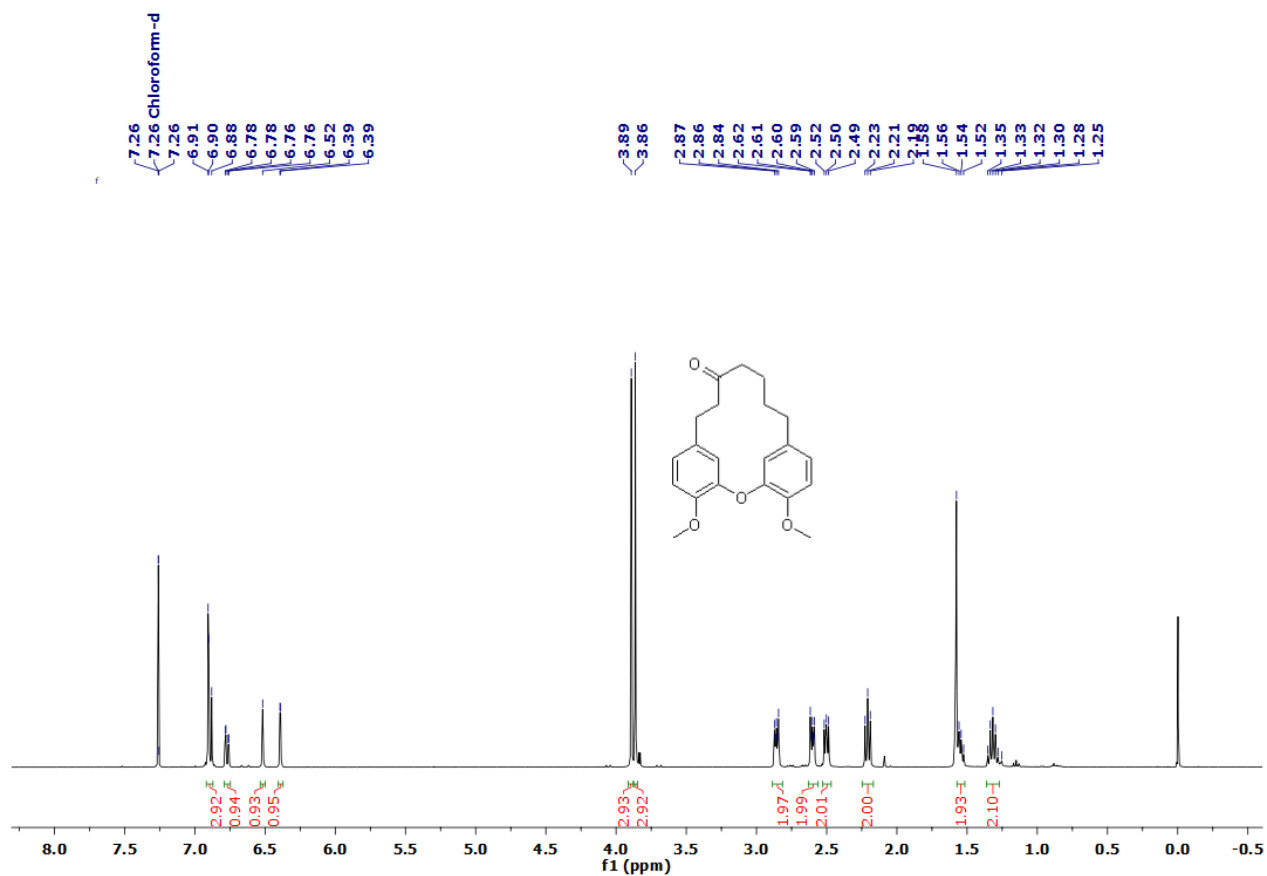


Figure 45. ¹H NMR spectra for compound **116**, 400 MHz, CDCl₃

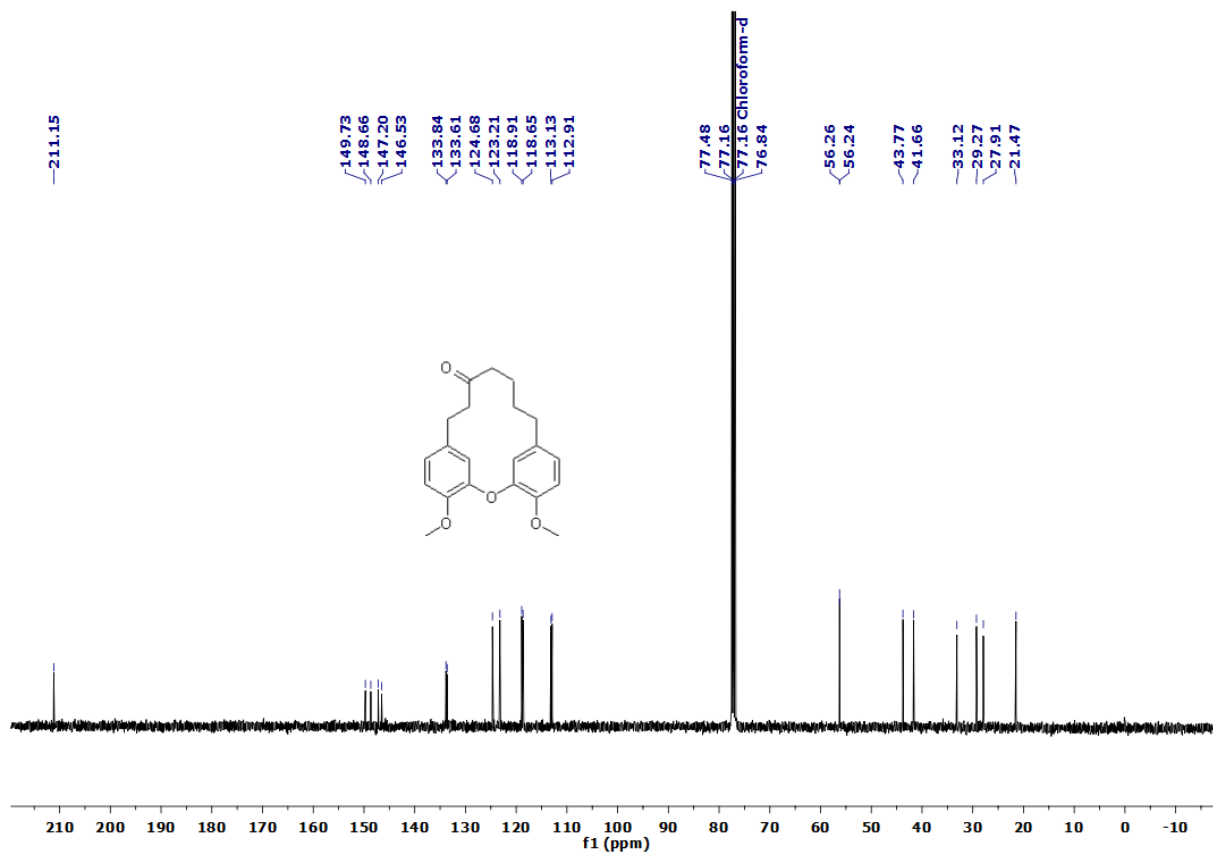


Figure 46. ¹³C NMR spectra for compound **116**, 100 MHz, CDCl₃

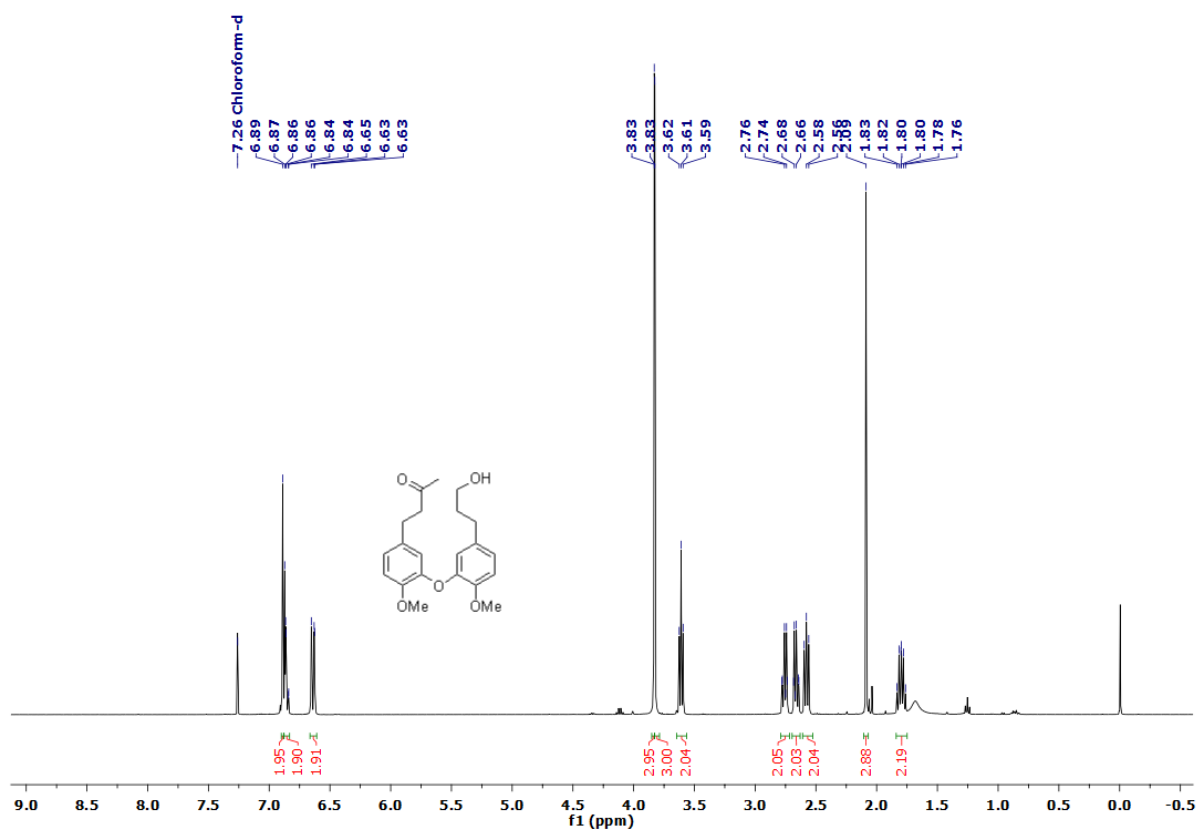


Figure 47. ¹H NMR spectra for compound 117, 400 MHz, CDCl₃

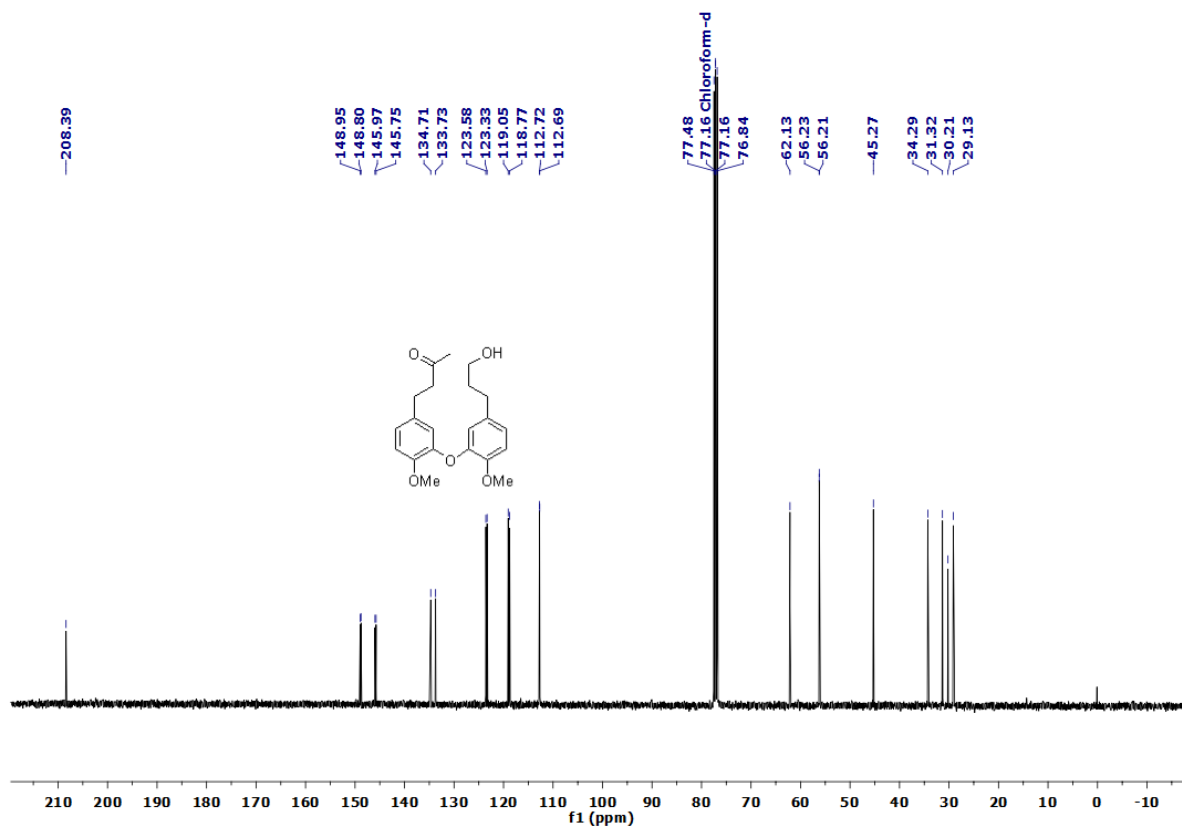


Figure 48. ¹³C NMR spectra for compound 117, 100 MHz, CDCl₃

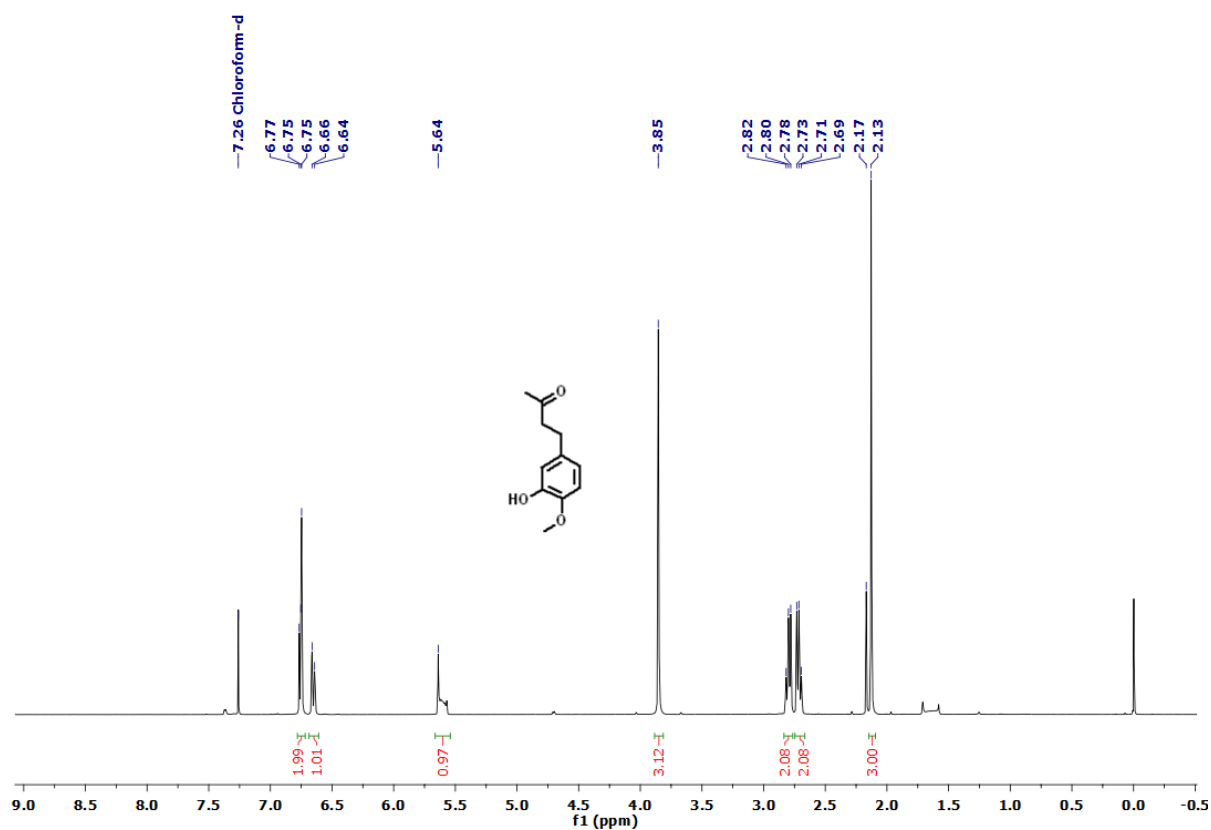


Figure 49. ¹H NMR spectra for compound **118**, 400 MHz, CDCl₃

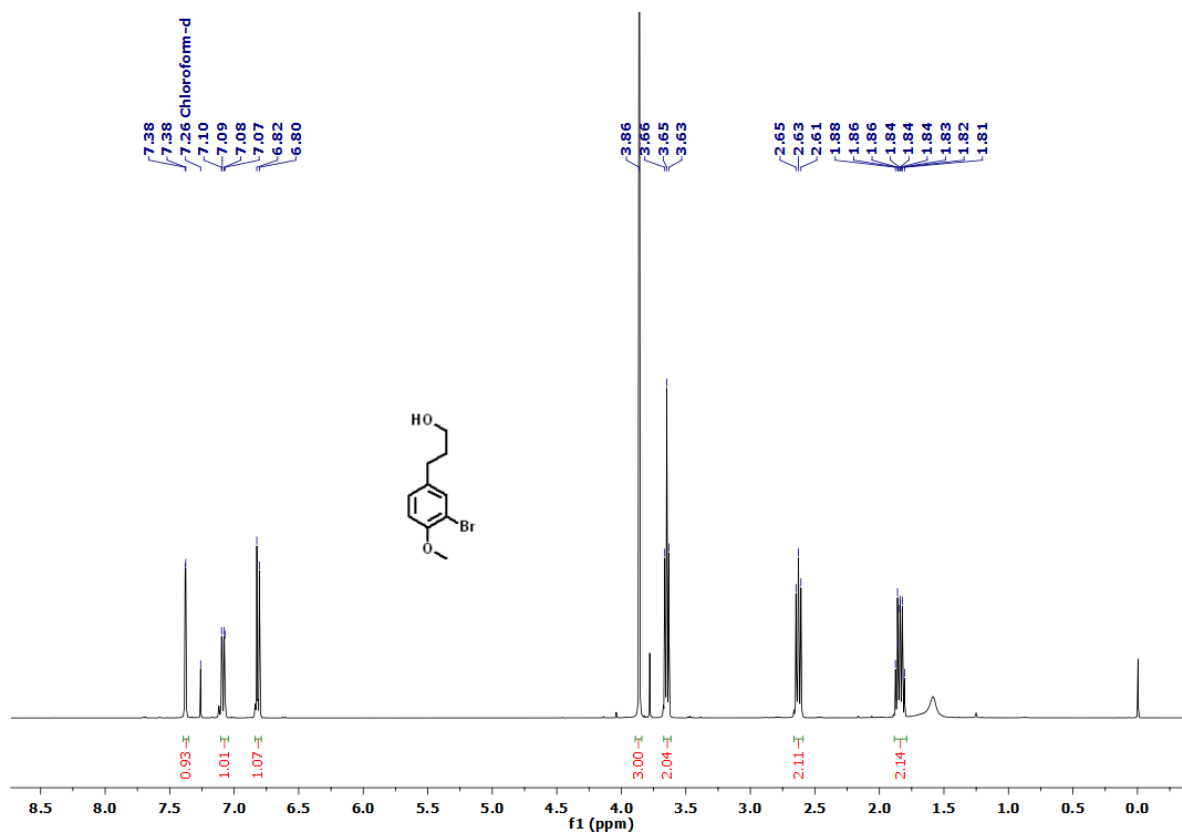


Figure 50. ¹H NMR spectra for compound **119**, 400 MHz, CDCl₃

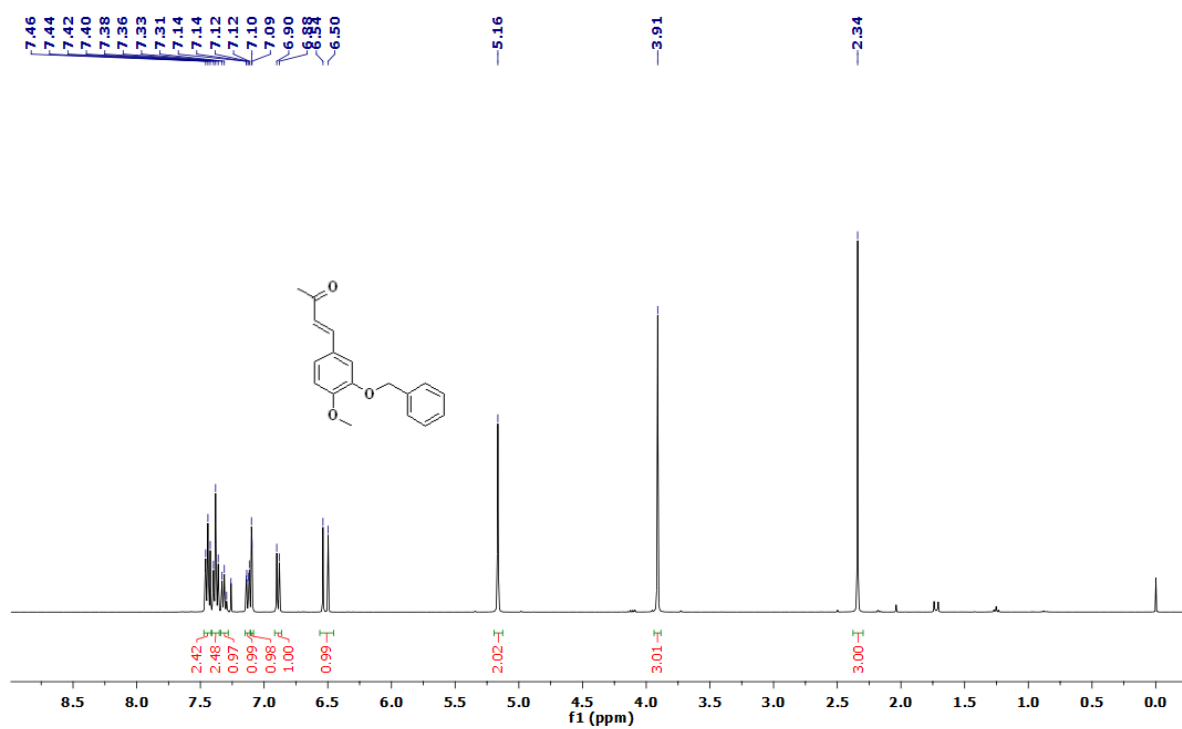
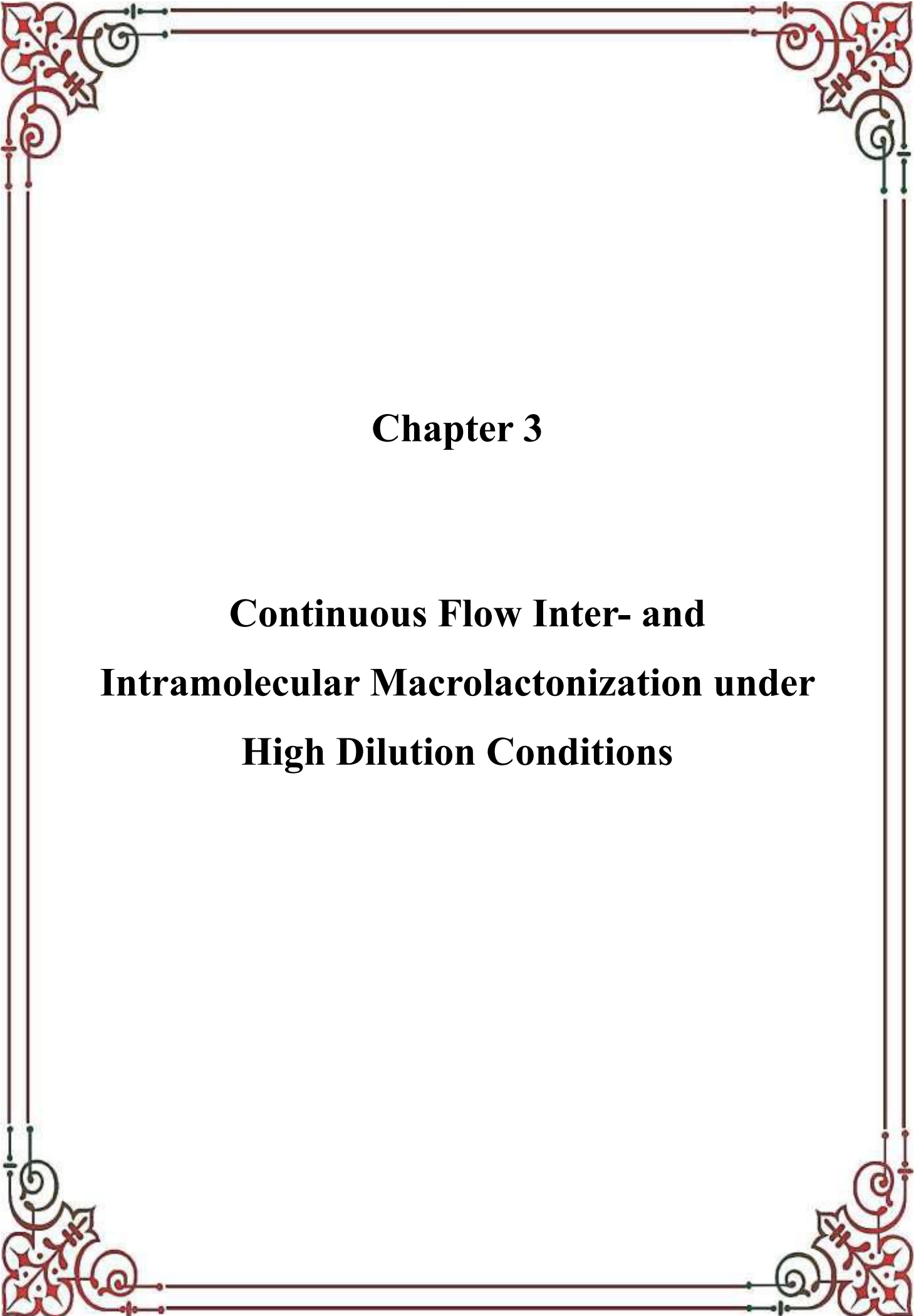


Figure 51. ^1H NMR spectra for compound **120**, 400 MHz, CDCl_3



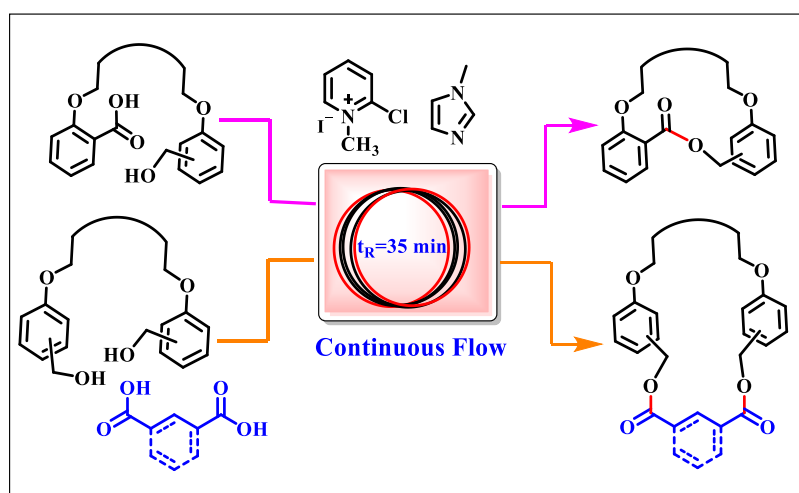
Chapter 3

Continuous Flow Inter- and Intramolecular Macrolactonization under High Dilution Conditions

3. Continuous Flow Inter- and Intramolecular Macrolactonization under High Dilution Conditions

3.1 Abstract

In this chapter, we have developed an efficient continuous flow process for the macrolactonization of seco acids and diacids using diols in the presence of Mukaiyama reagent (*N*-methyl-2-chloropyridinium iodide) for medium to large-sized macrocyclic lactones. Compared to alternative methods, the continuous flow process delivers good to high yields within a short reaction time. Using this methodology, a diverse array of compounds including macrocyclic lactones (11 compounds) from intramolecular reaction of seco-acids, dilactones (15 compounds), and tetralactone derivatives (2 compounds) from intermolecular diols and diacids spanning the ring sizes from 12 to 26 members were synthesized within a residence time as short as 35 minutes. Moreover, the continuous flow process for macrolactonization offers the distinct advantage of effectively managing high reactant dilution within a precisely confined volume of a perfluoroalkoxy alkanes (PFA) tube reactor (7 mL), demonstrating its elegance.



3.2 Introduction to Macrolactonization

Macrocyclic lactone core is recognized as a structurally significant motif in numerous natural¹²¹ and synthetic compounds,¹²² including biologically active drug molecules.¹²³ As a

result, these privileged molecular frameworks have significantly contributed to pharmaceuticals,¹²⁴ agrochemicals,¹²⁵ supramolecular chemistry,¹²⁶ fungicides,¹²⁷ and insecticides.¹²⁸ Furthermore, macrocyclic lactones have gained significant utility in both the fragrance industry¹²⁹ and the cosmetic industry.¹³⁰ Over the past decade, numerous macrolactonization methods have been developed. In addition, several reports are available on the synthesis of intramolecular macrocyclic lactones by using seco-acids via activation of alcohol or acid group (Figure 52). These reports primarily focus on the Yamaguchi reaction,¹³¹ Shiina macrolactonization,¹³² Corey-Nicolaou strategy,¹³³ Steglich-Boden-Keck reaction,¹³⁴ Mitsunobu reaction,¹³⁵ and Mukaiyama esterification.¹³⁶ Among these, Mukaiyama esterification stands out as particularly cost-effective and user-friendly.

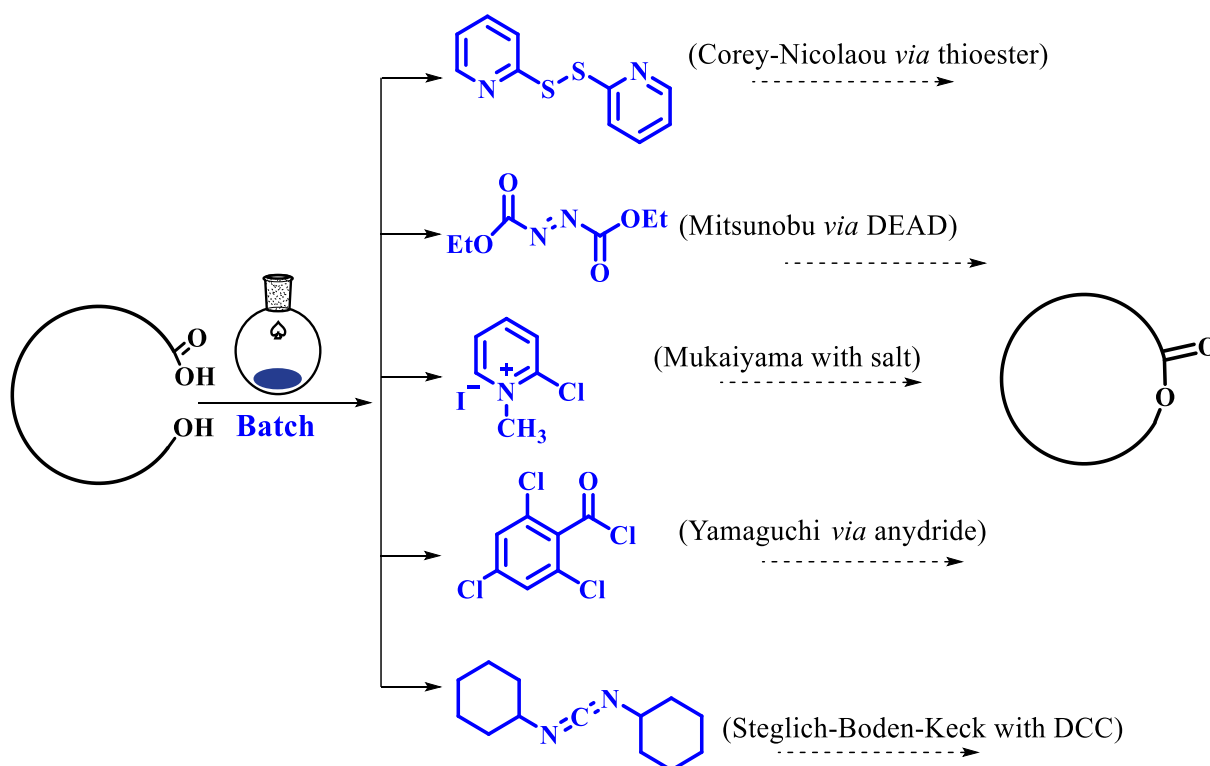


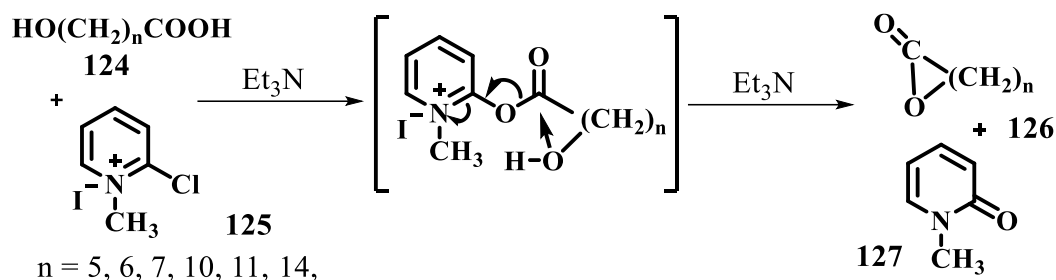
Figure 52. Prevalent strategies for macrolactonization

Additionally, there are reports of intermolecular macrocyclic di-lactonization using di-alcohol and dicarboxylic acid.

3.3 Literature Overview on Macrolactonization

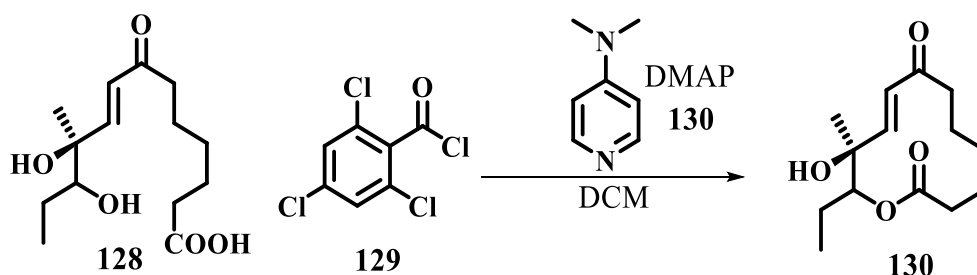
In 1976, Mukaiyama et al. introduced *N*-methyl-2-chloropyridinium iodide **125** as an effective reagent for macrolactonization. A series of hydroxy acids or seco acids, $\text{HO}(\text{CH}_2)_n\text{COOH}$ **124** with $n = 5, 6, 7, 10, 11, 14$, was employed to prepare medium and large ring lactones **126** generated by product **127** as illustrated in Scheme 49.¹³⁷ Since then, this

approach has been expanded to synthesize a variety of macrocyclic lactone and lactam-containing natural products.



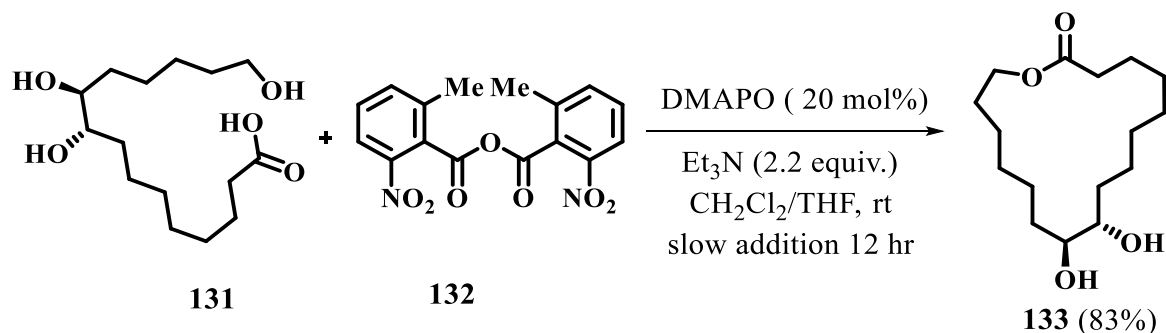
Scheme 49. Mukaimaya's macrolactonization using *N*-methyl-2-chloropyridinium iodide

Moreover, the synthesis of macrocyclic lactone **131** from seco-acid **128** with 2,4,6-trichloro benzoyl chloride **129** to form a mixed anhydride which, upon reaction with an alcohol in the presence of the stoichiometric amount of 4-dimethylaminopyridine **130** (DMAP), produced the desired ester. This reaction was reported by Yamaguchi and coworkers (Scheme 50).¹³¹



Scheme 50. Yamaguchi macrolactomization using 2,4,6-trichloro benzoyl chloride

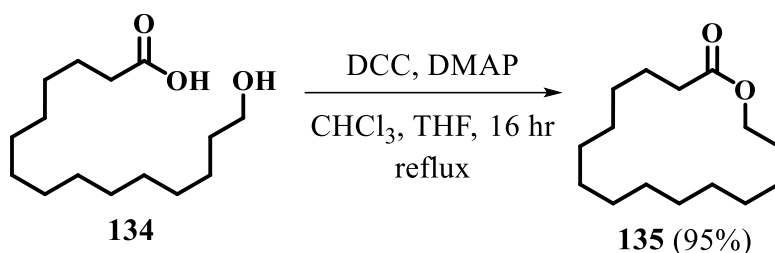
Next, Shiina and coworkers subsequently reported a highly effective macrolactonization method. The seco-acid **132** was converted into macrolactone **133** using 2-methyl-6-nitrobenzoic anhydride (MNBA) **18**, along with 4-(dimethylamino)pyridine 1-oxide (DAMPO) and triethylamine as a base in DCM solvent, in 83% yield (Scheme 51).¹³²



Scheme 51. Shiina macrolactonization using substituted benzoic anhydride

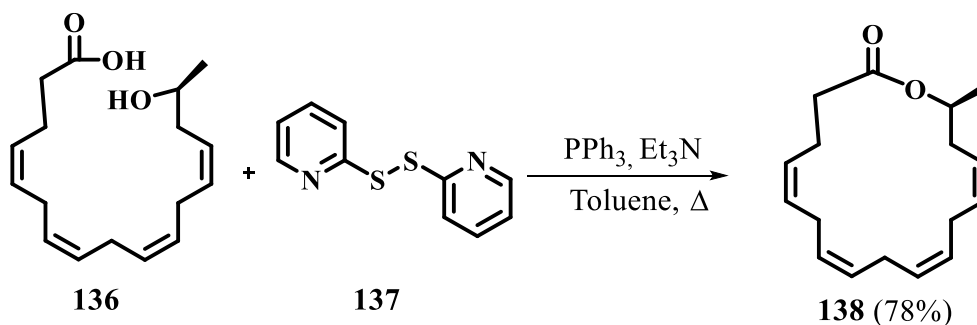
Also, Boden and Keck developed a synthetic methodology for preparing large-ring lactones from corresponding ω -hydroxy acids. In this reaction, DCC and DMAP were added

in a round-bottom flask, followed by the slow addition of seco-acid **134** in THF. After refluxing, the resulting macrocyclic lactone **135** was obtained in a 95% yield (Scheme 52).¹³⁴



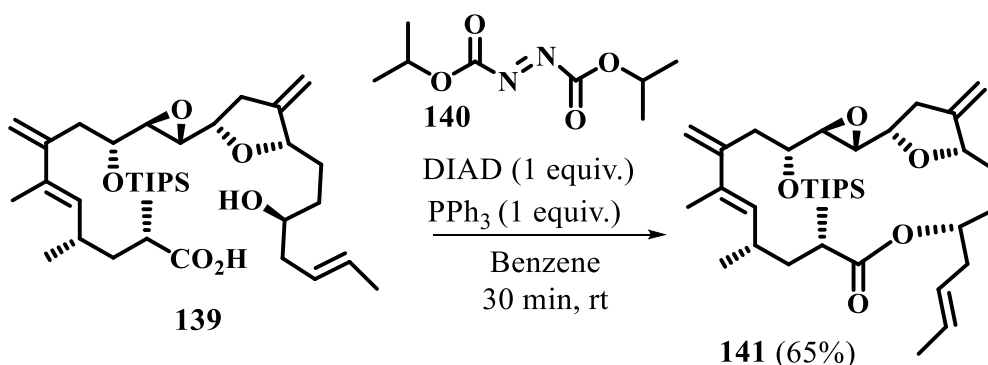
Scheme 52. Boden and Keck's macrolactonization using DCC and DMAP

Corey-Nicolaou reported macrolactonization reaction. Stenstrøm and coworkers used for the first total synthesis of (–) aplyolide A **138**. The reaction involves intramolecular macrocyclic esterification of seco-acid **136** using 2,2-dipyridyl disulfide **137**, PPh₃, and Et₃N in refluxing toluene, yielding macrocyclic lactone **138** in 78% yield (Scheme 53).¹³³



Scheme 53. Corey-Nicolaou macrolactonization using 2,2-dipyridyl disulfide

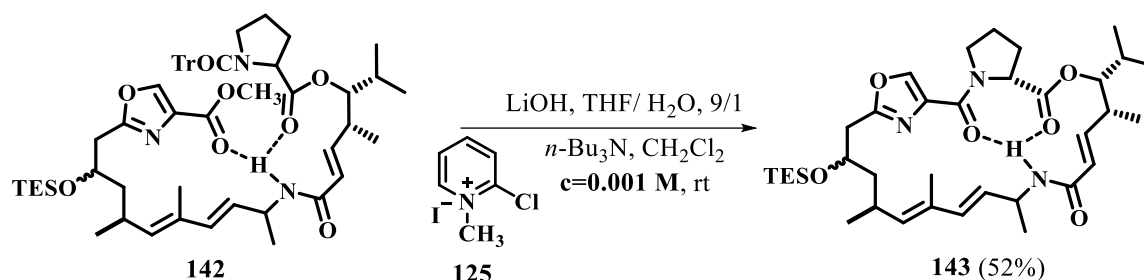
In 1976 Mitsunobu described a macrolactonization protocol to obtain medium and large macrolactones. This methodology is based on the activation of the seco-acid alcohol **139** using diisopropyl azodicarboxylate **140** (DIAD) and triphenylphosphine (PPh₃) in benzene solvent furnished 65% yield of macrolactone **141** within 30 min for reaction time (Scheme 54).¹³⁵



Scheme 54. Mitsunobu's macrolactonization using diethyl azodicarboxylate and PPh₃

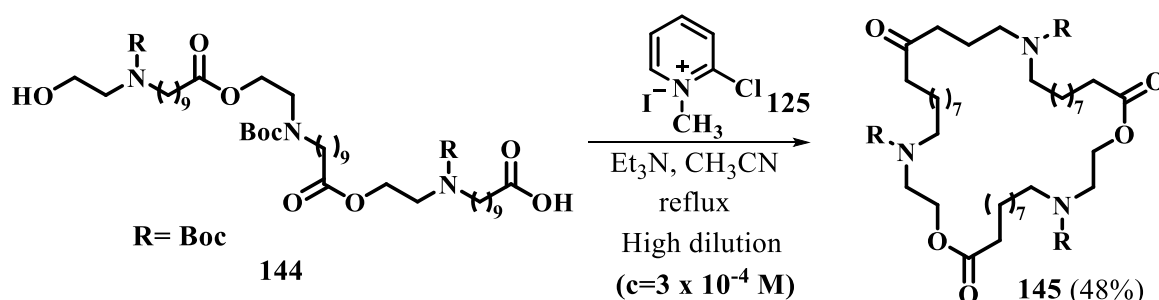
Among these reactions, Mukaiyama esterification is highly cost-effective and easy to handle. Furthermore, this Mukaimaya salt **125** was used in the total synthesis of (–)

Virginiamycin M2 by Yu-Jang Li and coworkers in 1996. In this reaction, LiOH hydrolyse the ester **142** to generate the acid and deprotection of amide. Finally, Mukaiyama reaction afforded the desired macrocyclic product **143** in a 52% yield (Scheme 55).¹³⁶



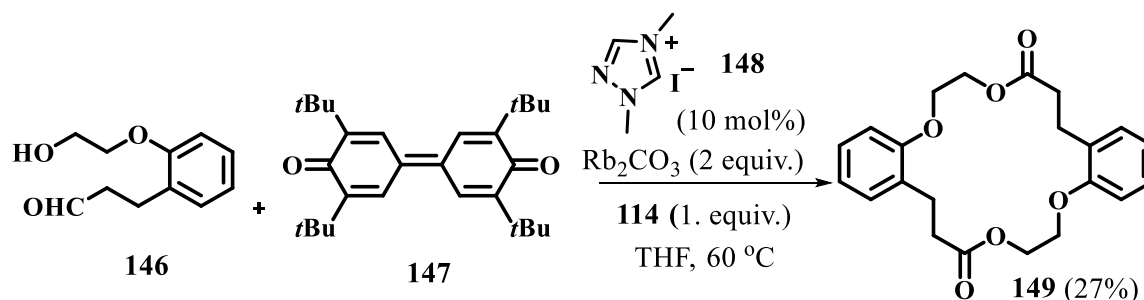
Scheme 55. Mukaimaya's amide coupling reaction

Subsequently, this approach has been extended to synthesize various macrocyclic lactone and lactam containing natural products. Meinwald and coworker reported Mukaiyama reagent **125** promoted the conversion of hydroxy acid **144** into 42-membered macrolactone **145** under high dilution conditions in refluxing acetonitrile in 48% yield (Scheme 56).¹³⁷



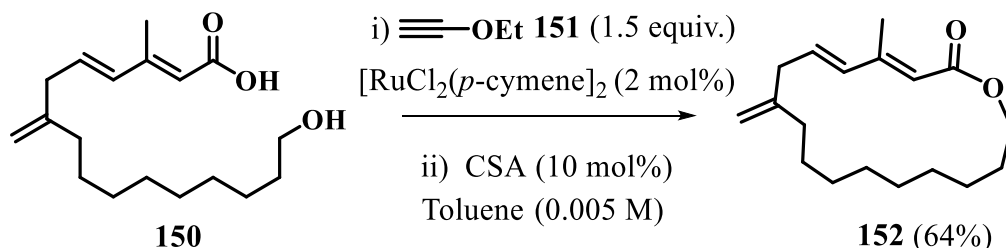
Scheme 56. Mukaimaya's ester coupling reaction

Moreover, *N*-heterocyclic carbene (NHC)-catalyzed oxidative esterification of aldehydes to macrocyclic di-lactone reported by Samanta and Studer. 18-membered macrocyclic lactone **149** was synthesized under oxidative esterification conditions. Aldehyde **146** reacted with NHC **148**, Rb_2CO_3 (2 equiv.), and diphenoquinone **147** in THF solvent at 60 °C for 20 hr afforded 27% yield of macrocyclic di-lactone **149** (Scheme 57).¹³⁸



Scheme 57. *N*-heterocyclic carbene catalyzed oxidative macrolactonization of aldehydes

Additionally, metal-catalysed macrolactonization was described by Trost and Chisholm in 2002. Subjecting a hydroxy acid **150** and ethoxy acetylene **151**, 2 mol % $[\text{RuCl}_2(p\text{-cymene})]_2$ in toluene followed by addition of 10 mol% camphor sulfonic acid (CSA) provided macrolactones **152** in 64 % yields (Scheme 58).¹³⁹



Scheme 58. Metal catalyzed macrolactonization

3.4 Aim and Rationale of Work

All these macrolactonization reactions were carried out under batch conditions using metal or non-metal catalysts. Typically, intramolecular or intermolecular cyclization reactions perform well under high dilution conditions with the slow addition of reactants. However, in all previous reports, batch strategies have been found to be highly inefficient for drug discovery and large-scale synthesis. These methods typically require long reaction times and high dilution, which directly impact the overall cost and the principles of green chemistry. Furthermore, the selective formation of macrocyclic lactones over other oligomeric mixtures often depends on the precisely controlled addition of reactants. Achieving this controlled addition with precision is challenging in batch processes, leading to issues with selectivity and yield. To address these issues, an improved chemical process is needed for the efficient production of macrocyclic lactones for a wide range of applications.

Thus, developing continuous flow chemistry for macrolactonization could address the various limitations inherent in batch reactions, such as long reaction times, high dilution requirements, and difficulty in precisely controlling reactant addition. Continuous flow chemistry offers several advantages, including improved reaction control, enhanced safety, and increased efficiency, making it an ideal approach for large-scale synthesis. Despite its potential, there is currently only one report in the literature on continuous flow macrolactonization using a coupling reagent.

3.5 Results and Discussion

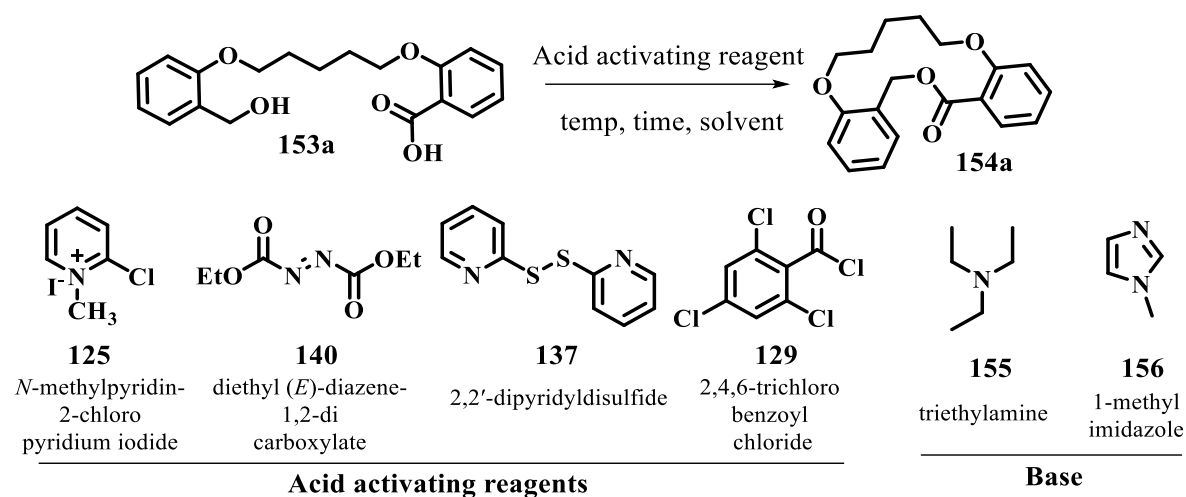
Herein, we report the continuous flow intermolecular macrolactonization of various dicarboxylic acids with diols, as well as the intramolecular macrolactonization of various seco

acids. These reactions utilize **125** (Mukaiyama salt) as an acid activator and 1-methyl imidazole (MIM) as a base under the continuous flow process. Unlike traditional batch processes, which require large volumes to achieve the necessary high dilution, continuous flow processes can be performed in much smaller reactor volumes. This smaller scale allows for more efficient handling of highly diluted reactants, which is critical for the successful formation of macrocyclic lactones. In our method, this approach yields macrocyclic lactones in moderate yield.

3.6 Optimization Studies for Macrolactone

3.6.1 Macrolactonization of Seco Acid using Different Acid Activators under Batch Conditions

We began our study toward macrolactonization by reacting **153a** intramolecularly to deliver the macrolactone **154a** by screening different solvents and various acid-activating agents in the batch reaction condition. Thus, this reaction with Mukaiyama reagent (2-chloro-1-methylpyridinium iodide) **125** and triethylamine **155** as a base and dichloromethane solvent provide the macrolactone **154a** in 10% yield, and 70% of the starting material seco acid **153a** was recovered (Table 3.1, entry 1). Other solvents in dichloroethane afforded 5% yield of **154a** (Table 3.1, entry 2). When THF and methanol were used as solvents, no product formation was observed after 1 day (Table 3.1, entries 3,4). An improved yield (17%) of macrolactone **154a** was observed when acetonitrile (CH₃CN) was used as a solvent (Table 3.1, entry 5). There was no product formation when using diisopropyl azodicarboxylate (DIAD) **140** and triphenylphosphine in either THF or CH₃CN as solvents at room temperature (Table 3.1, entries 6 and 7). This suggests that the combination of **140** and triphenylphosphine is ineffective under these conditions for promoting the desired macrolactonization reaction. Besides, macrolactone **154a** did not form when the reaction was conducted with the Corey-Nicolaou reagent **137** (2,2'-dipyridyldisulfide and triphenylphosphine) in THF at 0 °C (Table 3.1, entry 8). This same reaction was performed in CH₃CN, which provided only a 7% yield of **154a** with unreacted starting material **153a** (Table 3.1, entry 9). Afterward, **154a** was subjected to a Yamaguchi reaction by utilizing 2,4,6-trichlorobenzoyl chloride **129** in THF supplying a 13% yield of **154a** and in acetonitrile affording a 15% yield of **154a** (Table 3.1, entries 10 and 11). Next, refluxing the reaction mixture with Mukaiyama salt and **155** afforded a 25% yield of **154a** (Table 3.1, entry 12). An improved yield (30%) was observed by changing the base 1-methylimidazole (MIM) **156** (Table 3.1, entry 13). Mitsunobu, Corey-Nicolaou, and Yamaguchi reactions under reflux conditions resulted in a lowering in the yield of product **154a** (Table 3.1, entries 14–16).

Table 3.1 Acid activator study in batch reaction conditions

Sr. No	Acid activating reagent	solvent	time (hr)	yield of 154a/153a (%)
1 ^{a,c}	125/155	DCM	24	10/70
2 ^{a,c}	125/155	DCE	24	5/92
3 ^{a,c}	125/155	THF	24	0/100
4 ^{a,c}	125/155	MeOH	24	0/60
5 ^{a,c}	125/155	CH ₃ CN	24	17/70
6 ^{a,d}	140/PPh₃	THF	24	0/100
7 ^{a,d}	140/PPh₃	CH ₃ CN	24	0/100
8 ^{a,e,g}	137/PPh₃	THF	24	0/100
9 ^{a,e}	137/PPh₃	CH ₃ CN	24	7/80
10 ^{a,f}	129/DMAP	THF	24	13/50
11 ^{a,f}	129/DMAP	CH ₃ CN	24	15/42
12 ^{b,c}	125/122	CH ₃ CN	24	25/65
13 ^{b,c}	125/123	CH ₃ CN	24	30/55
14 ^{b,d}	1140/PPh₃	CH ₃ CN	24	12/65
15 ^{b,e}	137/PPh₃	CH ₃ CN	24	9/78
16 ^{b,f}	129/DMAP	CH ₃ CN	24	15/40

Reaction conditions: ^aCompound **153a** (0.015 M in CH₃CN) and acid activator reagent (see. table) were taken in a sealed tube and reacted for 24 hr at room temp. ^breflux condition; ^cMukaiyama reagent; ^dMitsunobu reagent; ^eCorey-Nicolaou reagent, ^fYamaguchi reagent. ^gat 0 °C condition. The mentioned yields are isolated yields.

All these experimental results indicate that Mukaiyama reagent with 1-methylimidazole is an efficient activator as compared to other acid activators.

To improve product yield, explore seamless scalability, and mitigate scaling-up challenges linked with batch processing, transitioned the optimized batch condition to a continuous flow approach. In our continuous flow setup, we integrated two Vapourtec SF-10 peristaltic pumps for solvent delivery, a T-piece for efficient mixing of the reaction components, perfluoro alkoxy alkanes (PFA) tubing for conducting the reaction, a water bath for a source of heating, and a back pressure regulator (BPR) to maintain consistent pressure conditions (Figure 53).

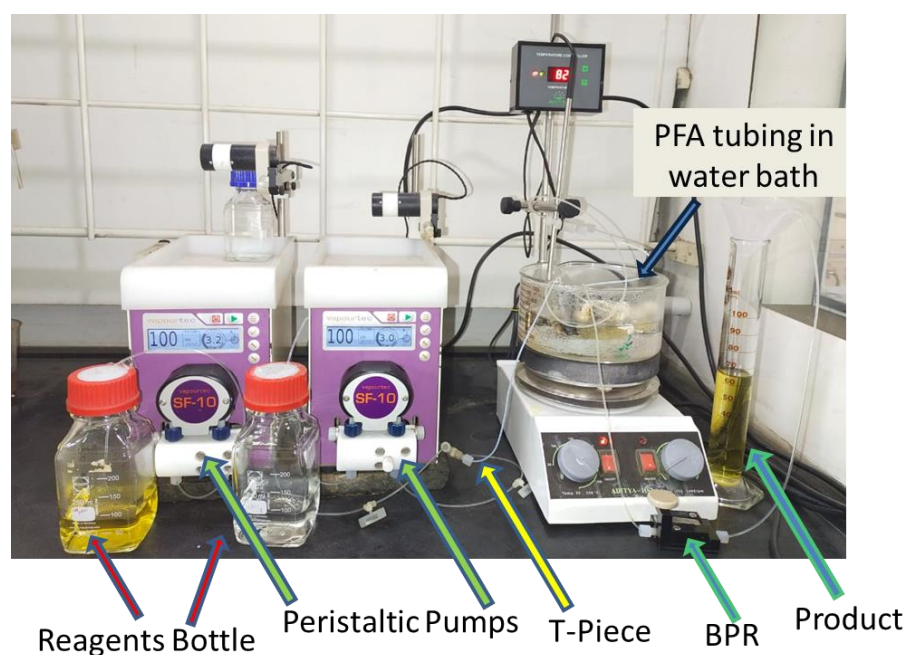


Figure 53. Continuous flow set up for macrolactonisation

This configuration allows us to precisely control the flow rates of solvents and reactants, optimize reaction conditions such as temperature and pressure, and ensure efficient mixing of reactants in the narrow tubing environment. The use of PFA tubing is particularly advantageous due to its excellent chemical resistance and compatibility with a wide range of solvents and reaction conditions.

3.6.2 Macrolactonization of Seco-acid using Different Acid Activators under Flow Conditions

To, screen macrolactonization in a continuous flow reactor in the presence of various acid activators, we initiated our investigation into macrolactonization using a continuous flow reactor, focusing on substrate **153a** as a model. Initially, a mixture of **125** and triethylamine

156 in CH₃CN was passed through 7 mL, length 890 cm of PFA tubing using a peristaltic pump at a flow rate of 0.1 mL/min at room temperature. After a 35-minute residence time, the yield of **154a** was 25% (Figure 54). Upon raising the reaction temperature to 80 °C, the yield of **154a** increased to 45% (Figure 54). However, when utilizing the Corey-Nicolau reagent as an alternative acid activator, a reduction in the yield of **154a** was observed (Figure 54). Additionally, the Mitsunobu reaction showed no product formation at room temperature, and only a 15% yield of **154a** was achieved at 80 °C (Figure 54). Subsequently, compound **153a** underwent the Yamaguchi reaction at room temperature and 80 °C, yielding 23% and 30%, respectively (Figure 54). Finally, employing Mukaiyama salt with 1-methylimidazole as a base produced **154a** in a higher yield of 45% compared to other activators. It is worth noting that the macrolactonization proceeded without requiring special reaction conditions such as a dry solvent or inert atmosphere (Figure 54).

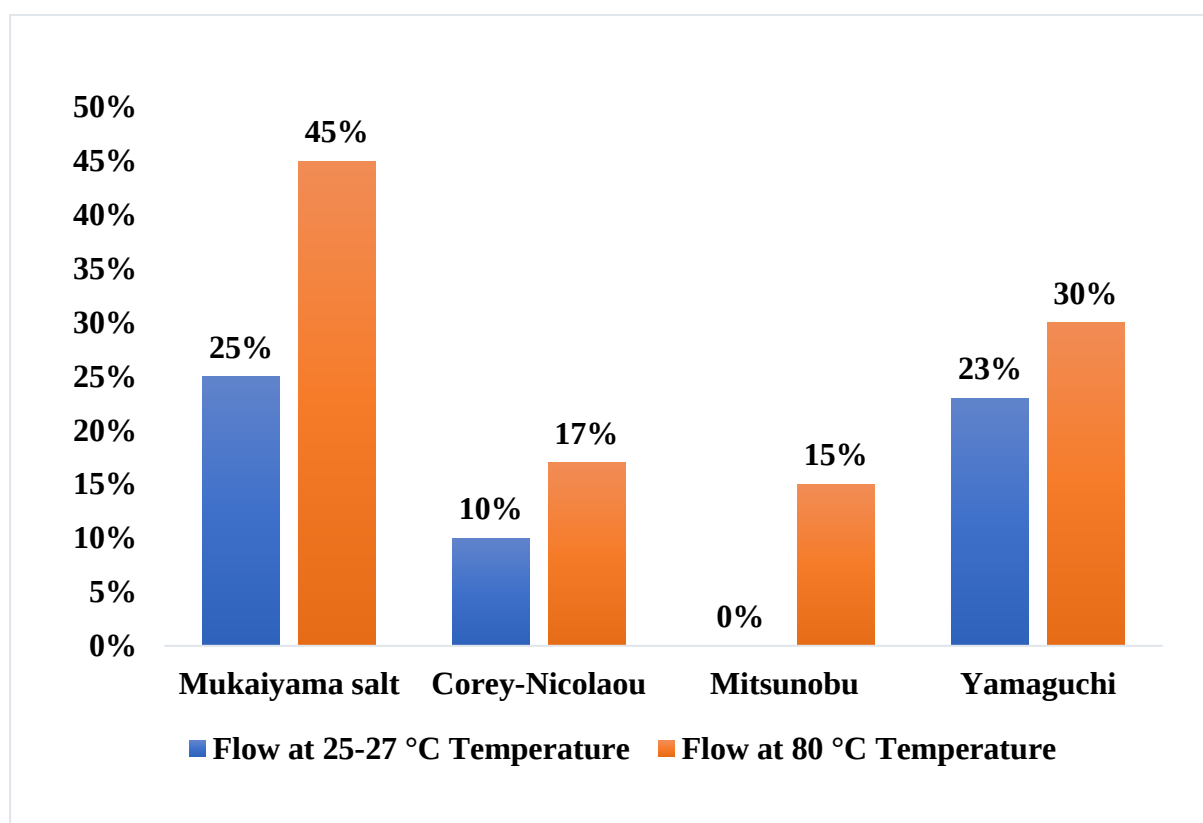
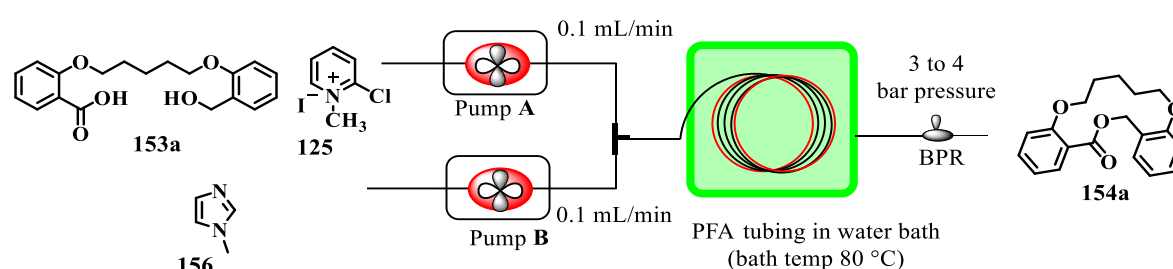


Figure 54. Acid activator study for macrolactonisation under continuous flow

“Reaction conditions: Peristaltic pump **A:** compound **153a** and activators in CH₃CN, Peristaltic pump **B:** base in CH₃CN were flown through to PFA tubing (id = 0.1 cm, 7 mL, length = 890 cm) at room temperature (25-27 °C) without any pressure and at 80 °C in the preheated water bath under 3-4 bar pressure. The mentioned yields are isolated yields.

Having identified Mukaiyama salt with 1-methylimidazole as an effective combination for macrolactonization, we initiated further optimization of reaction conditions in a flow reactor. Initially, substrate **153a** and Mukaiyama salt **125** were introduced into pump A, while compound **156** in CH₃CN was fed into pump B. Both streams were passed through 9 mL of PFA tubing (inner diameter = 0.1 cm, length=1150 cm) at a flow rate of 0.1 mL/min, maintaining a residence time of 45 minutes at 80 °C, resulting in a 45% yield of **154a** (Table 3.2, entry 1).

Table 3.2. Optimization of the Reaction for Intramolecular Macrolactonization of Seco Acids



Sr. No	153a (M)	125 (M)	156 (M)	fr pump (A: B) (mL/min)	t _R = min	yield (%) 154a/153a
1 ^{a,b}	0.015	0.036	0.015	0.1:0.1	45	45/40
2 ^a	0.015	0.036	0.015	0.1:0.1	35	45/40
3 ^a	0.015	0.036	0.03	0.1:0.1	35	54/32
4 ^a	0.015	0.036	0.036	0.1:0.1	35	54/32
5 ^a	0.015	0.06	0.03	0.1:0.1	35	52/36
6 ^a	0.02	0.048	0.04	0.1:0.1	35	50/38
7 ^a	0.01	0.024	0.02	0.1:0.1	35	54/32
8 ^a	0.015	0.036	0.03	0.15:0.15	23.3	49/20
9 ^a	0.015	0.036	0.03	0.2:0.2	17.5	30/59
10 ^a	0.015	0.036	0.03	0.3:0.3	11.6	12/76
11 ^a	0.015	0.036	0.03	0.05:0.05	70	55/40

^a**Reaction Conditions:** Peristaltic pump A: compound **153a** and **125** in CH₃CN, Peristaltic pump B: base **156** in CH₃CN were flown through to PFA tubing (id = 0.1 cm 7 mL, length = 890 cm) at 80 °C in the preheated water bath under 3 to 4 bar pressure. ^bflown through PFA tubing (id = 0.1 cm, 9 mL, length = 1150 cm) at 80 °C in the preheated water bath under 3-4 bar pressure; f_R=flow rate; t_R= residence time. The mentioned yields are isolated yields.

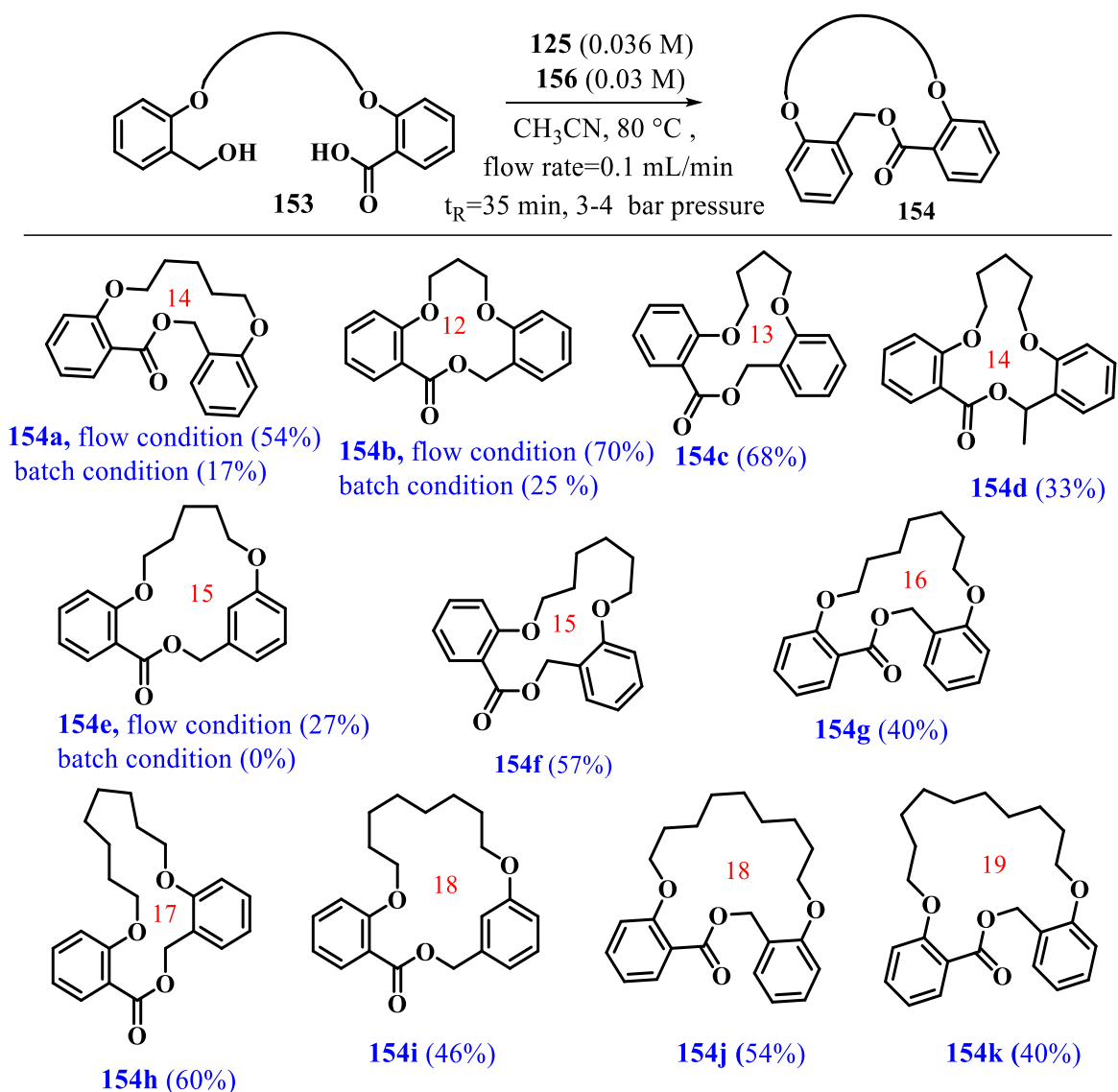
Subsequently, by reducing the length of PFA tubing to 890 cm and determining the residence time accordingly, a comparable yield of **121a** was achieved (Table 3.2, entry 2). Upon, increasing the base concentration to 0.03 M, a notable improvement in the yield of **154a** (54%) was observed (Table 3.2, entry 3). Further increasing the base concentration to 0.036 M maintained the yield in 54% (Table 3.2, entry 4). However, increasing the concentration of Mukaiyama salt to 0.06 M resulted in a slight decrease in the yield of **154a** (52%, Table 3.2, entry 5). Higher concentrations of substrates **153a**, Mukaiyama salt **125**, and base **156** led to a decrease in the yield of **154a** (Table 3.2, entry 6). Conversely, increasing the dilution of **153a** resulted in a 54% yield of **154a** (Table 3.2, entry 7). Moreover, increasing the flow rate of each pump led to reduced conversion of **153a** to product **154a** (Table 3.2, entries 8 to 10). Subsequently, decreasing the flow rate and increasing the residence time resulted in a slight increase in the yield of **154a** to 55% (Table 3.2, entry 11).

3.6.3 Substrate Scope for Intramolecular Macrolactonization

With the optimal result from Table 3.2, entry 3 in hand, we proceeded to investigate the flow macrolactonization of various seco acid derivatives. Flow macrolactonization of 2-(3-(2-(hydroxymethyl)phenoxy)propoxy)benzoic acid with a propyl spacer (**153b**) increased the yield of **154b** to 70% (Scheme 59), with no formation of the corresponding side product macrodiolide. In contrast, performing this reaction under batch conditions yielded only 25% (Scheme 59). In contrast, **154c** with a butyl spacer (0.15 mmol) provided a yield of 68%. Intramolecular macrolactonization of a secondary alcohol and acid (**153d**) resulted in a 33% yield of **154d** (Scheme 59). However, positional isomers such as *meta*-substituted seco acid (**153e**) yielded a lower 27% yield of macrolactone **154e** and showed no product formation under batch conditions (Scheme 59). Additionally, substrates with longer spacer lengths ranging from hexyl to decyl gave moderate to good yields (40–60%) of macrolactones **154f–154k**. (Scheme 59). These studies indicate that the yield of the macrolactone product correlates with the length of the spacer chain.

➤ Gram-scale synthesis of macrolactone **154c**:

For gram-scale, 2-(4-(2-(hydroxymethyl)phenoxy)butoxy)benzoic acid **153c** (0.015 M, 3.41 gm, 10.80 mmol) and Mukaiyama salt (0.036 M, 6.6 gm, 25.88 mmol) was dissolved with CH₃CN in a reagent bottle. Then, 1-methylimidazole **156** (0.03 M, 1.77 mg, 21.55 mmol) was

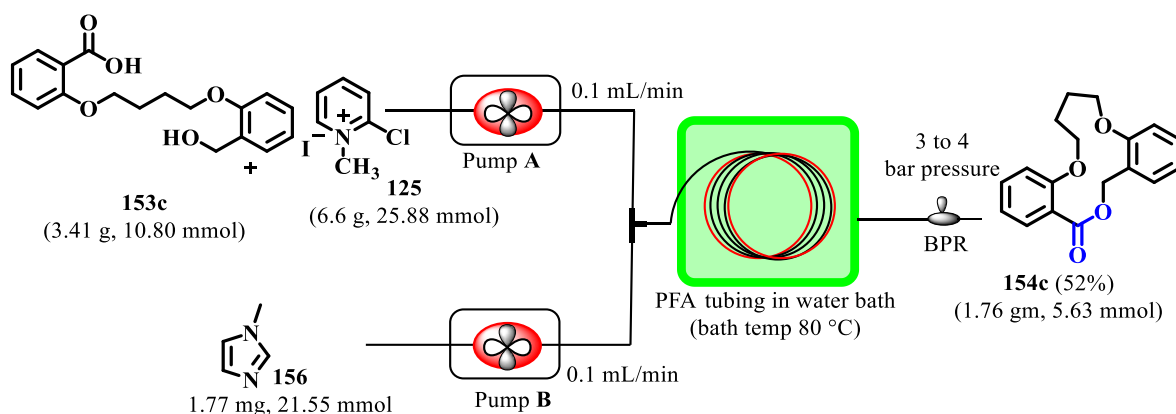


Scheme 59. Substrate scope for intramolecular macrolactonization

Flow reaction condition: Peristaltic pump **A**: compound **153** (0.015 M, 0.15 mmol), **125** (0.036 M) in CH₃CN, peristaltic pump **B**: **156** (0.03 M) in CH₃CN were flown through PFA tubing (id = 0.1 cm, 7 mL, length = 890 cm) with 0.1 mL/min flow rate at 80 °C in the preheated water bath for residence time 35 min. under 3-4 bar pressure. **Batch reaction condition:** Compound **153** (0.015 M, 0.15 mmol), **125** (0.036 M) and **156** (0.03 M) in CH₃CN were heated at 80 °C in the preheated oil bath for 24 hr. The mentioned yields are isolated yields.

dissolved in another reagent bottle with CH₃CN. Both the reagent solutions were flown through the PFA tubing (id = 0.1 cm 7 mL, length = 890 cm) in 80 °C in a preheated water bath with 3-4 bar pressure. After workup, the residue was purified by column chromatography (EtOAc/n-

hexane = 10:90) as the eluent to afford the desired product of **154c** (1.76 gm, 5.63 mmol, 52 %) as an oily product and starting material recovered of **153a** (1.03 gm, 32%).



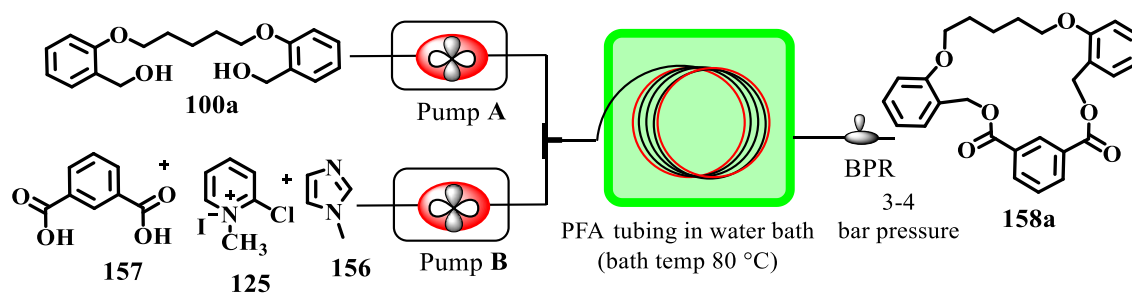
Scheme 69. Gram-scale synthesis of **154c** intramolecular macrolactonization

Next, we proceeded to explore the applicability of this transformation with substituted diol and diacid derivatives for the synthesis of macrocyclic dilactones using continuous flow chemistry. Initially, we utilized the optimized conditions developed for macrocyclic lactone **154** to synthesize compound **158a**. However, combining solutions **100**, **157**, and **125** in pump A with solution **156** in pump B resulted in a poor yield of 20%. Subsequently, we reoptimized the flow conditions for the synthesis of **158a**.

3.7 Optimization for Intermolecular Macrocyclic di-lactonization

Initially, optimized reaction conditions were used to ((pentane-1,5-diylbis(oxy))bis(2,1-phenylene))dimethanol (**100a**) and isophthalic acid (**157**) to produce the expected product (**158**). However, solutions **100a** in pump A with solution **156**, **157**, and **125** in pump B resulted in a lower result of 24% (Table 3.3, entry 1). Additionally, increasing the base loading did not improve the yield (Table 3.3, entries 2 to 4). But, increasing the concentration of the acid activator to 0.06 M and 0.072 M resulted in a slight yield improvement of **158a**, achieving 26% and 28% respectively (Table 3.3, entries 5 and 6). Later, increasing the residence time of the reaction did not affect the yield of **158a** (Table 3.3, entry 7). When reducing the **100a**, **125**, **156**, and **157** concentrations resulted in a slight yield improvement (Table 3.3, entry 8). Subsequently, extending the reaction time by 50 minutes showed no change in the yield of compound **158a** (Table 3.3, entry 9). Further, increasing the flow rate of both peristaltic pumps resulted in lower product conversion (Table 3.3, entries 10 and 11). Furthermore, increasing the flow rate of peristaltic pump B while keeping the flow rate of pump

Table 3.3. Optimization of the Reaction for Intramolecular Macrolactonization using diols and diacids



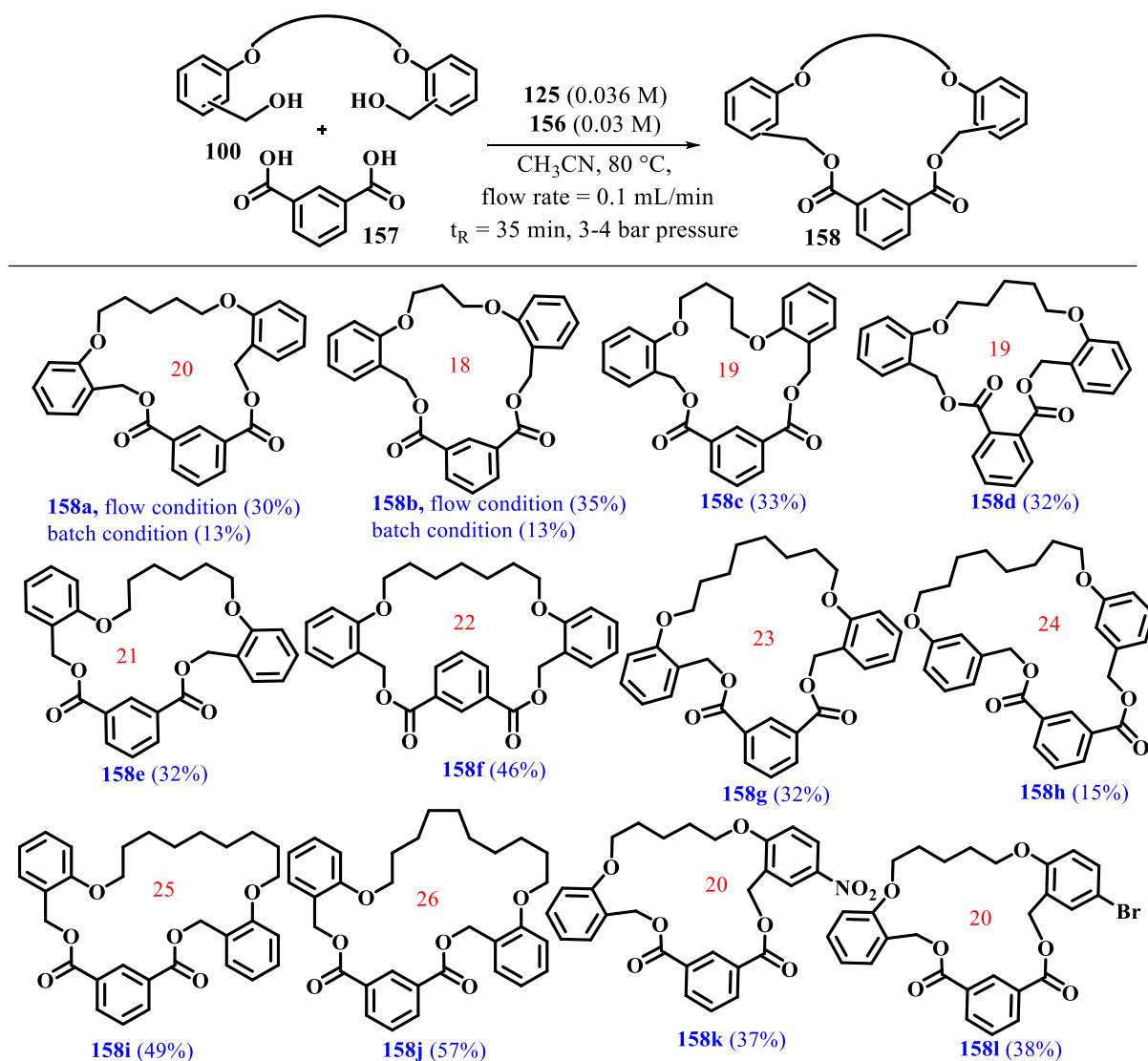
Sr. NO	Conc ⁿ of 100a (M)	Conc ⁿ of 157 (M)	Conc ⁿ of 125(M)	Conc ⁿ of 156 (M)	f _R pump (A:B) (mL/min)	t _R = min	yield (158a/100a) (%)
1 ^a	0.015	0.015	0.036	0.03	0.1:0.1	35	24/40
2 ^a	0.015	0.015	0.036	0.045	0.1:0.1	35	24/35
3 ^a	0.015	0.015	0.036	0.06	0.1:0.1	35	24/30
4 ^a	0.015	0.015	0.036	0.09	0.1:0.1	35	20/30
5 ^a	0.015	0.015	0.06	0.06	0.1:0.1	35	26/28
6 ^a	0.015	0.015	0.072	0.06	0.1:0.1	35	28/15
7 ^{a,b}	0.015	0.015	0.072	0.06	0.1:0.1	50	28/20
8 ^a	0.0075	0.0075	0.036	0.03	0.1:0.1	35	30/20
9 ^{a,b}	0.0075	0.0075	0.036	0.03	0.1:0.1	50	30/12
10 ^a	0.0075	0.0075	0.036	0.03	0.2:0.2	17.5	23/32
11 ^a	0.0075	0.0075	0.036	0.03	0.3:0.3	11.6	7/80
12 ^a	0.0075	0.0075	0.036	0.03	0.1:0.2	23.3	20/34
13 ^a	0.0075	0.0075	0.036	0.03	0.1:0.3	17	12/40
14 ^a	0.0075	0.0075	0.036	0.03	0.2:0.1	17	14/39

^aReaction conditions: for peristaltic pump A: compound **100a** in CH₃CN and, for peristaltic pump B: **125**, **157** and **156** in CH₃CN were flown through the PFA tubing (id = 0.1 cm, 7 mL, length = 890 cm) at 80 °C in the preheated water bath for residence time (see in Table 3.3) under 3-4 bar pressure. ^bpassed through the PFA tubing (id = 0.1 cm, 10 mL); f_R=flow rate; t_R=residence time. The mentioned yields are isolated yields.

A constant did not improve the product yield (Table 3.3, entries 12 and 13). Subsequently, keeping the flow rate of pump B constant while increasing the flow rate of pump A led to reduced conversion of **100a** to product **158a** (Table 3.3, entry 14).

3.7.1 Substrate Scope for the Intermolecular Macrocylic Di-lactonization

Next, to generalize this intermolecular macrolactonization under a flow system, we explored the substrate scope using various diol and diacid derivatives. A pentyl spacer diol with isophthalic acid yielded 30% of **158a** (Scheme 61). The same reaction performed under batch conditions afforded a 13% yield of **158a** (Scheme 61). Using a diol with a propyl spacer (**124b**)



Scheme 61. Substrate scope for the intermolecular macrolactonization

Flow reaction condition: Peristaltic pump A: diol **100** (0.0075 M, 0.15 mmol) in CH₃CN, and Peristaltic pump B: diacid **157** (0.0075 M) in CH₃CN, **125** (0.036 M) and **156** (0.03 M) in CH₃CN were flown with 0.1 mL/min from each pump at 80 °C in the preheated water bath for

residence time 35 min under 3-4 bar pressure. **Batch reaction condition:** diol **100** (0.0075 M, 0.15 mmol), diacid **157** (0.0075 M), and **156** (0.03 M) in CH₃CN were heated at 80 °C in the preheated oil bath for 24 hr. The mentioned yields are isolated yields.

and treating it with isophthalic acid resulted in the macrocyclic dilactone **158b** with a 35% yield under flow conditions and a 16% yield under batch conditions (Scheme 61). This reaction produced the 19-membered macrolactone **158c** in a 33% yield (Scheme 61). The diol with a pentyl spacer (**100a**) and phthalic acid gave a 32% yield of **158d** (Scheme 61). Moreover, the 21-membered macrocyclic dilactone **158e** was obtained in a 32% yield (Scheme 61). In the case of the 22-membered macrocyclic dilactone **158f**, a yield of 46% was observed, and its structure was confirmed by X-ray analysis (Figure 55).

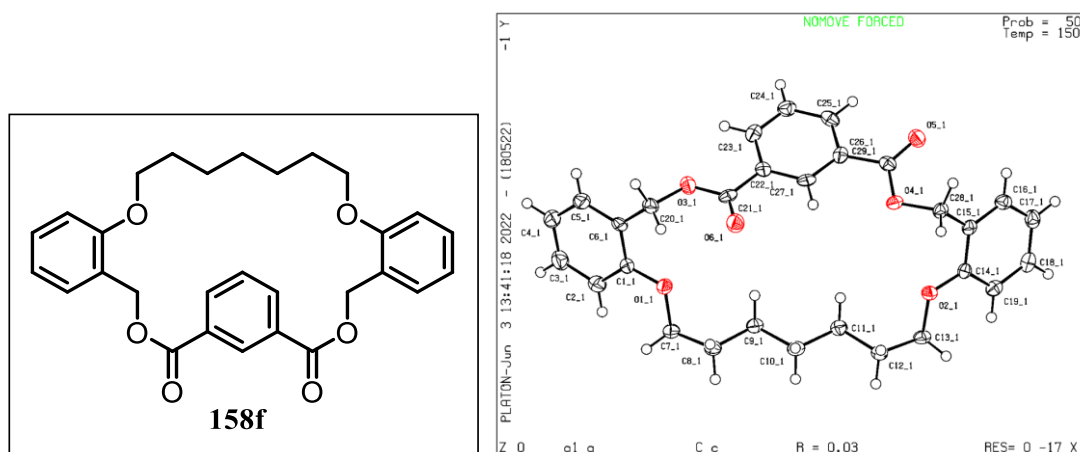


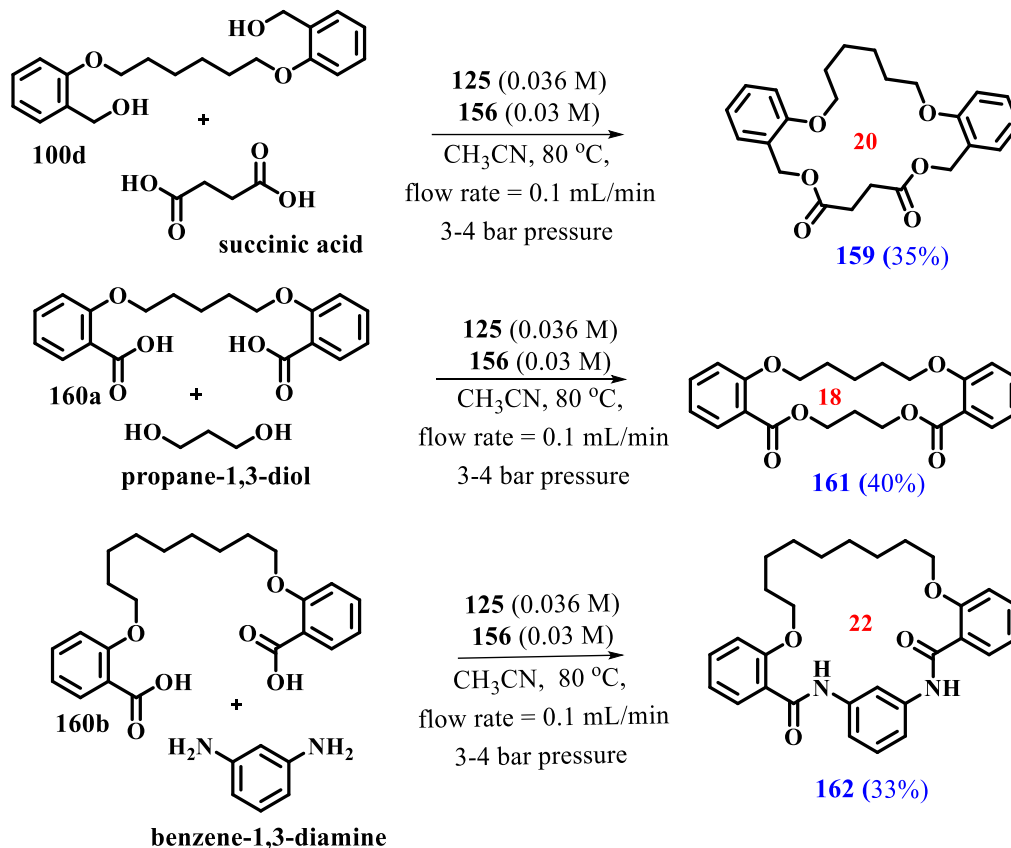
Figure 55. ORTEP crystal structure of **158f** showing thermal ellipsoids at the 50% probability level

Using a diol with an octyl spacer resulted in a 32% yield of macrolactone **158g** (Scheme 61). A *meta*-substituted diol derivative furnished a poor yield of the macrocyclic dilactone **158h** (Scheme 61). Increasing the spacer length of the diol led to higher yields of macrolactones **158i** (49%) and **158j** (57%) (Scheme 61). Finally, nitro- and bromo-substituted diol derivatives treated with isophthalic acid furnished a 37% yield of **158k** and 38% yield of **158l**, respectively (Scheme 61).

3.7.2 Substrate Scope for the Intermolecular Macrocyclic Di-lactonization

To expand this strategy, an intermolecular macrolactonization was performed with a diol and succinic acid (Scheme 62). The macrocyclic dilactone was successfully achieved by the intermolecular coupling of heptyl spacer diol (**100d**) with succinic acid, affording the 21-

membered macro-dilactone **159** in a 35% yield (Scheme 62). A diacid bearing a pentyl spacer (**160a**) with propanediol resulted in the 18-membered macrocyclic dilactone **161** in a 40% yield (Scheme 62). Additionally, 22-membered macrocyclic di-lactam **162** was synthesized in a 32% yield by intermolecular coupling **160b** with *m*-phenylenediamine (Scheme 62).



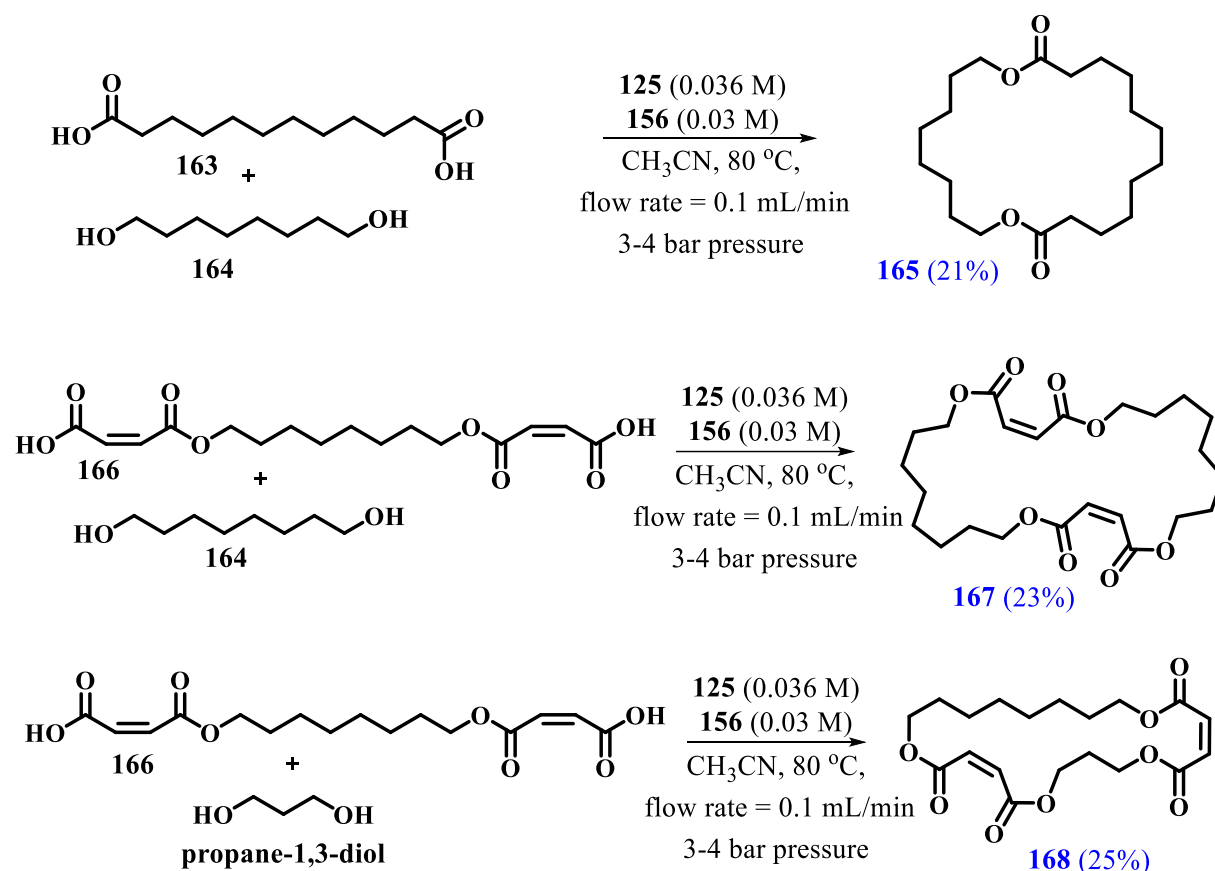
Scheme 62. Intermolecular macrolactonization/macrolactamization using different compounds: diol, diacid, and diamine

Reaction conditions: Peristaltic pump **A**: compound **100d** or **160a** or **160b** (0.0075 M) in CH₃CN, and peristaltic pump **B**: succinic acid or propanediol or *m*-phenylenediamine (0.0075 M) in CH₃CN, **125** (0.036 M) and **156** (0.03 M) were flown with 0.1 mL/min from each pump at 80 °C in the preheated water bath for residence time 35 min under 3-4 bar pressure. The mentioned yields are isolated yields.

3.7.3 Substrate Scope for Intermolecular Macrolactonization using Aliphatic Diol and Diacid

Next, we explored continuous flow macrolactonization with aliphatic diacids **130** and diols **131** (Scheme 63). The 20-membered macrocyclic dilactone **130a** was obtained from dodecanedioic acid and octanediol in a 21% yield (Scheme 63). Furthermore, the 24- and 18-

membered macrocyclic tetralactones **134** and **135** were obtained in 23% and 25% yields, respectively (Scheme 63).



Scheme 72. Inter-molecular macrolactonization using aliphatic diol and diacid

Reaction conditions: Peristaltic pump A: octanediol or propanediol (0.0075 M) in CH_3CN , and peristaltic pump B: dodecanedioic acid **163** or **166** (0.0075 M) in CH_3CN , **108** (0.036 M) and **123** (0.03 M) were flown 0.1 mL/min. from each pump to the PFA tubing (0.1 cm, 7 mL, length = 890 cm) at 80 °C in the preheated water bath for a residence time of 35 min under 3-4 bar pressure. The mentioned yields are isolated yields.

3.8 Conclusion

In conclusion, we have developed an innovative method for the efficient synthesis of macrocyclic lactones and dilactones using a continuous flow system. This approach effectively manages the high dilution typically required for macrolactonization by utilizing a confined volume within a customized perfluoroalkoxy alkane (PFA) tube. The flow-mediated macrolactonization demonstrated versatility by producing a broad range of macrocyclic lactones, encompassing ring sizes from 12 to 26 members, with moderate yields. This method

is not only efficient but also scalable, allowing for gram-scale synthesis while maintaining high reproducibility. Our continuous flow process facilitated the synthesis of various macrocyclic dilactones and tetralactones through the intermolecular coupling of diacids and diols. Additionally, the process proved successful in synthesizing macrocyclic dilactams under continuous flow conditions. The significant advantages of this methodology include its scalability, reproducibility, and ability to handle a wide variety of substrates, making it a valuable tool for the synthesis of complex macrocyclic structures in both academic and industrial settings. This advancement opens new avenues for the efficient and scalable production of macrocyclic compounds, which are important in various fields, including pharmaceuticals and materials science.

3.9 Experimental Section and Data Collection

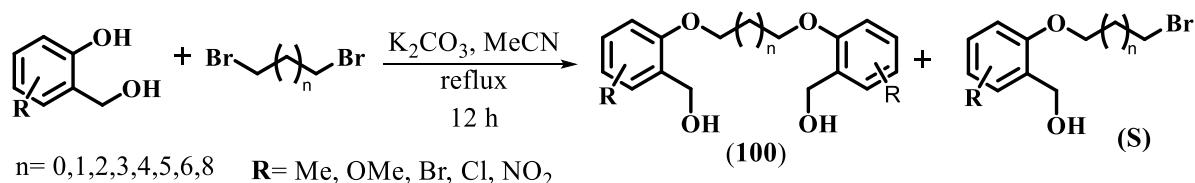
3.9.1. General Information

The *N*-methyl-2-chloropyridinium iodide (CAS number-14338-32-0, SIGMA), 1-methylimidazole (MIM) (CAS number- 616-47-7, SIGMA), Triethylamine (TEA) (CAS number-121-44-8, SIGMA), Ethyl salicylate (CAS number-118-61-6, SIGMA), 2-hydroxy benzyl alcohol (CAS number- 166952, SIGMA) and all dibromo compounds were purchased from Sigma-Aldrich. The column chromatography separations were performed over 100-200 mesh silica-gel. Visualization was accomplished with UV light. The flow chemistry experiments were carried out on Vapourtec SF-10 reagent pump and homogeneous reactions were performed in customized PFA tubing (7, 10, 12 mL). ¹H and ¹³C NMR spectra were recorded on 400 and 100 MHz respectively, using Bruker or JEOL spectrometers in CDCl₃ (CAS number-865-49-6 SIGMA) and DMSO(d₆) (CAS number-2206-27-1, SIGMA). Chemical shifts (δ) for ¹H and ¹³C-NMR spectra are given in ppm relative to tetramethyl silane (TMS) [δ 7.27 for ¹H (chloroform-d), δ 77.0 for ¹³C (chloroform-d); δ 2.50 for ¹H (DMSO-d₆). Abbreviations used in the NMR follow-up experiments: b, broad; s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet. High-Resolution Mass Spectra were recorded with waters-synapt G2 using electrospray ionization (ESI-TOF). All UV-Visible absorption spectra were recorded by a spectrophotometer (PerkinElmer) model Lambda 25, with the use of 1.0 cm quartz cells in a dichloromethane medium (1x10⁻⁵M). Infrared (ATR) spectra were obtained with a Bruker Alpha-E infrared spectrometer. Melting points were recorded on DBK programmable melting point instrument. All melting points were measured in an open glass capillary tube. Single-crystal diffraction analysis data were collected at 100 K with a Bruker

Kappa Apex III CCD Duo diffractometer (operated at 1500 W power: 50 kV, 30 mA) using graphite monochromatic Mo K α radiation. More information on crystal structures (**158f**) can be obtained from the Cambridge Crystallographic Data Centre (CCDC) via deposition number 2176849.

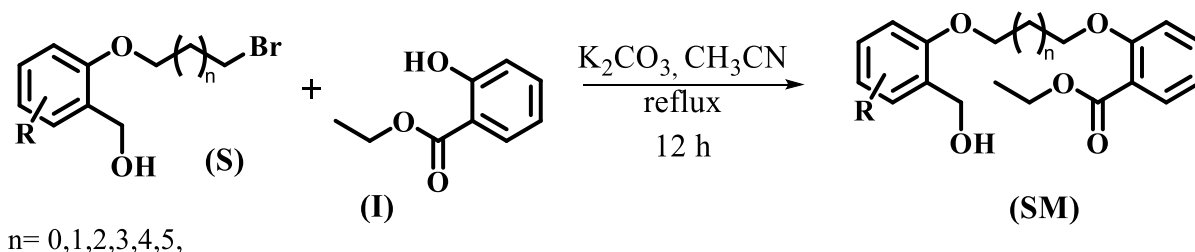
3.9.2. Experimental Section

A) General experimental procedure for mono- and di-alkylation of 2-hydroxybenzylalcohol



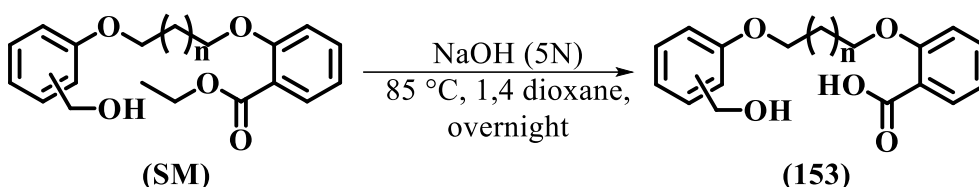
In a 100 mL round bottom flask were added 2-hydroxybenzylalcohol (1 equiv.), dibromoalkanes (1.5 equiv.), and potassium carbonate (2 equiv.) in acetonitrile. The solution was refluxed at 85 °C temperature for 12-16 h in oil bath. The progress of the reaction was monitored by the thin-layer chromatography technique. After completion of the reaction, the mixture of products (mono- and dialkylated) was extracted in water and dichloromethane. The dichloromethane layers were combined and dried over Na₂SO₄. Dichloromethane was evaporated and the residue was directly purified by silica gel chromatography by using EtOAc: *n*-hexane = 15:85 [for mono-alkylated product (S)] and 40:60 [for di-alkylated product (**100**)].

B) General experimental procedure for ester alcohol derivatives¹⁴³



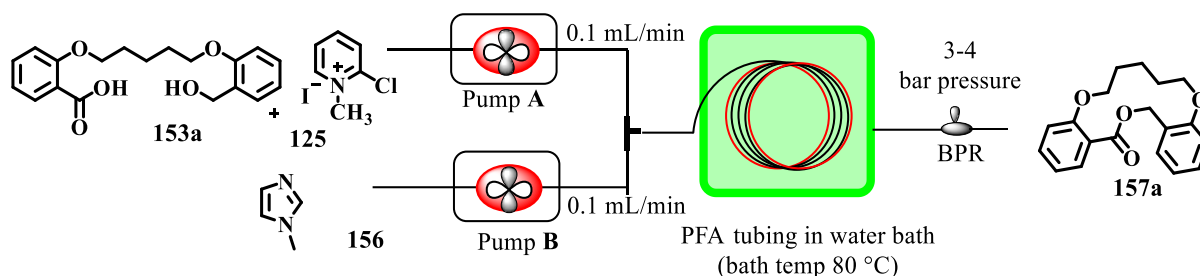
In a 100 mL round bottom flask, (S) (1 equiv.), ethyl 2-hydroxybenzoate (I) (1 equiv.), and potassium carbonate (K₂CO₃) (1 equiv.) in acetonitrile were added. The solution was refluxed at 85 °C temperature for 16 h in oil bath. The progress of the reaction was monitored by thin layer chromatography. The resulting mixture was extracted with ethyl acetate for two times using 30 mL of solvent each time. The ethyl acetate layer were combined and dried over Na₂SO₄. After removing the solvent under reduced pressure, the residue was purified by using column chromatography (EtOAc:*n*-hexane = 40:60) for the product SM.

C) General experimental procedure for seco-acid derivatives¹⁴⁰



To a 1,4-dioxane solution of **SM** 5N NaOH solution was added. The mixture was stirred at 85 °C overnight in oil bath. The reaction mixture was extracted with EtOAc. 1.0 M HCl solution was added to the aqueous solution to adjust the pH until pH adjusted to 2, and then extracted with EtOAc three times. The ethyl acetate layer was dried over anhydrous Na₂SO₄ and evaporated using a vacuum. The residue was directly purified by silica gel chromatography using EtOAc: *n*-hexane = 70:30 to afford the product **153**.

D) General experimental procedure for intramolecular macrolactonization



Intramolecular macrolactonisation using mukaiyama salt in flow: The mixture of 0.015 M of seco-acids **153a** and 0.036 M of Mukaiyama salt **125** in acetonitrile was flown through pump A and 0.03 M of 1-methylimidazole **156** in acetonitrile were flown through pump B with the flow rate of 0.1 mL/min each and both the reaction mixture connected through the T-piece for mixing. The resulting mixture was then allowed to react in PFA tubing (id = 0.1 cm, 7 mL, length = 890 cm) preheated in a water bath at 80 °C maintained with 3-4 bar pressure using BPR with a residence time of 35 min. The volatile components of the crude reaction mixture were evaporated using vacuum, extracted in ethyl acetate (10x2 mL), and washed with sodium thiosulphate solution in water. Further, the ethyl acetate layer was concentrated under reduced pressure followed by column chromatography (EtOAc:*n*-hexane= 5:95) purification afforded the corresponding **154a**.

Intramolecular macrolactonisation in batch: A mixture of seco-acids **153a** (50 mg, 0.15 mmol) and Mukaiyama reagent **125** (183 mg, 0.36 mmol) were suspended in acetonitrile (20 mL). To this reaction mixture was added 1-methylimidazole **156** (49 mg, 0.3 mmol) in sequence. The resulting reaction mixture was allowed to reflux in an oil bath or room temperature for 24 h. The volatile components of the crude reaction mixture were evaporated using vacuum, extracted in ethyl acetate (10x2 mL) and washed with sodium thiosulphate

solution in water. Further, the ethyl acetate layer was concentrated under reduced pressure followed by column chromatography (EtOAc:*n*-hexane = 5:95) purification afforded the corresponding **154a**.

Corey-Nicolaou macrolactonization in flow: For intramolecular macrolactonization in flow, the mixture of 0.015 M of seco-acids **153a** in acetonitrile was flown through pump A and 0.036 M of 2,2'-dipyridyldisulfide **137** and 0.036 M of triphenylphosphine in acetonitrile which was flown through pump B at 0.1 mL/min each. Both the reaction mixture connected through the T-piece for mixing. The resulting mixture was then allowed to react in PFA tubing preheated in a water bath at room temp without any bar pressure or 80 °C (id = 0.1 cm, 7 mL, length = 890 cm) 3-4 bar pressure with residence time 35 min before passing through a back pressure regulator and collection in a flask. The volatile components of the crude reaction mixture was concentrated under vacuum. The residue was dissolved in ethyl acetate (20 mL) and washed with water (2x50 mL). Further, the ethyl acetate layer was concentrated under reduced pressure by purified by column chromatography (EtOAc:*n*-hexane = 5:95) the corresponding product **154a**.

Corey-Nicolaou macrolactonization in batch: A mixture of seco-acids **153a** (50 mg, 0.15 mmol) and 2,2'-dipyridyldisulfide **125** (79 mg, 0.36 mmol) were suspended in acetonitrile (20 mL). To this reaction mixture was added triphenylphosphine (94 mg, 0.3 mmol) in sequence. The resulting reaction mixture was allowed to reflux in oil bath or room temperature for 24 h. The volatile components of the crude reaction mixture was evaporated used vacuum and extracted in ethyl acetate (10x2 mL). The combined ethyl acetate was washed with sodium thiosulphate solution in water. Further, the ethyl acetate layer was concentrated under reduced pressure by purified by column chromatography (EtOAc:*n*-hexane = 5:95) the corresponding product **154a**.

Yamaguchi macrolactonization in flow: For intramolecular Yamaguchi macrolactonization in flow, the mixture of 0.015 M of seco-acids **153a**, 0.03 M of 1-methylimidazole, and 0.036 M of 2,4,6-trichlorobenzoyl chloride **129** in acetonitrile were flown through pump A and 0.03 M of 4-Dimethylaminopyridine in acetonitrile which was flown through pump B at 0.1 mL/min each. Both the reaction mixture connected through the T-piece for mixing. The resulting mixture was then allowed to react in PFA tubing preheated in a water bath at room temp without any bar pressure or 80 °C (id = 0.1 cm, 7 mL, length = 890 cm) 3-4 bar pressure with residence time 35 min before passing a back pressure regulator and collection in a flask. The volatile components of the crude reaction mixture were evaporated under vacuum. The residue was

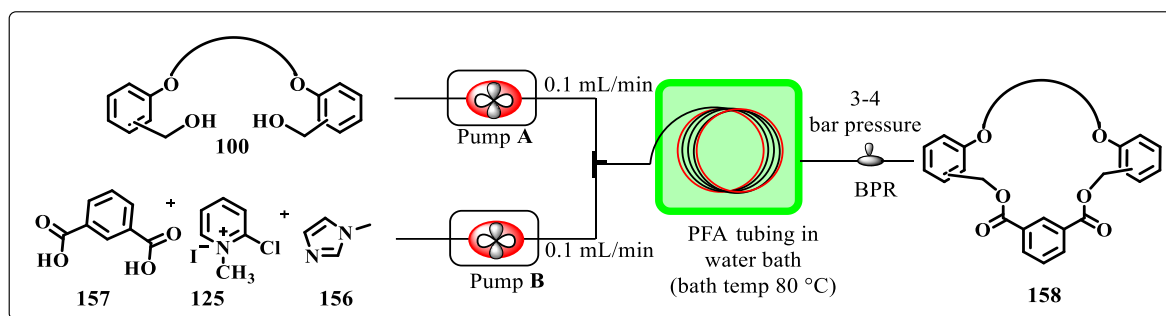
dissolved in ethyl acetate (20 mL) and washed with water (2x50 mL). Further, the ethyl acetate layer was concentrated under reduced pressure by purified by column chromatography (EtOAc:*n*-hexane= 5:95) the corresponding product **154a**.

Yamaguchi macrolactonization in batch: A mixture of seco-acids **153a** (50 mg, 0.15 mmol), (24.6 mg, 0.3 mmol) of 1-methylimidazole and 2,4,6-trichlorobenzoyl chloride **129** (87 mg, 0.36 mmol) was suspended in acetonitrile (20 mL). To this reaction mixture was added 4-dimethylaminopyridine (36 mg, 0.3 mmol) in sequence. The resulting reaction mixture was allowed to reflux under an oil bath or room temperature for 24 h. The volatile components of the crude reaction mixture were evaporated under a vacuum. After extracted in ethyl acetate (10x2 mL) and washed with sodium thiosulphate solution in water. Further, the ethyl acetate layer was concentrated under reduced pressure by purified by column chromatography (EtOAc:*n*-hexane= 5:95) the corresponding product **154a**.

Mitsunobu macrolactonization in flow: For intramolecular macrolactonization in flow, the mixture of 0.015 M of seco-acids **153a**, 0.036 M of triphenylphosphine, and 0.036 M of diisopropyl azodicarboxylate **105D** in acetonitrile were flown through pump A and acetonitrile solvent which was flown through pump B at 0.1mL/min each and both the reaction mixture connected through the T-piece for mixing. The resulting mixture was then allowed to react in PFA tubing preheated in a water bath at room temp without any bar pressure or 80 °C (id = 0.1 cm, 7 mL, length = 890 cm) 3-4 bar pressure, residence time 35 min before passing through a back pressure regulator and collection in a flask. The volatile components of the crude reaction mixture were evaporated under vacuum. The crude residue was dissolved in ethyl acetate (20 mL) and washed with water (2x50 mL). Further, the ethyl acetate layer was concentrated under reduced pressure by purified by column chromatography (EtOAc:*n*-hexane= 5:95) the corresponding product **154a**.

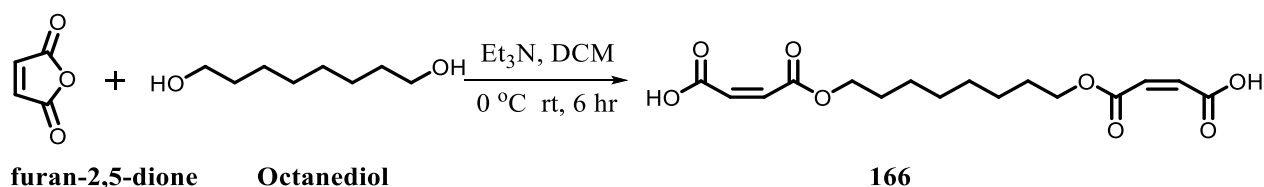
Mitsunobu macrolactonization in batch: A mixture of seco-acids **153a** (50 mg, 0.15 mmol) and diisopropyl azodicarboxylate **140** (45 mg, 0.22 mmol) was suspended in acetonitrile (20 mL). To this reaction mixture was added triphenylphosphine (59 mg, 0.22 mmol) in sequence. The resulting reaction mixture was allowed to reflux under an oil bath or room temperature for 24 hr. The volatile components of the crude reaction mixture were evaporated using a vacuum, extracted in ethyl acetate (10x2 mL), and washed with sodium thiosulphate solution in water. Further, the ethyl acetate layer was concentrated under reduced pressure by purified by column chromatography (EtOAc:*n*-hexane= 5:95) the corresponding product **154a**.

E) General experimental procedure for intermolecular macrocyclic dilactonisation



For intermolecular macro-di-lactonization in flow, the mixture of 0.0075 M of **100** in acetonitrile was flown through pump A and 0.0075 M of isophthalic **157** acid or succinic acid, 0.036 M of Mukaiyama salt **125** and 0.03 M of 1-methylimidazole **156** in acetonitrile was flown through pump B at 0.1 mL/min each. Both the reaction mixtures connected through the T-piece for mixing. The resulting mixture was then allowed to react in PFA tubing preheated in a water bath at 80 °C (id = 0.1 cm, 7 mL, length = 890 cm) 3-4 bar pressure with residence time 35 min before passing through a back pressure regulator and collection in a flask. The volatile components of the crude reaction mixture were evaporated using a vacuum and dissolved in ethyl acetate (20 mL) and washed with sodium thiosulphate solution in water. Further, the ethyl acetate layer was concentrated under reduced pressure by purified by column chromatography (EtOAc:*n*-hexane = 5:95) the corresponding product **158**.

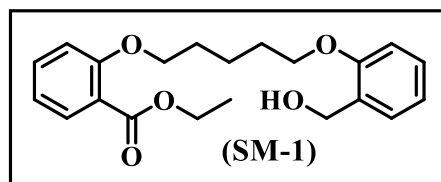
F) General experimental procedure for dicarboxylic acid synthesis¹⁴⁴



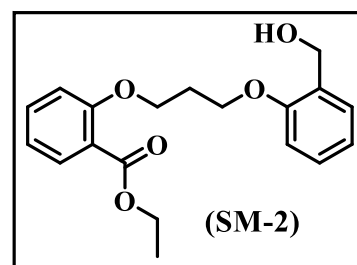
In 250 mL round bottomed flask under nitrogen was charged with furan-2,5-dione (2 gm, 20 mmol) and octanediol (1.4 gm, 10 mmol) in dry dichloromethane (100 mL). The stirred reaction mixture was cooled to 0 °C in ice bath and triethylamine (2 gm, 20.4 mmol) added. The reaction was continued for 4 h at 0 °C and further at room temperature for 5 hrs. Reaction was monitored by TLC. The residue was cooled to 0 °C in an ice bath and 200 mL of saturated sodium bicarbonate solution and extracted with ether. The aqueous layer was cooled to 0 °C in an ice bath and acidified with dilute hydrochloric acid followed by the extraction with diethyl ether or dichloromethane (4 x 100 mL). The entire organic layer combined and evaporated under reduced pressure to provide the corresponding pure dicarboxylic acid **166** in 61% yield.

3.9.3 Analytical Data of Product

Ethyl 2-((5-(2-(hydroxymethyl)phenoxy)pentyl)oxy)benzoate (SM-1): Prepared according to general experimental procedure 3.9.2B, using (2-((5-bromopentyl)oxy)phenyl)methanol (500 mg, 1.08 mmol), potassium carbonate (K_2CO_3) (281.9 mg, 1.08 mmol) and ethyl 2-hydroxybenzoate (**I**) (304 mg, 1.08 mmol). The residue was purified by using column chromatography (EtOAc/*n*-hexane = 40:60) as the eluent to afford desired product ethyl 2-((5-(2-(hydroxymethyl)phenoxy)pentyl)oxy)benzoate **SM-1** (580 mg, 1.62 mmol, 88% yield) as a semi-solid. ^1H NMR (400 MHz, $CDCl_3$) δ 7.77 (dd, J = 7.6, 1.8 Hz, 1H), 7.46 – 7.39 (m, 1H), 7.27 (ddd, J = 6.4, 5.4, 1.5 Hz, 2H), 6.99 – 6.90 (m, 3H), 6.87 (d, J = 8.2 Hz, 1H), 4.69 (s, 2H), 4.34 (q, J = 7.2 Hz, 2H), 4.06 (dt, J = 6.3, 4.4 Hz, 4H), 1.90 (dt, J = 13.6, 6.8 Hz, 4H), 1.72 (ddd, J = 16.2, 9.5, 6.2 Hz, 2H), 1.36 (t, J = 7.1 Hz, 3H), OH peak exchanged with deuterium of $CDCl_3$; ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.7, 158.5, 156.9, 133.4, 131.6, 129.0, 128.8, 120.8, 120.7, 120.2, 113.2, 111.1, 68.6, 67.8, 62.2, 60.9, 29.1, 22.9, 14.5, 14.3; FTIR (neat): 3500, 2941, 1713, 1600, 1492, 1243 cm^{-1} ; HRMS (ESI-TOF) m/z : $[M + Na]^+$ calcd for $C_{21}H_{26}O_5Na$, 381.1677, found 381.1676.



Ethyl 2-(3-(2-(hydroxymethyl)phenoxy)propoxy)benzoate (SM-2): Prepared according to general experimental procedure 3.9.2B, using (2-(3-bromopropoxy)phenyl)methanol (500 mg, 2 mmol),

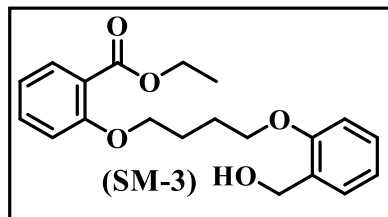


potassium carbonate (K_2CO_3) (281.9 mg, 2 mmol) and ethyl 2-hydroxybenzoate (339 mg, 1.08 mmol), the residue was purified by using column chromatography (EtOAc:*n*-hexane = 40:60) as the eluent to afford desired product ethyl 2-((3-(2-(hydroxymethyl)phenoxy)propoxy)benzoate **SM-2** (611 mg, 1.85 mmol, 90% yield) as a semi solid. ^1H NMR (400 MHz, $CDCl_3$) δ 7.78 (dd, J = 7.9, 1.8 Hz, 1H), 7.47 – 7.40 (m, 1H), 7.28 (dd, J = 7.1, 1.7 Hz, 1H), 7.25 (dd, 1H), 7.00 – 6.98 (m, 1H), 6.97 – 6.95 (m, 1H), 6.95 – 6.90 (m, 2H), 4.67 (s, 2H), 4.35 – 4.27 (m, 4H), 4.24 (t, J = 5.9 Hz, 2H), 2.39 – 2.29 (m, 2H), 1.34 (t, J = 7.2 Hz, 3H), OH peak exchanged with deuterium of $CDCl_3$; ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.4, 158.4, 156.7, 133.5, 131.7, 129.3, 129.1, 128.8, 120.9, 120.6, 113.4, 111.4, 65.4, 64.7, 62.1, 60.9, 29.4, 14.5; FTIR (neat): 3508, 2926,

2854, 1715, 1253, 1228 cm^{-1} ; HRMS (ESI-TOF) m/z : $[\text{M} + \text{Na}]^+$ calcd for $\text{C}_{19}\text{H}_{22}\text{O}_5\text{Na}$, 353.1364, found 353.1364.

Ethyl 2-(4-(2-(hydroxymethyl)phenoxy)butoxy)benzoate

(SM-3): Prepared according to general experimental procedure 3.9.2B, using (2-(4-bromobutoxy)phenyl)methanol (500 mg, 1.93 mmol), potassium carbonate (K_2CO_3) (266.6 mg, 1.93 mmol) and



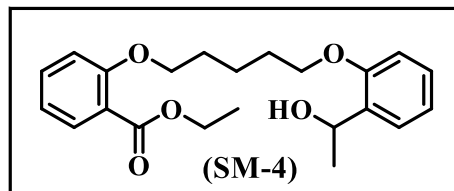
ethyl 2-hydroxybenzoate (320 mg, 1.93 mmol), the residue was purified by using column chromatography ($\text{EtOAc}:\text{n-hexane} = 40:60$) as the eluent to afford desired product ethyl 2-(4-(2-(hydroxymethyl)phenoxy)butoxy)benzoate **SM-3** (594 mg, 1.72 mmol, 89% yield) as a semi solid. ^1H NMR (400 MHz, CDCl_3) δ 7.80 – 7.74 (m, 1H), 7.46 – 7.39 (m, 1H), 7.25 (dt, $J = 9.4, 7.6$ Hz, 2H), 6.99 – 6.90 (m, 3H), 6.88 (d, $J = 8.2$ Hz, 1H), 4.67 (s, 2H), 4.37 – 4.28 (m, 2H), 4.10 (t, $J = 5.6$ Hz, 4H), 2.51 (s, 1H), 2.11 – 1.98 (m, 4H), 1.39 – 1.31 (m, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 166.5, 158.4, 156.8, 133.4, 131.7, 129.2, 129.0, 128.8, 120.8, 120.7, 120.3, 113.1, 111.1, 68.2, 67.6, 62.1, 60.9, 26.2, 14.4; FTIR (neat): 3435, 2938, 1708, 1600, 1491, 1209 cm^{-1} ; HRMS (ESI-TOF) m/z : $[\text{M} + \text{Na}]^+$ calcd for $\text{C}_{20}\text{H}_{24}\text{O}_5\text{Na}$, 367.1521, found 367.1522.

Ethyl

2-((5-(2-(1-

hydroxyethyl)phenoxy)pentyl)oxy)benzoate (SM-

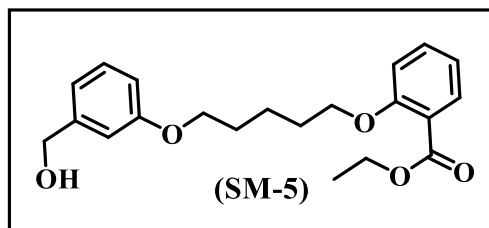
4): Prepared according to general experimental procedure 3.9.2B, using 1-(2-((5-



bromopentyl)oxy)phenyl)ethan-1-ol (500 mg, 1.74 mmol), potassium carbonate (K_2CO_3) (240.6 mg, 1.74 mmol) and ethyl 2-hydroxybenzoate (289 mg, 1.74 mmol), the residue was purified by using column chromatography ($\text{EtOAc}:\text{n-hexane} = 40:60$) as the eluent to afford desired product ethyl 2-((5-(2-(1-hydroxyethyl)phenoxy)pentyl)oxy)benzoate **SM-4** (590 mg, 1.58 mmol, 91% yield) as a semi solid. ^1H NMR (400 MHz, CDCl_3) δ 7.77 (d, $J = 7.5$ Hz, 1H), 7.43 (t, $J = 7.7$ Hz, 1H), 7.35 (d, $J = 7.3$ Hz, 1H), 7.22 (t, $J = 7.6$ Hz, 1H), 6.95 (d, $J = 7.3$ Hz, 3H), 6.86 (d, $J = 8.1$ Hz, 1H), 5.16 – 5.05 (m, 1H), 4.34 (q, $J = 6.8$ Hz, 2H), 4.06 (t, $J = 5.6$ Hz, 4H), 2.75 (s, 1H), 1.98 – 1.86 (m, 4H), 1.71 (dd, $J = 13.9, 7.5$ Hz, 2H), 1.50 (d, $J = 5.5$ Hz, 3H), 1.36 (t, $J = 6.5$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 166.7, 158.5, 156.1, 133.7, 133.3, 131.6, 128.3, 126.2, 121.0, 120.8, 120.2, 113.2, 111.3, 68.7, 67.8, 66.6, 60.9, 29.11, 23.0, 14.5; FTIR (neat): 3501, 2940, 2845, 1718, 1600, 1491, 1242 cm^{-1} ; HRMS (ESI-TOF) m/z : $[\text{M} + \text{Na}]^+$ calcd for $\text{C}_{22}\text{H}_{28}\text{O}_5\text{Na}$, 395.1834, found 395.1830.

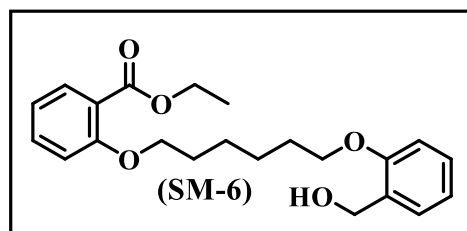
Ethyl**2-((5-(3-****(hydroxymethyl)phenoxy)pentyl)oxy)benzoate**

(SM-5): Prepared according to general experimental procedure 3.9.2B, using (3-((5-bromopentyl)oxy)phenyl)methanol (500 mg, 1.84



mmol), potassium carbonate (K_2CO_3) (253 mg, 1.84 mmol) and ethyl 2-hydroxybenzoate (304 mg, 1.84 mmol), the residue was purified by using column chromatography (EtOAc:*n*-hexane = 40:60) as the eluent to afford desired product ethyl 2-((5- **SM-5** (500 mg, 1.39 mmol, 75% yield) as a semi solid. ^1H NMR (400 MHz, $CDCl_3$) δ 7.78 (dd, J = 7.6, 1.7 Hz, 1H), 7.47 – 7.40 (m, 1H), 7.26 (dd, J = 13.0, 5.5 Hz, 1H), 6.95 (dt, J = 17.2, 7.3 Hz, 4H), 6.85 – 6.80 (m, 1H), 4.66 (s, 2H), 4.36 (q, J = 7.1 Hz, 2H), 4.07 (t, J = 6.3 Hz, 2H), 4.01 (t, J = 6.4 Hz, 2H), 1.97 – 1.84 (m, 4H), 1.76 – 1.65 (m, 2H), 1.38 (t, J = 7.1 Hz, 3H), OH peak exchanged with deuterium of $CDCl_3$; ^{13}C NMR (100 MHz, $CDCl_3$) 166.8, 159.4, 158.5, 142.7, 133.3, 131.6, 129.6, 120.9, 120.2, 119.1, 113.8, 113.2, 112.9, 68.7, 67.8, 65.2, 60.9, 29.0, 22.7, 14.3 (d, J = 14.7 Hz). FTIR (neat): 3507, 2941, 2845, 1718, 1601, 1491, 1240 cm^{-1} ; HRMS (ESI-TOF) m/z : $[M + Na]^+$ calcd for $C_{21}H_{26}O_5Na$, 381.1677, found 381.1676.

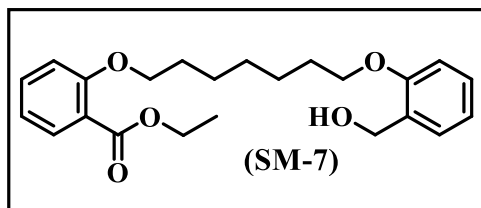
Ethyl 2-((6-(2-(hydroxymethyl)phenoxy)hexyl)oxy)benzoate (SM-6) : Prepared according to general experimental procedure 3.9.2B, using (2-((6-bromohexyl)oxy)phenyl)methanol (500 mg, 1.74 mmol), potassium carbonate (K_2CO_3) (240 mg, 1.74 mmol) and ethyl 2-hydroxybenzoate (290 mg, 1.74 mmol), the residue was purified by using



column chromatography (EtOAc:*n*-hexane = 40:60) as the eluent to afford desired product ethyl 2-((6-(2-(hydroxymethyl)phenoxy)hexyl)oxy)benzoate **SM-6** (510 mg, 1.37 mmol, 78% yield) as a semi-solid. ^1H NMR (400 MHz, $CDCl_3$) δ 7.76 (dd, J = 7.8, 1.7 Hz, 1H), 7.45 – 7.39 (m, 1H), 7.29 – 7.21 (m, 2H), 6.98 – 6.90 (m, 3H), 6.86 (d, J = 8.1 Hz, 1H), 4.68 (d, J = 3.1 Hz, 2H), 4.33 (q, J = 7.1 Hz, 2H), 4.03 (dd, J = 11.1, 6.3 Hz, 4H), 2.48 (s, 1H), 1.86 (dd, J = 14.2, 6.4 Hz, 4H), 1.63 – 1.49 (m, 4H), 1.36 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.7, 158.5, 156.9, 133.3, 131.6, 129.3, 128.9, 128.7, 120.9, 120.6, 120.1, 113.2, 111.1, 68.7, 67.9, 62.2, 60.8, 29.3, 29.2, 26.0, 25.8, 14.4. FTIR (neat): 3501, 2940, 2845, 1718, 1600, 1491, 1242 cm^{-1} ; HRMS (ESI-TOF) m/z : $[M + Na]^+$ calcd for $C_{22}H_{28}O_5Na$, 395.1834, found 395.1830.

Ethyl 2-((7-(2-(hydroxymethyl)phenoxy)heptyl)oxy)benzoate (SM-7): Prepared according

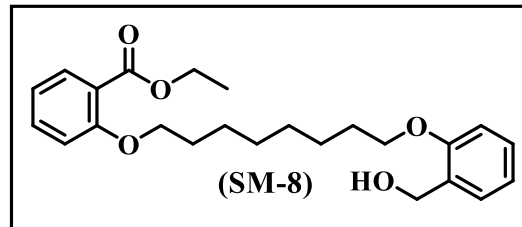
to general experimental procedure 3.9.2B, using (2-((7-bromoheptyl)oxy)phenyl)methanol (500 mg, 1.66 mmol), potassium carbonate (K_2CO_3) (229 mg, 1.66 mmol) and ethyl 2-hydroxybenzoate (276 mg,



1.66 mmol), the residue was purified by using column chromatography (EtOAc:*n*-hexane = 40:60) as the eluent to afford desired product ethyl 2-((7-(2-(hydroxymethyl)phenoxy)heptyl)oxy)benzoate **SM-7** (590 mg, 1.49 mmol, 89% yield) as a semi solid. ^1H NMR (400 MHz, $CDCl_3$) δ 7.79 (dd, J = 7.5, 1.7 Hz, 1H), 7.45 (ddd, 1H), 7.30 – 7.28 (m, 1H), 7.01 – 6.98 (m, 1H), 6.97 – 6.92 (m, 3H), 6.85 (dd, 1H), 4.69 (s, 2H), 4.37 (q, J = 7.0 Hz, 2H), 4.06 (t, J = 6.5 Hz, 2H), 3.99 (t, J = 6.5 Hz, 2H), 1.92 – 1.79 (m, 4H), 1.61 – 1.45 (m, 6H), 1.42 – 1.37 (m, 3H), OH peak exchanged with deuterium of $CDCl_3$; ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.2, 159.9, 158.9, 143.0, 133.6, 131.9, 130.0, 121.3, 120.4, 119.4, 114.3, 113.6, 113.3, 69.2, 68.3, 65.8, 61.2, 29.6, 26.4, 14.8; FTIR (neat): 3503, 2925, 2853, 1714, 1253, 1228 cm^{-1} ; HRMS (ESI-TOF) m/z : $[M + Na]^+$ calcd for $C_{23}H_{30}O_5Na$, 409.1990, found 409.1990.

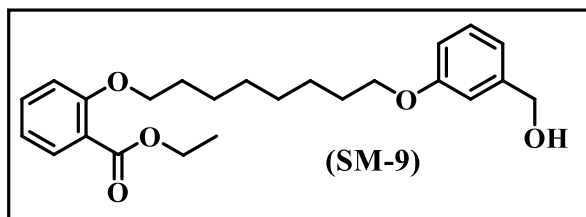
Ethyl 2-((8-(2-(hydroxymethyl)phenoxy)octyl)oxy)benzoate (SM-8): Prepared according to

general experimental procedure 3.9.2B, using (2-((8-bromooctyl)oxy)phenyl)methanol (500 mg, 1.59 mmol), potassium carbonate (K_2CO_3) (219 mg, 1.59 mmol) and ethyl 2-hydroxybenzoate (263 mg, 1.59 mmol), the residue was purified by



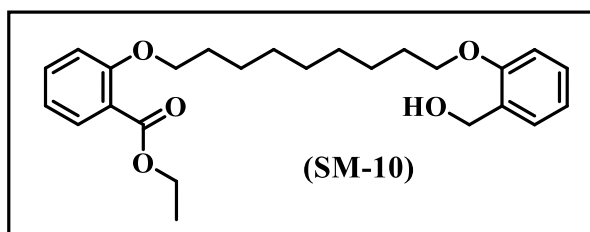
using column chromatography (EtOAc:*n*-hexane = 40:60) as the eluent to afford desired product ethyl 2-((8-(2-(hydroxymethyl)phenoxy)octyl)oxy)benzoate **SM-8** (540 mg, 1.35 mmol, 85% yield) as a semi solid. ^1H NMR (400 MHz, $CDCl_3$) δ 7.68 (dd, J = 8.0, 1.8 Hz, 1H), 7.36 – 7.30 (m, 1H), 7.20 – 7.13 (m, 2H), 6.89 – 6.81 (m, 3H), 6.78 (d, J = 8.1 Hz, 1H), 4.61 (d, J = 5.7 Hz, 2H), 4.26 (q, J = 7.1 Hz, 2H), 3.93 (dd, J = 11.8, 6.4 Hz, 4H), 2.43 (s, 1H), 1.78 – 1.69 (m, 4H), 1.48 – 1.36 (m, 4H), 1.33 – 1.31 (m, 4H), 1.28 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.8, 158.6, 157.0, 133.2, 131.5, 129.3, 128.9, 128.7, 120.9, 120.6, 120.1, 113.2, 111.1, 68.9, 68.0, 62.3, 60.8, 29.4, 29.3, 29.3, 29.3, 26.2, 26, 14.4; FTIR (neat): 3508, 2940, 2845, 1718, 1603, 1491, 1242 cm^{-1} ; HRMS (ESI-TOF) m/z : $[M + Na]^+$ calcd for $C_{24}H_{32}O_5Na$, 423.2147, found 423.2149.

Ethyl 2-((8-(3-(hydroxymethyl)phenoxy)octyl)oxy)benzoate (SM-9): Prepared according to general experimental procedure 3.9.2B, using 3-((8-bromooctyl)oxy)phenylmethanol (500 mg, 1.59 mmol), potassium carbonate (K₂CO₃) (219 mg, 1.59 mmol) and ethyl 2-hydroxybenzoate (263 mg, 1.59 mmol), the



residue was purified by using column chromatography (EtOAc:*n*-hexane = 40:60) as the eluent to afford desired product ethyl 2-((8-(3-(hydroxymethyl)phenoxy)octyl)oxy)benzoate **SM-9** (575 mg, 1.44 mmol, 90% yield) as a semi-solid; ¹H NMR (400 MHz, CDCl₃) δ 7.79 (dd, *J* = 7.9, 1.7 Hz, 1H), 7.49 – 7.42 (m, 1H), 7.29 (dd, *J* = 4.5, 3.1 Hz, 1H), 6.97 (dd, *J* = 13.9, 6.1 Hz, 4H), 6.86 – 6.82 (m, 1H), 4.69 (s, 2H), 4.37 (q, *J* = 7.1, 1.9 Hz, 2H), 4.04 (t, *J* = 5.6, 4.9 Hz, 2H), 3.98 (t, *J* = 6.5 Hz, 2H), 1.89 – 1.80 (m, *J* = 18.7, 10.0, 4.8 Hz, 4H), 1.59 – 1.47 (m, *J* = 21.6, 14.5, 7.2 Hz, 4H), 1.45 – 1.37 (m, 7H), OH peak exchanged with deuterium of CDCl₃; ¹³C NMR (100 MHz, CDCl₃) δ 166.8, 159.5, 158.6, 142.7, 133.3, 131.6, 129.7, 121.0, 120.1, 119, 113.9, 113.2, 113, 68.9, 68.0, 65.4, 60.9, 29.6, 29.1, 26.1, 14.4; FTIR (neat): 3501, 2935, 2860, 1710, 1601, 1419, 1254 cm⁻¹; HRMS (ESI-TOF) *m/z*: [M + Na]⁺ calcd for C₂₄H₃₂O₅Na, 423.2147, found 423.2149.

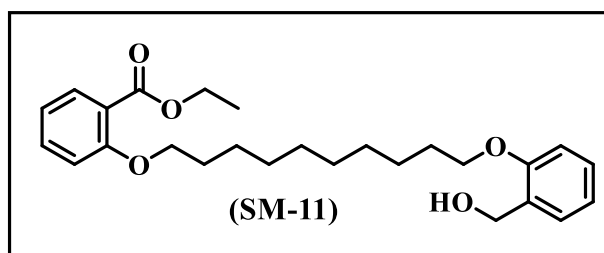
Ethyl 2-((9-(2-(hydroxymethyl)phenoxy)nonyl)oxy)benzoate (SM-10): Prepared according to general experimental procedure 3.9.2B, using 2-((9-bromononyl)oxy)phenylmethanol (500 mg, 1.52 mmol), potassium carbonate (K₂CO₃) (209 mg, 1.52 mmol) and ethyl 2-



hydroxybenzoate (252 mg, 1.52 mmol), the residue was purified by using column chromatography (EtOAc:*n*-hexane = 40:60) as the eluent to afford desired product **SM-10** (545 mg, 1.31 mmol, 86% yield) as a semi-solid. ¹H NMR (400 MHz, CDCl₃) δ 7.82 – 7.77 (m, 1H), 7.48 – 7.41 (m, 1H), 7.29 (ddd, *J* = 8.0, 5.4, 0.8 Hz, 2H), 7.01 – 6.93 (m, 3H), 6.90 (d, *J* = 8.1 Hz, 1H), 4.72 (s, 2H), 4.38 (q, *J* = 7.1 Hz, 2H), 4.04 (dd, *J* = 11.3, 6.4 Hz, 4H), 2.56 (s, 1H), 1.89 – 1.81 (m, 4H), 1.56 – 1.47 (m, 4H), 1.40 (dd, *J* = 8.5, 5.7 Hz, 9H); ¹³C NMR (100 MHz, CDCl₃) δ 166.8, 158.6, 157.0, 133.2, 131.6, 129.3, 128.9, 128.7, 120.9, 120.6, 120, 113.2, 111.1, 68.9, 68.0, 62.3, 60.8, 29.5, 29.4, 29.3, 26.2, 26.1, 14.4; FTIR (neat): 3441, 2929, 2856, 1706, 1600, 1491, 1237 cm⁻¹; HRMS (ESI-TOF) *m/z*: [M + Na]⁺ calcd for C₂₅H₃₄O₅Na, 437.2303, found 437.2301.

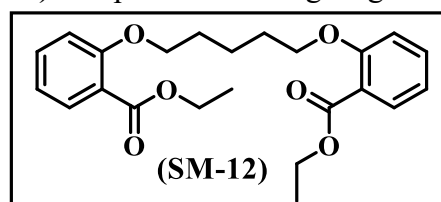
Ethyl 2-((10-(2-(hydroxymethyl)phenoxy)decyl)oxy)benzoate (SM-11): Prepared

according to general experimental procedure 3.9.2B, using (2-((10-bromodecyl)oxy)phenyl)methanol (500 mg, 1.46 mmol), potassium carbonate (K_2CO_3) (201 mg, 1.46 mmol) and ethyl 2-hydroxybenzoate (242 mg, 1.46 mmol), the



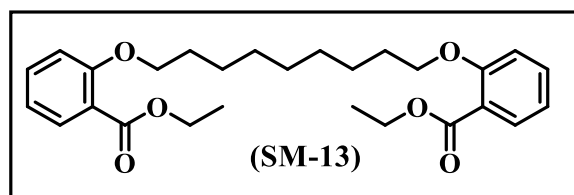
residue was purified by using column chromatography (EtOAc:*n*-hexane = 40:60) as the eluent to afford desired product **SM-11** (560 mg, 1.31 mmol, 89% yield) as a semi-solid. ^1H NMR (400 MHz, $CDCl_3$) δ 7.76 (dd, J = 7.9, 1.8 Hz, 1H), 7.43 – 7.37 (m, 1H), 7.24 (ddd, J = 9.6, 7.7, 1.5 Hz, 2H), 6.95 – 6.89 (m, 3H), 6.85 (d, J = 7.9 Hz, 1H), 4.68 (s, 2H), 4.34 (q, J = 7.2 Hz, 2H), 3.99 (q, J = 6.4 Hz, 4H), 2.60 (s, 1H), 1.84 – 1.76 (m, 4H), 1.48 (dt, J = 12.9, 7.2 Hz, 4H), 1.35 (dd, J = 14.1, 6.9 Hz, 11H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.8, 158.5, 156.9, 133.2, 131.5, 129.2, 128.8, 128.6, 120.8, 120.5, 120.0, 113.1, 111, 68.9, 67.9, 62.2, 60.8, 29.5, 29.4, 29.3, 29.2, 26.2, 26.0, 14.7; FTIR (neat): 3501, 2938, 2855, 1708, 1600, 1491, 1242 cm^{-1} ; HRMS (ESI-TOF) m/z : $[M + Na]^+$ calcd for $C_{26}H_{36}O_5Na$, 451.2460, found 451.2454.

Diethyl 2,2'-(pentane-1,5-diylbis(oxy))dibenzoate (SM-12): Prepared according to general experimental procedure 3.9.2B, using ethyl 2-hydroxybenzoate (1.0 gm, 6.0 mmol), potassium carbonate (K_2CO_3) (831 mg, 1.66 mmol) and 1,5-dibromo pentane (691 mg, 3.0 mmol), the residue was



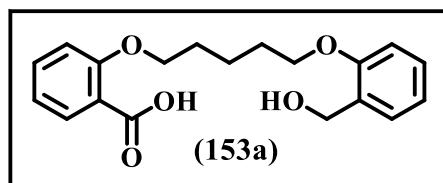
purified by using column chromatography (EtOAc:*n*-hexane = 30:70) as the eluent to afford desired product **SM-12** (1.9 gm, 4.74 mmol, 79% yield) as a semi-solid. ^1H NMR (400 MHz, $CDCl_3$) δ 7.77 (dd, J = 7.6, 1.8 Hz, 2H), 7.42 (td, J = 7.9, 1.8 Hz, 2H), 6.95 (t, J = 7.8 Hz, 4H), 4.34 (q, J = 7.2 Hz, 4H), 4.06 (t, J = 6.4 Hz, 4H), 1.96 – 1.86 (m, 4H), 1.77 – 1.67 (m, 2H), 1.36 (t, J = 7.1 Hz, 6H), ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.7, 158.6, 133.3, 131.6, 120.9, 120.2, 113.2, 68.8, 60.9, 29.0, 22.7, 14.5, FTIR (neat): 2941, 2853, 1723, 1600, 1490, 1245 cm^{-1} ; HRMS (ESI-TOF) m/z : $[M + Na]^+$ calcd for $C_{23}H_{28}O_6Na$, 423.1783, found 423.1781.

Diethyl 2,2'-(nonane-1,9-diylbis(oxy))dibenzoate (SM-13): Prepared according to general experimental procedure 3.9.2B, using ethyl 2-hydroxybenzoate (700 mg, 4.21 mmol), potassium carbonate (K_2CO_3) (582 mg, 4.21 mmol) and 1,5-dibromopentane (1.2 gm, 4.21



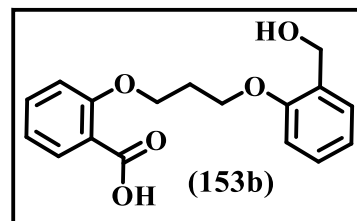
mmol), the residue was purified by using column chromatography (EtOAc:*n*-hexane = 30:70) as the eluent to afford desired product diethyl **SM-13** (1.5 gm, 3.29 mmol, 78% yield) as a semi-solid. ¹H NMR (400 MHz, CDCl₃) δ 7.76 (dd, *J* = 8.0, 1.8 Hz, 2H), 7.41 (td, *J* = 8.2, 1.7 Hz, 2H), 6.94 (t, *J* = 7.4 Hz, 4H), 4.34 (q, *J* = 7.1 Hz, 4H), 4.01 (t, *J* = 6.5 Hz, 4H), 1.86 – 1.78 (m, 4H), 1.53 – 1.44 (m, 4H), 1.36 (dd, *J* = 9.2, 5.0 Hz, 12H); ¹³C NMR (100 MHz, CDCl₃) δ 166.8, 158.6, 133.2, 131.5, 120.9, 120.1, 113.2, 68.9, 60.8, 29.6, 29.7, 29.2, 29.4, 26.1, 14.4. FTIR (neat): 2980, 2850, 1725, 1600, 1491, 1245 cm⁻¹; HRMS (ESI-TOF) *m/z*: [M + Na]⁺ calcd for C₂₇H₃₆O₆Na, 479.2409, found 479.2406.

2-((5-(2-(hydroxymethyl)phenoxy)pentyl)oxy)benzoic acid (153a): Prepared according to general experimental procedure 3.9.2C, 1,4-dioxane (2.0 mL) solution of ethyl **SM-1** (200 mg, 0.55 mmol), 5N NaOH solution (5.0 mL) was added. The reaction mixture was stirred at 80 °C in an oil bath for overnight.



After, the residue was purified by using column chromatography (EtOAc/*n*-hexane = 60:40) as the eluent to afford **153a** (168 mg, 91% yield) as a solid. melting point: 74–76 °C; ¹H NMR (400 MHz, CDCl₃) δ 8.14 (dd, *J* = 4.5, 3.3 Hz, 1H), 7.54 (td, *J* = 8.5, 1.8 Hz, 1H), 7.23 (d, *J* = 7.8 Hz, 1H), 7.11 (t, *J* = 7.6 Hz, 1H), 7.03 (d, *J* = 8.3 Hz, 1H), 6.95 – 6.88 (m, 2H), 6.80 (dd, *J* = 8.2, 1.9 Hz, 1H), 4s.66 (s, 2H), 4.26 (t, *J* = 6.5 Hz, 2H), 4.00 (t, *J* = 6.1 Hz, 2H), 1.98 (dd, *J* = 14.7, 7.0 Hz, 2H), 1.90 – 1.82 (m, 2H), 1.72 – 1.65 (m, 2H), OH and COOH peaks are exchanged with deuterium of CDCl₃; ¹³C NMR (100 MHz, CDCl₃) δ 165.9, 157.7, 156.6, 135.1, 133.6, 129.1, 129.1, 128.8, 122.1, 120.7, 118.0, 112.8, 111.1, 69.9, 67.5, 61.9, 60.5, 28.9, 22.8, 21.1, 14.3; FTIR (neat): 3257, 2931, 2857, 1721, 1601, 1455, 1270 cm⁻¹; HRMS (ESI-TOF) *m/z*: [M + H]⁺ calcd for C₁₉H₂₃O₅Na, 331.1545, found 331.1542.

2-(3-(2-(hydroxymethyl)phenoxy)propoxy)benzoic acid (153b): Prepared according to general experimental procedure 3.9.2C, 1,4-dioxane (2.0 mL) solution of **SM-2** (200 mg, 0.60 mmol), 5.N NaOH solution (5.0 mL) was added. The reaction mixture was stirred at 80 °C in oil bath for overnight. After, the residue was purified by using column chromatography (EtOAc:*n*-hexane = 60:40) as

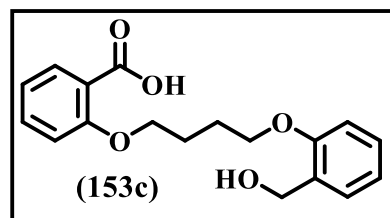


the eluent to afford **153b** (170 mg, 93% yield) as a solid. melting point: 130–132 °C; ¹H NMR (400 MHz, CDCl₃) δ 8.17 (dd, *J* = 7.8, 1.8 Hz, 1H), 7.59 – 7.52 (m, 1H), 7.29 (dd, 2H), 7.17 – 7.11 (m, 1H), 7.08 (d, *J* = 8.4 Hz, 1H), 6.98 (t, *J* = 7.2 Hz, 1H), 6.90 (d, *J* = 8.2 Hz, 1H), 4.70 (s, 2H), 4.48 (t, *J* = 6.2 Hz, 2H), 4.25 (t, *J* = 5.8 Hz, 2H), 2.44 (p, *J* = 6.0 Hz, 2H), OH and

COOH peaks are exchanged with deuterium of CDCl₃; ¹³C NMR (100 MHz, CDCl₃) δ 165.5, 157.5, 156.3, 135.2, 134.0, 129.3, 129.2, 129.1, 122.5, 121.5, 118.1, 112.8, 111.5, 67.2, 64.3, 61.7, 29.2; FTIR (neat): 3274, 2926, 2854, 1722, 1600, 1490, 1291 cm⁻¹; HRMS (ESI-TOF) *m/z*: [M + Na]⁺ calcd for C₁₇H₁₈O₅Na, 325.1052, found 325.1046.

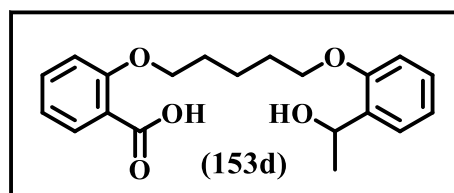
2-(4-(2-(hydroxymethyl)phenoxy)butoxy)benzoic acid

(153c): Prepared according to general experimental procedure 3.9.2C, 1,4-dioxane (2.0 mL) solution of **SM-3** (200 mg, 0.58 mmol), 5N NaOH solution (5.0 mL) was added. The reaction mixture was stirred at 80 °C in an oil



bath for overnight. After, the residue was purified by using column chromatography (EtOAc:*n*-hexane = 60:40) as the eluent to afford **153c** (160 mg, 87% yield) as a solid. melting point: 118-120 °C; ¹H NMR (400 MHz, CDCl₃) δ 8.16 (dd, *J* = 7.9, 1.8 Hz, 1H), 7.55 (ddd, *J* = 8.4, 7.5, 1.8 Hz, 1H), 7.32 – 7.28 (m, 1H), 7.28 – 7.23 (m, 1H), 7.16 – 7.10 (m, 1H), 7.06 (d, *J* = 8.4 Hz, 1H), 6.96 (t, *J* = 7.5 Hz, 1H), 6.87 (d, *J* = 8.1 Hz, 1H), 4.70 (s, 2H), 4.34 (t, *J* = 6.2 Hz, 2H), 4.11 (t, *J* = 5.8 Hz, 2H), 2.18 – 2.10 (m, 2H), 2.09 – 2.00 (m, 2H), OH and COOH peaks are exchanged with deuterium of CDCl₃; ¹³C NMR (100 MHz, CDCl₃) δ 165.8, 157.6, 156.5, 135.1, 133.8, 129.1, 128.9, 122.3, 121.0, 117.9, 112.7, 111.1, 69.8, 67.1, 61.9, 26.2, 26.1; FTIR (neat): 3274, 2926, 2854, 1722, 1455, 1253 cm⁻¹; HRMS (ESI-TOF) *m/z*: [M + Na]⁺ calcd for C₁₈H₂₀O₅Na, 339.1208, found 339.1208.

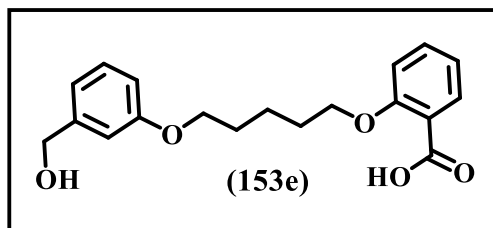
2-((5-(2-(1-hydroxyethyl)phenoxy)pentyl)oxy)benzoic acid (153d): Prepared according to general experimental procedure 3.9.2C, 1,4-dioxane (3.0 mL) solution of ethyl 2-((5-(2-(1-hydroxyethyl)phenoxy)pentyl)oxy)benzoate **SM-4** (600 mg, 1.6 mmol), 5N NaOH solution (5.0 mL) was



added. The reaction mixture was stirred at 80 °C in oil bath for overnight. After, the residue was purified by using column chromatography (EtOAc:*n*-hexane = 60:40) as the eluent to afford **153d** (475 mg, 85% yield) as a semi solid. ¹H NMR (400 MHz, CDCl₃) δ 8.17 (dd, *J* = 7.8, 1.8 Hz, 1H), 7.55 (ddd, *J* = 8.4, 7.4, 1.8 Hz, 1H), 7.36 (dd, *J* = 7.5, 1.6 Hz, 1H), 7.25 – 7.19 (m, 1H), 7.16 – 7.09 (m, 1H), 7.04 (d, *J* = 8.4 Hz, 1H), 6.99 (s, 1H), 6.85 (t, *J* = 8.2 Hz, 1H), 5.19 – 5.01 (q, 1H), 4.29 (t, *J* = 6.4 Hz, 2H), 4.06 (t, *J* = 6.1 Hz, 2H), 2.05 – 1.97 (m, 2H), 1.97 – 1.89 (m, *J* = 12.3, 6.4 Hz, 2H), 1.80 – 1.65 (m, 2H), 1.49 (t, *J* = 7.4 Hz, 3H), OH and COOH peaks are exchanged with deuterium of CDCl₃; ¹³C NMR (100 MHz, CDCl₃) δ 165.5, 157.5, 155.7, 134.9, 133.8, 133.4, 128.3, 126.1, 122.2, 120.9, 117.9, 112.6, 111.1, 69.9, 67.3,

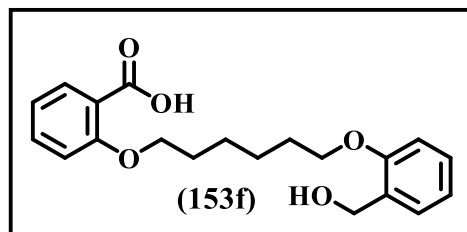
66.3, 29.0, 28.8, 23.1, 22.8; FTIR (neat): 3330, 2944, 2873, 1636, 1559 cm^{-1} ; HRMS (ESI-TOF) m/z : $[M + H]^+$ calcd for $\text{C}_{20}\text{H}_{25}\text{O}_5$, 345.1702, found 345.1705.

2-((5-(3-(hydroxymethyl)phenoxy)pentyl)oxy)benzoic acid (153e): Prepared according to general experimental procedure 3.9.2C, 1,4-dioxane (3.0 mL) solution of **SM-5** (300 mg, 0.83 mmol), 5N NaOH solution (5.0 mL) was added. The reaction mixture was stirred at 80 °C in an oil bath for overnight. After, the residue was purified by using



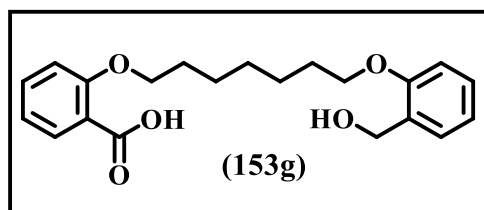
column chromatography (EtOAc:*n*-hexane =60:40) as the eluent to afford **153e** (250 mg, 90%) as a solid. melting point: 75-77 °C; ^1H NMR (400 MHz, CDCl_3) δ 8.17 (dd, J = 7.8, 1.7 Hz, 1H), 7.55 (ddd, J = 8.3, 7.6, 1.8 Hz, 1H), 7.29 – 7.22 (m, 1H), 7.15 – 7.09 (m, 1H), 7.04 (d, J = 8.5 Hz, 1H), 6.92 (d, J = 7.4 Hz, 2H), 6.84 – 6.78 (m, 1H), 4.67 (s, 2H), 4.28 (t, J = 6.5 Hz, 2H), 4.01 (t, J = 6.1 Hz, 2H), 1.99 (dd, J = 15.0, 6.8 Hz, 2H), 1.93 – 1.83 (m, 2H), 1.74 – 1.65 (m, 2H), OH and COOH peaks are exchanged with deuterium of CDCl_3 ; ^{13}C NMR (100 MHz, CDCl_3) δ 165.6, 159.2, 157.6, 142.7, 135.2, 133.9, 129.7, 122.3, 119.3, 117.8, 113.8, 113.1, 112.7, 70.1, 67.4, 65.3, 28.8, 22.7; FTIR (neat): 3257, 2931, 2857, 1721, 1601, 1487, 1257 cm^{-1} ; HRMS (ESI-TOF) m/z : $[M + \text{Na}]^+$ calcd for $\text{C}_{19}\text{H}_{22}\text{O}_5\text{Na}$, 353.1364, found 353.1356.

2-((6-(2-(hydroxymethyl)phenoxy)hexyl)oxy)benzoic acid (153f): Prepared according to general experimental procedure 3.9.2C, 1,4-dioxane (3.0 mL) solution of **SM-6** (350 mg, 0.93 mmol), 5N NaOH solution (5.0 mL) was added. The reaction mixture was stirred at 80 °C in an oil bath for overnight. After, the residue was purified by using column



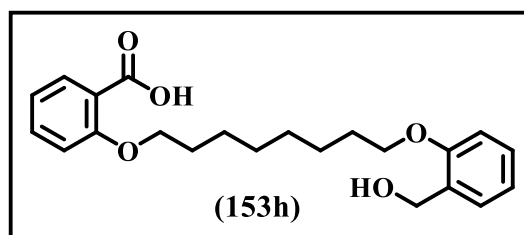
chromatography (EtOAc/*n*-hexane = 60:40) as the eluent to afford **153f** (300 mg, 92% yield) as a solid. melting point: 83-85 °C; ^1H NMR (400 MHz, CDCl_3) δ 8.17 (dd, J = 7.8, 1.8 Hz, 1H), 7.55 (ddd, J = 8.4, 7.4, 1.8 Hz, 1H), 7.29 – 7.23 (m, 2H), 7.15 – 7.10 (m, 1H), 7.04 (d, J = 8.1 Hz, 1H), 6.93 (td, J = 7.5, 0.8 Hz, 1H), 6.87 (d, J = 8.1 Hz, 1H), 4.69 (s, 2H), 4.26 (t, J = 6.5 Hz, 2H), 4.04 (t, J = 6.3 Hz, 2H), 2.62 (s, 1H), 2.00 – 1.91 (m, 2H), 1.86 (dd, J = 12.5, 6.1 Hz, 2H), 1.62 – 1.55 (m, 4H), COOH peak exchanged with deuterium of CDCl_3 ; ^{13}C NMR (100 MHz, CDCl_3) δ 165.6, 157.6, 156.9, 135.1, 133.9, 129.2, 129.1, 128.8, 122.3, 120.8, 117.9, 112.7, 111.2, 70.2, 67.7, 62.3, 29.2, 29.1, 26.3, 25.8; FTIR (neat): 3253, 2937, 2864, 1723, 1491, 1238 cm^{-1} ; HRMS (ESI-TOF) m/z : $[M + H]^+$ calcd for $\text{C}_{20}\text{H}_{25}\text{O}_5$, 345.1702, found 345.1705.

2-((7-(2-(hydroxymethyl)phenoxy)heptyl)oxy)benzoic acid (153g): Prepared according to general experimental procedure 3.9.2C, 1,4-dioxane (2.0 mL) solution of **SM-7** (250 mg, 0.64 mmol), 5N NaOH solution (5.0 mL) was added. The reaction mixture was stirred at 80 °C in an oil bath for overnight. After, the residue was purified by using



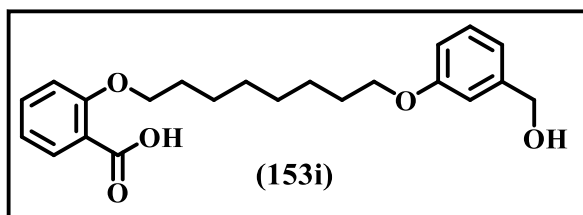
column chromatography (EtOAc:*n*-hexane = 60:40) as the eluent to afford **153g** (205 mg, 88% yield) as a semi-solid. ¹H NMR (400 MHz, CDCl₃) δ 8.18 (dd, *J* = 7.8, 1.8 Hz, 1H), 7.58 – 7.52 (m, 1H), 7.26 (m, 1H), 7.13 (t, *J* = 7.5 Hz, 2H), 7.04 (d, *J* = 8.4 Hz, 1H), 6.93 (t, *J* = 7.3 Hz, 1H), 6.87 (d, *J* = 8.0 Hz, 1H), 4.70 (s, 2H), 4.26 (t, *J* = 6.5 Hz, 2H), 4.03 (t, *J* = 6.4 Hz, 2H), 2.00 – 1.90 (m, 2H), 1.88 – 1.78 (m, 2H), 1.57 – 1.45 (m, 6H); OH and COOH peaks are exchanged with deuterium of CDCl₃; ¹³C NMR (100 MHz, CDCl₃) δ 165.6, 157.69, 157.0, 135.1, 133.9, 129.2, 129.1, 128.8, 122.3, 120.7, 117.9, 112.7, 111.2, 70.3, 67.9, 62.5, 29.3, 29.3, 28.9, 26.1, 25.9; FTIR (neat): 3257, 2935, 2839, 1725, 1602, 1456 cm⁻¹; HRMS (ESI-TOF) *m/z*: [M + Na]⁺ calcd for C₂₁H₂₆O₅Na, 381.1672, found 381.1662.

2-((8-(2-(hydroxymethyl)phenoxy)octyl)oxy)benzoic acid (153h): Prepared according to general experimental procedure 3.9.2C, 1,4-dioxane (2.0 mL) solution of **SM-8** (200 mg, 0.5 mmol), 5N



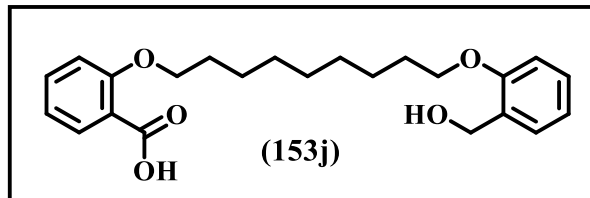
NaOH solution (5.0 mL) was added. The reaction mixture was stirred at 80 °C in an oil bath for overnight. After, the residue was purified by using column chromatography (EtOAc:*n*-hexane = 60:40) as the eluent to afford **153h** (170 mg, 91% yield) as a solid. melting point: 77-78 °C; ¹H NMR (400 MHz, CDCl₃) δ 8.18 (dd, 1H), 7.55 (ddd, 1H), 7.29 – 7.22 (m, 2H), 7.16 – 7.09 (m, 1H), 7.04 (d, *J* = 8.3 Hz, 1H), 6.92 (t, *J* = 7.4 Hz, 1H), 6.87 (d, *J* = 8.1 Hz, 1H), 4.70 (s, 2H), 4.24 (t, 2H), 4.01 (t, *J* = 8.5, 4.2 Hz, 2H), 1.96 – 1.87 (m, 2H), 1.86 – 1.77 (m, 2H), 1.50 (dd, *J* = 14.0, 7.0 Hz, 4H), 1.42 (d, *J* = 3.0 Hz, 4H), OH and COOH peaks are exchanged with deuterium of CDCl₃; ¹³C NMR (100 MHz, CDCl₃) δ 165.7, 157.7, 157, 135.1, 133.8, 129.2, 129.0, 128.7, 122.2, 120.6, 117.8, 112.7, 111.1, 70.3, 67.9, 62.4, 60.5, 29.4, 29.3, 29.2, 29.1, 26.2, 25.9, 21.2; FTIR (neat): 3254, 2930, 2856, 1722, 1600, 1455, 1236 cm⁻¹; HRMS (ESI-TOF) *m/z*: [M + Na]⁺ calcd for C₂₂H₂₈O₅Na, 395.1834, found 395.1835.

2-((8-(3-(hydroxymethyl)phenoxy)octyl)oxy)benzoic acid (153i): Prepared according to general experimental procedure 3.9.2C, 1,4-dioxane (2.0 mL) solution of **SM-9** (250 mg, 0.62 mmol), 5N NaOH solution (5.0 mL) was added. The reaction mixture was stirred at 80



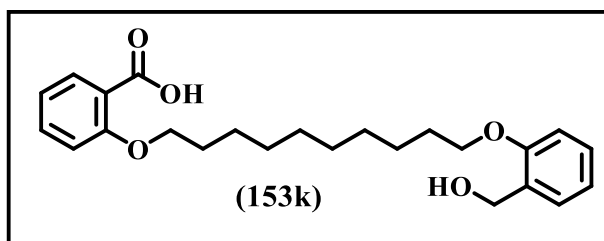
°C in an oil bath for overnight. After, the residue was purified by using column chromatography (EtOAc:*n*-hexane = 60:40) as the eluent to afford **153i** (169 mg, 90% yield) as a solid. melting point: 78-80 °C; ¹H NMR (400 MHz, CDCl₃) δ 8.16 (dd, *J* = 7.8, 1.8 Hz, 1H), 7.53 (ddd, *J* = 8.6, 7.4, 1.9 Hz, 1H), 7.23 (dd, *J* = 10.0, 5.3 Hz, 1H), 7.13 – 7.07 (m, 1H), 7.04 – 7.00 (m, 1H), 6.93 – 6.87 (m, 2H), 6.79 (dd, *J* = 7.9, 2.3 Hz, 1H), 4.64 (s, 2H), 4.23 (t, *J* = 6.5 Hz, 2H), 3.94 (t, *J* = 6.5 Hz, 2H), 1.95 – 1.85 (m, 2H), 1.80 – 1.72 (m, 2H), 1.53 – 1.43 (m, 4H), 1.43 – 1.36 (m, 4H), OH and COOH peaks are exchanged with deuterium of CDCl₃; ¹³C NMR (100 MHz, CDCl₃) δ 165.6, 159.4, 157.7, 142.7, 135.1, 133.9, 129.6, 122.2, 119.1, 117.7, 113.8, 113, 112.7, 70.3, 67.9, 65.3, 29.3, 29.2, 29.0, 26.2, 25.9; FTIR (neat): 3258, 2931, 2857, 1722, 1601, 1457 cm⁻¹; HRMS (ESI-TOF) *m/z*: [M + Na]⁺ calcd for C₂₂H₂₈O₅Na, 395.1834, found 395.1835.

2-((9-(2-(hydroxymethyl)phenoxy)nonyl)oxy)benzoic acid (153j): Prepared according to general experimental procedure 3.9.2C, 1,4-dioxane (2.0 mL) solution of **SM-10** (230 mg, 0.55 mmol), 5N NaOH solution (5.0 mL) was added. The reaction mixture was stirred



at 80 °C in an oil bath for overnight. After, the residue was purified by using column chromatography (EtOAc:*n*-hexane = 60:40) as the eluent to afford **120j** (200 mg, 93% yield) as a solid. melting point: 172-174 °C; ¹H NMR (400 MHz, CDCl₃) δ 8.18 (dd, *J* = 7.8, 1.8 Hz, 1H), 7.54 (ddd, *J* = 8.4, 7.5, 1.8 Hz, 1H), 7.27 – 7.21 (m, 2H), 7.12 (dd, *J* = 11.2, 4.0 Hz, 1H), 7.03 (d, *J* = 8.4 Hz, 1H), 6.92 (dd, *J* = 11.1, 3.8 Hz, 1H), 6.86 (d, *J* = 7.9 Hz, 1H), 4.68 (s, 2H), 4.24 (t, *J* = 6.5 Hz, 2H), 4.01 (t, *J* = 6.4 Hz, 2H), 1.90 (dd, *J* = 14.8, 6.8 Hz, 2H), 1.80 (dd, *J* = 14.6, 6.6 Hz, 2H), 1.54 – 1.43 (m, 4H), 1.40-1.38 (m, 6H), OH and COOH peaks are exchanged with deuterium of CDCl₃; ¹³C NMR (100 MHz, CDCl₃) δ 165.5, 157.7, 157.1, 135.1, 133.9, 129.2, 129.1, 128.8, 122.3, 120.6, 117.8, 112.7, 111.2, 70.4, 68.0, 62.5, 29.4, 29.4, 29.3, 29.2, 29.1, 26.2, 25.9; FTIR (neat): 3256, 2926, 2854, 1726, 1602, 1490, 1235 cm⁻¹; HRMS (ESI-TOF) *m/z*: [M + Na]⁺ calcd for C₂₃H₃₀O₅Na, 409.1990, found 409.1985.

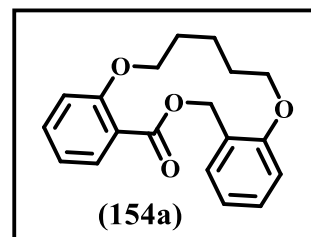
2-((10-(2-(hydroxymethyl)phenoxy)decyl)oxy)benzoic acid (153k): Prepared according to general experimental procedure 3.9.2C, 1,4-dioxane (5.0 mL) solution of **SM-11** (380 mg, 0.88 mmol), 5N NaOH solution (15 mL) was added. The reaction mixture was stirred at 80 °C in an oil bath for overnight.



After workup, the residue was purified by using column chromatography (EtOAc:*n*-hexane = 60:40) as the eluent to afford **153k** (320 mg, 90% yield) as a solid. melting point: 80-82 °C; ¹H NMR (400 MHz, CDCl₃) δ 8.15 (s, 1H), 7.53 (d, *J* = 0.7 Hz, 1H), 7.26 (d, *J* = 7.1 Hz, 2H), 7.10 (s, 1H), 7.03 (s, 1H), 6.90 (s, 1H), 6.86 (s, 1H), 4.68 (s, 2H), 4.22 (t, *J* = 6.5 Hz, 2H), 3.99 (t, *J* = 6.4 Hz, 2H), 1.94 – 1.84 (m, 2H), 1.79 (dq, *J* = 13.0, 6.5 Hz, 2H), 1.52 – 1.41 (m, 4H), 1.40 – 1.27 (m, *J* = 21.5 Hz, 8H), OH and COOH peaks are exchanged with deuterium of CDCl₃; ¹H NMR (400 MHz, DMSO) δ 12.50 (s, 1H), 7.60 (d, *J* = 7.6 Hz, 1H), 7.48 – 7.43 (m, 1H), 7.36 (d, *J* = 7.2 Hz, 1H), 7.20 – 7.14 (m, 1H), 7.09 (d, *J* = 8.4 Hz, 1H), 6.97 (dd, *J* = 11.0, 3.9 Hz, 1H), 6.91 (t, *J* = 7.2 Hz, 2H), 4.95 (s, 1H), 4.49 (s, 2H), 4.00 (t, *J* = 6.3 Hz, 2H), 3.94 (t, *J* = 6.3 Hz, 2H), 1.74 – 1.64 (m, 4H), 1.48 – 1.36 (m, 4H), 1.29 (s, 8H). ¹³C NMR (100 MHz, CDCl₃) δ 165.6, 157.7, 157, 135.1, 133.8, 129.2, 128.9, 128.6, 122.1, 120.5, 117.8, 112.7, 111.1, 70.4, 67.9, 62.3, 29.4, 29.3, 29.32, 29.2, 28.9, 26.2, 25.9; FTIR (neat): 3256, 2926, 2854, 1726, 1602, 1490, 1235 cm⁻¹; HRMS (ESI-TOF) *m/z*: [M + Na]⁺ calcd for C₂₄H₃₂O₅Na, 423.2147, found 423.2149.

7,8,9,10-tetrahydro-6*H*,16*H*,18*H*-dibenzo[*b,g*][1,5,9]trioxacyclotetradecin-16-one

(154a)²⁵: Prepared according to general experimental procedure 3.9.2D, a solution of **153a** (0.015 M, 49.5 mg) and (0.036 M, 91.8 mg) of Mukaiyama salt with CH₃CN in a vial. 1-methylimidazole (0.03 M, 25 mg) was dissolved in another vial with CH₃CN. Both reagent solutions were flown through the 7 mL PFA tubing at 80

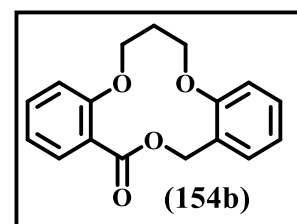


°C in a preheated water bath with 3-4 bar pressure. After workup, the residue was purified by using column chromatography (EtOAc:*n*-hexane = 10:90) as the eluent to afford the desired product **154a** (25.5 mg, 54% yield) as a solid and starting material recovered **153a** (11.6 mg, 35.11 %). **In batch condition:** compound **153a** (0.015 M, 49.5 mg) and (0.036 M, 91.8 mg) of Mukaiyama salt and 1-methylimidazole (0.03 M, 25 mg) in CH₃CN solvent were heated at 80 °C in the preheated oil path for 24 hrs to afford the desired product **154a** (8.4 mg, 17 % yield). melting point: 86-89 °C. ¹H NMR (400 MHz, CDCl₃) 7.77 (dd, *J* = 7.7, 1.8 Hz, 1H), 7.44 (dd,

$J = 7.4, 1.7$ Hz, 1H), 7.38 (ddd, $J = 8.4, 7.4, 1.8$ Hz, 1H), 7.34 – 7.28 (m, 1H), 6.96 – 6.92 (m, 1H), 6.90 (ddd, $J = 8.2, 3.2, 2.2$ Hz, 2H), 6.84 (d, $J = 8.3$ Hz, 1H), 5.39 (s, 2H), 4.13 (t, $J = 5.3$ Hz, 2H), 3.98 (t, 2H), 1.98 – 1.86 (m, $J = 11.1, 5.6$ Hz, 4H), 1.80 – 1.69 (m, $J = 10.5, 5.5$ Hz, 2H). ^{13}C NMR (100 MHz, CDCl_3) δ 168.5, 158.5, 158.2, 133.1, 131.9, 130.6, 123.9, 121.3, 120.2, 120.1, 112.6, 111.4, 67.8, 64.9, 63.6, 27.2, 26.6, 20.5; FTIR (neat): 1695, 1598, 1245, 1121 cm^{-1} . HRMS (ESI-TOF) m/z : $[\text{M} + \text{Na}]^+$ calcd for $\text{C}_{19}\text{H}_{20}\text{O}_4\text{Na}$, 335.1259, found 335.1253.

7,8-dihydro-6*H*,14*H*,16*H*-dibenzo[*b,g*][1,5,9]trioxacyclododecin-14-one (154b)²⁵:

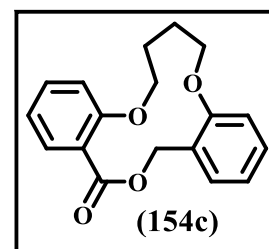
Prepared according to general experimental procedure 3.9.2D, a solution of **153b** (0.015 M, 45.3 mg) and (0.036 M, 91.8 mg) of Mukaiyama salt with CH_3CN in a vial. 1-methylimidazole (0.03 M, 25 mg) was dissolved in another vial with CH_3CN . Both reagent solutions were flown through the 7 mL PFA tubing at 80 °C in a



preheated water bath with 3-4 bar pressure. After workup, the residue was purified by using column chromatography ($\text{EtOAc}/n\text{-hexane} = 10:90$) as the eluent to afford the desired product **154b** (30 mg, 70% yield) as a solid and starting material recovered **153b** (4 mg, 13%). **In batch condition:** compound **153b** (0.015 M, 45.3 mg) and (0.036 M, 91.8 mg) of Mukaiyama salt and 1-methylimidazole (0.03 M, 25 mg) in CH_3CN solvent were heated at 80 °C in the preheated oil path for 24 hrs to afford the desired product **154b** (11 mg, 25 % yield); melting point: 107-109 °C; ^1H NMR (400 MHz, CDCl_3) δ 7.69 (dd, $J = 7.7, 1.7$ Hz, 1H), 7.38 (dd, $J = 7.2, 1.5$ Hz, 2H), 7.31 (td, $J = 8.1, 1.7$ Hz, 1H), 7.01 (dd, $J = 7.5, 0.8$ Hz, 1H), 6.94 (ddd, $J = 8.3, 7.6, 2.0$ Hz, 3H), 5.37 (s, 2H), 4.18 (t, $J = 5.0$ Hz, 2H), 4.08 (t, $J = 5.1$ Hz, 2H), 2.09 – 1.94 (m, $J = 15.0, 8.3, 3.9$ Hz, 4H). ^{13}C NMR (100 MHz, CDCl_3) δ 167.9, 158.8, 158.4, 132.9, 132.3, 131.0, 130.5, 125.3, 123.7, 121.5, 120.9, 116.9, 113.9, 68.5, 64.4, 27.2, 26.6. FTIR (neat): 1709, 1600, 1254, 1128 cm^{-1} ; HRMS (ESI-TOF) m/z : $[\text{M} + \text{Na}]^+$ calcd for $\text{C}_{17}\text{H}_{18}\text{O}_4\text{Na}$, 307.0946, found 307.0936.

6,7,8,9-tetrahydro-15*H*,17*H*-dibenzo[*b,g*][1,5,9]trioxacyclotridecin-15-one (154c)²⁵:

Prepared according to general experimental procedure 3.9.2D, (0.015 M, 47.4 mg) of **153c** and (0.036 M, 91.8 mg) of Mukaiyama salt with CH_3CN in a vial. 1-methylimidazole (0.03 M, 25 mg) was dissolved in another vial with CH_3CN . Both reagent solutions were flown through the 7 mL PFA tubing at 80 °C in preheated water bath with 3-4 bar pressure. After workup, the residue was purified by using column chromatography

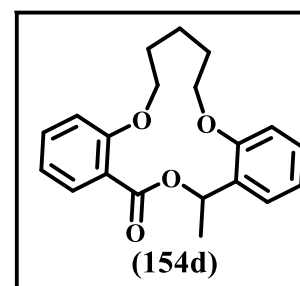


(EtOAc:*n*-hexane = 10:90) as the eluent to afford the desired product of **154c** (30.4 mg, 68 %) as an oily product.

Large-scale synthesis of compound 154c: For large scale, 2-(4-(2-(hydroxymethyl)phenoxy)butoxy)benzoic acid **153c** (0.015 M, 3.41 gm, 10.80 mmol) and Mukaiyama salt (0.036 M, 6.6 gm, 25.88 mmol) was dissolved with CH₃CN in a reagent bottle. Then, 1-methylimidazole (0.03 M, 1.77 mg, 21.55 mmol) was dissolved in another reagent bottle with CH₃CN. Both the reagent solutions were flown through the 7 mL PFA tubing in 80 °C in a preheated water bath with 3-4 bar pressure. After workup, the residue was purified by using column chromatography (EtOAc:*n*-hexane = 10:90) as the eluent to afford the desired product of **154c** (1.76 gm, 5.63 mmol, 52%) as an oily product and starting material recovered of **153a** (1.03 gm, 32%). ¹H NMR (400 MHz, CDCl₃) δ 7.69 (dd, *J* = 7.7, 1.7 Hz, 1H), 7.38 (dd, *J* = 7.2, 1.5 Hz, 2H), 7.31 (td, *J* = 8.1, 1.7 Hz, 1H), 7.01 (dd, *J* = 7.5, 0.8 Hz, 1H), 6.94 (ddd, *J* = 8.3, 7.6, 2.0 Hz, 3H), 5.37 (s, 2H), 4.18 (t, *J* = 5.0 Hz, 2H), 4.08 (t, *J* = 5.1 Hz, 2H), 2.09 – 1.94 (m, *J* = 15.0, 8.3, 3.9 Hz, 4H); ¹³C NMR (100 MHz, CDCl₃) δ 167.9, 158.8, 158.4, 132.9, 132.3, 131.0, 130.5, 125.3, 123.7, 121.5, 120.9, 116.9, 113.9, 71.1, 69.0, 64.4, 27.2, 26.6; FTIR (neat): 1706, 1599, 1250, 1121 cm⁻¹; HRMS (ESI-TOF) *m/z*: [M + Na]⁺ calcd for C₁₈H₁₈O₄Na, 321.1102, found 321.1101.

18-methyl-7,8,9,10-tetrahydro-6*H*,16*H*,18*H*-dibenzo[*b,g*][1,5,9]trioxacyclotetradecin-16-

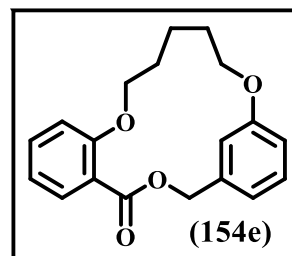
one (154d): Prepared according to general experimental procedure 3.9.2D, a solution of **153d** (0.015 M, 51.6 mg) and (0.036 M, 91.8 mg) of Mukaiyama salt with CH₃CN in a vial. 1-methylimidazole (0.03 M, 25 mg) was dissolved in another vial with CH₃CN. Both the reagent solutions were flown through the 7 mL PFA tubing in 80 °C in preheated water bath with 3-4 bar pressure. After workup,



the residue was purified by using column chromatography (EtOAc:*n*-hexane = 10:90) as the eluent to afford the desired product **154d** (16 mg, 32%) as sticky oil product and starting material recovered **153d** (5mg, 14%) ¹H NMR (400 MHz, CDCl₃) δ 7.68 (dd, *J* = 7.7, 1.8 Hz, 1H), 7.43 (dd, *J* = 7.5, 1.7 Hz, 1H), 7.36 (ddd, *J* = 8.4, 7.5, 1.8 Hz, 1H), 7.30 – 7.25 (m, 1H), 6.95 – 6.90 (m, 2H), 6.87 (dd, *J* = 8.4, 4.3 Hz, 2H), 6.34 (q, *J* = 6.7 Hz, 1H), 4.18 (dt, *J* = 8.6, 4.2 Hz, 1H), 4.10 – 4.00 (m, 2H), 3.93 (td, *J* = 9.4, 2.6 Hz, 1H), 2.14 – 1.80 (m, 7H), 1.76 – 1.65 (m, 2H); ¹³C NMR (100 MHz, CDCl₃) δ 167.5, 158.2, 132.7, 131.3, 130.3, 129.9, 127.5, 122.6, 120.2, 120, 113.7, 111.4, 71.6, 68.6, 65.3, 27.5, 26.9, 21.1, 18.4; FTIR (neat): 2931,

2871, 1723, 1699, 1601, 1234 cm^{-1} . HRMS (ESI-TOF) m/z : $[\text{M} + \text{Na}]^+$ calcd for $\text{C}_{20}\text{H}_{22}\text{O}_4\text{Na}$, 349.1415, found 349.1416.

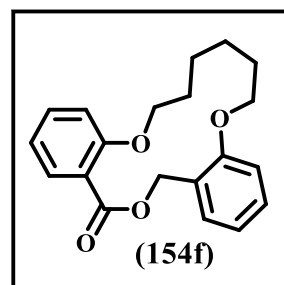
3,6,12-trioxa-1(1,2),5(1,3)-dibenzenacyclododecaphan-2-one (154e)²⁵: Prepared according to general experimental procedure 3.9.2D, a solution of **153e** (0.015 M, 49.5 mg) and (0.036 M, 91.8 mg) of Mukaiyama salt with CH_3CN in a vial and 1-methylimidazole (0.03 M, 25 mg) was dissolved in another vial with CH_3CN . Both reagent solutions were



flowed through the 7 mL PFA tubing in 80 °C in a preheated water bath with 3-4 bar pressure. After workup, the residue was purified by using column chromatography ($\text{EtOAc}:n\text{-hexane} = 10:90$) as the eluent to afford the desired product **154e** (12.6 mg, 27% yield) as a solid, melting point: 86-88 °C; and starting material recovered **153e** (9.5 mg, 28%) **In batch condition**: compound **153e** (0.015 M, 49.5 mg) and (0.036 M, 91.8 mg) of Mukaiyama salt and 1-methylimidazole (0.03 M, 25 mg) in CH_3CN solvent were heated at 80 °C in the preheated oil path for 24 hrs to no product formation **154e**. ^1H NMR (400 MHz, CDCl_3) δ 7.79 (dd, $J = 7.7, 1.8$ Hz, 1H), 7.50 – 7.44 (m, 1H), 7.30 (dd, $J = 9.7, 6.2$ Hz, 2H), 7.03 (dd, $J = 11.5, 4.1$ Hz, 2H), 6.98 (d, $J = 4.8$ Hz, 1H), 6.95 (dd, $J = 8.2, 2.4$ Hz, 1H), 5.42 (s, 2H), 4.28 (t, $J = 5.8$ Hz, 2H), 4.11 (t, 2H), 1.92 (dt, $J = 10.3, 5.8$ Hz, 2H), 1.83 (dd, $J = 12.3, 6.0$ Hz, 2H), 1.79 – 1.71 (m, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 167.7, 159.7, 158, 138.1, 133.2, 131.6, 129.5, 121.3, 120.8, 120.3, 118.5, 114.8, 113.1, 69.1, 68.8, 66.8, 29.2, 28.7, 23.4; FTIR (neat): 1724, 1595, 1261, 1160 cm^{-1} . HRMS (ESI-TOF) m/z : $[\text{M} + \text{Na}]^+$ calcd for $\text{C}_{19}\text{H}_{20}\text{O}_4$, 335.1259, found 335.1256.

6,7,8,9,10,11-hexahydro-17H,19H-dibenzo[*b,g*][1,5,9]trioxacyclopentadecin-17-one

(154f)²⁵: Prepared according to general experimental procedure 3.9.2D, a solution of **153f** (0.015 M, 51.6 mg) and (0.036 M, 91.8 mg) of Mukaiyama salt with CH_3CN in a vial and 1-methylimidazole (0.03 M, 25 mg) was dissolved in another vial with CH_3CN . Both the reagent solutions were

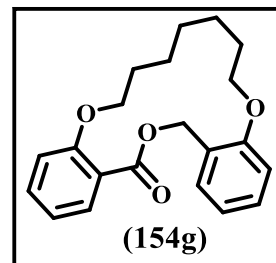


flowed through the 7 mL PFA tubing in 80 °C in a preheated water bath with 3-4 bar pressure. After workup, the residue was purified by using column chromatography ($\text{EtOAc}:n\text{-hexane} = 6:94$) as the eluent to afford the desired product **154f** (27.9 mg, 57% yield) as a semi solid and starting material recovered **153f** (8.4 mg, 24%); ^1H NMR (400 MHz, CDCl_3) δ 7.71 (dd, $J = 8.0, 1.8$ Hz, 1H), 7.46 (dd, $J = 7.4, 1.7$ Hz, 1H), 7.40 – 7.34 (m, 1H), 7.32 – 7.27 (m, 1H), 6.93 (dd, $J = 4.9, 3.8$ Hz, 2H), 6.90 – 6.86 (m, 2H), 5.42 (s, 2H), 4.11 (t, 2H), 4.07 (t, 2H), 1.89 – 1.81 (m, 2H), 1.81

– 1.72 (m, J = 6.8, 4.0 Hz, 4H), 1.70 – 1.62 (m, 2H); $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3) δ 167.9, 158.3, 157.5, 132.9, 132.8, 131.5, 130.4, 124.3, 121.9, 120.2, 120.0, 112.8, 111.5, 68.7, 68.6, 62.8, 28.8, 27.4, 26.9; FTIR (neat): 1699, 1598, 1247, 1124 cm^{-1} ; HRMS (ESI-TOF) m/z : $[\text{M} + \text{Na}]^+$ calcd for $\text{C}_{20}\text{H}_{22}\text{O}_4\text{Na}$, 349.1415, found 349.1417.

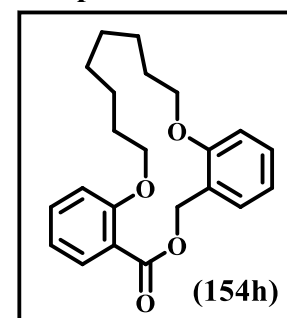
7,8,9,10,11,12-hexahydro-6*H*,18*H*,20*H*-dibenzo[*b,g*][1,5,9]trioxacyclohexadecin-18-one (154g)²⁵:

Prepared according to general experimental procedure D, a solution of **153g** (0.015 M, 53.7 mg) and (0.036 M, 91.8 mg) of Mukaiyama salt with CH_3CN in a vial. 1-methylimidazole (0.03 M, 25 mg) was dissolved in another vial with CH_3CN . Both the reagent solutions were flown through the 7 mL PFA tubing in 80 °C in a preheated water bath with 3-4 bar pressure. After workup, the residue was purified by using column chromatography ($\text{EtOAc}:n\text{-hexane}$ = 10:90) as the eluent to afford the desired product **154g** (20.5 mg, 40% yield) as semi-solid and starting material recovered **153g** (13 mg, 36%); ^1H NMR (400 MHz, CDCl_3) δ 7.69 (dd, J = 8.0, 1.8 Hz, 1H), 7.47 (dd, J = 7.5, 1.7 Hz, 1H), 7.40 – 7.34 (m, 1H), 7.32 – 7.27 (m, 1H), 6.96 – 6.87 (m, 4H), 5.42 (s, 2H), 4.06 (t, J = 5.5 Hz, 2H), 4.02 (t, J = 5.4 Hz, 2H), 1.80 (m, J = 12.1, 5.8 Hz, 4H), 1.58 (m, J = 12.6, 6.2 Hz, 6H). ^{13}C NMR (100 MHz, CDCl_3) δ 167.6, 158.3, 158.1, 132.8, 132.7, 131.4, 130.4, 129.5, 124.6, 120.5, 120.3, 114.0, 112.4, 69.1, 68.4, 62.4, 28.4, 28.2, 27.2, 26.4, 26.2; FTIR (neat): 1714, 1598, 1249, 1125 cm^{-1} . HRMS (ESI-TOF) m/z : $[\text{M} + \text{Na}]^+$ calcd for $\text{C}_{21}\text{H}_{24}\text{O}_4\text{Na}$, 363.1572, found 363.1565.



6,7,8,9,10,11,12,13-octahydro-19*H*,21*H*-dibenzo[*b,g*][1,5,9]trioxacycloheptadecin-19-one (154h)²⁵:

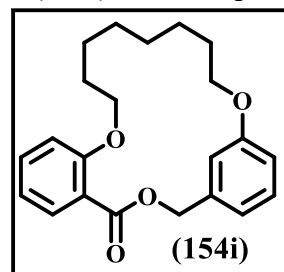
Prepared according to general experimental procedure 3.9.2D, a solution of **153h** (0.015 M, 55 mg) and (0.036 M, 91.8 mg) of Mukaiyama salt with CH_3CN in a vial. 1-methylimidazole (0.03 M, 25 mg) was dissolved in another vial with CH_3CN . Both the reagent solutions were flown through the 7 mL PFA tubing in 80 °C in a preheated water bath with 3-4 bar pressure. After workup, the residue was purified by using column chromatography ($\text{EtOAc}:n\text{-hexane}$ = 10:90) as the eluent to afford the desired product **154h** (31.6 mg, 60% yield) as a solid and starting material recovered **153h** (6.5 mg, 17%). melting point: 75-76 °C; ^1H NMR (400 MHz, CDCl_3) δ 7.65 (dd, J = 7.7, 1.7 Hz, 1H), 7.43 (dd, J = 7.4, 1.6 Hz, 1H), 7.40 – 7.34 (m, 1H), 7.30 (td, J = 8.1, 1.7 Hz, 1H), 6.95 (dd, J = 8.9, 1.3 Hz, 1H), 6.92 (dd, J = 4.8, 1.8 Hz, 1H), 6.90 – 6.84 (m, 2H), 5.39 (s, 2H), 4.10 (t, 2H), 3.98 (t, 2H), 1.81 – 1.67 (m, 4H), 1.63 – 1.52 (m, 4H), 1.45 – 1.34 (m, 4H); ^{13}C



NMR (100 MHz, CDCl₃) δ 166.9, 158.1, 157.9, 132.8, 132.1, 131.3, 130.3, 124.3, 121.6, 120.3, 119.8, 112.8, 111.6, 67.9, 67.7, 62.6, 29.1, 28.6, 28.2, 27.3, 24.9, 24.6; FTIR (neat): 1720, 1597, 1243, 1123 cm⁻¹; HRMS (ESI-TOF) m/z : [M + Na]⁺ calcd for C₂₂H₂₆O₄Na, 377.1728, found 377.1727.

3,6,15-trioxa-1(1,2),5(1,3)-dibenzenacyclopentadecaphan-2-one

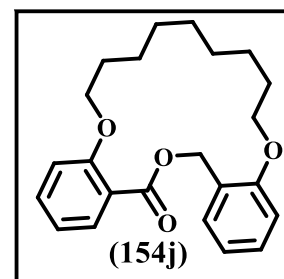
(154i): Prepared



according to general experimental procedure 3.9.2D, a solution of **153i** (0.015 M, 55 mg) and (0.036 M, 91.8 mg) of Mukaiyama salt with CH₃CN in a vial. 1-methylimidazole (0.03 M, 25 mg) was dissolved in another vial with CH₃CN. Both the reagent solutions were flown through the 7 mL PFA tubing in 80 °C in preheated water bath with 3-4 bar pressure. After workup, the residue was purified by using column chromatography (EtOAc:*n*-hexane = 10:90) as the eluent to afford the desired product **154i** (24.1 mg, 46% yield) as gummy liquid and starting material recovered **153i** (8.9 mg, 23%); ¹H NMR (400 MHz, CDCl₃) δ 7.65 (dd, J = 7.7, 1.8 Hz, 1H), 7.43 (dd, J = 7.4, 1.7 Hz, 1H), 7.40 – 7.35 (m, 1H), 7.32 – 7.28 (m, 1H), 6.96 – 6.93 (m, 1H), 6.93 – 6.90 (m, 1H), 6.87 (dd, J = 10.4, 4.0 Hz, 2H), 5.39 (s, 2H), 4.10 (t, 2H), 3.97 (t, 2H), 1.76 (dt, J = 6.8, 6.0 Hz, 2H), 1.70 (dt, J = 10.3, 5.0 Hz, 4H), 1.63 – 1.52 (m, 4H), 1.44 – 1.33 (m, 2H); ¹³C NMR (100 MHz, CDCl₃) δ 169.9, 158.1, 157.9, 132.8, 132.1, 131.3, 130.3, 124.3, 121.6, 120.2, 119.8, 112.8, 111.6, 67.9, 67.7, 62.6, 29.1, 28.6, 28.2, 27.3, 24.9, 24.6; FTIR (neat): 1724, 1594, 1278, 1163 cm⁻¹; HRMS (ESI-TOF) m/z : [M + Na]⁺ calcd for C₂₂H₂₆O₄Na, 377.1729, found 377.1726.

6,7,8,9,10,11,12,13-octahydro-19*H*,21*H*-dibenzo[*b,g*][1,5,9]trioxacycloheptadecin-19-one

(154j)²⁵: Prepared according to general experimental procedure 3.9.2D, a Solution of **153j** (0.015 M, 58 mg) and (0.036 M, 91.8 mg) of Mukaiyama salt with CH₃CN in a vial. 1-methylimidazole (0.03 M, 25 mg) was dissolved in another vial with CH₃CN. Both the reagent solutions were flown through the 7 mL PFA tubing in 80 °C in a preheated water bath with 3-4 bar pressure. After workup, the

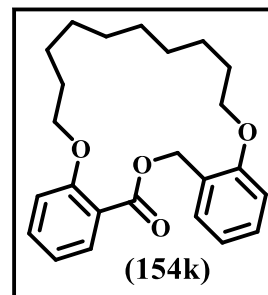


residue was purified by using column chromatography (EtOAc:*n*-hexane = 10:90) as to afford the desired product **154j** (30 mg, 54% yield) as a solid and starting material recovered **153j** (7.6 mg, 19%). melting point: 106-108 °C; ¹H NMR (400 MHz, CDCl₃) δ 7.68 (dd, J = 7.6, 1.7 Hz, 1H), 7.44 (dd, J = 7.5, 1.7 Hz, 1H), 7.38 (ddd, J = 8.5, 7.4, 1.8 Hz, 1H), 7.31 – 7.26 (m, 1H), 6.94 (ddd, J = 5.7, 5.0, 1.2 Hz, 2H), 6.88 (dd, J = 8.4, 7.6 Hz, 2H), 5.43 (s, 2H), 4.06 (t, 2H), 4.02 (t, 2H), 1.84 – 1.74 (m, 4H), 1.56 – 1.48 (m, 4H), 1.48 – 1.40 (m, J = 9.4, 5.3 Hz,

4H), 1.39 – 1.34 (m, $J = 11.5, 5.6$ Hz, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 166.7, 158.4, 157.5, 132.9, 131.2, 129.9, 124.8, 121.5, 120.5, 119.9, 112.9, 111.9, 69.2, 68.8, 61.7, 29.6, 29.3, 29.1, 28.8, 28.4, 27.1, 26.6; FTIR (neat): 1717, 1600, 1295, 1126 cm^{-1} ; HRMS (ESI-TOF) m/z : $[\text{M} + \text{Na}]^+$ calcd for $\text{C}_{23}\text{H}_{28}\text{O}_4\text{Na}$, 391.1885, found 391.1884.

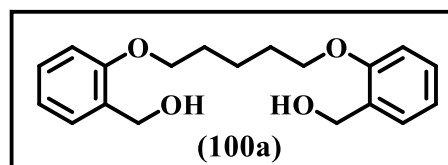
6,7,8,9,10,11,12,13,14,15-decahydro-21*H*,23*H*-dibenzo[*b,g*][1,5,9]trioxacyclononadecin-21-one (154k): Prepared according to general experimental procedure

3.9.2D, a solution of **153k** (0.015 M, 60 mg) and (0.036 M, 91.8 mg) of Mukaiyama salt with CH_3CN in a vial. 1-methylimidazole (0.03 M, 25 mg) was dissolved in another vial with CH_3CN . Both the reagent solutions were flown through the 7 mL PFA tubing in 80 °C in preheated water bath with 3-4 bar pressure. After workup, the residue



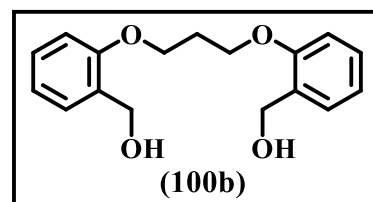
was purified by using column chromatography ($\text{EtOAc}:n\text{-hexane} = 10:90$) as to afford the desired product **154k** (22.8 mg, 40% yield) as a semisolid and starting material recovered **153k** (6.9 mg, 17%); ^1H NMR (400 MHz, CDCl_3) δ . 7.74 (dd, $J = 7.7, 1.8$ Hz, 1H), 7.41 (ddd, $J = 9.3, 5.7, 1.9$ Hz, 2H), 7.31 – 7.26 (m, 1H), 6.98 – 6.90 (m, 3H), 6.88 (dd, $J = 9.0, 4.6$ Hz, 1H), 5.42 (s, 2H), 4.06 (t, $J = 5.4$ Hz, 2H), 4.01 (t, $J = 5.4$ Hz, 2H), 1.77 (dt, $J = 5.0, 3.8$ Hz, 2H), 1.71 (dt, $J = 10.6, 4.5$ Hz, 2H), 1.63 – 1.50 (m, 4H), 1.37 – 1.29 (m, 8H); ^{13}C NMR (100 MHz, CDCl_3) δ 166.3, 158.8, 157.2, 133.1, 131.4, 129.9, 129.4, 125.1, 121.1, 120.3, 119.9, 113.1, 111.6, 68.2, 68, 62.1, 28.8, 28.8, 27.9, 27.9, 27.6, 27.5, 25.6, 25.2; FTIR (neat): 2939, 2871, 1712, 1601, 1493, 1290, 1254 cm^{-1} ; HRMS (ESI-TOF) m/z : $[\text{M} + \text{Na}]^+$ calcd for $\text{C}_{24}\text{H}_{30}\text{O}_4\text{Na}$, 405.2041, found 405.2039.

((pentane-1,5-diylbis(oxy))bis(2,1-phenylene))dimethanol (100a)²⁹: Prepared according to general experimental procedure 3.9.2A, using 2-(hydroxymethyl)phenol (500 mg, 4.03 mmol), potassium carbonate (K_2CO_3) (556 mg, 4.03 mmol) and 1,5-dibromo pentane (926.1 mg, 4.03 mmol). The

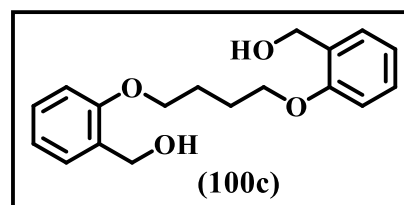


residue was purified by using column chromatography ($\text{EtOAc}:n\text{-hexane} = 40:60$) as the eluent to afford desired product **(100a)** (700 mg, 2.21 mmol, 55% yield) as a solid, melting point: 59-61 °C; ^1H NMR (400 MHz, CDCl_3) δ 7.29 (dd, $J = 8.8, 4.5$ Hz, 2H), 7.26 – 7.22 (m, 2H), 6.94 (t, $J = 7.4$ Hz, 2H), 6.87 (d, $J = 8.2$ Hz, 2H), 4.70 (s, 4H), 4.05 (t, $J = 5.9$ Hz, 4H), 2.88 (s, 2H), 1.98 – 1.84 (m, 4H), 1.77 – 1.65 (m, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 156.8, 129.3, 128.9, 128.8, 120.7, 111.2, 67.7, 62.0, 29.1, 23.1; HRMS (ESI-TOF) m/z : $[\text{M} + \text{Na}]^+$ calcd for $\text{C}_{19}\text{H}_{24}\text{O}_4\text{Na}$, 339.1572, found 339.1566.

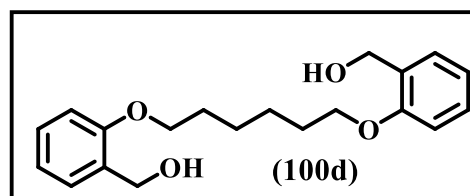
((propane-1,3-diylbis(oxy))bis(2,1-phenylene))dimethanol (100b)²⁹: Prepared according to general experimental procedure 3.9.2A, using 2-(hydroxymethyl)phenol (500 mg, 4.03 mmol), potassium carbonate (K₂CO₃) (556 mg, 4.03 mmol) and 1,3-dibromopropane (569.2 mg, 2.82 mmol). The residue was purified by using column chromatography (EtOAc/*n*-hexane =40:60) as the eluent to afford desired product **(100b)** (1.04 mg, 3.61 mmol, 89% yield) as a solid, melting point: 94-95 °C; ¹H NMR (400 MHz, CDCl₃) δ 7.28 (d, *J* = 6.4 Hz, 2H), 7.27 – 7.23 (m, 2H), 6.96 (d, *J* = 7.4 Hz, 2H), 6.90 (d, *J* = 8.1 Hz, 2H), 4.67 (s, 2H), 4.66 (s, 2H), 4.23 (t, *J* = 5.9 Hz, 4H), 2.52 (s, 2H), 2.34 (p, *J* = 5.9 Hz, 2H); ¹³C NMR (100 MHz, CDCl₃) δ 156.6, 129.3, 129.1, 121.1, 111.4, 65.2, 61.9, 29.4; HRMS (ESI-TOF) *m/z*: [M + Na]⁺ calcd for C₁₇H₂₀O₄Na, 311.1260 found, 311.1258.



((butane-1,4-diylbis(oxy))bis(2,1-phenylene))dimethanol (100c)²⁹: Prepared according to general experimental procedure 3.9.2A, using 2-(hydroxymethyl)phenol (500 mg, 4.03 mmol), potassium carbonate (K₂CO₃) (556 mg, 4.03 mmol) and 1,4-dibromobutane (608.7 mg, 2.82 mmol). The residue was purified by using column chromatography (EtOAc/*n*-hexane =40:60) as the eluent to afford desired product **(124c)** (1.02 gm, 3.37 mmol, 84% yield) as a solid. melting point:94-95 °C; ¹H NMR (400 MHz, CDCl₃) δ 7.28 (d, *J* = 1.5 Hz, 1H), 7.27 – 7.25 (m, 1H), 7.23 (dd, *J* = 7.5, 2.1 Hz, 2H), 6.93 (td, *J* = 7.5, 0.9 Hz, 2H), 6.86 (d, *J* = 8.2 Hz, 2H), 4.65 (s, 2H), 4.11 – 4.06 (m, 4H), 2.55 (s, 2H), 2.04 – 1.99 (m, 4H); ¹³C NMR (100 MHz, CDCl₃) δ 156.7, 129.2, 129.0, 128.9, 120.8, 111.2, 67.5, 62.0, 26.3; HRMS (ESI-TOF) *m/z*: [M +Na]⁺ calcd for C₁₈H₂₂O₄Na, 325.1415, found 325.1409.

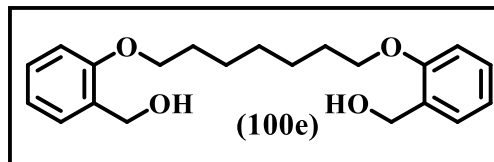


((hexane-1,6-diylbis(oxy))bis(2,1-phenylene))dimethanol (100d)²⁹: Prepared according to general experimental procedure 3.9.2A, using 2-(hydroxymethyl)phenol (500 mg, 4.03 mmol), potassium carbonate (K₂CO₃) (556 mg, 4.03 mmol) and 1,6-dibromohexane (687.8 mg, 2.82 mmol). The residue was purified by using column chromatography (EtOAc:*n*-hexane = 40:60) as the eluent to afford desired product **(100d)** (1.03 gm, 3.12 mmol, 77% yield) as a solid. melting point: 63-64 °C; ¹H NMR (400 MHz, CDCl₃) δ 7.31 – 7.22 (m, 4H), 6.94 (t, *J* = 7.4 Hz, 2H), 6.87 (d, *J* = 8.0 Hz, 2H), 4.68 (s, 4H), 4.03 (t, *J* = 6.3 Hz, 4H), 2.61 (s, 2H), 1.90 – 1.81 (m, 4H), 1.61



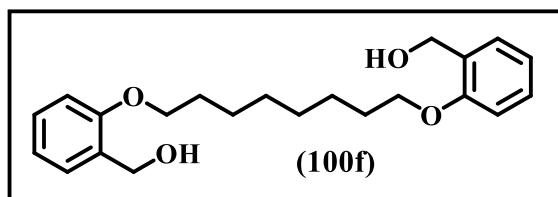
– 1.53 (m, 4H); ^{13}C NMR (100 MHz, CDCl_3) δ 156.9, 129.2, 128.93, 128.7, 120.6, 111.1, 67.8, 62.1, 29.2, 26.0; HRMS (ESI-TOF) m/z : $[\text{M} + \text{Na}]^+$ calcd for $\text{C}_{20}\text{H}_{26}\text{O}_4\text{Na}$, 353.1728, found 353.1719.

((heptane-1,7-diylbis(oxy))bis(2,1-phenylene))dimethanol (100e)²⁹: Prepared according to general experimental procedure 3.9.2A, using 2-(hydroxymethyl)phenol (500 mg, 4.03 mmol), potassium carbonate (K_2CO_3) (556 mg, 4.03 mmol) and 1,7-dibromoheptane (727.4 mg, 2.82 mmol).



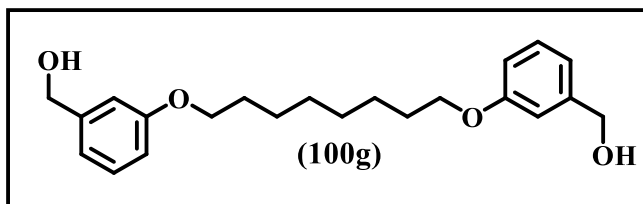
The residue was purified by using column chromatography ($\text{EtOAc}:\text{n-hexane}$ = 40:60) as the eluent to afford desired product **(100e)** (1.2 gm, 3.48 mmol, 86% yield) as a solid. melting point: 62-63 °C; ^1H NMR (400 MHz, CDCl_3) δ 7.30 – 7.27 (m, 2H), 7.26 – 7.23 (m, 2H), 6.94 (td, J = 7.4, 0.8 Hz, 2H), 6.87 (d, J = 8.1 Hz, 2H), 4.70 (s, 4H), 4.02 (t, J = 6.4 Hz, 4H), 2.58 (s, 2H), 1.83 (dt, J = 13.0, 6.6 Hz, 4H), 1.57 – 1.42 (m, 6H); ^{13}C NMR (100 MHz, CDCl_3) δ 156.9, 129.2, 128.9, 128.7, 120.6, 111.1, 67.9, 62.3, 29.2, 29.10, 26.2; HRMS (ESI-TOF) m/z : $[\text{M} + \text{Na}]^+$ calcd for $\text{C}_{21}\text{H}_{28}\text{O}_4\text{Na}$, 367.1885, found, 367.1880.

((octane-1,8-diylbis(oxy))bis(2,1-phenylene))dimethanol (124f)²⁹: Prepared according to general experimental procedure 3.9.2A, using 2-(hydroxymethyl)phenol (500 mg, 4.03 mmol), potassium carbonate (K_2CO_3) (556 mg, 4.03 mmol) and 1,8-dibromooctane (766.9 mg, 2.82 mmol).



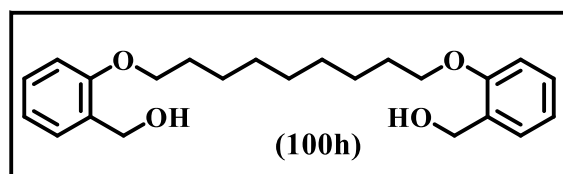
The residue was purified by using column chromatography ($\text{EtOAc}:\text{n-hexane}$ = 40:60) as the eluent to afford desired product **(100g)** (1.23 gm, 3.43 mmol, 85% yield) as a solid. melting point: 69-70 °C; ^1H NMR (400 MHz, CDCl_3) δ 7.30 – 7.26 (m, 2H), 7.26 – 7.22 (m, 2H), 6.93 (td, J = 7.5, 0.9 Hz, 2H), 6.88 (d, J = 8.1 Hz, 2H), 4.70 (s, 2H), 4.69 (s, 2H), 4.02 (t, J = 6.4 Hz, 4H), 2.59 (s, 2H), 1.83 (dt, J = 14.4, 6.4 Hz, 4H), 1.54 – 1.45 (m, 4H), 1.45 – 1.38 (m, 4H), OH peak are exchanged with deuterium of CDCl_3 ; ^{13}C NMR (100 MHz, CDCl_3) δ 156.9, 129.2, 128.9, 128.7, 120.6, 111.1, 67.9, 62.3, 29.4, 26.2; HRMS (ESI-TOF) m/z : $[\text{M} + \text{Na}]^+$ calcd for $\text{C}_{22}\text{H}_{32}\text{O}_4\text{Na}$, 381.2041, found 381.2036.

((octane-1,8-diylbis(oxy))bis(3,1-phenylene))dimethanol (100g)²⁹: Prepared according to general experimental procedure 3.9.2A, using 3-hydroxybenzyl alcohol (500 mg, 4.03 mmol), potassium carbonate (K_2CO_3) (556 mg, 4.03 mmol) and 1,8-



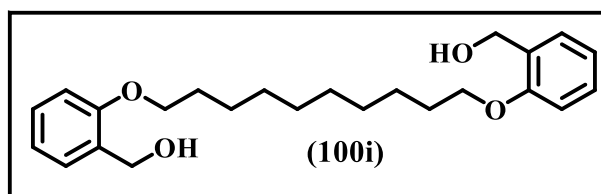
dibromooctane (766.9 mg, 2.82 mmol). The residue was purified by using column chromatography (EtOAc:*n*-hexane = 40:60) as the eluent to afford desired product (**100g**) (1.23 gm, 3.43 mmol, 85% yield) as a solid, melting point; 66-67 °C; ¹H NMR (400 MHz, CDCl₃) δ 7.28 – 7.23 (m, 2H), 6.93 – 6.90 (m, 4H), 6.84 – 6.82 (m, 1H), 6.81 (d, *J* = 2.2 Hz, 1H), 4.66 (s, 4H), 3.96 (t, *J* = 6.5 Hz, 4H), 1.83 – 1.74 (m, 4H), 1.71 (s, 2H), 1.52 – 1.44 (m, 4H), 1.40 (dd, *J* = 6.9, 3.6 Hz, 4H); ¹³C NMR (100 MHz, CDCl₃) δ 159.6, 142.6, 129.7, 119.1, 113.9, 113.1, 68.1, 65.5, 29.4, 26.1; HRMS (ESI-TOF) *m/z*: [M +Na]⁺ calcd for C₂₂H₃₂O₄Na, 381.2041, found 381.2036.

((nonane-1,9-diylbis(oxy))bis(2,1-phenylene))dimethanol (100h)²⁹: Prepared according to general experimental procedure 3.9.2A, using 2-(hydroxymethyl)phenol (500 mg, 4.03 mmol), potassium carbonate (K₂CO₃) (556 mg, 4.03 mmol) and 1,9-dibromononane (806



mg, 2.82 mmol). The residue was purified by using column chromatography (EtOAc/*n*-hexane =40:60) as the eluent to afford desired product (**100h**) (1.37 gm, 3.68 mmol, 91% yield) as a solid. melting point; 74-75 °C; ¹H NMR (400 MHz, CDCl₃) δ 7.28 – 7.24 (m, 2H), 7.24 – 7.21 (m, 2H), 6.91 (t, *J* = 7.4 Hz, 2H), 6.86 (d, *J* = 7.9 Hz, 2H), 4.68 (s, 2H), 4.67 (s, 2H), 4.01 (t, *J* = 6.4 Hz, 4H), 2.43 (s, 2H), 1.85 – 1.76 (m, 4H), 1.51 – 1.41 (m, 4H), 1.38 (d, *J* = 15.1 Hz, 2H); ¹³C NMR (100 MHz, CDCl₃) δ 157.0, 129.2, 128.9, 128.7, 120.6, 111.2 68.1, 62.4, 29.5, 29.4, 26.2; HRMS (ESI-TOF) *m/z*: [M +Na]⁺ calcd for C₂₃H₃₂O₄Na, 395.2198, found 395.2192.

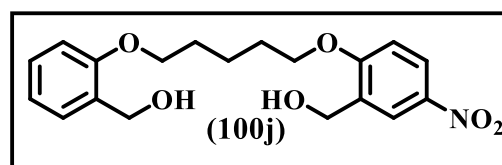
((decane-1,10-diylbis(oxy))bis(2,1-phenylene))dimethanol (100i)²⁹: Prepared according to general experimental procedure 3.9.2A, using 2-(hydroxymethyl)phenol (500 mg, 4.03 mmol), potassium carbonate (K₂CO₃) (556 mg, 4.03 mmol) and 1,10-



dibromononane (846 mg, 2.82 mmol). The residue was purified by using column chromatography (EtOAc/*n*-hexane =40:60) as the eluent to afford desired product (**100i**) (1.21 gm, 3.13 mmol, 77% yield) as a solid, melting point; 73-75 °C; ¹H NMR (400 MHz, CDCl₃) δ 7.26 (d, *J* = 6.6 Hz, 2H), 7.25 – 7.22 (m, 2H), 6.92 (t, *J* = 7.4 Hz, 2H), 6.87 (d, *J* = 8.0 Hz, 2H), 4.69 (s, 4H), 4.02 (t, *J* = 6.4 Hz, 4H), 2.49 (s, 2H), 1.85 – 1.77 (m, 4H), 1.46 (dd, *J* = 14.4, 6.7 Hz, 4H), 1.40 – 1.30 (m, *J* = 17.5 Hz, 8H); ¹³C NMR (100 MHz, CDCl₃) δ 157.1, 129.3, 129.0, 128.8, 120.6, 111.2, 68.1, 62.5, 29.5, 29.4, 29.4, 26.3; HRMS (ESI-TOF) *m/z*: [M +Na]⁺ calcd for C₂₄H₃₄O₄Na, 409.2355, found 409.2349.

(2-((5-(2-(hydroxymethyl)-4-**nitrophenoxy)pentyl)oxy)phenyl)methanol**

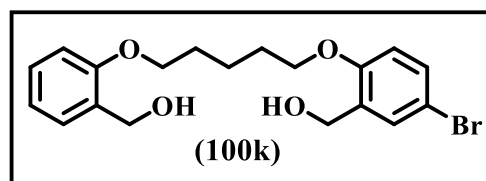
(124j): Prepared according to general experimental procedure 3.9.2A, using (2-((5-



bromopentyl)oxy)phenyl)methanol (500 mg, 1.83 mmol), potassium carbonate (K_2CO_3) (252 mg, 1.83 mmol) and 2-(hydroxymethyl)-4-nitrophenol (309 mg, 1.83 mmol). The residue was purified by using column chromatography (EtOAc:*n*-hexane = 40:60) as the eluent to afford desired product (2-((5-(2-(hydroxymethyl)-4-nitrophenoxy)pentyl)oxy)phenyl)methanol **(124j)** (513 mg, 1.42 mmol, 77% yield) as a solid, melting point; 79-78 °C ^1H NMR (400 MHz, $CDCl_3$) δ 8.28 (s, 1H), 8.16 (d, J = 9.0 Hz, 1H), 7.30 – 7.22 (m, 2H), 6.94 (t, J = 7.4 Hz, 1H), 6.88 (t, J = 8.7 Hz, 2H), 4.73 (s, 2H), 4.69 (s, 2H), 4.15 (t, J = 6.1 Hz, 2H), 4.07 (t, J = 6.0 Hz, 2H), 2.71 (s, 1H), 2.55 (s, 1H), 1.99 – 1.86 (m, 4H), 1.76 – 1.69 (m, 2H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 161.2, 156.8, 141.4, 130.7, 129.1, 128.9, 125.0, 123.7, 120.8, 111.2, 110.5, 68.7, 67.6, 62.1, 29.1, 28.8, 23.0.; FTIR (neat): 3345, 2923, 1588, 1277, 1149 cm^{-1} ; HRMS (ESI-TOF) m/z : $[M + Na]^+$ calcd for $C_{19}H_{23}NO_6Na$, 384.1422, found 384.1424.

(5-bromo-2-((5-(2-(hydroxymethyl)phenoxy)pentyl)oxy)phenyl)methanol**(100k):**

Prepared according to general experimental procedure 3.9.2B, using (2-((5-bromopentyl)oxy)phenyl)methanol (700 mg, 2.56 mmol), potassium carbonate (K_2CO_3) (254 mg, 2.56

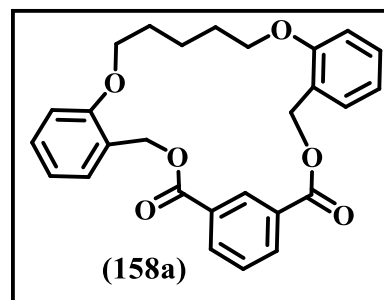


mmol) and 4-bromo-2-(hydroxymethyl)phenol (520 mg, 2.56 mmol). The residue was purified by using column chromatography (EtOAc:*n*-hexane = 40:60) as the eluent to afford desired product (5-bromo-2-((5-(2-(hydroxymethyl)phenoxy)pentyl)oxy)phenyl)methanol **(100k)** (856 mg, 2.17 mmol, 84% yield) as a semi-solid; ^1H NMR (400 MHz, $CDCl_3$) δ 7.46 (d, J = 2.5 Hz, 1H), 7.35 (dd, J = 8.7, 2.5 Hz, 1H), 7.31 – 7.25 (m, 2H), 6.99 – 6.93 (m, 1H), 6.89 (d, J = 8.1 Hz, 1H), 6.75 (d, J = 8.7 Hz, 1H), 4.71 (s, 2H), 4.66 (s, 2H), 4.08 (t, J = 6.1 Hz, 2H), 4.03 (t, J = 6.2 Hz, 2H), 1.95 – 1.86 (m, 4H), 1.75 – 1.66 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.8, 155.6, 131.6, 131.3, 129.1, 129.0, 128.9, 120.7, 112.9, 112.9, 111.1, 68.0, 67.6, 62.1, 60.9, 29.1, 28.9, 23.0. FTIR (neat): 3326, 2934, 1486, 1238, 734 cm^{-1} ; HRMS (ESI-TOF) m/z : $[M + Na]^+$ calcd for $C_{19}H_{23}O_4BrNa$, 417.0677, found 417.0671.

3,7,10,16-tetraoxa-1,9(1,2),5(1,3)-tribenzenacyclohexadecaphane-4,6-dione**(158a):**

Prepared according to general experimental procedure 3.9.2E, a solution of **100a** (0.0075 M, 47.5 mg) with CH_3CN in a vial and (0.0075 M, 25mg) of isophthalic acid **157**, (0.036 M, 183

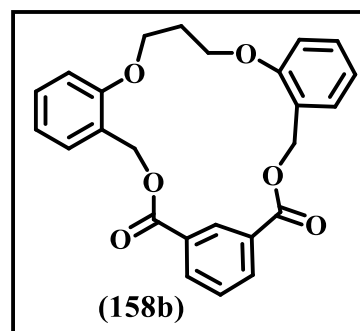
mg) of Mukaiyama salt and (0.03 M, 49 mg) of 1-methylimidazole were dissolved in another vial with CH₃CN. Both reagent solutions were flown through the 7 mL PFA tubing at 80 °C in a preheated water bath with 3-4 bar pressure. After workup, the residue was purified by using column chromatography (EtOAc:*n*-hexane = 10:90) to afford



the desired product **158a** (20 mg, 30% yield) as a solid and starting material recovered **100a** (5.1 mg, 16%). **In batch condition:** compound **100a** (0.0075 M, 47.5 mg), (0.0075 M, 25mg) of isophthalic acid **157** and (0.036 M, 183 mg) of Mukaiyama salt (0.03 M, 49 mg) of 1-methylimidazole in CH₃CN solvent were heated at 80 °C in the preheated oil path for 24 hrs to afford the desired product **158a** (9.2 mg, 13%) yield. melting point: 136-137 °C; ¹H NMR (400 MHz, CDCl₃) δ 8.59 (t, *J* = 1.7 Hz, 1H), 8.21 (dd, *J* = 7.8, 1.6 Hz, 2H), 7.53 – 7.46 (m, 3H), 7.32 (td, *J* = 7.9, 1.7 Hz, 2H), 6.96 (dd, *J* = 7.6, 5.0 Hz, 4H), 5.43 (s, 4H), 4.08 (t, *J* = 5.1 Hz, 4H), 1.94 – 1.82 (m, 6H); ¹³C NMR (100 MHz, CDCl₃) δ 166.1, 158.7, 134.3, 132.9, 131.0, 130.6, 130.3, 128.6, 124.8, 120.7, 113.1, 69.2, 63.5, 30.1, 23.7; FTIR (neat): 2927, 2869, 1717, 1604, 1456, 1251 cm⁻¹; HRMS (ESI-TOF) *m/z*: [M + H]⁺ calcd for C₂₇H₂₈O₆, 447.1807, found 447.1811.

3,7,10,14-tetraoxa-1,9(1,2),5(1,3)-tribenzenacyclotetradecaphane-4,6-dione (158b):

Prepared according to general experimental procedure 3.9.2E, a solution of **100b** (0.0075 M, 43.2 mg) with CH₃CN in a vial and (0.0075 M, 25 mg) of isophthalic acid **157**, (0.036 M, 183 mg) of Mukaiyama salt and (0.03 M, 49 mg) of 1-methylimidazole were dissolved in another vial with CH₃CN. Both reagent solutions were flown through the 7 mL PFA tubing in 80 °C in a preheated water bath with 3-4 bar pressure. After workup, the

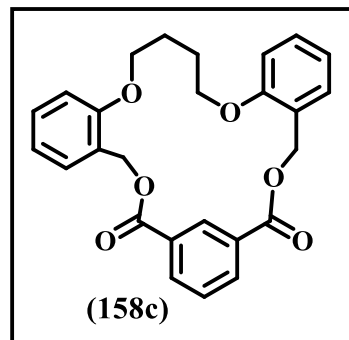


residue was purified by using column chromatography (EtOAc:*n*-hexane = 10:90) to afford the desired product **158b** (22.2 mg, 35% yield) as a solid and starting material recovered **100b** (6.9 mg, 24%). **In batch condition:** compound **100b** (0.0075 M, 43.2 mg), (0.0075 M, 25mg) of isophthalic acid **157** and (0.036 M, 183 mg) of Mukaiyama salt (0.03 M, 49 mg) of 1-methylimidazole in CH₃CN solvent were heated at 80 °C in the preheated oil path for 24 hrs to afford the desired product **158b** (10.3 mg, 16%) yield. melting point: 175-176 °C; ¹H NMR (400 MHz, CDCl₃) δ 8.72 (t, *J* = 1.6 Hz, 1H), 8.21 (dd, *J* = 7.8, 1.7 Hz, 2H), 7.51 (t, *J* = 7.8 Hz, 1H), 7.43 (dd, *J* = 7.4, 1.7 Hz, 2H), 7.36 (td, *J* = 8.1, 1.7 Hz, 2H), 6.98 (td, *J* = 7.5,

2.6 Hz, 4H), 5.38 (s, 4H), 4.33 (t, $J = 6.8$ Hz, 4H), 2.40 (p, $J = 6.7$ Hz, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 165.7, 158.9, 134.01, 132.1, 130.9, 130.9, 130.7, 128.8, 124.9, 121.1, 113.5, 66.7, 64.3, 31.1; FTIR (neat): 2948, 2858, 1745, 1604, 1300, 1251 cm^{-1} ; HRMS (ESI-TOF) m/z : $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{25}\text{H}_{23}\text{O}_6$, 419.1494, found 419.1487.

3,7,10,15-tetraoxa-1,9(1,2),5(1,3)-tribenzenacyclopentadecaphane-4,6-dione (158c):

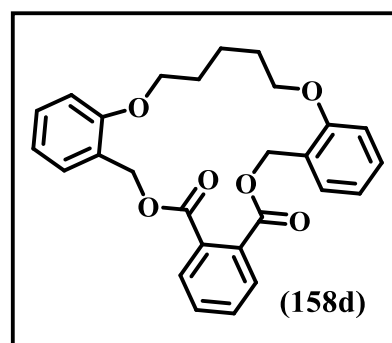
Prepared according to general experimental procedure 3.9.2E, a solution of ((butane-1,4-diylbis(oxy))bis(2,1-phenylene))dimethanol **100c** (0.0075 M, 43.2 mg) with CH_3CN in a vial and (0.0075 M, 25 mg) of isophthalic acid **157**, (0.036 M, 183 mg) of Mukaiyama salt and (0.03 M, 49 mg) of 1-methylimidazole were dissolved in another vial with CH_3CN . Both reagent solutions were flown through the 7 mL PFA



tubing at 80 °C in a preheated water bath with 3-4 bar pressure. After workup, the residue was purified by using column chromatography ($\text{EtOAc}/n\text{-hexane} = 10:90$) to afford desired product **158c** (21.6 mg, 33% yield) as a solid and starting material recovered **100c** (12 mg, 39%). melting point: 122-123 °C; ^1H NMR (400 MHz, CDCl_3) δ 8.58 (t, $J = 1.6$ Hz, 1H), 8.22 (dd, $J = 7.8, 1.6$ Hz, 2H), 7.51 (dd, $J = 7.3, 1.7$ Hz, 2H), 7.48 (d, $J = 7.8$ Hz, 1H), 7.32 (td, $J = 8.0, 1.7$ Hz, 2H), 6.95 – 6.91 (m, 2H), 6.90 (d, $J = 8.1$ Hz, 2H), 5.45 (s, 4H), 4.14 (dd, $J = 7.9, 2.9$ Hz, 4H), 2.18 – 2.13 (m, 4H); ^{13}C NMR (100 MHz, CDCl_3) δ 166.1, 158.2, 134.3, 132.9, 131.1, 130.6, 130, 128.6, 123.9, 120.2, 110.9, 66.9, 63.2, 25.8; FTIR (neat): 2919, 2851, 1715, 1699, 1225, 1201 cm^{-1} ; HRMS (ESI-TOF) m/z : $[\text{M} + \text{Na}]^+$ calcd for $\text{C}_{26}\text{H}_{24}\text{O}_6\text{Na}$, 455.1470, found 455.1483.

14,15,16,17-tetrahydro-7H,13H,23H-tribenzo[*b,g,l*][1,5,10,14]tetraoxacyclononadecine-5,25-dione (158d):

Prepared according to general experimental procedure 3.9.2E, a solution of ((pentane-1,5-diylbis(oxy))bis(2,1-phenylene))dimethanol **100a** (0.0075 M, 47.4 mg) with CH_3CN in a vial and (0.0075 M, 25 mg) of phthalic acid, (0.036 M, 183 mg) of Mukaiyama salt and (0.03 M, 49 mg) of 1-methylimidazole were dissolved in another vial with CH_3CN . Both reagent solutions were flown

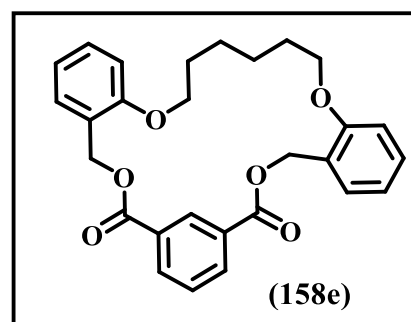


through the 7 mL PFA tubing at 80 °C in a preheated water bath with 3-4 bar pressure. After workup, the residue was purified by using column chromatography ($\text{EtOAc}/n\text{-hexane} = 10:90$) to afford desired product **158d** (21.2 mg, 32% yield) as a solid and starting material recovered

100a (5.3, 17%). melting point: 135-138 °C; ^1H NMR (400 MHz, CDCl_3) δ 7.64 (dt, $J = 6.2$, 3.1 Hz, 2H), 7.41 (dd, $J = 5.7$, 3.2 Hz, 2H), 7.32 (d, $J = 7.5$ Hz, 2H), 7.23 – 7.17 (m, 2H), 6.87 (t, $J = 7.4$ Hz, 2H), 6.80 (d, $J = 8.3$ Hz, 2H), 5.34 (s, 4H), 3.98 (t, $J = 5.4$ Hz, 4H), 1.86 – 1.77 (m, 4H), 1.71 (dd, $J = 14.1$, 7.2 Hz, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 167.9, 157.2, 132.5, 131.1, 130.6, 129.8, 129.1, 124.3, 120.6, 111.7, 68.3, 62.5, 29.3, 23.9; FTIR (neat): 2937, 2869, 1716, 1601, 1450, 1253 cm^{-1} ; HRMS (ESI-TOF) m/z : $[\text{M} + \text{Na}]^+$ calcd for $\text{C}_{27}\text{H}_{26}\text{O}_6\text{Na}$ 469.1623, found 449.1616.

3,7,10,17-tetraoxa-1,9(1,2),5(1,3)-tribenzenacycloheptadecaphane-4,6-dione (158e):

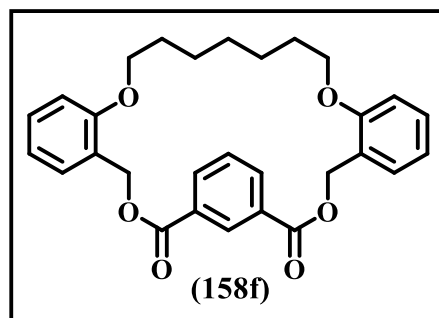
Prepared according to general experimental procedure 3.9.2E, a solution of ((hexane-1,6-diylbis(oxy))bis(2,1-phenylene))dimethanol **100d** (0.0075 M, 49.5 mg) with CH_3CN in a vial and (0.0075 M, 25 mg) of isophthalic acid, (0.036 M, 183 mg) of Mukaiyama salt and (0.03 M, 49 mg) of 1-methylimidazole were dissolved in another vial with CH_3CN .



Both reagent solutions were flown through the 7 mL PFA tubing at 80 °C in a preheated water bath with 3-4 bar pressure. After workup, the residue was purified by using column chromatography ($\text{EtOAc}:\text{n-hexane} = 10:90$) to afford the desired product **158e** (22.4 mg, 32% yield) as a solid and starting material recovered **100d** (6.4 mg, 19%). melting point: 158-160 °C; ^1H NMR (400 MHz, CDCl_3) δ 8.68 (t, $J = 1.7$ Hz, 1H), 8.16 (dd, $J = 7.8$, 1.7 Hz, 2H), 7.44 (s, 1H), 7.41 (dd, $J = 7.4$, 1.5 Hz, 2H), 7.35 – 7.30 (m, 2H), 6.95 (dd, $J = 7.4$, 0.8 Hz, 2H), 6.88 (d, $J = 8.2$ Hz, 2H), 5.43 (s, 4H), 3.99 (t, $J = 6.2$ Hz, 4H), 1.73 – 1.63 (m, 4H), 1.45 – 1.40 (m, 4H); ^{13}C NMR (100 MHz, CDCl_3) δ 165.9, 158.3, 133.8, 132.2, 131.2, 131.0, 130.6, 128.5, 124.2, 120.2, 111.6, 67.8, 63.9, 29.0, 25.6; FTIR (neat): 2937, 2860, 1716, 1294, 1253 cm^{-1} ; HRMS (ESI-TOF) m/z : $[\text{M} + \text{Na}]^+$ calcd for $\text{C}_{28}\text{H}_{28}\text{O}_6\text{Na}$, 483.1783, found: 483.1782.

3,7,10,18-tetraoxa-1,9(1,2),5(1,3)-tribenzenacyclooctadecaphane-4,6-dione (158f):

Prepared according to general experimental procedure 3.9.2E, a solution of **100e** (0.0075 M, 51.6 mg) with CH_3CN in a vial and (0.0075 M, 25 mg) of isophthalic acid, (0.036 M, 183 mg) of Mukaiyama salt and (0.03 M, 49 mg) of 1-methylimidazole were dissolved in another vial with CH_3CN .

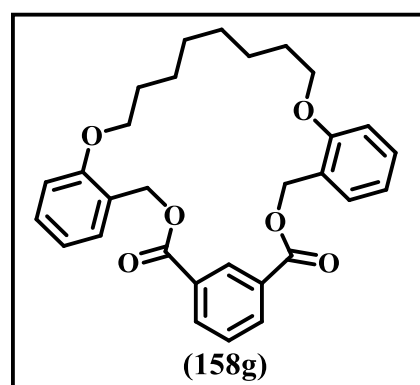


Both reagent solutions were flown through the 7 mL PFA tubing at 80 °C in a preheated water bath with 3-4 bar pressure. After workup, the residue was purified by using column chromatography ($\text{EtOAc}:\text{n-hexane} = 10:90$)

to afford the desired product **158f** (32.6 mg, 46% yield) as a solid and starting material recovered **100e** (9.8 mg, 28%). melting point: 169-171 °C; ^1H NMR (400 MHz, CDCl_3) δ 8.72 (t, $J = 1.6$ Hz, 1H), 8.16 (dd, $J = 7.8, 1.8$ Hz, 2H), 7.44 (d, $J = 7.8$ Hz, 1H), 7.39 (dd, $J = 7.4, 1.8$ Hz, 2H), 7.37 – 7.32 (m, 2H), 6.95 (td, $J = 7.3, 0.8$ Hz, 2H), 6.89 (d, $J = 8.2$ Hz, 2H), 5.40 (s, 4H), 3.94 (t, $J = 5.4$ Hz, 4H), 1.71 – 1.63 (m, 4H), 1.25 – 1.19 (m, $J = 6.8$ Hz, 6H); ^{13}C NMR (100 MHz, CDCl_3) δ 165.8, 158.5, 133.8, 131.9, 131.1, 131.1, 130.6, 128.4, 124.1, 120.1, 111.6, 68.2, 64.1, 30.4, 30.0, 26.8; FTIR (neat): 2932, 2855, 1721, 1605, 1254, 1227 cm^{-1} ; HRMS (ESI-TOF) m/z : $[\text{M} + \text{Na}]^+$ calcd for $\text{C}_{29}\text{H}_{30}\text{O}_6\text{Na}$, 497.1939, found: 497.1939; **Crystal preparation**: The crystals are grown by simple recrystallization method where pure compounds isolated after column chromatography and dissolved in dichloromethane and layered with hexane, kept at room temperature to get compound **158f** pure crystal. More information on crystal structures can also be obtained from the Cambridge Crystallographic Data Centre (CCDC) with deposition number 2176849.

3,7,10,19-tetraoxa-1,9(1,2),5(1,3)-tribenzenacyclononadecaphane-4,6-dione (158g):

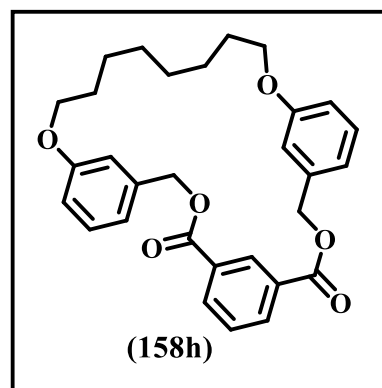
Prepared according to general experimental procedure 3.9.2E, a solution of **100f** (0.0075 M, 53.7 mg) with CH_3CN in a vial and (0.0075 M, 25 mg) of isophthalic acid, (0.036 M, 183 mg) of Mukaiyama salt and (0.03 M, 49 mg) of 1-methylimidazole were dissolved in another vial with CH_3CN . Both reagent solutions were flown through the 7 mL PFA tubing in 80 °C in preheated water bath with 3-4 bar pressure. After workup, the residue was purified by



using column chromatography ($\text{EtOAc}:\text{n-hexane} = 10:90$) as to afford the desired product **158g** (23.8 mg, 32% yield) as a solid and starting material recovered **100f** (12.2 mg, 34%). melting point: 107-108 °C; ^1H NMR (400 MHz, CDCl_3) δ 8.70 (t, $J = 1.7$ Hz, 1H), 8.17 (dd, $J = 7.8, 1.8$ Hz, 2H), 7.43 (t, $J = 7.8$ Hz, 1H), 7.39 – 7.33 (m, 4H), 6.96 (td, $J = 7.4, 0.8$ Hz, 2H), 6.94 – 6.88 (m, 2H), 5.37 (s, 4H), 3.98 (t, $J = 5.9$ Hz, 4H), 1.62 – 1.55 (m, 4H), 1.27 – 1.21 (m, 4H), 1.00 – 0.93 (m, 4H); ^{13}C NMR (100 MHz, CDCl_3) δ 165.9, 158.5, 133.8, 131.8, 131.4, 131.0, 130.6, 128.4, 124.2, 120.3, 112.1, 68.1, 64.3, 29.5, 29.2, 26.0; FTIR (neat): 2923, 2853, 1721, 1605, 1290, 1252 cm^{-1} ; HRMS (ESI-TOF) m/z : $[\text{M} + \text{Na}]^+$ calcd for $\text{C}_{30}\text{H}_{32}\text{O}_6\text{Na}$, 511.2096, found: 511.2097.

3,7,10,19-tetraoxa-1,5,9(1,3)-tribenzenacyclononadecaphane-4,6-dione (158h): Prepared

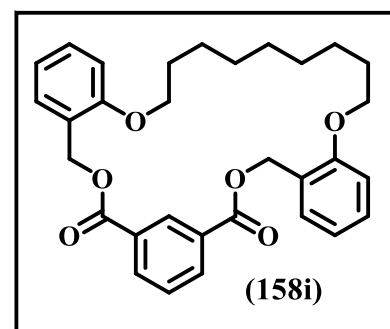
according to general experimental procedure 3.9.2E, a solution of **100g** (0.0075 M, 53.7 mg) with CH₃CN in a vial and (0.0075 M, 25mg) of isophthalic acid, (0.036 M, 183 mg) of Mukaiyama salt and (0.03 M, 49 mg) of 1-methylimidazole were dissolved in another vial with CH₃CN. Both reagent solutions were flown through the 7 mL PFA tubing at 80 °C in a preheated water bath with 3-4 bar pressure. After workup, the residue was purified by using



column chromatography (EtOAc:*n*-hexane = 10:90) to afford the desired product **158h** (11.4 mg, 15% yield) as a solid and starting material recovered **100h** (15.5 mg, 43%). melting point: 112-113 °C; ¹H NMR (400 MHz, CDCl₃) δ 8.69 (t, *J* = 1.6 Hz, 1H), 8.25 (dd, *J* = 7.8, 1.8 Hz, 2H), 7.51 (t, *J* = 7.8 Hz, 1H), 7.25 – 7.21 (m, 2H), 6.98 (d, *J* = 2.0 Hz, 2H), 6.96 (d, *J* = 7.7 Hz, 2H), 6.83 (dd, *J* = 8.2, 2.5 Hz, 2H), 5.34 (s, 4H), 3.93 (t, *J* = 6.0 Hz, 4H), 1.77 – 1.68 (m, 4H), 1.49 – 1.40 (m, 4H), 1.38 – 1.31 (m, 4H); ¹³C NMR (100 MHz, CDCl₃) δ 165.8, 159.6, 137.5, 134.4, 130.9, 130.7, 129.6, 128.8, 120.9, 115.2, 114.1, 67.7, 67.0, 29.1, 28.8, 25.7; FTIR (neat): 2937, 2855, 1706, 1227 cm⁻¹; HRMS (ESI-TOF) *m/z*; [M +Na]⁺ calcd for C₃₀H₃₂O₆Na, 511.2096, found: 511.2093.

3,7,10,20-tetraoxa-1,9(1,2),5(1,3)-tribenzenacycloicosaphane-4,6-dione (158i): Prepared

according to general experimental procedure 3.9.2E, a solution of **100h** (0.0075 M, 55.8 mg) with CH₃CN in a vial and (0.0075 M, 25 mg) of isophthalic acid, (0.036 M, 183 mg) of Mukaiyama salt and (0.03 M, 49 mg) of 1-methylimidazole were dissolved in another vial with CH₃CN. Both reagent solutions were flown through the 10 mL PFA tubing at 80 °C in a preheated water bath with 3-4 bar pressure. After workup,



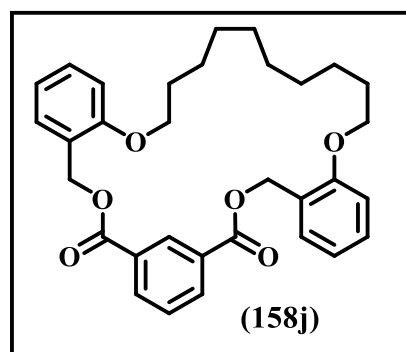
the residue was purified by using column chromatography (EtOAc:*n*-hexane = 10:90) to afford the desired product **158i** (37 mg, 49% yield) as a solid and starting material recovered **100h** (8.9 mg, 24%). melting point: 167-169 °C; ¹H NMR (400 MHz, CDCl₃) δ 8.77 (t, *J* = 1.5 Hz, 1H), 8.15 (dd, *J* = 7.8, 1.7 Hz, 2H), 7.41 (d, *J* = 7.8 Hz, 1H), 7.38 – 7.33 (m, 4H), 6.95 (td, *J* = 7.5, 0.9 Hz, 2H), 6.88 (d, *J* = 8.5 Hz, 2H), 5.35 (s, 4H), 3.95 (t, *J* = 5.5 Hz, 4H), 1.66 – 1.60 (m, 4H), 1.22 – 1.12 (m, *J* = 9.4, 7.5 Hz, 4H), 1.09 – 0.98 (m, *J* = 10.8, 7.6 Hz, 4H), 0.57 – 0.46 (m, *J* = 15.5, 7.8 Hz, 2H); ¹³C NMR (100 MHz, CDCl₃) δ 165.9, 158.5, 133.9, 131.8,

131.3, 131.1, 130.7, 128.4, 123.7, 120.1, 111.2, 67.6, 64.4, 29.7, 29.6, 29.5, 26.8; FTIR (neat): 2924, 2853, 1715, 1255, 1225 cm^{-1} ; HRMS (ESI-TOF) m/z : $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{31}\text{H}_{35}\text{O}_6$, 503.2434, found: 503.2436.

3,7,10,21-tetraoxa-1,9(1,2),5(1,3)-

tribenzenacyclohenicosaphane-4,6-dione (158j):

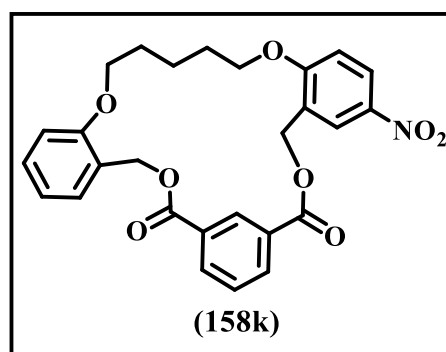
Prepared according to general experimental procedure 3.9.2E, a solution of **100i** (0.0075 M, 58 mg) with CH_3CN in a vial and (0.0075 M, 25 mg) of isophthalic acid, (0.036 M, 183 mg) of Mukaiyama salt and (0.03 M, 49 mg) of 1-methylimidazole were dissolved in another



vial with CH_3CN . Both reagent solutions were flown through the 7 mL PFA tubing at 80 °C in a preheated water bath with 3-4 bar pressure. After workup, the residue was purified by using column chromatography ($\text{EtOAc}:\text{n-hexane} = 10:90$) to afford the desired product **158j** (43.9 mg, 57% yield) as a solid and starting material recovered **100i** (11 mg, 28%). melting point: 167-169 °C; ^1H NMR (400 MHz, CDCl_3) δ 8.72 (t, $J = 1.7$ Hz, 1H), 8.18 (dd, $J = 7.8, 1.8$ Hz, 2H), 7.43 (t, $J = 7.8$ Hz, 1H), 7.38 – 7.34 (m, 4H), 7.01 – 6.88 (m, 4H), 5.35 (s, 4H), 4.01 (t, $J = 5.6$ Hz, 4H), 1.80 – 1.51 (m, $J = 11.1, 9.5, 5.8$ Hz, 4H), 1.33 – 1.26 (m, $J = 15.5, 7.5, 5.0$ Hz, 4H), 1.13 – 1.06 (m, $J = 10.1, 4.9$ Hz, 4H), 0.87 – 0.81 (m, 4H); ^{13}C NMR (100 MHz, CDCl_3) δ 165.9, 158.5, 133.9, 131.7, 131.3, 130.9, 130.6, 128.4, 123.9, 120.2, 111.8, 68.2, 64.3, 29.6, 29.1, 26.5; FTIR (neat): 2925, 2853, 1714, 1253, 1228 cm^{-1} ; HRMS (ESI-TOF) m/z : $[\text{M} + \text{Na}]^+$ calcd for $\text{C}_{32}\text{H}_{36}\text{O}_6\text{Na}$, 539.2410, found: 539.2415.

15-nitro-3,7,10,16-tetraoxa-1,9(1,2),5(1,3)-tribenzenacyclohexadecaphane-4,6-dione

(126k): Prepared according to general experimental procedure 3.9.2E, a solution of **100j** (0.0075 M, 58 mg) with CH_3CN in a vial and (0.0075 M, 25 mg) of isophthalic acid, (0.036 M, 183 mg) of Mukaiyama salt and (0.03 M, 49 mg) of 1-methylimidazole were dissolved in another vial with CH_3CN . Both reagent solutions were flown through the 7 mL PFA tubing at

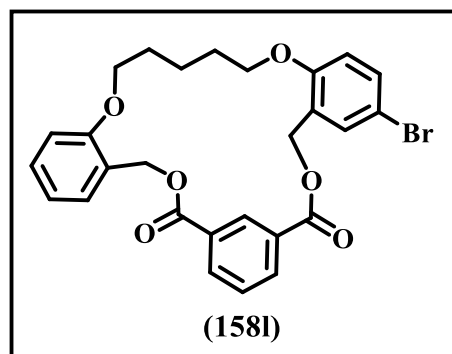


80 °C in a preheated water bath with 3-4 bar pressure. After workup, the residue was purified by using column chromatography ($\text{EtOAc}:\text{n-hexane} = 10:90$) as to afford the desired product **100k** (27.4 mg, 37% yield) as a solid. melting point: 180-183 °C; ^1H NMR (400 MHz, CDCl_3) δ 8.56 (t, $J = 1.5$ Hz, 1H), 8.42 (d, $J = 2.8$ Hz, 1H), 8.25 (dd, $J = 8.2, 2.0$ Hz, 1H), 8.21 (ddd, J

= 9.3, 4.6, 3.1 Hz, 2H), 7.54 – 7.46 (m, 2H), 7.36 – 7.29 (m, 1H), 6.96 (ddd, J = 6.5, 5.9, 4.1 Hz, 3H), 5.45 (s, 2H), 5.43 (s, 2H), 4.19 (t, J = 5.3 Hz, 2H), 4.09 (t, J = 5.3 Hz, 2H), 1.99 – 1.83 (m, J = 18.5, 9.7 Hz, 6H); ^{13}C NMR (100 MHz, CDCl_3) δ 165.9, 165.8, 163.5, 158.7, 141.0, 134.6, 134.4, 133.1, 131.0, 130.7, 130.4, 130.2, 128.8, 128.6, 126.9, 125.2, 124.9, 120.9, 113.3, 111.7, 69.6, 69.3, 63.5, 62.4, 30.2, 29.8, 23.7; FTIR (neat): 2944, 2870, 1716, 1300, 1269 cm^{-1} ; HRMS (ESI-TOF) m/z : $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{27}\text{H}_{26}\text{O}_8$, 492.1658, found: 492.1657.

15-bromo-3,7,10,16-tetraoxa-1,9(1,2),5(1,3)-tribenzenacyclohexadecaphane-4,6-dione (158l):

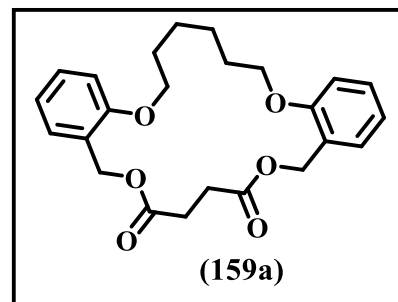
Prepared according to general experimental procedure 3.9.2E, a solution of (5-bromo-2-((5-(2-(hydroxymethyl)phenoxy)pentyl)oxy)phenyl)methanol **100k** (0.0075 M, 58 mg) with CH_3CN in a vial and (0.0075 M, 25 mg) of isophthalic acid, (0.036 M, 183



mg) of Mukaiyama salt and (0.03 M, 49 mg) of 1-methylimidazole were dissolved in another vial with CH_3CN . Both reagent solutions were flown through the 7 mL PFA tubing at 80 °C in a preheated water bath with 3-4 bar pressure. After workup, the residue was purified by using column chromatography ($\text{EtOAc}:n\text{-hexane}$ = 10:90) as to afford the desired product **158l** (30.4 mg, 38% yield) as a solid. melting point: 137-138 °C; ^1H NMR (400 MHz, CDCl_3) δ 8.57 (s, 1H), 8.25 – 8.18 (m, 2H), 7.63 (d, J = 2.0 Hz, 1H), 7.53 – 7.46 (m, 2H), 7.41 (dd, J = 8.7, 1.8 Hz, 1H), 7.32 (t, J = 7.8 Hz, 1H), 6.95 (t, J = 7.2 Hz, 2H), 6.82 (d, J = 8.7 Hz, 1H), 5.43 (s, 2H), 5.36 (s, 2H), 4.08 (t, J = 4.5 Hz, 2H), 4.04 (t, J = 5.0 Hz, 2H), 1.94 – 1.80 (m, 6H); ^{13}C NMR (100 MHz, CDCl_3) δ 166, 165.9, 158.7, 157.8, 135.4, 134.4, 134.3, 133.2, 132.9, 131.0, 130.7, 130.6, 130.2, 128.7, 126.8, 124.8, 120.8, 114.7, 113.1, 112.7, 69.5, 69.1, 63.4, 62.6, 30.1, 30.0, 23.7; FTIR (neat): 2944, 2869, 1716, 1250, 1226 cm^{-1} ; HRMS (ESI-TOF) m/z : $[\text{M} + \text{Na}]^+$ calcd for $\text{C}_{27}\text{H}_{25}\text{O}_6\text{Br}$, 547.0732, found: 547.0727.

6,7,8,9,10,11,20,21-octahydro-17H,24H-dibenzo[b,l][1,5,10,14]tetraoxacycloicosine-19,22-dione (159):

Prepared according to general experimental procedure 3.9.2E, a solution of **100d** (0.0075 M, 49.5 mg) with CH_3CN in a vial and (0.0075 M, 17.7 mg) of succinic acid, (0.036 M, 183 mg) of Mukaiyama salt and (0.03 M, 49 mg) of 1-methylimidazole were dissolved in another vial with CH_3CN . Both reagent solutions were flown

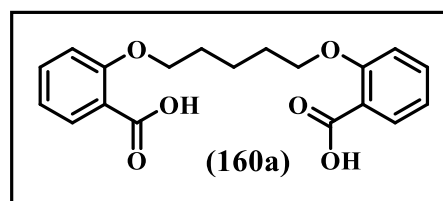


through the 7 mL PFA tubing in 80 °C in a preheated water bath with 3-4 bar pressure. After

workup, the residue was purified by using column chromatography (EtOAc:*n*-hexane = 5:95) to afford the desired product **159** (21.4 mg, 35% yield) as a solid and starting material recovered **100d** (5.6 mg, 17%). melting point: 156-157 °C; ¹H NMR (400 MHz, CDCl₃) δ 7.30 (ddd, *J* = 5.4, 4.8, 1.7 Hz, 3H), 7.27 – 7.23 (m, 1H), 6.94 – 6.87 (m, 3H), 6.86 (d, *J* = 3.0 Hz, 1H), 5.15 (s, 4H), 4.00 (t, *J* = 5.9 Hz, 4H), 2.65 (s, 4H), 1.79 (dd, *J* = 13.2, 6.0 Hz, 4H), 1.61 – 1.51 (m, 4H); ¹³C NMR (100 MHz, CDCl₃) δ 172.1, 158.3, 131.6, 130.5, 124.1, 120.3, 111.8, 77.5, 76.8, 67.9, 63.4, 29.4, 29.4, 25.9; FTIR (neat): 2926, 2857, 1710, 1291, 1152 cm⁻¹; HRMS (ESI-TOF) *m/z*; [M + Na]⁺ calcd for C₂₄H₂₈O₆Na, 435.1783 found: 435.1781.

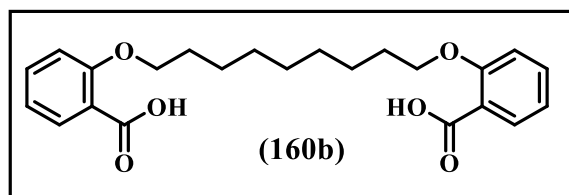
2,2'-(pentane-1,5-diylbis(oxy))dibenzoic acid (**160a**)

: Prepared according to general experimental procedure 3.9.2C, 1,4-dioxane (4.0 mL) solution of diethyl 2,2'-(pentane-1,5-diylbis(oxy))dibenzoate (300 mg, 0.75 mmol), 5N NaOH solution (10.0 mL) was added. The



reaction mixture was stirred at 80 °C in oil bath for overnight. After, the residue was purified by using column chromatography (EtOAc:*n*-hexane = 60:40) as the eluent to afford **160a** (210 mg, 81% yield) as a solid. melting point: 106-107 °C; ¹H NMR (400 MHz, CDCl₃) δ 8.16 (dd, *J* = 7.8, 1.8 Hz, 2H), 7.55 (ddd, *J* = 8.4, 7.4, 1.8 Hz, 2H), 7.16 – 7.09 (m, 2H), 7.04 (d, *J* = 8.2 Hz, 2H), 4.29 (t, *J* = 6.4 Hz, 4H), 2.03 (dt, *J* = 14.5, 6.5 Hz, 4H), 1.78 – 1.68 (m, *J* = 10.4, 6.5 Hz, 2H), COOH peaks are exchanged with deuterium of CDCl₃; ¹³C NMR (100 MHz, CDCl₃) δ 165.9, 165.8, 157.6, 135.2, 133.8, 122.3, 117.9, 112.8, 69.7, 28.7, 22.6; FTIR (neat): 3291, 2941, 1726, 1601, 1456 cm⁻¹; HRMS (ESI-TOF) *m/z*: [M + Na]⁺ calcd for C₁₉H₂₀O₆Na, 367.1153, found: 367.1155.

2,2'-(nonane-1,9-diylbis(oxy))dibenzoic acid (160b**):** Prepared according to general experimental procedure 3.9.2C, 1,4-dioxane (4.0 mL) solution of diethyl 2,2'-(nonane-1,9-diylbis(oxy))dibenzoate (650 mg, 1.42 mmol), 5N NaOH solution (10.0 mL) was added. The



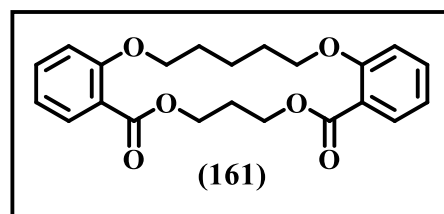
reaction mixture was stirred at 80 °C in an oil bath for overnight. After, the residue was purified by using column chromatography (EtOAc:*n*-hexane = 60:40) as the eluent to afford **160b** (510 mg, 89% yield) as a solid. melting point: 92-94 °C; ¹H NMR (400 MHz, CDCl₃) δ 8.17 (dd, *J* = 7.8, 1.3 Hz, 2H), 7.55 (dd, *J* = 11.2, 4.5 Hz, 2H), 7.15 – 7.08 (m, 2H), 7.04 (d, *J* = 8.4 Hz, 2H), 4.25 (t, *J* = 6.4 Hz, 4H), 1.96 – 1.87 (m, 4H), 1.49 (dd, *J* = 14.0, 6.4 Hz, 4H), 1.43 – 1.35 (m, 6H), COOH peaks are exchanged with deuterium of CDCl₃; ¹³C NMR (100 MHz, CDCl₃)

δ 165.9, 157.8, 135.2, 133.8, 122.2, 117.8, 112.8, 70.3, 29.3, 29.1, 29, 25.9; FTIR (neat): 3261, 2930, 2856, 1735, 1602, 1458 cm^{-1} ; HRMS (ESI-TOF) m/z : $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{23}\text{H}_{29}\text{O}_6$, 401.1964, found: 401.1970.

7,8,9,10,19,20-hexahydro-6*H*,16*H*,18*H*,22*H*-

dibenzo[*b,k*][1,5,9,13]tetraoxacyclooctadecine-16,22-dione (161): Prepared according to

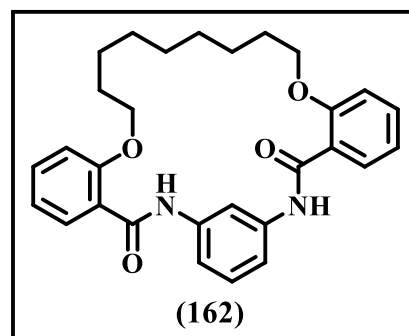
general experimental procedure 3.9.2E, a solution of propane-1,3-diol (0.0075 M, 11.4 mg) with CH_3CN in a vial and (0.0075 M, 51.6 mg) of 2,2'-(pentane-1,5-diylbis(oxy))dibenzoic acid (0.036 M, 183 mg) of



of Mukaiyama salt and (0.03 M, 49 mg) of 1-methylimidazole were dissolved in another vial with CH_3CN . Both reagent solutions were flown through the 7 mL PFA tubing in 80 °C in a preheated water bath with 3-4 bar pressure. After workup, the residue was purified by using column chromatography ($\text{EtOAc}:\textit{n}$ -hexane = 5:95) as to afford the desired product **161a** (23 mg, 40% yield) as a semi-solid (6.4 mg, 18%). ^1H NMR (400 MHz, CDCl_3) δ 7.73 (dd, J = 7.6, 1.5 Hz, 2H), 7.43 (t, J = 7.9 Hz, 2H), 6.96 (dd, J = 17.9, 8.0 Hz, 4H), 4.47 (t, J = 6.3 Hz, 4H), 4.06 (t, J = 5.4 Hz, 4H), 2.24 (dd, J = 12.6, 6.3 Hz, 2H), 1.90 (dd, J = 12.4, 7.0 Hz, 2H), 1.79 (d, J = 6.4 Hz, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 167.9, 158.0, 133.2, 131.6, 121.1, 120.1, 112.6, 69.1, 61.3, 30.0, 29.7, 28.4, 24.8; FTIR (neat): 2930, 2807, 1715, 1291, 1128 cm^{-1} ; HRMS (ESI-TOF) m/z : $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{22}\text{H}_{25}\text{O}_6$, 385.1651, found: 385.1646.

8,18-dioxa-3,5-diaza-1,7(1,2),4(1,3)-tribenzenacyclooctadecaphane-2,6-dione (162):

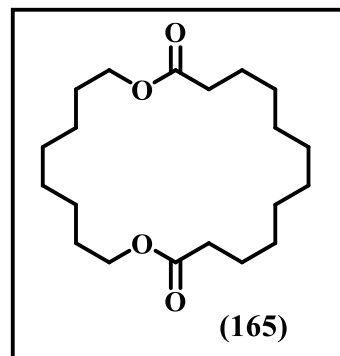
Prepared according to general experimental procedure 3.9.2E, a solution of (0.0075 M, 19 mg) of *m*-phenylenediamine with CH_3CN in a vial and (0.0075 M, 68 mg) of 2,2'-(nonane-1,9-diylbis(oxy)) dibenzoic acid (0.036 M, 183 mg) of Mukaiyama salt and (0.03 M, 49 mg) of 1-methylimidazole were dissolved in another vial with CH_3CN . Both reagent solutions were flown through the 7



mL PFA tubing at 80 °C in a preheated water bath with 3-4 bar pressure. After workup, the residue was purified by using column chromatography ($\text{EtOAc}:\textit{n}$ -hexane = 5:95) to afford the desired product **162** (26.3 mg, 33% yield) as a semi-solid. ^1H NMR (400 MHz, CDCl_3) δ 9.61 (s, 2H), 8.21 (dd, J = 7.8, 1.8 Hz, 2H), 7.84 (dd, J = 8.2, 2.0 Hz, 2H), 7.47 (ddd, J = 8.4, 7.4, 1.8 Hz, 2H), 7.41 (t, J = 8.2 Hz, 1H), 7.14 – 7.09 (m, 3H), 7.02 (d, J = 8.4 Hz, 2H), 4.22 (t, J

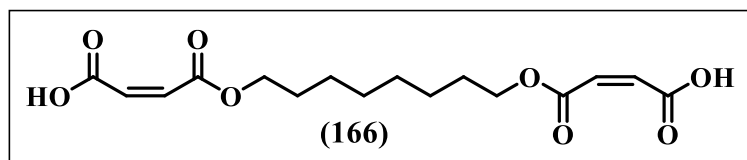
= 5.8 Hz, 4H), 1.88 (dt, J = 15.1, 5.9 Hz, 4H), 1.49 (dd, J = 15.2, 7.6 Hz, 4H), 1.39 – 1.32 (m, 4H), 1.29 (dd, J = 8.5, 2.5 Hz, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 163.9, 156.8, 138.8, 133.2, 132.5, 130.1, 122.6, 121.7, 118.0, 113.2, 112.6, 70.3, 69.8, 29.4, 28.7, 28.9, 28.7, 28.6, 26.3, 25.9; FTIR (neat): 2928, 2855, 1666, 1601, 1485, 1300, 1233 cm^{-1} ; HRMS (ESI-TOF) m/z : $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{29}\text{H}_{33}\text{N}_2\text{O}_4$, 473.2440, found: 473.2446.

1,10-dioxacyclodocosane-11,22-dione (165): Prepared according to general experimental procedure 3.9.2E, a solution of octane-1,8-diol **131** (0.0075 M, 43 mg) with CH_3CN in a vial and (0.0075 M, 69 mg) of dodecanedioic acid **163**, (0.036 M, 183 mg) of Mukaiyama salt and (0.03 M, 49 mg) of 1-methylimidazole were dissolved in another vial with CH_3CN . Both reagent solutions were flown through the 7 mL PFA tubing in 80 °C in the preheated water



bath with 3-4 bar pressure. After workup, the residue was purified by using column chromatography ($\text{EtOAc}:\text{n-hexane}$ = 5:95) to afford the desired product **165** (21 mg, 21% yield) as a semisolid. ^1H NMR (400 MHz, CDCl_3) δ 4.11 (t, J = 5.8 Hz, 4H), 2.34 – 2.28 (m, 4H), 1.68 – 1.56 (m, 12H), 1.36 (ddd, J = 12.3, 8.3, 4.6 Hz, 14H); ^{13}C NMR (100 MHz, CDCl_3) δ 174.2, 64.2, 34.5, 29.0, 28.6, 26.2, 25.2; FTIR (neat): 1716, 1421, 1214, 1116 cm^{-1} ; HRMS (ESI-TOF) m/z : $[\text{M} + \text{Na}]^+$ calcd for $\text{C}_{20}\text{H}_{36}\text{O}_4\text{Na}$, 363.2511, found: 363.2514.8

(2Z,2'Z)-4,4'-(octane-1,8-diylbis(oxy))bis(4-oxobut-2-enoic acid (166): In 250ml round bottomed flask under nitrogen was charged with anhydride (2 gm, 20 mmol) and diol (1,4 gm, 10 mmol) in anhydrous

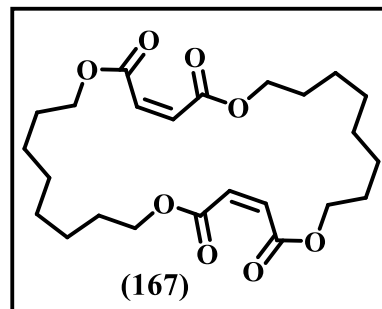


dichloromethane (100 ml). The stirred reaction mixture was cooled to 0 °C in an ice bath and (2 gm, 20.4 mmol of triethylamine) was added. The reaction was continued for 4 hrs at 0 °C and further at room temperature for 5 hr. The reaction was monitored by TLC. After all the anhydride was reacted, the solvent was evaporated. The residue was cooled to 0 °C in an ice bath and added 200 mL of saturated sodium bicarbonate solution and extracted with ether. The aqueous layer was cooled to 0 °C in an ice bath and acidified with dilute hydrochloric acid followed by the extraction with diethyl ether or dichloromethane (4 x 100 mL). The entire organic layers were combined and evaporated under reduced pressure to provide the corresponding pure dicarboxylic acid **166** (61%, 12.5 mmol) yield as a white solid. melting point: 103-105 °C; ^1H NMR (400 MHz, CDCl_3) δ 6.37 (s, 4H), 4.26 (t, J = 6.5 Hz, 4H), 1.75 –

1.66 (m, 4H), 1.41 – 1.33 (m, 8H); COOH peak exchanged with deuterium of CDCl₃; ¹³C NMR (100 MHz, CDCl₃) δ 167.2, 166.8, 133.6, 130.5, 66.6, 28.90, 28.3, 25.6; FTIR (neat): 2923, 2854, 1716, 1421, 1214 cm⁻¹; HRMS (ESI-TOF) *m/z*: [M +Na]⁺ calcd for C₁₆H₂₂O₄Na, 365.1212, found: 365.1210.

(3Z,17Z)-1,6,15,20-tetraoxacyclooctacos-3,17-diene-2,5,16,19-tetraone (167): Prepared

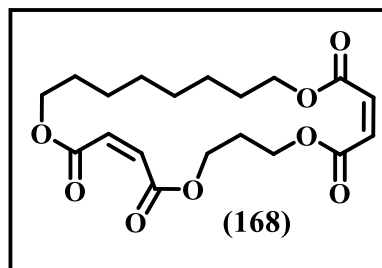
according to general experimental procedure 3.9.2E, a solution of (0.0075 M, 17.61 mg) of octanediol **164** with CH₃CN in a vial and (0.0075 M, 51.3 mg) of (**166**), (0.036 M, 183 mg) of Mukaiyama salt and (0.03 M, 49 mg) of 1-methylimidazole were dissolved in another vial with CH₃CN. Both reagent solutions were flown through the 7 mL PFA



tubing in 80 °C in a preheated water bath with 3-4 bar pressure. After workup, the residue was purified by using column chromatography (EtOAc:*n*-hexane = 5:95) to afford the desired product **167** (16.1 mg, 23% yield) as a semi-solid and 12 mg starting material recorded. ¹H NMR (400 MHz, CDCl₃) δ 6.85 (s, 4H), 4.23 (t, *J* = 5.8 Hz, 8H), 1.73 – 1.64 (m, 8H), 1.38 (m, 16H); ¹³C NMR (100 MHz, CDCl₃) δ 165.28, 133.76, 65.44, 29.84, 29.19, 28.7, 25.9; FTIR (neat): 2926, 2854, 1716, 1642, 1263, cm⁻¹; HRMS (ESI-TOF) *m/z*: [M +Na]⁺ calcd for C₂₄H₃₆O₈Na, 475.2307, found: 475.2307.

(7Z,21Z)-1,5,10,19-tetraoxacyclotricosa-7,21-diene-6,9,20,23-tetraone (168): Prepared

according to general experimental procedure 3.9.2E, a solution of (0.0075 M, 11.4 mg) of propanediol with CH₃CN in a vial and (0.0075 M, 51.3 mg) of (**166**), (0.036 M, 183 mg) of Mukaiyama salt and (0.03 M, 49 mg) of 1-methylimidazole were dissolved in another vial with CH₃CN.



Both reagent solutions were flown through the 7 mL PFA tubing in 80 °C in preheated water bath with 3-4 bar pressure. After workup, the residue was purified by using column chromatography (EtOAc:*n*-hexane = 5:95) to afford the desired product **168** (14 mg, 25% yield) as a semi-solid ¹H NMR (400 MHz, CDCl₃) δ 6.82 (d, *J* = 15.8 Hz, 2H), 6.76 (d, *J* = 15.8 Hz, 2H), 4.40 – 4.36 (m, 4H), 4.27 – 4.22 (m, 4H), 2.15 (dd, *J* = 11.2, 5.8 Hz, 2H), 1.69 – 1.63 (m, 4H), 1.37 (s, 6H); ¹³C NMR (100 MHz, CDCl₃) δ 165.1, 165.0, 132.9, 65.5, 63.9, 28.5, 28.3, 27.6, 25.2.; FTIR (neat): 2927, 2855, 1715, 1644, 1265, cm⁻¹; HRMS (ESI-TOF) *m/z*: [M +H]⁺ calcd for C₁₉H₂₇O₈, 383.1706 found: 383.1702.

3.9.4 X-ray structure

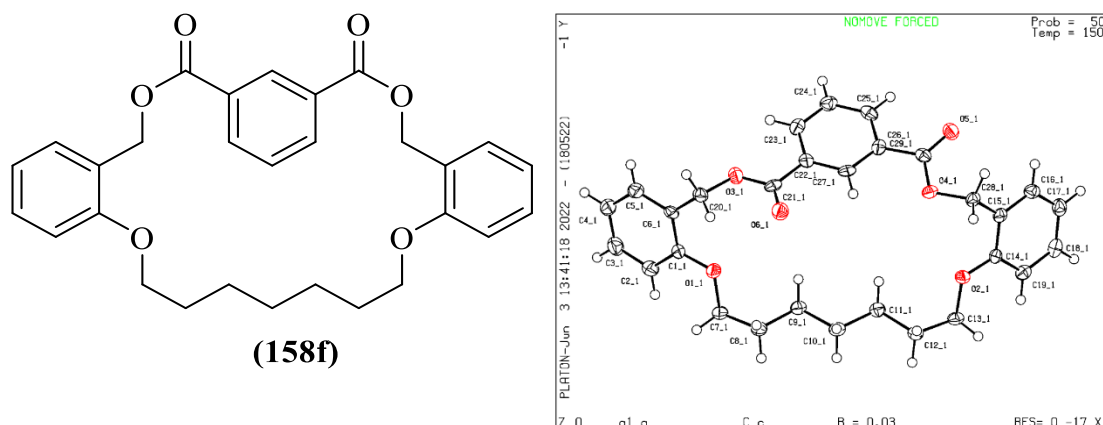


Figure 76. ORTEP crystal structure of **158f** showing thermal ellipsoids at the 50% probability level

Crystallographic parameters of **158f**

Parameters	158f
Empirical formula	C ₂₉ H ₃₀ O ₆
Formula Mass/g mol	474.53
Experimental crystal description	Crystalline Solid
Colour	white
D _{calc} /g cm ⁻³	1.275
Crystal system	monoclinic
Space group	C c
a/ Å	18.870(2)
b/ Å	16.0859(18)
c/ Å	8.1501(9)
α/ deg	90
β/ deg	92.106(4)
γ/ deg	90
V/Å ³	2472.2(5)
Z	4
T / K	150 K
Diffraction Source	CuKα

Diffraction radiation wavelength/ Å	1.54178
Diffraction reflection theta full	0.998
Reflection number total	3464
Reflection number gt	3406
μ/mm^{-1}	0.720
F(000)	1008.0
$R_1, wR_2 [I > 2\sigma(I)]$	0.0345, 0.1033
$R_1, wR_2(\text{all data})$	0.0350, 0.1036
GoF	1.281

Crystal preparation: The crystals are grown by simple recrystallization method where pure compounds isolated after column chromatography are dissolved in dichloromethane and layered with hexane, kept at room temperature to get compound **158f** pure crystal. More information on crystal structures can also be obtained from the Cambridge Crystallographic Data Centre (CCDC) with deposition numbers 2176849.

3.10. Appendix II: Copies of ^1H and ^{13}C NMR spectra of Representative Compounds.

Entry	Data	Figure No
SM-1	^1H and ^{13}C	56-57
153a	^1H and ^{13}C	58-59
153b	^1H and ^{13}C	60-61
154a	^1H and ^{13}C	62-63
154b	^1H and ^{13}C	64-65
100a	^1H and ^{13}C	66-67
100b	^1H and ^{13}C	68-69
158a	^1H and ^{13}C	70-71
158b	^1H and ^{13}C	72-73
160	^1H and ^{13}C	74-75

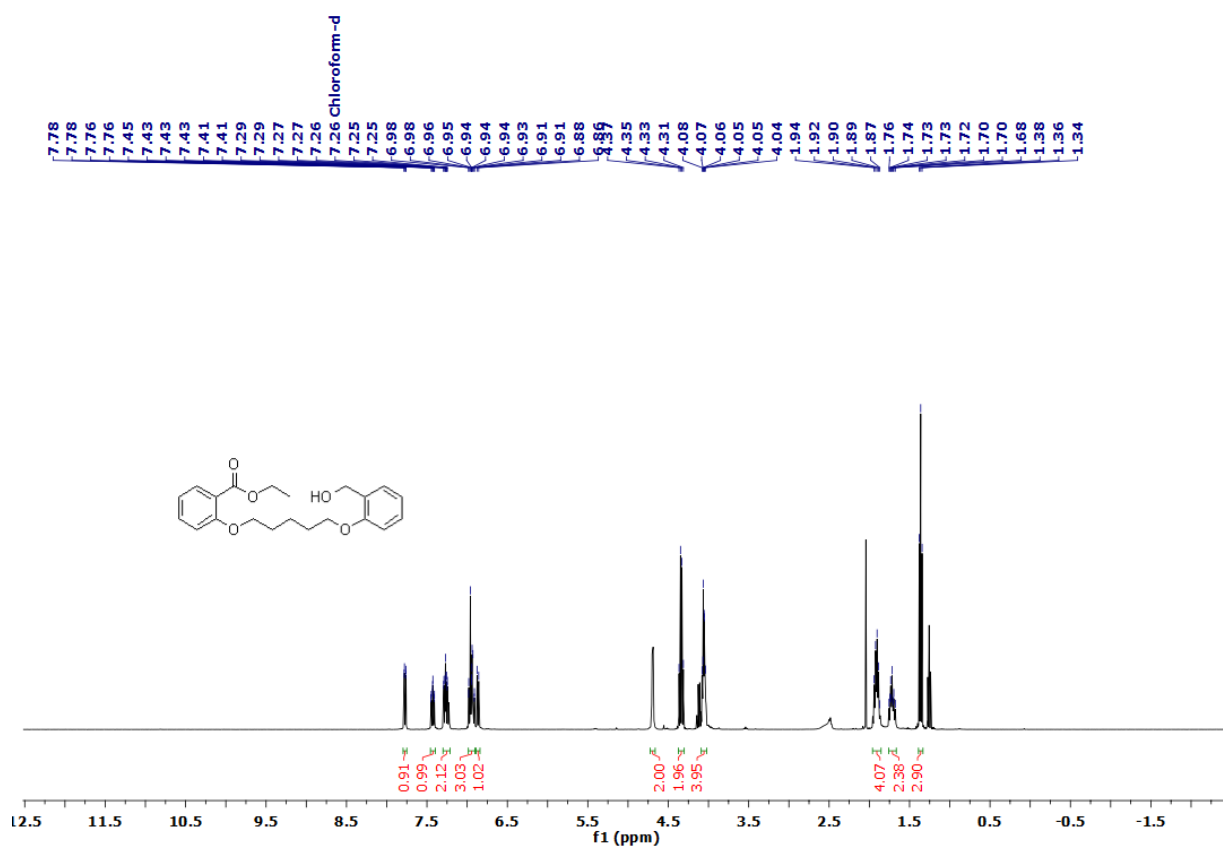


Figure 56. ¹H NMR spectra for compound **SM-1**, 400 MHz, CDCl₃

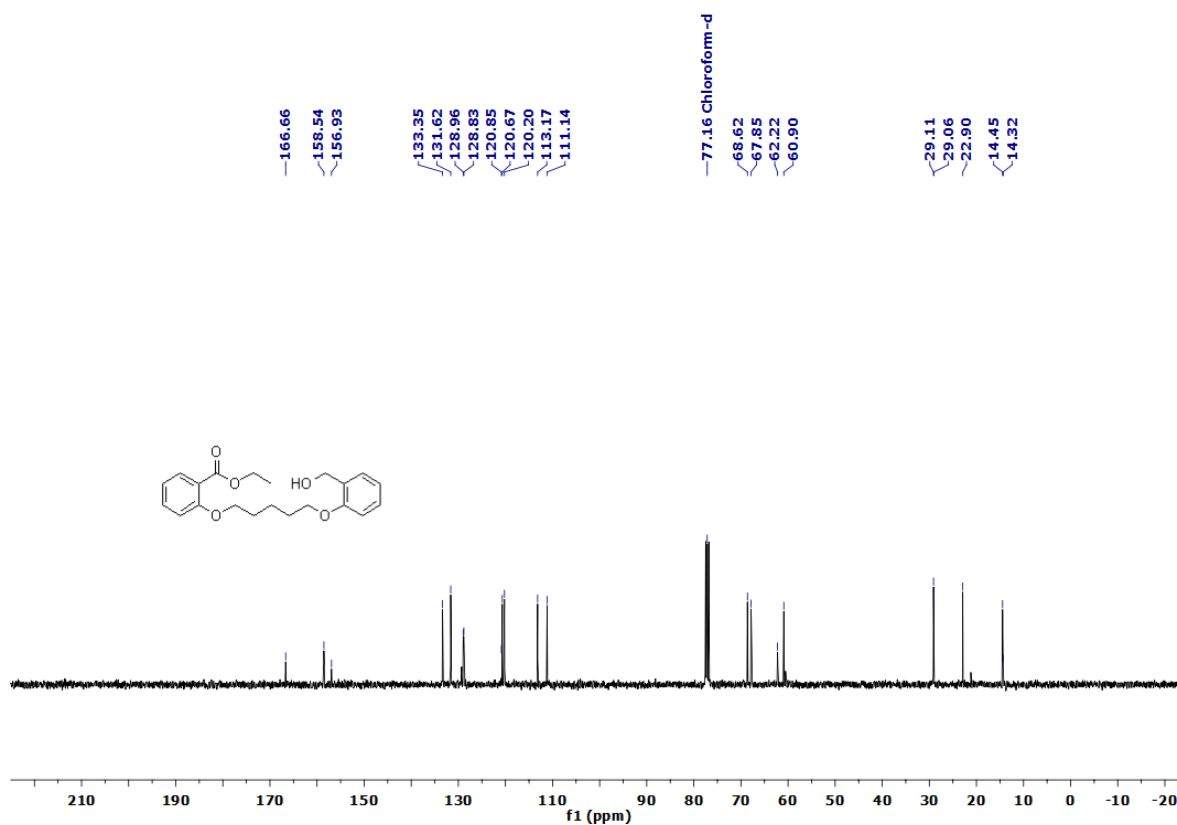


Figure 57. ¹³C NMR spectra for compound **SM-1**, 100 MHz, CDCl₃

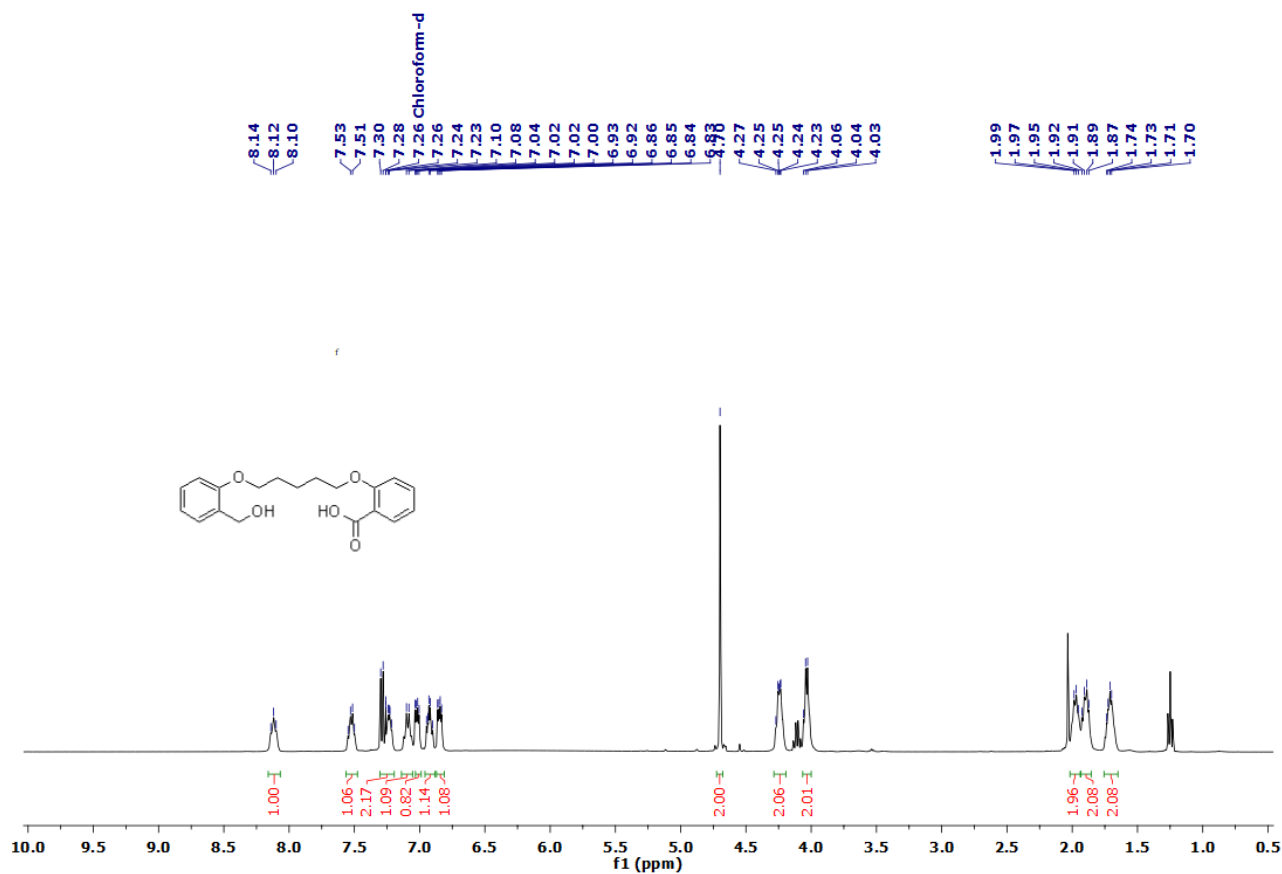


Figure 58. ¹H NMR spectra for compound **153a**, 400 MHz, CDCl₃

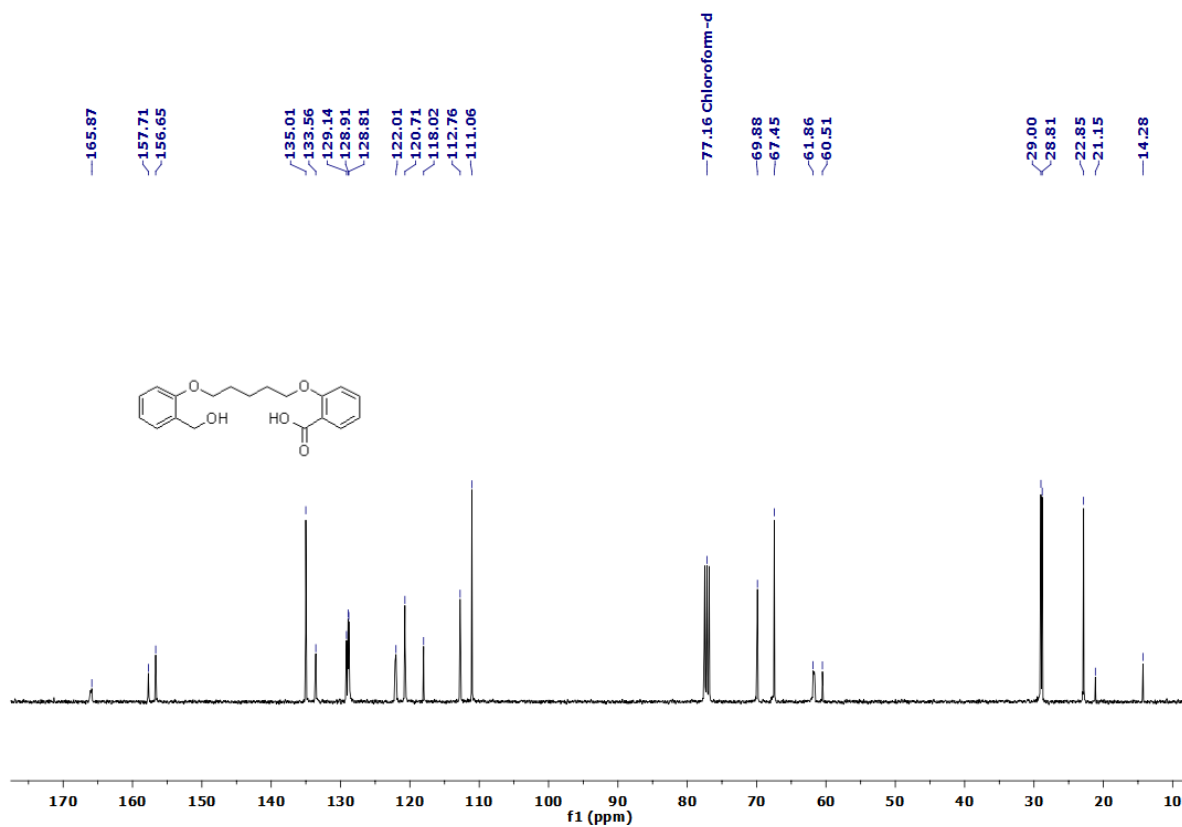


Figure 59. ¹³C NMR spectra for compound **153a**, 100 MHz, CDCl₃

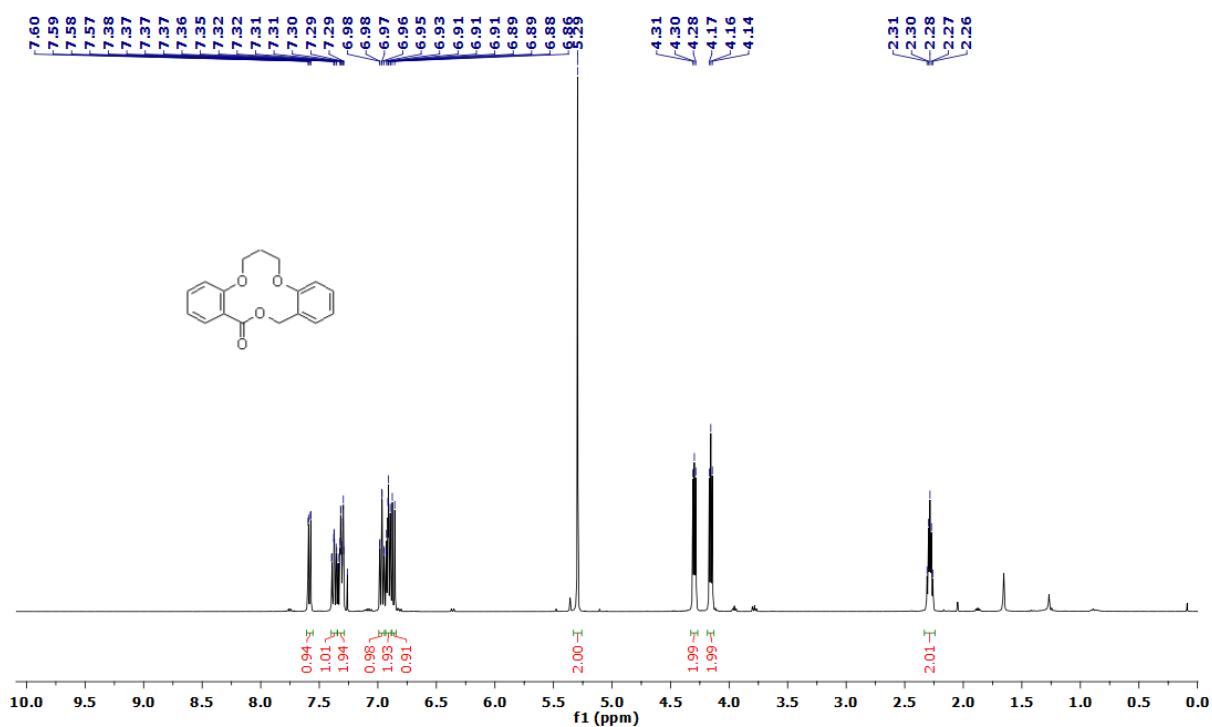


Figure 60. ¹H NMR spectra for compound **154b**, 400 MHz, CDCl₃

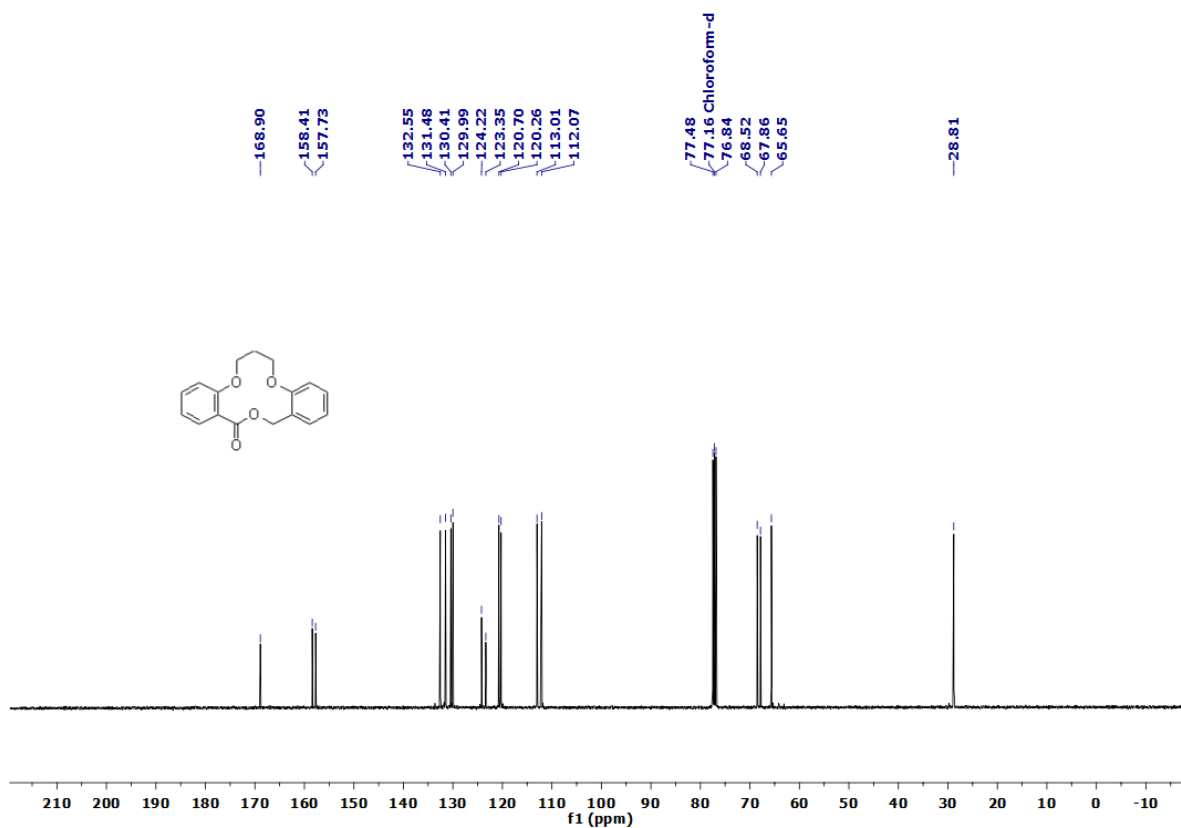


Figure 61. ¹³C NMR spectra for compound **154b**, 100 MHz, CDCl₃

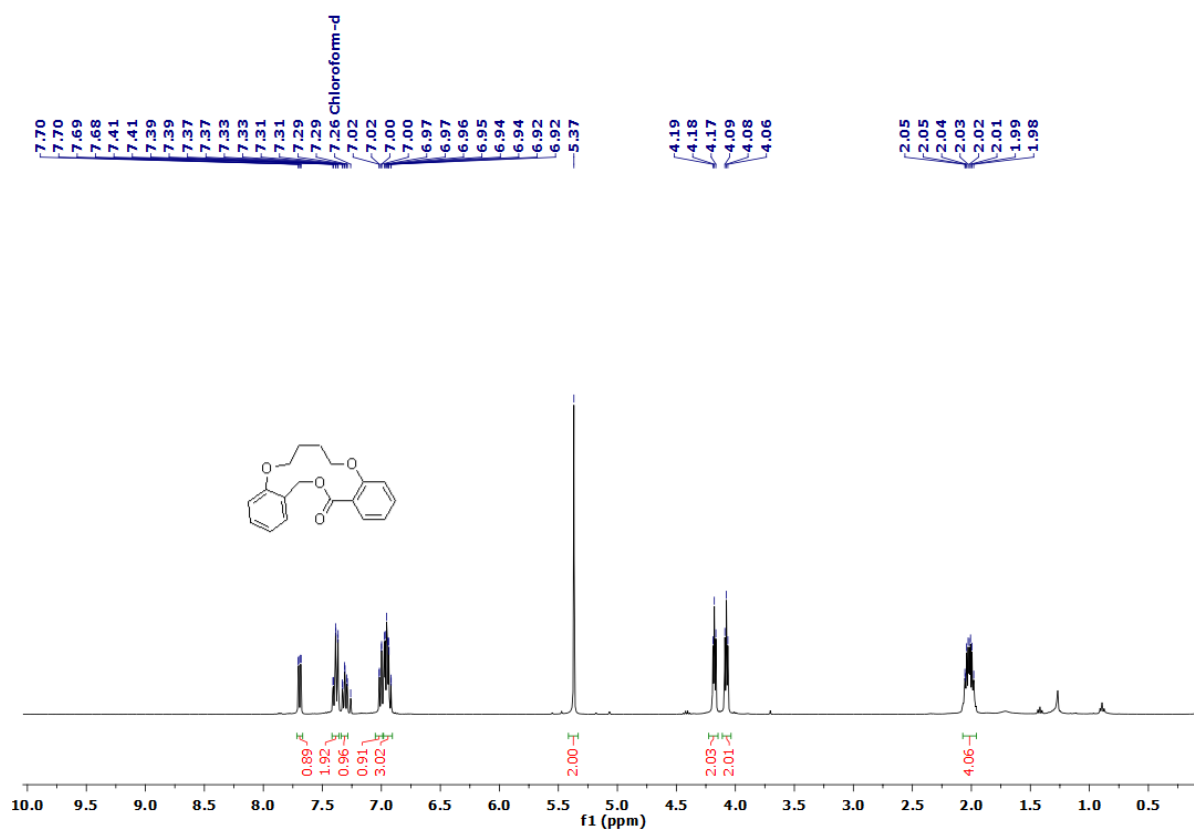


Figure 62. ¹H NMR spectra for compound **154c**, 400 MHz, CDCl₃

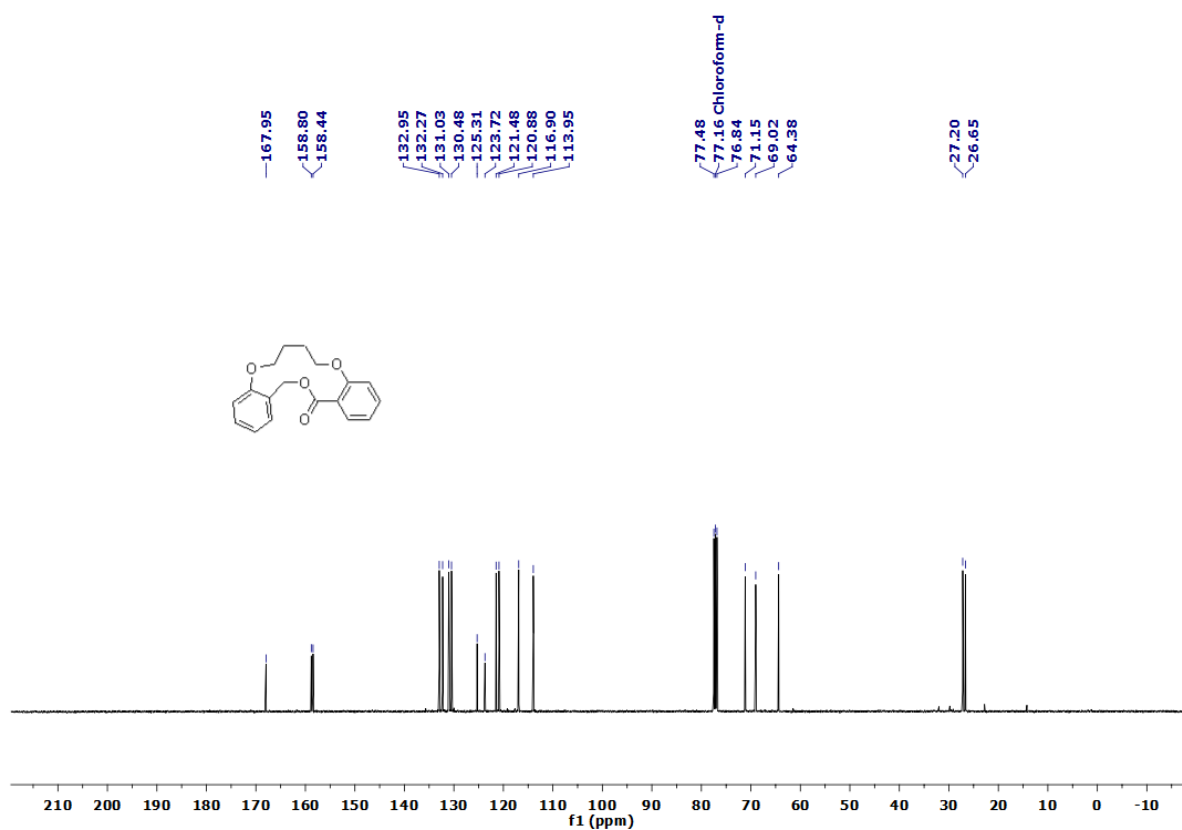


Figure 63. ¹³C NMR spectra for compound **154c**, 100 MHz, CDCl₃

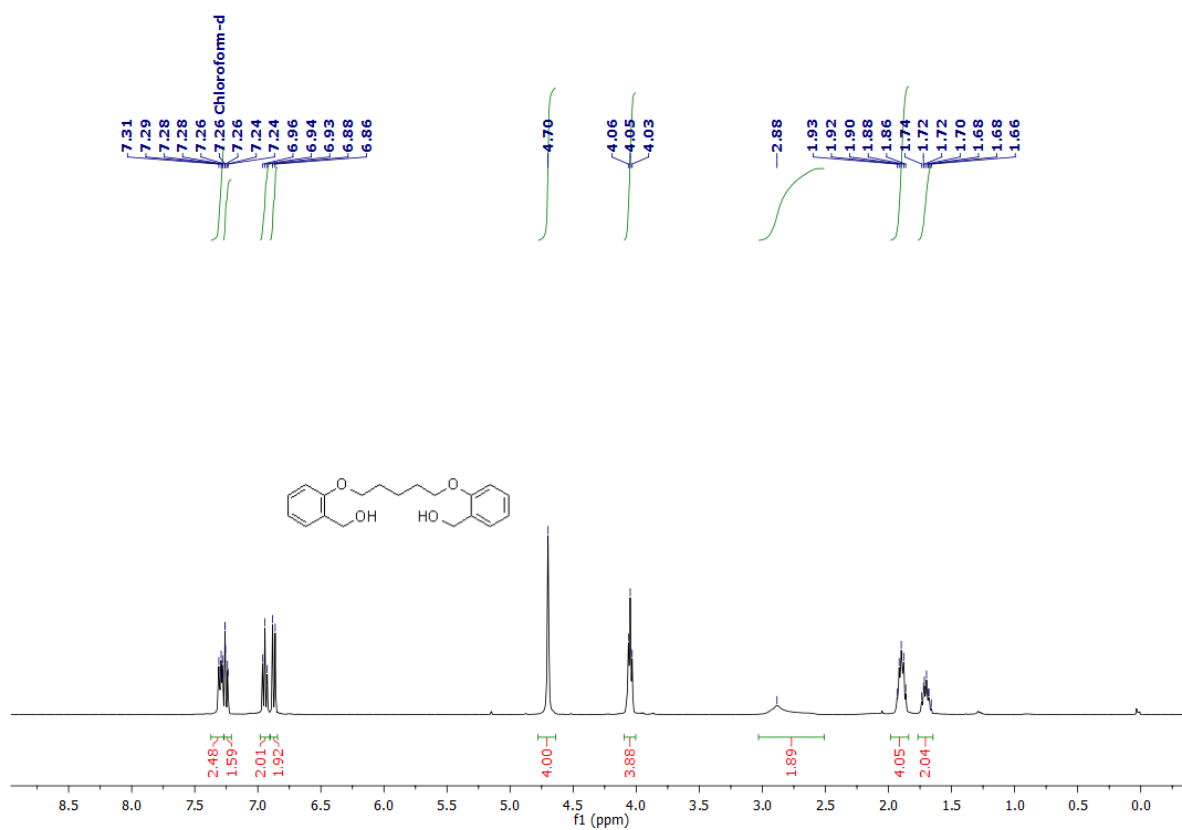


Figure 64. ¹H NMR spectra for compound **100a**, 400 MHz, CDCl₃

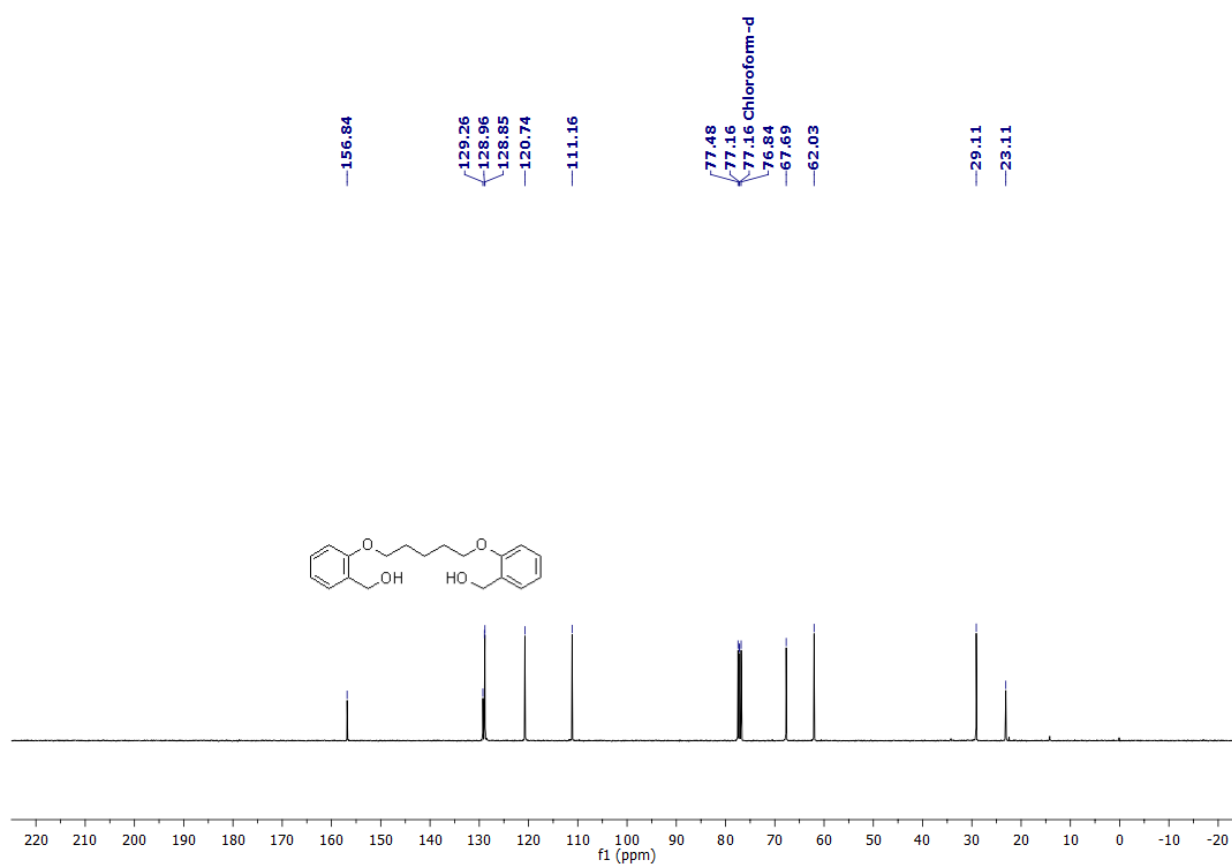


Figure 65. ¹³C NMR spectra for compound **100a**, 100 MHz, CDCl₃

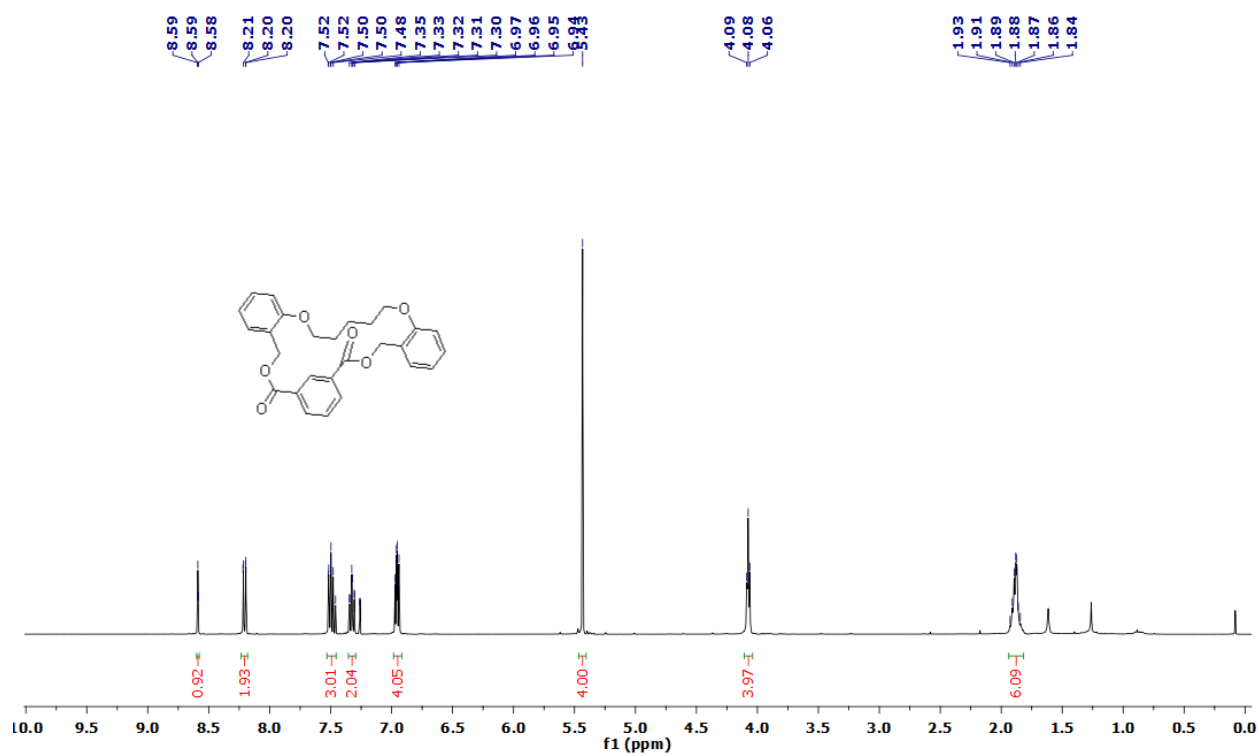


Figure 66. ¹H NMR spectra for compound **158a**, 400 MHz, CDCl₃

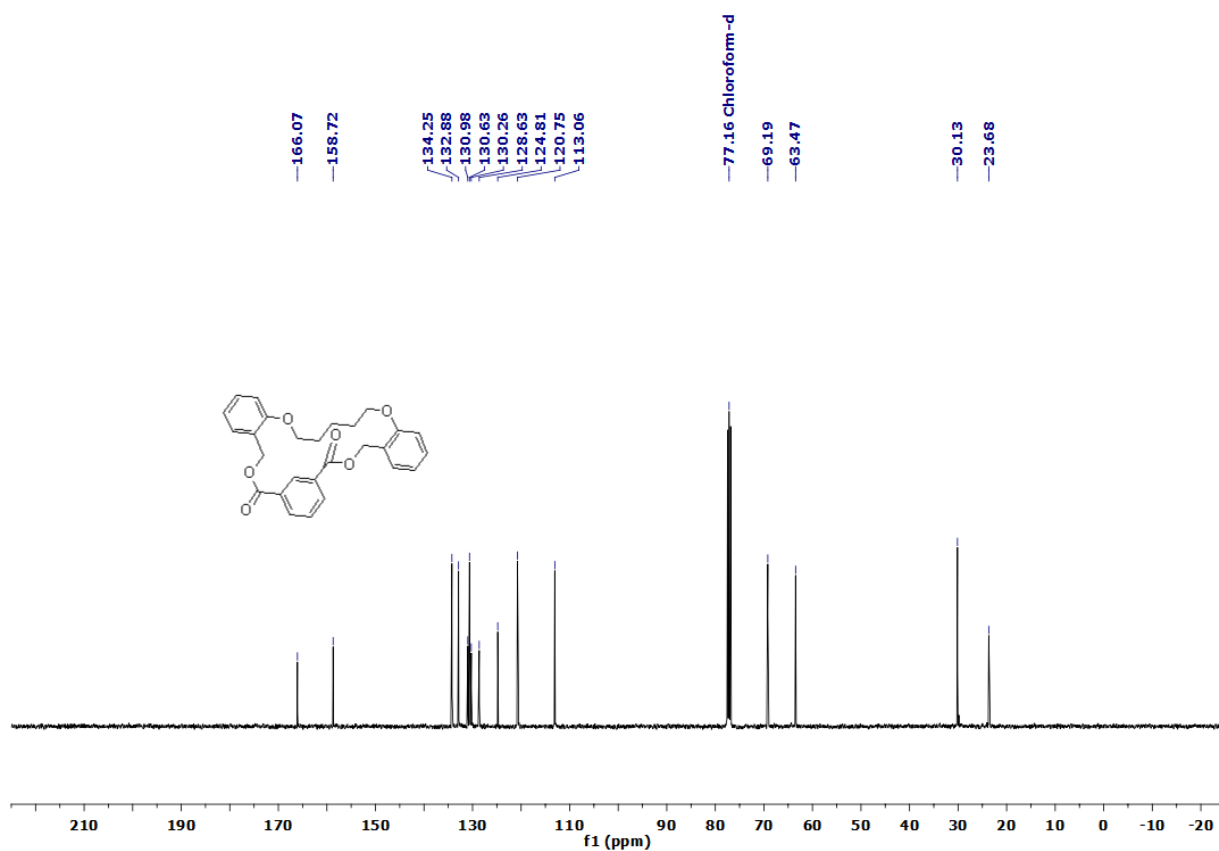


Figure 67. ¹³C NMR spectra for compound **158a**, 100 MHz, CDCl₃

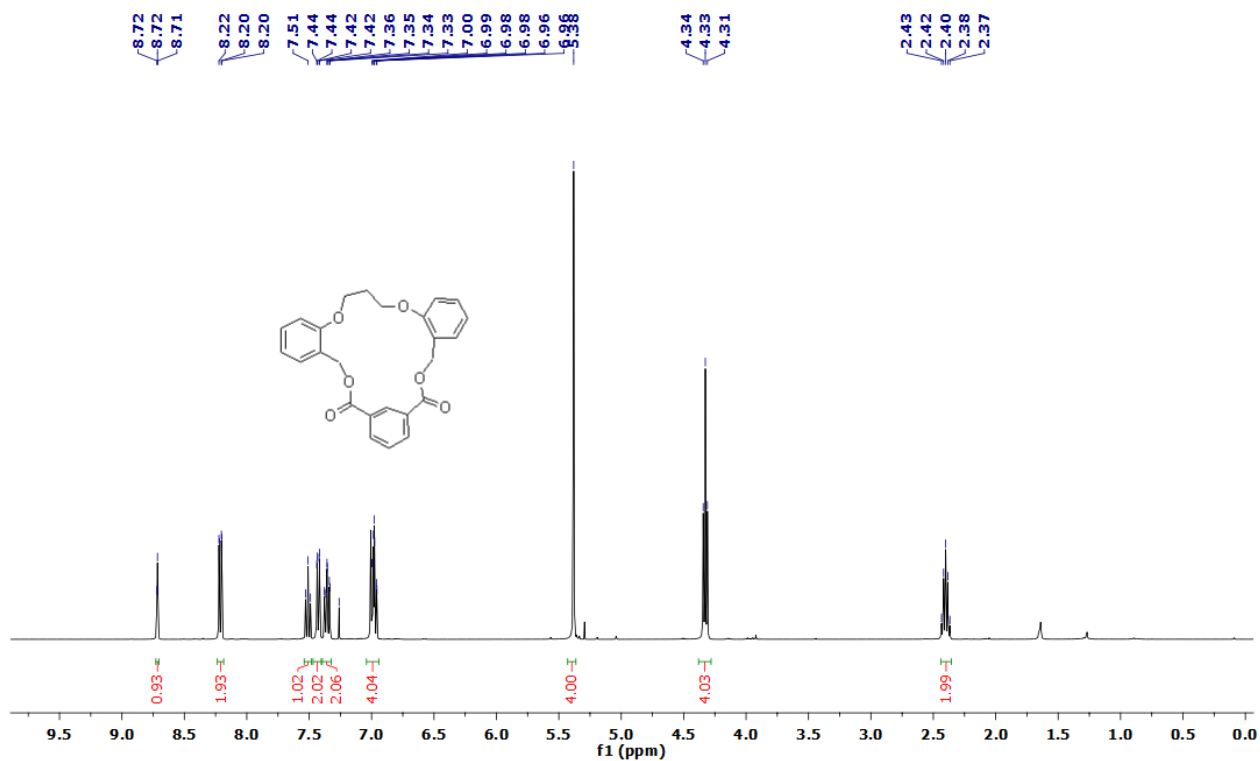


Figure 68. ^1H NMR spectra for compound **158b**, 400 MHz, CDCl_3

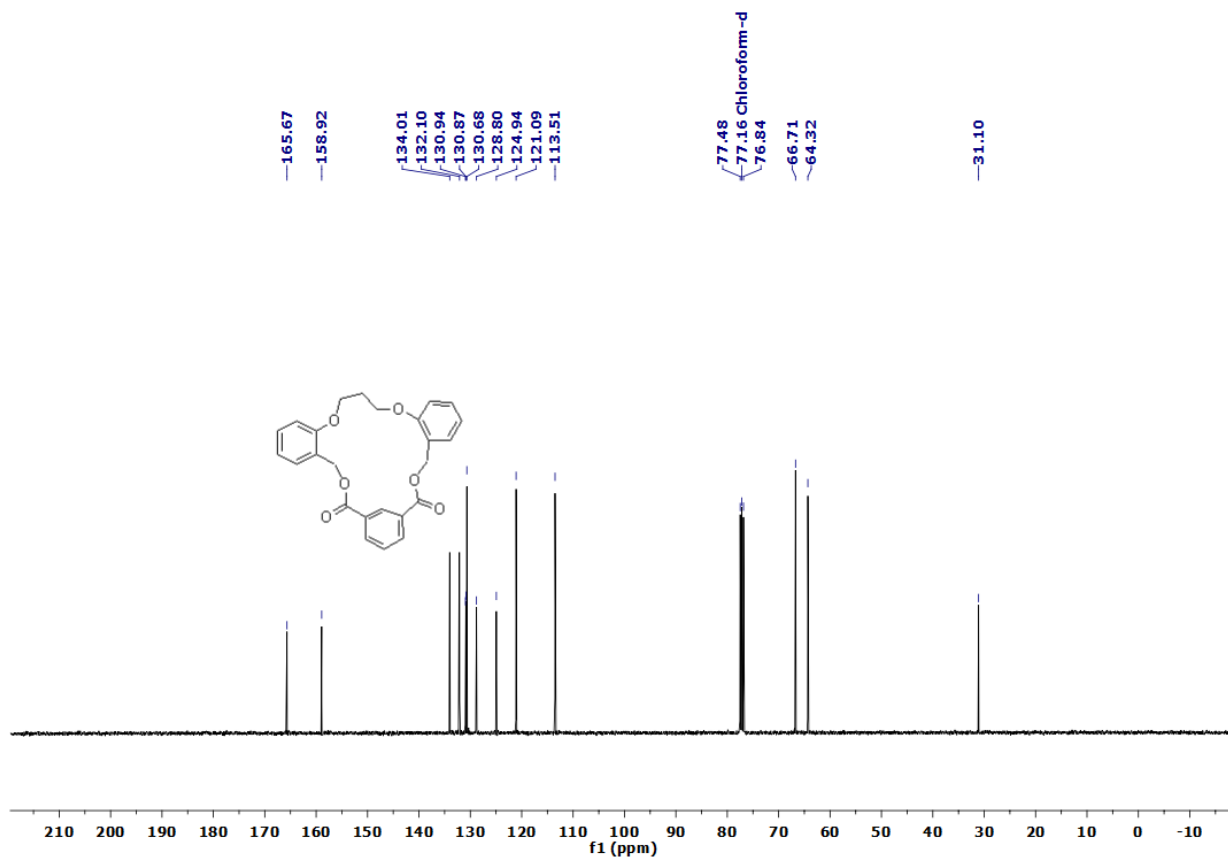


Figure 69. ^{13}C NMR spectra for compound **158b**, 100 MHz, CDCl_3

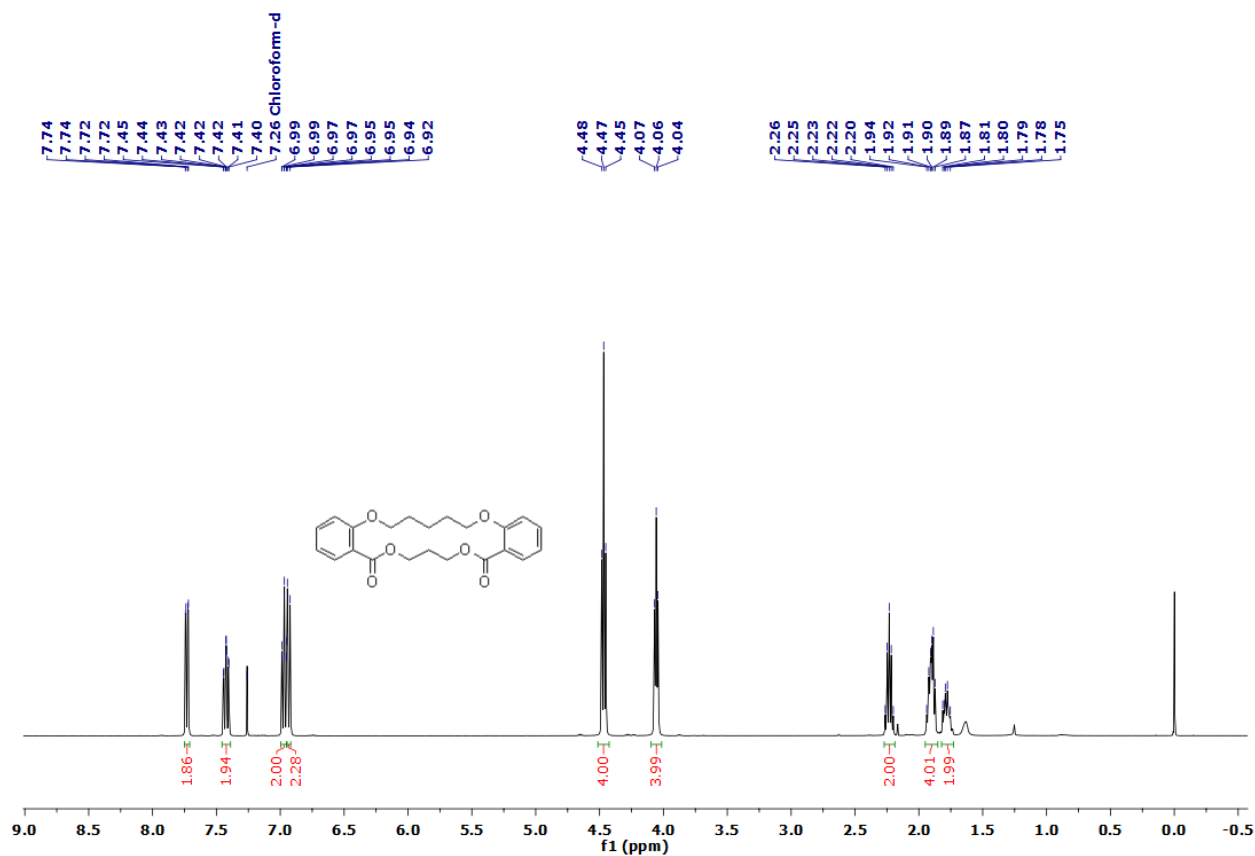


Figure 70. ¹H NMR spectra for compound **159**, 400 MHz, CDCl₃

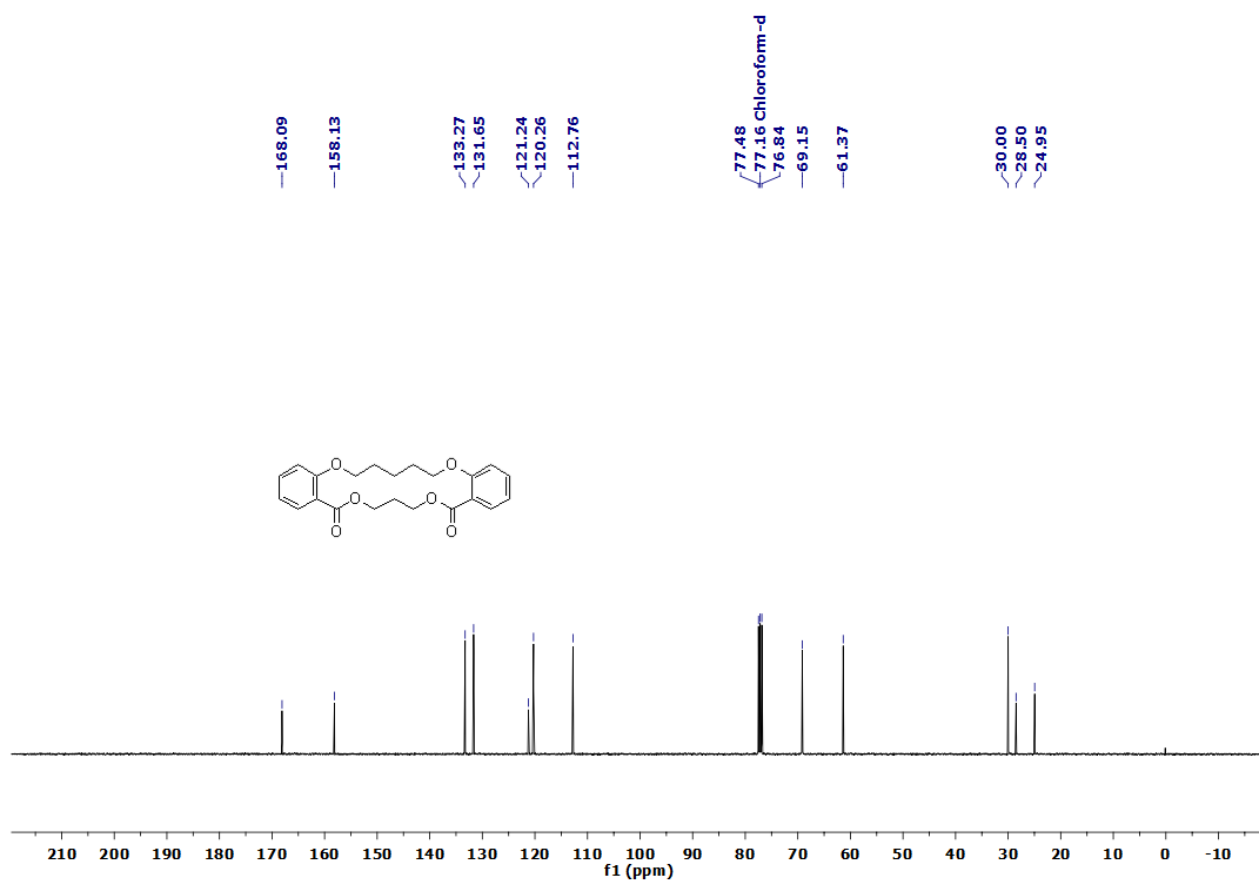


Figure 71. ¹³C NMR spectra for compound **159**, 100 MHz, CDCl₃

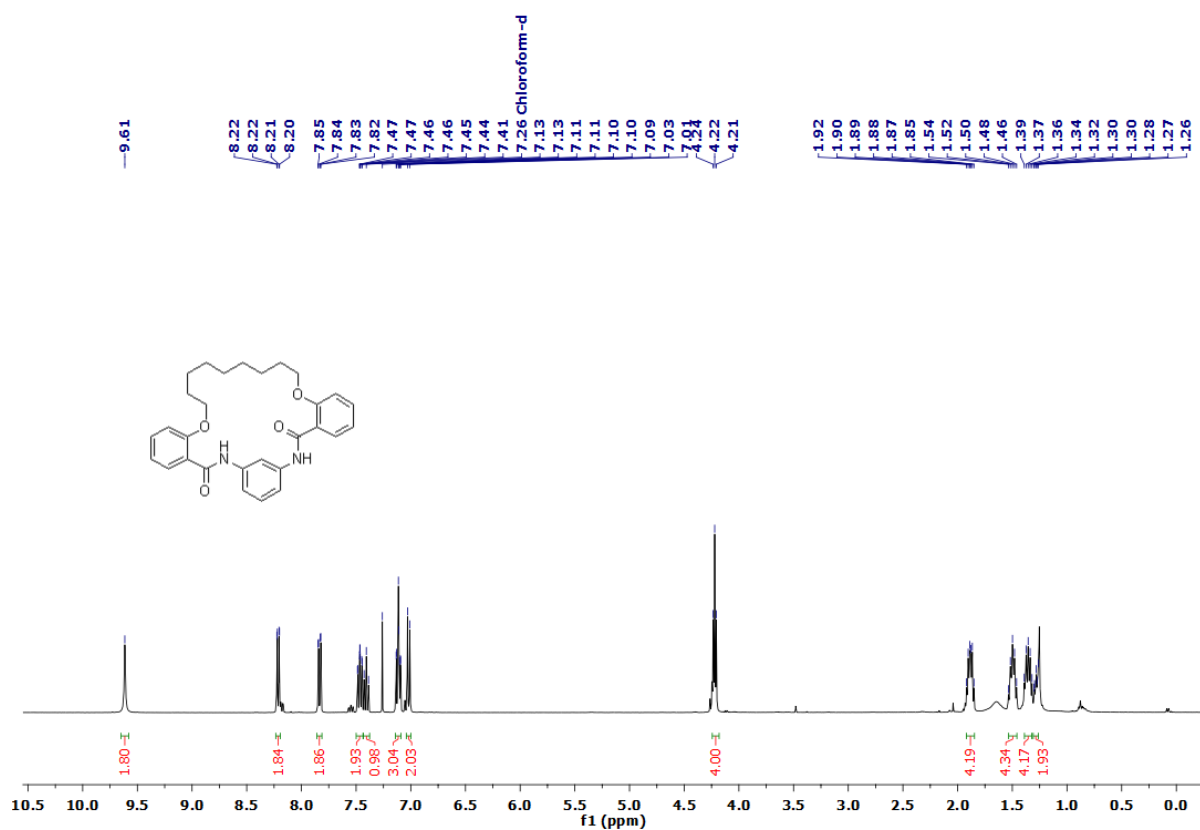


Figure 72. ¹H NMR spectra for compound **162** 400 MHz, CDCl₃

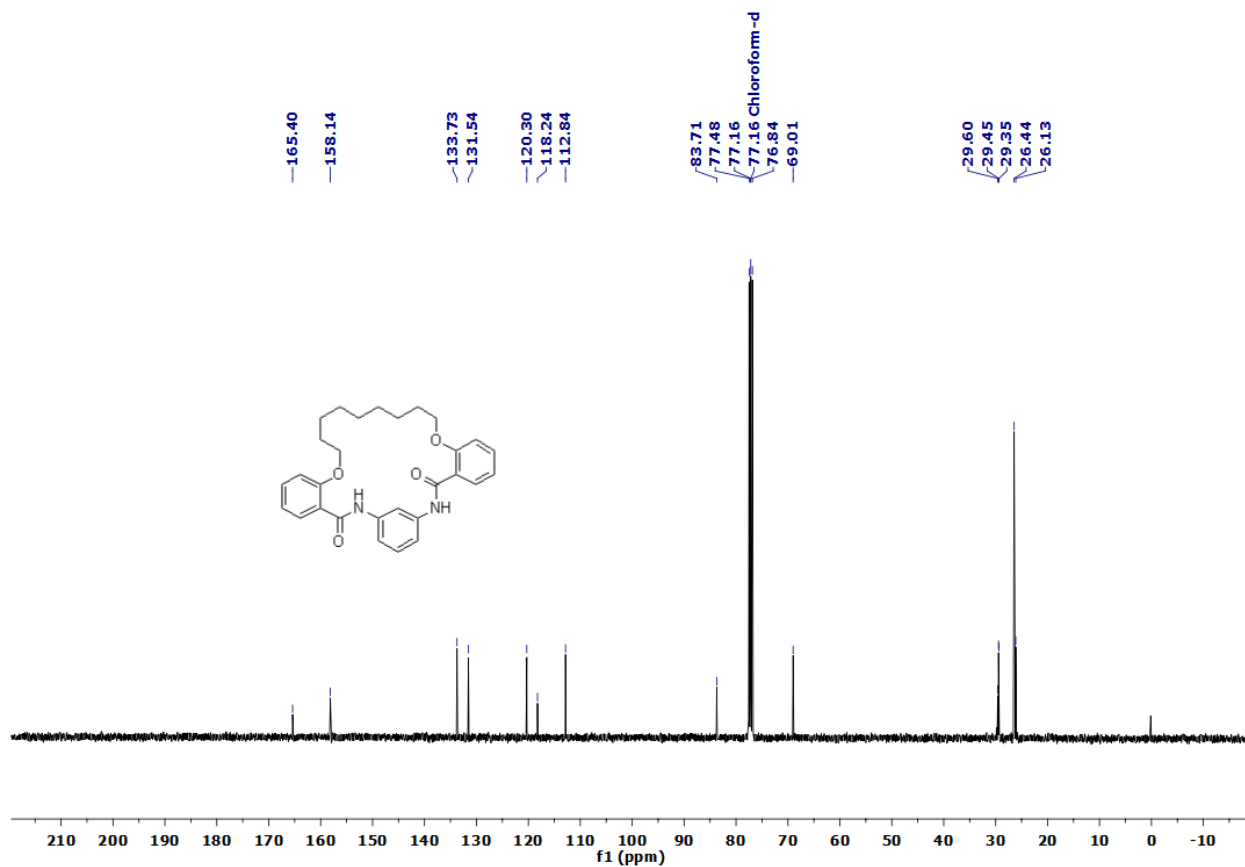


Figure 73. ¹³C NMR spectra for compound **162**, 100 MHz, CDCl₃

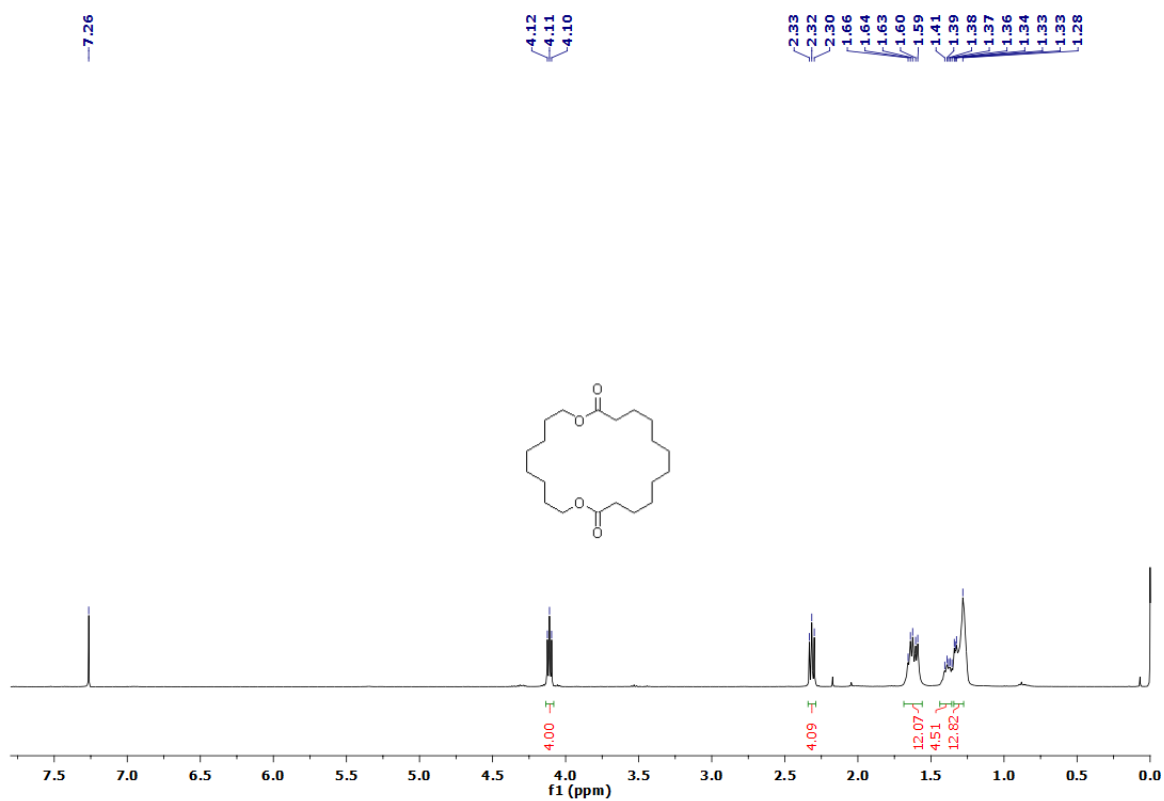
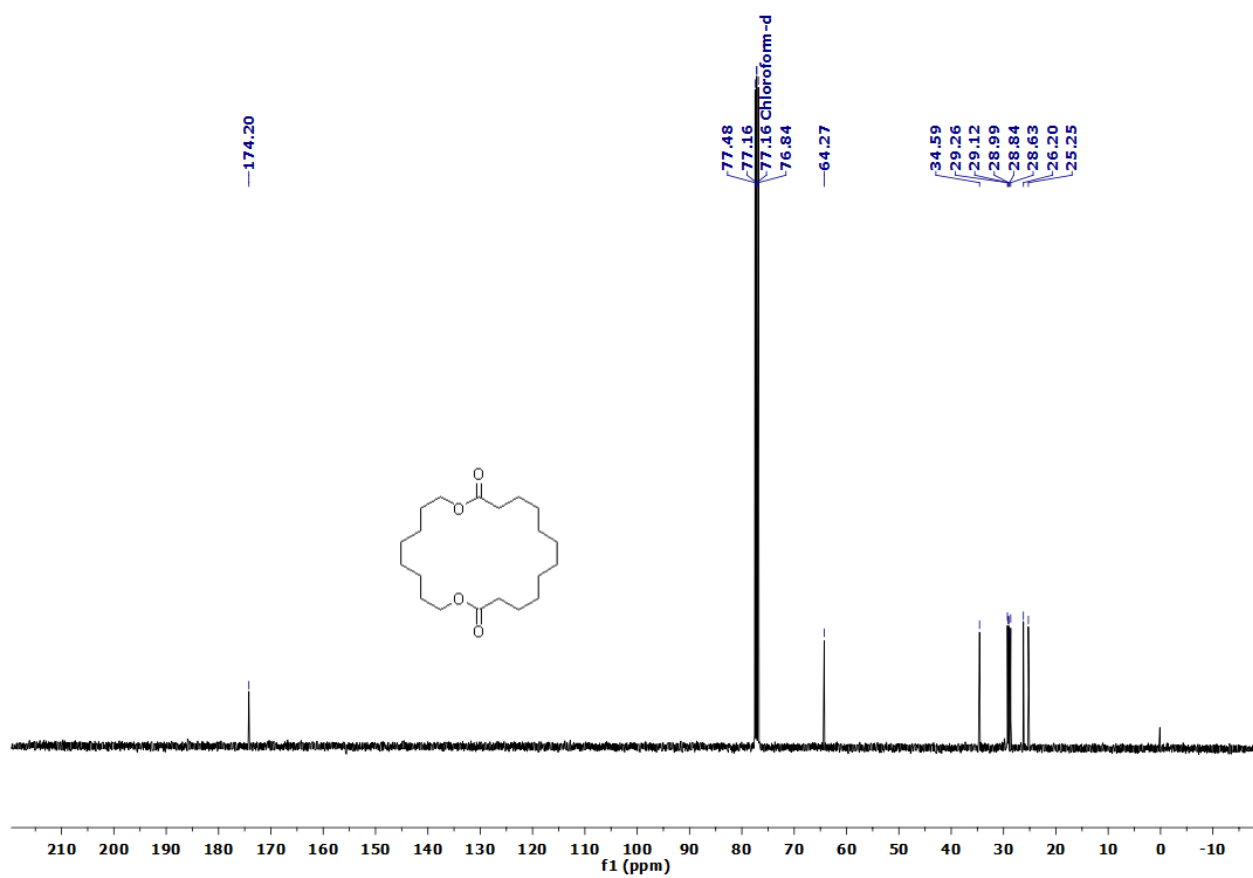
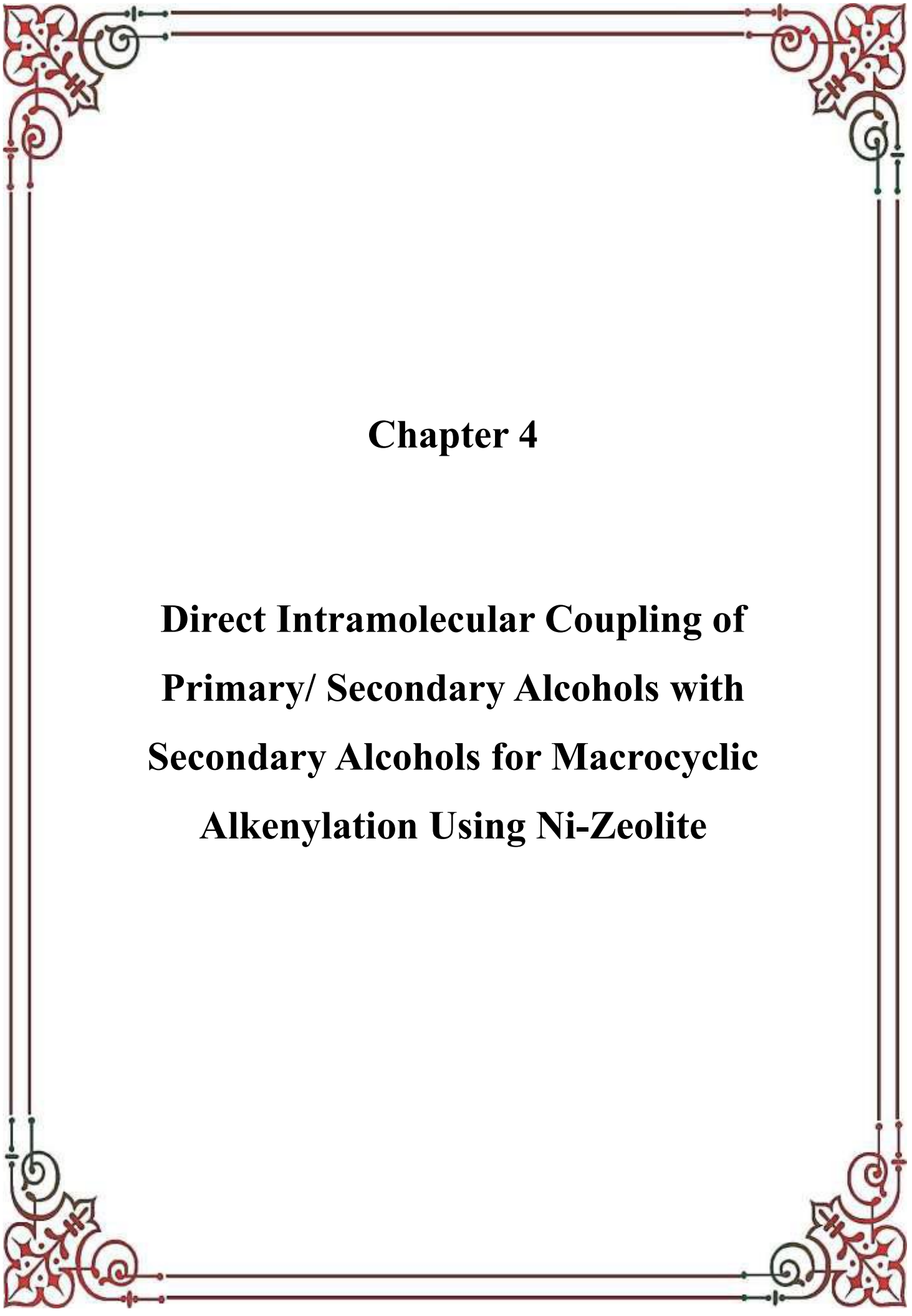


Figure 74. ¹H NMR spectra for compound **165**, 400 MHz, CDCl₃





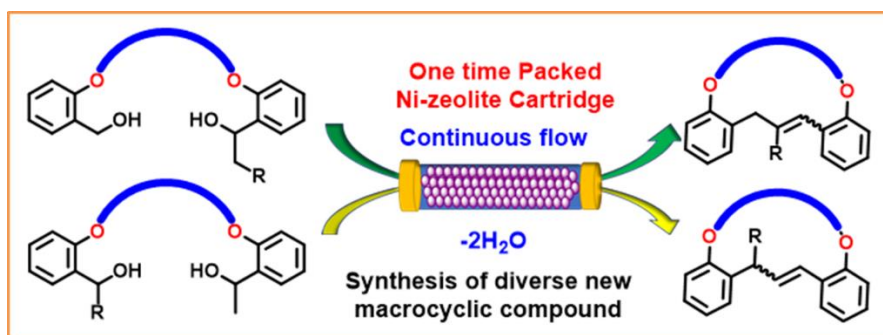
Chapter 4

Direct Intramolecular Coupling of Primary/ Secondary Alcohols with Secondary Alcohols for Macrocyclic Alkenylation Using Ni-Zeolite

4. Direct Intramolecular Coupling of Primary/Secondary Alcohols with Secondary Alcohols for Macrocylic Alkenylation Using Ni-Zeolite

4.1 Abstract

In this chapter, we described direct intramolecular coupling of primary and secondary alcohols to synthesize selectively macrocyclic olefins using a Ni-Zeolite catalyst in a continuous flow system. The reaction mechanism involves two key steps: first, the dehydration of secondary alcohols to form alkenes, and second, the intramolecular dehydrative coupling of these alkenes with primary alcohols. This method efficiently produces macrocyclic olefins with moderate yields. Notably, this approach is versatile and can be extended to the intramolecular coupling of secondary-secondary alcohols and alkene-alcohols, resulting in a wide array of macrocyclic olefin products. This innovative approach offers several benefits, including step economy, no need for additives or pre-functionalization, use of an inexpensive and reusable catalyst, and successful application to 23 macrocycles with different ring sizes.



4.2 Introduction to Macrocyclic-alkenes

Macrocyclic alkenes are fundamental structural motifs found in biologically active natural products,¹⁴¹ pharmaceutically active compounds,¹⁴² and perfume industry.¹⁴³ Beyond their medicinal applications for example, Salicylihalamide A macrocyclic alkene compound found in natural products,¹⁴⁴ (*R,Z*)-5-muscenone useful in the perfume industry,¹⁴⁵ and Pacritinib used in drugs¹⁴⁶ (Figure 77). These structurally distinct macrocyclic alkenes are valuable in various fields of chemistry. The significant structural and biological importance of macrocycles has motivated synthetic chemists to develop efficient methods for their synthesis. However, the synthesis of macrocyclic alkene *via* inter- or intramolecular cyclization presents

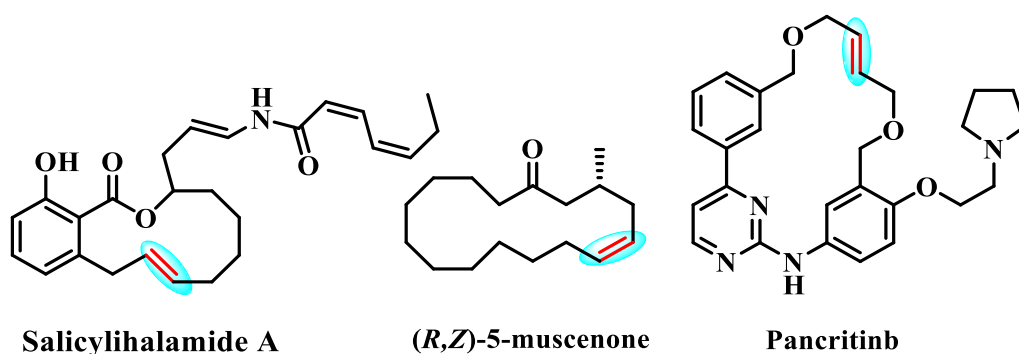
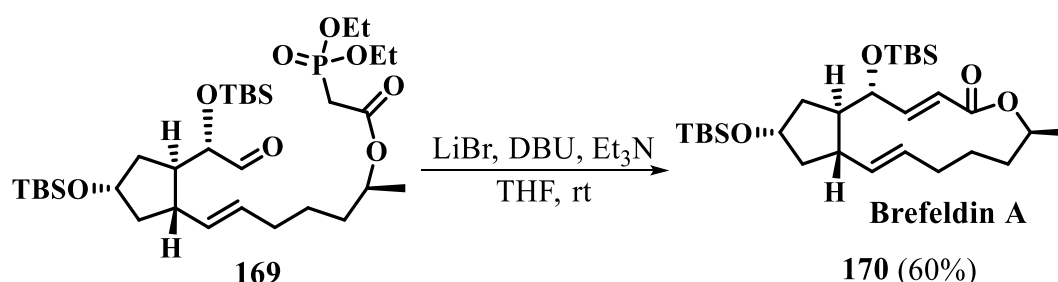


Figure 77. Examples of macrocyclic alkene compound

significant challenges making it a complex area in synthetic organic chemistry. Several strategies have been developed for the synthesis of macrocyclic alkenes by using catalytic and non-catalytic reactions.

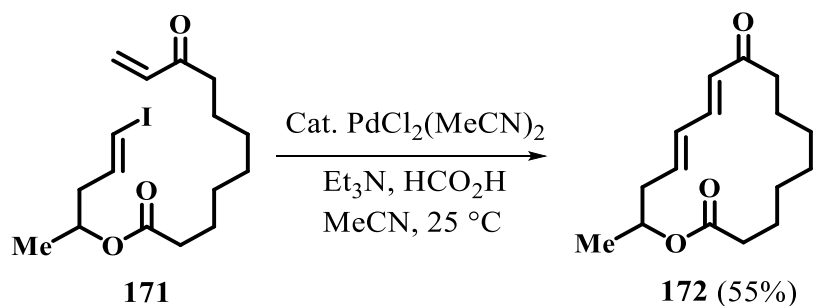
4.3 Literature Report on Macrocyclic-alkene

The macrocyclic Brefeldin A **170** was synthesized from **169** using Roush–Masamune conditions (LiBr, DBU, and Et₃N), to achieve 60% yield. This reaction was reported by Raghavan and Yelleni in 2016 (Scheme 73).¹⁴⁷



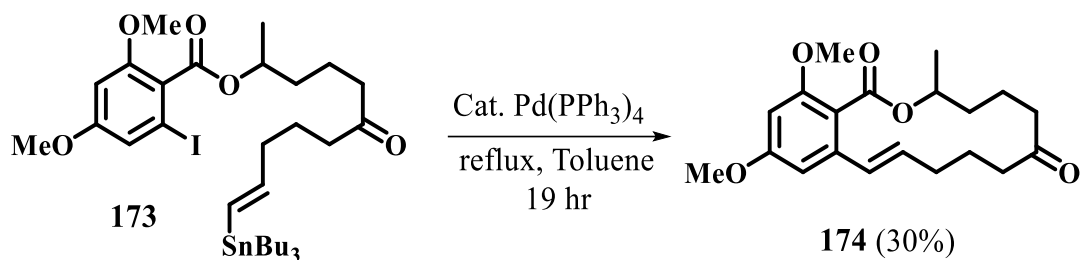
Scheme 73. Synthesis of Brefeldin A **170** using Roush–Masamune conditions

In 1981, Ziegler and coworkers reported the Heck macrocyclization to synthesize compound **172**. The reaction utilized vinyl ketone **171** coupled intramolecularly at 25 °C under high dilution conditions, with PdCl₂(MeCN)₂, formic acid, and triethylamine. This setup enabl-



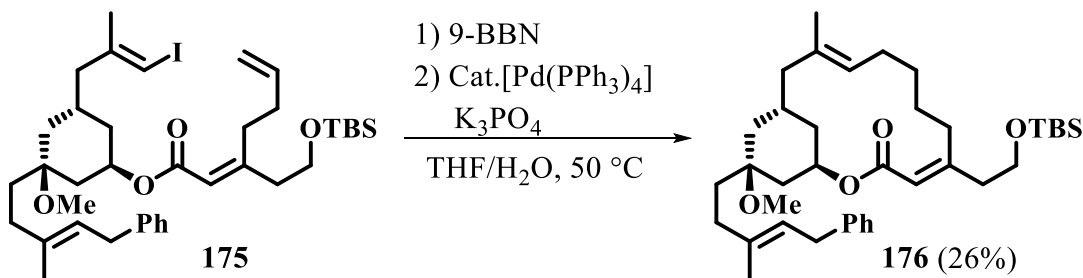
Scheme 74. Pd-catalyzed intramolecular Heck reaction for macrocyclic alkenylation

-ed the macrocyclization process, forming a C-C bond and producing macrocyclic lactone **170** with a 55% yield (Scheme 74).¹⁴⁸



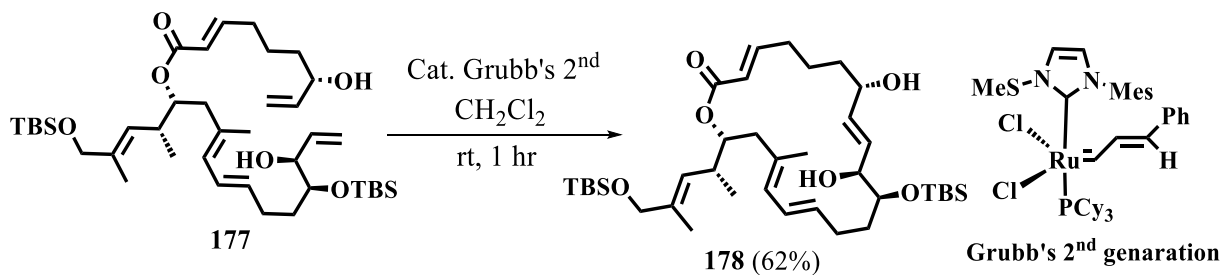
Scheme 75. Pd-catalyzed intramolecular Still reaction for macrocyclic alkenylation

Next, Stille and coworkers described the intramolecular coupling reactions used in the total synthesis of zearalenone. In this reaction, the intramolecular coupling of an aryl iodide with a vinylstannane **173** was performed using Pd(PPh₃)₄ as the catalyst in toluene at a high dilution (1 x 10⁻³ M). The reaction mixture was refluxed for 19 hr, resulting in the formation of the macrocyclic alkene **174** with a 30% yield (Scheme 75).¹⁴⁹



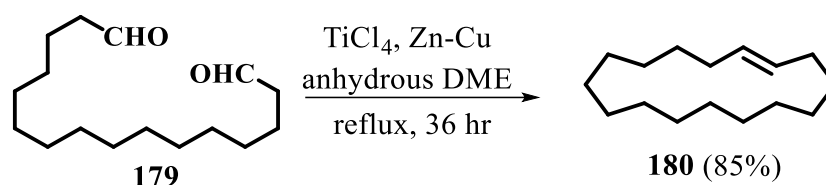
Scheme 76. Synthesis of Ripostatin analog *via* intramolecular Suzuki reaction

Furthermore, In 2014, Prusov and coworkers synthesized macrocyclic compound **176** in 26% yield. They have used 9-BBN with compound **175** and catalyst Pd(PPh₃)₄ in presence of base at 50 °C to obtain **176** (Scheme 76).¹⁵⁰



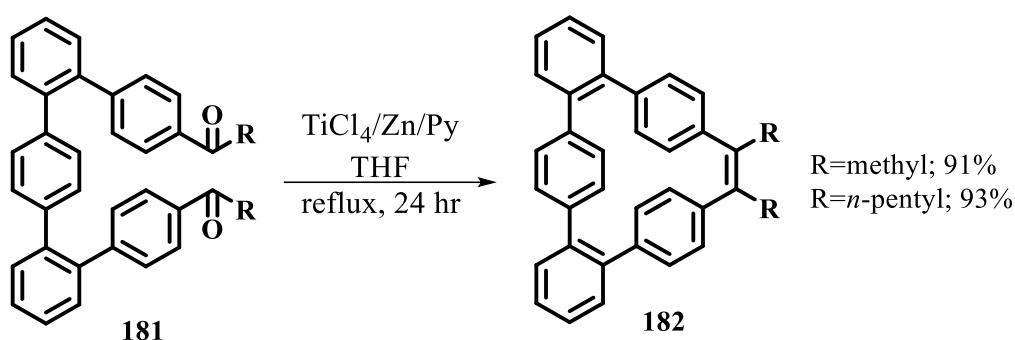
Scheme 77. Cyclization step using RCM Grubb's 2nd catalyst to Palmerolide A

After that, the macrocyclic compound Palmerolide A **178** was synthesized using ring-closing metathesis (RCM) by Prasad and coworkers in 2012. They treated compound **177** with Grubb's second-generation catalyst in dichloromethane at room temperature for 1 hr, resulting in the formation of the macrocycle **178** with a 62% yield (Scheme 77).¹⁵¹



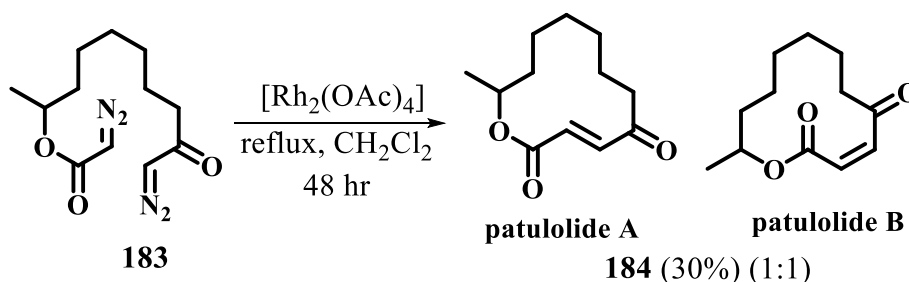
Scheme 78. Intramolecular McMurry reaction from dialdehyde

In 1977, McMurry and coworkers reported an intramolecular macrocyclization reaction. In this procedure, TiCl_4 was combined with Zn-Cu in anhydrous dimethoxyethane (DME) solvent and refluxed for 1 hr. Then, **179** was added, and the mixture was refluxed again for 35 hr, resulting in macrocyclic alkene **180** in 85% yield (Scheme 78).¹⁵²



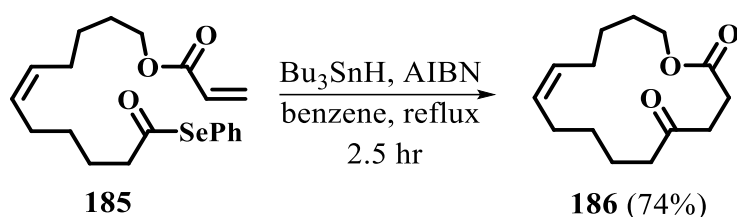
Scheme 79. Intramolecular McMurry reaction from diketone

After that, in 2009, Debroy et al. reported an intramolecular McMurry reaction converting diketone **181** to macrocyclic alkene **182** with a 91-93% yield. This reaction was carried out using $\text{TiCl}_4/\text{Zn}/\text{Py}$ in THF solvent and the reaction mixture was refluxed for 24 hr (Scheme 79).¹⁵³



Scheme 80. Synthesis of the macrocycles patulolides A and B

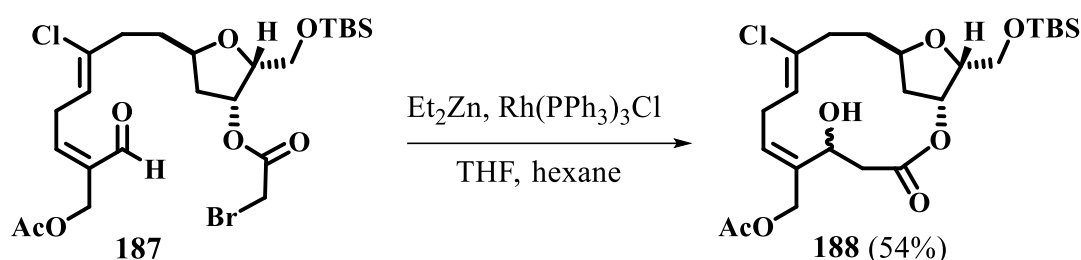
Doyle et al. detailed the synthesis of macrocycles patulolides A and B *via* the catalytic formation of a carbene dimer. They employed established method for the intermolecular coupling of bisdiazoketone **183**, which yielded 30% of both (*E*)- and (*Z*)-alkenes **184** when reacted with a rhodium acetate catalyst (Scheme 80).¹⁵⁴



Scheme 81. Intramolecular acyl radical-alkene reaction

Next, Boger and coworker reported an intramolecular acyl radical-alkene reaction. In this reaction, starting material **185** was refluxed in benzene with Bu_3SnH and AIBN, resulting in a 74% yield of the **186** (Scheme 81).¹⁵⁵

Moreover, In 2021, Britton and coworkers devised a method to synthesize a 14-membered macrocycle using Reformatsky reaction.¹⁶¹ This process intramolecular reaction of an α -bromoester with an aldehyde **187**, catalyzed by Et_2Zn and $\text{Rh}(\text{PPh}_3)_3\text{Cl}$ to furnish macrocyclic compound **188** with a yield of 54% (Scheme 82).¹⁵⁶



Scheme 82. Synthesis of 14-membered macrocycle *via* Reformatsky reaction.

4.4 Objective of this Work

The macrocyclic alkene compounds are essential in various fields, but synthesis of macrocyclic alkene is very challenging. The above literature methods for macrocyclic alkenylation, often demand preactivated substrates and specially designed alkene precursors. These processes not only produce genotoxic stoichiometric waste but also face challenges with selectivity, yields, and scalability issues in batch conditions. Additionally, all these reported catalytic reactions have used non-recyclable and expensive metal catalysts.

The objective of this work is to develop a new synthetic route for the synthesis of macrocyclic alkene compounds. To address these challenges, we aim to develop alternative catalytic approaches that utilize recyclable catalysts and continuous flow systems for large-scale synthesis. Our objective is to synthesize a macrocyclic alkene from alcohol using a continuous flow system with a heterogeneous catalyst based on metal-supported zeolites.

4.5 Result and Discussion

Nex, to develop a new approach for the synthesis of macrocyclic alkene *via* intramolecular dehydrative coupling of primary/secondary diols, initially, we synthesized various metal-zeolite-based heterogeneous catalysts using a reported procedure. Further, we screened these catalysts for their effectiveness in intramolecular macrocyclic alkene synthesis from unsymmetric diols under batch and continuous flow conditions.

➤ General Experimental Procedure for Synthesis of Heterogeneous Metal-Zeolite Catalysts¹⁵⁷

Preparation of Fe-Zeolite catalyst: Following the reported procedure, in 20 mL of deionized water, 5 gm of β -Zeolite were suspended. A 10% solution of metal chloride ($\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$) was prepared in deionized water. The suspension was stirred for 6 hr using a rotary evaporator to ensure uniform dispersion. Water was then removed under vacuum, and the metal-loaded samples were dried at 120 °C for 2 hr. Lastly, the dehydrated samples underwent an 8 hrs calcination at 500 °C. Metal loading of 2.63% onto the zeolite samples was achieved by adding the appropriate amount of the stock metal chloride solution.

Preparation of Ru-Zeolite catalyst: Following the reported procedure, in 20 mL of deionized water, 5 gm of β -Zeolite were suspended. A 10% solution of metal chloride ($\text{RuCl}_3 \cdot x\text{H}_2\text{O}$) was prepared in deionized water. The suspension was stirred for 6 hr using a rotary evaporator to ensure uniform dispersion. Water was then removed under vacuum, and the metal-loaded samples were dried at 120 °C for 2 hr. Lastly, the dehydrated samples underwent an 8 hrs calcination at 500 °C. Metal loading of 1.93% onto the zeolite samples was achieved by adding the appropriate amount of the stock metal chloride solution.

Preparation of Ni-Zeolite catalyst: Following the reported procedure, in 20 mL of deionized water, 5 gm of β -Zeolite were suspended. A 10% solution of metal chloride ($\text{NiCl}_3 \cdot 6\text{H}_2\text{O}$) was prepared in deionized water. The suspension was stirred for 6 hr using a rotary evaporator to ensure uniform dispersion. Water was then removed under vacuum, and the metal-loaded samples were dried at 120 °C for 2 hr. Lastly, the dehydrated samples underwent an 8 hrs calcination at 500 °C.

Characterization of Ni-Zeolite catalyst: From ICP-AES analysis of the freshly prepared and used Ni-Zeolite found a consistent 2.85% of Ni bound on the zeolite.

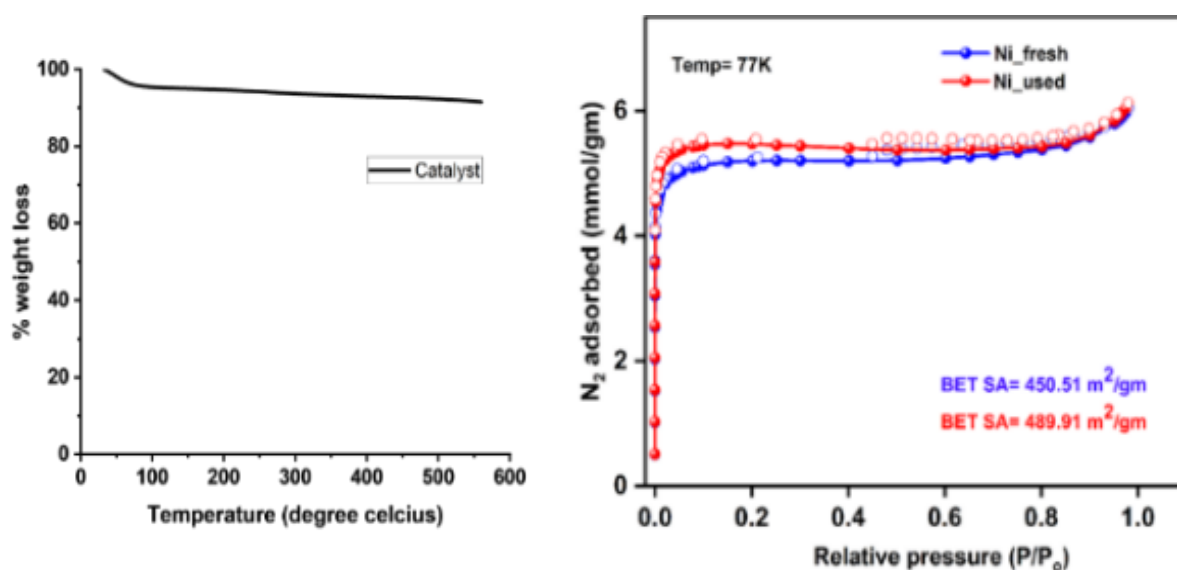


Figure 78. a) HRTEM images of Ni-Zeolite catalyst; b) Selected area of Ni-Zeolite; c)–f) Ni, Al, Si and O, respectively.

The morphology of the freshly prepared Ni-Zeolite was analyzed using HRTEM (Figure 78). The surfactant-directed zeolite showed an amorphous morphology¹⁵⁸. Selected area images of the catalyst demonstrated uniform distribution of Ni, Al, Si, and O (Figure 71a–f). Comparing TEM images of the used catalyst, we observed no change in morphology. Thus, the catalyst retained its morphology throughout continuous flow catalysis.

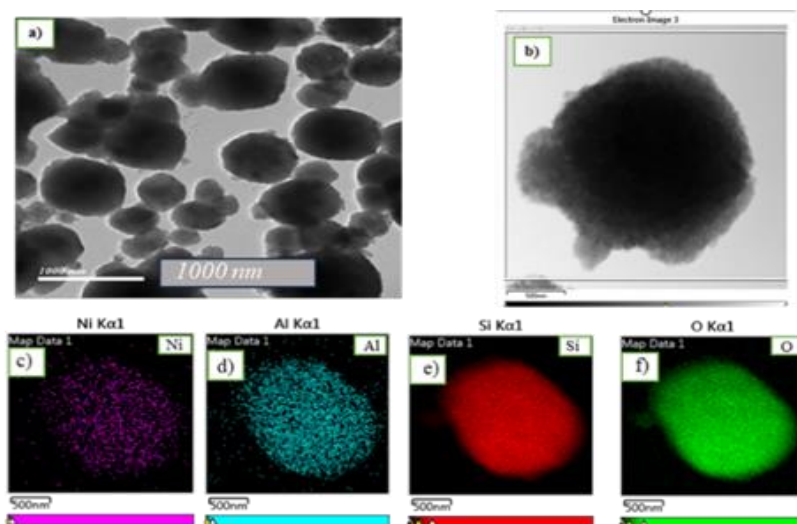


Figure 79. a) Thermogravimetric analysis (TGA) of Ni-Zeolite; b) BET surface area of fresh and used Ni-Zeolite

Furthermore, the thermal stability of the Ni-Zeolite was analyzed using thermogravimetric analysis (TGA) (Figure 79a). As depicted in Figure 79a, a slight weight loss

occurred below 150 °C, likely due to the evaporation of adsorbed water. No further weight loss was observed with increasing temperature. This study indicates that the Ni-Zeolite catalyst exhibits excellent stability at high temperatures up to 600 °C. Next, the specific surface area of the fresh and used 2.85% Ni-Zeolite catalyst was characterized using N₂ adsorption-desorption measurements. The N₂ adsorption-desorption isotherms of the catalyst are shown in Figure 24b. The fresh Ni-Zeolite catalyst and the used Ni-Zeolite catalyst exhibited BET-specific surface areas of 450.51 m²/g and 489.91 m²/g, respectively (Figure 79b). This suggests that the catalyst's surface area did not change significantly after prolonged use.

Powder X-ray diffraction (XRD) profiles of the zeolite and calcinated zeolite patterns exhibited diffraction peaks in the 2 θ range of 23° to 29°, consistent with those of the zeolite phase.¹⁵⁹ Both freshly prepared and used Ni-Zeolite samples showed the presence of Ni in the form of NiO. Specifically, peaks corresponding to NiO were observed at 2 θ values of 37°, 43.26°, and 62.73°. These peaks indicate the presence of NiO distributed on the surface of the Zeolite (Figure 80). This synthesized and characterized metal-zeolite is used for macrocyclization.

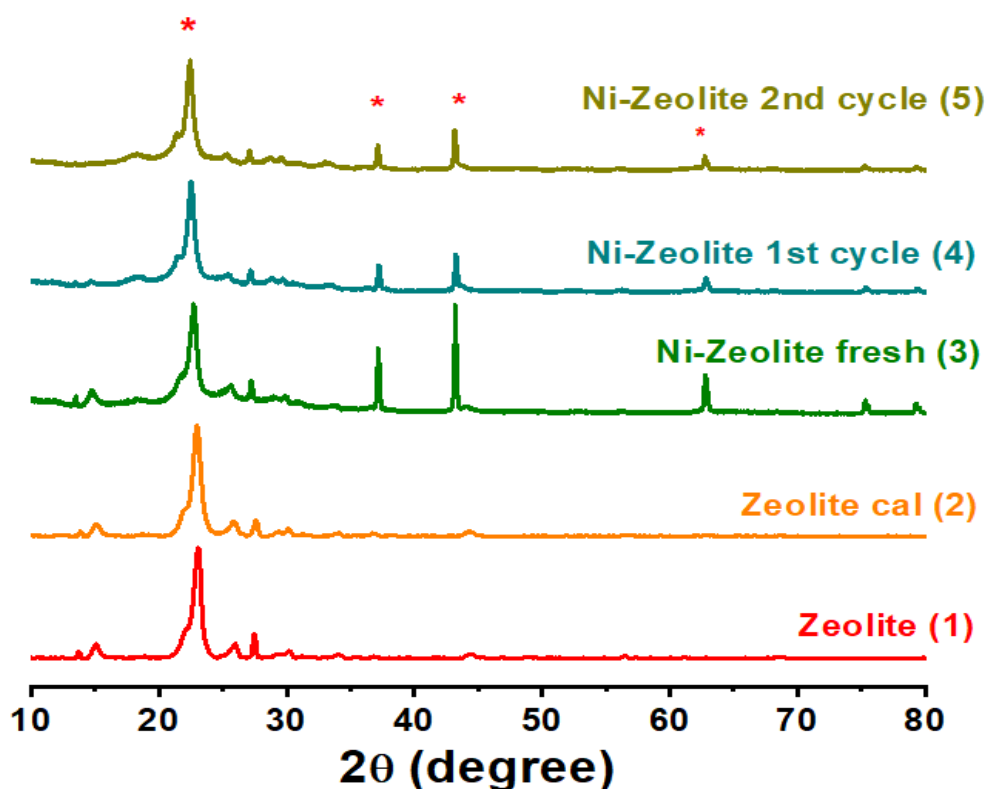
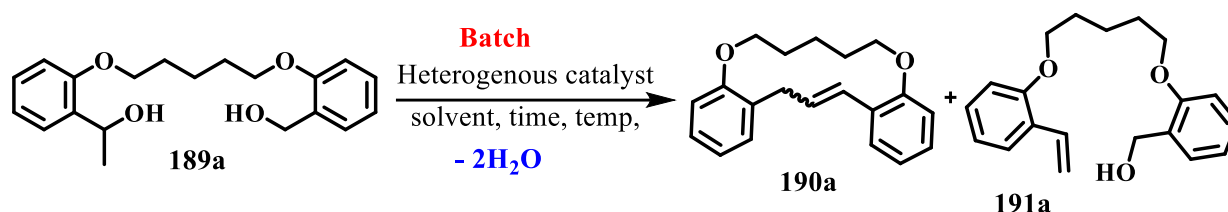


Figure 80. PXRD diffraction profiles 1) β -Zeolite, 2) β -Zeolite calcinated, 3) freshly prepared Ni-Zeolite, 4) Ni-Zeolite 1st cycle and 5) Ni-Zeolite 2nd cycle

4.5.1 Optimization for the Macrocyclic Olefination using Intramolecular Coupling of Alcohols under Batch Conditions

We began our investigation by performing the intramolecular dehydrative coupling of compound **189a** (1-(2-((5-(2-(hydroxymethyl)phenoxy)pentyl)oxy)phenyl)ethan-1-ol) as a benchmark substrate to produce the macrocyclic alkene **190a** (7,8,9,10-tetrahydro-6*H*,16*H*-dibenzo[*h,m*][1,7]dioxacyclotetradecine) and the acyclic alkene **191a** ((2-((5-(2-vinylphenoxy)pentyl)oxy)phenyl)methanol).

Table 4.1 Optimization for the macrocyclic olefination under batch conditions



Entry	Catalyst	Solvent	Time (hr)	Temp (°C)	Yield 190a/191a %
1 ^a	β -Zeolite	1, 4-dioxane	24	120	36/22
2 ^a	Fe-Zeolite	1, 4-dioxane	24	120	31/25
3 ^a	Ru-Zeolite	1, 4-dioxane	24	120	47/39
4 ^a	Ni-Zeolite	1, 4-dioxane	24	120	49/31
5 ^a	Ni-Zeolite	THF	24	120	40/50
6 ^a	Ni-Zeolite	Toluene	24	120	29/30
7 ^a	Ni-Zeolite	1, 4-dioxane	24	140	49/12
8 ^a	Ni-Zeolite	1, 4-dioxane	24	160	47/10
9 ^a	Ni-Zeolite	1, 4-dioxane	24	100	45/30
10 ^b	Ni-Zeolite	1, 4-dioxane	24	120	49/34
11 ^c	$\text{NiCl}_2 \cdot 6\text{H}_2\text{O}$	1, 4-dioxane	24	120	-
12 ^c	$\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$	1, 4-dioxane	24	120	18/25
13 ^c	$\text{RuCl}_3 \cdot x\text{H}_2\text{O}$	1, 4-dioxane	24	120	27/29
14	Ni-Zeolite	1, 4-dioxane	48	120	49/30

^a**Reaction conditions:** Compound **189a** (0.15 mmol) in 2 mL of solvent and 50 mg of catalyst were stirred in a sealed vial at an appropriate temperature for 24 hrs. ^b0.05 M of **189a** used; ^c3 mol% of catalyst. The mentioned yields are isolated yields.

We optimized this reaction by screening solvents, and temperatures with synthesized heterogeneous catalysts under batch reaction conditions. In this reaction, using a heterogeneous Zeolite catalyst (w/w) in 1, 4-dioxane at 120 °C for 24 hrs, 36% yield of macrocyclic alkene **190a** and a 22% yield of the acyclic alkene **191a** was obtained (Table 4.1, entry 1). This macrocyclic alkene **190a** was obtained as an *E:Z* mixture (98:2), confirmed by ^1H NMR data. Employing Fe-Zeolite as a catalyst provided a 31% yield of **190a** and a 25% yield of **191a** (Table 4.1, entry 2). When Ru-Zeolite was used, we observed a moderate yield (47%) of the macrocyclic alkene **190a** (Table 4.1, entry 3). Other heterogeneous catalysts, such as Ni-Zeolite, demonstrated higher efficiency in promoting macrocyclization, yielding 49% of compound **190a** (Table 1, entry 4). We also investigated the effect of various solvents such as when THF and toluene, was used the yields decreased to 40% and 29%, respectively (Table 4.1, entries 5 and 6). Moreover, yields increasing the reaction temperature to 140 °C and 160 °C resulted in 49% and 47%, respectively (Table 4.1, entries 7 and 8). Conversely, lowering the reaction temperature led to a 45% yield of compound **190a** (Table 4.1, entry 9). The dilution of compound **189a** to 0.05 M had minimal impact on the yield (Table 4.1, entry 10). Additionally, using a homogeneous metal catalyst, $\text{NiCl}_2 \cdot 6\text{H}_2\text{O}$, did not produce the desired product (Table 4.1, entry 11). The yield decreased further when $\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$ and $\text{RuCl}_3 \cdot x\text{H}_2\text{O}$ were used as catalysts (Table 4.1, entries 12 and 13). Extending the reaction time to 48 hrs did not improve the yield (Table 4.1, entry 14). The space-time yield for the batch reaction conditions after 24 hrs was found to be $1.98 \text{ g L}^{-1} \text{ h}^{-1}$.

To enhance product yield and address the scale-up challenges inherent in batch processes, we reoptimized our approach to a continuous flow process. For this continuous flow setup, we integrated several key components: a Vapourtec SF-10 peristaltic pump for reactant

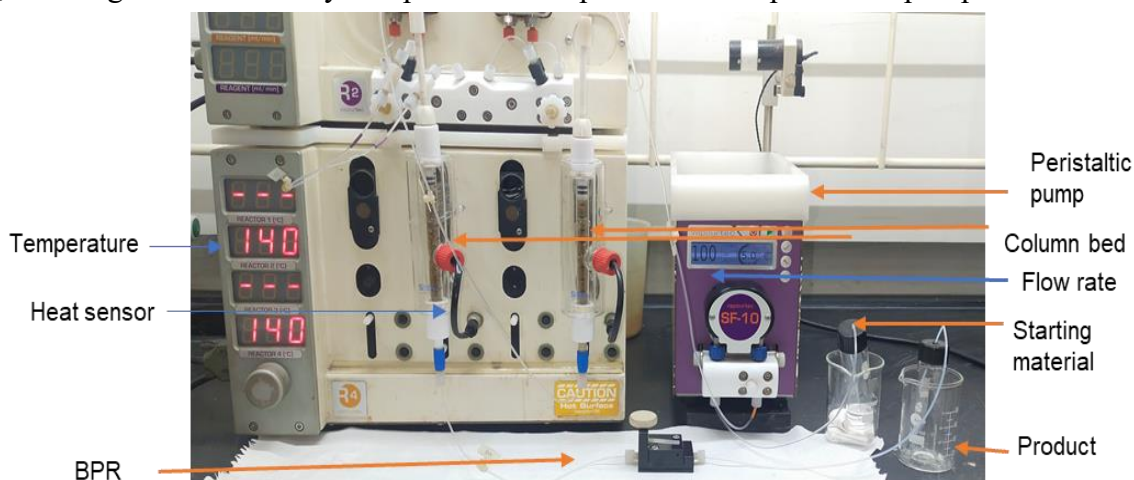
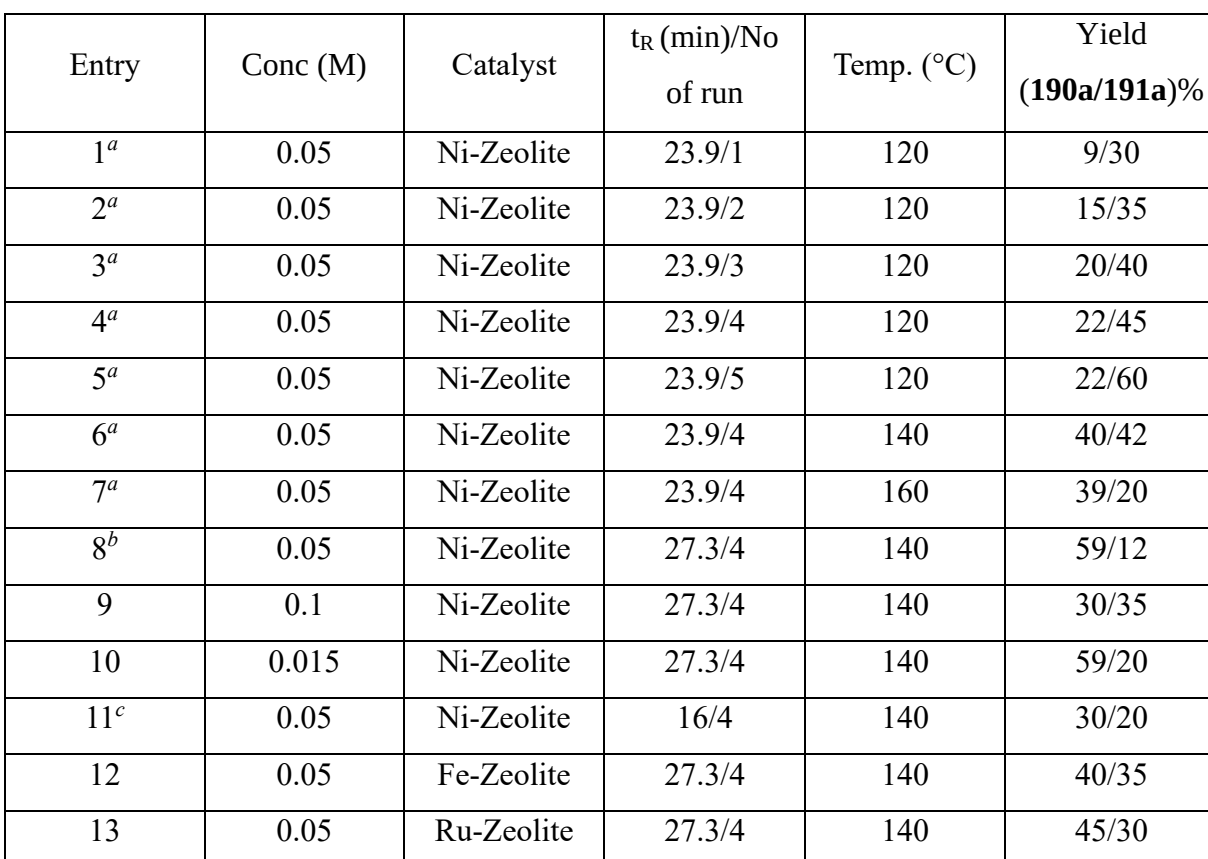


Figure 81. Continuous flow setup

4.5.2 Optimization for the Macrocyclic Olefination using Intramolecular Coupling of Alcohols under Continuous Flow Conditions

Table 4.2. Optimization for macrocyclic olefination under continuous flow conditions



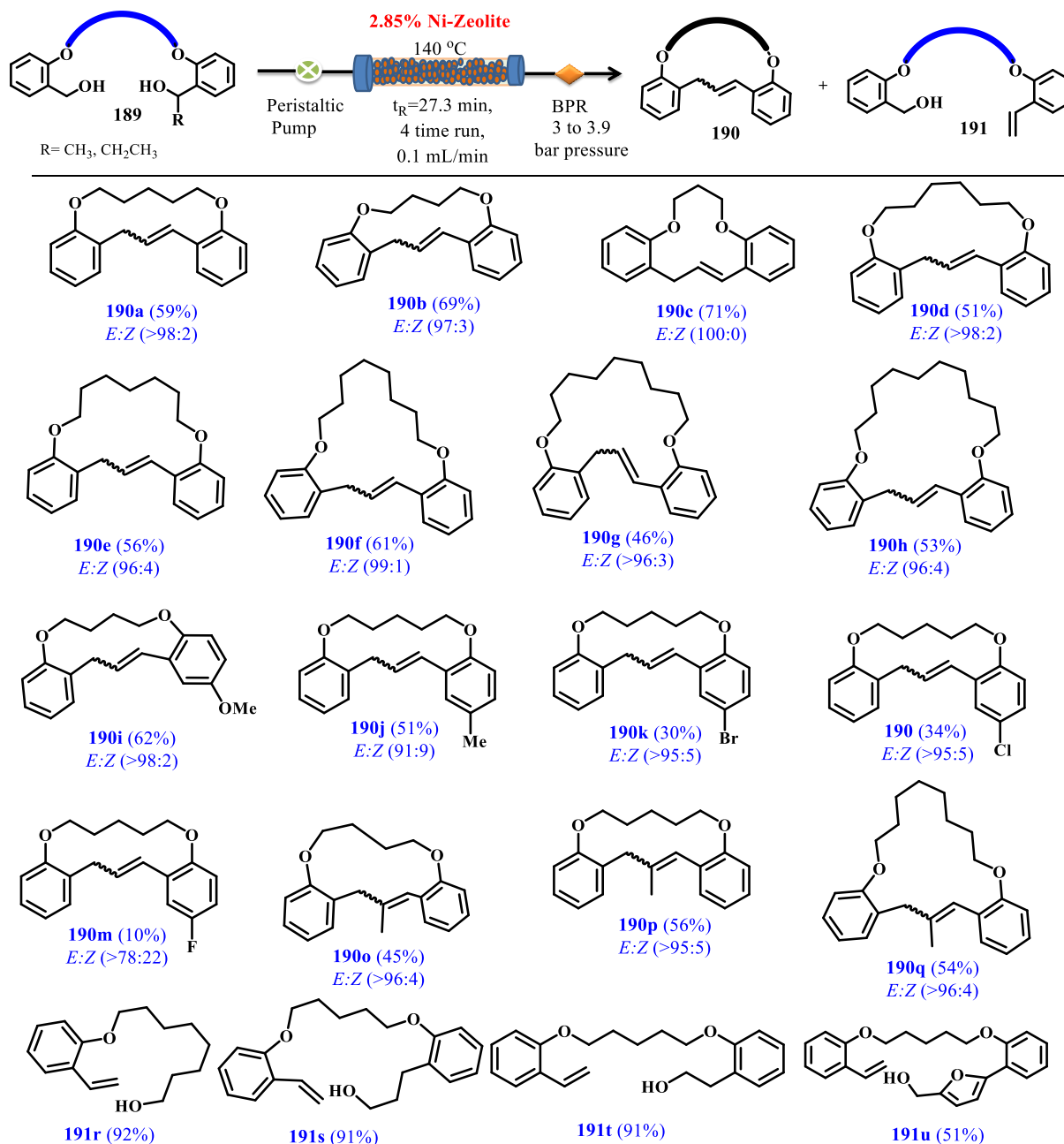
Reaction conditions: A solution of **189a** in 1, 4-dioxane solvent was prepared and flown (0.1 mL/min flow rate) through the Omnifit® column (6.6 × 150 mm) containing the catalysts ^a(1.7 g) or ^b(1.9 g) at an appropriate temperature for residence time and run. The mentioned yields are isolated yields. ^c0.15 mL/min flow rate.

23.9 minutes. After one cycle, this process yielded 9% of the desired macrocyclic product **190a** and 30% of the acyclic alkene **191a**, with the starting material being partially recovered (Table 4.2, entry 1). To improve the yield of product **190a**, we extended the run time and performed two cycles, which increased the yield of **190a** to 13% (Table 4.2, entry 2). When the reaction was conducted three times, the yield of the desired product increased to 20% (Table 4.2, entry 3). Running the reaction four and five times yielded 22% (Table 4.2, entries 4 and 5, respectively). Exploring the effect of temperature on the reaction, we found that 140 °C resulted 40% yield (Table 4.2, entry 6). However, further increasing the temperature to 160 °C led to a decreased 39% yield (Table 4.2, entry 7). Extending the residence time to 27.3 minutes and running the reaction four times resulted in a notable improvement in (59%) for the product **190a** (Table 4.2, entry 8). Conversely, increasing the concentration of compound **189a** to 0.1 M resulted in 30% yield of **190a** (Table 4.2, entry 9). High dilution conditions, with a concentration of 0.015 M, produced 59% yield (Table 4.2, entry 10). Shorter residence times reduced the yield of **190a** to 30% (Table 4.2, entry 11). Further, other supported catalysts, such as Fe-Zeolite and Ru-Zeolite, revealed lower efficiencies for macrocyclization, yielding 40% and 45% of the macrocyclic alkene **190a**, respectively (Table 4.2, entries 12 and 13). The optimal reaction conditions were achieved using Ni-Zeolite as the catalyst at a temperature of 140 °C in 1, 4-dioxane solvent, as detailed in Table 2, entry 8. Under these conditions, we observed a higher space-time yield of 26.45 g/L/h, which is a significant improvement compared to the yields obtained under batch conditions.

4.5.3 Substrate Scope for Macrocyclic Alkene from Unsymmetrical-diol

This optimization highlights the efficiency of the continuous flow process in enhancing product yield and throughput. After optimizing the reaction conditions, we investigated the macrocyclization of various diol derivatives in a continuous flow system. The ring-closing macrocyclization of diol **189b**, which has a butyl spacer, produced macrocycle **190b** in a 69% yield as an *E:Z* mixture (97:3) according to ¹H NMR analysis (Scheme 83). The structure was further confirmed by single-crystal XRD (Figure 82). Furthermore, the 12-membered macrocyclic alkene **190c** was formed in a 71% yield exclusively as the *E* isomer from the

corresponding diol **189c** (Scheme 83). Diol derivatives with six to eight carbon-chain spacers yielded macrocycles **190d–190f** in 54–63% yield, respectively (Scheme 83). Additionally, Furthermore, 18- and 19-membered macrocyclic alkenes **190g** and **190h** were formed the



Scheme 83. Substrate scope for macrocyclic alkene from unsymmetrical diol

Reaction conditions: 0.05 M solution of **189a** in 1, 4-dioxane was prepared and flown through the Omnifit® column (6.6 x 150 mm) containing Ni-Zeolite heterogeneous catalysts (1.7 g, 9 cm), heated at 140 °C, for residence time 27.3 min and run 4 times. The mentioned yields are isolated yields.

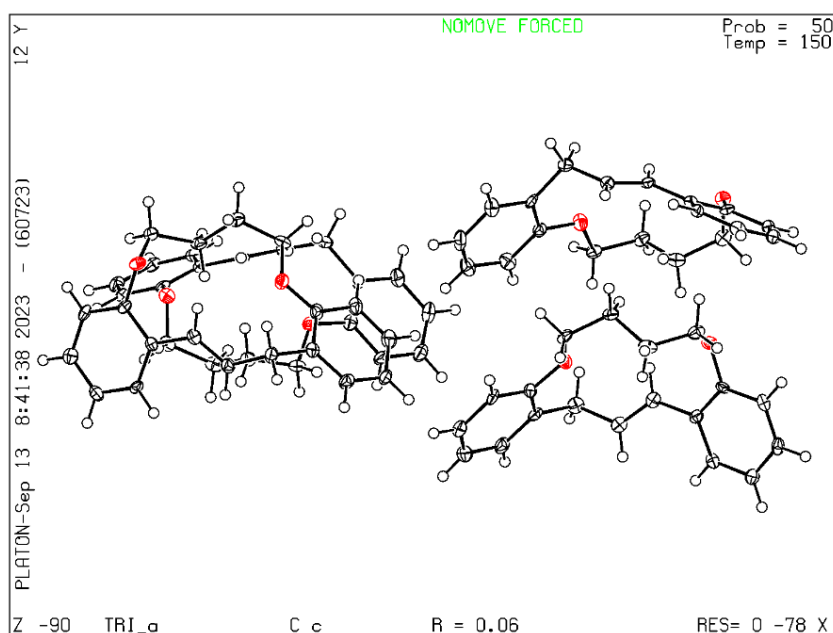
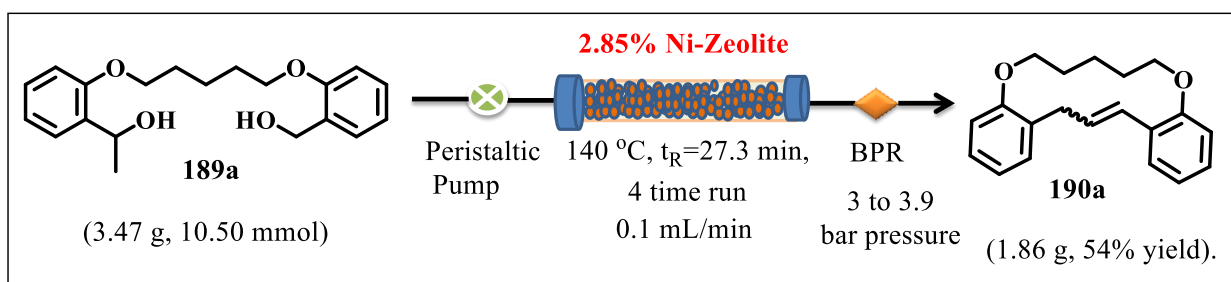


Figure 82. Crystal structure of **190b**.

respective diol in 43–46% yields (Scheme 83). Diols having electron-donating groups such as -OMe, -Me afforded 62% and 51% yield of **190i** and **190j** respectively (Scheme 83). With Br, Cl, and F the yield of respective macrocycle formation was decreased (**190k–m**, Scheme 83). Next, nitro-substituted diol did not produce the corresponding macrocycle **190n**. A diol with a butyl spacer, along with primary and secondary propane-1-ol groups, yielded the macrocycle **190o** from the corresponding diols **189o** in 45% yields (Scheme 83). Moreover, diol with a pentyl spacer yielded macrocycle **190p** with a 56% yield (Scheme 83). Interestingly, a 15-membered macrocyclic alkene **190q** was produced in a 54% yield from the same reaction (Scheme 83). When linear alcohol **189r** was used, it resulted in an 82% yield of the acyclic alkene **191r** (Scheme 83). Diols containing non-benzylic and benzylic alcohols only yielded non-cyclic alkenes **191s** and **191t** in 91% yields, respectively (Scheme 83). However, the reaction failed to produce a macrocyclic alkene from a diol containing a heteroatom (furan), resulting in a 51% yield of the acyclic alkene **191u** (Scheme 83). The catalytic activity of the singly packed Ni-Zeolite bed remained effective throughout the reactions, successfully producing all the aforementioned macrocyclic alkenes **190** without any loss in catalytic reactivity.

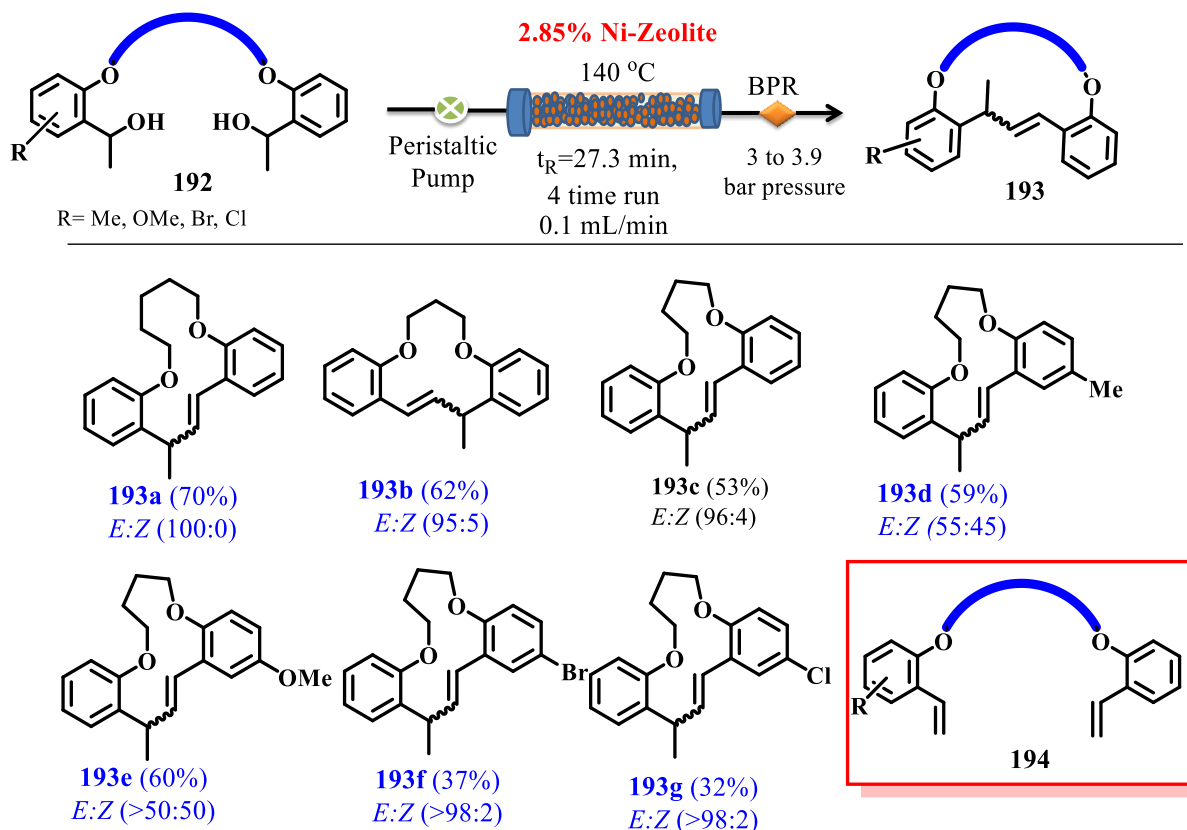
In addition, this optimized reaction condition was also performed on a large scale (10.5 mmol of **189**) to furnish a 54% yield of compound **190a** and a minor amount of **191a** was observed (Scheme 84).



Scheme 84. large-scale synthesis for macrocyclic alkene

4.5.4 Substrate Scope for Macrocyclic Alkene from Secondary-diol

Next, the cyclization was conducted using secondary diols. Under the specified conditions, intramolecular dehydrative coupling of diols **192a** yielded macrocyclic alkene **193a** in 70% yield with *E* selectivity (Scheme 59). A secondary diol with a propyl spacer gave **193b** in 62% yield as an *E*:*Z* mixture (95:5) (Scheme 59). Additionally, 13-membered macrocyclic



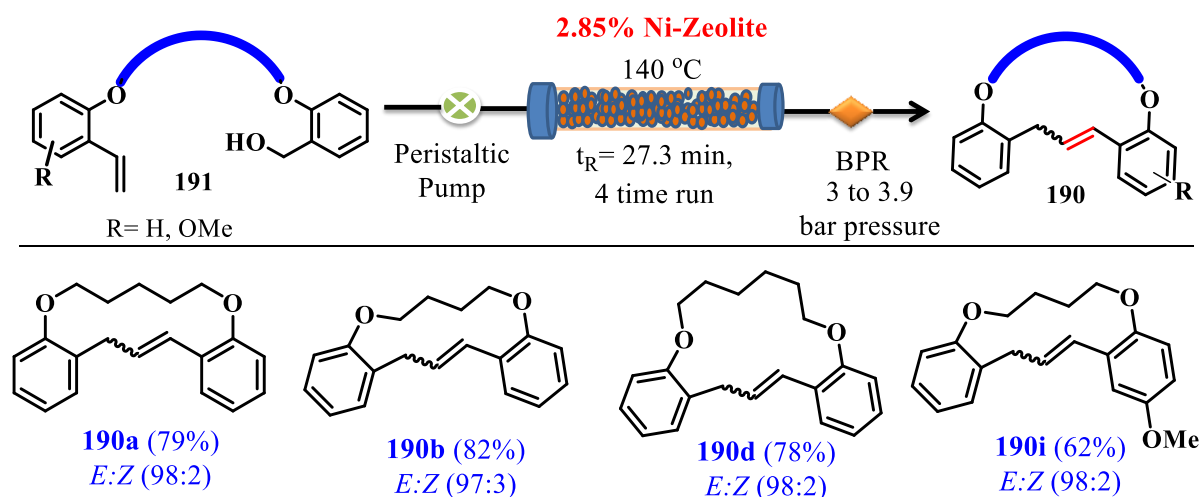
Scheme 85. Substrate scope for macrocyclic alkene from secondary diol.

Reaction conditions: 0.05 M solution of **192** in 1, 4-dioxane was prepared and flown through the Omnifit® column (6.6 x 150 mm) containing the Ni-Zeolite heterogeneous catalysts (1.7 g, 9 cm), at 140 °C, for residence time 27.3 min

alkene **193c** was obtained in 53% yield (Scheme 59). Diols with electron-donating substituents like -Me and -OMe provided compounds **193d** and **193e** in 59% and 60% yields, respectively (Scheme 59). However, diols substituted with Br or Cl resulted in lower yields: **193f** was obtained in 37% yield (Scheme 59) and **193g** in 32% yield (Scheme 59). Using a longer heptyl spacer diol led to an inseparable mixture of noncyclic dialkene **194** and macrocyclic alkene **193**. A Ni-Zeolite bed packed once delivered all macrocycles **193** without losing catalytic activity.

4.5.5 Substrate Scope for Macrocyclic Alkene from Intramolecular Coupling Alcohol and Alkene

To further demonstrate this novel coupling reaction, various alcohols **191** containing alkenes were prepared. Compound **191a** underwent an intramolecular dehydrative coupling reaction using Ni-Zeolite in a continuous flow system over two runs, yielding 79% of product **190a** (Scheme 86). This coupling reaction produced a 13-membered macrocyclic alkene **190b** in 82% yield with an *E:Z* ratio of 97:3 from the corresponding alcohol **191b** (Scheme 86). Additionally, the macrocyclic alkene with a heptyl spacer **190d** was formed in a 78% yield (Scheme 86). In this, electron-donating -OMe substituted compound **190i** delivered macrocyclic alkene **190i** in a 62% yield (Scheme 86). All the macrocycles **190** in Scheme 86 were synthesized using a single-packed Ni-Zeolite bed without any loss of catalytic activity.



Scheme 86. Substrate scope for macrocyclic alkene from intramolecular coupling of alcohol and alkene

^a**Reaction conditions:** 0.05 M solution of **158** in 1, 4-dioxane was prepared and flowed through the Omnifit® column (6.6 x 150 mm) containing the Ni-Zeolite heterogeneous catalysts (1.7 g, 9 cm), at 140 °C, for residence time 27.3 min and run two times. The mentioned yields are isolated yields.

4.6 Catalyst Reusability

To check the catalyst reusability, the reaction of 1,1'-((pentane-1,5-diylbis(oxy))bis(2,1-phenylene))bis(ethan-1-ol) **189a** was conducted under optimized conditions (Table 2, entry 8). A 0.05 M solution of substrate **189a** in 1, 4-dioxane solvent was pumped through Omnifit® column (6.6×150 mm) packed with 1.9 g of fresh Ni-Zeolite, preheated to 140°C and filled up to 9 cm. The flow rate was maintained at 0.1 mL/min with a back pressure of 3.5–3.9 psi, resulting in a residence time (t_R) of 27.3 min. The collected organic layer was concentrated under reduced pressure, and the crude product was purified by column chromatography, yielding 58% of product **190a**. After completing the reaction, the catalyst bed was washed with 1,4-dioxane and dried at 140°C. The same catalyst bed was reused, yielding 59% of product **190a** in subsequent runs: the first, second, third, fourth, and fifth times, maintaining consistent yields. Remarkably, the catalyst maintained its efficiency even after 10 cycles without any decline in activity (Figure 83). ICP-AES analysis of the reaction supernatant showed a minimal Ni content of 0.000177%.

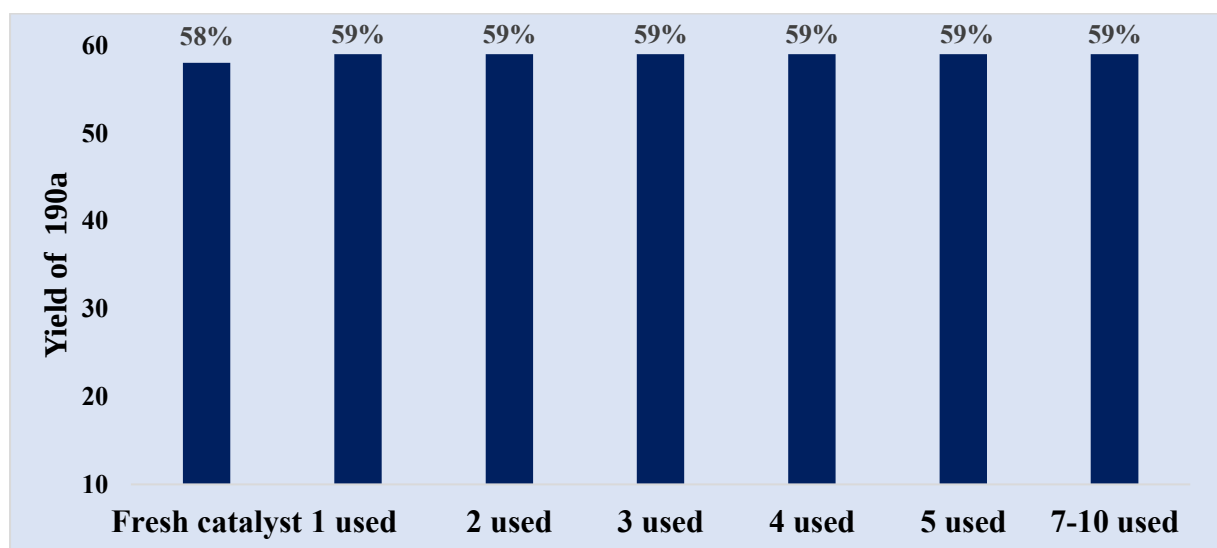
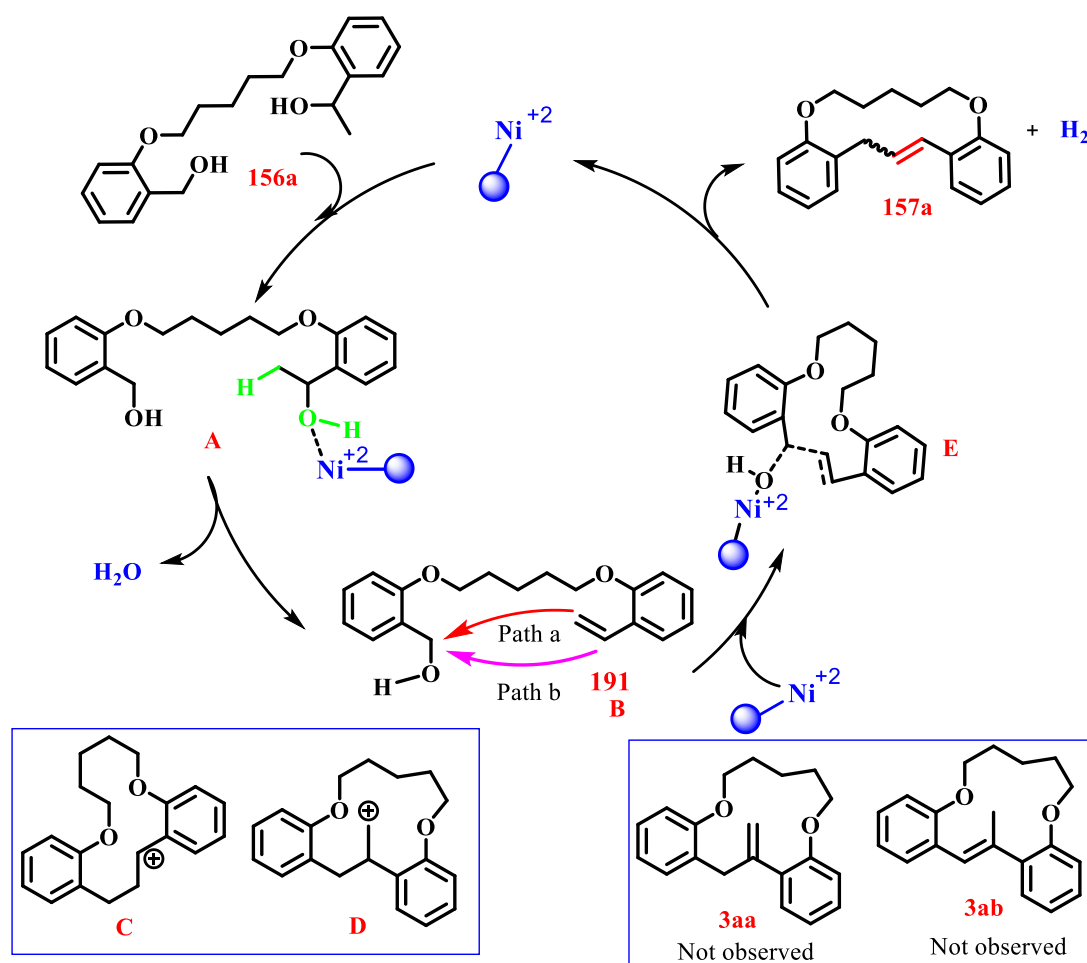


Figure 83. Ni-Zeolite catalyst reusability under continuous-flow

4.7 Plausible Mechanism for Macrocyclic Olefination

The proposed mechanism for this macrocyclization is illustrated in Scheme 87. Initially, compound **189a** reacts with 2.85% Ni-Zeolite, activating the alcohol to form complex **A**. Subsequently, complex **A** undergoes dehydration of the secondary alcohol, yielding **191** intermediate **B**. Ni coordination with intermediate **B** facilitates nucleophilic attack by the

alkene, by two possible pathways (a) or (b). The nucleophilic alkene attack proceeds with regioselectivity on the alcohol, generating intermediate **E**, which then undergoes dehydration to yield product **190a**. The regioselectivity in product formation is attributed to the formation of a more stable benzylic carbocation intermediate **C**. Other expected products, such as **3aa** and **3ab** via intermediate **D**, are not observed due to the lesser stabilization of intermediate **D** in this reaction.



Scheme 87. Plausible mechanism for macrocyclization

4.8 Conclusion

In this study, we developed an innovative method for the regioselective synthesis of predominantly macrocyclic (*E*) alkenes via the intramolecular coupling of alcohols, utilizing a sustainable Ni-Zeolite catalyst under continuous flow conditions. This catalytic system effectively couples both primary and secondary alcohols, demonstrating the synthesis of diverse macrocyclic alkenes with a broad substrate scope and high yields. A single time-packed Ni-Zeolite catalyst was employed efficiently to produce various macrocyclic alkenes,

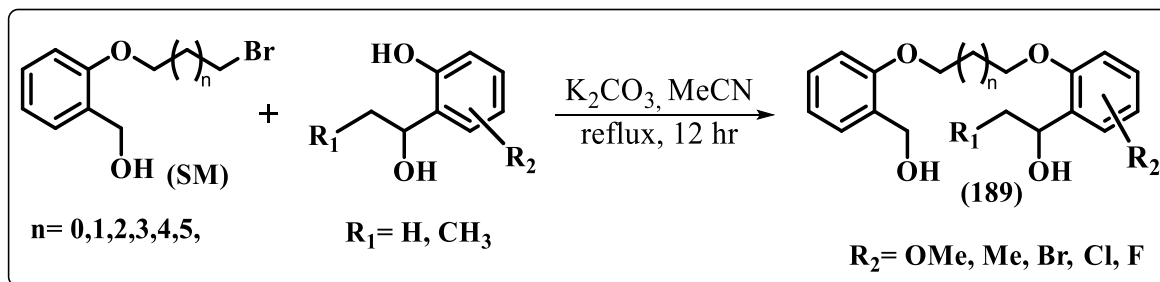
highlighting the simplicity and effectiveness of catalyst recyclability under continuous flow conditions. This approach offers several advantages: it operates without the need for additives, and stoichiometric reagents, specialized reaction conditions, and promotes step economy in synthesis. Furthermore, the method has been successfully demonstrated on a gram scale and shows reproducibility, underscoring its potential for practical applications in organic synthesis. The combination of high selectivity towards macrocyclic alkenes, efficient catalyst utilization, and scalability makes this approach promising for sustainable and efficient chemical manufacturing processes.

4.9 General Information and Data Collection

The Iron (III) chloride hexahydrate (CAS number-10025-77-1, SIGMA), Nickel (II) chloride hexahydrate (CAS number- 7791-20-0, SIGMA), Ruthenium (III) chloride hexahydrate (CAS number-14898-67-0,) were purchased from SIGMA. The column chromatographic separations were performed over 100-200 mesh size Silica-gel. Visualization was accomplished with UV light. The flow chemistry experiments were carried out on Vapourtec SF-10 reagent pump reactions performed in Omnifit® column (6.6 x 150 mm) and heating jacket. ¹H and ¹³C NMR spectra were recorded on 400 and 100 MHz respectively, using Bruker or JEOL spectrometers. Abbreviations used in the NMR follow-up experiments: b, broad; s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet. High-Resolution Mass Spectra were recorded with waters-synapt G2 using electrospray ionization (ESI-TOF). Infrared (ATR) spectra were obtained with a Bruker Alpha-E infrared spectrometer. Melting points were recorded on DBK programmable melting point instrument. All melting points were measured in an open glass capillary tube. Single-crystal diffraction analysis data were collected at 273 K with a Bruker Kappa Apex III CCD Duo diffractometer (operated at 1500 W power: 50 kV, 30 mA) using graphite monochromatic CuK α radiation. More information on crystal structures (**190b**) can also be obtained from the Cambridge Crystallographic Data Centre (CCDC) via deposition number 2294705.

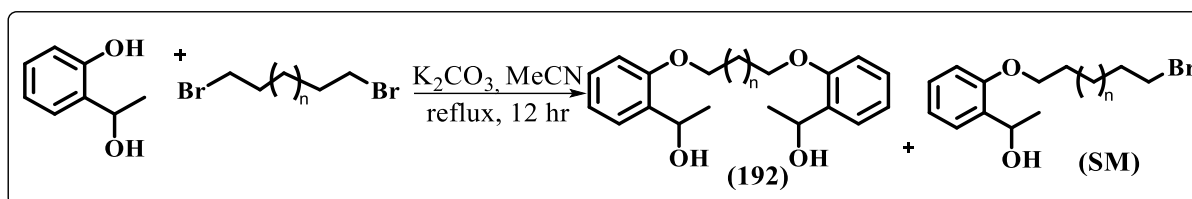
4.9.1 Experimental Section

A) General experimental procedure for primary and secondary diol derivatives.



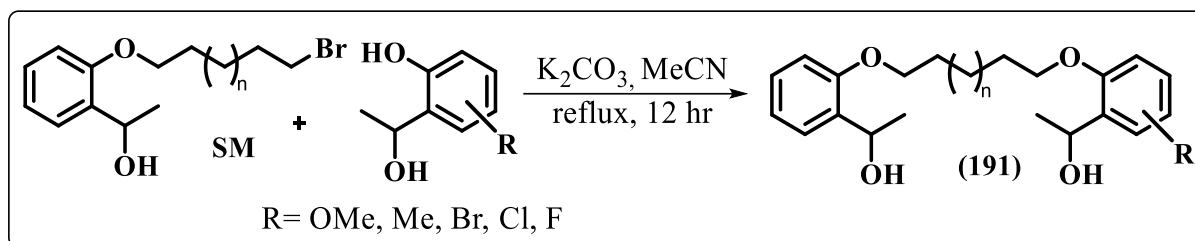
In a 100 mL round bottom flask (SM) (1 equiv.), 2-(1-hydroxyethyl)phenol or 2-(1-hydroxypropyl)phenol (1 equiv.), was added, along with potassium carbonate (K_2CO_3) (2 equiv.) in acetonitrile. In an oil bath, the solution was refluxed at 90 °C for 12 hr. The progress of the reaction was monitored using thin-layer chromatography. The resulting mixture was extracted with ethyl acetate two times using 30 mL of solvent each time. The ethyl acetate layer was combined and dried over Na_2SO_4 . After removing the solvent under reduced pressure, the residue was purified through column chromatography (EtOAc:*n*-hexane = 40:60) for product **189**.

B1) General experimental procedure for diol derivative:



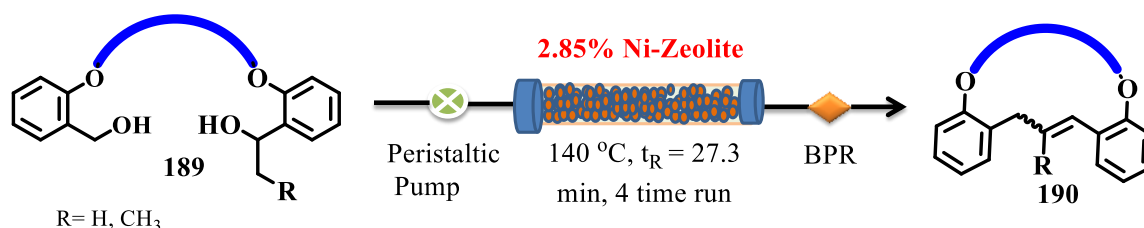
In a 100 mL round bottom flask, 2-(1-hydroxyethyl) phenol (1 equiv.), 1,5-dibromopentane (0.5 equiv.), and potassium carbonate (K_2CO_3) (2 equiv.) in acetonitrile were added. The solution was refluxed at 90 °C temperature for 12 hr in an oil bath. The progress of the reaction was monitored through the thin-layer chromatography technique. The resulting mixture was extracted with ethyl acetate two times using 30 mL of solvent each time. The ethyl acetate layer was combined and dried over Na_2SO_4 . After removing the solvent under reduced pressure, the residue was purified by using column chromatography (EtOAc:*n*-hexane = 50:40) for product **191**.

B2) General experimental procedure for diol derivative:



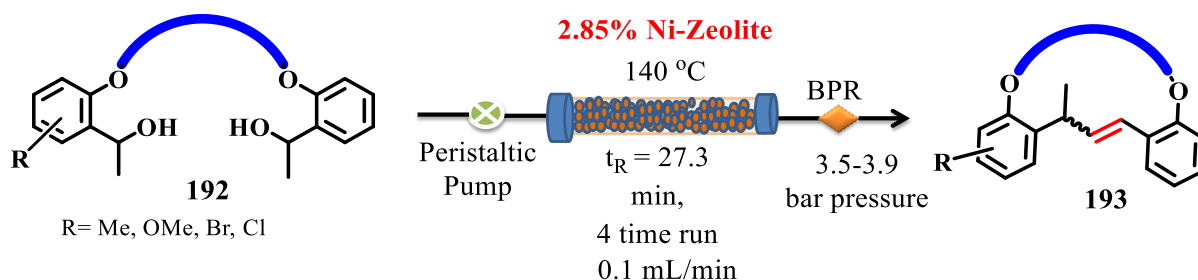
In a 100 mL round bottom flask, **SM** (1 equiv.), 2-(1-hydroxyethyl)phenol (substituted derivative) (1 equiv.), and potassium carbonate (K_2CO_3) (2 equiv.) in acetonitrile were added. In an oil bath, the solution was refluxed at 90 °C temperature for 12 hr. Reaction progress was monitored using thin-layer chromatography. The resulting mixture was extracted with ethyl acetate two times using 30 mL of solvent each time. The ethyl acetate layer was combined and dried over Na_2SO_4 . After removing the solvent under reduced pressure, the residue was purified by using column chromatography (EtOAc:*n*-hexane = 50:40) for product **192**.

C) General experimental procedure for preparation of macrocyclic alkene compounds (157) Using Ni-Zeolite flow under condition:



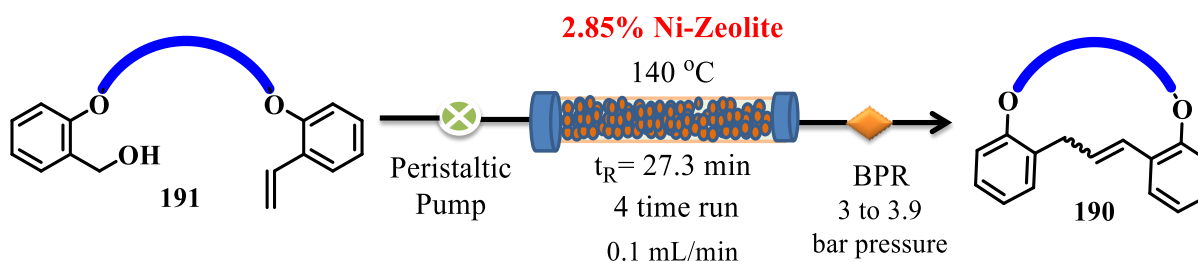
A 0.05 M solution of the diol substrate **189** in 1, 4-dioxane solvent was pumped using a syringe pump through a Omnifit® column (6.6 × 150 mm) packed bed containing 1.9 g of Ni-Zeolite filled up to 9 cm. It was preheated to 140 °C at a flow rate of 0.1 mL/min with 3.5 to 3.9 back pressure, and $t_R = 27.3$ min. After a four-time run, the collected organic layer was concentrated under reduced pressure, and the crude product was purified through column chromatography using (EtOAc/*n*-hexane = 0:100 to 2:98) as an eluent to afford the macrocyclic alkene **190**. After the reaction was complete, the catalyst bed was washed with 1,4-dioxane dried at 140 °C and used for the next reaction.

D) General experimental procedure for preparation of macrocyclic alkene compounds (193) Using Ni-Zeolite flow under condition:



A 0.05 M solution of both secondary diol **192** substrates in 1, 4-dioxane solvent was pumped using a syringe pump through a Omnifit® column (6.6 × 150 mm) packed bed containing 1.9 gm of Ni-Zeolite filled up to 9 cm. It was preheated at 140 °C at a flow rate of 0.1 mL/min with 3.5-3.9 back pressure and residence time $t_R = 27.3$ min. After a four-time run, the collected organic layer was concentrated under reduced pressure, and the crude product was purified by column chromatography using (EtOAc:*n*-hexane = 0:100 to 1:99) as an eluent to afford the macrocyclic alkene **193**. After the completion of the catalyst bed was washed with 1,4-dioxane dried at 140 °C and used for the next reaction.

E) General experimental procedure for preparation of macrocyclic alkene from the intramolecular coupling of alcohol and alkene by using Ni-Zeolite under flow condition:



A 0.05 M solution of **191** substrates in 1, 4-dioxane solvent was pumped using a syringe pump through a Omnifit® column (6.6 × 150 mm) packed bed containing 1.9 g of Ni-Zeolite filled up to 9 cm. It was preheated to 140 °C at a flow rate of 0.1 mL/min with 3 to 3.9 back pressure and $t_R = 27.3$ min. After a two-time run, the collected organic layer was concentrated under reduced pressure, and the crude product was through column chromatography using (EtOAc:*n*-hexane = 0:100 to 1:99) as an eluent to afford the macrocyclic alkene **190**. After completion of the reaction, the catalyst bed was washed with 1,4-dioxane dried at 140 °C and used for the next reaction.

Calculation of Space Time Yield and Weight Hourly Space Velocity (WHSV):

$$\text{Space Time Yield (STY)} = \frac{\text{desired concentration of Product} \times \text{Molecular weight of product} \times (\text{yield}/100)}{\text{Residence time}}$$

$$\text{Weight Hourly Space Velocity (WHSV)} = \frac{\text{mass of feed per hour}}{\text{mass of catalyst}}$$

4.9.2 Analytical Data for the Products

1,1'-((pentane-1,5-diylbis(oxy))bis(2,1-phenylene))bis(ethan-1-ol) (189a): Prepared

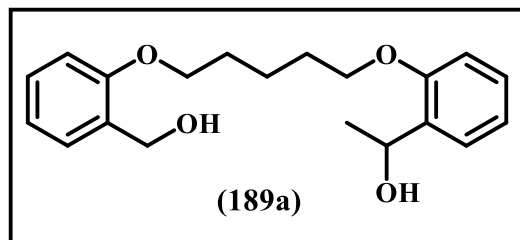
according to general experimental procedure

4.9.1A, using (2-((5-

bromopentyl)oxy)phenyl)methanol (500 mg, 1.83

mmol), potassium carbonate (K₂CO₃) (505 mg,

3.66 mmol) and 2-(1-hydroxyethyl)phenol (252



mg, 1.83 mmol). The residue was purified by using column chromatography (EtOAc:*n*-hexane = 40:60) as the eluent to afford desired (**189a**) (520 mg, 1.57 mmol, 86% yield) as a semisolid;

¹H NMR (400 MHz, CDCl₃) δ 7.36 – 7.27 (m, 2H), 7.26 – 7.19 (m, 2H), 6.95 (td, *J* = 7.5, 0.9 Hz, 2H), 6.87 (dd, *J* = 8.1, 2.2 Hz, 2H), 5.12 (q, *J* = 6.5 Hz, 1H), 4.69 (s, 2H), 4.06 (t, *J* = 6.2 Hz, 4H), 1.96 – 1.87 (m, 4H), 1.76 – 1.66 (m, 2H), 1.51 (d, *J* = 6.5 Hz, 3H), OH peaks are exchanged with deuterium of CDCl₃; ¹³C NMR (100 MHz, CDCl₃) δ 156.9, 155.9, 133.6, 129.3, 129.0, 128.9, 128.4, 126.3, 120.9, 120.8, 111.3, 111.2, 67.7, 67.6, 66.6, 62.0, 29.2, 29.1, 23.2, 23.1; FTIR (neat): 3386, 2933, 2868, 1488, 1452, 1232 cm⁻¹; HRMS (ESI-TOF) *m/z*: [M + Na]⁺ calcd for C₂₀H₂₆O₄Na, 353.1729 found 353.1729.

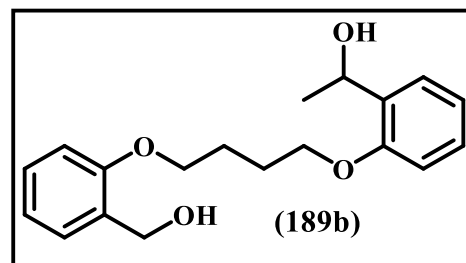
1-(2-(4-(2-

(hydroxymethyl)phenoxy)butoxy)phenyl)ethan-1-

ol (189b): Prepared according to general experimental

procedure 4.9.1A, using (2-(4-

bromobutoxy)phenyl)methanol (500 mg, 1.93 mmol),



potassium carbonate (K₂CO₃) (533 mg, 3.86 mmol) and 2-(1-hydroxyethyl)phenol (266 mg,

1.93 mmol). The residue was purified by using column chromatography (EtOAc:*n*-hexane =

40:60) as the eluent to afford desired product (**189b**) (521 mg, 1.65 mmol, 85% yield) as a

semisolid; ¹H NMR (400 MHz, CDCl₃) δ 7.34 (dd, *J* = 7.5, 1.3 Hz, 1H), 7.29 – 7.25 (m, 1H),

7.25 – 7.17 (m, 2H), 6.93 (q, *J* = 7.3 Hz, 2H), 6.85 (dd, *J* = 8.1, 2.2 Hz, 2H), 5.09 (q, *J* = 6.4

Hz, 1H), 4.64 (s, 2H), 4.07 (d, *J* = 1.4 Hz, 4H), 2.82 (s, 1H), 2.58 (s, 1H), 2.04 – 1.97 (m, 4H),

1.47 (d, *J* = 6.5 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 156.7, 155.8, 133.6, 129.3, 128.9,

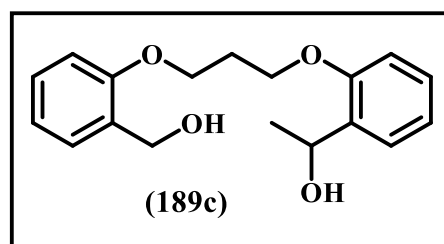
128.8, 128.3, 126.2, 120.9, 120.8, 111.2, 111.1, 67.4, 66.3, 61.8, 26.3, 23.1; FTIR (neat): 3068,

2934, 2868, 1488, 1454, 1234 cm⁻¹; HRMS (ESI-TOF) *m/z*: [M + Na]⁺ calcd for C₁₉H₂₄O₄Na,

339.1572 found 339.1563.

1-(2-(3-(2-(hydroxymethyl)phenoxy)propoxy)phenyl)ethan-1-ol (189c): Prepared

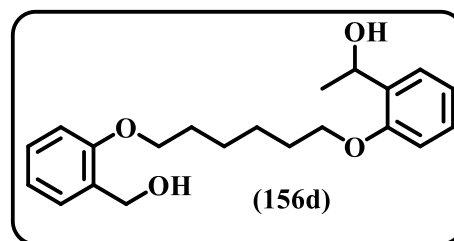
according to general experimental procedure 4.9.1A, using (2-(3-bromopropoxy)phenyl)methanol (500 mg, 2.04 mmol), potassium carbonate (K_2CO_3) (563 mg, 4.08 mmol) and 2-(1-hydroxyethyl)phenol (281 mg, 2.04 mmol). The residue was purified by using column



chromatography (EtOAc/*n*-hexane = 40:60) as the eluent to afford desired product 1-(2-(3-(2-(hydroxymethyl)phenoxy)propoxy)phenyl)ethan-1-ol (**189c**) (499 mg, 1.65 mmol, 81% yield) as a semisolid; ^1H NMR (400 MHz, $CDCl_3$) δ 7.36 (dd, J = 7.5, 1.6 Hz, 1H), 7.31 – 7.28 (m, 1H), 7.27 – 7.25 (m, 1H), 7.24 – 7.20 (m, 1H), 6.97 (td, J = 7.5, 0.9 Hz, 2H), 6.92 – 6.87 (m, 2H), 5.12 (q, J = 6.5 Hz, 1H), 4.67 (s, 2H), 4.24 (dd, J = 11.2, 5.8 Hz, 4H), 2.69 (s, 1H), 2.34 (p, J = 6.0 Hz, 2H), 1.48 (d, J = 6.5 Hz, 3H), OH peak exchanged with deuterium of $CDCl_3$; ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.6, 155.6, 133.7, 129.4, 129.1, 128.4, 126.3, 121.2, 121.1, 111.4, 111.4, 66.1, 65.1, 65.0, 61.7, 29.5, 23.1; FTIR (neat): 3355, 2926, 2878, 1662, 1489, 1453, 1286 cm^{-1} ; HRMS (ESI-TOF) m/z : $[M + Na]^+$ calcd for $C_{18}H_{22}O_4Na$, 325.1416 found 325.1405.

1-(2-(((6-(2-(hydroxymethyl)phenoxy)hexyl)oxy)phenyl)ethan-1-ol (189d): Prepared according to general experimental procedure 4.9.1A, using (2-(((6-bromohexyl)oxy)phenyl)methanol (700 mg,

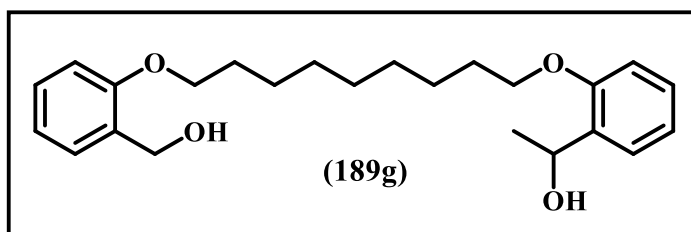
2.44 mmol), potassium carbonate (K_2CO_3) (673 mg, 4.88 mmol) and 2-(1-hydroxyethyl)phenol (336 mg, 2.04 mmol). The residue was purified by using column chromatography (EtOAc/*n*-hexane = 40:60) as the eluent to afford desired product 1-(2-(((6-(2-(hydroxymethyl)phenoxy)hexyl)oxy)phenyl)ethan-1-ol (**156d**) (621mg, 1.80 mmol, 74% yield) as a semisolid;



^1H NMR (400 MHz, $CDCl_3$) δ 7.34 (dd, J = 7.5, 1.6 Hz, 1H), 7.30 – 7.23 (m, 2H), 7.22 (dd, J = 8.0, 1.7 Hz, 1H), 6.99 – 6.91 (m, 2H), 6.87 (d, J = 8.2 Hz, 2H), 5.10 (q, J = 6.5 Hz, 1H), 4.67 (s, 2H), 4.04 (td, J = 6.3, 1.4 Hz, 4H), 2.76 (s, 1H), 2.50 (s, 1H), 1.91 – 1.82 (m, 4H), 1.58 (dt, J = 7.1, 3.5 Hz, 4H), 1.50 (d, J = 6.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.9, 156.1, 133.6, 129.3, 129.0, 128.8, 128.4, 126.2, 120.8, 120.7, 111.3, 111.2, 67.8, 67.7, 66.8, 62.3, 29.3, 26.1, 26.0, 23.0; FTIR (neat): 3385, 2934, 2865, 1454, 1234 cm^{-1} ; HRMS (ESI-TOF) m/z : $[M + Na]^+$ calcd for $C_{21}H_{28}O_4Na$, 367.1885 found 367.1873.

1-(2-((9-(2-(hydroxymethyl)phenoxy)nonyl)oxy)phenyl)ethan-1-ol (189g): Prepared

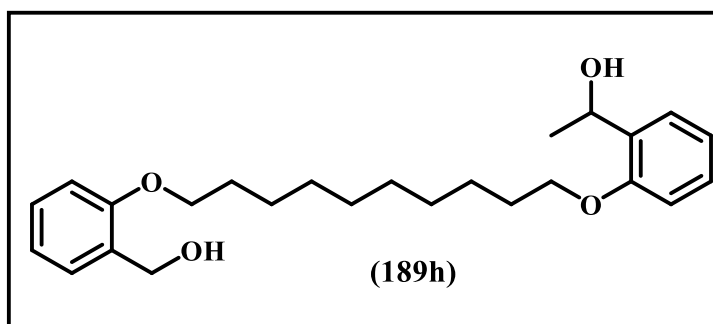
according to general experimental procedure 4.9.1A, using (2-((9-bromononyl)oxy)phenyl)methanol (500 mg, 1.52 mmol), potassium carbonate (K₂CO₃) (419 mg, 3.04



mmol) and 2-(1-hydroxyethyl)phenol (209 mg, 1.52 mmol). The residue was purified by using column chromatography (EtOAc/*n*-hexane =40:60) as the eluent to afford desired product 1-(2-((9-(2-(hydroxymethyl)phenoxy)nonyl)oxy)phenyl)ethan-1-ol (**156g**) (480 mg, 1.24 mmol, 81% yield) as a semisolid; ¹H NMR (400 MHz, CDCl₃) δ 7.31 (dd, *J* = 7.5, 1.5 Hz, 1H), 7.26 – 7.17 (m, 3H), 6.92 (td, *J* = 7.5, 0.8 Hz, 2H), 6.87 – 6.83 (m, 2H), 5.08 (q, *J* = 6.5 Hz, 1H), 4.68 (s, 2H), 4.00 (td, *J* = 6.4, 1.8 Hz, 4H), 1.85 – 1.76 (m, *J* = 6.5, 3.2 Hz, 4H), 1.50 (d, *J* = 6.5 Hz, 4H), 1.49 – 1.43 (m, 4H), 1.41 – 1.33 (m, 6H); OH peaks are exchanged with deuterium of CDCl₃; ¹³C NMR (100 MHz, CDCl₃) δ 157.1, 156.2, 133.5, 129.3, 129.0, 128.8, 128.4, 126.2, 120.7, 120.6, 111.3, 111.2, 68.1, 68.0, 67.0, 62.5, 29.6, 29.4, 29.4, 29.4, 26.3, 26.3, 23.0; FTIR (neat): 3397, 2927, 2857, 1487, 1454, 1234 cm⁻¹; HRMS (ESI-TOF) *m/z*: [M + Na]⁺ calcd for C₂₄H₃₄O₄Na, 409.2355 found 409.2344.

1-(2-((10-(2-(hydroxymethyl)phenoxy)decyl)oxy)phenyl)ethan-1-ol (189h): Prepared

according to general experimental procedure 4.9.1A, using (2-((10-bromodecyl)oxy)phenyl)methanol (500 mg, 1.46 mmol), potassium carbonate (K₂CO₃) (402 mg, 2.91 mmol) and 2-(1-hydroxyethyl)phenol (201 mg, 1.46

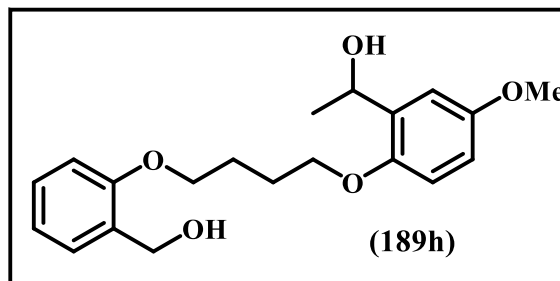


mmol). The residue was purified by using column chromatography (EtOAc/*n*-hexane = 40:60) as the eluent to afford desired product 1-(2-((10-(2-(hydroxymethyl)phenoxy)decyl)oxy)phenyl)ethan-1-ol (**189h**) (511 mg, 1.28 mmol, 87% yield) as a semisolid; ¹H NMR (400 MHz, CDCl₃) δ 7.33 (dd, *J* = 7.5, 1.7 Hz, 1H), 7.28 (s, 1H), 7.26 – 7.23 (m, 1H), 7.22 (dd, *J* = 7.9, 1.8 Hz, 1H), 6.97 – 6.91 (m, 2H), 6.89 – 6.84 (m, 2H), 5.09 (q, *J* = 6.5 Hz, 1H), 4.69 (s, 2H), 4.02 (td, *J* = 6.4, 1.7 Hz, 4H), 2.86 (s, 1H), 2.53 (s, 1H), 1.87 – 1.77 (m, 4H), 1.52 (d, *J* = 6.6 Hz, 3H), 1.51 – 1.43 (m, 4H), 1.37 (d, *J* = 17.5 Hz, 8H); ¹³C NMR (100 MHz, CDCl₃) δ 157.0, 156.2, 133.5, 129.3, 128.9, 128.7, 128.3, 126.2,

120.7, 120.6, 111.3, 111.1, 68.0, 67.9, 67.0, 62.4, 29.5, 29.4, 26.3, 26.3, 23.0; FTIR (neat): 3371, 2926, 1488, 1453, 1235 cm^{-1} ; HRMS (ESI-TOF) m/z : $[\text{M} + \text{Na}]^+$ calcd for $\text{C}_{25}\text{H}_{36}\text{O}_4\text{Na}$, 423.2511, found 423.2503.

1-(2-(4-(2-(hydroxymethyl)phenoxy)butoxy)-5-methoxyphenyl)ethan-1-ol (189i):

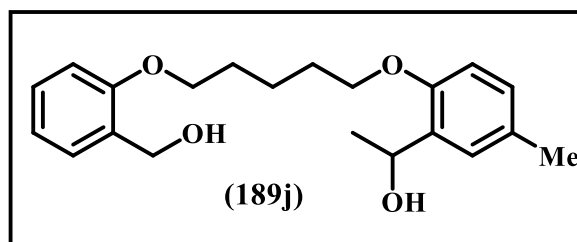
Prepared according to general experimental procedure 4.9.1A, using (2-(4-bromobutoxy)phenyl)methanol (500 mg, 1.93 mmol), potassium carbonate (K_2CO_3) (533 mg, 3.86 mmol) and 2-(1-hydroxyethyl)-4-methoxyphenol (324 mg, 1.93 mmol). The



residue was purified by using column chromatography ($\text{EtOAc}/n\text{-hexane} = 40:60$) as the eluent to afford the desired product 1-(2-(4-(2-(hydroxymethyl)phenoxy)butoxy)-5-methoxyphenyl)ethan-1-ol (**156i**) (580 mg, 1.67 mmol, 87% yield) as a semisolid; ^1H NMR (400 MHz, CDCl_3) δ 7.27 (dt, $J = 6.7, 6.2$ Hz, 2H), 6.98 – 6.92 (m, 2H), 6.88 (d, $J = 8.1$ Hz, 1H), 6.80 (d, $J = 8.8$ Hz, 1H), 6.74 (dd, $J = 8.8, 3.0$ Hz, 1H), 5.08 (q, $J = 6.5$ Hz, 1H), 4.67 (s, 2H), 4.13 – 4.09 (m, 2H), 4.05 (t, $J = 5.4$ Hz, 2H), 3.78 (s, 3H), 2.04 – 1.97 (m, 4H), 1.48 (d, $J = 6.5$ Hz, 3H), OH peaks are exchanged with deuterium of CDCl_3 ; ^{13}C NMR (100 MHz, CDCl_3) δ 156.8, 154.0, 149.9, 135.0, 129.3, 129.1, 129.0, 120.9, 112.6, 112.5, 112.4, 111.2, 68.1, 67.5, 66.4, 62.1, 55.9, 26.5, 26.4, 23.2. FTIR (neat): 3398, 2935, 1454, 1237 cm^{-1} ; HRMS (ESI-TOF) m/z : $[\text{M} + \text{Na}]^+$ calcd for $\text{C}_{20}\text{H}_{26}\text{O}_5\text{Na}$, 369.1677, found 369.1667.

1-(2-((5-(2-(hydroxymethyl)phenoxy)pentyl)oxy)-5-methylphenyl)ethan-1-ol (189j):

Prepared according to general experimental procedure 4.9.1A, using (2-((5-bromopentyl)oxy)phenyl)methanol (500 mg, 1.83 mmol), potassium carbonate (K_2CO_3) (505 mg, 3.66 mmol) and 2-(1-

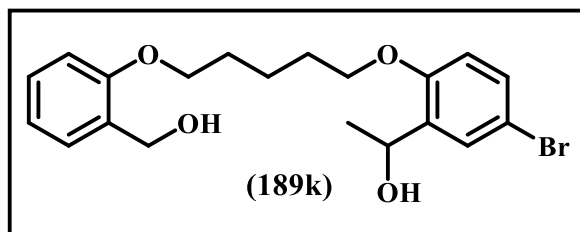


hydroxyethyl)-4-methyl phenol (278 mg, 1.83 mmol). The residue was purified by using column chromatography ($\text{EtOAc}/n\text{-hexane} = 40:60$) as the eluent to afford the desired product 1-(2-((5-(2-(hydroxymethyl)phenoxy)pentyl)oxy)-5-methylphenyl)ethan-1-ol (**189j**) (540 mg, 1.57 mmol, 86% yield) as a semisolid; ^1H NMR (400 MHz, CDCl_3) δ 7.33 – 7.22 (m, 2H), 7.14 (d, $J = 2.0$ Hz, 1H), 7.01 (dd, $J = 8.3, 1.8$ Hz, 1H), 6.93 (dd, $J = 10.8, 4.1$ Hz, 1H), 6.87 (d, $J = 8.1$ Hz, 1H), 6.76 (d, $J = 8.3$ Hz, 1H), 5.08 (dd, $J = 5.9, 3.7$ Hz, 1H), 4.69 (d, $J = 4.3$ Hz, 2H), 4.10 – 3.99 (m, 4H), 2.87 (d, $J = 3.9$ Hz, 1H), 2.56 (s, 1H), 2.29 (s, 3H), 1.95 – 1.85 (m, 4H),

1.75 – 1.67 (m, 2H), 1.50 (d, $J = 6.5$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 156.9, 153.9, 133.3, 130.1, 129.3, 129.0, 128.9, 128.5, 127.0, 120.8, 111.3, 111.2, 67.8, 67.7, 66.7, 62.1, 29.2, 29.1, 23.2, 20.7. FTIR (neat): 3372, 2927, 1480, 1456, 1229 cm^{-1} ; HRMS (ESI-TOF) m/z : $[\text{M} + \text{Na}]^+$ calcd for $\text{C}_{21}\text{H}_{28}\text{O}_4\text{Na}$, 367.1885, found 367.1881.

1-(5-bromo-2-((5-(2-(hydroxymethyl)phenoxy)pentyl)oxy)phenyl)ethan-1-ol (189k):

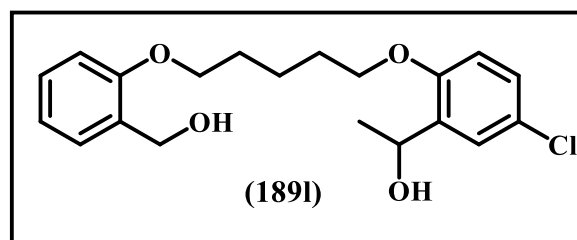
Prepared according to general experimental procedure 4.9.1A, using (2-((5-bromopentyl)oxy)phenyl)methanol (500 mg, 1.83 mmol), potassium carbonate (K_2CO_3) (505 mg, 3.66 mmol) and 4-bromo-2-(1-



hydroxyethyl)phenol (397 mg, 1.83 mmol). The residue was purified by using column chromatography ($\text{EtOAc}/n\text{-hexane} = 40:60$) as the eluent to afford the desired product 1-(5-bromo-2-((5-(2-(hydroxymethyl)phenoxy)pentyl)oxy)phenyl)ethan-1-ol (**189k**) (610 mg, 1.49 mmol, 81% yield) as a semisolid; ^1H NMR (400 MHz, CDCl_3) δ 7.31 – 7.22 (m, 3H), 7.10 (d, $J = 1.8$ Hz, 1H), 6.98 (d, $J = 1.8$ Hz, 1H), 6.94 (s, 1H), 6.87 (d, $J = 8.1$ Hz, 1H), 5.08 (dd, $J = 12.4$, 6.1 Hz, 1H), 4.69 (s, 2H), 4.09 – 4.00 (m, 4H), 2.70 (s, 1H), 2.51 (s, 1H), 1.95 – 1.87 (m, 4H), 1.70 (dt, $J = 12.4$, 5.9 Hz, 2H), 1.45 (d, $J = 6.5$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 156.9, 156.4, 133.0, 129.2, 129.1, 128.9, 127.5, 123.8, 121.4, 120.8, 114.9, 111.2, 68.0, 67.7, 65.7, 62.2, 29.1, 29.0, 23.2, 23.1; FTIR (neat): 3398, 2924, 1452, 1233 cm^{-1} ; HRMS (ESI-TOF) m/z : $[\text{M} + \text{Na}]^+$ calcd for $\text{C}_{20}\text{H}_{25}\text{O}_4\text{ClNa}$, 431.0833, found 431.0843.

1-(5-chloro-2-((5-(2-(hydroxymethyl)phenoxy)pentyl)oxy)phenyl)ethan-1-ol (189l):

Prepared according to general experimental procedure 4.9.1A, using (2-((5-bromopentyl)oxy)phenyl)methanol (500 mg, 1.83 mmol), potassium carbonate (K_2CO_3) (505 mg, 3.66 mmol) and 4-chloro-2-(1-

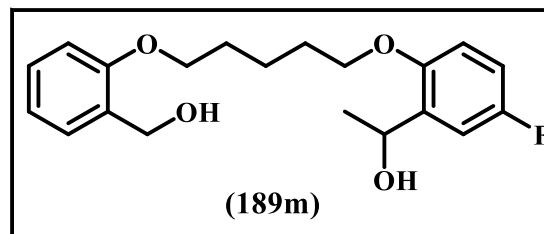


hydroxyethyl)phenol (316 mg, 1.83 mmol). The residue was purified by using column chromatography ($\text{EtOAc}/n\text{-hexane} = 40:60$) as the eluent to afford the desired product 1-(5-chloro-2-((5-(2-(hydroxymethyl)phenoxy)pentyl)oxy)phenyl)ethan-1-ol (**189l**) (410 mg, 1.12 mmol, 61% yield) as a semisolid; ^1H NMR (400 MHz, CDCl_3) δ 7.36 (d, $J = 2.6$ Hz, 1H), 7.31 – 7.22 (m, 2H), 7.16 (dd, $J = 8.7$, 2.7 Hz, 1H), 6.94 (td, $J = 7.5$, 0.8 Hz, 1H), 6.87 (d, $J = 8.1$ Hz, 1H), 6.77 (d, $J = 8.7$ Hz, 1H), 5.09 (q, $J = 6.5$ Hz, 1H), 4.68 (s, 2H), 4.08 – 3.98 (m, 4H), 2.75 (s, 1H), 2.53 (s, 1H), 1.90 (dq, $J = 13.3$, 6.7 Hz, 4H), 1.70 (dt, $J = 12.1$, 7.0 Hz, 2H), 1.46

(d, $J = 6.5$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 156.9, 154.3, 135.7, 129.2, 129.1, 128.9, 127.8, 126.4, 125.9, 120.8, 112.5, 111.2, 68.1, 67.7, 65.7, 62.2, 29.1, 29.1, 23.2, 23.1; FTIR (neat): 3397, 2926, 1481, 1452, 1233 cm^{-1} ; HRMS (ESI-TOF) m/z : $[\text{M} + \text{Na}]^+$ calcd for $\text{C}_{20}\text{H}_{25}\text{O}_4\text{ClNa}$, 387.1339, found 387.1329.

1-(5-fluoro-2-((5-(2-(hydroxymethyl)phenoxy)pentyl)oxy)phenyl)ethan-1-ol (189m):

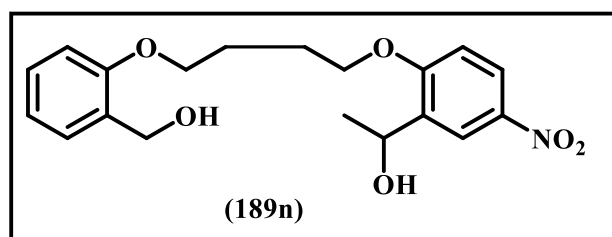
Prepared according to general experimental procedure 4.9.1A, using (2-((5-bromopentyl)oxy)phenyl)methanol (500 mg, 1.83 mmol), potassium carbonate (K_2CO_3) (505 mg, 3.66 mmol) and 4-fluoro-2-(1-



hydroxyethyl)phenol (285 mg, 1.83 mmol). The residue was purified by using column chromatography ($\text{EtOAc}/n\text{-hexane} = 40:60$) as the eluent to afford the desired product 1-(5-fluoro-2-((5-(2-(hydroxymethyl)phenoxy)pentyl)oxy)phenyl)ethan-1-ol (**156m**) (560 mg, 1.61 mmol, 88% yield) as a semisolid; ^1H NMR (400 MHz, CDCl_3) δ 7.30 – 7.23 (m, 2H), 7.11 (dd, $J = 9.2, 3.1$ Hz, 1H), 6.94 (td, $J = 7.5, 0.7$ Hz, 1H), 6.87 (d, $J = 7.5$ Hz, 2H), 6.77 (dd, $J = 8.9, 4.4$ Hz, 1H), 5.10 (q, $J = 6.5$ Hz, 1H), 4.69 (s, 2H), 4.06 (t, $J = 6.2$ Hz, 2H), 4.01 (td, $J = 6.2, 2.7$ Hz, 2H), 2.82 (s, 1H), 2.54 (s, 1H), 1.95 – 1.85 (m, 4H), 1.73 – 1.67 (m, 2H), 1.46 (d, $J = 6.5$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 158.6, 156.9, 156.2, 151.8, 135.8, 135.7, 129.2, 129.1, 128.9, 120.8, 114.0, 113.8, 113.4, 113.2, 112.2, 112.1, 111.2, 68.3, 67.7, 65.8, 62.2, 29.2, 29.1, 23.2, 23.1; FTIR (neat): 3398, 2931, 2870, 1609, 1454 cm^{-1} ; HRMS (ESI-TOF) m/z : $[\text{M} + \text{Na}]^+$ calcd for $\text{C}_{20}\text{H}_{25}\text{O}_4\text{FNa}$, 371.1634, found 371.1624.

1-(2-(4-(2-(hydroxymethyl)phenoxy)butoxy)-5-nitrophenyl)ethan-1-ol (189n): Prepared

according to general experimental procedure 4.9.1A, using (2-((4-bromobutoxy)phenyl)methanol (500 mg, 1.93 mmol), potassium carbonate (K_2CO_3) (505 mg, 3.66 mmol) and 2-(1-

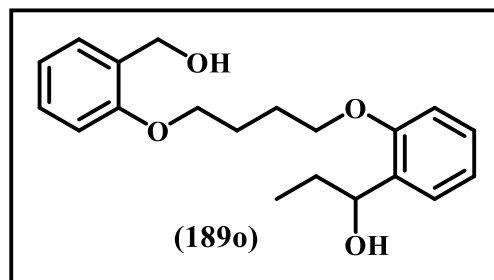


hydroxyethyl)-4-nitrophenol (285 mg, 1.83 mmol). The residue was purified by using column chromatography ($\text{EtOAc}/n\text{-hexane} = 40:60$) as the eluent to afford the desired product 1-(2-((5-(2-(hydroxymethyl)phenoxy)pentyl)oxy)-5-nitrophenyl)ethan-1-ol (**156n**) (530 mg, 1.41 mmol, 77% yield) as a semisolid; ^1H NMR (400 MHz, CDCl_3) δ 8.28 (d, $J = 2.1$ Hz, 1H), 8.17 (dd, $J = 9.0, 2.5$ Hz, 1H), 7.35 (dd, $J = 7.5, 1.1$ Hz, 1H), 7.23 (dd, $J = 7.9, 1.4$ Hz, 1H), 6.98 (t, $J = 7.5$ Hz, 1H), 6.89 (dd, $J = 14.3, 8.6$ Hz, 2H), 5.10 (q, $J = 6.5$ Hz, 1H), 4.70 (s, 2H), 4.20 (t,

$J = 5.5$ Hz, 2H), 4.12 (t, $J = 5.5$ Hz, 2H), 2.75 (s, 1H), 2.50 (s, 1H), 2.11 – 2.01 (m, 4H), 1.50 (d, $J = 6.5$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 161.2, 155.8, 141.5, 133.4, 130.7, 128.5, 126.4, 125.2, 124.0, 121.2, 111.3, 110.6, 68.6, 67.3, 66.7, 60.3, 26.3, 26.2, 23.0; FTIR (neat): 3400, 2929, 1498, 1452, 1236 cm^{-1} ; HRMS (ESI-TOF) m/z : $[\text{M} + \text{Na}]^+$ calcd for $\text{C}_{19}\text{H}_{23}\text{NO}_6\text{Na}$, 384.1423, found 384.1413.

1-(2-(4-(2-(hydroxymethyl)phenoxy)butoxy)phenyl)propan-1-ol (189o): Prepared

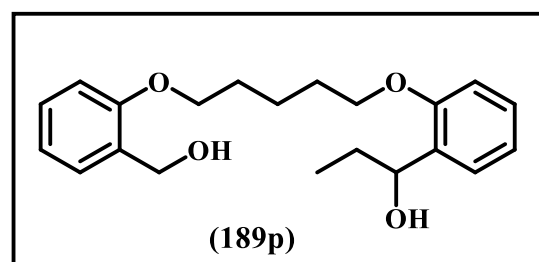
according to general experimental procedure 4.9.1A, using (2-(4-bromobutoxy)phenyl)methanol (500 mg, 1.93 mmol), potassium carbonate (K_2CO_3) (530 mg, 3.86 mmol) and 2-(1-hydroxypropyl)phenol (293 mg, 1.46 mmol). The residue was purified by using column chromatography (EtOAc/*n*-hexane = 40:60)



as the eluent to afford desired product 1-(2-(4-(2-(hydroxymethyl)phenoxy)butoxy)phenyl)propan-1-ol (**189o**) (513 mg, 1.55 mmol, 80% yield) as a semisolid; ^1H NMR (400 MHz, CDCl_3) δ 7.30 (ddd, $J = 12.7, 7.4, 3.6$ Hz, 3H), 7.25 – 7.20 (m, 1H), 6.99 – 6.92 (m, 2H), 6.88 (dd, $J = 8.1, 4.6$ Hz, 2H), 4.82 (t, $J = 6.6$ Hz, 1H), 4.67 (s, 2H), 4.11 (dt, $J = 7.5, 5.7$ Hz, 4H), 2.61 (s, 1H), 2.40 (s, 1H), 2.03 (dt, $J = 5.7, 2.8$ Hz, 4H), 1.86 – 1.76 (m, 2H), 0.94 (t, $J = 7.4$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 156.8, 156.0, 132.5, 129.3, 129.1, 129.0, 128.3, 127.2, 120.9, 120.9, 111.4, 111.2, 72.3, 67.5, 67.5, 62.1, 30.4, 26.4, 26.4, 10.6; FTIR (neat): 3369, 294, 2865, 1488, 1453, 1232 cm^{-1} ; HRMS (ESI-TOF) m/z : $[\text{M} + \text{Na}]^+$ calcd for $\text{C}_{20}\text{H}_{26}\text{O}_4\text{Na}$, 353.1729, found 353.1730

1-(2-((5-(2-(hydroxymethyl)phenoxy)pentyl)oxy)phenyl)propan-1-ol (189p): Prepared

according to general experimental procedure 4.9.1A, using (2-((5-bromopentyl)oxy)phenyl)methanol (500 mg, 1.83 mmol), potassium carbonate (K_2CO_3) (505 mg, 3.66 mmol) and 2-(1-

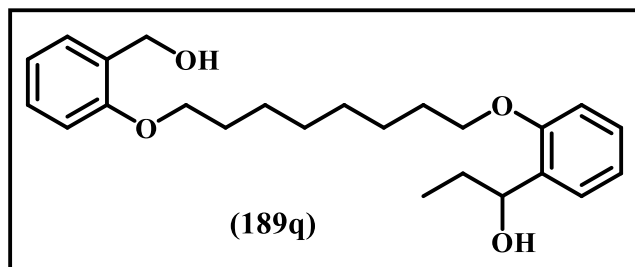


hydroxypropyl)phenol (278 mg, 1.86 mmol). The residue was purified by using column chromatography (EtOAc/*n*-hexane = 40:60) as the eluent to afford desired product 1-(2-((5-(2-(hydroxymethyl)phenoxy)pentyl)oxy)phenyl)propan-1-ol (**189p**) (559 mg, 1.33 mmol, 72% yield) as a semisolid; ^1H NMR (400 MHz, CDCl_3) δ 7.30 (td, $J = 7.3, 1.2$ Hz, 2H), 7.26 – 7.18 (m, 2H), 6.94 (tdd, $J = 7.4, 3.4, 0.9$ Hz, 2H), 6.90 – 6.84 (m, 2H), 4.82 (dd, $J = 11.6, 6.1$ Hz, 1H), 4.69 (d, $J = 4.8$ Hz, 2H), 4.09 – 4.02 (m, 4H), 2.80 (s, 1H), 2.55 (s, 1H), 1.91 (dq, $J =$

13.4, 6.7 Hz, 4H), 1.86 – 1.77 (m, 2H), 1.73 – 1.66 (m, 2H), 0.94 (t, $J = 7.4$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 156.9, 156.0, 132.5, 129.3, 129.0, 128.9, 128.3, 127.2, 120.8, 111.3, 111.2, 72.4, 67.7, 67.6, 62.1, 30.5, 29.2, 29.1, 23.2, 10.6; FTIR (neat): 3363, 2935, 2870, 1454, 1231 cm^{-1} ; HRMS (ESI-TOF) m/z : $[\text{M} + \text{Na}]^+$ calcd for $\text{C}_{21}\text{H}_{28}\text{O}_4\text{Na}$, 367.1885 found 367.1875.

1-(2-((8-(2-(hydroxymethyl)phenoxy)octyl)oxy)phenyl)propan-1-ol (189q): Prepared

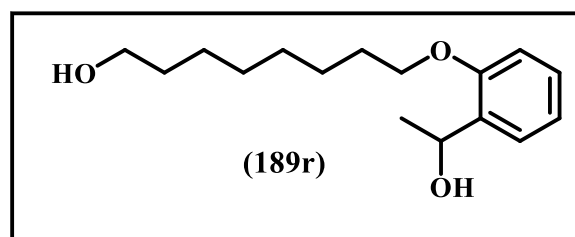
according to general experimental procedure 4.9.1A, using (2-((8-bromooctyl)oxy)phenyl)methanol (500 mg, 1.59 mmol), potassium carbonate (K_2CO_3) (438 mg, 3.17 mmol) and 2-(1-hydroxypropyl)phenol (219 mg, 1.59



mmol). The residue was purified by using column chromatography ($\text{EtOAc}/n\text{-hexane} = 40:60$) as the eluent to afford desired product 1-(2-((8-(2-(hydroxymethyl)phenoxy)octyl)oxy)phenyl)ethan-1-ol (**189q**) (509 mg, 1.37 mmol, 86% yield) as a semisolid; ^1H NMR (400 MHz, CDCl_3) δ 7.28 (dd, $J = 7.2, 1.7$ Hz, 2H), 7.22 (dd, $J = 7.9, 1.5$ Hz, 2H), 6.93 (td, $J = 7.3, 2.5$ Hz, 2H), 6.87 (dd, $J = 8.1, 3.7$ Hz, 2H), 4.78 (t, $J = 6.5$ Hz, 1H), 4.69 (s, 2H), 4.05 – 3.97 (m, 4H), 2.73 (s, 1H), 2.48 (s, 1H), 1.86 – 1.78 (m, 6H), 1.54 – 1.46 (m, 4H), 1.41 (dd, $J = 6.7, 3.6$ Hz, 4H), 0.95 (t, $J = 7.4$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 157.07, 156.24, 132.43, 129.28, 129.01, 128.80, 128.29, 127.26, 120.67, 111.39, 111.19, 72.96, 68.04, 67.95, 62.48, 30.42, 29.42, 29.40, 26.28, 26.26, 10.67; FTIR (neat): 3389, 2930, 2862, 1454, 1235 cm^{-1} ; HRMS (ESI-TOF) m/z : $[\text{M} + \text{Na}]^+$ calcd for $\text{C}_{24}\text{H}_{34}\text{O}_4\text{Na}$, 409.2355 found 409.2348.

8-(2-(1-hydroxyethyl)phenoxy)octan-1-ol (189r): Prepared according to general

experimental procedure 4.9.1A, using 2-(1-hydroxyethyl)phenol (500 mg, 3.62 mmol), potassium carbonate (K_2CO_3) (500 mg, 3.62 mmol) and 8-bromooctan-1-ol (756.8 mg, 3.62 mmol). The residue was purified by using

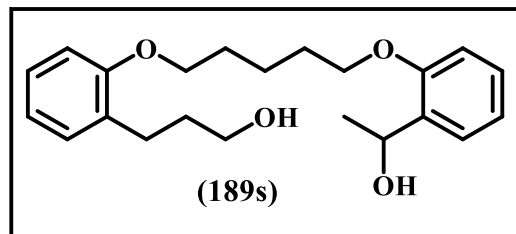


column chromatography ($\text{EtOAc}/n\text{-hexane} = 60:40$) as the eluent to afford desired product (**189r**) (870 mg, 3.27 mmol, 90% yield) as a semisolid; ^1H NMR (400 MHz, CDCl_3) δ 7.32 (dd, $J = 7.5, 1.5$ Hz, 1H), 7.22 (td, $J = 8.1, 1.6$ Hz, 1H), 6.94 (t, $J = 7.5$ Hz, 1H), 6.86 (d, $J = 8.2$ Hz, 1H), 5.09 (d, $J = 6.2$ Hz, 1H), 4.01 (t, $J = 6.4$ Hz, 2H), 3.63 (t, $J = 6.4$ Hz, 2H), 2.87 (s, 1H), 1.88 – 1.76 (m, 2H), 1.60 – 1.54 (m, 2H), 1.50 (dd, $J = 14.0, 7.2$ Hz, 5H), 1.36 (s, 6H);

^{13}C NMR (100 MHz, CDCl_3) 156.2, 133.5, 128.2, 126.3, 120.7, 111.3, 68.0, 67.0, 63.1, 32.8, 29.4, 29.3, 26.2, 25.7, 23.0; FTIR (neat): 3380, 2935, 2862, 1460, 1230 cm^{-1} ; HRMS (ESI-TOF) m/z : $[\text{M} + \text{Na}]^+$ calcd for $\text{C}_{16}\text{H}_{26}\text{O}_3\text{Na}$, 289.1779 found 289.1772.

3-(2-((5-(2-(1-hydroxyethyl)phenoxy)pentyl)oxy)phenyl)propan-1-ol (189s): Prepared

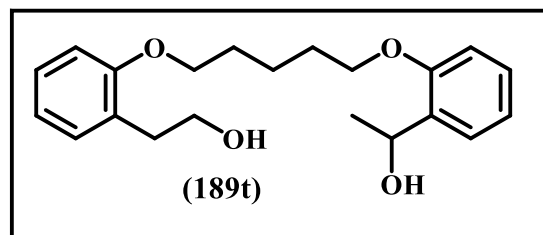
according to general experimental procedure 4.9.1A, using 2-(3-hydropropyl)phenol (264.9 mg, 1.74 mmol), potassium carbonate (K_2CO_3) (240 mg, 1.74 mmol) and 1-(2-((5-bromopentyl)oxy)phenyl)ethan-1-ol (500 mg, 1.74



mmol). The residue was purified by using column chromatography ($\text{EtOAc}/n\text{-hexane} = 60:40$) as the eluent to afford desired product (**189s**) (510 mg, 1.42 mmol, 82% yield) as a semisolid; ^1H NMR (400 MHz, CDCl_3) δ 7.35 (dd, $J = 7.5, 1.4$ Hz, 1H), 7.23 (td, $J = 8.0, 1.7$ Hz, 1H), 7.17 (ddd, $J = 7.4, 6.8, 2.7$ Hz, 2H), 6.96 (td, $J = 7.5, 0.7$ Hz, 1H), 6.89 (ddd, $J = 18.2, 11.2, 4.8$ Hz, 3H), 5.13 (q, $J = 6.5$ Hz, 1H), 4.06 (t, $J = 6.2$ Hz, 2H), 4.02 (t, $J = 6.2$ Hz, 2H), 3.05 (s, 1H), 2.32 (s, 1H), 1.91 (ddd, $J = 9.7, 8.5, 4.7$ Hz, 4H), 1.88 – 1.81 (m, 2H), 1.77 – 1.66 (m, 2H), 1.51 (d, $J = 6.5$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 156.9, 156.0, 133.6, 130.3, 130.2, 128.3, 127.2, 126.2, 120.8, 120.7, 111.3, 67.8, 66.6, 62.1, 33.1, 29.32, 29.36, 26.2, 23.3, 23.1; FTIR (neat): 3387, 2929, 2861, 1458, 1241 cm^{-1} ; HRMS (ESI-TOF) m/z : $[\text{M} + \text{Na}]^+$ calcd for $\text{C}_{22}\text{H}_{30}\text{O}_4\text{Na}$, 381.2041 found 381.2025

2-(2-((5-(2-(1-hydroxyethyl)phenoxy)pentyl)oxy)phenyl)ethan-1-ol (189t): Prepared

according to general experimental procedure 4.9.1A, using 2-(2-hydroxyethyl)phenol (240 mg, 1.74 mmol), potassium carbonate (K_2CO_3) (241 mg, 1.74 mmol) and 1-(2-((5-bromopentyl)oxy)phenyl)ethan-1-ol (500 mg,



1.74 mmol). The residue was purified by using column chromatography ($\text{EtOAc}/n\text{-hexane} = 60:40$) as the eluent to afford desired product (**189t**) (494 mg, 1.43 mmol, 82% yield) as a semisolid; ^1H NMR (400 MHz, CDCl_3) δ 7.33 (d, $J = 7.4$ Hz, 1H), 7.26 – 7.14 (m, 3H), 6.96 (t, $J = 7.5$ Hz, 1H), 6.88 (ddd, $J = 15.4, 11.0, 7.8$ Hz, 3H), 5.12 (q, $J = 5.9$ Hz, 1H), 4.07 (t, $J = 6.0$ Hz, 2H), 4.02 (t, $J = 6.0$ Hz, 2H), 3.81 (t, $J = 6.7$ Hz, 2H), 3.09 (s, 1H), 2.92 (t, $J = 6.9$ Hz, 2H), 2.42 (s, 1H), 1.96 – 1.85 (m, 4H), 1.78 – 1.68 (m, 2H), 1.52 (d, $J = 6.5$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 157.1, 156.1, 133.4, 131.0, 128.4, 127.8, 127.2, 126.3, 120.9, 120.7, 111.25, 111.21, 67.70, 67.67, 66.8, 62.9, 34.4, 29.32, 29.27, 23.4, 22.9; FTIR (neat): 3381,

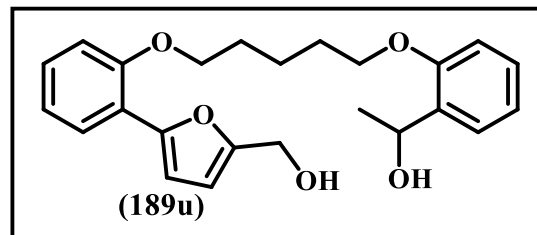
2932, 2860, 1449, 1245 cm^{-1} ; HRMS (ESI-TOF) m/z : $[\text{M} + \text{Na}]^+$ calcd for $\text{C}_{21}\text{H}_{28}\text{O}_4\text{Na}$, 367.1885 found 367.1859.

1-(2-((5-(2-(5-(hydroxymethyl)furan-2-yl)phenoxy)pentyl)oxy)phenyl)ethan-1-ol

(189u): In a 100 mL round bottom flask, we added

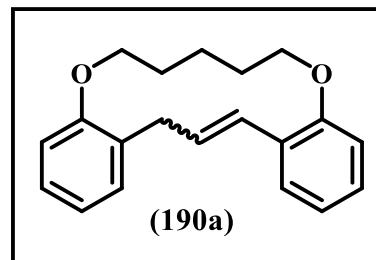
5-(2-((5-(2-

acetylphenoxy)pentyl)oxy)phenyl)furan-2-



carbaldehyde (120 mg, 0.3 mmol, 1 equiv.) 30 ml ethanol at 0 °C and added pinch by pinch NaBH_4 (17 mg, 0.45 mmol, 1.5 equiv.) for 3 hr. The progress of the reaction was monitored through the thin-layer chromatography technique. The resulting mixture quiche in NH_4Cl solution and extracted with ethyl acetate two times using 30 mL of solvent each time. The ethyl acetate layer was combined and dried over Na_2SO_4 . After removing the solvent under reduced pressure, the residue was purified by using column chromatography ($\text{EtOAc}/n\text{-hexane} = 30:70$) as the eluent to afford desired product **(156u)** 80 mg, 0.20 mmol, 66% yield) as a semisolid; ^1H NMR (400 MHz, CDCl_3) δ 7.87 (dd, $J = 7.8, 1.6$ Hz, 1H), 7.35 (dd, $J = 7.5, 1.5$ Hz, 1H), 7.22 (td, $J = 8.2, 1.7$ Hz, 2H), 7.04 – 6.98 (m, 1H), 6.98 – 6.92 (m, 2H), 6.90 (d, $J = 3.2$ Hz, 1H), 6.85 (d, $J = 8.0$ Hz, 1H), 6.34 (d, $J = 3.2$ Hz, 1H), 5.07 (q, $J = 6.5$ Hz, 1H), 4.65 (s, 2H), 4.17 – 4.06 (m, 2H), 4.03 (t, $J = 6.2$ Hz, 2H), 2.67 (s, 1H), 2.25 (s, 1H), 2.06 – 1.86 (m, 4H), 1.81 – 1.70 (m, 2H), 1.45 (d, $J = 6.5$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 156.7, 155.8, 154.7, 152.7, 132.9, 131.9, 130.3, 129.9, 129.6, 129.5, 126.9, 121.5, 120.78 120.2, 114.7, 113.8, 108.2, 107.0, 71.9, 70.3, 34.7, 31.2, 29.8, 28.8, 23.9. FTIR (neat): 3396, 2942, 2259, 1439, 1241 cm^{-1} ; HRMS (ESI-TOF) m/z : $[\text{M} + \text{Na}]^+$ calcd for $\text{C}_{24}\text{H}_{28}\text{O}_5\text{Na}$, 419.1834, found 419.1834.

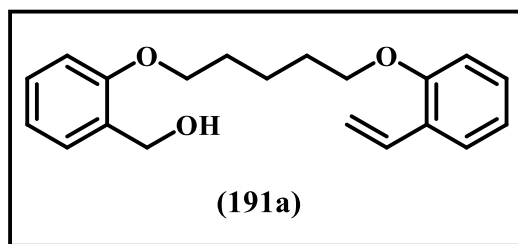
(E)-7,8,9,10-tetrahydro-6H,16H-dibenzo[*h,m*][1,7]dioxacyclotetradecine (190a): Prepared according to general experimental procedure 4.9.1C, a 0.05 M solution of **189a** (66.0 mg, 0.199 mmol) in (4 mL) in 1, 4-dioxane solvent was pumped using a syringe pump through Omnifit® column (6.6 x 150 mm) packed bed containing 1.9 gm of Ni-zeolite filled up to 9 cm and preheated at 140 °C with the flow rate of 0.1 mL/min at 3.5 to 3.9 back pressure and residence time $t_R = 27.3$ min. After a four-time run, the collected organic layer was concentrated under reduced pressure, and the crude product was purified by column chromatography using ($\text{EtOAc}/n\text{-hexane} = 2:98$) as an eluent to afford the compound **190a** as a white solid (34.5 mg, 59% yield, >98:2 *E:Z*); melting



point: 112-115 °C; and acyclic alkene (2-((5-(2-vinylphenoxy)pentyl)oxy) phenyl) methanol **191a** (7.7 mg, 12 %) as a semisolid. **(190a)**: ^1H NMR (400 MHz, CDCl_3) δ 7.28 – 7.23 (m, 1H), 7.20 – 7.08 (m, 3H), 6.90 – 6.80 (m, 4H), 6.73 (d, J = 16.0 Hz, 1H), 6.64 (dt, J = 15.9, 6.5 Hz, 1H), 4.07 (t, J = 5.1 Hz, 2H), 4.04 (t, J = 5.0 Hz, 2H), 3.52 (d, J = 6.5 Hz, 2H), 1.89 (dd, J = 5.9, 3.0 Hz, 4H), 1.80 (dd, J = 11.0, 6.0 Hz, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 157.62, 157.34, 131.85, 130.57, 128.96, 128.20, 28.11, 127.63, 126.57, 121.13, 120.33, 113.98, 110.95, 77.16, 69.37, 65.83, 37.30, 28.27, 27.94, 22.26. FTIR (neat): 2928, 2870, 1488, 1452, 1241 cm^{-1} ; HRMS (ESI-TOF) m/z : $[\text{M} + \text{Na}]^+$ calcd for $\text{C}_{20}\text{H}_{23}\text{O}_2$, 295.1698 found 295.1693.

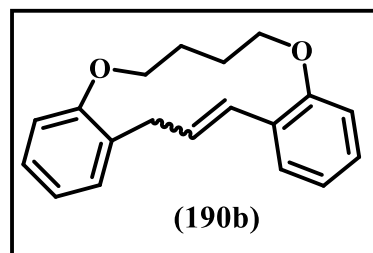
Large-scale reaction condition: A 0.05 M solution of **189a** (3.47 gm, 10.50 mmol) in (210 mL) in 1, 4-dioxane solvent was pumped using a syringe pump through two Omnifit® column (6.6 x 150 mm) packed bed containing 1.9 gm of Ni-zeolite filled up to 9 cm each column bed and preheated at 140 °C with the flow rate of 0.1 mL/min at 5 back pressure and residence time t_R = 30.7 min each column bed. After a two-time run, the collected organic layer was concentrated under reduced pressure, and the crude product was purified by column chromatography using (EtOAc/*n*-hexane = (2:98) as an eluent to afford the compound **190a** as a white solid (1.86 gm, 54% yield, >98:2 *E:Z*). Productivity per day: 0.05 X 0.1 X 60 X 24 X 294.3 X 0.54/1000. Productivity *g/day* = 1.14 *g/day*; Continuous flow 1.86 g (54%), and space time yield 12.82 $\text{g L}^{-1} \text{h}^{-1}$.

(2-((5-(2-vinylphenoxy)pentyl)oxy) phenyl) methanol (191a): ^1H NMR (400 MHz, CDCl_3) δ 7.48 (dd, J = 7.6, 1.7 Hz, 1H), 7.31 – 7.25 (m, 2H), 7.25 – 7.19 (m, 1H), 7.07 (dd, J = 17.8, 11.2 Hz, 1H), 6.96 – 6.90 (m, 2H), 6.87 (t, J = 7.6 Hz, 2H), 5.75 (dd, J = 17.8, 1.5 Hz, 1H), 5.25 (dd, J = 11.1, 1.5 Hz, 1H), 4.70 (d, J = 4.2 Hz, 2H), 4.06 (t, J = 6.4 Hz, 2H), 4.03 (t, J = 6.3 Hz, 2H), 2.33 (s, 1H), 1.97 – 1.86 (m, 4H), 1.75 – 1.66 (m, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 157.0, 156.2, 131.8, 129.3, 129.0, 128.9, 128.8, 126.9, 126.6, 120.7, 120.7, 114.4, 112.0, 111.2, 68.1, 67.9, 62.4, 29.2, 23.1; FTIR (neat): 3393, 2936, 2869, 1486, 1455, 1237 cm^{-1} ; HRMS (ESI-TOF) m/z : $[\text{M} + \text{Na}]^+$ calcd for $\text{C}_{20}\text{H}_{24}\text{O}_3\text{Na}$, 335.1622 found 335.1635.



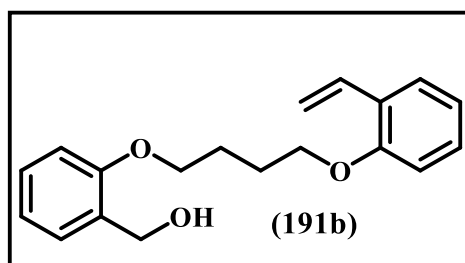
6,7,8,9-tetrahydro-15H-dibenzo[*g,l*][1,6]dioxacyclotridecine (190b): Prepared according to general experimental procedure 4.9.1C, a 0.05 M solution of **189b** (63.20 mg, 0.199 mmol) in (4 mL) in 1, 4-dioxane solvent was pumped using a syringe pump through Omnifit® column

(6.6 x 150 mm) packed bed containing 1.9 gm of Ni-zeolite filled up to 9 cm and preheated at 140 °C with the flow rate of 0.1 mL/min at 3.5 to 3.9 psi back pressure and residence time $t_R = 27.3$ min. After a four-time run, the collected organic layer was concentrated under reduced pressure, and the crude product was purified by column chromatography using (EtOAc/*n*-hexane = 1:99) as an eluent to afford the compound **190b** as a white solid (38.7 mg, 69% yield, 97:3 E:Z); melting point: 105-108 °C; and acyclic alkene (2-(4-(2-vinylphenoxy)butoxy)phenyl)methanol **191b** (3 mg, 5%) as a semisolid. Continuous flow 0.037 g (69%), space-time yield 26.45 g L⁻¹ h⁻¹. Productivity *g/day* = 1.14 g/day.

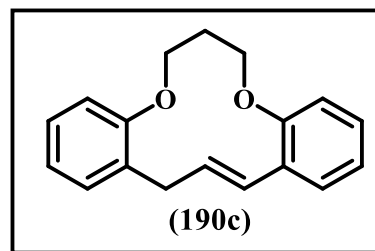


¹H NMR (400 MHz, CDCl₃) δ 7.36 (dd, *J* = 7.8, 1.6 Hz, 1H), 7.22 – 7.13 (m, 3H), 7.03 – 6.95 (m, 3H), 6.88 (td, *J* = 7.4, 1.0 Hz, 1H), 6.82 (t, *J* = 6.4 Hz, 1H), 6.02 (dt, *J* = 15.7, 7.1 Hz, 1H), 4.02 (dd, *J* = 10.3, 5.3 Hz, 4H), 3.50 (d, *J* = 6.9 Hz, 2H), 2.13 (dt, *J* = 7.5, 6.2 Hz, 2H), 1.82 (dt, *J* = 17.6, 6.2 Hz, 2H); ¹³C NMR (100 MHz, CDCl₃) δ 157.9, 157.5, 132.6, 130.6, 129.5, 128.7, 128.3, 127.9, 126.6, 123.8, 121.7, 120.5, 111.5, 75.0, 67.4, 36.8, 28.0, 26.2; FTIR (neat): 29490, 2871, 1483, 1241 cm⁻¹; HRMS (ESI-TOF) *m/z*: [M + H]⁺ calcd for C₁₉H₂₁O₂, 281.1542, found 281.1522.

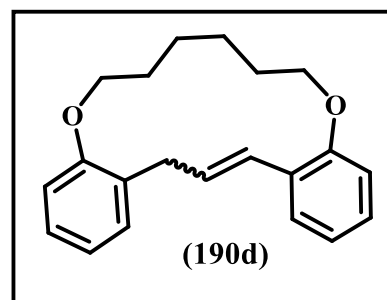
(2-(4-(2-vinylphenoxy)butoxy)phenyl)methanol (191b): ¹H NMR (400 MHz, CDCl₃) δ 7.49 (dd, *J* = 7.6, 1.6 Hz, 1H), 7.32 – 7.26 (m, 2H), 7.25 – 7.20 (m, 1H), 7.06 (dd, *J* = 17.8, 11.2 Hz, 1H), 6.97 – 6.92 (m, 2H), 6.88 (t, *J* = 8.4 Hz, 2H), 5.75 (dd, *J* = 17.8, 1.5 Hz, 1H), 5.25 (dd, *J* = 11.2, 1.5 Hz, 1H), 4.71 (s, 2H), 4.12 (t, *J* = 5.9 Hz, 2H), 4.08 (t, *J* = 5.7 Hz, 2H), 2.08 – 2.00 (m, *J* = 6.0, 3.2 Hz, 4H); OH peak exchanged with deuterium of CDCl₃; ¹³C NMR (100 MHz, CDCl₃) δ 156.8, 156.1, 131.7, 129.0, 128.9, 128.8, 126.6, 120.8, 120.7, 114.5, 111.9, 111.2, 67.8, 67.6, 62.2, 26.4, 26.2. FTIR (neat): 3382, 2939, 2872, 6, 1455, 1233 cm⁻¹; FTIR (neat): 3382, 2939, 2872, 1452, 1233 cm⁻¹; HRMS (ESI-TOF) *m/z*: [M + H]⁺ calcd for C₁₉H₂₃O₂, 299.1642, found 299.1644.



(E)-7,8-dihydro-6H,14H-dibenzo[f,k][1,5]dioxacyclododecine (190c): Prepared according to general experimental procedure 4.9.1C, a 0.05 M solution of 1-(2-(3-(2-(hydroxymethyl)phenoxy)propoxy)phenyl)ethan-1-ol **189c** (60.4 mg, 0.199 mmol) in (4 mL) 1, 4-dioxane solvent was pumped using a syringe pump through Omnifit® column (6.6 x 150 mm) packed bed containing 1.9 gm of Ni-Zeolite filled up to 9 cm and preheated at 140 °C with the flow rate of 0.1 mL/min at 3.5 to 3.9 back pressure and residence time $t_R = 27.3$ min. After a four-time run, the collected organic layer was concentrated under reduced pressure, and the crude product was purified by column chromatography using (EtOAc/*n*-hexane = 1:99) as an eluent to afford the compound **157c** as a semisolid (37.1 mg, 70% yield, 100:0 *E:Z*). Continuous flow 0.037 g (70%), space-time yield 28.42 g L⁻¹ h⁻¹. Productivity *g/day* = 1.39 g/day; ¹H NMR (400 MHz, CDCl₃) δ 7.31 – 7.27 (m, 1H), 7.23 (dd, *J* = 7.5, 5.9 Hz, 2H), 7.18 (dd, *J* = 7.7, 1.8 Hz, 1H), 7.08 (td, *J* = 7.4, 1.1 Hz, 1H), 7.03 (dd, *J* = 7.9, 1.1 Hz, 1H), 7.01 – 6.94 (m, 2H), 6.46 (d, *J* = 16.1 Hz, 1H), 6.02 (dt, *J* = 16.0, 5.3 Hz, 1H), 4.29 (t, 2H), 4.07 (t, *J* = 5.8 Hz, 2H), 3.58 (dd, *J* = 5.3, 1.7 Hz, 2H), 2.29 – 2.22 (m, 2H); ¹³C NMR (100 MHz, CDCl₃) δ 158.1, 157.3, 133.6, 131.3, 130.5, 128.2, 128.0, 127.9, 127.8, 127.7, 124.2, 121.1, 113.0, 76.8, 70.1, 64.7, 36.2, 29.4; FTIR (neat): 3382, 2939, 2872, 1452, 1233 cm⁻¹; HRMS (ESI-TOF) *m/z*; [M + H]⁺ calcd for C₁₈H₁₉O₂, 267.1385, found 267.1386.



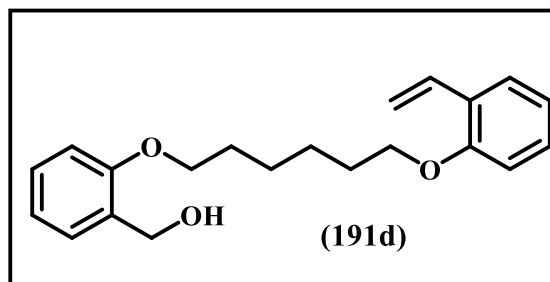
6,7,8,9,10,11-hexahydro-17H-dibenzo[i,n][1,8]dioxacyclopentadecine (190d): Prepared according to general experimental procedure 4.9.1C, a 0.05 M solution of 1-(2-((6-(2-(hydroxymethyl)phenoxy)hexyl)oxy)phenyl)ethan-1-ol **189d** (69.0 mg, 0.2 mmol) in (4 mL) 1, 4-dioxane solvent was pumped using a syringe pump through Omnifit® column (6.6 x 150 mm) packed bed containing 1.9 gm of Ni-Zeolite filled up to 9 cm and preheated at 140 °C with the flow rate of 0.1 mL/min at 3.5 to 3.9 back pressure and residence time $t_R = 27.3$ min. After a four-time run, the collected organic layer was concentrated under reduced pressure, and the crude product was purified by column chromatography using (EtOAc/*n*-hexane = 1:99) as an eluent to afford the compound **190d** as a white solid (31.6 mg, 51% yield, 98:2 *E:Z*); melting point: 88-89 °C; and non-cyclic alkene (2-((6-(2-vinylphenoxy)hexyl)oxy)phenyl)methanol **191d** (5 mg, 8%) as a semisolid. Continuous flow 0.031 g (51%), space-time yield 20.51 g L⁻¹ h⁻¹. Productivity *g/day* = 1.13



g/day; ^1H NMR (400 MHz, CDCl_3) δ 7.35 (dd, $J = 7.6, 1.7$ Hz, 1H), 7.21 (dd, $J = 7.3, 1.7$ Hz, 1H), 7.19 – 7.10 (m, 2H), 6.91 – 6.82 (m, 5H), 6.31 (dt, $J = 15.7, 7.2$ Hz, 1H), 4.10 – 4.05 (m, 2H), 4.05 – 4.01 (m, 2H), 3.54 (dd, $J = 7.2, 1.0$ Hz, 2H), 1.86 (qd, $J = 6.2, 2.7$ Hz, 4H), 1.83 – 1.74 (m, 2H), 1.72 – 1.64 (m, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 157.3, 156.1, 130.6, 130.4, 129.4, 127.9, 127.8, 127.5, 127.2, 126.1, 120.9, 120.4, 112.7, 111.5, 69.4, 67.8, 35.8, 29.5, 28.5, 27.7, 27.1; FTIR (neat): 2920, 2861, 1592, 1236 cm^{-1} ; HRMS (ESI-TOF) m/z : $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{21}\text{H}_{25}\text{O}_2$, 309.1855, found 309.1850.

(2-((6-(2-vinylphenoxy) hexyl)oxy)phenyl)

methanol (191d): ^1H NMR (400 MHz, CDCl_3) δ 7.48 (dd, $J = 7.6, 1.6$ Hz, 1H), 7.30 – 7.18 (m, 3H), 7.06 (dd, $J = 17.8, 11.2$ Hz, 1H), 6.93 (dd, $J = 12.8, 7.5$ Hz, 2H), 6.90 – 6.84 (m, 2H), 5.75 (dd, $J = 17.8, 1.5$ Hz, 1H), 5.24 (dd, $J = 11.2,$



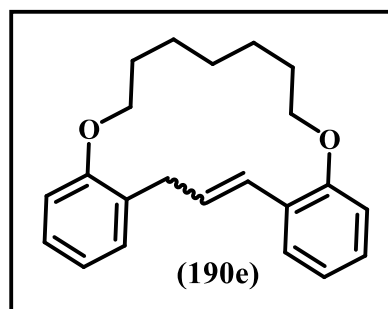
1.5 Hz, 1H), 4.69 (s, 2H), 4.04 (t, $J = 6.5$ Hz, 2H), 4.01 (t, $J = 6.4$ Hz, 2H), 2.38 (s, 1H), 1.92 – 1.81 (m, 4H), 1.62 – 1.54 (m, 4H); ^{13}C NMR (100 MHz, CDCl_3) δ 157.0, 156.3, 131.8, 129.3, 129.0, 128.9, 128.8, 126.9, 126.6, 120.7, 120.6, 114.3, 112.0, 111.2, 68.2, 67.9, 62.5, 29.4, 26.1; FTIR (neat): 3400, 2934, 2865, 1453, 1236 cm^{-1} ; HRMS (ESI-TOF) m/z : $[\text{M} + \text{Na}]^+$ calcd for $\text{C}_{21}\text{H}_{26}\text{O}_2\text{Na}$, 349.1780, found 349.1779.

7,8,9,10,11,12-hexahydro-6H,18H-dibenzo[b,g][1,9]dioxacyclohexadecine (190e):

Prepared according to general experimental procedure 4.9.1C, a 0.05 M solution of **189e** (71.7 mg, 0.2 mmol) in (4 mL) 1, 4-dioxane solvent was pumped using a syringe pump through Omnifit® column (6.6 x 150 mm) packed bed containing 1.9 gm of Ni-zeolite filled up to 9 cm and preheated at 140 °C with the flow rate of 0.1 mL/min at 3.5 to 3.9 back pressure and residence time $t_R = 27.3$ min. After a four-time run, the collected organic layer was concentrated under reduced pressure, and the crude product was purified by column chromatography using (EtOAc/*n*-hexane = 1:99) as an eluent to afford the compound **190e** as a white solid (35.9 mg, 56% yield, 96:4 E:Z); melting point: 88-89 °C; and non-cyclic alkene (2-((7-(2-vinylphenoxy)heptyl)oxy)phenyl)methanol **191e** (6 mg, 9%) as a semisolid. Continuous flow 0.035 g (56%), space-time yield 27.8 $\text{g L}^{-1} \text{h}^{-1}$. Productivity $\text{g/day} = 1.30$ g/day;

7,8,9,10,11,12-hexahydro-6*H*,18*H*-dibenzo[*b,g*][1,9]dioxacyclohexadecine (190e). ¹H

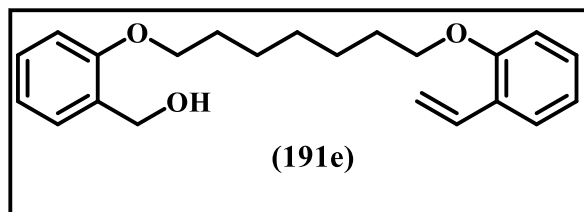
NMR (400 MHz, CDCl₃) δ 7.35 (dd, *J* = 7.6, 1.6 Hz, 1H), 7.22 (dd, *J* = 7.4, 1.7 Hz, 1H), 7.18 – 7.09 (m, 2H), 6.91 – 6.82 (m, 4H), 6.80 (d, *J* = 7.1 Hz, 1H), 6.36 (dt, *J* = 15.7, 7.2 Hz, 1H), 4.01 (dd, *J* = 7.9, 4.0 Hz, 4H), 3.55 (dd, *J* = 7.2, 1.0 Hz, 2H), 1.88 (dt, *J* = 13.4, 6.5 Hz, 2H), 1.81 (dd, *J* = 12.1, 5.7 Hz, 2H), 1.69 – 1.60 (m, 4H), 1.54 – 1.48 (m, 2H); ¹³C



NMR (100 MHz, CDCl₃) δ 157.2, 156.3, 130.6, 130.4, 129.5, 127.8, 127.4, 127.4, 127.3, 125.8, 120.6, 120.6, 112.4, 112.1, 68.2, 67.7, 34.9, 28.8, 28.0, 27.2, 25.9, 25.7; FTIR (neat): 2929, 2861, 1592, 1242 cm⁻¹; HRMS (ESI-TOF) *m/z*: [M + H]⁺ calcd for C₂₂H₂₇O₂, 323.2011, found 323.2007.

(2-((7-(2-vinylphenoxy)heptyl)oxy)phenyl)methanol (191e): ¹H NMR (400 MHz, CDCl₃) δ

7.48 (dd, *J* = 7.6, 1.7 Hz, 1H), 7.29 – 7.19 (m, 3H), 7.07 (dd, *J* = 17.8, 11.2 Hz, 1H), 6.96 – 6.89 (m, 2H), 6.86 (dd, *J* = 11.1, 3.8 Hz, 2H), 5.75 (dd, *J* = 17.8, 1.6 Hz, 1H), 5.25 (dd, *J* =



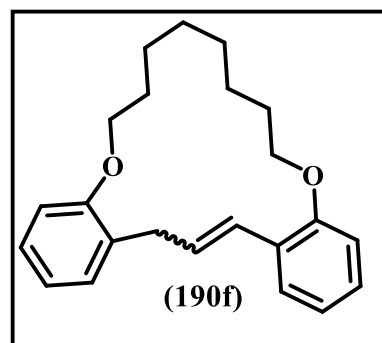
11.2, 1.6 Hz, 1H), 4.70 (s, 2H), 4.03 (t, *J* = 6.5 Hz, 2H), 3.99 (t, *J* = 6.4 Hz, 2H), 2.39 (s, 1H), 1.88 – 1.80 (m, 4H), 1.56 – 1.43 (m, 6H); ¹³C NMR (100 MHz, CDCl₃) δ 157.1, 156.4, 131.9, 129.3, 129.0, 128.9, 128.8, 126.9, 126.6, 120.7, 120.6, 114.3, 112.0, 111.2, 68.3, 68.0, 62.6, 29.4, 29.2, 26.2; FTIR (neat): 3399, 2933, 2862, 1455, 1238 cm⁻¹; HRMS (ESI-TOF) *m/z*: [M + H]⁺ calcd for C₂₂H₂₉O₃, 341.2117, found 341.2110.

6,7,8,9,10,11,12,13-octahydro-19*H*-dibenzo[*b,g*][1,9]dioxacycloheptadecine (190f):

Prepared according to general experimental procedure 4.9.1C, a 0.05 M solution of 1-(2-((8-(2-(hydroxymethyl)phenoxy)octyl)oxy)phenyl)ethan-1-ol **189f** (74.5 mg, 0.2 mmol) in (4 mL) 1, 4-dioxane solvent was pumped using a syringe pump through Omnifit® column (6.6 x 150 mm) packed bed containing 1.9 gm of Ni-zeolite filled up to 9 cm and preheated at 140 °C with the flow rate of 0.1 mL/min with 3.5 to 3.9 back pressure and residence time *t_R* = 27.3 min. After a four-time run, the collected organic layer was concentrated under reduced pressure, and the crude product was purified by column chromatography using (EtOAc/*n*-hexane = 1:99) as an eluent to afford the compound **190f** as a white solid (41.1 mg, 61% yield, 99:1 *E:Z*); melting point: 83-85 °C; and acyclic alkene (2-((8-(2-vinylphenoxy)octyl)oxy)phenyl)methanol **191f** very trace amount and stating material recovered. Continuous flow 0.041 g (61%), space-time yield 24.86 g L⁻¹ h⁻¹. Productivity *g/day* = 1.47 g/day.

6,7,8,9,10,11,12,13-octahydro-19*H*-dibenzo[*b,g*][1,9] dioxacyclo heptadecine (190f): ^1H

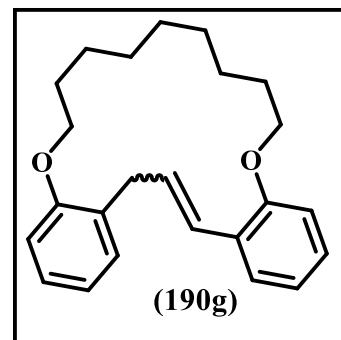
NMR (400 MHz, CDCl_3) δ 7.39 (dd, $J = 7.5, 1.4$ Hz, 1H), 7.24 (dd, $J = 7.4, 1.7$ Hz, 1H), 7.20 – 7.10 (m, 2H), 6.90 (ddd, $J = 7.4, 3.7, 2.1$ Hz, 2H), 6.84 (t, $J = 7.8$ Hz, 3H), 6.31 (dt, $J = 15.7, 7.3$ Hz, 1H), 4.07 – 4.01 (m, 2H), 3.98 – 3.93 (m, 2H), 3.58 (dd, $J = 7.3, 1.0$ Hz, 2H), 1.79 (ddt, $J = 18.6, 14.5, 4.7$ Hz, 4H), 1.71 – 1.60 (m, 4H), 1.52 – 1.44 (m, 4H); ^{13}C NMR (100 MHz, CDCl_3) δ 157.3, 156.0, 130.4, 129.8, 129.3, 127.8,



127.4, 126.8, 126.6, 125.1, 120.4, 120.4, 111.8, 111.5, 67.9, 67.4, 34.9, 29.6, 28.7, 28.1, 27.5, 25.4, 25.1; FTIR (neat): 2932, 2854, 1455, 1242 cm^{-1} ; HRMS (ESI-TOF) m/z : $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{23}\text{H}_{29}\text{O}_2$, 337.2168 found 337.2154.

7,8,9,10,11,12,13,14-octahydro-6*H*,20*H*-dibenzo[*b,g*][1,9]dioxacyclooctadecine (190g):

Prepared according to general experimental procedure 4.9.1C, a 0.05 M solution of 1-(2-((9-(2-(hydroxymethyl)phenoxy)nonyl)oxy)phenyl)ethan-1-ol **189g** (77.3 mg, 0.2 mmol) in (4 mL) 1, 4-dioxane solvent was pumped using a syringe pump through Omnifit® column (6.6 x 150 mm) packed bed containing 1.9 gm of Ni-Zeolite filled up to 9 cm and preheated at 140 °C with the flow rate of 0.1 mL/min with 3.5 to

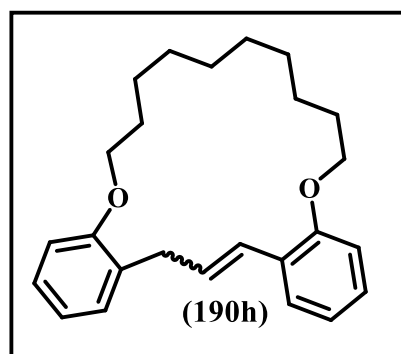


3.9 back pressure and residence time $t_R = 27.3$ min. After a four-time run, the collected organic layer was concentrated under reduced pressure, and the crude product was purified by column chromatography using (EtOAc/*n*-hexane = 1:99) as an eluent to afford the compound **157g** as a white solid (31.9 mg, 46% yield, 96:4 *E:Z*); melting point: 92-95 °C; and acyclic alkene observed trace amount. Continuous flow 0.0319 g (46%), space-time yield 18.57 $\text{g L}^{-1} \text{h}^{-1}$. Productivity $\text{g/day} = 1.16 \text{ g/day}$. ^1H NMR (400 MHz, CDCl_3) δ 7.40 (dd, $J = 7.6, 1.6$ Hz, 1H), 7.27 (dd, $J = 7.4, 0.9$ Hz, 1H), 7.19 – 7.10 (m, 2H), 6.90 (ddd, $J = 12.9, 9.6, 5.4$ Hz, 2H), 6.86 – 6.80 (m, 3H), 6.33 (dt, $J = 15.6, 7.3$ Hz, 1H), 4.04 – 4.00 (m, 2H), 4.00 – 3.96 (m, 2H), 3.61 (dd, $J = 7.3, 0.8$ Hz, 2H), 1.88 – 1.81 (m, 2H), 1.78 (ddd, $J = 10.8, 7.4, 3.6$ Hz, 2H), 1.66 – 1.40 (m, 12H); ^{13}C NMR (100 MHz, CDCl_3) δ 157.0, 156.1, 130.2, 130.1, 129.4, 127.9, 127.3, 126.8, 126.5, 124.9, 120.5, 120.4, 111.8, 111.7, 68.8, 68.3, 33.8, 29.9, 29.0, 28.9, 28.8, 28.5, 27.4, 26.1; FTIR (neat): 2930, 2856, 1454, 1241 cm^{-1} ; HRMS (ESI-TOF) m/z : $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{24}\text{H}_{31}\text{O}_2$, 351.2324 found 351.2326.

6,7,8,9,10,11,12,13,14,15-decahydro-21H-dibenzo[*b,g*][1,9]dioxacyclononadecine (190h):

Prepared according to general experimental procedure 4.9.1C, A 0.05 M solution of 1-(2-((10-(2-(hydroxymethyl)phenoxy)decyl)oxy)phenyl)ethan-1-ol

189h (80 mg, 0.199 mmol) in (4 mL) 1, 4-dioxane solvent was pumped using a syringe pump through Omnifit® column (6.6 x 150 mm) packed bed containing 1.9 gm of Ni-zeolite filled up to 9 cm and preheated at 140 °C with



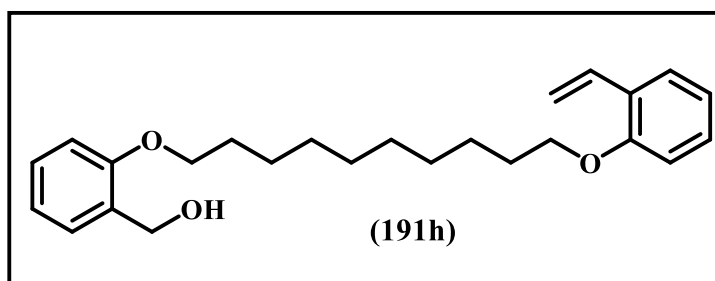
the flow rate of 0.1 mL/min with 3.5 to 3.9 back pressure was and residence time $t_R = 27.3$ min. After a four-time run, the collected organic layer was concentrated under reduced pressure, and the crude product was purified by column chromatography using (EtOAc/*n*-hexane = 1:99) as an eluent to afford the compound **190h** as a white solid (38.8 mg, 53% yield, 96:4 E:Z); melting point: 82-83 °C; and acyclic alkene (2-((9-(2-vinylphenoxy)nonyl)oxy)phenyl)methanol **191h** (6 mg, 8%) as a semisolid. Continuous flow 0.0388 g (53%), space-time yield 21.72 g L⁻¹ h⁻¹. Productivity *g/day* = 1.39 g/day.

7,8,9,10,11,12,13,14-octahydro-6H,20H-dibenzo[*b,g*][1,9] dioxacyclooctadecine (190h):

¹H NMR (400 MHz, CDCl₃) δ 7.41 (dd, *J* = 7.6, 1.6 Hz, 1H), 7.25 (dd, *J* = 7.1, 0.9 Hz, 2H), 7.16 (dd, *J* = 7.7, 1.8 Hz, 2H), 6.93 – 6.87 (m, 2H), 6.85 (dd, *J* = 8.6, 6.3 Hz, 3H), 6.34 (dt, *J* = 15.8, 7.2 Hz, 1H), 4.03 – 3.99 (m, 2H), 3.99 – 3.95 (m, 2H), 3.62 (d, *J* = 7.3 Hz, 2H), 1.78 (ddd, *J* = 13.8, 8.7, 5.4 Hz, 4H), 1.64 – 1.54 (m, 6H), 1.41 (s, 6H); ¹³C NMR (100 MHz, CDCl₃) δ 170.5, 157.1, 156.1, 129.7, 129.5, 129.5, 127.9, 127.7, 127.2, 127.1, 126.7, 125.7, 120.5, 120.4, 112.1, 111.6, 76.8, 68.0, 67.9, 34.0, 29.2, 28.9, 28.1, 28.0, 27.8, 27.7, 26.1, 25.6; FTIR (neat): 2930, 2857, 1455, 1240 cm⁻¹; HRMS (ESI-TOF) *m/z*: [M + H]⁺ calcd for C₂₅H₃₃O₂, 365.2481 found 365.2488.

(2-((10-(2-vinylphenoxy)decyl)oxy)phenyl)methanol (191h): ¹H NMR (400 MHz, CDCl₃) δ

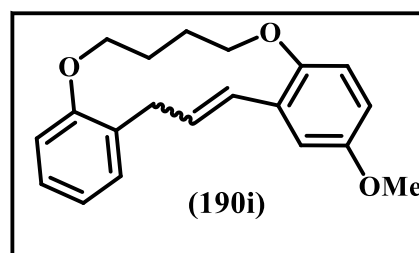
7.47 (dd, *J* = 7.6, 1.6 Hz, 1H), 7.29 – 7.18 (m, 2H), 7.07 (dd, *J* = 17.8, 11.2 Hz, 1H), 6.93 (dt, *J* = 13.2, 4.0 Hz, 2H), 6.87 (t, *J* = 7.4 Hz, 2H), 5.76 (dd, *J* = 17.8, 1.6 Hz, 1H), 5.25 (dd, *J* = 11.2, 1.5 Hz, 1H),



4.70 (s, 2H), 4.02 (t, *J* = 6.5 Hz, 2H), 3.98 (t, *J* = 6.5 Hz, 2H), 2.41 (s, 1H), 1.86 – 1.77 (m, 4H), 1.52 – 1.44 (m, 4H), 1.35 (s, 8H); ¹³C NMR (100 MHz, CDCl₃) δ 157.1, 156.4, 131.9,

129.3, 129.0, 128.9, 128.8, 126.9, 126.6, 120.6, 120.6, 114.3, 112.0, 111.2, 68.4, 68.1, 62.6, 29.6, 29.5, 29.4, 29.4, 26.3, 26.3; FTIR (neat): 3388, 2930, 2857, 1455, 1240 cm^{-1} ; HRMS (ESI-TOF) m/z : $[\text{M} + \text{Na}]^+$ calcd for $\text{C}_{25}\text{H}_{34}\text{O}_3$, 405.2405 found 405.2428.

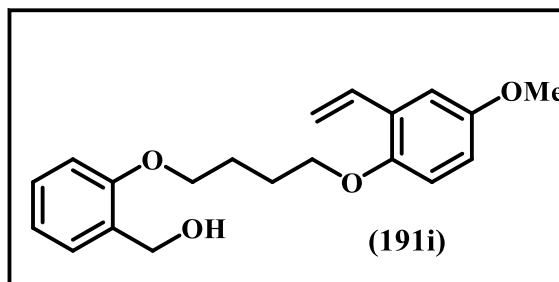
2-methoxy-6,7,8,9-tetrahydro-15H-dibenzo[*g,l*][1,6]dioxacyclotridecine (190i): Prepared according to general experimental procedure 4.9.1C, a 0.05 M solution of 1-(2-(4-(2-(hydroxymethyl)phenoxy)butoxy)-5-methoxyphenyl)ethan-1-ol **189i** (69 mg, 0.199 mmol) in (4 mL) 1, 4-dioxane solvent was pumped using a syringe pump through Omnifit® column (6.6 x 150 mm) packed bed containing 1.9 gm of Ni-zeolite filled up to 9 cm and preheated at 140 °C with the flow rate of 0.1 mL/min at 3.5 to 3.9 back pressure and residence time $t_R = 27.3$ min. After a four-time run, the collected organic layer was concentrated under reduced pressure, and the crude product was purified by column chromatography using (EtOAc/*n*-hexane = 1:99) as an eluent to afford the compound (**190i**) as a semisolid (38.5 mg, 62% yield, 98:2 *E:Z*); and non-cyclic alkene (**191i**). Continuous flow 0.0385 g (62%), space-time yield 25.31 $\text{g L}^{-1} \text{h}^{-1}$. Productivity $\text{g/day} = 1.38 \text{ g/day}$.



(E)-2-methoxy-6,7,8,9-tetrahydro-15H-

dibenzo[*g,l*][1,6]dioxacyclotridecine (190i): ^1H NMR (400 MHz, CDCl_3) δ 7.22 – 7.15 (m, 2H), 6.97 (d, $J = 15.7$ Hz, 1H), 6.93 (d, $J = 8.8$ Hz, 1H), 6.90 – 6.86 (m, 2H), 6.81 (d, $J = 8.0$ Hz, 1H), 6.71 (dd, $J = 8.8, 3.1$ Hz, 1H), 6.01 (dt, $J = 15.6, 7.1$ Hz, 1H), 4.04 – 3.99 (m, 2H), 3.99 – 3.94 (m, 2H), 3.76 (s, 3H), 3.49 (d, $J = 7.1$ Hz, 2H), 2.12 (dt, $J = 7.5, 6.2$ Hz, 2H), 1.80 (dt, $J = 12.2, 6.5$ Hz, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 157.88, 155.81, 151.33, 133.23, 130.57, 129.47, 128.50, 128.05, 127.81, 122.69, 120.46, 114.11, 111.36, 110.74, 77.48, 77.16, 77.16, 76.84, 75.39, 67.38, 55.69, 36.71, 28.00, 26.22. FTIR (neat): 2919, 2873, 1598 1492, 1451 cm^{-1} ; HRMS (ESI-TOF) m/z : $[\text{M} + \text{Na}]^+$ calcd for $\text{C}_{20}\text{H}_{22}\text{O}_3\text{Na}$, 333.1468, found 333.1461.

(2-(4-(4-methoxy-2-vinylphenoxy)butoxy)phenyl)methanol (191i): ^1H NMR (400 MHz, CDCl_3) δ 7.31 – 7.23 (m, 2H), 7.03 (td, $J = 11.5, 5.9$ Hz, 2H), 6.95 (dd, $J = 11.1, 3.7$ Hz, 1H), 6.89 (d, $J = 8.2$ Hz, 1H), 6.84 – 6.79 (m, 1H), 6.77 (dd, $J = 8.9, 2.8$ Hz, 1H), 5.73 (dd, $J = 17.8, 1.3$ Hz, 1H), 5.25 (dd, $J = 11.1, 1.3$ Hz, 1H), 4.70 (s, 2H), 4.11 (t, $J = 5.9$ Hz, 2H), 4.02

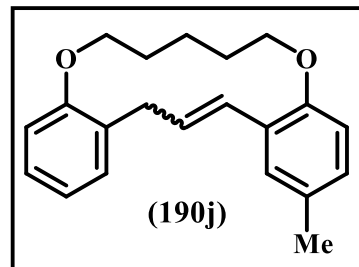


(t, $J = 5.7$ Hz, 2H), 3.79 (s, 3H), 2.06 – 1.96 (m, 4H); ^{13}C NMR (100 MHz, CDCl_3) δ 156.9,

153.9, 150.6, 131.6, 129.1, 128.8, 120.8, 114.7, 114.0, 113.7, 111.8, 111.2, 68.8, 67.6, 62.3, 55.9, 26.4, 26.3; FTIR (neat): 3388, 2921, 2871, 1601, 1491 cm^{-1} ; HRMS (ESI-TOF) m/z : $[\text{M} + \text{Na}]^+$ calcd for $\text{C}_{20}\text{H}_{24}\text{O}_4\text{Na}$, 351.1573, found 351.1562.

2-methyl-7,8,9,10-tetrahydro-6*H*,16*H*-dibenzo[*h,m*][1,7]dioxacyclotetradecine (190j):

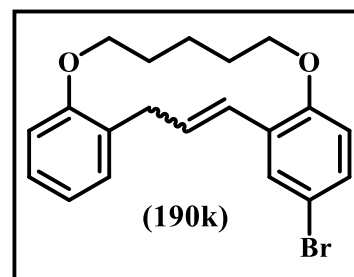
Prepared according to general experimental procedure 4.9.1C, a 0.05 M solution of 1-(2-((5-(2-(hydroxymethyl)phenoxy)pentyl)oxy)-5-methylphenyl)ethan-1-ol **189j** (69 mg, 0.199 mmol) in (4 mL) 1, 4-dioxane solvent was pumped using a syringe pump through Omnifit® column



(6.6 x 150 mm) packed bed containing 1.9 gm of Ni-Zeolite filled up to 9 cm and preheated at 140 °C with the flow rate of 0.1 mL/min at 3.5 to 3.9 back pressure and residence time t_R = 27.3 min. After a four-time run, the collected organic layer was concentrated under reduced pressure, and the crude product was purified by column chromatography (EtOAc/*n*-hexane = 1:99) as an eluent to afford the compound **(190j)** as a semisolid (31.5 mg, 51% yield, 98:2 *E:Z*); and non-cyclic alkene observed. Continuous flow 0.0315 g (51%), space-time yield 20.84 g $\text{L}^{-1} \text{h}^{-1}$. Productivity g/day = 1.13 g/day. ^1H NMR (400 MHz, CDCl_3) δ 7.16 (dd, J = 12.3, 4.6 Hz, 2H), 7.08 (d, J = 1.9 Hz, 1H), 6.91 (dd, J = 8.2, 1.8 Hz, 1H), 6.84 (dd, J = 17.2, 7.7 Hz, 2H), 6.73 (dd, J = 12.1, 3.7 Hz, 2H), 6.54 (dt, J = 15.9, 6.9 Hz, 1H), 4.07 – 4.00 (m, 4H), 3.51 (d, J = 7.5 Hz, 2H), 2.24 (s, 3H), 1.87 (dd, J = 5.7, 3.5 Hz, 4H), 1.76 (dd, J = 11.2, 5.9 Hz, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 157.7, 155.3, 131.3, 130.6, 128.3, 128.1, 127.6, 126.5, 120.3, 114.4, 110.9, 69.9, 65.9, 37.2, 28.4, 28.1, 22.4, 20.7; FTIR (neat): 2918, 2875, 1596, 1491, 1451 cm^{-1} ; HRMS (ESI-TOF) m/z : $[\text{M} + \text{Na}]^+$ calcd for $\text{C}_{21}\text{H}_{24}\text{O}_2\text{Na}$, 331.1674, found 331.1664.

2-bromo-7,8,9,10-tetrahydro-6*H*,16*H*-dibenzo[*h,m*][1,7]dioxacyclotetradecine (190k):

Prepared according to general experimental procedure 4.9.1C, a 0.05 M solution of **189k** (82 mg, 0.2 mmol) in (4 mL) 1, 4-dioxane solvent was pumped using a syringe pump through Omnifit® column (6.6 x 150 mm) packed bed containing 1.9 gm of Ni-zeolite filled up to 9 cm and preheated at 140 °C with the

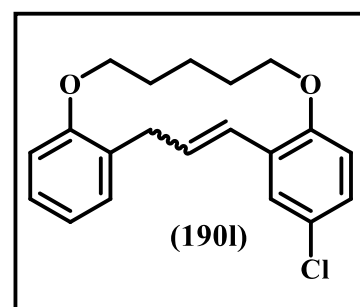


flow rate of 0.1 mL/min at 3.5 to 3.9 back pressure and residence time t_R = 27.3 min. After a four-time run, the collected organic layer was concentrated under reduced pressure, and the crude product was purified by column chromatography using (EtOAc/*n*-hexane = 1:99) as an eluent to afford the compound **(190k)** as a semisolid (22.4 mg, 30% yield, 98:2 *E:Z*); and

acyclic alkene observed. Continuous flow 0.022 g (30%), space-time yield 12.24 g L⁻¹ h⁻¹. Productivity *g/day* = 0.80 g/day. ¹H NMR (400 MHz, CDCl₃) δ 7.18 (t, *J* = 7.5 Hz, 2H), 7.08 (d, *J* = 8.2 Hz, 1H), 6.99 (dd, *J* = 8.2, 1.9 Hz, 1H), 6.95 (d, *J* = 1.8 Hz, 1H), 6.89 – 6.82 (m, 2H), 6.69 (dd, *J* = 14.6, 7.9 Hz, 1H), 6.59 (d, *J* = 16.0 Hz, 1H), 4.05 (t, *J* = 4.8 Hz, 4H), 3.50 (d, *J* = 6.6 Hz, 2H), 1.88 (dd, *J* = 8.3, 6.7 Hz, 4H), 1.79 (dt, *J* = 10.0, 4.9 Hz, 2H); ¹³C NMR (100 MHz, CDCl₃) δ 157.8, 157.5, 132.8, 130.6, 129.4, 128.7, 127.7, 127.2, 125.7, 124.1, 120.4, 120.3, 117.1, 111.0, 69.5, 65.7, 37.4, 28.1, 27.6, 22.1; FTIR (neat): 2921, 2877, 1591, 1495, 1457 cm⁻¹; HRMS (ESI-TOF) *m/z*: [M + H]⁺ calcd for C₂₀H₂₂O₂Br, 373.0803 found 373.0800.

2-chloro-7,8,9,10-tetrahydro-6*H*,16*H*-dibenzo[*h,m*][1,7]dioxacyclotetradecine (190l):

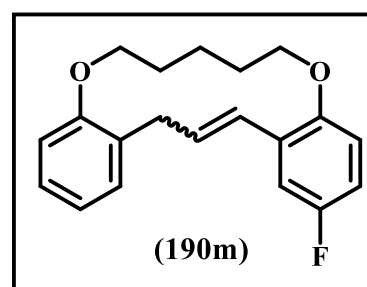
Prepared according to general experimental procedure 4.9.1C, a 0.05 M solution of **189l** (73 mg, 0.2 mmol) in (4 mL) 1, 4-dioxane solvent was pumped using a syringe pump through Omnifit® column (6.6 x 150 mm) packed bed containing 1.9 gm of Ni-zeolite filled up to 9 cm and preheated at 140 °C with the flow rate of 0.1 mL/min at 3.5 to 3.9 back pressure and residence



time *t_R* = 27.3 min. After a four-time run, the collected organic layer was concentrated under reduced pressure, and the crude product was purified by column chromatography using (EtOAc/*n*-hexane = 99) as an eluent to afford the compound (**190l**) as a semisolid (22.6 mg, 34% yield); and non-cyclic alkene observed. continuous flow 0.022 g (34%), space-time yield 14.02 g L⁻¹ h⁻¹. Productivity *g/day* = 0.80 g/day. ¹H NMR (400 MHz, CDCl₃) δ 7.22 (d, *J* = 2.6 Hz, 1H), 7.20 – 7.15 (m, 2H), 7.05 (dd, *J* = 8.6, 2.6 Hz, 1H), 6.90 – 6.86 (m, 1H), 6.83 (d, *J* = 8.5 Hz, 1H), 6.74 (d, *J* = 8.6 Hz, 1H), 6.66 – 6.60 (m, 2H), 4.04 (t, *J* = 5.0 Hz, 4H), 3.51 (d, *J* = 5.4 Hz, 2H), 1.89 – 1.82 (m, 4H), 1.78 (dt, *J* = 9.9, 4.8 Hz, 2H). ¹³C NMR (100 MHz, CDCl₃) δ 157.6, 155.9, 133.2, 130.6, 129.9, 128.5, 127.8, 127.6, 127.1, 126.0, 125.5, 120.4, 115.3, 110.9, 69.8, 65.8, 37.2, 28.2, 27.8, 22.2; FTIR (neat): 2925, 2868, 1579, 1494, 1442 cm⁻¹; HRMS (ESI-TOF) *m/z*: [M + Na]⁺ calcd for C₂₀H₂₁ClO₂Na, 351.1128, found 351.1121.

2-fluoro-7,8,9,10-tetrahydro-6*H*,16*H*-dibenzo[*h,m*][1,7]dioxacyclotetradecine (190m):

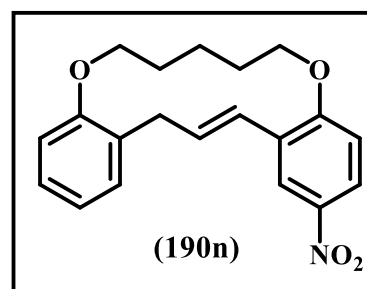
Prepared according to general experimental procedure 4.9.1C, a 0.05 M solution of **189m** (69 mg, 0.198 mmol) in (4 mL) 1, 4-dioxane solvent was pumped using a syringe pump through Omnifit® column (6.6 x 150 mm) packed bed containing 1.9 gm of Ni-zeolite filled up to 9 cm and



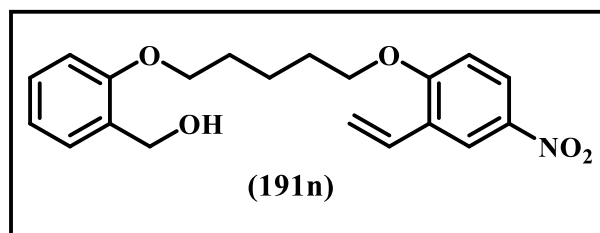
preheated at 140 °C with the flow rate of 0.1 mL/min at 3.5 to 3.9 back pressure and residence time $t_R = 27.3$ min. After a four-time run, the collected organic layer was concentrated under reduced pressure, and the crude product was purified by column chromatography using (EtOAc/*n*-hexane = 1:99) as an eluent to afford the compound (**190m**) as a semisolid (6.8 mg, 10% yield, 78:22 *E:Z*) and a trace amount of non-cyclic alkene was observed. Continuous flow 0.0068 g (10%), space-time yield 4.44 g L⁻¹ h⁻¹. Productivity *g/day* = 0.22 g/day. ¹H NMR (400 MHz, CDCl₃) δ 7.20 – 7.15 (m, 2H), 6.97 (dd, *J* = 9.6, 2.9 Hz, 1H), 6.90 – 6.85 (m, 1H), 6.85 – 6.81 (m, 1H), 6.80 – 6.75 (m, 2H), 6.72 (d, *J* = 11.7 Hz, 1H), 6.52 (dt, *J* = 15.8, 6.9 Hz, 1H), 4.04 (dd, *J* = 9.8, 4.8 Hz, 4H), 3.51 (d, *J* = 6.1 Hz, 2H), 1.86 (dd, *J* = 7.5, 4.5 Hz, 4H), 1.76 (dt, *J* = 8.1, 4.6 Hz, 2H); ¹³C NMR (100 MHz, CDCl₃) δ 157.6, 157.3, 132.7, 130.6, 127.8, 125.8, 120.4, 113.8, 110.9, 70.5, 65.9, 37.0, 28.3, 28.1, 22.4; FTIR (neat): 2920, 2870, 1589, 1490, 1452 cm⁻¹; HRMS (ESI-TOF) *m/z*: [M + H]⁺ calcd for C₂₀H₂₂FO₂, 313.1604, found 313.1612.

2-nitro-7,8,9,10-tetrahydro-6*H*,16*H*-

dibenzo[*h,m*][1,7]dioxacyclotetradecine (191n): Prepared according to general experimental procedure 4.9.1C, a 0.05 M solution of **189n** (75 mg, 0.199 mmol) in (4 mL) 1, 4-dioxane solvent was pumped using a syringe pump through Omnifit® column (6.6 x 150 mm) packed bed containing 1.9 gm of Ni-



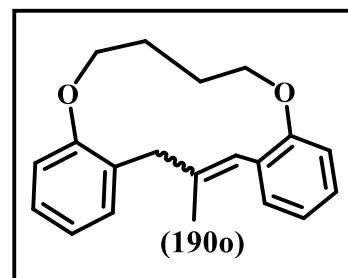
zeolite filled up to 9 cm and preheated at 140 °C with the flow rate of 0.1 mL/min at 3.5 to 3.9 back pressure and residence time $t_R = 27.3$ min. After a four-time run, the collected organic layer was concentrated under reduced pressure, and the crude product was observed only noncyclic alkene (**191n**) but did not observe macrocyclic alkene **190n**.



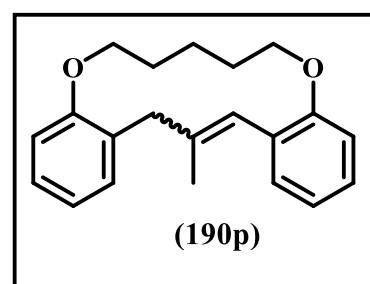
The compound (**191n**) as a semisolid (60 mg, 84% yield). ¹H NMR (400 MHz, CDCl₃) δ 8.28 (d, *J* = 2.7 Hz, 1H), 8.17 (dd, *J* = 9.0, 2.8 Hz, 1H), 7.48 (dd, *J* = 7.6, 1.6 Hz, 1H), 7.22 (d, *J* = 0.7 Hz, 1H), 7.03 (dd, *J* = 17.8, 11.2 Hz, 1H), 6.97 – 6.84 (m, 3H), 5.73 (dd, *J* = 17.8, 1.5 Hz, 1H), 5.22 (dd, *J* = 11.2, 1.5 Hz, 1H), 4.72 (s, 2H), 4.21 (t, *J* = 6.0 Hz, 2H), 4.09 (t, *J* = 5.7 Hz, 2H), 2.12 – 1.99 (m, 4H); ¹³C NMR (100 MHz, CDCl₃) δ 161.2, 155.9, 141.5, 131.6, 130.6, 129.0, 126.9, 126.7, 125.1, 123.7, 120.9, 114.5, 111.9, 110.6, 68.7, 67.6, 60.5, 26.2, 26.1. FTIR (neat): 3391, 2925, 2878, 1602, 1491,

1459 cm^{-1} ; HRMS (ESI-TOF) m/z ; $[\text{M} + \text{Na}]^+$ calcd for $\text{C}_{20}\text{H}_{23}\text{NO}_5\text{Na}$, 380.1474, found 380.1465.

16-methyl-6,7,8,9-tetrahydro-15H-dibenzo[*g,l*][1,6]dioxacyclotridecine (190o): Prepared according to general experimental procedure 4.9.1C, a 0.05 M solution of **189o** (66 mg, 0.199 mmol) in (4 mL) 1, 4-dioxane solvent was pumped using a syringe pump through Omnifit® column (6.6 x 150 mm) packed bed containing 1.9 gm of Ni-zeolite filled up to 9 cm and preheated at 140 °C with the flow rate of 0.1 mL/min at 3.5 to 3.9 back pressure and residence time $t_R = 27.3$ min. After a four-time run, the collected organic layer was concentrated under reduced pressure, and the crude product was purified by column chromatography using (EtOAc/*n*-hexane = 1:99) as an eluent to afford the compound **190o** as a semisolid (26.5 mg, 45% yield, 96:4 *E:Z*); and non-cyclic alkene was observed very traces amount. Continuous flow 0.0265 g (45%), space-time yield $18.37 \text{ L}^{-1} \text{ h}^{-1}$. Productivity $\text{g/day} = 0.95 \text{ g/day}$. ^1H NMR (400 MHz, CDCl_3) δ 7.24 – 7.17 (m, 3H), 7.15 (dd, $J = 7.6, 1.7 \text{ Hz}$, 1H), 7.06 – 6.99 (m, 2H), 6.90 (dd, $J = 11.1, 4.6 \text{ Hz}$, 1H), 6.85 (d, $J = 8.4 \text{ Hz}$, 1H), 6.49 (s, 1H), 6.41 (s, 1H), 4.05 (t, 2H), 3.94 (t, 2H), 3.48 (s, 2H), 2.10 (td, $J = 10.4, 5.4 \text{ Hz}$, 2H), 1.89 (td, $J = 11.2, 5.8 \text{ Hz}$, 2H), 1.72 (d, $J = 1.1 \text{ Hz}$, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 158.3, 158.0, 137.0, 132.3, 131.9, 130.4, 128.4, 127.8, 127.7, 123.2, 122.4, 121.6, 120.4, 111.8, 73.9, 68.5, 43.2, 29.3, 25.3, 16.9; FTIR (neat): 2931, 2867, 1487, 1451, 1239 cm^{-1} ; HRMS (ESI-TOF) m/z ; $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{20}\text{H}_{23}\text{O}_2$, 295.1698 found 295.1693.

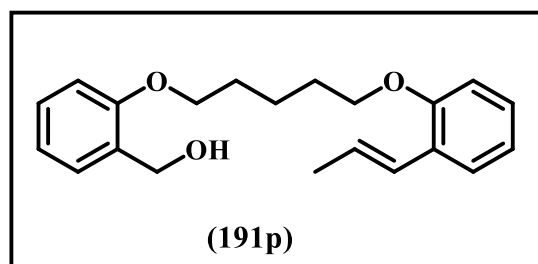


17-methyl-7,8,9,10-tetrahydro-6H,16H-dibenzo[*h,m*][1,7]dioxacyclotetradecine (190p): Prepared according to general experimental procedure 4.9.1C, a 0.05 M solution of 1-(2-((5-(2-(hydroxymethyl)phenoxy)pentyl)oxy)phenyl)propan-1-ol **189p** (69 mg, 0.2 mmol) in (4 mL) 1, 4-dioxane solvent was pumped using a syringe pump through Omnifit® column (6.6 x 150 mm) packed bed containing 1.9 gm of Ni-zeolite filled up to 9 cm and preheated at 140 °C with the flow rate of 0.1 mL/min at 3.5 to 3.9 back pressure and residence time $t_R = 27.3$ min. After a four-time run, the collected organic layer was concentrated under reduced pressure, and the crude product was purified by column chromatography using (EtOAc/*n*-hexane = 1:99) as an eluent to afford the compound **190p** as a semisolid (34.4 mg, 56% yield, 95:5 *E:Z*); and non-cyclic alkene (E)-(2-((5-(2-(prop-1-en-1-

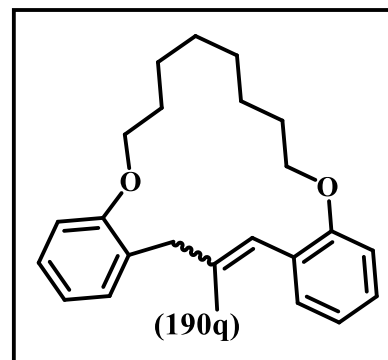


yl)phenoxy)pentyl)oxy)phenyl)methanol **191p** (7 mg, 11%) as a semisolid. Continuous flow 0.034.4 g (56%), space-time yield 22.76 g L⁻¹ h⁻¹. Productivity *g/day* = 1.24 g/day. 17-methyl-7,8,9,10-tetrahydro-6*H*,16*H*-dibenzo[*h,m*][1,7] dioxacyclotetradecine (**190p**): ¹H NMR (400 MHz, CDCl₃) δ 7.21 (dd, *J* = 12.2, 4.6 Hz, 3H), 7.15 (td, *J* = 7.8, 1.6 Hz, 1H), 6.93 – 6.88 (m, 2H), 6.86 (d, *J* = 8.8 Hz, 2H), 6.36 (s, 1H), 4.02 (dd, *J* = 10.9, 5.7 Hz, 4H), 3.52 (s, 2H), 1.89 – 1.74 (m, 6H), 1.70 (d, *J* = 1.1 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 158.2, 157.2, 137.2, 132.1, 130.2, 129.3, 128.1, 127.7, 127.2, 121.2, 120.5, 120.0, 113.4, 111.2, 68.2, 66.6, 42.4, 28.0, 27.3, 21.7, 17.3; FTIR (neat): 2921, 1487, 1240 cm⁻¹; HRMS (ESI-TOF) *m/z*; [M + H]⁺ calcd for C₂₁H₂₅O₂, 309.1855 found 309.1845.

(*E*)-(2-((5-(2-(prop-1-en-1-yl)phenoxy)pentyl)oxy)phenyl)methanol (**191p**): ¹H NMR (400 MHz, CDCl₃) δ 7.41 (dd, *J* = 7.6, 1.6 Hz, 1H), 7.31 – 7.24 (m, 2H), 7.19 – 7.13 (m, 1H), 6.98 – 6.91 (m, 1H), 6.91 – 6.85 (m, 2H), 6.78 – 6.69 (m, 1H), 6.24 (dq, *J* = 15.8, 6.6 Hz, 1H), 4.71 (s, 2H), 4.07 (t, *J* = 6.4 Hz, 2H), 4.02 (t, *J* = 6.3 Hz, 2H), 2.36 (s, 1H), 1.98 – 1.91 (m, 4H), 1.91 – 1.88 (m, 3H), 1.71 (tt, *J* = 10.3, 6.1 Hz, 2H). ¹³C NMR (100 MHz, CDCl₃) δ 156.9, 155.6, 129.3, 129.0, 128.8, 127.8, 127.2, 126.5, 126.4, 125.7, 120.7, 112.0, 111.2, 68.1, 67.8, 62.4, 29.2, 23.0, 19.1; FTIR (neat): 2936, 2869, 1487, 1492 cm⁻¹; HRMS (ESI-TOF) *m/z*; [M + Na]⁺ calcd for C₂₁H₂₆O₃Na, 349.1779 found 349.1778.



(*E*)-20-methyl-6,7,8,9,10,11,12,13-octahydro-19*H*-dibenzo[*b,g*][1,9]dioxacycloheptadecane (**190q**): Prepared according to general experimental procedure 4.9.1C, a 0.05 M solution of 1-(2-((8-(2-(hydroxymethyl)phenoxy)octyl)oxy)phenyl)propan-1-ol **189q** (77 mg, 0.199 mmol) in (4 mL) 1, 4-dioxane solvent was pumped using a syringe pump through Omnifit® column (6.6

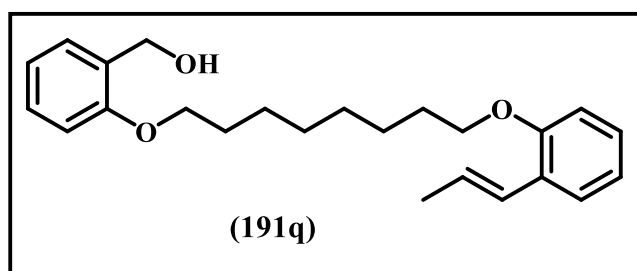


x 150 mm) packed bed containing 1.9 gm of Ni-zeolite filled up to 9 cm and preheated at 140 °C with the flow rate of 0.1 mL/min at 3.5 to 3.9 back pressure and residence time *t_R* = 27.3 min. After a four-time run, the collected organic layer was concentrated under reduced pressure, and the crude product was purified by column chromatography using (EtOAc/*n*-hexane = 1:99) as an eluent to afford the compound **190q** (37.7 mg, 54%) as a semisolid; and non-cyclic alkene **191q** (5 mg, 7%) as a semisolid. Continuous flow 0.0377 g (54%), space-time yield 21.95 g L⁻¹ h⁻¹. Productivity *g/day* = 1.36 g/day. ¹H NMR (400 MHz, CDCl₃) δ 7.23 (dd, *J* = 7.3, 1.6 Hz,

1H), 7.19 (dd, $J = 11.1, 4.7$ Hz, 2H), 7.13 (dd, $J = 7.8, 1.6$ Hz, 1H), 6.90 (dd, $J = 7.4, 1.0$ Hz, 1H), 6.89 – 6.81 (m, 3H), 6.63 (s, 1H), 4.07 (t, $J = 5.2$ Hz, 2H), 3.94 (t, $J = 4.4$ Hz, 2H), 3.56 (s, 2H), 1.89 (d, $J = 1.2$ Hz, 3H), 1.85 – 1.78 (m, 2H), 1.74 – 1.62 (m, 6H), 1.50 – 1.44 (m, 4H); OH peak exchanged with deuterium of CDCl₃; ¹³C NMR (100 MHz, CDCl₃) δ 157.7, 156.6, 136.9, 131.1, 130.3, 128.7, 127.9, 127.4, 127.2, 121.4, 120.0, 119.8, 111.5, 111.4, 68.0, 67.3, 41.8, 29.4, 28.6, 28.2, 26.9, 25.0, 24.8, 18.4. FTIR (neat): 2927, 2858, 1488, 1451, 1241 cm⁻¹; HRMS (ESI-TOF) m/z : [M + H]⁺ calcd for C₂₄H₃₁O₂, 351.2324 found 351.2317.

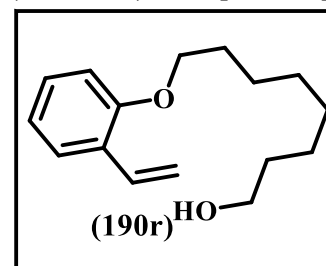
(E)-(2-((8-(2-(prop-1-en-1-yl)phenoxy)octyl)oxy)phenyl)methanol (191q): ¹H NMR (400

MHz, CDCl₃) δ 7.38 (dd, $J = 7.6, 1.5$ Hz, 1H), 7.27 – 7.20 (m, 2H), 7.16 – 7.10 (m, 1H), 6.94 – 6.85 (m, 3H), 6.86 – 6.80 (m, 2H), 6.71 (dd, $J = 15.9, 1.4$ Hz, 1H), 6.22 (dq, $J = 15.8, 6.6$ Hz, 1H), 4.68 (s, 2H), 4.00 (d, $J = 6.5$ Hz, 2H), 3.96 (t, $J = 6.5$



Hz, 2H), 2.42 (s, 1H), 1.88 (dd, $J = 6.6, 1.6$ Hz, 3H), 1.84 – 1.78 (m, 4H), 1.48 (d, $J = 3.4$ Hz, 4H), 1.40 (dd, $J = 6.9, 3.8$ Hz, 4H); ¹³C NMR (100 MHz, CDCl₃) δ 157.1, 155.8, 129.3, 129.0, 128.8, 127.8, 127.2, 126.5, 126.3, 125.9, 120.6, 112.0, 111.2, 68.4, 68.0, 62.5, 29.4, 29.4, 26.2, 26.2, 19.1; FTIR (neat): 2931, 2862, 483, 1450, 1235 cm⁻¹; HRMS (ESI-TOF) m/z : [M + Na]⁺ calcd for C₂₄H₃₂O₃Na, 391.22489 found 391.2267.

8-(2-vinylphenoxy)octan-1-ol (191r): Prepared according to general experimental procedure 4.9.1C, a 0.05 M solution of 8-(2-(1-hydroxyethyl)phenoxy)octan-1-ol **189r** (80 mg, 0.3 mmol) in (6 mL) 1, 4-dioxane solvent was pumped using a syringe pump

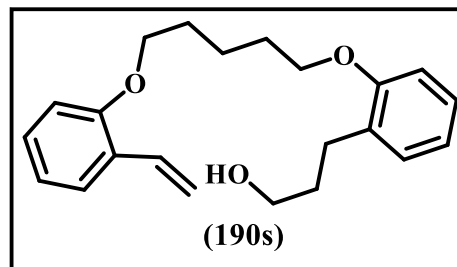


through Omnifit® column (6.6 x 150 mm) packed bed containing 1.9 gm of Ni-zeolite filled up to 9 cm and preheated at 140 °C with the flow rate of 0.1 mL/min at 3.5 to 3.9 back pressure and residence time $t_R = 27.3$ min. After a four-time run, the collected organic layer was concentrated under reduced pressure, and the crude product was purified by column chromatography using (EtOAc/*n*-hexane = 20:80) as an eluent to afford the compound acyclic alkene **191r** (68.6 mg, 92%) as a semisolid. Continuous flow 0.068 g (92%), space-time yield 56.36 g L⁻¹ h⁻¹. Productivity $g/day = 1.64$ g/day. ¹H NMR (400 MHz, CDCl₃) δ 7.47 (dd, $J = 7.6, 1.5$ Hz, 1H), 7.24 – 7.18 (m, 1H), 7.07 (dd, $J = 17.8, 11.2$ Hz, 1H), 6.92 (t, $J = 7.5$ Hz, 1H), 6.86 (d, $J = 8.2$ Hz, 1H), 5.80 – 5.71 (m, 1H), 5.25 (dd, $J = 11.2, 1.5$ Hz, 1H), 3.98 (t, $J = 6.4$ Hz, 2H), 3.64 (t, $J = 6.6$ Hz, 2H), 1.81 (dd, $J = 14.6, 6.7$ Hz, 2H), 1.62 – 1.45 (m, 6H), 1.37 (d,

$J = 1.8$ Hz, 6H); ^{13}C NMR (100 MHz, CDCl_3) δ 156.4, 131.9, 128.9, 126.6, 120.6, 114.3, 112.0, 68.4, 63.1, 32.9, 29.5, 29.4, 26.2, 25.8; FTIR (neat): 2920, 2851, 1479, 1451, 1245 cm^{-1} ; HRMS (ESI-TOF) m/z : $[\text{M} + \text{Na}]^+$ calcd for $\text{C}_{16}\text{H}_{24}\text{O}_2\text{Na}$, 271.1673 found 271.1649.

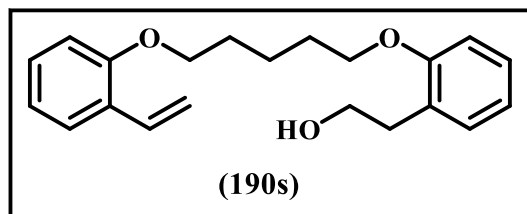
3-(2-((5-(2-vinylphenoxy)pentyl)oxy)phenyl)propan-1-ol (191s): Prepared according to general experimental procedure 4.9.1C, a 0.05 M solution of 3-(2-((5-(2-(1-hydroxyethyl)phenoxy)pentyl)oxy)phenyl)propan-1-ol

189s (72 mg, 0.2 mmol) in (4 mL) 1, 4-dioxane solvent was pumped using a syringe pump through Omnifit® column (6.6 x 150 mm) packed bed containing 1.9 gm of Ni-zeolite filled up to 9 cm and preheated at 140 °C with the flow rate of 0.1 mL/min at 3.5 to 3.9 back



pressure and residence time $t_R = 27.3$ min. After a four-time run, the collected organic layer was concentrated under reduced pressure, and the crude product was purified by column chromatography using (EtOAc/*n*-hexane = 20:80) as an eluent to afford the compound acyclic alkene **191s** (62.1 mg, 91%) as a semisolid. Continuous flow 0.062 g (91%), space-time yield 37.22 $\text{g L}^{-1} \text{h}^{-1}$. Productivity $\text{g/day} = 2.23$ g/day. ^1H NMR (400 MHz, CDCl_3) δ 7.49 (dd, $J = 7.6$, 1.5 Hz, 1H), 7.25 – 7.14 (m, 3H), 7.08 (dd, $J = 17.8$, 11.2 Hz, 1H), 6.97 – 6.89 (m, 2H), 6.89 – 6.83 (m, 2H), 5.76 (dd, $J = 17.8$, 1.5 Hz, 1H), 5.26 (dd, $J = 11.2$, 1.5 Hz, 1H), 4.03 (td, $J = 6.3$, 2.2 Hz, 4H), 3.59 (t, $J = 6.3$ Hz, 2H), 2.75 (t, $J = 7.3$ Hz, 2H), 1.95 – 1.84 (m, 6H), 1.76 – 1.67 (m, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 156.9, 156.3, 131.8, 130.3, 130.2, 128.9, 127.3, 126.9, 126.6, 120.7, 120.7, 114.4, 112.0, 111.3, 68.2, 67.9, 62.0, 33.1, 29.2, 29.2; FTIR (neat): 2929, 2850, 1474, 1449, 1243 cm^{-1} ; HRMS (ESI-TOF) m/z : $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{22}\text{H}_{29}\text{O}_3\text{Na}$, 341.2116 found 341.2119.

2-(2-((5-(2-vinylphenoxy)pentyl)oxy)phenyl)ethan-1-ol (191t): Prepared according to general experimental procedure 4.9.1C, a 0.05 M solution of 2-(2-((5-(2-(1-hydroxyethyl)phenoxy)pentyl)oxy)phenyl)ethan-1-ol **189t** (69 mg, 0.2 mmol) in (4 mL) 1, 4-

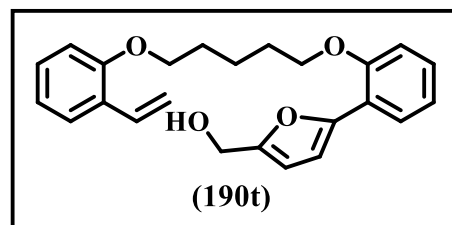


dioxane solvent was pumped using a syringe pump through Omnifit® column (6.6 x 150 mm) packed bed containing 1.9 gm of Ni-zeolite filled up to 9 cm and preheated at 140 °C with the flow rate of 0.1 mL/min at 3.5 to 3.9 back pressure was maintained in the reaction and residence time $t_R = 27.3$ min. After a four-time run, the collected organic layer was concentrated under reduced pressure, and the crude product was purified by column chromatography using

(EtOAc/*n*-hexane = 20:80) as an eluent to afford the compound non-cyclic alkene **191t** (59.6 mg, 91%) as a semisolid. Continuous flow 0.059 g (91%), space-time yield 37.26 g L⁻¹ h⁻¹. Productivity *g/day* = 2.13 g/day. ¹H NMR (400 MHz, CDCl₃) δ 7.49 (dd, *J* = 7.6, 1.5 Hz, 1H), 7.25 – 7.14 (m, 3H), 7.08 (dd, *J* = 17.8, 11.2 Hz, 1H), 6.97 – 6.90 (m, 2H), 6.90 – 6.84 (m, 2H), 5.76 (dd, *J* = 17.8, 1.4 Hz, 1H), 5.25 (dd, *J* = 11.2, 1.4 Hz, 1H), 4.03 (td, *J* = 6.3, 4.4 Hz, 4H), 3.84 (t, *J* = 6.4 Hz, 2H), 2.92 (t, *J* = 6.4 Hz, 2H), 1.95 – 1.87 (m, 4H), 1.75 – 1.69 (m, 2H), OH peak exchanged with deuterium of CDCl₃; ¹³C NMR (100 MHz, CDCl₃) δ 157.1, 156.3, 131.8, 131.1, 128.9, 127.9, 127.3, 126.9, 126.6, 120.7, 114.4, 112.0, 111.4, 68.1, 67.8, 63.0, 34.3, 29.2, 29.2, 23.1; FTIR (neat): 2929, 2850, 1474, 1449, 1243 cm⁻¹; HRMS (ESI-TOF) *m/z*: [M + H]⁺ calcd for C₂₁H₂₆O₃Na, 349.1780 found 349.1737.

(5-(2-((5-(2-vinylphenoxy)pentyl)oxy)phenyl)furan-2-yl)methanol (191u): Prepared

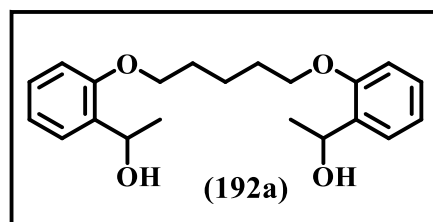
according to general experimental procedure 4.9.1C, a 0.05 M solution of **189u** (79 mg, 0.199 mmol) in (3 mL) 1, 4-dioxane solvent was pumped using a syringe pump through Omnifit® column (6.6 x 150 mm) packed bed containing 1.9 gm of Ni-zeolite filled up to 9 cm and



preheated at 140 °C with the flow rate of 0.1 mL/min at 3.5 to 3.9 back pressure and residence time *t_R* = 27.3 min. After a two-time run, the collected organic layer was concentrated under reduced pressure, and the crude product was purified by column chromatography using (EtOAc/*n*-hexane = 1:99) as an eluent to afford the compound (**191u**) as a semisolid 37 mg, 51% yield). Continuous flow 0.037 g (51%), space-time yield 20.94 g L⁻¹ h⁻¹. Productivity *g/day* = 1.32 g/day. ¹H NMR (400 MHz, CDCl₃) δ 7.38 (d, *J* = 2.1 Hz, 1H), 7.29 (dd, *J* = 7.6, 1.7 Hz, 1H), 7.24 – 7.18 (m, 1H), 7.14 (dd, *J* = 8.3, 2.1 Hz, 1H), 7.11 – 7.02 (m, 2H), 6.93 – 6.87 (m, 1H), 6.83 (d, *J* = 8.3 Hz, 1H), 6.31 (d, *J* = 3.1 Hz, 1H), 6.26 (d, *J* = 3.1 Hz, 1H), 5.74 (dd, *J* = 17.8, 1.3 Hz, 1H), 5.25 (dd, *J* = 11.1, 1.3 Hz, 1H), 4.30 – 4.25 (m, 2H), 3.96 (s, 2H), 3.69 – 3.62 (m, 1H), 3.61 – 3.54 (m, 1H), 1.85 – 1.77 (m, 1H), 1.70 (tdd, *J* = 11.1, 7.2, 3.6 Hz, 1H), 1.24 – 1.15 (m, 4H); ¹³C NMR (100 MHz, CDCl₃) δ 156.7, 155.8, 154.7, 152.7, 132.9, 131.9, 130.3, 129.9, 129.6, 129.5, 126.9, 121.5, 120.8, 120.2, 114.7, 113.8, 108.2, 107.0, 71.9, 70.3, 34.7, 31.2, 29.8, 28.8, 23.9. FTIR (neat): 3100, 2857, 1474, 1451, 1247 cm⁻¹; HRMS (ESI-TOF) *m/z*: [M + H]⁺ calcd for C₂₄H₂₇O₄, 379.1909, found 379.1912.

1,1'-((pentane-1,5-diylbis(oxy))bis(2,1-phenylene))bis(ethan-1-ol) (192a): Prepared

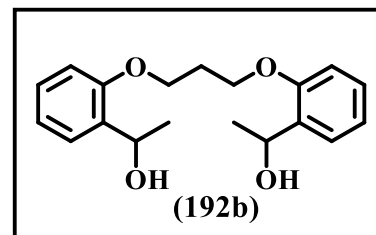
according to general experimental procedure 4.9.1B1, using 2-(1-hydroxyethyl) phenol (500 mg, 3.62 mmol), 1,5-dibromo pentane (416 mg, 1.81 mmol), and potassium carbonate (K_2CO_3) (1 gm, 7.24 mmol), The residue was purified by using column chromatography (EtOAc/*n*-



hexane = 40:60) as the eluent to afford desired product **(192a)** (1.01 gm, 2.93 mmol, 81% yield) as a semisolid; ^1H NMR (400 MHz, $CDCl_3$) δ 7.39 – 7.33 (m, 2H), 7.23 (td, J = 7.9, 1.7 Hz, 2H), 6.96 (t, J = 7.3 Hz, 2H), 6.87 (d, J = 8.2 Hz, 2H), 5.18 – 5.07 (m, 2H), 4.06 (t, J = 6.2 Hz, 4H), 2.89 (s, 2H), 1.96 – 1.86 (m, 4H), 1.76 – 1.69 (m, 2H), 1.51 (d, J = 4.3 Hz, 3H), 1.49 (d, J = 4.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.9, 133.6, 128.3, 126.2, 120.9, 111.2, 67.7, 67.6, 66.5, 29.2, 29.1, 23.2, 23.1, 23.1, 23.1; FTIR (neat): 3400, 2932, 2869, 1451, 1235 cm^{-1} ; HRMS (ESI-TOF) m/z : $[M + Na]^+$ calcd for $C_{21}H_{28}O_4Na$, 367.1885 found 367.1885.

1,1'-((propane-1,3-diylbis(oxy))bis(2,1-phenylene))bis(ethan-1-ol) (192b): Prepared

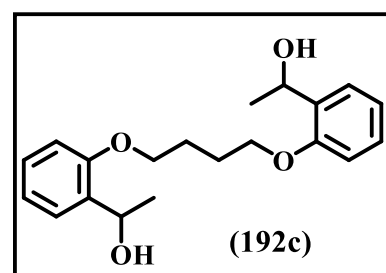
according to general experimental procedure 4.9.1B1, using 2-(1-hydroxyethyl) phenol (500 mg, 3.62 mmol), 1,3-dibromopropane (365 mg, 1.81 mmol), and potassium carbonate (K_2CO_3) (1 gm, 7.24 mmol), The residue was purified by using column chromatography (EtOAc/*n*-hexane



= 40:60) as the eluent to afford desired product 1,1'-((pentane-1,5-diylbis(oxy))bis(2,1-phenylene))bis(ethan-1-ol) (**159b**) (710 mg, 62 mmol, 62% yield) as a semisolid; ^1H NMR (400 MHz, $CDCl_3$) δ 7.38 (d, J = 7.5 Hz, 2H), 7.28 – 7.20 (m, 2H), 6.98 (q, J = 7.0 Hz, 2H), 6.90 (d, J = 8.2 Hz, 2H), 5.12 (dd, J = 12.3, 6.1 Hz, 2H), 4.23 (t, J = 6.0 Hz, 4H), 2.74 (d, J = 7.5 Hz, 2H), 2.35 (dq, J = 11.9, 5.9 Hz, 2H), 1.48 (dd, J = 6.5, 3.0 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.6, 155.6, 133.8, 133.8, 128.4, 128.4, 126.2, 126.2, 121.2, 121.2, 111.4, 111.3, 66.0, 66.0, 64.9, 29.5, 29.5, 23.2, 23.1; FTIR (neat): 3389, 2931, 2873, 1600, 1499 cm^{-1} ; HRMS (ESI-TOF) m/z : $[M + Na]^+$ calcd for $C_{19}H_{24}O_4Na$, 339.1573, found 339.1571.

1,1'-((butane-1,4-diylbis(oxy))bis(2,1-phenylene))bis(ethan-1-ol) (192c): Prepared

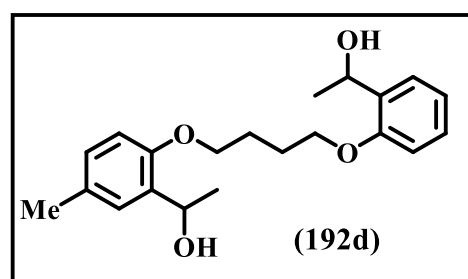
according to general experimental procedure 4.9.1B1, using 2-(1-hydroxyethyl) phenol (500 mg, 3.62 mmol), 1,4-dibromobutane (390 mg, 1.81 mmol), and potassium carbonate (K_2CO_3) (1 gm, 7.24 mmol), The residue was purified by using column chromatography (EtOAc/*n*-hexane



= 40:60) as the eluent to afford desired product 1,1'-((butane-1,4-diylbis(oxy))bis(2,1-phenylene))bis(ethan-1-ol) (**159c**) (909 mg, 2.75 mmol, 76% yield) as a semisolid; ^1H NMR (400 MHz, CDCl_3) δ 7.31 (dt, $J = 7.5, 1.9$ Hz, 2H), 7.24 – 7.19 (m, 2H), 7.00 – 6.92 (m, 2H), 6.86 (d, $J = 8.2$ Hz, 2H), 5.13 – 5.03 (m, 2H), 4.26 – 4.16 (m, 4H), 3.97 – 3.86 (m, 4H), 3.58 (s, 2H), 1.50 (dd, $J = 6.6, 1.1$ Hz, 6H); ^{13}C NMR (100 MHz, CDCl_3) δ 156.2, 156.1, 134.1, 128., 126.6, 126.6, 121.4, 112.2, 112.2, 69.9, 69.8, 67.8, 67.7, 66.3, 66.2, 22.4, 22.3; FTIR (neat): 3401, 2919, 2870, 1454, 1231 cm^{-1} ; HRMS (ESI-TOF) m/z : $[\text{M} + \text{Na}]^+$ calcd for $\text{C}_{20}\text{H}_{26}\text{O}_4\text{Na}$, 353.1728 found 353.1721.

1-(2-(4-(2-(1-hydroxyethyl)-4-methylphenoxy)butoxy)phenyl)ethan-1-ol (159d**)(dr=1:1):**

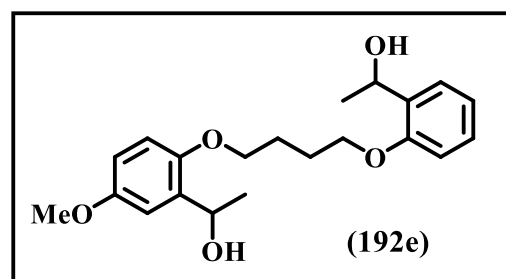
Prepared according to general experimental procedure 4.9.1B2, using 1-(2-(4-bromobutoxy)phenyl)ethan-1-ol (800 mg, 2.93 mmol), 2-(1-hydroxyethyl)-4-methylphenol (390 mg, 1.81 mmol), and potassium carbonate (K_2CO_3) (808 mg, 5.86 mmol), The residue



was purified by using column chromatography ($\text{EtOAc}/n\text{-hexane} = 40:60$) as the eluent to afford desired product 1-(2-(4-(2-(1-hydroxyethyl)-4-methylphenoxy)butoxy)phenyl)ethan-1-ol (**159d**) (730 mg, 2.12 mmol, 72% yield) as a semisolid; ^1H NMR (400 MHz, CDCl_3) δ 7.36 (d, $J = 7.5$ Hz, 1H), 7.25 – 7.20 (m, 1H), 7.16 (s, 1H), 7.02 (dd, $J = 8.3, 1.9$ Hz, 1H), 6.96 (td, $J = 7.5, 0.8$ Hz, 1H), 6.87 (d, $J = 8.2$ Hz, 1H), 6.77 (dd, $J = 8.3, 1.3$ Hz, 1H), 5.08 (dt, $J = 10.4, 6.6$ Hz, 2H), 4.09 (dt, $J = 10.9, 5.5$ Hz, 4H), 2.66 (s, 2H), 2.29 (s, 3H), 2.06 – 2.00 (m, $J = 5.5, 2.8$ Hz, 4H), 1.52 – 1.45 (m, 6H); ^{13}C NMR (100 MHz, CDCl_3) δ 154.0, 153.8, 133.6, 133.4, 133.3, 130.3, 130.2, 128.9, 128.4, 127.02, 127.0, 126.3, 126.2, 121.0, 120.99, 111.4, 111.3, 111.2, 67.6, 67.5, 66.6, 66.5, 66.4, 66.3, 26.5, 23.23, 23.1, 23.1, 23.04, 20.7; FTIR (neat): 3389, 2934, 2873, 1450, 1239 cm^{-1} ; HRMS (ESI-TOF) m/z : $[\text{M} + \text{Na}]^+$ calcd for $\text{C}_{21}\text{H}_{28}\text{O}_4\text{Na}$, 367.1885 found 367.1883.

1-(2-(4-(2-(1-hydroxyethyl)-4-methoxyphenoxy)butoxy)phenyl)ethan-1-ol (159e**) (dr=1:1):**

Prepared according to general experimental procedure 4.9.1B2, using 1-(2-(4-bromobutoxy)phenyl)ethan-1-ol (800 mg, 2.93 mmol), 2-(1-hydroxyethyl)-4-methoxyphenol

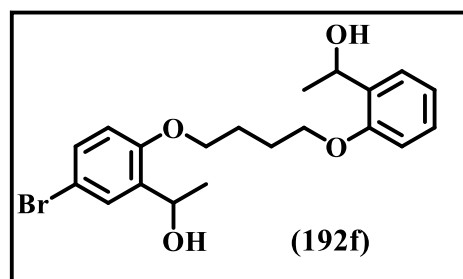


(492 mg, 2.93 mmol), and potassium carbonate (K_2CO_3) (808 mg, 5.86 mmol), The residue was purified by using column chromatography ($\text{EtOAc}/n\text{-hexane} = 40:60$) as the eluent to

afford desired product 1-(2-(4-(2-(1-hydroxyethyl)-4-methoxyphenoxy)butoxy)phenyl)ethan-1-ol (**159e**) (647 mg, 2.12 mmol, 61% yield) as a semisolid; ^1H NMR (400 MHz, CDCl_3) δ 7.36 (d, $J = 7.5$ Hz, 1H), 7.23 (td, $J = 7.9$, 1.7 Hz, 1H), 6.99 – 6.94 (m, 2H), 6.87 (d, $J = 8.2$ Hz, 1H), 6.80 (dd, $J = 8.9$, 1.2 Hz, 1H), 6.74 (dd, $J = 8.8$, 3.0 Hz, 1H), 5.07 (dd, $J = 15.5$, 6.6 Hz, 2H), 4.10 (t, $J = 5.3$ Hz, 2H), 4.05 (t, $J = 5.2$ Hz, 2H), 3.78 (s, 3H), 2.71 (s, 2H), 2.03 (dd, $J = 6.9$, 4.2 Hz, 4H), 1.48 (ddd, $J = 8.2$, 6.5, 4.8 Hz, 6H); ^{13}C NMR (100 MHz, CDCl_3) δ 155.9, 155.8, 154.0, 145.0, 149.9, 135.1, 135.0, 133.7, 133.6, 128.4, 126.3, 126.2, 121.0, 120.9, 112.54, 112.51, 112.44, 112.4, 111.3, 111.2, 68.1, 68.1, 67.5, 66.5, 66.4, 66.3, 66.2, 55.9, 26.5, 26.5, 26.4, 23.2, 23.2, 23.1, 23.0; FTIR (neat): 3316, 2935, 1454, 1237, 1019 cm^{-1} ; HRMS (ESI-TOF) m/z : $[\text{M} + \text{Na}]^+$ calcd for $\text{C}_{21}\text{H}_{28}\text{O}_5\text{Na}$, 383.1834 found 383.1829.

1-(2-(4-(4-bromo-2-(1-hydroxyethyl)phenoxy)butoxy)phenyl)ethan-1-ol (159f**) (dr=1:1):**

Prepared according to general experimental procedure 4.9.1B2, using 1-(2-(4-bromobutoxy)phenyl)ethan-1-ol (800 mg, 2.93 mmol), 4-bromo-2-(1-hydroxyethyl)phenol (635 mg, 2.93 mmol), and potassium carbonate (K_2CO_3) (808 mg, 5.86 mmol).

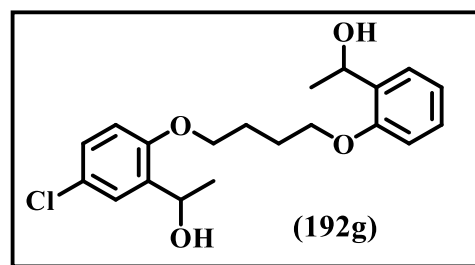


The residue was purified by using column

chromatography ($\text{EtOAc}/n\text{-hexane} = 40:60$) as the eluent to afford desired product 1-(2-(4-(2-(1-hydroxyethyl)-4-methoxyphenoxy)butoxy)phenyl)ethan-1-ol (**159f**) (723 mg, 1.77 mmol, 60% yield) as a semisolid; ^1H NMR (400 MHz, CDCl_3) δ 7.50 (t, $J = 2.4$ Hz, 1H), 7.36 (d, $J = 7.5$ Hz, 1H), 7.31 (dd, $J = 8.7$, 2.5 Hz, 1H), 7.23 (td, $J = 8.0$, 1.7 Hz, 1H), 6.97 (t, $J = 7.5$ Hz, 1H), 6.87 (d, $J = 8.2$ Hz, 1H), 6.73 (dd, $J = 8.7$, 1.0 Hz, 1H), 5.09 (dq, $J = 12.7$, 6.4 Hz, 2H), 4.09 (dd, $J = 12.2$, 6.4 Hz, 4H), 2.07 – 1.99 (m, 4H), 1.49 (dd, $J = 6.5$, 5.4 Hz, 3H), 1.45 (dd, $J = 6.4$, 5.3 Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 155.7, 155.7, 154.6, 154.6, 136.1, 136.0, 133.5, 130.8, 129.1, 128.3, 126.2, 126.1, 120.9, 120.9, 113.34, 113.3, 112.9, 112.8, 111.2, 111.1, 77.3, 77.0, 76.7, 67.72, 67.7, 67.3, 66.5, 66.2, 65.5, 65.3, 26.3, 26.2, 23.11, 23.0, 22.9, 22.8; FTIR (neat): 3398, 2935, 2870, 1454, 1235 cm^{-1} ; HRMS (ESI-TOF) m/z : $[\text{M} + \text{Na}]^+$ calcd for $\text{C}_{20}\text{H}_{25}\text{O}_4\text{BrNa}$, 431.0833 found 431.0830.

1-(5-chloro-2-(4-(2-(hydroxymethyl)phenoxy)butoxy)phenyl)ethan-1-ol (159g): (dr=1:1):

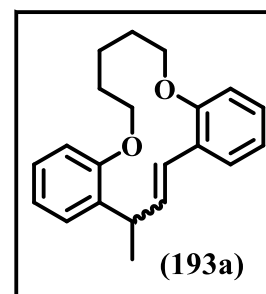
Prepared according to general experimental procedure 4.9.1B2, using 1-(2-(4-bromobutoxy)phenyl)ethan-1-ol (800 mg, 2.93 mmol), 4-chloro-2-(1-hydroxyethyl)phenol (505 mg, 2.93 mmol), and potassium carbonate (K_2CO_3) (808 mg, 5.86 mmol),



The residue was purified by using column chromatography (EtOAc/*n*-hexane = 40:60) as the eluent to afford desired product 1-(5-chloro-2-(4-(2-(hydroxymethyl)phenoxy)butoxy)phenyl)ethan-1-ol (**159g**) (630 mg, 1.73 mmol, 59% yield) as a semisolid; ^1H NMR (400 MHz, $CDCl_3$) δ 7.36 (dd, J = 6.3, 4.2 Hz, 2H), 7.23 (td, J = 8.0, 1.6 Hz, 1H), 7.17 (dd, J = 8.7, 2.6 Hz, 1H), 6.97 (t, J = 7.5 Hz, 1H), 6.87 (d, J = 8.2 Hz, 1H), 6.77 (d, J = 8.7 Hz, 1H), 5.14 – 5.01 (m, 2H), 4.09 (dd, J = 11.7, 5.9 Hz, 4H), 2.04 (d, J = 5.7 Hz, 4H), 1.49 (dd, J = 6.4, 5.4 Hz, 3H), 1.45 (dd, J = 6.4, 5.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.8, 155.8, 154.2, 154.2, 135.83, 135.8, 133.6, 128.4, 127.9, 126.36, 126.3, 126.2, 126.0, 121.1, 121.0, 112.52, 112.5, 111.3, 111.2, 67.9, 67.9, 67.5, 66.5, 66.3, 65.6, 65.5, 26.39, 26.36, 26.3, 23.23, 23.2, 23.1, 23.0; FTIR (neat): 3397, 2934, 2873, 1602, 1454 cm^{-1} ; HRMS (ESI-TOF) m/z ; $[M + Na]^+$ calcd for $C_{20}H_{25}O_4ClNa$, 387.1338, found 387.1330.

16-methyl-7,8,9,10-tetrahydro-6H,16H-dibenzo[*h,m*][1,7]dioxacyclotetradecine (193a):

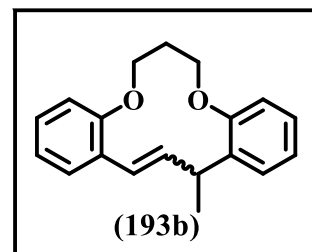
Prepared according to general experimental procedure 4.9.1D, a 0.05 M solution of **192a** (69 mg, 0.199 mmol) in (4 mL) 1, 4-dioxane solvent was pumped using a syringe pump through Omnifit® column (6.6 x 150 mm) packed bed containing 1.9 gm of Ni-zeolite filled up to 9 cm and preheated at 140 °C with the flow rate of 0.1 mL/min at 3.5 to 3.9 back pressure was maintained in the reaction and residence time t_R = 27.3



min. After a four-time run, the collected organic layer was concentrated under reduced pressure. The crude product was purified by column chromatography using (EtOAc/*n*-hexane = 1:99) as an eluent to afford the compound **193a** as a semisolid (43.3 mg, 70% yield, 100:0 *E:Z*) and non-cyclic alkene was observed very traces amount. Continuous flow 0.043 g (70%), space-time yield 28.65 $g\ L^{-1}\ h^{-1}$. Productivity g/day = 1.55 g/day . ^1H NMR (400 MHz, $CDCl_3$) δ 7.27 – 7.21 (m, 3H), 7.16 (td, J = 7.8, 1.6 Hz, 1H), 7.11 (td, J = 7.8, 1.6 Hz, 1H), 6.89 (dd, J = 12.8, 4.2 Hz, 2H), 6.84 (dd, J = 8.2, 4.3 Hz, 2H), 6.77 (dd, J = 16.0, 7.4 Hz, 1H), 6.69 (d, J = 16.0 Hz, 1H), 4.18 – 4.12 (m, 1H), 4.04 (td, J = 6.5, 3.3 Hz, 2H), 4.02 – 3.96 (m, 1H), 3.83 (p, J = 7.1 Hz, 1H), 2.04 – 1.83 (m, 4H), 1.83 – 1.75 (m, 2H), 1.52 (d, J = 7.1 Hz, 3H); ^{13}C NMR

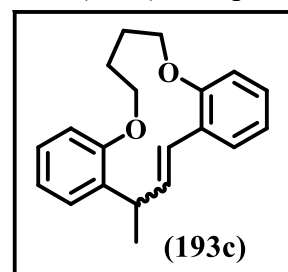
(100 MHz, CDCl₃) δ 157.4, 157.2, 137.5, 133.5, 128.4, 128.0, 127.8, 127.6, 127.3, 124.7, 121.1, 120.4, 113.8, 111.0, 69.3, 65.6, 40.8, 28.2, 27.7, 22.2, 19.2; FTIR (neat): 2933, 2871, 1602, 1499, 1452 cm⁻¹; HRMS (ESI-TOF) m/z ; [M + H]⁺ calcd for C₂₁H₂₅O₂, 309.1855 found 309.1850.

14-methyl-7,8-dihydro-6*H*,14*H*-dibenzo[*f,k*][1,5]dioxacyclododecine (160b): Prepared according to general experimental procedure 4.9.1D, a 0.05 M solution of 1,1'-((propane-1,3-diylbis(oxy))bis(2,1-phenylene))bis(ethan-1-ol) **192b** (63 mg, 0.199 mmol) in (4 mL) 1, 4-dioxane solvent was pumped using a syringe pump through Omnifit® column (6.6 x 150 mm) packed bed containing 1.9 gm of



Ni-zeolite filled up to 9 cm and preheated at 140 °C with the flow rate of 0.1 mL/min at 3.5 to 3.9 back pressure was maintained in the reaction and residence time t_R = 27.3 min. After a four-time run, the collected organic layer was concentrated under reduced pressure. The crude product was purified by column chromatography using (EtOAc/*n*-hexane = 1:99) as an eluent to afford the compound **193b** as a semisolid (34.7 mg, 62% yield, 95:5 *E:Z*) and non-cyclic alkene was observed very traces amount. Continuous flow 0.0347 g (62%), space-time yield 25.25 g L⁻¹ h⁻¹. Productivity *g/day* = 1.25 g/day. ¹H NMR (400 MHz, CDCl₃) δ 7.24 – 7.16 (m, 3H), 7.14 (td, *J* = 7.7, 1.7 Hz, 1H), 7.02 (dd, *J* = 8.0, 7.0 Hz, 1H), 6.98 – 6.91 (m, 3H), 6.36 (d, *J* = 16.1 Hz, 1H), 6.09 (dd, *J* = 16.1, 5.7 Hz, 1H), 4.29 (ddd, *J* = 9.8, 6.2, 3.8 Hz, 1H), 4.24 – 4.17 (m, 1H), 4.10 (ddd, *J* = 9.1, 7.0, 4.8 Hz, 1H), 3.96 (ddd, *J* = 9.1, 6.4, 4.8 Hz, 1H), 3.79 – 3.70 (m, 1H), 2.28 – 2.15 (m, 2H), 1.50 (d, *J* = 7.2 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 157.6, 157.4, 137.8, 133.2, 133.1, 128.9, 128.7, 127.8, 127.7, 125.4, 123.9, 121.0, 120.4, 113.1, 69.9, 65.0, 40.6, 29.4, 19.5; FTIR (neat): 2931, 2860, 1602, 1498 cm⁻¹; HRMS (ESI-TOF) m/z ; [M + H]⁺ calcd for C₁₉H₂₁O₂, 281.1541 found 281.1536.

15-methyl-6,7,8,9-tetrahydro-15*H*-dibenzo[*g,l*][1,6]dioxacyclotridecine (193c): Prepared according to general experimental procedure 4.9.1D, a 0.05 M solution of **192c** (66 mg, 0.199 mmol) in (4 mL) 1, 4-dioxane solvent was pumped using a syringe pump through Omnifit® column (6.6 x 150 mm) packed bed containing 1.9 gm of Ni-zeolite filled up to 9 cm and preheated at 140 °C with the flow rate of 0.1 mL/min at 3.5

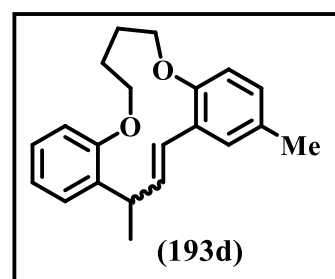


to 3.9 back pressure was maintained in the reaction and residence time t_R = 27.3 min. After a four-time run, the collected organic layer was concentrated under reduced pressure. The crude product was purified by column chromatography using ethyl acetate: hexane (1:99) as an eluent

to afford the compound **193c** as a semisolid (31.3 mg, 53% yield, 96:4 *E:Z*) and non-cyclic alkene was observed very traces amount. Continuous flow 0.0313 g (53%), space-time yield 21.83 g L⁻¹ h⁻¹. Productivity *g/day* = 1.12 g/day. ¹H NMR (400 MHz, CDCl₃) δ 7.31 (ddd, *J* = 9.1, 7.9, 1.7 Hz, 2H), 7.16 (td, *J* = 9.3, 1.7 Hz, 2H), 7.02 – 6.90 (m, 4H), 6.81 (d, *J* = 8.1 Hz, 1H), 5.93 (dd, *J* = 15.7, 8.5 Hz, 1H), 4.13 – 4.04 (m, 2H), 4.01 – 3.89 (m, 3H), 2.34 – 2.23 (m, 1H), 2.07 – 1.97 (m, 1H), 1.88 – 1.78 (m, 2H), 1.49 (d, *J* = 7.1 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 157.41, 135.78, 133.20, 132.39, 128.14, 127.38, 126.89, 126.72, 125.50, 123.72, 121.41, 120.58, 111.58, 74.65, 67.55, 38.76, 27.96, 26.26, 18.7; FTIR (neat): 2917, 2867, 1598, 1492 cm⁻¹; HRMS (ESI-TOF) *m/z*; [M + H]⁺ calcd for C₂₀H₂₃O₂, 295.1698 found 295.1709.

2,15-dimethyl-6,7,8,9-tetrahydro-15H-dibenzo[*g,l*][1,6]dioxacyclotridecine (193d):

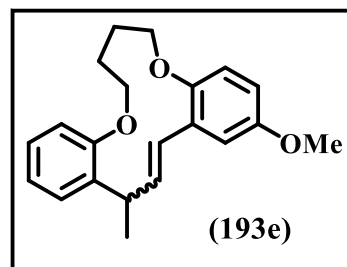
Prepared according to general experimental procedure 4.9.1C2, a 0.05 M solution of 1-(2-(4-(2-(1-hydroxyethyl)-4-methylphenoxy)butoxy)phenyl)ethan-1-ol **192d** (69 mg, 0.2 mmol) in (4 mL) 1, 4-dioxane solvent was pumped using a syringe pump through Omnifit® column (6.6 x 150 mm) packed bed containing 1.9 gm of Ni-zeolite filled up to 9 cm and



preheated at 140 °C with the flow rate of 0.1 mL/min at 3.5 to 3.9 back pressure was maintained in the reaction and residence time *t_R* = 27.3 min. After a four-time run, the collected organic layer was concentrated under reduced pressure. The crude product was purified by column chromatography using (EtOAc/*n*-hexane = 1:99) as an eluent to afford the compound **193d** as a semisolid (36.4 mg, 59% yield, 55:45 *E:Z*) and non-cyclic alkene was observed very traces amount. Continuous flow 0.0364 g (59%), space-time yield 24.08 g L⁻¹ h⁻¹. Productivity *g/day* = 1.30 g/day. ¹H NMR (400 MHz, CDCl₃) δ 7.39 – 7.34 (m, 1H), 7.29 (dd, *J* = 7.5, 1.5 Hz, 1H), 7.20 – 7.12 (m, 2H), 7.09 (s, 1H), 7.03 – 6.88 (m, 5H), 6.85 – 6.78 (m, 1H), 6.73 (d, *J* = 8.2 Hz, 1H), 5.94 – 5.85 (m, 1H), 4.13 – 4.03 (m, 2H), 4.00 – 3.86 (m, 4H), 2.32 (s, 2H), 2.28 (s, 3H), 2.08 – 1.85 (m, 2H), 1.86 – 1.75 (m, 2H), 1.50 (dd, *J* = 7.1, 4.1 Hz, 4H). ¹³C NMR (100 MHz, CDCl₃) δ 157.4, 155.2, 136.0, 135.8, 135.6, 135.4, 133.14, 133.11, 133.1, 133.0, 132.3, 131.98, 131.9, 129.9, 129.7, 128.78, 128.7, 128.13, 128.1, 127.8, 127.6, 127.5, 127.4, 127.3, 127.1, 127.0, 126.87, 126.8, 126.7, 125.5, 125.4, 125.3, 123.7, 123.6, 121.4, 121.3, 121.2, 121.1, 120.5, 111.9, 111.7, 111.4, 74.8, 74.1, 67.8, 67.7, 67.4, 38.7, 38.6, 27.9, 27.8, 26.24, 26.2, 20.9, 20.8, 18.8, 18.7, 18.6; FTIR (neat): 2932, 2864, 1596, 1491, 14551 cm⁻¹; HRMS (ESI-TOF) *m/z*; [M + H]⁺ calcd for C₂₁H₂₅O₂, 309.1855 found 309.1848.

2-methoxy-15-methyl-6,7,8,9-tetrahydro-15H-**dibenzo[*g,l*][1,6]dioxacyclotridecine (193e):**

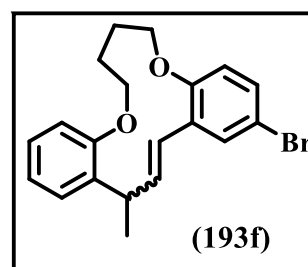
Prepared according to general experimental procedure 4.9.1D, a 0.05 M solution of 1-(2-(4-(2-(1-hydroxyethyl)-4-methoxyphenoxy)butoxy)phenyl)ethan-1-ol **192e** (69 mg, 0.2 mmol) in (4 mL) 1, 4-dioxane solvent was pumped using a



syringe pump through Omnifit® column (6.6 x 150 mm) packed bed containing 1.9 gm of Ni-zeolite filled up to 9 cm and preheated at 140 °C with the flow rate of 0.1 mL/min at 3.5 to 3.9 back pressure was maintained in the reaction and residence time $t_R = 27.3$ min. After a four-time run, the collected organic layer was concentrated under reduced pressure. The crude product was purified by column chromatography using (EtOAc/*n*-hexane = 1:99) as an eluent to afford the compound **193e** as a semisolid (36.6 mg, 60% yield, 55:45 *E:Z*) and non-cyclic alkene was observed very traces amount. Continuous flow 0.0366 g (60%), space-time yield 23.03 g L⁻¹ h⁻¹. Productivity *g/day* = 1.40 g/day. ¹H NMR (400 MHz, CDCl₃) δ 7.33 (dd, *J* = 7.9, 1.6 Hz, 1H), 7.30 – 7.25 (m, 1H), 7.16 (ddd, *J* = 7.7, 6.9, 2.4 Hz, 1H), 7.09 (ddd, *J* = 9.6, 6.4, 1.7 Hz, 1H), 6.98 (dt, *J* = 11.3, 5.0 Hz, 3H), 6.95 – 6.89 (m, 2H), 6.88 – 6.82 (m, 2H), 6.82 – 6.77 (m, 1H), 6.75 (d, *J* = 8.8 Hz, 1H), 6.68 (td, *J* = 8.3, 3.1 Hz, 2H), 6.56 (dd, *J* = 12.4, 8.4 Hz, 1H), 5.94 (dd, *J* = 15.7, 8.6 Hz, 1H), 5.86 (dd, *J* = 15.7, 8.5 Hz, 1H), 4.16 (t, *J* = 4.3 Hz, 1H), 4.11 – 3.99 (m, 4H), 3.96 – 3.82 (m, 5H), 3.77 (s, 3H), 3.75 (s, 2H), 2.33 – 2.19 (m, 2H), 2.06 – 1.96 (m, 2H), 1.93 – 1.82 (m, 2H), 1.79 (ddd, *J* = 10.9, 7.1, 3.6 Hz, 2H), 1.48 (dd, *J* = 9.5, 7.1 Hz, 5H); ¹³C NMR (100 MHz, CDCl₃) δ 157.8, 157.4, 155.8, 153.8, 152.0, 151.6, 151.3, 147.8, 147.0, 135.8, 135.6, 135.0, 134.4, 134.0, 133.1, 132.9, 132.1, 131.4, 128.1, 127.4, 127.2, 126.9, 126.7, 125.6, 125.5, 123.6, 122.6, 121.0, 120.5, 119.7, 119.6, 114.0, 113.9, 113.1, 111.7, 111.3, 110.8, 110.7, 109.8, 75.1, 74.1, 73.0, 68.4, 67.7, 67.4, 55.9, 55.8, 55.7, 48.7, 41.7, 40.7, 38.9, 38.5, 27.9, 27.6, 26.2, 26.1, 25.9, 25.7, 22.3, 18.8, 18.5; FTIR (neat): 2920, 2873, 1596, 1492, 1453 cm⁻¹; HRMS (ESI-TOF) *m/z*: [M + Na]⁺ calcd for C₂₁H₂₄O₃, 347.1623 found 347.1628.

3-bromo-15-methyl-6,7,8,9-tetrahydro-15H-dibenzo[*g,l*][1,6]dioxacyclotridecine (160f):

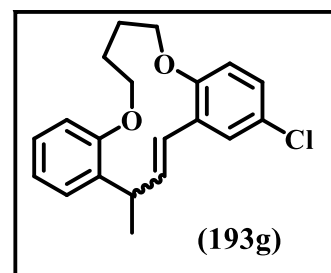
Prepared according to general experimental procedure 4.9.1D, a 0.05 M solution of **159f** (82 mg, 0.2 mmol) in (4 mL) 1, 4-dioxane solvent was pumped using a syringe pump through Omnifit® column (6.6 x 150 mm) packed bed containing 1.9 gm of Ni-zeolite filled up to 9 cm and preheated at 140 °C with the flow rate of 0.1



mL/min at 3.5 to 3.9 back pressure was maintained in the reaction and residence time $t_R = 27.3$ min. After a four-time run, the collected organic layer was concentrated under reduced pressure. The crude product was purified by column chromatography using (EtOAc/*n*-hexane = 1:99) as an eluent to afford the compound **160f** as a semisolid (27.7 mg, 37% yield, 98:2 *E:Z*) and non-cyclic alkene was observed very traces amount. Continuous flow 0.0277 g (37%), space-time yield $15.14 \text{ g L}^{-1} \text{ h}^{-1}$. Productivity $g/day = 0.99 \text{ g/day}$. ^1H NMR (400 MHz, CDCl_3) δ 7.35 (t, $J = 4.2 \text{ Hz}$, 2H), 7.27 – 7.24 (m, 1H), 7.16 (d, $J = 2.1 \text{ Hz}$, 1H), 7.03 – 6.93 (m, 1H), 6.67 (d, $J = 8.7 \text{ Hz}$, 3), 5.87 (dd, $J = 15.7, 8.5 \text{ Hz}$, 1H), 4.07 (ddd, $J = 6.9, 6.1, 3.3 \text{ Hz}$, 2H), 3.99 – 3.93 (m, 1H), 3.89 (td, $J = 8.5, 2.4 \text{ Hz}$, 2H), 2.33 – 2.22 (m, 1H), 2.06 – 1.96 (m, 1H), 1.85 – 1.76 (m, 2H), 1.46 (d, $J = 7.1 \text{ Hz}$, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 157.4, 156.5, 135.5, 134.8, 132.1, 129.9, 129.9, 128.4, 126.7, 126.1, 123.8, 121.4, 113.2, 112.9, 74.6, 67.9, 38.7, 27.9, 26.2, 18.6; FTIR (neat): 2933, 2872, 1487, 1477, 1285 cm^{-1} ; HRMS (ESI-TOF) m/z : $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{20}\text{H}_{22}\text{BrO}_2$, 373.0803 found 373.0813.

2-chloro-15-methyl-6,7,8,9-tetrahydro-15H-dibenzo[*g,l*][1,6]dioxacyclotridecine (160g):

Prepared according to general experimental procedure 4.9.1D, a 0.05 M solution of 1-(2-(4-(4-chloro-2-(1-hydroxyethyl)phenoxy)butoxy)phenyl)ethan-1-ol **191g** (82 mg, 0.2 mmol) in (4 mL) 1, 4-dioxane solvent was pumped using a syringe pump through Omnifit® column (6.6 x 150 mm) packed bed containing 1.9 gm of Ni-zeolite filled up to 9 cm and preheated

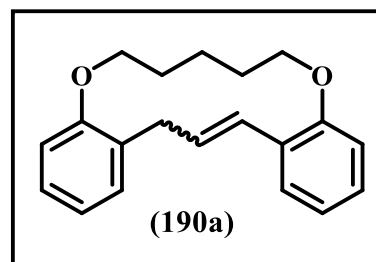


at 140°C with the flow rate of 0.1 mL/min at 3.5 to 3.9 back pressure was maintained in the reaction and residence time $t_R = 27.3$ min. After a four-time run, the collected organic layer was concentrated under reduced pressure. The crude product was purified by column chromatography using (EtOAc/*n*-hexane = 1:99) as an eluent to afford the compound **193g** as a semisolid (21.1 mg, 32% yield, 98:2 *E:Z*) and non-cyclic alkene was observed very traces amount. Continuous flow 0.021 g (32%), space-time yield $13.03 \text{ g L}^{-1} \text{ h}^{-1}$. Productivity $g/day = 0.75 \text{ g/day}$. ^1H NMR (400 MHz, CDCl_3) δ 7.35 (dd, $J = 7.9, 1.5 \text{ Hz}$, 1H), 7.22 (d, $J = 2.6 \text{ Hz}$, 1H), 7.19 – 7.13 (m, 1H), 7.12 (dd, $J = 8.6, 2.6 \text{ Hz}$, 1H), 7.02 – 6.99 (m, 1H), 6.98 – 6.92 (m, 2H), 6.72 (d, $J = 8.7 \text{ Hz}$, 1H), 5.87 (dd, $J = 15.7, 8.5 \text{ Hz}$, 1H), 4.11 – 4.04 (m, 2H), 3.96 (td, $J = 6.6, 3.1 \text{ Hz}$, 1H), 3.94 – 3.85 (m, 2H), 2.32 – 2.22 (m, 1H), 2.05 – 1.96 (m, 1H), 1.82 (tdd, $J = 10.7, 7.4, 3.7 \text{ Hz}$, 2H), 1.47 (d, $J = 7.1 \text{ Hz}$, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 157.4, 156.0, 135.1, 134.8, 132.1, 128.3, 127.0, 126.9, 126.7, 126.1, 125.5, 123.8, 121.4, 112.7, 74.6, 68.0,

38.6, 27.9, 26.2, 18.6; FTIR (neat): 2927, 1583, 1490, 1472, 1241 cm^{-1} ; HRMS (ESI-TOF) m/z ; $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{20}\text{H}_{22}\text{ClO}_2$, 329.1308 found 329.1287.

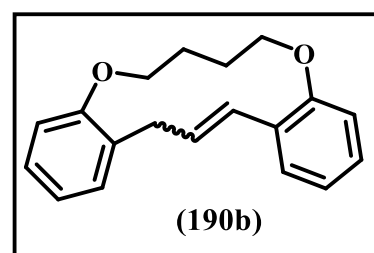
7,8,9,10-tetrahydro-6*H*,16*H*-

dibenzo[*h,m*][1,7]dioxacyclotetradecine (190a): Prepared according to general experimental procedure 4.9.1E, a 0.05 M solution of (2-((5-(2-vinylphenoxy)pentyl)oxy)phenyl)methanol **191a** (62 mg, 0.2 mmol) in (4 mL) 1, 4-dioxane solvent was pumped using a



syringe pump through Omnifit® column (6.6 x 150 mm) packed bed containing 1.9 gm of Ni-zeolite filled up to 9 cm and preheated at 140 °C with the flow rate of 0.1 mL/min at 3.5 to 3.9 back pressure was maintained in the reaction and residence time $t_R = 27.3$ min. After a two-time run, the collected organic layer was concentrated under reduced pressure, and the crude product was purified by column chromatography using (EtOAc/*n*-hexane = 1:99) as an eluent to afford the compound **190a** as a semisolid (46.2 mg, 79% yield, 98:2 *E:Z*). Continuous flow 0.0462 g (79%), space-time yield 32.02 $\text{g L}^{-1} \text{h}^{-1}$. Productivity $\text{g/day} = 1.367$ g/day. ^1H NMR (400 MHz, CDCl_3) δ 7.28 – 7.23 (m, 1H), 7.20 – 7.08 (m, 3H), 6.90 – 6.80 (m, 4H), 6.73 (d, $J = 16.0$ Hz, 1H), 6.64 (dt, $J = 15.9, 6.5$ Hz, 1H), 4.07 (t, $J = 5.1$ Hz, 2H), 4.04 (t, $J = 5.0$ Hz, 2H), 3.52 (d, $J = 6.5$ Hz, 2H), 1.89 (dd, $J = 5.9, 3.0$ Hz, 4H), 1.80 (dd, $J = 11.0, 6.0$ Hz, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 157.62, 157.3, 131.8, 130.6, 128.9, 128.2, 128.1, 127.6, 126.6, 121.1, 120.3, 113.9, 110.9, 77.2, 69.4, 65.8, 37.3, 28.2, 27.9, 22.2. FTIR (neat): 2928, 2870, 1488, 1452, 1241 cm^{-1} ; HRMS (ESI-TOF) m/z ; $[\text{M} + \text{Na}]^+$ calcd for $\text{C}_{20}\text{H}_{23}\text{O}_2$, 295.1698 found 295.1693.

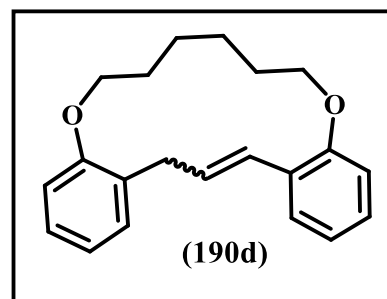
6,7,8,9-tetrahydro-15*H*-dibenzo[*g,l*][1,6]dioxacyclotridecine (190b): Prepared according to general experimental procedure 4.9.1E, a 0.05 M solution of **191b** (45.00 mg, 0.150 mmol) in (3 mL) in 1, 4-dioxane solvent was pumped using a syringe pump through Omnifit® column (6.6 x 150 mm) packed bed containing 1.9 gm of Ni-zeolite filled up to 9 cm and preheated at 140 °C with the flow rate of 0.1 mL/min at 3.5 to 3.9 back pressure was maintained



in the reaction and residence time $t_R = 27.3$ min. After a two-time run, the collected organic layer was concentrated under reduced pressure. The crude product was purified by column chromatography using (EtOAc/*n*-hexane = 1:99) as an eluent to afford the compound **190b** as a white solid (34.5 mg, 82% yield, 97:3 *E:Z*); Melting point: 105-108 °C. Continuous flow

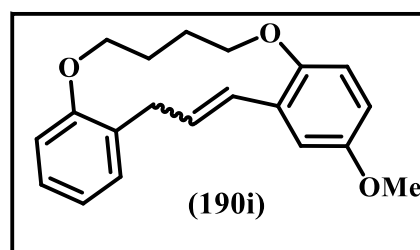
0.034 g (82%), space-time yield 30.76 g L⁻¹ h⁻¹. Productivity *g/day* = 1.65 g/day. ¹H NMR (400 MHz, CDCl₃) δ 7.36 (dd, *J* = 7.8, 1.6 Hz, 1H), 7.22 – 7.13 (m, 3H), 7.03 – 6.95 (m, 3H), 6.88 (td, *J* = 7.4, 1.0 Hz, 1H), 6.82 (t, *J* = 6.4 Hz, 1H), 6.02 (dt, *J* = 15.7, 7.1 Hz, 1H), 4.02 (dd, *J* = 10.3, 5.3 Hz, 4H), 3.50 (d, *J* = 6.9 Hz, 2H), 2.13 (dt, *J* = 7.5, 6.2 Hz, 2H), 1.82 (dt, *J* = 17.6, 6.2 Hz, 2H); ¹³C NMR (100 MHz, CDCl₃) δ 157.9, 157.5, 132.6, 130.6, 129.5, 128.7, 128.3, 127.7, 126.6, 123.8, 121.7, 120.5, 111.5, 75.0, 67.4, 36.8, 28.0, 26.2; FTIR (neat): 29490 2871, 1483, 1241 cm⁻¹; HRMS (ESI-TOF) *m/z*; [M + H]⁺ calcd for C₁₉H₂₁O₂, 281.1542, found 281.1522.

6,7,8,9,10,11-hexahydro-17*H*-dibenzo[*i,n*][1,8]dioxacyclopentadecine (190d): Prepared according to general experimental procedure 4.9.1E, a 0.05 M solution of (2-((6-(2-vinylphenoxy)hexyl)oxy)phenyl)methanol **191d** (49.0 mg, 0.150 mmol) in (4 mL) 1, 4-dioxane solvent was pumped using a syringe pump through Omnifit® column (6.6 x 150 mm) packed bed containing 1.9 gm of Ni-zeolite filled up to 9 cm and preheated at 140 °C with the flow rate of 0.1 mL/min



at 3.5 to 3.9 back pressure was maintained in the reaction and residence time *t_R* = 27.3 min. After a two-time run, the collected organic layer was concentrated under reduced pressure, and the crude product was purified by column chromatography using (EtOAc/*n*-hexane = 1:99) as an eluent to afford the compound **190d** as a white solid (36.1 mg, 78% yield, 98:2 *E:Z*); melting point: 88-89 °C. continuous flow 0.036 g (78%), space-time yield 32.82 g L⁻¹ h⁻¹. Productivity *g/day* = 1.373 g/day. ¹H NMR (400 MHz, CDCl₃) δ 7.35 (dd, *J* = 7.6, 1.7 Hz, 1H), 7.21 (dd, *J* = 7.3, 1.7 Hz, 1H), 7.19 – 7.10 (m, 2H), 6.91 – 6.82 (m, 5H), 6.31 (dt, *J* = 15.7, 7.2 Hz, 1H), 4.10 – 4.05 (m, 2H), 4.05 – 4.01 (m, 2H), 3.54 (dd, *J* = 7.2, 1.0 Hz, 2H), 1.86 (qd, *J* = 6.2, 2.7 Hz, 4H), 1.83 – 1.74 (m, 2H), 1.72 – 1.64 (m, 2H); ¹³C NMR (100 MHz, CDCl₃) δ 157.3, 156.1, 130.6, 130.4, 129.4, 127.9, 127.8, 127.5, 127.2, 126.1, 120.9, 120.4, 112.7, 111.5, 69.4, 67.8, 35.8, 29.5, 28.5, 27.7, 27.1; FTIR (neat): 2920, 2861, 1592, 1236 cm⁻¹; HRMS (ESI-TOF) *m/z*; [M + H]⁺ calcd for C₂₁H₂₅O₂, 309.1855, found 309.1850.

2-methoxy-6,7,8,9-tetrahydro-15*H*-dibenzo[*g,l*][1,6]dioxacyclotridecine (190i): Prepared according to general experimental procedure 4.9.1E, a 0.05 M solution of (2-(4-(4-methoxy-2-vinylphenoxy)butoxy)phenyl)methanol **191i** (49 mg, 0.149 mmol) in (3 mL) 1, 4-dioxane solvent was pumped using a syringe pump through (Omnifit® column (6.6 x



150 mm) packed bed containing 1.9 gm of Ni-zeolite filled up to 9 cm and preheated at 140 °C with the flow rate of 0.1 mL/min at 3.5 to 3.9 back pressure was maintained in the reaction and residence time $t_R = 27.3$ min. After a two-time run, the collected organic layer was concentrated under reduced pressure, and the crude product was purified by column chromatography using (EtOAc/*n*-hexane = 1:99) as an eluent to afford the compound (**190i**) as a semisolid (28.5 mg, 62% yield, 98:2 *E:Z*). Continuous flow 0.028 g (62%), space-time yield 18.73 g L⁻¹ h⁻¹. Productivity *g/day* = 1.38 g/day. ¹H NMR (400 MHz, CDCl₃) δ 7.22 – 7.15 (m, 2H), 6.97 (d, *J* = 15.7 Hz, 1H), 6.93 (d, *J* = 8.8 Hz, 1H), 6.90 – 6.86 (m, 2H), 6.81 (d, *J* = 8.0 Hz, 1H), 6.71 (dd, *J* = 8.8, 3.1 Hz, 1H), 6.01 (dt, *J* = 15.6, 7.1 Hz, 1H), 4.04 – 3.99 (m, 2H), 3.99 – 3.94 (m, 2H), 3.76 (s, 3H), 3.49 (d, *J* = 7.1 Hz, 2H), 2.12 (dt, *J* = 7.5, 6.2 Hz, 2H), 1.80 (dt, *J* = 12.2, 6.5 Hz, 2H); ¹³C NMR (100 MHz, CDCl₃) δ 157.8, 155.8, 151.3, 133.2, 130.6, 129.5, 128.5, 128.0, 127.8, 122.7, 120.5, 114.1, 111.4, 110.7, 75.3, 67.4, 55.7, 36.7, 28.0, 26.2. FTIR (neat): 2919, 2873, 1598 1492, 1451 cm⁻¹; HRMS (ESI-TOF) *m/z*; [M + Na]⁺ calcd for C₂₀H₂₂O₃Na, 333.1468, found 333.1461.

4.9.3 Crystal data:

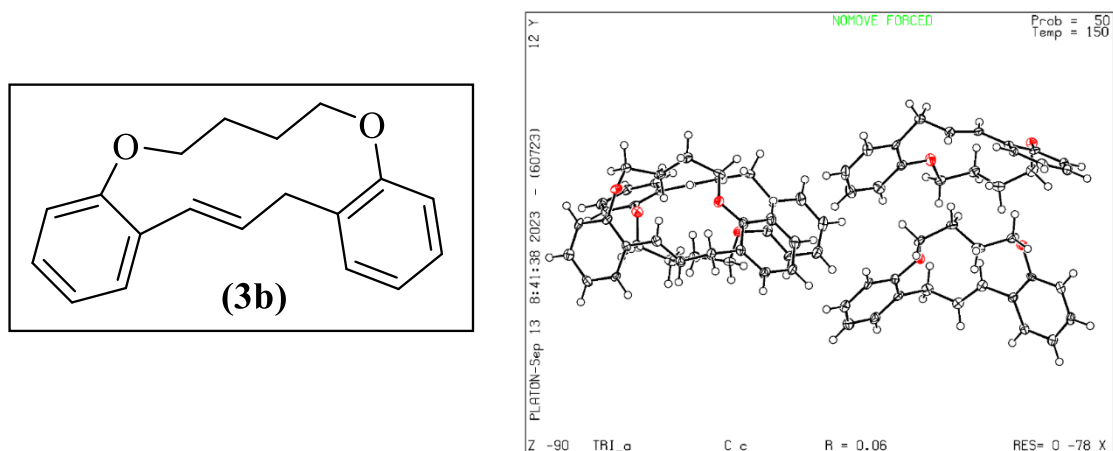


Figure 127. ORTEP crystal structure of 157b showing thermal ellipsoids at the 50% probability level:

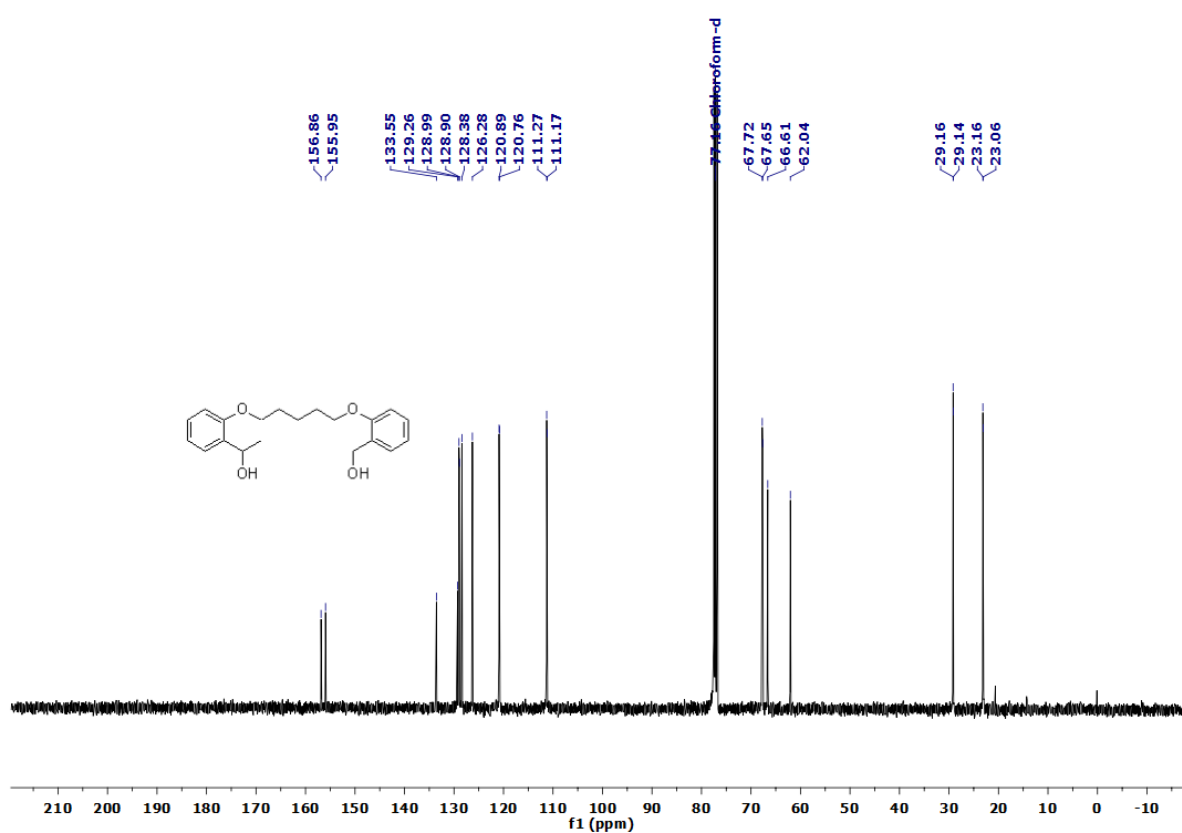
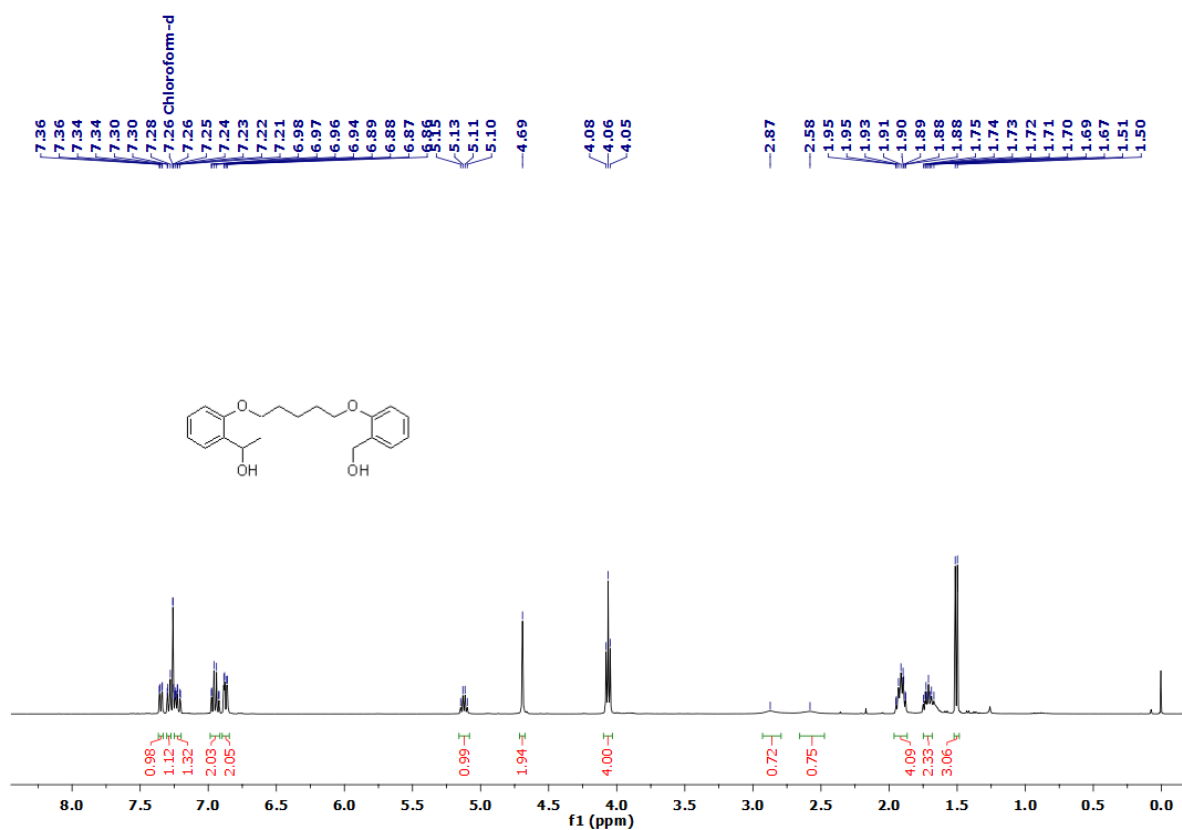
Crystallographic parameters of **3b**:

Parameters	157b
Empirical formula	C ₁₉ H ₂₀ O ₂
Formula Mass/g mol	280.35
Experimental crystal description	Crystalline Solid
Colour	white
D _{calcd} /g cm ⁻³	1.289
Crystal system	Monoclinic
Space group	C c
<i>a</i> / Å	11.5864(15)

b/ Å	11.5914(13)
c/ Å	43.019(5)
α / deg	90
β / deg	90.267(4)
γ / deg	90
V/Å ³	5777.5(12)
Z	16
T / K	150 K
Diffraction Source	MoK\alpha
Diffraction radiation wavelength/ Å	0.71073
Diffraction reflection theta full	0.996
Reflection number total	8244
Reflection number gt	7355
μ /mm-1	0.0582
F(000)	2400.0
R ₁ ,wR ₂ [I>2 σ (I)]	0.0582,
	0.1739
R ₁ ,wR ₂ (all data)	0.0665,
	0.1845
GoF	0.775

4.10 Appendix IV: Copies of ^1H and ^{13}C NMR Spectra of Representative Compounds

Entry	Data	Figure No
156a	^1H and ^{13}C	84-85
156b	^1H and ^{13}C	86-87
157a	^1H and ^{13}C	88-89
157b	^1H and ^{13}C	90-91
158a	^1H and ^{13}C	92-93
159a	^1H and ^{13}C	94-95
159b	^1H and ^{13}C	96-97
160a	^1H and ^{13}C	98-99
160b	^1H and ^{13}C	100-101
160c	^1H and ^{13}C	102-103



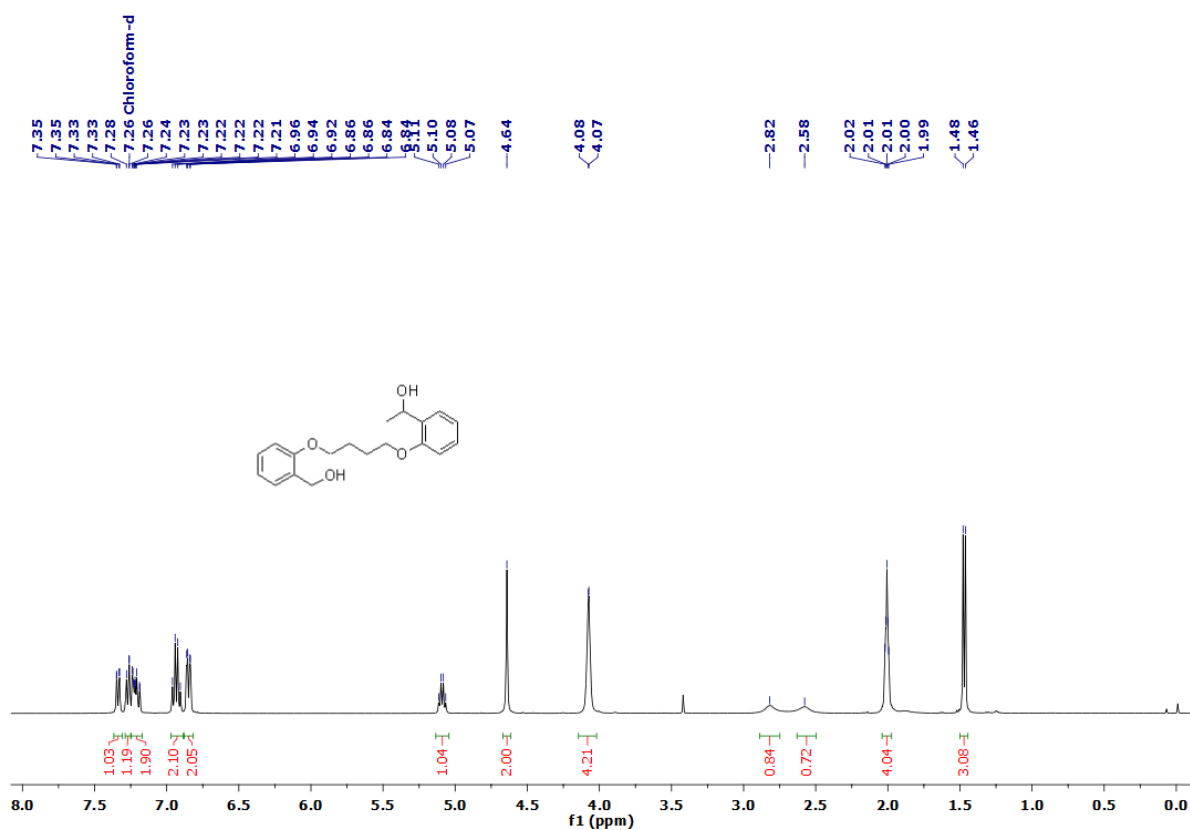


Figure 86. ¹H NMR spectra for compound **156b**, 400 MHz, CDCl₃

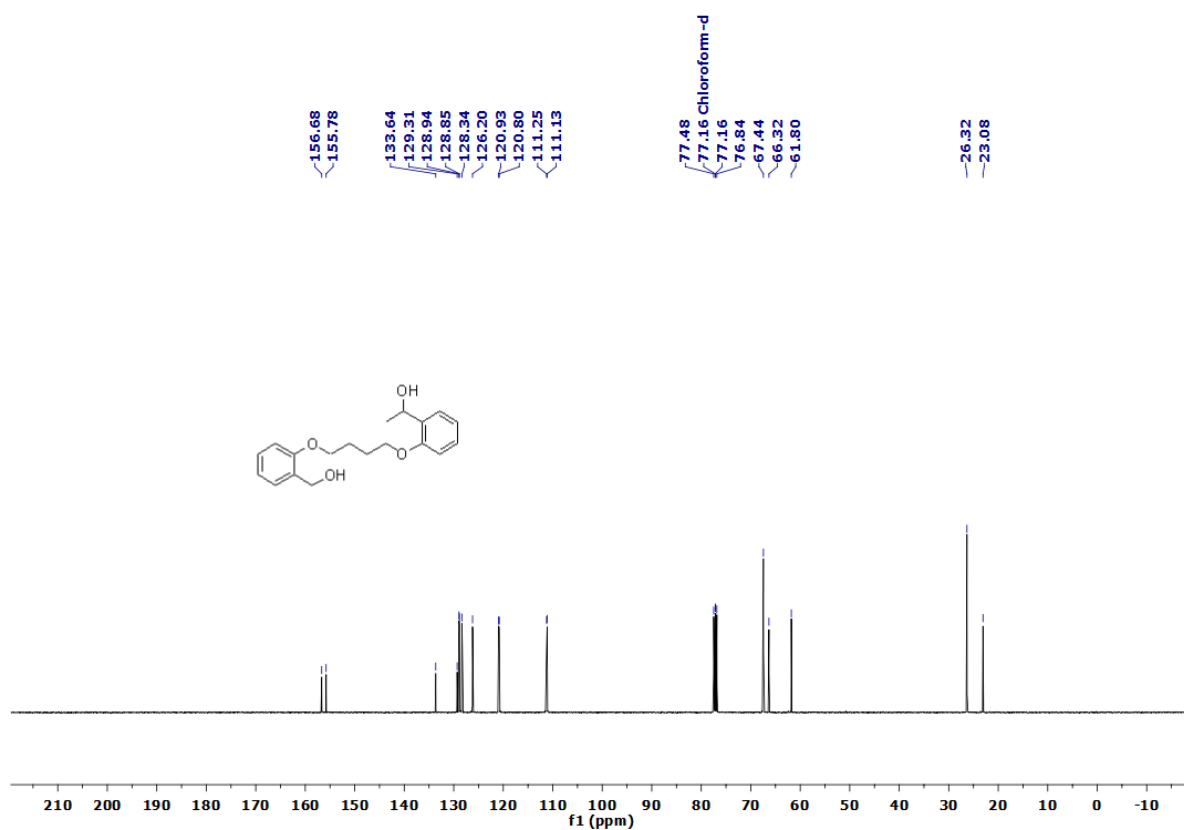
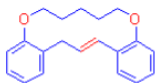


Figure 87. ¹³C NMR spectra for compound **156b**, 100 MHz, CDCl₃



Chemical structure: O=C1C=CC(OC2=CC=C(C=C2)OC3=CC=CC=C3C(=O)C4=CC=CC=C4OC5=CC=CC=C5C=C5)C=C1

¹³C NMR peaks (ppm):

- 157.62, 157.34 (Aromatic carbonyl carbons)
- 131.85, 130.57, 128.96, 128.20, 128.11, 127.63, 126.57, 121.13, 120.33, 113.98, 110.95 (Aromatic and alkene carbons)
- 77.48, 77.36, 77.16, 76.84, 69.37, 65.83 (Solvent and ether carbons)
- 37.30, 28.27, 27.94, 22.26 (Alkyl carbons)

240

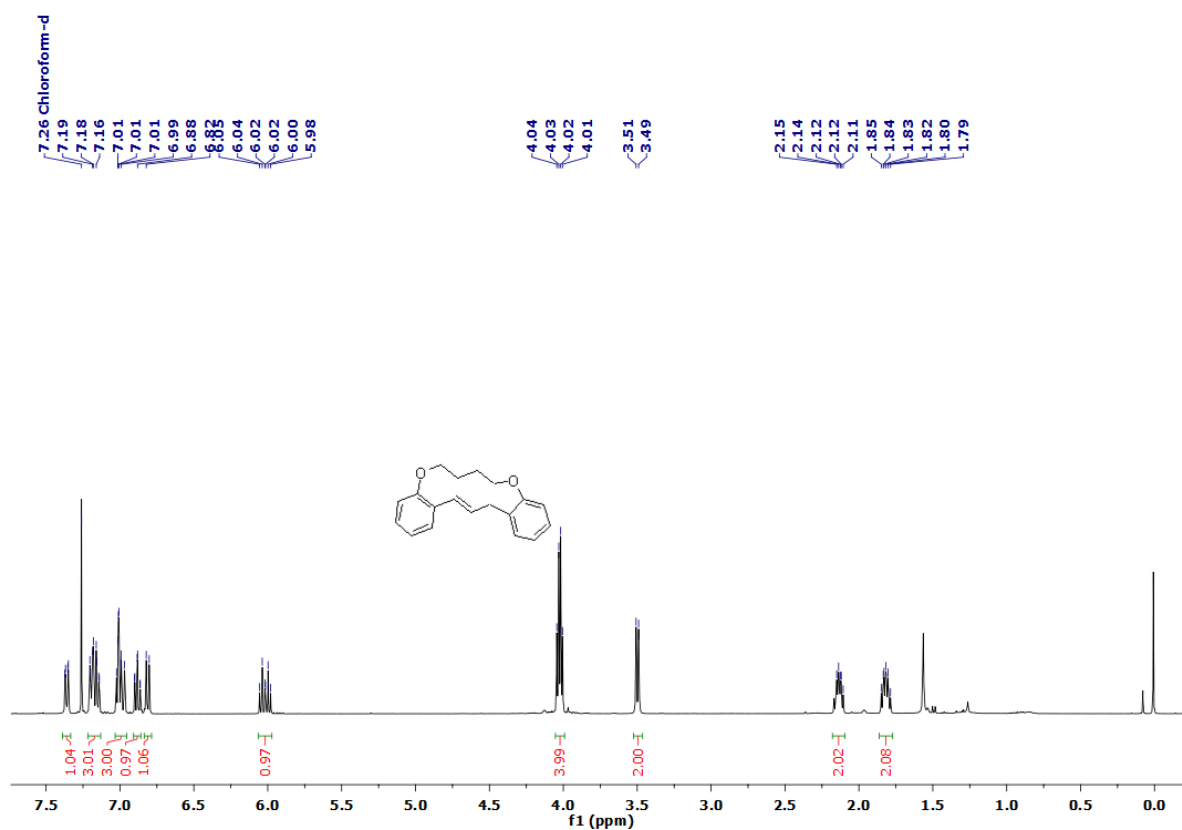


Figure 90. ¹H NMR spectra for compound **157b**, 400 MHz, CDCl₃

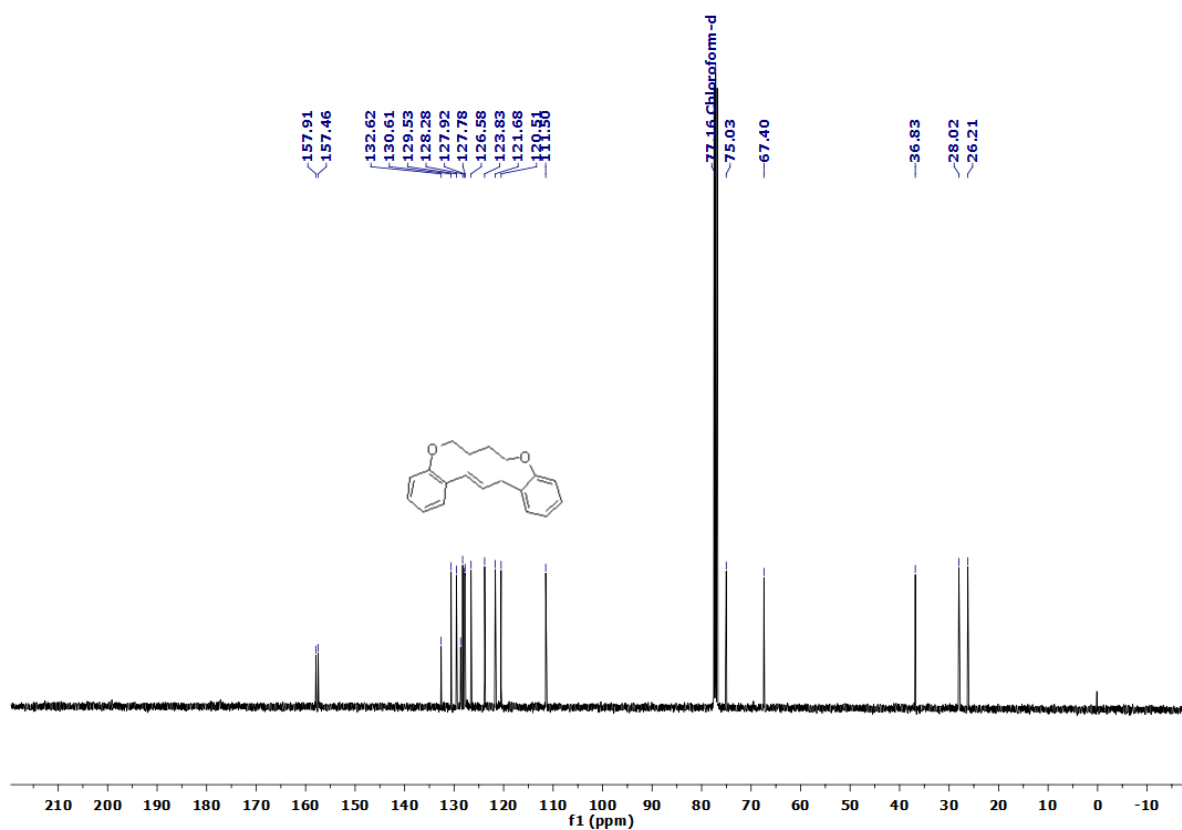


Figure 91. ¹³C NMR spectra for compound **157b**, 100 MHz, CDCl₃

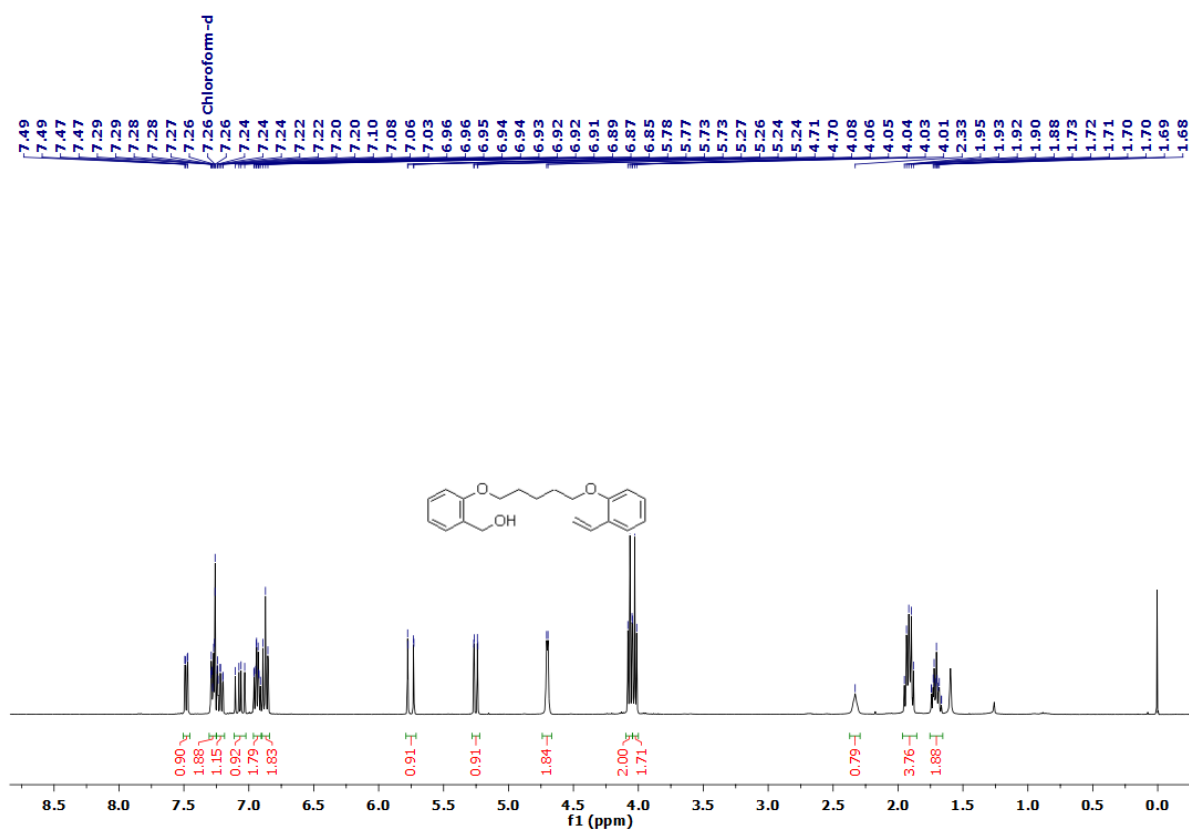


Figure 92. ¹H NMR spectra for compound **158a**, 400 MHz, CDCl₃

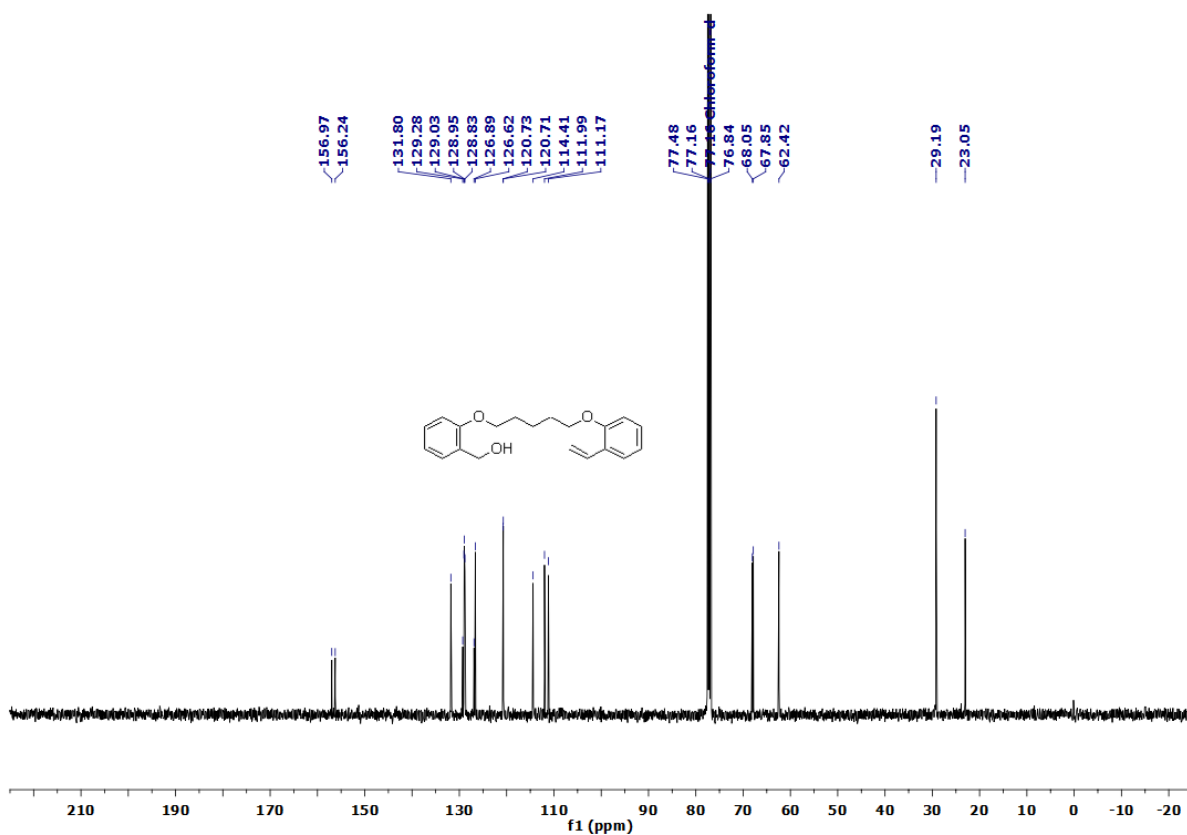


Figure 93. ¹³C NMR spectra for compound **158a**, 100 MHz, CDCl₃

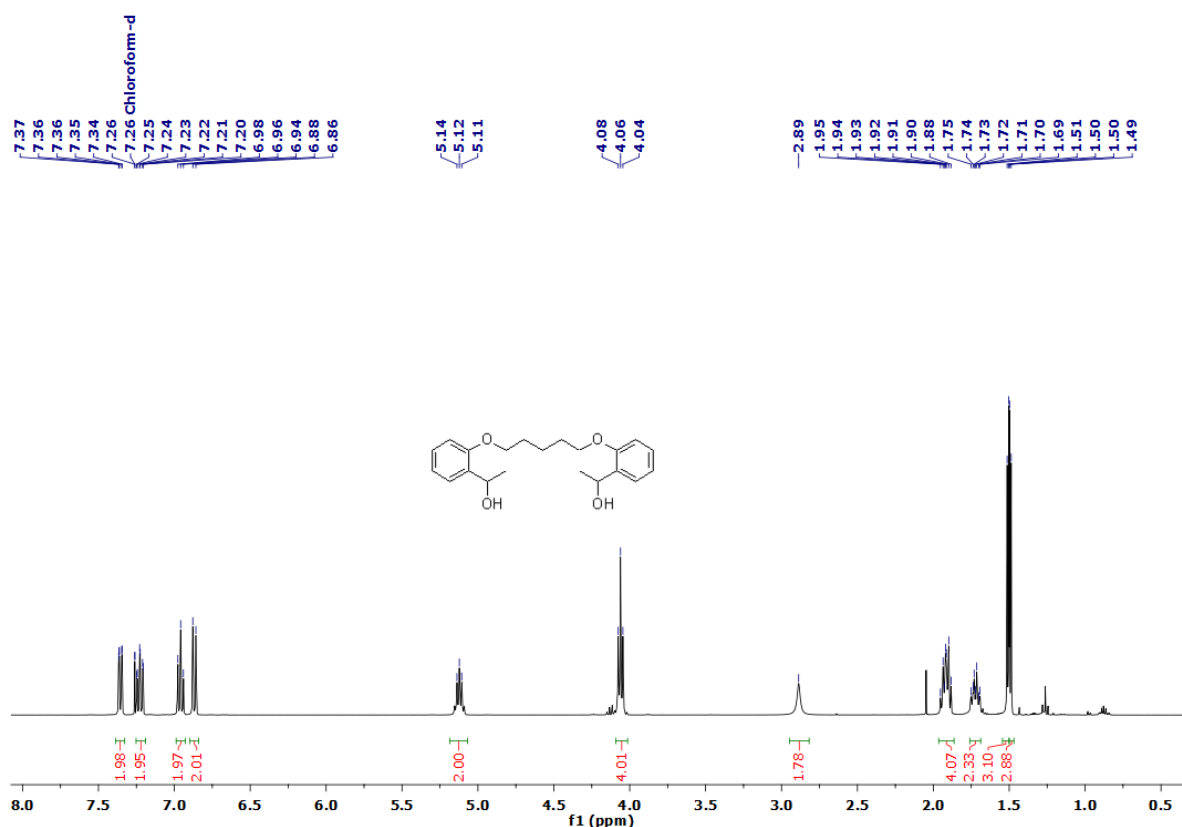


Figure 94. ¹H NMR spectra for compound **159a**, 400 MHz, CDCl₃

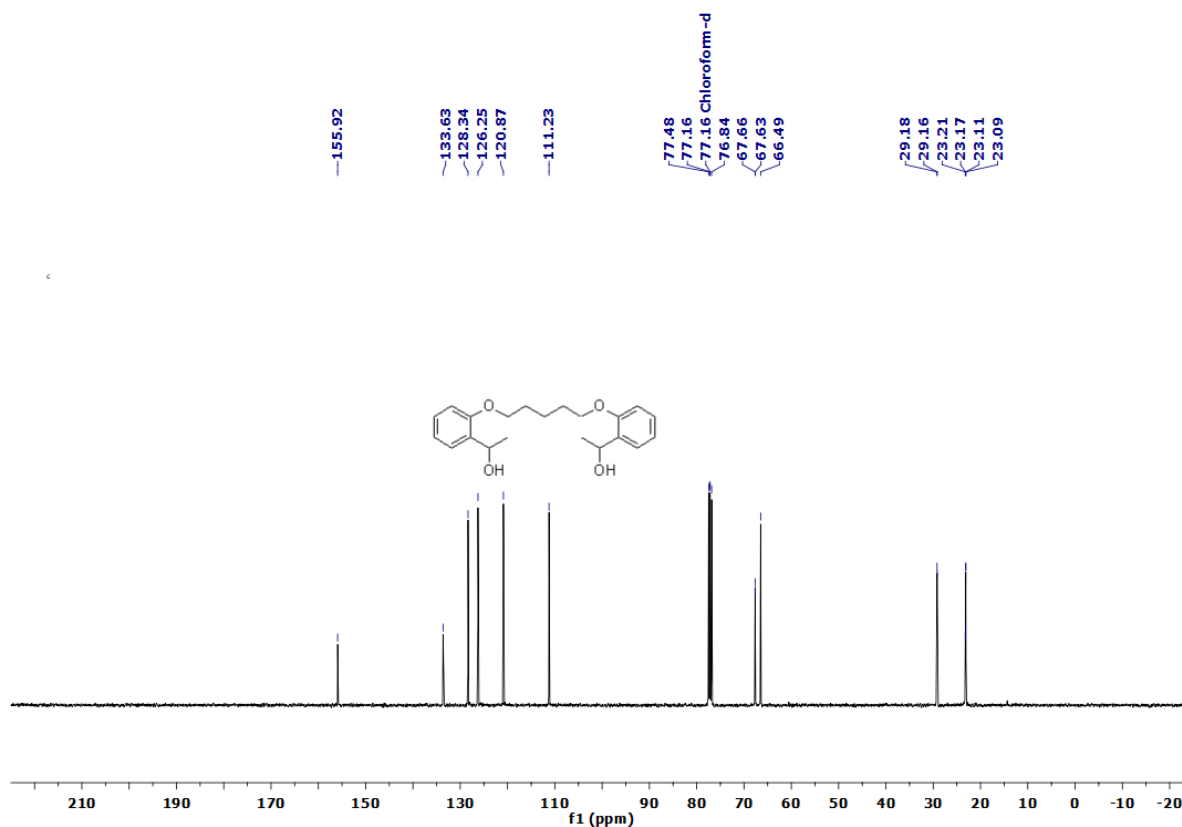


Figure 95. ¹³C NMR spectra for compound **159a**, 100 MHz, CDCl₃

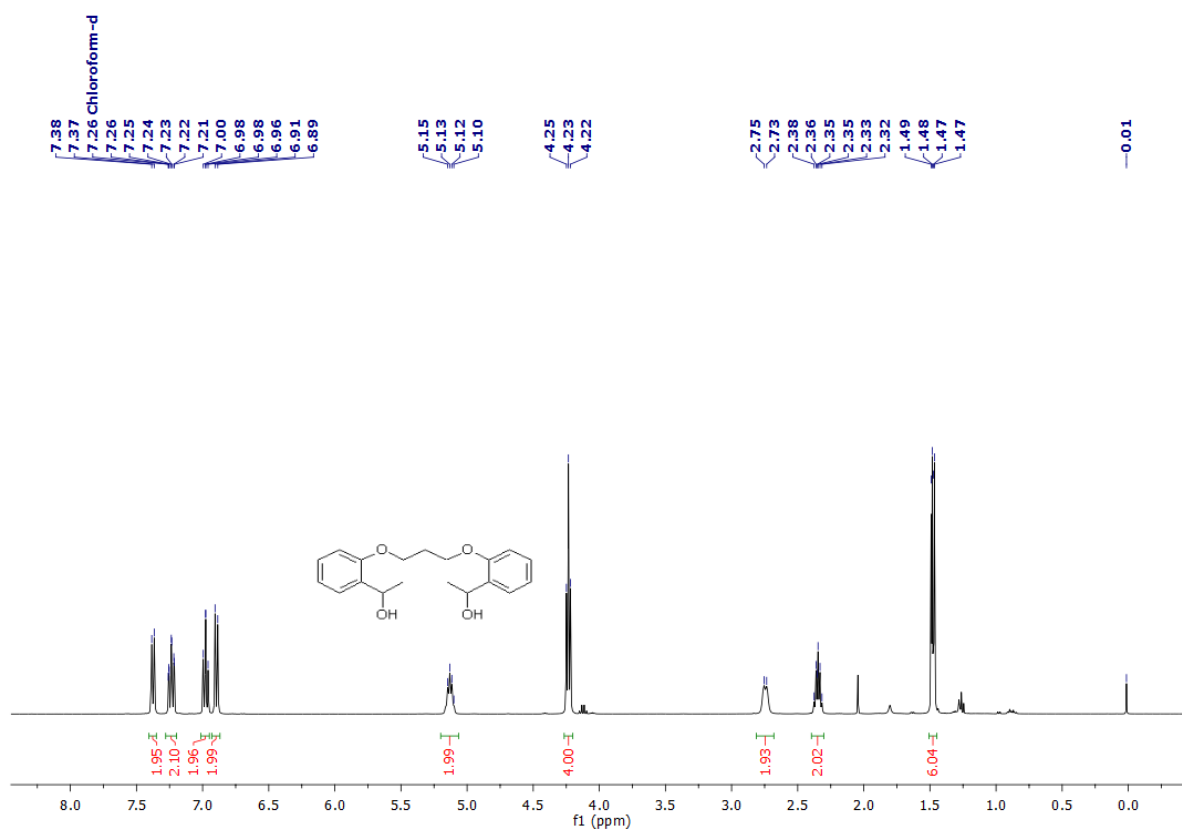


Figure 96. ¹H NMR spectra for compound **159b**, 400 MHz, CDCl₃

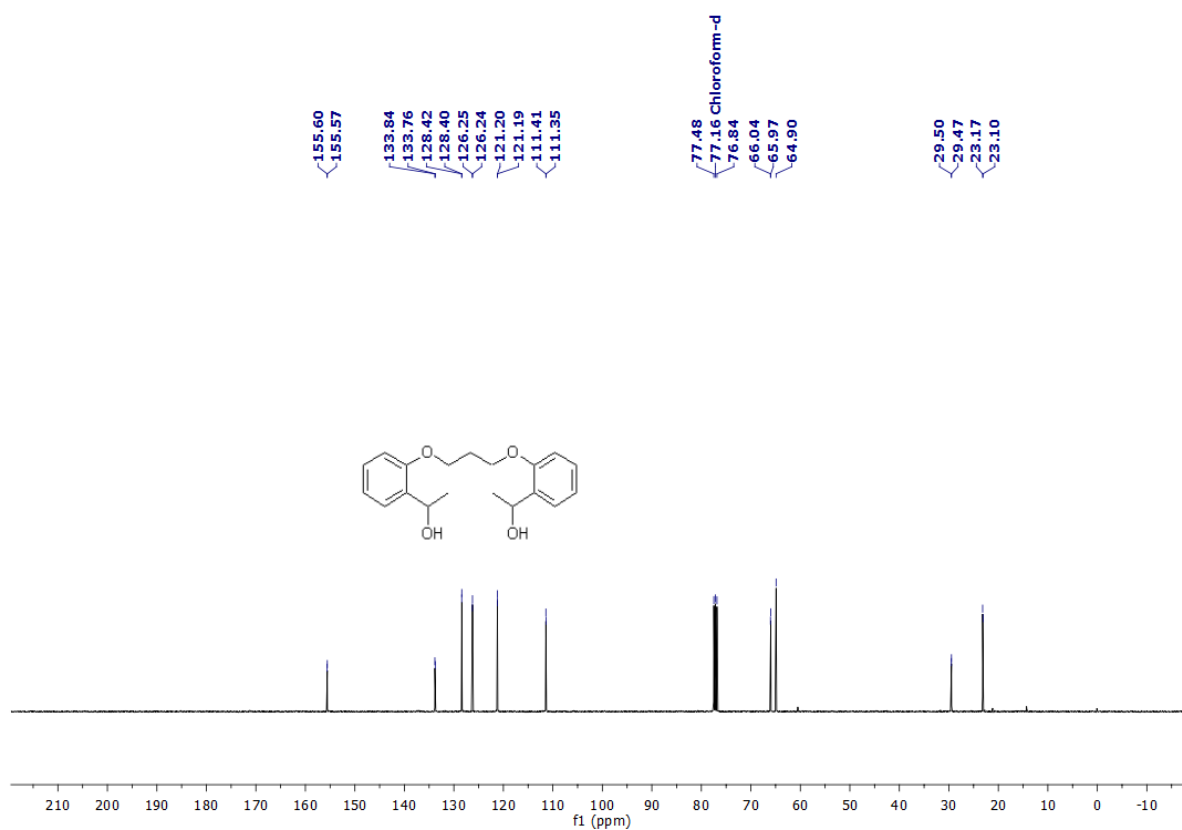


Figure 97. ¹³C NMR spectra for compound **159b**, 100 MHz, CDCl₃

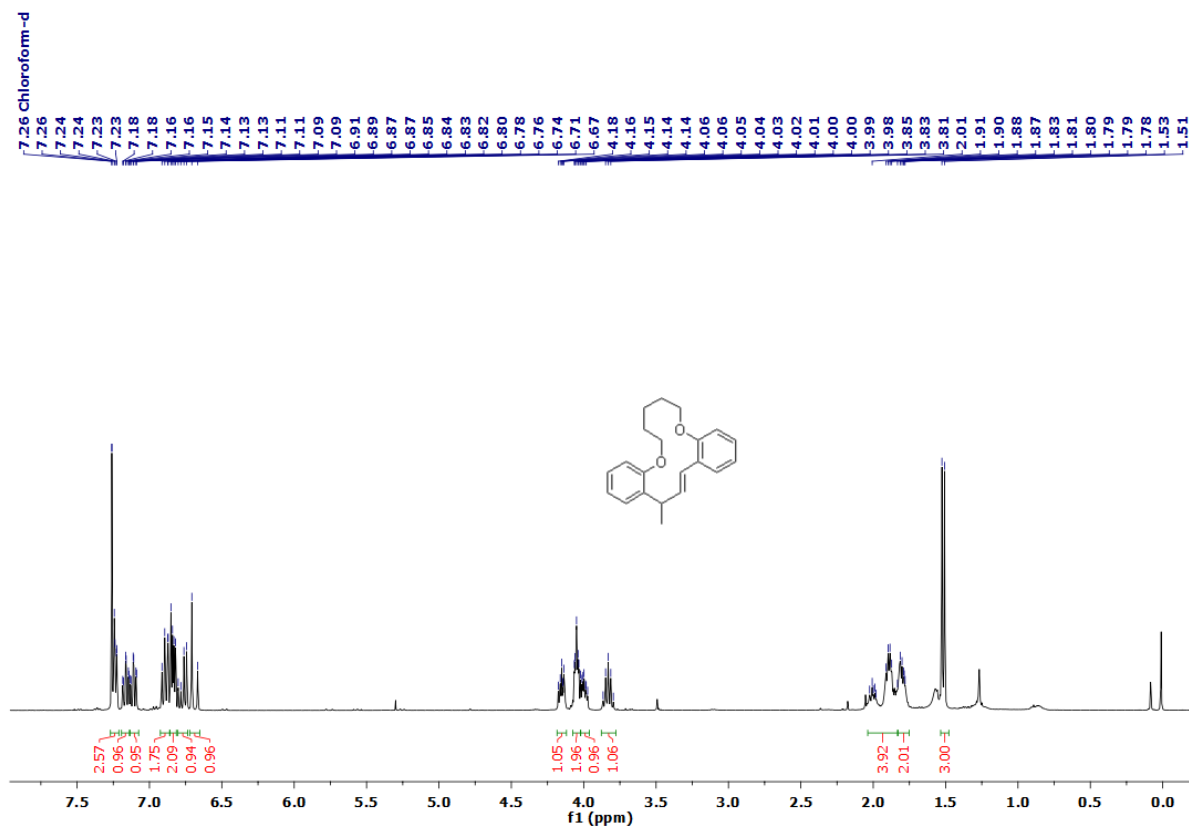


Figure 98. ¹H NMR spectra for compound **160a**, 400 MHz, CDCl₃

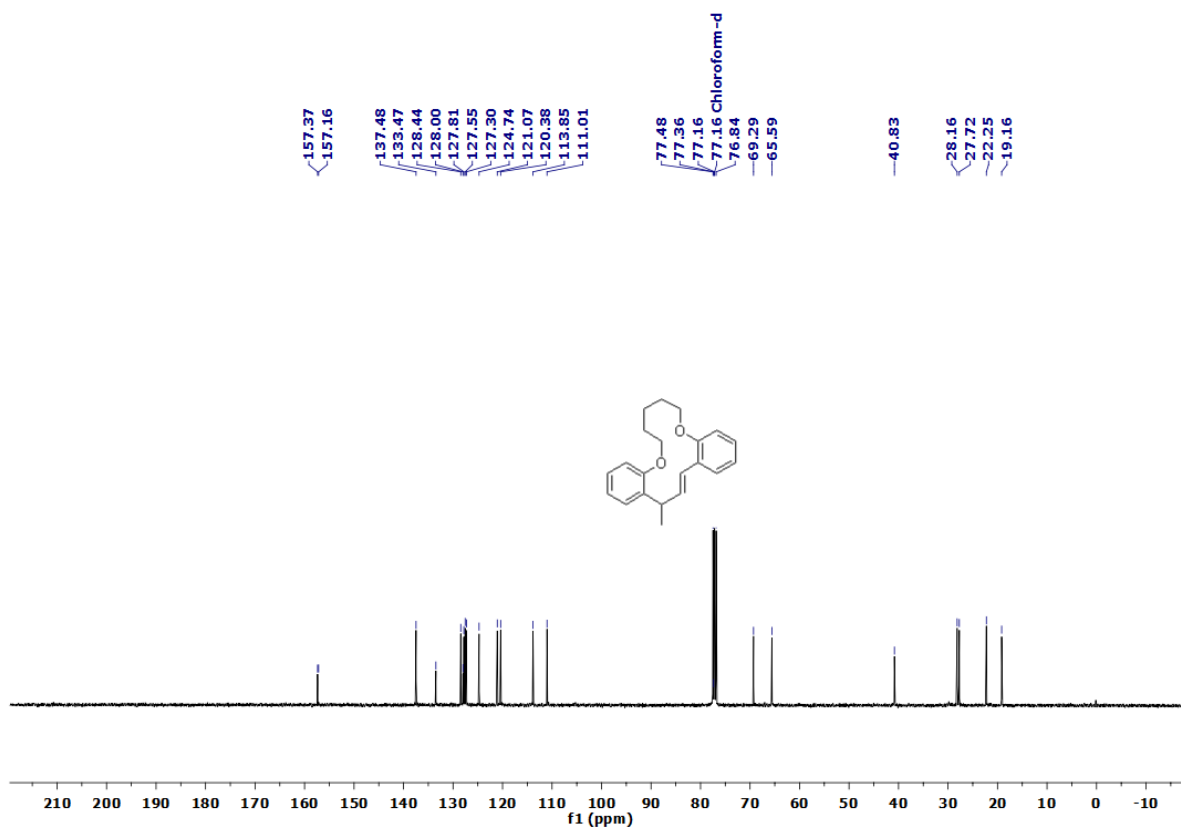


Figure 99. ¹³C NMR spectra for compound **160a**, 100 MHz, CDCl₃

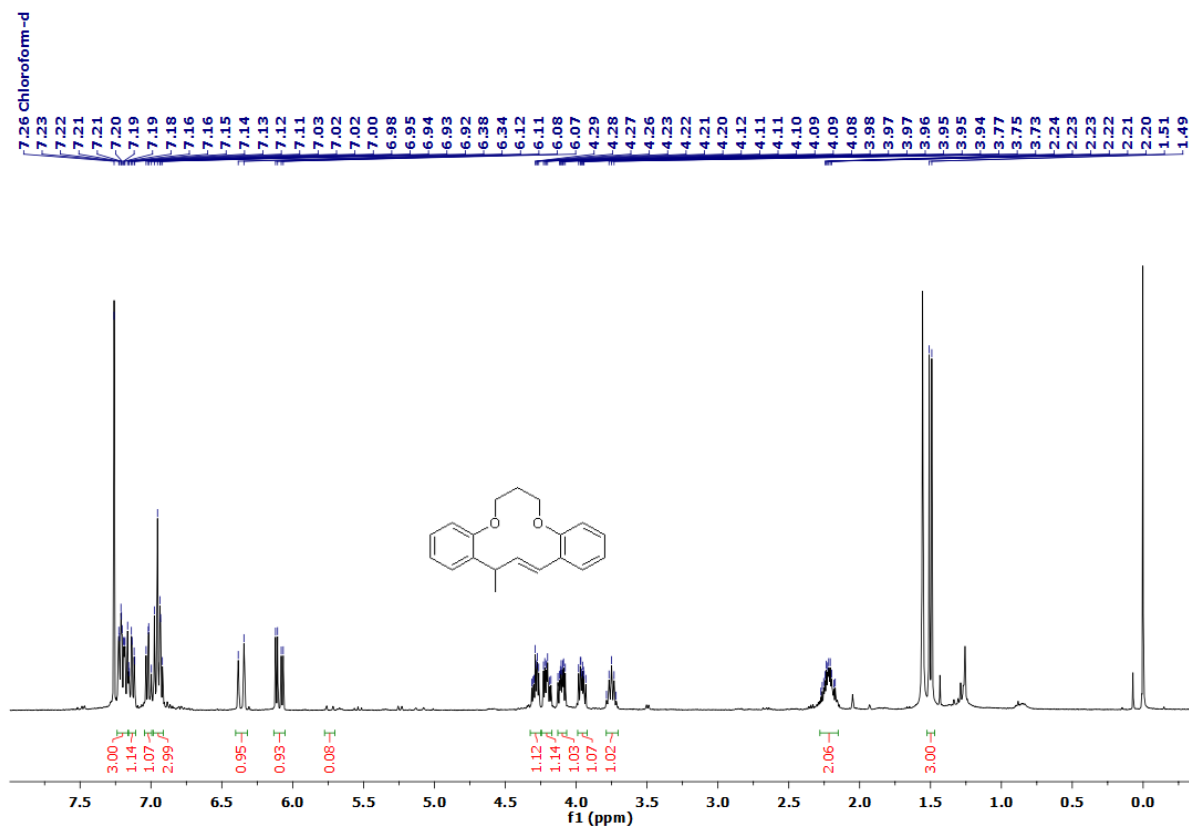


Figure 100. ¹H NMR spectra for compound **160b**, 400 MHz, CDCl₃

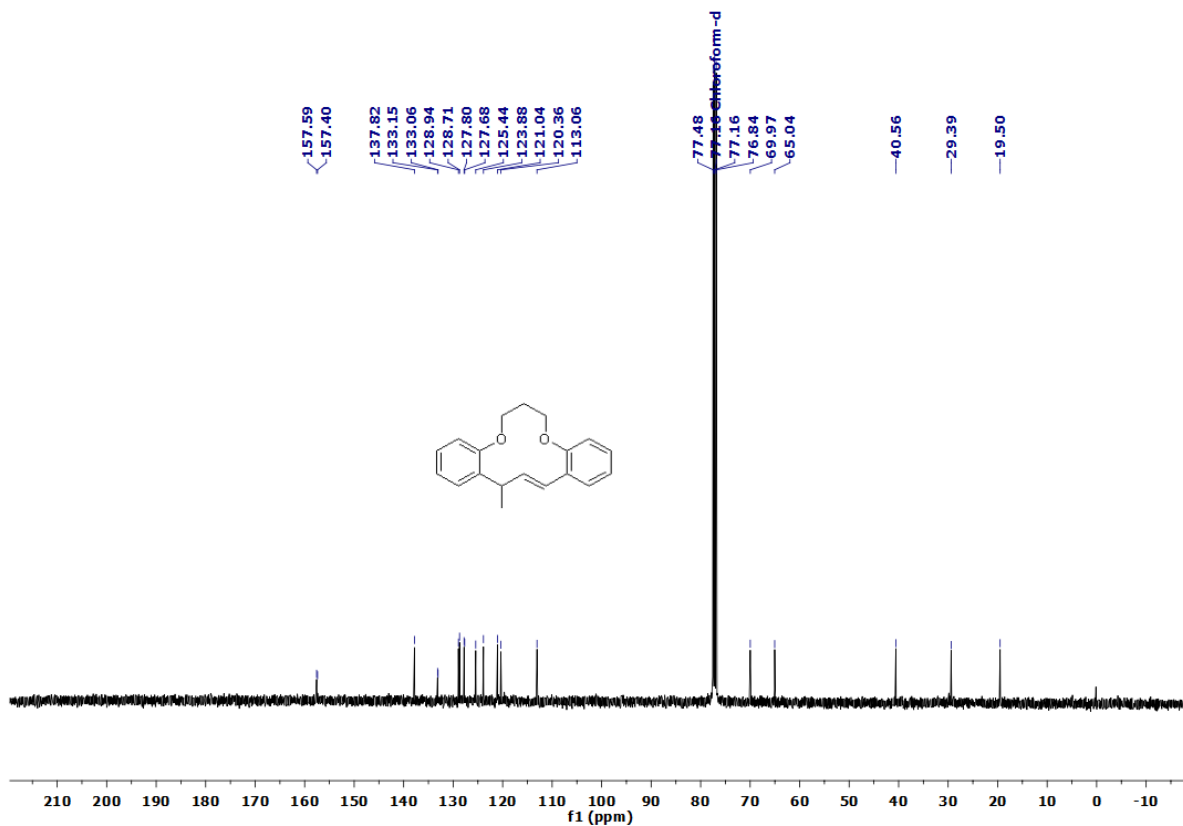
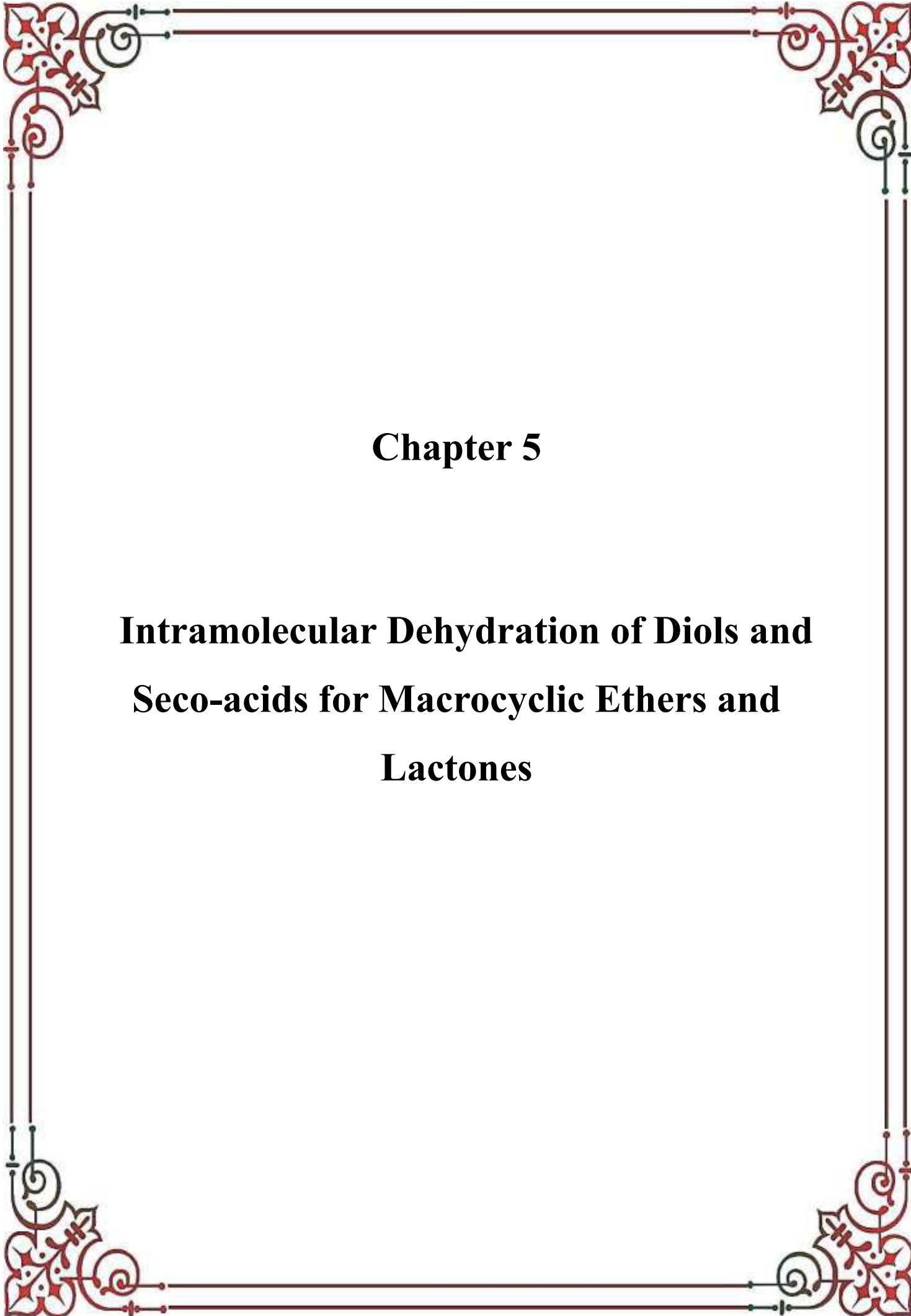


Figure 101. ¹³C NMR spectra for compound **160b**, 100 MHz, CDCl₃



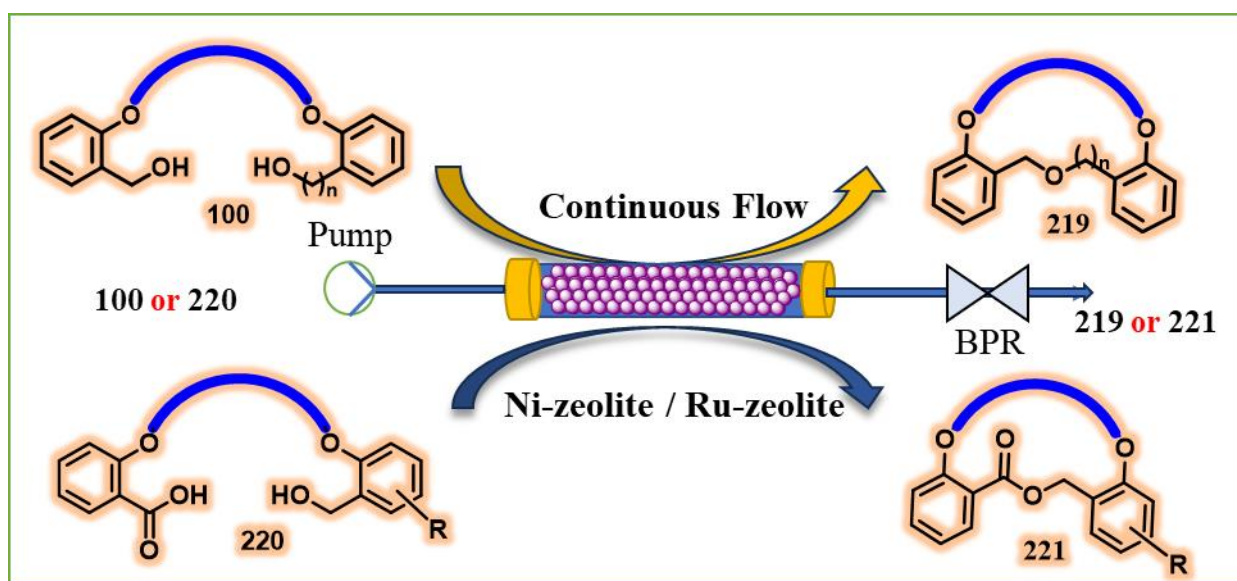
Chapter 5

Intramolecular Dehydration of Diols and Seco-acids for Macrocyclic Ethers and Lactones

5. Intramolecular Dehydration of Diols and Seco-acids for Macrocyclic Ethers and Lactones

5.1 Abstract

In this chapter, we have presented a highly effective method for the intramolecular dehydrative coupling of symmetrical and unsymmetrical diols to synthesize macrocyclic ethers, utilizing a heterogeneous Ni-Zeolite catalyst under a continuous flow system. Additionally, this technique proves to be an efficient protocol for the intramolecular dehydrative macrolactonization of seco-acids using either Ni-Zeolite or Ru-Zeolite catalysts. This approach under continuous flow is broadly applicable, with a wide range of substrates passed through a one-time packed Ni-Zeolite, resulting in the production of 20 macrocyclic polyethers and 11 examples of macrolactones, with water as the sole byproduct.



5.2 Introduction to Macrocyclic Ether

Macrocyclic ether compounds are significant synthetic targets due to their wide applications in organic/inorganic chemistry and material science.^{39,40} Moreover, these polyethers are used as phase transfer catalysts¹⁶⁰ and have ion selectivity to trap various metal ions.⁴¹ In addition, various macrocyclic ethers have special cavity diameters that offer better binding with cancer cells¹⁶¹ and serve as supramolecular receptors.¹⁶² For example, monosaccharide-based¹⁶³ crown ether **195** is used in catalysis reactions, and aza-crown ethers

196, used for cancer treatments¹⁶⁴ (Scheme 61). Notably, several crown ethers have shown biological applications, such as anticancer, antifungal, and antimalarial activities¹⁷². This makes them valuable in drug discovery.

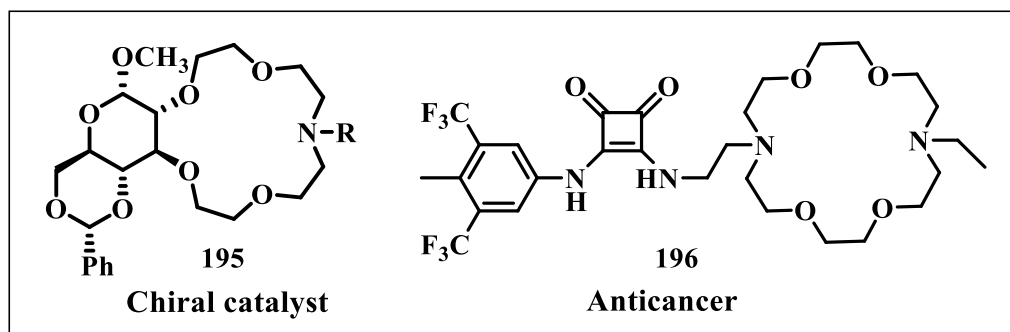
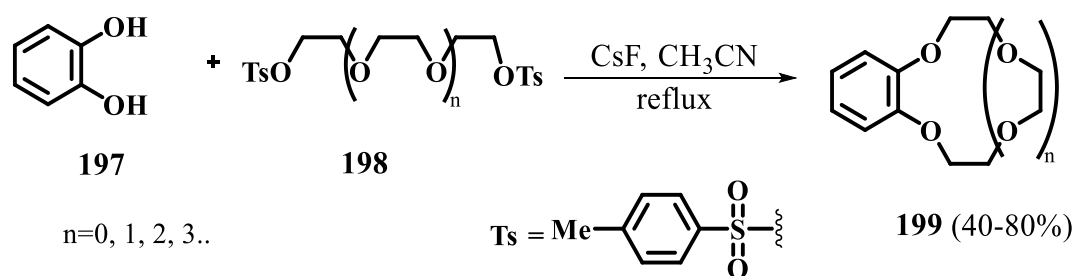


Figure 104. Application of macrocyclic polyether

In this context, several reports are available for inter- or intramolecular macrocyclic etherification *via* catalytic and non-catalytic reactions.

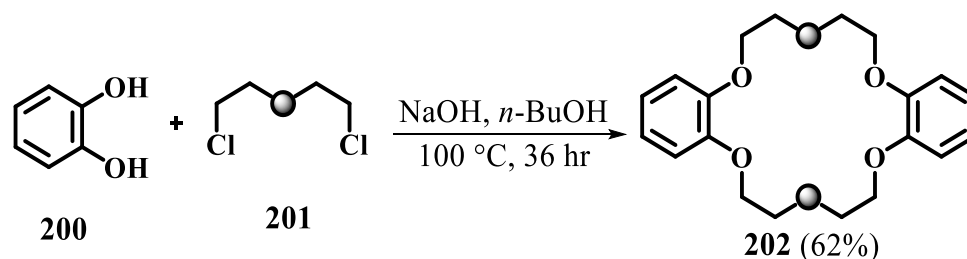
5.3 Literature Report on Macrocyclic Etherification

The examples given below include, both inter and intramolecular macrocyclic etherification *via* nucleophilic substitution reactions. In 1885, Bartsch and coworkers synthesized various macrocyclic ethers **199** using catechol **197** and a tosylated diol **198** in the presence of caesium fluoride (CsF). This reaction was conducted under reflux conditions in acetonitrile (CH₃CN) solvent to provide moderate to good yield of macrocyclic ethers **199** (Scheme 88).¹⁶⁵



Scheme 88. Bartsch's approach for synthesizing macrocyclic ethers

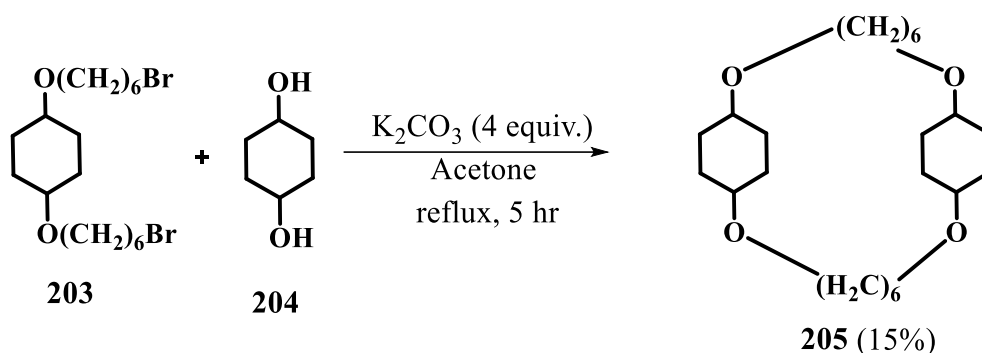
Next, in 1967 Pedersen synthesized macrocyclic polyethers by using catechol **200** and



Scheme 89. Pedersen's methodology for crown ether synthesis

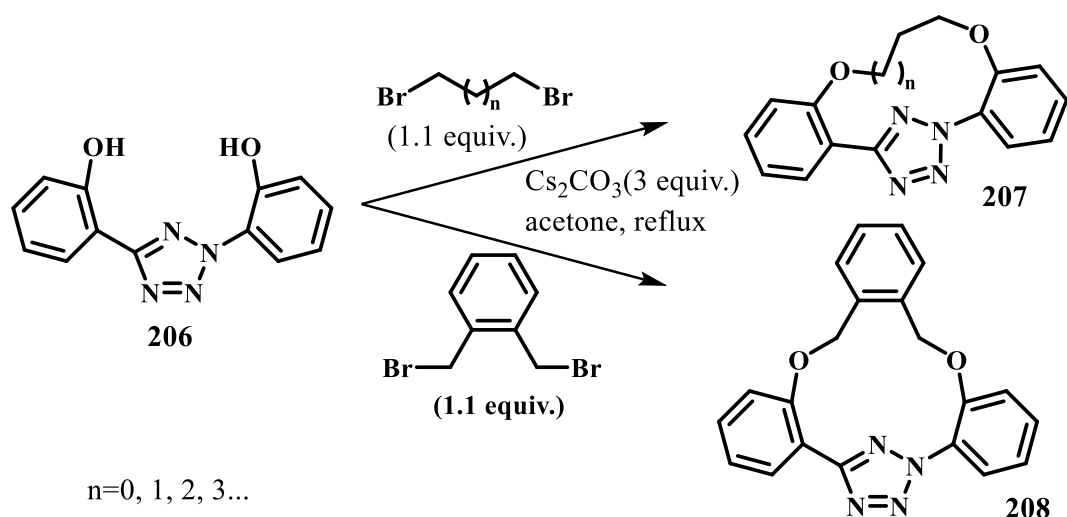
bis(2-chloroethyl) ether **201** in the presence of sodium hydroxide as a base and butanol as a solvent, to produce dibenzo-18-crown-6 **202** in 62% yield (Scheme 89).¹⁶⁶

In 1941, Adams and Whitehell synthesized a macrocyclic ether by refluxing hydroquinone **204** with a dibromo compound **203** in the presence of potassium carbonate (K_2CO_3) in acetone solvent for 5 hrs. This reaction afforded macrocyclic ethers **205** in 15% yield (Scheme 90).¹⁶⁷



Scheme 90. Intermolecular macrocyclic ether synthesis

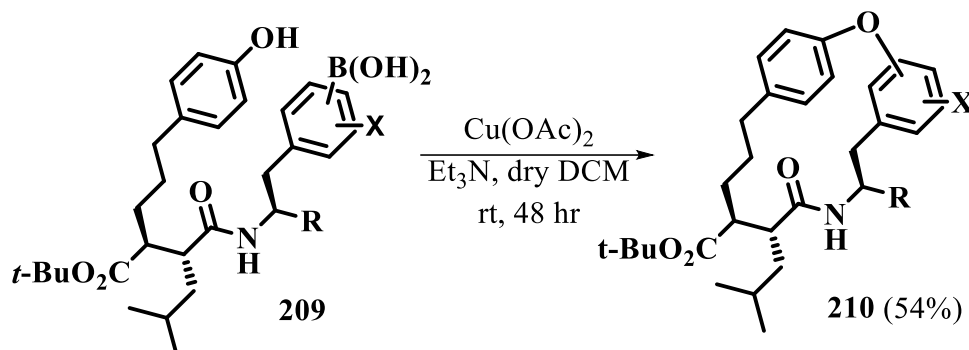
Next, the classical S_N2 reaction involving bis-*O*-alkylation was used to synthesize **207** or **208**. This was achieved by refluxing tetrazole **206** with dibromo alkanes (1.1 equiv.) and Cs_2CO_3 (3 equiv.) in acetone. This reaction procedure was reported by Qing Lin and coworkers as in Scheme 91.¹⁶⁸



Scheme 91. Synthesis of the macrocyclic compounds *via O*-alkylation

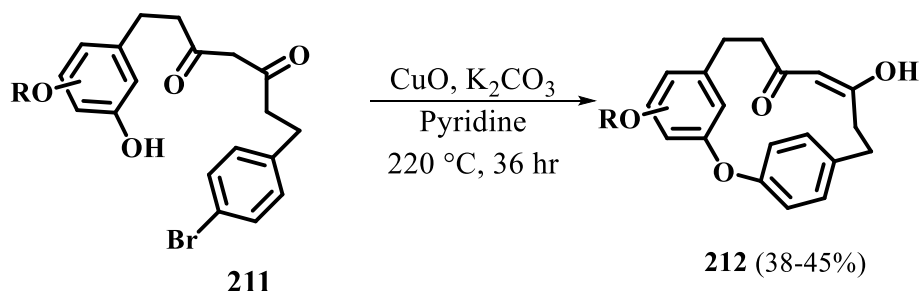
These traditional approaches required stoichiometric base, genotoxic halides/mesylate/tosylate as substrates, and resulted in formation of copious waste, which make them non-sustainable and less atom economic reactions. On the other hand, very few catalytic methods for macrocyclic etherification have been reported in the last few decades.

In 2001, Decicco and coworkers reported the Cu-mediated synthesis of macrocyclic biphenyl ether using intramolecular *O*-arylation of phenols with phenylboronic acid **209**. This reaction involved the use $\text{Cu}(\text{OAc})_2$, and triethylamine as a base in dry DCM, at room temperature for 48 hr obtained in a 54% yield of **210** (Scheme 92).¹⁶⁹



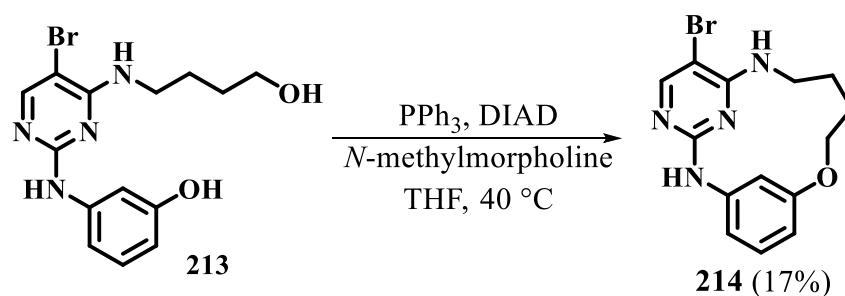
Scheme 92. Synthesis of the macrocyclic compounds *via O*-arylation

Next, Beaudry and colleagues conducted macrocyclic etherification by employing the intramolecular Ullmann coupling of phenol and aryl halide **211** under harsh reaction conditions (Scheme 64). They utilized CuO as a catalyst and K_2CO_3 as a base in pyridine solvent at 120 °C, to furnish product **212** in 38-45% yield (Scheme 93).¹⁷⁰



Scheme 93. Intramolecular Ullmann coupling reaction for etherification

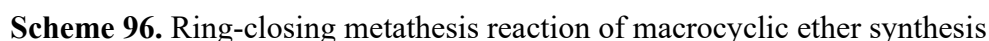
Furthermore, Lücking and colleagues utilized Mitsunobu reaction conditions to deliver **214**. In this reaction, they employed **213** in the presence of triphenylphosphine and diisopropyl azodicarboxylate (DIAD) in THF solvent, resulting in 17% yield of **214** (Scheme 94).¹⁷¹



Scheme 94. Mitsunobu reaction conditions for the synthesis ether bond



Grubbs and coworkers reported the synthesis of an ether compound using ring-closing metathesis. In this process, the macrocyclic alkene **217** was refluxed with a ruthenium catalyst, resulting in the formation of the **218** in 50% yield (Scheme 96).¹⁷³



5.4 Aim and Rationale of Work

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activators or special reactants/conditions. Furthermore, homogeneous catalytic systems have been well studied for the direct etherification of alcohols *via* dehydrative coupling. Many of these catalytic reactions are limited to form acyclic and small cyclic ethers.¹⁸³ However, there are no reports for the intramolecular catalytic dehydrative macrocyclization using symmetrical and unsymmetrical diols.

We aim to synthesize macrocyclic ethers from symmetrical/unsymmetrical diols using reusable heterogeneous catalysts under continuous flow conditions. In the previous chapter, we have revealed the efficiency of Ni-Zeolite as a catalyst for double dehydrative coupling to form C=C bonds in macrocyclic alkenylation. In this chapter, we describe the Ni-Zeolite catalyzed dehydrative coupling of diols to form macrocyclic polyethers under continuous flow conditions. Additionally, we extend this scope for macrocyclic lactones synthesis *via* dehydrative intramolecular coupling to form seco-acids using Ru-Zeolite as a recyclable catalyst under continuous flow.

5.5 Result and Discussion

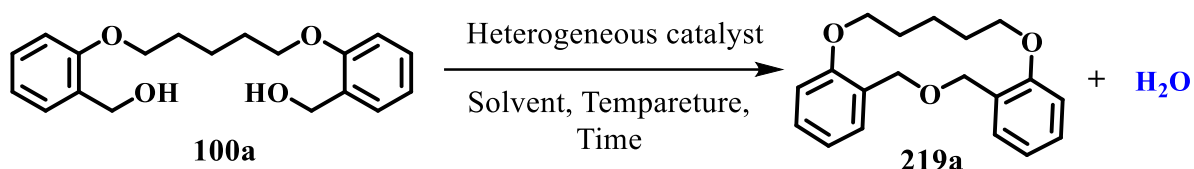
We began our research by synthesizing macrocyclic ether compound **219a** from diphenyldimethanol **100a**, employing a heterogeneous metal-Zeolite catalyst under both batch and continuous flow conditions. The starting material was subjected to various reaction conditions, including different catalysts, temperatures, and solvents, in both batch and flow setups. Through comprehensive screening, we identified Ni-Zeolite catalyst and 1, 4-dioxane as an effective solvent under batch/flow conditions. With these results, we proceeded with optimization studies under both batch and flow conditions, aiming to maximize yield and facilitate large-scale production of the macrocyclic ether.

5.5.1 Optimization for the Macrocyclic Ether under Batch Conditions

We commenced the optimization study by preparing various metal-Zeolite based catalysts (Fe-Zeolite, Ni-Zeolite, and Ru-Zeolite) using the reported procedure.¹⁵⁷ Initially, diphenyldimethanol **100a** was employed as a model substrate to synthesize the macrocyclic ether **219a**, by examining various solvents, temperatures, and heterogeneous/homogeneous catalysts under batch reaction conditions. Use of 2.83% Fe-Zeolite (w/w = weight of starting material by weight of catalyst) in toluene was heated at 160 °C for 24 hr to provide 8% of **219a** (Table 5.1, entry 1). Switching the solvent to 1,4-dioxane increased the yield to 10% (Table 5.1, entry 2). Further, an improvement to 16% yield was achieved when 2.85% Ni-Zeolite employed as a catalyst at 120 °C (Table 5.1, entry 3). Increasing the catalyst concentration to

w/2w and w/3w did not significantly alter the yield (Table 5.1, entries 4 and 5). A control experiment with β -Zeolite alone resulted in only trace amounts of **219a** (Table 5.1, entry 6). Metal precursor such as $\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$, $\text{NiCl}_2 \cdot 6\text{H}_2\text{O}$, and $\text{RuCl}_3 \cdot x\text{H}_2\text{O}$ produced poor yields (Table 5.1, entries 7, 8, 9), and no product was formed with NiO as the catalyst (Table 5.1, entry 10).

Table 5.1. Optimization for the macrocyclic ether under batch conditions



Entry	Catalyst	Solvent	Temp (°C)	Yield of 219a (%)
1 ^a	Fe-Zeolite	Toluene	160	8
2 ^a	Fe-Zeolite	1,4-dioxane	160	10
3 ^a	Ni-Zeolite	1,4-dioxane	120	16
4 ^b	Ni-Zeolite	1,4-dioxane	120	18
5 ^c	Ni-Zeolite	1,4-dioxane	120	18
6 ^b	β -Zeolite	1,4-dioxane	120	NR
7 ^b	$\text{NiCl}_2 \cdot 6\text{H}_2\text{O}$	1,4-dioxane	120	5
8 ^b	$\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$	1,4-dioxane	120	5
9 ^b	$\text{RuCl}_3 \cdot x\text{H}_2\text{O}$	1,4-dioxane	120	4
10 ^a	NiO	1,4-dioxane	120	NR

Reaction in batch conditions: Compound **100a** (0.15 mmol) in solvents (2 mL, see table 5.1) and ^a50, ^b100, ^c150 mg of catalyst were stirred in a sealed vial at various temperatures (see table 5.1) for 24 hr. The mentioned yields are isolated yields. NR= no reaction.

To address yield and scale-up issues associated with the batch process we optimized this reaction using a fixed-bed continuous flow setup. In this continuous flow system, a Vapourtec SF-10 peristaltic pump is used for continuous pumping of starting material dissolved in a solvent, An Omnifit® column (6.6 × 150 mm) was used for packing the heterogeneous catalysts. Our research group modified a heating block to provide the necessary heat. We

employed perfluoroalkoxy alkane (PFA) tubing for feeding the reactant and a back pressure regulator (BPR) to maintain the desired pressure (Figure 105).

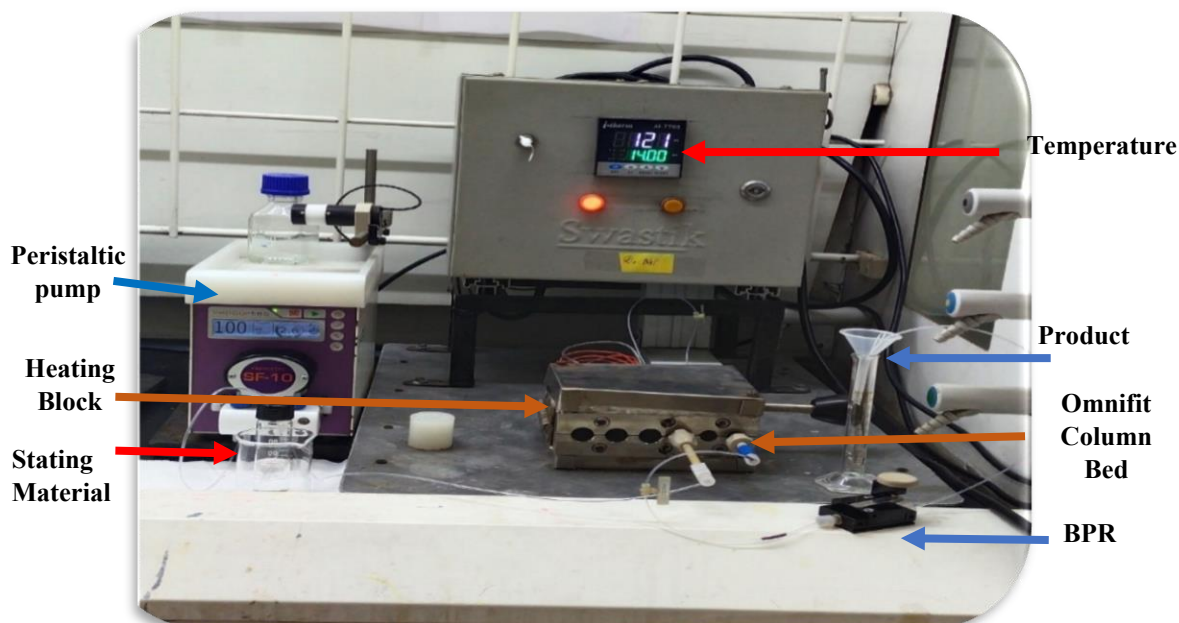


Figure 105. Customized continuous flow setup

5.5.2 Optimization for the Macrocyclic Ether under Continuous Flow Conditions

A vial containing a 0.05 M solution of **100a** in 1,4-dioxane was passed through a pre-heated (100 °C) Omnifit-packed bed reactor filled with Fe-Zeolite (1.5 gm, bed height= 5 cm) with a flow rate of 0.1 mL/min resulted in a 10% yield of the macrocyclic compound **219a** with residence time of 17.1 minutes (Table 5.2, entry 1). The structure of this compound was confirmed by single-crystal XRD (Figure 106). Further details on the crystal structure can be

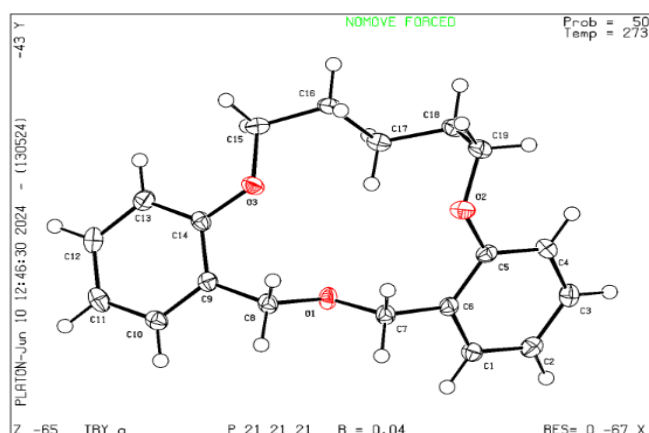
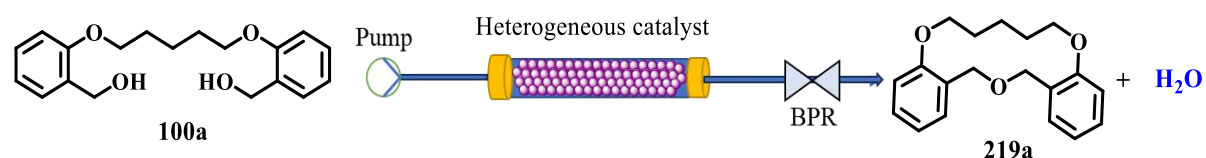


Figure 106. ORTEP crystal structure of **219a** showing thermal ellipsoids at the 50% probability level

found at the Cambridge Crystallographic Data Centre (CCDC) under deposition number 2266303.

Table 5.2. Optimization for the macrocyclic etherification in a continuous flow



Sr. No	Conc (M)	Catalyst	Residence time (t _R) min/run	Temp (°C)	Yield of 219a (%)
1 ^a	0.05	Fe-Zeolite	17.1/1	100	10
2 ^a	0.05	Fe-Zeolite	17.1/2	120	13
3 ^a	0.05	Ru-Zeolite	17.1/2	120	27
4 ^a	0.05	Ni-Zeolite	17.1/2	120	48
5 ^a	0.05	Ni-Zeolite	17.1/3	120	61
6 ^a	0.05	Ni-Zeolite	17.1/4	120	65
7 ^a	0.05	Ni-Zeolite	17.1/5	120	65
8 ^a	0.1	Ni-Zeolite	17.1/4	120	32
9 ^a	0.05	Ni-Zeolite	17.1/4	140	46
10 ^a	0.05	Ni-Zeolite	17.1/4	160	20
11 ^b	0.05	Ni-Zeolite	17.1/4	120	58
12 ^c	0.05	Ni-Zeolite	17.1/4	120	21
13 ^d	0.05	Ni-Zeolite	17.1/4	120	45
14 ^{a,e}	0.05	Ni-Zeolite	27.3/4	120	68

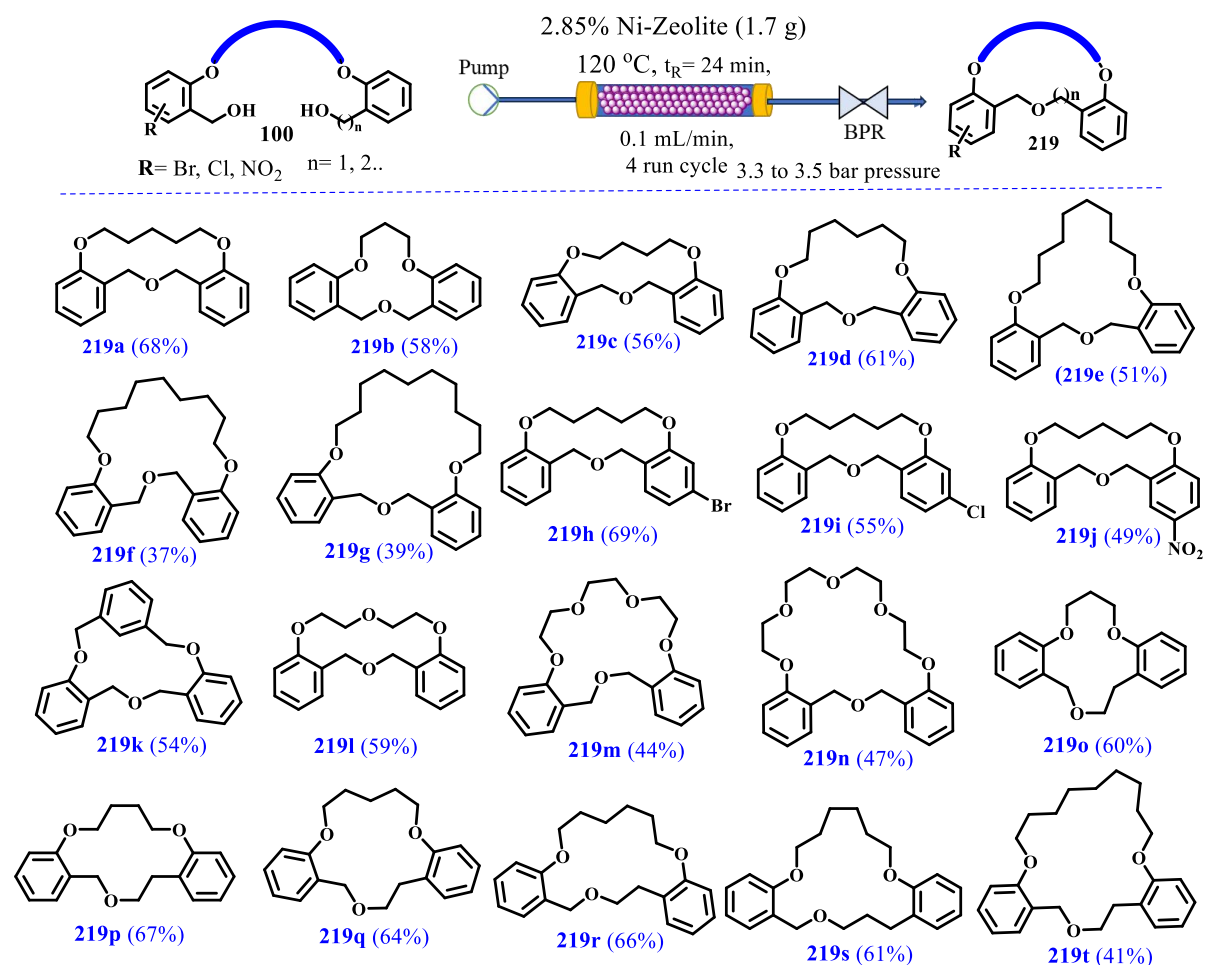
^aReaction conditions: A solution of **100a** in a 1,4-dioxane solvents was prepared and flown through (0.1 mL/min flow rate with 3-4 bar pressure), Omnifit® column (6.6 × 150 mm) containing the heterogeneous catalysts (1.5 g, 5 cm height), at specified temperatures and residence time (see table 5.2). ^bTHF, ^cbenzene, ^dtoluene was used as a solvent. ^e1.7 g, 7 cm height of catalysts used. at 3.3 to 3.5 bar back pressure. The mentioned yields are isolated yields.

Further increasing the temperature and conducting a two-run cycle with a residence time of 17.1 minutes, the yield of product **219a** increased to 13% and 27%, respectively (Table

5.2, entries 2 and 3). Using Ni-Zeolite as the catalyst, the yield of product **219a** further increased to 48% (Table 5.2, entry 4). When the run cycle was increased to 3 and 4, the yield increased to 61% and 65%, respectively, with Ni-Zeolite fixed bed as the catalyst (Table 5.2, entries 5 and 6). Increasing the run cycle to 5 times did not yield improvement (Table 5.2, entry 7). Performing the reaction with a 0.1 M concentration of compound **100a** resulted in a 32% yield (Table 5.2, entry 8). Temperature studies revealed that 140 and 160 °C were not optimal for converting **100a** into product **219a** (Table 5.2, entries 9 and 10). Other solvents, such as THF, benzene, and toluene, were unsuitable (Table 5.2, entries 11, 12, and 13). The best-optimized condition was achieved by increasing the catalyst amount to 1.7 g, resulting in a 68% yield of product **219a** (Table 5.2, entry 14).

5.5.3 Substrate Scope for Macrocyclic Etherification

To generalize this approach, we explored the substrate scope with various diols **100** derivatives (Scheme 97). Diphenyldimethanol containing propyl spacer **219b** resulted in a 58% yield of **219b** (Scheme 71). Diols **100c** and **100d**, with butyl and hexyl spacers, led to **219c** and



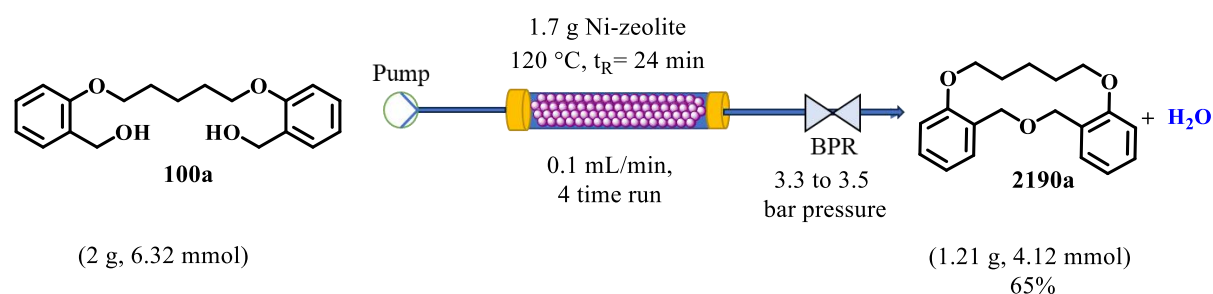
Scheme 97. Substrate scope for macrocyclic etherification

Reaction conditions: 0.05 M solution of **100** in 1,4-dioxane solvent prepared and flown through (0.1 mL/min flow rate with 3-4 bar pressure), Omnifit® column (6.6 × 150 mm) containing Ni-Zeolite (1.7 g, 7 cm), 120 °C, for residence time 27.3 min, 0.1 mL/min, at 3.3 to 3.5 bar back pressure and run 4 time.

219d with yields of 56% and 61%, respectively (Scheme 97). Increasing the spacer length in diols **100e-g**, such as octyl, nonyl, and decyl, resulted in a linear decrease in yield from 51% to 39% for macrocyclic ethers **219e-g** (Scheme 97). Additionally, bromo-substituted diol **100h** delivered 69% yield of **219h** (Scheme 97). Chloro- and nitro-substituted diol derivatives afforded 55% and 49% yields of macrocyclic ethers **219i** and **219j** respectively. Another substrate, **100k** with a benzene-1,3-dimethylene spacer delivered a 54% yield of macrocyclic ether **219k** (Scheme 97).

Furthermore, a four-oxygen containing cyclic ether **219l** was formed in 59% yield (Scheme 97). Polyether derivatives **219m-n** with triethylene glycol and tetraethylene glycol spacers were obtained in moderate yields with variable ring sizes (17 and 20) (Scheme 97). Subsequently, unsymmetrical diols with propyl, butyl, pentyl, and hexyl spacers **219o-r** afforded macrocyclic ethers **219o-r** with yields of 60%, 67%, 64%, and 66%, respectively (Scheme 97). Longer spacer length in **100s** and **100t**, containing benzylic and non-benzylic diols, subjected to dehydrative macrocyclization under flow conditions, afforded macrocyclic ethers **219s** and **219t** with ring sizes ranging from 17 to 19 in moderate yields (Scheme 97).

Additionally, this optimized reaction condition was applied to a gram scale 6.2 mmol of **100a**, to afford 65% yield of compound **219a** (Scheme 98).



Scheme 98. Gram-scale synthesis of macrocyclic etherification

5.6 Optimization for the Macrolactonization under Continuous Flow Conditions

The continuous flow catalytic dehydration process is not limited to macrocyclic ether formation but also extended its application to the synthesis of macrocyclic lactones. To facilitate intramolecular macrolactonization, various seco-acids **220** were prepared and optimized. Initially, this reaction was examined using seco-acid **220a** as a model substrate to produce macrolactone **221a**, with different catalysts, solvents, and temperatures under batch and flow conditions. β -Zeolite alone resulted **221a**, in 3% yield under batch conditions and 14% yield under continuous flow conditions (Figure 107). Further catalyst studies, was carried out with metal-loaded Zeolites specifically Fe-Zeolite, Ru-Zeolite, and Ni-Zeolite. Among these catalysts, Ru-Zeolite proved to be an effective catalyst for the dehydrative macrolactonization of seco-acid **220a** to macrolactone **221a**, provided 51% yields under batch conditions and 65% yields under flow conditions (Figure 107). In contrast, the Amberlyst®15 delivered lower yield of macrolactone **221a** (Figure 107). Furthermore, solvent study suggests that, 1,4-dioxane is the optimal solvent and afforded the best yield of **221a** (Figure 107).

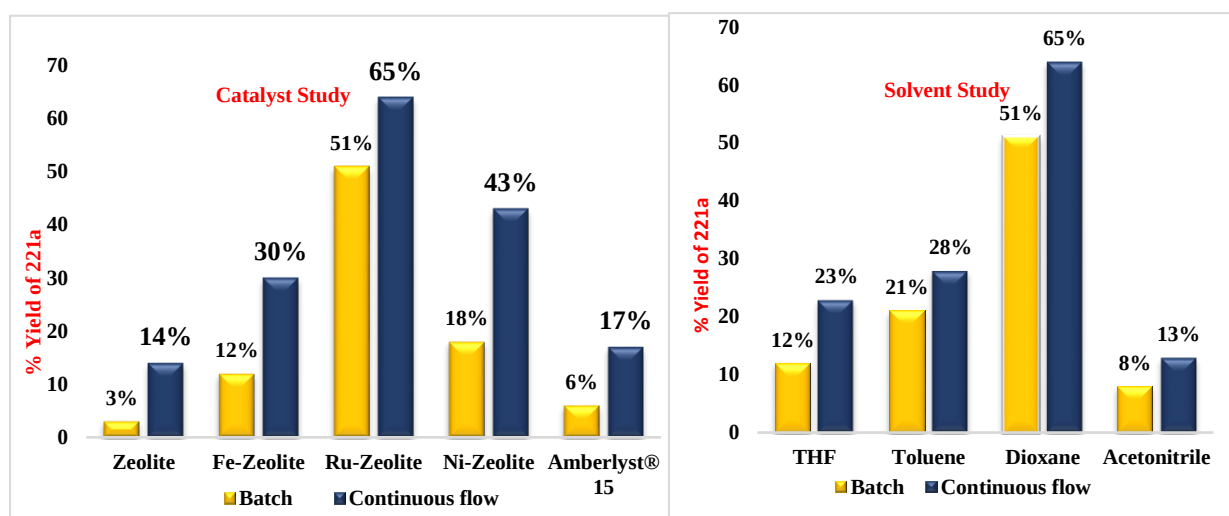


Figure 107. Catalyst and solvent studies under batch and continuous flow for the macrolactonization

Reactions in batch conditions: Compound **3a** (0.15 mmol) in solvents (2 mL, see figure 4) and 50 mg of catalyst were stirred in a sealed cap vial at 120 °C for 24 h. The mentioned yields are isolated yields. **Reactions in continuous flow conditions:** A solution of **3a** in (4 mL) solvents was prepared and flowed (0.1 mL/min flow rate) through the Omnifit column

containing the heterogeneous catalysts (1.7 g, 7 cm height), 0.1 mL/min, at 3.3 to 3.5 bar back pressure, at 120 °C. The mentioned yields are isolated yields

Various concentrations of compound **220a** were tested for macrolactonization: 0.01 M, 0.05 M, 0.1 M, and 0.2 M, resulting in yields of 65%, 65%, 57%, and 39% of compound **221a**, respectively (Figure 108). The similar yield of **221a** was obtained at a concentration of 0.05 M and 0.01 M. Employing 0.05 M concentration, the temperature study was also conducted at 100 °C, 120 °C, 140 °C, and 160 °C with flow rate of 0.1 mL/min yielding 53%, 65%, 65%, and 66% of compound **221a**, respectively. The optimal temperature for macrolactonization was found to be 120 °C, providing the best yield (Figure 108).

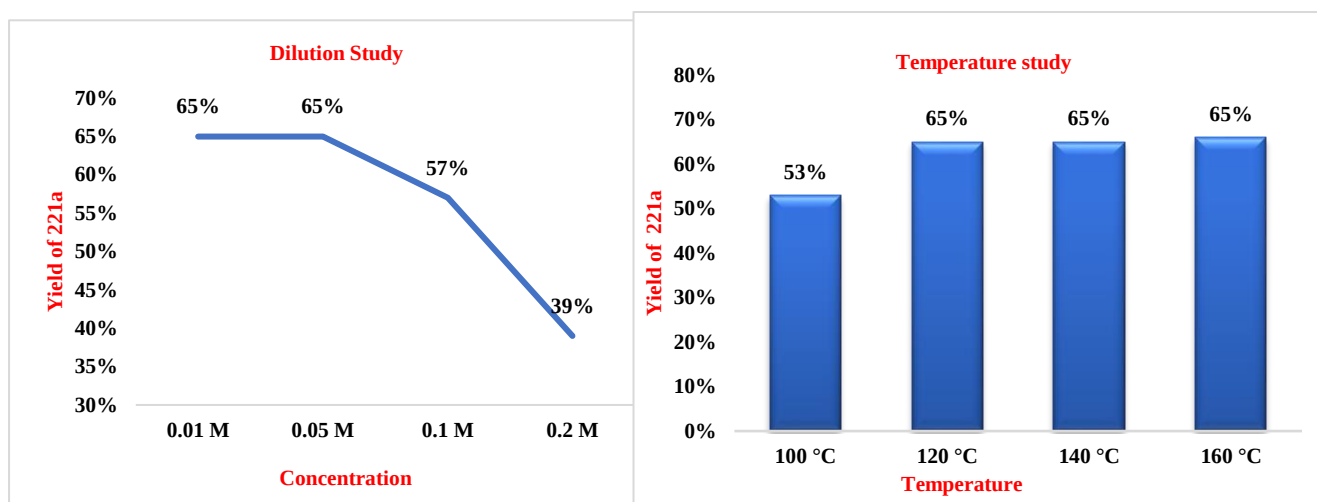
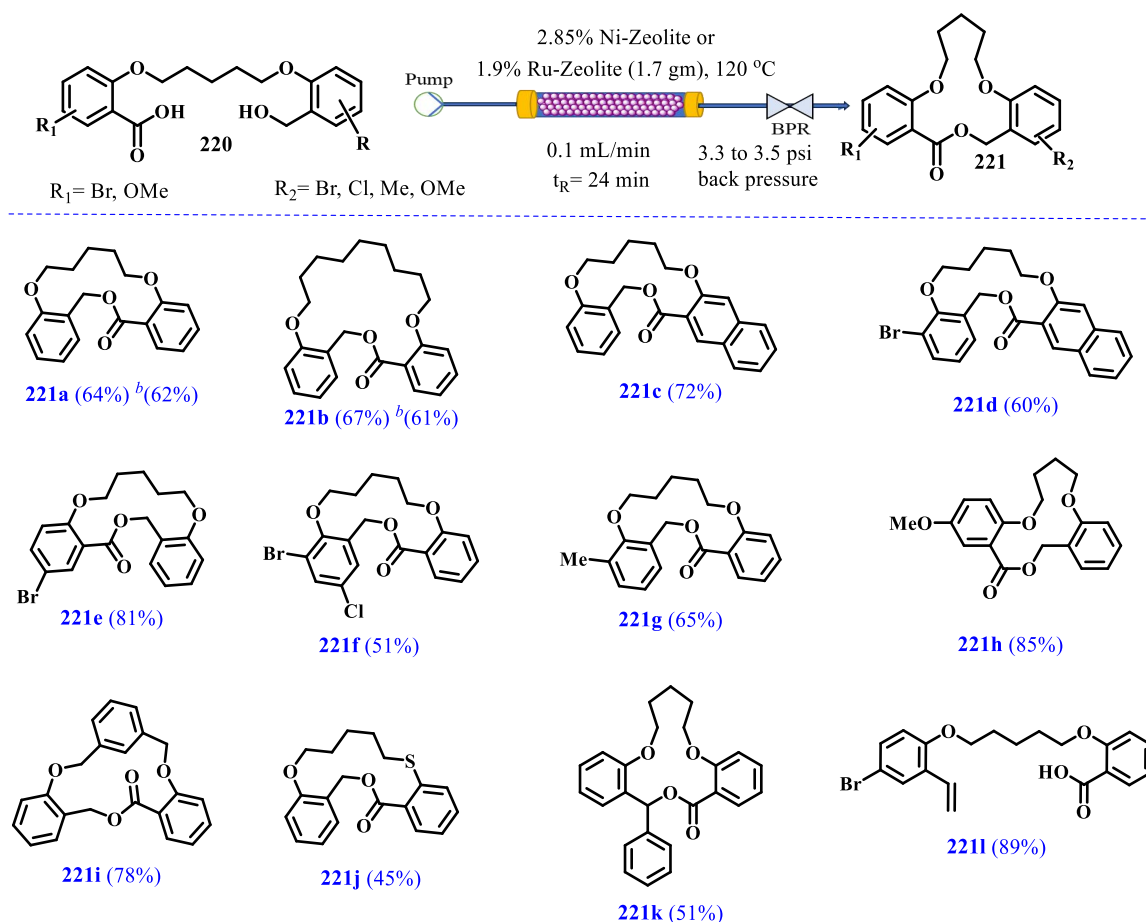


Figure 108. Temperature and dilution studies under batch and continuous flow for the macrolactonization

Reaction in continuous flow conditions: A solution of **3a** in dioxane solvents was prepared and flowed (0.1 mL/min flow rate) through the Omnifit column containing the heterogeneous catalysts (1.7 g, 7 cm height), 3.3 to 3.5 bar back pressure, at different temperatures, and concentration (see figure 4). The mentioned yields are isolated yields

5.6.1 Substrate Scope for Macrolactonization

Subsequently, the substrate scope for macrolactonization was explored with various seco-acids of different structures (Scheme 98). The octyl spacer seco-acid **220b** yielded macrolactone **221b** in 67% yield (Scheme 99). Naphthoic acid-containing seco

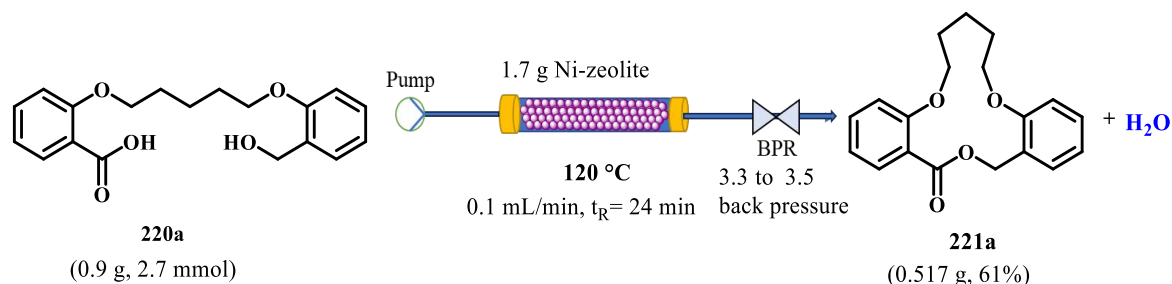


Scheme 99. Substrate scope for macrolactonization

^a**Reaction conditions:** 0.05 M solution of **100** in 1,4-dioxane solvent was flown through (0.1 mL/min flow rate and maintain 3.3 to 3.5 bar pressure) 4 mL of the Omnifit® column (6.6 × 150 mm) containing Ru-Zeolite heterogeneous catalysts (1.7 gm, 7 cm), 0.1 mL/min flow rate, at 3.3 to 3.5 bar back pressure, at 120 °C for residence time $t_R = 27.3$ min. ^bIn case of Ni-Zeolite, the reaction mixture was flown for 4 run cycle.

-acid **220c** provided compound **221c** in 72% yield (Scheme 99). Bromo-substituted seco-acids **220d**, **220e**, and **220f** yielded macrolactones **221d**, **221e**, and **221f** in yields of 60%, 81%, and 51%, respectively (Scheme 99). Electron-donating -Me and -OMe substituted seco-acids **220g** and **220h** furnished macrocyclic lactones **221g** and **221h** with yields of 65% and 85%, respectively (Scheme 99). Aryl spacer seco-acid **220i** delivered compound **221i** with a yield of 78% (Scheme 99). However, a decrease in yield was observed when thiobenzoic acid-containing seco-acid **220j** was used to form macrolactone **221j** (Scheme 99). Additionally, the reaction successfully proceeded with secondary alcohol, yielding product **221k** in 51% yield (Scheme 99). Conversely, bromo-substituted methyl secondary alcohol yielded only the alkene

product **221i** (Scheme 99). Additionally, the optimized reaction conditions were successfully scaled up to 2.7 mmol of **220a**, resulting in a 61% yield of compound **221a** (Scheme 100).



Scheme 100. Large scale reaction for macrolactonization

5.6.2 Reusability of Ni-Zeolite Catalyst

Furthermore, to check the reusability of Ni-Zeolite catalyst 10 reaction cycles were performed using one-time packed Omnifit® column filled with fresh Ni-Zeolite. First reaction cycle delivered a 68% yield of macrocyclic ether **219a** (Figure 109). Next, 2nd and 3rd reaction cycles provided the same yield of **219a** (Figure 109). Subsequent cycles upto 7th cycle furnished similar yields. Intriguingly, the 8th cycles furnished 67% yield of **219a**. Remarkably, even after the 10th time use, the catalyst remained active, maintaining its reactivity (Figure 109). After the 10th reaction cycle, we checked the Ni-binding on Zeolite by ICP analysis study and confirmed that 2.85% of Ni on Zeolite.

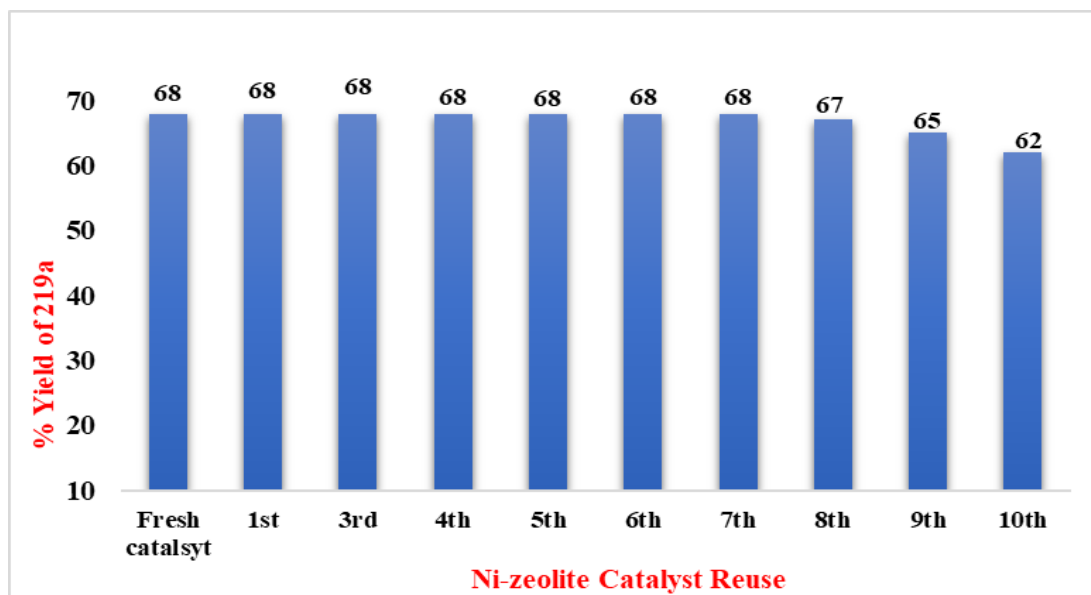
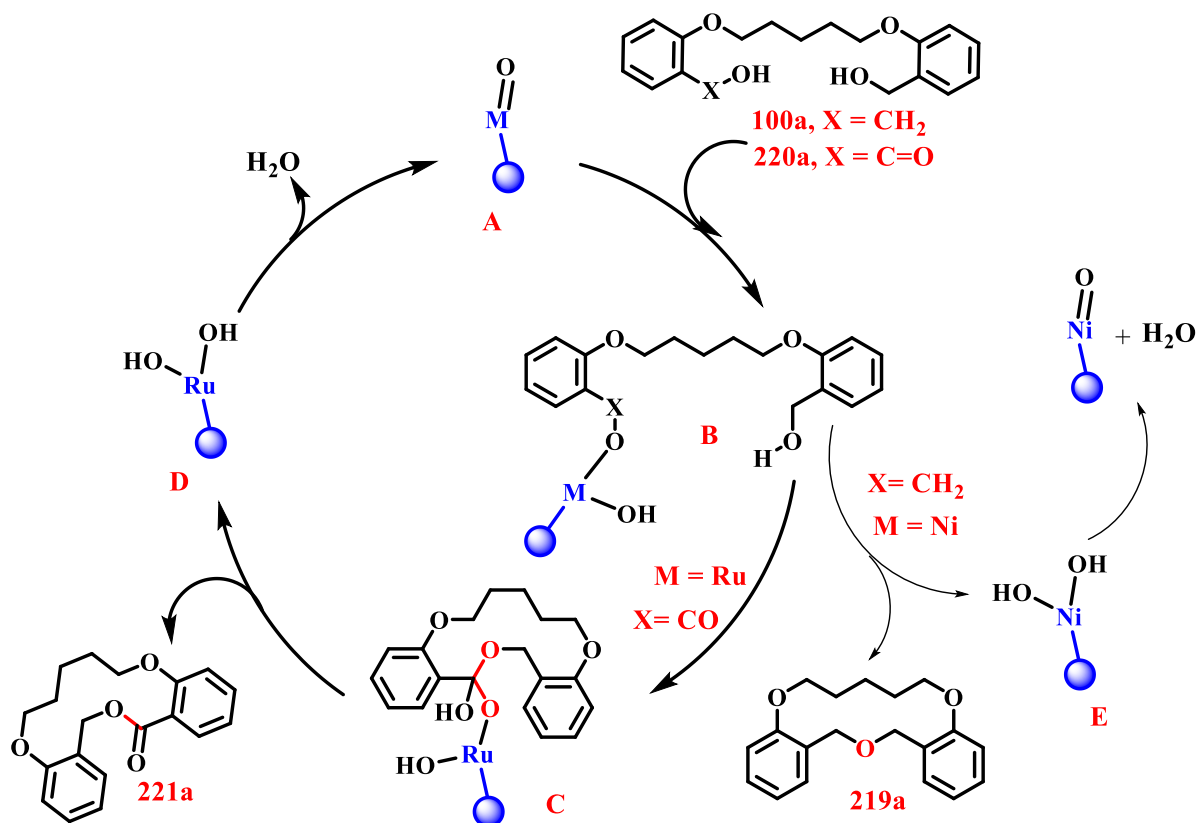


Figure 109. Ni-Zeolite catalyst reusability under continuous flow

5.7 Plausible Mechanism for Macrolactonization and Macrolactonization

The plausible activation mode and the recycling of the Ru-Zeolite and Ni-Zeolite are illustrated in Scheme 101. Initially, carboxylic acid **220a** or diol **100a** reacts with Ru=O (+4) or Ni=O (+2) to form respective addition intermediates **B**. Intermediate **C** undergoes elimination to



Scheme 101. Plausible mechanism for macrolactonization and macrocyclic ether formation yield intermediate **D** and macrocyclic lactone **221a**. Intermediate **D**, then eliminates a water molecule and facilitated to recycle the Ru-Zeolite catalyst. For macrocyclic ether formation **100a**, the intramolecular attack of alcohol on Ni-alkoxide forms intermediate **E**. Intermediate **E** subsequently undergoes thermolytic dehydration to regenerate the Ni-Zeolite catalyst.

5.8 Conclusion

In conclusion, we have developed a continuous flow catalytic method for the intramolecular dehydration of diols and seco-acids, enabling the synthesis of macrocyclic polyethers and lactones. A one-time packed Ni-Zeolite cartridge effectively catalyzed the reaction of diols, yielding a variety of macrocyclic polyethers with diverse ring sizes. Ru-Zeolite catalyst is used to convert seco-acids into a range of macrocyclic lactones with different

ring sizes. This method eliminated the need for predefined substrates and special reaction conditions. Moreover, the method has been successfully applied to numerous substrates, demonstrated scalability to gram-scale, and highlighted the recyclability of both catalysts. The advantages of this approach include highly reusable, scalable heterogeneous catalysts and shows high compatibility with diverse substrates of different ring sizes with the generation of water as a by-product.

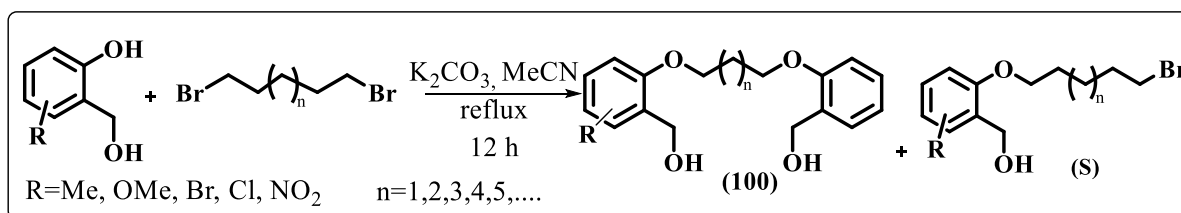
5.9 Experimental Section and Data Collection

5.9.1. General Information

The Iron (III) chloride hexahydrate (CAS number-10025-77-1, SIGMA), Nickel (II) chloride hexahydrate (CAS number-7791-20-0, SIGMA), Ruthenium (III) chloride hydrate (CAS number-14898-67-0, SIGMA). The column chromatographic separations were performed over 100-200 mesh size Silica-gel. Visualization was accomplished with UV light. The flow chemistry experiments were carried out using Vapourtec SF-10 reagent pump, PFA tubing, and Omnifit® column (6.6 x 150 mm). ^1H and ^{13}C NMR spectra were recorded on 400 and 100 MHz respectively, using Bruker or JEOL spectrometers. Abbreviations used in the NMR follow-up experiments: b, broad; s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet. High-Resolution Mass Spectra were recorded with waters-synapt G2 using electrospray ionization (ESI-TOF). Infrared (ATR) spectra were obtained with a Bruker Alpha-E infrared spectrometer. Melting points were recorded on DBK programmable melting point instrument. All melting points were measured in an open glass capillary tube. Single-crystal diffraction analysis data were collected at 273 K with a Bruker Kappa Apex III CCD Duo diffractometer (operated at 1500 W power: 50 kV, 30 mA) using graphite monochromatic CuK α radiation. More information on crystal structures (**219a**) can be obtained from the Cambridge Crystallographic Data Centre (CCDC) via deposition number 2266303.

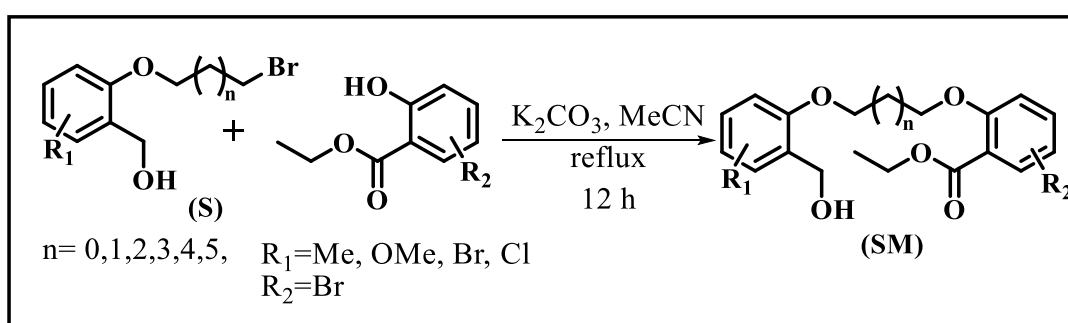
5.9.2. Experimental Section

A) General experimental procedure for mono- and dialkylation of 2-hydroxy benzyl alcohol.¹¹²



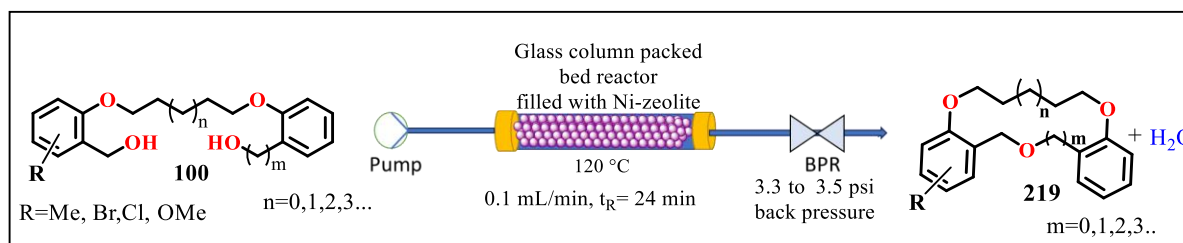
In a 100 mL round bottom flask were added derivatives of 2-hydroxy benzyl alcohol (1 equiv), dibromo alkanes (1.5 equiv), and potassium carbonate (K_2CO_3) (2 equiv.) in acetonitrile. The solution was refluxed at 85 °C for 12–16 h in an oil bath. The progress of the reaction was monitored by the thin-layer chromatography technique. After completion of the reaction, the mixture of products (mono- and dialkylated) was extracted in water and dichloromethane. The dichloromethane layers were combined and dried over Na_2SO_4 . Dichloromethane was evaporated, and the residue was directly purified by silica gel chromatography by using EtOAc:*n*-hexane = 15:85 (for monoalkylated product [S]) and 40:60 (for dialkylated product [100]).

B) General experimental procedure for ester alcohol derivatives.¹⁸⁵



In a 100 mL round-bottom flask were added compound (SM) (1 equiv), ethyl 2-hydroxybenzoate/derivative (1 equiv.), and potassium carbonate (1 equiv.) in acetonitrile. The solution was refluxed at 85 °C for 16 h in an oil bath. The progress of the reaction was monitored by the thin-layer chromatography technique. The resulting mixture was extracted with ethyl acetate twice using 30 mL of solvent each time. The ethyl acetate layer was combined and dried over Na_2SO_4 . After removing the solvent under reduced pressure, the residue was purified using column chromatography (EtOAc:*n*-hexane = 20:80 to 30:70) for the product SM.

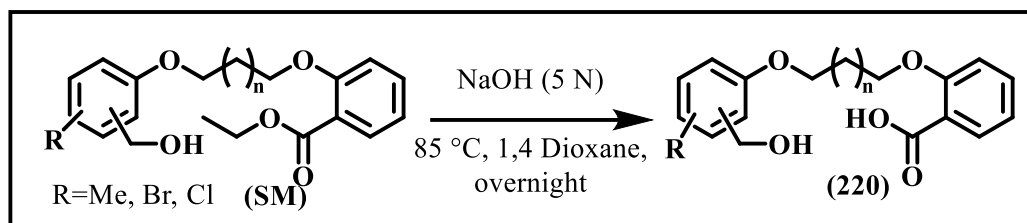
C) General experimental procedure for intramolecular macroetherification



In 10-20 mL vial 0.05 M solution of **100** diol in 1,4-dioxane solvent was prepared and pumped using a syringe pump through Omnifit® column (6.6 x 150 mm) packed bed containing 1.7 g of Ni-Zeolite filled up to 7 cm and preheated at 120 °C with the flow rate of

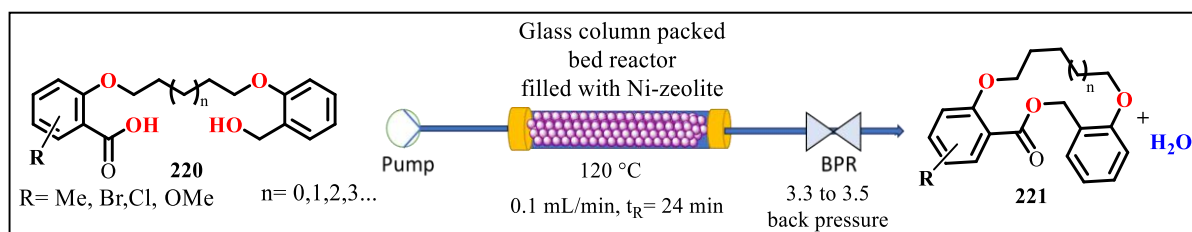
0.1 mL/min at 3.3 to 3.5 psi back pressure and residence time $t_R = 27.3$ min. After a four-time run. The collected organic layer was concentrated under reduced pressure and the crude product was purified by column chromatography using (EtOAc:*n*-hexane = 05:95 to 20:80) as an eluent to afford the compound **219**.

D) General experimental procedure for seco-acid derivatives.¹⁸⁵



To a 1,4-dioxane solution of ester (**SM**) was added a 5N NaOH solution. The mixture was stirred at 85 °C overnight in an oil bath. The reaction mixture was extracted with EtOAc. 1.0 M HCl solution was added to the aqueous solution to adjust the pH to 2, and then, the mixture was extracted with EtOAc three times. The ethyl acetate layer was dried over anhydrous Na₂SO₄ and evaporated using a vacuum. The residue was directly purified by silica gel chromatography using (EtOAc:*n*-hexane = 40-60 to 70:30) to afford product **220**.

E) General experimental procedure for intramolecular macrolactonization



In 10-20 mL vial 0.05 M solution of seco-acids **220** in 1,4-dioxane solvent was prepared and pumped using a syringe pump through Omnifit® column (6.6 x 150 mm) packed bed containing 1.7 g of Ru-Zeolite filled up to 7 cm and preheated at 120 °C with the flow rate of 0.1 mL/min at 3.3 to 3.5 back pressure. The collected organic layer was concentrated under reduced pressure and the crude product was purified by column chromatography using (EtOAc:*n*-hexane = 05:95 to 10:90) as an eluent to afford the compound **221**.

F) Run time Study in Continuous flow: One time run in continuous flow: A 0.05 M solution of the diol **1a** in dioxane solvent was pumped using a syringe pump through a glass column (Omnifit® (6.6 x 150 mm) packed bed and preheated at 120 °C with the flow rate of 0.1 mL/min at 3.3 to 3.5 bar back pressure was maintained in the reaction and residence time $t_R = 23.94$ min in one cycle. The collected organic layer was concentrated and further purification afforded a 20% yield of compound **219** (Figure 110).

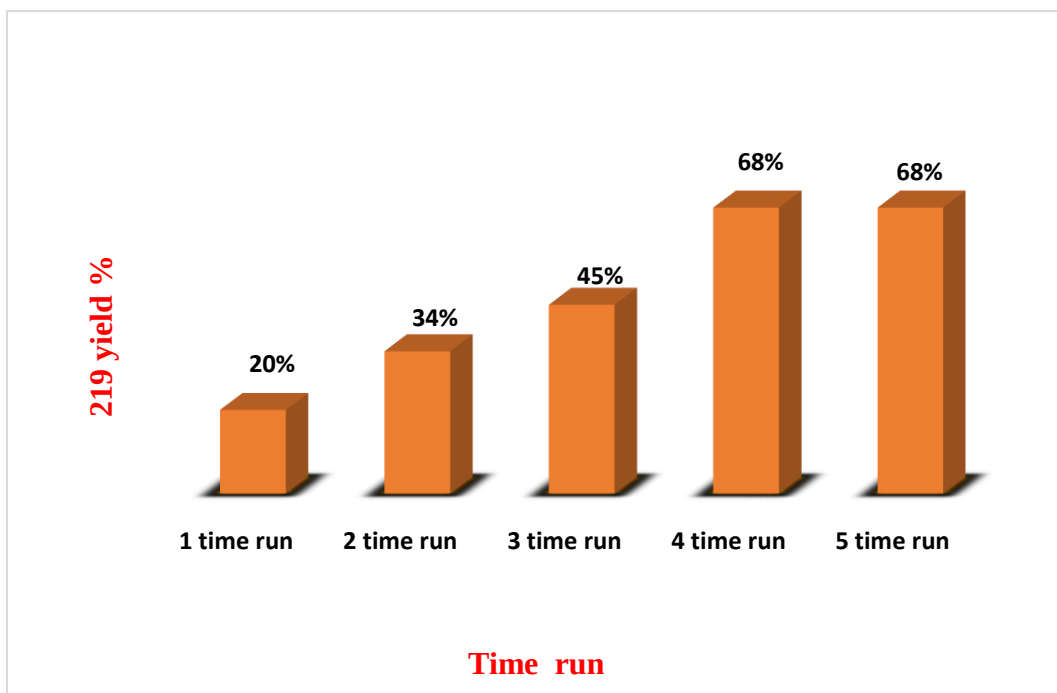


Figure 110. Ni-Zeolite catalyst time run under continuous-flow

Second time run in continuous flow: A 0.05 M solution of the diol **1a** in dioxane solvent was pumped using syringe pump through glass column (Omnifit® (6.6 x 150 mm) packed bed and preheated at 120 °C with the flow rate of 0.1 mL/min at 3.3 to 3.5 bar back pressure was maintained in the reaction and residence time $t_R = 23.94$ min in one cycle. After one cycle same reaction mixture passed through same column bed (without activation of catalyst). The collected organic layer was concentrated and further purification afforded a 34% yield of compound **219** (Figure 110).

Third time run in continuous flow: After two cycles same reaction mixture passed through the same column bed (without activation of catalyst). The collected organic layer was concentrated and further purification afforded a 45% yield of compound **219** (Figure 110).

Fourth time run in continuous flow: After three cycles same reaction mixture passed through the same column bed (without activation of catalyst). The collected organic layer was concentrated and further purification affords a 68% yield of compound **219** (Figure 110).

Fifth time run in continuous flow: After four cycles same reaction mixture passed through the same column bed (without activation of catalyst). The collected organic layer was concentrated and further purification affords a 68% yield of compound **219** (Figure 110).

Calculation of Space Time Yield and Weight Hourly Space Velocity (WHSV):

Space Time Yield (STY)

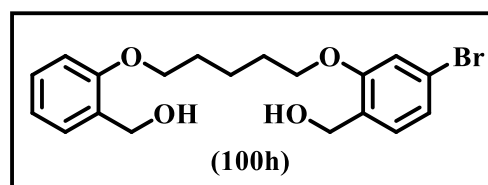
$$\frac{\text{desired concentration of Product} \times \text{Molecular weight of product} \times (\text{yield}/100)}{\text{Residence time}}$$

$$\text{Weight Hourly Space Velocity (WHSV)} = \frac{\text{mass of feed per hour}}{\text{mass of catalyst}}$$

5.9.3 Analytical Data of Product

(4-bromo-2-((5-(2-(hydroxymethyl)phenoxy)pentyl)oxy)phenyl)methanol (100h):

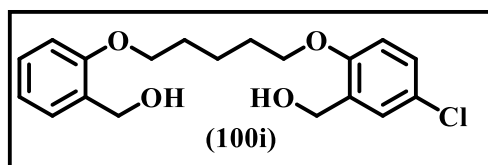
Prepared according to general experimental procedure 5.9.2A, using (2-((5-bromopentyl)oxy)phenyl)methanol (700 mg, 2.56 mmol), potassium carbonate (K₂CO₃) (354 mg, 2.56



mmol) and 5-bromo-2-(hydroxymethyl)phenol (520 mg, 2.56 mmol). The residue was purified by using column chromatography (EtOAc/*n*-hexane = 40:60) as the eluent to afford desired product (4-bromo-2-((5-(2-(hydroxymethyl)phenoxy)pentyl)oxy)phenyl)methanol (**100h**) (890 mg, 2.25 mmol, 87% yield) as semi solid; ¹H NMR (400 MHz, CDCl₃) δ 7.44 (d, *J* = 2.5 Hz, 1H), 7.33 (dd, *J* = 8.7, 2.5 Hz, 1H), 7.29 – 7.27 (m, 1H), 7.26 – 7.23 (m, 1H), 6.94 (td, *J* = 7.5, 0.9 Hz, 1H), 6.87 (d, *J* = 8.1 Hz, 1H), 6.73 (d, *J* = 8.7 Hz, 1H), 4.69 (s, 2H), 4.64 (s, 2H), 4.06 (t, *J* = 6.1 Hz, 2H), 4.02 (t, *J* = 6.2 Hz, 2H), 2.61 (s, 2H), 1.89 (qd, *J* = 6.3, 3.2 Hz, 4H), 1.71 – 1.65 (m, 2H); ¹³C NMR 100 MHz, CDCl₃) δ 156.8, 155.6, 131.5, 131.2, 131.2, 129.1, 128.9, 128.8, 120.7, 112.9, 112.7, 111.1, 67.9, 67.6, 62.1, 60.9, 29.0, 28.9, 23.0; FTIR (neat): 3357, 2938, 2870, 1483, 1236 cm⁻¹; HRMS (ESI-TOF) *m/z*: calculated for C₁₉H₂₃BrO₄Na [M + Na]⁺: 417.0677, found: 417.0673.

(5-chloro-2-((5-(2-(hydroxymethyl)phenoxy)pentyl)oxy)phenyl)methanol (100i):

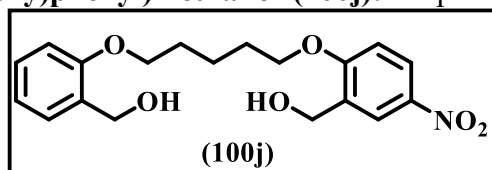
Prepared according to general experimental procedure 5.9.2A, using (2-((5-bromopentyl)oxy)phenyl)methanol (500 mg, 1.83 mmol), potassium carbonate (K₂CO₃) (252 mg, 1.83



mmol) and 2-(hydroxymethyl)-5-chlorophenol (309 mg, 1.83 mmol). The residue was purified by using column chromatography (EtOAc/*n*-hexane = 40:60) as the eluent to afford desired product (2-((5-(2-(hydroxymethyl)-5-nitrophenoxy)pentyl)oxy)phenyl)methanol (**100i**) (513

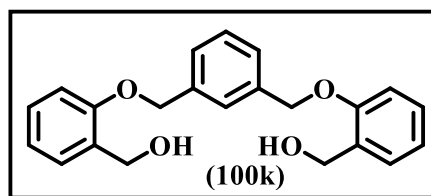
mg, 1.42 mmol, 77% yield) as a semisolid, ^1H NMR (400 MHz, CDCl_3) δ 7.27 (ddd, $J = 4.5$, 3.6, 0.8 Hz, 1H), 7.26 – 7.22 (m, 1H), 7.21 (d, $J = 8.0$ Hz, 1H), 6.94 (dd, $J = 7.4$, 0.8 Hz, 1H), 6.90 (dd, $J = 8.1$, 2.0 Hz, 1H), 6.85 (d, $J = 8.1$ Hz, 1H), 6.82 (d, $J = 1.9$ Hz, 1H), 4.68 (d, $J = 4.2$ Hz, 2H), 4.61 (d, $J = 4.1$ Hz, 2H), 4.02 (t, $J = 6.1$ Hz, 2H), 3.97 (t, $J = 6.1$ Hz, 2H), 3.12 (s, 1H), 3.01 (s, 1H), 1.92 – 1.80 (m, 4H), 1.73 – 1.60 (m, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 156.9, 156.6, 133.8, 129.1, 128.8, 128.6, 127.9, 120.6, 120.4, 111.7, 111.0, 67.9, 67.5, 61.6, 60.5, 28.9, 28.8, 22.9; FTIR (neat): 3360, 2933, 2872, 1497, 1389, 1262 cm^{-1} ; HRMS (ESI-TOF) m/z : calculated for $\text{C}_{19}\text{H}_{23}\text{O}_4\text{ClNa}$, $[\text{M} + \text{Na}]^+$ 373.1184, found: 373.1189.

(2-((5-(2-(hydroxymethyl)-4-nitrophenoxy)pentyl)oxy)phenyl)methanol (100j): Prepared according to general experimental procedure 5.9.2A, using 2-((5-bromopentyl)oxy)phenyl)methanol (500 mg, 1.83 mmol), potassium carbonate (K_2CO_3) (252



mg, 1.83 mmol) and 2-(hydroxymethyl)-4-nitrophenol (309 mg, 1.83 mmol). The residue was purified by using column chromatography ($\text{EtOAc}/n\text{-hexane} = 40:60$) as the eluent to afford the desired product (2-((5-(2-(hydroxymethyl)-4-nitrophenoxy)pentyl)oxy)phenyl)methanol (**100j**) (513 mg, 1.42 mmol, 77% yield) as a solid, melting point; 79–78 $^\circ\text{C}$; ^1H NMR (400 MHz, CDCl_3) δ 8.24 (s, 1H), 8.11 (dd, $J = 9.0$, 2.8 Hz, 1H), 7.28 – 7.22 (m, 2H), 6.92 (t, $J = 7.4$ Hz, 1H), 6.88 – 6.83 (m, 2H), 4.69 (s, 2H), 4.68 (s, 2H), 4.12 (t, $J = 6.1$ Hz, 2H), 4.05 (t, $J = 6.0$ Hz, 2H), 3.07 (s, 1H), 2.76 (s, 1H), 1.90 (dt, $J = 8.3$, 7.3 Hz, 4H), 1.75 – 1.65 (m, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 161.1, 156.8, 141.3, 130.8, 129.1, 128.9, 128.8, 124.9, 123.7, 120.8, 111.1, 110.4, 68.7, 67.6, 62.3, 62.2, 29.0, 28.8, 23.0; FTIR (neat): 3361, 2939, 2872, 1499, 1388, 1260 cm^{-1} ; HRMS (ESI-TOF) m/z : calculated for $\text{C}_{19}\text{H}_{23}\text{NO}_6\text{Na}$, $[\text{M} + \text{Na}]^+$ 384.1423, found: 384.1411.

((1,3-phenylenebis(methylene))bis(oxy))bis(2,1-phenylene))dimethanol (100k): Prepared according to general experimental procedure 5.9.2A, using 2-hydroxybenzyl alcohol (700 mg, 5.64 mmol, 1 equiv.), potassium carbonate (K_2CO_3) (1.56 g, 11.2 mmol, 2 equiv.) and 1,3-bis(bromomethyl)benzene (744.2 mg,

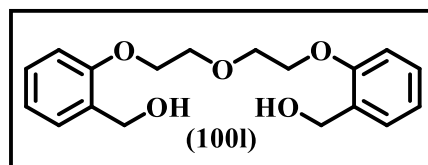


2.82 mmol, 0.5 equiv.) reflux in CH_3CN solvent. The residue was purified by using column chromatography ($\text{EtOAc}/n\text{-hexane} = 40:60$) as the eluent to afford desired product (((1,3-phenylenebis(methylene))bis(oxy))bis(2,1-phenylene))dimethanol (**100k**) (850 mg, 2.43 mmol, 86% yield) as white solid; melting point = 79–81 $^\circ\text{C}$. ^1H NMR (400 MHz, CDCl_3) δ 7.54 (s, 1H), 7.41 (d, $J = 5.9$ Hz, 1H), 7.38 – 7.31 (m, 4H), 7.29 – 7.23 (m, 2H), 6.97 (td, $J = 7.5$,

0.8 Hz, 2H), 6.93 (d, $J = 8.2$ Hz, 2H), 5.14 (s, 4H), 4.73 (s, 4H), 2.65 (s, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 156.4, 137.6, 129.6, 129.0, 128.9, 126.9, 125.8, 121.2, 111.7, 69.8, 61.8; FTIR (neat): 3352, 2936, 2871, 1450, 1227 cm^{-1} ; HRMS (ESI-TOF) m/z : calculated for $\text{C}_{22}\text{H}_{22}\text{O}_4\text{Na}$, $[\text{M} + \text{Na}]^+$ 373.1416, found: 373.1407.

(((oxybis(ethane-2,1-diyl))bis(oxy))bis(2,1-phenylene))dimethanol (100l): Prepared

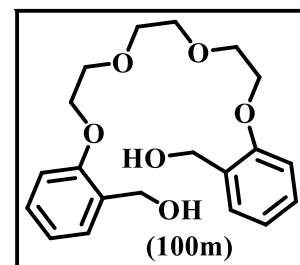
according to general experimental procedure 5.9.2A, using 2-hydroxybenzyl alcohol (800 mg, 6.44 mmol, 1 equiv.), potassium carbonate (K_2CO_3) (1.8 g, 12.9 mmol, 2 equiv.), and 1-bromo-2-(2-bromoethoxy)ethane (747.3



mg, 3.22 mmol, 1 equiv.), reflux in CH_3CN solvent. The residue was purified by using column chromatography ($\text{EtOAc}/n\text{-hexane} = 40:60$) as the eluent to afford desired product **(((oxybis(ethane-2,1-diyl))bis(oxy))bis(2,1-phenylene))dimethanol (100l)** (980 mg, 3.08 mmol, 95% yield) as colourless semisolid; ^1H NMR (400 MHz, CDCl_3) δ 7.27 – 7.20 (m, 4H), 6.94 (td, $J = 7.5, 0.8$ Hz, 2H), 6.89 – 6.84 (m, 2H), 4.63 (s, 4H), 4.21 (dd, $J = 5.3, 3.5$ Hz, 4H), 3.91 – 3.87 (m, 4H), OH peaks are exchanged with deuterium of CDCl_3 ; ^{13}C NMR (100 MHz, CDCl_3) δ 157.1, 130.3, 129.7, 129.1, 121.4, 112.3, 69.9, 67.9, 61.9; FTIR (neat): 3390, 2939, 2871, 1589, 1240 cm^{-1} ; HRMS (ESI-TOF) m/z : calculated for $\text{C}_{18}\text{H}_{22}\text{O}_5\text{Na}$, $[\text{M} + \text{Na}]^+$ 341.1364, found: 341.1361.

(((ethane-1,2-diylbis(oxy))bis(ethane-2,1-diyl))bis(oxy))bis(2,1-phenylene))dimethanol (100m): Prepared according to general experimental procedure

5.9.2A, using 2-hydroxybenzyl alcohol (700 mg, 5.64 mmol), potassium carbonate (K_2CO_3) (1.55 g, 11.28 mmol) and 1,2-bis(2-bromoethoxy)ethane (778.0 mg, 2.82 mmol) reflux in CH_3CN solvent. The residue was purified by using column chromatography ($\text{EtOAc}:n\text{-hexane} = 40:60$) as the eluent to afford desired product

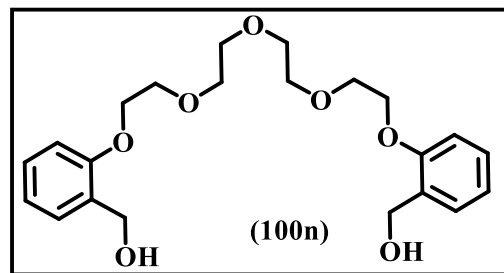


(((ethane-1,2-diylbis(oxy))bis(ethane-2,1-diyl))bis(oxy))bis(2,1-phenylene))dimethanol (100m) (990 mg, 2.73 mmol, 96% yield) as colourless semisolid; ^1H NMR (400 MHz, CDCl_3)

δ 7.26 – 7.19 (m, 4H), 6.96 – 6.90 (m, 2H), 6.86 (d, $J = 8.4$ Hz, 2H), 4.63 (s, 4H), 4.21 – 4.15 (m, 4H), 3.88 – 3.81 (m, 4H), 3.71 (s, 4H), OH peaks are exchanged with deuterium of CDCl_3 . ^{13}C NMR (100 MHz, CDCl_3) δ 157.2, 130.3, 129.4, 129.0, 121.3, 112.5, 76.8, 70.8, 69.8, 68.0, 62.3; FTIR (neat): 3390, 2937, 2845, 1588, 1236 cm^{-1} ; HRMS (ESI-TOF) m/z : calculated for $\text{C}_{20}\text{H}_{26}\text{O}_6\text{Na}$, $[\text{M} + \text{Na}]^+$ 385.1626, found: 385.1622.

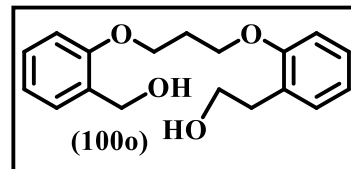
(((oxybis(ethane-2,1-diyl))bis(oxy))bis(ethane-2,1-diyl))bis(oxy))bis(2,1-phenylene)) dimethanol

(100n): Prepared according to general experimental procedure 5.9.2A, using 2-hydroxybenzyl alcohol (500 mg, 4.03 mmol),



potassium carbonate (K_2CO_3) (557 mg, 4.03 mmol) and 1-bromo-2-(2-(2-(2-bromoethoxy)ethoxy)ethoxy)ethane (644.4 mg, 2.01 mmol) reflux in CH_3CN solvent. The residue was purified by using column chromatography (EtOAc:*n*-hexane = 40:60) as the eluent to afford desired product **(100n)** (980 mg, 3.08 mmol, 81% yield) as colourless semisolid; ^1H NMR (400 MHz, $CDCl_3$) δ 7.30 – 7.23 (m, 4H), 6.96 (td, J = 7.5, 0.7 Hz, 2H), 6.91 – 6.85 (m, 2H), 4.67 (s, 4H), 4.19 (dd, J = 5.4, 3.8 Hz, 4H), 3.88 – 3.83 (m, 4H), 3.74 – 3.69 (m, 4H), 3.69 – 3.65 (m, 4H), 3.45 (s, 1H), OH peaks are exchanged with deuterium of $CDCl_3$. ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.1, 130.4, 129.2, 128.9, 121.2, 112.3, 70.7, 70.7, 69.6, 67.9, 62.1; FTIR (neat): 3363, 2934, 2856, 1584, 1260 cm^{-1} ; HRMS (ESI-TOF) m/z : calculated for $C_{22}H_{31}O$, $[M + H]^+$ 407.2070, found 407.2068.

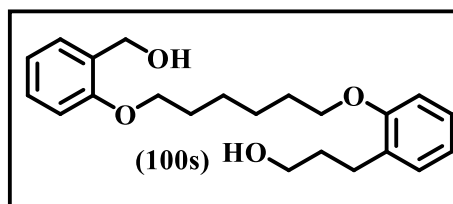
2-(2-(3-(2-(hydroxymethyl)phenoxy)propoxy)phenyl)ethan-1-ol (100o): Prepared according to general experimental procedure 5.9.2A, using (2-(3-bromopropoxy)phenyl)methanol (1 g, 4.0 mmol), potassium carbonate (K_2CO_3) (1.1 g, 8.0 mmol) and 2-(2-hydroxyethyl)phenol (563 mg, 4.0 mmol). The residue was



purified by using column chromatography (EtOAc/*n*-hexane = 40:60) as the eluent to afford the desired product **(100o)** (780 mg, 2.58 mmol, 63% yield) as a semisolid, ^1H NMR (400 MHz, $CDCl_3$) δ 7.27 (ddd, J = 8.6, 4.7, 4.3 Hz, 2H), 7.23 – 7.15 (m, 2H), 6.95 (dd, J = 14.3, 6.5 Hz, 2H), 6.90 (t, J = 7.5 Hz, 2H), 4.68 (s, 2H), 4.24 (t, J = 6.0 Hz, 2H), 4.20 (t, J = 5.9 Hz, 2H), 3.79 (t, J = 6.5 Hz, 2H), 2.89 (t, J = 6.6 Hz, 2H), 2.33 (p, J = 6.0 Hz, 2H), OH peaks are exchanged with deuterium of $CDCl_3$. ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.8, 156.6, 131.1, 129.3, 129.1, 128.9, 127.9, 127.2, 121.0, 121.0, 111.6, 111.3, 64.8, 64.7, 62.8, 34.1, 29.4; FTIR (neat): 3340, 2931, 2877, 1489, 1236 cm^{-1} ; HRMS (ESI-TOF) m/z : calculated for $C_{18}H_{22}O_4Na$, $[M + Na]^+$ 325.1415, found 325.1405.

3-(2-((6-(2-(hydroxymethyl)phenoxy)hexyl)oxy)phenyl)propan-1-ol (100s): Prepared

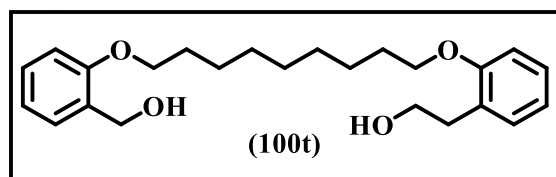
according to general experimental procedure 5.9.2A, using (2-((6-bromohexyl)oxy)phenyl)methanol (1.0 g, 3.48 mmol, 1 equiv.), potassium carbonate (K_2CO_3) (960 mg, 6.96 mmol, 2 equiv.) and 2-(3-



hydroxypropyl)phenol (539 mg, 3.48 mmol, 1 equiv.). The residue was purified by using column chromatography (EtOAc/*n*-hexane = 40:60) as the eluent to afford desired product (**100s**) (990 mg, 2.73 mmol, 79% yield); as a semisolid; ^1H NMR (400 MHz, $CDCl_3$) δ 7.30 – 7.23 (m, 2H), 7.16 (ddd, J = 14.5, 7.4, 1.7 Hz, 2H), 6.94 (dt, J = 8.3, 4.2 Hz, 1H), 6.91 – 6.83 (m, 3H), 4.69 (s, 2H), 4.04 (t, J = 6.3 Hz, 2H), 4.00 (t, J = 6.4 Hz, 2H), 3.57 (t, J = 6.2 Hz, 2H), 2.71 (t, J = 7.3 Hz, 2H), 1.89 – 1.80 (m, 6H), 1.60 – 1.55 (m, 4H), OH peaks are exchanged with deuterium of $CDCl_3$. ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.0, 156.9, 130.3, 130.2, 129.3, 129.0, 128.8, 127.3, 120.8, 120.7, 111.4, 111.2, 67.9, 67.9, 62.3, 62.0, 33.1, 29.4, 29.3, 26.1, 26.0; FTIR (neat): 3384, 2936, 1452, 1234 cm^{-1} ; HRMS (ESI-TOF) m/z : calculated for $C_{22}H_{31}O_4$, $[M + H]^+$ 359.2222, found: 359.2221.

2-(2-((9-(2-(hydroxymethyl)phenoxy)nonyl)oxy)phenyl)ethan-1-ol (100t): Prepared

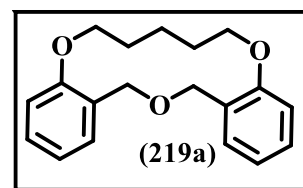
according to general experimental procedure 5.9.2A, using (2-((9-bromononyl)oxy)phenyl)methanol (1.0 g, 3.4 mmol, 1 equiv.), potassium carbonate (K_2CO_3)



(938 mg, 6.8 mmol, 2 equiv.) and 2-(2-hydroxyethyl)phenol (419 mg, 3.4 mmol, 1 equiv.). The residue was purified by using column chromatography (EtOAc/*n*-hexane = 40:60) as the eluent to afford desired product (**100t**) (970 mg, 2.51 mmol, 82% yield); as a semisolid; ^1H NMR (400 MHz, $CDCl_3$) δ 7.30 – 7.24 (m, 2H), 7.24 – 7.19 (m, 1H), 7.18 – 7.14 (m, 1H), 6.97 – 6.89 (m, 2H), 6.87 (dd, J = 8.0, 4.3 Hz, 2H), 4.69 (s, 2H), 4.02 (t, J = 6.4 Hz, 2H), 3.97 (t, J = 6.4 Hz, 2H), 3.84 (t, J = 6.4 Hz, 2H), 2.92 (t, J = 6.4 Hz, 2H), 1.81 (tt, J = 12.9, 6.5 Hz, 4H), 1.47 (dd, J = 14.1, 6.4 Hz, 4H), 1.37 (s, 6H), OH peaks are exchanged with deuterium of $CDCl_3$. ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.2, 157.0, 131.0, 129.2, 129.0, 128.7, 127.8, 127.2, 120.6, 120.6, 111.3, 111.1, 68.0, 63.0, 62.5, 34.3, 29.5, 29.4, 29.3, 26.2; FTIR (neat): 3385, 2931, 1456, 1242 cm^{-1} ; HRMS (ESI-TOF) m/z : calculated for $C_{24}H_{34}O_4Na$, $[M + Na]^+$ 409.2354, found: 409.2347.

7,8,9,10-tetrahydro-6*H*,16*H*,18*H*-dibenzo[*b,g*][1,5,9]trioxacyclotetradecine (219a):

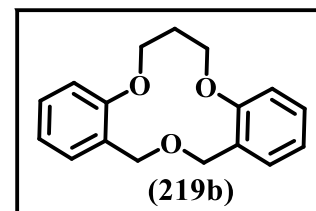
Prepared according to general experimental procedure 5.9.2C, a 0.05 M solution of **100a** (63 mg, 0.199 mmol) in (127 mL) 1,4-dioxane solvent was pumped using syringe pump through Omnifit® column (6.6 x 150 mm) packed bed containing 1.7 g of Ni-zeolite filled up to



7 cm and preheated at 120 °C with the flow rate of 0.1 mL/min at 3.3 to 3.5 back pressure and residence time $t_R = 27.3$ min after a four-time run. The collected organic layer was concentrated under reduced pressure and the crude product was purified by column chromatography using (EtOAc/*n*-hexane = 5:95) as an eluent to afford the compound **219a** (40.3 mg, 68%) as a white solid, weight hourly space velocity (WHSV) = 53 h⁻¹, space-time yield = 17.59 g L⁻¹ h⁻¹, melting point: 80-83 °C; **Large scale reaction for macrocyclic ether:** Prepared according to general experimental procedure C, a 0.05 M solution of **100a** ((pentane-1,5-diylbis(oxy))bis(2,1-phenylene))dimethanol (2 gm, 6.32 mmol) in 1,4-dioxane solvent was pumped using a syringe pump through two Omnifit® column (6.6 x 150 mm) packed bed containing 1.7 gm of Ni-Zeolite filled up to 7 cm each column bed and preheated at 120 °C with the flow rate of 0.1 mL/min at 4-5 back pressure was and residence time $t_R = 27.3$ min each column bed. After a two-time run, the collected organic layer was concentrated under reduced pressure, and the crude product was purified by column chromatography using (EtOAc/*n*-hexane = 5:95) as an eluent to afford the compound **219a** (1.231 g, 4.12 mmol, 65%) as a white solid, weight hourly space velocity (WHSV) = 53 h⁻¹, space-time yield = 17.57 g L⁻¹ h⁻¹, ¹H NMR (400 MHz, CDCl₃) δ 7.47 (dd, $J = 7.4, 1.7$ Hz, 2H), 7.41 – 7.36 (m, 2H), 7.03 (t, $J = 7.4$ Hz, 2H), 6.98 (d, $J = 8.1$ Hz, 2H), 4.75 (s, 4H), 4.21 (t, $J = 5.1$ Hz, 4H), 2.08 – 2.01 (m, 2H), 1.98 (dd, $J = 11.4, 5.9$ Hz, 4H); ¹³C NMR (100 MHz, CDCl₃) δ 158.2, 131.9, 129.6, 126.7, 120.2, 111.9, 69.3, 66.9, 28.0, 21.4; FTIR (neat): 2931, 2864, 1596, 1246 cm⁻¹; HRMS (ESI-TOF) m/z : calculated for C₁₉H₂₂O₃Na, [M + Na]⁺321.1466, found 321.1469.

7,8-dihydro-6*H*,14*H*,16*H*-dibenzo[*b,g*][1,5,9]trioxacyclododecine (219b): Prepared

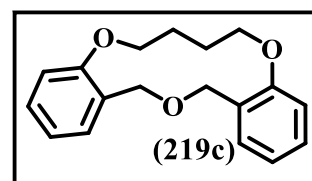
according to general experimental procedure 5.9.2C, a 0.05 M solution of **100b** (57.7 mg, 0.20 mmol) in (4 mL) 1,4-dioxane solvent was pumped using syringe pump through Omnifit® column (6.6 x 150 mm) packed bed containing 1.7 g of Ni-zeolite filled up



to 7 cm and preheated at 120 °C with the flow rate of 0.1 mL/min at 3.3 to 3.5 back pressure. The collected organic layer was concentrated under reduced pressure and the crude product was purified by column chromatography using (EtOAc:*n*-hexane = 5:95) as an eluent to afford

the compound **219b** (31.3 mg, 58%) as a white solid, weight hourly space velocity (WHSV) = 48 h^{-1} , space-time yield = $11.64 \text{ g L}^{-1} \text{ h}^{-1}$, and starting material recovered **100b** (23 mg, 40 %), melting point: 65-70 °C; ^1H NMR (400 MHz, CDCl_3) δ 7.28 (dd, $J = 7.7, 1.3 \text{ Hz}$, 2H), 7.26 – 7.22 (m, 2H), 6.92 – 6.83 (m, 4H), 4.60 (s, 4H), 4.28 – 4.22 (m, 4H), 2.31 – 2.25 (m, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 158.2, 131.3, 129.6, 127.3, 120.3, 111.6, 69.4, 68.1, 28.5; FTIR (neat): 2930, 2860, 1596, 1246 cm^{-1} ; HRMS (ESI-TOF) m/z : calculated for $\text{C}_{17}\text{H}_{18}\text{O}_3\text{Na}$, $[\text{M} + \text{Na}]^+$ 293.1153, found 293.1154.

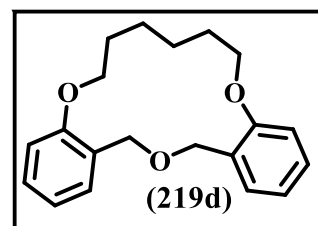
6,7,8,9-tetrahydro-15H,17H-dibenzo[b,g][1,5,9]trioxacyclotridecine (219c): Prepared according to general experimental procedure 5.9.2C, a 0.05 M solution of **100c** (60.5 mg, 0.20 mmol) in (4 mL) 1,4-dioxane solvent was pumped using syringe pump through Omnifit® column (6.6 x 150 mm) packed bed containing 1.7 g of Ni-zeolite filled up



to 7 cm and preheated at 120 °C with the flow rate of 0.1 mL/min at 3.3 to 3.5 back pressure. The collected organic layer was concentrated under reduced pressure and the crude product was purified by column chromatography using (EtOAc/*n*-hexane = 5:95) as an eluent to afford the compound **219c** (32 mg, 56%) as a white solid, weight hourly space velocity (WHSV) = 50 h^{-1} , space-time yield = $11.50 \text{ g L}^{-1} \text{ h}^{-1}$, and starting material recovered **100c** (25 mg, 41%), as semisolid; ^1H NMR (400 MHz, CDCl_3) δ 7.33 (dd, $J = 7.8, 1.7 \text{ Hz}$, 2H), 7.28 – 7.23 (m, 2H), 6.95 (dd, $J = 10.7, 4.4 \text{ Hz}$, 4H), 4.63 (s, 4H), 4.14 (t, $J = 7.4, 3.2 \text{ Hz}$, 4H), 2.07 (td, $J = 5.4, 2.6 \text{ Hz}$, 4H); ^{13}C NMR (100 MHz, CDCl_3) δ 158.7, 131.8, 129.8, 128.7, 121.7, 115.9, 70.7, 69.3, 27.0. FTIR (neat): 2926, 2856, 1455, 1240 cm^{-1} ; HRMS (ESI-TOF) m/z ; calculated for $\text{C}_{18}\text{H}_{20}\text{O}_3\text{Na}$, $[\text{M} + \text{Na}]^+$ 307.1309, found 307.1305.

6,7,8,9,10,11-hexahydro-17H,19H-dibenzo[b,g][1,5,9]trioxacyclopentadecine (219d):

Prepared according to general experimental procedure 5.9.2C, a 0.05 M solution of ((hexane-1,6-diylbis(oxy))bis(2,1-phenylene))dimethanol **100d** (59.3 mg, 0.15 mmol) in (3 mL) 1,4 dioxane solvent was pumped using syringe pump through Omnifit® column (6.6 x 150 mm) packed bed containing 1.7 g of

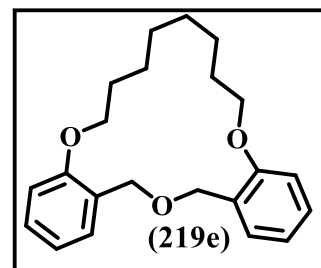


Ni-zeolite filled up to 7 cm and preheated at 120 °C with the flow rate of 0.1 mL/min at 3.3 to 3.5 back pressure. The collected organic layer was concentrated under reduced pressure and the crude product was purified by column chromatography using EtOAc/*n*-hexane (5:95) as an eluent to afford the compound **219d** (34.3 mg, 61%) as a white solid, weight hourly space velocity (WHSV) = 55 h^{-1} , space-time yield = $17.9 \text{ g L}^{-1} \text{ h}^{-1}$, and starting material recovered

100d (34.3 mg, 61%). melting point: 66-68 °C; ¹H NMR (400 MHz, CDCl₃) δ 7.40 (dd, *J* = 7.4, 1.7 Hz, 2H), 7.25 – 7.19 (m, 2H), 6.92 (td, *J* = 7.4, 1.0 Hz, 2H), 6.85 (d, *J* = 8.2 Hz, 2H), 4.66 (s, 4H), 4.06 (t, 4H), 1.83 (dd, *J* = 9.9, 5.3 Hz, 4H), 1.76 – 1.69 (m, 4H); ¹³C NMR (100 MHz, CDCl₃) δ 157.1, 130.7, 129.0, 127.6, 120.6, 111.61, 68.4, 68.1, 28.9, 27.2; FTIR (neat): 2925, 2854, 1453, 1239 cm⁻¹; HRMS (ESI-TOF) *m/z*; calculated for C₂₀H₂₄O₃Na, [M + Na]⁺ 335.1622, found: 335.1624.

6,7,8,9,10,11,12,13-octahydro-19*H*,21*H*-dibenzo[*b,g*][1,5,9]trioxacycloheptadecine

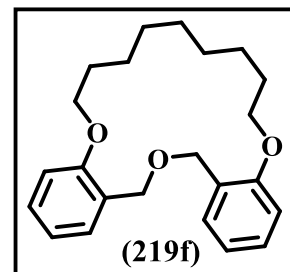
(219e): Prepared according to general experimental procedure 5.9.2C, a 0.05 M solution of **100e** (71.7 mg, 0.2 mmol) in (4 mL) 1,4-dioxane solvent was pumped using syringe pump through Omnifit® column (6.6 x 150 mm) packed bed containing 1.7 g of Ni-Zeolite filled up to 7 cm and preheated at 120 °C with the flow rate of 0.1 mL/min at 3.3 to 3.5 back pressure. The collected



organic layer was concentrated under reduced pressure and the crude product was purified by column chromatography using (EtOAc:*n*-hexane = 5:95) as an eluent to afford the compound **219e** (34.6 mg, 51%) as a white solid, weight hourly space velocity (WHSV) = 55 h⁻¹, space-time yield = 11.31 g L⁻¹ h⁻¹, and starting material recovered **100e** (10 mg, 14 %). melting point: 60-63 °C; ¹H NMR (400 MHz, CDCl₃) δ 7.46 (d, *J* = 7.4 Hz, 2H), 7.26 – 7.19 (m, 2H), 6.95 (t, *J* = 7.4 Hz, 2H), 6.85 (d, *J* = 8.2 Hz, 2H), 4.71 (s, 4H), 4.06 – 4.00 (m, 4H), 1.84 – 1.76 (m, 4H), 1.65 (dd, *J* = 14.5, 7.0 Hz, 4H), 1.48 (dd, *J* = 8.5, 5.2 Hz, 4H); ¹³C NMR (100 MHz, CDCl₃) δ 156.8, 129.6, 128.6, 127.6, 120.4, 111.0, 67.7, 67.6, 28.9, 27.7, 25.2; FTIR (neat): 2930, 2859, 1455, 1286 cm⁻¹; HRMS (ESI-TOF) *m/z*: calculated for C₂₂H₂₉O₃, [M + H]⁺ 341.2116, found 341.2115.

7,8,9,10,11,12,13,14-octahydro-6*H*,20*H*,22*H*-dibenzo[*b,g*][1,5,9]trioxacyclooctadecine

(219f): Prepared according to general experimental procedure 5.9.2C, a 0.05 M solution of **100f** (74.5 mg, 0.2 mmol) in (4 mL) 1,4-dioxane solvent was pumped using syringe pump through Omnifit® column (6.6 x 150 mm) packed bed containing 1.7 g of Ni-Zeolite filled up to 7 cm and preheated at 120 °C with the flow

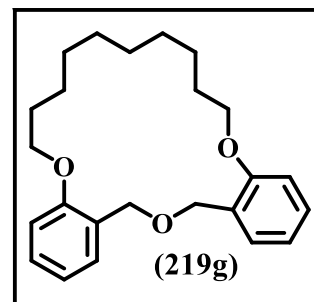


rate of 0.1 mL/min at 3.3 to 3.5 back pressure. The collected organic layer was concentrated under reduced pressure and the crude product was purified by column chromatography using (EtOAc:*n*-hexane = 5:95) as an eluent to afford the compound **219f** (26.2 mg, 37%) as a white solid, weight hourly space velocity (WHSV) = 62 h⁻¹, space-time yield = 6.21 g L⁻¹ h⁻¹, and

starting material recovered **100f** (9.5 mg, 13%), as a semisolid; ^1H NMR (400 MHz, CDCl_3) δ 7.46 (dd, $J = 7.5, 1.6$ Hz, 2H), 7.23 (td, $J = 8.1, 1.8$ Hz, 2H), 6.96 (td, $J = 7.4, 0.9$ Hz, 2H), 6.86 (d, $J = 8.2$ Hz, 2H), 4.70 (s, 4H), 4.02 (t, 4H), 1.84 – 1.77 (m, 4H), 1.63 – 1.55 (m, 4H), 1.47 (ddd, $J = 12.0, 8.9, 4.7$ Hz, 6H); ^{13}C NMR (100 MHz, CDCl_3) δ 156.9, 129.5, 128.6, 127.5, 120.5, 111.3, 68.4, 67.3, 29.4, 29.1, 28.7, 26.7; FTIR (neat): 2931, 2858, 1455, 1240 cm^{-1} ; HRMS (ESI-TOF) m/z : calculated for $\text{C}_{23}\text{H}_{30}\text{O}_3\text{Na}$, $[\text{M} + \text{Na}]^+$ 377.2092, found: 377.2087.

6,7,8,9,10,11,12,13,14,15-decahydro-21H,23H-dibenzo[b,g][1,5,9]trioxacyclononadecine

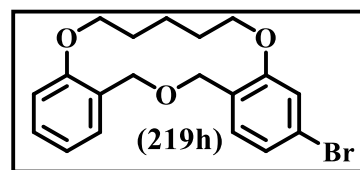
(219g): Prepared according to general experimental procedure 5.9.2C, a 0.05 M solution of **100g** (73.4 mg, 0.199 mmol) in (4 mL) 1,4 dioxane solvent was pumped using syringe pump through Omnifit® column (6.6 x 150 mm) packed bed containing 1.7 g of Ni-Zeolite filled up to 7 cm and preheated at 120 °C with the flow rate of 0.1 mL/min at 3.3 to 3.5 back pressure. The collected



organic layer was concentrated under reduced pressure and the crude product was purified by column chromatography using EtOAc:*n*-hexane (5:95) as an eluent to afford the compound **219g** (27.4 mg, 39%) as a semi solid, weight hourly space velocity (WHSV) = 65 h^{-1} , space-time yield = 6.90 $\text{g L}^{-1} \text{h}^{-1}$, and starting material recovered **100g** (14.3 mg, 19%); ^1H NMR (400 MHz, CDCl_3) δ 7.51 – 7.47 (m, 2H), 7.26 – 7.20 (m, 2H), 6.99 – 6.93 (m, 2H), 6.85 (d, $J = 8.0$ Hz, 2H), 4.72 (s, 4H), 4.01 (t, $J = 5.3$ Hz, 4H), 1.78 (dt, $J = 10.7, 5.9$ Hz, 4H), 1.57 (d, $J = 3.8$ Hz, 4H), 1.40 (d, $J = 8.5$ Hz, 8H); ^{13}C NMR (100 MHz, CDCl_3) δ 156.7, 128.4, 128.4, 127.6, 120.4, 111.2, 67.9, 67.8, 28.9, 28.0, 27.9, 25.9; FTIR (neat): 2925, 2854, 1453, 1239 cm^{-1} ; HRMS (ESI-TOF) m/z : calculated for $\text{C}_{24}\text{H}_{32}\text{O}_3\text{Na}$, $[\text{M} + \text{Na}]^+$ 391.2249 found 391.2263.

3-bromo-7,8,9,10-tetrahydro-6H,16H,18H-dibenzo[b,g][1,5,9]trioxacyclotetradecine

(219h): Prepared according to general experimental procedure 5.9.2C, a 0.05 M solution of **100h** (79 mg, 0.199 mmol) in (4 mL) 1,4-dioxane solvent was pumped using syringe pump through Omnifit® column (6.6 x 150 mm) packed bed

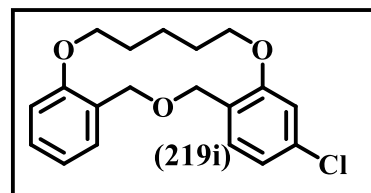


containing 1.7 g of Ni-Zeolite filled up to 7 cm and preheated at 120 °C with the flow rate of 0.1 mL/min at 3.3 to 3.5 back pressure. The collected organic layer was concentrated under reduced pressure and the crude product was purified by column chromatography using (EtOAc:*n*-hexane = 8:92) as an eluent to afford the compound **219h** (52.1 mg, 69 %) as a white solid, weight hourly space velocity (WHSV) = 67 h^{-1} , space-time yield = 23.04 $\text{g L}^{-1} \text{h}^{-1}$, and starting material recovered **100h** (8.5 mg, 11%). melting point: 139-142 °C; ^1H NMR (400

MHz, CDCl₃) δ 7.44 (d, J = 2.5 Hz, 1H), 7.31 (ddd, J = 6.2, 4.7, 2.1 Hz, 2H), 7.23 (dd, J = 7.8, 1.5 Hz, 1H), 6.88 (td, J = 7.4, 1.0 Hz, 1H), 6.83 (d, J = 8.2 Hz, 1H), 6.71 (d, J = 8.7 Hz, 1H), 4.58 (s, 2H), 4.54 (s, 2H), 4.04 (dd, J = 10.3, 5.5 Hz, 4H), 1.91 – 1.77 (m, 6H); ¹³C NMR (100 MHz, CDCl₃) δ 158.2, 157.3, 134.5, 132.2, 132.0, 129.8, 128.9, 126.4, 120.3, 113.8, 112.3, 111.9, 69.5, 68.6, 67.4, 66.8, 27.9, 27.9, 21.3; FTIR (neat): 2925, 2866, 1456, 1270 cm⁻¹; HRMS (ESI-TOF) m/z : calculated for C₁₉H₂₁BrO₃Na, [M + Na]⁺ 399.0572, found 399.0568.

3-chloro-7,8,9,10-tetrahydro-6*H*,16*H*,18*H*-dibenzo[*b,g*][1,5,9]trioxacyclotetradecine

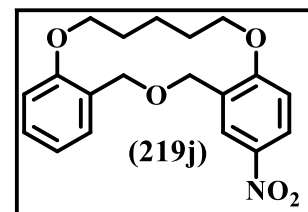
(219i): Prepared according to general experimental procedure 5.9.2C, a 0.05 M solution of **100i** (53 mg, 0.151 mmol) in (3 mL) dioxane solvent was pumped using syringe pump through Omnifit® column (6.6 x 150 mm) packed bed containing 1.7 g



of Ni-zeolite filled up to 7 cm and preheated at 120 °C with the flow rate of 0.1 mL/min at 3.3 to 3.5 back pressure was maintained in the reaction. The collected organic layer was concentrated under reduced pressure and the crude product was purified by column chromatography using EtOAc:*n*-hexane (5:95) as an eluent to afford the compound **219i** (27.6 mg, 55%) as a white solid, weight hourly space velocity (WHSV) = 59 h⁻¹, space-time yield = 12.97 g L⁻¹ h⁻¹, and starting material recovered **100i** (17.8 mg, 32%), as a semisolid. ¹H NMR (400 MHz, CDCl₃) δ 7.35 (dd, J = 7.4, 1.7 Hz, 1H), 7.31 – 7.25 (m, 2H), 6.96 – 6.87 (m, 3H), 6.86 (d, J = 1.9 Hz, 1H), 4.61 (s, 2H), 4.58 (s, 2H), 4.08 (dt, J = 6.8, 5.1 Hz, 4H), 1.99 – 1.80 (m, 6H); ¹³C NMR (100 MHz, CDCl₃) δ 158.8, 158.2, 134.9, 132.6, 131.9, 129.8, 126.4, 125.3, 120.3, 120.2, 112.7, 111.9, 69.4, 68.7, 67.2, 66.7, 27.9, 27.8, 21.2. FTIR (neat): 2934, 2871, 1503, 1272 cm⁻¹; HRMS (ESI-TOF) m/z : calculated for C₁₉H₂₁O₃ClNa, [M + Na]⁺ 355.1078, found 355.1072.

2-nitro-7,8,9,10-tetrahydro-6*H*,16*H*,18*H*-dibenzo[*b,g*][1,5,9]trioxacyclotetradecine

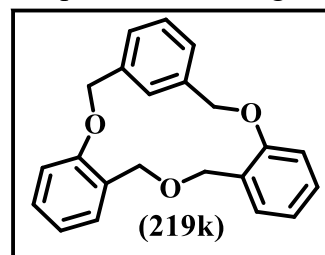
(219j): Prepared according to general experimental procedure 5.9.2C, a 0.05 M solution of **1j** (54.2 mg, 0.15 mmol) in (3 mL) 1,4-dioxane solvent was pumped using syringe pump through Omnifit® column (6.6 x 150 mm) packed bed containing 1.7 g of Ni-zeolite



filled up to 7 cm and preheated at 120 °C with the flow rate of 0.1 mL/min at 3.3 to 3.5 back pressure. The collected organic layer was concentrated under reduced pressure and the crude product was purified by column chromatography using EtOAc/*n*-hexane (5:95) as an eluent to afford the compound **219j** (25.4 mg, 49%) as a white solid, weight hourly space velocity (WHSV) = 61 h⁻¹, space-time yield = 10.64 g L⁻¹ h⁻¹, and starting material recovered **100j** (9.8

mg, 18 %). melting point: 157-158 °C; ^1H NMR (400 MHz, CDCl_3) δ 8.25 (d, $J = 2.8$ Hz, 1H), 8.17 (dd, $J = 9.0, 2.8$ Hz, 1H), 7.32 (dd, $J = 7.4, 1.7$ Hz, 1H), 7.28 – 7.21 (m, 1H), 6.89 (ddd, $J = 11.8, 6.4, 2.7$ Hz, 2H), 6.83 (d, $J = 8.2$ Hz, 1H), 4.61 (s, 2H), 4.61 (s, 2H), 4.15 (t, $J = 4.7$ Hz, 2H), 4.06 (t, $J = 5.0$ Hz, 2H), 1.92 – 1.80 (m, 6H); ^{13}C NMR (100 MHz, CDCl_3) δ 163.4, 158.1, 140.8, 132.1, 130.1, 127.7, 127.5, 126.2, 125.9, 120.4, 111.87, 111.4, 69.7, 68.7, 67.9, 66.4, 27.7, 27.5, 21.0; FTIR (neat): 2934, 2871, 1503, 1272 cm^{-1} ; HRMS (ESI-TOF) m/z : calculated for $\text{C}_{19}\text{H}_{22}\text{NO}_5$, $[\text{M} + \text{H}]^+$ 344.1499, found 344.1502.

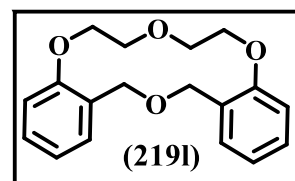
2,6,9-trioxa-1,7(1,2),4(1,3)-tribenzenacyclodecaphane (219k): Prepared according to general experimental procedure 5.9.2C, a 0.05 M solution of **100k** (70.0 mg, 0.199 mmol) in (4 mL) dioxan solvent was pumped using syringe pump through Omnifit® column (6.6 x 150 mm) packed bed containing 1.7 g of Ni-zeolite filled up to 7 cm and preheated at 120 °C with the flow rate of 0.1 mL/min at 3.3 to 3.5



back pressure. The collected organic layer was concentrated under reduced pressure and the crude product was purified by column chromatography using EtOAc/*n*-hexane (5:95) as an eluent to afford the compound **219k** (35.7 mg, 54%) as a white solid, weight hourly space velocity (WHSV) = 59 h^{-1} , space-time yield = 12.36 $\text{g L}^{-1} \text{h}^{-1}$, melting point: 143-145 °C; ^1H NMR (400 MHz, CDCl_3) δ 8.19 (s, 1H), 7.38 (dd, $J = 7.3, 1.6$ Hz, 2H), 7.24 (td, $J = 7.9, 1.8$ Hz, 3H), 7.13 (d, $J = 7.5$ Hz, 2H), 6.91 (dd, $J = 11.7, 5.3$ Hz, 4H), 5.20 (s, 4H), 4.67 (s, 4H); ^{13}C NMR (100 MHz, CDCl_3) δ 157.8, 138.6, 132.5, 129.9, 127.7, 126.7, 126.2, 124.8, 120.8, 112.8, 69.3, 69.1; FTIR (neat): 2913, 2878, 1495, 1254 cm^{-1} ; HRMS (ESI-TOF) m/z : calculated for $\text{C}_{22}\text{H}_{20}\text{O}_3\text{Na}$, $[\text{M} + \text{Na}]^+$ 355.1310, found 355.1316.

6,7,10,11-tetrahydro-9H,17H,19H-dibenzo[*e,j*][1,4,8,12]tetraoxacyclopentadecine (219l):

Prepared according to general experimental procedure 5.9.2C, a 0.05 M solution of **100l** (63.8 mg, 0.199 mmol) in (4 mL) dioxan solvent was pumped using syringe pump through Omnifit® column (6.6 x 150 mm) packed bed containing 1.7 g of Ni-zeolite filled up to 7 cm

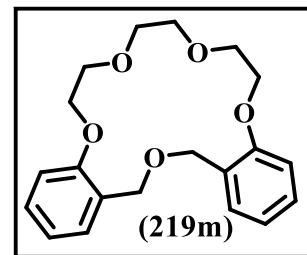


and preheated at 120 °C with the flow rate of 0.1 mL/min at 3.3 to 3.5 back pressure. The collected organic layer was concentrated under reduced pressure and the crude product was purified by column chromatography using (EtOAc:*n*-hexane = 10:90) as an eluent to afford the compound **219l** (35.7 mg, 59%) as a white solid, weight hourly space velocity (WHSV) = 53 h^{-1} , space-time yield = 13.50 $\text{g L}^{-1} \text{h}^{-1}$, melting point: 112-114 °C; ^1H NMR (400 MHz, CDCl_3) δ 7.40 – 7.35 (m, 2H), 7.27 – 7.20 (m, 2H), 6.94 (t, $J = 7.4$ Hz, 2H), 6.85 (d, $J = 8.2$ Hz, 2H),

4.68 (s, 4H), 4.20 – 4.14 (m, 4H), 3.92 – 3.87 (m, 4H); ^{13}C NMR (100 MHz, CDCl_3) δ 157.5, 131.3, 129.3, 127.8, 120.9, 112.4, 69.9, 68.5, 67.9; FTIR (neat): 2871, 1492, 1249 cm^{-1} ; HRMS (ESI-TOF) m/z : calculated for $\text{C}_{18}\text{H}_{20}\text{O}_4\text{Na}$, $[\text{M} + \text{Na}]^+$ 323.1259, found 323.1253.

6,7,9,10,12,13-hexahydro-19*H*,21*H*-dibenzo[*k,p*][1,4,7,10,14]pentaoxacycloheptadecine

(219m): Prepared according to general experimental procedure 5.9.2C, a 0.05 M solution of **100m** (72.4 mg, 0.199 mmol) in (4 mL) 1,4-dioxane solvent was pumped using syringe pump through Omnifit® column (6.6 x 150 mm) packed bed containing 1.7 g of Ni-zeolite filled up to 7 cm and preheated at 120 °C with the flow

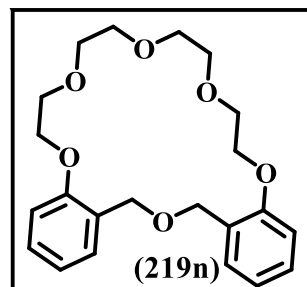


rate of 0.1 mL/min at 3.3 to 3.5 back pressure. The collected organic layer was concentrated under reduced pressure and the crude product was purified by column chromatography using (EtOAc/*n*-hexane = 15:85) as an eluent to afford the compound **219m** (30.5 mg, 44%) as a semisolid, weight hourly space velocity (WHSV) = 61 h^{-1} , space-time yield = 8.60 $\text{g L}^{-1} \text{h}^{-1}$, ^1H NMR (400 MHz, CDCl_3) δ 7.42 (dd, J = 7.5, 1.6 Hz, 2H), 7.23 (td, J = 8.0, 1.8 Hz, 2H), 6.96 (td, J = 7.4, 0.9 Hz, 2H), 6.85 (d, J = 8.2 Hz, 2H), 4.73 (s, 4H), 4.17 – 4.13 (m, 4H), 3.92 – 3.89 (m, 4H), 3.78 (s, 4H); ^{13}C NMR (100 MHz, CDCl_3) δ 156.7, 130.1, 128.7, 128.1, 121.0, 111.7, 70.8, 69.8, 68.1, 67.5; FTIR (neat): 2912, 2871, 1451, 1243 cm^{-1} ; HRMS (ESI-TOF) m/z ; calculated for $\text{C}_{20}\text{H}_{24}\text{O}_5\text{Na}$, $[\text{M} + \text{Na}]^+$ 367.1521, found 367.1515.

6,7,9,10,12,13,15,16-octahydro-22*H*,24*H*-

dibenzo[*n,s*][1,4,7,10,13,17]hexaoxacycloicosine (219n):

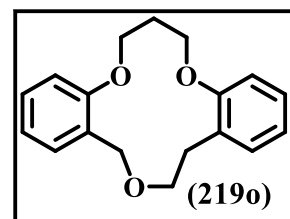
Prepared according to general experimental procedure 5.9.2C, a 0.05 M solution of **100n** (81.3 mg, 0.2 mmol) in (4 mL) 1,4-dioxane solvent was pumped using syringe pump through Omnifit® column (6.6 x 150 mm) packed bed containing 1.7 g of Ni-Zeolite filled up



to 7 cm and preheated at 120 °C with the flow rate of 0.1 mL/min at 3.3 to 3.5 back pressure. The collected organic layer was concentrated under reduced pressure and the crude product was purified by column chromatography using (EtOAc:*n*-hexane = 10:90) as an eluent to afford the compound **219n** (36.4 mg, 47%) as a white solid, weight hourly space velocity (WHSV) = 69 h^{-1} , space-time yield = 10.97 $\text{g L}^{-1} \text{h}^{-1}$, melting point: 90-92 °C; ^1H NMR (400 MHz, CDCl_3) δ 7.48 (dd, J = 7.4, 1.6 Hz, 2H), 7.23 (td, J = 7.9, 1.7 Hz, 2H), 7.01 – 6.95 (m, 2H), 6.88 – 6.83 (m, 2H), 4.73 (s, 4H), 4.19 – 4.12 (m, 4H), 3.88 – 3.84 (m, 4H), 3.82 – 3.76 (m, 4H), 3.76 – 3.70 (m, 4H); ^{13}C NMR (100 MHz, CDCl_3) δ 156.4, 128.9, 128.5, 128.0, 121.1, 111.8, 71.5,

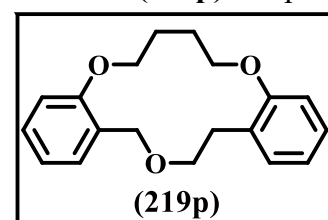
70.8, 69.8, 68.6, 67.6; FTIR (neat): 2869, 1452, 1244 cm^{-1} ; HRMS (ESI-TOF) m/z : calculated for $\text{C}_{22}\text{H}_{28}\text{O}_6\text{Na}$, $[\text{M} + \text{Na}]^+$ 411.1783, found: 411.1779.

7,8,16,17-tetrahydro-6*H*,14*H*-dibenzo[*c,j*][1,5,9]trioxacyclotridecine (219o): Prepared according to general experimental procedure C, a 0.05 M solution of 2-(2-(3-(2-(hydroxymethyl)phenoxy)propoxy)phenyl)ethan-1-ol **100o** (60 mg, 0.188 mmol) in (4 mL) 1,4-dioxane solvent was pumped using syringe pump through Omnifit® column (6.6 x 150 mm) packed bed containing 1.7 g of Ni-zeolite filled up to 7 cm and



preheated at 120 °C with the flow rate of 0.1 mL/min at 3.3 to 3.5 back pressure. The collected organic layer was concentrated under reduced pressure and the crude product was purified by column chromatography using EtOAc/*n*-hexane (5:95) as an eluent to afford the compound **219o** (34.1 mg, 60%) as a white solid, weight hourly space velocity (WHSV) = 47 h^{-1} , space-time yield = 13.12 $\text{g L}^{-1} \text{h}^{-1}$, melting point: 61-65 °C; ^1H NMR (400 MHz, CDCl_3) δ 7.43 – 7.37 (m, 1H), 7.30 – 7.23 (m, 1H), 7.16 (t, J = 8.2 Hz, 2H), 6.96 (t, J = 7.5 Hz, 1H), 6.89 – 6.82 (m, 2H), 6.79 (d, J = 8.0 Hz, 1H), 4.71 (s, 2H), 4.22 – 4.14 (m, 4H), 3.61 – 3.54 (m, 2H), 3.03 (dd, J = 9.3, 6.7 Hz, 2H), 2.36 (dt, J = 9.6, 4.8 Hz, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 157.6, 157.2, 132.7, 131.1, 129.5, 127.6, 127.3, 127.0, 120.8, 120.6, 110.8, 110.4, 68.3, 68.1, 67.9, 63.8, 30.6, 29.4; FTIR (neat): 2929, 2865, 1455, 1240 cm^{-1} ; HRMS (ESI-TOF) m/z : calculated for $\text{C}_{18}\text{H}_{20}\text{O}_3\text{Na}$, $[\text{M} + \text{Na}]^+$ 307.1309, found 307.1307.

6,7,8,9,17,18-hexahydro-15*H*-dibenzo[*b,h*][1,5,10]trioxacyclotetradecine (219p): Prepared according to general experimental procedure 5.9.2C, a 0.05 M solution of **100p** (63.2 mg, 0.199 mmol) in (4 mL) 1,4-dioxane solvent was pumped using syringe pump through Omnifit® column (6.6 x 150 mm) packed bed containing 1.7 g of Ni-zeolite

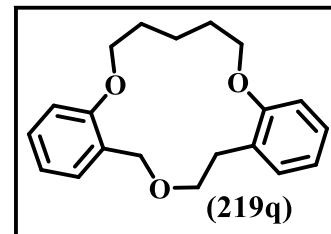


filled up to 7 cm and preheated at 120 °C with the flow rate of 0.1 mL/min at 3.3 to 3.5 back pressure. The collected organic layer was concentrated under reduced pressure and the crude product was purified by column chromatography using (EtOAc/*n*-hexane = 5:95) as an eluent to afford the compound **219p** (39.8 mg, 67%) as a semisolid, weight hourly space velocity (WHSV) = 53 h^{-1} , space-time yield = 17.10 $\text{g L}^{-1} \text{h}^{-1}$, ^1H NMR (400 MHz, CDCl_3) δ 7.35 (dd, J = 7.3, 1.6 Hz, 1H), 7.30 – 7.24 (m, 1H), 7.18 (td, J = 7.9, 1.7 Hz, 1H), 7.14 (dd, J = 7.4, 1.5 Hz, 1H), 6.95 (dd, J = 12.0, 4.6 Hz, 2H), 6.88 (dd, J = 7.4, 0.9 Hz, 1H), 6.82 (d, J = 8.1 Hz, 1H), 4.64 (s, 2H), 4.16 (t, J = 5.2 Hz, 2H), 4.05 (t, J = 4.9 Hz, 2H), 3.86 – 3.79 (m, 2H), 2.99 – 2.91 (m, 2H), 2.13 – 2.07 (m, 4H); ^{13}C NMR (100 MHz, CDCl_3) δ 157.9, 157.6, 130.9, 130.8,

129.4, 128.7, 127.7, 127.4, 121.1, 120.6, 113.7, 111.8, 71.4, 68.9, 68.6, 67.9, 32.5, 27.1, 26.3. FTIR (neat): 2928, 2861, 1455 cm^{-1} ; HRMS (ESI-TOF) m/z : calculated for $\text{C}_{19}\text{H}_{22}\text{O}_3\text{Na}$, $[\text{M} + \text{Na}]^+$ 321.1466, found 321.1459.

7,8,9,10,18,19-hexahydro-6*H*,16*H*-dibenzo[*b,h*][1,5,10]trioxacyclopentadecine (219q):

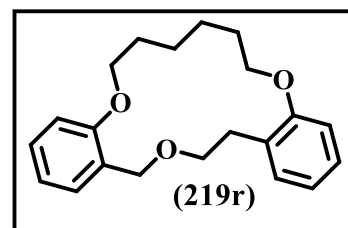
Prepared according to general experimental procedure C, a 0.05 M solution of 2-((5-(2-(hydroxymethyl)phenoxy)pentyl)oxy)phenyl)ethan-1-ol **100q** (66.1 mg, 0.2 mmol) in (4 mL) 1,4-dioxane solvent was pumped using syringe pump through Omnifit® column (6.6 x 150 mm)



packed bed containing 1.7 g of Ni-Zeolite filled up to 7 cm and preheated at 120 °C with the flow rate of 0.1 mL/min at 3.3 to 3.5 back pressure. The collected organic layer was concentrated under reduced pressure and the crude product was purified by column chromatography using (EtOAc/*n*-hexane = 5:95) as an eluent to afford the compound **219q** (39.8 mg, 64%) as a semisolid, weight hourly space velocity (WHSV) = 52 h^{-1} , space-time yield = 16.33 $\text{g L}^{-1} \text{h}^{-1}$, and starting material recovered **100m** (7.3 mg, 11%). ^1H NMR (400 MHz, CDCl_3) δ 7.37 (dd, J = 7.4, 1.6 Hz, 1H), 7.27 (ddd, J = 6.8, 5.7, 1.7 Hz, 1H), 7.18 (ddd, J = 7.3, 6.7, 2.6 Hz, 2H), 6.97 – 6.83 (m, 4H), 4.63 (s, 2H), 4.11 (t, J = 5.1 Hz, 2H), 4.03 (t, 2H), 3.77 – 3.70 (m, 2H), 3.04 – 2.96 (m, 2H), 1.96 (d, J = 7.3 Hz, 2H), 1.87 (ddd, J = 12.0, 8.8, 4.8 Hz, 4H); ^{13}C NMR (100 MHz, CDCl_3) δ 157.5, 157.3, 131.0, 130.5, 129.2, 127.7, 127.6, 127.3, 120.6, 120.5, 111.8, 111.8, 71.16, 67.8, 67.1, 67.0, 32.1, 28.9, 28.8, 22.7; FTIR (neat): 2929, 2865, 1455, 1240 cm^{-1} ; HRMS (ESI-TOF) m/z : calculated for $\text{C}_{20}\text{H}_{24}\text{O}_3\text{Na}$, $[\text{M} + \text{Na}]^+$ 335.1622, found 335.1620.

6,7,8,9,10,11,19,20-octahydro-17*H*-dibenzo[*b,h*][1,5,10]trioxacyclohexadecine (219r):

Prepared according to general experimental procedure 5.9.2C, a 0.05 M solution of **100r** (67.0 mg, 0.194 mmol) in (4 mL) 1,4-dioxane solvent was pumped using syringe pump through Omnifit® column (6.6 x 150 mm) packed bed containing 1.7 g

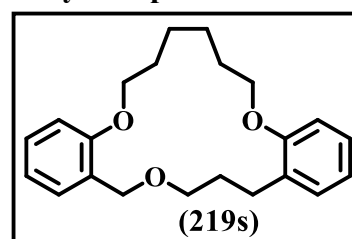


of Ni-Zeolite filled up to 7 cm and preheated at 120 °C with the flow rate of 0.1 mL/min at 3.3 to 3.5 back pressure. The collected organic layer was concentrated under reduced pressure and the crude product was purified by column chromatography using (EtOAc: *n*-hexane = 5:95) as an eluent to afford the compound **219r** (42.1 mg, 66%) as a semisolid, weight hourly space velocity (WHSV) = 55 h^{-1} , space-time yield = 17.81 $\text{g L}^{-1} \text{h}^{-1}$, and starting material recovered **100r** (5.8 mg, 8%). ^1H NMR (400 MHz,

CDCl₃) δ 7.37 (d, J = 7.4 Hz, 1H), 7.31 – 7.24 (m, 1H), 7.22 – 7.15 (m, 2H), 6.95 (t, J = 7.4 Hz, 1H), 6.89 (t, J = 7.2 Hz, 2H), 6.84 (d, J = 8.1 Hz, 1H), 4.60 (s, 2H), 4.11 – 4.05 (m, 2H), 4.05 – 3.96 (m, 2H), 3.75 – 3.66 (m, 2H), 3.05 – 2.95 (m, 2H), 1.93 – 1.83 (m, 4H), 1.78 (dd, J = 6.0, 2.9 Hz, 4H). ¹³C NMR (100 MHz, CDCl₃) δ 157.6, 157.4, 130.8, 130.3, 129.2, 127.7, 126.9, 126.8, 120.4, 120.3, 111.3, 110.8, 70.9, 68.8, 68.6, 68.4, 31.5, 29.7, 29.6, 28.5, 28.4; FTIR (neat): 2925, 2859, 1456, 1238 cm⁻¹; HRMS (ESI-TOF) m/z : calculated for C₂₁H₂₇O₃, [M + H]⁺ 327.1960, found: 327.1956.

6,7,8,9,10,11,20,21-octahydro-17*H*,19*H*-dibenzo[*b,i*][1,5,11]trioxacycloheptadecine

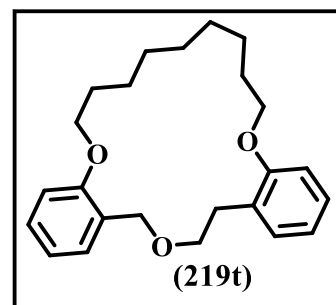
(219s): Prepared according to general experimental procedure 5.9.2C, a 0.05 M solution of **100s** (71.7 mg, 0.2 mmol) in (4 mL) 1,4-dioxane solvent was pumped using syringe pump through Omnifit® column (6.6 x 150 mm) packed bed containing 1.7 g of Ni-Zeolite filled up to 7 cm and preheated at 120 °C with the



flow rate of 0.1 mL/min at 3.3 to 3.5 back pressure. The collected organic layer was concentrated under reduced pressure and the crude product was purified by column chromatography using (EtOAc:*n*-hexane = 5:95) as an eluent to afford the compound **219s** (41.7 mg, 61%) as a white solid, weight hourly space velocity (WHSV) = 57 h⁻¹, space-time yield = 16.31 g L⁻¹ h⁻¹, and starting material recovered **219s** (12.2 mg, 17%). melting point: 62-64 °C; ¹H NMR (400 MHz, CDCl₃) δ 7.33 (dd, J = 7.4, 1.6 Hz, 1H), 7.29 – 7.23 (m, 1H), 7.18 – 7.09 (m, 2H), 6.94 (td, J = 7.4, 0.9 Hz, 1H), 6.91 – 6.82 (m, 3H), 4.55 (s, 2H), 4.09 – 3.99 (m, 4H), 3.63 (t, J = 6.6 Hz, 2H), 2.71 – 2.63 (m, 2H), 1.97 – 1.89 (m, 2H), 1.89 – 1.80 (m, 4H), 1.70 (dd, J = 6.4, 3.4 Hz, 4H); ¹³C NMR (100 MHz, CDCl₃) δ 157.6, 157.1, 131.3, 130.6, 130.0, 129.1, 127.6, 127.0, 120.6, 120.4, 112.4, 111.4, 70.4, 68.9, 68.0, 67.7, 30.0, 29.7, 29.6, 27.9, 27.3, 27.1; FTIR (neat): 2930, 2859, 1491, 1240 cm⁻¹; HRMS (ESI-TOF) m/z : calculated for C₂₂H₂₉O₃, [M + H]⁺ 341.2116, found 341.2114.

7,8,9,10,11,12,13,14,22,23-decahydro-6*H*,20*H*

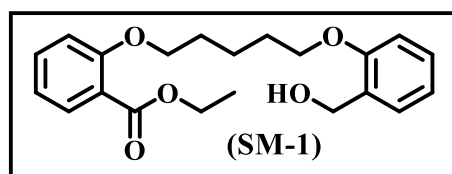
dibenzo[*b,h*][1,5,10]trioxacyclononadecine (219t): Prepared according to general experimental procedure 5.9.2C, a 0.05 M solution of **100t** (77.0 mg, 0.199 mmol) in (4 mL) dioxan solvent was pumped using syringe pump through Omnifit® column (6.6 x 150 mm) packed bed containing 1.7 g of Ni-zeolite filled up to



7 cm and preheated at 120 °C with the flow rate of 0.1 mL/min at 3.3 to 3.5 back pressure. The collected organic layer was concentrated under reduced pressure and the crude product was

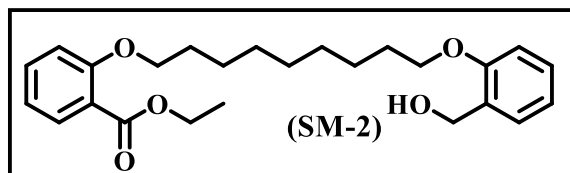
purified by column chromatography using (EtOAc:*n*-hexane = 5:95) as an eluent to afford the compound **219t** (30.3 mg, 41%) as a semisolid, weight hourly space velocity (WHSV) = 62 h⁻¹, space-time yield = 7.96 g L⁻¹ h⁻¹, ¹H NMR (400 MHz, CDCl₃) δ 7.43 (dd, *J* = 7.5, 1.5 Hz, 1H), 7.26 – 7.22 (m, 1H), 7.22 – 7.16 (m, 2H), 6.95 (td, *J* = 7.4, 0.8 Hz, 1H), 6.89 (td, *J* = 7.5, 1.0 Hz, 1H), 6.84 (dd, *J* = 11.2, 3.9 Hz, 2H), 4.65 (s, 2H), 4.05 – 4.01 (m, 2H), 4.01 – 3.97 (m, 2H), 3.84 – 3.77 (m, 2H), 3.10 – 3.02 (m, 2H), 1.86 – 1.78 (m, 4H), 1.62 – 1.53 (m, 4H), 1.51 – 1.42 (m, 6H); ¹³C NMR (100 MHz, CDCl₃) δ 157.4, 156.7, 130.9, 129.0, 128.6, 127.6, 127.2, 126.8, 120.4, 120.3, 111.1, 110.9, 70.9, 68.5, 67.9, 67.7, 31.6, 29.8, 29.2, 28.7, 28.4, 27.2, 26.9. FTIR (neat): 2926, 2856, 1492, 1239 cm⁻¹; HRMS (ESI-TOF) *m/z*: calculated for C₂₄H₃₂O₃Na, [M + Na]⁺ 391.5249, found: 391.5240.

Ethyl 2-((5-(2-(hydroxymethyl)phenoxy)pentyl)oxy)benzoate (SM-1): Prepared according to general experimental procedure 5.9.2B, using (2-((5-bromopentyl)oxy)phenyl)methanol (500 mg, 1.08 mmol), potassium carbonate (K₂CO₃) (281.9 mg, 1.08 mmol), and ethyl 2-hydroxybenzoate (304 mg, 1.08



mmol). The residue was purified by using column chromatography with EtOAc/*n*-hexane (40:60) as the eluent to afford the desired product **SM-1** (580 mg, 1.62 mmol, 88% yield) as a semisolid. ¹H NMR (400 MHz, CDCl₃) δ 7.77 (dd, *J* = 7.7, 1.7 Hz, 1H), 7.46 – 7.39 (m, 1H), 7.30 – 7.26 (m, 1H), 7.24 (dd, *J* = 7.9, 1.7 Hz, 1H), 6.99 – 6.94 (m, 2H), 6.94 – 6.90 (m, 1H), 6.87 (d, *J* = 8.1 Hz, 1H), 4.70 (d, *J* = 5.8 Hz, 2H), 4.34 (q, *J* = 7.1 Hz, 2H), 4.06 (td, *J* = 6.3, 4.6 Hz, 4H), 1.97 – 1.86 (m, 4H), 1.76 – 1.67 (m, 2H), 1.36 (t, *J* = 7.1 Hz, 3H), OH peak have exchanged with deuterium of CDCl₃; ¹³C NMR (100 MHz, CDCl₃) δ 166.7, 158.6, 156.9, 133.3, 131.6, 129.3, 129.0, 128.8, 120.9, 120.7, 120.2, 113.2, 111.2, 68.6, 67.9, 62.2, 60.9, 29.1, 29.1, 22.9, 14.4; FTIR (neat): 3500, 2941, 1713, 1600, 1492, 1243 cm⁻¹; HRMS (ESI-TOF) *m/z*: calculated for C₂₁H₂₆O₅Na, [M + Na]⁺ 381.1677, found 381.1670.

Ethyl 2-((9-(2-(hydroxymethyl)phenoxy)nonyl)oxy)benzoate (SM-2): Prepared according to general experimental procedure 5.9.2B, using (2-((9-bromononyl)oxy)phenyl)methanol (600 mg, 1.90 mmol), potassium carbonate (K₂CO₃)

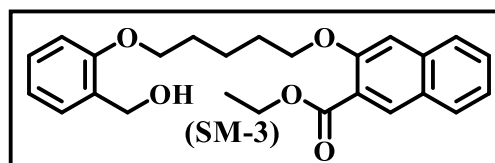


(262.2 mg, 1.90 mmol), and ethyl 2-hydroxybenzoate (316.2 mg, 1.90 mmol). The residue was purified by using column chromatography with EtOAc/*n*-hexane (40:60) as the eluent to afford the desired product **SM-2** (660 mg, 1.65 mmol, 86% yield) as a semisolid. ¹H NMR (400 MHz,

CDCl₃) δ 7.77 (dd, J = 8.0, 1.8 Hz, 1H), 7.42 (ddd, J = 8.3, 7.5, 1.8 Hz, 1H), 7.25 (ddd, J = 9.7, 6.9, 3.8 Hz, 2H), 6.98 – 6.90 (m, 3H), 6.87 (d, J = 8.1 Hz, 1H), 4.69 (d, J = 5.7 Hz, 2H), 4.35 (q, J = 7.1 Hz, 2H), 4.02 (td, J = 6.5, 3.4 Hz, 4H), 2.45 (s, 1H), 1.81 (dt, J = 13.4, 6.7 Hz, 4H), 1.48 (dd, J = 10.7, 7.8 Hz, 4H), 1.37 (dd, J = 8.7, 5.6 Hz, 9H); ¹³C NMR (100 MHz, CDCl₃) δ 166.8, 158.6, 157.1, 133.3, 131.6, 129.3, 129.0, 128.7, 121.0, 120.6, 120.1, 113.2, 111.2, 68.9, 68.0, 62.5, 60.7, 29.6, 29.4, 29.3, 26.3, 26.1, 14.4; FTIR (neat): 3456, 2930, 1700, 1610, 1490 cm⁻¹; HRMS (ESI-TOF) m/z : calculated for C₂₅H₃₄O₅Na, [M + Na]⁺ 437.2303, found 437.2303.

Ethyl 3-((5-(2-(hydroxymethyl)phenoxy)pentyl)oxy)-2-naphthoate (SM-3): Prepared according to general experimental procedure 5.9.2B,

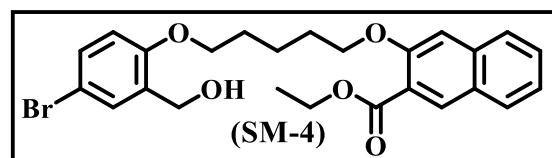
using 2-((5-bromopentyl)oxy)phenylmethanol (560 mg, 2.05 mmol), potassium carbonate (K₂CO₃) (549 mg, 3.98 mmol), and ethyl 3-hydroxy-2-naphthoate



(443 mg, 2.05 mmol). The residue was purified by using column chromatography with EtOAc/*n*-hexane = 40:60 as the eluent to afford the desired product **SM-3** (740 mg, 1.81 mmol, 88% yield) as a semisolid. ¹H NMR (400 MHz, CDCl₃) δ 8.27 (s, 1H), 7.81 (d, J = 8.1 Hz, 1H), 7.71 (d, J = 8.2 Hz, 1H), 7.50 (ddd, J = 8.2, 6.9, 1.2 Hz, 1H), 7.41 – 7.32 (m, 1H), 7.30 – 7.22 (m, 2H), 7.18 (s, 1H), 6.93 (td, J = 7.4, 0.8 Hz, 1H), 6.88 (d, J = 8.2 Hz, 1H), 4.71 (d, J = 5.7 Hz, 2H), 4.41 (q, J = 7.1 Hz, 2H), 4.17 (t, J = 6.3 Hz, 2H), 4.07 (t, J = 6.3 Hz, 2H), 2.03 – 1.89 (m, 4H), 1.82 – 1.72 (m, 2H), 1.41 (t, J = 7.1 Hz, 3H), OH peak have exchanged with deuterium of CDCl₃; ¹³C NMR (100 MHz, CDCl₃) δ 156.9, 155.1, 136.1, 132.5, 129.4, 129.0, 128.8, 128.8, 128.3, 127.7, 126.5, 124.4, 122.7, 120.7, 111.2, 107.7, 68.5, 67.9, 62.2, 61.2, 29.1, 29.0, 23.0, 14.5; FTIR (neat): 3233, 2940, 2851, 1739, 1705, 1600, 1246 cm⁻¹; HRMS (ESI-TOF) m/z : [M + Na]⁺ calculated for C₂₅H₂₈O₅Na, 431.1834, found 431.1825.

Ethyl 3-((5-(4-bromo-2-(hydroxymethyl)phenoxy)pentyl)oxy)-2-naphthoate (SM-4):

Prepared according to general experimental procedure 5.9.2B, using (5-bromo-2-((5-bromopentyl)oxy)phenyl)methanol (700 mg, 1.99 mmol), potassium carbonate (K₂CO₃) (549

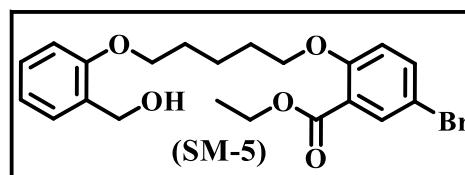


mg, 3.98 mmol), and ethyl 3-hydroxy-2-naphthoate (430 mg, 1.99 mmol). The residue was purified by using column chromatography with EtOAc/*n*-hexane = 40:60 as the eluent to afford the desired product **SM-4** (810 mg, 1.66 mmol, 84% yield) as a semisolid. ¹H NMR (400 MHz, CDCl₃) δ 8.26 (s, 1H), 7.81 (d, J = 8.1 Hz, 1H), 7.71 (d, J = 8.2 Hz, 1H), 7.54 – 7.46 (m, 1H),

7.44 (d, $J = 2.5$ Hz, 1H), 7.39 – 7.29 (m, 2H), 7.17 (s, 1H), 6.72 (d, $J = 8.6$ Hz, 1H), 4.66 (d, $J = 5.7$ Hz, 2H), 4.40 (q, $J = 7.1$ Hz, 2H), 4.16 (t, $J = 6.1$ Hz, 2H), 4.02 (dd, $J = 7.0, 3.9$ Hz, 2H), 2.45 (s, 1H), 2.01 – 1.86 (m, 4H), 1.79 – 1.69 (m, 2H), 1.41 (t, $J = 7.1$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 166.6, 155.7, 155.1, 136.1, 132.5, 131.7, 131.2, 128.8, 128.4, 127.6, 126.5, 124.4, 122.6, 112.9, 112.8, 107.7, 68.4, 68.2, 61.2, 28.9, 29.0, 22.9, 14.5; FTIR (neat): 3335, 2948, 2850, 1721, 1254 cm^{-1} ; HRMS (ESI-TOF) m/z : calculated for $\text{C}_{25}\text{H}_{27}\text{BrO}_5\text{Na}$, $[\text{M} + \text{Na}]^+$ 509.0940, found 509.0939.

Ethyl 5-bromo-2-((5-(2-(hydroxymethyl)phenoxy)pentyl)oxy)benzoate (SM-5): Prepared

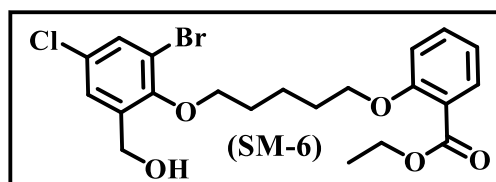
according to general experimental procedure 5.9.2B, using (2-((5-bromopentyl)oxy)phenyl)methanol (700 mg, 2.56 mmol), potassium carbonate (K_2CO_3) (706 mg, 5.12 mmol), and ethyl 5-bromo-2-



hydroxybenzoate (628 mg, 2.56 mmol). The residue was purified by using column chromatography with $\text{EtOAc}/n\text{-hexane} = 40:60$ as the eluent to afford the desired product **SM-5** (873 mg, 2.00 mmol, 78% yield) as a semisolid. ^1H NMR (400 MHz, CDCl_3) δ 7.87 (d, $J = 2.6$ Hz, 1H), 7.51 (dd, $J = 8.9, 2.6$ Hz, 1H), 7.30 – 7.22 (m, 2H), 6.93 (td, $J = 7.5, 0.8$ Hz, 1H), 6.85 (dd, $J = 12.7, 8.5$ Hz, 2H), 4.69 (d, $J = 6.3$ Hz, 2H), 4.33 (q, $J = 7.1$ Hz, 2H), 4.05 (q, $J = 6.4$ Hz, 4H), 1.91 (dq, $J = 12.5, 6.3$ Hz, 4H), 1.75 – 1.66 (m, 2H), 1.36 (t, $J = 7.1$ Hz, 3H), OH peak have exchanged with deuterium of CDCl_3 ; ^{13}C NMR (100 MHz, CDCl_3) δ 165.2, 157.7, 156.9, 135.9, 134.2, 129.3, 129.0, 128.9, 122.6, 120.7, 115.0, 112.3, 111.2, 69.1, 67.8, 62.3, 61.3, 29.1, 29.0, 22.9, 14.4. FTIR (neat): 3449, 2939, 2925, 1705, 1600, 1248 cm^{-1} ; HRMS (ESI-TOF) m/z : calculated for $\text{C}_{21}\text{H}_{26}\text{O}_5\text{Br}$, $[\text{M} + \text{H}]^+$ 437.0964, found 437.0959.

Ethyl 2-((5-(2-bromo-4-chloro-6-(hydroxymethyl)phenoxy)pentyl)oxy)benzoate (SM-6):

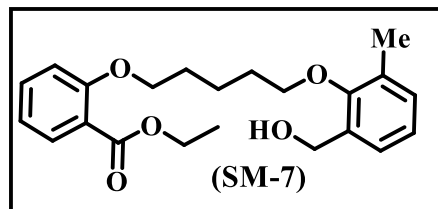
Prepared according to general experimental procedure 5.9.2B, using ethyl 2-((5-hydroxypentyl)oxy)benzoate (500 mg, 2.11 mmol), potassium carbonate (K_2CO_3) (582 mg, 4.22 mmol),



and 2-bromo-4-chloro-6-(hydroxymethyl)phenol (531 mg, 2.11 mmol). The residue was purified by using column chromatography with $\text{EtOAc}/n\text{-hexane} = 40:60$ as the eluent to afford the desired product **SM-6** (823 mg, 1.74 mmol, 83% yield) as a semisolid. ^1H NMR (400 MHz, CDCl_3) δ 7.76 (dd, $J = 7.9, 1.8$ Hz, 1H), 7.46 (dd, $J = 6.1, 2.2$ Hz, 1H), 7.44 – 7.41 (m, 1H), 7.36 (dd, $J = 4.7, 2.3$ Hz, 1H), 6.99 – 6.92 (m, 2H), 4.71 (d, $J = 4.1$ Hz, 2H), 4.34 (q, $J = 7.1$ Hz, 2H), 4.08 (t, $J = 6.1$ Hz, 2H), 3.98 (t, $J = 6.3$ Hz, 2H), 2.49 (s, 1H), 1.97 – 1.85 (m, 4H),

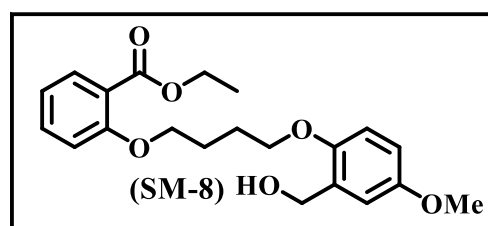
1.77 (ddd, $J = 12.6, 7.2, 2.4$ Hz, 2H), 1.37 (t, $J = 7.1$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 166.8, 158.6, 152.8, 137.5, 133.4, 132.2, 131.6, 130.1, 128.2, 120.9, 120.2, 117.8, 113.3, 74.1, 68.8, 61.0, 60.6, 23.0, 29.2, 22.8, 14.5; FTIR (neat): 3469, 2939, 2925, 1705, 1600, 1248 cm^{-1} ; HRMS (ESI-TOF) m/z : calculated for $\text{C}_{21}\text{H}_{24}\text{O}_5\text{BrClNa}$, $[\text{M} + \text{Na}]^+$ 493.0393, found 493.0390.

Ethyl 2-((5-(2-(hydroxymethyl)-6-methylphenoxy)pentyl)oxy)benzoate (SM-7): Prepared according to general experimental procedure 5.9.2B, using ethyl 2-((5-bromopentyl)oxy)benzoate (600 mg, 1.90 mmol), potassium carbonate (K_2CO_3) (524 mg, 3.8 mmol), and 2-(hydroxymethyl)-6-methyl phenol (263 mg, 1.90 mmol). The residue was purified by using



column chromatography with $\text{EtOAc}/n\text{-hexane} = 20:80$ as the eluent to afford the desired product **SM-7** (605 mg, 1.62 mmol, 85% yield) as a semisolid. ^1H NMR (400 MHz, CDCl_3) δ 7.77 (dd, $J = 7.6, 1.8$ Hz, 1H), 7.46 – 7.39 (m, 1H), 7.09 (d, $J = 1.8$ Hz, 1H), 7.04 (dd, $J = 8.3, 1.8$ Hz, 1H), 6.95 (dd, $J = 12.2, 4.8$ Hz, 2H), 6.76 (d, $J = 8.3$ Hz, 1H), 4.66 (d, $J = 5.2$ Hz, 2H), 4.34 (q, $J = 7.1$ Hz, 2H), 4.06 (t, $J = 6.3$ Hz, 2H), 4.02 (t, $J = 6.4$ Hz, 2H), 2.48 (s, 1H), 2.28 (s, 3H), 1.96 – 1.84 (m, 4H), 1.76 – 1.66 (m, 2H), 1.36 (t, $J = 7.1$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 166.7, 158.6, 154.8, 133.3, 131.6, 129.9, 129.6, 129.1, 120.9, 120.2, 113.2, 111.2, 68.7, 68.0, 62.2, 60.9, 29.6, 29.1, 22.9, 20.6, 14.4. FTIR (neat): 3266, 2940, 2879, 1719, 1448, 1226 cm^{-1} ; HRMS (ESI-TOF) m/z : calculated for $\text{C}_{22}\text{H}_{28}\text{O}_5\text{Na}$, $[\text{M} + \text{Na}]^+$ 395.1834 found 395.1830.

Ethyl 2-(4-(2-(hydroxymethyl)-4-methoxyphenoxy)butoxy)benzoate (SM-8): Prepared according to general experimental procedure 5.9.2B, using ethyl 2-((5-bromopentyl)oxy)benzoate (700 mg, 2.22 mmol), potassium carbonate (K_2CO_3) (612 mg, 4.44 mmol), and 2-(hydroxymethyl)-4-methoxyphenol (342 mg, 2.22 mmol). The residue

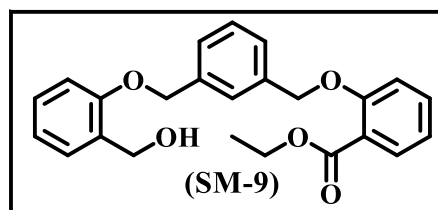


was purified by using column chromatography with $\text{EtOAc}:n\text{-hexane} = 20:80$ as the eluent to afford the desired product **SM-8** (730 mg, 1.88 mmol, 85% yield) as a semisolid; ^1H NMR (400 MHz, CDCl_3) δ 7.78 (dd, $J = 7.7, 1.8$ Hz, 1H), 7.46 – 7.36 (m, 1H), 7.17 (d, $J = 8.2$ Hz, 1H), 7.04 – 6.89 (m, 2H), 6.51 – 6.38 (m, 2H), 4.60 (d, $J = 3.8$ Hz, 2H), 4.34 (q, $J = 7.1$ Hz, 2H), 4.09 (dt, $J = 11.6, 5.9$ Hz, 4H), 3.79 (s, 3H), 2.31 (s, 1H), 2.11 – 1.98 (m, 4H), 1.36 (t, $J = 7.1$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 166.5, 160.7, 158.5, 158.0, 133.4, 131.7, 129.7, 122.0, 120.8, 120.3, 113.1, 104.1, 99.4, 68.3, 67.7, 61.7, 60.9, 55.5, 26.1, 26.1, 14.4; FTIR

(neat): 3320, 2945, 1715, 1601, 1490, 1243 cm^{-1} ; HRMS (ESI-TOF) m/z ; calculated for $\text{C}_{21}\text{H}_{26}\text{O}_6\text{Na}$, $[\text{M} + \text{Na}]^+$ 397.1627 found 397.1621.

Ethyl 2-((3-((2-(hydroxymethyl)phenoxy)methyl)benzyl)oxy)benzoate (SM-9): Prepared according to general experimental procedure 5.9.2B,

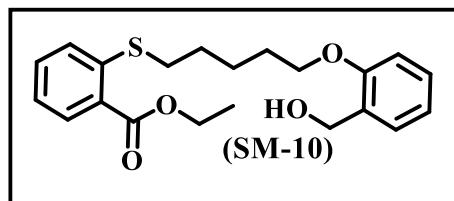
using ethyl (2-((3-(bromomethyl)benzyl)oxy)phenyl)methanol (540 mg, 1.76 mmol), potassium carbonate (K_2CO_3) (486 mg, 3.52



mmol), and ethyl 2-hydroxybenzoate (292 mg, 1.76 mmol). The residue was purified by using column chromatography with $\text{EtOAc}:\text{n-hexane} = 20:80$ as the eluent to afford the desired product **SM-9** (520 mg, 1.33 mmol, 75% yield) as a semisolid. ^1H NMR (400 MHz, CDCl_3) δ 7.85 – 7.81 (m, 1H), 7.58 (s, 1H), 7.48 (d, $J = 7.4$ Hz, 1H), 7.46 – 7.39 (m, 2H), 7.38 – 7.31 (m, 2H), 7.25 (ddd, $J = 9.5, 6.5, 1.7$ Hz, 1H), 7.04 – 6.98 (m, 2H), 6.95 (dd, $J = 12.1, 4.5$ Hz, 2H), 5.19 (s, 2H), 5.13 (s, 2H), 4.74 (s, 2H), 4.35 (t, $J = 7.1$ Hz, 2H), 1.34 (t, $J = 7.1$ Hz, 3H); OH peak have exchanged with deuterium of CDCl_3 ; ^{13}C NMR (100 MHz, CDCl_3) δ 166.6, 158.0, 156.6, 137.4, 137.3, 133.4, 131.8, 129.6, 129.0, 128.9, 126.8, 125.8, 121.2, 121.1, 120.7, 113.9, 111.7, 70.5, 70.0, 61.9, 61.0, 14.4; FTIR (neat): 3231, 2946, 2845, 1710, 1610, 1472, 1223 cm^{-1} ; HRMS (ESI-TOF) m/z : calculated for $\text{C}_{24}\text{H}_{24}\text{O}_5\text{Na}$, $[\text{M} + \text{Na}]^+$ 415.1522, found 415.1527.

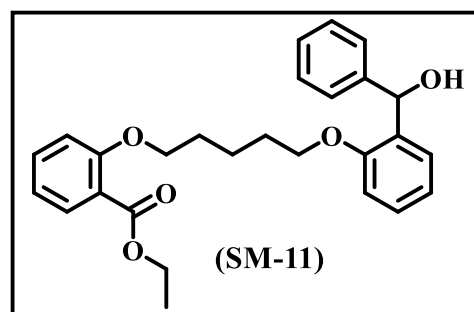
Ethyl 2-((5-(2-(hydroxymethyl)phenoxy)pentyl)thio)benzoate (SM-10): Prepared according to general experimental procedure 5.9.2B,

using (2-((5-bromopentyl)oxy)phenyl)methanol (700 mg, 2.56 mmol), potassium carbonate (K_2CO_3) (706 mg, 5.12 mmol), and ethyl 2-hydroxybenzoate (467 mg,



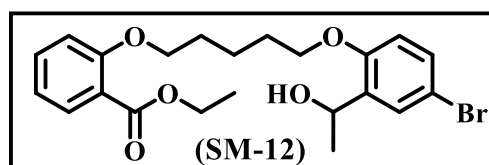
2.56 mmol). The residue was purified by using column chromatography with $\text{EtOAc}/\text{n-hexane} = 20:80$ as the eluent to afford the desired product **SM-10** (763 mg, 2.04 mmol, 79% yield) as a semisolid. ^1H NMR (400 MHz, CDCl_3) δ 7.96 (dd, $J = 7.8, 1.5$ Hz, 1H), 7.46 – 7.38 (m, 1H), 7.29 (dd, $J = 10.4, 8.1$ Hz, 2H), 7.24 (dd, $J = 7.9, 1.7$ Hz, 1H), 7.18 – 7.12 (m, 1H), 6.94 (td, $J = 7.4, 0.7$ Hz, 1H), 6.86 (d, $J = 8.1$ Hz, 1H), 4.70 (d, $J = 5.3$ Hz, 2H), 4.38 (q, $J = 7.1$ Hz, 2H), 4.03 (t, $J = 6.3$ Hz, 2H), 2.96 (t, $J = 7.2$ Hz, 2H), 2.38 (s, 1H), 1.91 – 1.78 (m, 4H), 1.74 – 1.64 (m, 2H), 1.40 (t, $J = 7.1$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 166.7, 156.9, 141.9, 132.3, 131.3, 129.3, 129.0, 128.8, 128.1, 125.7, 123.9, 120.7, 111.2, 67.7, 62.3, 61.2, 32.1, 29.0, 28.0, 25.8. FTIR (neat): 3401, 2945, 2871, 1735, 1459, 1256 cm^{-1} ; HRMS (ESI-TOF) m/z ; calculated for $\text{C}_{21}\text{H}_{26}\text{O}_5\text{SNa}$, $[\text{M} + \text{Na}]^+$ 397. 1449, found 397. 1440.

Ethyl 2-((5-(2-(hydroxy(phenyl)methyl)phenoxy)pentyl)oxy)benzoate (SM-11): Prepared according to general experimental procedure 5.9.2B, using ethyl 2-((5-bromopentyl)oxy)benzoate (520 mg, 1.65 mmol), potassium carbonate (K_2CO_3) (455 mg, 3.30 mmol), and phenol 2-(hydroxy(phenyl)methyl)phenol (387 mg, 1.65 mmol). The residue was purified by using column



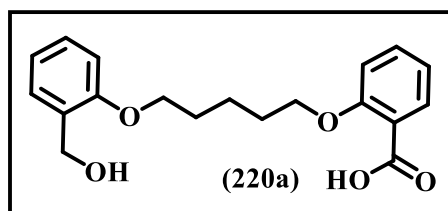
chromatography with EtOAc:*n*-hexane = 20:80 as the eluent to afford the desired product **SM-11** (512 mg, 1.09 mmol, 66% yield) as a semisolid. ^1H NMR (400 MHz, $CDCl_3$) δ 7.77 (dd, J = 7.7, 1.8 Hz, 1H), 7.44 (ddd, J = 8.4, 7.5, 1.8 Hz, 1H), 7.37 (d, J = 7.3 Hz, 2H), 7.31 – 7.25 (m, 4H), 7.24 – 7.17 (m, 1H), 6.99 – 6.91 (m, 3H), 6.86 (d, J = 8.1 Hz, 1H), 6.04 (d, J = 5.5 Hz, 1H), 4.32 (q, J = 7.1 Hz, 2H), 4.04 – 3.92 (m, 4H), 3.14 (d, J = 5.9 Hz, 1H), 1.88 – 1.74 (m, 4H), 1.54 (ddd, J = 9.8, 7.0, 2.3 Hz, 2H), 1.34 (t, J = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.6, 158.6, 156.2, 143.8, 133.3, 132.1, 131.6, 128.8, 128.2, 128.1, 127.2, 126.6, 120.9, 120.8, 120.2, 113.2, 111.6, 72.6, 68.6, 67.9, 60.9, 29.02, 28.98, 22.7, 14.4. FTIR (neat): 3274, 2942, 1728, 1455, 1237 cm^{-1} ; HRMS (ESI-TOF) m/z : calculated for $C_{27}H_{30}O_5Na$, $[M + Na]^+$ 457.1991, found: 457.1984.

Ethyl 5-bromo 2-((5-(2-(1-hydroxyethyl)phenoxy)pentyl)oxy)benzoate (SM-12): Prepared according to general experimental procedure 5.9.2B, using ethyl 2-((5-bromopentyl)oxy)benzoate (740 mg, 2.35 mmol), potassium carbonate (K_2CO_3) (648.6 mg, 4.7 mmol), and 4-bromo-2-(1-



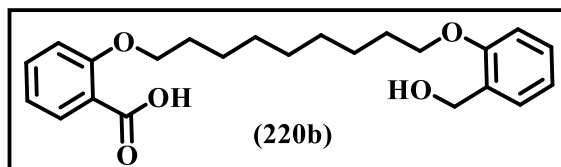
hydroxyethyl)phenol (509.59 mg, 2.35 mmol). The residue was purified by using column chromatography with EtOAc/*n*-hexane = 20:80 as the eluent to afford the desired product **SM-12** (965 mg, 2.14 mmol, 91% yield) as a semisolid. ^1H NMR (400 MHz, $CDCl_3$) δ 7.76 (dd, J = 7.7, 1.8 Hz, 1H), 7.49 (d, J = 2.4 Hz, 1H), 7.42 (ddd, J = 8.3, 7.5, 1.8 Hz, 1H), 7.29 (dd, J = 8.7, 2.5 Hz, 1H), 6.95 (ddd, J = 11.4, 6.2, 2.4 Hz, 2H), 6.71 (d, J = 8.7 Hz, 1H), 5.12 – 5.03 (m, 1H), 4.33 (dt, J = 14.3, 5.3 Hz, 2H), 4.08 – 3.96 (m, 4H), 2.63 (d, J = 4.6 Hz, 1H), 1.93 – 1.84 (m, 4H), 1.74 – 1.66 (m, 2H), 1.45 (d, J = 6.5 Hz, 3H), 1.35 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.6, 158.5, 154.9, 136.2, 133.3, 131.6, 130.8, 129.1, 120.9, 120.2, 113.2, 113.1, 112.9, 68.6, 68.2, 65.6, 60.9, 29.0, 29.0, 23.2, 22.9, 14.4; FTIR (neat): 3500, 2941, 1713, 1600, 1492, 1243 cm^{-1} ; HRMS (ESI-TOF) m/z : calculated for $C_{22}H_{27}BrO_5Na$, $[M + Na]^+$ 473.0941, found: 473.0945.

2-((5-(2-(hydroxymethyl)phenoxy)pentyl)oxy)benzoic acid (220a): Prepared according to general experimental procedure 5.9.2D, a 1,4-dioxane (20 mL) solution of ethyl 2-((5-(2-(hydroxymethyl)phenoxy)pentyl)oxy)benzoate (4 g, 11.16 mmol), 5N NaOH solution (25.0 mL), was added.



The reaction mixture was stirred at 80 °C in an oil bath overnight. After, the residue was purified using column chromatography with EtOAc:*n*-hexane = 60:40 as the eluent to afford **220a** (3.43 g, 93% yield) as a solid. melting point: 74–76 °C; ¹H NMR (400 MHz, CDCl₃) δ 8.16 (dd, *J* = 7.8, 1.8 Hz, 1H), 7.58 – 7.50 (m, 1H), 7.32 – 7.21 (m, 2H), 7.12 (t, *J* = 7.6 Hz, 1H), 7.04 (d, *J* = 8.4 Hz, 1H), 6.94 (t, *J* = 7.4 Hz, 1H), 6.86 (d, *J* = 8.2 Hz, 1H), 4.70 (s, 2H), 4.28 (t, *J* = 6.4 Hz, 2H), 4.06 (t, *J* = 6.1 Hz, 2H), 2.06 – 1.96 (m, 2H), 1.95 – 1.87 (m, 2H), 1.78 – 1.66 (m, 2H), OH and COOH peaks are exchanged with deuterium of CDCl₃; ¹³C NMR (100 MHz, CDCl₃) δ 165.7, 157.6, 156.7, 135.1, 133.8, 129.2, 129.0, 128.9, 122.3, 120.8, 118.1, 112.8, 111.2, 70.0, 67.5, 62.0, 29.1, 28.9, 22.9; FTIR (neat): 3259, 2911, 2840, 1720, 1601, 1451, 1271 cm⁻¹; HRMS (ESI-TOF) *m/z*; calculated for C₁₉H₂₃O₅, [M + H]⁺ 331.1545, found 331.1542.

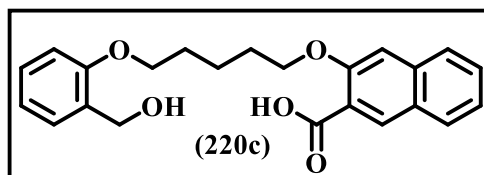
2-((9-(2-(hydroxymethyl)phenoxy)nonyl)oxy)benzoic acid (220b): Prepared according to general experimental procedure 5.9.2D, a 1,4-dioxane (3 mL) solution of ethyl 2-((9-(2-(hydroxymethyl)phenoxy)nonyl)oxy)benzoate (750 mg, 1.81 mmol), 5N NaOH solution (5



mL), was added. The reaction mixture was stirred at 80 °C in an oil bath for overnight. After, the residue was purified using column chromatography with EtOAc/*n*-hexane = 60:40 as the eluent to afford **220b** (620 mg, 88% yield) as a solid; melting point: 172–174 °C; ¹H NMR (400 MHz, CDCl₃) δ 8.21 (dd, *J* = 7.8, 1.8 Hz, 1H), 7.58 (ddd, *J* = 8.4, 7.4, 1.8 Hz, 1H), 7.32 – 7.27 (m, 1H), 7.18 – 7.12 (m, 1H), 7.08 (d, *J* = 8.3 Hz, 1H), 6.96 (dd, *J* = 7.2, 4.8 Hz, 2H), 6.85 (dd, *J* = 8.2, 2.1 Hz, 1H), 4.69 (s, 2H), 4.28 (t, *J* = 6.5 Hz, 2H), 3.99 (t, *J* = 6.5 Hz, 2H), 2.00 – 1.90 (m, 2H), 1.81 (dd, *J* = 14.6, 6.7 Hz, 2H), 1.51 (dt, *J* = 13.2, 6.1 Hz, 4H), 1.45 – 1.34 (m, 6H), OH and COOH peaks are exchanged with deuterium of CDCl₃; ¹³C NMR (100 MHz, CDCl₃) δ 165.8, 159.4, 157.7, 142.7, 135.1, 133.8, 129.6, 122.2, 119.0, 117.7, 113.9, 112.9, 112.7, 70.3, 67.9, 65.3, 29.5, 29.4, 26.1, 25.9, 25.8; FTIR (neat): 3251, 2923, 2855, 1720, 1602, 1491, 1230 cm⁻¹; HRMS (ESI-TOF) *m/z*: calculated for C₂₃H₃₀O₅Na, [M + Na]⁺ 409.1990, found 409.1985.

3-((5-(2-(hydroxymethyl)phenoxy)pentyl)oxy)-2-naphthoic acid (220c):

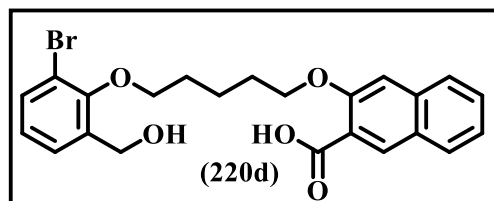
Prepared according to general experimental procedure 5.9.2D, a 1,4-dioxane (3 mL) solution of ethyl 3-((5-(2-



(hydroxymethyl)phenoxy)pentyl)oxy)-2-naphthoate (350 mg, 0.856 mmol), 5N NaOH solution (5 mL), was added. The reaction mixture was stirred at 80 °C in an oil bath overnight. After, the residue was purified using column chromatography with EtOAc/*n*-hexane = 60:40 as the eluent to afford **220c** (298 mg, 91% yield) as a solid. melting point: 80-84 °C; ¹H NMR (400 MHz, CDCl₃) δ 8.75 (s, 1H), 7.90 (d, *J* = 8.1 Hz, 1H), 7.76 (d, *J* = 8.1 Hz, 1H), 7.57 (t, *J* = 4.1 Hz, 1H), 7.48 – 7.41 (m, 1H), 7.32 – 7.28 (m, 2H), 7.25 (dd, *J* = 7.2, 0.9 Hz, 2H), 6.95 (dt, *J* = 8.2, 4.1 Hz, 1H), 6.88 (d, *J* = 8.2 Hz, 1H), 4.72 (s, 2H), 4.38 (t, *J* = 6.4 Hz, 2H), 4.09 (t, *J* = 6.1 Hz, 2H), 2.12 – 2.03 (m, 2H), 1.99 – 1.92 (m, 2H), 1.82 – 1.74 (m, 2H), OH and COOH peaks are exchanged with deuterium of CDCl₃; ¹³C NMR (100 MHz, CDCl₃) δ 156.8, 153.9, 136.7, 136.1, 129.5, 129.4, 129.0, 129.8, 128.5, 126.6, 125.5, 120.9, 111.2, 108.1, 69.9, 67.5, 62.1, 29.1, 28.9, 23.0; FTIR (neat): 3479, 2939, 2867, 1706, 1603, 1438, 1241 cm⁻¹; HRMS (ESI-TOF) *m/z*: calculated for C₂₃H₂₄O₅Na, [M + Na]⁺ 403. 1521, found 403. 1520.

1-((5-(2-bromo-6-(hydroxymethyl)phenoxy)pentyl)oxy)-2-naphthoic acid (220d):

Prepared according to general experimental procedure 5.9.2D, a 1,4-dioxane (3 mL) solution of ethyl 1-((5-(2-bromo-6-(hydroxymethyl)phenoxy)pentyl)oxy)-2-naphthoate



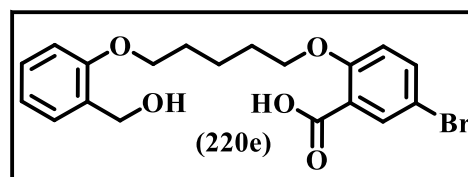
(340 mg, 0.667 mmol), 5N NaOH solution (5 mL), was added. The reaction mixture was stirred at 80 °C in an oil bath overnight. After, the residue was purified using column chromatography with EtOAc/*n*-hexane = 60:40 as the eluent to afford **220d** (298 mg, 93% yield) as a solid. melting point: 80-82 °C; ¹H NMR (400 MHz, CDCl₃) δ 8.73 (s, 1H), 7.89 (d, *J* = 8.2 Hz, 1H), 7.74 (d, *J* = 8.2 Hz, 1H), 7.57 (dd, *J* = 11.1, 4.0 Hz, 1H), 7.44 (dd, *J* = 9.0, 5.3 Hz, 2H), 7.35 – 7.22 (m, 2H), 6.72 (d, *J* = 8.7 Hz, 1H), 4.68 (s, 2H), 4.36 (t, *J* = 6.3 Hz, 2H), 4.02 (t, *J* = 6.1 Hz, 2H), 2.09 – 2.01 (m, 2H), 1.97 – 1.89 (m, 2H), 1.81 – 1.70 (m, 2H), OH and COOH peaks are exchanged with deuterium of CDCl₃; ¹³C NMR 100 MHz, CDCl₃) δ 165.9, 155.6, 153.8, 136.6, 136.1, 131.5, 131.3, 131.3, 129.5, 128.4, 126.6, 125.5, 118.4, 113.1, 112.7, 108.1, 69.9, 67.8, 61.0, 29.0, 28.8, 22.9; FTIR (neat): 3320, 2945, 1710, 1608, 1490, 1241 cm⁻¹; HRMS (ESI-TOF) *m/z*: calculated for C₂₃H₂₃O₅BrNa, [M + Na]⁺ 481.0627 found 481.0628.

5-bromo-2-((5-(2-(hydroxymethyl)phenoxy)pentyl)oxy)benzoic acid (220e): Prepared

according to general experimental procedure 5.9.2E, a

1,4-dioxane (3 mL) solution of ethyl 5-bromo-2-((5-(2-(hydroxymethyl)phenoxy)pentyl)oxy)benzoate (620

mg, 1.42 mmol), 5N NaOH solution (5 mL), was



added. The reaction mixture was stirred at 80 °C in an oil bath overnight. After, the residue

was purified using column chromatography with EtOAc/*n*-hexane = 60:40 as the eluent to

afford **220e** (503 mg, 87% yield) as a solid. melting point: 110-115°C; ¹H NMR (400 MHz,

CDCl₃) δ 8.21 (d, *J* = 2.1 Hz, 1H), 7.61 (dd, *J* = 8.8, 2.6 Hz, 1H), 7.32 – 7.21 (m, 2H), 6.93

(dd, *J* = 14.5, 8.1 Hz, 2H), 6.86 (d, *J* = 8.2 Hz, 1H), 4.71 (s, 2H), 4.22 (t, *J* = 6.3 Hz, 2H), 4.06

(t, *J* = 6.0 Hz, 2H), 2.03 – 1.94 (m, 2H), 1.94 – 1.87 (m, 2H), 1.77 – 1.68 (m, 2H), OH and

COOH peaks are exchanged with deuterium of CDCl₃; ¹³C NMR (100 MHz, CDCl₃) δ 164.8,

156.8, 137.4, 136.0, 129.2, 129.1, 129.0, 120.8, 120.2, 114.7, 114.4, 111.2, 70.3, 67.5, 62.0,

29.1, 28.9, 22.9; FTIR (neat): 3273, 2938, 2870, 1705, 1601, 1261 cm⁻¹; HRMS (ESI-TOF)

m/z: calculated for C₁₉H₂₁O₅BrNa, [M + Na]⁺ 431.0469, found 431.0466.

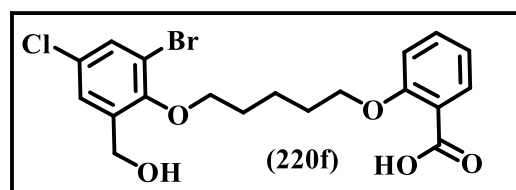
2-((5-(2-bromo-4-chloro-6-(hydroxymethyl)phenoxy)pentyl)oxy)benzoic acid (220f):

Prepared according to general experimental

procedure 5.9.2D, 1,4-dioxane (4 mL)

solution of ethyl 2-((5-(2-bromo-4-chloro-6-

(hydroxymethyl)phenoxy)pentyl)oxy)benzoate



(530 mg, 1.12 mmol), 5N NaOH solution (5 mL), was added. The reaction mixture was stirred

at 80 °C in an oil bath overnight. After, the residue was purified using column chromatography

with EtOAc/*n*-hexane = 60:40 as the eluent to afford **220f** (450 mg, 90% yield) as a semisolid.

¹H NMR (400 MHz, CDCl₃) δ 8.14 (d, *J* = 7.8 Hz, 1H), 7.57 – 7.52 (m, 1H), 7.44 (d, *J* = 2.3

Hz, 1H), 7.37 (d, *J* = 2.5 Hz, 1H), 7.12 (t, *J* = 7.6 Hz, 1H), 7.05 (d, *J* = 8.4 Hz, 1H), 4.70 (s,

2H), 4.29 (t, *J* = 6.4 Hz, 2H), 3.96 (t, *J* = 6.2 Hz, 2H), 2.05 – 1.96 (m, 2H), 1.95 – 1.85 (m,

2H), 1.80 – 1.69 (m, 2H), OH and COOH peaks are exchanged with deuterium of CDCl₃; ¹³C

NMR (100 MHz, CDCl₃) δ 165.9, 157.7, 152.5, 137.5, 135.2, 133.8, 132.1, 130.2, 128.1, 122.3,

117.9, 117.7, 112.8, 73.6, 70.1, 60.4, 29.8, 28.9, 22.7; FTIR (neat): 3266, 2940, 2878, 1719,

1448, 1226 cm⁻¹; HRMS (ESI-TOF) *m/z*: calculated for C₁₉H₂₁O₅BrClNa, [M + H]⁺ 443.0261,

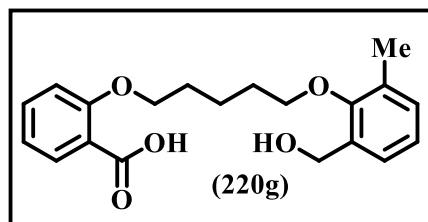
found 443.0252.

2-((5-(2-(hydroxymethyl)-6-methylphenoxy)pentyl)oxy)benzoic acid (220g): Prepared

according to general experimental procedure 5.9.2D, a 1,4-dioxane (4 mL) solution of ethyl

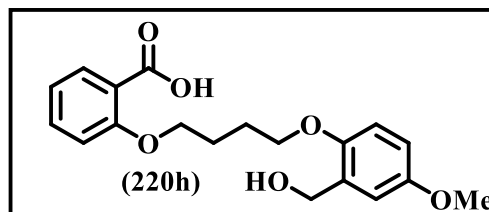
2-((5-(2-(hydroxymethyl)-6-

methylphenoxy)pentyl)oxy)benzoate (500 mg, 1.34 mmol), 5N NaOH solution (5 mL), was added. The reaction mixture was stirred at 80 °C in an oil bath overnight. After, the residue was purified using column



chromatography with EtOAc/*n*-hexane = 60:40 as the eluent to afford **220g** (443 mg, 96% yield) as a semisolid. ¹H NMR (400 MHz, DMSO) δ 11.65 (s, 1H), 6.78 (dd, *J* = 7.6, 1.8 Hz, 1H), 6.67 – 6.60 (m, 1H), 6.34 (s, 1H), 6.28 (d, *J* = 8.4 Hz, 1H), 6.15 (t, *J* = 7.5 Hz, 2H), 4.07 (s, 1H), 5.97 (d, *J* = 8.3 Hz, 1H), 3.64 (s, 2H), 3.22 (t, *J* = 6.3 Hz, 2H), 3.10 (t, *J* = 6.3 Hz, 2H), 1.40 (s, 3H), 0.93 (dt, *J* = 13.9, 6.9 Hz, 4H), 0.80 – 0.72 (m, 2H); ¹³C NMR (100 MHz, DMSO) δ 167.5, 157.4, 153.2, 132.8, 130.5, 130.3, 128.5, 127.6, 121.8, 120.0, 113.5, 111.0, 68.2, 67.5, 57.7, 28.4, 28.3, 22.1, 20.3; FTIR (neat): 3460, 2925, 2861, 1603, 1246 cm⁻¹; HRMS (ESI-TOF) *m/z*: calculated for C₂₀H₂₄O₅Na, [M + Na]⁺ 367.1521 found 367.1520.

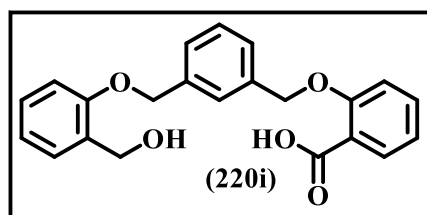
2-(4-(2-(hydroxymethyl)-4-methoxyphenoxy)butoxy)benzoic acid (220h): Prepared according to general experimental procedure 5.9.2D, a 1,4-dioxane (4 mL) solution of ethyl 2-(4-(2-(hydroxymethyl)-4-



methoxyphenoxy)butoxy)benzoate (560 mg, 1.44 mmol), 5N NaOH solution (6 mL), was added. The reaction mixture was stirred at 80 °C in an oil bath overnight. After, the residue was purified using column chromatography with EtOAc/*n*-hexane = 60:40 as the eluent to afford **220h** (490 mg, 94% yield) as a semisolid. ¹H NMR (400 MHz, CDCl₃) δ 8.14 (d, *J* = 7.3 Hz, 1H), 7.53 (dt, *J* = 15.7, 4.3 Hz, 1H), 7.22 – 7.15 (m, 1H), 7.11 (dd, *J* = 12.7, 5.2 Hz, 1H), 7.08 – 7.00 (m, 1H), 6.48 – 6.42 (m, 2H), 4.61 (s, 2H), 4.32 (t, *J* = 6.2 Hz, 2H), 4.07 (t, *J* = 5.8 Hz, 2H), 3.79 (s, 3H), 2.12 (dd, *J* = 13.6, 6.6 Hz, 2H), 2.07 – 1.98 (m, 2H), OH and COOH peaks are exchanged with deuterium of CDCl₃; ¹³C NMR (100 MHz, CDCl₃) δ 165.9, 160.8, 157.7, 157.7, 135.2, 133.8, 130.0, 122.2, 121.8, 118.1, 112.8, 104.3, 99.4, 69.7, 67.3, 61.4, 55.5, 26.1, 25.9; FTIR (neat): 3266, 2941, 2877, 1729, 1600, 1291 cm⁻¹; HRMS (ESI-TOF) *m/z*: calculated for C₁₉H₂₂O₆Na, [M + Na]⁺ 369.1313, found 369.1312.

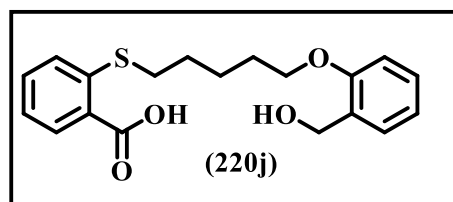
2-((3-((2-(hydroxymethyl)phenoxy)methyl)benzyl)oxy)benzoic acid (220i): Prepared

according to general experimental procedure 5.9.2D, a 1,4-dioxane (4 mL) solution of ethyl 2-((3-((2-(hydroxymethyl)phenoxy)methyl)benzyl)oxy)benzoate (510 mg, 1.30 mmol), 5N NaOH solution (6 mL), was added. The reaction mixture was stirred at 80 °C in an oil



bath overnight. After, the residue was purified using column chromatography with EtOAc/*n*-hexane = 60:40 as the eluent to afford **220i** (449 mg, 94% yield) as a white solid, Melting point: 109-112°C; ¹H NMR (400 MHz, CDCl₃) δ 8.13 (dd, *J* = 7.8, 1.4 Hz, 1H), 7.62 (s, 1H), 7.56 – 7.48 (m, 1H), 7.42 (t, *J* = 6.9 Hz, 2H), 7.33 (dd, *J* = 7.4, 1.4 Hz, 2H), 7.25 (ddd, *J* = 9.2, 6.2, 1.6 Hz, 1H), 7.11 (dd, *J* = 14.1, 7.8 Hz, 2H), 6.96 (t, *J* = 7.4 Hz, 1H), 6.91 (d, *J* = 8.2 Hz, 1H), 5.28 (s, 2H), 5.14 (s, 2H), 4.76 (s, 2H), OH and COOH peaks are exchanged with deuterium of CDCl₃; ¹³C NMR (100 MHz, CDCl₃) δ 166.1, 157.5, 156.4, 138.1, 135.5, 134.9, 133.7, 129.4, 129.3, 129.2, 129.1, 127.7, 127.3, 126.4, 122.3, 121.3, 118.8, 113.3, 111.7, 71.7, 69.7, 61.7; FTIR (neat): 3500, 2941, 2870, 1722, 1445, 1254 cm⁻¹; HRMS (ESI-TOF) *m/z*: calculated for C₂₂H₂₀O₅, [M + Na]⁺ 387.1208, found 387.1218.

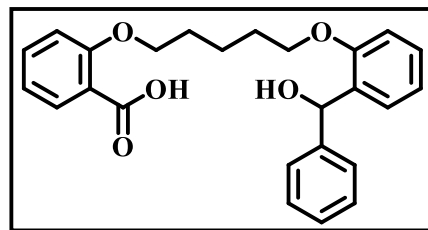
2-((5-(2-(hydroxymethyl)phenoxy)pentyl)thio)benzoic acid (220j): Prepared according to general experimental procedure 5.9.2D, a 1,4-dioxane (2 mL) solution of ethyl 2-((5-(2-(hydroxymethyl)phenoxy)pentyl)thio)benzoate (550 mg, 1.47 mmol), 5N NaOH solution (5 mL), was added.



The reaction mixture was stirred at 80 °C in an oil bath overnight. After, the residue was purified using column chromatography with EtOAc/*n*-hexane = 60:40 as the eluent to afford **220j** (495 mg, 97% yield) as a semisolid. melting point: 83-85°C; ¹H NMR (400 MHz, CDCl₃) δ 8.09 (dd, *J* = 7.9, 1.5 Hz, 1H), 7.50 – 7.43 (m, 1H), 7.34 (d, *J* = 7.8 Hz, 1H), 7.31 – 7.26 (m, 1H), 7.24 (dd, *J* = 7.9, 1.6 Hz, 1H), 7.21 – 7.15 (m, 1H), 6.96 – 6.90 (m, 1H), 6.86 (d, *J* = 8.2 Hz, 1H), 4.74 (s, 2H), 4.03 (t, *J* = 6.2 Hz, 2H), 2.97 (t, *J* = 7.1 Hz, 2H), 1.90 – 1.78 (m, 4H), 1.70 (ddt, *J* = 14.2, 9.3, 4.8 Hz, 2H) OH and COOH peaks are exchanged with deuterium of CDCl₃; ¹³C NMR (100 MHz, CDCl₃) δ 170.8, 156.9, 142.6, 133.1, 132.4, 129.1, 129.0, 128.8, 127.1, 126.1, 124.1, 120.7, 111.2, 67.7, 62.2, 32.3, 29.0, 27.9, 25.7; FTIR (neat): 3460, 2932, 2862, 1682, 1454, 1238 cm⁻¹; HRMS (ESI-TOF) *m/z*: calculated for C₁₉H₂₂O₄SNa, [M + Na]⁺ 369.1136, found 369.1133.

2-((5-(2-(hydroxy(phenyl)methyl)phenoxy)pentyl)oxy)benzoic acid (220k): Prepared

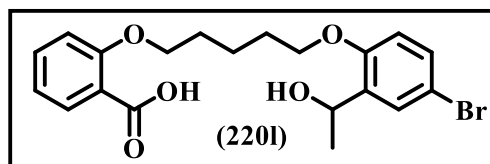
according to general experimental procedure 5.9.2D, a 1,4-dioxane (2 mL) solution of ethyl 2-((5-(2-(hydroxy(phenyl)methyl)phenoxy)pentyl)oxy)benzoate (780 mg, 1.80 mmol), 5N NaOH solution (5 mL), was added. The reaction mixture was stirred at 80 °C in an oil



bath overnight. After, the residue was purified using column chromatography with EtOAc/*n*-hexane = 60:40 as the eluent to afford **220k** (698 mg, 95% yield) as a semisolid. ¹H NMR (400 MHz, CDCl₃) δ 8.17 (dd, *J* = 7.8, 1.8 Hz, 1H), 7.56 (ddd, *J* = 9.0, 7.5, 1.8 Hz, 1H), 7.39 – 7.31 (m, 3H), 7.30 – 7.23 (m, 3H), 7.17 (dd, *J* = 11.6, 4.3 Hz, 1H), 7.16 – 7.10 (m, 1H), 7.01 (d, *J* = 8.3 Hz, 1H), 6.97 (td, *J* = 7.5, 0.7 Hz, 1H), 6.86 (d, *J* = 8.1 Hz, 1H), 6.03 (s, 1H), 4.16 (t, *J* = 6.6 Hz, 2H), 4.04 – 3.91 (m, 2H), 1.93 – 1.83 (m, 2H), 1.83 – 1.74 (m, 2H), 1.47 (dt, *J* = 19.6, 9.6 Hz, 2H), OH and COOH peaks are exchanged with deuterium of CDCl₃; ¹³C NMR (100 MHz, CDCl₃) δ 165.6, 157.6, 156.0, 143.8, 135.1, 133.9, 131.8, 128.9, 128.25, 128.16, 127.2, 126.7, 122.3, 120.9, 117.9, 112.7, 111.5, 72.6, 70.1, 67.4, 60.5, 28.9, 28.7, 22.6; FTIR (neat): 3254, 2942, 2870, 1725, 1455, 1237 cm⁻¹; HRMS (ESI-TOF) *m/z*: calculated for C₂₅H₂₆NaO₅, [M + Na]⁺ 429.1677 found 429.1674.

2-((5-(4-bromo-2-(1-hydroxyethyl)phenoxy)pentyl)oxy)benzoic acid (220l): Prepared

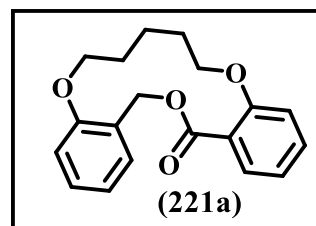
according to general experimental procedure 5.9.2D, a 1,4-dioxane (2 mL) solution of ethyl 2-((5-(4-bromo-2-(1-hydroxyethyl)phenoxy)pentyl)oxy)benzoate (500 mg, 1.11 mmol), 5N NaOH solution (5 mL), was added. The reaction mixture



was stirred at 80 °C in an oil bath overnight. After, the residue was purified using column chromatography with EtOAc/*n*-hexane = 60:40 as the eluent to afford **220l** (410 mg, 87% yield) as a solid. melting point: 92-95 °C; ¹H NMR (400 MHz, CDCl₃) δ 8.14 (dd, *J* = 7.8, 1.6 Hz, 1H), 7.59 – 7.46 (m, 2H), 7.33 – 7.23 (m, 1H), 7.11 (t, *J* = 7.6 Hz, 1H), 7.03 (d, *J* = 8.4 Hz, 1H), 6.70 (d, *J* = 8.7 Hz, 1H), 5.11 (q, *J* = 6.5 Hz, 1H), 4.27 (t, *J* = 6.3 Hz, 2H), 3.99 (qt, *J* = 9.4, 4.9 Hz, 2H), 1.98 (dd, *J* = 14.7, 6.9 Hz, 2H), 1.93 – 1.85 (m, 2H), 1.75 – 1.63 (m, 2H), 1.45 (d, *J* = 6.5 Hz, 3H), OH and COOH peaks are exchanged with deuterium of CDCl₃; ¹³C NMR (100 MHz, CDCl₃) δ 165.8, 157.6, 154.6, 136.1, 135.1, 133.8, 130.8, 129.1, 122.3, 117.9, 113.4, 112.9, 112.7, 69.9, 67.7, 65.4, 28.9, 28.8, 23.3, 22.8; FTIR (neat): 3440, 2941, 2872, 1716, 1248 cm⁻¹; HRMS (ESI-TOF) *m/z*: calculated for C₂₀H₂₃O₅BrNa, [M + Na]⁺ 445.0626 found 445.0632.

7,8,9,10-tetrahydro-6*H*,16*H*,18*H*-dibenzo[*b,g*][1,5,9]trioxacyclotetradecin-16-one (221a):

Prepared according to general experimental procedure 5.9.2E, a 0.05 M solution of **220a** 2-((5-(2-(hydroxymethyl)phenoxy)pentyl)oxy)benzoic acid (66 mg, 0.199 mmol) in (4 mL) 1,4-dioxane solvent was pumped using syringe pump through Omnifit® column (6.6 x 150 mm) packed bed

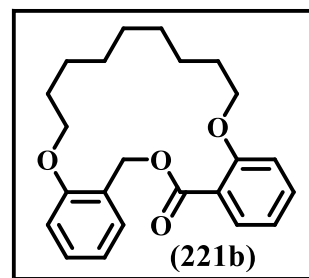


containing 1.7 g of Ru-Zeolite filled up to 7 cm and preheated at 120 °C with the flow rate of 0.1 mL/min at 3.3 to 3.5 back pressure. The collected organic layer was concentrated under reduced pressure and the crude product was purified by column chromatography using EtOAc/*n*-hexane = 10:90 as an eluent to afford the compound **4a** (39.9 mg, 64%) as a white solid, weight hourly space velocity (WHSV) = 52 h⁻¹, space-time yield = 16.37 g L⁻¹ h⁻¹, melting point: 86–89 °C.

Large-scale reaction for macrocyclic ether: Prepared according to general experimental procedure 5.9.2E, a 0.05 M solution of **220a** 2-((5-(2-(hydroxymethyl)phenoxy)pentyl)oxy)benzoic acid (0.9 gm, 2.72 mmol) in 1,4-dioxane solvent was pumped using a syringe pump through two Omnifit® column (6.6 x 150 mm) packed bed containing 1.7 gm of Ru-Zeolite filled up to 7 cm each column bed and preheated at 120 °C with the flow rate of 0.1 mL/min at 3.3 to 3.5 back pressure and residence time t_R = 27.3 min each column bed. After a two-time run, the collected organic layer was concentrated under reduced pressure, and the crude product was purified by column chromatography using EtOAc/*n*-hexane = 10:90 as an eluent to afford the compound **221a** (0.517 g, 1.67 mmol, 61%) as a white solid, weight hourly space velocity (WHSV) = 52 h⁻¹, space-time yield = 15.98 g L⁻¹ h⁻¹, ¹H NMR (400 MHz, CDCl₃) δ 7.77 (dd, J = 7.7, 1.8 Hz, 1H), 7.44 (dd, J = 7.3, 1.7 Hz, 1H), 7.38 (ddd, J = 8.4, 7.4, 1.8 Hz, 1H), 7.31 (td, J = 8.0, 1.8 Hz, 1H), 6.96 – 6.92 (m, 1H), 6.90 (ddd, J = 8.2, 3.3, 2.1 Hz, 2H), 6.84 (d, J = 8.3 Hz, 1H), 5.39 (s, 2H), 4.13 (t, J = 5.3 Hz, 2H), 4.01 – 3.91 (m, 2H), 1.92 (tt, J = 11.0, 5.6 Hz, 4H), 1.74 (td, J = 10.4, 5.5 Hz, 2H); ¹³C NMR (100 MHz, CDCl₃) δ 168.5, 158.6, 158.2, 133.1, 131.9, 130.6, 123.9, 121.3, 120.2, 120.1, 112.6, 111.4, 67.8, 64.9, 63.6, 27.2, 26.6, 20.5. FTIR (neat): 2941, 1691, 1601, 1240 cm⁻¹; HRMS (ESI-TOF) m/z : calculated for C₁₉H₂₀O₄Na, [M + Na]⁺ 335.1259, found 335.1253.

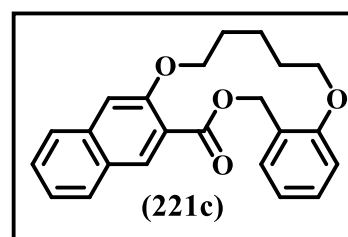
7,8,9,10,11,12,13,14-octahydro-6*H*,20*H*,22*H*-dibenzo[*b,g*][1,5,9]trioxacyclooctadecin-20-one (221b):

Prepared according to general experimental procedure 5.9.2E, a 0.05 M solution of **220b** 2-((9-(2-(hydroxymethyl)phenoxy)nonyl)oxy)benzoic acid (58 mg, 0.150 mmol) in (3 mL) 1,4-dioxane solvent was pumped using syringe pump through Omnifit® column (6.6 x 150 mm) packed bed containing 1.7 g of Ru-zeolite filled up to 7 cm and preheated at 120 °C with the flow rate of 0.1 mL/min at 3.3 to 3.5 back pressure. The collected organic layer was concentrated under reduced pressure and the crude product was purified by column chromatography using EtOAc/*n*-hexane = 10:90 as an eluent to afford the compound **221b** (37.1 mg, 67%) as a white solid, weight hourly space velocity (WHSV) = 62 h⁻¹, space-time yield = 21.25 g L⁻¹ h⁻¹, ¹H NMR (400 MHz, CDCl₃) δ 7.70 (dd, *J* = 7.6, 1.7 Hz, 1H), 7.45 (dd, *J* = 7.5, 1.6 Hz, 1H), 7.42 – 7.36 (m, 1H), 7.32 – 7.27 (m, 1H), 6.97 (dd, *J* = 10.9, 4.0 Hz, 1H), 6.90 (dd, *J* = 16.0, 8.3 Hz, 3H), 5.44 (s, 2H), 4.09 – 4.04 (m, 2H), 4.04 – 3.99 (m, 2H), 1.86 – 1.73 (m, 4H), 1.54 (dt, *J* = 11.1, 6.6 Hz, 4H), 1.49 – 1.41 (m, 4H), 1.38 (dd, *J* = 11.6, 5.6 Hz, 2H); ¹³C NMR (100 MHz, CDCl₃) δ 166.2, 158.8, 157.2, 133.1, 131.4, 129.9, 129.4, 125.1, 121.1, 120.3, 119.9, 113.1, 111.6, 68.2, 68.0, 62.0, 28.85, 28.78, 28.0, 27.9, 27.6, 27.5, 25.6, 25.2. FTIR (neat): 1717, 1600, 1295, 1126 cm⁻¹; HRMS (ESI-TOF) *m/z*: calculated for C₂₃H₂₈O₄Na, [M + Na]⁺ 391.1885, found 391.1884.



7,8,9,10-tetrahydro-6*H*,18*H*,20*H*-benzo[*b*]naphtho[2,3-*g*][1,5,9]trioxacyclotetradecin-18-one (221c):

Prepared according to general experimental procedure 5.9.2E, a 0.05 M solution of **220c** 1-((5-(2-(hydroxymethyl)phenoxy)pentyl)oxy)-2-naphthoic acid (76 mg, 0.199 mmol) in (4 mL) 1,4-dioxane solvent was pumped using syringe pump through Omnifit® column (6.6 x 150 mm) packed bed containing 1.7 g of Ru-Zeolite filled up to 7 cm and preheated at 120 °C with the flow rate of 0.1 mL/min at 3.3 to 3.5 back pressure. The collected organic layer was concentrated under reduced pressure and the crude product was purified by column chromatography using EtOAc/*n*-hexane = 10:90 as an eluent to afford the compound **221c** (52.1 mg, 72%) as a white solid, weight hourly space velocity (WHSV) = 61 h⁻¹, space-time yield = 24.05 g L⁻¹ h⁻¹, ¹H NMR (400 MHz, CDCl₃) δ 8.27 (s, 1H), 7.80 (d, *J* = 8.1 Hz, 1H), 7.67 (d, *J* = 8.2 Hz, 1H), 7.47 (ddd, *J* = 7.9, 4.4, 1.2 Hz, 2H), 7.36 – 7.29 (m, 2H), 7.08 (s, 1H), 6.96 – 6.87 (m, 2H), 5.44 (s, 2H), 4.14 (t, *J* = 5.4 Hz, 2H), 4.11 – 4.05 (m, 2H), 2.01 – 1.88 (m, 4H), 1.81 (td, *J* = 10.5, 5.5

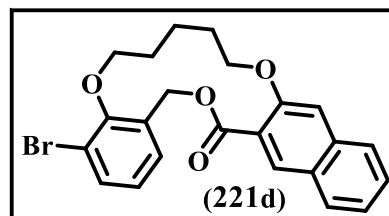


Hz, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 168.5, 158.6, 155.0, 136.1, 133.2, 132.8, 130.7, 128.8, 128.1, 127.7, 126.4, 124.2, 123.8, 123.4, 120.2, 111.4, 107.1, 67.7, 64.9, 64.0, 27.2, 26.6, 20.6; FTIR (neat): 2919, 2869, 1696, 1200 cm^{-1} ; HRMS (ESI-TOF) m/z : calculated for $\text{C}_{23}\text{H}_{23}\text{O}_4$, $[\text{M} + \text{H}]^+$ 363.1596, found 363.1591.

4-bromo-7,8,9,10-tetrahydro-6*H*,18*H*,20*H*-benzo[*b*]naphtho[2,3-

***g*][1,5,9]trioxacyclotetradecin-18-one (221d):** Prepared

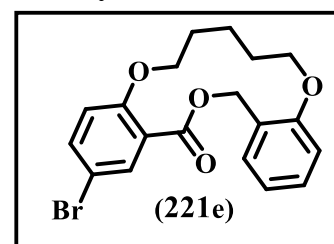
according to general experimental procedure 5.9.2E, a 0.05 M solution of **221d** (69 mg, 0.150 mmol) in (3 mL) 1,4-dioxane solvent was pumped using syringe pump through



Omnifit® column (6.6 x 150 mm) packed bed containing 1.7 g of Ru-zeolite filled up to 7 cm and preheated at 120 °C with the flow rate of 0.1 mL/min at 3.3 to 3.5 back pressure. The collected organic layer was concentrated under reduced pressure and the crude product was purified by column chromatography using EtOAc/*n*-hexane = 10:90 as an eluent to afford the compound **221d** (40 mg, 60%) as a white solid. weight hourly space velocity (WHSV) = 75 h^{-1} , space-time yield = 20.51 $\text{g L}^{-1} \text{h}^{-1}$, melting point: 95-110 °C; ^1H NMR (400 MHz, CDCl_3) δ 8.28 (s, 1H), 7.81 (d, J = 8.1 Hz, 1H), 7.66 (s, 1H), 7.60 (d, J = 2.5 Hz, 1H), 7.47 (ddd, J = 8.2, 6.9, 1.2 Hz, 1H), 7.41 (dd, J = 8.7, 2.5 Hz, 1H), 7.34 (ddd, J = 8.1, 6.9, 1.1 Hz, 1H), 7.08 (s, 1H), 6.78 (d, J = 8.8 Hz, 1H), 5.36 (s, 2H), 4.15 – 4.04 (m, 4H), 2.00 – 1.87 (m, 4H), 1.79 (td, J = 10.4, 5.5 Hz, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 168.3, 157.7, 154.9, 136.2, 135.8, 133.2, 133.0, 128.9, 128.3, 127.7, 126.4, 125.9, 124.3, 122.9, 113.2, 112.1, 107.2, 67.6, 65.4, 63.0, 27.1, 26.5, 20.5; FTIR (neat): 2921, 2839, 1725, 1240 cm^{-1} ; HRMS (ESI-TOF) m/z : calculated for $\text{C}_{23}\text{H}_{21}\text{O}_4\text{BrNa}$, $[\text{M} + \text{Na}]^+$ 463.0521, found 463.0514.

14-bromo-7,8,9,10-tetrahydro-6*H*,16*H*,18*H*-dibenzo[*b,g*][1,5,9]trioxacyclotetradecin-16-one (221e): Prepared according to general experimental

procedure E, A 0.05 M solution of **220e** (61.5 mg, 0.199 mmol) in (3 mL) 1,4-dioxane solvent was pumped using syringe pump through Omnifit® column (6.6 x 150 mm) packed bed containing 1.7 g of Ru-Zeolite filled up to 7 cm and preheated at 120 °C with

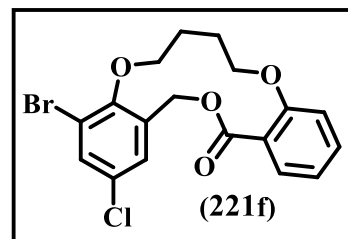


the flow rate of 0.1 mL/min at 3.3 to 3.5 back pressure. The collected organic layer was concentrated under reduced pressure and the crude product was purified by column chromatography using EtOAc/*n*-hexane = 10:90 as an eluent to afford the compound **221e** (47.5 mg, 81%) as a sticky. weight hourly space velocity (WHSV) = 66 h^{-1} , space-time yield = 32.88 $\text{g L}^{-1} \text{h}^{-1}$, ^1H NMR (400 MHz, CDCl_3) δ 7.87 (d, J = 2.6 Hz, 1H), 7.44 (ddd, J = 9.1, 8.1,

2.2 Hz, 2H), 7.32 (td, $J = 8.0, 1.7$ Hz, 1H), 6.94 – 6.86 (m, 2H), 6.73 (d, $J = 8.8$ Hz, 1H), 5.38 (s, 2H), 4.12 (t, $J = 5.1$ Hz, 2H), 3.98 – 3.93 (m, 2H), 1.95 – 1.86 (m, 4H), 1.80 – 1.69 (m, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 167.0, 158.5, 157.3, 135.7, 134.4, 133.1, 130.7, 123.6, 123.1, 120.3, 114.5, 112.1, 111.4, 68.2, 64.8, 63.9, 27.1, 26.5, 20.4; FTIR (neat): 2921, 2870, 1674, 1600, 1299, 1261 cm^{-1} ; HRMS (ESI-TOF) m/z : calculated for $\text{C}_{19}\text{H}_{19}\text{O}_4\text{BrNa}$, $[\text{M} + \text{Na}]^+$ 413.0364, found 413.0358.

4-bromo-2-chloro-6,7,8,9-tetrahydro-15*H*,17*H*-dibenzo[*b,g*][1,5,9]trioxacyclotridecin-

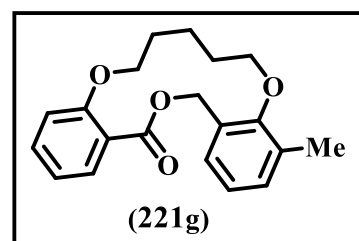
15-one (221f): Prepared according to general experimental procedure 5.9.2E, a 0.05 M solution of **220f** 2-(4-(2-bromo-4-chloro-6-(hydroxymethyl)phenoxy)butoxy)benzoic acid (66.5 mg, 0.149 mmol) in (3 mL) 1,4-dioxane solvent was pumped using syringe pump through Omnifit® column (6.6 x 150 mm)



packed bed containing 1.7 g of Ru-Zeolite filled up to 7 cm and preheated at 120 °C with the flow rate of 0.1 mL/min at 3.3 to 3.5 back pressure was maintained in the reaction. The collected organic layer was concentrated under reduced pressure and the crude product was purified by column chromatography using EtOAc/*n*-hexane = 10:90 as an eluent to afford the compound **221f** (32.4 mg, 51%) as a white solid, weight hourly space velocity (WHSV) = 72 h^{-1} , space-time yield = 14.12 $\text{g L}^{-1} \text{h}^{-1}$, ^1H NMR (400 MHz, CDCl_3) δ 7.74 (dd, $J = 7.7, 1.8$ Hz, 1H), 7.56 (d, $J = 2.6$ Hz, 1H), 7.45 – 7.39 (m, 2H), 7.00 (td, $J = 7.6, 0.9$ Hz, 1H), 6.94 (d, $J = 8.3$ Hz, 1H), 5.30 (s, 2H), 4.30 (t, $J = 7.2$ Hz, 2H), 4.08 (t, $J = 5.4$ Hz, 2H), 2.20 – 2.11 (m, 2H), 1.96 (dt, $J = 11.5, 5.5$ Hz, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 168.0, 157.8, 155.9, 134.0, 133.5, 132.1, 131.9, 131.6, 129.4, 121.6, 121.0, 118.9, 113.8, 74.4, 69.2, 63.4, 27.8, 23.7; FTIR (neat): 2941, 2835, 11722, 1604, 1205 cm^{-1} ; HRMS (ESI-TOF) m/z : calculated for $\text{C}_{18}\text{H}_{16}\text{BrClO}_4\text{Na}$, $[\text{M} + \text{Na}]^+$ 432.9818, found 432.9810.

4-methyl-7,8,9,10-tetrahydro-6*H*,16*H*,18*H*-dibenzo[*b,g*][1,5,9]trioxacyclotetradecin-16-

one (221g): Prepared according to general experimental procedure 5.9.2E, a 0.05 M solution of **220g** 2-((5-(2-(hydroxymethyl)-6-methylphenoxy)pentyl)oxy)benzoic acid (52 mg, 0.150 mmol) in (3 mL) 1,4-dioxane solvent was pumped using syringe pump through Omnifit® column (6.6 x

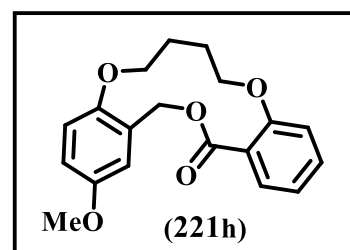


150 mm) packed bed containing 1.7 g of Ru-Zeolite filled up to 7 cm and preheated at 120 °C with the flow rate of 0.1 mL/min at 3.3 to 3.5 back pressure. The collected organic layer was concentrated under reduced pressure and the crude product was purified by column

chromatography using EtOAc/*n*-hexane = 10:90 as an eluent to afford the compound **221g** (32.1 mg, 65%) as a semisolid, weight hourly space velocity (WHSV) = 55 h⁻¹, space-time yield = 17.84 g L⁻¹ h⁻¹, ¹H NMR (400 MHz, CDCl₃) δ 7.77 (dd, *J* = 7.7, 1.5 Hz, 1H), 7.42 – 7.35 (m, 1H), 7.29 – 7.24 (m, 1H), 7.10 (dd, *J* = 8.3, 1.7 Hz, 1H), 6.94 (t, *J* = 7.5 Hz, 1H), 6.82 (dd, *J* = 18.6, 8.3 Hz, 2H), 5.37 (s, 2H), 4.11 (t, *J* = 5.2 Hz, 2H), 4.01 – 3.93 (m, 2H), 2.27 (s, 3H), 1.97 – 1.84 (m, 4H), 1.74 (td, *J* = 10.5, 5.5 Hz, 2H); ¹³C NMR (100 MHz, CDCl₃) δ 168.5, 158.2, 156.4, 133.8, 133.1, 131.9, 130.8, 129.4, 123.6, 121.3, 120.0, 112.6, 111.3, 67.8, 65.0, 63.5, 27.2, 26.7, 20.5, 20.4; FTIR (neat): 2921, 2869, 1695, 1601, 1299, 1260 cm⁻¹; HRMS (ESI-TOF) *m/z*: calculated for C₂₀H₂₃O₄, [M + H]⁺ 327.1596, found 327.1588.

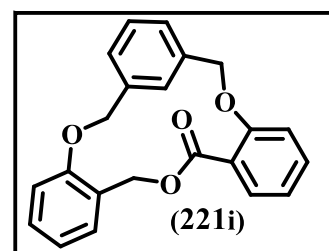
2-methoxy-6,7,8,9-tetrahydro-15*H*,17*H*-dibenzo[*b,g*][1,5,9]trioxacyclotridecin-15-one

(221h): Prepared according to general experimental procedure E, A 0.05 M solution of **220h** (54 mg, 0.149 mmol) in (3 mL) 1,4-dioxane solvent was pumped using syringe pump through Omnifit® column (6.6 x 150 mm) packed bed containing 1.7 g of Ru-Zeolite filled up to 7 cm and preheated at 120 °C with the



flow rate of 0.1 mL/min at 3.3 to 3.5 back pressure. The collected organic layer was concentrated under reduced pressure and the crude product was purified by column chromatography using EtOAc/*n*-hexane = 10:90 as an eluent to afford the compound **221h** (43.5 mg, 85%) as a sticky, weight hourly space velocity (WHSV) = 55 h⁻¹, space-time yield = 31.60 g L⁻¹ h⁻¹, ¹H NMR (400 MHz, CDCl₃) δ 7.68 (dd, *J* = 7.7, 1.7 Hz, 1H), 7.38 (ddd, *J* = 8.2, 7.4, 1.8 Hz, 1H), 7.29 (d, *J* = 8.3 Hz, 1H), 6.99 (td, *J* = 7.6, 1.0 Hz, 1H), 6.95 (d, *J* = 8.3 Hz, 1H), 6.52 (d, *J* = 2.4 Hz, 1H), 6.45 (dd, *J* = 8.3, 2.4 Hz, 1H), 5.30 (s, 2H), 4.16 (t, *J* = 4.9 Hz, 2H), 4.06 (t, *J* = 5.1 Hz, 2H), 3.79 (s, 2H), 2.08 – 1.93 (m, 4H); ¹³C NMR (100 MHz, CDCl₃) δ 168.0, 161.7, 159.8, 158.5, 132.9, 131.1, 123.8, 121.5, 118.0, 116.9, 104.7, 101.5, 71.1, 69.0, 64.1, 55.5, 27.3, 26.5. FTIR (neat): 2924, 2831, 1735, 1606, 1236 cm⁻¹; HRMS (ESI-TOF) *m/z*: calculated for C₁₉H₂₀O₅Na, [M + Na]⁺ 351.1208, found 351.1200.

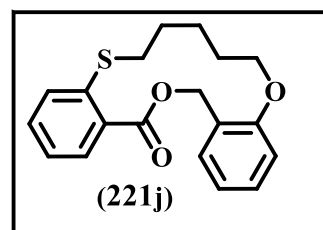
2,6,9-trioxa-1,7(1,2),4(1,3)-tribenzenacyclodecaphan-8-one (221i): Prepared according to general experimental procedure 5.9.2E, a 0.05 M solution of **220i** (55.0 mg, 0.150 mmol) in (3 mL) 1,4-dioxane solvent was pumped using syringe pump through Omnifit® column (6.6 x 150 mm) packed bed containing 1.7 g of Ru-zeolite filled up to 7 cm and preheated at 120 °C with the flow rate of 0.1 mL/min at 3.3 to 3.5 back pressure. The collected organic layer was concentrated under reduced pressure and



the crude product was purified by column chromatography using EtOAc/*n*-hexane = 10:90 as an eluent to afford the compound **221i** (40.8 mg, 78%) as a semisolid, weight hourly space velocity (WHSV) = 59 h⁻¹, space-time yield = 27.22 g L⁻¹ h⁻¹, ¹H NMR (400 MHz, CDCl₃) δ 8.27 (s, 1H), 7.88 (dd, *J* = 7.7, 1.8 Hz, 1H), 7.51 – 7.41 (m, 2H), 7.29 – 7.20 (m, 2H), 7.15 (d, *J* = 7.5 Hz, 1H), 7.08 – 7.00 (m, 2H), 6.97 (d, *J* = 8.3 Hz, 2H), 6.91 (td, *J* = 7.4, 0.8 Hz, 1H), 5.62 (s, 2H), 5.41 (s, 2H), 5.11 (s, 2H); ¹³C NMR (100 MHz, CDCl₃) δ 168.1, 157.5, 156.9, 138.0, 137.7, 133.5, 133.4, 132.3, 130.5, 127.8, 125.2, 125.1, 124.8, 124.1, 121.7, 121.3, 120.8, 113.3, 113.0, 69.3, 68.4, 62.3; FTIR (neat): 2925, 2875, 1645, 1608, 1269, 1209 cm⁻¹; HRMS (ESI-TOF) *m/z*: calculated for C₂₂H₁₉O₄, [M + H]⁺ 347.1283, found 347.1288.

7,8,9,10-tetrahydro-6*H*,16*H*,18*H*-dibenzo[*b,g*][1,5]dioxo[9]thiacyclotetradecin-16-one

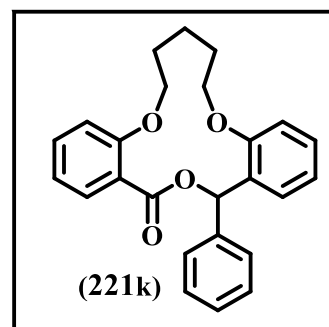
(221j): Prepared according to general experimental procedure 5.9.2E, a 0.05 M solution of **220j** (66.5 mg, 0.149 mmol) in (3 mL) 1,4-dioxane solvent was pumped using syringe pump through Omnifit® column (6.6 x 150 mm) packed bed containing 1.7 g of Ru-Zeolite filled up to 7 cm and preheated at 120 °C with the flow



rate of 0.1 mL/min at 3.3 to 3.5 back pressure. The collected organic layer was concentrated under reduced pressure and the crude product was purified by column chromatography using EtOAc/*n*-hexane = 10:90 as an eluent to afford the compound **221j** (32.4 mg, 51%) as a white solid, weight hourly space velocity (WHSV) = 58 h⁻¹, space-time yield = 12.5 g L⁻¹ h⁻¹, Melting point: 106-105°C; ¹H NMR (400 MHz, CDCl₃) δ 7.57 (dd, *J* = 7.9, 0.8 Hz, 1H), 7.46 (dd, *J* = 7.7, 1.4 Hz, 1H), 7.38 – 7.33 (m, 2H), 7.33 – 7.29 (m, 1H), 7.21 (td, *J* = 7.6, 1.2 Hz, 1H), 6.94 (td, *J* = 7.4, 0.9 Hz, 1H), 6.86 (d, *J* = 8.2 Hz, 1H), 5.35 (s, 2H), 4.02 – 3.97 (m, 2H), 2.96 (t, *J* = 5.8 Hz, 2H), 1.71 (dd, *J* = 10.5, 5.7 Hz, 2H), 1.61 (dt, *J* = 6.4, 3.2 Hz, 4H); ¹³C NMR (100 MHz, CDCl₃) δ 168.3, 158.3, 137.8, 135.5, 135.0, 132.1, 130.8, 130.7, 128.4, 127.1, 123.8, 120.3, 111.6, 67.4, 64.9, 37.9, 28.9, 28.7, 24; FTIR (neat): 2923, 2837, 1722, 1607, 1202 cm⁻¹; HRMS (ESI-TOF) *m/z*: calculated for C₁₉H₂₁O₃S, [M + H]⁺ 329.1211, found 329.1207.

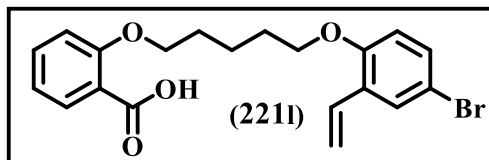
18-phenyl-7,8,9,10-tetrahydro-6*H*,16*H*,18*H*-dibenzo[*b,g*][1,5,9]trioxacyclotetradecin-16-one

(221k): Prepared according to general experimental procedure 5.9.2E, a 0.05 M solution of **220k** (66.5 mg, 0.149 mmol) in (3 mL) 1,4-dioxane solvent was pumped using syringe pump through Omnifit® column (6.6 x 150 mm) packed bed containing 1.7 g of Ru-Zeolite filled up to 7 cm and preheated at 120 °C with the flow rate of 0.1 mL/min at 3.3 to 3.5 back



pressure. The collected organic layer was concentrated under reduced pressure and the crude product was purified by column chromatography using EtOAc/*n*-hexane = 10:90 as an eluent to afford the compound **221k** (32.4 mg, 51%) as a white solid, weight hourly space velocity (WHSV) = 66 h⁻¹, space-time yield = 29.22 g L⁻¹ h⁻¹, ¹H NMR (400 MHz, CDCl₃) δ 7.70 (dd, *J* = 7.7, 1.7 Hz, 1H), 7.45 (d, *J* = 7.4 Hz, 2H), 7.42 – 7.33 (m, 4H), 7.29 (d, *J* = 7.1 Hz, 1H), 7.25 (dd, *J* = 5.6, 0.8 Hz, 1H), 7.09 (dd, *J* = 7.8, 1.6 Hz, 1H), 6.95 (dd, *J* = 13.2, 7.9 Hz, 2H), 6.83 (dd, *J* = 7.5, 6.1 Hz, 2H), 4.25 – 4.19 (m, 1H), 4.08 – 3.89 (m, 3H), 1.92 – 1.63 (m, 6H); ¹³C NMR (100 MHz, CDCl₃) δ 166.8, 158.4, 157.9, 140.0, 132.8, 131.8, 130.9, 130.2, 128.2, 127.4, 127.2, 126.5, 122.7, 120.4, 119.8, 114.3, 111.2, 74.9, 69.0, 65.7, 27.4, 27.2, 21.3; FTIR (neat): 2925, 2829, 1720, 1601, 1210 cm⁻¹; HRMS (ESI-TOF) *m/z*: calculated for C₂₅H₂₄O₄Na, [M + Na]⁺ 411.1572 found 411.1572.

2-((5-(4-bromo-2-(1-hydroxyvinyl)phenoxy)pentyl)oxy)benzoic acid (221l): Prepared according to general experimental procedure 5.9.2E, a 0.05 M solution of **220l** (63 mg, 0.148 mmol) in (3 mL) 1,4-dioxane solvent was pumped using syringe



pump through Omnifit® column (6.6 x 150 mm) packed bed containing 1.7 g of Ru-Zeolite filled up to 7 cm and preheated at 120 °C with the flow rate of 0.1 mL/min at 3.3 to 3.5 back pressure. The collected organic layer was concentrated under reduced pressure and the crude product was purified by column chromatography using EtOAc/*n*-hexane = 10:90 as an eluent to afford the compound **221l** (56 mg, 89%) as a semisolid, weight hourly space velocity (WHSV) = 68 h⁻¹, space-time yield = 42.5 g L⁻¹ h⁻¹, ¹H NMR (400 MHz, CDCl₃) δ 8.18 (dd, *J* = 7.8, 1.8 Hz, 1H), 7.58 – 7.50 (m, 2H), 7.29 (dd, *J* = 8.7, 2.5 Hz, 1H), 7.17 – 7.09 (m, 1H), 7.03 (d, *J* = 8.3 Hz, 1H), 6.94 (dd, *J* = 17.7, 11.2 Hz, 1H), 6.71 (d, *J* = 8.8 Hz, 1H), 5.72 (dd, *J* = 17.7, 1.2 Hz, 1H), 5.29 (dd, *J* = 11.1, 1.1 Hz, 1H), 4.28 (t, *J* = 6.5 Hz, 2H), 3.99 (t, *J* = 6.1 Hz, 2H), 2.05 – 1.97 (m, 2H), 1.94 – 1.86 (m, 2H), 1.75 – 1.64 (m, 2H), COOH peak have exchanged with deuterium of CDCl₃; ¹³C NMR (100 MHz, CDCl₃) δ 165.5, 157.6, 155.1, 135.2, 133.9, 131.4, 130.5, 129.2, 129.0, 122.4, 117.8, 115.8, 113.66, 113.1, 112.7, 70.1, 68.1, 28.9, 28.8, 22.8; FTIR (neat): 3356, 2928, 2841, 1725, 1601, 1212 cm⁻¹; HRMS (ESI-TOF) *m/z*: calculated for C₂₀H₂₁O₄Br, [M + Na]⁺ 427.0521, found 427.0518.

5.9.4. Crystal data

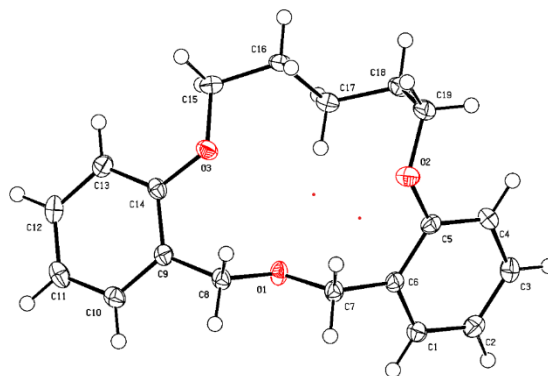
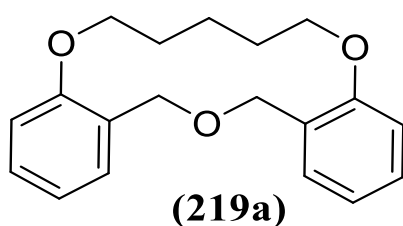


Figure 75. ORTEP crystal structure of **219a** showing thermal ellipsoids at the 50% probability level

Crystallographic parameters of **219a**:

Parameters	219a
Empirical formula	C ₁₉ H ₂₂ O ₃
Formula Mass/g mol	298.36
Experimental crystal description	Crystalline Solid
Colour	white
D _{calc} /g cm ⁻³	1.278
Crystal system	orthorhombic
Space group	P 21 21 21
a/ Å	7.8414(15)
b/ Å	9.058(2)
c/ Å	21.828(5)
α/ deg	90
β/ deg	90
γ/ deg	90
V/Å ³	1550.4(6)
Z	4
T / K	273 K
Diffraction Source	CuKα
Diffraction radiation wavelength/ Å	0.71073
Diffraction reflection theta full	0.997
Reflection number total	3900
Reflection number gt	3323
μ/mm-1	0.085
F(000)	640.0
R ₁ ,wR ₂ [I>2σ(I)]	0.0432,
	0.0852
R ₁ ,wR ₂ (all data)	0.0554,
	0.0896
GoF	1.220

Crystal preparation: The crystals are grown by a simple recrystallization method where pure compounds isolated after column chromatography are dissolved in dichloromethane and layered with hexane, kept at room temperature to get compound **219a** pure crystal. More information on crystal structures can also be obtained from the Cambridge Crystallographic Data Centre (CCDC) with deposition number **2266303**.

5.10. Appendix V: Copies of ^1H and ^{13}C NMR Spectra of Representative Compounds

Entry	Data	Figure No
100h	^1H and ^{13}C	110 and 111
100i	^1H and ^{13}C	112 and 113
219a	^1H and ^{13}C	114 and 115
219b	^1H and ^{13}C	116 and 117
219c	^1H and ^{13}C	118 and 119
220a	^1H and ^{13}C	120 and 121
220b	^1H and ^{13}C	122 and 123
221a	^1H and ^{13}C	124 and 125
221b	^1H and ^{13}C	126 and 127
221c	^1H and ^{13}C	128 and 129

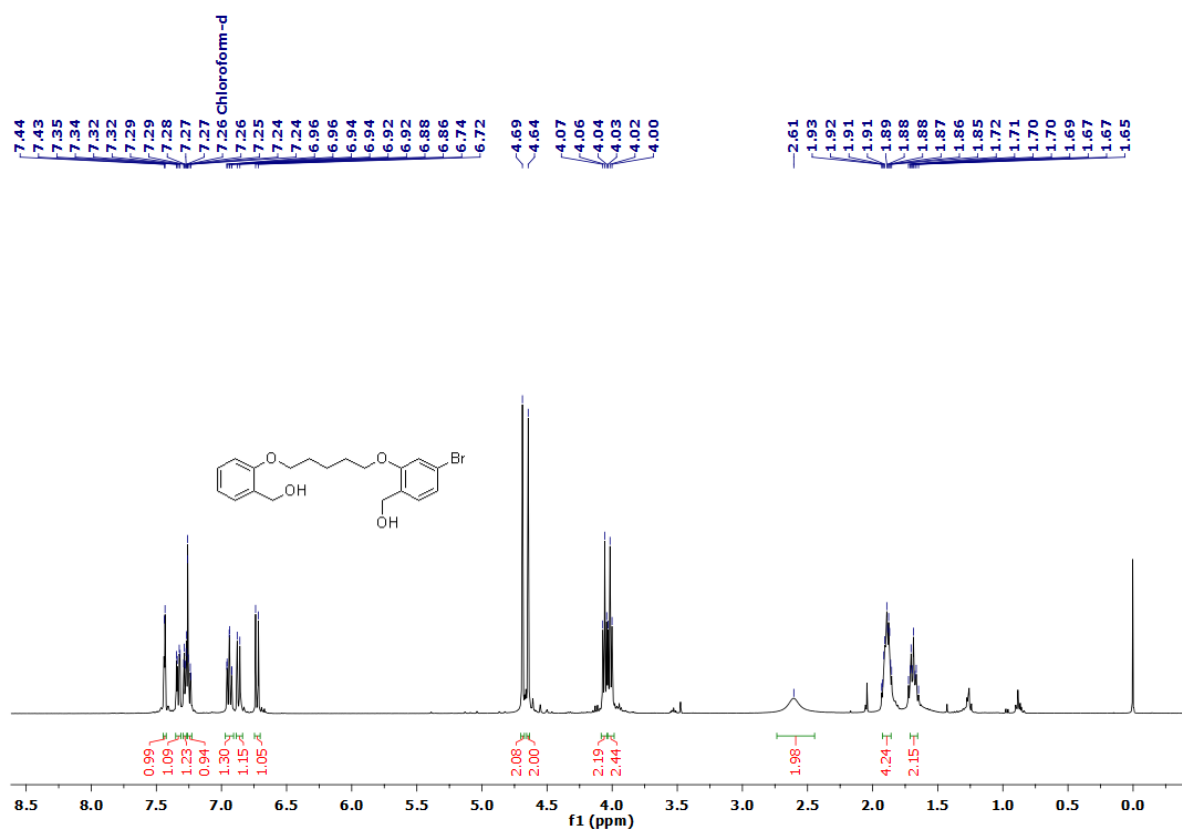


Figure 110. ¹H NMR spectra for compound **100h**, 400 MHz, CDCl₃

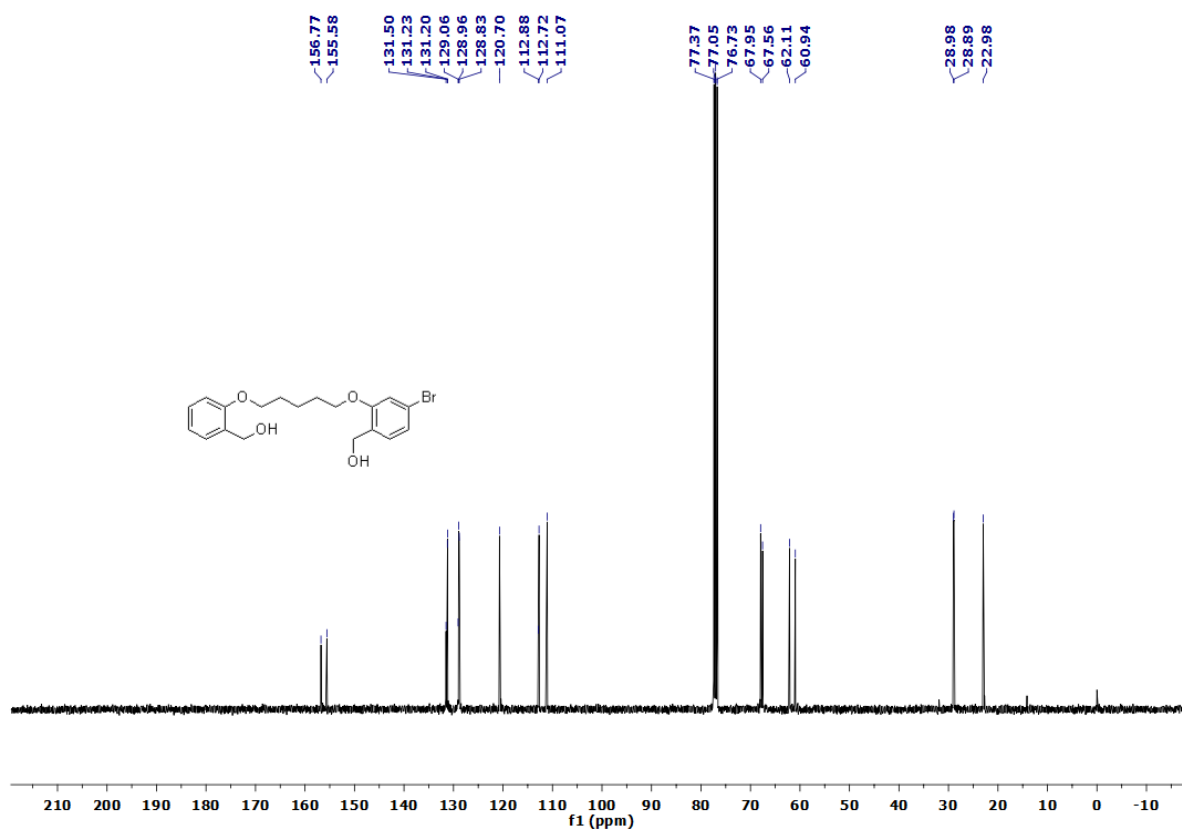


Figure 111. ¹³C NMR spectra for compound **100h**, 100 MHz, CDCl₃

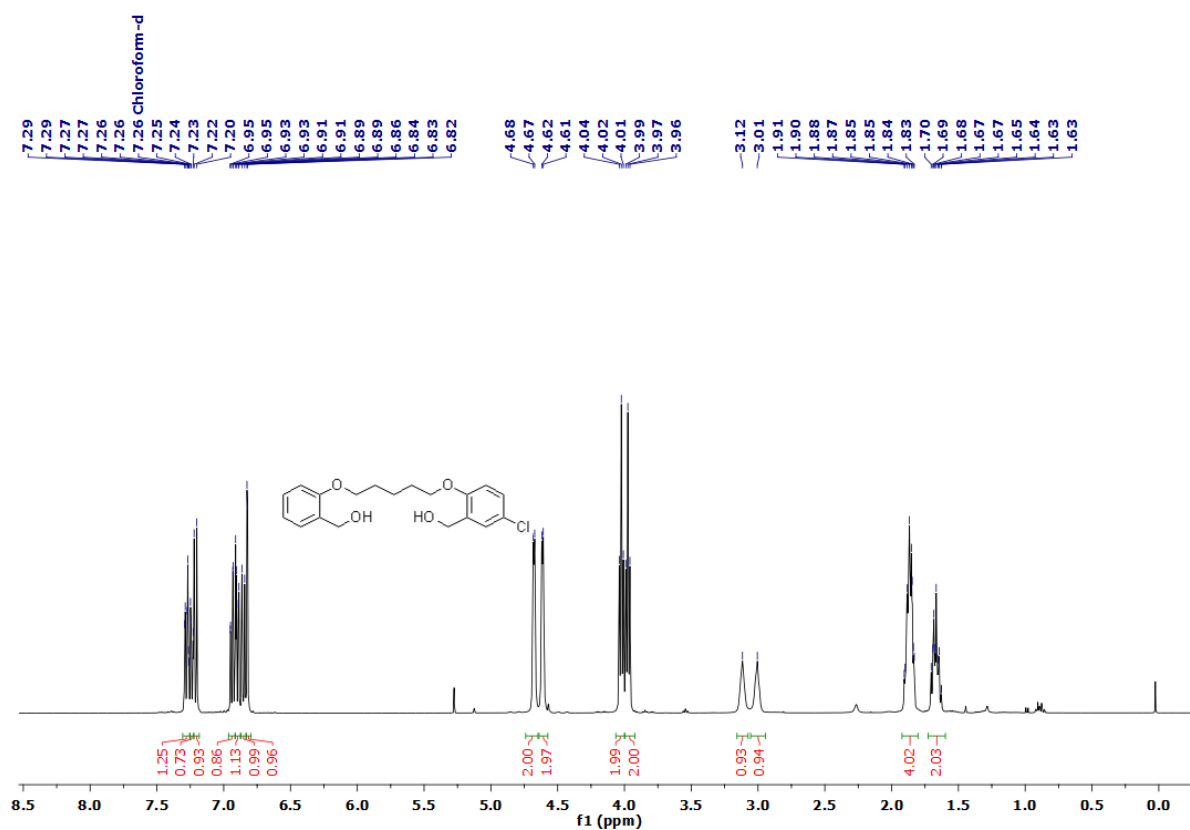


Figure 112. ¹H NMR spectra for compound **100i**, 400 MHz, CDCl₃

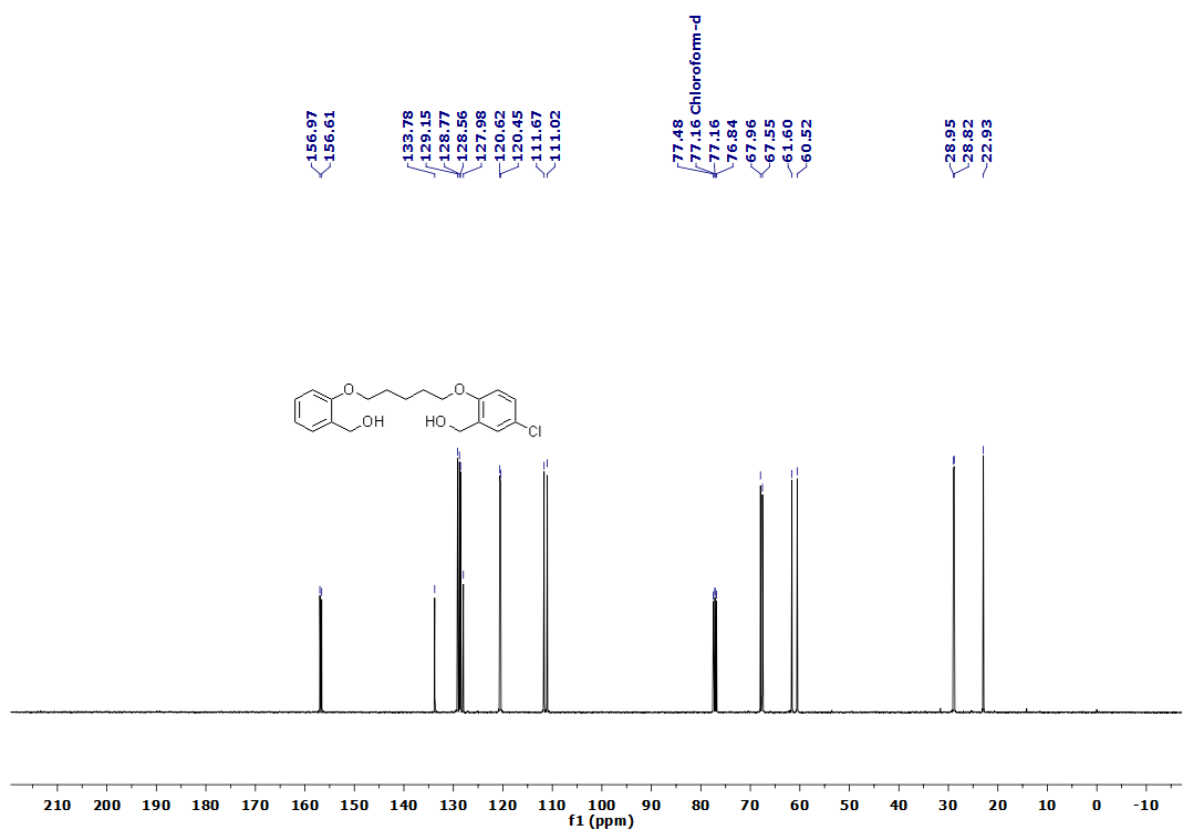


Figure 113. ¹³C NMR spectra for compound **100i**, 100 MHz, CDCl₃

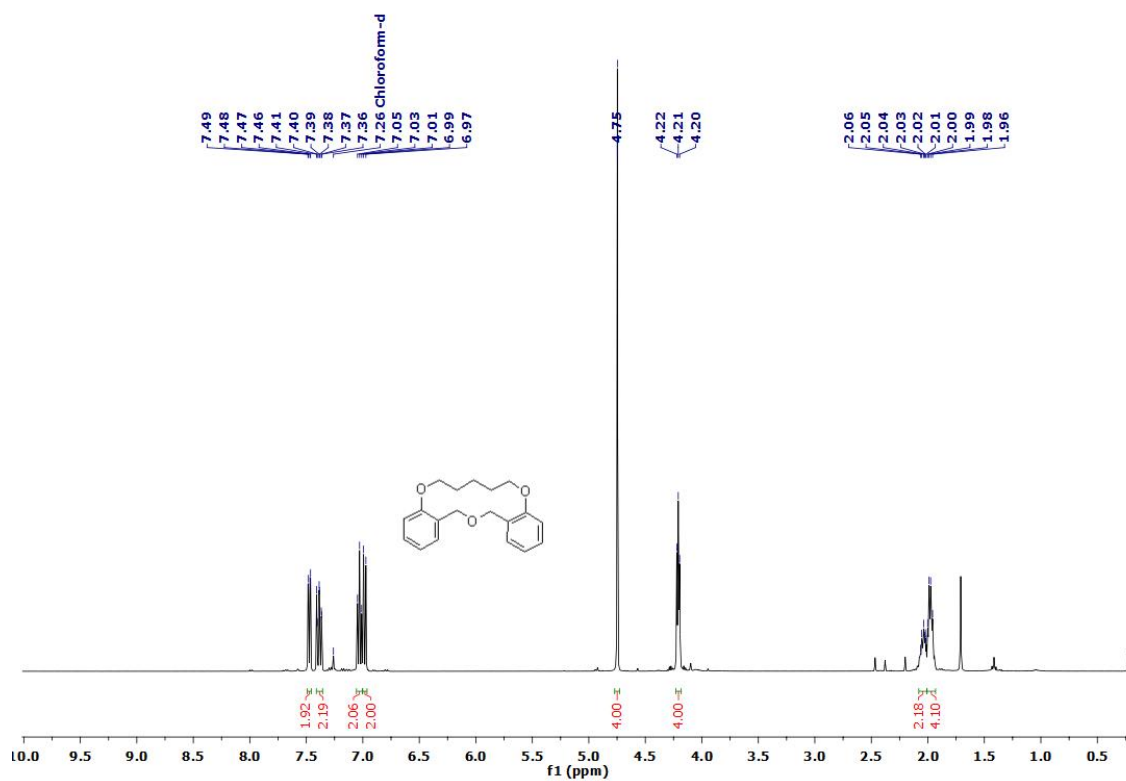


Figure 114. ¹H NMR spectra for compound **219a**, 400 MHz, CDCl₃

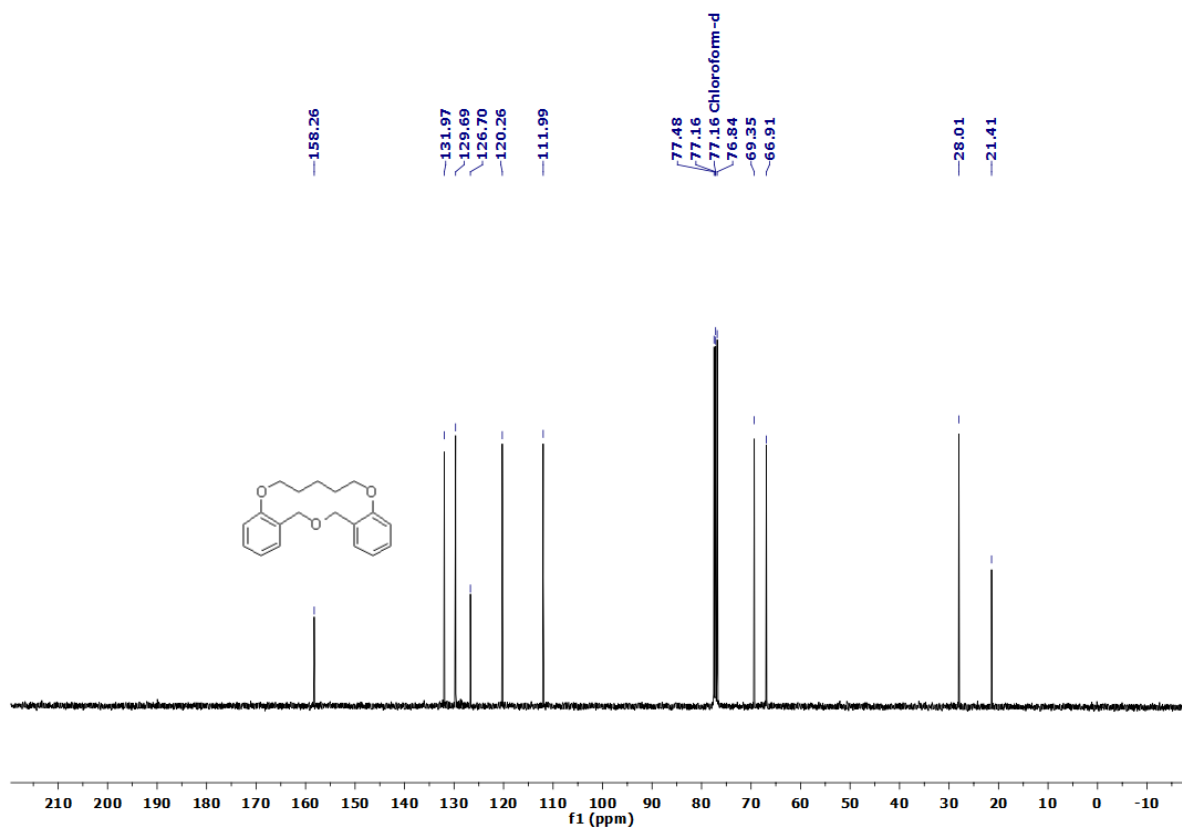


Figure 115. ¹³C NMR spectra for compound **219a**, 100 MHz, CDCl₃

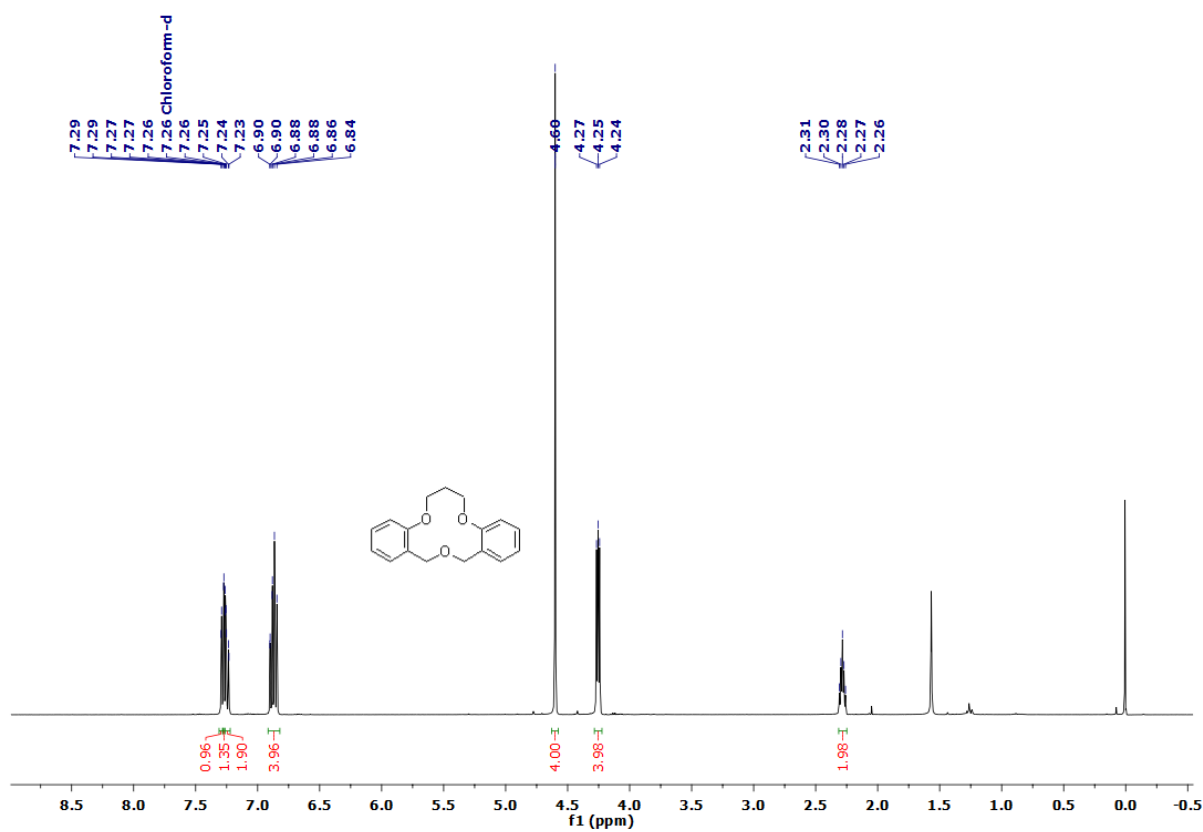


Figure 116. ¹H NMR spectra for compound **219b**, 400 MHz, CDCl₃

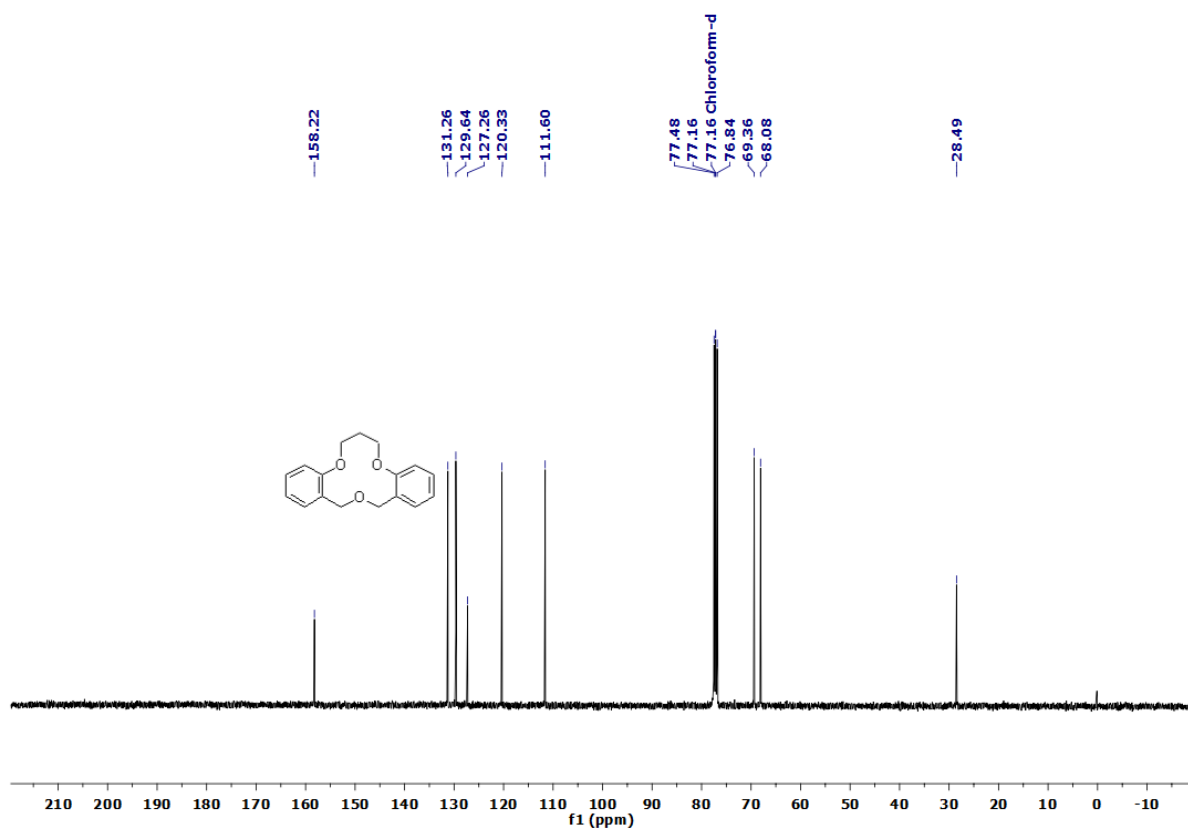


Figure 117. ¹³C NMR spectra for compound **219b**, 100 MHz, CDCl₃

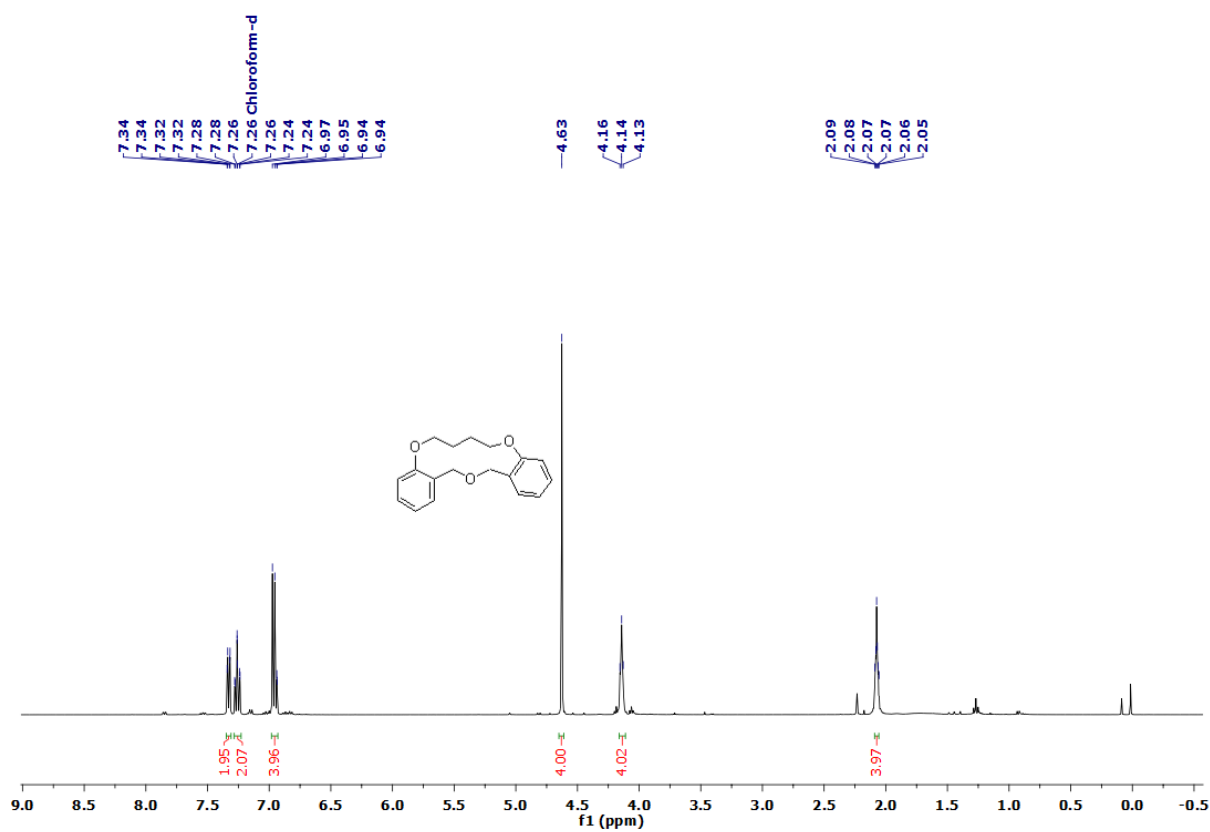


Figure 118. ¹H NMR spectra for compound **219c**, 400 MHz, CDCl₃

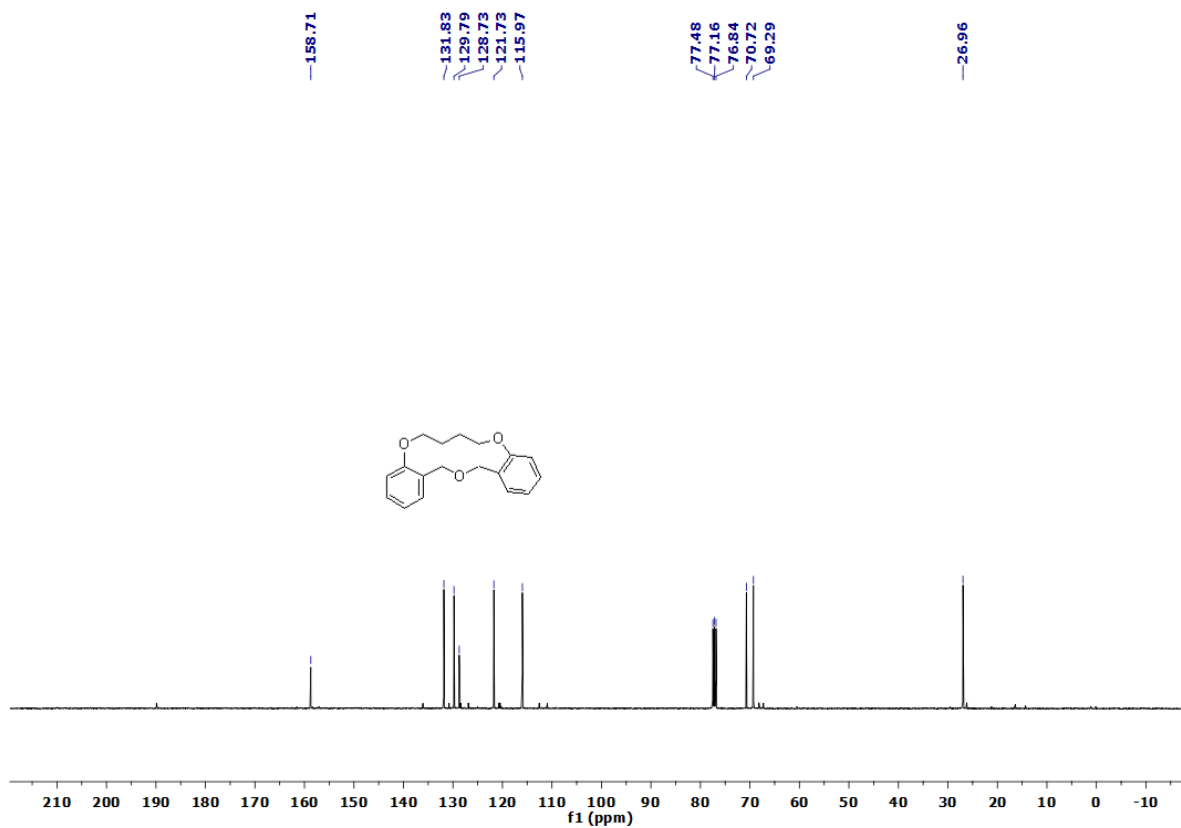


Figure 119. ¹³C NMR spectra for compound **219c**, 100 MHz, CDCl₃

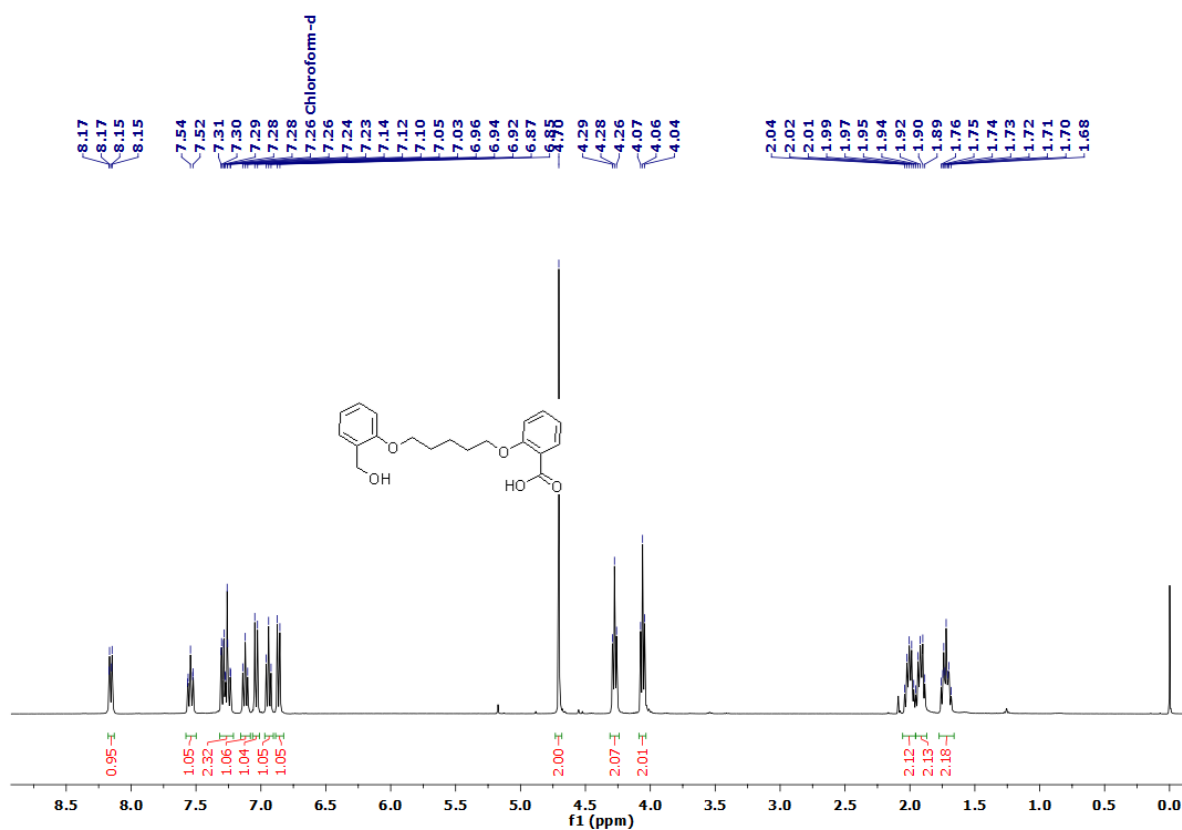


Figure 120. ¹H NMR spectra for compound **220a**, 400 MHz, CDCl₃

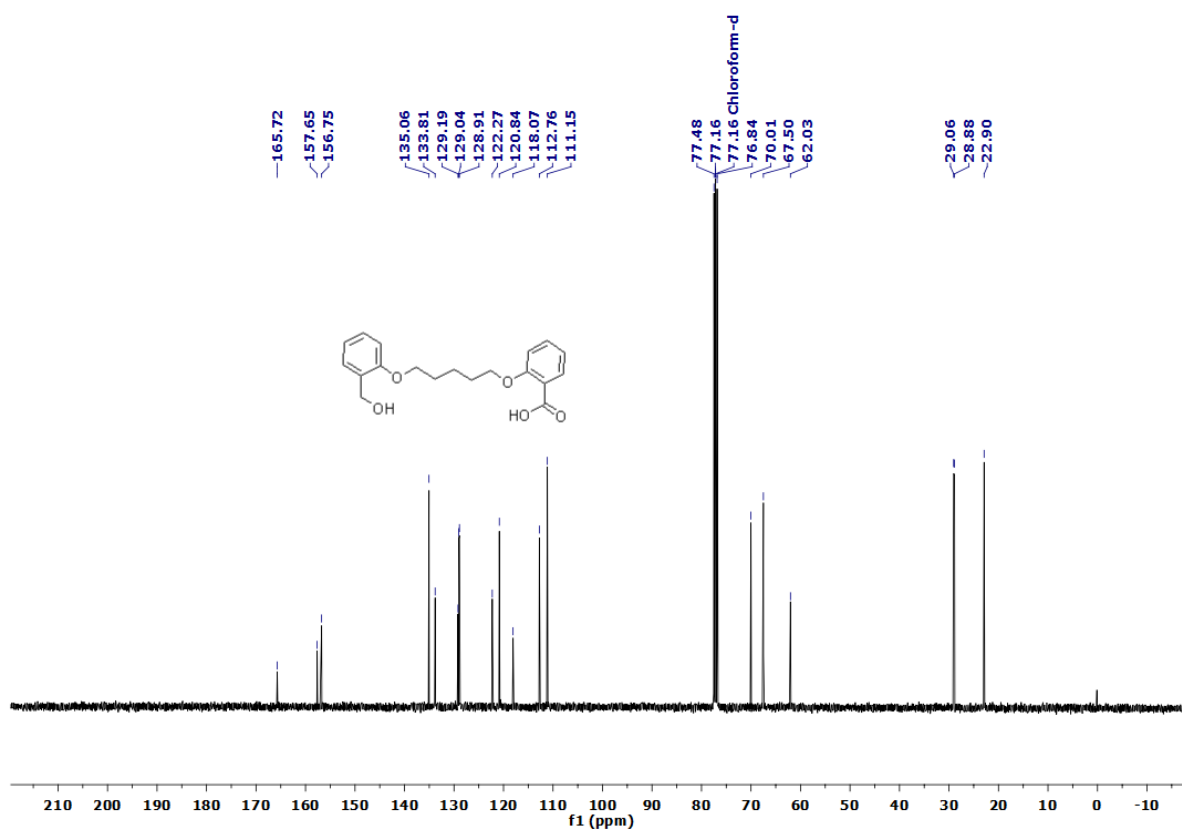


Figure 121. ¹³C NMR spectra for compound **220a**, 100 MHz, CDCl₃

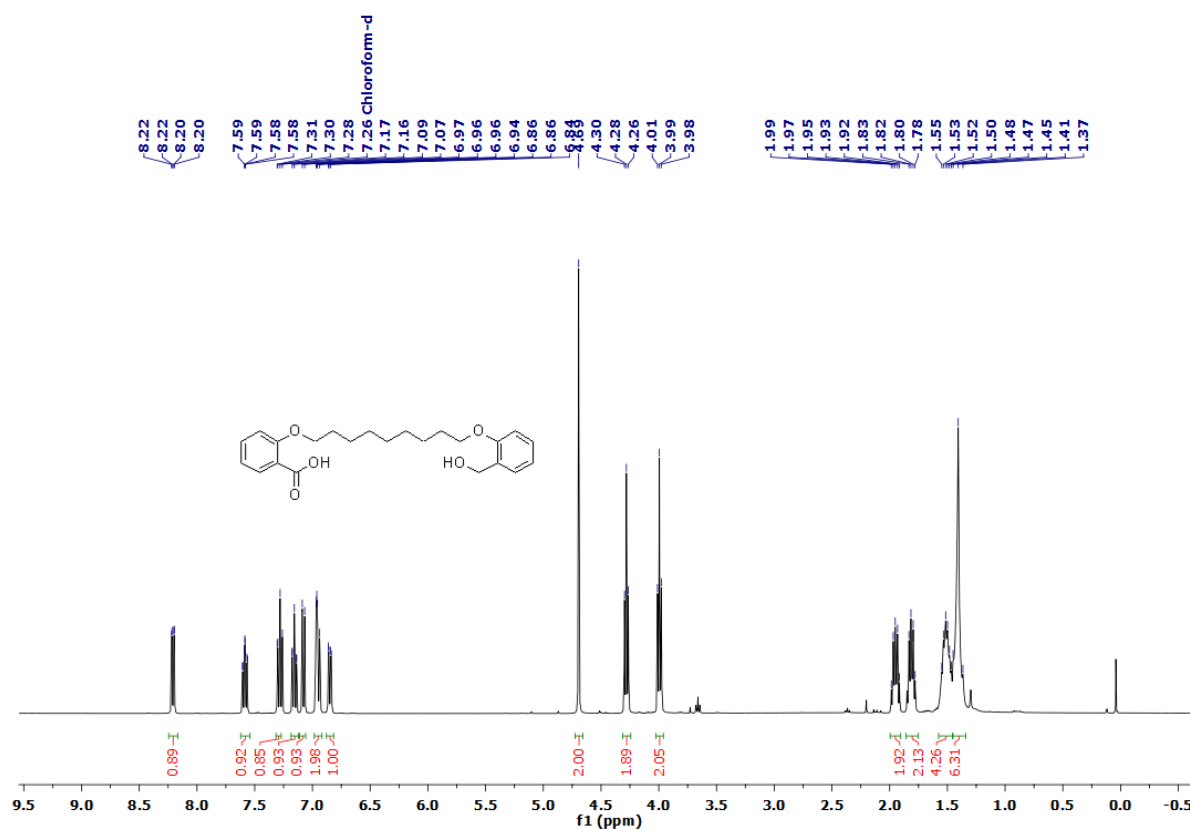


Figure 122. ¹H NMR spectra for compound **220b**, 400 MHz, CDCl₃

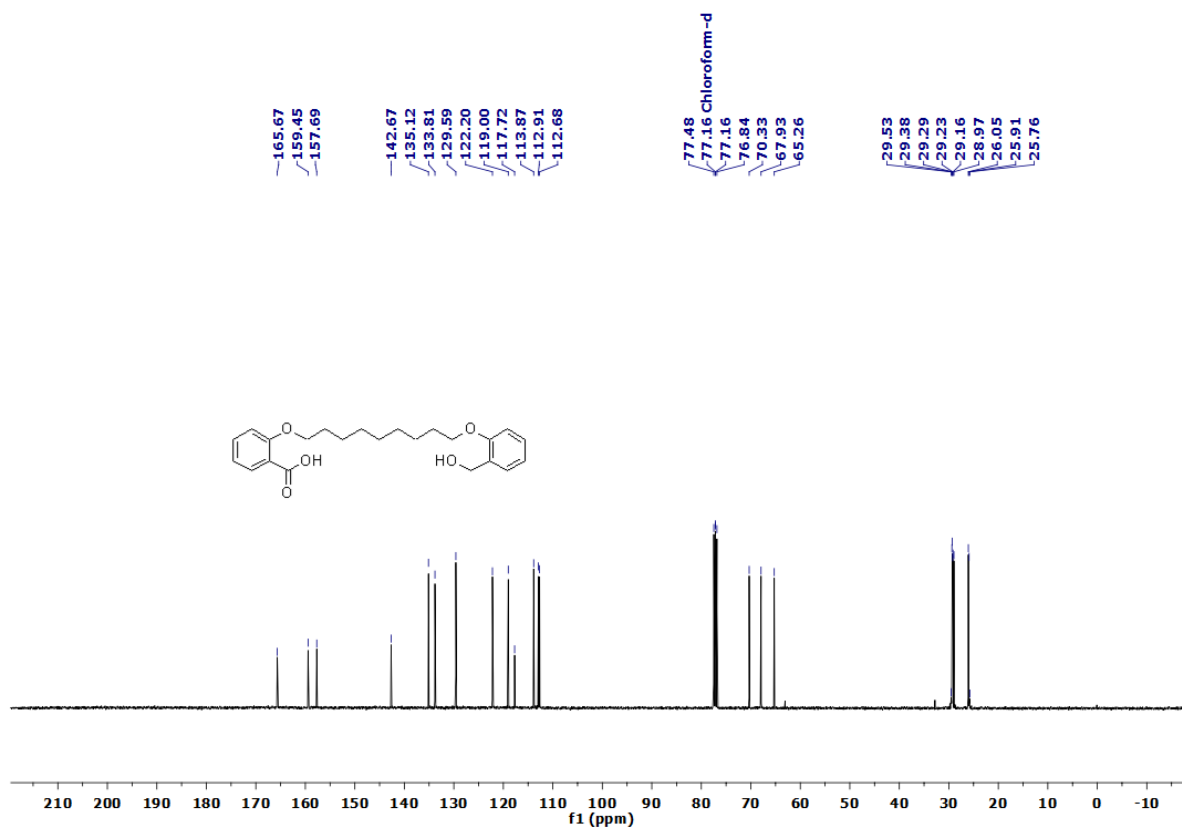


Figure 123. ¹³C NMR spectra for compound **220b**, 100 MHz, CDCl₃

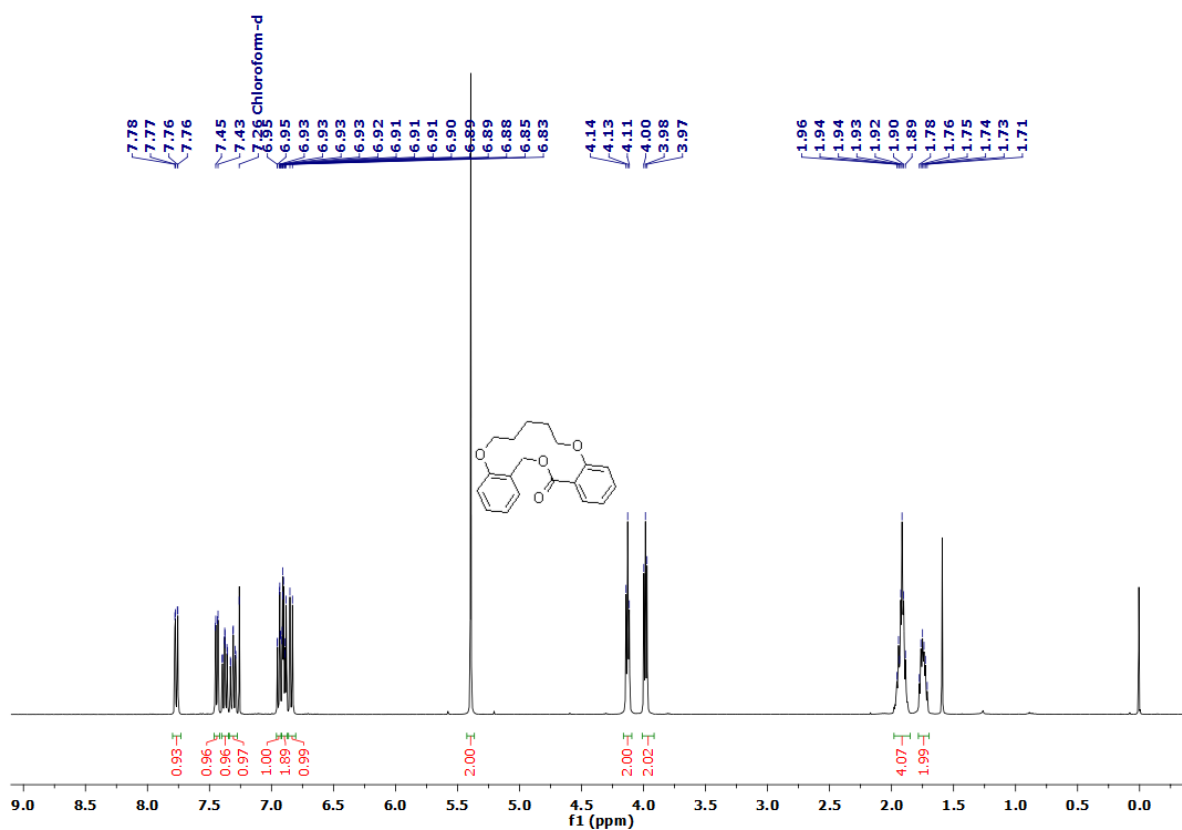


Figure 124. ¹H NMR spectra for compound **221a**, 400 MHz, CDCl₃

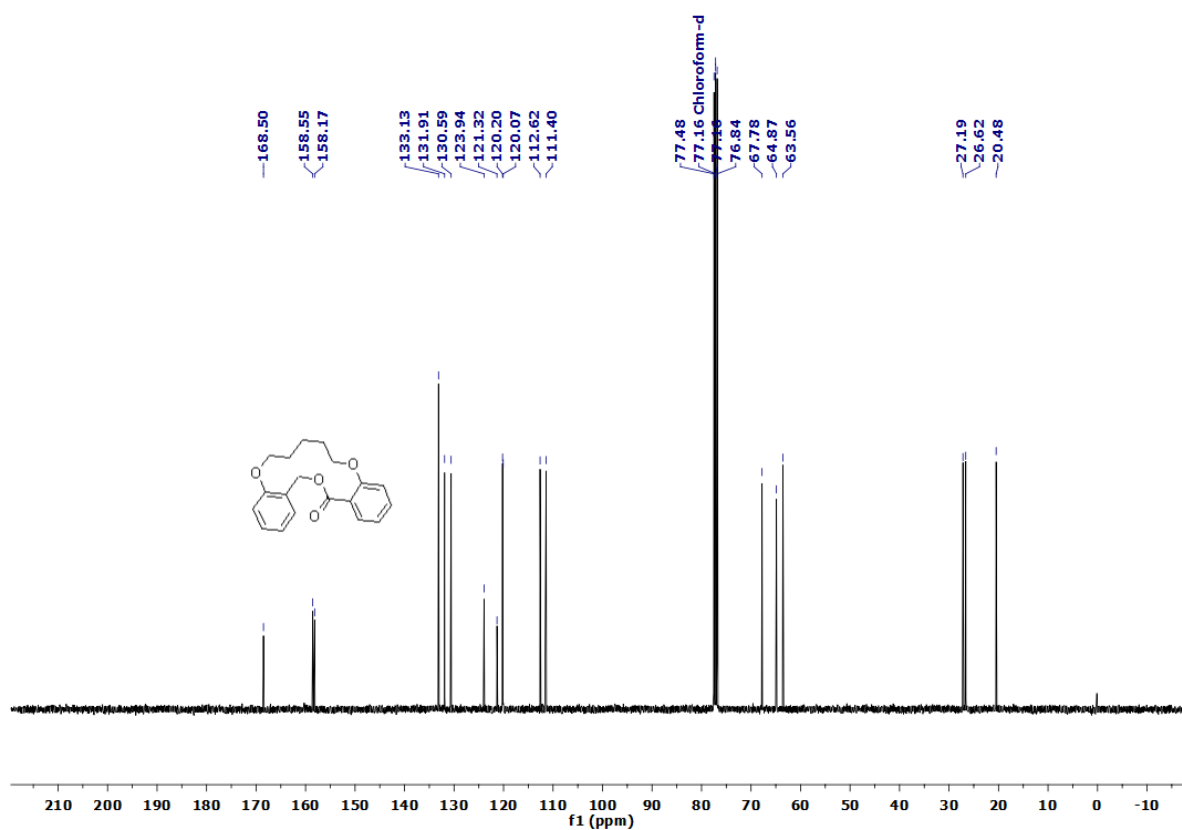


Figure 125. ¹³C NMR spectra for compound **221a**, 100 MHz, CDCl₃

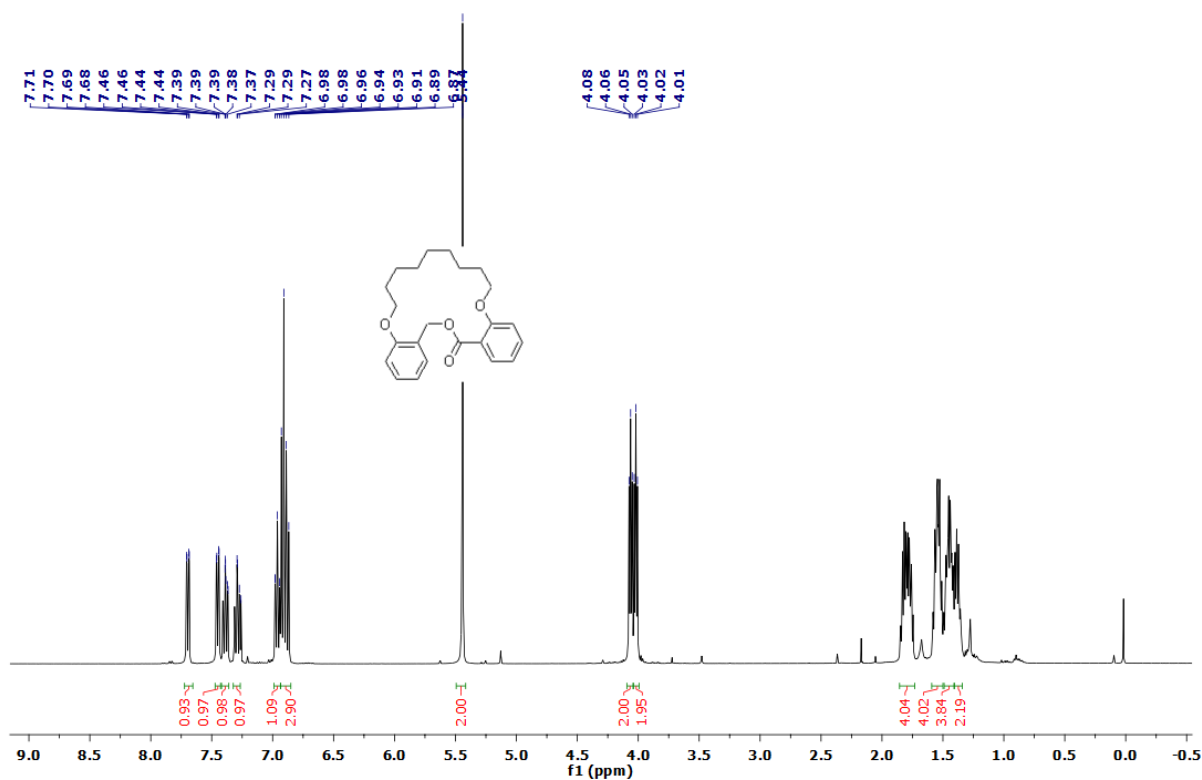


Figure 126. ¹H NMR spectra for compound **221b**, 400 MHz, CDCl₃

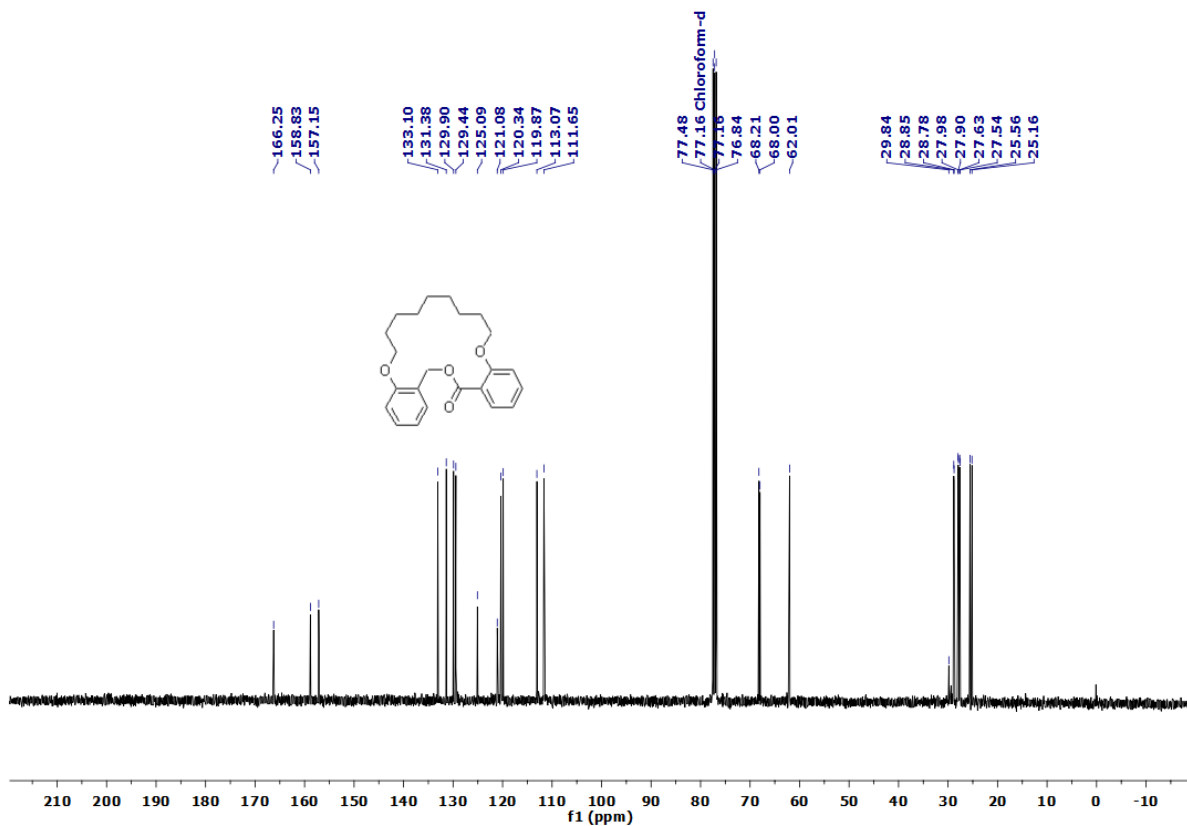


Figure 127. ¹³C NMR spectra for compound **221b**, 100 MHz, CDCl₃

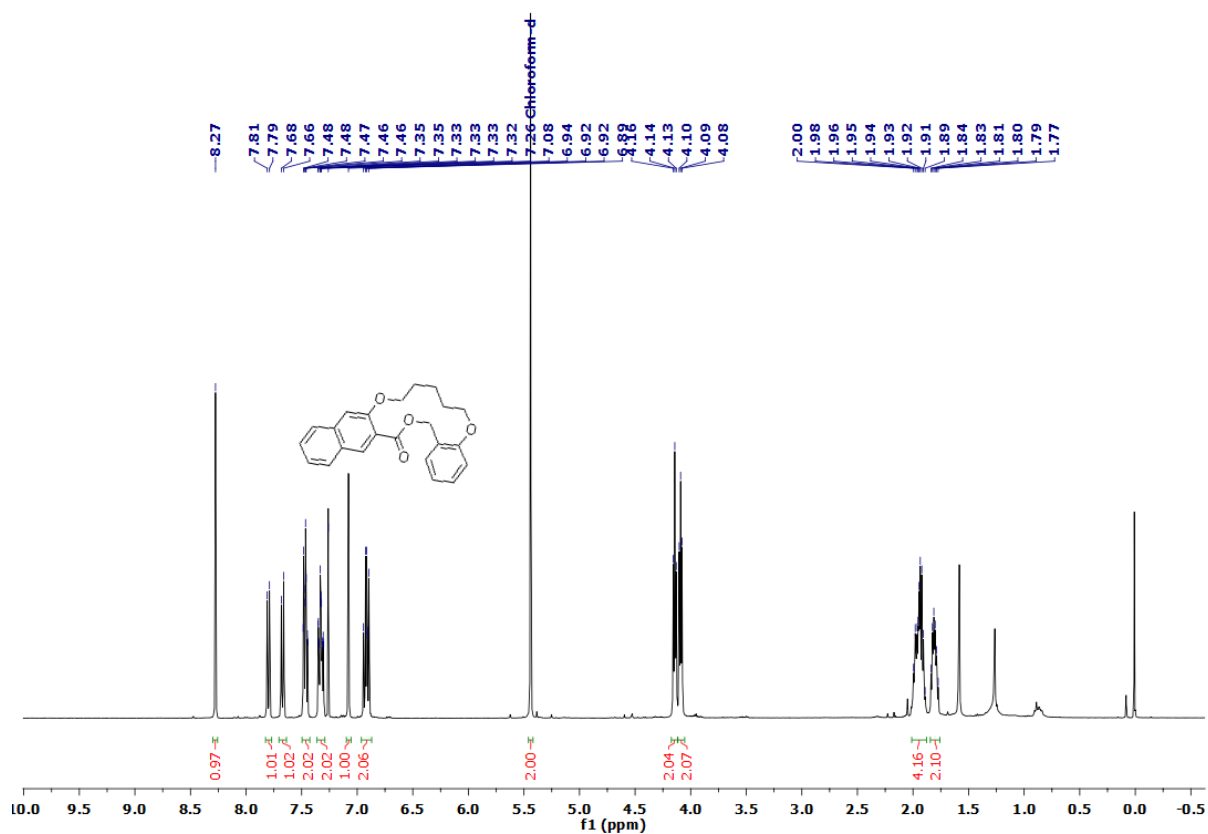


Figure 128. ¹H NMR spectra for compound 221c, 400 MHz, CDCl₃

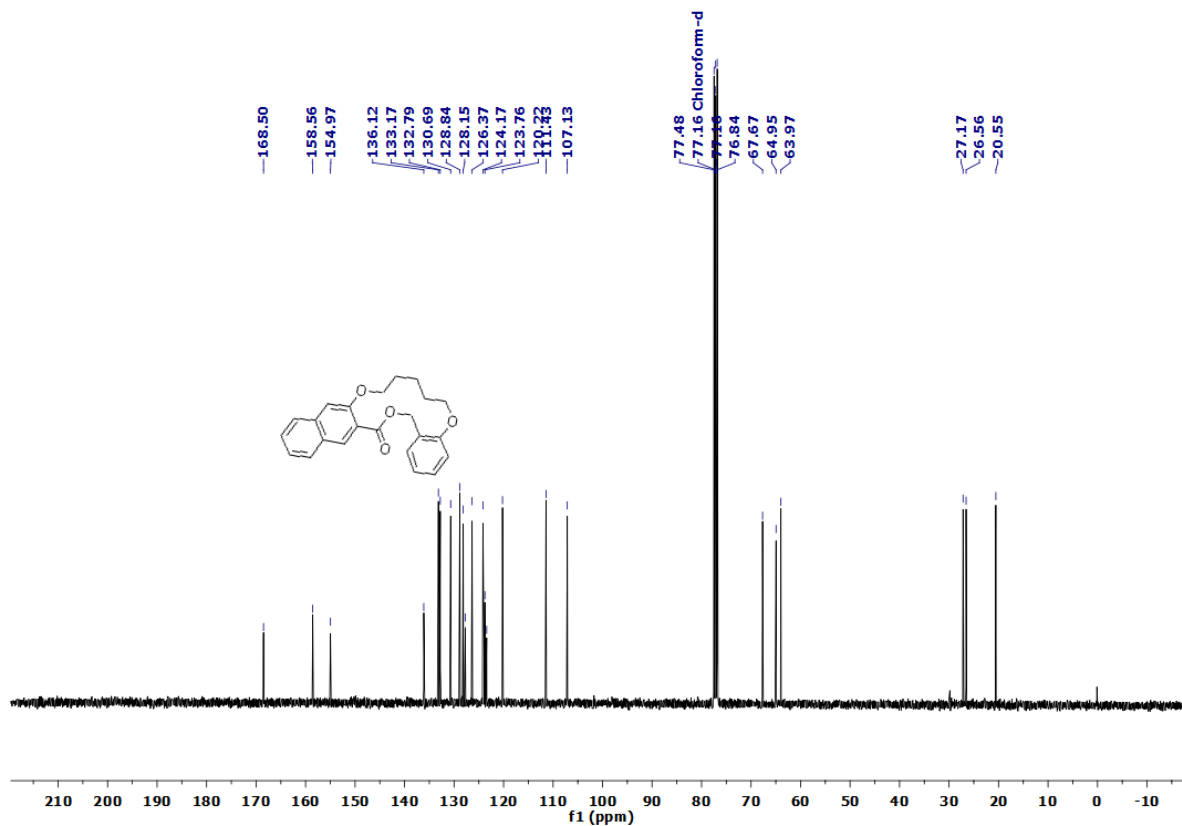


Figure 129. ¹³C NMR spectra for compound 221c, 100 MHz, CDCl₃

SUMMARY AND OUTLOOK

Chapter 1: In the first chapter, an overview of macrocycles, which includes their classification, significance, and a variety of applications is provided. Additionally, the challenges associated with macrocyclization reactions and highlight key strategies for the synthesis of macrocycles are addressed. Furthermore, how the catalysis and continuous flow techniques are advancing macrocycle synthesis by significantly improving reaction efficiency, selectivity, and scalability are examined. These methods play a pivotal role in overcoming traditional limitations, offering enhanced control over reaction conditions, and enabling more sustainable and scalable processes.

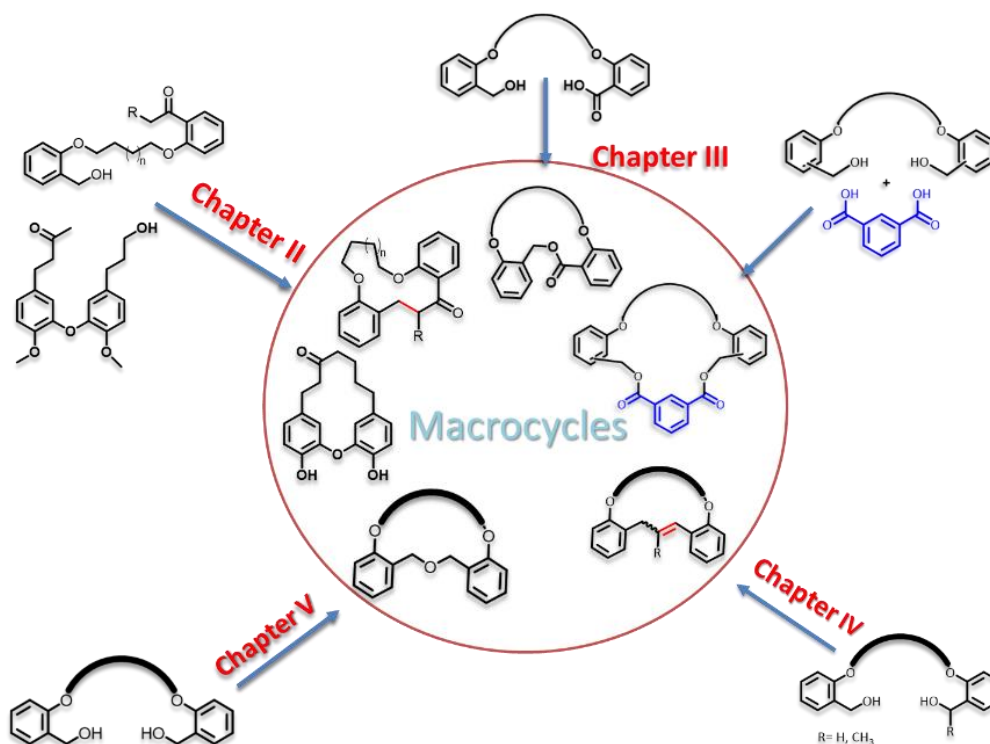
Chapter 2: In this chapter, a new method for the synthesis of macrocyclic ketone compounds using the borrowing hydrogen concept has been developed. This concept is step economic, environmentally friendly, sustainable, and generates only water as a by-product. The metal-catalyzed process applies to a wide range of substrates, highlighting its versatility in the synthesis of natural products. Furthermore, this borrowing hydrogen macrocyclization approach is utilized for the synthesis of the natural product Engelhardione.

Chapter 3: In this chapter, the intermolecular and intermolecular macrolactonization reaction under a continuous flow process is explored using seco-acid and diacid with diols. This reaction, utilized Mukaiyama reagent (*N*-methyl-2-chloropyridinium iodide) for acid activation in the presence of 1- methyl imidazole base. Moreover, macrocyclic lactones from the intramolecular reaction of seco-acid and dilactones and tetralactone from the intermolecular reaction of diols and diacids have been synthesized with a short residence time of 35 minutes.

Chapter 4: In this chapter, a new method for the synthesis of macrocyclic alkenes from primary and secondary alcohols using a Ni-Zeolite catalyst under continuous flow system is developed. The Ni-Zeolite catalyst offers easy recovery and reusability, facilitating the production of 23 macrocyclic alkenes with moderate yields. This method also enables the intramolecular coupling of secondary-secondary alcohols and alkene-alcohols, resulting in a diverse range of macrocyclic alkenes. Key advantages of this approach include step economy, and the generation of water as the sole by-product.

Chapter 5: In the final chapter, a straightforward and effective method for the synthesis of macrocyclic ethers by intramolecular dehydrative coupling of symmetrical and unsymmetrical

diols using a reusable Ni-Zeolite catalyst under continuous-flow system have been developed. This method uses a highly reusable and recoverable Ni/Ru-Zeolite heterogeneous catalyst, that shows effectiveness of this process for the synthesis of macrolactones from seco-acids under continuous flow conditions. Notable advantage of this method is, the generation of water as the sole by-product.



OUTLOOK

The work presented in this thesis highlights the significant progress made in the field of macrocycle synthesis through the development of innovative catalytic methods for the synthesis of macrocyclic ketone and natural product. Furthermore, it underscores the transformative potential of catalysis and continuous flow techniques in macrocycle synthesis, like macrolactone, macrocyclic alkene and macrocyclic ether. These approaches not only improve the efficiency and sustainability of synthetic processes but also offer new opportunities for the synthesis of structurally diverse and biologically relevant macrocyclic compounds. Future research should continue to focus on organic synthesis and contribute to the development of more sustainable and scalable chemical processes.

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- 1) **Sutar, D. V.**; Jamdade, A. B.; Swami, G. B.; P. M. Jadhav and Gnanaprakasam, B*. Continuous-Flow Fixed-Bed Catalysis for Intramolecular Dehydration of Diols and Seco-acids for Asymmetrical Macrocyclic Ether and macrocyclic lactone using Ni/Ru-Zeolite Catalyst. *Manuscript accepted in Journal of Organic Chemistry* **2024**.
- 2) **Sutar, D. V.**; Swami, G. B.; Jamdade, A. B.; and Gnanaprakasam, B*. Direct Intramolecular Coupling of Primary/Secondary Alcohols with Secondary Alcohols for Macrocyclic Alkenylation Using Ni-Zeolite Catalyst Under Continuous-Flow Conditions. *Adv. Synth. Catal.* **2024**, *366*, 1–11.
- 3) **Sutar, D. V.**; Sarang, N. U.; Jamdade, A. B. and Gnanaprakasam, B*. Continuous Flow Inter- and Intramolecular Macrolactonization under High Dilution Conditions. *J. Org. Chem.* **2023**, *88*, 3740–3759.
- 4) Jamdade, A. B.; **Sutar, D. V.**; and Gnanaprakasam, B*. Synthesis of Macrolactams from Macrolactones Using Ru-/Ir-Catalytic System under Neutral Conditions. *Org. Lett.* **2023**, *25*, 9058–9063.
- 5) Jamdade, A. B.; **Sutar, D. V.**; and Gnanaprakasam, B*. Dehydrogenative Intramolecular Macrolactonization of Dihydroxy Compounds Using Ru-MACHO Catalyst. *Org. Lett.* **2022**, *24*, 4394–4398.
- 6) Jamdade, A. B.; **Sutar, D. V.**; Bisht, G. S.; and Gnanaprakasam, B*. Ru-MACHO-Catalyzed Direct Inter/Intramolecular Macrocyclization of Alcohols and Ketones. *Org. Lett.* **2021**, *23*, 7386–7390.
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- 8) Jamdade, A. B.; Swami, G. B.; **Sutar, D. V.**; and Gnanaprakasam, B*. Ru-zeolite Catalyzed Dehydrative N-Alkylation of Amides for the Construction of Macrolactams under Continuous Flow Module. *Manuscript Submitted to E-JOC*

Ru-MACHO-Catalyzed Direct Inter/Intramolecular Macrocyclization of Alcohols and Ketones

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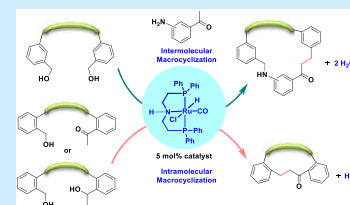


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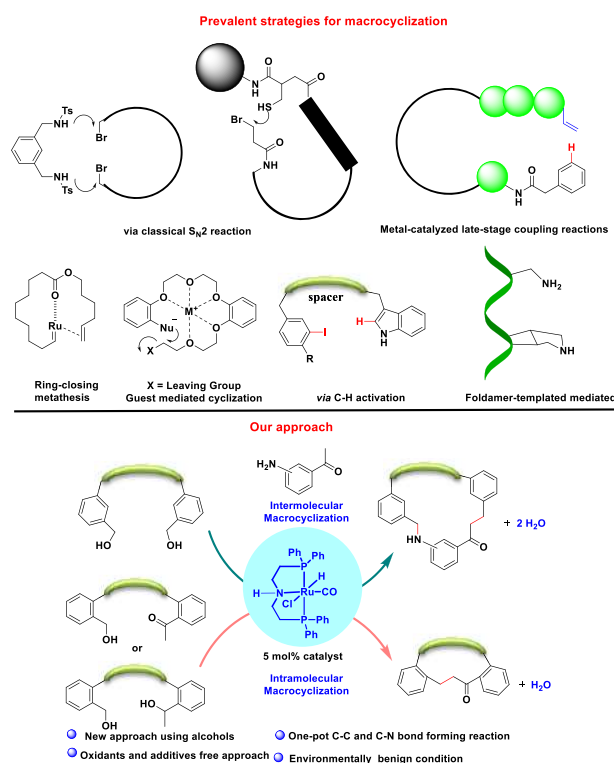
Supporting Information

ABSTRACT: Herein we describe a new approach for end-to-end cyclization to construct macrocycles through the inter/intramolecular dehydrogenative coupling of alcohols and ketones in the presence of a Ru-MACHO catalyst. This method is highly atom economical and sustainable and can be used for many substrates. Additionally, this method results in the generation of only water as the byproduct. Moreover, in this approach, high dilution of the reactants is crucial for cyclization and high-yield macrocycle synthesis.

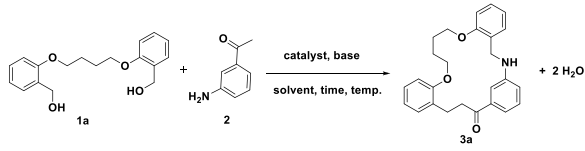


In chemistry, macrocycles constitute a special class of chemical compounds with ubiquitous structural motifs. Macrocycles of 12 or more atoms form a cyclic ring system in many natural products,¹ and they are widely used in pharmaceutical,² material,³ and supramolecular chemistry.⁴ However, the synthesis of macrocycles through the ring closure of end groups of linear long chains is challenging because of the highly complex entropy process⁵ involved, which possibly leads to competing undesired intermolecular reactions and oligomerization.⁶ Selectivity during macrocyclization is difficult because of possible side reactions, which decrease the yield of the desired product. Despite various challenges in macrocyclization, a significant number of approaches have been developed for the construction of macrocycles. In classical approaches, stoichiometric reagents are required to activate the functional group, and toxic halogenated reagents are used for inter/intramolecular macrocyclization.⁷ These approaches thus result in the generation of a considerable amount of waste byproducts and are unsustainable.⁸ In contemporary macrocyclization approaches, transition-metal-catalyzed reactions have been reported with various end-group functionalities. These approaches have gained considerable attention because of their advantages such as their selectivity, efficiency, high atom economy, low byproduct generation, and sustainability.⁹ Thus numerous approaches have been developed for inter/intramolecular macrocyclization using transition metals as catalysts. Notable synthesis strategies include ring-closing metathesis (RCM),¹⁰ cycloaddition reactions using alkyne–azide,¹¹ the guest-mediated synthesis of the macrocycle,¹² the foldamer-templated-mediated reaction,¹³ the multicomponent reaction,¹⁴ cross-coupling reactions,¹⁵ and C–H activation¹⁶ (Scheme 1). However, the development of a novel synthesis method for efficient macrocyclization with high selectivity and sustainability is highly desirable. In the 21st century, metal-catalyzed transformations proceeding through the borrowing hydrogen concept (BHC) have emerged as a superlative approach for the C–C and C–N bond-forming reactions¹⁷ because of advantages

Scheme 1. State-of-the-Art Schematics of Various Macrocyclization Strategies



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Table 1. Optimization of Reaction Conditions^a


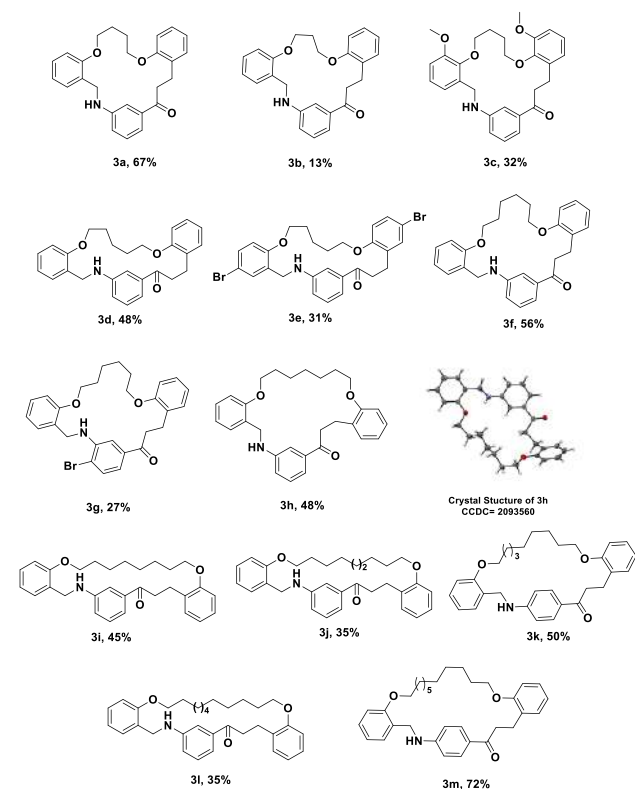
entry	catalyst (5 mol %)	base (equiv)	conc. (1:2) in toluene (M)	time (h)	yield of 3a (%)
1		KOH (2)	0.1:0.1	16	trace
2	Ru-MACHO		0.1:0.1	16	
3	Ru-MACHO	NaOH (1)	0.1:0.1	16	17
4	Ru-MACHO	NaOH (2)	0.1:0.1	16	13
5 ^b	Ru-MACHO	NaOH (1)	0.1:0.1	16	14
6 ^c	Ru-MACHO	NaOH (1)	0.1:0.1	16	30
7 ^c	Ru-MACHO	NaOH (1)	0.08:0.04	24	36
8 ^c	Ru-MACHO	NaOH (2)	0.08:0.04	24	38
9 ^c	Ru-MACHO	KO ^t Bu (2)	0.08:0.04	24	40
10 ^c	Ru-MACHO	KOH (2)	0.08:0.04	24	42
11 ^c	Ru-MACHO	KOH (2)	0.05:0.02	24	49
12 ^c	Ru-MACHO	KOH (2)	0.05:0.02	48	54
13 ^{c,d}	Ru-MACHO	KOH (2)	0.05:0.02	48	44
14 ^c	RuCl ₃ ·xH ₂ O	KOH (2)	0.05:0.02	48	trace
15 ^c	Ru-PNN	KOH (2)	0.05:0.02	48	28
16 ^c	RuH ₂ (CO)(PPh ₃) ₃	KOH (2)	0.05:0.02	48	30
17 ^c	Ru-NHC	KOH (2)	0.05:0.02	48	34
18 ^c	Ru-MACHO	KOH (2)	0.01:0.01	48	67
19 ^c		KOH (2)	0.01:0.01	48	trace

^aReaction conditions: Compounds **1a** and **2** (M solution in toluene, see table), Ru-MACHO (5 mol %), and base (see table) were stirred in an oil bath preheated to 160 °C for different time periods (see table). ^bReaction conditions: Reaction mixture heated to 140 °C. ^cReaction conditions: Reaction mixture heated to 180 °C. ^dReaction conditions: 1,4-Dioxane was used as a solvent.

such as minimal byproduct formation, mutagenic-reagent-free reactions, low *E* factor, and sustainability. Although fundamental reactions for BHC with several catalytic systems have been investigated, the application of this approach toward macrocycle synthesis has not been studied until now.

In this study, we report a novel approach for end-to-end cyclization toward the synthesis of macrocycles by using BHC. This study is the first to describe an approach for the synthesis of macrocycles by using alcohols and ketones through inter- and intramolecular borrowing alkylation.

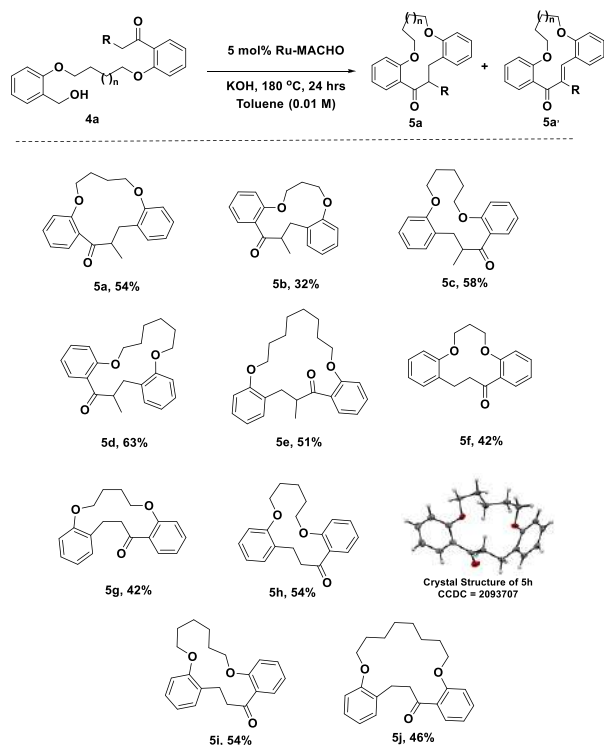
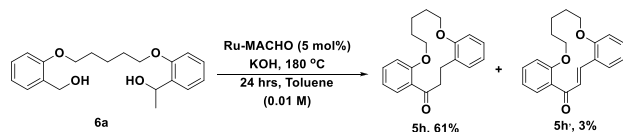
We initiated our investigation by performing dehydrogenative coupling of compound **1a** and 1-(3-aminophenyl)ethan-1-one as a model reaction. In addition, we performed a controlled experiment, which revealed that both the catalyst and the base are essential for this transformation (Table 1, entries 1 and 2). Notably, 5 mol % of Ru-MACHO [carbonylchlorohydrido{bis-[2-(diphenylphosphino)ethyl]amino}ethyl]amino-ruthenium(II)]¹⁸ catalyst and 1 equiv of NaOH base provided a 17% isolated yield of product **3a** (Table 1, entry 3). The use of 2 equiv of NaOH base resulted in a decrease in the product yield (Table 1, entry 4). A yield enhancement was observed upon increasing the reaction temperature up to 180 °C (Table 1, entry 6). Moreover, when the concentrations of both starting materials were reduced, the product yield increased. Macrocyclization was found to be highly dependent on dilution (Table 1, entry 7). Furthermore, the use of 2 equiv of the base resulted in a slight increase in the product yield. Bases KO^tBu and KOH

Scheme 2. Substrate Scope for Intermolecular Macrocyclization^a

^aReaction conditions: Diphenyldimethanol derivatives (0.01 M in toluene), aminoacetophenone (0.01 M in toluene), Ru-MACHO (5 mol %), and KOH (0.166 mmol) were taken in a sealed tube. The reaction mixture was heated to 180 °C for 48 h.

resulted in a 40 and 42% yield, respectively (Table 1, entries 9 and 10). High dilution of both starting materials up to 0.05:0.02 M substantially increased the product yield (Table 1, entry 11). When the reaction was maintained for a long time period, a slight increment in the product yield was observed (Table 1, entry 12). Furthermore, other solvents, such as 1,4-dioxane, were found to be inefficient for this transformation after screening. Subsequently, various Ru catalysts such as RuCl₃·xH₂O, Ru-PNN, RuH₂(CO)(PPh₃)₃, and Ru-NHC used for the formation of this macrocycle resulted in a poor-to-moderate yield (Table 1, entries 14–17). The product yield increased substantially when the concentration of the starting material was decreased to 0.01 M (Table 1, entry 18). The absence of catalyst resulted in no reaction (Table 1, entry 19).

Inspired by the optimized results, we investigated the substrate scope for this method with various diphenyldimethanol derivatives. The experimental results revealed that the macrocycle yield depends on the chain length of the spacer. The diphenyldimethanol containing butyl spacer in **3a** resulted in a 67% yield. The propyl-substituted spacer resulted in **3b** in a poor yield (13%). However, diphenyldimethanols with ethyl and methyl spacers could not promote macrocyclization. Other substrates exhibiting a long spacer length resulted in a 45–56% yield of macrocycles **3c–i**, with the exception of bromo-substituted derivatives, **3e** and **3g**, and methoxy derivative **3c**, whose yield percentages were 31, 27, and 32%, respectively (Scheme 2). However, diols with nonyl and undecyl spacers with 4-amino acetophenone resulted in macrocycles **3k** (50%)

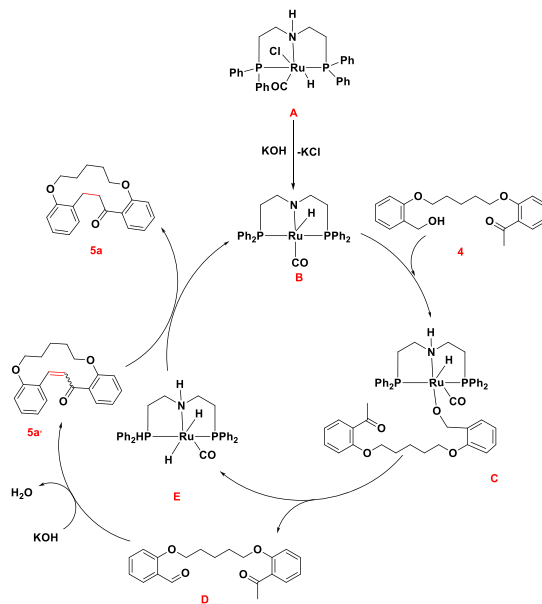
Scheme 3. Substrate Scope for Intramolecular Macrocyclization^aScheme 4. Intramolecular Macrocyclization Using Primary and Secondary Alcohols^a

^aReaction conditions: Compound **6a** (0.01 M solution in toluene), Ru-MACHO (5 mol %), and KOH (1 equiv) were taken in a sealed tube. The reaction mixture was heated to 180 °C in an oil bath for 24 h.

and **3m** (72%), respectively. Positional isomers (para- and meta-substituted) of diphenyldimethanols did not react with 3-aminoacetophenone or 4-amino acetophenone.

Next, we applied this strategy for the intramolecular macrocyclization reaction. Although the Ru-MACHO-catalyzed alkylation of ketones and amides using alcohols was reported,¹⁹ applications in macrocyclization were not studied. We used 1-(2-(4-(2-(hydroxymethyl)phenoxy)butoxy)phenyl)propan-1-one **4a** as a model substrate. A controlled experiment revealed that the catalyst and base were crucial for this transformation because in the absence of the catalyst and base in the reaction mixture, no reaction was observed. (See the SI, Table 1, entries 1 and 2.) Notably, heating of the reaction mixture containing 1 mol % of Ru-MACHO catalyst and stoichiometry KOH as a base yielded macrocycle **5a** (30%) along with (*E*)-16-methyl-6,7,8,9-tetrahydro-15*H*-dibenzo[*g,l*][1,6]dioxacyclotridecin-15-one **5a'** as a minor product. (See the SI, Table 1, entry 3.) When this reaction mixture was heated to 160 and 180 °C, 40 and 46%

Scheme 5. Plausible Mechanism for Macrocyclization



yields of product **5a** (see the SI, Table 1, entries 4 and 5), respectively, were obtained. When NaOH was used as a base, the product yield decreased. (See the SI, Table 1, entry 6.) Notably, upon an increase in the amount of catalyst (5 mol %), an increase in the yield of product **5a** was observed. A two-fold decrease in the concentration of starting material **4a** increased the yield of product **5a**. (See the SI, Table 1, entry 7.) Other catalysts such as $\text{RuH}_2\text{CO}(\text{PPh}_3)_3$ and $[\text{Ru}-(\text{COD})\text{Cl}_2]_n$ were found to be inefficient for macrocyclization. (See the SI, Table 1, entries 8 and 9.)

Next, we investigated the generality of this transformation with other ketone–alcohol derivatives. A propyl spacer compound resulted in a 32% yield of macrocycle **5b**. Moderate yields of macrocycles **5c–e** were obtained using respective alcohols having ethyl ketone through the intramolecular BHC reaction. An increase in the chain length in the spacer of ketone–alcohol **4** directly influenced the yield of the macrocycle. Thus with four to six chain spacers, the yield of macrocycles **5f–i** increased to 54%. An octyl spacer resulted in a 46% yield of macrocycle **5j** (Scheme 3). Furthermore, in most of these reactions, traces of the alkene macrocycle were observed. To expand the scope of the application of this strategy, we performed intramolecular macrocyclization with unsymmetric diols (Scheme 4). Thus the macrocyclization was successfully achieved through the intramolecular coupling of **6** with primary and secondary alcohols, following which products **5h** and **5h'** were obtained (Scheme 4). This reaction was allowed with another substrate **6b** to obtain product **5g** (56%).

On the basis of literature reports,²⁰ a plausible mechanism for this transformation is depicted in Scheme 5. At the outset, KOH and Ru-MACHO catalyst **A** were used to generate active catalyst **B**.²¹ Furthermore, active catalyst **B** reacted with alcohol **4** to produce alkoxy-coordinated intermediate **C**. Subsequently, β -hydride elimination in intermediate **C** formed aldehyde **D** and hydride intermediate **E**. Next, compound **D** underwent an intramolecular aldol condensation reaction to generate compound **5a'**. Finally, the hydrogenation of compound **5a'** resulted in the desired macrocycle **5a**. A plausible mechanism for

intermolecular cyclization to form **3** based on literature²⁰ is also depicted. (See the SI.)

In conclusion, we developed a novel approach for the synthesis of macrocycles through inter- and intramolecular cyclization by using dimethanol and ketone–alcohol in the presence of a Ru-MACHO catalyst. Moderate yields of numerous macrocycles with 12- to 26-membered rings were obtained using this approach. We also found that high dilution and the spacer length are pivotal to efficient macrocyclization. The proposed approach is highly sustainable, atom economical, and easily synthesizable and results in the generation of water as the only byproduct. The feasibility of this approach for the synthesis of natural products and drugs is being investigated in our laboratory.

■ ASSOCIATED CONTENT

SI Supporting Information

The Supporting Information is available free of charge at <https://pubs.acs.org/doi/10.1021/acs.orglett.1c02569>.

Experimental procedures, compound characterization data, copies of NMR for the compounds, and X-ray crystallographic data (PDF)

FAIR data, including the primary NMR FID files, for compounds **1a–j**, **3a–m**, **4a–j**, **5a–j**, and **6a,b** (ZIP)

Accession Codes

CCDC 2093560 and 2093707 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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Continuous Flow Inter- and Intramolecular Macrolactonization under High Dilution Conditions

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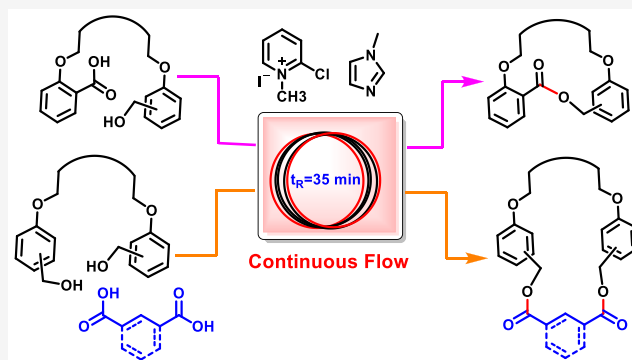


Article Recommendations



Supporting Information

ABSTRACT: An efficient continuous flow process for the macrolactonization of seco acids and diacids using diols in the presence of Mukaiyama reagent (*N*-methyl-2-chloropyridinium iodide) has been developed for medium to large sized macrocyclic lactones. In comparison with other methods, the continuous flow process provided good to high yield in a short reaction time. By using this methodology, a wide range of macrocyclic lactones (11 compounds), dilactones (15 compounds), and tetralactone derivatives (2 compounds) with various ring sizes (12–26 atoms in the core) were synthesized in just 35 min of residence time. Advantageously, macrolactonization under the flow process is very elegant to handle the high dilution of reactants with a defined perfluoroalkoxy alkanes (PFA) tube reactor volume (7 mL).



INTRODUCTION

The macrocyclic lactones have been considered as structurally important motifs in many natural/unnatural products¹ and biologically active drug molecules.² Therefore, these privileged molecular frameworks have made a great contribution in the fields of pharmaceuticals,³ agrochemicals,⁴ supramolecular chemistry,⁵ fungicides, and insecticides.⁶ Moreover, macrocyclic lactones have also found intense utility in the fragrance industry⁷ and cosmetic industry.⁸ In the past decade, a wide range of macrolactonization approaches have been developed. In addition, pioneering reports are available on the synthesis of macrolactones by using seco acids via either activation of the carboxylic acid or activation of the hydroxy group (Scheme 1A). These reports mainly focused on the Corey-Nicolaou strategy,⁹ Yamaguchi reaction,¹⁰ Shiina macrolactonization,¹¹ Steglich-Boden-Keck reaction,¹² Mitsunobu reaction,¹³ and Mukaiyama esterification¹⁴ reaction. Among these reactions, Mukaiyama esterification is very cost-effective and easy to handle. So, it has been used for several macrocyclic lactone syntheses. In 1976, Mukaiyama et al. reported *N*-methyl-2-chloropyridinium iodide as an elegant reagent for macrolactonization.¹⁴ Subsequently, this approach has been extended to synthesize various macrocyclic lactone and lactam-containing natural products.^{15,16} Furthermore, Meinwald et al. synthesized a 98-membered macrolactone in 48% yield using Mukaiyama reagent.¹⁷ It is also useful for the total synthesis of (+)-quadron,¹⁸ (+)-sorangicin A,¹⁹ (+)-tubelactomicin,²⁰ (–)-bastimolide,²¹ and prostaglandin F2 α .²² Later, to conduct a heterogeneous system for simplifying the product

purification, liquid state Mukaiyama reagent was immobilized on the polymer support (such as Wang resin).²³ All these transformations were carried out under batch reaction using metal/nonmetal catalysts,²⁴ catalytic dehydrogenative intramolecular macrolactonization,²⁵ and *N*-heterocyclic carbene (NHC)-catalyzed oxidative esterification of aldehydes.²⁶

Generally, macrocyclization reactions work well under high dilution conditions with the slow addition of reactants. In all previous reports, both batch and microwave strategies have been found to be highly inefficient in drug discovery and large-scale synthesis, where a long reaction time and high dilution are required. This directly affects the cost and green chemistry perspectives. Moreover, selective formation of macrocyclic lactone over the other oligomer mixture is generally associated with controlled addition, which is difficult to control precisely by the batch process. To overcome these issues, a better chemical process is required to produce macrocyclic lactone for a wide range of applications. Thus, developing continuous flow chemistry for the macrolactonization could control the various limitations that arise from the batch reactions. However, to the best of our knowledge, there is only one

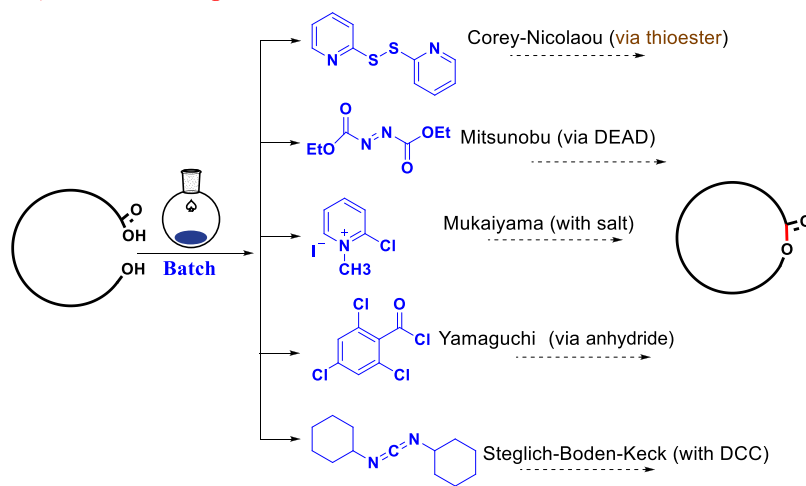
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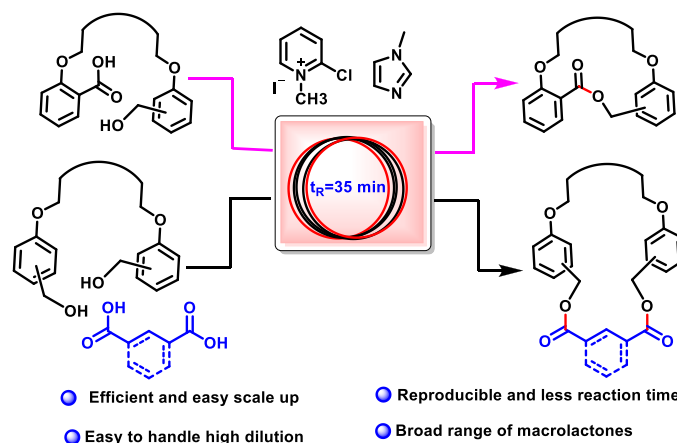
Scheme 1. State of the Art for the Macrolactonization by Using Different Acid Activators

A) Prevalent strategies for macrolactonization



B) This work

Continuous Flow



recent report available in the literature for continuous flow macrolactonization using a coupling reagent.²⁷

Continuous flow chemistry is a well-established technique used for the large-scale production of intermediates and pharmaceutical drugs.²⁸ On the other hand, the traditional batch method required very harsh reaction conditions as the reflux setups with round-bottom flasks (RBFs) where the scale-up of the optimized process is very challenging due to the need for many other additional adjustments. Thus, the new chemical process using continuous flow for the synthesis of industrially important molecules has attracted much attention due to its easy large-scale synthesis and precise control of reaction conditions like temperature, time, and dilution. Superior process window, efficiency, and most importantly improved safety are also additional advantages in the continuous flow process.²⁹

Herein, we report the continuous flow intermolecular macrolactonization of various dicarboxylic acids with diols and intramolecular macrolactonization of various seco acids using **3a** (Mukaiyama salt) as an acid activator and 1-methyl imidazole (MIM) as a base under the continuous flow process (Scheme 1B). Unlike the batch process, this requires a smaller volume of the reactor to run the highly diluted reactant to afford the macrocyclic lactone in moderate yield. A series of macrocyclic lactone and macrocyclic dilactones have been synthesized under a continuous flow process.

RESULTS AND DISCUSSION

Macrolactonization of Seco Acid Using Different Acid Activators under Batch Conditions.

We started our investigation toward macrolactonization by reacting **1a** intramolecularly to provide the macrolactone **2a** by screening different solvents and various acid activating agents in the batch reaction condition. Thus, this reaction with Mukaiyama reagent [2-chloro-1-methylpyridinium iodide, **3a**] and triethylamine **4a** as a base and dichloromethane solvent delivered the macrolactone **2a** in 10% yield, and 70% of the starting material **1a** was recovered (Table 1, entry 1). This reaction in dichloroethane afforded 5% yield of **2a** (Table 1, entry 2). When THF and methanol were used as solvent, no product formation was observed after 24 h (Table 1, entries 3 and 4). An improved yield (17%) of macrolactone **2a** (70% of the starting material **1a** recovered, Table 1, entry 5) was observed when ACN was used as a solvent. There was no product formation while using DIAD [diisopropyl azodicarboxylate] **3b** and triphenylphosphine in THF and acetonitrile as solvent at room temperature (Table 1, entries 6 and 7). Similarly, the macrolactone **2a** was not formed when the reaction was performed by using Corey-Nicolaou reagent [2,2'-dipyridyldisulfide and triphenylphosphine] **3c** in THF solvent at 0 °C (Table 1, entry 8). The same reaction was performed in acetonitrile, which provided only a 7% yield of **2a** with unreacted starting material **1a** (Table 1, entry 9). Later, **1a** was

Table 1. Acid Activator Study in Batch Reaction Conditions

entry	acid activating reagent	solvent	time (h)	yield of 2a/1a (%)
1 ^{a,c}	3a/4a	DCM	24	10/70
2 ^{a,c}	3a/4a	DCE	24	5/92
3 ^{a,c}	3a/4a	THF	24	0/100
4 ^{a,c}	3a/4a	MeOH	24	0/60
5 ^{a,c}	3a/4a	CH ₃ CN	24	17/70
6 ^{a,d}	3b/PPh ₃	THF	24	0/100
7 ^{a,d}	3b/PPh ₃	CH ₃ CN	24	0/100
8 ^{a,e,g}	3c/PPh ₃	THF	24	0/100
9 ^{a,e}	3c/PPh ₃	CH ₃ CN	24	7/80
10 ^{a,f}	3d/DMAP	THF	24	13/50
11 ^{a,f}	3d/DMAP	CH ₃ CN	24	15/42
12 ^{b,c}	3a/4a	CH ₃ CN	24	25/65
13 ^{b,c}	3a/4b	CH ₃ CN	24	30/55
14 ^{b,d}	3b/PPh ₃	CH ₃ CN	24	12/65
15 ^{b,e}	3c/PPh ₃	CH ₃ CN	24	9/78
16 ^{b,f}	3d/DMAP	CH ₃ CN	24	15/40

^aReaction conditions: Compound **1a** (0.015 M in CH₃CN) and acid activator reagent (in table) were taken in a sealed tube and reacted for 24 h at room temperature. The mentioned yields are isolated yields. ^bAt reflux condition. ^cMukaiyama reagent. ^dMitsunobu reagent. ^eCorey-Nicolaou reagent. ^fYamaguchi reagent. ^gAt 0 °C condition.

subjected to a Yamaguchi reaction by using 2,4,6-trichlorobenzoyl chloride **3d** in THF furnishing a 13% yield of **2a** and in acetonitrile affording a 15% yield of **2a** (Table 1, entries 10 and 11). Moreover, refluxing the reaction mixture with Mukaiyama salt and triethylamine **4a** afforded 25% yield of **2a** (Table 1, entry 12). An improved yield (30%) was observed by changing the base [1-methylimidazole] **4b** (Table 1, entry 13). Mitsunobu, Corey-Nicolaou, and Yamaguchi reactions under reflux conditions resulted in a decrease in the yield of product **2a** (Table 1, entries 14–16). These experimental results indicate that Mukaiyama reagent with 1-methylimidazole is an efficient activator as compared to other acid activators. To increase the product yield, investigate seamless scalability, and reduce the inherent scaling-up issues associated with a batch process, we transferred the optimized batch process to a continuous flow process. For the continuous flow setup, we have integrated two Vapourtec SF-10 peristaltic pumps for pumping solvent, a T-piece for mixing the reaction mixture, perfluoroalkoxy alkanes (PFA) tubing for the reaction, a water bath for the heating, and the back pressure regulator to maintain the pressure (Figure 1).

Next, to screen macrolactonization in a continuous flow reactor in the presence of various acid activators, we started



Figure 1. Continuous flow setup for macrolactonization.

our investigation by using **1a** as a model substrate. The vial containing **3a** and triethylamine **4a** in CH₃CN is passed through the PFA tubing (7 mL) by using the peristaltic pump with a 0.1 mL/min flow rate at room temperature for a 35 min residence time gave 25% yield of **2a** (Figure 2). Upon changing the reaction temperature to 80 °C, the yield of **2a** was further

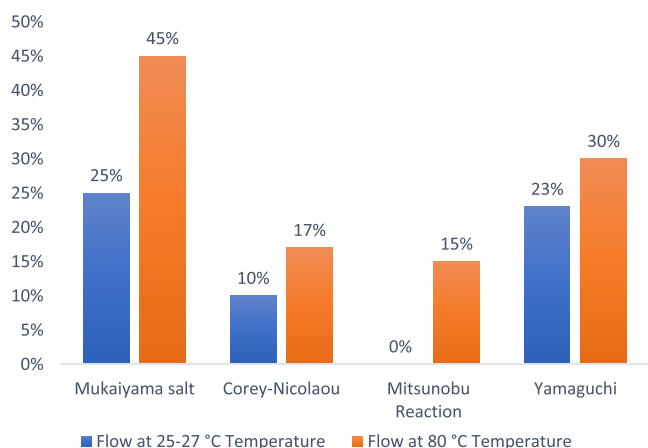


Figure 2. Acid activator study for macrolactonization under continuous flow. ^aReaction conditions: For peristaltic pump A, compound **1a** and activators in CH₃CN and, for peristaltic pump B, base in CH₃CN were flowed through PFA tubing (id = 0.1 cm, 7 mL) at room temperature (25–27 °C) without any pressure and at 80 °C in the preheated water bath under 3–4 bar pressure. The mentioned yields are isolated yields.

increased to 45% (Figure 2). With the other acid activator such as the Corey-Nicolaou reagent, a decrease in the yield of **2a** was observed (Figure 2). Moreover, the Mitsunobu reaction resulted in no product formation at room temperature, whereas at 80 °C only 15% yield of **2a** was observed (Figure 2). Later, compound **1a** was subjected to the Yamaguchi reaction at room temperature and at 80 °C, which gave 23% and 30% yields, respectively (Figure 2). Eventually, Mukaiyama salt **3a** with a 1-methylimidazole (**4b**) as a base delivered **2a** in 45% yield, which is higher as compared to other activators. Of note, the macrolactonization did not require any

special reaction conditions such as the use of a dry solvent and inert reaction condition.

Since Mukaiyama salt **3a** with the MIM **4b** as a base was found efficient for macrolactonization, we started our investigation for the further optimization of reaction conditions in a flow reactor. Initially, by employing two peristaltic pumps, substrate **1a** with Mukaiyama salt **3a** in pump A and compound **4b** in CH₃CN in pump B were passed through 9 mL PFA (perfluoroalkoxy alkanes) tubing (id = 0.1 cm) with a 0.1 mL/min flow rate to maintain a residence time of 45 min at 80 °C to afford 45% yield of **2a** (Table 2, entry 1). Next, by shortening the length of PFA tubing to 7 mL and decreasing the residence time, a similar yield of **2a** was obtained (Table 2, entry 2).

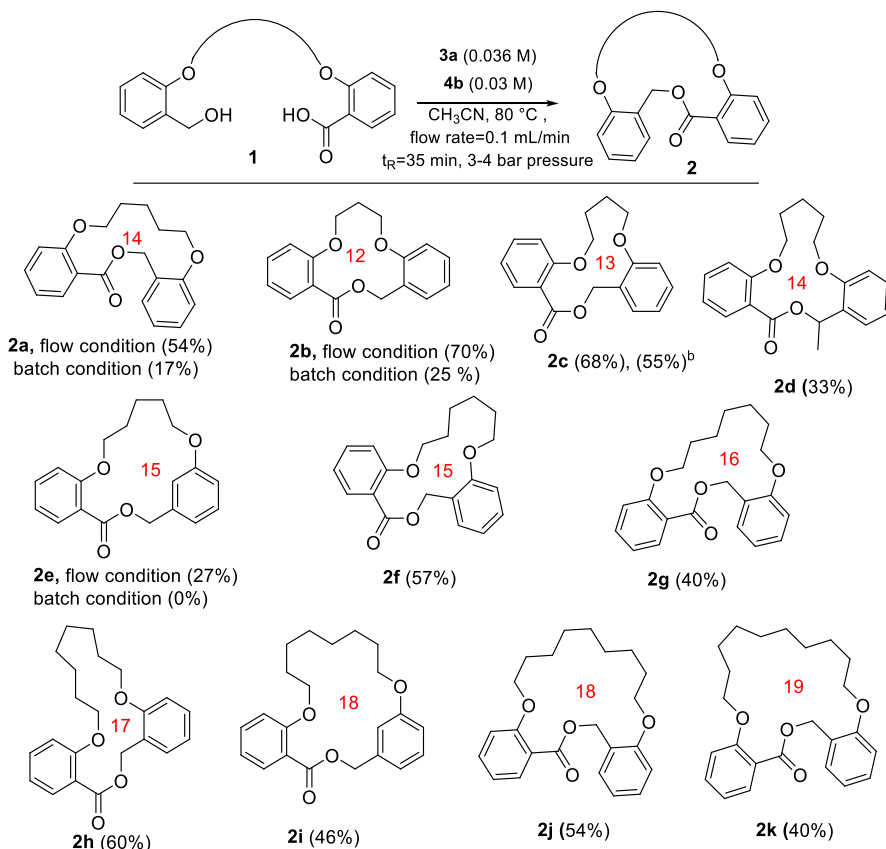
Increasing the base concentration to 0.03 M, an improvement in the yield (54%) of **2a** was observed (Table 2, entry 3). Furthermore, with an increase in the base concentration to 0.036 M, 54% yield was observed (Table 2, entry 4). Also, the increased concentration of Mukaiyama salt to 0.06 M showed a slight decrease in the yield of **2a** (52%) (Table 2, entry 5). With increasing concentrations of **1a**, **3a**, and **4b**, a decrease in the yield of **2a** was observed (Table 2, entry 6). Moreover, increasing the dilution of **1a**, a 54% yield of **2a** was observed (Table 2, entry 7). Furthermore, increasing the flow rate of each pump, less conversion of **1a** to the product **2a** was observed (Table 2, entries 8–10). Later, decreasing the flow rate and increasing the residence time resulted the slight increase of **2a** with 55% yield (Table 2, entry 11).

Having the best optimized result in hand (Table 2, entry 3), we further investigated the macrolactonization of various seco acid derivatives in a continuous flow. Flow macrolactonization of 2-(3-(2-(hydroxymethyl)phenoxy) propoxy)benzoic acid-bearing (**1b**) propyl spacer increased the yield of **2b** to 70% (Scheme 2) without formation of the corresponding side

Table 2. Optimization of the Reaction for Intramolecular Macrolactonization of Seco Acids^a

entry	1a (M)	3a (M)	4b (M)	f_R pump (A/B) (mL/min)	t_R = min	yield (%) 2a/1a
1 ^{b,c}	0.015	0.036	0.015	0.1:0.1	45	45/40
2 ^b	0.015	0.036	0.015	0.1:0.1	35	45/40
3 ^b	0.015	0.036	0.03	0.1:0.1	35	54/32
4 ^b	0.015	0.036	0.036	0.1:0.1	35	54/32
5 ^b	0.015	0.06	0.03	0.1:0.1	35	52/36
6 ^b	0.02	0.048	0.04	0.1:0.1	35	50/38
7 ^b	0.01	0.024	0.02	0.1:0.1	35	54/32
8 ^b	0.015	0.036	0.03	0.15:0.15	23.3	49/20
9 ^b	0.015	0.036	0.03	0.2:0.2	17.5	30/59
10 ^b	0.015	0.036	0.03	0.3:0.3	11.6	12/76
11 ^b	0.015	0.036	0.03	0.05:0.05	70	55/40

^a f_R = flow rate; t_R = residence time. The mentioned yields are isolated yields. ^bReaction conditions: For peristaltic pump A, compounds **1a** and **3a** in CH₃CN and, for peristaltic pump B, base **4b** in CH₃CN were flowed through PFA tubing (id = 0.1 cm, 7 mL) at 80 °C in the preheated water bath under 3–4 bar pressure. ^cReaction conditions: For peristaltic pump A, compounds **1a** and **3a** in CH₃CN and, for peristaltic pump B, base **4b** in CH₃CN were flowed through PFA tubing (id = 0.1 cm, 9 mL) at 80 °C in the preheated water bath under 3–4 bar pressure.

Scheme 2. Substrate Scope for Intramolecular Macrolactonization^a

^aFlow reaction conditions: For peristaltic pump A, compound **1** (0.015 M, 0.15 mmol) and **3a** (0.036 M) in CH_3CN and, for peristaltic pump B, **4b** (0.03 M) in CH_3CN were flowed through PFA tubing (id = 0.1 cm, 7 mL) with a 0.1 mL/min flow rate at 80°C in the preheated water bath for a residence time of 35 min under 3–4 bar pressure. Batch reaction conditions: Compound **1** (0.015 M, 0.15 mmol), **3a** (0.036 M), and **4b** (0.03 M) in CH_3CN were heated at 80°C in the preheated oil bath for 24 h. The mentioned yields are isolated yields. ^bWith 10.8 mmol.

product macrodilactone. However, this reaction under batch conditions afforded 25% yield (Scheme 2).

On the other hand, seco acid bearing a butyl spacer (**1c**, 0.15 mmol) furnished a 68% yield whereas a gram-scale reaction with 10.8 mmol gave 55% yield of **2c** (Scheme 2). Next, intramolecular macrolactonization of a secondary alcohol (**1d**) and acid resulted in a 33% yield of **2d** (Scheme 2). Moreover, positional isomers such as meta-substituted seco acid (**1e**) afforded less yield (27%) of macrolactone **2e** and no product formation under batch conditions (Scheme 2). Other substrates having longer spacer lengths from hexyl to decyl gave moderate to good yield (40–60%) of macrolactones **2f–2k** (Scheme 2). From these studies, it has been observed that the yield of the macrolactone product depends on the chain length of the spacer.

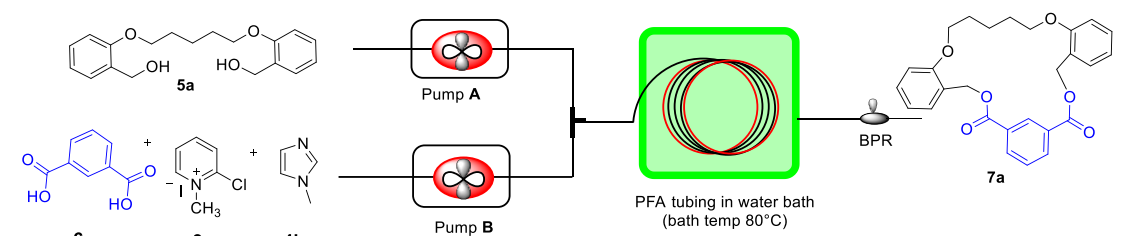
Next, we investigated the generality of this transformation with substituted diol and diacid derivatives to synthesize macrocyclic dilactones in continuous flow chemistry. We have used the optimized condition of compound **2** for the synthesis of compound **7a**. However, flowing the solution of **3a**, **5a**, and **6** in pump A and the solution of **4b** in pump B resulted in poor yield (20%). Therefore, we have again optimized the flow condition for **7a**.

Initially, optimized reaction conditions were applied to ((pentane-1,5-diylbis(oxy))bis(2,1-phenylene))dimethanol **5a** and isophthalic acid **6** to deliver product **7a**, but the intermolecular macrocyclic dilactone (**7a**) furnished a lower

yield (24%, Table 3, entry 1). Further, when the base loading was increased, no improvement in the yield was observed (Table 3, entries 2–4). Increasing the concentration of acid activator up to 0.06 and 0.072 M resulted in a slightly increased yield of **7a** (26% and 28%, Table 3, entries 5 and 6). Later, when the residence time of the reaction was increased, no change in the yield of **7a** was observed (Table 3, entry 7). However, when the concentrations of **5a**, **6**, **3a**, and **4a** were decreased, a slight improvement in the yield was observed (Table 3, entry 8). Then, we increased the reaction time by 50 min, and no change was observed in the yield of compound **7a** (Table 3, entry 9). Additionally, less conversion of the product was found after increasing the flow rate of both the peristaltic pumps (Table 3, entries 10 and 11). Furthermore, increasing the flow rate of peristaltic pump B and keeping the flow rate of pump A constant resulted in no improvement in the yield of the product (Table 3, entries 12 and 13). Later, by keeping the flow rate of pump B constant and increasing the flow rate of pump A, less conversion of **5a** to the product **7a** was observed (Table 3, entry 14).

Next, to generalize this intermolecular macrolactonization under flow system, we investigated the substrate scope with various diol and diacid derivatives. A pentyl spacer diol with isophthalic acid delivered 30% yield of **7a** (Scheme 3). Furthermore, this reaction under batch condition afforded a 13% yield of **7a** (Scheme 3). The diol-bearing propyl spacer (**5b**) treated with isophthalic acid resulted in the macro-

Table 3. Optimization Study in Flow for Intermolecular Macro-Dilactonization



entry	5a (M)	6 (M)	3a (M)	4b (M)	f_R pump (A/B) (mL/min)	t_R = min	yield (%) 7a/5a
1 ^a	0.015	0.015	0.036	0.03	0.1:0.1	35	24/40
2 ^a	0.015	0.015	0.036	0.045	0.1:0.1	35	24/35
3 ^a	0.015	0.015	0.036	0.06	0.1:0.1	35	24/30
4 ^a	0.015	0.015	0.036	0.09	0.1:0.1	35	20/30
5 ^a	0.015	0.015	0.06	0.06	0.1:0.1	35	26/28
6 ^a	0.015	0.015	0.072	0.06	0.1:0.1	35	28/15
7 ^{a,b}	0.015	0.015	0.072	0.06	0.1:0.1	50	28/20
8 ^a	0.0075	0.0075	0.036	0.03	0.1:0.1	35	30/20
9 ^{a,b}	0.0075	0.0075	0.036	0.03	0.1:0.1	50	30/12
10 ^a	0.0075	0.0075	0.036	0.03	0.2:0.2	17.5	23/32
11 ^a	0.0075	0.0075	0.036	0.03	0.3:0.3	11.6	7/80
12 ^a	0.0075	0.0075	0.036	0.03	0.1:0.2	23.3	20/34
13 ^a	0.0075	0.0075	0.036	0.03	0.1:0.3	17	12/40
14 ^a	0.0075	0.0075	0.036	0.03	0.2:0.1	23.3	14/39

^aReaction conditions: for peristaltic pump A, compound 5a in CH₃CN and, for peristaltic pump B, 3a, 6, and 4b in CH₃CN were flowed through the PFA tubing (id = 0.1 cm, 7 mL) at 80 °C in the preheated water bath for the residence time (see table) under 3–4 bar pressure. f_R = flow rate; t_R = residence time. The mentioned yields are isolated yields. ^bPassed through the PFA tubing (id = 0.1 cm, 10 mL).

dilactone 7b in 35% yield under flow conditions and 16% yield under batch conditions (Scheme 3). This reaction afforded 19-membered macrolactone 7c in 33% yield (Scheme 3). Diol having a pentyl spacer (5a) with phthalic acid gave a 32% yield of 7d (Scheme 3). Moreover, 21-membered macrocyclic dilactone 7e was obtained in 32% yield (Scheme 3). In the case of 22-membered macrocyclic dilactone 7f, 46% yield was observed (Scheme 3). The structure of 7f was confirmed by X-ray analysis (Figure 3). An octyl-spacer diol (5f) resulted in 32% yield of macrolactone 7g (Scheme 3). Metasubstituted diol derivative furnished a poor yield of macrocyclic dilactone 7h (Scheme 3). The increased spacer length of diol led to an increase in the yield of macrolactones 7i (49%) and 7j (57%) (Scheme 3). Eventually, nitro and bromo substituted diol derivatives were treated with isophthalic acid to furnish 37% yield of 7k and 38% yield of 7l, respectively (Scheme 3).

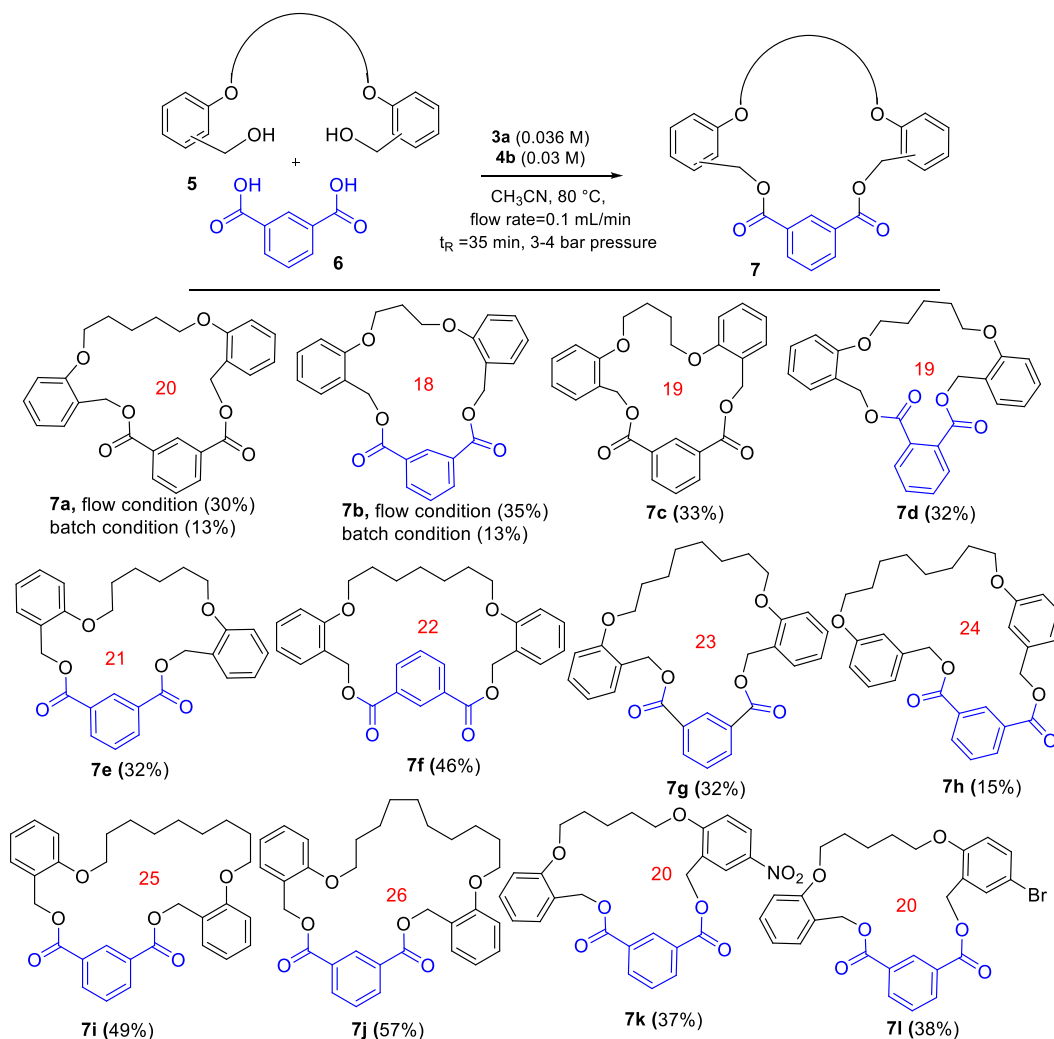
Further, to expand this strategy, intermolecular macro-lactonization was performed with a diol and succinic acid (Scheme 4). Thus, macrocyclic dilactone was also successfully achieved by intermolecular coupling of heptyl spacer diol (5d) with succinic acid affording the 21-membered macro-dilactone 8a in 35% yield (Scheme 4). Diacid-bearing pentyl spacer (9a) with propanediol resulted in the 18-membered macrocyclic dilactone 10a in 40% yield (Scheme 4). Moreover, 22-membered macrocyclic dilactam 10b was synthesized in 32% yield by intermolecular coupling of 9b with *m*-phenylenediamine (Scheme 4). Next, we have explored the continuous flow macrolactonization with aliphatic diacids and diols (Scheme 5). Thus, 20 membered macrocyclic dilactone 11a was obtained from dodecanedioic acid and octanediol in 21% yield (Scheme 5). The 24 and 18 membered macrocyclic tetralactone 13a and 13b was obtained in 23% and 25% yield, respectively (Scheme 5).

CONCLUSION

In conclusion, we have developed a new tool for the efficient synthesis of new macrocyclic lactone and dilactone under continuous flow mode. This approach successfully demonstrated handling of the high dilution in the flow-mediated macrolactonization under a confined volume of the customized PFA tube. Furthermore, this flow macrolactonization was demonstrated with a broad range of macrolactone having a 12- to 26-membered ring size up to moderate yield. Moreover, this reaction was easily scalable in grams and found to be highly reproducible. In addition, various macrocyclic dilactones and tetralactones were synthesized via intermolecular coupling of diacids and diols under a continuous flow process. Further, this process was also successful for the synthesis of macrocyclic dilactam under continuous flow.

EXPERIMENTAL SECTION

General Information and Data Collection. *N*-Methyl-2-chloropyridinium iodide (CAS number 14338-32-0, SIGMA), 1-methylimidazole (MIM) (CAS number 616-47-7, SIGMA), triethylamine (TEA) (CAS number 121-44-8, SIGMA), ethyl salicylate (CAS number 118-61-6, SIGMA), 2-hydroxybenzylalcohol (CAS number 166952, SIGMA), and all dibromo compounds were purchased from Sigma-Aldrich. The column chromatography separations were performed over 100–200 mesh silica gel. Visualization was accomplished with UV light. The flow chemistry experiments were carried out on a Vapourtec SF-10 reagent pump, and homogeneous reactions were performed in customized PFA tubing (7, 10, 12 mL). ¹H and ¹³C NMR spectra were recorded on 400 and 100 MHz, respectively, using Bruker or JEOL spectrometers in CDCl₃ (CAS number 865-49-6 SIGMA) and DMSO-*d*₆ (CAS number 2206-27-1, SIGMA). Chemical shifts (δ) for ¹H and ¹³C NMR spectra are given in ppm relative to tetramethyl silane (TMS) [δ 7.27 for ¹H (chloroform-*d*), δ 77.16 for ¹³C (chloroform-*d*); δ 2.50 for ¹H (DMSO-*d*₆). Abbreviations used in the NMR follow-up experiments:

Scheme 3. Substrate Scope for the Intermolecular Macrolactonization^a

^aFlow reaction conditions: For peristaltic pump A, diol 5 (0.0075 M, 0.15 mmol) in CH₃CN and, for peristaltic pump B, diacid 6 (0.0075 M) in CH₃CN, 3a (0.036 M), and 4b (0.03 M) in CH₃CN were flowed at 0.1 mL/min from each pump at 80 °C in the preheated water bath for a residence time of 35 min under 3–4 bar pressure. Batch reaction conditions: diol 5 (0.0075 M, 0.15 mmol), diacid 6 (0.0075 M), and 4b (0.03 M) in CH₃CN were heated at 80 °C in the preheated oil bath for 24 h. The mentioned yields are isolated yields.

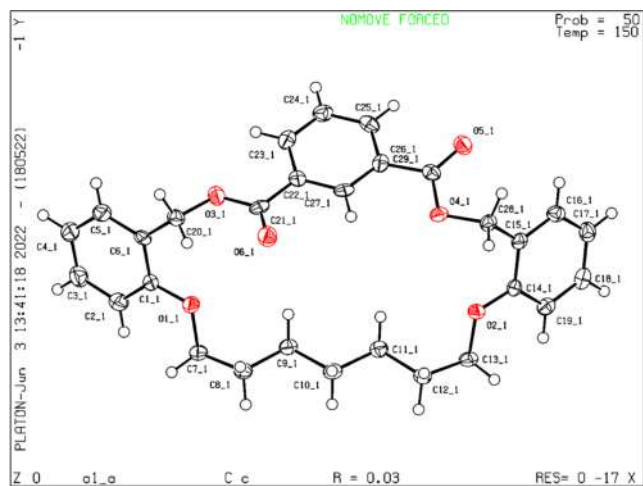
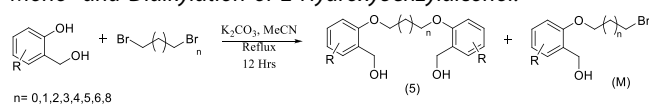


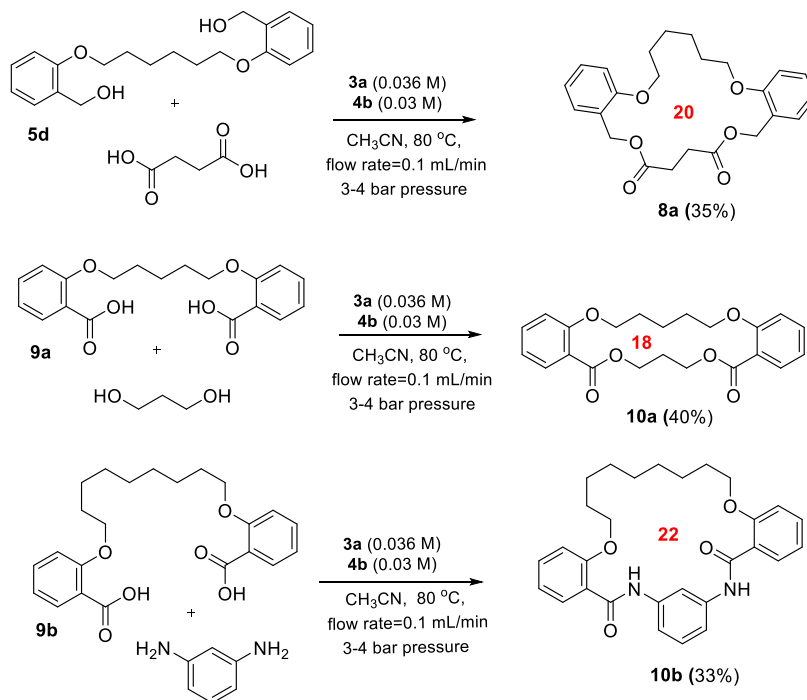
Figure 3. ORTEP crystal structure of 7f showing thermal ellipsoids at the 50% probability level.

b, broad; s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet. High-resolution mass spectra were recorded with waters-synapt G2 using electrospray ionization (ESI-TOF). All UV–visible absorption spectra were recorded by a spectrophotometer (PerkinElmer) model Lambda 25 with the use of 1.0 cm quartz cells in a dichloromethane medium (1×10^{-5} M). Infrared (ATR) spectra were obtained with a Bruker Alpha-E infrared spectrometer. Melting points were recorded on DBK programmable melting point instrument. All melting points were measured in an open glass capillary tube. Single-crystal diffraction analysis data were collected at 100 K with a Bruker Kappa Apex III CCD Duo diffractometer (operated at 1500 W power: 50 kV, 30 mA) using graphite monochromatic Mo K α radiation. More information on crystal structures (7f) can also be obtained from the Cambridge Crystallographic Data Centre (CCDC) via deposition number 2176849.

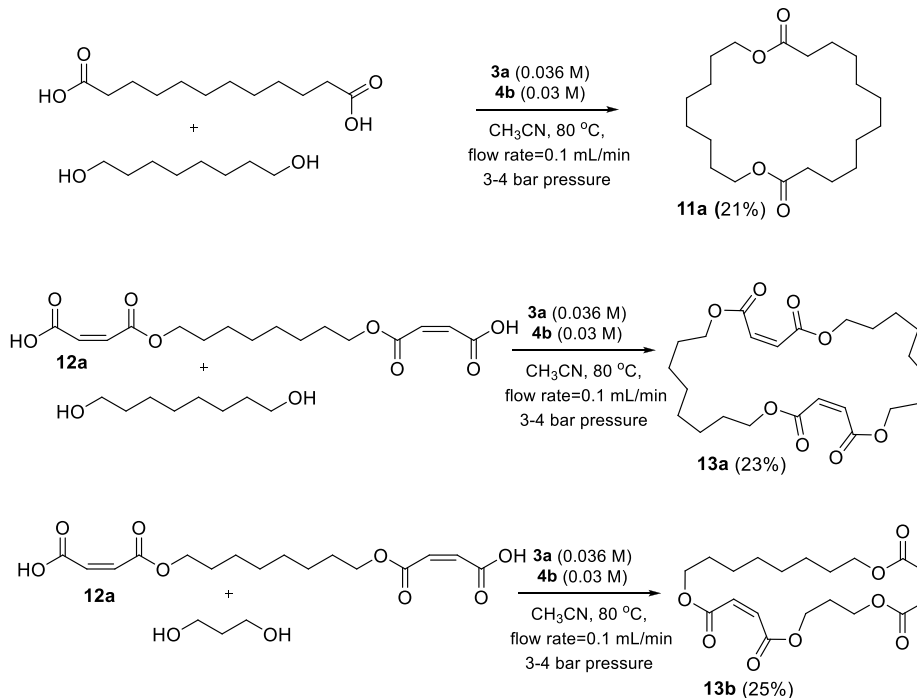
Experimental Section. A) General Experimental Procedure for Mono- and Dialkylation of 2-Hydroxybenzylalcohol.^{25,30}



In a 100 mL round-bottom flask were added 2-hydroxybenzylalcohol (1 equiv), dibromoalkanes (1.5 equiv), and potassium carbonate (2

Scheme 4. Intermolecular Macrolactonization/Macrolactamization Using Different Compounds: Diol, Diacid, and Diamine^a

^aReaction conditions: for peristaltic pump A, compound 5d, or 9a, or 9b (0.0075 M) in CH₃CN and, for peristaltic pump B, succinic acid, propanediol, or *m*-phenylenediamine (0.0075 M) in CH₃CN, 3a (0.036 M), and 4b (0.03 M) were flowed at 0.1 mL/min from each pump at 80 °C in the preheated water bath for a residence time of 35 min under 3–4 bar pressure. The mentioned yields are isolated yields.

Scheme 5. Intermolecular Macrolactonization Using Aliphatic Diol and Diacid^a

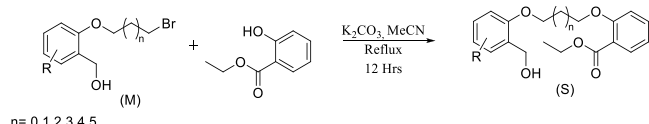
^aReaction conditions: for peristaltic pump A, octanediol or propanediol (0.0075 M) in CH₃CN and, for peristaltic pump B, dodecanedioic acid or 12a (0.0075 M) in CH₃CN, 3a (0.036 M), and 4b (0.03 M) were flowed at 0.1 mL/min from each pump to the PFA tubing (0.1 cm, 7 mL) at 80 °C in the preheated water bath for a residence time of 35 min under 3–4 bar pressure. The mentioned yields are isolated yields.

equiv) in acetonitrile. The solution was refluxed at 85 °C for 12–16 h in an oil bath. The progress of the reaction was monitored by the thin-layer chromatography technique. After completion of the reaction, the

mixture of products (mono- and dialkylated) was extracted in water and dichloromethane. The dichloromethane layers were combined and dried over Na₂SO₄. Dichloromethane was evaporated, and the

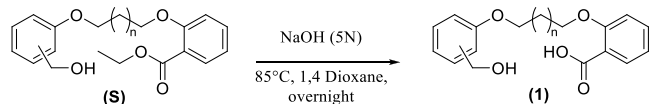
residue was directly purified by silica gel chromatography by using EtOAc/*n*-hexane = 15:85 (for monoalkylated product {M}) and 40:60 (for dialkylated product {S}).

B) General Experimental Procedure for Ester Alcohol Derivatives.³⁰



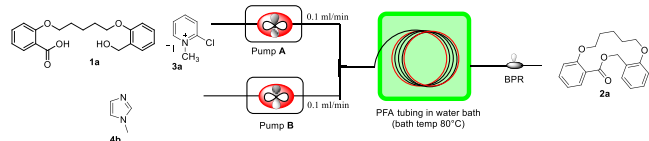
In a 100 mL round-bottom flask were added (M) (1 equiv), ethyl 2-hydroxybenzoate (1 equiv), and potassium carbonate (K_2CO_3) (1 equiv) in acetonitrile. The solution was refluxed at 85 °C for 16 h in an oil bath. The progress of the reaction was monitored by the thin layer chromatography technique. The resulting mixture was extracted with ethyl acetate for two times using 30 mL of solvent each time. The ethyl acetate layer was combined and dried over Na_2SO_4 . After removing the solvent under reduced pressure, the residue was purified by using column chromatography (EtOAc/*n*-hexane = 40:60) for the product S.

C) General Experimental Procedure for Seco Acid Derivatives.³¹



To a 1,4-dioxane solution of S was added a 5N NaOH solution. The mixture was stirred at 85 °C overnight in an oil bath. The reaction mixture was extracted with EtOAc. 1.0 M HCl solution was added to the aqueous solution to adjust the pH to 2, and then, the mixture was extracted with EtOAc three times. The ethyl acetate layer was dried over anhydrous Na_2SO_4 and evaporated using a vacuum. The residue was directly purified by silica gel chromatography using EtOAc/*n*-hexane = 70:30 to afford the product 1.

D) General Experimental Procedure for Intramolecular Macrolactonization.



Intramolecular Macrolactonization Using Mukaiyama Salt in Flow. The mixture of 0.015 M seco acids 1a and 0.036 M Mukaiyama salt 3a in acetonitrile was flowed through pump A and 0.03 M 1-methylimidazole 4b in acetonitrile was flowed through pump B with a flow rate of 0.1 mL/min each. Both the reaction mixtures were connected to a T-piece for mixing. The resulting mixture was then allowed to react in PFA tubing (id = 0.1 cm, 7 mL), which is preheated in a water bath at 80 °C maintained at 3–4 bar pressure using BPR with a residence time of 35 min. The volatile components of the crude reaction mixture were evaporated using vacuum, extracted in ethyl acetate (10 × 2 mL), and washed with sodium thiosulfate solution in water. Further, the ethyl acetate layer was concentrated under reduced pressure followed by column chromatography (EtOAc/*n*-hexane = 5:95) purification to afford the corresponding 2a.

Intramolecular Macrolactonization in Batch. A mixture of seco acids 1a (50 mg, 0.15 mmol) and Mukaiyama reagent 3a (183 mg, 0.36 mmol) was suspended in acetonitrile (20 mL). To this reaction mixture was added 1-methylimidazole 4b (49 mg, 0.3 mmol) in sequence. The resulting reaction mixture was allowed to reflux in an oil bath or at room temperature for 24 h. The volatile components of the crude reaction mixture were evaporated using vacuum, extracted in ethyl acetate (10 × 2 mL), and washed with sodium thiosulfate solution in water. Further, the ethyl acetate layer was concentrated under reduced pressure followed by column chromatography (EtOAc/*n*-hexane = 5:95) purification to afford the corresponding 2a.

Corey-Nicolaou Macrolactonization in Flow. For intramolecular macrolactonization in flow, the mixture of 0.015 M seco acids 1a in

acetonitrile was flowed through pump A and 0.036 M 2,2'-dipyridyldisulfide 3c and 0.036 M triphenylphosphine in acetonitrile was flowed through pump B at 0.1 mL/min each. Both the reaction mixtures were connected to a T-piece for mixing. The resulting mixture was then allowed to react in PFA tubing preheated in a water bath at room temperature without any pressure or at 80 °C (id = 0.1 cm, 7 mL, 3–4 bar pressure, residence time of 35 min) before passing a back pressure regulator and collection in a flask. The volatile components of the crude reaction mixture were evaporated using vacuum. The residue was dissolved in ethyl acetate (20 mL) and washed with water (2 × 50 mL). Further, the ethyl acetate layer was concentrated under reduced pressure followed by column chromatography (EtOAc/*n*-hexane = 5:95) purification to afford the corresponding product 2a.

Corey-Nicolaou Macrolactonization in Batch. A mixture of seco acids 1a (50 mg, 0.15 mmol) and 2,2'-dipyridyldisulfide 3b (79 mg, 0.36 mmol) was suspended in acetonitrile (20 mL); to this reaction mixture was added triphenylphosphine (94 mg, 0.3 mmol) in sequence. The resulting reaction mixture was allowed to reflux in an oil bath or at room temperature for 24 h. The volatile components of the crude reaction mixture were evaporated using vacuum and extracted in ethyl acetate (10 × 2 mL). The combined ethyl acetate was washed with sodium thiosulfate solution in water. Further, the ethyl acetate layer was concentrated under reduced pressure followed by column chromatography (EtOAc/*n*-hexane = 5:95) purification to afford the corresponding product 2a.

Yamaguchi Macrolactonization in Flow. For intramolecular macrolactonization in flow, the mixture of 0.015 M seco acids 1a, 0.03 M 1-methylimidazole, and 0.036 M 2,4,6-trichlorobenzoyl chloride 3d in acetonitrile was flowed through pump A and 0.03 M 4-(dimethylamino)pyridine in acetonitrile was flowed through pump B at 0.1 mL/min each. Both reaction mixtures were connected to a T-piece for mixing. The resulting mixture was then allowed to react in PFA tubing preheated in a water bath at room temperature without any pressure or at 80 °C (id = 0.1 cm, 7 mL, 3–4 bar pressure, residence time of 35 min) before passing a back pressure regulator and collection in a flask. The volatile components of the crude reaction mixture were evaporated using vacuum. The residue was dissolved in ethyl acetate (20 mL) and washed with water (2 × 50 mL). Further, the ethyl acetate layer was concentrated under reduced pressure followed by column chromatography (EtOAc/*n*-hexane = 5:95) purification to afford the corresponding product 2a.

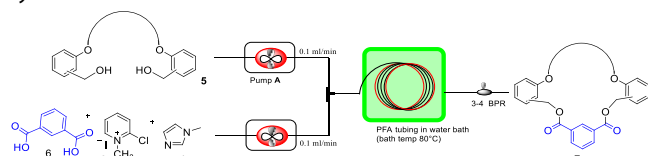
Yamaguchi Macrolactonization in Batch. A mixture of seco acids 1 (50 mg, 0.15 mmol), 1-methylimidazole (24.6 mg, 0.3 mmol), and 2,4,6-trichlorobenzoyl chloride 3d (87 mg, 0.36 mmol) was suspended in acetonitrile (20 mL). To this reaction mixture was added 4-(dimethylamino)pyridine (36 mg, 0.3 mmol) in sequence. The resulting reaction mixture was allowed to reflux under an oil bath or at room temperature for 24 h. The volatile components of the crude reaction mixture were evaporated using vacuum and extracted in ethyl acetate (10 × 2 mL) and washed with sodium thiosulfate solution in water. Further, the ethyl acetate layer was concentrated under reduced pressure followed by column chromatography (EtOAc/*n*-hexane = 5:95) purification to afford the corresponding product 2a.

Mitsunobu Macrolactonization in Flow. For intramolecular macrolactonization in flow, the mixture of 0.015 M seco acids 1, 0.036 M triphenylphosphine, and 0.036 M diisopropyl azodicarboxylate 3b in acetonitrile was flowed through pump A and acetonitrile solvent was flowed through pump B at 0.1 mL/min each. Both reaction mixtures were connected to a T-piece for mixing. The resulting mixture was then allowed to react in PFA tubing preheated in a water bath at room temperature without any pressure or at 80 °C (id = 0.1 cm, 7 mL, 3–4 bar pressure, residence time of 35 min) before passing a back pressure regulator and collection in a flask. The volatile components of the crude reaction mixture were evaporated using vacuum. The crude residue was dissolved in ethyl acetate (20 mL) and washed with water (2 × 50 mL). Further, the ethyl acetate layer was concentrated under reduced pressure followed by column

chromatography (EtOAc/*n*-hexane= 5:95) purification to afford the corresponding product **2a**.

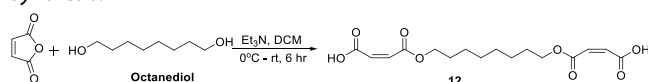
Mitsunobu Macrolactonization in Batch. A mixture of seco acids **1a** (50 mg, 0.15 mmol) and diisopropyl azodicarboxylate **3b** (45 mg, 0.22 mmol) was suspended in acetonitrile (20 mL). To this reaction mixture was added triphenylphosphine (59 mg, 0.22 mmol) in sequence. The resulting reaction mixture was allowed to reflux under an oil bath or at room temperature for 24 h. The volatile components of the crude reaction mixture were evaporated using vacuum and extracted in ethyl acetate (10 × 2 mL) and washed with sodium thiosulfate solution in water. Further, the ethyl acetate layer was concentrated under reduced pressure followed by column chromatography (EtOAc/*n*-hexane= 5:95) purification to afford the corresponding product **2a**.

E) General Experimental Procedure for Intermolecular Macrocyclic Dilactonization.



For intermolecular macro-dilactonization in flow, the mixture of 0.0075 M **5** in acetonitrile was flowed through pump A and 0.0075 M isophthalic **6** acid or succinic acid, 0.036 M Mukaiyama salt **3a**, and 0.03 M 1-methylimidazole **4b** in acetonitrile was flowed through pump B at 0.1 mL/min each. Both reaction mixtures were connected to a T-piece for mixing. The resulting mixture was then allowed to react in PFA tubing preheated in a water bath at 80 °C (id = 0.1 cm, 7 mL, 3–4 bar pressure, residence time of 35 min) before passing a back pressure regulator and collection in a flask. The volatile components of the crude reaction mixture were evaporated using vacuum and dissolved in ethyl acetate (20 mL) and washed with sodium thiosulfate solution in water. Further, the ethyl acetate layer was concentrated under reduced pressure followed by column chromatography (EtOAc/*n*-hexane= 7:93) purification to afford the corresponding product **7a**.

F) General Experimental Procedure for Dicarboxylic Acid Synthesis.³²



A 250 mL round bottomed flask under nitrogen was charged with anhydride (2 g, 20 mmol) and diol (1.4 g, 10 mmol) in anhydrous dichloromethane (100 mL). The stirred reaction mixture was cooled to 0 °C in an ice bath, and triethylamine (2 g, 20.4 mmol) was added. The reaction was continued for 4 h at 0 °C and further at room temperature for 5 h. The reaction was monitored by TLC. After all the anhydride was reacted, the solvent was evaporated. The residue was cooled to 0 °C in an ice bath, and 200 mL of saturated sodium bicarbonate solution was added; then, it was extracted with ether. The aqueous layer was cooled to 0 °C in an ice bath and acidified with dilute hydrochloric acid followed by extraction with diethyl ether or dichloromethane (4 × 100 mL). The entire organic layer was combined and evaporated under reduced pressure to provide the corresponding pure dicarboxylic acid.

Analytical Data of Product. Ethyl 2-((5-(2-(Hydroxymethyl)phenoxy)pentyl)oxy)benzoate (**Sa**). Prepared according to general procedure B using (2-((5-bromopentyl)oxy)phenyl)methanol (500 mg, 1.08 mmol), potassium carbonate (K_2CO_3) (281.9 mg, 1.08 mmol), and ethyl 2-hydroxybenzoate (304 mg, 1.08 mmol). The residue was purified by using column chromatography with EtOAc/*n*-hexane = 40:60 as the eluent to afford the desired product ethyl 2-((5-(2-(hydroxymethyl)phenoxy)pentyl)oxy)benzoate **Sa** (580 mg, 1.62 mmol, 88% yield) as a semisolid. ^1H NMR (400 MHz, $CDCl_3$) δ 7.77 (dd, J = 7.6, 1.8 Hz, 1H), 7.46–7.39 (m, 1H), 7.27 (ddd, J = 6.4, 5.4, 1.5 Hz, 2H), 6.99–6.90 (m, 3H), 6.87 (d, J = 8.2 Hz, 1H), 4.69 (s, 2H), 4.34 (q, J = 7.2 Hz, 2H), 4.06 (dt, J = 6.3, 4.4 Hz, 4H), 1.90 (dt, J = 13.6, 6.8 Hz, 4H), 1.72 (ddd, J = 16.2, 9.5, 6.2 Hz, 2H), 1.36 (t, J

= 7.1 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 166.7, 158.5, 156.9, 133.4, 131.6, 129.0, 128.8, 120.8, 120.7, 120.2, 113.2, 111.1, 68.6, 67.8, 62.2, 60.9, 29.1, 22.9, 14.5, 14.3; FTIR (neat): 3500, 2941, 1713, 1600, 1492, 1243 cm^{-1} ; HRMS (ESI-TOF) m/z : $[M + Na]^+$ calcd for $C_{21}H_{26}O_5Na$, 381.1677, found 381.1676.

Ethyl 2-(3-(2-(Hydroxymethyl)phenoxy)propoxy)benzoate (Sb**).** Prepared according to general procedure B using (2-(3-bromopropoxy)phenyl)methanol (500 mg, 2 mmol), potassium carbonate (K_2CO_3) (281.9 mg, 2 mmol), and ethyl 2-hydroxybenzoate (339 mg, 1.08 mmol). The residue was purified by using column chromatography with EtOAc/*n*-hexane = 40:60 as the eluent to afford desired product ethyl 2-(3-(2-(hydroxymethyl)phenoxy)propoxy)benzoate **Sb** (611 mg, 1.85 mmol, 90% yield) as a semisolid. ^1H NMR (400 MHz, $CDCl_3$) δ 7.78 (dd, J = 7.9, 1.8 Hz, 1H), 7.47–7.40 (m, 1H), 7.28 (dd, J = 7.1, 1.7 Hz, 1H), 7.25 (dd, 1H), 7.00–6.98 (m, 1H), 6.97–6.95 (m, 1H), 6.95–6.90 (m, 2H), 4.67 (s, 2H), 4.35–4.27 (m, 4H), 4.24 (t, J = 5.9 Hz, 2H), 2.39–2.29 (m, 2H), 1.34 (t, J = 7.2 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 166.4, 158.4, 156.7, 133.5, 131.7, 129.3, 129.1, 128.8, 120.9, 120.6, 113.4, 111.4, 65.4, 64.7, 62.1, 60.9, 29.4, 14.5; FTIR (neat): 3508, 2926, 2854, 1715, 1253, 1228 cm^{-1} ; HRMS (ESI-TOF) m/z : $[M + Na]^+$ calcd for $C_{19}H_{22}O_5Na$, 353.1364, found 353.1364.

Ethyl 2-(4-(2-(Hydroxymethyl)phenoxy)butoxy)benzoate (Sc**).** Prepared according to general procedure B using (2-(4-bromobutoxy)phenyl)methanol (500 mg, 1.93 mmol), potassium carbonate (K_2CO_3) (266.6 mg, 1.93 mmol), and ethyl 2-hydroxybenzoate (320 mg, 1.93 mmol). The residue was purified by using column chromatography with EtOAc/*n*-hexane = 40:60 as the eluent to afford desired product ethyl 2-(4-(2-(hydroxymethyl)phenoxy)butoxy)benzoate (**Sc**) (594 mg, 1.72 mmol, 89% yield) as a semisolid.

^1H NMR (400 MHz, $CDCl_3$) δ 7.80–7.74 (m, 1H), 7.46–7.39 (m, 1H), 7.25 (dt, J = 9.4, 7.6 Hz, 2H), 6.99–6.90 (m, 3H), 6.88 (d, J = 8.2 Hz, 1H), 4.67 (s, 2H), 4.37–4.28 (m, 2H), 4.10 (t, J = 5.6 Hz, 4H), 2.51 (s, 1H), 2.11–1.98 (m, 4H), 1.39–1.31 (m, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 166.5, 158.4, 156.8, 133.4, 131.7, 129.2, 129.0, 128.8, 120.8, 120.7, 120.3, 113.1, 111.1, 68.2, 67.6, 62.1, 60.9, 26.2, 14.4; FTIR (neat): 3435, 2938, 1708, 1600, 1491, 1209 cm^{-1} ; HRMS (ESI-TOF) m/z : $[M + Na]^+$ calcd for $C_{20}H_{24}O_5Na$, 367.1521, found 367.1522.

Ethyl 2-((5-(2-(1-Hydroxyethyl)phenoxy)pentyl)oxy)benzoate (Sd**).** Prepared according to general procedure B using 1-2-((5-bromopentyl)oxy)phenyl)ethan-1-ol (500 mg, 1.74 mmol), potassium carbonate (K_2CO_3) (240.6 mg, 1.74 mmol), and ethyl 2-hydroxybenzoate (289 mg, 1.74 mmol). The residue was purified by using column chromatography with EtOAc/*n*-hexane = 40:60 as the eluent to afford desired product ethyl 2-((5-(2-(1-hydroxyethyl)phenoxy)pentyl)oxy)benzoate **Sd** (590 mg, 1.58 mmol, 91% yield) as a semisolid.

^1H NMR (400 MHz, $CDCl_3$) δ 7.77 (d, J = 7.5 Hz, 1H), 7.43 (t, J = 7.7 Hz, 1H), 7.35 (d, J = 7.3 Hz, 1H), 7.22 (t, J = 7.6 Hz, 1H), 6.95 (d, J = 7.3 Hz, 3H), 6.86 (d, J = 8.1 Hz, 1H), 5.16–5.05 (m, 1H), 4.34 (q, J = 6.8 Hz, 2H), 4.06 (t, J = 5.6 Hz, 4H), 2.75 (s, 1H), 1.98–1.86 (m, 4H), 1.71 (dd, J = 13.9, 7.5 Hz, 2H), 1.50 (d, J = 5.5 Hz, 3H), 1.36 (t, J = 6.5 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 166.7, 158.5, 156.1, 133.7, 133.3, 131.6, 128.3, 126.2, 121.0, 120.8, 120.2, 113.2, 111.3, 68.7, 67.8, 66.6, 60.9, 29.11, 23.0, 14.5; FTIR (neat): 3501, 2940, 2845, 1718, 1600, 1491, 1242 cm^{-1} ; HRMS (ESI-TOF) m/z : $[M + Na]^+$ calcd for $C_{22}H_{28}O_5Na$, 395.1834, found 395.1830.

Ethyl 2-((5-(3-(Hydroxymethyl)phenoxy)pentyl)oxy)benzoate (Se**).** Prepared according to general procedure B using (3-((5-bromopentyl)oxy)phenyl)methanol (500 mg, 1.84 mmol), potassium carbonate (K_2CO_3) (253 mg, 1.84 mmol), and ethyl 2-hydroxybenzoate (304 mg, 1.84 mmol). The residue was purified by using column chromatography with EtOAc/*n*-hexane = 40:60 as the eluent to afford desired product ethyl 2-((5-(2-(1-hydroxyethyl)phenoxy)pentyl)oxy)benzoate **Se** (500 mg, 1.39 mmol, 75% yield) as a semisolid.

^1H NMR (400 MHz, CDCl_3) δ 7.78 (dd, $J = 7.6, 1.7$ Hz, 1H), 7.47–7.40 (m, 1H), 7.26 (dd, $J = 13.0, 5.5$ Hz, 1H), 6.95 (dt, $J = 17.2, 7.3$ Hz, 4H), 6.85–6.80 (m, 1H), 4.66 (s, 2H), 4.36 (q, $J = 7.1$ Hz, 2H), 4.07 (t, $J = 6.3$ Hz, 2H), 4.01 (t, $J = 6.4$ Hz, 2H), 1.97–1.84 (m, 4H), 1.76–1.65 (m, 2H), 1.38 (t, $J = 7.1$ Hz, 3H); $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3) 166.8, 159.4, 158.5, 142.7, 133.3, 131.6, 129.6, 120.9, 120.2, 119.1, 113.8, 113.2, 112.9, 68.7, 67.8, 65.2, 60.9, 29.0, 22.7, 14.3 (d, $J = 14.7$ Hz); FTIR (neat): 3507, 2941, 2845, 1718, 1601, 1491, 1240 cm^{-1} ; HRMS (ESI-TOF) m/z ; $[\text{M} + \text{Na}]^+$ calcd for $\text{C}_{21}\text{H}_{26}\text{O}_5\text{Na}$, 381.1677, found 381.1676.

Ethyl 2-((6-(2-(Hydroxymethyl)phenoxy)hexyl)oxy)benzoate (Sf). Prepared according to general procedure B using (2-((6-bromohexyl)oxy)phenyl)methanol (500 mg, 1.74 mmol), potassium carbonate (K_2CO_3) (240 mg, 1.74 mmol), and ethyl 2-hydroxybenzoate (290 mg, 1.74 mmol). The residue was purified by using column chromatography with EtOAc/*n*-hexane = 40:60 as the eluent to afford desired product ethyl 2-((6-(2-(hydroxymethyl)phenoxy)hexyl)oxy)benzoate Sf (510 mg, 1.37 mmol, 78% yield) as a semisolid.

^1H NMR (400 MHz, CDCl_3) δ 7.76 (dd, $J = 7.8, 1.7$ Hz, 1H), 7.45–7.39 (m, 1H), 7.29–7.21 (m, 2H), 6.98–6.90 (m, 3H), 6.86 (d, $J = 8.1$ Hz, 1H), 4.68 (d, $J = 3.1$ Hz, 2H), 4.33 (q, $J = 7.1$ Hz, 2H), 4.03 (dd, $J = 11.1, 6.3$ Hz, 4H), 2.48 (s, 1H), 1.86 (dd, $J = 14.2, 6.4$ Hz, 4H), 1.63–1.49 (m, 4H), 1.36 (t, $J = 7.1$ Hz, 3H); $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3) δ 166.7, 158.5, 156.9, 133.3, 131.6, 129.3, 128.9, 128.7, 120.9, 120.6, 120.1, 113.2, 111.1, 68.7, 67.9, 62.2, 60.8, 29.3, 29.2, 26.0, 25.8, 14.4; FTIR (neat): 3501, 2940, 2845, 1718, 1600, 1491, 1242 cm^{-1} ; HRMS (ESI-TOF) m/z ; $[\text{M} + \text{Na}]^+$ calcd for $\text{C}_{22}\text{H}_{28}\text{O}_5\text{Na}$, 395.1834, found 395.1830.

Ethyl 2-((7-(2-(Hydroxymethyl)phenoxy)heptyl)oxy)benzoate (Sg). Prepared according to general procedure B using (2-((7-bromoheptyl)oxy)phenyl)methanol (500 mg, 1.66 mmol), potassium carbonate (K_2CO_3) (229 mg, 1.66 mmol), and ethyl 2-hydroxybenzoate (276 mg, 1.66 mmol). The residue was purified by using column chromatography with EtOAc/*n*-hexane = 40:60 as the eluent to afford desired product ethyl 2-((7-(2-(hydroxymethyl)phenoxy)heptyl)oxy)benzoate Sg (590 mg, 1.49 mmol, 89% yield) as a semisolid.

^1H NMR (400 MHz, CDCl_3) δ 7.79 (dd, $J = 7.5, 1.7$ Hz, 1H), 7.45 (ddd, 1H), 7.30–7.28 (m, 1H), 7.01–6.98 (m, 1H), 6.97–6.92 (m, 3H), 6.85 (dd, 1H), 4.69 (s, 2H), 4.37 (q, $J = 7.0$ Hz, 2H), 4.06 (t, $J = 6.5$ Hz, 2H), 3.99 (t, $J = 6.5$ Hz, 2H), 1.92–1.79 (m, 4H), 1.61–1.45 (m, 6H), 1.42–1.37 (m, 3H); $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, CDCl_3) δ 167.2, 159.9, 158.9, 143.0, 133.6, 131.9, 130.0, 121.3, 120.4, 119.4, 114.3, 113.6, 113.3, 69.2, 68.3, 65.8, 61.2, 29.6, 26.4, 14.8; FTIR (neat): 3503, 2925, 2853, 1714, 1253, 1228 cm^{-1} ; HRMS (ESI-TOF) m/z ; $[\text{M} + \text{Na}]^+$ calcd for $\text{C}_{23}\text{H}_{30}\text{O}_5\text{Na}$, 409.1990, found 409.1990.

Ethyl 2-((8-(2-(Hydroxymethyl)phenoxy)octyl)oxy)benzoate (Sh). Prepared according to general procedure B using (2-((8-bromooctyl)oxy)phenyl)methanol (500 mg, 1.59 mmol), potassium carbonate (K_2CO_3) (219 mg, 1.59 mmol), and ethyl 2-hydroxybenzoate (263 mg, 1.59 mmol). The residue was purified by using column chromatography with EtOAc/*n*-hexane = 40:60 as the eluent to afford desired product ethyl 2-((8-(2-(hydroxymethyl)phenoxy)octyl)oxy)benzoate Sh (540 mg, 1.35 mmol, 85% yield) as a semisolid.

^1H NMR (400 MHz, CDCl_3) δ 7.68 (dd, $J = 8.0, 1.8$ Hz, 1H), 7.36–7.30 (m, 1H), 7.20–7.13 (m, 2H), 6.89–6.81 (m, 3H), 6.78 (d, $J = 8.1$ Hz, 1H), 4.61 (d, $J = 5.7$ Hz, 2H), 4.26 (q, $J = 7.1$ Hz, 2H), 3.93 (dd, $J = 11.8, 6.4$ Hz, 4H), 2.43 (s, 1H), 1.78–1.69 (m, 4H), 1.48–1.36 (m, 4H), 1.33–1.31 (m, 4H), 1.28 (t, $J = 7.1$ Hz, 3H); $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3) δ 166.8, 158.6, 157.0, 133.2, 131.5, 129.3, 128.9, 128.7, 120.9, 120.6, 120.1, 113.2, 111.1, 68.9, 68.0, 62.3, 60.8, 29.4, 29.3, 29.3, 26.2, 26, 14.4; FTIR (neat): 3508, 2940, 2845, 1718, 1603, 1491, 1242 cm^{-1} ; HRMS (ESI-TOF) m/z ; $[\text{M} + \text{Na}]^+$ calcd for $\text{C}_{24}\text{H}_{32}\text{O}_5\text{Na}$, 423.2147, found 423.2149.

Ethyl 2-((8-(3-(Hydroxymethyl)phenoxy)octyl)oxy)benzoate (Si). Prepared according to general procedure B using (3-((8-bromooctyl)oxy)phenyl)methanol (500 mg, 1.59 mmol), potassium carbonate (K_2CO_3) (219 mg, 1.59 mmol), and ethyl 2-hydroxybenzoate (263

mg, 1.59 mmol). The residue was purified by using column chromatography with EtOAc/*n*-hexane = 40:60 as the eluent to afford desired product ethyl 2-((8-(3-(hydroxymethyl)phenoxy)octyl)oxy)benzoate Si (575 mg, 1.44 mmol, 90% yield) as a semisolid.

^1H NMR (400 MHz, CDCl_3) δ 7.79 (dd, $J = 7.9, 1.7$ Hz, 1H), 7.49–7.42 (m, 1H), 7.29 (dd, $J = 4.5, 3.1$ Hz, 1H), 6.97 (dd, $J = 13.9, 6.1$ Hz, 4H), 6.86–6.82 (m, 1H), 4.69 (s, 2H), 4.37 (q, $J = 7.1, 1.9$ Hz, 2H), 4.04 (t, $J = 5.6, 4.9$ Hz, 2H), 3.98 (t, $J = 6.5$ Hz, 2H), 1.89–1.80 (m, $J = 18.7, 10.0, 4.8$ Hz, 4H), 1.59–1.47 (m, $J = 21.6, 14.5, 7.2$ Hz, 4H), 1.45–1.37 (m, 7H); $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3) δ 166.8, 159.5, 158.6, 142.7, 133.3, 131.6, 129.7, 121.0, 120.1, 119, 113.9, 113.2, 113, 68.9, 68.0, 65.4, 60.9, 29.6, 29.1, 26.1, 14.4; FTIR (neat): 3501, 2935, 2860, 1710, 1601, 1419, 1254 cm^{-1} ; HRMS (ESI-TOF) m/z ; $[\text{M} + \text{Na}]^+$ calcd for $\text{C}_{24}\text{H}_{32}\text{O}_5\text{Na}$, 423.2147, found 423.2149.

Ethyl 2-((9-(2-(Hydroxymethyl)phenoxy)nonyl)oxy)benzoate (Sj). Prepared according to general procedure B using (2-((9-bromononyl)oxy)phenyl)methanol (500 mg, 1.52 mmol), potassium carbonate (K_2CO_3) (209 mg, 1.52 mmol), and ethyl 2-hydroxybenzoate (252 mg, 1.52 mmol). The residue was purified by using column chromatography with EtOAc/*n*-hexane = 40:60 as the eluent to afford desired product ethyl 2-((9-(2-(hydroxymethyl)phenoxy)nonyl)oxy)benzoate Sj (545 mg, 1.31 mmol, 86% yield) as a semisolid.

^1H NMR (400 MHz, CDCl_3) δ 7.82–7.77 (m, 1H), 7.48–7.41 (m, 1H), 7.29 (ddd, $J = 8.0, 5.4, 0.8$ Hz, 2H), 7.01–6.93 (m, 3H), 6.90 (d, $J = 8.1$ Hz, 1H), 4.72 (s, 2H), 4.38 (q, $J = 7.1$ Hz, 2H), 4.04 (dd, $J = 11.3, 6.4$ Hz, 4H), 2.56 (s, 1H), 1.89–1.81 (m, 4H), 1.56–1.47 (m, 4H), 1.40 (dd, $J = 8.5, 5.7$ Hz, 9H); $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3) δ 166.8, 158.6, 157.0, 133.2, 131.6, 129.3, 128.9, 128.7, 120.9, 120.6, 120, 113.2, 111.1, 68.9, 68.0, 62.3, 60.8, 29.5, 29.4, 29.3, 26.2, 26.1, 14.4; FTIR (neat): 3441, 2929, 2856, 1706, 1600, 1491, 1237 cm^{-1} ; HRMS (ESI-TOF) m/z ; $[\text{M} + \text{Na}]^+$ calcd for $\text{C}_{25}\text{H}_{34}\text{O}_5\text{Na}$, 437.2303, found 437.2301.

Ethyl 2-((10-(2-(Hydroxymethyl)phenoxy)decyl)oxy)benzoate (Sk). Prepared according to general procedure B using (2-((10-bromodecyl)oxy)phenyl)methanol (500 mg, 1.46 mmol), potassium carbonate (K_2CO_3) (201 mg, 1.46 mmol), and ethyl 2-hydroxybenzoate (242 mg, 1.46 mmol). The residue was purified by using column chromatography with EtOAc/*n*-hexane = 40:60 as the eluent to afford desired product ethyl 2-((10-(2-(hydroxymethyl)phenoxy)decyl)oxy)benzoate Sk (560 mg, 1.31 mmol, 89% yield) as a semisolid.

^1H NMR (400 MHz, CDCl_3) δ 7.76 (dd, $J = 7.9, 1.8$ Hz, 1H), 7.43–7.37 (m, 1H), 7.24 (ddd, $J = 9.6, 7.7, 1.5$ Hz, 2H), 6.95–6.89 (m, 3H), 6.85 (d, $J = 7.9$ Hz, 1H), 4.68 (s, 2H), 4.34 (q, $J = 7.2$ Hz, 2H), 3.99 (q, $J = 6.4$ Hz, 4H), 2.60 (s, 1H), 1.84–1.76 (m, 4H), 1.48 (dt, $J = 12.9, 7.2$ Hz, 4H), 1.35 (dd, $J = 14.1, 6.9$ Hz, 11H); $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3) δ 166.8, 158.5, 156.9, 133.2, 131.5, 129.2, 128.8, 128.6, 120.8, 120.5, 120.0, 113.1, 111, 68.9, 67.9, 62.2, 60.8, 29.5, 29.4, 29.3, 29.2, 26.2, 26.0, 14.7; FTIR (neat): 3501, 2938, 2855, 1708, 1600, 1491, 1242 cm^{-1} ; HRMS (ESI-TOF) m/z ; $[\text{M} + \text{Na}]^+$ calcd for $\text{C}_{26}\text{H}_{36}\text{O}_5\text{Na}$, 451.2460, found 451.2454.

Diethyl 2,2'-(Pentane-1,5-diylbis(oxy))dibenzoate (Sl). Prepared according to general procedure B using ethyl 2-hydroxybenzoate (1.0 g, 6.0 mmol), potassium carbonate (K_2CO_3) (831 mg, 1.66 mmol), and 1,5-dibromopentane (691 mg, 3.0 mmol). The residue was purified by using column chromatography with EtOAc/*n*-hexane = 30:70 as the eluent to afford desired product diethyl 2,2'-(pentane-1,5-diylbis(oxy))dibenzoate Sl (1.9 g, 4.74 mmol, 79% yield) as a semisolid.

^1H NMR (400 MHz, CDCl_3) δ 7.77 (dd, $J = 7.6, 1.8$ Hz, 2H), 7.42 (td, $J = 7.9, 1.8$ Hz, 2H), 6.95 (t, $J = 7.8$ Hz, 4H), 4.34 (q, $J = 7.2$ Hz, 4H), 4.06 (t, $J = 6.4$ Hz, 4H), 1.96–1.86 (m, 4H), 1.77–1.67 (m, 2H), 1.36 (t, $J = 7.1$ Hz, 6H); $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3) δ 166.7, 158.6, 133.3, 131.6, 120.9, 120.2, 113.2, 68.8, 60.9, 29.0, 22.7, 14.5; FTIR (neat): 2941, 2853, 1723, 1600, 1490, 1245 cm^{-1} ; HRMS (ESI-TOF) m/z ; $[\text{M} + \text{Na}]^+$ calcd for $\text{C}_{23}\text{H}_{28}\text{O}_6\text{Na}$, 423.1783, found 423.1781.

Diethyl 2,2'-(Nonane-1,9-diylbis(oxy))dibenzoate (5m). Prepared according to general procedure B using ethyl 2-hydroxybenzoate (700 mg, 4.21 mmol), potassium carbonate (K_2CO_3) (582 mg, 4.21 mmol), and 1,5-dibromopentane (1.2 g, 4.21 mmol). The residue was purified by using column chromatography with EtOAc/*n*-hexane = 30:70 as the eluent to afford desired product diethyl 2,2'-(nonane-1,9-diylbis(oxy))dibenzoate **5m** (1.5 g, 3.29 mmol, 78% yield) as a semisolid.

^1H NMR (400 MHz, $CDCl_3$) δ 7.76 (dd, J = 8.0, 1.8 Hz, 2H), 7.41 (td, J = 8.2, 1.7 Hz, 2H), 6.94 (t, J = 7.4 Hz, 4H), 4.34 (q, J = 7.1 Hz, 4H), 4.01 (t, J = 6.5 Hz, 4H), 1.86–1.78 (m, 4H), 1.53–1.44 (m, 4H), 1.36 (dd, J = 9.2, 5.0 Hz, 12H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 166.8, 158.6, 133.2, 131.5, 120.9, 120.1, 113.2, 68.9, 60.8, 29.6, 29.7, 29.2, 29.4, 26.1, 14.4; FTIR (neat): 2980, 2850, 1725, 1600, 1491, 1245 cm^{-1} ; HRMS (ESI-TOF) m/z ; $[M + Na]^+$ calcd for $C_{27}H_{36}O_6Na$, 479.2409, found 479.2406.

2-((5-(2-(Hydroxymethyl)phenoxy)pentyl)oxy)benzoic Acid (1a). Prepared according to general procedure C; a 1,4-dioxane (2.0 mL) solution of ethyl 2-(3-(2-(hydroxymethyl)phenoxy)propoxy)benzoate **5a** (200 mg, 0.55 mmol), 5.0 mol/L NaOH solution (5.0 mL), was added. The reaction mixture was stirred at 80 °C in an oil bath overnight. After, the residue was purified by using column chromatography with EtOAc/*n*-hexane = 60:40 as the eluent to afford **1a** (168 mg, 91% yield) as a solid. Melting point: 74–76 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 8.14 (dd, J = 4.5, 3.3 Hz, 1H), 7.54 (td, J = 8.5, 1.8 Hz, 1H), 7.23 (d, J = 7.8 Hz, 1H), 7.11 (t, J = 7.6 Hz, 1H), 7.03 (d, J = 8.3 Hz, 1H), 6.95–6.88 (m, 2H), 6.80 (dd, J = 8.2, 1.9 Hz, 1H), 4.66 (s, 2H), 4.26 (t, J = 6.5 Hz, 2H), 4.00 (t, J = 6.1 Hz, 2H), 1.98 (dd, J = 14.7, 7.0 Hz, 2H), 1.90–1.82 (m, 2H), 1.72–1.65 (m, 2H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 165.9, 157.7, 156.6, 135.1, 133.6, 129.1, 129.1, 128.8, 122.1, 120.7, 118.0, 112.8, 111.1, 69.9, 67.5, 61.9, 60.5, 28.9, 22.8, 21.1, 14.3; FTIR (neat): 3257, 2931, 2857, 1721, 1601, 1455, 1270 cm^{-1} ; HRMS (ESI-TOF) m/z ; $[M + H]^+$ calcd for $C_{19}H_{23}O_5Na$, 331.1545, found 331.1542.

2-(3-(2-(Hydroxymethyl)phenoxy)propoxy)benzoic Acid (1b). Prepared according to general procedure C; a 1,4-dioxane (2.0 mL) solution of ethyl 2-(3-(2-(hydroxymethyl)phenoxy)propoxy)benzoate **5b** (200 mg, 0.60 mmol), 5.0 mol/L NaOH solution (5.0 mL), was added. The reaction mixture was stirred at 80 °C in an oil bath overnight. After, the residue was purified by using column chromatography with EtOAc/*n*-hexane = 60:40 as the eluent to afford **1b** (170 mg, 93% yield) as a solid. Melting point: 130–132 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 8.17 (dd, J = 7.8, 1.8 Hz, 1H), 7.59–7.52 (m, 1H), 7.29 (dd, 2H), 7.17–7.11 (m, 1H), 7.08 (d, J = 8.4 Hz, 1H), 6.98 (t, J = 7.2 Hz, 1H), 6.90 (d, J = 8.2 Hz, 1H), 4.70 (s, 2H), 4.48 (t, J = 6.2 Hz, 2H), 4.25 (t, J = 5.8 Hz, 2H), 2.44 (p, J = 6.0 Hz, 2H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 165.5, 157.5, 156.3, 135.2, 134.0, 129.3, 129.2, 129.1, 122.5, 121.5, 118.1, 112.8, 111.5, 67.2, 64.3, 61.7, 29.2; FTIR (neat): 3274, 2926, 2854, 1722, 1600, 1490, 1291 cm^{-1} ; HRMS (ESI-TOF) m/z ; $[M + Na]^+$ calcd for $C_{17}H_{18}O_5Na$, 325.1052, found 325.1046.

2-(4-(2-(Hydroxymethyl)phenoxy)butoxy)benzoic acid (1c). Prepared according to general procedure C; a 1,4-dioxane (2.0 mL) solution of ethyl 2-(4-(2-(hydroxymethyl)phenoxy)butoxy)benzoate **5c** (200 mg, 0.58 mmol), 5.0 mol/L NaOH solution (5.0 mL), was added. The reaction mixture was stirred at 80 °C in an oil bath overnight. After, the residue was purified by using column chromatography with EtOAc/*n*-hexane = 60:40 as the eluent to afford **1c** (160 mg, 87% yield) as a solid. Melting point: 118–120 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 8.16 (dd, J = 7.9, 1.8 Hz, 1H), 7.55 (ddd, J = 8.4, 7.5, 1.8 Hz, 1H), 7.32–7.28 (m, 1H), 7.28–7.23 (m, 1H), 7.16–7.10 (m, 1H), 7.06 (d, J = 8.4 Hz, 1H), 6.96 (t, J = 7.5 Hz, 1H), 6.87 (d, J = 8.1 Hz, 1H), 4.70 (s, 2H), 4.34 (t, J = 6.2 Hz, 2H), 4.11 (t, J = 5.8 Hz, 2H), 2.18–2.10 (m, 2H), 2.09–2.00 (m, 2H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 165.8, 157.6, 156.5, 135.1, 133.8, 129.1, 128.9, 122.3, 121.0, 117.9, 112.7, 111.1, 69.8, 67.1, 61.9, 26.2, 26.1; FTIR (neat): 3274, 2926, 2854, 1722, 1455, 1253 cm^{-1} ; HRMS (ESI-TOF) m/z ; $[M + Na]^+$ calcd for $C_{18}H_{20}O_5Na$, 339.1208, found 339.1208.

2-((5-(2-(1-Hydroxyethyl)phenoxy)pentyl)oxy)benzoic Acid (1d). Prepared according to general procedure C; a 1,4-dioxane (3.0 mL) solution of ethyl 2-((5-(2-(1-hydroxyethyl)phenoxy)pentyl)oxy)benzoate **5d** (600 mg, 1.6 mmol), 5.0 mol/L NaOH solution (5.0 mL), was added. The reaction mixture was stirred at 80 °C in an oil bath overnight. After, the residue was purified by using column chromatography with EtOAc/*n*-hexane = 60:40 as the eluent to afford **1d** (475 mg, 85% yield) as a semisolid. ^1H NMR (400 MHz, $CDCl_3$) δ 8.17 (dd, J = 7.8, 1.8 Hz, 1H), 7.55 (ddd, J = 8.4, 7.4, 1.8 Hz, 1H), 7.36 (dd, J = 7.5, 1.6 Hz, 1H), 7.25–7.19 (m, 1H), 7.16–7.09 (m, 1H), 7.04 (d, J = 8.4 Hz, 1H), 6.99 (s, 1H), 6.85 (t, J = 8.2 Hz, 1H), 5.19–5.01 (q, 1H), 4.29 (t, J = 6.4 Hz, 2H), 4.06 (t, J = 6.1 Hz, 2H), 2.05–1.97 (m, 2H), 1.97–1.89 (m, J = 12.3, 6.4 Hz, 2H), 1.80–1.65 (m, 2H), 1.49 (t, J = 7.4 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 165.5, 157.5, 155.7, 134.9, 133.8, 133.4, 128.3, 126.1, 122.2, 120.9, 117.9, 112.6, 111.1, 69.9, 67.3, 66.3, 29.0, 28.8, 23.1, 22.8; FTIR (neat): 3330, 2944, 2873, 1636, 1559 cm^{-1} ; HRMS (ESI-TOF) m/z ; $[M + H]^+$ calcd for $C_{20}H_{25}O_5$, 345.1702, found 345.1705.

2-((5-(3-(Hydroxymethyl)phenoxy)pentyl)oxy)benzoic Acid (1e). Prepared according to general procedure C; a 1,4-dioxane (3.0 mL) solution of ethyl 2-((5-(3-(hydroxymethyl)phenoxy)pentyl)oxy)benzoate **5e** (300 mg, 0.83 mmol), 5.0 mol/L NaOH solution (5.0 mL), was added. The reaction mixture was stirred at 80 °C in an oil bath overnight. After, the residue was purified by using column chromatography with EtOAc/*n*-hexane = 60:40 as the eluent to afford **1e** (250 mg, 90%) as a solid. Melting point: 75–77 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 8.17 (dd, J = 7.8, 1.7 Hz, 1H), 7.55 (ddd, J = 8.3, 7.6, 1.8 Hz, 1H), 7.29–7.22 (m, 1H), 7.15–7.09 (m, 1H), 7.04 (d, J = 8.5 Hz, 1H), 6.92 (d, J = 7.4 Hz, 2H), 6.84–6.78 (m, 1H), 4.67 (s, 2H), 4.28 (t, J = 6.5 Hz, 2H), 4.01 (t, J = 6.1 Hz, 2H), 1.99 (dd, J = 15.0, 6.8 Hz, 2H), 1.93–1.83 (m, 2H), 1.74–1.65 (m, 2H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 165.6, 159.2, 157.6, 142.7, 135.2, 133.9, 129.7, 122.3, 119.3, 117.8, 113.8, 113.1, 112.7, 70.1, 67.4, 65.3, 28.8, 22.7; FTIR (neat): 3257, 2931, 2857, 1721, 1601, 1487, 1257 cm^{-1} ; HRMS (ESI-TOF) m/z ; $[M + Na]^+$ calcd for $C_{19}H_{22}O_5Na$, 353.1364, found 353.1356.

2-((6-(2-(Hydroxymethyl)phenoxy)hexyl)oxy)benzoic Acid (1f). Prepared according to general procedure C; a 1,4-dioxane (3.0 mL) solution of ethyl 2-((6-(2-(hydroxymethyl)phenoxy)hexyl)oxy)benzoate **5f** (350 mg, 0.93 mmol), 5.0 mol/L NaOH solution (5.0 mL), was added. The reaction mixture was stirred at 80 °C in an oil bath overnight. After, the residue was purified by using column chromatography with EtOAc/*n*-hexane = 60:40 as the eluent to afford **1f** (300 mg, 92% yield) as a solid. Melting point: 83–85 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 8.17 (dd, J = 7.8, 1.8 Hz, 1H), 7.55 (ddd, J = 8.4, 7.4, 1.8 Hz, 1H), 7.29–7.23 (m, 2H), 7.15–7.10 (m, 1H), 7.04 (d, J = 8.1 Hz, 1H), 6.93 (td, J = 7.5, 0.8 Hz, 1H), 6.87 (d, J = 8.1 Hz, 1H), 4.69 (s, 2H), 4.26 (t, J = 6.5 Hz, 2H), 4.04 (t, J = 6.3 Hz, 2H), 2.62 (s, 1H), 2.00–1.91 (m, 2H), 1.86 (dd, J = 12.5, 6.1 Hz, 2H), 1.62–1.55 (m, 4H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 165.6, 157.6, 156.9, 135.1, 133.9, 129.2, 129.1, 128.8, 122.3, 120.8, 117.9, 112.7, 111.2, 70.2, 67.7, 62.3, 29.2, 29.1, 26.3, 25.8; FTIR (neat): 3253, 2937, 2864, 1723, 1491, 1238 cm^{-1} ; HRMS (ESI-TOF) m/z ; $[M + H]^+$ calcd for $C_{20}H_{25}O_5$, 345.1702, found 345.1705.

2-((7-(2-(Hydroxymethyl)phenoxy)heptyl)oxy)benzoic Acid (1g). Prepared according to general procedure C; a 1,4-dioxane (2.0 mL) solution of 2-((7-(2-(hydroxymethyl)phenoxy)heptyl)oxy)benzoic acid benzoate **5g** (250 mg, 0.64 mmol), 5.0 mol/L NaOH solution (5.0 mL), was added. The reaction mixture was stirred at 80 °C in an oil bath overnight. After, the residue was purified by using column chromatography with EtOAc/*n*-hexane = 60:40 as the eluent to afford **1g** (205 mg, 88.4% yield) as a semisolid. ^1H NMR (400 MHz, $CDCl_3$) δ 8.18 (dd, J = 7.8, 1.8 Hz, 1H), 7.58–7.52 (m, 1H), 7.26 (m, 1H), 7.13 (t, J = 7.5 Hz, 2H), 7.04 (d, J = 8.4 Hz, 1H), 6.93 (t, J = 7.3 Hz, 1H), 6.87 (d, J = 8.0 Hz, 1H), 4.70 (s, 2H), 4.26 (t, J = 6.5 Hz, 2H), 4.03 (t, J = 6.4 Hz, 2H), 2.00–1.90 (m, 2H), 1.88–1.78 (m, 2H), 1.57–1.45 (m, 6H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 165.6, 157.69, 157.0, 135.1, 133.9, 129.2, 129.1, 128.8, 122.3, 120.7, 117.9, 112.7, 111.2, 70.3, 67.9, 62.5, 29.3, 29.3, 28.9, 26.1, 25.9; FTIR

(neat): 3257, 2935, 2839, 1725, 1602, 1456 cm^{-1} ; HRMS (ESI-TOF) m/z ; $[\text{M} + \text{Na}]^+$ calcd for $\text{C}_{21}\text{H}_{26}\text{O}_5\text{Na}$, 381.1672, found 381.1662.

2-((8-(2-(Hydroxymethyl)phenoxy)octyl)oxy)benzoic Acid (1h). Prepared according to general procedure C; a 1,4-dioxane (2.0 mL) solution of ethyl 2-((8-(2-(hydroxymethyl)phenoxy)octyl)oxy)-benzoate **Sh** (200 mg, 0.5 mmol), 5.0 mol/L NaOH solution (5.0 mL), was added. The reaction mixture was stirred at 80 °C in an oil bath overnight. After, the residue was purified by using column chromatography with EtOAc/*n*-hexane = 60:40 as the eluent to afford **1h** (170 mg, 91% yield) as a solid. Melting point: 77–78 °C; ^1H NMR (400 MHz, CDCl_3) δ 8.18 (dd, 1H), 7.55 (ddd, 1H), 7.29–7.22 (m, 2H), 7.16–7.09 (m, 1H), 7.04 (d, J = 8.3 Hz, 1H), 6.92 (t, J = 7.4 Hz, 1H), 6.87 (d, J = 8.1 Hz, 1H), 4.70 (s, 2H), 4.24 (t, 2H), 4.01 (t, J = 8.5, 4.2 Hz, 2H), 1.96–1.87 (m, 2H), 1.86–1.77 (m, 2H), 1.50 (dd, J = 14.0, 7.0 Hz, 4H), 1.42 (d, J = 3.0 Hz, 4H); $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3) δ 165.7, 157.7, 157, 135.1, 133.8, 129.2, 129.0, 128.7, 122.2, 120.6, 117.8, 112.7, 111.1, 70.3, 67.9, 62.4, 60.5, 29.4, 29.3, 29.2, 29.1, 26.2, 25.9, 21.2; FTIR (neat): 3254, 2930, 2856, 1722, 1600, 1455, 1236 cm^{-1} ; HRMS (ESI-TOF) m/z ; $[\text{M} + \text{Na}]^+$ calcd for $\text{C}_{22}\text{H}_{28}\text{O}_5\text{Na}$, 395.1834, found 395.1835.

2-((8-(3-(Hydroxymethyl)phenoxy)octyl)oxy)benzoic Acid (1i). Prepared according to general procedure C; a 1,4-dioxane (2.0 mL) solution of ethyl 2-((8-(3-(hydroxymethyl)phenoxy)octyl)oxy)-benzoate **Si** (250 mg, 0.62 mmol), 5.0 mol/L NaOH solution (5.0 mL), was added. The reaction mixture was stirred at 80 °C in an oil bath overnight. After, the residue was purified by using column chromatography with EtOAc/*n*-hexane = 60:40 as the eluent to afford **1i** (169 mg, 90% yield) as a solid. Melting point: 78–80 °C; ^1H NMR (400 MHz, CDCl_3) δ 8.16 (dd, J = 7.8, 1.8 Hz, 1H), 7.53 (ddd, J = 8.6, 7.4, 1.9 Hz, 1H), 7.23 (dd, J = 10.0, 5.3 Hz, 1H), 7.13–7.07 (m, 1H), 7.04–7.00 (m, 1H), 6.93–6.87 (m, 2H), 6.79 (dd, J = 7.9, 2.3 Hz, 1H), 4.64 (s, 2H), 4.23 (t, J = 6.5 Hz, 2H), 3.94 (t, J = 6.5 Hz, 2H), 1.95–1.85 (m, 2H), 1.80–1.72 (m, 2H), 1.53–1.43 (m, 4H), 1.43–1.36 (m, 4H); $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3) δ 165.6, 159.4, 157.7, 142.7, 135.1, 133.9, 129.6, 122.2, 119.1, 117.7, 113.8, 113, 112.7, 70.3, 67.9, 65.3, 29.3, 29.2, 29.0, 26.2, 25.9; FTIR (neat): 3258, 2931, 2857, 1722, 1601, 1457 cm^{-1} ; HRMS (ESI-TOF) m/z ; $[\text{M} + \text{Na}]^+$ calcd for $\text{C}_{22}\text{H}_{28}\text{O}_5\text{Na}$, 395.1834, found 395.1835.

2-((9-(2-(Hydroxymethyl)phenoxy)nonyl)oxy)benzoic Acid (1j). Prepared according to general procedure C; a 1,4-dioxane (2.0 mL) solution of ethyl 2-((9-(2-(hydroxymethyl)phenoxy)nonyl)oxy)-benzoate **Sj** (230 mg, 0.55 mmol), 5.0 mol/L NaOH solution (5.0 mL), was added. The reaction mixture was stirred at 80 °C in an oil bath overnight. After, the residue was purified by using column chromatography with EtOAc/*n*-hexane = 60:40 as the eluent to afford **1j** (200 mg, 93% yield) as a solid. Melting point: 172–174 °C; ^1H NMR (400 MHz, CDCl_3) δ 8.18 (dd, J = 7.8, 1.8 Hz, 1H), 7.54 (ddd, J = 8.4, 7.5, 1.8 Hz, 1H), 7.27–7.21 (m, 2H), 7.12 (dd, J = 11.2, 4.0 Hz, 1H), 7.03 (d, J = 8.4 Hz, 1H), 6.92 (dd, J = 11.1, 3.8 Hz, 1H), 6.86 (d, J = 7.9 Hz, 1H), 4.68 (s, 2H), 4.24 (t, J = 6.5 Hz, 2H), 4.01 (t, J = 6.4 Hz, 2H), 1.90 (dd, J = 14.8, 6.8 Hz, 2H), 1.80 (dd, J = 14.6, 6.6 Hz, 2H), 1.54–1.43 (m, 4H), 1.40–1.38 (m, 6H); $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3) δ 165.5, 157.7, 157.1, 135.1, 133.9, 129.2, 129.1, 128.8, 122.3, 120.6, 117.8, 112.7, 111.2, 70.4, 68.0, 62.5, 29.4, 29.4, 29.3, 29.2, 29.1, 26.2, 25.9; FTIR (neat): 3256, 2926, 2854, 1726, 1602, 1490, 1235 cm^{-1} ; HRMS (ESI-TOF) m/z ; $[\text{M} + \text{Na}]^+$ calcd for $\text{C}_{23}\text{H}_{30}\text{O}_5\text{Na}$, 409.1990, found 409.1985.

2-((10-(2-(Hydroxymethyl)phenoxy)decyl)oxy)benzoic Acid (1k). Prepared according to general procedure C; a 1,4-dioxane (5.0 mL) solution of ethyl 2-((10-(2-(hydroxymethyl)phenoxy)decyl)oxy)-benzoate **Sk** (380 mg, 0.88 mmol), 5.0 mol/L NaOH solution (15 mL), was added. The reaction mixture was stirred at 80 °C in an oil bath overnight. After the workup, the residue was purified by using column chromatography with EtOAc/*n*-hexane = 60:40 as the eluent to afford **1k** (320 mg, 90% yield) as a solid. Melting point: 80–82 °C; ^1H NMR (400 MHz, CDCl_3) δ 8.15 (s, 1H), 7.53 (d, J = 0.7 Hz, 1H), 7.26 (d, J = 7.1 Hz, 2H), 7.10 (s, 1H), 7.03 (s, 1H), 6.90 (s, 1H), 6.86 (s, 1H), 4.68 (s, 2H), 4.22 (t, J = 6.5 Hz, 2H), 3.99 (t, J = 6.4 Hz, 2H), 1.94–1.84 (m, 2H), 1.79 (dq, J = 13.0, 6.5 Hz, 2H), 1.52–1.41 (m, 4H), 1.40–1.27 (m, J = 21.5 Hz, 8H); ^1H NMR (400

MHz, DMSO) δ 12.50 (s, 1H), 7.60 (d, J = 7.6 Hz, 1H), 7.48–7.43 (m, 1H), 7.36 (d, J = 7.2 Hz, 1H), 7.20–7.14 (m, 1H), 7.09 (d, J = 8.4 Hz, 1H), 6.97 (dd, J = 11.0, 3.9 Hz, 1H), 6.91 (t, J = 7.2 Hz, 2H), 4.95 (s, 1H), 4.49 (s, 2H), 4.00 (t, J = 6.3 Hz, 2H), 3.94 (t, J = 6.3 Hz, 2H), 1.74–1.64 (m, 4H), 1.48–1.36 (m, 4H), 1.29 (s, 8H); $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3) δ 165.6, 157.7, 157, 135.1, 133.8, 129.2, 128.9, 128.6, 122.1, 120.5, 117.8, 112.7, 111.1, 70.4, 67.9, 62.3, 29.4, 29.3, 29.32, 29.2, 28.9, 26.2, 25.9; FTIR (neat): 3256, 2926, 2854, 1726, 1602, 1490, 1235 cm^{-1} ; HRMS (ESI-TOF) m/z ; $[\text{M} + \text{Na}]^+$ calcd for $\text{C}_{24}\text{H}_{32}\text{O}_5\text{Na}$, 423.2147, found 423.2149.

7,8,9,10-Tetrahydro-6H,16H,18H-dibenzo[b,g][1,5,9]-trioxacyclotetradecin-16-one (2a).²⁵ Prepared according to general procedure D; a solution of **1a** (0.015 M, 49.5 mg) and Mukaiyama salt (0.036 M, 91.8 mg) was dissolved with ACN in a vial. 1-Methylimidazole (0.03 M, 25 mg) was dissolved in another vial with ACN. Both reagent solutions were flowed through the 7 mL PFA tubing in an 80 °C in preheated water bath at 3–4 bar pressure. After workup, the residue was purified by using column chromatography with EtOAc/*n*-hexane = 10:90 as the eluent to afford the desired product **2a** (25.5 mg, 54% yield) as a solid and the starting material **1a** (11.6 mg, 35.11%) was recovered. Batch reaction: compound **1a** (0.015 M, 49.5 mg), Mukaiyama salt (0.036 M, 91.8 mg), and 1-methylimidazole (0.03 M, 25 mg) in ACN solvent were heated at 80 °C in the preheated oil bath for 24 h to afford the desired product **2a** (8.4 mg, 17% yield). Melting point: 86–89 °C. ^1H NMR (400 MHz, CDCl_3) δ 7.77 (dd, J = 7.7, 1.8 Hz, 1H), 7.44 (dd, J = 7.4, 1.7 Hz, 1H), 7.38 (ddd, J = 8.4, 7.4, 1.8 Hz, 1H), 7.34–7.28 (m, 1H), 6.96–6.92 (m, 1H), 6.90 (ddd, J = 8.2, 3.2, 2.2 Hz, 2H), 6.84 (d, J = 8.3 Hz, 1H), 5.39 (s, 2H), 4.13 (t, J = 5.3 Hz, 2H), 3.98 (t, 2H), 1.98–1.86 (m, J = 11.1, 5.6 Hz, 4H), 1.80–1.69 (m, J = 10.5, 5.5 Hz, 2H); $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3) δ 168.5, 158.5, 158.2, 133.1, 131.9, 130.6, 123.9, 121.3, 120.2, 120.1, 112.6, 111.4, 67.8, 64.9, 63.6, 27.2, 26.6, 20.5; FTIR (neat): 1695, 1598, 1245, 1121 cm^{-1} ; HRMS (ESI-TOF) m/z ; $[\text{M} + \text{Na}]^+$ calcd for $\text{C}_{19}\text{H}_{20}\text{O}_4\text{Na}$, 335.1259, found 335.1253.

7,8-Dihydro-6H,14H,16H-dibenzo[b,g][1,5,9]trioxacyclododecin-14-one (2b).²⁵ Prepared according to general procedure D; a solution of **1b** (0.015 M, 45.3 mg) and Mukaiyama salt (0.036 M, 91.8 mg) was dissolved with ACN in a vial. 1-Methylimidazole (0.03 M, 25 mg) was dissolved in another vial with ACN. Both reagent solutions were flowed through the 7 mL PFA tubing in an 80 °C in preheated water bath at 3–4 bar pressure. After workup, the residue was purified by using column chromatography with EtOAc/*n*-hexane = 10:90 as the eluent to afford the desired product **2b** (30 mg, 70% yield) as a solid and starting material **1b** (4 mg, 13%) was recovered. Batch reaction: compound **1b** (0.015 M, 45.3 mg), Mukaiyama salt (0.036 M, 91.8 mg), and 1-methylimidazole (0.03 M, 25 mg) in ACN solvent were heated at 80 °C in the preheated oil bath for 24 h to afford the desired product **2b** (11 mg, 25% yield). Melting point: 107–109 °C; ^1H NMR (400 MHz, CDCl_3) δ 7.69 (dd, J = 7.7, 1.7 Hz, 1H), 7.38 (dd, J = 7.2, 1.5 Hz, 2H), 7.31 (td, J = 8.1, 1.7 Hz, 1H), 7.01 (dd, J = 7.5, 0.8 Hz, 1H), 6.94 (ddd, J = 8.3, 7.6, 2.0 Hz, 3H), 5.37 (s, 2H), 4.18 (t, J = 5.0 Hz, 2H), 4.08 (t, J = 5.1 Hz, 2H), 2.09–1.94 (m, J = 15.0, 8.3, 3.9 Hz, 4H); $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3) δ 167.9, 158.8, 158.4, 132.9, 132.3, 131.0, 130.5, 125.3, 123.7, 121.5, 120.9, 116.9, 113.9, 68.5, 64.4, 27.2, 26.6; FTIR (neat): 1709, 1600, 1254, 1128 cm^{-1} ; HRMS (ESI-TOF) m/z ; $[\text{M} + \text{Na}]^+$ calcd for $\text{C}_{17}\text{H}_{18}\text{O}_4\text{Na}$, 307.0946, found 307.0936.

6,7,8,9-Tetrahydro-15H,17H-dibenzo[b,g][1,5,9]-trioxacyclotridecin-15-one (2c).²⁵ Prepared according to general procedure D; 2-(4-(2-(hydroxymethyl)phenoxy)butoxy)benzoic acid **1c** (0.015 M, 47.4 mg) and Mukaiyama salt (0.036 M, 91.8 mg) were dissolved with ACN in a vial. 1-Methylimidazole (0.03 M, 25 mg) was dissolved in another vial with ACN. Both reagent solutions were flowed through the 7 mL PFA tubing in an 80 °C preheated water bath at 3–4 bar pressure. After workup, the residue was purified by using column chromatography with EtOAc/*n*-hexane = 10:90 as the eluent to afford the desired product of **2c** (30.4 mg, 68%) as an oily product.

Large Scale Synthesis of Compound 2c. For large scale, 2-(4-(2-(hydroxymethyl)phenoxy)butoxy)benzoic acid **1c** (0.015 M, 3.41 g, 10.80 mmol) and Mukaiyama salt (0.036 M, 6.6 g, 25.88 mmol) were dissolved with ACN in a reagent bottle. Then, 1-methylimidazole (0.03 M, 1.77 mg, 21.55 mmol) was dissolved in another reagent bottle with ACN. Both the reagent solutions were flowed through the 7 mL PFA tubing in an 80 °C preheated water bath at 3–4 bar pressure. After workup, the residue was purified by using column chromatography with EtOAc/*n*-hexane = 10:90 as the eluent to afford the desired product of **2c** (1.76 g, 5.63 mmol, 52%) as an oily product and the starting material **1a** (1.03 g, 32%) was recovered. ¹H NMR (400 MHz, CDCl₃) δ 7.69 (dd, *J* = 7.7, 1.7 Hz, 1H), 7.38 (dd, *J* = 7.2, 1.5 Hz, 2H), 7.31 (td, *J* = 8.1, 1.7 Hz, 1H), 7.01 (dd, *J* = 7.5, 0.8 Hz, 1H), 6.94 (ddd, *J* = 8.3, 7.6, 2.0 Hz, 3H), 5.37 (s, 2H), 4.18 (t, *J* = 5.0 Hz, 2H), 4.08 (t, *J* = 5.1 Hz, 2H), 2.09–1.94 (m, *J* = 15.0, 8.3, 3.9 Hz, 4H); ¹³C{¹H} NMR (101 MHz, CDCl₃) δ 167.9, 158.8, 158.4, 132.9, 132.3, 131.0, 130.5, 125.3, 123.7, 121.5, 120.9, 116.9, 113.9, 71.1, 69.0, 64.4, 27.2, 26.6; FTIR (neat): 1706, 1599, 1250, 1121 cm⁻¹; HRMS (ESI-TOF) *m/z*; [M + Na]⁺ calcd for C₁₈H₁₈O₄Na, 321.1102, found 321.1101.

18-Methyl-7,8,9,10-tetrahydro-6H,16H,18H-dibenzo[b,g][1,5,9]-trioxacyclotetradecin-16-one (2d). Prepared according to general procedure D; a solution of **1d** (0.015 M, 51.6 mg) and Mukaiyama salt (0.036 M, 91.8 mg) was dissolved with ACN in a vial. 1-Methylimidazole (0.03 M, 25 mg) was dissolved in another vial with ACN. Both the reagent solutions were flowed through the 7 mL PFA tubing in an 80 °C preheated water bath at 3–4 bar pressure. After workup, the residue was purified by using column chromatography with EtOAc/*n*-hexane = 10:90 as the eluent to afford the desired product **2d** (16 mg, 32.7%) as a thick oil product and the starting material **1d** (5 mg, 14%) was recovered. ¹H NMR (400 MHz, CDCl₃) δ 7.68 (dd, *J* = 7.7, 1.8 Hz, 1H), 7.43 (dd, *J* = 7.5, 1.7 Hz, 1H), 7.36 (ddd, *J* = 8.4, 7.5, 1.8 Hz, 1H), 7.30–7.25 (m, 1H), 6.95–6.90 (m, 2H), 6.87 (dd, *J* = 8.4, 4.3 Hz, 2H), 6.34 (q, *J* = 6.7 Hz, 1H), 4.18 (dt, *J* = 8.6, 4.2 Hz, 1H), 4.10–4.00 (m, 2H), 3.93 (td, *J* = 9.4, 2.6 Hz, 1H), 2.14–1.80 (m, 7H), 1.76–1.65 (m, 2H); ¹³C{¹H} NMR (101 MHz, CDCl₃) δ 167.5, 158.2, 132.7, 131.3, 130.3, 129.9, 127.5, 122.6, 120.2, 120, 113.7, 111.4, 71.6, 68.6, 65.3, 27.5, 26.9, 21.1, 18.4; FTIR (neat): 2931, 2871, 1723, 1699, 1601, 1234 cm⁻¹; HRMS (ESI-TOF) *m/z*; [M + Na]⁺ calcd for C₂₀H₂₂O₄Na, 349.1415, found 349.1416.

3,6,12-Trioxa-1(1,2),5(1,3)-dibenzenacyclododecaphan-2-one (2e).²⁵ Prepared according to general procedure D; a solution of **1e** (0.015 M, 49.5 mg) and Mukaiyama salt (0.036 M, 91.8 mg) was dissolved with ACN in a vial, and 1-methylimidazole (0.03 M, 25 mg) was dissolved in another vial with ACN. Both reagent solutions were flowed through 7 mL PFA tubing in an 80 °C in preheated water bath at 3–4 bar pressure. After workup, the residue was purified by using column chromatography with EtOAc/*n*-hexane = 10:90 as the eluent to afford the desired product **2e** (12.6 mg, 27% yield) as a solid and the starting material **1e** (9.5 mg, 28%) was recovered. Batch reaction: compound **1e** (0.015 M, 49.5 mg), Mukaiyama salt (0.036 M, 91.8 mg), and 1-methylimidazole (0.03 M, 25 mg) in ACN solvent were heated at 80 °C in a preheated oil path for 24 h to afford product **2e**. Melting point: 86–88 °C; ¹H NMR (400 MHz, CDCl₃) δ 7.79 (dd, *J* = 7.7, 1.8 Hz, 1H), 7.50–7.44 (m, 1H), 7.30 (dd, *J* = 9.7, 6.2 Hz, 2H), 7.03 (dd, *J* = 11.5, 4.1 Hz, 2H), 6.98 (d, *J* = 4.8 Hz, 1H), 6.95 (dd, *J* = 8.2, 2.4 Hz, 1H), 5.42 (s, 2H), 4.28 (t, *J* = 5.8 Hz, 2H), 4.11 (t, 2H), 1.92 (dt, *J* = 10.3, 5.8 Hz, 2H), 1.83 (dd, *J* = 12.3, 6.0 Hz, 2H), 1.79–1.71 (m, 2H); ¹³C{¹H} NMR (101 MHz, CDCl₃) δ 167.7, 159.7, 158, 138.1, 133.2, 131.6, 129.5, 121.3, 120.8, 120.3, 118.5, 114.8, 113.1, 69.1, 68.8, 66.8, 29.2, 28.7, 23.4; FTIR (neat): 1724, 1595, 1261, 1160 cm⁻¹; HRMS (ESI-TOF) *m/z*; [M + Na]⁺ calcd for C₁₉H₂₀O₄, 335.1259, found 335.1256.

6,7,8,9,10,11-Hexahydro-17H,19H-dibenzo[b,g][1,5,9]-trioxacyclopentadecin-17-one (2f).²⁵ Prepared according to general procedure D; a solution of **1f** (0.015 M, 51.6 mg) and Mukaiyama salt (0.036 M, 91.8 mg) was dissolved with ACN in a vial, and 1-methylimidazole (0.03 M, 25 mg) was dissolved in another vial with ACN. Both the reagent solutions were flowed through 7 mL PFA tubing in an 80 °C preheated water bath at 3–4 bar pressure. After

workup, the residue was purified by using column chromatography with EtOAc/*n*-hexane = 6:94 as the eluent to afford the desired product **2f** (27.9 mg, 57% yield) as a semisolid and the starting material **1f** (8.4 mg, 24%) was recovered; ¹H NMR (400 MHz, CDCl₃) δ 7.71 (dd, *J* = 8.0, 1.8 Hz, 1H), 7.46 (dd, *J* = 7.4, 1.7 Hz, 1H), 7.40–7.34 (m, 1H), 7.32–7.27 (m, 1H), 6.93 (dd, *J* = 4.9, 3.8 Hz, 2H), 6.90–6.86 (m, 2H), 5.42 (s, 2H), 4.11 (t, 2H), 4.07 (t, 2H), 1.89–1.81 (m, 2H), 1.81–1.72 (m, *J* = 6.8, 4.0 Hz, 4H), 1.70–1.62 (m, 2H); ¹³C{¹H} NMR (100 MHz, CDCl₃) δ 167.9, 158.3, 157.5, 132.9, 132.8, 131.5, 130.4, 124.3, 121.9, 120.2, 120.0, 112.8, 111.5, 68.7, 68.6, 62.8, 28.8, 27.4, 26.9; FTIR (neat): 1699, 1598, 1247, 1124 cm⁻¹; HRMS (ESI-TOF) *m/z*; [M + Na]⁺ calcd for C₂₀H₂₂O₄Na, 349.1415, found 349.1417.

7,8,9,10,11,12-Hexahydro-6H,18H,20H-dibenzo[b,g][1,5,9]-trioxacyclohexadecin-18-one (2g).²⁵ Prepared according to general procedure D; a solution of **1g** (0.015 M, 53.7 mg) and Mukaiyama salt (0.036 M, 91.8 mg) was dissolved with ACN in a vial. 1-Methylimidazole (0.03 M, 25 mg) was dissolved in another vial with ACN. Both the reagent solutions were flowed through 7 mL PFA tubing in an 80 °C preheated water bath at 3–4 bar pressure. After workup, the residue was purified by using column chromatography with EtOAc/*n*-hexane = 10:90 as the eluent to afford the desired product **2g** (20.5 mg, 40% yield) as semisolid and the starting material **1g** (13 mg, 36%) was recovered; ¹H NMR (400 MHz, CDCl₃) δ 7.69 (dd, *J* = 8.0, 1.8 Hz, 1H), 7.47 (dd, *J* = 7.5, 1.7 Hz, 1H), 7.40–7.34 (m, 1H), 7.32–7.27 (m, 1H), 6.96–6.87 (m, 4H), 5.42 (s, 2H), 4.06 (t, *J* = 5.5 Hz, 2H), 4.02 (t, *J* = 5.4 Hz, 2H), 1.80 (m, *J* = 12.1, 5.8 Hz, 4H), 1.58 (m, *J* = 12.6, 6.2 Hz, 6H); ¹³C{¹H} NMR (100 MHz, CDCl₃) δ 167.6, 158.3, 158.1, 132.8, 132.7, 131.4, 130.4, 129.5, 124.6, 120.5, 120.3, 114.0, 112.4, 69.1, 68.4, 62.4, 28.4, 28.2, 27.2, 26.4, 26.2; FTIR (neat): 1714, 1598, 1249, 1125 cm⁻¹; HRMS (ESI-TOF) *m/z*; [M + Na]⁺ calcd for C₂₁H₂₄O₄Na, 363.1572, found 363.1565.

6,7,8,9,10,11,12,13-Octahydro-19H,21H-dibenzo[b,g][1,5,9]-trioxacycloheptadecin-19-one (2h).²⁵ Prepared according to general procedure D; a solution of **1h** (0.015 M, 55 mg) and Mukaiyama salt (0.036 M, 91.8 mg) was dissolved with ACN in a vial. 1-Methylimidazole (0.03 M, 25 mg) was dissolved in another vial with ACN. Both the reagent solutions were flowed through 7 mL PFA tubing in an 80 °C preheated water bath at 3–4 bar pressure. After workup, the residue was purified by using column chromatography with EtOAc/*n*-hexane = 10:90 as the eluent to afford the desired product **2h** (31.6 mg, 60.3% yield) as a solid and the starting material **1h** (6.5 mg, 17%) was recovered. Melting point: 75–76 °C; ¹H NMR (400 MHz, CDCl₃) δ 7.65 (dd, *J* = 7.7, 1.7 Hz, 1H), 7.43 (dd, *J* = 7.4, 1.6 Hz, 1H), 7.40–7.34 (m, 1H), 7.30 (td, *J* = 8.1, 1.7 Hz, 1H), 6.95 (dd, *J* = 8.9, 1.3 Hz, 1H), 6.92 (dd, *J* = 4.8, 1.8 Hz, 1H), 6.90–6.84 (m, 2H), 5.39 (s, 2H), 4.10 (t, 2H), 3.98 (t, 2H), 1.81–1.67 (m, 4H), 1.63–1.52 (m, 4H), 1.45–1.34 (m, 4H); ¹³C{¹H} NMR (101 MHz, CDCl₃) δ 166.9, 158.1, 157.9, 132.8, 132.1, 131.3, 130.3, 124.3, 121.6, 120.3, 119.8, 112.8, 111.6, 67.9, 67.7, 62.6, 29.1, 28.6, 28.2, 27.3, 24.9, 24.6; FTIR (neat): 1720, 1597, 1243, 1123 cm⁻¹; HRMS (ESI-TOF) *m/z*; [M + Na]⁺ calcd for C₂₂H₂₆O₄Na, 377.1728, found 377.1727.

3,6,15-Trioxa-1(1,2),5(1,3)-dibenzenacyclopentadecaphan-2-one (2i).²⁵ Prepared according to general procedure D; a solution of **1i** (0.015 M, 55 mg) and Mukaiyama salt (0.036 M, 91.8 mg) was dissolved with ACN in a vial. 1-Methylimidazole (0.03 M, 25 mg) was dissolved in another vial with ACN. Both the reagent solutions were flowed through 7 mL PFA tubing in an 80 °C preheated water bath at 3–4 bar pressure. After workup, the residue was purified by using column chromatography with EtOAc/*n*-hexane = 10:90 as the eluent to afford the desired product **2i** (24.1 mg, 46% yield) as gummy liquid and the starting material **1i** (8.9 mg, 23%) was recovered; ¹H NMR (400 MHz, CDCl₃) δ 7.65 (dd, *J* = 7.7, 1.8 Hz, 1H), 7.43 (dd, *J* = 7.4, 1.7 Hz, 1H), 7.40–7.35 (m, 1H), 7.32–7.28 (m, 1H), 6.96–6.93 (m, 1H), 6.93–6.90 (m, 1H), 6.87 (dd, *J* = 10.4, 4.0 Hz, 2H), 5.39 (s, 2H), 4.10 (t, 2H), 3.97 (t, 2H), 1.76 (dt, *J* = 6.8, 6.0 Hz, 2H), 1.70 (dt, *J* = 10.3, 5.0 Hz, 4H), 1.63–1.52 (m, 4H), 1.44–1.33 (m, 2H); ¹³C{¹H} NMR (101 MHz, CDCl₃) δ 169.9, 158.1, 157.9, 132.8, 132.1, 131.3, 130.3, 124.3, 121.6, 120.2, 119.8, 112.8, 111.6, 67.9, 67.7, 62.6, 29.1, 28.6, 28.2, 27.3, 24.9, 24.6; FTIR (neat): 1724, 1594,

1278, 1163 cm^{-1} ; HRMS (ESI-TOF) m/z ; $[\text{M} + \text{Na}]^+$ calcd for $\text{C}_{22}\text{H}_{26}\text{O}_4\text{Na}$, 377.1729, found 377.1726.

6,7,8,9,10,11,12,13-Octahydro-19H,21H-dibenzo[b,g][1,5,9]-trioxacycloheptadecin-19-one (2j).²⁵ Prepared according to general procedure D; a solution of **1j** (0.015 M, 58 mg) and Mukaiyama salt (0.036 M, 91.8 mg) was dissolved with ACN in a vial. 1-Methylimidazole (0.03 M, 25 mg) was dissolved in another vial with ACN. Both the reagent solutions were flowed through 7 mL PFA tubing in an 80 °C preheated water bath at 3–4 bar pressure. After workup, the residue was purified by using column chromatography with EtOAc/*n*-hexane = 10:90 as the eluent to afford the desired product **2j** (30 mg, 54% yield) as a solid and the starting material **1j** (7.6 mg, 19%) was recovered. Melting point: 106–108 °C; ^1H NMR (400 MHz, CDCl_3) δ 7.68 (dd, J = 7.6, 1.7 Hz, 1H), 7.44 (dd, J = 7.5, 1.7 Hz, 1H), 7.38 (ddd, J = 8.5, 7.4, 1.8 Hz, 1H), 7.31–7.26 (m, 1H), 6.94 (ddd, J = 5.7, 5.0, 1.2 Hz, 2H), 6.88 (dd, J = 8.4, 7.6 Hz, 2H), 5.43 (s, 2H), 4.06 (t, 2H), 4.02 (t, 2H), 1.84–1.74 (m, 4H), 1.56–1.48 (m, 4H), 1.48–1.40 (m, J = 9.4, 5.3 Hz, 4H), 1.39–1.34 (m, J = 11.5, 5.6 Hz, 2H); $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3) δ 166.7, 158.4, 157.5, 132.9, 131.2, 129.9, 124.8, 121.5, 120.5, 119.9, 112.9, 111.9, 69.2, 68.8, 61.7, 29.6, 29.3, 29.1, 28.8, 28.4, 27.1, 26.6; FTIR (neat): 1717, 1600, 1295, 1126 cm^{-1} ; HRMS (ESI-TOF) m/z ; $[\text{M} + \text{Na}]^+$ calcd for $\text{C}_{23}\text{H}_{28}\text{O}_4\text{Na}$, 391.1885, found 391.1884.

6,7,8,9,10,11,12,13,14,15-Decahydro-21H,23H-dibenzo[b,g][1,5,9]trioxacyclononadecin-21-one (2k). Prepared according to general procedure D; a solution of **1k** (0.015 M, 60 mg) and Mukaiyama salt (0.036 M, 91.8 mg) was dissolved with ACN in a vial. 1-Methylimidazole (0.03 M, 25 mg) was dissolved in another vial with ACN. Both the reagent solutions were flowed through 7 mL PFA tubing in an 80 °C preheated water bath at 3–4 bar pressure. After workup, the residue was purified by using column chromatography with EtOAc/*n*-hexane = 10:90 as the eluent to afford the desired product **2k** (22.8 mg, 40% yield) as a semisolid and the starting material **1k** (6.9 mg, 17%) was recovered; ^1H NMR (400 MHz, CDCl_3) δ 7.74 (dd, J = 7.7, 1.8 Hz, 1H), 7.41 (ddd, J = 9.3, 5.7, 1.9 Hz, 2H), 7.31–7.26 (m, 1H), 6.98–6.90 (m, 3H), 6.88 (dd, J = 9.0, 4.6 Hz, 1H), 5.42 (s, 2H), 4.06 (t, J = 5.4 Hz, 2H), 4.01 (t, J = 5.4 Hz, 2H), 1.77 (dt, J = 5.0, 3.8 Hz, 2H), 1.71 (dt, J = 10.6, 4.5 Hz, 2H), 1.63–1.50 (m, 4H), 1.37–1.29 (m, 8H); $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3) δ 166.3, 158.8, 157.2, 133.1, 131.4, 129.9, 129.4, 125.1, 121.1, 120.3, 119.9, 113.1, 111.6, 68.2, 68, 62.1, 28.8, 28.8, 27.9, 27.9, 27.6, 27.5, 25.6, 25.2; FTIR (neat): 2939, 2871, 1712, 1601, 1493, 1290, 1254 cm^{-1} ; HRMS (ESI-TOF) m/z ; $[\text{M} + \text{Na}]^+$ calcd for $\text{C}_{24}\text{H}_{30}\text{O}_4\text{Na}$, 405.2041, found 405.2039.

((Pentane-1,5-diylbis(oxy))bis(2,1-phenylene))dimethanol (5a).²⁹ Prepared according to general procedure B using 2-(hydroxymethyl)-phenol (500 mg, 4.03 mmol), potassium carbonate (K_2CO_3) (556 mg, 4.03 mmol), and 1,5-dibromopentane (926.1 mg, 4.03 mmol). The residue was purified by using column chromatography with EtOAc/*n*-hexane = 40:60 as the eluent to afford desired product (**5a**) (700 mg, 2.21 mmol, 55% yield) as a solid. Melting point: 59–61 °C; ^1H NMR (400 MHz, CDCl_3) δ 7.29 (dd, J = 8.8, 4.5 Hz, 2H), 7.26–7.22 (m, 2H), 6.94 (t, J = 7.4 Hz, 2H), 6.87 (d, J = 8.2 Hz, 2H), 4.70 (s, 4H), 4.05 (t, J = 5.9 Hz, 4H), 2.88 (s, 2H), 1.98–1.84 (m, 4H), 1.77–1.65 (m, 2H); $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3) δ 156.8, 129.3, 128.9, 128.8, 120.7, 111.2, 67.7, 62.0, 29.1, 23.1; HRMS (ESI-TOF) m/z ; $[\text{M} + \text{Na}]^+$ calcd for $\text{C}_{19}\text{H}_{24}\text{O}_4\text{Na}$, 339.1572, found 339.1566.

((Propane-1,3-diylbis(oxy))bis(2,1-phenylene))dimethanol (5b).²⁹ Prepared according to general procedure B using 2-(hydroxymethyl)-phenol (500 mg, 4.03 mmol), potassium carbonate (K_2CO_3) (556 mg, 4.03 mmol), and 1,3-dibromopropane (569.2 mg, 2.82 mmol). The residue was purified by using column chromatography with EtOAc/*n*-hexane = 40:60 as the eluent to afford desired product (**5b**) (1.04 mg, 3.61 mmol, 89% yield) as a solid. Melting point: 94–95 °C; ^1H NMR (400 MHz, CDCl_3) δ 7.28 (d, J = 6.4 Hz, 2H), 7.27–7.23 (m, 2H), 6.96 (d, J = 7.4 Hz, 2H), 6.90 (d, J = 8.1 Hz, 2H), 4.67 (s, 2H), 4.66 (s, 2H), 4.23 (t, J = 5.9 Hz, 4H), 2.52 (s, 2H), 2.34 (p, J = 5.9 Hz, 2H); $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3) δ

156.6, 129.3, 129.1, 121.1, 111.4, 65.2, 61.9, 29.4; HRMS (ESI-TOF) m/z ; $[\text{M} + \text{Na}]^+$ calcd for $\text{C}_{17}\text{H}_{20}\text{O}_4\text{Na}$, 311.1260 found, 311.1258.

((Butane-1,4-diylbis(oxy))bis(2,1-phenylene))dimethanol (5c).²⁹ Prepared according to general procedure B using 2-(hydroxymethyl)-phenol (500 mg, 4.03 mmol), potassium carbonate (K_2CO_3) (556 mg, 4.03 mmol), and 1,4-dibromobutane (608.7 mg, 2.82 mmol). The residue was purified by using column chromatography with EtOAc/*n*-hexane = 40:60 as the eluent to afford desired product (**5c**) (1.02 g, 3.37 mmol, 84% yield) as a solid. Melting point: 94–95 °C; ^1H NMR (400 MHz, CDCl_3) δ 7.28 (d, J = 1.5 Hz, 1H), 7.27–7.25 (m, 1H), 7.23 (dd, J = 7.5, 2.1 Hz, 2H), 6.93 (td, J = 7.5, 0.9 Hz, 2H), 6.86 (d, J = 8.2 Hz, 2H), 4.65 (s, 2H), 4.11–4.06 (m, 4H), 2.55 (s, 2H), 2.04–1.99 (m, 4H); $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3) δ 156.7, 129.2, 129.0, 128.9, 120.8, 111.2, 67.5, 62.0, 26.3; HRMS (ESI-TOF) m/z ; $[\text{M} + \text{Na}]^+$ calcd for $\text{C}_{18}\text{H}_{22}\text{O}_4\text{Na}$, 325.1415, found 325.1409.

((Hexane-1,6-diylbis(oxy))bis(2,1-phenylene))dimethanol (5d).²⁹ Prepared according to general procedure B using 2-(hydroxymethyl)-phenol (500 mg, 4.03 mmol), potassium carbonate (K_2CO_3) (556 mg, 4.03 mmol), and 1,6-dibromohexane (687.8 mg, 2.82 mmol). The residue was purified by using column chromatography with EtOAc/*n*-hexane = 40:60 as the eluent to afford desired product (**5d**) (1.03 g, 3.12 mmol, 77% yield) as a solid. Melting point: 63–64 °C; ^1H NMR (400 MHz, CDCl_3) δ 7.31–7.22 (m, 4H), 6.94 (t, J = 7.4 Hz, 2H), 6.87 (d, J = 8.0 Hz, 2H), 4.68 (s, 4H), 4.03 (t, J = 6.3 Hz, 4H), 2.61 (s, 2H), 1.90–1.81 (m, 4H), 1.61–1.53 (m, 4H); $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3) δ 156.9, 129.2, 128.93, 128.7, 120.6, 111.1, 67.8, 62.1, 29.2, 26.0; HRMS (ESI-TOF) m/z ; $[\text{M} + \text{Na}]^+$ calcd for $\text{C}_{20}\text{H}_{26}\text{O}_4\text{Na}$, 353.1728, found 353.1719.

((Heptane-1,7-diylbis(oxy))bis(2,1-phenylene))dimethanol (5e).²⁹ Prepared according to general procedure B using 2-(hydroxymethyl)-phenol (500 mg, 4.03 mmol), potassium carbonate (K_2CO_3) (556 mg, 4.03 mmol), and 1,7-dibromoheptane (727.4 mg, 2.82 mmol). The residue was purified by using column chromatography with EtOAc/*n*-hexane = 40:60 as the eluent to afford desired product (**5e**) (1.2 g, 3.48 mmol, 86% yield) as a solid. Melting point: 62–63 °C; ^1H NMR (400 MHz, CDCl_3) δ 7.30–7.27 (m, 2H), 7.26–7.23 (m, 2H), 6.94 (td, J = 7.4, 0.8 Hz, 2H), 6.87 (d, J = 8.1 Hz, 2H), 4.70 (s, 4H), 4.02 (t, J = 6.4 Hz, 4H), 2.58 (s, 2H), 1.83 (dt, J = 13.0, 6.6 Hz, 4H), 1.57–1.42 (m, 6H); $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3) δ 156.9, 129.2, 128.9, 128.7, 120.6, 111.1, 67.9, 62.3, 29.2, 29.10, 26.2; HRMS (ESI-TOF) m/z ; $[\text{M} + \text{Na}]^+$ calcd for $\text{C}_{21}\text{H}_{28}\text{O}_4\text{Na}$, 367.1885, found, 367.1880.

((Octane-1,8-diylbis(oxy))bis(2,1-phenylene))dimethanol (5f).²⁹ Prepared according to general procedure B using 2-(hydroxymethyl)-phenol (500 mg, 4.03 mmol), potassium carbonate (K_2CO_3) (556 mg, 4.03 mmol), and 1,8-dibromooctane (766.9 mg, 2.82 mmol). The residue was purified by using column chromatography with EtOAc/*n*-hexane = 40:60 as the eluent to afford desired product (**5f**) (1.23 g, 3.43 mmol, 85% yield) as a solid. Melting point: 69–70 °C; ^1H NMR (400 MHz, CDCl_3) δ 7.30–7.26 (m, 2H), 7.26–7.22 (m, 2H), 6.93 (td, J = 7.5, 0.9 Hz, 2H), 6.88 (d, J = 8.1 Hz, 2H), 4.70 (s, 2H), 4.69 (s, 2H), 4.02 (t, J = 6.4 Hz, 4H), 2.59 (s, 2H), 1.83 (dt, J = 14.4, 6.4 Hz, 4H), 1.54–1.45 (m, 4H), 1.45–1.38 (m, 4H); $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3) δ 156.9, 129.2, 128.9, 128.7, 120.6, 111.1, 67.9, 62.3, 29.4, 26.2; HRMS (ESI-TOF) m/z ; $[\text{M} + \text{Na}]^+$ calcd for $\text{C}_{22}\text{H}_{30}\text{O}_4\text{Na}$, 381.2041, found 381.2036.

((Octane-1,8-diylbis(oxy))bis(3,1-phenylene))dimethanol (5g).²⁹ Prepared according to general procedure B using 3-hydroxybenzyl alcohol (500 mg, 4.03 mmol), potassium carbonate (K_2CO_3) (556 mg, 4.03 mmol), and 1,8-dibromooctane (766.9 mg, 2.82 mmol). The residue was purified by using column chromatography with EtOAc/*n*-hexane = 40:60 as the eluent to afford desired product (**5g**) (1.23 g, 3.43 mmol, 85% yield) as a solid. Melting point: 66–67 °C; ^1H NMR (400 MHz, CDCl_3) δ 7.28–7.23 (m, 2H), 6.93–6.90 (m, 4H), 6.84–6.82 (m, 1H), 6.81 (d, J = 2.2 Hz, 1H), 4.66 (s, 4H), 3.96 (t, J = 6.5 Hz, 4H), 1.83–1.74 (m, 4H), 1.71 (s, 2H), 1.52–1.44 (m, 4H), 1.40 (dd, J = 6.9, 3.6 Hz, 4H); $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3) δ 159.6, 142.6, 129.7, 119.1, 113.9, 113.1, 68.1, 65.5, 29.4, 26.1; HRMS (ESI-TOF) m/z ; $[\text{M} + \text{Na}]^+$ calcd for $\text{C}_{22}\text{H}_{32}\text{O}_4\text{Na}$, 381.2041, found 381.2036.

*((Nonane-1,9-diylbis(oxy))bis(2,1-phenylene))dimethanol (5h).*²⁹

Prepared according to general procedure B using 2-(hydroxymethyl)-phenol (500 mg, 4.03 mmol), potassium carbonate (K_2CO_3) (556 mg, 4.03 mmol), and 1,9-dibromononane (806 mg, 2.82 mmol). The residue was purified by using column chromatography with EtOAc/*n*-hexane = 40:60 as the eluent to afford desired product **5h** (1.37 g, 3.68 mmol, 91% yield) as a solid. Melting point; 74–75 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.28–7.24 (m, 2H), 7.24–7.21 (m, 2H), 6.91 (t, J = 7.4 Hz, 2H), 6.86 (d, J = 7.9 Hz, 2H), 4.68 (s, 2H), 4.67 (s, 2H), 4.01 (t, J = 6.4 Hz, 4H), 2.43 (s, 2H), 1.85–1.76 (m, 4H), 1.51–1.41 (m, 4H), 1.38 (d, J = 15.1 Hz, 2H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 157.0, 129.2, 128.9, 128.7, 120.6, 111.2, 68.1, 62.4, 29.5, 29.4, 26.2; HRMS (ESI-TOF) m/z ; $[M + Na]^+$ calcd for $C_{23}H_{32}O_4Na$, 395.2198, found 395.2192.

*((Decane-1,10-diylbis(oxy))bis(2,1-phenylene))dimethanol (5i).*²⁹

Prepared according to general procedure B using 2-(hydroxymethyl)-phenol (500 mg, 4.03 mmol), potassium carbonate (K_2CO_3) (556 mg, 4.03 mmol), and 1,10-dibromononane (846 mg, 2.82 mmol). The residue was purified by using column chromatography with EtOAc/*n*-hexane = 40:60 as the eluent to afford desired product **5i** (1.21 g, 3.13 mmol, 77% yield) as a solid. Melting point; 73–75 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.26 (d, J = 6.6 Hz, 2H), 7.25–7.22 (m, 2H), 6.92 (t, J = 7.4 Hz, 2H), 6.87 (d, J = 8.0 Hz, 2H), 4.69 (s, 4H), 4.02 (t, J = 6.4 Hz, 4H), 2.49 (s, 2H), 1.85–1.77 (m, 4H), 1.46 (dd, J = 14.4, 6.7 Hz, 4H), 1.40–1.30 (m, J = 17.5 Hz, 8H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 157.1, 129.3, 129.0, 128.8, 120.6, 111.2, 68.1, 62.5, 29.5, 29.4, 29.4, 26.3; HRMS (ESI-TOF) m/z ; $[M + Na]^+$ calcd for $C_{24}H_{34}O_4Na$, 409.2355, found 409.2349.

(2-((5-(2-(Hydroxymethyl)-4-nitrophenoxy)pentyl)oxy)phenyl)methanol (5j). Prepared according to general procedure B using 2-((5-bromopentyl)oxy)phenyl)methanol (500 mg, 1.83 mmol), potassium carbonate (K_2CO_3) (252 mg, 1.83 mmol), and 2-(hydroxymethyl)-4-nitrophenol (309 mg, 1.83 mmol). The residue was purified by using column chromatography with EtOAc/*n*-hexane = 40:60 as the eluent to afford desired product **5j** (513 mg, 1.42 mmol, 77% yield) as a solid. Melting point; 79–78 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 8.28 (s, 1H), 8.16 (d, J = 9.0 Hz, 1H), 7.30–7.22 (m, 2H), 6.94 (t, J = 7.4 Hz, 1H), 6.88 (t, J = 8.7 Hz, 2H), 4.73 (s, 2H), 4.69 (s, 2H), 4.15 (t, J = 6.1 Hz, 2H), 4.07 (t, J = 6.0 Hz, 2H), 2.71 (s, 1H), 2.55 (s, 1H), 1.99–1.86 (m, 4H), 1.76–1.69 (m, 2H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 161.2, 156.8, 141.4, 130.7, 129.1, 128.9, 125.0, 123.7, 120.8, 111.2, 110.5, 68.7, 67.6, 62.1, 29.1, 28.8, 23.0; FTIR (neat): 3345, 2923, 1588, 1277, 1149 cm^{-1} ; HRMS (ESI-TOF) m/z ; $[M + Na]^+$ calcd for $C_{19}H_{23}NO_6Na$, 384.1422, found 384.1424.

(5-Bromo-2-((5-(2-(hydroxymethyl)phenoxy)pentyl)oxy)phenyl)methanol (5k). Prepared according to general procedure B using 2-((5-bromopentyl)oxy)phenyl)methanol (700 mg, 2.56 mmol), potassium carbonate (K_2CO_3) (254 mg, 2.56 mmol), and 4-bromo-2-(hydroxymethyl)phenol (520 mg, 2.56 mmol). The residue was purified by using column chromatography with EtOAc/*n*-hexane = 40:60 as the eluent to afford desired product **5k** (856 mg, 2.17 mmol, 84% yield) as a semisolid; ^1H NMR (400 MHz, $CDCl_3$) δ 7.46 (d, J = 2.5 Hz, 1H), 7.35 (dd, J = 8.7, 2.5 Hz, 1H), 7.31–7.25 (m, 2H), 6.99–6.93 (m, 1H), 6.89 (d, J = 8.1 Hz, 1H), 6.75 (d, J = 8.7 Hz, 1H), 4.71 (s, 2H), 4.66 (s, 2H), 4.08 (t, J = 6.1 Hz, 2H), 4.03 (t, J = 6.2 Hz, 2H), 1.95–1.86 (m, 4H), 1.75–1.66 (m, 2H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.8, 155.6, 131.6, 131.3, 129.1, 129.0, 128.9, 120.7, 112.9, 112.9, 111.1, 68.0, 67.6, 62.1, 60.9, 29.1, 28.9, 23.0; FTIR (neat): 3326, 2934, 1486, 1238, 734 cm^{-1} ; HRMS (ESI-TOF) m/z ; $[M + Na]^+$ calcd for $C_{19}H_{23}O_4BrNa$, 417.0677, found 417.0671.

3,7,10,16-Tetraoxa-1,9(1,2),5(1,3)-tribenzenacyclohexadecaphane-4,6-dione (7a). Prepared according to general procedure E; a solution of ((pentane-1,5-diylbis(oxy))bis(2,1-phenylene))-dimethanol **5a** (0.0075 M, 47.5 mg) was dissolved with ACN in a vial, and isophthalic acid (0.0075 M, 25 mg), Mukaiyama salt (0.036 M, 183 mg), and 1-methylimidazole (0.03 M, 49 mg) were dissolved

in another vial with ACN. Both reagent solutions were flowed through 7 mL PFA tubing in an 80 °C preheated water bath at 3–4 bar pressure. After workup, the residue was purified by using column chromatography with EtOAc/*n*-hexane = 10:90 as the eluent to afford the desired product **7a** (20 mg, 30% yield) as a solid and the starting material **5a** (5.1 mg, 16%) was recovered. Batch reaction: compound **5a** (0.0075 M, 47.5 mg), isophthalic acid (0.0075 M, 25 mg), Mukaiyama salt (0.036 M, 183 mg), and 1-methylimidazole (0.03 M, 49 mg) in ACN solvent were heated at 80 °C in a preheated oil path for 24 h to afford the desired product **7a** (9.2 mg, 13%). Melting point: 136–137 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 8.59 (t, J = 1.7 Hz, 1H), 8.21 (dd, J = 7.8, 1.6 Hz, 2H), 7.53–7.46 (m, 3H), 7.32 (td, J = 7.9, 1.7 Hz, 2H), 6.96 (dd, J = 7.6, 5.0 Hz, 4H), 5.43 (s, 4H), 4.08 (t, J = 5.1 Hz, 4H), 1.94–1.82 (m, 6H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 166.1, 158.7, 134.3, 132.9, 131.0, 130.6, 130.3, 128.6, 124.8, 120.7, 113.1, 69.2, 63.5, 30.1, 23.7; FTIR (neat): 2927, 2869, 1717, 1604, 1456, 1251 cm^{-1} ; HRMS (ESI-TOF) m/z ; $[M + H]^+$ calcd for $C_{27}H_{25}O_6$, 447.1807, found 447.1811.

3,7,10,14-Tetraoxa-1,9(1,2),5(1,3)-tribenzenacyclotetradecaphane-4,6-dione (7b). Prepared according to general procedure E; a solution of ((propane-1,3-diylbis(oxy))bis(2,1-phenylene))-dimethanol **5b** (0.0075 M, 43.2 mg) was dissolved with ACN in a vial, and of isophthalic acid (0.0075 M, 25 mg), Mukaiyama salt (0.036 M, 183 mg), and 1-methylimidazole (0.03 M, 49 mg) were dissolved in another vial with ACN. Both reagent solutions were flowed through 7 mL PFA tubing in an 80 °C preheated water bath at 3–4 bar pressure. After workup, the residue was purified by using column chromatography with EtOAc/*n*-hexane = 10:90 as the eluent to afford the desired product **7b** (22.2 mg, 35% yield) as a solid and the starting material **5b** (6.9 mg, 24%) was recovered. Batch reaction: compound **5b** (0.0075 M, 43.2 mg), isophthalic acid (0.0075 M, 25 mg), Mukaiyama salt (0.036 M, 183 mg), and 1-methylimidazole (0.03 M, 49 mg) in ACN solvent were heated at 80 °C in a preheated oil path for 24 h to afford the desired product **7b** (10.3 mg, 16%). Melting point: 175–176 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 8.72 (t, J = 1.6 Hz, 1H), 8.21 (dd, J = 7.8, 1.7 Hz, 2H), 7.51 (t, J = 7.8 Hz, 1H), 7.43 (dd, J = 7.4, 1.7 Hz, 2H), 7.36 (td, J = 8.1, 1.7 Hz, 2H), 6.98 (td, J = 7.5, 2.6 Hz, 4H), 5.38 (s, 4H), 4.33 (t, J = 6.8 Hz, 4H), 2.40 (p, J = 6.7 Hz, 2H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 165.7, 158.9, 134.01, 132.1, 130.9, 130.9, 130.7, 128.8, 124.9, 121.1, 113.5, 66.7, 64.3, 31.1; FTIR (neat): 2948, 2858, 1745, 1604, 1300, 1251 cm^{-1} ; HRMS (ESI-TOF) m/z ; $[M + H]^+$ calcd for $C_{25}H_{23}O_6$, 419.1494, found 419.1487.

3,7,10,15-Tetraoxa-1,9(1,2),5(1,3)-tribenzenacyclopentadecaphane-4,6-dione (7c). Prepared according to general procedure E; a solution of ((butane-1,4-diylbis(oxy))bis(2,1-phenylene))-dimethanol **5c** (0.0075 M, 43.2 mg) was dissolved with ACN in a vial, and isophthalic acid (0.0075 M, 25 mg), Mukaiyama salt (0.036 M, 183 mg), and 1-methylimidazole (0.03 M, 49 mg) were dissolved in another vial with ACN. Both reagent solutions were flowed through 7 mL PFA tubing in an 80 °C preheated water bath at 3–4 bar pressure. After workup, the residue was purified by using column chromatography with EtOAc/*n*-hexane = 10:90 as the eluent to afford desired product **7c** (21.6 mg, 33% yield) as a solid and the starting material **5c** (12 mg, 39%) was recovered. Melting point: 122–123 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 8.58 (t, J = 1.6 Hz, 1H), 8.22 (dd, J = 7.8, 1.6 Hz, 2H), 7.51 (dd, J = 7.3, 1.7 Hz, 2H), 7.48 (d, J = 7.8 Hz, 1H), 7.32 (td, J = 8.0, 1.7 Hz, 2H), 6.95–6.91 (m, 2H), 6.90 (d, J = 8.1 Hz, 2H), 5.45 (s, 4H), 4.14 (dd, J = 7.9, 2.9 Hz, 4H), 2.18–2.13 (m, 4H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 166.1, 158.2, 134.3, 132.9, 131.1, 130.6, 130, 128.6, 123.9, 120.2, 110.9, 66.9, 63.2, 25.8; FTIR (neat): 2919, 2851, 1715, 1699, 1225, 1201 cm^{-1} ; HRMS (ESI-TOF) m/z ; $[M + Na]^+$ calcd for $C_{26}H_{24}O_6Na$, 455.1470, found 455.1483.

14,15,16,17-Tetrahydro-7H,13H,23H-tribenzo[b,g,l][1,5,10,14]-tetraoxacyclononadecine-5,25-dione (7d). Prepared according to general procedure E; a solution of ((pentane-1,5-diylbis(oxy))bis(2,1-phenylene))-dimethanol **5a** (0.0075 M, 47.4 mg) was dissolved with ACN in a vial, and phthalic acid (0.0075 M, 25 mg), Mukaiyama salt (0.036 M, 183 mg), and 1-methylimidazole (0.03 M, 49 mg) were dissolved in another vial with ACN. Both reagent solutions were

flowed through 7 mL PFA tubing in an 80 °C preheated water bath at 3–4 bar pressure. After workup, the residue was purified by using column chromatography with EtOAc/*n*-hexane = 10:90 as the eluent to afford desired product **7d** (21.2 mg, 32% yield) as a solid and the starting material **5a** (5.3, 17%) was recovered. Melting point: 135–138 °C; ¹H NMR (400 MHz, CDCl₃) δ 7.64 (dt, *J* = 6.2, 3.1 Hz, 2H), 7.41 (dd, *J* = 5.7, 3.2 Hz, 2H), 7.32 (d, *J* = 7.5 Hz, 2H), 7.23–7.17 (m, 2H), 6.87 (t, *J* = 7.4 Hz, 2H), 6.80 (d, *J* = 8.3 Hz, 2H), 5.34 (s, 4H), 3.98 (t, *J* = 5.4 Hz, 4H), 1.86–1.77 (m, 4H), 1.71 (dd, *J* = 14.1, 7.2 Hz, 2H); ¹³C{¹H} NMR (100 MHz, CDCl₃) δ 167.9, 157.2, 132.5, 131.1, 130.6, 129.8, 129.1, 124.3, 120.6, 111.7, 68.3, 62.5, 29.3, 23.9; FTIR (neat): 2937, 2869, 1716, 1601, 1450, 1253 cm^{−1}; HRMS (ESI-TOF) *m/z*; [M + Na]⁺ calcd for C₂₇H₂₆O₆Na, 469.1623, found 449.1616.

3,7,10,17-Tetraoxa-1,9(1,2),5(1,3)-tribenzenacycloheptadecaphane-4,6-dione (7e). Prepared according to general procedure E; a solution of ((hexane-1,6-diylbis(oxy))bis(2,1-phenylene))dimethanol **5d** (0.0075 M, 49.5 mg) was dissolved with ACN in a vial, and isophthalic acid (0.0075 M, 25 mg), Mukaiyama salt (0.036 M, 183 mg), and 1-methylimidazole (0.03 M, 49 mg) were dissolved in another vial with ACN. Both reagent solutions were flowed through 7 mL PFA tubing in an 80 °C preheated water bath at 3–4 bar pressure. After workup, the residue was purified by using column chromatography with EtOAc/*n*-hexane = 10:90 as the eluent to afford the desired product **7e** (22.4 mg, 32% yield) as a solid and the starting material **5d** (6.4 mg, 19%) was recovered. Melting point: 158–160 °C; ¹H NMR (400 MHz, CDCl₃) δ 8.68 (t, *J* = 1.7 Hz, 1H), 8.16 (dd, *J* = 7.8, 1.7 Hz, 2H), 7.44 (s, 1H), 7.41 (dd, *J* = 7.4, 1.5 Hz, 2H), 7.35–7.30 (m, 2H), 6.95 (dd, *J* = 7.4, 0.8 Hz, 2H), 6.88 (d, *J* = 8.2 Hz, 2H), 5.43 (s, 4H), 3.99 (t, *J* = 6.2 Hz, 4H), 1.73–1.63 (m, 4H), 1.45–1.40 (m, 4H); ¹³C{¹H} NMR (100 MHz, CDCl₃) δ 165.9, 158.3, 133.8, 132.2, 131.2, 131.0, 130.6, 128.5, 124.2, 120.2, 111.6, 67.8, 63.9, 29.0, 25.6; FTIR (neat): 2937, 2860, 1716, 1294, 1253 cm^{−1}; HRMS (ESI-TOF) *m/z*; [M + Na]⁺ calcd for C₂₈H₂₈O₆Na, 483.1783, found 483.1782.

3,7,10,18-Tetraoxa-1,9(1,2),5(1,3)-tribenzenacyclooctadecaphane-4,6-dione (7f). Prepared according to general procedure E; a solution of ((heptane-1,7-diylbis(oxy))bis(2,1-phenylene))-dimethanol **5e** (0.0075 M, 51.6 mg) was dissolved with ACN in a vial, and isophthalic acid (0.0075 M, 25 mg), Mukaiyama salt (0.036 M, 183 mg), and 1-methylimidazole (0.03 M, 49 mg) were dissolved in another vial with ACN. Both reagent solutions were flowed through 7 mL PFA tubing in an 80 °C preheated water bath at 3–4 bar pressure. After workup, the residue was purified by using column chromatography with EtOAc/*n*-hexane = 10:90 as the eluent to afford the desired product **7f** (32.6 mg, 46% yield) as a solid and the starting material **5e** (9.8 mg, 28%) was recovered. Melting point: 169–171 °C; ¹H NMR (400 MHz, CDCl₃) δ 8.72 (t, *J* = 1.6 Hz, 1H), 8.16 (dd, *J* = 7.8, 1.8 Hz, 2H), 7.44 (d, *J* = 7.8 Hz, 1H), 7.39 (dd, *J* = 7.4, 1.8 Hz, 2H), 7.37–7.32 (m, 2H), 6.95 (td, *J* = 7.3, 0.8 Hz, 2H), 6.89 (d, *J* = 8.2 Hz, 2H), 5.40 (s, 4H), 3.94 (t, *J* = 5.4 Hz, 4H), 1.71–1.63 (m, 4H), 1.25–1.19 (m, *J* = 6.8 Hz, 6H); ¹³C{¹H} NMR (100 MHz, CDCl₃) δ 165.8, 158.5, 133.8, 131.9, 131.1, 131.1, 130.6, 128.4, 124.1, 120.1, 111.6, 68.2, 64.1, 30.4, 30.0, 26.8; FTIR (neat): 2932, 2855, 1721, 1605, 1254, 1227 cm^{−1}; HRMS (ESI-TOF) *m/z*; [M + Na]⁺ calcd for C₂₉H₃₀O₆Na, 497.1939, found 497.1939; Crystal preparation: The crystals are grown by a simple recrystallization method where pure compounds are isolated after column chromatography, dissolved in dichloromethane, layered with hexane, and kept at room temperature to get compound **7f** as a pure crystal. More information on crystal structures can also be obtained from the Cambridge Crystallographic Data Centre (CCDC) with deposition number 2176849.

3,7,10,19-Tetraoxa-1,9(1,2),5(1,3)-tribenzenacyclononadecaphane-4,6-dione (7g). Prepared according to general procedure E; a solution of ((octane-1,8-diylbis(oxy))bis(2,1-phenylene))dimethanol **5f** (0.0075 M, 53.7 mg) was dissolved with ACN in a vial, and isophthalic acid (0.0075 M, 25 mg), Mukaiyama salt (0.036 M, 183 mg), and 1-methylimidazole (0.03 M, 49 mg) were dissolved in another vial with ACN. Both reagent solutions were flowed through 7

mL PFA tubing in an 80 °C preheated water bath at 3–4 bar pressure. After workup, the residue was purified by using column chromatography with EtOAc/*n*-hexane = 10:90 as the eluent to afford the desired product **7g** (23.8 mg, 32% yield) as a solid and the starting material **5f** (12.2 mg, 34%) was recovered. Melting point: 107–108 °C; ¹H NMR (400 MHz, CDCl₃) δ 8.70 (t, *J* = 1.7 Hz, 1H), 8.17 (dd, *J* = 7.8, 1.8 Hz, 2H), 7.43 (t, *J* = 7.8 Hz, 1H), 7.39–7.33 (m, 4H), 6.96 (td, *J* = 7.4, 0.8 Hz, 2H), 6.94–6.88 (m, 2H), 5.37 (s, 4H), 3.98 (t, *J* = 5.9 Hz, 4H), 1.62–1.55 (m, 4H), 1.27–1.21 (m, 4H), 1.00–0.93 (m, 4H); ¹³C{¹H} NMR (100 MHz, CDCl₃) δ 165.9, 158.5, 133.8, 131.8, 131.4, 131.0, 130.6, 128.4, 124.2, 120.3, 112.1, 68.1, 64.3, 29.5, 29.2, 26.0; FTIR (neat): 2923, 2853, 1721, 1605, 1290, 1252 cm^{−1}; HRMS (ESI-TOF) *m/z*; [M + Na]⁺ calcd for C₃₀H₃₂O₆Na, 511.2096, found 511.2097.

3,7,10,19-Tetraoxa-1,5,9(1,3)-tribenzenacyclononadecaphane-4,6-dione (7h). Prepared according to general procedure E; a solution of ((octane-1,8-diylbis(oxy))bis(3,1-phenylene))dimethanol **5g** (0.0075 M, 53.7 mg) was dissolved with ACN in a vial, and isophthalic acid (0.0075 M, 25 mg), Mukaiyama salt (0.036 M, 183 mg), and 1-methylimidazole (0.03 M, 49 mg) were dissolved in another vial with ACN. Both reagent solutions were flowed through 7 mL PFA tubing in an 80 °C preheated water bath at 3–4 bar pressure. After workup, the residue was purified by using column chromatography with EtOAc/*n*-hexane = 10:90 as the eluent to afford the desired product **7h** (11.4 mg, 15% yield) as a solid and the starting material **5h** (15.5 mg, 43%) was recovered. Melting point: 112–113 °C; ¹H NMR (400 MHz, CDCl₃) δ 8.69 (t, *J* = 1.6 Hz, 1H), 8.25 (dd, *J* = 7.8, 1.8 Hz, 2H), 7.51 (t, *J* = 7.8 Hz, 1H), 7.25–7.21 (m, 2H), 6.98 (d, *J* = 2.0 Hz, 2H), 6.96 (d, *J* = 7.7 Hz, 2H), 6.83 (dd, *J* = 8.2, 2.5 Hz, 2H), 5.34 (s, 4H), 3.93 (t, *J* = 6.0 Hz, 4H), 1.77–1.68 (m, 4H), 1.49–1.40 (m, 4H), 1.38–1.31 (m, 4H); ¹³C{¹H} NMR (100 MHz, CDCl₃) δ 165.8, 159.6, 137.5, 134.4, 130.9, 130.7, 129.6, 128.8, 120.9, 115.2, 114.1, 67.7, 67.0, 29.1, 28.8, 25.7; FTIR (neat): 2937, 2855, 1706, 1227 cm^{−1}; HRMS (ESI-TOF) *m/z*; [M + Na]⁺ calcd for C₃₀H₃₂O₆Na, 511.2096, found 511.2093.

3,7,10,20-Tetraoxa-1,9(1,2),5(1,3)-tribenzenacycloicosaphane-4,6-dione (7i). Prepared according to general procedure E; a solution of ((nonane-1,9-diylbis(oxy))bis(2,1-phenylene))dimethanol **5h** (0.0075 M, 55.8 mg) was dissolved with ACN in a vial, and isophthalic acid (0.0075 M, 25 mg), Mukaiyama salt (0.036 M, 183 mg), and 1-methylimidazole (0.03 M, 49 mg) were dissolved in another vial with ACN. Both reagent solutions were flowed through 10 mL PFA tubing in an 80 °C preheated water bath at 3–4 bar pressure. After workup, the residue was purified by using column chromatography with EtOAc/*n*-hexane = 10:90 as the eluent to afford the desired product **7i** (37 mg, 49% yield) as a solid and the starting material **5h** (8.9 mg, 24%) was recovered. Melting point: 167–169 °C; ¹H NMR (400 MHz, CDCl₃) δ 8.77 (t, *J* = 1.5 Hz, 1H), 8.15 (dd, *J* = 7.8, 1.7 Hz, 2H), 7.41 (d, *J* = 7.8 Hz, 1H), 7.38–7.33 (m, 4H), 6.95 (td, *J* = 7.5, 0.9 Hz, 2H), 6.88 (d, *J* = 8.5 Hz, 2H), 5.35 (s, 4H), 3.95 (t, *J* = 5.5 Hz, 4H), 1.66–1.60 (m, 4H), 1.22–1.12 (m, *J* = 9.4, 7.5 Hz, 4H), 1.09–0.98 (m, *J* = 10.8, 7.6 Hz, 4H), 0.57–0.46 (m, *J* = 15.5, 7.8 Hz, 2H); ¹³C{¹H} NMR (100 MHz, CDCl₃) δ 165.9, 158.5, 133.9, 131.8, 131.3, 131.1, 130.7, 128.4, 123.7, 120.1, 111.2, 67.6, 64.4, 29.7, 29.6, 29.5, 26.8; FTIR (neat): 2924, 2853, 1715, 1255, 1225 cm^{−1}; HRMS (ESI-TOF) *m/z*; [M + H]⁺ calcd for C₃₁H₃₅O₆, 503.2434, found 503.2436.

3,7,10,21-Tetraoxa-1,9(1,2),5(1,3)-tribenzenacycloheneicosaphane-4,6-dione (7j). Prepared according to general procedure E; a solution of ((decane-1,10-diylbis(oxy))bis(2,1-phenylene))-dimethanol **5i** (0.0075 M, 58 mg) with ACN in a vial, and isophthalic acid (0.0075 M, 25 mg), Mukaiyama salt (0.036 M, 183 mg), and 1-methylimidazole (0.03 M, 49 mg) were dissolved in another vial with ACN. Both reagent solutions were flowed through 7 mL PFA tubing in an 80 °C preheated water bath at 3–4 bar pressure. After workup, the residue was purified by using column chromatography with EtOAc/*n*-hexane = 10:90 as the eluent to afford the desired product **7j** (43.9 mg, 57% yield) as a solid and the starting material **5i** (11 mg, 28%) was recovered. Melting point: 167–169 °C; ¹H NMR (400 MHz, CDCl₃) δ 8.72 (t, *J* = 1.7 Hz, 1H), 8.18 (dd, *J* = 7.8, 1.8 Hz,

2H), 7.43 (t, $J = 7.8$ Hz, 1H), 7.38–7.34 (m, 4H), 7.01–6.88 (m, 4H), 5.35 (s, 4H), 4.01 (t, $J = 5.6$ Hz, 4H), 1.80–1.51 (m, $J = 11.1$, 9.5, 5.8 Hz, 4H), 1.33–1.26 (m, $J = 15.5$, 7.5, 5.0 Hz, 4H), 1.13–1.06 (m, $J = 10.1$, 4.9 Hz, 4H), 0.87–0.81 (m, 4H); $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3) δ 165.9, 158.5, 133.9, 131.7, 131.3, 130.9, 130.6, 128.4, 123.9, 120.2, 111.8, 68.2, 64.3, 29.6, 29.1, 26.5; FTIR (neat): 2925, 2853, 1714, 1253, 1228 cm^{-1} ; HRMS (ESI-TOF) m/z ; $[\text{M} + \text{Na}]^+$ calcd for $\text{C}_{32}\text{H}_{36}\text{O}_6\text{Na}$, 539.2410, found 539.2415.

15-Nitro-3,7,10,16-tetraoxa-1,9(1,2),5(1,3)-tribenzenacyclohexadecaphane-4,6-dione (7k). Prepared according to general procedure E; a solution of (2-((5-(2-(hydroxymethyl)-4-nitrophenoxy)pentyl)-oxy)phenyl)methanol **5j** (0.0075 M, 58 mg) was dissolved with ACN in a vial, and isophthalic acid (0.0075 M, 25 mg), Mukaiyama salt (0.036 M, 183 mg), and 1-methylimidazole (0.03 M, 49 mg) were dissolved in another vial with ACN. Both reagent solutions were flowed through 7 mL PFA tubing in an 80 °C preheated water bath at 3–4 bar pressure. After workup, the residue was purified by using column chromatography with EtOAc/*n*-hexane = 10:90 as the eluent to afford the desired product **5j** (27.4 mg, 37% yield) as a solid. Melting point: 180–183 °C; ^1H NMR (400 MHz, CDCl_3) δ 8.56 (t, $J = 1.5$ Hz, 1H), 8.42 (d, $J = 2.8$ Hz, 1H), 8.25 (dd, $J = 8.2$, 2.0 Hz, 1H), 8.21 (ddd, $J = 9.3$, 4.6, 3.1 Hz, 2H), 7.54–7.46 (m, 2H), 7.36–7.29 (m, 1H), 6.96 (ddd, $J = 6.5$, 5.9, 4.1 Hz, 3H), 5.45 (s, 2H), 5.43 (s, 2H), 4.19 (t, $J = 5.3$ Hz, 2H), 4.09 (t, $J = 5.3$ Hz, 2H), 1.99–1.83 (m, $J = 18.5$, 9.7 Hz, 6H); $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, CDCl_3) δ 165.9, 165.8, 163.5, 158.7, 141.0, 134.6, 134.4, 133.1, 131.0, 130.7, 130.4, 130.2, 128.8, 128.6, 126.9, 125.2, 124.9, 120.9, 113.3, 111.7, 69.6, 69.3, 63.5, 62.4, 30.2, 29.8, 23.7; FTIR (neat): 2944, 2870, 1716, 1300, 1269 cm^{-1} ; HRMS (ESI-TOF) m/z ; $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{27}\text{H}_{26}\text{O}_8$, 492.1658, found 492.1657.

15-Bromo-3,7,10,16-tetraoxa-1,9(1,2),5(1,3)-tribenzenacyclohexadecaphane-4,6-dione (7l). Prepared according to general procedure E; a solution of (5-bromo-2-((5-(2-(hydroxymethyl)phenoxy)pentyl)oxy)phenyl)methanol **5k** (0.0075 M, 58 mg) was dissolved with ACN in a vial, and isophthalic acid (0.0075 M, 25 mg), Mukaiyama salt (0.036 M, 183 mg), and 1-methylimidazole (0.03 M, 49 mg) were dissolved in another vial with ACN. Both reagent solutions were flowed through 7 mL PFA tubing in an 80 °C preheated water bath at 3–4 bar pressure. After workup, the residue was purified by using column chromatography with EtOAc/*n*-hexane = 10:90 as the eluent to afford the desired product **7l** (30.4 mg, 38% yield) as a solid. Melting point: 137–138 °C; ^1H NMR (400 MHz, CDCl_3) δ 8.57 (s, 1H), 8.25–8.18 (m, 2H), 7.63 (d, $J = 2.0$ Hz, 1H), 7.53–7.46 (m, 2H), 7.41 (dd, $J = 8.7$, 1.8 Hz, 1H), 7.32 (t, $J = 7.8$ Hz, 1H), 6.95 (t, $J = 7.2$ Hz, 2H), 6.82 (d, $J = 8.7$ Hz, 1H), 5.43 (s, 2H), 5.36 (s, 2H), 4.08 (t, $J = 4.5$ Hz, 2H), 4.04 (t, $J = 5.0$ Hz, 2H), 1.94–1.80 (m, 6H); $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3) δ 166, 165.9, 158.7, 157.8, 135.4, 134.4, 134.3, 133.2, 132.9, 131.0, 130.7, 130.6, 130.2, 128.7, 126.8, 124.8, 120.8, 114.7, 113.1, 112.7, 69.5, 69.1, 63.4, 62.6, 30.1, 30.0, 23.7; FTIR (neat): 2944, 2869, 1716, 1250, 1226 cm^{-1} ; HRMS (ESI-TOF) m/z ; $[\text{M} + \text{Na}]^+$ calcd for $\text{C}_{27}\text{H}_{25}\text{O}_6\text{Br}$, 547.0732, found 547.0727.

6,7,8,9,10,11,20,21-Octahydro-17H,24H-dibenzo[b,l][1,5,10,14]-tetraoxacycloicosine-19,22-dione (8a). Prepared according to general procedure E; a solution of ((hexane-1,6-diylbis(oxy))bis-(2,1-phenylene))dimethanol **5d** (0.0075 M, 49.5 mg) was dissolved with ACN in a vial, and succinic acid (0.0075 M, 17.7 mg), Mukaiyama salt (0.036 M, 183 mg), and 1-methylimidazole (0.03 M, 49 mg) were dissolved in another vial with ACN. Both reagent solutions were flowed through 7 mL PFA tubing in an 80 °C preheated water bath at 3–4 bar pressure. After workup, the residue was purified by using column chromatography with EtOAc/*n*-hexane = 5:95 as the eluent to afford the desired product **8a** (21.4 mg, 35% yield) as a solid and the starting material **5d** (5.6 mg, 17%) was recovered. Melting point: 156–157 °C; ^1H NMR (400 MHz, CDCl_3) δ 7.30 (ddd, $J = 5.4$, 4.8, 1.7 Hz, 3H), 7.27–7.23 (m, 1H), 6.94–6.87 (m, 3H), 6.86 (d, $J = 3.0$ Hz, 1H), 5.15 (s, 4H), 4.00 (t, $J = 5.9$ Hz, 4H), 2.65 (s, 4H), 1.79 (dd, $J = 13.2$, 6.0 Hz, 4H), 1.61–1.51 (m, 4H); $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3) δ 172.1, 158.3, 131.6, 130.5, 124.1, 120.3, 111.8, 77.5, 76.8, 67.9, 63.4, 29.4, 29.4, 25.9;

FTIR (neat): 2926, 2857, 1710, 1291, 1152 cm^{-1} ; HRMS (ESI-TOF) m/z ; $[\text{M} + \text{Na}]^+$ calcd for $\text{C}_{24}\text{H}_{28}\text{O}_6\text{Na}$, 435.1783, found 435.1781.

2,2'-(Pentane-1,5-diylbis(oxy))dibenzoic acid (9a). Prepared according to general procedure C; a 1,4-dioxane (4.0 mL) solution of diethyl 2,2'-(pentane-1,5-diylbis(oxy))dibenzoate **SI** (300 mg, 0.75 mmol) and a 5N NaOH solution (10.0 mL) were added. The reaction mixture was stirred at 80 °C in an oil bath overnight. After, the residue was purified by using column chromatography with EtOAc/*n*-hexane = 60:40 as the eluent to afford **9a** (210 mg, 81% yield) as a solid. Melting point: 106–107 °C; ^1H NMR (400 MHz, CDCl_3) δ 8.16 (dd, $J = 7.8$, 1.8 Hz, 2H), 7.55 (ddd, $J = 8.4$, 7.4, 1.8 Hz, 2H), 7.16–7.09 (m, 2H), 7.04 (d, $J = 8.2$ Hz, 2H), 4.29 (t, $J = 6.4$ Hz, 4H), 2.03 (dt, $J = 14.5$, 6.5 Hz, 4H), 1.78–1.68 (m, $J = 10.4$, 6.5 Hz, 2H); $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3) δ 165.9, 165.8, 157.6, 135.2, 133.8, 122.3, 117.9, 112.8, 69.7, 28.7, 22.6; FTIR (neat): 3291, 2941, 1726, 1601, 1456 cm^{-1} ; HRMS (ESI-TOF) m/z ; $[\text{M} + \text{Na}]^+$ calcd for $\text{C}_{19}\text{H}_{20}\text{O}_6\text{Na}$, 367.1153, found 367.1155.

2,2'-(Nonane-1,9-diylbis(oxy))dibenzoic Acid (9b). Prepared according to general procedure C; a 1,4-dioxane (4.0 mL) solution of diethyl 2,2'-(nonane-1,9-diylbis(oxy))dibenzoate **SI** (650 mg, 1.42 mmol) and a 5N NaOH solution (10.0 mL) were added. The reaction mixture was stirred at 80 °C in an oil bath overnight. After, the residue was purified by using column chromatography with EtOAc/*n*-hexane = 60:40 as the eluent to afford **9b** (510 mg, 89% yield) as a solid. Melting point: 92–94 °C; ^1H NMR (400 MHz, CDCl_3) δ 8.17 (dd, $J = 7.8$, 1.3 Hz, 2H), 7.55 (dd, $J = 11.2$, 4.5 Hz, 2H), 7.15–7.08 (m, 2H), 7.04 (d, $J = 8.4$ Hz, 2H), 4.25 (t, $J = 6.4$ Hz, 4H), 1.96–1.87 (m, 4H), 1.49 (dd, $J = 14.0$, 6.4 Hz, 4H), 1.43–1.35 (m, 6H); $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3) δ 165.9, 157.8, 135.2, 133.8, 122.2, 117.8, 112.8, 70.3, 29.3, 29.1, 29, 25.9; FTIR (neat): 3261, 2930, 2856, 1735, 1602, 1458 cm^{-1} ; HRMS (ESI-TOF) m/z ; $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{23}\text{H}_{29}\text{O}_6$, 401.1964, found 401.1970.

7,8,9,10,19,20-Hexahydro-6H,16H,18H,22H-dibenzo[b,k]-[1,5,9,13]tetraoxacyclooctadecine-16,22-dione (10a). Prepared according to general procedure E; a solution of propane-1,3-diol (0.0075 M, 11.4 mg) was dissolved with ACN in a vial, and 2,2'-(pentane-1,5-diylbis(oxy))dibenzoic acid **9a** (0.0075 M, 51.6 mg), Mukaiyama salt (0.036 M, 183 mg), and 1-methylimidazole (0.03 M, 49 mg) were dissolved in another vial with ACN. Both reagent solutions were flowed through 7 mL PFA tubing in an 80 °C preheated water bath at 3–4 bar pressure. After workup, the residue was purified by using column chromatography with EtOAc/*n*-hexane = 5:95 as the eluent to afford the desired product **10a** (23 mg, 40% yield) as a semisolid and the starting material **9a** (6.4 mg, 18%) was recovered. ^1H NMR (400 MHz, CDCl_3) δ 7.73 (dd, $J = 7.6$, 1.5 Hz, 2H), 7.43 (t, $J = 7.9$ Hz, 2H), 6.96 (dd, $J = 17.9$, 8.0 Hz, 4H), 4.47 (t, $J = 6.3$ Hz, 4H), 4.06 (t, $J = 5.4$ Hz, 4H), 2.24 (dd, $J = 12.6$, 6.3 Hz, 2H), 1.90 (dd, $J = 12.4$, 7.0 Hz, 4H), 1.79 (d, $J = 6.4$ Hz, 2H); $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3) δ 167.9, 158.0, 133.2, 131.6, 121.1, 120.1, 112.6, 69.1, 61.3, 30.0, 29.7, 28.4, 24.8; FTIR (neat): 2930, 2807, 1715, 1291, 1128 cm^{-1} ; HRMS (ESI-TOF) m/z ; $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{22}\text{H}_{25}\text{O}_6$, 385.1651, found 385.1646.

8,18-Dioxa-3,5-diaza-1,7(1,2),4(1,3)-tribenzenacyclooctadecaphane-2,6-dione (10b). Prepared according to general procedure E; a solution of *m*-phenylenediamine (0.0075 M, 19 mg) was dissolved with ACN in a vial, and 2,2'-(nonane-1,9-diylbis(oxy))dibenzoic acid (**Sm**) (0.0075 M, 68 mg), Mukaiyama salt (0.036 M, 183 mg), and 1-methylimidazole (0.03 M, 49 mg) were dissolved in another vial with ACN. Both reagent solutions were flowed through 7 mL PFA tubing in an 80 °C preheated water bath at 3–4 bar pressure. After workup, the residue was purified by using column chromatography with EtOAc/*n*-hexane = 5:95 as the eluent to afford the desired product **10b** (26.3 mg, 33% yield) as a semisolid. ^1H NMR (400 MHz, CDCl_3) δ 9.61 (s, 2H), 8.21 (dd, $J = 7.8$, 1.8 Hz, 2H), 7.84 (dd, $J = 8.2$, 2.0 Hz, 2H), 7.47 (ddd, $J = 8.4$, 7.4, 1.8 Hz, 2H), 7.41 (t, $J = 8.2$ Hz, 1H), 7.14–7.09 (m, 3H), 7.02 (d, $J = 8.4$ Hz, 2H), 4.22 (t, $J = 5.8$ Hz, 4H), 1.88 (dt, $J = 15.1$, 5.9 Hz, 4H), 1.49 (dd, $J = 15.2$, 7.6 Hz, 4H), 1.39–1.32 (m, 4H), 1.29 (dd, $J = 8.5$, 2.5 Hz, 2H); $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3) δ 163.9, 156.8, 138.8, 133.2, 132.5, 130.1, 122.6, 121.7, 118.0, 113.2, 112.6, 70.3, 69.8, 29.4, 28.7, 28.9, 28.7,

28.6, 26.3, 25.9; FTIR (neat): 2928, 2855, 1666, 1601, 1485, 1300, 1233 cm^{-1} ; HRMS (ESI-TOF) m/z ; $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{29}\text{H}_{33}\text{N}_2\text{O}_4$, 473.2440, found 473.2446.

1,10-Dioxacyclodocosane-11,22-dione (11a). Prepared according to general procedure E; a solution of octane-1,8-diol (0.0075 M, 43 mg) was dissolved with ACN in a vial, and dodecanedioic acid (0.0075 M, 69 mg), Mukaiyama salt (0.036 M, 183 mg), and 1-methylimidazole (0.03 M, 49 mg) were dissolved in another vial with ACN. Both reagent solutions were flowed through 7 mL PFA tubing in an 80 °C preheated water bath at 3–4 bar pressure. After workup, the residue was purified by using column chromatography with EtOAc/*n*-hexane = 5:95 as the eluent to afford the desired product **11a** (21 mg, 21% yield) as a semisolid. ^1H NMR (400 MHz, CDCl_3) δ 4.11 (t, J = 5.8 Hz, 4H), 2.34–2.28 (m, 4H), 1.68–1.56 (m, 12H), 1.36 (ddd, J = 12.3, 8.3, 4.6 Hz, 12H); ^{13}C { ^1H } NMR (100 MHz, CDCl_3) δ 174.2, 64.2, 34.5, 29.0, 28.6, 26.2, 25.2; FTIR (neat): 1716, 1421, 1214, 1116 cm^{-1} ; HRMS (ESI-TOF) m/z ; $[\text{M} + \text{Na}]^+$ calcd for $\text{C}_{20}\text{H}_{36}\text{O}_4\text{Na}$, 363.2511, found 363.2514.

(2Z,2'Z)-4,4'-(Octane-1,8-diylbis(oxy))bis(4-oxobut-2-enoic Acid) (12a). A 250 mL round bottomed flask under nitrogen was charged with anhydride (2 g, 20 mmol) and diol (1.4 g, 10 mmol) in anhydrous dichloromethane (100 mL). The stirred reaction mixture was cooled to 0 °C in an ice bath, and 2 g of 20.4 mmol of triethylamine was added. The reaction was continued for 4 h at 0 °C and further at room temperature for 5 h. The reaction was monitored by TLC. After all the anhydride was reacted, the solvent was evaporated. The residue was cooled to 0 °C in an ice bath, and 200 mL of saturated sodium bicarbonate solution was added before being extracted with ether. The aqueous layer was cooled to 0 °C in an ice bath and acidified with dilute hydrochloric acid followed by extraction with diethyl ether or dichloromethane (4 × 100 mL). The entire organic layer was combined and evaporated under reduced pressure to provide the corresponding pure dicarboxylic acid **12a** (61%, 12.5 mmol) yield as a white solid. Melting point: 103–105 °C; ^1H NMR (400 MHz, CDCl_3) δ 6.37 (s, 4H), 4.26 (t, J = 6.5 Hz, 4H), 1.75–1.66 (m, 4H), 1.41–1.33 (m, 8H); ^{13}C NMR (101 MHz, CDCl_3) δ 167.2, 166.8, 133.6, 130.5, 66.6, 28.90, 28.3, 25.6; FTIR (neat) 2923, 2854, 1716, 1421, 1214 cm^{-1} ; HRMS (ESI-TOF) m/z ; $[\text{M} + \text{Na}]^+$ calcd for $\text{C}_{20}\text{H}_{36}\text{O}_4\text{Na}$, 365.1212, found 365.1210.

(3Z,17Z)-1,6,15,20-Tetraoxacyclooctacos-3,17-diene-2,5,16,19-tetraone (13a). Prepared according to general procedure E; a solution of octanedioic acid (0.0075 M, 17.61 mg) was dissolved with ACN in a vial, and (2Z,2'Z)-4,4'-(octane-1,8-diylbis(oxy))bis(4-oxobut-2-enoic acid) (**12a**) (0.0075 M, 51.3 mg), Mukaiyama salt (0.036 M, 183 mg), and 1-methylimidazole (0.03 M, 49 mg) were dissolved in another vial with ACN. Both reagent solutions were flowed through 7 mL PFA tubing in an 80 °C preheated water bath at 3–4 bar pressure. After workup, the residue was purified by using column chromatography with EtOAc/*n*-hexane = 5:95 as the eluent to afford the desired product **13a** (16.1 mg, 23.7% yield) as a semisolid (12 mg of starting material recovered). ^1H NMR (400 MHz, CDCl_3) δ 6.85 (s, 4H), 4.23 (t, J = 5.8 Hz, 8H), 1.73–1.64 (m, 8H), 1.38 (m, 16H); ^{13}C { ^1H } NMR (100 MHz, CDCl_3) δ 165.28, 133.76, 65.44, 29.84, 29.19, 28.7, 25.9; FTIR (neat): 2926, 2854, 1716, 1642, 1263 cm^{-1} ; HRMS (ESI-TOF) m/z ; $[\text{M} + \text{Na}]^+$ calcd for $\text{C}_{24}\text{H}_{36}\text{O}_8\text{Na}$, 475.2307, found 475.2307.

(7Z,21Z)-1,5,10,19-Tetraoxacyclotricosa-7,21-diene-6,9,20,23-tetraone (13b). Prepared according to general procedure E; a solution of propanedioic acid (0.0075 M, 11.4 mg) was dissolved with ACN in a vial, and (2Z,2'Z)-4,4'-(octane-1,8-diylbis(oxy))bis(4-oxobut-2-enoic acid) (**12a**) (0.0075 M, 51.3 mg), Mukaiyama salt (0.036 M, 183 mg), and 1-methylimidazole (0.03 M, 49 mg) were dissolved in another vial with ACN. Both reagent solutions were flowed through 7 mL PFA tubing in an 80 °C preheated water bath at 3–4 bar pressure. After workup, the residue was purified by using column chromatography with EtOAc/*n*-hexane = 5:95 as the eluent to afford the desired product **13b** (14 mg, 25% yield) as a semisolid and the starting material **12a** (7.6 mg, 23%) was recovered. ^1H NMR (400 MHz, CDCl_3) δ 6.82 (d, J = 15.8 Hz, 2H), 6.76 (d, J = 15.8 Hz, 2H), 4.40–4.36 (m, 4H), 4.27–4.22 (m, 4H), 2.15 (dd, J = 11.2, 5.8 Hz, 2H),

1.69–1.63 (m, 5H), 1.37 (s, 8H). ^{13}C { ^1H } NMR (100 MHz, CDCl_3) δ 165.1, 165.0, 132.9, 65.5, 63.9, 28.5, 28.3, 27.6, 25.2; FTIR (neat): 2927, 2855, 1715, 1644, 1265 cm^{-1} ; HRMS (ESI-TOF) m/z ; $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{19}\text{H}_{27}\text{O}_8$, 383.1706, found 383.1702.

■ ASSOCIATED CONTENT

Data Availability Statement

The data underlying this study are available in the published article and its [Supporting Information](#).

Supporting Information

The Supporting Information is available free of charge at <https://pubs.acs.org/doi/10.1021/acs.joc.2c03000>.

Copies of ^1H and ^{13}C NMR, HRMS, and UV-vis spectra and crystallographic data ([PDF](#))

FAIR data, including the primary NMR FID files, for compounds **Sa**, **Sb**, **Sc**, **Sd**, **Se**, **Sf**, **Sg**, **Sh**, **Si**, **Sj**, **Sk**, **Sl**, **Sm**, **1a**, **1b**, **1c**, **1d**, **1e**, **1f**, **1g**, **1h**, **1i**, **1j**, **1k**, **2a**, **2b**, **2c**, **2d**, **2e**, **2f**, **2g**, **2h**, **2i**, **2j**, **2k**, **5a**, **5b**, **5c**, **5d**, **5e**, **5f**, **5g**, **5h**, **5i**, **5j**, **5k**, **7a**, **7b**, **7c**, **7d**, **7e**, **7f**, **7g**, **7h**, **7i**, **7j**, **7k**, **7l**, **8a**, **9a**, **9b**, **10a**, **10b**, **11a**, **12a**, **13a**, and **13b** ([ZIP](#))

Accession Codes

CCDC 2176849 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

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Direct Intramolecular Coupling of Primary/Secondary Alcohols with Secondary Alcohols for Macrocyclic Alkenylation Using Ni-Zeolite Catalyst Under Continuous-Flow Conditions

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Abstract: Herein, we report the direct intramolecular coupling of primary and secondary alcohols for the selective synthesis of macrocyclic olefins in the presence of Ni-zeolite catalyst under continuous flow. This reaction proceeds via dehydration of secondary alcohols to alkenes, which subsequently undergo intramolecular dehydrative coupling reaction with a primary alcohol to obtain moderate yields of macrocyclic olefins. This reaction is also effective for the coupling of secondary-secondary alcohols and alkene-alcohols to produce diverse macrocyclic olefin products. This unique approach has various advantages including step-economy, no additives and pre-functionalization required, inexpensive and reusable catalyst, and exemplification with 23 macrocycles in different ring sizes. The continuous flow macrocyclisation afforded higher productivity and space-time yield than the batch reaction conditions.

Keywords: Ni-zeolite; Continuous flow; Macrocyclisation; Alkenylation; Cross-coupling reaction

Introduction

Macrocyclic compounds are primitive structural motifs in biologically active natural products,^[1] pharmaceutically active compounds^[2,3] and the perfume industry.^[4] In addition to the medicinal applications, structurally distinct macrocycles have applications in chemistry, such as supramolecular chemistry,^[5] materials science^[6] and phase transfer catalysis.^[7,8] Macrocyclic conformation with heteroatoms also has greater binding affinity over linear chain structures.^[9] The structural assortment and the diverse binding affinity of the macrocycles have contributed to their diverse biological applications such as anti-carcinogenic effects,^[10] DNA interaction,^[11] and antitumor activity.^[12] The structural and biological importance of macrocycles has attracted synthetic chemists to develop efficient approaches for macrocycles. However, the synthesis of macrocycles

by inter or intramolecular cyclisation is challenging because of high disorders in the structure and entropy, resulting in more challenges in synthetic chemistry.^[13] To combat the challenges in macrocyclisation, several approaches have been developed, including catalytic and non-catalytic reactions.^[14] Although several macrocyclisation approaches have been reported to generate wide macrocyclic lactone and lactam, macrocyclisation via intramolecular alkenylation is limited (Figure 1). In this regard, one of the common practices for macrocyclic alkenylation involves Pd-catalysed intramolecular Heck reaction and Stille's reaction, which can yield many natural products and drugs (Figure 1a and b).^[15] Another important and most exploited strategy for macrocyclic alkenylation involves catalytic intramolecular ring-closing olefin metathesis, and it has been widely acclaimed in the synthesis of drug and natural product applications (Figure 1d).^[16] Recently, Loh

Previous approach: Macrocyclic alkenylation using prefunctionalised substrates

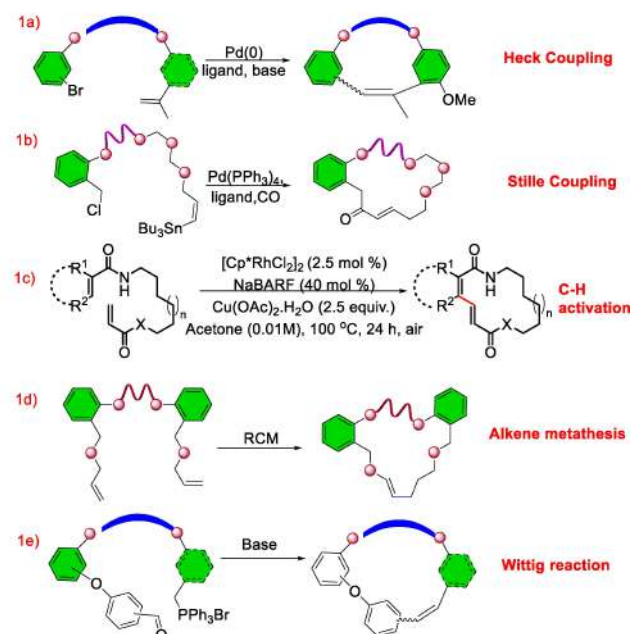


Figure 1. State-of-the-art for macrocyclic alkenylation.

research group reported intramolecular alkene-alkene cross-coupling using Rh(III) as a catalyst for the synthesis of macrocyclic alkenes (Figure 1c).^[17] However, few other conventional macrocyclic alkenylation reactions in the absence of metals have been reported using Wittig related reactions,^[18] which consider intramolecular coupling of carbonyl with the phosphorous ylide reagent (Figure 1e) and intramolecular aldehyde-aldehyde coupling reactions using McMurry coupling reactions.^[19]

These aforementioned methods require preactivated substrates and specially designed alkene precursors. They also generate genotoxic stoichiometric waste. Moreover, selectivity, yields, and scalability are primary concerns in some of the reported macrocyclic alkenylation reactions. All these reported catalytic reactions require non-recyclable and expensive metal catalysts. To circumvent these challenges, alternative new catalytic approaches that use readily accessible and recyclable catalysts must be developed. Furthermore, dehydration of alcohols to olefins is a fundamental reaction, which requires either high temperature or acid catalysts.^[20] However, this transformation is

less efficient because of other competing etherification reactions.^[21] In catalysis, zeolite and metal supported on zeolite can be used as catalysts in many chemical transformations because of their excellent reactivity and selectivity, easy preparation, and low cost.^[22] Zeolite and metal-supported zeolite have also been used as a catalyst for dehydration reactions because of their excellent acidic properties and selectivity.^[23] Although several catalytic applications have been demonstrated using zeolites, double dehydrative coupling of alcohol versus alcohol to form C=C bonds has not been reported. Herein, we report intramolecular dehydrative coupling of primary and secondary alcohols to form macrocyclic alkenes in the presence of Ni-zeolite under continuous flow conditions. This reaction is also efficient for the coupling of secondary-secondary alcohols and alcohol-alkene groups. This novel approach does not require any additives, stoichiometry reagents, activation, or prefunctionalisation of the substrates, and it produces environmentally benign water as a by-product.

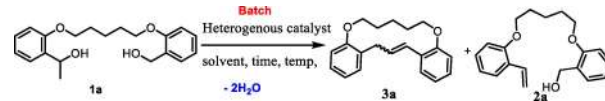
Results and Discussion

We initiated our investigation by performing intramolecular dehydrative coupling of compound **1a** (1-(2-((5-(2-(hydroxymethyl)phenoxy)pentyl)oxy)phenyl)ethan-1-ol) as a benchmark substrate to provide the macrocyclic alkene **3a** (7,8,9,10-tetrahydro-6H,16H-dibenzo[h,m][1,7]dioxacyclotetradecine) and the non-cyclic alkene **2a** ((2-((5-(2-vinylphenoxy)pentyl)oxy)phenyl)methanol). We did this by screening different solvents, temperatures, and catalysts in batch reaction conditions.

Thus, this reaction with heterogeneous catalyst zeolite (weight/weight) in dioxane at 120 °C after 24 h, delivered 36% of the macrocyclic alkene **3a** and 22% of the non-cyclic alkene compound **2a** (Table 1, entry 1). Compound **3a** was obtained as *E:Z* mixture (98:2) and confirmed by NMR data. Fe-Zeolite provided 31% yield of compound **3a** and 25% of compound **2a** (Table 1, entry 2). Ru-Zeolite gave a moderate yield of compound **3a** (Table 1, entry 3). Other heterogeneous catalysts such as Ni-zeolite showed higher efficiency towards macrocyclization, and afforded 49% yield of compound **3a** (Table 1, entry 4). The solvent effect was also examined. With solvents such as THF and toluene, the yield decreased to 40% and 29% respectively (Table 1, entries 5, and 6, respectively). Increasing the temperature to 140 °C and 160 °C resulted 49% and 47% yield (Table 1, entries 7, and 8 respectively). Decreasing the reaction temperature afforded 45% of compound **3a** (Table 1, entry 9).

Dilution (0.05 M) of compound **1a** had little impact on the outcome (Table 1, entry 10). Afterwards, this reaction with the homogeneous metal catalyst

Table 1. Optimization for the macrocyclic olefination using intramolecular coupling of alcohols under batch conditions.



Sr. No	Catalyst	Solvent	Time (hr)	Temp (°C)	Yield 3 a / 2 a %
1 ^[a]	Zeolite	Dioxane	24	120	36/22
2 ^[a]	Fe-zeolite	Dioxane	24	120	31/25
3 ^[a]	Ru-zeolite	Dioxane	24	120	47/39
4 ^[a]	Ni-zeolite	Dioxane	24	120	49/31
5 ^[a]	Ni-zeolite	THF	24	120	40/50
6 ^[a]	Ni-zeolite	Toluene	24	120	29/30
7 ^[a]	Ni-zeolite	Dioxane	24	140	49/12
8 ^[a]	Ni-zeolite	Dioxane	24	160	47/10
9 ^[a]	Ni-zeolite	Dioxane	24	100	45/30
10 ^[b]	Ni-zeolite	Dioxane	24	120	49/34
11 ^[c]	NiCl ₂ ·6H ₂ O	Dioxane	24	120	-
12 ^[c]	FeCl ₃ ·6H ₂ O	Dioxane	24	120	18/25
13 ^[c]	RuCl ₃ ·xH ₂ O	Dioxane	24	120	27/29
14	Ni-zeolite	Dioxane	48	120	49/30

^[a] Reaction conditions: Compound **1 a** (0.15 mmol) in 2 mL of solvent (Table 1) and 50 mg of catalyst were stirred in a sealed cap vial at an appropriate temperature (Table 1) for 24 hrs.

^[b] 0.05 M of **1 a** used;

^[c] 3 mol% of catalyst; The mentioned yields are isolated yields.

NiCl₂·6H₂O did not afford any desired product (Table 1, entry 11). However, the yield decreased when FeCl₃·6H₂O and RuCl₃·xH₂O were used (Table 1, entries 12, and 13, respectively). The yield did not improve when the reaction time was increased to 48 h (Table 1, entry 14). The space time yield for the batch reaction conditions after 24 hrs was found to be 1.98 g L⁻¹ h⁻¹.

To improve product yield and the inherent scaling-up issues associated with a batch process, we re-optimized the batch process to a continuous flow process. For the continuous flow setup, we integrated a Vapourtec SF-10 peristaltic pump for pumping solvent, an Omnifit column for packing the heterogeneous catalyst, perfluoro alkoxy alkanes (PFA) tubing for the reaction, a heating jacket for the heating, and a back pressure regulator to maintain the pressure (Figure 2). To screen the parameters for macrocyclic alkenes in a

continuous flow reactor, we used **1 a** as the ideal starting substrate in the presence of various heterogeneous catalysts. A vial containing 0.05 M solution of **1 a** in dioxane was passed through a pre-heated Omnifit packed bed reactor (filled with catalyst up to 7 cm) by using the peristaltic pump with 0.1 mL/min flow rate at 120 °C for 23.9 min residence time, 9% yield of product **3 a** and 30% yield of non-cyclic alkene **2 a** were obtained along with starting material recovered after one cycle (Table 2, entry 1). Further, increasing run time and two-run cycles afforded 13% yield of product **3 a** (Table 2, entry 2).

When the reaction was run three times, 20% yield was obtained (Table 2, entry 3). Four and five times yielded 22% each (Table 2, entries 4, and 5 respectively). In terms of screening temperature, at 140 °C a 40% yield was obtained (Table 2, entry 6), while at 160 °C the yield decreased (Table 2, entry 7). Further increasing the residence time of the reaction to 27.3 min after a four-time run, a notable 59% yield of **3 a** was observed (Table 2, entry 8). When the concentration of compound **1 a** was increased to 0.1 M, the yield of **3 a** was decreased (Table 2, entry 9). The high dilution (0.015 M) of **1 a** gave 59% yield (Table 2, entry 10). The shorter residence time decreased the yield of **3 a** to 30% (Table 2, entry 11). Other supported catalysts, namely, Fe-zeolite and Ru-zeolite, showed lower efficiency towards macrocyclization yielding 40% and 45% of macrocyclic alkene **3 a** (Table 2, entries 12, and 13 respectively). Best optimized reaction conditions were achieved by Ni-zeolite at 140 °C

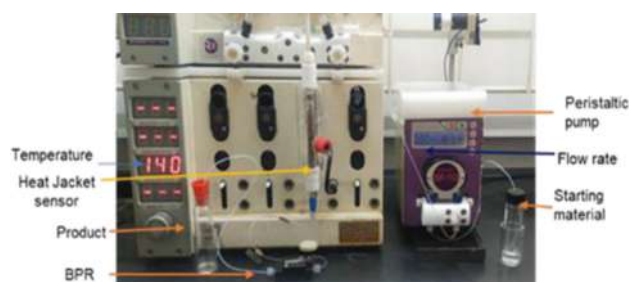
**Figure 2.** Continuous flow setup.

Table 2. Optimization for macrocyclic olefination using intramolecular coupling of alcohols under continuous flow conditions.

Sr. No	Conc (M)	Catalyst	tR (min)/ time run	Temp (°C)	Yield (3 a / 2 a) %
1 ^[a]	0.05	Ni-zeolite	23.9/1	120	9/30
2 ^[a]	0.05	Ni-zeolite	23.9/2	120	15/35
3 ^[a]	0.05	Ni-zeolite	23.9/3	120	20/40
4 ^[a]	0.05	Ni-zeolite	23.9/4	120	22/45
5 ^[a]	0.05	Ni-zeolite	23.9/5	120	22/60
6 ^[a]	0.05	Ni-zeolite	23.9/4	140	40/42
7 ^[a]	0.05	Ni-zeolite	23.9/4	160	39/20
8 ^[b]	0.05	Ni-zeolite	27.3/4	140	59/12
9	0.1	Ni-zeolite	27.3/4	140	30/35
10	0.015	Ni-zeolite	27.3/4	140	59/20
11 ^[c]	0.05	Ni-zeolite	16/4	140	30/20
12	0.05	Fe-zeolite	27.3/4	140	40/35
13	0.05	Ru-zeolite	27.3/4	140	45/30

Reaction conditions: A solution of **1 a** in dioxane solvent was prepared and flowed (0.1 mL/min flow rate) through the Omnifit column containing the catalysts.

^[a] (1.7 g) or

^[b] (1.9 g) at an appropriate temperature for residence time and run (Table 2). The mentioned yields are isolated yields.

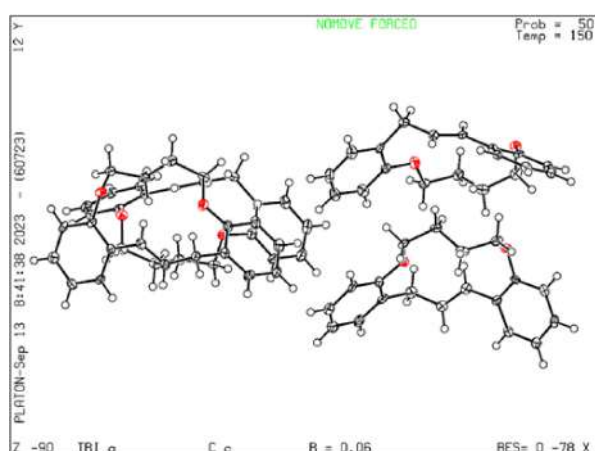
^[c] 0.15 mL/min flow rate.

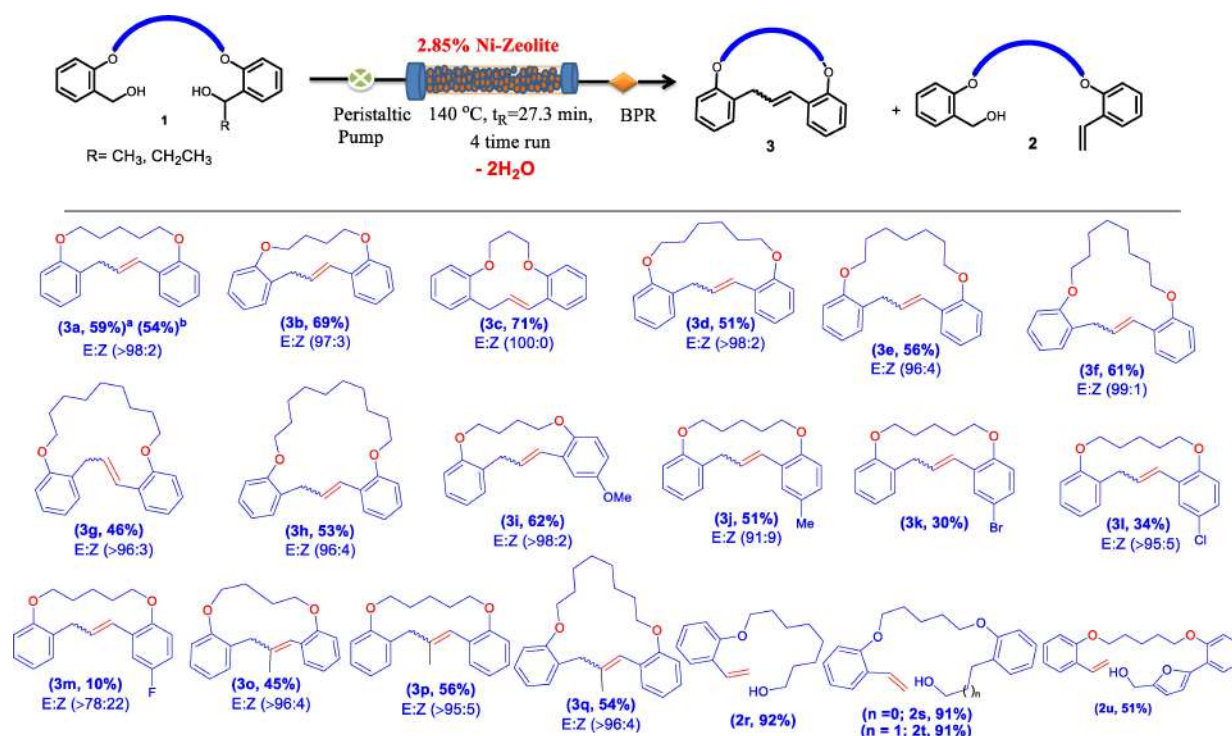
in dioxane solvent (Table 2, entry 8) and higher space-time yield 26.45 g L⁻¹ h⁻¹ compared to batch conditions.

After determining the best optimized results, we further investigated the macrocyclization of various diol derivatives in a continuous flow. Ring-closing macrocyclization of diol **1 b** having butyl spacer provided the macrocycle **3 b** in 69% yield (Scheme 1) as an *E:Z* mixture (97:3) based on the ¹H-NMR. This structure was further confirmed by single crystal XRD (Figure 3). Furthermore, the 12-membered macrocyclic alkene **3 c** formed in 71% yield was exclusively a *E*

isomer from the respective diol **1 c** (Scheme 1). Diol derivatives with six to eight carbon-chain spacers afforded 54–63% yield of macrocycles **3 d–3 f** respectively (Scheme 1). Furthermore, 18- and 19-membered macrocyclic alkenes **3 g** and **3 h** were formed from the respective diol in 43–46% yields (Scheme 1). Diols having electron-donating groups such as OMe, Me afforded 62% and 51% yield of **3 i** and **3 j** respectively (Scheme 1). With Br, Cl, and F the yield of respective macrocycle formation was decreased (**3 k–m**, Scheme 1). Nitro-substituted alcohol did not produce the respective macrocycle **3 n**. Diol with butyl spacer, primary and secondary propane-1-ol delivered the macrocycle **3 o** in 45% yield (Scheme 1). Diol with pentyl spacer gave 56% yield of **3 p** (Scheme 1). Interestingly, 15-membered macrocyclic alkene **3 q** was obtained in 54% yield in this reaction (Scheme 1). A linear alcohol **1 r** resulted 82% yield of non-cyclic alkene **2 r** (Scheme 1). The diols containing non-benzylic alcohol and benzylic alcohol delivered only non-cyclic alkenes **2 s** and **2 t** in 91% yield (Scheme 1). However, this reaction is failed to produce the macrocyclic alkene with heteroatom furan containing diol, which afforded 51% of non-cyclic alkene **2 u**. The singly packed Ni-zeolite bed delivered all the above macrocyclic alkene **3** without losing the catalytic activity.

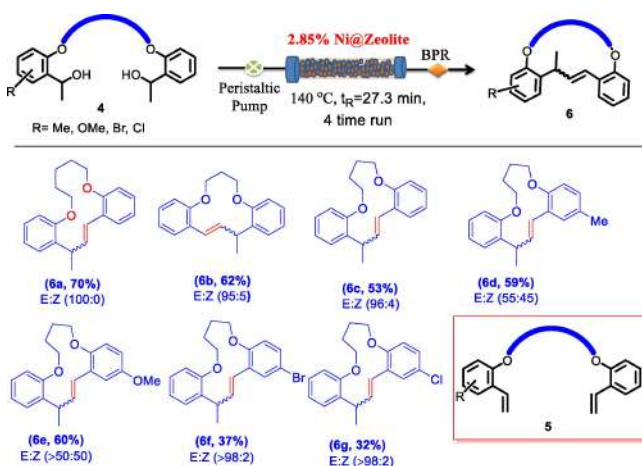
Next, this macrocyclization was performed with secondary diols. The intramolecular dehydrative coupling of secondary diol **4 a** under the set condition

**Figure 3.** Crystal structure of **3 b**.



Scheme 1. Substrate scope for macrocyclic alkene from unsymmetrical diol. ^[a] Reaction conditions: 0.05 M solution of **1** in dioxane was prepared and flowed through the Omnifit column containing Ni-zeolite heterogeneous catalysts (1.7 g, 9 cm), heated at 140 °C, for residence time 27.3 min and run 4 times. ^[b] Reaction performed in 10.5 mmol of **1a**. The mentioned yields are isolated yields.

afforded the corresponding macrocyclic alkene **6a** in 70% yield with E selectivity (Scheme 2). Secondary diol with propyl spacer afforded 62% yield of **6b** as a mixture of E:Z (95:5) (Scheme 2). Furthermore, 13-

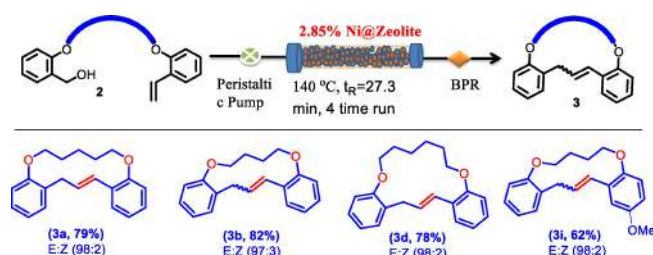


Scheme 2. Substrate scope for macrocyclic alkene from secondary diol. ^[a] Reaction conditions: 0.05 M solution of **4** in dioxane was prepared and flowed through the Omnifit column containing the Ni-zeolite heterogeneous catalysts (1.7 g, 9 cm), 140 °C, for residence time 27.3 min and run four times. The mentioned yields are isolated yields.

membered macrocyclic alkene **6c** was obtained in 53% yield (Scheme 2). Secondary diol with electron-donating substituents, viz. Me, OMe gave 59% and 60% yield of compounds **6d** and **6e** respectively (Scheme 2). The Br and Cl substituted diols delivered less conversion to the respective macrocyclic alkenes. The Br-substituted diol gave 37% yield of **6f** (Scheme 2), whereas Cl-substituted diol delivered 32% yield of compound **6g** (Scheme 2). By using a longer heptyl spacer diol gave an inseparable mixture of noncyclic dialkene and macrocyclic alkene. One-time packed Ni-zeolite bed delivered all the macrocycles **6** without losing the catalytic activity.

To further demonstrate this novel coupling reaction, various alcohols **2** having alkene were prepared. Compound **2a** reacted in the intramolecular dehydrative coupling reaction using Ni-zeolite after two times runs in a continuous flow, yielding 79% of product **3a** (Scheme 3). This coupling reaction afforded 13-membered macrocyclic alkene **3b** in 82% yield with an E:Z ratio (97:3) from the respective alcohol **2b** (Scheme 3). Macrocyclic alkene with heptyl spacer **3d** was formed in 78% yield (Scheme 3).

Electron donating -OMe substituted compound **2i** delivered macrocyclic alkene **3i** in 62% yield (Scheme 3). All the macrocycles **3** in Scheme 3 were synthesized using a one-time packed Ni-zeolite bed without any loss of catalytic activity. The ICP-AES of



Scheme 3. Substrate scope for macrocyclic alkene from intramolecular coupling of alcohol and alkene. ^[a]Reaction conditions: 0.05 M solution of **2** in dioxane was prepared and flowed through the Omnifit column containing the Ni-zeolite heterogeneous catalysts (1.7 g, 9 cm), 140 °C, for residence time 27.3 min and run two times. The mentioned yields are isolated yields.

the freshly prepared and used Ni-zeolite indicated 2.85% of Ni on the zeolite. This indicates that this catalyst is highly stable and sustainable under the experimental conditions for the prolonged catalytic reaction to deliver diverse macrocyclic alkenes.

The morphology of freshly prepared Ni-zeolite was analysed using TEM and XRD (Figure 4). The surfactant-directed zeolite exhibited an amorphous

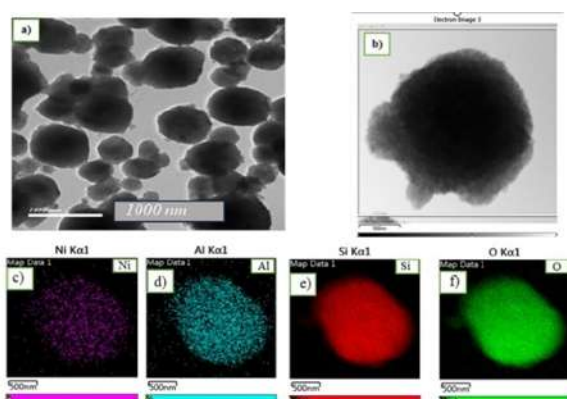


Figure 4. a) HRTEM images of Ni-zeolite catalyst; b) Selected area of Ni-zeolite; c)–f) Ni, Al, Si and O, respectively.

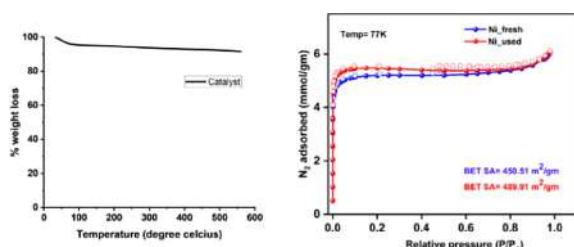


Figure 5. a) Thermogravimetric analysis (TGA) of Ni-zeolite; b) BET surface area of fresh and used Ni-zeolite.

morphology.^[24] Selected area images of the catalyst revealed that Ni, Al, Si, and O were uniformly distributed (Figure 4a–f). We compared TEM images of the used catalyst and observed the same morphology. Thus, the morphology of the catalyst was not affected during continuous flow catalysis.

Further, the thermal stability of the Ni-zeolite was analysed using thermogravimetric analysis (TGA, Figure 5). As shown in Figure 5a, a slight weight loss was observed below 150 °C. This could be attributed to the evaporation of adsorbed water. With further increase in the temperature, no weight loss was observed. The findings of this study indicate that Ni-zeolite catalyst has an excellent stability at high temperatures up to 600 °C. The specific surface area of fresh and used 2.85% Ni-zeolite catalyst was characterized using N₂ adsorption–desorption measurements. The N₂ adsorption–desorption isotherm of the catalyst is displayed in Figure 5b. The fresh Ni-zeolite catalyst and the used Ni-zeolite catalyst showed BET-specific surface area of 450.51 m²/g and 489.91 m²/g respectively (Figure 5b). Thus, the surface area of exhibit the catalyst did not change much after prolonged usage.

Powder XRD profiles of the zeolite and calcinated zeolite XRD patterns showed diffraction peaks at ranges of $2\theta = 23^\circ - 29^\circ$, which matched well with those of the phase zeolite.^[25] Freshly and used Ni-zeolite revealed the existence of Ni in the form of NiO. The peaks of Ni oxide were detected at $2\theta = 37^\circ, 43.26^\circ$, and 62.73° . This could be attributed to the NiO component which was distributed on the zeolite surface (Figure 6).

The reusability of the catalyst was checked by the reaction of 1,1'-((pentane-1,5-diylbis(oxy))bis(2,1-

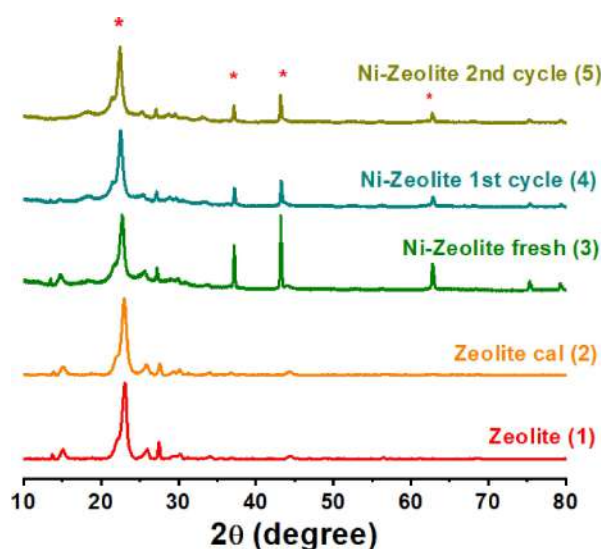


Figure 6. PXRD diffraction profiles 1) zeolite, 2) zeolite calcinated, 3) freshly prepared Ni-zeolite, 4) Ni-zeolite 1st cycle and 5) Ni-zeolite 2nd cycle.

phenylene))bis(ethan-1-ol) **1a** under the optimized reaction conditions (Table 2, entry 8). A 0.05 M solution of the substrate **1a** in dioxane solvent was pumped using a peristaltic pump through a glass column (Omnifit® (6.6×150 mm²) packed bed containing 1.9 g of fresh Ni-zeolite filled up to 9 cm and preheated to 140 °C. The flow rate was 0.1 mL/min, and the back pressure was maintained at 3.5–3.9 psi. with residence time t_R = 27.3 min. The collected organic layer was concentrated under reduced pressure, and the crude product was purified through column chromatography to afford a 58% yield of **3a**. After reaction completion, the catalyst bed was washed with 1,4-dioxane and dried at 140 °C. This bed catalyst was used again for the next reaction. The catalyst bed used

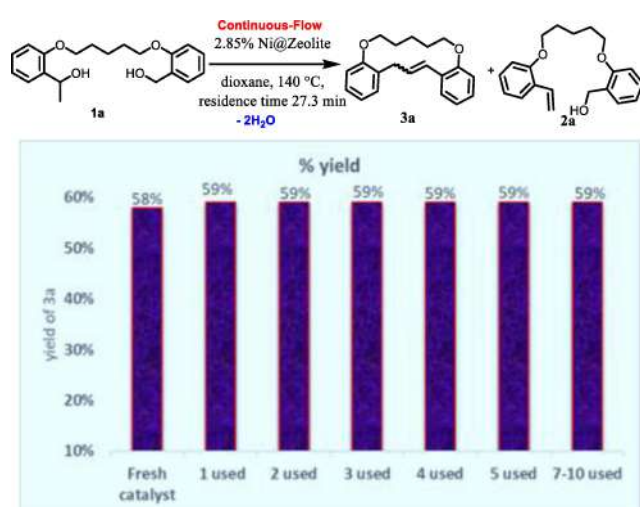
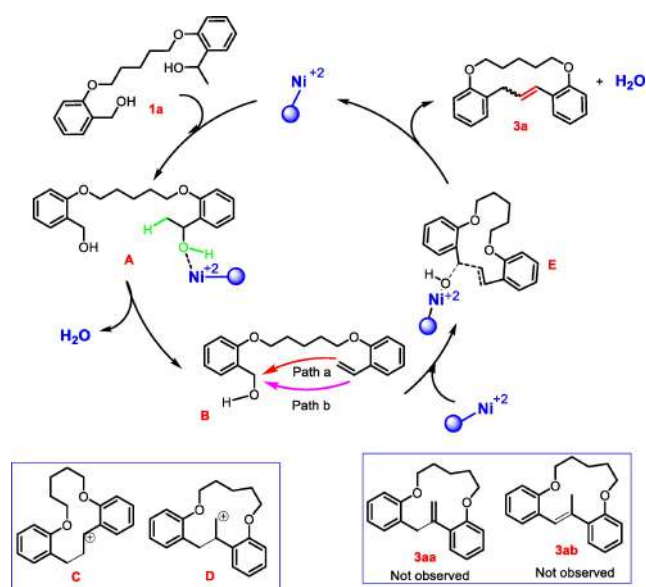


Figure 7. Ni-Zeolite catalyst reusability under continuous-flow.



Scheme 4. Plausible mechanism for macrocyclization.

once gave a 59% yield of **3a**. It was washed again with 1,4-dioxane and dried at 140 °C. When used for the second time, it gave a 59% yield of **3a**. When used for three to five times, it gave a 59% yield of **3a**. This catalyst was reused 10 times without any change in the activity (Figure 7). ICP-AES was used to determine amount of Ni in the reaction supernatant 0.000177%.

The plausible mechanism for this transformation is depicted in Scheme 4. First, compound **1a** reacted with 2.85% Ni-zeolite and activated the alcohol to generate complex **A**. Then, complex **A** underwent dehydration of secondary alcohol to produce the intermediate **B**. Further, Ni coordination with the intermediate **B**, and subsequently, there were nucleophile alkene attacks on activated alcohol in two possible pathways, a) or b). However, nucleophilic alkene attack led to regioselectivity on alcohol to generate the intermediate **E**, which underwent dehydration to form product **3a**. The regioselective product was obtained because of the formation of a more stable benzylic carbocation intermediate **C**. Whereas other expected products **3aa** and **3ab** through intermediate **D** were not observed in this reaction because of less stabilization of the intermediate.

Conclusion

In this study, we developed a modern approach for the regioselective synthesis of predominantly macrocyclic (E) alkenes through intramolecular coupling of alcohols by using a sustainable Ni-zeolite catalyst under continuous flow. In this reaction, both primary and secondary alcohols were effectively coupled and demonstrated to synthesize macrocyclic alkenes with broad substrate scope in very good yields. One time-packed Ni-zeolite catalyst was efficiently used to generate diverse macrocyclic alkenes and the advantage of the simple recyclability of the catalyst under flow were ascertained. This method has various advantages including no need for additives, stoichiometry reagents or special reaction conditions, and step economy. This reaction is demonstrated in gram-scale and also reproducible.

Experimental Section

All experimental details, including experimental procedures, characterization data for new compounds, X-ray crystallographic data, and NMR spectra for new compounds, can be found in Supporting Information.

A) General Experimental Procedure for Metal-Zeolite Catalyst Preparation^[26]

Fe-Zeolite^[26a] Catalyst Preparation

Zeolite (5 g) was suspended in 20 mL of deionized water. A 10% metal chloride ($\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$) solution was prepared in deionized water. Metal loading of 2.63% over zeolite samples was achieved by using the corresponding amounts of stock solution. This suspension was stirred for 6 h in a rotary evaporator for uniform dispersion. Water was removed under vacuum, and the metal-loaded samples were dried at 120 °C for 2 h. The dried samples were calcined at 500 °C for 8 h.

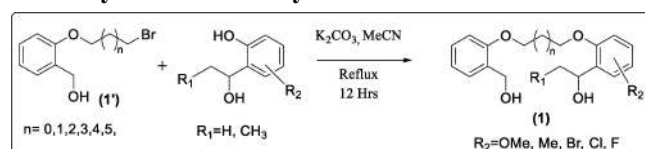
Ni-Zeolite^[26b] Catalyst Preparation

Zeolite (5 g) was suspended in 20 mL of deionized water. A 10% metal chloride ($\text{NiCl}_2 \cdot 6\text{H}_2\text{O}$) solution was prepared in deionized water. Metal loading of 2.85% over zeolite samples was achieved by using the corresponding amounts of stock solution. This suspension was stirred for 6 h in a rotary evaporator for uniform dispersion. Water was removed under vacuum, and the metal-loaded samples were dried at 120 °C for 2 h. The dried samples were calcined at 500 °C for 8 h.

Ru-Zeolite catalyst preparation

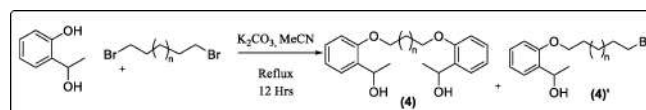
Zeolite (5 g) was suspended in 20 mL of deionized water. A 10% metal chloride ($\text{RuCl}_3 \cdot x\text{H}_2\text{O}$) solution was prepared in deionized water. Metal loading of 2%-3% over zeolite samples was achieved by using the corresponding amounts of stock solution. This suspension was stirred for 6 h in a rotary evaporator for uniform dispersion. Water was removed under vacuum, and the metal-loaded samples were dried at 120 °C for 2 h. The dried samples were calcined at 500 °C for 8 h.

B1) Reported General Experimental Procedure for Primary and Secondary Diol Derivatives^[14]



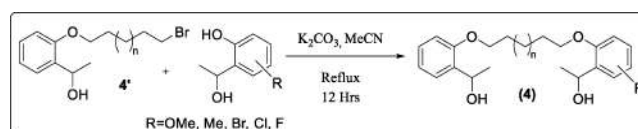
In a 100 mL round bottom flask (1') (1 equiv.), 2-(1-hydroxyethyl)phenol or 2-(1-hydroxypropyl)phenol (1 equiv.), was added, along with potassium carbonate (K_2CO_3) (2 equiv.) in acetonitrile. In an oil bath, the solution was refluxed at 90 °C for 12 h. The progress of the reaction was monitored using thin-layer chromatography. The resulting mixture was extracted with ethyl acetate two times using 30 mL of solvent each time. The ethyl acetate layer was combined and dried over Na_2SO_4 . After removing the solvent under reduced pressure, the residue was purified through column chromatography (EtOAc/n-hexane = 40:60) for product 1.

B2) General Experimental Procedure for Diol Derivative



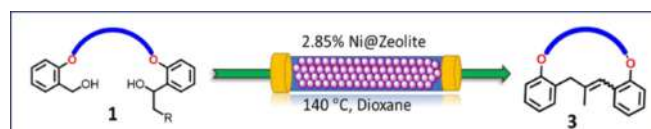
In a 100 mL round bottom flask, we added 2-(1-hydroxyethyl)phenol (1 equiv.), 1,5-dibromopentane (0.5 equiv.), and potassium carbonate (K_2CO_3) (2 equiv.) in acetonitrile. The solution was refluxed at 90 °C temperature for 12 hrs in an oil bath. The progress of the reaction was monitored through the thin-layer chromatography technique. The resulting mixture was extracted with ethyl acetate two times using 30 mL of solvent each time. The ethyl acetate layer was combined and dried over Na_2SO_4 . After removing the solvent under reduced pressure, the residue was purified by using column chromatography (EtOAc/n-hexane = 50:40) for product 4.

B3) General Experimental Procedure for Diol Derivative



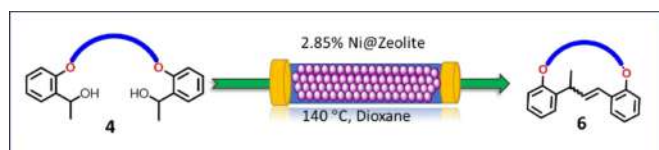
In a 100 mL round bottom flask, we added 4' (1 equiv.), 2-(1-hydroxyethyl)phenol (substituted derivative) (1 equiv.), and potassium carbonate (K_2CO_3) (2 equiv.) in acetonitrile. In an oil bath, the solution was refluxed at 90 °C temperature for 12 h. Reaction progress was monitored using thin-layer chromatography. The resulting mixture was extracted with ethyl acetate two times using 30 mL of solvent each time. The ethyl acetate layer was combined and dried over Na_2SO_4 . After removing the solvent under reduced pressure, the residue was purified by using column chromatography (EtOAc/n-hexane = 50:40) for product 4.

C1) General Procedure for Preparation of Macrocyclic Alkene Compounds (3) using Ni-Zeolite Flow Condition



A 0.05 M solution of the diol substrate in dioxane solvent was pumped using a syringe pump through a glass column (Omnifit® (6.6×150 mm²) packed bed containing 1.9 g of Ni-zeolite filled up to 9 cm. It was preheated to 140 °C at a flow rate of 0.1 mL/min back pressure of 3.5 to 3.9 psi, and t_R = 27.3 min. After a four-time run, the collected organic layer was concentrated under reduced pressure, and the crude product was purified through column chromatography using ethyl acetate: hexane (0:100) to (2:98) as an eluent to afford the macrocyclic alkene product. After the reaction was complete, the catalyst bed was washed with 1,4-dioxane dried at 140 °C and used for the next reaction.

C2) General Procedure for Preparation of Macro-cyclic Alkene Compounds (6) using Ni-Zeolite Flow Condition

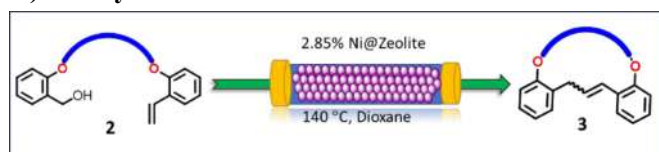


A 0.05 M solution of both secondary diol substrates in dioxane solvent was pumped using a syringe pump through a glass column (Omnifit® (6.6×150 mm²) packed bed containing 1.9 g of Ni-zeolite filled up to 9 cm. It was preheated at 140 °C at a flow rate of 0.1 mL/min back pressure of 3.5–3.9 psi was maintained in the reaction and residence time t_R = 27.3 min. After a four-time run, the collected organic layer was concentrated under reduced pressure, and the crude product was purified by column chromatography using ethyl acetate: hexane (0:100) to (1:98) as an eluent to afford the macrocyclic alkene product. After the reaction was complete, the catalyst bed was washed with 1,4-dioxane dried at 140 °C and used for the next reaction.

C3) General Procedure for Preparation of Macro-cyclic Alkene from the Intramolecular 3 of alcohol and 3 by using Ni-Zeolite in Flow Condition

A 0.05 M solution of 2 substrates in dioxane solvent was pumped using a syringe pump through a glass column (Omnifit® (6.6×150 mm²) packed bed containing 1.9 g of Ni-zeolite filled up to 9 cm. It was and preheated to 140 °C at a flow rate of 0.1 mL/min back pressure at 3–3.9 psi and t_R = 27.3 min. After a two-time run, the collected organic layer was concentrated under reduced pressure, and the crude product was through column chromatography using ethyl acetate: hexane (0:100) to (1:98) as an eluent to afford the macrocyclic alkene product. After reaction completion, the catalyst bed was washed with 1,4-dioxane dried at 140 °C and used for the next reaction.

D) Catalyst Characterization



Elemental analysis study of Ni %: w/w of Ni-zeolite: ppm = ug/g = 28563.57 ug/1 g sample = 28.56 mg/1 g sample = 28563.5 mg/100 g sample = 28.56 g/100 g sample = 2.85% wt/wt

E) Flow Set-Up for Large-Scale Reaction

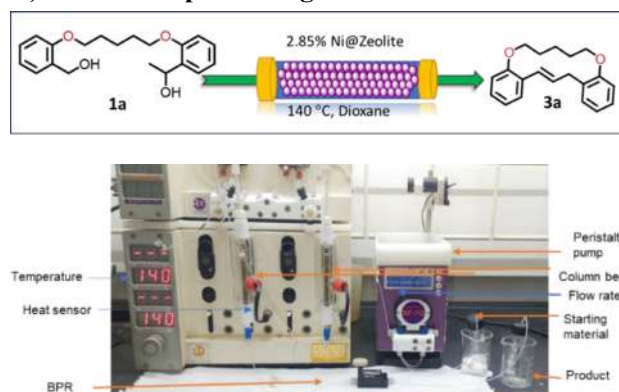


Figure E: Continuous Flow Step for Macrocyclization.

A 0.05 M solution of 1-(2-((5-(2-(hydroxymethyl)phenoxy)pentyl)oxy)phenyl)ethan-1-ol **1a** (3.47 g, 10.50 mmol) in (210 mL) in dioxane solvent was pumped using a syringe pump through a two glass column (Omnifit® (6.6×150 mm) packed bed containing 1.9 g of Ni-zeolite filled up to 9 cm. Each column bed was preheated to 140 °C at a flow rate of 0.1 mL/min, back pressure of 5 psi, and t_R of = 27.3 min. After a two-time run, the collected organic layer was concentrated under reduced pressure, and the crude product was purified by column chromatography using ethyl acetate: hexane (2:98) as an eluent to afford compound **3a** as a white solid (1.86 g, 54% yield).

CCDC-2294705 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/structures.

Acknowledgements

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RESEARCH ARTICLE

Direct Intramolecular Coupling of Primary/Secondary Alcohols with Secondary Alcohols for Macrocyclic Alkenylation Using Ni-Zeolite Catalyst Under Continuous-Flow Conditions

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 D. V. Sutar, G. B. Swami, A. B. Jamdade, Dr. B. Gnanaprakasam*



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