

A Strategic Approach to α,β -Unsaturated γ -Lactam Synthesis *via Trans-cis* Isomerization of Carbon-Carbon Double Bonds in Vinylogous γ -Amino Acids

विद्या वाचस्पति की
उपाधि की अपेक्षाओं की आंशिक पूर्ति में प्रस्तुत शोध प्रबंध

**A thesis submitted in partial fulfillment of the requirements
of the degree of Doctor of Philosophy**

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भारतीय विज्ञान शिक्षा एवं अनुसंधान संस्थान पुणे
INDIAN INSTITUTE OF SCIENCE EDUCATION AND RESEARCH PUNE
2023

Dedicated to Our Teachers and Family

CERTIFICATE

This is to certify that the work incorporated in the thesis entitled “**A Strategic Approach to α,β -Unsaturated γ -Lactam Synthesis via *Trans-cis* Isomerization of Carbon-Carbon Double Bonds in Vinylogous γ -Amino Acids**” submitted by **Manjeet Singh (ID No. 20173533)** carried out by the candidate at the Indian Institute of Science Education and Research (IISER), Pune, 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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Declaration

I hereby declare that the thesis entitled “**A Strategic Approach to α,β -Unsaturated γ -Lactam Synthesis via *Trans-cis* Isomerization of Carbon-Carbon Double Bonds in Vinylogous γ -Amino Acids**” submitted for the degree of Doctor of Philosophy in Chemistry at Indian Institute of Science Education and Research (IISER), Pune has not been submitted by me to any other University or Institution. This work was carried out at Indian Institute of Science Education and Research (IISER), Pune, India under the supervision of Prof. Hosahudya N. Gopi.

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Abbreviations

Ac₂O = Acetic anhydride

ACN = Acetonitrile

AcOH = Acetic acid

Aib = α -Amino isobutyric acid

Aic = 4-amino isocaproic acid

aq. = Aqueous

Bn = Benzyl

Boc = tert-Butoxycarbonyl

(Boc)₂O = Boc anhydride

^tBu = tertiary Butyl

Calcd. = Calculated

CCDC no. = Cambridge Crystallographic Data Centre number

CIF = Crystallographic Information File

d γ = dehydro gamma

dr = Diastereomeric ratio

DCC = N, N' -Dicyclohexylcarbodiimide

DCM = Dichloromethane

DIPEA = Diisopropylethyl Amine

DMAP = 4-Dimethylaminopyridine

DMF = Dimethylformamide

DMSO = Dimethylsulfoxide

er = Enantiomeric ratio

Et = Ethyl

EtOAc = Ethyl acetate

EtOH = Ethanol

Fmoc = 9-Fluorenylmethoxycarbonyl

Fmoc-OSu = N-(9-Fluorenylmethoxycarbonyloxy) succinimide

g = gram

h = hours

H-bond = Hydrogen bond

HATU = Hexafluorophosphate Azabenzotriazole Tetramethyl Uronium

HBTU = 2-(1H-benzotriazol-1-yl)-1, 1, 3, 3-tetramethyluronium hexafluorophosphate

HCl = Hydrochloric acid

HOBT = Hydroxybenzotriazole

IBX = 2-Iodoxybenzoic acid

IR = Infrared Spectroscopy

LAH = Lithium Aluminium Hydride

M = Molar

MALDI-TOF/TOF = Matrix-Assisted Laser Desorption/Ionization-Time of Flight

Me = Methyl

MeOH = Methanol

mg = Milligram

min = Minutes

μ L = Micro liter

mL = Milliliter

mM = MilliMolar

mmol = millimoles

MS = Mass Spectroscopy

N = Normal

nM = NanoMolar

NHS = N-hydroxy succinimide

NMP = N-methyl pyrrolidone

NMR = Nuclear Magnetic Resonance

ORTEP = Oak Ridge Thermal-Ellipsoid Plot Program

PG = Protecting Group

ppm = Parts per million

Py = Pyridine

R_f = Retention factor

RP- HPLC = Reversed Phase-High Performance Liquid Chromatography

R_t = Retention time

RT = Room Temperature

TFA = Trifluoroacetic acid

THF = Tetrahydrofuran

UV = Ultraviolet–Visible Spectroscopy

Z γ = Z-dehydro gamma

Abstract

The α,β -unsaturated γ -lactams represent important synthetic targets due to their presence in natural products, diverse biological activities, and their utility as building blocks for the synthesis of other compounds. These compounds have proven to be valuable scaffolds in many biologically active peptide natural products. Despite their wide range of applications, there are currently limited methods available for synthesizing α,β -unsaturated γ -lactams. We have been interested in understanding the conformation and chemical reactivity of α,β -unsaturated γ -amino acids. Previously, we studied the conformations of polypeptides composed of α,β -unsaturated γ -amino acids and also demonstrated base-mediated cyclization of α,β -unsaturated γ -amino acid amides into γ -lactams, involving multiple migrations of carbon-carbon double bonds. In this work, we have demonstrated the cyclization of α,β -unsaturated γ -amino acids under mild conditions. We have shown the spontaneous transformation of N-protected α,β -unsaturated γ -amino acid active esters into N-protected *Z*- α,β -unsaturated γ -lactams in the presence of a mild base. We studied the kinetics of the transformation. Further, we demonstrated the synthesis of *Z*- γ -lactams through in situ activation of *E*- α,β -unsaturated γ -amino acids using the peptide coupling reagent HBTU, DMF, and DIPEA at room temperature. Both methods gave excellent yields. Importantly, this transformation involves the remarkable *E* $\rightarrow$ *Z* isomerization of double bonds, a process uncommon in nature. This strategy also demonstrates the *trans-cis* isomerization of carbon-carbon double bonds without light or catalyst. By employing this strategy, we generated a library of α,β -unsaturated γ -lactams with diverse side chains in monomers and peptides with excellent yields. We also extended this strategy for the transformation of *E*-vinyllogous amino acids into *Z*-vinyllogous amino acids. We further applied this strategy for the synthesis of lactones. The analysis of the products and mechanistic analysis revealed the complete racemization of the products. To overcome the racemization of *Z*- γ -lactams, we redesigned the strategy and used (*Z*)-vinyllogous amino acids as starting materials instead of *E*-vinyllogous amino acids. The new strategy gave optically pure *Z*- γ -lactams. Overall, we have developed novel, mild, and effective strategies for the synthesis of *Z*- γ -lactams from both *E*- and *Z*-vinyllogous amino acids and peptides through carboxylic acid activation. The lactamization involves the *E* $\rightarrow$ *Z* isomerization of carbon-carbon double bonds. This strategy can be applied for the synthesis of *Z*-vinyllogous amino acids from *E*-vinyllogous amino acids and also for the synthesis of lactones.

Publications

1. **M. Singh**, M. Kumar, S. A. Nalawade, D. R. Puneeth Kumar and H. N. Gopi, Cyclization of N-Boc-(*E*)- α,β -Unsaturated γ -Amino Acid Active Esters into N-Boc-(*Z*)- α,β -Unsaturated γ -Lactams through *E* $\rightarrow$ *Z* Isomerization. *Org. Biomol. Chem.*, 2023, **21**, 3766-3769.
2. **M. Singh**, S. A. Nalawade, D. R. Puneeth Kumar, K. Veeresh, S. Pahan, S. Dey and H. N. Gopi, HBTU Mediated Synthesis of α,β -Unsaturated γ -Lactams from *E*- α,β -Unsaturated γ -Amino Acids, *Eur. J. Org. Chem.*, 2023, **26**, e202300682.
3. K. Veeresh, **M. Singh** and H. N. Gopi. Impact of substituent effects on the design of β -sheet mimetics and β -double helices from (*E*)-vinyllogous γ -amino acid oligomers, *Org. Biomol. Chem.*, 2019, **17**, 9226-9231.
4. S. A. Nalawade, **M. Singh**, D. R. Puneeth Kumar, S. Dey and H. N. Gopi. Stereoselective synthesis of backbone extended π -conjugated amino esters, *Org. Biomol. Chem.*, 2023, **21**, 2586.
5. D. R. Puneeth Kumar, R. M. Reja, D. K. Senapati, **M. Singh**, S. A. Nalawade, G. George, G. Kaul, A. Akhir, S. Chopra, S. Raghothama and H. N. Gopi. A cationic amphiphilic peptide chaperone rescues A β 42 aggregation and cytotoxicity, *RSC Med. Chem.*, 2023, **14**, 332-340.
6. D. R. Puneeth Kumar, S. A. Nalawade, S. Pahan, **M. Singh**, D. Senapati, S. Roy, S. Dey, S. Toraskar, S. Raghothama and H. N. Gopi. Proteolytically Stable $\alpha\gamma$ -Hybrid Peptides Inhibits the Aggregation and Cytotoxicity of A β 42, *ACS Chem. Neurosci.*, 2023, *ACS Chem. Neurosci.*, 2023, **14**, 18, 3398–3408.

Chapter 1

General Introduction of Lactams and their Precursor Vinylogous Amino Acids

1.1 Introduction

Lactams belong to one of the most important classes of organic compounds, the versatility of these compounds is reflected by their presence in a vast number of natural and pharmaceutical products.¹ They can be defined as “cyclic amides of amino carboxylic acids having 1-azacycloalkan-2-one or 1-azacycloalken-2-one as a core structure and some analogs of these rings substitute one or more C-atoms by the heteroatoms”. Lactam exists in various forms such as α -lactam (3-member ring), β -lactam (4-member ring), γ -lactam (5-member ring), δ -lactam (6-member ring) and ϵ -lactam (7-member ring), out of these β - and γ -lactams are most common in nature (Figure 1). Generally γ -lactam can be synthesized through the cyclization of γ -amino acids (γ -AAs), commonly known as the lactamization reaction.² One of the most important member (β -lactam) of this family was discovered by Sir Alexander Fleming in 1928 in penicillin,³ which is the first known β -lactam antibiotic originally obtained from *Penicillium chrysogenum* fungus species. Other than penicillin, penems or thiopenems, cephalosporins, monobactams and carbapenems also belong to β -lactam antibiotics.⁴ The presence of the β - and γ -lactam moieties is widespread among both natural and synthetic biologically active compounds (Figures 2 and 3). These structural elements impart a diverse array of biological activities, making them highly relevant in medicinal chemistry.⁵ Consequently, functionalized γ -lactams are of significant interest, holding considerable potential for the development of bioactive molecules.

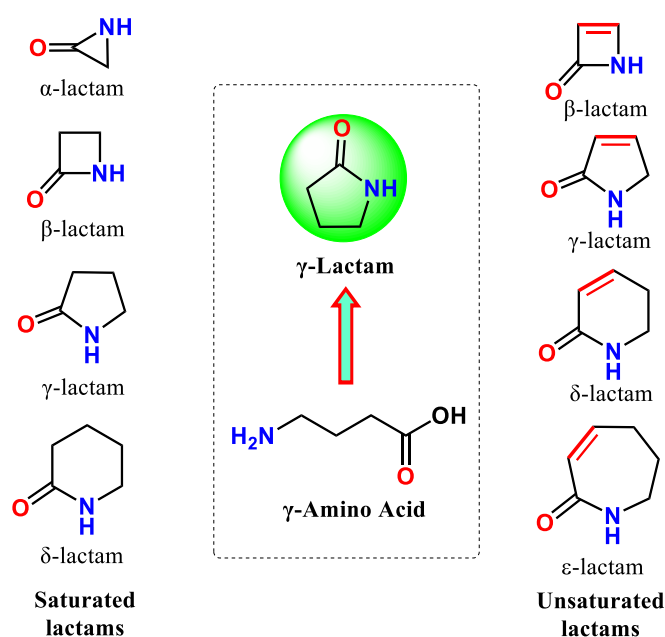


Figure 1. Different types of saturated and unsaturated lactams.

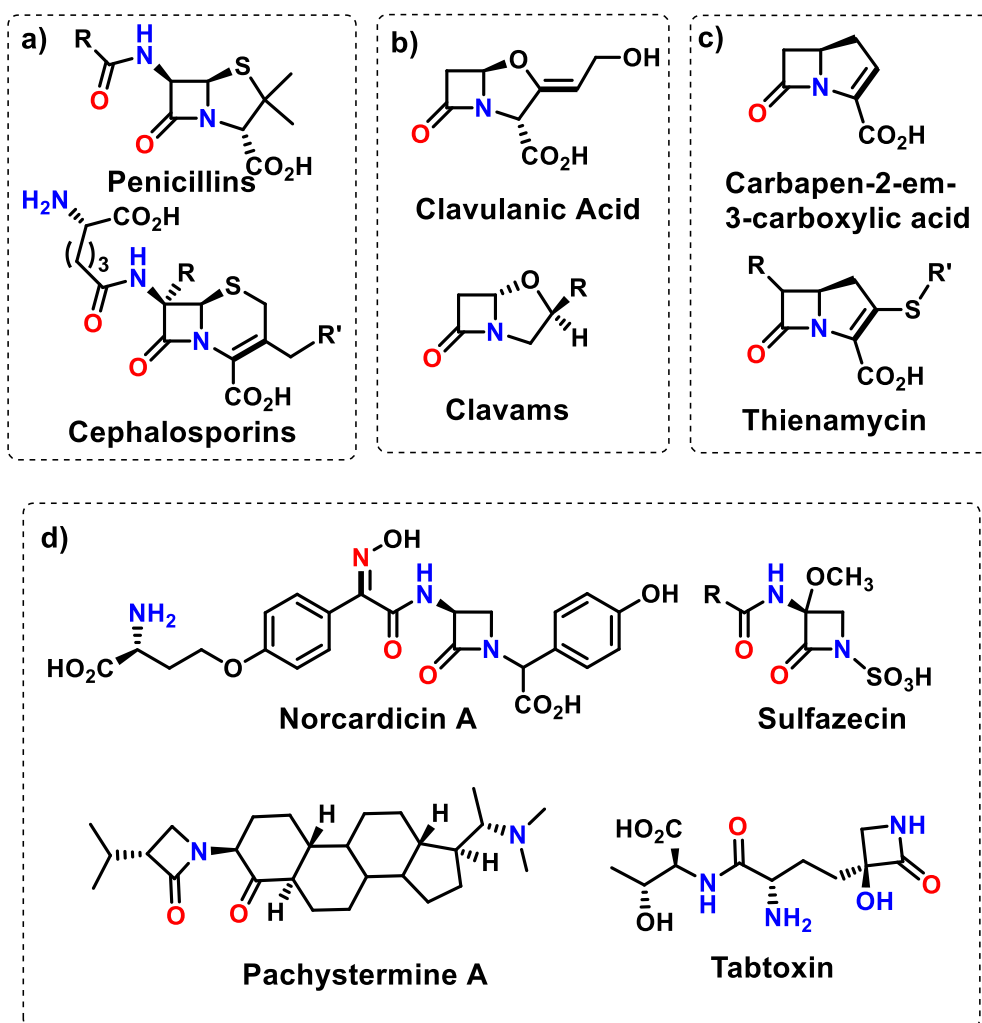


Figure 2. Selected examples of β -lactam compounds.

The exploration of γ -lactam scaffold stemmed from the recognition of rising bacterial resistance to conventional β -lactam antibiotics. Presently bacterial resistance is a major challenge associated with β -lactam antibiotics, now it is necessary to shift from the β -lactam core to some other structures. Recognizing the vital role of an activated amide bond for activity (beyond the β -lactam ring), the focus naturally shifted to γ -lactams and their analogs. Bicyclic γ -lactams, particularly penem derivatives, emerged as a specific area of interest in this context. The γ -lactam analogs of penicillins can also act as active antibiotics were first reported, by Baldwin and co-workers, and also researchers from Eli Lilly in the same year 1986.⁶ Unfortunately, due to their low antibacterial activity, these compounds were ultimately not brought into the market. However, their presence sparked inspiration among chemists, leading to the design of novel biologically active compounds featuring the γ -lactam ring.⁷

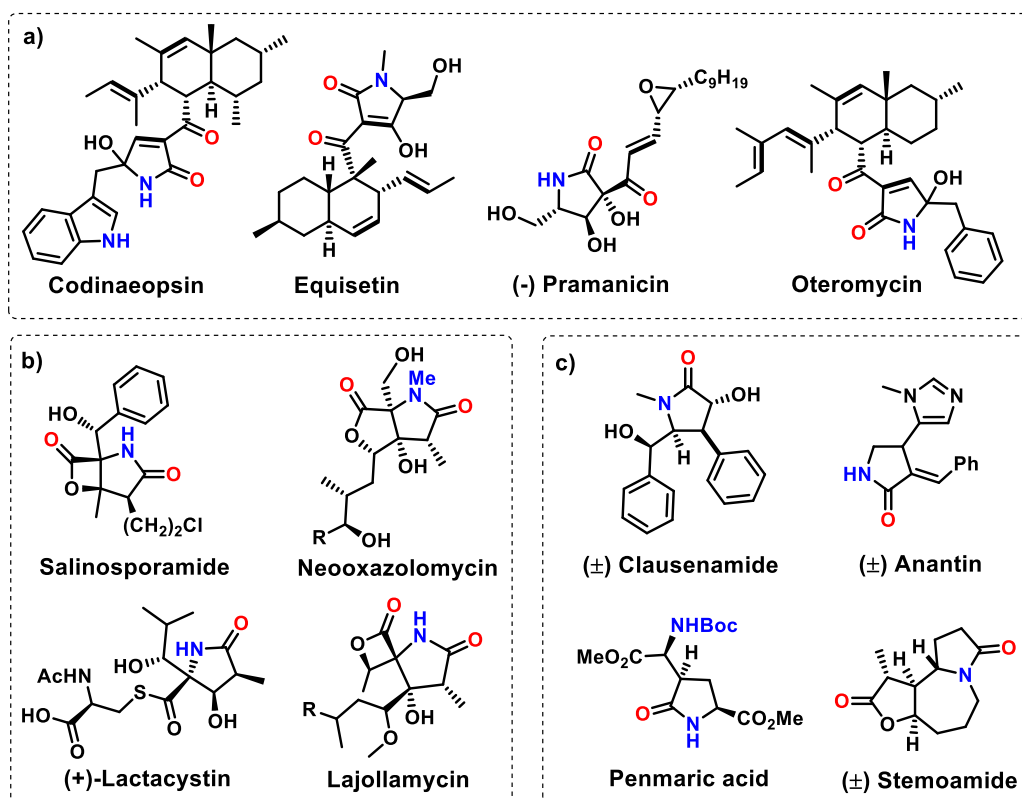


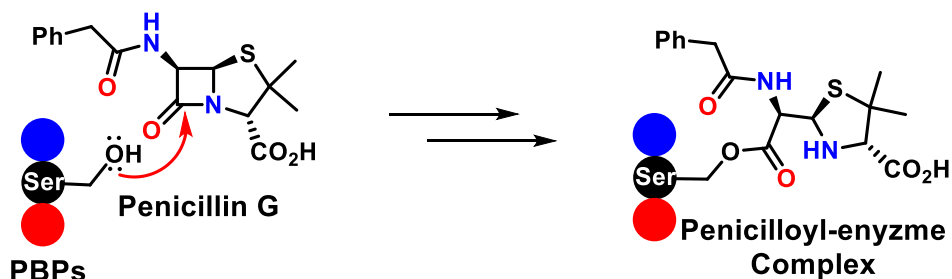
Figure 3. Some examples of γ -lactam containing compounds (a) from fungi, (b) from bacteria and (c) from plant sources.

1.2 Significance of Lactams

Lactams are an important class of compounds in organic chemistry and are widely used in the synthesis of various pharmaceuticals and other organic products. The rich chemistry of lactams is associated with their ability to undergo a variety of reactions, such as ring-opening, cycloaddition reaction, Michael addition reaction and substitution reactions, leading to a plethora of functionalized derivatives. These compounds find applications regularly in various fields and some of the important areas discussed below:

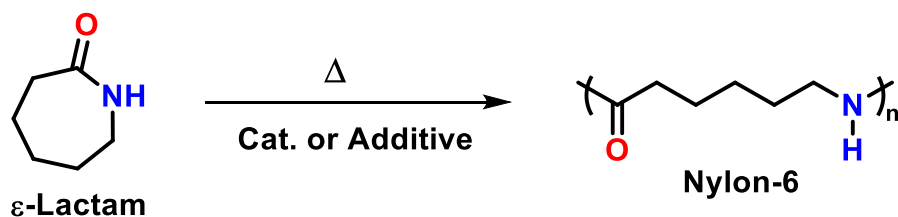
(i) Medicinal Chemistry or Pharmaceuticals: Many natural and synthetic compounds are having lactam rings is integral part of their structures, these compounds have been serving as anti-bacterial, anti-inflammatory, anti-viral, anti-diabetic, antimalarial, and anti-cancer.⁸ For example, β -lactam antibiotics like penicillins and cephalosporins are widely used in medicine and contain β -lactam in their structure. Blumberg and Strominger proposed the mechanism of action of penicillin in 1974, they proposed that all β -lactam antibiotics act as inhibitors of bacterial cell wall synthesis.^{8a} The transpeptidase generally called the penicillin binding

proteins (PBPs) is indispensable in the late stage of bacterial cell wall synthesis. In general, the amide bond of the β -lactam is electrophilic compared to a normal amide bond due to the ring strain of a 4-membered ring. Thus, it is highly susceptible to nucleophilic attack. The recognition of penicillin by the Serine amino acid of PBPs is a chemoselective phenomenon depicted in Scheme 1.



Scheme 1. Pictorial representation of the mechanism of action of β -lactam antibiotics.

(ii) Polymer Chemistry: Lactams are used in the production of different types of polyamide polymers such as nylon. Lactam ring opening polymerization (ROP) reaction is the most commonly used approach for synthesizing polyamides. The nylon polymers are the most significant polyamides produced at a scale exceeding 3 metric tons annually. These polyamides play a crucial role in a wide range of consumer products across various industry sectors, boasting a rich history dating back to the early 1900^s. Nylon 6, first synthesized by Paul Schlack in 1938, is characterized by a 5-methylene spacer between the amide linkages.⁹ Another commercially important polyamide nylon 12, is synthesized through the ring ROP of dodecalactam.¹⁰ In the initial stages, the industry employed H_2O -catalyzed ROP at high temperatures (250 °C). Over time, advancements in ROP techniques have been implemented, with notable improvements such as the use of acylated caprolactam or acylating agents which act as activators.¹¹ Higher members of this family such as nylon-11 and nylon-12 are frequently used for the automotive fuel lines, wire and cable insulation due to their unique properties.¹⁰ Additionally, the polymers nylon-6, nylon-6,6 and nylon-12 are prevalent in biomedical applications such as catheters, wound dressings, dental implants and sutures.¹²



Scheme 2. Synthesis of nylon-6 polymer from ϵ -lactam *via* ROP.

(iii) Natural Products: Nature has consistently served as a valuable reservoir of lactam-based natural products, some of these natural compounds being directly utilized in traditional medicine because of their pharmacological properties or serving as inspiration for chemists in the synthesis of analogs with enhanced biological properties. This motif is prevalent in various organisms, including bacteria, fungi, plants, and even animals, as shown in Figure 3. The γ -lactam structural feature plays the utmost role in numerous biologically active natural compounds, reflecting the diverse range of biological activities they exhibit. Despite the abundance of natural γ -lactams such as oligopyrrole natural products,¹³ peptidic natural products,¹⁴ terpenoid natural products,¹⁵ and non-peptidic natural products,¹⁶ there is limited information on the biosynthesis of these compounds.¹⁷ It can be speculated, that glutamic acid, glutathione, proline, and γ -aminobutyric acid (GABA) serve as the primary precursor compounds for γ -lactams in living cells.^{17,18}

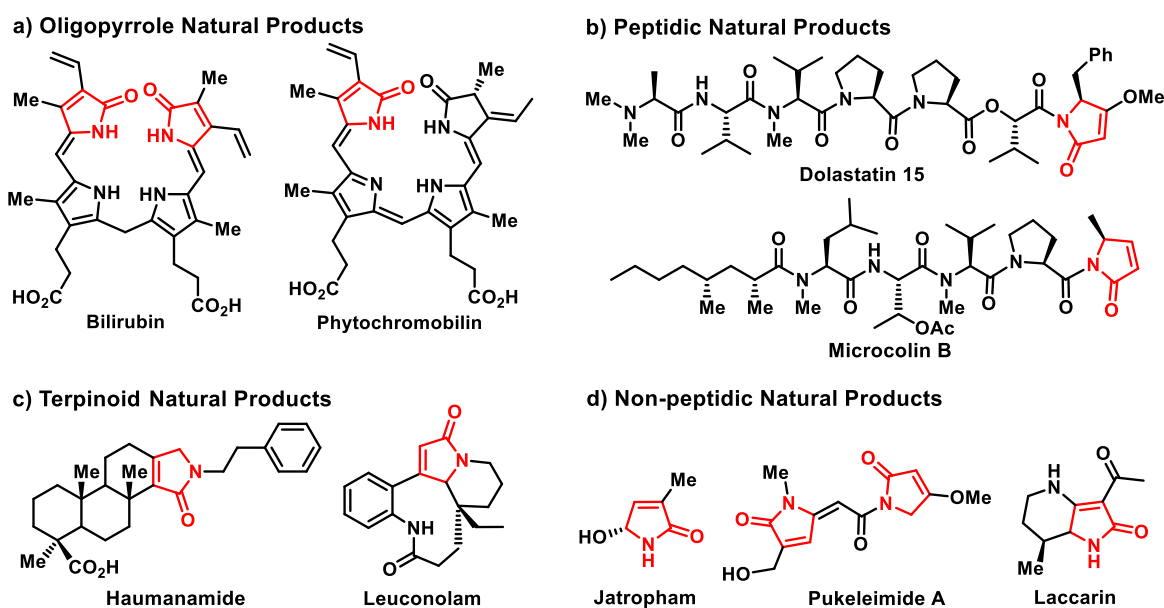
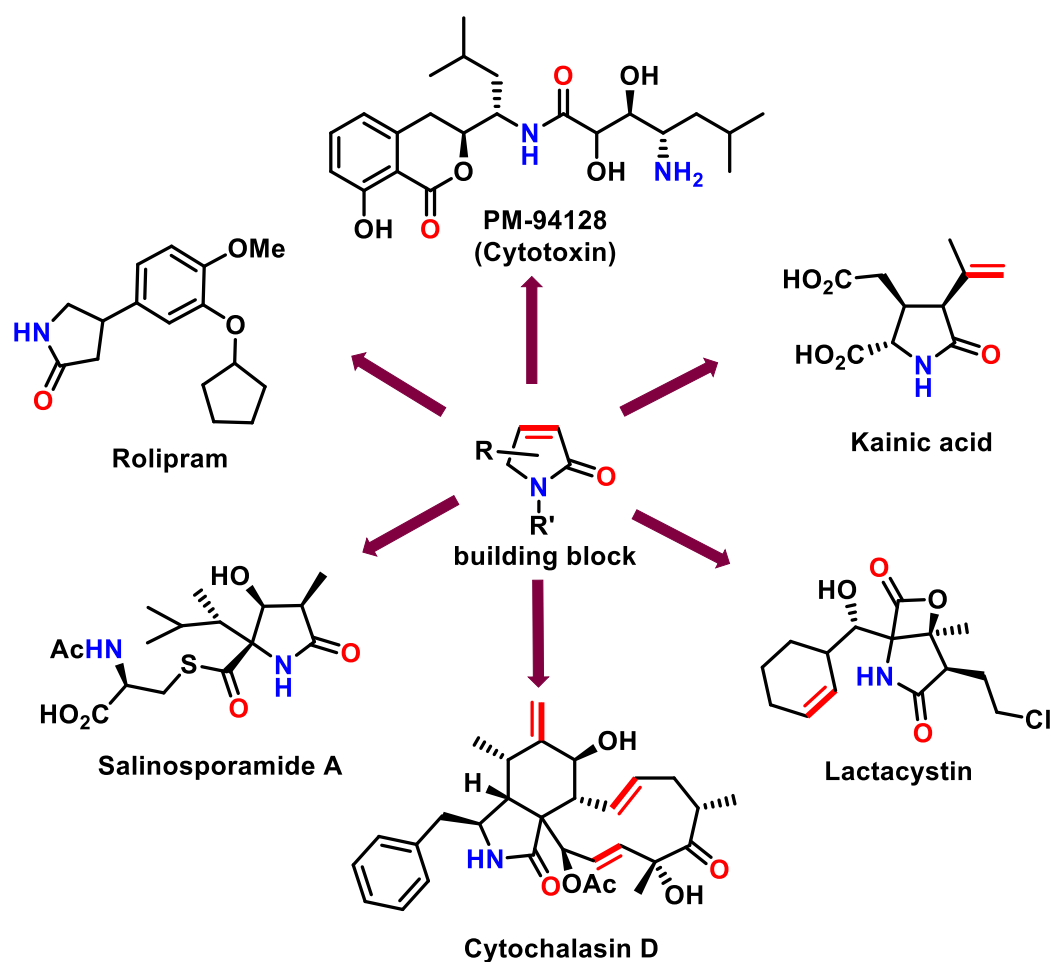


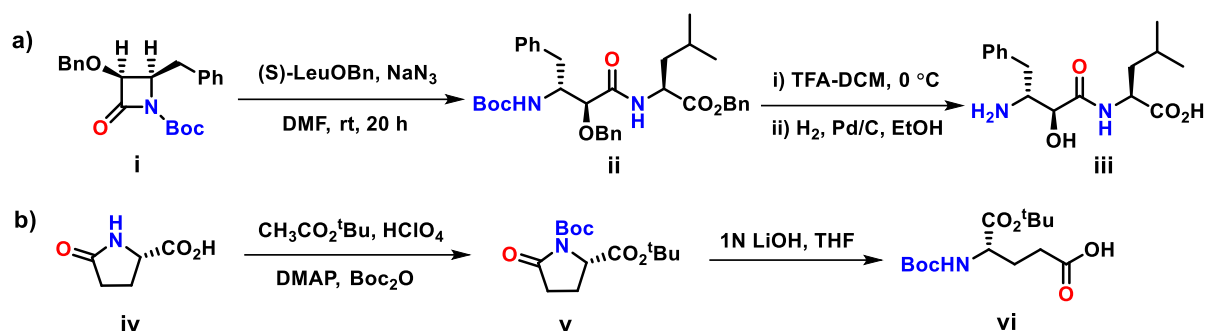
Figure 4. Selected examples of natural products with γ -lactams as a structural motif.

(iv) Organic Synthesis: Organic molecules containing nitrogen element are undeniably crucial in organic chemistry, as evidenced by their fundamental roles in various biological activities. Proteins, enzymes, nucleic acids (DNA and RNA), nucleobase and alkaloids, for instance, showcase the significance of nitrogen-containing compounds in biological systems.¹⁹ To synthesize molecules like amino acids, polymers, alkaloids, pharmaceutical compounds and natural products particularly β - and γ -lactams have gained prominence as a suitable building

blocks, depicted in Scheme 3 and 4. Recently, both racemic and asymmetric synthetic procedures of N-containing compounds with biological relevance have emerged, β - and γ -lactams serve as precursors to essential compounds such as, β/γ -amino alcohols or non natural β/γ -amino acids.^{20,21} These products, in turn, become valuable starting materials for peptides that incorporate non-natural amino acids. Notably, β -lactams have been instrumental in introducing the hydrophobic side chain of paclitaxel (taxol), an anticancer compound, and its related analogs. Additionally, total synthesis of lankacidin C utilizes the β -lactam compounds as predecessor for their δ -lactone core and lankacidin C acts as a macrolide antibiotic with antitumor properties,²² and constrained peptidomimetics have been synthesized using γ -lactam templates.²³



Scheme 3. Application of α,β -unsaturated γ -lactam in synthesis.



Scheme 4. Synthetic applications of β/γ -lactams (a) β -amino acid synthesis and (b) γ -amino acid synthesis.

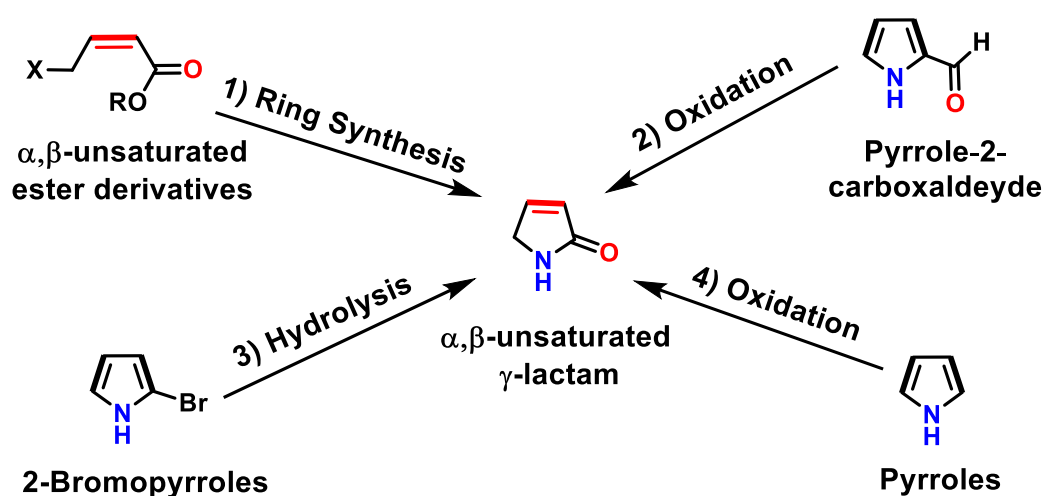
Due to these applications, lactams have been getting attention since the discovery of penicillin, and vast literature is known for the synthesis of the β -lactams.²⁴ The γ -lactam particularly α,β -unsaturated γ -lactam despite its paramount importance due to its significant implications in medicinal chemistry, drug development, and organic synthesis is less explored. Many biologically active compounds and pharmaceuticals incorporate α,β -unsaturated γ -lactam moieties, making the development of efficient synthetic methods crucial for the creation of novel drugs with therapeutic potential. Moreover, the methodologies developed for α,β -unsaturated γ -lactam synthesis often extend to broader applications in organic chemistry, providing valuable tools for constructing complex molecular structures. Their synthesis not only enhances our understanding of organic chemistry and reaction mechanisms but also has practical implications in catalysis, green chemistry, and the design of drug delivery systems. Overall, the study of α,β -unsaturated γ -lactam synthesis is essential for advancing both synthetic organic chemistry and medicinal chemistry.

1.3 Synthesis of α,β -Unsaturated γ -Lactam

The synthesis of α,β -unsaturated γ -lactams holds an important place in synthetic organic chemistry. α,β -unsaturated γ -lactams can be obtained through various synthetic protocols. These methods can be classified into two categories based on the order of development which are the following:

1.3.1 The Classical Methods for α,β -Unsaturated γ -Lactam Synthesis

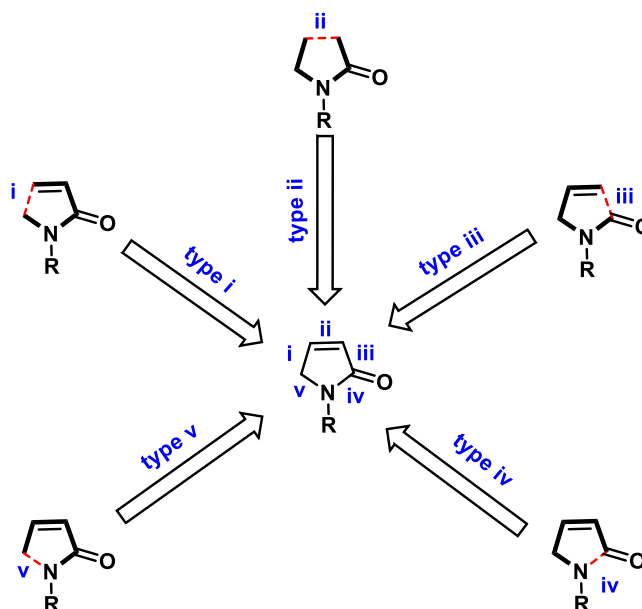
The initial interest in lactam synthesis was primarily driven by their presence in oligopyrrole bile pigments as a terminal groups. In 1964, Atkinson and colleagues provided a comprehensive overview of the historical development of lactam synthesis.²⁵ During that era, four primary synthetic routes to lactam were prominent: (1) ring synthesis,^{26a} (2) pyrrole-2-carboxaldehyde oxidation,^{26b} (3) 2-bromopyrroles hydrolysis^{26c} and (4) pyrroles oxidation^{26d}. All methods are collectively delineated in Scheme 5. These approaches continue to be among the most widely employed procedures for the *de novo* synthesis of α,β -unsaturated γ -lactam.



Scheme 5. Traditional approaches to α,β -unsaturated γ -lactam synthesis.

The synthesis of α,β -unsaturated γ -lactam can be achieved through intramolecular and intermolecular cyclization. In the intramolecular synthesis of lactam, the key reactions occur within a single molecule, leading to the formation of the α,β -unsaturated γ -lactam. This method often involves the closure of a ring through reactions between functional groups within the same molecular framework, for example, a reaction between amine and carboxylic acid functional groups. On the other hand, intermolecular lactam synthesis involves reactions between distinct molecular entities, resulting in the formation of α,β -unsaturated γ -lactam. Both intramolecular and intermolecular approaches offer unique advantages and challenges, providing chemists with versatile tools to access a wide range of lactam structures for various applications. The ring synthesis in the design of α,β -unsaturated γ -lactams through intramolecular reactions is among the most commonly used methods, depicted in Scheme 6. The α,β -unsaturated γ -lactams synthesis can be achieved through following five intramolecular cyclizations: (i) Michael addition type reaction and Aldol type condensation,²⁷ (ii) Metathesis

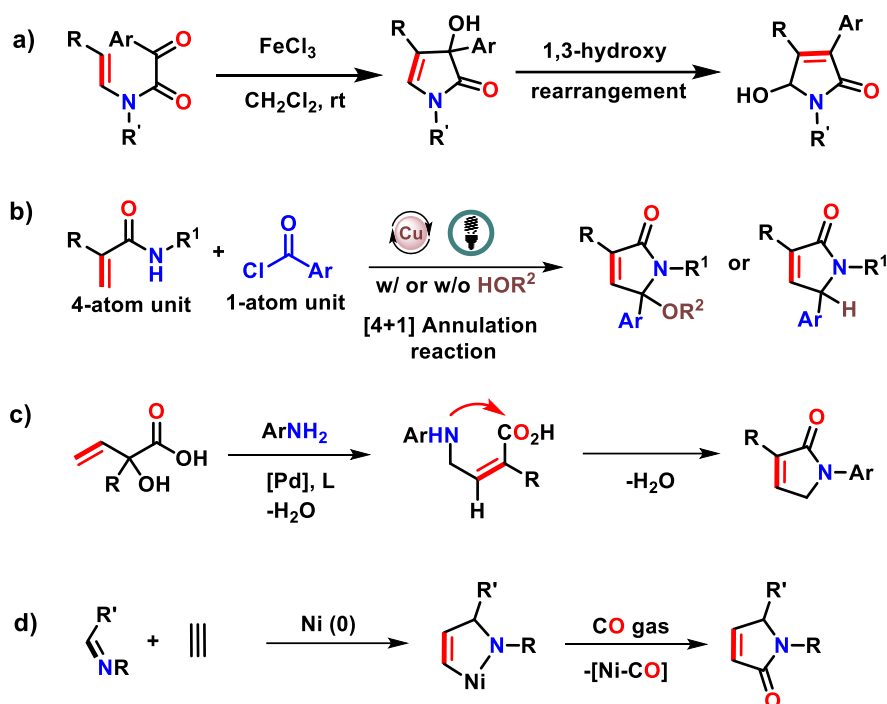
and Wittig type reactions,²⁸ (iii) Seleno- and cyano-amidation reaction,²⁹ (iv) intramolecular condensation reaction,³⁰ and (v) radical cyclization and metal-salt catalyzed cyclocondensation reactions.³¹



Scheme 6. Strategies used to synthesize α,β -unsaturated γ -lactam by intramolecular cyclization.

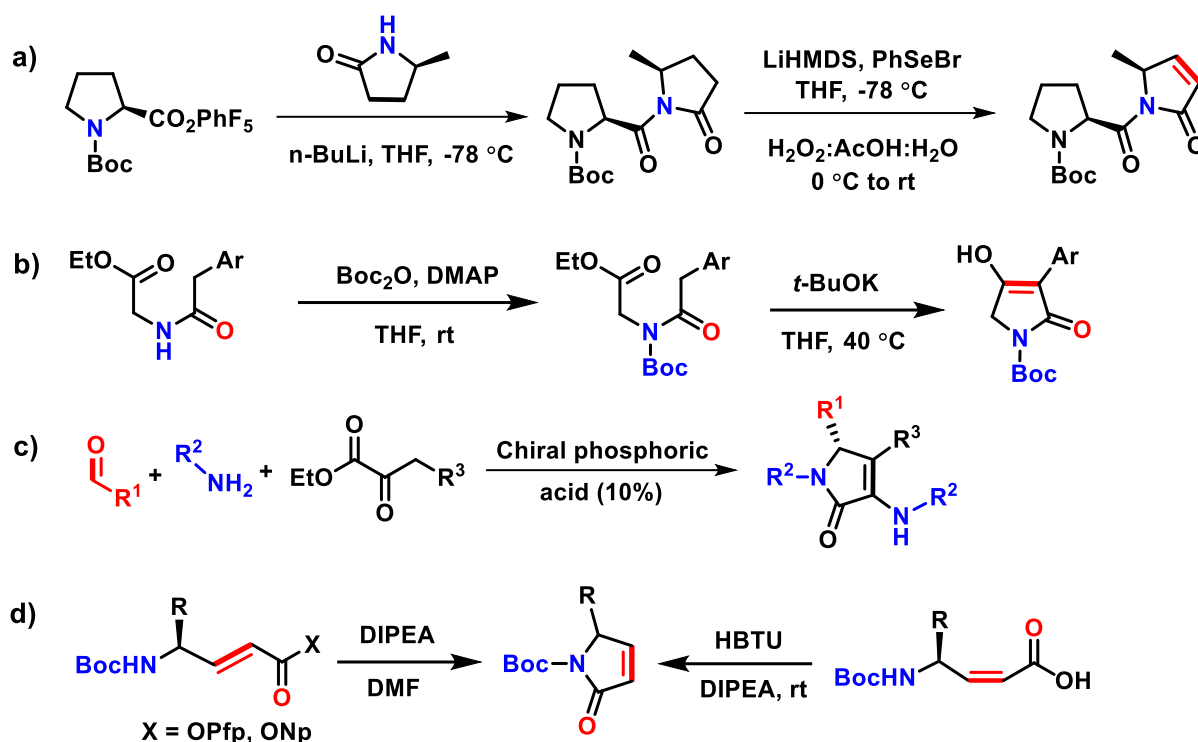
1.3.2 The Modern Synthetic Methods for α,β -Unsaturated γ -Lactam Synthesis

(i) Transition Metal-Catalyzed Synthesis of α,β -Unsaturated γ -Lactam: In recent years, the development of efficient and sustainable synthetic methodologies for the construction of α,β -unsaturated γ -lactams has garnered considerable attention within the scientific community. Transition metal-catalyzed transformations have emerged as powerful tools in this context, providing atom-efficient and versatile routes to access these valuable compounds. The ability of transition metals to facilitate key bond-forming steps, coupled with their inherent catalytic efficiency, positions them as catalysts of choice for the synthesis of complex organic structures. To synthesize α,β -unsaturated γ -lactams, Wang *et al.* introduce the FeCl_3 -catalyzed intramolecular enaminic addition strategy followed by 1,3-hydroxy rearrangement,³² Ngai *et al.* introduce Cu-catalyzed [4+1] annulation reaction of acrylamides and aroyl chlorides,³³ Kleij *et al.* introduce Pd-catalyzed domino synthesis *via* amination of tertiary allylic alcohol,³⁴ Ogoshi *et al.* introduce Ni-catalyzed [2+2+1] cycloaddition reaction of alkynes and imines in the presence of phenyl formate as a CO source,³⁵ and others,³⁶ all these synthetic protocols are delineated in Scheme 7.



Scheme 7. Metal catalyzed synthesis of α,β -unsaturated γ -lactams.

(ii) **Non-Transition Metal-Catalyzed Synthesis of α,β -Unsaturated γ -Lactam:** While transition metal catalysis has made significant strides in the construction of α,β -unsaturated γ -lactams, the exploration of non-metal-catalyzed routes represents an exciting and complementary avenue in the pursuit of sustainable synthetic methodologies. The absence of transition metals in catalysis not only address concerns related to metal waste but also presents an opportunity to expand the toolbox of synthetic methods, allowing for a more diverse range of substrates and reaction conditions. For the synthesis of Z - α,β -unsaturated γ -lactams, Gerwick *et al.* introduce the selenoxide elimination strategy of chiral pyrrolidone,³⁷ Pelkey *et al.* introduce base-mediated reaction of Boc-protected acetamides,³⁸ Palacios *et al.* introduce three-component Brønsted-acid-catalyzed reaction of aldehydes, amines, and pyruvate derivatives,³⁹ we recently introduced α,β -unsaturated γ -amino acids and active esters of α,β -unsaturated γ -amino acids for α,β -unsaturated γ -lactams formation which encompasses remarkable $E \rightarrow Z$ isomerization,⁴⁰ and others,⁴¹ all these synthetic protocols are delineated in Scheme 8.



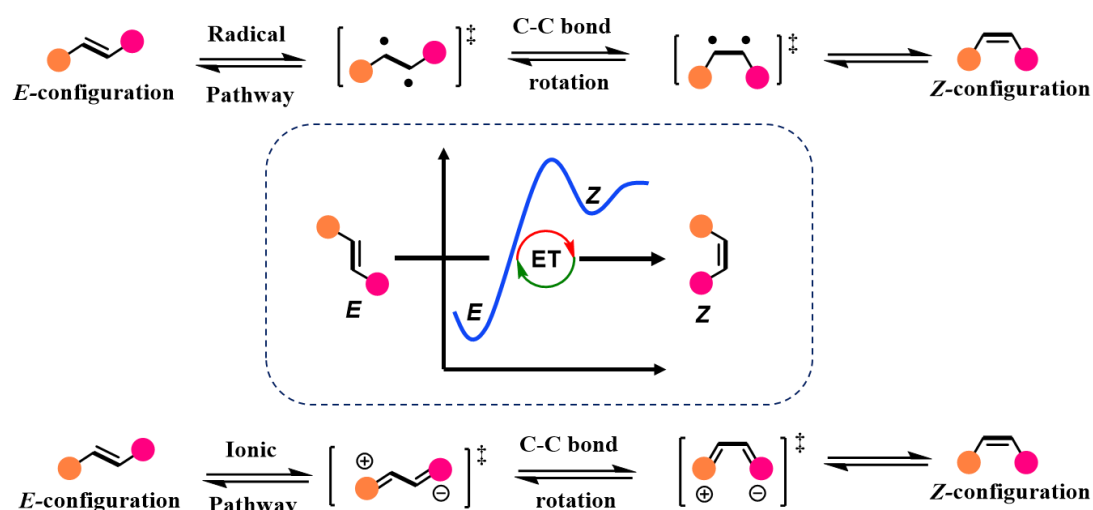
Scheme 8. Non-metal-catalyzed synthesis of α,β -unsaturated γ -lactam.

1.4 $E \rightarrow Z$ Isomerization

The chemical reactivity of the alkenes functional group in the organic molecules never fails to astonish the chemists. The isomerization phenomenon exhibited by these molecules provides an extra platform for their chemical reactivity. The isomerization of alkenes is generally described in terms of $E \rightarrow Z$ and $Z \rightarrow E$ configurational changes. As a result, the spatial orientation of the alkene's substituents changes which is the main cause of the diverse properties and different chemical reactivity of the E and Z isomer. During the transformation of E -vinyllogous amino acid into α,β -unsaturated γ -lactam the $E \rightarrow Z$ isomerization was the crucial step of reaction Scheme 8d. Although the thermal stability of the E -configuration of alkene is more compared to the Z -configuration, as depicted in Scheme 9, under suitable reaction conditions and structural parameters of the product and intermediate restricted the transformation of Z -configuration back to E -configuration once formed.⁴²

1.4.1 Mechanisms of $E \rightarrow Z$ Isomerization: There are several mechanisms proposed in the literature to describe this phenomenon. Most common pathways of isomerization follow homolytic and heterolytic approaches.⁵² In the homolytic mechanism, the breaking of the

double bond results into the formation of a diradical intermediate where each carbon atom retains one of the two electrons from the π -bond. It can undergo C-C bond rotation followed by radical recombination leading to another isomeric form, generally shown by the olefin molecules.^{42b} Whereas in the heterolytic mechanism, the double bond cleavage in such a way that one carbon atom retains both electrons from the π -bond, while the other loses its electrons, forming an ionic intermediate. This ionic intermediate can undergo C-C bond rotation followed by rearrangement of bonds leading to another isomer, generally shown by push-pull alkenes (electron donating group at one end and electron withdrawing group at other end of alkene), these isomerization processes are delineated in Scheme 9. In addition to the chemical structure, several other factors also influence the $E \rightarrow Z$ isomerization such as temperature, light, solvent, catalyst (enzyme), substituents, and pH.⁴³

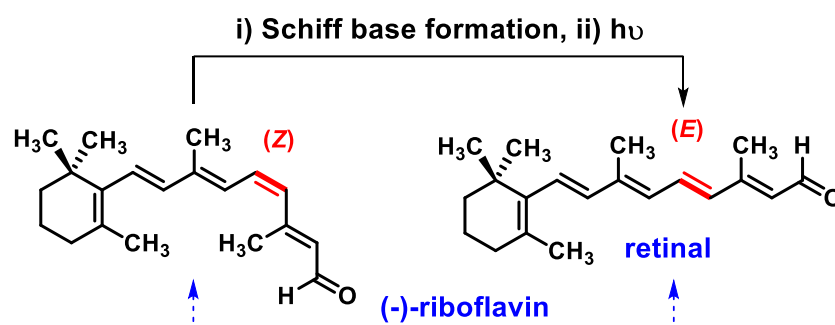


Scheme 9. General pathways of the $E \rightarrow Z$ Isomerization.

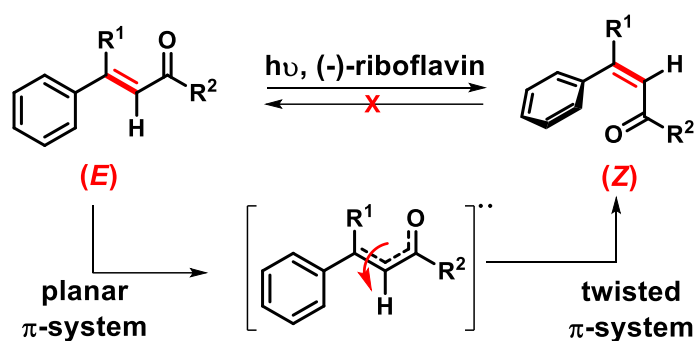
1.4.2 $E \leftrightarrow Z$ Isomerization in Natural and Artificial Systems: The inherent tendency of natural systems predominantly favors the E -isomer, which can be seen in natural photochemical process ($Z \rightarrow E$) involved in the isomerization of the retinal, depicted in Scheme 10a.⁴⁴ In a remarkable study conducted by Walker and Radda in 1967, it was observed that the riboflavin catalyses the reverse photoisomerization ($E \rightarrow Z$) of the retinal.⁴⁵ This significant discovery opened doors for further exploration of the method in organic compounds. In continuation, Gilmour *et al.* successfully utilize this technique in small molecule models, achieving a remarkable (Z)-selective catalytic isomerization of activated olefins, depicted in Scheme 10b.^{42a} The transformation is assisted by (-)-riboflavin as a key catalyst, resulting in an impressive selectivity of up to 99:1 of Z/E . Finally, polyene retinoids represent a crucial

class of biologically active molecules with diverse implications in various aspects of human physiology. Retinoids consist of retinol, retinal, and retinoic acid, playing crucial roles in vertebrate growth and development, vision, embryonic development, cell differentiation, reproduction, and immune response.⁴⁶

a) Natural System ($Z \rightarrow E$):



b) Activated Olefins ($E \rightarrow Z$):



Scheme 10. (a) Process of $Z \rightarrow E$ isomerization in the natural system (retinal) and (b) process of $E \rightarrow Z$ isomerization in activated olefin systems.

1.5 Vinylogous γ -Amino Acids

The three-dimensional structure of biomolecules namely proteins, lipids, nucleic acids, and carbohydrates is mainly considered to be responsible for their biological functions. Among these, proteins are the most important because of their involvement in almost all living processes in an organism. Amino acids are the fundamental building blocks of proteins, these 20 amino acids are also known as ribosomal or natural amino acids. Within this important field, a distinctive class of non-natural amino acids (nnAA) known as vinylogous amino acids due to their unique properties such as proteolytic stability, conformational diversity and site-specific labeling, has emerged as a subject of intense investigation. Vinylogous γ -amino acids or α,β -unsaturated γ -amino acids can be defined as amino acids containing $-\text{CH}=\text{CH}-$ group between

C $^{\alpha}$ and C=O in their chemical structure. The α,β -unsaturated γ -amino acids have been employed as initial compounds for producing γ -amino acids,⁴⁷ and serving as substrates in diverse organic reactions such as 1,4-conjugate addition,⁴⁸ epoxidation,⁴⁹ and the Diels-Alder reaction,⁵⁰ contributing to the creation of functional derivatives of γ -amino acids. Based on the configuration of the double bonds these vinylogous γ -amino acids can be *E*- and *Z*-vinylogous γ -amino acids, sometimes heteroaromatic γ -amino acids which have a *Z*-configuration by default, are depicted in Figure 5. The foldamer of vinylogous γ -amino acids is still less explored, this is mainly because of the challenges associated with obtaining stereochemically pure vinylogous γ -amino acids and their analogs.

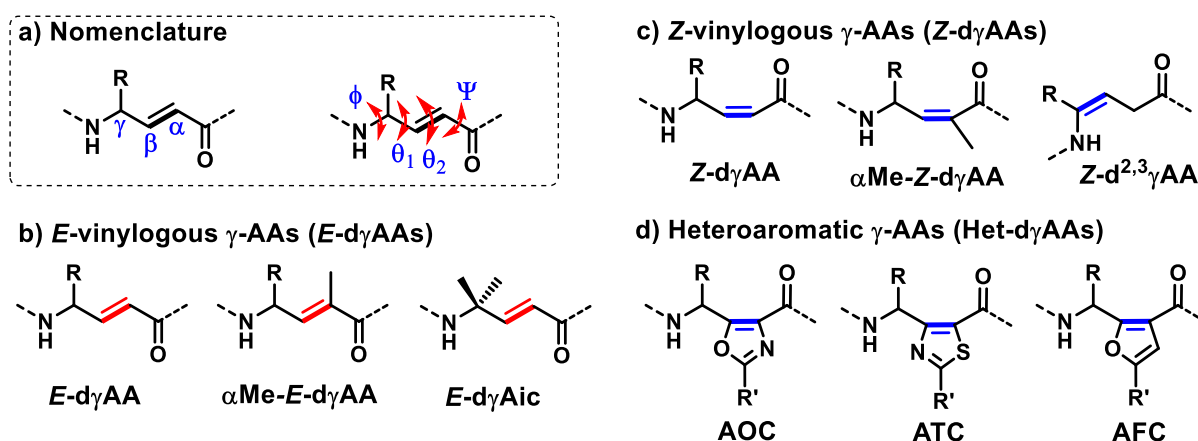


Figure 5. Different types of α,β -unsaturated γ -amino acids, (a) nomenclature, (b) *E*- α,β -unsaturated γ -amino acids, (c) *Z*- α,β -unsaturated γ -amino acids and (d) heteroaromatic γ -amino acids.

1.5.1 Natural Occurrence of Vinylogous Amino Acids and their Biological Importance

In the nineties, different *E*-vinylogous γ -amino acid residues were discovered in various natural secondary metabolites, with many of them found to be serving as inhibitors of serine and/or cysteine proteases.⁵¹ For example, miraziridine A, a non-ribosomal amino acid containing peptide natural product extracted from the marine sponge *Theonella aff. mirabilis* is known for its a potent cathepsin B inhibitor, because of the electrophilic nature of *E*-vinylogous arginine (Arg) residue present at C-terminus.⁵² Similarly, Gallinamide A^{52d} and Luminmycin A,^{52e} are derived from a marine cyanobacterium and belong to the Glidobactin peptide family respectively. They strongly inhibit the cysteine protease cathepsin L and the proteasome because of their irreversible inhibitory mechanism of action, both compounds accommodate

an *E*-vinyllogous alanine in their structure.⁵³ Among the most intriguing molecules in terms of structure-activity are the macrocyclic pentapeptides known as Cyclotheonamides, obtained from *Theonella* sponge species.^{51a} They are mainly functioning as serine proteases inhibitors in the trypsin family, the α -keto homoarginine and *E*-vinyllogous tyrosine is the key structural feature of these pentapeptides. The complex of Cyclotheonamide A with trypsin and thrombin binding was elucidated through X-ray diffraction (XRD) studies conducted by the research groups of Schreiber and Clardy,⁵⁴ and Fusetani,⁵⁵ separately.

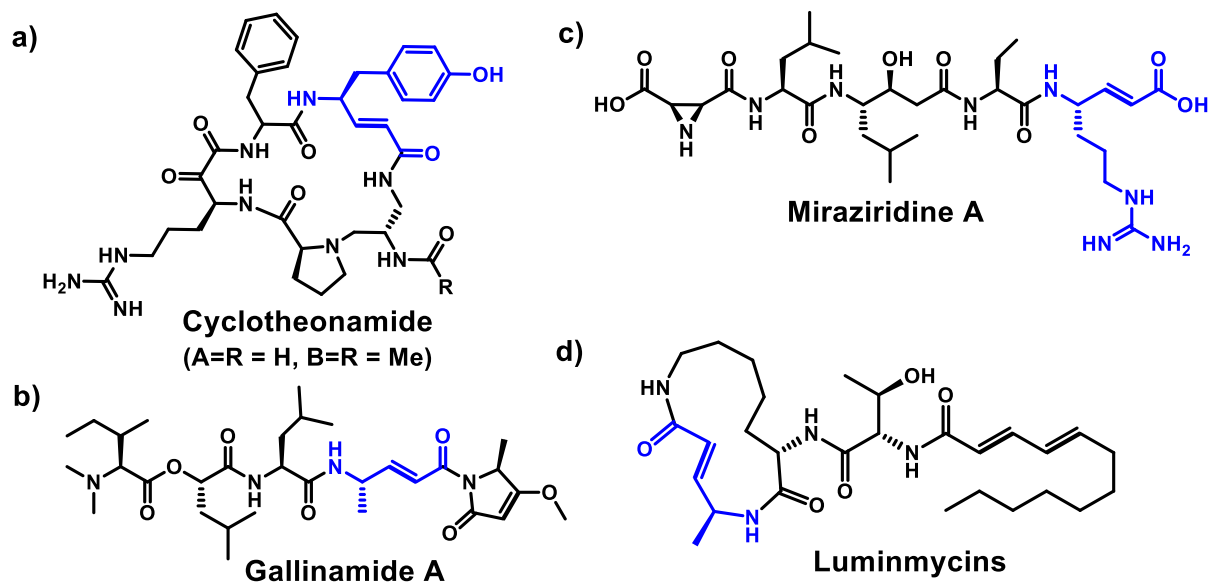


Figure 6. Selected examples of vinyllogous γ -amino acid-containing natural products.

1.5.2 Chemically Synthesized Vinyllogous γ -Peptides as Protease Inhibitors

Motivated by the bioactivity displayed by naturally available peptides with vinyllogous γ -amino acid as integral part of their structure, several research groups put effort to developed synthetic peptides incorporating vinyllogous γ -amino esters to specifically achieve the inhibition of serine and cysteine proteases.⁵⁶ In 1984, Hanzlik *et al.* pioneered a novel approach by replacing the scissile amide carbonyl with a Michael acceptor in peptidic substrates, which leads to a distinct class of peptidyl thiol protease inhibitors utilizing vinyllogous amino esters.^{56a,b} Later on, Kong *et al.* demonstrated the effective inactivation of HRV 3C protease using vinyllogous γ -glutamine esters.^{56c} Furthermore, numerous other studies have highlighted the design and development of protease inhibitor peptides based on Michael acceptors, particularly those incorporating vinyllogous residues.^{56d-g}

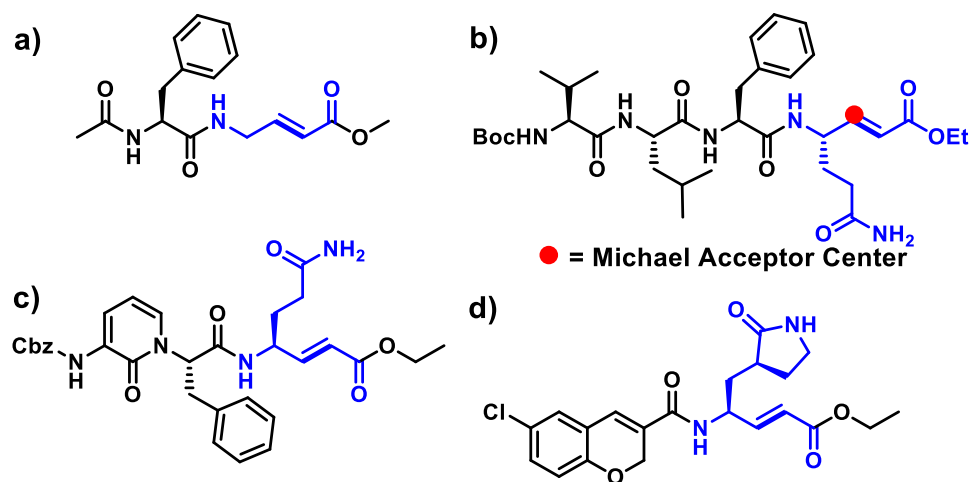
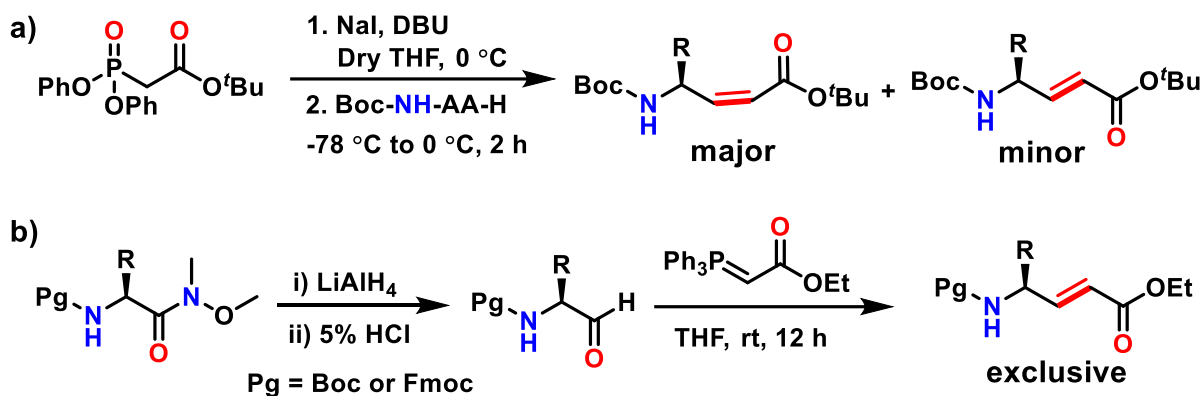


Figure 7. Selected examples of peptides utilizing (*E*)-vinyl groups for different protease inhibitors.

1.5.3 Synthetic Perspectives of Vinyl groups γ -Amino Esters

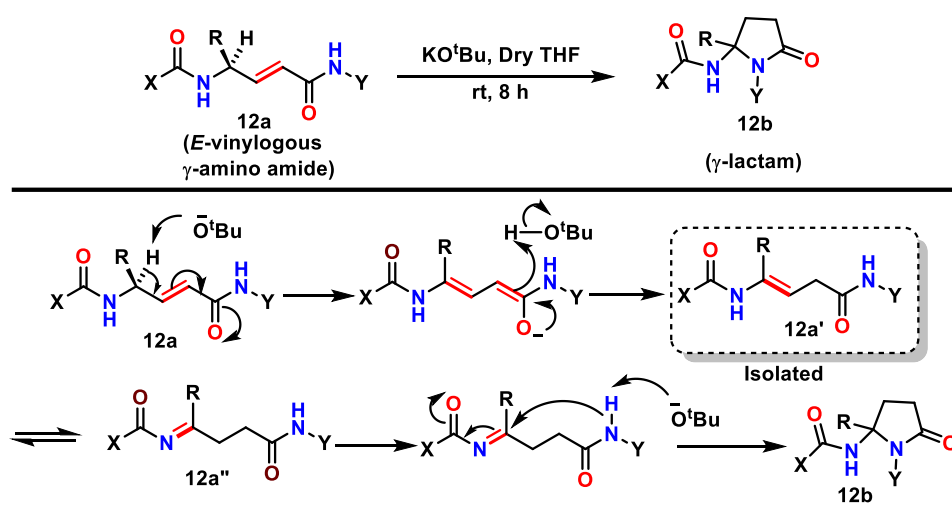
Various methods, namely Wittig,⁵⁷ Peterson,⁵⁸ and Julia,⁵⁹ and Horner-Wadsworth-Emmons (HWE)⁶⁰ reaction, have been reported for the synthesis of vinyl groups. Notably, the HWE reaction, a derivative of the Wittig reaction, has found extensive application in the formation of vinyl groups amino acids (as depicted in Scheme 11a).⁶¹ In this process, alkali metal bases like butyl lithium (BuLi) and sodium hydride (NaH) are commonly employed to make the reactive metalated-phosphonate intermediate. To enhance stereoselectivity, reactions often incorporate metal salts such as NaI and organic bases such as DBU and Et₃N.⁶² The group of Seebach *et al.* demonstrated the formation of methyl esters of *N*-Boc- α,β -unsaturated γ -amino acids with an *E/Z* ratio ranging from 3:1 to 7:1 using NaH as a base within the HWE framework.⁶³ Grison *et al.*, on the other hand, utilized Horner reagents as starting materials for the stereoselective synthesis of both *E*- and *Z*-vinyl groups γ -amino acids.⁶⁴ The *Z*-stereoselectivity was accomplished through reaction *tert*-butyl 2-(diphenoxyphosphoryl)-acetate with DBU in the presence of sodium iodide (NaI) followed by treatment of *in-situ* formed ylide with aldehyde at -78 °C temperature. Subsequently, from our group we showed an efficient approach for synthesizing vinyl groups γ -amino esters with remarkable *E*-stereoselectivity starting from the *N*-protected amino aldehydes taking advantage of the Wittig reaction, the pictorial representation of the reaction is depicted in Scheme 11b.⁶⁵ Moreover, the reaction shows excellent compatibility with diverse side chains and with different protecting groups such as Boc and Fmoc.



Scheme 11. Different strategies to synthesize vinylogous γ -amino esters.

1.5.4 *E*-vinylogous Amino Amide Rearrangement for γ -Lactam Synthesis

In order to show the actual potential of the *E*-vinylogous amino amide **12a** in the synthesis of organic compounds of practical applications, our group proposed the base-mediated transformation of *E*-vinylogous amino amide **12a** into their corresponding γ -lactams likely involves a sequential series of double-bond migrations. The reaction scheme and plausible mechanism for the rearrangement of **12a** into **12b** is delineated in Scheme 12.⁶⁶ Potassium *tert*-butoxide base initiate the reaction by the abstraction of the acidic γ -proton of **12a** triggers the $\alpha,\beta \rightarrow \beta,\gamma$ double-bond migration, resulting in the formation of intermediate **12a'**. It exists in equilibrium with **12b'** through enamine-imine tautomerism. Ultimately, the labile imide **12b'** undergoes a thermodynamically favoured 5-exo-trig cyclization, assisted by deprotonated C-terminus amide, leading to the γ -lactam formation.



Scheme 12. γ -Lactam synthesis through base-mediated rearrangement.

1.6 Modulating Conformation of Vinylogous γ -Amino Acids and Vinylogous γ -Peptides

1.6.1 Mimicking of β -Sheet Structures using *E*-vinylogous γ -amino acids: In the early nineties, Schreiber and colleagues conducted the first comprehensive investigation into the conformational preferences of *E*- α,β -unsaturated γ -amino acids (*E*-vinylogous γ -amino acid).⁶⁷ Their study involved a notable comparison between the folding tendencies of *E*- α,β -unsaturated γ -amino acids and their α -methylated counterparts, denoted as $\alpha(\text{Me})$ -*E*- α,β -unsaturated γ -amino acids. The single crystal structure analysis of Boc-*E*-d^{2,3} γ -Ala-NH-*i*Pr (Figure 8a) revealed an elongated sheet-like configuration, stabilized through hydrogen bonding between strands. The conformational behavior of the dipeptide does not change with the introduction of an additional substituent (-CH₃ group) at the α -position. However, it did induce a reversal in the directionality of the strands, resulting in the formation of antiparallel sheet-type structures (Figure 8b). Notably, the presence of the -CH₃ group not only hindered strand association but also destabilized the overall structure, particularly in the case of longer oligomers.⁶⁷ This distinct conformational preference was later examined by our group in the homooligomer of *E*- α,β -unsaturated γ -amino acids and α,γ -hybrid peptides consisting of *E*- α,β -unsaturated γ -amino acids.^{65,68}

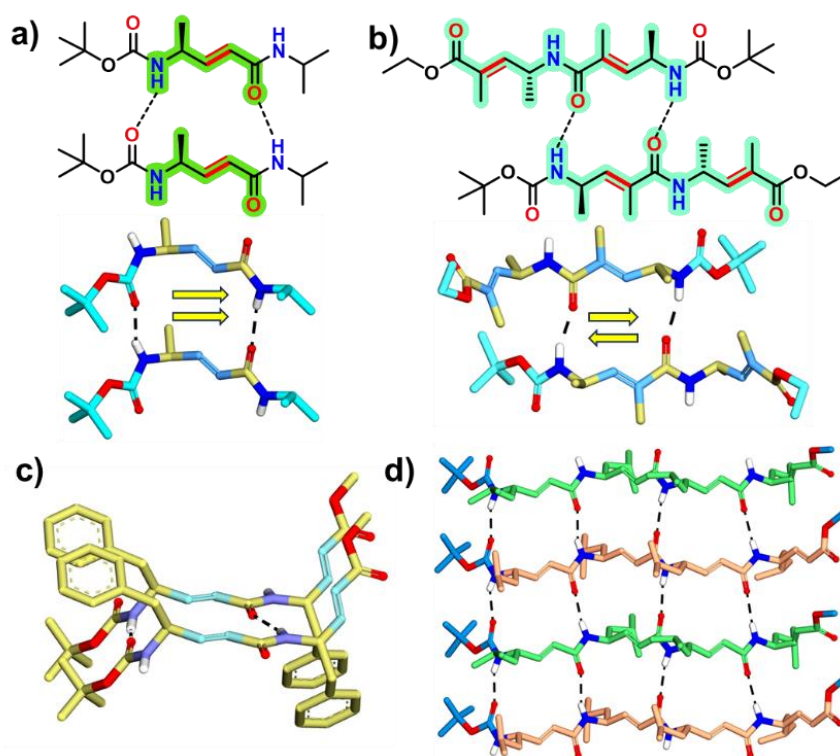
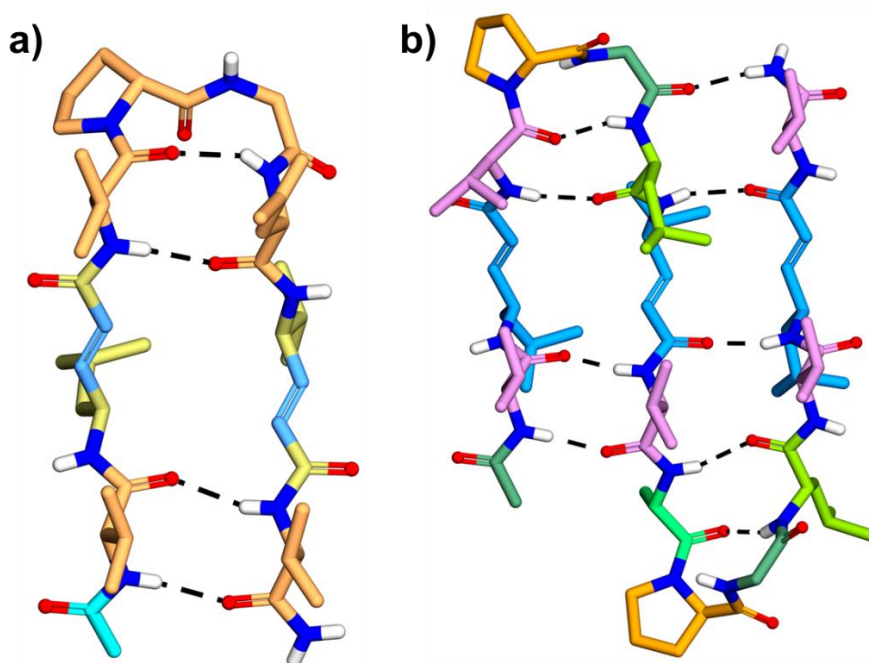


Figure 8. Extended conformation of (*E*)-vinylogous amino acid: (a) extended sheet-type structure for monomer, (b) antiparallel sheet structure for α -(Me)-*E*-vinylogous γ -dipeptide

(c) parallel sheet structure for *E*-vinyllogous γ -dipeptide and (d) parallel β -sheet structure for homooligomer of (*E*)-vinyllogous leucine amino acid.

Previously our group has exploited the sheet-inducing property of *E*- α,β -unsaturated γ -amino acids, using selective incorporation of it into the hybrid peptides it is possible to design extended structures like β -hairpin,^{68a} three-stranded antiparallel β -sheet,^{68b} and β -meander structures,⁶⁹ depicted in Figure 9. The α,γ -hybrid peptides depicted in Figures 9a and 9b containing the *E*- α,β -unsaturated γ -amino acids were strategically placed into facing positions to form β -strands, connected by the ^DPro-Gly dipeptide known for its β -turn promoting tendencies. Surprisingly, peptide **9a** and the N-terminal segments of peptide **9b** shared the same set of amino acid sequences, but the β -turns exhibited by them are completely different **9a** represents a type II' turn in β -hairpin structure whereas **9b** represents type I' turn in the three-stranded sheet. The *E*- α,β -unsaturated γ -amino acids present in these peptides displayed a similar preference for specific torsion angles, approximately $\phi = -120^\circ$, $\theta_1 = 120^\circ$, $\theta_2 = 180^\circ$, and $\psi = 180^\circ$. We additionally, explored the unique conformational characteristics of $\alpha\alpha E$ -vinyllogous hybrid hexapeptides in miniature β -meander type structures, which offer an opportunity to explore well-organized protein super secondary structures memetics beyond the traditional secondary structures such as helices, beta-sheets, and turns.⁶⁹



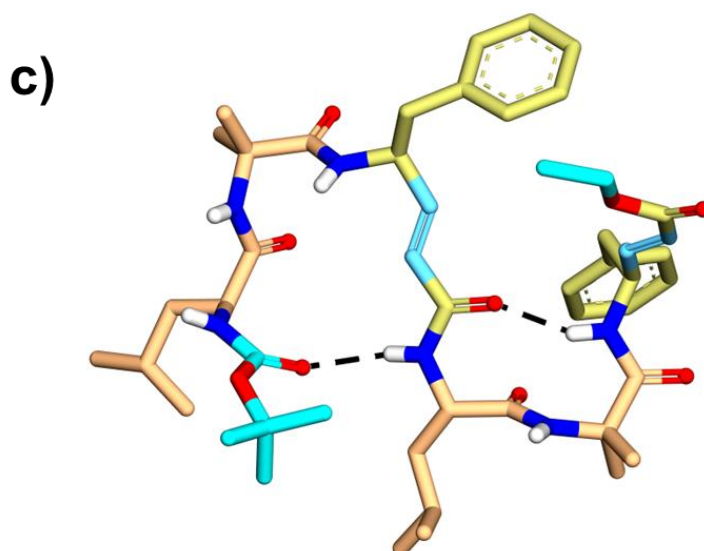


Figure 9. α,γ -hybrid peptide containing *E*-vinyllogous amino acid forming: (a) β -hairpin structure (b) three-stranded antiparallel β -sheet structure and (c) β -meander structures.

In a related study, Kunwar and colleagues demonstrated the utility of *E*-vinyllogous γ -proline (*E*-d γ P) and its α -Me analog, (α Me)-vinyllogous γ -proline, in mimicking a type VI β -turn.⁷⁰ They strategically incorporated *E*-vinyllogous amino acids at the core of peptide sequences **10a** and **10b**. The vinyllogous γ -residues play a significant role in promoting hairpin nucleation, by assisting the formation of a 12-membered pseudocycle that involves the interaction between the C=O (*i*-1) of the preceding residue and the HN (*i*+1) (depicted in Figure 10). This unique feature was attributed to the propensity of *E*-vinyllogous proline residues to adopt a *cis* prolyl amide conformation. Moreover, the study highlighted a prevailing occurrence of *s-trans* conformers within the enamide moiety of the vinyllogous γ -amino acids in the structures of both peptides.

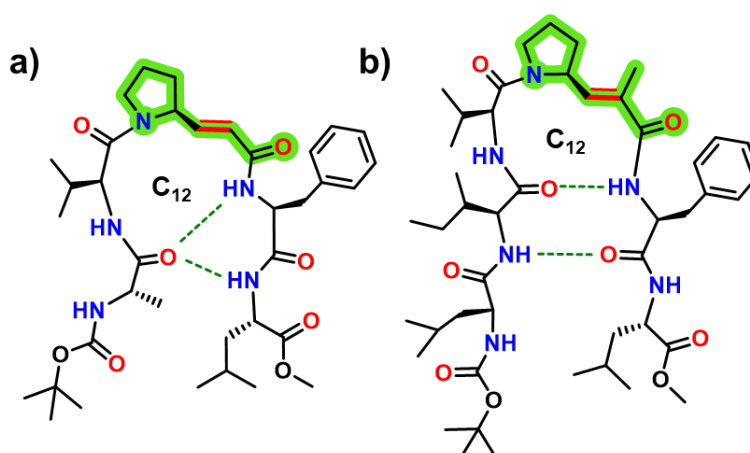


Figure 10. β -Hairpin structures: reverse turns are stabilized by a 12-membered H-bond.

(ii) **Mimicking of Helical Structures using *E*-vinyllogous γ -amino acids:** The helical structure is the most abundant in the protein secondary structure. Hofmann and colleagues predicted the helical architectural arrangements for homo-oligomers of *E*-vinyllogous γ -amino acid for the first time using theoretical calculation.⁷¹ They further predicted that the higher oligomers of *E*-vinyllogous γ -amino acid with C_{22} - and C_{27} -helical structures (Figure 11a and 11b) have a comparable inner diameter of gramicidin A, which is well recognized for its ion channel property. These structures are ultimately stabilized by intramolecular hydrogen-bonded 22- and 27-membered pseudocycles, as depicted in Figures 11a and 11b. Furthermore, we displayed that achiral (*E*)- α,β -unsaturated 4,4-dimethyl γ -amino acids (*E*-d γ Aic) can trigger the formation of achiral β -double helix.⁷² Notably, these architectural arrangements are not very common in the peptide and protein structure except gramicidin A.⁷³ However, these structural motifs with intermolecular hydrogen bonding are distinctive features of nucleic acid (DNA) and polysaccharides. Just like extended structures *s-cis* enamide moiety significantly constrains the θ_2 and ψ torsion angles, irrespective of the local environment around *E*- α,β -unsaturated γ -amino acids. In contrast, the other angles, ϕ and θ_1 are much more flexible. The values of ϕ and θ_1 can vary depending on the C_γ substitution pattern. For instance, in the case of the achiral (*E*)- α,β -unsaturated 4,4-dimethyl γ -amino acids (*E*-d γ Aic), specific values were observed for homooligomer **11c**, such as $\phi = 70^\circ$ and $\theta_1 = 20^\circ$. As a result, homooligomer **11c** did not adopt an extended conformation but instead folded into a large helix, which spontaneously self-assembled into a parallel β -double helical structure, further stabilized by intermolecular hydrogen bonds (depicted in Figure 11c).

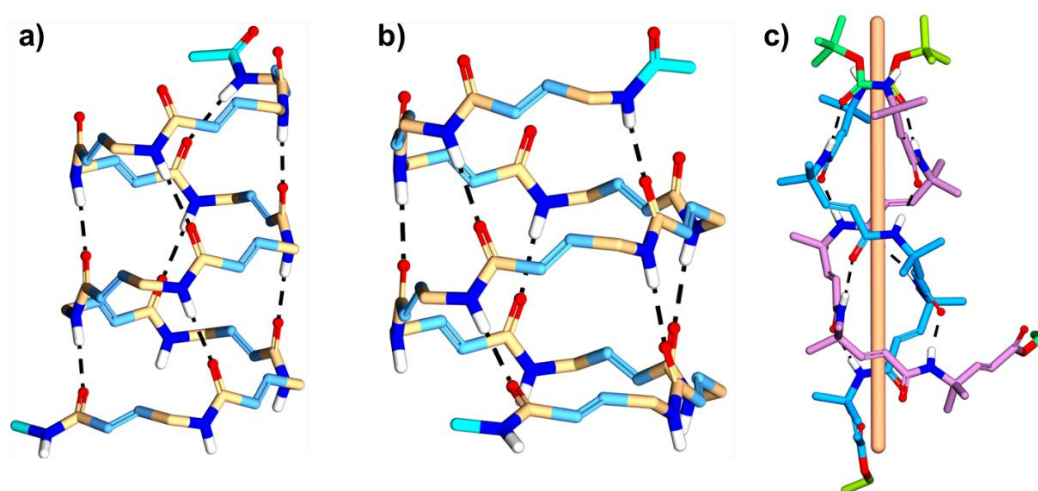


Figure 11. Helical structure from *E*-vinyllogous amino acids: (a and b) theoretically predicted structure of higher homooligomer of *E*-vinyllogous amino acids C₂₂- and C₂₇-helix respectively and (c) β -double helix structure utilizing *E*-d γ -Aic amino acid.

1.6.2 Foldamers of *Z*-vinyllogous γ -Amino Acids

(i) β -turn structure of *Z*-vinyllogous γ -amino acids: In the late nineties, Grison *et al.* and Coutrot *et al.*, explored the conformational behaviors of *Z*-vinyllogous γ -amino acids (*Z*-d γ AAs).⁷⁴ Unlike *E*-vinyllogous γ -amino acids, which tend to adopt extended conformations, *Z*-vinyllogous γ -amino acids were found to prefer compact structures reminiscent of type I β -turns. The crystal structures of monomer amides (α Me)-*Z*-d γ Pro-NH-*i*Pr **12a** and (α Me)-*Z*-d γ Ala-NH-*i*Pr **12b**, revealed a distinctive "*cis*-vinyllog turn" stabilized by a 9-membered hydrogen bond between the carbonyl group and the amine group surrounding the γ -amino acids (Figure 12). Additionally, a favored conformation similar to the *E*-isomer was observed, where the H-C $^{\gamma}$ -C $^{\beta}$ =C $^{\alpha}$ eclipsed conformation was prominent. The same research group also delved into the conformational preferences of α,γ - and γ,α -hybrid di- and tri-peptides. In the crystal structure of the γ,α -dipeptide Boc-(α Me)-*Z*-d γ Pro-Ala-NH-*i*Pr, **12c** an additional hydrogen bond was observed, involving the Boc carbonyl and *i*Pr amide groups, resulting in the formation of a 9- and 12-membered pseudocycle (Figure 12c).^{74a,c} This bidentate C_{9/12} hydrogen bond played a crucial role in further stabilizing the overall structure of the dipeptide, however the same dipeptide with *E*-vinyllogous.

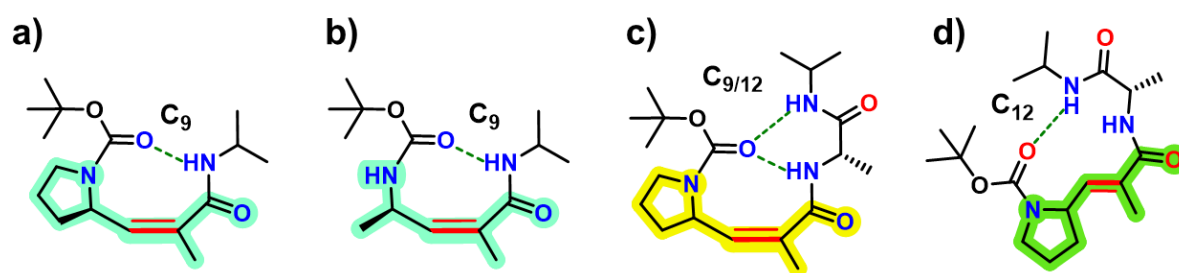


Figure 12. Comparison of turns structure exhibited by (a and b) *Z*-vinyllogous proline amino amide and *Z*-vinyllogous alanine amino amide (c) *Z*-vinyllogous amino acid containing dipeptide and (d) *E*-vinyllogous amino acid containing dipeptide.

(ii) Mimicking of Helical structure using *Z*-vinyllogous γ -amino acids: In 2003, Hoffmann and colleagues proposed, based on computational studies, that *Z*- α,β -unsaturated γ -amino acid oligomers might promote tight helix structures stabilized by small 7- or 9-membered pseudocycles.⁷¹ They predicted the unique conformational preferences and structural

implications of Z-vinylogous γ -amino acids, providing valuable insights into their potential roles in peptide folding and helix stabilization.

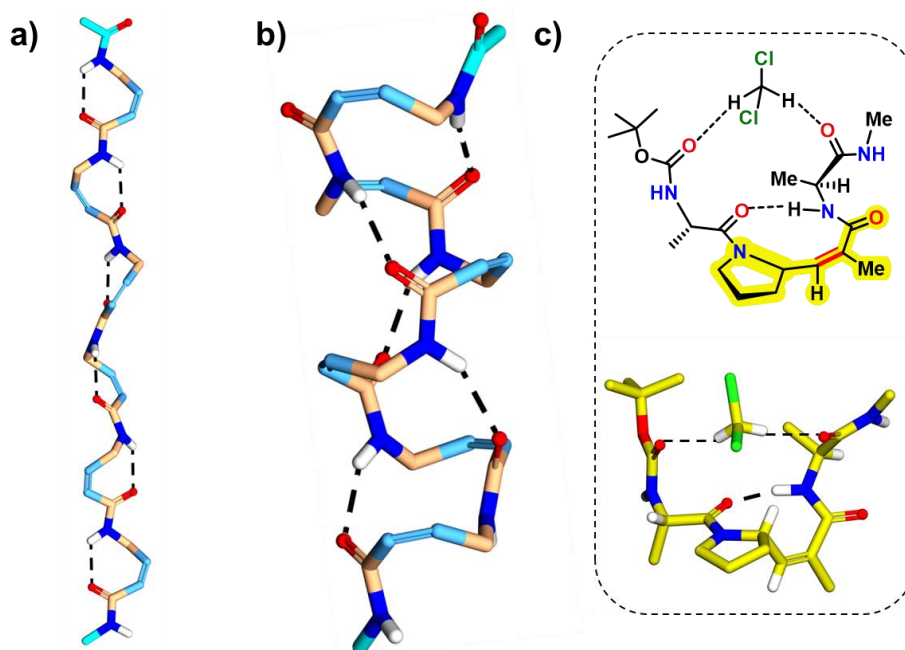


Figure 13. Helical structures incorporating Z-vinylogous amino acid (a) C₇-helix (b) C₁₂-helix and (c) β -turn consisting of Z-vinylogous amino acids.

Additionally, we have shown selective incorporation of the compact Z- α,β -unsaturated γ -amino acids into the α,γ -hybrid peptides. The geometrical constraints of these Z- α,β -unsaturated γ -amino acids stimulate the helicity through the backbone hybrid peptide. The outcome is reflected in the formation of a non-classical helix formation.⁷⁵ Notably, the α,γ -vinylogous peptides are generally considered to be unstructured or nonhelical.^{76,77} So the introduction of Z- α,β -unsaturated γ -amino acids in α,γ -hybrid peptide involves the formation of C₁₂-helix conformation similar to that of all γ -amino acid containing α,γ -hybrid peptide. The structural analysis revealed these conformations are stabilized by 6 intramolecular hydrogen bonds between i (C=O) and $i + 3$ (NH) residues, depicted in Figure 14a. It is evident from these observations that changing *E*-vinylogous amino acid to Z-vinylogous amino acid in a hybrid peptide is one of the deciding factors of their conformation. To support this we demonstrated a facile rearrangement of the nonhelical *E*-vinylogous hybrid tripeptide to helical helical Z-vinylogous hybrid tripeptide involving α,β to β,γ double bond shift using potassium tertiary butoxide as a base.⁷⁷ As a result of rearrangement *E*- α,β -unsaturated γ -amino acid residue in **14b** changed to the Z- β,γ -unsaturated γ -amino acid residue in **14c**. Similar trends were

displayed by other α,γ -hybrid peptides also, composed of alternating α - and E -vinyllogous amino acids. However, the type of Z -vinyllogous amino acid residues are different in **14a** and **14c** still their conformations are the same that is C_{12} -helix.

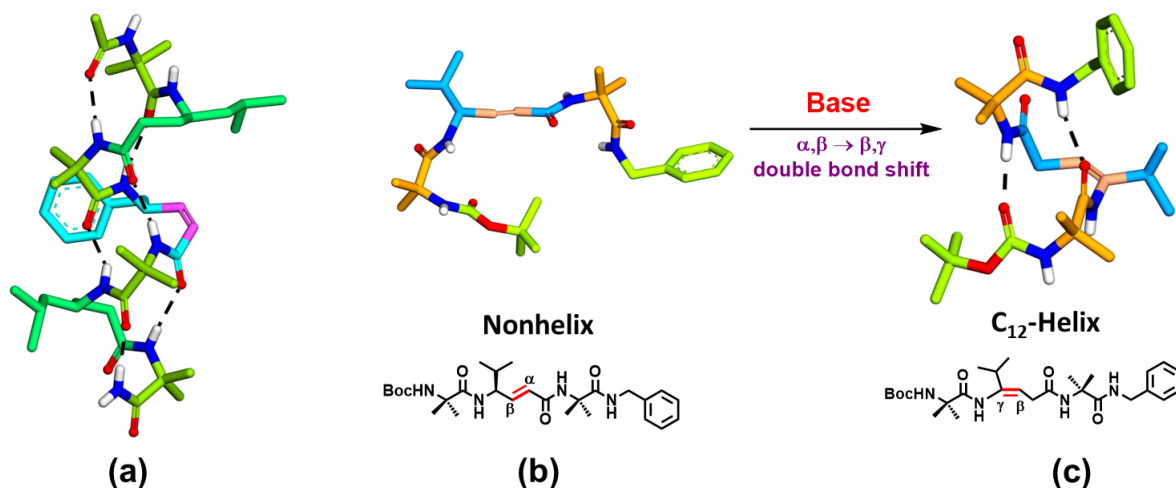


Figure 14. The helical architecture of Z -vinyllogous amino acids, (a) C_{12} -helical α,γ -hybrid peptide containing Z -vinyllogous amino acid, and (b) transformation of nonhelical E -vinyllogous tripeptide to C_{12} -helical Z -vinyllogous tripeptide peptide.

1.7 References

- (a) M. C. Wilson, S.-J. Nam, T. A. M. Gulder, C.A. Kauffman, P. R. Jensen, W. Fenical and B. S. Moore, *J. Am. Chem. Soc.*, 2011, **133**, 1971–1977; (b) S. Sarkar, A. Banerjee, J. A. Shah, U. Mukherjee, N. C. Frederiks, C. J. Johnson and M.-Y. Ngai, *J. Am. Chem. Soc.*, 2022, **144**, 20884–20894; (c) Z. Feng, F. Chu, Z. Guo and P. Sun, *Bioorg. Med. Chem. Lett.*, 2009, **19**, 2270–2272; (d) U. A. Pereira, L. C. A. Barbosa, C. R. A. Maltha, A. J. Demuner, M. A. Masood, and A. L. Pimenta, *Bioorg. Med. Chem. Lett.*, 2014, **24**, 1052–1056; (e) E. Choi, C. Lee, M. Cho, J. J. Seo, J. S. Yang, S. J. Oh, K. Lee, S.-K. Park, H. M. Kim, H. J. Kwon and G. Han, *J. Med. Chem.*, 2012, **55**, 10766–10770; (f) C. Peifer, R. Selig, K. Kinkel, D. Ott, F. Totzke, C. Schachtele, R. Heidenreich, M. Rocken, D. Schollmeyer and S. Laufer, *J. Med. Chem.*, 2008, **51**, 3814–3824; (g) Y. Okazaki, A. Ishizuka, A. Ishihara, T. Nishioka and H. Iwamura, *J. Org. Chem.*, 2007, **72**, 3830–3839; (h) R. H. Feling, G. O. Buchanan, T. J. Mincer, C. A. Kauffman, P. R. Jensen and W. Fenical, *Angew. Chem., Int. Ed.*, 2003, **42**, 355–357; (i) Y. Ai, Y. Hu, F. Kang, Y. Lai, Y. Jia, Z. Huang, S. Peng, H. Ji, J. Tian and Y. Zhang, *J. Med. Chem.*, 2015, **58**, 4506–4520; (j) J. Caruano, G. G. Muccioli and R.

- Robiette, *Org. Biomol. Chem.*, 2016, **14**, 10134–10156; (k) L.-W. Ye, C. Shu and F. Gagosz, *Org. Biomol. Chem.*, 2014, **12**, 1833–1845; (l) C. Kammerer, G. Prestat, D. Madec and G. Poli, *Acc. Chem. Res.*, 2014, **47**, 3439–3447.
2. (a) P.-L. Lam, Y. Wu and K.-L. Wong, *Org. Biomol. Chem.*, 2022, **20**, 2601-2604; (b) C. Baglioni, *Biochem. Biophys. Res. Commun.*, 1970, **38**, 212–219; (c) D. S. Rehder, T. M. Dillon, G. D. Pipes and P. V. Bondarenko, *J. Chromatogr. A*, 2006, **1102**, 164–175; (d) D. R. Twardzik and A. Peterkofsky, *Proc. Natl. Acad. Sci. U.S.A.*, 1972, **69**, 274–277; (e) G. H. Jones, *Biochemistry*, 1974, **13**, 855–860.
 3. (a) A. Fleming, *Br. J. Exp. Pathol.*, 1929, **10**, 226–236; (b) A. Fleming, *Rev. Infect. Dis.*, 1980, **2**, 129-139.
 4. (a) L. M. Lima, B. N. M. da Silva, G. Barbosa and E. J. Barreiro, *Eur. J. Med. Chem.*, 2020, **208**, 112829; (b) P. Liras and J.F. Martín, *Academic Press INC.*, 2009, pp. 274-289; (c) R. R. Watkins and R. A. Bonomo, *Infect. Dis.*, 2017, pp. 1203-1216.
 5. (a) K. Tahlan, and S. Jensen, *J. Antibiot.*, 2013, **66**, 401–410; (b) J. Caruano, G. G. Muccioli and R. Robiette, *Org. Biomol. Chem.*, 2016, **14**, 10134–10156.
 6. (a) J. E. Baldwin, C. Lowe, C. J. Schofield and E. Lee, *Tetrahedron Lett.*, 1986, **27**, 3461–3464; (b) D. B. Boyd, T. K. Elzey, L. D. Hatfield, M. D. Kinnick and J. M. Morin Jr., *Tetrahedron Lett.*, 1986, **27**, 3453–3456; (c) D. B. Boyd, B. J. Foster, L. D. Hatfield, W. J. Hornback, N. D. Jones, J. E. Munroe and J. K. Swartzendruber, *Tetrahedron Lett.*, 1986, **27**, 3457–3460.
 7. M. B. Smith, in *Three carbon-heteroatom bonds: Amides and derivatives; Peptides; Lactams*, ed. G. T. Verlag, 2005, **21**, pp. 647–711.
 8. (a) P. M. Blumberg and J. L. Strominger, *Bacteriol. Rev.*, 1974, **38**, 291-335; (b) E. J. E. Caro-Diaz, F. A. Valeriote and W. H. Gerwick, *Org. Lett.*, 2019, **21**, 793–796; (c) P. Zarantonello, C. P. Leslie, R. Ferritto and W. M. Kazmierski, *Bioorg. Med. Chem. Lett.*, 2002, **12**, 561-565; (d) T. Conroy, J. T. Guo, N. Elias, K. M. Cergol, J. Gut, J. Legac, L. Khatoon, Y. Liu, S. McGowan, P. J. Rosenthal, N. H. Hunt and R. J. Payne, *J. Med. Chem.*, 2014, **57**, 10557–10563; (e) T. Conroy, J. T. Guo, N. H. Hunt and R. J. Payne, *Org. Lett.*, 2010, **12**, 5576–5579; (f) M. Jiang, S. Chen, J. Li and L. Liu, *Mar. Drugs*, 2020, **18**, 114; (g) R. Ratnayake, S. P. Gunasekera, J. J. Ma, L. H. Dang, T. J. Carney, V. J. Paul and

- H. Luesch, *ChemBioChem*, 2020, **21**, 2356–2366; (h) S. Sarkar, A. Banerjee, J. A. Shah, U. Mukherjee, N. C. Frederiks, C. J. Johnson and M.-Y. Ngai, *J. Am. Chem. Soc.* 2022, **144**, 20884–20894; (i) Z. Feng, F. Chu, Z. Guo and P. Sun, *Bioorg. Med. Chem. Lett.*, 2009, **19**, 2270–2272; (j) U. A. Pereira, L. C. A. Barbosa, C. R. A. Maltha, A. J. Demuner, M. A. Masood, and A. L. Pimenta, *Bioorg. Med. Chem. Lett.*, 2014, **24**, 1052–1056.
9. P. Matthies and W. F. Seydl, in *High Performance Polymers: Their Origin and Development*, eds. R. B. Seymour and G. S. Kirshenbaum, Springer Netherlands, Dordrecht, 1986, pp. 39–53.
 10. G. B. Apgar and M. J. Koskoski, in *High Performance Polymers: Their Origin and Development*, eds. R. B. Seymour and G. S. Kirshenbaum, Springer Netherlands, Dordrecht, 1986, pp. 55–65.
 11. S. Hanshelmut, S. Joachim, S. Hermann and I. Otto, USPTO, 1965.
 12. (a) R. Shamey and K. Sinha, *Review of Progress in Coloration and Related Topics*, 2003, **33**, 93–107; (b) M. Shakiba, E. Rezvani Ghomi, F. Khosravi, S. Jouybar, A. Bigham, M. Zare, M. Abdouss, R. Moaref and S. Ramakrishna, *Polymers for Advanced Technologies*, 2021, **32**, 3368–3383; (c) D. J. Barillo, M. Pozza and M. Margaret-Brandt, *Burns*, 2014, **40**, 24–29.
 13. S. K. Dey, and D. A. Lightner, *J. Org. Chem.*, 2008, **73**, 2704–2714.
 14. H.-B. Yu, E. Glukhov, Y. Li, A. Iwasaki, L. Gerwick, P. C. Dorrestein, B.-H. Jiao and W. H. Gerwick, *J. Nat. Prod.*, 2019, **82**, 2608–2619.
 15. Z. Xu, Q. Wang and J. Zhu, *J. Am. Chem. Soc.*, 2013, **135**, 19127–19130.
 16. K. Takabe, M. Suzuki, T. Nishi, M. Hiyoshi, Y. Takamori, H. Yodaa and N. Mase, *Tetrahedron Lett.*, 2000, **41**, 9859–9863.
 17. (a) S. Maiya, A. Grundmann, X. Li, S.-M. Li and G. Turner, *ChemBioChem*, 2007, **8**, 1736–1743; (b) A. Kumar and A. K. Bachhawat, *Curr. Sci.*, 2012, **102**, 288; (c) R. B. Hamed, J. R. Gomez-Castellanos, L. Henry, C. Ducho, M. A. McDonough and C. J. Schofield, *Nat. Prod. Rep.*, 2013, **30**, 21–107.
 18. Q. Bodson, R. Denooz, P. Serpe and C. Charlier, *Acta Clin. Belg.*, 2008, **63**, 200–208.

19. (a) S. M. Hecht, *Bioorganic Chemistry: Peptides and Proteins*, Oxford University Press: Oxford, 1998; (b) M. Hesse, In *Alkaloids: Nature's Curse or Blessing?*, Wiley-VCH: New York, 2000.
20. (a) B. Alcaide, P. Almendros and C. Aragoncillo, *Chem. Rev.*, 2007, **107**, 4437-4492; (b) T. C. Boge and G. I. Georg, In *Enantioselective Synthesis of β -Amino Acids*, E. Juaristi, Ed., Wiley-VCH: New York, 1997, pp 1-43; (c) C. Palomo, J. M. Aizpurua and I. Ganboa, In *Enantioselective Synthesis of β -Amino Acids*, E. Juaristi, Ed., Wiley-VCH: New York, 1997, pp 279-357; (d) I. Ojima, In *The Organic Chemistry of β -Lactams*, G. I. Georg, VCH: New York, 1993, pp 197-255.
21. (a) S. A. Khan and B. W. Erickson, *J. Am. Chem. Soc.* 1984, **106**, 798-799; (b) N. V. Lyutenko, A. E. Sorochinsky and V. A. Soloshonok, *Chem. Heterocycl. Comp.*, 2023, **59**, 332-340; (c) C. Najera and M. Yus, *Tetrahedron: Asymmetry*, 1999, **10**, 2245-2303; (d) S. K. Panday, J. Prasad and D. K. Dikshit, *Tetrahedron: Asymmetry*, 2009, **20**, 1581-1632.
22. A. S. Kende, K. Liu, I. Kaldor, G. Dorey and K. Koch, *J. Am. Chem. Soc.*, 1995, **117**, 8258.
23. A. Geranurimi and W. D. Lubell, *Org. Lett.*, 2018, **20**, 6126- 6129.
24. (a) C. R. Pitts and T. Lectka, *Chem. Rev.*, 2014, **114**, 7930-7953; (b) H. Alper, F. Urso and D. J. H. Smith, *J. Am. Chem. Soc.*, 1983, **105**, 6737; (c) S. Calet, F. Urso and H. Alper, *J. Am. Chem. Soc.*, 1989, **111**, 931; (d) E. J. Corey and A. M. Felix, *J. Am. Chem. Soc.*, 1965, **87**, 2518; (e) D. M. Brunwin, G. Lowe and J. Parker, *J. Chem. Soc. C*, 1971, 3756; (f) J. Marco-Contelles, *Angew. Chem., Int. Ed.*, 2004, **43**, 2198; (g) M. M. C. Lo and G. C. Fu, *J. Am. Chem. Soc.*, 2002, **124**, 4572; (h) R. Shintani and G. C. Fu, *Angew. Chem., Int. Ed.*, 2003, **42**, 4082; (i) M. C. Ye, J. Zhou, Z. Z. Huang and Y. Tang, *Chem. Commun.*, 2003, 2554; (j) M. C. Ye, J. Zhou and Y. J. Tang, *J. Org. Chem.*, 2006, **71**, 3576.
25. J. H. Atkinson, R. S. Atkinson and A. W. Johnson, *J. Chem. Soc.*, 1964, 5999.
26. (a) H. Plieninger and M. Decker, *Liebigs Ann. Chem.*, 1956, **598**, 198; (b) A. Huni and F. Frank, *Z. Physiol. Chem.*, 1947, **282**, 96; (c) W. Siedel, *Liebigs Ann. Chem.*, 1943, **554**, 144; (d) H. Fischer, T. Yoskioka and P. Hartmann, *Z. Physiol. Chem.*, 1932, **212**, 146.
27. (a) J. Clayden, R. Turnbull and I. Pinto, *Org. Lett.*, 2004, **6**, 609-611; (b) W. Hess and J. W. Burton, *Adv. Synth. Cat.*, 2011, **353**, 2966-2970; (c) R. Naitoh, Y. Nakamura, E. Katano, Y. Nakamura, E. Okada, and M. Asaoka, *Heterocycles*, 2004, **63**, 1009-1012; (d) S. G.

- Parameswarappa and F.C. Pigge, *J. Org. Chem.*, 2012, **77**, 8038-8048; (e) A. I. Lansakara, D. P. Farrell, and F. C. Pigge, *Org. Biomol. Chem.*, 2014, **12**, 1090-1099.
28. (a) A. Mallagaray, G. Domínguez, A. Gradillas, and J. Pérez-Castells, *Org. Lett.*, 2008, **10**, 597-600; (b) M. Daly, K. Gill, M. Sime, G. L. Simpson, and A. Sutherland, *Org. Biomol. Chem.*, 2011, **9**, 6761-6770.
29. (a) M. Toyofuku, E. Murase, H. Nagai, S.-ichi Fujiwara, T. Shin-ike, H. Kuniyasu and N. Kambe, *Eur. J. Org. Chem.*, 2009, **19**, 3141–3144; (b) Y. Kobayashi, H. Kamisaki, R. Yanada, and Y. Takemoto, *Org. Lett.*, 2006, **8**, 2711–2713.
30. (a) A. J. Pearson, H. Sun and X. Wang, *J. Org. Chem.*, 2007, **72**, 2547–2557; (b) F. Palacios, A. M. O. de Retana and A. V. del Burgo *J. Org. Chem.*, 2011, **76**, 9472–9477; (c) R. T. Watson, V. K. Gore, K. R. Chandupatla, R. K. Dieter and J. P. Snyder, *J. Org. Chem.*, 2004, **69**, 6105–6114.
31. (a) F. Nishino, K. Miki, Y. Kato, K. Ohe, and S. Uemura, *Org. Lett.*, 2003, **5**, 2615–2617; (b) M. Lautens, W. Han, and J. H.-C. Liu, *J. Am. Chem. Soc.* 2003, **125**, 4028–4029; (c) G. B. Bajracharya, P. S. Koranne, R. N. Nadaf, R. K. M. Gabr, K. Takenaka, S. Takizawa and H. Sasai, *Chem. Commun.*, 2010, **46**, 9064-9066; (d) Y. Tang and C. Li, *Org. Lett.*, 2004, **6**, 3229–3231.
32. L. Yang, C.-H. Lei, D.-X. Wang, Z.-T. Huan and M.-X. Wang, *Org. Lett.*, 2010, **12**, 3918–3921.
33. S. Sarkar, A. Banerjee, J. A. Shah, U. Mukherjee, N. C. Frederiks, C. J. Johnson and M.-Y. Ngai, *J. Am. Chem. Soc.*, 2022, **144**, 20884– 20894.
34. J. Xie, S. Xue, E. C. Escudero-Adan and A. W. Kleij, *Angew. Chem. Int. Ed.*, 2018, **57**, 16727–16731.
35. Y. Hoshimoto, T. Ohata, Y. Sasaoka M. Ohashi and S. Ogoshi, *J. Am. Chem. Soc.*, 2014, **136**, 15877–15880.
36. (a) T. Morimoto, N. Chatani, S. Murai, *J. Am. Chem. Soc.*, 1999, **121**, 1758– 1759; (b) S.-K. Kang, K.-J. Kim, C.-M. Yu, J.-W. Hwang and Y.-K. Do, *Org. Lett.*, 2001, **3**, 2851– 2853; (c) S. Ma and H. Xie, *J. Org. Chem.*, 2002, **67**, 6575– 6578; (d) Z. Zhou, G. Liu, and X. Lu, *Org. Lett.*, 2016, **18**, 5668– 5671; (e) M. I. D. Mardjan, J.

- L. Parrain, L. Commeiras, *Adv. Synth. Catal.*, 2016, **358**, 543–548; (g) J. Chang, B. Liu, Y. Yang and M. Wang, *Org. Lett.*, 2016, **18**, 3984–3987; (h) S. G. Wang, Y. Liu and N. Cramer, *Angew. Chem., Int. Ed.*, 2019, **131**, 18304–18308; (i) W.-J. Yoo, W. Chen, T. V. Nguyen and S. Kobayashi, *Org. Lett.*, 2020, **22**, 2328–2332.
37. E. J. E. Caro-Diaz, F. A. Valeriote and W. H. Gerwick, *Org. Lett.*, 2019, **21**, 793–796.
38. A. A. van Loon, M. K. Holton, C. R. Downey, T. M. White, C. E. Rolph, S. R. Bruening, G. Li, K. M. Delaney, S. J. Pelkey and E. T. Pelkey, *J. Org. Chem.*, 2014, **79**, 8049–8058.
39. X. del Corte, A. Maestro, J. Vicario, E. M. de Marigorta and F. Palacios, *Org. Lett.* 2018, **20**, 317–320.
40. (a) M. Singh, M. Kumar, S. A. Nalawade, D. R. Puneeth Kumar and H. N. Gopi, *Org. Biomol. Chem.*, 2023, **21**, 3766–3769; (b) M. Singh, S. A. Nalawade, D. R. Puneeth Kumar, K. Veeresh, S. Pahan, S. Dey and H. N. Gopi, *Eur. J. Org. Chem.* 2023, **26**, e202300682.
41. (a) M. Adib, M. Mahdavi, M. A. Noghania and H. R. Bijanzadeh, *Tetrahedron Lett.*, 2007, **48**, 8056–8059; (b) J. Clayden, R. Turnbulla and I. Pinto, *Tetrahedron: Asymmetry*, 2005, **16**, 2235–2241; (c) B. B. Snider and B. J. Neubert, *J. Org. Chem.*, 2004, **69**, 8952–8955; (d) F. Gaviña, A. M. Costero, M. R. Andreu, M. Carda and S. V. Luis, *J. Am. Chem. Soc.*, 1998, 4017–4018; (e) H. Kakeya, C. Onozawa, M. Sato, K. Arai and H. Osada, *J. Med. Chem.*, 1997, **40**, 391–394; (e) T. Conroy, J. T. Guo, N. H. Hunt and R. J. Payne, *Org. Lett.*, 2010, **12**, 5576–5579; (f) T. Conroy, J. T. Guo, R. G. Linington, N. H. Hunt and R. J. Payne, *Chem. Eur. J.*, 2011, **17**, 13544–13552; (g) J. K. Howard, C. J. T. Hyland, J. Just and J. A. Smith, *Org. Lett.*, 2013 **15**, 1714–1717.
42. (a) J. B. Metternich and R. Gilmour, *J. Am. Chem. Soc.*, 2015, **137**, 11254–11257; (b) T. Nevesely, M. Wienhold, J. J. Molloy and R. Gilmour, *Chem. Rev.*, 2022, **122**, 2650–2694.
43. C. Dugave and L. Demange, *Chem. Rev.*, 2003, **103**, 2475–2532.
44. (a) F. Gai, K. C. Hasson, J. C. MacDonald and P. A. Anfinrud, *Science*, 1998, **279**, 1886–1891; (b) B. O'Leary, B. Duke and J. E. Eilers, *Nature*, 1973, **246**, 166–167; (c) G. Bassolino, T. Sovdat, M. Liebel, C. Schnedermann, B. Odell, T. D. W. Claridge, P. Kukura and S. P. Fletcher, *J. Am. Chem. Soc.*, 2014, **136**, 2650–2658.
45. A. G. Walker and G. K. Radda, *Nature*, 1967, **215**, 1483.
46. (a) S. Kahremany, C. L. Sander, G. P. Tochtrop, A. Kubas and K. Palczewski, *Org. Biomol. Chem.*, 2019, **17**, 8125–8139; (b) V. Dupe, N. B. Ghyselinck, V. Thomazy, L. Nagy, P. J.

- Davies, P. Chambon and M. Mark, *Dev. Biol.*, 1999, **208**, 30–43; (c) A. Canete, E. Cano, R. Munoz-Chapuli and R. Carmona, *Nutrients*, 2017, **9**, 159–176; (d) K. Palczewski, *J. Biol. Chem.*, 2012, **287**, 1612–1619; (e) J. von Lintig, P. D. Kiser, M. Golczak and K. Palczewski, *Trends Biochem. Sci.*, 2010, **35**, 400–410; (f) L. Hofmann and K. Palczewski, *Prog. Retinal Eye Res.*, 2015, **49**, 46–66; (g) L. Jiang, R. Dong, M. Ying, Q. He, J. Cao and B. Yang, *Br. J. Pharmacol.*, 2018, **175**, 4285–4294; (h) J. S. Khillan, *Nutrients*, 2014, **6**, 1209–1222.
47. (a) T. Hintermann, K. Gademann, B. Jaun and D. Seebach, *Helv. Chim. Acta*, 1998, **81**, 983–1002; (b) M. Brenner and D. Seebach, *Helv. Chim. Acta*, 2001, **84**, 1181–1189.
48. (a) M. M. M. Santos and R. Moreira, *Mini-Rev. Med. Chem.*, 2007, **7**, 1040–1050; (b) J. S. Plummer, L. A. Emery, M. A. Stier and M. J. Suto, *Tetrahedron Lett.*, 1993, **34**, 7529–7532.
49. Y. Fu, B. Xu, X. Zou, C. Ma, X. Yang, K. Mou, G. Fu, Y. Lu and P. Xu, *Bioorg. Med. Chem. Lett.*, 2007, **17**, 1102–1106.
50. M. T. Reetz, *Angew. Chem., Int. Ed. Engl.*, 1991, **30**, 1531–1546.
51. (a) N. Fusetani, S. Matsunaga, H. Matsumoto and Y. Takebayashi, *J. Am. Chem. Soc.*, 1990, **112**, 7053–7054; (b) J. E. Coleman, E. D. d Silva, F. Kong, R. J. Andersen and T. M. Allen, *Tetrahedron*, 1995, **51**, 10653–10662; (c) N. Schaschke, *Bioorg. Med. Chem. Lett.*, 2004, **14**, 855–857; (d) R. G. Linington, B. R. Clark, E. E. Trimble, A. Almanza, L.-D. Urena, D. E. Kyle and W. H. Gerwick, *J. Nat. Prod.*, 2009, **72**, 14–17; (e) X. Bian, A. Plaza, Y. Zhang and R. Muller, *J. Nat. Prod.*, 2012, **75**, 1652–1655; (f) J. A. Nieman, J. E. Coleman, D. J. Wallace, E. Piers, L. Y. Lim, M. Roberge and R. J. Andersen, *J. Nat. Prod.*, 2003, **66**, 183–199.
52. P. Tabares, B. Degel, N. Schaschke, U. Hentschel and T. Schirmeister, *Pharmacognosy Res.*, 2012, **4**, 63–66.
53. B. Miller, A. J. Friedman, H. Choi, J. Hogan, J. A. McCammon, V. Hook and W. H. Gerwick, *J. Nat. Prod.*, 2014, **77**, 92–99.
54. A. Y. Lee, M. Hagihara, R. Karmacharya, M. W. Albers and S. L. Schreiber, J. Clardy, *J. Am. Chem. Soc.*, 1993, **115**, 12619–12620.
55. B. E. Maryanoff, X. Qiu, K. P. Padmanabhan, A. Tulinsky, H. R. A. Jr, P. Andrade-Gordon, M. N. Greco, J. A. Kauffman, K. C. Nicolaou, A. Liu, P. H. Brungs, N. Fusetani, *Proc. Natl. Acad. Sci. USA*, 1993, **90**, 8048–8052.
56. (a) R. P. Hanzlik and S. A. Thompson, *J. Med. Chem.*, 1984, **27**, 711–712; (b) S. Liu and R. P. Hanzlik, *J. Med. Chem.*, 1992, **35**, 1067–1075; (c) J.-S. Kong, S. Venkatraman, K. Furness, S. Nimkar, T. A. Shepherd, Q. M. Wang, J. Aube, R. P. Hanzlik, *J. Med. Chem.*,

- 1998, **41**, 2579-2587; (d) M. M. M. Santos and R. Moreira, *Mini-Rev. Med. Chem. Lett.*, 2007, **7**, 1040-1050; (e) A. Breuning, B. Degel, F. Schulz, C. Buchold, M. Stempka, U. Machon, S. Heppner, C. Gelhaus, M. Leippe, M. Leyh, C. Kisker, J. Rath, A. Stich, J. Gut, P. J. Rosenthal, C. Schmuck and T. Schirmeister, *J. Med. Chem.*, 2010, **53**, 1951-1963; (f) N. Schaschke and C. P. Sommerhoff, *ChemMedChem*, 2010, **5**, 367-370; (g) H. M. M. Bastiaans, J. L. van der Baan and H. C. J. Ottenheijm, *J. Org. Chem.*, 1997, **62**, 3880-3889.
57. (a) G. Wittig and G. Geissler, *Justus Liebigs Ann. Chem.*, 1953, **580**, 44-68; (b) G. Wittig and U. Schollkopf, *Chem. Ber.*, 1954, **87**, 1318-1330; (c) G. Wittig, *Science*, 1980, **210**, 600-604; (d) A. Maerckar, *Org. React.*, 1965, **14**, 270-490; (e) B. E. Maryanoff and A. B. Reitz, *Chem. Rev.*, 1989, **89**, 863-927; (f) O. I. Kolodiazhnyi, *Phosphorus Ylides, Chemistry and Application in Organic Synthesis*, Wiley-VCH, Weinheim, Germany, 1999; (g) E. Vedejs and C. F. Marth, *J. Am. Chem. Soc.*, 1990, **112**, 3905-3909; (h) A. El-Batta, C. Jiang, W. Zhao, R. Anness, A. L. Cooksy and M. Bergdahl, *J. Org. Chem.*, 2007, **72**, 5244-5259.
58. (a) D. J. Peterson, *J. Org. Chem.*, 1968, **33**, 780-784; (b) D. J. Ager, *Synthesis*, 1984, 384-398; (c) D. J. Ager, *Org. React.*, 1990, **38**, 1-223.
59. (a) M. Julia and J. M. Paris, *Tetrahedron Lett.*, 1973, **14**, 4833-4836; (b) J. B. Baudin, G. Hareau, S. A. Julia and O. Ruel, *Tetrahedron Lett.*, 1991, **32**, 1175-1178; (c) P. J. Kocienski, *Phosphorus Sulfur Relat. Elem.*, 1985, **24**, 97-127; (d) P. R. Blakemore, *J. Chem. Soc., Perkin Trans. I*, 2002, 2563-2585.
60. (a) D. P. Rotella, *J. Am. Chem. Soc.*, 1996, **118**, 12246-12247; (b) S. Oishi, T. Kamano, A. Niida, Y. Odagaki, N. Hamanaka, M. Yamamoto, K. Ajito, H. Tamamura, A. Otaka and N. Fujii, *J. Org. Chem.*, 2002, **67**, 6162-6173; (c) V. R. Chintareddy, A. Ellern and J. G. Verkade, *J. Org. Chem.*, 2010, **75**, 7166-7174.
61. L. K. Blasdel and A. G. Myers, *Org. Lett.*, 2005, **7**, 4281-4283.
62. (a) T. D. W. Claridge, S. G. Davies, J. A. Lee, R. L. Nicholson, P. M. Roberts, A. J. Russell, A. D. Smith and S. M. Toms, *Org. Lett.*, 2008, **10**, 5437-5440; (b) M. A. Blanchette, W. Choy, J. T. Davis, A. P. Essinfeld, S. Masamune, W. R. Roush and T. Sakai, *Tetrahedron Lett.*, 1984, **25**, 2183-2186; (c) M. W. Rathke and M. Nowak, *J. Org. Chem.*, 1985, **50**, 2624-2626.
63. (a) T. Hintermann, K. Gademann, B. Jaun and D. Seebach, *Helv. Chim. Acta*, 1998, **81**, 983-1002; (b) M. Brenner and D. Seebach, *Helv. Chim. Acta*, 2001, **84**, 1181-1189.

64. (a) C. Grison, P. Coutrot, S. Geneve, C. Didierjean and M. Marraud, *J. Org. Chem.*, 2005, **70**, 10753–10764; (b) C. Grison, S. Geneve, E. Halbin and P. Coutrot, *Tetrahedron*, 2001, **57**, 4903–4923.
65. S. M. Mali, A. Bandyopadhyay, S. V. Jadhav, M. G. Kumar and H. N. Gopi, *Org. Biomol. Chem.*, 2011, **9**, 6566–6574.
66. M. G. Kumar, K. Veeresh, S. A. Nalawade, R. V. Nithun and H. N. Gopi, *J. Org. Chem.*, 2019, **84**, 15145–15153.
67. M. Hagihara, N. J. Anthony, T. J. Stout, J. Clardy, S. L. Schreiber, *J. Am. Chem. Soc.*, 1992, **114**, 6568–6570.
68. (a) A. Bandyopadhyay, S. M. Mali, P. Lunawat, K. M. P. Raja and H. N. Gopi, *Org. Lett.*, 2011, **13**, 4482–4485; (b) A. Bandyopadhyay, R. Misra and H. N. Gopi, *Chem. Commun.*, 2016, **52**, 4938–4941; (c) K. Veeresh, M. Singh and H. N. Gopi, *Org. Biomol. Chem.*, 2019, **17**, 9226–9231.
69. M. G. Kumar, S. N. Benke, K. M. P. Raja and H. N. Gopi, *Chem. Commun.*, 2015, **51**, 13397–13399.
70. T. K. Chakraborty, A. Ghosh, S. K. Kumar, A. C. Kunwar, *J. Org. Chem.*, 2003, **68**, 6459–6462.
71. C. Baldauf, R. Gunther, and H.-J. Hofmann, *J. Org. Chem.* 2005, **70**, 5351–5361.
72. R. Misra, S. Dey, R. M. Reja and H. N. Gopi, *Angew. Chem. Int. Ed.*, 2018, **57**, 1057–1061.
73. (a) D. A. Langes, *Science*, 1988, **241**, 188–191; (b) D. W. Urry, J. D. Glickson, D. F. Mayers, J. Haider, *Biochemistry*, 1972, **11**, 487–493; (c) B. A. Wallace, K. Ravikumar, *Science*, 1988, **241**, 182–187; (d) S. V. Sychev, L. I. Barsukov, V. T. Ivanov, *J. Pept. Sci.*, 2013, **19**, 452–458; (e) D. A. Kelkar, A. Chattopadhyay, *Biochim. Biophys. Acta Biomembr.*, 2007, **1768**, 2011–2025; (f) S. V. Sychev, L. I. Barsukov, V. T. Ivanov, *Eur. Biophys. J.*, 1993, **22**, 279–288.
74. (a) P. Coutrot, C. Grison, S. Geneve, C. Didierjean, A. Aubry, A. Vicherat and M. Marraud, *Lett. Pept. Sci.*, 1997, **4**, 415–422; (b) C. Grison, S. Geneve, S. Claudel, P. Coutrot and M. Marraud, *Tetrahedron, Lett.*, 2003, **44**, 2297–2300; (c) C. Grison, P. Coutrot, S. Geneve, C. Didierjean and M. Marraud, *J. Org. Chem.*, 2005, **70**, 10753–10764.
75. M. G. Kumar, V. J. Thombare, M. M. Katariya, K. Veeresh, K. M. P. Raja and H. N. Gopi, *Angew. Chem. Int. Ed.*, 2016, **128**, 7978–7982.
76. A. Bandyopadhyay and H. N. Gopi, *Org. Lett.*, 2012, **14**, 2770–2773.
77. K. Veeresh and H. N. Gopi, *Org. Lett.* 2019, **21**, 4500–4504.

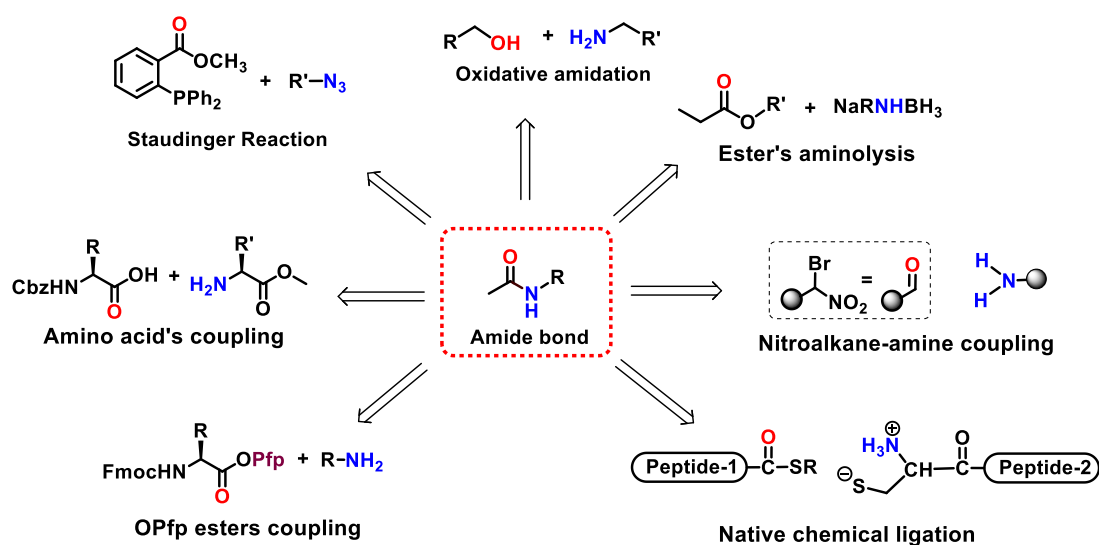
Chapter 2

Cyclization of *N*-Boc-(*E*)- α,β -Unsaturated γ -Amino Acid Active Esters into *N*-Boc-(*Z*)- α,β -Unsaturated γ -Lactams through *E* $\rightarrow$ *Z* Isomerization

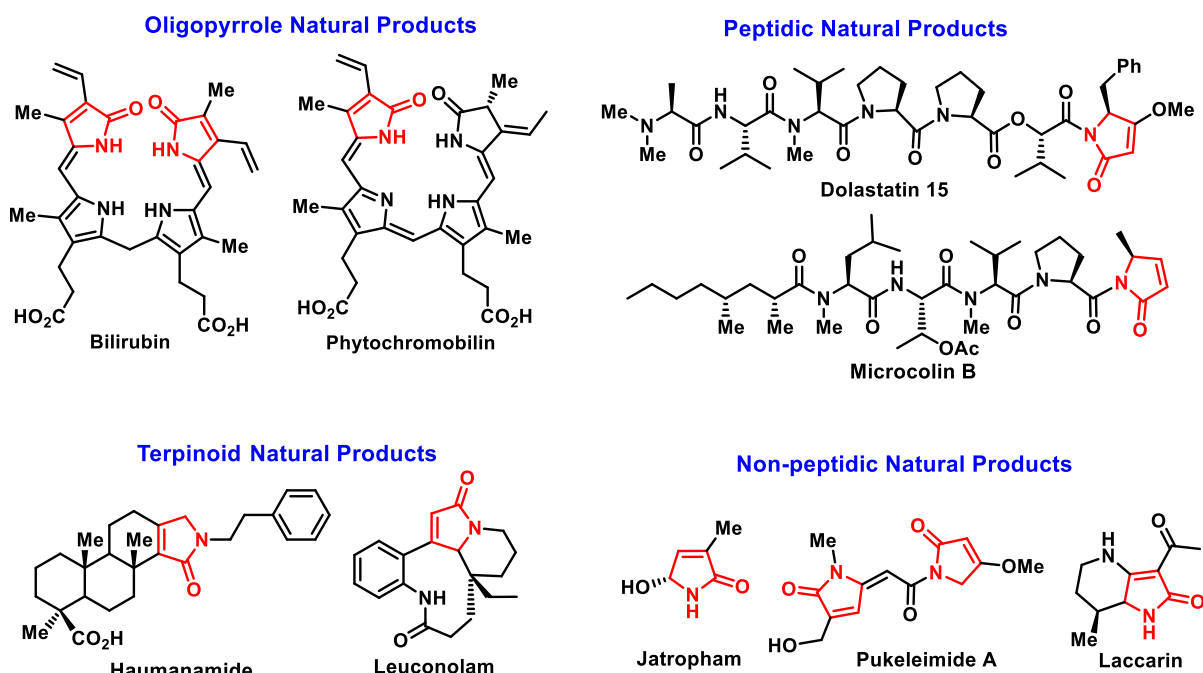
The original work of this chapter has been published in the “Organic & Biomolecular Chemistry ” journal. Here, we adopted the text from Ref. M. Singh, M. Kumar, S. A. Nalawade, D. R. Puneeth Kumar and H. N. Gopi, *Org. Biomol. Chem.*, 2023, **21**, 3766–3769 with permission from the Royal Society of Chemistry. A copy of the permission letter is attached at the end of the chapter.

2.1 Introduction

The aminolysis of esters is a classical method for the synthesis of amide bonds,¹ along with this conventional method alternative approaches to amide synthesis have been developed, including Staudinger ligation,² native chemical ligation,³ nitroalkane-amine coupling⁴ and direct oxidative-amidation of alcohols⁵ as shown in Scheme 1. In addition to the various substituted phenyl esters, the pentafluorophenyl (OPfp) esters and the *p*-nitrophenol (ONp) esters of N-protected amino acids have served as ideal coupling agents in peptide synthesis.^{6,7} In continuation of our interest in peptides composed of α,β -unsaturated γ -amino acids,^{8,9} we sought to examine the suitability of the OPfp esters of N-protected vinylogous amino acids as coupling agents in peptide synthesis. In the process of the development of the pentafluorophenyl active esters of α,β -unsaturated γ -amino acids, we encountered an unusual and spontaneous transformation of these esters into the corresponding α,β -unsaturated γ -lactams at room temperature in the presence of a weak base, DIPEA. Strikingly, the transformation involves the unfavorable *E* $\rightarrow$ *Z* isomerization of carbon-carbon double bonds. α,β -Unsaturated γ -lactams are very important structural constituents of a variety of natural products including oligopyrroles, heme metabolites, terpenoids and peptidic natural products,¹⁰ some of them are shown in Scheme 2. The widespread biological applications of α,β -unsaturated γ -lactams have attracted considerable attention towards their synthesis.¹¹ A variety of synthetic routes have been developed for N-aryl/alkylated α,β -unsaturated γ -lactam synthesis.^{10,12–20} Despite this wide range of applications of α,β -unsaturated γ -lactams, currently there are not many methods available for the synthesis of N-acylated α,β -unsaturated γ -lactams with broad side-chain specificity.



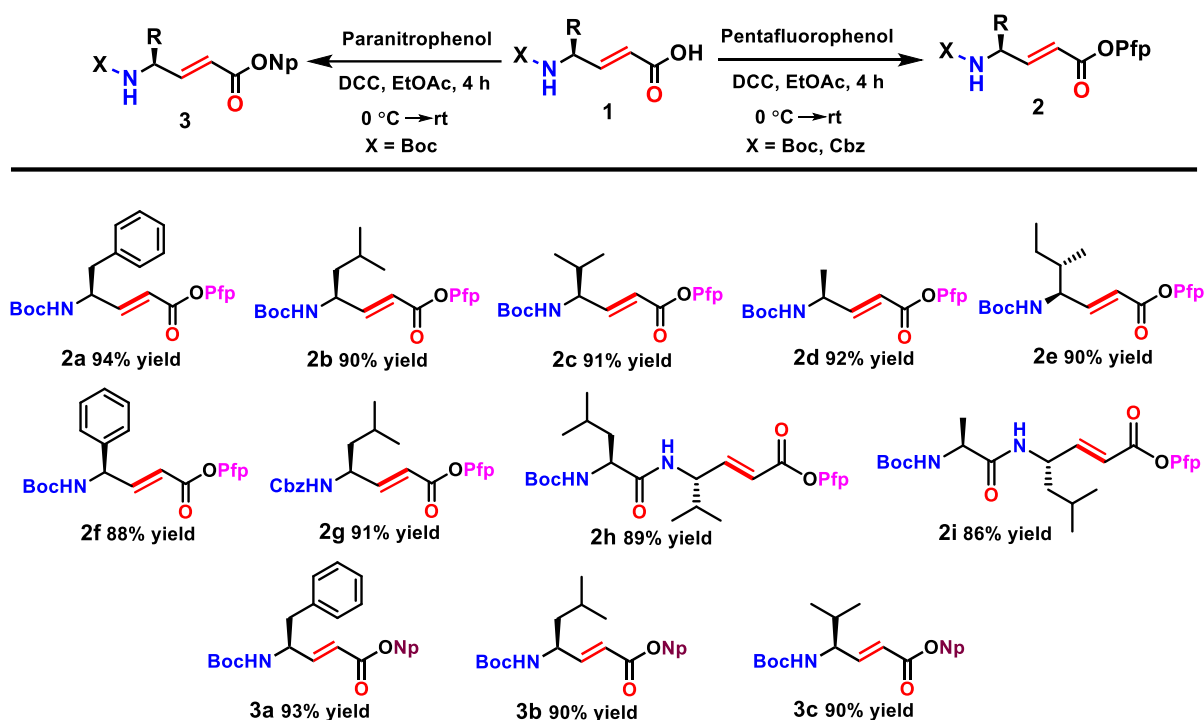
Scheme 1. Different methods for the synthesis of amide bond-containing compounds.



Scheme 2. Natural products containing α,β -unsaturated γ -lactams as their core structural motifs.

2.2 Aim and Rationale of the Present Work

To perform a remarkable transformation of the pentafluorophenyl esters and *p*-nitrophenyl esters of N-protected (*E*)- α,β -unsaturated γ -amino acids into N-protected (*Z*)- α,β -unsaturated γ -lactams at room temperature and 50 °C respectively in the presence of a weak base. In this context, we synthesized a series of pentafluorophenyl esters (**2a-2i**) and *p*-nitrophenyl esters (**3a-3c**) starting from corresponding vinylogous amino acids and pentafluorophenol or *p*-nitrophenol. The esterification reactions were performed using the coupling agent DCC and pentafluorophenol. The schematic representation of the active ester formation reaction is shown in Scheme 3. All active esters were isolated in good yield and characterized. These active esters readily undergo aminolysis reaction with their free amine counterparts at room temperature in the presence of DIPEA. However, upon a delay in the addition of free amine, we encountered an unusual (*Z*)- α,β -unsaturated γ -lactam product in the reaction. These surprising results motivated us for a detailed investigation of the transformation.



Scheme 3. Synthesis of active ester of Boc/Cbz-(*E*)- α,β -unsaturated γ -amino acids.

2.3 Results and Discussion

To validate intramolecular cyclization in the absence of free amine, the OPfp ester **2a** with a phenylalanine side-chain was stirred in DMF for about 2 h in the presence of DIPEA. We observed the complete transformation of OPfp ester **2a** with *trans* carbon–carbon double bonds into α,β -unsaturated γ -lactam **4a** with *cis* carbon–carbon double bonds. Starting material (**2a**) as well as a final product (**4a**) was purified by silica-gel chromatography, where the progression of the reaction was monitored by TCL analysis. Further, the confirmation of the synthesized compounds was done by ^1H NMR, ^{13}C NMR and HRMS spectra analysis. The schematic representation of the cyclization reaction is shown in Scheme 4. The most important facet of the transformation is the *E* $\rightarrow$ *Z* isomerization of carbon–carbon double bonds. The isomerization of double bonds from *E* $\rightarrow$ *Z* is a thermodynamically unfavorable process.^{21,22} Furthermore, the chiral HPLC analysis revealed that all γ -lactams derived from active esters were racemized during cyclization. These enantiomers can be separated using chiral HPLC. The single crystal structure of the pentafluorophenyl ester (**2a** and **2d**) and *p*-nitrophenyl ester (**3a** and **3c**) is shown in Figure 1, suggesting the stability of these active esters.

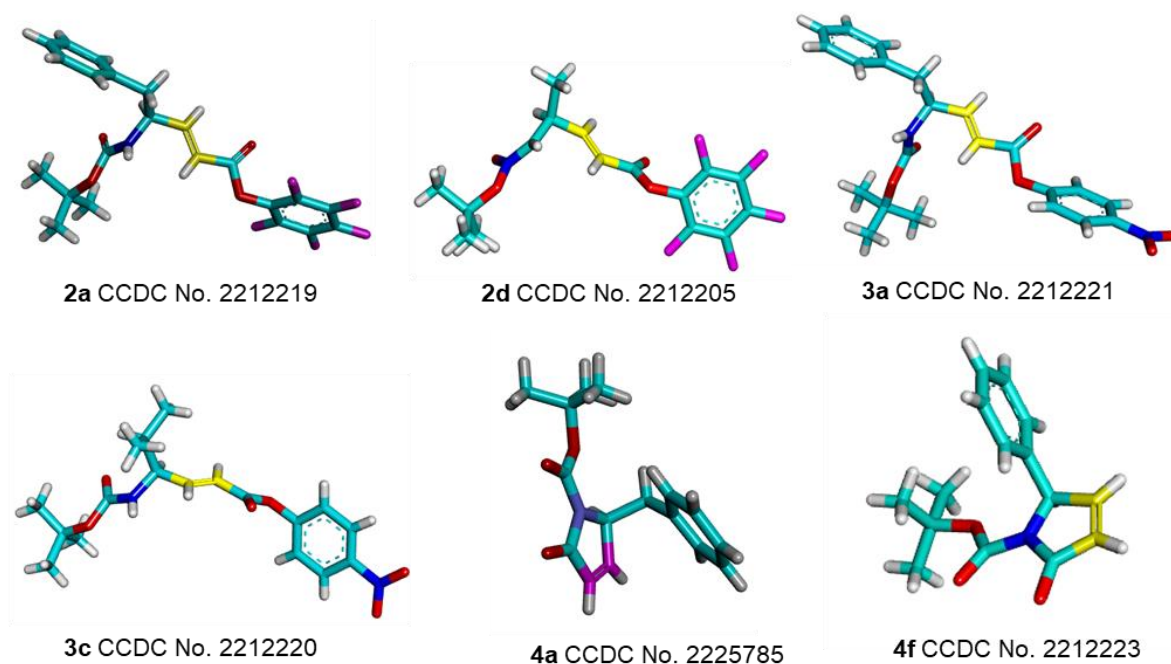
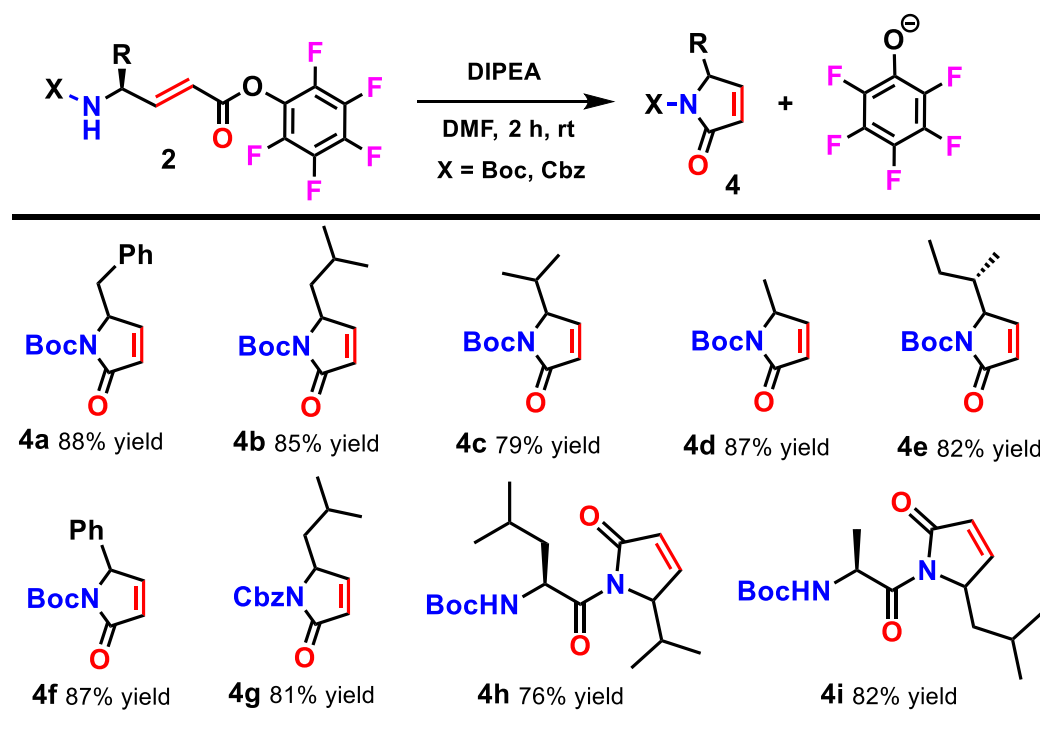


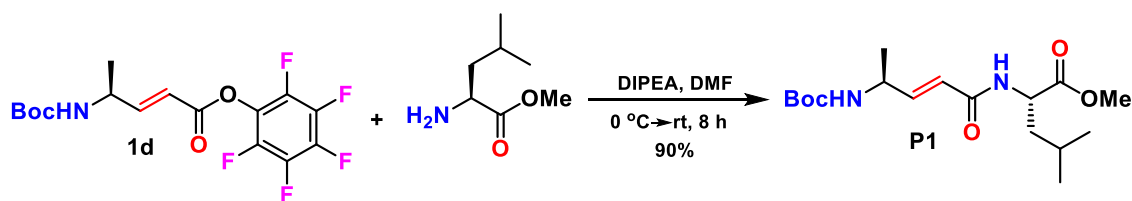
Figure 1. Single crystal structure of active esters and α,β -unsaturated γ -lactam.

Encouraged by this transformation of (*E*)- α,β -unsaturated γ -amino acids into (*Z*)- α,β -unsaturated γ -lactams, we subjected other OPfp esters **2b–2f** to lactamization by just stirring the solution of these active esters in DMF for about 2 h in the presence of DIPEA. The (*Z*)- α,β -unsaturated γ -lactams, **4b–4f**, were isolated in excellent yields. The single crystal structure of the α,β -unsaturated γ -lactams (**4a** and **4f**), is shown in Figure 1. Furthermore, to examine whether or not the OPfp esters of N-Cbz-protected α,β -unsaturated γ -amino acids can undergo lactamization similar to the OPfp esters of Boc-protected amino acids, we synthesized compound **2g** and subjected it to cyclization. The N-Cbz-protected α,β -unsaturated γ -lactam **4g** was isolated in a very good yield. These results suggested that the lactamization reaction is compatible with both Boc- and Cbz-protecting groups. The cyclization reaction was clean and no other by-products were observed in the reaction.



Scheme 4. Synthesis of N-protected- α,β -unsaturated γ -lactams (**4a-4i**) from the OPfp ester of N-protected-(*E*)- α,β -unsaturated γ -amino acids (**2a-2i**).

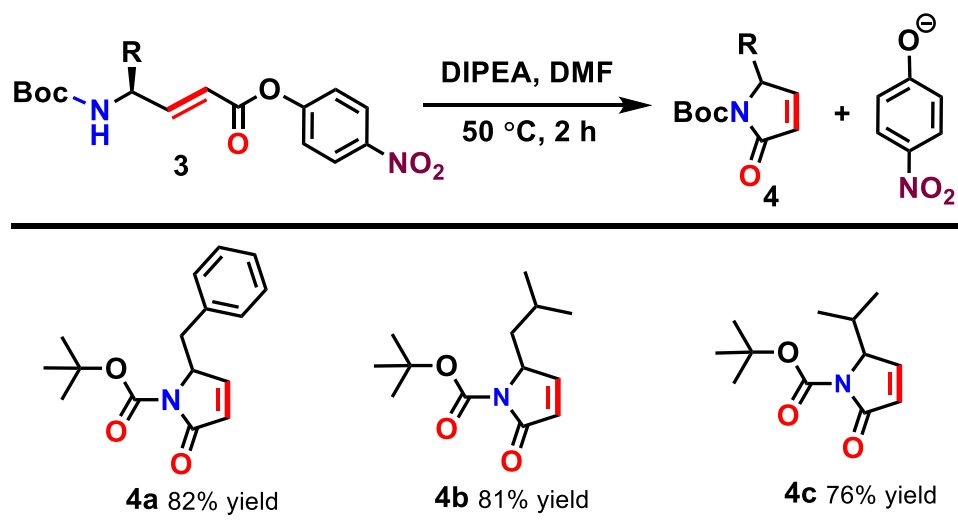
Furthermore, active ester (**1d**) treated with H-Leu-OMe to give dipeptide (**P1**) under a similar reaction condition of lactamization, depicted in Scheme 5. No lactamization was observed in the absence of the base DIPEA even after stirring the reaction mixture continuously for about 24 h. These observations suggested that the base triggers the intramolecular cyclization.



Scheme 5. Aminolysis reaction of Boc-(*S, E*)d^{2,3} γ Ala-OPfp (**1d**) in presence of a free amine.

Motivated by the transformation of (*E*)-vinyllogous amino acids into *Z*- γ -lactams mediated by pentafluorophenyl esters, we aimed to investigate whether this conversion is exclusive to pentafluorophenyl esters or other active esters, such as *p*-nitrophenyl esters of (*E*)-vinyllogous amino acids, can also facilitate this transformation. In this context, we synthesized several *p*-nitrophenyl esters of (*E*)-vinyllogous amino acids using *p*-nitrophenol and DCC, similar to the synthesis of pentafluorophenyl esters. The pictorial representation of the reaction is depicted in Scheme 3. The list of *p*-nitrophenyl esters of (*E*)-vinyllogous amino acids (**3a-3c**) is also

provided in Scheme 3. The *p*-nitrophenyl esters (**3a–3c**) were subjected to a cyclization reaction similar to pentafluorophenyl esters. The pictorial representation of the reaction is shown in Scheme 6.



Scheme 6: Synthesis of N-protected- α,β -unsaturated γ -lactams (**4a–4c**) from the ONp ester of N-protected-(*E*)- α,β -unsaturated γ -amino acids (**3a–3c**).

The examination of the cyclization reaction revealed that the transformation of ONp esters into their corresponding α,β -unsaturated γ -lactams (**3a–3c**) required 50 °C for lactamization. The reactivity pattern of these OPfp esters and ONp esters can be understood by comparing the IR and ^1H NMR spectra with their parent *E*- α,β -unsaturated γ -amino acids. The active esters and *E*- α,β -unsaturated γ -amino acid follow the reactivity order: **1a** < **3a** < **2a**. It is evident from the IR stretching frequency of Boc-dg-Phe-OPfp (**2a**) 1766 cm^{-1} , Boc-dg-Phe-ONp (**3a**) 1743 cm^{-1} and Boc-dg-Phe-OH (**1a**) 1699 cm^{-1} , **2a** contain most electrophilic center and **1a** have least electrophilic center among these three compounds, shown in Figure 2 (i). The more electron-withdrawing property of the -Pfp group makes **2a** more susceptible to nucleophilic attack compared to the -Np group, attributed by observed IR stretching frequency.²³ The comparison of ^1H NMR spectra of Boc-dg-Leu-OH (**1b**), Boc-dg-Leu-OPfp (**2b**) and Boc-dg-Leu-ONp (**3b**) shows a significant increase in chemical shift of protons H1 and H2 in active esters due to the strong electron-withdrawing nature of -Np and -Pfp groups shown in Figure 2 (ii). The difference in chemical shift values is more in the case of **2b** compared to **3b** with respect to **1b**. The values of chemical shift change are shown in Table 1, where H2 protons shift more compared to H1 because H2 protons are present near the electron-withdrawing groups. Comparative IR and NMR studies suggest, why OPfp esters react at room temperature however ONp esters require 50 °C for lactamization.

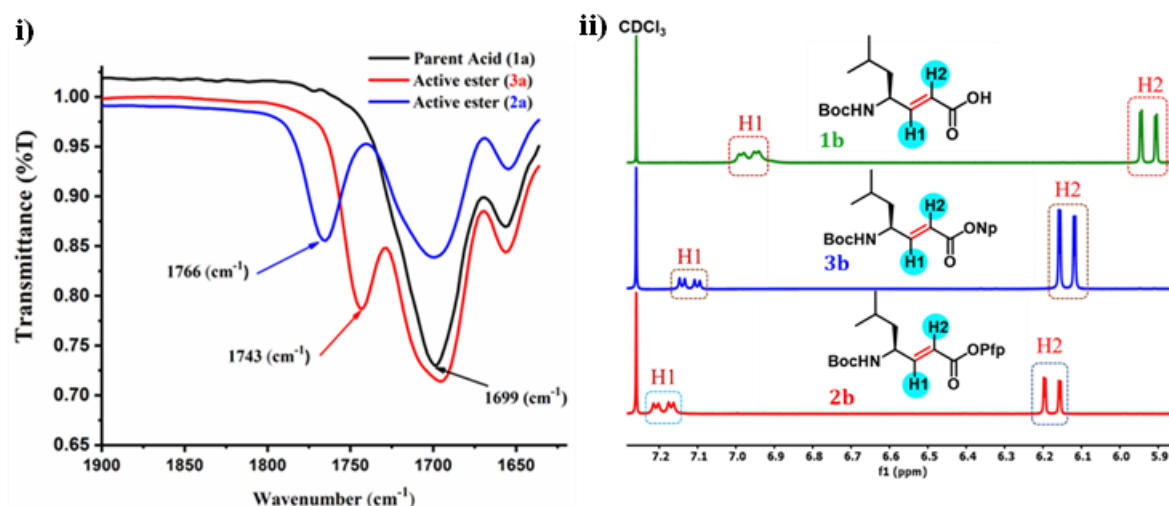


Figure 2 (i) Combined Partial IR spectra of **1a**, **2a** and **3a** and (ii) Combined Partial ^1H NMR spectra of **1b**, **2b** and **3b**.

Table 1. The values of chemical shift difference between the active esters and parent *E*- α,β -unsaturated γ -amino acid.

Active Ester	$\Delta\delta = (\delta_{\text{active ester}} - \delta_{\text{acid}})$	
	H1	H2
ONp	0.15	0.21
OPfp	0.22	0.25

2.4 Kinetics Analysis of the Lactamization Reaction

Using *p*-nitrophenol as a UV probe, we studied the kinetics of the lactamization of **3a**, **3b** and **3c** *p*-nitrophenol esters. The reaction was monitored at 431 nm and the lactamization reaction was initiated by the addition of DIPEA to the solution (29.42 μM) of ONp esters in DMF. The first-order rate constants for the formation of **4a**, **4b** and **4c** from the corresponding ONp esters were determined by plotting the concentrations of ONp esters vs. time (s). The molar extinction coefficient (ϵ) for the 4-nitrophenolate ion was obtained 4110 $\text{M}^{-1} \text{cm}^{-1}$ by plotting the absorbance against concentration, under the reaction condition. The rate constants are given in Table 2. The first-order equation reduces to $\ln[A] = \ln[A]_0 - kt$ ($[A]$: concentration of a reactant at time t ; $[A]_0$: initial concentration of reactant; k : rate constant). The standard curve was first generated to determine the product concentration at a given time from the observed absorbance at 431 nm. The observed absorbance was used to determine the value of $[A]$. Plotting $\ln[A]$

against time yielded the rate constant, using the linear fit method.²⁴ The kinetic profile of **3a**, **3b** and **3c** is shown in Figure 3. The rate constant for the cyclization of **3a** to **4a** was found to be $6.03 \times 10^{-4} \text{ s}^{-1}$. Similarly, **3b** and **3c** transformed into their corresponding γ -lactams **4b** and **4c** with rate constants $5.83 \times 10^{-4} \text{ s}^{-1}$ and $4.82 \times 10^{-4} \text{ s}^{-1}$, respectively. All three ONp esters gave almost similar rate constant values, which indicates that all three ONp esters follow a similar pathway of cyclization. All the kinetic experiments were performed at 50 °C.

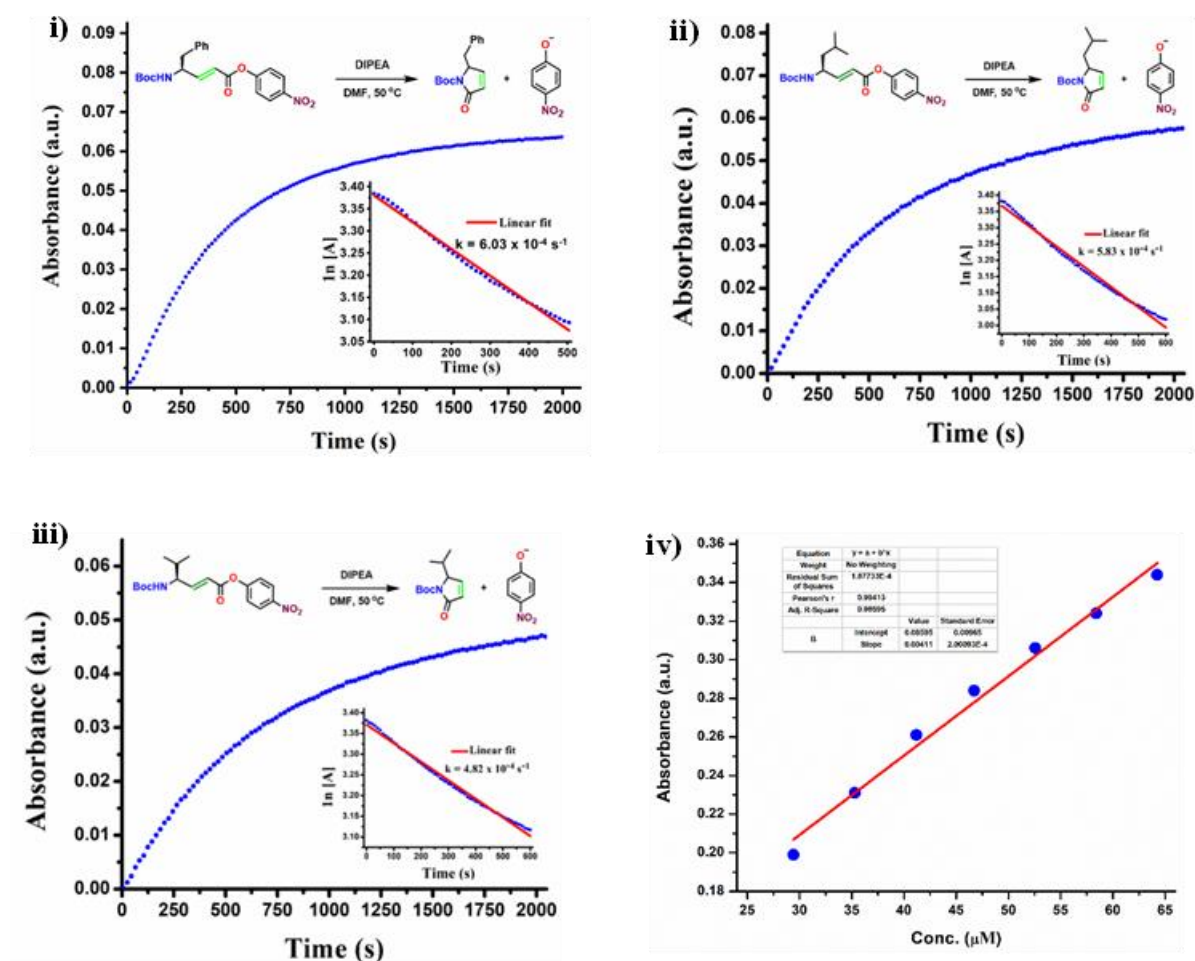


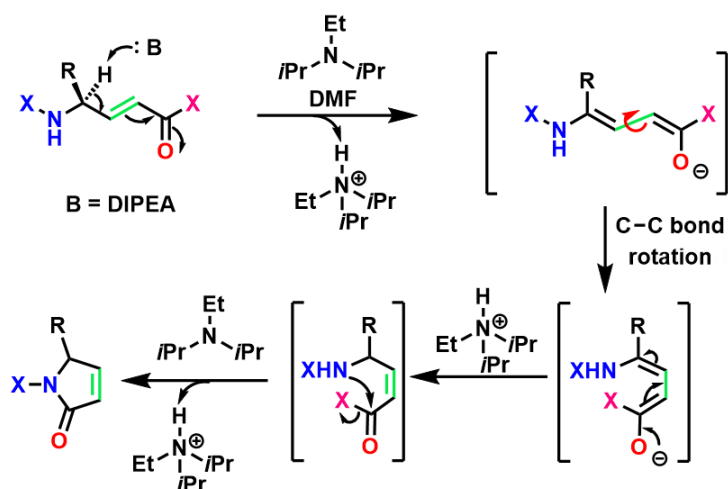
Figure 3. Kinetic analysis for the transformation of ONp esters into the corresponding α,β -unsaturated γ -lactams, (i) **3a** $\rightarrow$ **4a**, (ii) **3b** $\rightarrow$ **4b**, (iii) **3c** $\rightarrow$ **4c** and (iv) Plot of absorbance vs concentration to yield molar absorption coefficient (ϵ).

Table 2. Rate constants for the transformation of ONp esters into corresponding lactams.

Entry	Transformation	Rate constant (k)
1	3a $\rightarrow$ 4a	$6.03 \pm 0.3 \times 10^{-4} \text{ s}^{-1}$
2	3b $\rightarrow$ 4b	$5.83 \pm 0.4 \times 10^{-4} \text{ s}^{-1}$
3	3c $\rightarrow$ 4c	$4.82 \pm 0.3 \times 10^{-4} \text{ s}^{-1}$

2.5 Plausible Reaction Mechanism

The striking manifestation of the cyclization of the active esters of (*E*)- α,β -unsaturated γ -amino acids to (*Z*)- α,β -unsaturated γ -lactams inspired us to delineate the possible mechanism of the reaction. In contrast to $Z \rightarrow E$ isomerization, $E \rightarrow Z$ isomerization of carbon-carbon double bonds is an energetically unfavorable process. Nevertheless, selective $E \rightarrow Z$ isomerization can be achieved through photochemical irradiation of the extended π -conjugated systems.^{21,22} To evaluate the role of visible light in the α,β -unsaturated γ -lactam synthesis, we repeated the cyclization of **2a** to **4a** under dark conditions. We found no difference in the yields of the products, confirming that there is no requirement of light in the $E \rightarrow Z$ isomerization and subsequent lactamization of **4a**. Similar results were also observed for the transformation of **2b** and **2c** to **4b** and **4c**, respectively. In addition, there is a complete loss in the stereochemistry at the γ -carbon. Based on these observations, we proposed the possible mechanism of lactamization and it is shown in Scheme 7.



Scheme 7. Possible mechanism of the intramolecular cyclization of (*E*)- α,β -unsaturated γ -amino acids through $E \rightarrow Z$ isomerization of carbon-carbon double bonds.

2.6 Conclusion

In conclusion, we demonstrated the spontaneous transformation of active esters of *N*-protected (*E*)- α,β -unsaturated γ -amino acids into corresponding *N*-protected-(*Z*)- α,β -unsaturated γ -lactams in the presence of a weak base under mild conditions. The transformation involves the uncommon $E \rightarrow Z$ isomerization of double bonds. The γ -amide NH is crucial for cyclization. As γ -CH is directly involved in the reaction that leads to racemization in the products. The involvement of unfavorable $E \rightarrow Z$ isomerization of carbon-carbon double bonds without light

or metal catalysts is the most striking feature of this lactamization. The transformation observed here emulates the biosynthesis of coumarin which involves $E \rightarrow Z$ isomerization of double bonds followed by spontaneous lactonization of coenzyme A (CoA-SH) ester of *o*-hydroxycinnamic acid in the absence of light.²⁵ Similar to γ -NH, the *o*-hydroxyl group is critical for $E \rightarrow Z$ isomerization and lactonization. The results reported here can be used to access the α,β -unsaturated lactams under mild conditions.

2.7 Experimental Section

General Method: All the cyclization reactions were performed under N₂ conditions. All the amino acids, Boc anhydride, Benzyl chloroformate, N-hydroxysuccinimide, NaBH₄, Oxone, HBTU, HOBT, Ethyl bromoacetate, Triphenyl Phosphine (PPh₃), Trifluoroacetic acid (TFA), N,N-Diisopropylethylamine (DIPEA), DMF, EtOAc, Hexane, were purchased from different commercial sources. Ethyl acetate, Hexane, and THF (over sodium) were distilled before use. Column chromatography was performed on silica gel (60-120). Reactions were monitored by analytical thin layer chromatography (TLC) and confirmed by UV light chamber and KMnO₄ or ninhydrin staining. ¹H NMR, ¹³C NMR, and ¹⁹F NMR spectra were recorded in deuterated solvents on 400 MHz, 101 MHz, and 377 MHz NMR machines respectively using the residual solvent signal as the internal standard (CDCl₃). Chemical shifts are reported in parts per million (ppm, δ) relative to tetramethyl silane (δ 0.00). ¹H NMR splitting patterns are assigned as singlet (s), doublet (d), broad singlet (bs), triplet (t), doublet of doublets (dd), and quintet (qn). Coupling constants (J) are reported in Hertz (Hz). Mass spectra were recorded using HRMS Electron Spray Ionization (ESI). IR spectra were recorded on an IR spectrometer. HPLC was done using a Chiralpak[®]-IC column (4.6 mm ϕ x 250 mmL) of particle size 5 μ m. The X-ray data were collected at low temperatures (100, 120 K and 150 K) on a Bruker APEX (II) DUO CCD diffractometer using Mo K α (λ = 0.71073 Å) and Cu K α radiation (λ = 1.54178 Å) graphite monochromated radiation.

2.7.1 Synthetic procedures for OPfp/ONp esters of (*E*)-vinyllogous amino acids.

The *N*-protected α,β -unsaturated γ -amino esters (Boc/CbzHN-(*S,E*)d^{2,3} γ Xxx-OEt) were prepared by the previously reported procedures.²⁶ Boc/Cbz and ethyl ester protecting groups were used to protect the N-terminus and C-terminus of the (*E*)-vinyllogous amino acids, respectively and the ethyl ester was deprotected by base hydrolysis using 1N NaOH, to obtain **1a-1g**. The synthetic details of OPfp esters synthesis is given below. The purification of final

OPfp esters was carried out through silica gel column chromatography using ethyl acetate and hexane solvent gradient as eluent in order of increasing polarity.

Boc/CbzHN-d^{2,3}γXxx-OH (2 mmol) was dissolved in 50 mL of EtOAc, to this solution DCC (459 mg, 2.2 mmol) was added under ice-cold conditions, after stirring the reaction mixture for about 5 min, pentafluorophenol (368 mg, 2 mmol) was added.²⁷ The reaction mixture was allowed to be stirred for 4 h at room temperature. After completion of the reaction (progress of the reaction monitored by TLC), filtration was done by using a sintered funnel to remove urea (DCU) from the reaction mixture in the form of residue. The filtrate part containing the product Boc/CbzHN-d^{2,3}γXxx-OPfp was concentrated under reduced pressure. The obtained crude product was purified through a silica gel (60-120 mesh) column by ethyl acetate and hexane mixture as eluent in order of increasing polarity to get pure **2a-2g**.

Boc-(S,E)-d^{2,3}γPhe-OPfp (2a): White solid in 94% yield, R_f = 0.85 (20% EtOAc in hexane). M.p. 102-104 °C. [α]_D²⁵ = +6 (c 0.1, MeOH). ¹H NMR (400 MHz, Chloroform-*d*) δ 7.36 – 7.31 (m, 2H), 7.31 – 7.26 (m, 1H), 7.26 – 7.21 (m, 1H), 7.19 (dd, *J* = 8.3, 1.5 Hz, 2H), 6.10 (dd, *J* = 15.7, 1.7 Hz, 1H), 4.73 (s, 1H), 4.61 (s, 1H), 2.96 (d, *J* = 6.9 Hz, 2H), 1.42 (s, 9H). ¹³C NMR (101 MHz, Chloroform-*d*) δ 161.82, 155.09, 153.40, 142.56, 140.87, 140.11, 139.28, 138.34, 136.74, 135.98, 129.48, 128.89, 127.30, 117.83, 80.44, 52.74, 40.70, 28.40. ¹⁹F NMR (377 MHz, Chloroform-*d*) δ -152.50, -158.07, -162.40. HRMS (ESI) calculated for C₂₂H₂₀F₅NO₄Na [M+Na]⁺ *m/z* 480.1209 found 480.1206. IR: 1765 cm⁻¹.

Boc-(S,E)-d^{2,3}γLeu-OPfp (2b): White solid in 90% yield, R_f = 0.85 (20% EtOAc in hexane). M.p. 97-99 °C. [α]_D²⁵ = -22 (c 0.1, MeOH). ¹H NMR (400 MHz, Chloroform-*d*) δ 7.16 (dd, *J* = 15.6, 5.1 Hz, 1H), 6.16 (dd, *J* = 15.6, 1.6 Hz, 1H), 4.53 (d, *J* = 8.4 Hz, 1H), 4.46 (s, 1H), 1.77 – 1.72 (m, 1H), 1.46 (s, 9H), 1.44 (d, *J* = 7.1 Hz, 2H), 0.97 (dd, *J* = 6.6, 0.9 Hz, 6H). ¹³C NMR (101 MHz, Chloroform-*d*) δ 162.06, 155.24, 154.80, 142.60, 140.86, 140.06, 139.29, 138.34, 136.75, 117.07, 80.24, 50.28, 43.61, 28.47, 24.94, 22.95, 22.12. ¹⁹F NMR (377 MHz, Chloroform-*d*) δ -152.40, -158.20, -162.42. HRMS (ESI) calculated for C₁₉H₂₂F₅NO₄Na [M+Na]⁺ *m/z* 446.1366 found 446.1361. IR: 1765 cm⁻¹.

Boc-(S,E)-d^{2,3}γVal-OPfp (2c): White solid in 91% yield, R_f = 0.86 (20% EtOAc in hexane). M.p. 129-131 °C. [α]_D²⁵ = -25 (c 0.1, MeOH). ¹H NMR (400 MHz, Chloroform-*d*) δ 7.19 (dd, *J* = 15.6, 5.1 Hz, 1H), 6.17 (dd, *J* = 15.6, 1.8 Hz, 1H), 4.64 (d, *J* = 9.2 Hz, 1H), 4.30 (s, 1H), 1.99 – 1.89 (m, 1H), 1.47 (s, 9H), 0.98 (dd, *J* = 12.5, 6.8 Hz, 6H). ¹³C NMR (101 MHz, Chloroform-*d*) δ 161.92, 155.48, 153.38, 142.71, 141.09, 140.11, 139.33, 138.36, 136.77,

118.23, 80.27, 57.15, 32.37, 28.49, 19.14, 18.19. ^{19}F NMR (377 MHz, Chloroform-*d*) δ -152.46, -158.15, -162.44. HRMS (ESI) calculated for $\text{C}_{18}\text{H}_{20}\text{F}_5\text{NO}_4\text{Na}$ $[\text{M}+\text{Na}]^+$ m/z 432.1209 found 432.1215. IR: 1759 cm^{-1} .

Boc-(*S,E*)- $\text{d}^{2,3}\gamma\text{Ala}$ -OPfp (2d): White solid in 92% yield, $R_f = 0.80$ (20% EtOAc in hexane). M.p. 91-93 $^{\circ}\text{C}$. $[\alpha]_{\text{D}}^{25} = -29$ (*c* 0.1, MeOH). ^1H NMR (400 MHz, Chloroform-*d*) δ 7.19 (dd, $J = 15.7, 4.8$ Hz, 1H), 6.14 (dd, $J = 15.7, 1.7$ Hz, 1H), 4.63 (s, 1H), 4.51 (s, 1H), 1.46 (s, 9H), 1.34 (d, $J = 7.0$ Hz, 3H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 162.04, 155.11, 155.04, 142.59, 140.86, 140.17, 139.28, 138.35, 136.75, 116.91, 80.30, 28.45, 20.12. ^{19}F NMR (377 MHz, Chloroform-*d*) δ -152.50, -158.16, -162.46. HRMS (ESI) calculated for $\text{C}_{16}\text{H}_{16}\text{F}_5\text{NO}_4\text{Na}$ $[\text{M}+\text{Na}]^+$ m/z 404.0896 found 404.0889. IR: 1764 cm^{-1} .

Boc-(*S,E*)- $\text{d}^{2,3}\gamma\text{Ile}$ -OPfp (2e): White solid in 90% yield, $R_f = 0.85$ (20% EtOAc in hexane). M.p. 100-102 $^{\circ}\text{C}$. $[\alpha]_{\text{D}}^{25} = -18.5$ (*c* 0.1, MeOH). ^1H NMR (400 MHz, Chloroform-*d*) δ 7.18 (dd, $J = 15.7, 5.2$ Hz, 1H), 6.17 (dd, $J = 15.7, 1.8$ Hz, 1H), 4.66 (d, $J = 9.1$ Hz, 1H), 4.39 (s, 1H), 1.73 – 1.66 (m, 1H), 1.54 – 1.48 (m, 1H), 1.47 (s, 9H), 1.19 (ddd, $J = 11.8, 8.3, 6.2$ Hz, 1H), 0.98 – 0.93 (m, 6H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 161.90, 155.41, 153.20, 140.09, 118.29, 80.24, 56.24, 39.14, 28.48, 25.49, 15.59, 11.75. ^{19}F NMR (377 MHz, Chloroform-*d*) δ -152.44, -158.17, -162.46. HRMS (ESI) calculated for $\text{C}_{19}\text{H}_{22}\text{F}_5\text{NO}_4\text{Na}$ $[\text{M}+\text{Na}]^+$ m/z 446.1366 found 446.1375. IR: 1764 cm^{-1} .

Boc-(*S,E*)- $\text{d}^{2,3}\gamma\text{Phg}$ -OPfp (2f): White solid in 88% yield, $R_f = 0.88$ (20% EtOAc in hexane). M.p. 136-138 $^{\circ}\text{C}$. $[\alpha]_{\text{D}}^{25} = +9$ (*c* 0.1, MeOH). ^1H NMR (400 MHz, Chloroform-*d*) δ 7.44 – 7.33 (m, 4H), 7.32 – 7.28 (m, 2H), 6.24 (dd, $J = 15.6, 1.9$ Hz, 1H), 5.54 (s, 1H), 4.95 (s, 1H), 1.47 (s, 9H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 161.87, 154.91, 152.76, 140.07, 139.32, 138.42, 136.73, 129.44, 128.75, 127.46, 125.13, 118.15, 80.76, 55.99, 28.47. ^{19}F NMR (377 MHz, Chloroform-*d*) δ -152.34, -157.99, -162.34. HRMS (ESI) calculated for $\text{C}_{21}\text{H}_{18}\text{F}_5\text{NO}_4\text{Na}$ $[\text{M}+\text{Na}]^+$ m/z 466.1053 found 466.1053. IR: 1764 cm^{-1} .

Cbz-(*S,E*)- $\text{d}^{2,3}\gamma\text{Leu}$ -OPfp (2g): White solid in 91% yield, $R_f = 0.82$ (20% EtOAc in hexane). $[\alpha]_{\text{D}}^{25} = -42$ (*c* 0.1, MeOH). ^1H NMR (400 MHz, Chloroform-*d*) δ 7.39 – 7.31 (m, 5H), 7.16 (dd, $J = 15.6, 5.3$ Hz, 1H), 6.17 (d, $J = 15.6$ Hz, 1H), 5.14 (s, 2H), 4.83 (d, $J = 8.4$ Hz, 1H), 4.53 (p, $J = 7.2$ Hz, 1H), 1.74 (m, 1H), 1.48 (t, $J = 7.3$ Hz, 2H), 0.97 (d, $J = 6.6$ Hz, 6H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 161.95, 155.84, 154.04, 142.69, 140.87, 140.06, 139.28, 138.36, 136.75, 136.20, 128.74, 128.48, 128.32, 117.38, 67.35, 50.80, 43.46, 24.89, 22.91,

22.08. ^{19}F NMR (377 MHz, Chloroform-*d*) δ -152.39, -158.08, -162.40. HRMS (ESI) calculated for $\text{C}_{22}\text{H}_{20}\text{F}_5\text{NO}_4\text{Na}$ $[\text{M}+\text{Na}]^+$ m/z 480.1210 found 480.1209. IR: 1765 cm^{-1} .

Boc-Leu-(*S,E*)- $\text{d}^{2,3}\gamma\text{Val}$ -OPfp (2h): Oily liquid in 91% yield, $R_f = 0.83$ (20% EtOAc in hexane). $[\alpha]_{\text{D}}^{25} = -42$ (c 0.1, MeOH). ^1H NMR (400 MHz, Chloroform-*d*) δ 7.19 (dd, $J = 15.7$, 5.1 Hz, 1H), 6.69 (s, 1H), 6.16 (dd, $J = 15.7$, 1.8 Hz, 1H), 4.90 (d, $J = 7.7$ Hz, 1H), 4.62 (dtd, $J = 9.0$, 5.3, 1.9 Hz, 1H), 4.15 – 4.09 (m, 1H), 1.97 (td, $J = 7.1$, 5.7 Hz, 1H), 1.76 – 1.68 (m, 2H), 1.56 – 1.50 (m, 1H), 1.45 (s, 9H), 0.99 – 0.93 (m, 12H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 172.55, 161.86, 156.31, 152.69, 142.53, 141.18, 140.12, 136.75, 118.37, 80.78, 55.40, 53.58, 40.0, 32.21, 28.40, 24.95, 23.00, 22.12, 19.20, 18.01. ^{19}F NMR (377 MHz, Chloroform-*d*) δ -152.42, -158.13, -162.38. HRMS (ESI) calculated for $\text{C}_{24}\text{H}_{31}\text{F}_5\text{N}_2\text{O}_5\text{Na}$ $[\text{M}+\text{Na}]^+$ m/z 545.2050 found 545.2052. IR: 1766 cm^{-1} .

Boc-Ala-(*S,E*)- $\text{d}^{2,3}\gamma\text{Leu}$ -OPfp (2i): Oily liquid in 89% yield, $R_f = 0.80$ (20% EtOAc in hexane). $[\alpha]_{\text{D}}^{25} = -31$ (c 0.1, MeOH). ^1H NMR (400 MHz, Chloroform-*d*) δ 7.16 (dd, $J = 15.7$, 4.9 Hz, 1H), 6.54 (s, 1H), 6.16 (dd, $J = 15.7$, 1.7 Hz, 1H), 5.00 – 4.88 (m, 1H), 4.77 (ddq, $J = 8.4$, 4.1, 2.2 Hz, 1H), 4.17 (dd, $J = 12.9$, 6.9 Hz, 1H), 1.74 – 1.69 (m, 1H), 1.52 – 1.48 (m, 2H), 1.46 (s, 9H), 1.39 (d, $J = 7.1$ Hz, 3H), 0.97 – 0.93 (m, 6H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 172.43, 162.00, 153.93, 147.19, 142.58, 140.08, 140.04, 139.26, 136.73, 117.26, 80.86, 48.60, 43.26, 29.84, 28.39, 24.94, 23.09, 21.90, 17.36. ^{19}F NMR (377 MHz, Chloroform-*d*) δ -152.43, -158.17, -162.44. HRMS (ESI) calculated for $\text{C}_{22}\text{H}_{27}\text{F}_5\text{N}_2\text{O}_5\text{Na}$ $[\text{M}+\text{Na}]^+$ m/z 517.1737 found 517.1743. IR: 1765 cm^{-1} .

BocHN- $\text{d}^{2,3}\gamma\text{Xxx}$ -OH (2 mmol) was dissolved in 50 mL of EtOAc, to this solution DCC (454 mg, 2.2 mmol) was added under ice-cold conditions, after stirring the reaction mixture for about 5 min, *p*-nitrophenol (278 mg, 2 mmol) was added.²⁷ The reaction mixture was allowed to be stirred for 4 h at room temperature. After completion of the reaction (progress of the reaction monitored by TLC), filtration was done by using a sintered funnel to remove urea (DCU) from the reaction mixture in the form of residue. The filtrate part containing the product BocHN- $\text{d}^{2,3}\gamma\text{Xxx}$ -ONp was concentrated under reduced pressure. The obtained crude product was purified through a silica gel (60-120 mesh) column by ethyl acetate and hexane mixture as eluent in order of increasing polarity to get pure **3a-3c**.

Boc-(*S,E*)- $\text{d}^{2,3}\gamma\text{Phe}$ -ONp (3a): White solid in 93% yield, $R_f = 0.86$ (20% EtOAc in hexane). M.p. 143-146 °C. $[\alpha]_{\text{D}}^{25} = -2$ (c 0.1, MeOH). ^1H NMR (400 MHz, Chloroform-*d*) δ 8.30 – 8.25

(m, 2H), 7.36 – 7.27 (m, 5H), 7.22 – 7.14 (m, 3H), 6.07 (dd, $J = 15.6, 1.7$ Hz, 1H), 4.70 (bs, 1H), 4.61 (s, 1H), 2.96 (d, $J = 6.8$ Hz, 2H), 1.42 (s, 9H). ^{13}C NMR (101 MHz, Chloroform- d) δ 163.59, 155.51, 155.11, 151.78, 145.45, 136.13, 129.47, 128.89, 127.27, 125.34, 122.56, 119.66, 80.35, 52.75, 40.75, 28.44. HRMS (ESI) calculated for $\text{C}_{22}\text{H}_{24}\text{N}_2\text{O}_6\text{Na}$ $[\text{M}+\text{Na}]^+$ m/z 435.1531 found 435.1522. IR: 1743 cm^{-1} .

Boc-(*S,E*)- $d^{2,3}\gamma$ Leu-ONp (3b): White solid in 91% yield, $R_f = 0.81$ (20% EtOAc in hexane). M.p. 67-69 °C. $[\alpha]_D^{25} = -40$ (c 0.1, MeOH). ^1H NMR (400 MHz, Chloroform- d) δ 8.28 (d, $J = 9.2$ Hz, 2H), 7.31 (d, $J = 9.1$ Hz, 2H), 7.09 (dd, $J = 15.6, 5.4$ Hz, 1H), 6.13 (dd, $J = 15.6, 1.5$ Hz, 1H), 4.55 (d, $J = 8.2$ Hz, 1H), 4.44 (t, $J = 6.5$, 1H), 1.73 (dq, $J = 13.5, 6.8$ Hz, 1H), 1.47 (s, 9H), 1.45 – 1.42 (m, 2H), 0.97 (dd, $J = 6.6, 1.3$ Hz, 6H). ^{13}C NMR (101 MHz, Chloroform- d) δ 163.83, 155.34, 153.04, 145.45, 126.32, 125.35, 122.59, 118.96, 115.77, 80.31, 50.30, 43.67, 28.51, 24.94, 22.89, 22.22. HRMS (ESI) calculated for $\text{C}_{19}\text{H}_{26}\text{N}_2\text{O}_6\text{Na}$ $[\text{M}+\text{Na}]^+$ m/z 401.1688 found 401.1682. IR: 1740 cm^{-1} .

Boc-(*S,E*)- $d^{2,3}\gamma$ Val-ONp (3c): White solid in 90% yield, $R_f = 0.80$ (20% EtOAc in hexane). M.p. 102-104 °C. $[\alpha]_D^{25} = -44$ (c 0.1, MeOH). ^1H NMR (400 MHz, Chloroform- d) δ 8.28 (d, $J = 9.2$ Hz, 2H), 7.32 (d, $J = 9.2$ Hz, 2H), 7.12 (dd, $J = 15.6, 5.4$ Hz, 1H), 6.14 (dd, $J = 15.7, 1.7$ Hz, 1H), 4.65 (d, $J = 9.0$ Hz, 1H), 4.27 (s, 1H), 1.93 (dt, $J = 12.8, 6.3$ Hz, 1H), 1.47 (s, 9H), 0.98 (dd, $J = 11.2, 6.8$ Hz, 6H). ^{13}C NMR (101 MHz, Chloroform- d) δ 163.68, 155.53, 151.64, 145.45, 126.36, 125.34, 122.59, 120.06, 115.92, 80.21, 57.16, 32.32, 28.50, 19.11, 18.23. HRMS (ESI) calculated for $\text{C}_{18}\text{H}_{24}\text{N}_2\text{O}_6\text{Na}$ $[\text{M}+\text{Na}]^+$ m/z 387.1531 found 387.1531. IR: 1740 cm^{-1} .

2.7.2 Transformation of OPfp active esters into α,β -unsaturated γ -lactam.

Boc/Cbz- $d^{2,3}\gamma$ Xxx-OPfp (1 mmol) was dissolved in 10 mL of DMF, to this solution DIPEA (0.87 mL, 5 mmol) was added. The reaction mixture was stirred for 2 h at room temperature. After completion of the reaction (monitored by TLC), workup was done by diluting the reaction mixture with ethyl acetate (2×50 mL), followed by successive washings with 10% HCl (3×40 mL), 10% Na_2CO_3 (3×40 mL) and brine solution (3×25 mL). The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The obtained crude product was purified through a silica gel (60-120 mesh) column by ethyl acetate and hexane mixture as eluent in order of increasing polarity to get **4a-4i**.

tert-butyl-2-benzyl-5-oxo-2,5-dihydro-1H-pyrrole-1-carboxylate (4a): White solid in 88% yield, $R_f = 0.55$ (20% EtOAc in hexane). M.p. 99-102 °C. $[\alpha]_D^{25} = +6$ (c 0.1, MeOH). ^1H NMR (400 MHz, Chloroform-*d*) δ 7.34 – 7.27 (m, 3H), 7.17 – 7.13 (m, 2H), 7.02 (dd, $J = 6.1, 2.0$ Hz, 1H), 6.02 (dd, $J = 6.1, 1.6$ Hz, 1H), 4.75 (ddt, $J = 9.5, 3.8, 1.8$ Hz, 1H), 3.55 (dd, $J = 13.1, 3.9$ Hz, 1H), 2.74 (dd, $J = 13.1, 9.5$ Hz, 1H), 1.63 (s, 9H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 169.20, 150.05, 149.64, 135.76, 129.51, 128.84, 127.30, 126.79, 83.34, 63.51, 38.74, 28.37. HRMS (ESI) calculated for $\text{C}_{16}\text{H}_{19}\text{NO}_3\text{Na}$ $[\text{M}+\text{Na}]^+$ m/z 296.1262, found 296.1262.

tert-butyl-2-isobutyl-5-oxo-2,5-dihydro-1H-pyrrole-1-carboxylate (4b): Oily liquid in 85% yield, $R_f = 0.60$ (20% EtOAc in hexane). $[\alpha]_D^{25} = +2$ (c 0.1, MeOH). ^1H NMR (400 MHz, Chloroform-*d*) δ 7.22 (dd, $J = 6.1, 2.0$ Hz, 1H), 6.08 (dd, $J = 6.1, 1.6$ Hz, 1H), 4.60 (ddt, $J = 9.9, 3.7, 1.8$ Hz, 1H), 1.67 (td, $J = 4.5, 2.3$ Hz, 1H), 1.56 (s, 9H), 1.47 – 1.41 (m, 2H), 0.99 (d, $J = 6.6$ Hz, 3H), 0.94 (d, $J = 6.6$ Hz, 3H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 169.43, 150.69, 149.45, 126.46, 83.01, 61.54, 41.27, 28.28, 25.29, 24.05, 22.29. HRMS (ESI) calculated for $\text{C}_{13}\text{H}_{21}\text{NO}_3\text{Na}$ $[\text{M}+\text{Na}]^+$ m/z 262.1418, found 262.1418.

tert-butyl-2-isopropyl-5-oxo-2,5-dihydro-1H-pyrrole-1-carboxylate (4c): oily liquid in 79% yield, $R_f = 0.58$ (20% EtOAc in hexane). $[\alpha]_D^{25} = +4$ (c 0.1, MeOH). ^1H NMR (400 MHz, Chloroform-*d*) δ 7.12 (dd, $J = 6.2, 2.0$ Hz, 1H), 6.14 (dd, $J = 6.2, 1.7$ Hz, 1H), 4.55 (dt, $J = 3.9, 1.8$ Hz, 1H), 2.59 (qt, $J = 6.9, 3.5$ Hz, 1H), 1.54 (s, 9H), 1.09 (d, $J = 7.1$ Hz, 3H), 0.66 (d, $J = 6.9$ Hz, 3H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 169.70, 149.73, 147.94, 127.92, 83.00, 67.41, 28.99, 28.23, 19.63, 14.98. HRMS (ESI) calculated for $\text{C}_{12}\text{H}_{19}\text{NO}_3\text{Na}$ $[\text{M}+\text{Na}]^+$ m/z 248.1262, found 248.1261.

tert-butyl-2-methyl-5-oxo-2,5-dihydro-1H-pyrrole-1-carboxylate (4d): Oily liquid in 87% yield, $R_f = 0.52$ (20% EtOAc in hexane). $[\alpha]_D^{25} = +6$ (c 0.1, MeOH). ^1H NMR (400 MHz, Chloroform-*d*) δ 7.09 (dd, $J = 6.1, 2.0$ Hz, 1H), 6.06 (dd, $J = 6.1, 1.7$ Hz, 1H), 4.61 (dt, $J = 6.7, 1.8$ Hz, 1H), 1.56 (s, 9H), 1.43 (d, $J = 6.7$ Hz, 3H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 169.30, 151.90, 149.53, 126.07, 83.04, 58.53, 28.28, 18.30. HRMS (ESI) calculated for $\text{C}_{10}\text{H}_{18}\text{NO}_3\text{Na}$ $[\text{M}+\text{Na}]^+$ m/z 220.0949, found 220.0955.

tert-butyl-2-((S)-sec-butyl)-5-oxo-2,5-dihydro-1H-pyrrole-1-carboxylate (4e): $R_f = 0.60$ (20% EtOAc in hexane). $[\alpha]_D^{25} = -6$ (c 0.1, MeOH). ^1H NMR (400 MHz, Chloroform-*d*, mixture of two isomers in ratio of 1:1) δ 7.12 (dd, $J = 6.2, 2.0$ Hz, 1H), 7.07 (dd, $J = 6.1, 2.1$ Hz, 1H), 6.12 (dd, $J = 6.2, 1.7$ Hz, 1H), 6.09 (dd, $J = 6.2, 1.8$ Hz, 1H), 4.64 (dt, $J = 4.0, 1.9$ Hz,

1H), 4.55 (dt, $J = 3.9, 1.9$ Hz, 1H), 2.30 (dddt, $J = 20.7, 10.5, 7.0, 3.2$ Hz, 2H), 1.53 (s, 18H), 1.44 – 1.23 (m, 4H), 1.06 (d, $J = 7.1$ Hz, 3H), 1.02 (t, $J = 7.4$ Hz, 3H), 0.82 (t, $J = 7.4$ Hz, 3H), 0.61 (d, $J = 6.9$ Hz, 3H). ^{13}C NMR (101 MHz, Chloroform- d) δ 169.79, 169.77, 149.66, 149.57, 148.31, 148.12, 127.86, 127.40, 82.94, 67.60, 66.10, 35.87, 35.81, 28.22, 28.20, 27.31, 22.59, 16.59, 12.66, 12.37, 12.26. HRMS (ESI) calculated for $\text{C}_{13}\text{H}_{21}\text{NO}_3\text{Na}$ $[\text{M}+\text{Na}]^+$ m/z 262.1418, found 262.1418.

tert-butyl-2-oxo-5-phenyl-2,5-dihydro-1H-pyrrole-1-carboxylate (4f): White solid in 87% yield, $R_f = 0.59$ (20% EtOAc in hexane). M.p. 102-104 °C. $[\alpha]_D^{25} = 0$ (c 0.1, MeOH). ^1H NMR (400 MHz, Chloroform- d) δ 7.38 – 7.31 (m, 3H), 7.21 – 7.18 (m, 2H), 7.06 (dd, $J = 6.0, 2.2$ Hz, 1H), 6.16 (dd, $J = 6.0, 1.7$ Hz, 1H), 5.53 (t, $J = 2.0$ Hz, 1H), 1.27 (s, 9H). ^{13}C NMR (101 MHz, Chloroform- d) δ 170.00, 150.31, 148.78, 135.85, 129.00, 128.62, 126.62, 125.44, 83.09, 66.39, 27.89. HRMS (ESI) calculated for $\text{C}_{15}\text{H}_{17}\text{NO}_3\text{Na}$ $[\text{M}+\text{Na}]^+$ m/z 282.1105, found 282.1103.

benzyl 2-isobutyl-5-oxo-2,5-dihydro-1H-pyrrole-1-carboxylate (4g): Oily liquid in 81% yield, $R_f = 0.55$ (30% EtOAc in hexane). $[\alpha]_D^{25} = +4$ (c 0.1, MeOH). ^1H NMR (400 MHz, Chloroform- d) δ 7.46 – 7.42 (m, 2H), 7.39 – 7.32 (m, 3H), 7.27 (dd, $J = 6.1, 2.0$ Hz 1H), 6.10 (dd, $J = 6.1, 1.7$ Hz, 1H), 5.36 (d, $J = 12.3$ Hz, 1H), 5.27 (d, $J = 12.3$ Hz, 1H), 4.66 (ddd, $J = 7.5, 3.8, 1.9$ Hz, 1H), 2.0 – 1.94 (m, 1H), 1.69 – 1.62 (m, 1H), 1.45 – 1.38 (m, 1H), 0.93 (d, $J = 6.6$ Hz, 3H), 0.88 (d, $J = 6.6$ Hz, 3H). ^{13}C NMR (101 MHz, Chloroform- d) δ 168.92, 151.42, 150.93, 135.42, 128.71, 128.52, 128.34, 126.17, 68.07, 61.60, 40.96, 25.24, 23.85, 22.14. HRMS (ESI) calculated for $\text{C}_{16}\text{H}_{20}\text{NO}_3$ $[\text{M}+\text{H}]^+$ m/z 274.1443, found 274.1439.

tert-butyl ((2S)-1-(2-isopropyl-5-oxo-2,5-dihydro-1H-pyrrol-1-yl)-4-methyl-1-oxopentan-2-yl)carbamate (4h): Oily liquid in 76% yield, $R_f = 0.51$ (20% EtOAc in hexane). $[\alpha]_D^{25} = -230$ (c 0.1, MeOH). ^1H NMR (400 MHz, Chloroform- d) δ 7.25 (d, $J = 4.2$ Hz, 1H), 6.13 (dd, $J = 6.2, 1.5$ Hz, 1H), 5.49 (t, $J = 9.0$ Hz, 1H), 5.05 (d, $J = 8.3$ Hz, 1H), 4.75 (s, 1H), 2.68 – 2.53 (m, 1H), 1.81 (ddt, $J = 13.6, 6.7, 3.8$ Hz, 1H), 1.62 – 1.53 (m, 1H), 1.41 (s, 9H), 1.39 – 1.33 (m, 1H), 1.06 (dd, $J = 12.4, 6.8$ Hz, 6H), 0.91 (d, $J = 6.7$ Hz, 3H), 0.59 (d, $J = 6.9$ Hz, 3H). ^{13}C NMR (101 MHz, Chloroform- d) δ 174.00, 169.83, 155.82, 150.12, 127.40, 79.62, 66.65, 53.31, 41.70, 28.41, 28.01, 25.15, 23.69, 21.13, 19.47, 14.99. HRMS (ESI) calculated for $\text{C}_{18}\text{H}_{30}\text{N}_2\text{O}_4\text{Na}$ $[\text{M}+\text{Na}]^+$ m/z 361.2103, found 361.2101.

tert-butyl ((2S)-1-(2-isobutyl-5-oxo-2,5-dihydro-1H-pyrrol-1-yl)-1-oxopropan-2-yl)carbamate (4i): Oily liquid in 84% yield, $R_f = 0.59$ (20% EtOAc in hexane). $[\alpha]_D^{25} = -69$ (c 0.1, MeOH). ^1H NMR (400 MHz, Chloroform- d) δ 7.39 (d, $J = 5.4$ Hz, 1H), 6.12 – 6.09 (m, 1H), 5.41 (q, $J = 7.3$ Hz, 1H), 5.23 (d, $J = 7.1$ Hz, 1H), 4.87 – 4.77 (m, 1H), 1.71 – 1.67 (m, 1H), 1.44 (s, 9H), 1.40 (d, $J = 6.9$ Hz, 3H), 1.25 (d, $J = 7.1$ Hz, 2H), 1.01 (d, $J = 6.6$ Hz, 3H), 0.93 (d, $J = 6.6$ Hz, 3H). ^{13}C NMR (101 MHz, Chloroform- d) δ 173.55, 169.46, 155.32, 153.03, 125.91, 79.76, 61.28, 60.88, 50.37, 40.41, 28.48, 25.37, 23.92, 22.27. HRMS (ESI) calculated for $\text{C}_{16}\text{H}_{26}\text{N}_2\text{O}_4\text{Na}$ $[\text{M}+\text{Na}]^+$ m/z 333.1790, found 333.1790.

2.7.3 Transformation of ONp active esters into α,β -unsaturated γ -lactam.

Boc-d^{2,3} γ Xxx-ONp (1 mmol) was dissolved in 10 mL of DMF, to this solution DIPEA (0.87 mL, 5 mmol) was added. The reaction mixture was stirred for 2 h at 50 °C. After completion of the reaction (monitored by TLC), workup was done by diluting the reaction mixture with ethyl acetate (50 mL), followed by successive washings with 10% HCl (3 $\times$ 40 mL), 10% Na_2CO_3 (3 $\times$ 40 mL) and brine solution (2 $\times$ 30 mL). The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The obtained crude product was purified through a silica gel (60-120 mesh) column by ethyl acetate and hexane mixture as eluent in order of increasing polarity to get pure **4a-4c**.

tert-butyl-2-benzyl-5-oxo-2,5-dihydro-1H-pyrrole-1-carboxylate (4a): White solid in 82% yield, $R_f = 0.59$ (20% EtOAc in hexane). M.p. 99-102 °C. $[\alpha]_D^{25} = +6$ (c 0.1, MeOH). ^1H NMR (400 MHz, Chloroform- d) δ 7.34 – 7.27 (m, 3H), 7.17 – 7.13 (m, 2H), 7.02 (dd, $J = 6.1$, 2.0 Hz, 1H), 6.02 (dd, $J = 6.1$, 1.6 Hz, 1H), 4.75 (ddt, $J = 9.5$, 3.8, 1.8 Hz, 1H), 3.55 (dd, $J = 13.1$, 3.9 Hz, 1H), 2.74 (dd, $J = 13.1$, 9.5 Hz, 1H), 1.63 (s, 9H). ^{13}C NMR (101 MHz, Chloroform- d) δ 169.20, 150.05, 149.64, 135.76, 129.51, 128.84, 127.30, 126.79, 83.34, 63.51, 38.74, 28.37. HRMS (ESI) calculated for $\text{C}_{16}\text{H}_{19}\text{NO}_3\text{Na}$ $[\text{M}+\text{Na}]^+$ m/z 296.1262, found 296.1262.

tert-butyl-2-isobutyl-5-oxo-2,5-dihydro-1H-pyrrole-1-carboxylate (4b): Oily liquid in 81% yield, $R_f = 0.60$ (20% EtOAc in hexane). $[\alpha]_D^{25} = +2$ (c 0.1, MeOH). ^1H NMR (400 MHz, Chloroform- d) δ 7.22 (dd, $J = 6.1$, 2.0 Hz, 1H), 6.08 (dd, $J = 6.1$, 1.6 Hz, 1H), 4.59 (ddt, $J = 9.9$, 3.7, 1.8 Hz, 1H), 1.69 (ddd, $J = 9.3$, 4.7, 2.5 Hz, 1H), 1.55 (s, 9H), 1.47 – 1.40 (m, 2H), 0.99 (d, $J = 6.6$ Hz, 3H), 0.94 (d, $J = 6.6$ Hz, 3H). ^{13}C NMR (101 MHz, Chloroform- d) δ 169.43, 150.69, 149.45, 126.46, 83.01, 61.54, 41.27, 28.28, 25.29, 24.05, 22.29. HRMS (ESI) calculated for $\text{C}_{13}\text{H}_{21}\text{NO}_3\text{Na}$ $[\text{M}+\text{Na}]^+$ m/z 262.1418, found 262.1418.

tert-butyl-2-isopropyl-5-oxo-2,5-dihydro-1H-pyrrole-1-carboxylate (4c): Oily liquid in 76% yield, $R_f = 0.58$ (20% EtOAc in hexane). $[\alpha]_D^{25} = +4$ (c 0.1, MeOH). ^1H NMR (400 MHz, Chloroform- d) δ 7.12 (dd, $J = 6.2, 2.0$ Hz, 1H), 6.14 (dd, $J = 6.2, 1.7$ Hz, 1H), 4.55 (dt, $J = 3.9, 1.8$ Hz, 1H), 2.59 (qt, $J = 6.9, 3.5$ Hz, 1H), 1.54 (s, 9H), 1.09 (d, $J = 7.1$ Hz, 3H), 0.66 (d, $J = 6.9$ Hz, 3H). ^{13}C NMR (101 MHz, Chloroform- d) δ 169.70, 149.73, 147.94, 127.92, 83.00, 67.41, 28.99, 28.23, 19.63, 14.98. HRMS (ESI) calculated for $\text{C}_{12}\text{H}_{19}\text{NO}_3\text{Na}$ $[\text{M}+\text{Na}]^+$ m/z 248.1262, found 248.1261.

2.7.4 Synthetic procedure for Boc- $\text{d}^{2,3}\gamma\text{Ala-Leu-OMe}$ (P1).

Boc- $\text{d}^{2,3}\gamma\text{Ala-OPfp}$ (**2d**, 381 mg, 1 mmol) was dissolved in 5 mL of DMF, to this solution DIPEA (0.870 mL, 5 mmol) was added. After stirring the reaction mixture for about 5 minutes at ice-cooled temperature, H-Leu-OMe (160 mg, 1.1 mmol) was added. The reaction mixture was stirred at room temperature for 8 h. After completion of the reaction (monitored by TLC), workup was done by diluting the reaction mixture with ethyl acetate (50 mL), followed by successive washings with 10% HCl (3×25 mL), 10% Na_2CO_3 (3×25 mL) and brine solution (3×25 mL). The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The obtained crude product was purified through a silica gel (60-120 mesh) column by ethyl acetate and hexane mixture as eluent in order of increasing polarity to get pure **P1**.

White solid in 90% yield, $R_f = 0.55$ (50% EtOAc in hexane). ^1H NMR (400 MHz, Chloroform- d) δ 6.72 (dd, $J = 15.3, 5.4$ Hz, 1H), 6.16 (dd, $J = 26.9, 8.3$ Hz, 1H), 5.91 (d, $J = 15.3$ Hz, 1H), 4.72 – 4.66 (m, 1H), 4.66 – 4.55 (m, 1H), 4.36 (s, 1H), 3.73 (s, 3H), 1.65 (ddd, $J = 9.7, 7.2, 3.9$ Hz, 2H), 1.58 – 1.52 (m, 1H), 1.43 (s, 9H), 1.24 (d, $J = 6.9$ Hz, 3H), 0.93 (dd, $J = 6.1, 4.1$ Hz, 7H). ^{13}C NMR (101 MHz, Chloroform- d) δ 173.81, 165.35, 155.13, 145.91, 122.35, 79.84, 52.47, 50.88, 41.84, 28.51, 24.96, 23.27, 22.90, 22.08, 20.60. HRMS (ESI) calculated for $\text{C}_{17}\text{H}_{30}\text{N}_2\text{O}_5\text{Na}$ $[\text{M}+\text{Na}]^+$ m/z 365.2052, found 365.2052.

2.8 Crystallographic Information.

Boc- $\text{d}^{2,3}\gamma\text{-Phe-OPfp}$ 2a: Crystals of **2a** were grown by slow evaporation from a solution of aqueous methanol at room temperature. A single crystal ($0.16 \times 0.05 \times 0.12$ mm) was mounted on a loop with a small amount of paraffin oil. The X-ray data were collected at 120K temperature on a Bruker APEX(II) DUO CCD diffractometer using Mo K_α radiation ($\lambda = 0.71073$ Å), ω -scans ($2\theta = 56.896$), for a total of 15970 independent reflections. Space group P 21, $a = 10.469$ (6), $b = 9.455$ (6), $c = 11.567$ (6), $\alpha = 90$, $\beta = 110.556$ (14), $\gamma = 90$, $V =$

1072.1(10) Å³, Monoclinic, Z = 2 for chemical formula C₂₂ H₂₀ F₅ N O₄, with one molecule in asymmetric unit; ρ calcd = 1.417 gcm⁻³, μ = 0.125 mm⁻¹, F (000) = 472, R_{int} = 0.1422. The structure was obtained by direct methods using SHELXS-97. The final R value was 0.0687 (wR₂ = 0.1476) 4988 observed reflections ($F_o \geq 4\sigma(|F_o|)$) and 293 variables, S = 0.893.

Boc-d^{2,3}γ-Ala-OPfp 2d: Crystals of **2d** were grown by slow evaporation from a solution of aqueous methanol at room temperature. A single crystal (0.14 × 0.1 × 0.06 mm) was mounted on a loop with a small amount of paraffin oil. The X-ray data were collected at 150K temperature on a Bruker APEX(II) DUO CCD diffractometer using Mo K_α radiation (λ = 0.71073 Å), ω -scans (2θ = 49.654), for a total of 16604 independent reflections. Space group P 1, a = 6.2002 (9), b = 9.3687 (12), c = 15.799 (2), α = 101.093 (4), β = 99.079 (4), γ = 105.428 (4), V = 846.7 (2) Å³, Triclinic, Z = 2 for chemical formula C₁₆ H₁₆ F₅ N O₄, with two molecules in asymmetric unit; ρ calcd = 1.496 gcm⁻³, μ = 0.142 mm⁻¹, F (000) = 392, R_{int} = 0.0407. The structure was obtained by direct methods using SHELXS-97. The final R value was 0.0326 (wR₂ = 0.0631) 5740 observed reflections ($F_o \geq 4\sigma(|F_o|)$) and 478 variables, S = 1.023.

Boc-d^{2,3}γ-Phe-ONp 3a: Crystals of **3a** were grown by slow evaporation from a solution of aqueous methanol at room temperature. A single crystal (0.15 × 0.07 × 0.06 mm) was mounted on a loop with a small amount of paraffin oil. The X-ray data were collected at 150K temperature on a Bruker APEX(II) DUO CCD diffractometer using Cu K_α radiation (λ = 1.54178 Å), ω -scans (2θ = 66.768), for a total of 26912 independent reflections. Space group P 21 21 21, a = 6.1910 (7), b = 14.7184 (16), c = 22.774 (3), α = 90, β = 90, γ = 90, V = 2075.2 (4) Å³, Orthorhombic, Z = 4 for chemical formula C₂₂ H₂₄ N₂ O₆, with one molecule in asymmetric unit; ρ calcd = 1.32 gcm⁻³, μ = 0.803 mm⁻¹, F (000) = 872, R_{int} = 0.1486. The structure was obtained by direct methods using SHELXS-97. The final R value was 0.0408 (wR₂ = 0.0922) 3681 observed reflections ($F_o \geq 4\sigma(|F_o|)$) and 275 variables, S = 1.037.

Boc-d^{2,3}γ-Val-ONp 3c: Crystals of **3c** were grown by slow evaporation from a solution of aqueous methanol at room temperature. A single crystal (0.12 × 0.07 × 0.05 mm) was mounted on a loop with a small amount of paraffin oil. The X-ray data were collected at 150K temperature on a Bruker APEX(II) DUO CCD diffractometer using Mo K_α radiation (λ =

0.71073 Å), ω -scans ($2\theta = 57.602$), for a total of 26912 independent reflections. Space group P 21, $a = 6.216$ (3), $b = 5.362$ (3), $c = 28.415$ (13), $\alpha = 90$, $\beta = 95.424$ (12), $\gamma = 90$, $V = 942.8$ (8) Å³, Monoclinic, $Z = 2$ for chemical formula C₁₈ H₂₄ N₂ O₆, with one molecule in asymmetric unit; ρ calcd = 1.284 gcm⁻³, $\mu = 0.097$ mm⁻¹, $F(000) = 388$, $R_{\text{int}} = 0.1842$. The structure was obtained by direct methods using SHELXS-97. The final R value was 0.0899 ($wR_2 = 0.2110$) 4704 observed reflections ($F_0 \geq 4\sigma(|F_0|)$) and 241 variables, $S = 1.085$.

tert-butyl 2-benzyl-5-oxo-2,5-dihydro-1H-pyrrole-1-carboxylate 4a: Crystals of **4a** were grown by slow evaporation from a solution of ethyl acetate-pet ether at room temperature. A single crystal ($0.11 \times 0.6 \times 0.08$ mm) was mounted on a loop with a small amount of paraffin oil. The X-ray data were collected at 100K temperature on a Bruker APEX(II) DUO CCD diffractometer using Mo K α radiation ($\lambda = 0.71073$ Å), ω -scans ($2\theta = 56.76$), for a total of 20509 independent reflections. Space group P 21/n, $a = 6.146$ (3), $b = 14.129$ (7), $c = 16.674$ (8), $\alpha = 90$, $\beta = 99.499$ (14), $\gamma = 90$, $V = 1427.9$ (12) Å³, Monoclinic, $Z = 4$ for chemical formula C₁₆ H₁₉ N O₃, with one molecule in the asymmetric unit; ρ calcd = 1.271 gcm⁻³, $\mu = 0.088$ mm⁻¹, $F(000) = 5$, $R_{\text{int}} = 0.0525$. The structure was obtained by direct methods using SHELXS-97. The final R value was 0.0723 ($wR_2 = 0.1772$) 3576 observed reflections ($F_0 \geq 4\sigma(|F_0|)$) and 185 variables, $S = 0.790$.

tert-butyl-2-oxo-5-phenyl-2,5-dihydro-1H-pyrrole-1-carboxylate 4f: Crystals of **4f** were grown by slow evaporation from a solution of ethyl acetate-pet ether at room temperature. A single crystal ($0.13 \times 0.8 \times 0.05$ mm) was mounted on a loop with a small amount of paraffin oil. The X-ray data were collected at 150K temperature on a Bruker APEX(II) DUO CCD diffractometer using Mo K α radiation ($\lambda = 0.71073$ Å), ω -scans ($2\theta = 56.76$), for a total of 20800 independent reflections. Space group P 21/c, $a = 6.2063$ (11), $b = 13.323$ (3), $c = 16.945$ (3), $\alpha = 90$, $\beta = 91.668$ (6), $\gamma = 90$, $V = 1400.6$ (4) Å³, Monoclinic, $Z = 4$ for chemical formula C₁₅ H₁₇ N O₃, with one molecule in the asymmetric unit; ρ calcd = 1.23 gcm⁻³, $\mu = 0.086$ mm⁻¹, $F(000) = 552$, $R_{\text{int}} = 0.0525$. The structure was obtained by direct methods using SHELXS-97. The final R value was 0.0416 ($wR_2 = 0.0915$) 3509 observed reflections ($F_0 \geq 4\sigma(|F_0|)$) and 176 variables, $S = 1.022$.

2.9 References

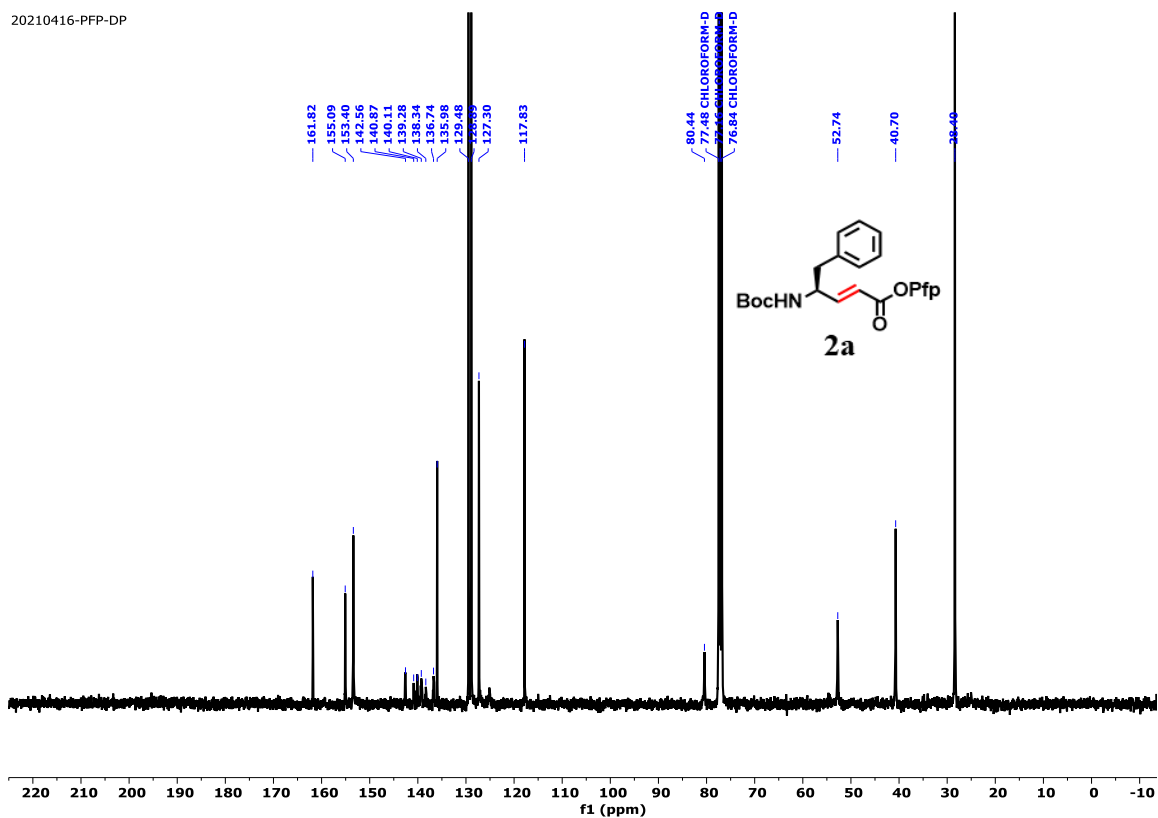
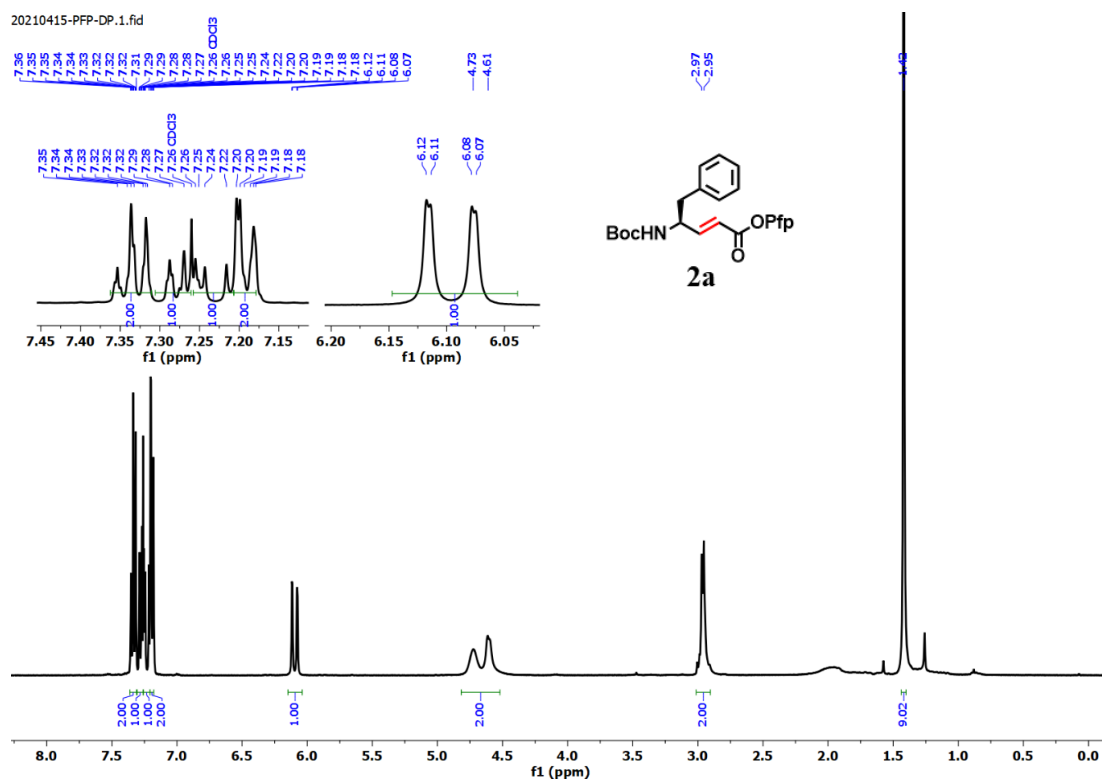
1. (a) Y. Guo, R.-Y. Wang, J.-X. Kang, Y.-N. Ma, C.-Q. Xu, J. Li, and X. Chen, *Nat. Commun.*, 2021, **12**, 5964; (b) L. L. Fellingner and L. F. Audrieth, *J. Am. Chem. Soc.*, 1938, **60**, 579–581; (c) M. Kawai, N. Fukuta, N. Ito, M. Ohya, Y. Butsugan, M. Maruyama, and Y. Kudo, *J. Chem. Soc., Chem. Commun.*, 1986, 955–956; (d) T. Högborg, P. Ström, M. Ebner and S. Rämsky, *J. Org. Chem.*, 1987, **52**, 2033–2036; (e) Y. Li, A. Yongye, M. Giulianotti, K. Martinez-Mayorga, Y. Yu and R. A. Houghten, *J. Comb. Chem.*, 2009, **11**, 1066–1072.
2. E. Saxon and C. R. Bertozzi, *Science*, 2000, **287**, 2007–2010.
3. P. E. Dawson, T. W. Muir, L. Clark-Lewis and S. B. H. Kent, *Science*, 1994, **266**, 776–779.
4. B. Shen, D. M. Makley and J. N. Johnston, *Nature*, 2010, **465**, 1027–1033.
5. C. Gunanathan, Y. Ben-David and D. Milstein, *Science*, 2007, **317**, 790–792.
6. L. Kisfaludy and I. Schön, *Synthesis*, 1983, **04**, 325–327.
7. M. Bodanszky, *Nature*, 1955, **175**, 685.
8. R. Misra, S. Dey, R. M. Reja and H. N. Gopi, *Angew. Chem. Int. Ed.*, 2018, **57**, 1057–1061.
9. M. G. Kumar, V. J. Thombare, M. M. Katariya, K. Veeresh, K. M. P. Raja and H. N. Gopi, *Angew. Chem. Int. Ed.*, 2016, **55**, 7847–7851.
10. E. T. Pelkey, S. J. Pelkey and J. G. Greger, In *Adv. Heterocycl. Chem.*, 2015, 115, 151.
11. (a) Z. Feng, F. Chu, Z. Guo and P. Sun, *Bioorg. Med. Chem. Lett.*, 2009, **19**, 2270–2272; (b) S. B. Singh, M. A. Goetz, E. T. Jones, G. F. Bills, R. A. Giacobbe, L. Herranz, S. Stevens-Miles and D. L. Williams, Jr., *J. Org. Chem.*, 1995, **60**, 7040–7042; (c) F. Micheli, A. Pasquarello, G. Tedesco, D. Hamprecht, G. Bonanomi, A. Checchia, A. Jaxa-Chamiec, F. Damiani, S. Davalli and D. Donati, *Bioorg. Med. Chem. Lett.*, 2006, **16**, 3906–3912; (d) J. Caruano, G. G. Muccioli and R. Robiette, *Org. Biomol. Chem.*, 2016, **14**, 10134–10156; (e) C. C. Cosner, J. T. Markiewicz, P. Bourbon, C. J. Mariani, O. Wiest, M. Rujoi, A. I. Rosenbaum, A. Y. Huang, F. R. Maxfield and P. Helquist, *J. Med. Chem.*, 2009, **52**, 6494–6498; (f) T. Kawasuji, M. Fuji, T. Yoshinaga, A. Sato, T. Fujiwarab and R. Kiyamaa, *Bioorg. Med. Chem.*, 2007, **15**, 5487–5492; (g) E. Choi, C. Lee, M. Cho, J. J. Seo, J. S. Yang, S. J. Oh, K. Lee, S.-K. Park, H. M. Kim, H. J. Kwon and G. Han, *J. Med. Chem.*, 2012, **55**, 10766–10770; (h) U. A. Pereira, L. C. A. Barbosa, C. R. A. Maltha, A. J. Demuner, M. A. Masood and A. L. Pimenta, *Bioorg. Med. Chem. Lett.*, 2014, **24**, 1052–1056.

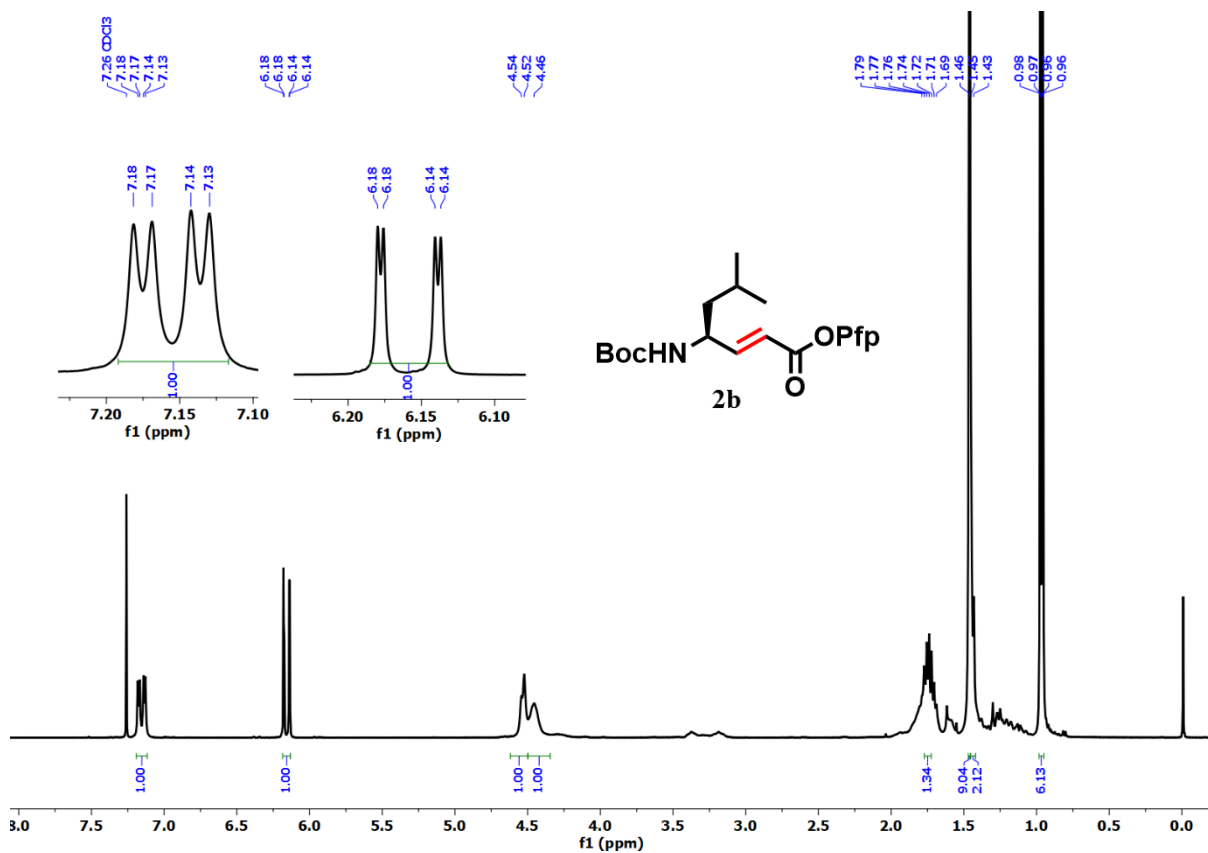
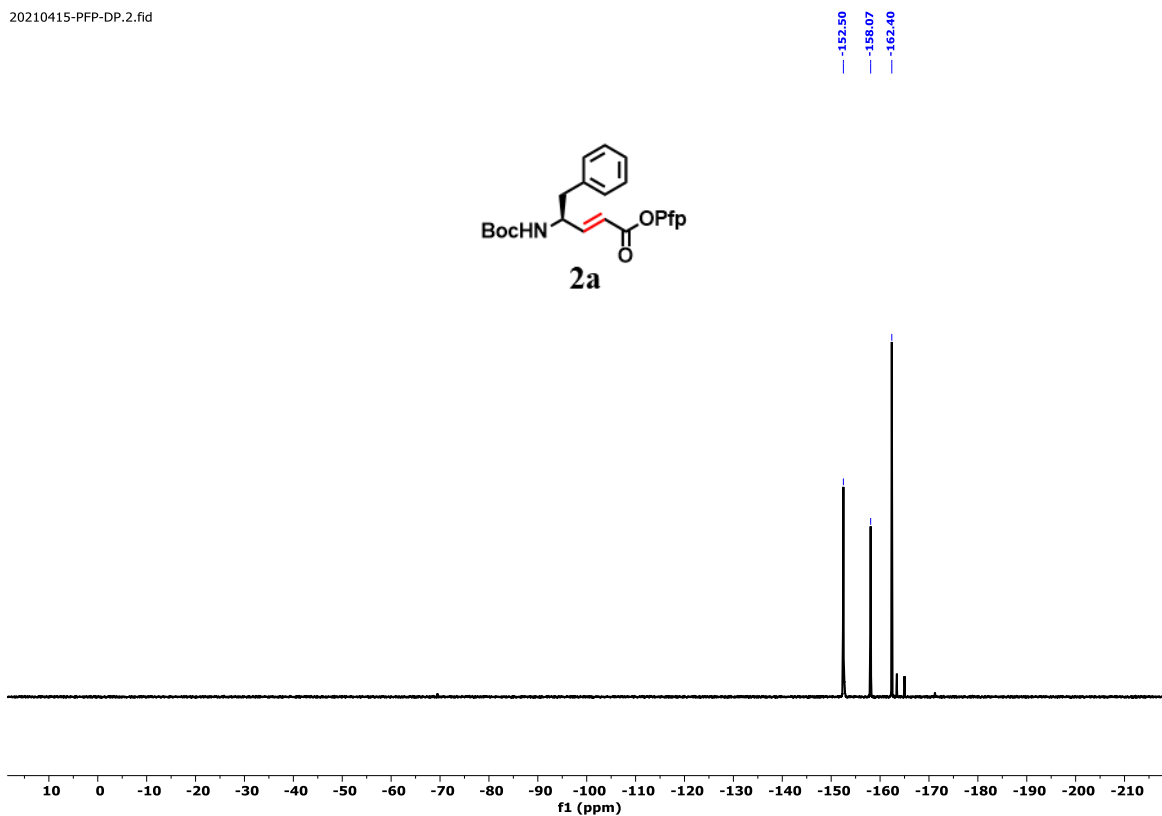
12. (a) B. B. Snider and B. J. Neubert, *J. Org. Chem.*, 2004, **69**, 8952–8955; (b) R. S. Coleman, M. C. Walczak and E. L. Campbell, *J. Am. Chem. Soc.*, 2005, **127**, 16038–16039; (c) F. Gaviña, A. Costero, M. Andreu, M. Carda and S. Luis, *J. Am. Chem. Soc.*, 1988, **110**, 4017–4018; (d) S.-K. Kang, K.-J. Kim, C.-M. Yu, J.-W. Hwang and Y.-K. Do, *Org. Lett.*, 2001, **3**, 2851–2853; (e) T. Morimoto, N. Chatani and S. Murai, *J. Am. Chem. Soc.*, 1999, **121**, 1758–1759.
13. J. Xie, S. Xue, E. C. Escudero-Adán and A. W. Kleij, *Angew. Chem., Int. Ed.*, 2018, **57**, 16727–16731.
14. S. Sarkar, A. Banerjee, J. A. Shah, U. Mukherjee, N. C. Frederiks, C. J. Johnson and M.-Y. Ngai, *J. Am. Chem. Soc.*, 2022, **144**, 20884–20894.
15. L. Yang, C.-H. Lei, D.-X. Wang, Z.-T. Huang and M.-X. Wang, *Org. Lett.*, 2010, **12**, 3918–3921.
16. X. del Corte, A. Maestro, J. Vicario, E. Martinez de Marigorta and F. Palacios, *Org. Lett.*, 2018, **20**, 317–320.
17. (a) A. K. Mandal, J. Hines, K. Kuramochia and C. M. Crews, *Bioorg. Med. Chem. Lett.*, 2005, **15**, 4043–4047; (b) Z.-B. Ye, J. Chen, W.-H. Meng and P.-Q. Haung, *Tetrahedron: Asymmetry*, 2010, **21**, 895–902; (c) T. Conroy, J. T. Guo, R. G. Linington, N. H. Hunt, and R. J. Payne, *Chem. Eur. J.*, 2011, **17**, 13544–13552; (d) T. Conroy, J. T. Guo, N. H. Hunt and R. J. Payne, *Org. Lett.*, 2010, **12**, 5576–5579.
18. E. J. E. Caro-Diaz, F. A. Valeriote and W. H. Gerwick, *Org. Lett.*, 2019, **21**, 793–796.
19. J. Chen, P.-Q. Huang and Y. Queneau, *J. Org. Chem.*, 2009, **74**, 7457–7463.
20. (a) Y. Xie, Y. Zhao, B. Qian, L. Yang, C. Xia and H. Huang, *Angew. Chem. Int. Ed.*, 2011, **50**, 5682–5686; (b) G. Hughes, M. Kimura and S. L. Buchwald, *J. Am. Chem. Soc.*, 2003, **125**, 11253–11258; (c) C. Shao, H.-J. Yu, N.-Y. Wu, P. Tian, R. Wang, C. G. Feng and G. Q. Lin, *Org. Lett.*, 2011, **13**, 788–791.
21. J. B. Metternich and R. Gilmour, *J. Am. Chem. Soc.*, 2015, **137**, 11254–11257.
22. C. Dugave and L. Demange, *Chem. Rev.*, 2003, **103**, 2475–2532.
23. G. Szokan, M. Almas, A. Kotai and A. R. Khlafula, *J. Chin. Chem. Soc.*, 1997, **44**, 519–526.
24. P. S. Addy, S. B. Erickson, J. S. Italia and A. Chatterjee, *J. Am. Chem. Soc.*, 2017, **139**, 11670–11673.
25. K. Kai, M. Mizutani, N. Kawamura, R. Yamamoto, M. Tamai, H. Yamaguchi, K. Sakata and B. I. Shimizu, *Plant J.*, 2008, **55**, 989–999.

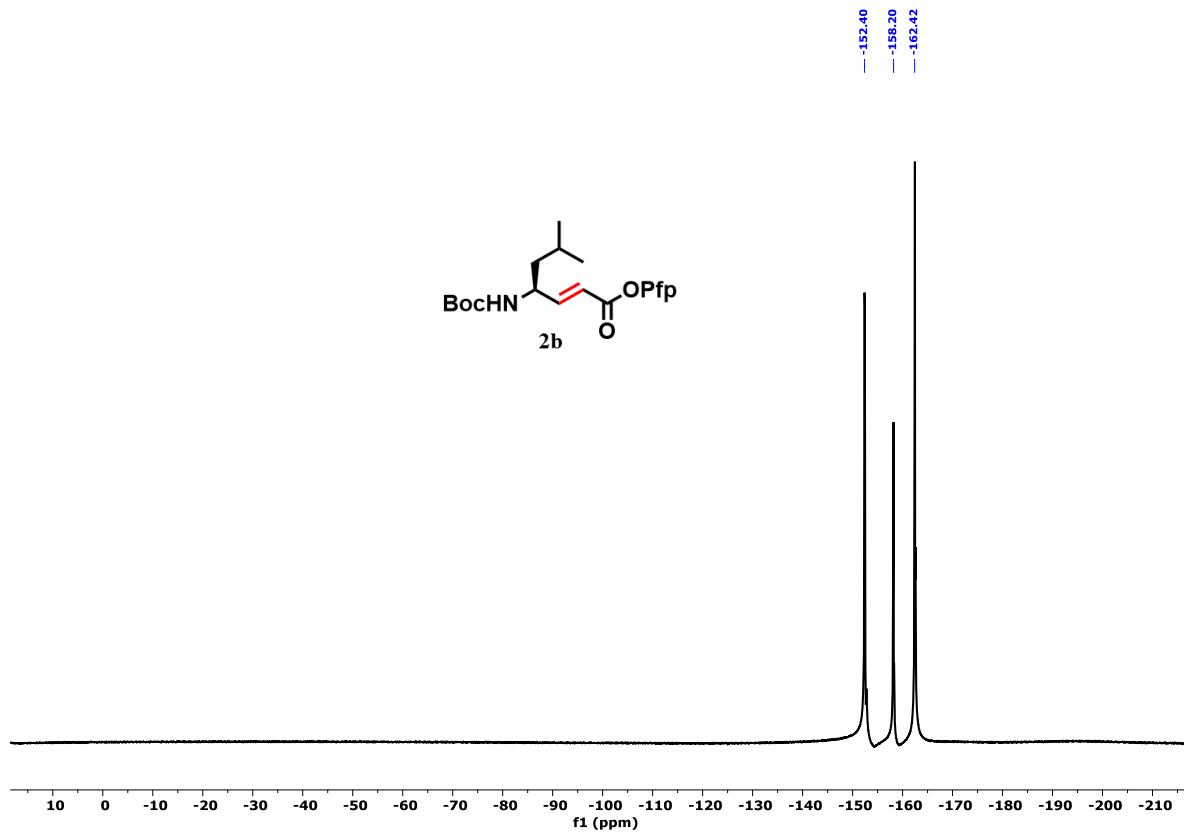
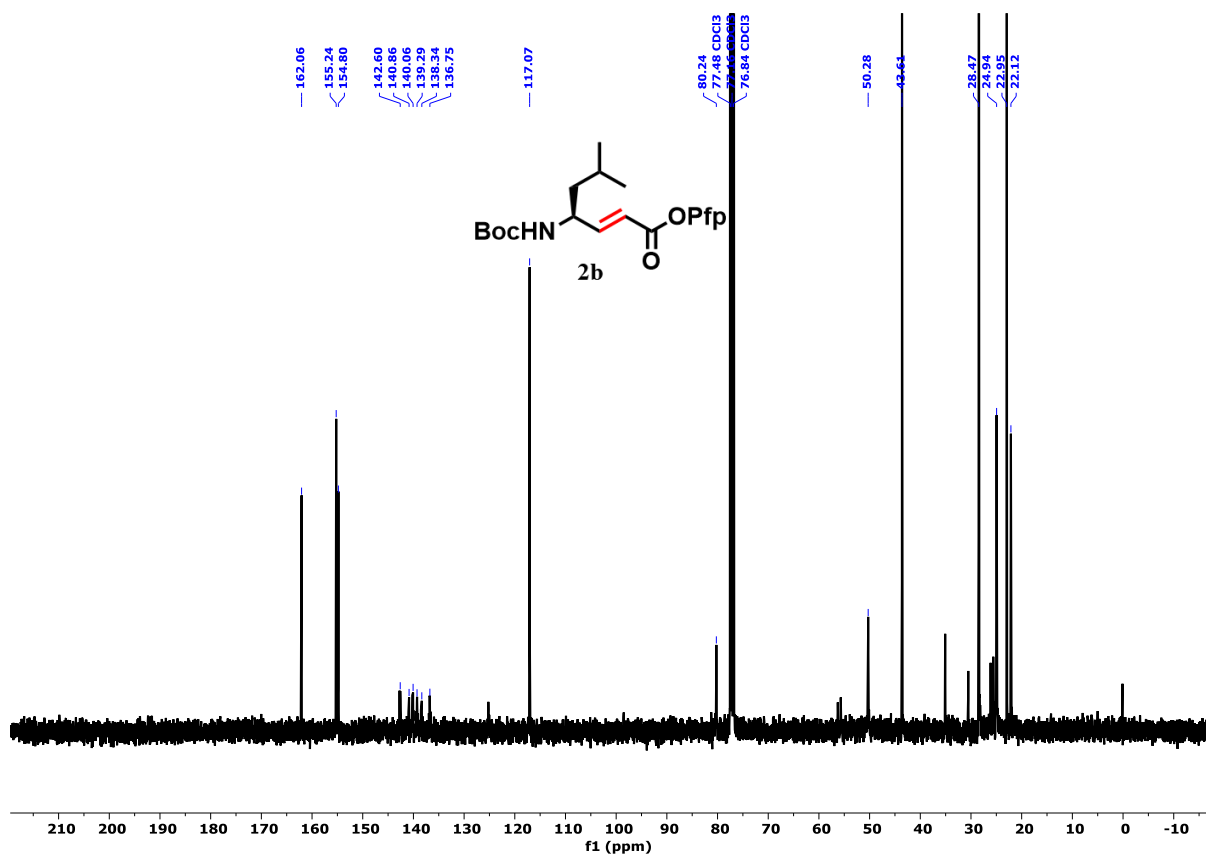
26. S. M. Mali, A. Bandyopadhyay, S. V. Jadhav, M. G. Kumar and H. N. Gopi, *Org. Biomol. Chem.*, 2011, **9**, 6566-6574.
27. H.-Q. Lan, J.-L. Ye, A.-E. Wang, Y.-P. Ruan and P.-Q. Huang, *Chem.-Eur. J.*, 2011, **17**, 958–968.

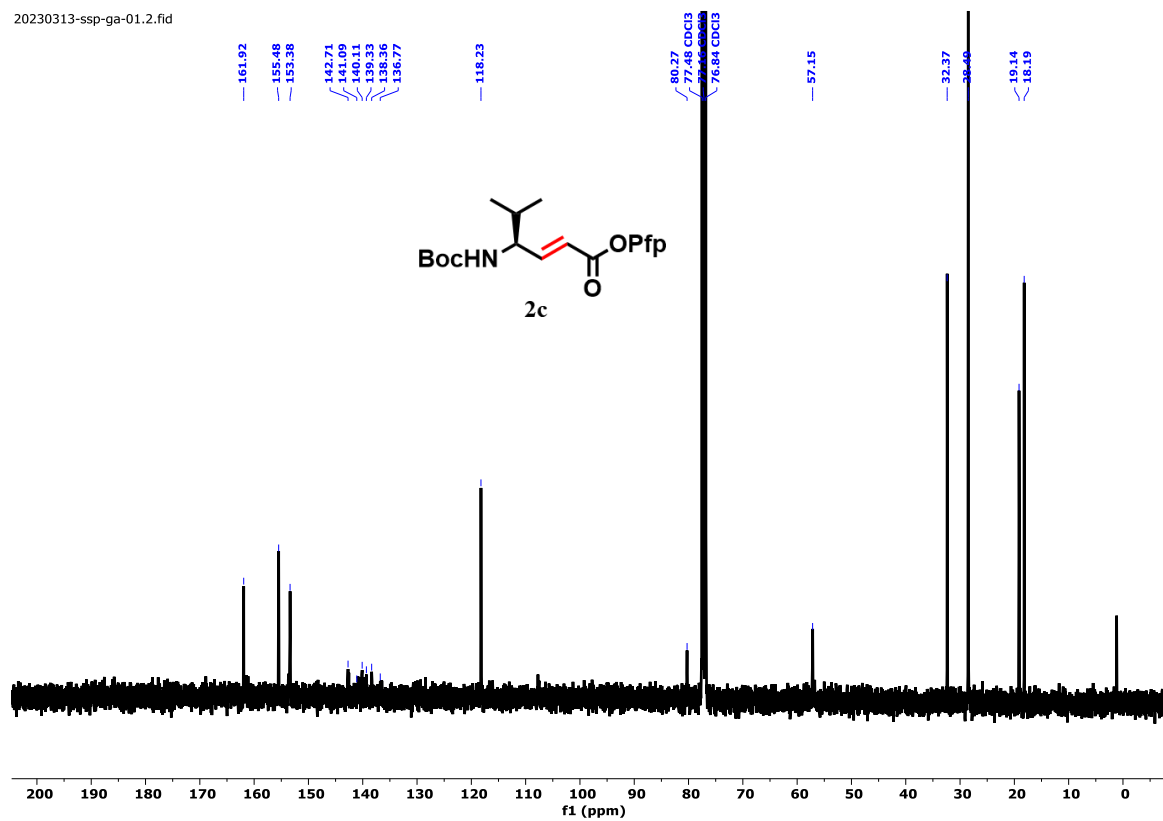
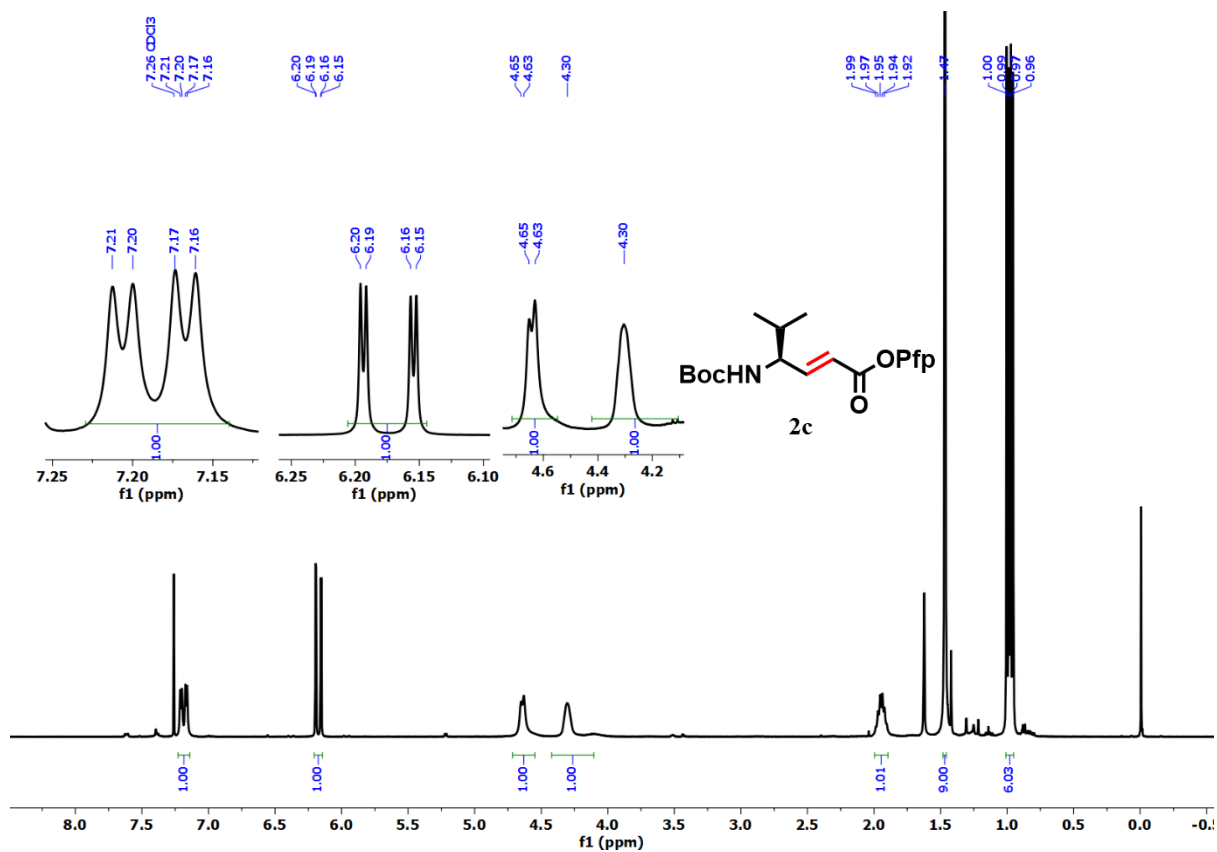
2.10 Appendix

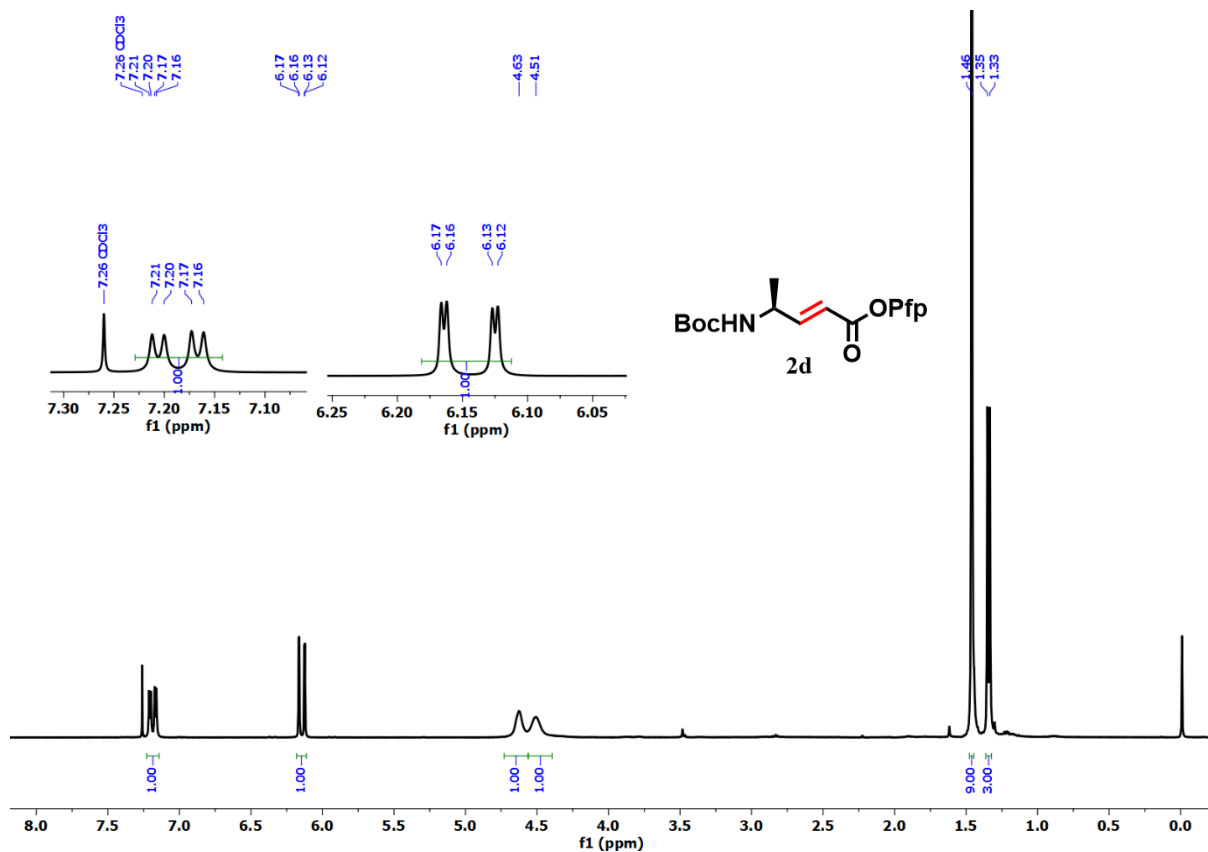
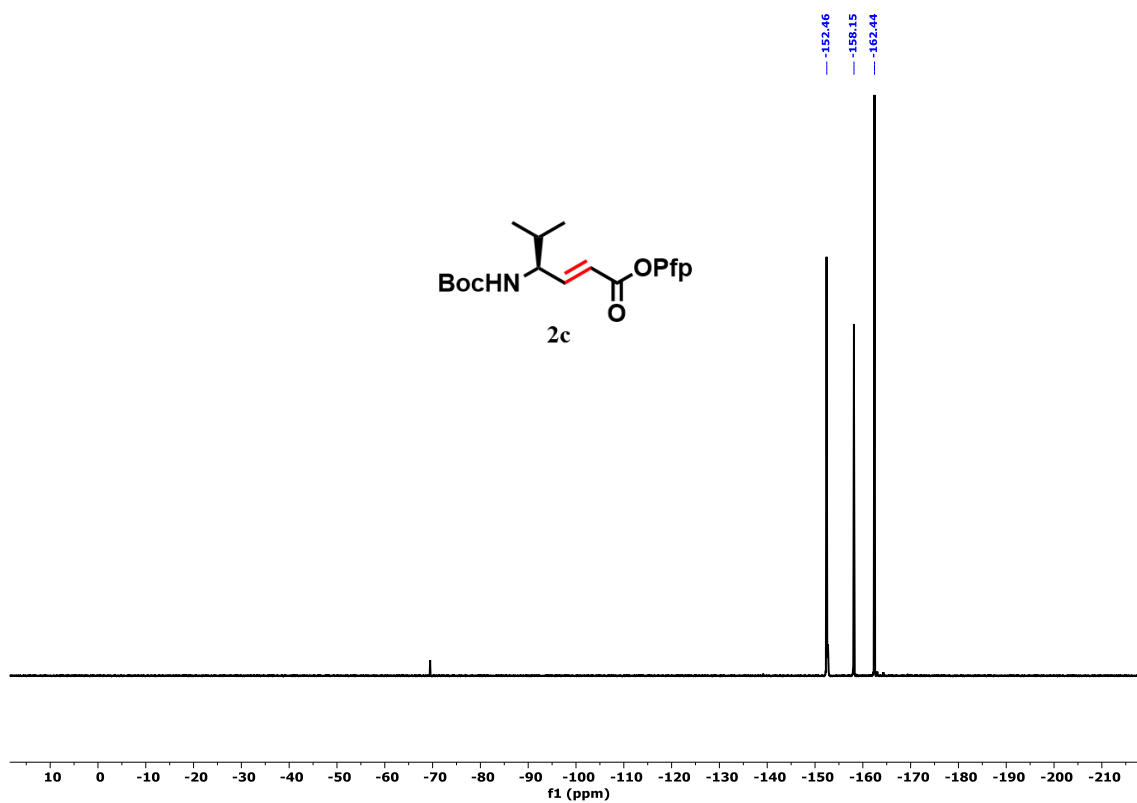
2.10.1 ^1H , ^{13}C and ^{19}F NMR of all compounds.

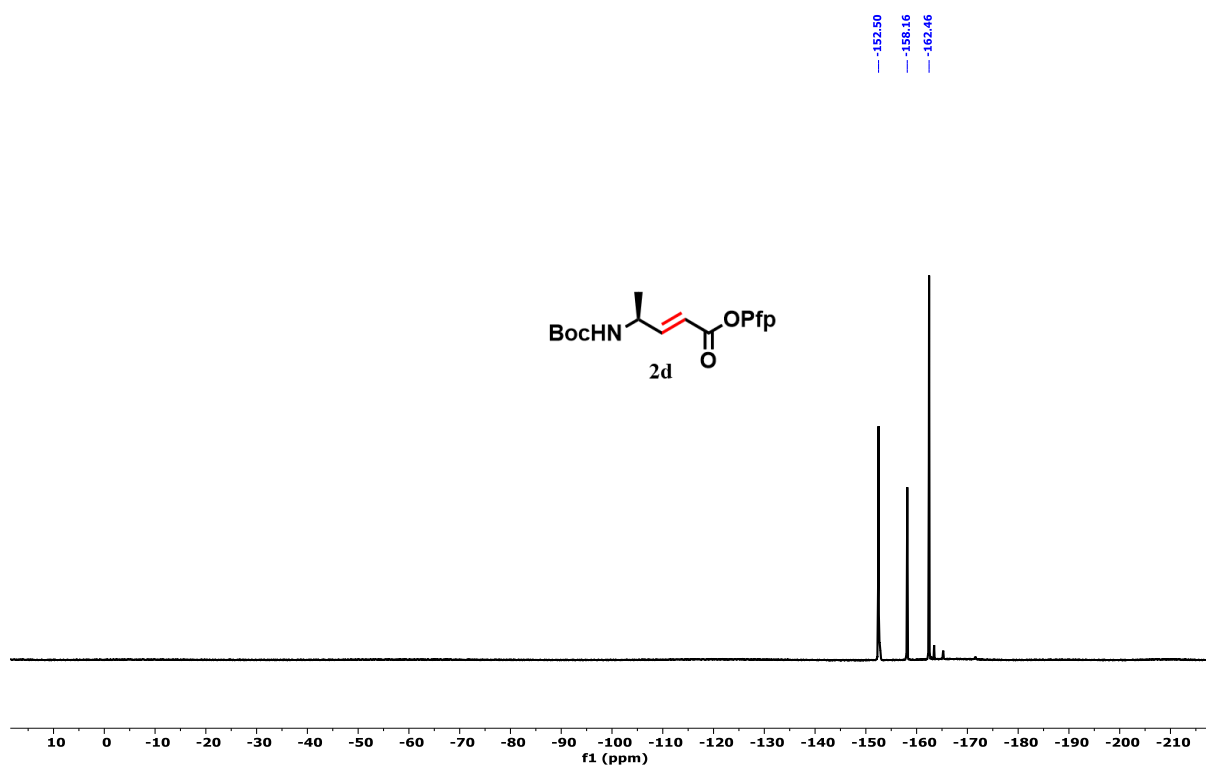
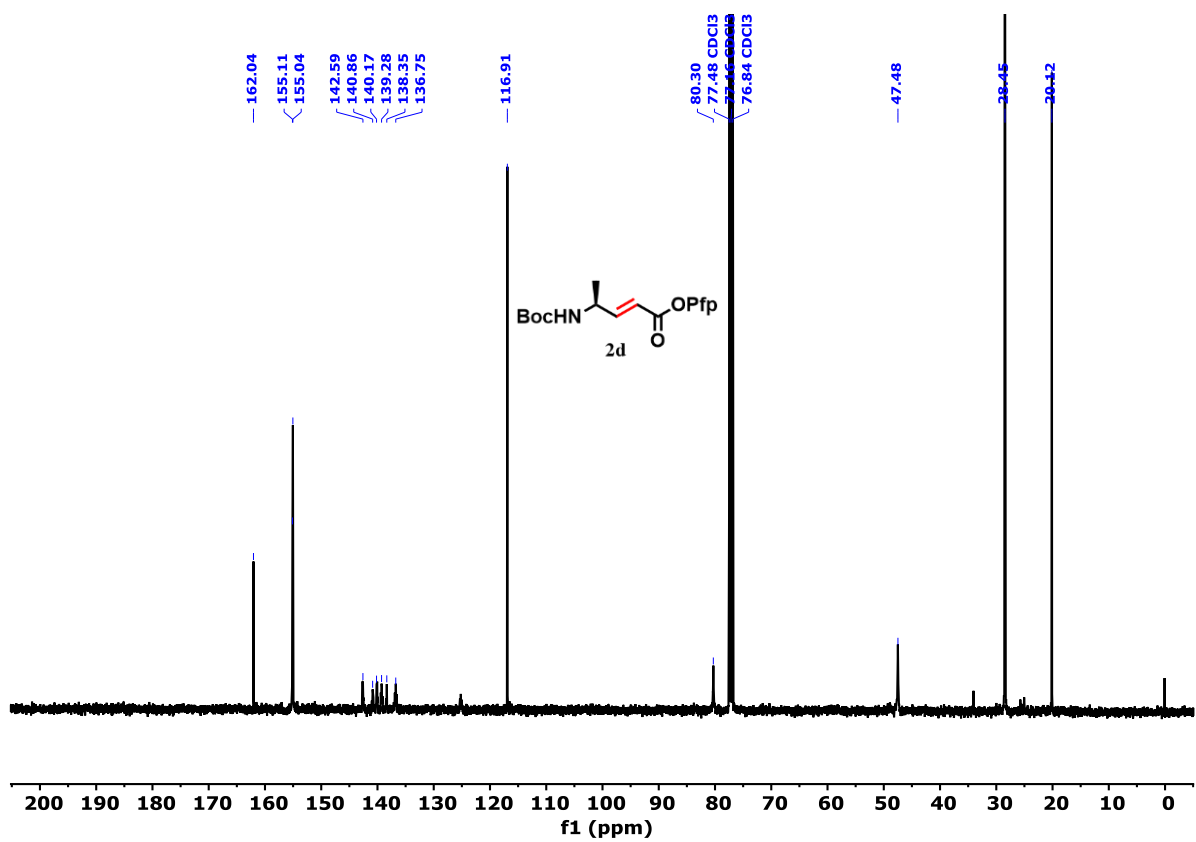


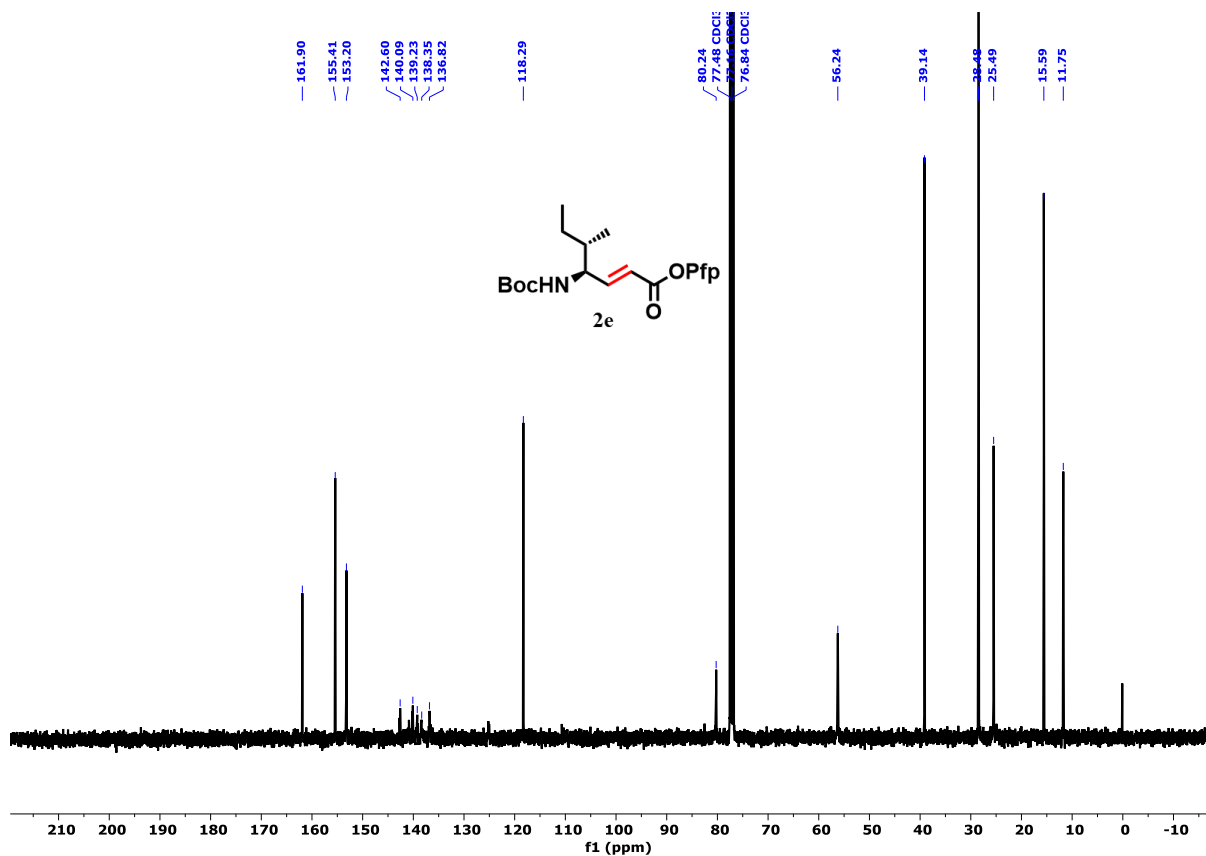
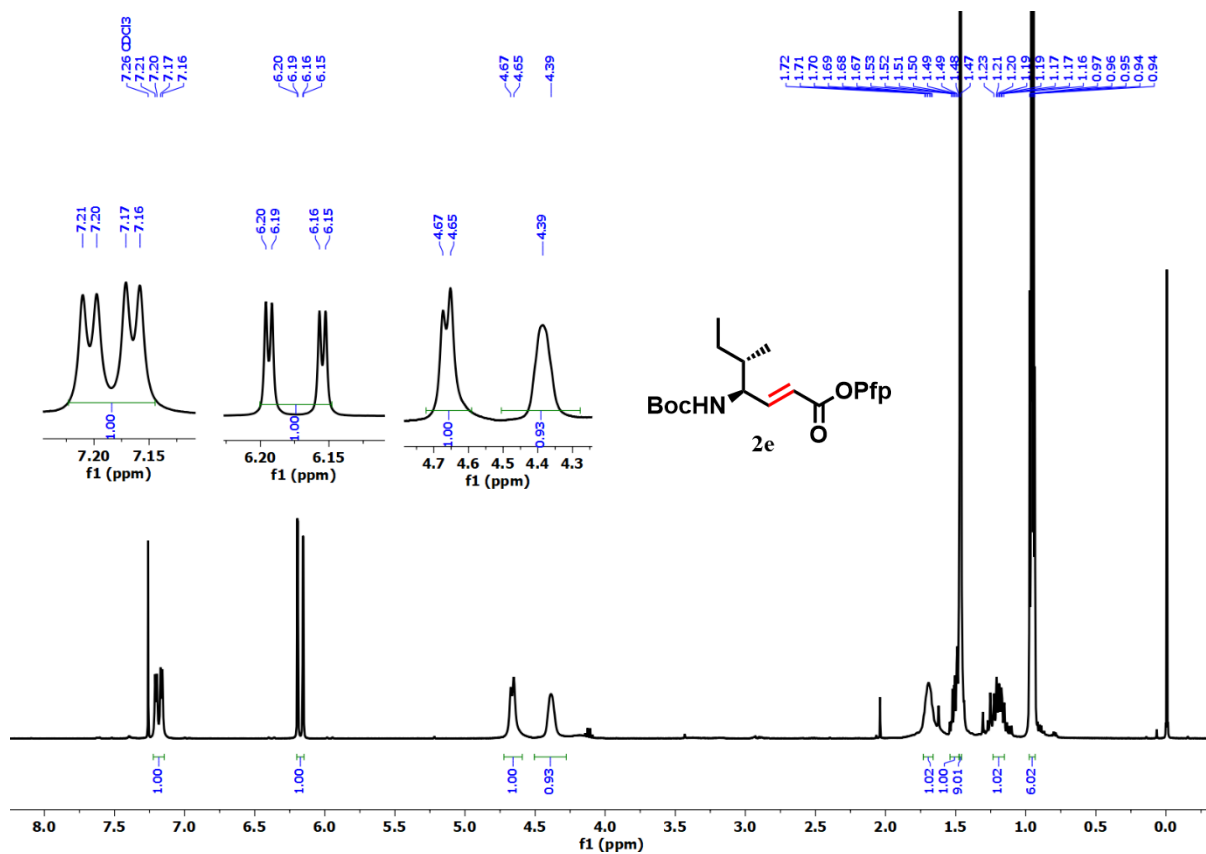


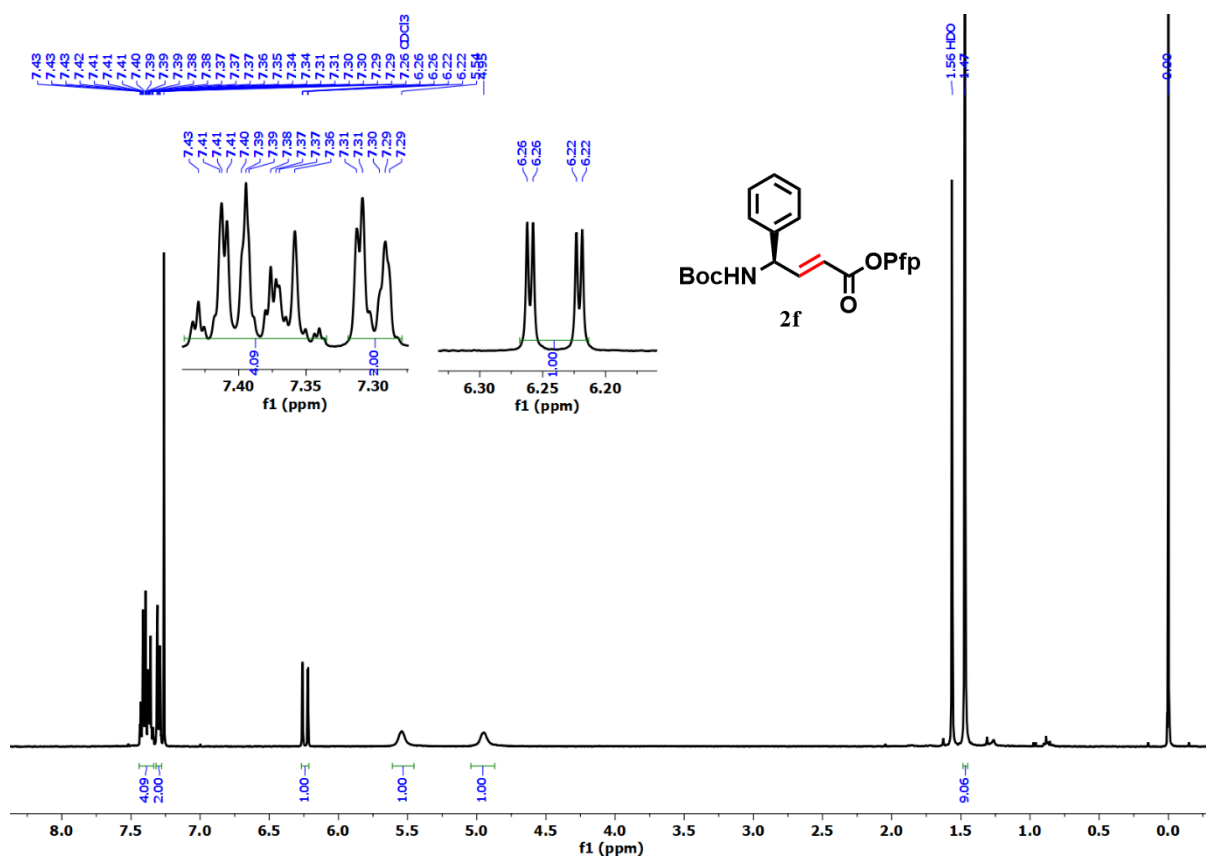
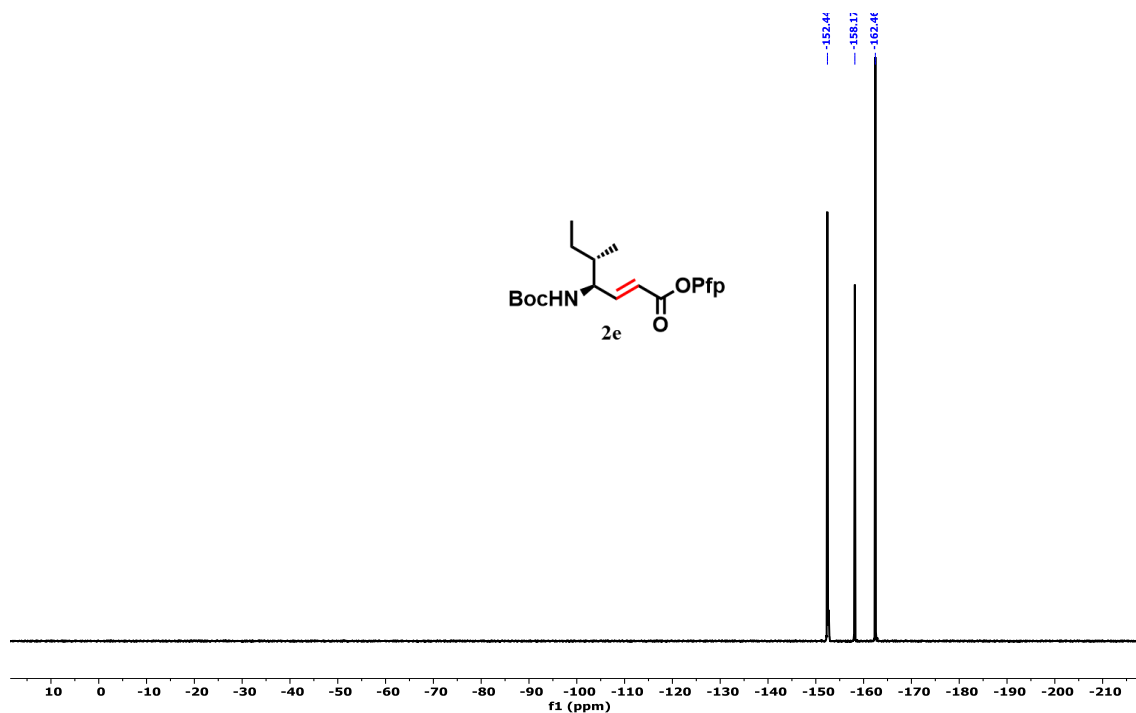




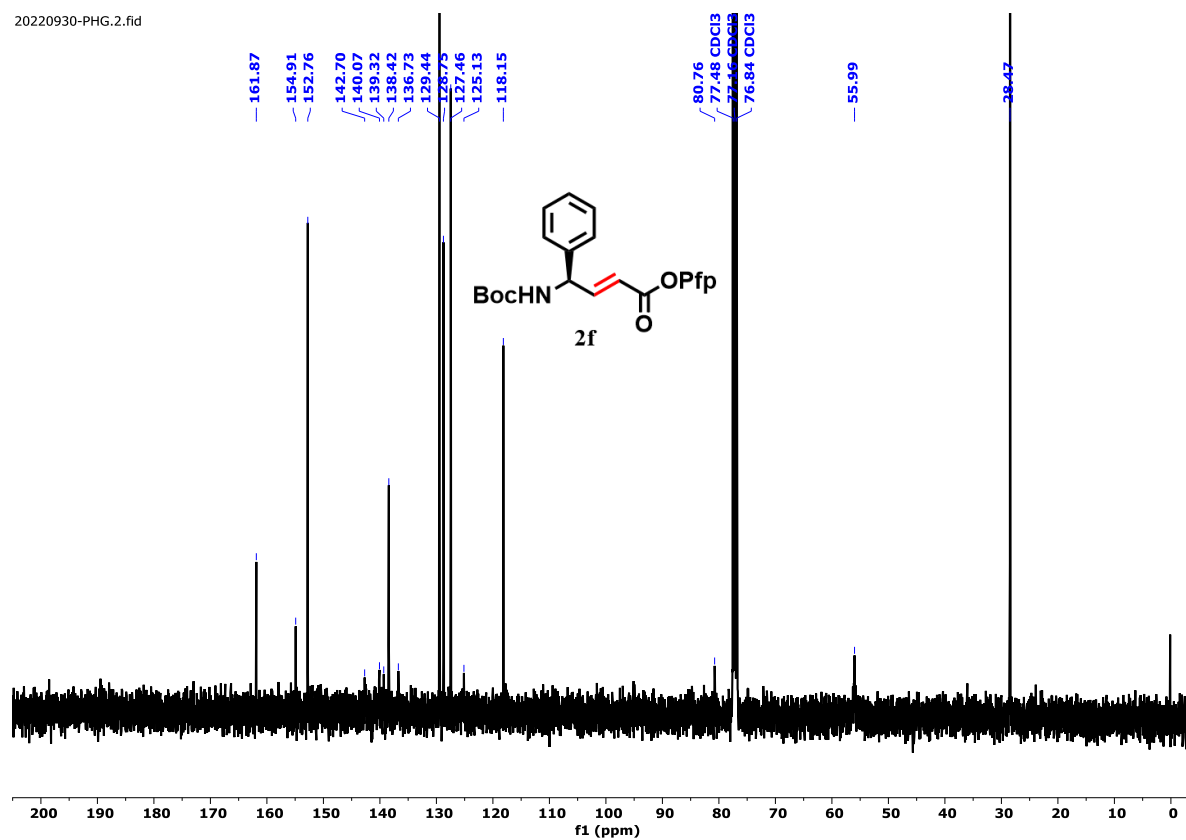




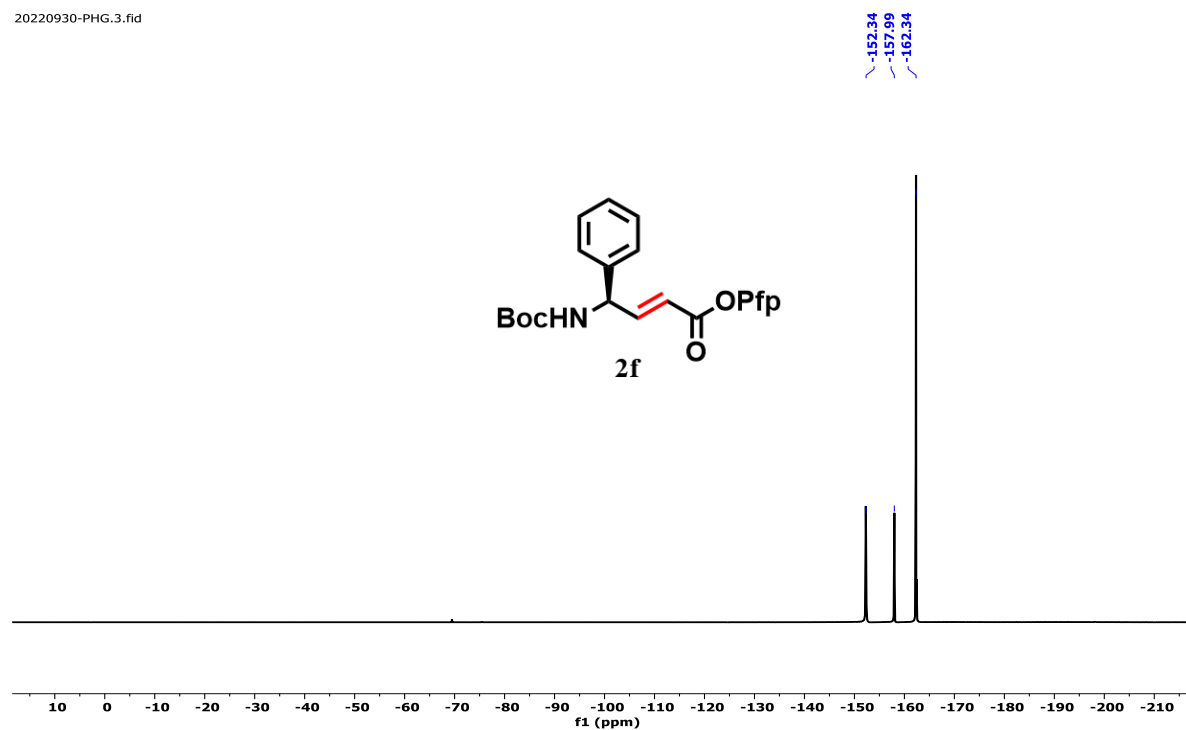




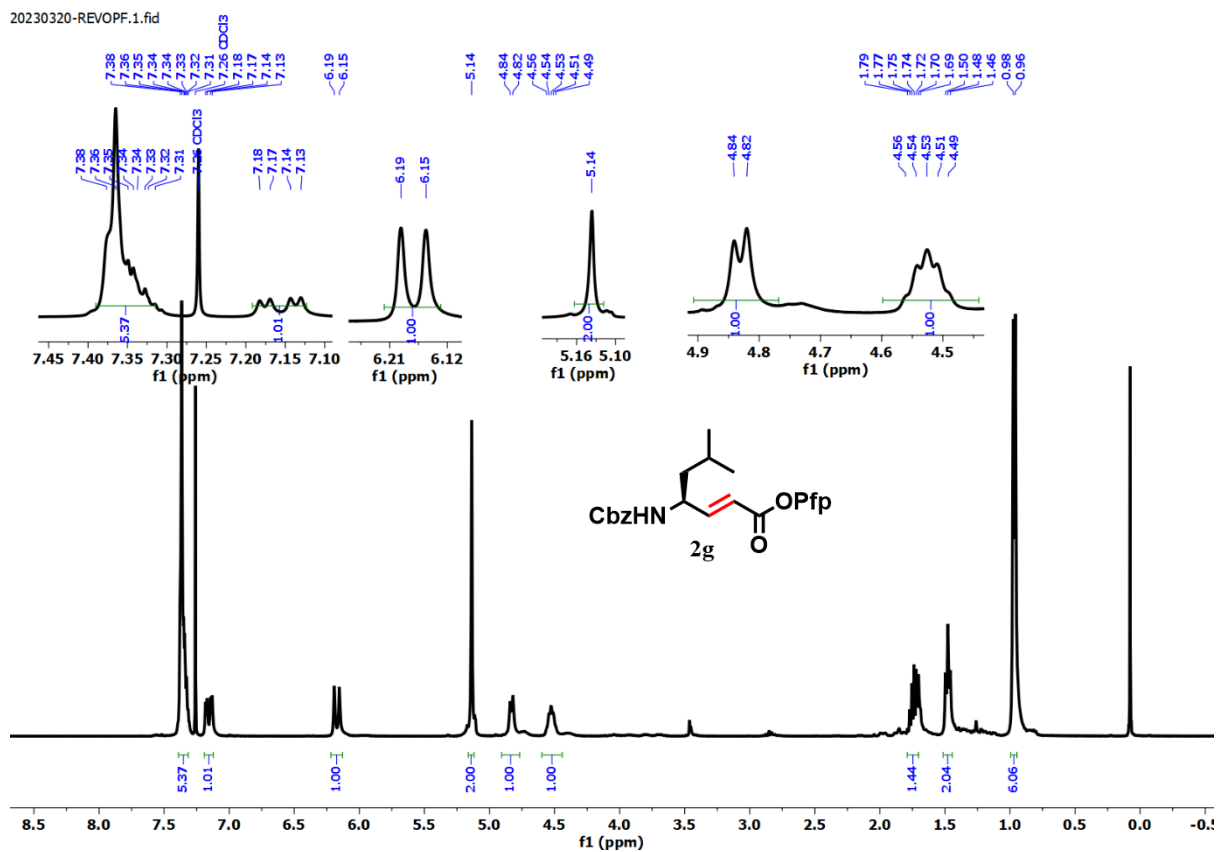
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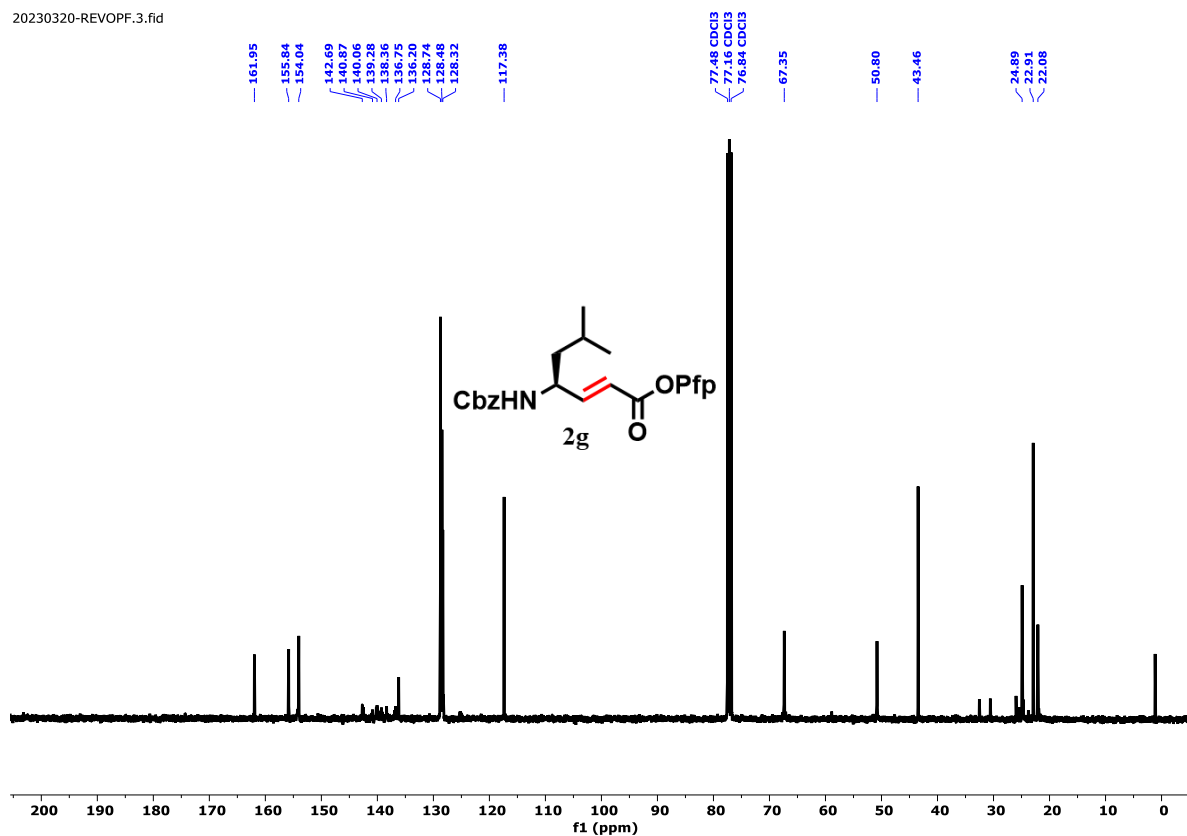
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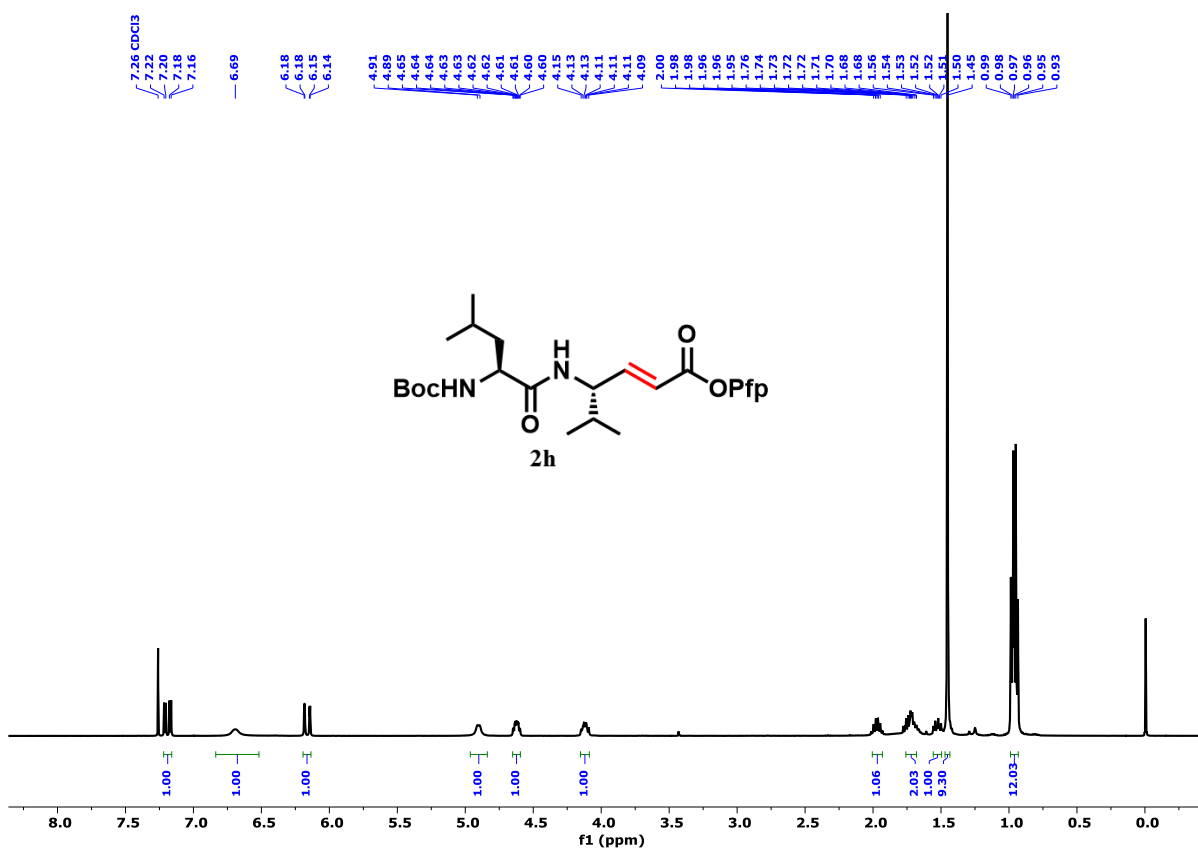
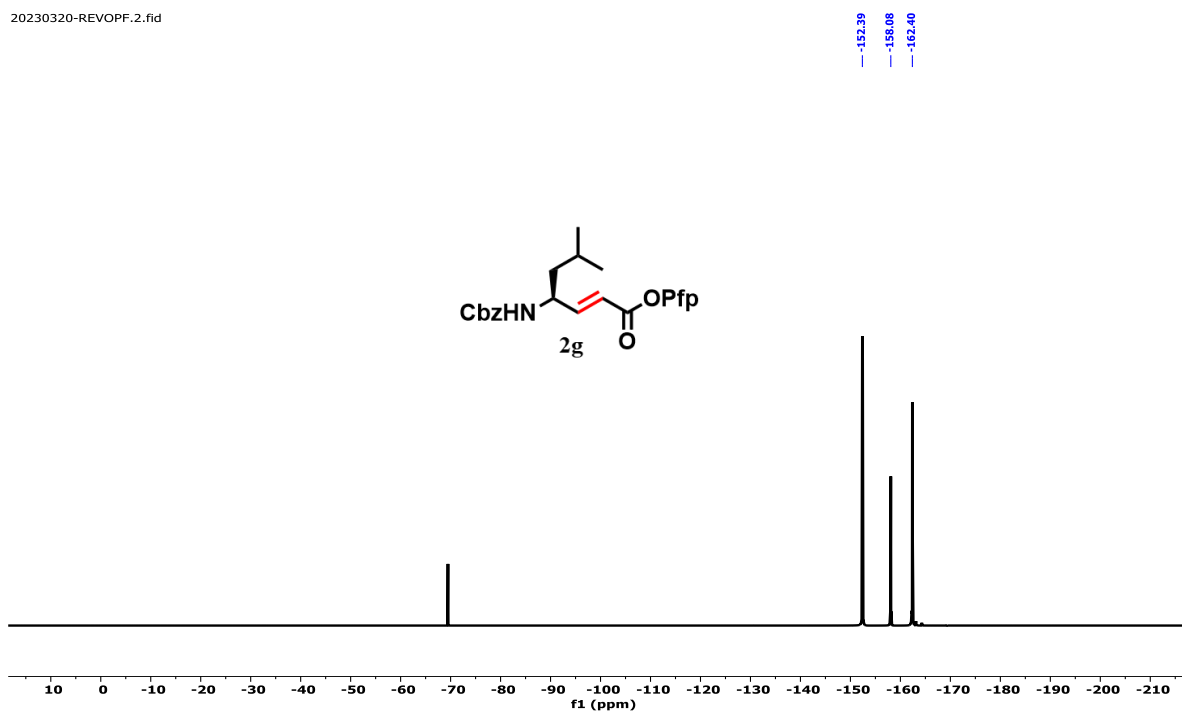


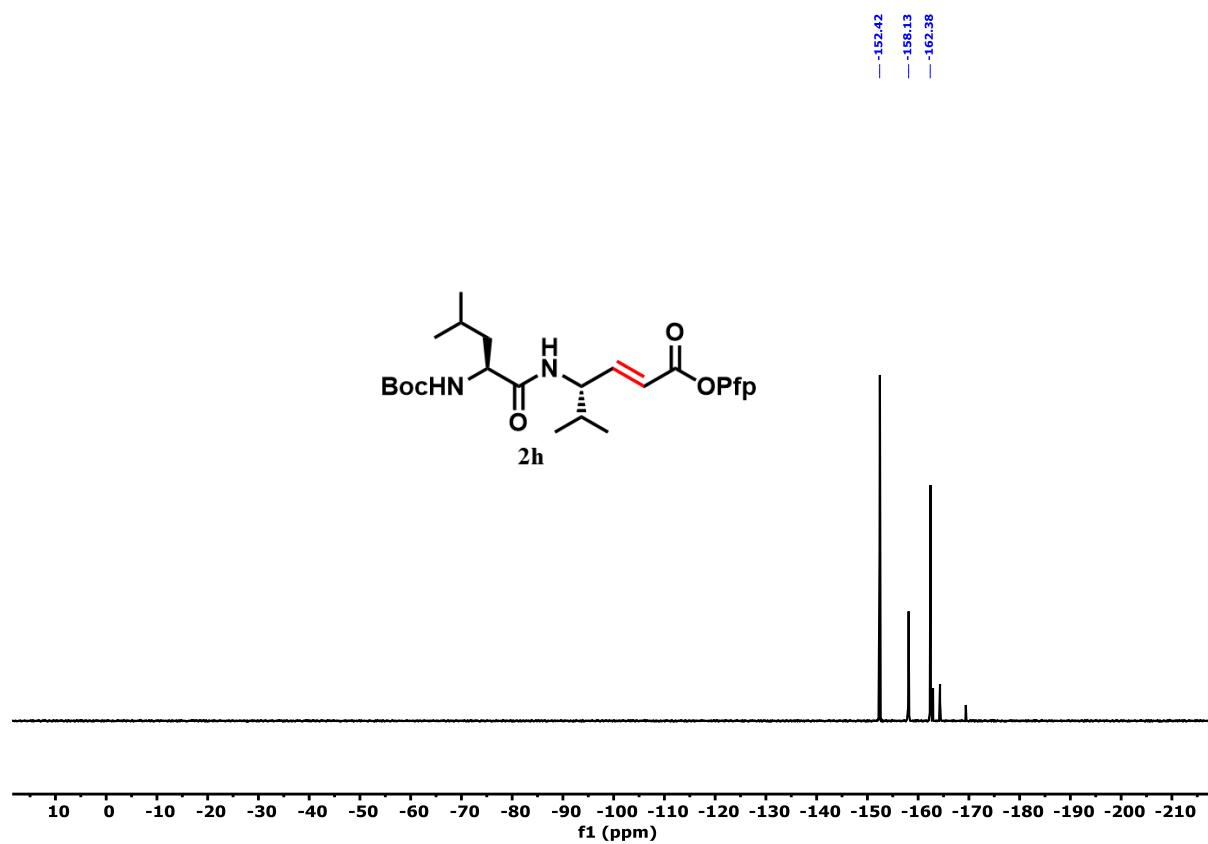
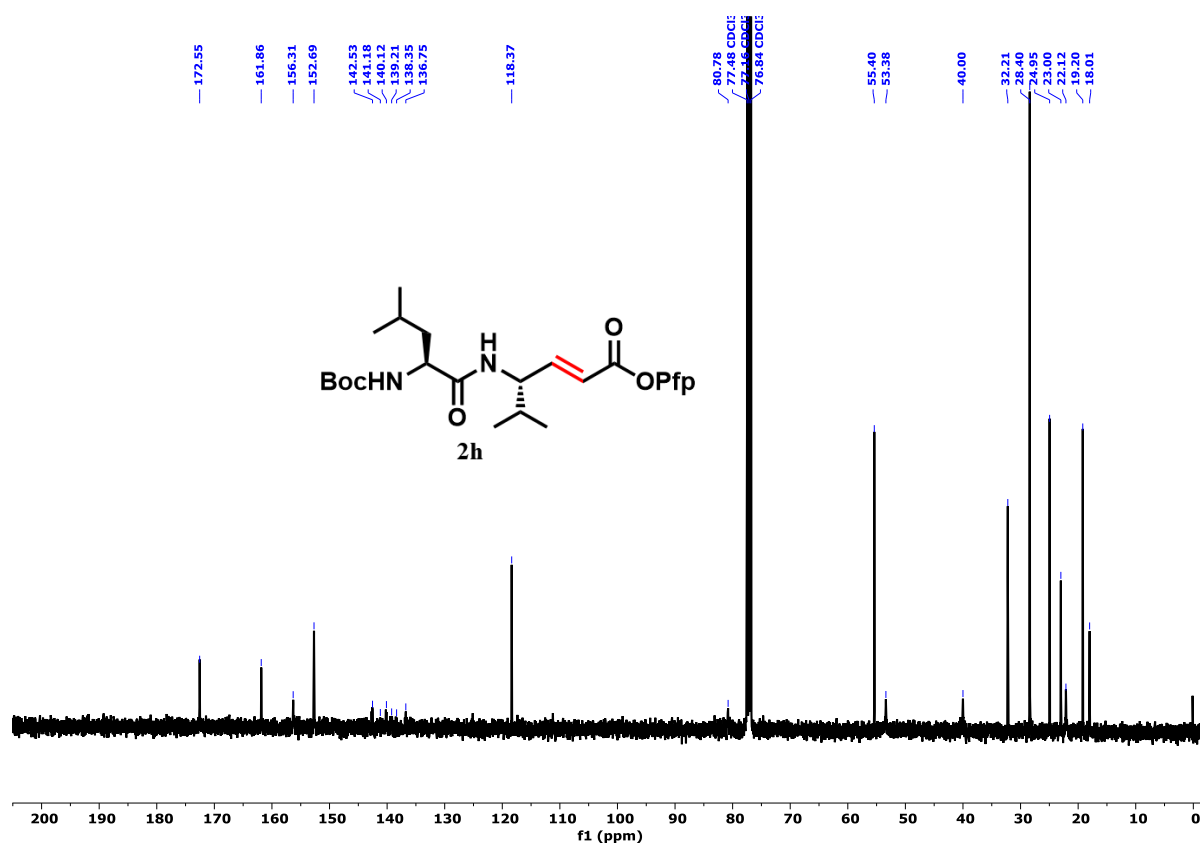
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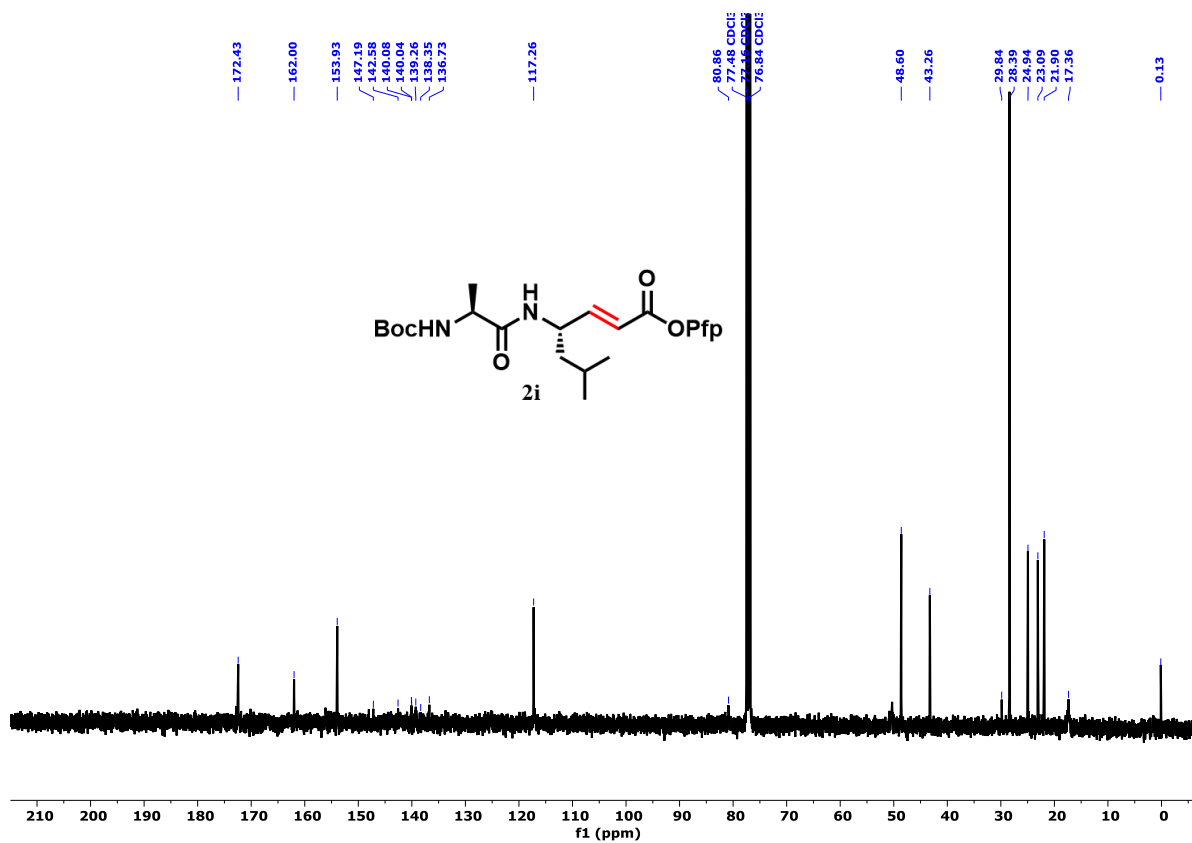
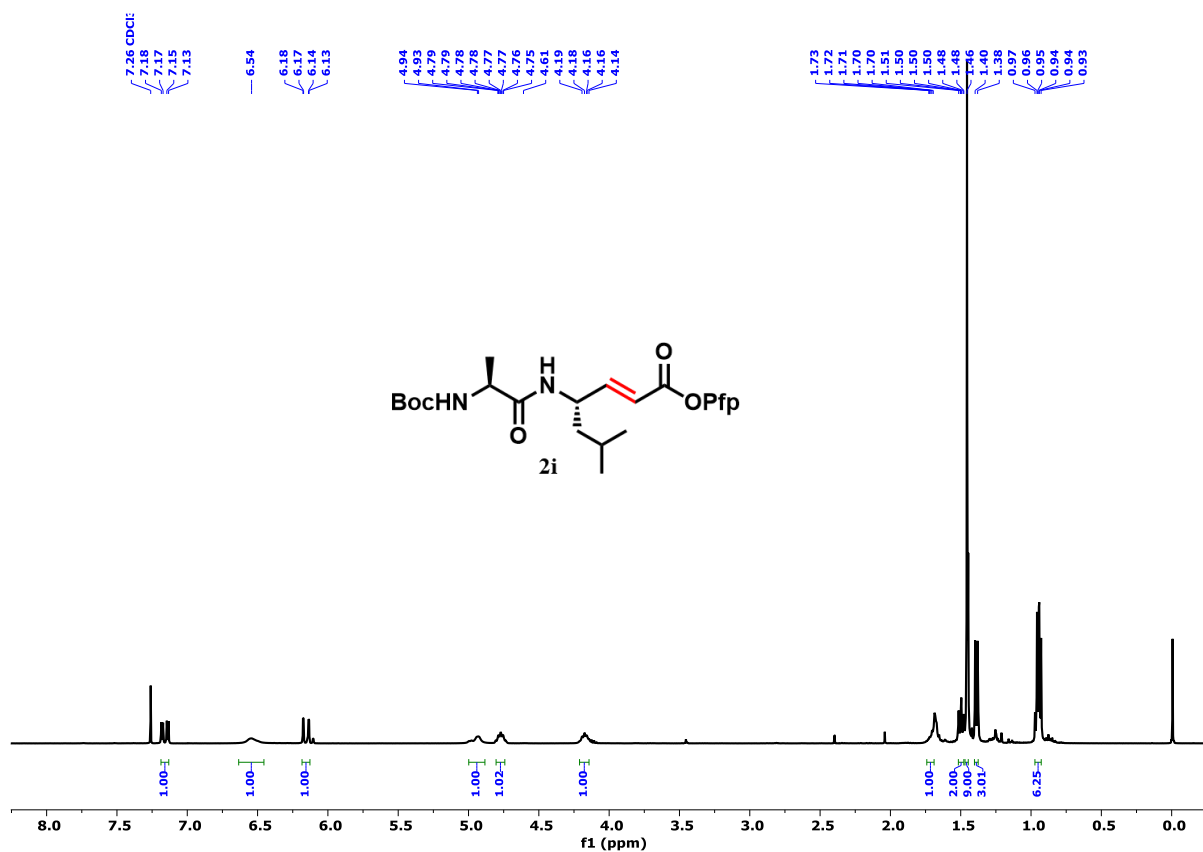


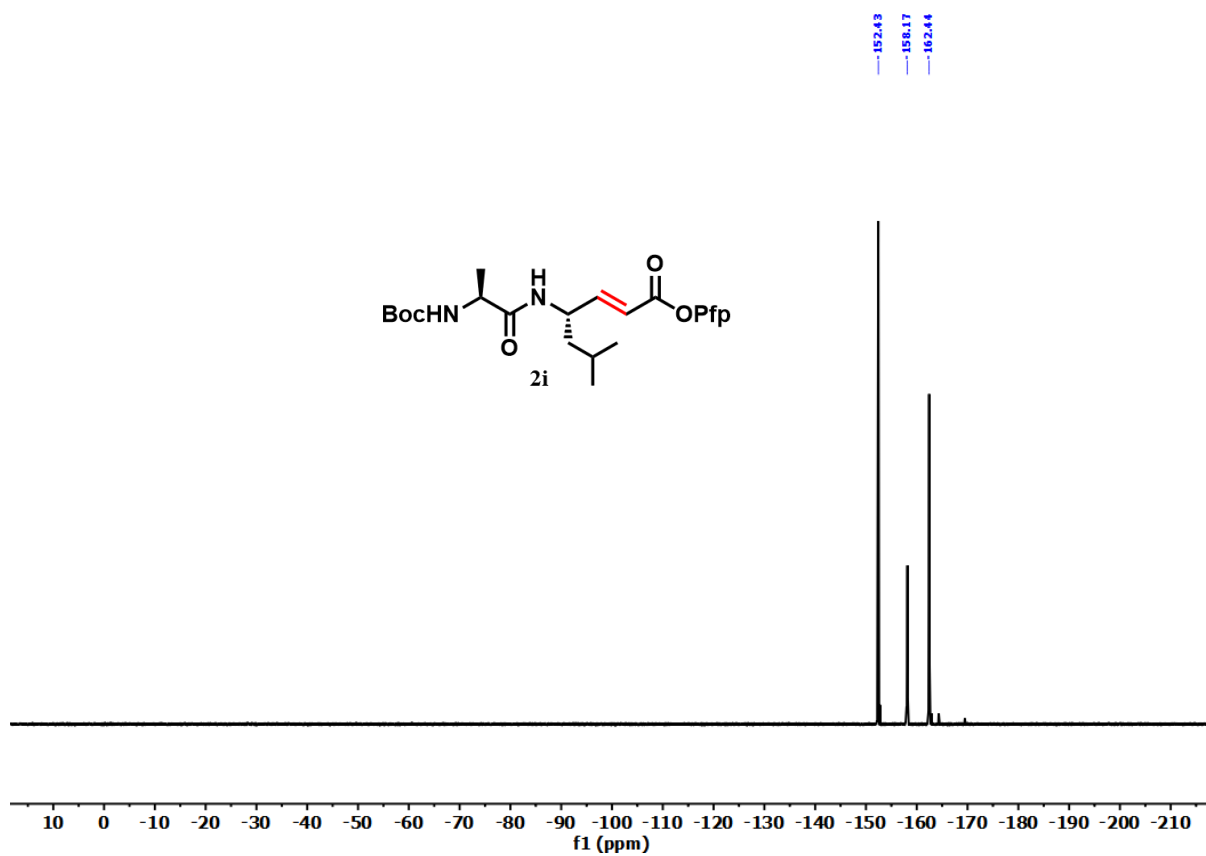
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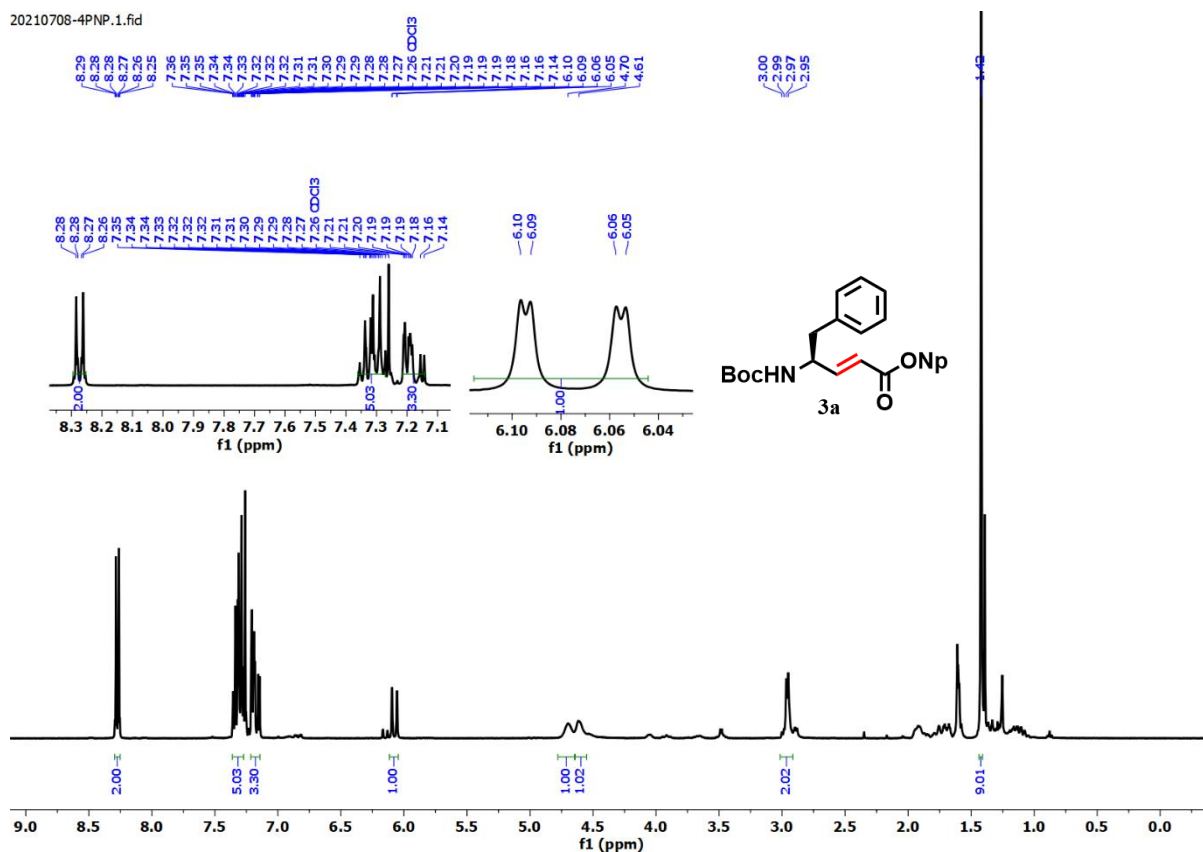




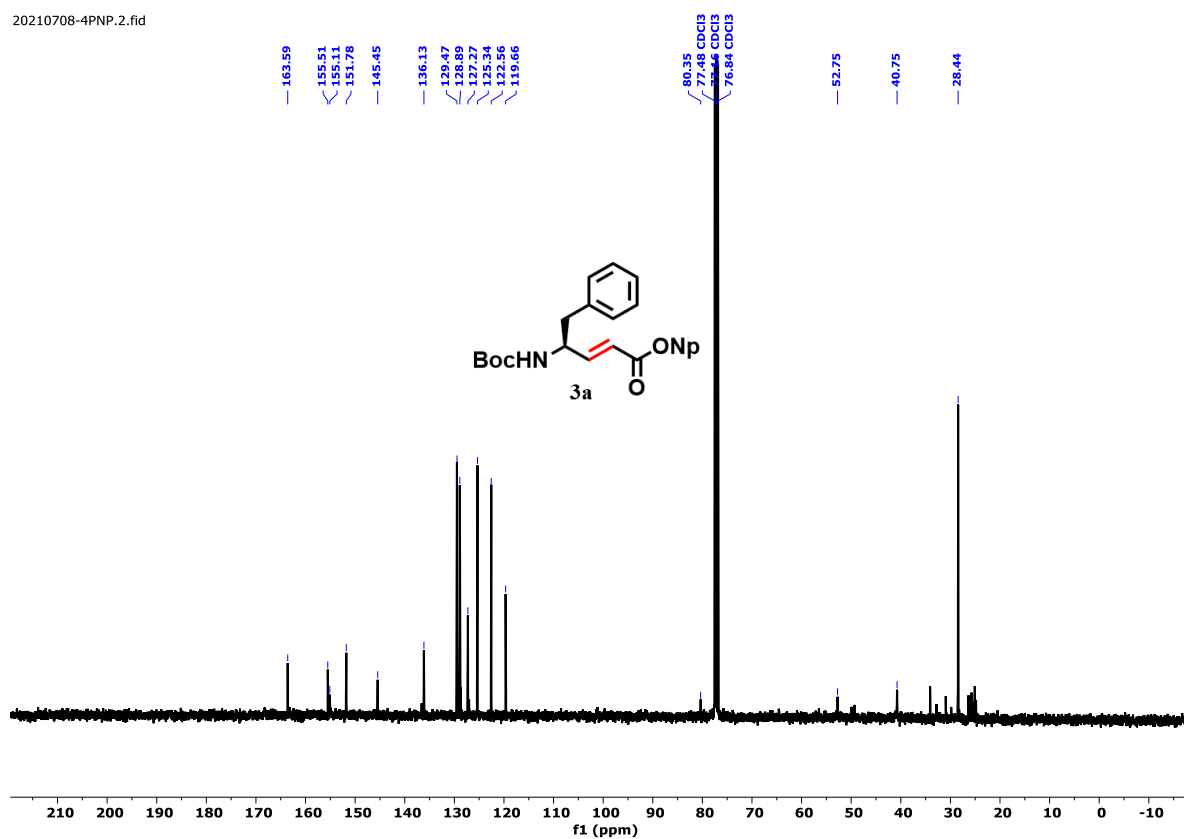


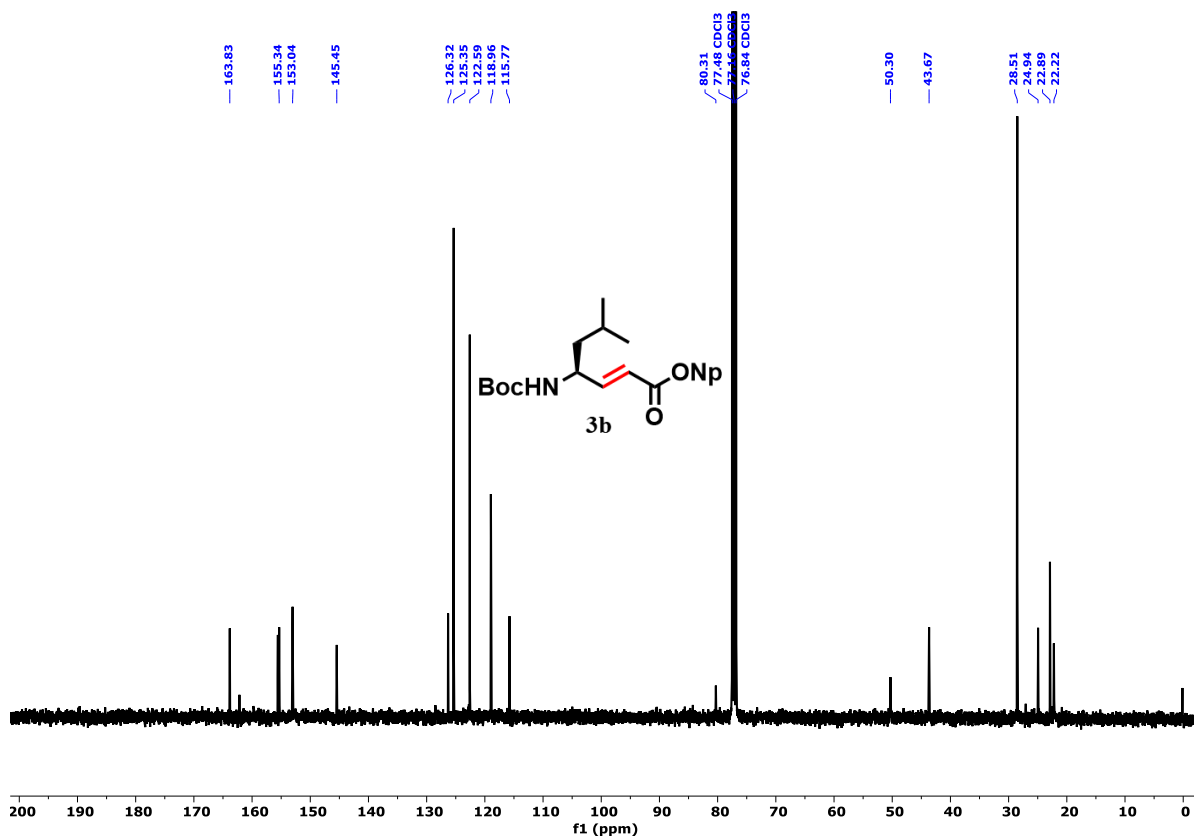
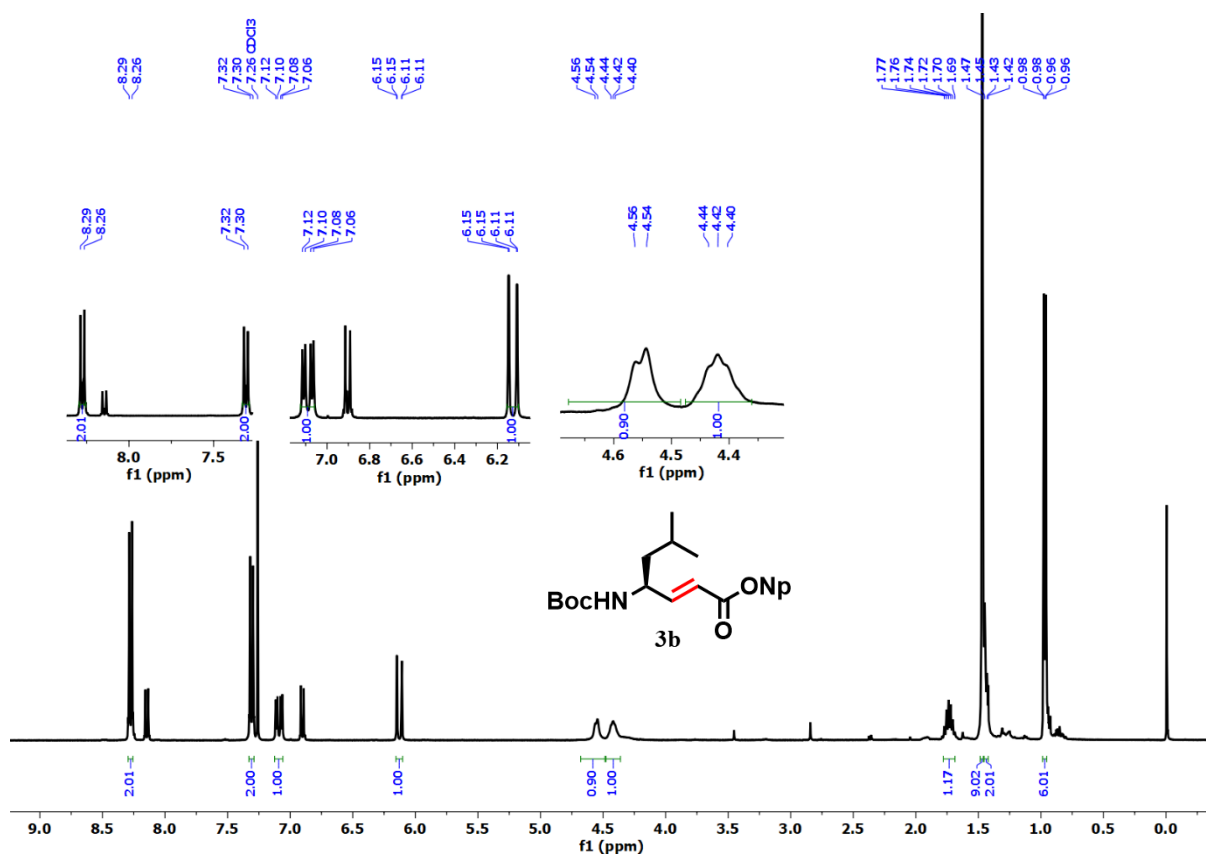


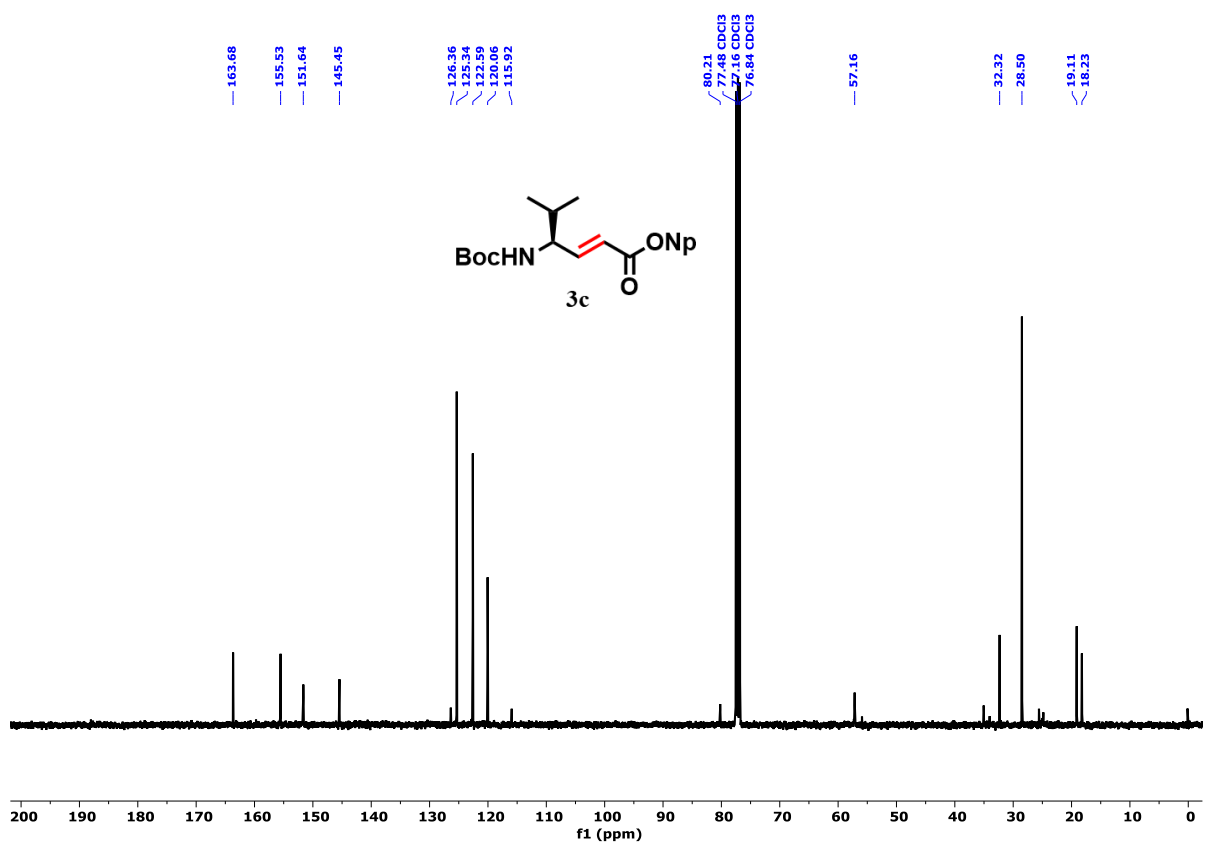
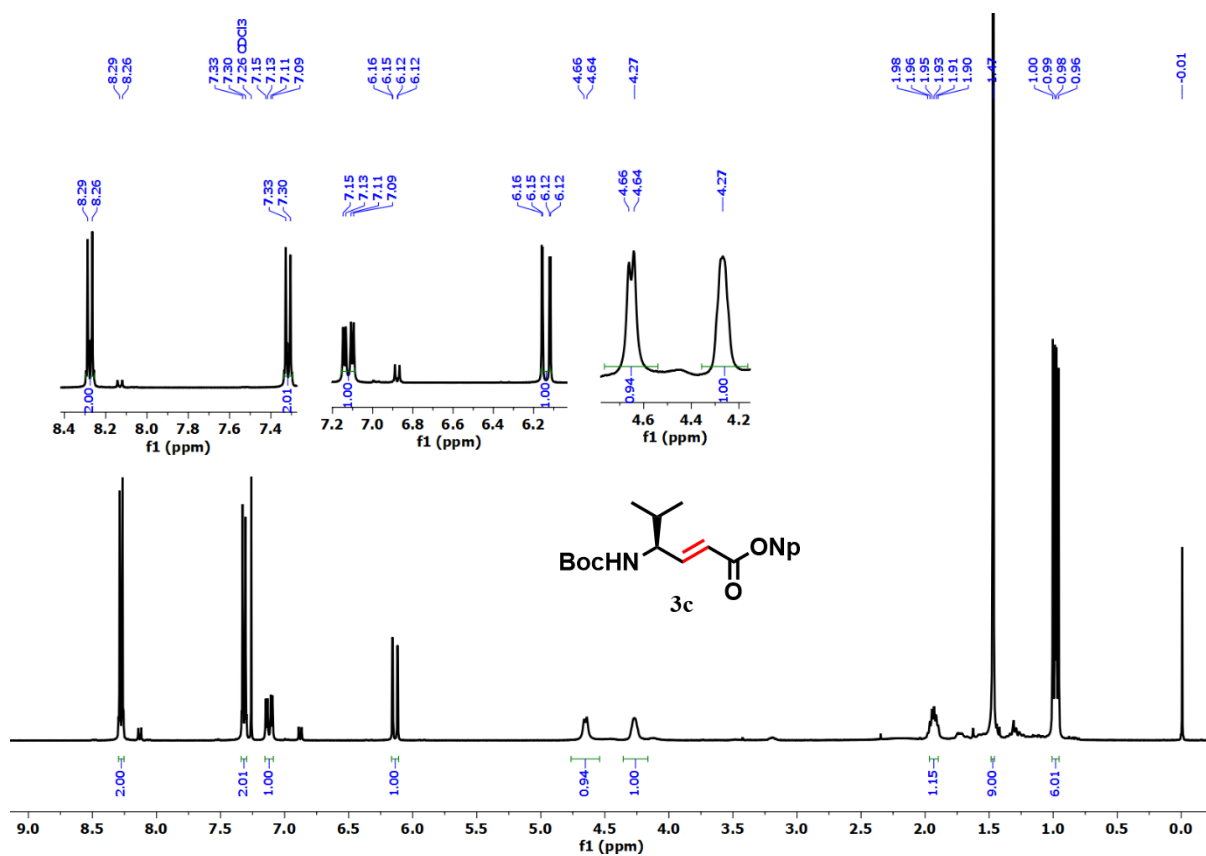
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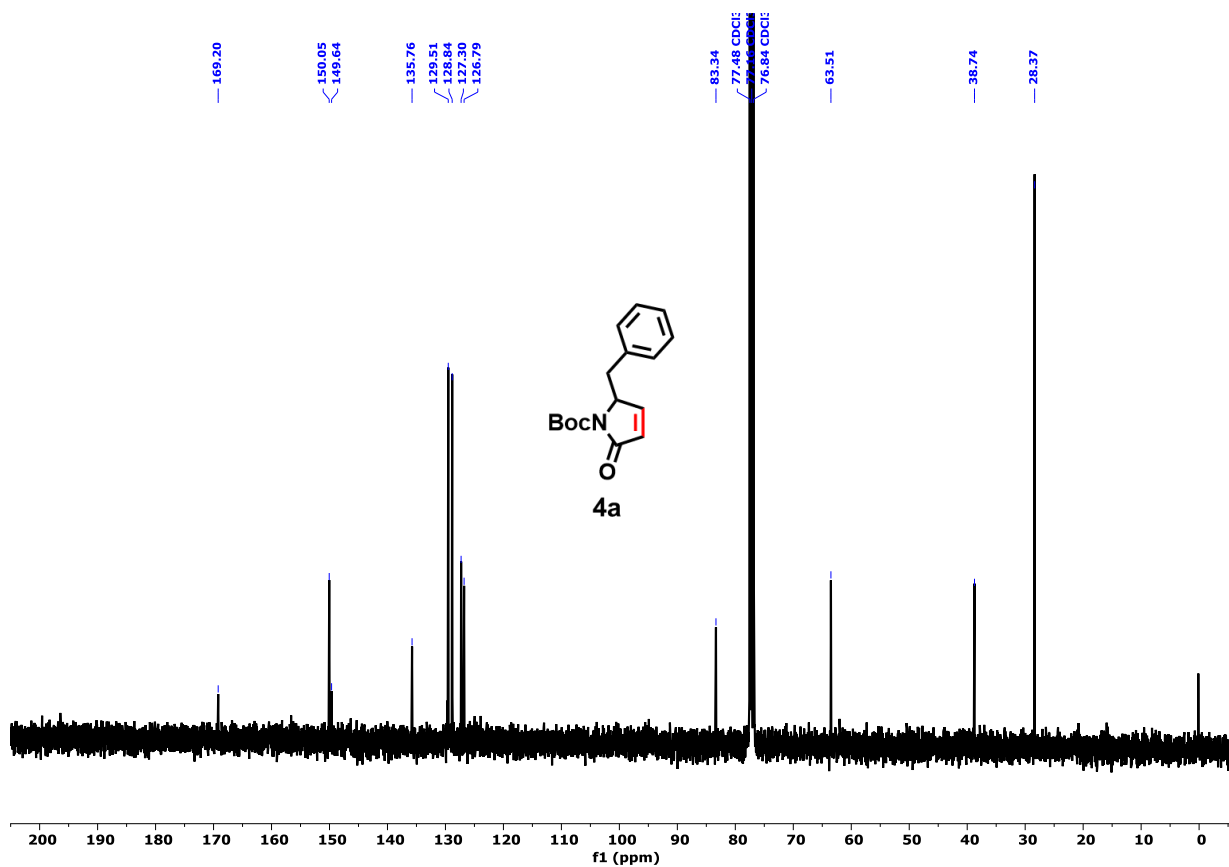
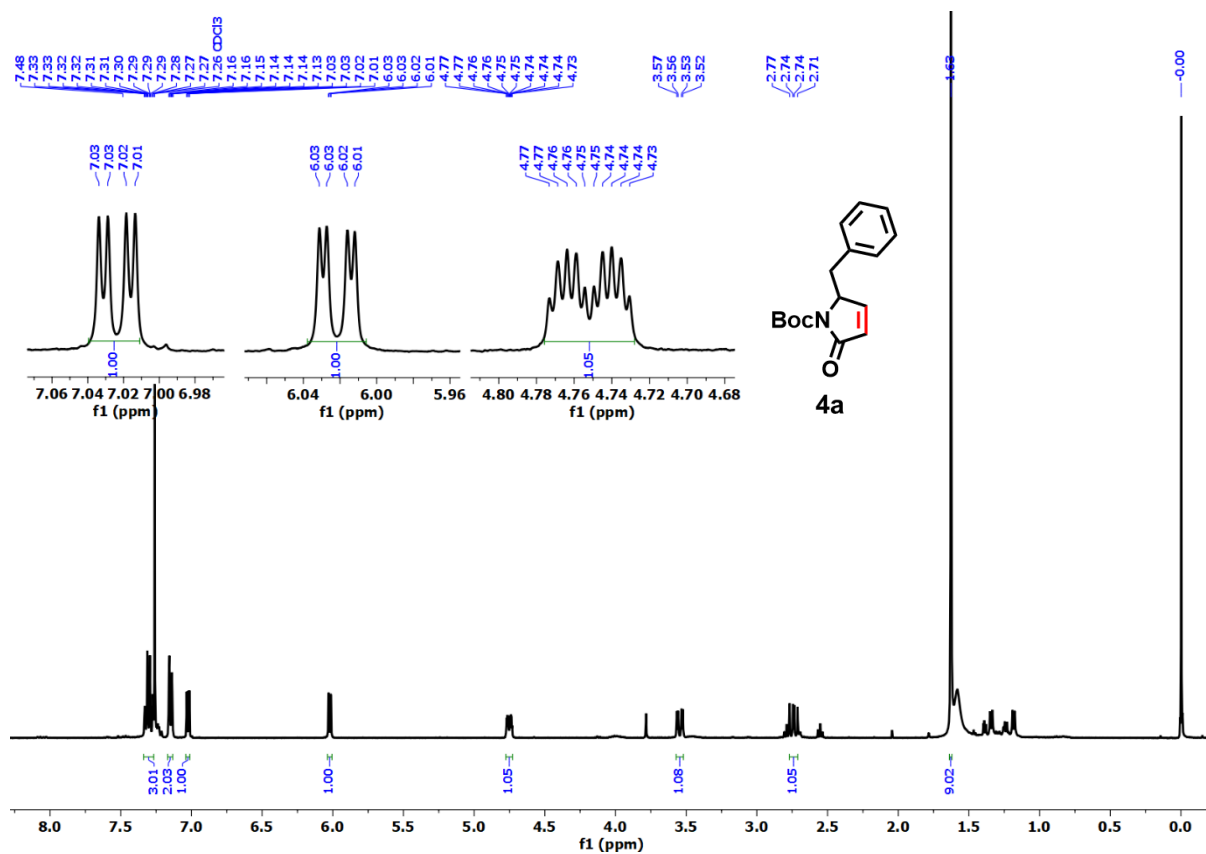


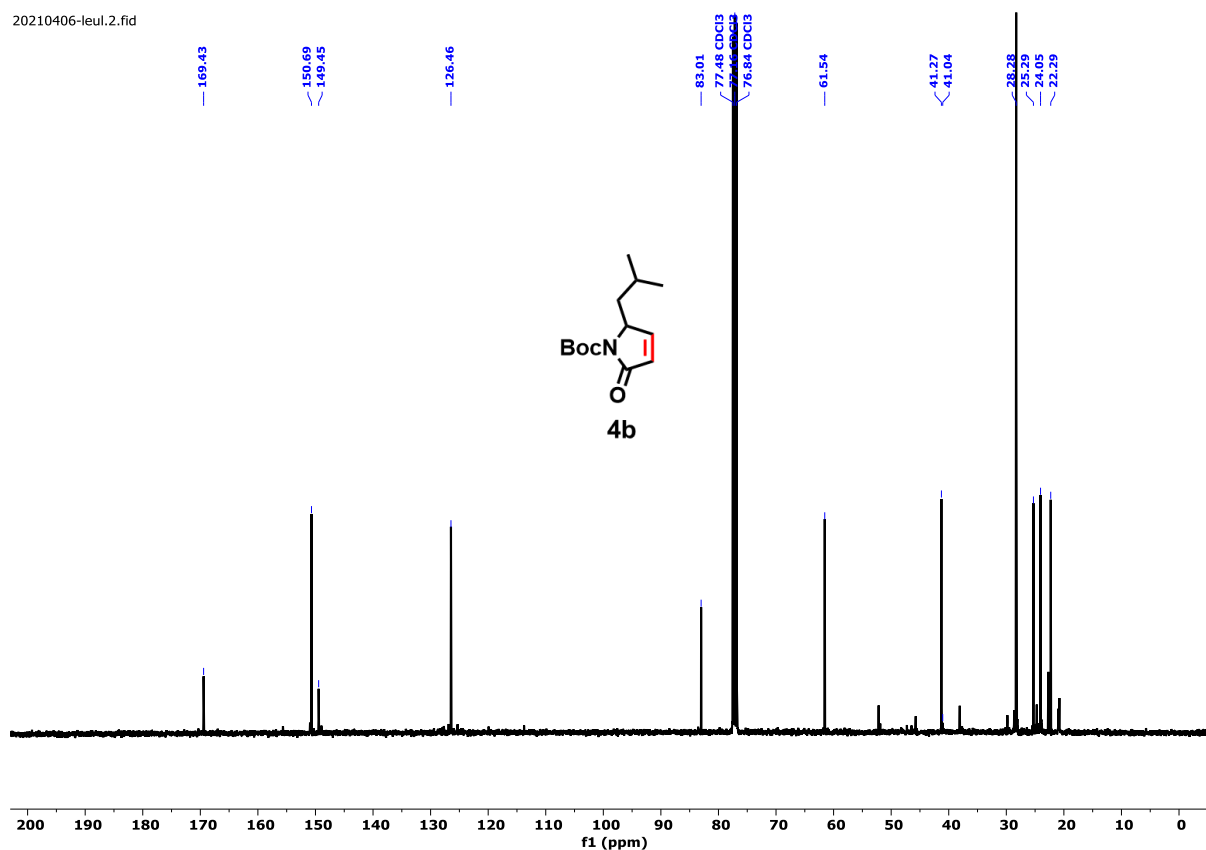
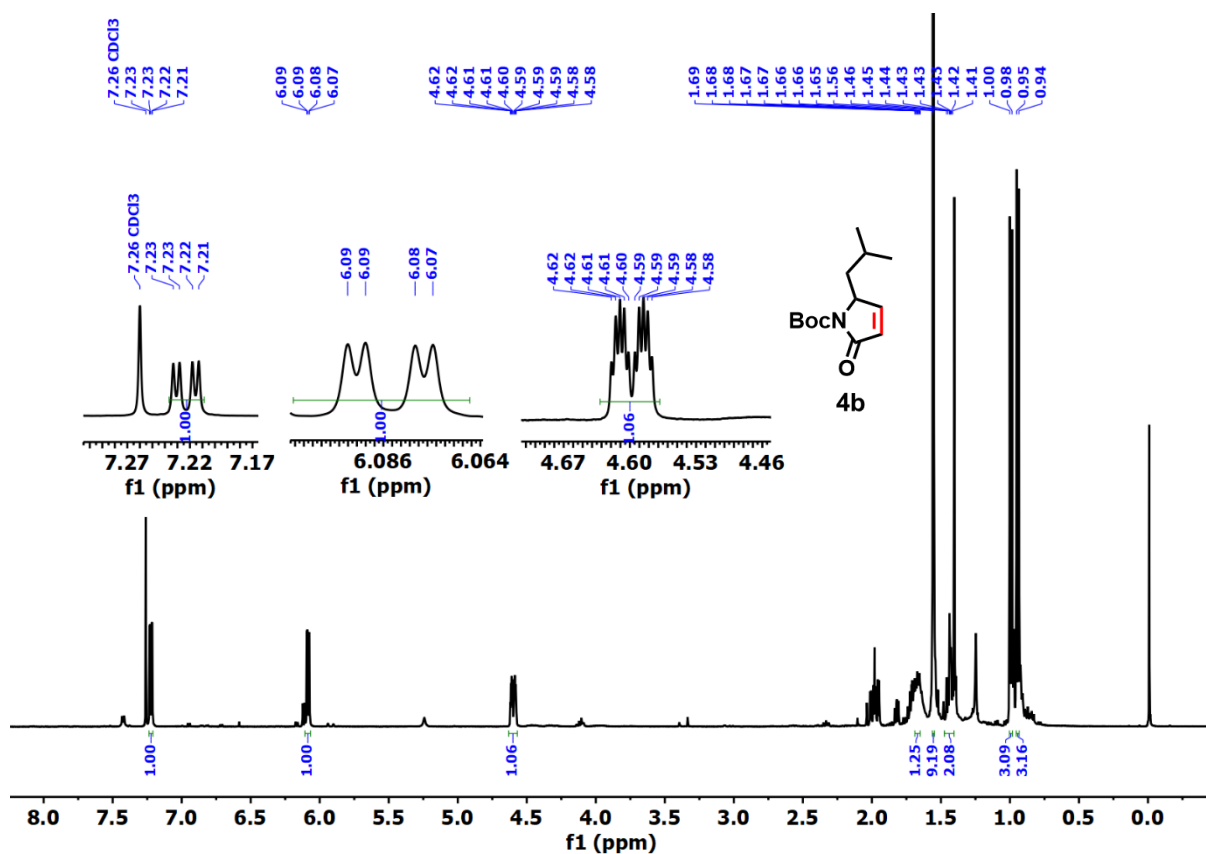
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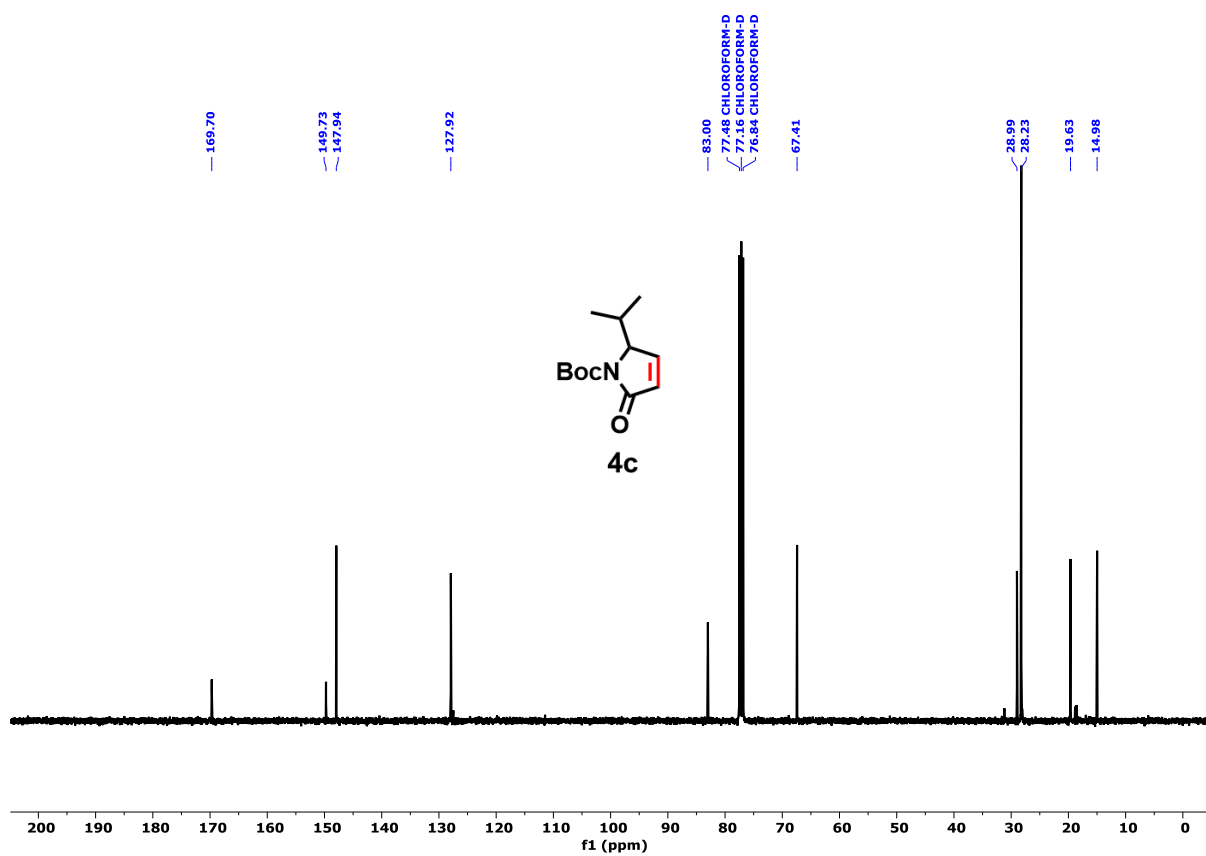
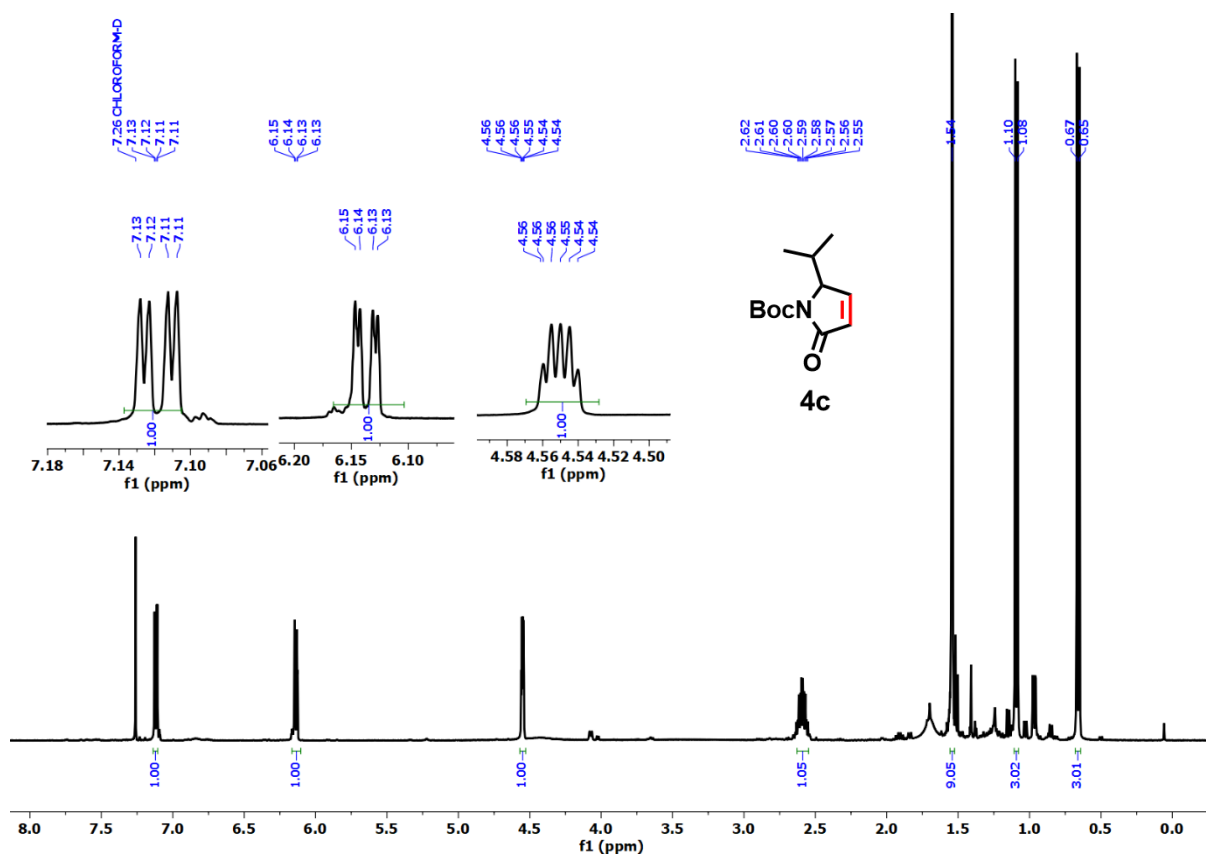


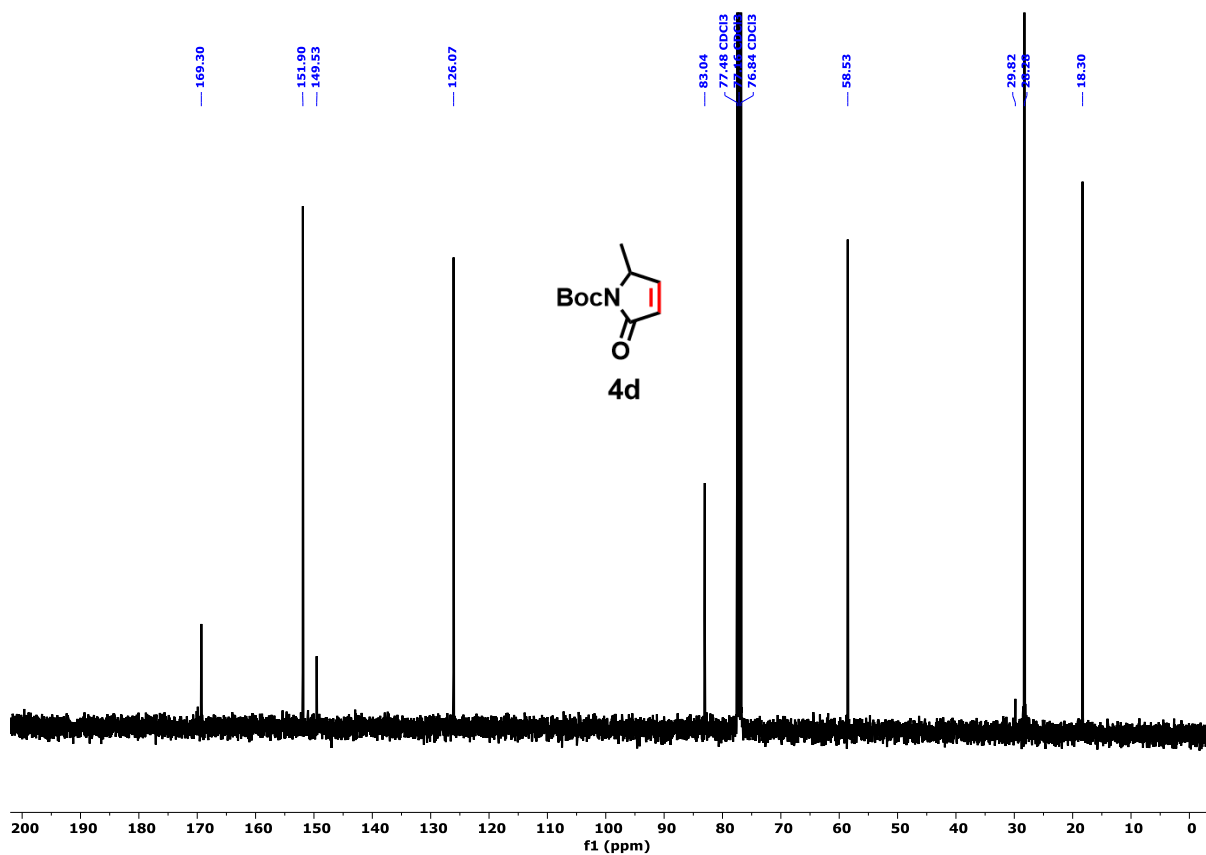
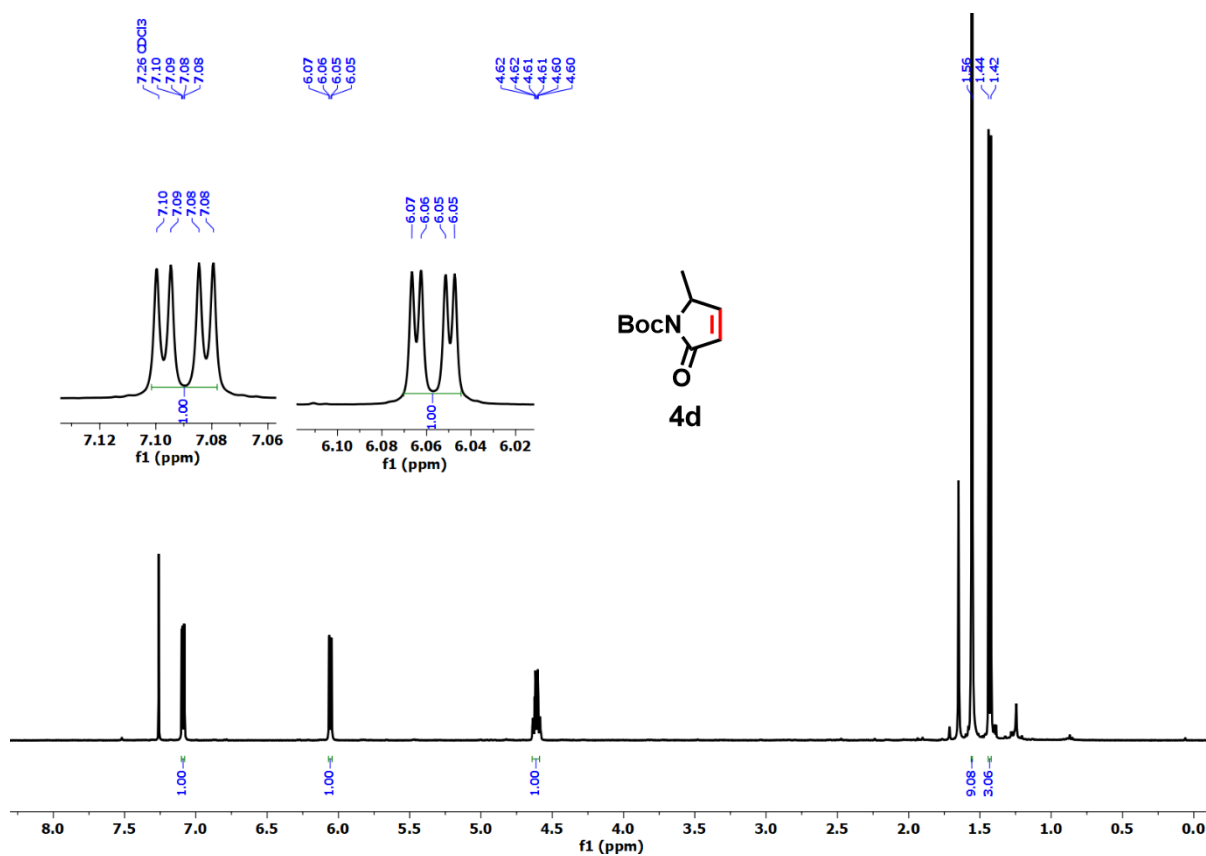


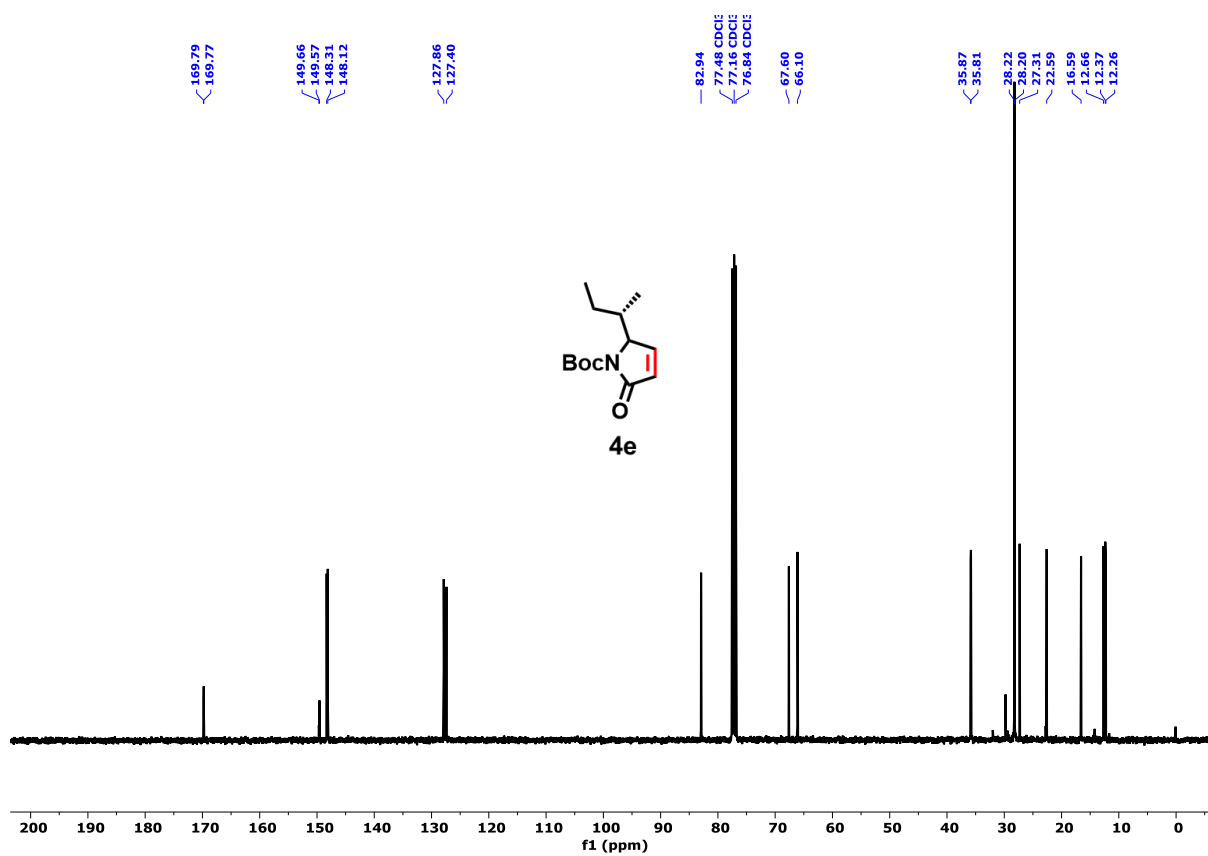
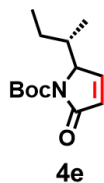
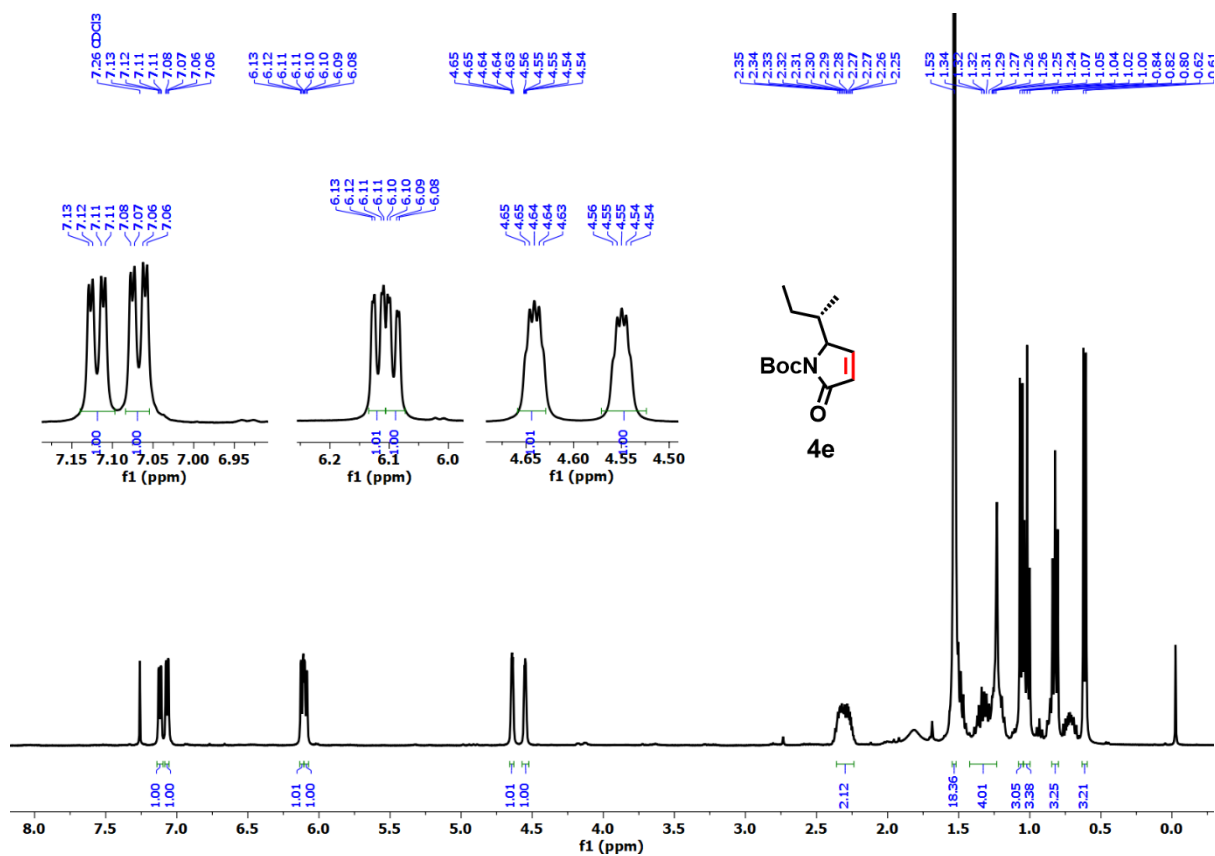


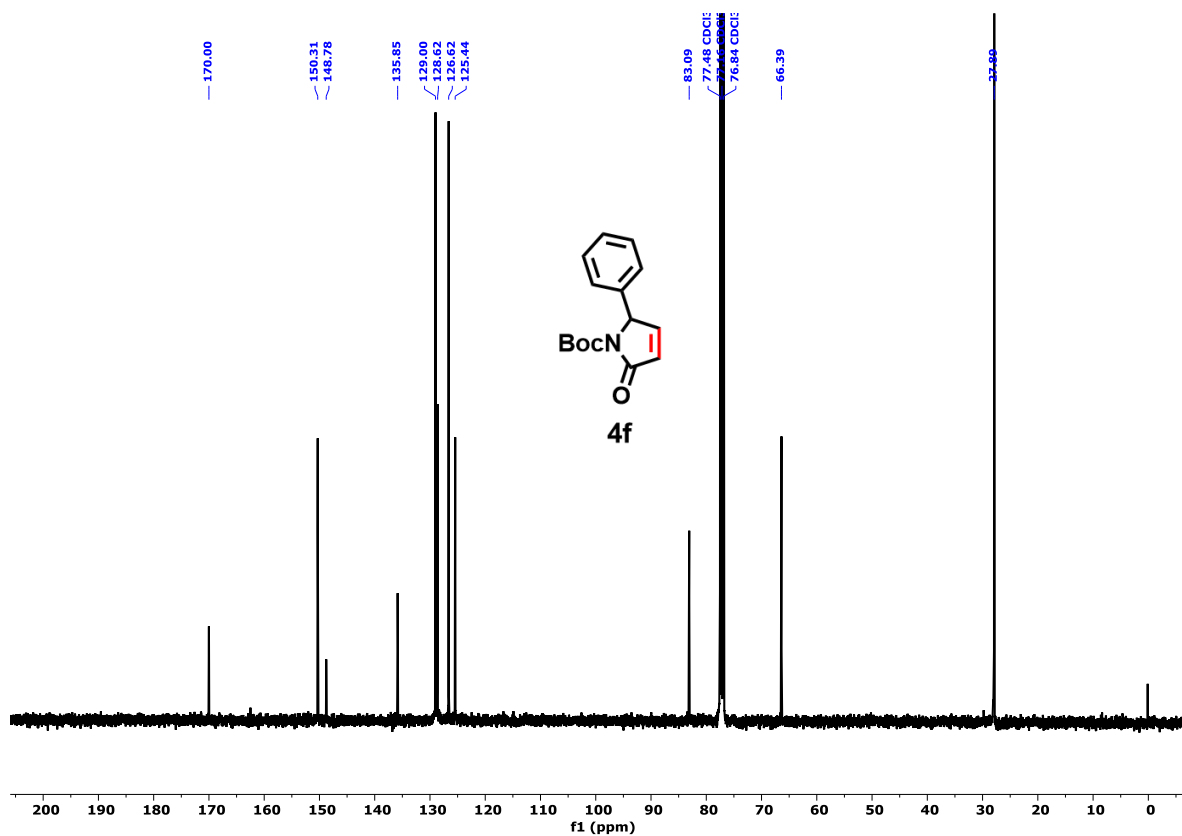
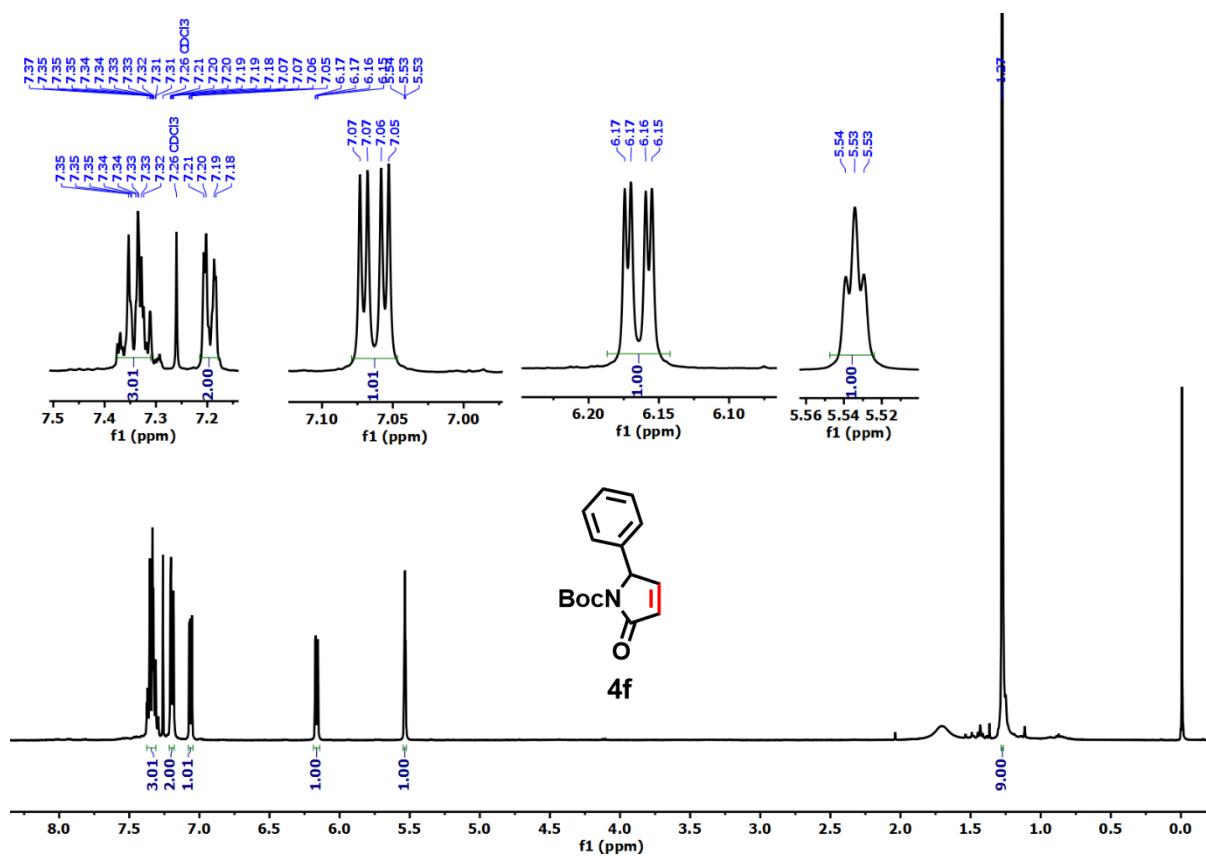


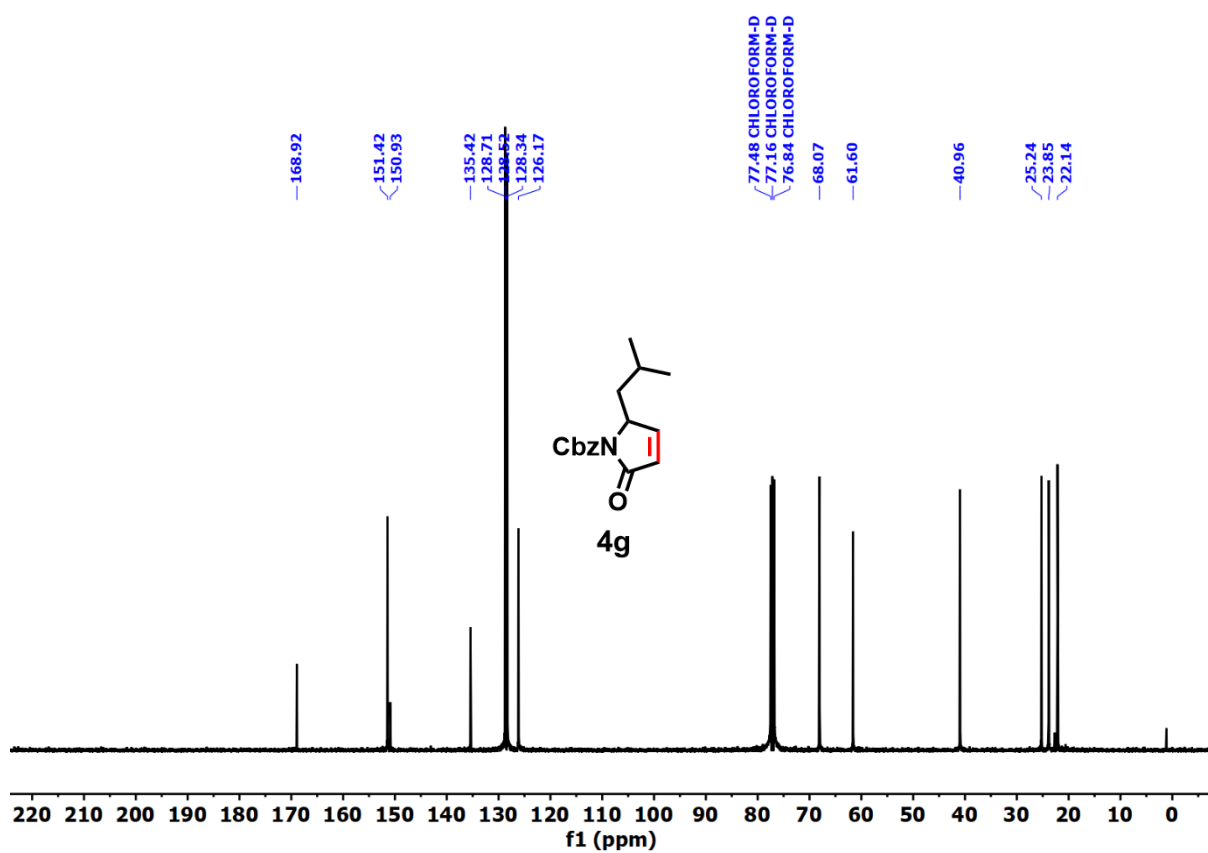
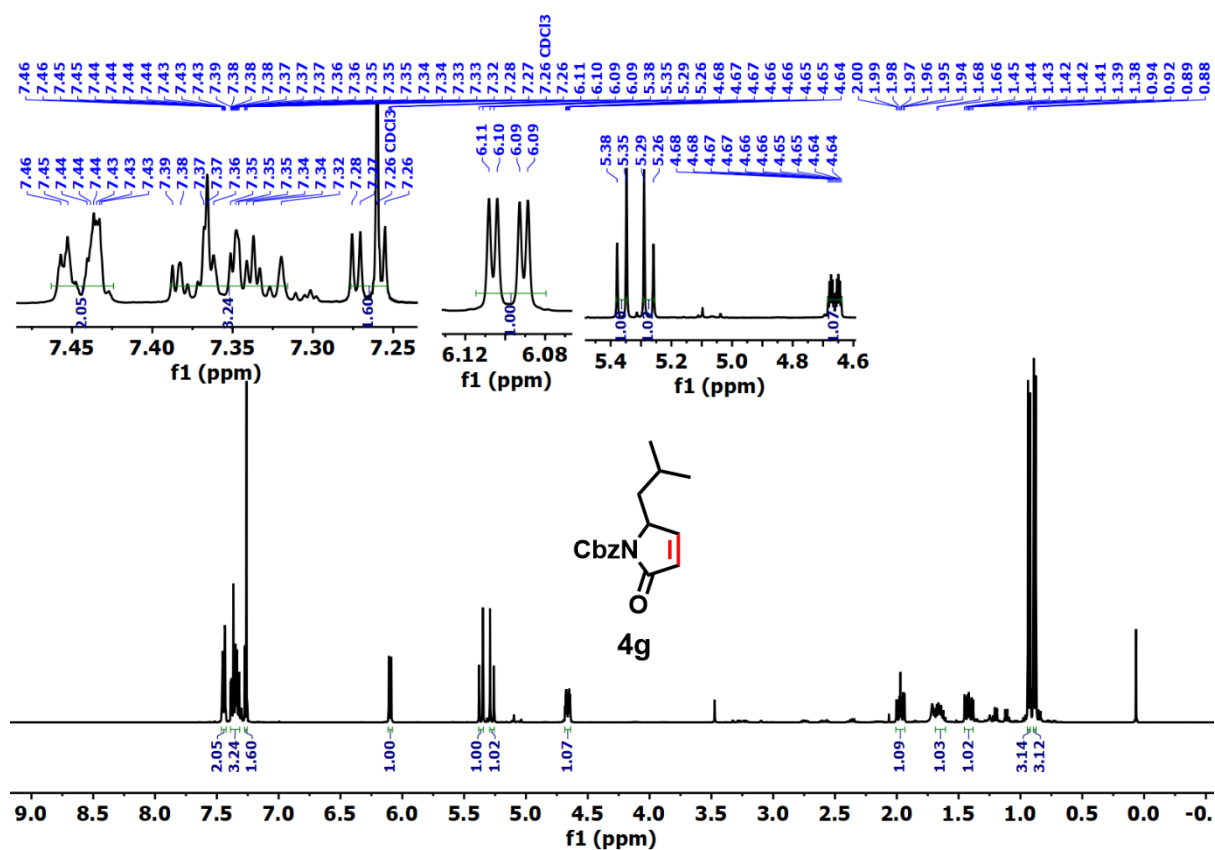


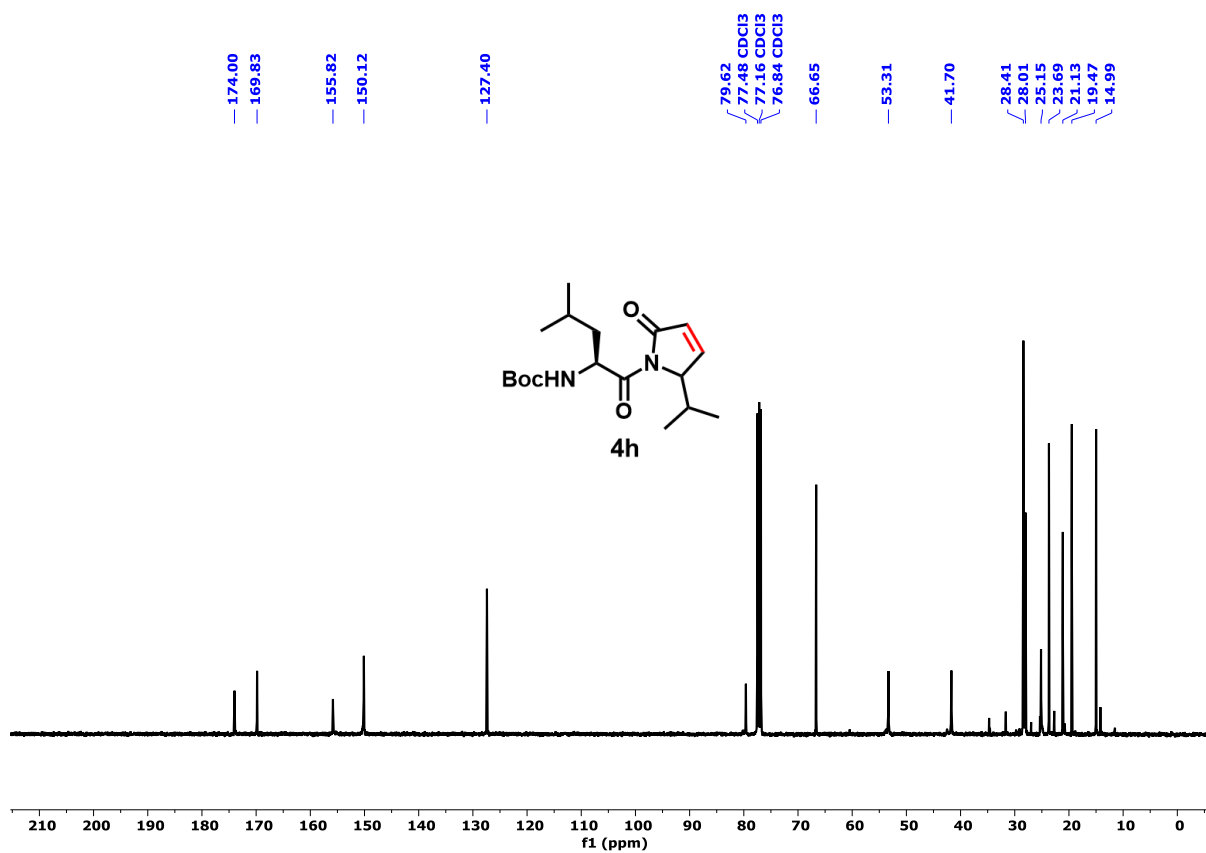
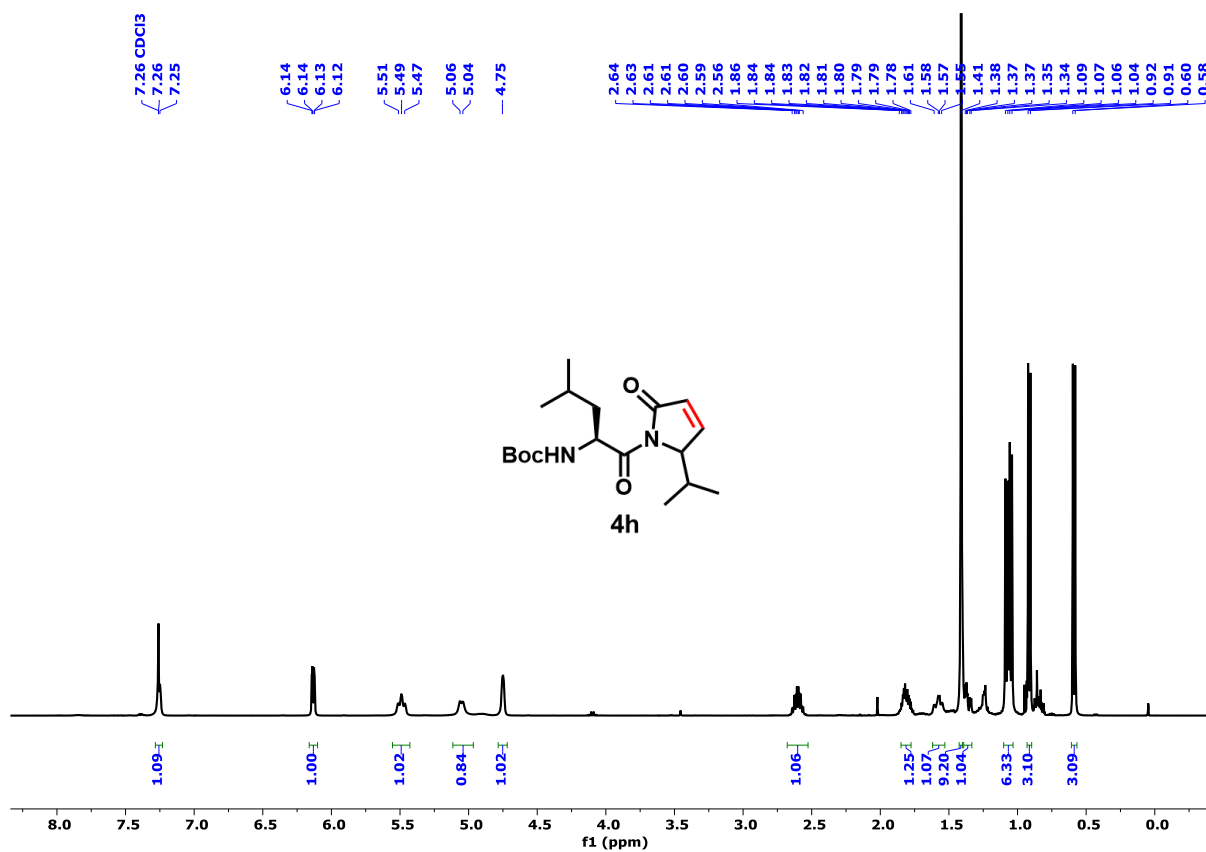




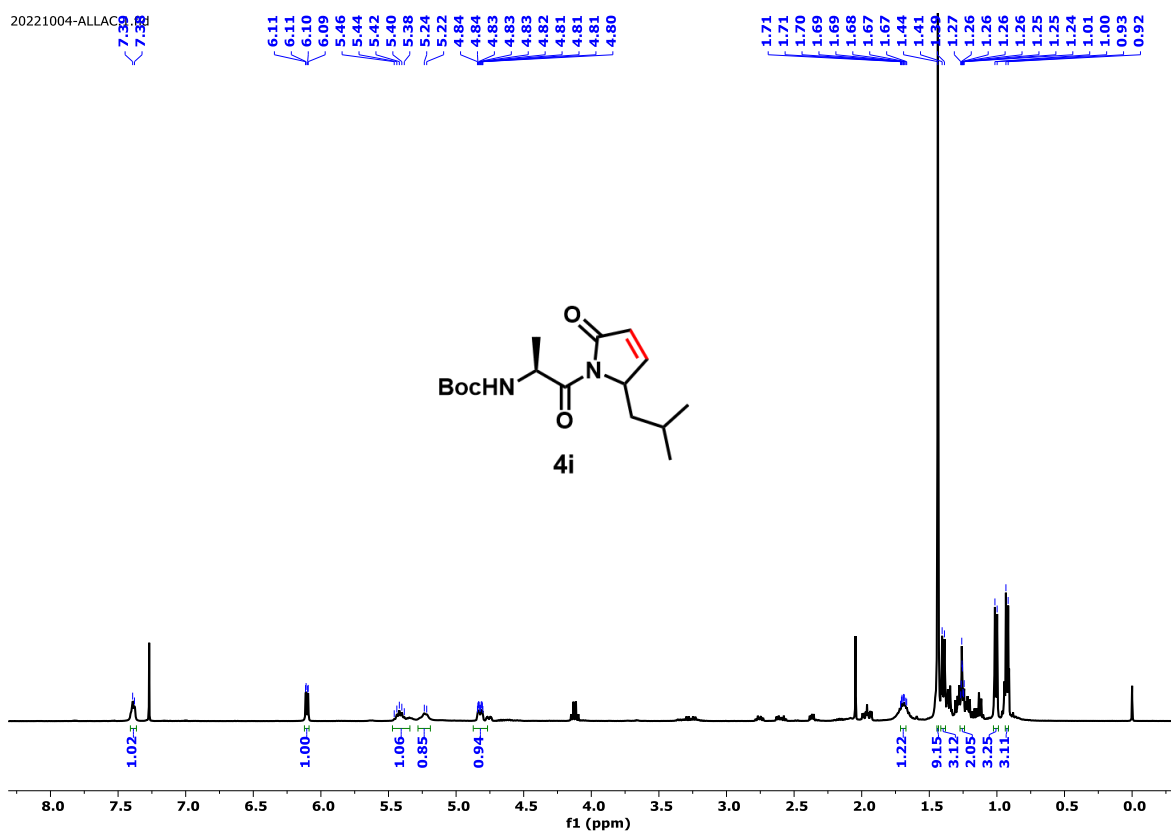




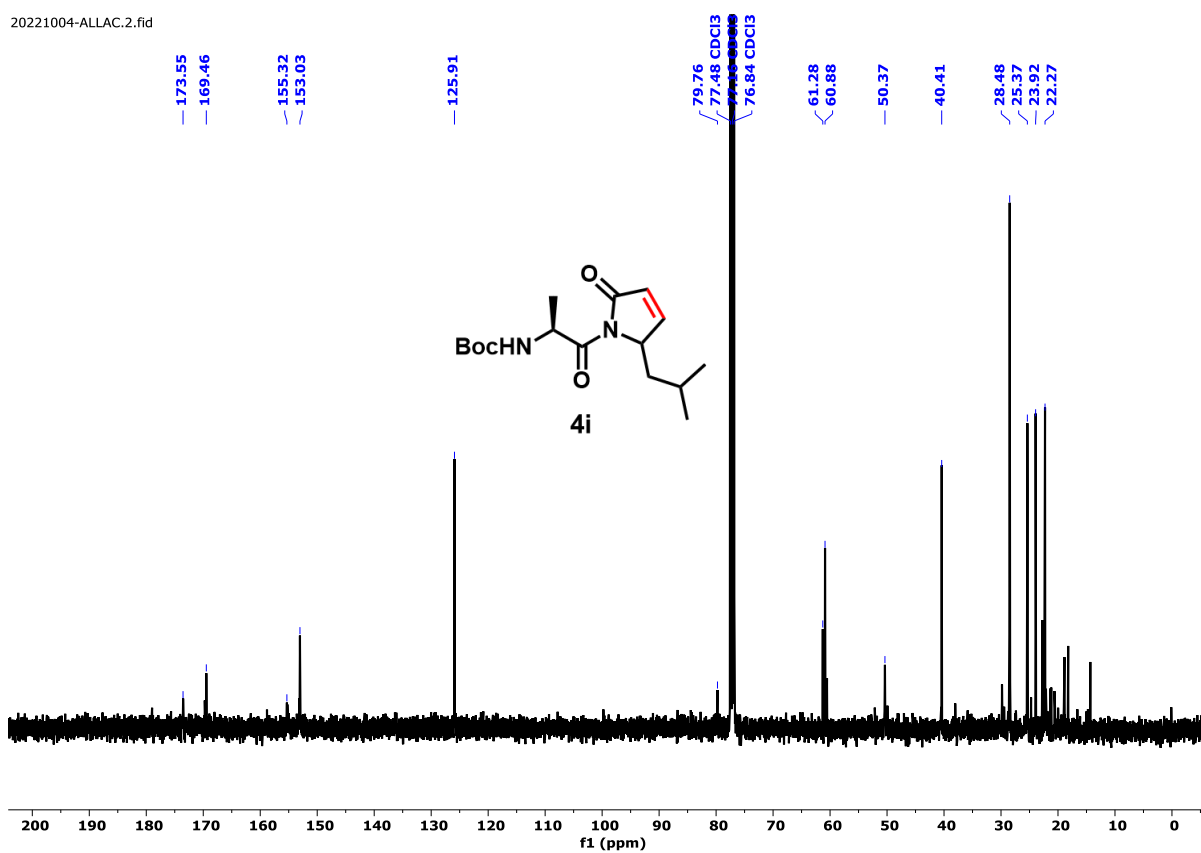


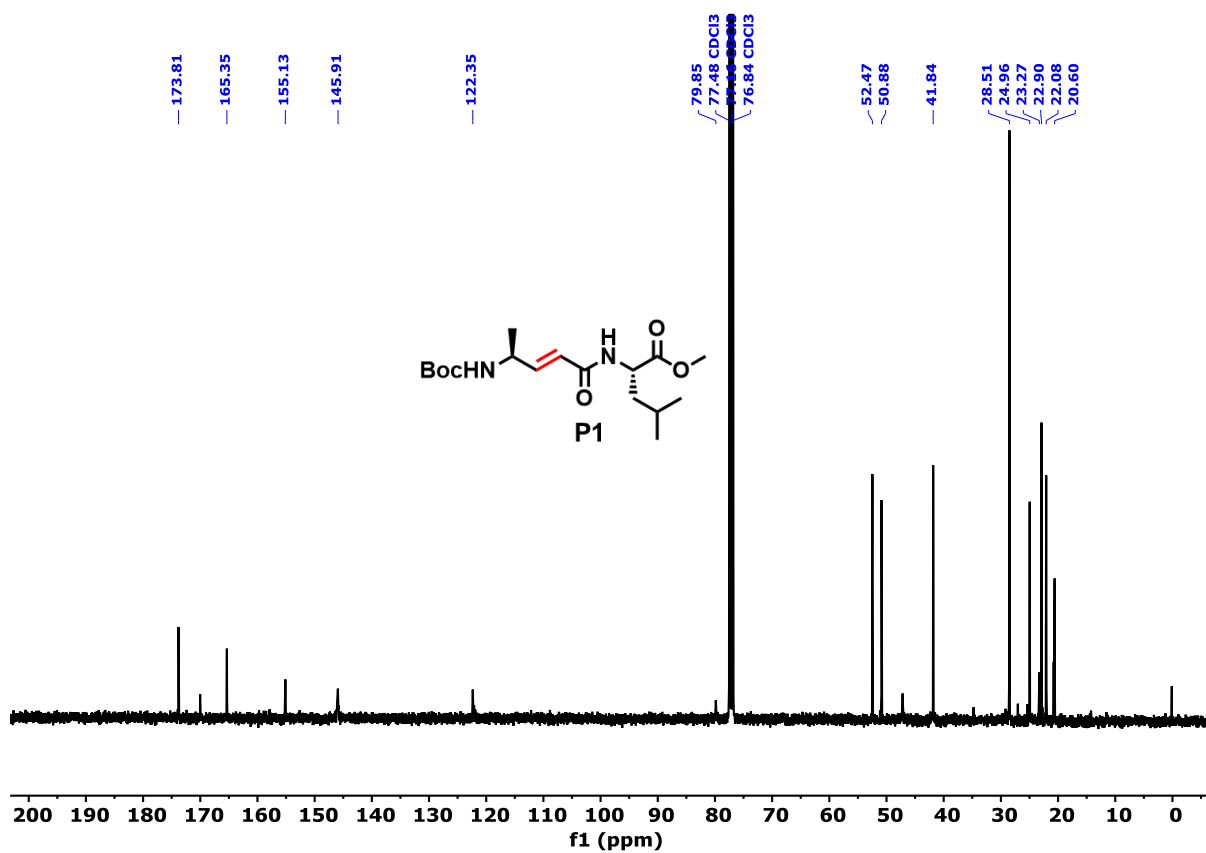
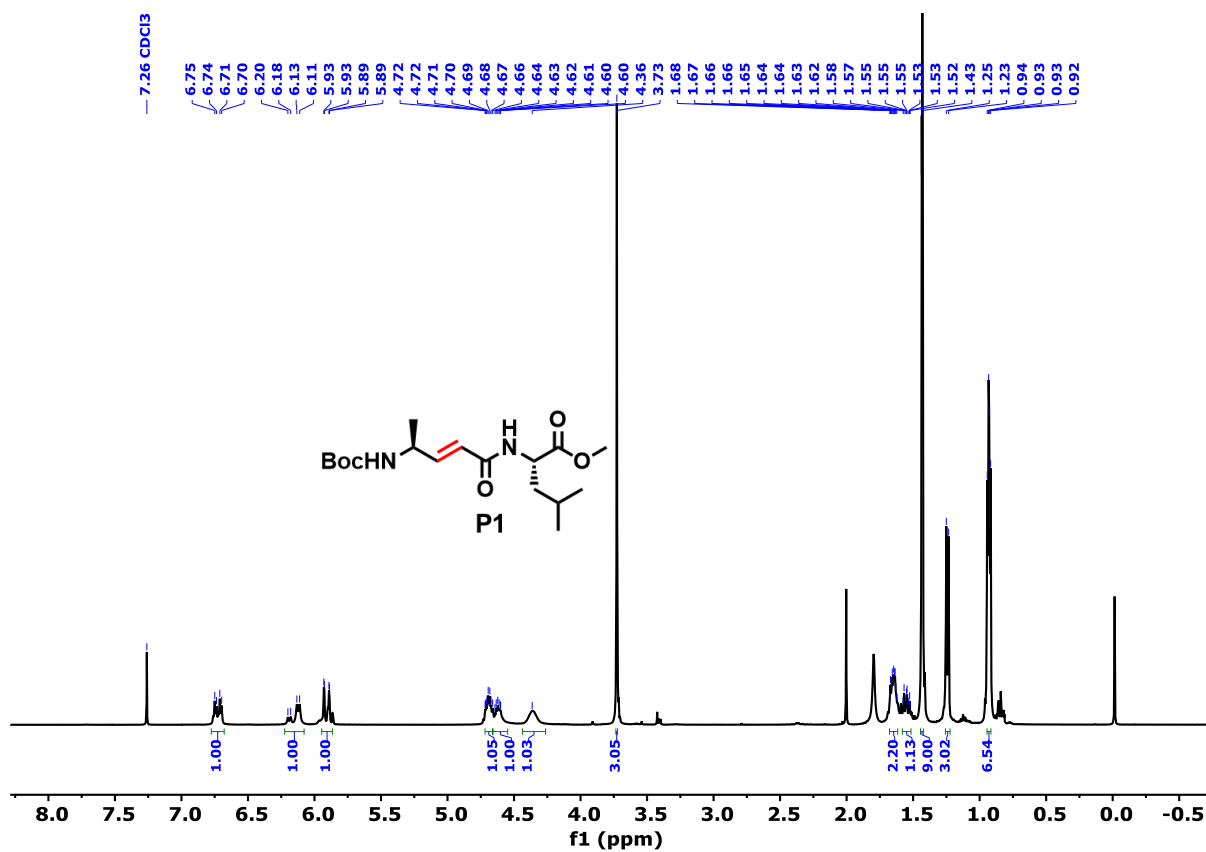


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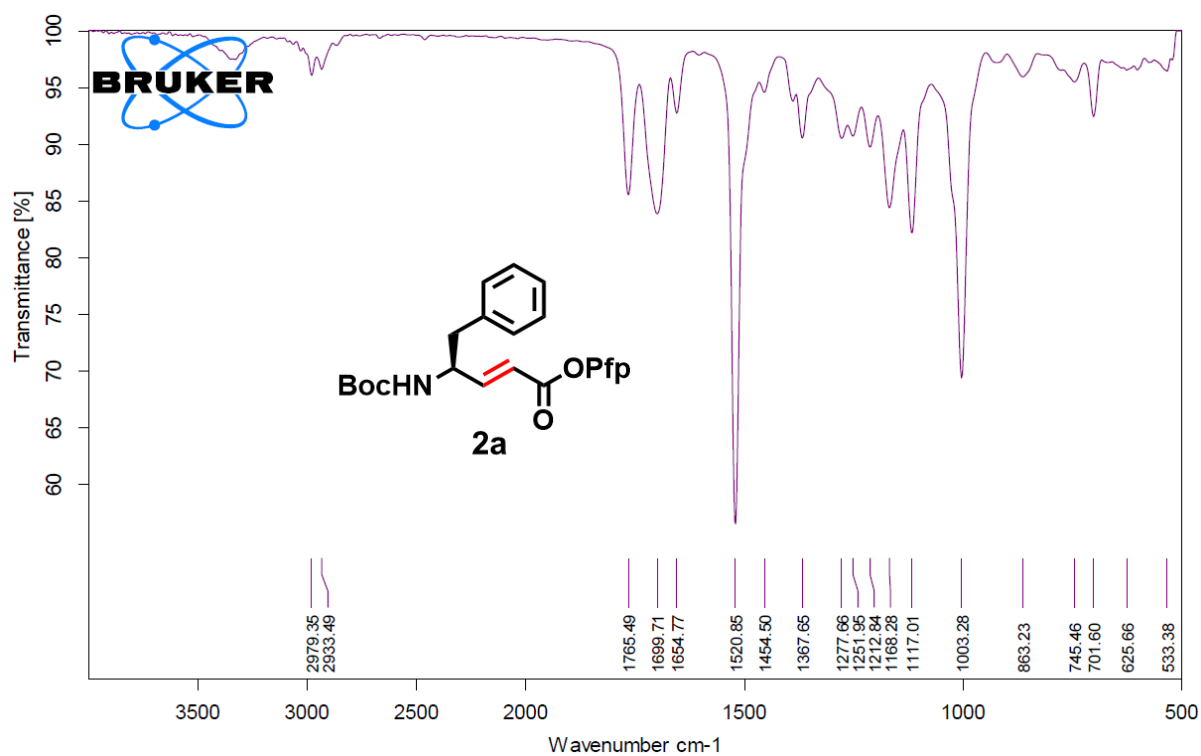
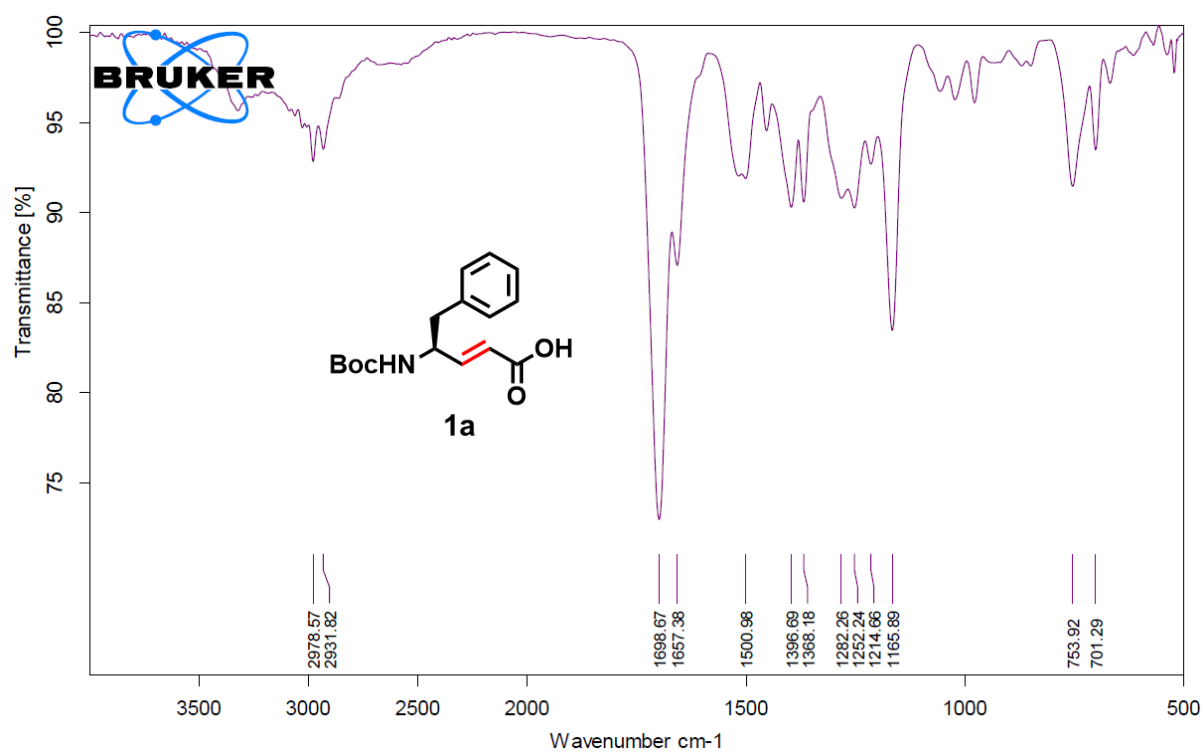


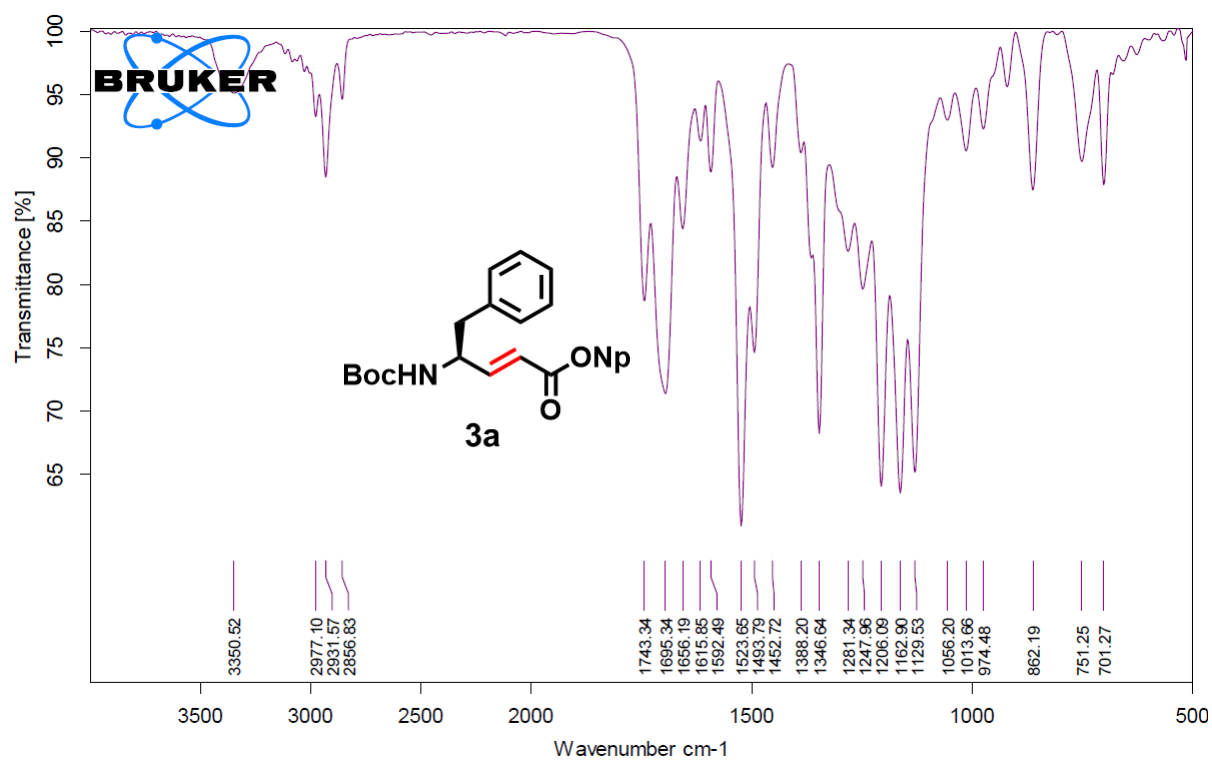
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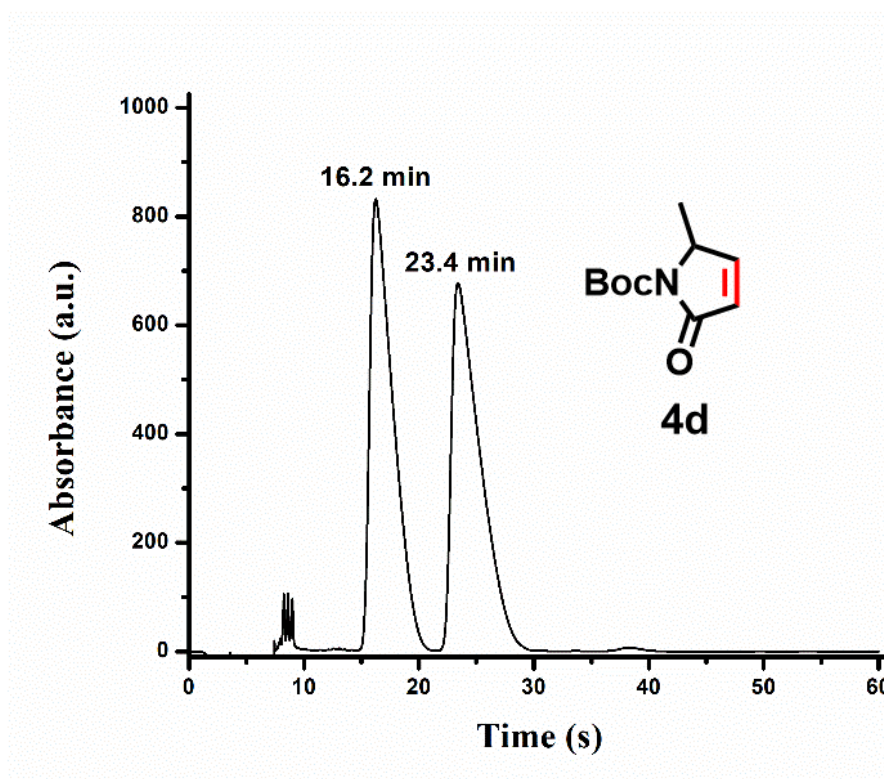


2.10.2 IR Spectra of Compounds





2.10.3 HPLC Peak (using chiral column)



2.10.4 Mass of all the synthesized compounds obtained from HRMS.

Entry	Compound	[M+Na/H] ⁺	Calculated Mass	Observed Mass	Δm
1	2a	C ₂₂ H ₂₀ F ₅ NO ₄ Na	480.1209	480.1206	0.0003
2	2b	C ₁₉ H ₂₂ F ₅ NO ₄ Na	446.1366	446.1361	0.0005
3	2c	C ₁₈ H ₂₀ F ₅ NO ₄ Na	432.1209	432.1215	0.0003
4	2d	C ₁₆ H ₁₆ F ₅ NO ₄ Na	404.0896	404.0889	0.0007
5	2e	C ₁₉ H ₂₂ F ₅ NO ₄ Na	446.1366	446.1375	0.0009
6	2f	C ₂₁ H ₁₈ F ₅ NO ₄ Na	466.1053	446.1053	0
7	2g	C ₂₂ H ₂₀ F ₅ NO ₄ Na	480.1210	480.1209	0.0001
8	2h	C ₂₄ H ₃₁ F ₅ N ₂ O ₄ Na	545.2050	545.2052	0.0002
9	2i	C ₂₂ H ₂₅ F ₅ N ₂ O ₄ Na	517.1737	517.1743	0.0006
10	3a	C ₂₂ H ₂₄ N ₂ O ₆ Na	435.1531	435.1522	0.0009
11	3b	C ₁₉ H ₂₆ N ₂ O ₆ Na	401.1688	401.1682	0.0006
12	3c	C ₁₈ H ₂₄ N ₂ O ₆ Na	387.1531	387.1531	0
13	4a	C ₁₆ H ₁₉ NO ₃ Na	296.1262	296.1262	0
14	4b	C ₁₃ H ₂₁ NO ₃ Na	262.1418	262.14.18	0
15	4c	C ₁₂ H ₁₉ NO ₃ Na	248.1262	248.1261	0.0001
16	4d	C ₁₀ H ₁₈ NO ₃ Na	220.0949	220.0955	0.0006
17	4e	C ₁₃ H ₂₁ NO ₃ Na	262.1418	262.14.18	0
18	4f	C ₁₅ H ₁₇ NO ₃ Na	282.1105	282.1103	0.0002
19	4g	C ₁₆ H ₂₀ NO ₃	274.1443	274.1439	0.0004
20	4h	C ₁₈ H ₃₀ N ₂ O ₄ Na	361.2103	361.2101	0.0002
21	4i	C ₁₆ H ₂₆ N ₂ O ₄ Na	333.1790	333.1790	0
22	P1	C ₁₇ H ₃₀ N ₂ O ₅ Na	365.2052	365.2052	0

Note: Δm = Mass difference, [M+Na/H]⁺ = Molecular ion.

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Cyclization of *N*-Boc-(*E*)- α,β -unsaturated γ -amino acid active esters into *N*-Boc-(*Z*)- α,β -unsaturated γ -lactams through *E* $\rightarrow$ *Z* isomerization†

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[Author affiliations](#)

Abstract

Here, we are reporting the spontaneous transformation of the active esters of *N*-Boc protected *E*- α,β -unsaturated γ -amino acids into the corresponding *Z*- α,β -unsaturated γ -lactams with concomitant *E* $\rightarrow$ *Z* isomerization in the presence of a weak base. No cyclization was observed in the absence of the base. Analysis revealed that amide γ -NH is crucial for both lactamization and *E* $\rightarrow$ *Z* isomerization. This mild transformation provides easy access to the synthetically challenging α,β -unsaturated γ -lactams and also gives new insights into the *E* $\rightarrow$ *Z* isomerization of double bonds.

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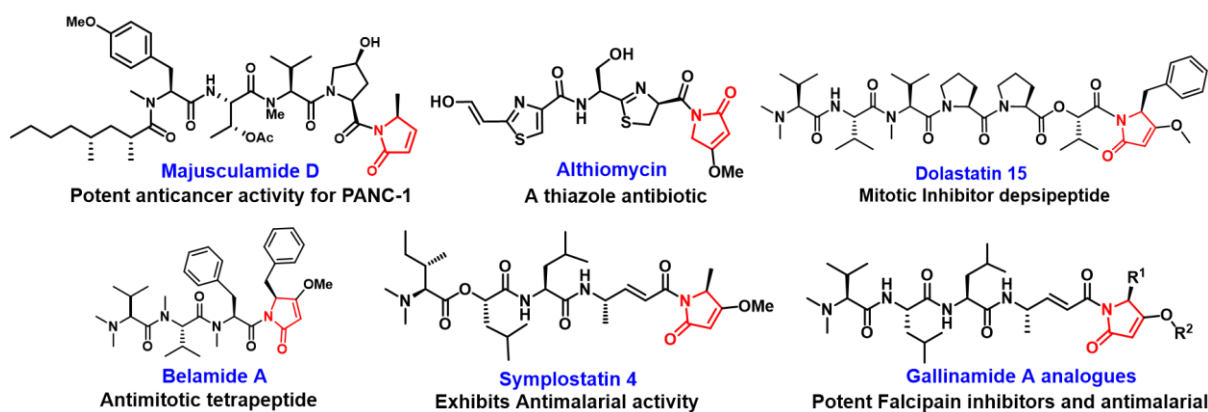
Chapter 3A

HBTU Mediated Synthesis of α,β -Unsaturated γ -Lactams from *E*- α,β -Unsaturated γ -Amino Acids

The original work of this chapter has been published in the “European Journal of Organic Chemistry” journal. Here, we adopted the text from Ref. M. Singh, S. A. Nalawade, D. R. Puneeth Kumar, K. Veeresh, S. Pahan, S. Dey and H. N. Gopi, *Eur. J. Org. Chem.* 2023, e202300682, with permission from the Chemistry Europe - Wiley Online Library. A copy of the permission letter is attached at the end of the chapter.

3A.1 Introduction

Several naturally occurring peptides with significant biological importance contain the α,β -unsaturated γ -amino acids as their ingredient core structure.¹ These amino acids have been serving as predecessors for the synthesis of γ^4 -amino acids.² In addition, α,β -unsaturated γ -amino acids have been serving as conformationally restricted templates to design a variety of helical structures,³ β -sheets,⁴ β -turns,⁵ and β -double helical structures.⁶ Further these α,β -unsaturated γ -amino acids have also been serving as substrates to derive a variety of functionalized γ -amino acids through conjugate addition.⁷ In the presence of a strong base, the amides of the α,β -unsaturated γ -amino acids can be transformed into the γ -lactams through the $\alpha,\beta \rightarrow \beta,\gamma$ migration of double bonds.⁸ Further, the double bond migrations have been explored to design helical structures from α,γ -hybrid peptides consisting of *E*- α,β -unsaturated γ -amino acids.⁹ Interestingly, the double bonds migrated from $\alpha,\beta \rightarrow \beta,\gamma$ position adopted *Z*-configuration and promoted helical structures with the loss of chirality.⁹ The carbon-carbon double bonds in the α,β -unsaturated γ -amino acid residues have shown very interesting properties. Recently we have shown the spontaneous lactamization of active esters of α,β -unsaturated γ -amino acids in the presence of a weak base through *trans-cis* isomerization of carbon-carbon double bonds.¹⁰ Previous results showed that in the case of amides, it requires a strong base to give saturated γ -lactams through 5-exo-trig cyclization, whereas the activate esters required a mild base to give α,β -unsaturated γ -lactams.^{8,10} The γ -lactams obtained in both methods are different. As the *E*-vinylogous active esters can be transformed into α,β -unsaturated γ -lactams, we speculated the *N*-protected *E*- α,β -unsaturated γ -amino acids can be transformed into corresponding α,β -unsaturated γ -lactams through *in-situ* carboxylic acid activation using the coupling reagent HBTU and DIPEA. The coupling reagent HBTU is known for *in-situ* activation of free carboxylic acids in the presence of DIPEA.¹¹ In addition, the reaction is also compatible with the peptides consisting of α,β -unsaturated γ -amino acids at the C-terminal. All *N*-protected- α,β -unsaturated γ -lactam and *N*-protected peptide α,β -unsaturated γ -lactams were isolated in very good yields. The reaction is compatible with various amino acid sidechains. Interestingly, no α,β -unsaturated γ -lactams were isolated in an identical control reaction consisting of free primary amine, instead dipeptides were isolated in excellent yields.



Scheme 1. Selected examples of γ -lactam peptidic natural products and their therapeutic applications.

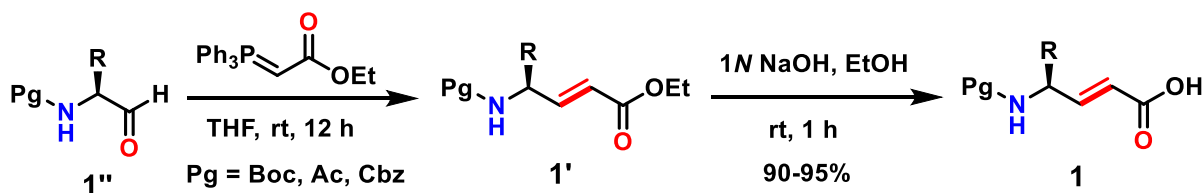
The diverse range of biological activities and widespread occurrence of α,β -unsaturated γ -lactams,^{1,12-17} have piqued the interest of synthetic chemists to explore viable methods for their synthesis. In literature various methods have been reported for the synthesis of this moiety,¹⁸ moreover α,β -unsaturated γ -lactams synthesis can be divided into five intramolecular cyclizations. (i) Michael addition type reaction and Aldol type condensation,^{19,20} (ii) Metathesis and Wittig type reactions,²¹ (iii) Seleno- and cyano-amidation reaction,²² (iv) intramolecular condensation reaction,²³ and (v) radical cyclization and metal-salt catalyzed cyclocondensation reactions.^{24,25}

3A.2 Aim and Rationale of the Present Work

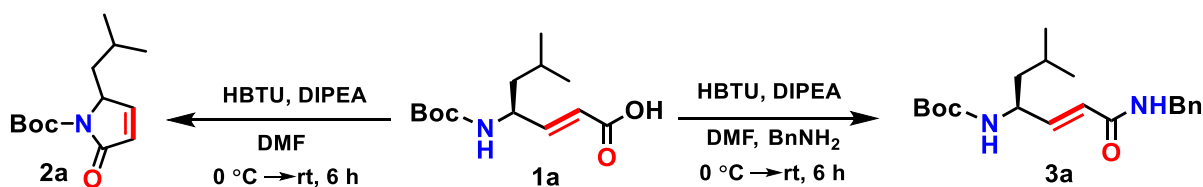
In the previous chapter, we have shown the spontaneous lactamization of active esters of α,β -unsaturated γ -amino acids in the presence of a weak base through *trans-cis* isomerization of carbon-carbon double bonds.¹⁰ In continuation, to check the effect of *in-situ* activation on cyclization we thoroughly investigate the substrate scope, reaction conditions and reaction mechanism of cyclization of α,β -unsaturated γ -amino acids using HBTU and DIPEA. In this chapter, we are reporting the intramolecular cyclization of *N*-protected-(*E*)- α,β -unsaturated γ -amino acids to corresponding *N*-protected- α,β -unsaturated γ -lactams in the presence of HBTU and DIPEA.

3A.3 Results and Discussion

As the *E*-vinylogous active esters can be transformed into α,β -unsaturated γ -lactams, we speculated the *N*-protected *E*- α,β -unsaturated γ -amino acids can be transformed into corresponding α,β -unsaturated γ -lactams through *in-situ* carboxylic acid activation using the coupling reagent HBTU and DIPEA. In order to understand the possibility of *in-situ* cyclization of *N*-protected *E*- α,β -unsaturated γ -amino acids, they were synthesized using the Wittig reaction followed by base-mediated ester hydrolysis. The pictorial representation of the reaction is shown in Scheme 2. All *N*-protected *E*- α,β -unsaturated γ -amino acids, **1a-1i**, were isolated in very good yield. To begin with, we subjected Boc-NH-(*E*)-d^{2,3} γ Leu-OH **1a** for the *in-situ* activation followed by cyclization using HBTU in the presence and absence of free amine. The pictorial representation of the reaction is depicted in Scheme 3. In the presence of 1.1 equivalent of benzylamine using coupling reagent HBTU which is known for *in-situ* activation of free carboxylic acids in the presence of DIPEA,¹¹ we isolated coupled product **3a** in excellent yield. Surprisingly, when **1a** was reacted under similar reaction conditions but in the absence of free amine (benzylamine) we got an entirely unexpected cyclized product **2a** which was confirmed through various spectroscopic analyses.



Scheme 2. The strategy used to synthesize *N*-protected α,β -unsaturated γ -amino acid (**1**).



Scheme 3. Strategies used to synthesize α,β -unsaturated γ -lactam **2a** and α,β -unsaturated γ -amino amide **3a**.

Further, to understand whether or not γ -lactams can be synthesized under identical conditions using the coupling agent EDC.HCl we subjected **1a** for lactamization. The reaction of **1a** with EDC.HCl also gave the lactam **2a**, however with lower yields. To understand the compatibility

of the solvents to the lactamization reaction, we studied the conversion of **1a** to **2a** using HBTU and DIPEA in THF, EtOAc, DCM and DMF. Out of all these solvents, we obtained good yields and purity of the α,β -unsaturated γ -lactams in dry DMF and dry DIPEA. We observed poor yields in other solvents. To understand the necessity of HBTU and DIPEA, two control reactions were performed using **1a** without HBTU as well as DIPEA. No products were observed in the absence of either DIPEA or HBTU. As in the peptide coupling reactions, both reagents were found to be crucial for the lactamization of *N*-protected- α,β -unsaturated γ -amino acids. After identifying the suitable conditions for the lactamization of **1a**, we subjected the *N*-protected *E*- α,β -unsaturated γ -amino acids **1b–1i** for the lactamization reaction using HBTU and DIPEA in DMF solvents to understand the compatibility of the reaction with Boc-, Cbz- and Ac-protecting groups. All the observed parameters of *N*-protected *E*- α,β -unsaturated γ -amino acids cyclization are tabulated in Table 1.

Table 1: Screening of different reaction conditions for synthesis of α,β -unsaturated γ -lactam **2a from **1a**.**

Entry	Solvent	Coupling Reagent	Base (eq.)	% Yield ^a
1	DMF	None	DIPEA (3)	0
2	DMF	EDC.HCl	DIPEA (3)	30
3	DMF	HBTU	DIPEA (1)	18
4	DMF	HBTU	DIPEA (3)	87
5	EtOAc	HBTU	DIPEA (3)	39
6	THF	HBTU	DIPEA (3)	35
7	DCM	HBTU	DIPEA (3)	25

Note: *a* = isolated yields, conc. = 0.1M, time = 6 h.

To evaluate the substrate scope *N*-protected-(*E*)- α,β -unsaturated γ -amino acids were transformed into corresponding α,β -unsaturated γ -lactams through *in-situ* activation of carboxylic acid, we synthesized a series of *N*-protected-(*E*)- α,β -unsaturated γ -amino acids with different amino acid side-chains starting from corresponding *N*-protected- α -amino aldehydes using the Wittig reaction as reported earlier.²⁶ The reaction mixture was stirred under an inert atmosphere for about 6 h. Remarkably, all the α,β -unsaturated γ -amino acids (**1a–1i**) were almost completely transformed into corresponding α,β -unsaturated γ -lactam (**2a–2i**), in very good yield. The pictorial representation of the reaction is depicted in Table 2. The α,β -unsaturated γ -lactam **2c** was crystallized, and their X-ray diffracted structures are shown in Figure 2.

Table 2: Synthesis of α,β -unsaturated γ -lactams (2a-2i) from corresponding *N*-protected-*E*- α,β -unsaturated γ -amino acids (1a-1i).

$\text{Pg-NH-CH(R)-CH=CH-COOH} \xrightarrow[\text{DMF, } 0^\circ\text{C} \rightarrow \text{rt, 6 h}]{\text{HBTU, DIPEA}} \text{X-N-CH(R)-CH=CH-CO}$

1 2

X = Ac/Cbz/Boc

Compound Code	α,β -unsaturated γ -amino acid (1)	α,β -unsaturated γ -lactam (2)	%Yield and Enantiomeric ratio (er)
a			69% yield (51:49 er)
b			85% yield (53:47 er)
c			72% yield (53:47 er)
d			71% yield (55:45 er)
e			82% yield (51:49 er)
f			10% yield
g			78% yield (52:48 er)
h			83% yield (51:49 er)
i			73% yield (52:48 er)

The enantiomeric ratio of the products (2a-2i) was calculated from the area of the HPLC peak, depicted in Figure 1. A chromatogram was obtained using a Chiralpak®-IC column (4.6 mm ϕ x 250 mmL) of particle size 5 μ m as a stationary phase. For the mobile phase isopropanol/n-hexane solvent system was used under isocratic elution, at a 1ml/min flow rate.

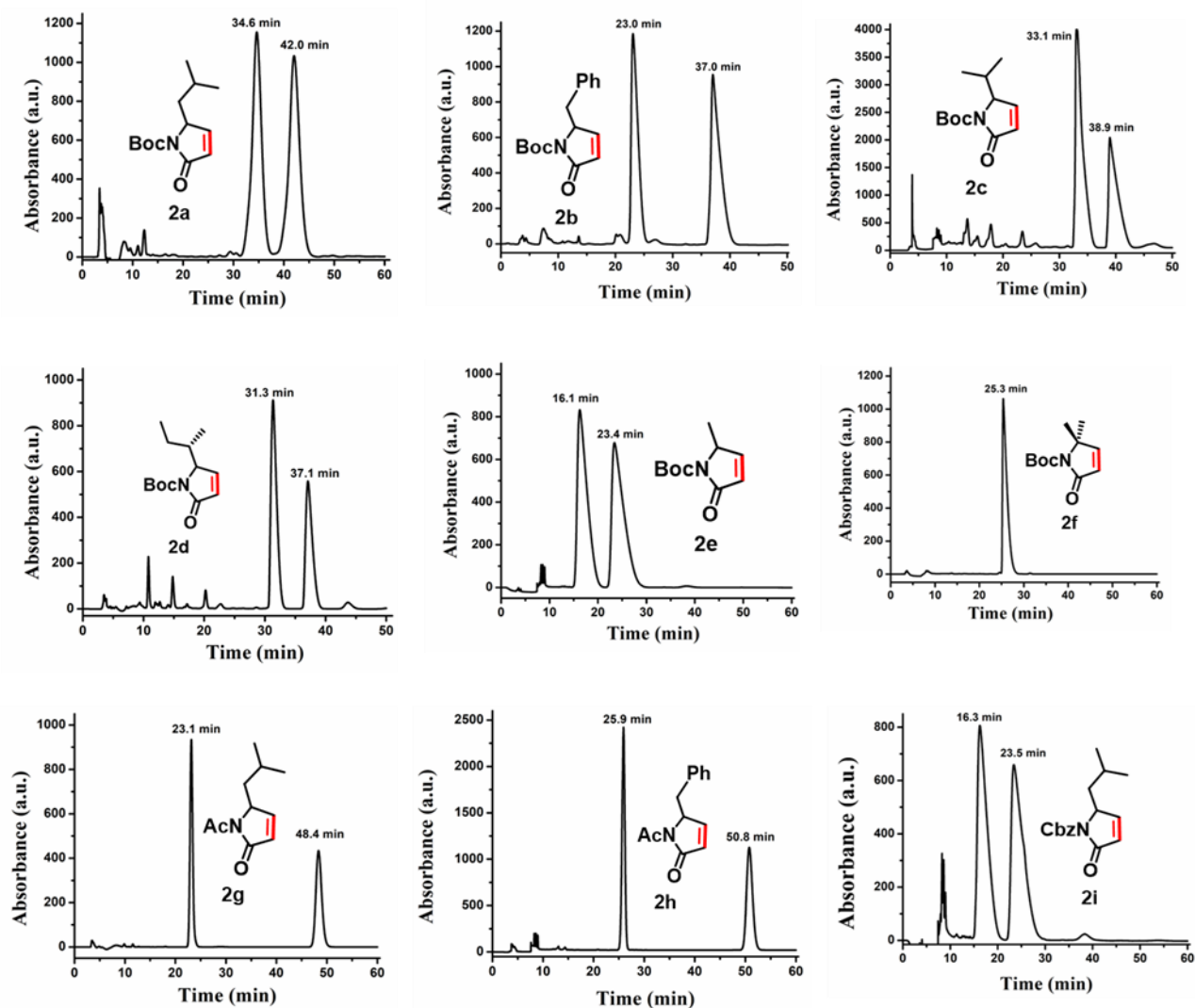
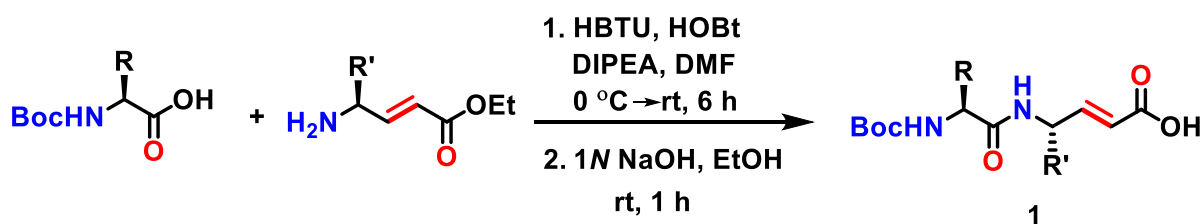


Figure 1. HPLC profiles of α,β -unsaturated γ -lactams (2a-2i).

3A.3.1 Synthesis of Dipeptide Lactams

Inspired by the transformation of *N*-protected- α,β -unsaturated γ -amino acids into corresponding *N*-protected- α,β -unsaturated γ -lactams, we sought to investigate whether α,β -unsaturated γ -lactams can be synthesized from the peptides consisting *E*- α,β -unsaturated γ -amino acids at the C-terminus. We synthesized a series of dipeptides, using solution phase peptide synthesis taking advantage of HBTU/HOBt and DIPEA followed by base hydrolysis of dipeptide esters, to obtain dipeptides **1j-1p**. The pictorial representation of the dipeptide acid synthesis from corresponding dipeptide esters is depicted in Scheme 4.



Scheme 4. Synthesis of dipeptide acids (**1j-1p**) from their corresponding dipeptide esters.

The dipeptide acid **1j** was treated with HBTU and DIPEA in DMF and the reaction mixture was stirred for about 6 h at room temperature. The peptide α,β -unsaturated γ -lactam, **2j**, was isolated in excellent yields. Similarly, all other dipeptide acids **1k-1p** with different amino acid side chains were transformed into peptide α,β -unsaturated γ -lactams **2k-2p** respectively with very good yields. These experiments suggested that similar to the α,β -unsaturated γ -amino acids, dipeptides can also be converted into the corresponding α,β -unsaturated γ -lactams using HBTU and DIPEA in DMF. The pictorial representation of the conversion of dipeptide acids (**1j-1p**) into peptide γ -lactams (**2j-2p**) is depicted in Table 3. The dipeptide α,β -unsaturated γ -lactam, **2m** and **2p** crystals obtained after slow evaporation of its solution in aqueous methanol and its single crystal structure are depicted in Figure 2.

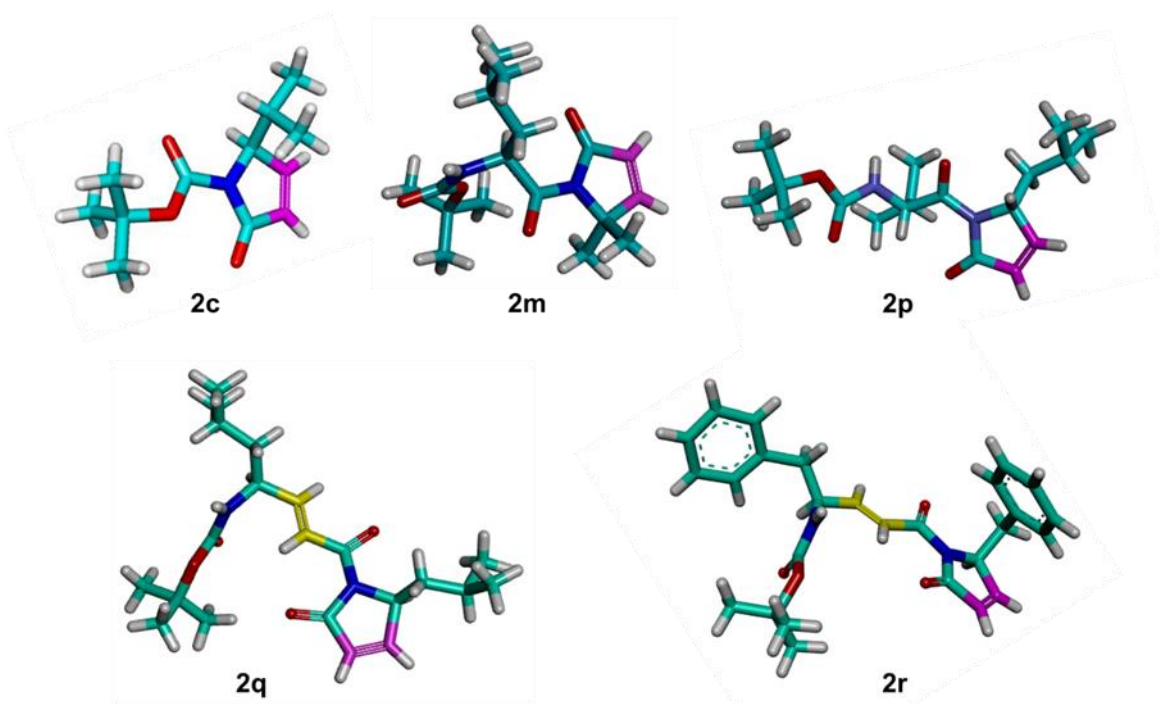


Figure 2. The X-ray diffracted structures of α,β -unsaturated γ -lactams **2c**, **2m**, **2p**, **2q** and **2r**.

Table 3: Synthesis of peptide γ -lactams (2j-2p) from corresponding dipeptide acids (1j-1p).

$\text{BocHN}-\text{CH}(\text{R})-\text{C}(=\text{O})-\text{NH}-\text{CH}(\text{R}')-\text{CH}=\text{CH}-\text{COOH} \xrightarrow[\text{DMF, } 0\text{ }^\circ\text{C} \rightarrow \text{rt, 6 h}]{\text{HBTU, DIPEA}} \text{BocHN}-\text{CH}(\text{R})-\text{C}(=\text{O})-\text{N}(\text{CH}(\text{R}')-\text{CH}=\text{CH})-\text{COOH}$

1 2

Compound Code	Dipeptide acid (1)	Peptide γ -lactam (2)	%Yield and Diastereomeric ratio (dr)
j			84% yield (53:47 dr)
k			83% yield (52:48 dr)
l			84% yield (54:46 dr)
m			78% yield (55:45 dr)
n			81% yield (55:45 dr)
o			83% yield (57:43 dr)
p			14% yield

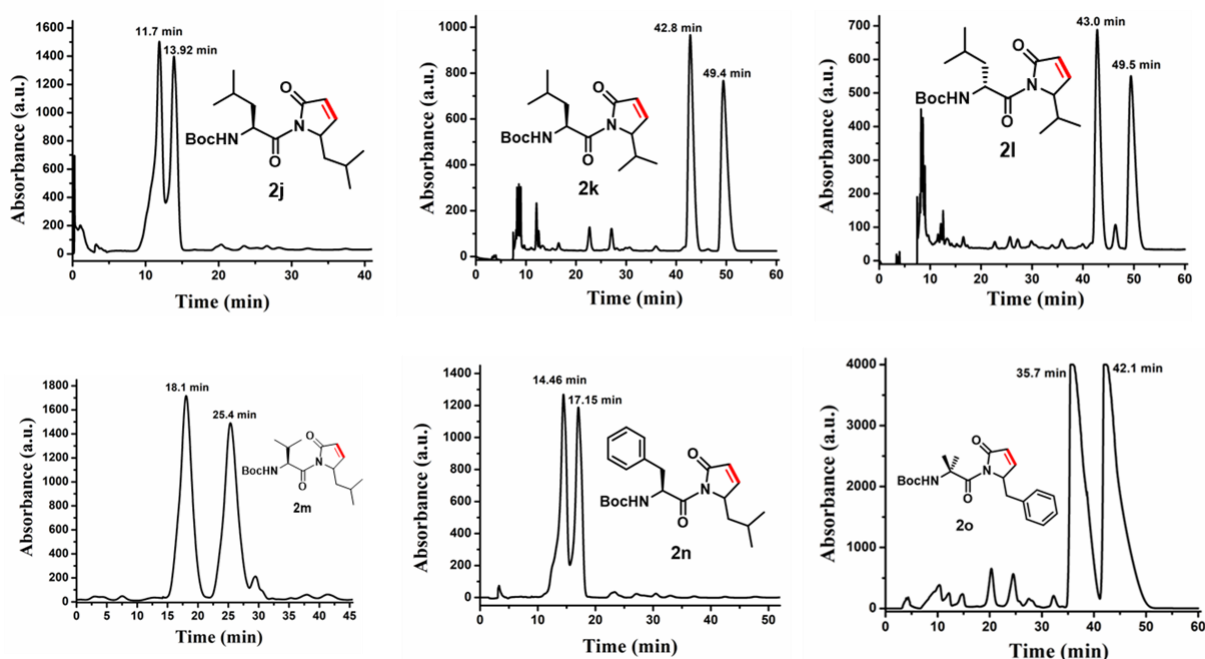


Figure 3. HPLC profiles of peptide γ -lactams (**2j-2o**).

3A.3.2 Synthesis of Dipeptide Lactams Consisting of α,β -Unsaturated γ -Amino Acids at the N-terminus.

Further, to understand the effect of α,β -unsaturated γ -lactam formation on other α,β -unsaturated γ -amino acid amides, from the dipeptides consisting of unsaturated amino acids to understand the behavior of *E*- α,β -unsaturated γ -amino amides during the α,β -unsaturated γ -lactam formation at the C-terminal residues. We synthesized the ethyl esters of dipeptides **1q** and **1r** using HBTU and HOBt-mediated coupling reactions and hydrolyzed. The free dipeptide acids **1q** and **1r** were subjected to α,β -unsaturated γ -lactam reaction mediated by the HBTU and DIPEA. The pictorial representation of the reaction is depicted in Table 4. The α,β -unsaturated γ -lactams **2q** and **2r** were isolated in excellent yields from **1q** and **1r**, respectively. Both α,β -unsaturated γ -lactams spontaneously gave a single crystal after the aqueous work-up and evaporation of the solvents. The X-ray structures are shown in Figure 2. The *E*-double bonds in the first residue remained intact during the lactamization and isomerization of the double bonds in the C-terminal residue.

Table 4: Synthesis of α,β -unsaturated γ -lactams (2q and 2r) from the dipeptides (1q and 1r) consisting of *E*- α,β -unsaturated γ -amino acids at the C-terminus.

Compound Code	Dipeptide acid (1)	Peptide γ -lactam (2)	%Yield and Diastereomeric ratio (dr)
q			80% yield (52:48 dr)
r			87% yield (52:48 dr)

The diastereomeric ratio of the products (2j–2s) was calculated from the area of the HPLC peak, depicted in Figures 3 and 4. A chromatogram was obtained using a Chiralpak®-IC column (4.6 mm ϕ x 250 mmL) of particle size 5 μ m as a stationary phase. For the mobile phase isopropanol/n-hexane solvent system was used under isocratic elution, at a 1ml/min flow rate.

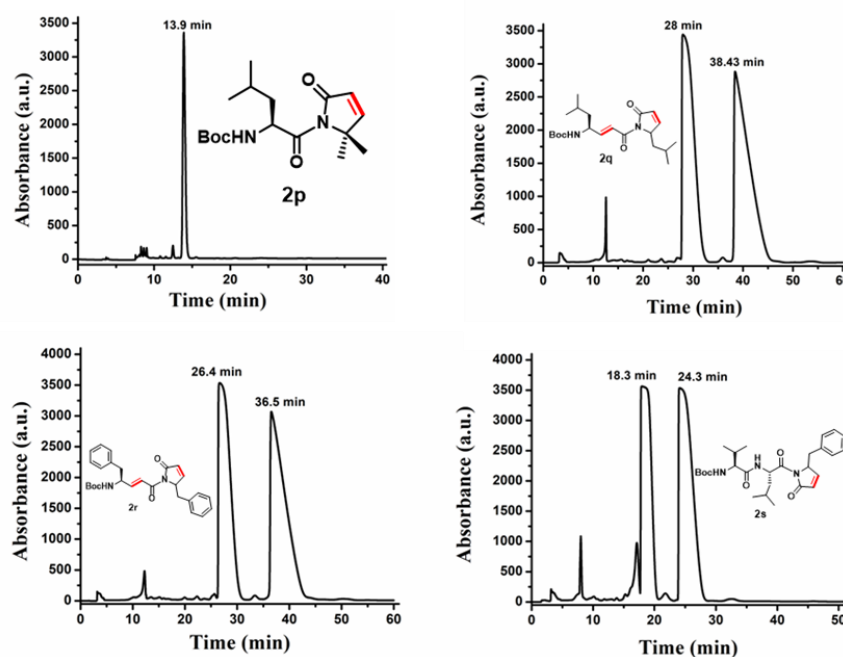
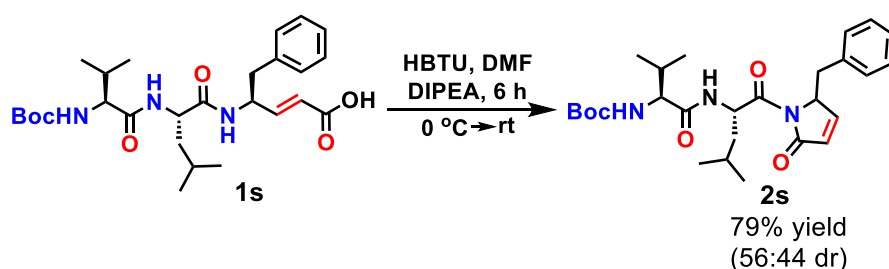


Figure 4. HPLC profiles of α,β -unsaturated γ -lactams (2p–2s).

3A.3.3 Synthesis of Tripeptide Lactams

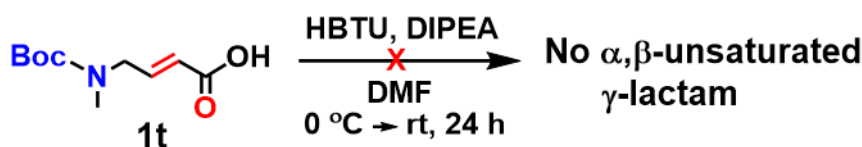
In order to understand whether or not the γ -lactams can be synthesized from tripeptide acids, we synthesized the tripeptide **1s** consisting of *E*- α,β -unsaturated γ -amino acid at C-terminus and studied the lactamization involving *trans* to *cis* isomerization of the double bond. The pictorial representation of the reaction is depicted in Scheme 5. Similar to the dipeptides, the tripeptide also readily undergoes a lactamization reaction mediated by HBTU and DIPEA. The tripeptide α,β -unsaturated γ -lactam **2s** was isolated in very good yields. These results suggested that the tripeptides consisting of C-terminal *E*-vinyllogous amino acids can be transformed into corresponding tripeptide γ -lactam without having any difficulties.



Scheme 5. Synthesis of α,β -unsaturated γ -lactam **2s** from the tripeptide **1s** consisting of *E*- α,β -unsaturated γ -amino acids at C-terminus.

3A.3.4 *Trans-Cis* Isomerization on *N*-methyl *E*-vinyllogous γ -Amino Acid

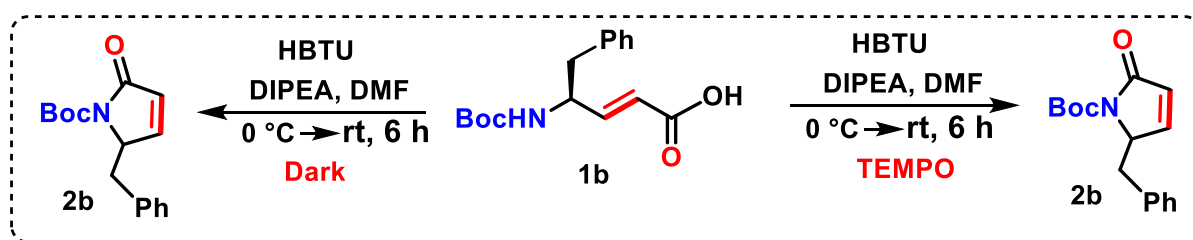
To understand whether or not the *N*-methyl *E*-vinyllogous γ -amino acids can undergo cyclization as well as to understand the possibilities of *E* $\rightarrow$ *Z* isomerization of the carbon-carbon double bonds we synthesized Boc-*N*(Me)-*E*- α,β -unsaturated γ -amino acid (**1t**) starting from *N*-Boc-sarcosine. Further to investigate whether it is possible to obtain *E* $\rightarrow$ *Z* isomerization of carbon-carbon double bonds instead of the α,β -unsaturated γ -lactam, we treated **1t** with HBTU and DIPEA and stirred the reaction mixture for about 24 h at room temperature. Interestingly, even after stirring the reaction mixture for 24 h, we did not observe any *E* $\rightarrow$ *Z* isomerization in **1t**, shown in Scheme 6. These results suggested that γ -amide NH plays a crucial role in the lactamization as well as *E* $\rightarrow$ *Z* isomerization of *N*-Boc- α,β -unsaturated γ -amino acids.



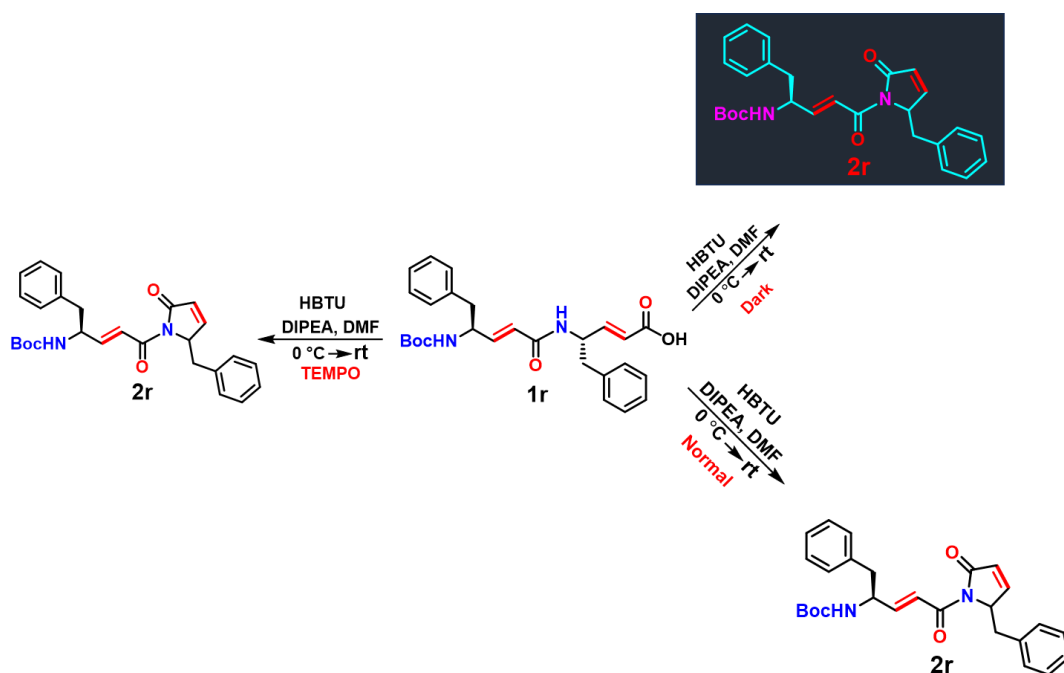
Scheme 6. The reaction of *N*-Me- α,β -unsaturated γ -amino acid (**1t**) with coupling reagents.

3A.3.5 Investigation of the Role of Radicals in the Cyclization Reaction

Further, to understand the formation of radicals during the reaction and its role in the cyclization, we did two control experiments, in the first experiment we treated **1b** and **1r** with HBTU and DIPEA under dark conditions, and in the second experiment, we treated **1b** and **1r** with HBTU and DIPEA in the presence of TEMPO, the pictorial representation is depicted in Scheme 7 and 8. In both cases reaction outcome was similar, which eliminates the formation of radicals during the reaction. Other than the TEMPO or dark condition the reaction follows the same optimized protocol mentioned in Table 1.



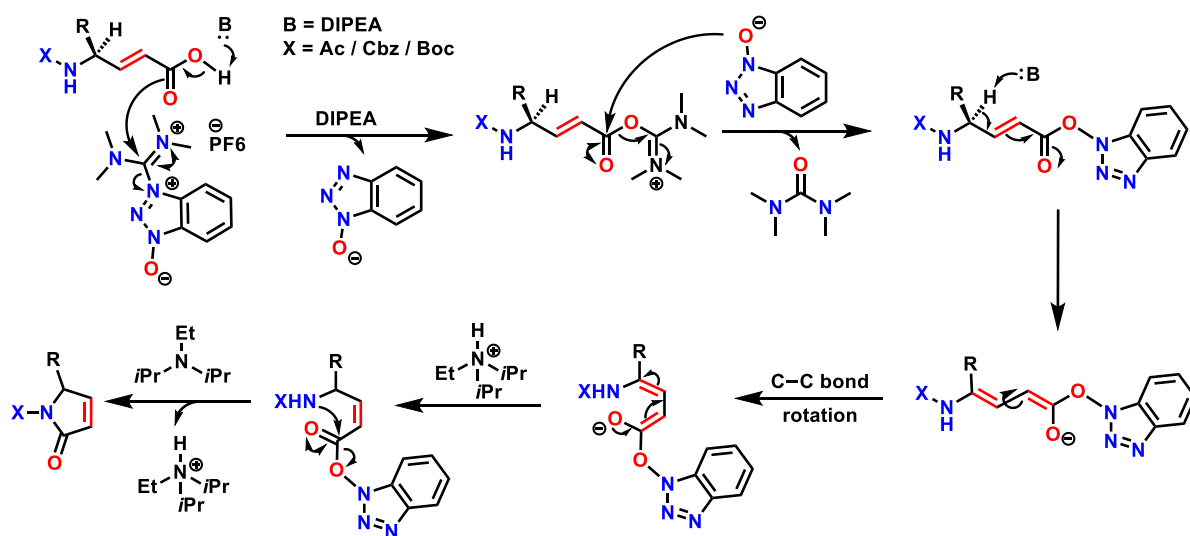
Scheme 7. Cyclization of BocNH-d $\gamma^{2,3}$ Phe-OH (**1b**) in different reaction conditions.



Scheme 8. Cyclization of dipeptide (**1r**) under different reaction conditions.

3A.4 Possible Reaction Mechanisms of the Cyclization.

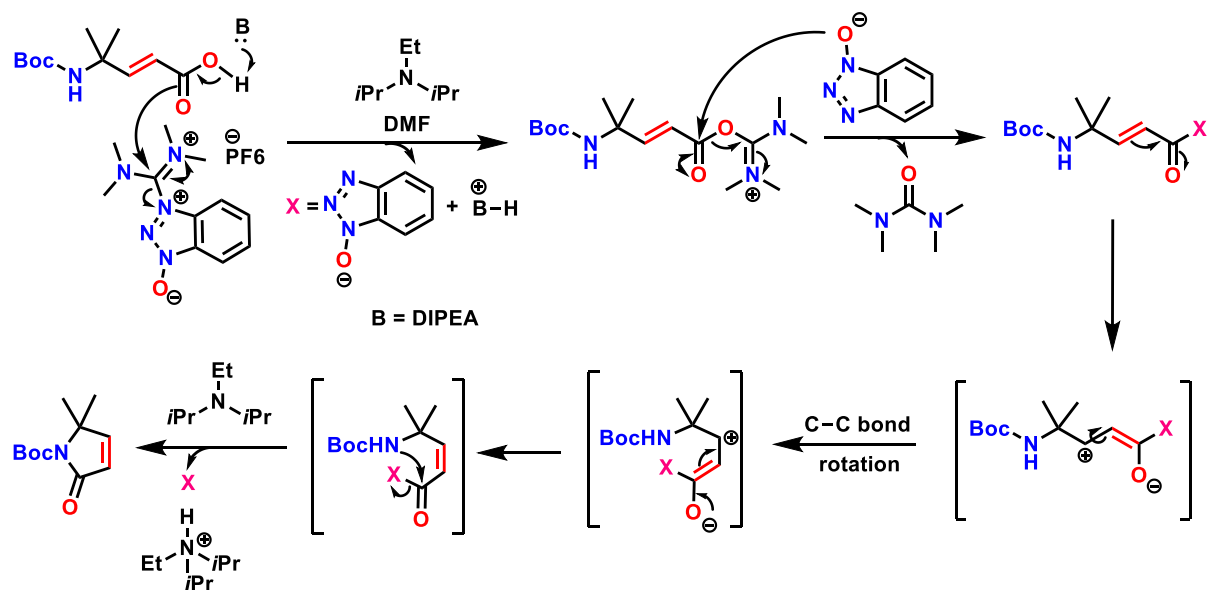
Even though the reaction conditions are very mild, we sought to investigate the chiral integrity of the products using chiral HPLC analysis. Similar to the pentafluorophenyl esters, the lactamization gave a racemic mixture of the α,β -unsaturated γ -lactams. Nevertheless, this procedure also provides an opportunity to acquire both stereoisomers of the α,β -unsaturated γ -lactams through chiral separation. Based on the experimental evidence, we propose the mechanism for lactamization of the *N*-protected α,β -unsaturated γ -amino acids as shown in Scheme 9.



Scheme 9. The possible reaction mechanism for the *N*-protected α,β -unsaturated γ -amino acids cyclization.

After confirming the importance of amide NH for the α,β -unsaturated γ -lactam formation, we turned our attention to understand the importance of the γ -CH in the lactamization. We speculated that if we replace γ -CH with γ -alkyl group, we may not get the α,β -unsaturated γ -lactam. To understand the role of γ -CH, we synthesized *N*-Boc-protected γ,γ -dimethyl α,β -unsaturated γ -amino acid, **1f**, and dipeptide acid **1p** consisting of *E*- α,β -unsaturated γ,γ -dimethyl substituted γ -amino acid. Both **1f** and **1p** were treated with HBTU and DIPEA in DMF. The pictorial representation of the reaction is depicted in Tables 2 and 3. Indeed, we isolated α,β -unsaturated γ -lactam products **2f** and **2p** from **1f** and **1p** respectively, however, with very low yields. The transformation of γ,γ -dimethyl α,β -unsaturated γ -amino acids into corresponding α,β -unsaturated γ -lactams indicates that γ -CH is important but not necessary for

lactamization. Based on these experimental evidences, we propose that *E*- α,β -unsaturated 4,4-disubstituted amino acids adopt different mechanisms depicted in Scheme 10.



Scheme 10. The possible reaction mechanism for the *E*- α,β -unsaturated-4,4-dimethyl substituted γ -amino acid cyclization.

3A.5 Conclusion

In conclusion, we have demonstrated a facile synthesis of α,β -unsaturated γ -lactams from *E*- α,β -unsaturated γ -amino acids through *in-situ* carboxylic acid activation using the coupling agent HBTU and base DIPEA. The reaction is compatible with Ac-, Boc-, and Cbz- N-protecting groups and various amino acid side-chains except for proline. This reaction is also compatible with peptides consisting of C-terminal α,β -unsaturated γ -amino acids. In the presence of a primary free amine coupling partner, the reaction gives only a peptide. In the absence of free amine, we observed a complete transformation of α,β -unsaturated γ -amino acids into α,β -unsaturated γ -lactams. Both γ -CH and amide NH are crucial for the smooth transformation into lactams. No α,β -unsaturated γ -lactams or *E*→*Z* isomerized double bond was observed in the case of *N*-protected *N*-Me-*E*- α,β -unsaturated γ -amino acids. The *E*- α,β -unsaturated γ,γ -dialkyl γ -amino acids can also be transformed into α,β -unsaturated γ -lactam, however with low yields. The α,β -unsaturated γ -amino acids with γ -CH follows different cyclization path. All amino acids with γ -CH gave a racemic mixture of α,β -unsaturated γ -lactams, which can be separated under a chiral environment. Overall, *E*- α,β -unsaturated γ -

amino acids can be transformed into α,β -unsaturated γ -lactams by *in-situ* activation of free carboxylic acids, involving *trans* to *cis* isomerization of double bonds.

3A.6 Experimental Section

General Information

All the chemical reagents, amino acids and solvents used for the synthesis were obtained from commercial suppliers and were used as received. The reaction progression was monitored by thin layer chromatography (TLC) using silica gel 60 F₂₅₄ precoated aluminum sheets and visualized by a 254 nm UV lamp, KMnO₄ and ninhydrin staining. All crude products passed through column chromatography for final purification using silica gel (60-120 and 100-200 mesh) and ethyl acetate/hexane as an eluent in increasing polarity. ¹H NMR and ¹³C NMR spectra were recorded on a Bruker Advance 400 MHz NMR spectrometer. The chemical shifts (δ) and coupling constants (*J*) of newly synthesized compounds were reported in ppm and Hz respectively. The abbreviations used for the multiplicity in ¹H NMR are singlet (s), broad singlet (bs), doublet (d), doublet of doublet (dd), doublet of doublet of doublet (ddd), triplet (t), quartet of doublet (qd), triplet of doublet (td), doublet of triplet (dt), quintet (qn) and multiplet (m). Mass samples were analyzed by high-resolution mass spectrometry (HRMS) technique using electrospray ionization (ESI) time-of-flight (TOF). The SC-XRD data of compounds was on collected Bruker APEX(II) DUO CCD diffractometer instrument at low temperature (100K and 150K) using the X-ray sources of Mo K α (λ = 0.71073 Å) and Cu K α (λ = 1.54178 Å) radiations. The *E*- α,β -unsaturated γ -amino acids (Boc/Ac/Cbz-(*E*)-d^{2,3} γ Xaa-OH) and dipeptides containing *E*- α,β -unsaturated γ -amino acids at C-terminal Boc-Xxx-(*E*)-d^{2,3} γ X'aa-OH and tripeptide Boc-Val-Leu-(*E*)-d^{2,3} γ -Phe-OH were prepared using the literature procedure.^{26,27}

3A.6.1 General Procedure for the Synthesis of *N*-protected (*E*)- α,β -unsaturated γ -amino acids (1a-1i)

Boc/Ac/Cbz-HN-d^{2,3} γ Xxx-OEt (3 mmol) was mixed with 25 mL of EtOH in a 100 mL round bottom (RB) flask, and to this solution, 1*N* NaOH was added, the reaction progression was monitored by TLC, the reaction was almost completed in 30 min at room temperature. Once the reaction was done, EtOH was evaporated using a rotary

evaporator, the resultant reaction mixture was acidified with 10% HCl to maintain the pH of the solution around 3-4 using pH paper, extracted three times with EtOAc (3 x 50 mL), and washed with brine solution (2 x 80 mL). The ethyl acetate layer was dried with anhydrous Na₂SO₄ and solvent was evaporated under reduced pressure. The products (**1a-1i**) obtained were used for synthesis without further purification.

(S,E)-4-((tert-butoxycarbonyl)amino)-6-methylhept-2-enoic acid (1a) Colorless solid, yield = 0.701 g (91%); **m.p.** 95-97 °C; [α]_D²⁵ = -22.0 (c 0.1, MeOH); ¹H NMR (400 MHz, Chloroform-*d*) δ 6.92 (d, *J* = 16.9 Hz, 1H), 5.91 (d, *J* = 15.5 Hz, 1H), 4.51 (s, 1H), 4.36 (s, 1H), 1.69 (sept, *J* = 6.8 Hz, 1H), 1.44 (s, 9H), 1.40 (d, *J* = 7.8 Hz, 2H), 0.93 (d, *J* = 6.8 Hz, 7H); ¹³C NMR (101 MHz, Chloroform-*d*) δ 171.27, 155.24, 151.44, 119.98, 80.00, 49.98, 43.79, 28.47, 24.87, 22.85, 22.27; HRMS (ESI-TOF) *m/z*: [M + Na]⁺ calculated for C₁₃H₂₃NO₄Na, 280.1524 found, 280.1528.

(S,E)-4-((tert-butoxycarbonyl)amino)-5-phenylpent-2-enoic acid (1b) White solid, yield = 0.811 g (93%); **m.p.** 149–152 °C; [α]_D²⁵ = -4.0 (c 0.1, MeOH); ¹H NMR (400 MHz, Chloroform-*d*) δ 7.33 – 7.29 (m, 2H), 7.26 – 7.22 (m, 1H), 7.18 – 7.15 (m, 2H), 7.00 (dd, *J* = 15.6, 4.9 Hz, 1H), 5.86 (d, *J* = 15.6 Hz, 1H), 4.65 (s, 1H), 4.56 (s, 1H), 2.90 (d, *J* = 6.6 Hz, 2H), 1.40 (s, 9H); ¹³C NMR (101 MHz, Chloroform-*d*) δ 170.63, 155.15, 150.23, 136.35, 129.53, 128.79, 127.10, 120.52, 80.20, 52.47, 40.89, 28.42; HRMS (ESI-TOF) *m/z*: [M + Na]⁺ calculated for C₁₆H₂₁NO₄Na, 314.1368 found, 314.1375.

(S,E)-4-((tert-butoxycarbonyl)amino)-5-methylhex-2-enoic acid (1c) Colorless solid, yield = 0.692 g (95%); **m.p.** 96-98 °C; [α]_D²⁵ = -8.0 (c 0.1, MeOH); ¹H NMR (400 MHz, Chloroform-*d*) δ 6.97 (dd, *J* = 15.6, 4.7 Hz, 1H), 5.93 (dd, *J* = 15.6, 1.7 Hz, 1H), 4.60 (d, *J* = 9.3 Hz, 1H), 4.22 (s, 1H), 1.88 (q, *J* = 6.5 Hz, 1H), 1.45 (s, 9H), 0.93 (dd, *J* = 11.2, 6.8 Hz, 6H); ¹³C {¹H} NMR (101 MHz, Chloroform-*d*) δ 171.07, 155.51, 150.10, 120.97, 80.02, 56.81, 32.35, 28.48, 19.00, 18.14; HRMS (ESI-TOF) *m/z*: [M + Na]⁺ calculated for C₁₂H₂₁NO₄Na, 266.1368 found, 266.1374.

(4S,5S,E)-4-((tert-butoxycarbonyl)amino)-5-methyl hept-2-enoic acid (1d) White solid, yield = 0.786 g (92%); **m.p.** 102-104 °C; [α]_D²⁵ = -20.0 (c 0.1, MeOH); ¹H NMR (400 MHz, Chloroform-*d*) δ 6.96 (dd, *J* = 15.7, 5.2 Hz, 1H), 5.93 (dd, *J* = 15.7, 1.7 Hz, 1H), 4.63 (d, *J* = 9.2 Hz, 1H), 4.31 (s, 1H), 1.67 – 1.60 (m, 1H), 1.44 (s, 9H), 1.44 – 1.39

(m, 1H), 1.19 – 1.10 (m, 1H), 0.95 – 0.87 (m, 6H); $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, Chloroform-*d*) δ 171.18, 155.42, 149.81, 121.11, 80.00, 55.86, 39.11, 28.48, 25.43, 15.44, 11.79. HRMS (ESI-TOF) m/z : $[\text{M} + \text{Na}]^+$ calculated for $\text{C}_{13}\text{H}_{23}\text{NO}_4\text{Na}$, 280.1524 found, 280.1526.

(*S,E*)-4-((*tert*-butoxycarbonyl)amino)pent-2-enoic acid (1e) Colorless solid, yield = 0.580 g (90%); **m.p.** 94-96 °C; $[\alpha]_{\text{D}}^{25} = -44.0$ (*c* 0.1, MeOH); ^1H NMR (400 MHz, Chloroform-*d*) δ 6.95 (dd, $J = 15.6, 4.5$ Hz, 1H), 5.89 (dd, $J = 15.6, 1.7$ Hz, 1H), 4.61 (s, 1H), 4.42 (s, 1H), 1.44 (s, 9H), 1.27 (d, $J = 7.0$ Hz, 3H). $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, Chloroform-*d*) δ 171.22, 155.09, 151.85, 119.73, 80.08, 47.17, 28.47, 20.27; HRMS (ESI-TOF) m/z : $[\text{M} + \text{Na}]^+$ calculated for $\text{C}_{10}\text{H}_{17}\text{NO}_4\text{Na}$, 238.1055 found, 238.1059.

(*E*)-4-((*tert*-butoxycarbonyl)amino)-4-methylpent-2-enoic acid (1f) Colorless solid, yield = 0.645 g (94%); **m.p.** 126-129 °C; $[\alpha]_{\text{D}}^{25} = 0$ (*c* 0.1, MeOH); ^1H NMR (400 MHz, Chloroform-*d*) δ 7.09 (d, $J = 15.9$ Hz, 1H), 5.83 (d, $J = 15.9$ Hz, 1H), 4.71 (s, 1H), 1.42 (s, 9H), 1.41 (s, 6H); $^{13}\text{C}\{^1\text{H}\}$ NMR (151 MHz, Chloroform-*d*) δ 171.66, 155.93, 154.27, 118.13, 79.72, 53.11, 28.48, 27.44; HRMS (ESI-TOF) m/z : $[\text{M} + \text{Na}]^+$ calculated for $\text{C}_{11}\text{H}_{19}\text{NO}_4\text{Na}$, 252.1211 found, 252.1217.

(*S,E*)-4-acetamido-6-methylhept-2-enoic acid (1g) Oily liquid, yield = 0.567 g (95%); $[\alpha]_{\text{D}}^{25} = -62.0$ (*c* 0.1, MeOH); ^1H NMR (400 MHz, Chloroform-*d*) δ 6.90 (dd, $J = 15.7, 5.5$ Hz, 1H), 5.89 (dd, $J = 15.7, 1.5$ Hz, 1H), 5.65 (d, $J = 8.6$ Hz, 1H), 4.70 (p, $J = 8.1, 7.5$ Hz, 1H), 2.03 (s, 3H), 1.66 (dp, $J = 13.5, 6.8$ Hz, 1H), 1.43 (t, $J = 7.5$ Hz, 2H), 0.93 (dd, $J = 6.6, 2.8$ Hz, 6H); $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, Chloroform-*d*) δ 170.61, 170.18, 150.36, 120.33, 48.67, 43.41, 24.94, 23.35, 22.84, 22.26; HRMS (ESI-TOF) m/z : $[\text{M} + \text{H}]^+$ calculated for $\text{C}_{10}\text{H}_{18}\text{NO}_3$, 200.1286 found 200.1287.

(*S,E*)-4-acetamido-5-phenylpent-2-enoic acid (1h) White solid, yield = 0.629 g (90%); **m.p.** 133–136 °C; $[\alpha]_{\text{D}}^{25} = -8.0$ (*c* 0.1, MeOH); ^1H NMR (400 MHz, Chloroform-*d*) δ 7.35 – 7.29 (m, 2H), 7.28 – 7.23 (m, 1H), 7.20 – 7.14 (m, 2H), 7.00 (dd, $J = 15.7, 5.1$ Hz, 1H), 5.82 (dd, $J = 15.7, 1.8$ Hz, 1H), 5.47 (d, $J = 8.5$ Hz, 1H), 5.05 – 4.96 (m, 1H), 2.94 (dd, $J = 6.8, 3.6$ Hz, 2H), 1.97 (s, 3H); $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, Chloroform-*d*) δ 170.19, 169.85, 149.40, 128.91, 127.30, 120.81, 50.91, 40.31, 23.37; HRMS (ESI-TOF) m/z : $[\text{M} + \text{H}]^+$ calculated for $\text{C}_{13}\text{H}_{16}\text{NO}_3$, 234.1130 found, 234.1132.

(*S,E*)-4-(((benzyloxy)carbonyl)amino)-6-methylhept-2-enoic acid (1i) Oily liquid, yield = 0.530 g (93%); $[\alpha]_D^{25} = -42.0$ (c 0.1, MeOH); ^1H NMR (400 MHz, Chloroform- d) δ 7.38 – 7.32 (m, 5H), 6.94 (dd, $J = 15.6, 5.5$ Hz, 1H), 5.94 (d, $J = 15.6$ Hz, 1H), 5.13 (d, $J = 13.3$ Hz, 2H), 4.85 (d, $J = 8.3$ Hz, 1H), 4.44 (t, $J = 7.2$ Hz, 1H), 1.69 (dp, $J = 13.5, 6.7$ Hz, 1H), 1.42 (t, $J = 7.2$ Hz, 2H), 0.98 – 0.90 (m, 6H); $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, Chloroform- d) δ 171.20, 155.91, 150.91, 136.23, 128.70, 128.41, 128.28, 120.21, 67.25, 50.55, 43.60, 24.81, 22.80, 22.19; HRMS (ESI-TOF) m/z : $[\text{M} + \text{H}]^+$ calculated for $\text{C}_{16}\text{H}_{21}\text{NO}_4\text{Na}$, 314.1368 found 314.1367.

3A.6.2 General procedure of peptides (1j-1p) synthesis

For the synthesis of dipeptide (BocHN-Xxx- $\text{d}^{2,3}\gamma\text{X'xx-OEt}$), first BocHN- $\text{d}^{2,3}\gamma\text{X'xx-OEt}$ (2 mmol) was treated with a 1:1 (v/v) mixture of DCM/TFA (10 mL) in a 25 mL RB at room temperature for 1 hour. Reaction progress was visualized by TLC, after the complete conversion of the starting material, the excess reagent and solvent were evaporated under reduced pressure. To remove the excess amount of TFA, the mixture was co-evaporated with DCM five times. The obtained TFA. $\text{H}_2\text{N-d}^{2,3}\gamma\text{X'xx-OEt}$ salt was further utilized for the coupling. In another 25 mL RB, the BocHN-Xxx-OH (2 mmol), HBTU (2 mmol) and HOBT (2 mmol) were dissolved in 8 to 10 mL of DMF. To this solution, DIPEA (6 mmol) was added and subsequently, the reaction mixture was allowed to react for 5 min at ice-cooled temperature, to this solution, TFA. $\text{H}_2\text{N-d}^{2,3}\gamma\text{X'xx-OEt}$ (2 mmol) is added. The reaction mixture was allowed to be at room temperature for 6 to 8 hours. After full consumption of starting materials (monitored by TLC), workup was done by diluting the reaction mixture with ethyl acetate (150 mL), followed by successive washings with 10% HCl (3×70 mL), 10% Na_2CO_3 (3×70 mL) and finally with brine solution (2×70 mL). The ethyl acetate layer was dried with anhydrous Na_2SO_4 and the solvent evaporated under reduced pressure. The obtained crude compounds were passed through a silica gel (60-120 mesh) column using ethyl acetate/hexane as eluent in increasing polarity. Hydrolysis of dipeptides was done similarly to that of monomers, the complete procedure is described above in section 3A.6.1.

(S,E)-4-((S)-2-((tert-butoxycarbonyl)amino)-4-methyl pentanamido)-6-methylhept-2-enoic acid (1j) White solid, yield = 0.965 g (87%); **m.p.** 130-135 °C; $[\alpha]_{\text{D}}^{25} = -34.0$ (*c* 0.1, MeOH); ^1H NMR (400 MHz, Chloroform-*d*) δ 6.92 (dd, *J* = 15.7, 5.5 Hz, 1H), 6.56 (s, 1H), 5.91 (dd, *J* = 15.7, 1.6 Hz, 1H), 5.02 (s, 1H), 4.69 (m, 1H), 4.08 (m, 1H), 1.74 – 1.57 (m, 3H), 1.52 – 1.47 (m, 1H), 1.44 (s, 9H), 1.43 – 1.36 (m, 2H), 0.99 – 0.87 (m, 12H); $^{13}\text{C}\{^1\text{H}\}$ NMR (151 MHz, Chloroform-*d*) δ 172.33, 170.00, 156.28, 150.34, 120.22, 80.66, 53.19, 48.42, 43.49, 40.50, 28.39, 24.87, 24.81, 22.98, 22.91, 22.29, 22.10; HRMS (ESI-TOF) *m/z*: $[\text{M} + \text{Na}]^+$ calculated for $\text{C}_{19}\text{H}_{34}\text{N}_2\text{O}_5\text{Na}$, 393.2365 found, 393.2368.

(S,E)-4-((S)-2-((tert-butoxycarbonyl)amino)-4-methyl pentanamid o)-5-methylhex-2-enoic acid (1k) White solid, yield = 0.961 g (90%); **m.p.** 123-126 °C; $[\alpha]_{\text{D}}^{25} = -36.0$ (*c* 0.1, MeOH); ^1H NMR (400 MHz, Chloroform-*d*) δ 6.96 (dd, *J* = 15.7, 5.7 Hz, 1H), 6.87 (d, *J* = 6.8 Hz, 1H), 5.93 (d, *J* = 15.7 Hz, 1H), 5.12 (s, 1H), 4.54 (m, 1H), 4.19 (m, 1H), 1.91 (h, *J* = 6.6 Hz, 1H), 1.76 – 1.60 (m, 2H), 1.56 – 1.49 (m, 1H), 1.44 (s, 9H), 1.01 – 0.78 (m, 12H); $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, Chloroform-*d*) δ 172.72, 169.85, 156.41, 148.68, 121.48, 80.70, 55.32, 53.26, 40.33, 32.34, 28.41, 24.93, 24.87, 22.87, 22.30, 18.93, 18.10, 18.00; HRMS (ESI-TOF) *m/z*: $[\text{M} + \text{Na}]^+$ calculated for $\text{C}_{18}\text{H}_{32}\text{N}_2\text{O}_5\text{Na}$, 379.2208 found, 379.2210.

(S,E)-4-((R)-2-((tert-butoxycarbonyl)amino)-4-methyl pentanamido)-5-methylhex-2-enoic acid (1l) White solid, yield = 0.993 g (93%); **m.p.** 118-122 °C; $[\alpha]_{\text{D}}^{25} = 28.0$ (*c* 0.1, MeOH); ^1H NMR (400 MHz, Chloroform-*d*) δ 6.96 (dd, *J* = 15.6, 5.7 Hz, 1H), 6.81 (d, *J* = 9.0 Hz, 1H), 5.93 (d, *J* = 15.6 Hz, 1H), 5.04 (d, *J* = 7.5 Hz, 1H), 4.57 – 4.49 (m, 1H), 4.16 (d, *J* = 7.0 Hz, 1H), 1.92 (m, 1H), 1.68 (m, 2H), 1.54 – 1.48 (m, 1H), 1.44 (s, 9H), 0.93 (ddd, *J* = 13.5, 6.8, 4.6 Hz, 12H); $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, Chloroform-*d*) δ 172.77, 169.74, 156.39, 148.57, 121.51, 80.60, 55.27, 53.23, 40.98, 40.41, 32.34, 28.39, 24.90, 24.84, 22.81, 22.30, 18.95, 18.91, 18.07, 17.99; HRMS (ESI-TOF) *m/z*: $[\text{M} + \text{Na}]^+$ calculated for $\text{C}_{18}\text{H}_{32}\text{N}_2\text{O}_5\text{Na}$, 379.2208 found, 379.2212.

(R,E)-4-((S)-2-((tert-butoxycarbonyl)amino)-3-methyl butanamido)-6-methylhept-2-enoic acid (1m) White solid, yield = 1.004 g (94%); **m.p.** 88-91 °C; $[\alpha]_{\text{D}}^{25} = 2.0$ (*c* 0.1, MeOH); ^1H NMR (400 MHz, DMSO-*d*₆) δ 12.22 (s, 1H), 7.98 (d, *J* = 8.4 Hz, 1H),

6.72 (d, $J = 15.6$, 5 Hz, 1H), 6.70 (d, $J = 10.5$ Hz, 1H), 5.82 (dd, $J = 15.6$, 1.7 Hz, 1H), 4.45 (tt, $J = 8.5$, 4.8 Hz, 1H), 3.77 – 3.64 (m, 1H), 1.89 (h, $J = 6.8$ Hz, 1H), 1.60 (dt, $J = 11.8$, 6.6 Hz, 1H), 1.38 (s, 9H), 1.31 (m, 2H), 0.88 – 0.81 (m, 12H); $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, DMSO- d_6) δ 171.10, 167.19, 155.44, 149.02, 120.45, 77.99, 60.25, 47.46, 42.20, 29.87, 28.17, 24.22, 23.01, 21.21, 19.20, 18.46; HRMS (ESI-TOF) m/z : $[\text{M} + \text{Na}]^+$ calculated for $\text{C}_{18}\text{H}_{32}\text{N}_2\text{O}_5\text{Na}$, 379.2208 found, 379.2211.

(*S,E*)-4-((*S*)-2-((*tert*-butoxycarbonyl)amino)-3-phenylpropanamido)-6-

methylhept-2-enoic acid (1n) White solid, yield = 1.066 g (88%); **m.p.** 152-155 °C; $[\alpha]_{\text{D}}^{25} = -24.0$ (c 0.1, MeOH); ^1H NMR (400 MHz, Chloroform- d) δ 7.29 (dd, $J = 8.0$, 6.4 Hz, 2H), 7.26 – 7.16 (m, 3H), 6.73 (d, $J = 15.6$ Hz, 1H), 6.13 (d, $J = 8.5$ Hz, 1H), 5.62 (d, $J = 15.6$ Hz, 1H), 5.28 (d, $J = 8.3$ Hz, 1H), 4.64 (d, $J = 8.9$ Hz, 1H), 4.33 (q, $J = 7.5$ Hz, 1H), 3.05 (d, $J = 7.3$ Hz, 2H), 1.60 – 1.51 (m, 1H), 1.41 (s, 9H), 1.33 (t, $J = 7.3$ Hz, 2H), 0.88 (dd, $J = 6.6$, 3.1 Hz, 6H); $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, Chloroform- d) δ 171.07, 170.16, 149.89, 129.42, 128.91, 127.31, 120.29, 80.68, 77.48, 76.84, 48.49, 43.37, 38.31, 28.37, 24.70, 22.88, 22.13; HRMS (ESI-TOF) m/z : $[\text{M} + \text{Na}]^+$ calculated for $\text{C}_{22}\text{H}_{32}\text{N}_2\text{O}_5\text{Na}$, 427.2208 found, 427.2209.

(*S,E*)-4-(2-((*tert*-butoxycarbonyl)amino)-2-methylprop anamido)-5 -phenylpent-2-

enoic acid (1o) White solid, yield = 1.071 g (95%); **m.p.** 123-126 °C; $[\alpha]_{\text{D}}^{25} = -16.0$ (c 0.1, MeOH); ^1H NMR (400 MHz, Chloroform- d) δ 7.31 – 7.27 (m, 2H), 7.25 – 7.16 (m, 3H), 7.00 (dd, $J = 15.7$, 4.9 Hz, 1H), 6.85 – 6.65 (m, 1H), 5.89 (dd, $J = 15.7$, 1.8 Hz, 1H), 5.11 – 4.79 (m, 2H), 2.92 (p, $J = 6.7$ Hz, 2H), 1.42 (s, 12H), 1.32 (s, 3H); $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, Chloroform- d) δ 174.17, 170.17, 149.23, 136.34, 129.32, 128.62, 126.97, 120.70, 81.98, 56.96, 50.93, 40.45, 28.29, 25.97, 25.34; HRMS (ESI-TOF) m/z : $[\text{M} + \text{Na}]^+$ calculated for $\text{C}_{20}\text{H}_{28}\text{N}_2\text{O}_5\text{Na}$, 399.1895 found, 399.1900.

(*S,E*)-4-(2-((*tert*-butoxycarbonyl)amino)-4-methylpent anamido)-4-methylpent-2-

enoic acid (1p) Colorless solid, yield = 0.944 g (92%); **m.p.** 143-147 °C; $[\alpha]_{\text{D}}^{25} = -38.0$ (c 0.1, MeOH); ^1H NMR (400 MHz, Chloroform- d) δ 7.06 (d, $J = 15.9$ Hz, 1H), 6.66 (s, 1H), 5.83 (d, $J = 15.9$ Hz, 1H), 5.12 (s, 1H), 4.08 (s, 1H), 1.69 – 1.57 (m, 2H), 1.48 (s, 3H), 1.47 (m, 1H), 1.44 (s, 12H), 0.93 (dd, $J = 8.2$, 6.2 Hz, 6H); $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, Chloroform- d) δ 172.27, 170.16, 156.43, 154.61, 118.43, 80.66, 60.56, 53.93, 40.70, 28.41, 27.14, 26.59, 24.87, 22.99, 22.26; HRMS (ESI-TOF) m/z : $[\text{M} + \text{Na}]^+$ calculated for $\text{C}_{17}\text{H}_{30}\text{N}_2\text{O}_5\text{Na}$, 365.2052 found, 365.2055.

3A.6.3 General procedure of peptides (1q, 1r and 1s) synthesis

Synthesis of peptides (1q, 1r and 1s) was done similarly to that of dipeptides, the complete process is described above in sections 3A.6.1 and 3A.6.2.

(S,E)-4-((S,E)-4-((tert-butoxycarbonyl)amino)-6-methylhept-2-en amido)-6-methylhept-2-enoic acid (1q) White solid, yield = 1.069 g (90%); **m.p.** 181-183 °C; $[\alpha]_D^{25} = -58.0$ (c 0.1, MeOH); ^1H NMR (400 MHz, DMSO- d_6) δ 12.29 (s, 1H), 8.13 (d, $J = 8.5$ Hz, 1H), 6.97 (d, $J = 8.7$ Hz, 1H), 6.72 (dd, $J = 15.6, 5.6$ Hz, 1H), 6.50 (dd, $J = 15.6, 6.0$ Hz, 1H), 5.95 (d, $J = 15.6$ Hz, 1H), 5.72 (dd, $J = 15.6, 1.6$ Hz, 1H), 4.53 (p, $J = 7.4, 6.8$ Hz, 1H), 4.12 (s, 1H), 1.61 – 1.51 (m, 2H), 1.38 (s, 9H), 1.34 (dd, $J = 8.7, 3.4$ Hz, 2H), 1.33 – 1.18 (m, 2H), 0.89 – 0.84 (m, 12H); $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, DMSO- d_6) δ 167.01, 164.23, 155.07, 148.96, 144.15, 122.63, 120.52, 77.71, 49.22, 47.52, 42.92, 42.43, 28.25, 24.36, 24.31, 22.80, 22.68, 21.83, 21.64; HRMS (ESI-TOF) m/z : $[\text{M} + \text{Na}]^+$ calculated for $\text{C}_{21}\text{H}_{36}\text{N}_2\text{O}_5\text{Na}$, 419.2521 found, 419.2521.

(S,E)-4-((S,E)-4-((tert-butoxycarbonyl)amino)-5-phenylpent-2-en amido)-5-phenylpent-2-enoic acid (1r) White solid, yield = 1.294 g (93%); **m.p.** 174-177 °C; $[\alpha]_D^{25} = -6.0$ (c 0.1, MeOH); ^1H NMR (400 MHz, DMSO- d_6) δ 12.32 (s, 1H), 8.27 (dd, $J = 8.4, 5.1$ Hz, 1H), 7.26 (dd, $J = 7.4, 3.6$ Hz, 4H), 7.21 (t, $J = 7.2$ Hz, 6H), 7.07 (dd, $J = 8.8, 4.5$ Hz, 1H), 6.80 (dd, $J = 15.6, 5.3$ Hz, 1H), 6.55 (dd, $J = 15.6, 5.5$ Hz, 1H), 5.91 (dd, $J = 15.6, 6.2$ Hz, 1H), 5.71 (ddd, $J = 15.6, 8.0, 1.7$ Hz, 1H), 4.77 – 4.67 (m, 1H), 4.28 (s, 1H), 2.90 (dt, $J = 13.7, 5.3$ Hz, 1H), 2.82 – 2.67 (m, 3H), 1.31 (s, 9H); $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, DMSO- d_6) δ 147.87, 143.28, 129.17, 128.22, 128.09, 126.34, 126.15, 123.02, 121.11, 77.80, 52.69, 28.21; HRMS (ESI-TOF) m/z : $[\text{M} + \text{Na}]^+$ calculated for $\text{C}_{27}\text{H}_{32}\text{N}_2\text{O}_5\text{Na}$, 487.2208 found, 487.2204.

(6S,9S,12S,E)-12-benzyl-9-isobutyl-6-isopropyl-2,2-dimethyl-4,7,10-trioxo-3-oxa-5,8,11-triaza pentadec-13-en-15-oic acid (1s) White solid, yield = 1.358 g (90%); **m.p.** 135-137 °C; $[\alpha]_D^{25} = -24.0$ (c 0.1, MeOH); ^1H NMR (400 MHz, Chloroform- d) δ 7.30 – 7.26 (m, 1H), 7.25 – 7.13 (m, 4H), 7.11 – 6.99 (m, 1H), 6.94 (dd, $J = 15.8, 5.5$ Hz, 1H), 5.85 (ddd, $J = 15.8, 6.5, 1.5$ Hz, 1H), 5.36 (s, 1H), 5.21 (s, 1H), 4.88 (q, $J = 7.2$ Hz, 1H), 4.52 (q, $J = 7.6$ Hz, 1H), 3.93 (q, $J = 8.4$ Hz, 1H), 2.98 – 2.77 (m, 2H), 2.17 – 1.99 (m, 1H), 1.63 – 1.47 (m, 2H), 1.42 (s, 9H), 1.40 – 1.30 (m, 1H), 0.96 – 0.78 (m, 12H); $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, Chloroform- d) δ 172.38, 171.78, 169.08, 156.27,

148.06, 136.49, 129.47, 129.40, 128.71, 128.68, 127.01, 121.39, 80.53, 60.41, 51.99, 51.79, 51.46, 40.78, 40.59, 28.42, 24.80, 24.69, 22.93, 22.01, 19.45; HRMS (ESI-TOF) m/z : $[M + Na]^+$ calculated for $C_{27}H_{42}N_3O_6Na$, 504.3073 found, 504.3075.

(E)-4-((tert-butoxycarbonyl)(methyl)amino)but-2-enoic acid (1t) Oily liquid, yield = 0.593 g (92%); $[\alpha]_D^{25} = 0$ (c 0.1, MeOH); 1H NMR (400 MHz, Chloroform- d) δ 7.77 (bs, 1H), 6.91 (dt, $J = 15.7, 5.0$ Hz, 1H), 5.83 (dt, $J = 15.7, 1.9$ Hz, 1H), 4.0 (bs, 1H), 3.96 (bs, 1H), 2.84 (s, 3H), 1.42 (s, 9H); $^{13}C\{^1H\}$ NMR (101 MHz, Chloroform- d) δ 170.7, 155.63, 145.98, 121.33, 80.41, 50.09, 34.54, 28.42; HRMS (ESI-TOF) m/z : $[M + Na]^+$ calculated for $C_{10}H_{17}NO_4Na$, 238.1055 found, 238.1054.

3A.6.4 General Procedure for the Synthesis of α,β -Unsaturated γ -Lactams (2a-2s)

To a 10 mL DMF (dimethylformamide) solution of Boc/Ac/Cbz-(E)- $d^{2,3}\gamma$ Xaa-OH / Boc-Xaa-(E)- $d^{2,3}\gamma$ Xaa-OH / Boc-Val-Leu-(E)- $d^{2,3}\gamma$ -Phe-OH (2mmol), N,N-diisopropyl ethylamine (6 mmol) was added. Subsequently, HBTU (2mmol) was added to the reaction mixture at ice-cold conditions. Under a nitrogen environment resultant reaction mixture was allowed to react further 6 hours at room temperature. The progression of the reaction was visualized by thin-layer chromatography (TLC) using a UV chamber, $KMnO_4$, and ninhydrin staining. Once the reaction was complete, the reaction mixture was diluted with ethyl acetate (150 mL) and washed with 10% HCl (3×60 mL), 10% Na_2CO_3 (3×60 mL), and finally with brine solution (3×60 mL). The ethyl acetate layer was dried with anhydrous Na_2SO_4 and the solvent evaporated under reduced pressure. The crude product obtained was passed through silica gel (100-200 mesh) column chromatography for final purification using an ethyl acetate/hexane solvent system in increasing polarity to get pure α,β -unsaturated γ -lactams (2a-2s).

tert-butyl 2-isobutyl-5-oxo-2,5-dihydro-1H-pyrrole-1-carboxylate (2a) Oily liquid, yield = 0.330 g (69%); $[\alpha]_D^{25} = 2.0$ (c 0.1, MeOH); 1H NMR (400 MHz, Chloroform- d) δ 7.22 (dd, $J = 6.1, 2.0$ Hz, 1H), 6.08 (dd, $J = 6.1, 1.6$ Hz, 1H), 4.59 (ddt, $J = 9.9, 3.7, 1.8$ Hz, 1H), 1.69 (ddd, $J = 9.3, 4.7, 2.5$ Hz, 1H), 1.55 (s, 9H), 1.47 – 1.40 (m, 2H), 0.99 (d, $J = 6.6$ Hz, 3H), 0.94 (d, $J = 6.6$ Hz, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, Chloroform- d) δ 169.43, 150.69, 149.45, 126.46, 83.01, 61.54, 41.27, 28.28, 25.29, 24.05, 22.29; HRMS (ESI-TOF) m/z : $[M + Na]^+$ calculated for $C_{13}H_{21}NO_3Na$, 262.1418 found, 262.1419.

tert-butyl 2-benzyl-5-oxo-2,5-dihydro-1H-pyrrole-1-carboxylate (2b) White solid, yield = 0.464 g (85%); **m.p.** 99-102 °C; $[\alpha]_{\text{D}}^{25} = 6.0$ (c 0.1, MeOH); ^1H NMR (400 MHz, Chloroform-*d*) δ 7.33 – 7.29 (m, 2H), 7.28 – 7.24 (m, 1H), 7.16 – 7.13 (m, 2H), 7.02 (dd, $J = 6.1, 2.0$ Hz, 1H), 6.02 (dd, $J = 6.1, 1.6$ Hz, 1H), 4.75 (ddt, $J = 9.5, 3.8, 1.9$ Hz, 1H), 3.54 (dd, $J = 13.1, 3.9$ Hz, 1H), 2.74 (dd, $J = 13.1, 9.5$ Hz, 1H), 1.62 (s, 9H); $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, Chloroform-*d*) δ 169.18, 150.04, 149.62, 135.74, 129.50, 128.82, 127.28, 126.77, 83.31, 63.49, 38.72, 28.35; HRMS (ESI-TOF) m/z : $[\text{M} + \text{Na}]^+$ calculated for $\text{C}_{16}\text{H}_{19}\text{NO}_3\text{Na}$, 296.1262 found, 296.1265.

tert-butyl 2-isopropyl-5-oxo-2,5-dihydro-1H-pyrrole-1-carboxylate (2c) Oily liquid, yield = 0.324 g (72%); $[\alpha]_{\text{D}}^{25} = 4.0$ (c 0.1, MeOH); ^1H NMR (400 MHz, Chloroform-*d*) δ 7.12 (dd, $J = 6.2, 2.1$ Hz, 1H), 6.14 (dd, $J = 6.2, 1.8$ Hz, 1H), 4.55 (dt, $J = 3.9, 1.9$ Hz, 1H), 2.59 (ddd, $J = 13.5, 6.9, 3.9$ Hz, 1H), 1.54 (s, 9H), 1.09 (d, $J = 7.1$ Hz, 3H), 0.66 (d, $J = 6.9$ Hz, 3H); $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, Chloroform-*d*) δ 169.66, 149.75, 147.91, 127.93, 82.99, 67.42, 29.00, 28.25, 19.63, 14.99; HRMS (ESI-TOF) m/z : $[\text{M} + \text{Na}]^+$ calculated for $\text{C}_{12}\text{H}_{19}\text{NO}_3\text{Na}$, 248.1262 found, 248.1261.

tert-butyl 2-((S)-sec-butyl)-5-oxo-2,5-dihydro-1H-pyrrole-1-carboxylate (2d) Oily liquid, yield = 0.375 g (71%); $[\alpha]_{\text{D}}^{25} = -6$ (c 0.1, MeOH). ^1H NMR (400 MHz, Chloroform-*d*, mixture of two isomers in ratio of 1:1) δ 7.12 (dd, $J = 6.2, 2.0$ Hz, 1H), 7.07 (dd, $J = 6.2, 2.0$ Hz, 1H), 6.13 (dd, $J = 6.2, 1.8$ Hz, 1H), 6.10 (dd, $J = 6.2, 1.8$ Hz, 1H), 4.65 (dd, $J = 3.9, 1.9$ Hz, 1H), 4.56 (dd, $J = 3.9, 1.9$ Hz, 1H), 2.35 (m, 1H), 2.28 (m, 1H), 1.54 (s, 18H), 1.39 – 1.29 (m, 2H), 1.27 – 1.20 (m, 2H), 1.07 (d, $J = 7.1$ Hz, 3H), 1.03 (t, $J = 7.4$ Hz, 3H), 0.83 (t, $J = 7.4$ Hz, 3H), 0.62 (d, $J = 6.9$ Hz, 3H); $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, Chloroform-*d*) δ 169.79, 169.77, 149.66, 149.57, 148.31, 148.12, 127.86, 127.40, 82.94, 67.60, 66.10, 35.87, 35.81, 28.22, 28.20, 27.31, 22.59, 16.59, 12.66, 12.37, 12.26. HRMS (ESI) calculated for $\text{C}_{13}\text{H}_{21}\text{NO}_3\text{Na}$ $[\text{M} + \text{Na}]^+ m/z$ 262.1418, found 262.1418.

tert-butyl 2-methyl-5-oxo-2,5-dihydro-1H-pyrrole-1-carboxylate (2e) Oily liquid, yield = 0.323 g (82%); $[\alpha]_{\text{D}}^{25} = 6.0$ (c 0.1, MeOH); ^1H NMR (400 MHz, Chloroform-*d*) δ 7.09 (dd, $J = 6.1, 2.0$ Hz, 1H), 6.06 (dd, $J = 6.1, 1.7$ Hz, 1H), 4.61 (dt, $J = 6.7, 1.8$ Hz, 1H), 1.56 (s, 9H), 1.43 (d, $J = 6.7$ Hz, 3H); $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, Chloroform-

d) δ 169.30, 151.90, 149.53, 126.07, 83.04, 58.53, 28.28, 18.30. HRMS (ESI-TOF) m/z : $[M + Na]^+$ calculated for $C_{10}H_{15}NO_3Na$, 220.0949 found, 220.0955.

***tert*-butyl 2,2-dimethyl-5-oxo-2,5-dihydro-1*H*-pyrrole-1-carboxyl ate (2f)** Colorless solid, yield = 0.042 g (10%); **m.p.** 63-66 °C; $[\alpha]_D^{25} = 0.0$ (*c* 0.1, MeOH); 1H NMR (600 MHz, Chloroform-*d*) δ 7.01 (d, $J = 6.0$ Hz, 1H), 5.99 (d, $J = 6.0$ Hz, 1H), 1.57 (s, 9H), 1.53 (s, 6H); $^{13}C\{^1H\}$ NMR (151 MHz, Chloroform-*d*) δ 169.49, 157.93, 149.63, 123.63, 82.93, 65.57, 28.36, 24.23; HRMS (ESI-TOF) m/z : $[M + Na]^+$ calculated for $C_{11}H_{17}NO_3Na$, 234.1105 found, 234.1106.

1-acetyl-5-isobutyl-1,5-dihydro-2*H*-pyrrol-2-one (2g) Oily liquid, yield = 0.282 g (78%); $[\alpha]_D^{25} = 8.0$ (*c* 0.1, MeOH); 1H NMR (400 MHz, Chloroform-*d*) δ 7.36 (dd, $J = 6.1, 2.0$ Hz, 1H), 6.10 (dd, $J = 6.1, 1.6$ Hz, 1H), 4.78 (ddt, $J = 9.6, 3.7, 1.8$ Hz, 1H), 2.53 (s, 3H), 2.07 (ddd, $J = 13.2, 9.3, 3.8$ Hz, 1H), 1.73 – 1.64 (m, 1H), 1.38 (ddd, $J = 13.2, 9.6, 4.8$ Hz, 1H), 1.01 (d, $J = 6.6$ Hz, 3H), 0.92 (d, $J = 6.6$ Hz, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, Chloroform-*d*) δ 170.41, 170.21, 152.59, 126.08, 60.89, 40.59, 25.37 (d, $J = 16.4$ Hz), 23.89, 22.25; HRMS (ESI-TOF) m/z : $[M + Na]^+$ calculated for $C_{10}H_{16}NO_2Na$, 204.1000 found, 204.0995.

1-acetyl-5-benzyl-1,5-dihydro-2*H*-pyrrol-2-one (2h) Oily liquid, yield = 0.357 g (83%); $[\alpha]_D^{25} = 4.0$ (*c* 0.1, MeOH); 1H NMR (400 MHz, Chloroform-*d*) δ 7.30 – 7.22 (m, 3H), 7.15 (dd, $J = 6.1, 2.1$ Hz, 1H), 7.12 (d, $J = 1.8$ Hz, 2H), 6.00 (dd, $J = 6.1, 1.7$ Hz, 1H), 4.93 (ddt, $J = 9.1, 3.7, 1.8$ Hz, 1H), 3.52 (dd, $J = 13.2, 3.7$ Hz, 1H), 2.82 (dd, $J = 13.2, 9.0$ Hz, 1H), 2.55 (s, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, Chloroform-*d*) δ 170.49, 170.24, 151.80, 135.54, 129.63, 128.66, 127.22, 126.45, 62.54, 37.65, 25.24; HRMS (ESI-TOF) m/z : $[M + Na]^+$ calculated for $C_{13}H_{13}NO_2Na$, 238.0843 found, 238.0843.

benzyl 2-isobutyl-5-oxo-2,5-dihydro-1*H*-pyrrole-1-carboxylate (2i) Oily liquid, yield = 0.398 g (73%); $[\alpha]_D^{25} = 6.0$ (*c* 0.1, MeOH); 1H NMR (400 MHz, Chloroform-*d*) δ 7.47 – 7.43 (m, 2H), 7.39 – 7.31 (m, 3H), 7.27 (dd, $J = 6.2, 2.0$ Hz, 1H), 6.10 (dd, $J = 6.2, 1.6$ Hz, 1H), 5.37 (d, $J = 12.3$ Hz, 1H), 5.28 (d, $J = 12.3$ Hz, 1H), 4.66 (ddt, $J = 9.7, 3.5, 1.7$ Hz, 1H), 1.97 (ddd, $J = 13.2, 9.3, 3.7$ Hz, 1H), 1.66 (ddt, $J = 7.2, 4.6, 2.3$ Hz, 1H), 1.42 (ddd, $J = 13.3, 9.7, 4.7$ Hz, 1H), 0.93 (d, $J = 6.5$ Hz, 3H), 0.89 (d, $J = 6.6$ Hz, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, Chloroform-*d*) δ 168.91, 151.41, 150.95, 135.44,

128.72, 128.52, 128.35, 126.19, 68.09, 61.62, 40.99, 25.26, 23.87, 22.17; HRMS (ESI-TOF) m/z : $[M + Na]^+$ calculated for $C_{16}H_{19}NO_3Na$, 296.1262 found 296.1266.

tert-butyl ((2S)-1-(2-isobutyl-5-oxo-2,5-dihydro-1H-pyrrol-1-yl)-4-methyl-1-oxopentan-2-yl)carbamate (2j) Oily liquid, yield = 0.605 g (84%); $[\alpha]_D^{25} = -134.0$ (c 0.1, MeOH); 1H NMR (400 MHz, Chloroform-*d*) δ 7.37 (dd, $J = 6.1, 2.0$ Hz, 1H), 6.07 (dd, $J = 6.1, 1.7$ Hz, 1H), 5.52 – 5.42 (m, 1H), 5.05 (d, $J = 9.5$ Hz, 1H), 4.78 (ddd, $J = 11.6, 3.7, 1.8$ Hz, 1H), 1.95 (ddd, $J = 13.3, 9.6, 3.8$ Hz, 1H), 1.84 – 1.77 (m, 1H), 1.67 (m, 1H), 1.60 – 1.51 (m, 1H), 1.41 (s, 9H), 1.37 – 1.29 (m, 2H), 1.05 (d, $J = 6.6$ Hz, 3H), 0.99 (d, $J = 6.6$ Hz, 3H), 0.91 (dd, $J = 6.7, 2.9$ Hz, 6H); $^{13}C\{^1H\}$ NMR (101 MHz, Chloroform-*d*) δ 173.89, 169.44, 155.83, 152.92, 125.94, 79.66, 60.86, 53.24, 41.69, 40.52, 28.45, 25.41, 25.17, 23.93, 23.74, 22.15, 21.19; HRMS (ESI-TOF) m/z : $[M + Na]^+$ calculated for $C_{19}H_{32}N_2O_4Na$, 375.2259 found, 375.2261.

tert-butyl ((2S)-1-(2-isopropyl-5-oxo-2,5-dihydro-1H-pyrrol-1-yl)-4-methyl-1-oxopentan-2-yl)carbamate (2k) Oily liquid, yield = 0.561 g (83%); $[\alpha]_D^{25} = -238.0$ (c 0.1, MeOH); 1H NMR (400 MHz, Chloroform-*d*) δ 7.25 (d, $J = 6.0$ Hz, 1H), 6.13 (dd, $J = 6.0, 1.5$ Hz, 1H), 5.49 (t, $J = 9.0$ Hz, 1H), 5.05 (d, $J = 8.3$ Hz, 1H), 4.75 (s, 1H), 2.68 – 2.53 (m, 1H), 1.81 (ddt, $J = 13.6, 6.7, 3.8$ Hz, 1H), 1.62 – 1.53 (m, 1H), 1.41 (s, 9H), 1.39 – 1.33 (m, 1H), 1.06 (dd, $J = 12.4, 6.8$ Hz, 6H), 0.91 (d, $J = 6.7$ Hz, 3H), 0.59 (d, $J = 6.9$ Hz, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, Chloroform-*d*) δ 174.00, 169.83, 155.82, 150.12, 127.40, 79.62, 77.48, 76.84, 66.65, 53.31, 41.70, 28.41, 28.01, 25.15, 23.69, 21.13, 19.47, 14.99; HRMS (ESI-TOF) m/z : $[M + Na]^+$ calculated for $C_{18}H_{30}N_2O_4Na$, 361.2103 found, 361.2101.

tert-butyl ((2R)-1-(2-isopropyl-5-oxo-2,5-dihydro-1H-pyrrol-1-yl)-4-methyl-1-oxopentan-2-yl)carbamate (2l) Oily liquid, yield = 0.597 g (84%); $[\alpha]_D^{25} = +212.0$ (c 0.1, MeOH); 1H NMR (400 MHz, Chloroform-*d*) δ 7.25 (d, $J = 6.0$ Hz, 1H), 6.13 (dd, $J = 6.0, 1.5$ Hz, 1H), 5.49 (t, $J = 9.0$ Hz, 1H), 5.06 (d, $J = 8.3$ Hz, 1H), 4.75 (s, 1H), 2.59 (ddd, $J = 13.9, 7.0, 4.2$ Hz, 1H), 1.81 (ddt, $J = 13.3, 10.4, 6.6$ Hz, 1H), 1.58 (t, $J = 11.1$ Hz, 1H), 1.41 (s, 9H), 1.39 – 1.33 (m, 1H), 1.06 (dd, $J = 12.5, 6.8$ Hz, 6H), 0.92 (d, $J = 6.7$ Hz, 3H), 0.59 (d, $J = 6.9$ Hz, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, Chloroform-*d*) δ 174.02, 169.85, 155.85, 150.13, 127.43, 79.66, 66.67, 53.34, 41.72, 28.44, 28.04, 25.18,

23.71, 21.15, 19.50, 15.01; HRMS (ESI-TOF) m/z : $[M + Na]^+$ calculated for $C_{18}H_{30}N_2O_4Na$, 361.2103 found, 361.2102.

tert-butyl ((2S)-1-(2-isobutyl-5-oxo-2,5-dihydro-1H-pyrrol-1-yl)-3-methyl-1-oxobutan-2-yl)carbamate (2m) Oily liquid, yield = 0.527 g (78%); $[\alpha]_D^{25} = -152.0$ (c 0.1, MeOH); 1H NMR (400 MHz, Chloroform-*d*) δ 7.38 (d, $J = 6.0$ Hz, 1H), 6.09 (dd, $J = 6.0, 1.7$ Hz, 1H), 5.45 (dd, $J = 9.7, 3.4$ Hz, 1H), 5.18 (d, $J = 9.8$ Hz, 1H), 4.82 (d, $J = 9.7$ Hz, 1H), 2.20 (s, 1H), 1.97 (ddd, $J = 13.3, 9.7, 3.8$ Hz, 1H), 1.73 – 1.66 (m, 1H), 1.44 (s, 9H), 1.38 – 1.32 (m, 1H), 1.08 (d, $J = 6.8$ Hz, 3H), 1.01 (d, $J = 6.6$ Hz, 3H), 0.93 (d, $J = 6.7$ Hz, 3H), 0.81 (d, $J = 7.0$ Hz, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, Chloroform-*d*) δ 172.70, 169.51, 156.15, 152.84, 125.96, 60.86, 58.56, 40.54, 30.98, 28.47, 25.44, 23.94, 22.14, 20.06, 16.18; HRMS (ESI-TOF) m/z : $[M + Na]^+$ calculated for $C_{18}H_{30}N_2O_4Na$, 361.2103 found, 361.2105.

tert-butyl ((2S)-1-(2-isobutyl-5-oxo-2,5-dihydro-1H-pyrrol-1-yl)-1-oxo-3-phenylpropan-2-yl)carbamate (2n) Oily liquid, yield = 0.625 g (81%); $[\alpha]_D^{25} = +12.0$ (c 0.1, MeOH); 1H NMR (400 MHz, Chloroform-*d*) δ 7.40 (d, $J = 6.1$ Hz, 1H), 7.31 – 7.26 (m, 4H), 7.25 – 7.22 (m, 1H), 6.13 (dd, $J = 6.1, 1.5$ Hz, 1H), 5.72 (td, $J = 8.6, 4.3$ Hz, 1H), 5.11 (d, $J = 8.2$ Hz, 1H), 4.81 (d, $J = 8.3$ Hz, 1H), 3.30 – 3.21 (m, 1H), 2.90 – 2.74 (m, 1H), 1.97 (ddd, $J = 13.3, 9.7, 3.8$ Hz, 1H), 1.71 (m, 1H), 1.36 (s, 9H), 1.23 – 1.19 (m, 1H), 1.01 (d, $J = 6.6$ Hz, 3H), 0.94 (d, $J = 6.6$ Hz, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, Chloroform-*d*) δ 172.62, 169.86, 155.30, 153.26, 136.78, 129.68, 129.49, 128.69, 128.51, 126.90, 125.90, 79.77, 61.35, 55.21, 40.54, 38.09, 28.34, 25.49, 23.88, 22.10; HRMS (ESI-TOF) m/z : $[M + Na]^+$ calculated for $C_{22}H_{30}N_2O_4Na$, 387.2284 found, 387.2299.

tert-butyl (1-(2-benzyl-5-oxo-2,5-dihydro-1H-pyrrol-1-yl)-2-methyl-1-oxopropan-2-yl)carbamate (2o) Viscous liquid, yield = 0.594 g (83%); $[\alpha]_D^{25} = +4.0$ (c 0.1, MeOH); 1H NMR (400 MHz, Chloroform-*d*) δ 7.31 (m, 2H), 7.26 – 7.19 (m, 3H), 7.13 (dd, $J = 6.0, 2.0$ Hz, 1H), 6.00 (dd, $J = 6.0, 1.5$ Hz, 1H), 5.75 (s, 1H), 4.98 (ddt, $J = 10.6, 4.0, 1.8$ Hz, 1H), 3.70 (dd, $J = 13.1, 4.1$ Hz, 1H), 2.46 (dd, $J = 13.2, 10.5$ Hz, 1H), 1.69 (s, 3H), 1.59 (s, 3H), 1.38 (s, 9H); $^{13}C\{^1H\}$ NMR (101 MHz, Chloroform-*d*) δ 175.96, 168.83, 155.49, 152.45, 136.65, 129.57, 128.77, 127.09, 125.93, 79.58, 64.99, 58.05,

38.45, 28.46, 25.91, 24.41; HRMS (ESI-TOF) m/z : $[M + Na]^+$ calculated for $C_{20}H_{26}N_2O_4Na$, 381.1790 found, 381.1795.

tert-butyl (S)-(1-(2,2-dimethyl-5-oxo-2,5-dihydro-1H-pyrrol-1-yl)-4-methyl-1-oxopentan-2-yl)carbamate (2p) Oily liquid, yield = 0.90 g (14%); $[\alpha]_D^{25} = -22.0$ (c 0.1, MeOH); 1H NMR (400 MHz, Chloroform-*d*) δ 7.14 (d, $J = 6.0$ Hz, 1H), 5.99 (d, $J = 6.0$ Hz, 1H), 5.56 – 5.49 (m, 1H), 5.10 (d, $J = 9.5$ Hz, 1H), 1.80 (m, 1H), 1.57 (s, 3H), 1.52 (s, 3H), 1.43 (s, 9H), 1.39 – 1.30 (m, 2H), 1.05 (d, $J = 6.6$ Hz, 3H), 0.92 (d, $J = 6.7$ Hz, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, Chloroform-*d*) δ 174.29, 169.71, 160.19, 155.81, 123.18, 79.61, 66.63, 53.24, 41.93, 29.84, 28.45, 25.14, 23.82, 23.59, 23.51, 21.31; HRMS (ESI-TOF) m/z : $[M + Na]^+$ calculated for $C_{17}H_{28}N_2O_4Na$, 347.1946 found, 347.1947.

tert-butyl ((4S,E)-1-(2-isobutyl-5-oxo-2,5-dihydro-1H-pyrrol-1-yl)-6-methyl-1-oxohept-2-en-4-yl)carbamate (2q) Colorless solid, yield = 0.604 g (80%); **m.p.** 156–158 °C; $[\alpha]_D^{25} = -28.0$ (c 0.1, MeOH); 1H NMR (400 MHz, Chloroform-*d*) δ 7.42 – 7.35 (m, 2H), 7.05 (d, $J = 15.9$ Hz, 1H), 6.09 (dd, $J = 6.1, 1.6$ Hz, 1H), 4.87 – 4.82 (m, 1H), 4.56 (d, $J = 8.0$ Hz, 1H), 4.43 (s, 1H), 2.07 (ddd, $J = 13.3, 9.5, 3.7$ Hz, 1H), 1.76 – 1.68 (m, 2H), 1.45 (s, 9H), 1.39 (m, 3H), 1.02 (d, $J = 6.6$ Hz, 3H), 0.94 (t, $J = 6.3$ Hz, 9H); $^{13}C\{^1H\}$ NMR (101 MHz, Chloroform-*d*) δ 170.26, 164.83, 155.29, 152.73, 150.08, 126.20, 121.56, 79.75, 61.10, 50.32, 43.99, 40.74, 28.52, 25.50, 24.92, 23.91, 22.86, 22.38, 22.19; HRMS (ESI-TOF) m/z : $[M + Na]^+$ calculated for $C_{21}H_{34}N_2O_4Na$, 401.2416 found, 401.2413.

tert-butyl ((2S,E)-5-(2-benzyl-5-oxo-2,5-dihydro-1H-pyrrol-1-yl)-5-oxo-1-phenylpent-3-en-2-yl)carbamate (2r) White solid, yield = 0.776 g (87%); **m.p.** 139–141 °C; $[\alpha]_D^{25} = +14.0$ (c 0.1, MeOH); 1H NMR (400 MHz, Chloroform-*d*) δ 7.41 – 7.27 (m, 5H), 7.26 – 7.10 (m, 8H), 5.99 (dd, $J = 6.1, 1.6$ Hz, 1H), 4.99 (d, $J = 7.1$ Hz, 1H), 4.72 (bs, 1H), 4.63 (bs, 1H), 3.55 (dd, $J = 11.0, 3.7$ Hz, 1H), 3.13 – 2.60 (m, 4H), 1.42 (s, 9H); $^{13}C\{^1H\}$ NMR (101 MHz, Chloroform-*d*) δ 170.10, 164.75, 155.18, 151.99, 149.22, 136.66, 135.62, 129.67, 129.65, 129.63, 129.58, 128.71, 128.69, 127.22, 126.97, 126.55, 126.52, 121.97, 79.94, 62.88, 37.82, 28.47; HRMS (ESI-TOF) m/z : $[M + Na]^+$ calculated for $C_{27}H_{30}N_2O_4Na$, 469.2103 found, 469.2104.

tert-butyl ((2S)-1-(((2S)-1-(2-benzyl-5-oxo-2,5-dihydro-1H-pyrrol-1-yl)-4-methyl-1-oxopentan-2-yl)amino) -3-methyl-1-oxobutan-2-yl)carbamate (2s) Viscous liquid, yield = 0.776 g (79%); $[\alpha]_{\text{D}}^{25} = -56.0$ (c 0.1, MeOH); ^1H NMR (400 MHz, Chloroform-*d*) δ 7.28 (d, $J = 5.9$ Hz, 1H), 7.26 – 7.23 (m, 2H), 7.20 (dd, $J = 6.1, 2.0$ Hz, 1H), 7.10 – 7.07 (m, 2H), 6.44 (d, $J = 7.9$ Hz, 1H), 6.03 (dd, $J = 6.1, 1.7$ Hz, 1H), 5.79 – 5.69 (m, 1H), 5.10 (d, $J = 9.0$ Hz, 1H), 4.96 (ddt, $J = 9.0, 3.7, 1.9$ Hz, 1H), 3.93 (dd, $J = 9.0, 6.5$ Hz, 1H), 3.43 (dd, $J = 13.3, 3.6$ Hz, 1H), 2.86 (dd, $J = 13.3, 9.0$ Hz, 1H), 2.15 – 2.07 (m, 1H), 1.75 – 1.69 (m, 1H), 1.50 – 1.47 (m, 1H) 1.45 (s, 9H), 1.00 (d, $J = 6.6$ Hz, 3H), 0.98 (d, $J = 6.6$ Hz, 3H) 0.95 (d, $J = 6.9$ Hz, 3H), 0.92 (d, $J = 6.9$ Hz, 3H); $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, Chloroform-*d*) δ 173.05, 171.61, 169.37, 156.02, 152.35, 135.08, 129.75, 128.64, 127.37, 126.38, 79.95, 62.55, 60.19, 51.87, 41.71, 37.41, 30.97, 28.44, 25.17, 23.72, 21.01, 19.46, 18.08; HRMS (ESI-TOF) m/z : $[\text{M} + \text{Na}]^+$ calculated for $\text{C}_{27}\text{H}_{39}\text{N}_3\text{O}_5\text{Na}$, 508.2787 found, 508.2790.

3A.6.5 General Procedure for the Synthesis of Benzylamine Coupled Product (3a)

Boc-(*E*)- $\text{d}^{2,3}\gamma$ -Leu-OH (0.514 g, 2 mmol) and HBTU (0.758 g, 2 mmol) were mixed with 5 mL of DMF, to this solution DIPEA (1.0 mL, 6 mmol) was added. After stirring the reaction mixture for 5 minutes at ice-cooled temperature, benzylamine (0.25 mL, 2.2 mmol) was added under a nitrogen environment. Subsequently, the reaction mixture was allowed to react further for 6 hours at room temperature, the reaction progression was visualized till completion using TLC (ethyl acetate/hexane, 1:1), work-up was done by diluting the reaction mixture with ethyl acetate (150 mL), followed by successive washings with 10% HCl (3 $\times$ 60 mL), 10% Na_2CO_3 (3 $\times$ 60 mL) and finally with brine solution (3 $\times$ 60 mL). The ethyl acetate layer was dried with anhydrous Na_2SO_4 and solvent evaporated under reduced pressure. For final purification, the obtained crude compound was passed through column chromatography (silica gel 60-120 mesh, ethyl acetate/hexane in increasing polarity) to isolate the pure coupled product **3a**.

tert-butyl (S,E)-(1-(benzylamino)-6-methyl-1-oxohept-2-en-4-yl)carbamate (3a) White solid, yield = 623 g (90%). **m.p.** 142-144 °C. $[\alpha]_{\text{D}}^{25} = -32$ (c 0.1, MeOH). ^1H NMR (400 MHz, Chloroform-*d*) δ 7.36 – 7.26 (m, 5H), 6.71 (dd, $J = 15.3, 6.1$ Hz, 1H), 5.89 (d, $J = 15.3$, Hz, 1H), 5.81 (s, 1H), 4.50 (d, $J = 5.7$ Hz, 2H), 4.44 (s, 1H), 4.29 (s, 1H), 1.68 (p, $J = 6.6$ Hz, 1H),

1.43 (s, 9H), 1.38 (t, $J = 7.2$ Hz, 2H), 0.92 (dd, $J = 6.6, 1.4$ Hz, 6H). $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, Chloroform- d) δ 165.53, 155.29, 144.94, 138.23, 128.83, 128.04, 127.67, 123.02, 79.71, 50.05, 44.12, 43.83, 28.51, 24.77, 22.74, 22.41. HRMS (ESI-TOF) calculated for $\text{C}_{20}\text{H}_{30}\text{N}_2\text{O}_3\text{Na}$ $[\text{M}+\text{Na}]^+$ m/z 369.2154, found 369.2146.

3A.7 Crystallographic Information

Compound 2c: Crystals of **2c** were grown by slow evaporation from a solution of aqueous methanol at room temperature. A single crystal ($0.21 \times 0.24 \times 0.55$ mm) was mounted on a loop with a small amount of paraffin oil. The X-ray data were collected at 150 K temperature on a Bruker APEX(II) DUO CCD diffractometer using Mo $K\alpha$ radiation ($\lambda = 0.71073$ Å), ω -scans ($2\theta = 56.802$), for a total of 33372 independent reflections. Space group $P 2_1/c$, $a = 16.146$ (2), $b = 8.9286$ (10), $c = 9.1670$ (11), $\alpha = 90$, $\beta = 104.92$ (4), $\gamma = 90$, $V = 1277.0$ (3) Å³, Monoclinic, $Z = 4$ for chemical formula $\text{C}_{12}\text{H}_{19}\text{NO}_3$, with one molecule in asymmetric unit; ρ calcd = 1.172 gcm⁻³, $\mu = 0.084$ mm⁻¹, $F(000) = 488.0$, $R_{\text{int}} = 0.1753$. The structure was obtained by direct methods using SHELXS-97. The final R value was 0.0633 ($wR_2 = 0.1189$) 3198 observed reflections ($F0 \geq 4\sigma(|F0|)$) and 151 variables, $S = 1.034$.

Compound 2m: Crystals of **2m** were grown by slow evaporation from a solution of aqueous methanol at room temperature. A single crystal ($0.25 \times 0.3 \times 0.5$ mm) was mounted on a loop with a small amount of paraffin oil. The X-ray data were collected at 100 K temperature on a Bruker APEX(II) DUO CCD diffractometer using Cu $K\alpha$ radiation ($\lambda = 1.54178$ Å), ω -scans ($2\theta = 72.966$), for a total of 40458 independent reflections. Space group $P 4_3 2_1 2$, $a = 8.6930$ (11), $b = 8.6930$ (11), $c = 52.192$ (8), $\alpha = 90$, $\beta = 90$, $\gamma = 90$, $V = 3944.1$ (12) Å³, Tetragonal, $Z = 8$ for chemical formula $\text{C}_{18}\text{H}_{30}\text{N}_2\text{O}_4$, with one molecule in asymmetric unit; ρ calcd = 1.140 gcm⁻³, $\mu = 0.649$ mm⁻¹, $F(000) = 1472.0$, $R_{\text{int}} = 0.1912$. The structure was obtained by direct methods using SHELXS-97. The final R value was 0.0712 ($wR_2 = 0.1912$) 3919 observed reflections ($F0 \geq 4\sigma(|F0|)$) and 225 variables, $S = 1.017$.

Compound 2p: Crystals of **2p** were grown by slow evaporation from a solution of EtOAc-chloroform at room temperature. A single crystal ($0.2 \times 0.12 \times 0.06$ mm) was mounted on loop with a small amount of paraffin oil. The X-ray data were collected at 150 K temperature on a Bruker APEX(II) DUO CCD diffractometer using Mo $K\alpha$ radiation ($\lambda = 0.71073$ Å), ω -scans ($2\theta = 56.682$), for a total of 9925 independent reflections. Space group $P 2_1$, $a = 10.6044$ (14), $b = 18.714$ (3), $c = 10.9305$ (16), $\alpha = 90$, $\beta = 116.303$ (4), $\gamma = 90$, $V = 1944.6$ (5) Å³, Monoclinic,

$Z = 4$ for chemical formula $C_{17}H_{28}N_2O_4$, with two molecules in asymmetric unit; ρ calcd = 1.108 g cm^{-3} , $\mu = 0.079 \text{ mm}^{-1}$, $F(000) = 704$, $R_{\text{int}} = 0.0852$. The structure was obtained by direct methods using SHELXS-97. The final R value was 0.0633 ($wR_2 = 0.1734$) 9674 observed reflections ($F0 \geq 4\sigma(|F0|)$) and 430 variables, $S = 0.934$.

Compound 2q: Crystals of **2q** were grown by slow evaporation from a solution of aqueous methanol at room temperature. A single crystal ($0.18 \times 0.14 \times 0.6 \text{ mm}$) was mounted on a loop with a small amount of paraffin oil. The X-ray data were collected at 100 K temperature on a Bruker APEX(II) DUO CCD diffractometer using Mo $K\alpha$ radiation ($\lambda = 0.71073 \text{ \AA}$), ω -scans ($2\theta = 56.976$), for a total of 16253 independent reflections. Space group $P 1$, $a = 6.102(4)$, $b = 11.771(8)$, $c = 16.676(11)$, $\alpha = 71.431(17)$, $\beta = 82.81(2)$, $\gamma = 78.90(2)$, $V = 1111.6(13) \text{ \AA}^3$, Triclinic, $Z = 2$ for chemical formula $C_{21}H_{34}N_2O_4$, with two molecules in asymmetric unit; ρ calcd = 1.131 g cm^{-3} , $\mu = 0.078 \text{ mm}^{-1}$, $F(000) = 412$, $R_{\text{int}} = 0.1852$. The structure was obtained by direct methods using SHELXS-97. The final R value was 0.0969 ($wR_2 = 0.2959$) 9051 observed reflections ($F0 \geq 4\sigma(|F0|)$) and 501 variables, $S = 0.912$.

Compound 2r: Colourless plate shape Crystals of **2r** were grown by slow evaporation from a solution of ethyl acetate and n-heptane. A good quality single crystal ($0.5 \times 0.43 \times 0.3 \text{ mm}$) was mounted on the head of a goniometer using a loop with a small amount of paraffin oil. The X-ray diffraction data of a single crystal were collected at 100K temperature on a Bruker APEX(II) DUO CCD diffractometer using Mo $K\alpha$ radiation ($\lambda = 0.71073 \text{ \AA}$), ω -scans ($2\theta = 50.52$), for a total of 15903 independent reflections. Space group $P n a 2_1$, $a = 21.706(4)$, $b = 17.838(4)$, $c = 6.233(2)$, $\beta = 90.00(3)$, $V = 2413.4(10) \text{ \AA}^3$, Orthorhombic, $Z = 4$ for chemical formula $C_{27}H_{30}N_2O_4$, with one molecule in asymmetric unit; ρ calcd = 1.229 g cm^{-3} , $\mu = 0.083 \text{ mm}^{-1}$, $F(000) = 952.0$, $R_{\text{int}} = 0.6039$. The structure was obtained by direct methods using SHELXL-97. The final R value was 0.1128 ($wR_2 = 0.3451$) 4250 observed reflections ($F0 \geq 4\sigma(|F0|)$) and 302 variables, $S = 0.869$.

3A.8 References

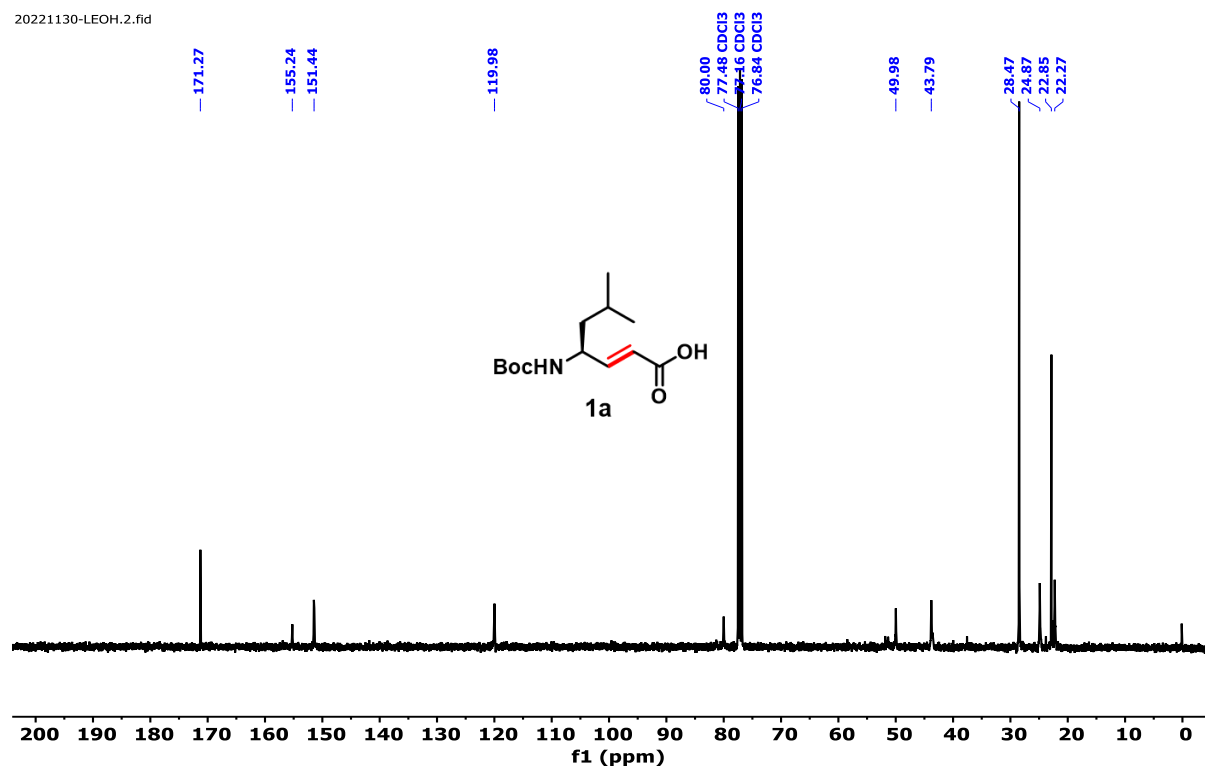
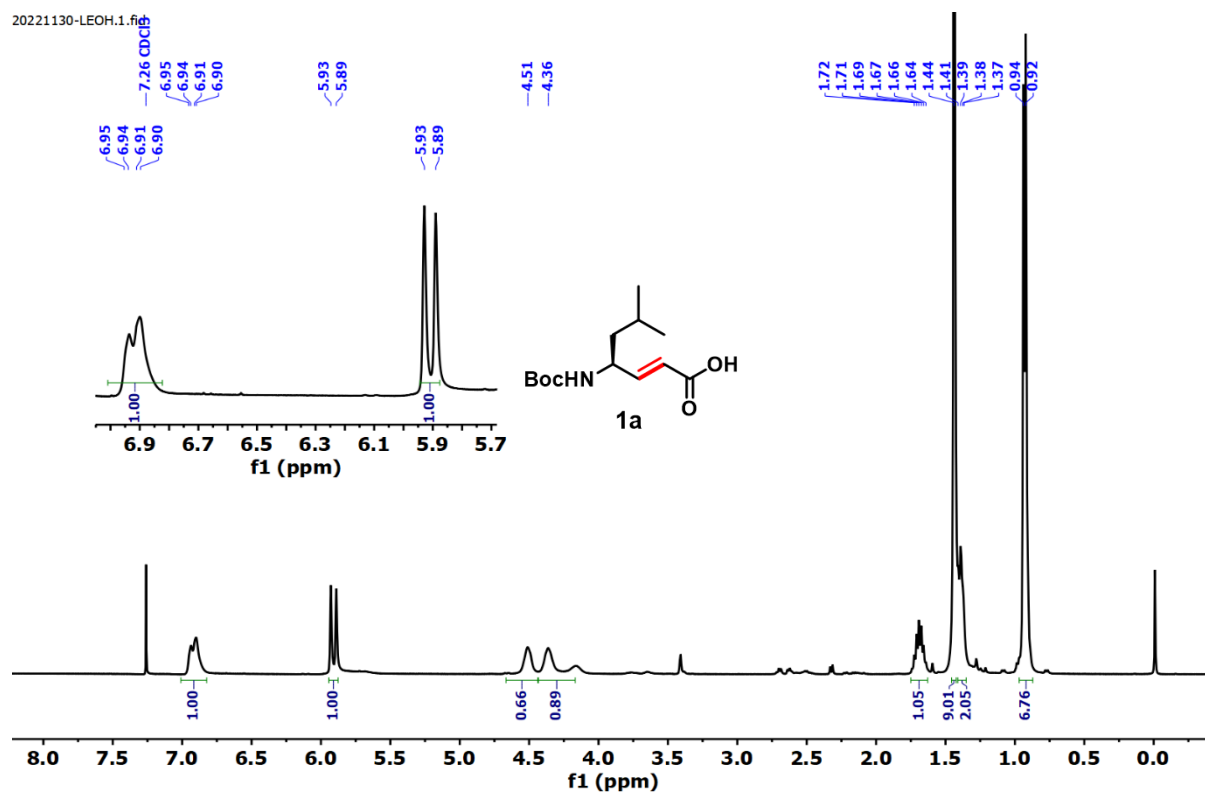
1. (a) R. G. Linington, B. R. Clark, E. E. Trimble, A. Almanza, L. Urena, D. E. Kyle and W. H. Gerwick, *J. Nat. Prod.*, 2009, **72**, 14–17; (b) J. E. Coleman, E. D. de Silva, F. Kong, R. J. Andersen and T. M. Allen, *Tetrahedron*, 1995, **51**, 10653-10662; (c) N. Schaschke, *Bioorg. Med. Chem. Lett.*, 2004, **14**, 855-857; (d) M. Hagihara and S. L. Schreiber, *J. Am. Chem. Soc.* 1992, **114**, 6570-6571; (e) J. A. Nieman, J. E. Coleman, D. J. Wallace, E. Piers, L. Y. Lim, M. Roberge and R. J. Andersen, *J. Nat. Prod.* 2003, **66**, 183–199; (f) E. J. E. Caro-Diaz, F. A. Valeriote and W. H. Gerwick, *Org. Lett.*, 2019, **21**, 793–796; (g) E. T. Pelkey, S. J. Pelkey and J. G. Greger, *In Adv. Heterocycl. Chem.*, 2015, **115**, 151.
2. (a) S. Hanessian and R. Schaum, *Tetrahedron Lett.*, 1997, **38**, 163-166; (b) S. V. Jadhav, A. Bandyopadhyay and H. N. Gopi, *Org. Biomol. Chem.*, 2013, **11**, 509–514; (c) A. Bandyopadhyay, S. V. Jadhav and H. N. Gopi, *Chem. Commun.*, 2012, **48**, 7170–7172.
3. (a) C. Baldauf, R. Gunther and H.-J. Hofmann, *J. Org. Chem.*, 2005, **70**, 5351–5361; (b) M. G. Kumar, V. J. Thombare, M. M. Katariya, K. Veeresh, K. M. P. Raja and H. N. Gopi, *Angew. Chem., Int. Ed.*, 2016, **55**, 7847–7851.
4. (a) M. Hagihara, N. J. Anthony, T. J. Stout, J. Clardy and S. L. Schreiber, *J. Am. Chem. Soc.*, 1992, **114**, 6568–6570; (b) A. Bandyopadhyay, S. M. Mali, P. Lunawat, K. M. P. Raja and H. N. Gopi, *Org. Lett.*, 2011, **13**, 4482–4485; (c) M. G. Kumar, S. N. Benke, K. M. P. Raja and H. N. Gopi, *Chem. Commun.*, 2015, **51**, 13397–13399; (d) A. Bandyopadhyay, R. Misra and H. N. Gopi, *Chem. Commun.*, 2016, **52**, 4938–4941.
5. (a) C. Grison, P. Coutrot, S. Geneve, C. Didierjean and M. Marraud, *J. Org. Chem.*, 2005, **70**, 10753–10764; (b) C. Grison, S. Geneve, E. Halbin and P. Coutrot, *Tetrahedron*, 2001, **57**, 4903-4923; (c) T. K. Chakraborty, A. Ghosh, S. K. Kumar, A. C. Kunwar, *J. Org. Chem.*, 2003, **68**, 6459–6462.
6. (a) R. Misra, S. Dey, R. M. Reja and H. N. Gopi, *Angew. Chem., Int. Ed.*, 2018, **57**, 1057–1061; (b) K. Veeresh, M. Singh and H. N. Gopi, *Org. Biomol. Chem.*, 2019, **17**, 9226-9231.
7. M. G. Kumar, S. M. Mali and H. N. Gopi, *Org. Biomol. Chem.*, 2013, **11**, 803-813.
8. M. G. Kumar, K. Veeresh, S. A. Nalawade, R. V. Nithun and H. N. Gopi, *J. Org. Chem.*, 2019, **84**, 15145–15153.

9. K. Veeresh and H. N. Gopi, *Org. Lett.*, 2019, **21**, 4500–4504.
10. M. Singh, M. Kumar, S. A. Nalawade, D. R. Puneeth Kumar and H. N. Gopi, *Org. Biomol. Chem.*, 2023, **21**, 3766–3769.
11. (a) V. Dourtoglou, J. C. Ziegler and B. Gross, *Tetrahedron Lett.*, 1978, **15**, 1269–1272; (b) V. Dourtoglou, B. Gross, V. Lambropoulou and C. Zioudrou, *Synthesis*, 1984, **07**, 572–574; (c) S. Adam, *Bioorg. Med. Chem. Lett.*, 1992, **2**, 571–574; (d) R. Knorr, A. Trzeciak, W. Bannwarth and D. Gillessen, *Tetrahedron Lett.*, 1989, **30**, 1927–1930.
12. E. J. E. Caro-Diaz, F. A. Valeriote and W. H. Gerwick, *Org. Lett.*, 2019, **21**, 793–796.
13. P. Zarantonello, C. P. Leslie, R. Ferritto and W. M. Kazmierski, *Bioorg. Med. Chem. Lett.*, 2002, **12**, 561–565.
14. T. Conroy, J. T. Guo, N. Elias, K. M. Cergol, J. Gut, J. Legac, L. Khatoon, Y. Liu, S. McGowan, P. J. Rosenthal, N. H. Hunt and R. J. Payne, *J. Med. Chem.*, 2014, **57**, 10557–10563.
15. T. Conroy, J. T. Guo, N. H. Hunt and R. J. Payne, *Org. Lett.*, 2010, **12**, 5576–5579.
16. M. Jiang, S. Chen, J. Li and L. Liu, *Mar. Drugs*, 2020, **18**, 114.
17. R. Ratnayake, S. P. Gunasekera, J. J. Ma, L. H. Dang, T. J. Carney, V. J. Paul and H. Luesch, *ChemBioChem*, 2020, **21**, 2356–2366.
18. (a) B. G. Van den Hoven and H. Alper, *J. Am. Chem. Soc.*, 2001, **123**, 10214–10220; (b) K. Tonogaki, K. Itami, and J.-ichi. Yoshida, *J. Am. Chem. Soc.*, 2006, **128**, 1464–1465; (c) A. Mallinger, B. Nadal, N. Chopin, and T. Le Gall, *Eur. J. Org. Chem.*, 2010, **5**, 1142–1048; (d) Y. Ujihara, K. Nakayama, T. Sengoku, M. Takahashi, and H. Yoda, *Org. Lett.*, 2012, **14**, 5142–5145.
19. (a) J. Clayden, R. Turnbull and I. Pinto, *Org. Lett.*, 2004, **6**, 609–611; (b) W. Hess and J. W. Burton, *Adv. Synth. Cat.*, 2011, **353**, 2966–2970; (c) R. Naitoh, Y. Nakamura, E. Katano, Y. Nakamura, E. Okada, and M. Asaoka, *Heterocycles*, 2004, **63**, 1009–1012.
20. (a) S. G. Parameswarappa and F.C. Pigge, *J. Org. Chem.*, 2012, **77**, 8038–8048; (b) A. I. Lansakara, D. P. Farrell, and F. C. Pigge, *Org. Biomol. Chem.*, 2014, **12**, 1090–1099.
21. (a) A. Mallagaray, G. Domínguez, A. Gradillas, and J. Pérez-Castells, *Org. Lett.*, 2008, **10**, 597–600; (b) M. Daly, K. Gill, M. Sime, G. L. Simpson, and A. Sutherland, *Org. Biomol. Chem.*, 2011, **9**, 6761–6770.
22. (a) M. Toyofuku, E. Murase, H. Nagai, S.-ichi Fujiwara, T. S.-ike, H. Kuniyasu and N. Kambe, *Eur. J. Org. Chem.* 2009, **19**, 3141–3144; (b) Y. Kobayashi, H. Kamisaki, R. Yanada, and Y. Takemoto, *Org. Lett.*, 2006, **8**, 2711–2713.

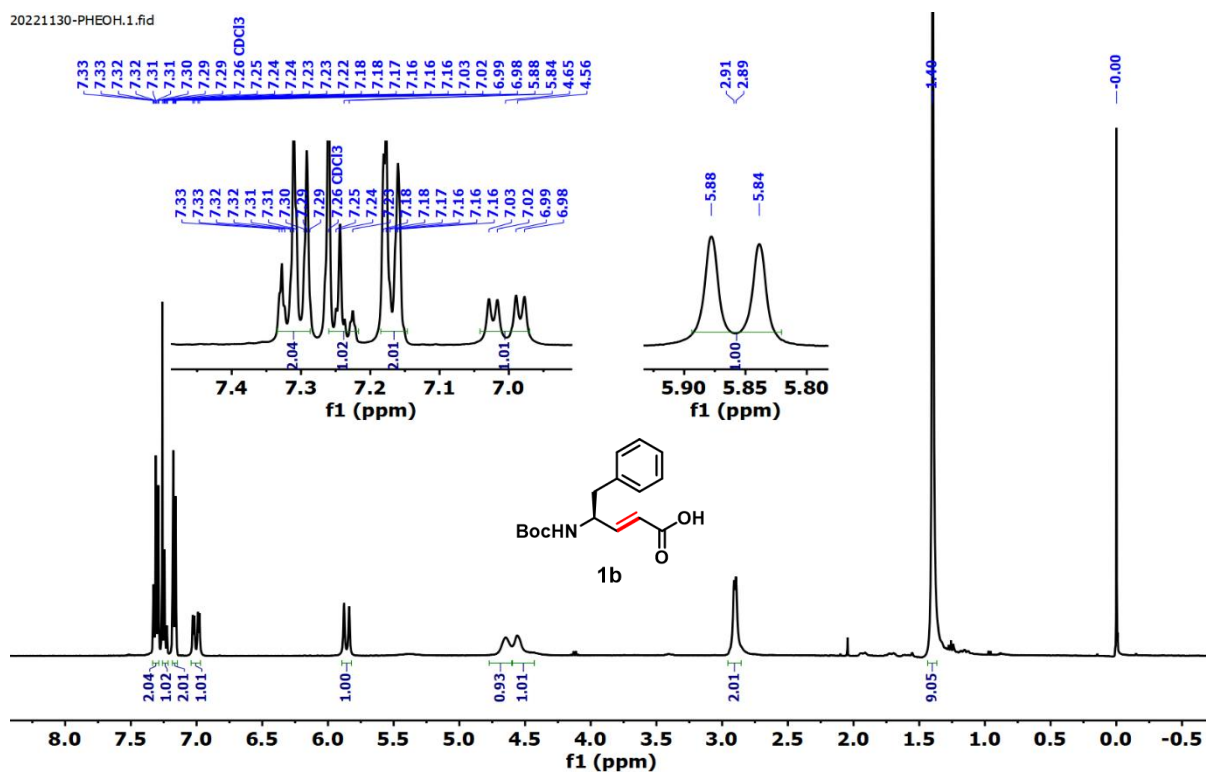
23. (a) A. J. Pearson, H. Sun and X. Wang, *J. Org. Chem.*, 2007, **72**, 2547–2557; (b) F. Palacios, A. M. Ochoa de Retana, and A. Vélez del Burgo *J. Org. Chem.*, 2011, **76**, 9472–9477; (c) R. T. Watson, V. K. Gore, K. R. Chandupatla, R. K. Dieter and J. P. Snyder, *J. Org. Chem.*, 2004, **69**, 6105–6114.
24. Y. Tang and C. Li, *Org. Lett.*, 2004, **6**, 3229–3231.
25. (a) F. Nishino, K. Miki, Y. Kato, K. Ohe, and S. Uemura, *Org. Lett.*, 2003, **5**, 2615–2617; (b) M. Lautens, W. Han, and J. H.-C. Liu, *J. Am. Chem. Soc.* 2003, **125**, 4028–4029; (c) G. B. Bajracharya, P. S. Koranne, R. N. Nadaf, R. K. M. Gabr, K. Takenaka, S. Takizawa and H. Sasai, *Chem. Commun.*, 2010, **46**, 9064-9066.
26. S. M. Mali, A. Bandyopadhyay, S. V. Jadhav, M. G. Kumar and H. N. Gopi, *Org. Biomol. Chem.*, 2011, **9**, 6566-6574.
27. M. Bodanszky and A. Bodanszky, *The Practice of Peptide Synthesis*; Springer-Verlag: New York, 1984, pp 1–282.

3A.9 Appendix

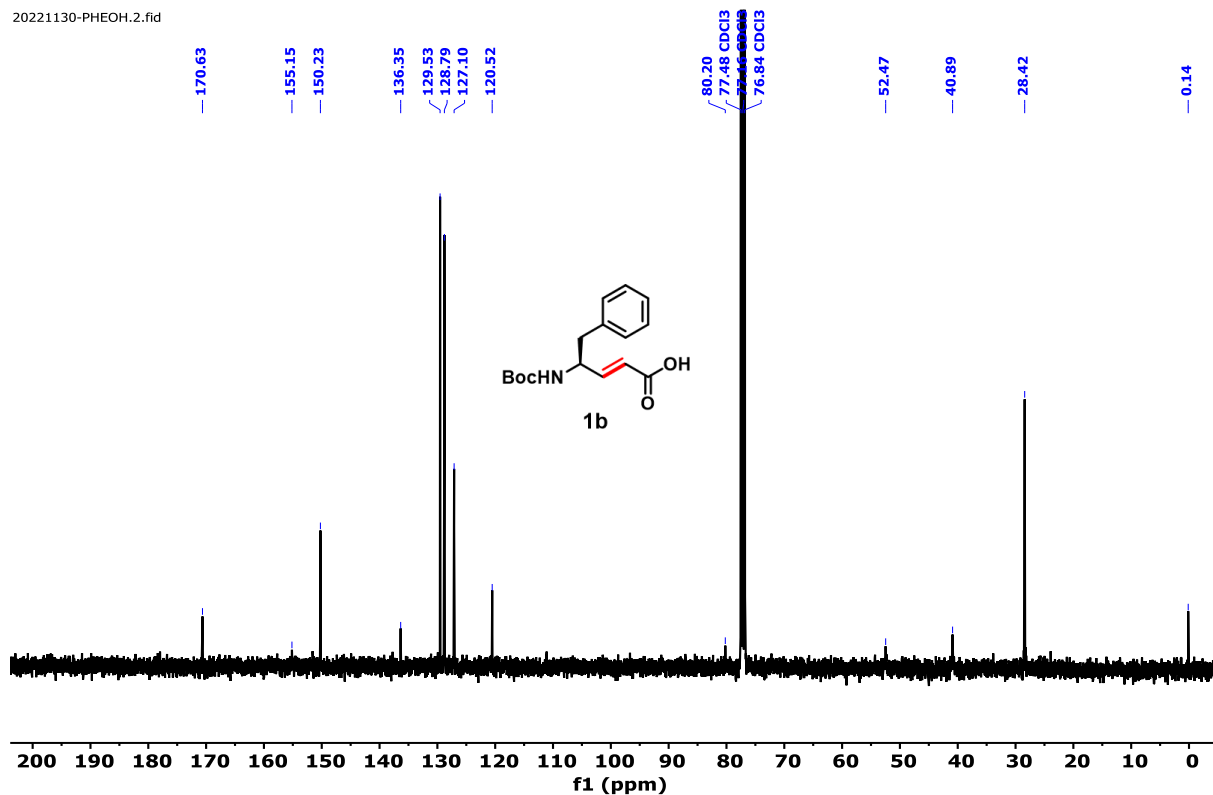
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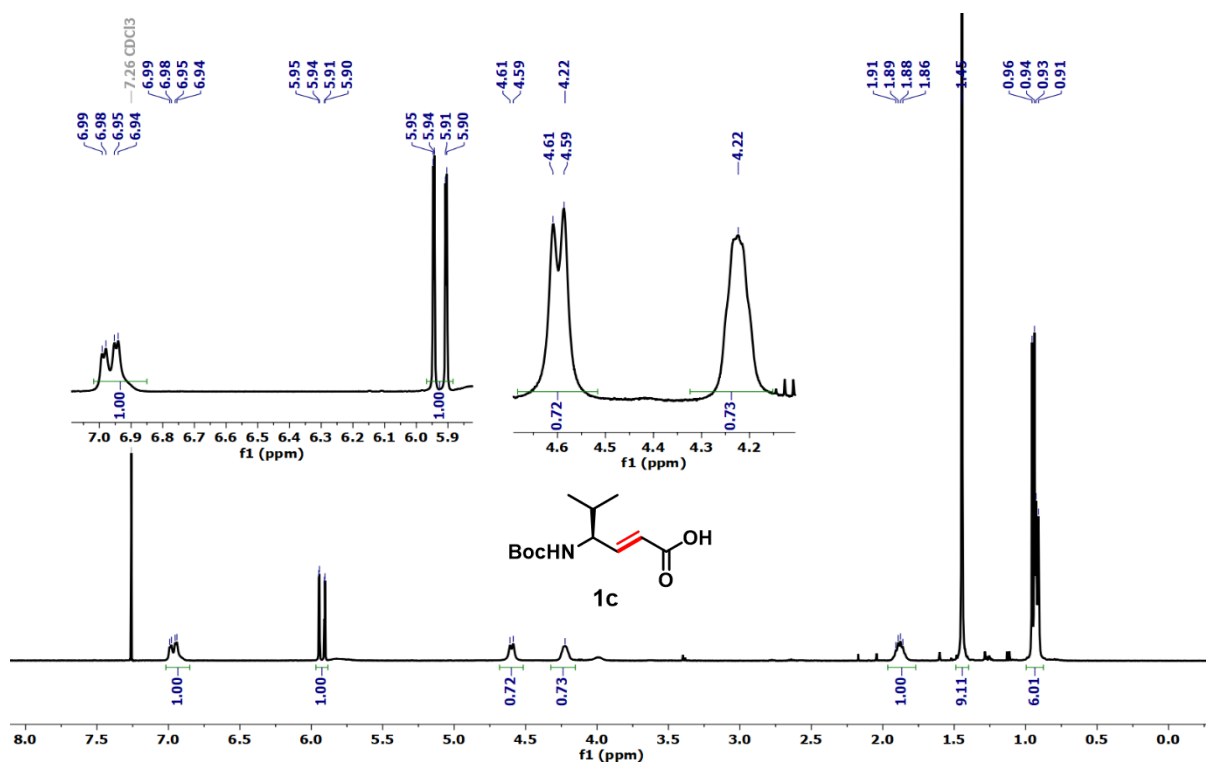


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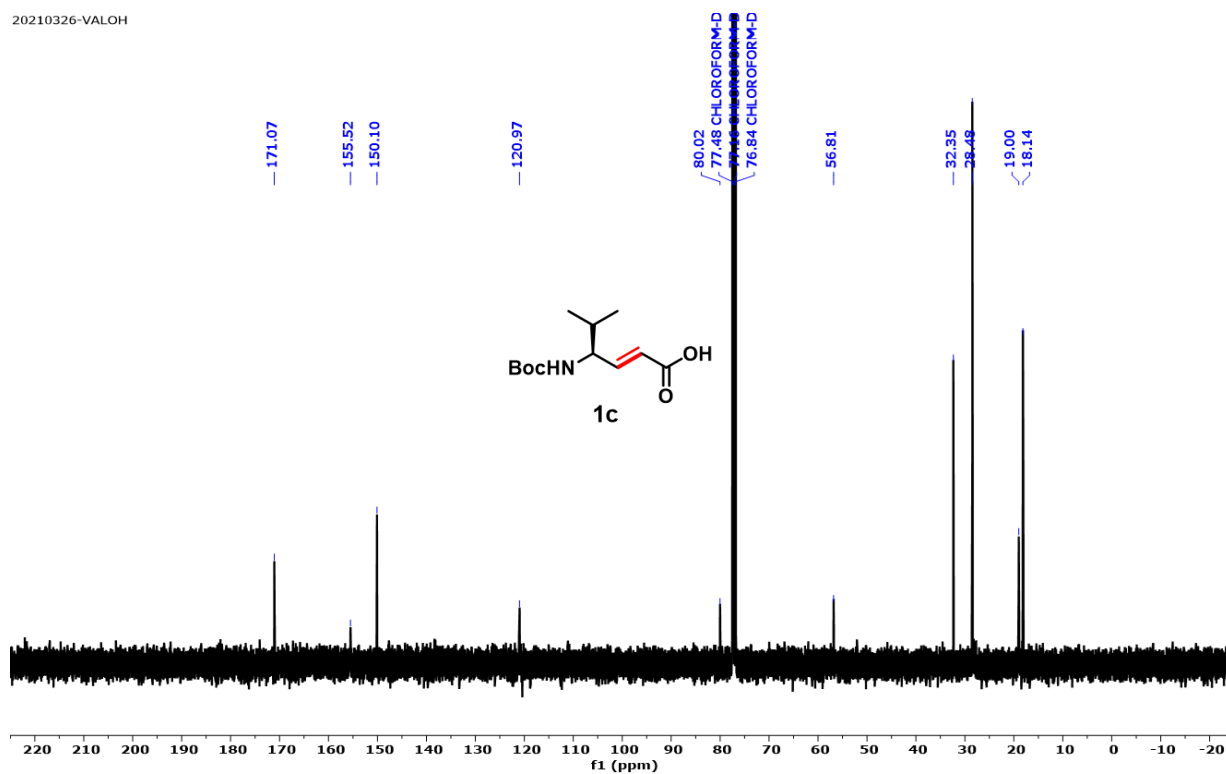


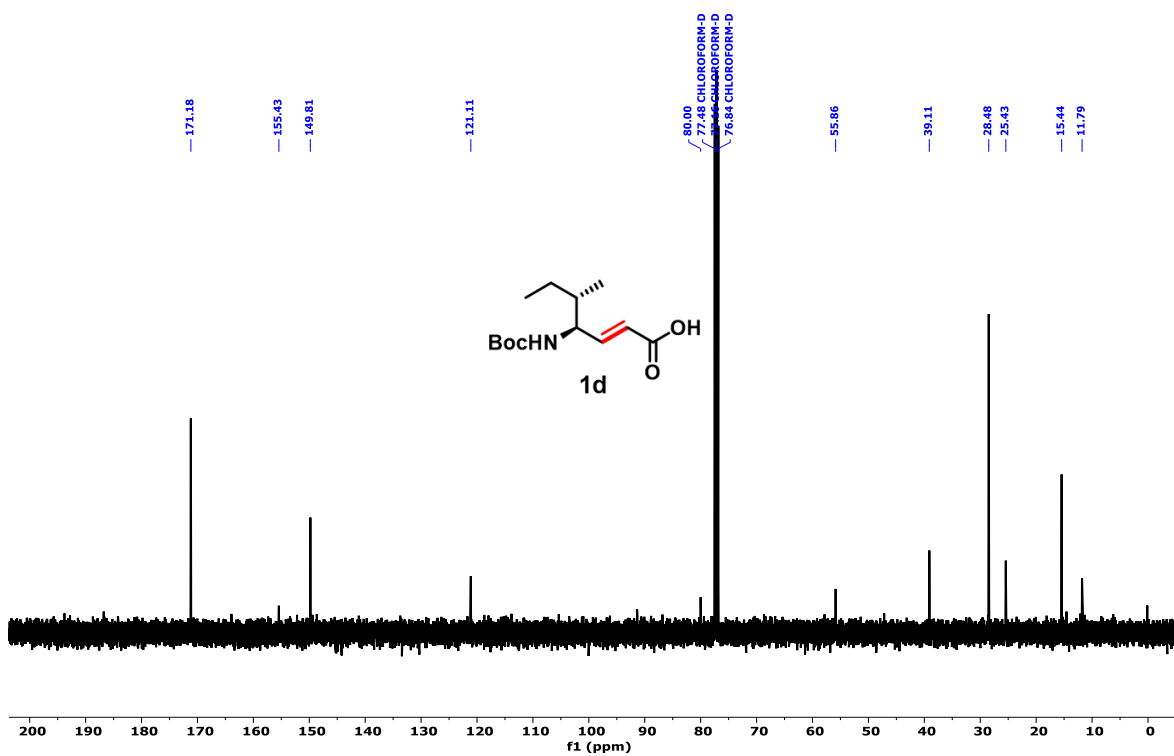
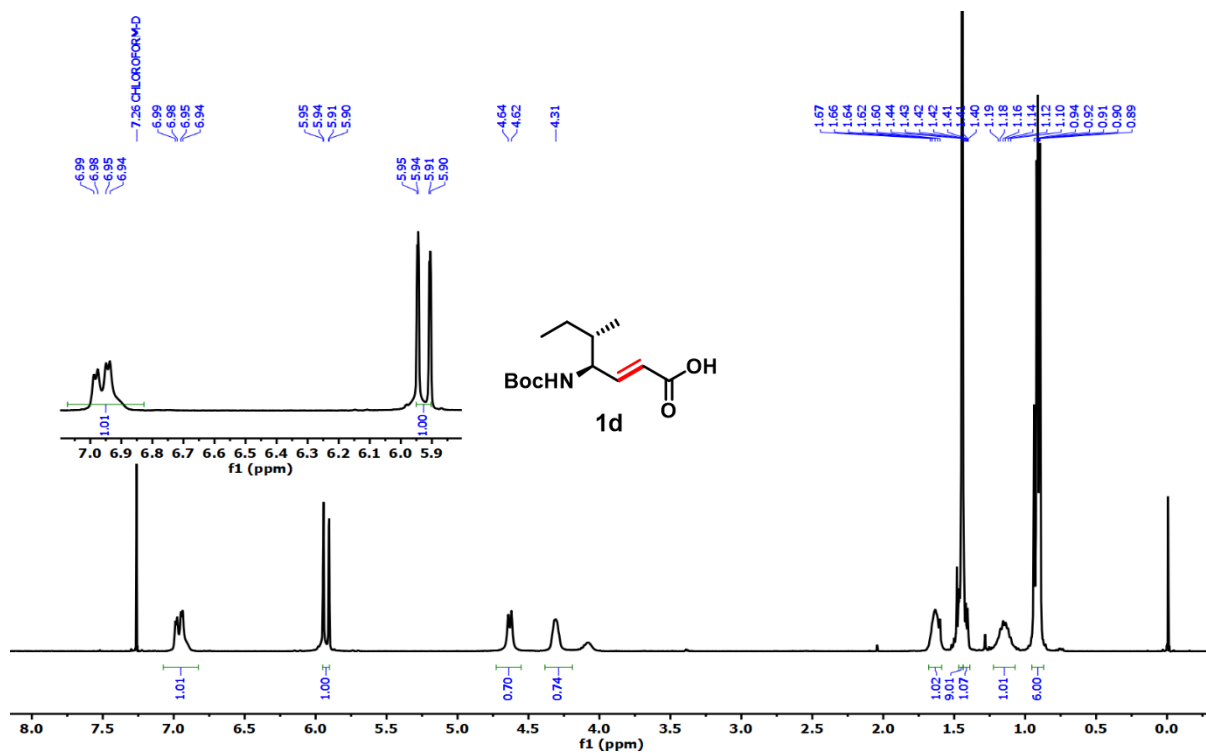
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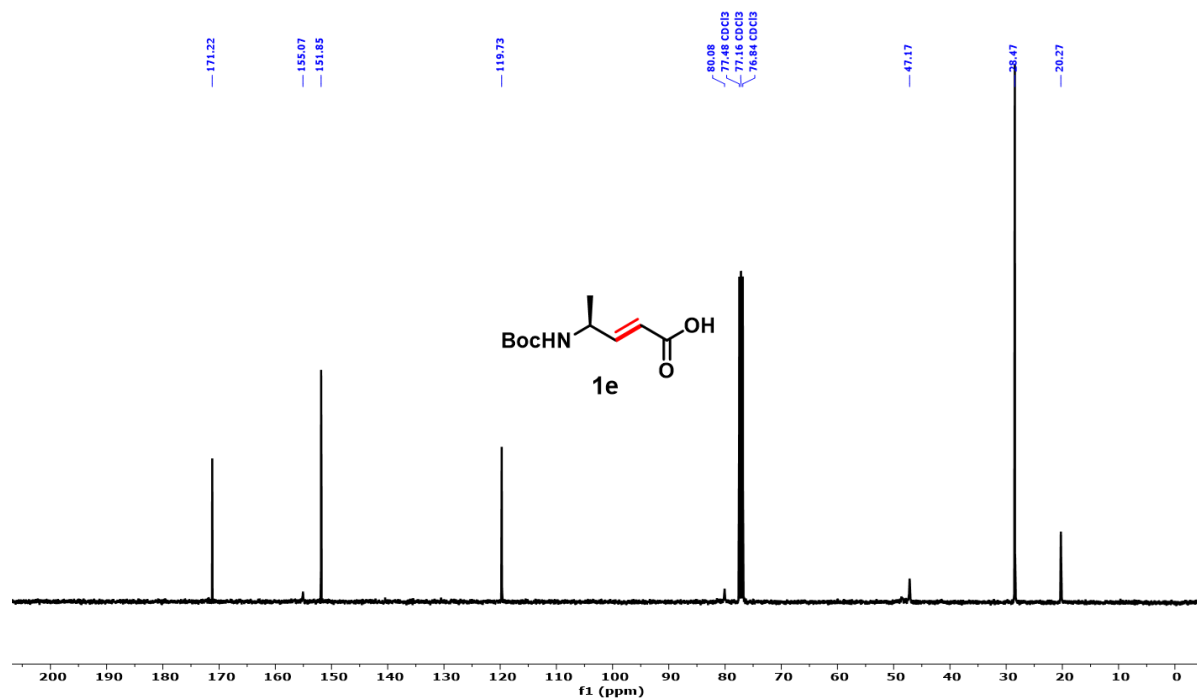
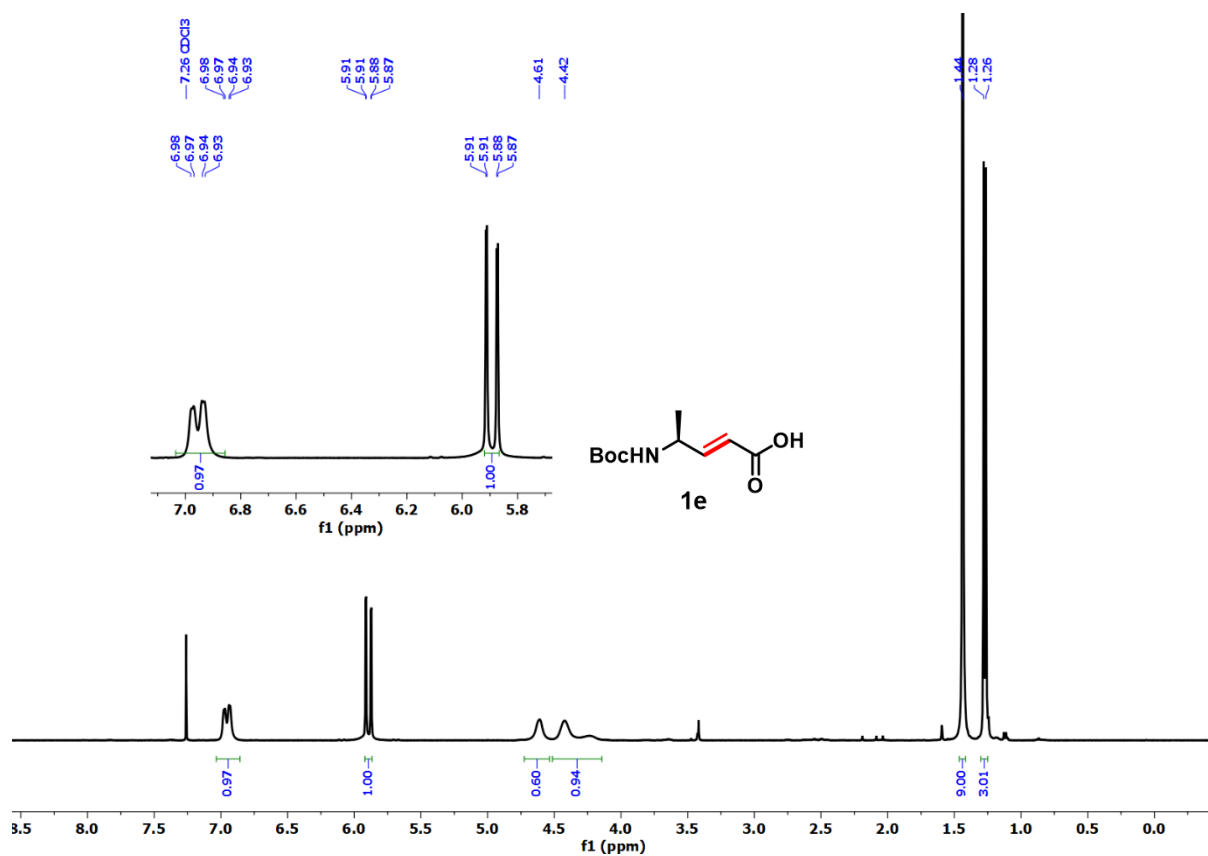


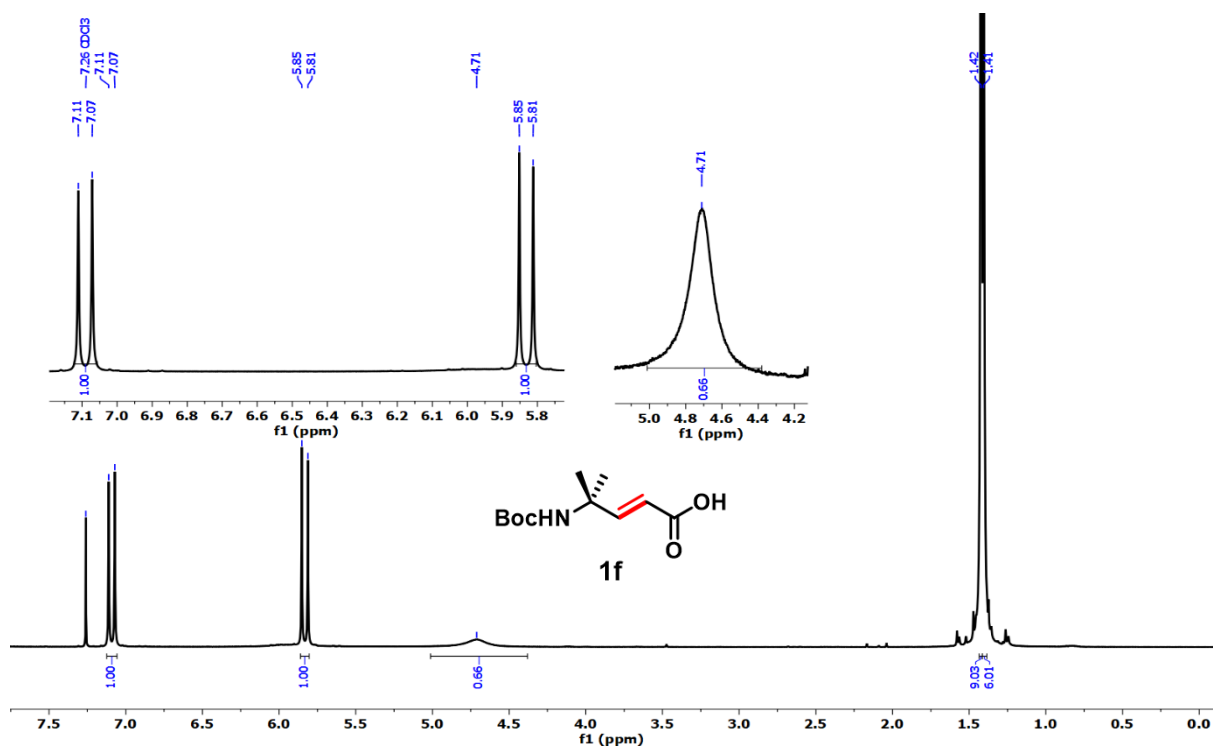


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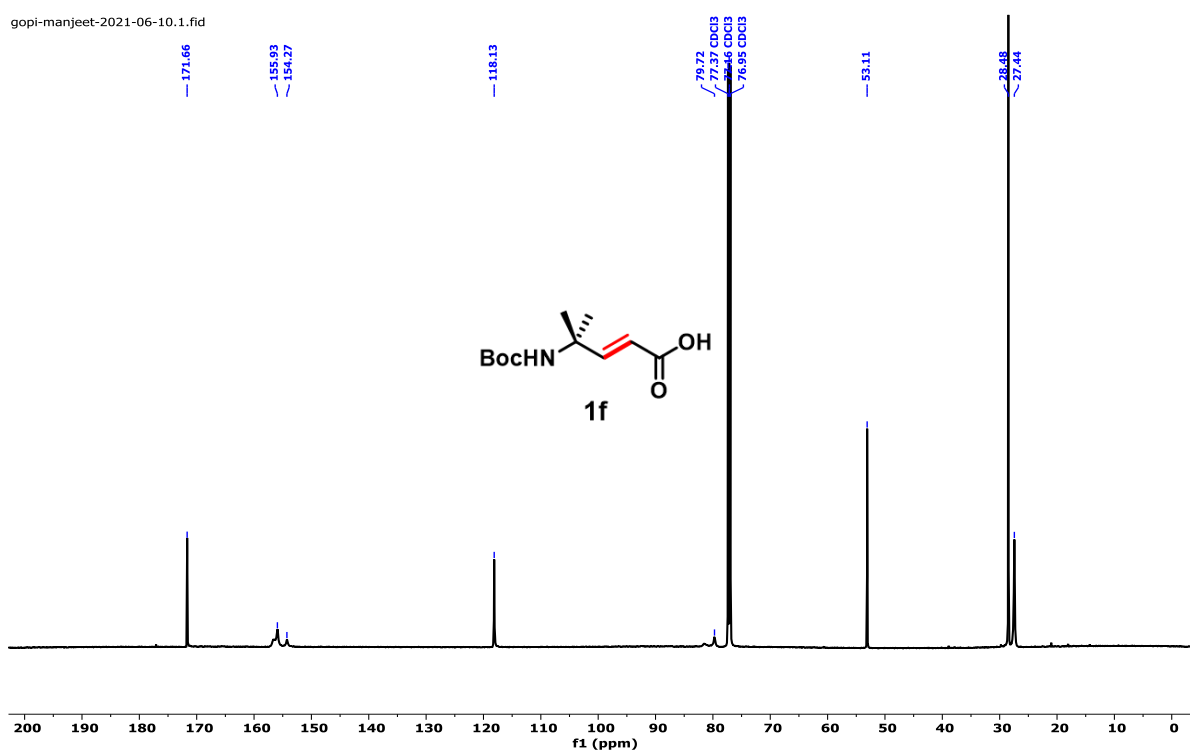


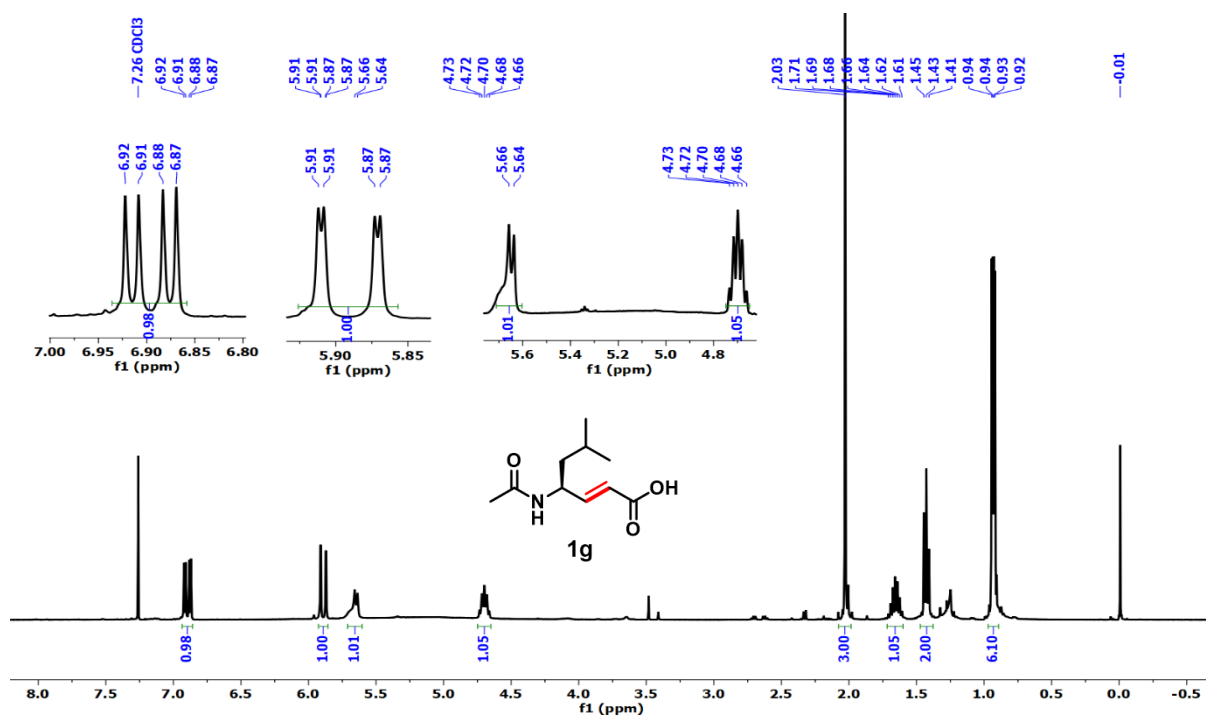




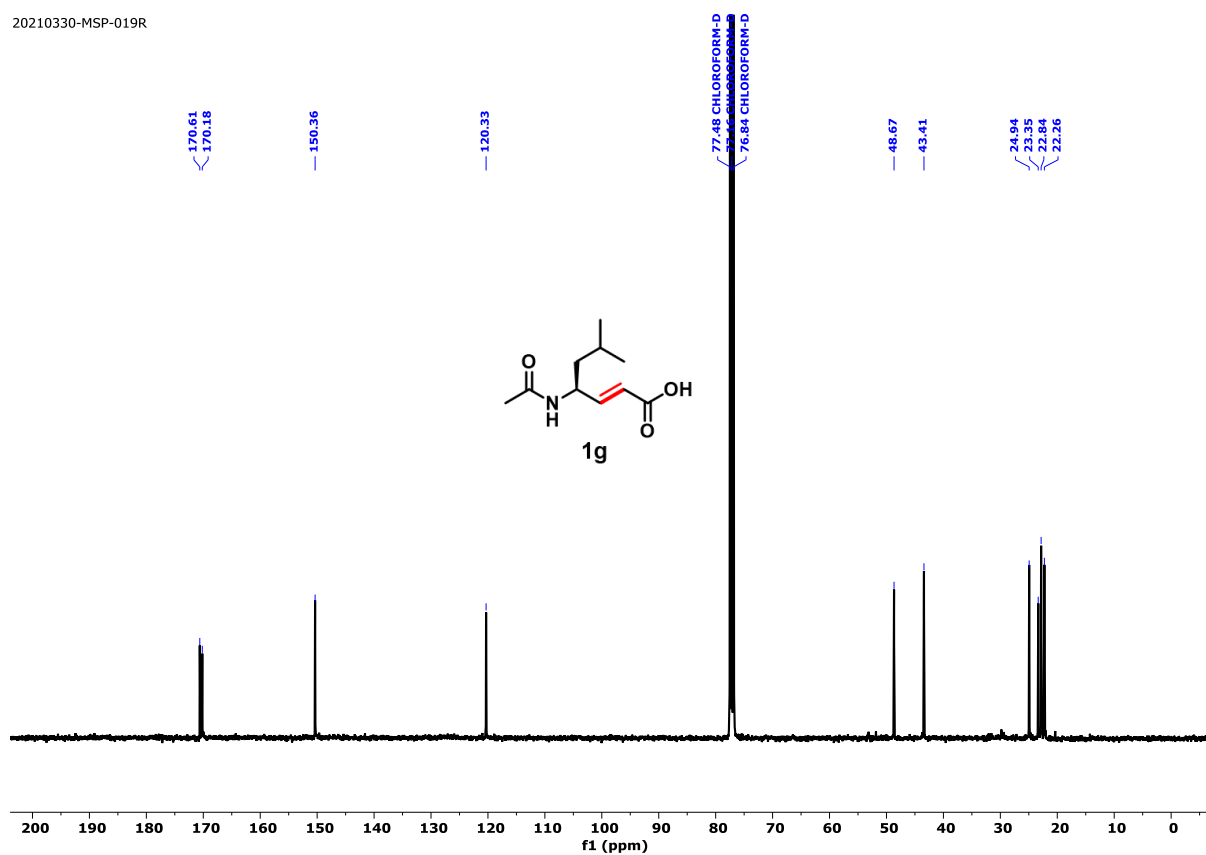


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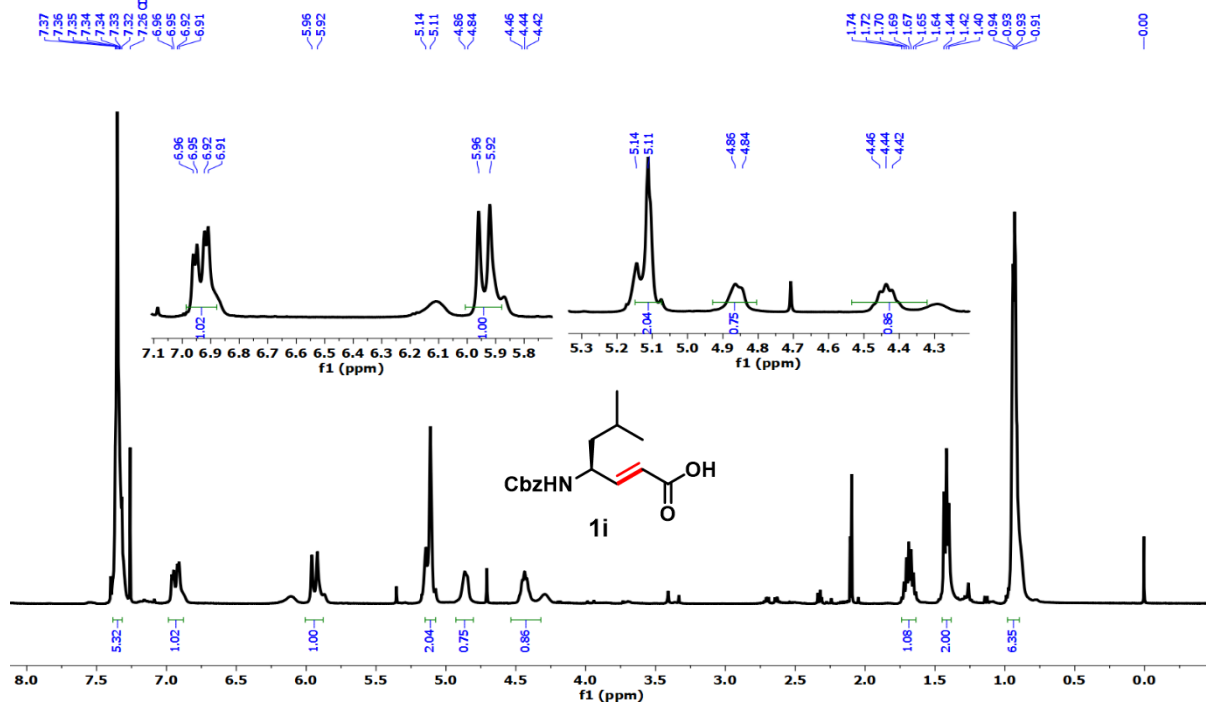




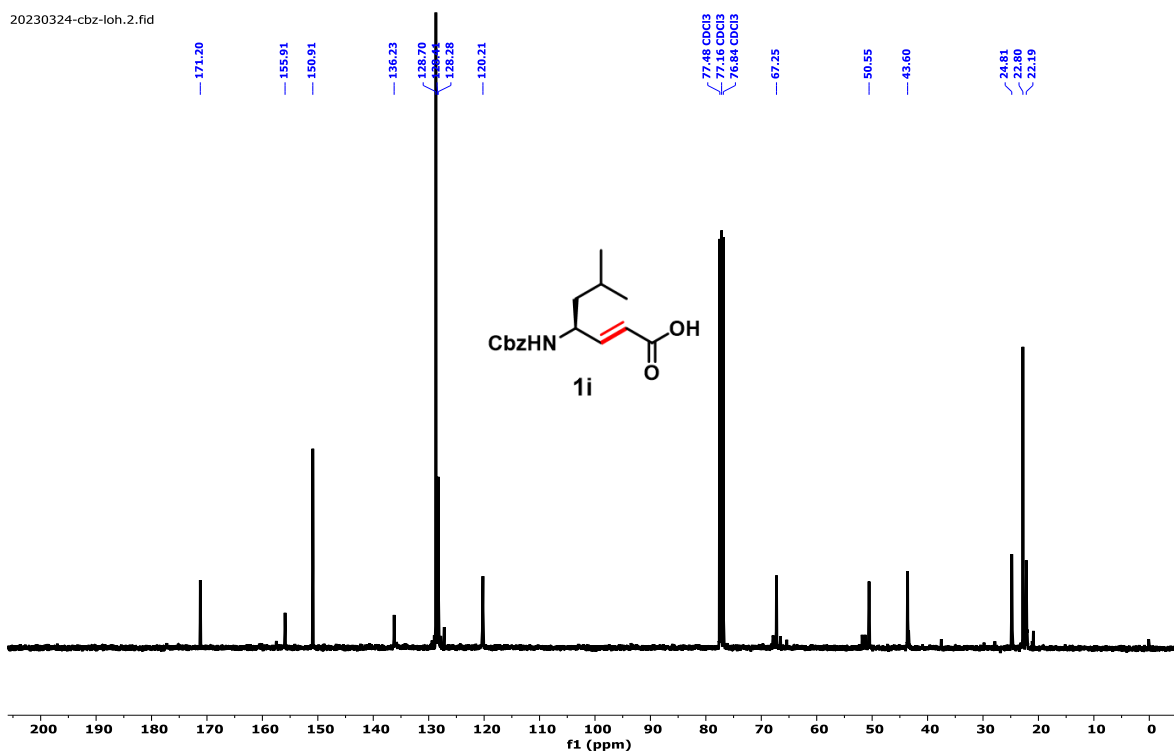
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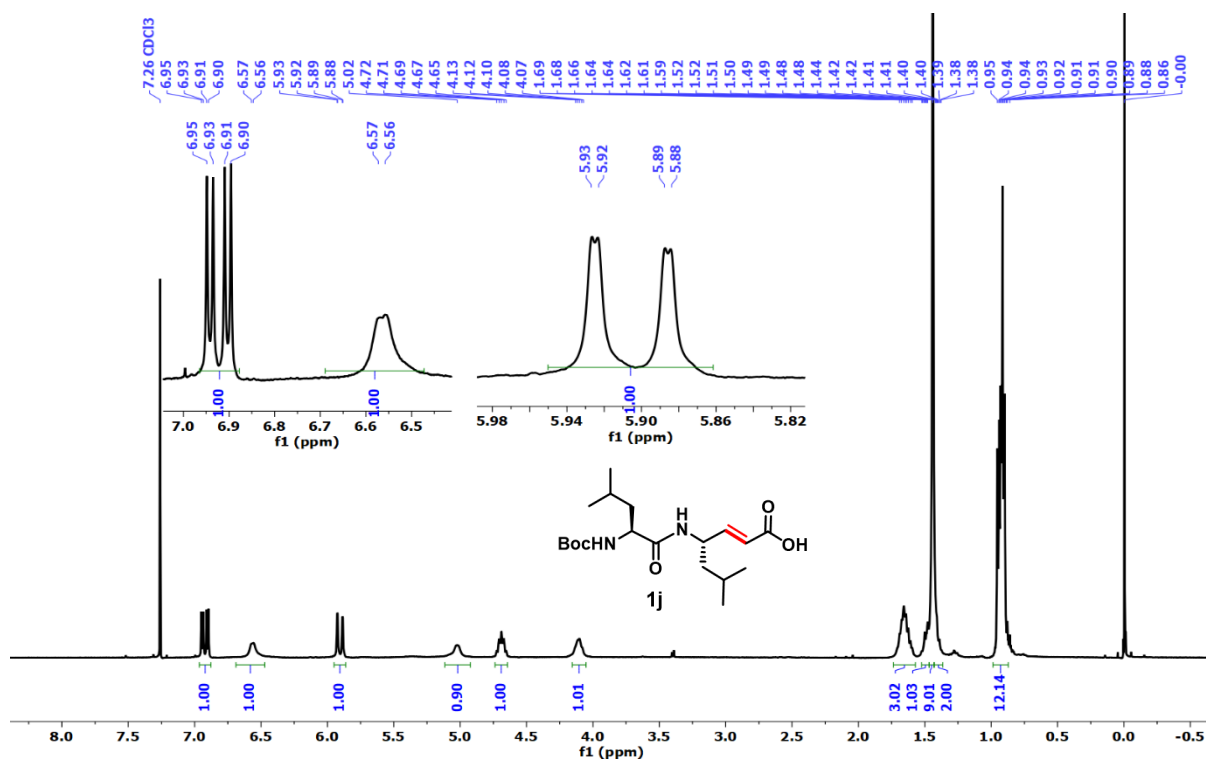


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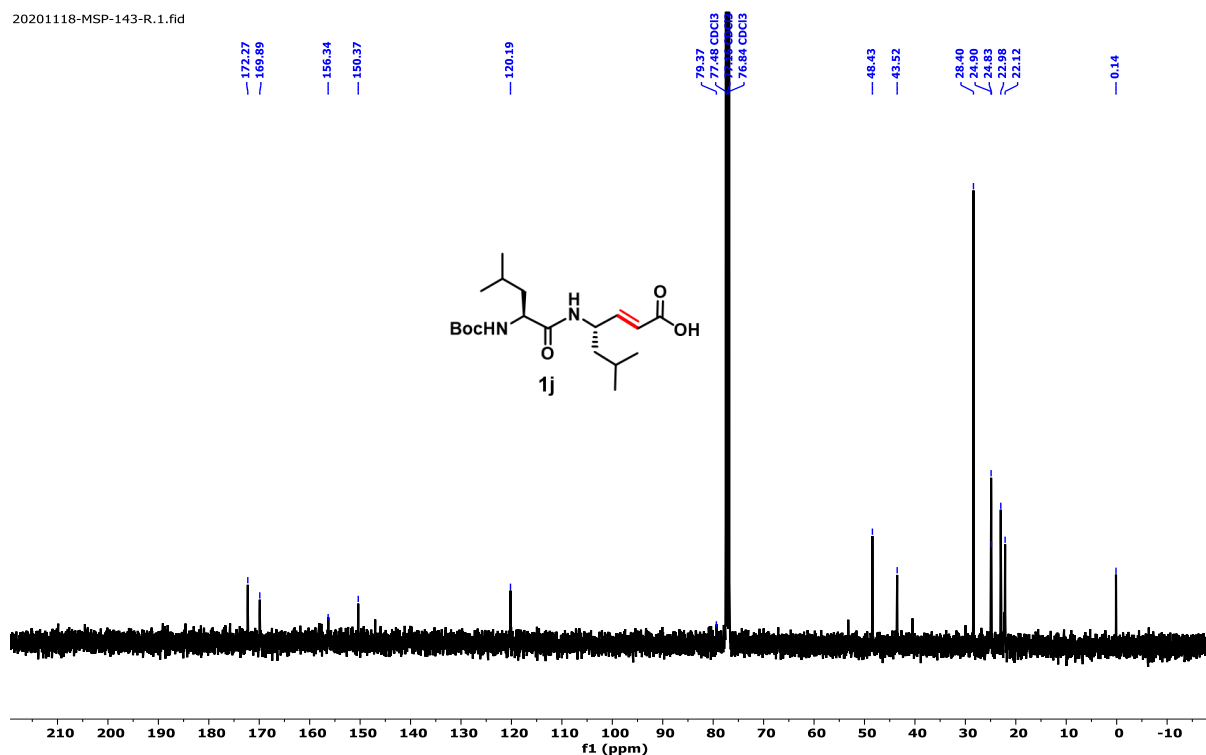


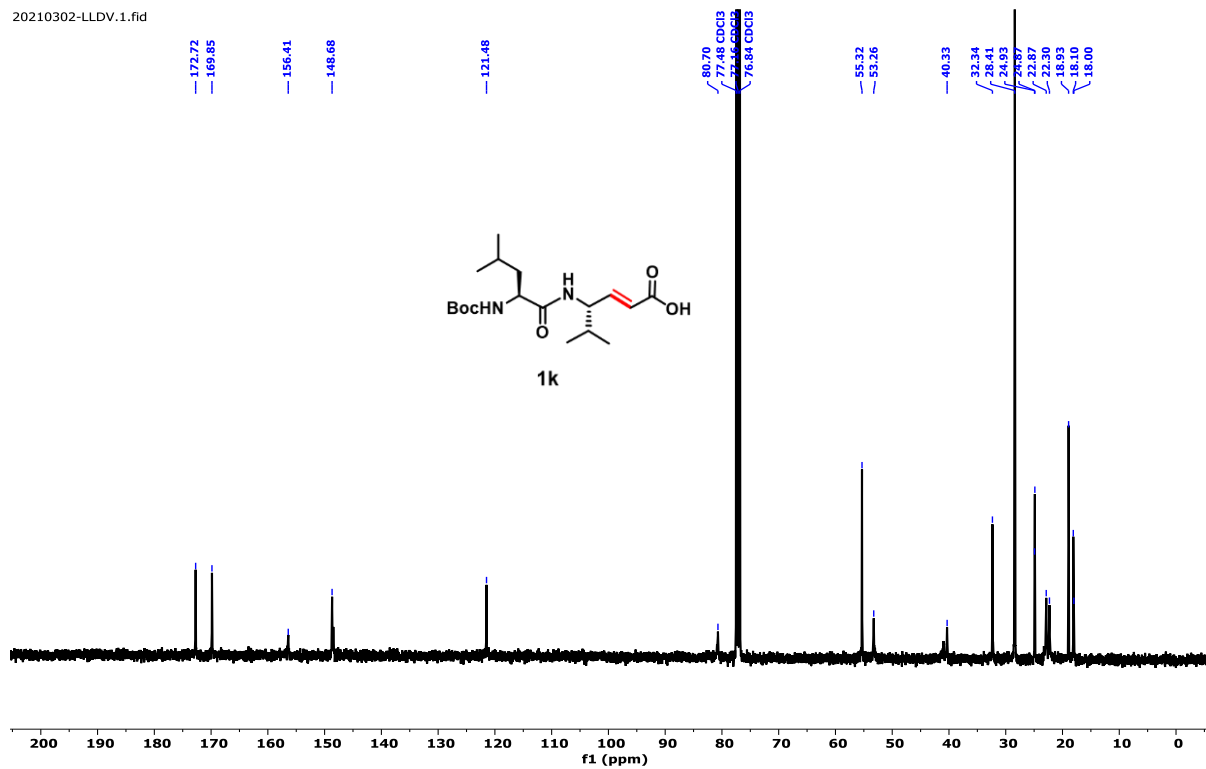
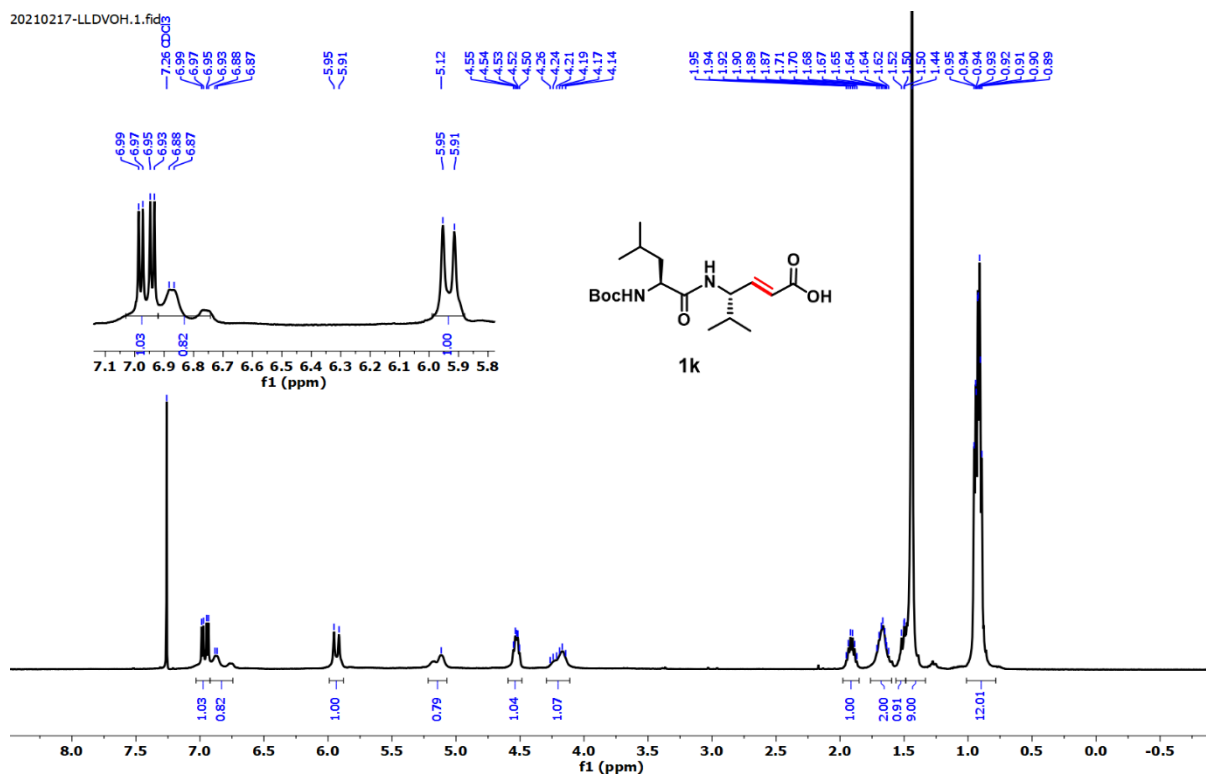
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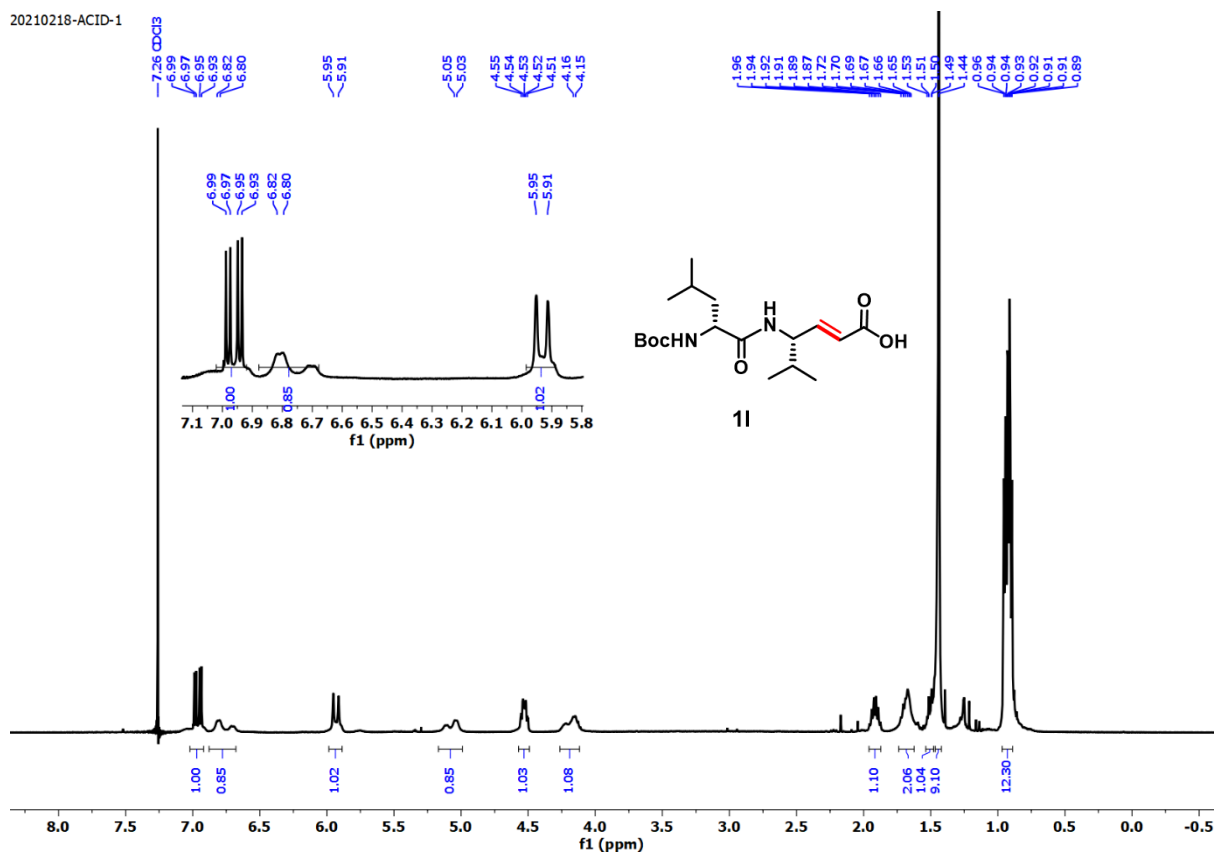


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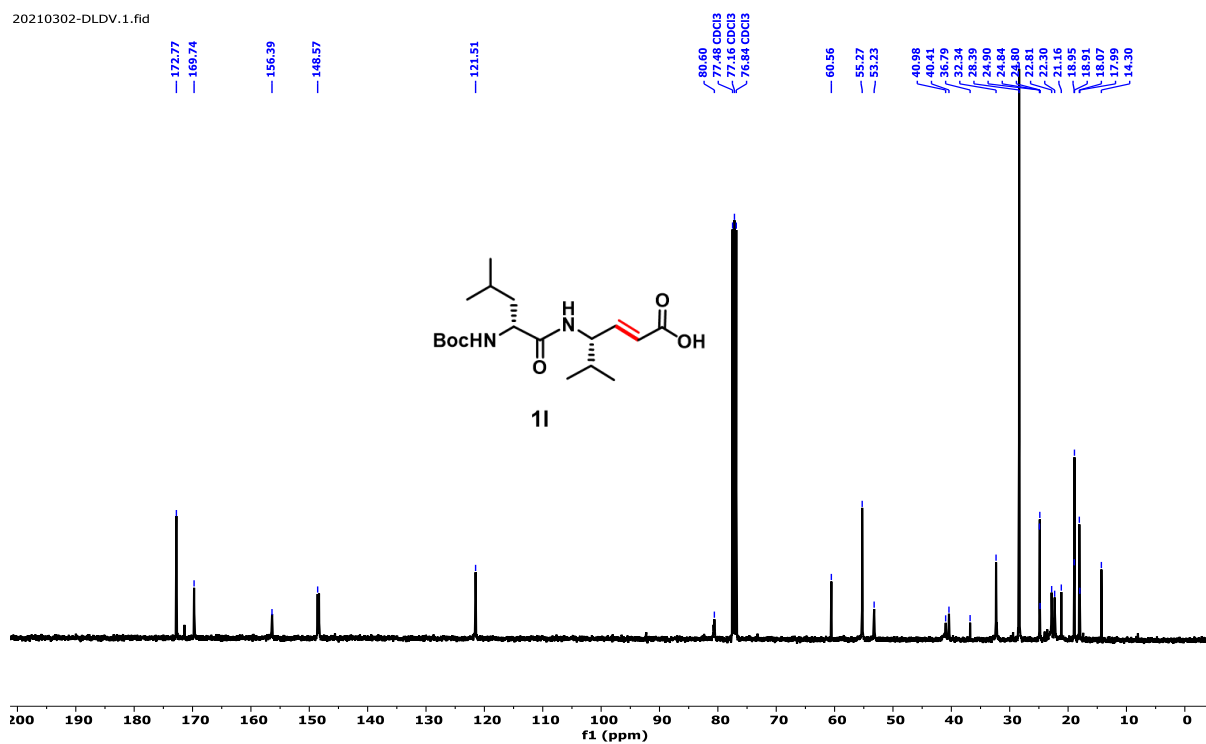




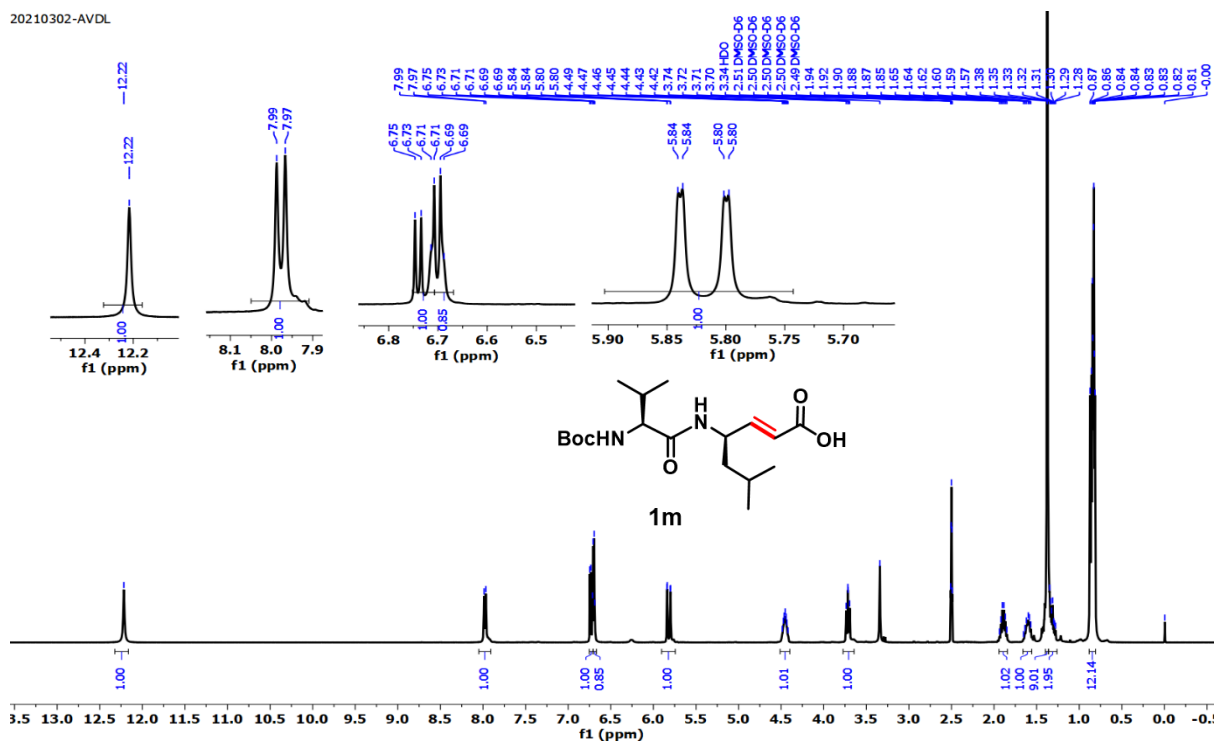
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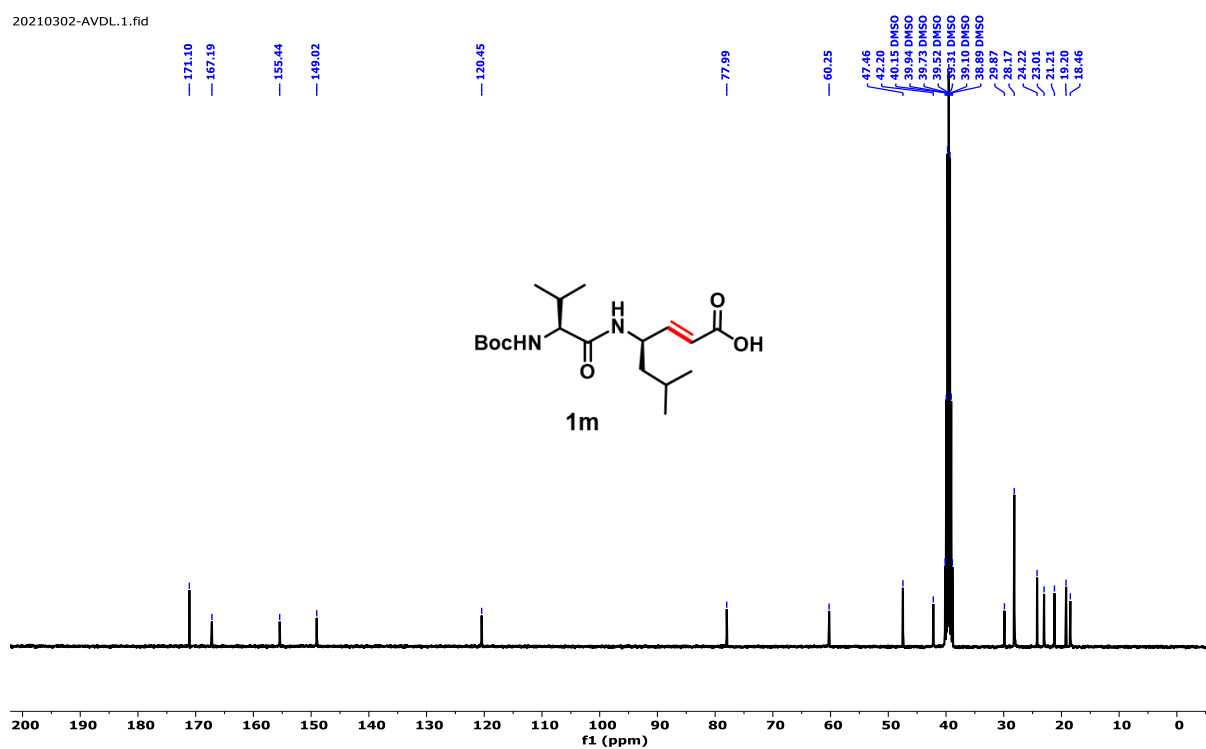
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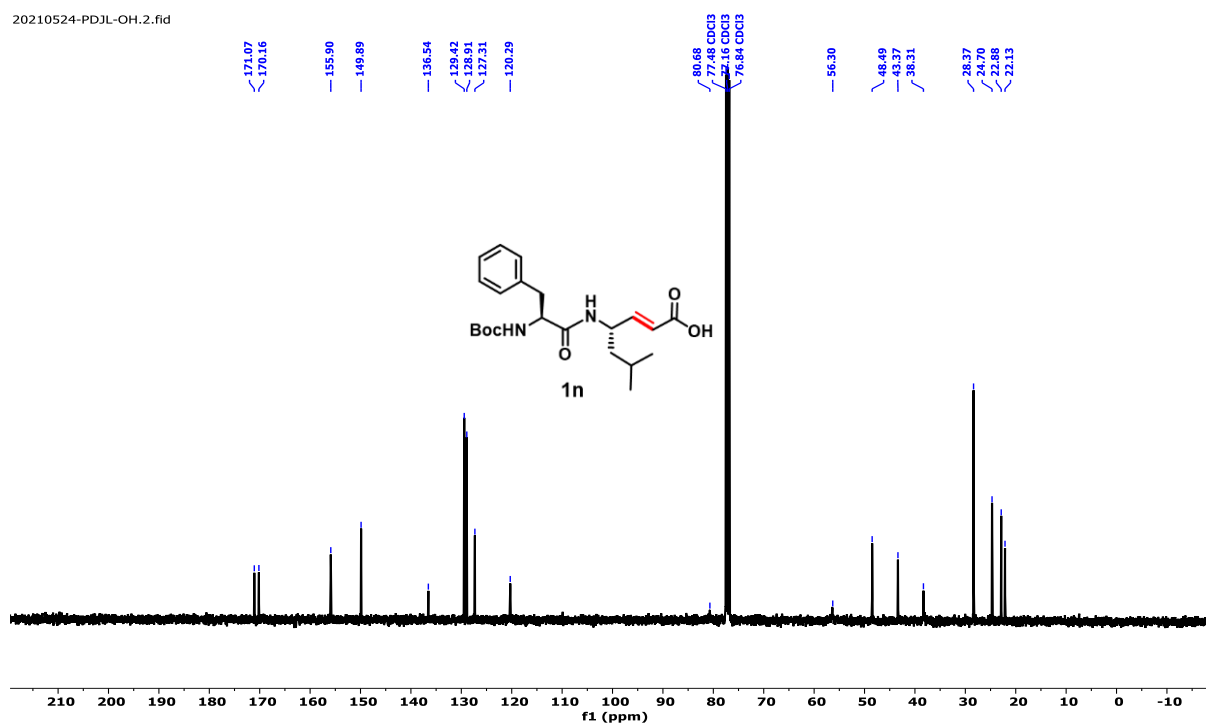
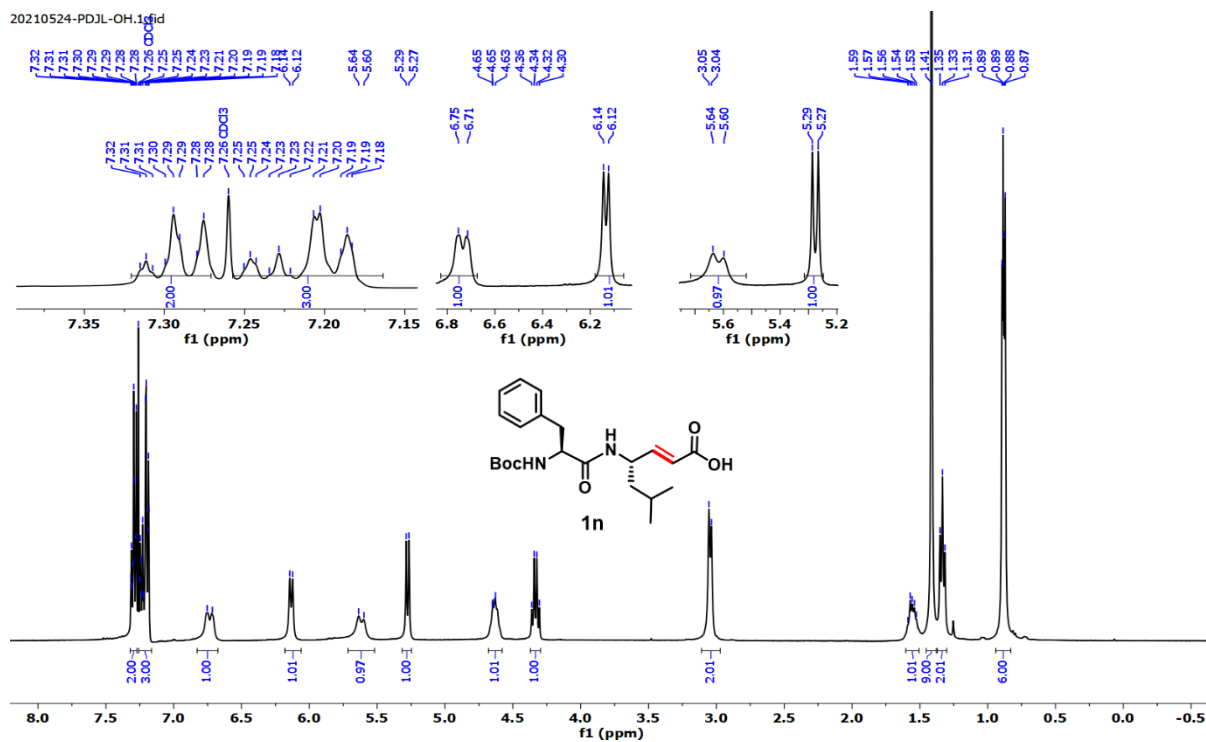


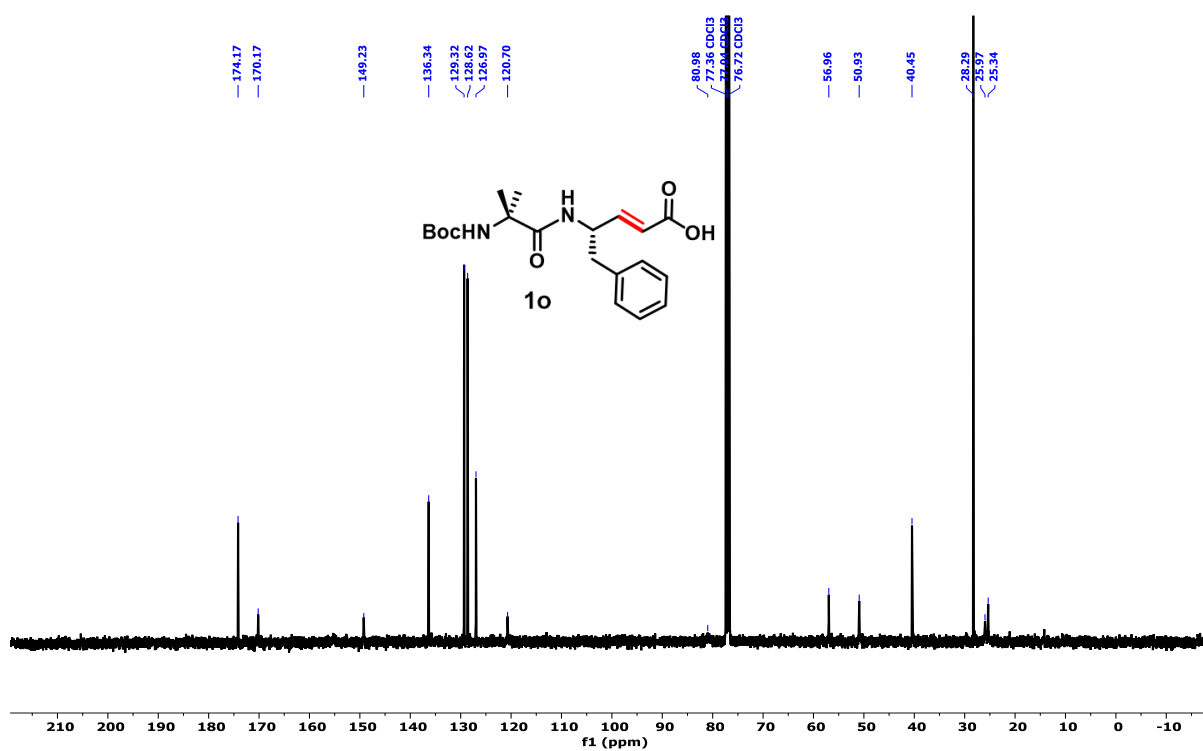
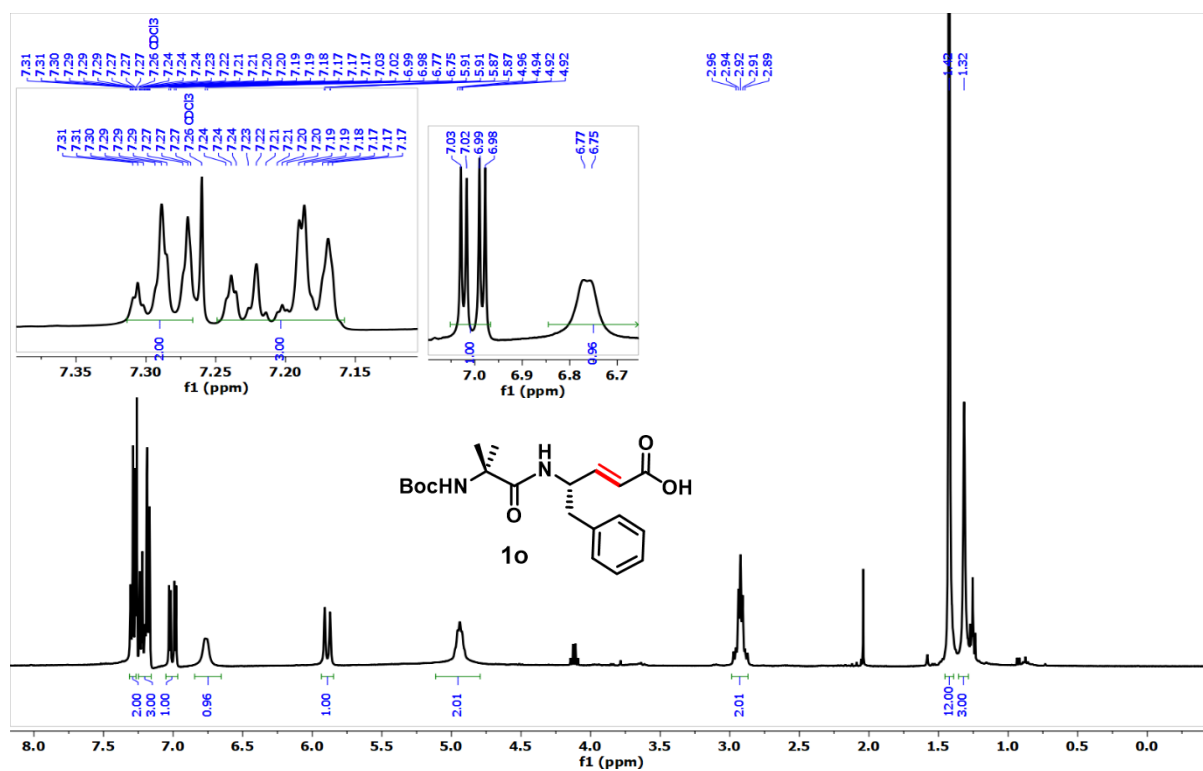
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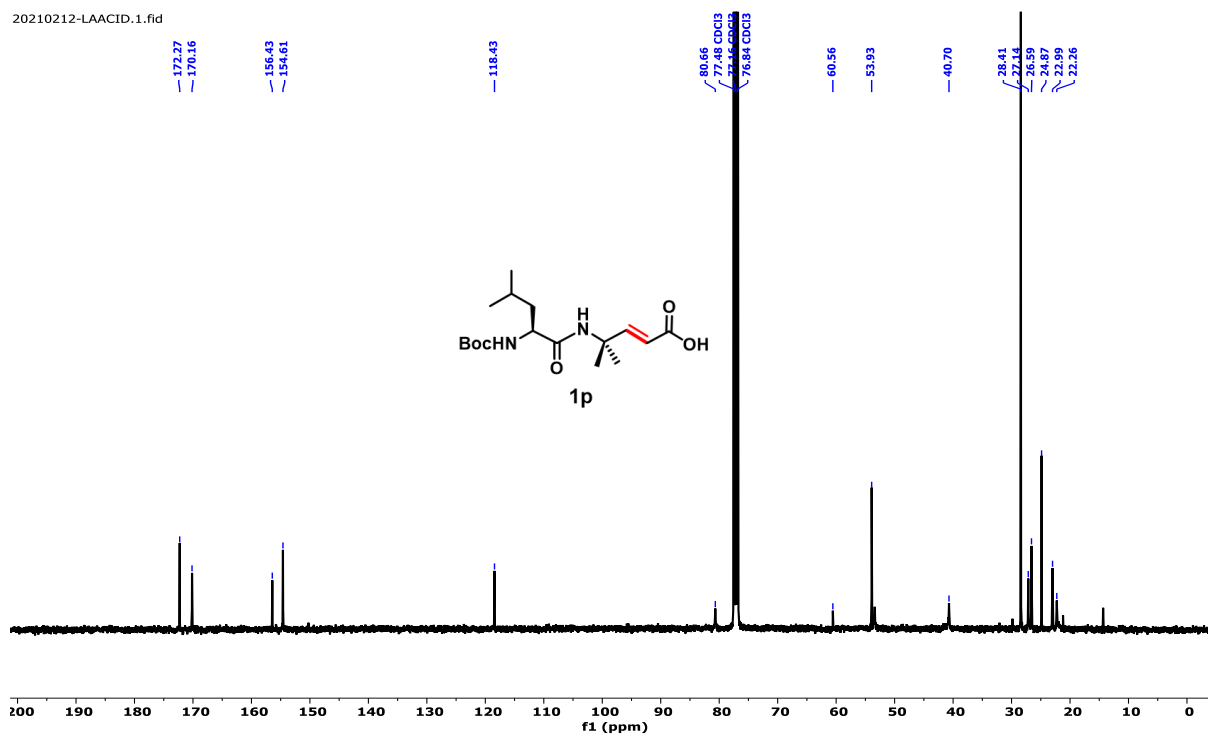
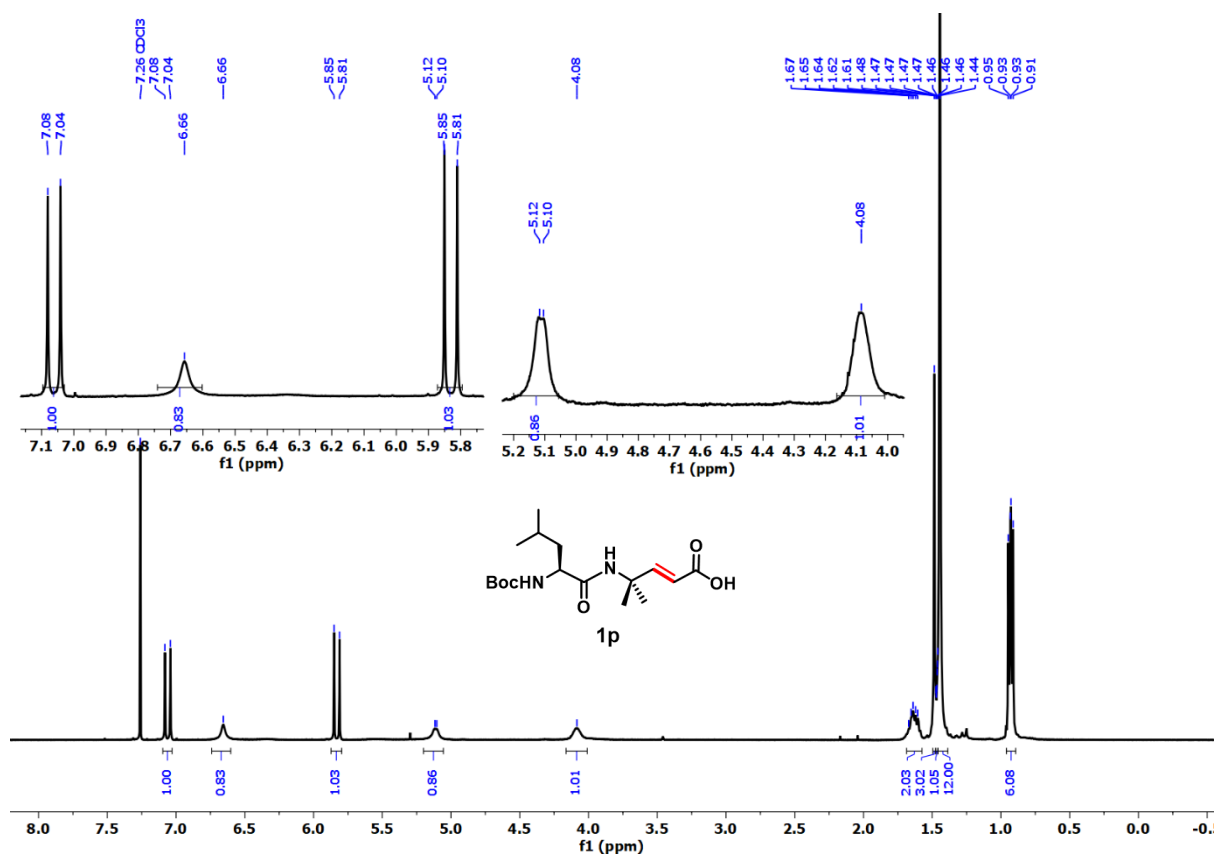


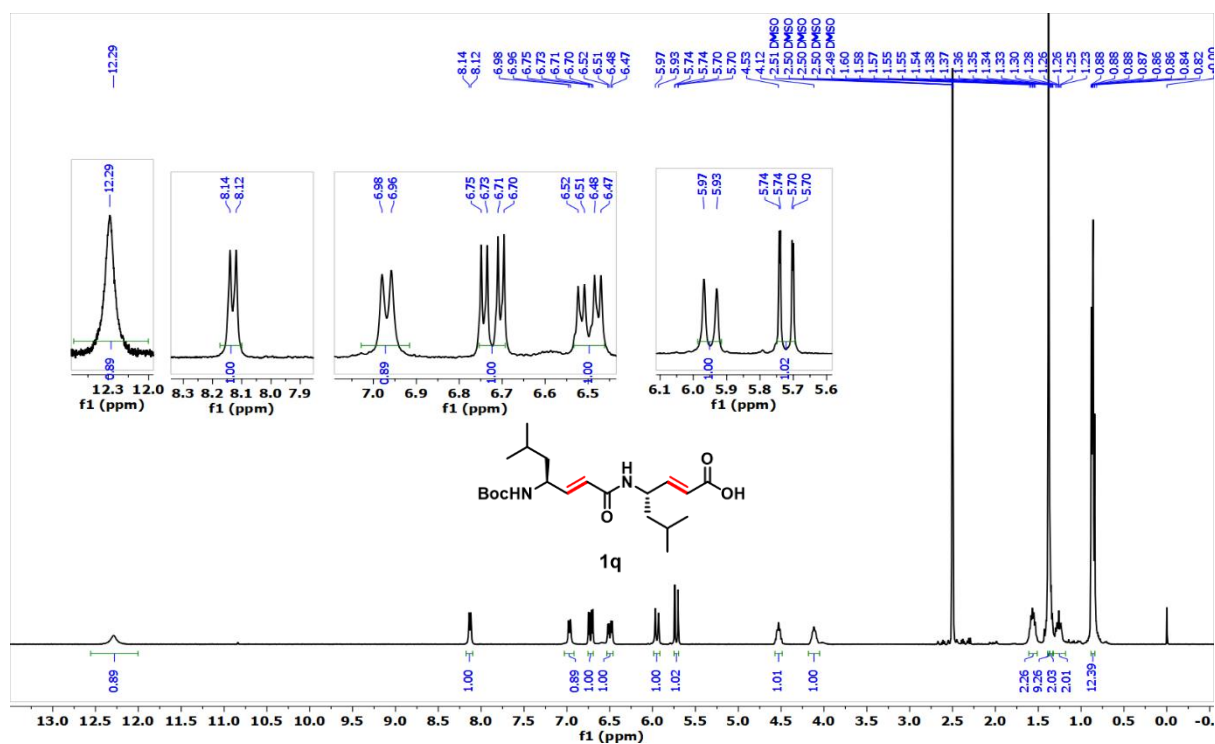
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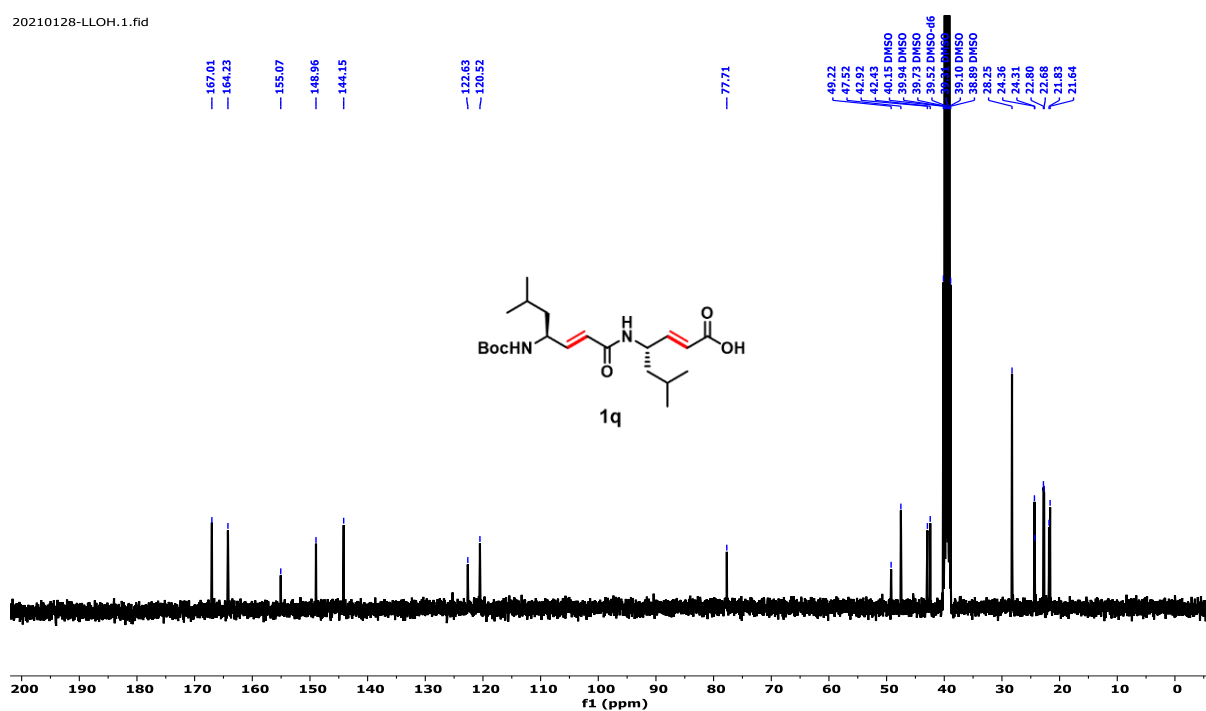


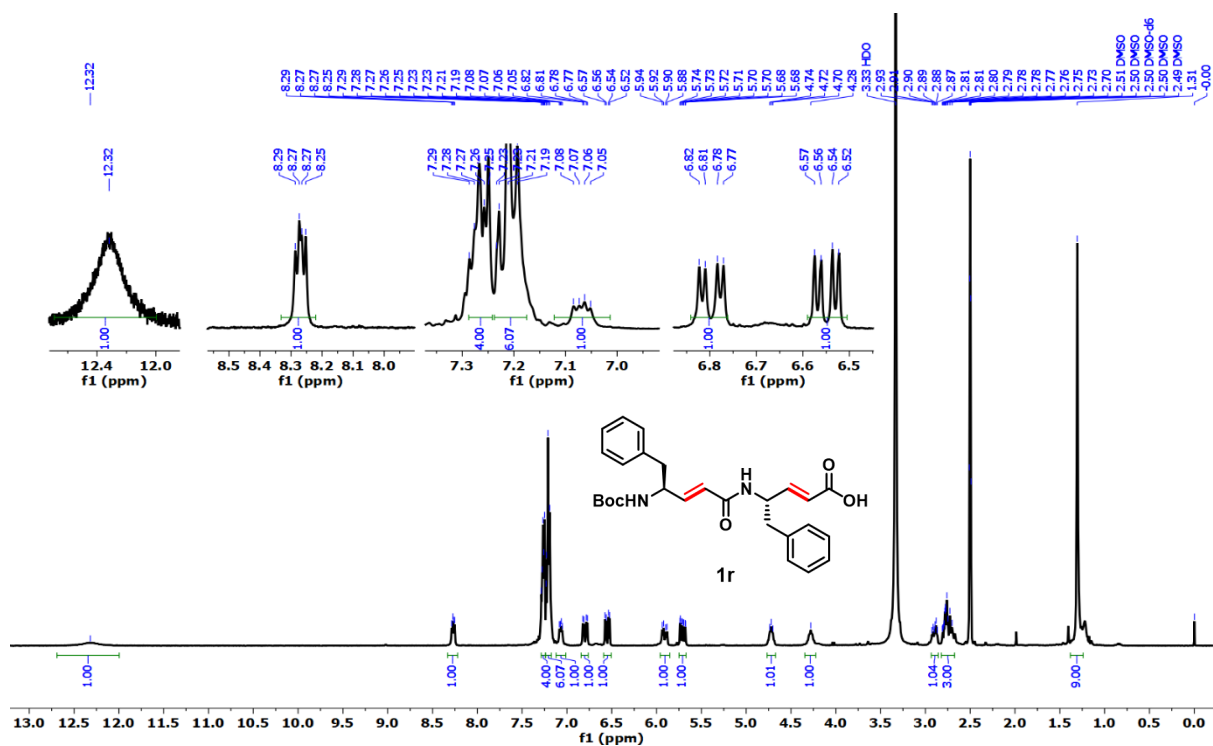




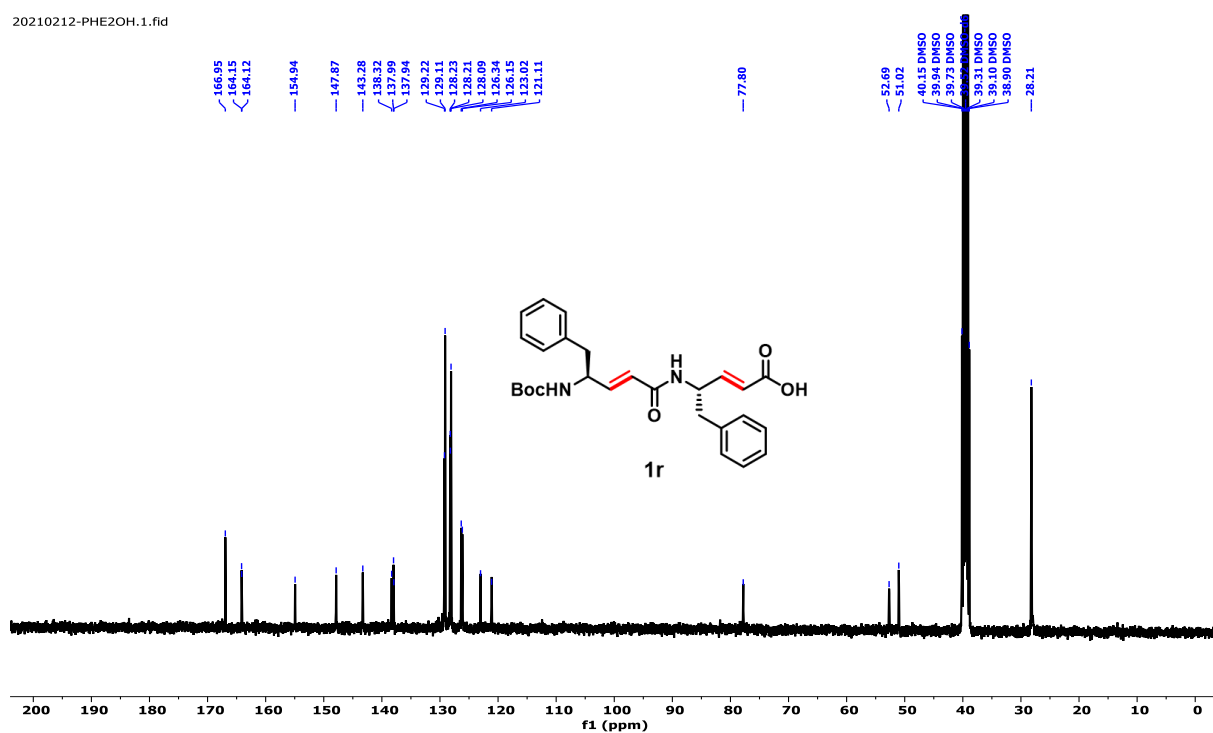


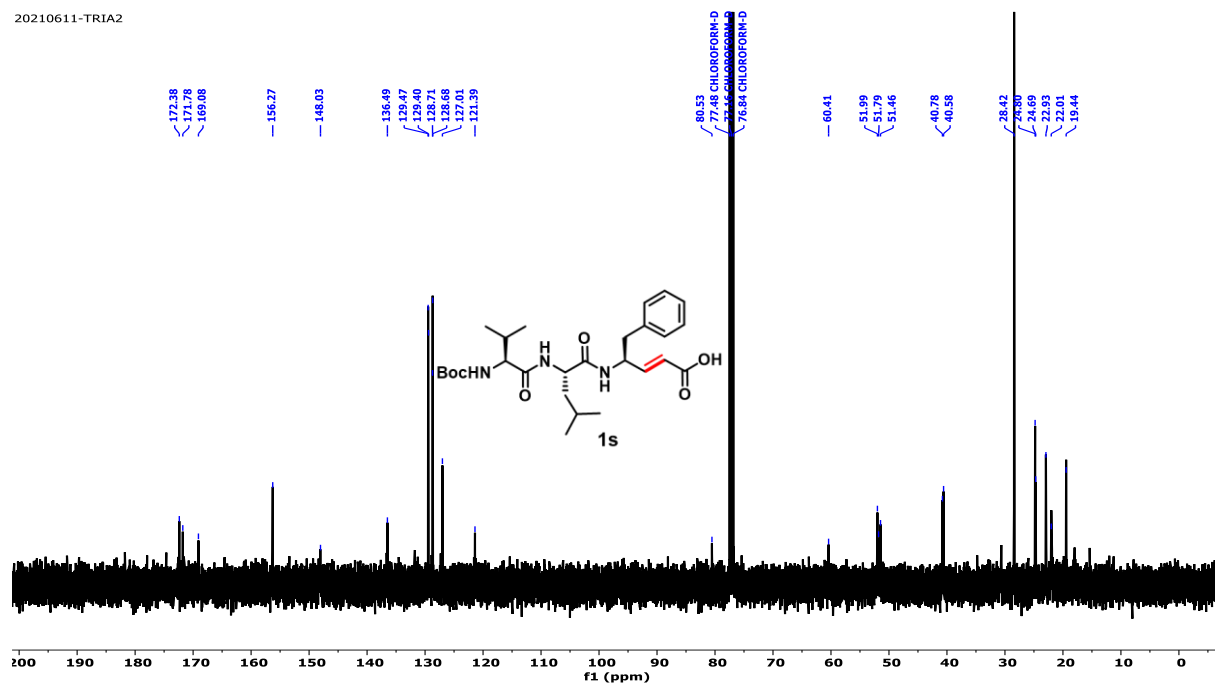
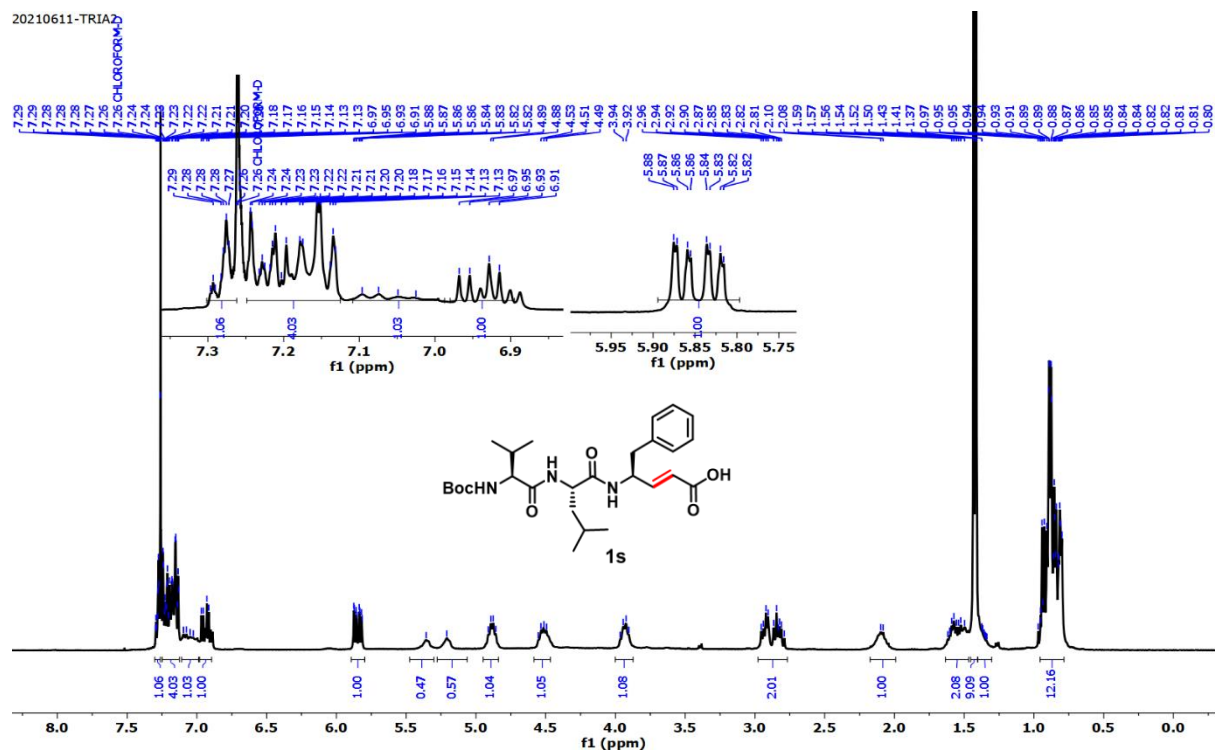
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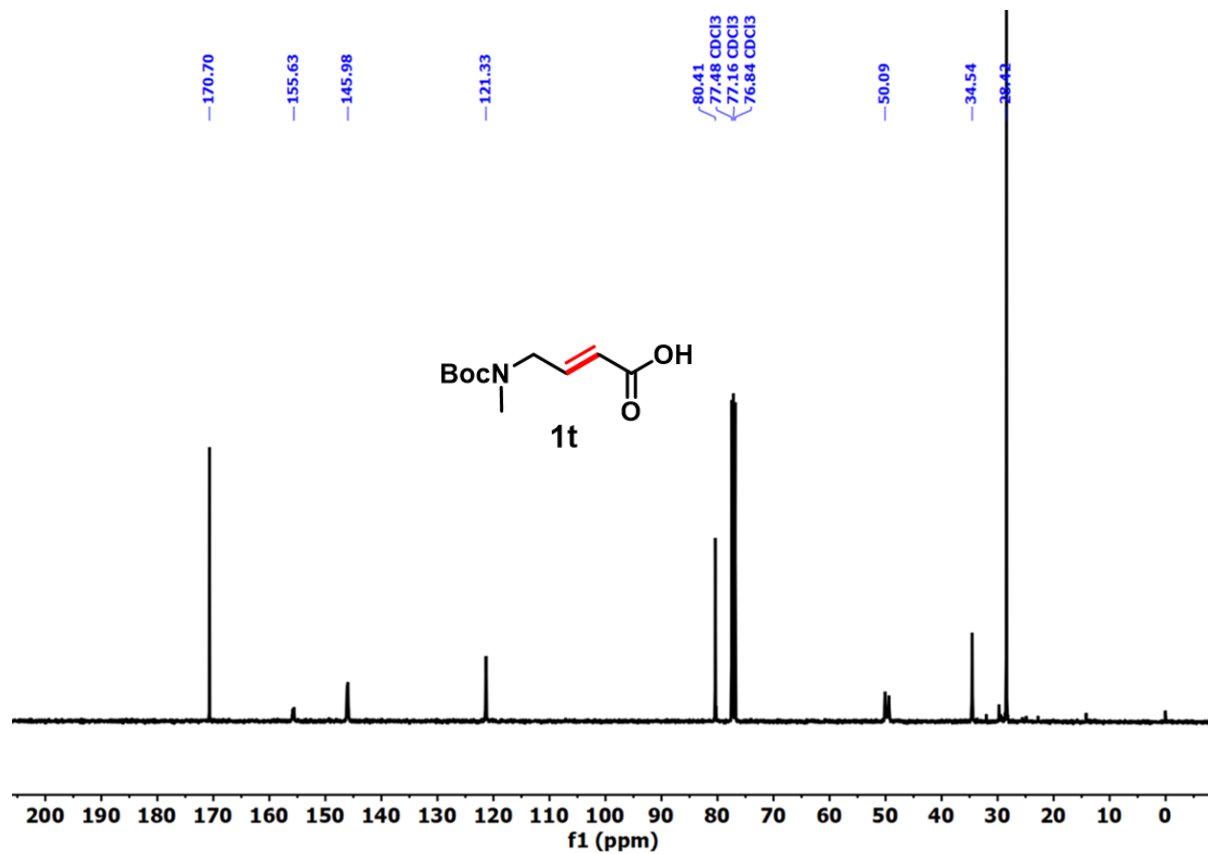
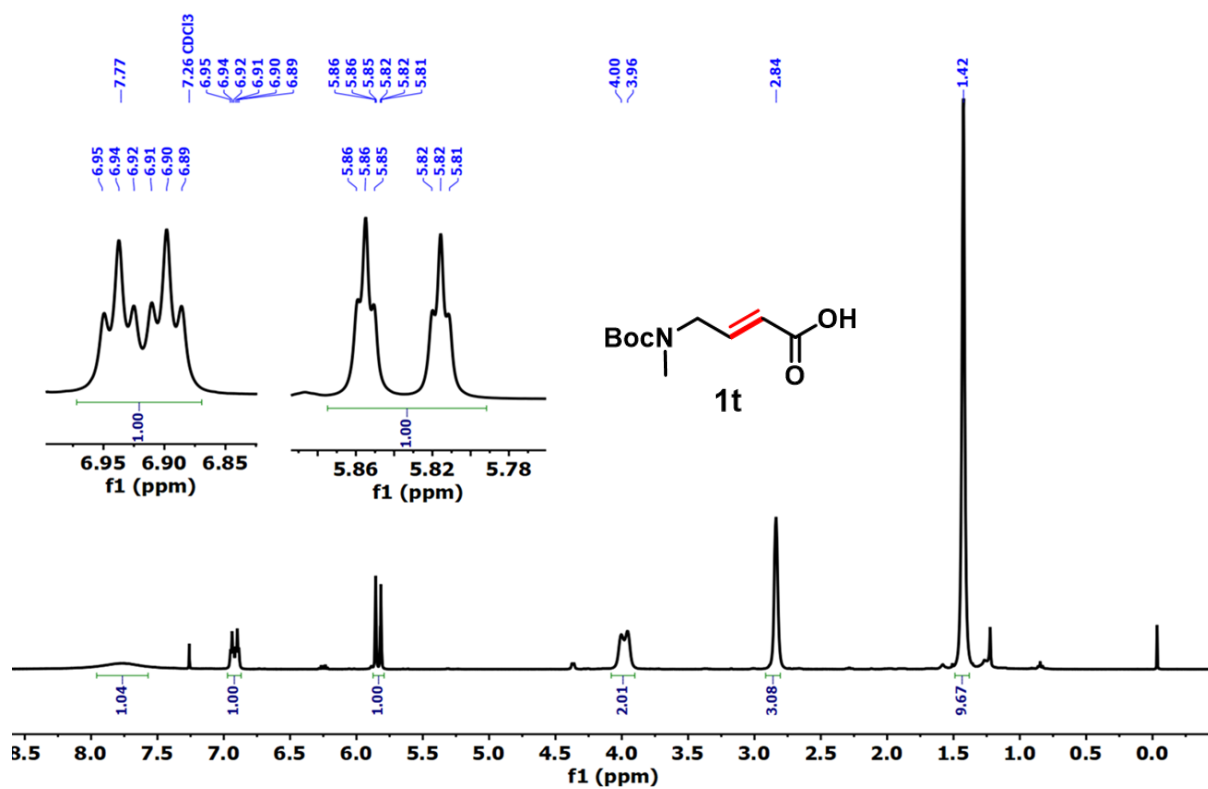


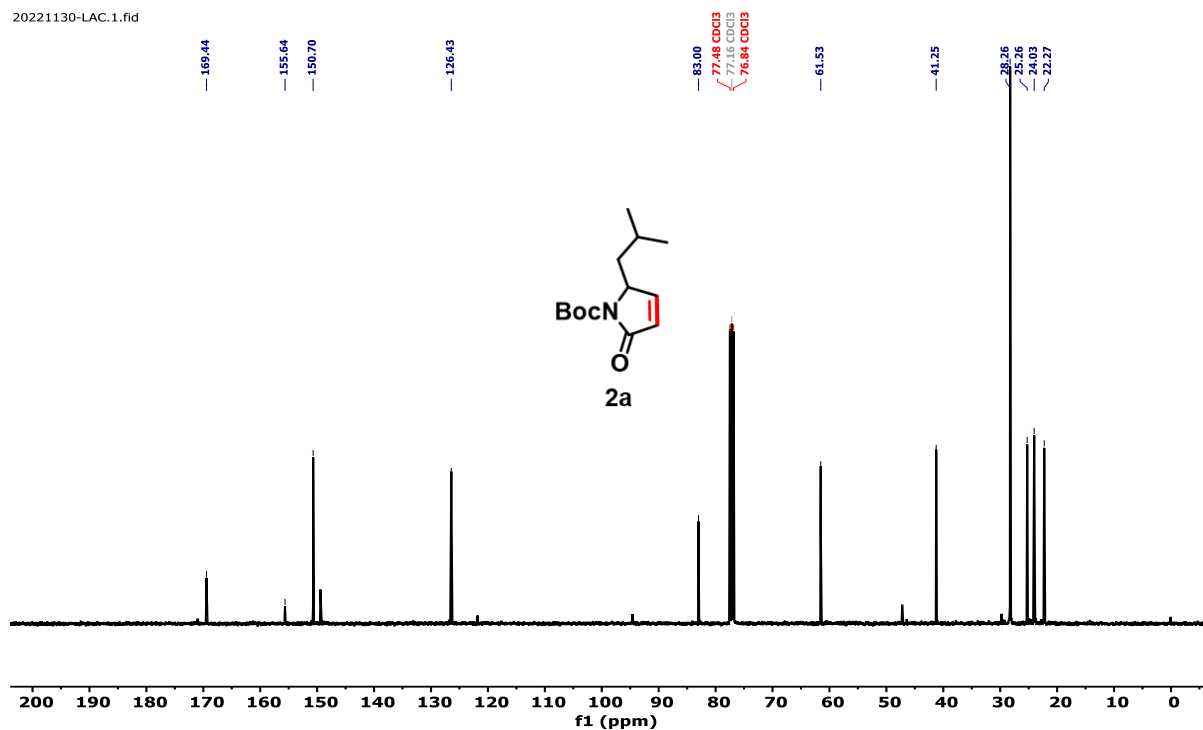
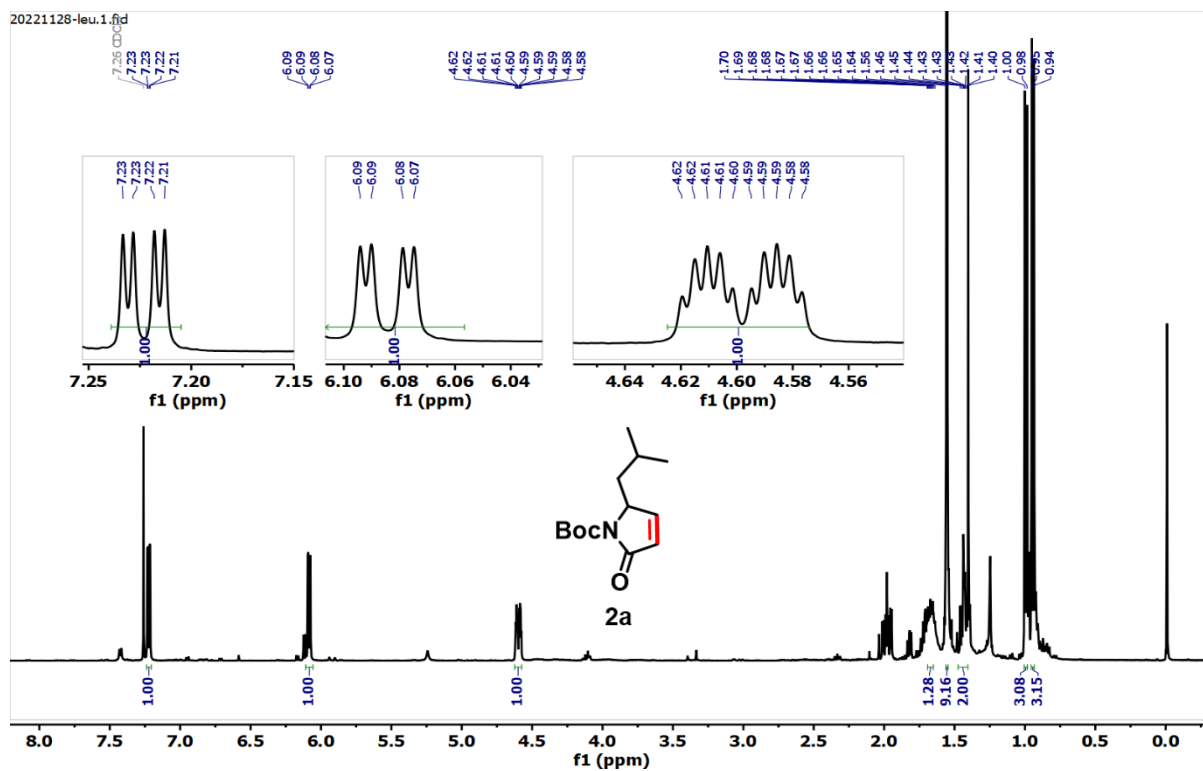


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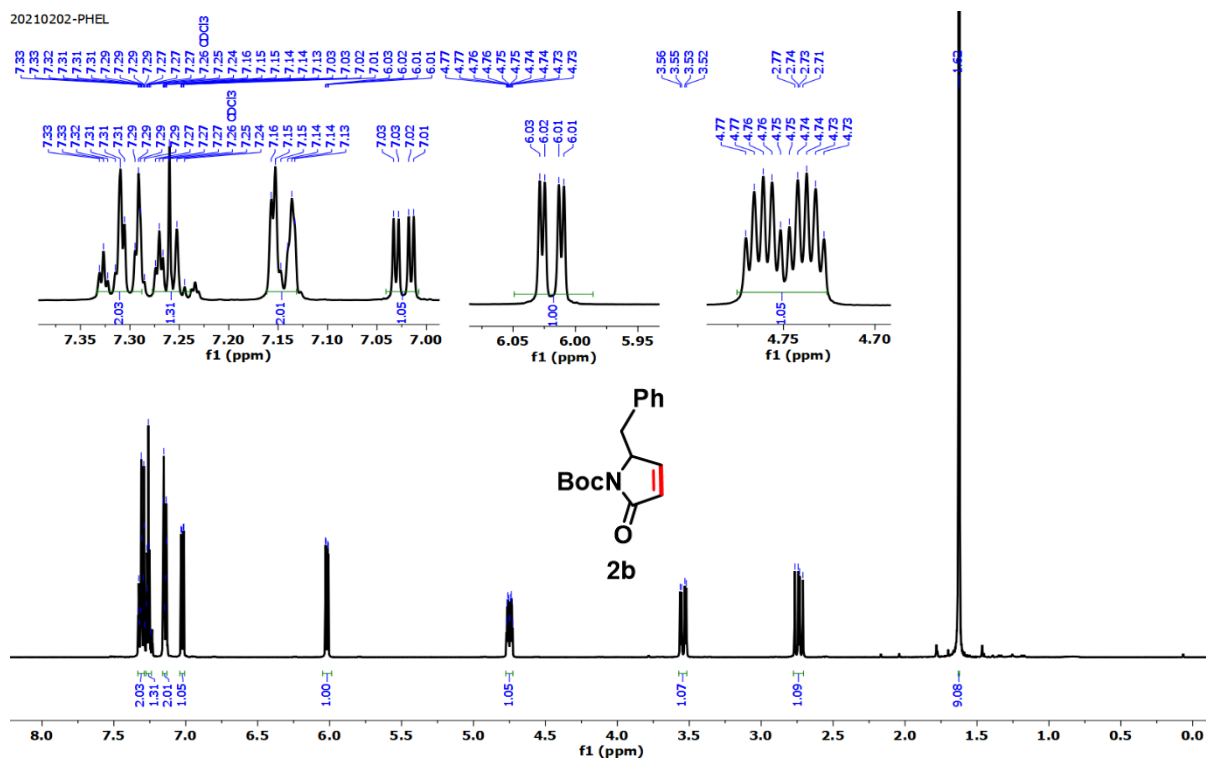




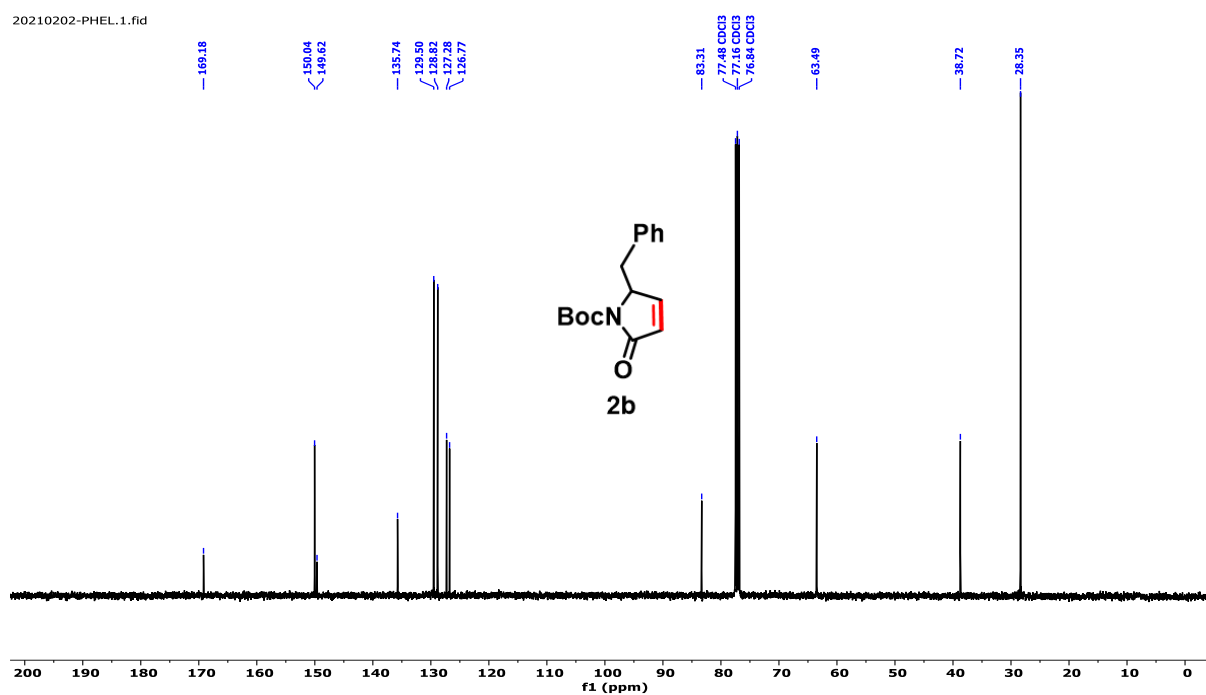




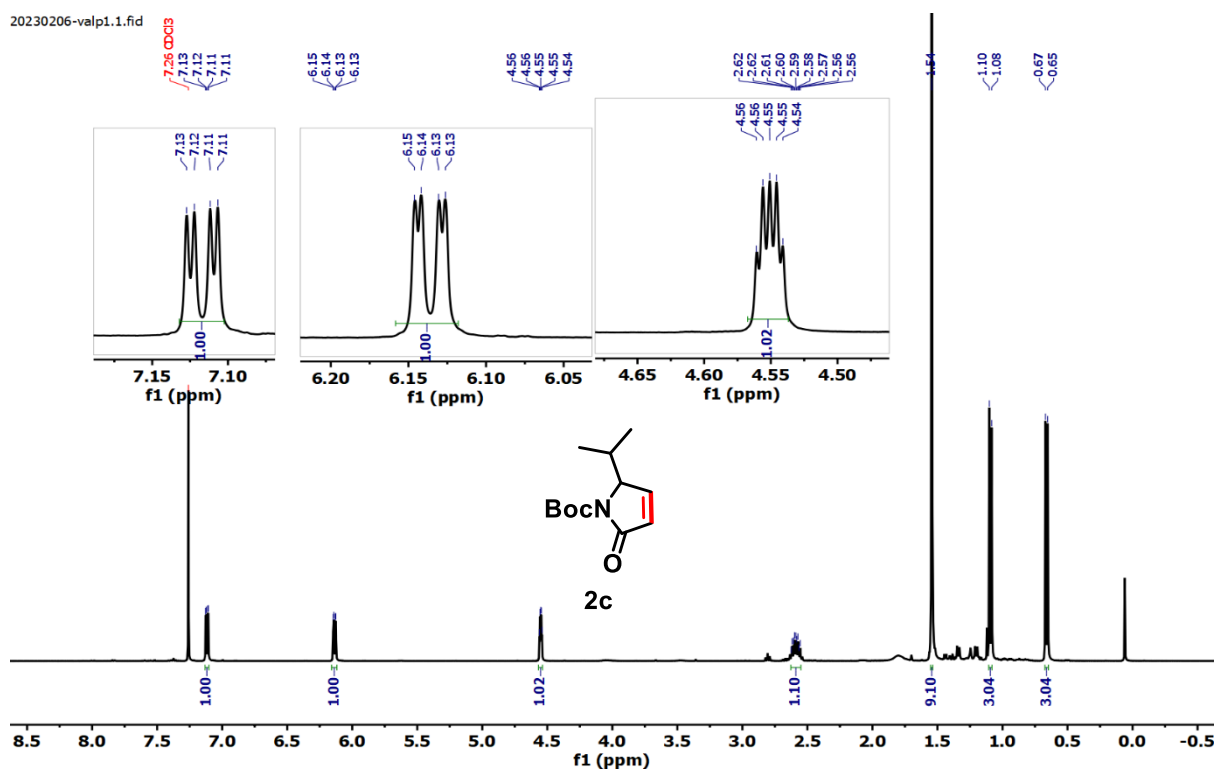
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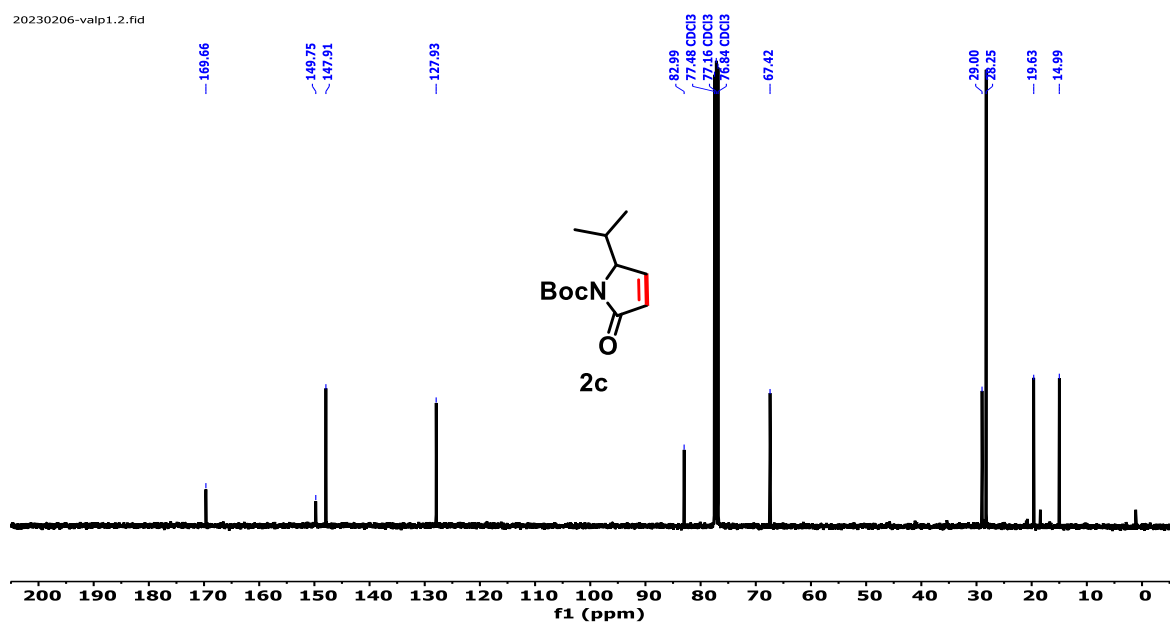
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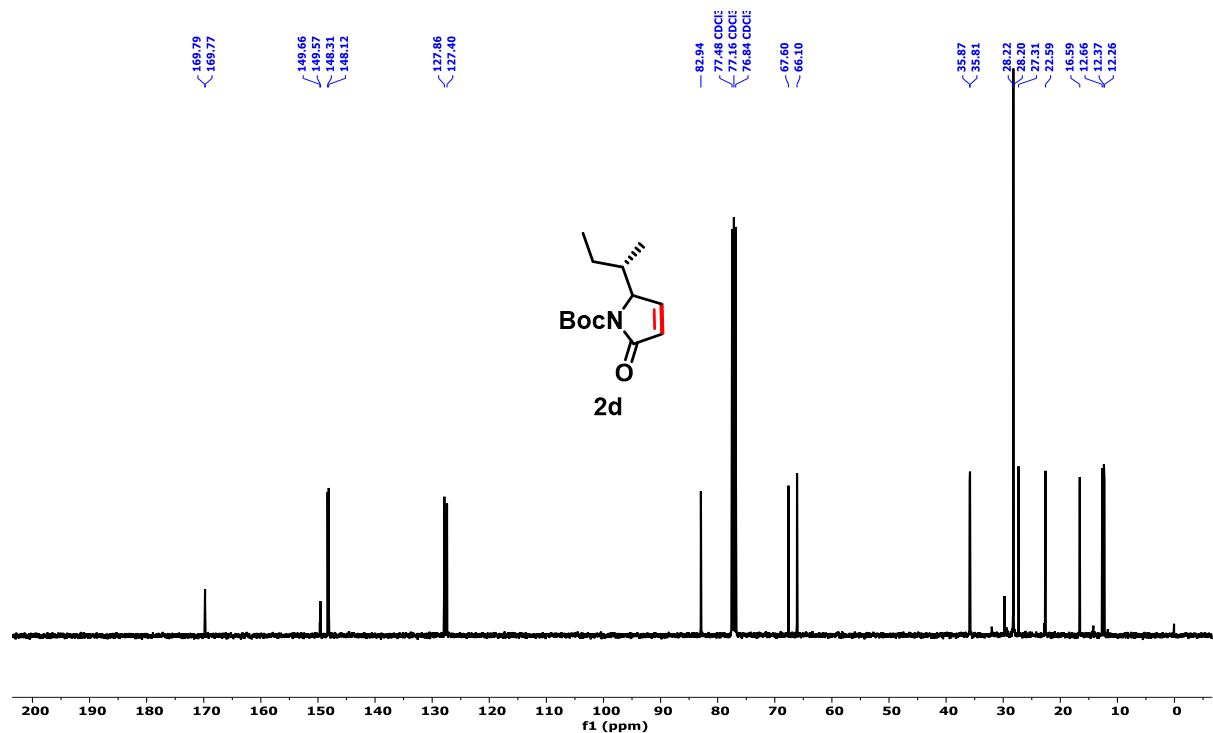
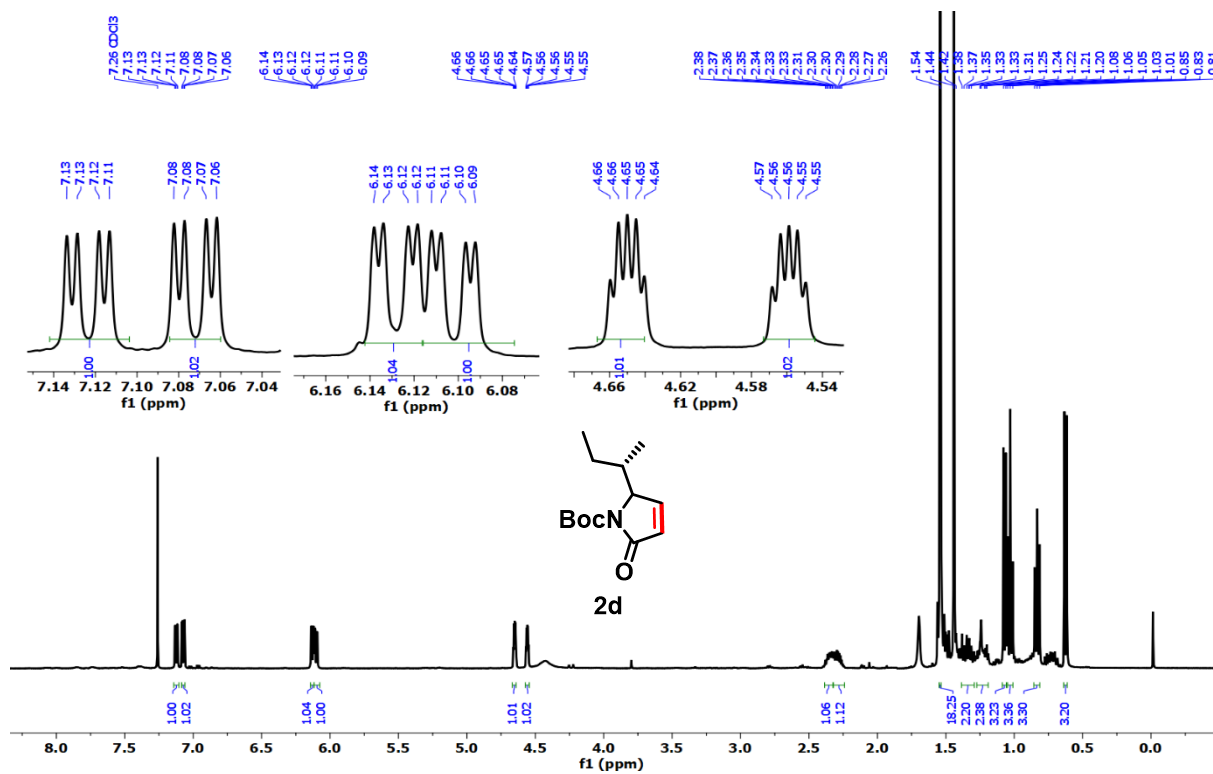


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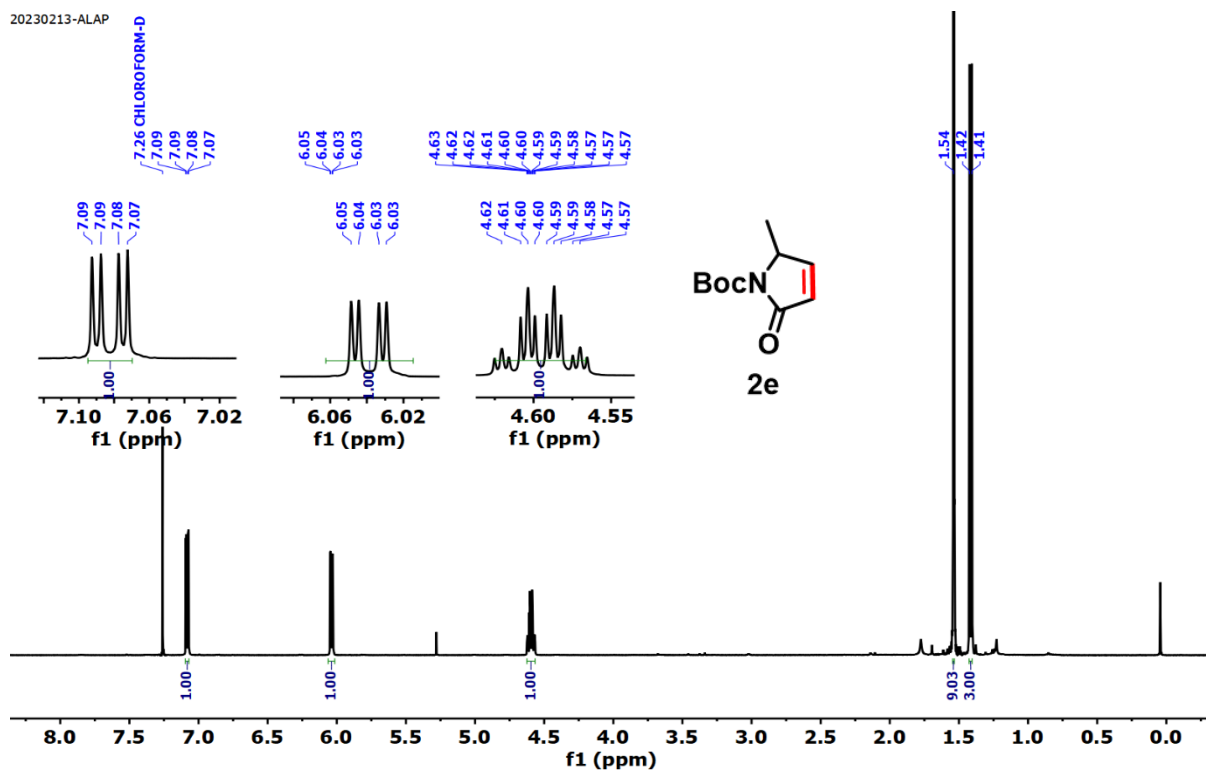


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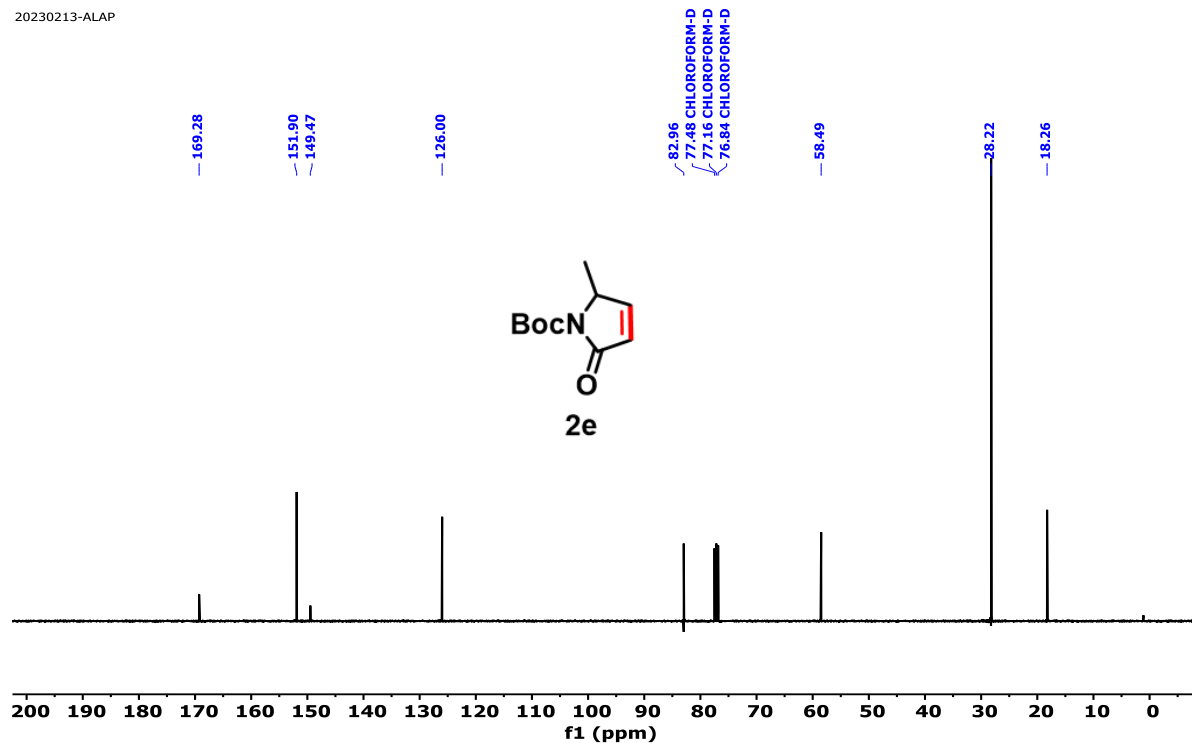


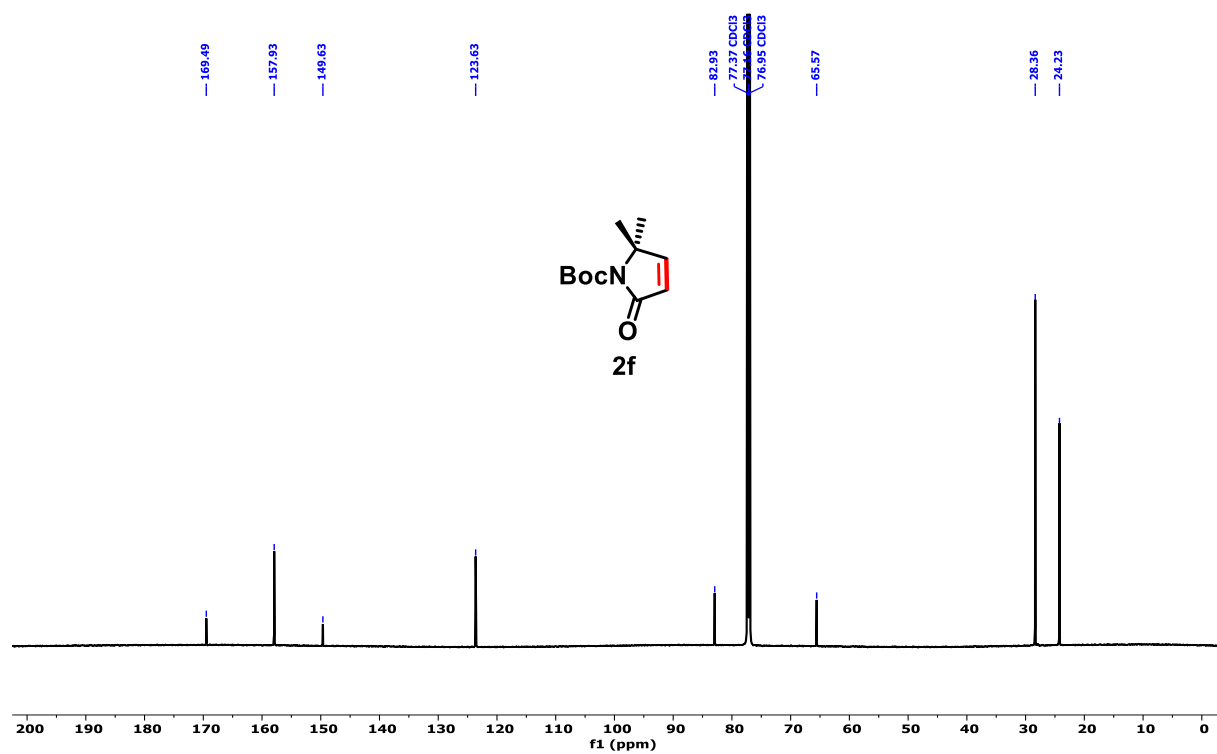
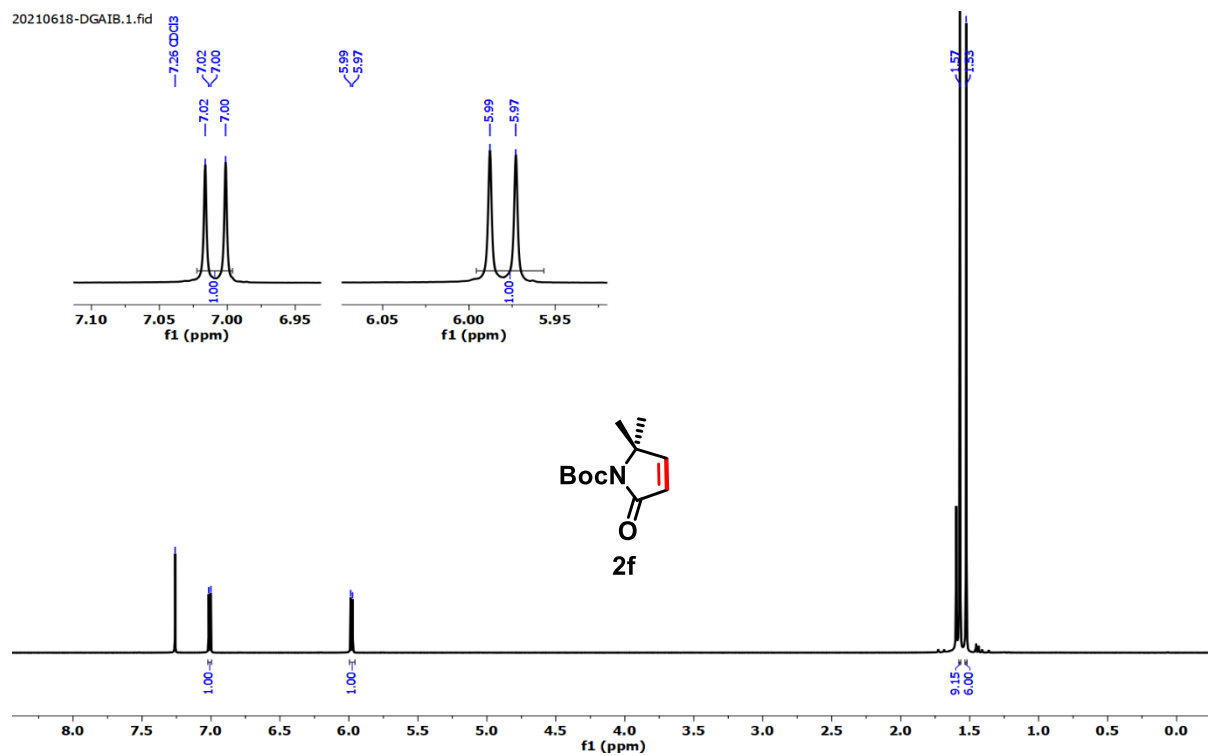


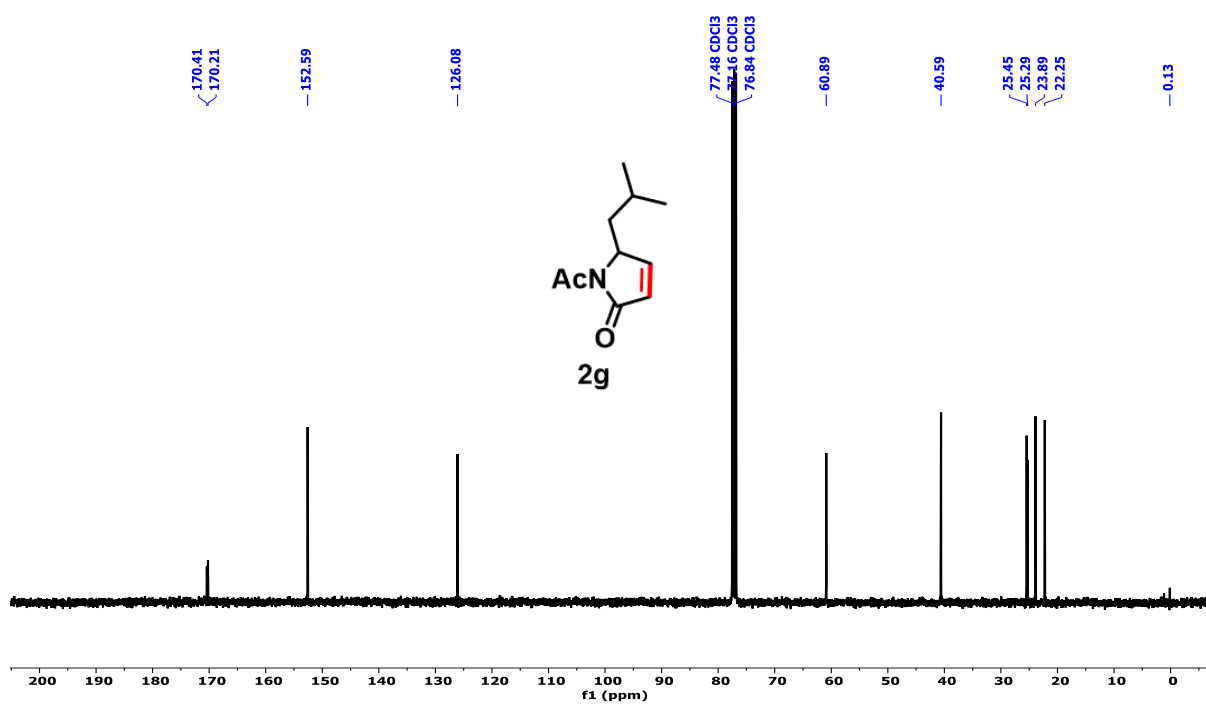
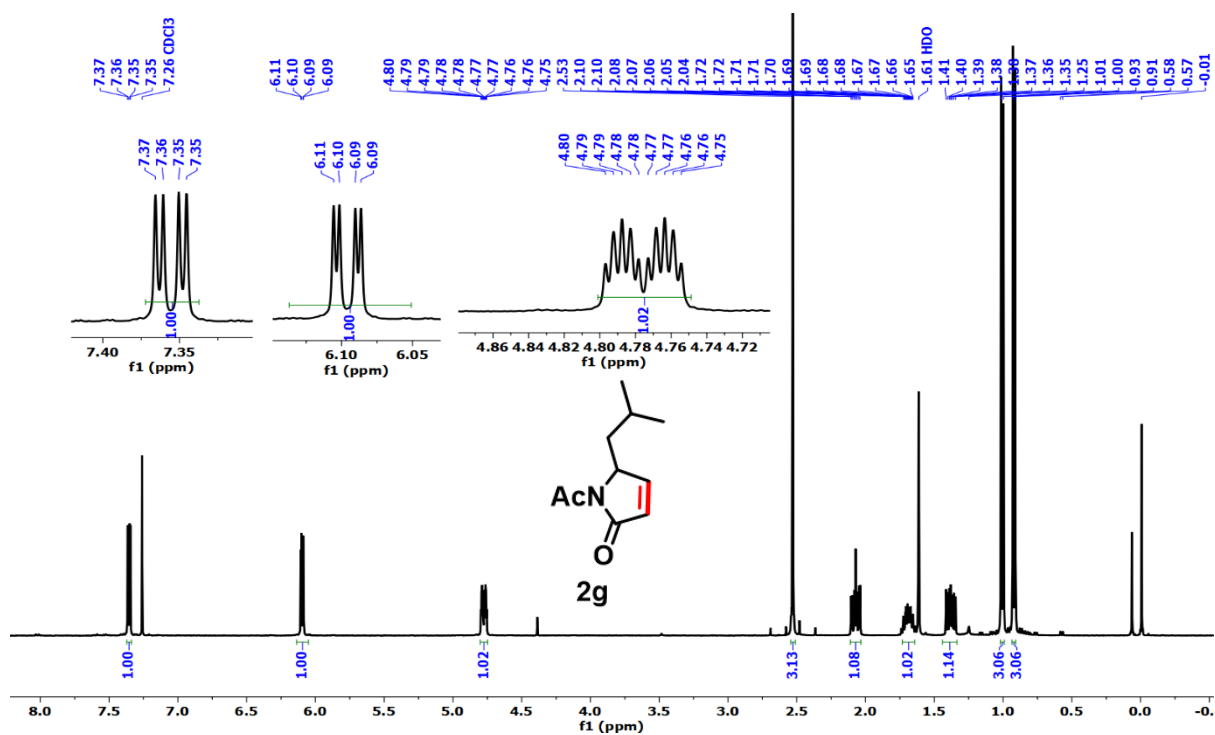
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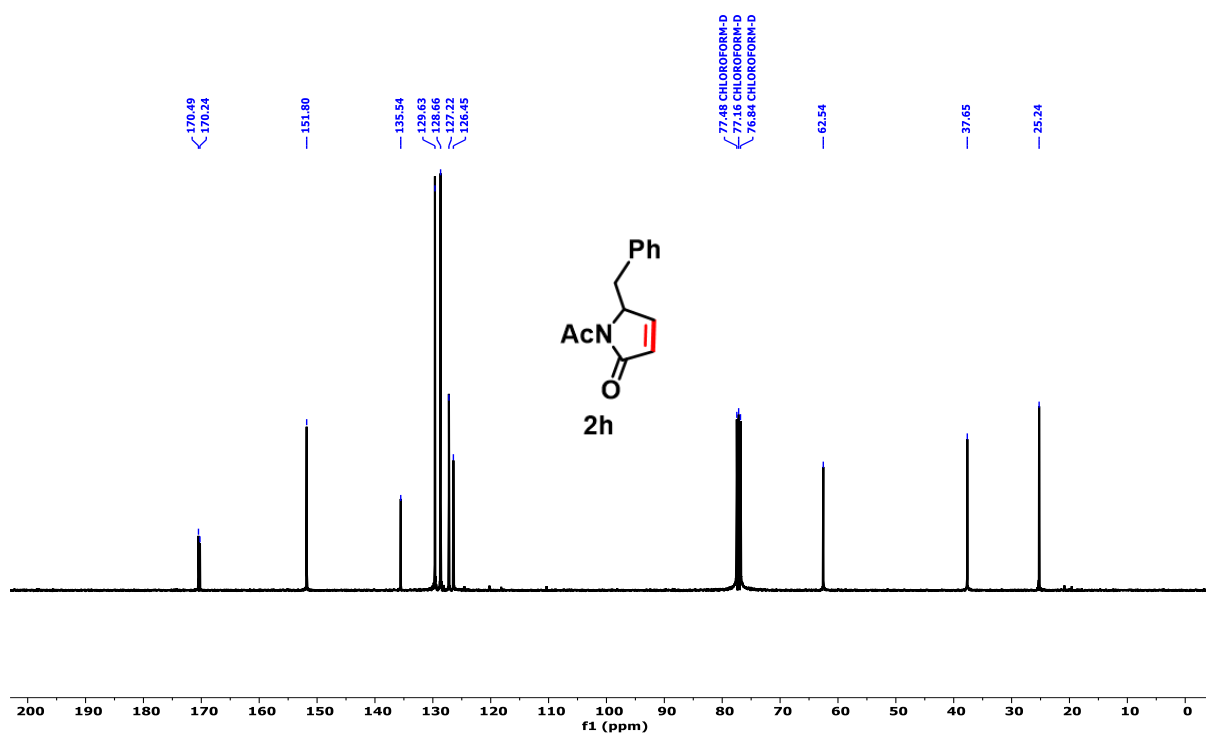
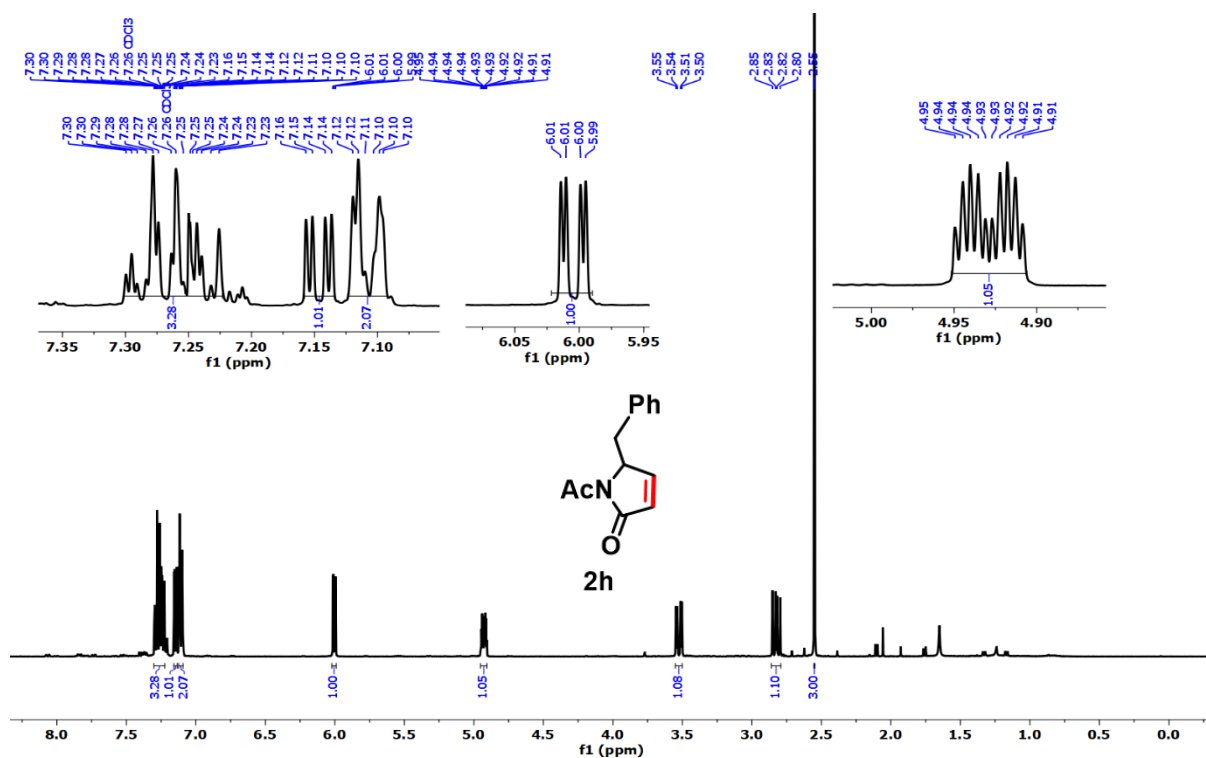


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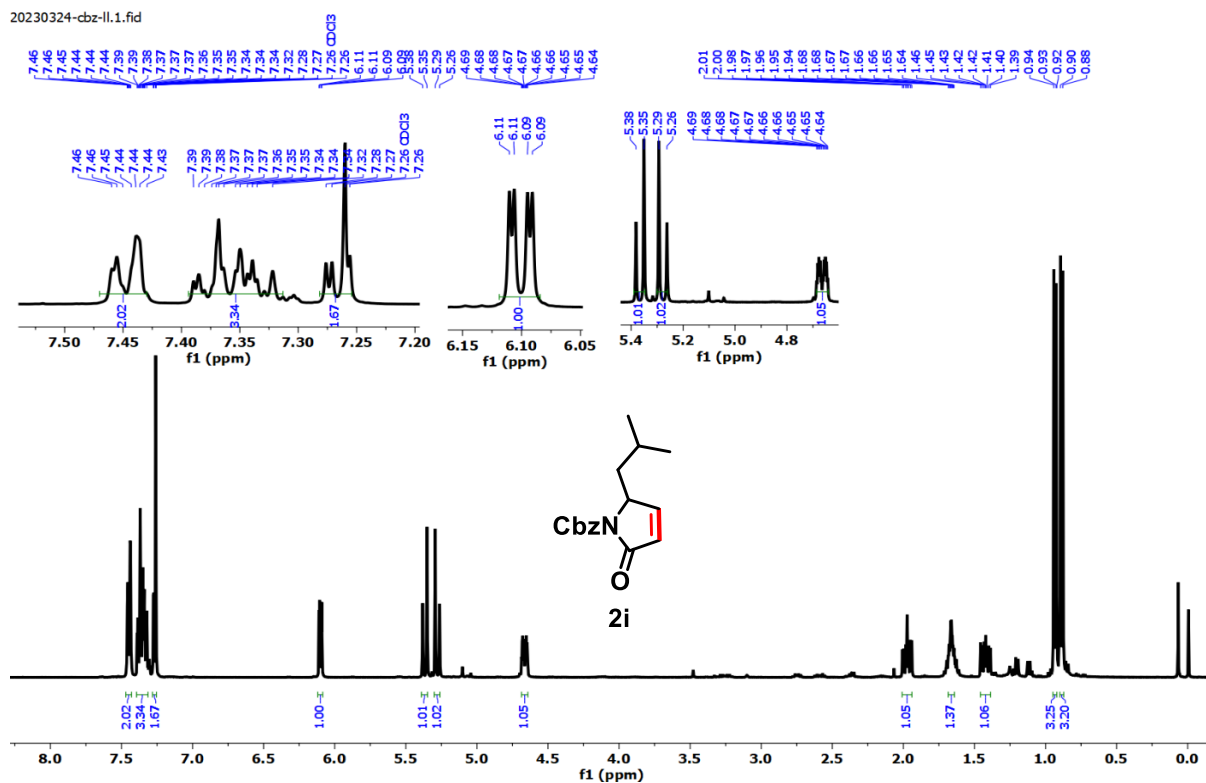




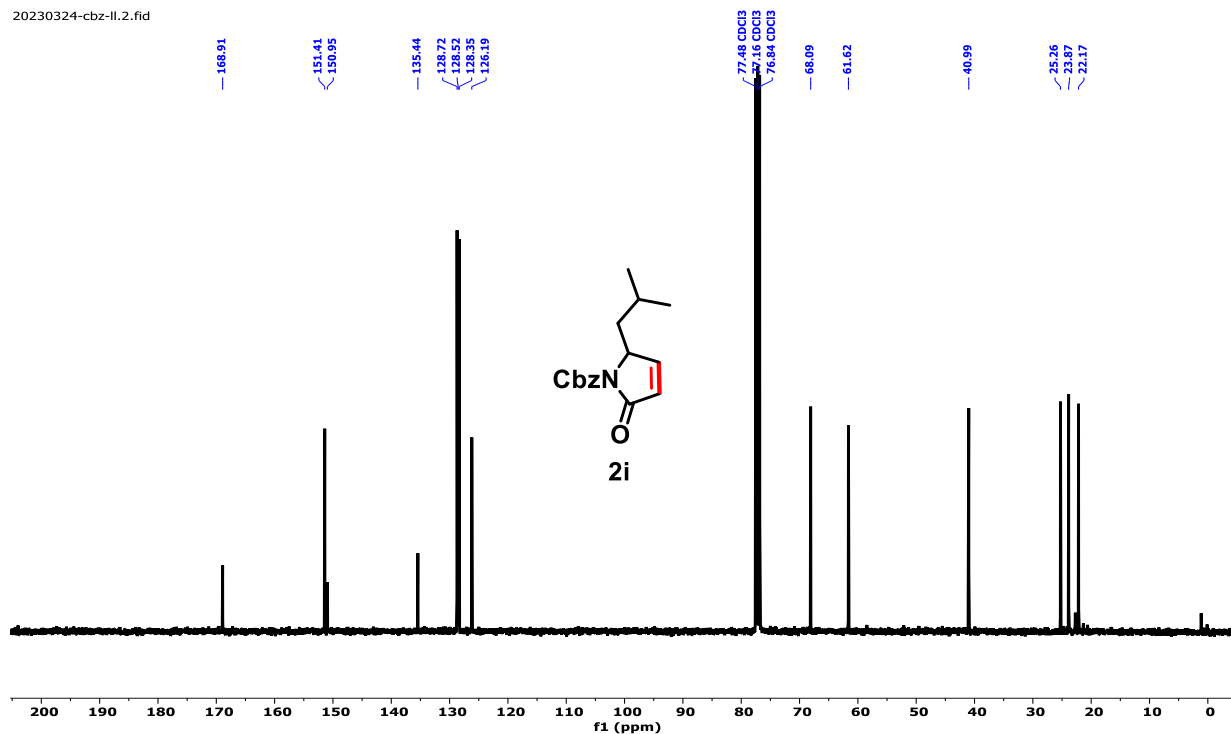


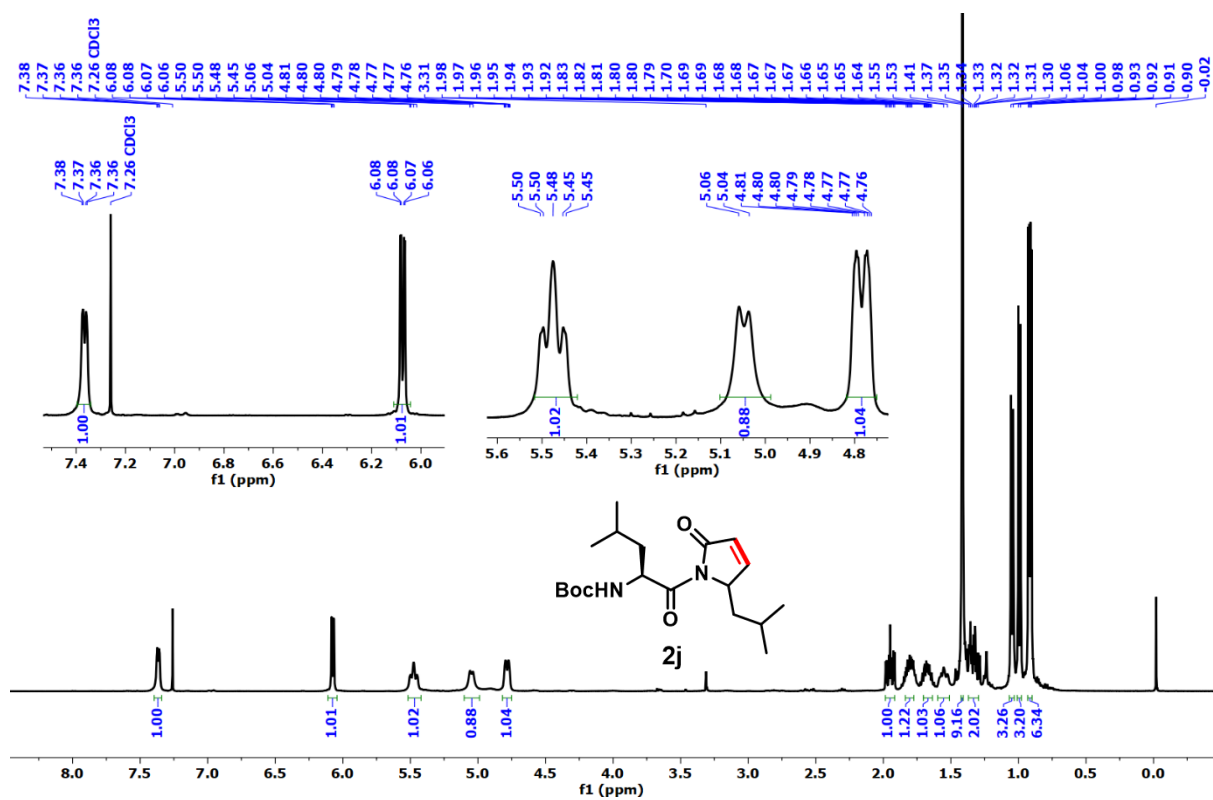


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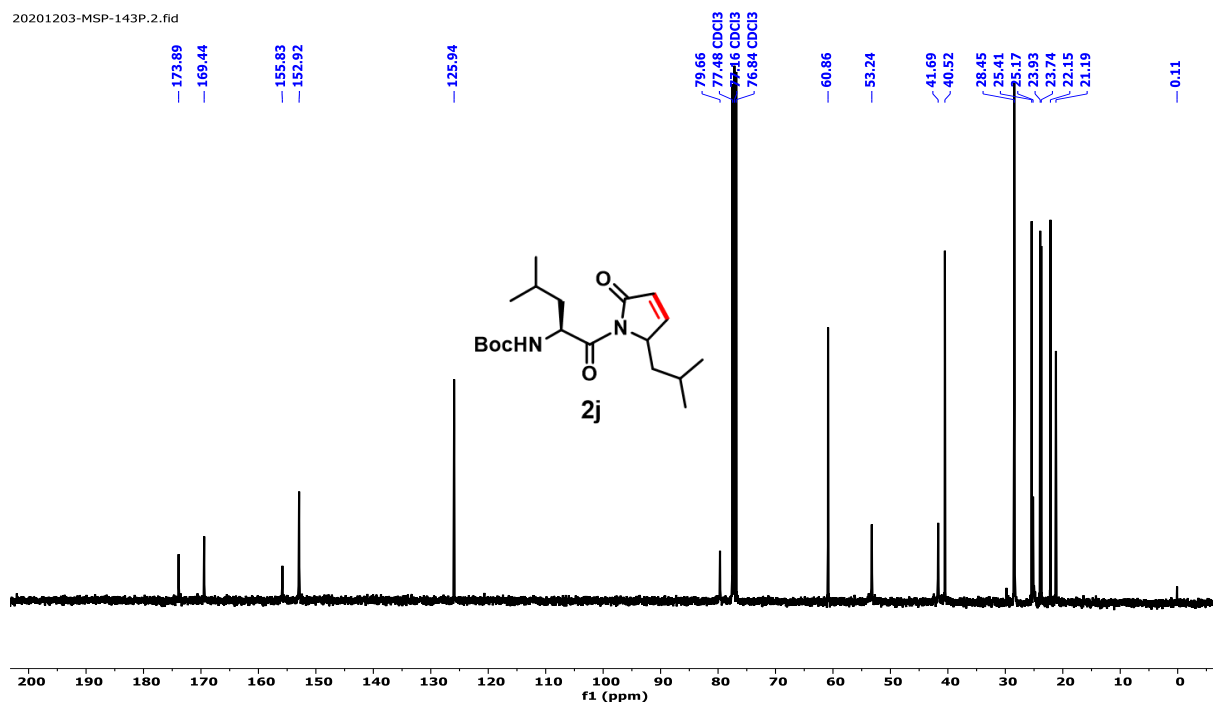


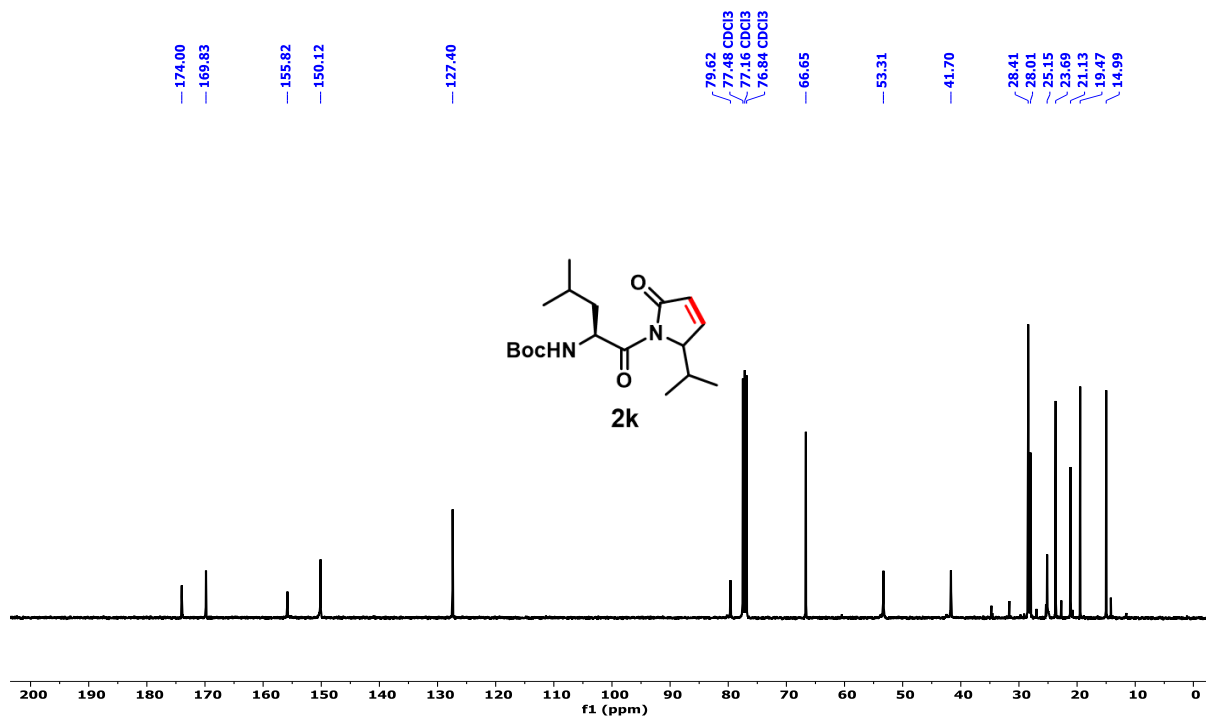
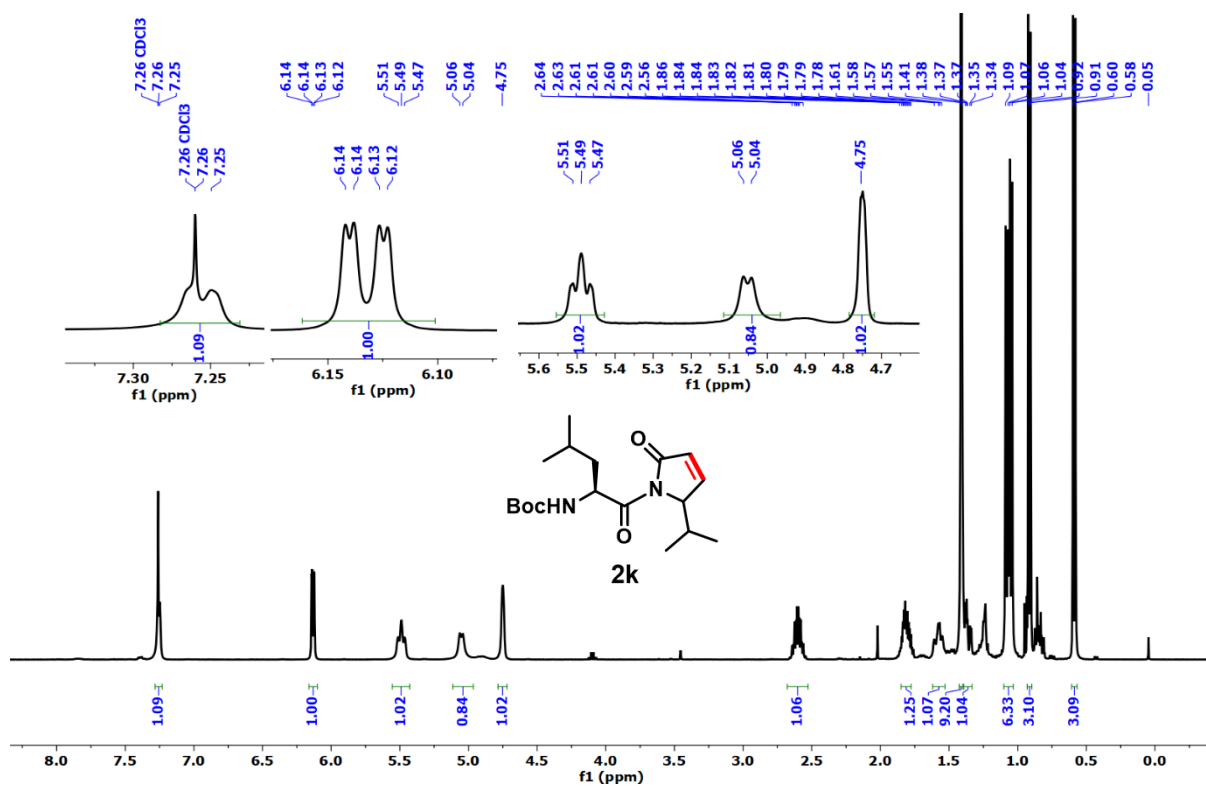
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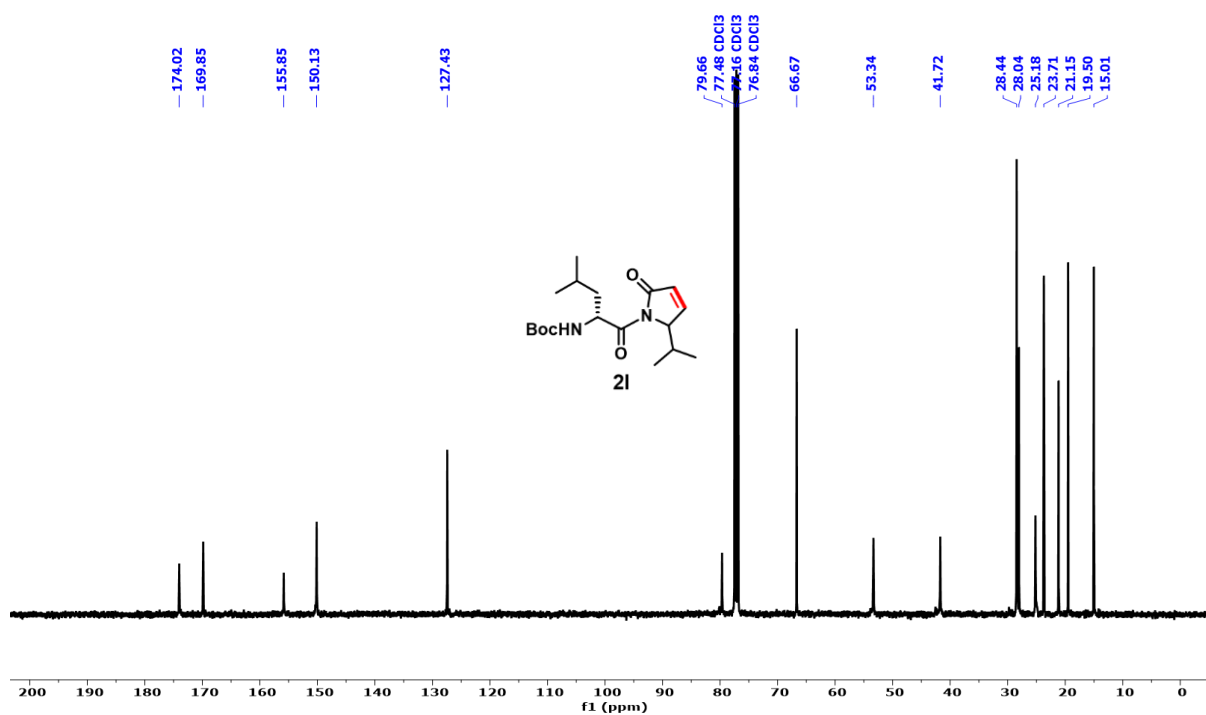
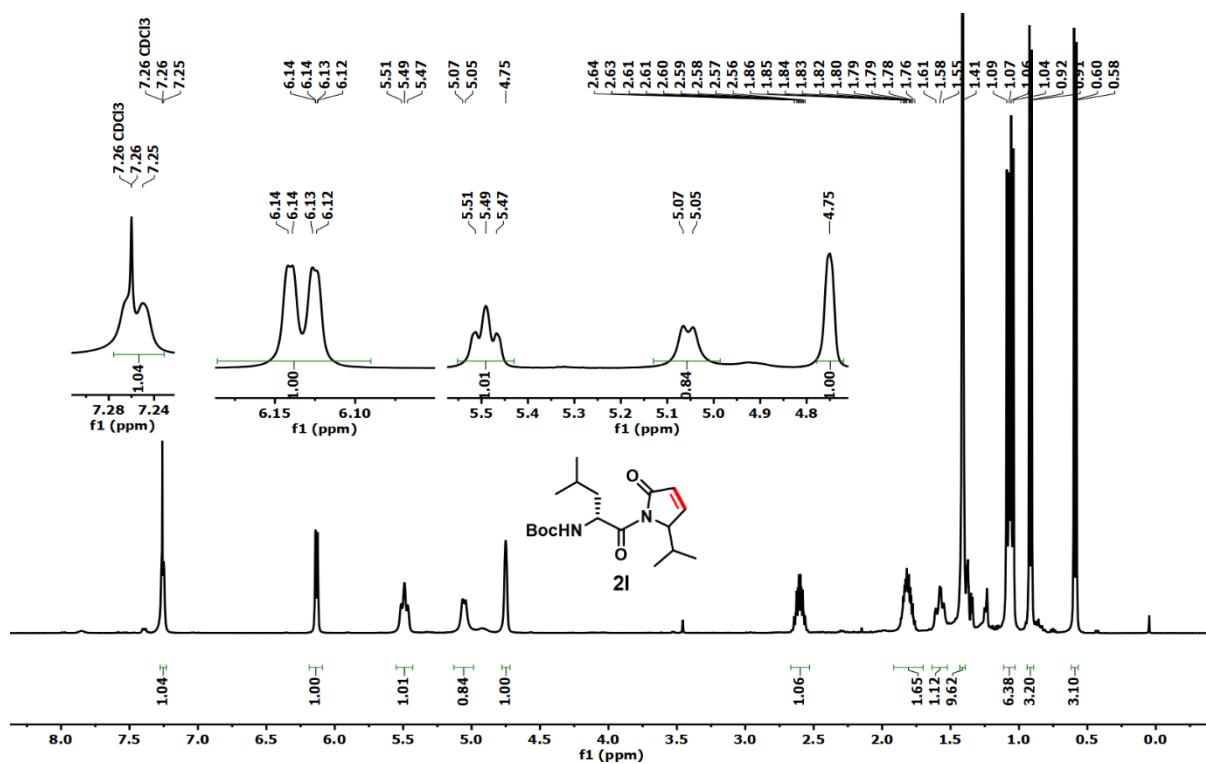


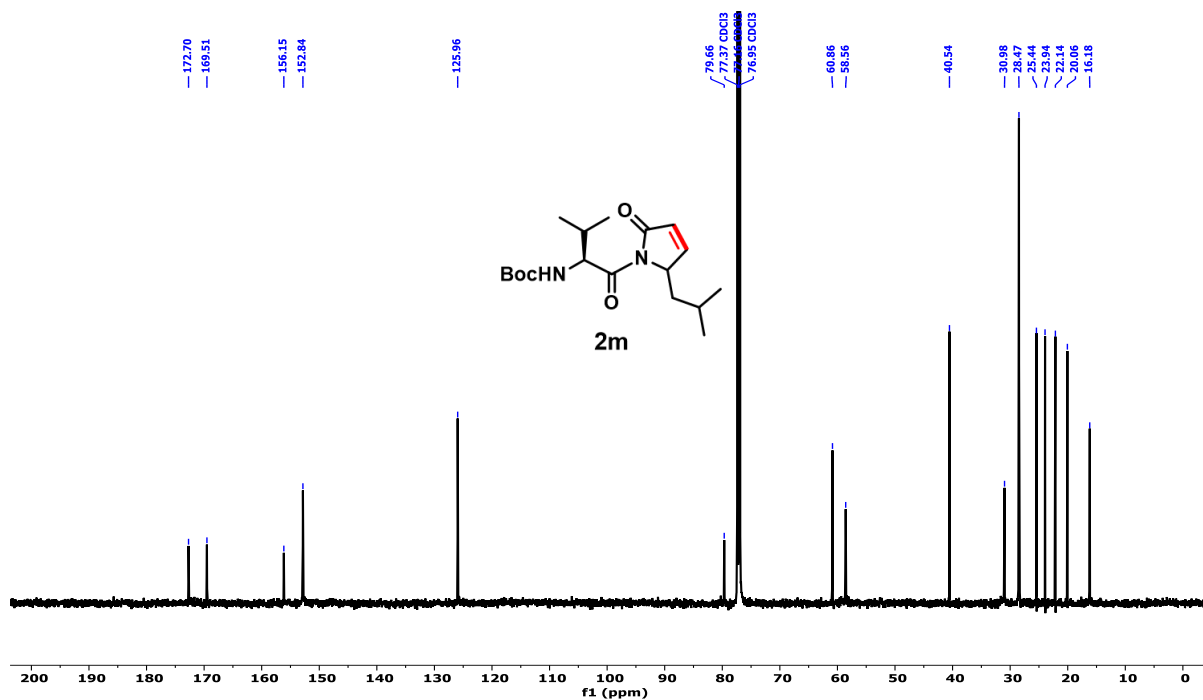
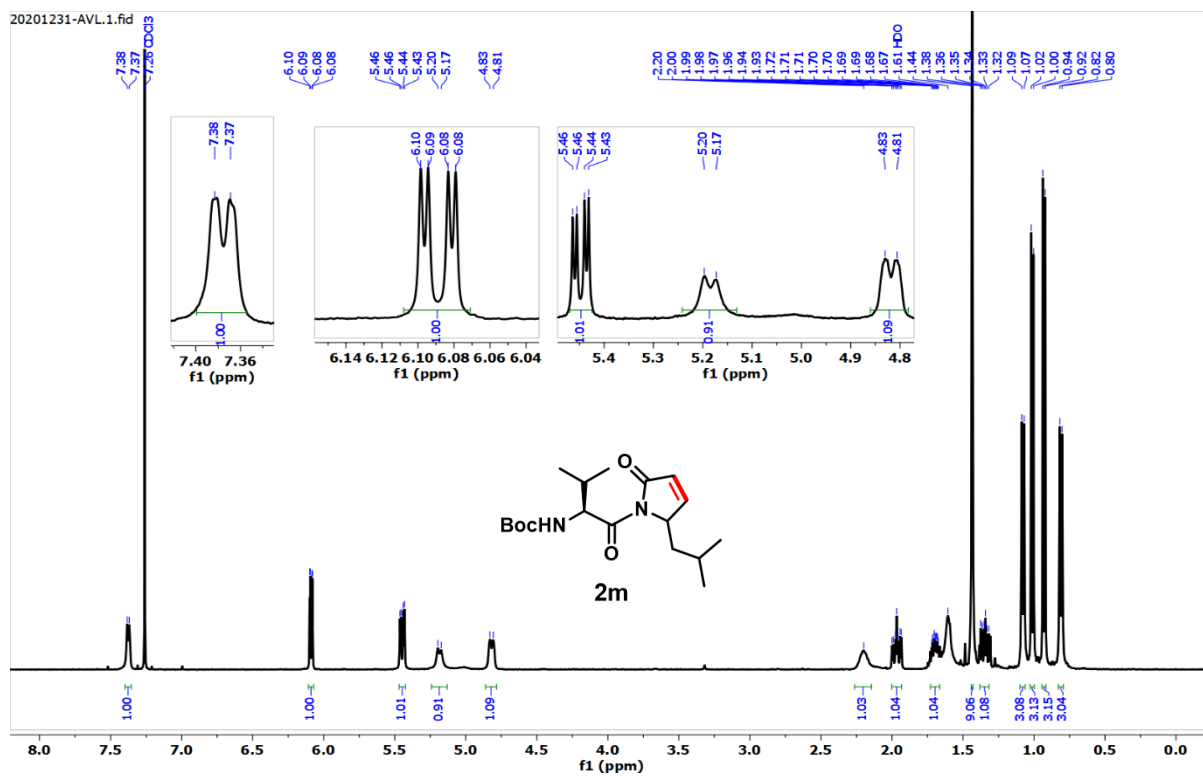


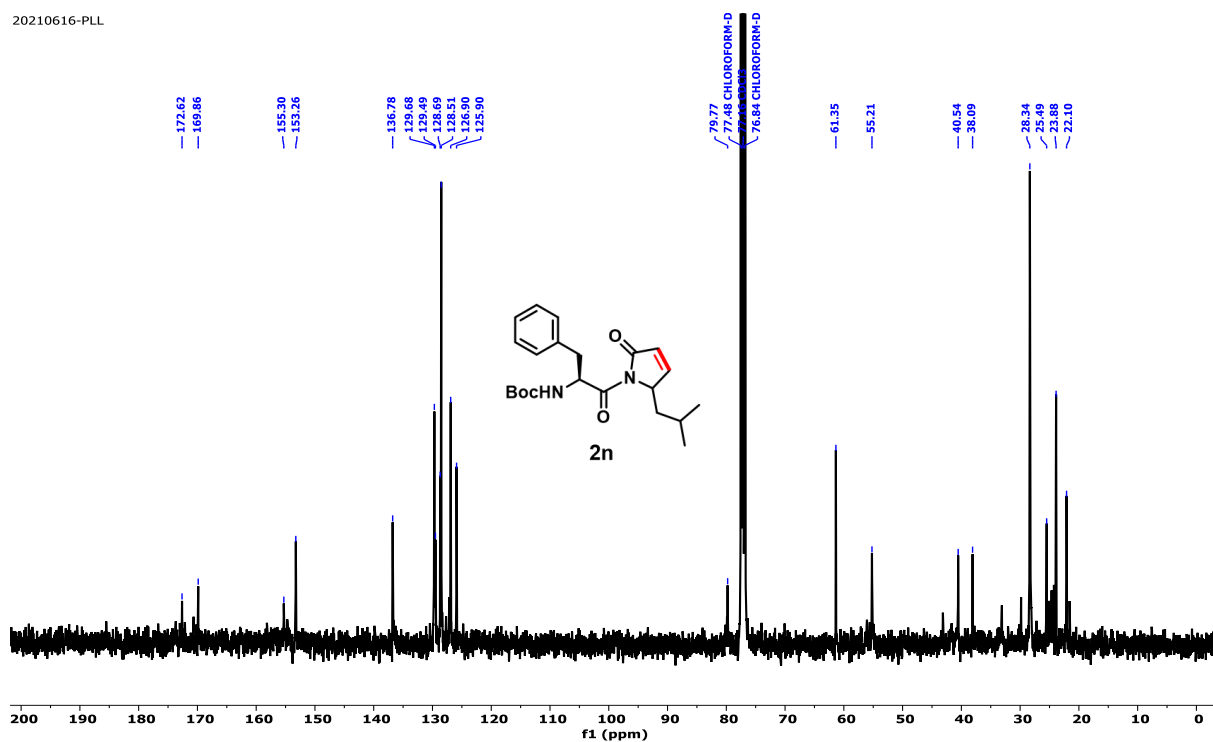
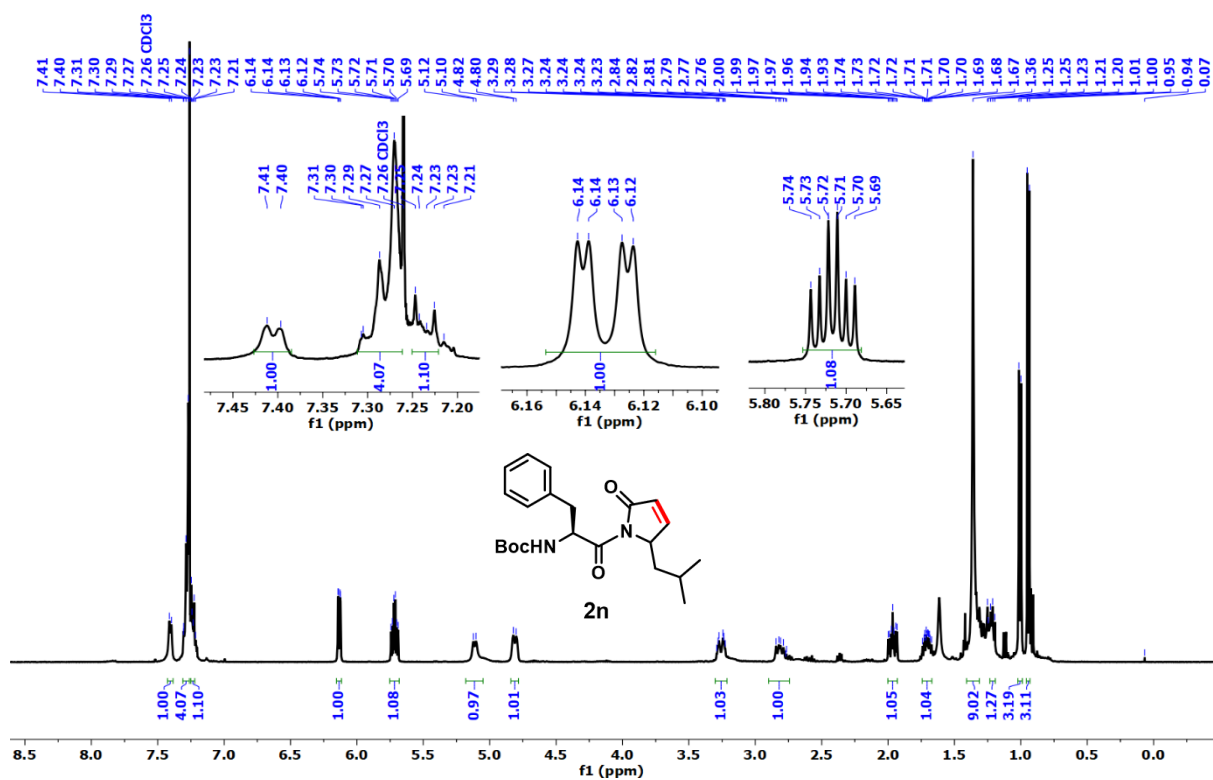
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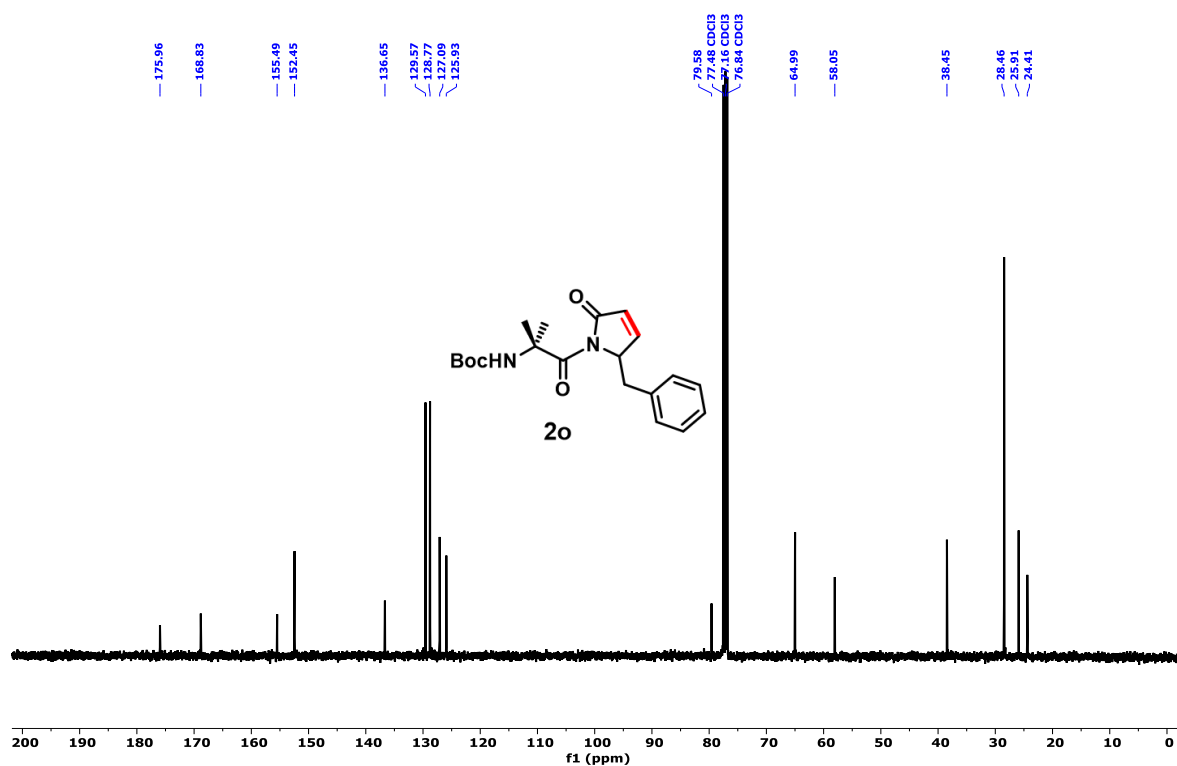
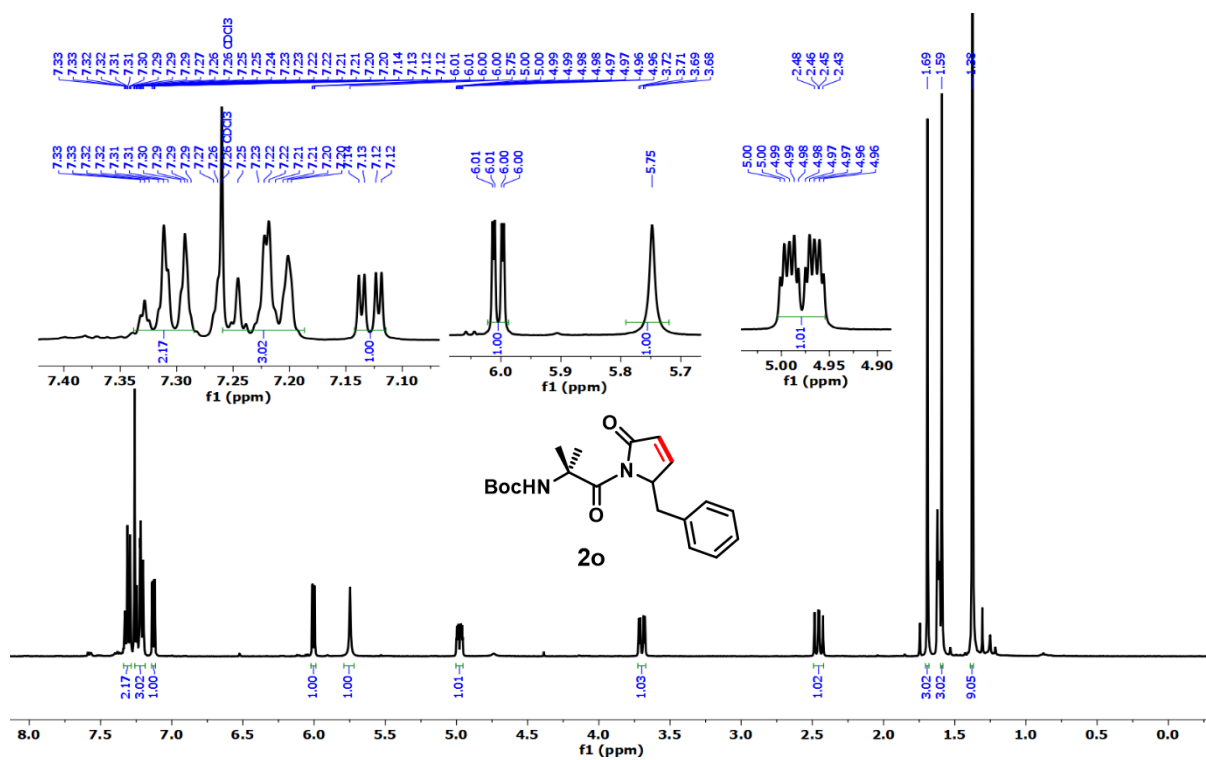


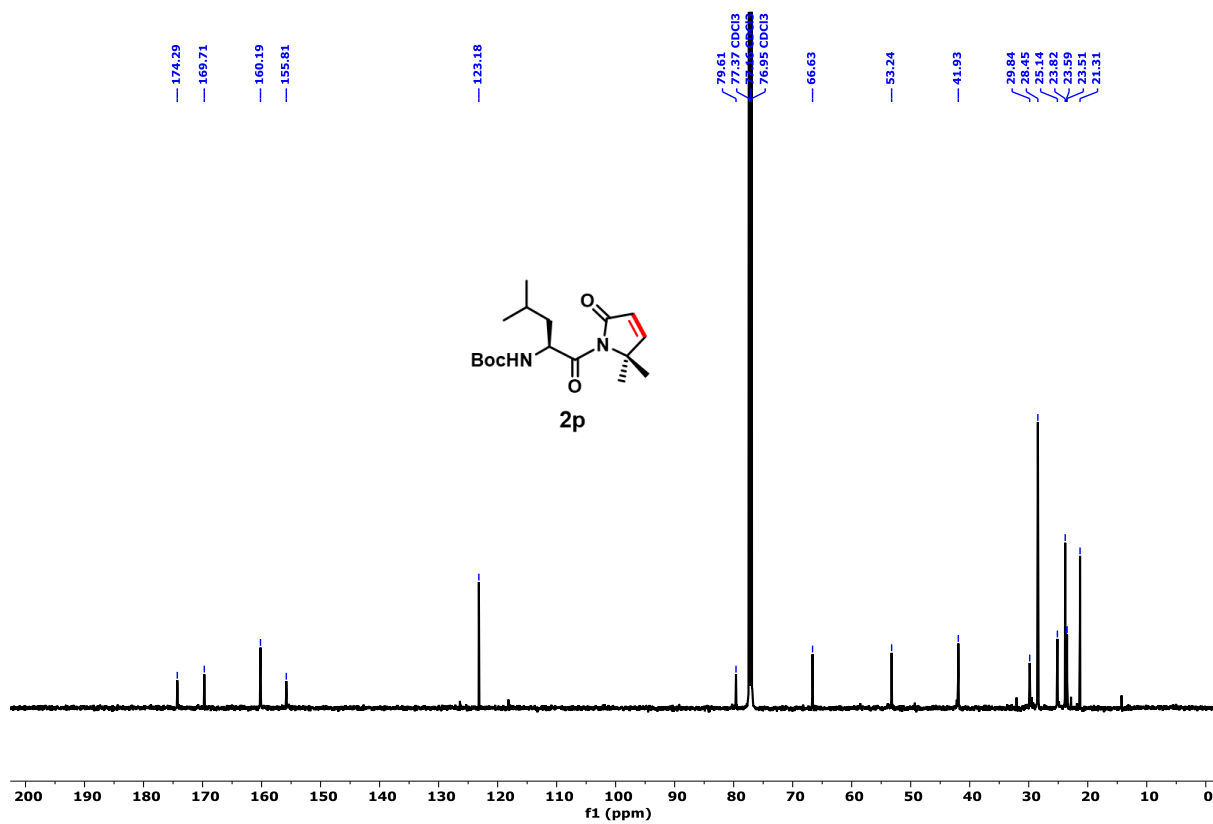
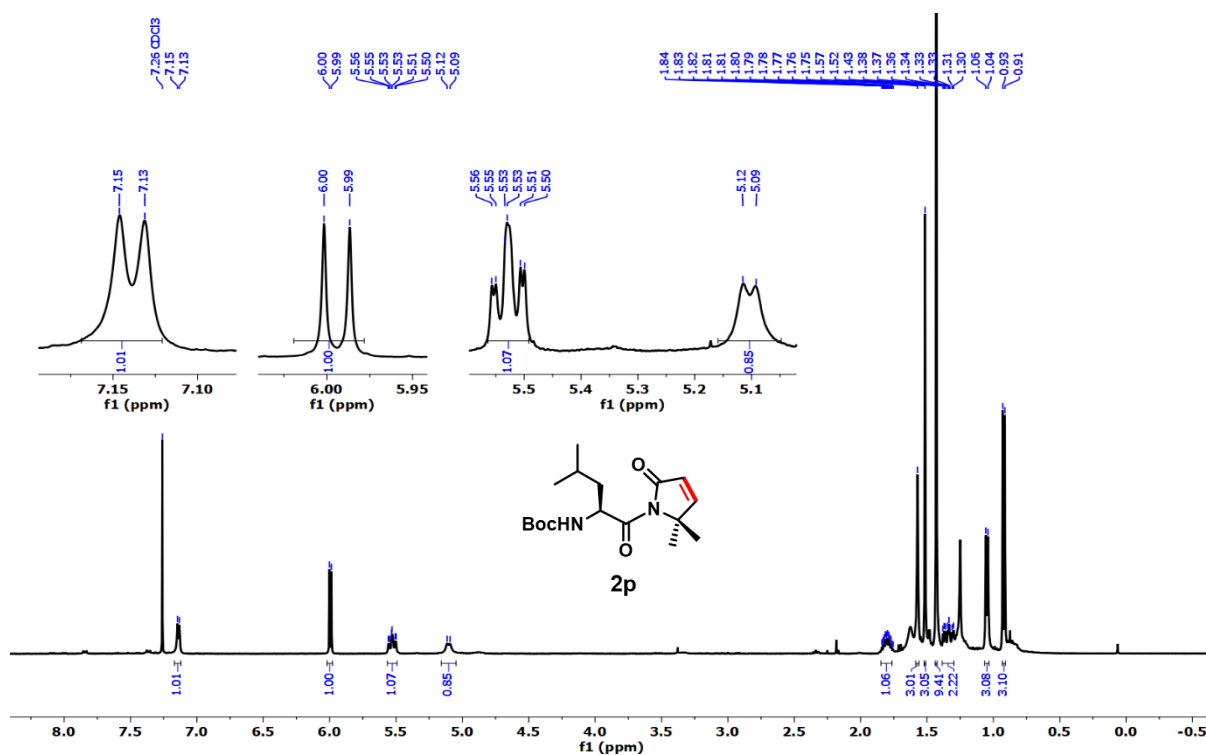


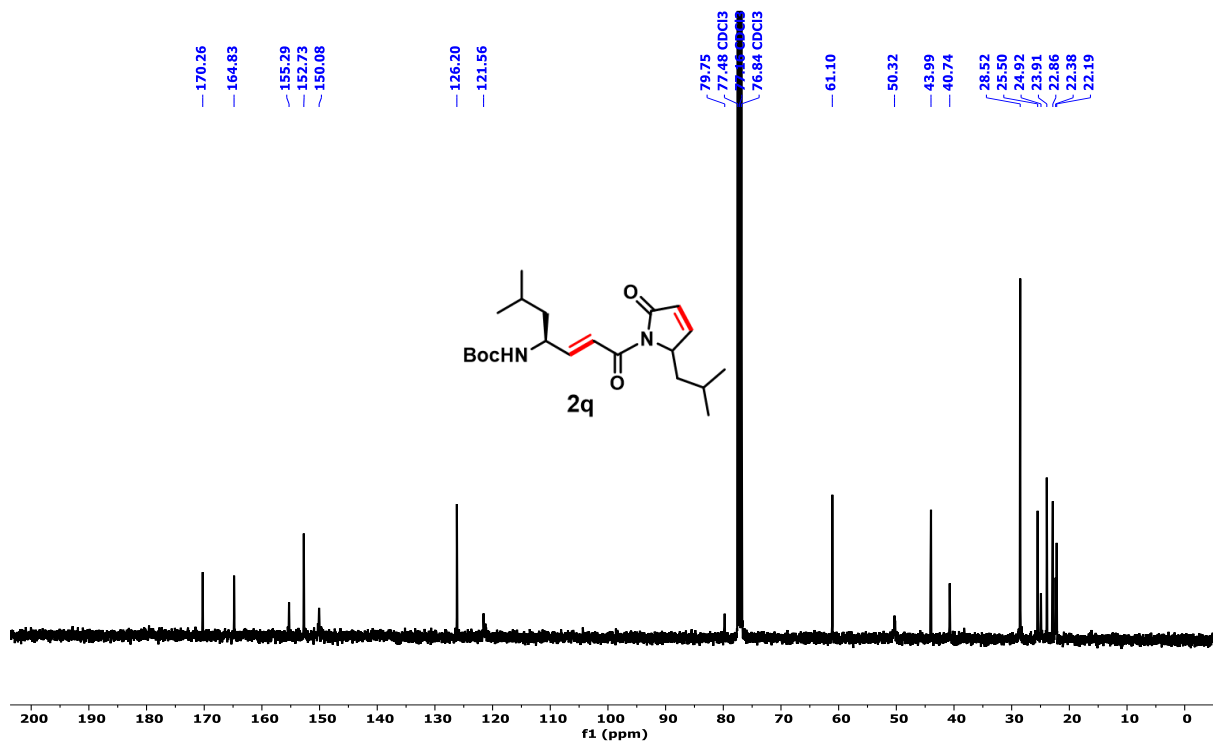
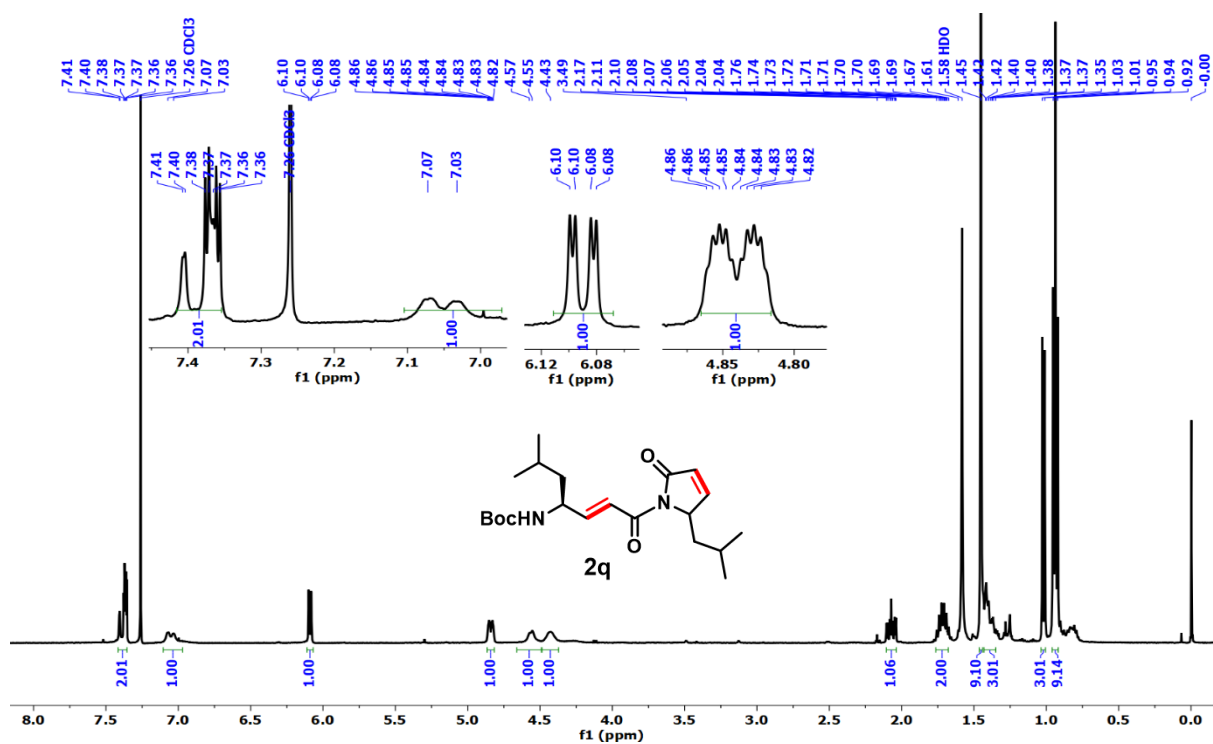


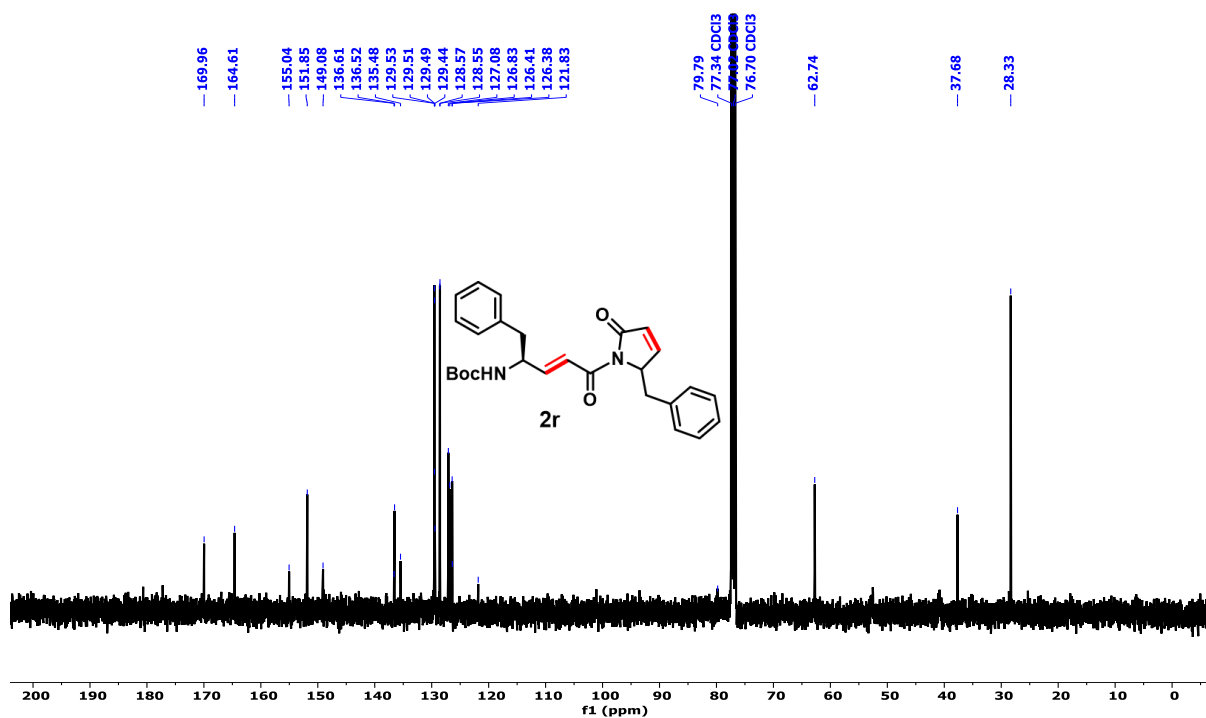
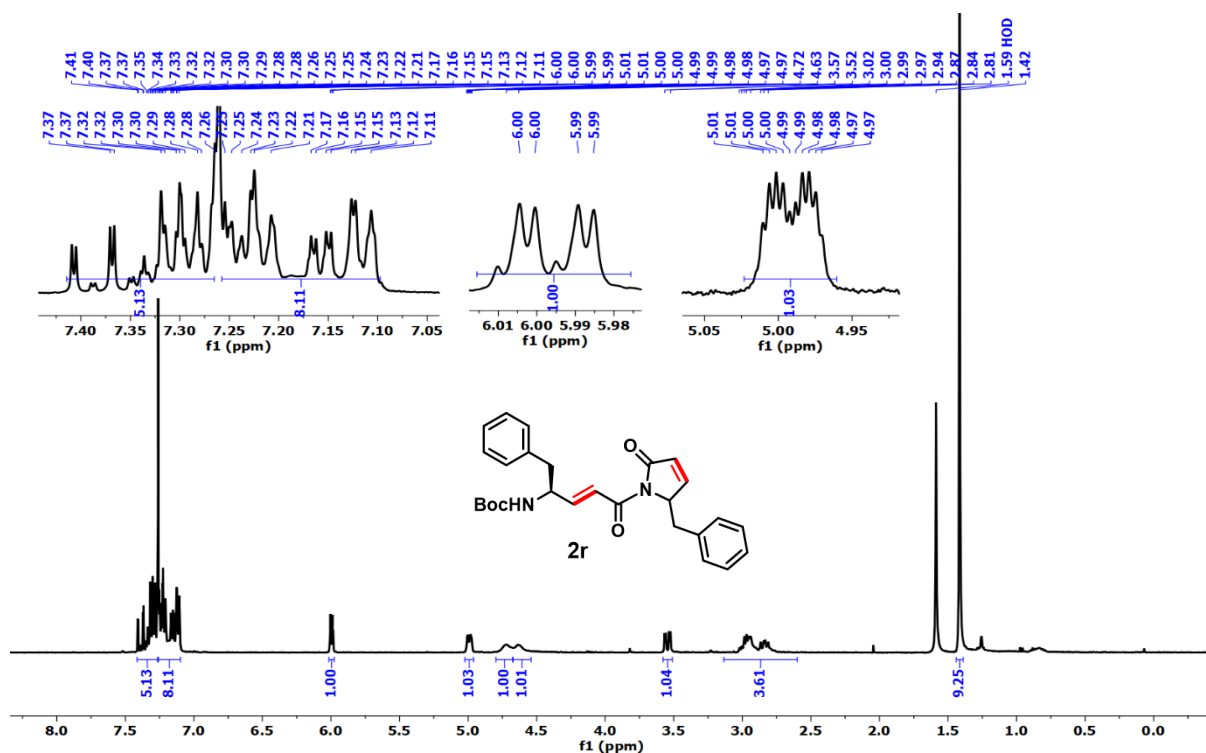


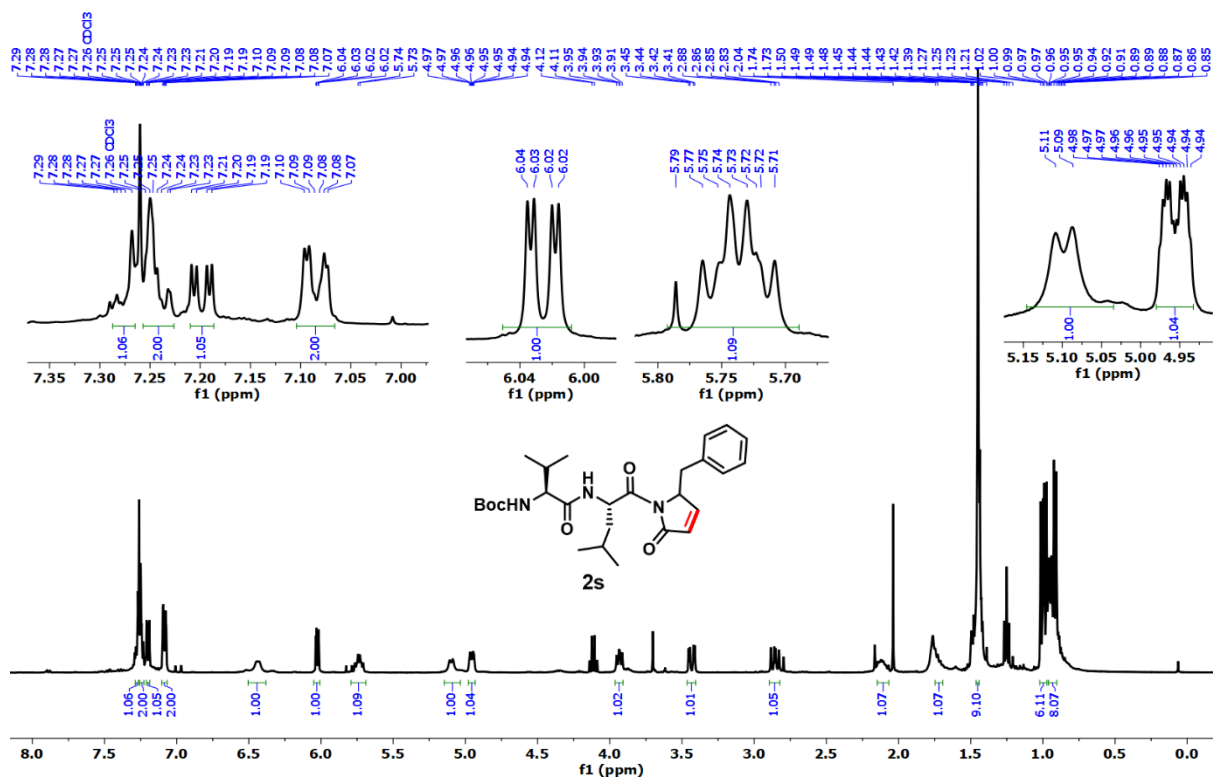




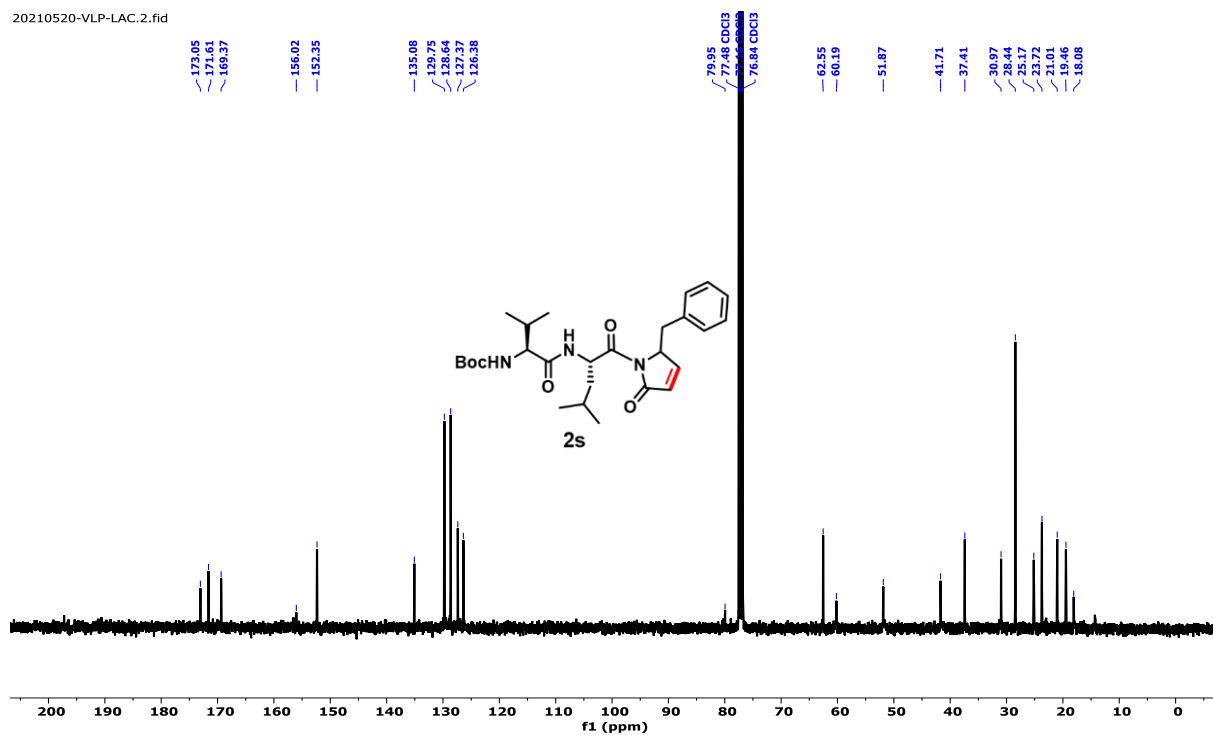


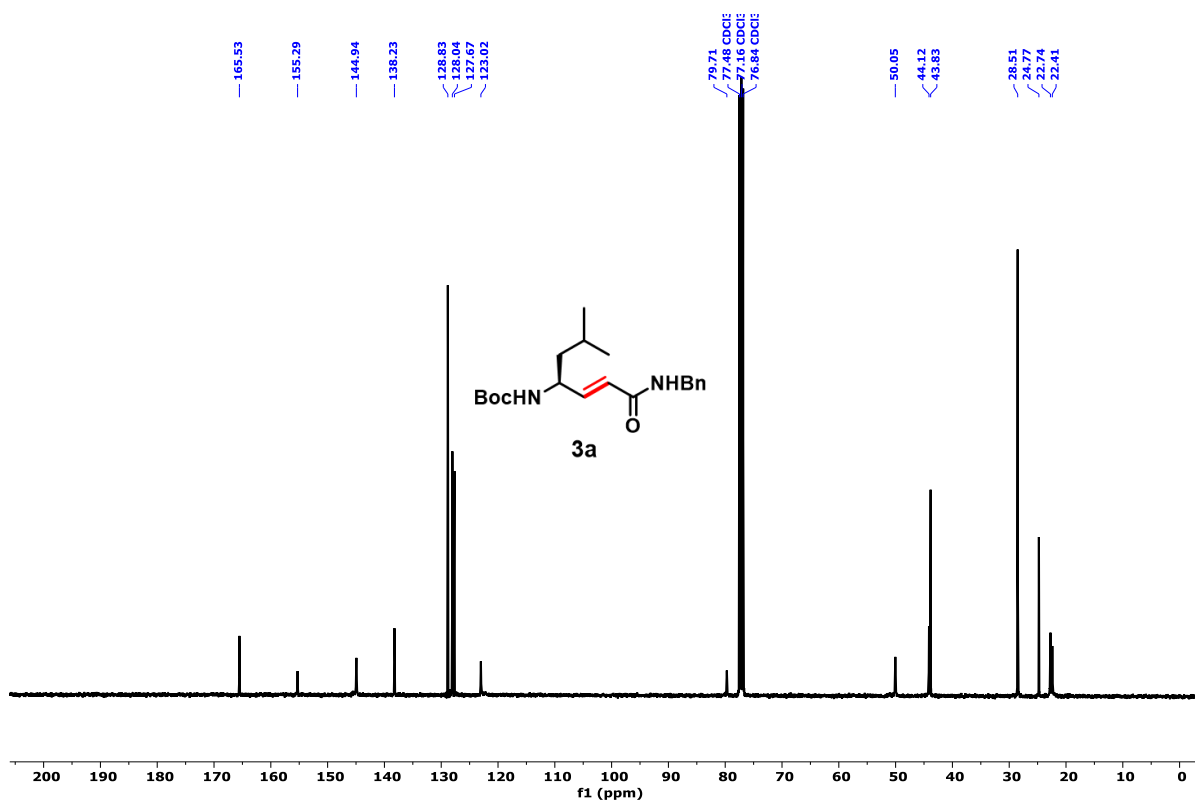
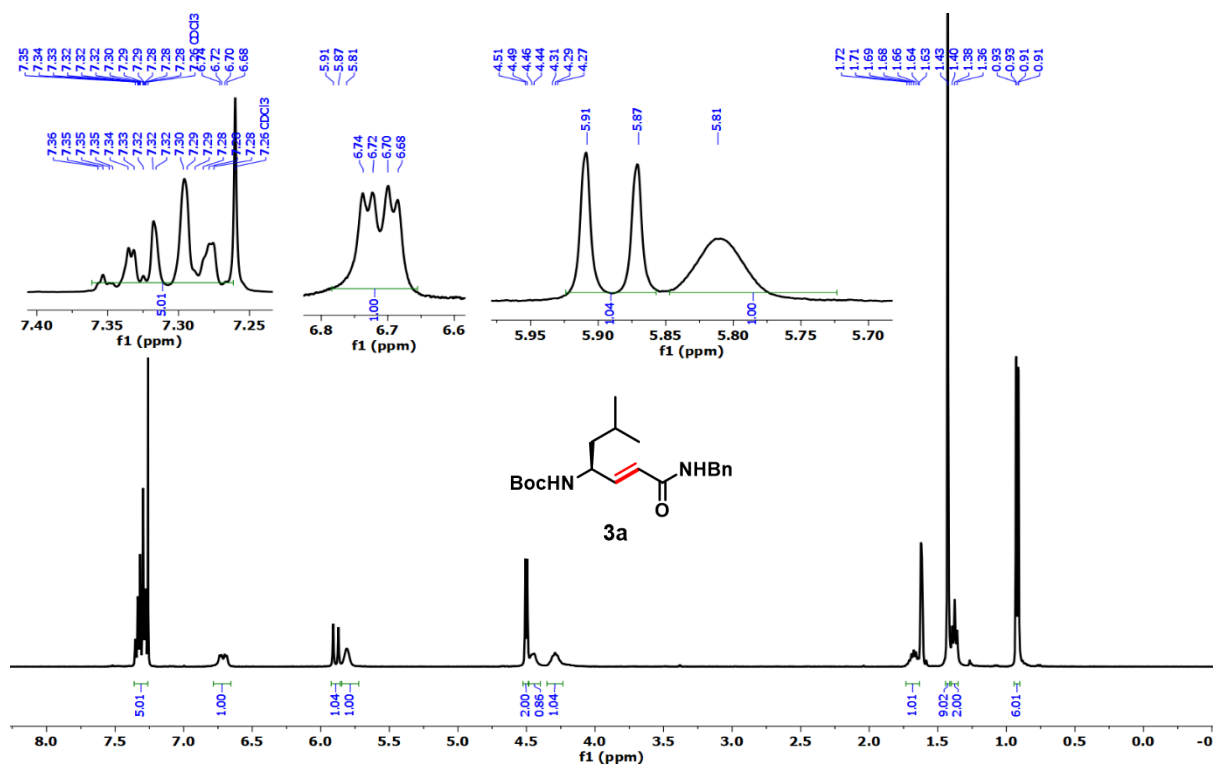






20210520-VLP-LAC.2.fid





3A.9.2 Mass of all the synthesized compounds obtained from HRMS

Entry	Compound	[M+Na/H] ⁺	Calculated Mass	Observed Mass	Δm
1	1a	C ₁₃ H ₂₃ NO ₄ Na	280.1524	280.1528	0.0004
2	1b	C ₁₆ H ₂₁ NO ₄ Na	314.1368	314.1375	0.0007
3	1c	C ₁₂ H ₂₁ NO ₄ Na	266.1368	266.1374	0.0006
4	1d	C ₁₃ H ₂₃ NO ₄ Na	280.1524	280.1526	0.0002
5	1e	C ₁₀ H ₁₇ NO ₄ Na	238.1055	238.1059	0.0004
6	1f	C ₁₁ H ₁₉ NO ₄ Na	252.1211	252.1217	0.0006
7	1g	C ₁₀ H ₁₈ NO ₃	200.1286	200.1287	0.0001
8	1h	C ₁₃ H ₁₆ NO ₃	234.1130	234.1132	0.0002
9	1i	C ₁₆ H ₂₁ NO ₄ Na	314.1368	314.1367	0.0001
10	1j	C ₁₉ H ₃₄ N ₂ O ₅ Na	393.2365	393.2368	0.0003
11	1k	C ₁₈ H ₃₂ N ₂ O ₅ Na	379.2208	379.2210	0.0002
12	1l	C ₁₈ H ₃₂ N ₂ O ₅ Na	379.2208	379.2212	0.0004
13	1m	C ₁₈ H ₃₂ N ₂ O ₅ Na	379.2208	379.2211	0.0003
14	1n	C ₂₂ H ₃₂ N ₂ O ₅ Na	427.2208	427.2209	0.0001
15	1o	C ₂₀ H ₂₈ N ₂ O ₅ Na	399.1895	399.1990	0.0005
16	1p	C ₁₇ H ₃₀ N ₂ O ₅ Na	365.2052	365.2055	0.0003
17	1q	C ₂₁ H ₃₆ N ₂ O ₅ Na	419.2521	419.2521	0
18	1r	C ₂₇ H ₃₂ N ₂ O ₅ Na	487.2208	487.2204	0.0004
19	1s	C ₂₇ H ₄₂ N ₃ O ₆ Na	504.3073	504.3075	0.0002
20	1t	C ₁₀ H ₁₇ NO ₄ Na	238.1055	238.1054	0.0001
21	2a	C ₁₃ H ₂₁ NO ₃ Na	262.1418	262.1419	0.0001
22	2b	C ₁₆ H ₁₉ NO ₃ Na	296.1262	296.1265	0.0003
23	2c	C ₁₂ H ₁₉ NO ₃ Na	248.1262	248.1261	0.0001
24	2d	C ₁₃ H ₂₁ NO ₃ Na	262.1418	262.1418	0
25	2e	C ₁₀ H ₁₅ NO ₃ Na	220.0949	220.0955	0.0006
26	2f	C ₁₁ H ₁₇ NO ₃ Na	234.1105	234.1106	0.0001
27	2g	C ₁₀ H ₁₆ NO ₂ Na	204.1000	204.0995	0.0005
28	2h	C ₁₃ H ₁₃ NO ₂ Na	238.0843	238.0843	0
29	2i	C ₁₆ H ₁₉ NO ₃ Na	296.1262	296.1266	0.0004
30	2j	C ₁₉ H ₃₂ N ₂ O ₄ Na	375.2259	375.2261	0.0002
31	2k	C ₁₈ H ₃₀ N ₂ O ₄ Na	361.2103	361.2101	0.0002
32	2l	C ₁₈ H ₃₀ N ₂ O ₄ Na	361.2103	361.2102	0.0001
33	2m	C ₁₈ H ₃₀ N ₂ O ₄ Na	361.2103	361.2105	0.0002
34	2n	C ₂₂ H ₃₀ N ₂ O ₄ Na	387.2284	387.2299	0.0015
35	2o	C ₂₀ H ₂₆ N ₂ O ₄ Na	381.1790	381.1795	0.0005
36	2p	C ₁₇ H ₂₈ N ₂ O ₄ Na	347.1946	347.1947	0.0001
37	2q	C ₂₁ H ₃₄ N ₂ O ₄ Na	401.2416	401.2413	0.0003
38	2r	C ₂₇ H ₃₀ N ₂ O ₄ Na	469.2103	469.2104	0.0001
39	2s	C ₂₇ H ₃₉ N ₃ O ₅ Na	508.2787	508.2790	0.0003
40	3a	C ₂₀ H ₃₀ N ₂ O ₃ Na	369.2154	369.2146	0.0008

Note: Δm = Mass difference, [M+Na/H]⁺ = Molecular ion.

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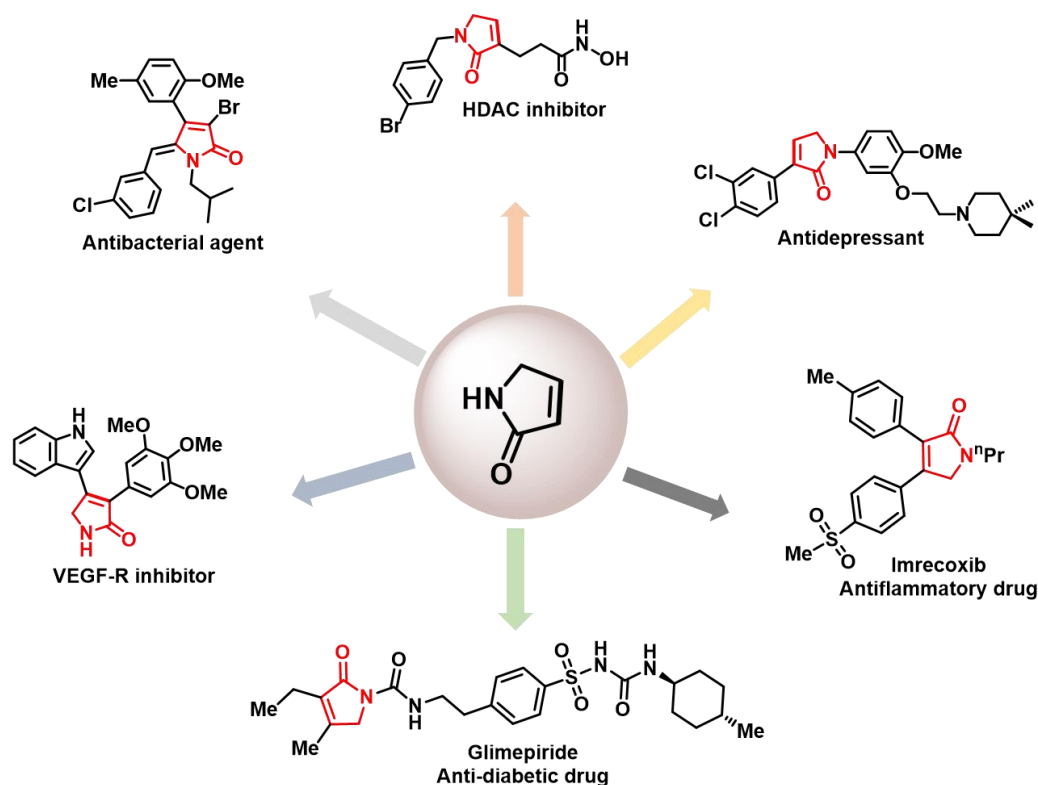
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Chapter 3B

Synthesis of Core Z- γ -Lactam Using HATU and DIPEA

3B.1 Introduction

The unique structural features of α,β -unsaturated γ -butyrolactams is responsible for their wide range of properties and reactivity, makes them valuable and versatile building blocks in the synthesis of various complex organic molecules.¹ For example, α,β -unsaturated γ -butyrolactams have been explored by M. Shibasaki *et al.* and others for the vinylogous additions to electrophiles,² D. J. Williams and co-workers, and others for the conjugate addition,³ and C. Riche *et al.* and D. Romo *et al.* for the pericyclic reactions.⁴ In addition, α,β -unsaturated γ -butyrolactams coupled with a tertiary amine to form the Morita–Baylis–Hillman-type products *via* organocatalysis.⁵ α,β -unsaturated γ -butyrolactams along with their synthetic application also have considerable biological significance, primarily due to their role as versatile scaffolds in the development of biologically active compounds and their involvement in the modulation of various biological processes.⁶ Some of the key aspects of their biological relevance are drug discovery,⁷ anti-inflammatory and antibacterial activity,^{8,9} and enzyme inhibition,¹⁰ some α,β -unsaturated γ -butyrolactams containing compounds along with their therapeutic applications are shown in the Scheme 1. Glimepiride as an antidiabetic drug and Imrecoxib as an anti-inflammatory drug is currently commercially available from this class of compounds.⁷ The progress in the area of efficiently synthesizing routes for the formation of α,β -unsaturated γ -butyrolactams has been always of enduring importance to synthetic chemists.¹¹ Among these synthetic methods, the metal-salt catalyzed reactions,^{7,12} and well-established selenoxide elimination of pyrrolidone are important and useful methods for the preparation of α,β -unsaturated γ -butyrolactams.¹³ Recently we have shown that α,β -unsaturated γ -butyrolactams can be formed from active esters of *N*-Boc-protected-(*E*)- α,β -unsaturated γ -amino acids,¹⁴ and also from the *in-situ* activation of *E*- α,β -unsaturated γ -amino acids with various side chains using HBTU and DIPEA as a coupling reagent and activator base respectively.¹⁵ Further to understand the effect of amino acid side chain and stronger coupling reagent HATU on cyclization, we studied the reactions of achiral *E*-vinylogous amino acids of glycine residue in monomers with different protecting groups and peptides. Moreover, these achiral *E*-vinylogous γ -amino acids were explored in the design of the single helix and β -double helix foldamers.¹⁶⁻¹⁸



Scheme 1. α,β -unsaturated γ -butyrolactams containing compounds with their biological activities.

3B.2 Aim and Rationale of the Present Work

Synthesis of α,β -unsaturated γ -butyrolactams involves either multiple steps or the use of toxic reagents.^{11,12} In the previous chapter we have seen the side chain of the *E*-vinyllogous amino acid also influences the cyclization reaction.¹⁵ To understand the effect of side chains and concentration of reaction mixture on cyclization, here we investigated the cyclization of achiral *E*-vinyllogous amino acid using HATU and DIPEA as a coupling reagent and activator base respectively. HATU is very frequently used for the synthesis of amide derivatives,^{19,20} because of its enhanced reactivity compared to the HBTU.²¹ Also in previous methods, we have seen lower yields in the case of monomers mainly, so here we have changed our strategy. In the present method, we used THF solvent instead of DMF under high dilution conditions to perform intra-molecular cyclization reactions.

3B.3 Results and Discussion

Our investigation commenced with the optimization of reaction conditions using *N*-protected-(*E*)- α,β -unsaturated γ -glycine amino acid **1a** as the model substrate. We synthesized *N*-protected-(*E*)- α,β -unsaturated γ -glycine amino acid **1a** by treating *N*-protected- α -amino

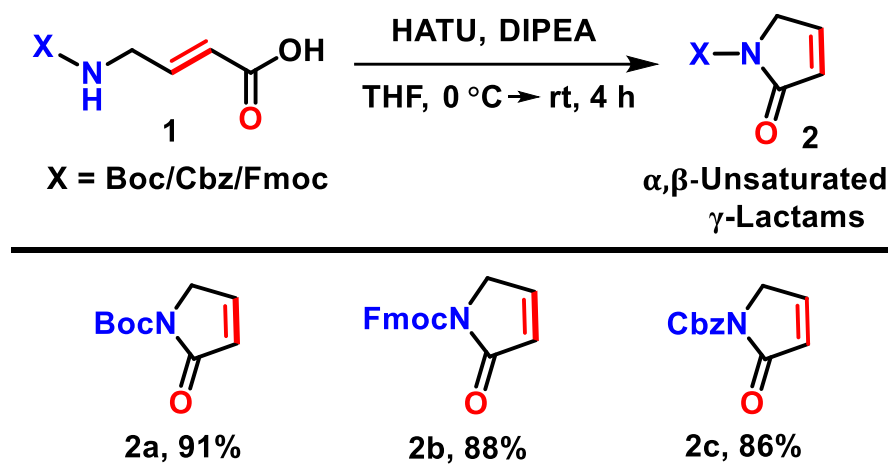
aldehydes with Wittig ylide using the procedure as reported earlier.²² A systematic screening was carried out to evaluate a range of solvents, varying reaction times, and the type of coupling reagent to establish a standard optimized procedure, given in Table 1. Under high dilution conditions, **1a** was treated with HATU and DIPEA in dried THF to get α,β -unsaturated γ -butyrolactam **2a**, the reaction progress was observed by TLC and product formation was analyzed by various spectroscopic techniques.

Table 1: Screening of different reaction conditions for 1a to 2a transformation.

Entry	Solvent	C. R.	Time (h)	% Yield ^a
1	DMF	HBTU	6	70
3	DMF	HATU	4	75
4	Dry THF	HBTU	6	64
5	DCM	HATU	4	36
6	EtOAc	HATU	4	32
7	Dry THF	HATU	4	91

^aConc = 0.01M, C. R. = Coupling Reagent

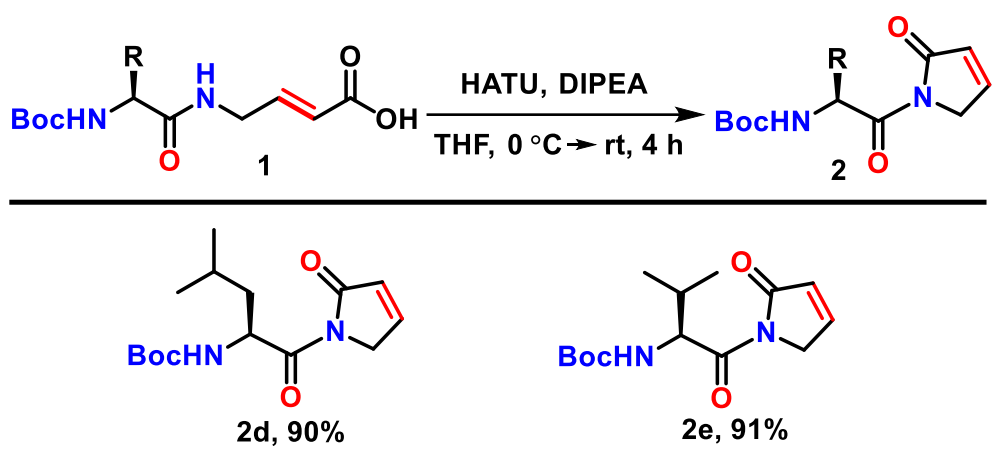
We were very pleased to see the best conversion of **1a** to **2a** above mentioned the optimized reaction condition, where we obtained **2a** in 91% yield. Similarly, **1b** and **1c** were transformed into **2b** and **2c** respectively using optimized reaction conditions, with excellent yields. We found that the reaction works well with *E*-vinyllogous amino acid with different protecting groups (-Boc, -Fmoc and -Cbz) of the amine functional group, depicted in Scheme 2.



Scheme 2. Synthesis of α,β -unsaturated γ -butyrolactams (**2a-2c**).

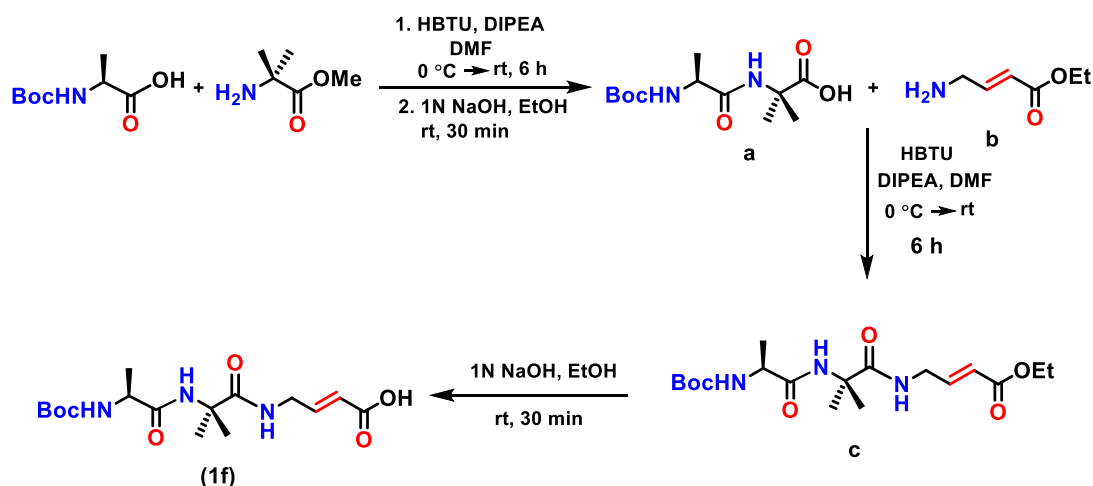
3B.3.1 Synthesis of Dipeptide γ -Lactams (2d-2e)

Inspired by these fascinating results, we sought to investigate whether achiral α,β -unsaturated γ -amino acid containing dipeptides and tripeptides at the C-terminus can be transformed into the peptide γ -lactam. We synthesized dipeptides **1d** and **1e**, using solution phase peptide synthesis taking advantage of HBTU and DIPEA followed by base hydrolysis of di-peptide esters, to obtain dipeptides **1d-1f**.^{22,23} Using the similar strategy of cyclization, dipeptides **1d** and **1e** was transformed into corresponding peptide γ -lactams **2d-2e** respectively. After having the optimized reaction conditions in hand, we explore the substrate scope of the cyclization reaction and the results are summarized in Schemes 3.

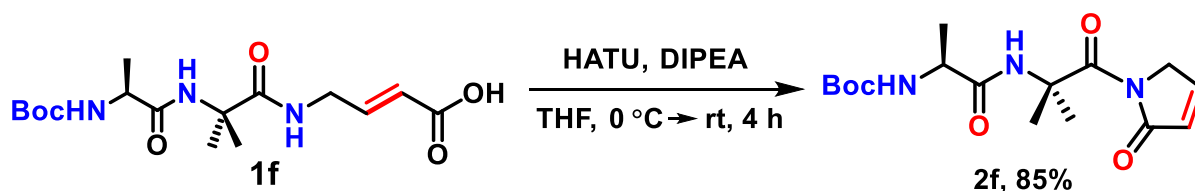


3B.3.2 Synthesis of Tripeptide γ -Lactams (2f)

Using solution phase peptide synthesis tripeptide ester (**c**) was synthesized which upon base hydrolysis gave tripeptide acid **1f**. The peptide **1f** was purified through column chromatography and characterized before further synthesis. Subsequently, **1f** was transformed into the corresponding peptide γ -lactams **2f** using HATU and DIPEA under high dilution conditions. A pictorial representation of the synthesis of **1f** starting from Boc-amino is depicted in Scheme 4.



Scheme 4. Pictorial representation of the synthesis of **1f** starting from Boc-amino acid.



Scheme 5. Pictorial representation of the transformation **1f** to tripeptide γ -lactam **2f**.

The ^1H NMR analysis of cyclization revealed that the achiral *E*-vinylous amino acid **1a** shows a chemical shift (δ_{H}) for the alkene protons at 6.99 and 5.93 ppm with the coupling constant value of 15.6 Hz. After cyclization chemicals shift changed to 7.18 and 6.15 ppm with a coupling constant of 6.1 Hz for the α,β -unsaturated γ -butyrolactams **2a**. Indicating the formation of a 5-membered lactam ring *via* intramolecular cyclization. Mass analysis of the cyclization indicates the 18-unit massless for the cyclized product compared to the starting substrate, which is well-coped with NMR analysis. We obtained crystal structure for the α,β -unsaturated γ -butyrolactams **2b** shown in the Figure 1.

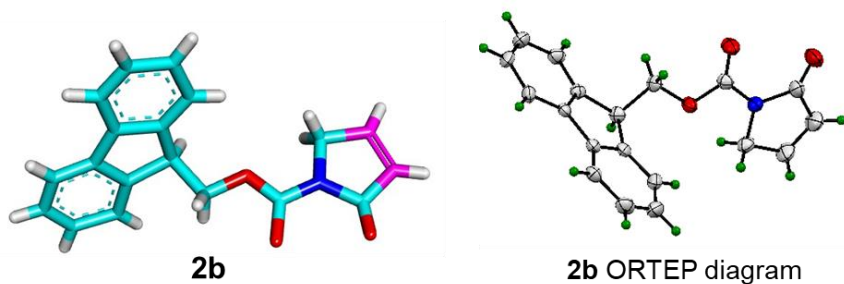
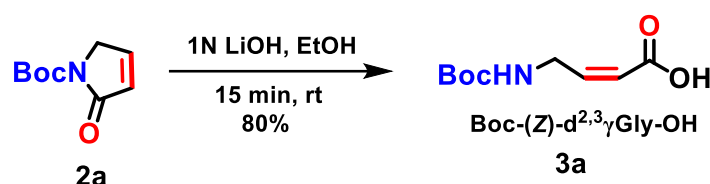


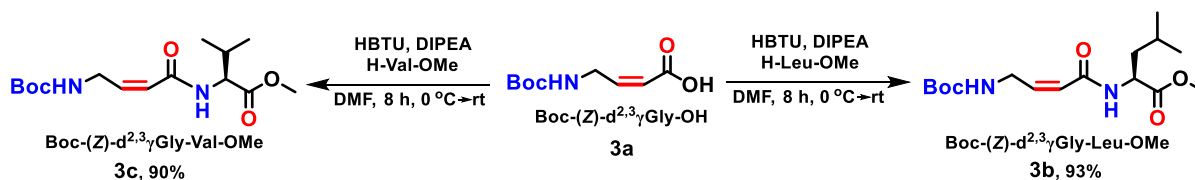
Figure 1. Crystal structure of α,β -unsaturated γ -butyrolactam **2b**.

3B.3.3 Application of α,β -Unsaturated γ -Butyrolactams in Peptide Synthesis

The saturated γ -lactams undergo base hydrolysis reaction,²⁴ taking advantage of this method we tested whether α,β -unsaturated γ -butyrolactams **2a** can undergo a similar hydrolysis reaction using 1N LiOH. After the purification of the hydrolyzed product, it was observed that the **2a** converted to the *N*-Boc-(*Z*)-d^{2,3} γ Gly-OH (**3a**) shown in Scheme 6. This was confirmed by ¹H NMR analysis of the **3a** indicating a coupling constant value of 11.5 Hz for alkene protons which correspond to the *Z*-configuration of the hydrolyzed product **3a**. *N*-Boc-(*Z*)-d^{2,3} γ Gly-OH (**3a**) was further utilized for the synthesis of dipeptide methyl esters **3b** and **3c** using the standard protocol of the solution phase peptide synthesis,²³ shown in Scheme 7.



Scheme 6. Synthesis of *N*-Boc-(*Z*)- α,β -unsaturated γ -glycine amino acid (**3a**).

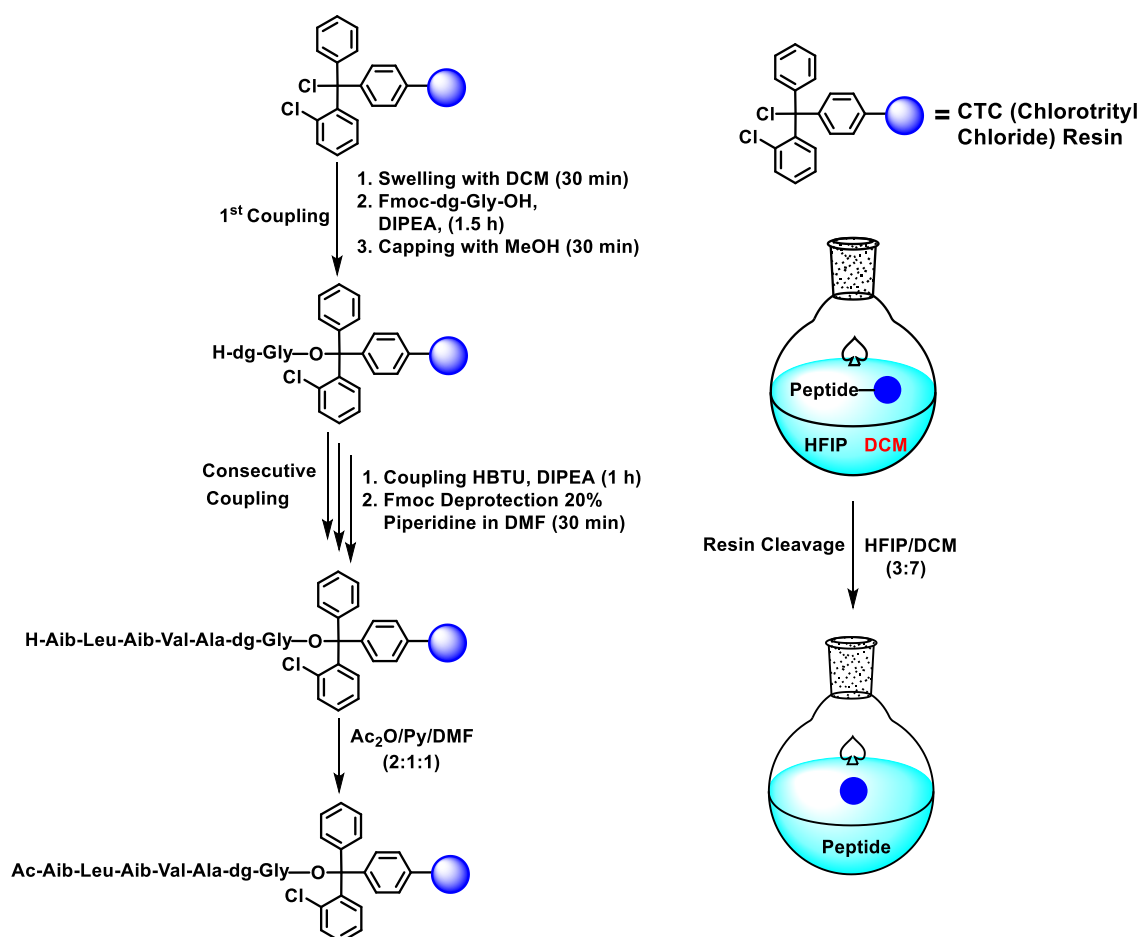


Scheme 7. Solution phase peptide synthesis of dipeptide methyl esters (**3b** and **3c**) using **3a**.

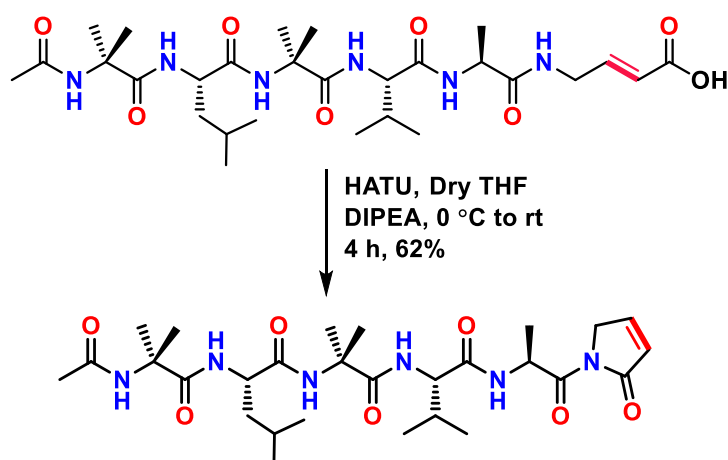
3B.3.4 SPPS Followed by Cyclization Reaction

The synthesis of peptides containing α,β -unsaturated γ -butyrolactams can be challenging in some cases.²⁵ To overcome these difficulties we have extended the current strategy to Solid Phase Peptide Synthesis (SPPS),²⁶ followed by cyclization of peptide synthesized by SPPS. 2-Chlorotrityl chloride resin and standard Fmoc chemistry have been used for the synthesis of peptide **1g**, containing *E*- α,β -unsaturated γ -glycine amino acid at the C-terminus, schematic representation of **1g** via SPPS strategy is shown in Scheme 8. The formation of **1g** was confirmed by MALDI-TOF/TOF analysis and **1g** was cyclized using previously optimized reaction conditions to get **2g**, which was purified through RP-HPLC using MeOH/Water as a solvent system, HPLC traces are shown in Figure 2. The conversion of **1g** to **2g** (shown in

Scheme 9) was analyzed by MALDI-TOF/TOF analysis, we found that as a result of cyclization 18 mass got reduced indicating the formation of α,β -unsaturated γ -butyrolactam at C-terminus of the peptide **1g**. The mechanism of the cyclization reaction also involves $E \rightarrow Z$ isomerization as discussed in the previous chapters.^{14,15}



Scheme 8. Schematic representation of SPPS of peptide **1g** using Fmoc chemistry.



Scheme 9. Pictorial representation of the synthesis of **2g** from peptide **1g**.

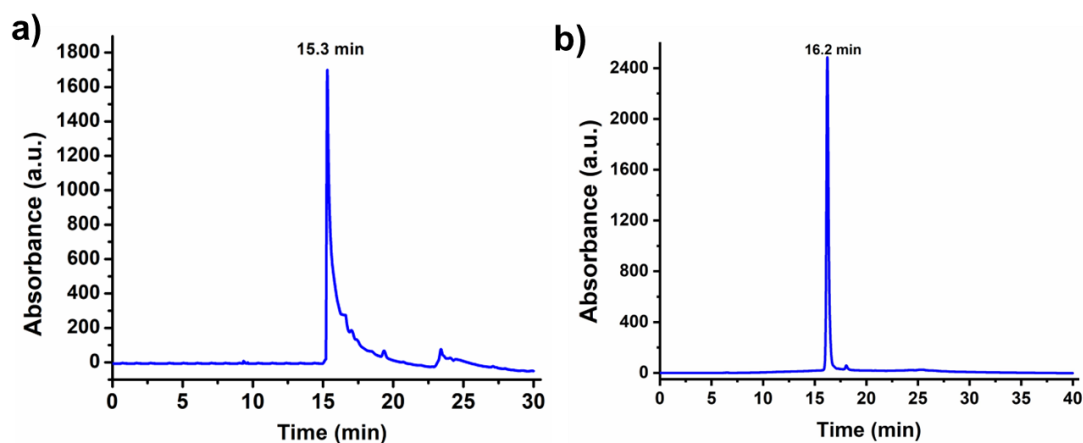


Figure 2. HPLC chromatograms of a) for hexapeptide acid (**1g**) and a) for hexapeptide γ -lactam (**2g**).

3B.4 Conclusion

In summary, the exploration of achiral *E*-vinyllogous γ -amino acids in organic synthesis represents a significant and promising avenue of synthetic tools. Throughout this study, it became evident that *E*-vinyllogous γ -amino acids offer a wide array of synthetic possibilities, allowing for the creation of diverse scaffolds and functional groups. In the transformations of achiral *E*-vinyllogous γ -amino acids to the α,β -unsaturated γ -butyrolactams HATU and DIPEA play an important role under high dilution conditions. Importantly, this strategy is quite handy and results in exceptionally good yields of all the synthesized cyclic compounds. The extension of the method provides a relatively smooth pathway for the synthesis of complex peptides, where we took advantage of solid phase peptide synthesis (SPPS). Overall, achiral α,β -unsaturated γ -amino acids can be transformed into α,β -unsaturated γ -butyrolactams through *in-situ* activation of free carboxylic acids, involving *E* $\rightarrow$ *Z* isomerization of double bonds as reported earlier.²⁷

3B.5 Experimental Section

General Method: All the cyclization reactions were performed under inert conditions of nitrogen. All the amino acids, Boc anhydride, Benzyl chloroformate, N-(9-Fluorenylmethoxycarbonyloxy)succinimide, LiAlH_4 , HBTU, HATU, HOBT, Ethyl bromoacetate, Triphenyl Phosphine (PPh_3), Trifluoroacetic acid (TFA), N,N-Diisopropylethylamine (DIPEA), DMF, THF, EtOAc, Hexane, were purchased from different

commercial sources. Ethyl acetate, Hexane, and THF (over sodium) were distilled before use. Column chromatography was performed on silica gel (60-120). Reactions were monitored by analytical thin layer chromatography (TLC) and confirmed by UV light chamber and KMnO₄ or ninhydrin staining. ¹H NMR and ¹³C NMR spectra were recorded in deuterated solvents on 400 MHz and 101 MHz NMR machines respectively using the residual solvent signal as the internal standard. Chemical shifts are reported in parts per million (ppm, δ) relative to tetramethyl silane (δ 0.00). ¹H NMR splitting patterns are assigned as singlet (s), doublet (d), broad singlet (bs), triplet (t), doublet of doublets (dd), and quintet (qn). Coupling constants (*J*) are reported in Hertz (Hz). Mass spectra were recorded using HRMS Electron Spray Ionization (ESI). The mass of the purified peptides was finally confirmed by MALDI-TOF/TOF analysis. The X-ray data were collected at low temperature (150 K) on a Bruker APEX (II) DUO CCD diffractometer using Mo K α (λ = 0.71073 Å) graphite monochromated radiation.

3B.5.1 Synthetic procedures for *N*-protected (*E*)-vinyllogous amino acids.

The *N*-protected α,β -unsaturated γ -amino esters (Boc/Fmoc/Cbz-(*E*)-d^{2,3} γ Gly-OEt) were prepared by the previously reported procedures.²⁶ Boc/Fmoc/Cbz and ethyl ester protecting groups were used to protect the N-terminus and C-terminus of the (*E*)-vinyllogous glycine amino acid, respectively. The ethyl ester group of Boc/Fmoc/Cbz-(*E*)-d^{2,3} γ Gly-OEt at 2 mmol scale was deprotected by base hydrolysis using 1N NaOH, to obtain **1a-1c**.

(*E*)-4-((*tert*-butoxycarbonyl) amino) but-2-enoic acid (**1a**)

Viscous liquid, yield = 360 mg (90%); ¹H NMR (400 MHz, CDCl₃) δ _H 6.99 (d, *J* = 15.6 Hz, 1H), 5.93 (d, *J* = 15.6 Hz, 1H), 4.92–4.74 (m, 1H), 3.94 (s, 2H), 1.44 (s, 9H); ¹³C NMR (101 MHz, CDCl₃) δ _C 170.81, 155.84, 147.25, 120.87, 80.19, 41.46, 28.43. HRMS: *m/z* for C₉H₁₅NO₄Na (M + Na)⁺, cal. 224.0898, found 224.0892.

(*E*)-4-(((9H-fluoren-9-yl) methoxy) carbonyl) amino) but-2-enoic acid (**1b**)

White solid, yield = 594 mg (92%); **m.p.** 158-161 °C; [α]_D²⁵ = -24.0 (*c* 0.1, MeOH); ¹H NMR (400 MHz, CD₃CN) δ _H 7.83 (d, *J* = 7.5 Hz, 2H), 7.66 (d, *J* = 7.5 Hz, 2H), 7.42 (t, *J* = 7.5 Hz, 2H), 7.34 (t, *J* = 7.3 Hz, 2H), 6.85 (dt, *J* = 15.7, 4.7 Hz, 1H), 5.93 (s, 1H), 5.84 (d, *J* = 15.7 Hz, 1H), 4.36 (d, *J* = 6.9 Hz, 2H), 4.24 (t, *J* = 6.9 Hz, 1H), 3.86 (t, *J* = 4.1 Hz, 2H); ¹³C NMR (101 MHz, CD₃CN) δ _C 167.35, 147.02, 145.17, 142.16, 128.71, 128.11, 126.14, 121.24,

121.00, 67.15, 48.12, 42.16, 1.94, 1.73. **HRMS:** m/z for $C_{19}H_{17}NO_4Na$ ($M + Na$)⁺, cal. 346.1055, found 346.1056.

(E)-4-(((benzyloxy) carbonyl) amino) but-2-enoic acid (1c)

Viscous liquid, yield = 418 mg (89%); **¹H NMR** (400 MHz, CDCl₃) δ_H 7.37 (d, J = 3.3 Hz, 5H), 6.96 (dt, J = 15.7, 4.8 Hz, 1H), 5.99 (dt, J = 15.7, 1.9 Hz, 1H), 5.18 (s, 1H), 5.12 (s, 1H), 4.92 (d, J = 4.8 Hz, 1H), 4.03–3.96 (m, 2H); **¹³C NMR** (101 MHz, CDCl₃) δ_C 144.90, 128.73, 128.43, 128.34, 121.47, 76.84, 66.53, 41.92. **HRMS:** m/z for $C_{12}H_{12}NO_4$ ($M - H$)⁻, cal. 234.0768, found 234.0769.

3B.5.2 General procedure of peptides (1d-1f) synthesis.

For the synthesis of dipeptide (BocHN-Leu/Val/-d^{2,3}γGly-OEt), first BocHN-d^{2,3}γGly-OEt (2.2 mmol) was treated with DCM-TFA mixture (1:1, 10 mL) in a 25 mL RB for deprotecting Boc-group. The reaction was performed for 30 minutes at room temperature. Reaction progress was monitored by TLC, after completion of the reaction, the solution was evaporated under reduced pressure using a rotary evaporator. To remove the excess amount of TFA, the mixture was co-evaporated with DCM four to five times at low temperatures. The obtained TFA.H₂N-d^{2,3}γGly-OEt salt was basified with a small amount of DIPEA before being utilized for the coupling. In another 25 mL RB, the BocHN-Leu/Val-OH (2 mmol) and HBTU (2 mmol) were dissolved in 8 mL of DMF. After some time DIPEA (6 mmol) was added to the reaction mixture. After stirring the reaction mixture for 5 min at ice-cooled temperature, H₂N-d^{2,3}γGly-OEt (**b**, 2 mmol) is added. The reaction mixture was stirred at room temperature for 6 h. After completion of the reaction which was visualized by TLC, workup was done by diluting the reaction mixture with ethyl acetate (150 mL), followed by successive washings with 10% HCl (3 × 80 mL), 10% Na₂CO₃ (3 × 80 mL) and brine solution (2 × 80 mL). The organic layer was dried on top of anhydrous Na₂SO₄ and concentrated under reduced pressure. The obtained crude compounds were purified through silica gel (60-120 mesh) column chromatography using ethyl acetate/pet-ether as eluent in increasing polarity. Hydrolysis of dipeptides was done using 1N NaOH followed by acid workup to get dipeptides **1d** and **1e**. A similar strategy was used to synthesize tripeptide **1f**, where first Boc-Ala-OH (2 mmol) was activated with HBTU (2 mmol) in a 25 mL round bottom flask in the presence of activator base DIPEA. Subsequently, a methyl ester of Aib amino acid (H-Aib-OMe) was added to the reaction mixture to obtain the dipeptide ester

Boc-Ala-Aib-OMe after the workup mentioned above. Which was further hydrolyzed by using 1N NaOH to get the dipeptide Boc-Ala-Aib-OH (**a**, 2 mmol). Which was treated with H₂N-d^{2,3}γGly-OEt (**b**, 2 mmol) under coupling reaction conditions of DMF, HBTU (2 mmol) and DIPEA (6 mmol). The reaction mixture diluted with 150 mL ethyl acetate was washed with diluted 10% HCl and 10% Na₂CO₃ followed by brine washing. The combined organic layer was dried over sodium sulfate and concentrated under a reduced vacuum to get crude Boc-Ala-Aib-dg-Gly-OEt (**c**). After performing column purification we obtained a good amount of tripeptide ester, which was base hydrolyzed to get the desired final tripeptide Boc-Ala-Aib-dg-Gly-OH (**1f**) shown in Scheme 4.

(*S,E*)-4-(2-((*tert*-butoxycarbonyl) amino)-4-methylpentanamido) but-2-enoic acid (1d)

Viscous liquid, yield = 577 mg (92%); ¹H NMR (400 MHz, Acetone-*d*₆) δ_H 8.95 (d, *J* = 10.6 Hz, 1H), 6.76 (dt, *J* = 15.7, 9.0 Hz, 1H), 6.23 (d, *J* = 8.3 Hz, 1H), 4.91 (dt, *J* = 15.7, 7.3 Hz, 1H), 4.21 (q, *J* = 7.8 Hz, 1H), 3.12 (dt, *J* = 7.4, 1.5 Hz, 2H), 1.72 (dq, *J* = 13.3, 6.6 Hz, 1H), 1.58 (dd, *J* = 8.4, 6.1 Hz, 2H), 1.41 (s, 9H), 0.93 (d, *J* = 6.6 Hz, 3H), 0.90 (d, *J* = 6.6 Hz, 3H); ¹³C NMR (101 MHz, Acetone-*d*₆) δ_C 172.58, 171.51, 156.65, 124.15, 103.76, 79.43, 53.77, 41.56, 31.56, 28.46, 25.36, 23.33, 21.82. **HRMS**: *m/z* for C₁₅H₂₅N₂O₅ (M - H)⁻, cal. 313.1764, found 313.1764.

(*S,E*)-4-(2-((*tert*-butoxycarbonyl) amino)-3-methylbutanamido) but-2-enoic acid (1e)

Viscous liquid, yield = 564 mg (94%); ¹H NMR (400 MHz, CD₃CN) δ_H 6.91 (s, 1H), 6.84 (d, *J* = 15.6 Hz, 1H), 5.85 (d, *J* = 15.6 Hz, 1H), 5.61 – 5.46 (m, 1H), 3.95 (d, *J* = 5.9 Hz, 2H), 3.83 (d, *J* = 7.5 Hz, 1H), 2.04 (h, *J* = 6.7 Hz, 1H), 1.41 (s, 9H), 0.92 (d, *J* = 6.8 Hz, 3H), 0.87 (d, *J* = 6.8 Hz, 3H); ¹³C NMR (101 MHz, CD₃CN) δ_C 172.86, 167.56, 156.87, 146.48, 121.45, 79.81, 61.10, 40.32, 31.30, 28.50, 19.63, 18.07, 1.88, 1.67. **HRMS**: *m/z* for C₁₄H₂₄N₂O₅Na (M + Na)⁺, cal. 323.1582, found: 323.1580.

(S,E)-2,2,6,9,9-pentamethyl-4,7,10-trioxo-3-oxa-5,8,11-triazapentadec-13-en-15-oic acid (1f)

Viscous liquid, yield = 621 mg (87%); $^1\text{H NMR}$ (400 MHz, Acetone- d_6) δ_{H} 7.61 (s, 1H), 7.53 (s, 1H), 6.87 (dt, J = 15.7, 4.5 Hz, 1H), 6.35 (s, 1H), 5.97 (d, J = 15.7 Hz, 1H), 3.95 (dd, J = 8.9, 4.6 Hz, 3H), 1.51 (s, 3H), 1.47 (s, 3H), 1.39 (s, 9H), 1.30 (d, J = 7.1 Hz, 3H); $^{13}\text{C NMR}$ (151 MHz, CD_3CN) δ_{C} 175.42, 173.98, 167.77, 157.25, 146.90, 121.38, 80.45, 57.71, 52.18, 40.83, 28.56, 26.22, 25.40, 17.48. **HRMS**: m/z for $\text{C}_{16}\text{H}_{27}\text{N}_3\text{O}_6\text{Na}$ ($\text{M} + \text{Na}$) $^+$, cal. 380.1797, found: 380.1794.

3B.5.3 Procedure for the Synthesis of Achiral α,β -Unsaturated γ -Lactams (2a-2f).

Boc/Fmoc/Cbz-(*E*)- $\text{d}^{2,3}\gamma\text{Gly-OH}$ or Boc-Leu/Val-(*E*)- $\text{d}^{2,3}\gamma\text{Gly-OH}$ or Boc-Ala-Aib-(*E*)- $\text{d}^{2,3}\gamma\text{Gly-OH}$ (2 mmol) was initially dissolved in 50 mL of THF then DIPEA (6 mmol) was added to the reaction mixture. The resultant reaction mixture was treated with HATU (2 mmol) at ice-cold conditions. The reaction mixture was stirred for 4 h at room temperature under an inert environment. The progress of the reaction was monitored by thin-layer chromatography (TLC). Once the reaction was complete, THF was evaporated using a rotary evaporator resultant reaction mixture was diluted with ethyl acetate (150 mL) and washed with 10% HCl (3 $\times$ 80 mL), 10% Na_2CO_3 (3 $\times$ 80 mL), and brine solution (3 $\times$ 80 mL). The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude product was purified using silica gel (60-120 mesh) column chromatography using an ethyl acetate/hexane solvent system in increasing polarity to get pure α,β -unsaturated γ -lactams (2a-2f).

***tert*-butyl 2-oxo-2,5-dihydro-1H-pyrrole-1-carboxylate (2a)**

Viscous liquid, yield = 311 mg (85%), R_{f} = 0.50 (40% EtOAc in hexane); $^1\text{H NMR}$ (400 MHz, CDCl_3) δ_{H} 7.18 (d, J = 6.1 Hz, 1H), 6.15 (dt, J = 6.1, 1.9 Hz, 1H), 4.34 (t, J = 2.0 Hz, 2H), 1.55 (s, 9H); $^{13}\text{C NMR}$ (101 MHz, CDCl_3) δ_{C} 169.32, 149.71, 145.27, 128.06, 83.16, 51.77, 28.21. **HRMS**: m/z for $\text{C}_9\text{H}_{13}\text{NO}_3\text{Na}$ ($\text{M} + \text{Na}$) $^+$, cal. 206.0786, found: 206.0791.

(9H-fluoren-9-yl) methyl 2-oxo-2,5-dihydro-1H-pyrrole-1-carboxylate (2b)

White solid, yield = 536 mg (88%), **m.p.** 147-149 $^\circ\text{C}$, R_{f} = 0.48 (40% EtOAc in hexane); $^1\text{H NMR}$ (400 MHz, CDCl_3) δ_{H} 7.77 (t, J = 6.8 Hz, 4H), 7.44–7.39 (m, 2H), 7.34 (td, J = 7.4, 1.0 Hz, 2H), 7.27–7.24 (m, 1H), 6.22 (dt, J = 6.1, 1.9 Hz, 1H), 4.55 (d, J = 7.3 Hz, 2H), 4.37 (t, J = 2.0 Hz, 2H), 4.34 (d, J = 7.3 Hz, 1H); $^{13}\text{C NMR}$ (101 MHz, CDCl_3) δ_{C} 168.67, 151.23,

146.02, 143.54, 141.38, 127.98, 127.76, 127.32, 125.44, 120.07, 68.66, 51.59, 46.76. **HRMS:** m/z for $C_{19}H_{15}NO_3Na$ ($M + Na$)⁺, cal. 328.0949, found: 328.0949.

Benzyl 2-oxo-2,5-dihydro-1H-pyrrole-1-carboxylate (2c)

Viscous liquid, yield = 373 mg (86%), R_f = 0.45 (40% EtOAc in hexane); **¹H NMR** (400 MHz, CDCl₃) δ_H 7.47–7.42 (m, 2H), 7.39–7.33 (m, 3H), 7.22 (dt, J = 6.2, 2.1 Hz, 1H), 6.18 (dt, J = 6.2, 2.0 Hz, 1H), 5.32 (s, 2H), 4.41 (t, J = 2.0 Hz, 2H); **¹³C NMR** (101 MHz, CDCl₃) δ_C 168.87, 151.01, 145.87, 135.41, 128.74, 128.59, 128.40, 127.81, 68.17, 51.66. **HRMS:** m/z for $C_{12}H_{11}NO_3Na$ ($M + Na$)⁺, cal. 240.0636, found 240.0632.

tert-butyl (S)-(4-methyl-1-oxo-1-(2-oxo-2,5-dihydro-1H-pyrrol-1-yl) pentan-2-yl) carbamate (2d)

Viscous liquid, yield = 532 mg (90%), R_f = 0.55 (50% EtOAc in hexane); **¹H NMR** (400 MHz, CDCl₃) δ_H 7.32 (d, J = 5.9 Hz, 1H), 6.16 (dt, J = 6.1, 1.9 Hz, 1H), 5.46 (dd, J = 6.1, 3.0 Hz, 1H), 5.09 (d, J = 9.2 Hz, 1H), 4.46 (dt, J = 12.7, 2.1 Hz, 1H), 4.33 (dt, J = 12.6, 2.0 Hz, 1H), 1.82 (ddd, J = 12.9, 6.6, 3.3 Hz, 1H), 1.56 (d, J = 11.9 Hz, 1H), 1.42 (s, 9H), 1.39–1.34 (m, 1H), 1.05 (d, J = 6.5 Hz, 3H), 0.92 (d, J = 6.7 Hz, 3H); **¹³C NMR** (101 MHz, CDCl₃) δ_C 174.16, 169.41, 155.79, 147.24, 127.64, 79.78, 52.75, 50.86, 41.35, 28.44, 25.12, 23.70, 21.19. **HRMS:** m/z for $C_{15}H_{24}N_2O_4Na$ ($M + Na$)⁺, cal. 319.1633, found 319.1633.

tert-butyl (S)-(3-methyl-1-oxo-1-(2-oxo-2,5-dihydro-1H-pyrrol-1-yl) butan-2-yl) carbamate (2e)

Viscous liquid, yield = 513 mg (91%), R_f = 0.52 (50% EtOAc in hexane); **¹H NMR** (400 MHz, CDCl₃) δ_H 7.32 (dt, J = 6.1, 2.0 Hz, 1H), 6.17 (dt, J = 6.1, 1.9 Hz, 1H), 5.44 (dd, J = 9.6, 3.7 Hz, 1H), 5.21 (d, J = 9.7 Hz, 1H), 4.49 (dt, J = 12.6, 2.0 Hz, 1H), 4.34 (dt, J = 12.6, 2.0 Hz, 1H), 2.16 (s, 1H), 1.43 (s, 9H), 1.07 (d, J = 6.8 Hz, 3H), 0.83 (d, J = 6.9 Hz, 3H); **¹³C NMR** (101 MHz, CDCl₃) δ_C 172.85, 169.48, 156.06, 147.16, 127.73, 79.77, 58.09, 50.84, 30.48, 28.46, 20.01, 16.21. **HRMS:** m/z for $C_{14}H_{22}N_2O_4Na$ ($M + Na$)⁺, cal. 305.1477, found: 305.1475.

***tert*-butyl (S)-1-((2-methyl-1-oxo-1-(2-oxo-2,5-dihydro-1*H*-pyrrol-1-yl) propan-2-yl) amino)-1-oxopropan-2-yl) carbamate (2f)**

Viscous liquid, yield = 576 mg (85%), R_f = 0.45 (50% EtOAc in hexane); $^1\text{H NMR}$ (400 MHz, CDCl_3) δ_{H} 7.28 – 7.25 (m, 2H), 6.86 (s, 1H), 6.06 (dt, J = 6.0, 1.9 Hz, 1H), 4.90 (d, J = 7.4 Hz, 1H), 4.46 (q, J = 1.9 Hz, 2H), 4.07 (t, J = 11.2 Hz, 1H), 1.65 (s, 3H), 1.64 (s, 3H), 1.44 (s, 9H), 1.23 (d, J = 7.1 Hz, 3H); $^{13}\text{C NMR}$ (151 MHz, CDCl_3) δ_{C} 174.27, 172.37, 168.82, 155.34, 147.32, 127.66, 80.09, 80.08, 57.59, 52.82, 50.20, 29.84, 28.46, 18.62. **HRMS**: m/z for $\text{C}_{16}\text{H}_{25}\text{N}_3\text{O}_5\text{Na}$ ($\text{M} + \text{Na}$) $^+$, cal. 362.1691, found: 362.1692.

3B.5.4 Hydrolysis of α,β -unsaturated lactam of Glycine

Compound **2a** (1 mmol) was dissolved in 20 mL of EtOH, subsequently, 1*N* LiOH was added to the reaction mixture. After performing the reaction for 15 minutes at room temperature, the reaction status was monitored in between using TLC. Once the reaction was completed the reaction mixture was acidified with diluted 10% HCl solution. Then extraction of the hydrolyzed product was done using EtOAc (50 ml x 3 times) and washing with brine solution (50 ml x 3 times). The hydrolyzed product was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude hydrolyzed product was purified using silica gel (60-120 mesh) column chromatography using an ethyl acetate/hexane solvent system in increasing polarity to get pure Boc-Z-d^{2,3}Gly-OH (**3a**).

(Z)-4-((tert-butoxycarbonyl) amino) but-2-enoic acid (3a)

Oily liquid, yield = 160 mg (80%); $^1\text{H NMR}$ (400 MHz, CDCl_3) δ_{H} 6.34 (dt, J = 11.5, 6.3 Hz, 1H), 5.88 (dt, J = 11.5, 1.9 Hz, 1H), 4.99 (s, 1H), 4.21 (d, J = 6.6 Hz, 2H), 1.45 (s, 9H); $^{13}\text{C NMR}$ (101 MHz, CDCl_3) δ_{C} 170.16, 156.38, 148.24, 120.95, 120.92, 39.45, 28.49. **HRMS**: m/z for $\text{C}_9\text{H}_{15}\text{NO}_4\text{Na}$ ($\text{M} + \text{Na}$) $^+$, cal. 224.0898, found: 224.0892.

3B.5.5 Synthesis of dipeptides 3a and 3b using hydrolyzed product 3a.

Boc-(Z)-d^{2,3}γGly-OH (**3a**, 0.5 mmol) was initially dissolved in 5 mL DMF, subsequently DIPEA (1.5 mmol), HBTU (0.5 mmol) and H-Leu-OMe or H-Val-OMe (0.56 mmol) was added to the reaction mixture. The coupling reaction was first kept at ice-cold conditions for 10 min, and further reaction proceeded at room temperature for 8 h monitored by TLC. After

completion of the reaction, workup was done by diluting the reaction mixture with ethyl acetate (100 mL), followed by successive washings with 10% HCl (3 × 50 mL), 10% Na₂CO₃ (3 × 50 mL) and brine solution (2 × 50 mL). The organic layer was dried on top of anhydrous Na₂SO₄ and concentrated under reduced pressure. The obtained crude compounds were purified through silica gel (60-120 mesh) column chromatography using ethyl acetate/hexane as eluent in increasing polarity to get pure depeptides **3b** and **3c**.

Methyl (Z)-(4-((tert-butoxycarbonyl) amino) but-2-enoyl)-L-leucinate (3b)

Oily liquid, yield = 152 mg (93%), R_f = 0.52 (50% EtOAc in hexane); ¹H NMR (400 MHz, CDCl₃) δ_H 6.59 (d, *J* = 8.5 Hz, 1H), 6.08–5.92 (m, 1H), 5.23 (s, 1H), 4.68–4.53 (m, 2H), 3.83–3.78 (m, 1H), 3.72 (s, 3H), 1.63 (dt, *J* = 4.6, 2.3 Hz, 2H), 1.56–1.50 (m, 1H), 1.44 (s, 9H), 0.93 (dd, *J* = 6.5, 2.1 Hz, 6H); ¹³C NMR (101 MHz, CDCl₃) δ_C 173.43, 169.45, 156.18, 139.03, 124.92, 80.50, 52.49, 50.76, 44.47, 41.65, 28.39, 24.92, 22.94, 21.99. HRMS: *m/z* for C₁₆H₂₈N₂O₅Na (M + Na)⁺, cal. 351.1895, found: 351.1892.

Methyl (Z)-(4-((tert-butoxycarbonyl) amino) but-2-enoyl)-L-valinate (3c)

Oily liquid, yield = 141 mg (90%), R_f = 0.48 (50% EtOAc in hexane); ¹H NMR (400 MHz, CDCl₃) δ_H 6.63 (d, *J* = 8.6 Hz, 1H), 6.01 (dd, *J* = 11.5, 6.1 Hz, 1H), 5.87 (d, *J* = 11.5 Hz, 1H), 5.15 (d, *J* = 19.5 Hz, 1H), 4.55 (ddd, *J* = 8.9, 5.0, 3.6 Hz, 2H), 3.85–3.79 (m, 1H), 3.73 (s, 3H), 2.21–2.15 (m, 1H), 1.46 (s, 9H), 0.94 (s, 3H), 0.89 (d, *J* = 6.9 Hz, 3H); ¹³C NMR (101 MHz, CDCl₃) δ_C 172.41, 172.26, 169.68, 156.27, 136.89, 124.63, 80.56, 57.12, 52.36, 44.59, 31.09, 28.40, 19.05, 17.76. HRMS: *m/z* for C₁₅H₂₆N₂O₅Na (M + Na)⁺, cal. 337.1739, found: 337.1737.

3B.5.6 Solid Phase Peptide Synthesis (SPPS) followed by Cyclization.

The solid phase peptide synthesis of the peptide **1g** was performed manually on 2-Chlorotrityl chloride resin at 0.3 mmol scale using Fmoc chemistry. For the synthesis of peptide **1g** first 2-chlorotrityl chloride resin was pre-swelled in DCM for 30 min and then treated with a mixture of Fmoc-d^{2,3}γGly-OH and DIPEA in DCM for 1 hour. Subsequently, all amino acids with Fmoc-group first dissolved in NMP solvent, then HBTU and DIPEA were added to the reaction mixture. The resultant reaction mixture was transferred to the SPPS synthesizer and coupling was done using the protocol of solid-phase peptide synthesis (SPPS). Each coupling was carried out at room temperature for 45 minutes coupling time. When the peptide synthesis

was completed, the peptide-bound resin was washed with DMF (5 mL x 3), DCM (5 mL x 3) and DMF (5 mL x 3) and dried under vacuum. To release the peptides from the resin, a mixture of HFIP:DCM (3:7, 10 mL) was added to the resin which was stirred for 2 hours at room temperature using a 25 mL round bottom flask. The resin was removed by filtration method and purification was performed before further synthesis. The crude peptide was again dissolved in a small amount (approx. 5 mL) of MeOH and purified using reversed-phase HPLC equipped with a C₁₈ column as a stationary phase. Methanol and water gradient systems at a 2 mL/min flow rate were used to purify the peptide. The mass of the purified peptides **1g** was further confirmed by MALDI-TOF analysis. Peptide **1g** was cyclized into **2g** (62%) using the above-optimized reaction condition mentioned in Scheme 9.

3B.6 Crystallographic Information.

Compound 2b: 10 mg of **2b** was dissolved in 2 mL of distilled methanol solvent in a 5 mL glass vial, to the resultant solution 2-3 drops of distilled water were added. After slow evaporation of aqueous methanol solution at room temperature for 2 to 3 days crystals of **2d** were grown. A plate-shaped single crystal of dimension (0.26 × 0.18 × 0.45 mm) was mounted on a loop of the SC-XRD goniometer. The SC-XRD data measurements were done at low temperature (150K) on a Bruker APEX(II) DUO CCD diffractometer device using Mo K α radiation source ($\lambda = 0.71073 \text{ \AA}$), ω -scans ($2\theta = 56.64$), for a total of 48621 independent reflections. The specific parameters of the crystal are, unit cell Monoclinic, Space group P n, $a = 6.1931 (5)$, $b = 9.5042 (9)$, $c = 25.547 (2)$, $\alpha = 90$, $\beta = 93.877 (3)$, $\gamma = 90$, Volume = 1500.3 (2) $\text{\AA}^3$, formula units $Z = 4$ for chemical formula C₁₉H₁₅NO₃, with two molecules in the asymmetric unit. Density $\rho_{\text{cal.}} = 1.352 \text{ g cm}^{-3}$, $\mu = 0.092 \text{ mm}^{-1}$, $F(000) = 640$, $R_{\text{int}} = 0.1087$. The crystal structure was obtained by using Bruker APEX(III) software and the method used was SHELXS-97. The final R_{factor} was 0.0529 ($wR2 = 0.1151$) 7168 observed reflections ($F0 \geq 4\sigma(|F0|)$) and 415 variables, goodness of fit $S = 1.043$.

3B.7 References

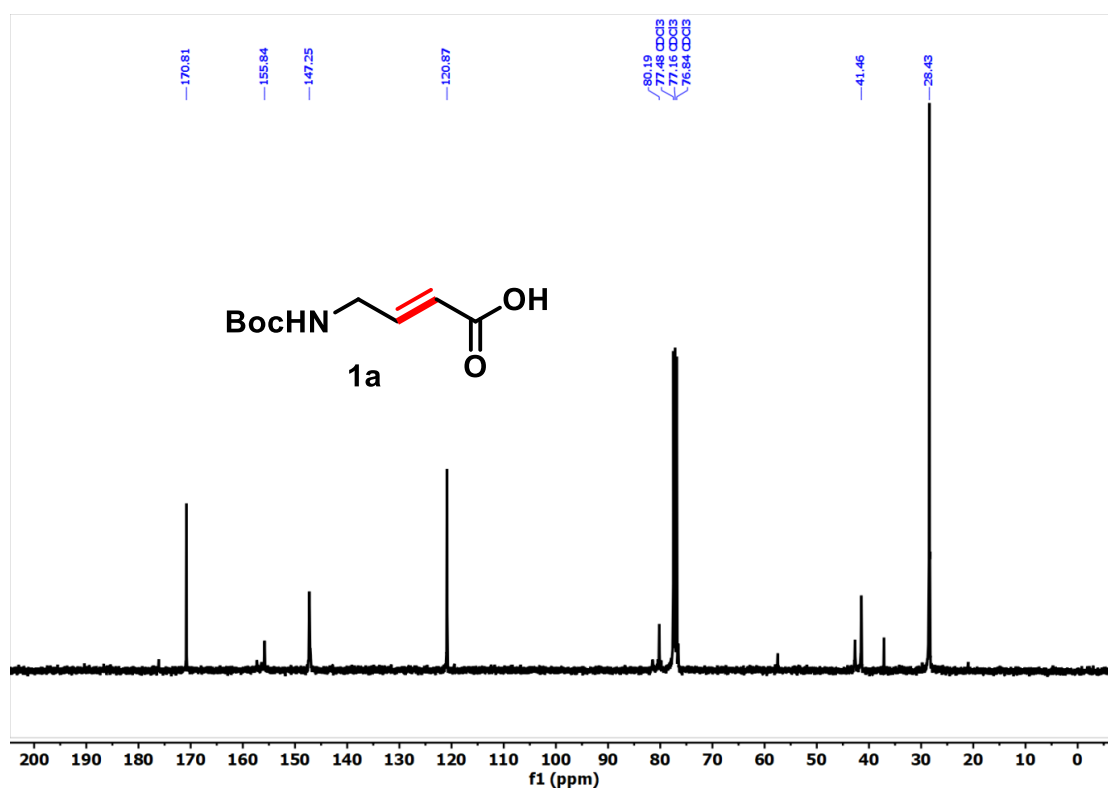
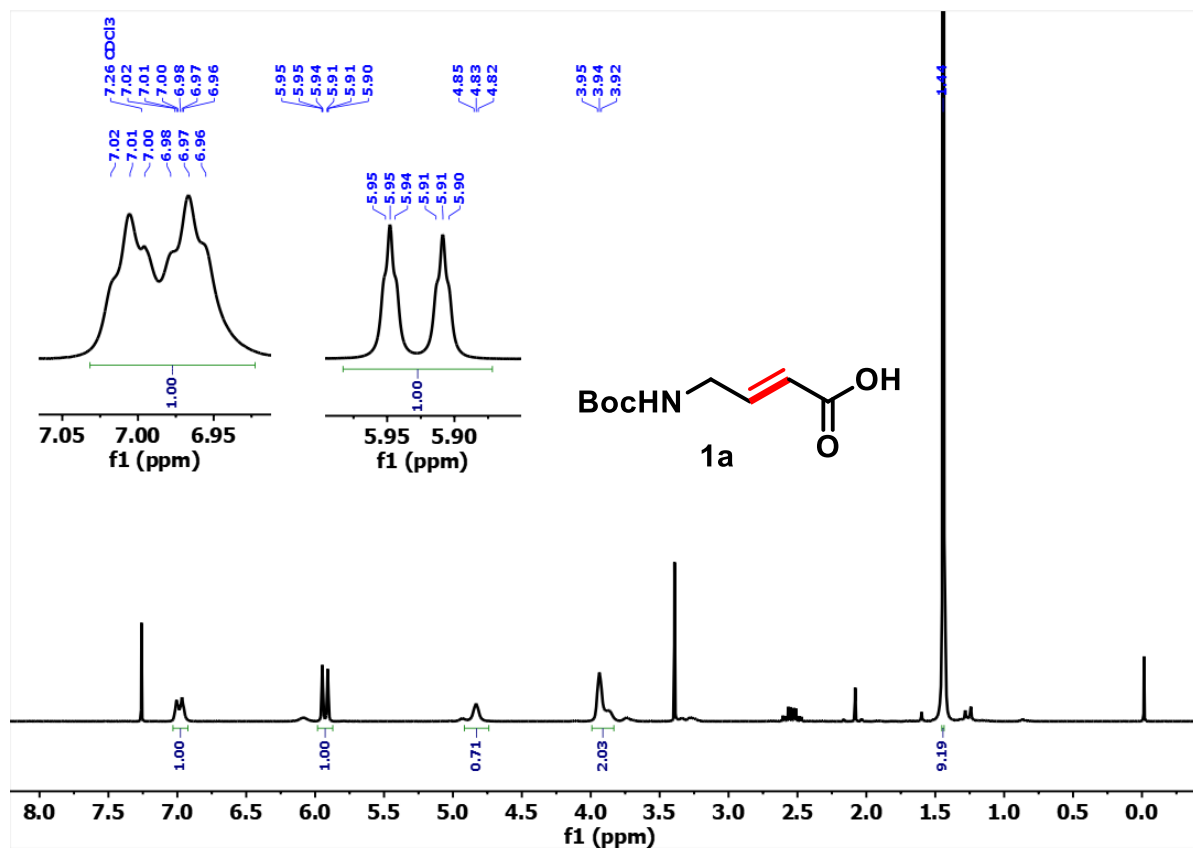
1. C. Curti, L. Battistini, A. Sartori and F. Zanardi, *Chem. Rev.*, 2020, **120**, 2448–2612.
2. (a) N. E. Shepherd, H. Tanabe, Y. Xu, S. Matsunaga and M. Shibasaki, *J. Am. Chem. Soc.* 2010, **132**, 3666–3667; (b) J. Zhang, X. Liu, X. Ma and R. Wang, *Chem. Commun.*, 2013, **49**, 9329–9331; (c) B. M. Trost and J. Hitce, *J. Am. Chem. Soc.*, 2009, **131**, 4572–4573; (d) S. P.-nok, C. Kuhakarn, M. Pohmakotr, V. Reutrakul and D. Soorukram, *Org. Biomol. Chem.*, 2015, **13**, 11087–11095; (e) C. Curti, A. Sartori, L. Battistini, G. Rassu, P. Burreddu, F. Zanardi and G. Casiraghi, *J. Org. Chem.*, 2008, **73**, 5446–5451; (f) C. Curti, L. Battistini, F. Zanardi, G. Rassu, V. Zambrano, L. Pinna and G. Casiraghi, *J. Org. Chem.*, 2010, **75**, 8681–8684; (g) R. P. Singh, B. M. Foxman and L. Deng, *J. Am. Chem. Soc.*, 2010, **132**, 9558–9560; (h) H. Huang, F. Yu, Z. Jin, W. Li, W. Wu, X. Liang and J. Ye, *Chem. Commun.*, 2010, **46**, 5957–5959; (i) S. V. Pansare and E. K. Paul, *Chem. Commun.*, 2011, **47**, 1027–1029; (j) V. Kumar and S. Mukherjee, *Chem. Commun.*, 2013, **49**, 11203–11205; (k) S. Nakamura, R. Yamaji and M. Hayashi, *Chem. – Eur. J.*, 2015, **21**, 9615–9618.
3. (a) A. G. M. Barrett, J. Head, M. L. Smith, N. S. Stock, A. J. P. White and D. J. Williams, *J. Org. Chem.*, 1999, **64**, 6005–6018; (b) A. Gheorghe, M. Schulte and O. Reiser, *J. Org. Chem.*, 2006, **71**, 2173–2176; (c) O. Ahmed, P. B. Hitchcock and D. W. Young, *Org. Biomol. Chem.*, 2006, **4**, 1596–1603; (d) J. F. Bower, S. Chakthong, J. Svende, A. J. Williams, R. M. Lawrence, P. Szeto and T. Gallagher, *Org. Biomol. Chem.*, 2006, **4**, 1868–1877.
4. (a) N. Langlois, N. Van Bac, N. Dahuron, J.-M. Delcroix, A. Deyine, D. Griffart-Brunet, A. Chiaroni and C. Riche, *Tetrahedron*, 1995, **51**, 3571–3586; (b) P. J. Dransfield, S. Wang, A. Dilley and D. Romo, *Org. Lett.*, 2005, **7**, 1679–1682.
5. (a) Y. Ma, G. Zhang, J. Zhang, D. Yang, and R. Wang, *Org. Lett.* 2014, **16**, 5358–5361; (b) X.-X. Wu, Y. He, X.-X. Qiao, T. Ma, C.-P. Zou, G. Li, and X.-J. Zhao, *J. Org. Chem.*, 2023, **88**, 6599–6610.
6. (a) D. Mostowicz, M. Dygas and Z. Kaluza, *J. Org. Chem.*, 2015, **80**, 1957–1963; (b) J. Bosch, T. Roca, J.-L. Catena, O. Llorens, J.-J. Pérez, C. Lagunas, A. G. Fernandez, I. Miquel, A. Fernandez-Serrat and C. Farrerons, *Bioorg. Med. Chem. Lett.*, 2000, **10**, 1745–1748; (c) S. S. Zimmerman, A. Khatri, E. C. Garnier-Amblard, P. Mullasseril, N. L. Kurtkaya, S. Gyoneva, K. B. Hansen, S. F. Traynelis and D. C. Liotta, *J. Med. Chem.*, 2014, **57**, 2334–2356; (d) R. Dayam, T. Sanchez, and N. Neamati, *J. Med. Chem.*, 2005, **48**, 8009–

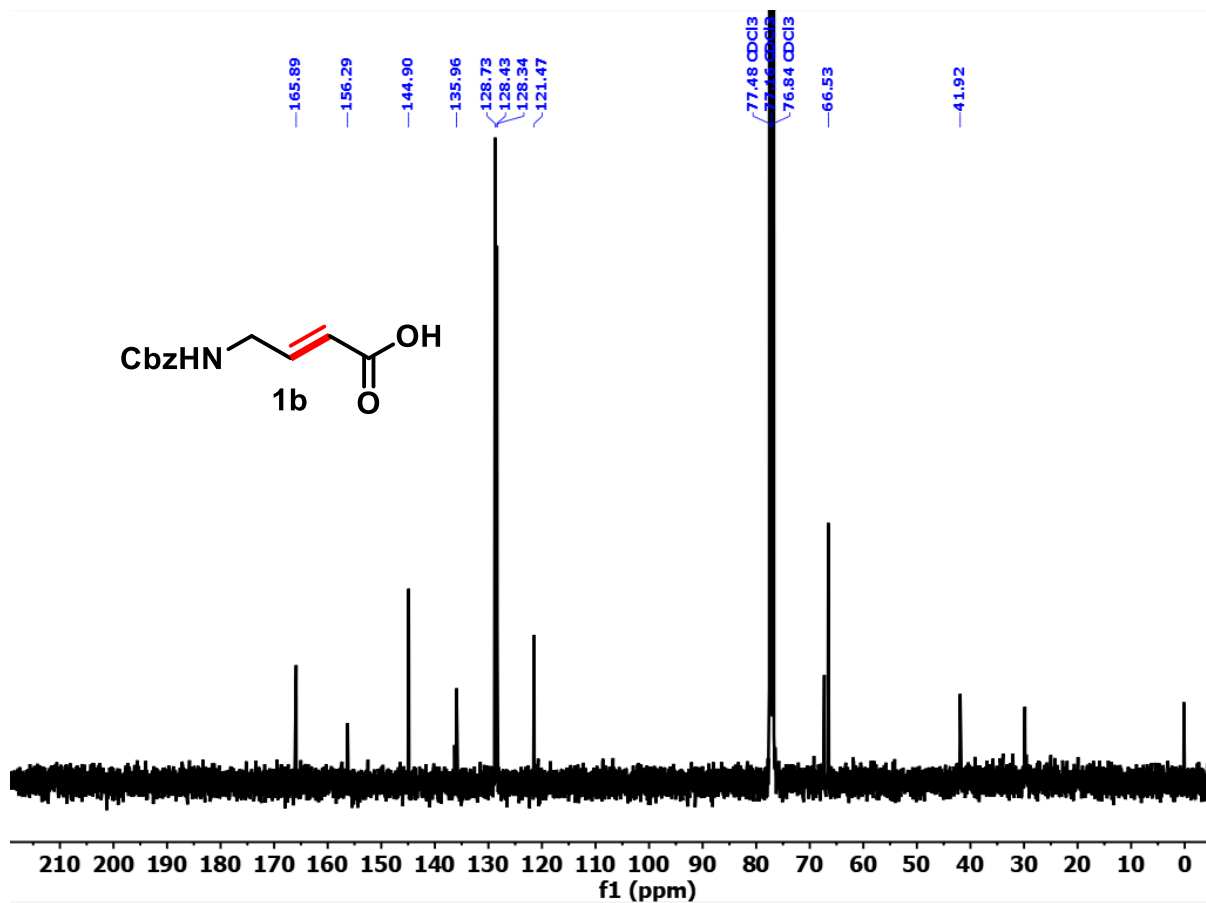
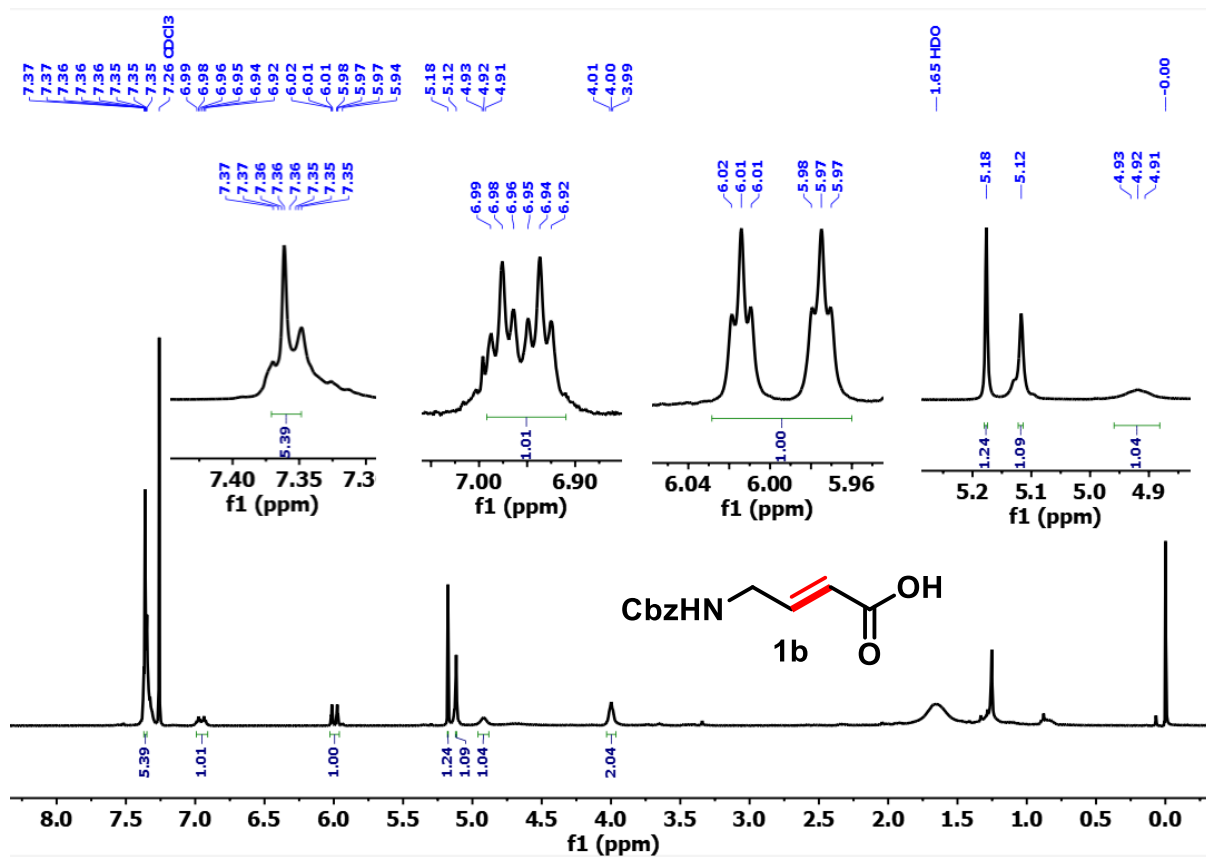
- 8015; (e) R. Dayam, L. Q. Al-Mawsawi and N. Neamati, *Bioorg. Med. Chem. Lett.*, 2007, **17**, 6155-6159.
7. S. Sarkar, A. Banerjee, J. A. Shah, U. Mukherjee, N. C. Frederiks, C. J. Johnson and M.-Y. Ngai, *J. Am. Chem. Soc.* 2022, **144**, 20884–20894.
 8. Z. Feng, F. Chu, Z. Guo and P. Sun, *Bioorg. Med. Chem. Lett.*, 2009, **19**, 2270-.2272.
 9. U. A. Pereira, L. C. A. Barbosa, C. R. A. Maltha, A. J. Demuner, M. A. Masood, and A. L. Pimenta, *Bioorg. Med. Chem. Lett.*, 2014, **24**, 1052-1056.
 10. (a) E. Choi, C. Lee, M. Cho, J. J. Seo, J. S. Yang, S. J. Oh, K. Lee, S.-K. Park, H. M. Kim, H. J. Kwon and G. Han, *J. Med. Chem.*, 2012, **55**, 10766-10770; (b) C. Peifer, R. Selig, K. Kinkel, D. Ott, F. Totzke, C. Schachtele, R. Heidenreich, M. Rocken, D. Schollmeyer and S. Laufer, *J. Med. Chem.*, 2008, **51**, 3814-3824.
 11. (a) G. Casiraghi, P. Spanu, G. Rassu, L. Pinna and F. Ulgheri, *J. Org. Chem.*, 1994, **59**, 2906-2909; (b) A. D. Cuiper, M. Brzostowska, J. K. Gawronski, W. J. J. Smeets, A. L. Spek, H. Hiemstra, R. M. Kellogg and B. L. Feringa, *J. Org. Chem.*, 1999, **64**, 2567-2570; (c) M. G. B. Drew, R. J. Harrison, J. Mann, A. J. Tench and R. J. Young, *Tetrahedron*, 1999, **55**, 1163-1172; (d) S. Roy and C. Spino, *Org. Lett.*, 2006, **8**, 939-942; (e) S. Spiess, C. Berthold, R. Weihofen and G. Helmchen, *Org. Biomol. Chem.*, 2007, **5**, 2357-2360; (f) M. Daly, K. Gill, M. Sime, G. L. Simpson and A. Sutherland, *Org. Biomol. Chem.*, 2011, **9**, 6761-6770; (g) Y. Hoshimoto, T. Ohata, Y. Sasaoka, M. Ohashi and S. Ogoshi, *J. Am. Chem. Soc.*, 2014, **136**, 15877-15880; (h) G. B. Bajracharya, P. S. Koranne, R. N. Nadaf, R. K. M. Gabr, K. Takenaka, S. Takizawa and H. Sasai, *Chem. Commun.*, 2010, **46**, 9064-9066; (i) X. Jusseau, L. Chabaud and C. Guillou, *Tetrahedron*, 2014, **70**, 2595-2615.
 12. (a) L. Yang, C.-H. Lei, D.-X. Wang, Z.-T. Huang, M.-X. Wang, *Org. Lett.* 2010, **12**, 3918–3921; (b) J. Xie, S. Xue, E. C. Escudero-Adan, A. W. Kleij, *Angew. Chem., Int. Ed.*, 2018, **57**, 16727–16731.
 13. E. J. E. Caro-Diaz, F. A. Valeriote and W. H. Gerwick, *Org. Lett.* 2019, **21**, 793–796.
 14. M. Singh, M. Kumar, S. A. Nalawade, D. R. Puneeth Kumar and H. N. Gopi, *Org. Biomol. Chem.*, 2023, **21**, 3766-3769.
 15. M. Singh, S. A. Nalawade, D. R. Puneeth Kumar, K. Veeresh, S. Pahan, S. Dey and H. N. Gopi, *Eur. J. Org. Chem.* 2023, **26**, e202300682.
 16. C. Baldauf, R. Gunther, and H.-J. Hofman, *J. Org. Chem.* 2005, **70**, 5351–5361.
 17. R. Misra, S. Dey, R. M. Reja and H. N. Gopi, *Angew. Chem., Int. Ed.*, 2018, **57**, 1057–1061.
 18. K. Veeresh, M. Singh and H. N. Gopi, *Org. Biomol. Chem.*, 2019, **17**, 9226-9231.

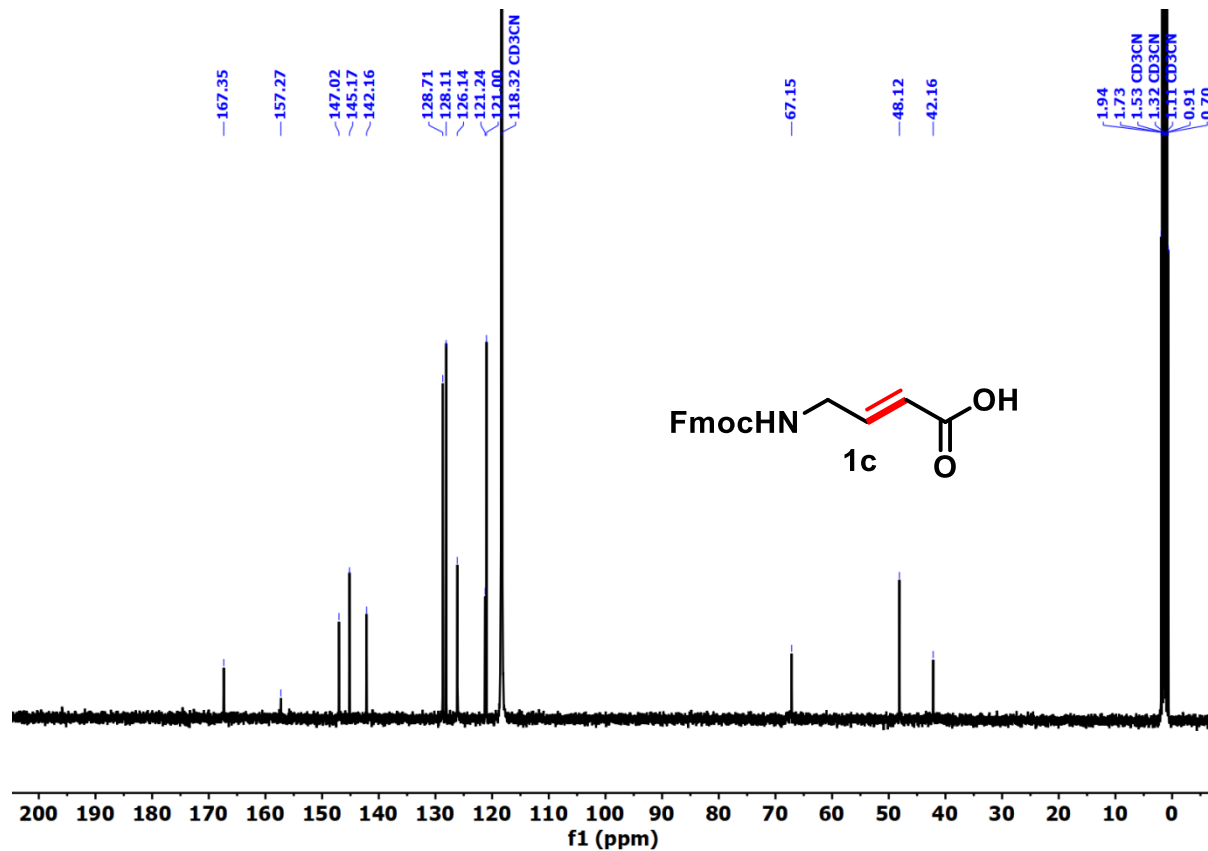
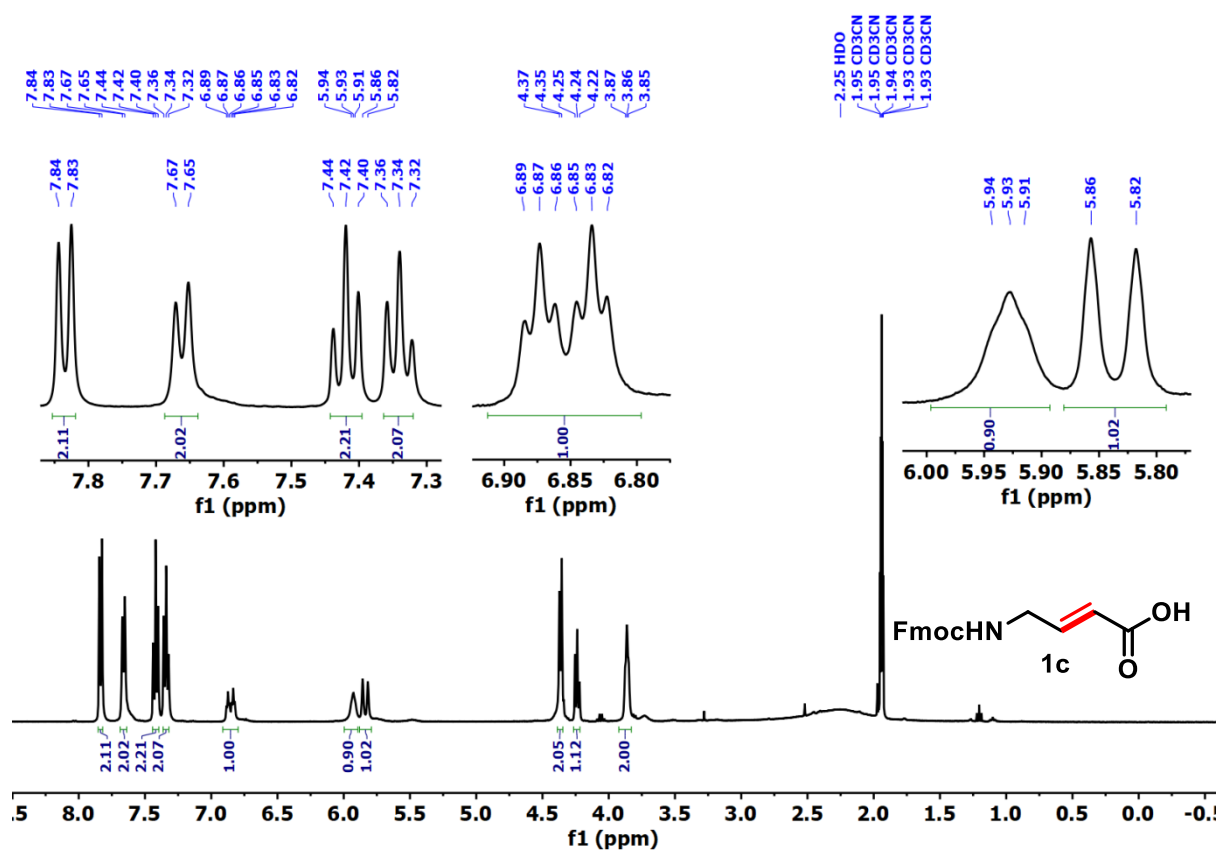
19. L. A. Carpino, H. Imazumi, A. El-Faham, F. J. Ferrer, C. Zhang, Y. Lee, B. M. Foxman, P. Henklein, C. Hanay, C. Mugge, H. Wenschuh, J. Klose, M. Beyermann and M. Bienert, *Angew. Chemie. Int. Ed.* 2002, **41**, 441–445.
20. L. A. Carpino, *J. Am. Chem. Soc.*, 1993, **115**, 4397–4398.
21. R. Knorr, A. Trzeciak, W. Bannworth and D. Gillessen, *Tetrahedron Lett.*, 1989, **30**, 1927-1930.
22. S. M. Mali, A. Bandyopadhyay, S. V. Jadhav, M. G. Kumar and H. N. Gopi, *Org. Biomol. Chem.*, 2011, **9**, 6566-6574.
23. M. Bodanszky and A. Bodanszky, *The Practice of Peptide Synthesis*; Springer-Verlag: New York, 1984, pp 1–282.
24. S. A. Khan and B. W. Erickson, *J. Am. Chem. Soc.* 1984, **106**, 798-799.
25. (a) Z.-B. Ye, J. Chen, W.-H. Meng, P.-Q. Huang, *Tetrahedron: Asymmetry*, **2010**, 21, 895-902; (b) F. E. Koehn, R. E. Longley and J. K. Reed, *J. Nat. Prod.*, 1992, **55**, 613–619; (c) H.-Q. Lan, J.-L. Ye, A.-E. Wang, Y.-P. Ruan and P.-Q. Huang, *Chem. Eur. J.*, 2011, **17**, 958 – 968.
26. (a) R. B. Merrifield, *J. Am. Chem. Soc.*, 1963, **85**, 2149-2154; (b) R. B. Merrifield, *Science*, 1986, **232**, 341-347.
27. (a) J. B. Metternich and R. Gilmour, *J. Am. Chem. Soc.*, 2015, **137**, 11254–11257; (b) C. Dugave and L. Demange, *Chem. Rev.*, 2003, **103**, 2475–2532.

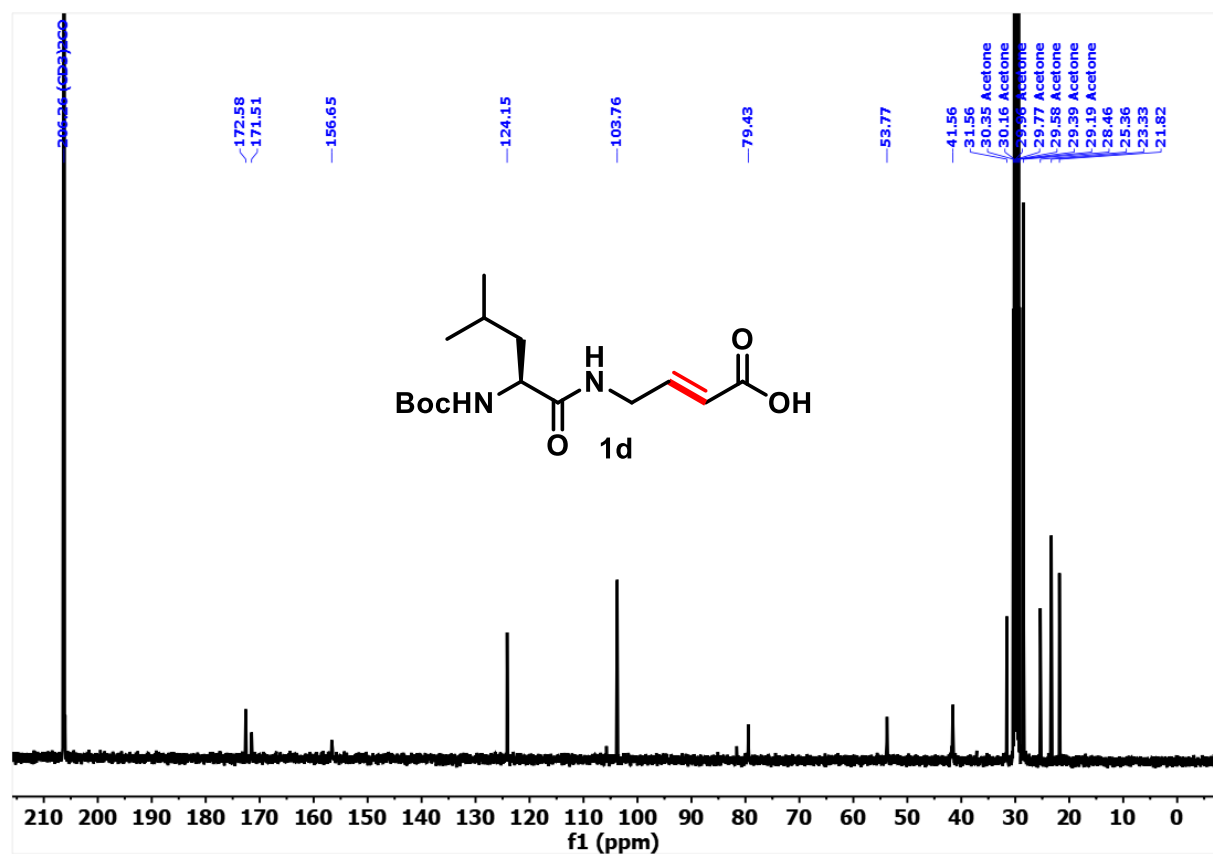
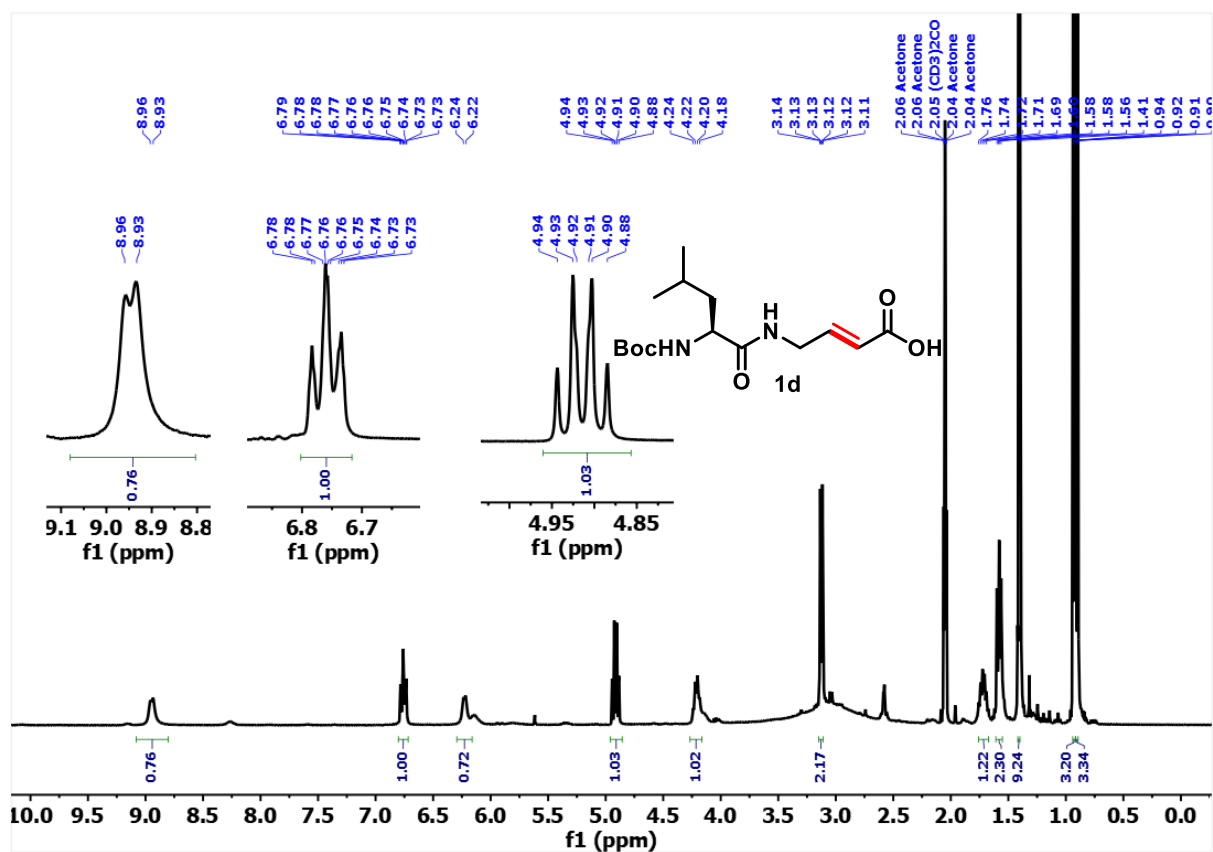
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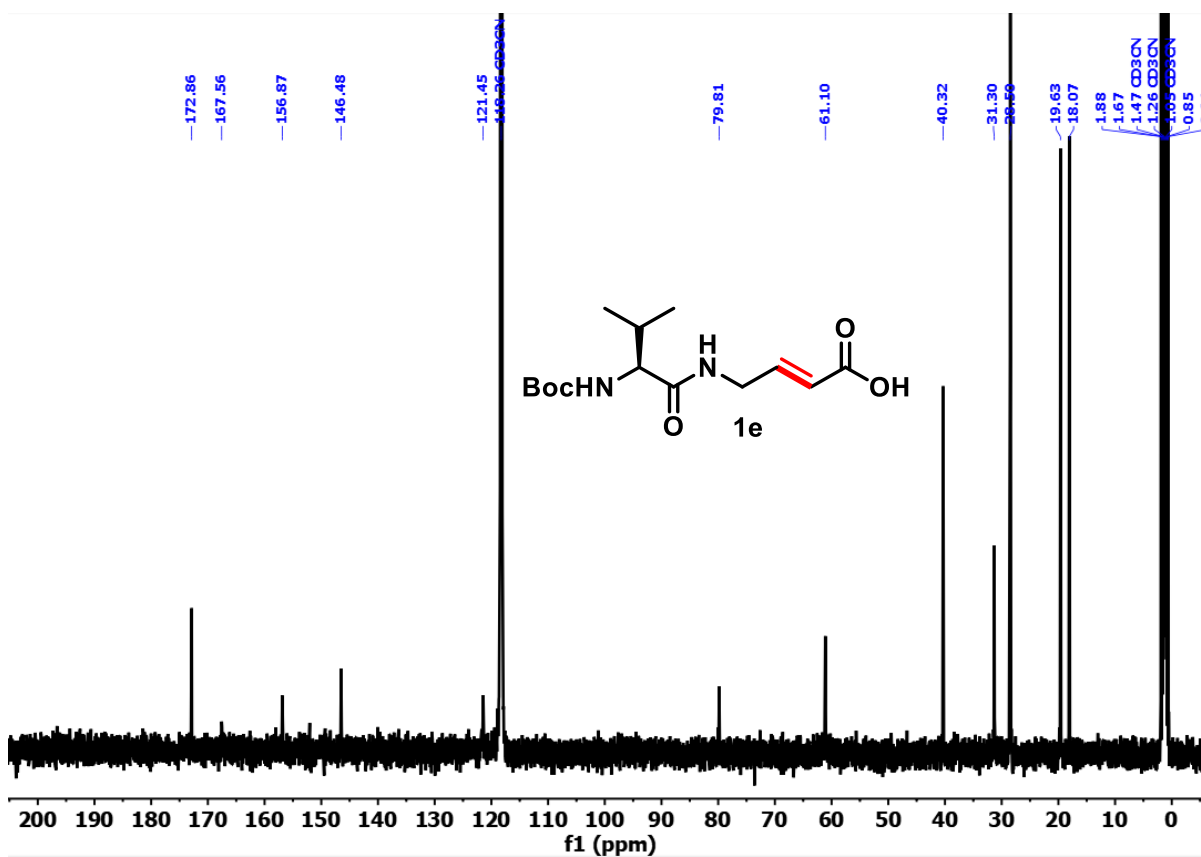
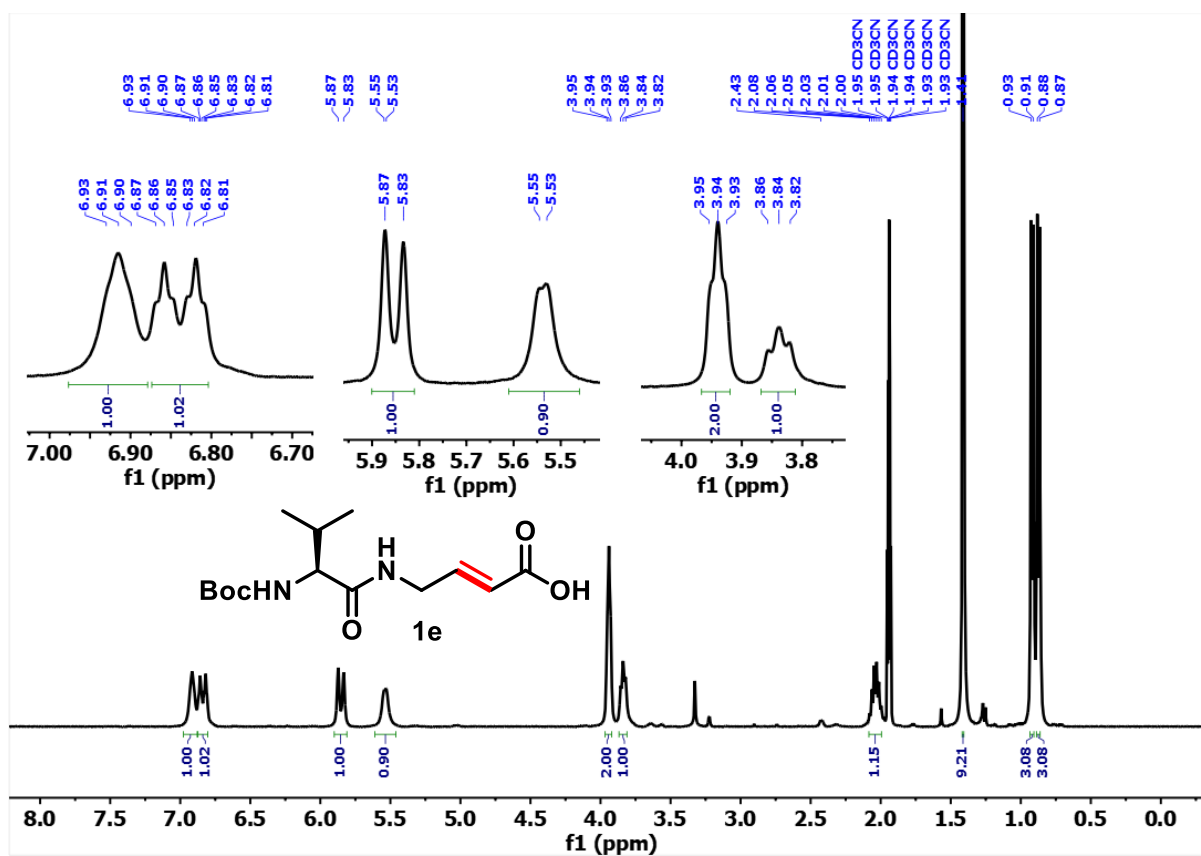
3B.8.1. ^1H and ^{13}C NMR of all compounds.

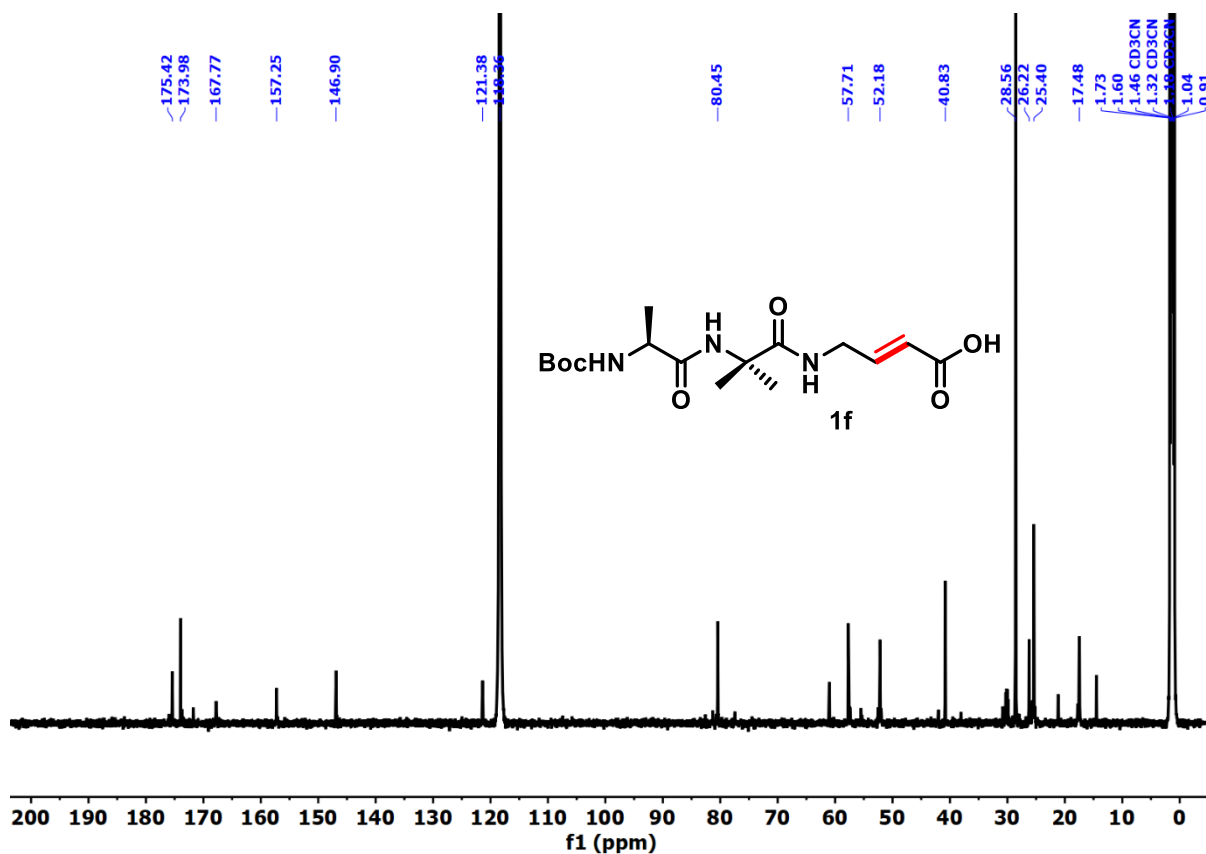
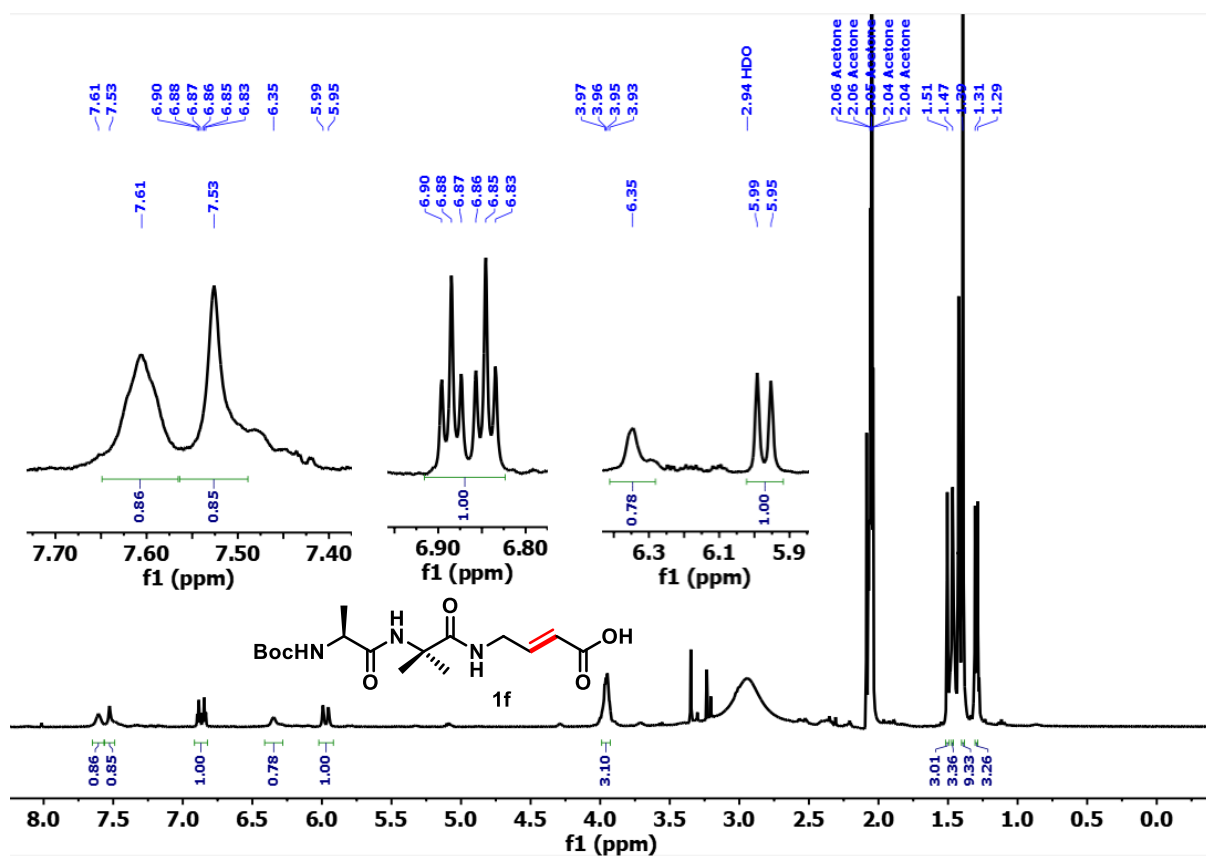




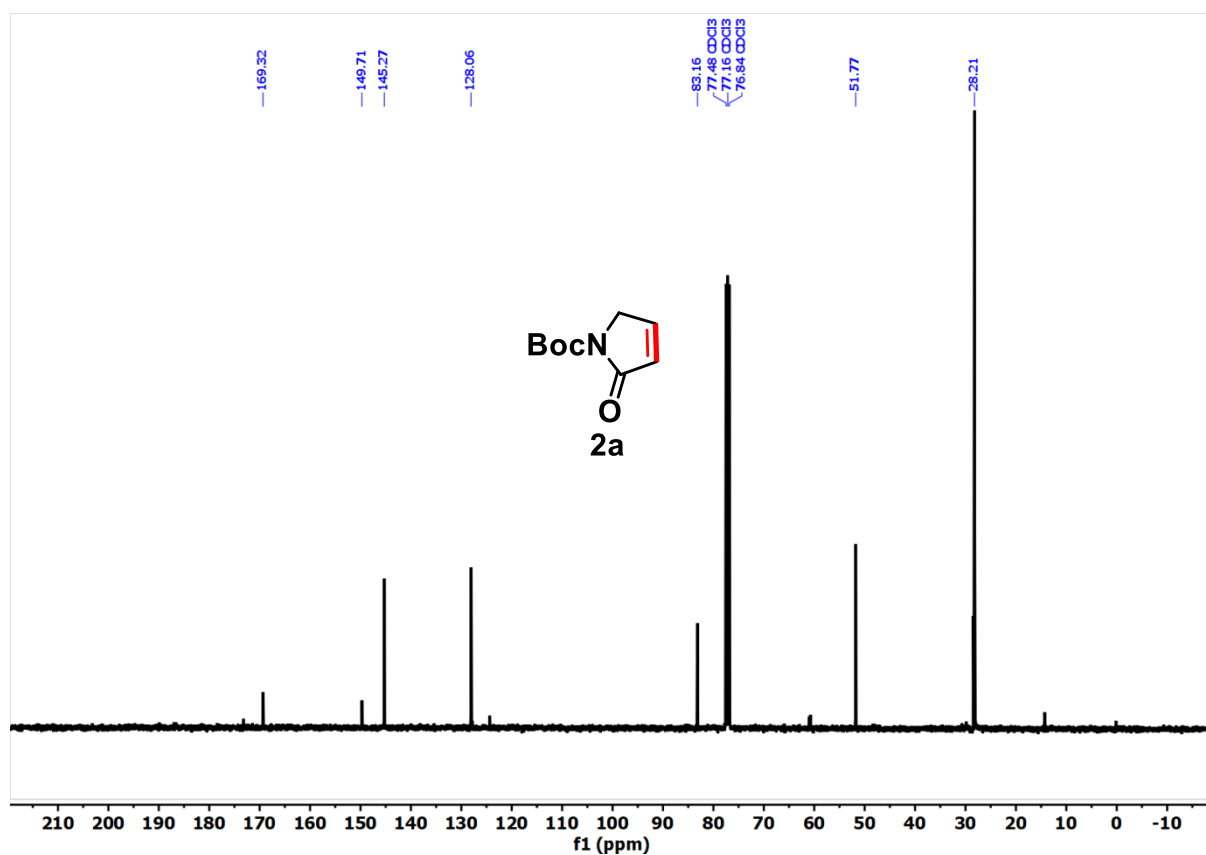
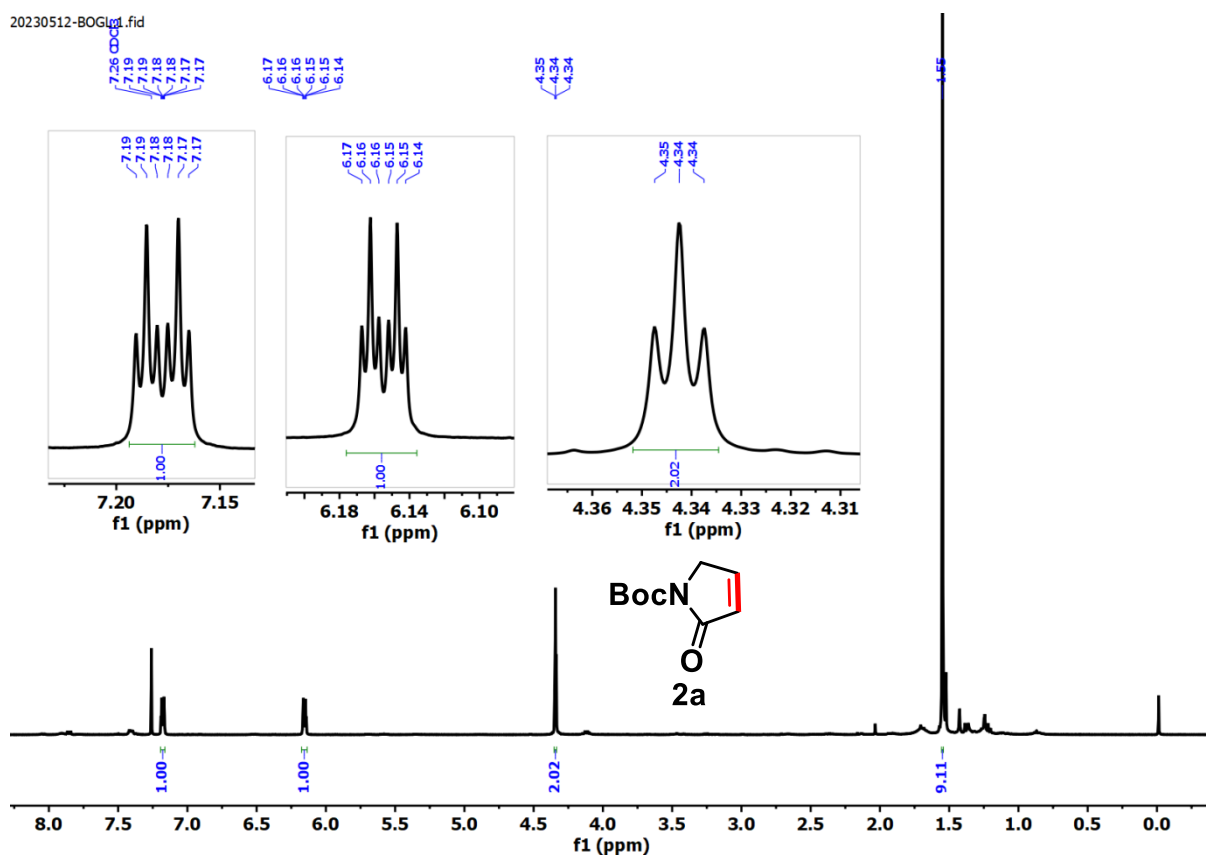




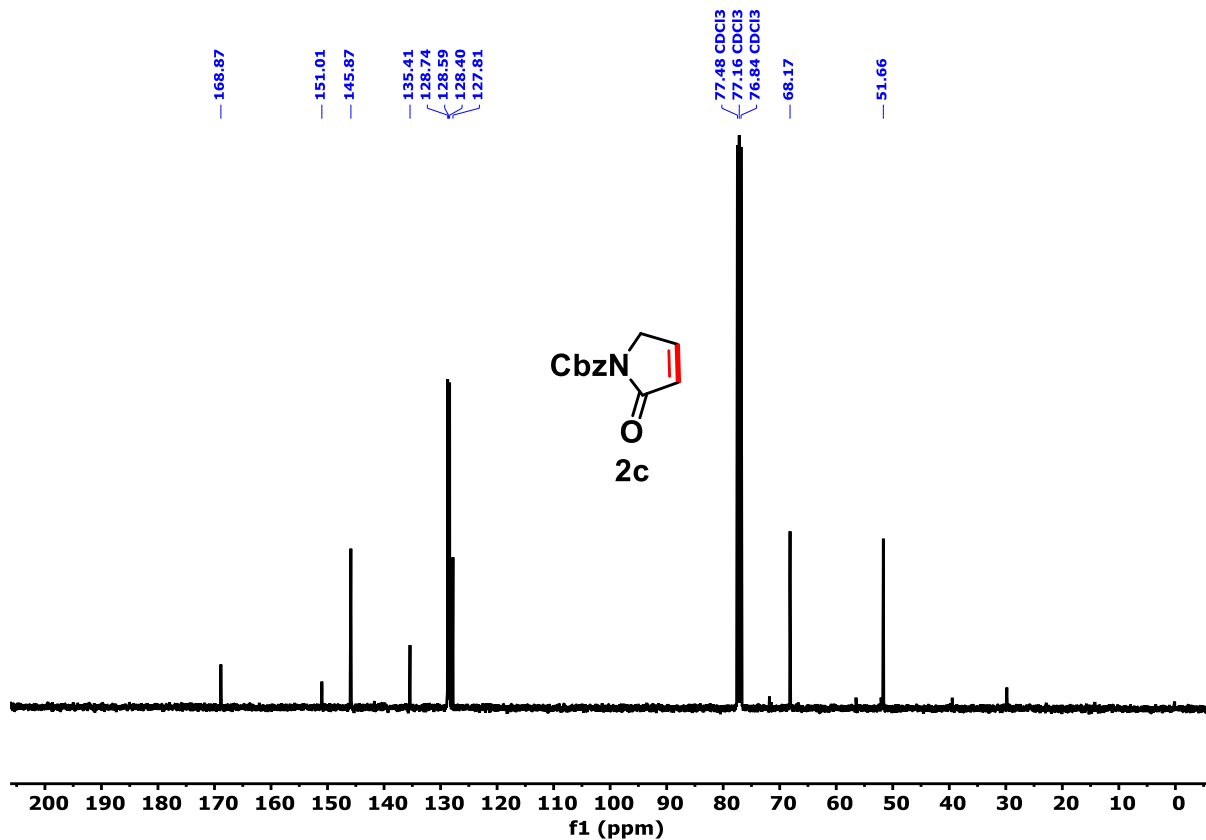
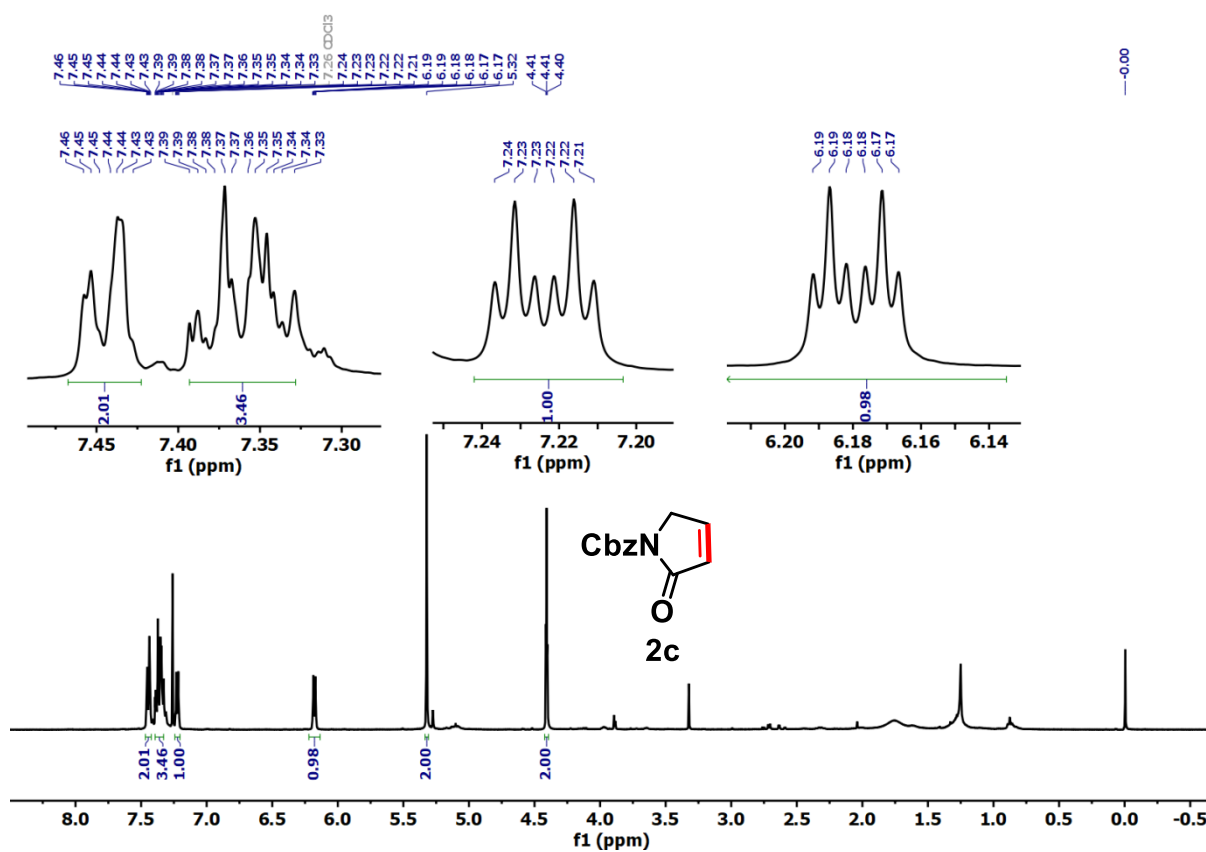


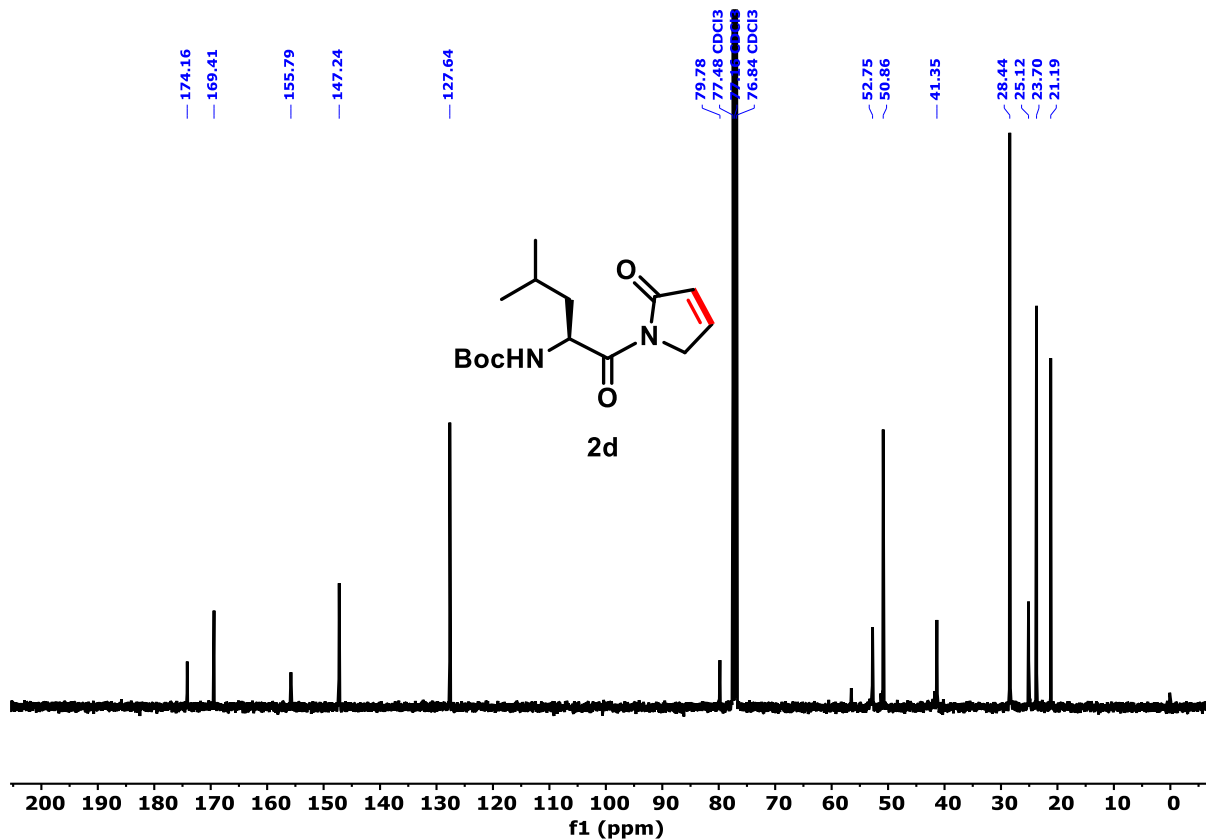
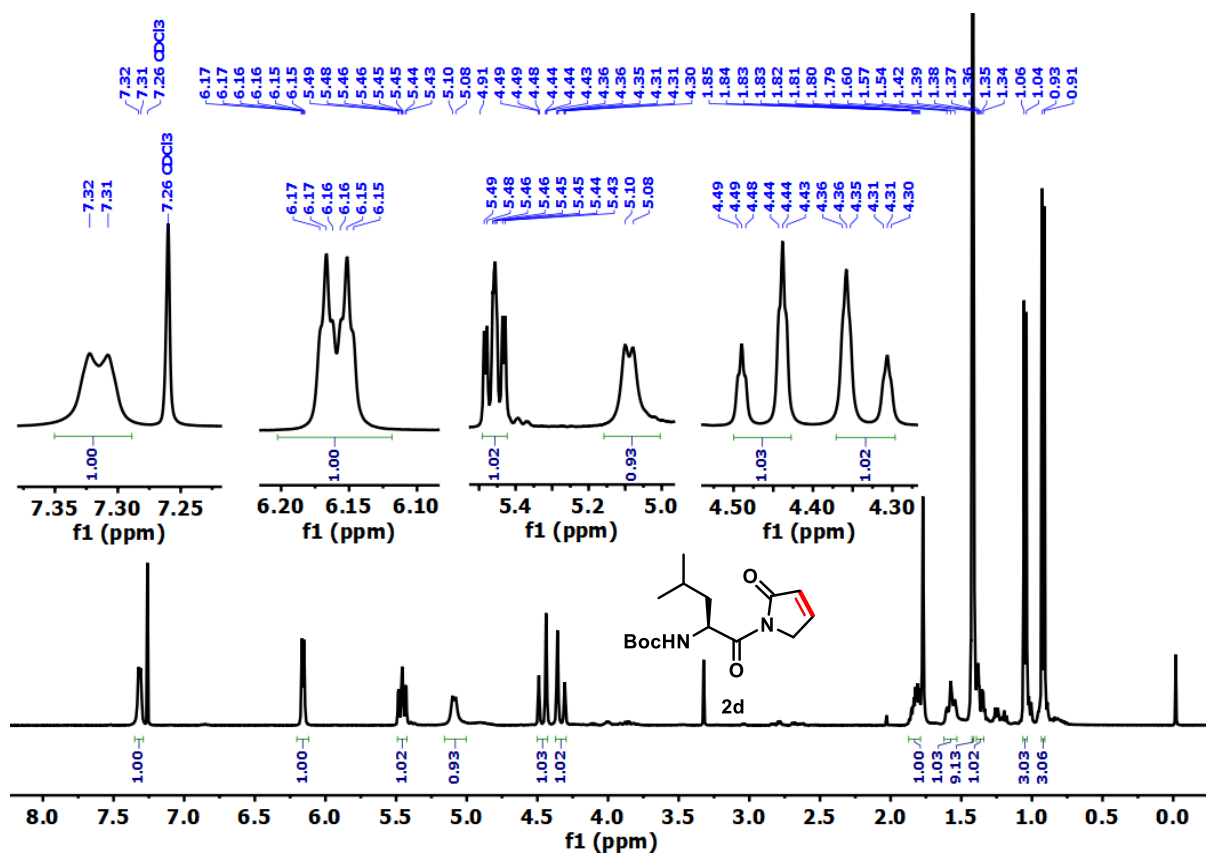


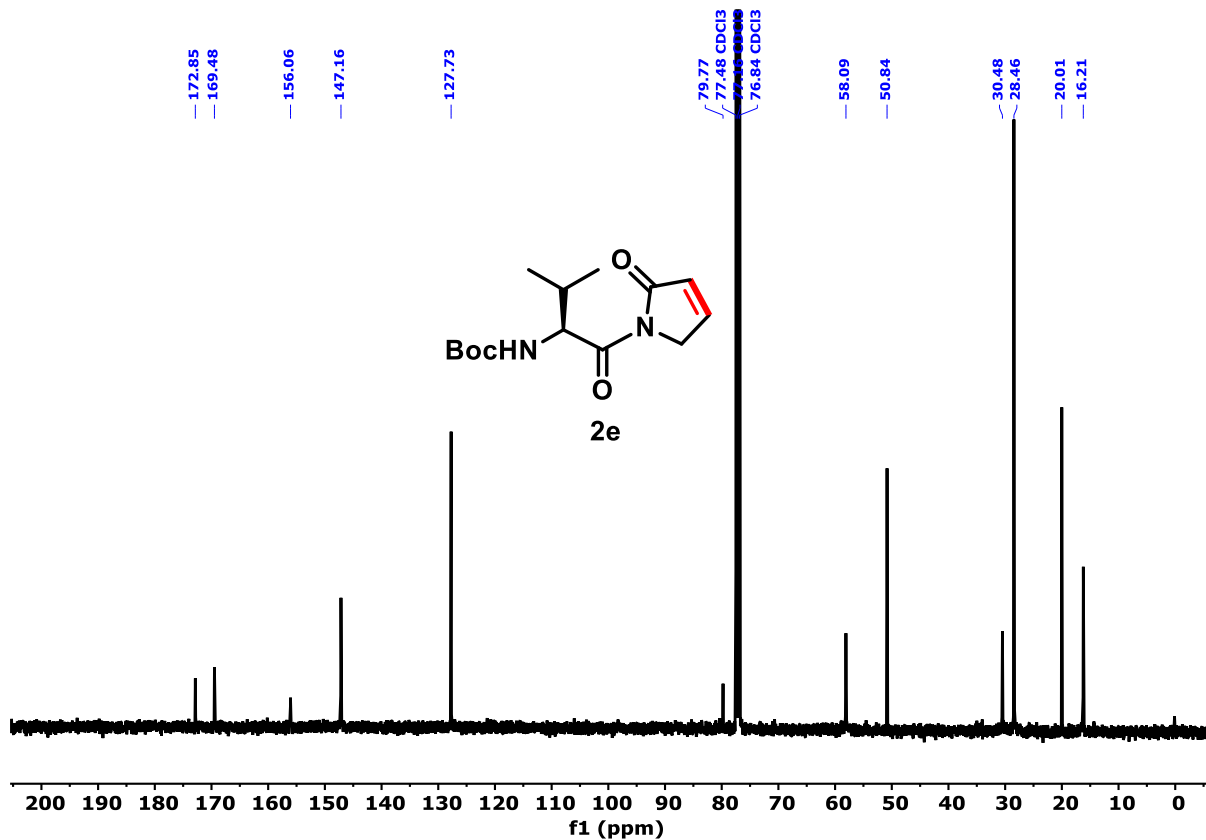
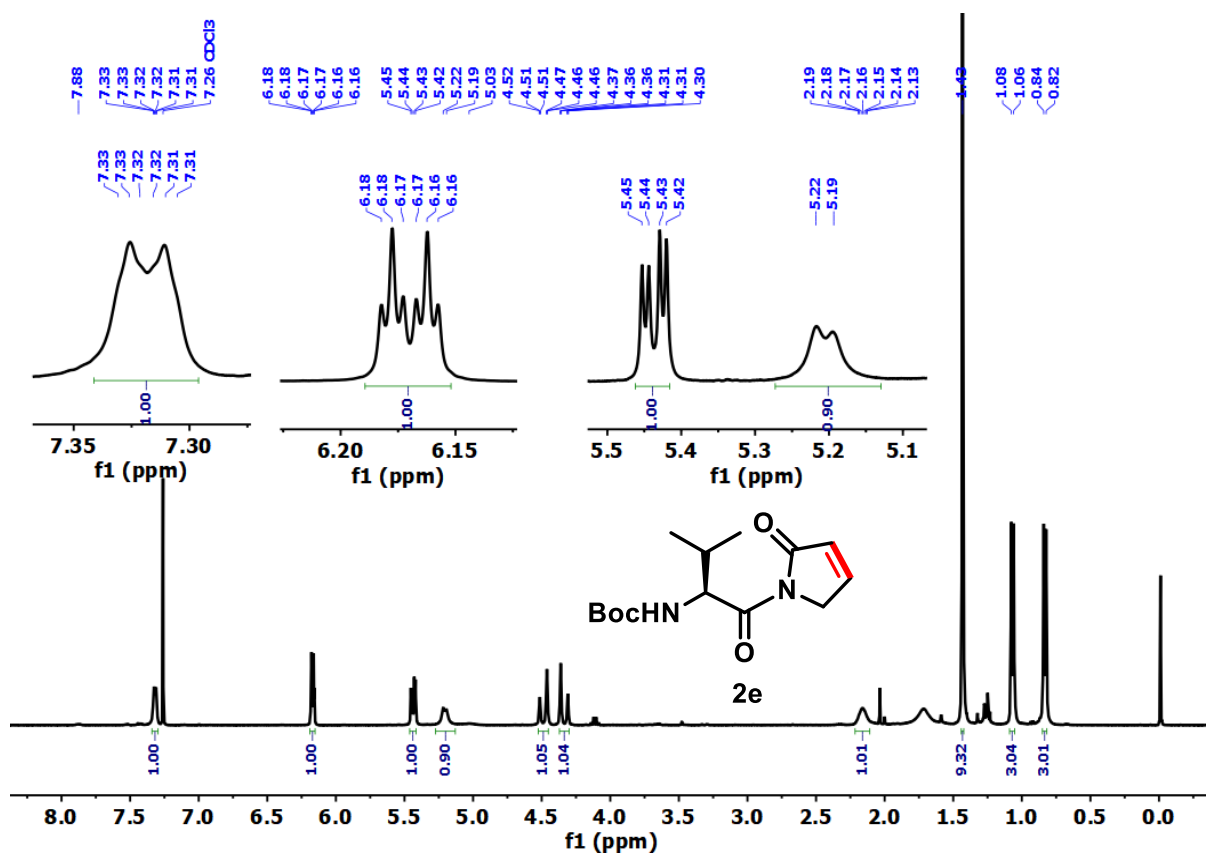
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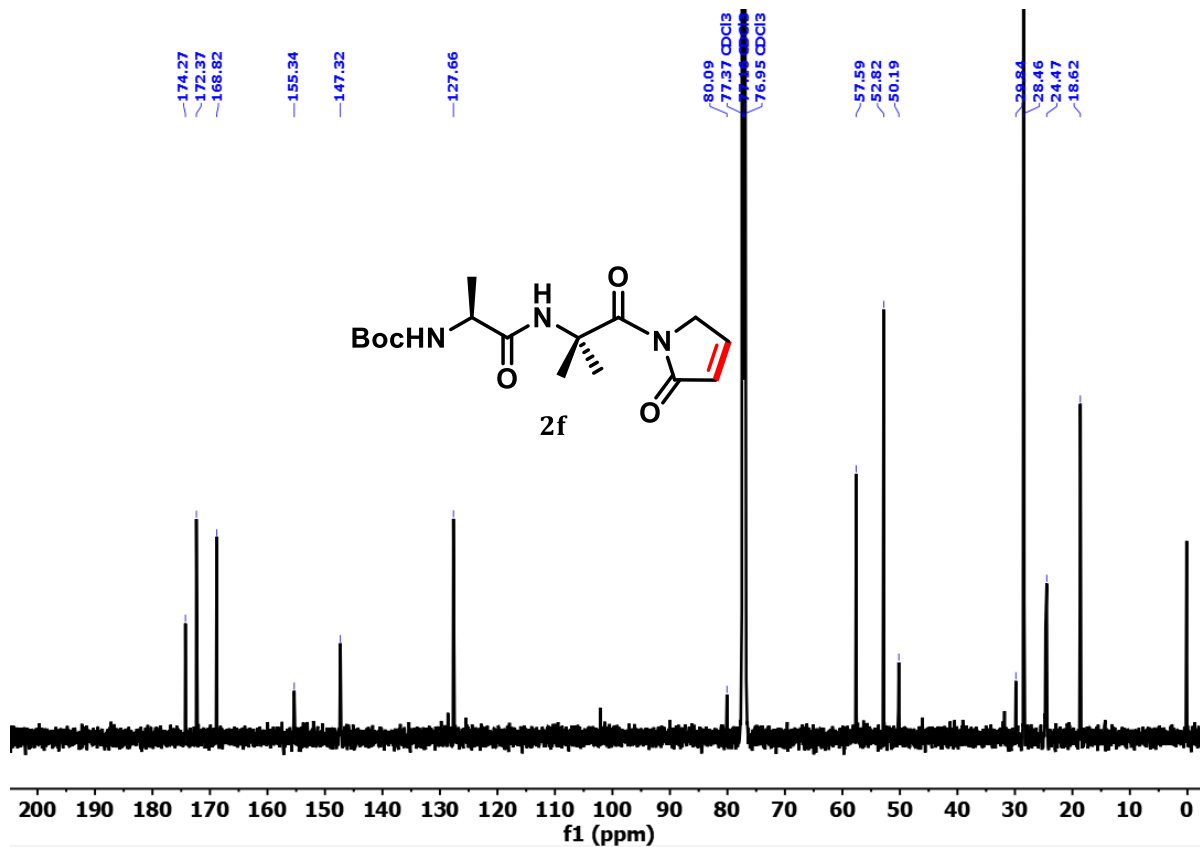
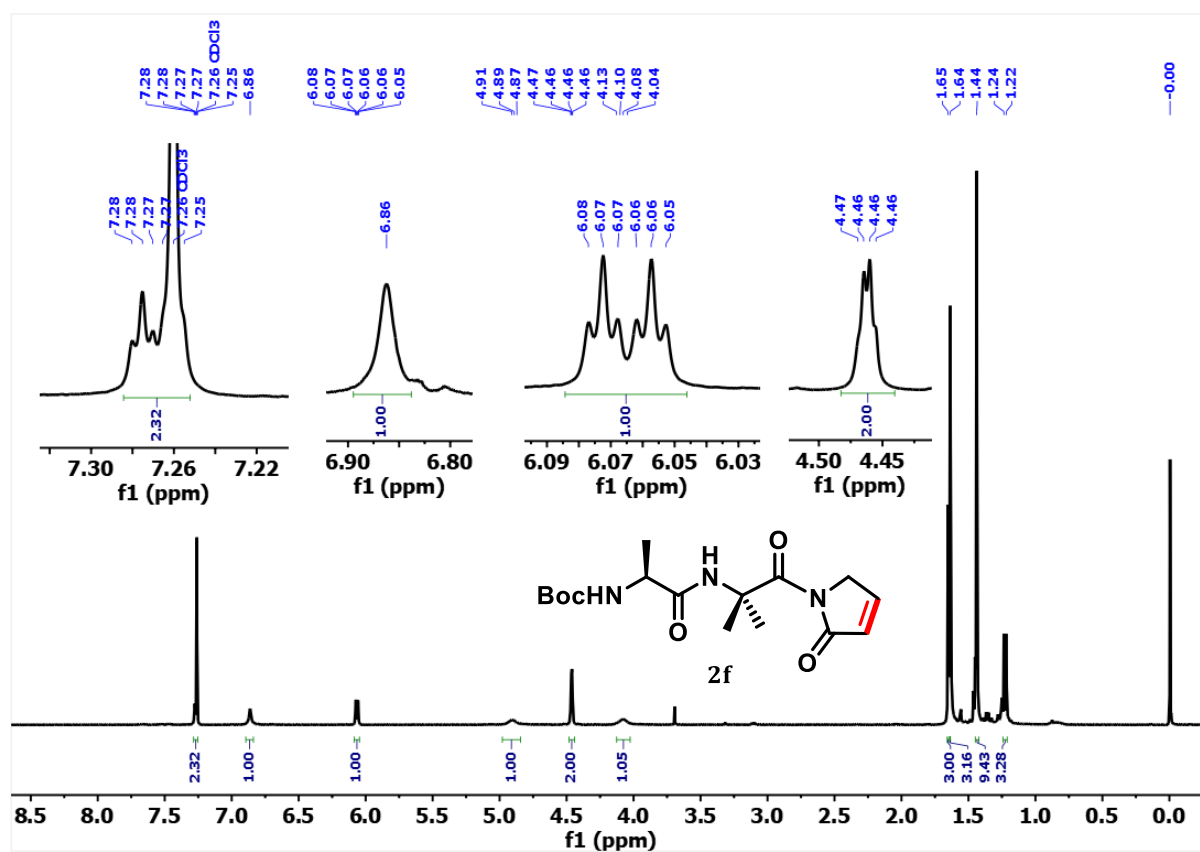


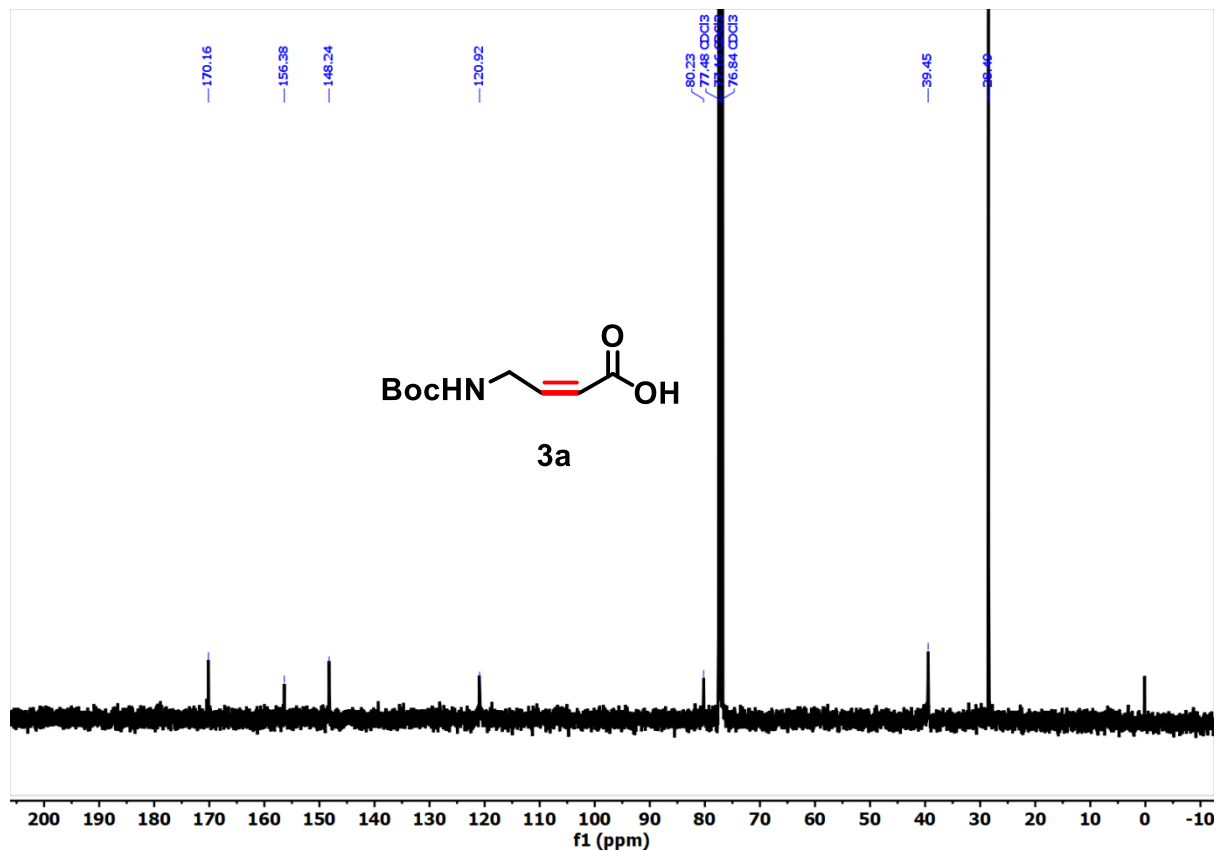
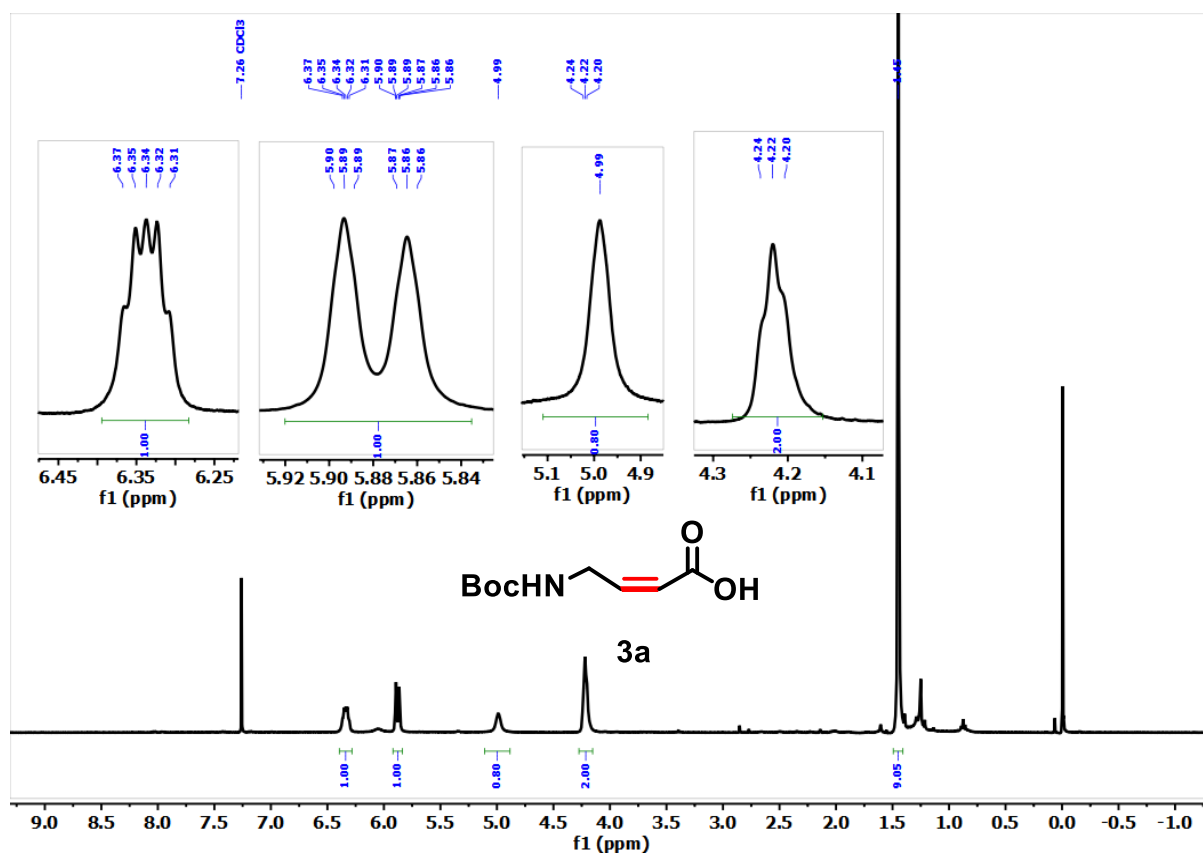


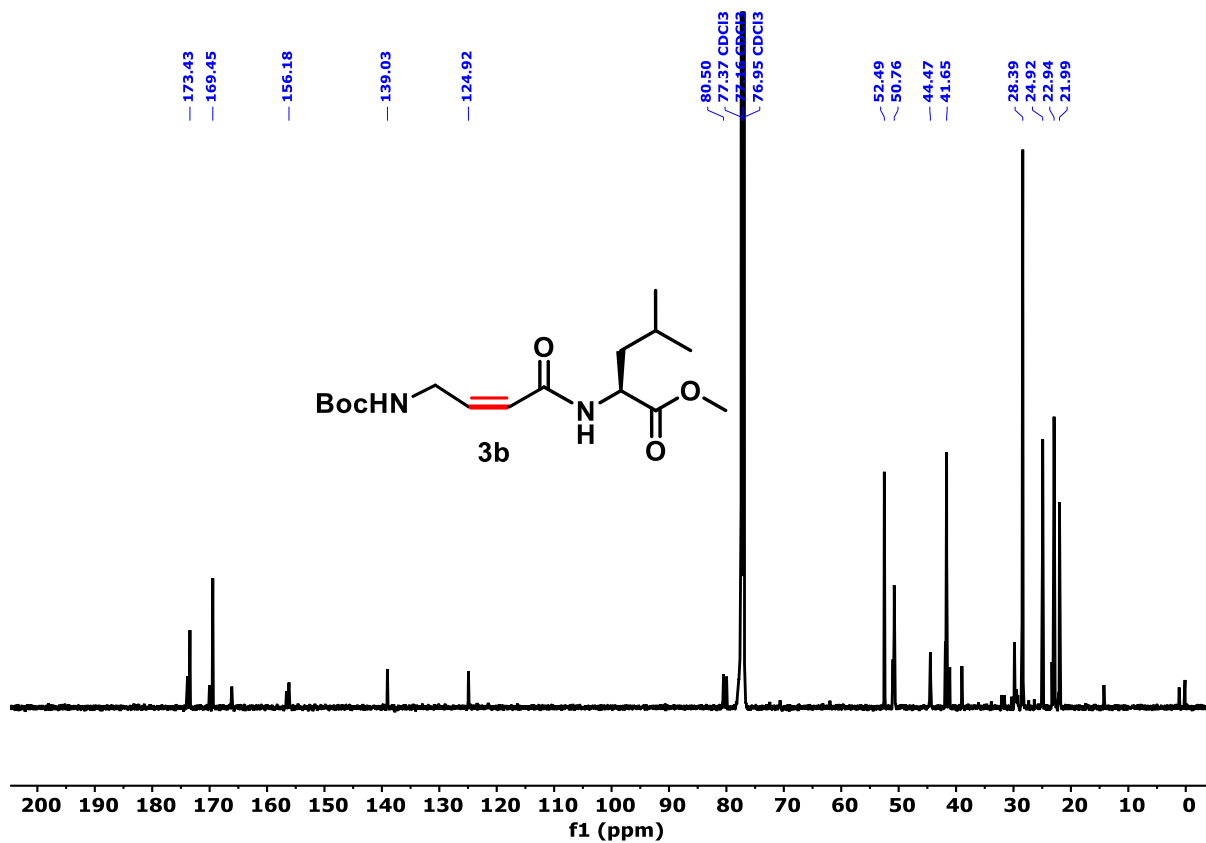
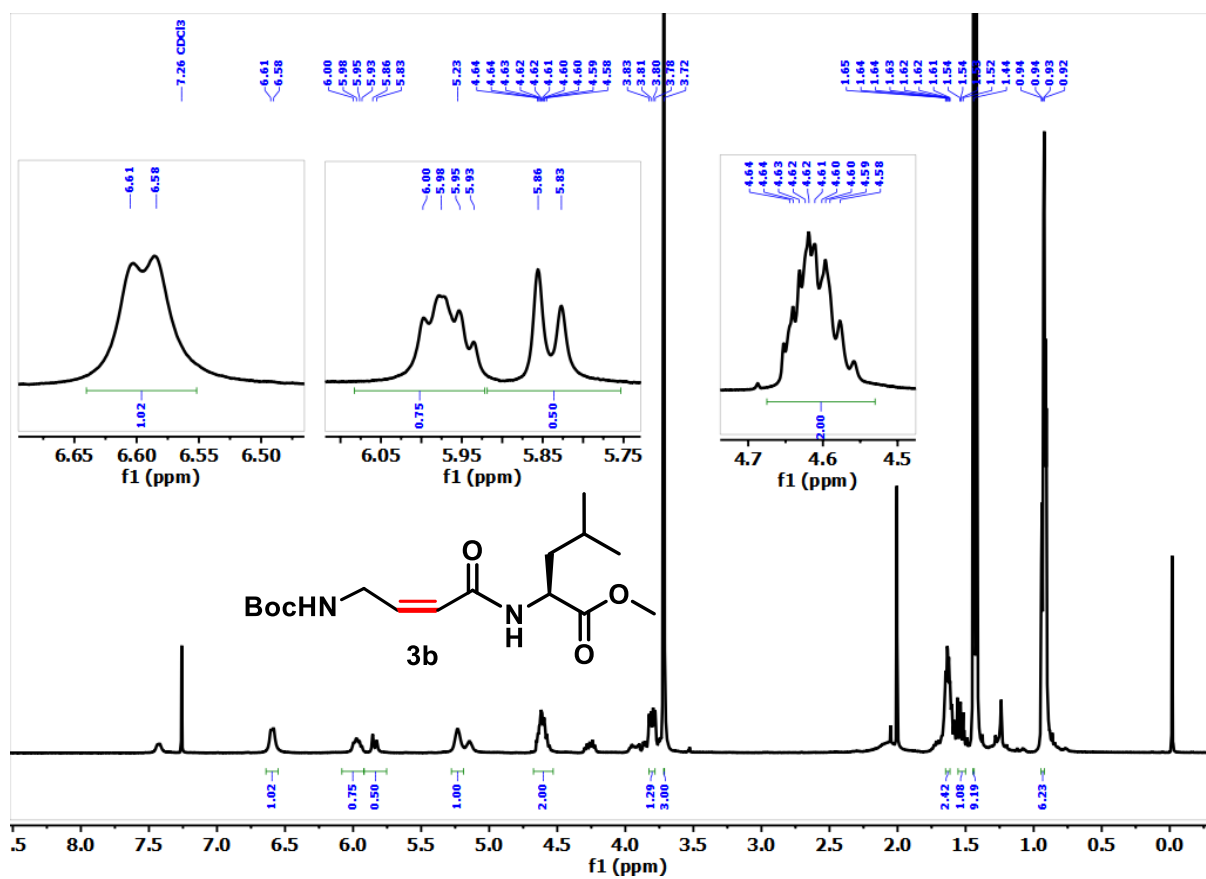


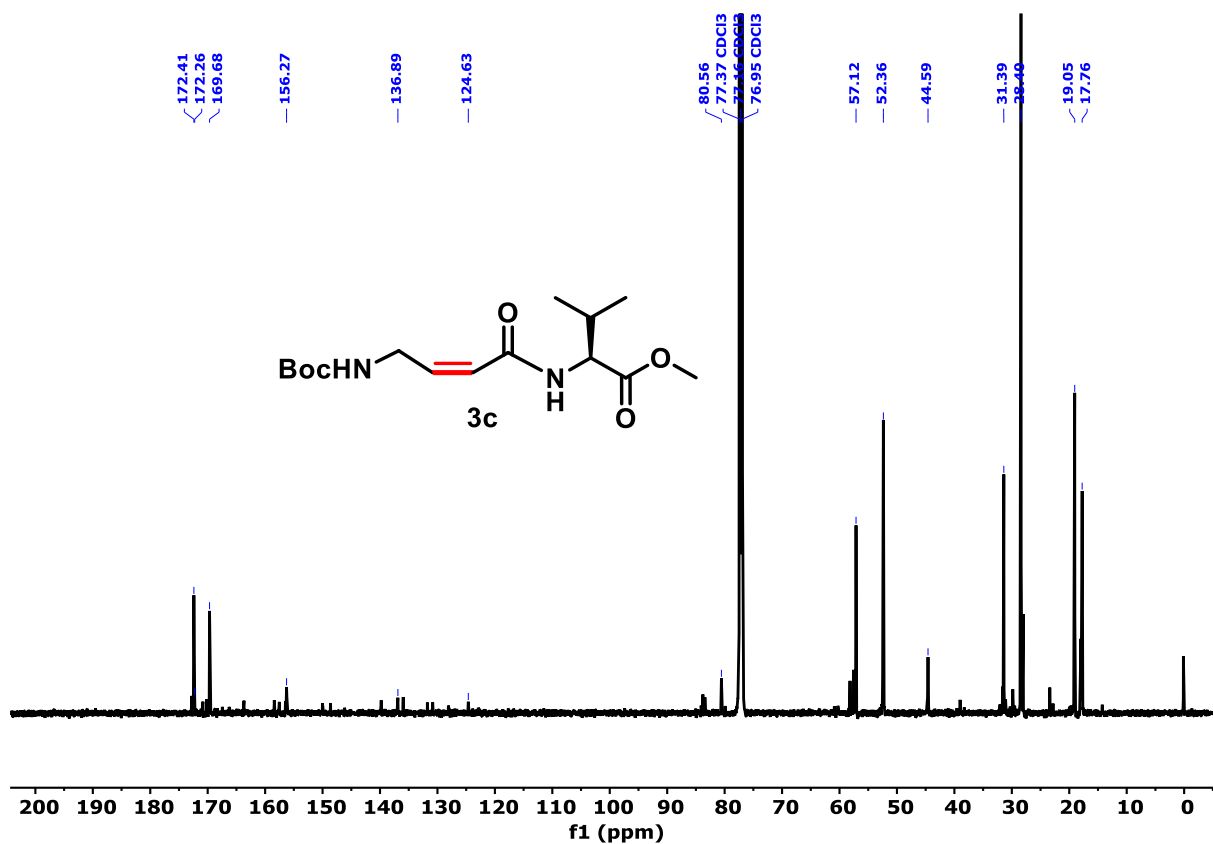
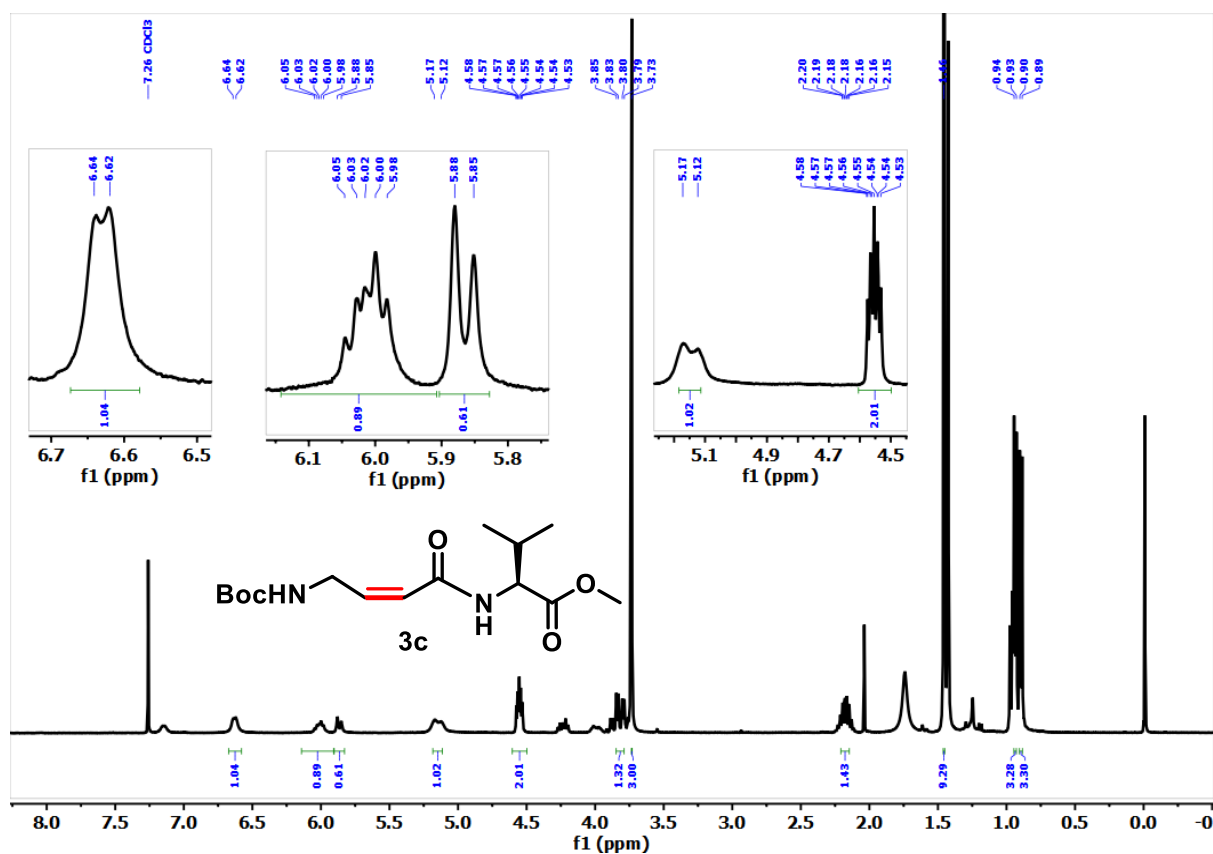










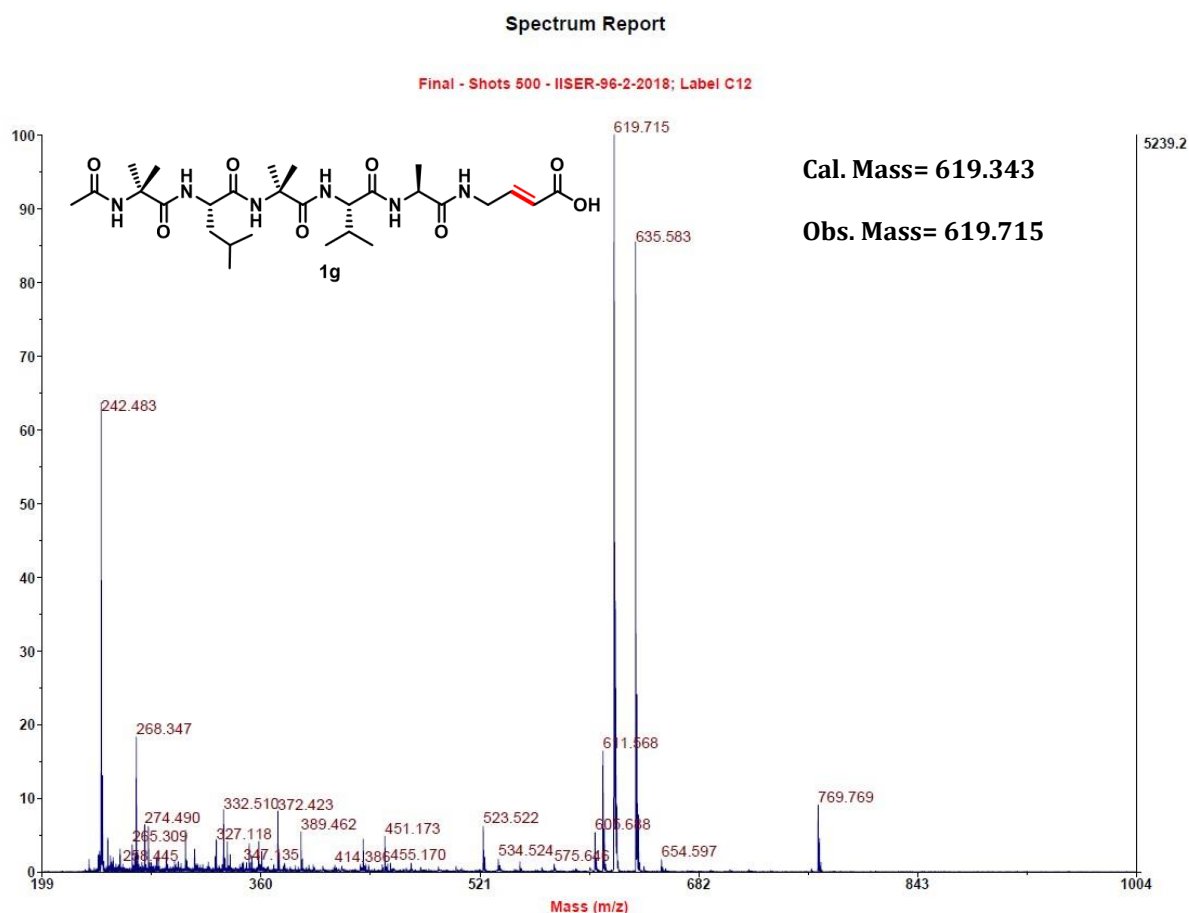


3B.8.2 Mass of all the synthesized compounds obtained from HRMS and MALDI-TOF

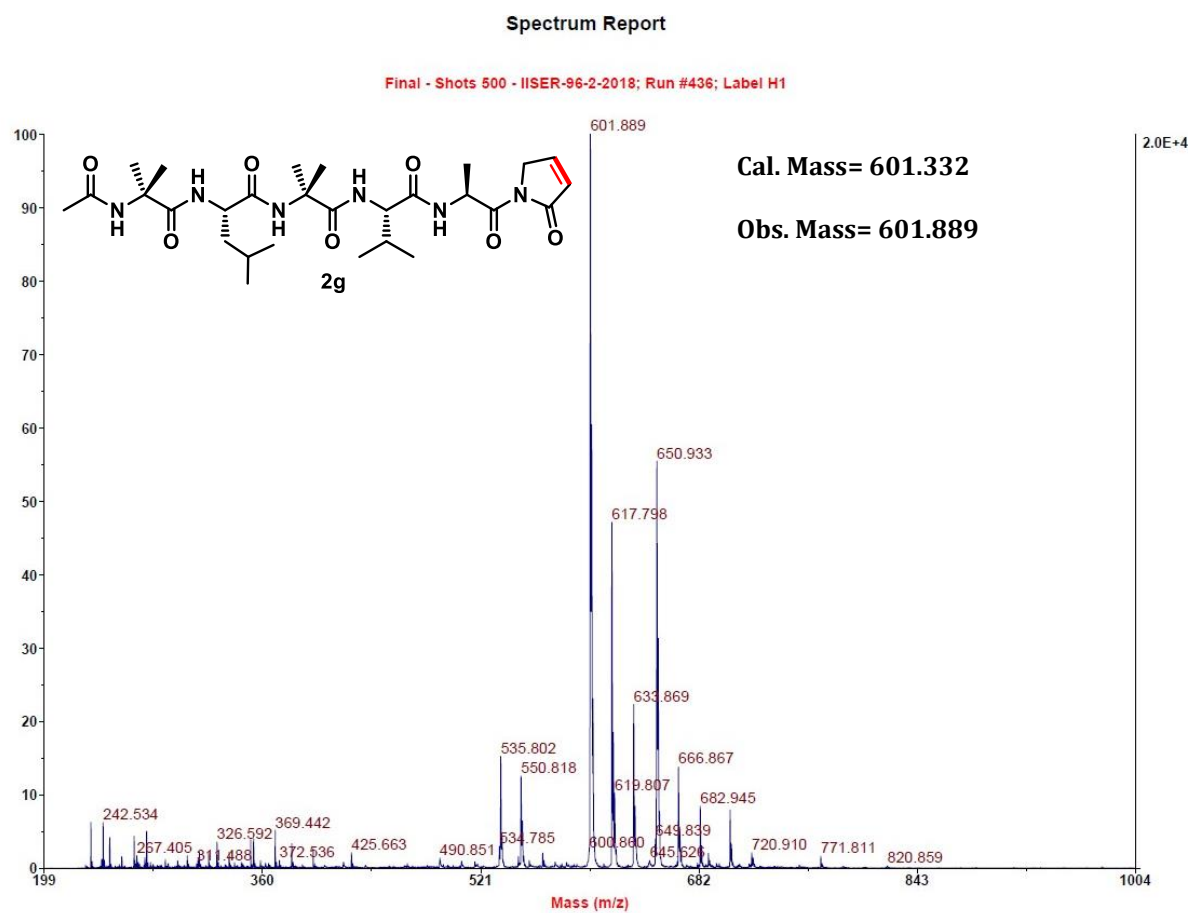
Entry	Compound	[M+Na/H] ⁺	Calculated Mass	Observed Mass	Δm
1	1a	C ₉ H ₁₅ NO ₄ Na	224.0898	224.0892	0.0006
2	1b	C ₁₉ H ₁₇ NO ₄ Na	346.1055	346.1056	0.0001
3	1c	C ₁₂ H ₁₂ NO ₄	234.0768	234.0769	0.0001
4	1d	C ₁₅ H ₂₅ N ₂ O ₅	313.1764	313.1764	0
5	1e	C ₁₄ H ₂₄ N ₂ O ₅ Na	323.1582	323.1580	0.0002
6	1f	C ₁₆ H ₂₇ N ₃ O ₆ Na	380.1797	380.1794	0.0003
7	2a	C ₉ H ₁₃ NO ₃ Na	206.0786	206.0791	0.0005
8	2b	C ₁₉ H ₁₅ NO ₃ Na	328.0949	328.0949	0
9	2c	C ₁₂ H ₁₁ NO ₃ Na	240.0636	240.0632	0.0004
10	2d	C ₁₅ H ₂₄ N ₂ O ₄ Na	319.1633	319.1633	0
11	2e	C ₁₄ H ₂₂ N ₂ O ₄ Na	305.1477	305.1475	0.0002
12	2f	C ₁₆ H ₂₅ N ₃ O ₅ Na	362.1691	362.1692	0.0001
13	3a	C ₉ H ₁₅ NO ₄ Na	224.0898	224.0892	0.0006
14	3b	C ₁₆ H ₂₈ N ₂ O ₅ Na	351.1895	351.1892	0.0003
15	3c	C ₁₅ H ₂₆ N ₂ O ₅ Na	337.1739	337.1737	0.0002

Note: Δm = Mass difference, [M+Na/H]⁺ = Molecular ion.

(i) MALDI-TOF spectra of **1g** (Ac-Aib-Leu-Aib-Val-Ala-d^{2,3}γ-Gly-OH) [M+Na]⁺ Cal. Mass 619.343 and obs. Mass 619.715.



(ii) MALDI-TOF spectra of **2g** (Ac-Aib-Leu-Aib-Val-Ala-d^{2,3}γ-Gly-Lactam) [M+Na]⁺ Cal. Mass 601.332 and obs. Mass 601.889.



Chapter 4A

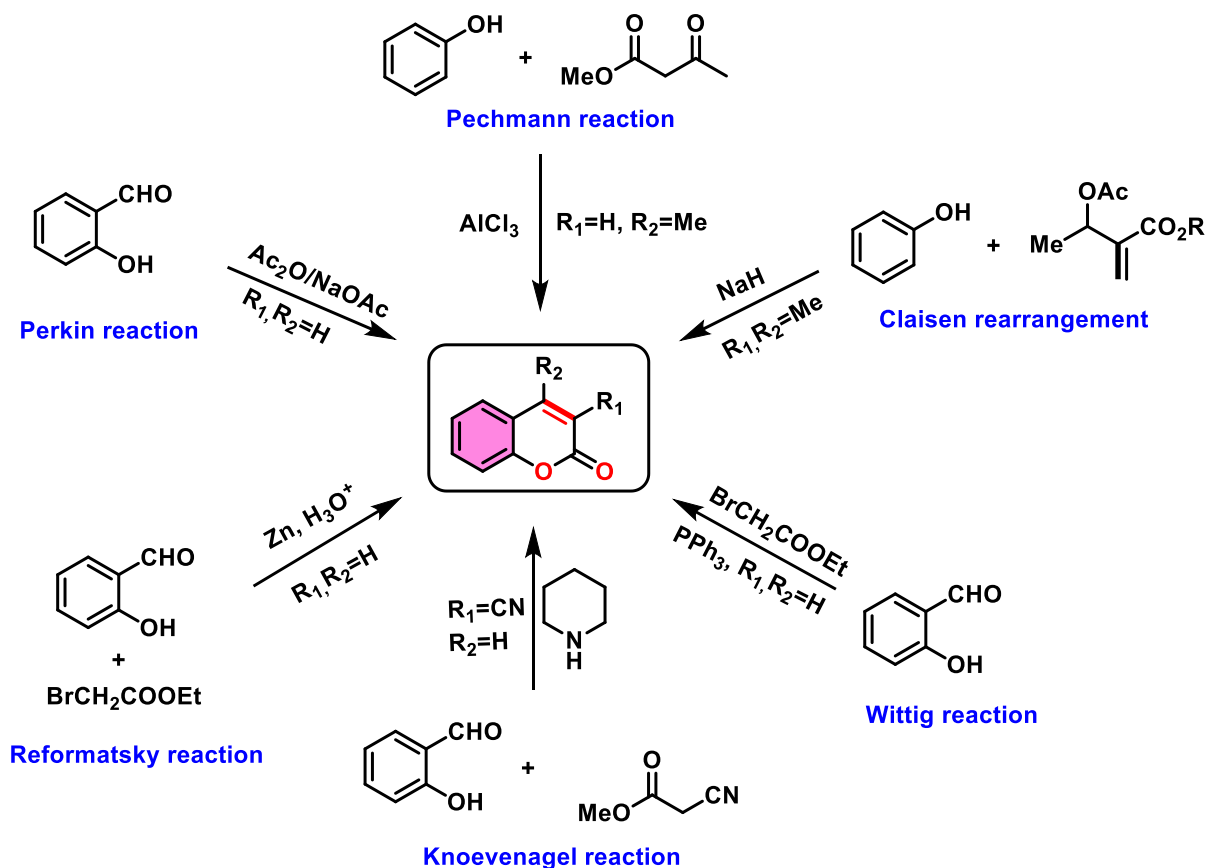
**A Concise Approach to Lactone Synthesis
from *o*-Hydroxy Cinnamic Acid Precursors
via HATU Activation**

4A.1 Introduction

IUPAC defines lactones as “cyclic esters of hydroxycarboxylic acids having 1-oxacycloalkan-2-one or 1-oxacycloalken-2-one as a core structure and some analogs of these rings substitute one or more C-atoms by the heteroatoms”.¹ Several secondary metabolites consist of lactones core structure because of their remarkable chemical architectures and biological activities. The most commonly known compounds of this class are α -, β -, γ -, δ -, and ω -lactones, which contain 3- to 7-membered rings respectively which are a small version of lactones,² out of these γ - and δ -lactones contain the most stable lactone rings as a result they are the most abundant in nature.^{3,4} One of the key features of these compounds is they serve as integral components in the scent of flowers, the flavor of fruits, and the odorants of butter and butter oil.⁵⁻⁷ Additionally, lactones are prevalent in various pharmaceuticals, often influencing the bioactivity and pharmacokinetics of drugs.⁸ Moreover, lactones are important intermediates in organic synthesis, enabling the construction of complex molecules with efficiency and precision.⁹

Coumarins belong to a sub-class of lactones first discovered by A. Vogel in legume plants and are known for their broad spectrum of biological activities and versatile applications.¹⁰ Coumarins and its derivatives play a significant role in both organic chemistry and natural product chemistry. Warfarin is a marketed drug from this family well known for its anticoagulant properties,¹¹ other substituted coumarin exhibits a plethora of biological activities such as anticancer,¹² antibacterial,¹³ antioxidant,¹⁴ antifungal,¹⁵ anti-inflammatory,¹⁶ antiviral,¹⁷ antidiabetic,¹⁸ anti-neurodegenerative,¹⁹ and anti-HIV activities.²⁰ Along with their diverse biological activities, these compounds also find application in the cosmetics,²¹ perfume industries,²² food industries,²³ and agrochemicals industries.²⁴ Due to their vast applications in different fields, various methods have been developed to synthesize coumarin derivatives. The synthesis of coumarin derivatives typically takes advantage of synthetic methodologies such as the Perkin reaction,²⁵ Pechmann condensation,²⁶ Wittig reaction,²⁷ Knoevenagel condensation,²⁸ Reformatsky reaction,²⁹ and Claisen rearrangement,³⁰ they all are collectively delineated in Scheme 1. These methods with several advantages also suffer from some drawbacks such as long reaction duration, use of toxic reagents, and harsh reaction conditions such as high reaction temperature. Consequently, recent advancements have introduced innovative techniques such as microwave chemistry and the employment of novel catalysts, enhancing the efficiency and sustainability of coumarin production.³¹ Recently we have shown synthesis of α,β -unsaturated γ -lactam,^{32,33} through activation of α,β -unsaturated γ -amino acids *via cis-trans* isomerization. Inspired by the spontaneous transformation of α,β -unsaturated γ -

amino acids into *Z*- γ -lactams, we sought to investigate whether the same strategy can be extended to α,β -unsaturated δ -lactone synthesis. In this chapter, we are extending previously established methods for the synthesis of α,β -unsaturated δ -lactone or coumarins from *o*-hydroxy cinnamic acid derivatives. We synthesized various substituted derivatives of coumarin from the activation of *o*-hydroxy cinnamic acid derivatives using HATU and DIPEA and subsequent lactonization at 50 °C. Lactonization reaction worked better at higher temperatures compared to room temperature.



Scheme 1. Commonly used methods for synthesizing coumarin and its derivatives.

4A.2 Aim and Rationale of the Present Work

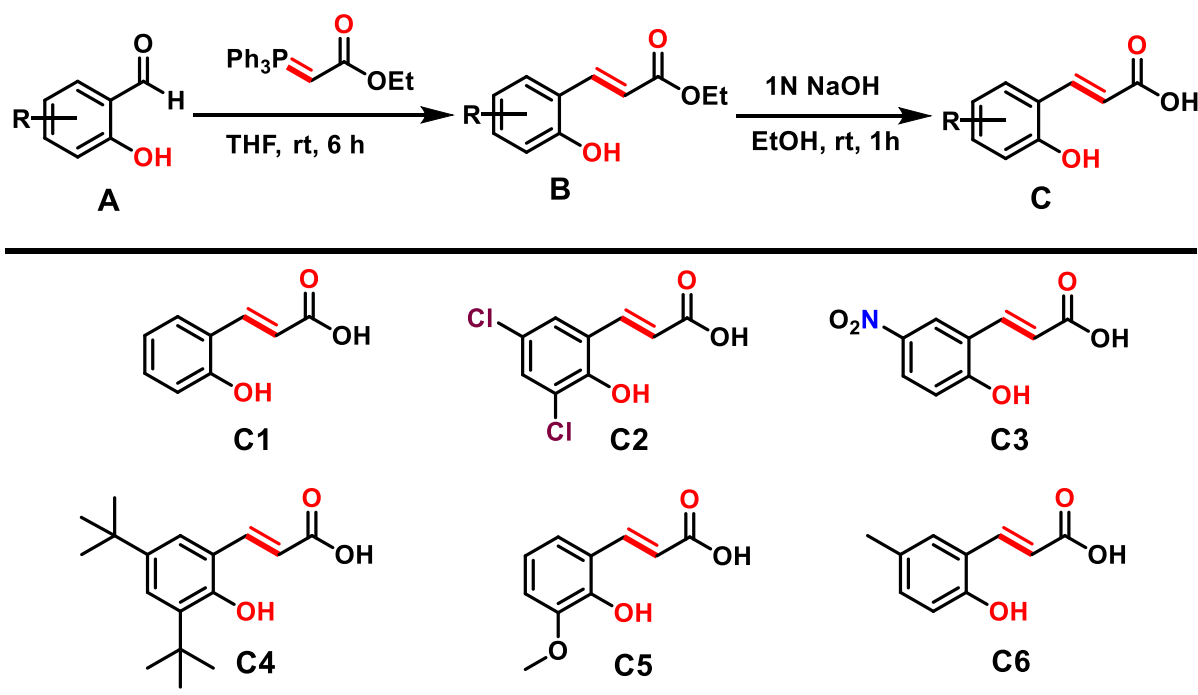
Previously, we showed that the urethane or acetyl-protected NH group can act as a nucleophile in the cyclization of active esters of *N*-protected-(*E*)- α,β -unsaturated γ -amino acids. In continuation, here we sought to investigate whether another function group such as the phenolic -OH group can act similarly to the NH group of the urethane group in order to obtain the cyclized product α,β -unsaturated δ -lactone. A detailed study of lactonization has been done in

the presence of various substituent groups attached to the benzene ring of the *o*-hydroxy cinnamic acid. This is the first report where we observed the formation of lactones from the cinnamic acid derivatives through activation using HATU and DIPEA under high dilution reaction conditions. For this purpose, we have synthesized different *o*-hydroxy cinnamic acid derivatives from previously established protocols,³⁴ and examined their chemical reactivity under suitable reaction conditions.

4A.3 Results and Discussion

4A.3.1 Synthesis of *o*-Hydroxy Cinnamic Acid Derivatives

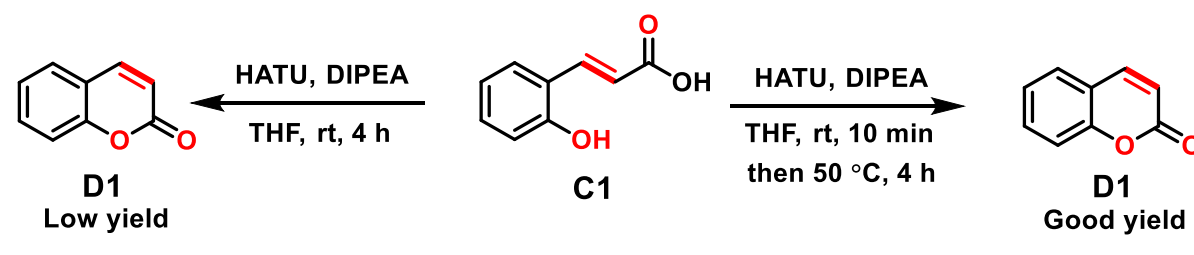
Routinely Wittig olefination reactions are used for the conversion of aldehyde and ketone to alkenes using Wittig ylide reagent.³⁴ In order to get the required starting *o*-hydroxy cinnamic acid derivatives, we sought to use the Wittig reaction. Initially, salicylaldehyde (**A1**) was treated with the Wittig ylide which led to the formation of ethyl-*o*-hydroxy-cinnamate (**B1**) which was confirmed by various spectroscopic techniques. Similarly, other salicylaldehyde derivatives (**A2-A6**) were converted to their corresponding ethyl-*o*-hydroxy-cinnamate derivatives (**B2-B6**) respectively. All these compounds were purified *via* column chromatography and isolated in very good yield (90-95%). Compounds **B1-B6** after base hydrolysis were converted to the desired starting material (**C1-C6**) respectively, a pictorial representation of their synthesis is shown in Scheme 2.



Scheme 2. Synthesis of desired starting materials (**C1-C6**) for lactonization.

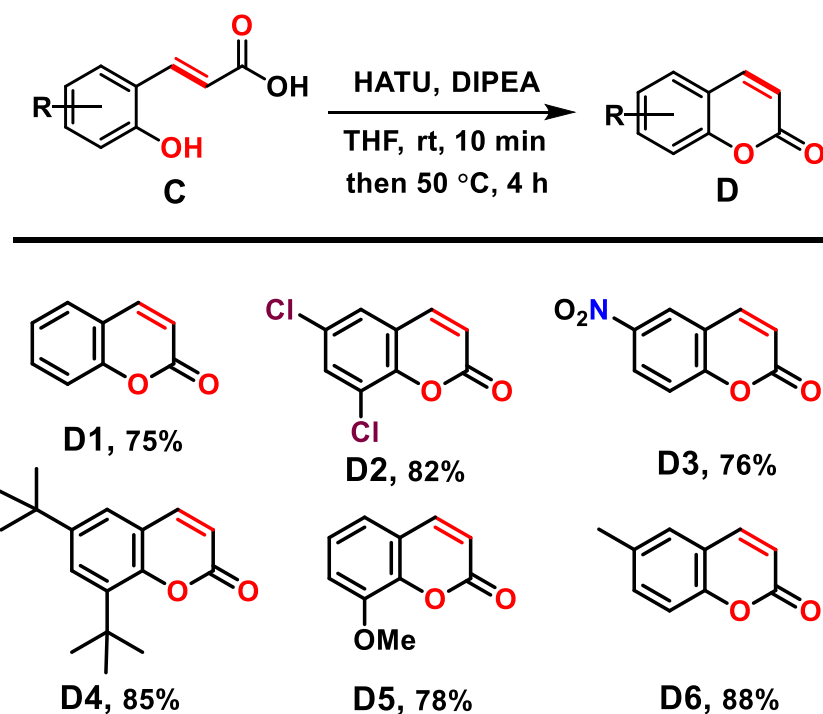
4A.3.2 Synthesis of α,β -Unsaturated δ -Lactones (Coumarin Derivatives)

Inspired by the previous results, where we transformed achiral *E*-vinyllogous amino acids into corresponding α,β -unsaturated γ -lactams using HATU and DIPEA. Very similarly *o*-hydroxy cinnamic acid (**C1**) was activated with HATU in the presence of DIPEA at room temperature and its transformation was monitored. Unfortunately, although we were able to identify the desired cyclized product (**D1**), it was obtained in a low yield of nearly 35%, which forced us to modify the cyclization reaction conditions. The most probable reasons for the lower yield are the lower nucleophilicity of the phenolic -OH group compared to the NH group and the formation of a 6-membered ring *via* 6-exo-trig cyclization. After several unsuccessful attempts to improve the yields of the lactonization reaction using different reaction conditions, we concluded that changing the temperature of the reaction from rt to 50 °C after the initial activation with HATU drastically changed the reaction outcome, as shown in Scheme 3.



Scheme 3. Cyclization of **C1** under different reaction conditions.

Furthermore, using similar optimized reaction conditions **C2-C6** were transformed into their corresponding lactones **D2-D6** respectively. The substrate scope of the lactonization reaction and the results are summarized in Scheme 4. During the course of the study, we found a single crystal for the **D6** after slow evaporation of aqueous methanol at room temperature, the crystal structure of the **D6** is shown in Figure 1. Both electron-donating substituents such as -OMe and electron-withdrawing substituents such as -NO₂ give similar yields suggesting that no significant interference of these groups on the yields of the reaction. In addition, we also observed no influence of bulky groups on the rate of the reaction.



Scheme 4. Substrate scope for the lactonization reaction.

HRMS and NMR spectroscopic techniques were mainly used to understand the fate of the lactonization reaction. The ^1H NMR analysis of lactonization revealed that the *o*-hydroxy cinnamic acid **C1** shows a chemical shift (δ_{H}) for the alkene protons at 7.89 and 6.51 ppm with the coupling constant value of 16.1 Hz. After lactonization chemical shift of alkene protons changed to 7.71 and 6.42 ppm with a coupling constant of 9.5 Hz for the coumarin **D1**. Indicating the formation of a 6-membered lactone ring *via* intramolecular cyclization. Mass analysis of the cyclization indicates the 18-unit massless for the cyclized product compared to the starting substrate, which is well-coped with NMR analysis.

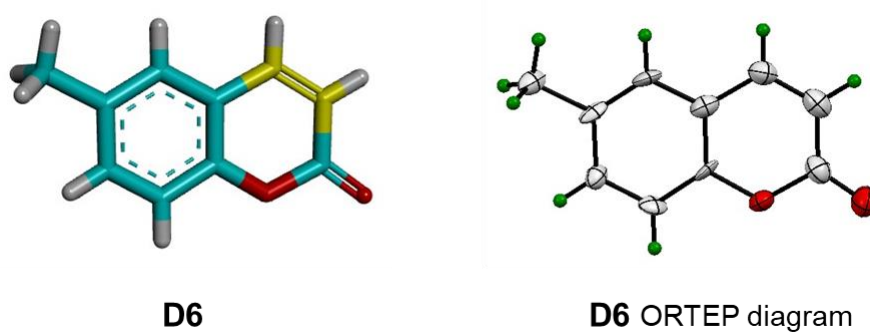


Figure 1. Single crystal structure and ORTEP diagram of **D6**.

Further to check the importance of the nucleophilic center (phenolic hydroxyl group) for cyclization of *o*-hydroxy cinnamic acid, we treated cinnamic acid (**C7**) with HATU and DIPEA where the hydroxyl group is absent. We did not observe any *cis-trans* isomerized product even after stirring the reaction for 24 hours, which was confirmed by coupling constant values of

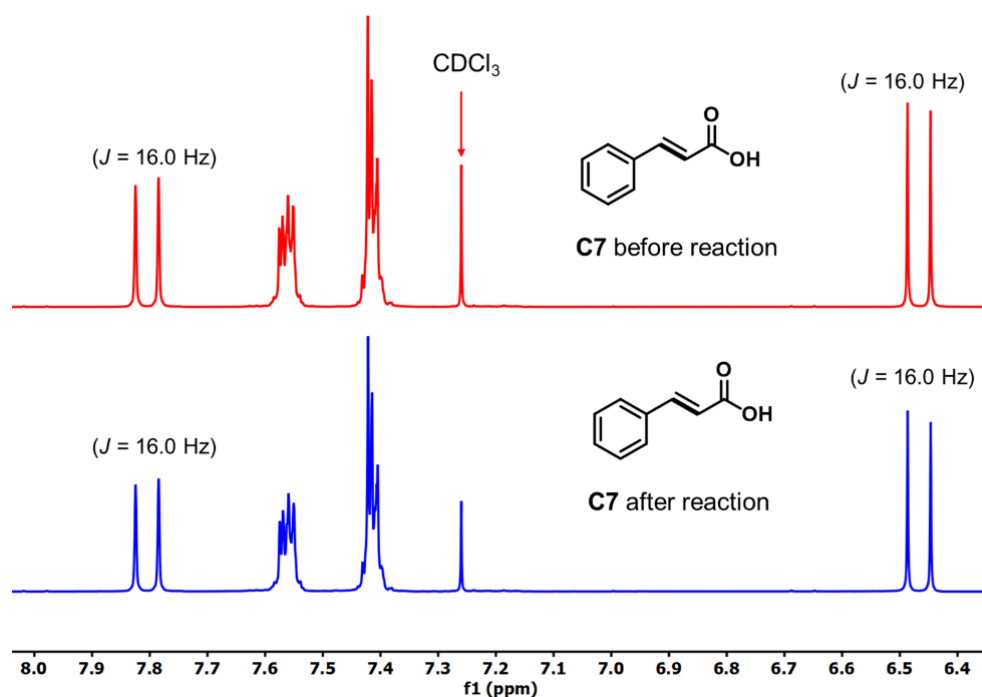
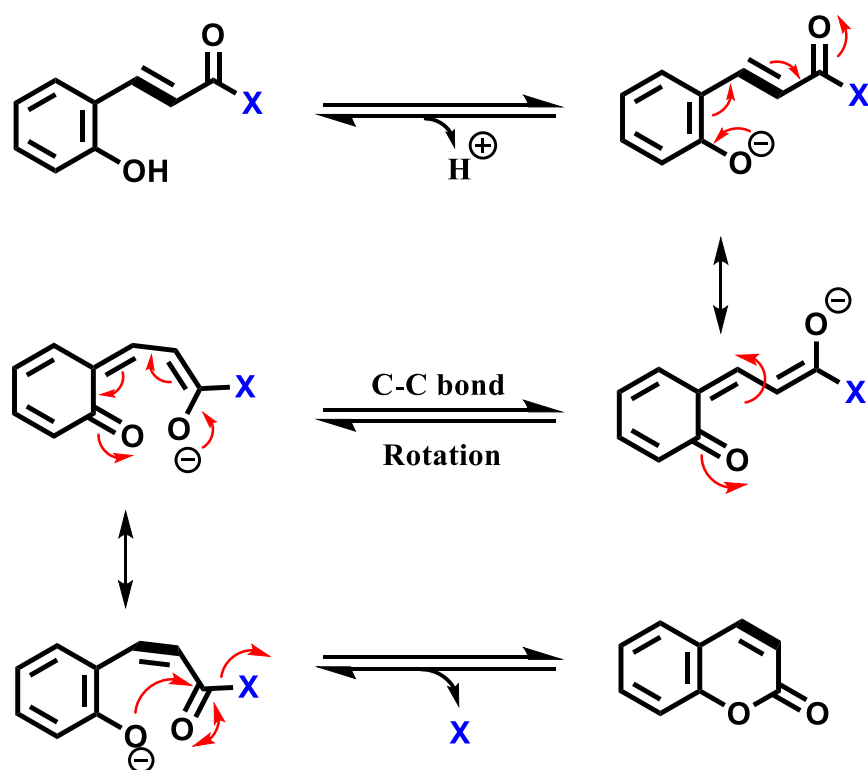


Figure 2. The combined partial ¹H NMR spectra of cinnamic acid (**C7**) before reaction and after reaction.

alkene protons of cinnamic acid. Suggesting phenolic hydroxyl group is very important for *cis-trans* isomerization as well as for lactonization reaction. The combined partial ¹H NMR spectra of cinnamic acid (**C7**) before reaction and after the reaction with HATU and DIPEA are given in Figure 2.

4A.4 Possible Reaction Mechanism

Shimizu *et al.* proposed that the thioester (X = CoAS) of cinnamic acid undergoes *cis*-to-*trans* isomerization involving the formation of an ionic intermediate through an ionic mechanism.³⁵ A result of *cis*-to-*trans* isomerization nucleophilic center and electrophilic center come in proximity. Finally, an attack of nucleophile (phenoxide ion) on the electrophilic center (thioester) gives coumarin, delineated in Scheme 5. It was believed that a similar pathway was adopted by an *in-situ* generated active ester of cinnamic acid derivatives which is the OAt-ester (X = OAt) to produce coumarin derivatives through HATU activation.



Scheme 5. Possible reaction mechanism of lactonization of *o*-hydroxy cinnamic acid (C1).

4A.5 Conclusion

In summary, we have established an efficient method for the synthesis of coumarin and its derivatives using HATU and DIPEA under very mild reaction conditions. The results suggest that changing nucleophiles from the NH group to the phenolic -OH group does not affect the extent of cyclization. However, in the absence of a nucleophilic center, we did not observe any *cis-trans* isomerization. The proposed mechanism of the reaction matches well with the earlier proposed mechanism of *o*-hydroxy cinnamic acid derivatives cyclization in biological systems.³⁵ Present method provide broad substrate scope with various substitution on the aromatic ring which rarely affect the reaction progress.

4A.6 Experimental Section

General Method:

All required amino acids, HATU, DIPEA, PPh_3 , $\text{BrCH}_2\text{COOEt}$ and THF solvent were purchased from commercial vendors and used without any purification. Solvents ethyl acetate and hexane were distilled before use. Purification of synthesized compounds was carried out through silica column chromatography using silica gel (60-120 mesh). Characterization of the

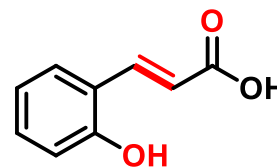
compounds was done using ^1H NMR (400 MHz) and ^{13}C NMR (101 MHz) on a Bruker Avance and JEOL spectrometer and Mass samples were analyzed by High-resolution mass spectrometry using ESI TOF in both +ve and -ve mode. The X-ray data were collected at 150K temperature on a Bruker APEX(II) DUO CCD diffractometer using Cu K_α radiation ($\lambda = 1.54178 \text{ \AA}$). The *o*-hydroxy cinnamic acid derivatives were prepared according to the previously reported protocols.³⁴

4A.6.1 Synthesis of *o*-hydroxy cinnamic acid derivatives (C1-C6)

General procedure for the synthesis of *o*-hydroxy cinnamic acid derivatives (C1-C6): To the 50 mL THF solution of salicylaldehyde derivatives (5 mmol) Wittig ylide ($\text{Ph}_3\text{PCHCO}_2\text{Et}$, 5.5 mmol) was added at room temperature. The reaction mixture was stirred for about 12 h and reaction progress was monitored by thin-layer chromatography (TLC). After completion of the reaction, THF was evaporated using a rotary evaporator. As a result, we obtained crude product ethyl-*o*-hydroxy-cinnamate derivatives, which were purified through column chromatography using EtOAc/hexane in increasing order of polarity starting from 2% to get pure ethyl-*o*-hydroxy-cinnamate derivatives (**B1-B6**). Subsequently, ethyl-*o*-hydroxy-cinnamate derivatives (**B1-B6**, 3 mmol) were dissolved in EtOH and treated with 1N NaOH at room temperature. The reaction mixture was stirred for about 1-2 h and reaction progress was monitored by TLC. After completion of the reaction, EtOH was evaporated using a rotary evaporator. The reaction mixture was then acidified with 10% HCl followed by dilution with EtOAc (150 mL) and washed with brine solution ($2 \times 80 \text{ mL}$). The organic layer was dried over anhydrous Na_2SO_4 for 6-8 h and concentrated under reduced pressure. Finally, we got *o*-hydroxy cinnamic acid derivatives (**C1-C6**) which were purified similar to their precursors and used further for synthesis.

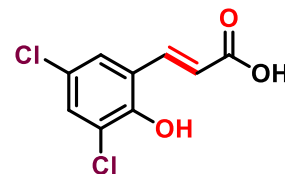
2-Hydroxy Cinnamic Acid (C1):

White solid, yield = 443 mg (90%), **m.p.** 202-204 °C; ^1H NMR (400 MHz, CD_3CN) δ_{H} 8.24 (bs, 1H), 7.89 (d, $J = 16.1 \text{ Hz}$, 1H), 7.54 (dd, $J = 8.0, 1.7 \text{ Hz}$, 1H), 7.26 (ddd, $J = 8.2, 7.3, 1.7 \text{ Hz}$, 1H), 7.01–6.80 (m, 2H), 6.51 (d, $J = 16.1 \text{ Hz}$, 1H); ^{13}C NMR (101 MHz, CD_3CN) δ_{C} 168.55, 156.90, 141.24, 132.58, 129.79, 122.19, 121.22, 118.50, 117.00; HRMS: m/z for $\text{C}_9\text{H}_7\text{O}_3$ ($\text{M} - \text{H}$), calcd: 163.0395, found: 163.0397.



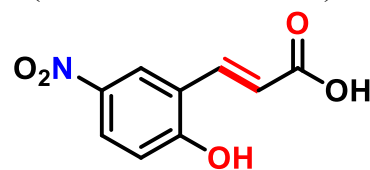
3,5-Dichloro 2-Hydroxy Cinnamic Acid (C2):

White solid, yield = 590 mg (85%), **m.p.** 258-260 °C; ^1H NMR (400 MHz, Acetone- d_6) δ_{H} 9.09 (s, 1H), 7.96 (d, J = 16.1 Hz, 1H), 7.70 (d, J = 2.5 Hz, 1H), 7.51 (d, J = 2.6 Hz, 1H), 6.70 (d, J = 16.1 Hz, 1H); ^{13}C NMR (101 MHz, Acetone- d_6) δ_{C} 166.75, 150.51, 137.61, 130.02, 126.66, 125.18, 124.73, 122.30, 121.21; HRMS: m/z for $\text{C}_9\text{H}_7\text{Cl}_2\text{O}_3$ ($\text{M} + \text{H}$) $^+$, calcd: 232.9772, found: 232.9769.



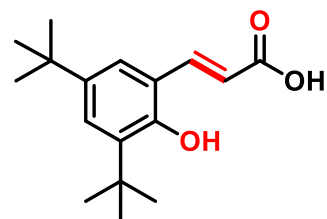
2-Hydroxy 5-Nitro Cinnamic Acid (C3):

White solid, yield = 582 mg (93%), **m.p.** 235-238 °C; ^1H NMR (400 MHz, Acetone- d_6) δ_{H} 10.80 (s, 1H), 8.52 (d, J = 2.8 Hz, 1H), 8.16 (dd, J = 9.0, 2.8 Hz, 1H), 7.97 (d, J = 16.2 Hz, 1H), 7.19 (d, J = 9.0 Hz, 1H), 6.80 (d, J = 16.2 Hz, 1H); ^{13}C NMR (101 MHz, Acetone- d_6) δ_{C} 166.86, 161.71, 137.87, 128.81, 128.69, 126.45, 124.69, 121.13, 116.48; HRMS: m/z for $\text{C}_9\text{H}_6\text{NO}_5$ ($\text{M} - \text{H}$) $^-$, calcd: 208.0246, found: 208.0249.



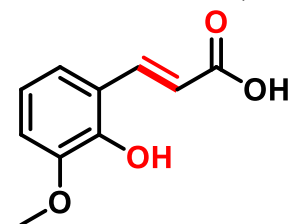
3,5-Di-*tert*-butyl 2-Hydroxy Cinnamic Acid (C4):

White solid, yield = 760 mg (92%), **m.p.** 161-163 °C; ^1H NMR (400 MHz, Acetone- d_6) δ_{H} 8.06 (d, J = 15.8 Hz, 1H), 7.50 (d, J = 2.4 Hz, 1H), 7.42 (d, J = 2.4 Hz, 1H), 6.42 (d, J = 15.8 Hz, 1H), 2.99 (s, 1H), 1.44 (s, 9H), 1.32 (s, 9H); ^{13}C NMR (101 MHz, Acetone- d_6) δ_{C} 168.08, 153.07, 143.47, 141.35, 138.98, 127.14, 123.95, 122.35, 118.79, 35.73, 34.97, 31.77, 30.20; HRMS: m/z for $\text{C}_{17}\text{H}_{23}\text{O}_3$ ($\text{M} - \text{H}$) $^-$, calcd: 275.1647, found: 275.1652.



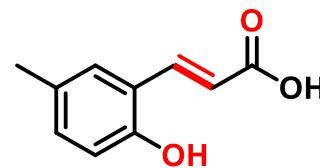
2-Hydroxy 3-Methoxy Cinnamic Acid (C5):

White solid, yield = 529 mg (91%), **m.p.** 165-167 °C; ^1H NMR (400 MHz, Acetone- d_6) δ_{H} 8.27 (s, 1H), 8.04 (d, J = 16.1 Hz, 1H), 7.22 (dd, J = 8.0, 1.4 Hz, 1H), 7.03 (dd, J = 8.1, 1.4 Hz, 1H), 6.86 (t, J = 8.0 Hz, 1H), 6.61 (d, J = 16.1 Hz, 1H), 3.89 (s, 3H); ^{13}C NMR (101 MHz, Acetone- d_6) δ_{C} 168.44, 148.66, 147.00, 140.74, 121.87, 121.02, 120.23, 119.15, 113.50, 56.48; HRMS: m/z for $\text{C}_{10}\text{H}_9\text{O}_4$ ($\text{M} - \text{H}$) $^-$, calcd: 193.0501, found: 193.0502.



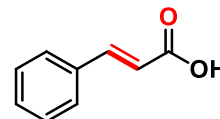
2-Hydroxy 5-Methyl Cinnamic Acid (C6):

White solid, yield = 480 mg (90%), **m.p.** 270-273 °C; ^1H NMR (400 MHz, Acetone- d_6) δ_{H} 9.05 (s, 1H), 8.00 (d, J = 16.1 Hz, 1H), 7.42 (d, J = 2.2 Hz, 1H), 7.07 (ddd, J = 8.3, 2.3, 0.8 Hz, 1H), 6.87 (d, J = 8.3 Hz, 1H), 6.59 (d, J = 16.1 Hz, 1H), 2.26 (s, 3H); ^{13}C NMR (101 MHz, Acetone- d_6) δ_{C} 167.66, 154.46, 140.34, 132.03, 128.86, 128.79, 121.14, 117.63, 116.03, 19.47; HRMS: m/z for $\text{C}_{10}\text{H}_{10}\text{O}_3\text{Na}$ ($\text{M} + \text{Na}$) $^+$, calcd: 201.0527, found: 201.0529.



Cinnamic Acid (C7):

White solid, **m.p.** 130-132 °C; ^1H NMR (400 MHz, Chloroform- d) δ_{H} 7.80 (d, J = 16.0 Hz, 1H), 7.59 – 7.53 (m, 2H), 7.45 – 7.38 (m, 3H), 6.47 (d, J = 16.0 Hz, 1H); ^{13}C NMR (101 MHz, Chloroform- d) δ_{C} 172.67, 147.25, 134.17, 130.90, 129.11, 128.52, 117.47; HRMS: m/z for $\text{C}_9\text{H}_9\text{O}_2$ ($\text{M} + \text{H}$) $^+$, calcd: 149.0603, found: 149.0604.

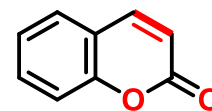


4A.6.2 Synthesis of α,β -Unsaturated δ -Lactones (Coumarin derivatives, D1-D6)

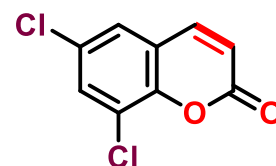
General procedure for the synthesis of Coumarin derivatives (D1-D6): *o*-Hydroxy cinnamic acid derivatives (**C1-C6**, 2 mmol) were initially dissolved in 50 mL of THF then DIPEA (6 mmol) was added to the reaction mixture. The resultant reaction mixture was treated with HATU (2 mmol) at room temperature for 10 minutes and the reaction mixture was further stirred for 4 h at 50 °C. The progression of the reaction was monitored by TLC. Once the reaction was complete, the reaction mixture was concentrated under reduced pressure using a rotary evaporator resultant reaction mixture was diluted with ethyl acetate (150 mL) and washed with 10% HCl (3 $\times$ 80 mL), 10% Na_2CO_3 (3 $\times$ 80 mL), and brine solution (3 $\times$ 80 mL). The combined organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude product was purified using silica gel (60-120 mesh) column chromatography using an ethyl acetate/hexane solvent system in increasing polarity to get pure coumarin derivatives (**D1-D6**).

Coumarin (D1):

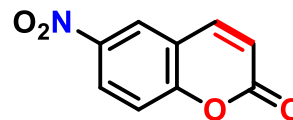
White solid, $R_f = 0.72$ (20% EtOAc in hexane), yield = 219 mg (75%), **m.p.** 75-77 °C; ^1H NMR (400 MHz, CDCl_3) δ_{H} 7.71 (dd, $J = 9.5, 0.7$ Hz, 1H), 7.56–7.47 (m, 2H), 7.35–7.26 (m, 2H), 6.42 (d, $J = 9.5$ Hz, 1H); ^{13}C NMR (101 MHz, CDCl_3) δ_{C} 160.95, 154.17, 143.59, 131.97, 128.00, 124.57, 118.95, 117.03, 116.82; HRMS: m/z for $\text{C}_9\text{H}_7\text{O}_2$ ($\text{M} + \text{H}$) $^+$, calcd: 147.0446, found: 147.0441.

**6,8-Dichloro Coumarin (D2):**

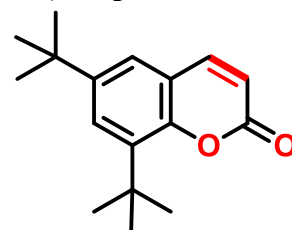
White solid, $R_f = 0.75$ (20% EtOAc in hexane), yield = 349 mg (82%), **m.p.** 71-73 °C; ^1H NMR (400 MHz, CDCl_3) δ_{H} 7.63 (d, $J = 9.6$ Hz, 1H), 7.60 (d, $J = 2.4$ Hz, 1H), 7.40 (d, $J = 2.3$ Hz, 1H), 6.52 (d, $J = 9.6$ Hz, 1H); ^{13}C NMR (101 MHz, CDCl_3) δ_{C} 158.95, 148.62, 142.08, 132.03, 129.72, 125.87, 122.96, 120.77, 118.71; HRMS: m/z for $\text{C}_9\text{H}_5\text{Cl}_2\text{O}_2$ ($\text{M} + \text{H}$) $^+$, calcd: 214.9666, found: 214.9666.

**6-Nitro Coumarin (D3):**

White solid, $R_f = 0.80$ (20% EtOAc in hexane), yield = 290 mg (76%), **m.p.** 80-82 °C; ^1H NMR (400 MHz, CDCl_3) δ_{H} 8.48–8.35 (m, 2H), 7.81 (d, $J = 9.6$ Hz, 1H), 7.48 (d, $J = 9.0$ Hz, 1H), 6.60 (d, $J = 9.6$ Hz, 1H); ^{13}C NMR (101 MHz, CDCl_3) δ_{C} 158.85, 157.58, 144.09, 142.21, 126.65, 123.76, 118.88, 118.83, 118.13; HRMS: m/z for $\text{C}_9\text{H}_6\text{NO}_4$ ($\text{M} + \text{H}$) $^+$, calcd: 192.0297, found: 192.0297.

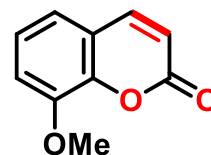
**6,8-Di-*tert*-butyl Coumarin (D4):**

Pale yellowish, $R_f = 0.82$ (20% EtOAc in hexane), yield = 438 mg (85%), **m.p.** 68-70 °C; ^1H NMR (400 MHz, CDCl_3) δ_{H} 7.69 (d, $J = 9.5$ Hz, 1H), 7.58 (d, $J = 2.4$ Hz, 1H), 7.29 (d, $J = 2.4$ Hz, 1H), 6.39 (d, $J = 9.5$ Hz, 1H), 1.52 (s, 9H), 1.36 (s, 9H); ^{13}C NMR (101 MHz, CDCl_3) δ_{C} 161.03, 150.91, 146.81, 145.00, 137.49, 127.22, 122.64, 118.81, 115.64, 35.24, 34.78, 31.51, 30.02; HRMS: m/z for $\text{C}_{17}\text{H}_{23}\text{O}_2$ ($\text{M} + \text{H}$) $^+$, calcd: 259.1698, found: 259.1691.



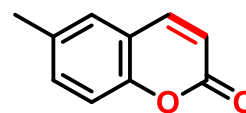
8-Methoxy Coumarin (D5):

White solid, $R_f = 0.76$ (20% EtOAc in hexane), yield = 274 mg (78%), **m.p.** 69-71 °C; ^1H NMR (400 MHz, CDCl_3) δ_{H} 7.69 (d, $J = 9.5$ Hz, 1H), 7.21 (t, $J = 7.9$ Hz, 1H), 7.08 (ddd, $J = 10.7, 8.0, 1.4$ Hz, 2H), 6.44 (d, $J = 9.5$ Hz, 1H), 3.97 (s, 3H); ^{13}C NMR (101 MHz, CDCl_3) δ_{C} 16.35, 147.41, 143.91, 143.73, 124.42, 119.61, 119.39, 117.09, 113.89, 56.39; HRMS: m/z for $\text{C}_{10}\text{H}_9\text{O}_3$ ($\text{M} + \text{H}$) $^+$, calcd: 177.0551, found: 177.0546.



6-Methyl Coumarin (D6):

White solid, $R_f = 0.75$ (20% EtOAc in hexane), yield = 281 mg (88%), **m.p.** 74-76 °C; ^1H NMR (400 MHz, CDCl_3) δ_{H} 7.64 (d, $J = 9.6$ Hz, 1H), 7.32 (dd, $J = 8.5, 2.1$ Hz, 1H), 7.25 (s, 1H), 7.21 (d, $J = 8.4$ Hz, 1H), 6.39 (d, $J = 9.6$ Hz, 1H), 2.39 (s, 3H); ^{13}C NMR (101 MHz, CDCl_3) δ_{C} 161.18, 152.29, 143.53, 134.24, 132.94, 127.80, 118.70, 116.71, 116.69, 20.83; HRMS: m/z for $\text{C}_{10}\text{H}_9\text{O}_2$ ($\text{M} + \text{H}$) $^+$, calcd: 161.0602, found: 161.0605.



4A.7 Crystallographic Information

Compound D6: 10 mg of **D6** was dissolved in 2 mL of methanol solvent in a 5 mL vial, to the resultant solution 2-3 drops of distilled water were added. After slow evaporation of aqueous methanol solution at room temperature crystals of **D6** were grown. A single crystal (0.23 × 0.14 × 0.40 mm) was mounted on a loop of the SC-XRD goniometer. The SC-XRD data measurements were done at 150K temperature on a Bruker APEX(II) DUO CCD diffractometer device using Cu K α radiation source ($\lambda = 1.54178$ Å), ω -scans ($2\theta = 47.85$), for a total of 12849 independent reflections. Space group $P 2_1 2_1 2_1$, $a = 4.7077$ (3), $b = 5.8232$ (4), $c = 28.223$ (2), $\alpha = 90$, $\beta = 90$, $\gamma = 90$, $V = 773.70$ (9) Å 3 , Orthorhombic, formula units $Z = 4$ for chemical formula $\text{C}_{10}\text{H}_8\text{O}_2$, with one molecule in asymmetric unit; ρ calcd = 1.375 gcm $^{-3}$, $\mu = 0.782$ mm $^{-1}$, $F(000) = 336$, $R_{\text{int}} = 0.0906$. The crystal structure was obtained by using Bruker APEX(III) software and the method used was SHELXS-97. The final R_{factor} was 0.0499, ($wR2 = 0.1492$) 724 observed reflections ($F0 \geq 4\sigma(|F0|)$) and 111 variables, goodness of fit $S = 1.34$.

4A.8 References

1. IUPAC, *Compendium of Chemical Terminology*, 2nd ed. (the “Gold Book”), Blackwell Science, Oxford, 1997; (b) IUPAC, *Compendium of Chemical Terminology*, 2020.

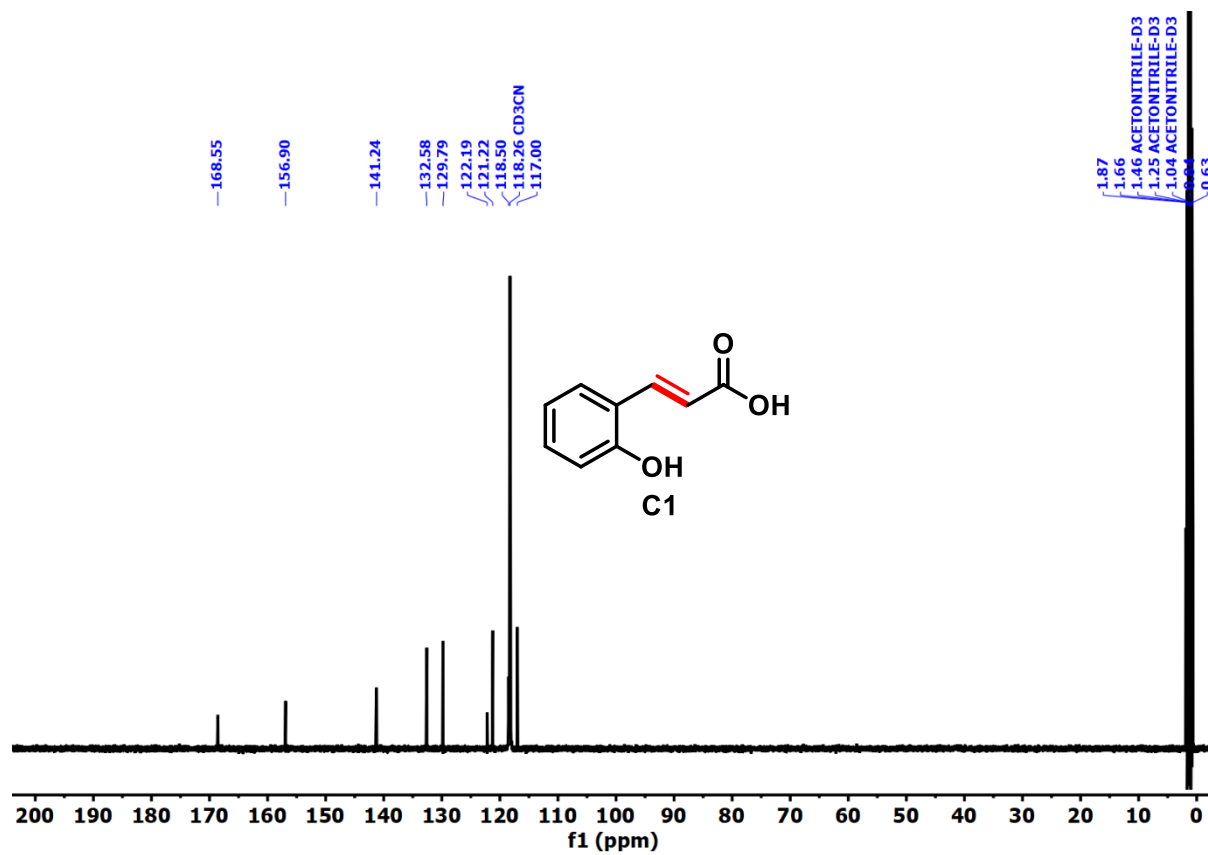
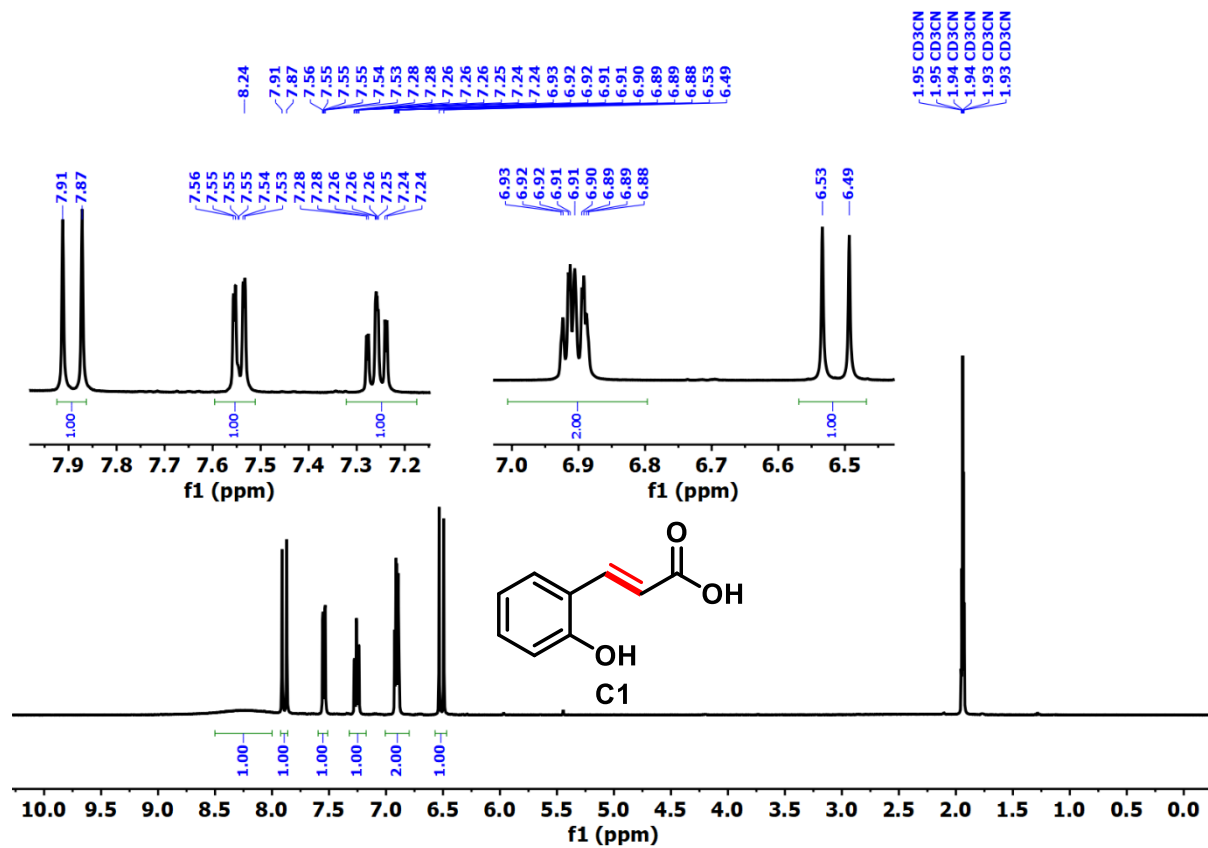
2. R. Alen, 2018, *Carbohydrate Chemistry: Fundamentals and Applications*, WSPC, Singapura.
3. D. Koszelewski, F. Borys, A. Brodzka and R. Ostaszewski, *Eur. J. Org Chem.*, 2019, 1653-1658.
4. M. Sardan, S. Sezer, A. Günel, M. Akkaya and C. Tanyeli, *Bioorg. Med. Chem. Lett.*, 2012, **22**, 5814-5818.
5. (a) S. Okui, M. Uchiyama and M. Mizugaki, *J. Biochem.*, 1963, **53**, 265–270; (b) J. Schrader, M. M. W. Etschmann, D. Sell, J. M. Hilmer and J. Rabenhorst, *Biotechnol. Lett.*, 2004, **26**, 463–472; (c) Y. Wache, M. Aguedo, J. M. Nicaud and J. M. Belin, *Appl. Microbiol. Biotechnol.*, 2003, **61**, 393–404.
6. E. Masson, R. Baumes, C. L. Guerneve and J. L. Puech, *J. Agric. Food Chem.*, 2000, **48**, 4306-4309.
7. (a) J. Boldingh and R. J. Taylor, *Nature*, 1962, **194**, 909–913; (b) P. S. Dimick, N. J. Walker, S. Patton, *J. Agric. Food Chem.*, 1969, **17**, 649–655; (c) D. A. Forss, *J. Agric. Food Chem.*, 1969, **17**, 681–685.
8. (a) M. Romero, P. Renard, D. Caignard, G. Atassi, X. Solans, P. Constans, C. Bailly and M. D. Pujol, *J. Med. Chem.*, 2007, **50**, 294-307; (b) C. M. Oliver, A. L. Schaefer, E. P. Greenberg and J. R. Sufrin, *J. Med. Chem.*, 2009, **52**, 1569-1575.
9. (a) A. Caretto, M. Noè, M. Selva and A. Perosa, *ACS Sustainable Chem. Eng.*, 2014, **2**, 2131-2141; (b) Z. Yang, J. Zhao, W. Yang and W. Deng, *Org. Lett.*, 2019, **21**, 1015-1020.
10. D. Cao, Z. Liu, P. Verwilt, S. Koo, P. Jangjili, J. S. Kim and W. Lin, *Chem. Rev.*, 2019, **119**, 10403- 10519.
11. (a) O. M. Radostits, G. P. Searcy and K. G. Mitchall, *Can. Vet. J.*, 1980, **21**, 155; (b) G. Satish, In *Advances in Structure and Activity Relationship of Coumarin Derivatives*, Penta, S. Ed., Academic Press: Boston, 2016, 151–159.
12. (a) R. S. Keri, B. S. Sasidhar, B. M. Nagaraja and M. A. Santos, *Eur. J. Med. Chem.*, 2015, **100**, 257–269; (b) S. Emami and S. Dadashpour, *Eur. J. Med. Chem.* 2015, **102**, 611–630.
13. (a) Y. Wei, S. Q. Li and H. Haos, *Nat. Prod. Res.*, 2018, **32**, 1824–1831; (b) R. H. Vekariya, K. D. Patel, D. P. Rajani, S. D. Rajani and D. H. Patel, *J. Assoc. Arab. Univ. Basic Appl.*

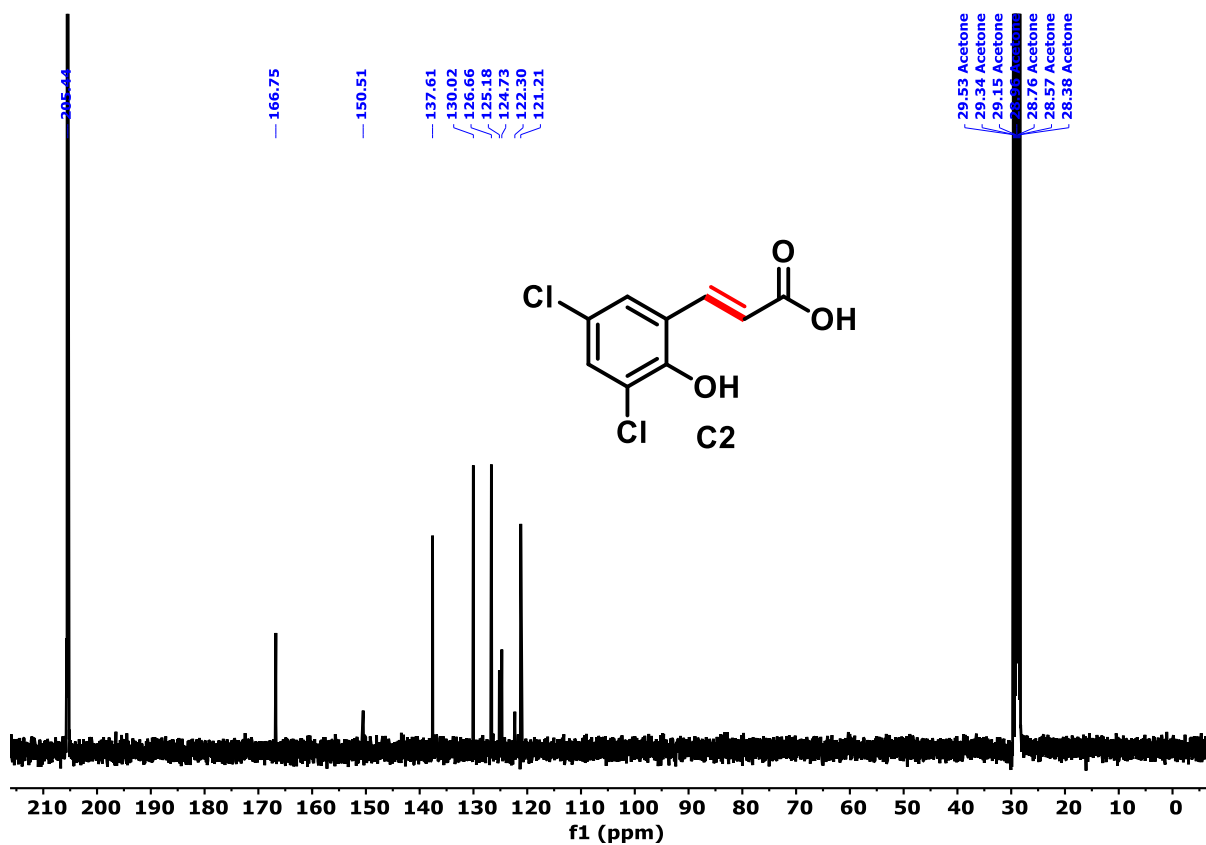
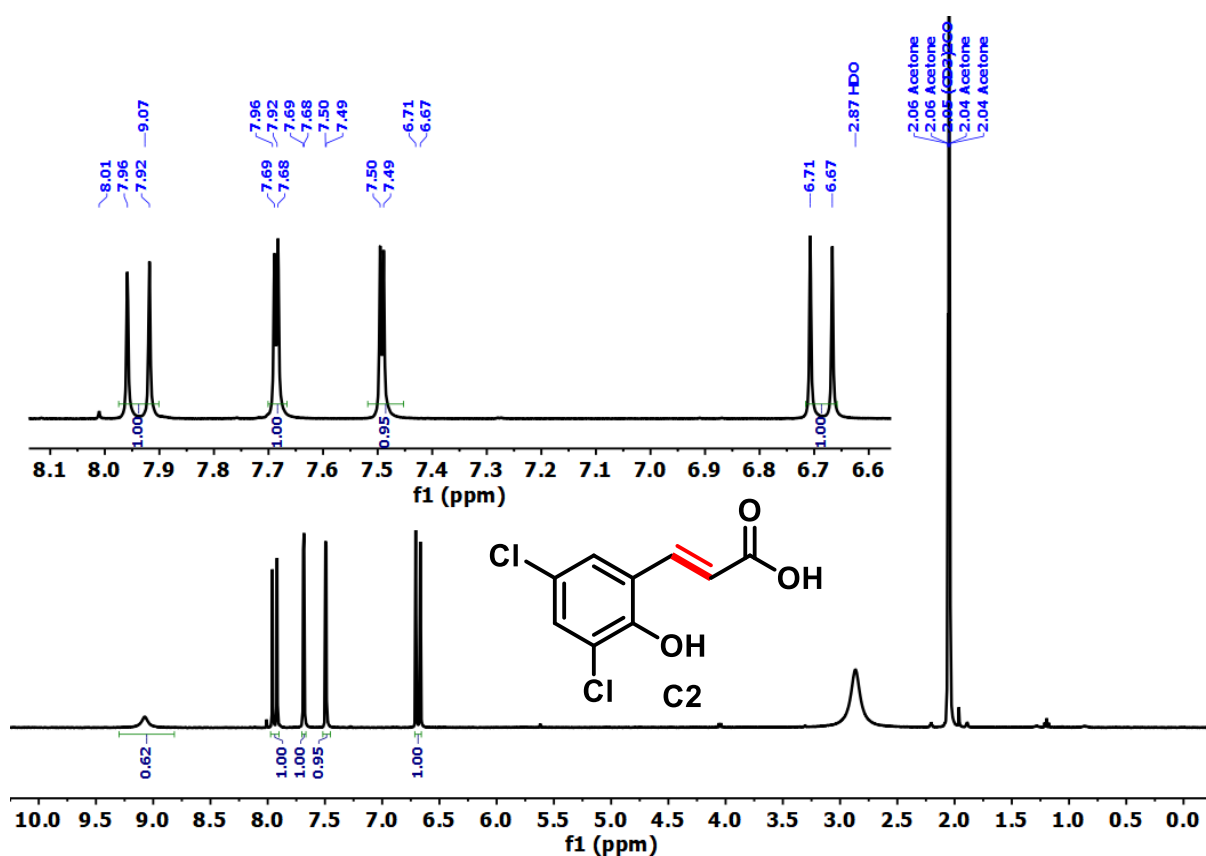
- Sci.*, 2017, **23**, 10–19; (c) Y. K. Al-Majedy, A. A. H. Kadhum, A. A. Al-Amiery and A. B. Mohamad, *Syst. Rev. Pharm.*, 2017, **8**, 62–70; (d) M. Basanagouda, K. Shivashankar, M. V. Kulkarni, V. P. Rasal, H. Patel, S. S. Mutha and A. A. Mohite, *Eur. J. Med. Chem.*, 2010, **45**, 1151–1157.
14. (a) R. K. Arora, N. Kaur, Y. Bansal and G. Bansal, *Acta Pharm. Sin. B*, 2014, **4**, 368–375; (b) W. Pu, Y. Lin, J. Zhang, F. Wang, C. Wang and G. Zhang, *Bioorg. Med. Chem. Lett.*, 2014, **24**, 5432–5434; (c) L. Z. Chen, W. Sun, W. Bol, J. Q. Wang, C. Xiu, W. J. Tang, J. B. Shi, H. P. Zhou and X. H. Liu, *Eur. J. Med. Chem.*, 2017, **138**, 170–181; (d) M. J. Matos, S. Vazquez-Rodriguez, A. Fonseca, E. Uriarte, L. Santana and F. Borges, *Curr. Org. Chem.*, 2017, **21**, 311–324.
15. (a) M. K. Kathiravan, A. B. Salake, A. S. Chothe, P. B. Dudhe, R. P. Watode, M. S. Mukta and S. Gadhwe, *Bioorg. Med. Chem.*, 2012, **20**, 5678–5698; (b) A. A. Al-Amiery, Y. K. Al-Majedy, A. A. H. Kadhum and B. Mohamad, *Sci. Rep.*, 2015, **5**, 1–7; (c) M. A. I. Salem, M. I. Marzouk and A. M. El-Kazak, *Molecules*, 2016, **21**, 249.
16. (a) D. Olmedo, R. Sancho, L. M. Bedoya, J. L. López-Pérez, E. Del Olmo, E. Muñoz, J. Alcamí, M. P. Gupta and A. S. Feliciano, *Molecules*, 2012, **17**, 9245–9257; (b) J. Grover and S. M. Jachak, *RSC Adv.*, 2015, **5**, 38892–38905.
17. (a) M. K. Gupta, S. Kumar and S. Chaudhary, *Pharm. Chem. J.*, 2020, **53**, 1122–1127; (b) R. Kenchappa, Y. D. Bodke, A. Chandrashekar, M. A. Sindhe and S. K. Peethambar, *Arab. J. Chem.*, 2017, **10**, 3895–3906; (c) M. Z. Hassan, H. Osman, M. A. Ali and M. J. Ahsan, *Eur. J. Med. Chem.*, 2016, **123**, 236–255.
18. (a) P. Anand, B. Singh and N. Singh, *Bioorg. Med. Chem.*, 2012, **20**, 1175–1180; (b) S. F. Razavi, M. Khoobi, H. Nadri, A. Sakhteman, A. Moradi, S. Emami, A. Foroumadi and A. Shafiee, *Eur. J. Med. Chem.*, 2013, **64**, 252–259; (c) W. D. Seo, J. Y. Kim, H. W. Ryu, J. H. Kim, S. I. Han, J. E. Ra, K. H. Seo, K. C. Jang and J. H. Lee, *J. Funct. Foods*, 2013, **5**, 1421–1431.
19. E. Jameel, T. Umar, J. Kumar and N. Hoda, *Chem. Biol. Drug Des.*, 2016, **87**, 21–38.
20. (a) S. Emami, S. Dadashpour, *Eur. J. Med. Chem.*, 2015, **102**, 611–630; (b) D. Yu, M. Suzuki, L. Xie, S. L. Morris-Natschke and K.-H. Lee, *Med. Res. Rev.*, 2003, **23**, 322–345; (c) I. Kostova, *Curr. HIV Res.*, 2006, **4**, 347–363; (d) P. Wadhwa, J. Priti, R. Santosh and R. A. J. Hemant, *Curr. Drug Discovery Technol.*, 2018, **15**, 2–19.

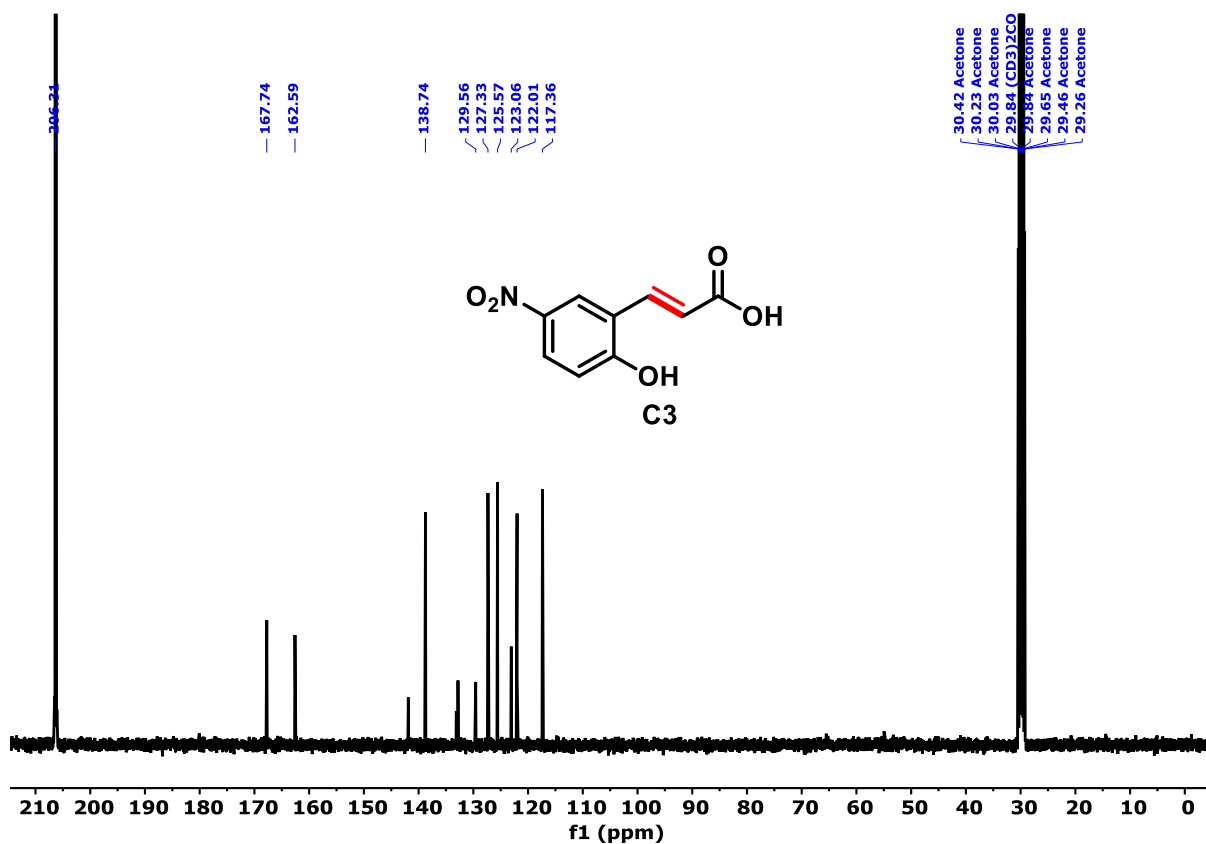
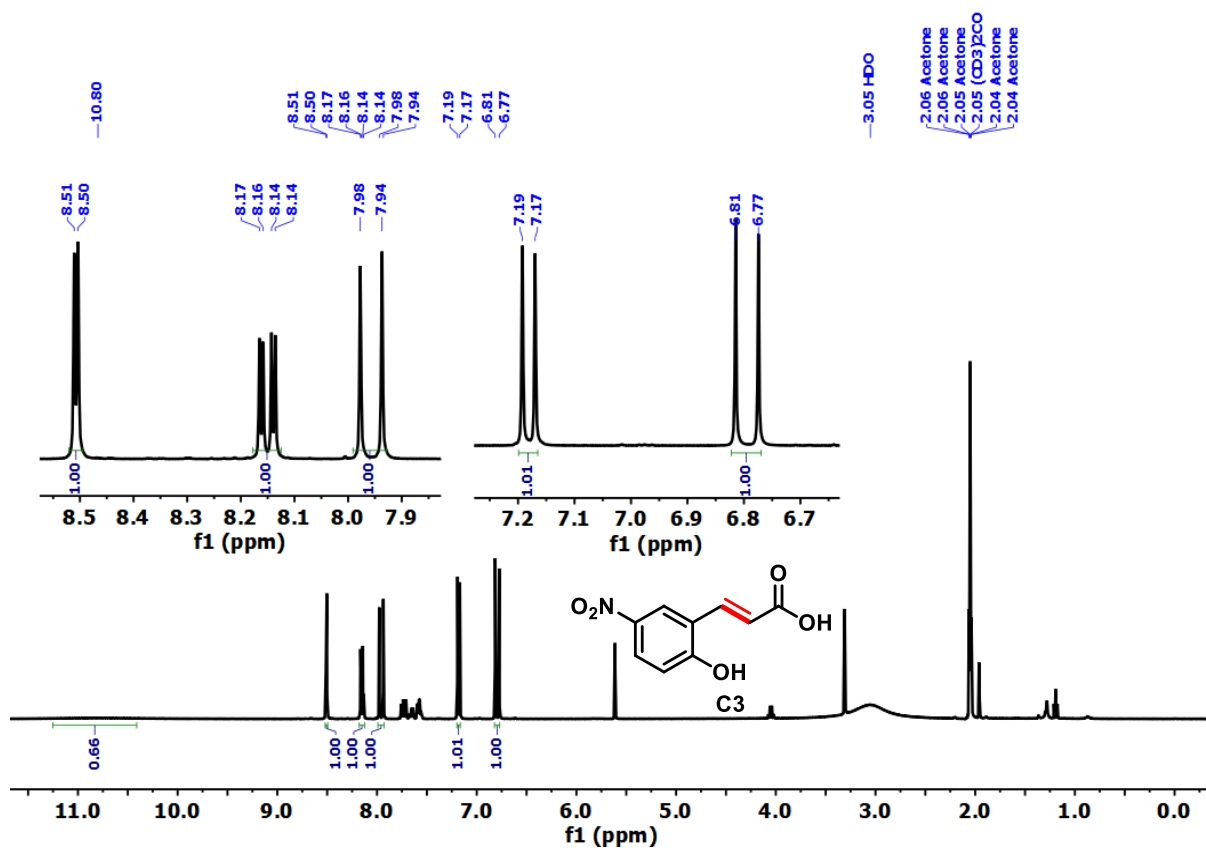
21. C. Stiefel, T. Schubert and G. E. Morlock, *ACS Omega*, 2017, **2**, 5242–5250.
22. F. Floc'h, F. Mauger, J.-R. Desmurs and A. Gard, *Perfum. Flavor.*, 2002, **27**, 32–36.
23. C. Sproll, W. Ruge, C. Andlauer, R. Godelmann and D. W. Lachenmeier, *Food Chemistry*, 2008, **109**, 462–469.
24. (a) V. B. Riatto, R. A. Pilli and M. M. Victor, *Tetrahedron*, 2008, **64**, 2279-2300; (b) H. M. C. Ferraz, F. I. Bombonato and L. S. Longo Jr., *Synthesis*, 2007, **21**, 3261-3285; (c) G. Rousseau, *Tetrahedron*, 1995, **51**, 2777-2849; (d) S. Mishra, S. Upadhyay, R. Shukla, *Front. Physiol.*, 2017, **7**, 691.
25. W. H. Perkin, *J. Chem. Soc.*, 1868, **21**, 53-63.
26. S. Tyndall, K. F. Wong and M. A. VanAlstine-Parris, *J. Org. Chem.*, 2015, **80**, 8951–8953.
27. D. H. A. Rocha, D. C. G. A. Pinto and A. M. S. Silva, *Eur. J. Org. Chem.*, 2018, 2443–2457.
28. F. Bigi, L. Chesini, R. Maggi and G. Sartori, *J. Org. Chem.* 1999, **64**, 1033-1035.
29. R. C. Fuson and N. Thomas, *J. Org. Chem.*, 1953, **18**, 1762–1766
30. C. Schultze and B. Schmidt, *J. Org. Chem.*, 2018, **83**, 5210-5224.
31. (a) K. Ahittin, M. Emre, *Curr. Microwave Chem.*, 2019, **5**, 162–178; (b) S. N. Mangasuli, K. M. Hosamani and P. B. Managutti, *Heliyon*, 2019, **5**, e01131; (c) J.-W. Jung, N.-J. Kim, H. Yun and Y. T. Han, *Molecules*, 2018, **23**, 2417.
32. M. Singh, M. Kumar, S. A. Nalawade, D. R. Puneeth Kumar and H. N. Gopi, *Org. Biomol. Chem.*, 2023, **21**, 3766-3769.
33. M. Singh, S. A. Nalawade, D. R. Puneeth Kumar, K. Veeresh, S. Pahan, S. Dey and H. N. Gopi, *Eur. J. Org. Chem.* 2023, **26**, e202300682.
34. S. M. Mali, A. Bandyopadhyay, S. V. Jadhav, M. G. Kumar and H. N. Gopi, *Org. Biomol. Chem.*, 2011, **9**, 6566-6574.
35. K. Kai, M. Mizutani, N. Kawamura, R. Yamamoto, M. Tamai, H. Yamaguchi, K. Sakata and B. I. Shimizu, *Plant J.*, 2008, **55**, 989–999.

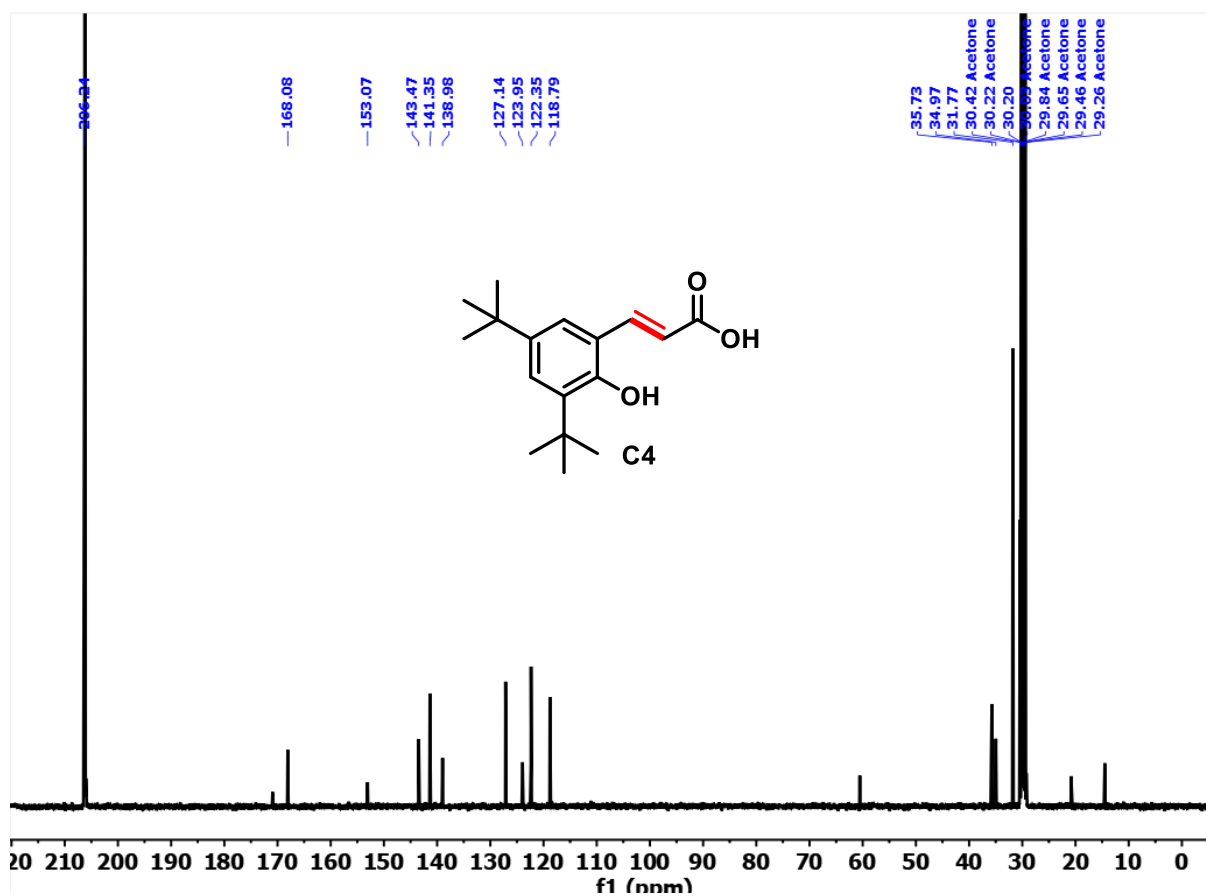
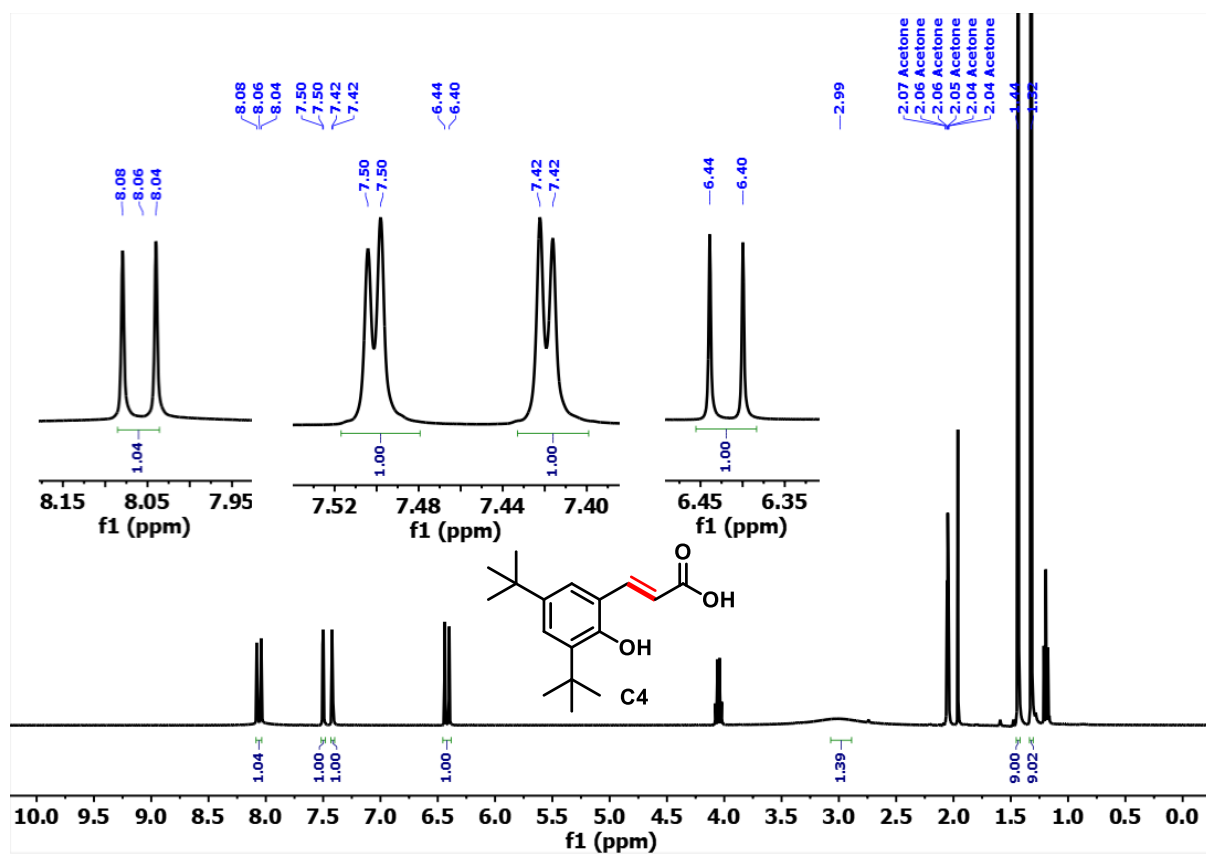
4A.9 Appendix

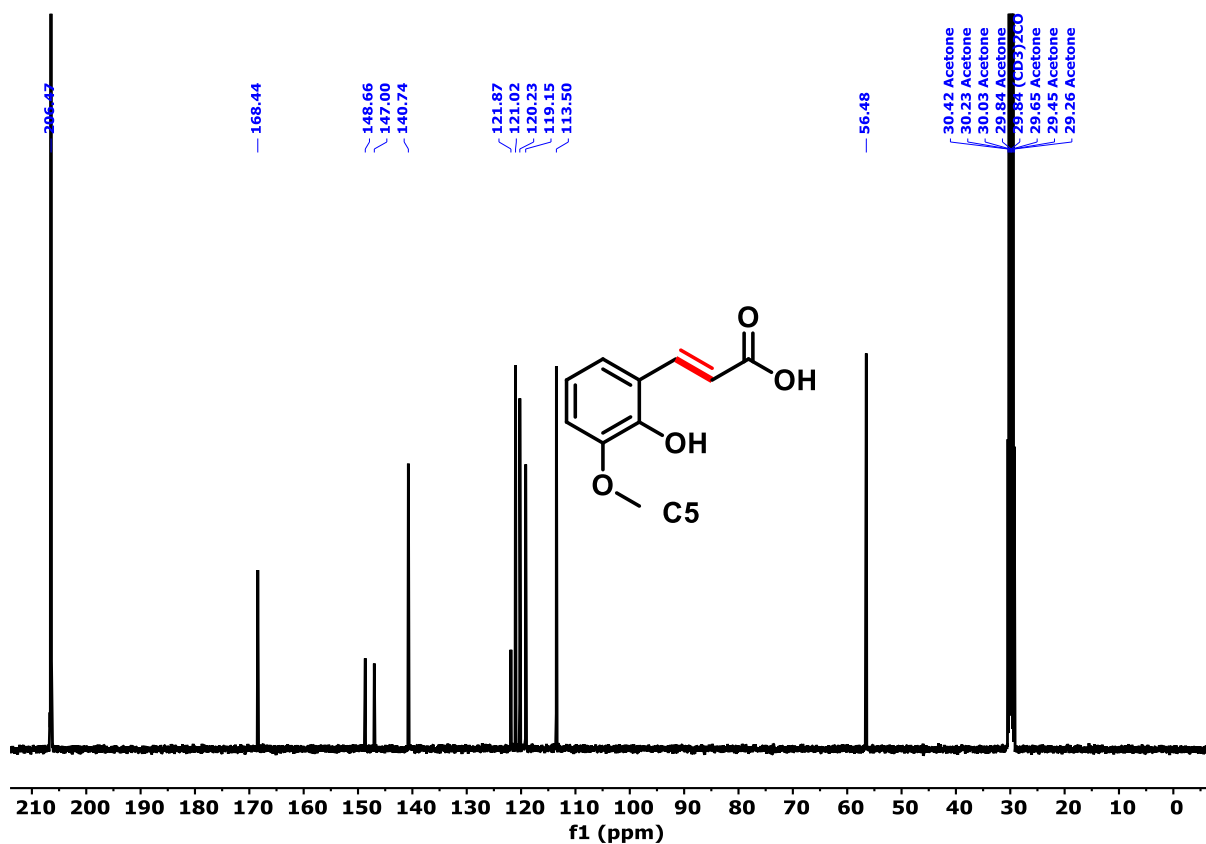
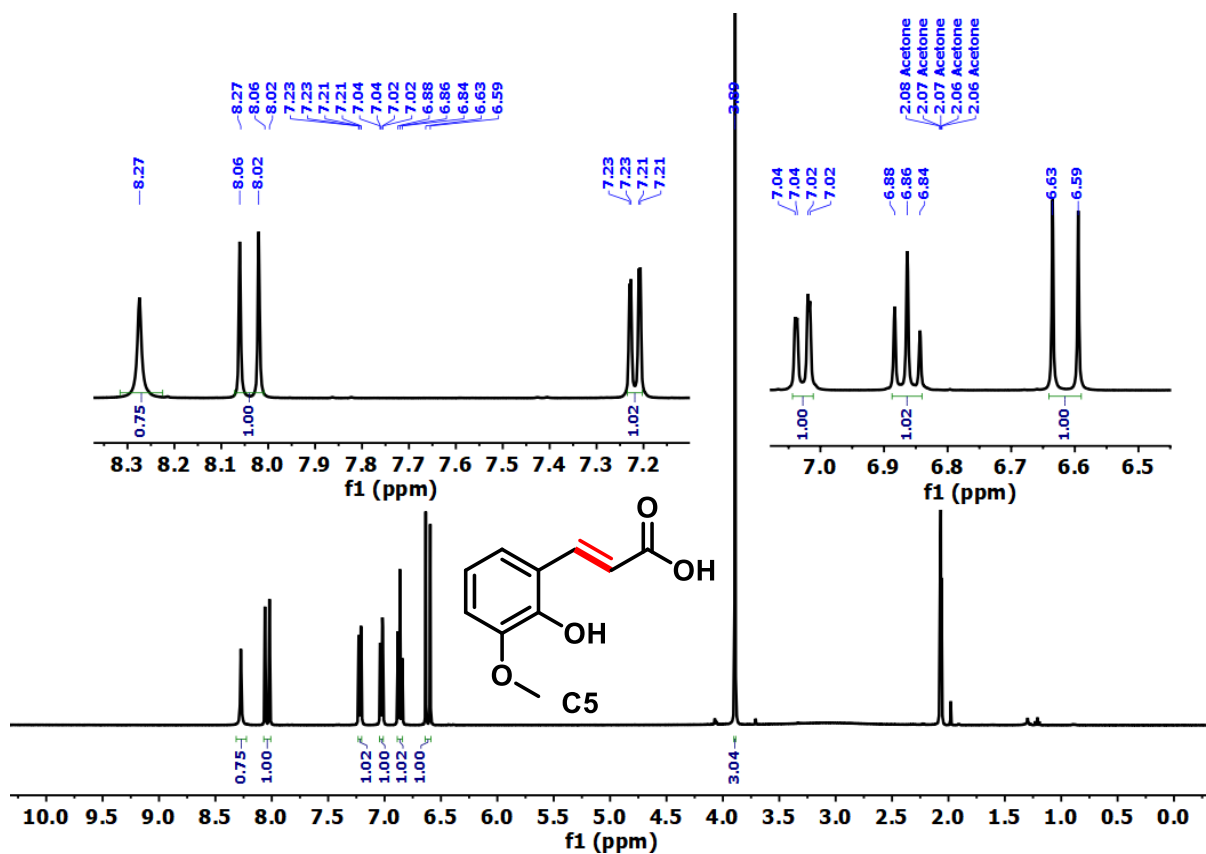
4A.9.1 ^1H and ^{13}C NMR of all compounds

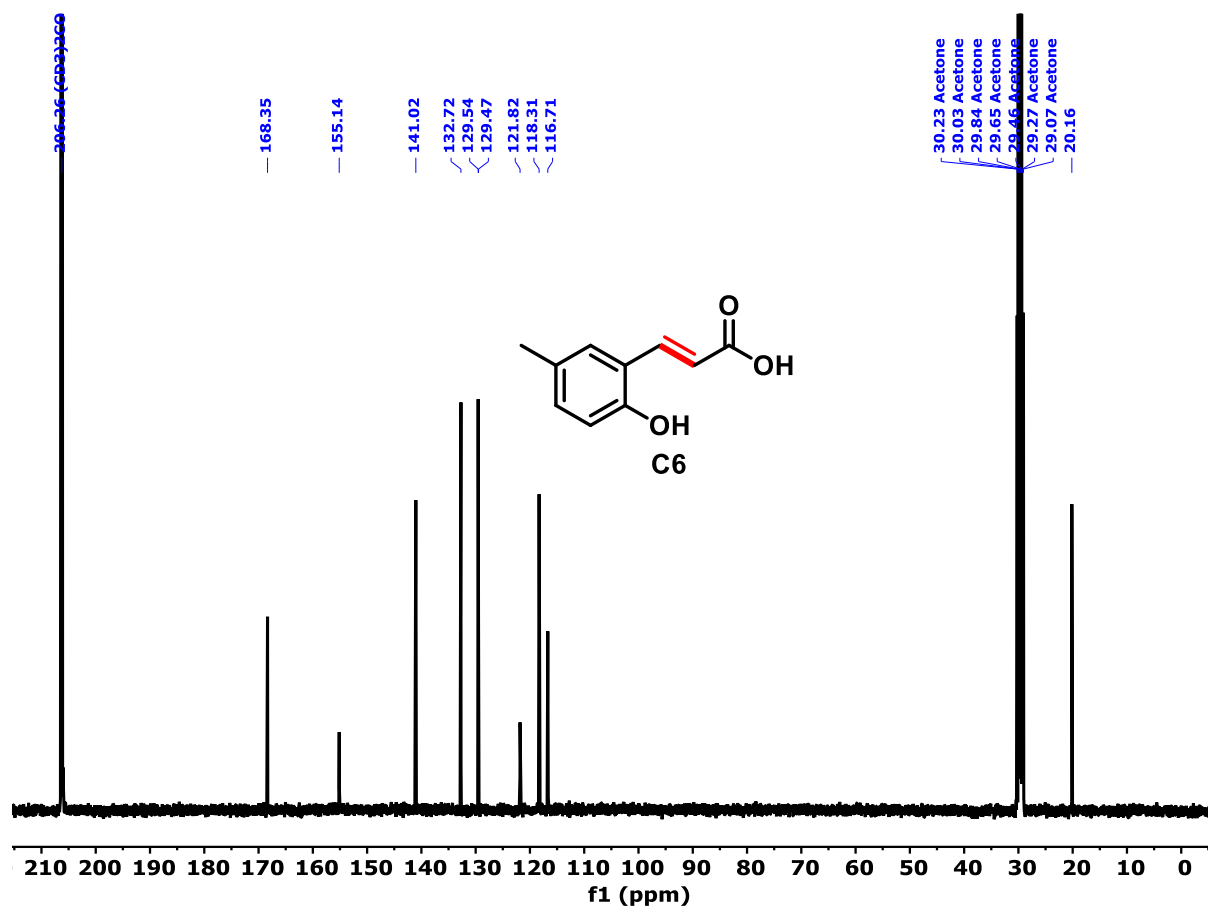
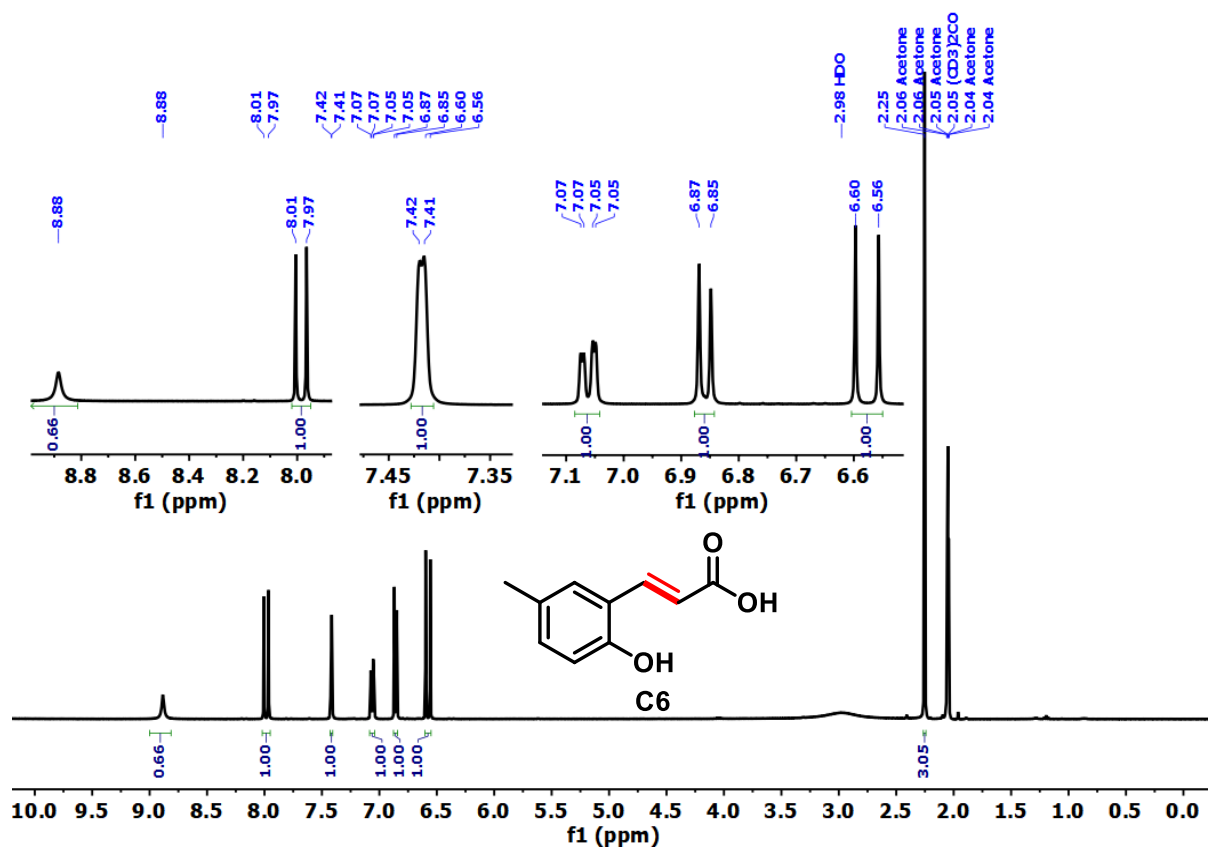


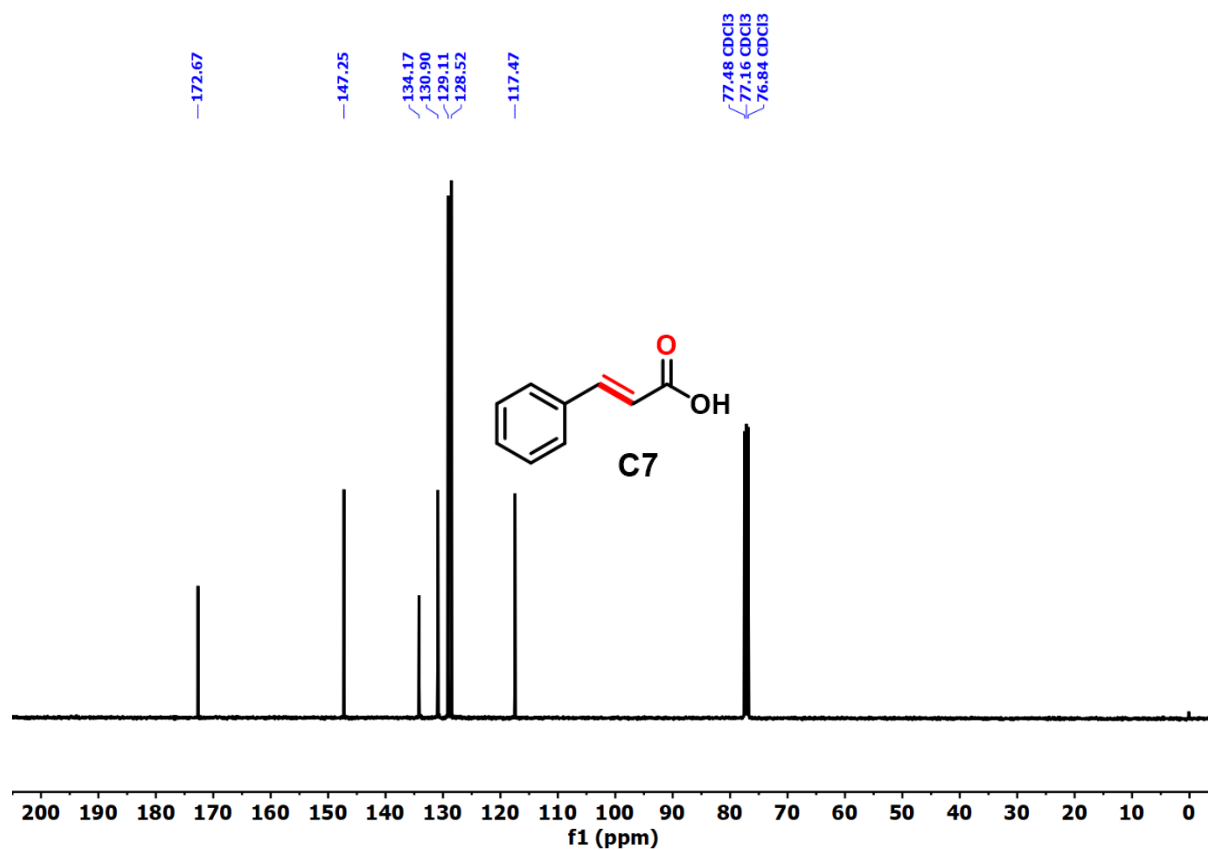
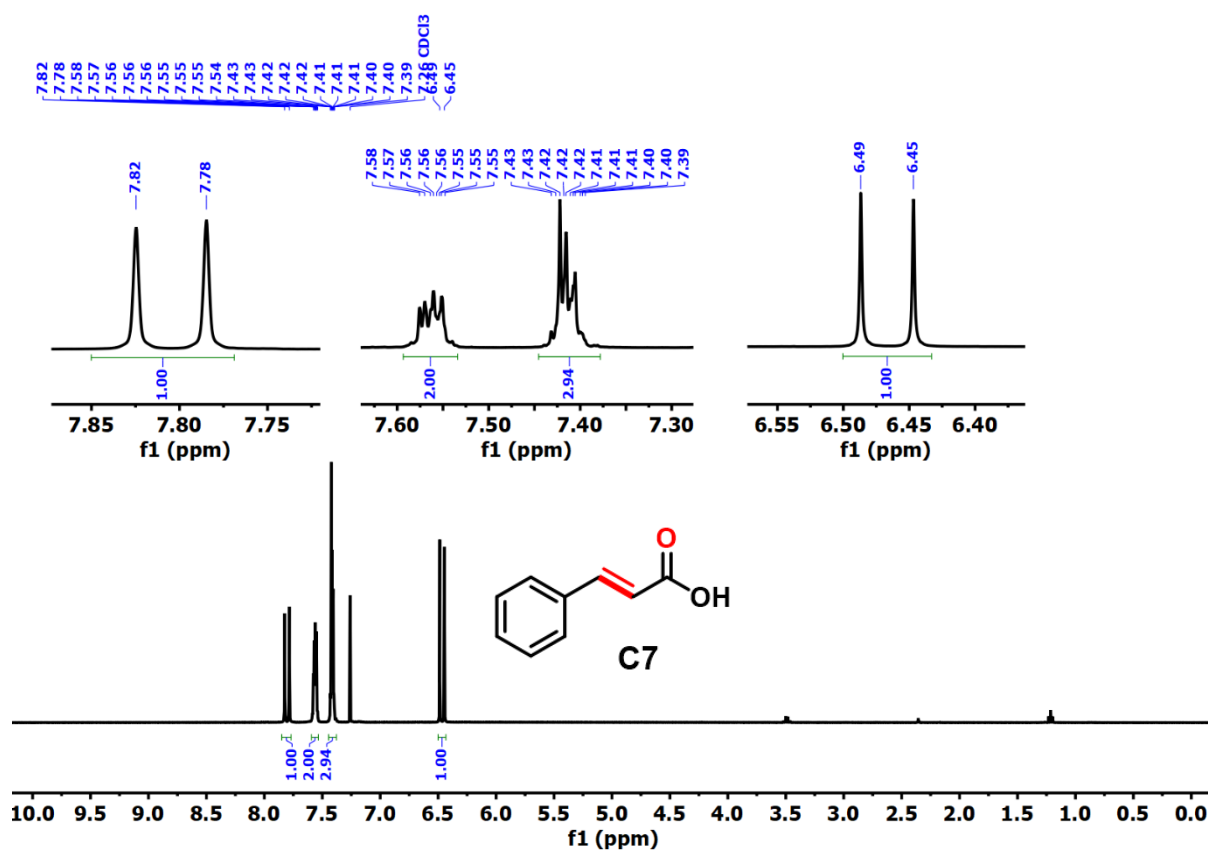


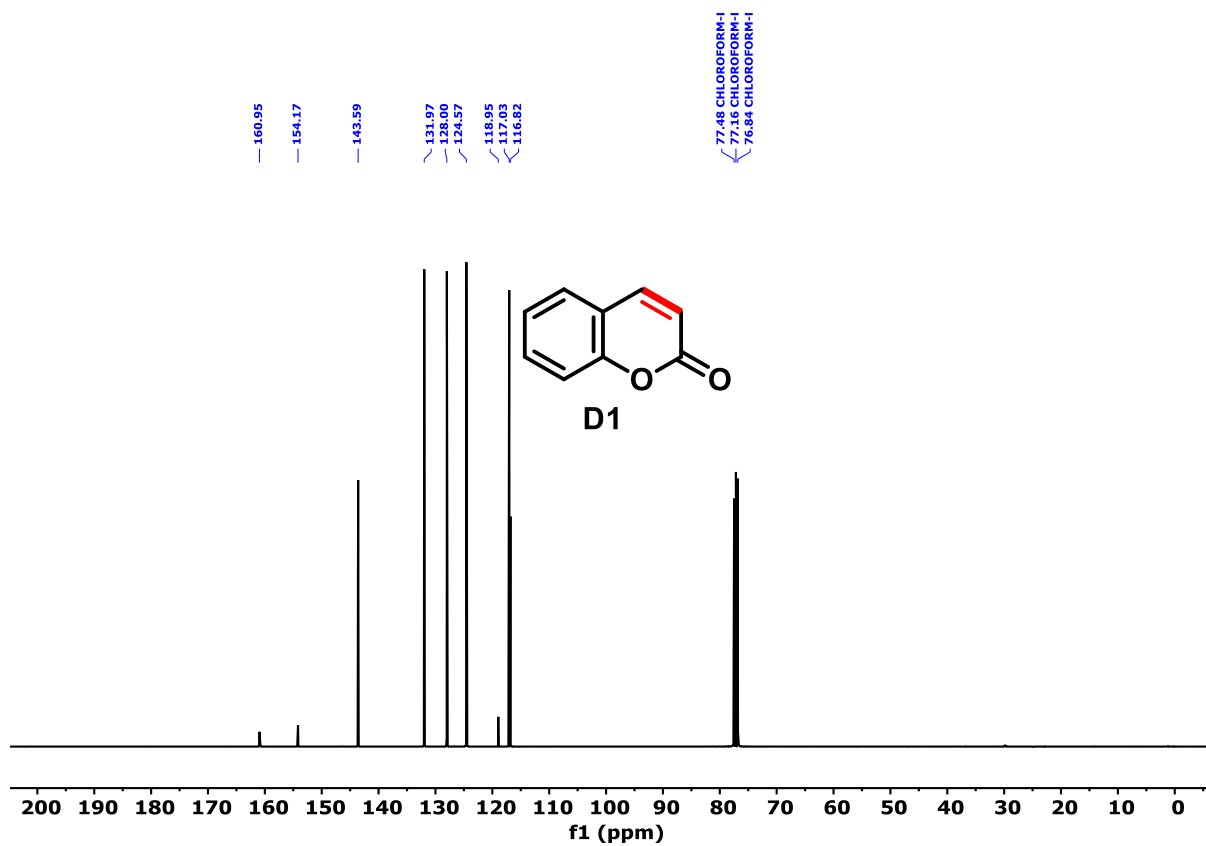
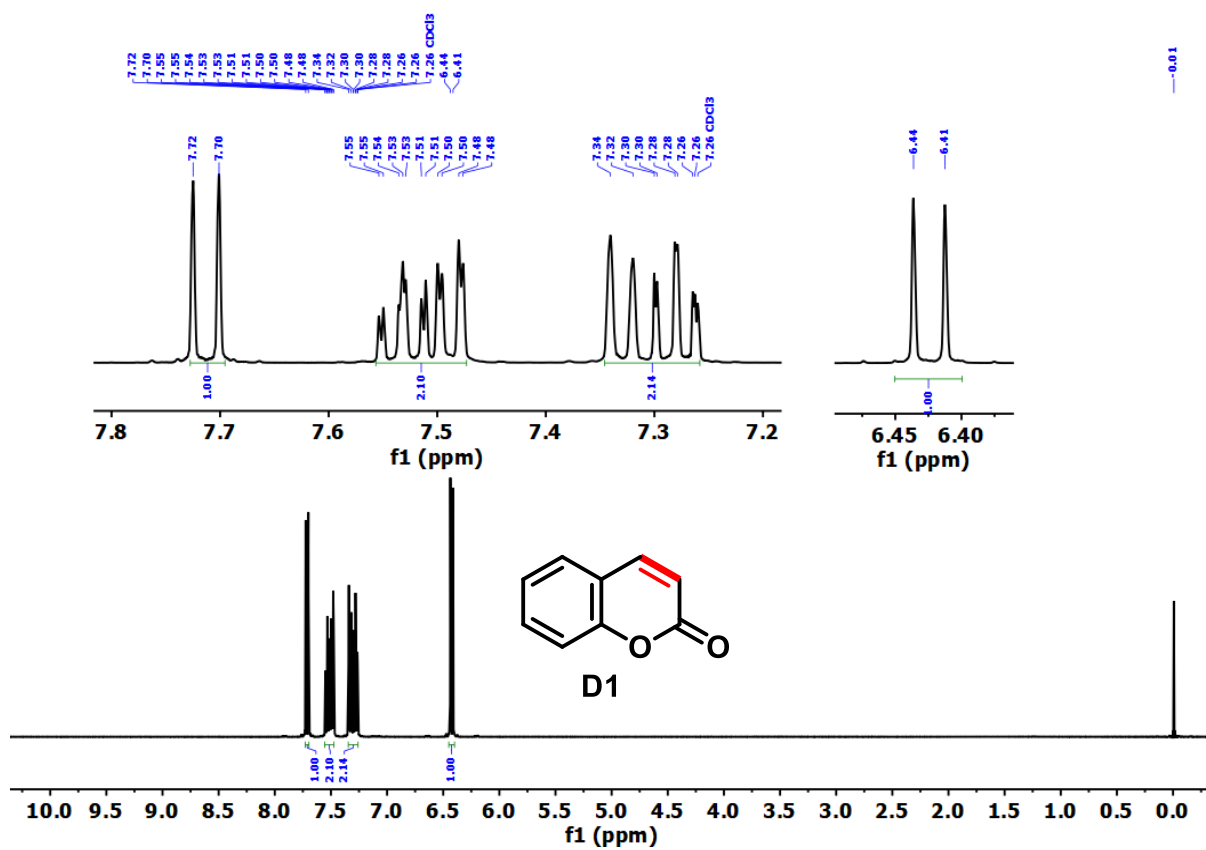


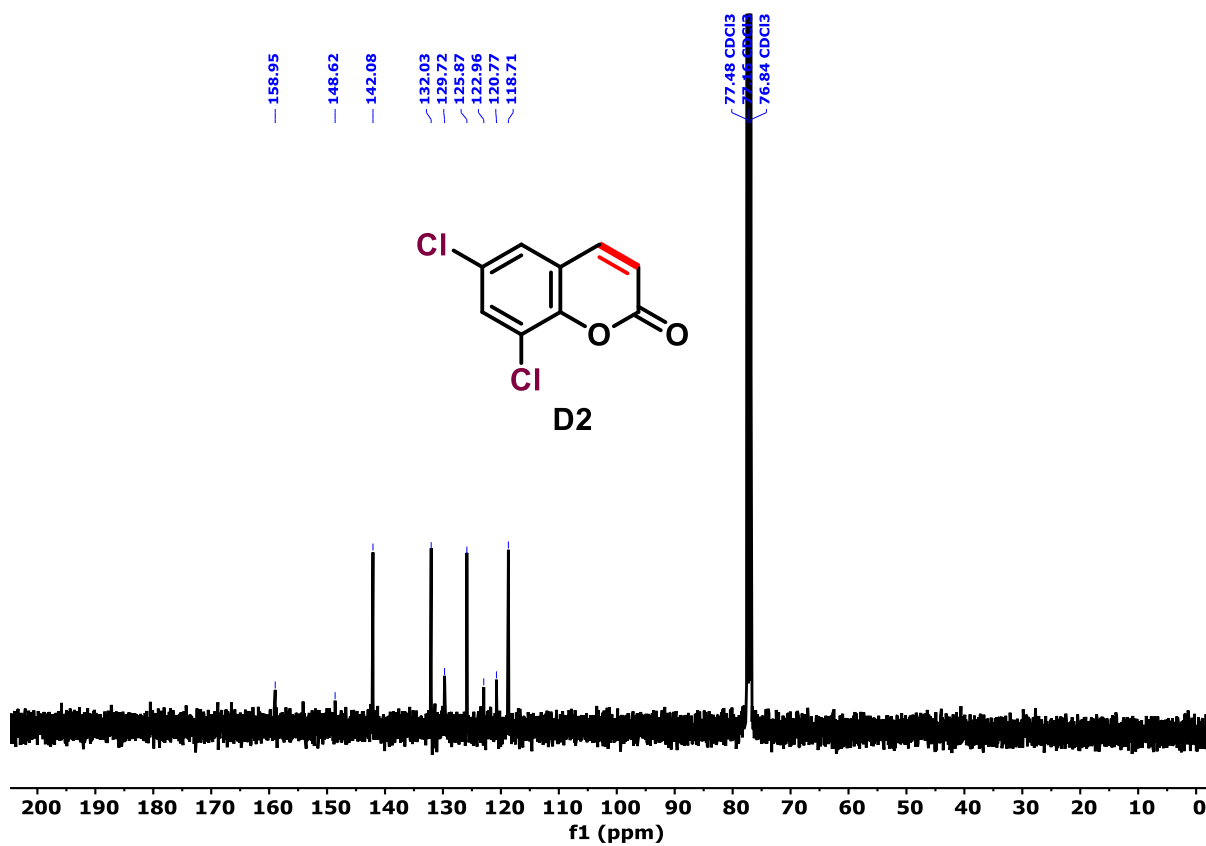
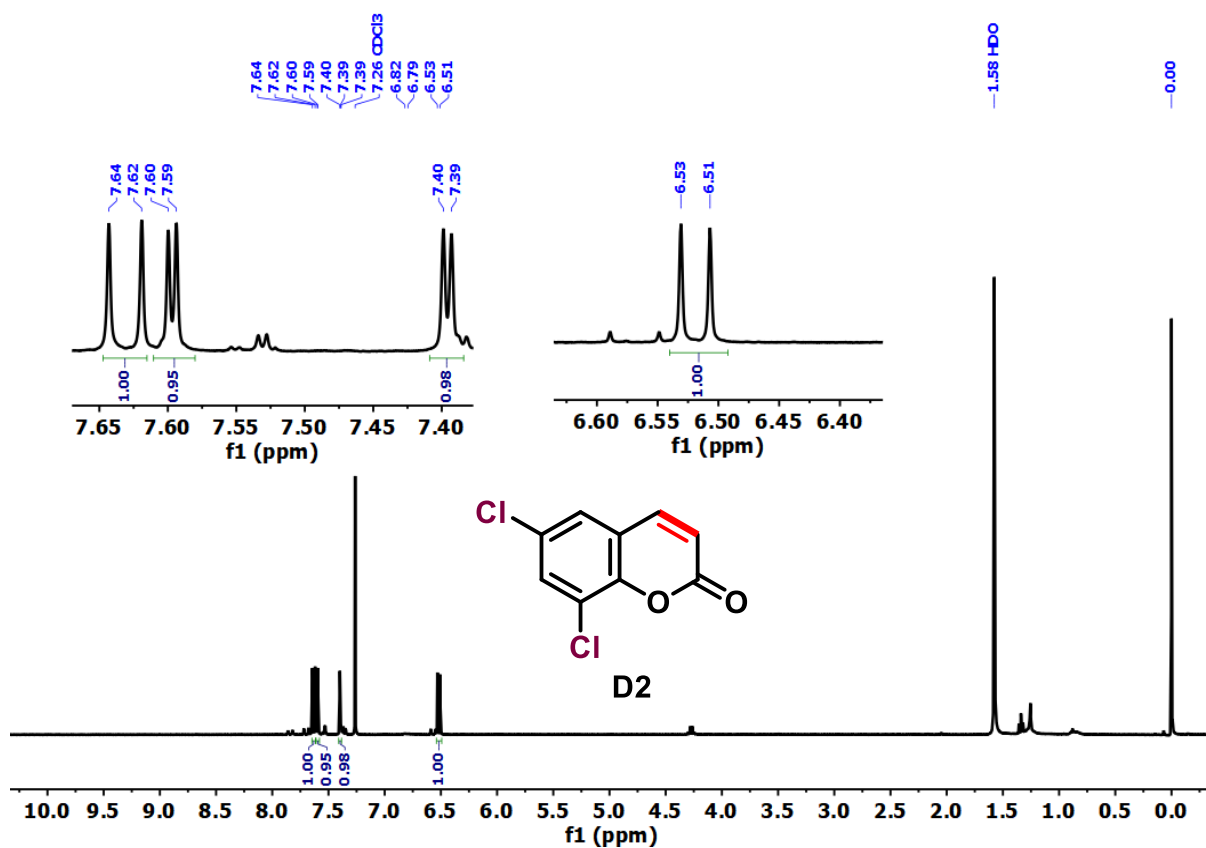


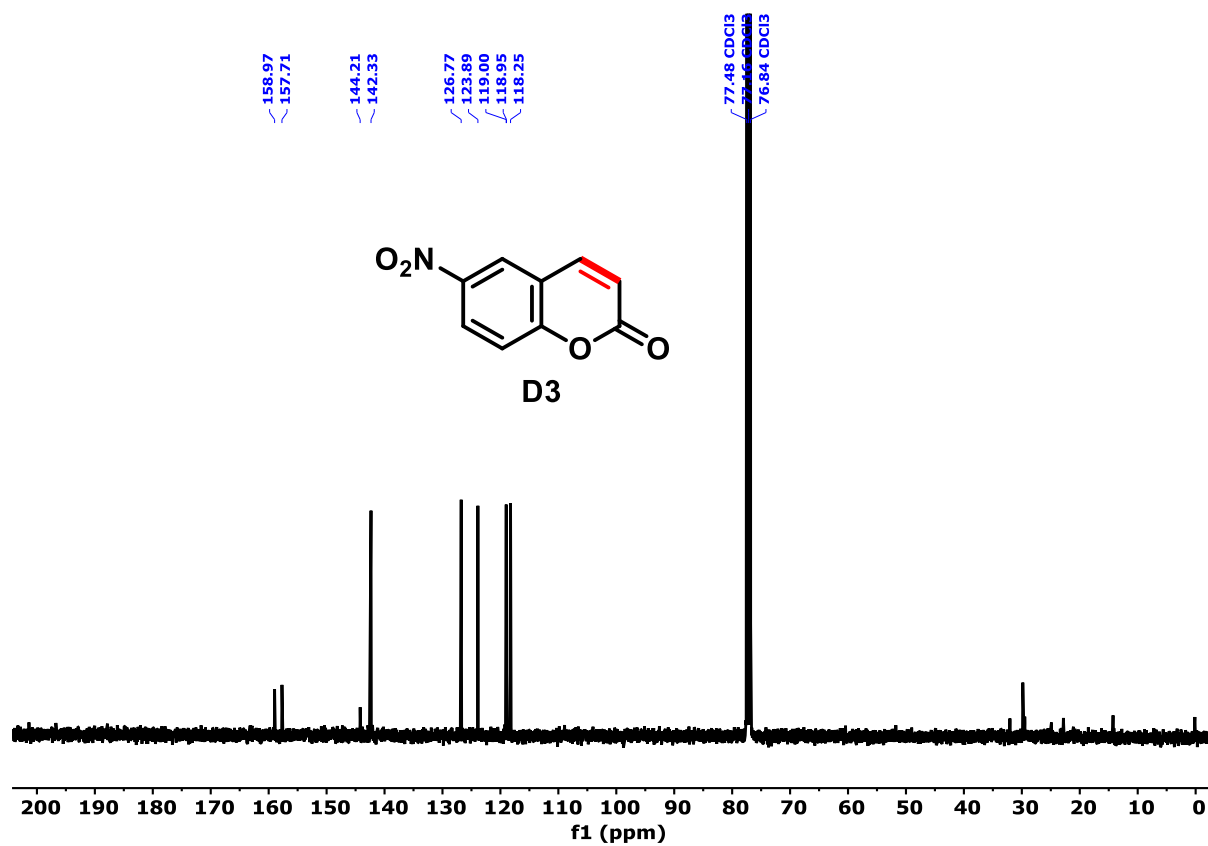
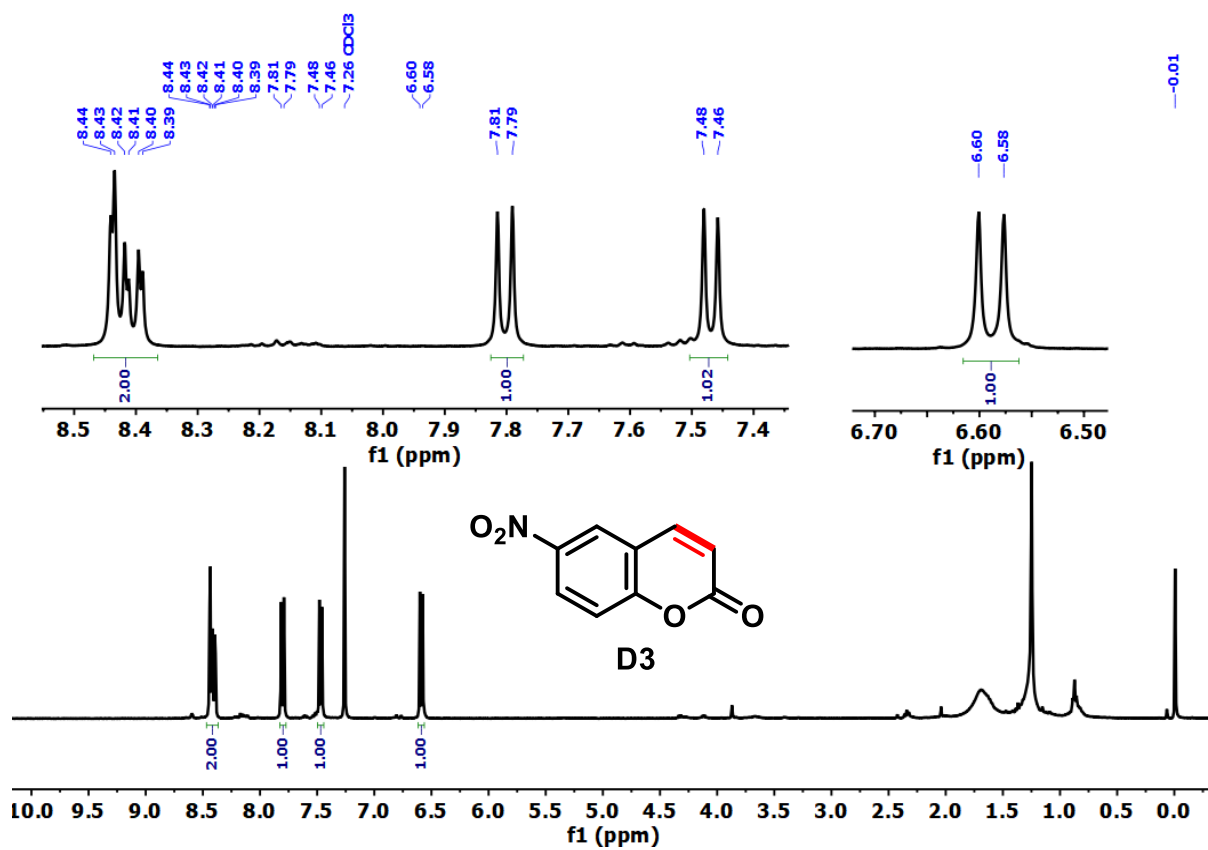


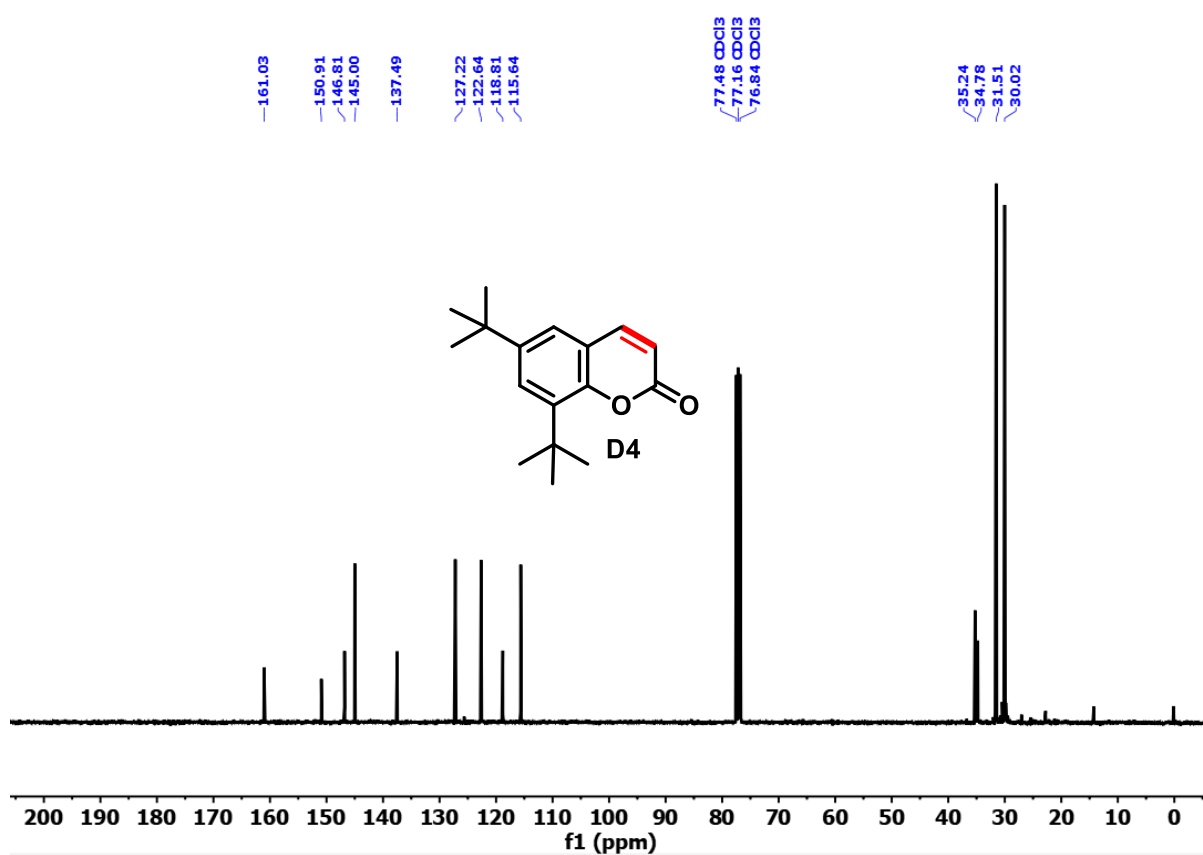
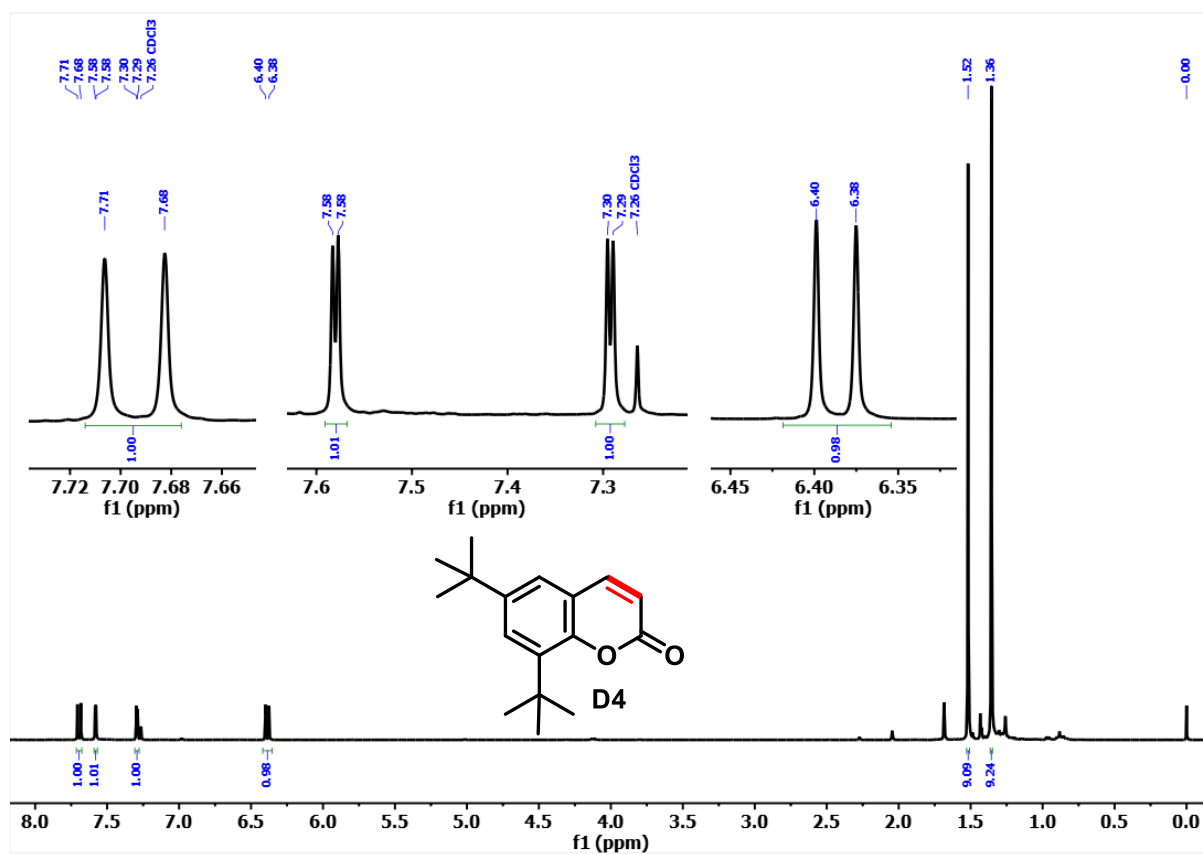


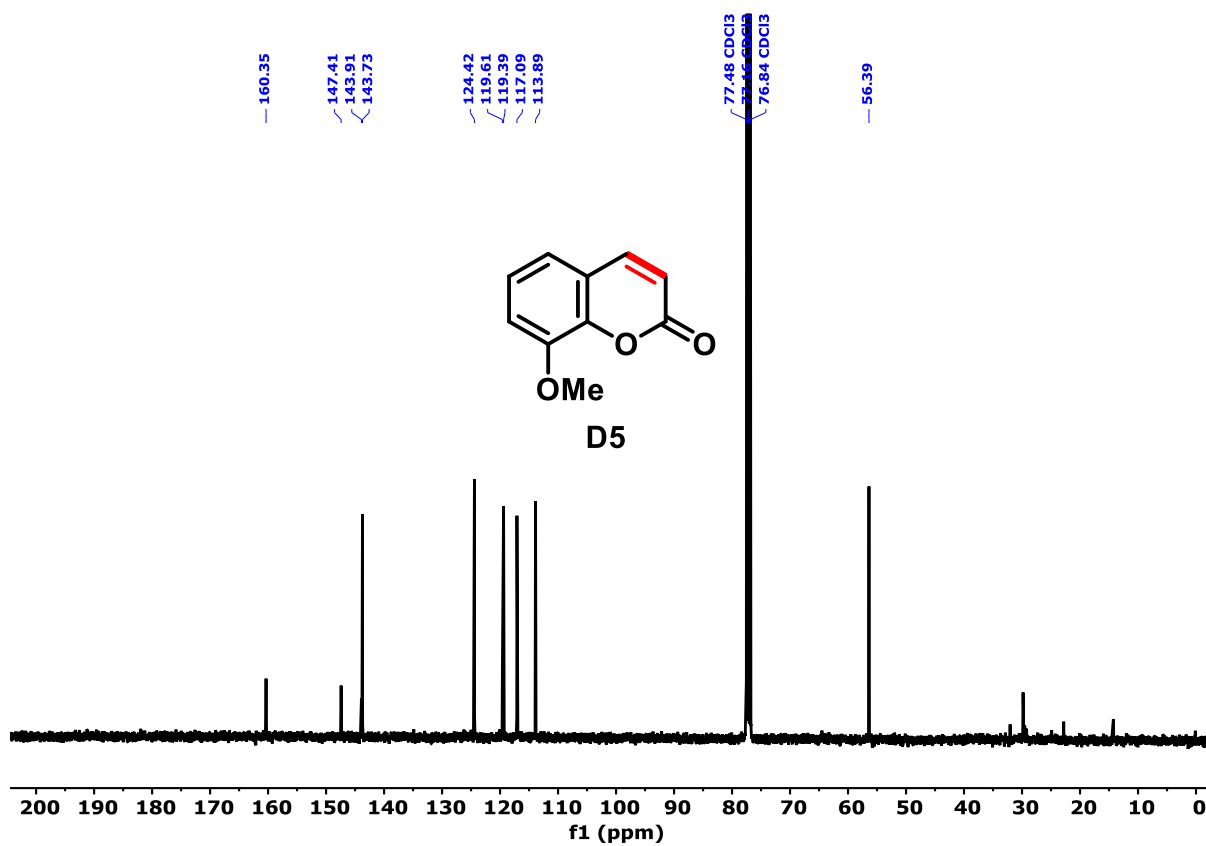
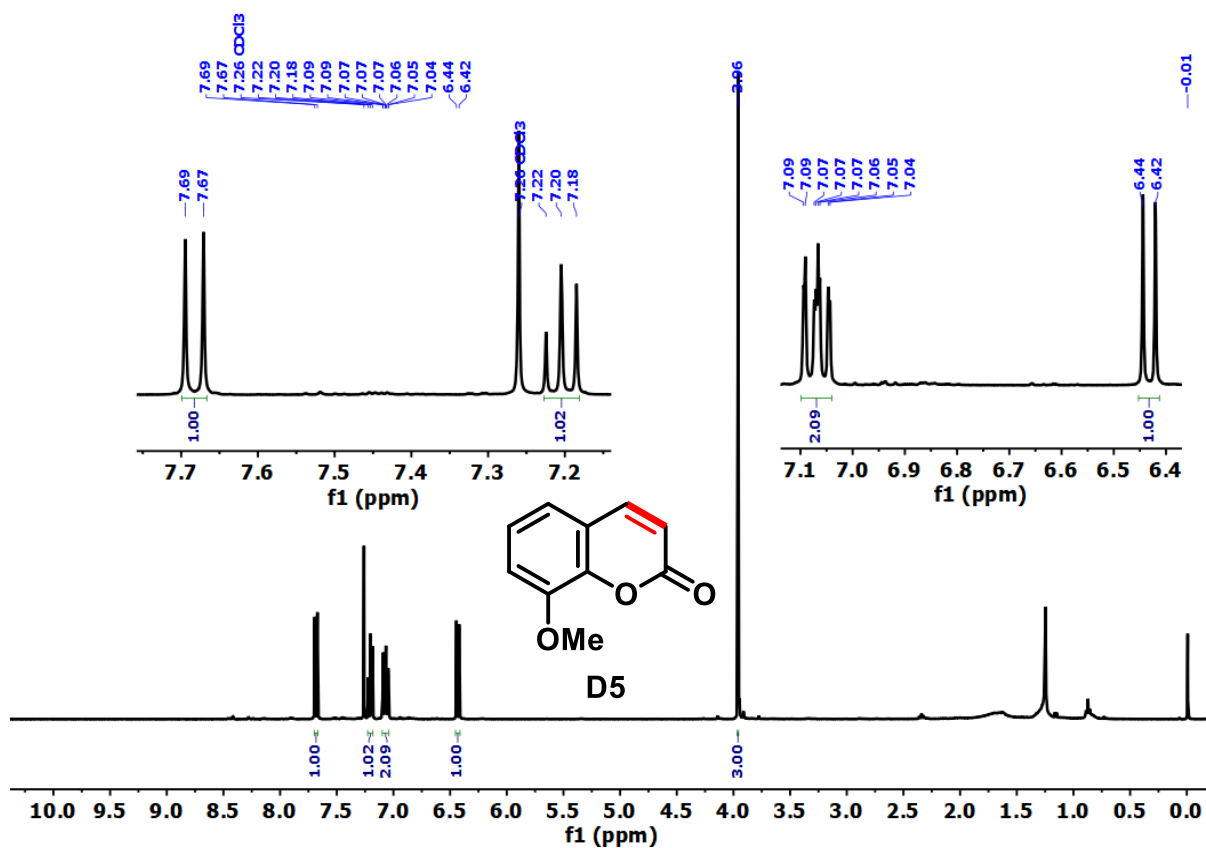


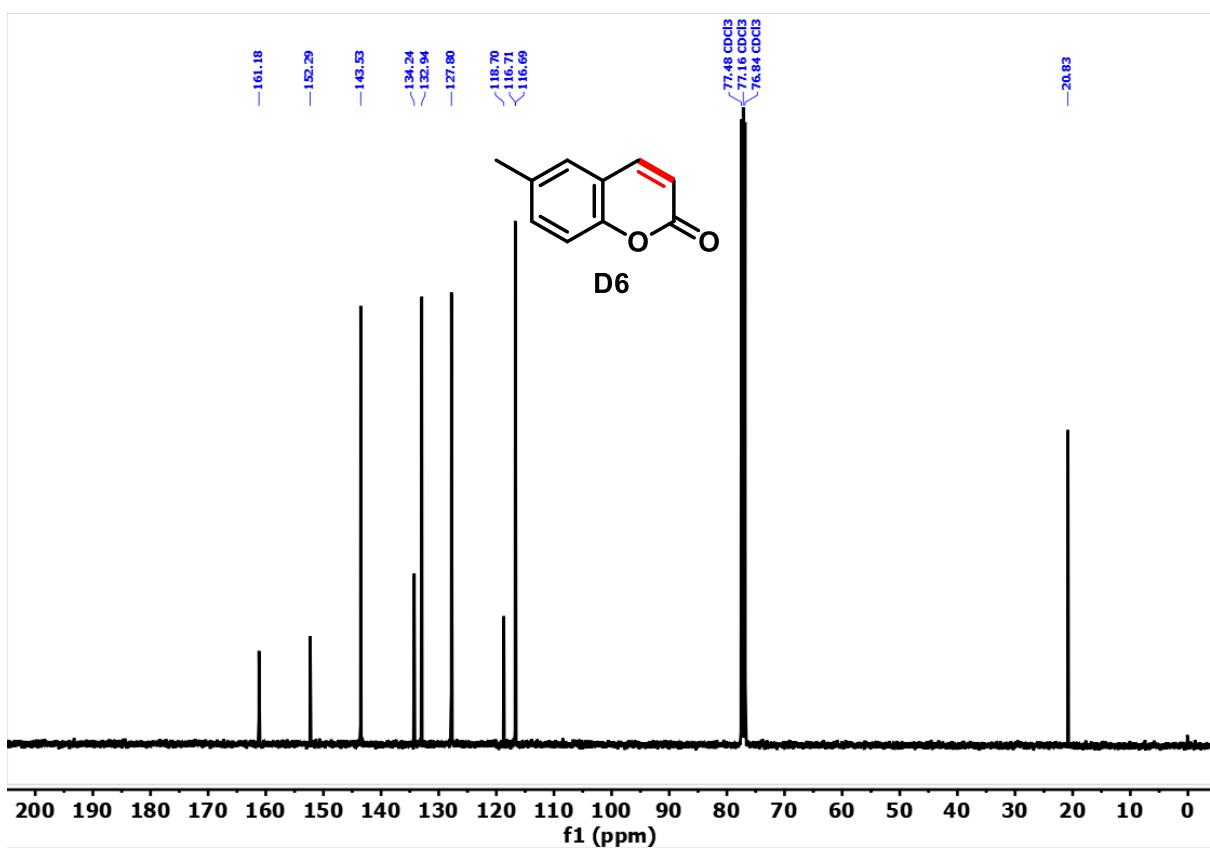
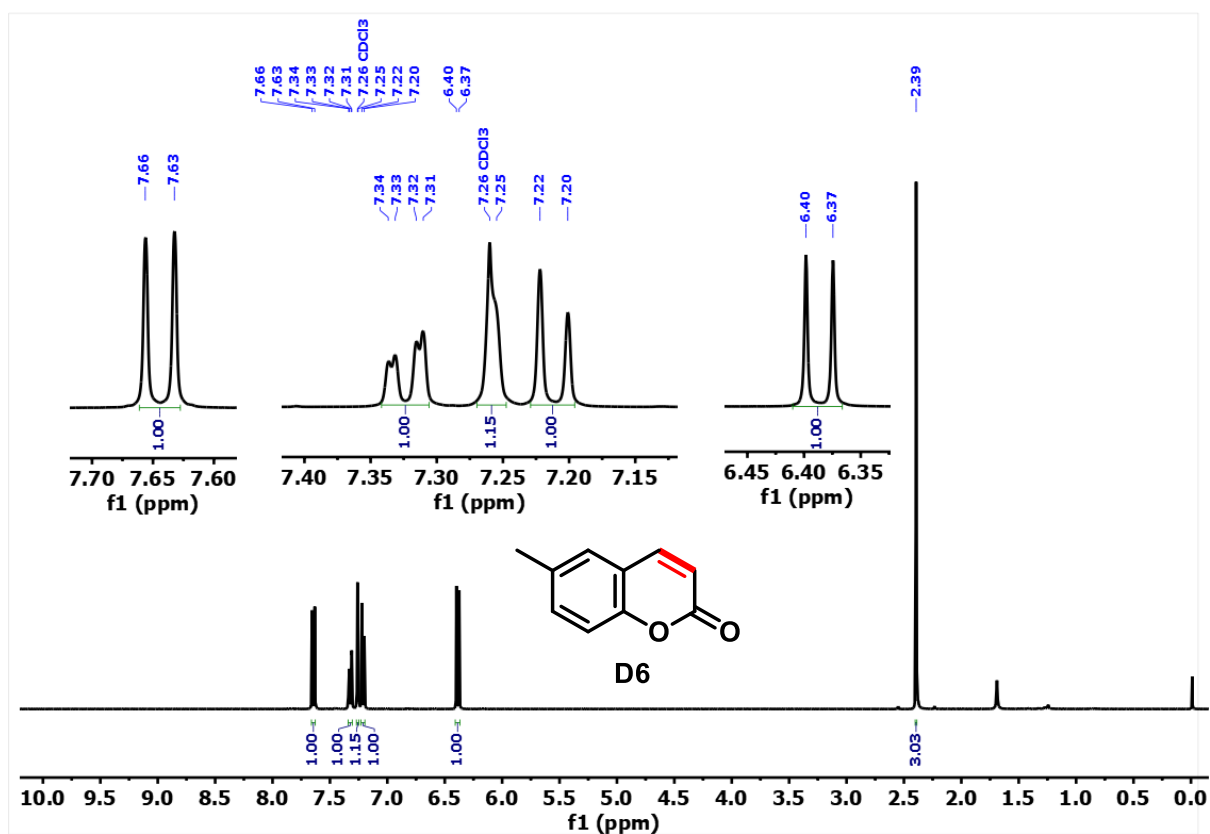












4A.9.2 Mass of all the synthesized compounds obtained from HRMS

Entry	Compound	$[M\pm Na/H]^{\pm}$	Calculated Mass	Observed Mass	Δm
1	C1	$C_9H_7O_3$	161.0602	161.0605	0.0003
2	C2	$C_9H_7Cl_2O_3$	232.9772	232.9769	0.0003
3	C3	$C_9H_6NO_5$	208.0246	208.0249	0.0003
4	C4	$C_{17}H_{23}O_3$	275.1647	275.1652	0.0005
5	C5	$C_{10}H_9O_4$	193.0501	1930.0502	0.0001
6	C6	$C_{10}H_{10}O_3Na$	201.0527	201.0529	0.0002
7	C7	$C_9H_9O_2$	149.0603	149.0604	0.0001
7	D1	$C_9H_7O_2$	147.0446	147.0441	0.0005
8	D2	$C_9H_5Cl_2O_2$	214.9666	214.9666	0
9	D3	$C_9H_6NO_4$	192.0297	192.0297	0
10	D4	$C_{17}H_{23}O_2$	259.1698	259.1698	0.0007
11	D5	$C_{10}H_9O_3$	177.0551	177.0546	0.0005
12	D6	$C_{10}H_9O_2$	161.0602	161.0605	0.0003

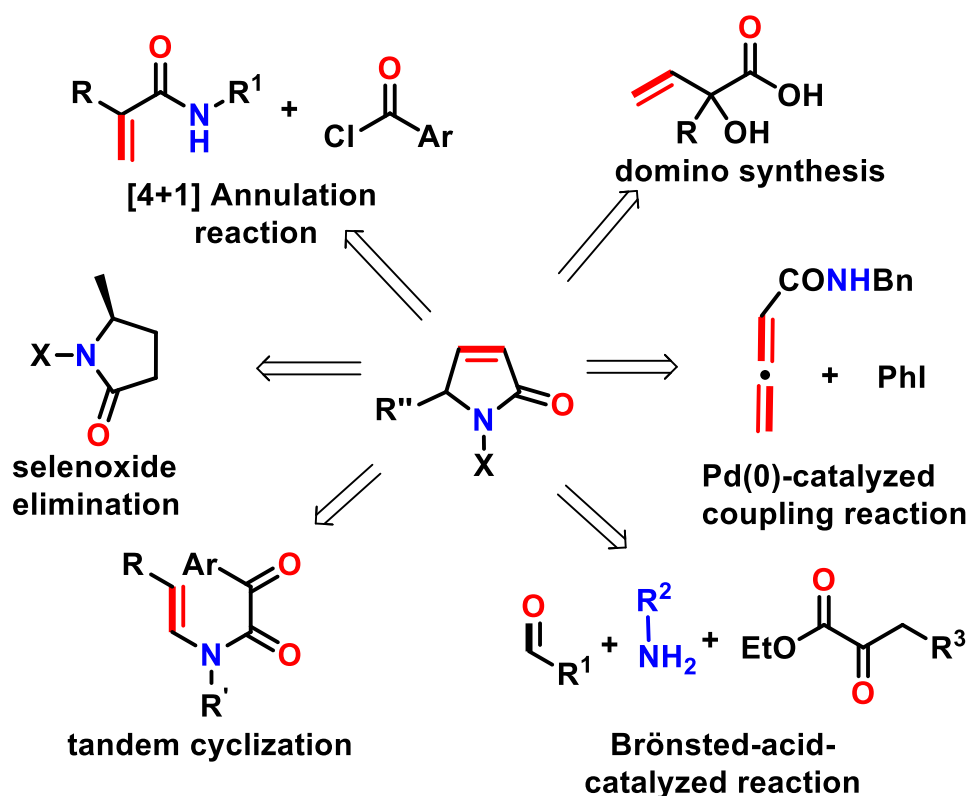
Note: Δm = Mass difference, $[M\pm Na/H]^{\pm}$ = Molecular ion.

Chapter 4B

Efficient Synthesis of Chiral α,β - Unsaturated- γ -Lactams from Z-Vinylogous Amino Acids

4B.1 Introduction

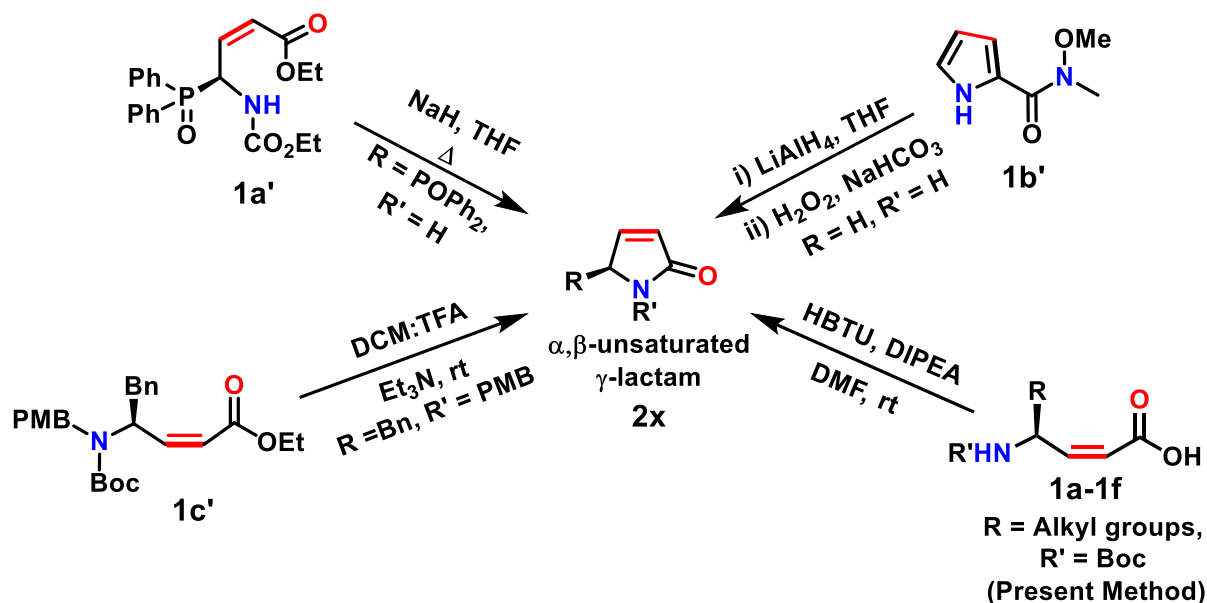
α,β -unsaturated γ -lactams are important structural components found in a diverse range of natural products, including heme metabolites, peptidic, and terpenoids natural products.¹ Their inherent structural significance has led to the development of numerous synthetic and natural products featuring the α,β -unsaturated γ -lactam core, demonstrating therapeutic potential as anti-diabetic, antimalarial, anti-inflammatory, anti-viral, anti-cancer, and anti-bacterial agents.² The widespread biological applications of α,β -unsaturated γ -lactams have sparked significant interest in their synthetic exploration. A variety of synthetic routes have been established for the synthesis of *N*-aryl/alkylated α,β -unsaturated γ -lactams.^{1,3} Recently, Kleij and coworkers⁴ reported the Pd-catalyzed domino synthesis of *N*-aryl- γ -lactams from the *in situ* generated *Z*-configured γ -amino acids. Ngai and colleagues⁵ reported the visible-light-induced excited state copper-catalyzed annulation reaction to synthesize α,β -unsaturated *N*-aryl- γ -lactam derivatives. Wang and colleagues⁶ reported the Fe-catalyzed tandem cyclization tertiary enamides to derive α,β -unsaturated *N*-alkyl- γ -lactams. In addition to the various transition metal catalysts, organocatalysts have also been developed for the synthesis of α,β -unsaturated *N*-alkyl- γ -lactams. Palacios and coworkers developed the Brönsted acid-catalyzed three-component coupling reaction for the synthesis of α,β -unsaturated *N*-aryl- γ -lactams.⁷ In addition, the synthesis of the *N*-acylated γ -lactams involves multiple steps with harsh reaction conditions. The most widely used protocol involves the acylation of saturated γ -lactam mediated by *n*-BuLi and the subsequent introduction of unsaturation.⁸⁻¹⁰ Using this protocol, Gerwick and colleagues recently reported the total synthesis of Majusculamide D.⁹ In addition, this method is only applicable to the γ -lactam consisting of an alanine side-chain. In continuation, Chen et al explored the Grignard reaction to introduce a tyrosine side-chain in the total synthesis of Ypaoamide.¹⁰ Along with their biological activity, α,β -unsaturated γ -lactams are also valuable precursors for the synthesis of saturated γ -lactams.¹¹ Despite this wide range of applications of α,β -unsaturated γ -lactams, currently there are not many methods available for the synthesis of *N*-acylated α,β -unsaturated γ -lactam with broad side-chain specificity. In the previous chapters, we have demonstrated *Z*- γ -lactams from (*E*)- α,β -unsaturated γ -amino acids with complete racemization. Based on the mechanism of the reaction, we anticipated that chiral *Z*- γ -lactams can be synthesized starting from *Z*- α,β -unsaturated γ -amino acids. In this chapter, we examined our hypothesis whether or not *Z*- α,β -unsaturated γ -amino acids can be transformed into chiral *Z*- γ -lactams.



Scheme 1. Selected reported protocols for the synthesis of α,β -unsaturated γ -lactams.

Previously only few reports are available on the cyclization of *Z*-vinyllogous compounds, the group of Palacios and colleagues treated *Z*-vinyllogous aminoalkylphosphine oxide (**1a'**) with sodium hydride followed by heating to generate α,β -unsaturated γ -lactams (**2a'**),^{12a} Pelkey and colleagues did the reduction of pyrrole Weinreb amides (**1b'**) followed by the oxidation of product formed using hydrogen peroxide in sodium bicarbonate to give α,β -unsaturated γ -lactams (**2b'**),^{12b} and Pearson and colleagues have introduced the deprotection strategy of *Z*-vinyllogous amino ester (**1c'**) using trifluoroacetic acid (TFA) to synthesize α,β -unsaturated γ -lactams (**2c'**).^{12c} All these methods are collectively depicted in Scheme 2. Moreover, we have displayed how *N*-protected *E*- α,β -unsaturated γ -amino acids can be transformed into corresponding α,β -unsaturated γ -lactams through *in-situ* carboxylic acid activation using the coupling reagents HBTU/HATU and DIPEA in chapter 3A and 3B, but unfortunately, we end up with racemized products in case of 3A.¹³ Based on the experimental evidence we proposed a reaction mechanism for the lactamization reaction in chapter 3A, where we observed that the last step in the cyclization process is the conversion of *N*-protected *Z*- α,β -unsaturated γ -amino acids into the α,β -unsaturated γ -lactams, depicted in Scheme 3.^{13a} With this idea we try to synthesize *Z*-vinyllogous amino acids using the Horner-Wadsworth-Emmons (HWE) reaction,¹⁴ and further we analyzed their cyclization reaction. The *N*-protected *Z*-amino acids do not

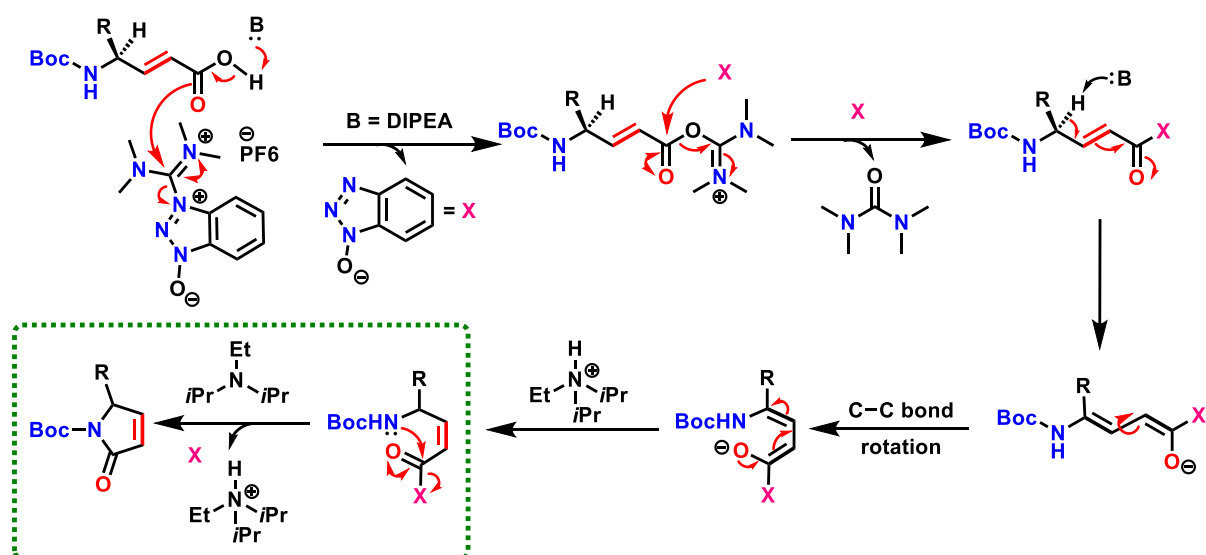
require *cis-trans* isomerization to produce α,β -unsaturated γ -lactams when treated with HBTU and DIPEA. We assumed that in this case, abstraction of a proton by base is not required to trigger the initiation of cyclization as a result we may obtain optically pure α,β -unsaturated γ -lactams.



Scheme 2. Different ways of synthesizing α,β -unsaturated γ -lactam using *Z*-vinylogous amino esters, *Z*-vinylogous amino acids, and pyrrole Weinreb amides.

4B.2 Aim and Rationale of the Present Work

To understand the configurational effect (*E* and *Z*) on the cyclization product of the α,β -unsaturated amino acids, the *Z*-isomers were synthesized. The *N*-Boc-*Z*- α,β -unsaturated amino acids were treated exactly similar to the *N*-Boc-*E*- α,β -unsaturated amino acids utilizing HBTU and DIPEA as a coupling reagent and activator base respectively. The outcome of the cyclization reaction was analyzed using various techniques. In peptide chemistry, coupling reagents such as HBTU (Hexafluorophosphate Benzotriazole Tetramethyl Uronium) are generally used to make amide bonds by activating the carboxylic group of amino acids for the nucleophilic attack.^{15,16}

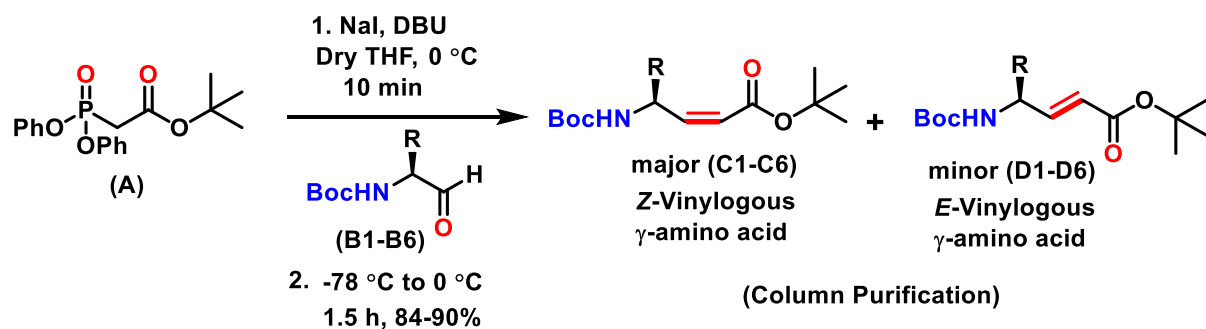


Scheme 3. The role of *Z*-configuration is highlighted in the last step of the cyclization reaction of *E*-vinylogous amino acid.

4B.3 Result and Discussion

4B.3.1 Synthesis of Boc-*Z*-vinylogous Amino Esters

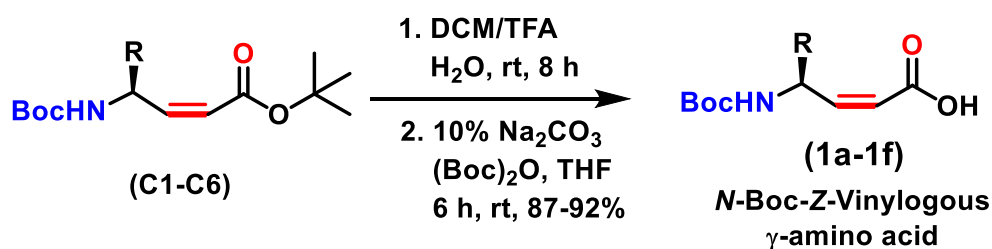
Synthesis of the *N*-protected *Z*-vinylogous amino acids from *N*-protected amino aldehyde is a tedious task. However, the *Z*- α,β -unsaturated amino esters can be prepared using the HWE reaction with little ease.¹⁴ In this reaction *tert*-butyl (diphenylphosphono)acetate **A** was treated with *N*-Boc-amino aldehyde (**B1-B6**) in the presence of NaI and DBU base at -78°C . The NaI salt acts as a transition state stabilizer which ultimately leads to the formation of *N*-protected-*Z*- α,β -unsaturated amino esters (**C1-C6**) as a major product, the reaction mixture was purified through column chromatography. The pictorial representation of the *Z*-vinylogous amino esters formation is depicted in Scheme 4.



Scheme 4. Synthesis of *N*-protected *Z*-vinylogous amino esters using HWE reaction.

4B.3.2 Synthesis of Boc-Z-vinylogous Amino Acids

These Z-vinylogous amino esters contain the Boc- group at the N-terminus and the tertiary butyl- group at the C-terminus. Further treatment of **C1-C6** with TFA in the presence of a catalytic amount of water removes both the protecting groups, which leads to unprotected Z-vinylogous amino acids. Subsequently, Boc- protection was done to get the desired final product, which is *N*-Boc-Z- α,β -unsaturated γ -amino acids (**1a-1f**), depicted in Scheme 5. All the compounds were purified and characterized before utilizing them for further synthesis. The analysis of the *N*-protected Z-vinylogous amino formation was done using the ^1H NMR technique, as this technique can distinguish between *E*-configuration and *Z*-configuration. The coupling constant (*J*) of the alkene protons differs remarkably for *E*- and *Z*-alkene, generally coupling constant value of *E*-alkenes is around 15-16 Hz whereas the coupling constant value of *Z*-alkenes is around 11-12 Hz. After cyclization, the coupling constant value of alkene protons in the product changed significantly and appeared around 6.0-6.2 Hz. However, the coupling constant values of *E/Z*-vinylogous amino acids are quite different from each other but their products have a similar set of coupling constant values.



Scheme 5. Synthesis of *N*-protected Z-vinylogous amino acids.

4B.3.3 Synthesis of α,β -Unsaturated γ -Lactams from Z-vinylogous Amino Acids

We exploited the optimized reaction conditions used for the cyclization of *E*-vinylogous amino acids except for the time parameter which is 2 hours less than that of the *E*-vinylogous amino acids, which may be because of the preorganized *cis* configuration of the reactant for the cyclization reaction. Having the desired starting material (**1a-1f**, *Z*-vinylogous amino acid) and optimized reaction conditions from Chapter 3A in hand, we examined the synthesis of α,β -unsaturated γ -lactams from the *N*-Boc-Z-vinylogous amino acids. In this context, **1a-1f** were treated with the HBTU and DIPEA under standard coupling conditions. It was assumed that *N*-Boc-Z-vinylogous amino acids would produce α,β -unsaturated γ -lactams similar to the *N*-Boc-*E*-vinylogous amino acids *via in-situ* activation. It was observed that the cyclization reaction was almost completed in the duration of 4 hours to produce α,β -unsaturated γ -lactams (**2a-2f**)

with good yields. The substrate of the reaction is depicted in Table 1. Interestingly it was found that α,β -unsaturated γ -lactams produced in this pathway were optically pure, which was confirmed by HPLC analysis using a chiral column as a stationary phase. The HPLC profile of **2a-2d** is depicted in Figure 1, suggesting the formation of a single isomer through a lactamization reaction. Very similar information was obtained through specific rotation $[\alpha]$ analysis of these compounds, where significant $[\alpha]$ values corresponding to the single isomer of α,β -unsaturated γ -lactams were obtained.

Table 1: Synthesis of optically pure γ -lactams from Z-vinylogous amino acids.

Reaction scheme showing the conversion of a Z-vinylogous amino acid (1) to an optically pure γ -lactam (2) using HBTU, DIPEA, and DMF at 0 °C to room temperature for 4 h.

Compound Code	Z-Vinylogous amino acid (1)	α,β -unsaturated γ -lactam (2)	%Yield
a			88%
b			87%
c			82%
d			90%
e			86%
f			84%

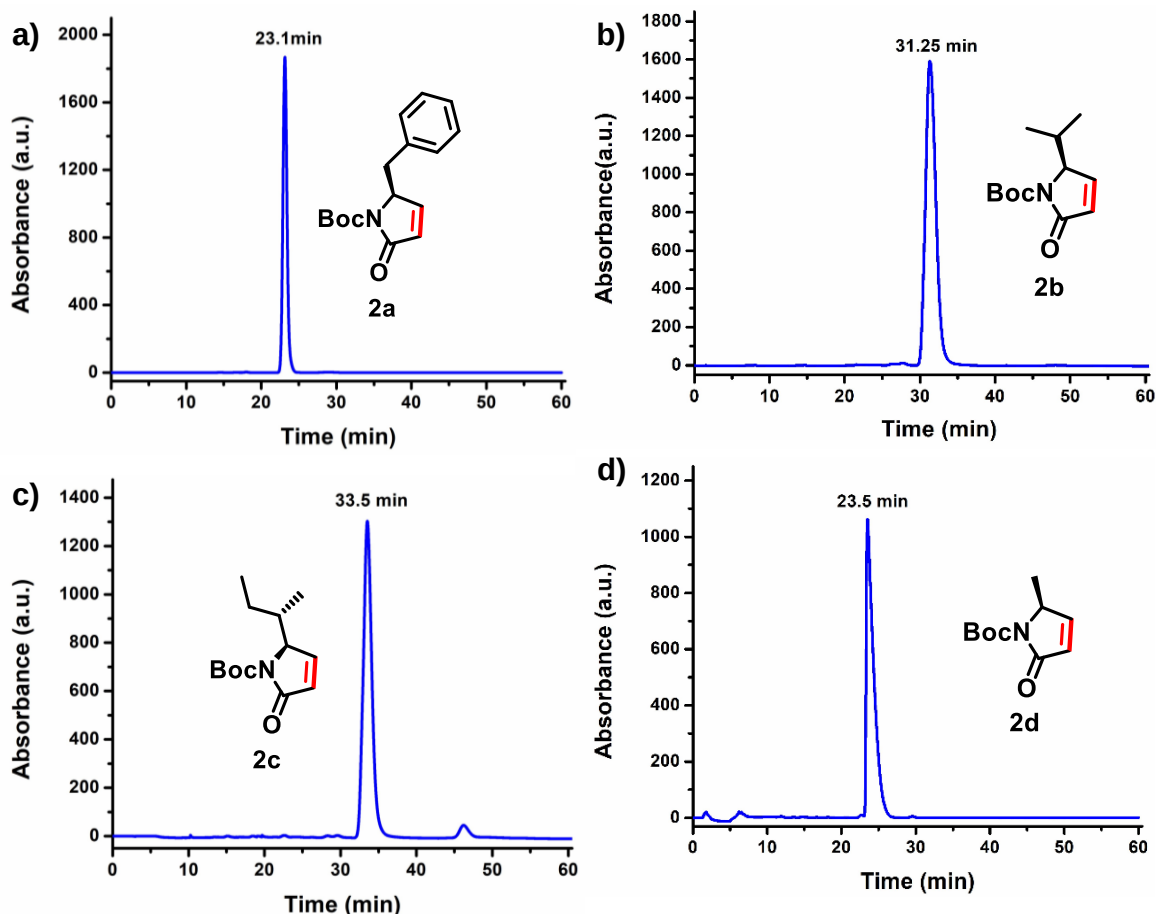
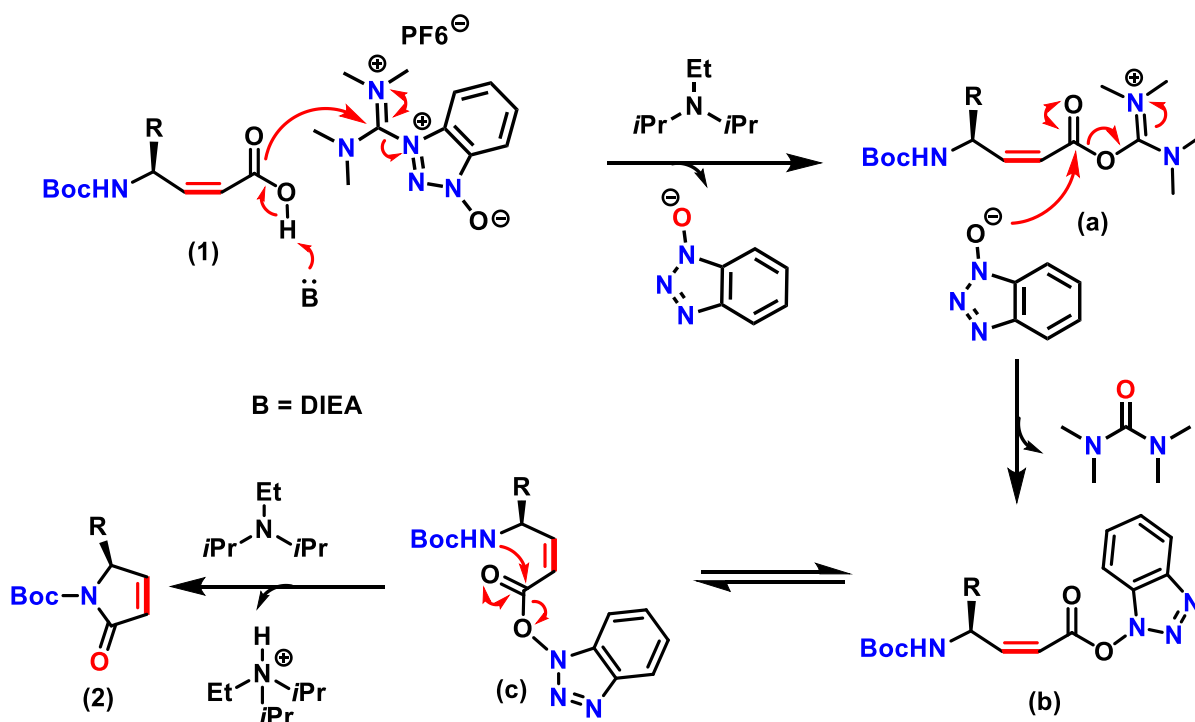


Figure 1. HPLC profile (a-d) represents the optical purity of the compounds **2a-2d**.

4B.4 Possible Reaction Mechanism

Boc-Z-vinylogous amino acid (**1**) reacts with HBTU in the presence of DIPEA to form intermediate (**a**). In the next step, OBt anion attacks intermediate (**a**) forming a new intermediate (**b**) and byproduct urea.^{11,12} The active ester (**b**) is the key intermediate in the context of the carboxylic group reactivity *via* activation, and can exist in various conformations due to its structural flexibility. Finally, the intermediate (**c**) with nucleophilic and electrophilic centers in proximity, leads to the formation of the final cyclized product (**1**) after the nucleophilic attack of the NH of the urethane group on the activated carboxylic center. The mechanistic details of the cyclization reaction are depicted in Scheme 6.



Scheme 6. Possible mechanism of the cyclization of *N*-Boc-*Z*-vinylogous amino acids.

4B.5 Conclusion

In conclusion, we have successfully synthesized *N*-Boc-*Z*-vinylogous amino acids with diverse side chains followed by their transformation into the α,β -unsaturated γ -lactams *via* activation with HBTU and mild base DIPEA. This method provides optically pure products which were confirmed by HPLC equipped with a chiral column. The optical purity of the product was further supported by specific rotation $[\alpha]$ analysis of the α,β -unsaturated γ -lactams. The present method provides an efficient method for the synthesis of α,β -unsaturated γ -lactams containing natural products and peptides.

4B.6 Experimental Section

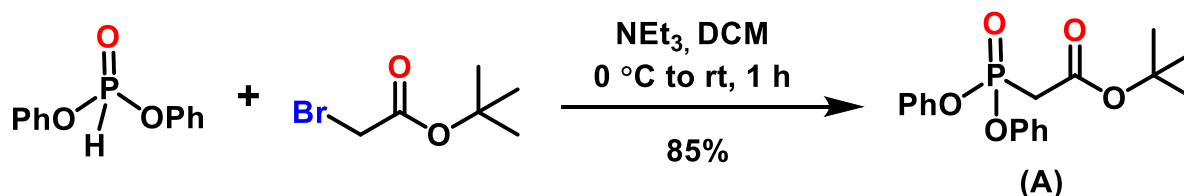
General Method

All the chemicals used were purchased from commercially available sources, which were directly used without further purification. Purification of the synthesized compounds was done by using column chromatography on silica gel of 60-120 mesh. Characterization of the compounds was done by using Bruker Avance 400 MHz spectrometer, ^1H NMR and ^{13}C NMR

recorded at 400 MHz and 101 MHz machines respectively. The mass of the compounds was analyzed by High-resolution mass spectrometry using ESI TOF.

4B.6.1 Synthetic procedure of *tert*-butyl (diphenylphosphono)acetate (A)

The diphenyl phosphite (10 mmol) was dissolved in 50 mL of dry dichloromethane in a 100 mL RB. To this solution, triethylamine (15 mmol) and *tert*-butyl bromoacetate were added at ice-cold conditions. Initially, a 15-20 min. the reaction mixture was stirred at ice-cold conditions then it was allowed to react further for 1 hour at room temperature.¹⁵ The reaction progress was visualized by TLC using a UV chamber and Ninhydrin staining. The unreacted reagents were quenched by the addition of water to the reaction vessel. DCM was evaporated using a rotary evaporator and the desired compound was extracted using 100 mL solvent (75ml EtOAc and 25 mL hexane) followed by washing with water and brine solution two times, dried with Na₂SO₄ and concentrated to get crude compound **A**, synthesis protocol of the compound is depicted in Scheme 7. It was purified through column chromatography to remove volatile impurities formed during synthesis, using the solvent system EtOAc/hexane in increasing polarity starting from 1% solvent system, compound **A** eluted from column nearly in solvent system 6-8% range.



Scheme 7. Synthesis of *tert*-butyl (diphenylphosphono)acetate **A**.

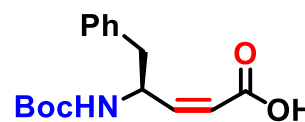
4B.6.2 Synthetic procedure of *N*-Boc-*Z*-vinyllogous amino acids

The *tert*-butyl (diphenylphosphono)acetate (**A**, 7.5 mmol) was dissolved in 50 mL dry THF at 0 °C in 100 mL RB as a reaction vessel. Thereafter, NaI (9 mmol) and DBU (7.5 mmol) were added sequentially to the solution of **A** at the same reaction condition. The resultant reaction mixture was stirred at 0 °C for 15 min. to ensure the formation of *Z*-ylide. In another reaction setup, Boc-amino aldehyde (**B1-B6**, 7.5 mmol) was dissolved in 50 mL of dry THF at -78 °C. After 15 min. *Z*-ylide was transferred to the RB containing Boc-amino aldehyde (**B1-B6**) solution, further reaction was stirred at -78 °C for 1.5 hours to get compound **C1-C6**, as shown in the reaction Scheme 4.² The progress of the reaction was visualized by TLC using a UV chamber, KMnO₄ and Ninhydrin staining. After completion of the reaction unreacted reagents

were quenched with saturated NH_4Cl solution. THF was evaporated before the workup. The final reaction mixture was extracted with EtOAc (75 mL) x 3 times followed by washing with brine solution (80 ml) x 2 times and dried with Na_2SO_4 and concentrated to get crude compound **C**. It was purified through column chromatography to remove minor isomer **D** formed during synthesis, using the solvent system EtOAc/hexane in increasing polarity starting from 1% solvent system, compound **C** eluted from column nearly in solvent system 3-5% range and good yield. Further treatment of **C** with TFA-DCM mixture (1:1, 10 mL) in the presence of a catalytic amount of water removes both the protecting groups (Boc- and -*t*-Butyl), the excess amount of the TFA co-evaporated with DCM five times leads to *Z*-vinyllogous amino acids. Subsequently, Boc- protection was done using 10% Na_2CO_3 and boc-anhydride to get the desired final product in good yield, which is *N*-Boc-*Z*- α,β -unsaturated γ -amino acids (**1a-1f**), the pictorial representation of their synthesis is depicted in Scheme 4.

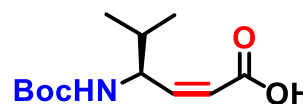
Boc-*Z*- $\text{d}^{2,3}\gamma\text{Phe-OH}$ (**1a**):

White solid, **M.p.** 178-180 °C, $[\alpha]_{\text{D}}^{25} = +60$ (c 0.1, MeOH); **^1H NMR** (400 MHz, $\text{DMSO-}d_6$) δ 12.42 (s, 1H), 7.22 (ddd, $J = 19.2, 13.3, 7.9$ Hz, 5H), 6.98 (d, $J = 8.6$ Hz, 1H), 6.14 (dd, $J = 11.5, 8.6$ Hz, 1H), 5.72 (dd, $J = 11.5, 1.3$ Hz, 1H), 5.23 (dt, $J = 15.0, 8.4$ Hz, 1H), 2.79 – 2.65 (m, 2H), 1.28 (s, 9H); **^{13}C NMR** (151 MHz, $\text{DMSO-}d_6$) δ 166.75, 154.90, 149.85, 138.33, 129.27, 127.96, 126.05, 119.76, 77.65, 50.28, 28.19; **HRMS** (ESI) cal. for $\text{C}_{16}\text{H}_{21}\text{NO}_4\text{Na}$ $[\text{M}+\text{Na}]^+ m/z$ 314.1368 obs. 314.1375.



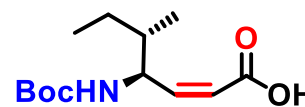
Boc-*Z*- $\text{d}^{2,3}\gamma\text{Val-OH}$ (**1b**):

Oily liquid, $[\alpha]_{\text{D}}^{25} = +22$ (c 0.1, MeOH); **^1H NMR** (400 MHz, $\text{Acetone-}d_6$) δ 6.19 (s, 1H), 6.13 (t, $J = 10.7$ Hz, 1H), 5.88 (dd, $J = 11.7, 1.0$ Hz, 1H), 5.00 (d, $J = 8.1$ Hz, 1H), 1.90 (dd, $J = 13.6, 6.9$ Hz, 1H), 1.40 (s, 9H), 0.97 (d, $J = 6.8$ Hz, 3H), 0.93 (d, $J = 6.8$ Hz, 3H); **^{13}C NMR** (101 MHz, $\text{Acetone-}d_6$) δ 206.46, 167.00, 156.43, 148.21, 121.17, 78.87, 54.55, 33.24, 28.52, 19.28, 18.62; **HRMS** (ESI) cal. for $\text{C}_{12}\text{H}_{21}\text{NO}_4\text{Na}$ $[\text{M}+\text{Na}]^+ m/z$ 266.1368 obs. 266.1366.

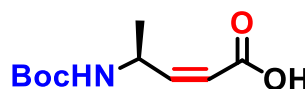


Boc-Z-d^{2,3}Ile-OH (1c):

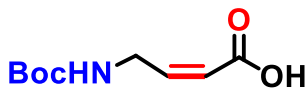
Oily liquid, $[\alpha]_{\text{D}}^{25} = -88$ (c 0.1, MeOH); **¹H NMR** (400 MHz, Acetonitrile-*d*₃) δ 5.98 (dd, $J = 11.6$ Hz, 1H), 5.84 (t, $J = 11.6$ Hz, 1H), 5.60 (d, $J = 10.4$ Hz, 1H), 4.84–4.60 (m, 1H), 1.64–1.47 (m, 2H), 1.40 (s, 9H), 1.11 (m, 1H), 0.89 (d, $J = 7.0$ Hz, 3H), 0.88–0.82 (m, 3H); **¹³C NMR** (101 MHz, Acetonitrile-*d*₃) δ 167.43, 157.39, 147.48, 80.23, 53.70, 39.50, 28.53, 26.60, 15.43, 11.42, 1.90, 1.69; HRMS (ESI) cal. for C₁₃H₂₃NO₄Na [M+Na]⁺ m/z 280.1524 obs. 280.1523.

**Boc-Z-d^{2,3}Ala-OH (1d):**

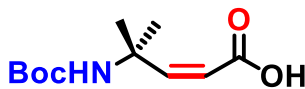
Oily liquid, $[\alpha]_{\text{D}}^{25} = +43$ (c 0.1, MeOH); **¹H NMR** (400 MHz, DMSO-*d*₆) δ 12.37 (s, 1H), 7.02 (d, $J = 7.9$ Hz, 1H), 6.07 (dd, $J = 11.5, 1.2$, 1H), 5.64 (dd, $J = 11.5, 1.3$ Hz, 1H), 5.05 (h, $J = 7.3$ Hz, 1H), 1.36 (s, 9H), 1.10 (d, $J = 6.8$ Hz, 3H); **¹³C NMR** (151 MHz, DMSO-*d*₆) δ 166.75, 151.29, 126.97, 113.42, 76.44, 48.61, 31.93, 29.23; HRMS (ESI) cal. for C₁₀H₁₇NO₄Na [M+Na]⁺ m/z 238.1055 obs. 238.1059.

**Boc-Z-d^{2,3}Gly-OH (1e):**

Oily liquid, $[\alpha]_{\text{D}}^{25} = 0$ (c 0.1, MeOH); **¹H NMR** (400 MHz, Chloroform-*d*) δ 6.34 (dt, $J = 11.5, 6.3$ Hz, 1H), 5.87 (dt, $J = 11.5, 1.9$ Hz, 1H), 5.00 (s, 1H), 4.22 (d, $J = 6.5$ Hz, 2H), 1.45 (s, 9H); **¹³C NMR** (101 MHz, Chloroform-*d*) δ 170.15, 156.37, 148.28, 120.92, 80.23, 39.45, 28.49; HRMS (ESI) cal. for C₉H₁₅NO₄Na [M+Na]⁺ m/z 224.0899 obs. 224.0898.

**Boc-Z-d^{2,3}Aib-OH (1f):**

Oily liquid, $[\alpha]_{\text{D}}^{25} = 0$ (c 0.1, MeOH); **¹H NMR** (400 MHz, Chloroform-*d*) δ 6.00 (d, $J = 12.3$ Hz, 1H), 5.82 (d, $J = 12.3$ Hz, 1H), 1.50 (s, 6H), 1.43 (s, 9H); **¹³C NMR** (101 MHz, Chloroform-*d*) δ 170.38, 157.97, 123.62, 119.85, 80.72, 52.69, 28.49, 28.36, 24.22; HRMS (ESI) cal. for C₁₁H₁₉NO₄Na [M+Na]⁺ m/z 252.1212 obs. 252.1211.

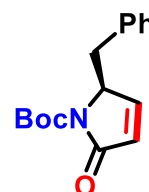


4B.6.3 Synthetic procedure of *N*-Boc- α,β -unsaturated γ -lactam from *N*-Boc-*Z*-vinyllogous amino acids

The *N*-Boc-*Z*-vinyllogous amino acids (**1a-1f**, 0.5 mmol) were dissolved in 1-2 mL of DMF. To this solution, DIPEA (1.5 mmol) and HBTU (0.5 mmol) were added subsequently at 0 °C. The progress of the reaction was visualized by TLC using a UV chamber, KMnO₄ and Ninhydrin staining. After completion of the reaction, workup was done by extracting the compound using EtOAc (50 mL) x 3 times followed by washing with 10% HCl and 10 % Na₂CO₃ (30 mL) x 3 times, finally with brine solution (30 mL) x 2 times. The organic layer containing the compound was dried with Na₂SO₄ and concentrated to get crude compound (**2a-2f**) in excellent yield, the pictorial representation of their synthesis is depicted in Table 1. The crude compound was transformed into a form of slurry using silica and DCM, which was transferred to the column for the final purification. The EtOAc-hexane solvent system was used in the increasing order of polarity starting from the 5% solvent system, all compounds were eluted from the column in the range of 8-12%, *N*-Boc- α,β -unsaturated γ -lactam (**2a-2f**).

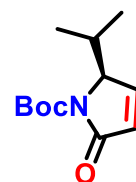
tert-butyl (*S*)-2-benzyl-5-oxo-2,5-dihydro-1*H*-pyrrole-1-carboxylate (**2a**):

White solid, **M.p.** 90-92 °C, *R_f* = 0.53 (20% EtOAc in hexane), Yield = 88%, [α]_D²⁵ = +19 (c 0.1, MeOH); ¹H NMR (400 MHz, Chloroform-*d*) δ 7.33 – 7.28 (m, 2H), 7.28 – 7.23 (m, 2H), 7.17 – 7.13 (m, 2H), 7.02 (dd, *J* = 6.1, 2.0 Hz, 1H), 6.02 (dd, *J* = 6.2, 1.6 Hz, 1H), 4.75 (ddt, *J* = 9.5, 3.8, 1.8 Hz, 1H), 3.54 (dd, *J* = 13.1, 3.9 Hz, 1H), 2.74 (dd, *J* = 13.1, 9.5 Hz, 1H), 1.63 (s, 9H); ¹³C NMR (101 MHz, Chloroform-*d*) δ 169.20, 150.05, 149.63, 135.75, 129.51, 128.83, 127.29, 126.78, 83.33, 63.50, 38.73, 28.36; **HRMS** (ESI) cal. for C₁₆H₁₉NO₃Na [M+Na]⁺ *m/z* 296.1262 obs. 296.1259.



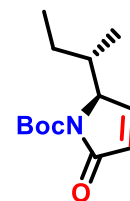
tert-butyl (*S*)-2-isopropyl-5-oxo-2,5-dihydro-1*H*-pyrrole-1-carboxylate (**2b**):

Viscous liquid, *R_f* = 0.58 (20% EtOAc in hexane), Yield = 87%, [α]_D²⁵ = +16 (c 0.1, MeOH); ¹H NMR (400 MHz, Chloroform-*d*) δ 7.12 (dd, *J* = 6.2, 2.0 Hz, 1H), 6.14 (dd, *J* = 6.1, 1.7 Hz, 1H), 4.55 (dt, *J* = 4.0, 1.9 Hz, 1H), 2.59 (ddd, *J* = 9.9, 7.0, 3.5 Hz, 1H), 1.55 (s, 9H), 1.10 (d, *J* = 7.1 Hz, 3H), 0.66 (d, *J* = 6.9 Hz, 3H); ¹³C NMR (101 MHz, Chloroform-*d*) δ 169.69, 149.75, 147.93, 127.93, 83.01, 67.43, 29.00, 28.26, 19.64, 15.00; **HRMS** (ESI) cal. for C₁₂H₁₉NO₃Na [M+Na]⁺ *m/z* 248.1262 obs. 248.1260.



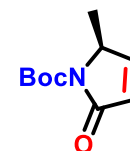
***tert*-butyl (S)-2-((S)-*sec*-butyl)-5-oxo-2,5-dihydro-1*H*-pyrrole-1-carboxylate (2c):**

Viscous liquid, $R_f = 0.61$ (20% EtOAc in hexane), Yield = 82%, $[\alpha]_D^{25} = -80$ (c 0.1, MeOH); (Mixture of two rotamers) $^1\text{H NMR}$ (400 MHz, Chloroform- d) δ 7.12 (dd, $J = 6.2, 2.0$ Hz, 1H), 7.07 (dd, $J = 6.2, 2.1$ Hz, 1H), 6.12 (dd, $J = 6.2, 1.8$ Hz, 1H), 6.10 (dd, $J = 6.2, 1.8$ Hz, 1H), 4.64 (dt, $J = 3.9, 1.9$ Hz, 1H), 4.55 (dt, $J = 3.8, 1.9$ Hz, 1H), 2.31 (ddtd, $J = 27.8, 13.8, 6.8, 3.7$ Hz, 2H), 1.53 (s, 17H), 1.47 – 1.41 (m, 1H), 1.33 (dd, $J = 14.5, 6.6$ Hz, 1H), 1.23 (tt, $J = 11.1, 3.7$ Hz, 2H), 1.06 (d, $J = 7.1$ Hz, 3H), 1.02 (t, $J = 7.4$ Hz, 3H), 0.85 – 0.80 (m, 3H), 0.62 (d, $J = 6.9$ Hz, 3H); $^{13}\text{C NMR}$ (101 MHz, Chloroform- d) δ 169.78, 169.76, 149.67, 149.58, 148.30, 148.11, 127.88, 127.41, 82.94, 67.60, 66.10, 35.87, 35.81, 28.23, 28.21, 27.32, 22.60, 16.60, 12.67, 12.37, 12.27; **HRMS** (ESI) cal. for $\text{C}_{13}\text{H}_{21}\text{NO}_3\text{Na}$ $[\text{M}+\text{Na}]^+$ m/z 262.1418 obs. 262.1414.



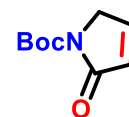
***tert*-butyl (S)-2-methyl-5-oxo-2,5-dihydro-1*H*-pyrrole-1-carboxylate (2d):**

Viscous liquid, $R_f = 0.50$ (20% EtOAc in hexane), Yield = 90%, $[\alpha]_D^{25} = +37$ (c 0.1, MeOH); $^1\text{H NMR}$ (400 MHz, Chloroform- d) δ 7.09 (dd, $J = 6.0, 2.0$ Hz, 1H), 6.05 (dd, $J = 6.1, 1.7$ Hz, 1H), 4.61 (qt, $J = 6.7, 1.8$ Hz, 1H), 1.55 (s, 9H), 1.43 (d, $J = 6.7$ Hz, 3H); $^{13}\text{C NMR}$ (101 MHz, Chloroform- d) δ 169.33, 151.92, 149.52, 126.05, 83.05, 58.54, 28.26, 18.29; **HRMS** (ESI) cal. for $\text{C}_{10}\text{H}_{15}\text{NO}_3\text{Na}$ $[\text{M}+\text{Na}]^+$ m/z 220.0949 obs. 220.0955.



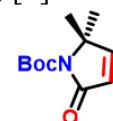
***tert*-butyl 2-oxo-2,5-dihydro-1*H*-pyrrole-1-carboxylate (2e):**

Viscous liquid, $R_f = 0.45$ (20% EtOAc in hexane), Yield = 86%, $[\alpha]_D^{25} = 0$ (c 0.1, MeOH); $^1\text{H NMR}$ (400 MHz, Chloroform- d) δ 7.18 (dt, $J = 6.2, 2.1$ Hz, 1H), 6.15 (dt, $J = 6.2, 2.0$ Hz, 1H), 4.34 (t, $J = 2.0$ Hz, 2H), 1.55 (s, 9H); $^{13}\text{C NMR}$ (101 MHz, Chloroform- d) δ 169.32, 149.71, 145.27, 128.06, 83.16, 51.77, 28.21; **HRMS** (ESI) cal. for $\text{C}_9\text{H}_{14}\text{NO}_3$ $[\text{M}+\text{H}]^+$ m/z 184.0973 obs. 184.0977.



***tert*-butyl 2,2-dimethyl-5-oxo-2,5-dihydro-1*H*-pyrrole-1-carboxylate (2f):**

Colorless solid, **M.p.** 123-125 °C, $R_f = 0.50$ (20% EtOAc in hexane), Yield = 84%, $[\alpha]_D^{25} = 0$ (c 0.1, MeOH); $^1\text{H NMR}$ (400 MHz, Chloroform- d) δ 7.01 (d, $J = 6.0$ Hz, 1H), 5.99 (d, $J = 6.0$ Hz, 1H), 1.58 (s, 10H), 1.53 (s, 6H); $^{13}\text{C NMR}$ (101 MHz, Chloroform- d) δ 169.48, 157.93, 152.78, 123.63, 82.94, 65.58, 28.36, 24.23; **HRMS** (ESI) cal. for $\text{C}_{11}\text{H}_{17}\text{NO}_3$ $[\text{M}+\text{Na}]^+$ m/z 234.1105 obs. 234.1106.



4B.7 References

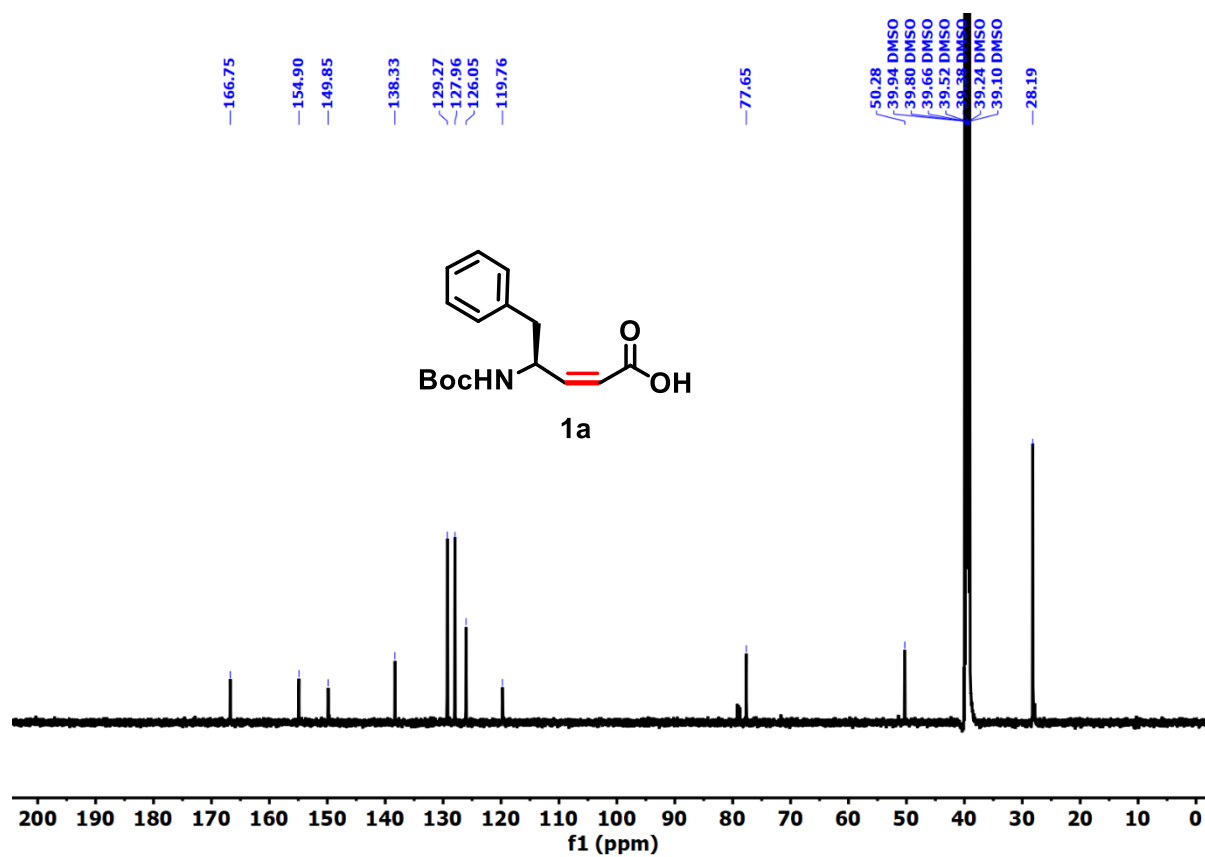
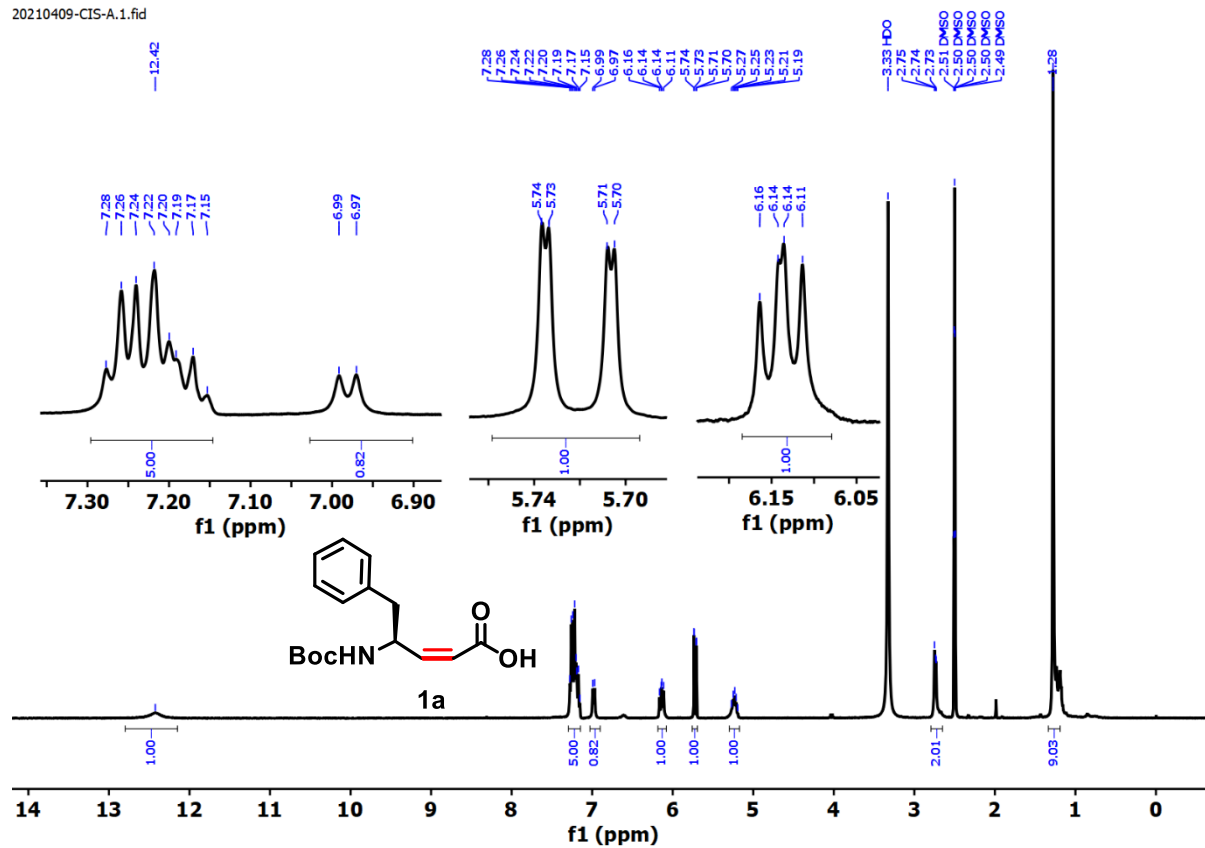
1. E. T. Pelkey, S. J. Pelkey and J. G. Greger, In *Adv. Heterocycl. Chem.*, 1st ed.; Academic Press, 2015, 115, 151.
2. (a) F. Micheli, A. Pasquarello, G. Tedesco, D. Hamprecht, G. Bonanomi, A. Checchia, A. Jaxa-Chamiec, F. Damiani, S. Davalli and D. Donati, *Bioorg. Med. Chem. Lett.*, 2006, **16**, 3906–3912; (b) J. Caruano, G. G. Muccioli and R. Robiette, *Org. Biomol. Chem.*, 2016, **14**, 10134–10156; (c) C. C. Cosner, J. T. Markiewicz, P. Bourbon, C. J. Mariani, O. Wiest, M. Rujoi, A. I. Rosenbaum, A. Y. Huang, F. R. Maxfield and P. Helquist, *J. Med. Chem.*, 2009, **52**, 6494–6498; (d) T. Kawasuji, M. Fuji, T. Yoshinaga, A. Sato, T. Fujiwarab and R. Kiyamaa, *Bioorg. Med. Chem.*, 2007, **15**, 5487–5492; (e) E. Choi, C. Lee, M. Cho, J. J. Seo, J. S. Yang, S. J. Oh, K. Lee, S.-K. Park, H. M. Kim, H. J. Kwon and G. Han, *J. Med. Chem.*, 2012, **55**, 10766–10770; (f) U. A. Pereira, L. C. A. Barbosa, C. R. A. Maltha, A. J. Demuner, M. A. Masood and A. L. Pimenta, *Bioorg. Med. Chem. Lett.*, 2014, **24**, 1052–1056; (g) Z. Feng, F. Chu, Z. Guo and P. Sun, *Bioorg. Med. Chem. Lett.*, 2009, **19**, 2270–2272; (h) S. B. Singh, M. A. Goetz, E. T. Jones, G. F. Bills, R. A. Giacobbe, L. Herranz, S. Stevens-Miles and D. L. Williams, Jr., *J. Org. Chem.*, 1995, **60**, 7040–7042.
3. (a) F. Gaviña, A. Costero, M. Andreu, M. Carda and S. Luis, *J. Am. Chem. Soc.*, 1988, **110**, 4017–4018; (b) S.-K. Kang, K.-J. Kim, C.-M. Yu, J.-W. Hwang and Y.-K Do, *Org. Lett.*, 2001, **3**, 2851–2853; (c) T. Morimoto, N. Chatani and S. Murai, *J. Am. Chem. Soc.*, 1999, **121**, 1758–1759; (d) B. B. Snider and B. J. Neubert, *J. Org. Chem.*, 2004, **69**, 8952–8955; (e) R. S. Coleman, M. C. Walczak and E. L. Campbell, *J. Am. Chem. Soc.*, 2005, **127**, 16038–16039.
4. J. Xie, S. Xue, E. C. Escudero-Adán and A. W. Kleij, *Angew. Chem., Int. Ed.*, 2018, **57**, 16727–16731.
5. S. Sarkar, A. Banerjee, J. A. Shah, U. Mukherjee, N. C. Frederiks, C. J. Johnson and M.-Y. Ngai, *J. Am. Chem. Soc.*, 2022, **144**, 20884–20894.
6. L. Yang, C.-H. Lei, D.-X. Wang, Z.-T. Huang and M.-X. Wang, *Org. Lett.*, 2010, **12**, 3918–3921.
7. X. del Corte, A. Maestro, J. Vicario, E. Martinez de Marigorta and F. Palacios, *Org. Lett.*, 2018, **20**, 317–320.
8. (a) Z.-B. Ye, J. Chen, W.-H. Meng and P.-Q. Haung, *Tetrahedron: Asymmetry*, 2010, **21**, 895–902; (b) T. Conroy, J. T. Guo, R. G. Linington, N. H. Hunt, and R. J. Payne, *Chem. Eur. J.*, 2011, **17**, 13544–13552; (c) T. Conroy, J. T. Guo, N. H. Hunt and R. J. Payne, *Org.*

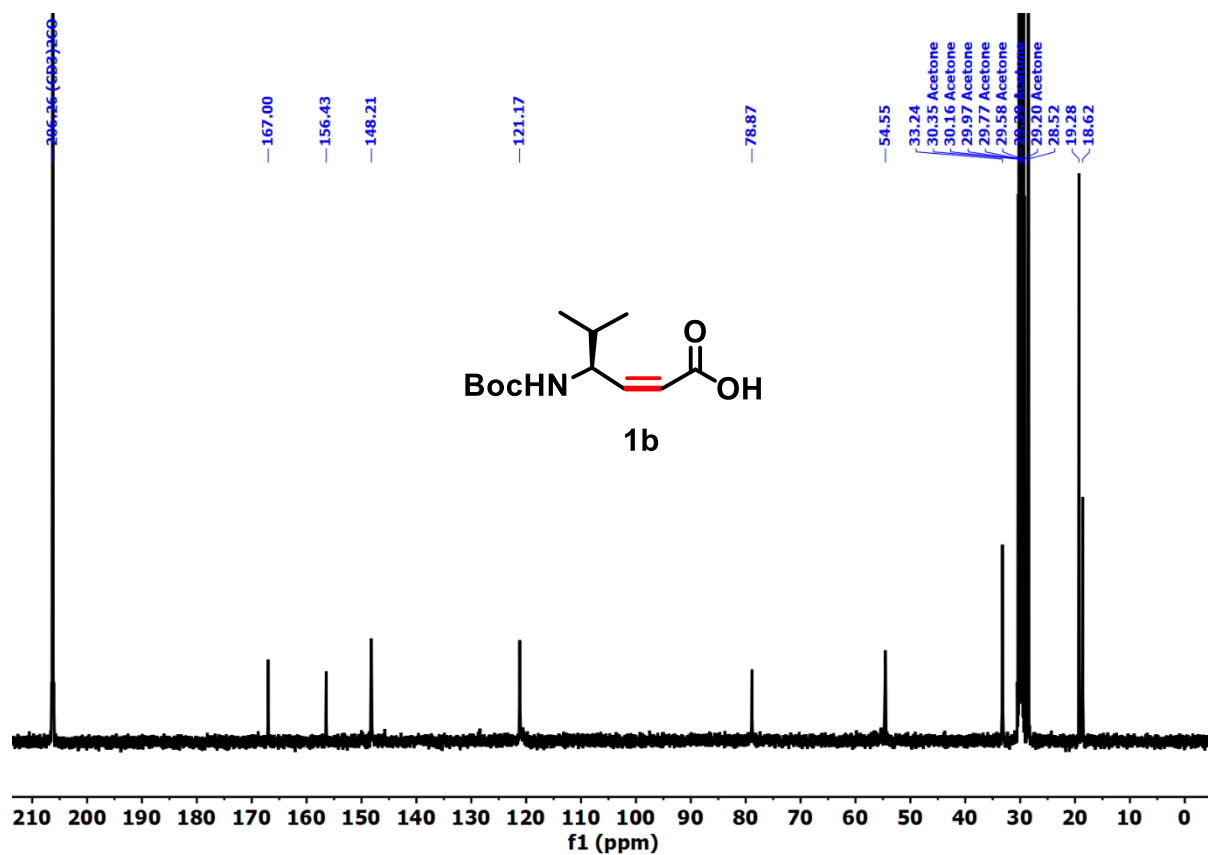
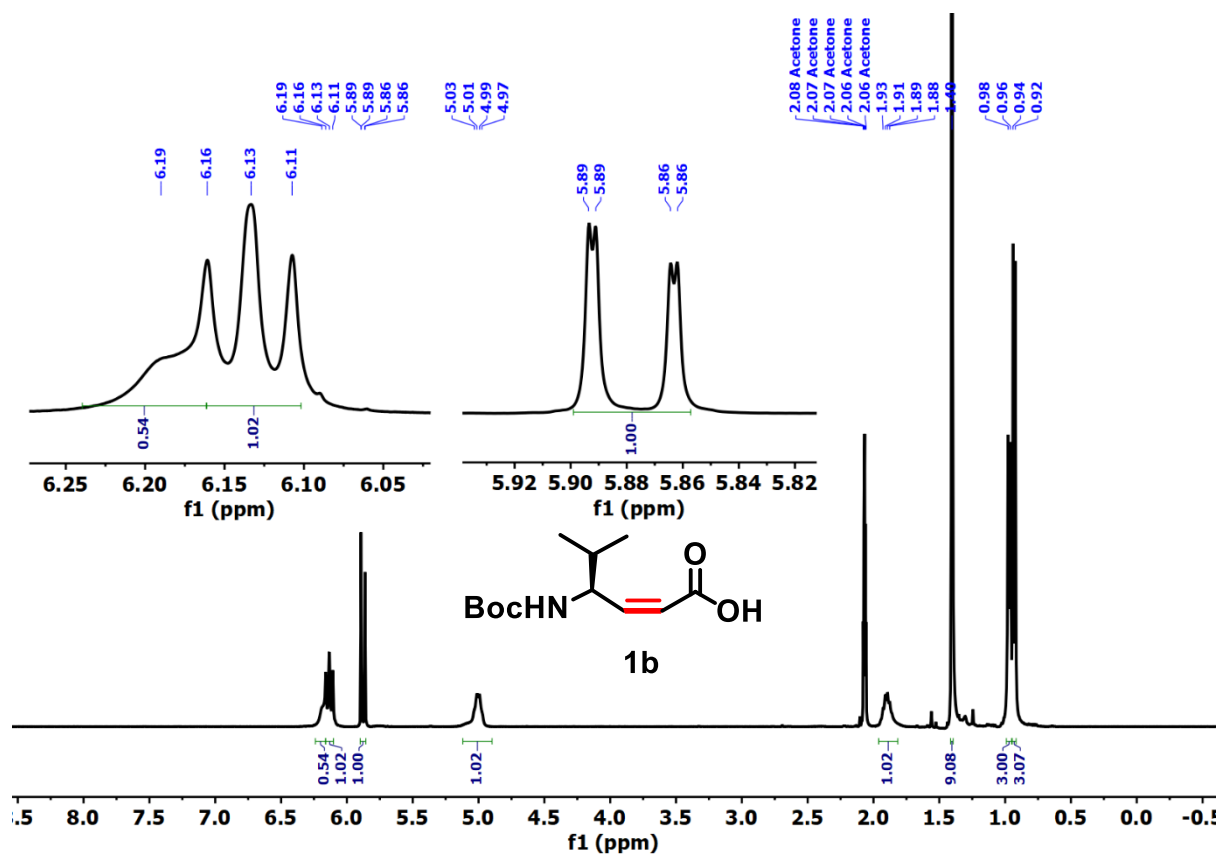
- Lett.*, 2010, **12**, 5576–5579; (d) A. K. Mandal, J. Hines, K. Kuramochia and C. M. Crews, *Bioorg. Med. Chem. Lett.*, 2005, **15**, 4043–4047
9. E. J. E. Caro-Diaz, F. A. Valeriote and W. H. Gerwick, *Org. Lett.*, 2019, **21**, 793–796.
 10. J. Chen, P.–Q. Huang and Y. Queneau, *J. Org. Chem.*, 2009, **74**, 7457–7463.
 11. (a) G. Hughes, M. Kimura and S. L. Buchwald, *J. Am. Chem. Soc.*, 2003, **125**, 11253–11258; (b) C. Shao, H.-J. Yu, N.-Y. Wu, P. Tian, R. Wang, C. G. Feng and G. Q. Lin, *Org. Lett.*, 2011, **13**, 788–791; (c) Y. Xie, Y. Zhao, B. Qian, L. Yang, C. Xia and H. Huang, *Angew. Chem. Int. Ed.*, 2011, **50**, 5682–5686.
 12. (a) F. Palacios, A. M. O. de Retana and A. V. del Burgo, *J. Org. Chem.*, 2011, **76**, 9472–9477; (b) A. R. Coffin, M. A. Roussell, E. Tserlin, and E. T. Pelkey, *J. Org. Chem.*, 2006, **71**, 6678–6681; (c) A. J. Pearson, H. Sun and X. Wang, *J. Org. Chem.*, 2007, **72**, 2547–2557.
 13. (a) M. Singh, S. A. Nalawade, D. R. Puneeth Kumar, K. Veeresh, S. Pahan, S. Dey and H. N. Gopi, *Eur. J. Org. Chem.* 2023, **26**, e202300682; (b) M. Singh, M. Kumar, S. A. Nalawade, D. R. Puneeth Kumar and H. N. Gopi, *Org. Biomol. Chem.*, 2023, **21**, 3766–3769.
 14. (a) K. Ando, T. Oishi, M. Hirama, H. Ohno and T. Ibuka, *J. Org. Chem.*, 2000, **65**, 4745–4749; (b) K. Ando, *J. Org. Chem.*, 1999, **64**, 8406–8408.
 15. V. Dourtoglou, J. C. Ziegler and B. Gross, *Tetrahedron Lett.*, 1978, **15**, 1269–1272.
 16. R. Knorr, A. Trzeciak, W. Bannwarth and D. Gillessen, *Tetrahedron Lett.*, 1989, **30**, 1927–1930.

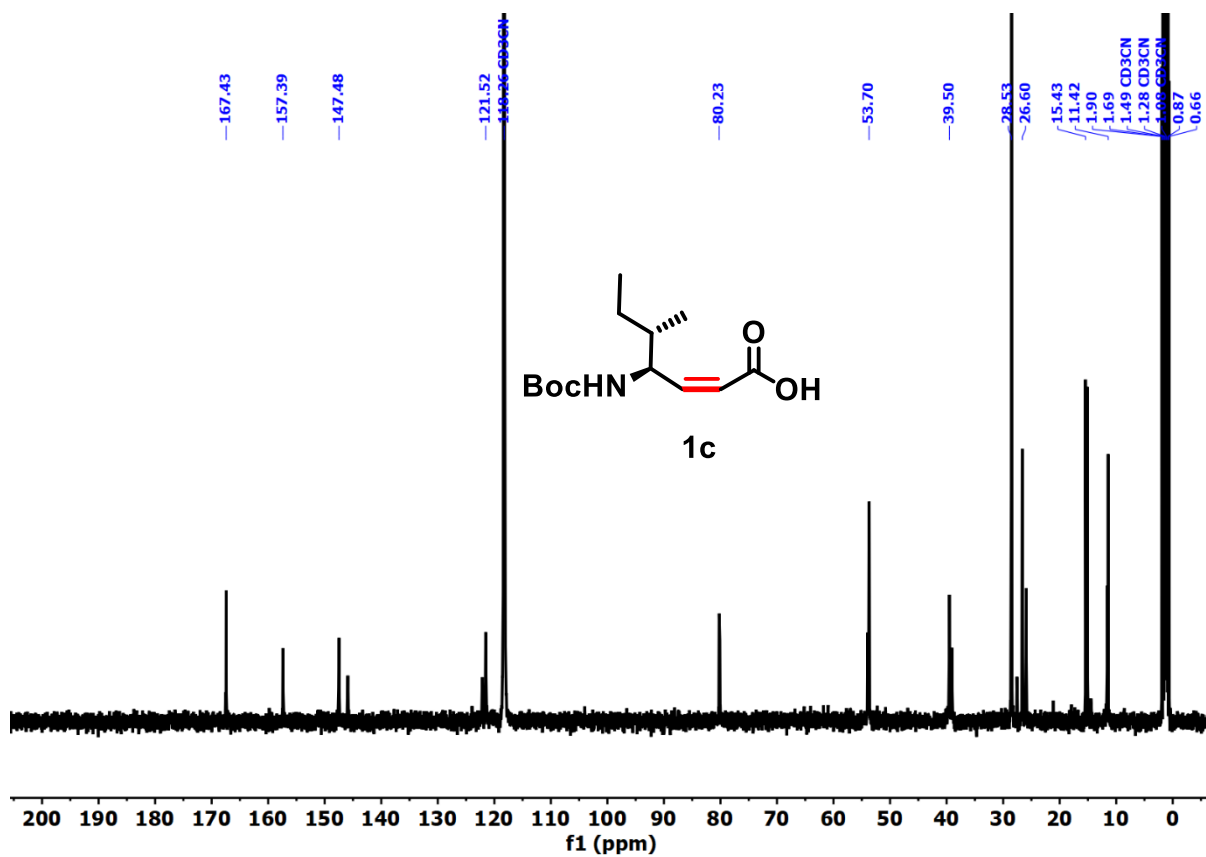
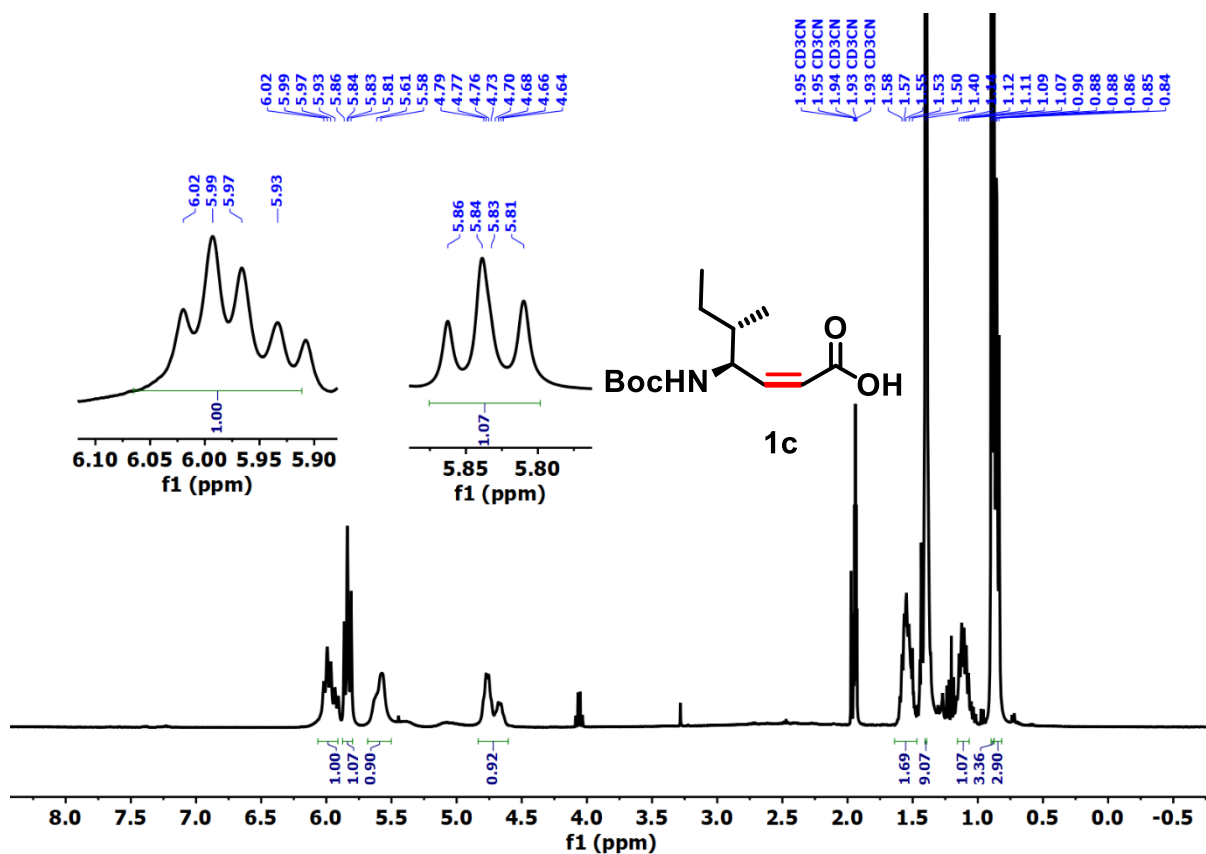
4B.8 Appendix

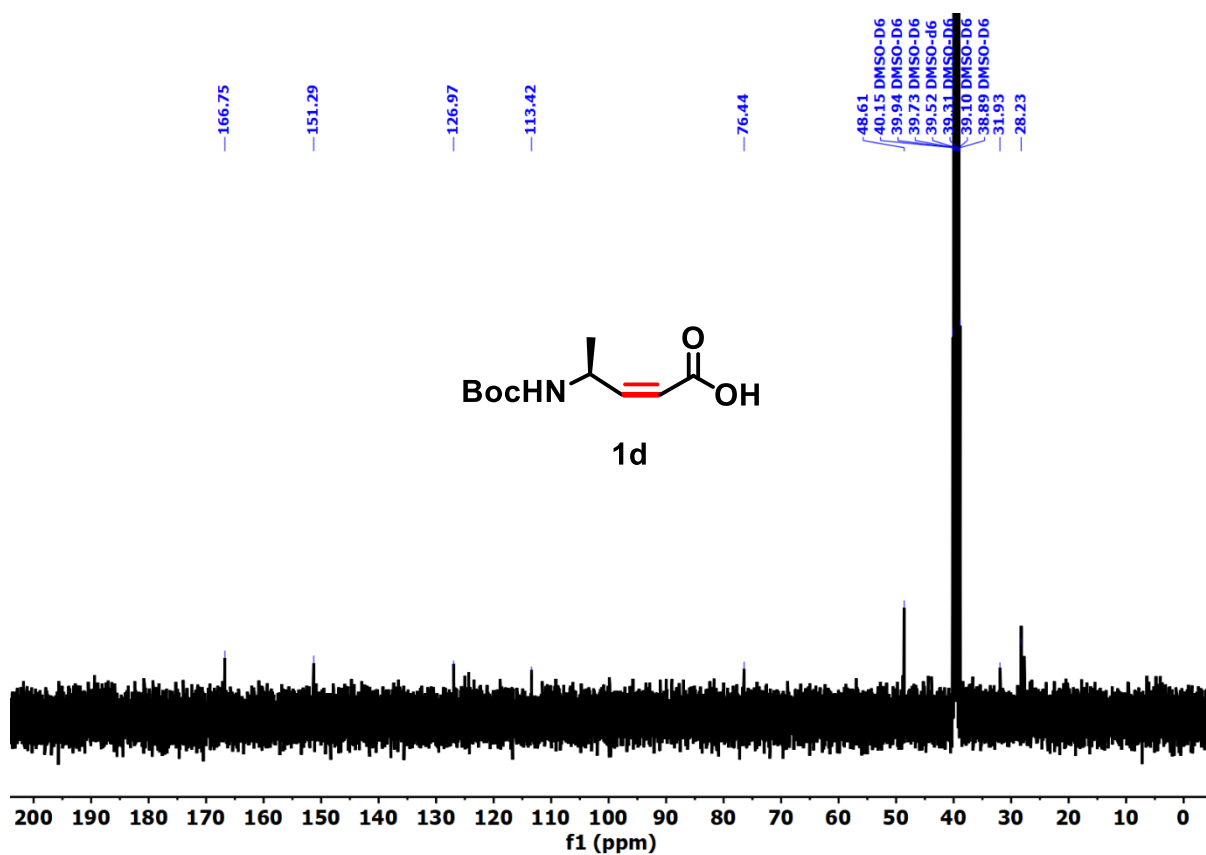
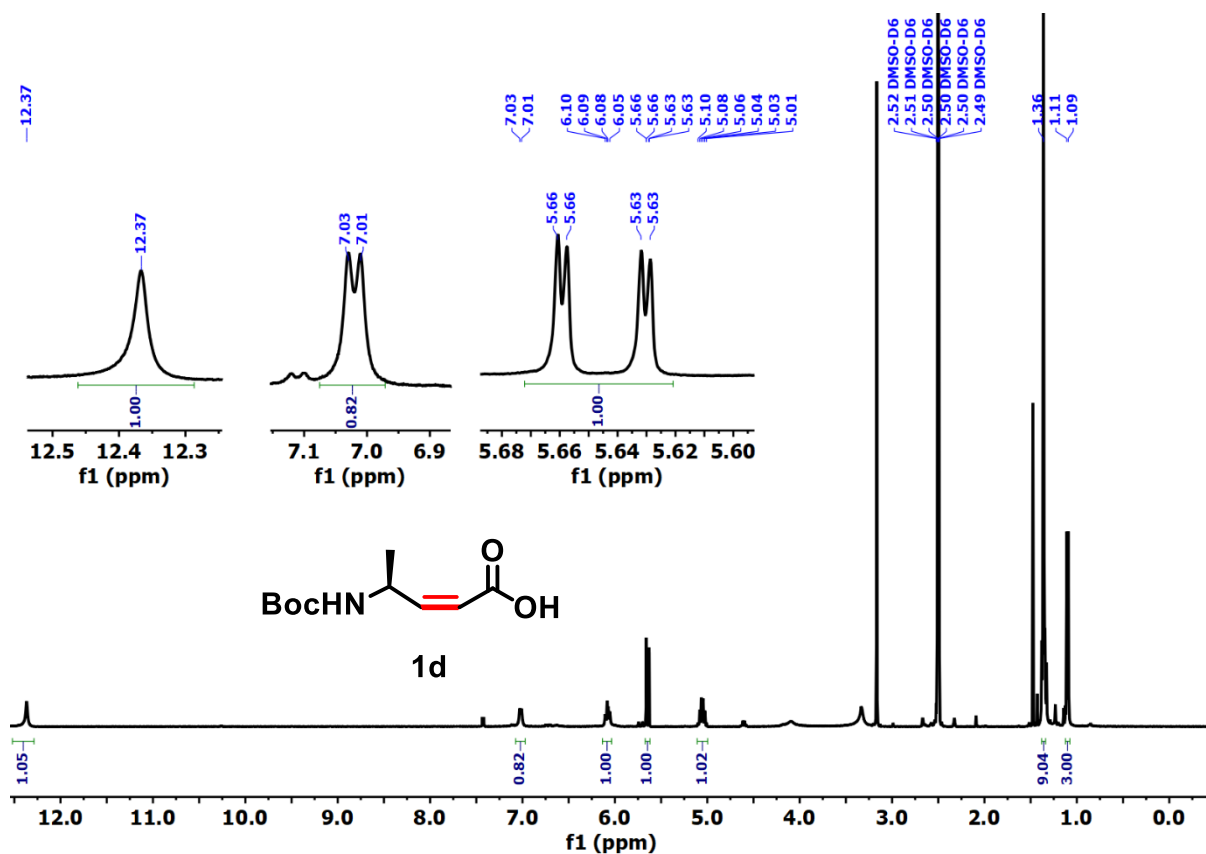
4B.8.1 ^1H NMR and ^{13}C NMR of all synthesized compounds

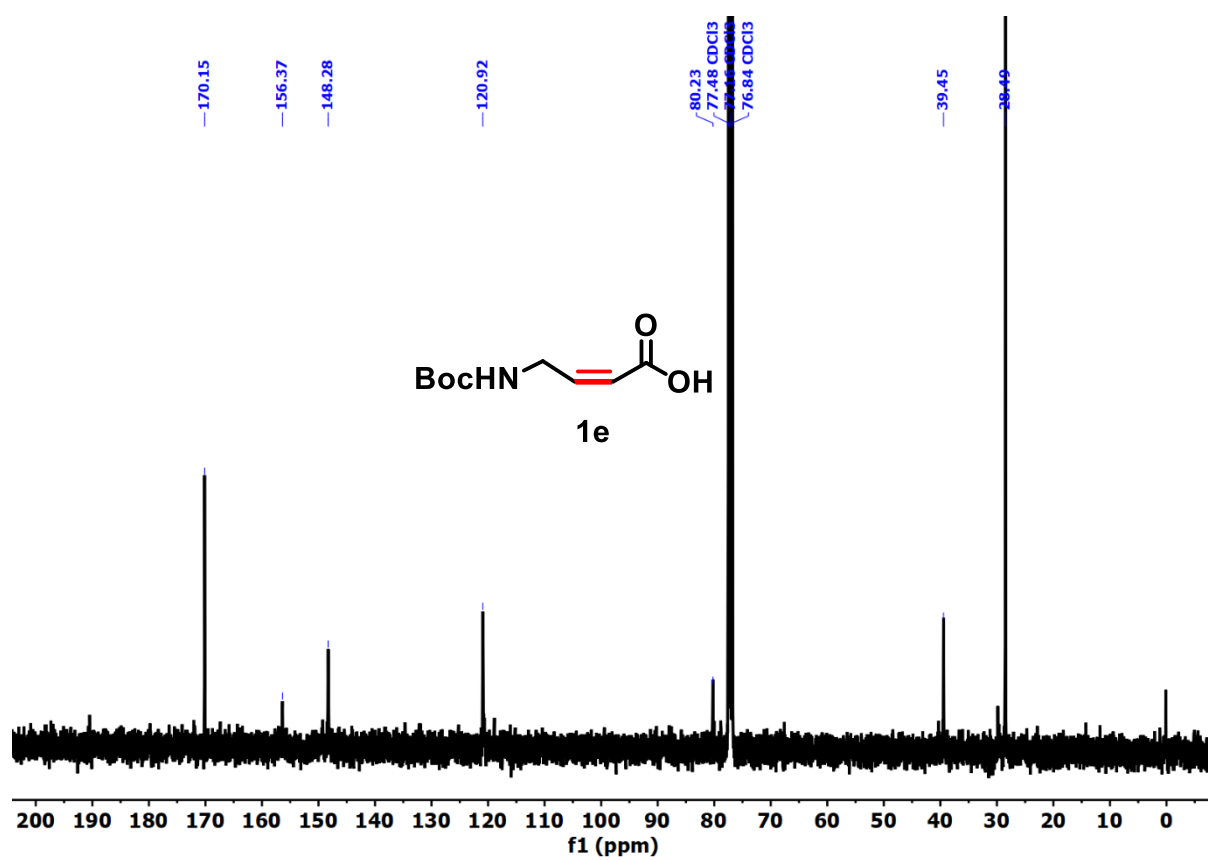
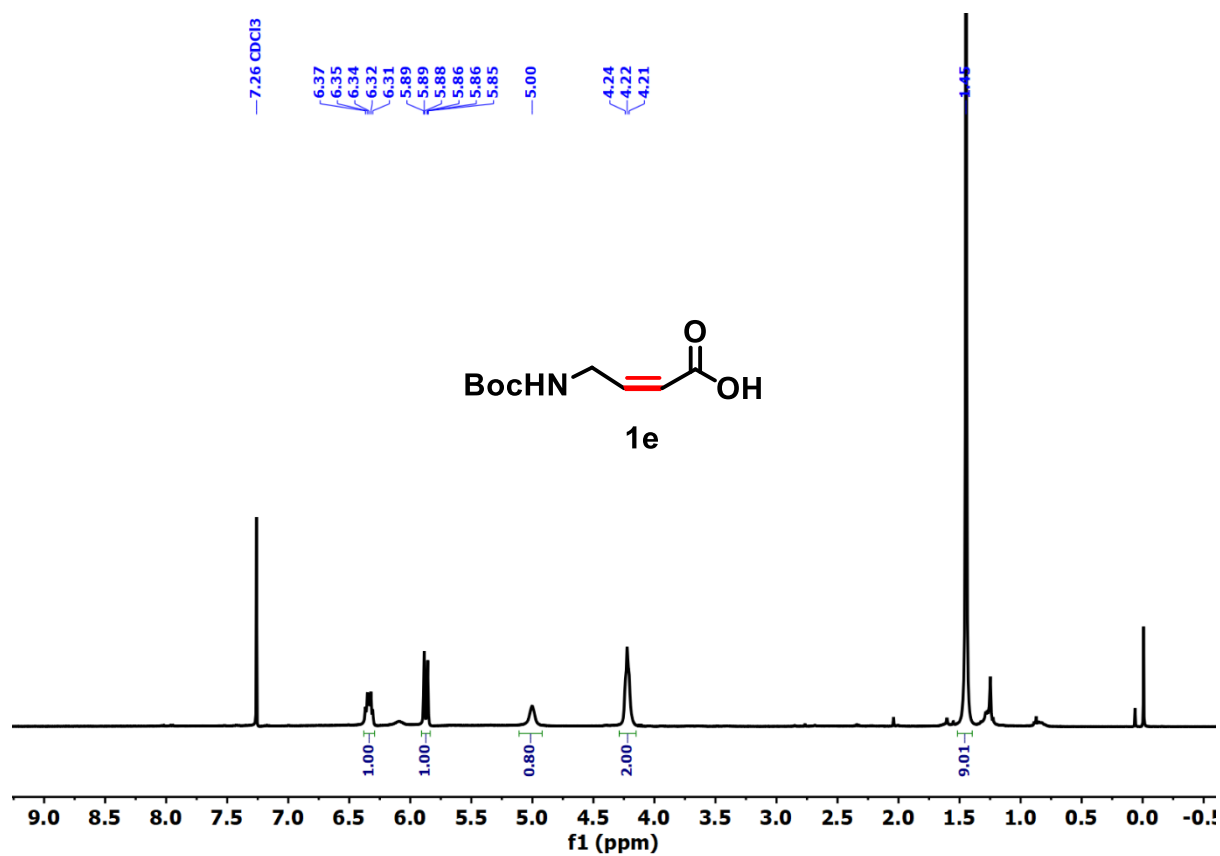
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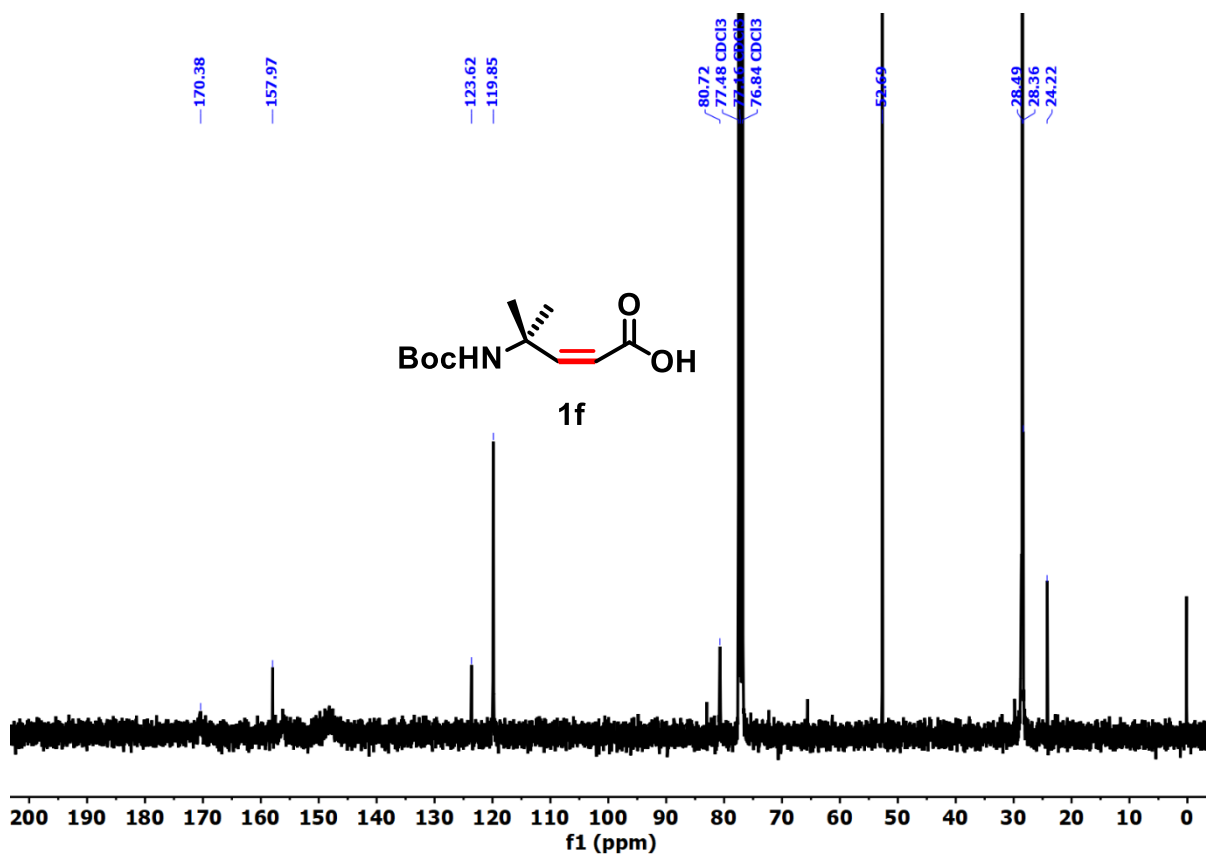
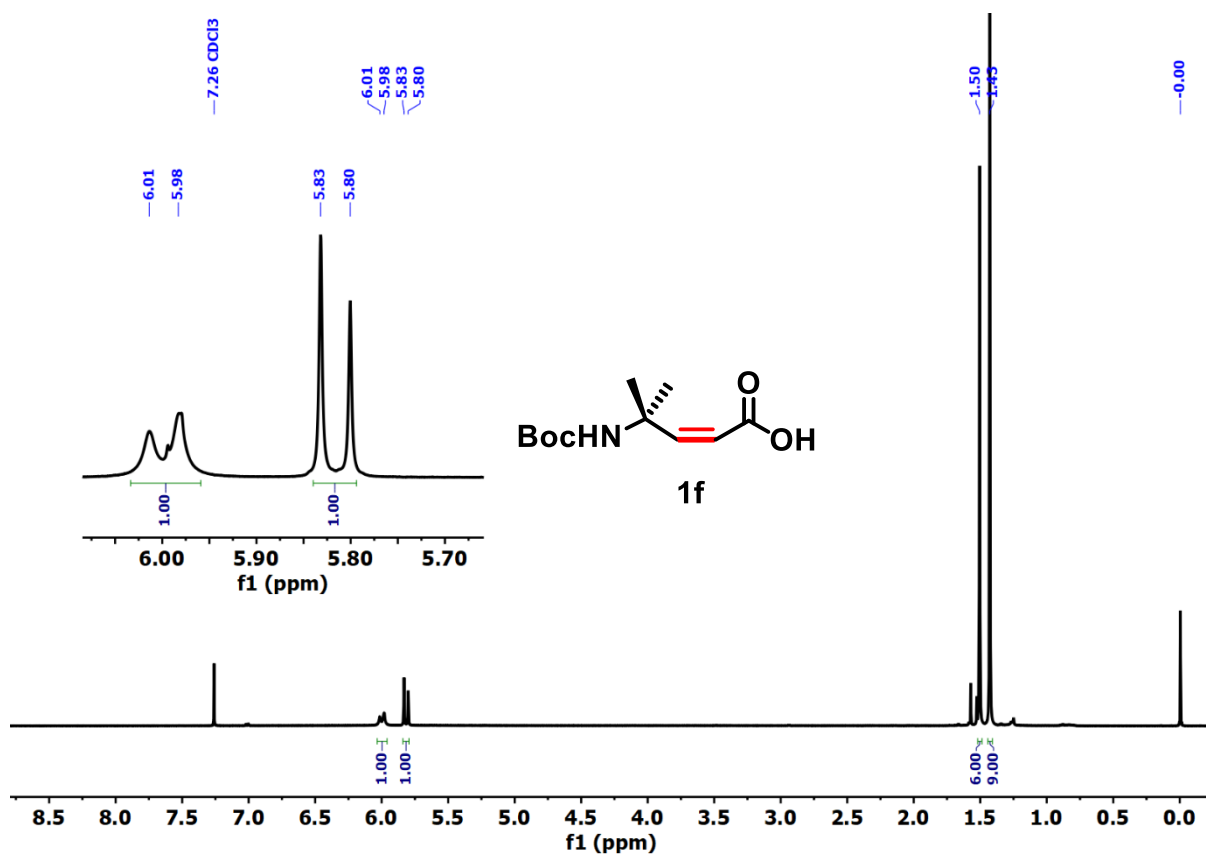


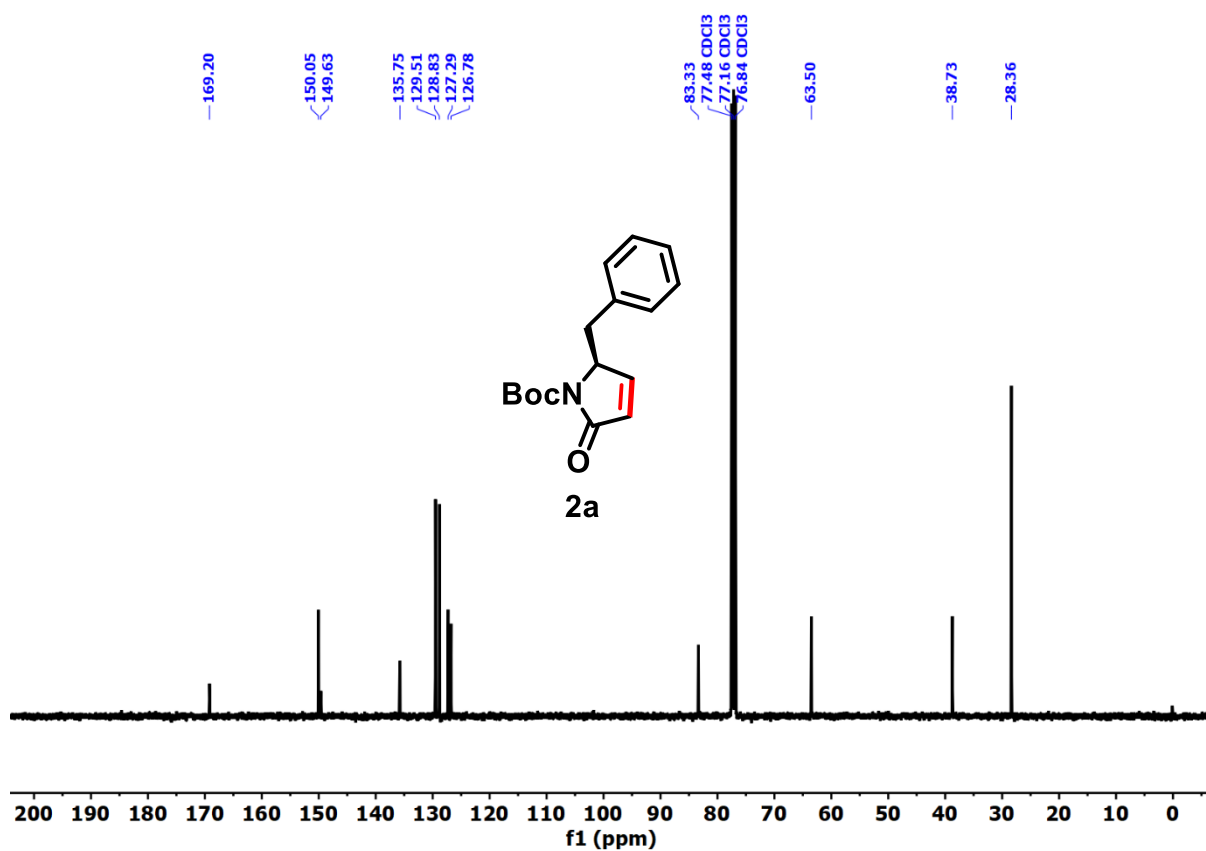
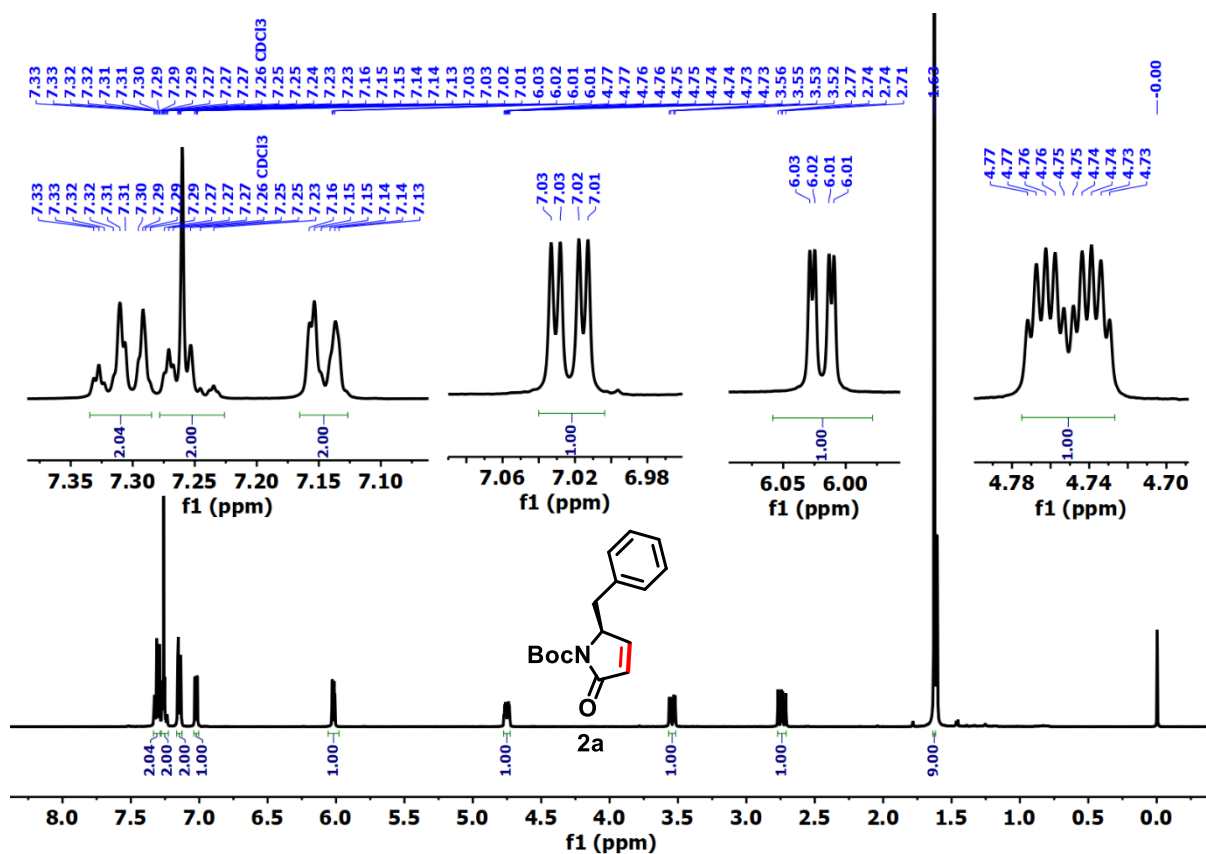


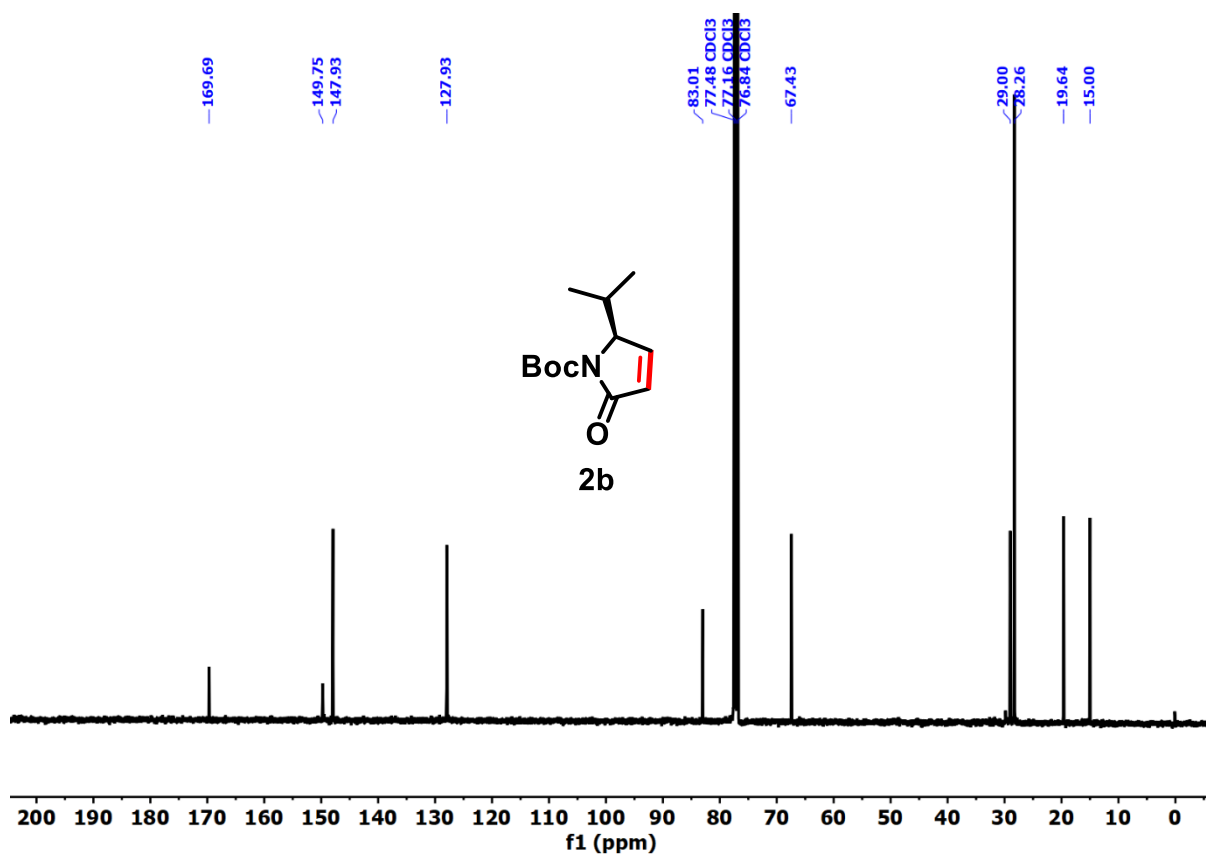
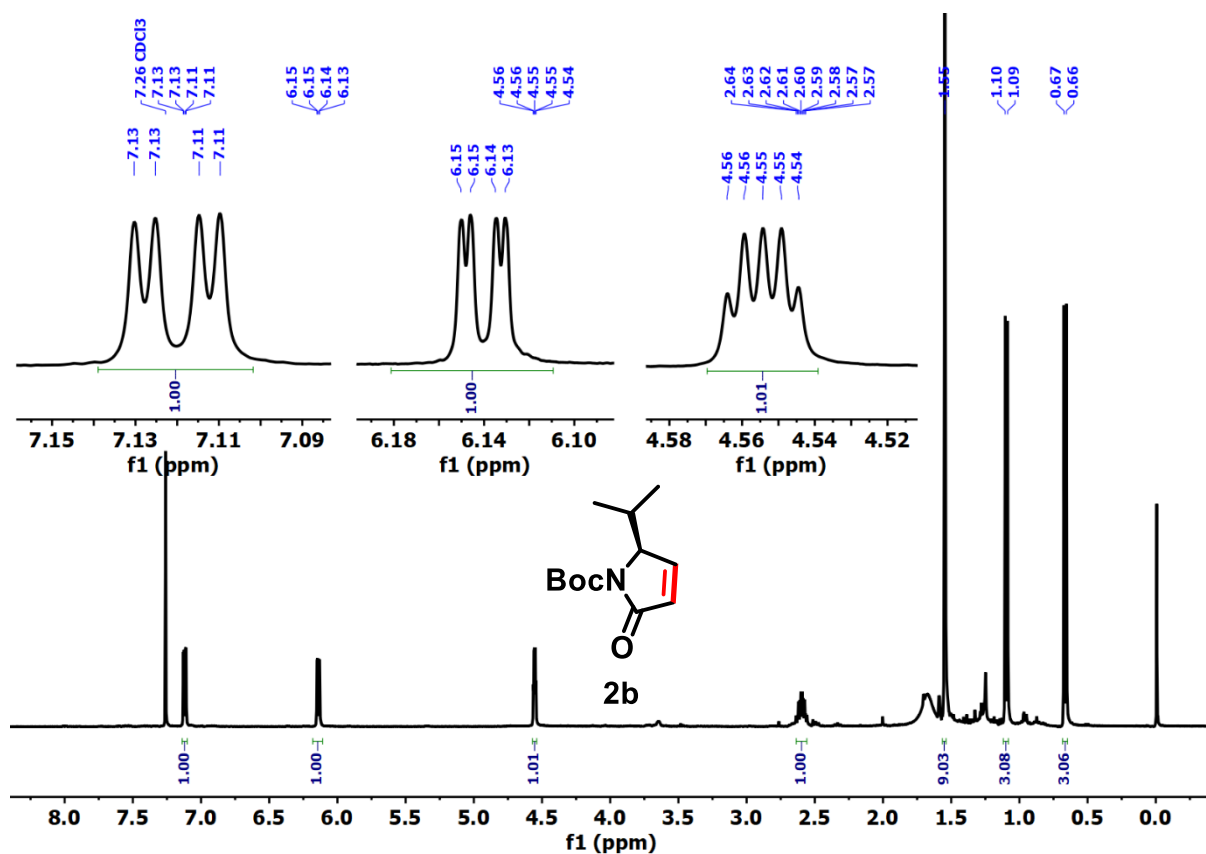


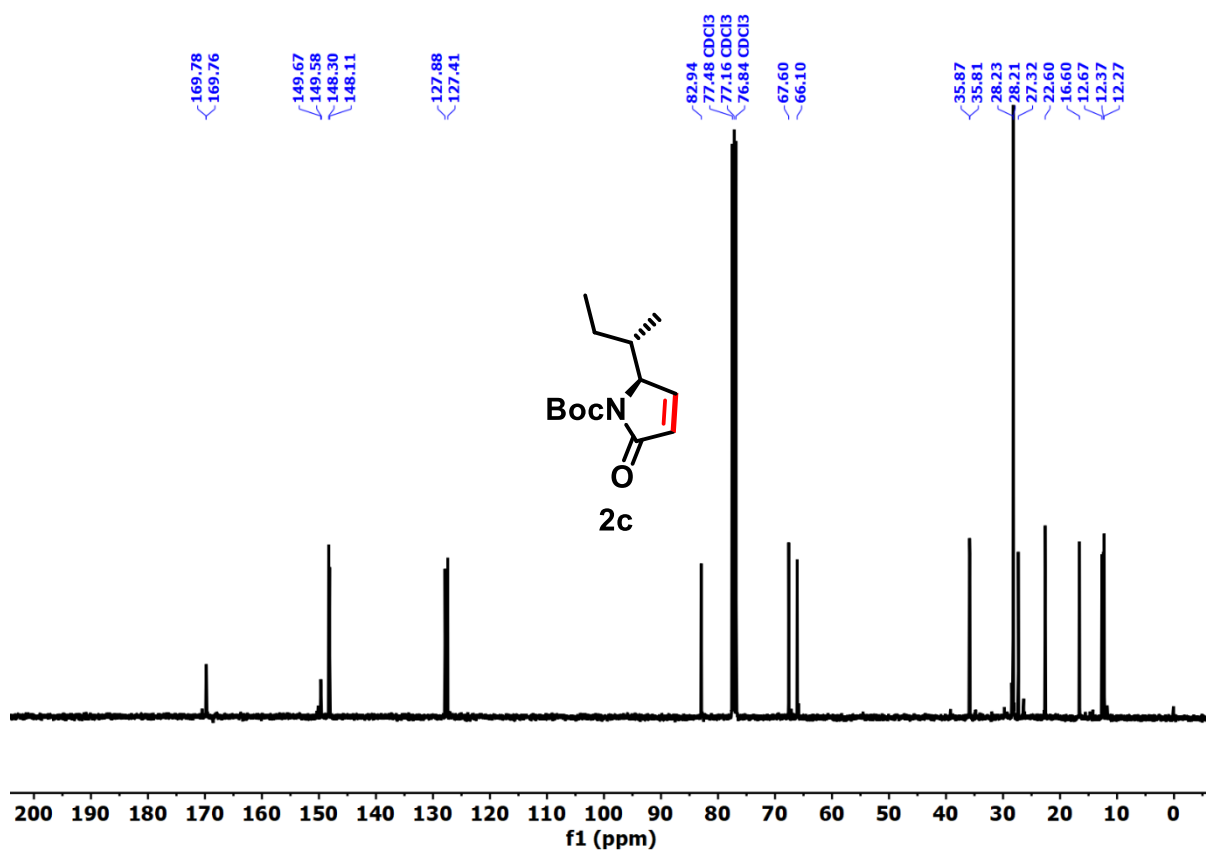
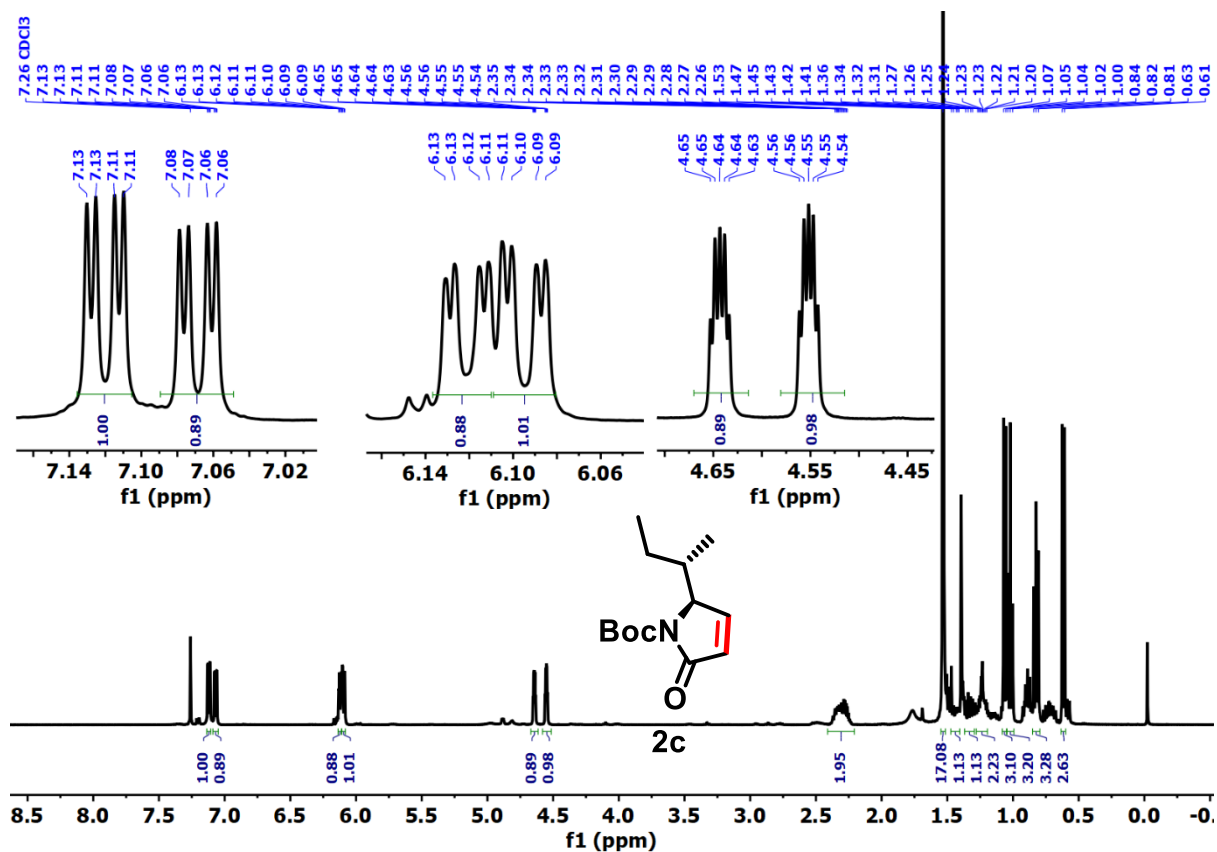


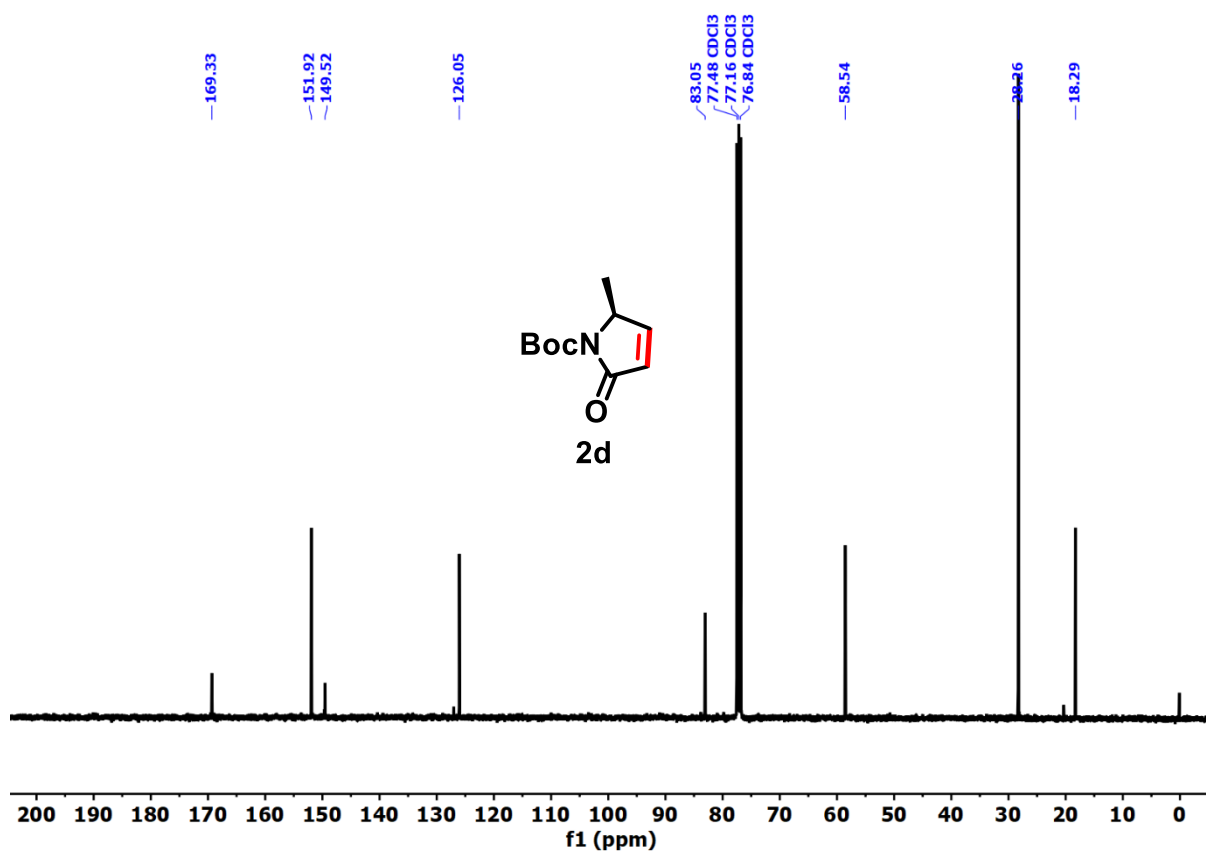
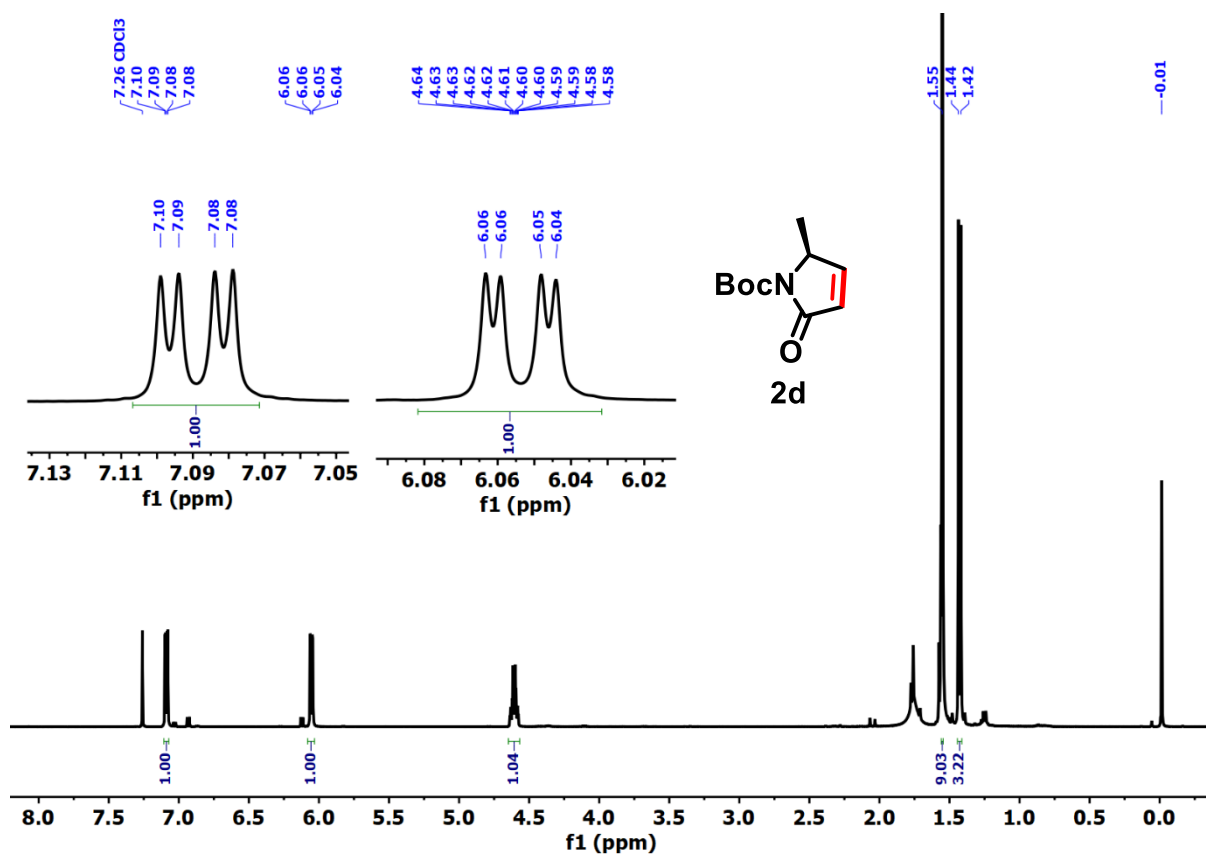




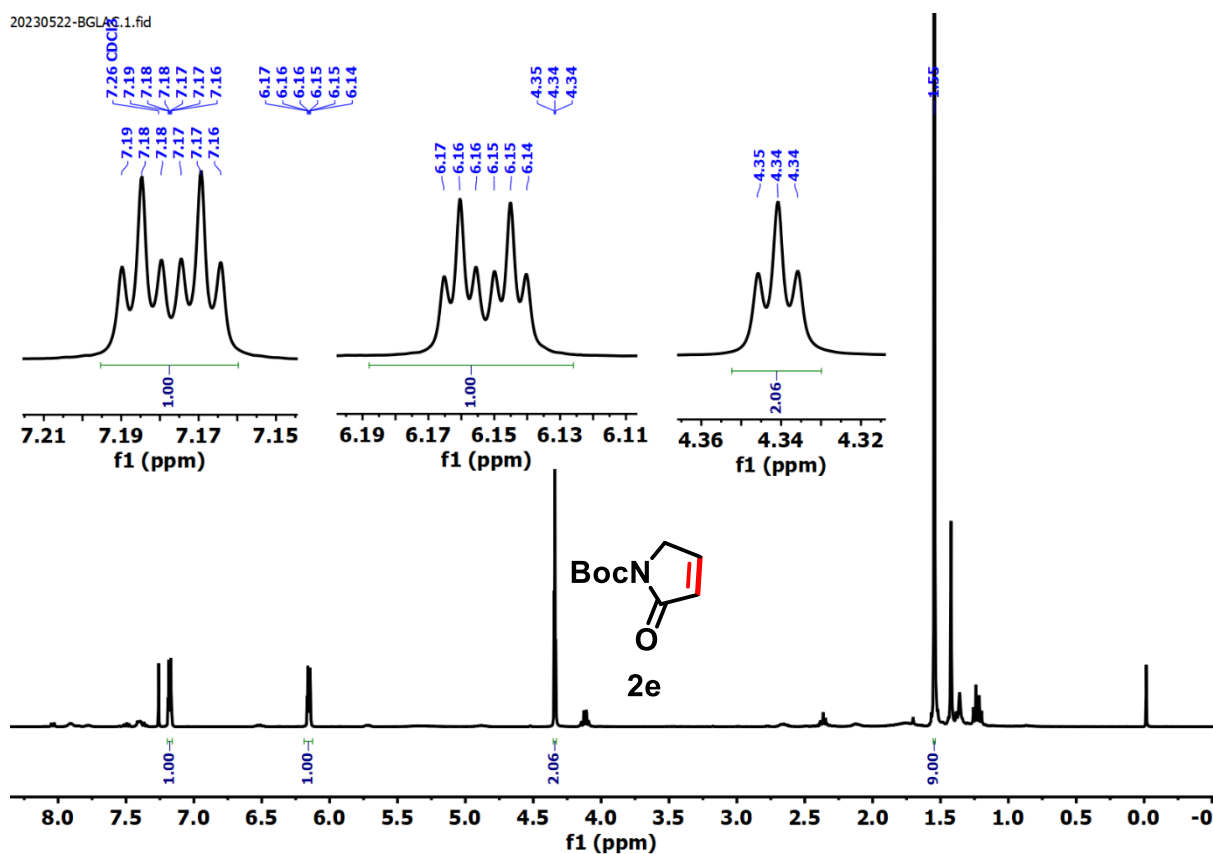




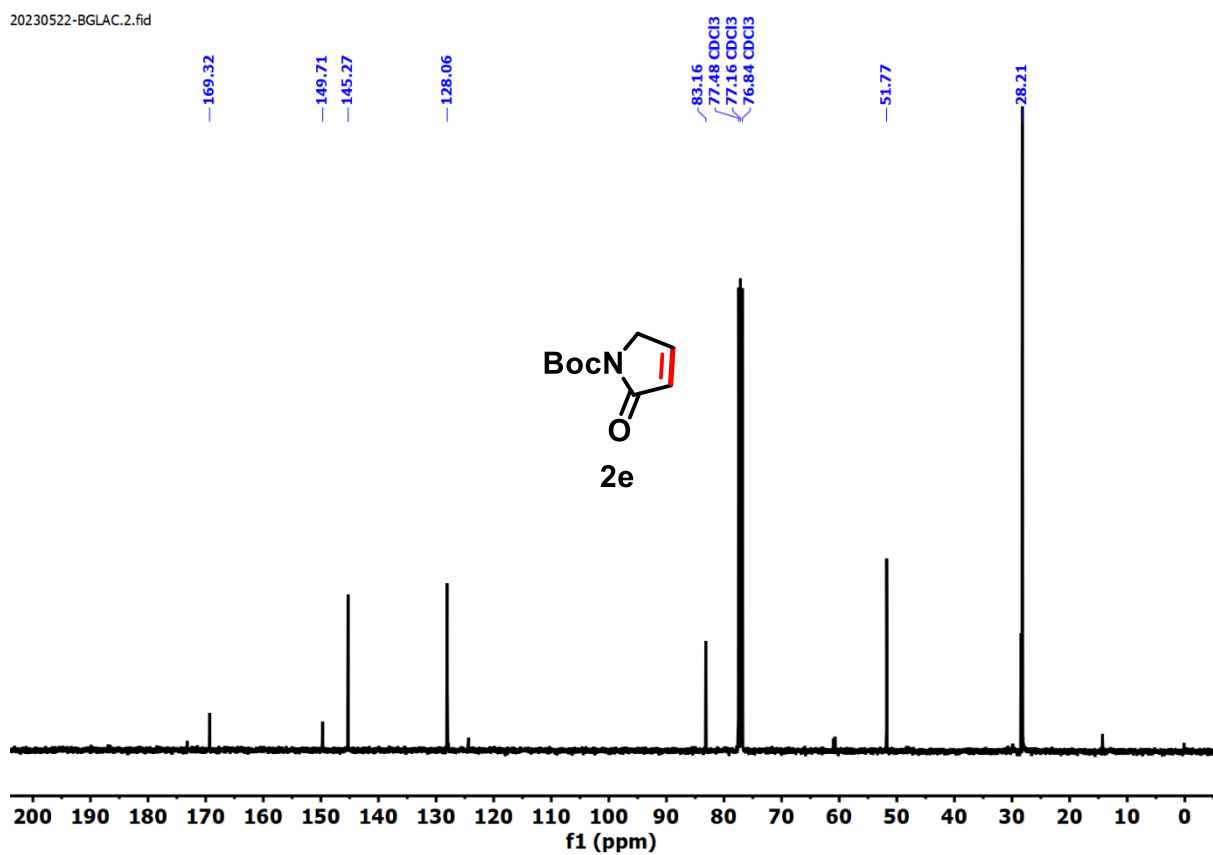


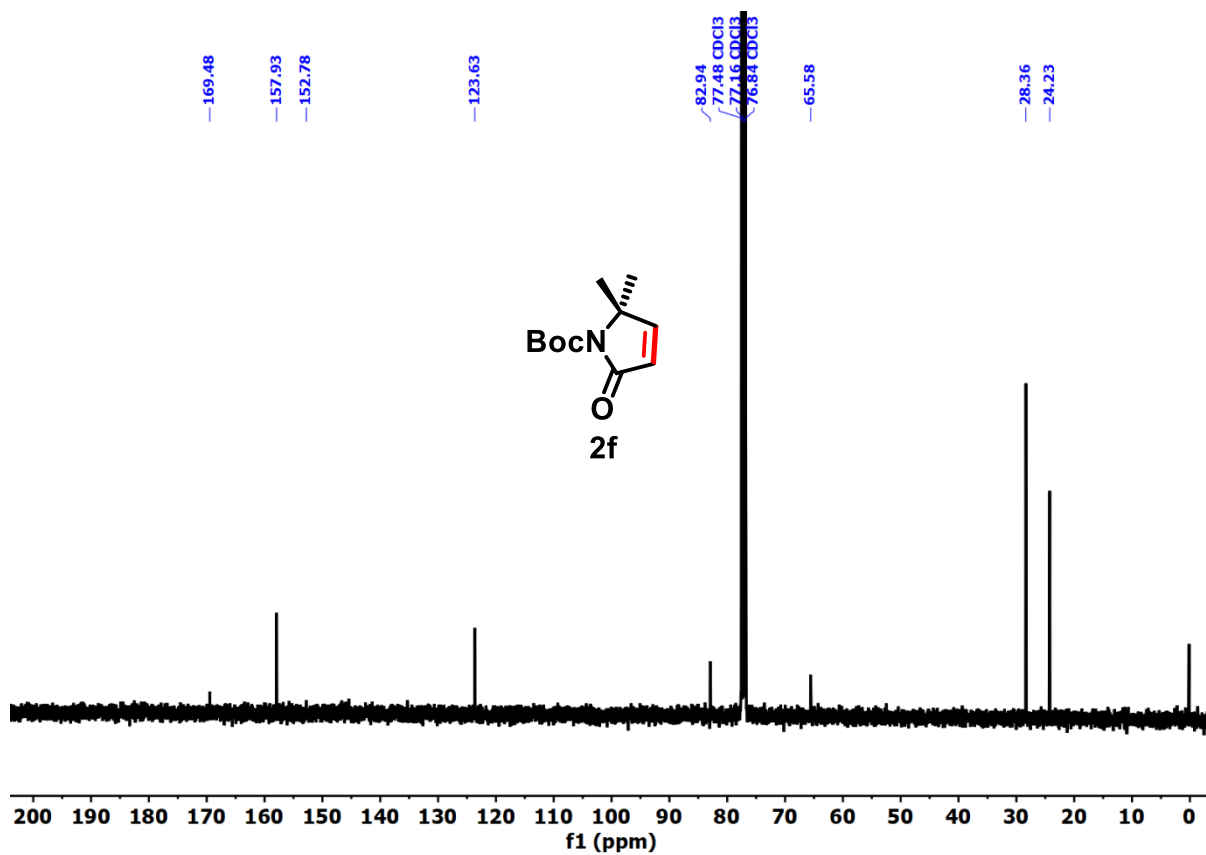
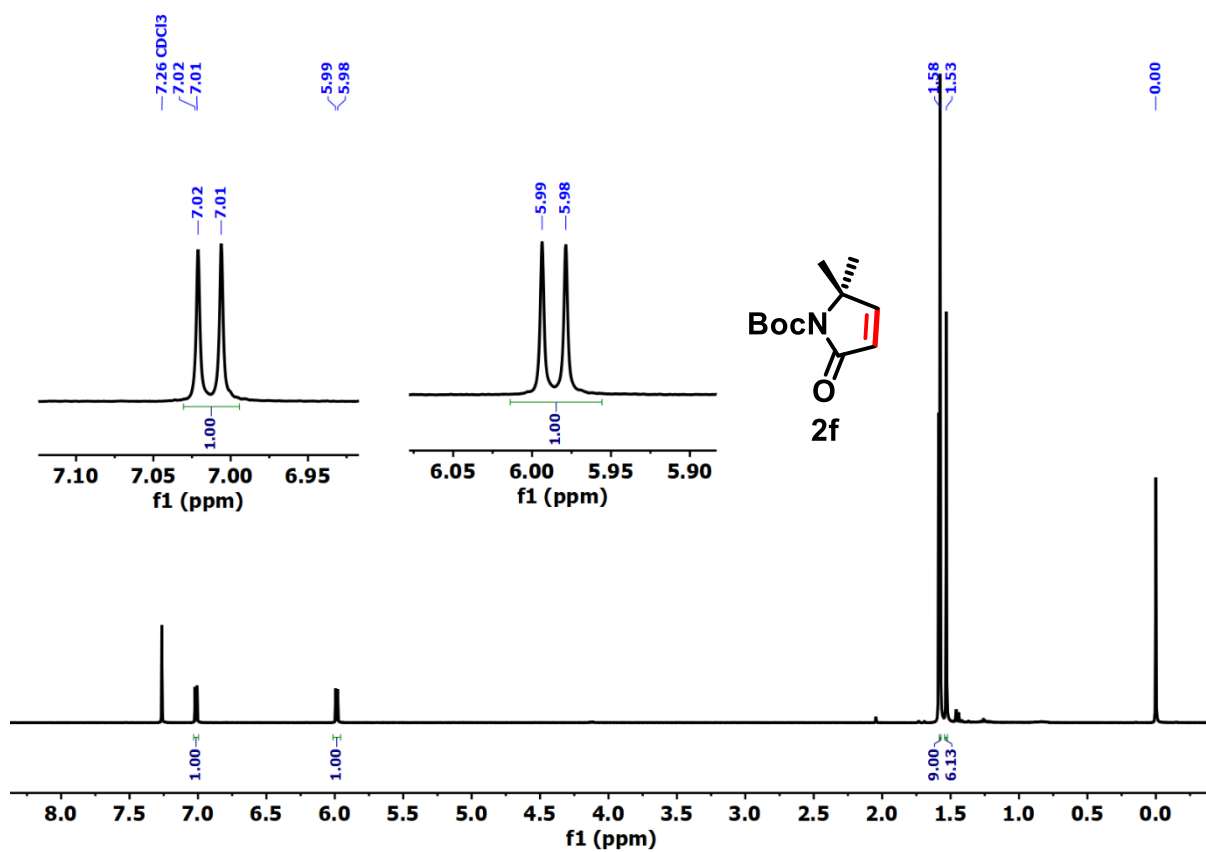


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4B.8.2 Mass of all the synthesized compounds obtained from HRMS

Entry	Compound	$[M \pm Na/H]^{\pm}$	Calculated Mass	Observed Mass	Δm
1	1a	$C_{16}H_{21}NO_4Na$	314.1368	314.1375	0.0007
2	1b	$C_{12}H_{21}NO_4Na$	266.1368	266.1366	0.0002
3	1c	$C_{13}H_{23}NO_4Na$	280.1524	280.1523	0.0001
4	1d	$C_{10}H_{17}NO_4Na$	238.1055	238.1059	0.0004
5	1e	$C_9H_{15}NO_4Na$	224.0899	224.0898	0.0001
6	1f	$C_{11}H_{19}NO_4Na$	252.1212	252.1211	0.0002
7	2a	$C_{16}H_{19}NO_3Na$	296.1262	296.1259	0.0003
8	2b	$C_{12}H_{19}NO_3Na$	248.1262	248.1260	0.0002
9	2c	$C_{13}H_{21}NO_3Na$	262.1418	262.1414	0.0004
10	2d	$C_{10}H_{15}NO_3Na$	220.0949	220.0955	0.0006
11	2e	$C_9H_{14}NO_3$	184.0973	184.0977	0.0004
12	2f	$C_{11}H_{17}NO_3$	234.1105	234.1106	0.0001

Note: Δm = Mass difference, $[M \pm Na/H]^{\pm}$ = Molecular ion.