A Formal Synthesis of (-)-Brasilenol

A Thesis

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By

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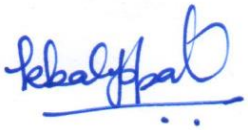
Certificate

This is to certify that this dissertation entitled “A Formal Synthesis of (-)-Brasilenol” towards the partial fulfillment of the BS-MS Dual Degree Programme at the Indian Institute of Science Education and Research, Pune, represents study/work carried out by Tirth Chauhan at Indian Institute of Technology, Bombay under the supervision of Prof. Krishna P. Kaliappan, Department of Chemistry, during the academic year 2023-2024.

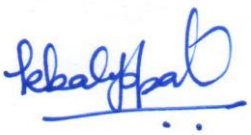
Prof. Srinivasa Hotha



Prof. Krishna P. Kaliappan

Declaration

I hereby declare that the matter embodied in the report entitled “A Formal Synthesis of (-)-Brasilenol” are the result of the work carried out by me at the Department of Chemistry, Indian Institute of Technology, Bombay, under the supervision of Prof. Krishna P. Kaliappan and the same has not been submitted elsewhere for any other degree. Wherever others contribute, every effort is made to clearly indicate this clearly, with due reference to the literature and acknowledgment of the collaborative research and discussions.



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Abstract

Our efforts towards a chiral pool synthesis of (-)-brasilenol from (-)-β-pinene is reported here. Starting from relatively abundant (-)-β-pinene, the unnatural enantiomer (-)-brasilenol was targeted in 11 steps. Use of stereospecific ring-opening was employed to ensure conservation of stereocenter at the isopropyl group, while hydrogenative stereospecific isomerization of exocyclic enone to endocyclic enone was utilized for prevention of racemization of the methyl group.

Acknowledgments

I am grateful to Prof. Krishna P. Kaliappan for providing me with an opportunity to conduct my MS thesis project in Prof. Kaliappan's research group. I also thank the IIT Bombay Department of Chemistry for the facilities. I thank the DST Inspire Scholarship for aiding me with the funding of this work. I thank my lab mates for their academic help and operation of instruments and my family for their motivational support.

Chapter 1

Introduction to Brasilenol

1.1. Introduction

Natural products often come in several (four main) types: terpenoids (derivatives of isoprene) like β-ionone; alkaloids (containing amine moiety) like nicotine; polyketides (acetate and malonate as building blocks) like fluostatin B; and phenylpropanoids (phenylalanine as a building block) like eugenol[1].

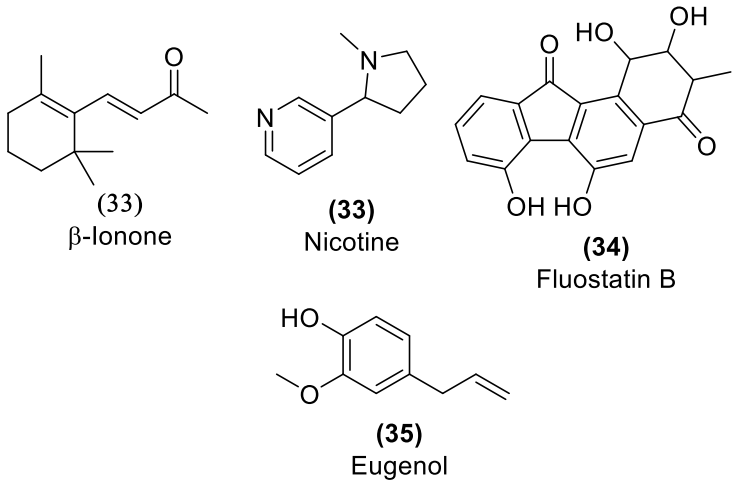

Figure 1: Some well-known natural products of each class of natural products

Brasilenol is a naturally occurring non-isoprenoid sesquiterpenoid (C_{15}), bicyclic, and allylic alcohol[2], with the natural isomer being (3*R*,4*S*,7*R*)-(+)-brasilenol[3]. The molecule belongs to brasilane-skeleton natural products consisting of fused bicyclic 5-6 hydrindane core.

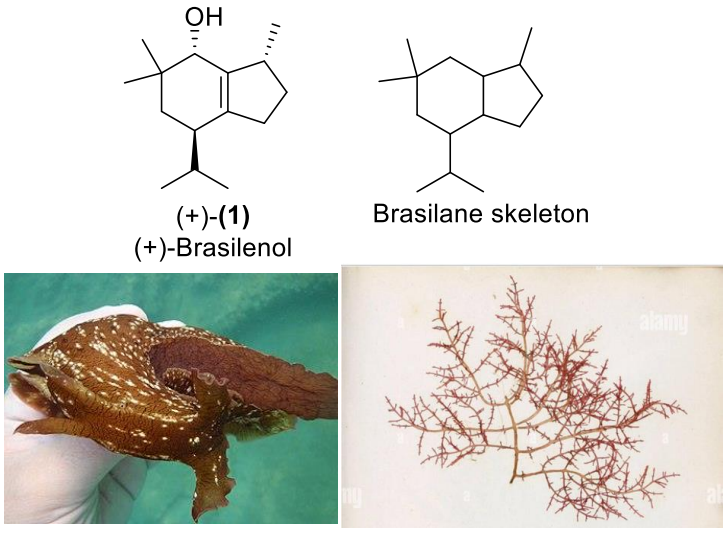

Figure 2: (From Top Left to Bottom Right) Natural brasilenol, brasilane skeleton, Aplysia brasiliana, Laurencia obtusa[4][5]

The brasilane core is present in a whole host of bioactive molecules, some of which are shown in Figure **3**.

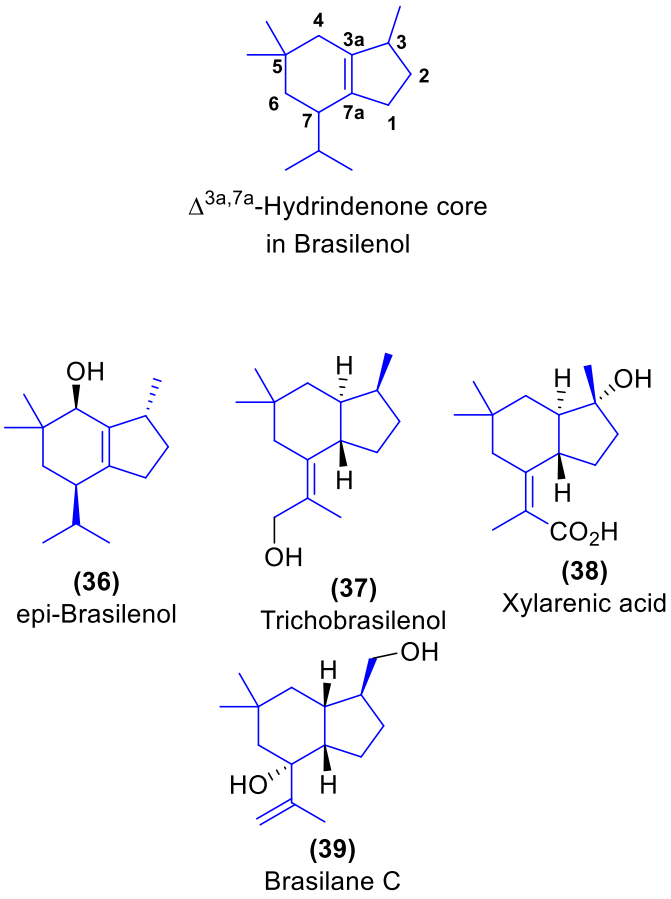

Figure 3: Some other Brasilane core natural products

epi-Brasilenol was isolated from *Aplysia brasiliana* by Stallard *et. al.*[2], trichobrasilenol was isolated from *Trichoderma* fungi by Murai *et. al.*[6], xylarenic acid is an anti-bacterial and cytostatic (against HepG2) natural product isolated from endophytic fungi *Xylaria* by Hu *et. al.*[7], and Brasilane C (along with Brasilane A and B) was isolated from basidiomycete *Coltricia sideroides* by Dong-Bao Hu *et. al.*[8].

(+)-Brasilenol was isolated and spectroscopically analyzed from the digestive gland of the Gulf of Mexico sea hare *Aplysia brasiliana* by Stallard *et al*. in 1977[2], along with epi-brasilenol and halogenated terpenes. They noticed that the sea hare had very few natural predators. When they painted the crab *Callinectes sapidus* with the sea hare's digestive gland extract, the crab became unappetizing to the octopus *Octopus vulgaris*[2]. This suggested an unknown anti-feedant present inside *A. brasiliana*, which was discovered to be brasilenol. Brasilenol is thought to be accumulated by the sea

hare from its food source, the red algae *Laurencia obtusa*, where it is present as a secondary metabolite.

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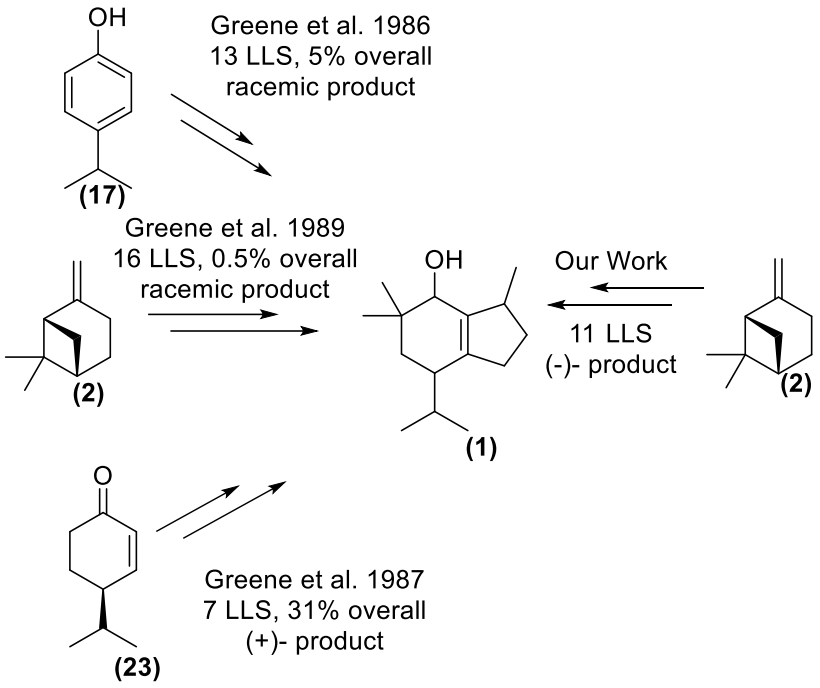
As our lab aims to discover concise and efficient syntheses of natural products that have value as potential medicines or perfumery compounds[9], we set out to carry out the total synthesis of the unnatural enantiomer of the natural product (+)-brasilenol.

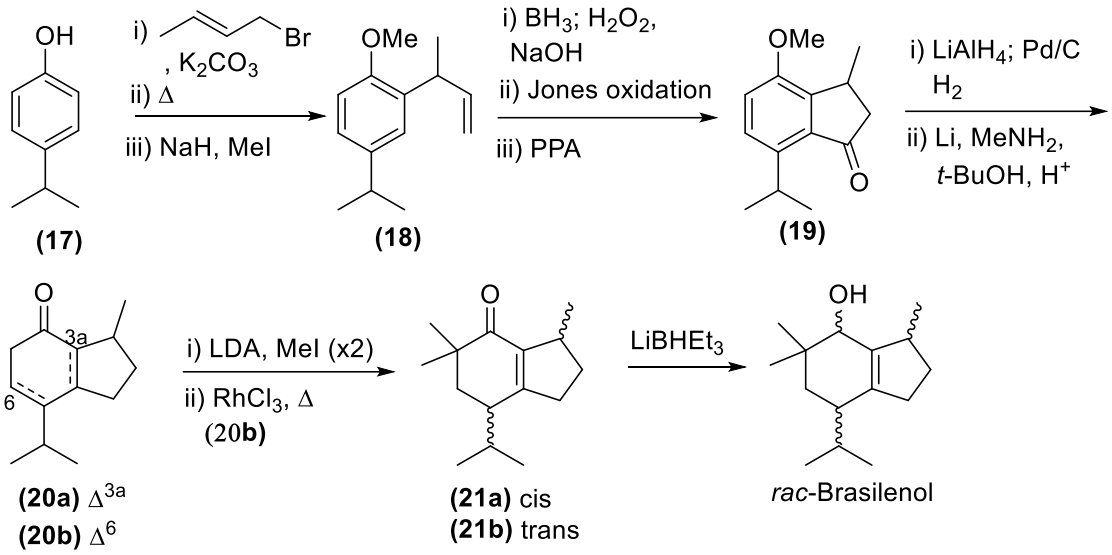
1.2. Literature Review

Greene *et al.*[3][10][11] have conducted significant research in Brasilenol synthesis utilizing achiral petrochemical and naturally available substrates, reporting its first synthesis in 1986[10].



Scheme 1: Previous brasilenol syntheses

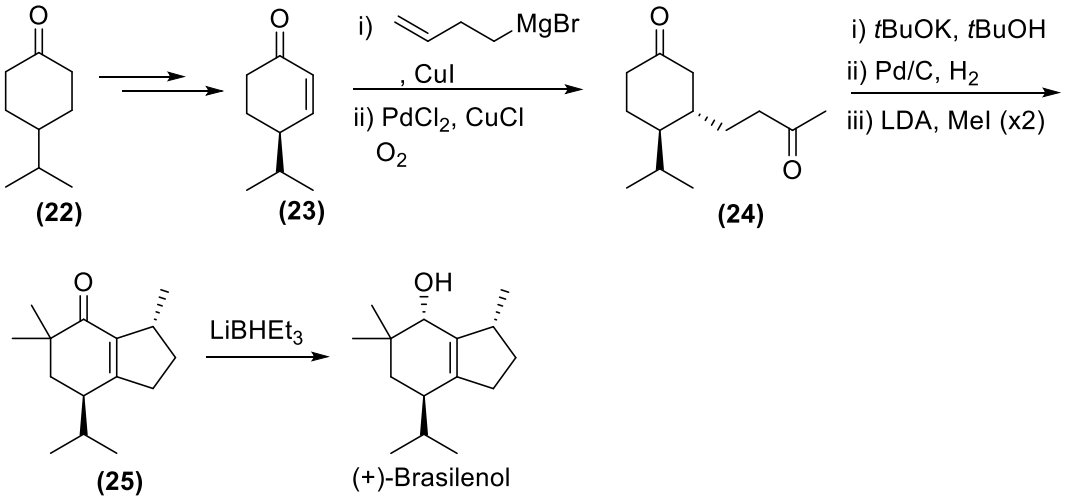
They employed 4-isopropylphenol **(17)** as the starting material and achieved the synthesis of *rac*-brasilenol in 13 steps with a 5% overall yield. They employed Friedel-Craft alkylation of terminal olefin **(18)** to form the cyclopentane ring **(19)**, Birch reduction to dearomatize the benzene ring, and $RhCl_3$-catalyzed olefinic rearrangement to form brasilenone **(21b)**.



Scheme 2: Brasilenol synthesis from 4-isopropylphenol

As the starting material was achiral and no enantioselective reactions were used, the product was naturally racemic.

Greene *et al*., in 1987[3], synthesized (+)-brasilenol in 7 steps in 31% overall yield, utilizing cryptone **(23)** as the starting material. The (racemic) cryptone was itself derived from β-pinene according to the protocols they mentioned.

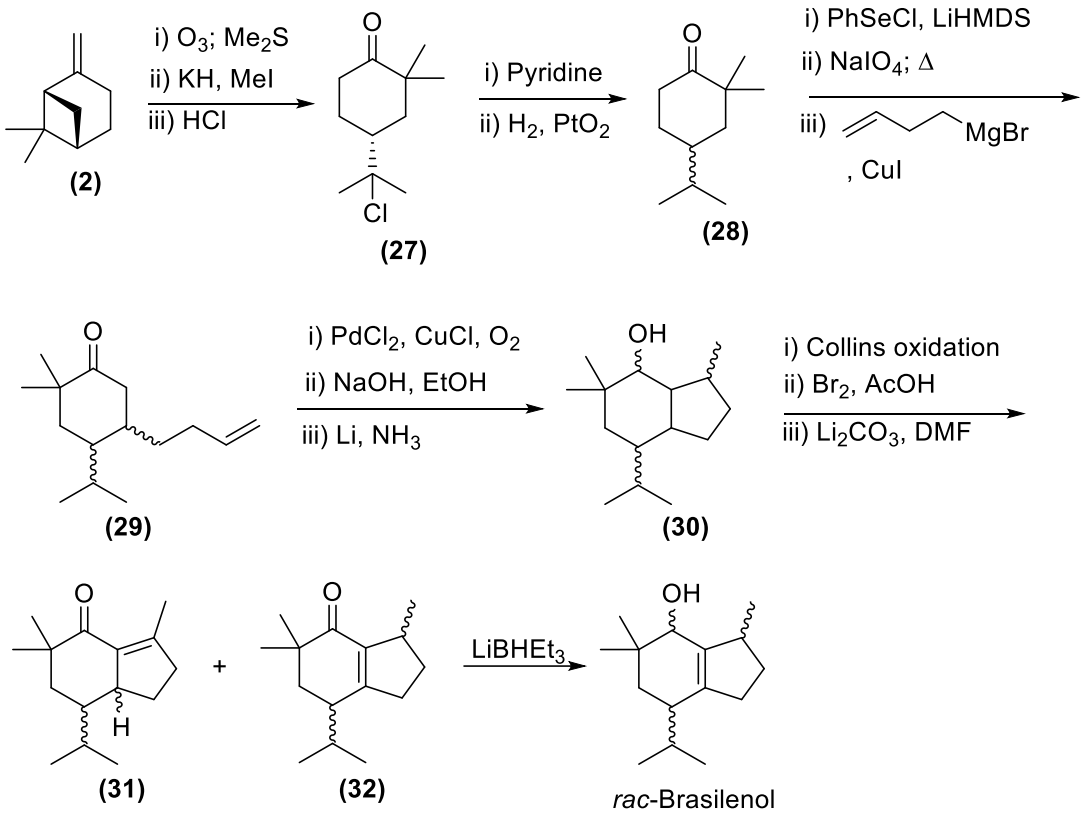


Scheme 3: Enantioselective synthesis of (+)-brasilenol

The ring opening of (+)-nopinone using $AlCl_3$ yields racemic cryptone, while preparation of (*R*)-(-)-cryptone requires additional steps from 4-isopropylcyclohexanone **(22)** utilizing (*R*)-(+)-N-isopropyl-N-(1-phenylethyl)amine as chiral base for enantioselective silylation, which would decrease overall yield from the

reported data. Their key reaction was the aldol ring-closing and hydrogenative enone isomerization to eventually give **(25)**.

Greene *et al.*, in 1989[11], synthesized *rac*-brasilenol in 16 steps and 0.5% overall yield, utilizing β-pinene **(2)** as the starting material.



Scheme 4: Brasilenol synthesis utilizing early-stage dimethylation

They used HCl-mediated ring opening of (+)-nopinone to form tertiary alkyl chloride **(27)** , forming the **(28)** after dehydrohalogenation and hydrogenation. These steps led to racemization. They conducted the dimethylation early in the synthesis, preventing Pd/C-catalyzed isomerization of exocyclic enone **(31)** due to steric crowding from the two geminal methyl groups, requiring enone reduction to ketone and dehydrohalogenation steps to form the required endocyclic enone **(32)**. These steps caused a massive reduction in overall yields.

From the above syntheses, it is evident that the overall yields are often low if starting from commercially available starting materials. It was also seen that no synthesis was helpful for the selective preparation of the unnatural enantiomer (-)-brasilenol in decent yields without racemization from enantiomerically pure starting material. This problem

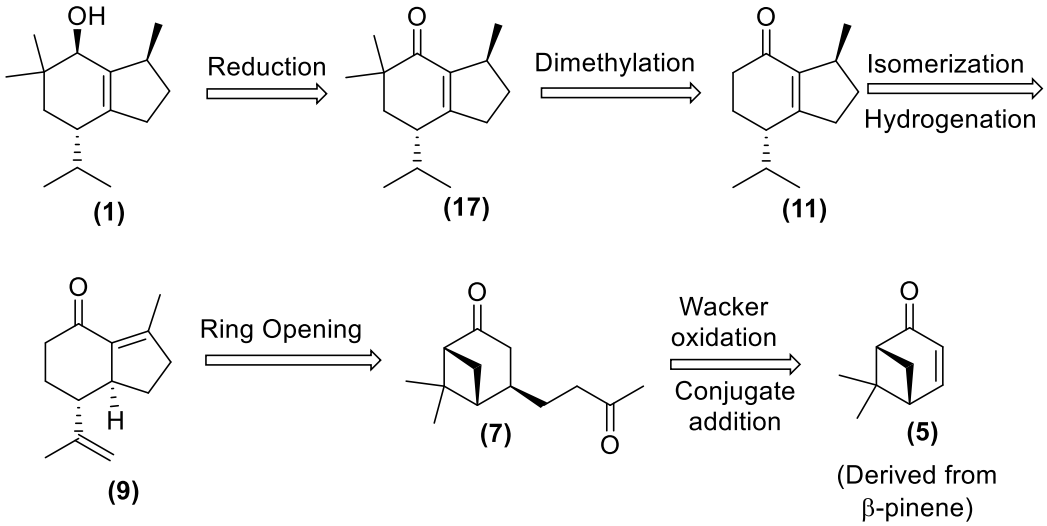
has been addressed in this project, as little-to-no racemization occurs in the conditions employed.

1.3. Objective

The objective of this work is to accomplish the total synthesis of the unnatural enantiomer of the sesquiterpene (-)-brasilenol from the commercially available monoterpene (-)-β-pinene without racemization of the existing chiral centers.

1.4. Retrosynthesis

(-)-Brasilenol was planned to be synthesized according to Scheme **5**. The alcohol could be accessed from the stereoselective reduction of the sterically hindered enone Brasilenone **(17)**. Brasilenone could be traced back to the dimethylation of the bicyclic endocyclic enone **(11)**. This enone could be prepared via the suprafacial hydrindenone C=C migration of the hydrogenated exocyclic enone olefin **(9)**.



Scheme 5: Retrosynthetic approach to (-)-brasilenol

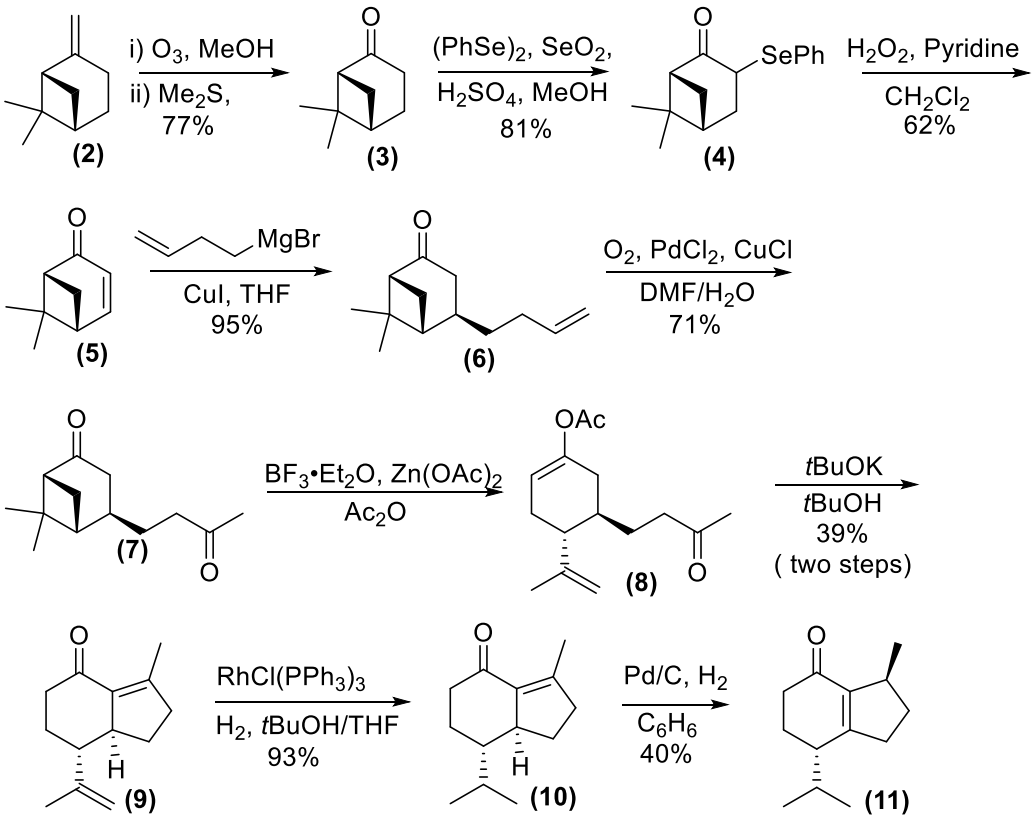
This olefin can be synthesized by the aldol condensation of the ring-opened product from the nopinone-derived diketone **(7)**. This diketone can be prepared from the Wacker oxidation of the 1,4-conjugate addition product of homoallyl Grignard and apoverbenone **(5)**. Apoverbenone has been reported to be made by the selenoxide elimination of nopinone, which was prepared by the ozonolysis of the commercially available β-pinene.

Chapter 2

Results and Discussion

2.1. Forward Synthesis

As proposed in our retrosynthesis, the forward synthesis began (Scheme **6**) with the preparation of apoverbenone **(5)**[12][13]. The monoterpene (-)-β-pinene **(2)**, containing the nopinane core, was first transformed to (+)-nopinone **(3)** by ozonolysis. The nopinone was then dehydrogenated to apoverbenone **(5)**.

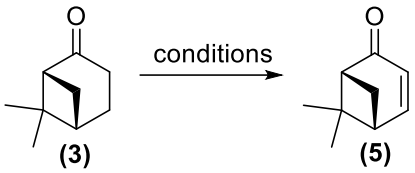


Scheme 6: Forward Synthesis of C-3 bis(desmethyl)brasilenone from β-pinene

Nicolau suggested the direct oxidation of ketones to enones using IBX complexes[16][17], but the method provided poor yields and conversion. A one-step cyclic ketone-to-enone conversion using ammonium chlorochromate[18] gave no conversion. Hence, the direct conversion of (+)-nopinone to (+)-apoverbenone was attempted but yielded sub-par yield and purity.

Phenylselenoxide elimination is a good yielding method where the phenylselenide intermediate can be separated from nopinone with relative ease. This method is known to give better yields in the selenoxide elimination step, but the steric hindrance of the bicyclic ring prevents facile *syn*-elimination of PhSeOH and allows side reactions like the Pummerer reaction, proton-mediated 1,3-diketone formation, and formation of

phenylselenylated enones. All these factors lead to yields of 50% in two steps from nopinone to apoverbenone.

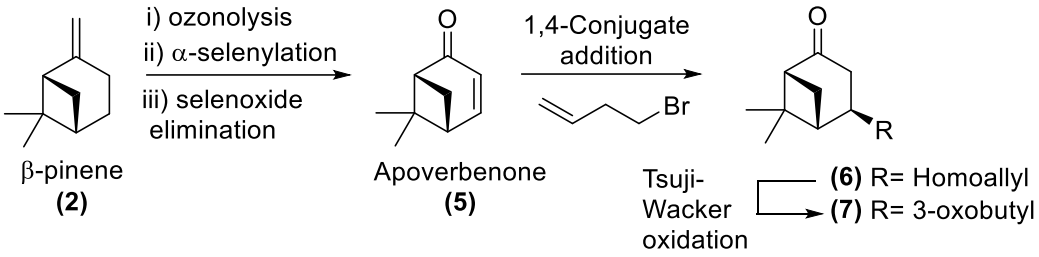


Sr. no.	Conditions	Yields of **(5)**
1.	2 equiv. IBX, DMSO, PhMe, 60 °C, 36 h	42%
2.	2 equiv. IBX, NMO•H_2O, DMSO, 45 °C, 24 h	13%
3.	1.5 equiv. NH_4CrO_3Cl, DMF	N.R.
4.	3 equiv. IBX, 30 mol% PTSA, DMSO, PhMe, 24 h	45%
5.	**i) $(PhSe)_2$, SeO_2, H_2SO_4, MeOH** **ii) H_2O_2, Pyridine, DCM**	**50%**

Table 1: Nopinone to Apoverbenone conversion

The product acquired this way was free of solvents and gave consistently excellent yields in the following step. A notable quality of this apoverbenone was its relatively high melting point above 5 °C.

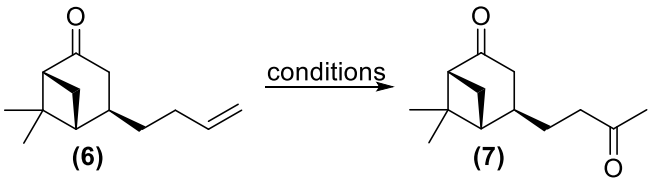
The key 1,4-conjugate addition of homoallyl Grignard-derived cuprate to apoverbenone gave the terminal olefin **(6)**[14] in excellent yields.



Scheme 7: Nopinane ring functional group interconversions

Wacker oxidation of **(6)** to **(7)** was then conducted. The Wacker-type oxidation of **(6)** to **(7)** was also tested for facile and economic synthesis with low Pd consumption. None of the methods tested, as noted below (Table **2**), were found to provide better yields than the standard method requiring 10mol% $PdCl_2$. The use of Pd/C-$KBrO_3$[19] was attractive due to the use of a relatively cheap catalyst and oxidant, but the reaction gave no conversion. $Pd(OAc)_2$-H_2O_2 oxidation[20] yielded the product in a short

duration and with very low catalyst loading, but the product was unstable in the presence of trace acid and hence degraded upon storage.

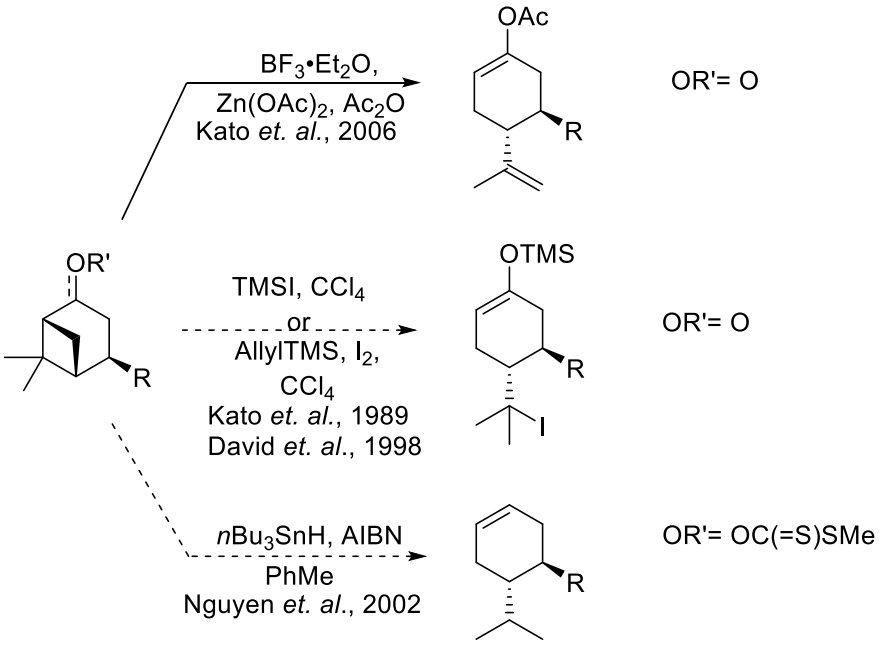


Sr. no.	Conditions	Yield of **(7)**
1.	Pd/C, $KBrO_3$, THF/H_2O, reflux, 24 h	N.R.
2.	$Pd(OAc)_2$, H_2O_2, AcOH, 80 °C, 6 h	30%
3.	$PdCl_2$, DMAc/H_2O, O_2, 80 °C, 48 h	50%
4.	**10 mol% $PdCl_2$, 1 equiv. CuCl, O_2, DMF/H_2O, r.t., 24 h**	**71%**

Table 2: Terminal olefin Wacker oxidation conditions

The use of $PdCl_2$ as the sole catalyst in DMAc-H_2O solvent was effective but complete conversion was not observed[21]. Finally, only the general Tsuji-Wacker oxidation with 1 equiv. CuCl, as a co-catalyst[22], gave good yields in an acceptable time. One point to be noted is that the product formed from 10mol% $PdCl_2$ had a slight brown tint and gave a small amount of slightly non-polar impurities not observed in methods without Cu co-catalyst, although this was inconsequential in the next steps. The DMAc: H_2O solvent and the absence of Cu cocatalyst allowed the formation of a very clean product, albeit at lower conversion.

The cyclobutyl ring was successfully opened under Lewis acid conditions to afford the enol acetate **(8)**. Various methods have been used for the cyclobutane ring opening of the nopinone moiety. Usually, these methods include the use of Bronsted or Lewis acids, but radical mechanisms have been reported, too. Among these methods, the boron trifluoride-mediated acetylative ring-opening[15] has the highest experimental data and proven substrate scope. The presence of substitution at C-3 of the nopinone ring gave an isopropenyl group upon ring scission in a stereospecific fashion.

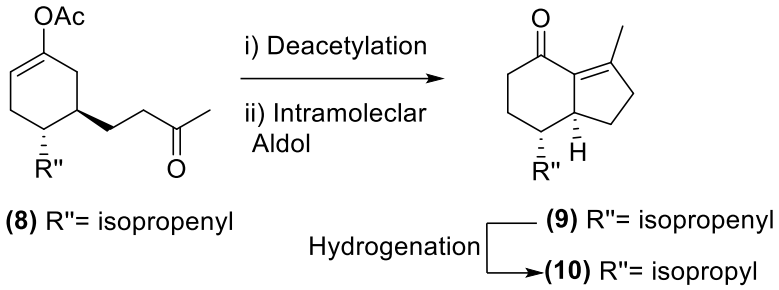


Scheme 8: Cyclobutyl ring opening of nopinone moiety

The use of TMSI[23][24] would give an unstable tertiary alkyl iodide, which would undergo dehydrohalogenation to the isopropylidene group, which would undergo hydrogenation to give a mix of diastereomers. The use of *n*Bu_3SnH radical dehalogenation would bring additional complexities. Hence, this method was not utilized.

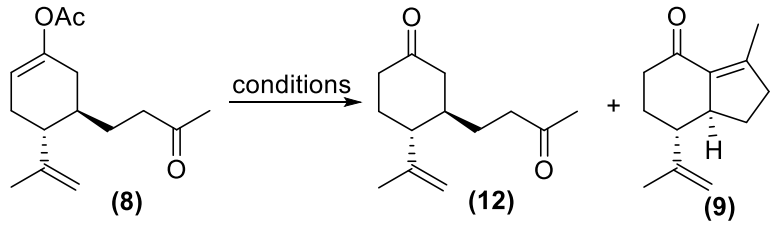
Other methods tend to increase the steps or complexity of purification, for example, the *n*Bu_3SnH-AIBN mediated ring opening of the xanthate ester of nopinol[25] to give cyclohexene ring with an isopropyl side-chain.

Deacetylation of the enol acetate **(8)** and intramolecular aldol condensation yielded the bicyclic olefin **(9)**. The deacetylation of the enol acetate **(8)** was attempted on the ring-opened diketone **(12)**. The logic was to either hydrogenate the diketone or conduct the aldol cyclization of the diketone. Upon treating the enol acetate with K_2CO_3 in methanol, the deacetylation via transesterification occurred, but with low yields, and yielded the aldol product in significant amounts.



Scheme 9: Hydrindenone core preparation and FGI

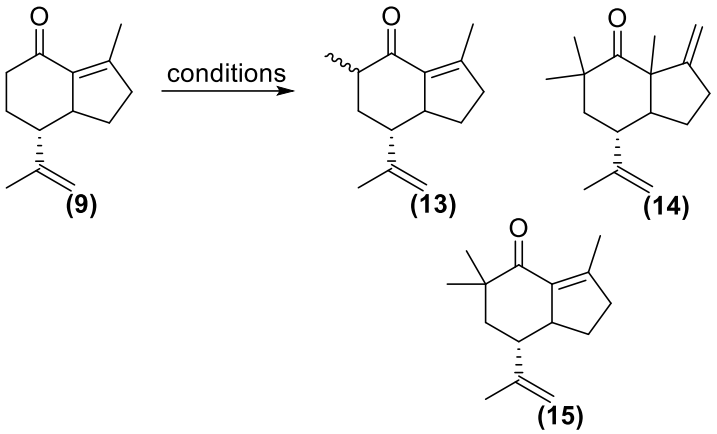
Attempts to conduct Pd metal-catalyzed deacetylation of enol ester[26] also failed to give the desired product. However, it was found that using *t*BuOK in *t*BuOH solution smoothly and quickly provided olefin enone **(9)** through tandem transesterification-aldol cyclization.



Sr. no.	Conditions	Yield
1.	K_2CO_3, MeOH, r.t., 1 h	**(12)**: 26%
2.	$Pd(MeCN)_2Cl_2$, *i*PrOH, reflux, 20 h	Dec.
3.	***t*BuOK, *t*BuOH, r.t., 15 min**	**(9): 80%**

Table 3: Deacetylation of the enol acetate intermediate

The dimethylation of **(9)** was attempted. Our plan was to hydrogenate the isopropenyl group later. Following the protocols from other reported syntheses, LDA and other strong bases were utilized to prepare the enolate, followed by methylation with MeI to get **(15)**. Despite the various methods of alkylation utilizing different bases and conditions, it was found that they all gave low conversion to **(13)** or tri-alkylation to γ-alkene **(14)**. This was likely due to the relative ease of deprotonation of sterically unhindered allylic methyl protons in the C_5 ring, making overalkylation facile. This caused us to revise the sequence and keep the dimethylation step in the late stage.

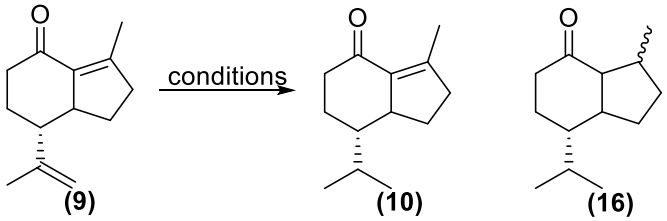


Sr. no.	Conditions	Yield
1.	LDA, MeI, THF, -78 °C (repeated twice)	Low conversion
2.	NaH, MeI, THF, 0 °C-r.t. (repeated twice)	**(13)** formed only
3.	*t*BuOK, MeI, PhMe, 0 °C	**(14)** formed predominantly
4.	LiHMDS, MeI, THF, -70 °C (repeated twice)	**(14)** formed predominantly

Table 4: Dimethylation attempts for the olefinic hydrindenone

Selective hydrogenation of the terminal alkene without isomerization of the double bond and over-reduction of the enone to the enone **(10)** was now our target. Hydrogenation of the isopropenyl group is a relatively facile reaction, but the presence of the enone functional group limited our options of catalysts and reagents.

Using the heterogenous Pt/C (Kaffer modification) catalyst in 1 atm H_2 atmosphere, it was found that this catalyst hydrogenated the isolated olefin group relatively quickly but was prone to the over-hydrogenation of the enone group to the ketone **(16)**. Diimide reduction with cheap, in-situ generated NBSH[27] was tested, but it led to the formation of hydrazone. Finally, Wilkinson's catalyst was employed after testing various solvent systems[28] to selectively and completely hydrogenate the isopropenyl group to the isopropyl group. It must be noted that the use of Pd and Ni catalysts was avoided due to their well-reported tendency to cause epimerization of the isopropyl group during the hydrogenation of the isopropenyl moiety[29].



Sr no.	Conditions	Yield of **(10)**
1.	Pt/C, H_2, EtOH, r.t., 12 h	**(16)** predominantly formed
2.	*o*-NBSCl, N_2H_4•H_2O, MeCN, r.t., 18 h	Hydrazone formed
3.	$RhCl(PPh_3)_3$, H_2, PhH, r.t., 12 h	N.R.
4.	$RhCl(PPh_3)_3$, H_2, PhMe, r.t., 24 h	N.R.
5.	$RhCl(PPh_3)_3$, H_2, PhH/EtOH, r.t., 48 h	30%
6.	**$RhCl(PPh_3)_3$, H_2, THF/*t*BuOH, r.t., 24 h**	**93%**

Table 5: Hydrogenation of olefinic hydrindenone

The exocyclic enone isomerized stereoselectively to the endocyclic enone **(11)** with Pd/C and H_2, but there exist avenues for improvement here as the conversion was often incomplete, indicating loss of activity of catalyst. This enone has already been successfully converted into brasilenol in a report by Greene *et al.*[3], and hence we have completed the formal asymmetric synthesis of brasilenol from apoverbenone in 6 steps.

2.2. Conclusion

The formal synthesis of the unnatural enantiomer of the natural product brasilenol was done in 11 steps with a 9.3% overall yield over 8 steps from β-pinene to the known molecule Δ^3-hydrindenone **(10)**. The ring-opening was conducted relatively late in the synthesis compared to other syntheses involving such a step. This synthesis provides a method of utilizing the readily available (-)-β-pinene, which can be obtained in high enantiomeric purity, to prepare highly enantiopure (-)-brasilenol. The important steps used in this synthesis are Tsuji-Wacker oxidation, Lewis acid-mediated enantiospecific cyclobutyl ring cleavage, and intramolecular aldol condensation.

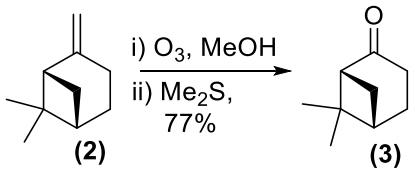
Chapter 3

Materials and Method

3.1. General Information

All reactions were conducted under nitrogen atmosphere using the Schlenk technique (unless noted otherwise). Solvents were dry (unless noted otherwise). Commercially available reagents were used directly without purification (unless noted otherwise). Column chromatography was conducted in Finar 100-200 mesh silica gel 60. TLC was conducted over aluminum-supported silica gel Merck G F254 directly from the box without activation. Petroleum ether 60-80 used in the mobile phase was distilled before use. NMR spectra were recorded in 5mm glass NMR tubes with 0.3-0.5 ml deuterated solvent ($CDCl_3$ or C_6D_6). The residual protonated solvent peak was used as a reference for ^1H and ^{13}C NMR. NMR spectra were recorded on Bruker Avance III 400 (400 MHz). The ^{13}C NMR chemical shifts are rounded off to the nearest decimal. High-Resolution Mass Spectroscopy (HRMS) was conducted on Agilent 6500 with ESI (+ve).

(1*R*,5*S*)-6,6-dimethylbicyclo[3.1.1]heptan-2-one (3)[12]:



26 g (191 mmol) of freshly distilled β-pinene **(2)** was dissolved in 200 ml methanol in a 250 ml 2-neck round-bottom flask equipped with a magnetic stirring bar. A gas inlet tube, with a water trap in between, was fixed in the side neck, while a gas outlet was fixed in the central neck, which was connected to a solvent trap and finally into an acidified KI scrubber. The flask was cooled to -50 °C using a lab chiller (Julabo). Ozonized oxygen was bubbled with stirring for 5 h till the reaction was completed, as observed by TLC. After completion of the reaction, 20 mL of dimethyl sulfide was added dropwise and the reaction was allowed to slowly warm up to r.t. with constant stirring over the course of 24 h. The solvent was removed, and purification was conducted with silica gel column chromatography using 95:5 PE: EtOAc as eluent followed by short-path vacuum distillation to provide 20.3 g (147 mmol) (+)-nopinone **(3)** as a sweet-smelling colorless oil in 77% yield.

^{1}H-NMR (400 MHz, $CDCl_3$) δ(ppm): 2.63 – 2.47 (m, 3H), 2.33 (ddd, *J* = 19.1, 9.1, 2.1 Hz, 1H), 2.23 (dq, *J* = 6.5, 4.1, 3.1 Hz, 1H), 2.04 (dddd, *J* = 13.2, 11.1, 3.9, 2.1 Hz,

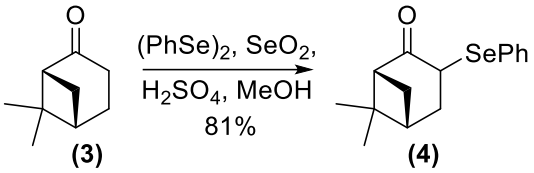
1H), 1.93 (dddd, *J* = 15.4, 8.5, 3.6, 1.8 Hz, 1H), 1.57 (d, *J* = 10.2 Hz, 1H), 1.32 (s, 3H), 0.84 (s, 3H)

^{13}C- NMR (100 MHz, $CDCl_3$) δ(ppm): 215.3, 58.1, 41.4, 40.5, 32.9, 26.0, 25.4, 22.3, 21.5.

HRMS (ESI +ve): $C_9H_{14}O$ Expected [M+H]: 139.1123, Found: 139.1123

R_f: 0.24 (Silica gel, 95:5 PE: EtOAc)

(1*R*,5*R*)-6,6-dimethyl-3-(phenylselanyl)bicyclo[3.1.1]heptan-2-one (4)[13]:



2 g (14.5 mmol) of nopinone **3** was dissolved in 30 mL of MeOH in a two-neck round-bottom flask equipped with a stirring bar. 2.49 g of diphenyl diselenide (7.98 mmol, 0.55 equiv.) and selenium dioxide (17.4 mmol, 1.2 equiv.) were added to this solution. 0.7 ml 98% H_2SO_4 was added as a catalyst and allowed to warm up to r.t. with stirring for 4 h. After the reaction was observed to be completed by TLC, sat. $NaHCO_3$ solution was added slowly and extracted with EtOAc. Purification was done by silica gel column chromatography using 95:5 PE: EtOAc as eluent to yield 3.45 g (11.7 mmol) of **(4)** as an odorous yellow oil with an 81% yield. The TLC on staining and heating with acidified ethanolic Brady's reagent yields a blackish spot that appears very different and slightly less polar than the starting material.

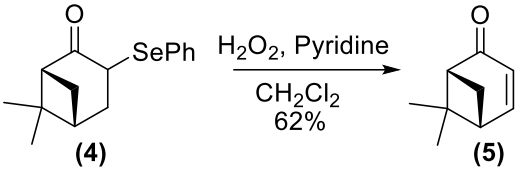
^{1}H-NMR (400 MHz, $CDCl_3$) δ(ppm): 7.71 – 7.64 (m, 2H), 7.31 (m, *J* = 5.0, 1.9 Hz, 3H), 3.86 (dd, *J* = 9.5, 2.1 Hz, 1H), 2.70 (t, *J* = 5.2 Hz, 1H), 2.63 – 2.50 (m, 2H), 2.28 – 2.18 (m, 2H), 1.87 (d, *J* = 10.9 Hz, 1H), 1.35 (s, 3H), 0.84 (s, 3H)

^{13}C-NMR (100 MHz, $CDCl_3$) δ(ppm): 210.3, 134.8, 130.6, 129.3, 128.4, 57.8, 42.3, 40.9, 40.4, 31.7, 26.0, 25.8, 22.2.

HRMS (ESI +ve): $C_{15}H_{17}OSe$ Expected [M+H]: 295.0601, Found: 295.0598

R_f: 0.37 (Silica gel, 95:5 PE: EtOAc)

(1*R*,5*R*)-6,6-dimethylbicyclo[3.1.1]hept-3-en-2-one (5)[13]:



In a round-bottom flask with a stirring bar, a solution of 3.45 g (11.78 mmol) **(4)** in 70 ml CH_2Cl_2, 3.5 mL of pyridine (43 mmol, 3.65 equiv.) was added. The solution was allowed to cool in an ice bath. With strong stirring, 11 mL (23.56 mmol, 2 equiv.) 7-8% aq. H_2O_2 was added drop wise to the above solution. The stirring was continued overnight at r.t., and progress was checked with TLC. Upon complete consumption of the starting material, the reaction was quenched with sat. $NaHSO_3$ solution, extracted with CH_2Cl_2, the combined organic phase was washed with water, dil. HCl (twice), and brine. The organic phases were dried with anhydrous Na_2SO_4, and the solvent was removed in a rotavapor. Purification was done with vacuum distillation, providing 1 g (62%) of apoverbenone as a yellow liquid.

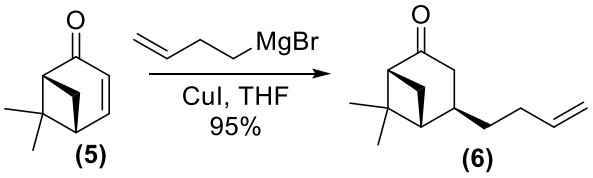
^{1}H-NMR (400 MHz, $CDCl_3$) δ(ppm): 7.52 (ddd, *J* = 8.9, 6.6, 1.0 Hz, 1H), 5.95 (ddd, *J* = 8.9, 1.9, 1.0 Hz, 1H), 2.85 (dtd, *J* = 9.1, 5.5, 1.0 Hz, 1H), 2.72 (td, *J* = 5.9, 1.9 Hz, 1H), 2.14 (d, *J* = 9.2 Hz, 1H), 1.51 (s, 3H), 1.04 (s, 3H)

^{13}C-NMR (100 MHz, $CDCl_3$) δ(ppm): 204.6, 157.3, 126.1, 59.0, 44.2, 42.3, 26.8, 22.6.

HRMS (ESI +ve): $C_9H_{12}O$ [M+H] Expected: 137.0966, Found: 137.0966

R_f: 0.24 (Silica gel, 95:5 PE: EtOAc)

(1*R*,4*R*,5*R*)-4-(but-3-en-1-yl)-6,6-dimethylbicyclo[3.1.1]heptan-2-one (6)[14]:



Homoallyl bromide was prepared by slowly adding HMPA with the help of an addition funnel into boiling 1,4-dibromobutane and continuously collecting the product, followed by re-distillation and storing over fused $CaCl_2$ lumps[30]. Homoallyl magnesium bromide was prepared according to the method outlined in a previous report[31].

In another flame-dried 2-neck round bottom flask, 1.54g (8.08 mmol, 1.1 equiv.) CuI was dried with a flame under a vacuum. 10 mL of dry THF was added to it, and the

suspension was cooled to -40 °C. After the drop-wise addition of the solution of homoallyl magnesium bromide at the same temperature, the suspension turned into a deep blue color. A solution of 1 g (7.34 mmol) apoverbenone in 4 mL of dry THF was added dropwise to the above cuprate reagent. This solution was left to stir at -40 °C for 2 h (monitored by TLC). After all the apoverbenone was consumed, the reaction was quenched with sat. NH_4Cl solution, filtered through a pad of Celite, and extracted with EtOAc (3 x 20 ml). The combined organic phase was washed with water and brine and dried over anhydrous Na_2SO_4. Purification was done by silica gel column chromatography using 95:5 PE: EtOAc as eluent to yield 1.34 g (6.97 mmol) **(6)** as a colorless oil in 95% yield.

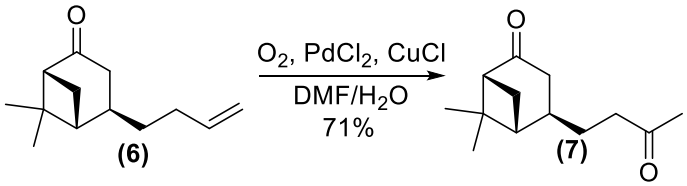
^{1}H-NMR (400 MHz, $CDCl_3$) δ(ppm): 5.79 (ddt, *J* = 16.9, 10.2, 6.7 Hz, 1H), 5.06 – 4.92 (m, 2H), 2.52 (t, *J* = 5.2 Hz, 1H), 2.49 – 2.35 (m, 2H), 2.16 – 1.99 (m, 5H), 1.58 (d, *J* = 10.8 Hz, 1H), 1.46 (q, *J* = 7.1 Hz, 2H), 1.32 (s, 3H), 0.82 (s, 3H)

^{13}C-NMR (100 MHz, $CDCl_3$) δ(ppm): 214.6, 138.4, 114.9, 58.2, 45.5, 41.7, 40.6, 34.3, 31.5, 31.5, 26.2, 22.6, 22.0

HRMS (ESI +ve): $C_{13}H_{20}O$ [M+H] Expected: 193.1592, Found: 193.1603

R_f: 0.31 (Silica gel, 95:5 PE: EtOAc)

(1*R*,4*R*,5*R*)-6,6-dimethyl-4-(3-oxobutyl)bicyclo[3.1.1]heptan-2-one (7):



A general method of Tsuji-Wacker oxidation was followed according to a known protocol[22].

To a round bottom flask with a stirring bar, 690 mg of CuCl (6.97 mmol, 1 equiv.), 123 mg (0.7 mmol, 0.1 equiv.) of $PdCl_2$ and 18 mL of 7:1 DMF: H_2O were added. The flask was flushed with pure O_2 for 2 h. After 2 h, the solution turned from blackish brown to murky green. 1.34 g (6.97 mmol) of **(6)** was added to the solution dropwise and the reaction mixture quickly turned black. The flask was fitted with an oxygen bladder and was vigorously stirred at r.t. for 24 h. The reaction mixture was diluted with EtOAc and washed with dil. HCl to remove Cu(II) and water to remove DMF. The organic layer

was treated with brine and dried over anhydrous Na_2SO_4. Purification was done by silica gel column chromatography with 95:5, 90:10, and 80:20 PE: EtOAc to yield **(7)** as a colorless oil (product number) with 1.01g (70%) yield.

^{1}H-NMR (400 MHz, C_6D_6) δ(ppm): 2.46 (t, *J* = 5.2 Hz, 1H), 2.22 (dd, *J* = 18.2, 8.1 Hz, 1H), 1.96 – 1.88 (m, 1H), 1.78 – 1.67 (m, 3H), 1.65 (s, 3H), 1.64 – 1.52 (m, 2H), 1.37 – 1.18 (m, 2H), 1.14 (d, *J* = 10.8 Hz, 1H), 0.97 (s, 3H), 0.62 (s, 3H)

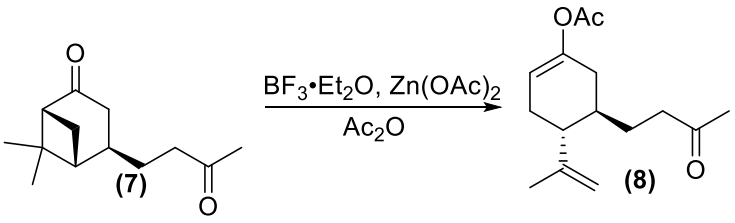
^{13}C-NMR (100 MHz, C_6D_6) δ(ppm): 210.4, 205.6, 57.6, 45.4, 40.8, 40.6, 40.0, 31.3, 29.1, 28.5, 25.6, 22.1, 21.4.

HRMS (ESI +ve): $C_{13}H_{20}O_2$ [M+H] Expected: 209.1542, Found: 209.1554

IR (cm^{-1}): 2952-2928 (sp^3 C-H str., strong), 1714, 1703 (C=O str., strong)

R_f: 0.17 (Silica gel, 80:20 PE: EtOAc)

(4*R*,5*R*)-5-(3-oxobutyl)-4-(prop-1-en-2-yl)cyclohex-1-en-1-yl acetate (8):

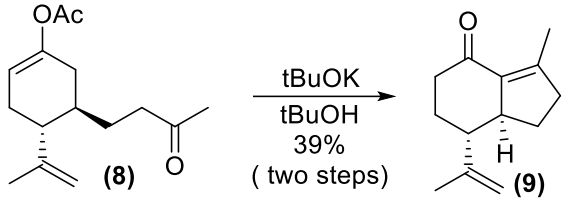


A slightly modified method used elsewhere was used for the cyclobutane ring-opening[15], the primary modification being reaction duration.

A solution of 1.01 g (4.85 mmol) of diketone **(7)** in 15 ml of Ac_2O was added to an oven-dried 2-neck round bottom flask with a stirring bar equipped with nitrogen flow. To this, 950mg (5.18mmol, 1.1 equiv.) of $Zn(OAc)_2$ was added, and to the above ice-cold suspension, 0.4 mL of BF_3•Et_2O was added slowly. The suspension was allowed to warm up to r.t. with stirring for 4h. The reaction was quenched with water and extracted with EtOAc, followed by washing with water, sat. $NaHCO_3$, and brine. The organic phase was collected and dried with Na_2SO_4. The solvent was removed under reduced pressure, and partial purification was done with silica gel column chromatography using 80:20 PE: EtOAc. Eluent to yield 1.13 g **(8)** of yellowish liquid. The NMR (^{1}H and ^{13}C) of this compound was impure but confirmational for the presence of isopropenyl, enol acetate, and aliphatic ketone groups. This crude product was carried forward as such in the next step

R_f: 0.38 (Silica gel, 80:20 PE: EtOAc)

(7*R*,7a*S*)-3-methyl-7-(prop-1-en-2-yl)-1,2,5,6,7,7a-hexahydro-4H-inden-4-one (9):



The method outlined elsewhere was used[3].

201 mg of the crude enol acetate obtained above was dissolved in 25 mL of *t*BuOH, and under stirring, 1.1 mL (2 equiv.) of 1M *t*BuOK in *t*BuOH was added drop wise. After 20 min. (TLC), the reaction mixture was quenched with sat. NH_4Cl solution and extracted with EtOAc. After treatment with brine and drying the solution with anhydrous Na_2SO_4, the solvent was removed under reduced pressure. Purification was done with silica gel column chromatography with 95:5 PE: EtOAc as eluent to yield 89 mg (39%, two steps) product **(9)** as a pale-yellow liquid.

^{1}H-NMR (400 MHz, $CDCl_3$) δ(ppm): 4.84 – 4.73 (m, 2H), 2.89 (m,1H), 2.50 (ddd, *J* = 17.4, 4.9, 2.3 Hz, 1H), 2.46 – 2.22 (m, 3H), 2.07 (dt, *J* = 2.5, 1.2 Hz, 3H), 2.06 – 1.96 (m, 2H), 1.93 – 1.85 (m, 1H), 1.85 – 1.74 (m, 1H), 1.74 – 1.69 (m, 3H), 1.41 (ddt, *J* = 12.7, 10.9, 9.6 Hz, 1H)

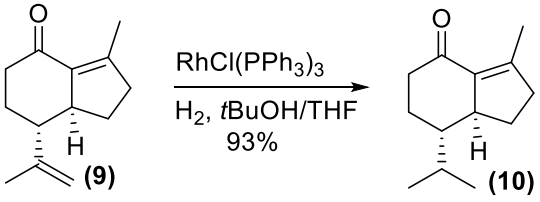
^{13}C-NMR (100 MHz, $CDCl_3$) δ(ppm): 200.2, 154.1, 147.0, 134.7, 111.1, 51.8, 49.9, 41.2, 38.5, 30.2, 30.0, 19.4, 16.5.

HRMS (ESI +ve): Expected [M+H]: 191.1435, Found: 191.1435

IR (cm^{-1}): 2928, 2871, 1678 (C=O str, strong), 1622, 1454, 1374, 1263

R_f: 0.27 (Silica gel, 95:5 PE: EtOAc)

(7*S*,7a*S*)-7-isopropyl-3-methyl-1,2,5,6,7,7a-hexahydro-4H-inden-4-one (10):



The conditions were used as reported elsewhere[29].

A solution of 105 mg olefin **(9)** in 3 mL of 1:1 *t*BuOH/THF was added to a round bottom flask with a stirring bar. The solution was degassed in nitrogen *via* vacuum-N_2 cycling (10 times), and 5 mol% $RhCl(PPh_3)_3$ was added. Then, the solution was degassed with hydrogen *via* vacuum-H_2 cycling (10 times). After 24 h (TLC), the solvent was removed, and purification was performed using silica gel column chromatography (95:5 PE: EtOAc) to yield 100 mg (93%) of the hydrogenated product **(10)** as a faintly yellow liquid. The data matches with the ones reported in a previous report [12].

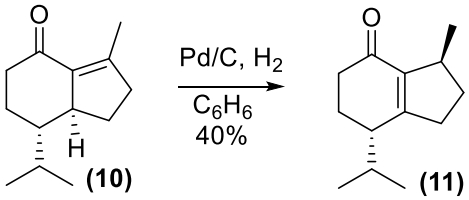
^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 2.75 (dddd, J = 14.6, 9.8, 5.0, 2.5 Hz, 1H), 2.53 – 2.36 (m, 2H), 2.33 – 2.18 (m, 2H), 2.16 – 2.09 (m, 1H), 2.07 (s, 3H), 1.84 (ttd, *J* = 11.5, 6.3, 5.7, 2.7 Hz, 2H), 1.52 – 1.37 (m, 2H), 1.31 (tt, *J* = 11.8, 2.9 Hz, 1H), 0.96 (d, *J* = 7.0 Hz, 3H), 0.83 (d, *J* = 7.0 Hz, 3H).

^{13}C-NMR (100 MHz, $CDCl_3$) δ(ppm): 200.9, 153.4, 135.4, 49.7, 48.7, 41.4, 38.7, 30.4, 28.4, 23.8, 21.5, 16.5, 16.2.

HRMS (ESI +ve): Expected [M+H]: 193.1592, Found: 193.1616

R_f: 0.69 (Silica gel, 95:5 PE: EtOAc, three times)

(3*S*,7*S*)-7-isopropyl-3-methyl-1,2,3,5,6,7-hexahydro-4H-inden-4-one (11)[13]:



According to the method used by Greene *et al.* 1987, to a 100 mg exocyclic enone solution in degassed dry benzene, 50 wt% of 10% Pd/C was added. The suspension was heated to 60 °C in a hydrogen atmosphere under slow stirring for 7 h. The product appeared as a slightly more polar spot under shortwave UV. The solution was then filtered through a pad of Celite and evaporated under reduced pressure. Purification was done by silica gel column chromatography with CH_2Cl_2 to yield the rearranged enone **(11)** as a volatile brownish solid in 40mg (40%) yield.

^{1}H-NMR (400 MHz, C_6D_6) δ(ppm): 3.22 – 3.10 (m, 1H), 2.36 (dt, *J* = 16.2, 4.8 Hz, 1H), 2.23 – 1.95 (m, 4H), 1.89 – 1.64 (m, 4H), 1.50 – 1.39 (m, 1H), 1.26 (d, *J* = 6.9 Hz, 3H), 0.71 (d, *J* = 6.9 Hz, 3H), 0.53 (d, *J* = 6.9 Hz, 3H)

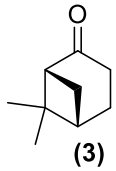
^{13}C-NMR (100 MHz, C_6D_6) δ(ppm): 196.1, 142.8, 114.5, 42.8, 38.3, 38.1, 33.8, 31.2, 29.3, 23.2, 20.8, 19.5, 17.5.

HRMS (ESI +ve): Expected [M+H]: 193.1592, Found: 193.1615

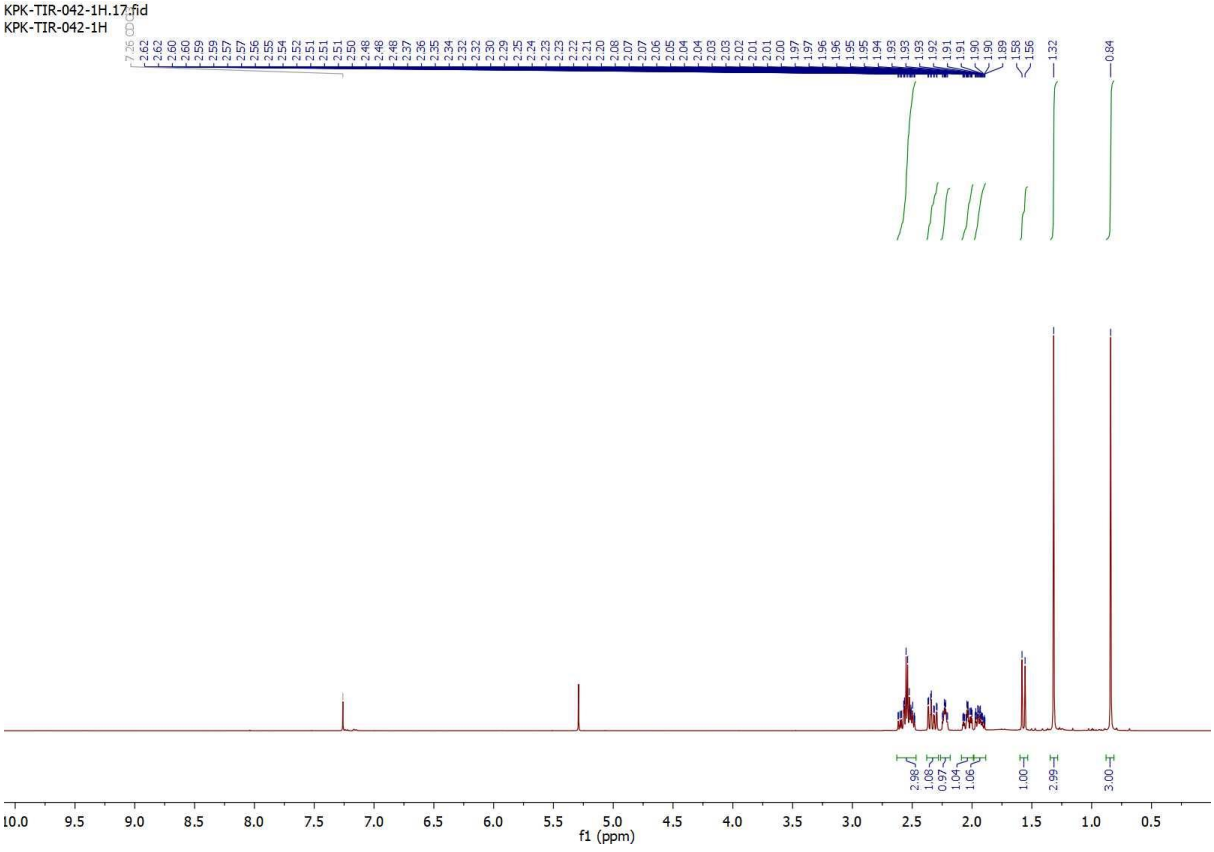
R_f: 0.24 (Silica gel, 95:5 PE: EtOAc)

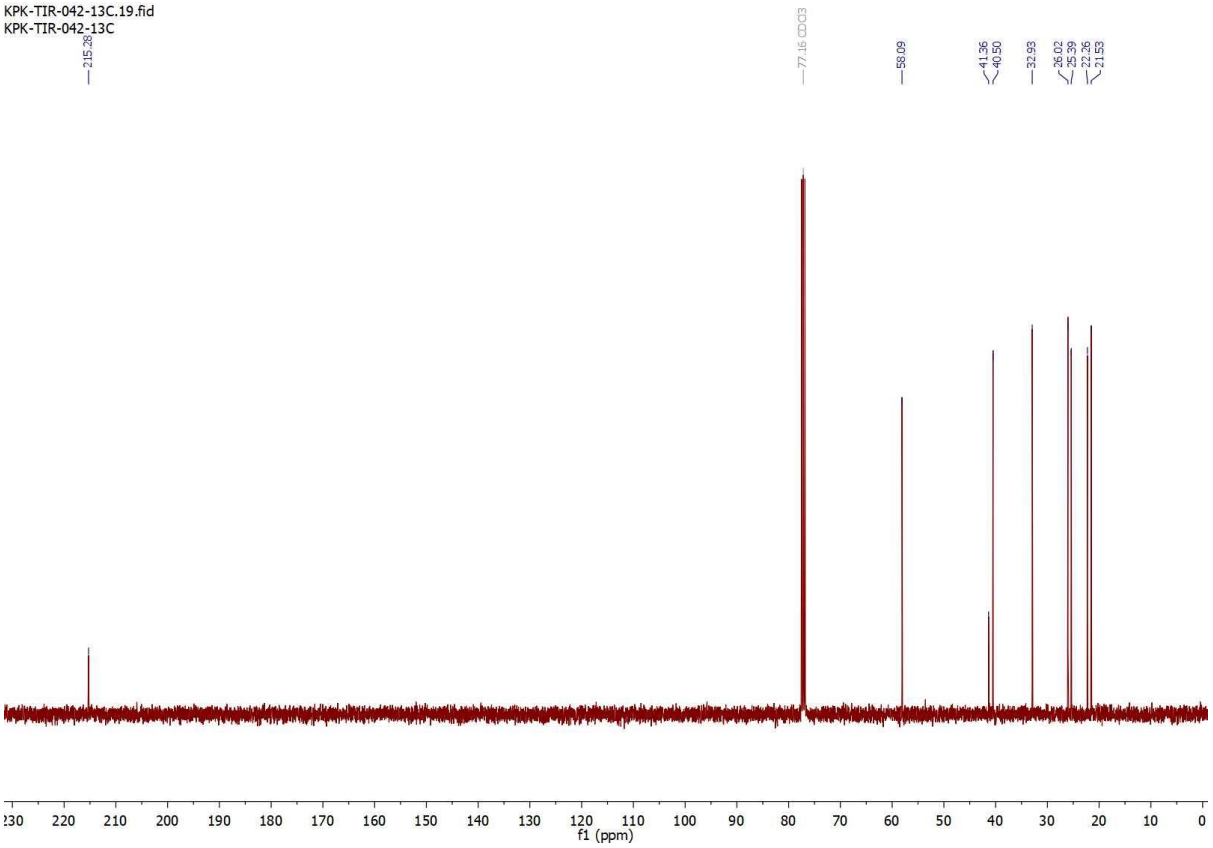
3.2. Spectral Data

(1*R*,5*S*)-6,6-dimethylbicyclo[3.1.1]heptan-2-one (3):

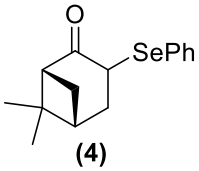


(3)

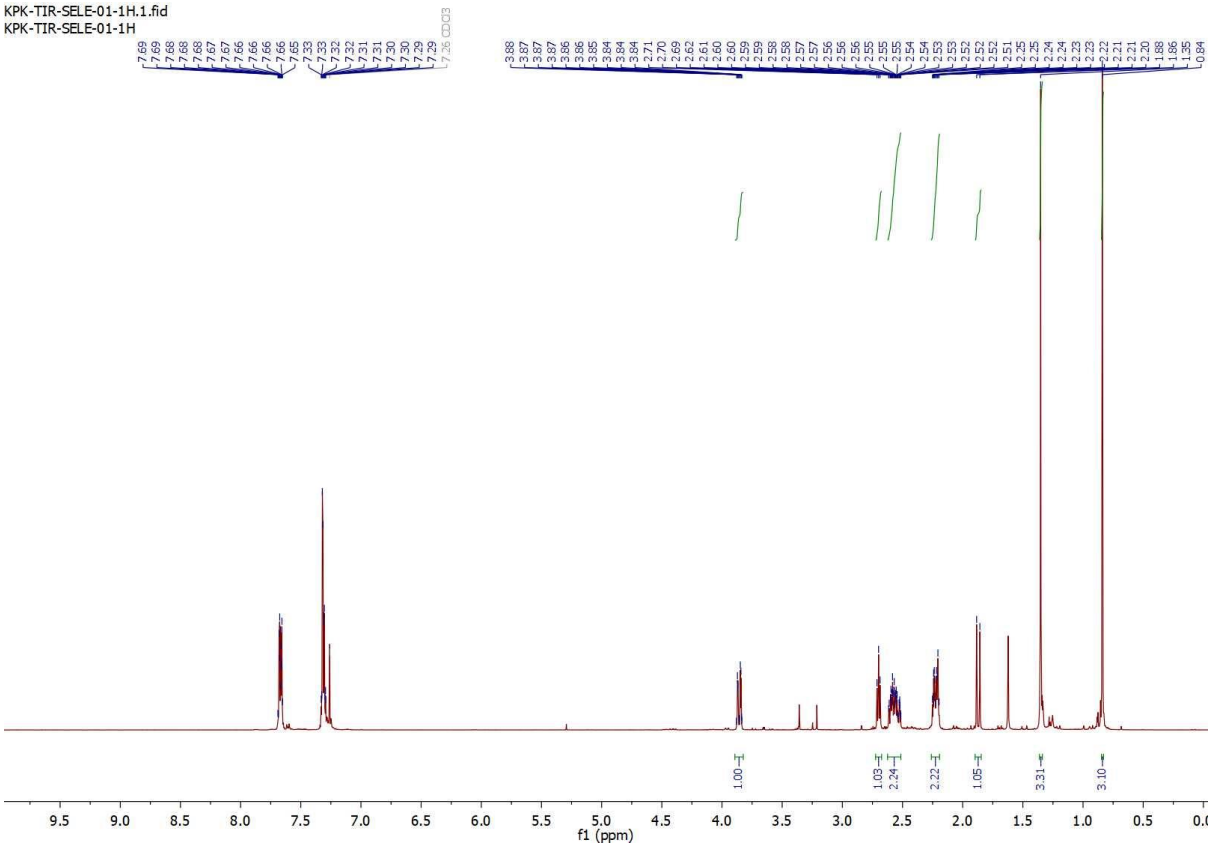


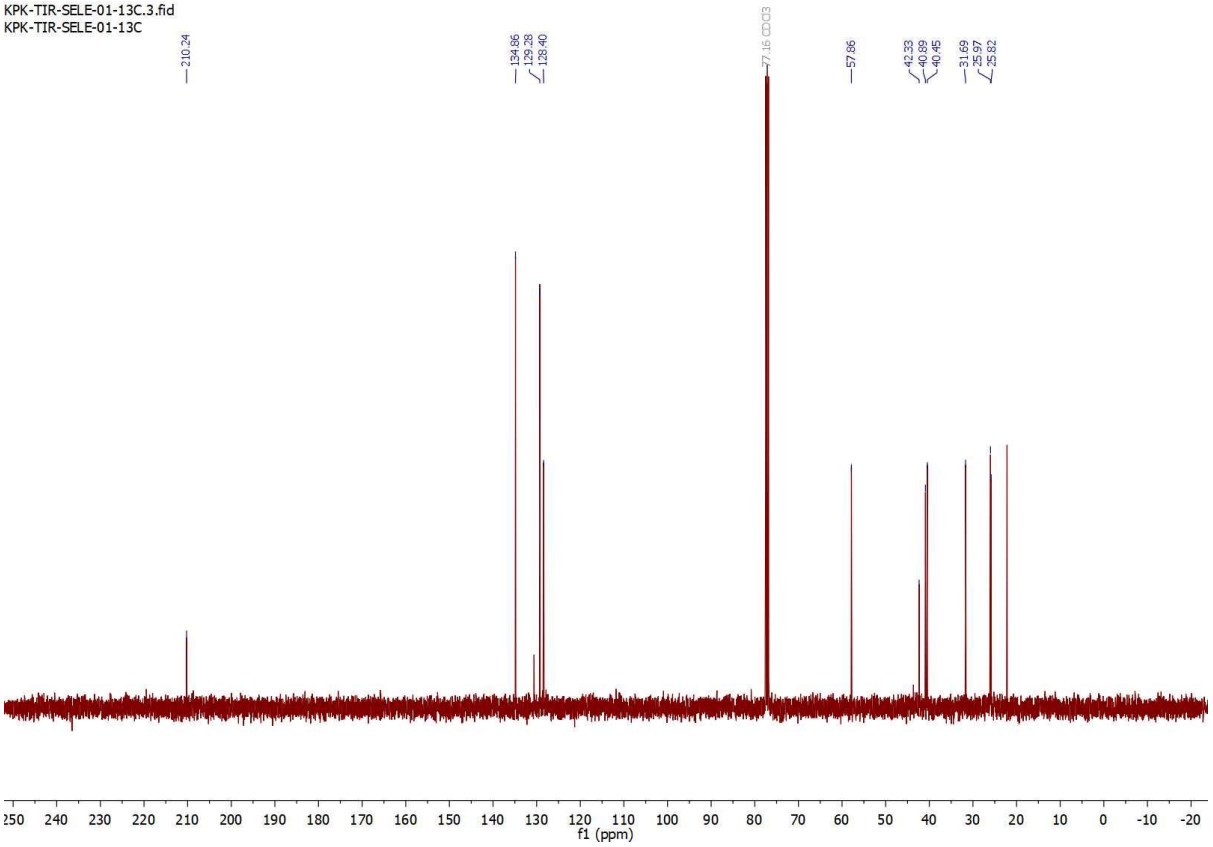


(1*R*,5*R*)-6,6-dimethyl-3-(phenylselanyl)bicyclo[3.1.1]heptan-2-one (4):

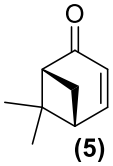


(4)

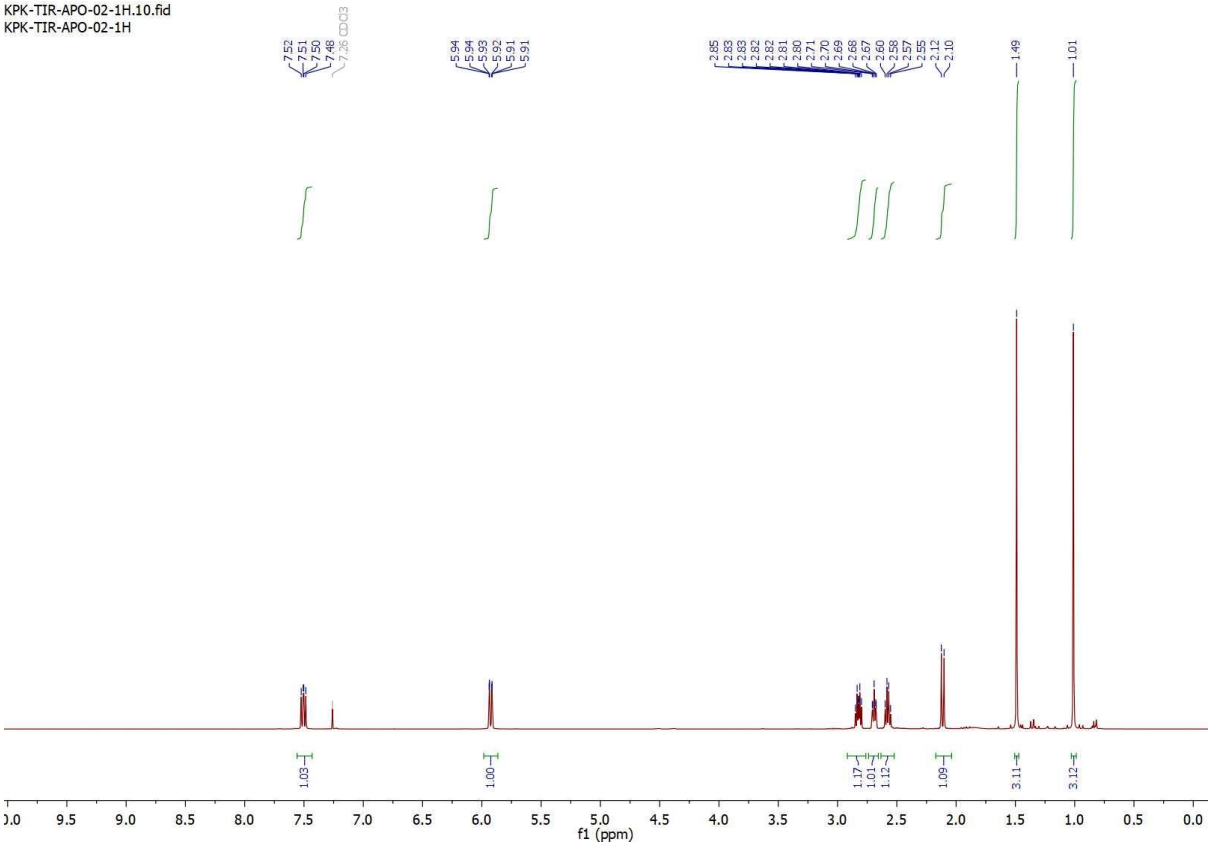




(1*R*,5*R*)-6,6-dimethylbicyclo[3.1.1]hept-3-en-2-one (5):



(5)


KPK-TIR-APO-02-1H.10.fid
KPK-TIR-APO-02-1H
7.52
7.51
7.50
7.48
7.26 CDCl3
5.94
5.94
5.93
5.92
5.91
5.91
2.85
2.83
2.83
2.82
2.82
2.81
2.80
2.71
2.70
2.69
2.68
2.67
2.60
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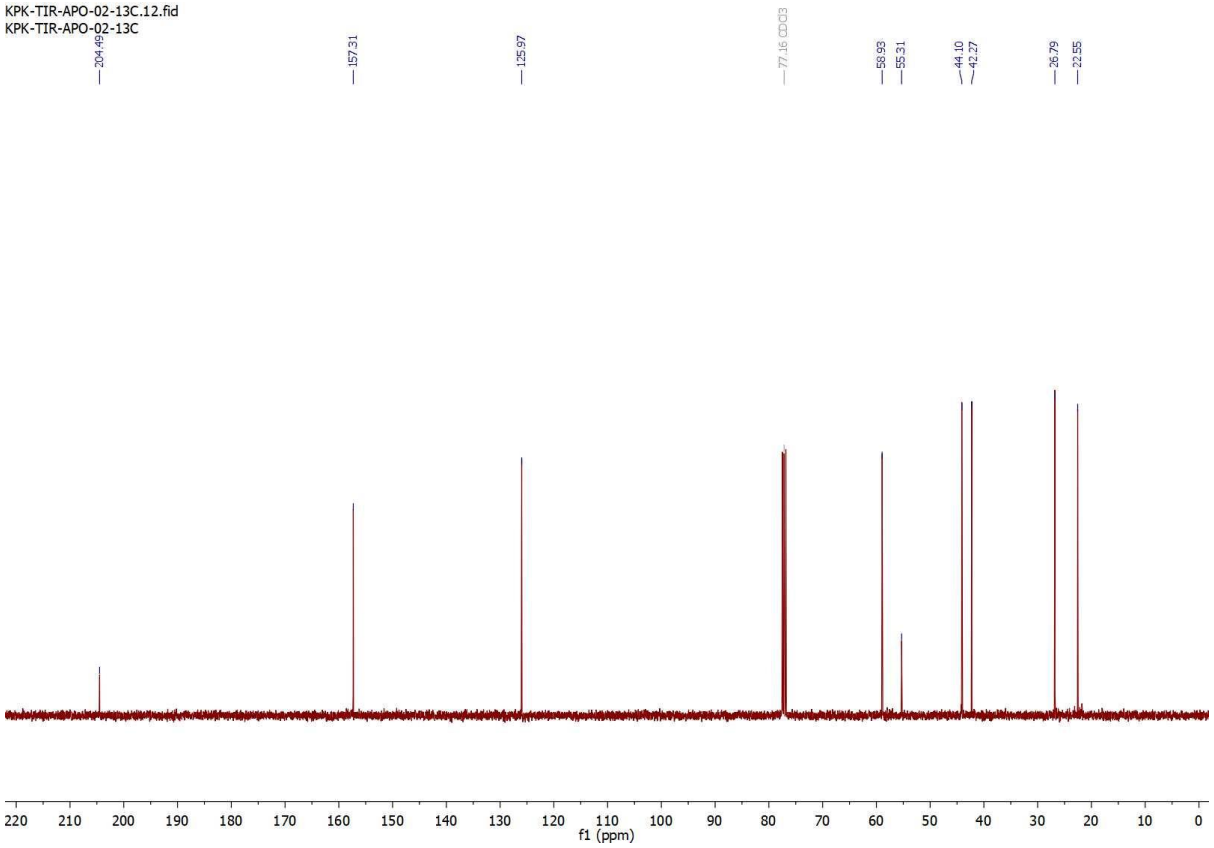
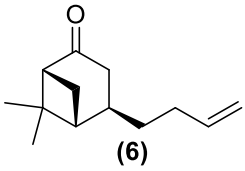
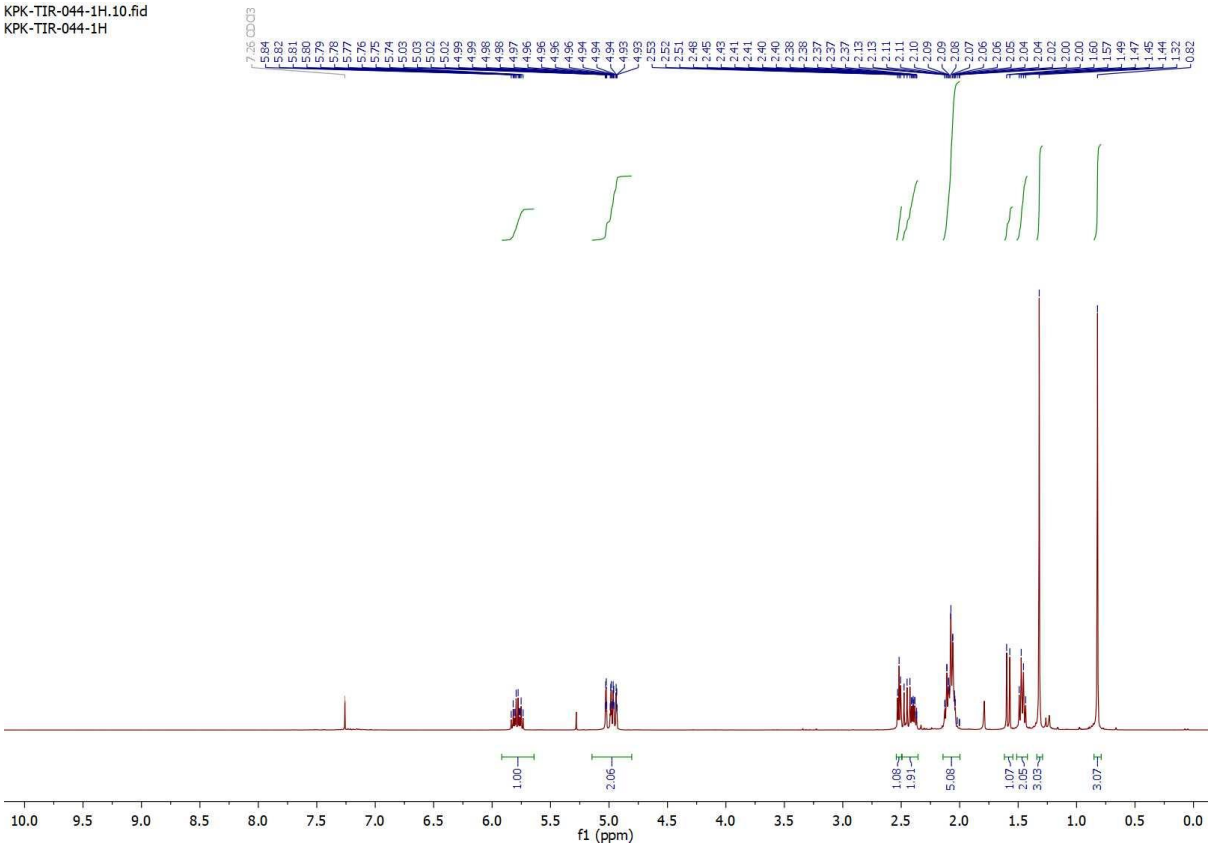
1.12
1.09
3.11
3.12
f1 (ppm)

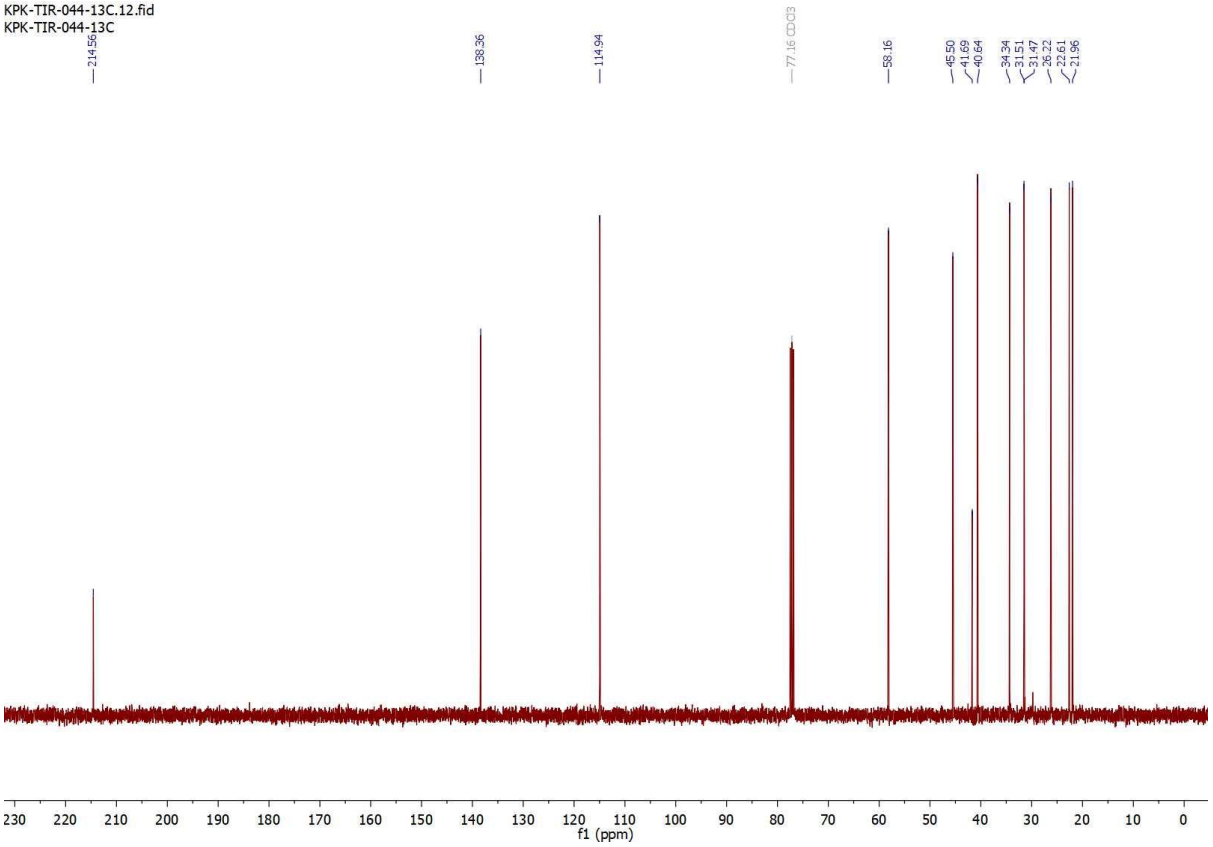


(1*R*,4*R*,5*R*)-4-(but-3-en-1-yl)-6,6-dimethylbicyclo[3.1.1]heptan-2-one (6):

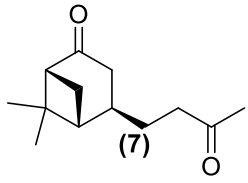


(6)

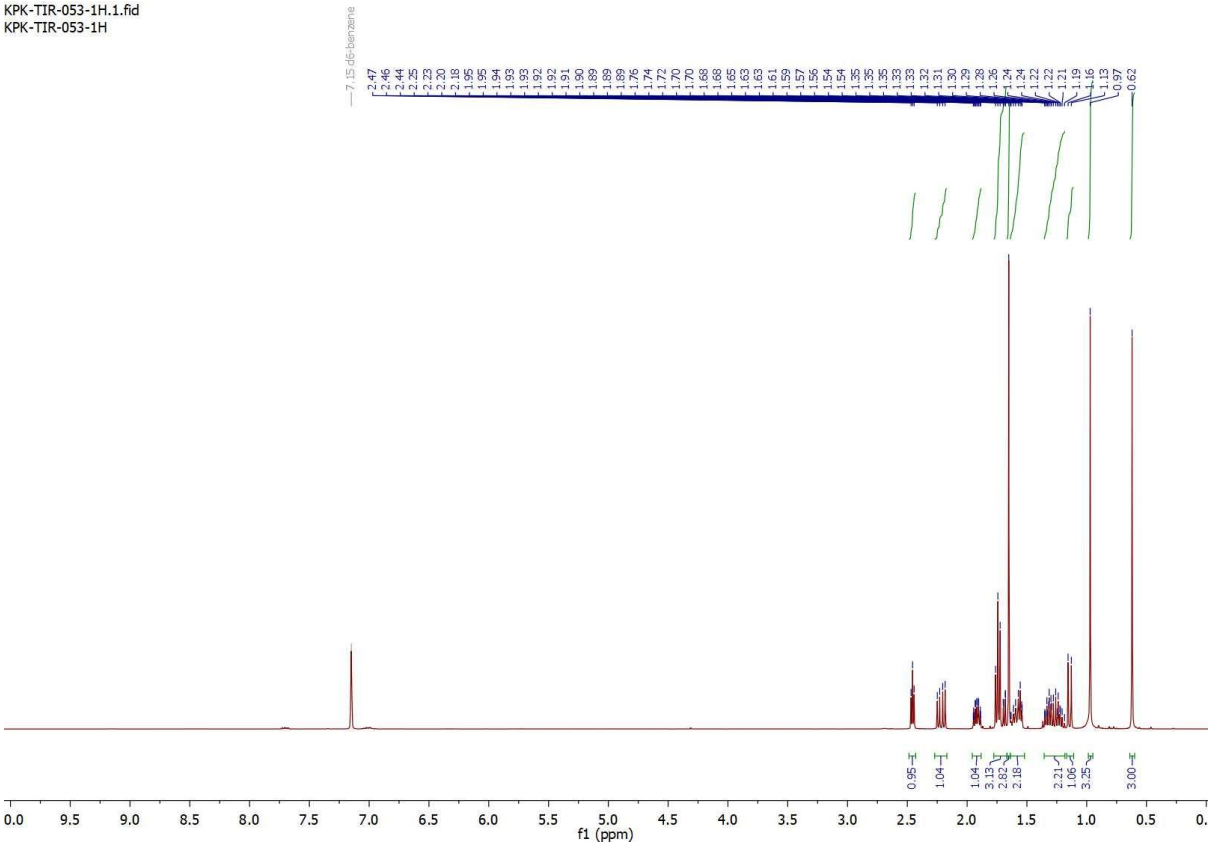


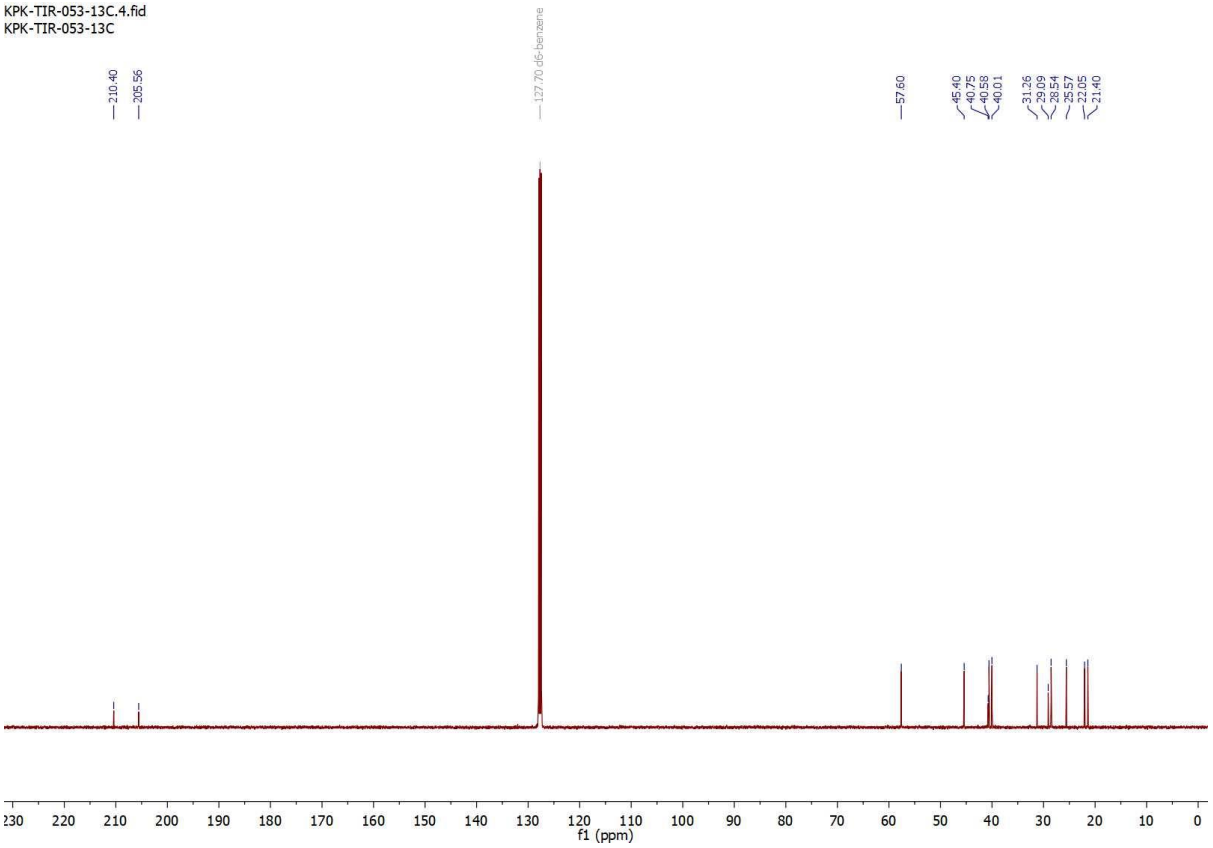


(1*R*,4*R*,5*R*)-6,6-dimethyl-4-(3-oxobutyl)bicyclo[3.1.1]heptan-2-one (7):

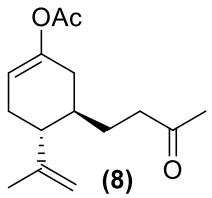


KPK-TIR-053-1H.1.fid
KPK-TIR-053-1H

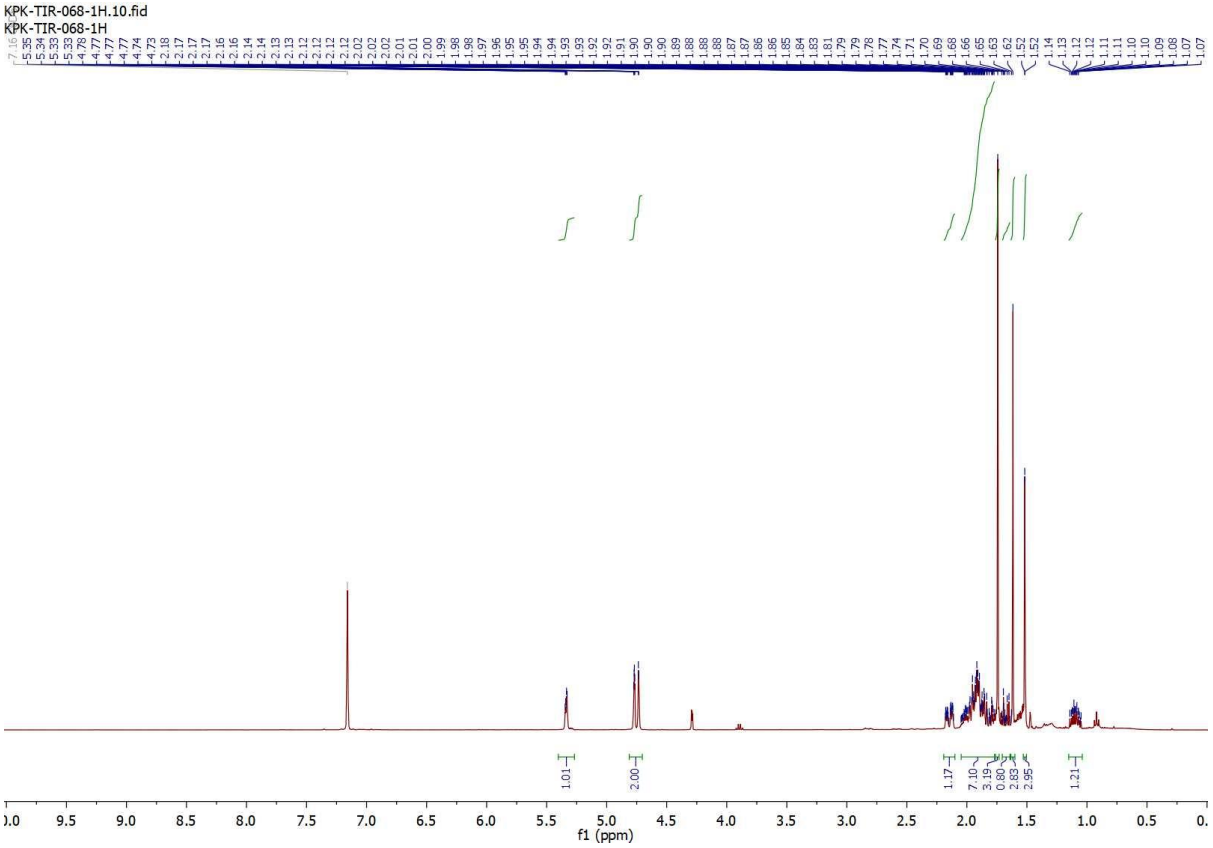


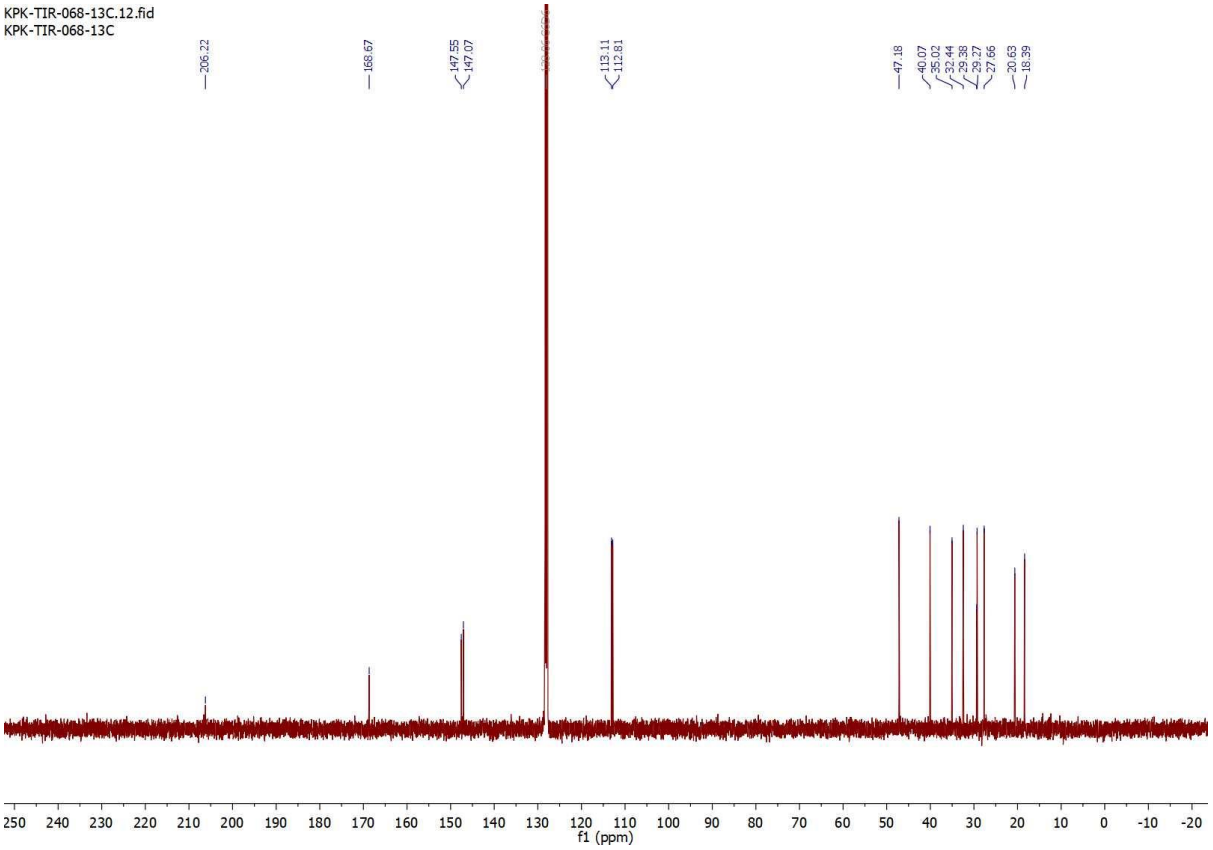


(4*R*,5*R*)-5-(3-oxobutyl)-4-(prop-1-en-2-yl)cyclohex-1-en-1-yl acetate (8):

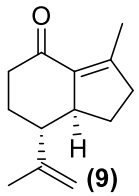


(8)

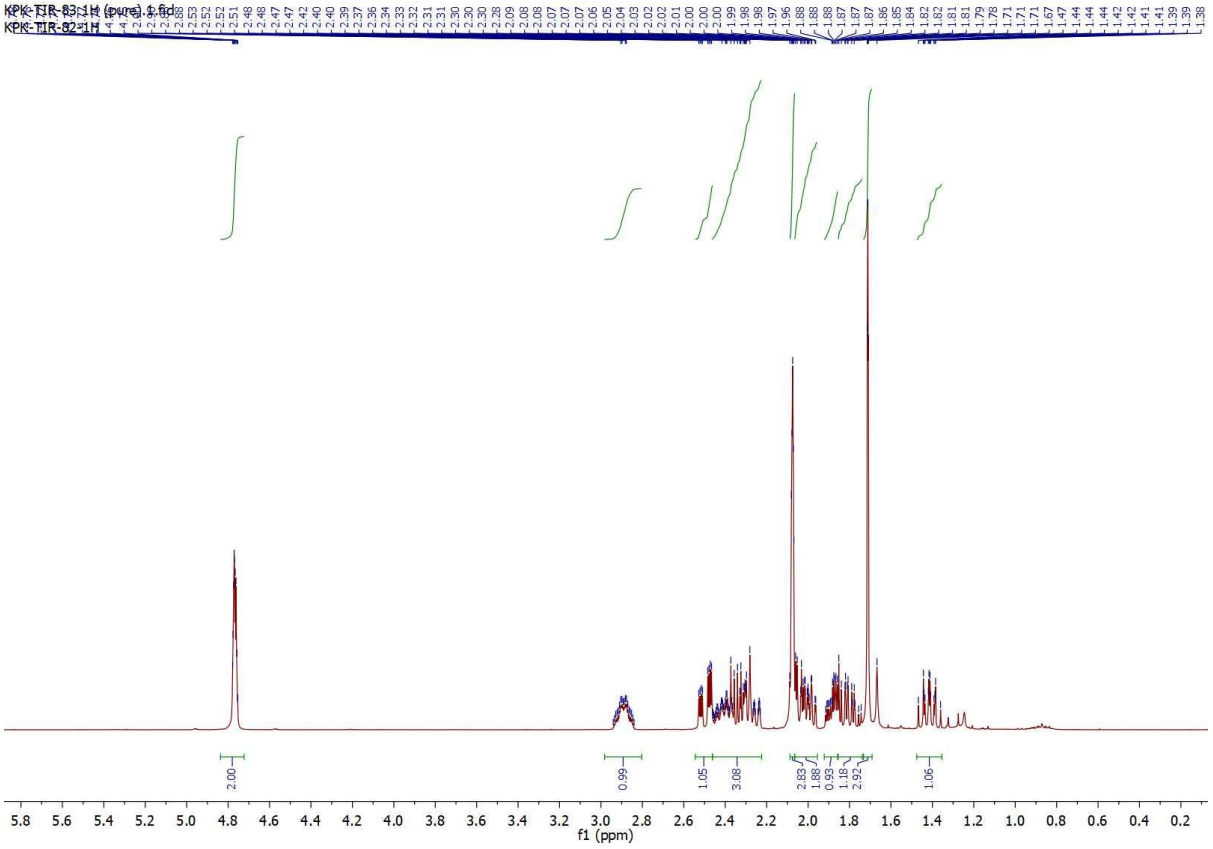


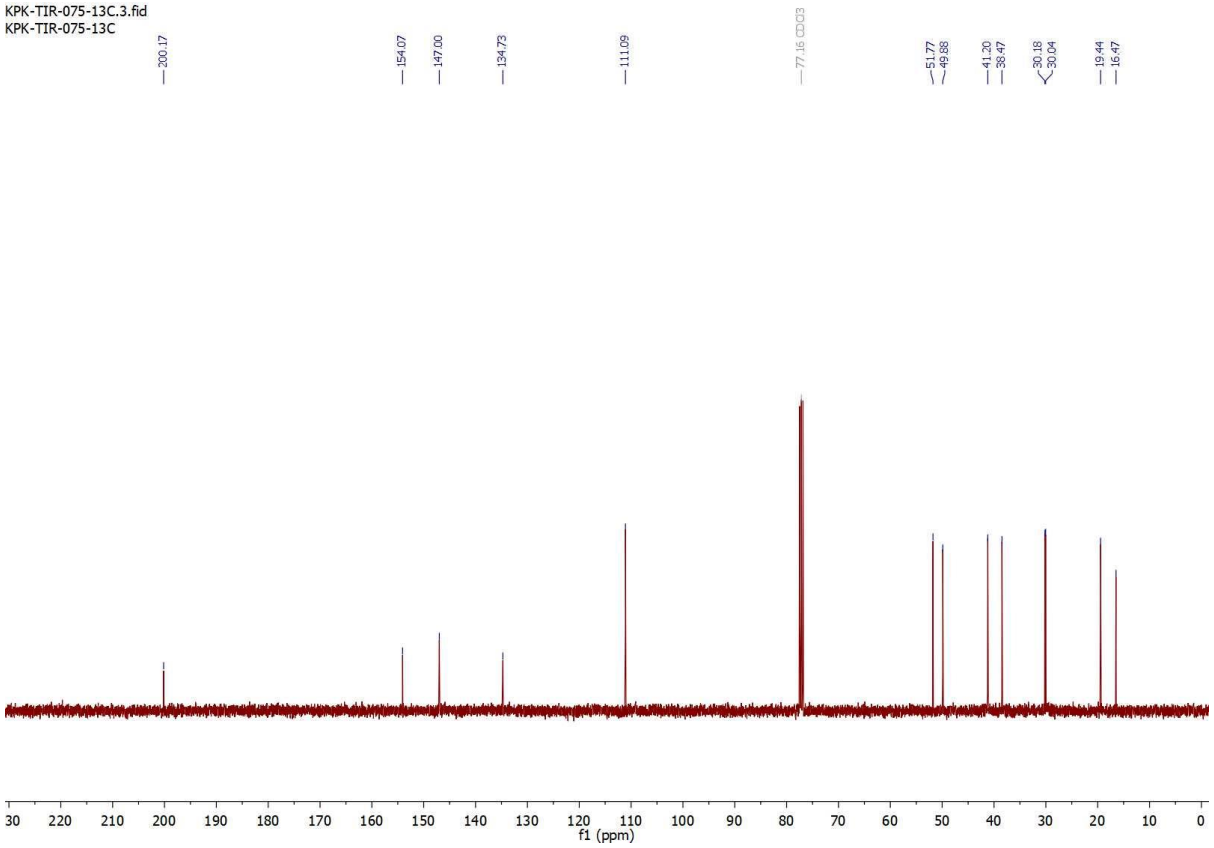


(7*R*,7a*S*)-3-methyl-7-(prop-1-en-2-yl)-1,2,5,6,7,7a-hexahydro-4H-inden-4-one (9):

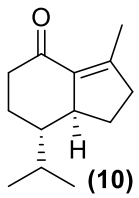

O
H

(9)

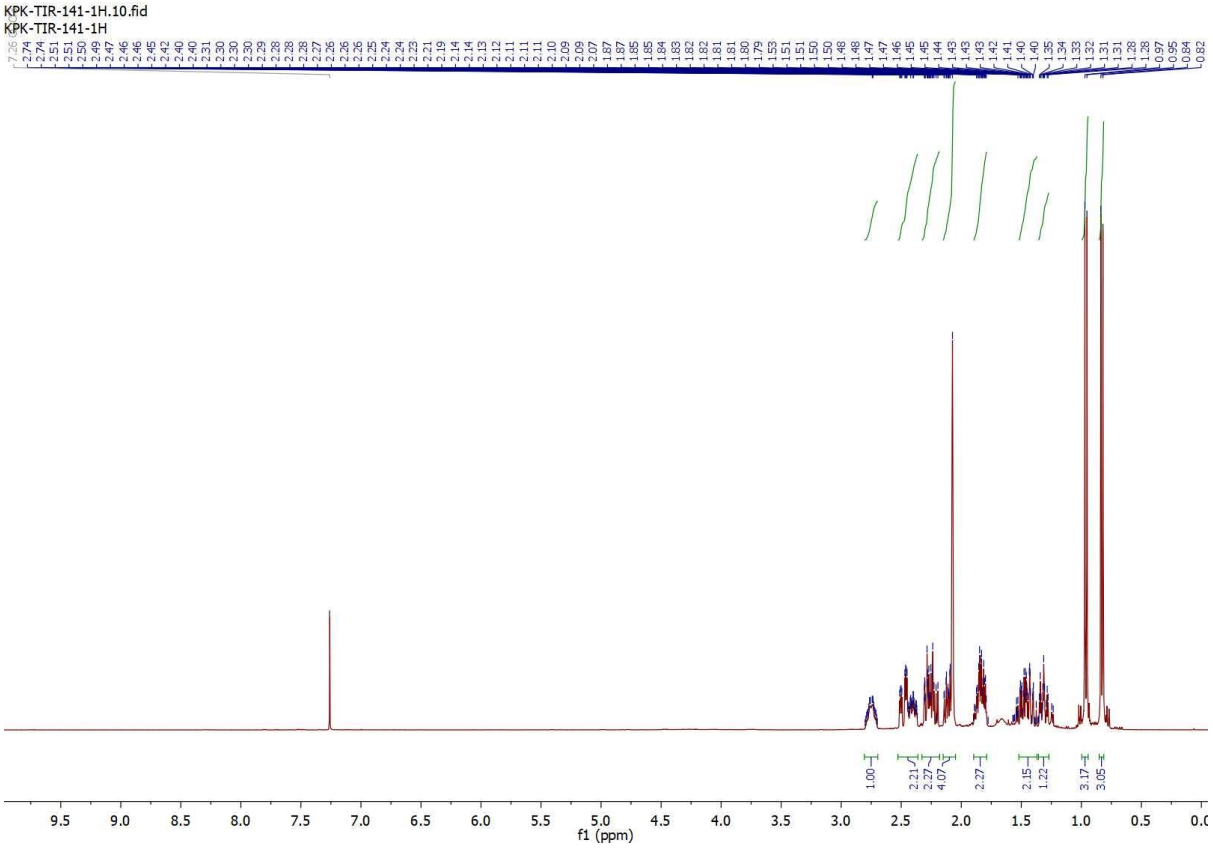

KPK-TIR-83-1H (pure).1.fid
KPK-TIR-82-1H
2.00
0.99
1.05
3.08
2.83
1.88
0.93
1.18
2.92
1.06
5.8 5.6 5.4 5.2 5.0 4.8 4.6 4.4 4.2 4.0 3.8 3.6 3.4 3.2 3.0 2.8 2.6 2.4 2.2 2.0 1.8 1.6 1.4 1.2 1.0 0.8 0.6 0.4 0.2
f1 (ppm)

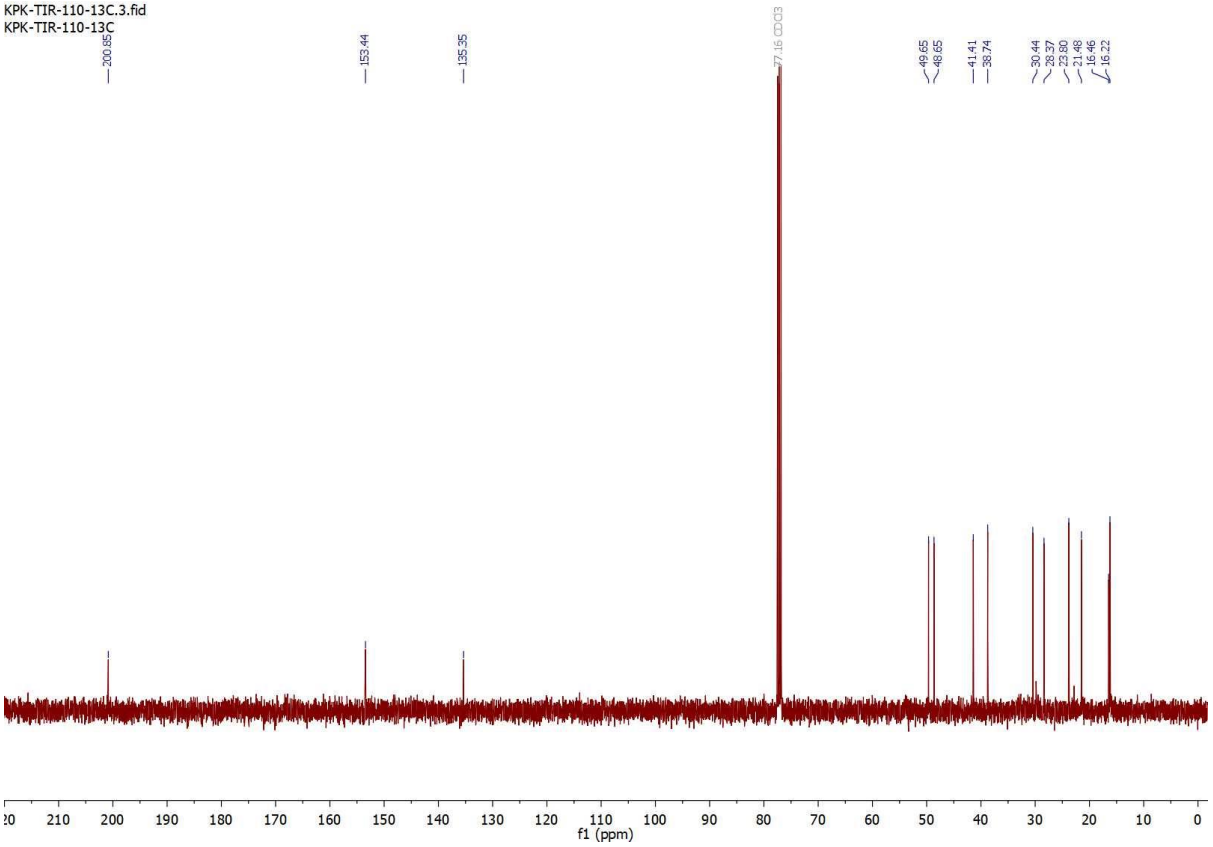


(7*S*,7a*S*)-7-isopropyl-3-methyl-1,2,5,6,7,7a-hexahydro-4H-inden-4-one (10):

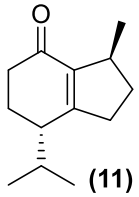


(10)

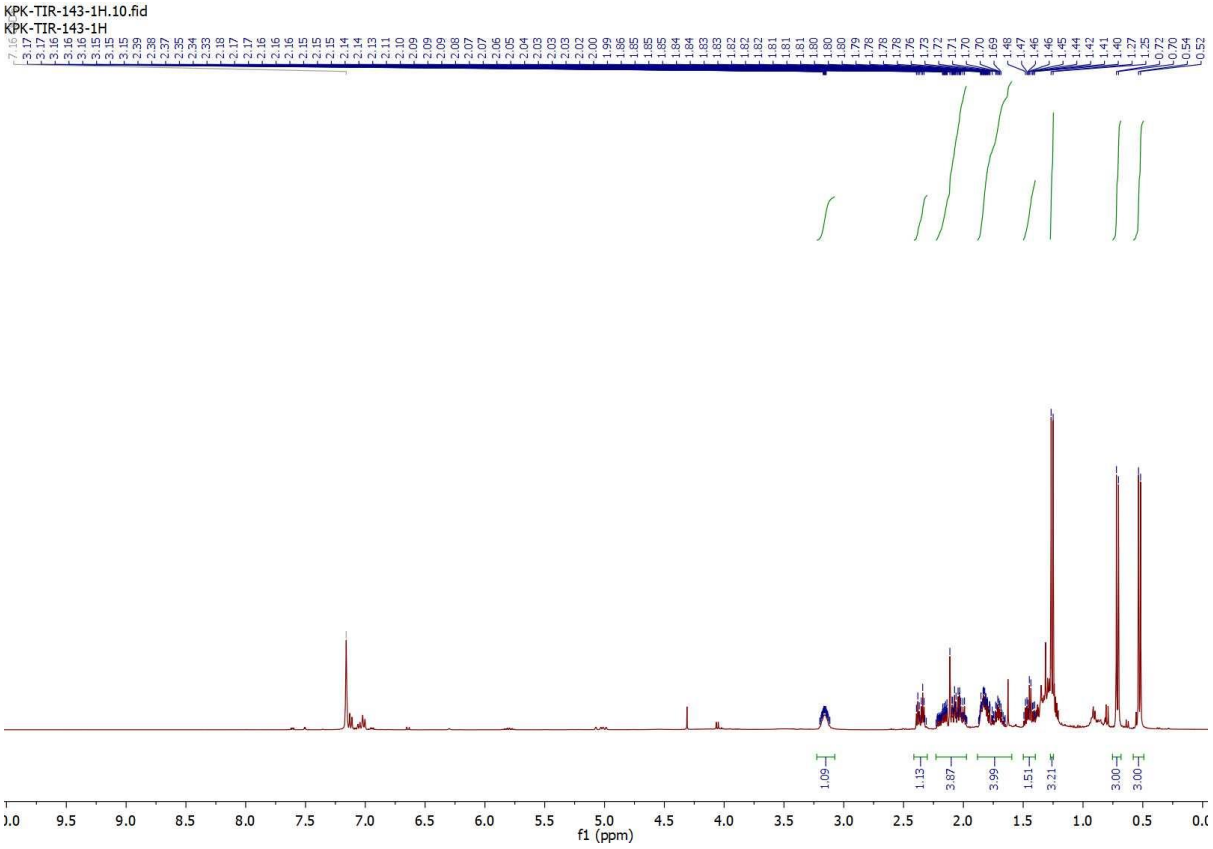


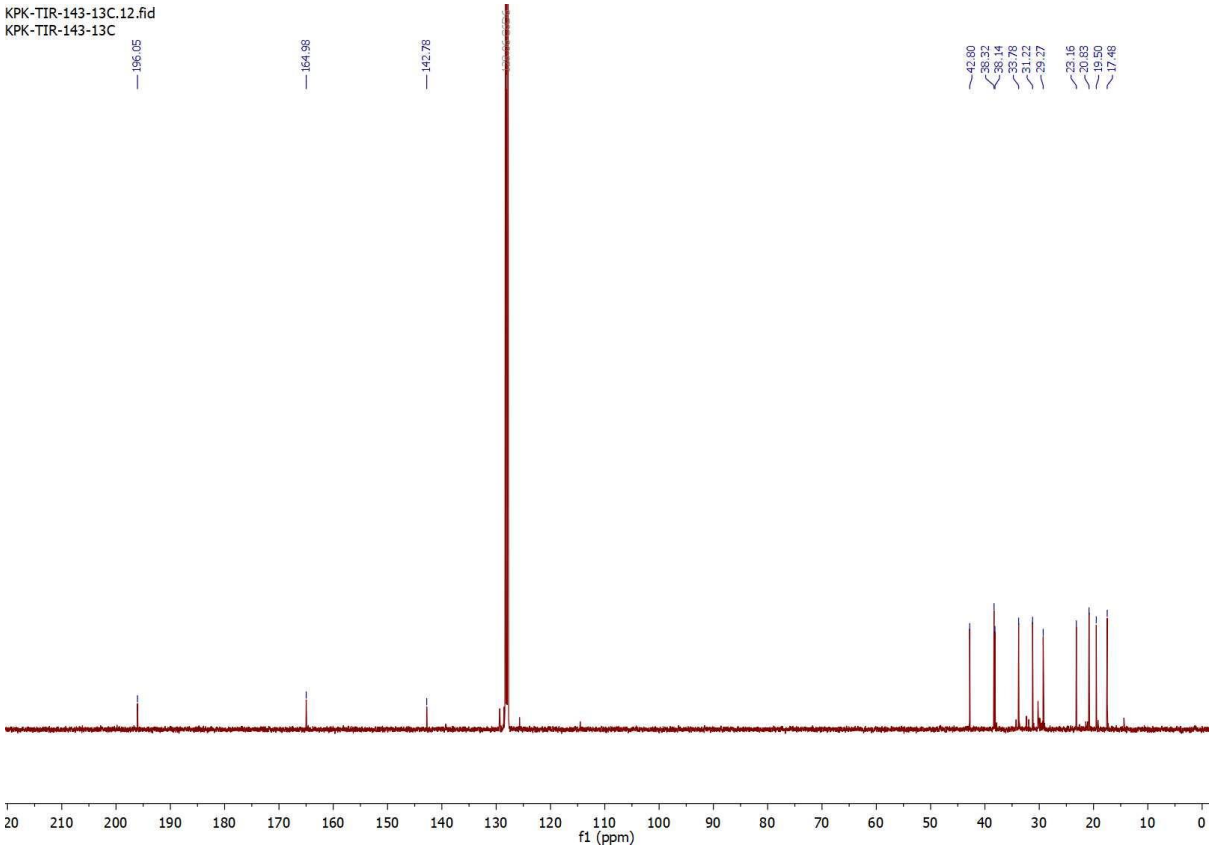


(3*S*,7*S*)-7-isopropyl-3-methyl-1,2,3,5,6,7-hexahydro-4H-inden-4-one (11):



(11)


KPK-TIR-143-1H.10.fid
KPK-TIR-143-1H
1.09
1.13
3.87
3.99
1.51
3.21
3.00
3.00
f1 (ppm)


KPK-TIR-143-13C.12.fid
KPK-TIR-143-13C
196.05
164.98
142.78
42.80
38.32
38.14
33.78
31.22
29.27
23.16
20.83
19.50
17.48
f1 (ppm)

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