Traceless Stereoinduction for the Enantiopure Synthesis of substituted cyclopent-2-enones: Total Synthesis of (-)-Teuclatriol and (+)-Orientalol-F

Dissertation
Zur Erlangung des Doktorgrades

Dr. rer. nat.

Der Fakultät für Chemie und Pharmazie

Der Universität Regensburg

Vorgelegt von
Nanaji Arisetti

aus Palakonda (Indien)

Regensburg 2105

Die Arbeit wurde angeleitet von: Prof. Dr. Oliver Reiser

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Prüfungsausschuss: Vorsitz: Prof. Dr. Axel Jacobi von Wangelin

1. Gutachter: Prof. Dr. Oliver Reiser

2. Gutachter: Prof. Dr. Sabine Amslinger

3. Gutachter: Prof. Dr. Robert Wolf

For All Chemistry Nobel Laureates

"A Man has always to be busy with his thoughts if anything is to be accomplished" **-Antonie van Leeuwenhoek**

Der experimentelle Teil der vorliegenden Arbeit wurde unter der Leitung von Herrn Prof. Dr. Oliver Reiser in der Zeit von Oktober 2011 bis März 2015 am Institute für Organische Chemie der Universität Regensburg angefertigt.

Herrn Prof. Dr. Oliver Reiser möchte ich herzlich für die Überlassung des äußerst interessanten Themas, die anregenden Diskussionen unde seine stete Unterstützung während der Durchführung Arbeit danken.

Contents

Abbreviations

Ar	Aryl
atm.	atmosphere
Bn	Benzyl
Boc	*tert*-butyloxycarbonyl
c	concentration
d	days
dba	dibenzylideneacetone
DCC	N,N`-dicyclohexylcarbodimide
DCM	dichloromethane
DIPEA	N,N-diisopropylethylamine
DMAP	dimethyl aminopyridine
DMSO	dimethylsulfoxide
EA	ethyl acetate
ee	enantiomeric excess
ent	enantiomer
eq.	Equation
equiv.	Equivalents
Et	ethyl
EtOH	Ethanol
g	gram
H	hours
HPLC	high pressure liquid Chromatography
HRMS	high resolution mass spectrometry
^{i}Pr	*iso*-propyl
^{i}PrOH	*iso*-propanol
IR	infrared spectroscopy
L	liter
LiHMDS	lithium bis(trimethylsilyl)amide
Me	Methyl
MeCN	acetonitrile
MeOH	methanol
mg	milligram
min	minutes
mmol	millimoles
mL	milliter
m.p.	melting point
MS	mass spectroscopy
^{n}Bu	n-butyl
NMR	nuclear magnetic resonance
Nu	nucleophile
PE	petrol ether
Ph	phenyl
quant.	Quantitative
rt	room temperature
rac	racemic
p	pressure
t	time

T	temperature
TBAF	tetrabutyl ammoniumfluoride
TBDMS	*tert*-butyldimethyl silyl
THF	tetrahydrofuran
V	volume
W	watt

A. INTRODUCTION

1. Bioactive substituted cyclopent-2-enone compounds and its derivatives

Cyclopent-2-enone is one of the most important core structure in many bioactive prostaglandin derivatives and sesquiterpenes. Prostaglandins are a group of physiologically active compounds having hormone like effects.[1] Every prostaglandin contains 20 carbon atoms. Prostaglandins show wide range of activities. They regulates cell growth, calcium ion levels, hormones, inflammation, and act on parietal cells in the stomach wall to inhibit acid secretion.[2] The biological activity of cyclopent-2-enone containing compounds is manifested in their ability to undergo conjugate addition with various biological nucleophiles such as L-cysteine or thiol containing enzymes (E-SH). Based on the SAR studies it was concluded that the cyclopent-2-enone moiety enhances the cytotoxic activity.[3] 5-(1′-hydroxy)-4-disubstituted cyclopent-2-enones **1** (Fig 1) act against malignant tumors.[4] Cyclopent-2-enone prostaglandin derivatives show anti-inflammatory and antiviral activity and inhibit NF-κB activation in human cell stimulated with tumor necrosis factor-α. The prostaglandin analog **2** acts against L1210 murine leukemia cells with IC_{50}= 4.0 (μg/mL).[5] TEI-9826 **3** was shown to retain *in vivo* activity against *cis*-platin-resistant tumors.[6] The IC_{50} value of TEI-9826 for the inhibition of human ovarian cancer is 7.5 μM. 15-deoxy -12-iso-Δ^7-PGA_1 **4** shows promising anti-proliferative activity with IC_{50}= 0.23 (μg/mL) on colon 26 cancer cells.[2] Prostaglandin-A_1 (PGA_1)[2] **5** causes renal vasodilation, increase urine sodium excretion and lower the arterial pressure in hypertensive patients (Fig 1).

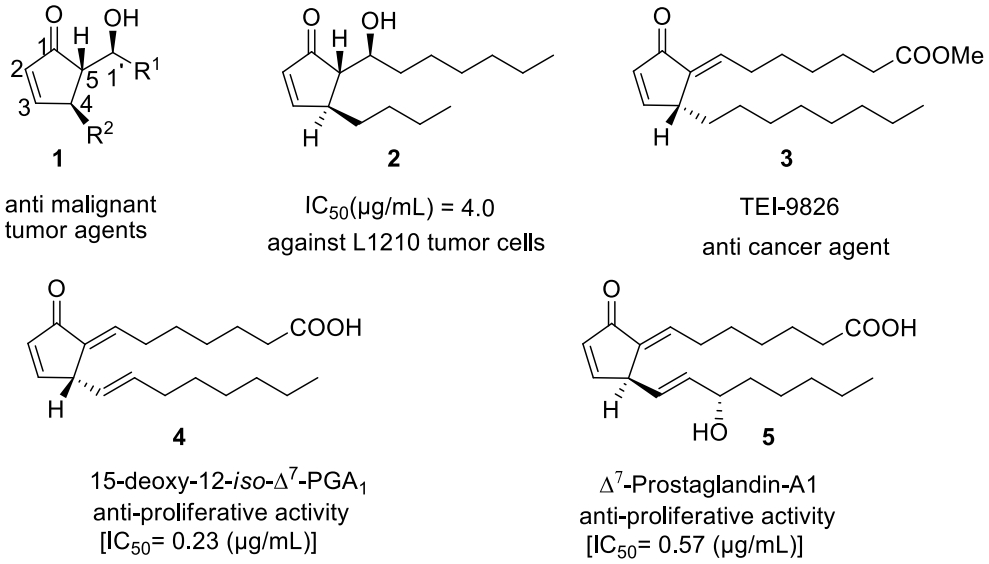
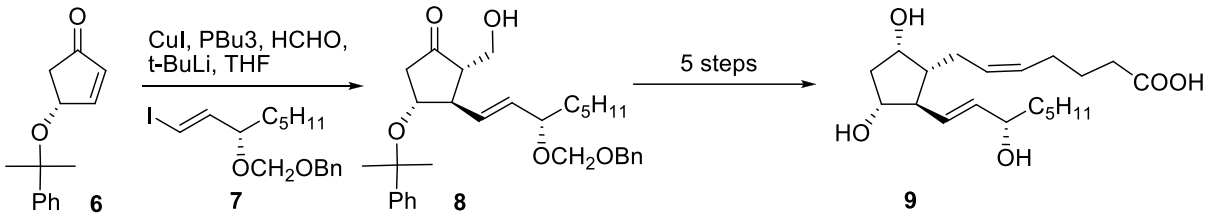


Figure 1: Bioactive cyclopent-2-enone prostaglandin derivatives.

2. Literature precedents for the synthesis of substituted cyclopent-2-enones and prostaglandin derivatives

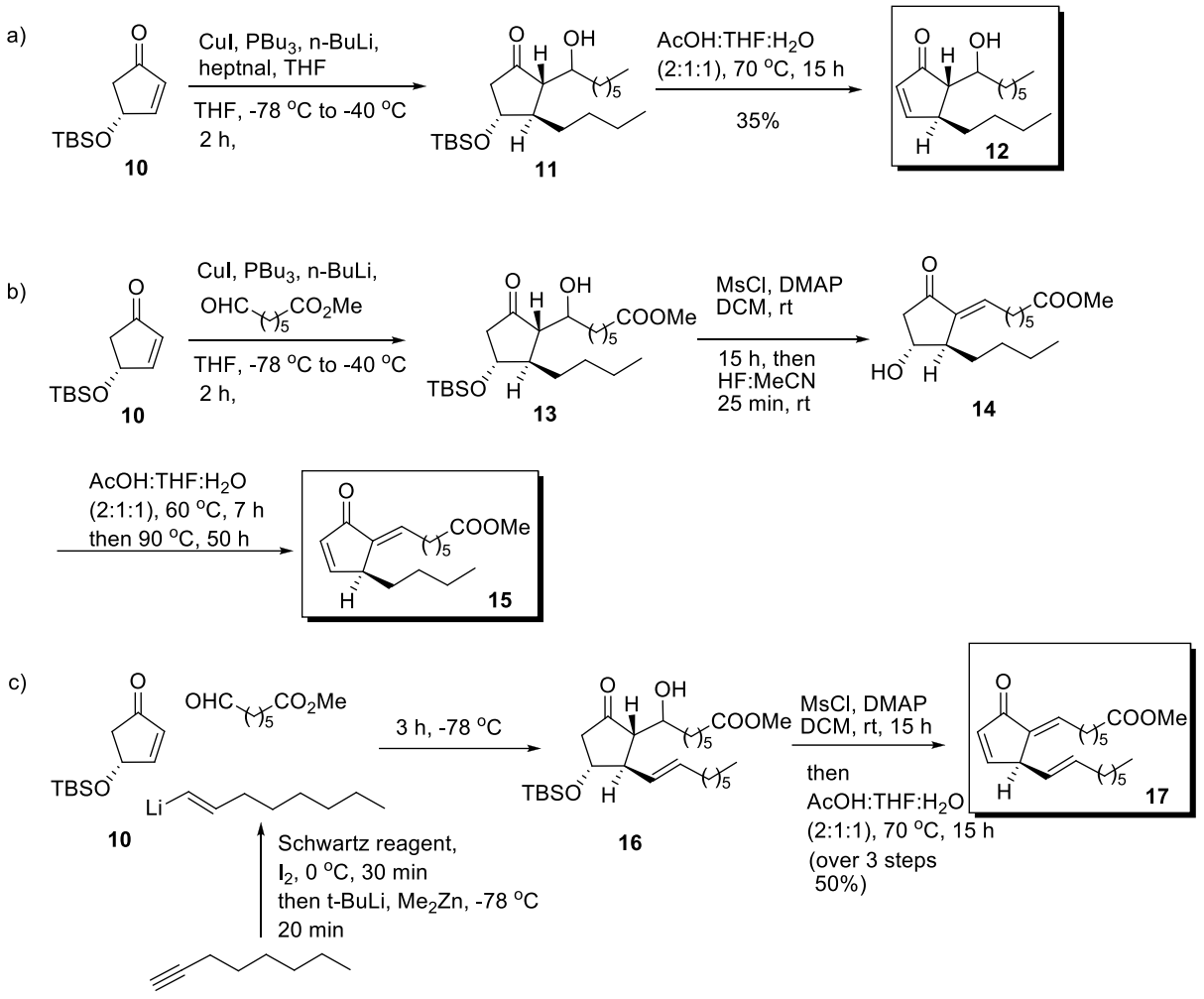
The consecutive addition of two side chains to the cyclopent-2-enone core (three-component coupling in one pot) is a well known procedure in prostaglandin synthesis. A one pot, high yield construction of the whole prostaglandin skeleton is accomplishable by combination of the copper-mediated conjugate addition of alkyl or alkenyl nucleophiles to 4-siloxy cyclopent-2-enones followed by trapping the intermediate enolate with aldehydes. Deprotection of 4-siloxy followed by dehydration gives prostaglandin derivatives. Since organo cuprates have been widely used for the addition of organic groups to the β-position of the α,β-unsaturated carbonyls, it is known that the cuprate mediated conjugate addition of nucleophiles, followed by trapping intermediate enolate with strong electrophiles useful for synthesis of substituted cyclopent-2-enones or prostaglandin derivatives.

In 1975, Gilbert Stork *et al.* reported the synthesis of $PGF_{2\alpha}$ **9** (Scheme 1) from **6** by using E-vinyl iodide **7** as nucleophile and HCHO[7] as electrophile. The resulting **8** was converted in 5 further steps to the prostaglandin **9**.[8]



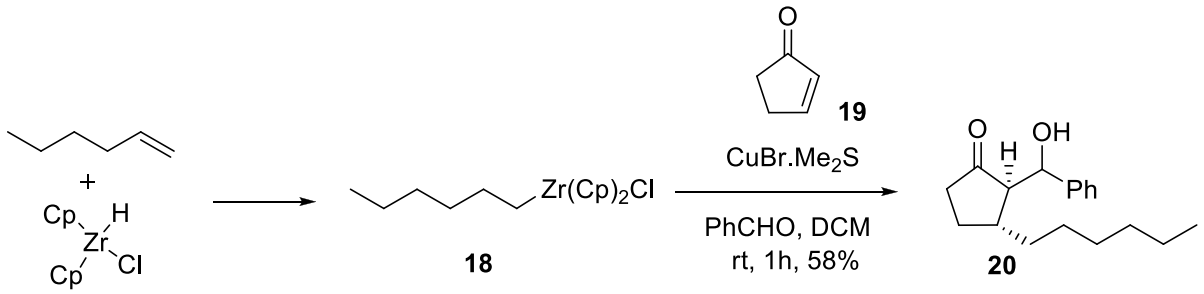
Scheme 1: Stork approach to the PGF_{2a}.

Ryoji Noyori *et al.* developed new routes for the prostaglandin derivatives **12**, **15**, and **17** from cyclopent-2-enone **10** (Scheme 2).[9] They synthesized various prostaglandin derivatives by trapping an intermediate enolate with different types of aldehydes followed by deprotection and dehydration of –OTBS group. The 1-octenyl substituent of **17**, was derived from 1-octyne through the 1-octenyl zirconocene, which has been formed *in situ* from 1-octyne and Schwartźs reagent,[10] followed by treatment with t-BuLi.



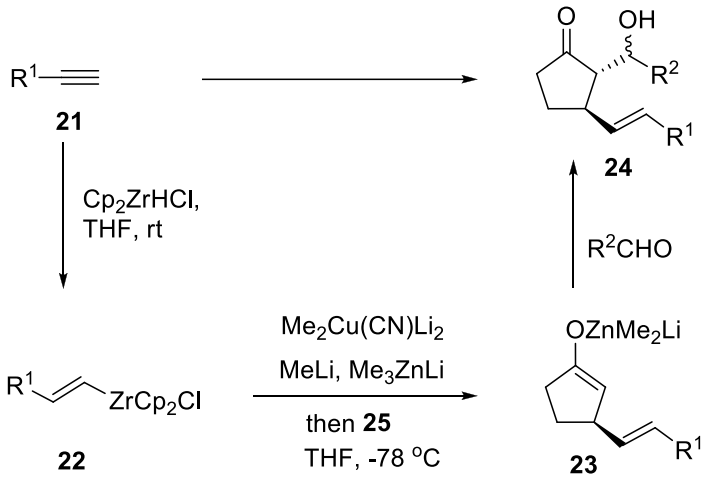
Scheme 2: Noyori approach towards the prostaglandin derivatives.

Smitrovich *et al.* developed a Cu(I) catalyzed addition of alkylzirconocenes to the α,β-unsaturated carbonyl compounds (Scheme 3).[11] This method allows the synthesis of substituted cyclopentanones from cyclopent-2-enoens. In the presence of 3-10 mol% of Cu(I) salts, alkylzirconocenes react readily with α,β-unsaturated carbonyl compounds. The reaction yields are sensitive to the presence of Lewis acids and bases. Steric hindrances as well as a broad range of functional groups are tolerated. Cyclopent-2-enone **19** readily underwent tandem conjugate addition with hexyl zirconocene **18** (which has been formed *in situ* from 1-hexene and Schwartz reagent) followed by aldol reaction with benzaldehyde in the presence of 10 mol% of $CuBr \cdot Me_2S$ gave **20** in 58% yield with 2:1 mixture of epimers.



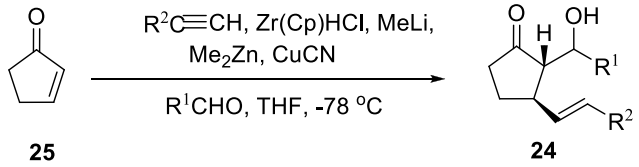
Scheme 3: Synthesis of substituted cyclopentanone by Smitrovich *et al*.

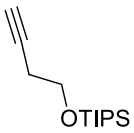
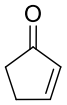
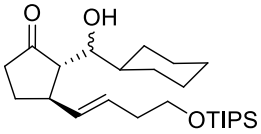
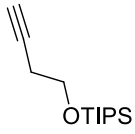
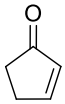
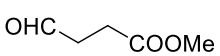
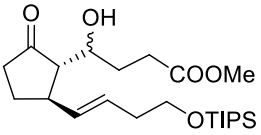
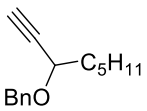
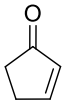
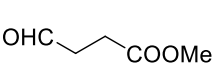
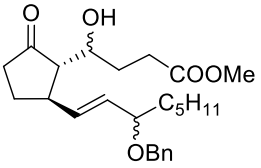
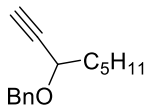
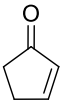
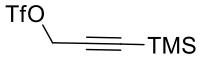
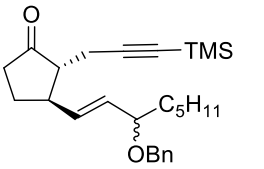
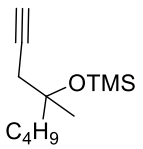
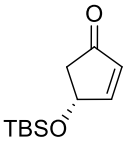
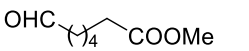
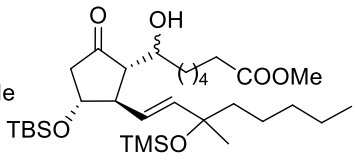
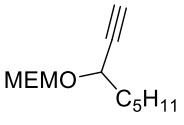
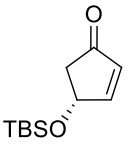
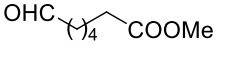
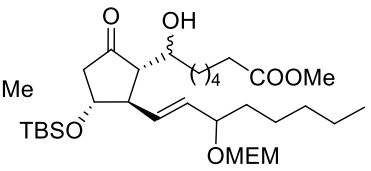
In the year, 1994 Lipshutz B. H. *et al.* reported enantiopure synthesis of substituted cyclopentanones and non-prostaglandin skeletal from cyclopent-2-enone **25**.[12] In this case, alkenyl zirconocene acts as nucleophiles, which has been derived from the corresponding terminal alkyne by using Schwartźs reagent. This was a one pot 6 steps sequence could be developed for the synthesis of prostaglandin and non-prostaglandin skeletons of type **24**. This method involves the *trans* metalation[13] between a organozirconium[14] to a cuprate species (Scheme 4). Alkenyl zirconocenes **22**, which upon exposure to Me_3ZnLi (which has been derived from Me_2Zn and MeLi) in THF at -78 °C effects the transmetaltion. After conjugate addition, the trapping of the resulting enolate **23** with aldehydes is rapid at -78 °C and affords aldol adduct **24** as mixture of diastereomers with respect to the newly formed stereo center (Table 1).



Scheme 4: Catalytic Cuprate-induced vinyl ligand 1,4-addition to **25** by Lipshutz *et al*.

Table 1: Synthesis of 4-alkenyl substituted cyclopentane derivatives by Lipshutz *et al*.



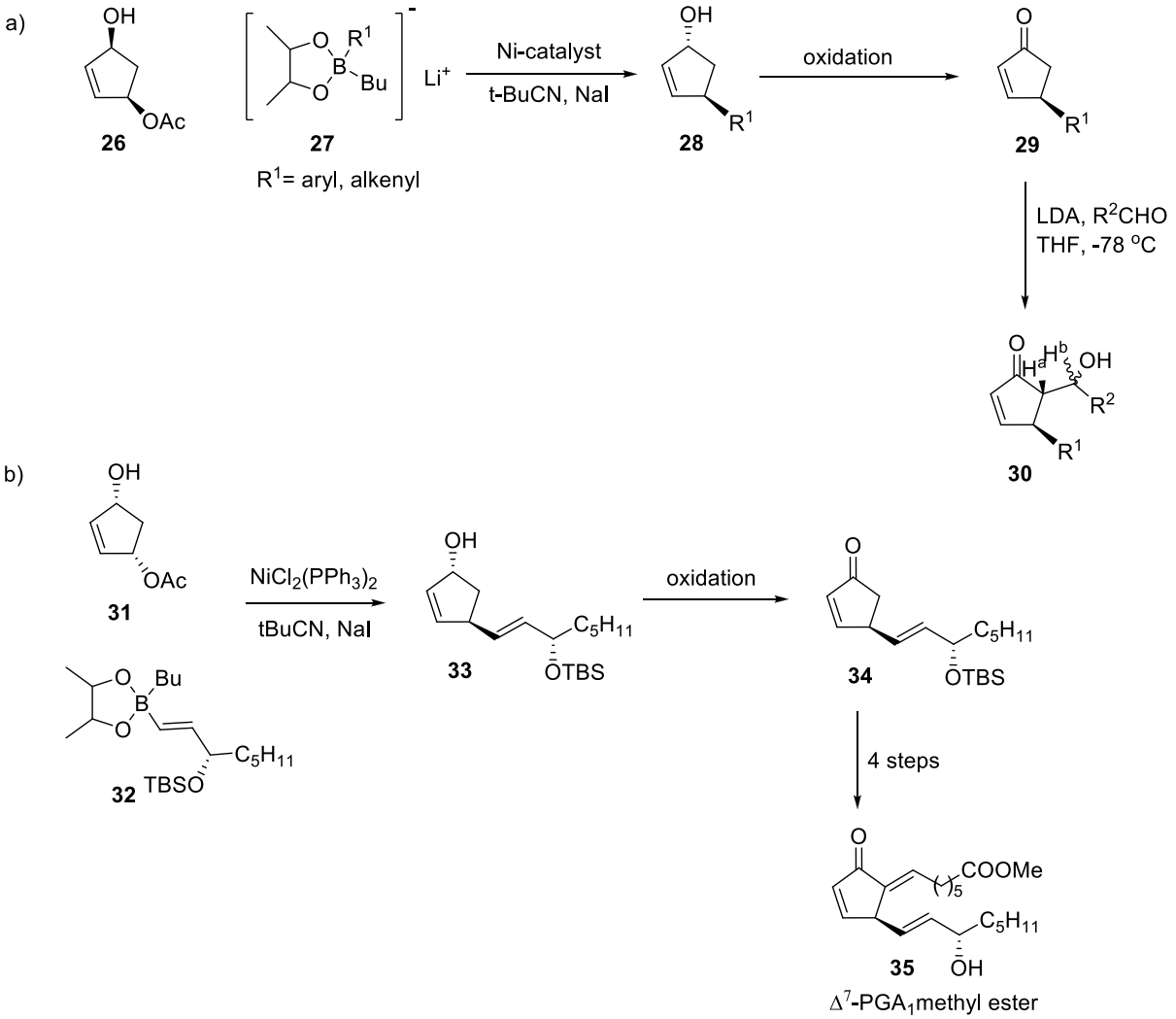
Entry	1-alkyne	enone	aldehyde	product	yield[%]
1					80[a]
2					74[b]
3					75[c]
4					74[b]
5					79[d]
6					83[b]

a) One isomer by ^{1}H-NMR. b) Two isomers by ^{1}H-NMR. c) Five isomers by ^{1}H-NMR. d) Four isomers by ^{1}H-NMR.

With cyclopent-2-enone as starting material, various successful examples were developed by combination of different alkynes and aldehydes providing yields between 70-80%. The number of

epimers was based on substituents on alkyne as well as aldehde. Alkyne with no substituents gave only one isomer (entry 1, Table 1) and alkyne with substituent's furnished epimers more than two (entry 2-6, Table 1).

In the year 2002, Kobayashi *et al.* reported the application of Ni-catalysis for the synthesis of enantiopure cyclopentanoid molecules **30**.[15] They have developed the installation of aryl and alkenyl groups on to the readily available monoacetate **26**[16] using lithium borate **27**[17] and nickel catalyst in the presence of additive gave 4-substituted hydroxy cyclopentenes **28**.



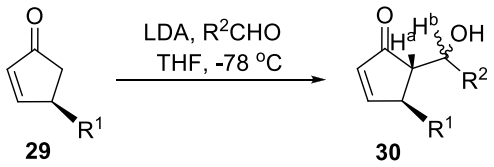
Scheme 5: a) General route for synthesis of aldol adducts **30**. b) Synthetic root to Δ^7-PGA_1 methyl ester by Kobayashi *et al.*

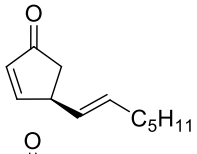
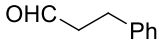
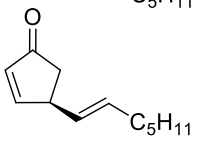
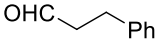
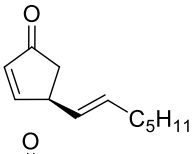
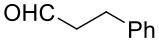
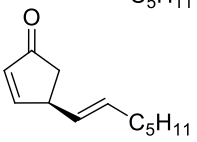
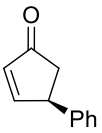
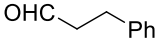
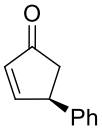
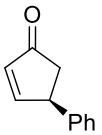
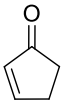
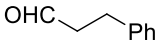
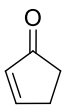
Among several additives t-BuCN and NaI in ratio of 13:1 was found to be the best additive. The oxidation of **28** furnished **29**, followed by trapping of the resulting enolate of **29** with aldehydes gave

4-substituted cyclopent-2-enone **30** (Table 2). After treatment with a base such as LDA at -78 ^{o}C followed by trapping of resulting enolate with aldehydes afforded an aldol adduct **30** (Table 2). They reported synthesis of Δ^{7}-PGA$_{1}$ methyl ester **35** from **31** and **32** by using this methodology as key step (Scheme 5)**.**

The yield of aldol adducts **30** depend on time and temperature, it was shown that the intermediate enolate is unstable . The authors found that 60 min and >-50 ^{o}C were suitable reaction parameters for aldol adduct formation. The assignment of the *anti* and *syn* aldols **30** was made by using coupling constants between H^{a} and H^{b}. The *anti*-aldols show $J_{a,b}$ =7-9 Hz and *syn*-aldols shows $J_{a,b}$ = 3 Hz. In all cases, aromatic aldehydes gave nearly the same ratio of epimers (entry 1-3, 5, 7 and 8, Table 2), where as aliphatic aldhehyde provided *anti*-aldol as the major diastereomer (entry 4, 6 and 9, Table 2).

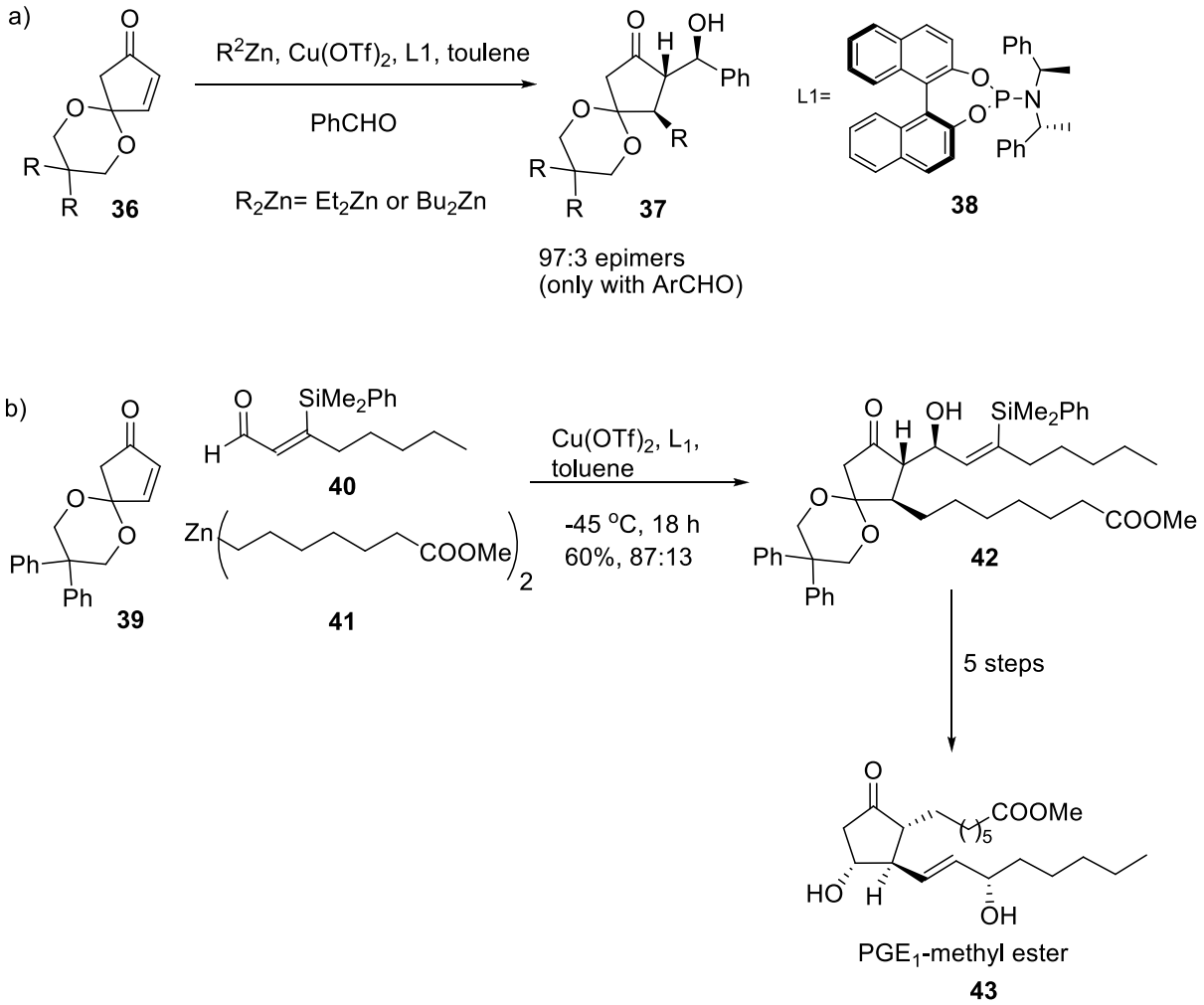
Table 2: Synthesis of 4,5-disubstituted cyclopent-2-enone derivatives **29** by Kobayashi *et al.*



Entry	enone[a]	base	aldehyde	yield[%][b]	*anti:syn*[c]
1		LDA		85	2:1
2		LiCA		88	4.8:1
3		LHMDS		86	3.5:1
4		LDA	iPrCHO	66	>20:1[d]
5		LDA		83	4.2:1
6		LDA	iPrCHO	72	>20:1[d]
7		LDA	PhCHO	74	2.5:1
8		LDA		72	2.4:1
9		LDA	iPrCHO	75	13:1

a) Synthesized from **29** by using oxidation. b) Calculated from the isolated yields. c) *Anti: syn* aldols determined by coupling constants. d) Determined by ^{1}H NMR.

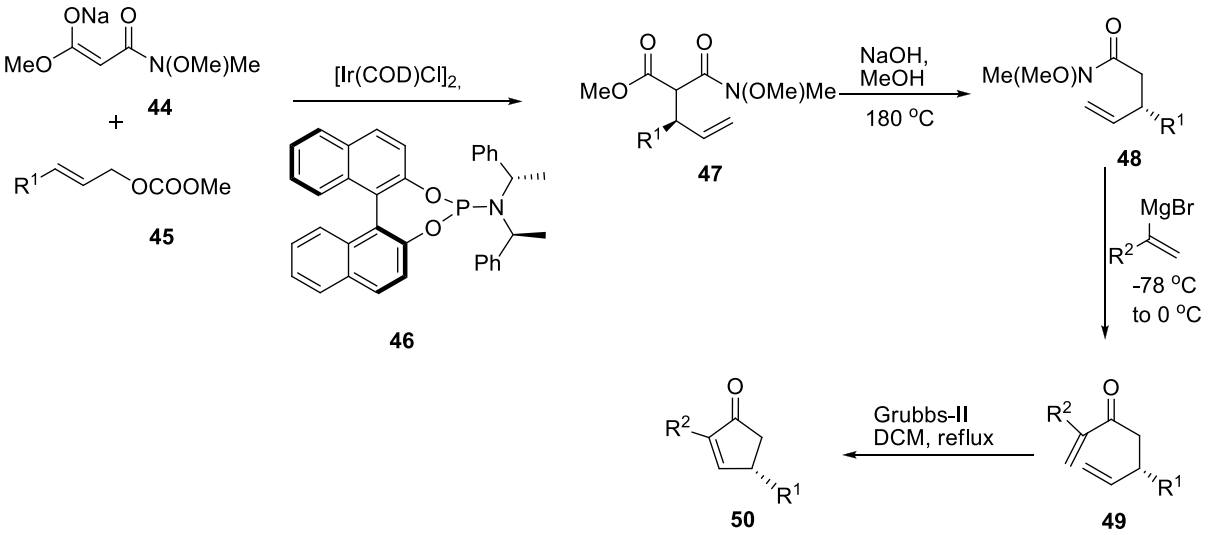
Approximately at the same time, Feringa *et al.* published their results of the synthesis of enantiopure substituted cyclopentanones **37** by using catalytic tandem 1,4-addition and aldol reaction in the presence of a catalyst generated *in situ* from $Cu(OTf)_2$ and phosphoramidate **38**.[18] They used alkyl zinc compounds[19] as nucleophiles in the presence of aromatic aldehydes. Enantioselectivities were obtained upto 94% and *de* upto 97:3. Alternatively, PGE_1 methyl ester **43** could be synthesized from the compound **39** and zinc compound **41** applying the conditions developed for the synthesis of **37**. The key compound **42** was obtained in 60% yield and a 87:13 ratio of epimers, which was further converted to PGE_1-methyl ester **43** in five steps (Scheme 6b).



Scheme 6: a) General method for synthesis of enantiopure substituted cyclopentanones by Feringa *et al*. b) Synthetic route to PGE_1-methyl ester.

In the year 2006, Helmchen *et al.* reported synthesis of enantiopure 2,4-disubstituted cyclopent-2-enones **50** by iridium catalyzed allylic alkylations.[20] The key steps involved in their synthesis are iridium catalyzed allyl alkylation, acylation and ring closing metathesis. In this case, sodium enolates

of Weinreb amides[21] **44**, allylic carbonates **45** and Grignard reagents are the starting materials. Enolate **44** and carbonate **45** are reacted with each other in the presence of iridium catalyst and ligand **46**[22-24] gave amide **47** with high stereoinduction through the catalyst. Saponification with NaOH and decarboxylation at 180 °C gave amide **48**. After Grignard reaction at -78 °C followed by ring closing metathesis[25] on **49** the 2,4-disubstituted cyclopent-2-enones **50** were obtained as products with high enantiomeric excess (Scheme 7) .



Scheme 7: Iridium catalyzed synthesis of substituted cyclopent-2-enones by Helmchen *et al.*

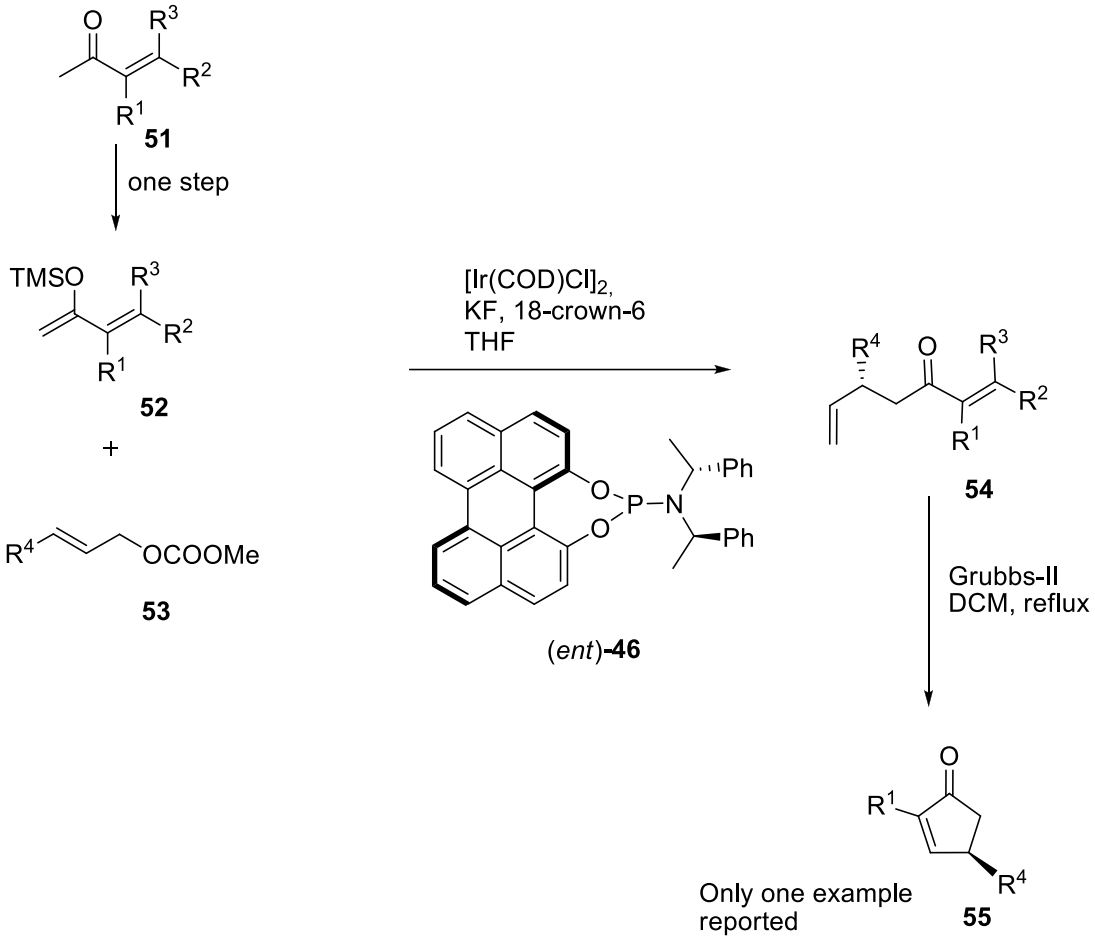
Table 3: Examples of 4-substituted cyclopent-2-enone derivatives by Helmchen *et al.*

Entry	Substr.	R^1	R^2	yield [%][a]	*ee*[%][b]
1	(*R*)-**47**	Ph	H	66	97
2	(*R*)-**47**	Ph	Ph	55	96
3	(*R*)-**47**	Me	Me	44	95
4	(*R*)-**47**	n-octyl	H	56	96
5	(*R*)-**47**	n-octyl	Me	56	n.d.

a) Yields based on 44+45. b) Determined by HPLC on chiral column.

On the other hand, in 2014 Hartwig *et al.* published enantioselective allylic substitution of unstabilized enolates **52** (derived from **51**) by using iridium catalysis.[26] In this case, unstabilized

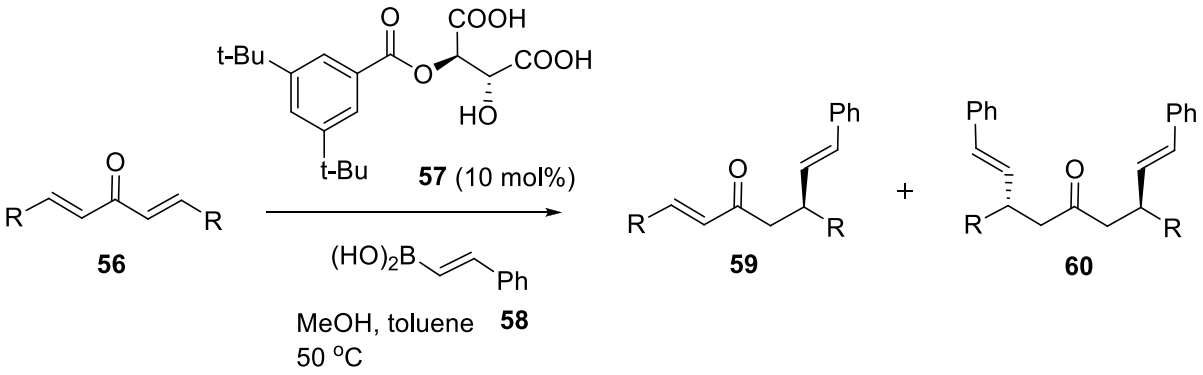
enolates **52** and allylic carbonates **53** are starting materials. These two starting materials reacts with each other in the presence of $[Ir(COD)Cl]_2$ and ligand (*ent*)-**46** to afford allylated products **54** having new stereo center at the β-position to the keto group. The additives played a key role for the reaction of allylic carbonate with enolate. Among the several additives tested, it was found that KF with 18-crown-6 is key to the success of the reaction. The β-allylated unsaturated ketone **54** should be useful intermediates for synthesis of enantiopure 4-substituted cyclopent-2-enones **55** by using ring-closing metathesis (Scheme 8).



Scheme 8: Iridium catalyzed synthesis of β-substituted unsaturated ketones by Hartwig *et al.*

Moreover, recently Nakajima group published synthesis of enantipoure 4-substituted cyclopent-2-enones **59** from dienones **56** (Table 4).[27] The key steps involved O-monoacyltartaric acid catalyzed enantioselective conjugate addition of boronic acids to dienones followed by Ru-catalyzed RCM.[28] With styryl boronic acid as starting material various successful examples are presented by changing the substituents on dienone providing mono styrylated products in 42-81% and ee with 86-94% along with bis styrylated product **60** (Table 4).

Table 4: Synthesis of mono-styryl enones by Nakajima *et al.*

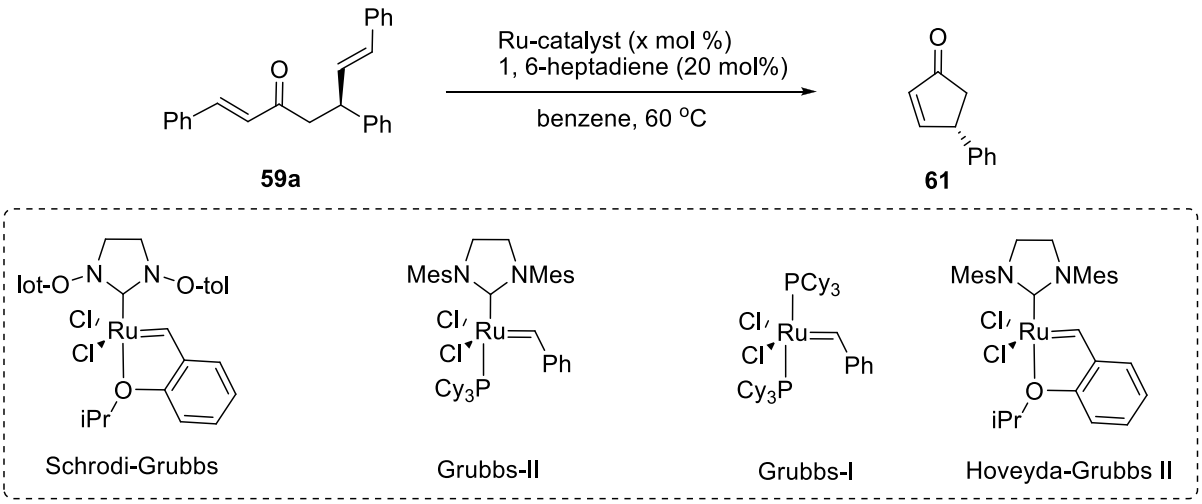


Entry	R	**58**[equiv]	MeOH[equiv]	**59**[%]	ee[%]	**60**[%]
1	Ph	1.2	2.4	79	86	16
2	Ph	1.0	2.0	78	86	16
3	Ph	1.0	2.0	81	86	9
4	Ph	2.1	4.2	42	86	58
5	*p*-Br-C_6H_4	1.0	2.0	52	86	21
6	*p*-OMe-C_6H_4	1.0	2.0	68	90	12
7	2-thienyl	1.0	2.0	76	88	8
8	1-naphthyl	1.0	2.0	68	94	15
9	n-octyl	1.0	2.0	56	89	15

The actual reaction time was 24 h. To suppress the amount of **60**, the reaction time was reduced to 14 h. On the other hand, using exactly 1 equivalent of boronic acid **58** significantly suppressed the yield of **60** (entry 3 and 7, Table 4). The higher amount of boronic acid favors the formation **60** in equal yield with respect to the **59** (entry 4, Table 4). With compound **59a** in their hand, they concentrated on the construction of cyclopent-2-enone by using RCM reaction. Various Ru-catalysts were tested for ring closing metathesis. The Schrodi-Grubbs catalyst[29] in the presence of 1, 6-heptadiene (additive) gave desired product in moderate yield (entry 1, Table 5). The Grubbs-II[30] also showed similar activity in the presence of additive (entry 2, Table 5). The Grubbs-I catalyst[31] failed completely in this RCM (entry 3, Table 5). When switched to Hoveyda-Grubbs II catalyst[32] gave better

results. 15 mol% of Hoveyda-Grubbs II furnished desired compound **61** in 84% yield after 48 h (entry 4, Table 5). Whereas lowers the amount to 10 mol% provides desired compound **61** in very good yield 98% after 24 h (entry 7, Table 5). The additive diene generates active Ru- species from the catalyst, which would promote less reactive enones into the RCM reaction.

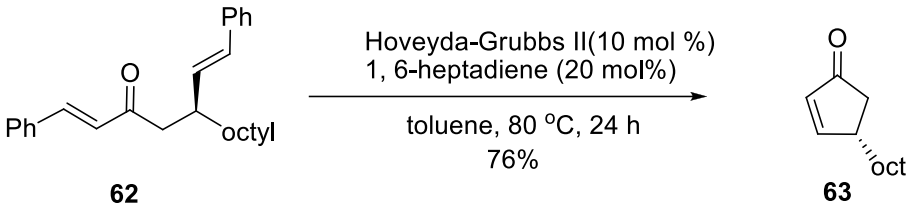
Table 5: Synthesis of 4-substituted cyclopent-2-enones using RCM by Nakajima *et al.*



Entry	Ru-catalyst	X	time[h]	yield[%]
1[a]	Schrodi-Grubbs	15	72	56
2[a]	Grubbs-II	15	72	56
3[a]	Grubbs-I	15	72	0
4[a]	Hoveyda-Grubbs II	15	72	84
5[b]	Hoveyda-Grubbs II	15	24	84
6[b]	Hoveyda-Grubbs II	10	24	73
7[b,c,d]	Hoveyda-Grubbs II	10	24	98
8[b,c,d]	Hoveyda-Grubbs II	10	24	85
9[b,c,e]	Hoveyda-Grubbs II	10	24	0
10[b,c,f]	Hoveyda-Grubbs II	10	24	81

a) The catalyst (5 mol %) was added every 24 h (15 mol %). b) The catalyst was added in one portion. c) In toluene at 80 ^{o}C. d) With 1, 6-heptadine (0.4 equiv). e) Without 1,6-heptadiene. f) With diallyl ether (0.2 equiv).

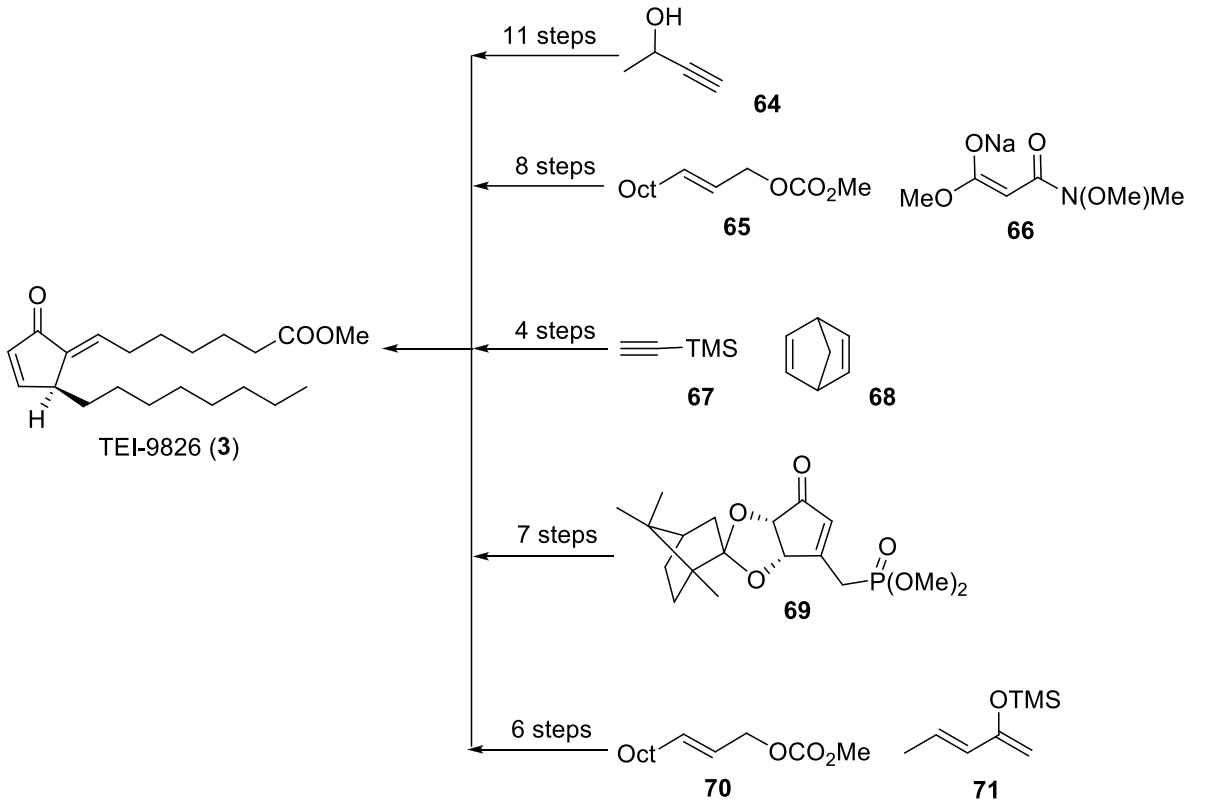
Entry 9 provides a derivative **62** with n-octyl group. After successive RCM with Hoveyda-Grubbs II in the presence of 1,6-heptadiene at 80 ^{o}C for 24 h furnished 4-octyl cyclopent-2-enone **63** in 76% yield, which is know intermediate for TEI-9826 (Scheme 9).



62 **63**

Scheme 9: Synthesis of enantiopure 4-octyl cyclopent-2-enone by Nakajima *et al*.

TEI-9826 **3** is one of the most prominent anti-cancer drugs. Many groups reported the synthesis of this anti-tumor agent. In 2003, Monneret *et al.* reported the synthesis of TEI-9826 from commercially available propargyl alcohol **64** in 11 steps.[33c] Key steps involved in their synthesis are a Claisen rearrangement[34] and a RCM. However, no experimental details have been published. In 2006, Helmchen *et al.* synthesized this molecule from (E)-methyl undec-2-enyl carbonate **65**, Weinreb amide **66** and vinyl magnesium bromide by using iridium catalyzed allylic substitution followed by Ru-catalyzed ring closing metathesis.[20]



Scheme 10: Various synthetic approaches towards the TEI-9826.

Iqbal and co-workers reported the synthesis of TEI-9826 by using Pauson-Khand reaction between TMS-acetylene **67** and norbornadiene **68**, which gave rise to cyclopent-2-enone core.[33b] Zurawinski *et al.* described the synthesis of TEI-9826 from cyclopent-2-enone derivative **69** in 7 steps.[33a] The key steps were involved here, Horner-Wardsworth-Emmons-olefination[35] followed by aldol reaction. Recently Hartwig *et al.* accomplished from silylenol ether **70** and compound **71** in 6 steps by using iridium catalyzed enantio selective allylic substitution of unstabilized silyl enol ethers and subsequent RCM with Grubbs-II catalyst (Scheme 10).[26] Moreover, all the above methods need more than two pots, harsh conditions and longer reaction time for the synthesis of prostaglandin derivatives.

3. Bio-active guaianes and guaianolides

Guaianes and guaianolides,[36] represent one of the largest subgroup of naturally occurring sesquiterpenes and lactones exhibiting strong biological activity.[37,38] Plants containing different guaianes and guaianolides as the active principles have been used in traditionally medicine for treating cancer, inflammatory etc. Guaianes consisting of 5,7-bicyclic hydroazulene system and guaianolides consisting 5,7,5-tricyclic system.

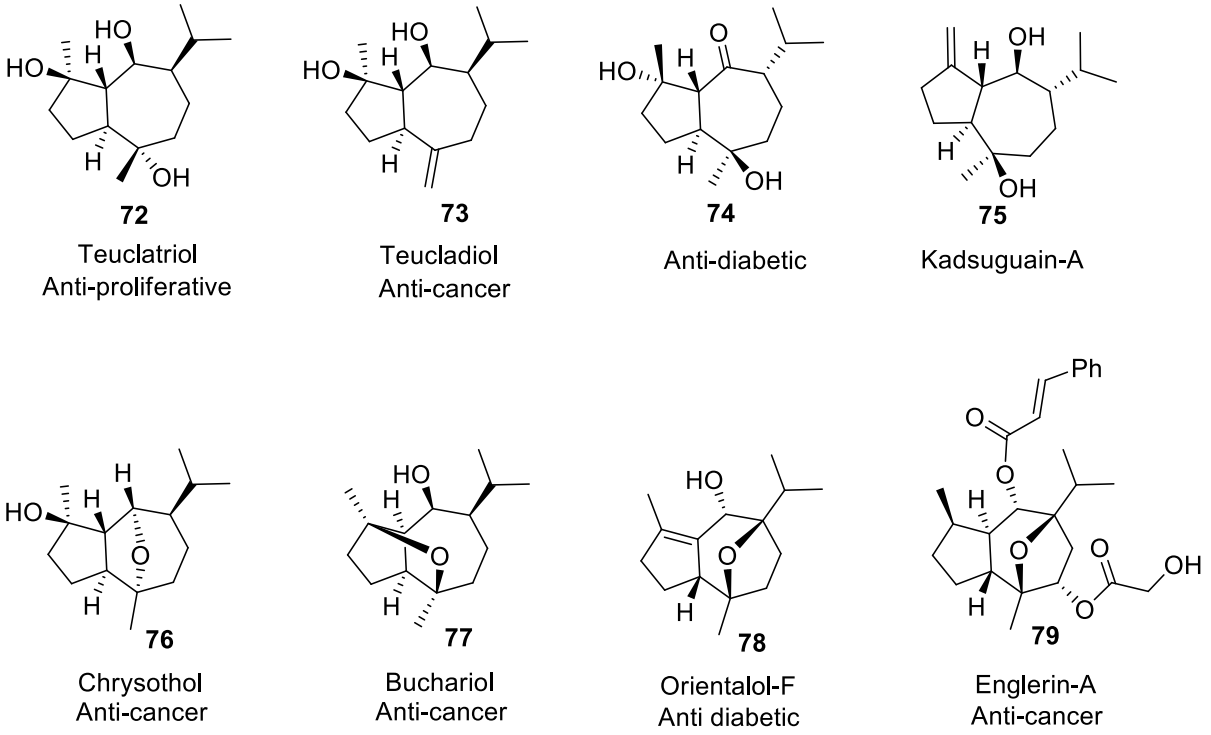


Figure 2: Bioactive guaiane sesquiterpens.

Guaianes are 5,7-bicyclic sesquiterpenes, widely obtained from many plants. These molecules exhibit strong anti-tumor, anti-inflammatory and anti diabetic activities.[39] The functionalities on guaiane core structure affect the nature of activity in biological systems. The representative members shown below exemplify the structural diversity found within this class of compounds. Teuclatriol **72** isolated from *teucrium leucocladum*,[40] shows a significant anti-proliferative activity against human activated peripheral blood lymphocytes with IC_{50} = 72.5 µg/mL.[41] Another guaiane molecule with exo-methelene group teucladiol **73** also isolated from *teucrium leucocladum*,[40] exhibit moderate anti-cancer activity on human breast cancer cell lines. Molecule **74** from acorus calamus, shows promising anti-diabetic activity on a insulin mediated glucose consumption model of HepG2 cells.[42] Kadsuguain-A **75** isolated from *piper kadsura*, shows moderate anti-neuroinflammatory activity.[43] Guaiane core structure with Oxygen bridge also exhibits strong bioactivity. Chrysothol **76** isolated from *chrysothamnus viscidiflorus*, shows anti-cancer activity on human breast cancer cells.[44,45] Buchariol **77** which was isolated from *salvia bucharica,* shows cytotoxic activity against a panel of human cancer lines.[46,47] Orientalol-F **78** isolated from *Alisma orientalis* acts anti-diabetic.[48] Another similar molecule englerin-A **79** was isolated from *phyllanthus engleri*, and shows anti cancer activity on human renal cancer cell lines[49] (Fig 2).

The pseudoguaianolide skeleton along with the 5,7-bicyclic hydroazulene ring system often contains a third ring, an unsaturated α-methylene-γ-butyro lactone fused to the 7 membered ring. Along with structural diversity guaianolides exhibit strong biological activity. Here we showed some bio-active molecules with guaian 8,12-olide core structure. Helenalin **81** is a sesquiterpene lactone found in *Arnica Montana* has a variety of observed anti-inflammatory and antitumor activities. Helenalin[50] has been shown to selectively inhibit the NF-κB, which plays a key role in the regulating immune response. The sesquiterpen lactone carpesiolin[51] **82** shows significant inhibitory activity against *Cochlioblous miyabeanus*. On the other hand, sesquiterpenoid lactone **80**[52] was found to be submicromolar inhibitors against LPS-induced nitric oxide production in RAW264.7 macrophages (Fig 3).

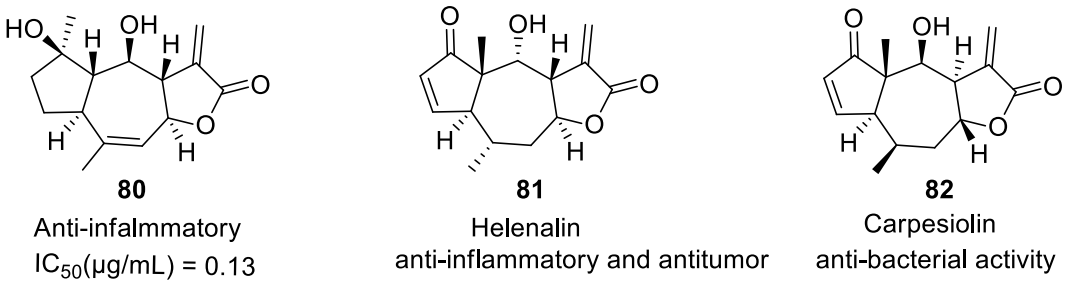
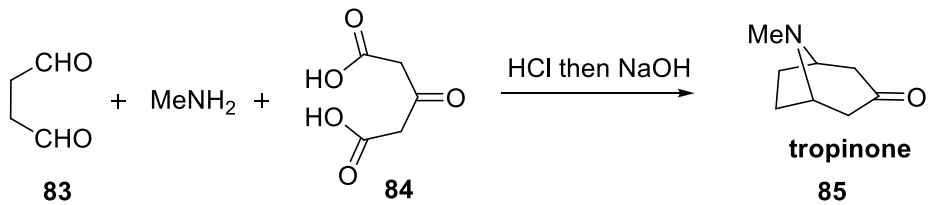


Figure 3: Bioactive pseudoguaianolide sesquiterpens

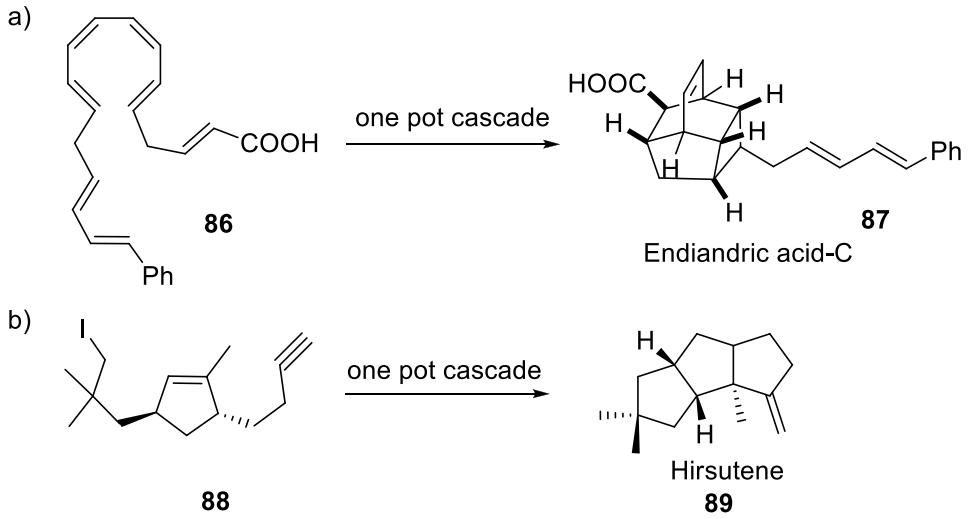
4. Pot economy in natural product synthesis by using cascade sequence

The total synthesis of natural products and biologically active compounds, such as pharmaceuticals and agrochemicals, has reached an extraordinary level of sophistication. The efficient total synthesis of natural products has always been a critical issue for organic chemists. A lot of effort has been devoted to the development of an ideal synthesis. When synthesizing molecules, one not only has to consider efficiency but also sustainability, such as atom economy, step economy, redox economy, Protecting-group-free[53] and toxic metal free synthesis also contributes to sustainability. Only a single reaction solvent, workup procedure, and purification step may be required to provide a product that would otherwise have to be made over the course of several individual steps.



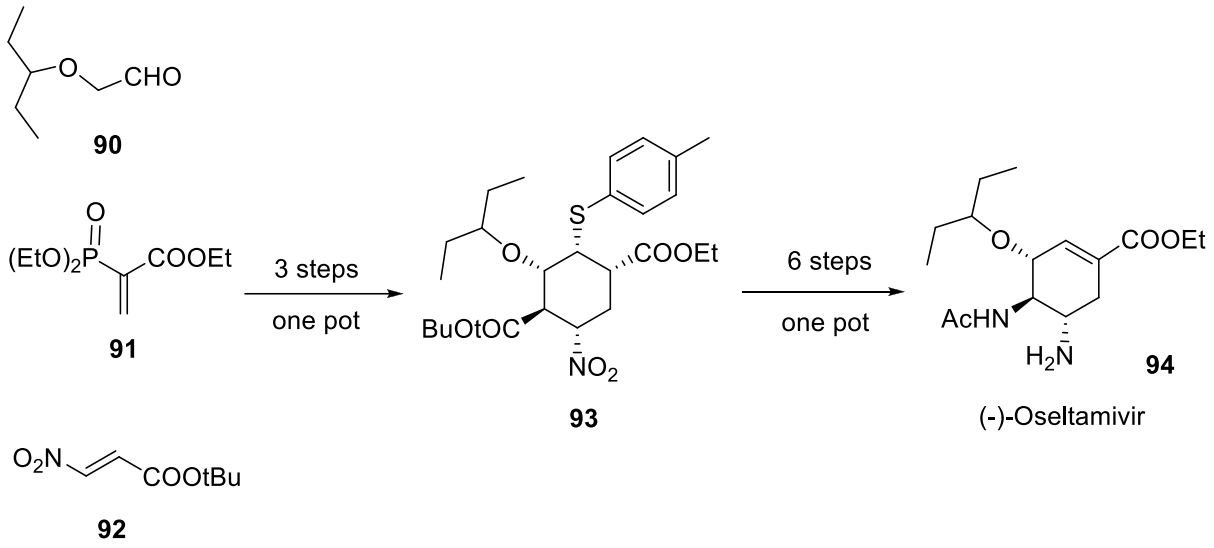
Scheme 11: Robinson approach to the tropinone.

As such, cascade reaction/ domino reaction/ tandem reaction can be considered as one pot economy reaction. A cascade reaction is an efficient method to achieve several transformations and by forming several bonds, while at the same time save purifications steps, and thus minimize chemical waste and time. Indeed, cascade reactions have attracted the attention of organic chemists, since Robinson`s one pot synthesis of tropinone (Scheme 11).[54] Subsequent classic examples include the endiandric acid-C **87**[55] cascade by Black and co-workers through the electrocyclic reactions (Scheme 12a).[56] Radical based synthesis of hirsutene[57] and other triquinane natural products by Curran and co-workers are the other prominent examples.[58] They used tandem radical approach starting from intermediate **88**, which leads to tricyclic core of hirsutene **89** in a one pot operation (Scheme 12b).



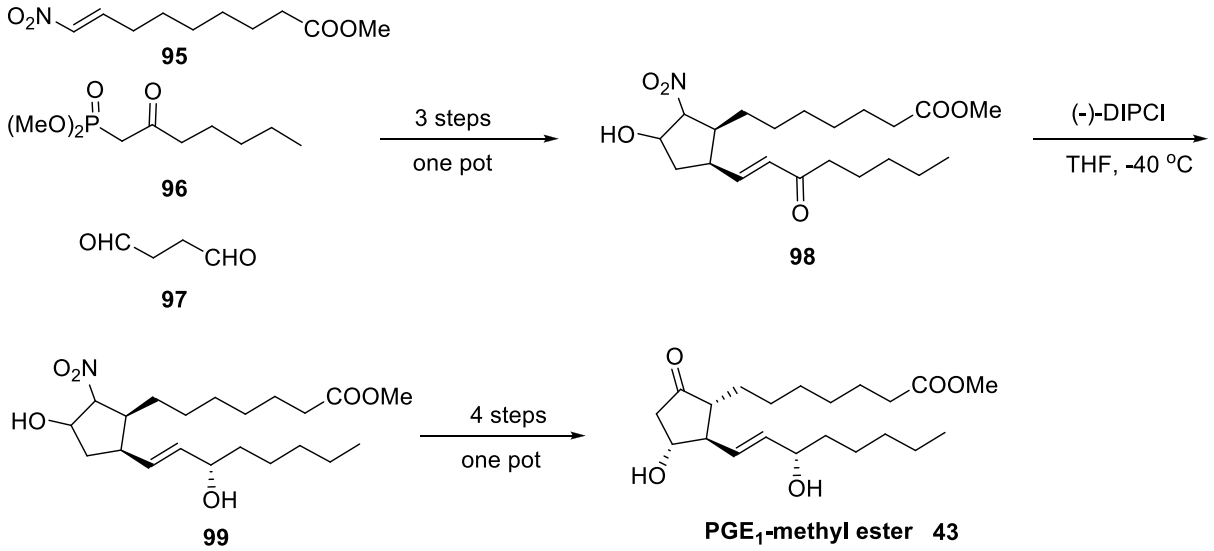
Scheme 12: a) Black electrocyclic cascade for endiandric acid-C. b) Radical cyclization cascade for hirsutene by Curran *et al*.

Hayashi and co-workers reported one-pot synthesis of (-)-oseltamivir[59,60] **94** by using an asymmetric Michael reaction of aldehyde **90** with (Z) - N-2-nitroethnylacetamide **92** catalyzed by diphenyl prolinol silyl ether. They used two one-pot sequences for the target. In the first one pot operation, they achieved core structure of (–)-oseltimivir **93** by using an asymmetric enantioselective Michael addition,[61] Horner-Wadsworth-Emmons reaction[35] followed by cyclization. In the next one pot operation, they achieved six further transformations, which led to the target **94** with good yield (Scheme 13).[62]



Scheme 13: Pot economy cascade for (-)-Oseltimivir by Hayashi *et al*.

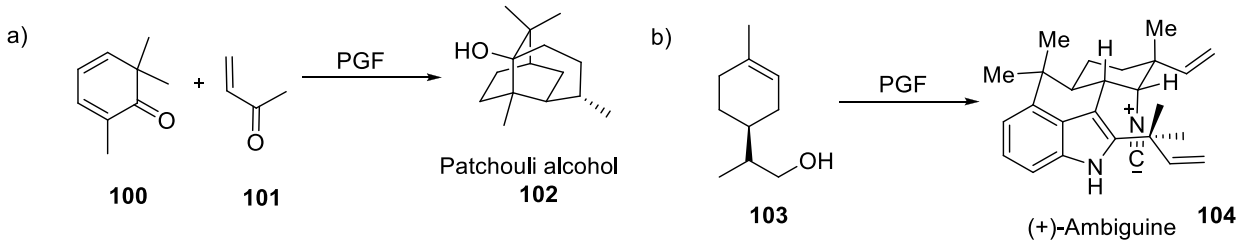
On the other hand, the same group reported synthesis of PGE_1-methyl ester **43** by using a three-pot cascade. In the first pot they achieved the synthesis of cyclopentane core **98** with two stereogenic centers by using an enantio selective Michael addition, Horner-Wadsworth-Emmons followed by cyclization, which was reduced selectively to **99** by using (-)-diisopinocamphenyl chloroborane. A further one pot protocol combining 4 transformations was then demonstrated, which led to PGE_1-methyl ester with 14% overall yield (Scheme 14).[63]



Scheme 14: Three pot economy for PGE_1-metghyl ester by Hayashi *et al*.

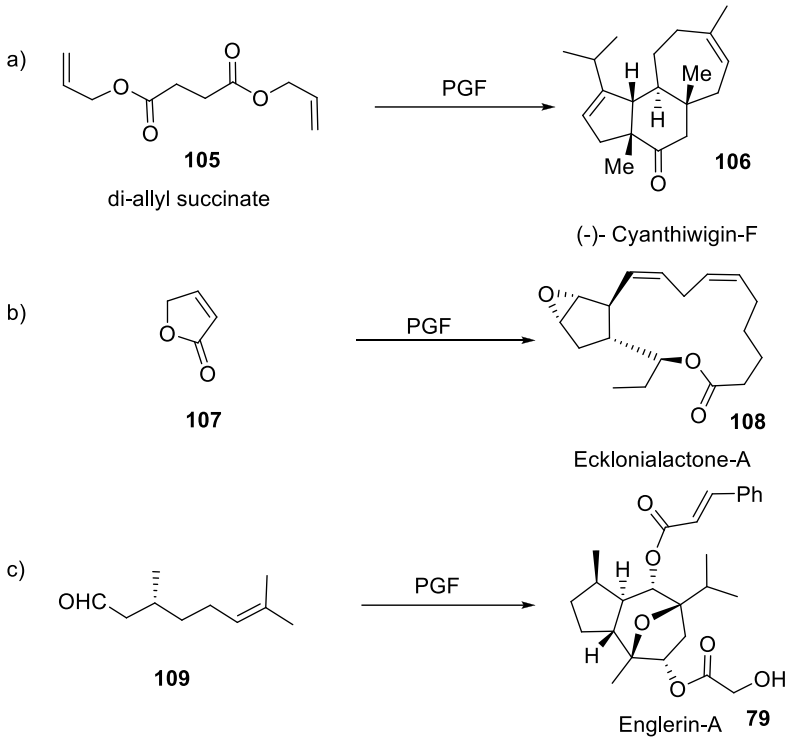
5. Protecting group free access to the natural product synthesis

Total synthesis is a big tool for synthesis of derivatives of naturally occurring bioactive molecules with different functionalization. When we start synthesis of some complex molecules, selectivity plays a crucial role. One strategy that allows the differentiation of similar functional groups is the use of protecting groups. Nevertheless, adding protecting group and removal of protecting group needs 2 steps, thus reducing yield and requiring more reagents. It is therefore desirable to develop reaction sequences that avoid the use of protecting groups. Some prominent examples are shown in the following: In 1917 Robinson reported the synthesis of tropinone from the simple starting materials succinaldehyde, methylamine and acetone di-carboxylic acid. This one may be considered first protecting group free synthesis as well as one pot synthesis. In 1968, Danieshfsky *et al.* reported the total synthesis of racemic patchouli alcohol **102** from **100** and **101** without using any protecting groups.[64] In his synthesis, each intermediate has limited reactive sites and diminishing chemo selective transformations (Scheme 15a). Phil. S. Baran *et al.* reported the first synthesis of ambiguine-H **104** by using a protecting group free strategy.[65] They used commercially available material **103** as starting material by using direct indole coupling in the presence of copper salts as key step[66] (Scheme 15b).



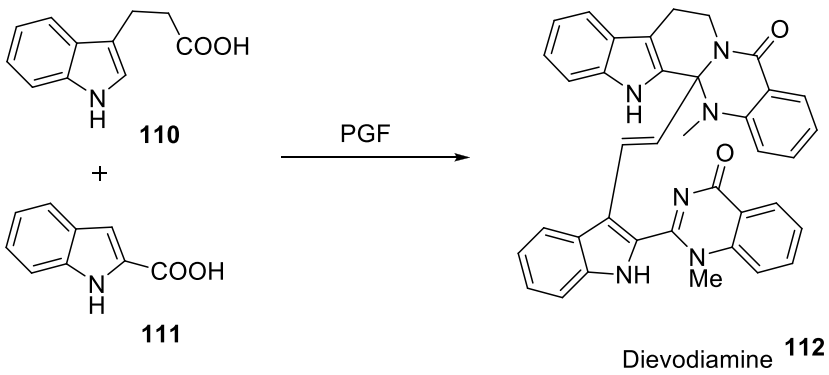
Scheme 15: Protecting group free strategy for Patchouli alcohol by Danishefsky *et al* (a), (+)-ambiguine-H by Baran *et al* (b).

Moreover, in 2008 B. M. Stoltz group reported first synthesis of cyantwigin-F **106** from di-allyl succinate **105** without using any protecting groups.[67] The key steps involved double enantioselective alkylation[68] in the presence of $Pd_2(dba)_3$ and PHOX ligand followed by RCM (Scheme 16a). Alois Fürstner *et al.* reported the total synthesis of ecklonialactone **108** without using any protecting groups and alkyne metathesis as key step (Scheme 16b).[69] In 2010, D. Ma *et al.* reported the total synthesis of englerin-A **79** from **109** by using gold-catalyzed cyclization of keto enynes and without using any protecting groups (Scheme 16c).[70] The protecting group free synthesis needs intermediates with active sites, which are diminishing chemoselective transformations.



Scheme 16: Protecting group free approach to the various natural products.

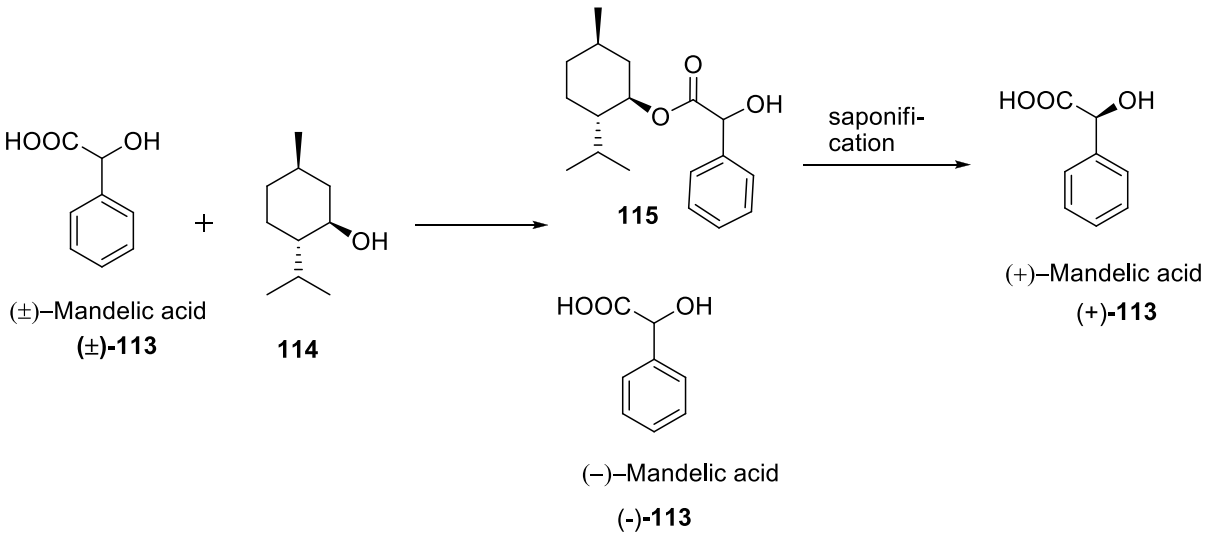
Recently J. K. Taylor *et al.* reported first total synthesis of Dievidiamine **112** from commercially available materials **110** and **111**. The key steps include the first example of an organometallic addition into a DHED adduct and Stille coupling between two sterically hindred alkenes. Moreover, they completed the synthesis without using any protecting groups; this could be an example of protecting group free synthesis (Scheme 17).[71]



Scheme 17: Protecting group free approach to theDievodiamine by Taylor *et al*.

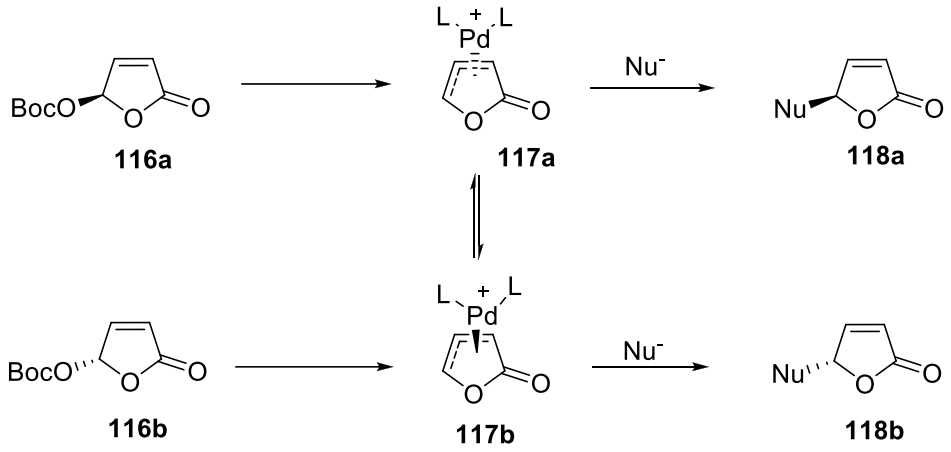
6. Kinetic resolution

Many of the building blocks in biological systems and bioactive natural products are mostly available in pure enantiomeric forms. Their synthesis as well as that of analogues needs an asymmetric synthetic strategy. The enantioselective synthesis can be achieved by using chiral catalysts or achiral catalysts with chiral ligands. Separation of enantiomers from racemic mixture by using kinetic resolution is a well known strategy in asymmetric synthesis. Two enantiomers in racemic mixture react with different rates with a chiral reagent, resulting in an enantiomeric excess of an unreacted enantiomer in a racemic mixture. The first kinetic resolution reported by Louis Pasteur.[72] However, Marckwald and McKenze reported the first synthetic kinetic resolution in 1899.[73] They separated enantiopure (+)-**113** from (±)-**113** by using enantiselective esterfication with **114**. In which (+)-**113** reacts faster than (-)-**113**, gave ester **115**, saponification on **115** furnished (+)**-113** in pure enantiomeric form (Scheme 18).



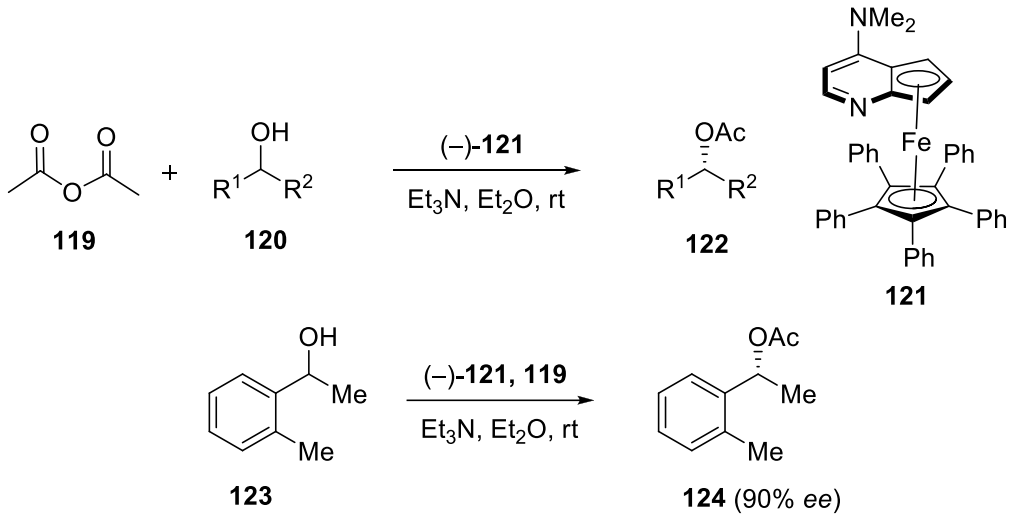
Scheme 18: Kinetic resolution of racemic mandelic acid by Marckwald and McKenze.

B. M. Trost *et al.* published asymmetric synthesis of butenolides **118**.[74] In this case, palladium catalyst forms a chiral complex with ligand **127**. The two enantiomers of butenolide generated π-allylpalladium complex **117a** and **117b** with Pd-catalyst. These 2 complexes undergo interconversion with each other. If interconversion is fast relative to nucloephilc addition one of the complexes reacts with nucleophile faster than the other, then effective dynamic kinetic resolution would be result (Scheme 19).



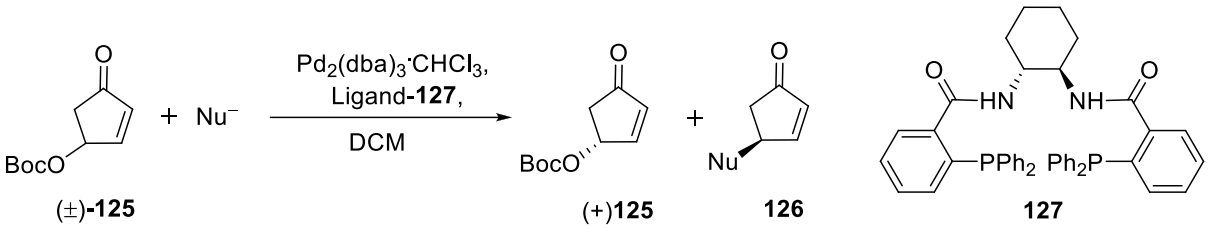
Scheme 19: Kinetic resolution of butenolides by using Pd-(*R,R)*-Trost complex by Trost *et al*.

G. Fu *et al*. reported kinetic resolution of secondary alcohols **120** as enantipure acetates **122** by using a planar-chiral DMAP analogue **121** in the presence of **119** (as acetylation agent) and triethyl amine gave selectivities ranging from 12-52. In these cases, enantioselectivity observed are better than previously reported non-enzymatic asymmetric acylation catalyst (Scheme 20).[75]



Scheme 20: Kinetic resolution of racemic secondary alcohols by G. Fu *et al.*

Recently O.Reiser *et al*. published enantioselective synthesis of 4-hetero substituted cyclopent-2-enones **126** from (±)-**125**. In this case, they used Pd-catalyzed kinetic resolution of (±)-**125** with various nucleophiles in the presence of ligand **127**. Excellent enantioselectivities of both substitution products **126** and recovered starting material (+)-**125** were obtained even at low catalyst loading (Scheme 21). This method could be useful for synthesis of various starting materials for cyclopentanoid bioactive molecules and prostaglandin derivatives.[76]



(±)-125 (+)125 126 127

Scheme 21: Kinetic resolution of racemic 4-Boc cyclopent-2-enones by using Pd- ligand **127** complex by Reiser *et al*.

7. Conclusion

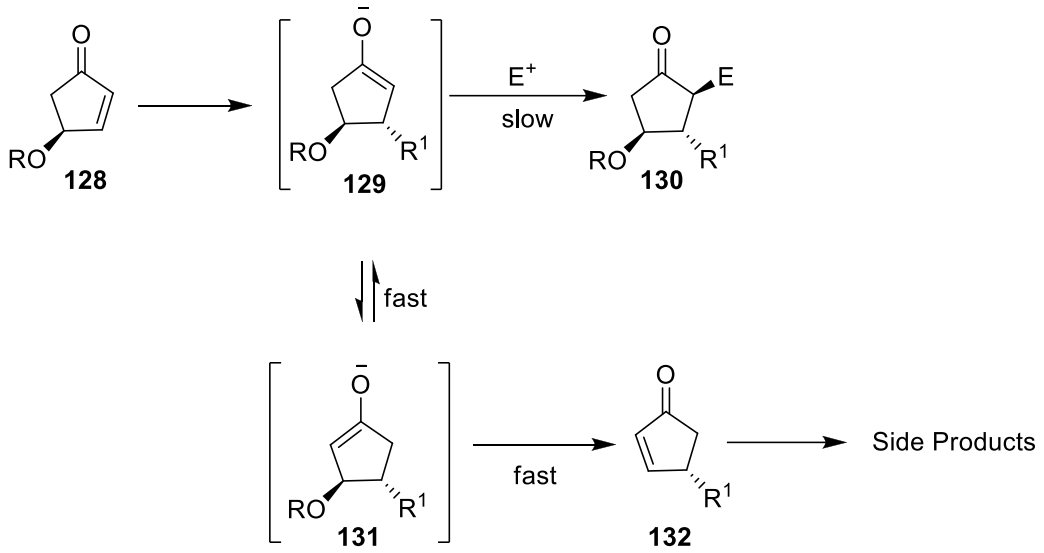
Since last 40 years, the synthesis of substituted cyclopent-2-enones was expanded significantly. Prostaglandins exhibit a broad range of biological activity and stimulate the development of research in their synthesis. As there are more and more number of prostaglandins discovered, the full evaluation of their bioactivity is still of current interest. Besides this, methods were developed to synthesize substituted cyclopent-2-enones from various starting materials, which were highly valuable in view of growing interest in their synthesis. On the other hand, cyclopentanoid sesquiterpenes are also exhibit a broad range of bioactivity. Therefore, the total synthesis of sesquiterpenes plays an important role in inventing new methods in organic synthesis.

B. Main Part

1. One pot synthesis of substituted cyclopent-2-enones by using a traceless stereoinducing directing group

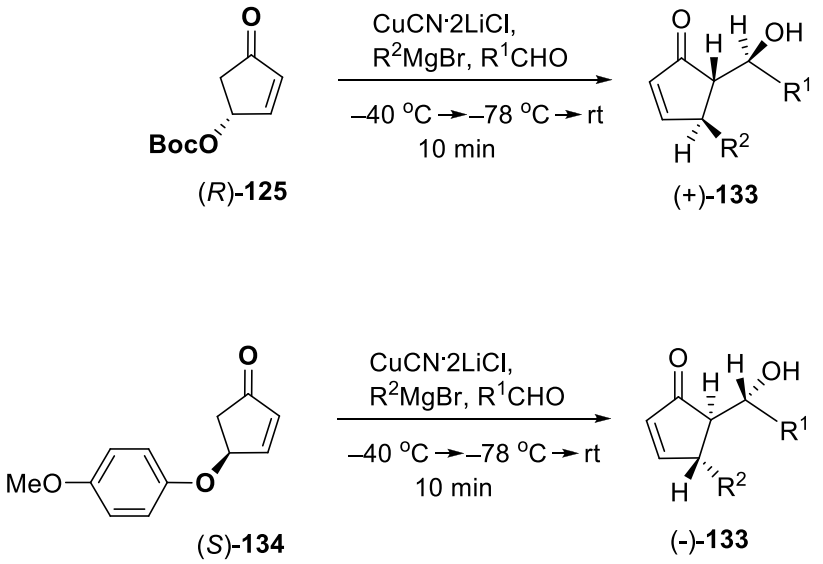
1.1 Introduction

Substituted cyclopent-2-enones represents one of the most important core structures in many bioactive prostaglandin derivatives and sesquiterpenes. Prostaglandins[1] are a group of physiologically active compounds having hormone like effects. They show wide range of activities, such as regulating cell growth, calcium ion levels, hormones, inflammation, and they act on parietal cells in the stomach wall to inhibit acid secretion.[2] Cyclopent-2-enone compounds have been shown, to react by conjugate addition with various biological nucleophiles such as L-cysteine or thiol containing enzymes (E-SH). Based on the SAR studies it was concluded that cyclopent-2-enone moiety enhances the cytotoxic activity. 5-(1-hydroxy)-4-substituted cyclopent-2-enones **1** (Fig 1, Introduction part) act against malignant tumors. Cyclopent-2-enone prostaglandin derivatives showed anti-inflammatory and antiviral activity, and inhibit NF-κB activation in human cells stimulated with tumor necrosis factor-α.[77] Based on the biological activity of such substituted cyclopent-2-enones many groups have reported the synthesis this moiety by using chiral pool, chiral reagents and various catalytically strategies.[78] Addition of organo lithium or Grignard reagents to cyclopent-2-enones in the presence of copper (I) salts followed by trapping of the resultion enolate intermediate with an aldehyde is a well known process for synthesis of prostaglandin derivatives. However, extensive studies along this line have revealed that such direct vicinal functionalization is not easy to achieve. The difficulty is presumably attributable to the complex nature of the reaction system, which causes a facile double bond migration of the initial formed enolate **129**, causing concomitant dehydration to give undesired products **132**. By using highly reactive electrophiles, such side reactions are avoided.[79]



Scheme 22: Consecutive addition of 2-side chains to the cyclopent-2-enoen and mechanistic proposal

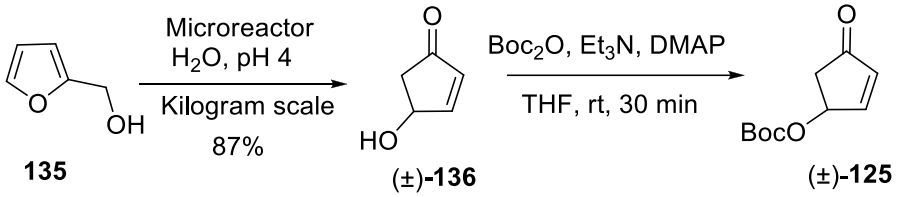
As I showed in introduction, with the pioneering work of Noyori *et al*. utilizing 4-siloxy-2-cyclopentenone **10** as a key building block for the synthesis of prostaglandins, a reliable strategy towards enantiopurecyclopentenones was established, being broadly applied by many. Conjugate *anti*-addition of nucleophiles to **10** in the 3-position controlled by the adjacent siloxy group followed by an aldol reaction in the 2-position *anti* to the nucleophile just introduced was developed. Subsequently, the siloxy group can be eliminated to generate the substituted 2-cyclopentenone. With the advent of asymmetric conjugate additions, it was demonstrated that 2-cyclopentenone could be used directly as a starting material for the synthesis of enantiopurecyclopentanones (Scheme 2, Introduction part). Other strategies towards the target structure have been reported as well, however, mixtures of epimers at C-1', often in ratios close to 1:1, are generally obtained with only few exceptions that require sterically demanding aldehydes. In my thesis I have found that the pseudoenantiomeric building blocks (*R*)-**125** and (*S*)-**134** are exceptional starting materials for the one-flask synthesis of the target structure (+)-**133** and (-)-**133** (both enantiomeric forms with excellent enantio- and diastereocontrol including the C-1' position. The 4-oxo-substitutents in (*R*)-**125** and (*S*)-**134**[80] act as traceless stereoinducing elements that not only relay 1,2- but also remote 1,4-stereocontrol in a cascade of nucleophile addition/ aldol reaction / elimination sequence (Scheme 23).



Scheme 23: Stereoselective synthesis of 5-(1-hydroxy)-4-substituted cyclopent-2-enones.

1.2 Synthesis of (*R*)**-125 and** (*S*)**-134:**

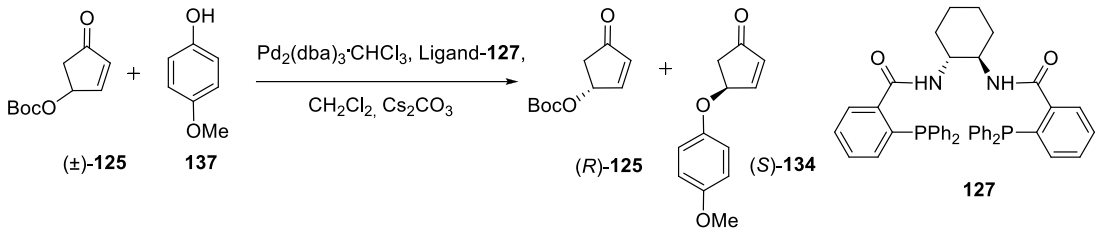
(*R*)-**125** and (*S*)**-134** are readily available in enantiopure form from the bulk chemical furfurylalcohol **135** in a two-step sequence. In the first step, (±)-**136** was synthesized on kilogram scale from **135** by an acid catalyzed Piancatelli rearrangement[81] carried out in a micro reactor setup afforded (±)-**136** in 87% yield, which was converted to (±)-**125** with $(Boc)_2O$ and Et_3N gave (±)-**125** in 85% yield (Scheme 24).[82]



Scheme 24: Synthesis of (±)-**125.**

With the compound (±)-**125** in our hand we decided to synthesize (*R*)-**125** and (*S*)**-134** via a Trost-Tsuji asymmetric allylation technology.[83,84] Reacting 4-methoxy phenol **137** as nucloephile with (±)-**125** in the presence of $Pd_2(dba)_3{\cdot}CHCl_3$ and **127**[85] gave corresponding 4-methoxy phenol substituted compound (*S*)-**134** along with unreacted (*R*)-**125**. The yield and *ee* of the (*R*)-**125** and (*S*)**-134** depend on the equivalents of the **137** (Table 6).

Table 6: Optimization studies for (*R*)-**125** and (*S*)-**129**.



Entry[a]	(±)-125 (mmol)	137 (mmol)	$Pd_2(dba)_3{\cdot}CHCl_3$[b] (mol%)	127[b] (mol%)	Cs_2CO_3[b] (equiv)	Yield (%)[c] (*R*)-125	Yield (%)[c] (*S*)-134	*ee* (%) (*R*)-125	*ee* (%) (*S*)-134
1	0.5	0.05	5.00	18.50	1.48	69	10	16	98
2	0.5	0.10	2.50	9.25	0.74	61	20	25	98
3	0.5	0.15	1.67	6.18	0.49	55	30	61	97
4	0.5	0.20	1.25	4.62	0.37	48	40	81	96
5	0.5	0.25	1.00	3.70	0.30	41	50	≥99	92
6	0.5	0.25	0.20	3.70	0.30	45	44	86	94
7	0.5	0.25	0.40	3.70	0.30	41	48	≥99	90

[a] General procedure: (±)-**125** (0.5 mmol), **137**, $Pd_2(dba)_3{\cdot}CHCl_3$, **127**, Cs_2CO_3, DCM (6 mL), 0 °C, 2.5 h. [b] $Pd_2(dba)_3{\cdot}CHCl_3$, **127**, Cs_2CO_3, based on **137**. [c] Isolated yields after column chromatography.

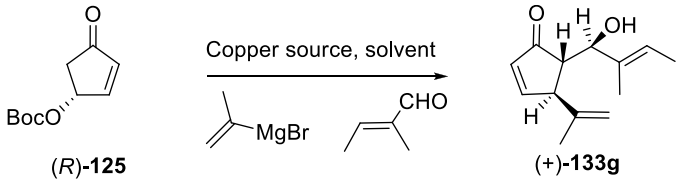
When we used **137** in lower amounts, the formation (*S*)-**134** with good enantiomeric excess but low yield is achieved (entry 1, Table 6). However, the higher amount of **137** favors the (*R*)-**125** with good yield and enantiomeric excess (entry 5, Table 6). Decreasing the amount of the Pd-catalyst from 1 mol% to 0.4 mol% was tolerated well, while a decrease to 0.2 mol% gave some better results for both (*R*)-**125** and (*S*)-**134** (entries 5, 6 and 7). We have resolved (±)-**125** on 50 g scale with **137** (0.5 equiv) under the condtions shown in entry 5, giving rise to (*R*)-**125** (42%, >99% *ee*) and (*S*)-**134** (48%, >92% *ee*).

1.3 Synthesis of (+)-133 and (-)-133

Copper (I)-catalyzed Grignard additions to (*R*)-**125** followed by trapping of the resulting enolate with aldehydes were investigated next. First it was set out to identify best copper (I) source for the envisioned one pot operation. Test reactions were performed with (*R*)-**125**, isopropenyl magnesiumbromide and *trans*-2-methyl-2-butenal (Table7): Using copper (I) iodide in THF,[86] the desired adduct (+)-**133g** was obtained with 48% yield (entry 1, Table 7). Switching to diethyl ether, the yield decreased to 38% (entry 2, Table 7). Variation of the copper(I)-species by adding PBu_3, which has been shown to be stabilize the intermediate oregano copper reagent,[87] also gave

disappointing yields(entries 4-6, Table 7). Higher order cyanocuprates[88] were examined next: Applying CuCN·2LiCl in combination with Grignard reagents in THF–afforded (+)-**133g** with an improved yield of 66% (entry 7, Table 7). Further variation of solvent demonstrated that the mixture of THF and diethyl ether led to lower yields than THF alone (entries 3, 6 and 9, Table 7). These results suggest that the CuCN·2LiCl mixture[89,90] in THF proved to be the best condition for the one-pot strategy, offering good yields in short reaction times.

Table 7: Optimization studies for one pot strategy.



(*R*)-**125** (+)-**133g**

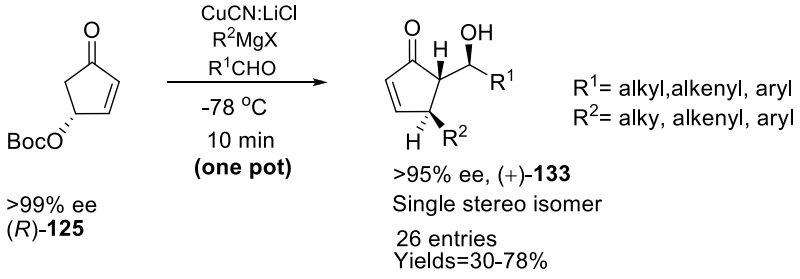
Entry	Copper source	Solvent	Temperature (°C)	Time (min)	Yield[d]
1[a]	CuI	THF	–78 °C, 30 min, then –45 °C to –78 °C	80 min	48%
2[a]	CuI	Et_2O	–78 °C, 30 min, then –45 °C to –78 °C	80 min	38%
3[a]	CuI	THF:Et_2O[e]	–78 °C	80 min	44%
4[b]	CuI+PBu_3	THF	rt to –78 °C	45 min	38%
5[b]	CuI+PBu_3	Et_2O	rt to –78 °C	45 min	32%
6[b]	CuI+PBu_3	THF:Et_2O[e]	rt to –78 °C	45 min	38%
7[c]	CuCN+LiCl	THF	–40 °C to –78 °C	10 min	66%
8[c]	CuCN+LiCl	Et_2O	–40 °C to –78 °C	15 min	45%
9[c]	CuCN+LiCl	THF:Et_2O[e]	–40 °C to –78 °C	15 min	51%

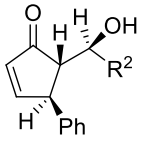
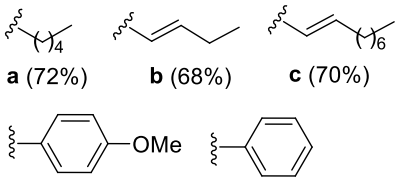
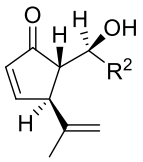
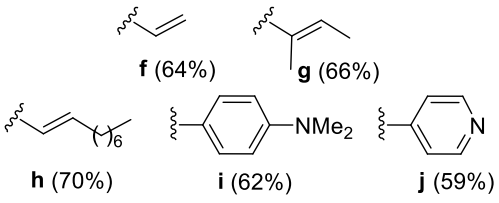
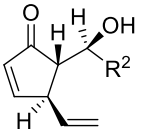
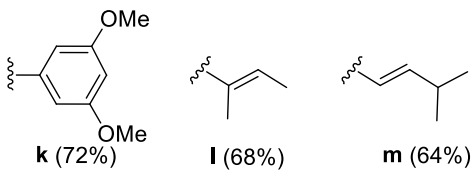
[a] (*R*)-**125** (0.38 mmol, 1 equiv), CuI (1.62 equiv), iso-propenylmagnesium bromide (1.62 equiv), aldehyde (1.68 equiv), solvent (8 mL). [b] (*R*)-**125** (0.38 mmol, 1 equiv), CuI (1 equiv), PBu_3(2 equiv), iso-propenylmagnesium bromide (1 equiv), aldehyde (1.68 equiv), solvent (8 mL). [c] (*R*)-**125** (0.38 mmol, 1 equiv), CuCN (3 equiv), LiCl (6 equiv), iso-propenylmagnesium bromide (3 equiv), aldehyde (1.68 equiv), solvent (10 mL). [d] Yields obtained after column chromatography. [e] THF:Et_2O (3:1, 10 mL).

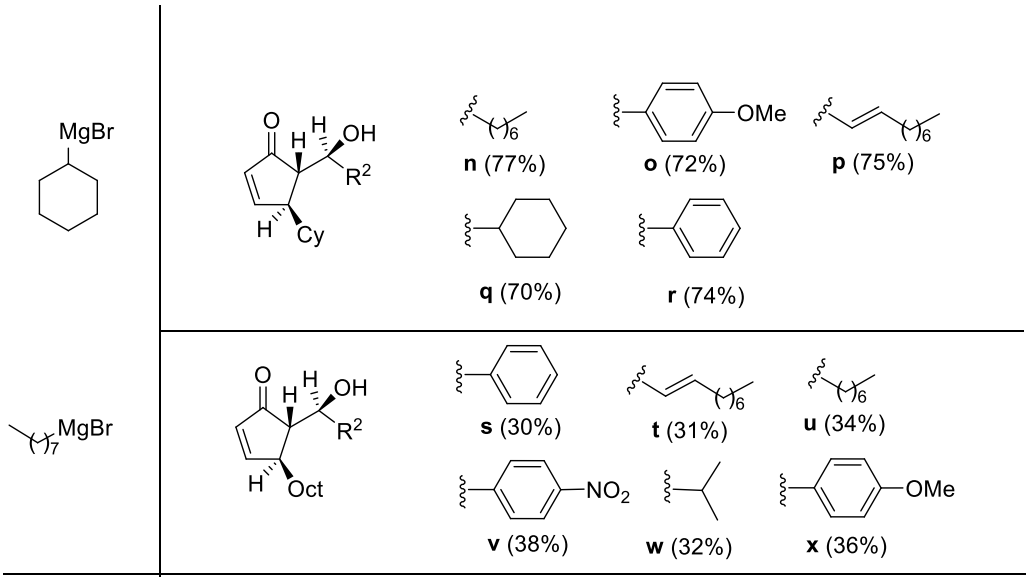
Under the optimized conditions, the addition of organometal compounds to (*R*)-**125** followed by trapping of the resulting intermediate enolates was investigated: Irrespective of the Grignard reagent

employed (aryl-, vinyl- and alkyl) or the aldehydes (aromatic, α,β-unsaturated or aliphatic) the adducts (-)-**133** were obtained with high stereoselectivity. The level of enantioselectivity is determined by the *anti*-selectivity of the Grignard reagent in the initial conjugate addition to (*R*)-**125**, and small differences in selectivity are observed correlating with its steric bulk (Table 8). Introducing a vinyl group as the smallest nucleophile investigated, the enantioselectvitiy was ≥95% *ee*, while octyl, isopropenyl, cyclohexyl and phenyl generally gave ≥99% *ee* with the exception of (+)-**133i** (98% *ee*). Good yields (59-77%) were obtained in all cases with the exception of octyl magnesiumbromide, which gave rise to (+)-**133s-x** (30-38%). It was subsequently found (vide infra) that this Grignard reagent gave considerable higher yields when (*S*)-**134,** being pseudo enantiomericto (*R*)-**125**, was used.

Table 8: One pot strategy of (*R*)-**125** with different Grignard reagents and aldehydes.



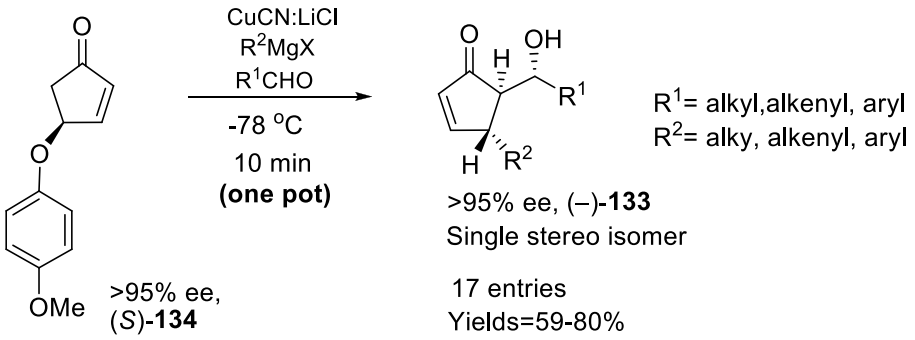
R^2MgBr	(+)-133	R^1
MgBr		 **a** (72%) **b** (68%) **c** (70%) **d** (78%) **e** (72%)
MgBr		 **f** (64%) **g** (66%) **h** (70%) **i** (62%) **j** (59%)
MgBr		 **k** (72%) **l** (68%) **m** (64%)

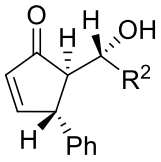
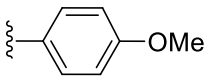
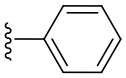
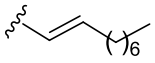
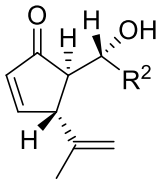
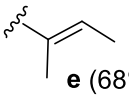
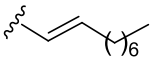
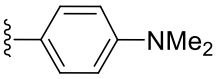
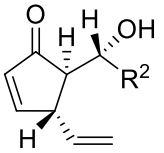
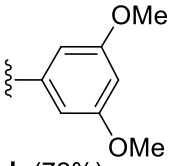
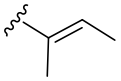
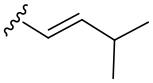
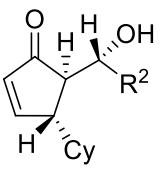
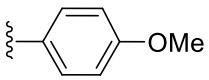
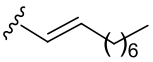


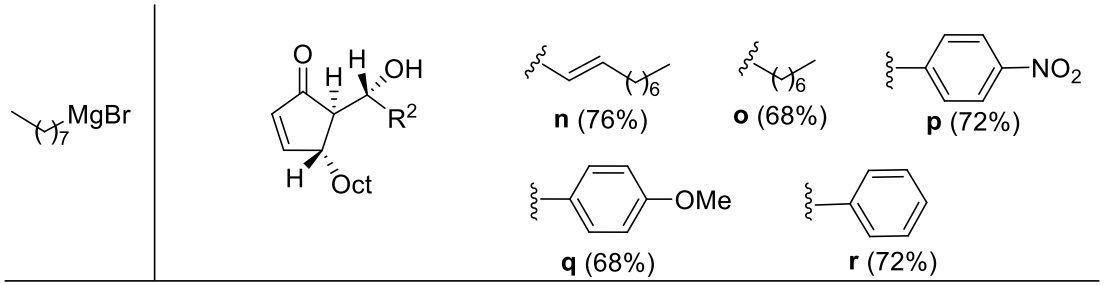
All products were obtained with ≥ 99% *de* as determined by ^{1}HNMR of the crude products. Enantioselectivities (**133a**-**d**, **133f-h**, **133n, o, p** and **r**, **133s**, **133t**: ≥ 99% *ee*, **133i**: 98% *ee*; **133k**: 96% *ee*, **133m**: ≥95% *ee*,) of (+)-**133** for each Grignard reagent were determined by chiral HPLC of the pure against a racemic reference samples of **133a-d**, **f-h**, **n-p** and **r, s, t** and from these data extrapolated to **133e**, **j**, **l**, **q** and **u-x.**

Employing the 4-OPMP derivative (*S*)-**134** as starting material gave access to the enantiomeric cycopentenones (-)-**133** with equally good selectivity. Gratifyingly, good yields were obtained in all cases, even for octyl magnesium bromide (Table 9).

Table 9: One pot strategy of (*S*)-**134** with different Grignard reagents and aldehydes.

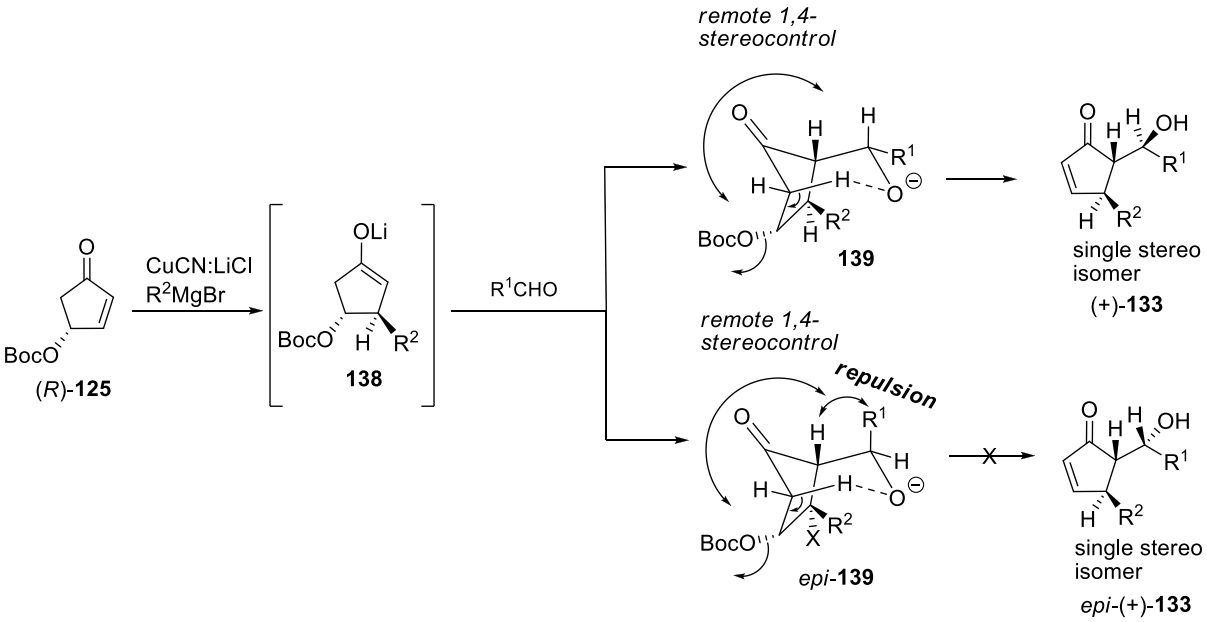


R^2MgBr	(-)-133	R^1		
MgBr		 **a** (72%)	 **b** (74%)	 **c** (68%)
MgBr		 **d** (66%)	 **e** (68%)	
		 **f** (68%)	 **g** (60%)	
MgBr		 **h** (72%)	 **i** (66%)	 **j** (65%)
MgBr		 **k** (75%)	 **l** (68%)	 **m** (80%)



[a]All products were obtained with ≥95%d.r.as determined by ^{1}HNMR of the crude products. (-)-**133a**, **c**, **d**, **g**, **h**, **j**, **k**, **l**, **n** and **r**: 94% *ee* (Chiral HPLC against reference samples reference).

As depicted in Scheme 25, upon addition of a nucleophile to (*R*)-**125**, the enantiopure enolate **138** is formed, which is then converted to the aldol adduct (+)-**133** by reacting with an aldehyde. The excellent stereocontrol achieved for (+)-**133** at the C-1'-position can be understood by the terminating *anti*-elimination of ROH (R=–OBoc,) from intermediate **139**, which we reckon is initially formed along with (*epi*)-**139** (Scheme 25).



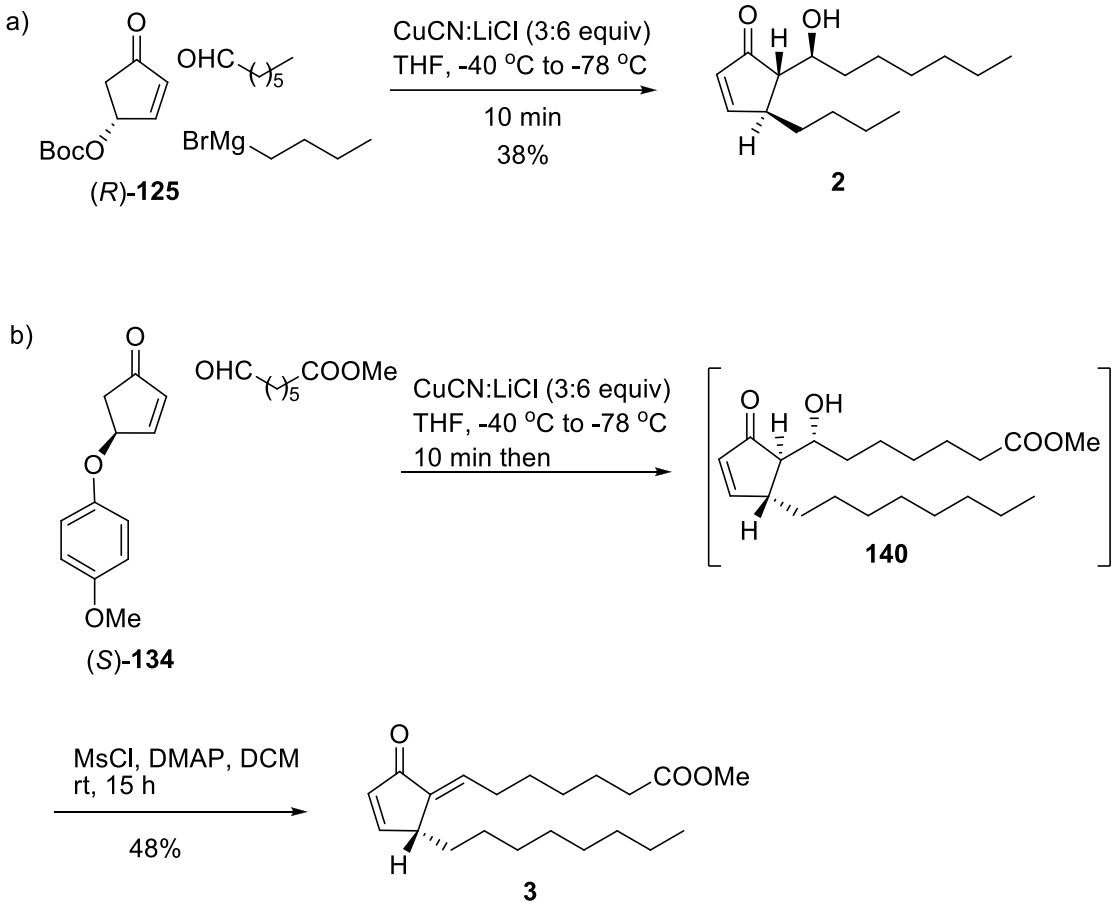
Scheme 25: Stereochemical model for the remote 1,4-stereocontrol of the –OBoc group.

139 can adopt a favorable conformation that triggers elimination to (+)-**133**, while in (*epi*)-**139**, the conformation that is required to invoke R-OH elimination suffers from steric repulsion caused by the axial position of R^1.[91-93]

1.4 Applications of the methodology towards biologically relevant cyclopent-2-enones

Prostaglandins are lipid compounds having hormone type activities that are found in many tissues and organs. They are produced following the sequential oxidation of arachidonic acid by

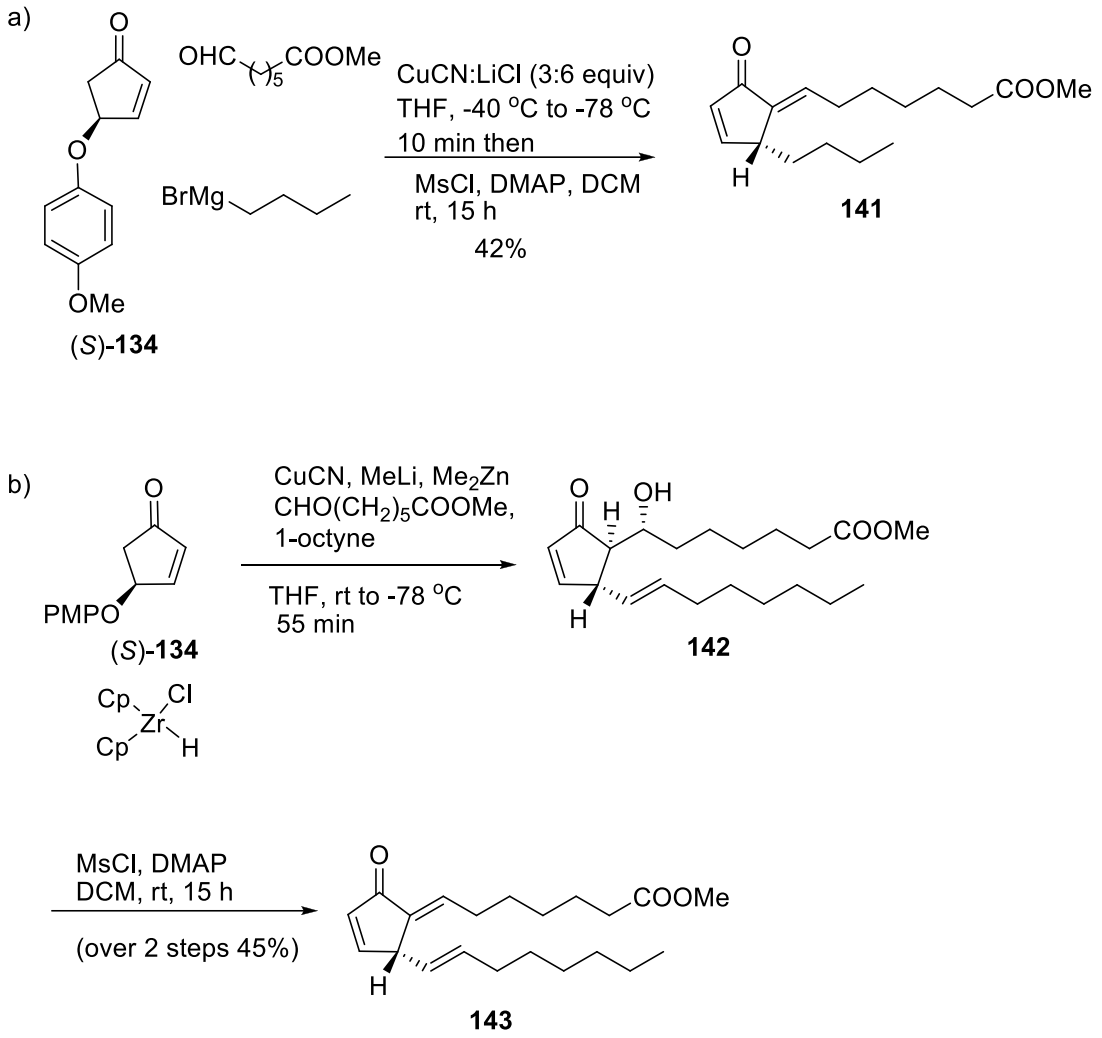
cyclooxygenase and have a wide variety of effects in bio-systems. Prostaglandins are responsible for constriction and dilation of vascular smooth muscle, regulate calcium movement, regulate hormones, and control cell growth.[94,95] Owing to the bioactivity of these compounds, many groups reported syntheses of these molecules by consecutive addition of two side chains to the enantiopure 4-oxo cyclopent-2-enones **10** in the presence of Cu (I)-salts (Scheme 2, Introduction part). All these methods need separate reaction steps, quite drastic reactionconditions and longer reaction times. To overcome these problems, we decided to use the strategy developed above for the synthesis of some prostaglandinsand derivatives thereof.



Scheme 26: One-pot synthesis of anti tumor agents **2** and **3**.

Compound **2**, acts against L1210 murine leukemia cells with IC_{50}= 4.0 (µg/mL),[5] could be obtained from (*R*)-**125** by using n-butyl magnesium bromide as Grignard reagent and heptanal as trapping reagent for the intermediate enolate in 38% yield. The anti-tumor agent **3** (TEI-9826) was synthesized from (*S*)-**134** by using n-octyl magnesiumbromide as Grignard reagent and trapping the resulting

enolate by methyl-6-formylhexanoate afforded **140**, which was used for the next dehydration with MsCl[96] in the same flask without further separation gave **3** in 48% yield (Scheme 26) .



Scheme 27: Synthesis of **141** and **143**.

Two more prostaglandin derivatives **141** (butyl derivative of **3**) and **143** (methyl ester of **4**) could be obtained starting from (*S*)-**134**. To synthesize **141** we used n-butyl magnesiumbromide as nucleophile and methyl-6-formylhexanoate. The resulting aldol adduct was then dehydrated by using MsCl and DMAP to give rise **141** in 42% yield. Using vinyl zirconium instead of Grignard reagents was also possible. We were able to synthesize **143** in 45 % yield starting from (*S*)-**134**, 1-octyne, Schwartźs reagent (Cp_2ZrHCl) and methyl-6-formylhexanoate giving rise to **142**, followed by dehydration to **143**. The later strategy could be in general useful for the synthesis of prostaglandin derivatives with alkenyl groups at C4, without the need to transmetallate another organometal precursor (Scheme 27).[97]

2. Studies towards the synthesis of teuclatriol and iso-teucladiol

2.1 Isolation and bioactivity

The second aim of this work is synthesis of some bioactive guaiane natural products by using the previously described one-pot strategy as key step. Here we successfully achieved the total synthesis of teucltriol **72**,[46] iso-teucladiol **144**,[46] (Fig 4).

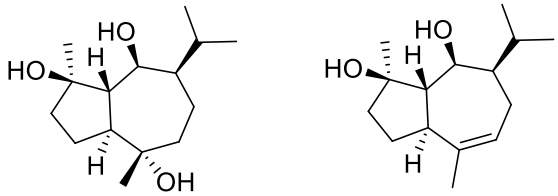
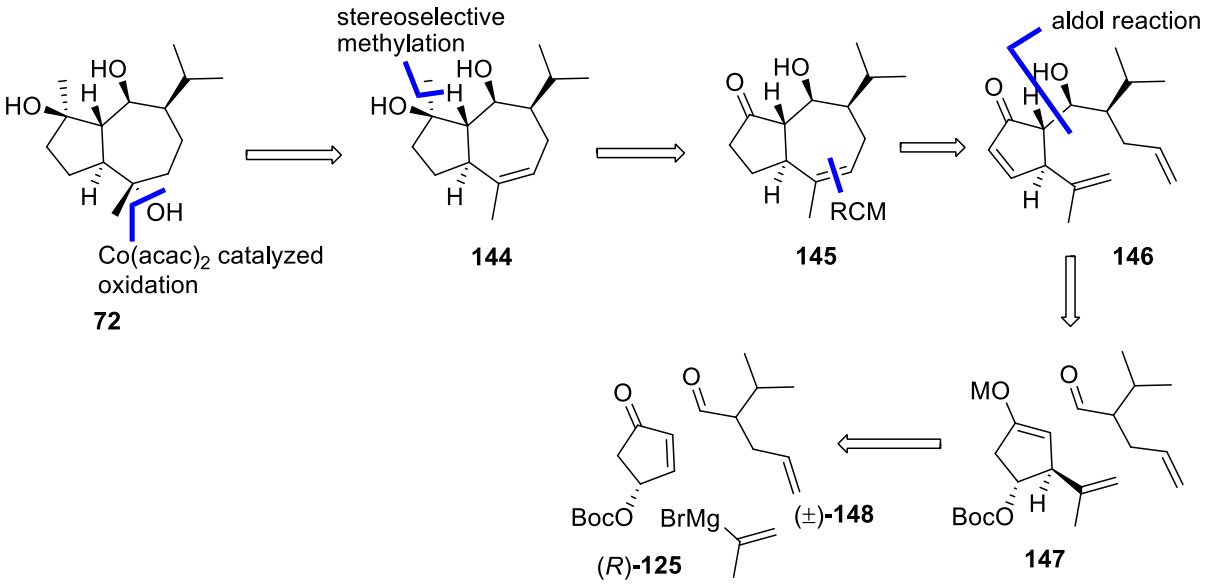


Figure 4: Structure of teuclatriol **72** and teucladiol **144**.

Teuclatriol (**72**) is another guaiane sesquiterpene was isolated from *teucrium leucocladum.* This compound showed a significant anti-proliferative activity on human activated peripheral blood lymphocytes with IC_{50} = 72.5 µg/ml. A number of sesquiterpene lactones have shown anti-inflammatory and anti-cancer activity. Various studies revealed that these lactones most likely induce their immunoinhibitory activity through apoptosis. Teuclatriol does not have a lactone ring, its anti-proliferative activity probably follows a different mode of action. Using bioassay-guided fractionation, it appears that teuclatriol is one of the responsible compounds for the immunoinhibitory activity of *Salvia mirzayanni*.

2.2 Retrosynthetic analysis

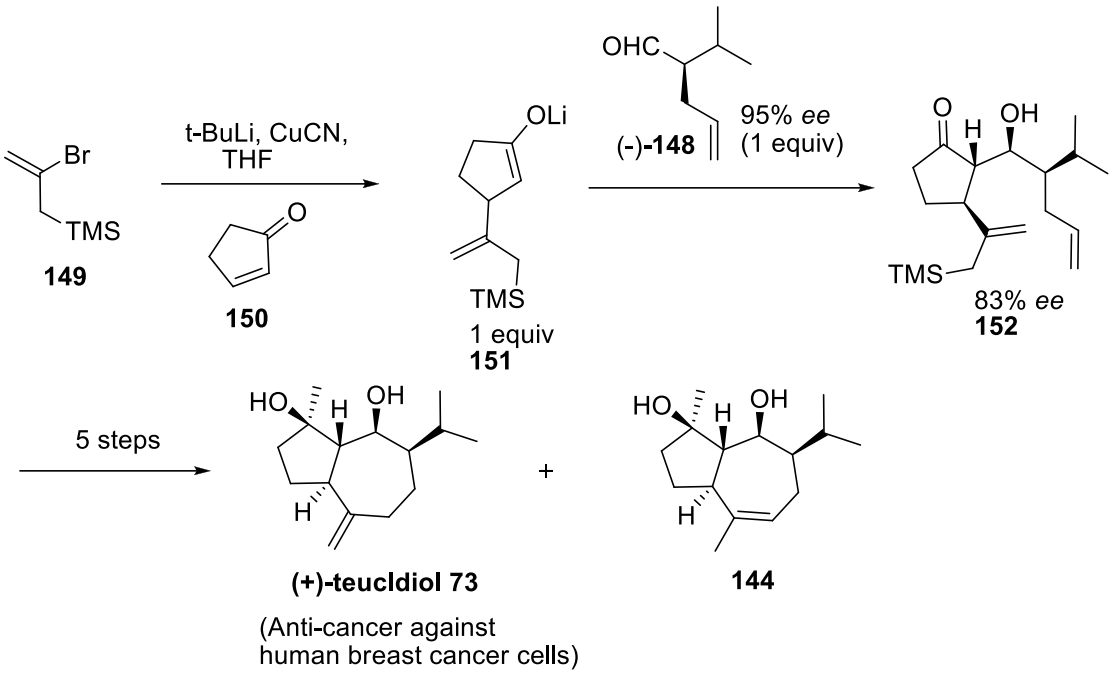
In our retro synthesis, the main goal was to achieve an adduct **146** with 4 contiguous stereo centers in a single step by using our one-pot strategy. We envisioned that the target molecule **72** can be obtained from compound **144** by hydration of the double bond.[98,99] **144** might be obtained from **145** via stereo selective methylation.[100-102] Compound **145** was expected to arise from aldol adduct **146** through ring closing metathesis followed by selective reduction of α,β-unsaturated double bond. Aldol adduct **146** could be accomplished by kinetic resolution of racemic achiral aldehyde (±)-**148**[103] with enantiopure enolate **147** (Scheme 28).



Scheme 28: Retrosynthetic analysis of teuclatriol **72**.

2.3 Kinetic resolution of racemic enolates

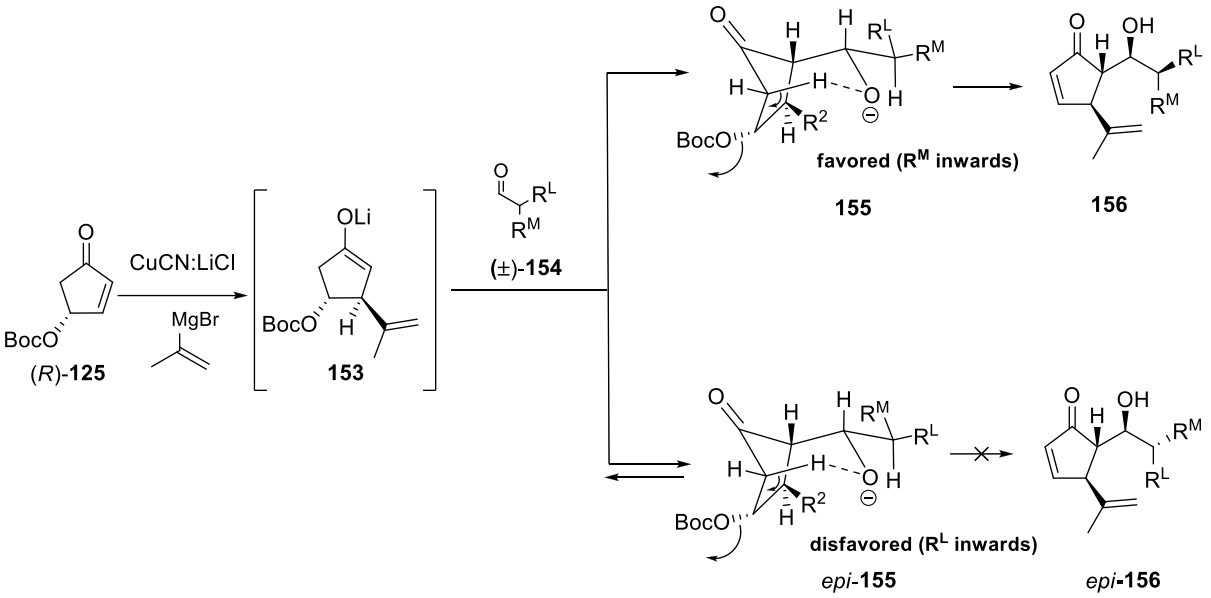
Kinetic resolution is a well known process for the separation of enantiomers from a racemic mixture. In this process, one of the enantiomer reacts faster than the other enantiomer with a chiral reagent . In 2010 Vanderwal and co-workers reported the kinetic resolution of racemic enolates **151** by using enantiopure achiral aldehyde (-)-**148**.[104] Using aldehyde (-)-**148** (95% *ee*) in the reaction of the racemic enolate **151** afforded aldol adduct **152** in 38% yield with 83% *ee*. Apparently, (–)-**148** underwent epimerization under the reaction conditions. *The authors therefore noted that an ideal enantioselective synthesis would incorporateenantioenrcihe enolate, but the asymmetric conjugate addition of sp2-hybridized organometallics to the cyclopentenone is not a well-developed process*. From adduct **152** five steps were needed to complete the synthesis of teucladiol **73** (Scheme 29).



Scheme 29: Vanderwal *et al*. approach towards the teucladiol **73**.

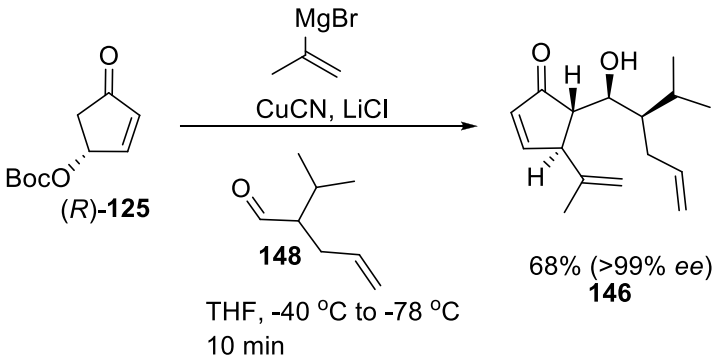
2.4 Kinetic resolution of racemic aldehyde (±)-**149 and synthesis of teuclatriol**

Using our one-pot strategy demonstrated that racemic α-chiral aldehydes (±)-**154** are resolved allowing the one-step construction of cyclopent-2-enones **156** with 4-contiguous stereocenters. Extending the stereochemical model to α-chiral aldehydes (±)-**154** suggests that **155** is favored over (*epi*)-**155:** By placing the smallest substituent (hydrogen) on the α-center axial to minimize 1,3-interactions with the cyclopentanone moiety allows R^L in **156** to orient away from the chair conformation, being most favorable to trigger the elimination of Boc-OH (Scheme 30).



Scheme 30: Stereochemical model for the remote 1,4-stereocontrol of the –OBoc group with achiral aldehydes.

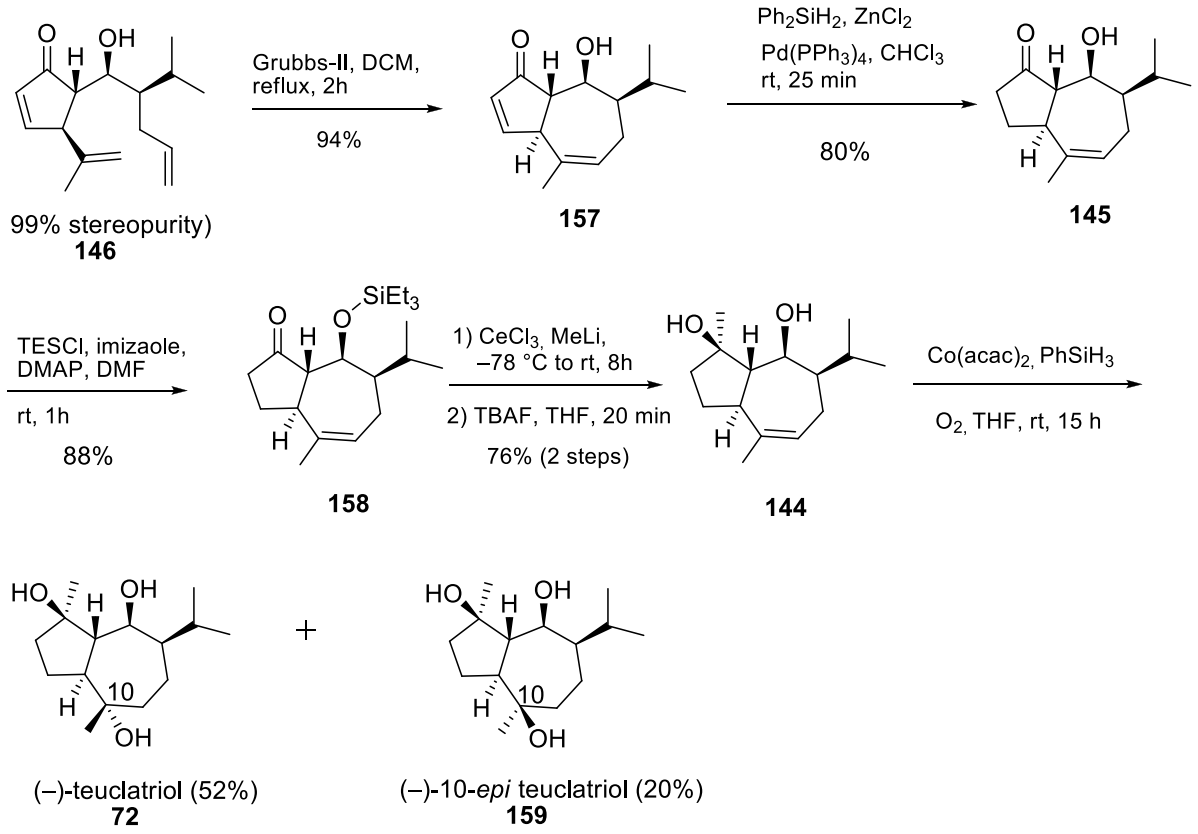
As depicted in the retrosynthetic analysis of **72** (Scheme 28), the guaiane core **145** could be obtained from aldol adduct **146**. Reacting (*R*)-**125**, isopropenyl magnesiumbromide and aldehyde (±)-**148** gave aldol adduct **146** in 68% yield and with >99% ee and. With this compound **146** in our hand, we further proceeded towards the teuclatriol **72** (Scheme 31).



Scheme 31: Kinetic resolution of aldehyde (±)-**148** by using enantiopure (*R*)-**125.**

With this compound **146** in our hand, we further proceeded towards the teuclatriol **72**. Ring closing metathesis (92% yield) gave rise to **157** followed by selective reduction of its α,β-unsaturated double bond using Ph_2SiH_2 in the presence of $Pd(TPP)_4$ afforded **145** in 80% yield.[105] The alcohol function in the resulting **145** was protected by reaction with TESCl to yield **158** in 88%.[106] Regio and stereoselective methylation of **158** by MeLi, $CeCl_3$ in THF at -78 °C followed by deprotection with

TBAF[107, 108] afforded diol **144** in 76% yield. The final step in our synthesis was hydration of the alkene double bond to a tertiary alcohol at C-10. Initially, oxymercuration-deoxymercuration[109] on **144** was applied, however compound **72** was obtained low yield and accompanied with undesired side products. Gratifyingly, cobalt-catalyzed hydration in the presence of $PhSiH_3$ and oxygen[110,111] afforded teuclatriol **72** in 52% yield along with 10-*epi* teuclatriol **159** in 20% yield (Scheme 32).



Scheme 32: End game for teuclatriol**.**

The spectroscopic data (^{1}H NMR, ^{13}C NMR, UV and HRMS) and optical rotation were in accordance with literature.[46]

Table 10. ^{1}H and ^{13}C NMR chemical shift comparison of synthetic and natural (-)-**teuclatriol**.

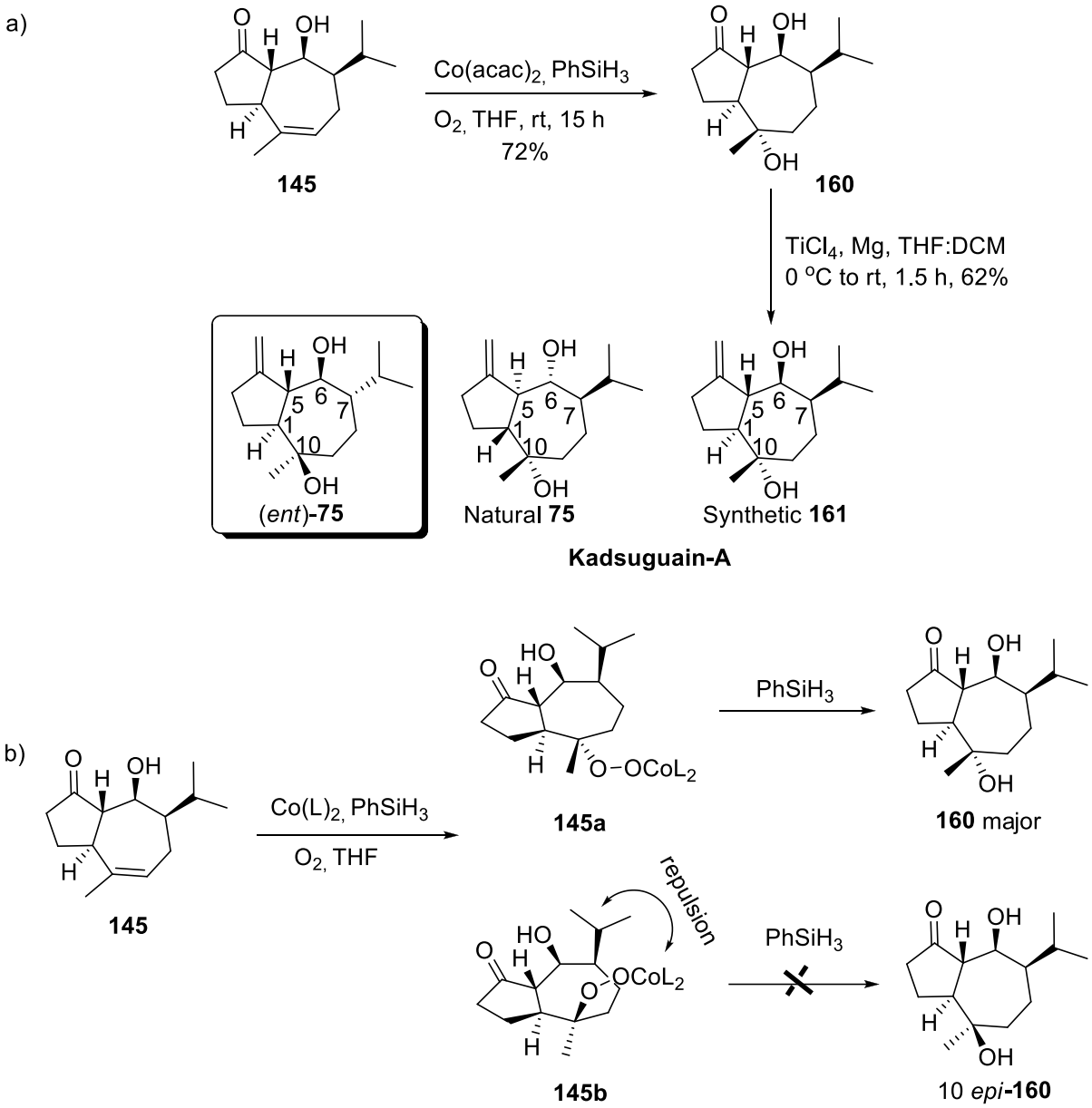
^{1}H NMR chemical shift comparision		^{13}C NMR chemical shift comparision	
^{1}H NMR synthetic ($CDCl_3$-600 MHz)	^{1}H NMR natural ($CDCl_3$-500 MHz)	^{13}C NMR synthetic ($CDCl_3$-150 MHz)	^{13}C NMR natural ($CDCl_3$-125 MHz)
4.13 (dt)	4.13 (dd)	81.11	81.12
1.98-1.93 (m)	1.94 (dd)	75.47	75.46
1.86 (td)	1.85 (m)	71.40	71.41
1.81-1.76 (m)	1.77 (m)	55.25	55.25
1.74 (d)	1.73 (m)	52.03	52.04
1.69 (dd)	1.68 (m)	47.99	48.02
1.59-156 (m)	1.56 (m)	45.48	45.48
1.39 (dd)	1.38 (m)	41.10	41.13
1.36 (dd)	1.36 (m)	29.56	29.56
1.26 (s)	1.27 (d)	23.16	23.17
1.25 (s)	1.23 (s)	23.07	23.09
1.08 (dd)	1.08 (m)	22.14	22.16
1.02 (d)	1.02 (d)	21.50	21.50
0.97 (d)	0.97 (d)	21.14	21.14
		20.50	20.51

Table 11. ^{1}H and ^{13}C NMR chemical shift comparison of synthetic and natural **(–)-10 *epi*-teuclatriol**.

^{1}H NMR chemical shift comparision		^{13}C NMR chemical shift comparision	
^{1}H NMR synthetic ($CDCl_3$-300 MHz)	^{1}H NMR natural ($CDCl_3$-300 MHz)	^{13}C NMR synthetic ($CDCl_3$-75 MHz)	^{13}C NMR natural ($CDCl_3$-50.3 MHz)
4.1 (dt)	4.11 (dd)	81.2	81.2
2.26-2.18 (m)	2.22 (dd)	73.1	73.0
1.29 (s)	1.29 (s)	71.3	71.3
1.17 (s)	1.20 (s)	54.0	53.9
1.00 (t)	1.02 (d)	51.6	51.6
0.96 (d)	0.97 (d)	46.8	47.1
		45.9	45.7
		40.9	41.0
		29.9	29.9
		29.8	29.7
		23.6	23.6
		23.3	23.3
		21.3	21.3
		21.2	21.2
		19.9	19.9

2.5 Studies towards Kadsuguain-A

Kadsuguian-A **75** is a guaianesesquiterpene, which was isolated from *piper kadsura*.[43] Based on our previous synthesis of **78**, we assume that an intermediate **145** could be useful starting material for the synthesis of C-7 epimer of (*ent*)-**75**. Reaction of **145** with Co $(acac)_2$ and $PhSiH_3$ in the presence of oxygen gave **160** in 72% yield. We expected that the newly formed C10-OH would be in *anti* position to the C1-H. Unfortunately, we have observed the newly formed C10-OH group was in *syn* to the C1-H. Based on the proposed mechanism (scheme 33b),[110] we thought that the intermediate peroxocobalt complex reacts with alkene from the less hindered side and form **145a**, which provides us **160** as a major compound. The next step of our synthesis was the introduction of an *exo*-methylene group in **160**. Wittig methylenation,[112,113] gave the expected product **161** only in low yield. Selective methylenation in the presence of $TiCl_4$ and magnesium in DCM/THF mixture afforded the desired target **161** in 62% yield (Scheme 33a).[114] However, the newly synthesized molecule **161** showed a different configuration at C7 and C10 positions with respect to (*ent*)-**75.**



Scheme 33: Synthesis of isomer of Kadsuguain-A.

3. Studies towards the orientalol-F 78 and englerin-A 79

3.1 Isolation and bioactivity

Guaianes are representatives of the largest group among naturally occurring sesquiterpenes.[115] Orientalol-F **78** is an oxo-bridged guaianesesquiterpene isolated from *Alismaorientalis* JUZEP and has been widely cultivated in China and Japan; its dried rhizomes have been used as folk medicines to treat diabetes. Another oxo-bridged guaianesesquiterpene is englerin-A **79**, which was isolated from

phyllanthusengleri in Zimbabwe and Tanzania region. It showed a 1000-fold selectivity against six of eight renal cancer cell lines with IC_{50} values 1-87 nM. The C-9 glycolate ester moiety is important for the anti-cancer activity for the engelrin-A,[116] because the glycolic acid is well known metabolite of ethylene glycol that causes acute renal toxicity in mammals (Fig 5).

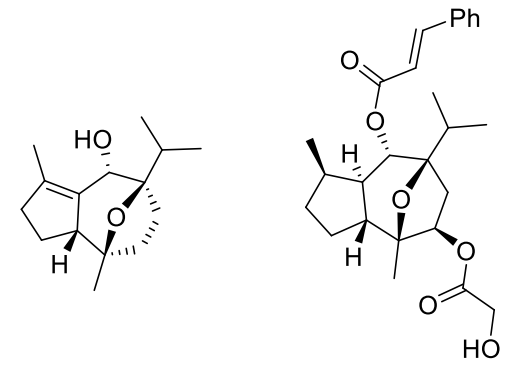
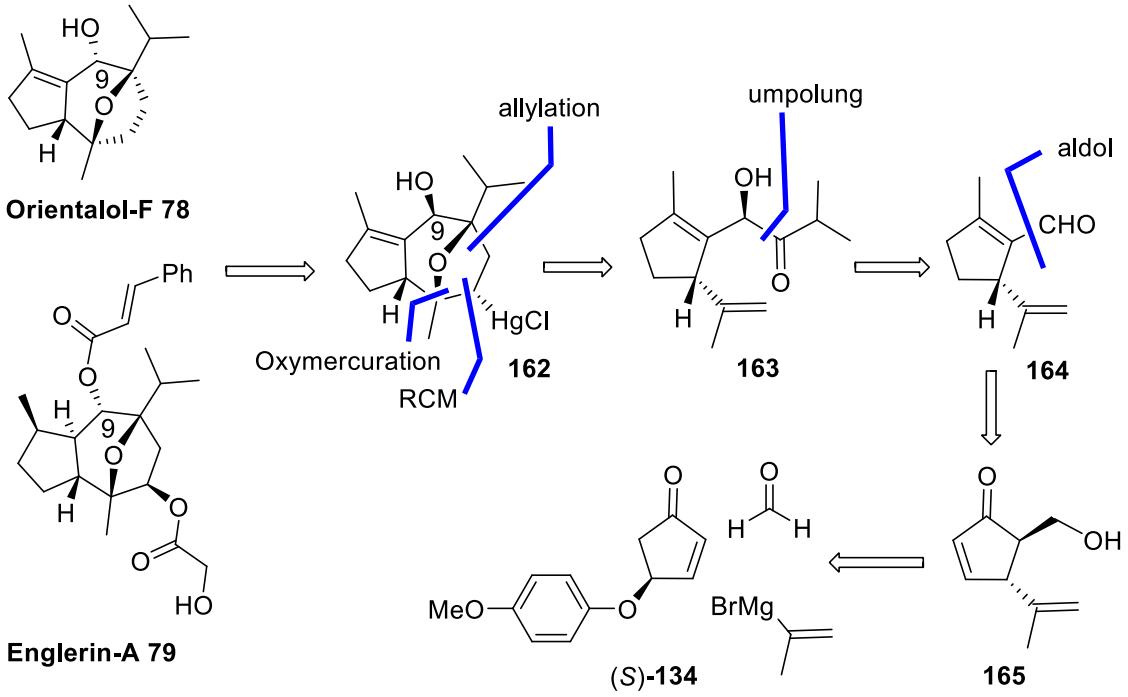


Figure 5: Structure of orientalol-F **78** and englerin-A **79**.

3.2 Retro synthetic analysis

As depicted in scheme 34, we envisioned that the mercuric salt **162** could be the common intermediate for the targets **78** and **79**. **78** could be obtained from **162** through reductive demercuration, followed by inversion of C9-OH.

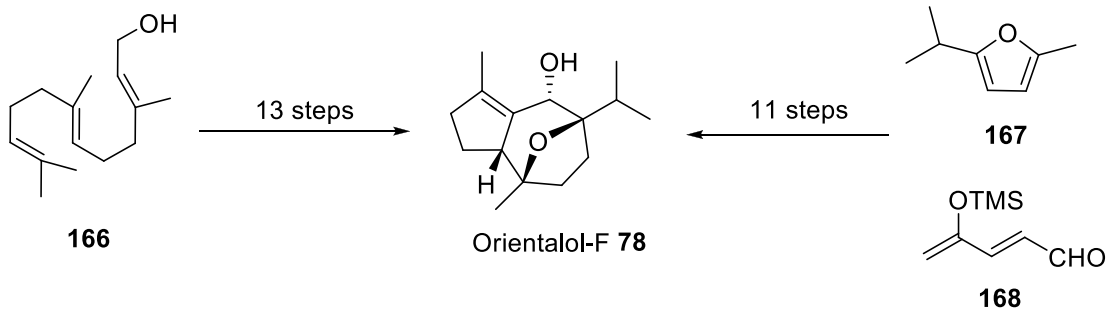


Scheme 34: Retrosynthetic analysis of orientalol-F **78** and englerin-A **79**.

162 was expected to arise from **163** by allylation, RCM[117] and subsequent oxymercuration. Ketone **163** might be accessed from an unsaturated aldehyde **164** by umpolung method. Aldehyde **164** could be assembled from enone **165** through the selective reduction of α,β-unsaturated double bond, methylation and subsequent oxidation.

3.3 Previous reports for orientalol-F and englerin-A

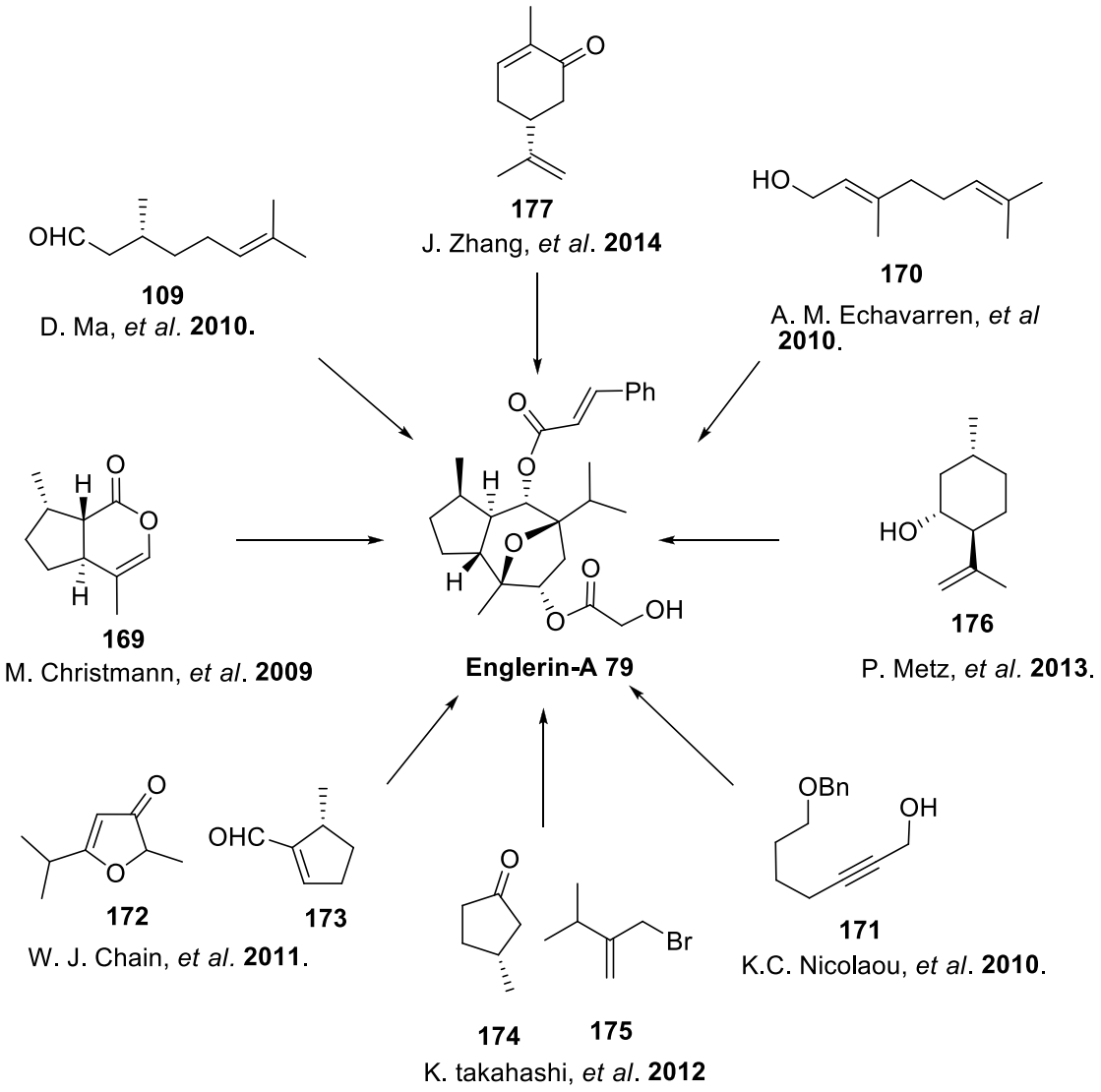
Up to date only two groups have reported the synthesis of the orientalol-F. In 2009, Echavarren *et al.* reported the first synthesis of oriental-F **78** from **166** by gold-catalyzed cycloaddition of functionalized ketoenynes.[118] In 2012, Wang *et al.* achieved the synthesis of **78** from **167** and **168** by 4+3 cycloaddition[119] catalyzed by a proline derivative in the key step (Scheme 35).



166 Orientalol-F **78** **167** **168**

Scheme 35: Previous reports for Orientalol-F.

Based on its strong bioactivity against renal cancer cell lines many groups focused on the synthesis of **79**. In 2009 M. Christmann *et al*. reported the first synthesis of **79** from commercially available nepatalactone **169** in 15 steps and found that the assignment of the absolute stereochemistry in naturally occurring **79** has been wrong.[120] In 2010, D. Ma *et al.* and Echavarren *et al.* achieved the synthesis of **79** by gold catalyzed cyclization of enynes as key step from **109** and **170**.[70,121] Notably the synthesis developed by D. Ma is protecting group free. In the same year, Nicolaou *et al.* reported the synthesis of **79** in 25 steps from **171**.[122]



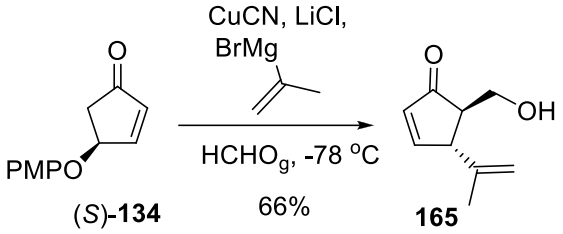
Scheme 36: Previous reports for Englerin-A.

The synthesis of W. J. Chain *et al.* (2012)[123] feuters SmI_2 mediated reductive cyclization between **172** and **173** as key step and K. Takahshi *et al.*(2012)[124] showcase $CrCl_2$ catalyzed enantio selective Barbier allylation[125] as key step for **79**. Moreover, P.Metz *et al.* (2013),[126] and J. Zhang *et al.* (2014)[127] also synthesized **79** starting from **176** and **177** (Scheme 36).

3.4 Towards the construction of guaiane core structure of 78 and 79

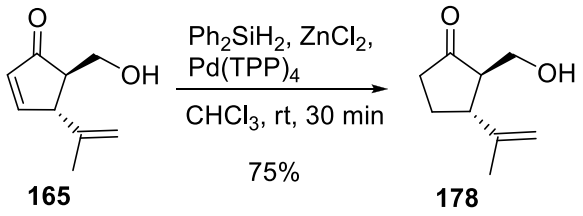
3.4.1 Synthesis of aldehyde 164

The total synthesis of **78** and **79**, began by subjecting (*S*)-**134**, isopropenyl magnesiumbromide and formaldehyde to the conditions developed for our one-pot operation to cyclopentenones, giving rise **165** in 66% yield as a single stereoisomer (Scheme 37).



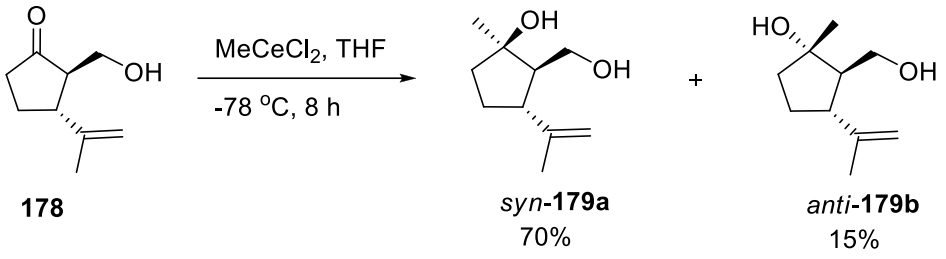
Scheme 37: Synthesis of enone **165** by using one pot strategy on (*S*)-**134**.

The next step of our synthesis consisted of the selective reduction of the α,β–unsaturated double bond in **165**. The combination of catalytic amounts of $ZnCl_2$ and to the $Pd(TPP)_4$ in the presence of stoichiometric amounts of a hydride source has proved to be efficient in conjugate reductions of α,β-unsaturated double bonds.[105,151,152] First Bu_3SnH was tried as hydride source, however no reduction was observed at room temperature after 24 h.[128] In contrast, Ph_2SiH_2 as hydride source furnished **178** in 75% yield after 30 minutes at room temperature (Scheme 38).[105]



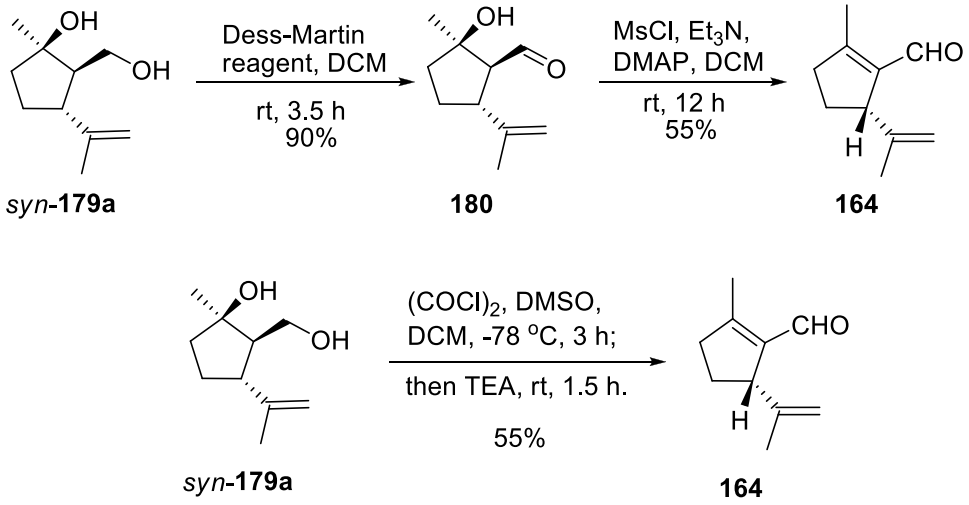
Scheme 38: Selective reduction of α,β–unsaturated double bond in **165**.

As the next step, the chemo selective methylation of **178** by MeLi, $CeCl_3$ in THF at -78 °C was carried out to afford *syn*-diol **179a** in 70% and *anti*-diol **179b** in 15% (Scheme 39).



Scheme 39: Synthesis of diol **179a** by using $MeCeCl_2$.

Next, we planned to do an oxidation of the primary alcohol on *syn*-**179a** followed by dehydration to arrive at aldehyde **164**. When compound **179a** was subjected to the conditions of the Dess-Martin oxidation[129] aldehyde **180** was obtained in 90% yield, which could be dehydrated to **164** in 55% yield in the presence of MsCl, Et_3N and DMAP. Alternatively, oxidation of **179a** under the conditions of a Swern oxidation[131] directly furnished **164**[130] in 54% yield. On the other hand, **179b** under the Swern conditions furnished *epi*-**180** in low yield (Scheme 40).

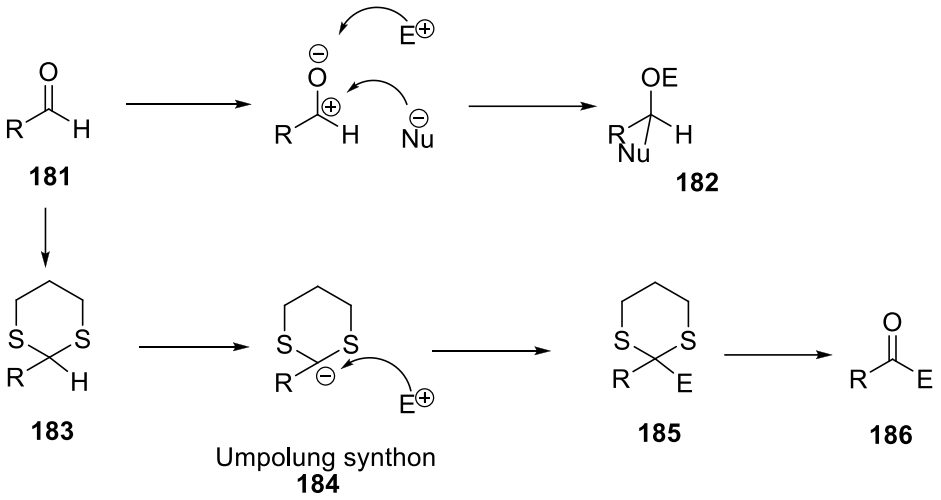


Scheme 40: Synthesis of aldehyde **164**.

3.4.2 Umpolung strategy

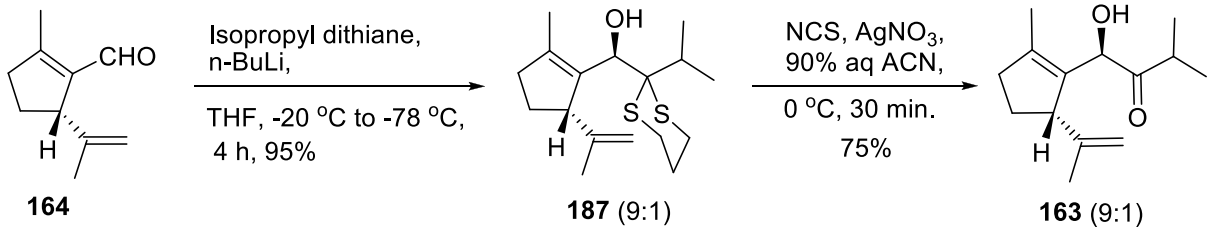
Umpolung is known as a chemical modification of a functional group with reversal of polarity, a concept that was developed D. Seebach and E. J. Corey.[132] It is a very important tool for the generation of carbanion synthons. A well-known Umpolung reagent in organic synthesis is the cyanide ion. For example, cyanide is a key catalyst in the benzoin condensation.[133] The net result in a benzoin condensation is that a bond is formed between two carbons that are normally electrophiles.

Moreover, dithiane chemistry is a classic example for Umpolung reaction. In aldehyde compounds, the carbonyl carbon behaves as an electrophile and oxygen behave like nucleophile, but if the aldehyde is converted to a 1,3-dithiane the polarity can be reversed by deprotanation, thus a carbanion synthon can be generated (Scheme 41).



Scheme 41: General Umpolung strategy in organic synthesis for the generation of carbanion synthons.

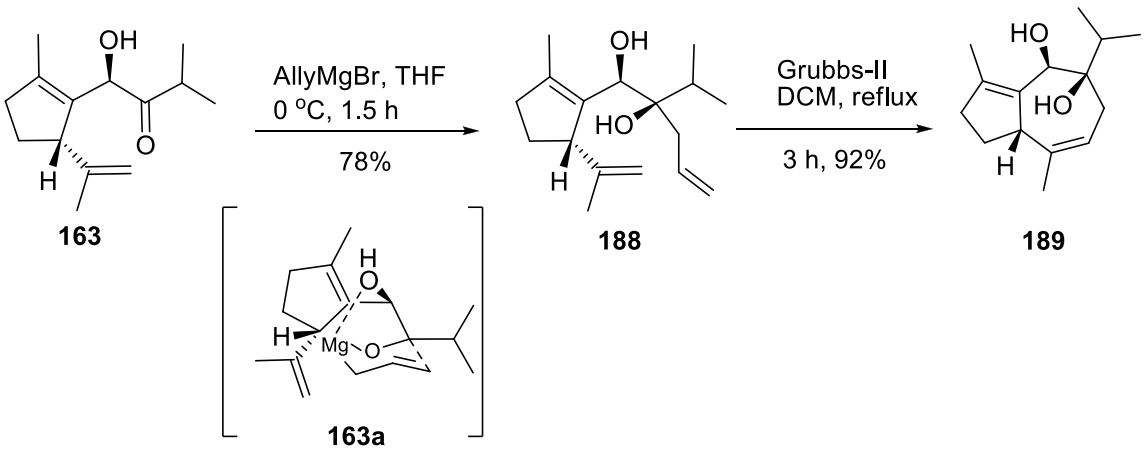
The next steps in our synthesis are concerned with the construction of the guaiane core structure being present in **78** and **79**. The reaction of aldehyde **164** with isopropyl dithiane (Umpolung synthon) in the presence of n-BuLi at -78 °C furnished **187** in 95% yield with 9:1 ratio.[134] Exposure of allylalcohol **187** to the conditions of deprotection (NCS, $AgNO_3$ in 9:1 ($MeCN:H_2O$)) gave hydroxyl ketone **163** in 75% yield (Scheme 42).[135]



Scheme 42: Synthesis of **163** by Umpolung.

The next aim was to achieve the stereoselective allylation of **163** followed by RCM. Barbier-type allylation of **163** with allyl bromide in the presence of zinc in DMF did not give the desired product after 24 h.[136] However, when allyl magnesiumbromide as an allylating agent at 0 °C was employed, diol **188** was obtained in 78% yield as a single diastereomer,[137] we thought that the presence of the

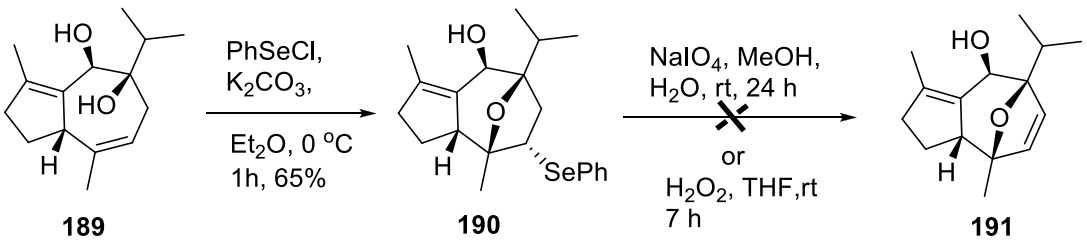
α-hydroxy group in **163** favors the addition of Grignard reagent through the **163a**, which provides us **188** as a major diastereomer. With **188** hand, the cyclization to obtain **189** was investigated. During the past decade, ring-closing metathesis developed as a powerful tool for the formation of carbon-carbon bonds with concurrent cyclization.[138] Which has been utilized for the synthesis of complex natural products. Reaction of diol **188** with Grubbs-II catalyst in DCM, after 3 h at refluxed temperature gave guaiane core **189** in 92% yield (Scheme 43).



Scheme 43: Synthesis of guaiane core compound **189**.

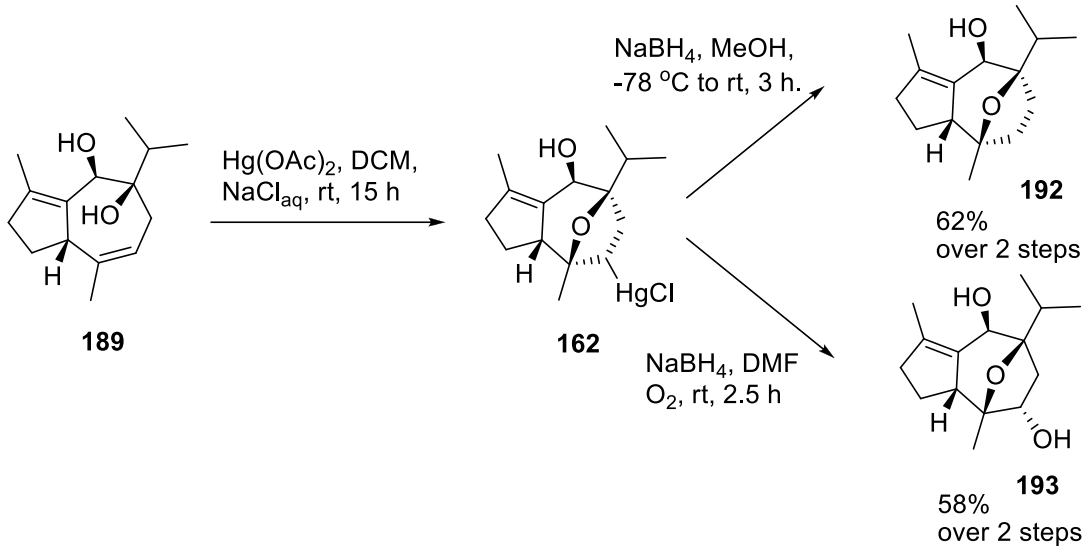
3.4.3 Construction of oxo-bridge ring

Having the guaiane core compound **189** in hand, the next aim was the construction of the oxo-bridge ring to complete the synthesis of **78** and **79**. Phenyl seleniumchloride was investigated to initiate the desired intramolecular cyclization.[139-141] Subjecting **189** to the PhSeCl and K_2CO_3 in DCM afforded the corresponding cyclized selenide compound **190** in 65% yield,[142] which was used directly for the next elimination step**.** $NaIO_4$ in MeOH-H_2O and H_2O_2 in THF were tested for the elimination of the PhSe-group in **190**. However, both of these procedures failed to produce compound **191** (Scheme 44). [143,144]



Scheme 44: Formation oxo-bridge core in **189** by using selenide chemistry.

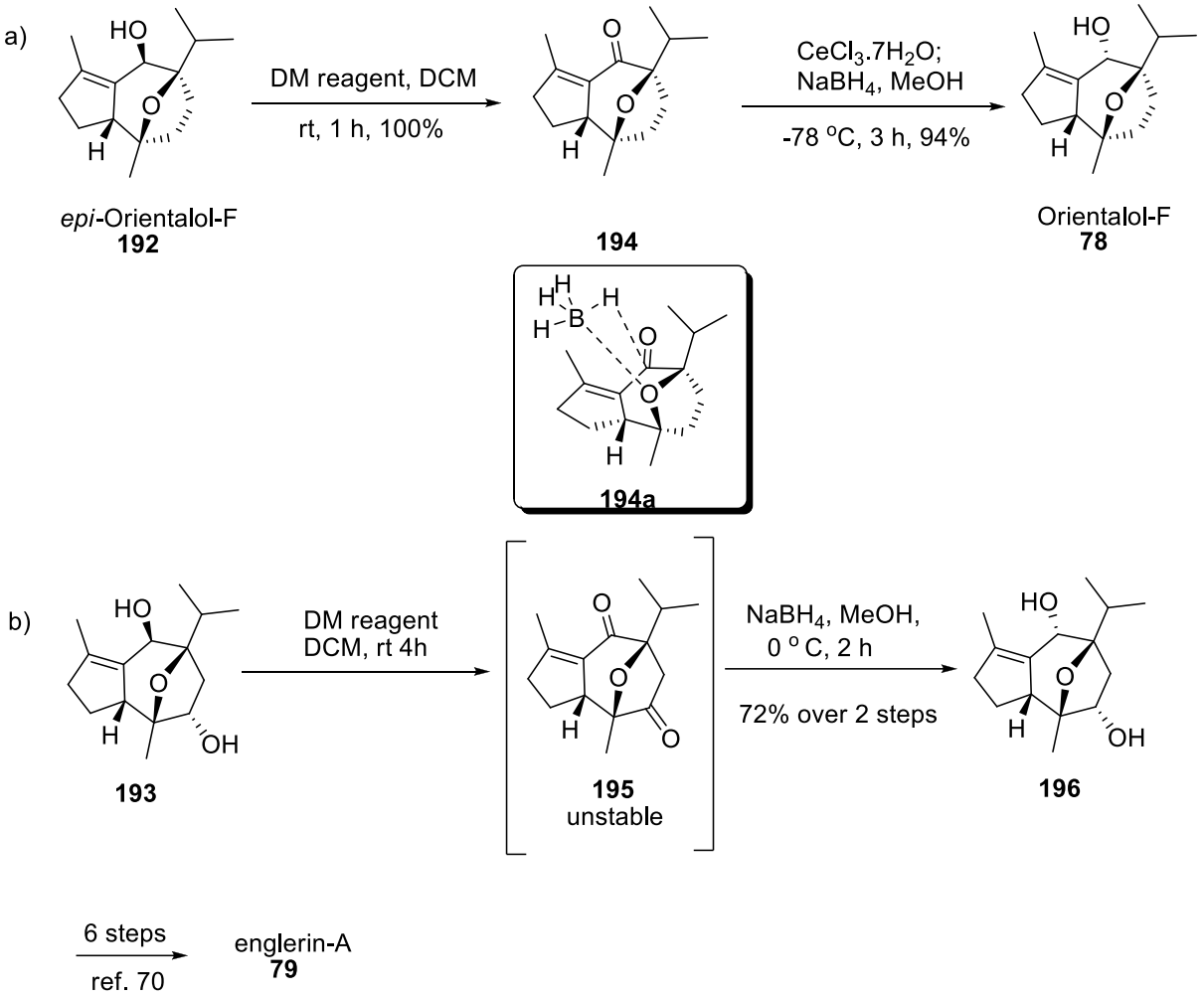
As an alternative, we turned our focus to an oxymercuration-deoxymercuration sequence. Reaction of compound **189** with Hg $(OAc)_2$ in DCM followed by treatment with aq. NaCl solution gave organo-mercuric compound **162** which was not further purified but directly subjected to the reduction with $NaBH_4$ at -78 °C in methanol to give rise to *epi*-orientalol-F **192** in 62% yield (over 2 steps). Alternatively, **162** could be converted to **193** by oxidation with $NaBH_4$, O_2 (bubbling) in DMF in 58% yield over two steps (Scheme 45).[145]



Scheme 45: Formation oxo-bridge core in **189** by oxymercuration method.

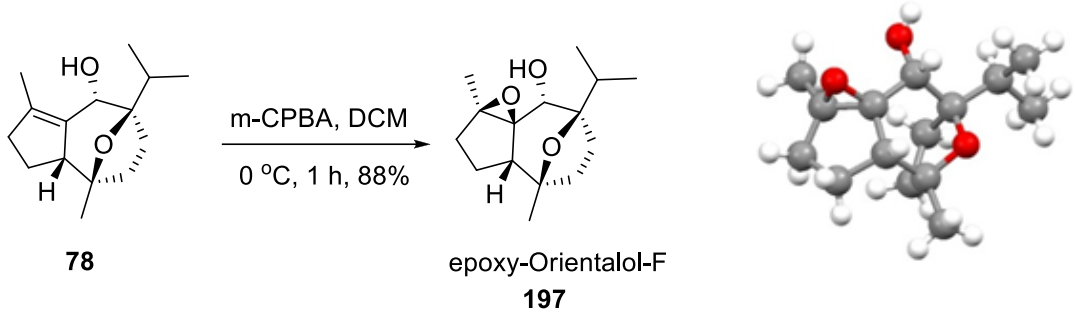
3.5 The end game for orientalol-F 78 and englerin-A 79

192 was oxidized with Dess-Martin reagent to give enone **194** in quantitative yield after 1 h at room temperature. Luche reduction[146,147] ($NaBH_4$, $CeCl_3 \cdot 7H_2O$) reduction of **194** the afforded final molecule orientalol-F **78** in 94% yield as a single stereoisomer (Scheme 46a). Alternatively, **193** was oxidized with Dess-Martin reagent followed by reduction with $NaBH_4$ in MeOH (72% over 2 steps) to give rise to **196** as a single stereoisomer. We thought that the oxo-bridge ring might form complex with intermediate borane (BH_4^-), which favors the attack of hydride nucleophile from the same side and leads to **78** and **196** as a majors. The diol-**196** is known intermediate for englerin-A **79**[70] (Scheme 46b).



Scheme 46: End game for orientalol-F and englerin-A.

The spectroscopic data (^{1}H NMR, ^{13}C NMR, UV and HRMS) and optical rotation were in accordance with literature.[48] In order to unambiguously prove the correct relative and absolute stereochemistry of (+)-orientalol-F **78** according to our synthetic route, a X-ray crystal structure was desired. Since orientalol-F **78** was obtained only as pale yellow oil, we synthesized a derivative, i.e. epoxy-orientalol-F **197** by treatment of **78** with m-CPBA in dry DCM at 0 °C in 88% yield,[148] which upon recrystallization from heptane afforded crystals suitable for X-ray analysis (Scheme 47).

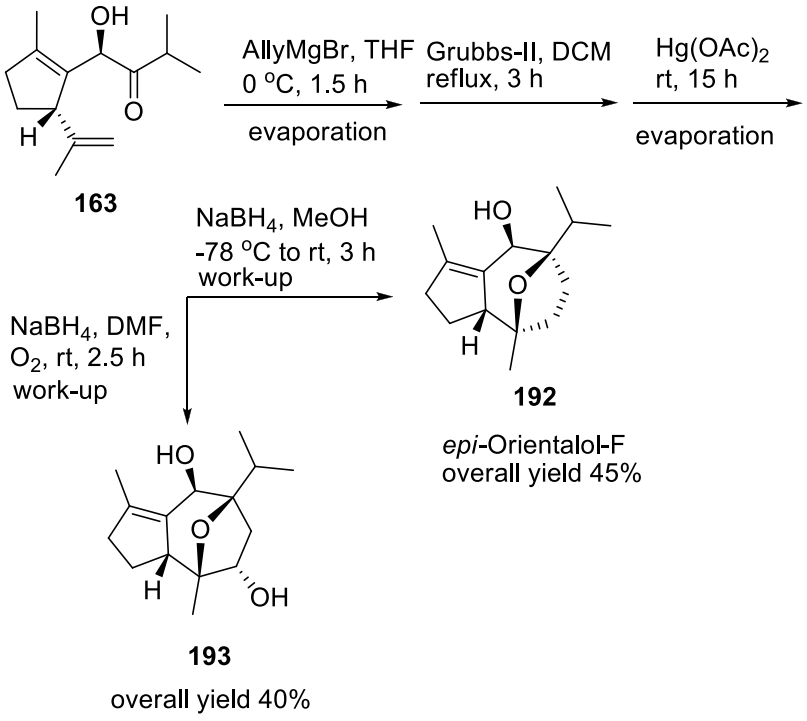


78

epoxy-Orientalol-F
197

Scheme 47: Synthesis of epoxy-orientalol-F **197** for X-ray analysis.

One-pot reactions are especially efficient method to rapidly achieve several transformations with the necessity for work-up and purification, which minimizes the generation of chemical waste and safes time. Our previous described individual steps showed only the desired transformations as clean spot-to-spot reactions on TLC. We therefore investigated if the guaiane core **192** or **193** can be constructed enroute to **78** and **79** from **163** without isolation of any intermediates. We started our one pot operation with allylation of **163** by using allylmagnesium bromide (1.5 equiv.) at 0 °C (the excess Grignard reagent was quenched by stirring the reaction in the open air).



163

192

epi-Orientalol-F
overall yield 45%

193

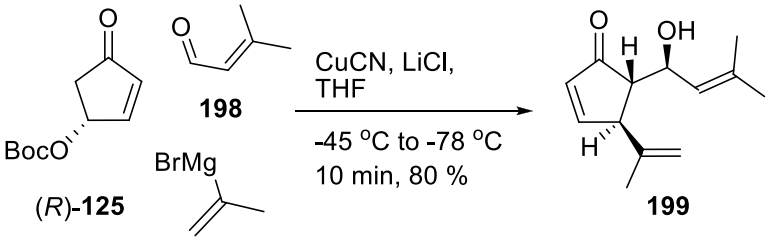
overall yield 40%

Scheme 48: Pot economy for **192** and **193**.

After 1.5 h the solvent was removed under reduced pressure, the crude was directly used for ring closing metathesis reaction with Grubbs-II catalyst in DCM in the same flask. After 3 h of reflux, $Hg(OAc)_2$ was added at room temperature to the same flask without evaporation of solvent. After 15 h at room temperature the reaction was quenched with aq. NaCl, yield in **162** (cf. Scheme 45) as crude product. In different reaction pots, **162** was done converted to **192** and **193** as described above. Overall **192** was obtained in 45% yield (over 4 steps starting from **163**) and **193** was obtained in 40% yield (over 4 steps starting from **162**) (Scheme 48).

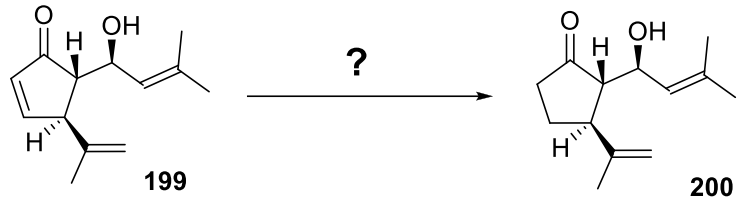
3.6 Other efforts for 78 and 79

With the successful synthesis of orientaol-F **78** (total synthesis) and englerin-A **79** (formal synthesis), we next turned our focus to different aldehydes for trapping the intermediate enolate that is generated after nucleophile addition to (*R*)-**125**, which would provide alternative intermediates that might be useful towards the target molecules **78** and **79**.

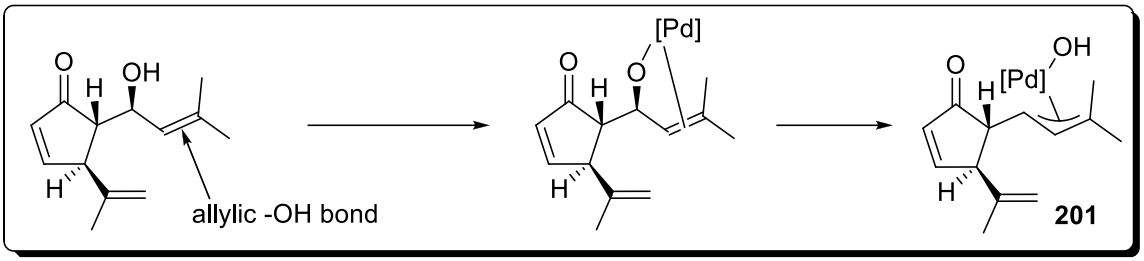


Scheme 49: Synthesis of **199**.

We began this study with the synthesis of **199**. We subjected compound (*R*)-**125**, isopropenyl magnesium bromide and **198** to our one pot conditions, giving rise to aldol adduct **199** in 80% yield (Scheme 49). The next step of our synthesis was the selective reduction of the α,β–unsaturated double bond in **199**. However, **199** possessing an allylic alcohol functionality gave **200** only in low yield under various reduction conditions with $Pd(TPP)_4$. It was thought that the presence of the allylic –OH system, which is very reactive towards the Pd (0) catalysts and forms Pd-allyl type complex **201**, interferes with the desired double bond reduction. Raney-Ni exhibits a good selectivity towards conjugate reduction of α,β–unsaturated double bonds in THF.[149] However, with **199** as substrate we observed no conversion after 24h at room temperature. Another alternative is the, Lewis acid catalyzed selective reduction of α,β–unsaturated double bonds.[150] Attempts to convert **199** to **200** by an $InCl_3$ catalyzed process with $NaBH_4$ as stoichiometric reductant was also met with no success (Scheme 50).[151]

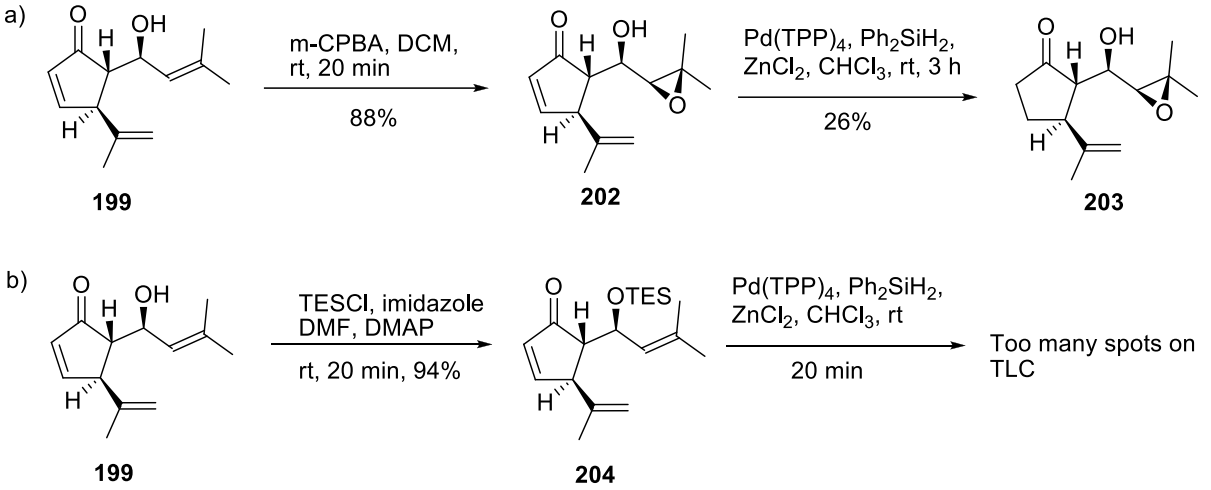


Condition	Status	Yield
$Pd(TPP)_4$, Ph_2SiH_2, $ZnCl_2$, $CHCl_3$, rt, 3 h	Yes	28%
$Pd(TPP)_4$, Bu_3SnH, $ZnCl_2$, $CHCl_3$, rt, 3 h	Yes	30%
$InCl_3$, $NaBH_4$, MeCN, rt, 24 h	No	-
Raney-Ni, THF 0 °C to rt, 24 h	No	-



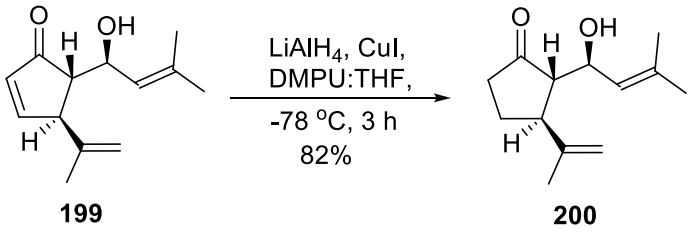
Scheme 50: Selective reduction of α,β-unsaturated double bond in **199**.

We therefore planned to protect the allylic alcohol double bond in **199** to prevent a reaction with Pd(0). We synthesized compound **202** from **199** using m-CPBA in DCM at 0 °C.[152] Subsequent reaction with $Pd(TPP)_4$, Ph_2SiH_2 in the presence of $ZnCl_2$ gave **203** in only 26% yield (Scheme 51a). Then we switched to protect free hydroxyl group in **199**. We treated compound **199** with TESCl giving rise to **204**. Subsequent treatment with $Pd(TPP)_4$, Ph_2SiH_2 and $ZnCl_2$ resulted on in decomposition of **204** after 30 min at room temperature (Scheme 51b).



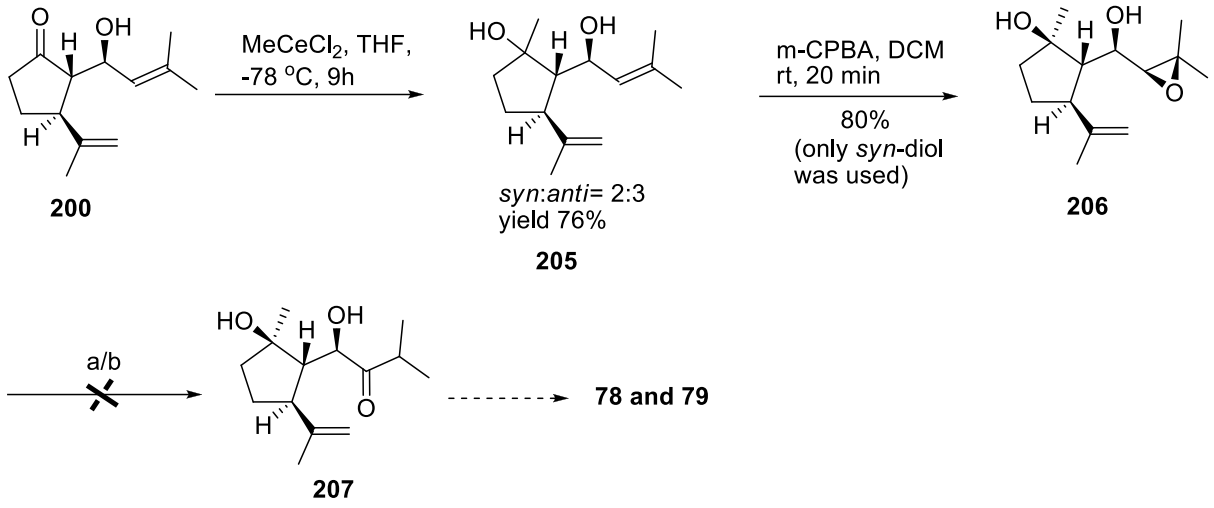
Scheme 51: Selective reduction of α,β–unsaturated bond in derivatives of **199**.

Addition of nucleophile to the α,β–unsaturated system in the presence of Cu (I) salts affords 1,4-addition products.[153-155] Copper hydrides however are not readily accessible. CuI catalyzed selective 1, 4- addition of hydride to the α,β–unsaturated system in the presence of $LiAlH_4$ is known. We subjected therefore, compound **199** to the combination of CuI and $LiAlH_4$ in a mixture of DMPU[156]: THF at -78 °C, yielding the desired **200** in 82 % yield after 3 h (Scheme 52).



Scheme 52: Selective reduction of α,β-unsaturated double bond in **199** with copper hydride.

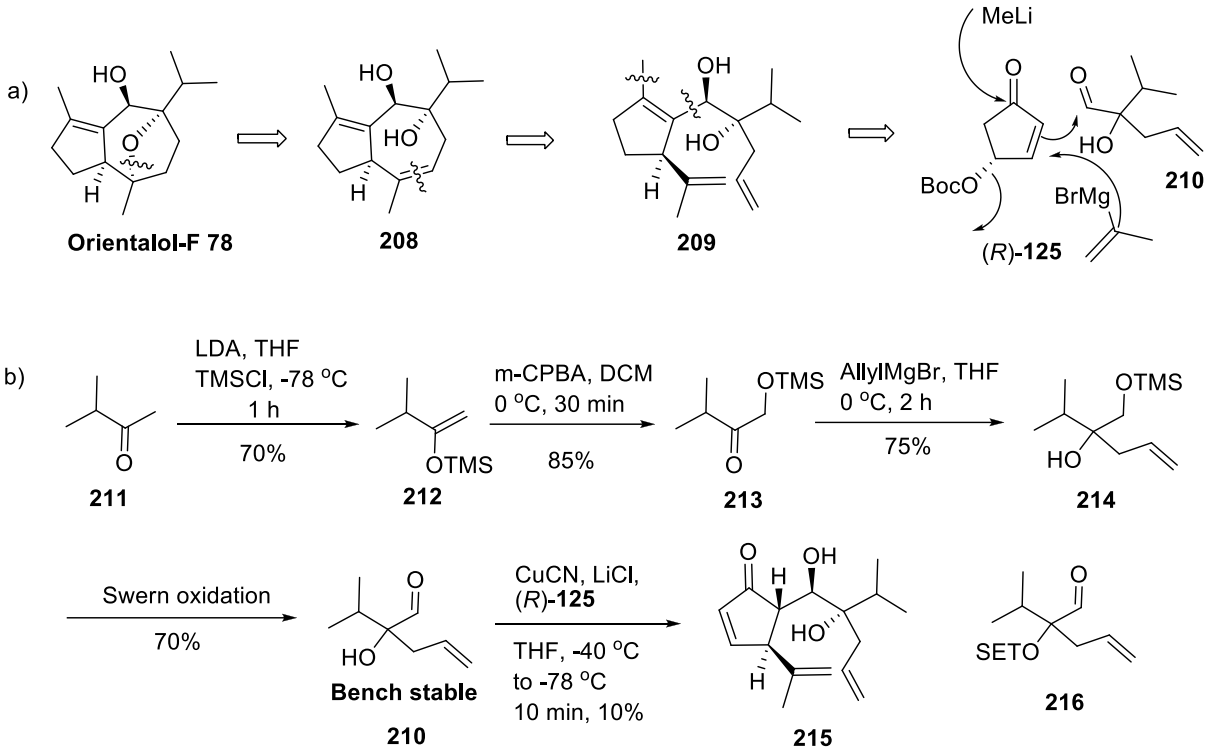
We next converted **200** to the methylated compound **205** with MeLi in the presence of $CeCl_3$ at -78 °C, which was obtained as a *syn*/*anti* mixture (2:3). The epoxide **206** was obatined from *syn*-**205** by epoxidation with m-CPBA in 80% yield. For the final rearrangement of epoxide to the ketone **207**, we planned to use an acid catalyzed rearrangement. We treated epoxide **206** with $BF_3{\cdot}Et_2O$ in DCM, which resulted in decomposition after 30 min at 0 °C[157] and also applying TfOH in DCM gave no better results.[158] Keto group formation could not be observed even after longer reaction time in both cases (Scheme 53).



a. $BF_3.Et_2O$, DCM, 0 °C, 30 min (decmposed)
b. CF_3SO_3H, DCM, 0 °C, 1 h (decomposed)

Scheme 53: Towards **78** and **79**.

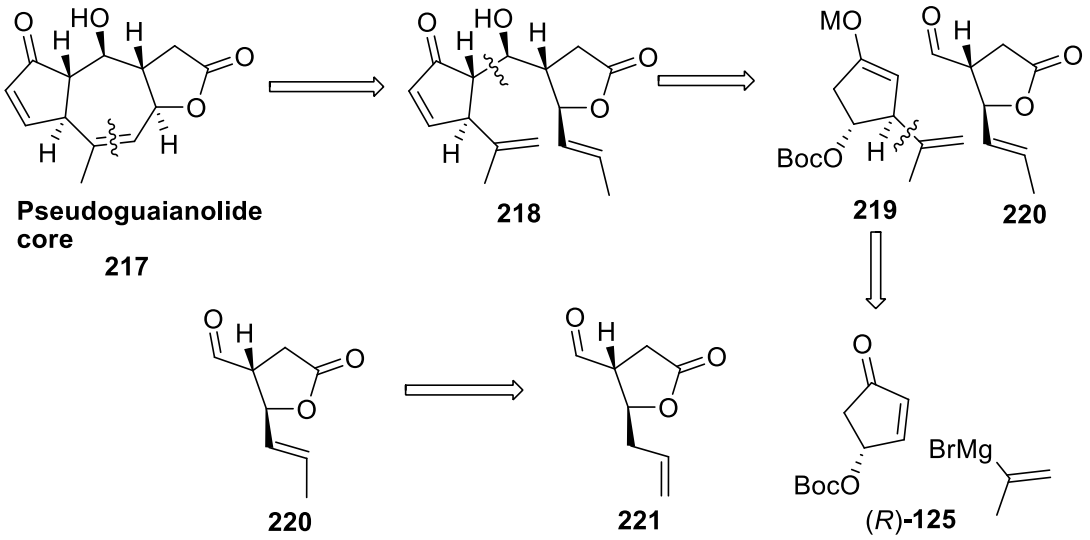
Having been unsuccessful to convert of **206** into **207**, we turned our focus to use aldehyde **210**, which is similar to the aldehyde **148** (with α-hydroxy group). As we have shown in our retrosynthetic analysis (Scheme 54a), compound **208** could be a useful intermediate for the construction oxo-bridged guaiane core of **78** by using ring-closing metathesis, which can then be used for the synthesis of **78** and **79**. **208** was expected to arise from (*R*)-**125**, isopropenyl magnesiumbromide and aldehyde **210**. Aldehyde **210** synthesized from commercially available methyl isopropyl ketone **211**. Silyl enol ether **212** was obtained from **211** by treatment with LDA followed by trapping the intermediate enolate with TMSCl in 70% yield.[159] This was used directly for the Rubottom oxidation[160,161] with m-CPBA affording **213** in 80% yield. **213** was converted to **210** by allylation with allyl magnesiumbromide (75% yield) followed by Swern oxidation (70% yield). **210** was found to be very stable at room temperature (Scheme 54b). The reaction of (*R*)-**125**, isopropenyl magnesiumbromide and aldehyde **210** according to our one-pot protocol gave the desired compound **215**, albeit in very low yield (10%). We thought that the protonation of the intermediate enolate might retard the formation of desired product in reasonable yield. Using the TES protected aldehyde **216** however gave also no conversion after 2 h at -78 °C (Scheme 54b).



Scheme 54: a) Retrosynthetic analysis of orientalol-F. b) Synthesis of aldehyde **210** and aldol adduct **209**.

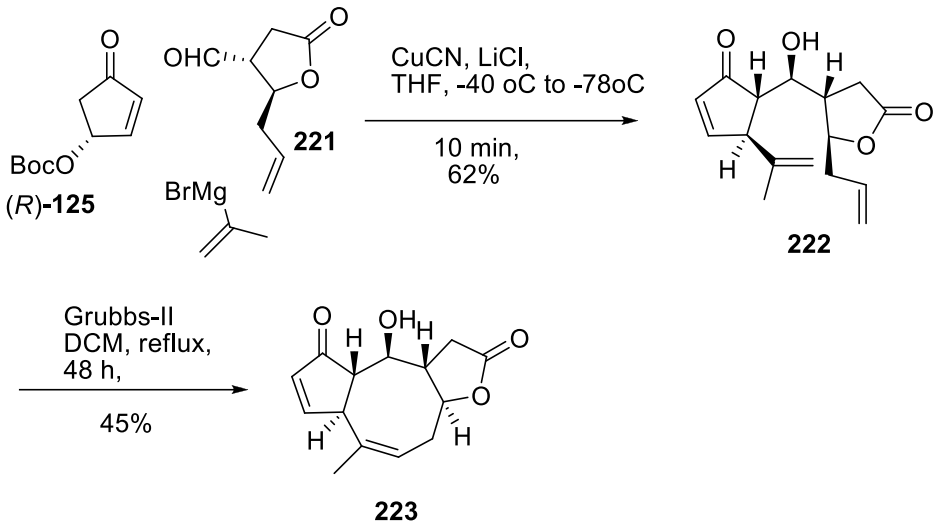
4. Studies towards the synthesis of pseudoguaianolide core structure

Based on SAR studies it has been shown that almost all known bioactive pseudoguaianolides possess an α,β-unsaturated lactone ring with an exomethylene group. This unsaturated lactone moiety enhances the cytotoxicity. The high toxicity can be attributed to the inhibition of DNA synthesis.[162] Based on this bioactivity we tried to construct pseudoguaianolide core structure for our building block by using our one pot strategy.



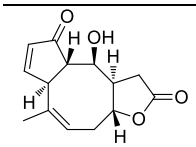
Scheme 55: Retrosynthetic analysis for pseudoguaianolide core.

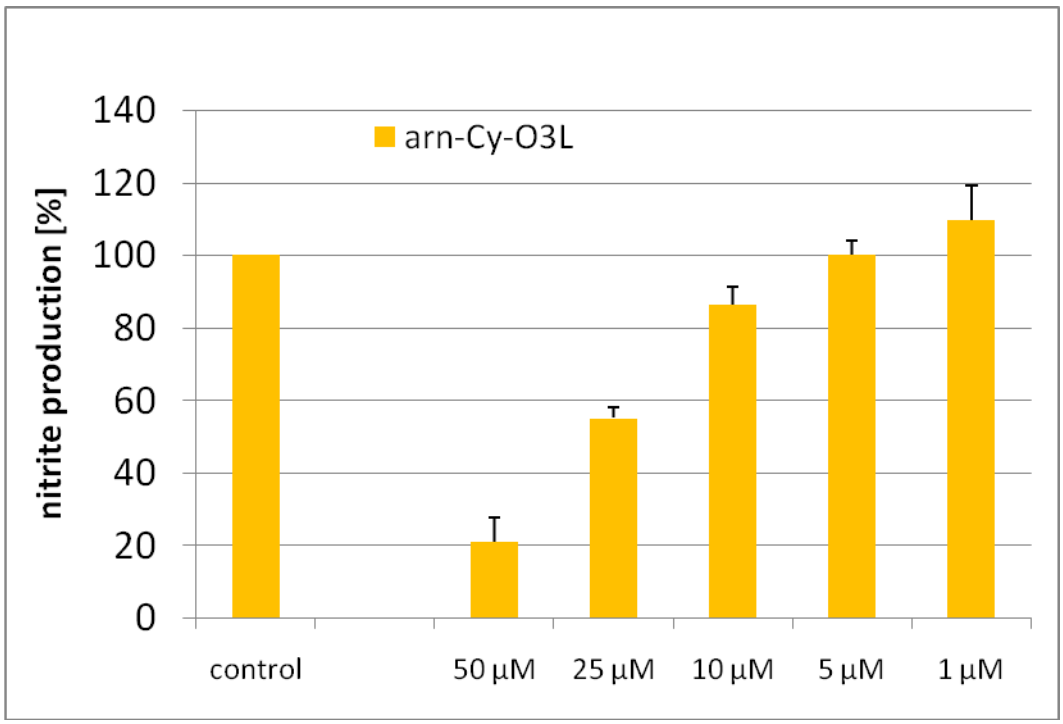
As outlined in scheme 55, aldehyde **220** was required for the construction of pseudoguaianolide core structure **217**. Before that, we first used known literature aldehyde **221**[163] for the trapping of the intermediate enolate that is formed after Grignard addition to (*R*)-**125**. We subjected compound (*R*)-**125**, isopropenyl magnesiumbromide and aldehyde **221** to the one-pot protocol to produce aldol adduct **222** in 62% yield. In the next step, we used Grubbs-II catalyzed ring closing metathesis to produce the unnatural pseudoguaianolide core structure **223**, having a 8-membered ring, in 45% yield (Scheme 56). However, the newly formed **223** was showed cyctotoxicity against RAW264 cell lines with 240 µM.



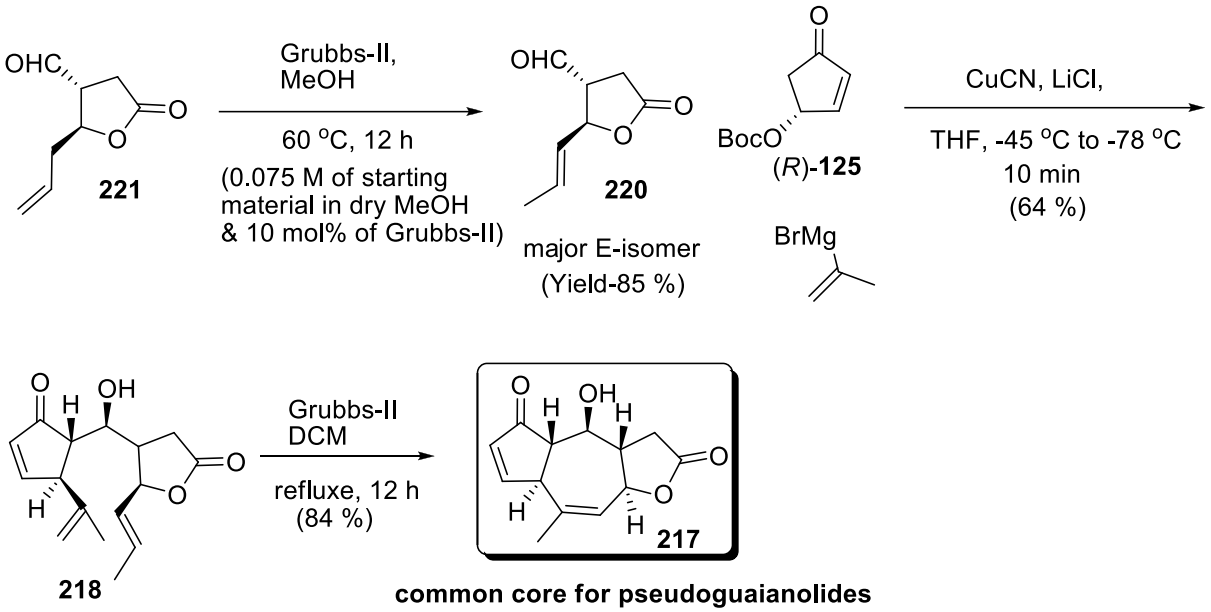
Scheme 56: Synthesis of unnatural pseudoguaianolide core structure **222**.

Table 12: Anti-inflammatory activity of **223.**

compound	MTT IC_{50} [µM]	inhibition of NO production [%]	
		minimum (conc [µM])	maximum (conc [µM])
	208.6 ± 11.7	44.8 ± 2.9 (25)	78.8 ± 6.6 (50)

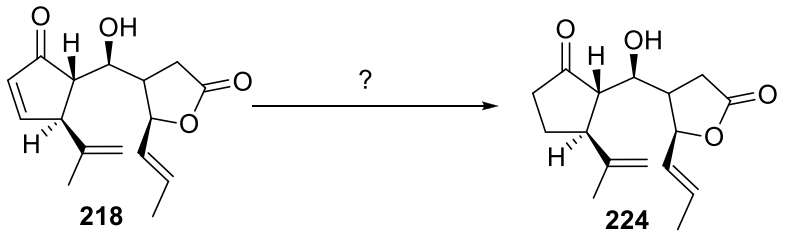


We next, focused on the construction of **217** with aldehyde **220**. As outlined in Scheme 55, the core structure **217** could be obtained from an aldol adduct **218**, which we can easily achieved from compound (*R*)-**125**, aldehyde **220** and isopropenyl magnesiumbromide. Aldehyde **220** can be easily accessed from aldehyde **221** by treatment with Grubbs-II catalyst and MeOH as solvent.[164] We used (*R*)-**125**, isopropenyl magnesiumbromide and aldehyde **220** to our one-pot protocol gave aldol adduct **218** in 64% yield. After successive ring closing metathesis with Grubbs-II catalyst afforded the natural pseudoguaianolide core structure **217** in 84% yield (Scheme 57).



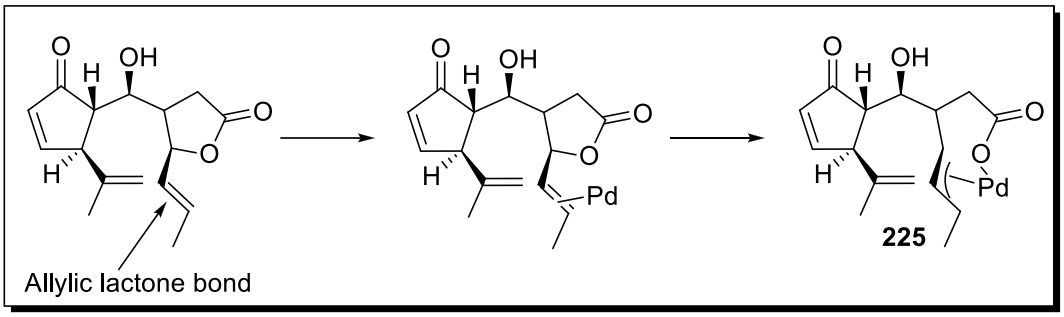
Scheme 57: Synthesis of pseudoguaianolide core structure.

With compound **218** in hand, we planned to synthesize anti-inflammatory drug **80**. We began our studies with selective reduction of α,β-unsaturated double bond in **218**. We first focused on Pd $(TPP)_4$ catalyzed selective reduction of α,β-unsaturated double bond in **218** in the presence of Ph_2SiH_2 as hydride source and obtained desired product **224** in very low yield. When we switched to Bu_3SnH under the above conditions, it gave decomposition after 1 h at room temperature. It was thought that the presence of allylic lactone system, which is very reactive towards the Pd (0) catalysts and forms Pd-allyl type complex **225**. This may retard the attack of Pd (0) to the α,β-unsaturated system (Scheme 58).



218 **224**

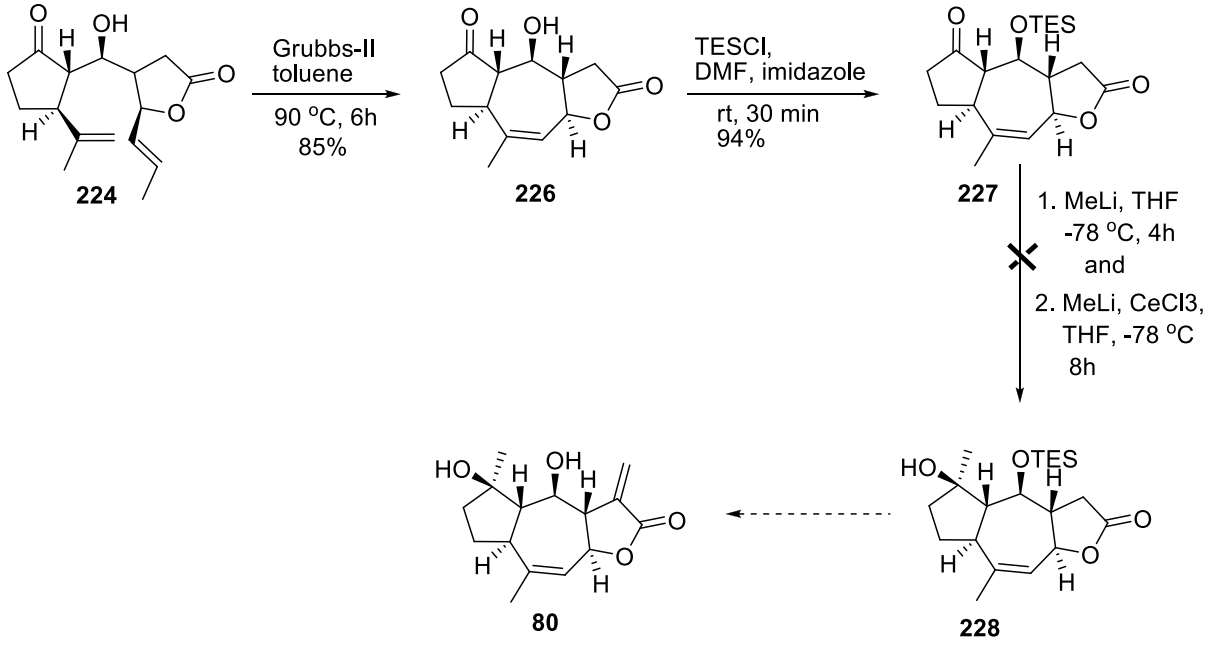
Condition	Status	Yield
$Pd(TPP)_4$, Ph_2SiH_2, $ZnCl_2$, $CHCl_3$, rt, 3 h	Yes	32%
$Pd(TPP)_4$, Bu_3SnH, $ZnCl_2$, $CHCl_3$, rt, 3 h	Yes	36%
$InCl_3$, $NaBH_4$, MeCN, rt, 24 h	NO	-
Raney-Ni, THF 0 °C to rt, 24 h	Yes	15%
CuI, $LiAlH_4$, DMPU:THF, -78 °C, 3 h	Yes	80%



Scheme 58: Selective reduction of α,β-unsaturated double bond in **217**.

Raney-Ni catalyzed selective conjugate reduction of α,β–unsaturated double bond in THF was met with no success. We next focused on copper hydride for selective reduction of α,β–unsaturated double bond in **218**. When we subjected, compound **218** to the CuI and $LiAlH_4$ in the mixture of DMPU: THF at -78 °C, the 1,4-adduct **224** was obtained in 80 % yield after 3 h (Scheme 58). After successful reduction of the unsaturated double bond in **218**, we directly applied Grubbs-II catalyzed ring closing metathesis to **224** in toluene at refluxed temperature to give rise to the pseudoguaianolide core structure **226** in 85% yield. **226** furnished **227** with TESCl and imidazole in

94% yield, and was then envisioned to be used for a stereoselective methylation to produce **228**. Unfortunately, all attempts of this methylation faield. When we applied methylation conditions (MeLi, THF, -78 °C, 4 h and MeLi, $CeCl_3$, -78 °C, 8 h), it gave many undesired spots on TLC (Scheme 59).



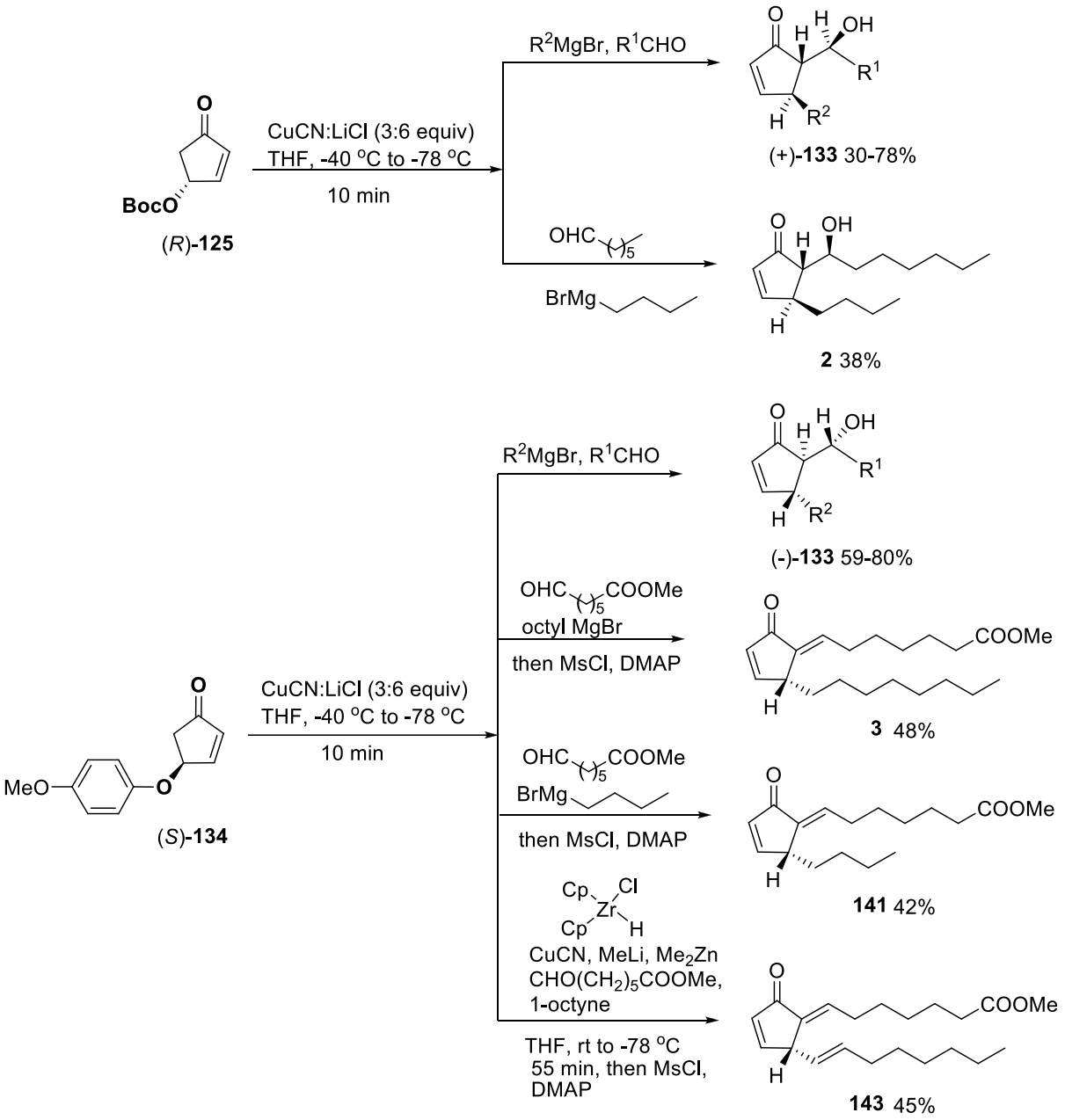
Scheme 59: Synthetic route to the **80**.

5. Conclusion

In conclusion, the readily available (*R*)-**125** and (*S*)-**134** allow the stereoselective synthesis of (+)-**133** and (-)-**133** with excellent selectivity and operational simplicity without using any harsh conditions, allowing the rapid assembly of natural scaffolds with complex architecture. The methodology described here offers a versatile approach for asymmetric synthesis of simple to complex various cyclopentanoid bioactive molecules. The first synthesis of (-)-teuclatriol **72** was achieved with 20% overall yield. This method allows the facile access to get guaiane and pseudoguaianolide core structures without using any protecting groups. On the other hand, with this method we have successfully finished total synthesis of (+)-orientalol-F **78** and formal synthesis of englerin-A **79** from our building block (*R*)-**125**.

C. Summary

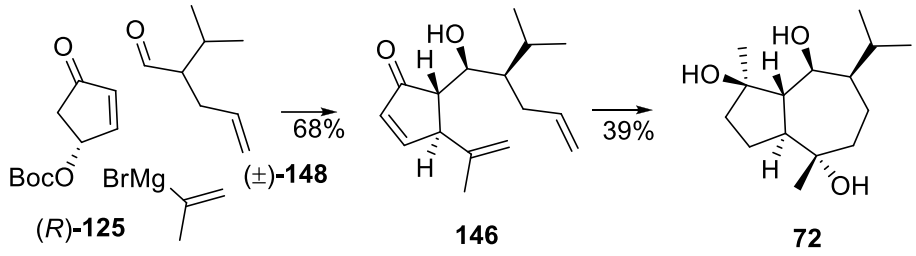
In the first chapter, an application for (*R*)-**125** and (*S*)-**134** on the basis of copper(I)-catalyzed Grignard additions followed by trapping of the resulting intermediate enolate with aldehydes were investigated. Adducts (+)-**133** and (-)-**133** could be synthesized from (*R*)-**125** and (*S*)-**134** in a facile procedure with a decent yields (Scheme 60).



Scheme 60: Over view of (+)-**133**, (-)-**133** and prostaglandin derivatives.

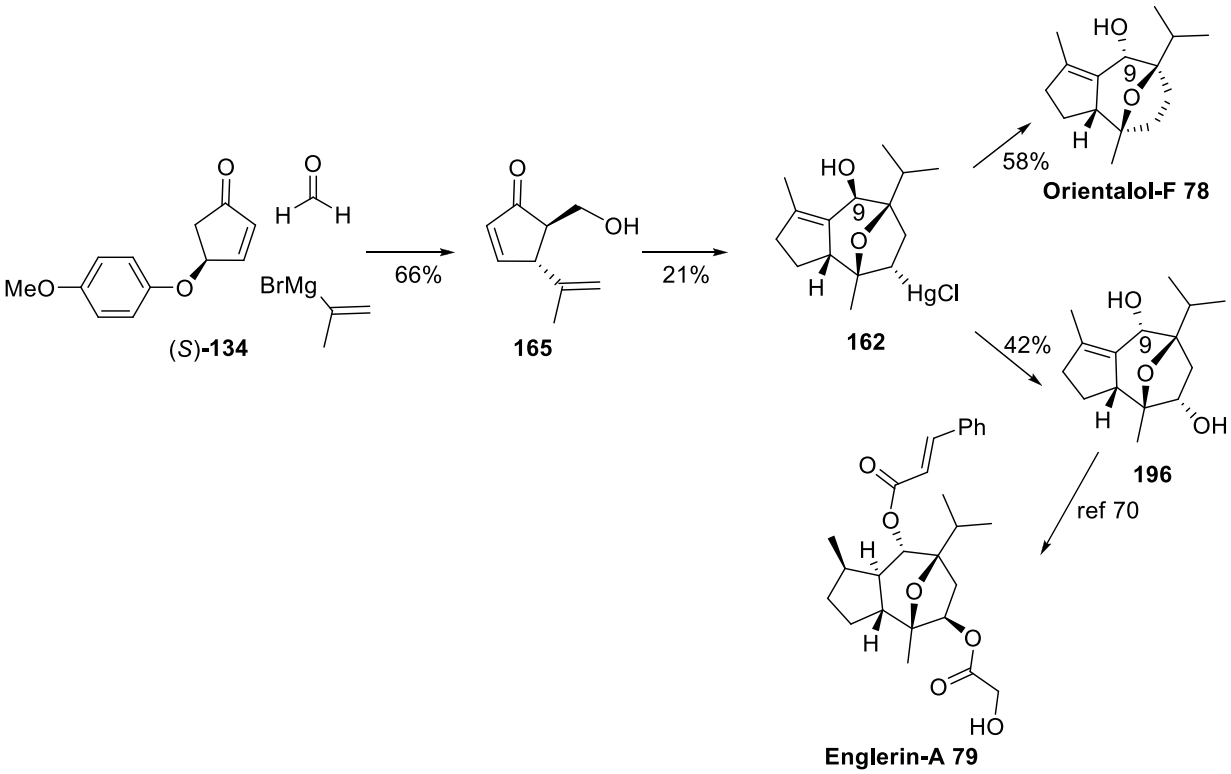
Excellent diastereo and enantioselectivities were obtained for adducts (+)-**133a**-**x** and (-)-**133 a-r**. The scope of participating Grignard reagents and aldehydes is very broad: aliphatic, aromatic and alkenyl organomagnesium compounds could be applied. This method provides a potentially useful access to a variety of bioactive cyclopentanoid prostaglandin derivatives such as TEI-9826 **3**, compound **2, 141** and **143** (Scheme 60).

In the second chapter, a successful synthesis of teuclatriol **72** from (*R*)**-125** has been demonstrated. The key steps involved, were a one-pot construction of cyclopent-2-enone **146** with 4 contiguous stereo centers, ring-closing metathesis, selective reduction of a α,β-unsaturated bond and subsequent chemoselective methylation. The first synthesis of (-)-teuclatriol **72** was achieved with 26% overall yield in six steps (Scheme 61).



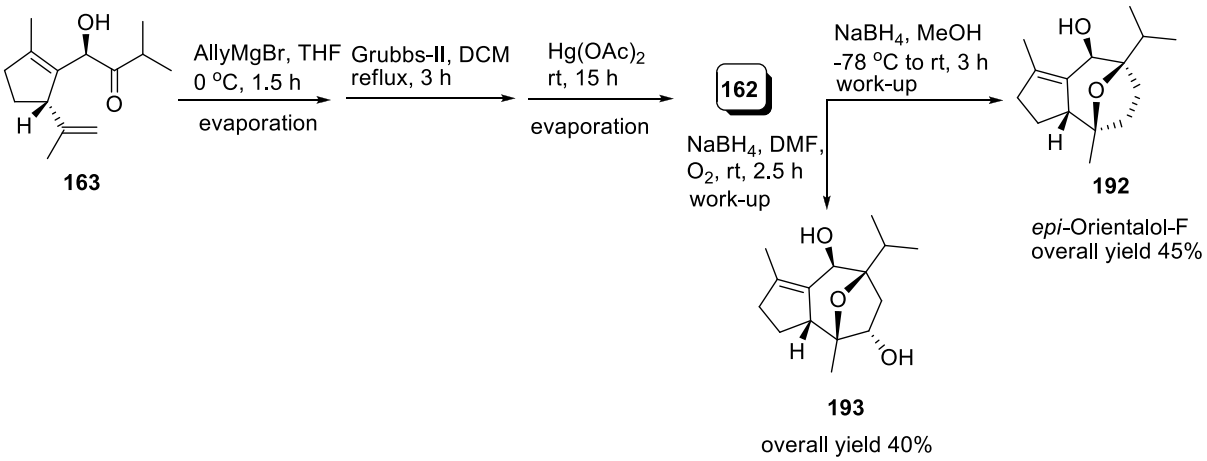
Scheme 61: Synthesis of **72**.

In the third chapter, a successful total synthesis of orientalol-F **78** from (*S*)-**134** has been demonstrated. The key steps involved were a, one-pot construction of **165**, an Umpolung, ring-closing metathesis and subsequent formation of an oxo-bridge ring by oxymercuration. Compound **162** furnished diol **196**, which is a known intermediate for englerin-A **79** (Scheme 62).



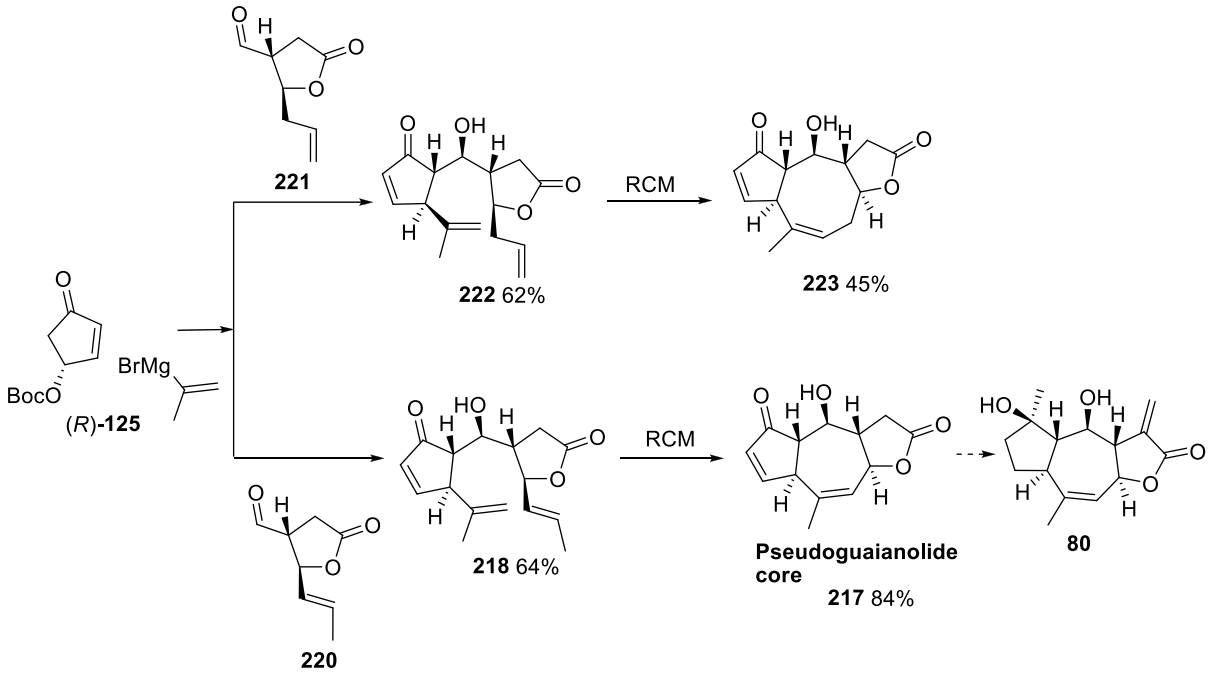
Scheme 62: Synthesis of **78** and **79**.

Moreover, different aldehydes have been used for trapping the intermediate enolate that is generated after nucleophile addition to (*R*)-**125**, which would provide alternative intermediates that might be useful towards the target molecules **78** and **79**. A study of a one-pot economy was carried out on **163** to get directly the desired **192** and **193** without isolation and purification of intermediates (Scheme 63).



Scheme 63: Overview of one pot operation on **163**.

In the fourth chapter, a successful construction of a pseudoguaianolide core structure **217** has been demonstrated.



Scheme 64: Synthesis of **217** and **223**.

In this synthesis, the new aldehyde **220** was synthesized from known aldehyde **221** via Grubbs-II catalyst. Later, selective reduction of the α,β-unsaturated bond was carried out on compound **218**, which could be a useful intermediate for compound **80**. Moreover, the synthesis of unnatural pseudoguaianolide core structure **223** and its bioactivity has been demonstrated (Scheme64).

D. Experimental Part

1. General

^{1}H-NMR-Spectra were recorded on Bruker Avance 300, Bruker Avance 400, Bruker Avance 600, Varian Inova 600, Bruker DRX-400 with a H/C/P/F QNP gradient probe and Bruker Avance 500 with a dual carbon/proton CPDUL cryoprobe. The chemical shift □□is given in [ppm], calibration is set on chloroform-d1 (7.26 ppm). The spectra were evaluated in 1st order and the coupling constants are given in Herth [Hz]. The following abbreviations for the spin multiplicity were used: s = singlet, d = doublet, t = triplet, q = quartet, qt = quintet, m = multiplet, dd = doublet of doublet, dt = doublet of triplet, ddd = doublet of double doublet, sept = septet. The sued deuterated solvents are given separately.

^{13}C-NMR-Spectra were recorded on Bruker Avance 300, Bruker Avance 400, Bruker Avance 600, Varian Inova 600, Bruker DRX-400 with a H/C/P/F QNP gradient probe and Bruker Avance 500 with a dual carbon/proton CPDUL cryoprobe. The chemical shift □□is given in [ppm], calibration is set on chloroform-d1 (77.16 ppm). The multiplicity of signals were detected by DEPT 135 and 90 (DEPT-Distortionless Enhancement by Polarization Transfer) and are given as: + = primary and tertiary C-atom (positive DEPT 135 signal; tertiary C-atom: DEPT 90 signal), - = secondary C-atom (negative DEPT 135 signal), Cq = quaternary C-atom (DEPT-signal intensity zero).

Melting points were measured on a Büchi SMP-20 in a silicon oil bath. The melting points are uncorrected.

Infrared-Spectra were recorded on a Bio-Rad Excalibur Series or Mattson Genesis Series FT-IR. Solid compounds were measured in KBr film, liquid compounds as a neat film between NaCl-plates. The wave numbers are given in [cm-1].

Masspectrometry was performed on a Varian MAT 311A, Finnigan MAT 95, Thermoquest Finnigan TSQ 7000, Nermag quadrupoles, VG-ZAB high resolution double focusing and VG Autospec-Q tandem hybrid with EBEqQ configuration. The percentage set in brackets gives the peak intensity related to the basic peak (I=100%). High Resolution Mass Spectrometry HRMS: The molecular formula was proven by the calculated precise mass.

Elemental Analysis was prepared by the micro analytic section University of Regensburg using a Vario EL III or Mikro-Rapid CHN (Heraeus).

Optical rotation was measured at room temperature on a 241 MC Perkin-Elmer polarimeter at a wavelength of 589 nm (Na-D) in a 1 dm or 0.1 dm cell. The concentration is given in (g/100 mL).

X-ray analysis was performed by the crystallography laboratory of the University of Regensburg (STOE-IPDS, Stoe & Cie GmbH).

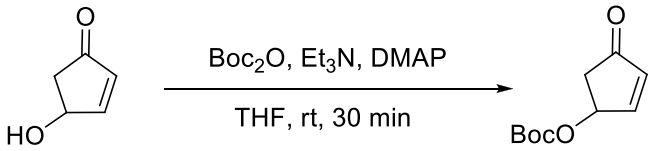
Chiral High Performance Liquid Chromatography was carried out using. Column: LabID 80/ Daicel Chemical Industries LTD./ CHIRALCEL (OD-H) (Lot No. ODH0CE-GB060)/ Cellulose tris (3,5-di methylphenyl carbamate) / coated on 5 m silica gel/ 250 mm x 4.6 mm ID/ part DAIC 14325 and CHIRALCEL OJ-H, 4.6 x 250 mm, 10 µm. LC system: Agilent 1100/3: DAD G1315B [DE03010828]/COLCOM G1316A [DE14925491] / ALS G1313A [DE23922434] / BIN pump GG1312A [DE43618259]/ HP 1050 DEGASSER.

Thin Layer Chromatography (TLC) was prepared on TLC- aluminium sheets (Merck, silica gel 60 F254, 0.2 mm). Detection in UV-light λ = 254 nm, staining with Iodine, Mostain, molybdatophosphoric acid (5% in ethanol), KMnO4 solution and vanillin-sulfuric acid.

Ozone-Generator For ozone generation a Fischer process technology ozone generator OZ 500 MM was used, supplied by an oxygen tank.

Solvents Absolute solvents were prepared according to usual lab procedures or taken from MB-SPS solvent purification system. EtOAc, Hexances and DCM were purified ny distillation before used. Further solvents and reagents were p.a. quality. Reaction with oxygen- and moisture sensitive reactants was performed in oven dried and in vacuo heated reaction flasks under pre-dried inert gas (nitrogen or argon) atmosphere. For cooling temperatures <-78 oC dry ice/acetone mixture was used.

2. Procedure for the synthesis of (*R*)-125 and (*S*)-134 in 50 gram scale:



(±)-**136** (±)-**125**

To a solution of 4-hydroxy-2-cyclopentenone (**±**)-**136** (36.76 g, 375 mmol) and Boc_2O (98.21 g, 450 mmol) in THF (375 mL) were added triethylamine (63 mL, 450 mmol) and DMAP (0.75 g). After the reaction mixture was stirred at room temperature for 30 min, the solvent was removed under reduced pressure. After purification on silica (hexanes/ EtOAc 5:1) obtained (**±)-125** (64.87 g, 87%).

Physical state: White solid;

TLC: R_f = 0.33 (hexanes/ EtOAc 9:1, UV-active, stains dark brown with vanillin);

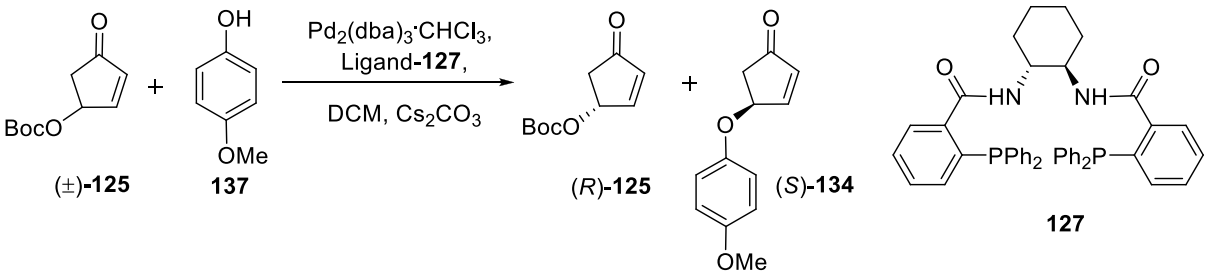
M.P= 39 °C;

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.60 (dd, *J* = 5.7, 2.4 Hz, 1H), 6.33 (dd, *J* = 5.7, 1.3 Hz, 1H), 5.71 (ddt, *J* = 3.6, 2.3, 1.8 Hz, 1H), 2.84 (dd, *J* = 18.7, 6.4 Hz, 1H), 2.40 (dd, *J* = 18.7, 2.2 Hz, 1H), 1.51 (s, 9H);

^{13}C NMR (75 MHz, $CDCl_3$): δ = 204.6, 158.6, 152.7, 137.2, 83.3, 74.2, 41.0, 27.8, 27.8, 27.8;

IR (neat) (cm^{-1}) ν_{max}: 1730, 1716;

HRMS (*m/z*): calcd for $C_{10}H_{14}O_4$ ($M^{\cdot+}$) 198.0892 , found 198.0896.



(±)-**125** **137** (*R*)-**125** (*S*)-**134** **127**

Under nitrogen atmosphere to a solution of (±)-**125** (50.00 g, 252.52 mmol, 2.0 equiv) **137** (15.67 g, 126.26 mmol, 1.0 equiv) and Cs_2CO_3 (12.17 g, 37.37 mmol, 0.296 equiv) in DCM (1000 mL) at 0 °C was added the catalyst solution, being separately prepared by stirring $Pd_2(dba)_3{\cdot}CHCl_3$ (1.31 g, 1.262 mmol, 1 mol% Pd based on **137**) and ligand (*R,R*)-**127** (3.07 g, 4.44 mmol, 0.035 equiv) in DCM (500 mL) until the initially purple solution turned yellow-brown (4-5 min). After 2.5 h of stirring at 0 °C,

solvent was removed under reduced pressure. After purification on silica (hexanes/ EtOAc 7:1 to 3:1) (*R*)-**125** (21.00 g, 42%, >99% *ee*) and (*S*)-**134** (24.75g, 48%, > 92% *ee*) were obtained.

Compound (*R*)-125:

Physical state: brown oil;

TLC: R_f = 0.33 (hexanes/ EtOAc 9:1, UV-active, stains dark brown with vanillin);

$[\alpha]_D^{25}$ = 94 (c 1.1, $CHCl_3$);

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.60 (dd, *J* = 5.7, 2.4 Hz, 1H), 6.33 (dd, *J* = 5.7, 1.3 Hz, 1H), 5.71 (ddt, *J* = 3.6, 2.3, 1.8 Hz, 1H), 2.84 (dd, *J* = 18.7, 6.4 Hz, 1H), 2.40 (dd, *J* = 18.7, 2.2 Hz, 1H), 1.51 (s, 9H);

^{13}C NMR (75 MHz, $CDCl_3$): δ = 204.6, 158.6, 152.7, 137.2, 83.3, 74.2, 41.0, 27.8, 27.8, 27.8;

IR (neat) (cm^{-1}) ν_{max}: 1730, 1716;

HRMS (*m/z*): calcd for $C_{10}H_{14}O_4$ ($M^{\cdot+}$) 198.0892 , found 198.0896.

Compound (*S*)-**134**:

Physical state: pale brown color solid;

TLC: R_f = 0.43 (hexanes/ EtOAc 3:1, UV-active, stains dark green with vanillin);

M.P. = 64 °C;

$[\alpha]_D^{25}$ = 8.62 (c 1.00, $CHCl_3$);

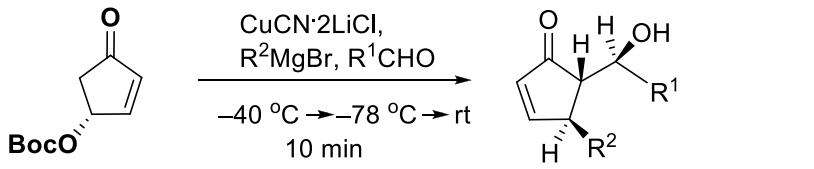
^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.70 (dd, *J*=5.7, 2.4 Hz, 1H), 6.98 – 6.71 (m, 4H), 6.35 (dd, *J*=5.7, 1.3 Hz, 1H), 5.37 (ddd, *J*=5.8, 3.4, 2.2 Hz, 1H), 3.78 (s, 3H), 2.85 (dd, *J*=18.4, 6.0 Hz 1H), 2.45 (dd, *J*=18.4, 2.2 Hz, 1H);

^{13}C NMR (75 MHz, $CDCl_3$): δ = 205.28, 159.90, 154.62, 151.31, 136.40, 116.71, 116.71, 114.89, 114.89, 76.07, 55.72, 41.90;

IR (neat) (cm^{-1}) ν_{max}: 1706, 1506, 1353, 1107, 1027, 821;

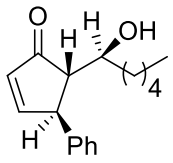
HRMS (*m/z*): calcd for $C_{12}H_{13}O_3$ $(M+H)^+$ 205.0859, found 205.0863.

3. Synthesis and characterization of (+)-133.



(*R*)-**125** (+)-**133** Yields (30-78%)

General Procedure A: To a stirred solution of CuCN (0.102 g, 1.14 mmol, 3.0 equiv) and anhydrous LiCl (0.096g, 2.28 mmol, 6.0 equiv) in THF (4 mL) was added the Grignard reagent (1.14 mmol, 3.0 equiv) dropwise at –40 °C. The reaction mixture was cooled to –78 °C upon which a solution of (*R*)-**125** (0.075 g, 0.38 mmol, 1.0 equiv) in THF (1 mL) was added. After 4 min of stirring, aldehyde (0.63 mmol, 1.68 equiv) was added. After the starting material had disappeared (ca. 5 min, monitored by TLC), NH_4Cl_{aq} (5 mL) was added and the reaction mixture was extracted with Et_2O (2x10 mL). The combined organic extracts were washed with brine (10 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude was purified by flash chromatography on silica.



Compound (+)-**133a:** The title compound was prepared from (*R*)-**125** (0.075 g, 0.38 mmol) phenylmagnesium bromide (0.94 M solution in THF, 1.2 mL, 1.14 mmol) and hexanal (0.063 g, 0.078 mL, 0.63 mmol) according to the general procedure A. After purification on silica (hexanes/ EtOAc 5:1 to 3:1) title compound was obtained in 72% yield (0.071 g).

Physical state: pale yellow oil;

TLC: R_f = 0.31 (hexanes/ EtOAc 5:1, UV-active, stains orange with vanillin);

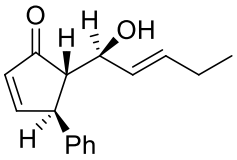
$[\alpha]_D^{25}$**:** 215.3 (c 0.32, $CHCl_3$);

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.62 (dd, *J* = 5.6, 2.4 Hz, 1H), 7.38 – 7.26 (m, 3H), 7.19 – 7.14 (m, 2H), 6.29 (dd, *J* = 5.6, 2.1 Hz, 1H), 3.87 (ddd, *J* = 7.4, 6.2, 2.4 Hz, 2H), 3.76 (s, 1H), 2.44 (dd, *J* = 8.2, 2.9 Hz, 1H), 1.66 – 1.47 (m, 2H), 1.33 – 1.12 (m, 6H), 0.82 (t, *J* = 6.8 Hz, 3H);

^{13}C NMR (75 MHz, $CDCl_3$) δ 212.96, 167.19, 140.52, 132.95, 129.11, 129.11, 127.51, 127.51, 127.51, 72.24, 59.01, 50.91, 35.26, 31.71, 24.55, 22.58, 14.02;

IR (neat) (cm^{-1}) ν_{max}: 3425, 2953, 2931, 2858, 1689, 1590, 1454, 1278, 1179, 1076, 1048, 1030, 757, 700, 616, 494;

HRMS (*m/z*)**:** calcd for $C_{17}H_{22}NaO_2$ $(M+Na)^+$ 281.1512, found 281.1510.



Compound (+)-**133b:** The title compound was prepared from (*R*)-**125** (0.075 g, 0.38 mmol) phenylmagnesium bromide (0.94 M solution in THF, 1.2 mL, 1.14 mmol) and *trans*-2-pentenal (0.053 g, 0.062 mL, 0.63 mmol) according to the general procedure A. After purification on silica (hexanes/ EtOAc 7:1 to 3:1) title compound was obtained in 68% yield (0.063 g).

Physical state: brown color oil;

TLC: R_f = 0.28 (hexanes/ EtOAc 5:1, UV-active, stains brown with vanillin);

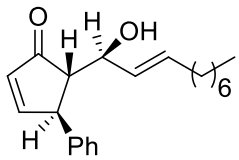
$[\alpha]_D^{25}$**:** 313.28 (c 0.28, $CHCl_3$);

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.64 (dd, *J* = 5.6, 2.5 Hz, 1H), 7.37 – 7.24 (m, 3H), 7.15 – 7.05 (m, 2H), 6.30 (dd, *J* = 5.6, 2.1 Hz, 1H), 5.85 (dt, *J* = 15.2, 6.1 Hz, 1H), 5.41 – 5.29 (m, 1H), 4.29 (t, *J* = 8.3 Hz, 1H), 3.91 – 3.81 (m, 2H), 2.48 (dd, *J* = 8.6, 2.7 Hz, 1H), 2.13 – 2.00 (m, 2H), 0.97 (t, *J* = 7.4 Hz, 3H);

^{13}C NMR (75 MHz, $CDCl_3$) δ 212.57, 167.37, 140.47, 136.20, 132.89, 128.91, 128.91, 128.80, 127.78, 127.78, 127.36, 74.29, 59.30, 50.51, 25.06, 12.98;

IR (neat) (cm^{-1}) ν_{max}: 3415, 2962, 1689, 1589, 1493, 1454, 1335, 1179, 1030, 969, 897, 758, 699, 533, 505;

HRMS (*m/z*)**:** calcd for $C_{16}H_{18}NaO_2$ $(M+Na)^+$ 265.1199, found 265.1200.



Compound (+)-**133c:** The title compound was prepared from (*R*)-**125** (0.075 g, 0.38 mmol) phenylmagnesium bromide (0.94 M solution in THF, 1.2 mL, 1.14 mmol) and *trans*-2-decenal (0.098 g, 0.11 mL, 0.63 mmol) according to the general procedure A. After purification on silica (hexanes/ EtOAc 7:1 to 3:1) title compound was obtained in 70% yield (0.083 g).

Physical state: yellow oil;

TLC: R_f = 0.31 (hexanes/ EtOAc 5:1, UV-active, stains dark red with vanillin);

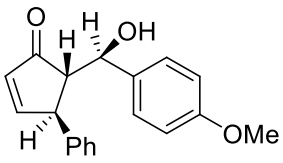
$[\alpha]_D^{25}$**:** 219.5 (c 0.56, $CHCl_3$);

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.64 (dd, *J* = 5.6, 2.5 Hz, 1H), 7.34 – 7.30 (m, 2H), 7.28 – 7.26 (m, 1H), 7.11 (dd, *J* = 5.2, 3.3 Hz, 2H), 6.29 (dd, *J* = 5.6, 2.1 Hz, 1H), 5.83 – 5.77 (m, 1H), 5.38 (ddt, *J* = 15.3, 7.8, 1.4 Hz, 1H), 4.30 (t, *J* = 8.1 Hz, 1H), 3.86 (dd, *J* = 4.8, 2.4 Hz,
1H), 2.50 (dd, *J* = 8.4, 2.7 Hz, 1H), 2.02 (qt, *J* = 10.8, 4.1 Hz, 2H), 1.34 (ddd, *J* = 12.0, 4.8, 2.3 Hz, 2H), 1.32 – 1.23 (m, 9H), 0.88 (t, *J* = 7.1 Hz, 3H);

^{13}C NMR (151 MHz, $CDCl_3$) δ 212.32, 167.25, 140.48, 134.83, 132.86, 129.56, 128.89, 128.89, 127.72, 127.72, 127.32, 74.18, 59.28, 50.43, 32.06, 31.77, 29.22, 29.14, 28.85, 22.65, 14.08;

IR (neat) (cm^{-1}) ν_{max}: 3361, 2926, 2855, 1690, 1511, 1454, 1234, 1036, 827, 700, 637, 537, 497;

HRMS (*m/z*): calcd for $C_{21}H_{28}NaO_2$ $(M+Na)^+$ 335.1982, found 335.1983.



Compound (+)**-133d:** The title compound was prepared (*R*)-**125** (0.075 g, 0.38 mmol) phenylmagnesium bromide (0.94 M solution in THF, 1.2 mL, 1.14 mmol) and 4-methoxy benzaldehyde (0.086 g, 0.076 mL, 0.63 mmol) according to the general procedure A. After purification on silica (hexanes/ EtOAc 5:1 to 3:1) title compound was obtained in 78% yield (0.087 g).

Physical state: green color oil;

TLC: R_f = 0.2 (hexanes/ EtOAc 5:1, UV-active, stains dark brown with vanillin);

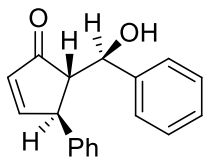
$[\alpha]_D^{25}$**:** 242.0 (c 0.53, $CHCl_3$);

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.60 (dd, *J* = 5.6, 2.5 Hz, 1H), 7.23 – 7.16 (m, 2H), 7.17 – 7.06 (m, 3H), 6.84 – 6.77 (m, 2H), 6.56 – 6.48 (m, 2H), 6.34 (dd, *J* = 5.6, 2.1 Hz, 1H), 4.74 (d, *J* = 9.5 Hz, 1H), 4.45 (s, 1H), 3.80 (s, 3H), 3.67 – 3.59 (m, 1H), 2.66 (dd, *J* = 9.5, 2.6 Hz, 1H);

^{13}C NMR (75 MHz, $CDCl_3$) δ 213.03, 167.52, 159.70, 140.05, 133.11, 132.88, 128.58, 128.58, 128.56, 128.56, 127.16, 127.16, 127.05, 113.81, 113.81, 75.03, 60.91, 55.40, 50.25;

IR (neat) (cm^{-1}) ν_{max}: 3445, 2836, 1689, 1612, 1587, 1513, 1454, 1247, 1174, 1031, 833, 701, 635, 538, 496;

HRMS (*m/z*): calcd for $C_{19}H_{18}NaO_2$ $(M+Na)^+$ 317.1148, found 317.1150.



Compound (+)**-133e:** The title compound was prepared (*R*)-**125** (0.075 g, 0.38 mmol) phenylmagnesium bromide (0.94 M solution in THF, 1.2 mL, 1.14 mmol) and benzaldehyde (0.067 g, 0.064 mL, 0.63 mmol) according to the general procedure A. After purification on silica (hexanes/ EtOAc 5:1 to 3:1) title compound was obtained in 72% yield (0.072 g).

Physical state: white powder;

TLC: R_f = 0.35 (hexanes/ EtOAc 5:1, UV-active, stains pale brown with vanillin);

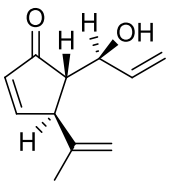
$[\alpha]_D^{25}$**:** 235.0 (c 0.16, $CHCl_3$);

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.62 (dd, *J* = 5.6, 2.5 Hz, 1H), 7.30 (d, *J* = 7.3 Hz, 5H), 7.15 – 7.04 (m, 3H), 6.49 – 6.41 (m, 2H), 6.36 (dd, *J* = 5.6, 2.0 Hz, 1H), 4.78 (d, *J* = 9.5 Hz, 1H), 4.69 – 4.35 (m, 1H), 3.66 (dd, *J* = 4.7, 2.4 Hz, 1H), 2.66 (dd, *J* = 9.5, 2.6 Hz, 1H);

^{13}C NMR (75 MHz, $CDCl_3$) δ 213.05, 167.61, 140.71, 139.92, 132.90, 128.56, 128.56, 128.49, 128.49, 128.46, 127.41, 127.41, 127.06, 127.06, 127.06, 75.55, 60.76, 50.10;

IR (neat) (cm^{-1}) ν_{max}: 3392, 1677, 1590, 1492, 1437, 1340, 1266, 1196, 1034, 902, 853, 796, 752, 695, 638, 555, 484;

HRMS (*m/z*): calcd for $C_{18}H_{16}NaO_2$ $(M+Na)^+$ 287.1150, found 287.1149.



Compound (+)-**133f:** The title compound was prepared from (*R*)-**125** (0.075 g, 0.38 mmol) isopropenylmagnesium bromide (1.0 M solution in THF, 1.14 mL, 1.14 mmol) and acrolein (0.036 g, 0.042 mL, 0.63 mmol) according to the general procedure A. After purification on silica (hexanes/ EtOAc 7:1 to 5:1) title compound was obtained in 64% yield (0.043 g).

Physical state: yellow oil;

TLC: R_f = 0.57 (hexanes/ EtOAc 3:1, UV-active, stains brown with vanillin);

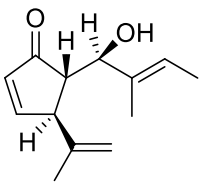
$[\alpha]_D^{25}$**:** 235.2 (c 0.14, $CHCl_3$);

^{1}H NMR (300 MHz, d_6-Acetone) δ 7.67 (dd, *J* = 5.7, 2.6 Hz, 1H), 6.14 (dd, *J* = 5.7, 2.0 Hz, 1H), 5.86 (ddd, *J* = 17.1, 10.5, 5.6 Hz, 1H), 5.35 – 5.24 (m, 1H), 5.12 – 5.05 (m, 1H), 4.84 – 4.80 (m, 1H), 4.76 (dd, *J* = 1.7, 0.8 Hz, 1H), 4.52 – 4.41 (m, 1H), 4.32 (d, *J* = 3.6 Hz, 1H), 3.50 (dd, *J* = 4.3, 2.0 Hz, 1H), 2.40 (dd, *J* = 5.3, 2.4 Hz, 1H), 1.79 – 1.75 (m, 3H);

^{13}C NMR (75 MHz, d_6-Acetone) δ 209.55, 167.52, 146.75, 138.73, 134.21, 115.84, 112.45, 73.32, 57.55, 51.24, 21.30;

IR (neat) (cm^{-1}) ν_{max}: 3468, 3390, 2973, 1689, 1645, 1587, 1438, 1378, 1273, 1184, 1052, 992,897, 785, 667, 535, 495;

HRMS (*m/z*)**:** calcd for $C_{11}H_{14}NaO_2$ $(M+Na)^+$ 201.099, found 201.098.



Compound (+)-**133g:** The title compound was prepared from (*R*)-**125** (0.075 g, 0.38 mmol) isopropenylmagnesium bromide (1.0 M solution in THF, 1.14 mL, 1.14 mmol) and *trans*-2-methyl-2-butenal (0.053 g, 0.06 mL, 0.63 mmol) according to the general procedure A. After purification on silica (hexanes/ EtOAc 7:1 to 5:1) title compound was obtained in 66% yield (0.052 g).

Physical state: yellow oil;

TLC: R_f = 0.62 (hexanes/ EtOAc 3:1, UV-active, stains brown with vanillin);

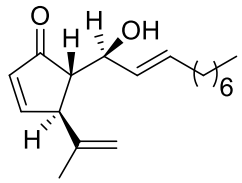
$[\alpha]_D^{25}$**:** 250.2 (c 0.37, $CHCl_3$);

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.47 (dd, *J* = 5.6, 2.5 Hz, 1H), 6.19 – 6.07 (m, 1H), 5.46 (qt, *J* = 19.5, 9.7 Hz, 1H), 4.86 – 4.76 (m, 1H), 4.67 (d, *J* = 0.7 Hz, 1H), 4.38 (s, 1H), 3.94 (d, *J* = 10.1 Hz, 1H), 3.13 (q, *J* = 2.3 Hz, 1H), 2.38 – 2.24 (m, 1H), 1.59 – 1.54 (m, 6H), 1.53 – 1.49 (m, 3H);

^{13}C NMR (75 MHz, $CDCl_3$) δ 212.89, 167.14, 141.82, 134.62, 131.78, 122.90, 113.03, 78.41, 51.61, 50.96, 18.16, 11.99, 9.68;

IR (neat) (cm^{-1}) ν_{max}: 3489, 3462, 2916, 1682, 1647, 1586, 1504, 1440, 1410, 1378, 1343, 1261, 1187, 1026, 943, 898,831, 793, 640, 624, 538, 464;

HRMS (*m/z*)**:** calcd for $C_{13}H_{18}NaO_2$ $(M+Na)^+$ 229.1199, found 229.1196.



Compound (+)**-133h:** The title compound was prepared from (*R*)-**125** (0.075 g, 0.38 mmol) isopropenylmagnesium bromide (1.0 M solution in THF, 1.14 mL, 1.14 mmol) and *trans*-2-decenal (0.098 g, 0.11 mL, 0.63 mmol) according to the general procedure A. After purification on silica (hexanes/ EtOAc 10:1) title compound was obtained in 70% yield (0.073 g).

Physical state: pale yellow oil;

TLC: R_f = 0.7 (hexanes/ EtOAc 5:1, UV-active, stains brown with vanillin);

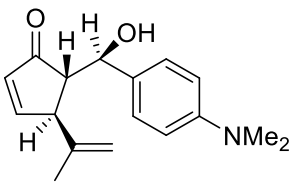
$[\alpha]_D^{25}$**:** 121.8 (c 0.71, $CHCl_3$);

^{1}H NMR (300 MHz, d_6-Acetone) δ 7.67 (dd, *J* = 5.7, 2.6 Hz, 1H), 6.13 (dd, *J* = 5.7, 2.0 Hz, 1H), 5.75 – 5.61 (m, 1H), 5.48 (ddt, *J* = 15.4, 6.5, 1.2 Hz, 1H), 4.86 – 4.80 (m, 1H), 4.75 (dd, *J* = 1.6, 0.8 Hz, 1H), 4.39 (dt, *J* = 9.4, 4.8 Hz, 1H), 3.50 (dd, *J* = 4.2, 2.0 Hz, 1H), 2.36 (dd, *J* = 5.5, 2.3 Hz, 1H), 2.07 – 2.02 (m, 1H), 2.02 – 1.95 (m, 2H), 1.78 – 1.74 (m, 3H), 1.35 – 1.24 (m, 10H), 0.88 (t, *J* = 6.7 Hz, 3H);

^{13}C NMR (75 MHz, d_6-Acetone): δ 210.00, 167.52, 134.21, 133.03, 130.53, 112.41, 73.33, 57.80, 51.43, 32.60, 32.84, 29.96, 29.96, 29.78, 29.78, 23.34, 21.32, 14.39.

IR (neat) (cm^{-1}) ν_{max}: 3420, 2925, 2855, 1689, 1586, 1510, 1440, 1348, 1233, 1100, 1037, 970, 900, 826, 632, 537, 497;

HRMS (*m/z*)**:** calcd for $C_{18}H_{28}NaO_2$ $(M+Na)^+$ 299.1982, found 299.1984.



Compound (+)**-133i:** The title compound was prepared from (*R*)-**125** (0.075 g, 0.38 mmol) isopropenylmagnesium bromide (1.0 M solution in THF, 1.14 mL, 1.14 mmol) and 4-dimethylamino benzaldehyde (0.095 g, 0.63 mmol) according to the general procedure A. After purification on silica (hexanes/ EtOAc 5:1) title compound was obtained in 62 % yield (0.064 g).

Physical state: yellow colored oil;

TLC: R_f = 0.13 (hexanes/ EtOAc 5:1, UV-active, stains dark green with vanillin);

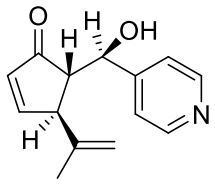
$[\alpha]_D^{25}$**:** 170.1 (c 0.6, $CHCl_3$);

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.51 (dd, *J* = 5.6, 2.6 Hz, 1H), 7.23 – 7.16 (m, 2H), 6.73 – 6.64 (m, 2H), 6.20 (dd, *J* = 5.6, 2.0 Hz, 1H), 4.59 (dd, *J* = 5.3, 3.8 Hz, 2H), 4.29 (d, *J* = 4.1 Hz, 2H), 3.13 (dd, *J* = 4.4, 2.2 Hz, 1H), 2.92 (s, 6H), 2.53 (dd, *J* = 9.2, 2.3 Hz, 1H), 1.34 (s, 3H);

^{13}C NMR (75 MHz, $CDCl_3$) δ 212.90, 168.07, 150.72, 143.64, 132.72, 129.19, 128.02, 128.02, 113.07, 112.41, 112.41, 75.26, 57.28, 51.57, 40.72, 40.72, 20.17;

IR (neat) (cm^{-1}) ν_{max}: 3445, 2968, 2855, 2798, 1685, 1614, 1522, 1444, 1346, 1219, 1185, 1163, 1055, 944, 899, 814, 739, 538;

HRMS (*m/z*)**:** calcd for $C_{17}H_{21}NaNO_2$ $(M+Na)^+$ 294.1572, found 294.1572.



Compound (+)**-133j:** The title compound was prepared from (*R*)-**125** (0.075 g, 0.38 mmol) isopropenylmagnesium bromide (1.0 M solution in THF, 1.14 mL, 1.14 mmol) and pyridine 4-carbaldehyde (0.068 g, 0.06 mL, 0.63 mmol) according to the general procedure A. After purification on silica (hexanes/ EtOAc 3:1 to 1:1) title compound was obtained in 59% yield (0.052 g).

Physical state: pale brown coloedr oil;

TLC: R_f = 0.25 (hexanes/ EtOAc 6:1, UV-active, stains green with vanillin);

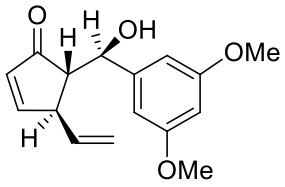
$[\alpha]_D^{25}$**:** 198.6 (c 0.18, $CHCl_3$);

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.53 (d, *J* = 4.5 Hz, 2H), 7.50 (dd, *J* = 5.7, 2.6 Hz, 1H), 7.28 (t, *J* = 5.5 Hz, 2H), 6.22 (dd, *J* = 5.7, 2.0 Hz, 1H), 4.79 (d, *J* = 8.5 Hz, 2H), 4.63 – 4.59 (m, 1H), 4.35 (s, 1H), 3.17 (dd, *J* = 4.7, 2.2 Hz, 1H), 2.52 (dd, *J* = 8.5, 2.7 Hz, 1H), 1.41 (s, 3H);

^{13}C NMR (75 MHz, $CDCl_3$) δ 211.41, 167.92, 149.97, 149.97, 149.52, 142.40, 132.89, 122.08, 122.08, 113.84, 74.14, 55.63, 51.29, 19.56;

IR (neat) (cm^{-1}) ν_{max}: 3424, 3174, 2358, 2326, 1699, 1603, 1559, 1416, 1271, 1186, 1067, 1003, 906, 815, 652, 574, 468;

HRMS (*m/z*)**:** calcd for $C_{14}H_{15}NaNO_2$ $(M+Na)^+$ 252.1101, found 252.110.



Compound (+)**-133k:** The title compound was prepared from (*R*)-**125** (0.075 g, 0.38 mmol) vinylmagnesium bromide (0.80 M solution in THF, 1.4 mL, 1.14 mmol) and 3, 5-di methoxy benzaldehyde (0.105 g, 0.63 mmol) according to

the general procedure A. After purification on silica (hexanes/ EtOAc 5:1 to 2:1) title compound was obtained in 72% yield (0.075 g).

Physical state: yellow oil;

TLC: R_f = 0.15 (hexanes/ EtOAc 5:1, UV-active, stains dark brown with vanillin);

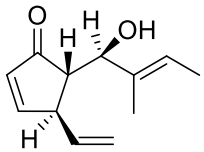
$[\alpha]_D^{25}$**:** 143.9 (c 0.14, $CHCl_3$);

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.59 (td, *J* = 5.5, 2.5 Hz, 1H), 6.53 (d, *J* = 2.3 Hz, 2H), 6.39 (t, *J* = 2.3 Hz, 1H), 6.23 (dd, *J* = 5.7, 2.0 Hz, 1H), 5.30 (ddd, *J* = 13.5, 10.2, 7.3 Hz, 1H), 4.85 (d, *J* = 10.2 Hz, 1H), 4.74 – 4.63 (m, 2H), 4.59 (s, 1H), 3.77 (d, *J* = 7.1 Hz, 6H), 3.22 – 3.14 (m, 1H), 2.42 (dd, *J* = 9.5, 3.0 Hz, 1H);

^{13}C NMR (75 MHz, $CDCl_3$) δ 212.11, 166.98, 160.84, 143.21, 136.41, 132.99, 116.17, 116.17, 104.99, 104.99, 100.25, 75.22, 57.79, 55.42, 55.42, 47.78;

IR (neat) (cm^{-1}) ν_{max}: 3465, 2939, 1686, 1596, 1507, 1463, 1430, 1346, 1295, 1204, 1153, 1058, 920, 837, 632, 538, 500;

HRMS (*m/z*)**:** calcd for $C_{16}H_{18}NaO_4$ $(M+Na)^+$ 297.1097, found 297.1099.



Compound (+)**-133l:** The title compound was prepared from (*R*)-**125** (0.075 g, 0.38 mmol) vinylmagnesium bromide (0.80 M solution in THF, 1.4 mL, 1.14 mmol) and *trans*-2-methyl-2-butenal (0.053 g, 0.06 mL, 0.63 mmol) according to the general procedure A. After purification on silica (hexanes/ EtOAc 7:1 to 3:1) title compound was obtained in 68% yield (0.050 g).

Physical state: pale red colored oil;

TLC: R_f = 0.35 (hexanes/ EtOAc 5:1, UV-active, stains dark brown with vanillin);

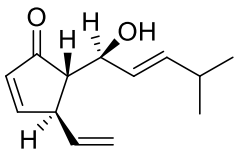
$[\alpha]_D^{25}$**:** 136.3 (c 0.45, $CHCl_3$);

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.52 (dt, *J* = 5.6, 3.0 Hz, 1H), 6.16 (dd, *J* = 5.6, 2.1 Hz, 1H), 5.65 – 5.47 (m, 2H), 5.08 – 4.94 (m, 2H), 4.00 (d, *J* = 10.2 Hz, 1H), 3.13 – 3.03 (m, 1H), 2.25 (dd, *J* = 10.2, 2.7 Hz, 1H), 1.74 – 1.62 (m, 1H), 1.62 – 1.55 (m, 6H);

^{13}C NMR (75 MHz, $CDCl_3$) δ 213.67, 167.15, 136.70, 135.24, 132.86, 124.00, 117.03, 79.14, 53.61, 49.03, 13.04, 10.71;

IR (neat) (cm^{-1}) ν_{max}: 3418, 2920, 1682, 1585, 1510, 1440, 1345, 1233, 1100, 1036, 912, 828, 734, 632, 536, 498;

HRMS (*m/z*)**:** calcd for $C_{12}H_{16}NaO_2$ $(M+Na)^+$ 215.1150, found 215.1150.



Compound (+)-**133m:** The title compound was prepared from (*R*)-**125** (0.075 g, 0.38 mmol) vinylmagnesium bromide (0.80 M solution in THF, 1.4 mL, 1.14 mmol) and *trans*-4-methyl-2-pentenal (0.062 g, 0.63 mmol) according to the general procedure A. After purification on silica (hexanes/ EtOAc 7:1 to 3:1) title compound was obtained in 64% yield (0.050 g).

Physical state: yellow oil;

TLC: R_f = 0.31 (hexanes/ EtOAc 5:1, UV-active, stains dark brown with vanillin);

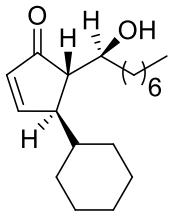
$[\alpha]_D^{25}$**:** 147.4 (c 0.11, $CHCl_3$);

^{1}H NMR (300 MHz, d_6-Acetone) δ 7.70 (dd, *J* = 5.7, 2.6 Hz, 1H), 6.12 (dd, *J* = 5.7, 2.1 Hz, 1H), 5.95 – 5.82 (m, 1H), 5.73 – 5.63 (m, 1H), 5.42 (ddd, *J* = 15.5, 6.5, 1.2 Hz, 1H), 5.11 (ddt, *J* = 12.9, 10.2, 1.3 Hz, 2H), 4.39 (dt, *J* = 9.3, 4.7 Hz, 1H), 3.55 – 3.46 (m, 1H), 2.32 (dd, *J* = 6.1, 2.6 Hz, 1H), 2.22 (dd, *J* = 13.5, 6.7 Hz, 1H), 2.08 – 2.03 (m, 1H), 0.94 (dd, *J* = 6.8, 0.9 Hz, 6H);

^{13}C NMR (75 MHz, d_6-Acetone) δ 210.03, 167.04, 139.83, 139.59, 134.07, 127.70, 115.95, 73.09, 58.21, 48.22, 31.50, 22.69, 22.64;

IR (neat) (cm^{-1}) ν_{max}: 3474, 2959, 2872, 1694, 1637, 1587, 1467, 1346, 1182, 974, 917, 790, 631, 539, 498;

HRMS (*m/z*)**:** calcd for $C_{13}H_{18}NaO_2$ $(M+Na)^+$ 229.1199, found 229.1194.



Compound (+)-**133n:** The title compound was prepared from (*R*)-**125** 0.075 g, 0.38 mmol) cyclohexylmagnesium bromide (0.8 M solution in THF, 1.4 mL, 1.14 mmol) and octanal (0.081 g, 0.098 mL, 0.63 mmol) according to the general procedure A. After purification on silica (hexanes/ EtOAc 10:1 to 5:1) title compound was obtained in 77% yield (0.085 g).

Physical state: pale green oil;

TLC: R_f = 0.52 (hexanes/ EtOAc 5:1, UV-active, stains brown with vanillin);

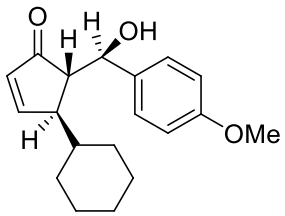
$[\alpha]_D^{25}$**:** 136.75 (c 0.25, $CHCl_3$);

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.70 (dd, *J* = 5.8, 2.6 Hz, 1H), 6.14 (dd, *J* = 5.8, 1.9 Hz, 1H), 3.63 (dd, *J* = 12.3, 6.4 Hz, 1H), 2.59 (td, *J* = 4.4, 2.1 Hz, 1H), 2.17 (dd, *J* = 7.7, 2.1 Hz, 1H), 1.81 – 1.74 (m, 2H), 1.72 – 1.65 (m, 3H), 1.55 (t, *J* = 5.5 Hz, 3H), 1.51 (s, 2H), 1.35 – 1.24 (m, 11H), 1.22 – 1.17 (m, 2H), 1.16 – 1.11 (m, 1H), 0.87 (d, *J* = 7.1 Hz, 3H);

^{13}C NMR (151 MHz, $CDCl_3$) δ 212.69, 167.57, 133.33, 72.70, 53.51, 50.99, 40.94, 35.58, 31.80, 31.55, 29.59, 29.53, 29.28, 26.50, 26.32, 26.30, 25.66, 22.63, 14.07;

IR (neat) (cm^{-1}) ν_{max}: 3440, 2922, 2852, 1687, 1449, 1183, 1052, 891, 631, 534, 496;

HRMS (*m/z*)**:** calcd for C19H32 NaO2 (M+Na)+ 315.2295, found 395.2286.



Compound (+)**-133o:** The title compound was prepared from (*R*)-**125** (0.075 g, 0.38 mmol) cyclohexylmagnesium bromide (0.8 M solution in THF, 1.4 mL, 1.14 mmol) and 4-methoxy benzaldehyde (0.086 g, 0.076 mL, 0.63 mmol) according to the general procedure A. After purification on silica (hexanes/ EtOAc 5:1 to 3:1) title compound was obtained in 72% yield (0.082 g).

Physical state: brown colored oil;

TLC: R_f = 0.22 (hexanes/ EtOAc 5:1, UV-active, stains dark brown with vanillin);

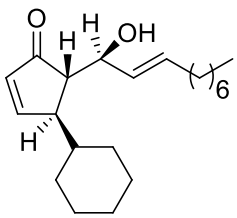
$[\alpha]_D^{25}$**:** 196.2 (c 0.48, $CHCl_3$);

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.65 (dd, *J* = 5.8, 2.6 Hz, 1H), 7.30 – 7.27 (m, 2H), 6.89 – 6.85 (m, 2H), 6.15 (dd, *J* = 5.8, 1.9 Hz, 1H), 4.57 (d, *J* = 9.3 Hz, 1H), 4.46 (s, 1H), 3.81 (s, 3H), 2.43 (d, *J* = 1.5 Hz, 1H), 2.39 (dd, *J* = 9.3, 2.2 Hz, 1H), 1.56 (dd, *J* = 14.0, 11.2 Hz, 3H), 1.35 – 1.29 (m, 2H), 1.02 – 0.94 (m, 3H), 0.88 – 0.82 (m, 2H), 0.63 (td, *J* = 11.9, 3.2 Hz, 1H);

^{13}C NMR (151 MHz, $CDCl_3$) δ 212.95, 168.22, 159.45, 133.71, 132.68, 128.06, 128.06, 113, 68, 113.68, 75.23, 55.33, 55.03, 50.45, 39.92, 31.09, 28.95, 26.34, 26.21, 26.17;

IR (neat) (cm^{-1}) ν_{max}: 3422, 2923, 2851, 1686, 1613, 1513, 1448, 1247, 1174, 1035, 632, 536, 495;

HRMS (*m/z*)**:** calcd for $C_{19}H_{24}NaO_3$ $(M+Na)^+$ 323.1618, found 323.1620.



Compound (+)**-133p:** The title compound was prepared from (*R*)-**125** (0.075 g, 0.38 mmol) cyclohexylmagnesium bromide (0.8 M solution in THF, 1.4 mL, 1.14 mmol) and *trans*-2-decenal (0.098 g, 0.11 mL, 0.63 mmol) according to the general procedure A. After purification on silica (hexanes/ EtOAc 7:1 to 5:1) title compound was obtained in 75% yield (0.090 g).

Physical state: yellow oil;

TLC: R_f = 0.48 (hexanes/ EtOAc 5:1, UV-active, stains dark brown with vanillin);

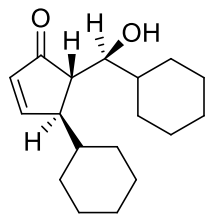
$[\alpha]_D^{25}$**:** 140.71 (c 0.73, $CHCl_3$);

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.69 (dd, *J* = 5.8, 2.6 Hz, 1H), 6.13 (dd, *J* = 5.8, 1.9 Hz, 1H), 5.70 (dt, *J* = 15.0, 6.7 Hz, 1H), 5.52 – 5.39 (m, 1H), 4.05 (t, *J* = 8.2 Hz, 1H), 3.77 (d, *J* = 9.8 Hz, 1H), 2.54 (td, *J* = 4.4, 2.1 Hz, 1H), 2.23 (dd, *J* = 8.6, 2.0 Hz, 1H), 2.09 – 1.99 (m, 2H), 1.72 (dd, *J* = 21.3, 8.2 Hz, 3H), 1.63 (d, *J* = 11.7 Hz, 3H), 1.48 (ddd, *J* = 11.5, 8.0, 3.5 Hz, 1H), 1.35 (dd, *J* = 13.2, 5.7 Hz, 2H), 1.24 (d, *J* = 12.7 Hz, 9H), 1.12 (ddd, *J* = 12.6, 9.6, 5.9 Hz, 3H), 0.87 (t, *J* = 6.6 Hz, 3H);

^{13}C NMR (151 MHz, $CDCl_3$) δ 212.70, 168.98, 134.40, 132.49, 129.73, 74.21, 55.94, 44.80, 33.73, 32.14, 31.83, 31.80, 29.69, 29.45, 29.23, 29.21, 29.17, 29.05, 27.14, 22.63, 14.07;

IR (neat) (cm^{-1}) ν_{max}: 3418, 2920, 2852, 1690, 1586, 1449, 970, 536;

HRMS (*m/z*)**:** calcd for $C_{21}H_{34}NaO_2$ $(M+Na)^+$ 341.2451, found 341.2451.



Compound (+)**-133q:** The title compound was prepared from (*R*)-**125** (0.075 g, 0.38 mmol) cyclohexylmagnesium bromide (0.8 M solution in THF, 1.4 mL, 1.14 mmol) and cyclohexanal (0.071 g, 0.63 mmol) according to the general procedure A. After purification on silica (hexanes/ EtOAc 7:1 to 5:1) title compound was obtained in 70% yield (0.073 g).

Physical state: yellow oil;

TLC: R_f = 0.42 (hexanes/ EtOAc 5:1, UV-active, stains orange with vanillin);

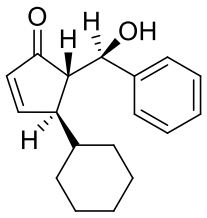
$[\alpha]_D^{25}$**:** 186.2 (c 0.75, $CHCl_3$);

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.70 (dd, *J* = 5.8, 2.5 Hz, 1H), 6.13 (dd, *J* = 5.8, 2.0 Hz, 1H), 3.44 – 3.37 (m, 1H), 3.16 (s, 1H), 2.63 (td, *J* = 4.6, 2.2 Hz, 1H), 2.36 (dd, *J* = 7.0, 2.4 Hz, 1H), 1.81 – 1.65 (m, 10H), 1.30 (t, *J* = 7.2 Hz, 2H), 1.21 (dd, *J* = 7.9, 4.2 Hz, 5H), 1.02 (d, *J* = 22.4 Hz, 3H), 0.91 – 0.84 (m, 2H);

^{13}C NMR (75 MHz, $CDCl_3$) δ 213.13, 167.39, 133.58, 77.37, 51.63, 50.04, 41.31, 40.73, 31.56, 30.53, 29.42, 27.17, 26.60, 26.47, 26.37, 26.37, 26.37, 26.03;

IR (neat) (cm^{-1}) ν_{max}: 3444, 2922, 2850, 1686, 1588, 1511, 1449, 1183, 1059, 636, 576, 420;

HRMS (*m/z*)**:** calcd for $C_{18}H_{28}NaO_2$ $(M+Na)^+$ 299.1982, found 299.1985.



Compound (+)**-133r:** The title compound was prepared from (*R*)-**125** (0.075 g, 0.38 mmol) cyclohexylmagnesium bromide (0.8 M solution in THF, 1.4 mL, 1.14 mmol) and benzaldehyde (0.067 g, 0.064 mL, 0.63 mmol) according to the general procedure A. After purification on silica (hexanes/ EtOAc 7:1 to 5:1) title compound was obtained in 74% yield (0.076 g).

Physical state: yellow oil;

TLC: R_f = 0.45 (hexanes/ EtOAc 5:1, UV-active, stains brown with vanillin);

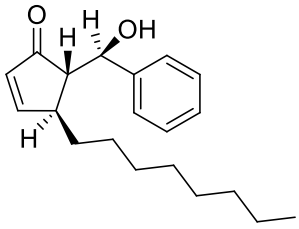
$[\alpha]_D^{25}$**:** 220.3 (c 0.39, $CHCl_3$);

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.65 (dd, *J* = 5.8, 2.6 Hz, 1H), 7.38 – 7.36 (m, 2H), 7.36 – 7.32 (m, 2H), 7.31 – 7.28 (m, 1H), 6.16 (dd, *J* = 5.8, 2.0 Hz, 1H), 4.62 (d, *J* = 9.3 Hz, 1H), 4.55 (s, 1H), 2.46 (td, *J* = 4.4, 2.2 Hz, 1H), 2.40 (dd, *J* = 9.3, 2.3 Hz, 1H), 1.61 – 1.52 (m, 3H), 1.28 (dd, *J* = 10.7, 8.9 Hz, 2H), 1.02 – 0.91 (m, 3H), 0.86 – 0.80 (m, 1H), 0.79 – 0.73 (m, 1H), 0.60 (qd, *J* = 12.2, 3.6 Hz, 1H);

^{13}C NMR (151 MHz, $CDCl_3$) δ 212.88, 168.23, 141.40, 132.67, 128.32, 128.32, 128.18, 126.88, 126.88, 75.67, 54.91, 50.34, 39.81, 31.02, 28.86, 26.31, 26.18, 26.15;

IR (neat) (cm^{-1}) ν_{max}: 3451, 2922, 2850, 1683, 1585, 1449, 1192, 1045, 903, 803, 760, 703, 550;

HRMS (*m/z*)**:** calcd for $C_{18}H_{22}NaO_2$ $(M+Na)^+$ 293.1512, found 293.1504.



Compound (+)**-133s:** The title compound was prepared from (*R*)-**125** (0.075 g, 0.38 mmol) octylmagnesium bromide (1.0 M solution in Et_2O, 1.14 mL, 1.14 mmol) and benzaldehyde (0.067 g, 0.064 mL, 0.63 mmol) according to the general procedure A. After purification on silica (hexanes/ EtOAc 10:1 to 5:1) title compound was obtained in 30% yield (0.035 g).

Physical state: pale yellow oil;

TLC: R_f = 0.44 (hexanes/ EtOAc 5:1, UV-active, stains pink with vanillin);

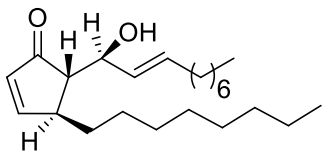
$[\alpha]_D^{25}$**:** 111.0 (c 0.15, $CHCl_3$);

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.65 (dd, *J* = 5.7, 2.5 Hz, 1H), 7.38 (dd, *J* = 8.2, 1.3 Hz, 2H), 7.36 – 7.33 (m, 2H), 7.32 – 7.28 (m, 1H), 6.17 (dd, *J* = 5.7, 1.9 Hz, 1H), 4.74 (s, 1H), 4.64 (d, *J* = 9.7 Hz, 1H), 2.50 (ddd, *J* = 7.4, 5.0, 2.4 Hz, 1H), 2.27 (dd, *J* = 9.7, 2.4 Hz, 1H), 1.26 (dd, *J* = 14.1, 6.7 Hz, 2H), 1.22 – 1.12 (m, 4H), 1.07 – 0.92 (m, 8H), 0.87 (t, *J* = 7.3 Hz, 3H);

^{13}C NMR (151 MHz, $CDCl_3$) δ 213.03, 169.22, 141.38, 132.27, 128.43, 128.43, 128.24, 126.88, 126.88, 75.43, 57.33, 44.53, 32.69, 31.76, 29.22, 29.10, 29.06, 26.19, 22.60, 14.07;

IR (neat) (cm^{-1}) ν_{max}: 3441, 2923, 2853, 1686, 1585, 1511, 1455, 1200, 1044, 702, 632, 544, 494;

HRMS (*m/z*)**:** calcd for $C_{20}H_{28}NaO_2$ $(M+Na)^+$ 323.1982, found 323.1980.



Compound (+)**-133t:** The title compound was prepared from (*R*)-**125** (0.075 g, 0.38 mmol) octylmagnesium bromide (1.0 M solution in Et_2O, 1.14 mL, 1.14 mmol) and *trans*-2-decenal (0.098 g, 0.11 mL, 0.63 mmol)

according to the general procedure A. After purification on silica (hexanes/ EtOAc 7:1 to 5:1) title compound was obtained in 31% yield (0.041 g).

Physical state: yellow oil;

TLC: R_f = 0.52 (hexanes/ EtOAc 5:1, UV-active, stains brown with vanillin);

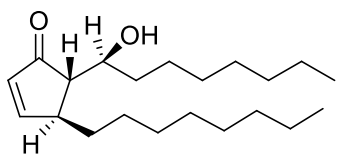
$[\alpha]_D^{25}$**:** 48.5 (c 0.18, $CHCl_3$);

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.69 (dd, *J* = 5.8, 2.6 Hz, 1H), 6.13 (dd, *J* = 5.8, 1.9 Hz, 1H), 5.72 – 5.67 (m, 1H), 5.48 – 5.43 (m, 1H), 4.05 (t, *J* = 8.2 Hz, 1H), 2.54 (dt, *J* = 4.3, 2.1 Hz, 1H), 2.23 (dd, *J* = 8.5, 2.0 Hz, 1H), 2.06 – 2.02 (m, 2H), 1.78 – 1.73 (m, 2H), 1.69 – 1.62 (m, 4H), 1.47 (ddd, *J* = 15.4, 7.8, 3.8 Hz, 1H), 1.40 – 1.31 (m, 3H), 1.28 (ddd, *J* = 14.7, 10.2, 5.6 Hz, 10H), 1.22 – 1.18 (m, 2H), 1.18 – 1.09 (m, 3H), 0.88 (t, *J* = 7.0 Hz, 6H);

^{13}C NMR (151 MHz, $CDCl_3$) δ 212.54, 168.02, 134.39, 132.93, 129.87, 74.55, 53.39, 50.59, 40.69, 32.13, 31.77, 31.45, 29.75, 29.17, 29.15, 29.09, 26.48, 26.30, 26.29, 22.65, 22.65, 14.07, 14.07;

IR (neat) (cm^{-1}) ν_{max}: 3430, 2922, 2852, 1692, 1464, 970, 909, 733, 631, 542, 498;

HRMS (m/z): calcd for C23H40 NaO2 (M+Na)+ 371.2921, found 371.2922.



Compound (+)**-133u:** The title compound was prepared from (*R*)-**125** (0.075 g, 0.38 mmol) octylmagnesium bromide (1.0 M solution in Et_2O, 1.14 mL, 1.14 mmol) and octanal (0.081 g, 0.098 mL, 0.63 mmol) according to the general procedure A. After purification on silica (hexanes/ EtOAc 7:1 to 5:1) title compound was obtained in 34% yield (0.042 g).

Physical state: pale yellow oil;

TLC: R_f = 0.58 (hexanes/ EtOAc 5:1, UV-active, stains pale brown with vanillin);

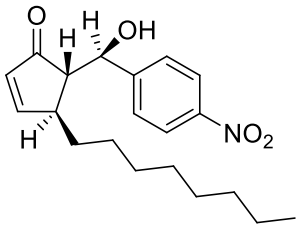
$[\alpha]_D^{25}$**:** 52.6 (c 0.85, $CHCl_3$);

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.69 (dd, *J* = 5.7, 2.5 Hz, 1H), 6.13 (dd, *J* = 5.7, 1.9 Hz, 1H), 3.79 (s, 1H), 3.67 (t, *J* = 8.1 Hz, 1H), 2.67 – 2.63 (m, 1H), 2.02 (dd, *J* = 8.4, 2.3 Hz, 1H), 1.64 (ddd, *J* = 10.7, 9.3, 5.3 Hz, 1H), 1.59 – 1.52 (m, 3H), 1.51 – 1.46 (m, 1H), 1.43 – 1.37 (m, 2H), 1.34 – 1.25 (m, 19H), 0.88 (td, *J* = 7.0, 3.6 Hz, 6H);

^{13}C NMR (151 MHz, $CDCl_3$) δ 213.03, 168.58, 132.84, 72.27, 55.94, 44.98, 35.59, 33.85, 31.82, 31.81, 29.66, 29.56, 29.41, 29.28, 29.21, 26.91, 25.39, 22.63, 22.63, 14.07, 14.07;

IR (neat) (cm^{-1}) ν_{max}: 3438, 2924, 2854, 1690, 1465, 1314, 1262, 1186, 634, 537, 497;

HRMS (*m/z*)**:** calcd for $C_{21}H_{38}NaO_2$ $(M+Na)^+$ 345.2764, found 345.2764.



Compound (+)**-133v:** The title compound was prepared from (*R*)-**125** (0.075 g, 0.38 mmol) octylmagnesium bromide (1.0 M solution in Et_2O, 1.14 mL, 1.14 mmol) and 4-nitro benzaldehyde (0.096 g, 0.63 mmol) according to the general procedure A. After purification on silica (hexanes/ EtOAc 7:1 to 3:1) title compound was obtained in 38% yield (0.050 g).

Physical state: pale yellow oil;

TLC: R_f = 0.23 (hexanes/ EtOAc 5:1, UV-active, stains pale brown with vanillin);

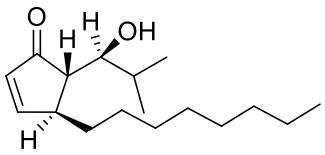
$[\alpha]_D^{25}$**:** 126.6 (c 0.85, $CHCl_3$);

^{1}H NMR (600 MHz, $CDCl_3$) δ 8.25 – 8.23 (m, 2H), 7.68 (dd, *J* = 5.7, 2.5 Hz, 1H), 7.60 – 7.58 (m, 2H), 6.20 (dd, *J* = 5.7, 1.9 Hz, 1H), 4.84 (s, 1H), 4.81 (d, *J* = 9.5 Hz, 1H), 2.52 (ddd, *J* = 7.4, 5.0, 2.4 Hz, 1H), 2.26 (dd, *J* = 9.5, 2.5 Hz, 1H), 1.27 – 1.23 (m, 2H), 1.20 – 1.12 (m, 4H), 1.03 (dd, *J* = 13.4, 7.7 Hz, 5H), 0.99 – 0.92 (m, 3H), 0.86 (t, *J* = 7.3 Hz, 3H);

^{13}C NMR (151 MHz, $CDCl_3$) δ 211.95, 169.06, 148.56, 147.77, 132.44, 127.79, 127.79, 123.71, 123.71, 74.47, 56.87, 44.17, 32.90, 31.71, 29.26, 29.16, 29.05, 26.31, 22.58, 14.03;

IR (neat) (cm^{-1}) ν_{max}: 3398, 2926, 2854, 1689, 1524, 1347, 1191, 856, 756, 536, 494;

HRMS (*m/z*)**:** calcd for $C_{21}H_{28}NO_6$ $(M+HCOO)^-$, 390.1922, found 390.1922.



Compound (+)**-133w:** The title compound was prepared from (*R*)-**125** (0.075 g, 0.38 mmol) octylmagnesium bromide (1.0 M solution in Et_2O, 1.14 mL, 1.14 mmol) and isobutanal (0.046 g, 0.058 mL, 0.63 mmol) according to the general procedure A. After purification on silica (hexanes/ EtOAc 7:1 to 3:1) title compound was obtained in 32% yield (0.033 g).

Physical state: pale brown oil;

TLC: R_f = 0.54 (hexanes/ EtOAc 5:1, UV-active, stains pale brown with vanillin);

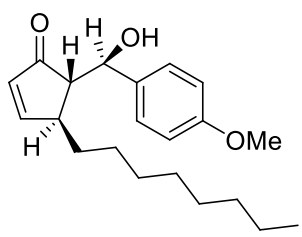
$[\alpha]_D^{25}$**:** 103.2 (c 0.65, $CHCl_3$);

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.70 (dd, *J* = 5.7, 2.4 Hz, 1H), 6.14 (dd, *J* = 5.7, 1.9 Hz, 1H), 3.80 (s, 1H), 3.47 (ddd, *J* = 8.6, 3.2, 2.4 Hz, 1H), 2.70 – 2.61 (m, 1H), 2.13 (dd, *J* = 8.6, 2.4 Hz, 1H), 1.86 (dtd, *J* = 9.4, 6.4, 2.9 Hz, 1H), 1.67 (s, 1H), 1.27 (s, 13H), 1.05 (d, *J* = 6.8 Hz, 3H), 0.96 (d, *J* = 6.7 Hz, 3H), 0.91 – 0.86 (m, 3H);

^{13}C NMR (75 MHz, $CDCl_3$) δ 213.72, 168.67, 132.95, 76.86, 53.21, 45.32, 33.37, 31.83, 31.44, 29.71, 29.43, 29.20, 26.70, 22.64, 20.33, 15.58, 14.09;

IR (neat) (cm^{-1}) ν_{max}:3486, 2925, 2856, 1686, 1512, 1465, 1236, 1042, 792, 632, 536, 501;

HRMS (*m/z*)**:** calcd for $C_{17}H_{30}NaO_2$ $(M+Na)^+$, 289.2138, found 289.2136.



Compound (+)**-133x:** The title compound was prepared from (*R*)-**125** (0.075 g, 0.38 mmol) octylmagnesium bromide (1.0 M solution in Et_2O, 1.14 mL, 1.14 mmol) and 4-methoxy benzaldehyde (0.086 g, 0.076 mL, 0.63 mmol) according to the general procedure A. After purification on silica (hexanes/ EtOAc 7:1 to 3:1) title compound was obtained in 36% yield (0.045 g).

Physical state: pale brown oil;

TLC: R_f = 0.25 (hexanes/ EtOAc 5:1, UV-active, stains deep brown with vanillin);

$[\alpha]_D^{25}$**:** 114.2 (c 0.65, $CHCl_3$);

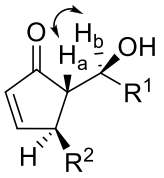
^{1}H NMR (600 MHz, $CDCl_3$) δ 7.65 (dd, *J* = 5.7, 2.5 Hz, 1H), 7.31 – 7.28 (m, 2H), 6.89 – 6.86 (m, 2H), 6.15 (dd, *J* = 5.7, 1.9 Hz, 1H), 4.69 (s, 1H), 4.58 (d, *J* = 9.7 Hz, 1H), 3.80 (s, 3H), 2.49 – 2.45 (m, 1H), 2.26 (dd, *J* = 9.7, 2.4 Hz, 1H), 1.26 (dd, *J* = 14.5, 7.2 Hz, 2H), 1.21 – 1.14 (m, 4H), 1.09 – 0.95 (m, 8H), 0.87 (t, *J* = 7.3 Hz, 3H);

^{13}C NMR (151 MHz, $CDCl_3$) δ 213.12, 169.24, 159.48, 133.69, 132.26, 128.04, 128.04, 113.75, 113.75, 74.96, 57.43, 55.24, 44.59, 32.74, 31.77, 29.25, 29.17, 29.10, 26.23, 22.60, 14.06;

IR (neat) (cm^{-1}) ν_{max}: 3463, 2926, 2854, 1686, 1613, 1513, 1464, 1303, 1246, 1173, 1036, 834, 632, 539, 497;

HRMS (*m/z*)**:** calcd for $C_{21}H_{30}NaO_3$ $(M+Na)^+$, 353.2087, found 353.209.

Table 11. Coupling constants $^3J_{Ha\text{-}Hb}$ of (+)-**133**.

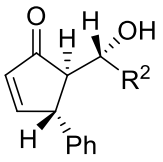


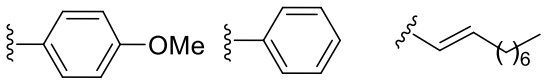
(+)-133 a-x

Compound	$^3J_{Ha\text{-}Hb}$	δ_{ppm}[a]	Compound	$^3J_{Ha\text{-}Hb}$	δ_{ppm}[a]
(+)-133a	8.21	2.44	(+)-133m	9.0	2.26
(+)-133b	8.68	2.48	(+)-133n	7.7	2.17
(+)-133c	8.6	2.5	(+)-133o	9.3	2.39
(+)-133d	9.46	2.66	(+)-133p	8.6	2.23
(+)-133e	9.5	2.66	(+)-133q	7.0	2.36
(+)-133f	8.2	2.36	(+)-133r	9.3	2.40
(+)-133g	10.1	2.31	(+)-133s	9.7	2.27
(+)-133h	8.4	2.33	(+)-133t	8.5	2.23
(+)-133i	9.2	2.53	(+)-133u	8.4	2.02
(+)-133j	8.5	2.52	(+)-133v	9.5	2.26
(+)-133k	9.5	2.42	(+)-133w	8.6	2.13
(+)-133l	10.2	2.25	(+)-133x	9.7	2.26

Kobayashi *et al*.[15] had established that for compound (+)-133 (*anti*-diols) $^3J_{Ha\text{-}Hb}$ is in the range of 8.4 to 9.7 Hz, while for the corresponding *syn*-diols $^3J_{Ha\text{-}Hb}$ is around 3 Hz.

All (-)-**133** derivatives were synthesized from (*S*)-**134** by using previous one pot conditions according to general procedure A.

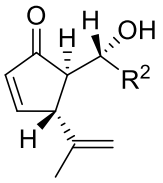


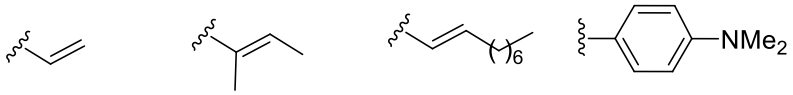


(-)-**133a** (72%) (-)-**133b** (74%) (-)-**133c** (68%)

Note: Characterization: Spectral data of (-)-**133 a**, **b** and **c** were matched with (+)-**133 d**, **e** and **c**.

$[\alpha]_D^{25}$: (-)-**133a** = -232.0 (c 0.53, $CHCl_3$), (-)-**133b** = -228.0 (c 0.15, $CHCl_3$), (-)-**133c** = -202.0 (c 0.56, $CHCl_3$).

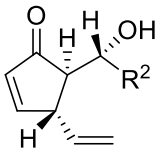


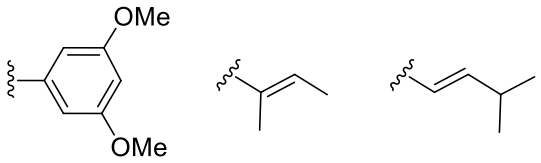


(-)-**133d** (66%) (-)-**133e** (68%) (-)-**133f** (68%) (-)-**133g** (60%)

Note: Characterization: Spectral data of (-)-**133 d**, **e**, **f** and **g** were matched with (+)-**133 f**, **g**, **h** and **i**.

$[\alpha]_D^{25}$: (-)-**133**d = -230.0 (c 0.14, $CHCl_3$), (-)-**133**b = -222.0 (c 0.37, $CHCl_3$), (-)-**133**c = -110.0 (c 0.71, $CHCl_3$), (-)-**133**g = n.d.

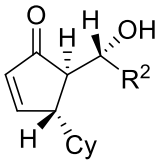


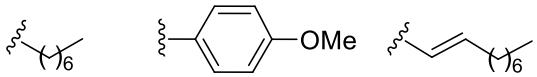


(-)-**133h** (72%) (-)-**133i** (66%) (-)-**133j** (65%)

Note: Characterization: Spectral data of (-)-**133 h**, **i** and **j** were matched with (+)-**133 k**, **l** and **m**.

$[\alpha]_D^{25}$: (-)-**133**h = -130.0 (c 0.14, $CHCl_3$), (-)-**133**i = n.d, (-)-**133**j = -141.0 (c 0.14, $CHCl_3$).

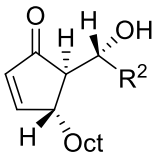




(-)-**133k** (75%) (-)-**133l** (68%) (-)-**133m** (80%)

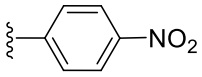
Note: Characterization: Spectral data of (-)-**133 k**, **l** and **m** were matched with (+)-**133 n**, **o** and **p**.

$[\alpha]_D^{25}$: (-)-**133**k = -127.0 (c 0.39, $CHCl_3$), (-)-**133**l = -188.0 (c 0.48, $CHCl_3$), (-)-**133**m = -129.0 (c 0.73, $CHCl_3$).

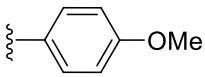


(-)-**133n** (76%)

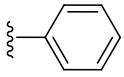
(-)-**133o** (68%)



(-)-**133p** (72%)



(-)-**133q** (68%)

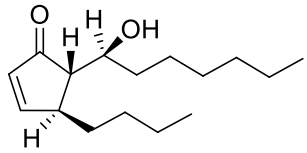


(-)-**133r** (72%)

Note Characterization: Spectral data of of (-)-**133 n**, **o**, **p**, **q** and **r** were matched with (+)-**133 t**, **u**, **v**, **x** and **s**.

$[\alpha]_D^{25}$**:** (-)-**133** n = -39.0 (c 0.19, $CHCl_3$), (-)-**133 o**, **p**, **q** and **r** = n.d.

4. Synthesis and characterization of natural products



Compound 2: The title compound was prepared from (*R*)-**125** (0.075 g, 0.38 mmol) n-butyl magnesiumbromide (0.90 M solution in THF, 1.24 mL, 1.14 mmol) and heptanal (0.068 g, 0.084 mL, 0.63 mmol) according to the general procedure A. After purification on silica (hexanes/EtOAc 10:1 to 5:1) **2** was obtained in 38% yield (0.037 g).

Physical state: pale yellow oil;

TLC: R_f = 0.4 (hexanes/EtOAc 5:1, UV-active, stains pale brown with vanillin);

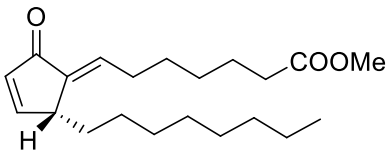
$[\alpha]_D^{25}$**:** 48.6 (c 0.18, $CHCl_3$);

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.70 (dd, *J* = 5.7, 2.5 Hz, 1H), 6.14 (dd, *J* = 5.7, 1.9 Hz, 1H), 3.87 (s, 1H), 3.68 (dd, *J* = 9.3, 4.8 Hz, 1H), 2.65 (ddd, *J* = 7.9, 5.6, 2.3 Hz, 1H), 2.04 – 2.00 (m, 1H), 1.67 – 1.62 (m, 1H), 1.58 – 1.47 (m, 4H), 1.38 – 1.24 (m, 11H), 0.93 – 0.85 (m, 6H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 213.20, 168.76, 132.86, 72.32, 55.94, 44.98, 35.59, 33.55, 31.85, 29.29, 29.09, 25.37, 22.79, 22.64, 14.11, 13.96;

IR (neat) (cm^{-1}) $\tilde{\nu}_{max}$: 3373, 2954, 2925, 2857, 1686, 1511, 1466, 1357, 1234, 1100, 1038, 827, 733, 529, 489;

HRMS (*m/z*)**:** calcd for $C_{16}H_{28}NaO_2$ $(M+Na)^+$ 275.1982, found 275.1982.



Compound 3 [(–)-TEI-9826]: To a stirred solution of CuCN (0.202 g, 2.25 mmol, 3.0 equiv) and anhydrous LiCl (0.190 g, 4.5 mmol, 6.0 equiv) in anhydrous THF (10 mL) was added octyl magnesiumbromide (0.9 M in Et_2O, 2.5 mL, 2.25 mmol, 3.0 equiv) dropwise at –40 °C under stirring. After the addition was completed, the reaction mixture was cooled to –78 °C. To this mixture was added a solution of (*S*)-**134** (0.153 g, 0.75 mmol, 1.0 equiv) in

anhydrous THF (6 mL) at–78 °C. After 4 min of stirring at –78 °C, methyl-6-formylhexanoate (0.199 g, 1.26 mmol, 1.68 equiv) was added. After the reaction was completed (ca. 5 min, monitored by TLC) the mixture was quenched by adding NH_4Cl_{aq} (5 mL) and allowed to warm to room temperature. The aqueous layer was removed with a pipette and the crude was dried under high *vacuum*. To a solution of the residue in DCM (10 mL) were added 4-(dimethylamino)-pyridine (0.486 g, 3.98 mmol) and methane sulfonylchloride (0.16 mL, 1.98 mmol) at ambient temperature. After stirring for 15 h, aqueous HCl solution was added. The layers were separated and the aqueous layer was extracted with EtOAc (3x 15 mL). The combined organic extracts were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (hexanes/EtOAc 5:1)) to give (–)-TEI-9826 **3** was obtained in 48% yield (0.12 g , 4 steps in one pot).

Physical state: yellow oil;

TLC: R_f = 0.36 (hexanes/EtOAc 5:1, UV-active, stains brown with vanillin);

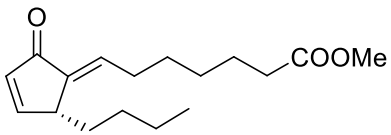
$[\alpha]_D^{25}$**:** –129.4 (c 0.43, $CHCl_3$); lit.[2] $[\alpha]_D^{24}$**:** –121 (c=0.58, $CHCl_3$), lit.[3] $[\alpha]_D^{25}$**:** 119 (c=1.10, $CHCl_3$, *ent*-**3**);

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 – 7.49 (m, 1H), 6.51 (t, *J* = 7.7 Hz, 1H), 6.31 (dd, *J* = 6.0, 1.8 Hz, 1H), 3.66 (s, 3H), 3.49 – 3.42 (m, 1H), 2.30 (t, *J* = 7.5 Hz, 2H), 2.28 – 2.15 (m, 2H), 1.81 (dd, *J* = 9.7, 4.0 Hz, 1H), 1.65 (dd, *J* = 15.5, 7.6 Hz, 2H), 1.55 – 1.47 (m, 3H), 1.41 – 1.34 (m, 2H), 1.30 – 1.21 (m, 12H), 0.87 (t, *J* = 6.9 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 197.2, 174.2, 162.2, 138.3, 135.4, 135.0, 51.7, 43.5, 34.1, 32.7, 32.0, 30.0, 29.6, 29.4, 29.1, 29.1, 28.5, 26.1, 25.0, 22.8, 14.3;

IR (neat) (cm^{-1}) $\tilde{\nu}_{max}$: 3373, 2954, 2925, 2857, 1686, 1511, 1466, 1357, 1234, 1100, 1038, 827, 733, 529, 489;

HRMS (*m/z*)**:** calcd for $C_{21}H_{34}O_3$ $(M)^+$ 334.2508, found 334.2504.



Compound 141: To a stirred solution of CuCN (0.33 g, 3.67 mmol, 3.0 equiv) and anhydrous LiCl (0.310 g, 7.35 mmol, 6.0 equiv) in anhydrous THF (13 mL) was added n-butyl magnesiumbromide (0.91 M in Et_2O, 4.0 mL, 3.67 mmol, 3.0 equiv) dropwise at –40 °C under stirring. After the addition was completed, the reaction mixture was cooled to –78 °C. To this mixture was added a solution of (*S*)-**134** (0.25 g, 1.225 mmol, 1.0 equiv) in anhydrous THF (2.5 mL) at–78 °C. After 4 min of stirring at –78 °C, methyl-6-formylhexanoate (0.32 g, 2.06 mmol, 1.68 equiv) was added. After the reaction was completed (ca. 5 min, monitored by TLC) the mixture was quenched by adding NH_4Cl_{aq} (10 mL) and allowed to warm to room temperature. The aqueous layer was removed with a pipette and the crude was dried under high *vacuum*. To a solution of the residue in DCM (18 mL)

were added 4-(dimethylamino)-pyridine (0.79 g, 6.90 mmol) and methane sulfonylchloride (0.25 mL, 3.45 mmol) at ambient temperature. After stirring for 15 h, aqueous HCl solution was added. The layers were separated and the aqueous layer was extracted with EtOAc (3x 20 mL). The combined organic extracts were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (hexanes/EtOAc 5:1) to give **141** in 42% yield (0.145 g, 4 steps in one pot).

Physical state: yellow oil;

TLC: R_f = 0.36 (hexanes/EtOAc 5:1, UV-active, stains brown with vanillin);

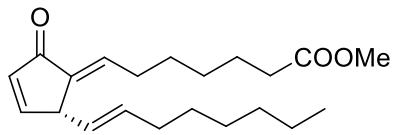
$[\alpha]_D^{25}$**:** –121.0 (c 0.5, $CHCl_3$);

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.48 (ddd, *J* = 6.0, 2.6, 0.9 Hz, 1H), 6.46 (t, *J* = 7.7 Hz, 1H), 6.26 (dd, *J* = 6.0, 1.9 Hz, 1H), 3.60 (s, 3H), 3.44 – 3.37 (m, 1H), 2.28 – 2.16 (m, 4H), 1.77 (ddd, *J* = 12.9, 5.8, 3.3 Hz, 1H), 1.64 – 1.54 (m, 2H), 1.51 – 1.41 (m, 3H), 1.36 – 1.17 (m, 6H), 0.84 – 0.79 (m, 3H);

^{13}C NMR (75 MHz, $CDCl_3$) δ 197.1, 174.1, 162.1, 138.1, 135.3, 134.8, 51.5, 43.3, 33.9, 32.1, 28.9, 28.9, 28.3, 28.0, 24.7, 22.8, 13.95;

IR (neat) (cm^{-1}) $\tilde{\nu}_{max}$: 3373, 2954, 2925, 2857, 1686, 1511, 1466, 1357, 1234, 1100, 1038, 827, 733, 529, 489;

HRMS (*m/z*)**:** calcd for $C_{17}H_{26}O_3$ $(M)^+$ 278.1882, found 278.1880.



Compound 143: To a 25 mL 3-neck round bottom flask equipped with a stir bar and septum was added $Cp_2Zr(H)Cl$ (0.39 g, 1.5 mmol) followed by 4 mL of THF and 1-octyne (0.225 mL, 1.5 mmol). Thw two-phase mixture shielded from light and allowed to stir for 30 min at room temperature. This mixture was the cooled to -78 °C, and at this temperature was added MeLi (1.6 M in Et_2O, 0.94 mL, 1.5 mmol), dropwise over 1 min. At the same time, to another round bottom flask was added CuCN (0.0068g, 0.075 mmol), followed by 1 mL of THF. The mixture was cooled to -78 °C, and Me_2Zn (2.0 M in heptanes, 0.39 mL, 0.75 mmol) was added dropwise, followed quickly by dropwise addition of MeLi (0.58 mL, 1.1 mmol). After 5 min this three phase slurry was placed in an ice-bath for 10 min. This solution was then cooled back to -78 °C and the solution containing methyl vinyl zirconocene, still at -78 °C was transferred to the flask, containing the zincate/catalytic cuprate mixture. After 5 min of stirring (*S*)-**134** (0.153 g, 0.75 mmol, 1.0 equiv) in 1.0 mL THF was added during 5 min. After 5 min of additional stirring methyl-6-formylhexanoate (0.2 g, 1.26 mmol) was added. After 5 min stirring the mixture was quenched with aq. NH_4Cl (5 mL). The layers were

separated and the aqueous layer was extracted with EtOAc (2X10 mL). The combined extracts were washed with brine (10 mL), dried, filtered and concentrated to give crude oil, which was directly subjected to the next step.

To a solution of the residue in DCM (12 mL) were added 4-(dimethylamino)-pyridine (0.52 g, 4.29 mmol) and methane sulfonylchloride (0.16 mL, 2.15 mmol) at ambient temperature. After stirring for 15 h, aqueous HCl solution was added. The layers were separated and the aqueous layer was extracted with EtOAc (3x 20 mL). The combined organic extracts were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (hexanes/EtOAc 5:1) to give **143** in 45% yield (0.113 g).

Physical state: yellow oil;

TLC: R_f = 0.63 (hexanes/EtOAc 3:1, UV-active, stains pale brown with vanillin);

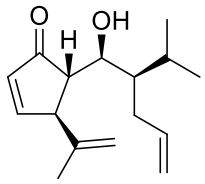
$[\alpha]_D^{25}$**:** –110.0 (c 0.5, $CHCl_3$);

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34 (ddd, *J* = 5.8, 2.6, 0.7 Hz, 1H), 6.58 (t, *J* = 7.7 Hz, 1H), 6.30 (dd, *J* = 5.9, 1.9 Hz, 1H), 5.63 (dd, *J* = 14.7, 7.3 Hz, 1H), 5.15 (ddt, *J* = 15.3, 8.5, 1.3 Hz, 1H), 3.96 (d, *J* = 8.5 Hz, 1H), 3.65 (s, 3H), 2.24 (ddd, *J* = 14.8, 13.8, 7.4 Hz, 4H), 2.01 (dd, *J* = 12.2, 5.7 Hz, 2H), 1.60 (dd, *J* = 15.1, 7.5 Hz, 2H), 1.49 – 1.40 (m, 2H), 1.36 – 1.23 (m, 10H), 0.87 (dd, *J* = 7.8, 4.7 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 196.8, 174.1, 161.1, 137.2, 136.9, 134.4, 133.8, 127.4, 51.6, 47.3, 33.9, 32.4, 31.7, 29.3, 28.9, 28.8, 28.6, 28.2, 24.7, 22.6, 14.1;

IR (neat) (cm^{-1}) $\tilde{\nu}_{max}$: 3373, 2954, 2925, 2857, 1686, 1511, 1357, 1110, 1038, 827, 733, 529;

HRMS (*m/z*)**:** calcd for $C_{21}H_{32}O_3$ $(M)^+$ 332.2351, found 332.2350.



Compound 146: To a stirred solution of CuCN (0.503 g, 5.61 mmol, 3.0 equiv) and anhydrous LiCl (0.472 g, 11.2 mmol, 6.0 equiv) in anhydrous THF (20 mL) was added iso propenyl magnesium bromide (0.83 M solution in THF, 5.61 mmol, 6.85 mL, 3.0 equiv) dropwise at –40 °C under stirring. After the addition was completed, the reaction mixture was cooled to –78 °C. To this mixture was added a solution of (*R*)-**125** (0.37 g, 1.87 mmol, 1.0 equiv) in anhydrous THF (5 mL) at –78 °C. After 4 min of stirring at -78 °C, **±-148** (0.471 g, 0.374 mmol, 2.0 equiv) was added. After the reaction was completed (ca. 5 min) the mixture was quenched by adding NH_4Cl_{aq} (30 mL). Then the mixture was allowed to warm to room temperature. The layers were separated, and the aqueous layer was extracted with Et_2O (2x15 mL). The combined organic extracts were dried over Na_2SO_4, filtered and

the solvent was removed under reduced pressure. After purification on silica (hexanes/EtOAc 7:1) **146** was obtained in 68% yield (0.316 g).

Physical state: brown color oil;

TLC: R_f = 0.62 (hexanes/EtOAc 5:1, UV-active, stains dark brown with vanillin);

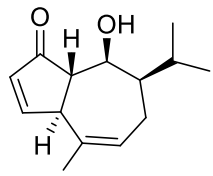
$[\alpha]_D^{25}$**:** 100.7 (c 0.42, $CHCl_3$);

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.60 – 7.49 (dd, *J*=5.6, 2.6 Hz, 1H), 6.21 (dd, *J* = 5.6, 2.1 Hz, 1H), 5.81 (ddt, *J* = 17.1, 10.0, 7.1 Hz, 1H), 5.04 (ddd, *J* = 17.1, 3.5, 1.6 Hz, 1H), 4.99 – 4.90 (m, 3H), 4.00 (t, *J* = 1.4 Hz, 1H), 3.93 – 3.83 (m, 1H), 3.24 (dd, *J* = 4.8, 2.4 Hz, 1H), 2.44 (dd, *J* = 9.2, 2.7 Hz, 1H), 2.25 – 2.14 (m, 2H), 1.88 (dtd, *J* = 13.8, 6.9, 4.8 Hz, 1H), 1.66 (d, *J* = 0.8 Hz, 3H), 1.51 (t, *J* = 5.5 Hz, 1H), 0.93 (dt, *J* = 13.2, 6.6 Hz, 6H);

^{13}C NMR (75 MHz, $CDCl_3$) δ 213.58, 167.62, 142.98, 139.01, 133.37, 115.46, 114.51, 72.76, 53.58, 51.39, 46.46, 30.96, 29.02, 20.87, 19.38, 18.97;

IR (neat) (cm^{-1}) $\tilde{\nu}_{max}$: 3473, 2957, 2928, 1743, 1686, 1589, 1414, 1369, 1279, 1177, 1056, 901, 795, 658, 624, 531, 496;

HRMS (*m/z*)**:** calcd for $C_{16}H_{24}NaO_2$ $(M+Na)^+$ 271.1669, found 271.1669.



Compound 157: A flask containing **146** (0.39 g, 1.57 mmol) was outfitted with a reflux condenser and evacuated and backfilled with dry nitrogen. Deoxygenated DCM (85 mL) was added, and the solution was heated to reflux (44 °C). A solution of Grubbs-II catalyst (0.09 g, 0.11 mmol) in deoxygenated DCM (5 mL) was added to the reaction mixture. The light brown reaction mixture was refluxed (44 °C) for 1.5 h and was then cooled to room temperature. The solvent was removed under reduced pressure. After purification on silica (hexanes/EtOAc 5:1 to 3:1) **157** was obtained in 94% yield (0.325 g).

Physical state: pale brown color oil;

TLC: R_f = 0.53 (hexanes/EtOAc 5:1, UV-active, stains dark brown with vanillin);

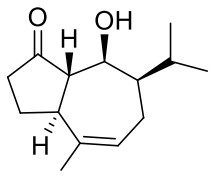
$[\alpha]_D^{25}$**:** –25.6 (c 0.25, $CHCl_3$);

^{1}H NMR (300 MHz, Acetone-d_6): δ 8.03 – 7.90 (dd, *J*=5.7, 2.6 Hz, 1H), 6.12 (dd, *J* = 5.9, 2.8 Hz, 1H), 5.57 – 5.49 (m, 1H), 4.23 – 4.15 (m, 1H), 3.60 (dd, *J* = 10.1, 8.8 Hz, 1H), 2.54 (dd, *J* = 9.7, 5.3 Hz, 1H), 2.04 (dt, *J* = 8.7, 4.3 Hz, 1H), 1.96 (t, *J* = 4.1 Hz, 1H), 1.87 (dd, *J* = 2.3, 0.9 Hz, 3H), 1.81 – 1.62 (m, 2H), 1.57 – 1.48 (m, 1H), 1.02 (d, *J* = 6.6 Hz, 3H), 0.93 (d, *J* = 5.8 Hz, 3H).

^{13}C NMR (75 MHz, Acetone-d_6) δ 212.17, 164.59, 136.88, 132.72, 127.66, 49.59, 49.54, 47.10, 29.56, 27.87, 26.58, 22.16, 21.68, 21.42;

IR (neat) (cm^{-1}) $\tilde{\nu}_{max}$: 3429, 2957, 2873, 1682, 1539, 1446, 1368, 1271, 1068, 976, 737, 632, 540, 497;

HRMS (*m/z*)**:** calcd for $C_{14}H_{20}NaO_2$ $(M+Na)^+$ 243.1463, found 243.1463



Compound 145: The **157** (0.21 g, 0.95 mmol, 1.0 equiv) was dissolved in $CHCl_3$ (7.5 mL, filtered through basic alumina) along with diphenylsilane (0.29 ml, 1.62 mmol, 1.7 equiv) and zinc chloride (0.067 g, 0.49 mmol, 0.52 equiv). Pd $(PPh_3)_4$ (0.015 g, 0.012 mmol, 0.013 equiv)[6] was added and the mixture was stirred (inert atmosphere was not required) at room temperature for 20 min. The solvent was removed under reduced pressure and the crude was purified by column chromatography (hexanes/EtOAc 5:1) **145** was obtained in 80% yield (0.170 g).

Physical state: white color solid;

TLC: R_f = 0.56 (hexanes/EtOAc 5:1, stains brown with vanillin);

$[\alpha]_D^{25}$: –63.5 (c 0.1, $CHCl_3$);

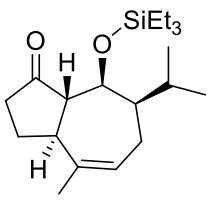
M.P.: 74 °C;

^{1}H NMR (300 MHz, $CDCl_3$): δ 5.58 (dd, *J* = 8.8, 1.3 Hz, 1H), 4.13 – 4.01 (m, 1H), 3.33 (t, *J* = 1.4 Hz, 1H), 2.57 (d, *J* = 11.6 Hz, 1H), 2.46 – 2.26 (m, 4H), 2.25 – 2.11 (m, 1H), 1.89 (dd, *J* = 17.4, 8.8 Hz, 1H), 1.71 (d, *J* = 7.0 Hz, 3H), 1.66 (ddd, *J* = 11.3, 7.7, 2.4 Hz, 1H), 1.61 – 1.49 (m, 1H), 1.29 (td, *J* = 10.1, 4.3 Hz, 1H), 1.00 (d, *J* = 6.6 Hz, 3H), 0.94 (d, *J* = 6.6 Hz, 3H);

^{13}C NMR (75 MHz, $CDCl_3$): δ 223.93, 137.29, 127.81, 71.21, 59.00, 49.21, 42.26, 37.85, 28.58, 26.93, 24.92, 21.98, 21.47, 20.99;

IR (neat) (cm^{-1}) $\tilde{\nu}_{max}$: 3525, 2964, 2870, 1721, 1443, 1408, 1284, 1241, 1159, 1064, 1033, 975, 864, 796, 636, 522;

HRMS (*m/z*)**:** calcd for $C_{14}H_{22}NaO_2$ $(M+Na)^+$ 245.1512, found 245.1513.



Compound 158: To a solution of **145** (0.044 g, 0.2 mmol) in anhydrous DMF (0.3 mL) was added imidazole (0.078 g, 1.15 mmol), DMAP (0.008 g, 0.06 mmol) and triethyl chlorosilane (1.46 mL, 0.83 mmol). The clear reaction mixture was stirred at room temperature for 1 h, then directly subjected to column chromatography (hexanes/EtOAc 10:1) without further work-up to afford **158** in 88% yield (0.059 g).

Physical state: yellow color oil;

TLC: R_f = 0.79 (hexanes/EtOAc 7:1, stains brown with vanillin staining);

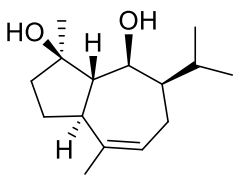
$[\alpha]_D^{25}$**:** –48.7 (c 0.14, $CHCl_3$);

^{1}H NMR (300 MHz, $CDCl_3$) δ 5.54 (dd, *J* = 8.1, 1.3 Hz, 1H), 4.20 (dt, *J* = 6.6, 2.0 Hz, 1H), 2.62 (d, *J* = 12.7 Hz, 1H), 2.51 – 2.39 (m, 1H), 2.37 – 2.16 (m, 3H), 2.13 – 1.97 (m, 1H), 1.86 (dd, *J* = 17.8, 8.1 Hz, 1H), 1.73 (d, *J* = 1.2 Hz, 3H), 1.61 – 1.50 (m, 2H), 1.25 (t, *J* = 7.4 Hz, 1H), 0.97 – 0.94 (m, 6H), 0.92 – 0.86 (m, 9H), 0.74 – 0.59 (m, 6H);

^{13}C NMR (75 MHz, $CDCl_3$) δ 219.56, 136.09, 127.75, 70.98, 62.55, 49.66, 43.01, 37.03, 28.71, 26.19, 25.35, 22.21, 21.38, 21.25, 7.31, 5.66;

IR (neat) (cm^{-1}) $\tilde{\nu}_{max}$: 2954, 2874, 1743, 1457, 1243, 1075, 999, 830, 738, 632, 534, 501;

HRMS (*m/z*)**:** calcd for $C_{20}H_{37}O_2Si$ $(M+H)^+$ 337.2485, found 337.2488.



Compound 144 [(–)-4β,6β-dihydroxy-1α,5β(H)-guai-9-ene]: $CeCl_3 \cdot 7H_2O$ (0.146 g, 0.39 mmol) was placed in 25 mL schlenck flask and, heated at 140 °C in *vacuo* (0.01 mmHg) for 3.5 h, and then cooled. Dry THF (1.7 mL) was added while stirring under N_2, and the solution was stirred for 2 h at room temperature under N_2 atmosphere. The resulting suspension was cooled to –78 °C, and MeLi (1.6 M solution in Et_2O, 0.24 mL, 0.17 mmol) was added. The resulting pale brown color mixture was stirred for 30 min, and then **158** (0.06 g, 0.18 mmol) in THF (1 mL) was added dropwise, and the mixture was stirred for a further 4 h at –78 °C. The reaction mixture was treated with a NH_4Cl_{aq} (15 mL), filtered through Celite and extracted with EtOAc (2x25 mL). The combined organic extracts were dried over Na_2SO_4 and evaporated under reduced pressure to give the crude product. Which was used for the next step without further purification.

Ta a solution of above crude in dry THF (2 mL) was added TABF (1 M solution in THF, 0.17 mL) at 0 °C during 5 min. The reaction mixture was stirred at room temperature until the starting material disappeared (ca. 30 min).The solvent was removed under reduced pressure and the residue was purified on silica (hexanes/EtOAc 10:1 to 3:1) to give rise to **144** in 76% yield (0.032 g, over 2 steps).

Physical state: pale yellow oil;

TLC: R_f = 0.13 (hexanes/EtOAc 2:1, stains deep blue with vanillin);

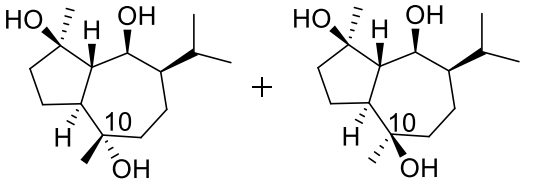
$[\alpha]_D^{25}$**:** –9.5 (c 0.44, $CHCl_3$); lit.[7] $[\alpha]_D^{25}$**:** 10.5 (c 0.60, $CHCl_3$)] for natural (+)-4β,6β-dihydroxy-1α,5β(H)-guai-9-ene;

^{1}H NMR (600 MHz, $CDCl_3$) δ 5.57 – 5.43 (m, 1H), 4.21 – 4.06 (m, 1H), 2.36 (d, *J* = 16.7 Hz, 2H), 2.34 – 2.19 (m, 2H), 2.08 (dd, *J* = 12.0, 9.5 Hz, 1H), 1.89 – 1.68 (m, 5H), 1.66 (s, 3H), 1.64 – 1.54 (m, 1H), 1.31 (s, 3H), 1.29 – 1.20 (m, 1H), 1.02 (d, *J* = 6.6 Hz, 3H), 0.98 – 0.93 (m, 3H);

^{13}C NMR (151 MHz, $CDCl_3$) δ 139.22, 126.18, 81.12, 72.42, 57.46, 50.49, 42.32, 39.90, 28.45, 26.59, 24.33, 24.17, 23.11, 21.41, 21.36;

IR (neat) (cm^{-1}) $\tilde{\nu}_{max}$: 3420, 3310, 2957, 2936, 2868, 1475, 1447, 1387, 1366, 1300, 1150, 1126, 1025, 963, 940, 885, 804, 690, 573, 543;

HRMS (*m/z*)**:** calcd for $C_{15}H_{26}NaO_2$ $(M+Na)^+$ 261.1825, found 261.1825.



(-)-Teuclatriol **72** (–)-10-*epi* teuclatriol **159**

(–)-Teuclatriol 72 and (–)-10-*epi* teuclatriol 159: **144** (0.056 g, 0.24 mmol) and cobalt acetylacetonate (0.012 g, 0.047 mmol) were dissolved in THF (2 mL). Oxygen was bubbled through the solution for 1 h at room temperature, upon which $PhSiH_3$ (0.15 mL, 0.94 mmol)[8] was added. The resulting reaction mixture was stirred at room temperature for 14 h in the presence of oxygen. The mixture was diluted with EtOAc, the solvent was evaporated and the crude was purified by column chromatography (hexanes/EtOAc 3:1to 1:1) to give rise to **72** in 52% yield (0.032 g) and **159** in 20% yield (0.012 g).

(–)-Teuclatriol:

Physical state: yellow color oil;

TLC: R_f = 0.23 (hexanes/EtOAc 2:1, stains blue with vanillin);

$[\alpha]_D^{25}$: –16.8 (c 0.59, $CHCl_3$), lit.[9] $[\alpha]_D^{24}$: 16.9 (c 0.43, $CHCl_3$) for natural (+)-teuclatriol ;

^{1}H NMR (600 MHz, $CDCl_3$): δ 4.13 (dt, *J* = 13.4, 4.6 Hz, 1H), 1.98 – 1.93 (m, 1H), 1.86 (td, *J* = 10.5, 3.1 Hz, 1H), 1.81 – 1.76 (m, 1H), 1.74 (d, *J* = 10.4 Hz, 1H), 1.69 (dd, *J* = 8.1, 6.0 Hz, 2H), 1.67 – 1.64 (m, 1H), 1.59 – 1.56 (m, 1H), 1.55 – 1.51 (m, 1H), 1.39 (dd, *J* = 6.2, 3.4 Hz, 2H), 1.36 (dd, *J* = 6.5, 3.3 Hz, 1H), 1.34 – 1.29 (m, 1H), 1.27 (d, *J* = 3.5 Hz, 3H), 1.25 (d, *J* = 4.2 Hz, 3H), 1.17 – 1.13 (m, 1H), 1.08 (dd, *J* = 8.3, 4.4 Hz, 1H), 1.02 (d, *J* = 6.6 Hz, 3H), 0.97 (d, *J* = 6.6 Hz, 3H);

^{13}C NMR (151 MHz, $CDCl_3$): δ 81.11, 75.47, 71.40, 55.25, 52.03, 47.99, 45.48, 41.10, 29.56, 23.16, 23.07, 22.14, 21.50, 21.14, 20.50;

IR (neat) (cm^{-1}): $\tilde{\nu}_{max}$: 3420, 2960, 2934, 2872, 1508, 1463, 1376, 1218, 1145, 1106, 1036, 902, 852, 789, 675, 635, 564, 471;

HRMS (*m/z*): calcd for $C_{15}H_{28}NaO_3$ $(M+Na)^+$ 279.193, found 279.1931.

(–)-10-*epi* teuclatriol:

Physical state: pale yellow color oil;

TLC: R_f = 0.15 (hexanes/EtOAc 2:1, stains deep blue with vanillin);

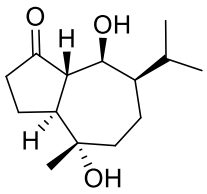
$[\alpha]_D^{25}$: –17.2 (c 0.39, $CHCl_3$), lit.[9] $[\alpha]_D^{24}$: +17.8 (c 0.29, $CHCl_3$) for natural (+)-10-*epi*teuclatriol;

^{1}H NMR (300 MHz, $CDCl_3$): δ 4.10 (dt, *J* = 8.5, 4.4 Hz, 1H), 2.26 – 2.18 (m, 1H), 1.92 – 1.84 (m, 1H), 1.80 – 1.72 (m, 2H), 1.72 – 1.67 (m, 2H), 1.67 – 1.60 (m, 2H), 1.58 (dd, *J* = 5.4, 2.5 Hz, 1H), 1.54 (dd, *J* = 7.1, 2.0 Hz, 1H), 1.39 (ddd, *J* = 17.1, 10.4, 3.2 Hz, 2H), 1.29 (s, 3H), 1.25 (s, 1H), 1.21 (s, 1H), 1.17 (d, *J* = 6.7 Hz, 3H), 1.14 (dd, *J* = 6.8, 2.6 Hz, 1H), 1.00 (t, *J* = 5.5 Hz, 3H), 0.96 (d, *J* = 6.6 Hz, 3H);

^{13}C NMR (75 MHz, $CDCl_3$): δ 81.28, 73.19, 71.37, 54.02, 51.63, 46.87, 45.90, 40.93, 29.93, 29.81, 23.67, 23.30, 21.37, 21.25, 19.97;

IR (neat) (cm^{-1}) $\tilde{\nu}_{max}$: 3420, 2960, 2934, 2872, 1508, 1463, 1376, 1218, 1145, 1106, 1036, 902, 852, 789, 675, 635, 564, 471;

HRMS (*m/z*): calcd for $C_{15}H_{28}NaO_3$ $(M+Na)^+$ 279.193, found 279.1931.



Compound 160: Compound **145** (0.025 g, 0.112 mmol) and $Co(acac)_2$ (0.006 g, 0.022 mmol) were dissolved in THF (1.2 mL), and the solution was cooled to 0 °C. Oxygen was bubbled through the solution for 2 h, and $PhSiH_3$ (0.055 mL, 0.448 mmol) was added afterwards. The reaction was stirred 18 h at room temperature in the presence of Oxygen balloon. Then the reaction was diluted with EtOAc and filtered through the silica gel. The solvent was removed and the crude was purified by column chromatography gave **160** in 62% yield (0.0165 g).

Physical state: white solid;

TLC: R_f = 0.21 (hexanes/EtOAc 1:1, stains deep brown with vanillin);

M.P.: 96 °C;

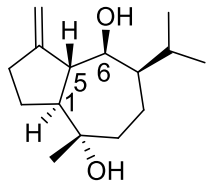
$[\alpha]_D^{25}$: n.d.;

^{1}H NMR (300 MHz, $CDCl_3$): δ 3.99 (d, *J* = 3.4 Hz, 1H), 2.59 (t, *J* = 9.1 Hz, 1H), 2.52 – 2.22 (m, 2H), 2.19 – 2.08 (m, 1H), 2.05 – 1.94 (m, 2H), 1.90 – 1.81 (m, 2H), 1.68 (dd, *J* = 15.7, 6.6 Hz, 2H), 1.53 – 1.28 (m, 3H), 1.25 (s, 3H), 1.16 (dd, *J* = 14.8, 8.2 Hz, 1H), 0.96 (dd, *J* = 9.9, 6.6 Hz, 6H);

^{13}C NMR (75 MHz, $CDCl_3$): δ 225.01, 71.6, 54.95, 51.07, 47.11, 46.63, 37.58, 29.66, 28.90, 23.84, 21.82, 21.41, 21.11, 20.26;

IR (neat) (cm^{-1}) $\tilde{\nu}_{max}$: n.d;

HRMS (*m/z*): calcd for $C_{14}H_{25}O_3$ $(M+H)^+$ 241.173, found 241.1731



Compound 161: To a suspension of Mg (0.0192 g, 0.8 mmol), $TiCl_4$ (0.022 mL, 0.2 mmol) in DCM (0.4 mL) at 0 °C was added over a 2 min of **160** (0.024 g, 0.1 mmol) in mixture of DCM: THF (0.3 mL: 0.2 mL). After being stirred for 1.5 h at the same temperature, quenched with aq. K_2CO_3 (1 mL). The resulting mixture was extracted with EtOAc (5 mL) followed by washed with brine. The solution was dried, filtered and concentrated under reduced pressure. The crude was purified by column chromatography (hexanes: EtOAc- 5:1) gave **161** in 48% yield (0.012 g).

Physical state: colorless oil;

TLC: R_f = 0.39 (hexanes/EtOAc 7:1, stains deep blue with vanillin);

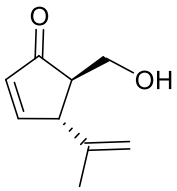
$[\alpha]_D^{25}$: n.d.;

^{1}H NMR (300 MHz, $CDCl_3$): δ 5.10 (s, 1H), 4.91 – 4.86 (m, 1H), 3.82 (dd, *J* = 7.8, 3.6 Hz, 1H), 2.67 (ddd, *J* = 10.1, 7.9, 2.2 Hz, 1H), 2.34 (dd, *J* = 15.3, 7.4 Hz, 1H), 2.28 – 2.16 (m, 1H), 1.89 – 1.82 (m, 2H), 1.78 – 1.69 (m, 2H), 1.69 – 1.59 (m, 3H), 1.50 – 1.43 (m, 2H), 1.42 – 1.30 (m, 3H), 1.20 (s, 3H), 0.97 (dd, *J* = 6.6, 3.0 Hz, 6H);

^{13}C NMR (75 MHz, $CDCl_3$): δ 156.81, 105.39, 75.60, 72.19, 51.07, 50.4, 48.59, 46.58, 33.45, 29.99, 29.91, 26.82, 21.39, 21.22, 20.4;

IR (neat) (cm^{-1}) $\tilde{\nu}_{max}$: n.d.;

HRMS (*m/z*): calcd for $C_{15}H_{27}O_2$ $(M+H)^+$ 239.193, found 239.1931.



Compound 165: To a suspension of CuI (4.53 g, 23.87 mmol, 1.623 equiv) in THF (140 mL) was added isopropenyl magnesiumbromide (0.6.M in THF, 39.8 ml, 23.87 mmol, 1.623 equiv) dropwise at -78 °C. The solution was allowed to warm up to -45 °C upon which a solution of (*S*)**-134** (3 g, 14.7 mmol, 1 equiv) in THF (36 mL) was added. After 10 min of stirring, the resulting solution was again cooled to -78 °C and HCHO (generated from 13.674 g, 441 mmol, 30 eq. of paraformaldehyde at 150°C) was passed through the above reaction mixture until disappearance of the starting material. Upon which the reaction was quenched with sat.NH_4Cl solution. Aqueous layer was extracted with ether (4×150 mL). The combined organic phases were washed with brine (200 mL), dried (Na_2SO_4) and the solvent was

removed under reduced pressure. The crude was purified by flash chromatography on silica (hexanes/ EtOAc 5:1 to 2:1) to give compound **165** in 66% yield (1.48 g).

Physical state: deep yellow oil;

TLC: R_f = 0.23 (hexanes/ EtOAc 3:1, UV-active, stains dark green with vanillin);

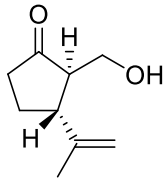
$[\alpha]_D^{25}$**:** 144.46 (c 1.00, $CHCl_3$);

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.64 (dd, *J* = 5.7, 2.4 Hz, 1H), 6.23 (dd, *J* = 5.7, 2.1 Hz, 1H), 4.93 – 4.83 (m, 1H), 4.81 (d, *J* = 0.5 Hz, 1H), 3.99 (dd, *J* = 10.7, 5.2 Hz, 1H), 3.83 – 3.65 (m, 1H), 3.38 (dd, *J* = 4.6, 2.3 Hz, 1H), 2.48 (s, 1H), 2.34 (ddd, *J* = 6.4, 4.7, 3.0 Hz, 1H), 1.73 (dt, *J* = 20.4, 10.2 Hz, 3H);

^{13}C NMR (75 MHz, $CDCl_3$): δ 211.27, 166.90, 144.04, 133.60, 112.84, 61.78, 52.82, 51.25, 20.46;

IR (neat) (cm^{-1}) ν_{max}: 3418, 1691, 1511, 1057, 895;

HRMS (*m/z*): calcd for $C_9H_{13}O_2$ $(M+H)^+$ 153.0910, found 153.0908.



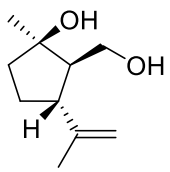
Compound 178: To a solution of **165** (2.28 g, 15.0 mmol) in $CHCl_3$ (120 ml) was added Ph_2SiH_2 (4.8 ml, 25.5 mmol, 1.7 equiv), $ZnCl_2$ (1.06 g, 7.8 mmol, 0.52 equiv) followed by $Pd(PPh_3)_4$ (225 mg, 0.2 mmol, 0.015 equiv). The resulting deep green colored mixture was stirred at room temperature for 30 min. The solvent was removed under reduced pressure and the crude was purified by flash column chromatography (hexanes/ EtOAc 5:1), **178** was obtained in 75% yield (1.74 g).

Physical state: deep brown oil;

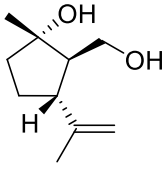
$[\alpha]_D^{23}$= 72.72 (c 1.00, $CHCl_3$);

^{1}H NMR (300 MHz, $CDCl_3$) δ = 4.88 – 4.86 (m, 1H), 4.84 (d, *J*=0.6 Hz, 1H), 3.84 (dd, *J*=11.3, 4.2 Hz, 1H), 3.65 (dd, *J*=11.3, 6.2 Hz, 1H), 2.66 (td, *J*=11.9, 5.8 Hz, 1H), 2.50 – 2.40 (m, 1H), 2.31 (dddd, *J*=11.9, 5.8, 3.9, 1.3 Hz, 2H), 2.23 – 2.08 (m, 2H), 1.77 (s, 3H), 1.74 – 1.64 (m, 1H);

^{13}C NMR (75 MHz, $CDCl_3$) δ = 221.01, 144.63, 111.83, 60.51, 54.07, 46.37, 38.04, 26.63, 19.37.



syn-diol



anti-diol

Compound 179: $CeCl_3.7H_2O$ (18.5 g, 49.8 mmol, 4.058 equiv) was placed in 500 mL three-necked flask and heated at 140^o in *vacuo* (0.1 mmHg) for 3 h, and then cooled to room temperature. THF (75 mL) was added, and the suspension was stirred at room temperature for 2.5 h under N_2 atmosphere. The resulting suspension was cooled to -78^{o}C, and methyl lithium (1.6 M in Et_2O, 30 ml, 49.2 mmol, 4.06 equiv) was added. The resulting pale brown colored mixture was stirred for 30 min, ketone **178** (1.88 g, 12.27 mmol, 1 equiv) in THF (45 mL) was

added dropwise, and the mixture stirred for a further 4 h at -78 °C. The reaction mixture was treated with a saturated solution of NH_4Cl, filtered through Celite and extracted with EtOAc (4×150 mL). The combined organic layers were dried (Na_2SO_4) and concentrated under reduce pressure. The crude was purified by flash column chromatography (hexanes/ EtOAc 7:1 to 3:1) to give **179a**-*syn* diol (1.48 g, 70%) **179b-***anti* diol (330 mg, 15%) as white solids.

Syn diol: **179a**

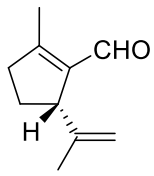
^{1}H NMR (300 MHz, $CDCl_3$) δ = 4.76 (s, 1H), 4.74 – 4.71 (m, 1H), 3.88 (dd, *J*=11.3, 3.1 Hz, 1H), 3.73 – 3.65 (m, 1H), 2.89 – 2.81 (m, 1H), 2.78 (d, *J*=4.8 Hz, 2H), 1.92 (dtd, *J*=12.6, 8.1, 6.1 Hz, 1H), 1.77 – 1.69 (m, 2H), 1.68 (s, 3H), 1.56 (ddd, *J*=10.9, 4.8, 3.3 Hz, 1H), 1.52 – 1.43 (m, 1H), 1.38 (s, 3H);

^{13}C NMR (75 MHz, $CDCl_3$) δ = 146.93, 110.67, 81.58, 60.75, 52.44, 46.86, 41.52, 28.34, 27.94, 19.28. Data was in accordance with literature.

Anti diol: **179b**

^{1}H NMR (300 MHz, $CDCl_3$) δ = 4.71 (s, 1H), 4.69 (dd, *J*=3.0, 1.6 Hz, 1H), 3.71 (dd, *J*=10.7, 4.7 Hz, 1H), 3.67 – 3.57 (m, 1H), 2.40 (s, 2H), 2.24 – 2.06 (m, 2H), 1.87 – 1.73 (m, 2H), 1.72 (s, 3H), 1.70 – 1.55 (m, 2H), 1.29 (s, 3H);

^{13}C NMR (75 MHz, $CDCl_3$) δ = 146.84, 110.74, 80.62, 63.13, 53.04, 47.50, 40.27, 26.94, 23.05, 18.75. Data was in accordance with literature.



Compound 164: To a solution of DMSO (3.06 g, 2.78 ml, 39 mmol, 5.27 equiv) in CH_2Cl_2 (16 mL) was added oxalyl chloride (1.66 ml, 20 mmol, 2.702 equiv) at -78° C. The resulting mixture was stirred at this temperature for 30 min and solution of **179a**-*syn* diol (1.258 g, 7.4 mmol, 1 equiv) in CH_2Cl_2 (10 mL) was added over 30 min. The resulting mixture was stirred for 3 h, Et_3N (11.8 mL, 84.32 mmol, 11.395 equiv) was added and the mixture was warmed to room temperature. The resulting mixture was diluted with cold water followed by extraction with DCM (4×50 mL). The combined organic layers were washed with brine (100mL) and dried. The solvent was removed under reduced pressure to give crude, which was purified by flash column chromatography (hexanes/ EtOAc 5:1) to give **164** in 52% yield (0.58 g).

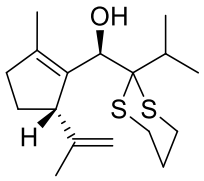
Physical state: deep pink color oil;

R_f = 0.75 (hexanes/ EtOAc 3:1, stains deep blue with vanilin);

$[\alpha]_D^{23}$= 58.7 (c 1, $CHCl_3$). (lit $[\alpha]_D^{23}$= 56.1 c 1, $CHCl_3$);

^{1}H NMR (300 MHz, $CDCl_3$) δ = 9.97 (s, 1H), 4.71 – 4.68 (m, 1H), 4.63 – 4.59 (m, 1H), 3.61 (d, *J*=9.3 Hz, 1H), 2.62 (dt, *J*=17.9, 8.2 Hz, 1H), 2.52 – 2.38 (m, 1H), 2.18 (d, *J*=1.2 Hz, 3H), 2.14 – 2.02 (m, 2H), 1.68 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ = 188.00, 163.74, 146.8, 139.13, 109.73 50.74, 39.43, 28.55, 20.48, 14.56. Data was in accordance with literature.



Compound 187: Under nitrogen atmosphere to a solution of 2-Isopropyl-1,3-dithinae (0.5 g, 2.975 mmol, 0.649 equiv) in THF (8.5 mL) was added dropwise n-BuLi (1.44 M, 3.15 mL, 4.533 mmol, 0.990 equiv) at -25 °C. The resultant clear solution was stirred at the same temperature for 2 h. After cooling down to -78° C, aldehyde **164** (0.687 g, 4.58 mmol, 1 equiv) in THF (3 mL) was added dropwise. The reaction mixture was stirred for 1 h, then quenched with saturated solution of NH_4Cl and warmed to ambient temperature. The layers were separated and aqueous layer was extracted with ether (3×50 mL). The combined organic layers were washed with brine (50 mL), dried (Na_2SO_4), filtered and concentrated under *vacuo*. The crude was purified by flash column chromatography (hexanes/ EtOAc 99.5:0.5 to 98:2) to give **187** in 70% yield (1.0 g).

Physical state: colorless syrup;

R_f = 0.64 (hexanes/ EtOAc 10:1, stains deep blue with vanilin);

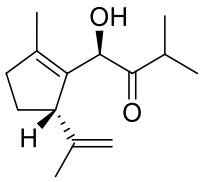
$[\alpha]_D^{23}$= 62.5 (c 0.85, $CHCl_3$);

^{1}H NMR (300 MHz, $CDCl_3$) δ = 4.92 (d, *J*=7.4 Hz, 2H), 4.78 – 4.71 (m, 1H), 4.00 (d, *J*=8.7 Hz, 1H), 2.97 (ddd, *J*=14.1, 9.0, 4.0 Hz, 1H), 2.89 – 2.81 (m, 2H), 2.79 – 2.71 (m, 2H), 2.50 – 2.30 (m, 2H), 2.20 (dd, *J*=16.3, 9.9 Hz, 1H), 2.12 – 2.02 (m, 1H), 1.93 (dd, *J*=12.0, 6.0 Hz, 2H), 1.80 – 1.74 (m, 6H), 1.63 – 1.57 (m, 1H), 1.24 (d, *J*=6.9 Hz, 3H), 1.14 (d, *J*=6.8 Hz, 3H);

^{13}C NMR (75 MHz, $CDCl_3$) δ = 152.42, 141.08, 134.28, 110.13, 74.66, 64.67, 53.74, 37.36, 35.16, 29.41, 26.43, 26.43, 24.41, 20.16, 19.11, 18.51, 15.17;

IR (neat) (cm^{-1}) νmax: 3539, 2922, 1637, 1436, 1380, 1017, 894, 803;

HRMS (ESI): calcd for $C_{17}H_{29}OS_2$ $(M+H)^+$ 313.1654, found 313.1653.



Compound 163: The α–hydroxydithiane **187** (1.079 g, 3.46 mmol) was dissolved in acetonitrile (5 mL) and was added at once to a well stirred solution of NCS (1.40 g, 10.4 mmol, 3 equiv) and $AgNO_3$ (2.05 g, 12.1 mmol, 3.497 equiv) in 50 mL of 90% aq.MeCN at 0 °C, stirring was continued for 30 min at the same temperature and then treated with sat.$Na_2S_2O_3$ solution (25 mL). The reaction mixture was extracted with ether (2×100 mL), then combined organic layers were washed with aq.Na_2CO_3 (50 mL), water (50 mL) and brine (50 mL), dried, filtered and concentrated under *vacuo*.

The crude was purified by flash column chromatography on silica (hexanes/ EtOAc 98:2) to give **163** in 75% yield (0.58 g).

Physical state: pale red color oil;

R_f = 0.36 (hexanes/ EtOAc 10:1, stains blue with vanilin);

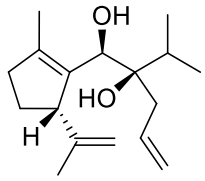
$[\alpha]_D^{23}$= 405.1 (c 0.52, $CHCl_3$);

^{1}H NMR (300 MHz, $CDCl_3$) δ = 5.06 (s, 1H), 4.67 (d, *J*=1.5 Hz, 1H), 4.61 (dd, *J*=2.1, 1.4, Hz 1H), 3.46 (s, 1H), 3.08 (d, *J*=9.2 Hz, 1H), 2.74 – 2.62 (m, 1H), 2.48 (dtd, *J*=10.0, 7.6, 1.1 Hz, 1H), 2.33 – 2.21 (m, 1H), 2.05 – 1.93 (m, 1H), 1.85 (d, *J*=1.2 Hz, 3H), 1.70 (ddd, *J*=8.3, 4.4, 2.1 Hz, 1H), 1.65 (s, 3H), 1.11 – 1.05 (m, 6H);

^{13}C NMR (75 MHz, $CDCl_3$) δ = 214.24, 149.62, 142.41, 132.19, 110.52, 72.94, 54.79, 37.90, 35.99, 28.33, 19.59, 18.21, 17.80, 14.42;

IR (neat) (cm^{-1}) ν_{max}: 3540, 2970, 2936, 1712, 1382, 1005, 884;

HRMS (EI-MS): calcd for $C_{14}H_{23}O_2$ $(M+H)^+$ 223.1693, found 223.1693.



Compound 188: Under nitrogen atmosphere to a solution of α–hydroxyketone **163** (475 mg, 2.14 mmol, 1 equiv) in THF (38 mL) was added a solution of allyl magnesiumbromide (0.55 M in Et_2O, 15.56 mL, 3.21 mmol, 1.5 equiv) at 0 °C, and was stirred at the same temperature for 1.5 h. The reaction mixture was quenched with saturated solution of NH_4Cl. The layers were separated and the aqueous layer was extracted with ether (2×50 mL). The combined organic extracts were washed with brine (50 mL) and dried. The solvent was removed under reduce pressure. The crude was purified by flash column chromatography (hexanes/ EtOAc 10:1) to give **188** in 72% yield (0.41 g).

Physical state: light red color oil;

R_f= 0.41 (hexanes/ EtOAc 7:1, stains blue with vanilin);

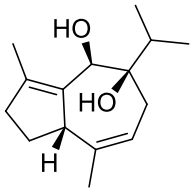
$[\alpha]_D^{23}$= 72.9 (c 0.48, $CHCl_3$);

^{1}H NMR (300 MHz, $CDCl_3$) δ = 6.03 (dqd, *J*=20.7, 10.4, 7.6 Hz, 1H), 5.17 – 5.00 (m, 2H), 4.83 (d, *J*=2.3 Hz, 1H), 4.69 (dd, *J*=2.4, 1.3 Hz, 1H), 4.54 (d, *J*=5.8 Hz, 1H), 3.68 (d, *J*=9.0 Hz, 1H), 2.44 – 2.34 (m, 3H), 2.26 – 2.11 (m, 2H), 2.06 – 1.94 (m, 1H), 1.80 – 1.72 (m, 6H), 1.62 – 1.53 (m, 1H), 1.29 – 1.24 (m, 1H), 0.99 (d, *J*=6.9 Hz, 3H), 0.90 – 0.85 (m, 1H), 0.83 (dd, *J*=6.7, 3.4 HZ, 3H);

^{13}C NMR (75 MHz, $CDCl_3$) δ = 152.70, 140.10, 135.77, 134.55, 117.5, 109.62, 77.99, 73.55, 53.66, 39.31, 37.31, 33.75, 29.19, 20.22, 17.48, 14.85;

IR (neat) (cm^{-1}) ν_{max}: 3547, 2939, 1638, 1439, 1371, 1059, 1371, 998, 893;

HRMS (EI-MS): calcd for $C_{17}H_{29}O_2$ $(M+H)^+$ 265.2162, found 265.2164.



Compound 189: A flask containing diol **188** (400 mg, 1.515 mmol, 1 equiv) was outfitted with a reflux condenser and evacuated and backfilled with dry N_2. DCM (100 mL) was added, and the solution was heated to reflux. A solution of Grubbs-II catalyst (66 mg, 0.0778 mmol, 0.117 equiv) in DCM (6.6 mL) was added to the reaction mixture, and the light brown color mixture was refluxed further for 3 h. The solvent was removed under reduced pressure and crude was purified by flash chromatography (hexanes/ EtOAc 5:1) to give **189** in 95% yield (0.34 g).

Physical state: Pale brown color oil;

R_f= 0.25 (hexanes/ EtOAc 5:1, stains deep blue with vanilin);

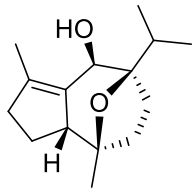
$[\alpha]_D^{23}$= 90.0 (c 1.07, $CHCl_3$);

^{1}H NMR (300 MHz, Acetone) δ = 5.37 – 5.29 (m, 1H), 4.43 (s, 1H), 3.72 (d, *J*=4.2 Hz, 1H), 3.24 (t, *J*=9.1 Hz, 1H), 2.33 (dd, *J*=5.1, 1.9 Hz, 1H), 2.28 (dt, *J*=3.7, 2.6 Hz, 1H), 2.18 – 2.09 (m, 1H), 2.06 (dd, *J*=4.5, 2.3 Hz, 1H), 2.03 – 1.96 (m, 3H), 1.89 (dd, *J*=1.9, 1.0 Hz, 3H), 1.79 – 1.74 (m, 1H), 1.72 (d, *J*=1.0 Hz, 3H), 1.06 (d, *J*=6.8 Hz, 3H), 0.91 – 0.86 (m, 3H);

^{13}C NMR (75 MHz, Acetone) δ = 141, 137.53, 134.16, 121, 81.75, 78.29, 53.40, 38.93, 35.98, 32.98, 29.75, 23.81, 18.72, 18.64, 15.81;

IR (neat) (cm^{-1}) νmax: 3472, 2961, 2914, 1741, 1445, 1373, 1072, 1013;

HRMS (EI-MS): calcd for $C_{15}H_{25}O_2$ $(M+H)^+$ 237.1849, found 237.1843.



Compound 192: Under nitrogen atmosphere to a solution of diol **189** (182 mg, 0.771 mmol, 1 equiv) in DCM (38 mL) was added Hg $(OAc)_2$ (302.5 mg, 0.951 mmol, 1.233 equiv) at room temperature .The reaction mixture was stirred for 15 h. To this resultant mixture was added water and extracted with ether (4×50 mL). The combined organic layers were washed with water (100 mL), brine (100 mL), dried (Na_2SO_4) and filtered. The solvent was removed under reduced pressure to give crude **162**. This was used for the next step without further purification.

To the above crude **162** in dry MeOH (23 mL), was added $NaBH_4$ (500 mg, 5.11 mmol) at -78 ^oC. The resulting mixture was warmed to room temperature and stirred for 3 h. The reaction mixture was treated with water, extracted with EtOAc (2×100 mL). The combined organic layers were washed with brine (50 mL), water (50 mL), dried and filtered. The crude was concentrated under reduced pressure and purified by flash chromatography (hexanes/ EtOAc 3:1) to give **192** in 62% yield (0.11 g).

Physical state: colorless oil;

R_f = 0.6 (hexanes/ EtOAc 5:1, stains blue with vanilin);

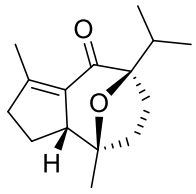
$[\alpha]_D^{23}$= 38.2 (c 0.25, $CHCl_3$);

^{1}H NMR (300 MHz, $CDCl_3$) δ = 4.44 (s, 1H), 2.68 (t, *J*=7.5 Hz, 1H), 2.26 (dt, *J*=24.9, 11.3 Hz, 2H), 1.94 (dd, *J*=13.1, 6.2 Hz, 1H), 1.89 (s, 3H), 1.85 – 1.74 (m, 2H), 1.73 – 1.59 (m, 2H), 1.51 (d, *J*=4.3 Hz, 1H), 1.36 – 1.23 (m, 2H), 1.19 (d, *J*=4.7 Hz, 3H), 1.03 (t, *J*=6.9 Hz, 6H);

^{13}C NMR (75 MHz, $CDCl_3$) δ = 133.49, 133.01, 86.66, 84.41, 73.89, 57.59, 39.05, 31.74, 31.68, 28.61, 24.00, 23.97, 18.12, 17.26, 14.64;

IR (neat) (cm^{-1}) ν_{max} = 3490, 2965, 2932, 2878, 1470, 1375, 1176, 1072, 1013, 901;

HRMS (EI-MS): calcd for 237.1849 $(M+H)^+$, found 237.1852.



Compound 194: Under nitrogen atmosphere to a solution of alcohol **192** (185 mg, 0.783 mmol, 1 equiv) in DCM (38 mL) was added Dess-Martin periodinane (370 mg, 0.870 mmol, 1.12 equiv) at 0^o C. The resulting mixture was warmed to ambient temperature and stirred for 1 h, then treated with saturated $Na_2S_2O_3$ solution (20 mL), followed by addition of sat. $NaHCO_3$ solution (20 mL) after 15 min. The resultant mixture was stirred for additional 15 min. The organic layer was separated and the aqueous layer was extracted with DCM (3×100 mL). The combined organic layers were washed with water (100 mL), brine (100 mL), dried over Na_2SO_4. The solvent was removed under reduced pressure, to give enone **194**, which was used for the next step without further purification (0.36 g, 98%).

R_f= 0.87 (hexanes/ EtOAc 5:1, stains brown with vanilin);

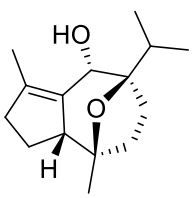
$[\alpha]_D^{23}$= -1.4 (c 0.47, $CHCl_3$);

^{1}H NMR (300 MHz, $CDCl_3$) δ = 3.22 (s, 1H), 2.59 – 2.42 (m, 1H), 2.35 – 2.23 (m, 1H), 2.16 (dt, *J*=13.7, 6.9 Hz, 1H), 2.08 (dd, *J*=3.3, 2.3 Hz, 3H), 2.05 – 1.85 (m, 3H), 1.68 – 1.61 (m, 1H), 1.54 – 1.35 (m, 2H), 1.33 (s, 3H), 1.03 (dd, *J*=6.9, 2.0 Hz, 6H);

^{13}C NMR (75 MHz, $CDCl_3$) δ = 199.88, 154.45, 131.90, 91.07, 84.39, 57.90, 38.86, 33.27, 30.57, 30.04, 25.98, 24.61, 18.41, 17.30, 15.96;

IR (neat) (cm^{-1}) ν_{max}= 2965, 2877, 1689, 1625, 1375, 1268, 1077, 1004, 883;

HRMS (EI-MS): calcd for $C_{15}H_{23}O_2$ $(M+H)^+$ 235.1693, found 235.1696.



Orientalol-F 78: Under nitrogen atmosphere to a stirred solution of crude **194** (81 mg, 0.346 mmol, 1 equiv) and $CeCl_3{\cdot}7H_2O$ (260 mg, 0.696 mmol, 2.011 equiv) in MeOH (10 mL) was added $NaBH_4$ (26.2 mg, 0.696 mmol, 2.011 equiv) at 0 ^{o}C. The mixture was stirred at room temperature for 20 h, then quenched by addition of water and extracted with EtOAc (2×50 mL). The combined organic layers were washed

with water (25 mL), brine (25 mL), dried, filtered and concentrated under reduce pressure. The crude was purified by flash chromatography (hexanes/ EtOAc 5:1) gave **78** (Orientalol-F) in 94% yield (0.076 g).

Physical state: pale yellow oil;

R_f= 0.6 (hexanes/ EtOAc 5:1, stains blue with vanilin);

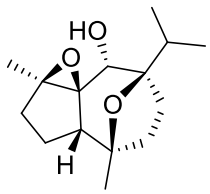
$[\alpha]_D^{23}$= 12.4 (c .67, DCM). (lit-$[\alpha]_D^{23}$= 12.2 (c 0.5, DCM);

^{1}H NMR (300 MHz, $CDCl_3$) δ = 4.47 – 4.39 (m, 1H), 2.73 – 2.63 (m, 1H), 2.39 – 2.15 (m, 2H), 1.96 (dd, *J*=13.8, 6.9 Hz, 1H), 1.89 (dd, *J*=3.2, 2.3 Hz, 3H), 1.85 – 1.75 (m, 2H), 1.73 – 1.60 (m, 2H), 1.58 – 1.46 (m, 1H), 1.28 (dddd, *J*=10.8, 9.7, 6.5, 2.5 Hz, 2H), 1.21 – 1.18 (m, 3H), 1.03 (t, *J*=6.9 Hz, 6H);

^{13}C NMR (75 MHz, $CDCl_3$) δ = 133.49, 133.0, 86.65, 84.41, 73.89, 57.59, 39.05, 31.73, 31.68, 28.60, 24.03, 23.97, 18.11, 17.26, 14.64;

IR (neat) (cm^{-1}) ν_{max}= 3490, 2965, 2931, 2878, 1469, 1375, 1177, 1072, 1013, 901;

HRMS (EI-MS): calcd for $C_{15}H_{25}O_2$ $(M+H)^+$ 237.1849, found 237.1852. Data was in accordance with literature.



Compound 197: Under nitrogen atmosphere m-CPBA (70%, 252 mg, 1.02 mmol, 1.2 equiv) was added to a stirred solution of **78** (200 mg, 0.85 mmol, 1 equiv) in DCM (4 mL) at 0^o C. The resultant mixture was stirred for 2 h at the same temperature, then quenched with saturated Na_2CO_3 solution (3 mL), and diluted with water (10 mL).The aqueous layer was extracted twice with DCM (2×15 mL). The combined organic extracts were washed with water (10 mL), brine (10 mL) dried and filtered. The solvent was removed under reduced pressure to give **197** as a white crystalline compound. This was used for the recrystallyzation from n-heptane without further purification.

R_f= 0.50 (hexanes/ EtOAc 3:1, stains deep blue with vanilin).

$[\alpha]_D^{23}$= 0.64 (c .36, $CHCl_3$);

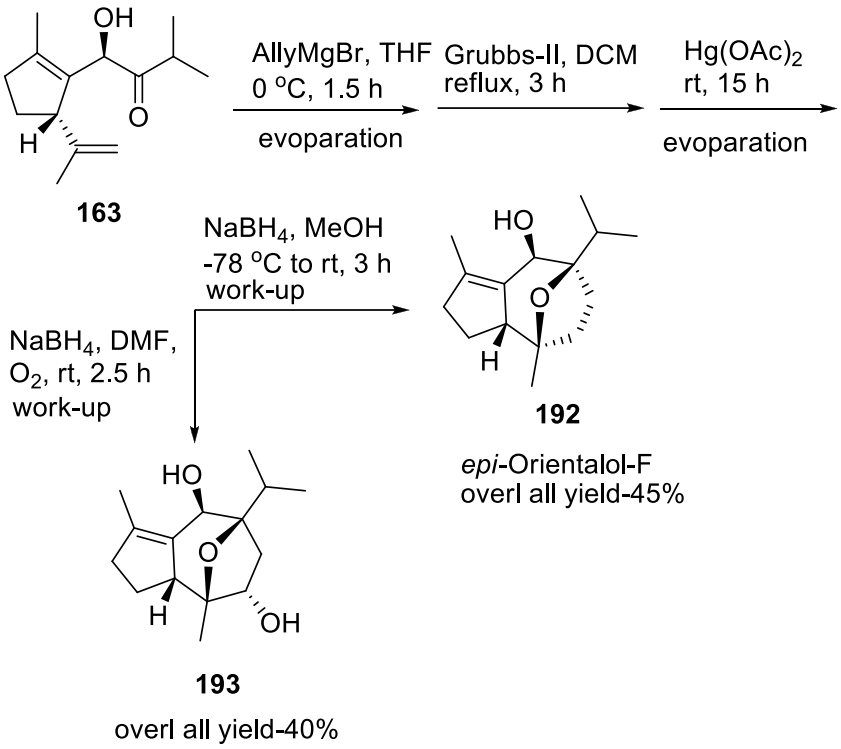
M.P = 68 ^{o}C;

^{1}H NMR (300 MHz, $CDCl_3$) δ = 4.34 (s, 1H), 2.16 (d, *J*=9.4 Hz, 1H), 2.04 – 1.75 (m, 6H), 1.75 – 1.68 (m, 1H), 1.67 (s, 3H), 1.65 – 1.40 (m, 3H), 1.26 (s, 3H), 1.03 (dd, *J*=8.9, 6.9 Hz, 6H);

^{13}C NMR (75 MHz, $CDCl_3$) δ = 86.67, 83.97, 73.55, 72.11, 71.76, 52.07, 34.58, 33.22, 31.99, 28.85, 24.54, 21.5, 17.81, 17.53, 16.72;

IR (neat) (cm^{-1}) ν_{max}= 3406, 2970, 2895, 1474, 1375, 1085, 1005, 888, 722;

HRMS (EI-MS): calcd for $C_{15}H_{25}O_3$ $(M+H)^+$ 253.1798, found 253.1797.



Under N_2 atmosphere allyl magnesiumbromide (0.55 M in Et_2O, 15.56 mL, 3.21 mmol, 1.5 equiv) was added to a solution of **163** (475 mg, 2.14 mmol, 1 equiv) in THF (38 mL) at 0 °C and stirring was continued for 1.5 h at the same temperature. The solvent was removed under reduced pressure, then dry DCM (100 mL) was added to this residue followed by addition Grubbs-II catalyst (66 mg, 0.0778 mmol, 0.117 equiv) in CH_2Cl_2 (6.6 mL) at room temperature. The resultant brown colored solution was refluxed for 3 h, to this solution was added Hg $(OAc)_2$ (520 mg, 1.622 mmol, 2.1 equiv) at ambient temperature. The resultant mixture was stirred for 15 h at the same temperature, and then quenched by addition of brine (75 mL). The aqueous layer was removed with pipette, and the resultant organic phase was concentrated in *vacuo.* To this residue in dry MeOH (50 mL) was added $NaBH_4$ (1 g, 10.2 mmol) at -78 °C. The reaction mixture was stirred at room temperature for 3 h, then the reaction was quenched with water, and extracted with EtOAc (4 X 50 mL). The combined organic layers were washed with brine (50 mL), water (50 mL) dried, filtered and concentrated in *vacuo.* The crude was purified by flash chromatography on silica (hexanes/ EtOAc 3:1) to give **192** (0.23 g, 45%) as colorless oil.

Oxygen was bubbled through the solution of $NaBH_4$ (210 mg, 5.55 mmol) in dry DMF (20 mL) for 45 min at room temperature, at which point suspension of residue (the crude obtained after

oxymercuration step from the above procedure) in dry DMF (20 mL) was introduced dropwise with syringe pump with continuous oxygen bubbling during 1 h. Upon, completion of the addition the resulting mixture was stirred with continuous oxygen bubbling at the same temperature for 30 min, and the reaction mixture was filtered through Celite pad, and washed celite pad with EtOAc, combined organic phases were washed with water, dried, filtered and concentrated in *vacuo.* The crude was purified by flash chromatography (hexanes/ EtOAc 3:1 to 1:1) to give **193** (0.22 g, 40%) as white color powder.

R_f= 0.25 (hexanes/ EtOAc 5:1, stains deep blue with vanilin).

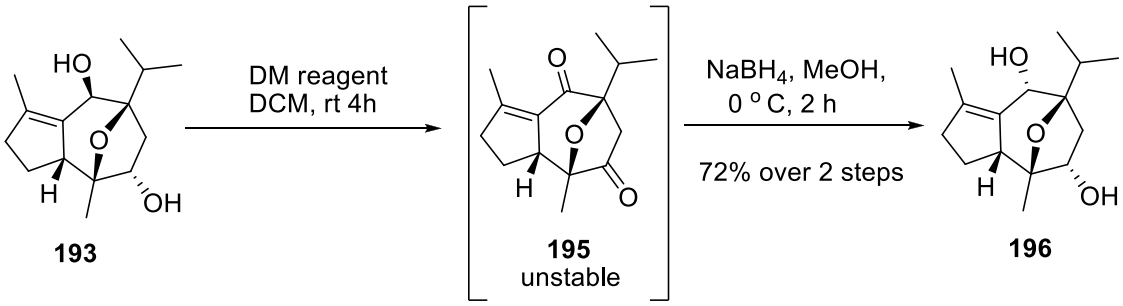
$[\alpha]_D^{23}$= 11.8 (c .49, CH_2Cl_2);

^{1}H NMR (300 MHz, $CDCl_3$) δ 4.39 (s, 1H), 3.93 (t, *J* = 6.7 Hz, 1H), 2.78 – 2.64 (m, 1H), 2.43 – 2.19 (m, 3H), 2.01 – 1.93 (m, 1H), 1.86 (d, *J* = 6.6 Hz, 3H), 1.64 – 1.49 (m, 3H), 1.37 (d, *J* = 8.7 Hz, 1H), 1.33 – 1.25 (m, 1H), 1.19 (s, 3H), 1.06 (dd, *J* = 6.9, 3.4 Hz, 6H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 133.7, 132.2, 86.8, 85.6, 73.5, 73.4, 56.1, 40.5, 38.9, 30.9, 23.6, 18.8, 17.8, 17.2, 14.6;

IR (neat) (cm^{-1}) ν_{max}= 3490, 3398, 2965, 2931, 2878, 1469, 1375, 1181, 1031, 901;

HRMS (EI-MS): calcd for $C_{15}H_{24}O_3$ $(M+H)^+$ 252.1726, found 253.173.



Under nitrogen atmosphere to a solution of diol **193** (252 mg, 1 mmol, 1 equiv) in DCM (20 mL) was added Dess-Martin periodinane (1.272 g, 3 mmol, 3 equiv) at 0° C. The resulting mixture was stirred for 4 h at the room temperature, then quenched with saturated $Na_2S_2O_3$ solution (40 mL) followed by addition of sat.$NaHCO_3$ solution (40 mL) after 15 min. The resulting mixture was stirred for additional 15 min. The organic layer was separated and the aqueous layer was extracted with DCM (3×100 mL). The combined organic layers were washed with water (100 mL), brine (100 mL), and dried over Na_2SO_4. Solvent was removed in *vacuo*, to give di ketone **195**, which was unstable at room temperature.

To a solution of the above crude di ketone **195** in dry MeOH (15 mL) was added $NaBH_4$ (38 mg, 1 mmol, 1 equiv) at 0 °C. After 30 min of stirring at the same temperature, the reaction mixture was quenched with saturated aq. NH_4Cl and extracted twice with EtOAc (20 mL). The combined organic phases were washed with brine and dried over Na_2SO_4. The residue was concentrated in *vacuo* and the crude was purified by flash chromatography (hexanes/ EtOAc 3:1 to 1:1) to give **196** as a white color powder in 72% yield (0.18 g).

R_f= 0.25 (hexanes/ EtOAc 5:1, stains deep blue with vanilin).

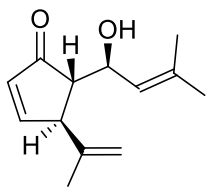
$[\alpha]_D^{23}$= 2.8 (c .49, CH_2Cl_2);

^{1}H NMR (300 MHz, $CDCl_3$) δ (300 MHz, $CDCl_3$) δ 4.55 (s, 1H), 3.95 (dd, *J* = 10.7, 6.2 Hz, 1H), 2.83 (s, 1H), 2.39 (dd, *J* = 10.3, 6.7 Hz, 2H), 2.29 – 2.21 (m, 1H), 2.16 – 2.08 (m, 1H), 2.07 – 1.99 (m, 1H), 1.91 (d, *J* = 5.1 Hz, 3H), 1.89 – 1.76 (m, 2H), 1.66 (dd, *J* = 13.5, 6.2 Hz, 2H), 1.26 (s, 3H), 1.00 (dd, *J* = 7.7, 7.1 Hz, 6H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 133.5, 133.4, 84.8, 81.9, 81.3, 74.1, 57.5, 39.3, 39.0, 31.1, 22.8, 21.6, 17.2, 16.8, 14.6;

IR (neat) (cm^{-1}) ν_{max}= 3490, 3398, 2965, 2931, 2878, 1469, 1375, 1181, 1031, 901;

HRMS (EI-MS): calcd for $C_{15}H_{24}O_3$ $(M+H)^+$ 252.1726, found 253.173.



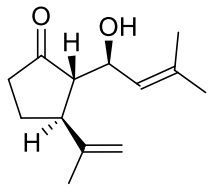
Compound 199: According to general procedure A: To a stirred solution of CuCN (3.12 g, 34.85 mmol, 3.0 equiv) and anhydrous LiCl (2.97 g, 69.69 mmol, 6.0 equiv) in THF (120 mL) was added iso propenylmagnesium bromide (1.18 M solution in THF, 34.85 mmol, 30 mL, 3.0 equiv) dropwise at –40 °C. The reaction mixture was cooled to –78 °C upon which a solution of (*R*)-**125** (2.3 g, 11.61 mmol, 1.0 equiv) in THF (15 mL) was added. After 4 min of stirring, **198** (1.96 g, 19.52 mmol, 1.68 equiv) was added. After the starting material had disappeared, aq. NH_4Cl (100 mL) was added and the reaction mixture was extracted with Et_2O (2x150 mL). The combined organic extracts were dried over Na_2SO_4, filtered and the solvent was removed under reduced pressure. After purification on silica (hexanes/EtOAc 5:1) **199** was obtained in 81% yield (1.95 g).

R_f= 0.33 (hexanes/ EtOAc 5:1, UV-active, stains bluish-green with vanilin).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.51 (dd, *J* = 5.7, 2.5 Hz, 1H), 6.16 (dd, *J* = 5.7, 2.0 Hz, 1H), 5.21 – 5.15 (m, 1H), 4.82 – 4.80 (m, 1H), 4.68 (s, 1H), 4.42 (t, *J* = 8.9 Hz, 1H), 3.69 (s, 1H), 3.14 (dd, *J* = 4.5, 2.2 Hz, 1H), 2.26 (dd, *J* = 8.6, 2.5 Hz, 1H), 1.67 (dd, *J* = 6.4, 1.3 Hz, 6H), 1.62 (s, 3H);

^{13}C NMR (75 MHz, $CDCl_3$) δ 212.4, 167.6, 143.8, 136.7, 133.2, 125.1, 113.4, 69.2, 55.4, 52.0, 25.7, 20.2, 18.5;

HRMS (EI-MS): calcd for $C_{13}H_{18}O_2Na$ $(M+Na)^+$ 229.1307, found 229.1310.



Compound 200: To a solution of α,β–unsaturated compound **199** (0.15 g, 0.728 mmol) in $CHCl_3$ (6 mL) was added Ph_2SiH_2 (0.23 ml, 1.24 mmol, 1.7 equiv), $ZnCl_2$ (0.051 g, 0.38 mmol, 0.52 equiv) and Pd $(PPh_3)_4$ (0.011 g, 0.011 mmol, 0.015 equiv). The mixture was stirred at room temperature for 3 h. The solvent was removed under reduced pressure, the crude was purified by flash column chromatography (hexanes/ EtOAc 5:1) to give **200** as pale brown oil in 28% yield (0.043 g).

To a solution of α,β–unsaturated compound **199** (0.029 g, 0.14 mmol) in THF (0.5 mL) was added Bu_3SnH (0.08 ml, 0.28 mmol, 2.0 equiv), $ZnCl_2$ (0.042 g, 0.308 mmol, 2.2 equiv) and Pd $(PPh_3)_4$ (0.005 g, 0.0042 mmol, 0.03 equiv). The mixture was stirred at room temperature for 3 h. The solvent was removed under reduced pressure, the crude was purified by flash column chromatography on silica (hexanes/ EtOAc 5:1) to give **200** as pale brown oil in 30% yield (0.045 g).

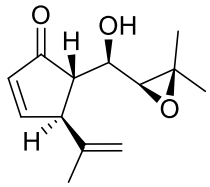
To a suspension of $LiAlH_4$ (0.332 g, 8.73 mmol) in THF (38 mL) at -78 °C was added CuI (1.66 g, 8.73 mmol) dissolved in THF: DMPU (4:1, 38 mL). The resulting mixture was stirred for 1 h at the sma temperature, and then added **199** (1.8 g, 8.73 mmol) in THF (4 mL). After stirring 2 h at -78 °C, the mixture was quenched with aq. NH_4Cl (50 mL) followed by ether (100 mL). The aqueous layer was extracted twice with Et_2O. The combined organic extracts were washed with brine, dried, filtered and concentrated under reduced pressure gave crude. The crude was purified by flash chromatography (hexanes/ EtOAc 3:1) gave **200** in 82% yield (1.5 g).

R_f= 0.25 (hexanes/ EtOAc 5:1, stains brown with vanilin).

^{1}H NMR (300 MHz, $CDCl_3$) δ 5.36 – 5.28 (m, 1H), 4.82 – 4.77 (m, 2H), 4.47 (ddd, *J* = 9.0, 6.0, 2.8 Hz, 1H), 3.12 (d, *J* = 3.3 Hz, 1H), 2.69 (td, *J* = 11.1, 6.6 Hz, 1H), 2.46 – 2.36 (m, 1H), 2.33 – 2.18 (m, 2H), 2.10 – 2.03 (m, 1H), 1.73 (s, 3H), 1.72 – 1.70 (m, 1H), 1.66 (dd, *J* = 9.7, 1.3 Hz, 6H);

^{13}C NMR (75 MHz, $CDCl_3$) δ 221.2, 145.5, 135.9, 124.9, 111.6, 68.4, 57.2, 47.3, 38.4, 26.9, 25.7, 19.1, 18.2;

HRMS (EI-MS): calcd for $C_{13}H_{20}O_2Na$ $(M+Na)^+$ 231.1466, found 231.1467.



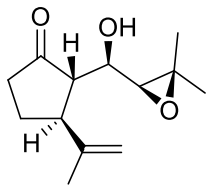
Compound 202: Under the nitrogen atmosphere to a solution of **199** (0.064 g, 0.31 mmol) in DCM (3 mL) at 0 °C was added m-CPBA (0.152 g, 2.0 equiv) at once. The reaction mixture was allowed to stir for 20 min at the same temperature. The solvent was removed under reduced pressure and the crude was purified by flash column chromatography (hexanes/ EtOAc 2:1) gave **202** in 88% yield (0.061 g).

R_f= 0.28 (hexanes/ EtOAc 3:1, UV-active, stains deep pink with vanilin).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.61 (dd, *J* = 5.7, 2.5 Hz, 1H), 6.24 (dd, *J* = 5.7, 2.1 Hz, 1H), 4.90 (p, *J* = 1.4 Hz, 1H), 4.83 (d, *J* = 0.6 Hz, 1H), 3.78 (dd, *J* = 7.7, 4.9 Hz, 1H), 3.56 (dd, *J* = 4.7, 2.2 Hz, 1H), 3.16 (d, *J* = 7.7 Hz, 1H), 2.43 (dd, *J* = 4.9, 2.9 Hz, 1H), 1.75 – 1.72 (m, 3H), 1.33 (d, *J* = 3.3 Hz, 6H);

^{13}C NMR (75 MHz, $CDCl_3$) δ 209.2, 166.7, 143.9, 134.0, 113.3, 70.1, 64.8, 60.5, 53.8, 51.7, 24.8, 20.2, 19.3;

HRMS (EI-MS): calcd for $C_{13}H_{19}O_3$ $(M+H)^+$ 223.126, found 223.1261.



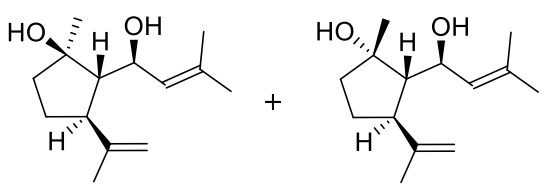
Compound 203: To a solution of α,β–unsaturated compound **202** (0.07 g, 0.315 mmol) in $CHCl_3$ (3 mL) was added Ph_2SiH_2 (0.099 ml, 0.535 mmol, 1.7 equiv), $ZnCl_2$ (0.022 g, 0.38 mmol, 0.16 equiv) and Pd $(PPh_3)_4$ (0.005 g, 0.004 mmol, 0.015 equiv), and the mixture was stirred at the room temperature for 30 min. The solvent was removed under reduced pressure, the crude was purified by flash column chromatography (hexanes/ EtOAc 5:1) to give **203** as pale brown oil in 28% yield (0.02 g).

R_f= 0.31 (hexanes/ EtOAc 7:1, stains blue with vanilin).

^{1}H NMR (300 MHz, $CDCl_3$) δ 4.96 – 4.88 (m, 2H), 4.26 – 4.16 (m, 2H), 3.74 (d, *J* = 4.6 Hz, 1H), 3.53 (d, *J* = 3.7 Hz, 1H), 3.02 – 2.87 (m, 1H), 2.52 – 2.42 (m, 1H), 2.33 – 2.28 (m, 1H), 2.28 – 2.16 (m, 2H), 1.79 (s, 3H), 1.64 (s, 3H), 1.54 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 223.4, 144.5, 112.6, 78.1, 72.3, 66.9, 57.4, 47.4, 39.0, 30.5, 27.0, 26.5, 19.2;

HRMS (EI-MS): calcd for $C_{13}H_{21}O_3$ $(M+H)^+$ 225.141, found 225.140.



Compound 205: $CeCl_3.7H_2O$ (1.63 g, 4.36 mmol, 4.05 equiv) was place in a 25 mL three-necked flask and heated at 140° in *vacuo* (0.1 mmHg) for 3 h, and then cooled to room temperature. THF (10 mL)

was added and stirring was continued for 2.5 h at room temperature. The resulting suspension was cooled to -78°C, and methyl lithium (1.49 M in Et_2O, 3.0 ml, 4.315 mmol, 4.01 equiv) was added. The resulting pale brown colored mixture was stirred for 1 h, ketone **200** (0.224 g, 1.07 mmol, 1.0 equiv) in THF (5 mL) was added, and the reaction mixture was stirred for further 4 h at the same temperature. The reaction mixture was quenched with aq.NH_4Cl solution, filtered through Celite and extracted with EtOAc (4×15 mL). The combined organic layers were dried (Na_2SO_4). The solvent was removed under reduce pressure, the products were separated by flash column chromatography (hexanes/ EtOAc 7:1 to 3:1) to give **205**-*syn* diol (0.074 g, 30%) **205-***anti* diol (0.11 g, 46%) as colorless oils.

205-*syn* diol:

R_f= 0.72 for *syn* and 0.6 for *anti* (hexanes/ EtOAc 5:1, stains pale blue with vanilin);

^{1}H NMR (300 MHz, $CDCl_3$) δ 5.36 – 5.26 (m, 1H), 4.68 (s, 2H), 4.52 (dd, *J* = 9.2, 6.6 Hz, 1H), 2.58 (dd, *J* = 17.1, 8.9 Hz, 1H), 1.90 – 1.81 (m, 1H), 1.78 – 1.72 (m, 2H), 1.68 (s, 3H), 1.66 (s, 6H), 1.57 – 1.44 (m, 2H), 1.42 (s, 3H), 1.39 – 1.24 (m, 2H);

^{13}C NMR (75 MHz, $CDCl_3$) δ 147.4, 134.3, 127.2, 110.4, 81.3, 70.3, 56.0, 49.7, 42.3, 31.0, 29.4, 25.7, 19.5, 18.2;

HRMS (EI-MS): calcd for $C_{14}H_{25}O_2$ $(M+H)^+$ 225.1776, found 225.177.

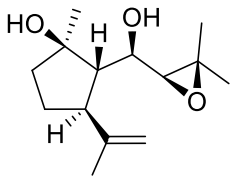
205-*anti* diol:

R_f= (hexanes: ethyl acetate=5:1).

^{1}H NMR (300 MHz, $CDCl_3$) δ 5.11 – 5.00 (m, 1H), 4.58 – 4.49 (m, 2H), 4.40 (t, *J* = 9.6 Hz, 1H), 3.36 (s, 1H), 2.26 – 2.14 (m, 1H), 1.96 (dd, *J* = 28.5, 18.0 Hz, 2H), 1.86 – 1.76 (m, 2H), 1.75 – 1.70 (m, 1H), 1.67 – 1.64 (m, 6H), 1.61 (d, *J* = 1.2 Hz, 3H), 1.51 – 1.43 (m, 1H), 1.36 (s, 3H);

^{13}C NMR (75 MHz, $CDCl_3$) δ 147.8, 135.1, 126.9, 109.9, 80.8, 71.1, 55.9, 47.1, 40.0, 27.9, 55.6, 23.0, 18.6, 18.4;

HRMS (EI-MS): calcd for $C_{14}H_{25}O_2$ $(M+H)^+$ 225.1776, found 225.177.



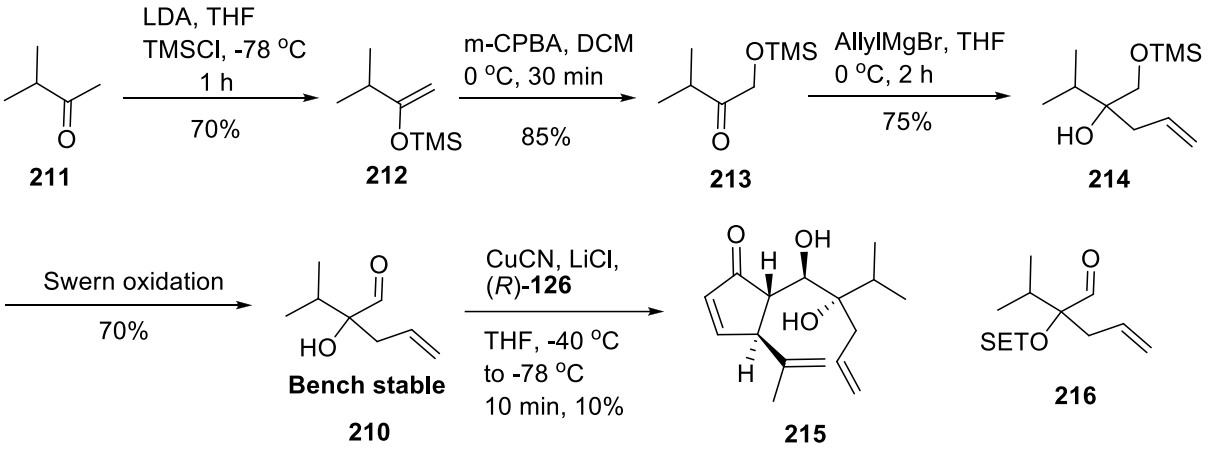
Compound 206: Under nitrogen to a solution of **205** *syn*-diol (0.052 g, 0.233 mmol) in DCM (3 mL) was added m-CPBA (0.084 g, 1.1 equiv) at once at 0 °C. The reaction mixture was allowed to stir for 20 min at the same temperature. The solvent was removed under reduced pressure and the crude was purified by flash column chromatography (hexanes/ EtOAc 2:1) gave **206** in 85% yield (0.046 g).

R_f= 0.35 (hexanes/ EtOAc 2:1, stains deep blue with vanilin);

^{1}H NMR (300 MHz, $CDCl_3$) δ 4.74 – 4.65 (m, 2H), 3.56 – 3.46 (m, 1H), 2.70 (d, *J* = 8.7 Hz, 1H), 2.32 – 2.23 (m, 1H), 2.22 – 2.15 (m, 1H), 1.91 – 1.79 (m, 2H), 1.75 (s, 3H), 1.73 – 1.65 (m, 1H), 1.61 – 1.38 (m, 2H), 1.31 (d, *J* = 6.5 Hz, 6H), 1.26 (d, *J* = 7.2 Hz, 1H), 1.22 (s, 3H);

^{13}C NMR (75 MHz, $CDCl_3$) δ 146.8, 110.7, 80.8, 72.5, 67.4, 62.2, 52.7, 46.3, 39.4, 28.5, 24.5, 23.0, 19.7, 19.3;

HRMS (EI-MS): calcd for $C_{14}H_{25}O_3$ $(M+H)^+$ 241.1725, found 241.1728.



To a solution of i-Pr_2NH (2.8 mL, 20 mmol) in THF (30 mL) was added n-BuLi (1.45 M in hexanes, 13.8 mL, 20 mmol) at 0 °C and the resulting solution was stirred for 30 min at the same temperature, then cooled to -78 °C. Ketone **211** (2.14 mL, 20 mmol) was added dropwise and the resulting mixture was stirred for 45 min at -78 °C, and was then added TMSCl (3.0 mL, 24 mmol) followed by quenched with aq. NH_4Cl. The reaction was warmed to room temperature. The aqueous layer was extracted with Et_2O. The combined organic extracts were washed with brine, dried, filtered and concentrated under reduced pressure gave crude **212** which we can use directly for the next step.

To the above crude **212** solution in DCM (125 mL) was added m-CPBA (5.94 g) at 0 °C. The reaction mixture was allowed to warm room temperature during 30 min, and was quenched with water. The aqueous layer was extracted with DCM. The combined organic extracts were washed with brine, dried, filtered and concentrated under reduced pressure gave crude **213**.

To the above crude **213** (0.83 g, 4.74 mmol) in Et_2O(30 mL) was added allyl magnesium bromide (0.74 M in Et_2O, 19 mL, 14.22 mmol) at 0 °C. The reaction was stirred at the same temperature for 30 min and was allowed to warm to room temperature for 30 min. The reaction was quenched with aq. NH_4Cl and extracted twice with Et_2O. The combined organics were washed with brine; dried, filtered

and removed solvent under reduced pressure gave crude. This crude was purified by flash column (hexanes/ EtOAc 7:1) gave diol **214** in 70% yield (0.72 g).

R_f= 0.64 (hexanes/ EtOAc 10:1, stains blue with vanilin).

^{1}H NMR (300 MHz, $CDCl_3$) δ 5.92 – 5.70 (m, 1H), 5.07 – 5.03 (m, 1H), 5.00 (ddd, *J* = 5.3, 2.3, 1.3 Hz, 1H), 3.48 – 3.35 (m, 2H), 2.18 (dddd, *J* = 13.4, 9.0, 7.0, 3.7 Hz, 3H), 1.80 (dq, *J* = 13.5, 6.8 Hz, 1H), 0.87 (d, *J* = 7.0 Hz, 6H), 0.11 – 0.04 (m, 9H);

^{13}C NMR (75 MHz, $CDCl_3$) δ 145.8, 118.0, 75.6, 65.9, 39.2, 33.5, 17.7, 17.4, 3X0.00(TMS);

HRMS (EI-MS): calcd for $C_{11}H_{25}O_2Si(M+H)^+$ 217.155, found 217.157.

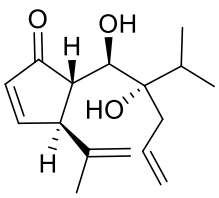
To the above diol **214** (0.084 g, 0.392 mmol) in DCM (1.2 mL) was added DMSO (0.29 mL, 4.11 mmol) followed by the addition of iPr_2NEt (0.35 mL, 2.03 mmol) after 15 min at 0 °C. To this solution was added $Py.SO_3$ complex (0.193 g, 1.21 mmol). The reaction mixture was stirred at the same temperature for an hour, and was quenched with aq. $NaHCO_3$ followed by extraction with DCM. The combined organics were washed with brine, dried, filtered and concentrated under reduced pressure. The resulting crude was purified by flash column (hexanes/ EtOAc 7:1) gave aldehyde **210** in 80% yield (0.045g).

R_f= 0.65 (hexanes/ EtOAc 5:1, stains pale brown with vanilin).

^{1}H NMR (300 MHz, $CDCl_3$) δ 9.53 (s, 1H), 5.78 – 5.57 (m, 1H), 5.16 – 5.12 (m, 1H), 5.09 (d, *J* = 1.1 Hz, 1H), 3.15 (s, 1H), 2.51 (dt, *J* = 1.9, 1.1 Hz, 1H), 2.49 (dd, *J* = 2.6, 1.2 Hz, 1H), 2.01 (dd, *J* = 13.7, 6.8 Hz, 1H), 1.01 (d, *J* = 6.8 Hz, 3H), 0.89 – 0.86 (m, 3H);

^{13}C NMR (75 MHz, $CDCl_3$) δ 205.2, 131.8, 119.4, 81.8, 38.8, 32.7, 17.0, 16.0;

HRMS (EI-MS): calcd for $C_{15}H_{24}O_3$ $(M+H)^+$, found.



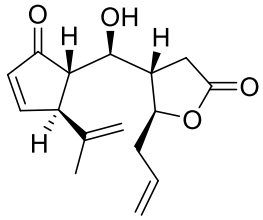
Compound 215: According to general procedure A: To a stirred solution of CuCN (0.051mmol, 0.561 mmol, 3.0 equiv) and anhydrous LiCl (0.048 g, 1.122 mmol, 6.0 equiv) in THF (2 mL) was added isopropenylmagnesium bromide (0.92 M solution in THF, 0.561 mmol, 0.61 mL, 3.0 equiv) dropwise at –40 °C. The reaction mixture was cooled to –78 °C upon which a solution of (*R*)-**125** (0.038 g, 0.187 mmol, 1.0 equiv) in THF (0.5 mL) was added. After 4 min of stirring at -78 °C, **210** (0.053 g, 0.37 mmol, 2.0 equiv) was added. After the reaction was completed (ca. 5 min), the mixture was quenched with NH_4Cl_{aq} (100 mL) and the aqueous layer was extracted with Et_2O (2x5 mL). The combined organic extracts were washed with brine, dried, filtered and the solvent was removed under reduced pressure. After purification on silica (hexanes/EtOAc 7:1-5:1) **215** was obtained in 12% yield (0.006 g).

R_f= 0.25 (hexanes/ EtOAc 5:1, UV-active, stains blue with vanilin);

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.68 (dd, *J* = 5.7, 2.2 Hz, 1H), 6.21 (dd, *J* = 5.7, 2.1 Hz, 1H), 6.09 – 5.94 (m, 1H), 5.15 – 5.01 (m, 2H), 4.95 (dd, *J* = 3.8, 2.3 Hz, 2H), 4.51 (s, 1H), 3.89 (d, *J* = 7.6 Hz, 1H), 3.81 (q, *J* = 2.5 Hz, 1H), 2.84 (d, *J* = 8.7 Hz, 1H), 2.63 (dd, *J* = 3.1, 1.7 Hz, 1H), 2.38 (dd, *J* = 14.5, 7.0 Hz, 2H), 1.95 (dd, *J* = 13.7, 6.9 Hz, 1H), 1.71 (s, 3H), 1.13 (d, *J* = 6.8 Hz, 3H), 0.83 (d, *J* = 7.0 Hz, 3H);

^{13}C NMR (75 MHz, $CDCl_3$) δ 212.1, 169.0, 142.9, 135.6, 134.0, 116.7, 114.8, 72.9, 54.1, 53.1, 37.6, 36.1, 23.9, 19.5, 17.5, 14.6;

HRMS (EI-MS): calcd for $C_{16}H_{24}O_3$ $(M+H)^+$ 264.1726, found 265.173.



Compound 222: According to general procedure A: To a stirred solution of CuCN (0.215 g, 2.4 mmol, 3.0 equiv) and dried LiCl (0.202 g, 4.8 mmol, 6.0 equiv) in THF (8 mL) was added isopropenylmagnesium bromide (0.92 M solution in THF, 2.4 mmol, 2.6 mL, 3.0 equiv) dropwise at –40 °C. The reaction mixture was cooled to –78 °C upon which a solution of (*R*)-**125** (0.16 g, 0.8 mmol, 1.0 equiv) in THF (2 mL) was added. After 4 min successive stirring at -78 °C, aldehyde **221** (0.21 g, 1.34 mmol, 1.68 equiv) was added. After the reaction was completed (ca. 10 min), the mixture was quenched with aq.NH_4Cl (10 mL), and the reaction mixture was extracted with Et_2O (2x25 mL). The combined organic extracts were washed with brine (25 mL), dried over Na_2SO_4, filtered and concentrated under *vacuo*. The crude was purified by flash chromatography on silica (hexanes/ EtOAc 5:1 to 2:1) obtained enone **222** in 66 % yield (0.145 g).

Physical state: deep yellow oil;

TLC: R_f = 0.3 (hexanes/ EtOAc 2:1, UV-active, stains pale green with vanillin);

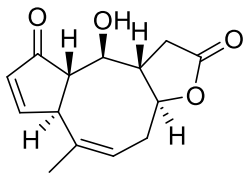
$[\alpha]_D^{25}$**:** n.d.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.49 (dd, *J* = 5.7, 2.4 Hz, 1H), 6.22 (dd, *J* = 5.6, 2.2 Hz, 1H), 5.85 – 5.69 (m, 1H), 5.15 (s, 1H), 5.12 – 5.08 (m, 1H), 4.96 – 4.92 (m, 1H), 4.90 (s, 1H), 4.68 – 4.58 (m, 2H), 3.77 – 3.72 (m, 1H), 3.16 (dd, *J* = 5.3, 2.6 Hz, 1H), 2.81 (dd, *J* = 16.9, 9.2 Hz, 1H), 2.49 – 2.33 (m, 3H), 2.19 (dd, *J* = 16.9, 9.1 Hz, 1H), 2.10 – 2.05 (m, 1H), 1.59 (s, 3H);

^{13}C NMR (75 MHz, $CDCl_3$) δ 212.31, 176.04, 167.66, 142.14, 133.32, 132.41, 119.15, 115.30, 79.76, 69.52, 52.65, 51.35, 43.95, 38.32, 28.29, 18.47;

IR (neat) (cm^{-1}) ν_{max}: 3485, 2919, 1773, 1686, 1440, 1229, 967, 905, 535, 494;

HRMS (*m/z*)**:** calcd for $C_{16}H_{21}O_4$ $(M+H)^+$ 277.1361, found 277.1362.



Compound 223: A flask containing enone **222** (0.146 g, 0.53 mmol) was outfitted with reflux condenser and evacuated and backfilled with N_2 3 times. Deoxygenated DCM (25 mL) was added, and the solution was heated to reflux (40 °C). A solution of Grubbs-II catalyst (0.045 g) in deoxygenated DCM (2.5 mL) was added to the reaction mixture. The light brown reaction mixture was refluxed for 48 h and was then cooled to room temperature. The solvent was removed under reduced pressure. After purification on silica (hexanes/ EtOAc 5:1 to 2:1) **223** was obtained in 45 % yield (0.059 g).

Physical state: pale yellow oil;

TLC: R_f = 0.5 (hexanes/ EtOAc 1:1, UV-active, stains deep brown with vanillin);

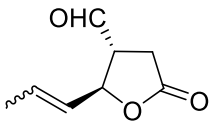
$[\alpha]_D^{25}$**:** n.d.;

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.66 (dd, *J* = 5.7, 2.2 Hz, 1H), 6.27 (dd, *J* = 5.7, 2.3 Hz, 1H), 5.33 (d, *J* = 6.6 Hz, 1H), 4.86 – 4.76 (m, 2H), 3.73 (t, *J* = 9.9 Hz, 1H), 3.46 (d, *J* = 1.6 Hz, 1H), 2.97 (ddt, *J* = 18.0, 5.4, 2.6 Hz, 1H), 2.85 – 2.67 (m, 2H), 2.60 – 2.49 (m, 1H), 2.37 – 2.24 (m, 1H), 2.11 (dd, *J* = 10.2, 4.3 Hz, 1H), 1.64 – 1.60 (m, 3H);

^{13}C NMR (75 MHz, $CDCl_3$) δ 211.16, 175.54, 165.95, 134.44, 133.88, 121.54, 80.22, 74.27, 56.26, 46.24, 44.75, 35.81, 33.77, 20.79;

IR (neat) (cm^{-1}) ν_{max}: 2923, 1780, 1690, 1578, 1414, 1261, 1227, 1045, 985, 898, 539, 497;

HRMS (*m/z*)**:** calcd for $C_{14}H_{17}O_4$ $(M+H)^+$ 249.105, found 249.1044.



Compound 220: To a solution of the aldehyde **221** (0.057 g, 0.37 mmol, 1 equiv) in dry MeOH (0.075 M) was added Grubbs-II catalyst (10 mol %) at room temperature. The suspension was then heated at 60° C. After 10 minutes, the catalyst completely dissolved and the resulting deep brown color solution was stirred at same temperature for further 15 h. After reaction was completed the solvent was removed under vacuo. The residue was purified by flash chromatography (hexanes/ EtOAc 5:1 to 2:1) the isomerized aldehyde **220** was obtained in 85 % yield (E/Z- 5:1, 0.049 g).

Physical state: deep brown oil;

TLC: R_f = 0.13 (hexanes/ EtOAc 2:1, stains deep green with vanillin);

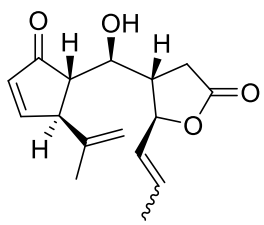
$[\alpha]_D^{25}$**:** 147.36 (c 0.11, $CHCl_3$);

^{1}H NMR (300 MHz, $CDCl_3$) δ; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.75 – 9.71 (m, 1H), 5.96 – 5.78 (m, 1H), 5.63 – 5.45 (m, 1H), 3.30 – 3.14 (m, 1H), 2.93 – 2.83 (m, 1H), 2.79 – 2.70 (m, 1H), 2.53 (dt, *J* = 14.4, 6.6 Hz, 1H), 1.79 – 1.72 (m, 3H);

^{13}C NMR (75 MHz, $CDCl_3$) δ 197.15, 173.99, 132.27, 127.11, 79.32, 53.13, 28.84, 17.72;

IR (neat) (cm^{-1}) ν_{max}: 3080, 2980, 2841, 1774, 1727, 1419, 1359, 1193, 921;

HRMS (*m/z*)**:** calcd for $C_8H_{11}O_3$ $(M+H)^+$ 155.0703, found 155.0702.



Compound 218: According to general procedure A: To a stirred solution of CuCN (0.215 g, 2.4 mmol, 3.0 equiv) and dried LiCl (0.202 g, 4.8 mmol, 6.0 equiv) in THF (8 mL) was added isopropenylmagnesium bromide (0.92 M solution in THF, 2.4 mmol, 2.6 mL, 3.0 equiv) dropwise at –40 °C. The reaction mixture was cooled to –78 °C upon which a solution of (*R*)-**125** (0.16 g, 0.8 mmol, 1.0 equiv) in THF (2 mL) was added. After 4 min successive stirring at -78 °C, aldehyde **220** (0.21 g, 1.34 mmol, 1.68 equiv) was added. After the reaction was completed (ca. 10 min), the mixture was quenched by adding aq.NH_4Cl (10 mL), and the reaction mixture was extracted with Et_2O (2x25 mL). The combined organic extracts were washed with brine (25 mL), dried over Na_2SO_4, filtered and concentrated under *vacuo*. The crude was purified by flash chromatography on silica (hexanes/ EtOAc 5:1 to 2:1) obtained enone **218** in 66 % yield (0.145 g).

Physical state: deep yellow oil;

TLC: R_f = 0.3 (hexanes/ EtOAc 2:1, UV-active, stains pale green with vanillin);

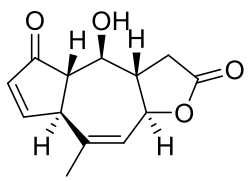
$[\alpha]_D^{25}$**:** 11.1 (c 0.11, $CHCl_3$);

^{1}H NMR (300 MHz, $CDCl_3$) δ; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.54 (dd, *J* = 5.6, 2.4 Hz, 1H), 6.28 – 6.23 (m, 1H), 5.95 – 5.77 (m, 1H), 5.49 – 5.37 (m, 1H), 5.00 – 4.96 (m, 2H), 4.91 (dd, *J* = 15.8, 7.4 Hz, 1H), 4.70 (d, *J* = 6.2 Hz, 1H), 3.75 (d, *J* = 5.4 Hz, 1H), 3.29 – 3.20 (m, 1H), 2.90 – 2.80 (m, 1H), 2.37 – 2.22 (m, 2H), 2.13 (dt, *J* = 10.2, 3.4 Hz, 1H), 1.75 – 1.71 (m, 3H), 1.64 (s, 3H);

^{13}C NMR (75 MHz, $CDCl_3$) δ 212.44, 175.95, 167.79, 142.16, 133.23, 132.92, 127.72, 115.32, 81.86, 68.21, 52.48, 51.51, 46.56, 28.42, 18.45, 17.86;

IR (neat) (cm^{-1}) ν_{max}: 3485, 2919, 1773, 1686, 1440, 1229, 1188, 967, 905, 728, 535, 494;

HRMS (*m/z*)**:** calcd for $C_{16}H_{21}O_4$ $(M+H)^+$ 277.1361, found 277.1362.



Compound 217: A flask containing enone **218** (0.145 g, 0.53 mmol) was outfitted with reflux condenser and evacuated and backfilled with N_2 3 times. Deoxygenated DCM (25 mL) was added, and the solution was heated to reflux (40 °C). A solution of Grubbs-II catalyst (0.045 g) in deoxygenated DCM (2.5 mL) was added to the reaction mixture.The light brown reaction mixture was refluxed for 15 h and was then cooled to room temperature. The solvent was removed under reduced pressure. After purification on silica (hexanes/ EtOAc 5:1 to 2:1) **217** was obtained in 84 % yield (0.104 g).

Physical state: deep brown oil;

TLC: R_f = 0.5 (hexanes/ EtOAc 1:1, UV-active, stains deep brown with vanillin);

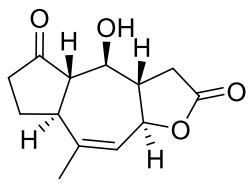
$[\alpha]_D^{25}$**:** 17.4 (c 0.18, $CHCl_3$);

^{1}H NMR (300 MHz, $CDCl_3$) δ; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.80 (dd, *J* = 5.9, 2.0 Hz, 1H), 6.30 (dd, *J* = 5.9, 2.6 Hz, 1H), 5.86 – 5.82 (m, 1H), 4.91 – 4.83 (m, 2H), 3.50 (d, *J* = 2.6 Hz, 1H), 2.95 – 2.87 (m, 1H), 2.49 – 2.44 (m, 1H), 2.24 (ddd, *J* = 10.1, 6.1, 2.5 Hz, 1H), 2.13 – 2.08 (m, 1H), 1.99 (td, *J* = 4.1, 2.2 Hz, 1H), 1.87 (s, 3H);

^{13}C NMR (75 MHz, $CDCl_3$) δ 209.77, 175.32, 162.15, 136.67, 134.12, 126.58, 78.63, 74.63, 55.04, 48.87, 45.41, 34.24, 19.97;

IR (neat) (cm^{-1}) ν_{max}: 2923, 1780, 1690, 1578, 1414, 1261, 1227, 1045, 985, 898, 734, 631, 539, 497;

HRMS (*m/z*)**:** calcd for $C_{13}H_{15}O_4$ $(M+H)^+$ 235.0969, found 235.0965.



Compound 226: To a suspension of $LiAlH_4$ (0.0038 g, 0.1 mmol) in THF (0.45 mL) at -78 °C was added CuI (0.019 g, 0.1 mmol) dissolved in THF: DMPU (4:1, 0.45 mL). The resulting mixture was stirred for 1 h at the same temperature, and then was added **217** (0.024 g, 0.1 mmol) in THF (0.1 mL). After stirring 2 h at -78 °C, the mixture was quenched with aq. NH_4Cl (5 mL) followed by ether (10 mL). The aqueous layer was extracted twice with Et_2O. The combined organic extracts were washed with brine, dried, filtered and concentrated under reduced pressure gave crude. The crude was purified by flash chromatography (hexanes/ EtOAc 3:1) gave **226** in 76% yield (0.018 g).

Physical state: pale yellow oil;

TLC: R_f = 0.48 (hexanes/ EtOAc 1:1, stains deep brown with vanillin);

$[\alpha]_D^{25}$**:** n.d.;

^{1}H NMR (300 MHz, $CDCl_3$) δ 5.77 (s, 1H), 5.14 (d, *J* = 10.4 Hz, 1H), 4.03 (dd, *J* = 9.1, 5.0 Hz, 1H), 3.54 (s, 1H), 3.11 – 2.99 (m, 1H), 2.67 – 2.56 (m, 2H), 2.43 (ddd, *J* = 22.7, 12.0, 5.8 Hz, 3H), 2.26 – 2.16 (m, 2H), 1.83 (d, *J* = 1.4 Hz, 3H);

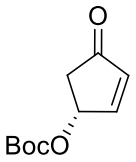
^{13}C NMR (75 MHz, $CDCl_3$) δ 221.0, 175.8, 139.1, 126.6, 76.0, 65.7, 59.1, 46.6, 42.2, 37.2, 29.6, 26.8, 22.0;

IR (neat) (cm^{-1}) ν_{max}: 2923, 1780, 1690, 1578, 1414, 1261, 1227, 1045, 985;

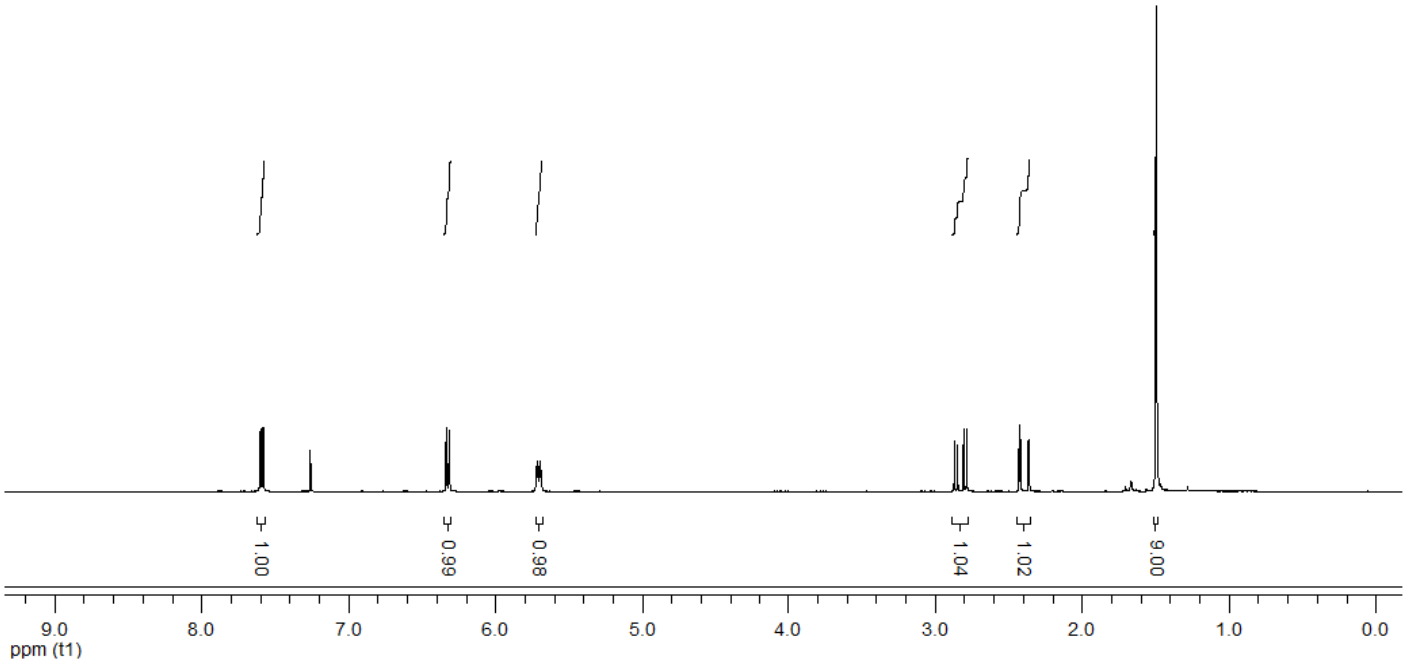
HRMS (*m/z*)**:** calcd for $C_{13}H_{17}O_4$ $(M+H)^+$ 237.105, found 237.1049.

E. Appendix

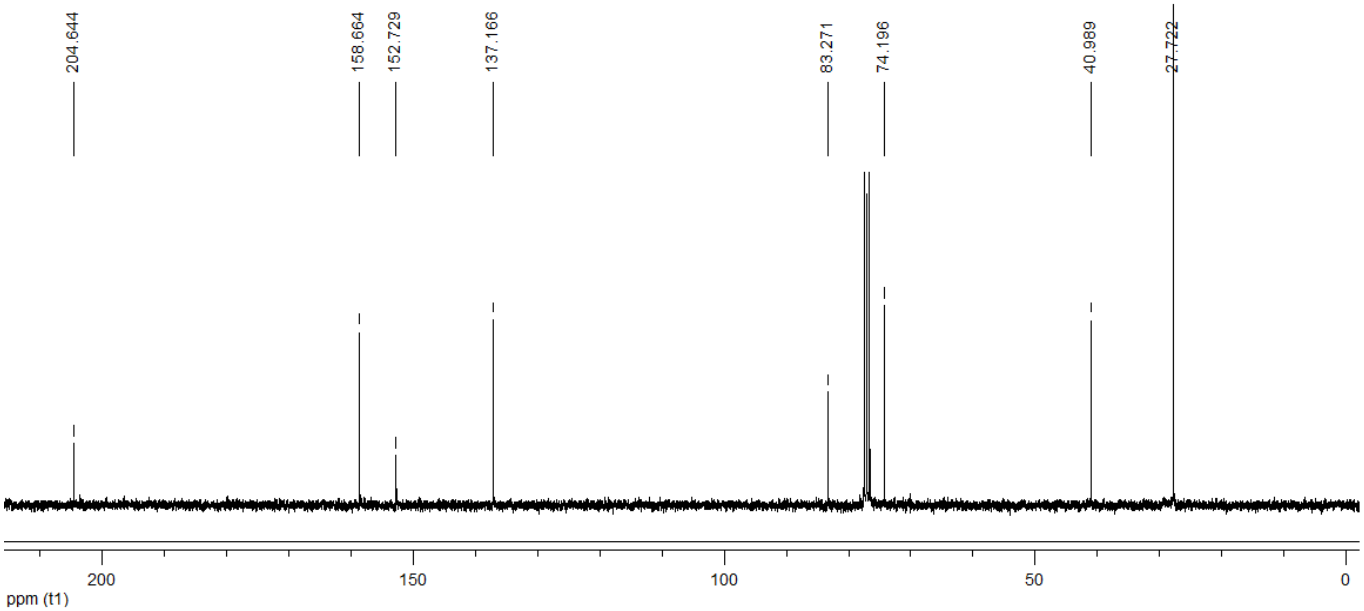
1. NMR Spectra:

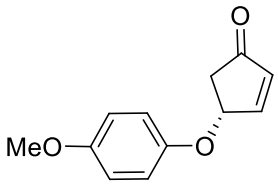


(*R*)-**125**, **$CDCl_3$, 300 MHz**

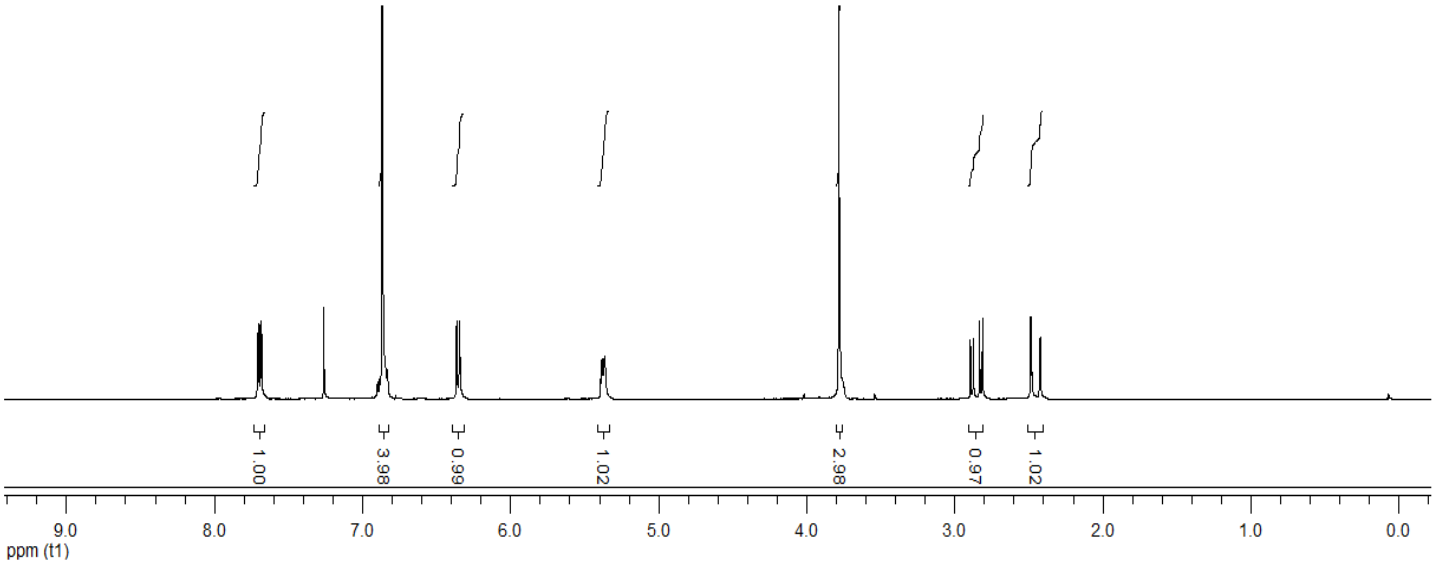


$CDCl_3$, 75 MHz

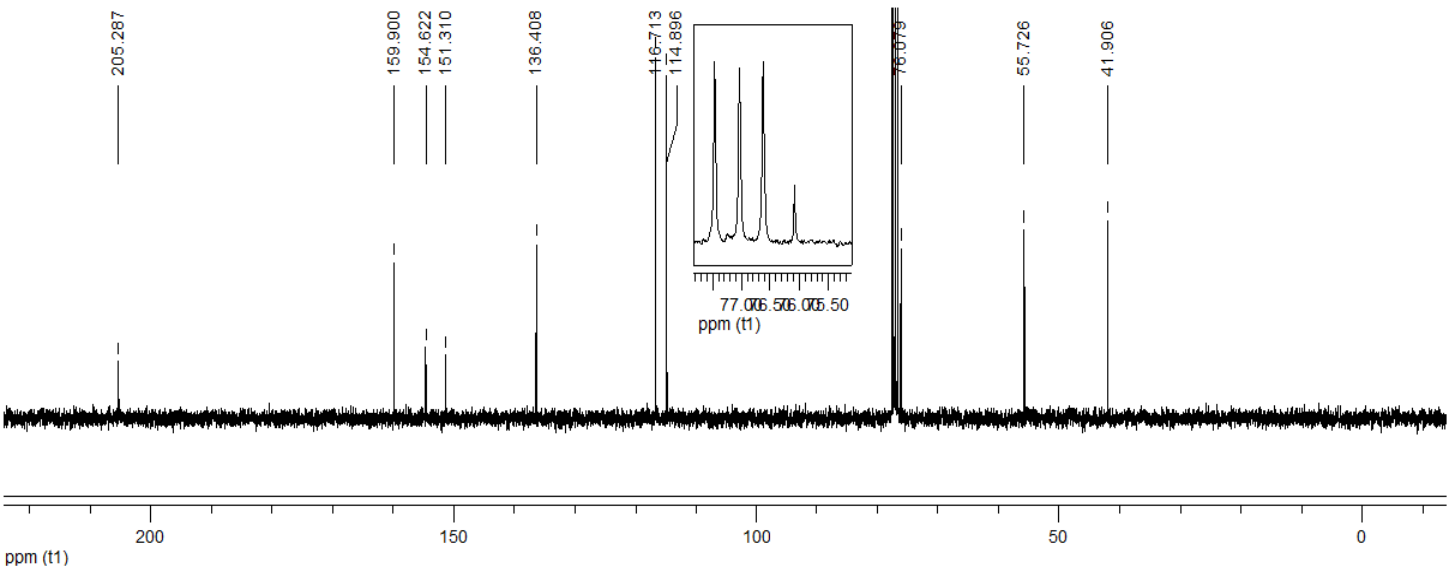


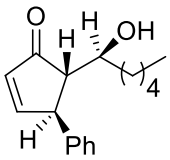


(*S*)-**134**, **$CDCl_3$, 300 MHz**

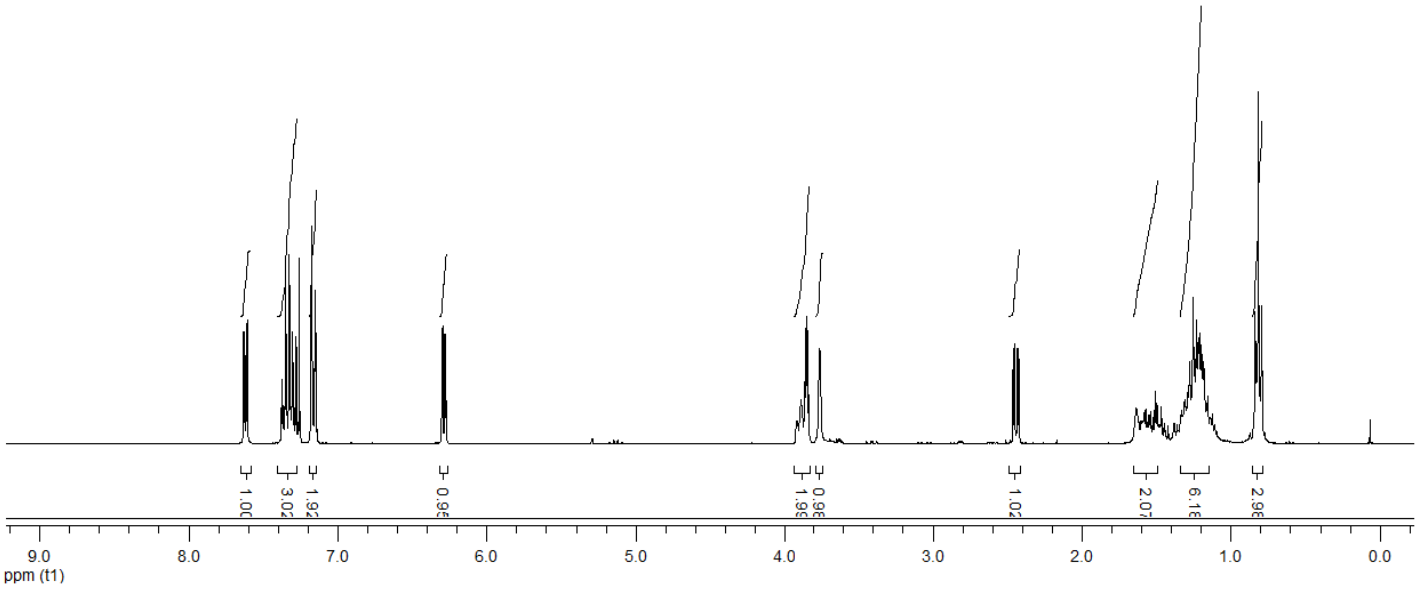


$CDCl_3$, 75 MHz

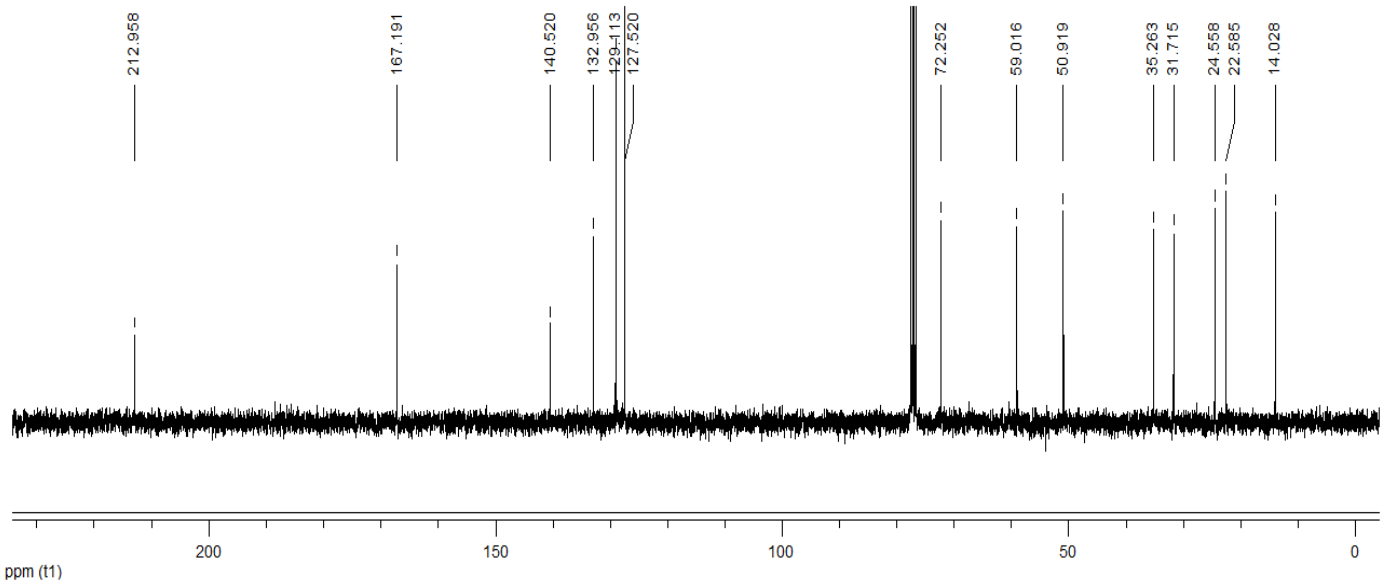


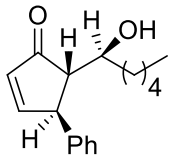


(+)-133a, $CDCl_3$, 300 MHz

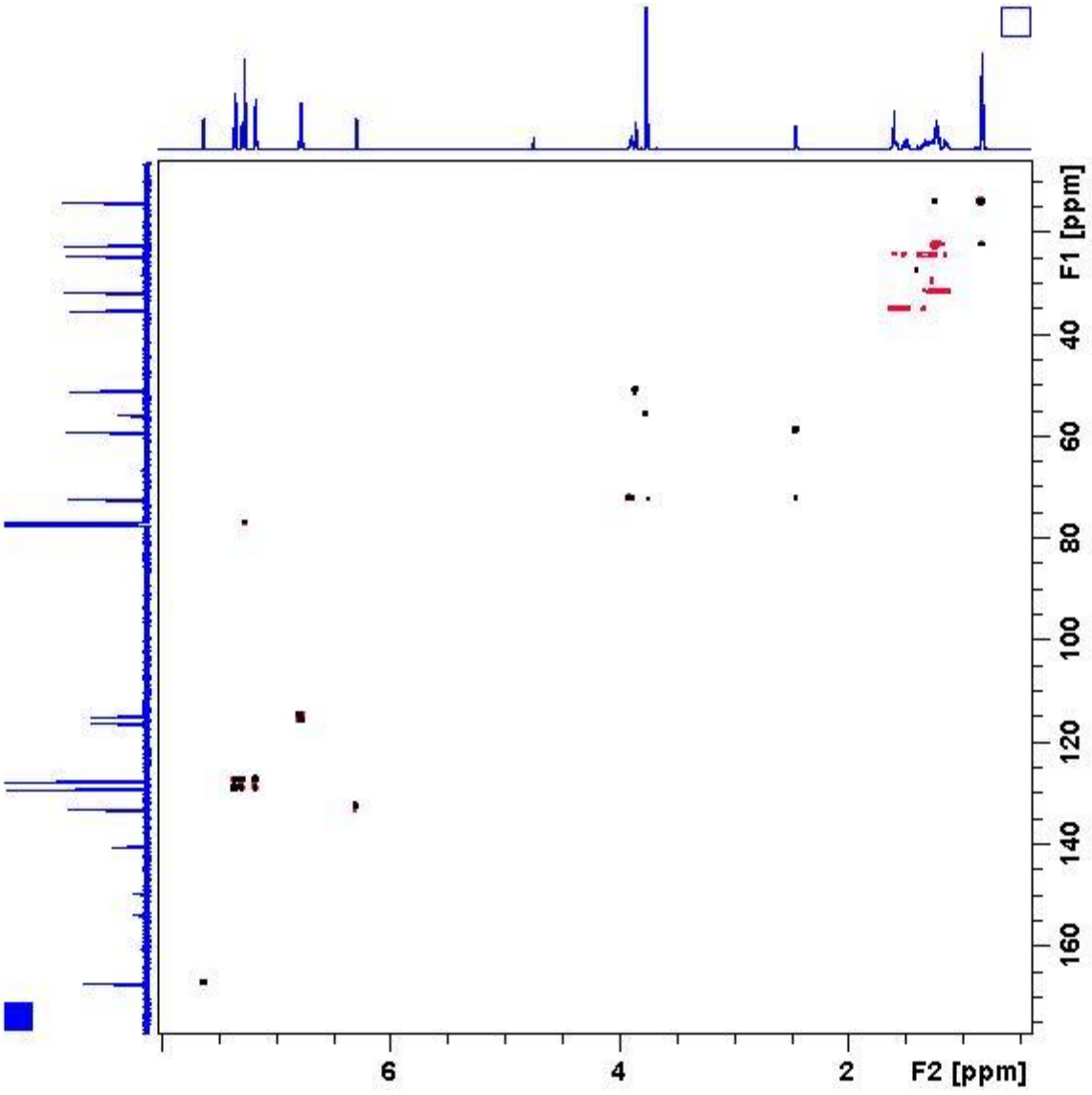


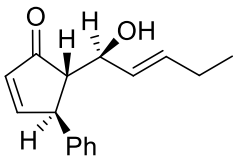
$CDCl_3$, 75 MHz



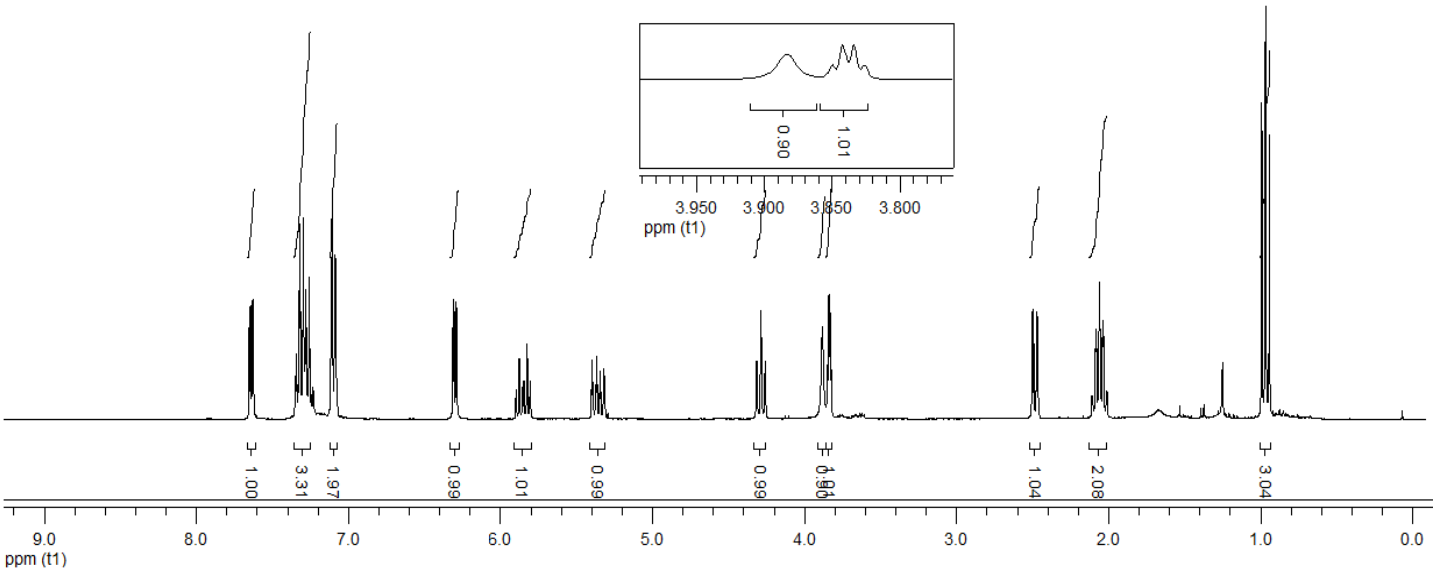


(+)-**133a, HSQC, $CDCl_3$, 600 MHz**

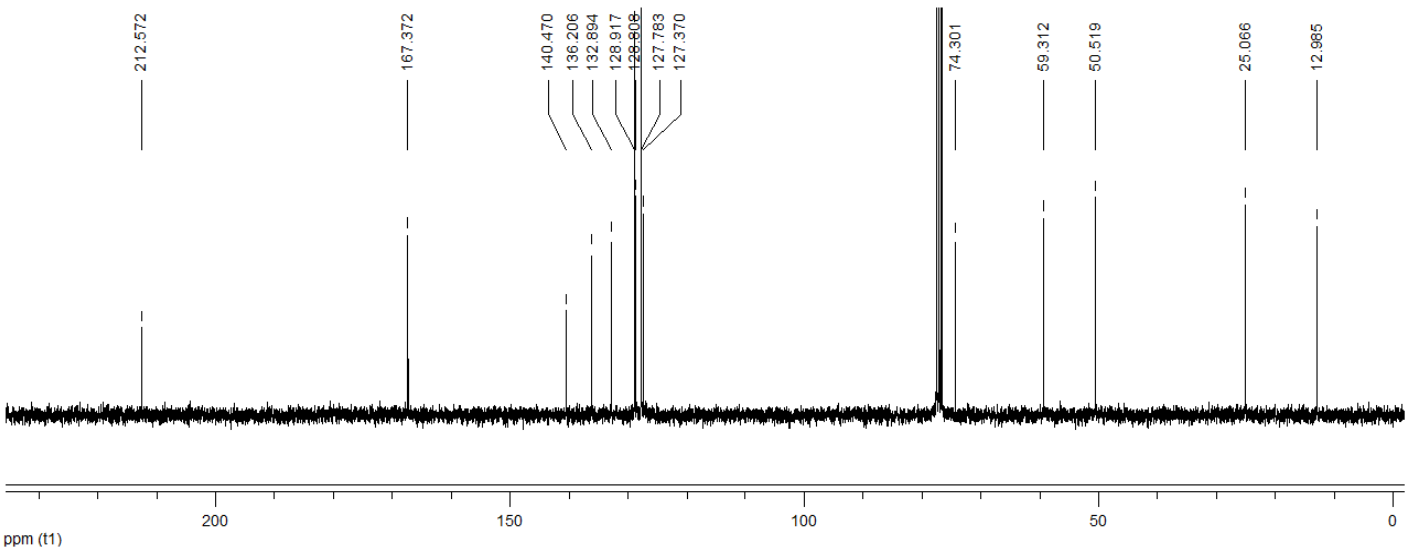


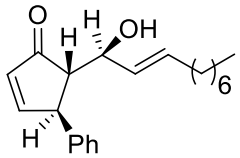


(+)-133b, $CDCl_3$, 300 MHz

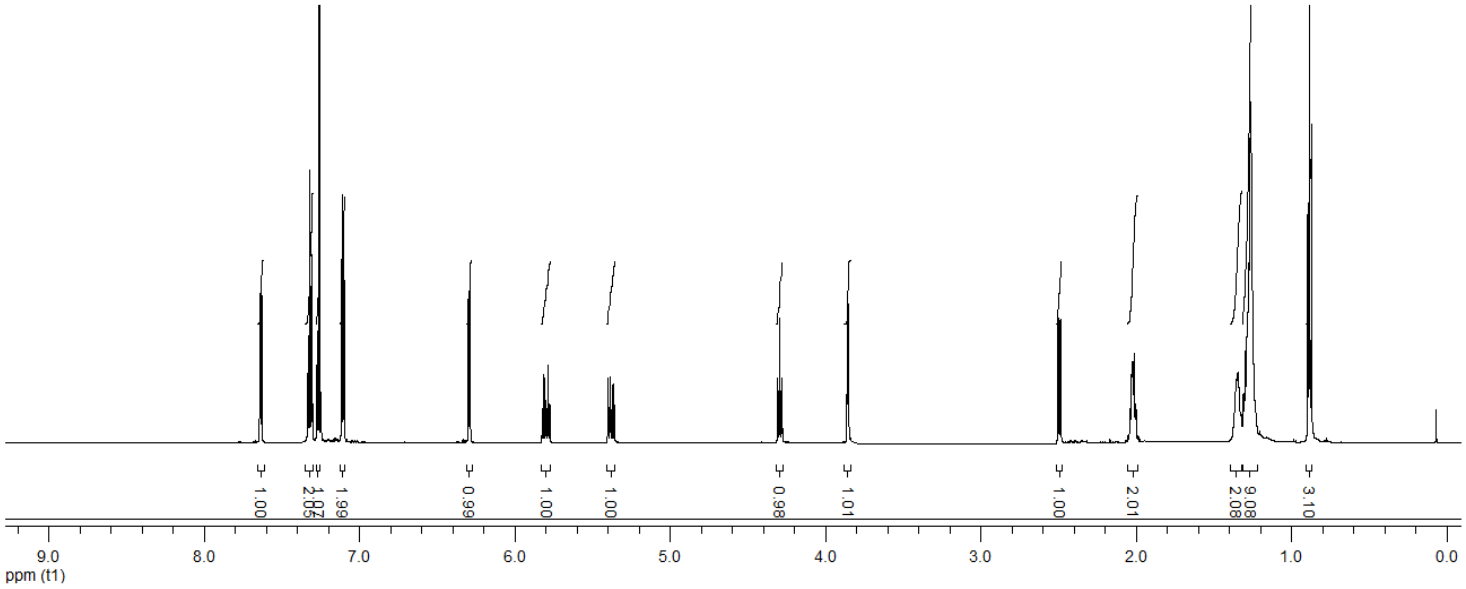


$CDCl_3$, 75 MHz

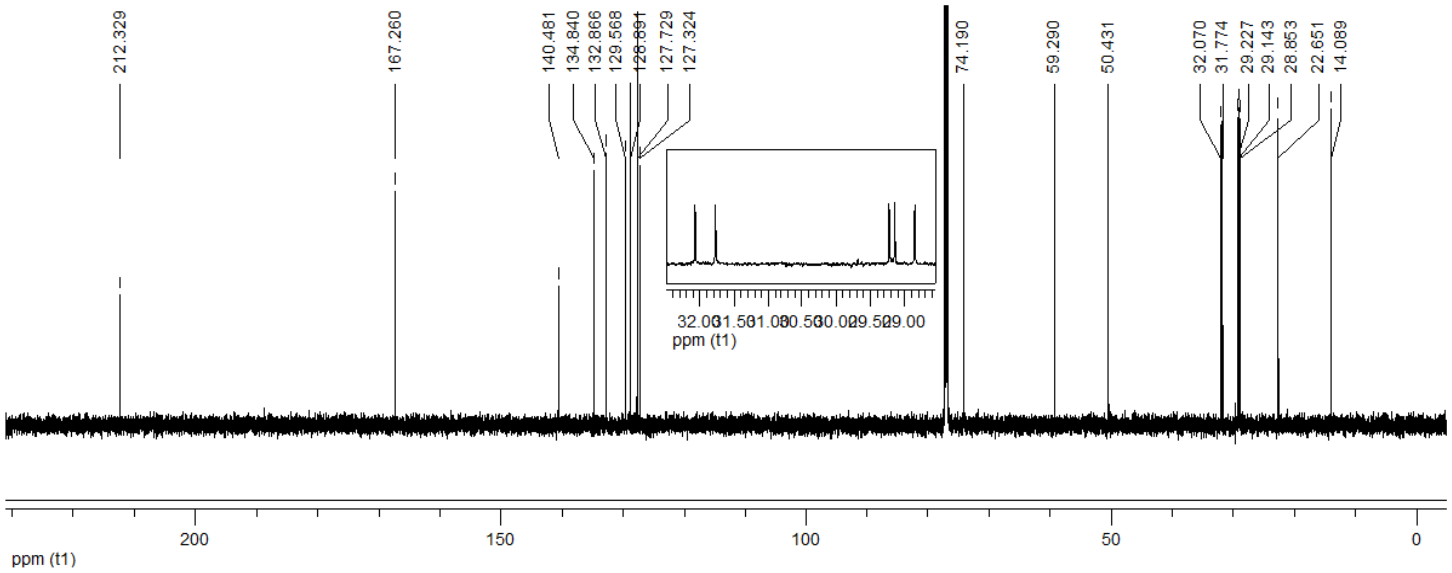


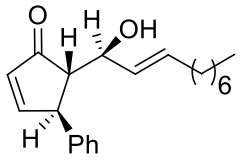


(+)-133c, $CDCl_3$, 600 MHz

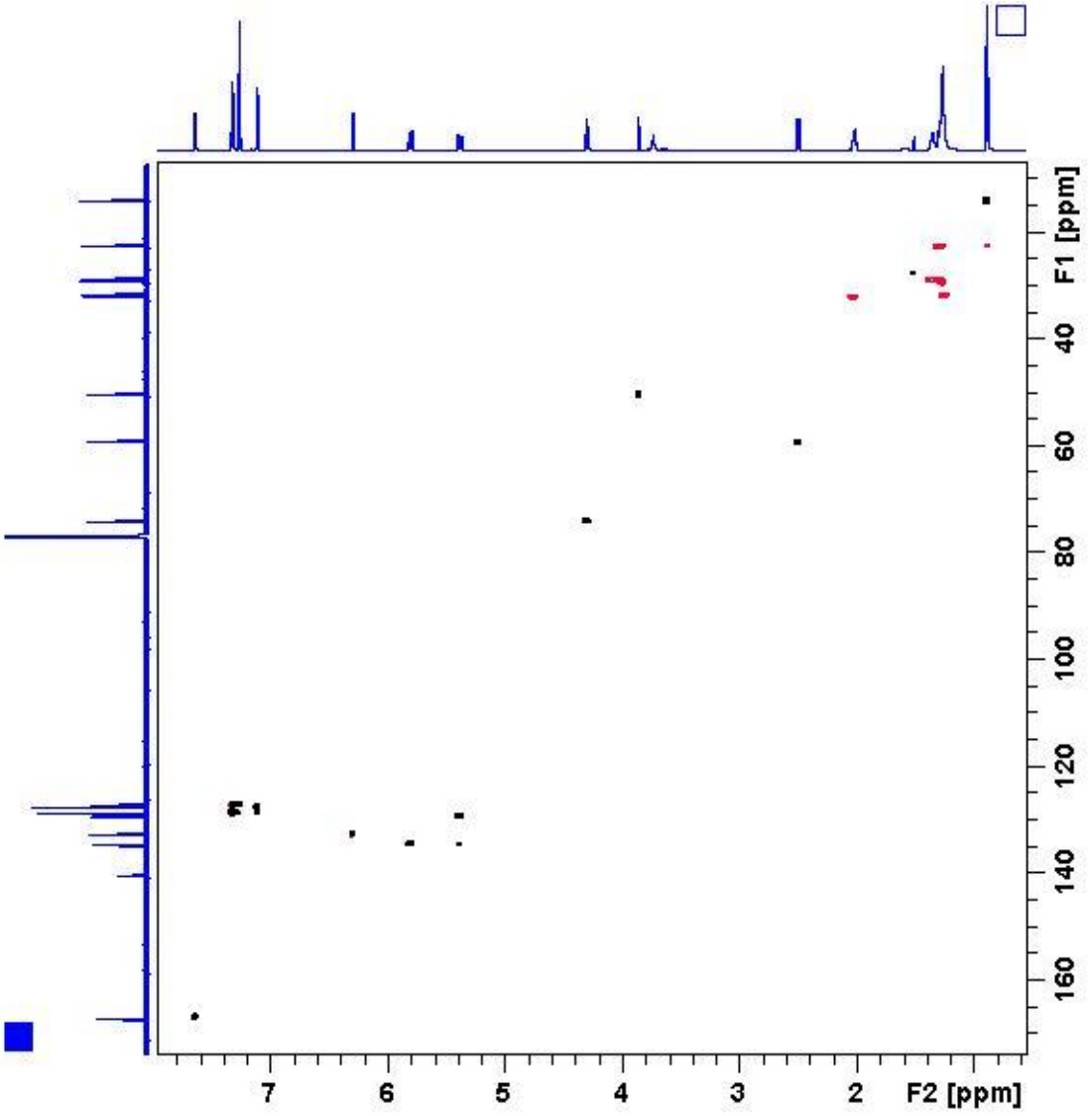


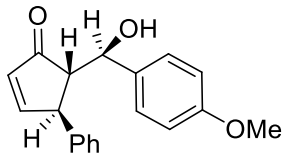
$CDCl_3$, 151 MHz



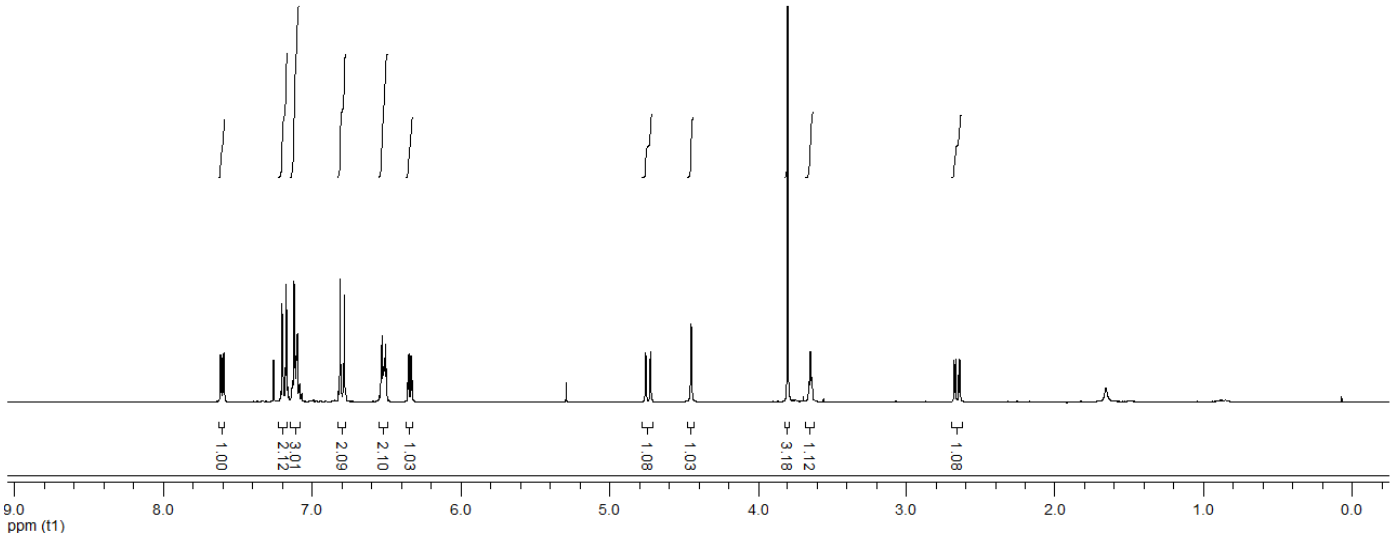


(+)-**133c, HSQC, $CDCl_3$, 600 MHz**

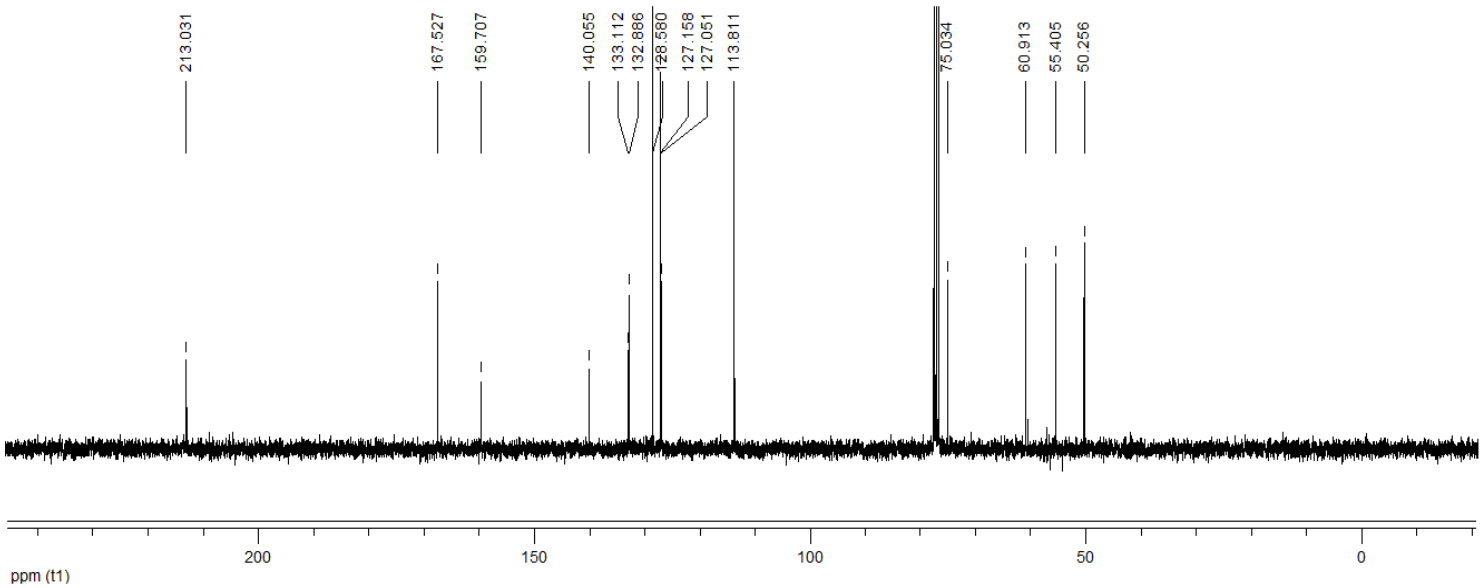


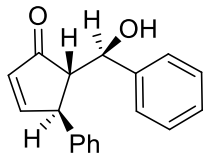


(+)-133d, $CDCl_3$, 300 MHz

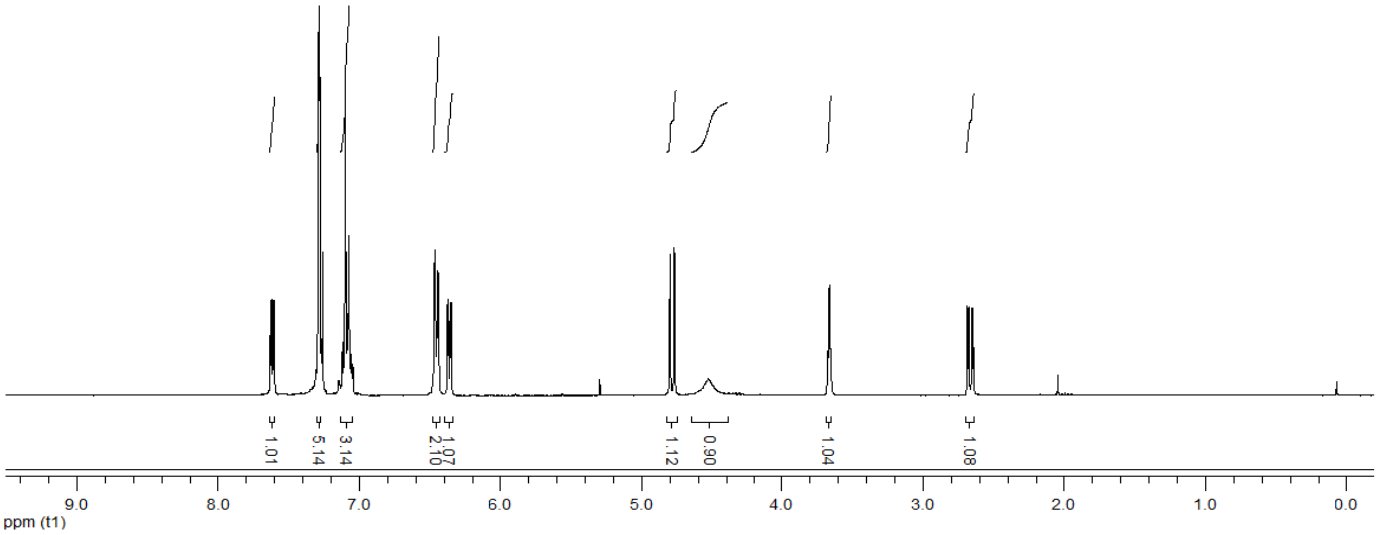


$CDCl_3$, 75 MHz

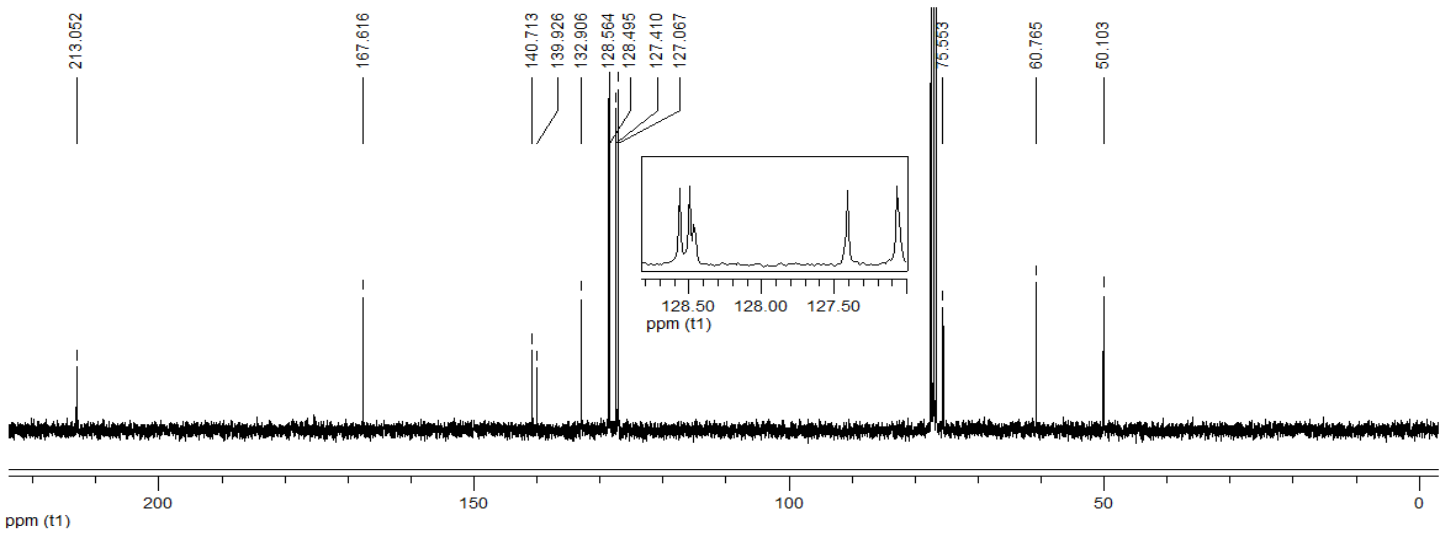


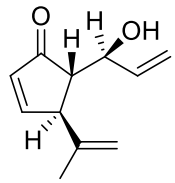


(+)-133e, $CDCl_3$, 300 MHz

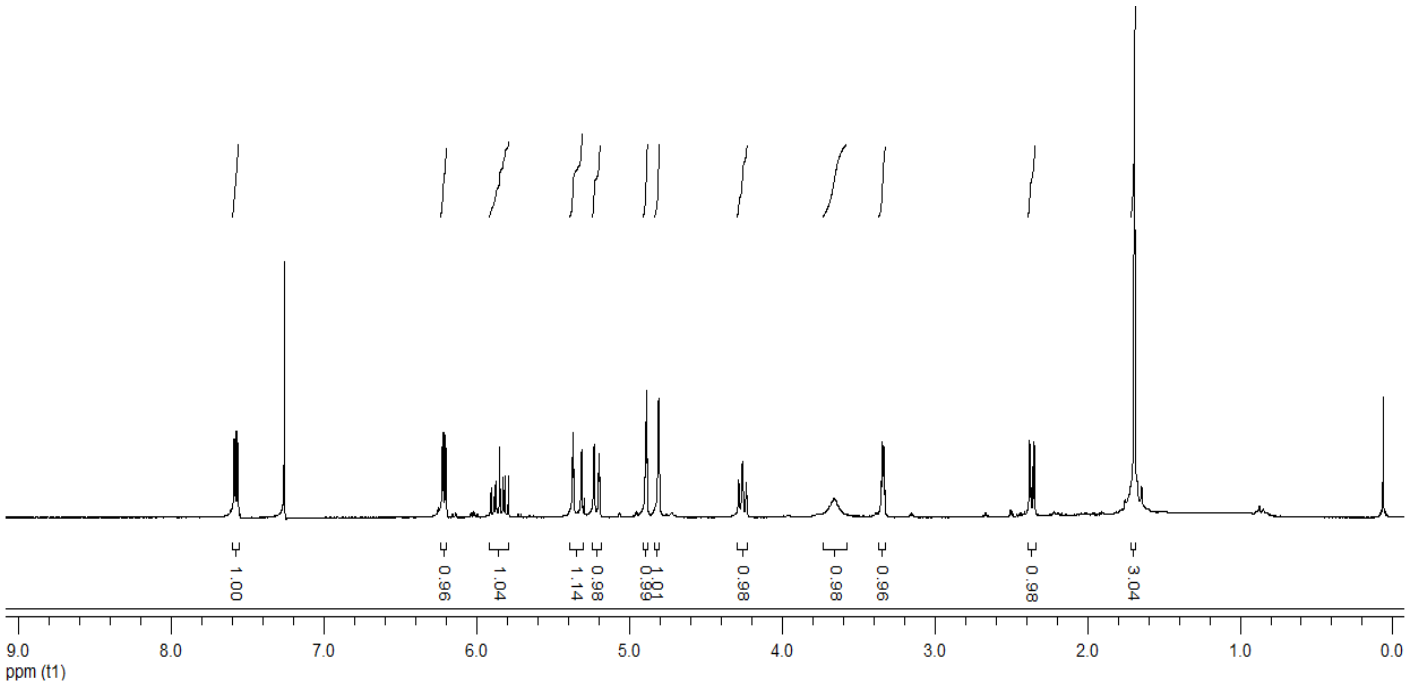


$CDCl_3$, 75 MHz

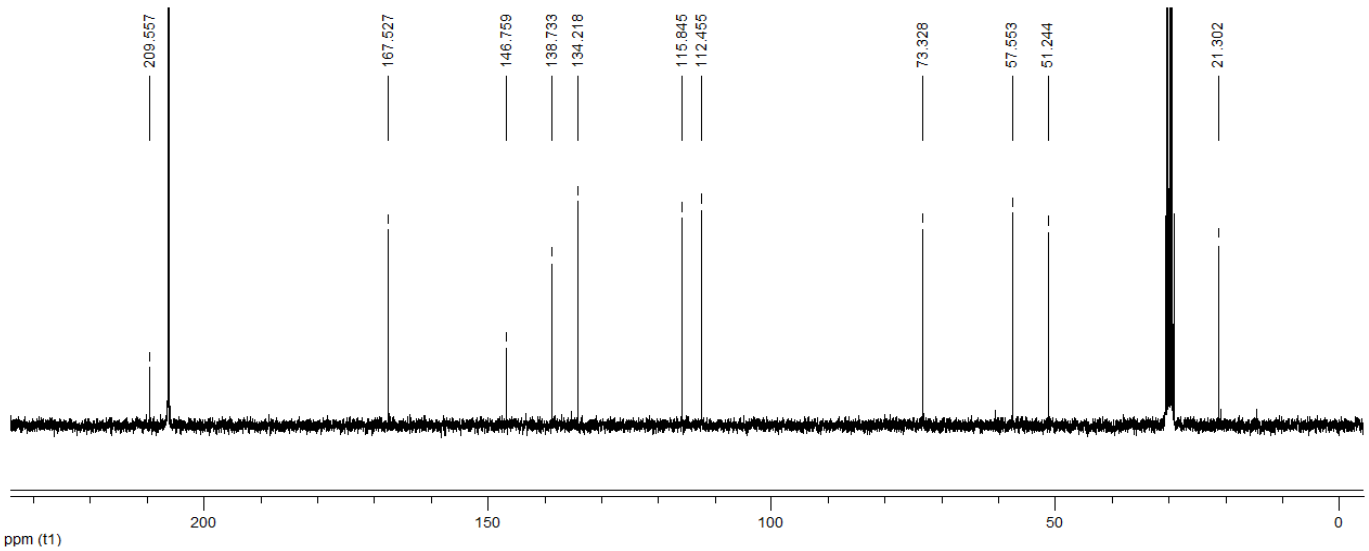


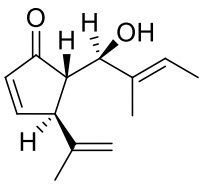


(+)-133f, d_6-Acetone, 300 MHz

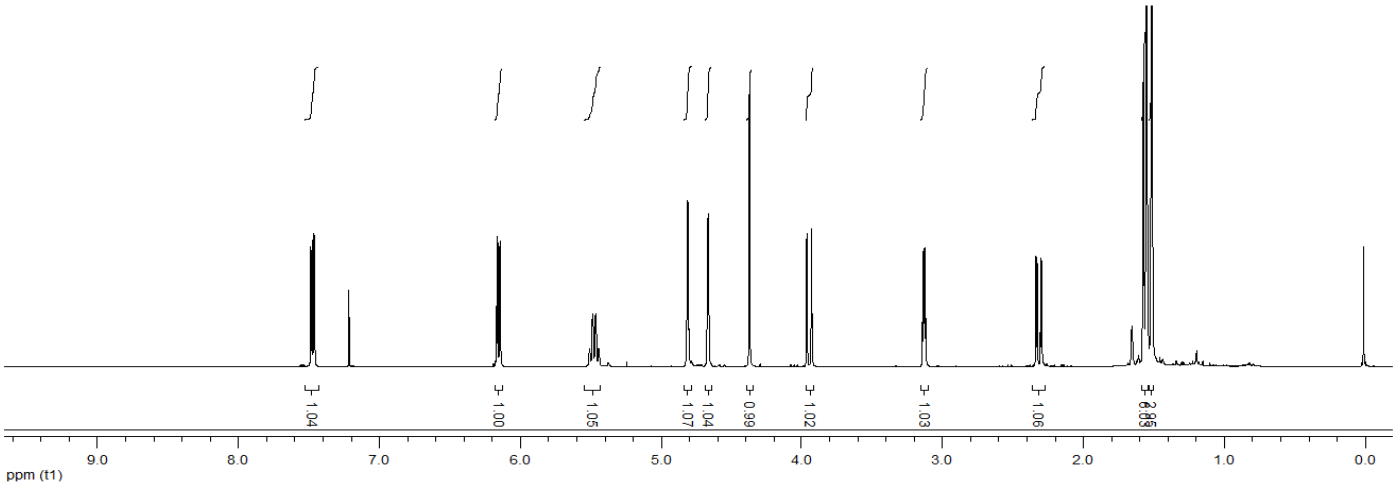


D_6-Acetone, 75 MHz

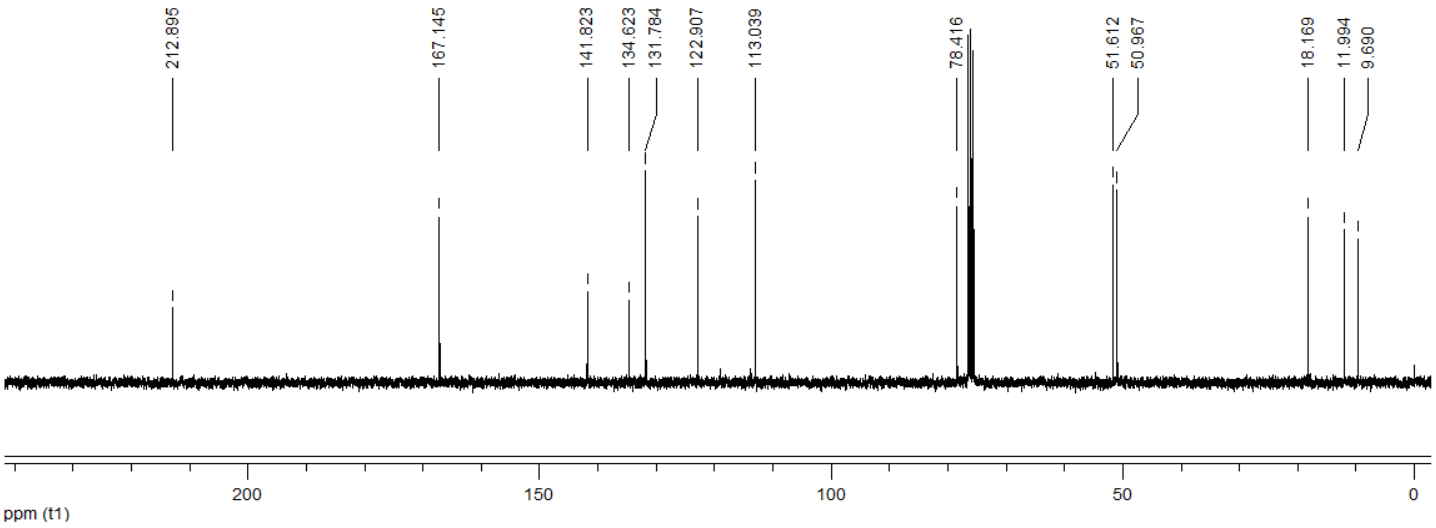


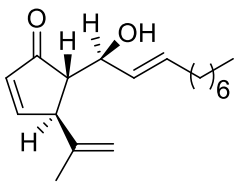


(+)-133g, $CDCl_3$, 300 MHz

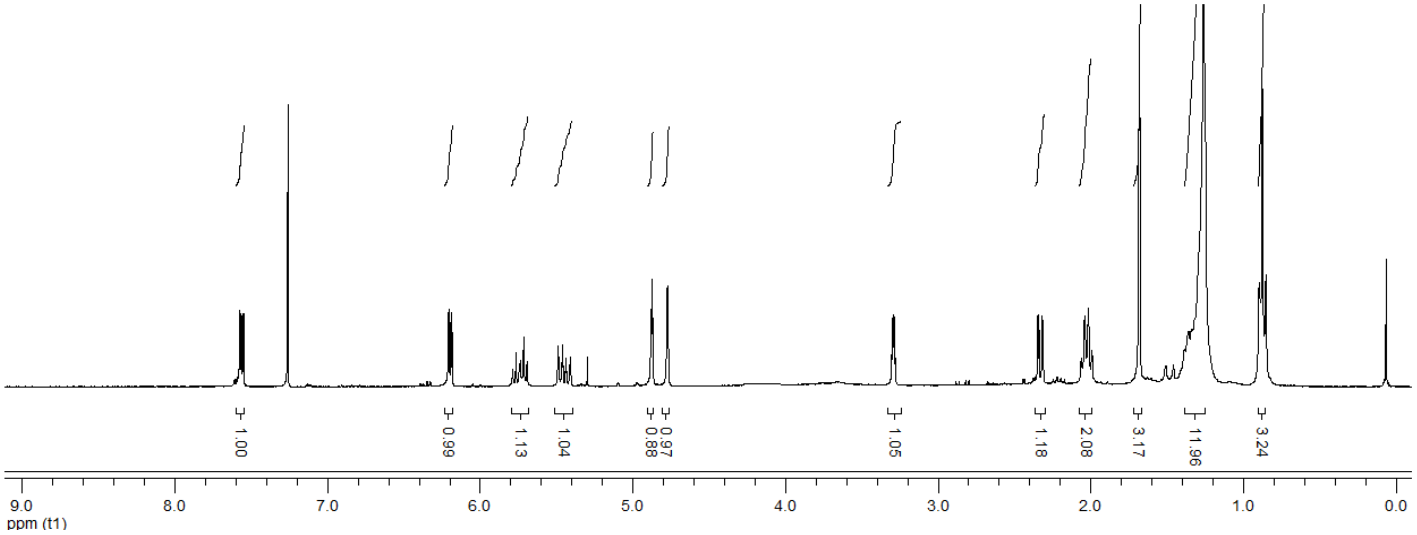


$CDCl_3$, 75 MHz

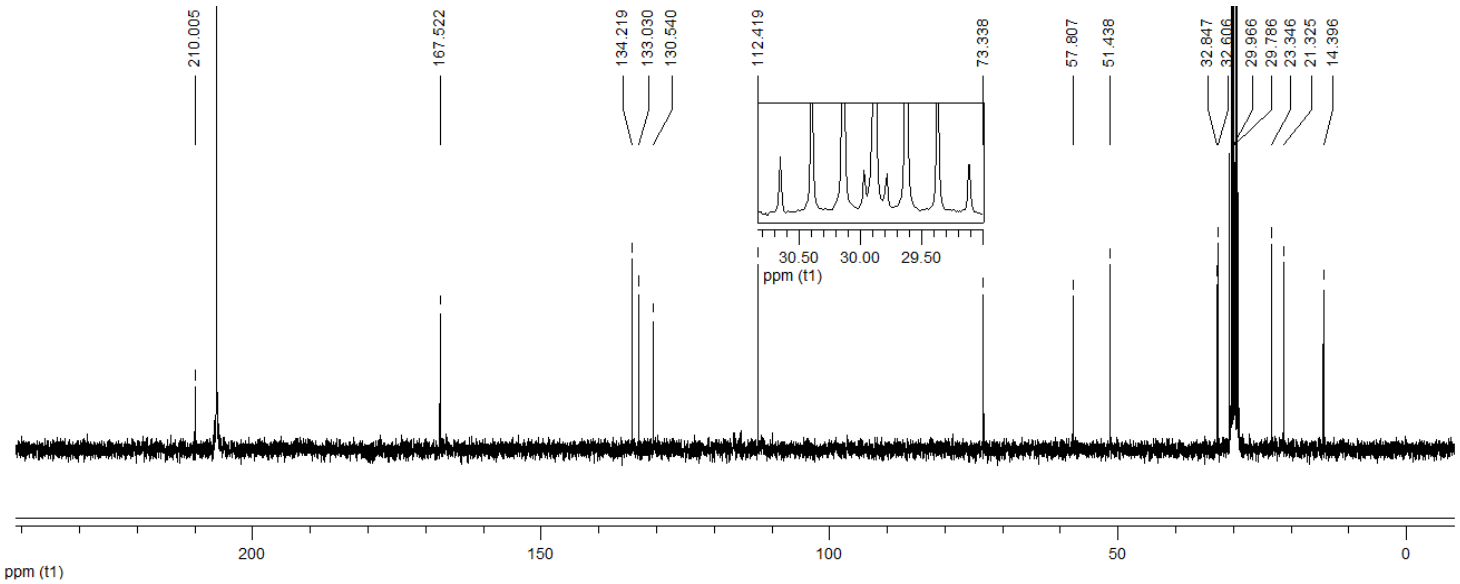


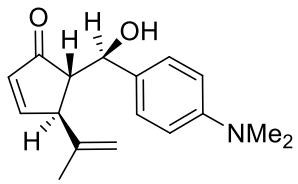


(+)-133h, d_6-Acetone, 300 MHz

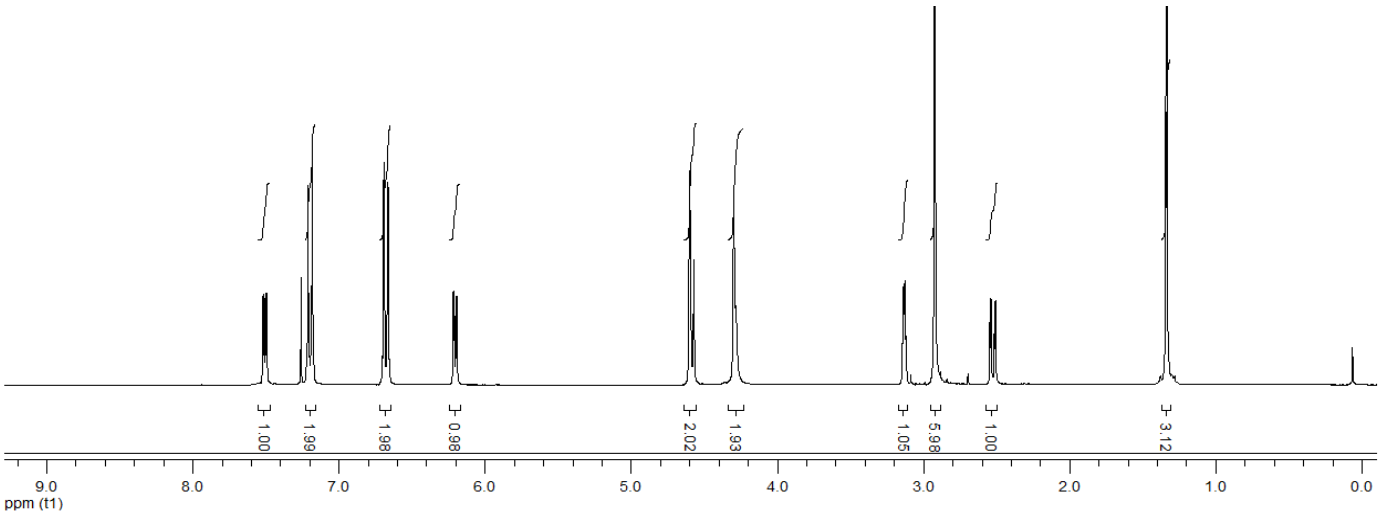


D_6-Acetone, 75 MHz

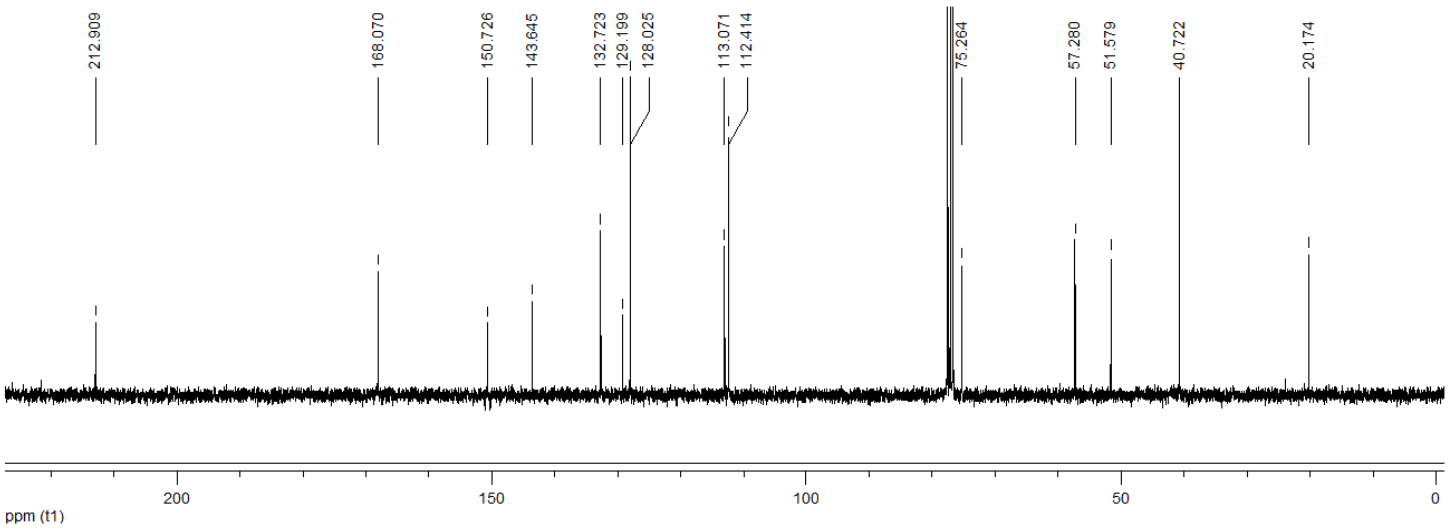


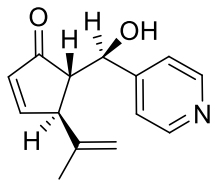


(+)-133i, $CDCl_3$, 300 MHz

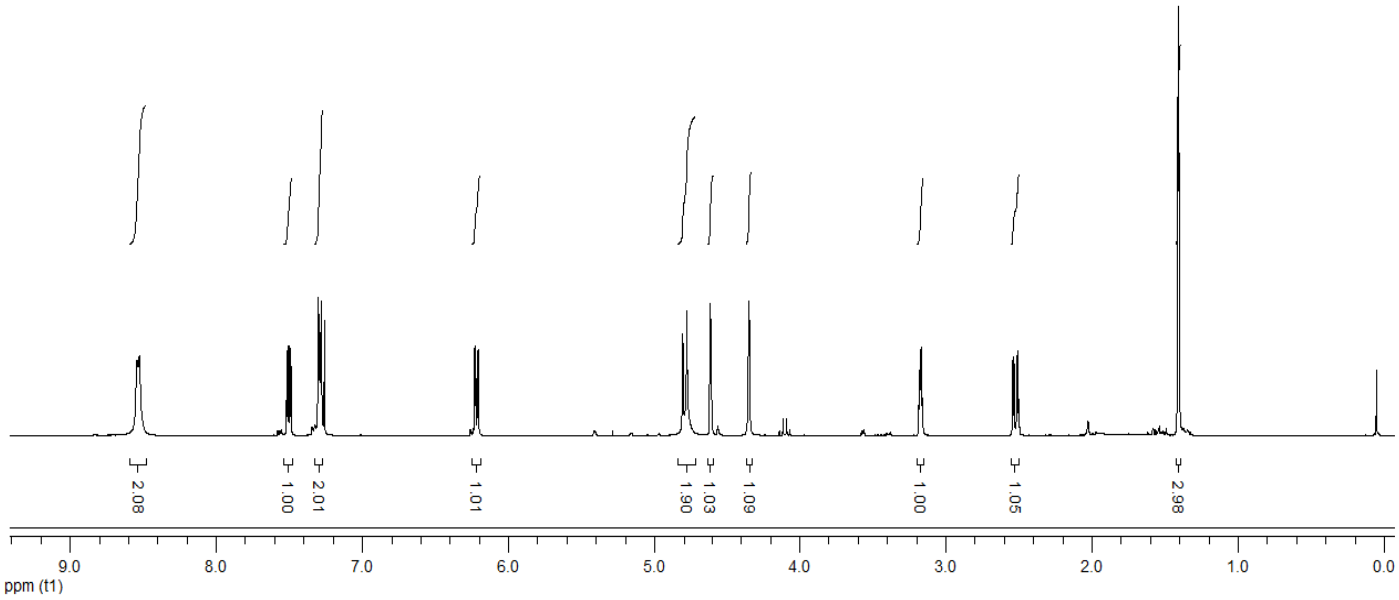


$CDCl_3$, 75 MHz

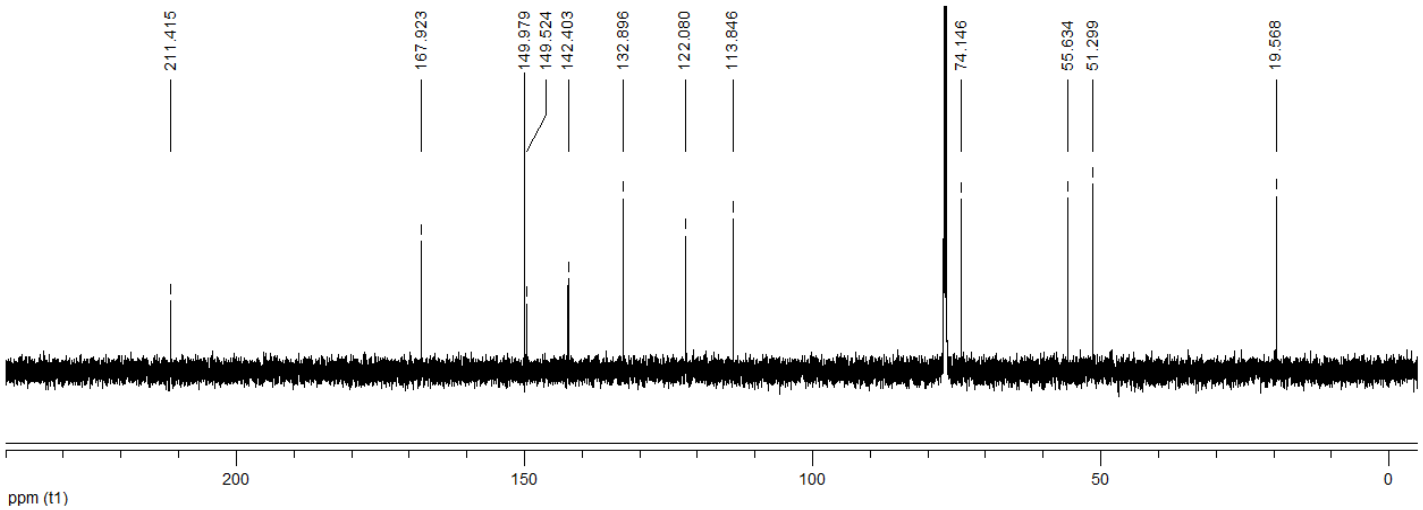


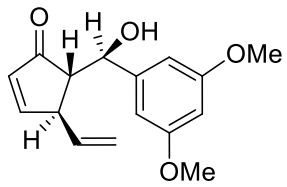


(+)-133j, $CDCl_3$, 300 MHz

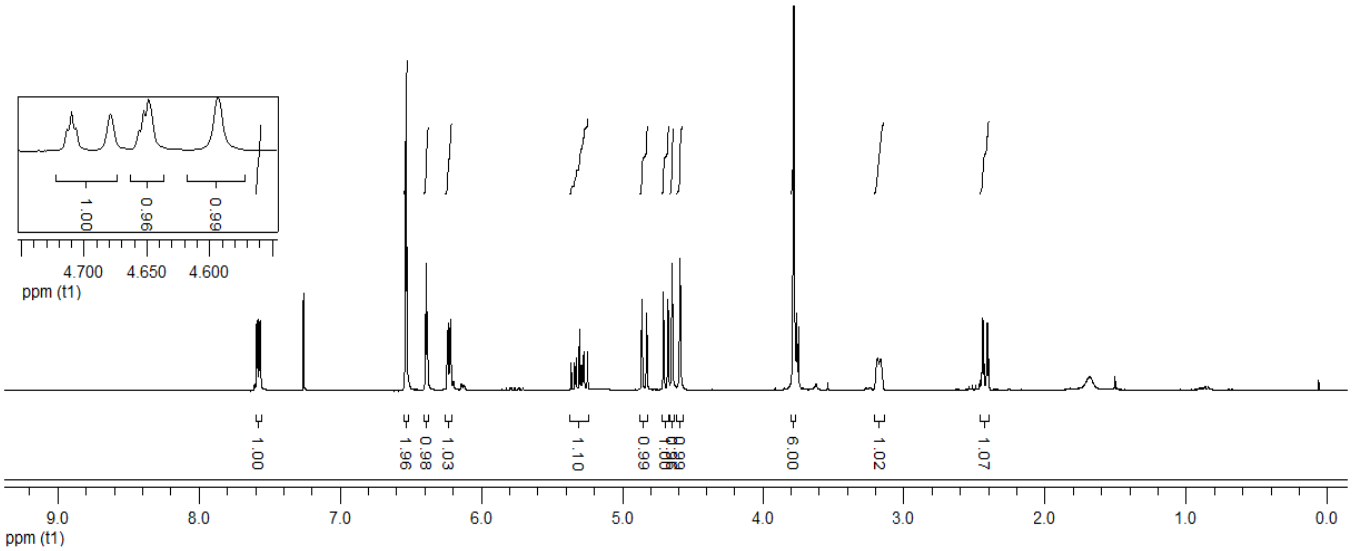


$CDCl_3$, 75 MHz

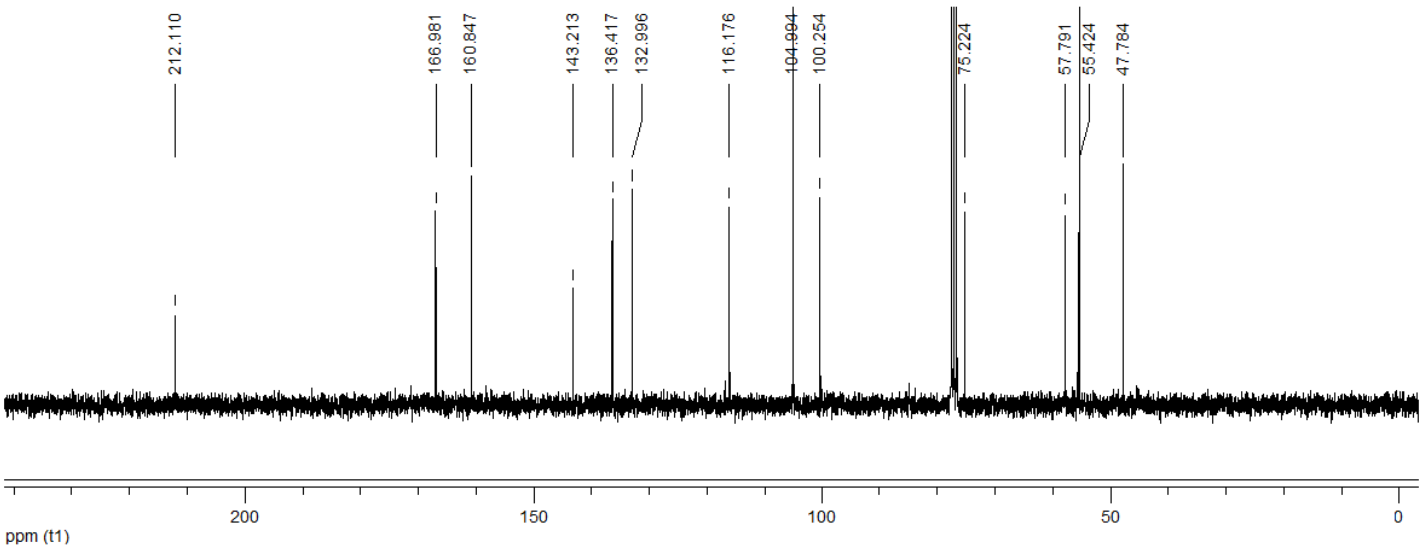


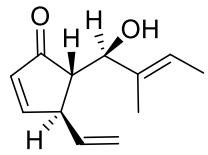


(+)-133k, $CDCl_3$, 300 MHz

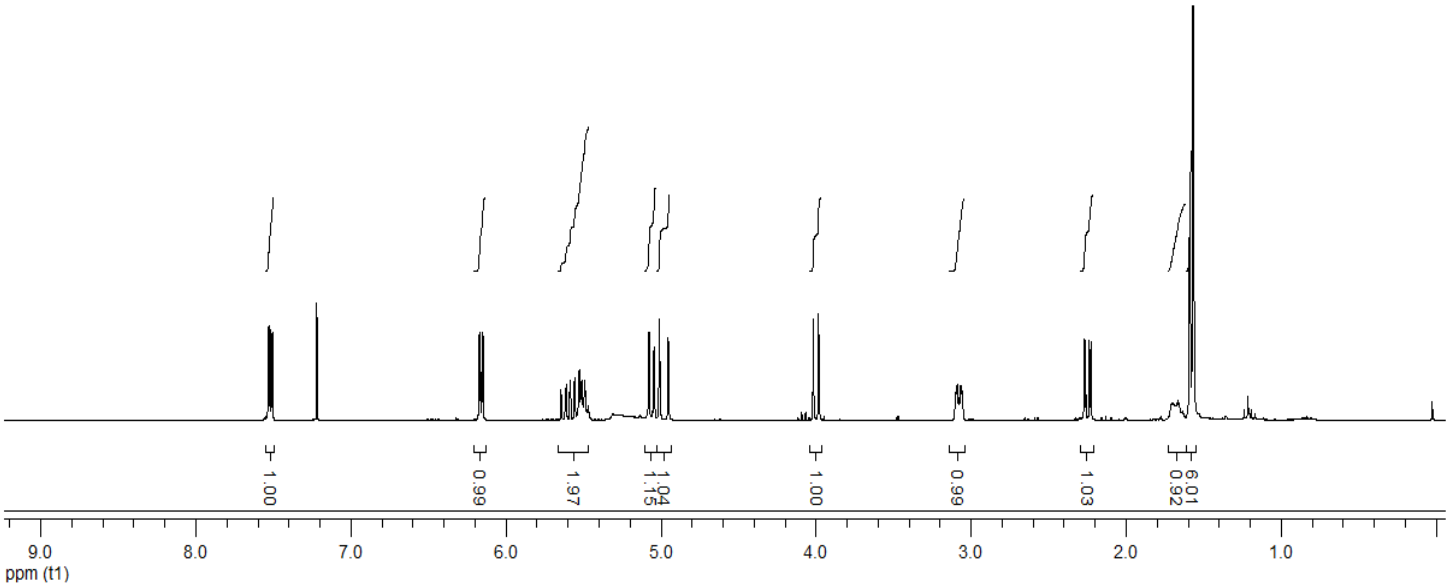


$CDCl_3$, 75 MHz

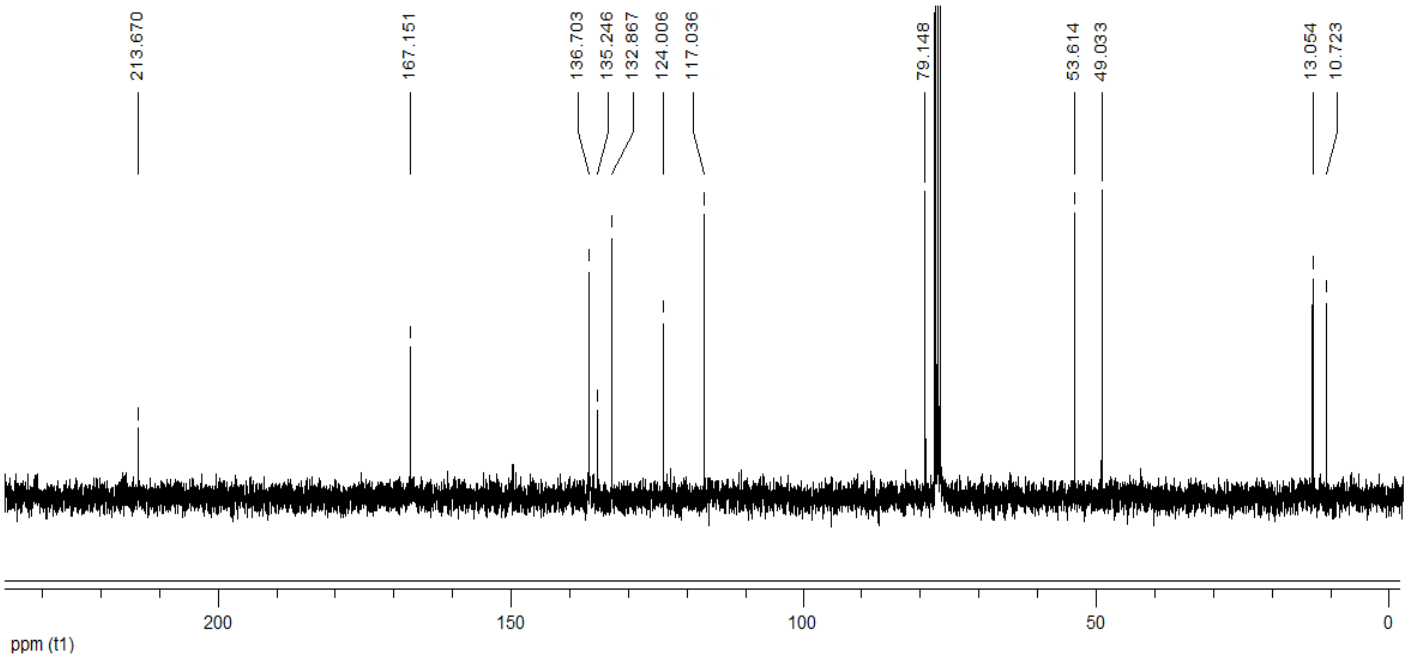


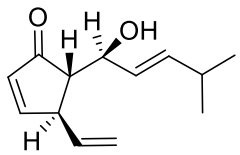


(+)-133l, $CDCl_3$, 300 MHz

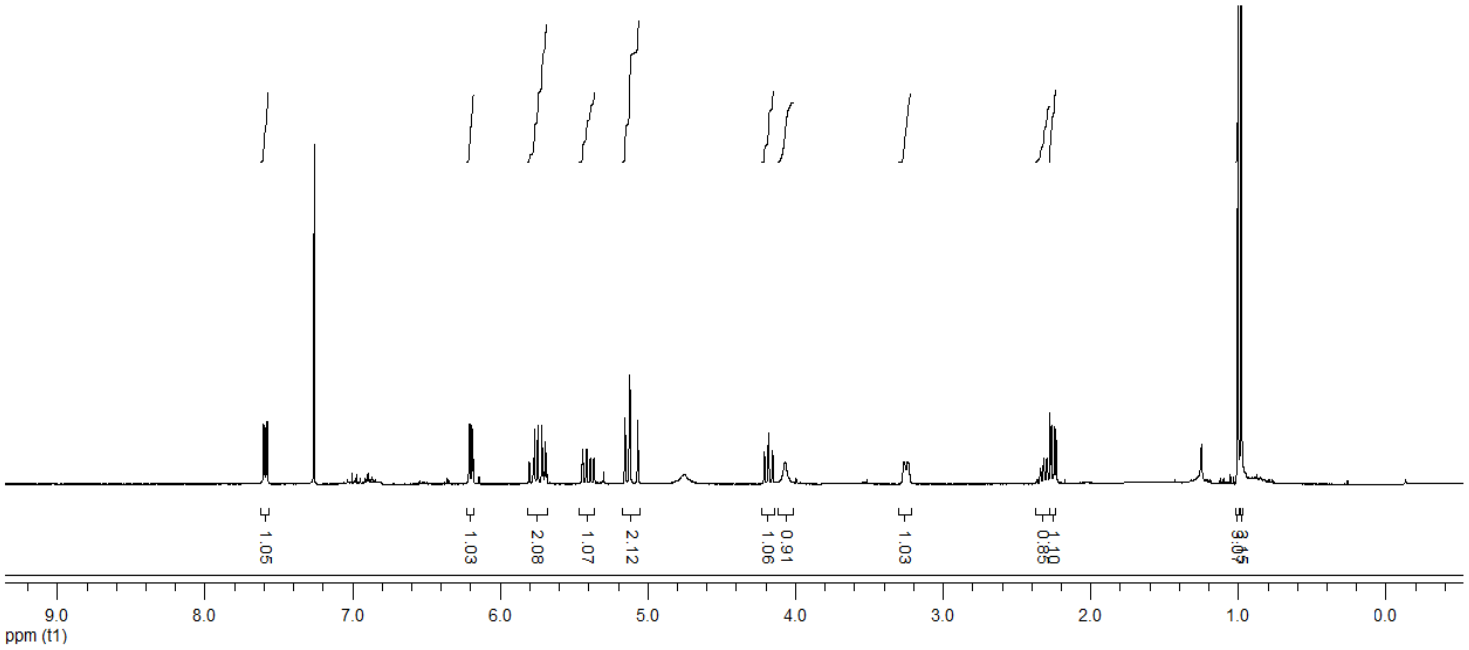


$CDCl_3$, 75 MHz

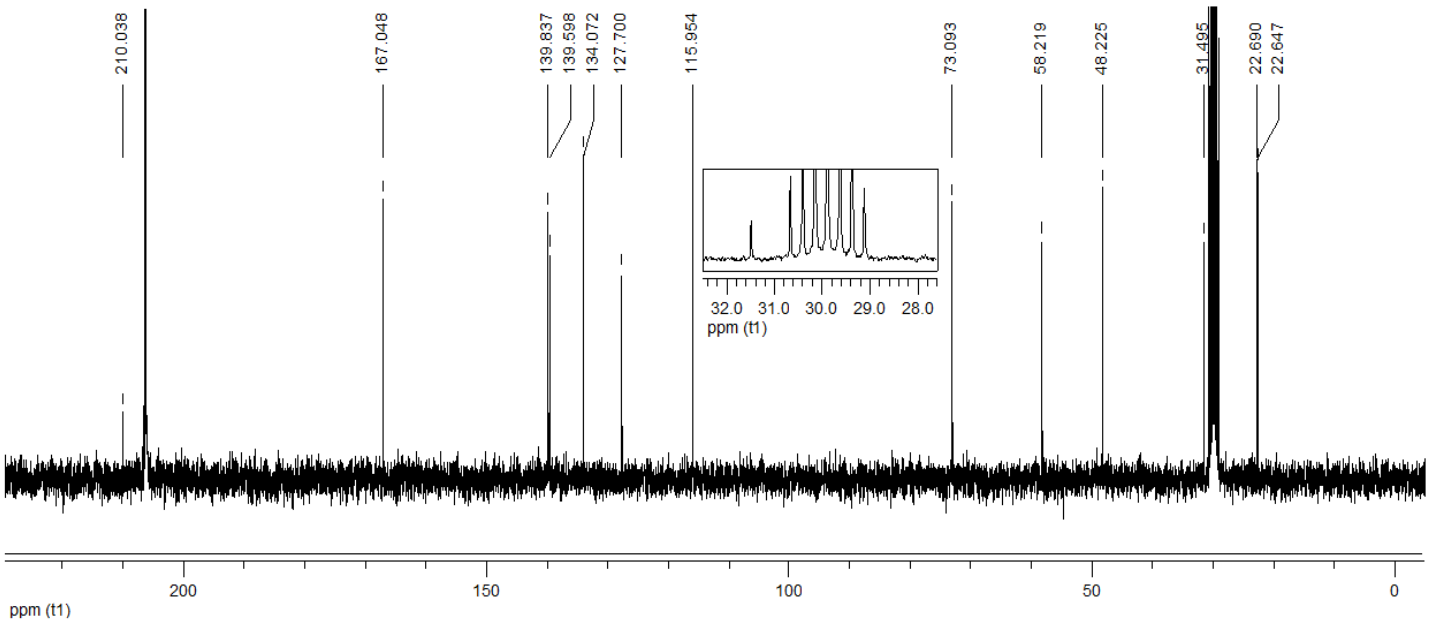


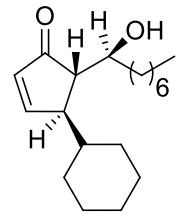


(+)-133m, d_6-Acetone, 300 MHz

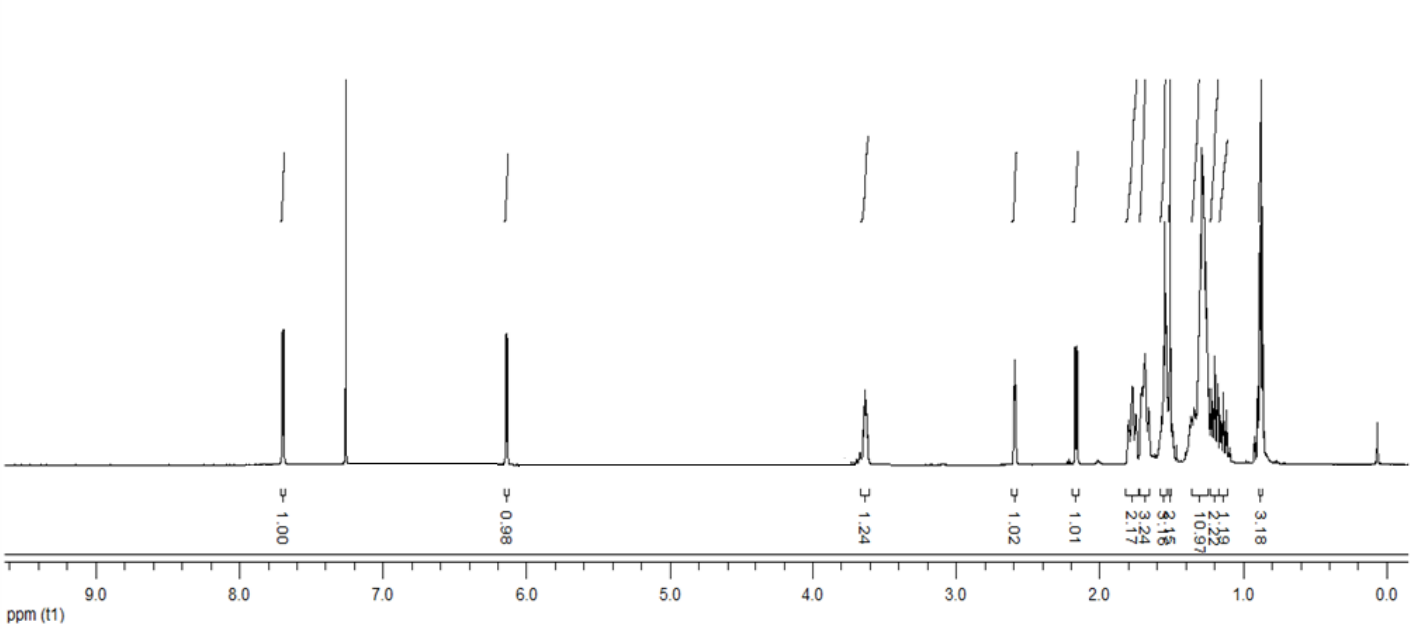


D_6-Acetone, 75 MHz

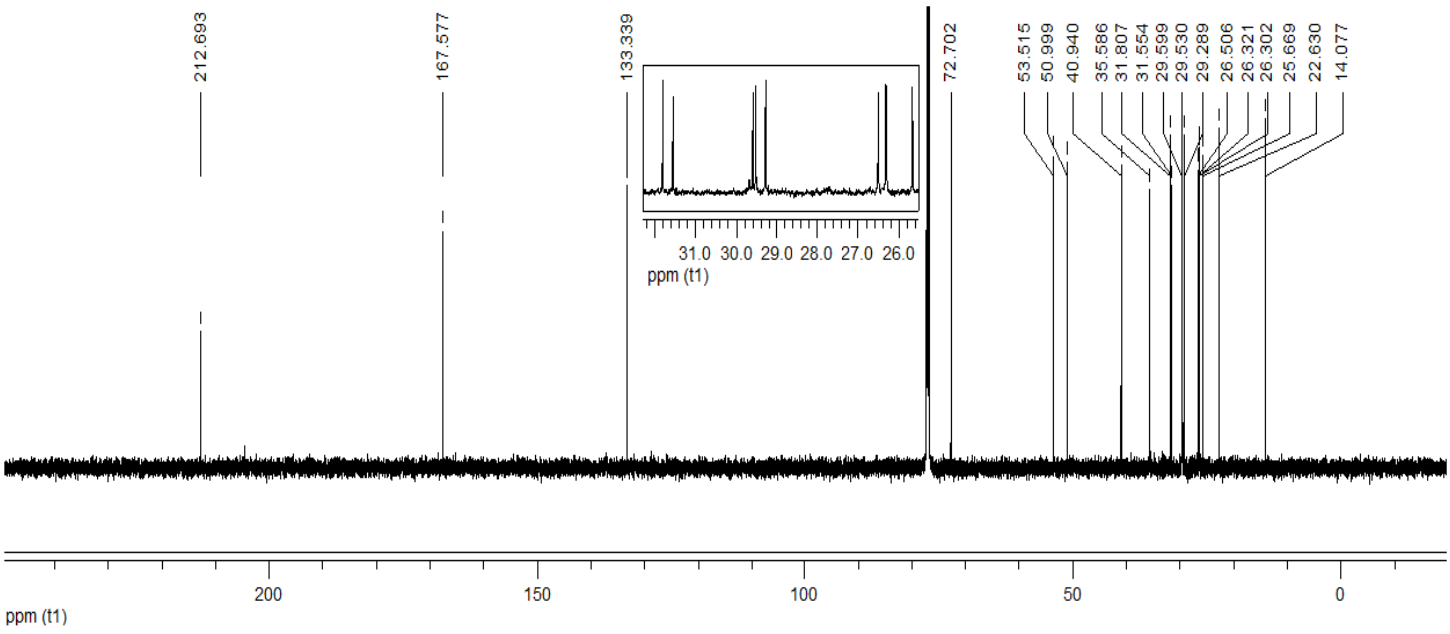


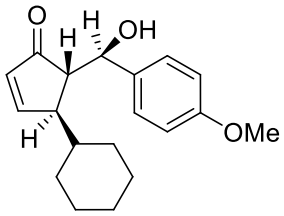


(+)-133n, $CDCl_3$, 600 MHz

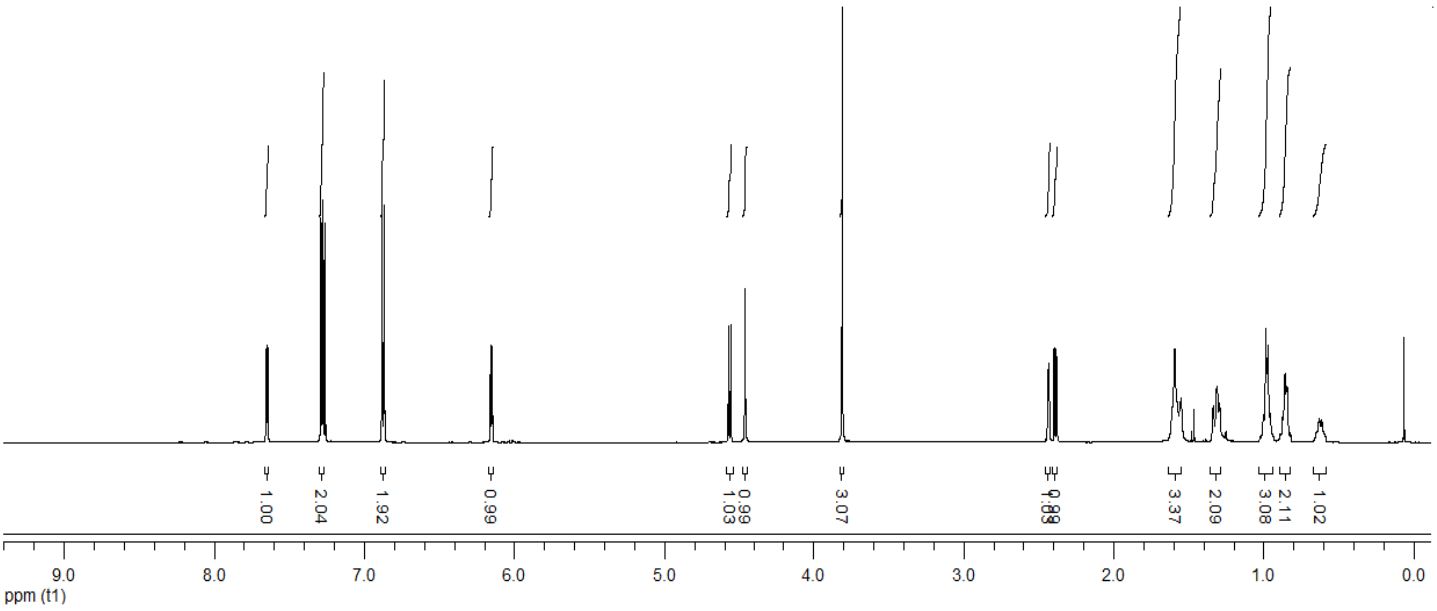


$CDCl_3$, 151 MHz

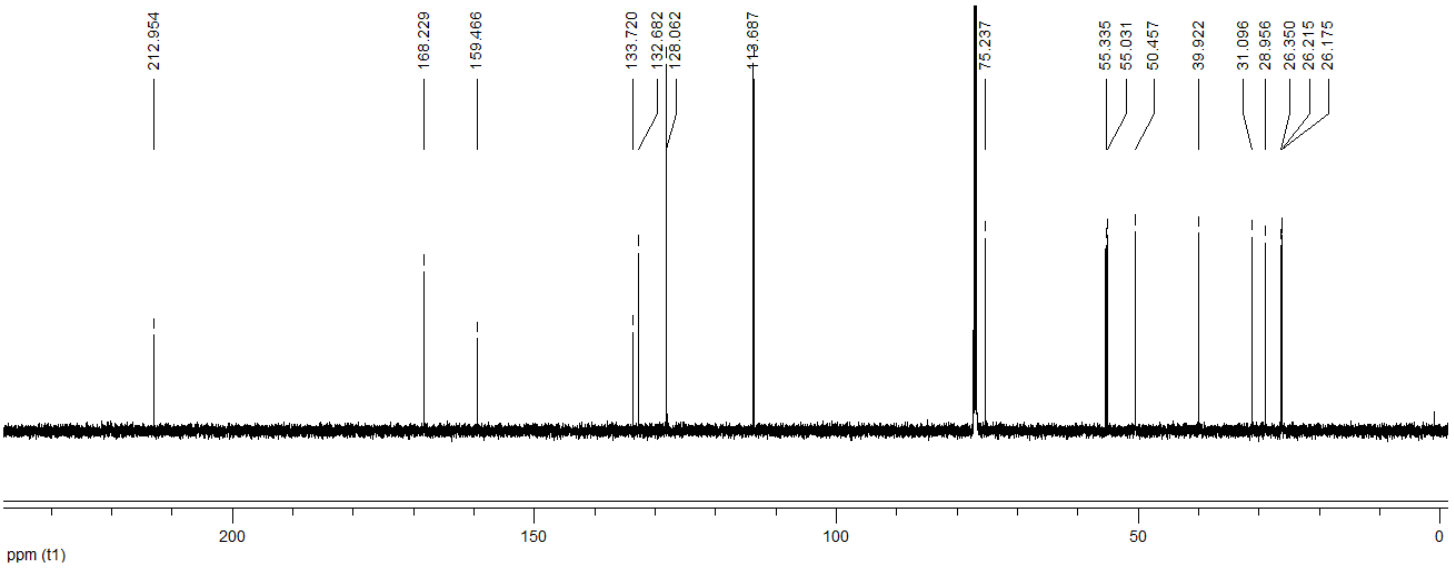


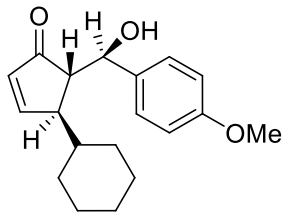


(+)-133o, $CDCl_3$, 600 MHz

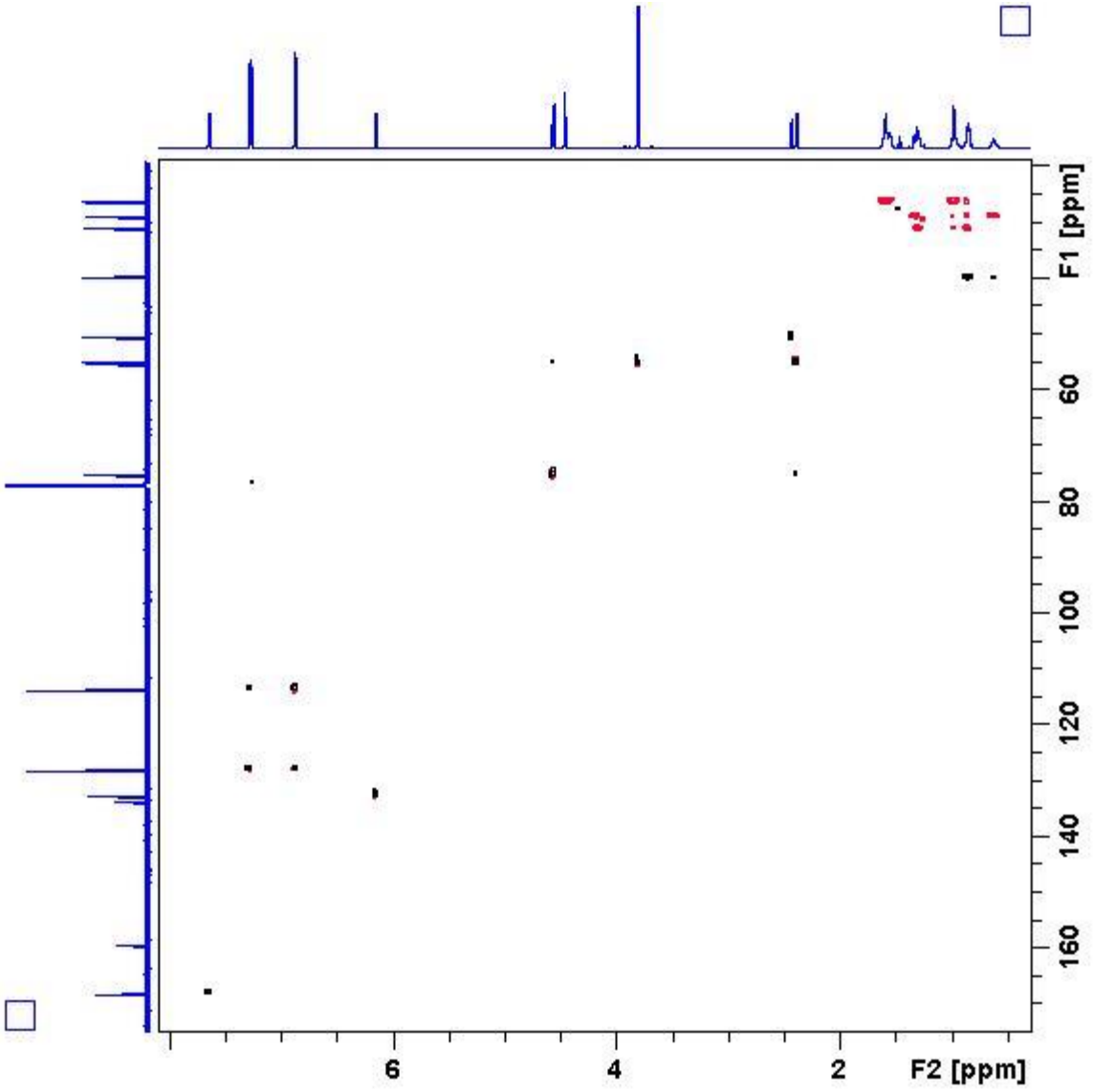


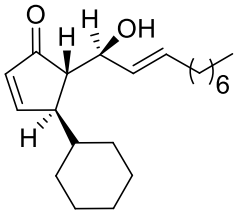
$CDCl_3$, 151 MHz



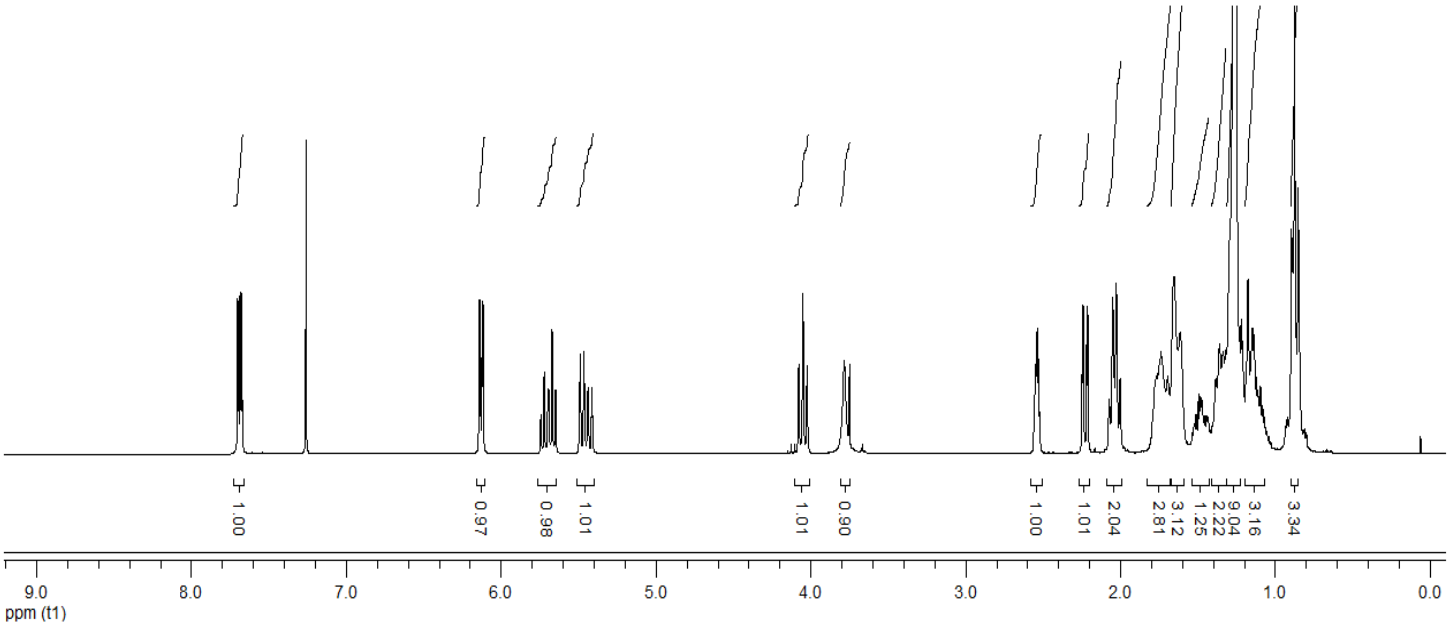


(+)-133o, HSQC, $CDCl_3$, 600 MHz

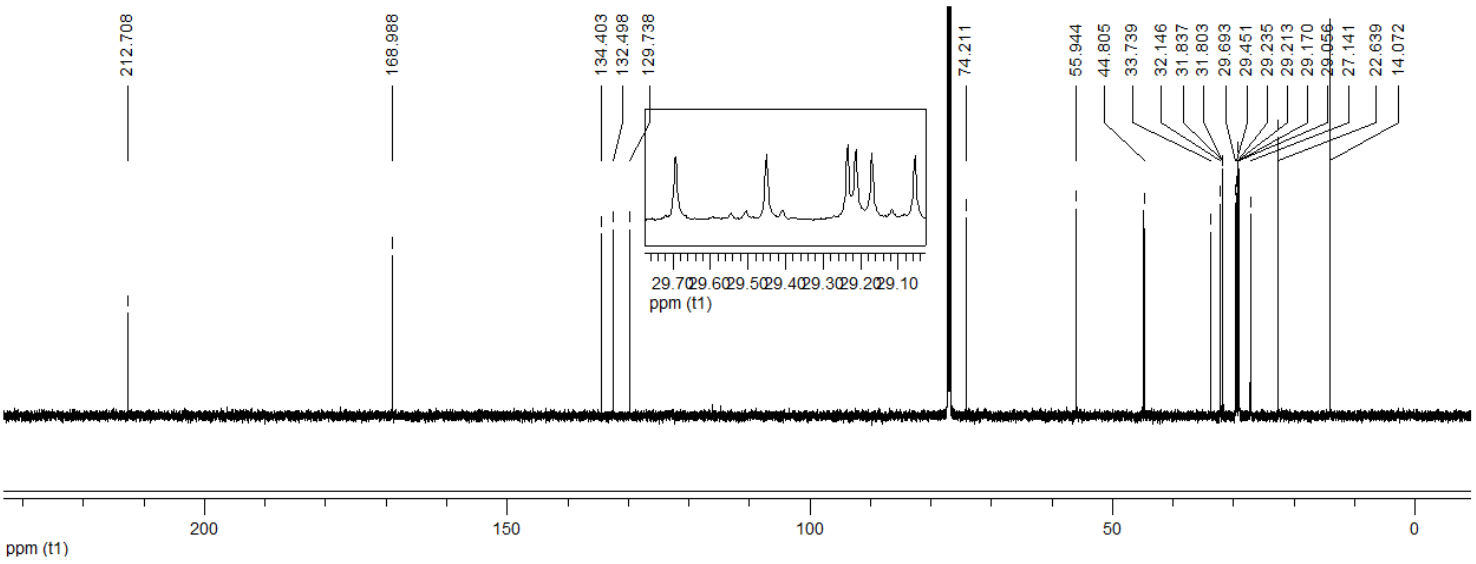


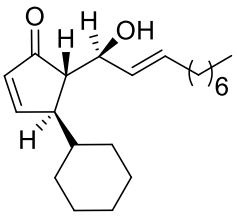


(+)-133p, $CDCl_3$, 600 MHz

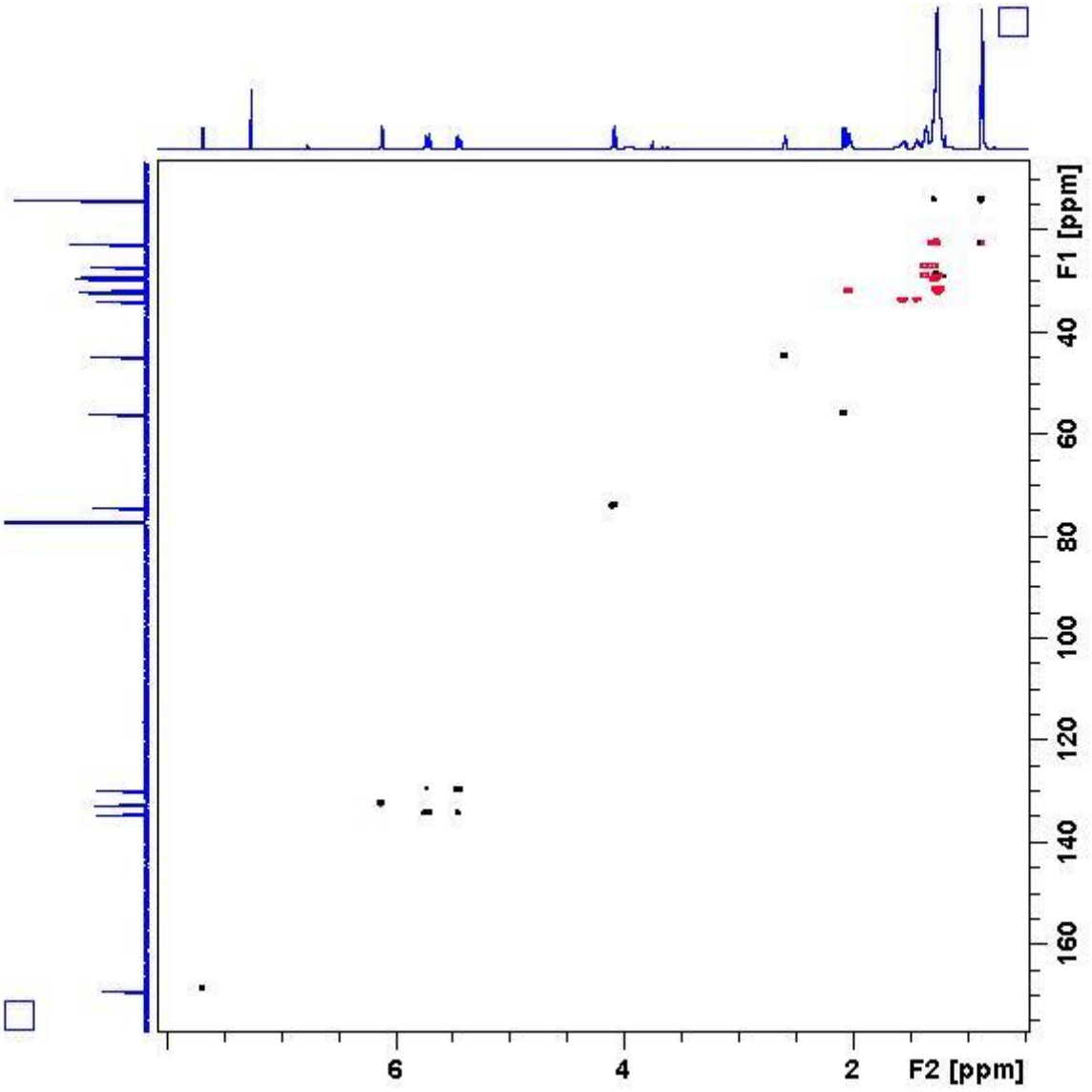


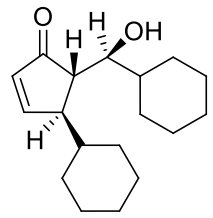
$CDCl_3$, 151 MHz



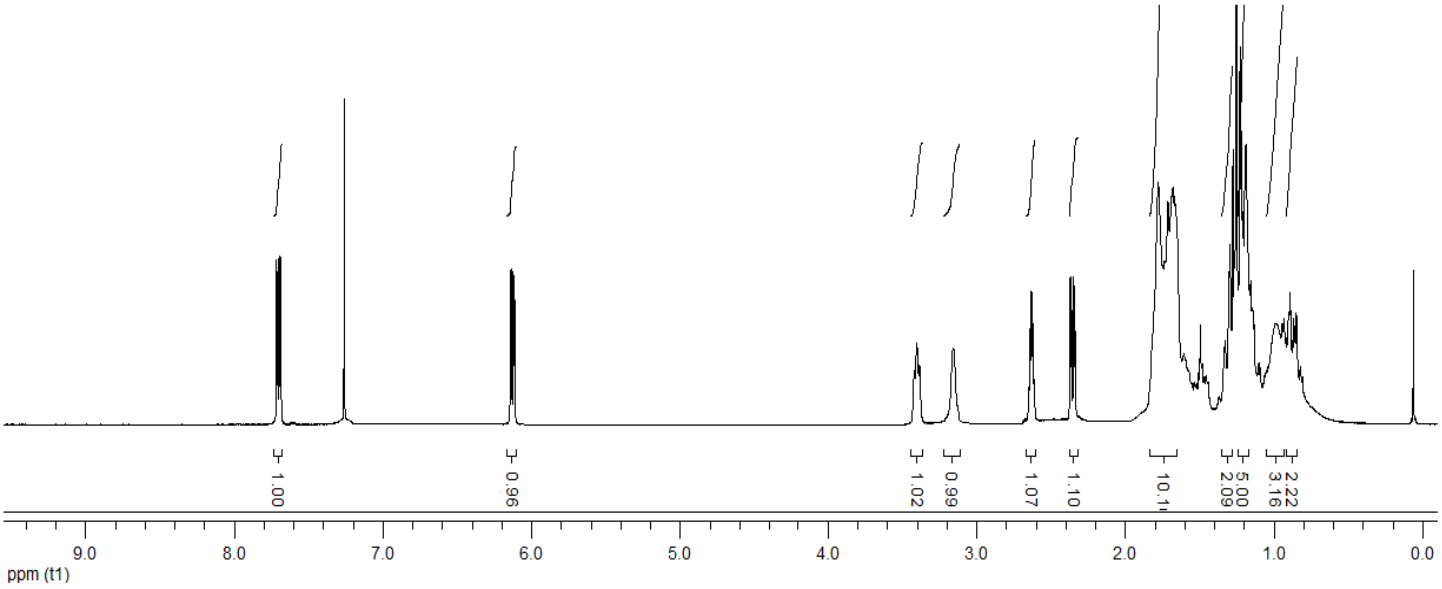


(+)-133p, HSQC, $CDCl_3$, 600 MHz

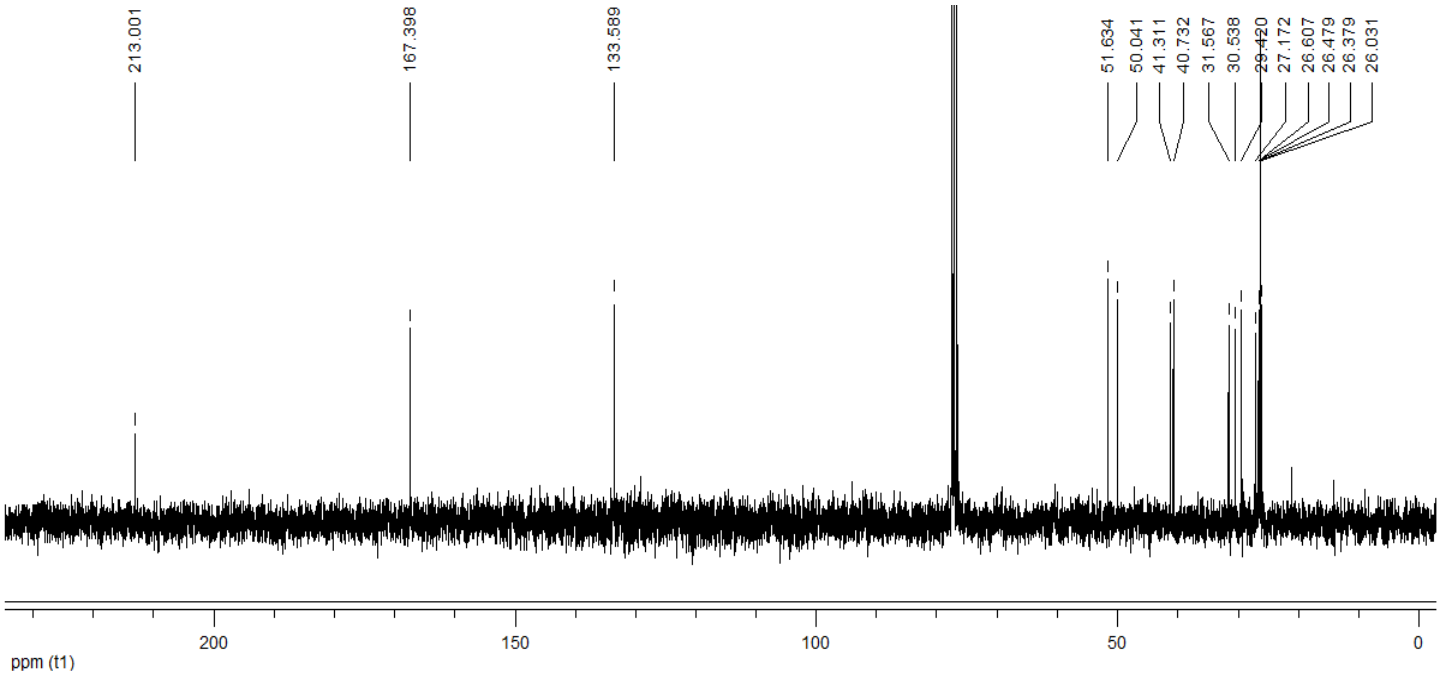


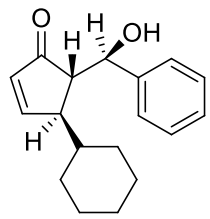


(+)-133q, $CDCl_3$, 300 MHz

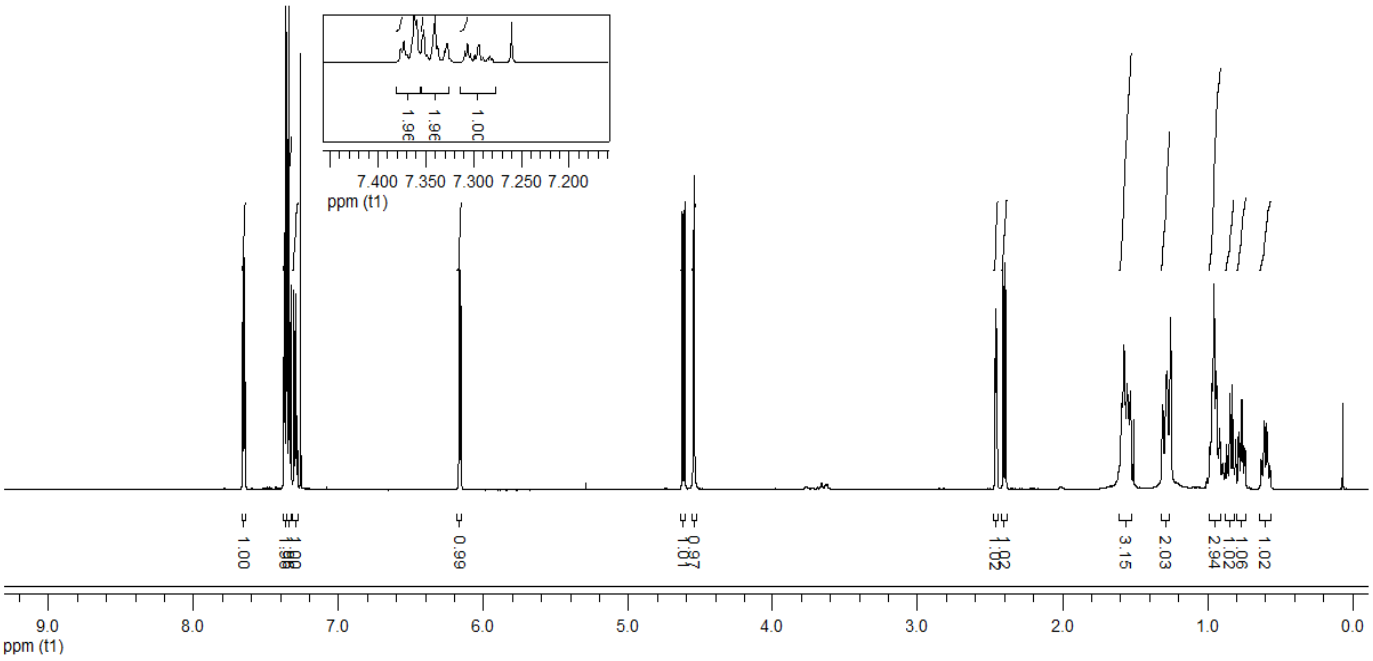


$CDCl_3$, 75 MHz

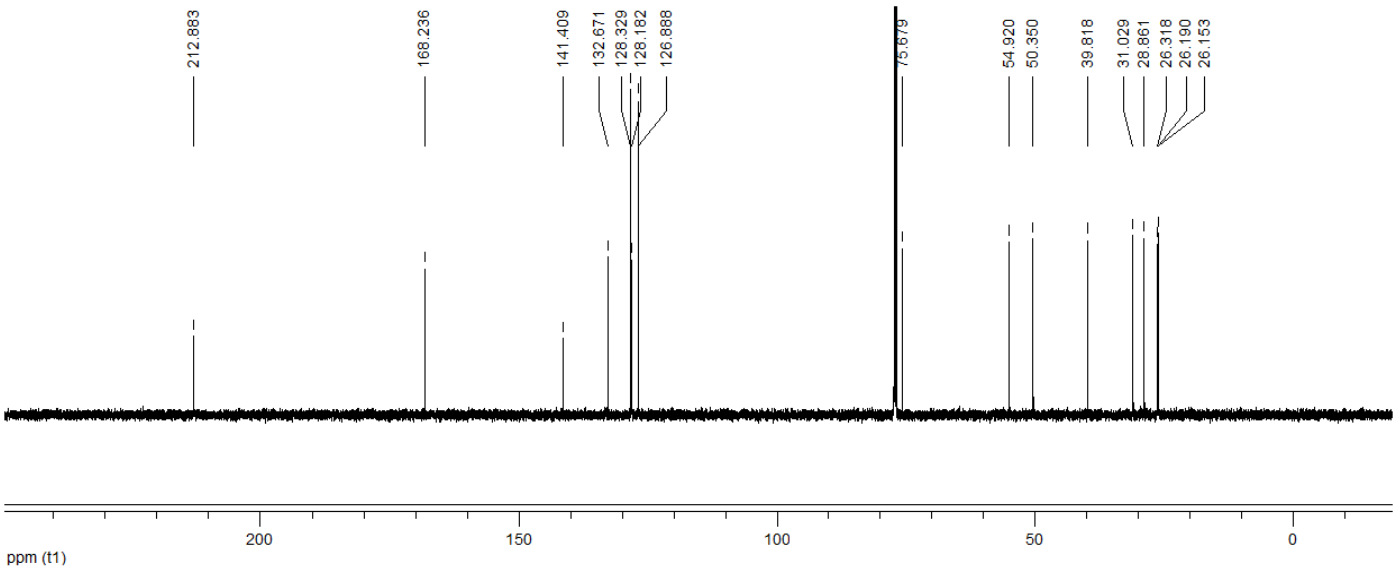


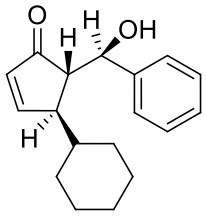


(+)-133r, $CDCl_3$, 600 MHz

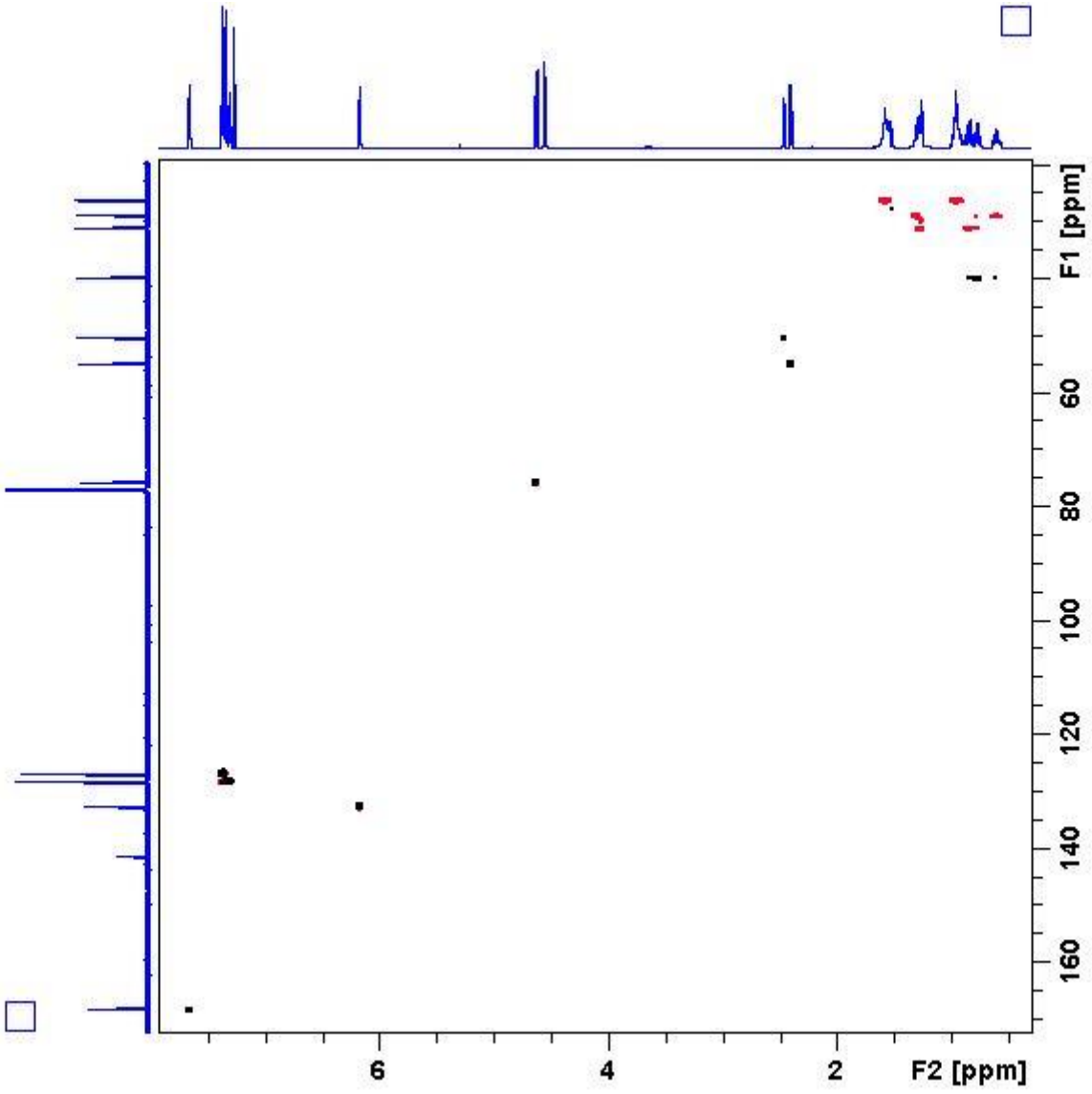


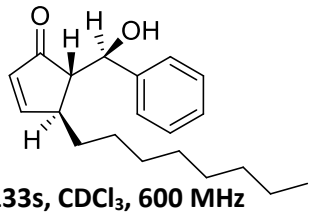
$CDCl_3$, 151 MHz



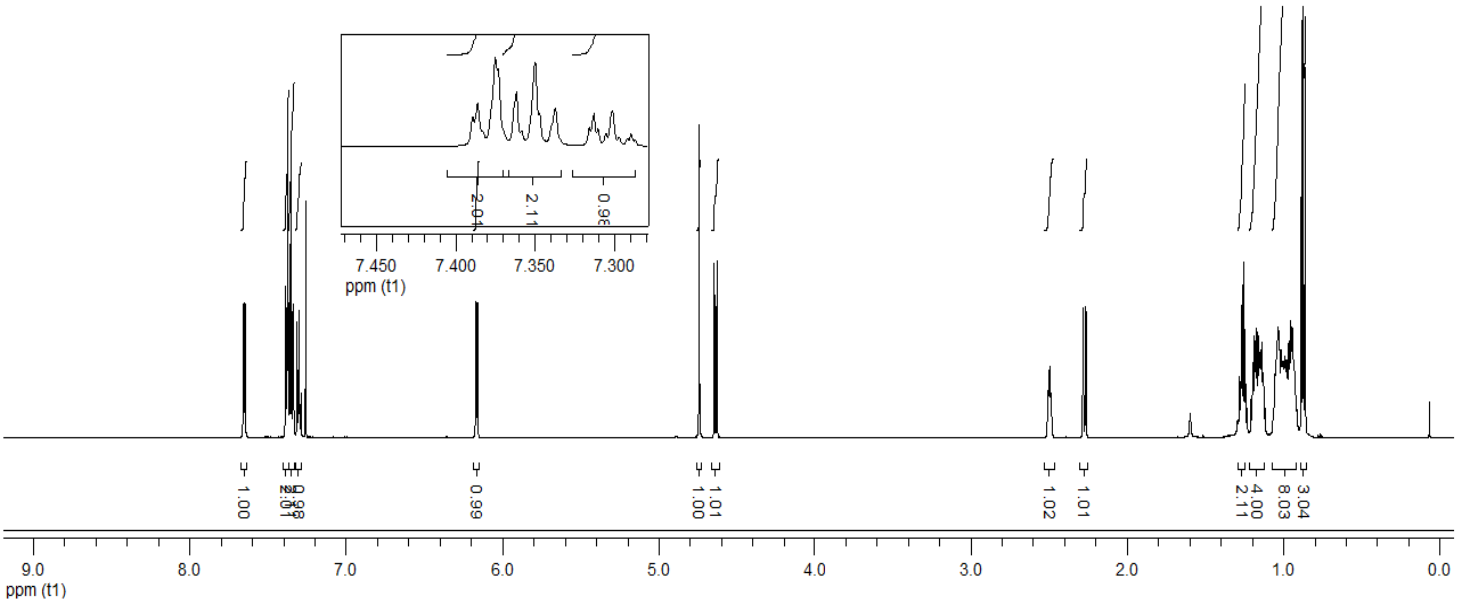


(+)-133r, HSQC, $CDCl_3$, 600 MHz

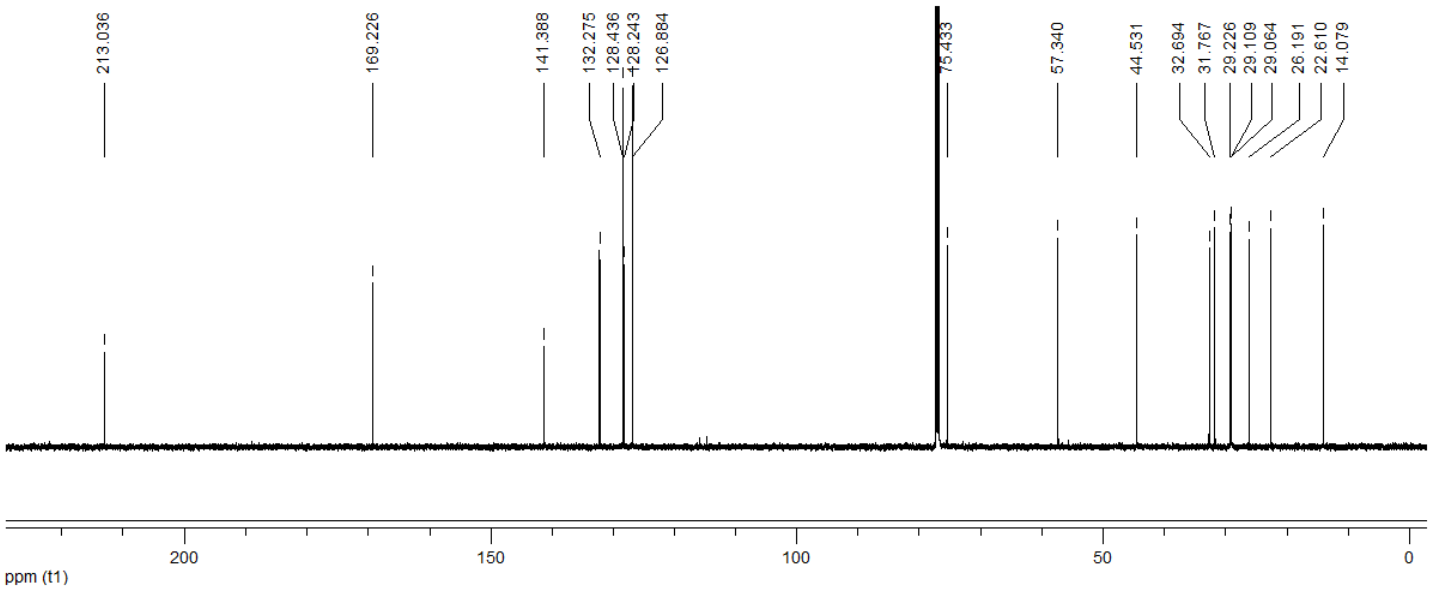


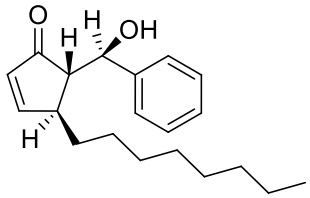


(+)-133s, $CDCl_3$, 600 MHz

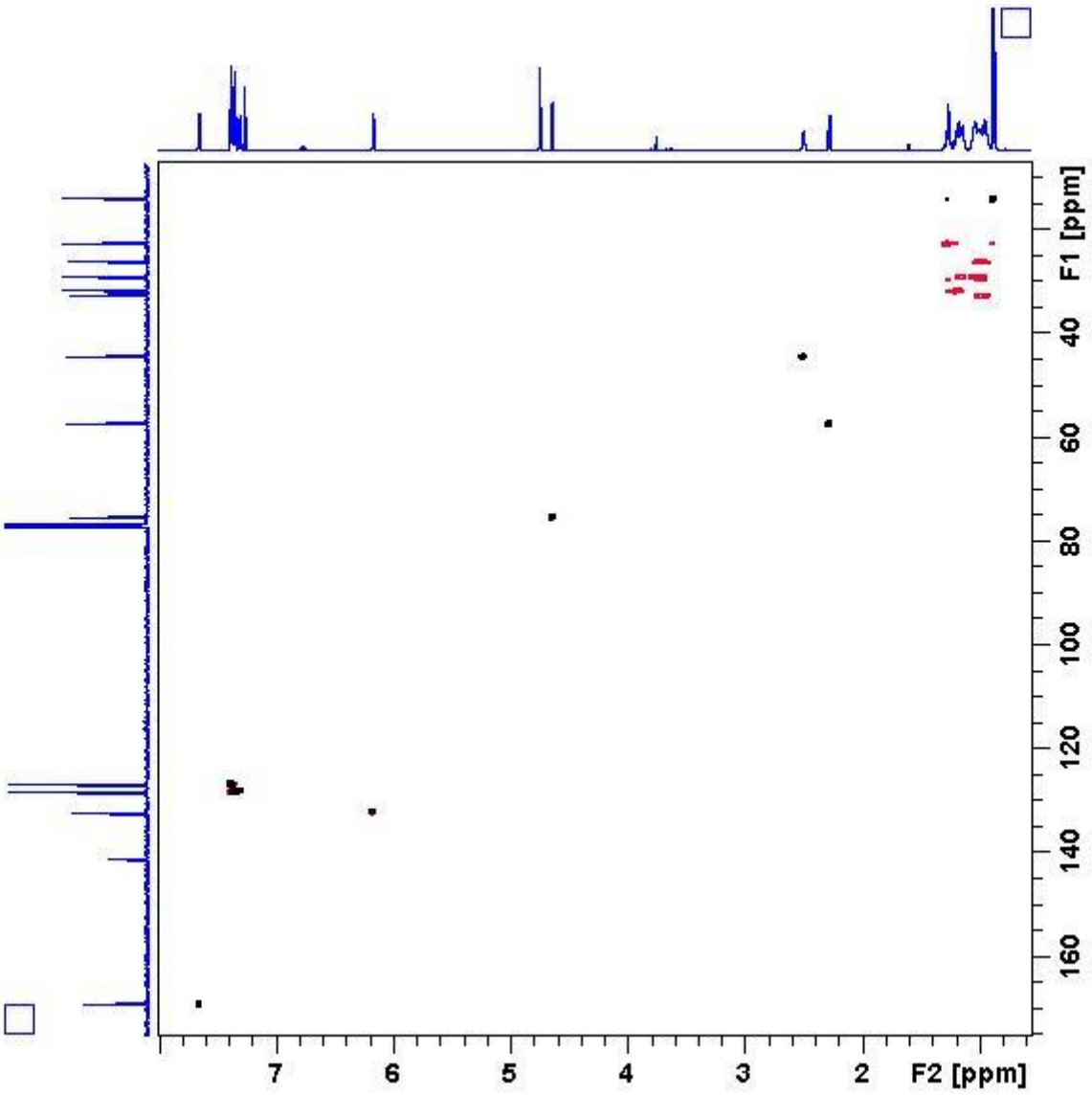


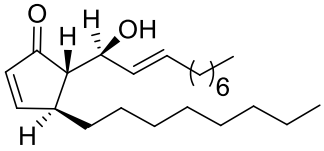
$CDCl_3$, 151 MHz



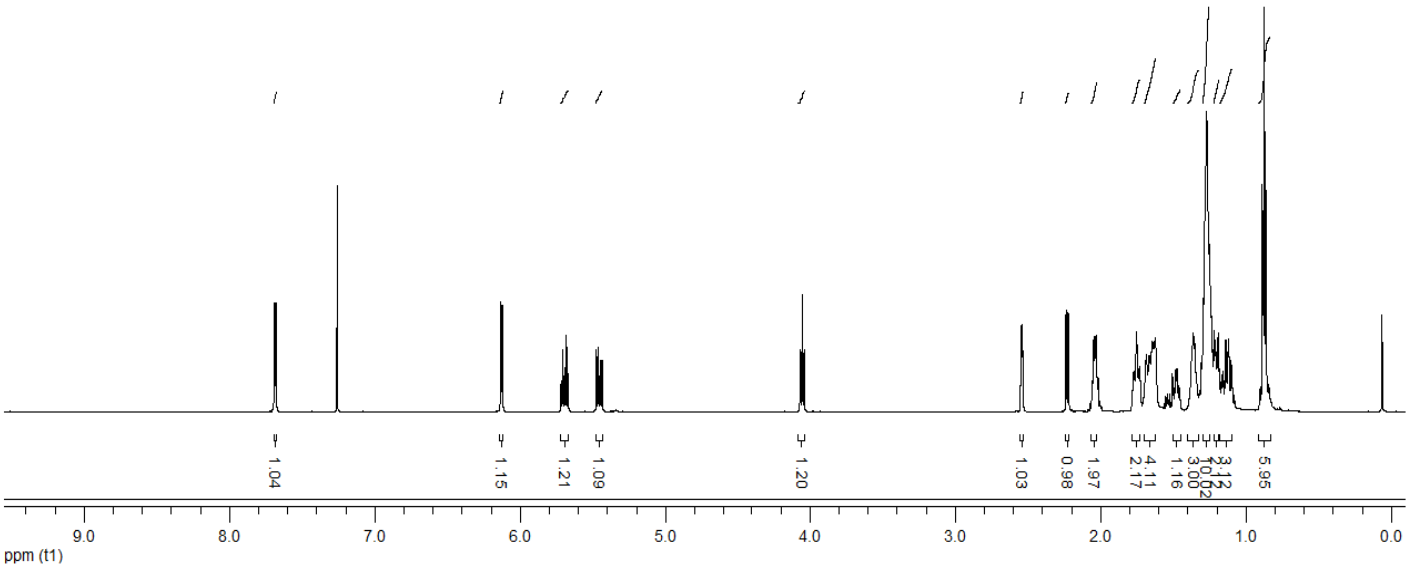


(+)-133s, HSQC, $CDCl_3$, 600 MHz

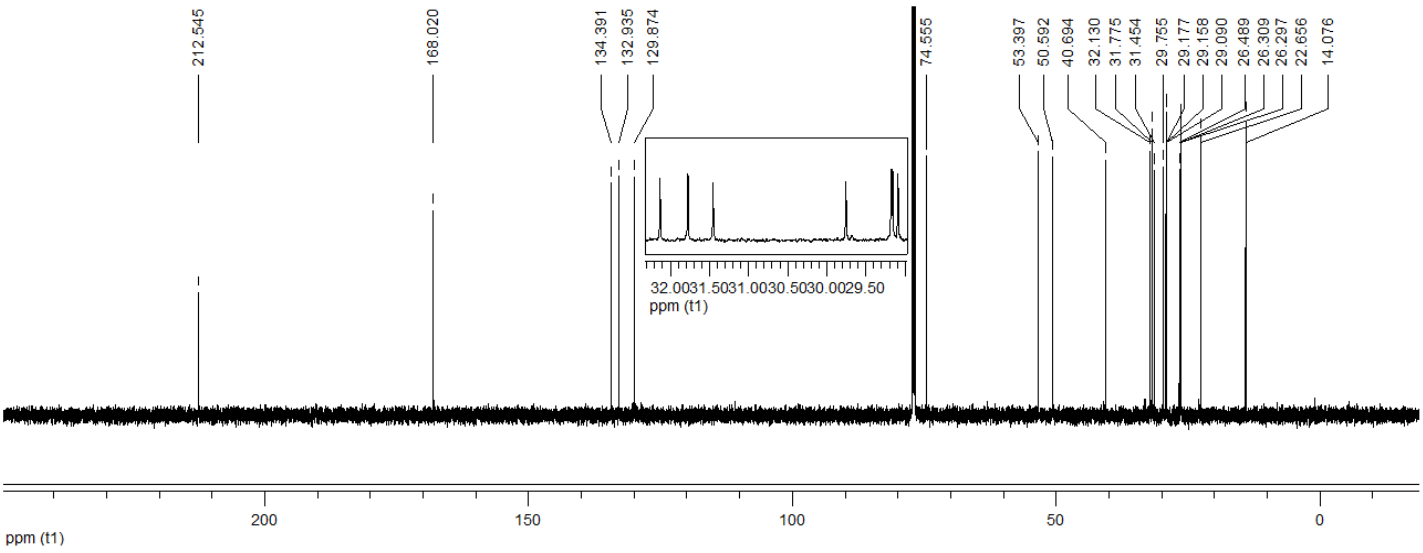


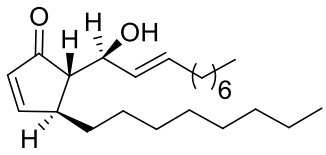


(+)-133t, $CDCl_3$, 600 MHz

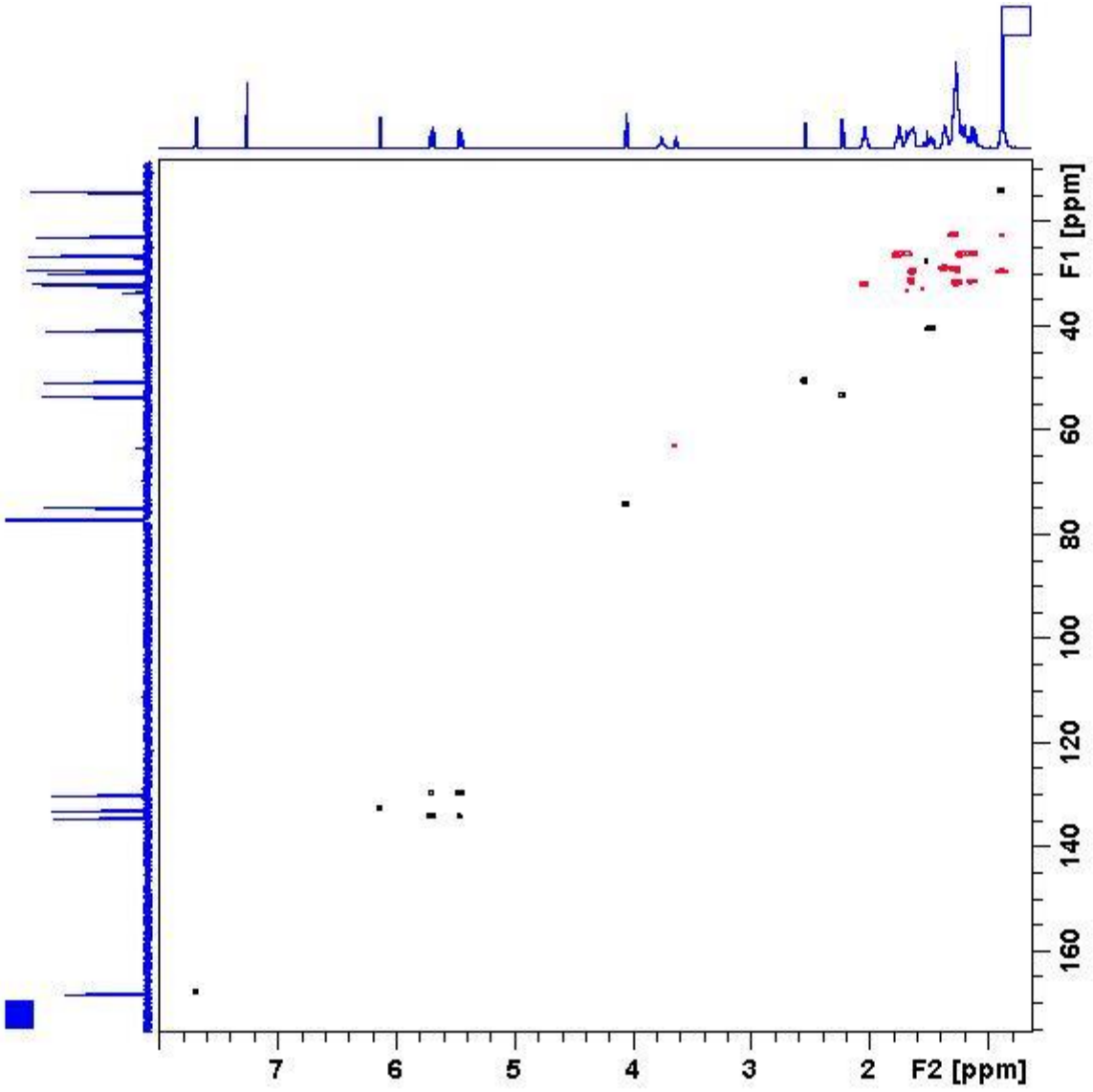


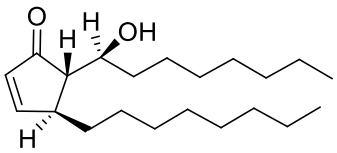
$CDCl_3$, 151 MHz



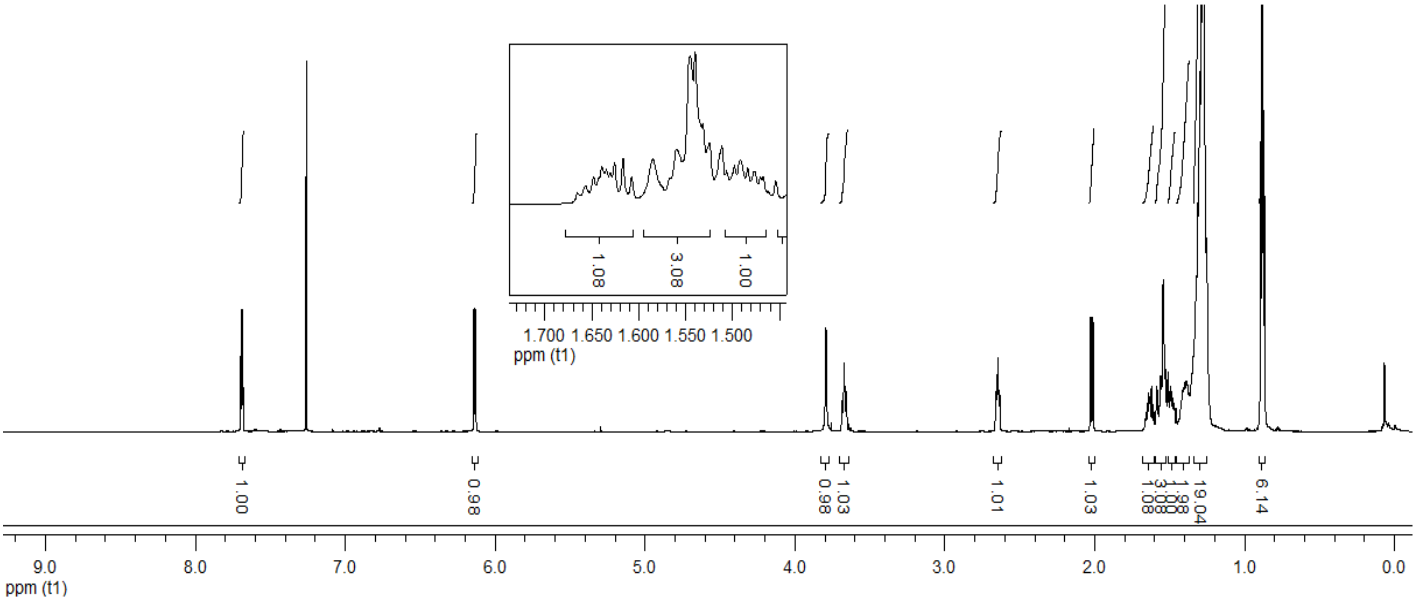


(+)-133t, HSQC, $CDCl_3$, 600 MHz

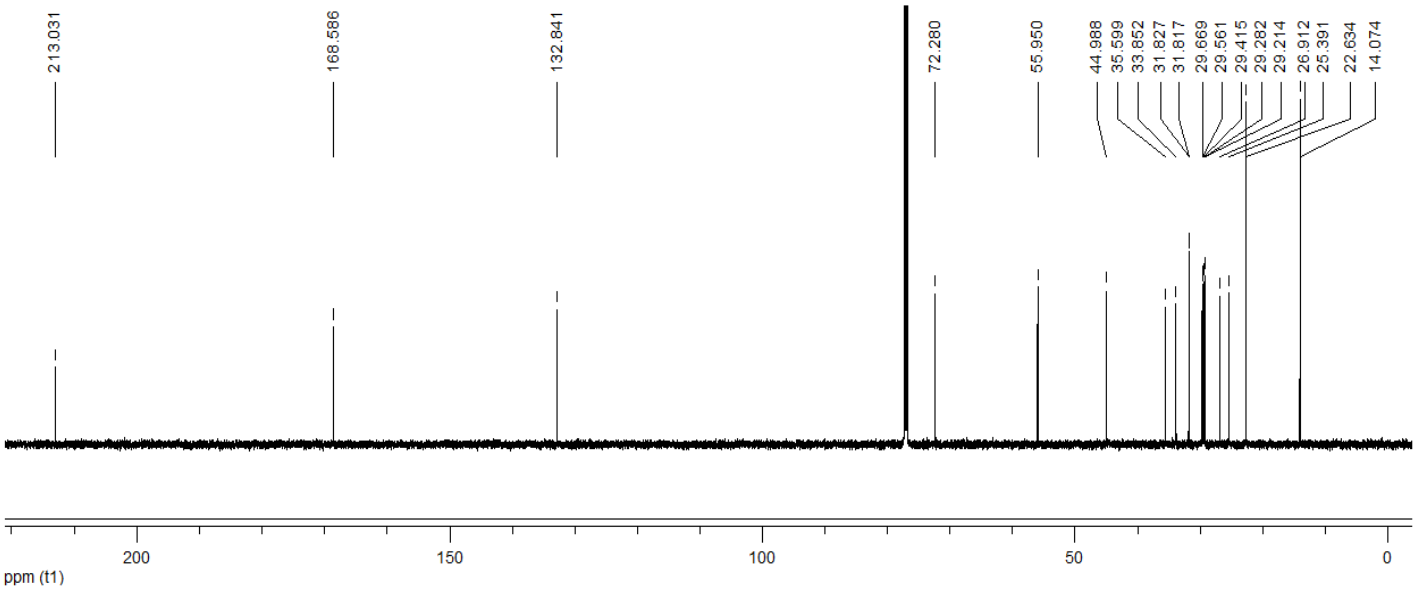


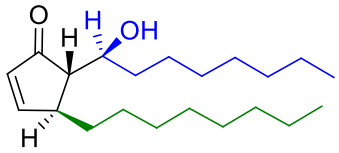


(+)-133u, $CDCl_3$, 600 MHz

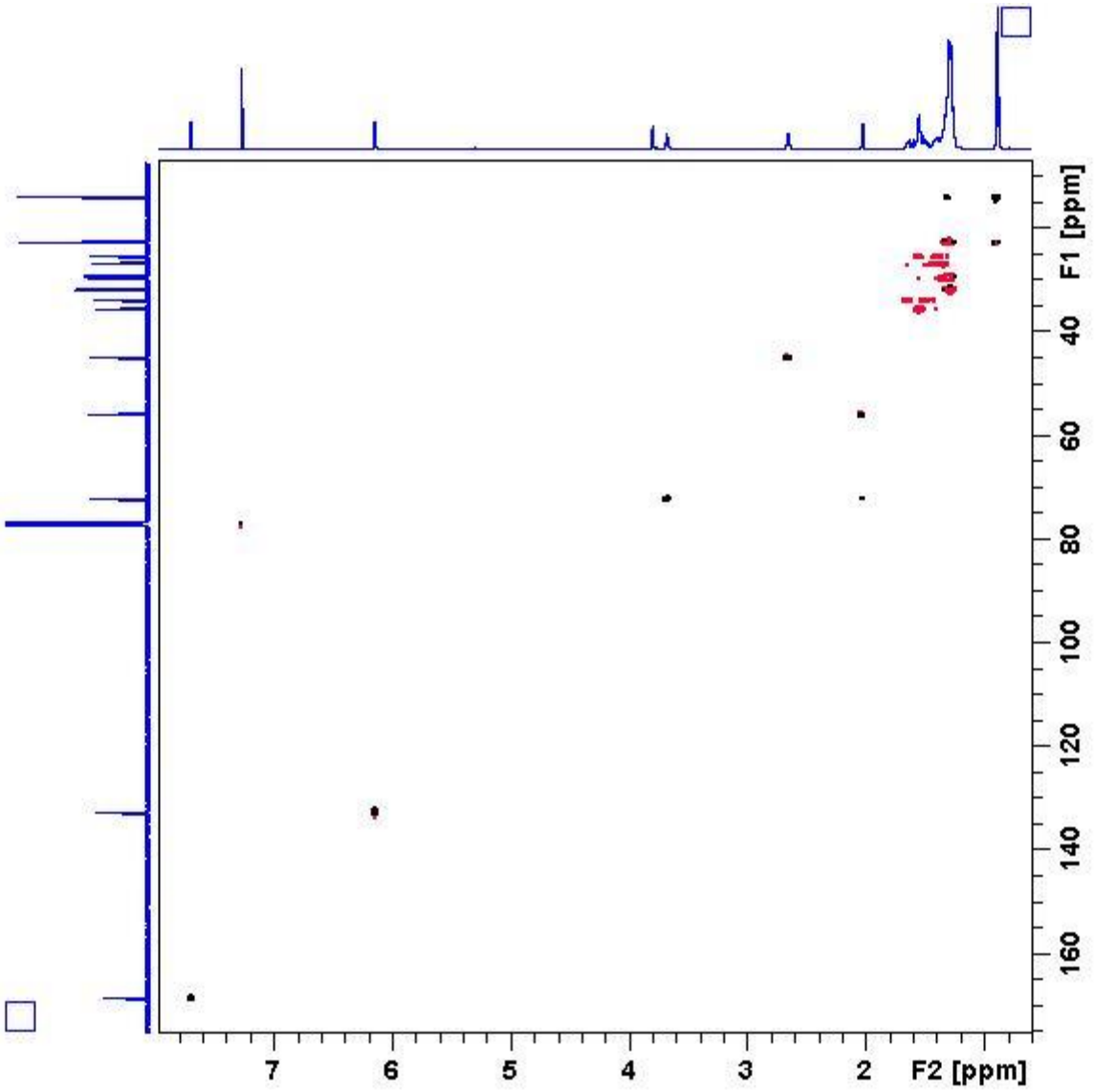


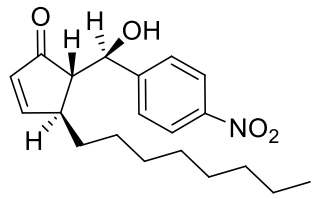
$CDCl_3$, 151 MHz



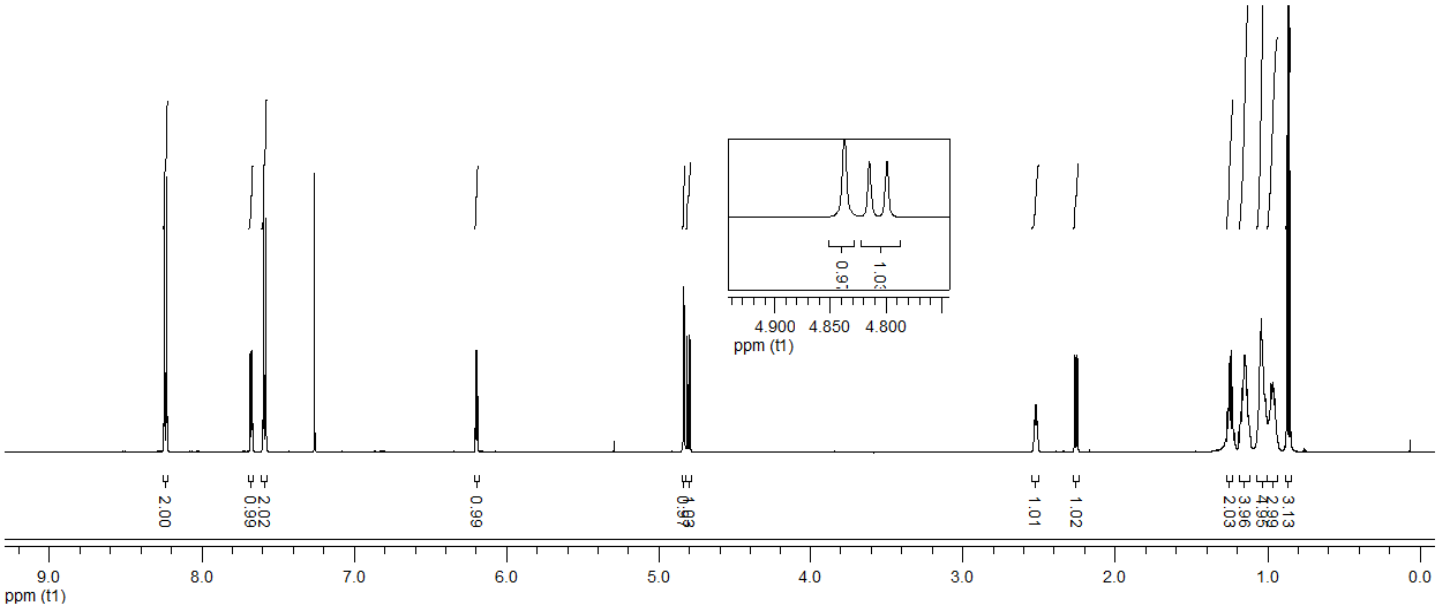


(+)-133u, HSQC, $CDCl_3$, 600 MHz

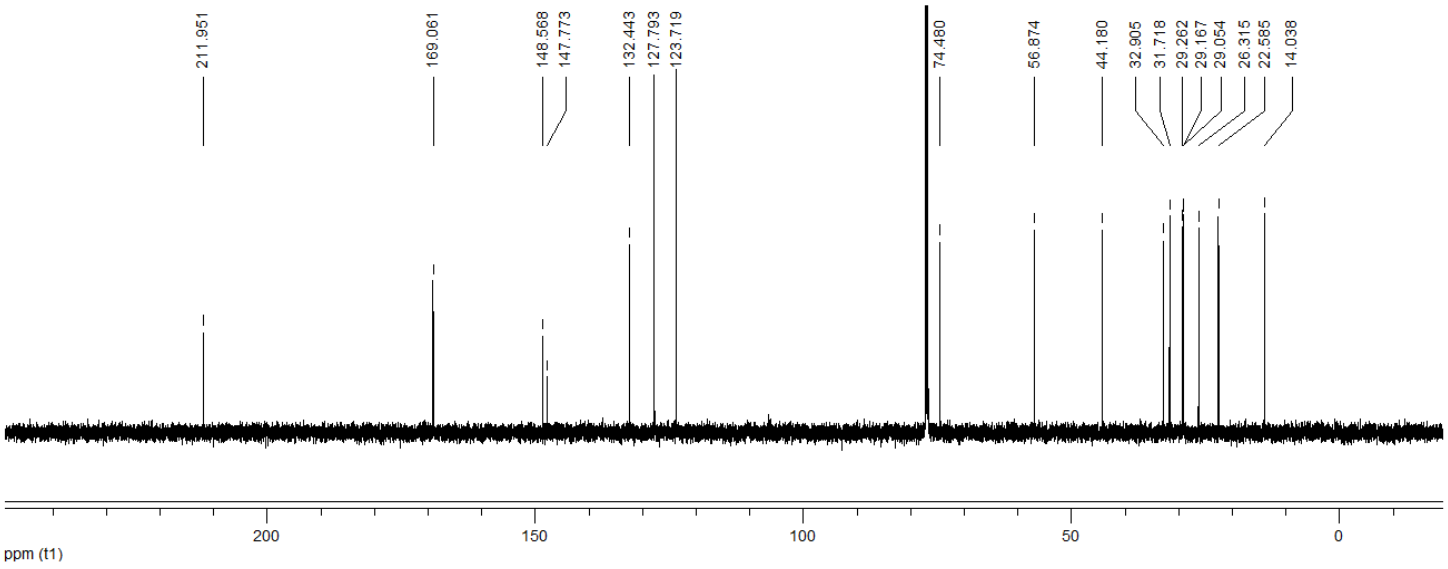


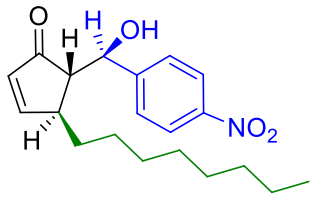


(+)-133v, $CDCl_3$, 600 MHz

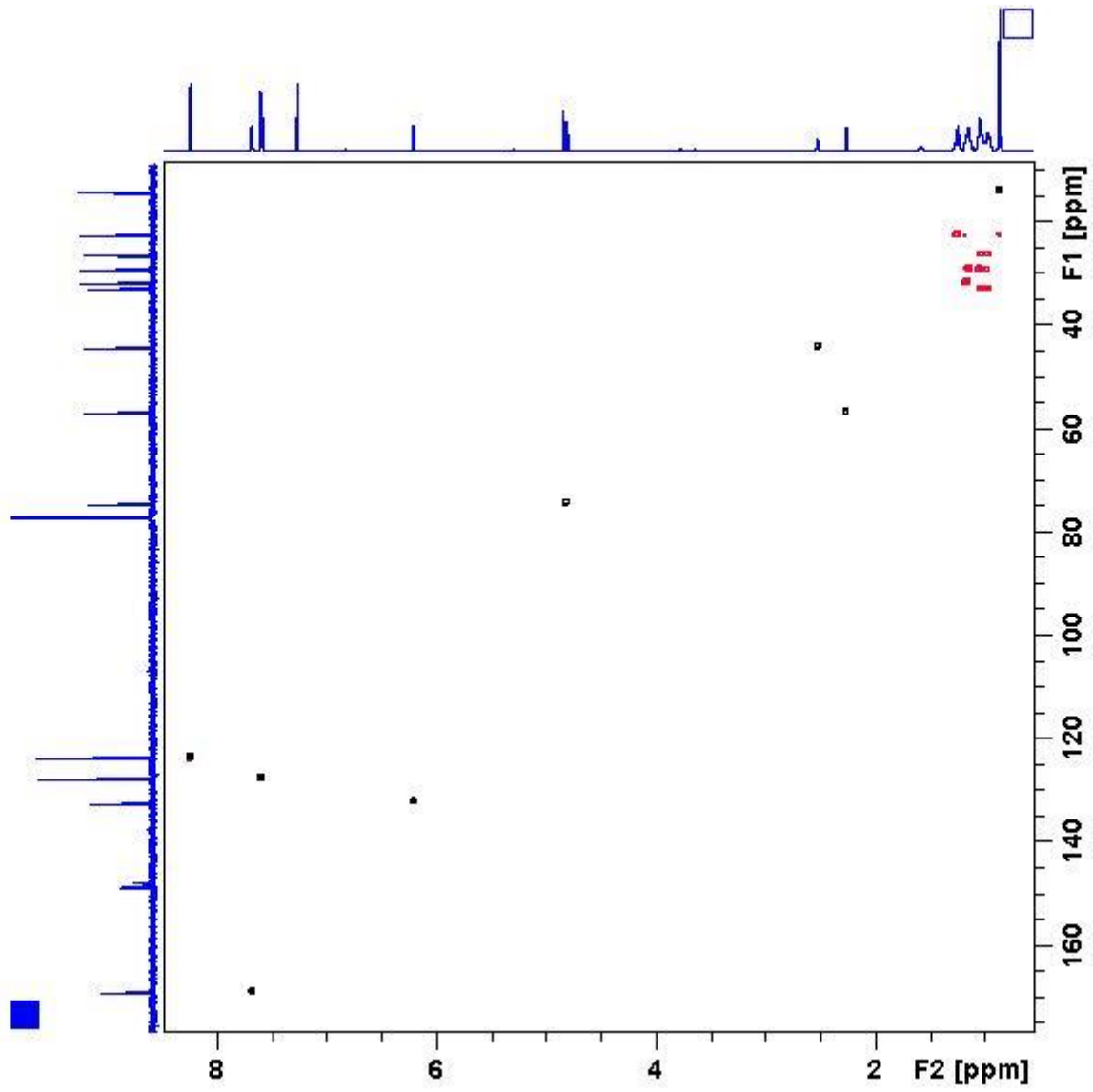


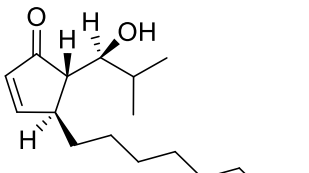
$CDCl_3$, 151 MHz



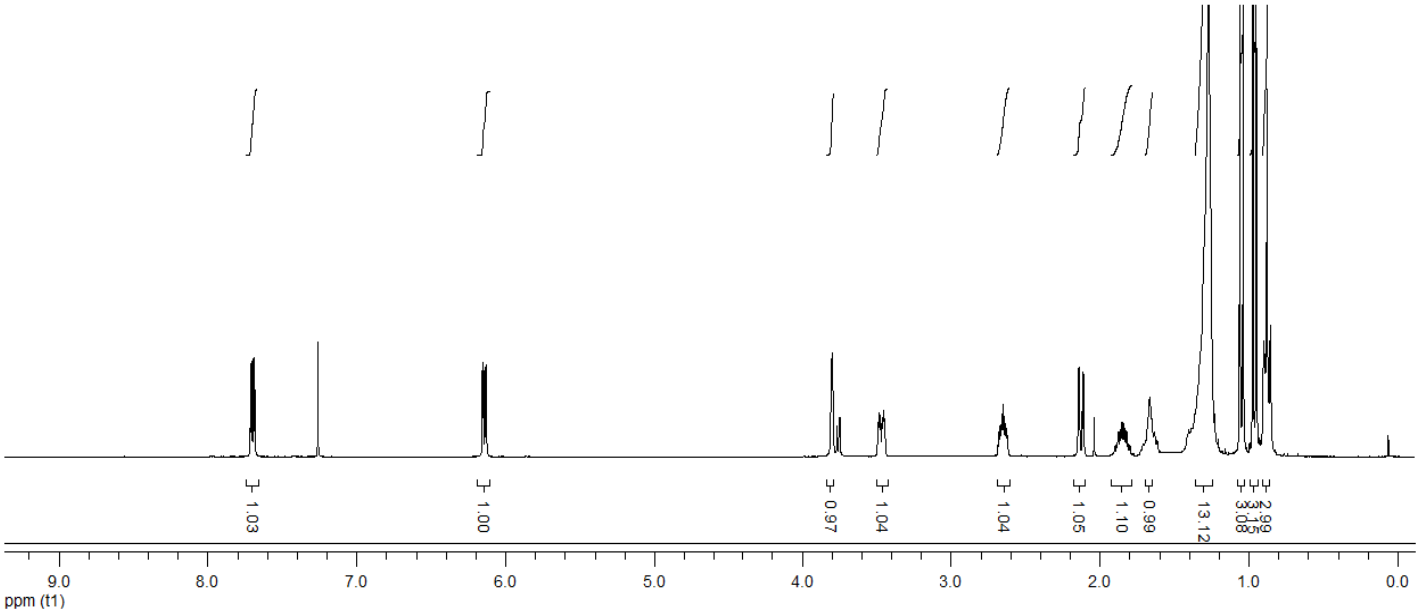


(+)-133v, HSQC, $CDCl_3$, 600 MHz

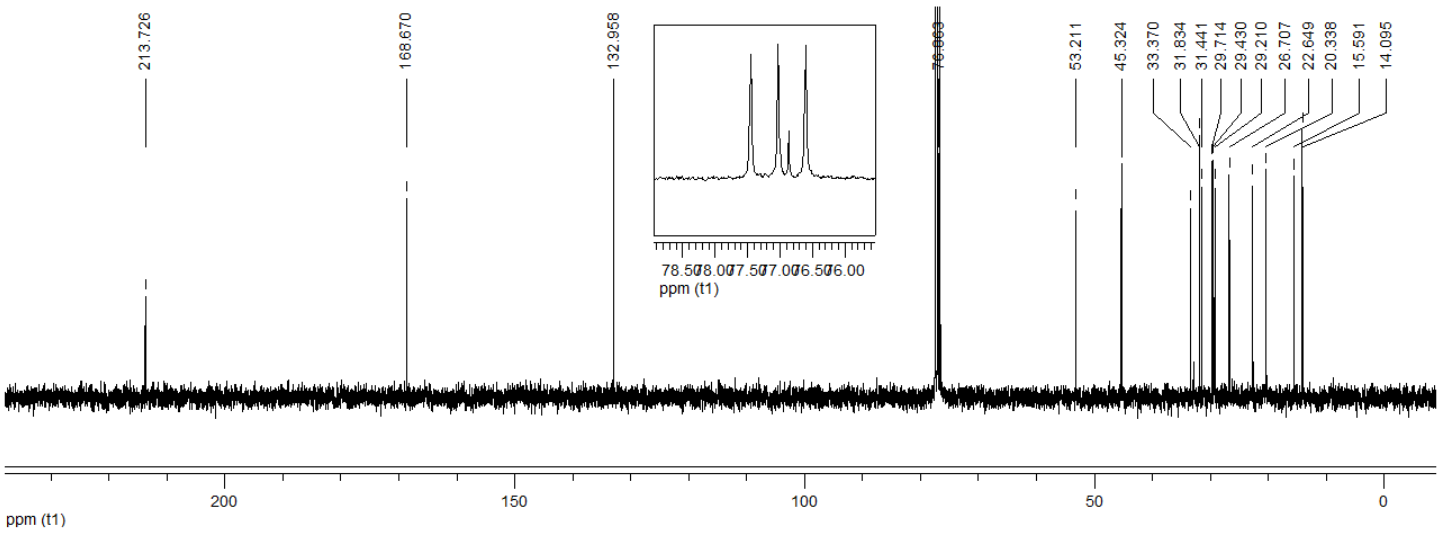


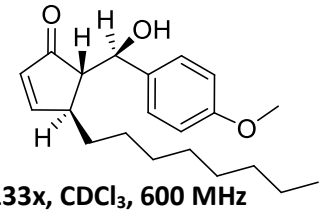


(+)-133w, $CDCl_3$, 300 MHz

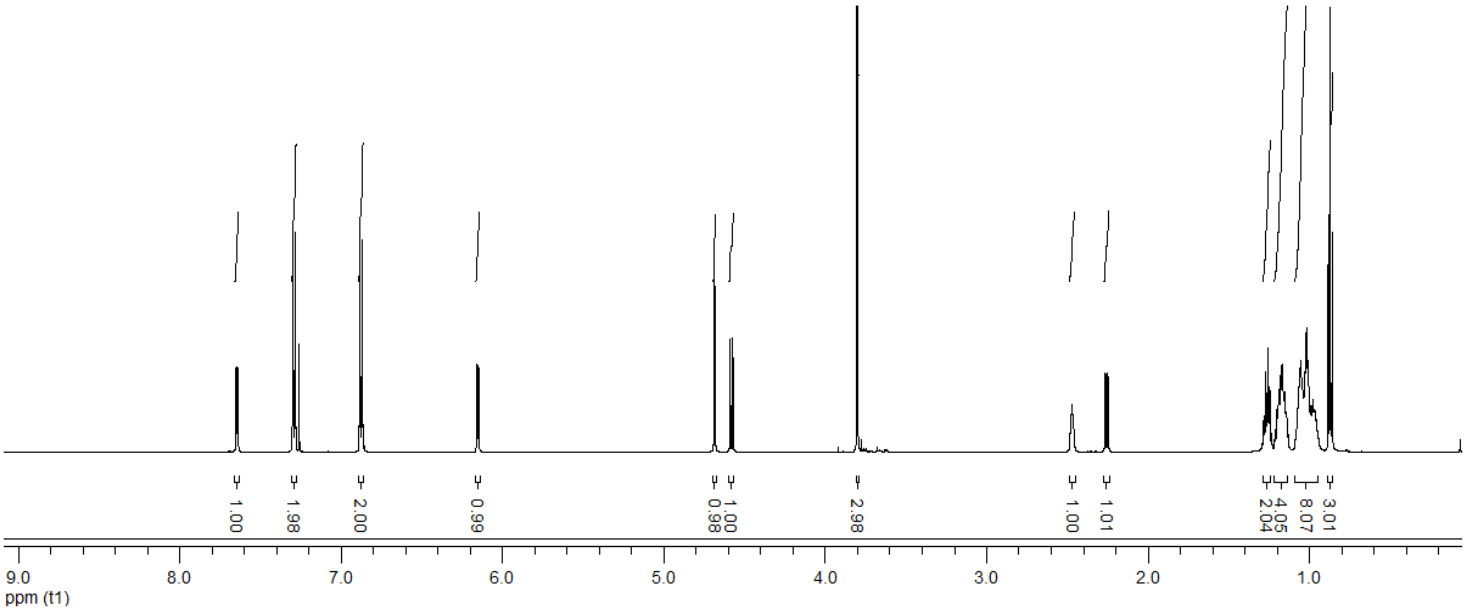


$CDCl_3$, 75 MHz

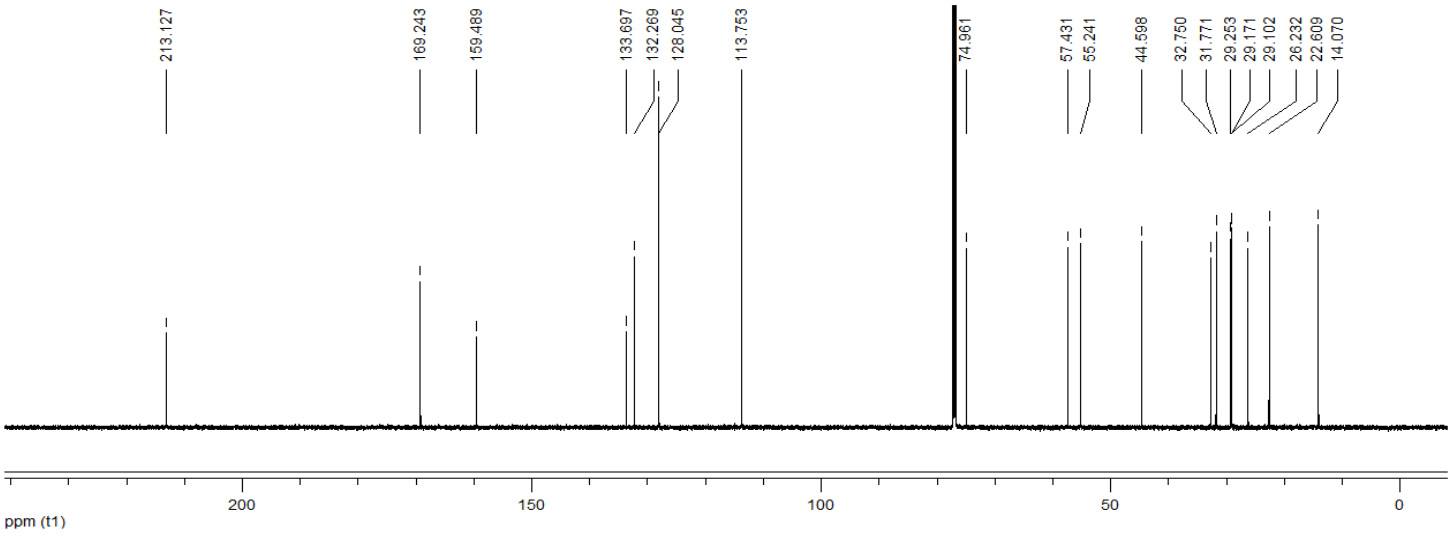


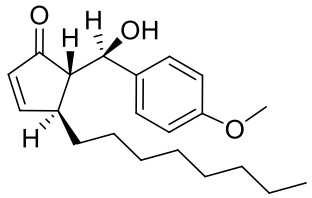


(+)-133x, $CDCl_3$, 600 MHz

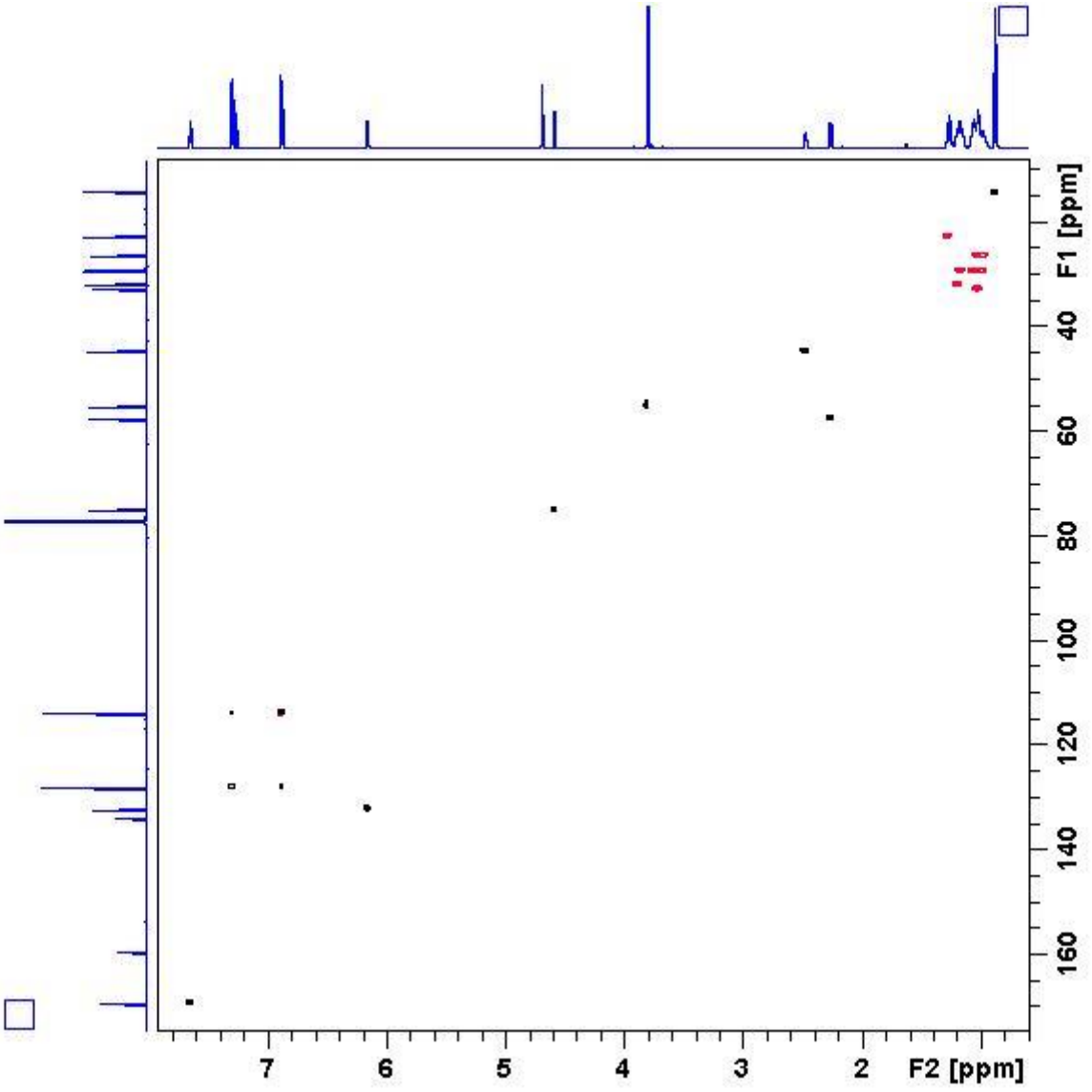


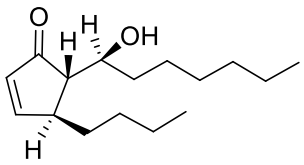
$CDCl_3$, 151 MHz



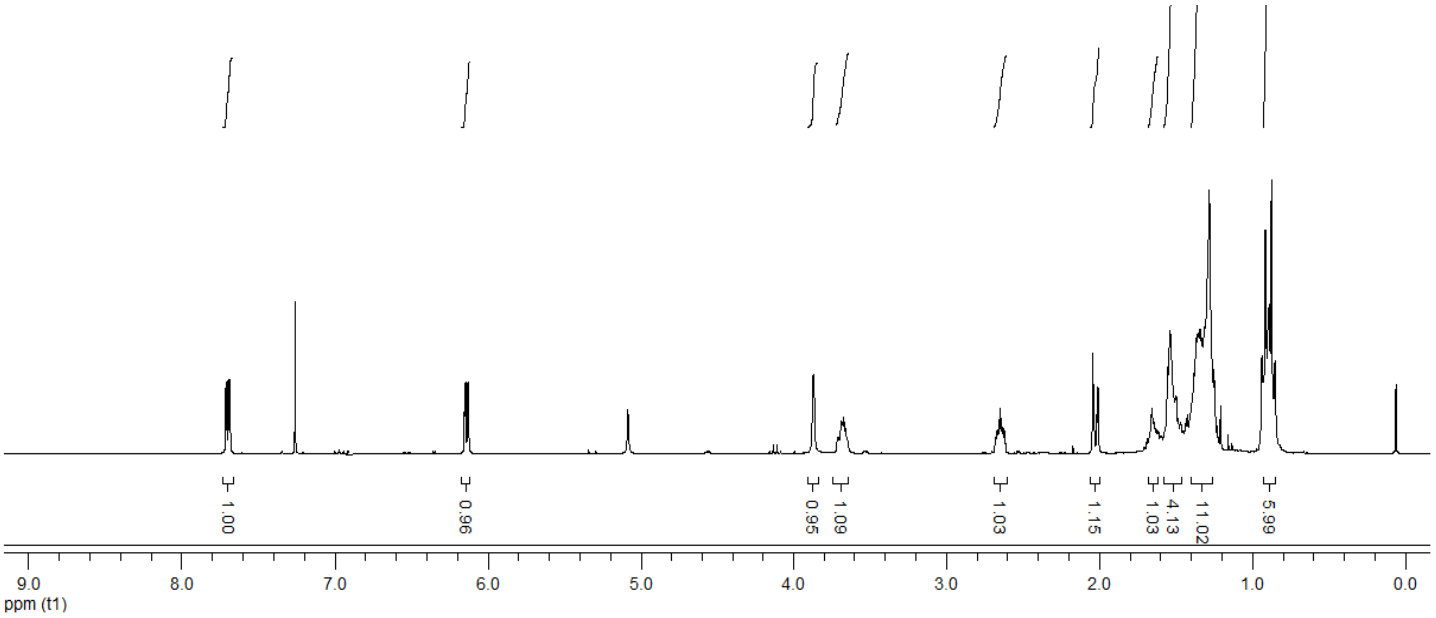


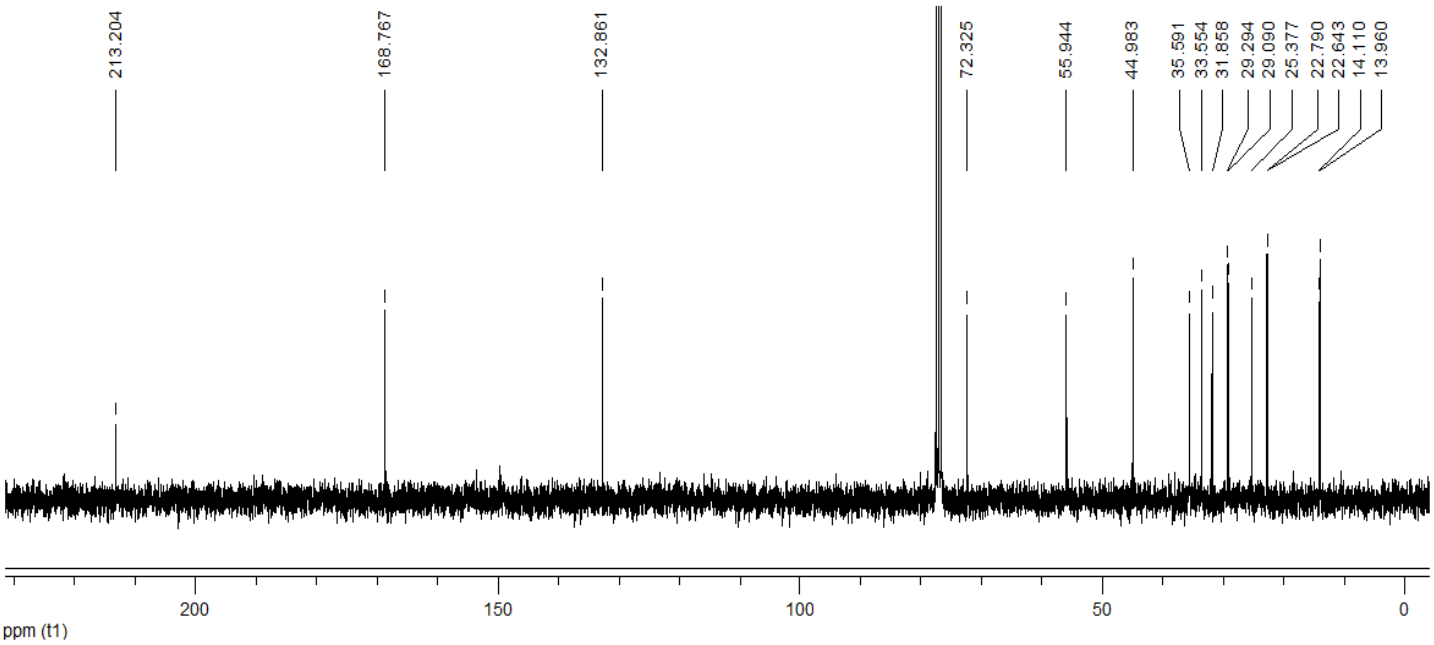
(+)-133x, HSQC, $CDCl_3$, 600 MHz

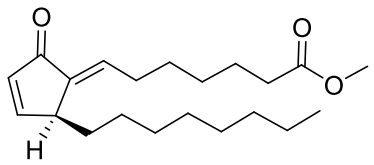




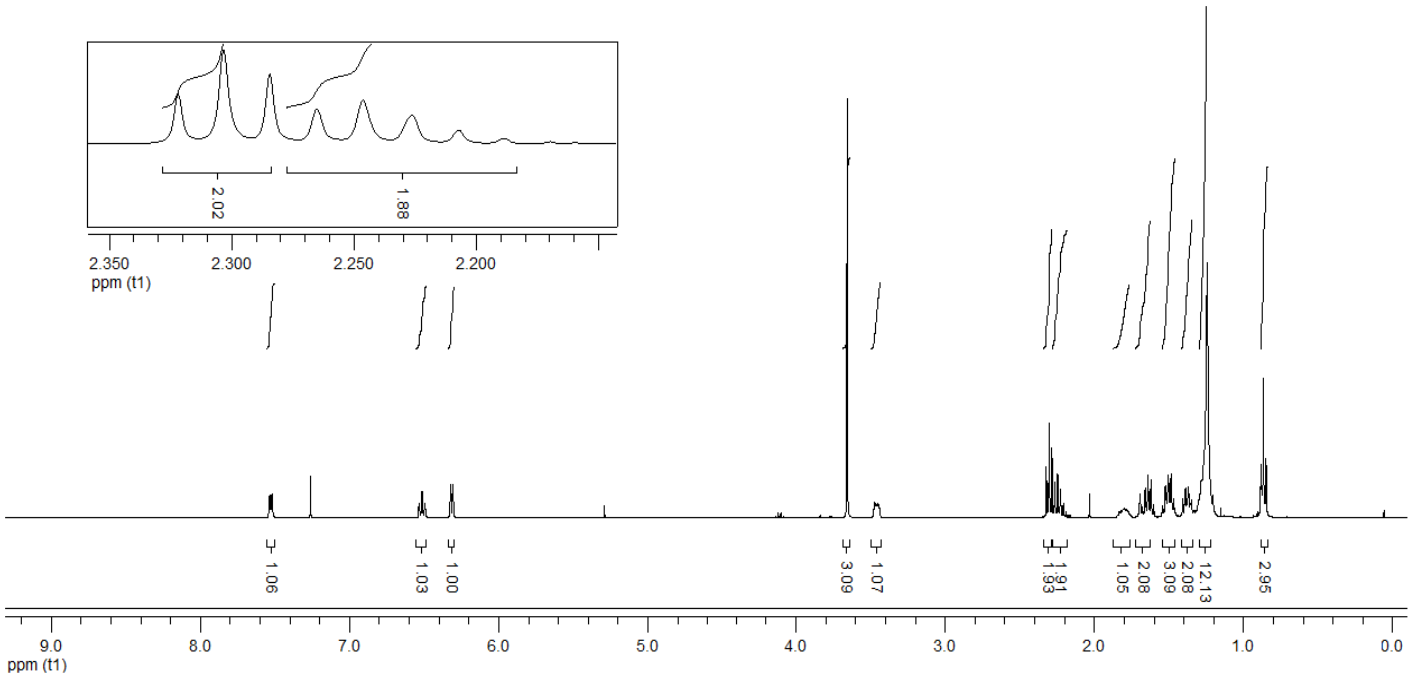
2, $CDCl_3$, 300 MHz



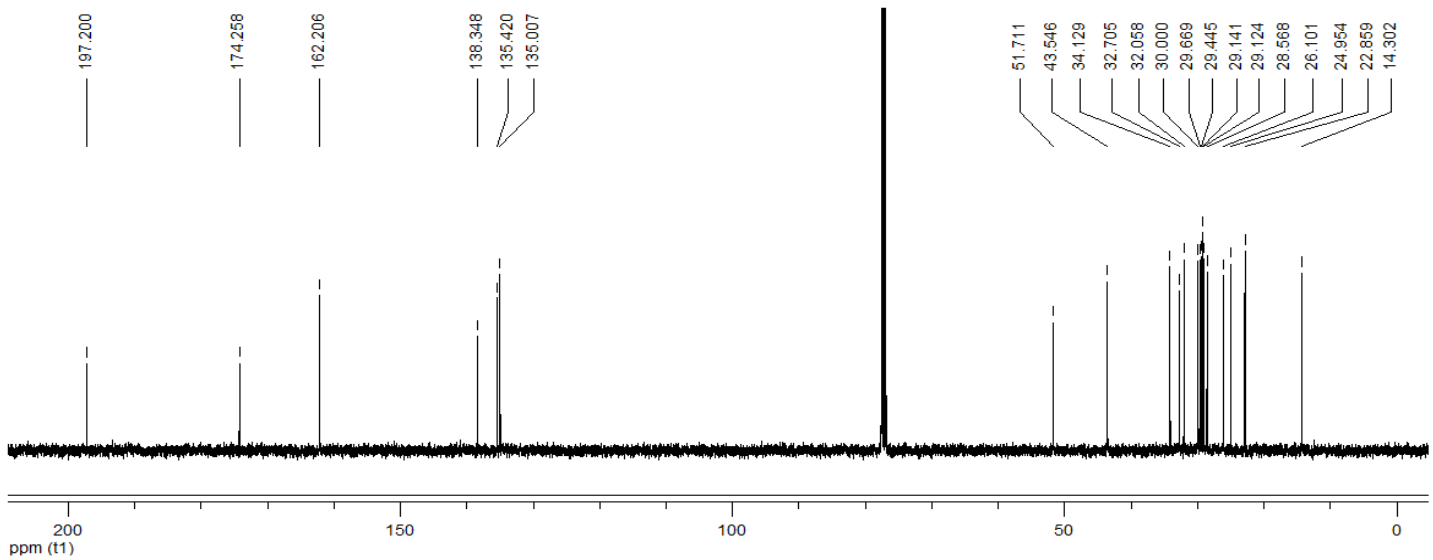


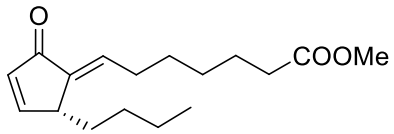


3, $CDCl_3$, 400 MHz

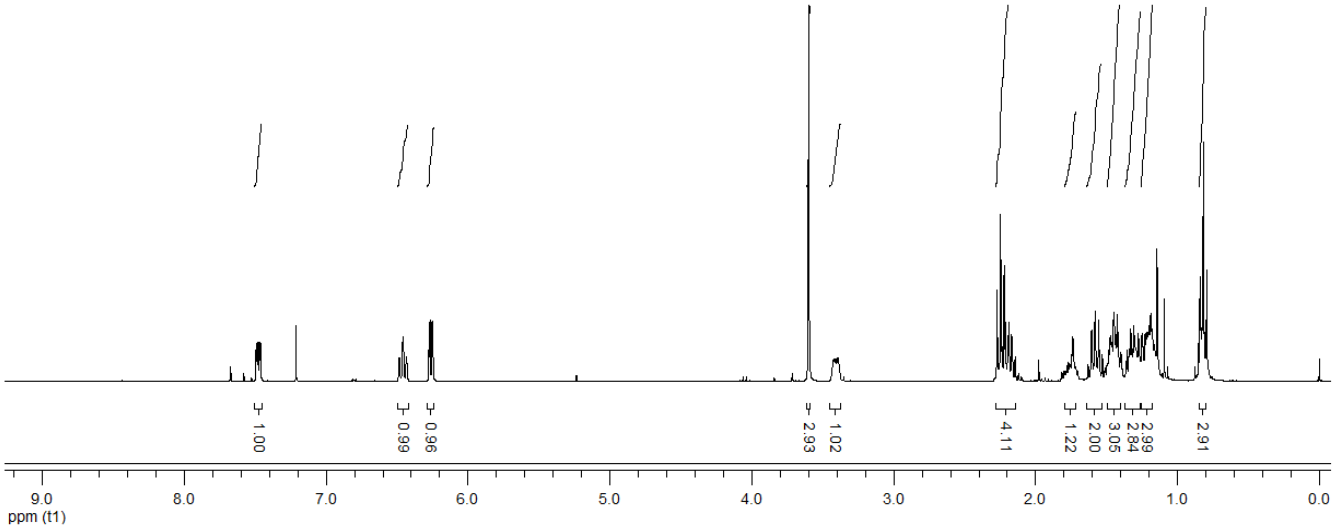


$CDCl_3$, 100 MHz

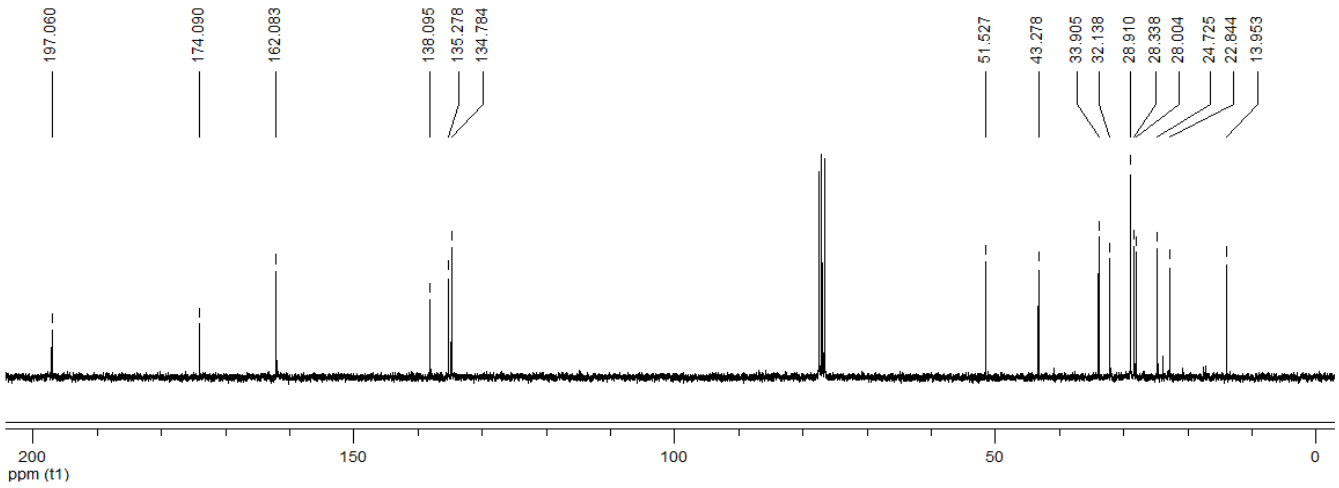


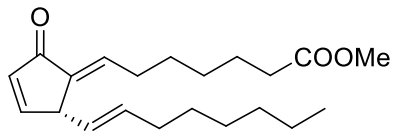


141, $CDCl_3$, 300 MHz

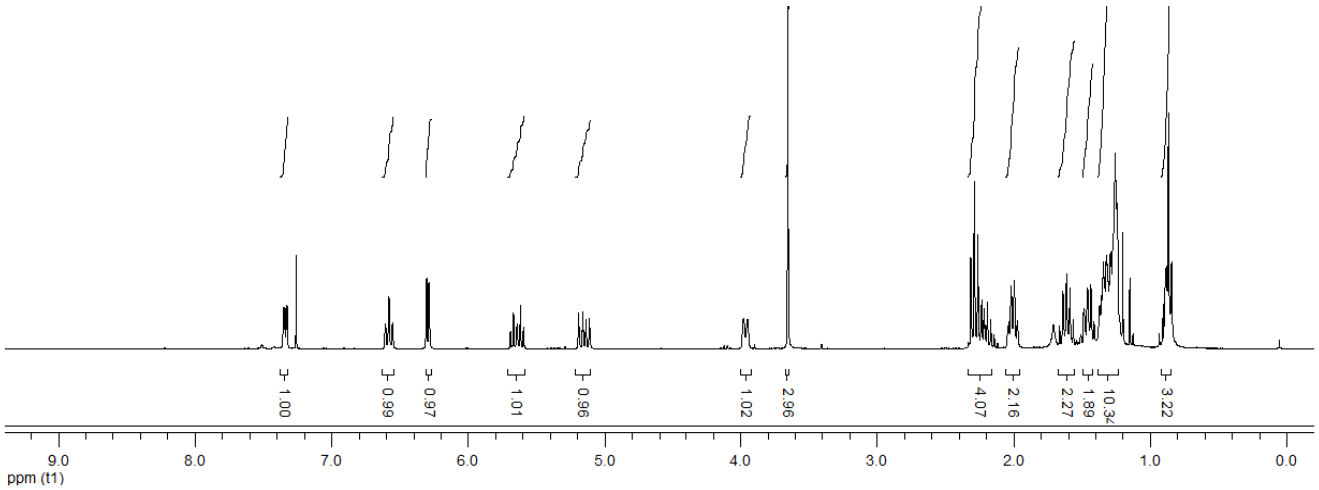


$CDCl_3$, 75 MHz

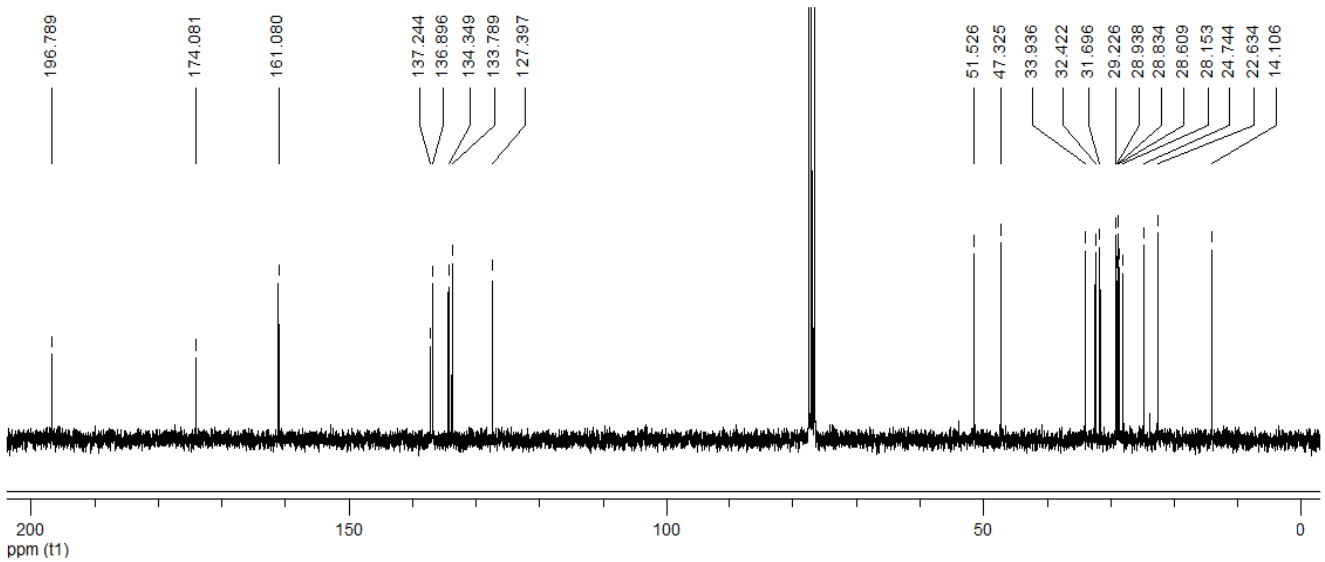


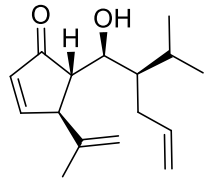


143, $CDCl_3$, 300 MHz

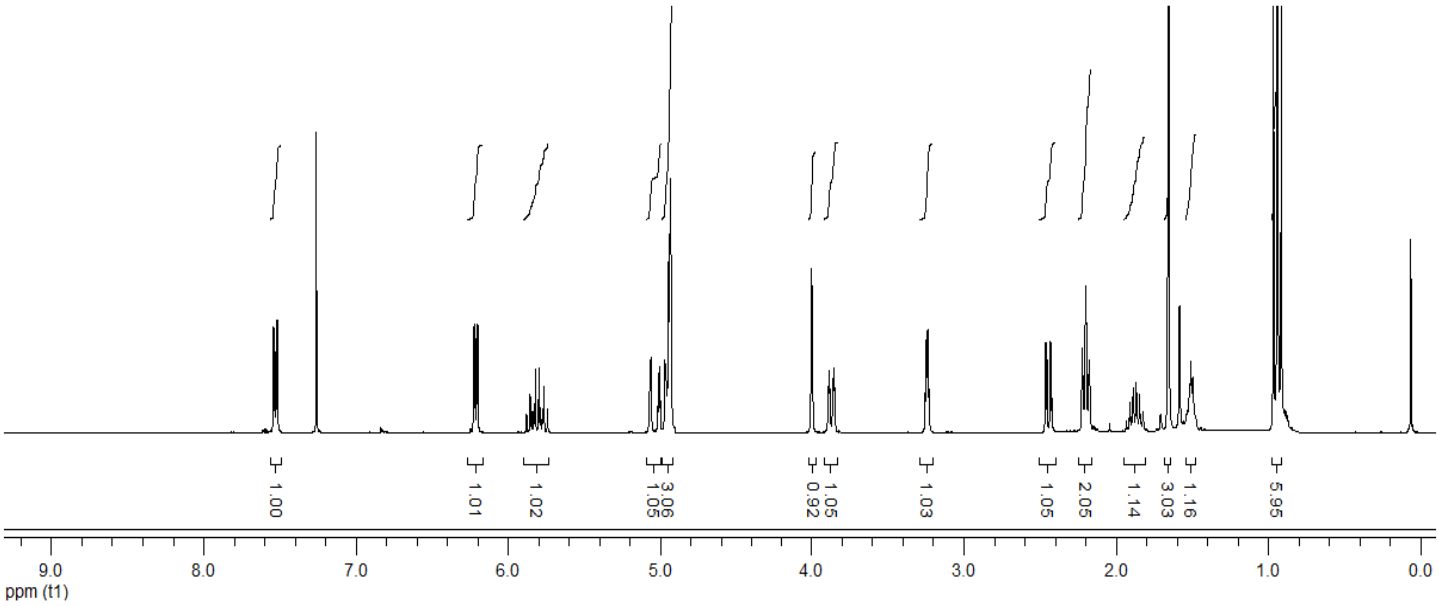


$CDCl_3$, 75 MHz

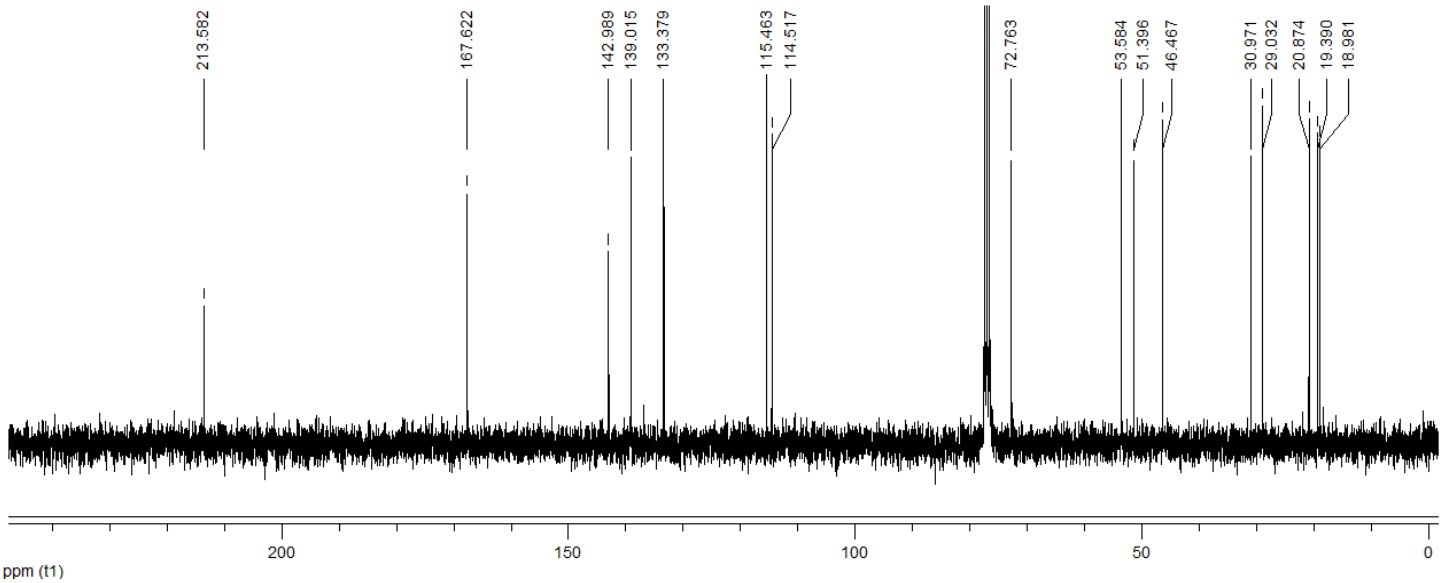


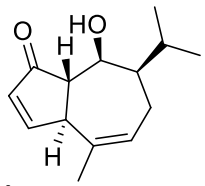


146, $CDCl_3$, 300 MHz

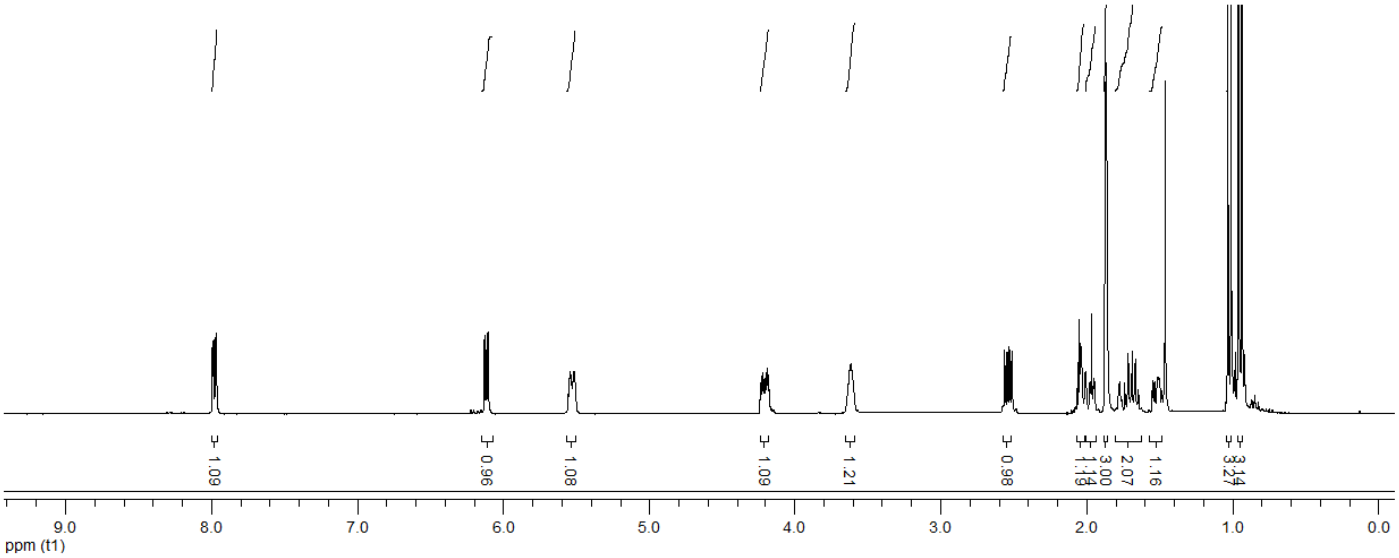


$CDCl_3$, 75 MHz

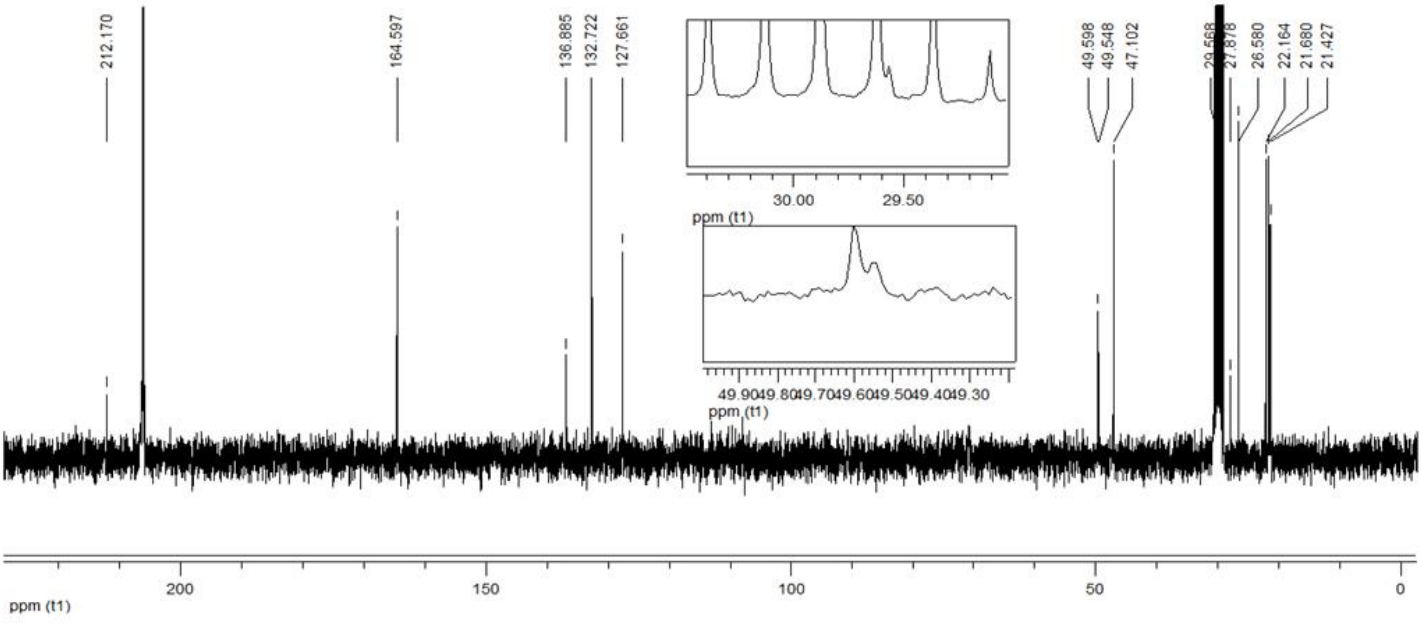


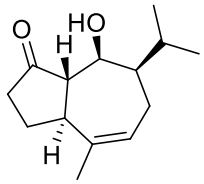


157, d6-Acetone, 300 MHz

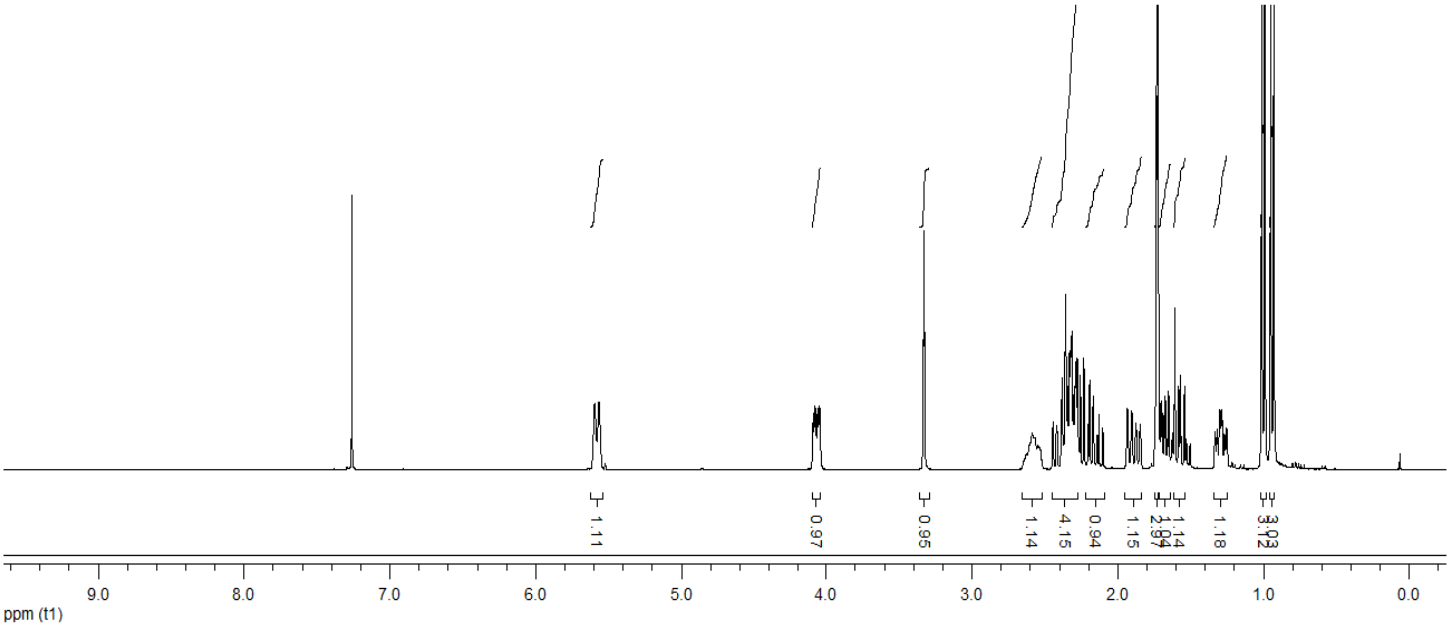


D_6-Acetone, 75 MHz

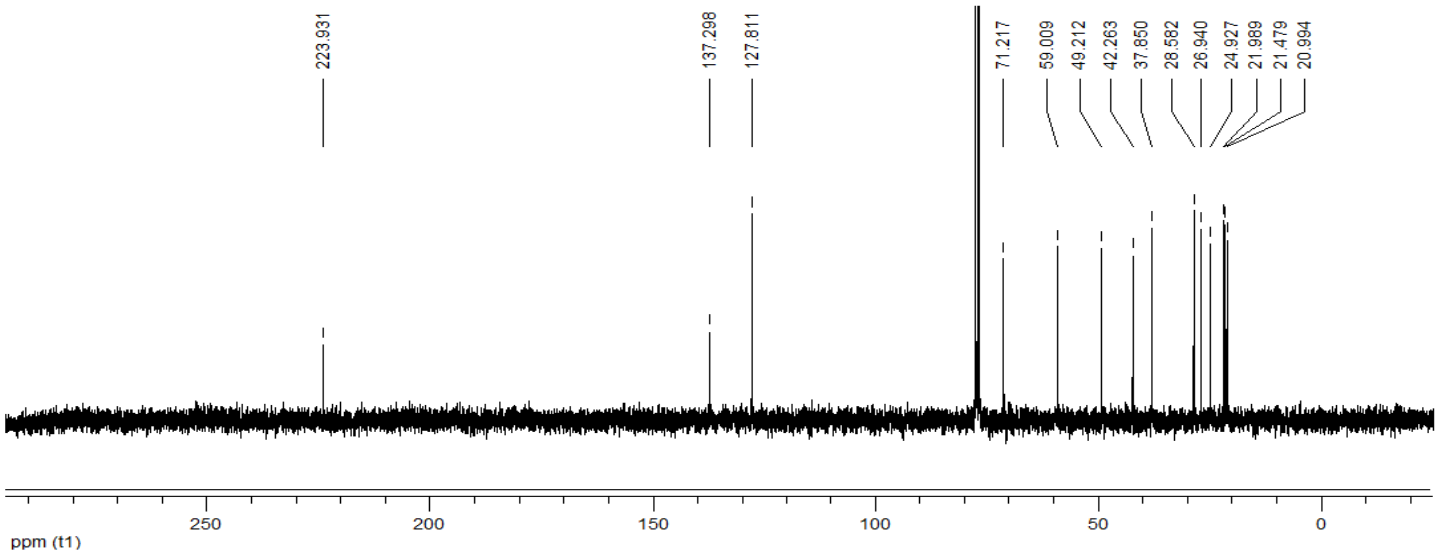


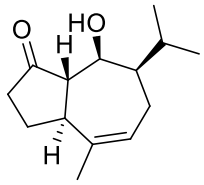


145, $CDCl_3$, 300 MHz

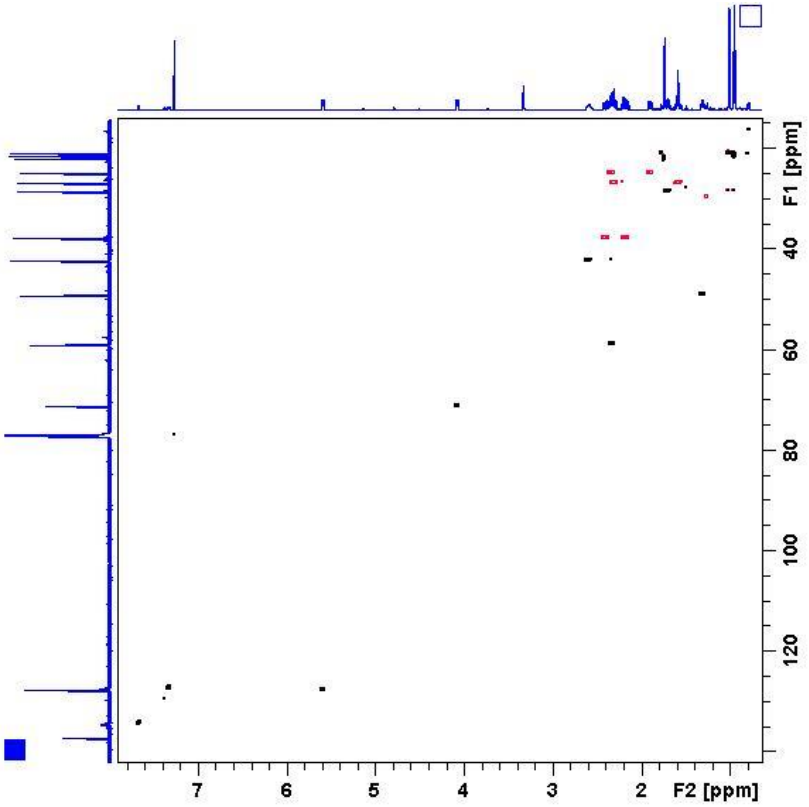


$CDCl_3$, 75 MHz

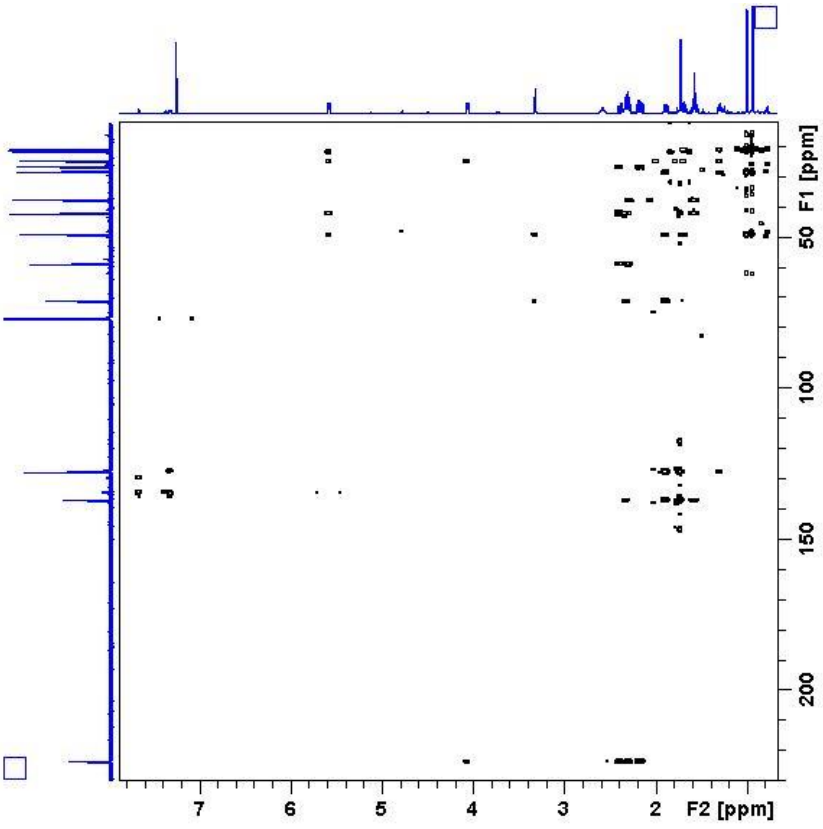


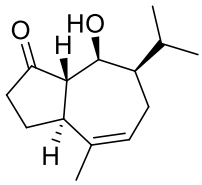


HSQC, $CDCl_3$, 600 MHz

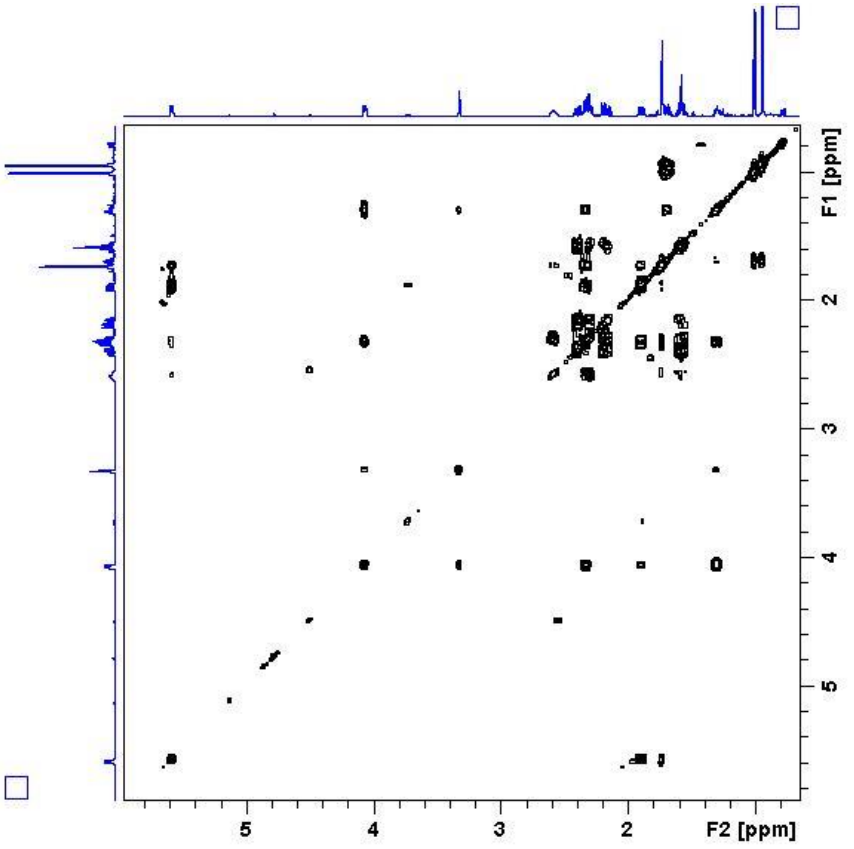


HMBC, $CDCl_3$, 600 MHz

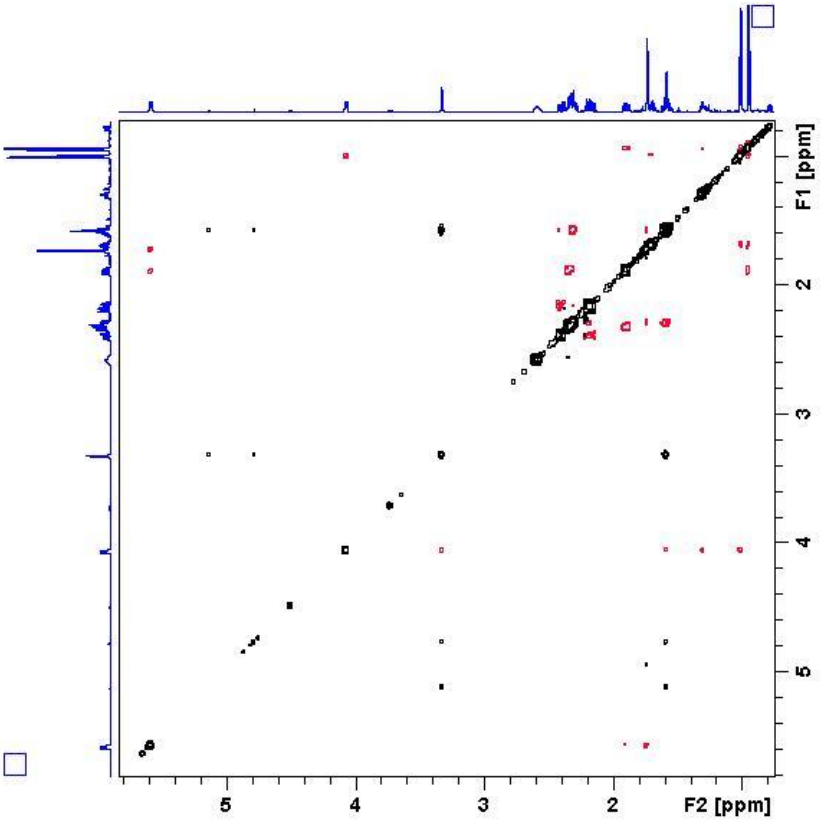


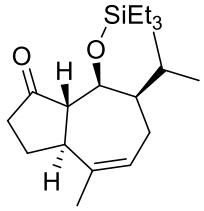


COSY, $CDCl_3$, 600 MHz

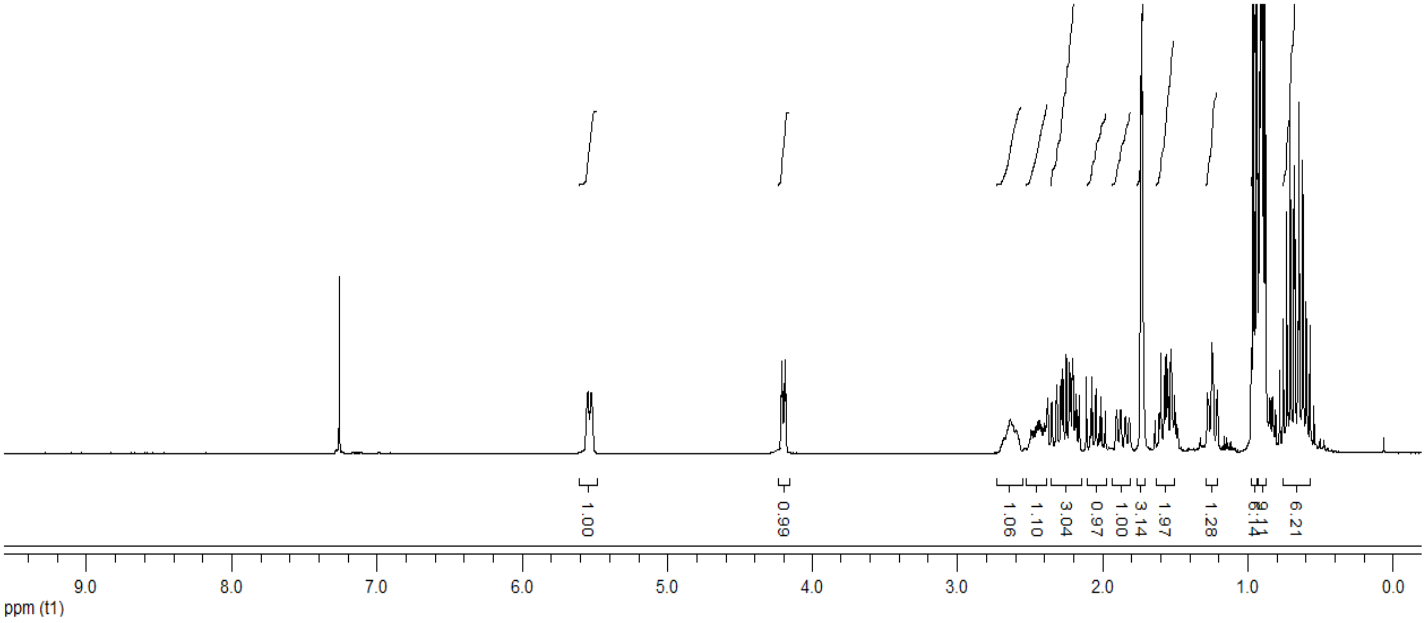


Noesy, $CDCl_3$, 600 MHz

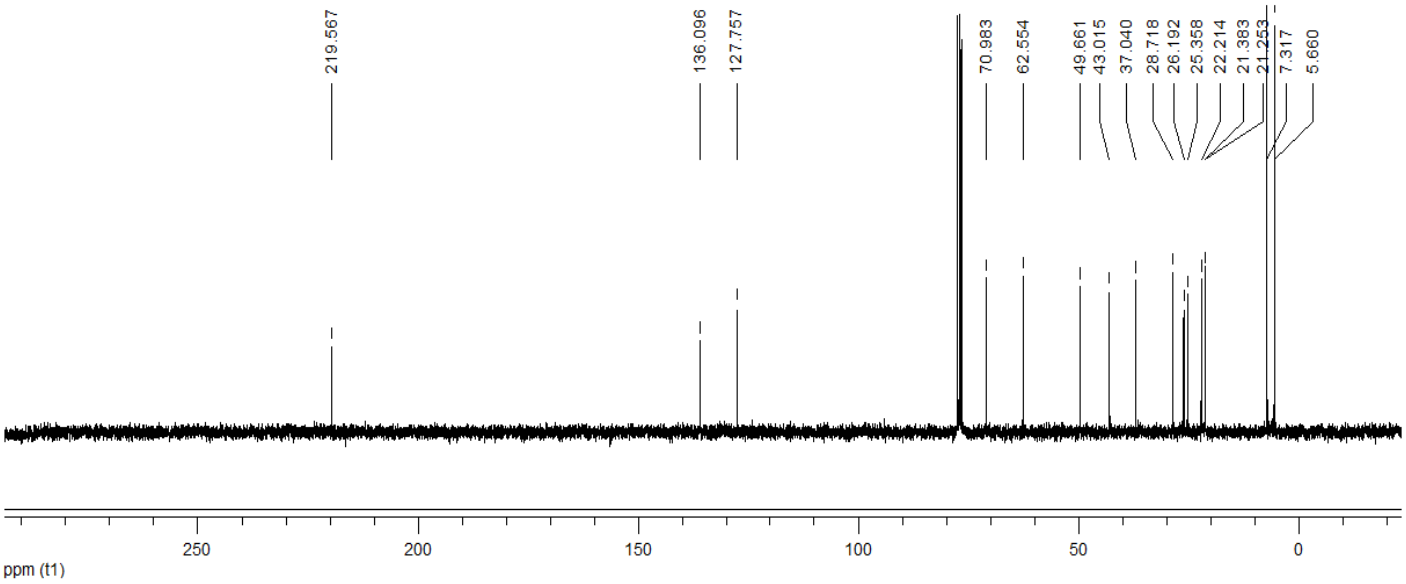


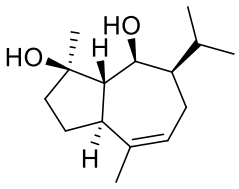


158, $CDCl_3$, 300 MHz

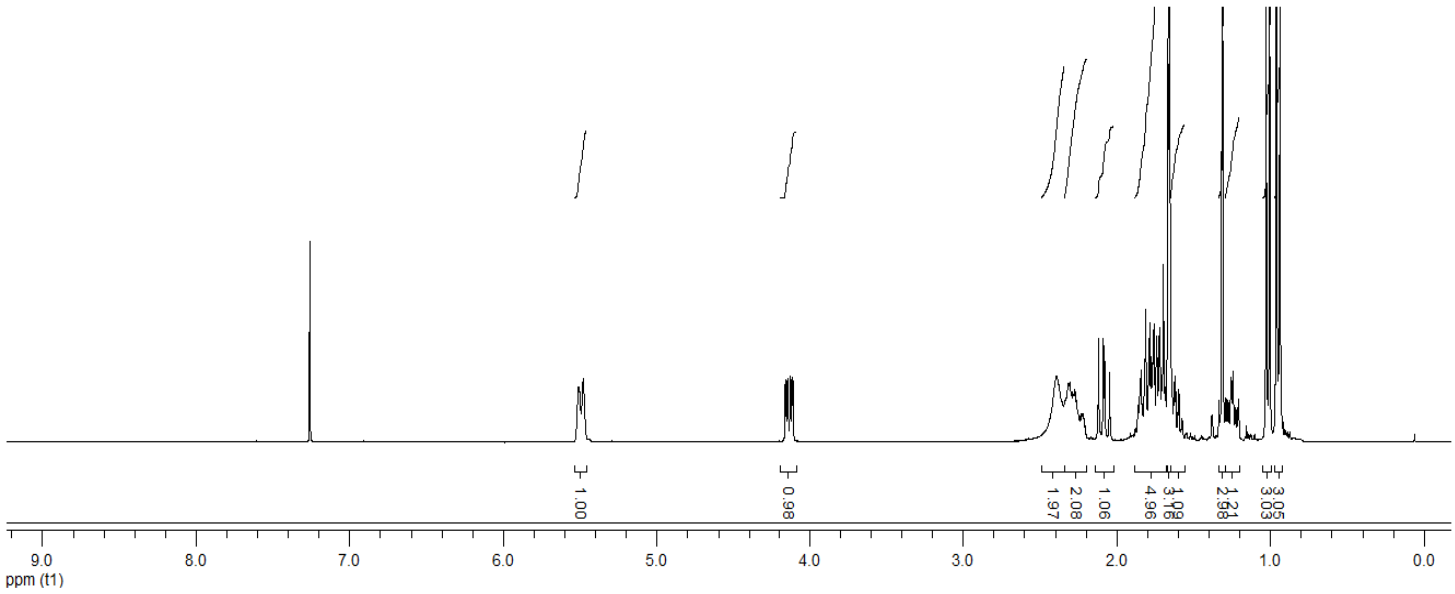


$CDCl_3$, 75 MHz

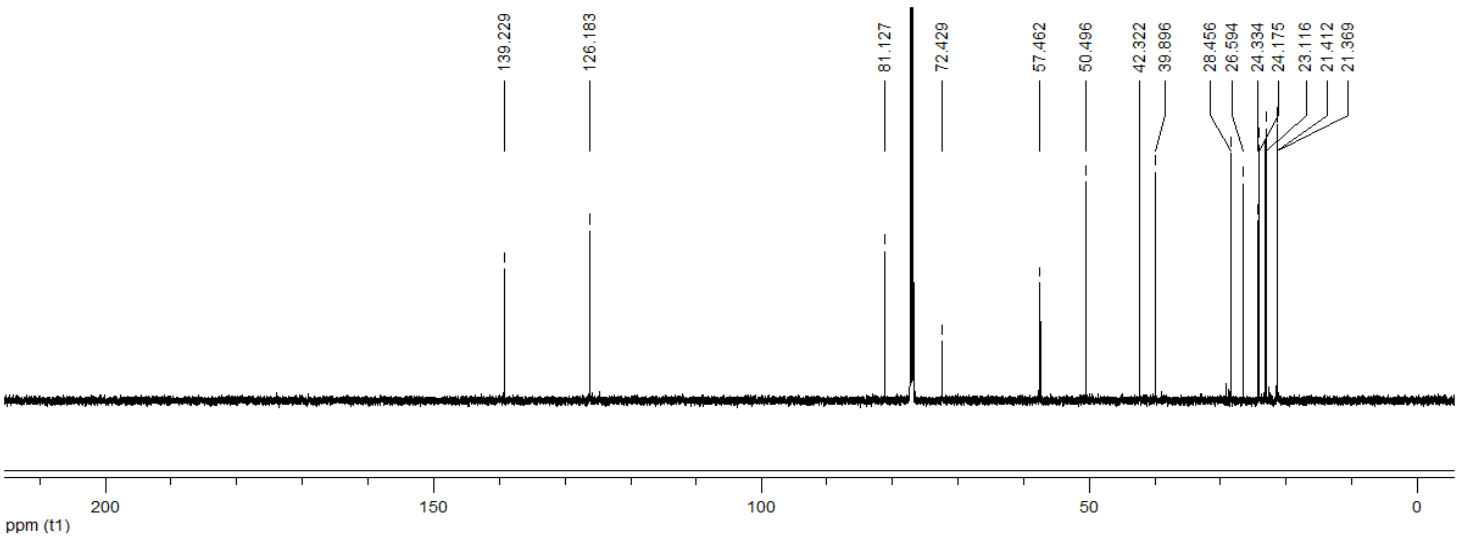


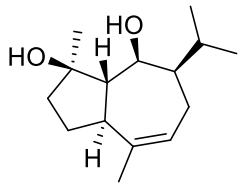


144, $CDCl_3$, 600 MHz

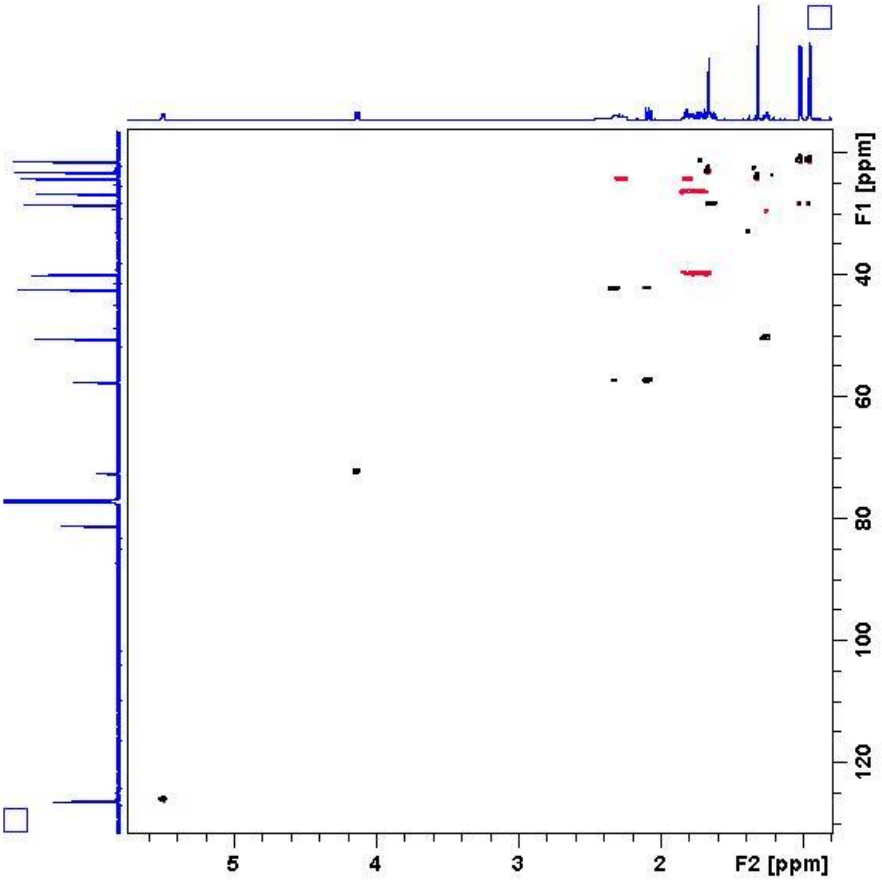


$CDCl_3$, 151 MHz

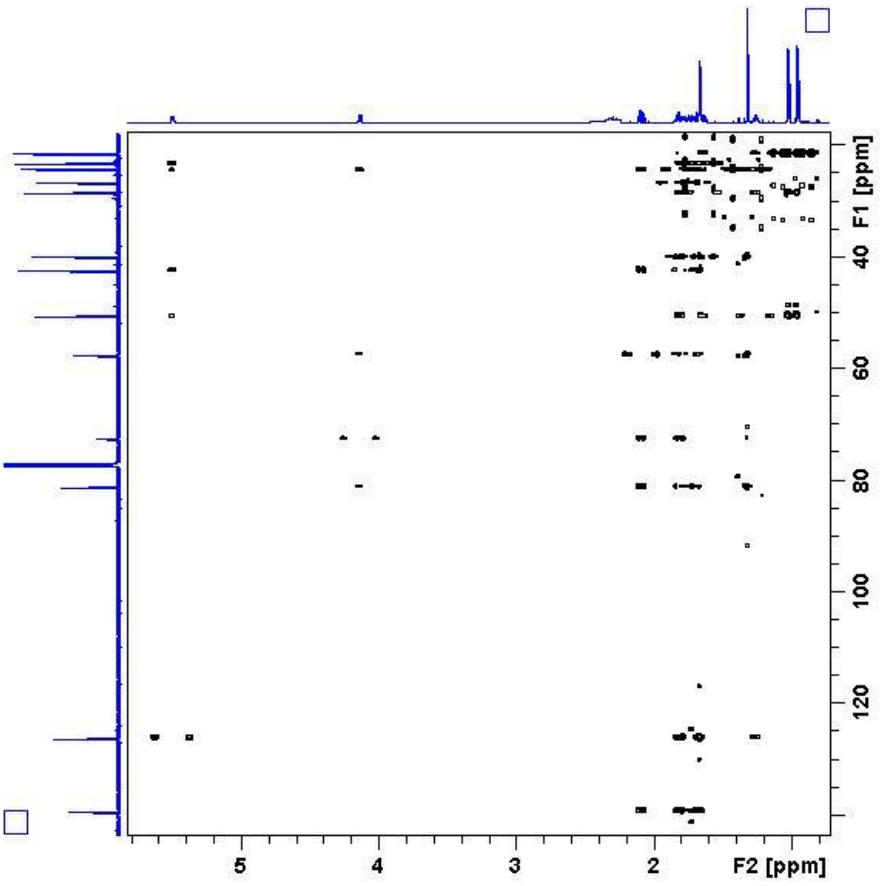


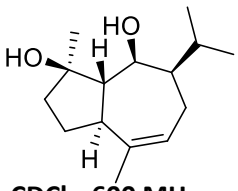


HSQC, $CDCl_3$, 600 MHz

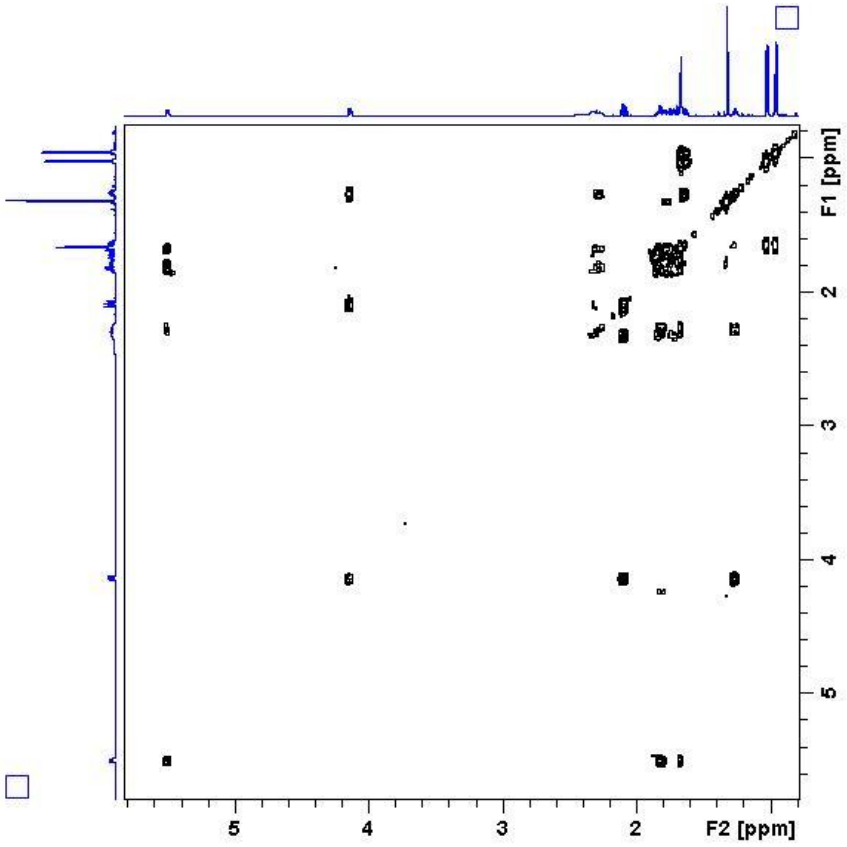


HMBC, $CDCl_3$, 600 MHz

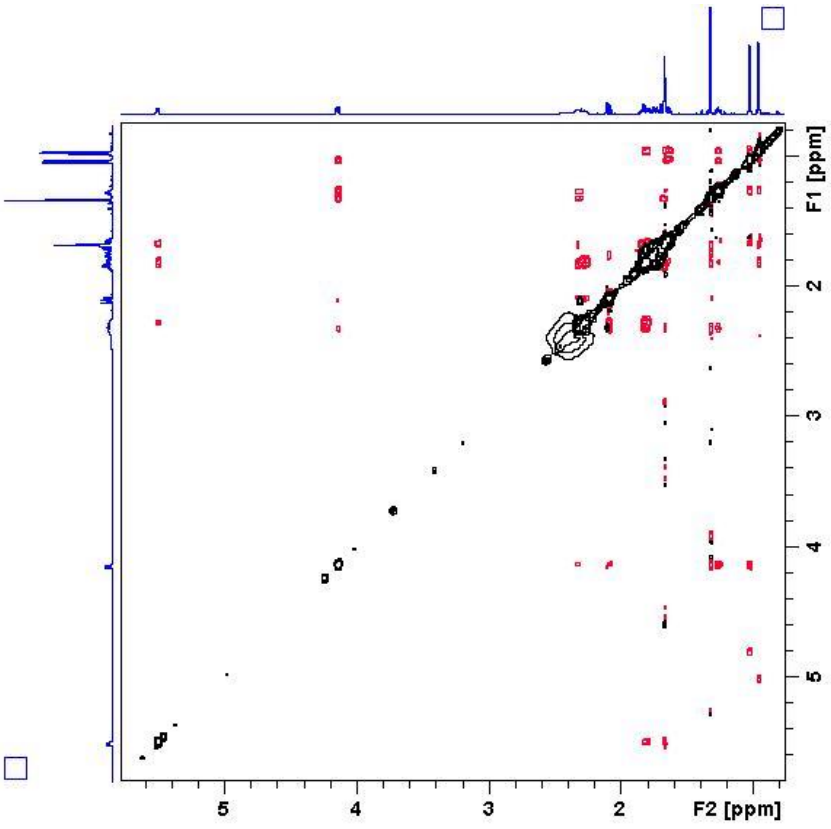


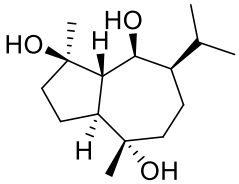


COSY, $CDCl_3$, 600 MHz



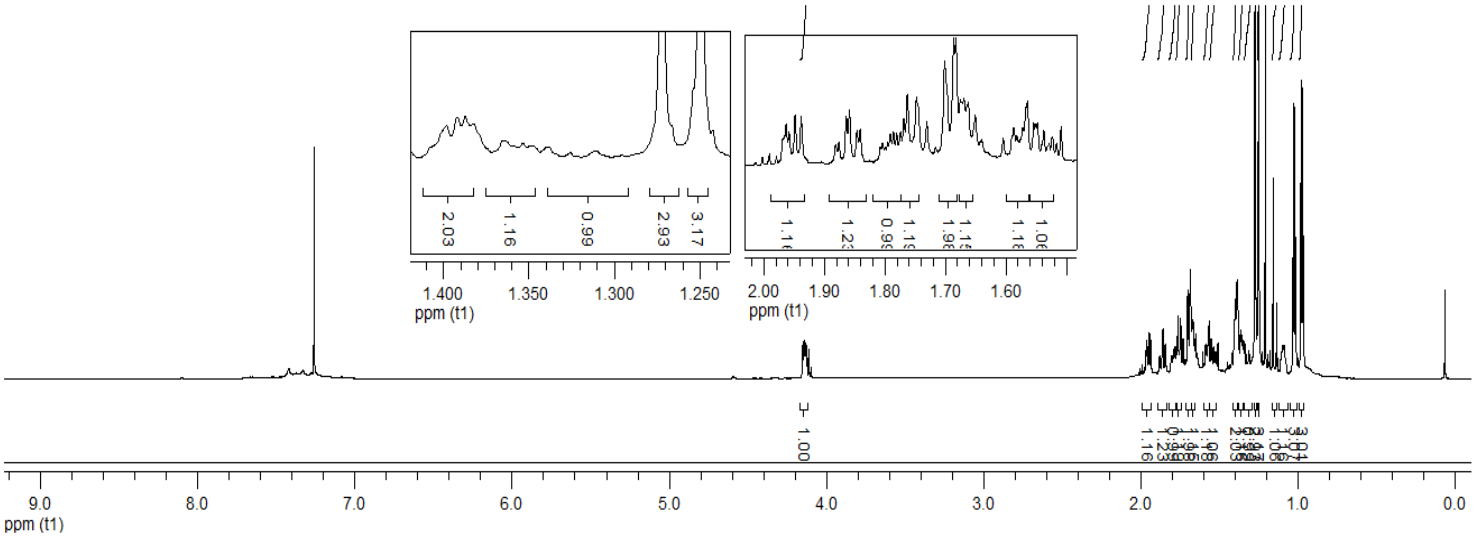
Noesy, $CDCl_3$, 600 MHz



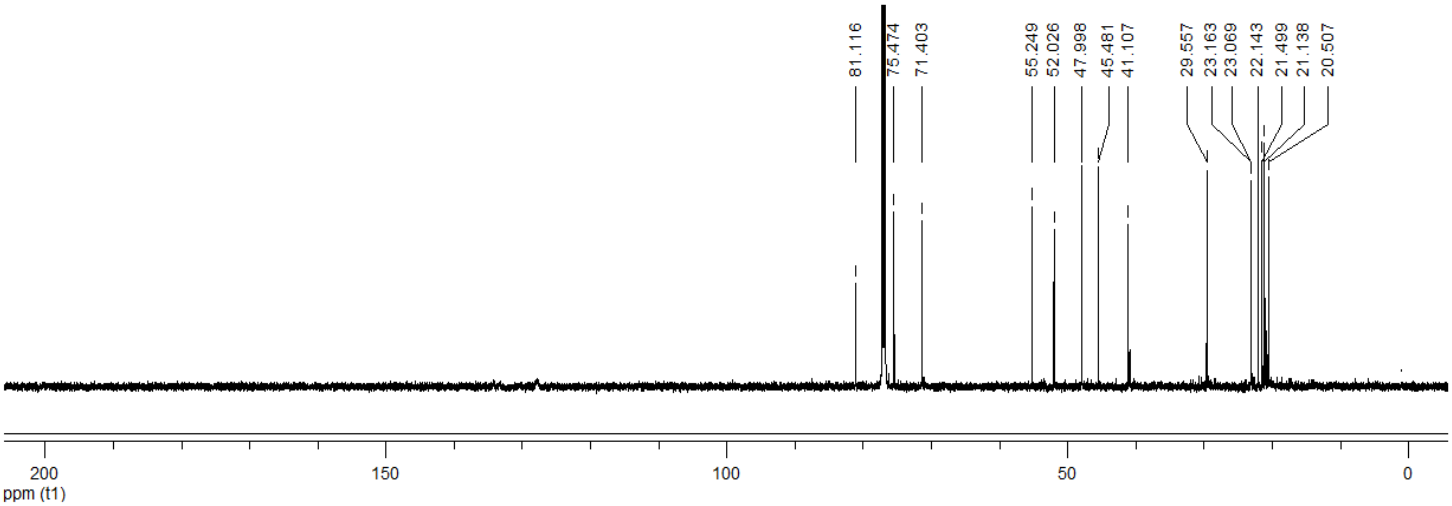


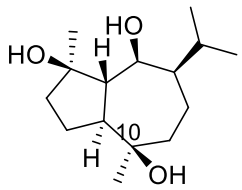
teuclatriol

72, $CDCl_3$, 600 MHz



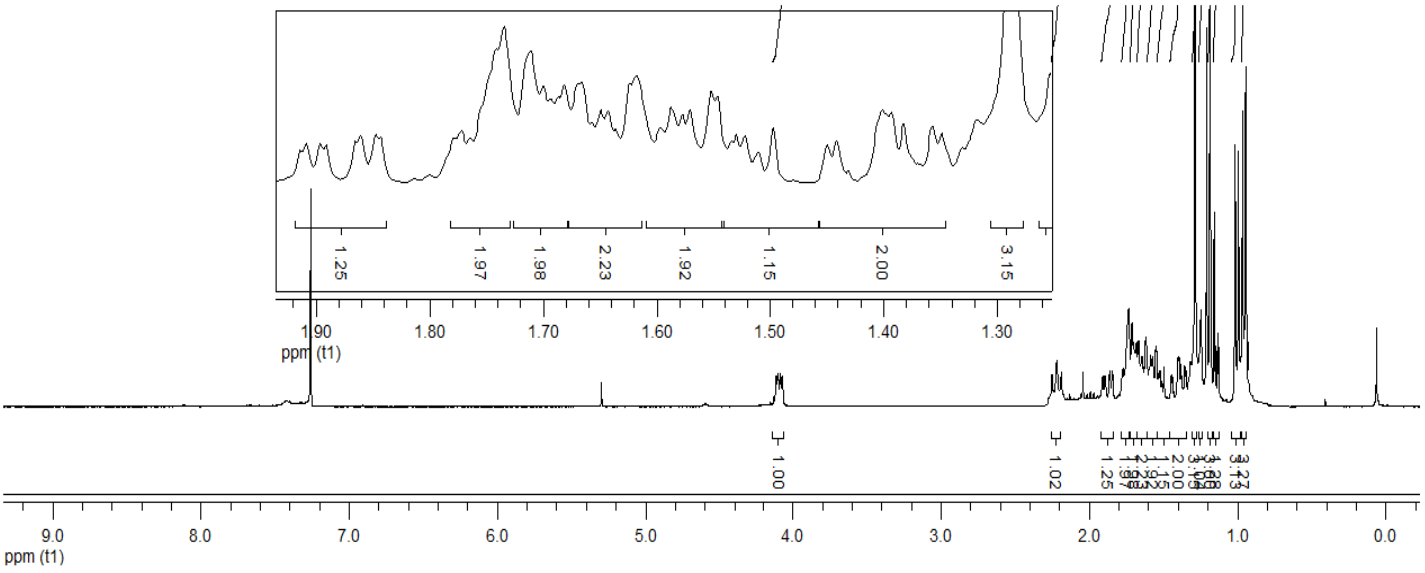
$CDCl_3$, 151 MHz



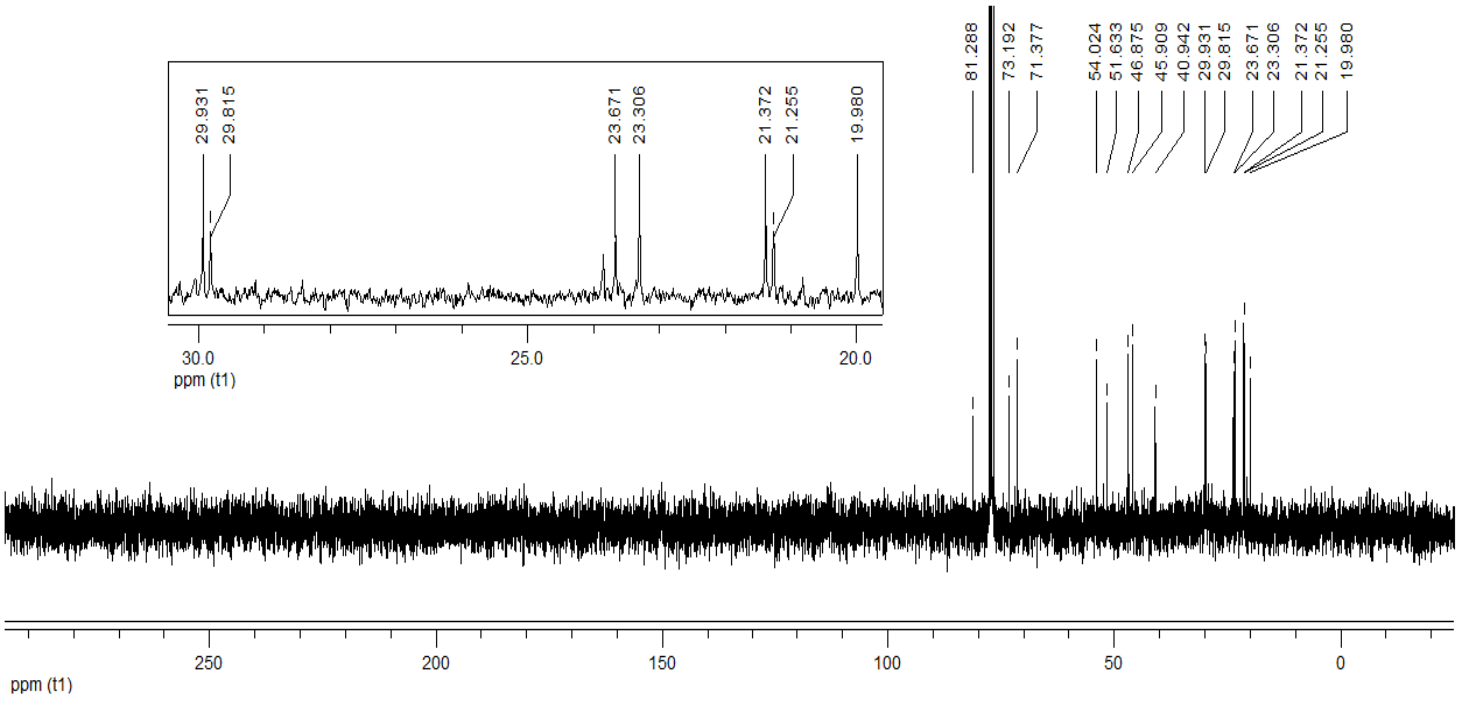


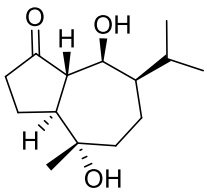
10 *epi*-teuclatriol

159, $CDCl_3$, 300 MHz

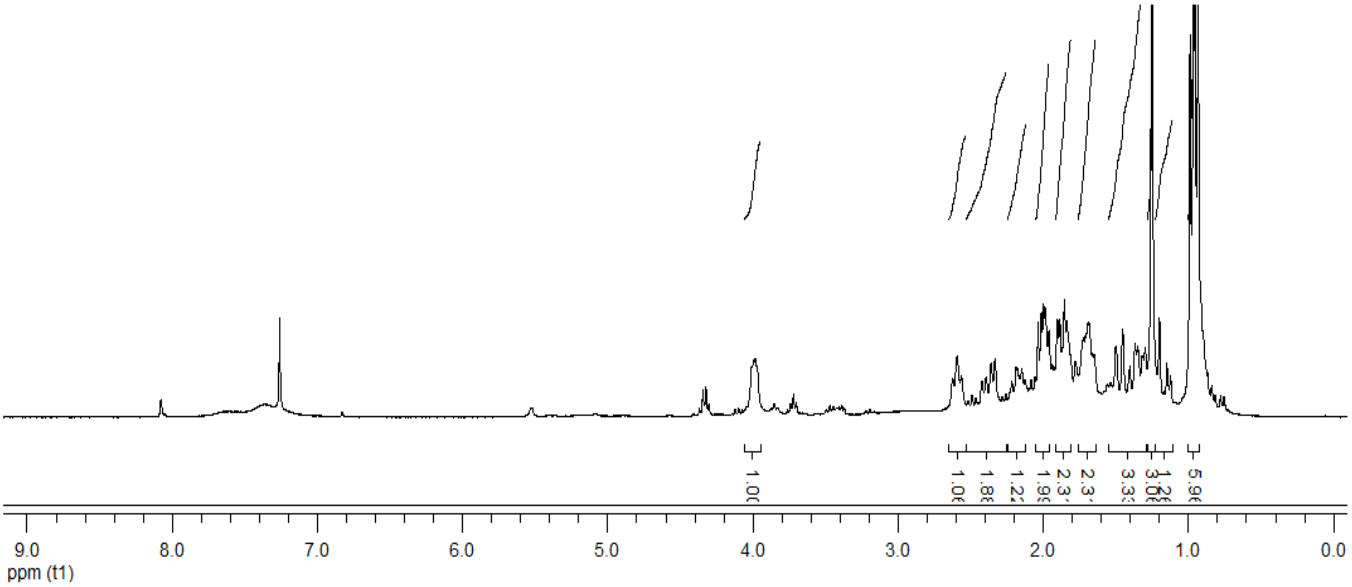


$CDCl_3$, 75 MHz

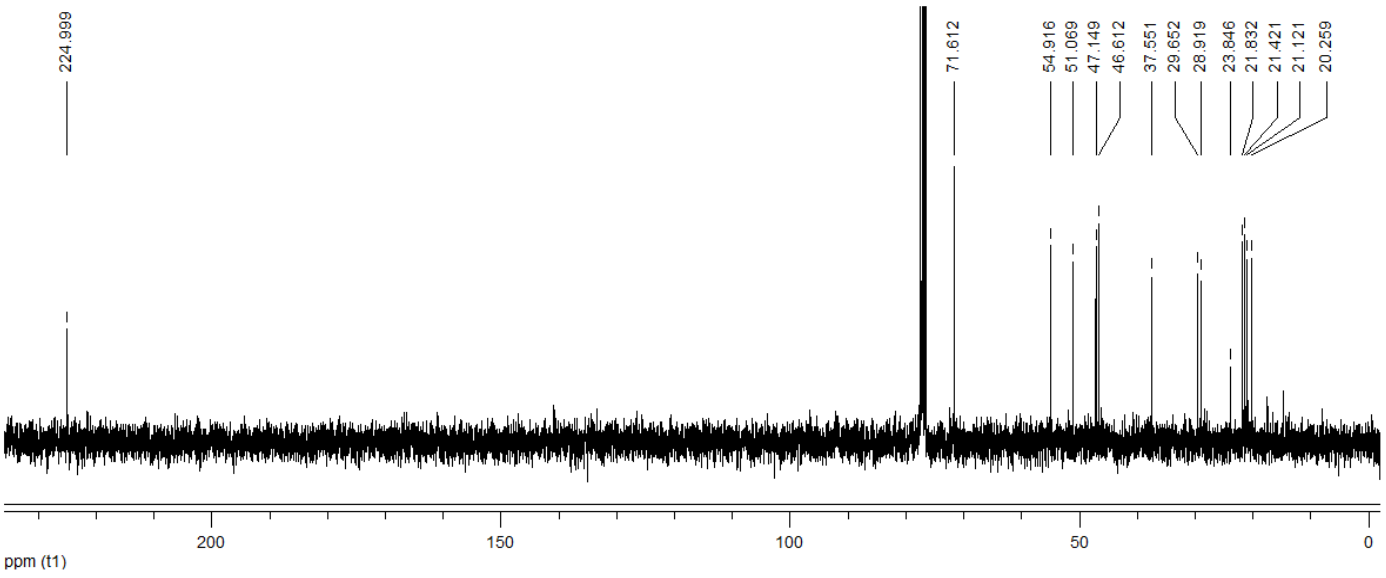


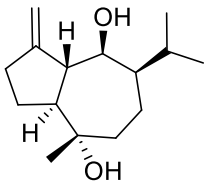


160, $CDCl_3$, 300 MHz

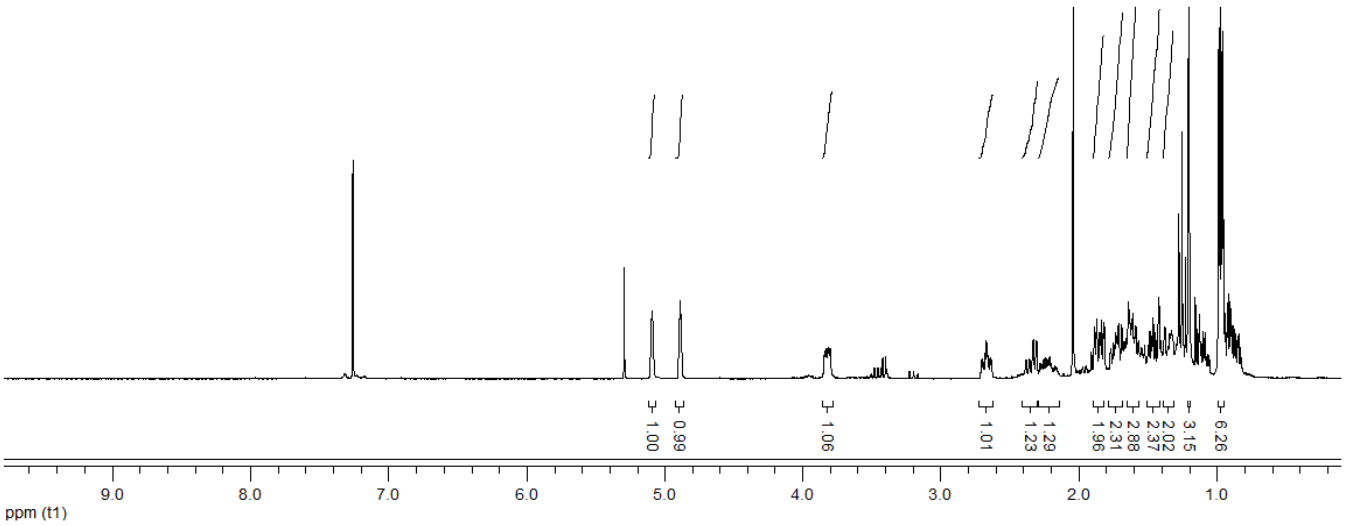


$CDCl_3$, 75 MHz

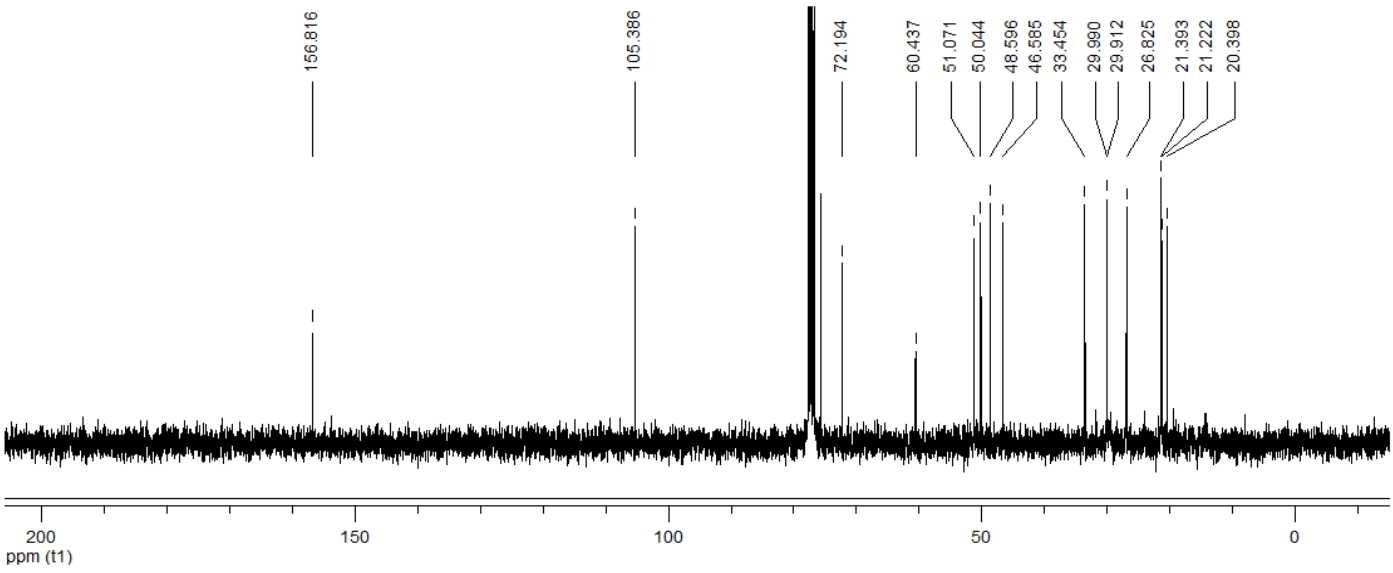


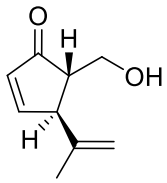


161, $CDCl_3$, 300 MHz

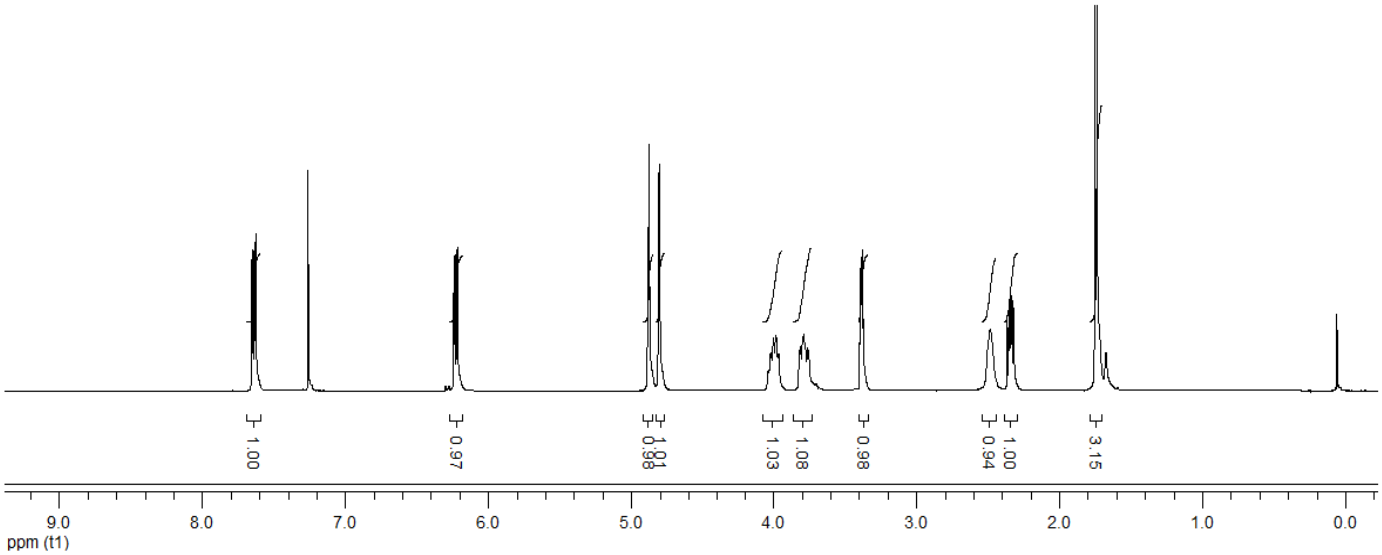


$CDCl_3$, 75 MHz

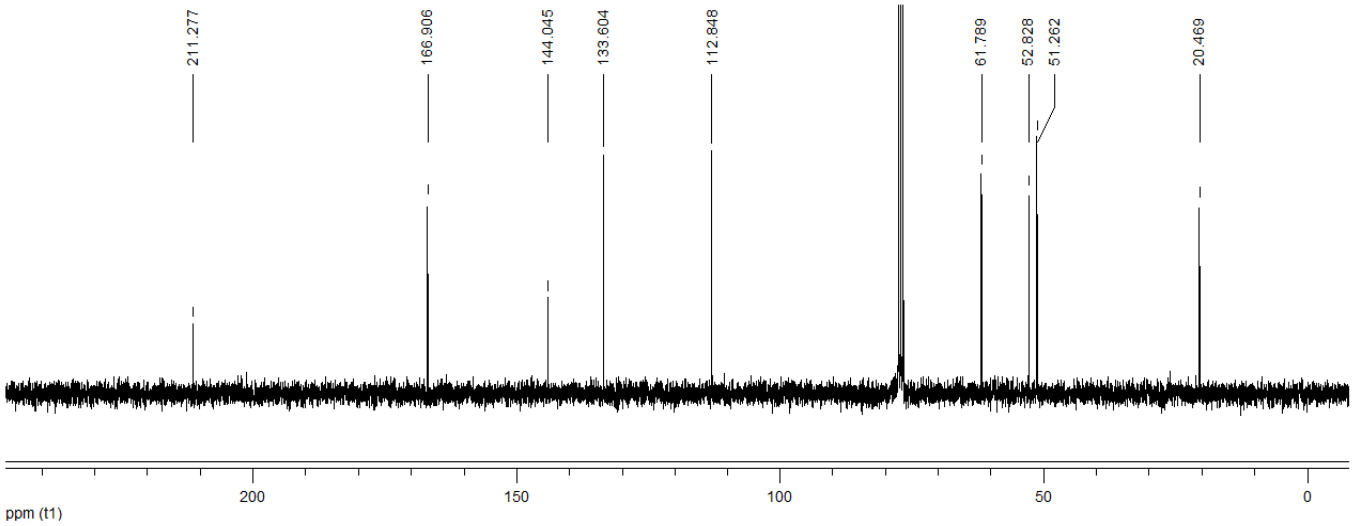


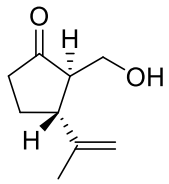


165, $CDCl_3$, 300 MHz

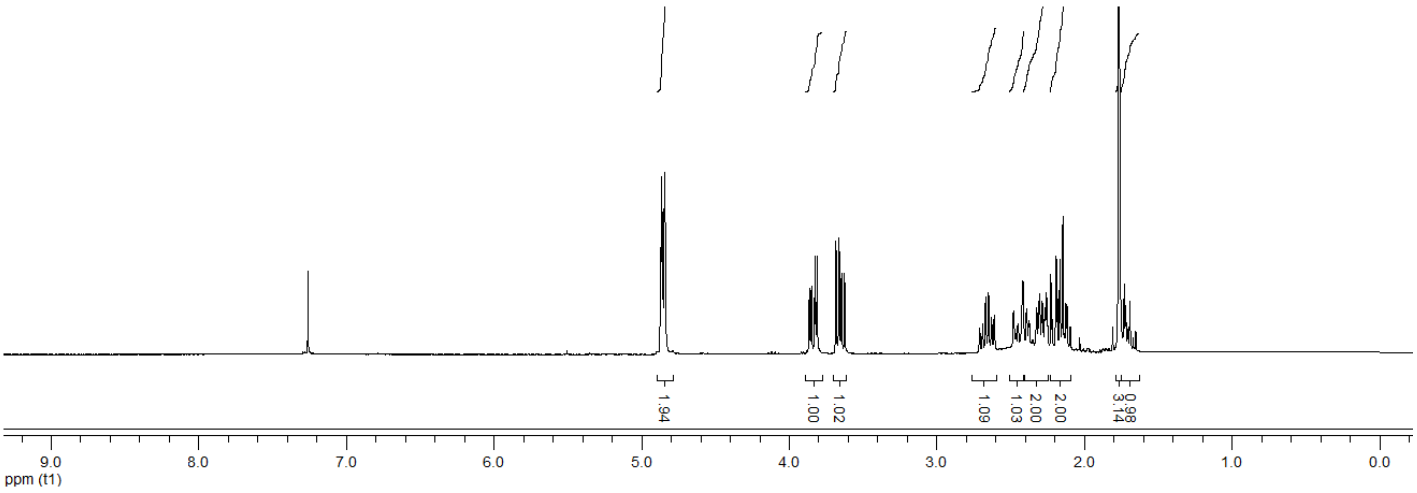


$CDCl_3$, 75 MHz

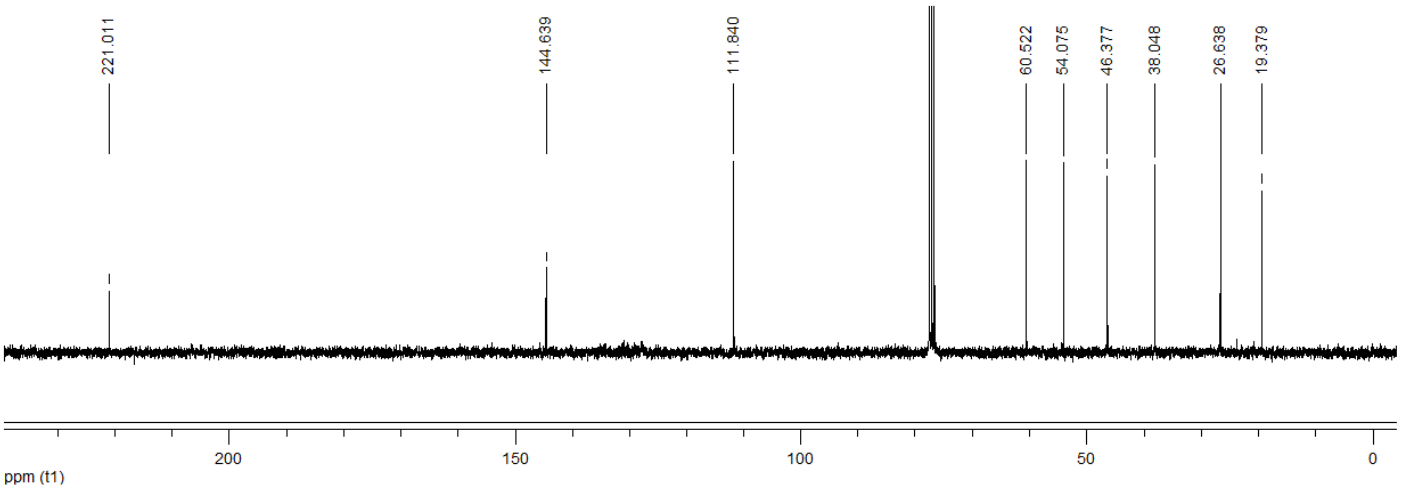


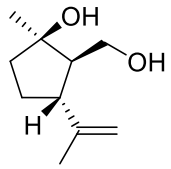


178, $CDCl_3$, 300 MHz

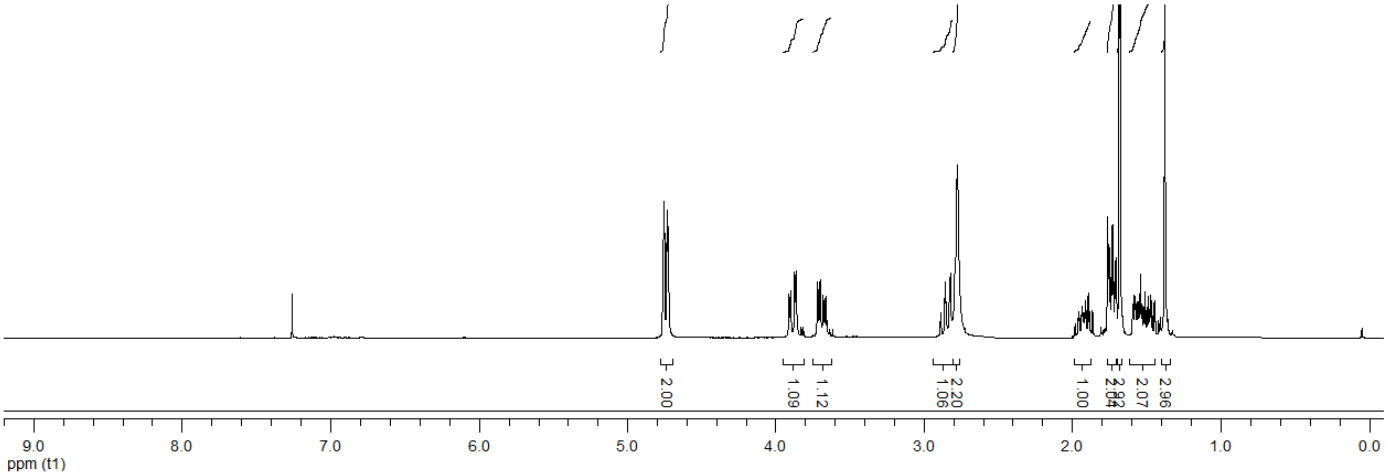


CDCl3, 75 MHz

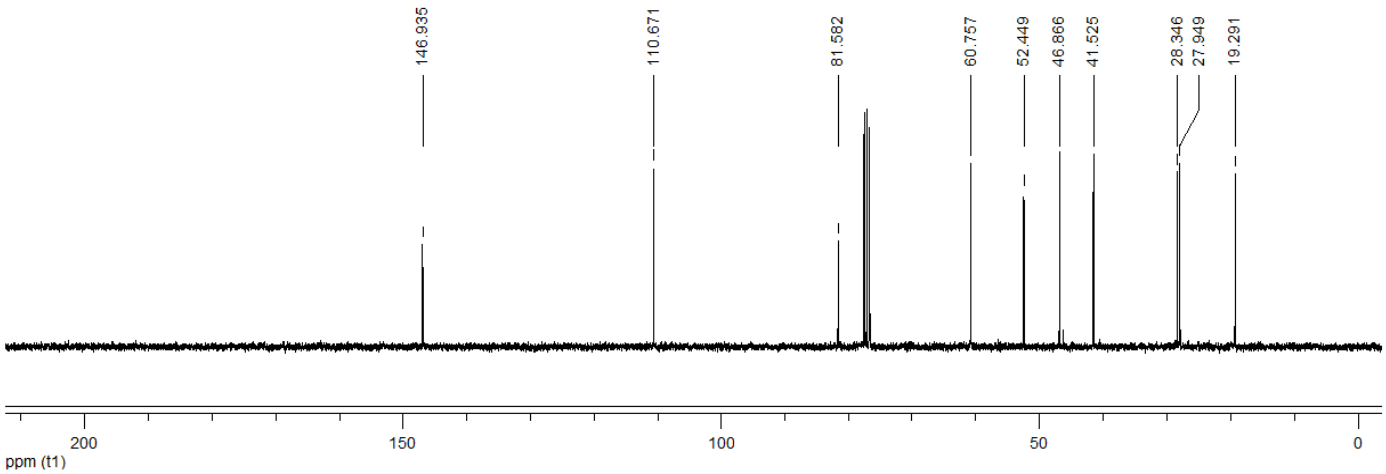


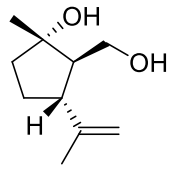


179a-*syn*, $CDCl_3$, 300 MHz

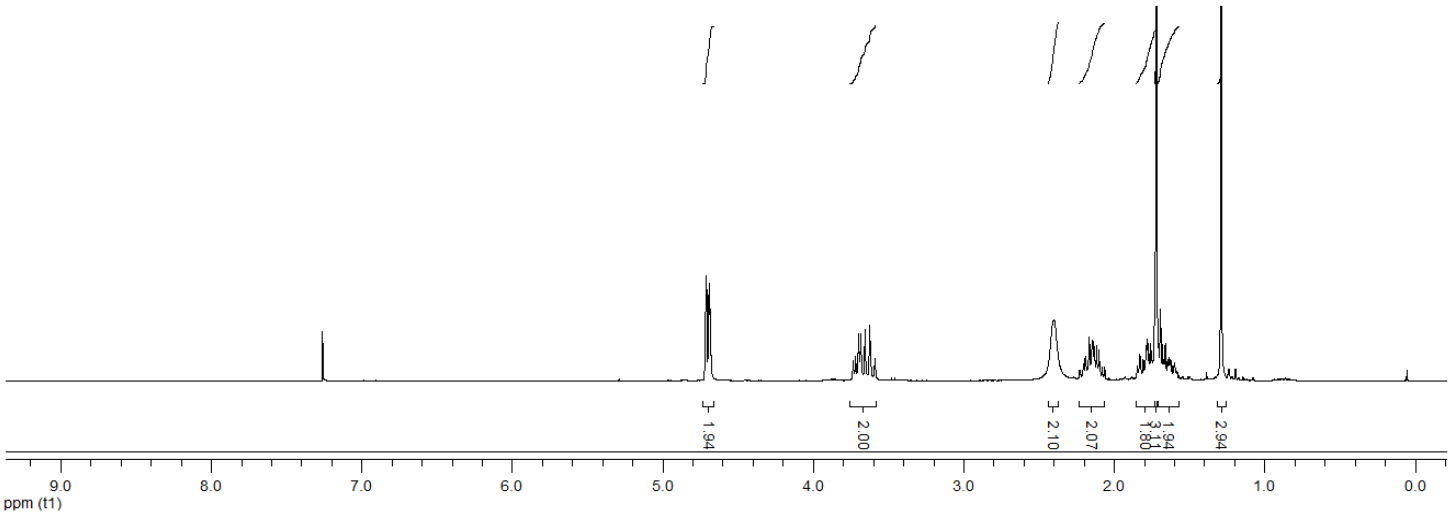


$CDCl_3$, 75 MHz

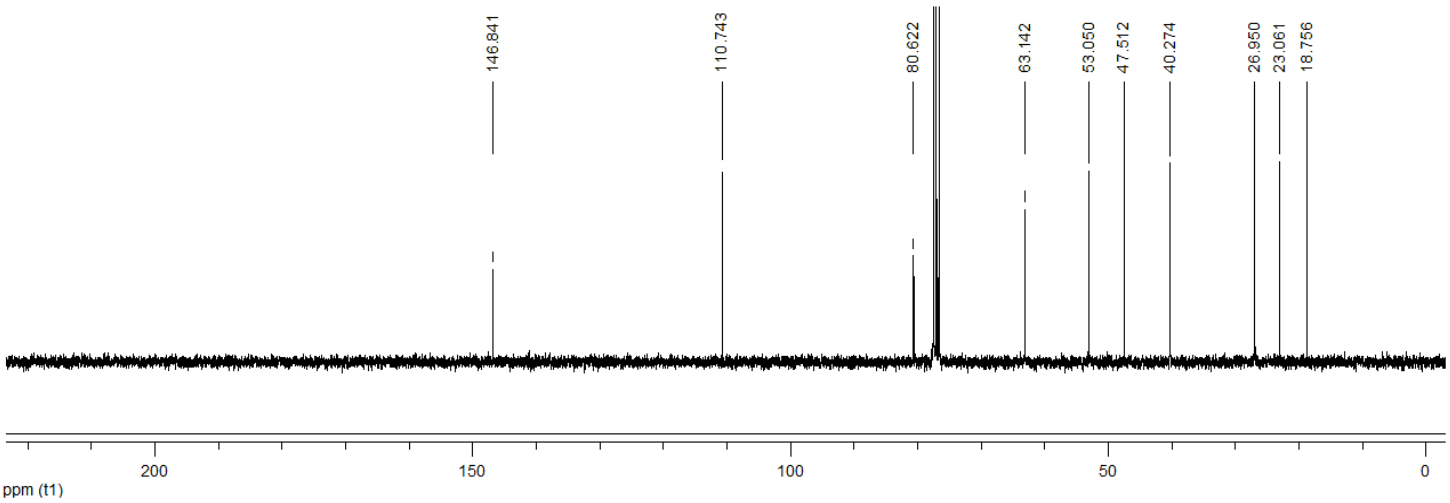


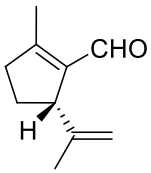


179b-*anti*, $CDCl_3$, 300 MHz

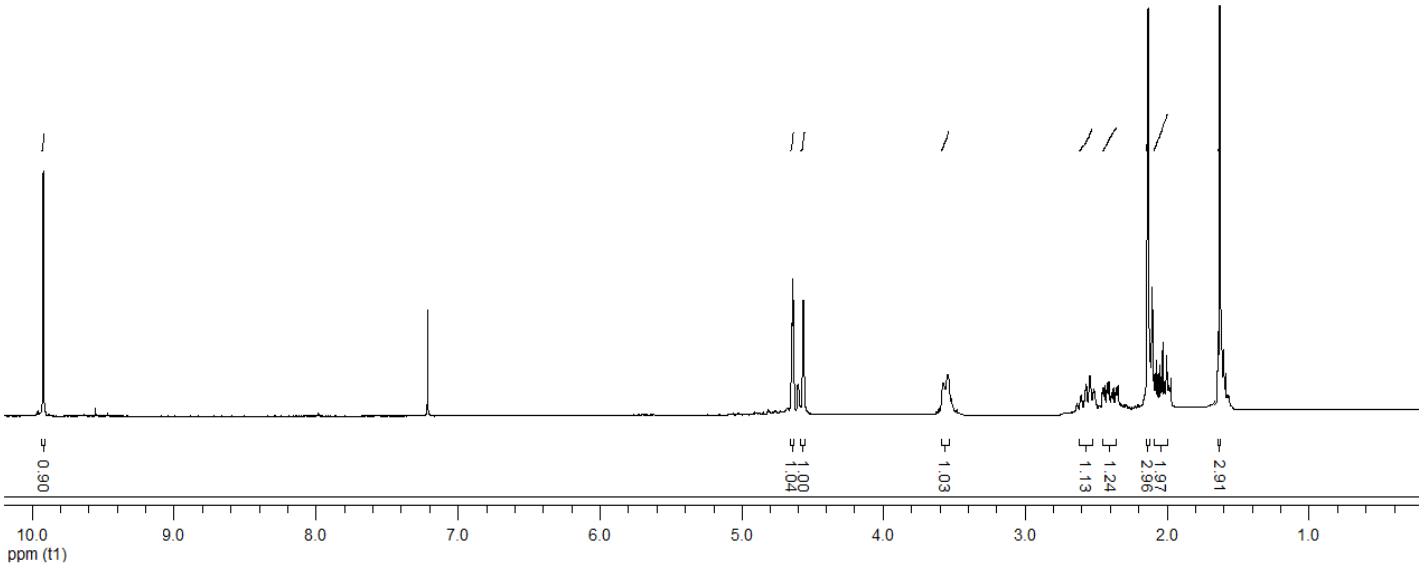


CDCl3, 75 MHz

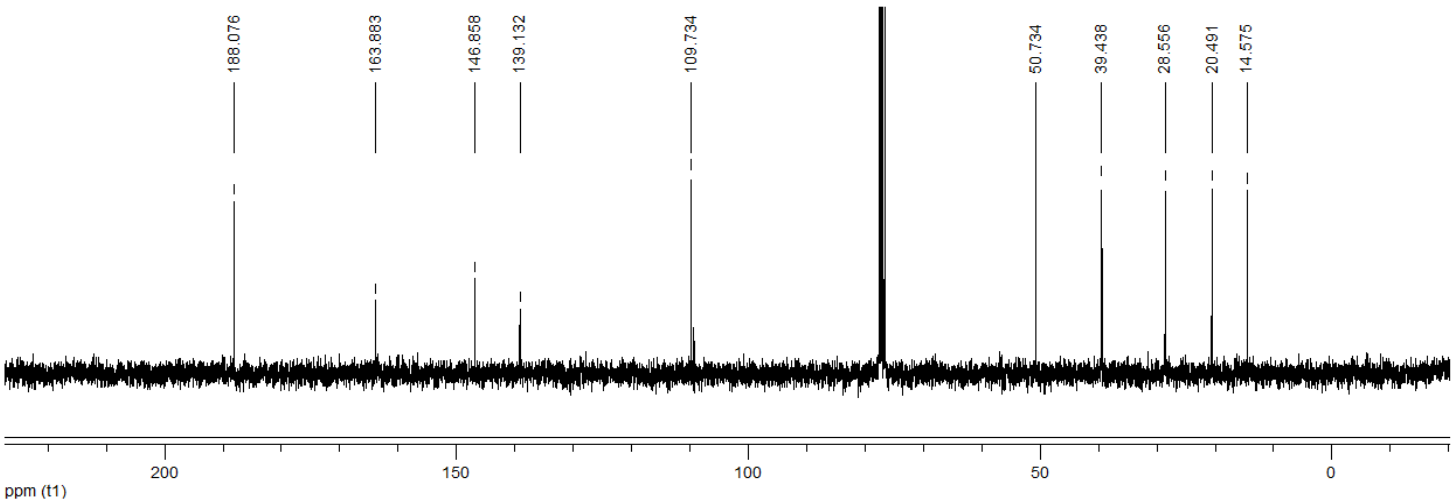


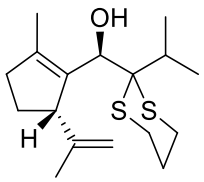


164, $CDCl_3$, 300 MHz

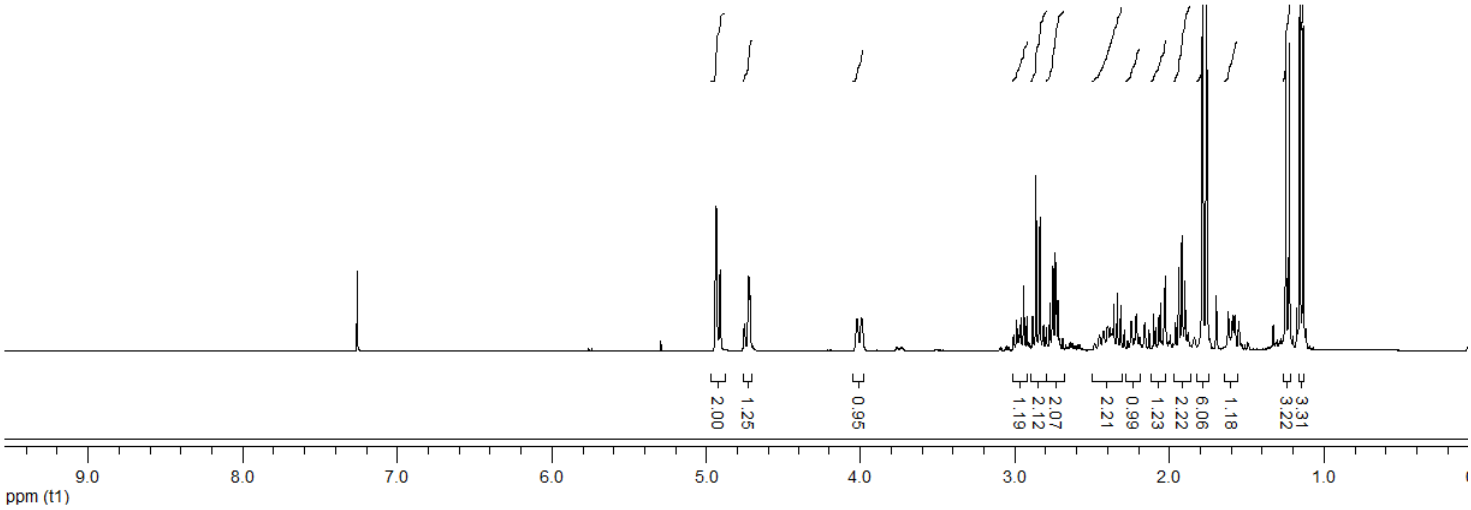


$CDCl_3$, 75 MHz

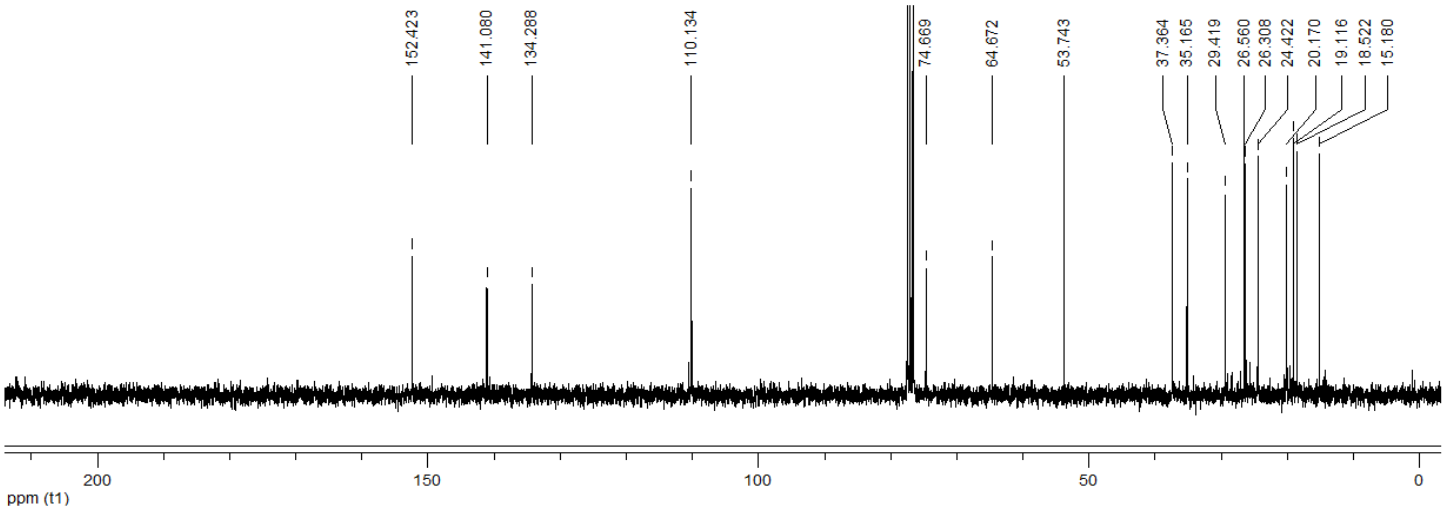


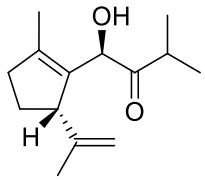


187, $CDCl_3$, 300 MHz

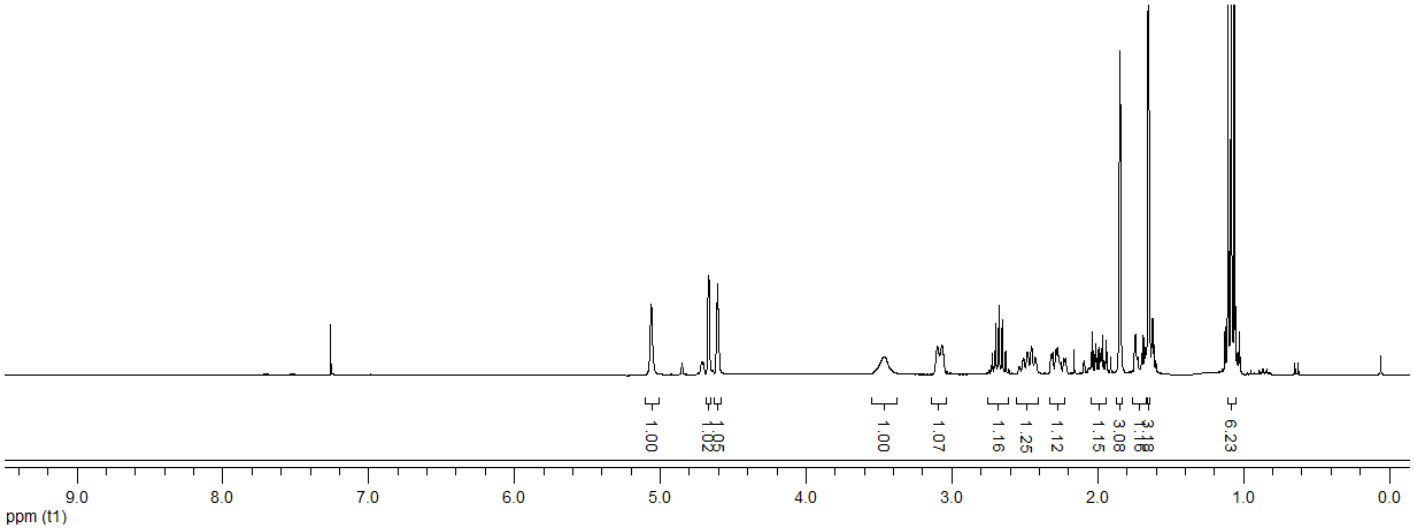


$CDCl_3$, 75 MHz

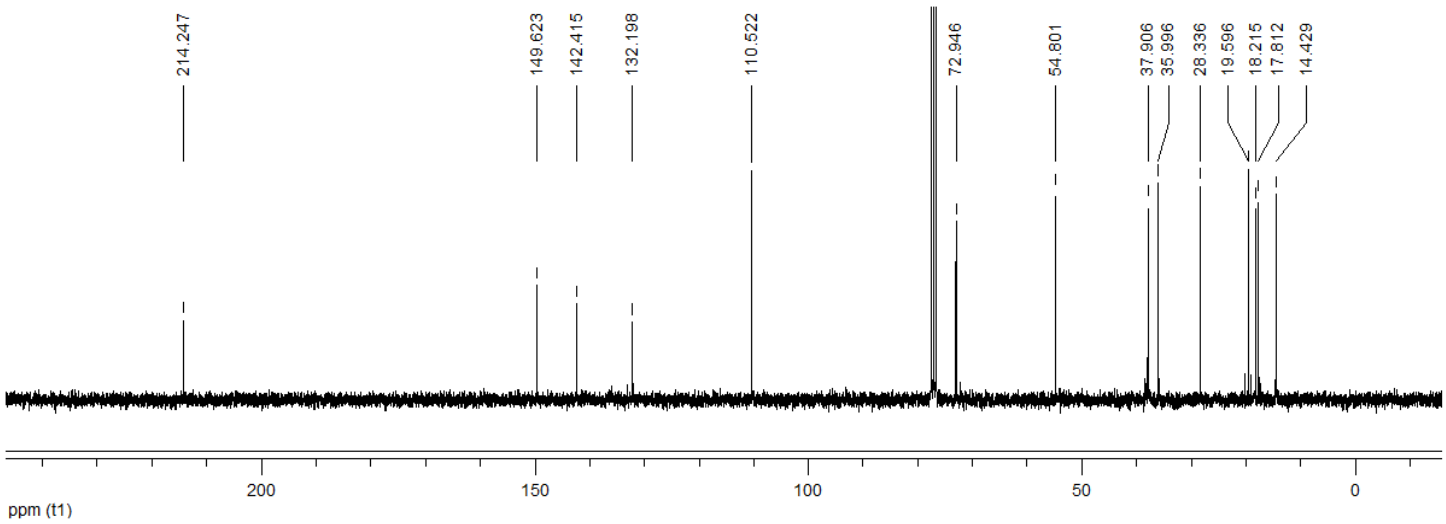


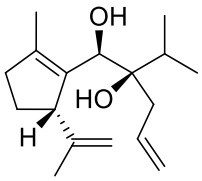


163, $CDCl_3$, 300 MHz

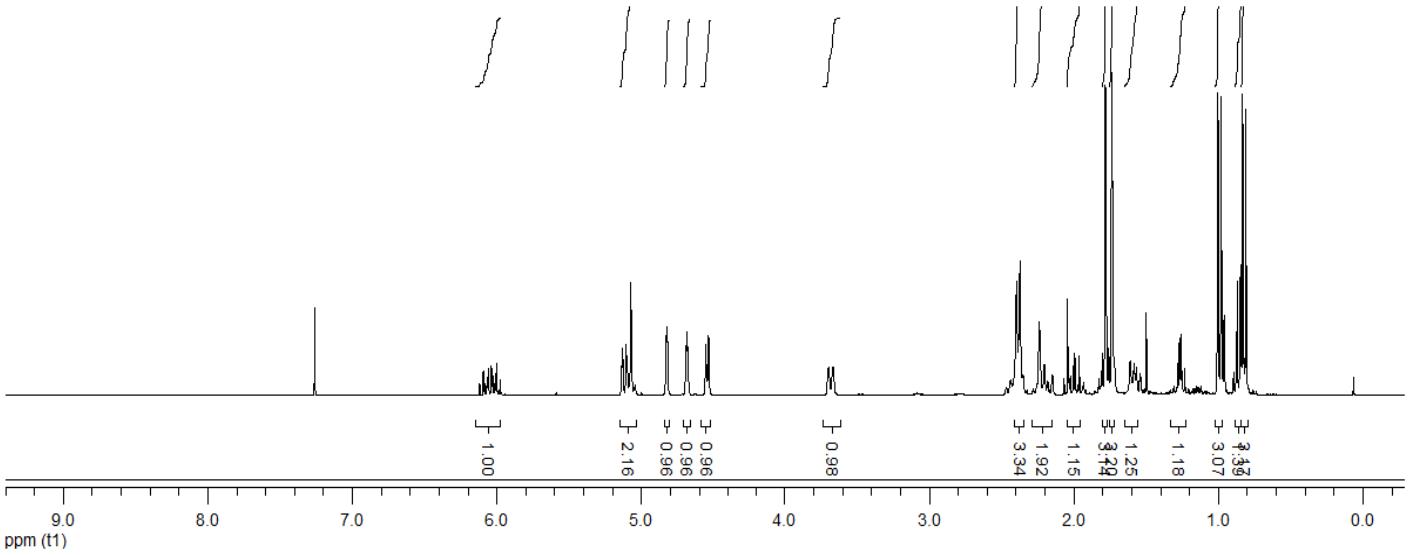


$CDCl_3$, 75 MHz

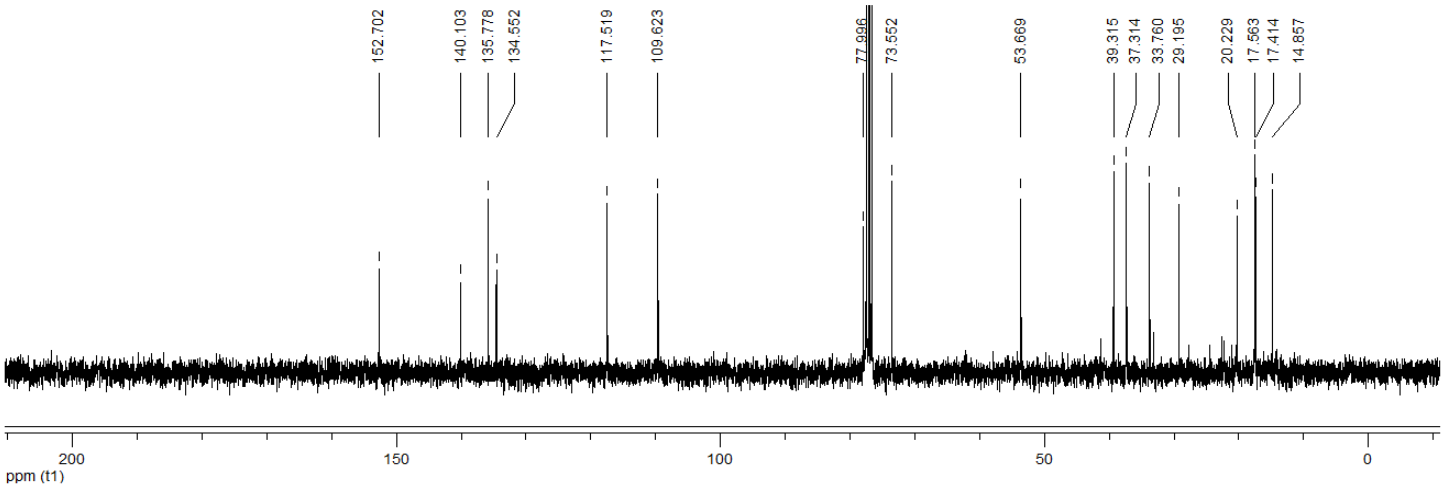


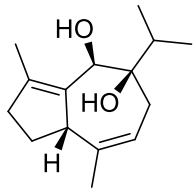


188, $CDCl_3$, 300 MHz

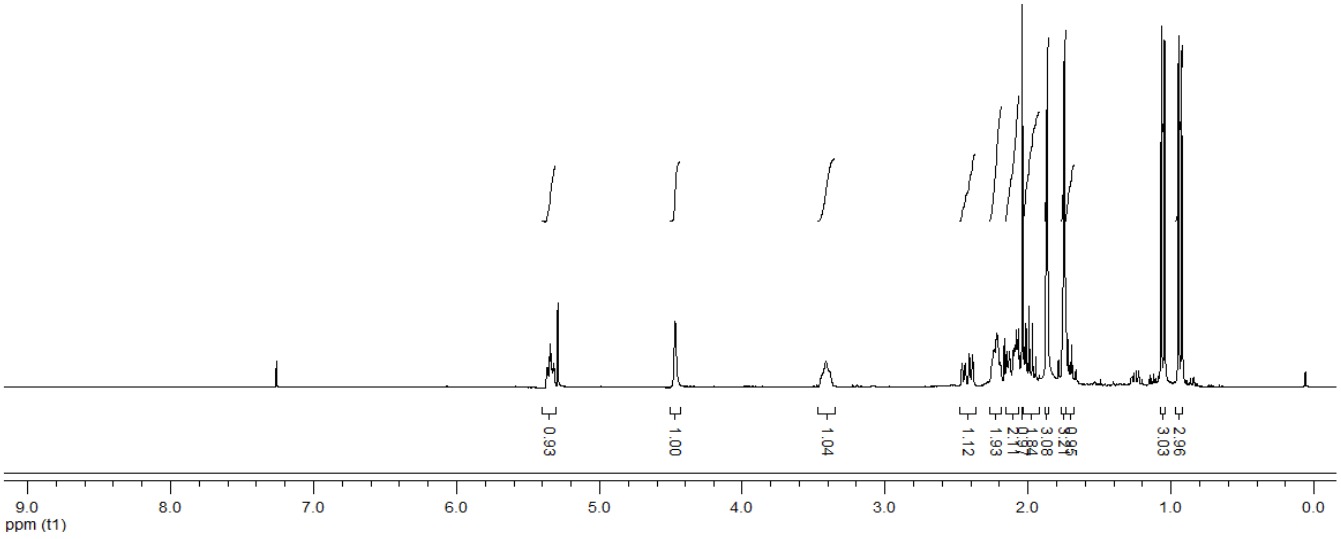


$CDCl_3$, 75 MHz

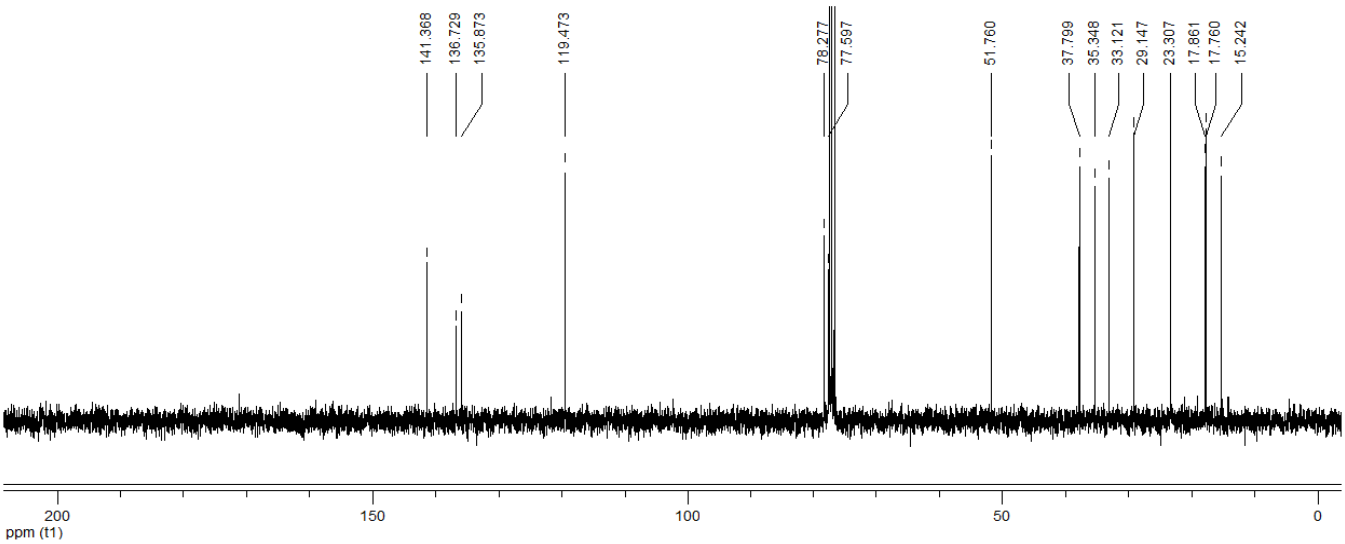


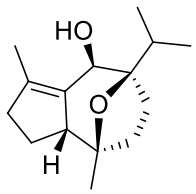


189, d_6-Acetone, 300 MHz

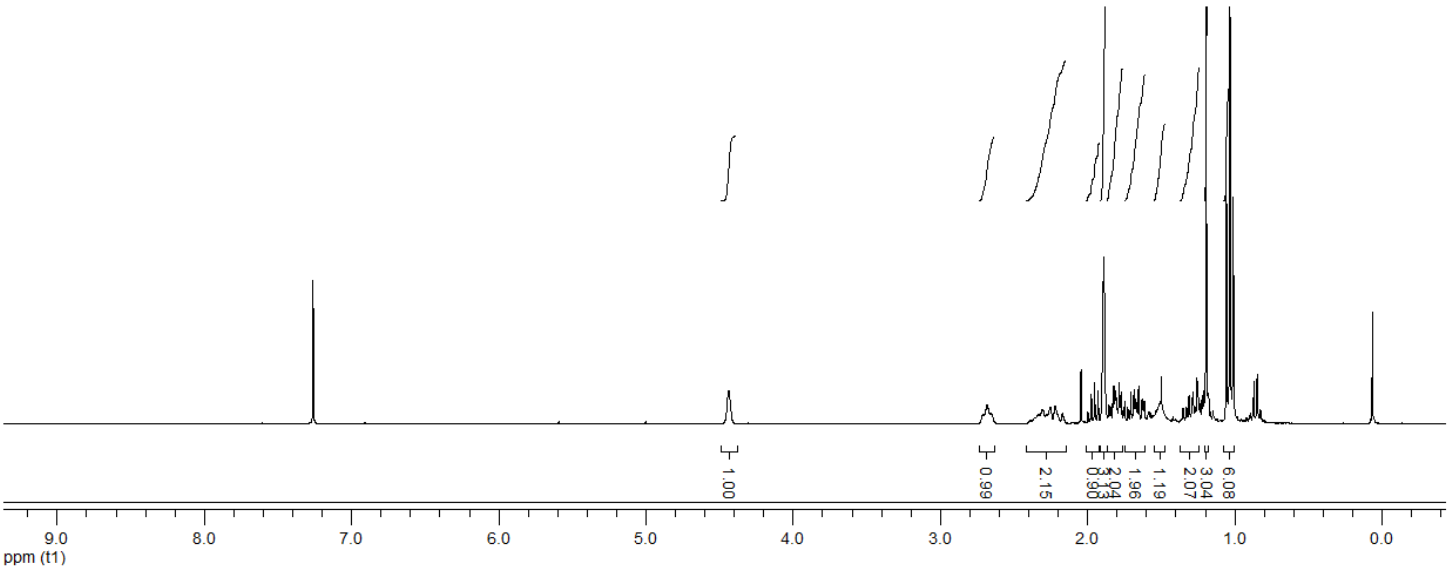


d_6-Acetone, 75 MHz

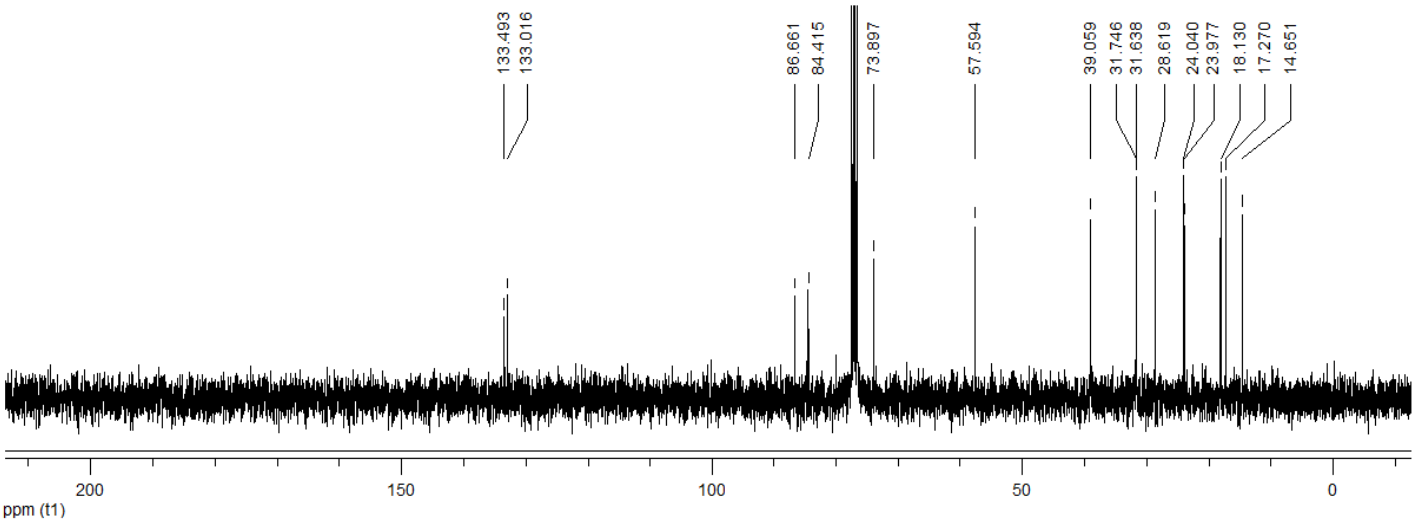


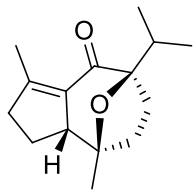


192, $CDCl_3$, 300 MHz

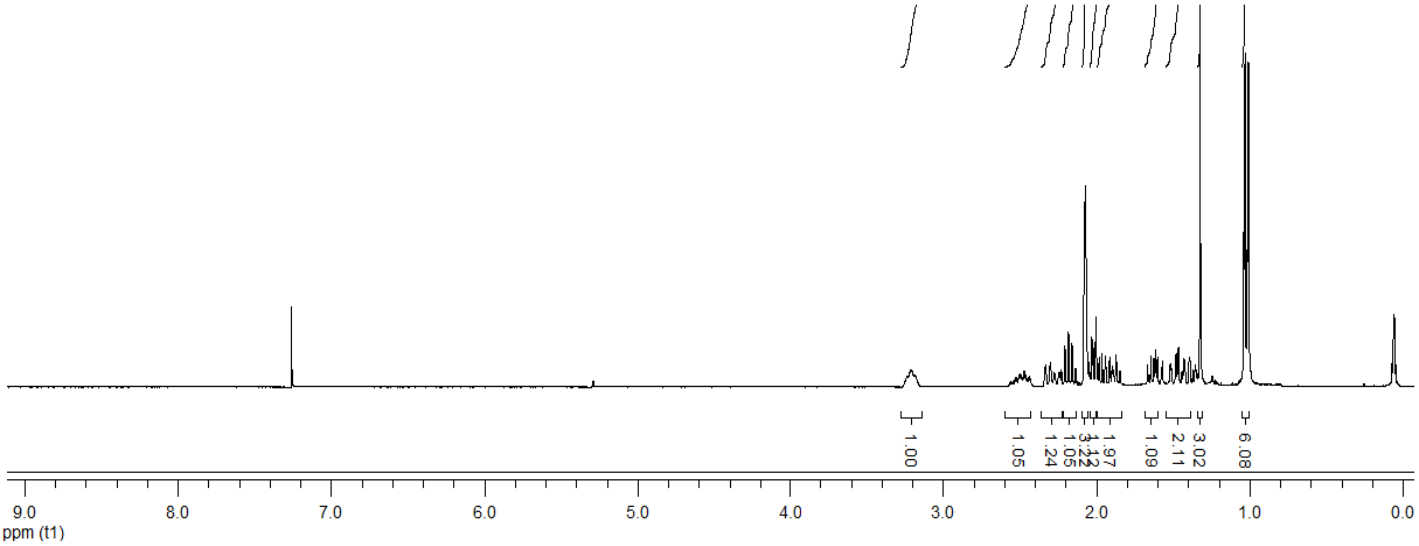


$CDCl_3$, 75 MHz

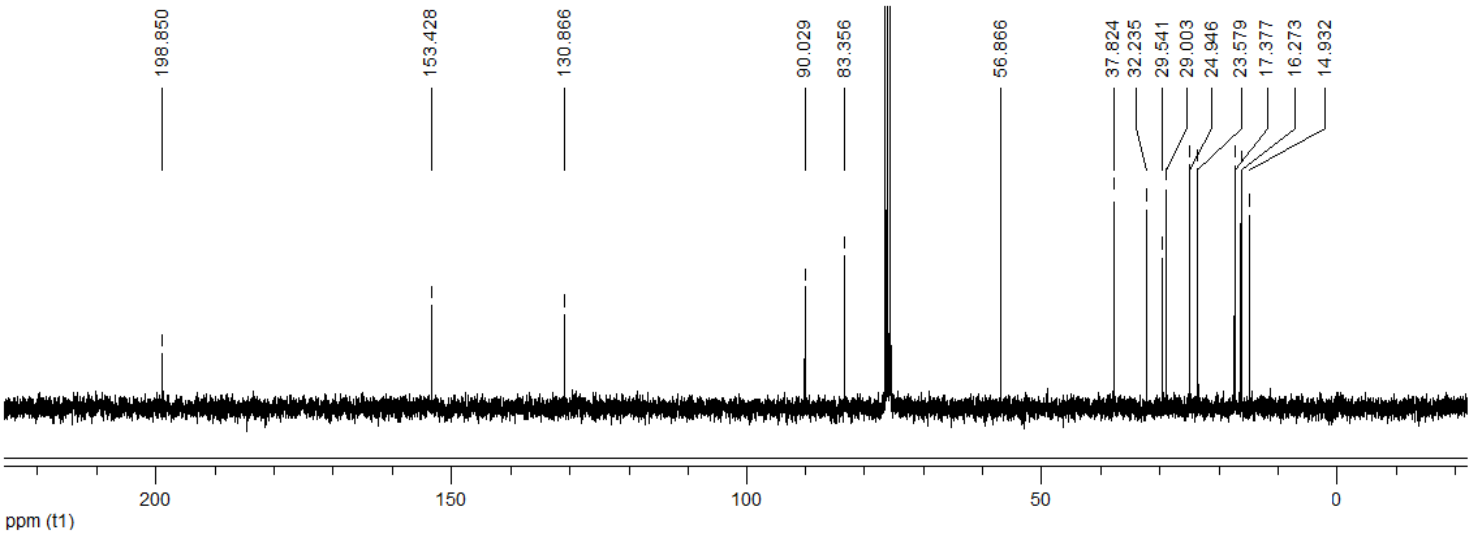


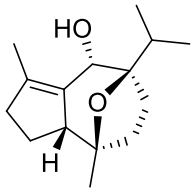


194, $CDCl_3$, 300 MHz

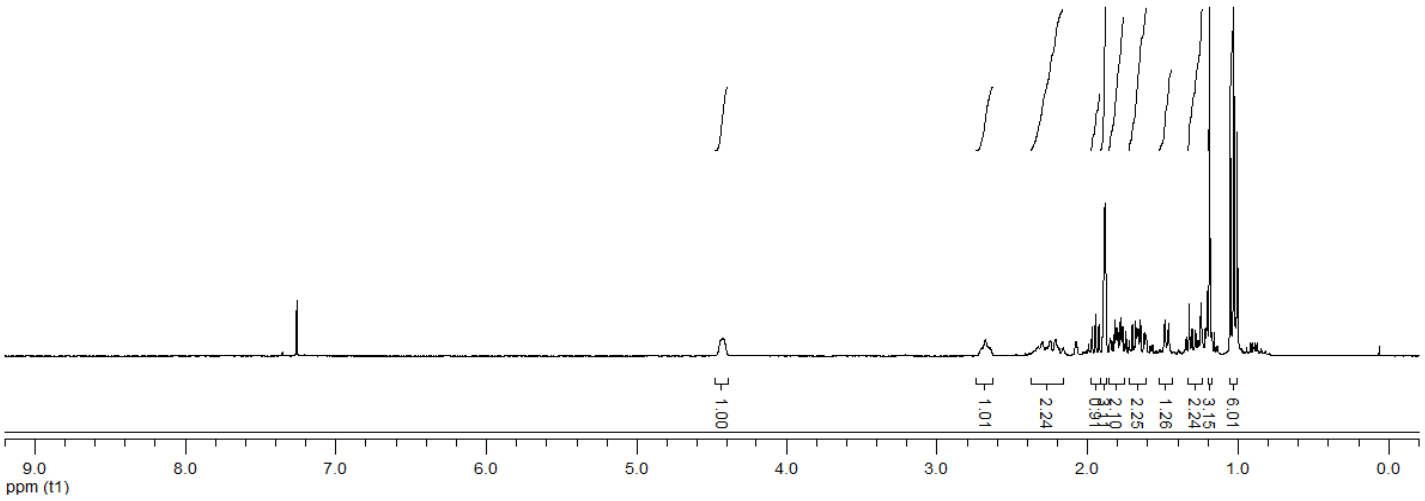


$CDCl_3$, 75 MHz

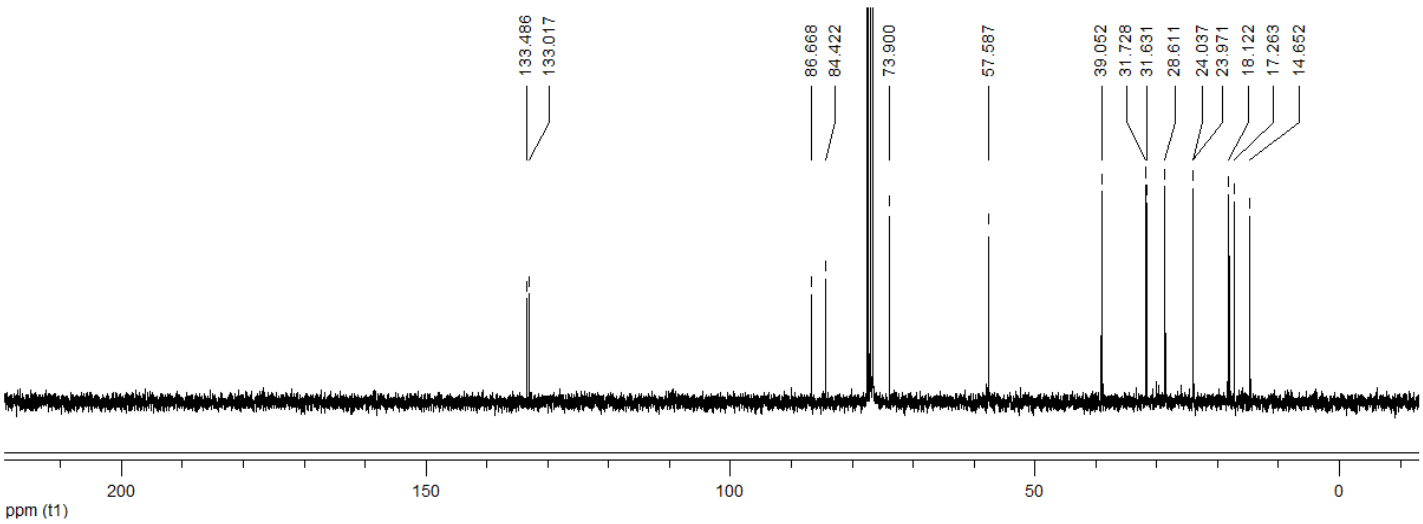


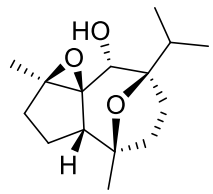


78 (+)-**Orientalol-F, $CDCl_3$, 300 MHz**

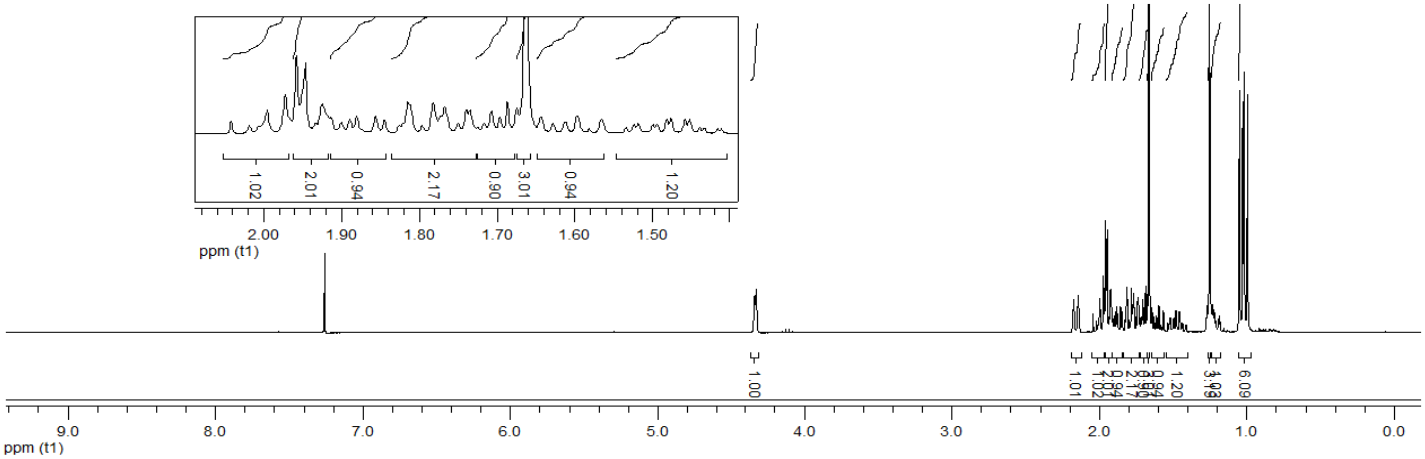


$CDCl_3$, 75 MHz

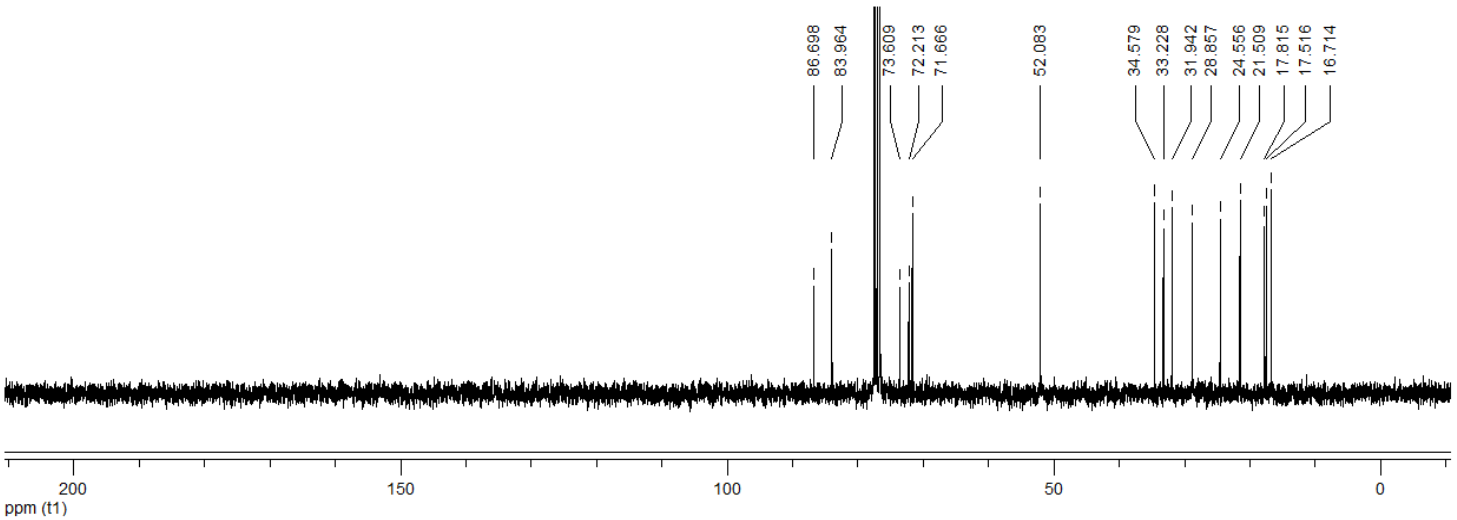


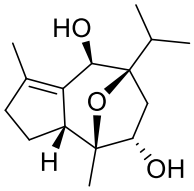


197, $CDCl_3$, 300 MHz

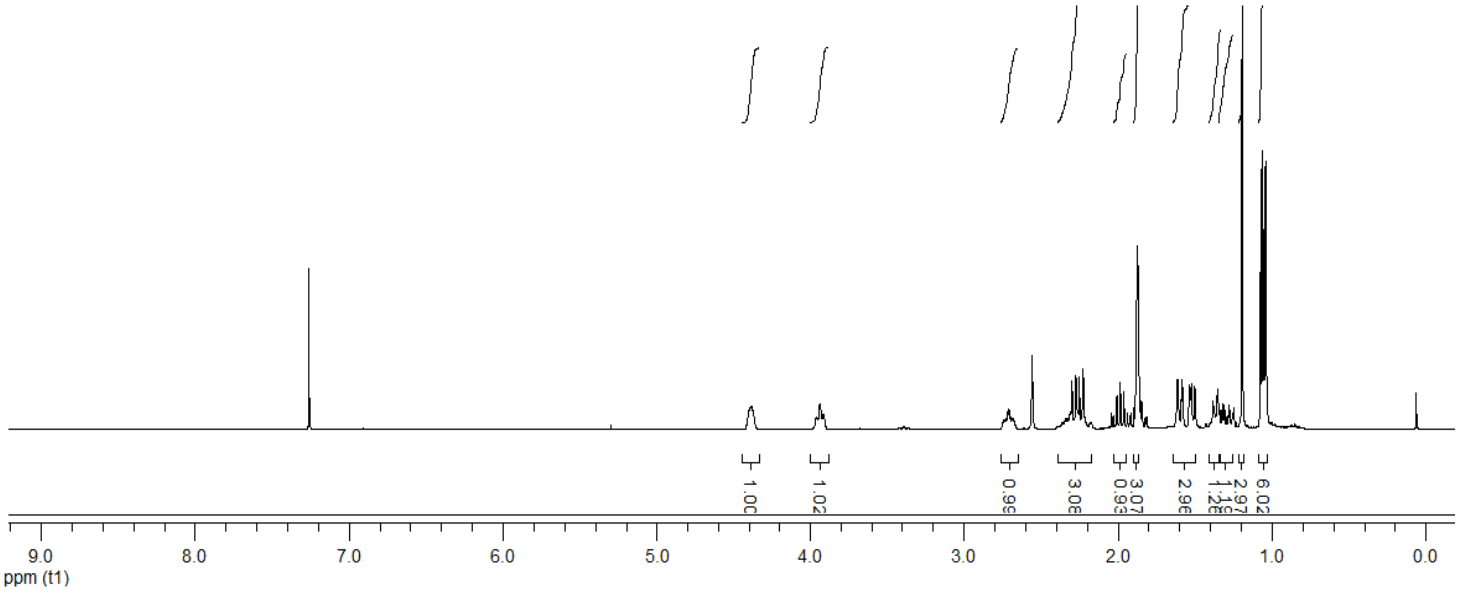


$CDCl_3$, 75 MHz

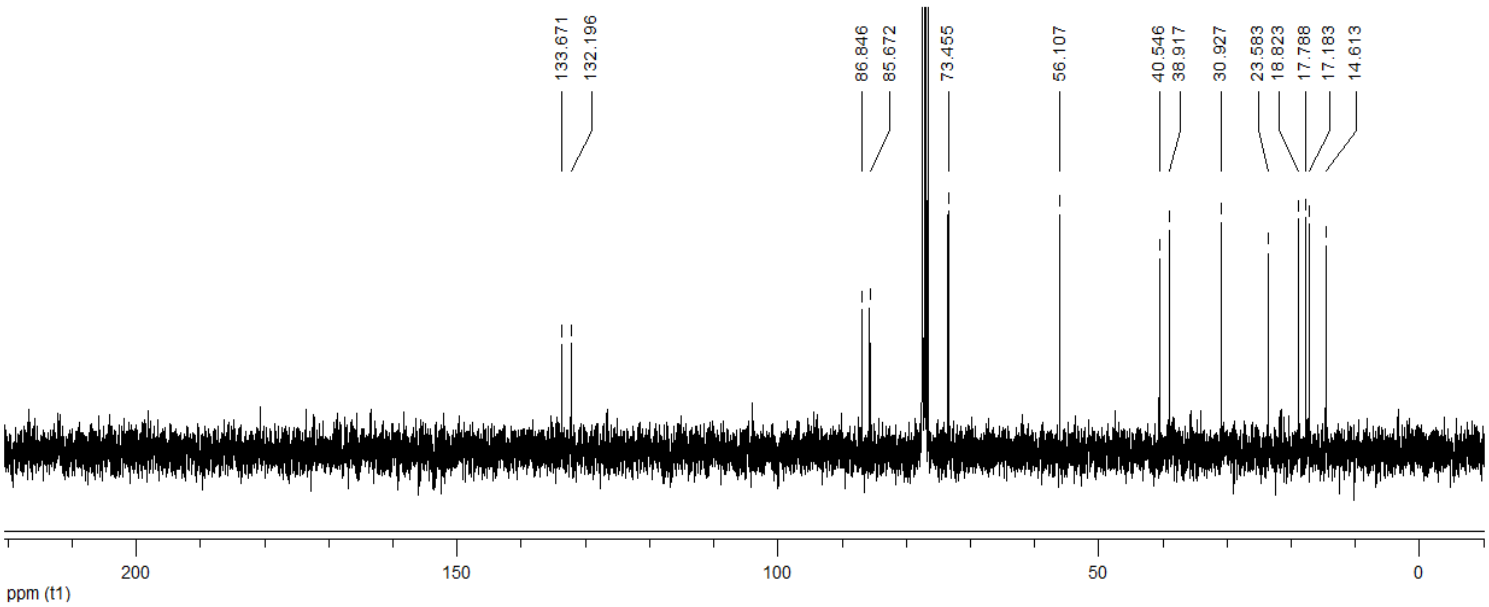


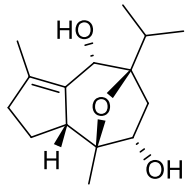


193, $CDCl_3$, 300 MHz

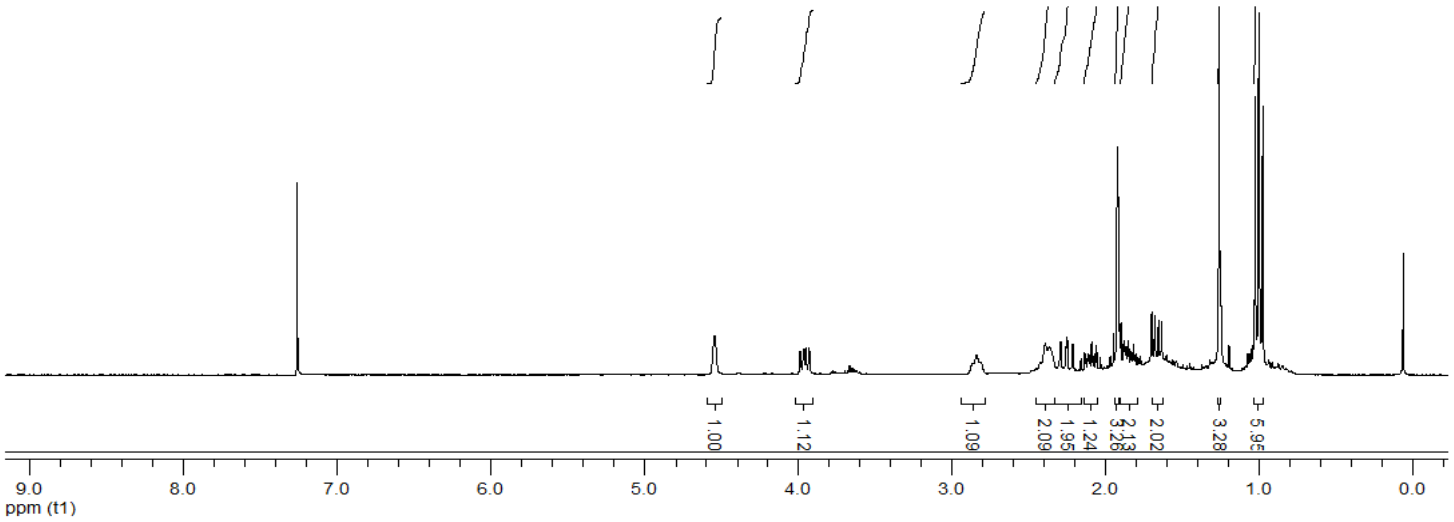


$CDCl_3$, 75 MHz

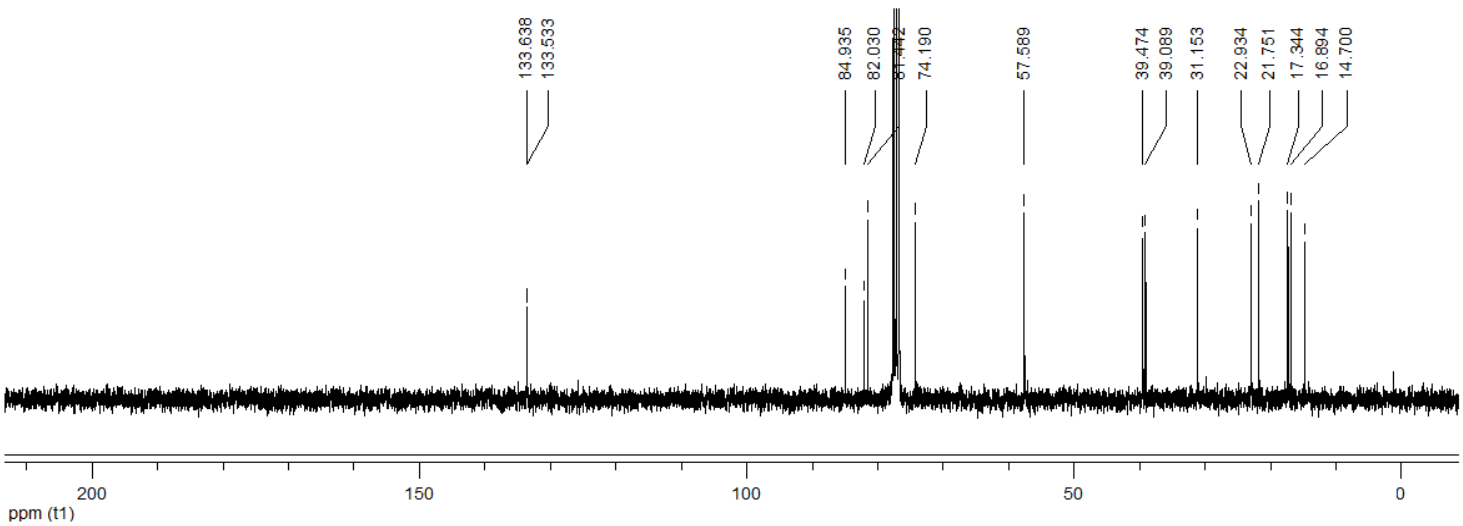


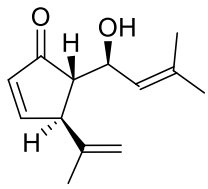


196, $CDCl_3$, 300 MHz

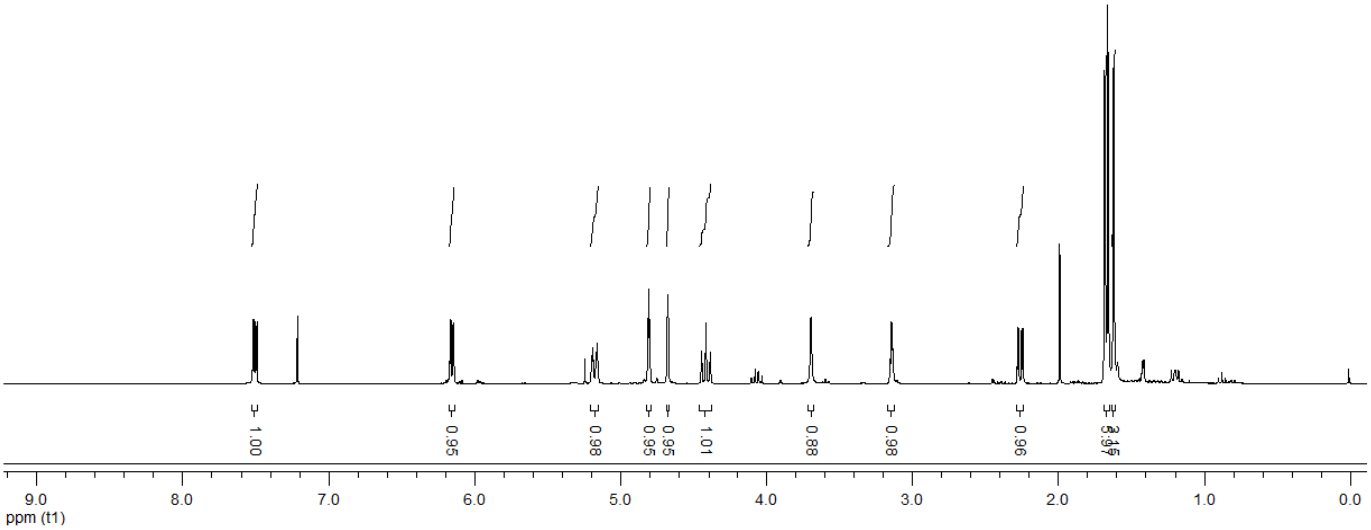


$CDCl_3$, 75 MHz

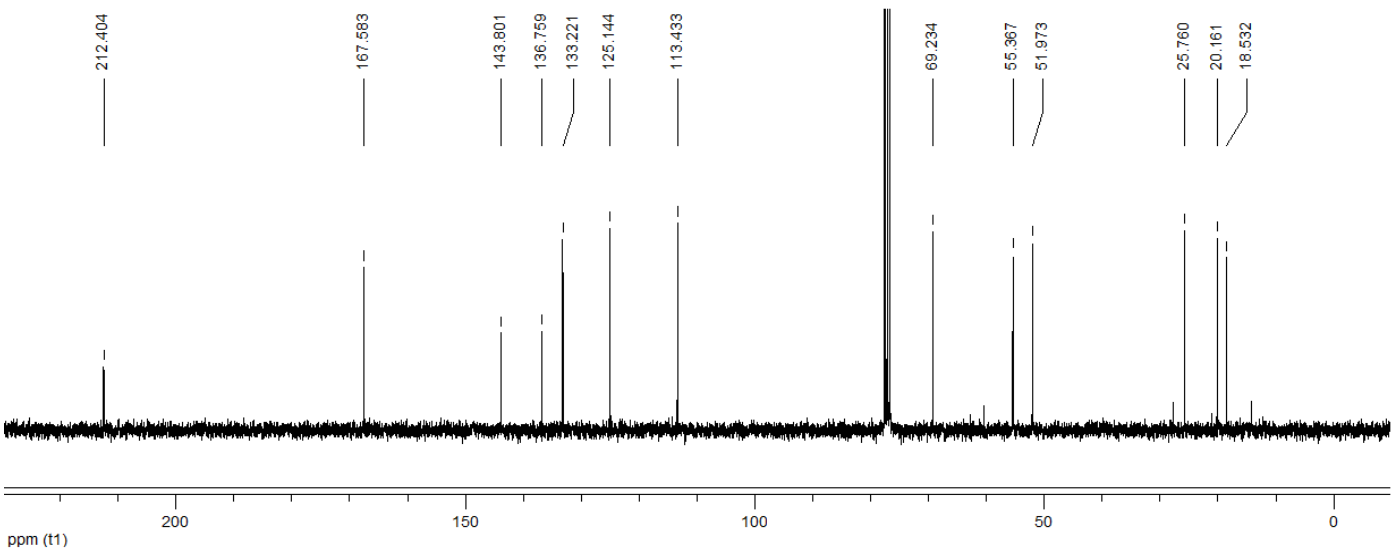


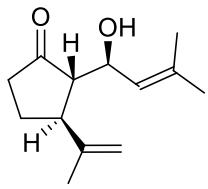


199, $CDCl_3$, 300 MHz

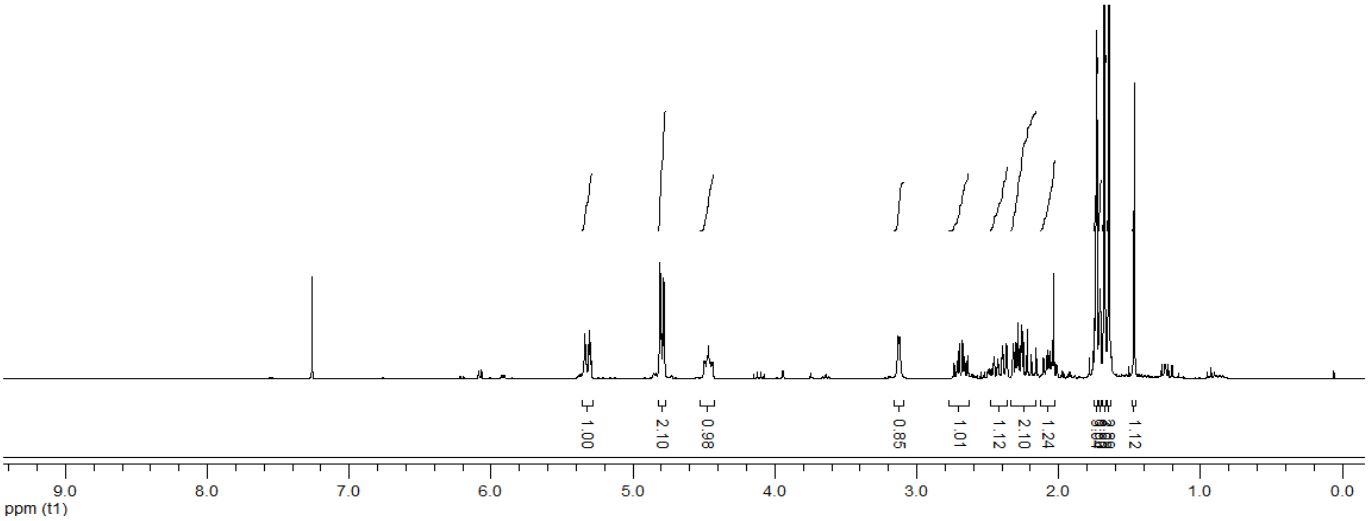


$CDCl_3$, 75 MHz

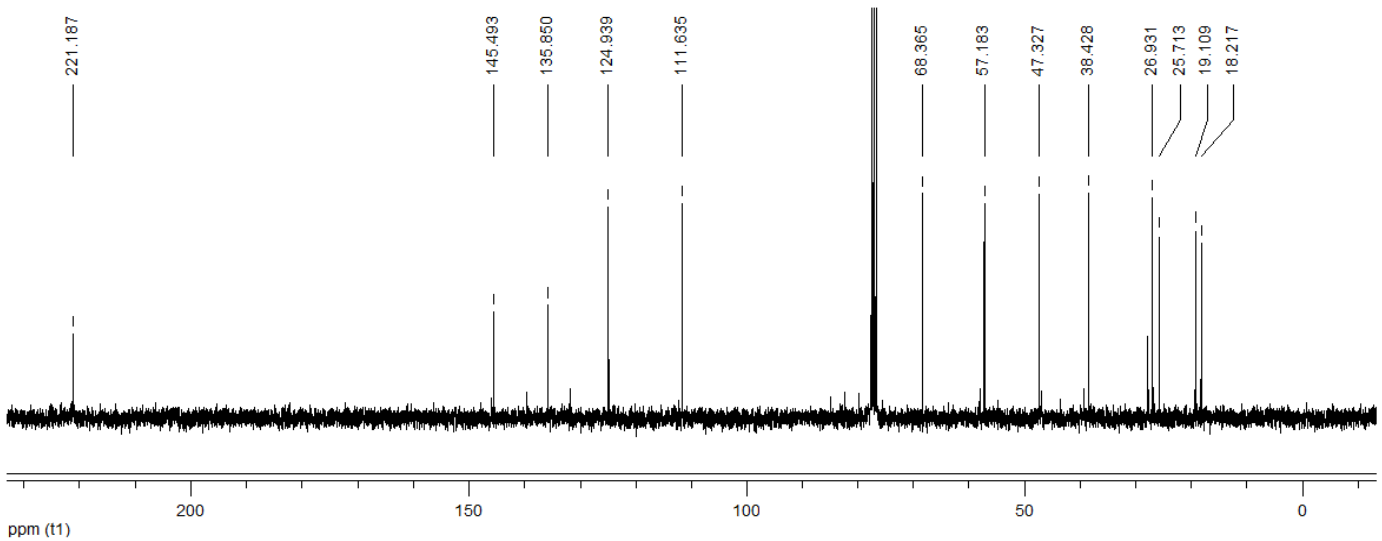


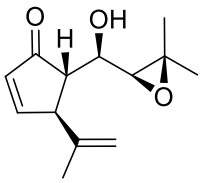


200, $CDCl_3$, 300 MHz

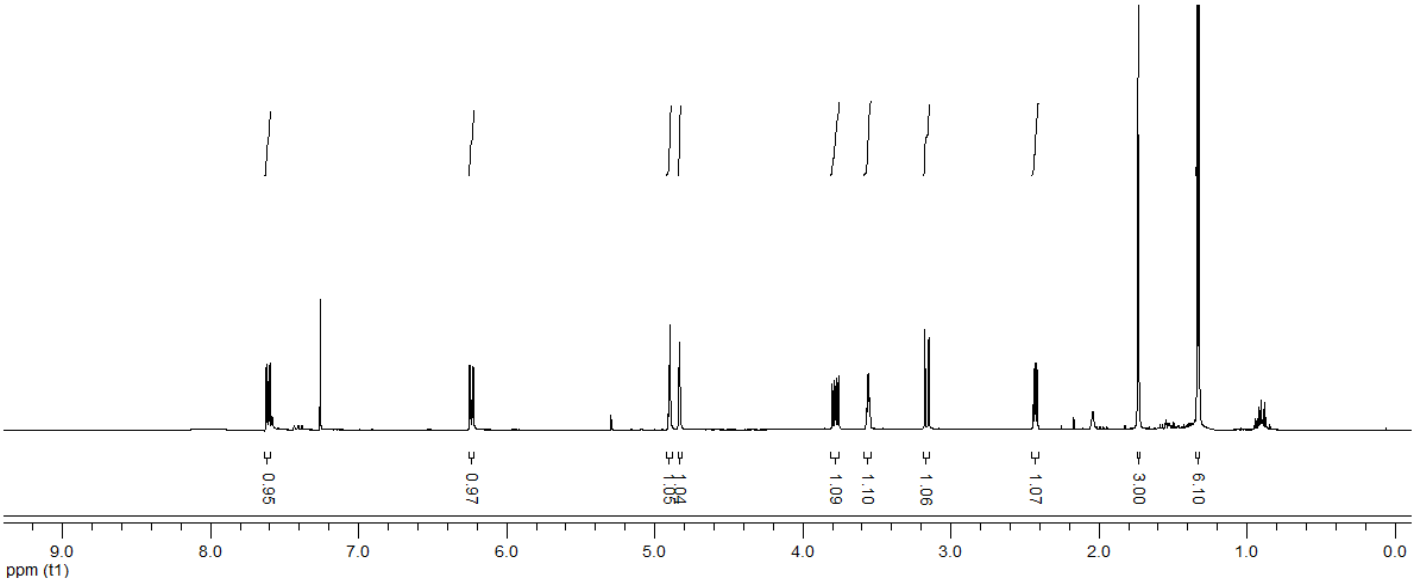


$CDCl_3$, 75 MHz

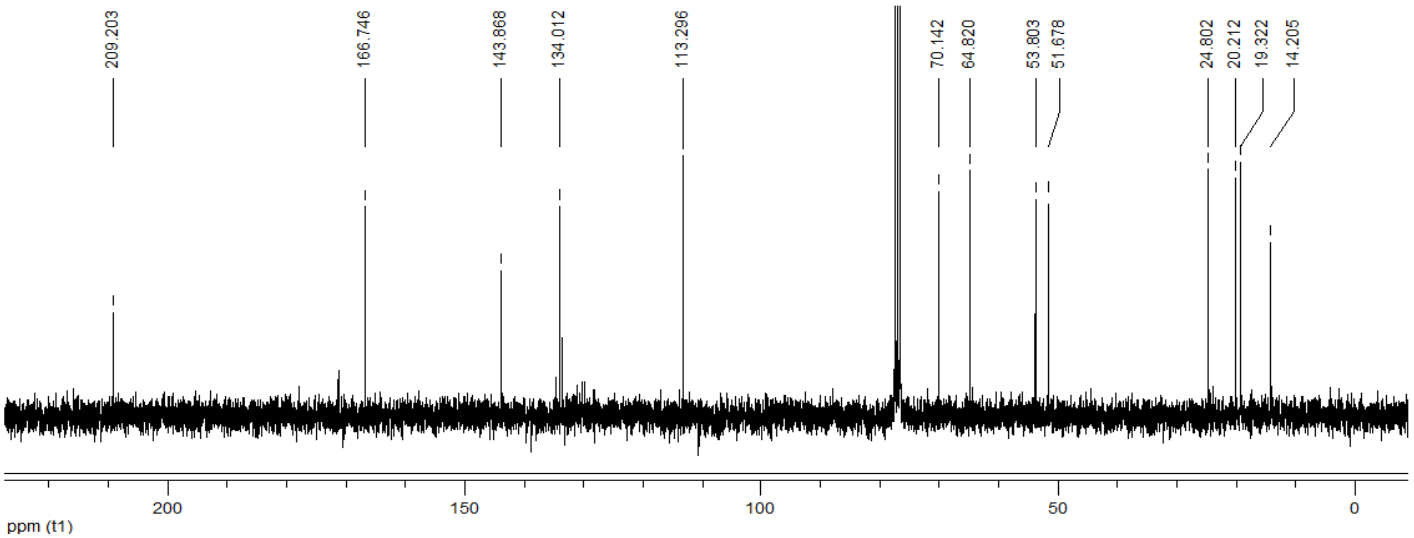


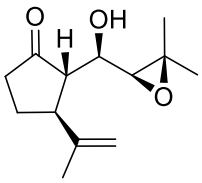


202, $CDCl_3$, 300 MHz

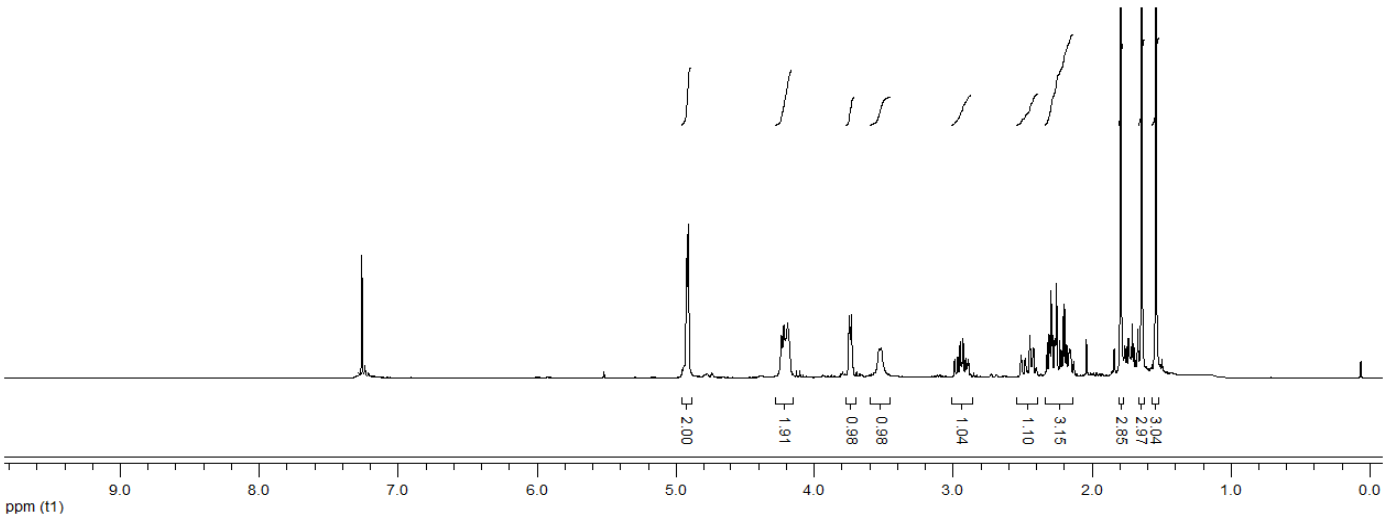


$CDCl_3$, 75 MHz

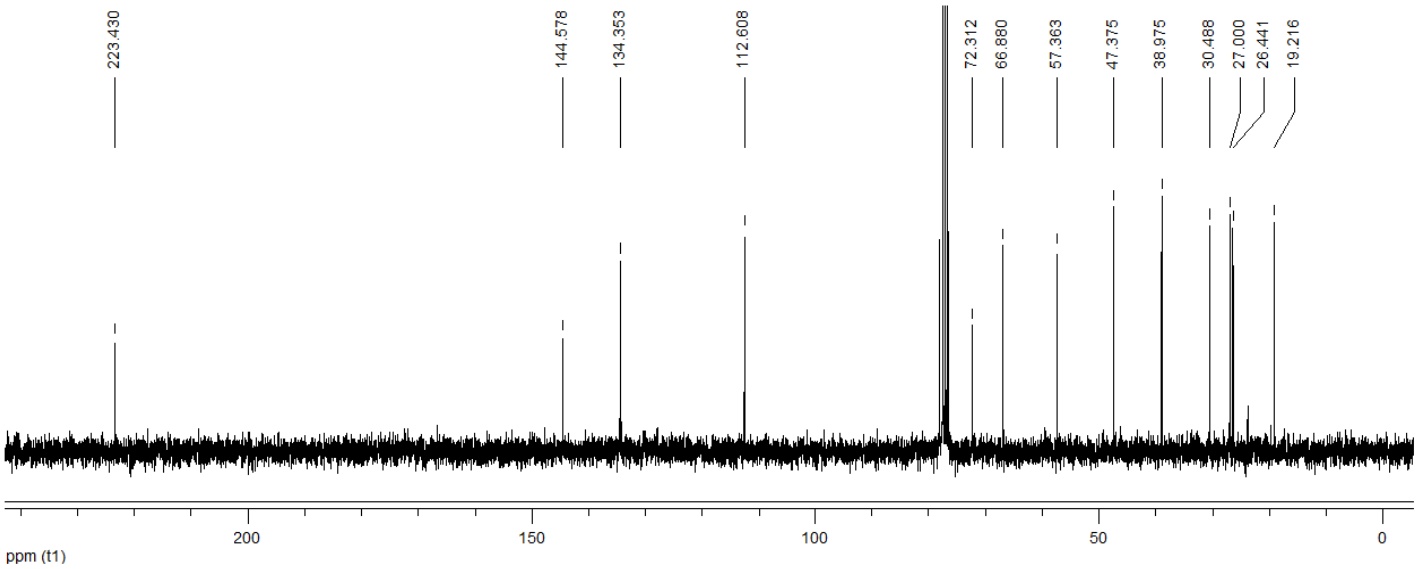


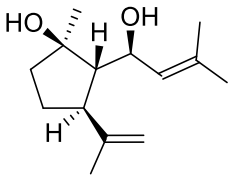


203, $CDCl_3$, 300 MHz

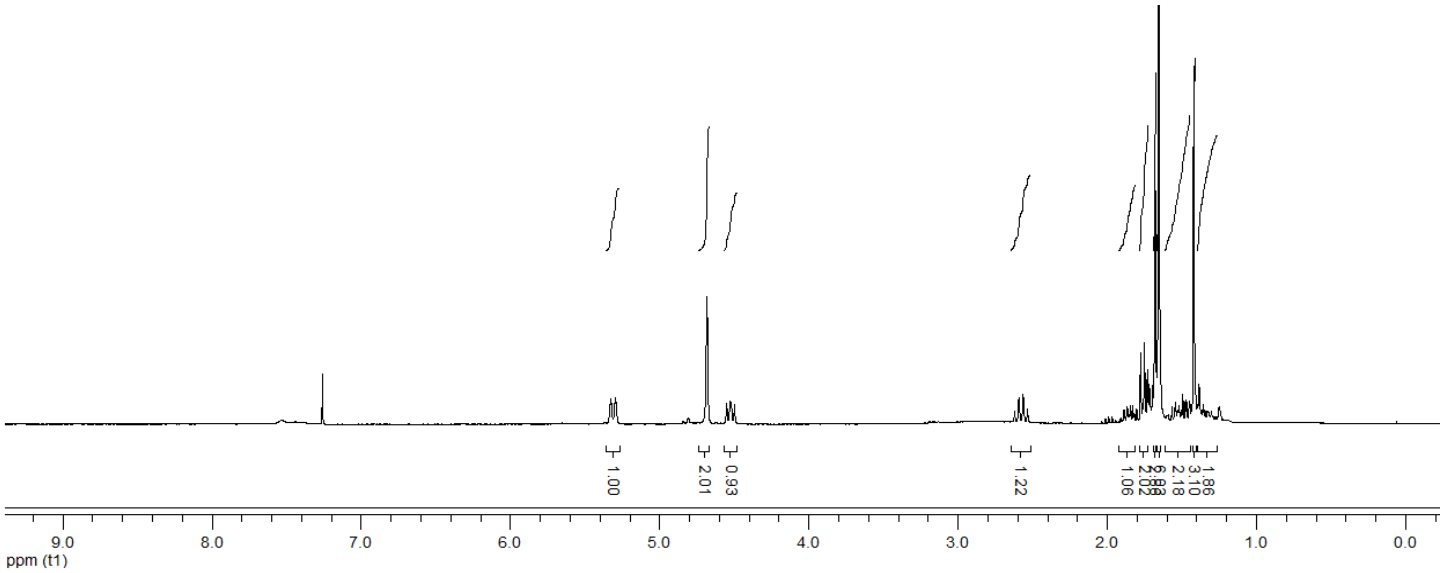


$CDCl_3$, 75 MHz

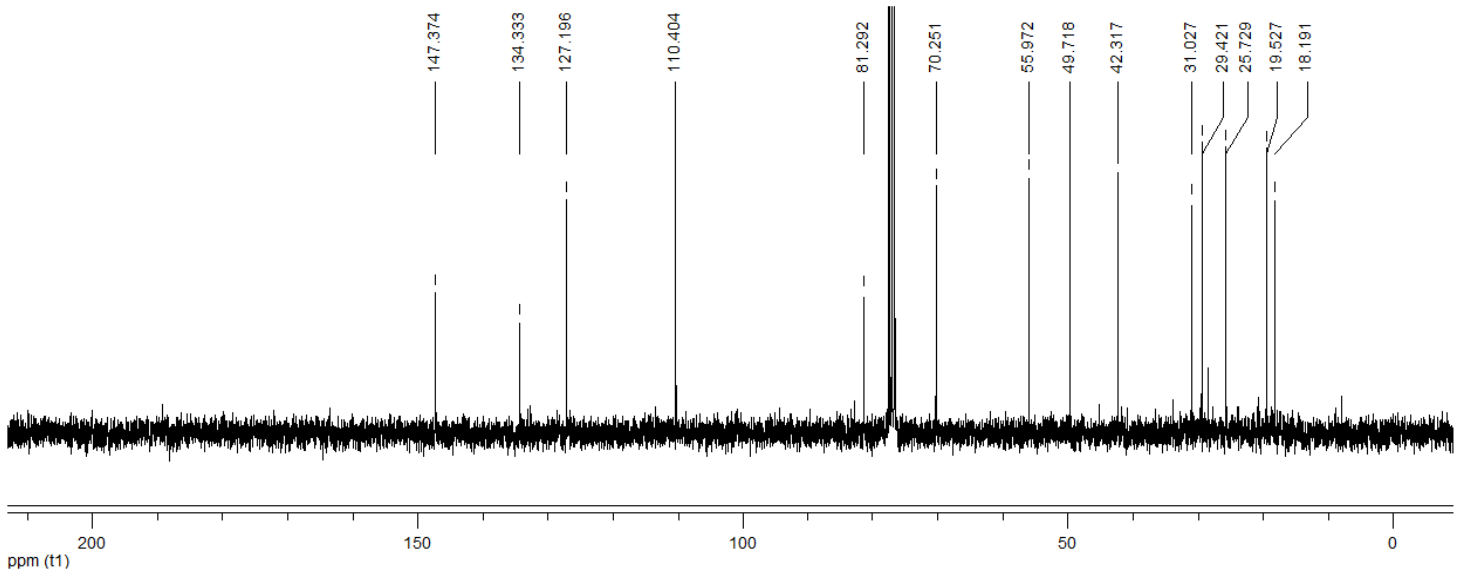


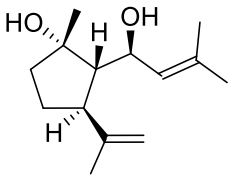


205-*syn*, $CDCl_3$, 300 MHz

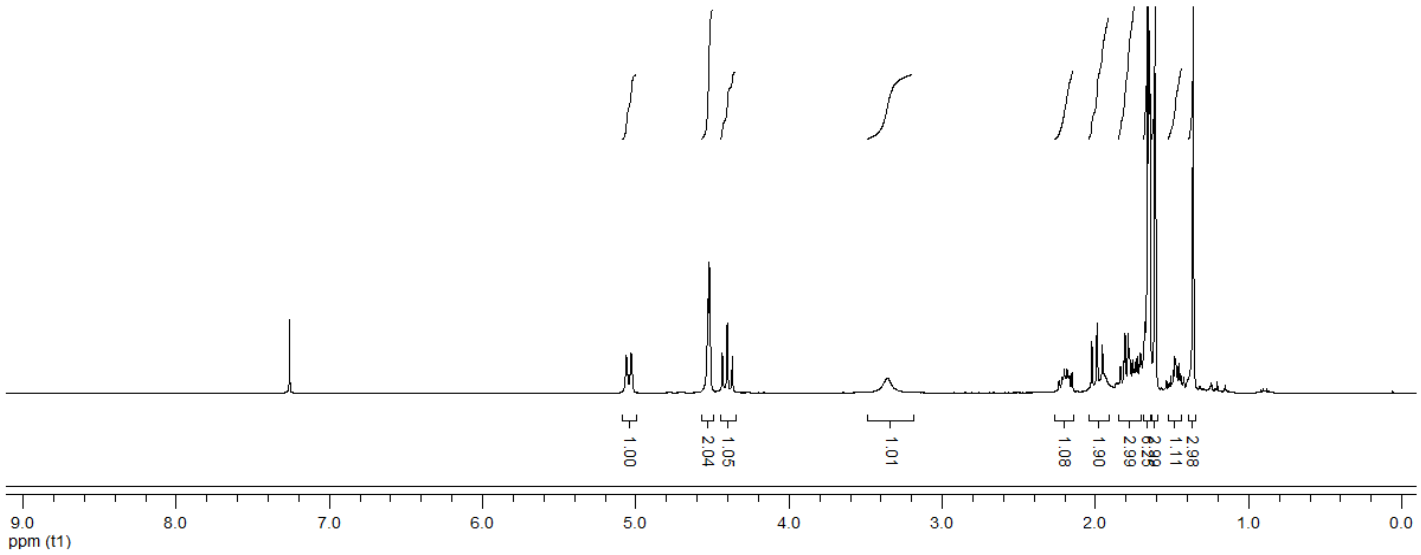


CDCl3, 75 MHz

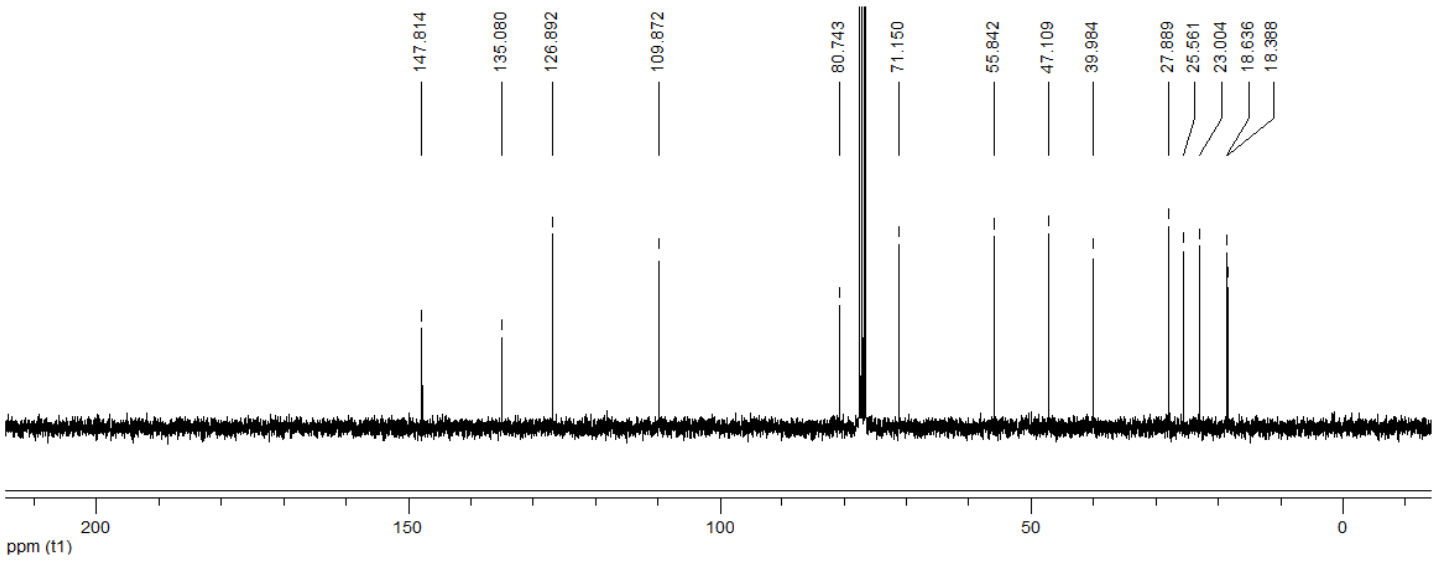


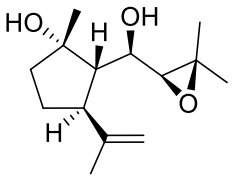


205-*anti*, $CDCl_3$, 300 MHz

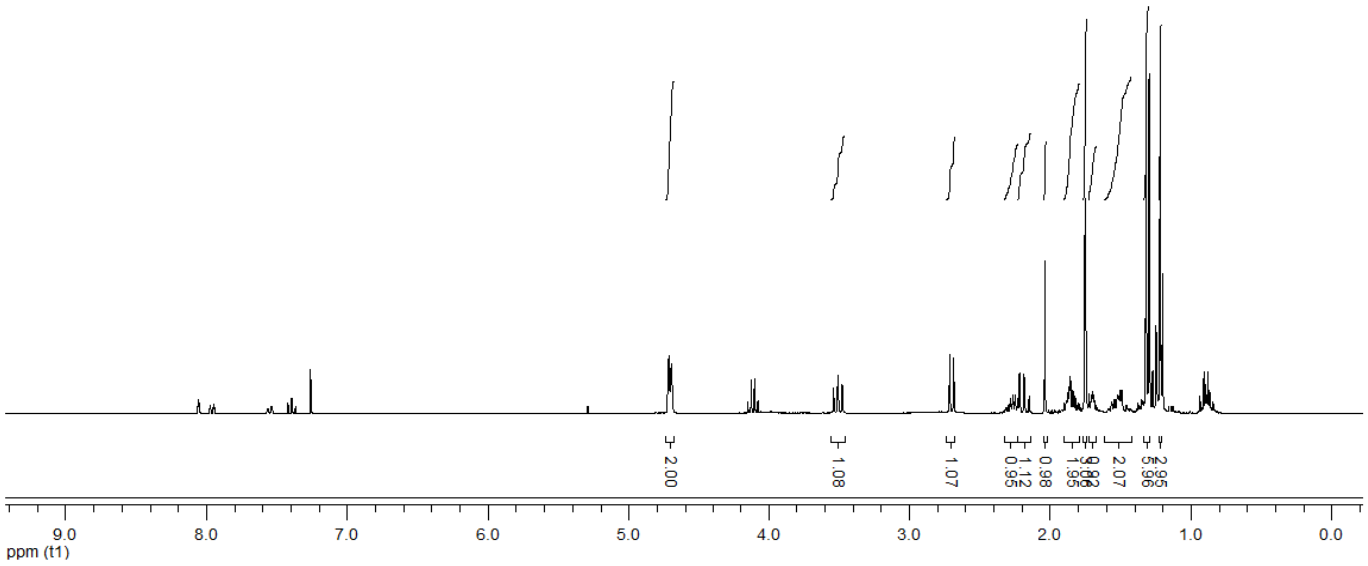


$CDCl_3$, 75 MHz

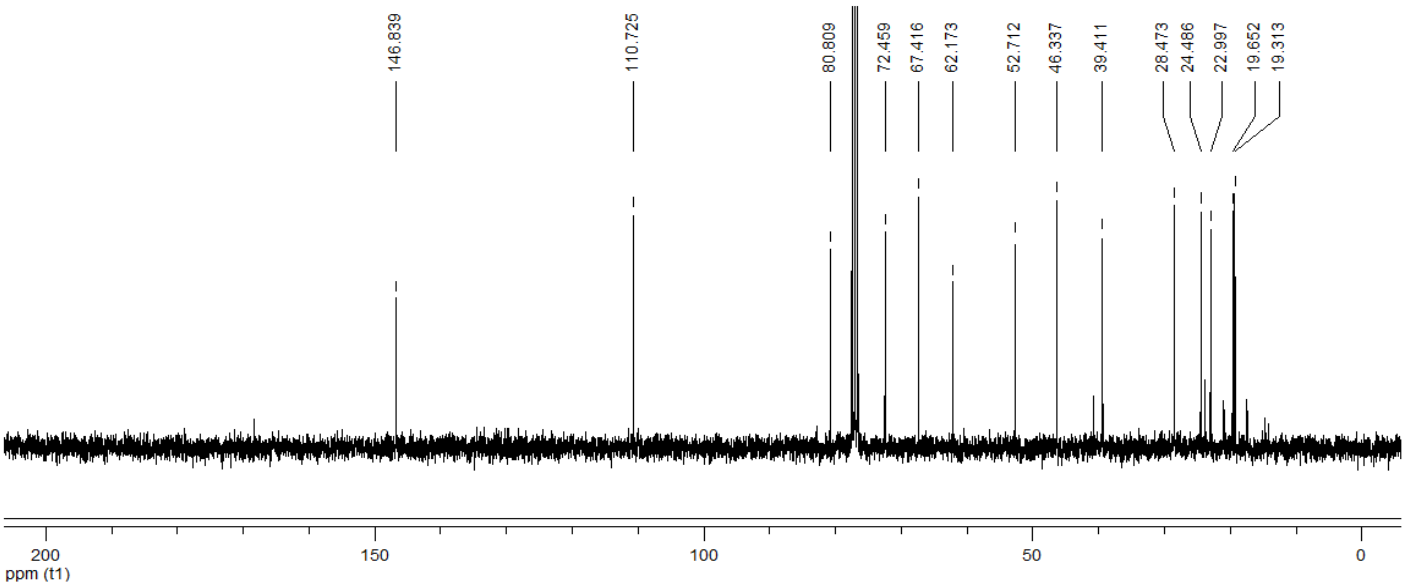


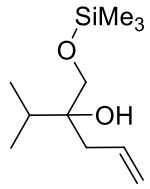


206, $CDCl_3$, 300 MHz

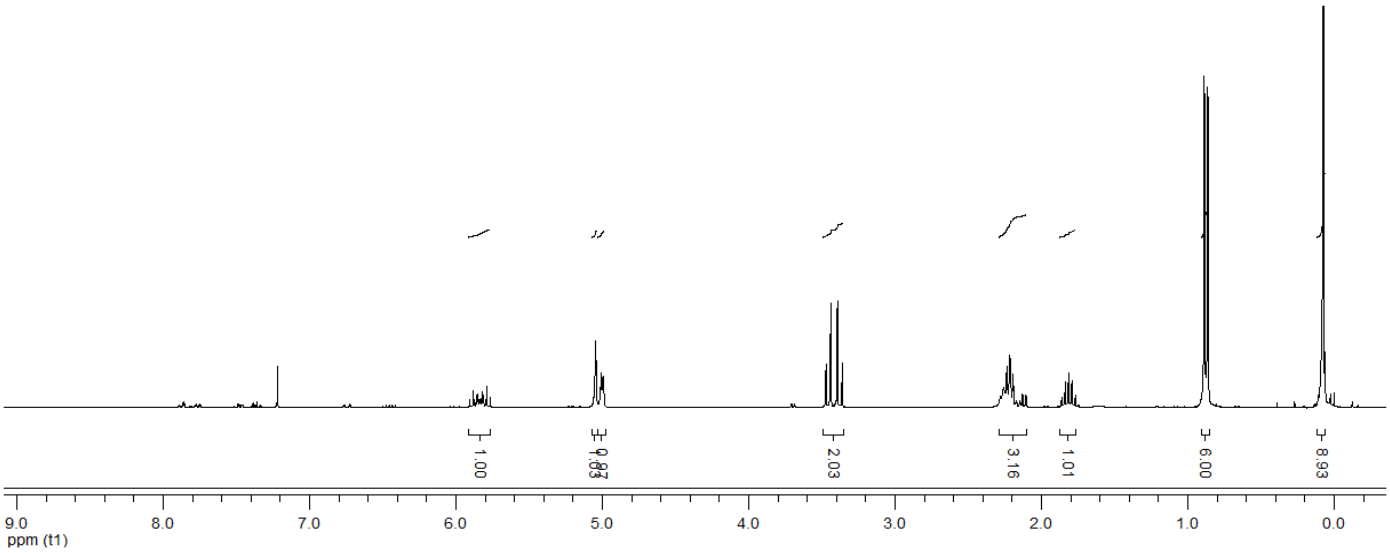


$CDCl_3$, 75 MHz

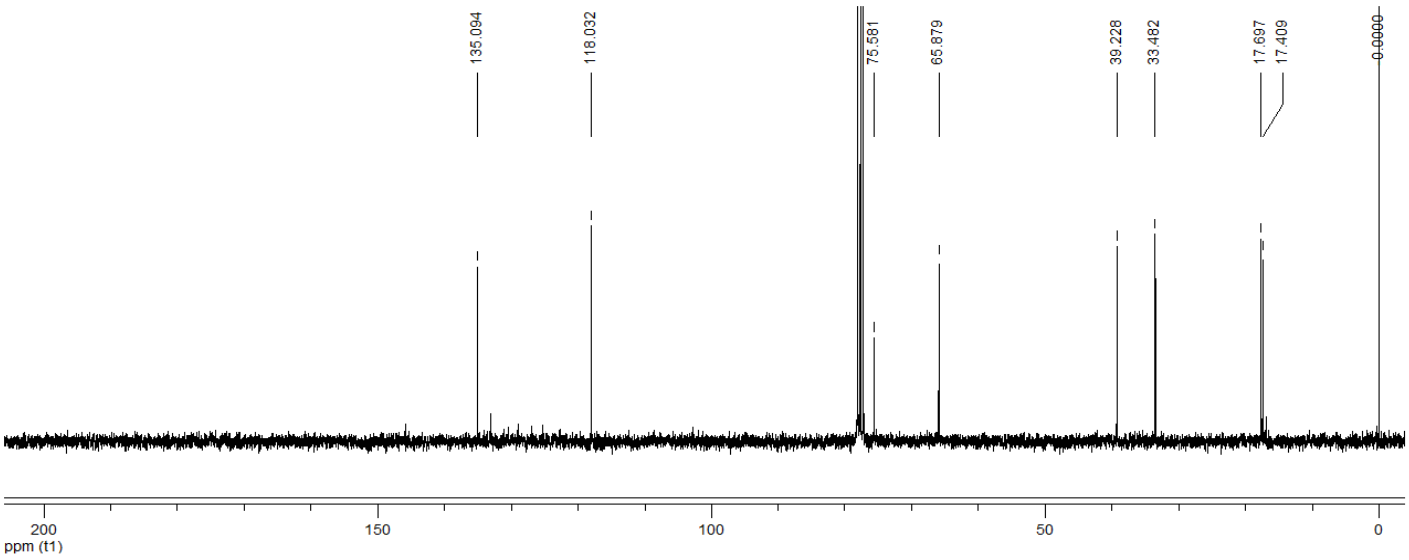


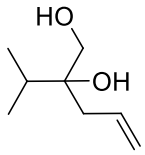


214a, $CDCl_3$, 300 MHz

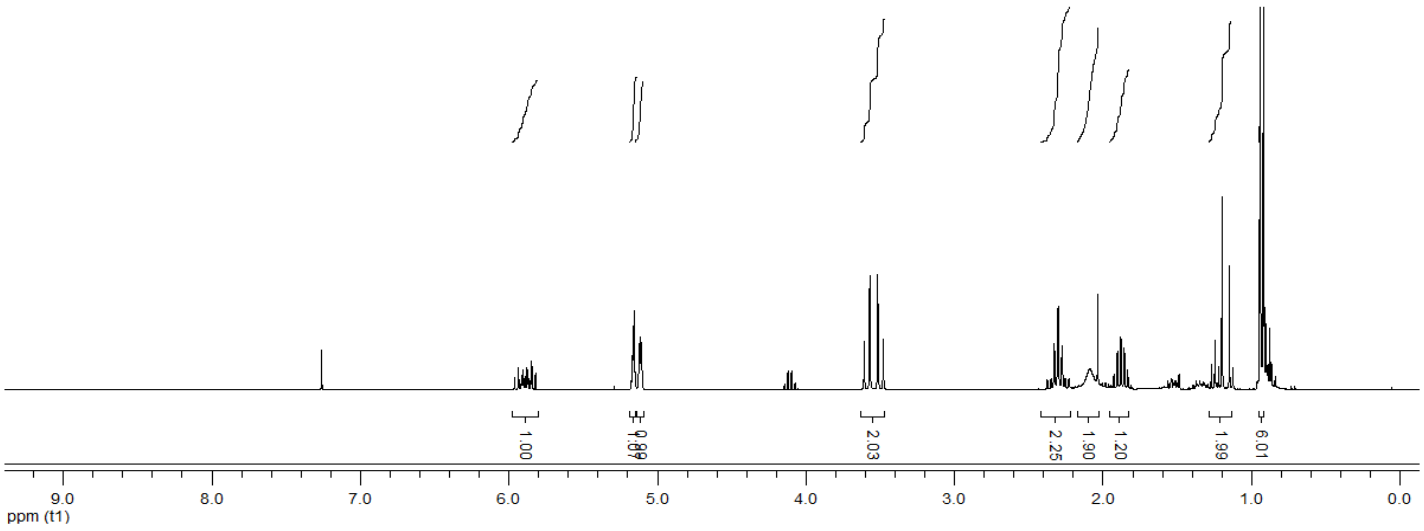


$CDCl_3$, 75 MHz

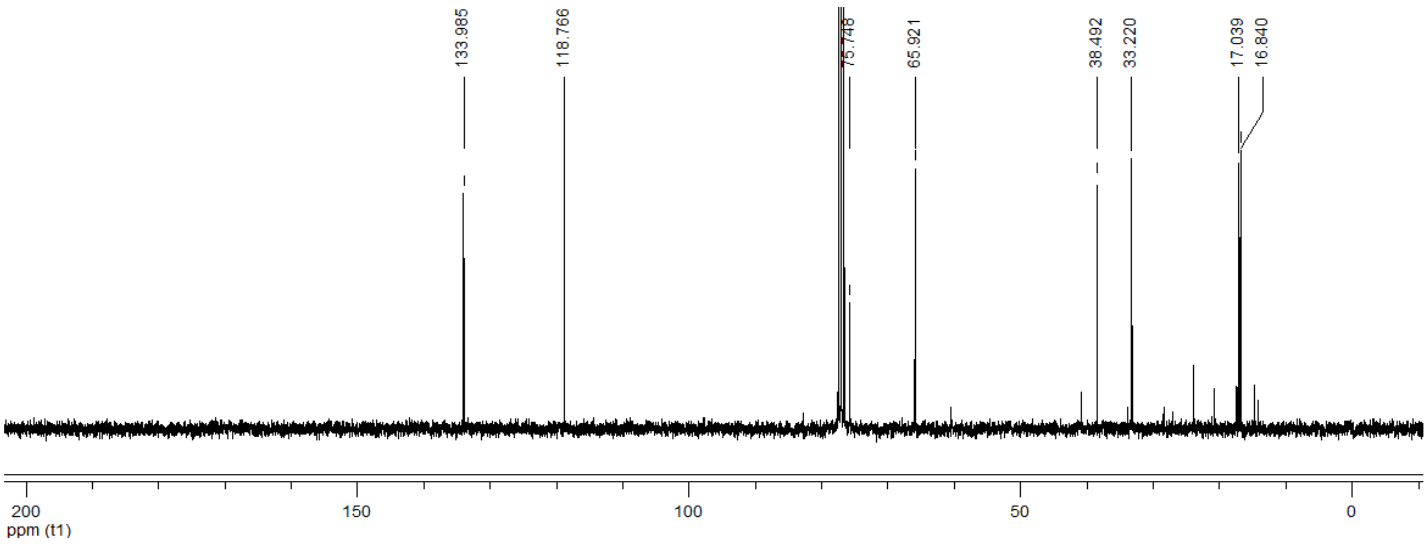


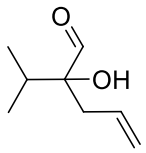


214b, $CDCl_3$, 300 MHz

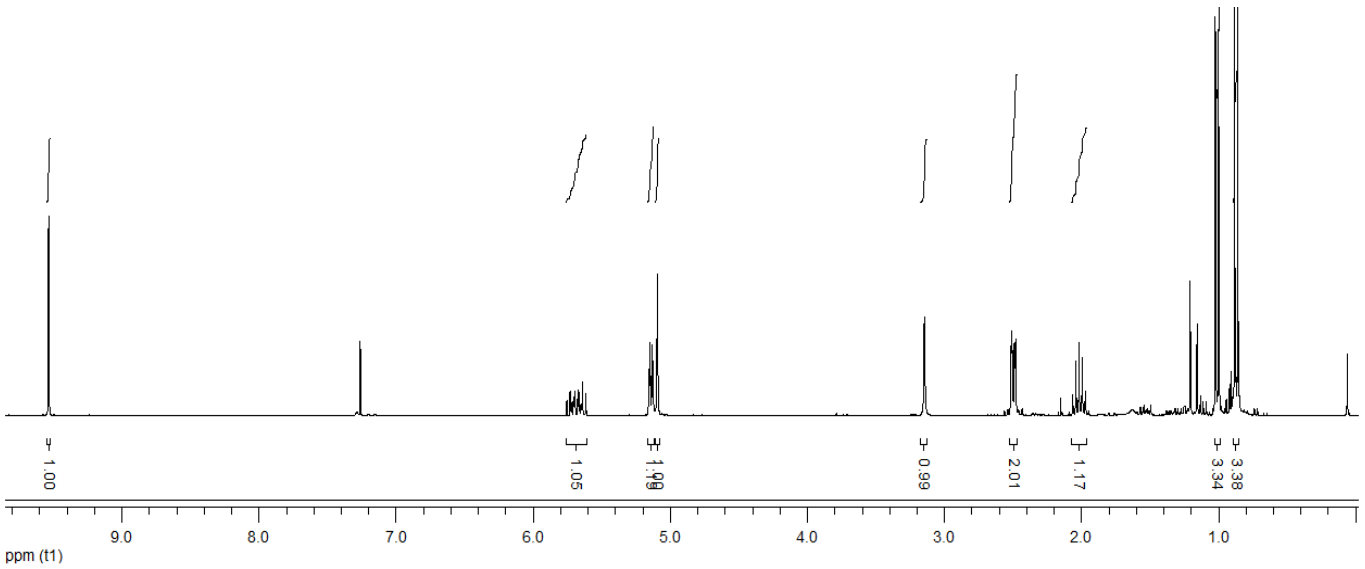


$CDCl_3$, 75 MHz

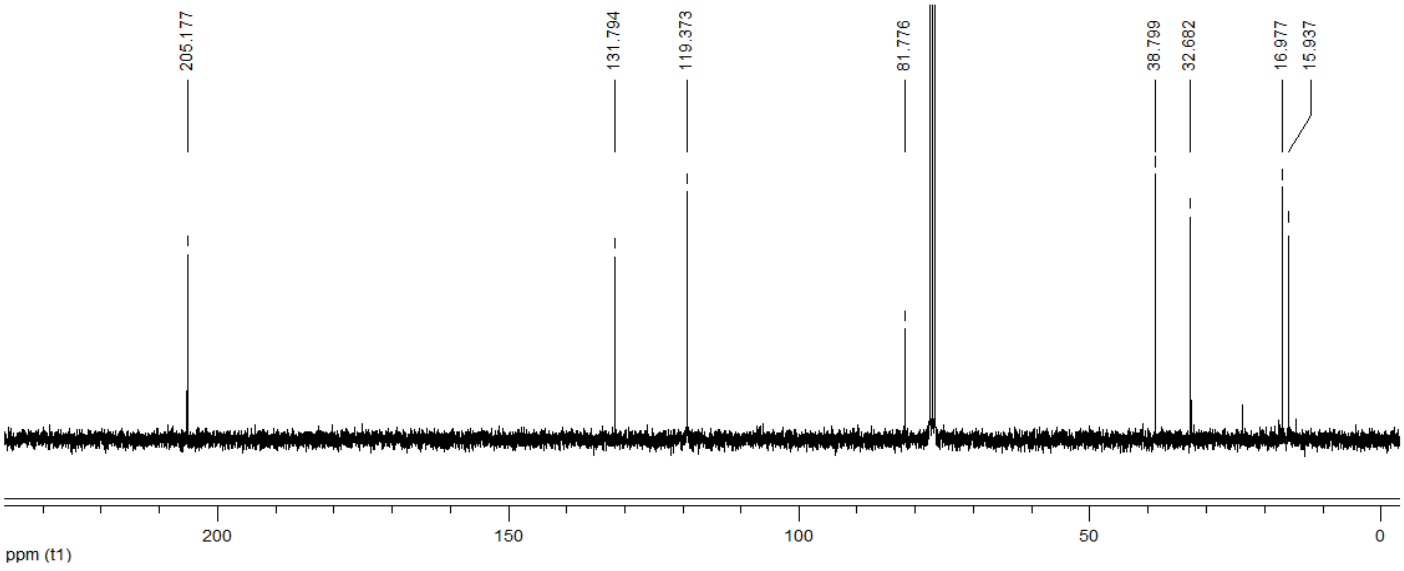


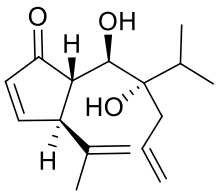


210, $CDCl_3$, 300 MHz

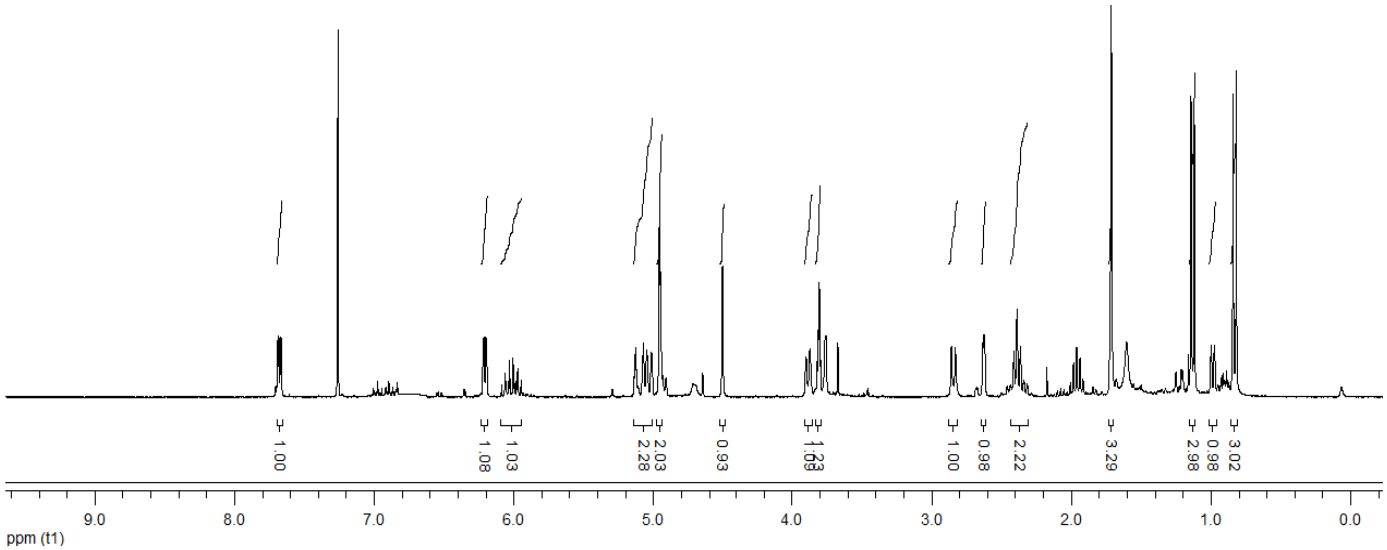


$CDCl_3$, 75 MHz

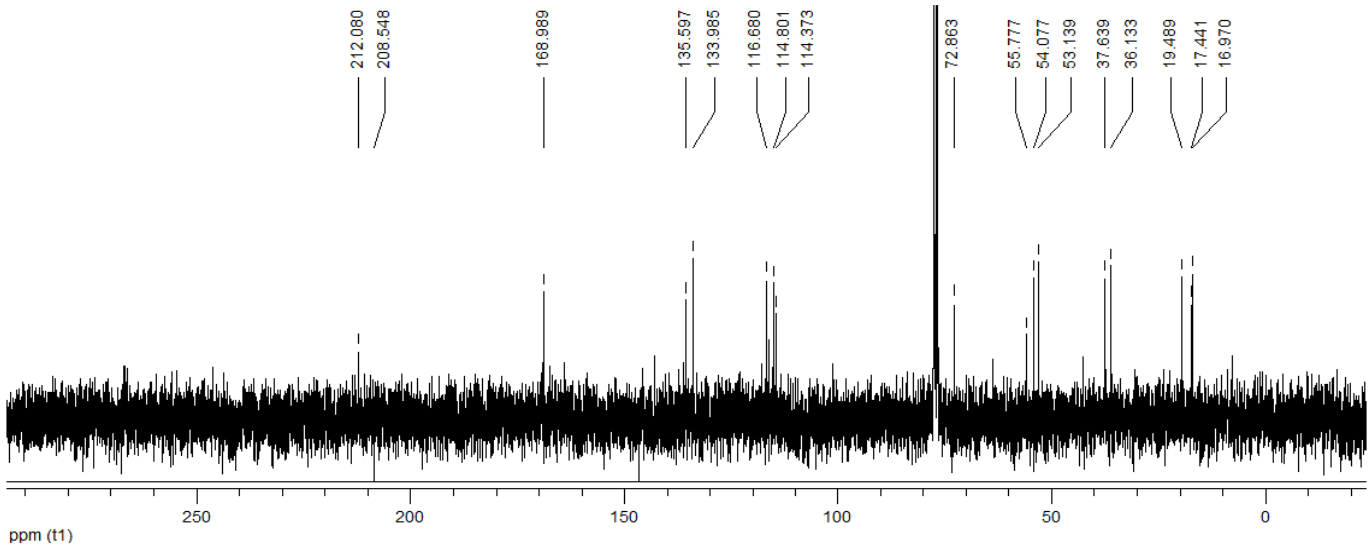


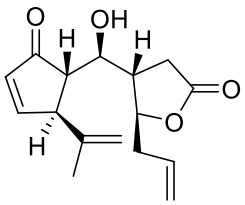


215, $CDCl_3$, 300 MHz

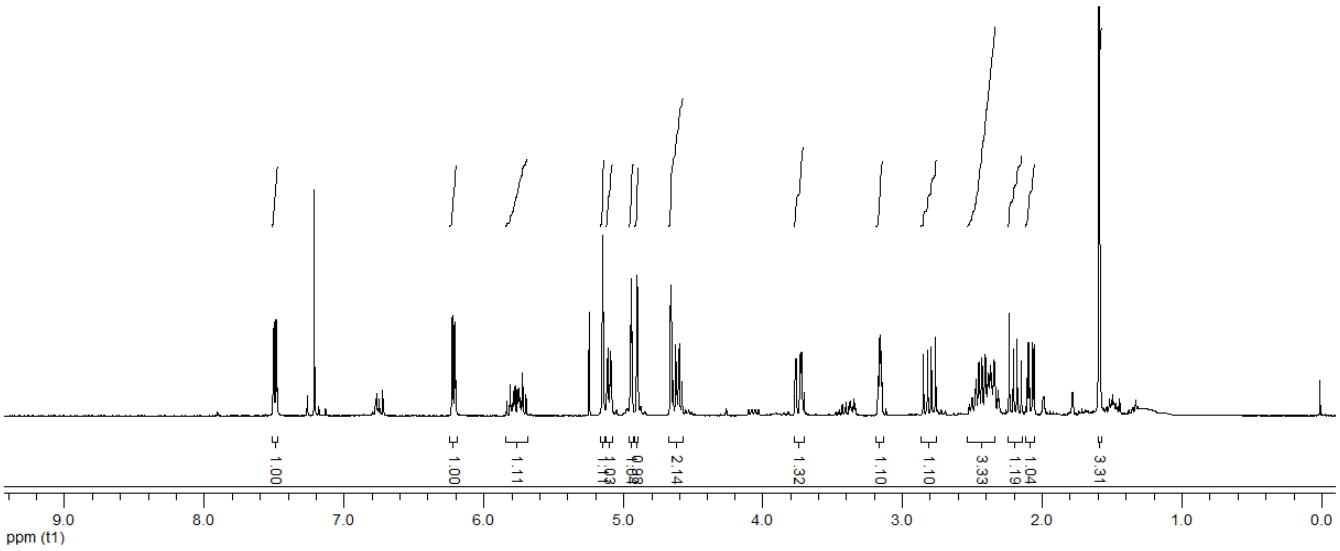


$CDCl_3$, 75 MHz

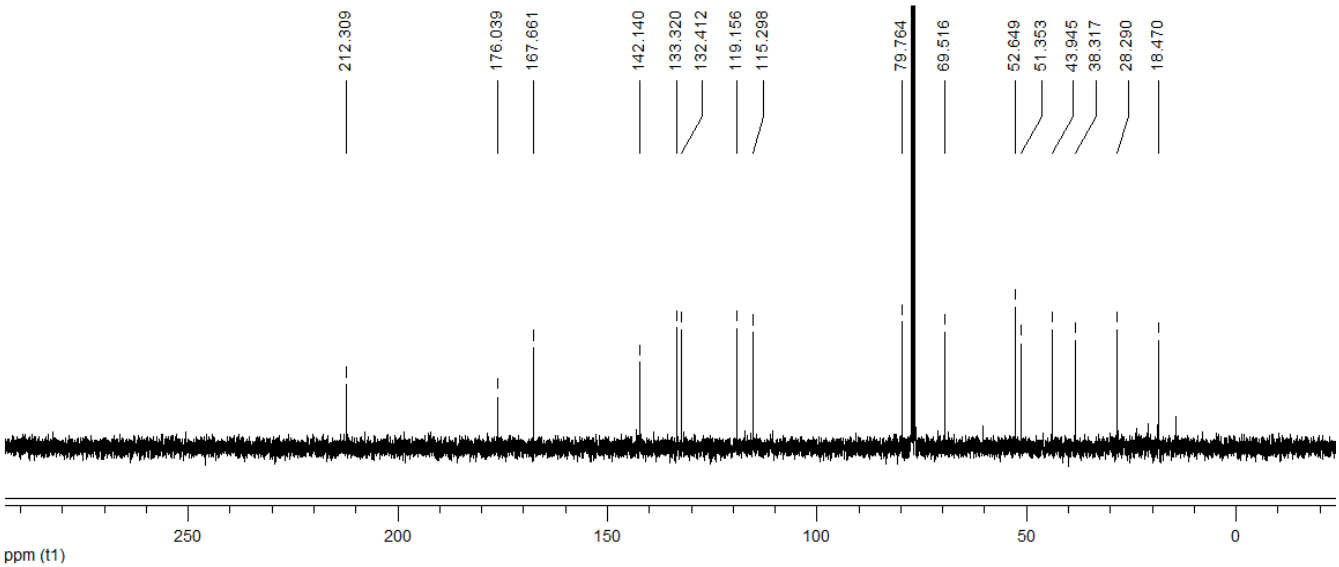


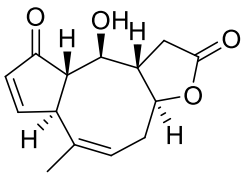


222, $CDCl_3$, 300 MHz

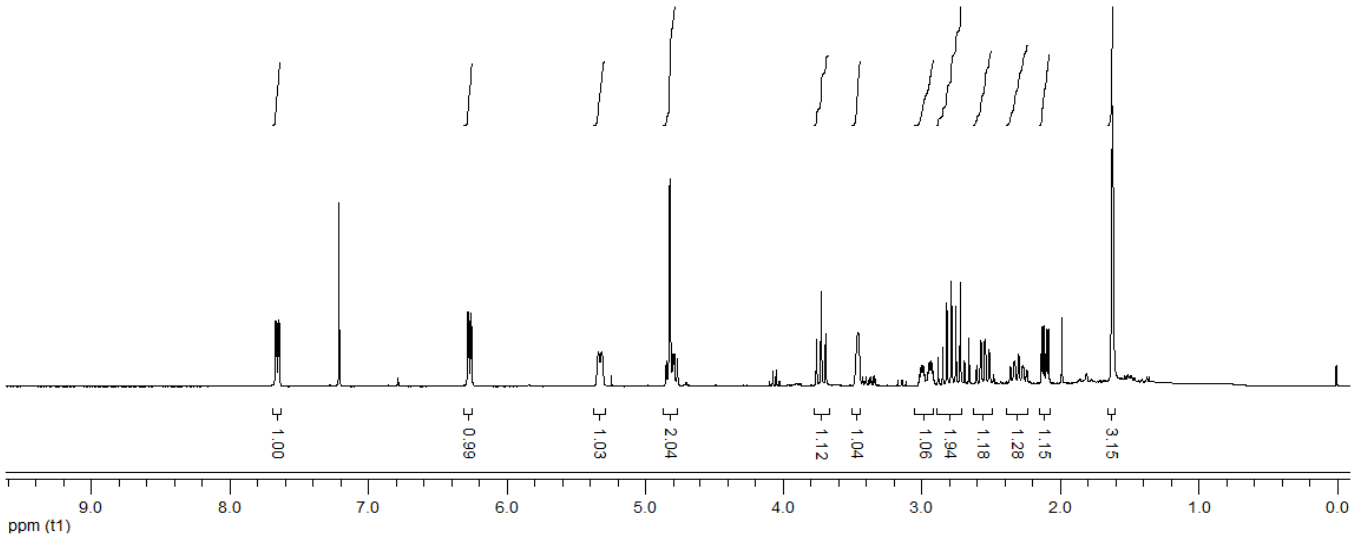


$CDCl_3$, 75 MHz

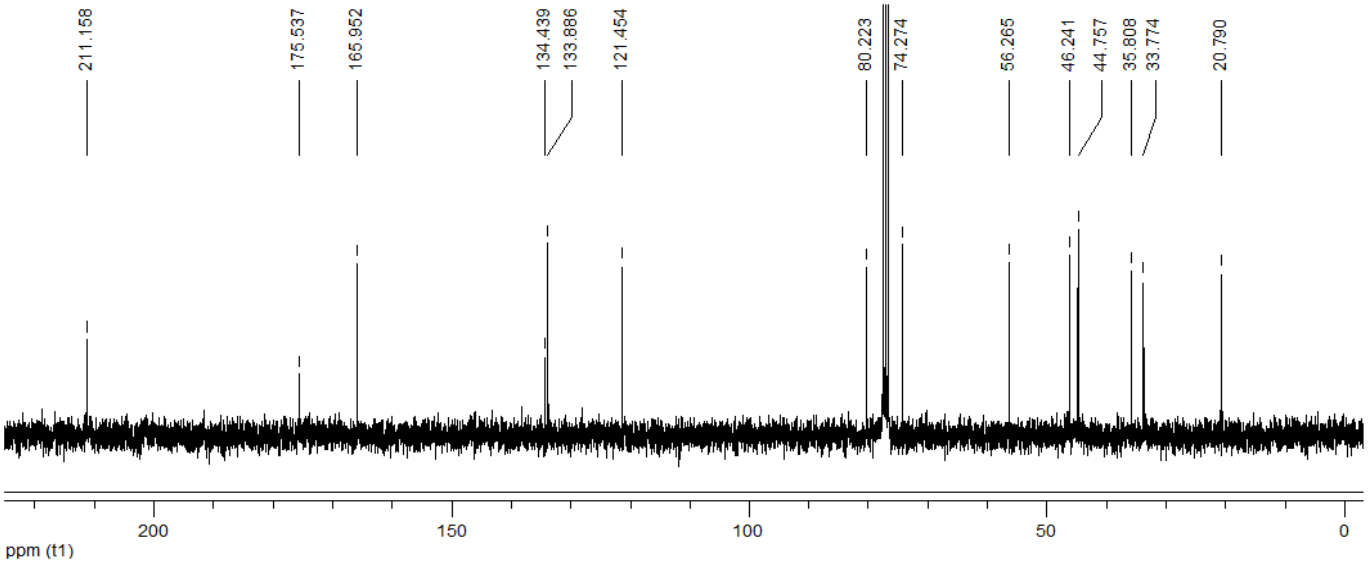


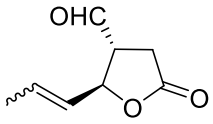


223, $CDCl_3$, 300 MHz

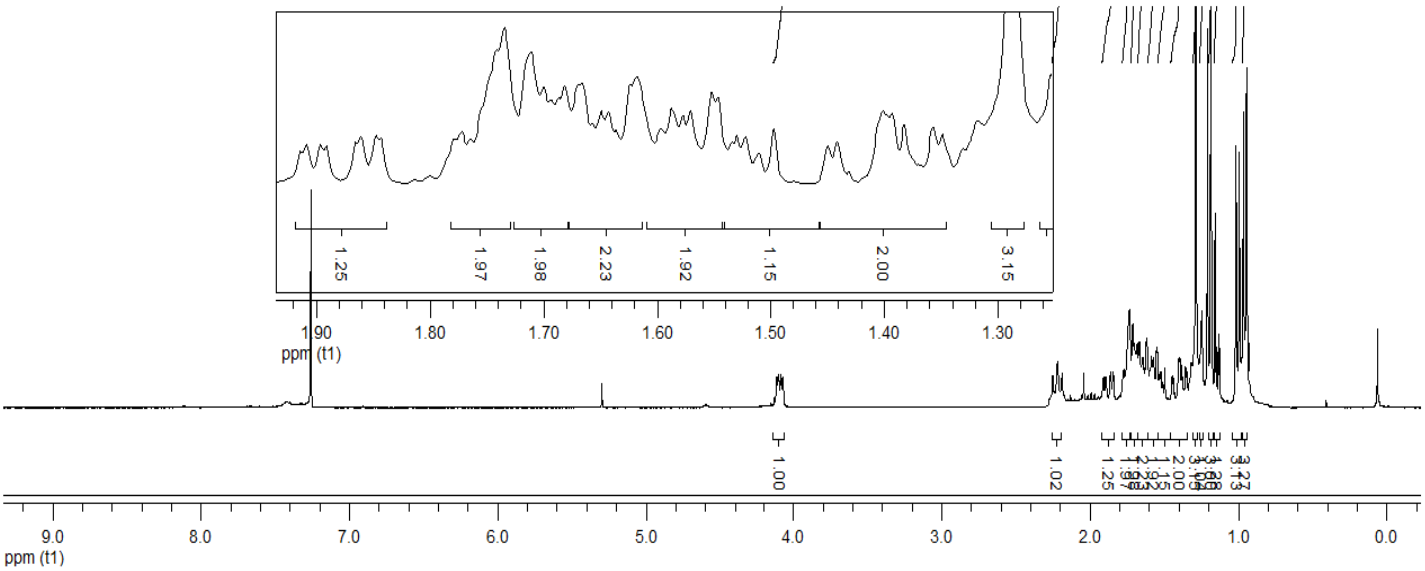


CDCl3, 75 MHz

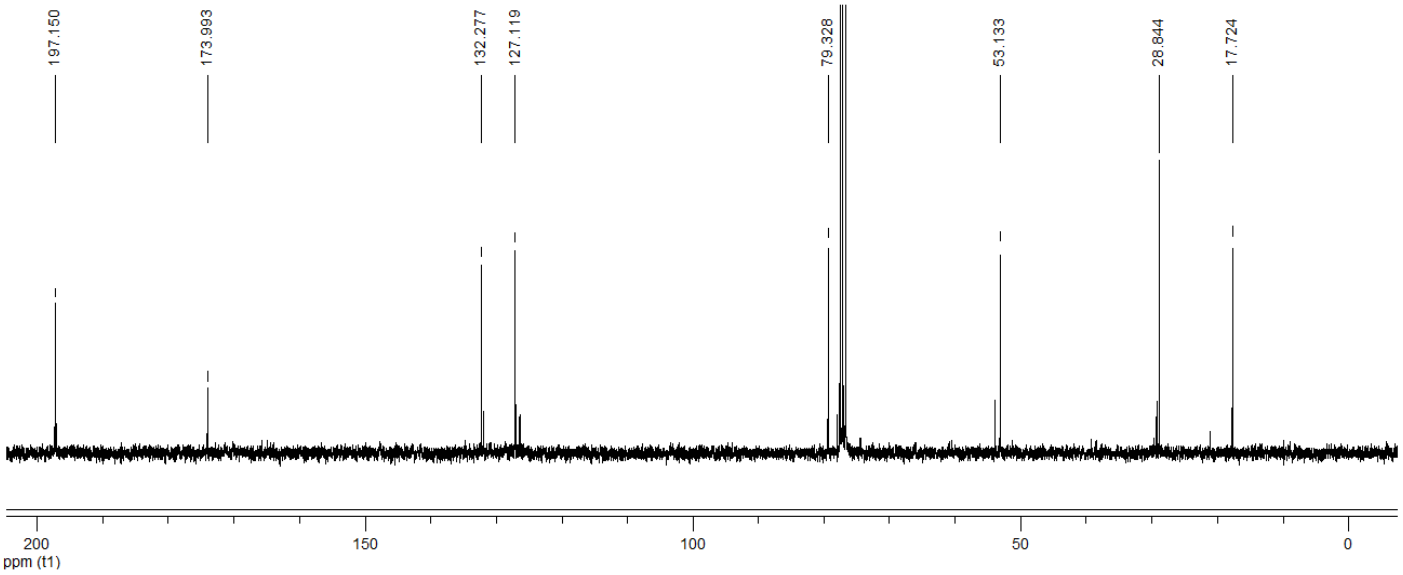


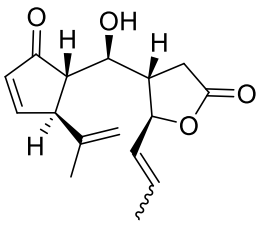


220, $CDCl_3$, 300 MHz

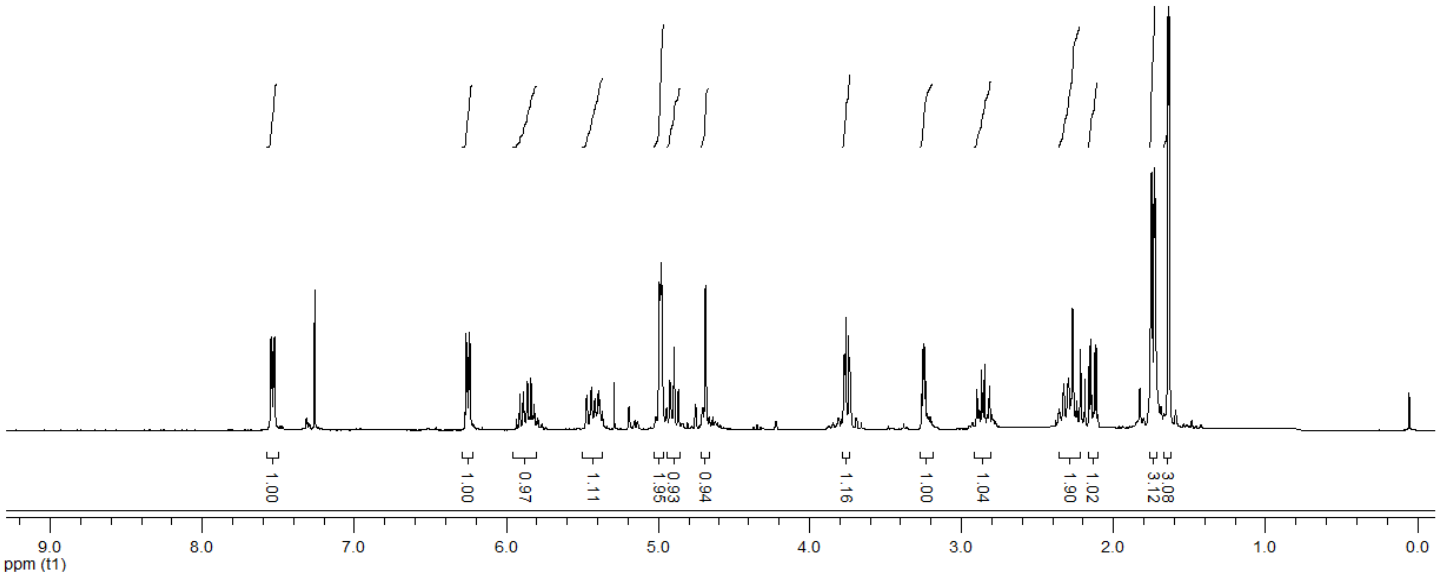


$CDCl_3$, 75 MHz

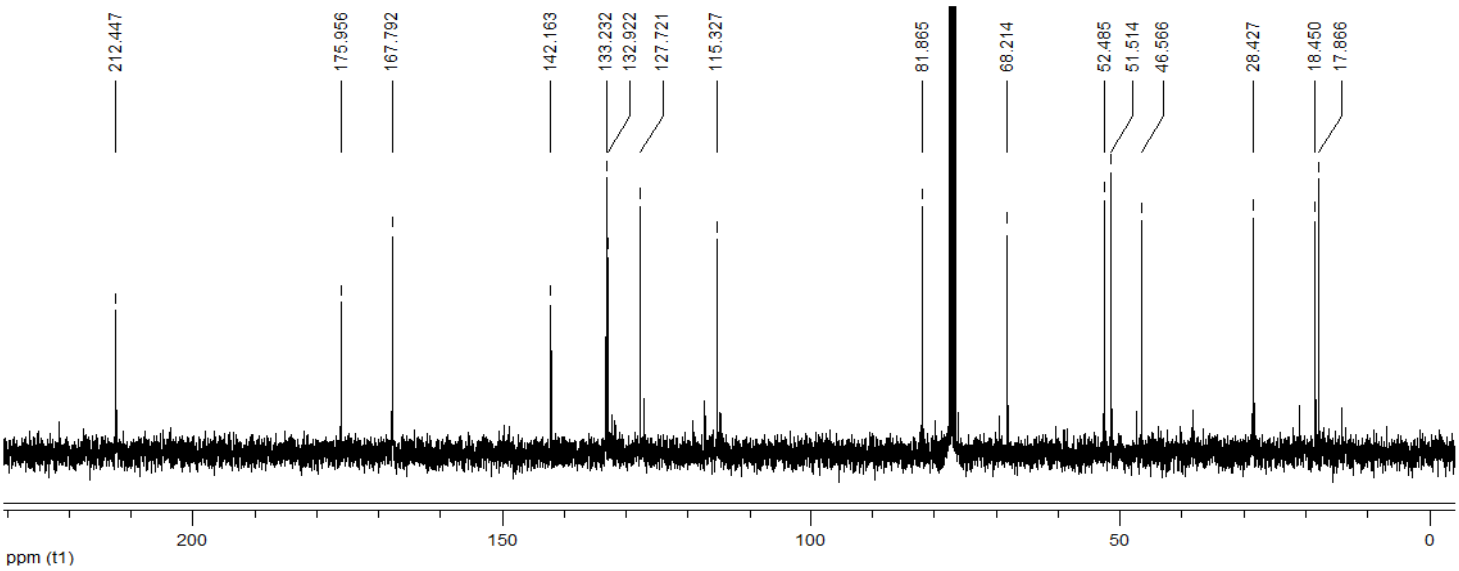


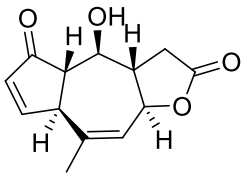


218, $CDCl_3$, 300 MHz

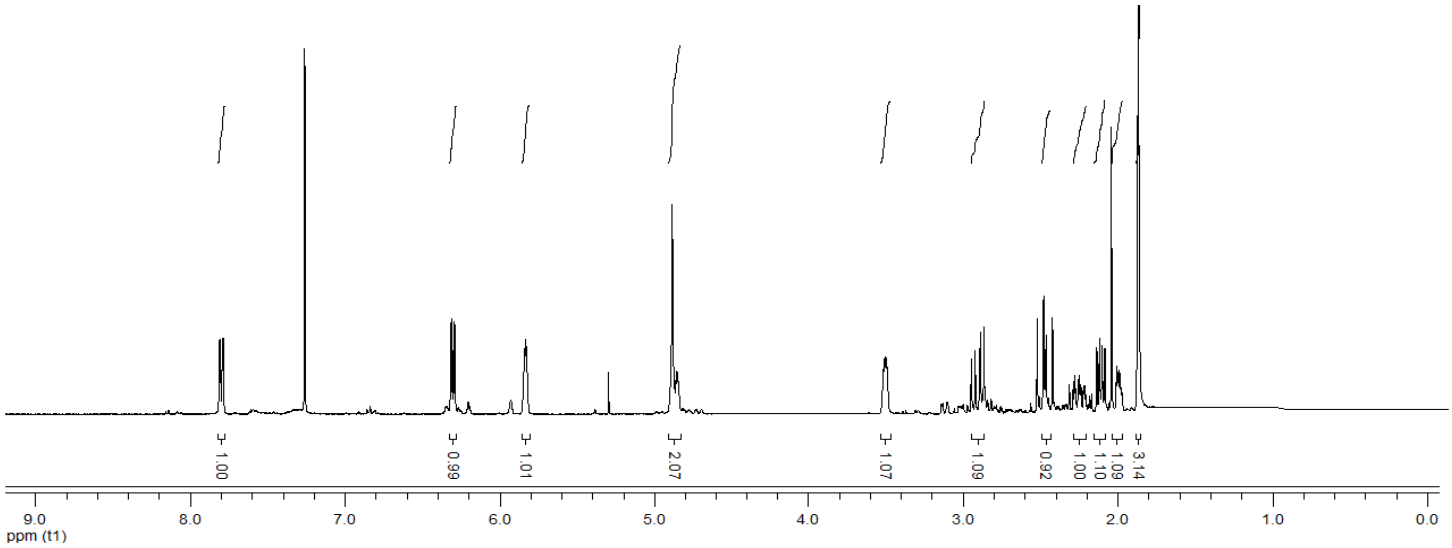


$CDCl_3$, 75 MHz

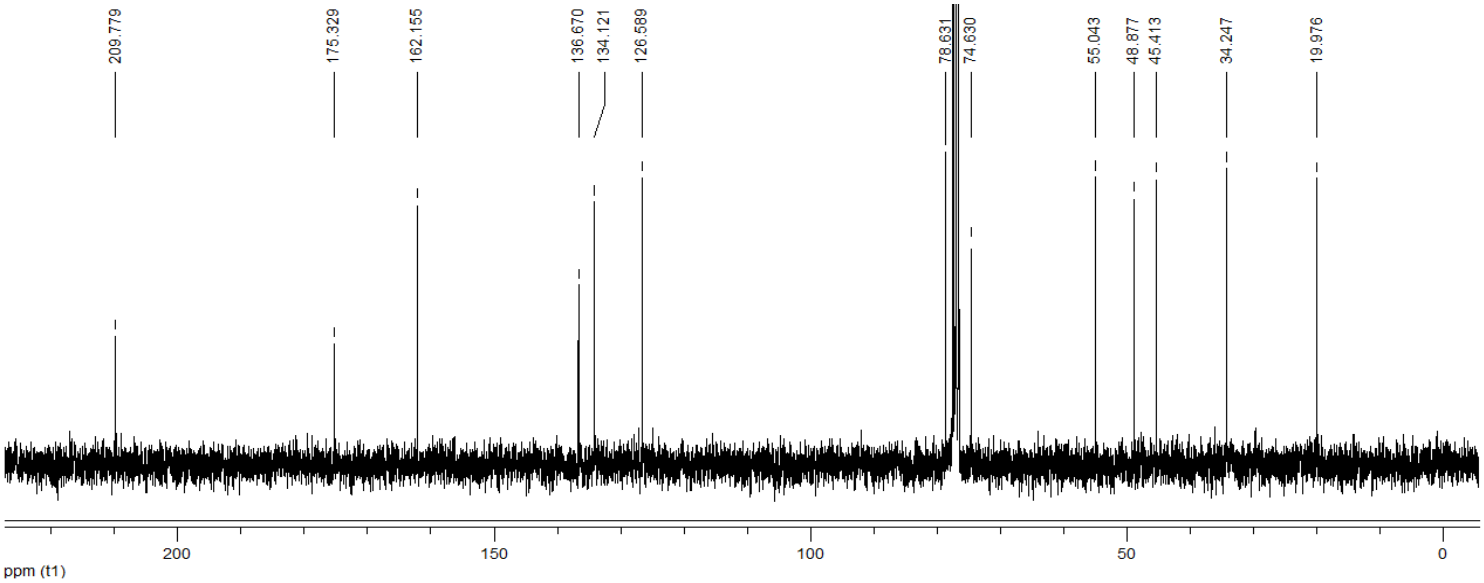


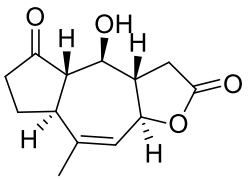


217, $CDCl_3$, 300 MHz

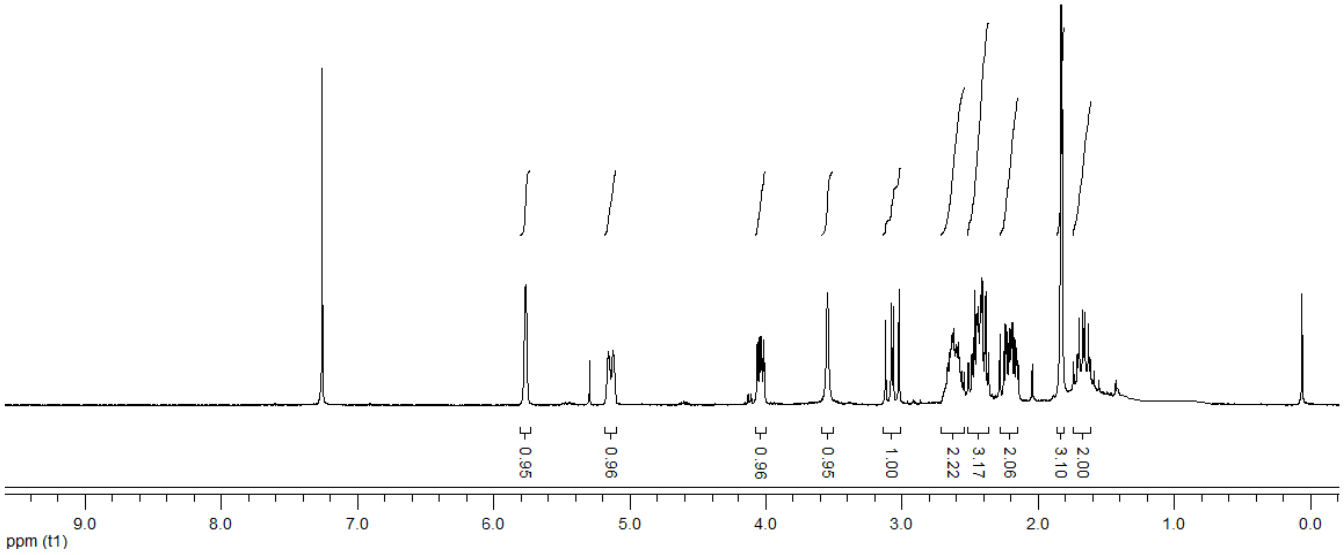


CDCl3, 75 MHz

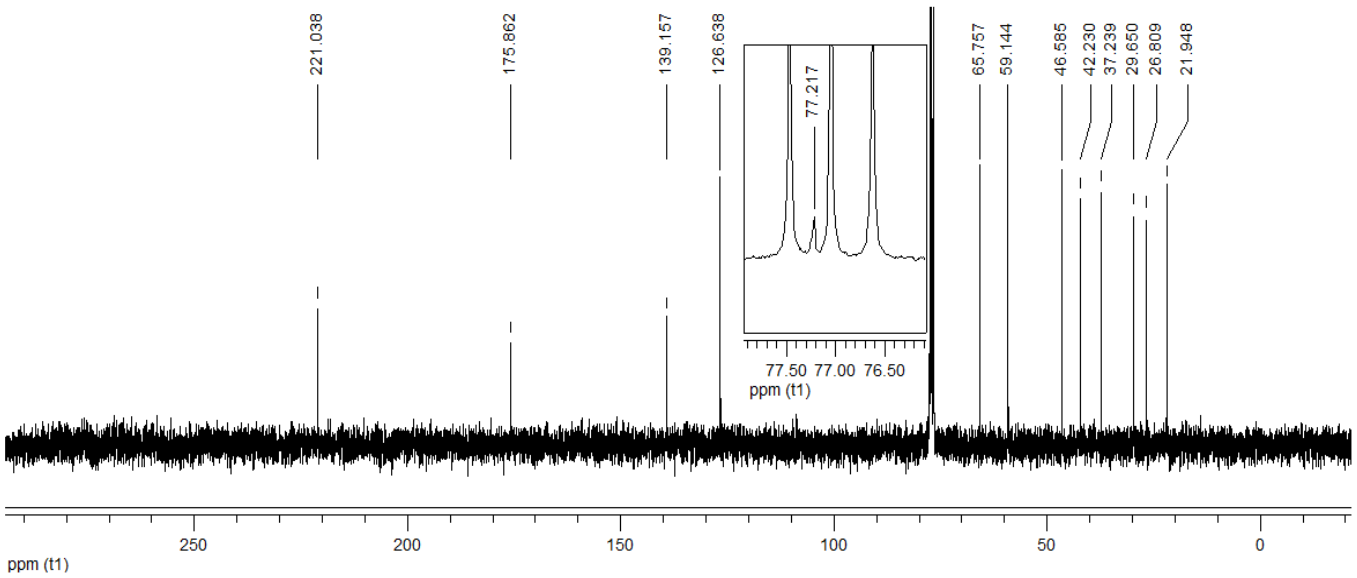




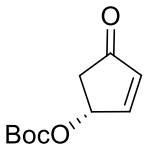
226, $CDCl_3$, 300 MHz



$CDCl_3$, 75 MHz



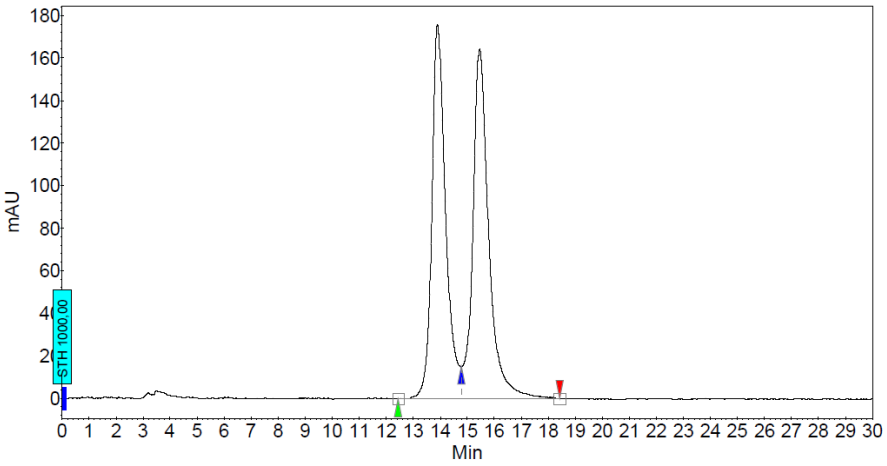
2. HPLC data:



(*R*)-**125**

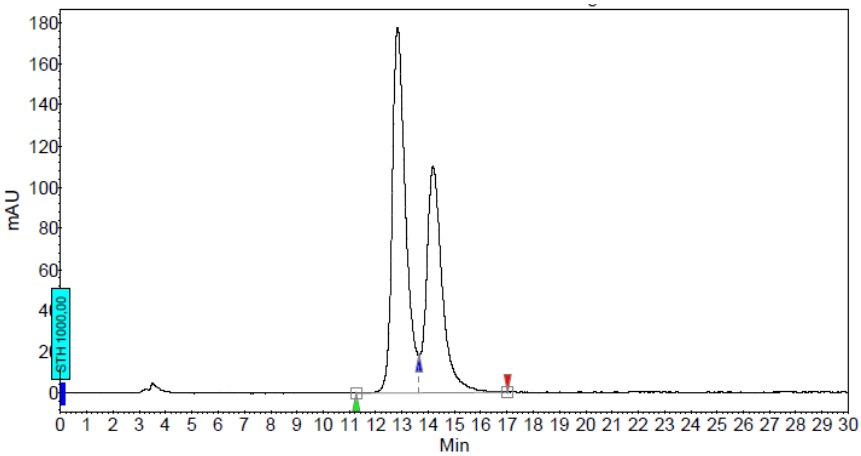
HPLC condition: (CHIRALCEL OJ-H, Hept: iPrOH-99:1, 1.0 mL/min, 215 nm)

Racemic



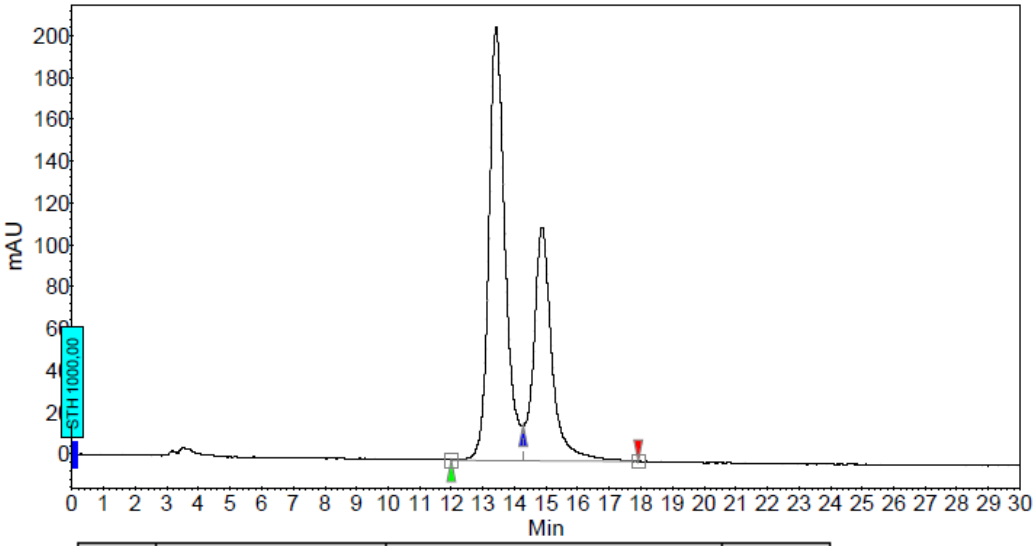
Index	Name	Time [Min]	Quantity [% Area]	Height [mAU]	Area [mAU.Min]	Area % [%]
1	UNKNOWN	13.90	48.13	175.8	104.3	48.127
2	UNKNOWN	15.46	51.87	164.3	112.4	51.873
Total			100.00	340.1	216.8	100.000

Table 6, entry-1



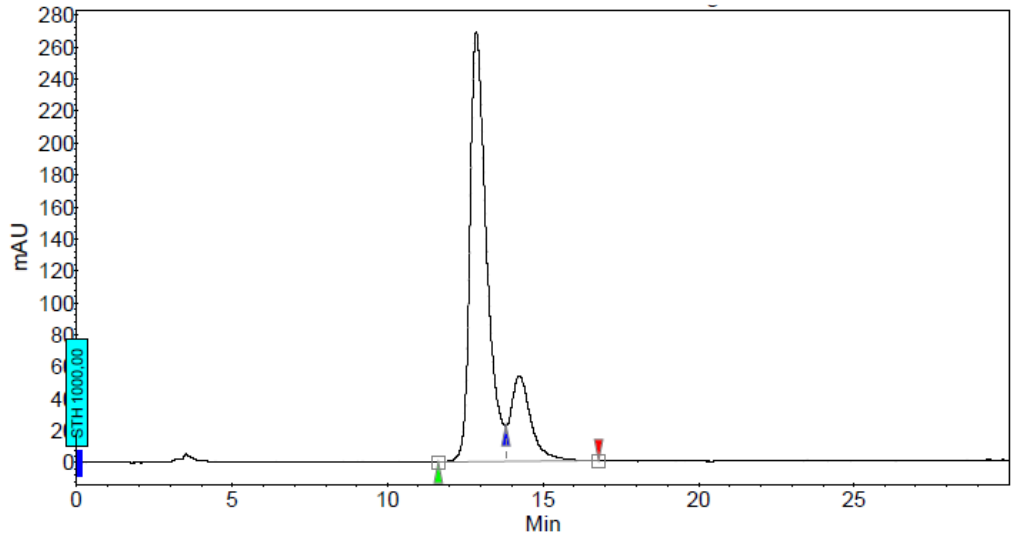
Index	Name	Time [Min]	Quantity [% Area]	Height [mAU]	Area [mAU.Min]	Area % [%]
1	UNKNOWN	12.83	57.86	177.3	104.7	57.859
2	UNKNOWN	14.19	42.14	109.9	76.3	42.141
Total			100.00	287.1	181.0	100.000

Table 6, entry-2



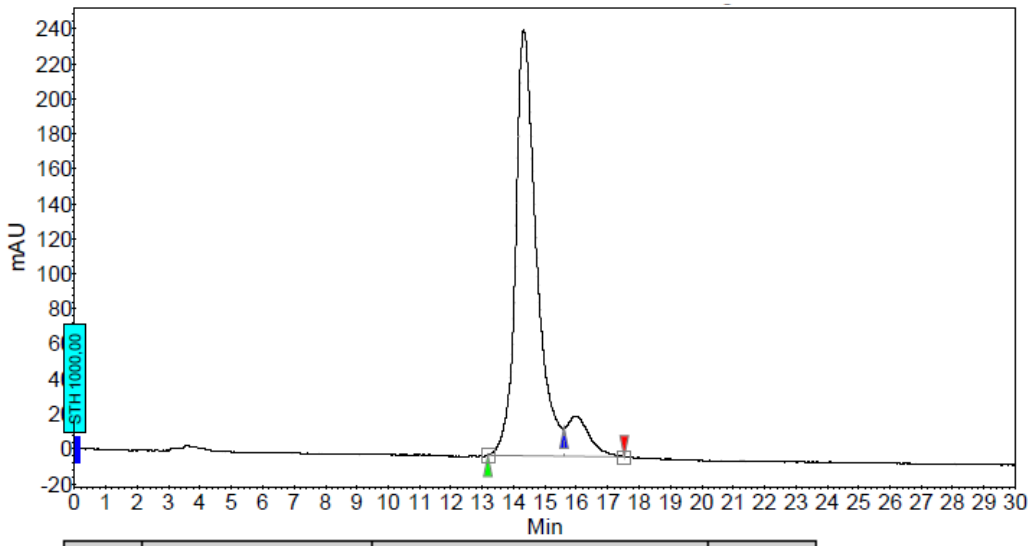
Index	Name	Time [Min]	Quantity [% Area]	Height [mAU]	Area [mAU.Min]	Area % [%]
1	UNKNOWN	13,42	62,38	207,1	123,3	62,382
2	UNKNOWN	14,87	37,62	111,7	74,3	37,618
Total			100,00	318,8	197,6	100,000

Table 6, entry-3



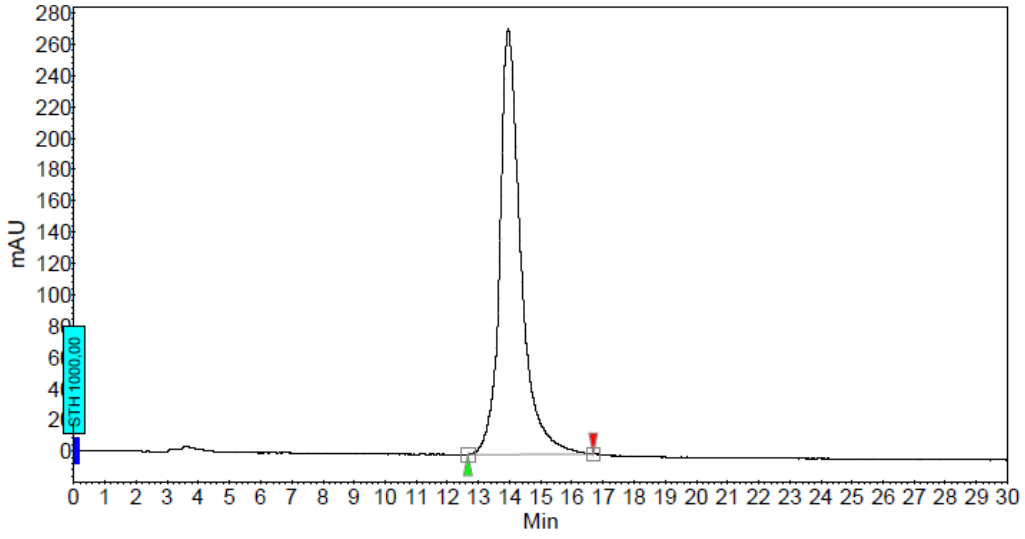
Index	Name	Time [Min]	Quantity [% Area]	Height [mAU]	Area [mAU.Min]	Area % [%]
1	UNKNOWN	12,85	80,50	268,9	166,7	80,498
2	UNKNOWN	14,24	19,50	53,4	40,4	19,502
Total			100,00	322,4	207,0	100,000

Table 6, entry-4



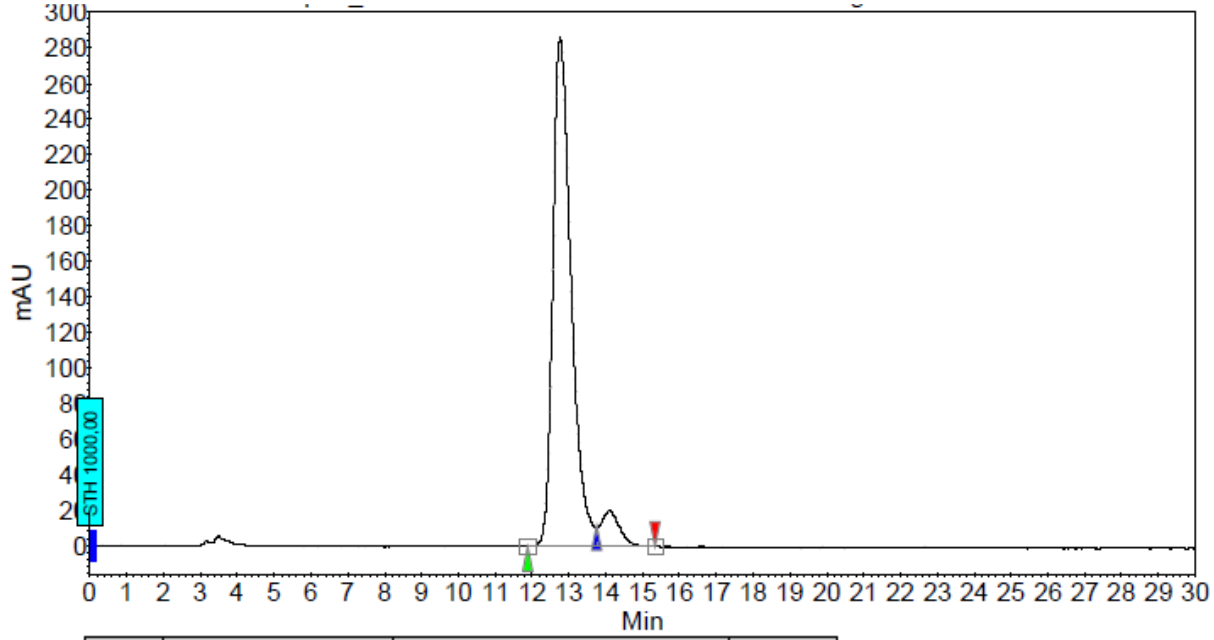
Index	Name	Time [Min]	Quantity [% Area]	Height [mAU]	Area [mAU.Min]	Area % [%]
1	UNKNOWN	14,32	90,76	243,0	186,9	90,760
2	UNKNOWN	16,02	9,24	22,9	19,0	9,240
Total			100,00	265,9	206,0	100,000

Table 6, entry-5



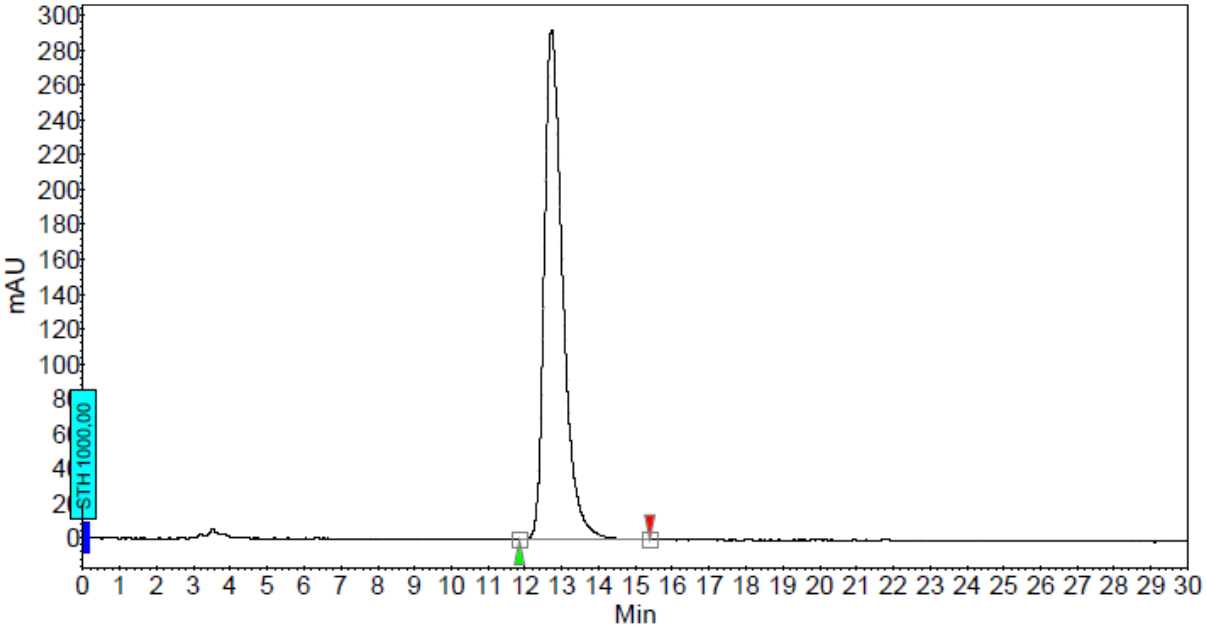
Index	Name	Time [Min]	Quantity [% Area]	Height [mAU]	Area [mAU.Min]	Area % [%]
1	UNKNOWN	13,95	100,00	272,2	213,6	100,000
Total			100,00	272,2	213,6	100,000

Table 6, entry-6



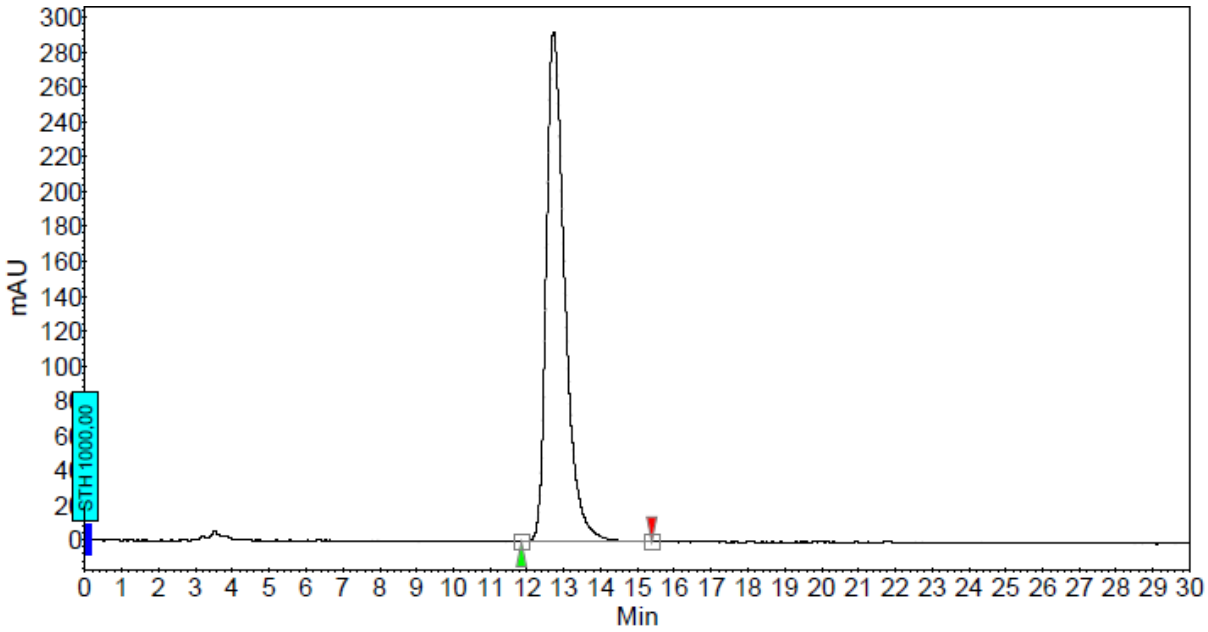
Index	Name	Time [Min]	Quantity [% Area]	Height [mAU]	Area [mAU.Min]	Area % [%]
1	UNKNOWN	12,76	93,19	286,6	164,9	93,189
2	UNKNOWN	14,11	6,81	20,0	12,1	6,811
Total			100,00	306,6	177,0	100,000

Table 6, entry-7

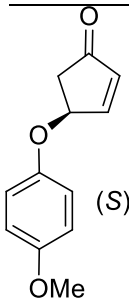


Index	Name	Time [Min]	Quantity [% Area]	Height [mAU]	Area [mAU.Min]	Area % [%]
1	UNKNOWN	12,72	100,00	292,5	171,1	100,000
Total			100,00	292,5	171,1	100,000

50 g scale

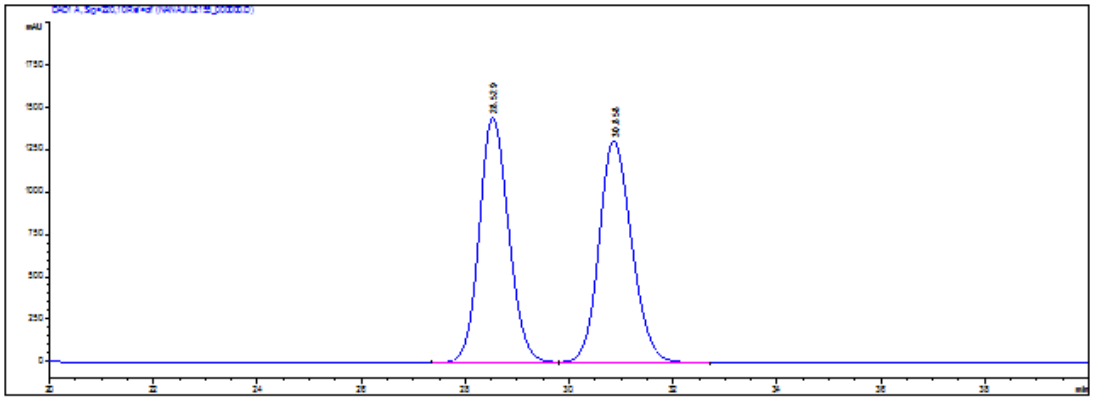


Index	Name	Time [Min]	Quantity [% Area]	Height [mAU]	Area [mAU.Min]	Area % [%]
1	UNKNOWN	12,72	100,00	292,5	171,1	100,000
Total			100,00	292,5	171,1	100,000



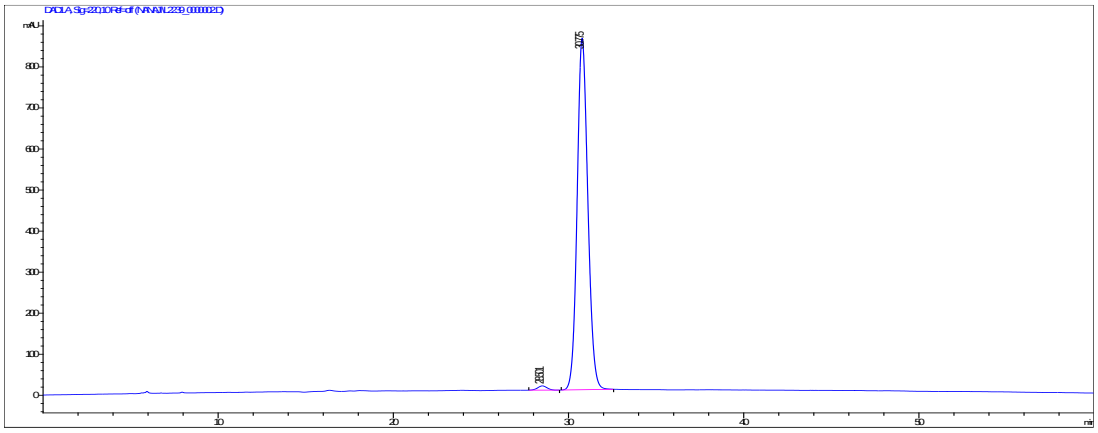
(*S*)-**134** HPLC condition: (Daicel CHIRALCEL OD-H, Hex: iPrOH-9:1, 0.5 mL/min, 220 nm)

Racemic



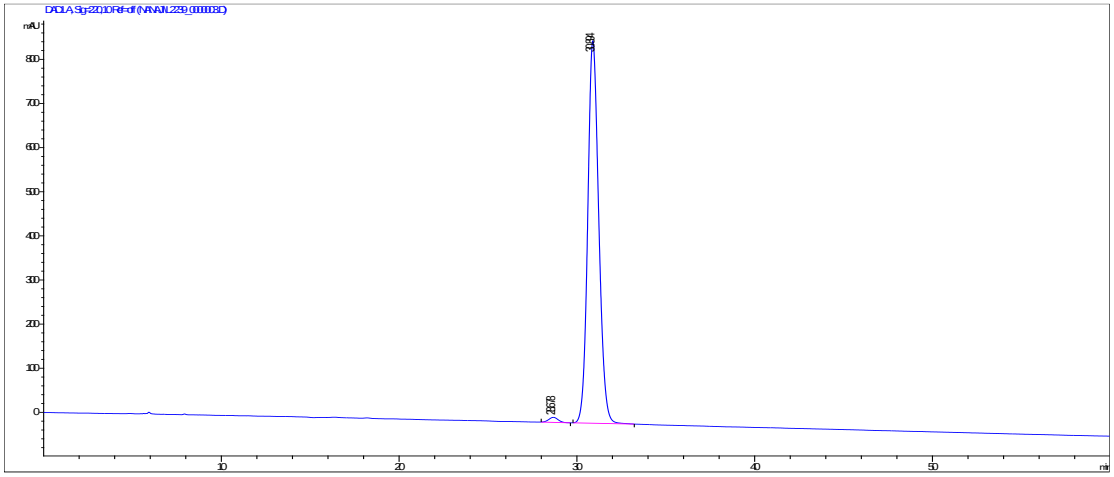
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	28.529	BV	0.6120	5.69962e4	1445.68945	49.8721
2	30.858	VB	0.6769	5.72885e4	1308.09363	50.1279
Totals :				1.14285e5	2753.78308	

Table 6, entry-1



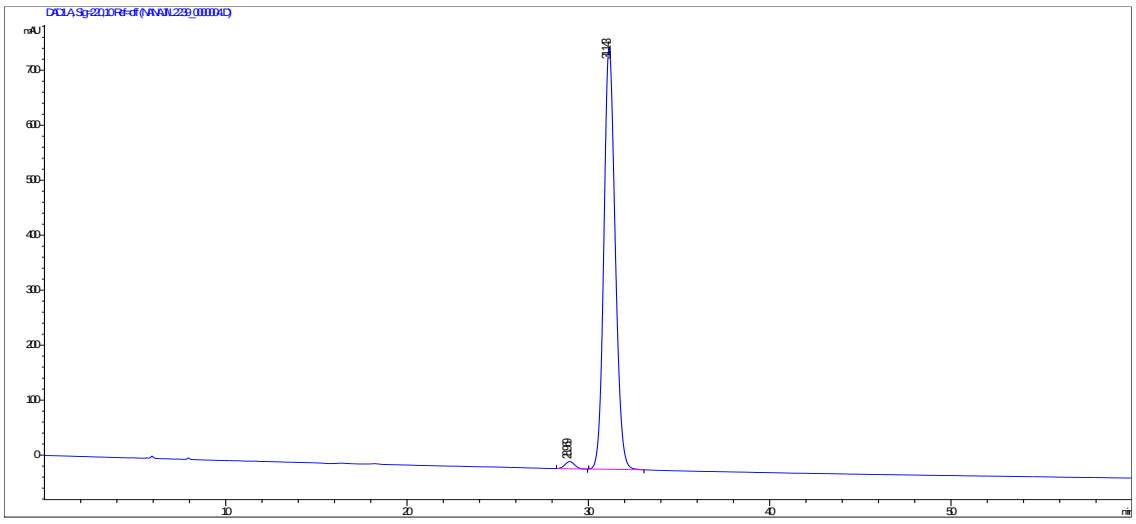
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	28.501	BB	0.5658	381.90018	10.36617	1.0384
2	30.775	BB	0.6580	3.63969e4	856.15778	98.9616
Totals :				3.67788e4	866.52394	

Table 6, entry-2



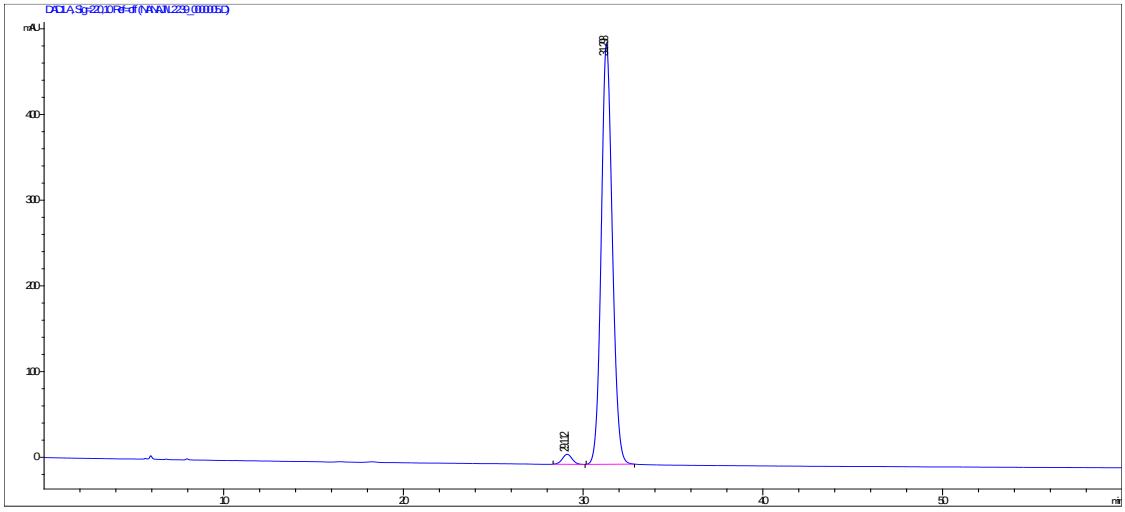
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	28.678	BB	0.5527	412.48117	11.38510	1.0947
2	30.894	BB	0.6656	3.72674e4	866.83331	98.9053
Totals :				3.76799e4	878.21841	

Table 6, entry-3



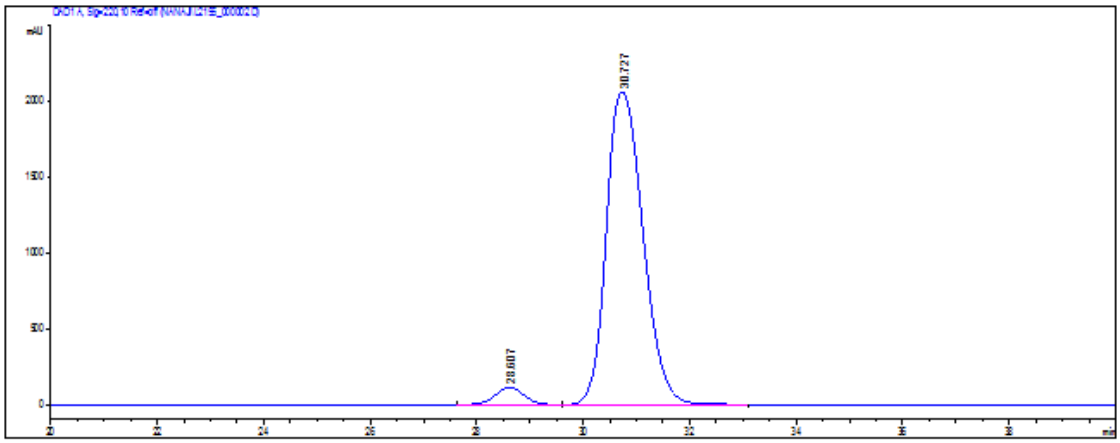
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	28.969	BB	0.5692	493.40097	13.22828	1.4578
2	31.143	BB	0.6704	3.33532e4	768.38739	98.5422
Totals :				3.38467e4	781.61567	

Table 6, entry-4



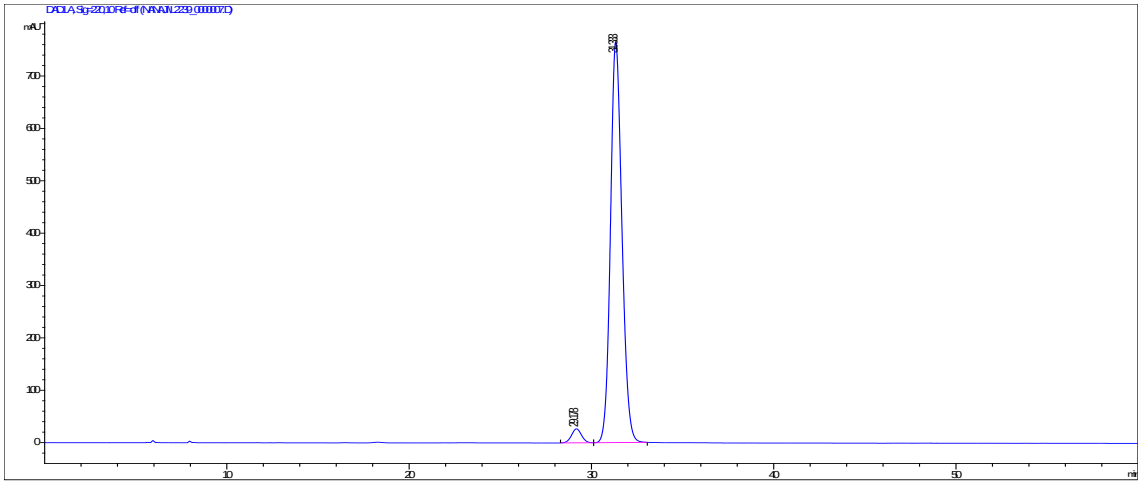
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	29.112	BB	0.5748	442.20560	11.70512	2.0492
2	31.298	BB	0.6663	2.11368e4	490.88638	97.9508
Totals :				2.15790e4	502.59151	

Table 6, entry-5



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	28.607	BB	0.5767	4304.28711	115.53338	4.1854
2	30.727	BB	0.7513	9.85356e4	2062.82935	95.8146
Totals :				1.02840e5	2178.3627	

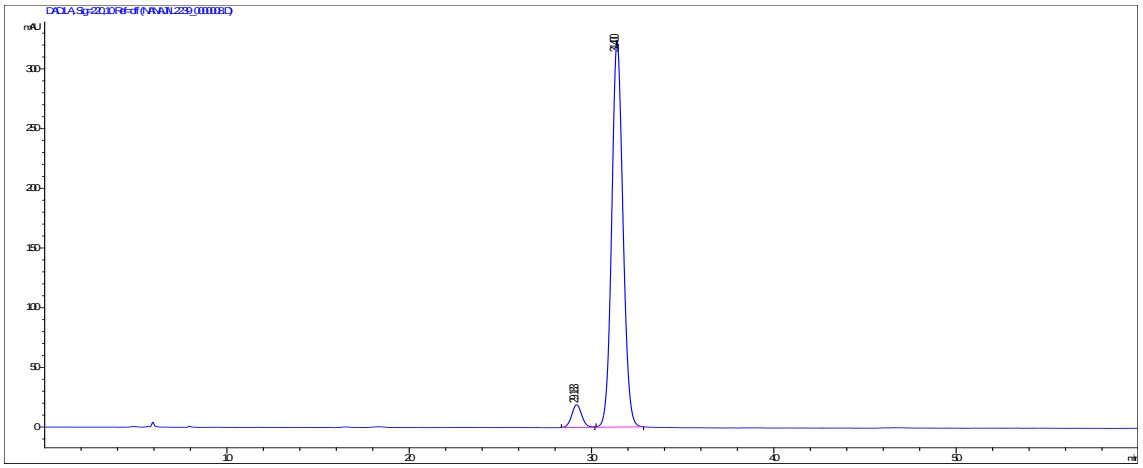
Table 6, entry-6



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	29.178	BV	0.5912	1018.88660	26.70000	2.9599
2	31.333	VB	0.6731	3.34046e4	765.46082	97.0401

Totals : 3.44234e4 792.16082

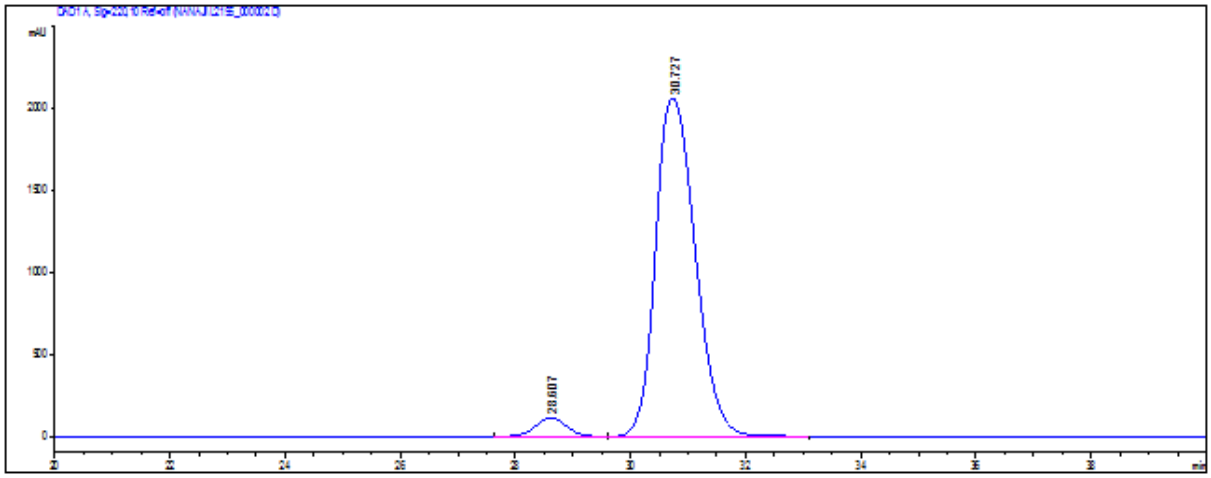
Table 6, entry-7



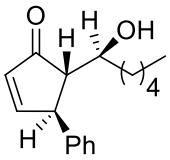
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	29.183	BB	0.5944	732.45392	19.05536	5.0130
2	31.400	BB	0.6611	1.38787e4	323.13040	94.9870

Totals : 1.46111e4 342.18576

50 g scale

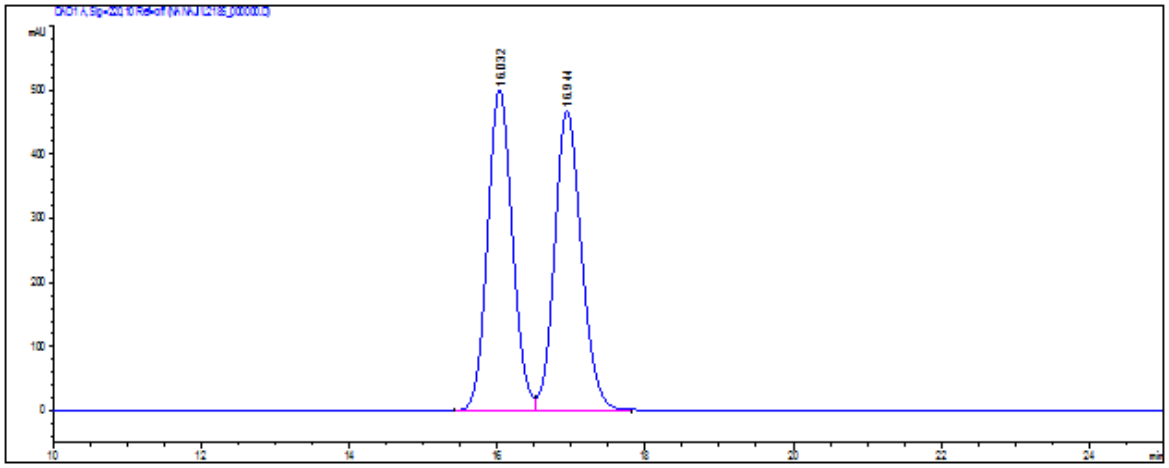


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	28.607	BB	0.5767	4304.28711	115.53338	4.1854
2	30.727	BB	0.7513	9.85356e4	2062.82935	95.8146
Totals :				1.02840e5	2178.3627	



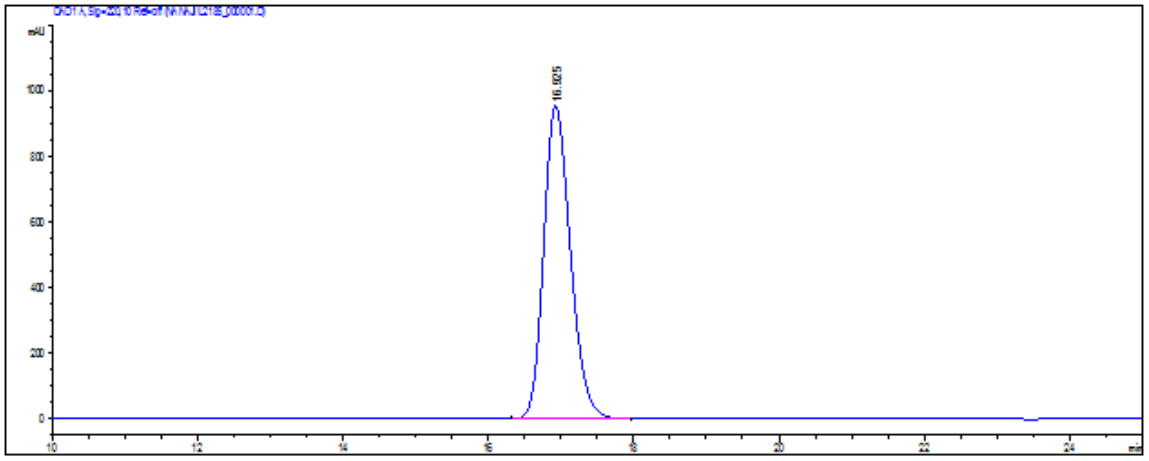
(+)-**133a**

Racemic (Daicel CHIRALCEL OD-H, Hex: iPrOH-9:1, 0.5 mL/min, 220 nm)

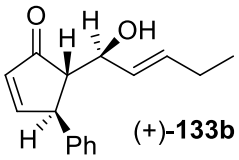


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	16.032	BV	0.3624	1.16628e4	499.58316	49.8767
2	16.944	VB	0.3867	1.17205e4	467.19119	50.1233
Totals :				2.33833e4	966.77435	

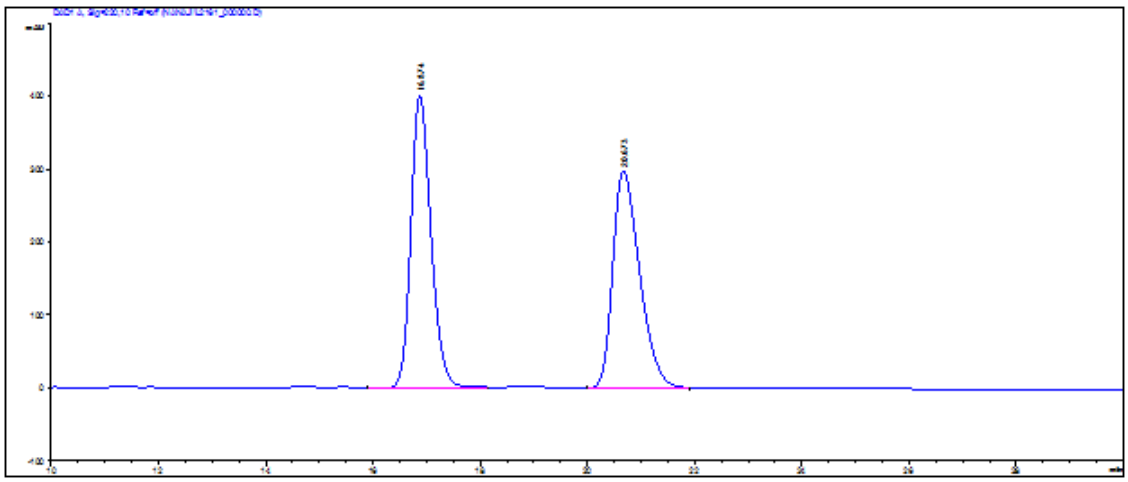
Pure



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	16.925	BB	0.3939	2.43745e4	954.45892	100.0000
Totals :				2.43745e4	954.45892	

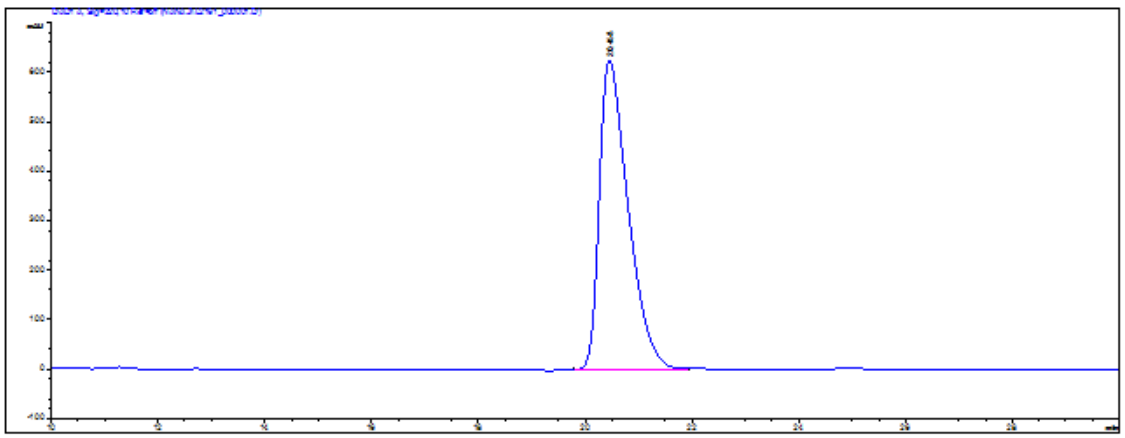


(+)-**133b** **Racemic** (Daicel CHIRALCEL OD-H, Hex: iPrOH-9:1, 0.5 mL/min, 220 nm)

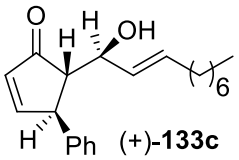


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	16.874	VB	0.4014	1.04194e4	400.64154	50.1847
2	20.673	BB	0.5337	1.03428e4	297.44733	49.8153
Totals:				2.07622e4	698.08887	

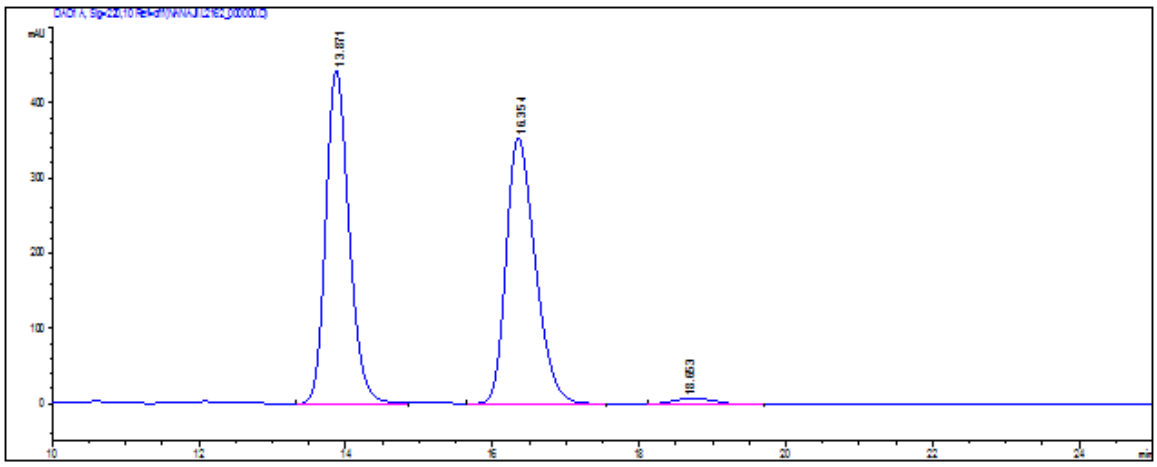
Pure



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	20.458	BB	0.5635	2.32976e4	624.16785	100.0000
Totals :				2.32976e4	624.16785	

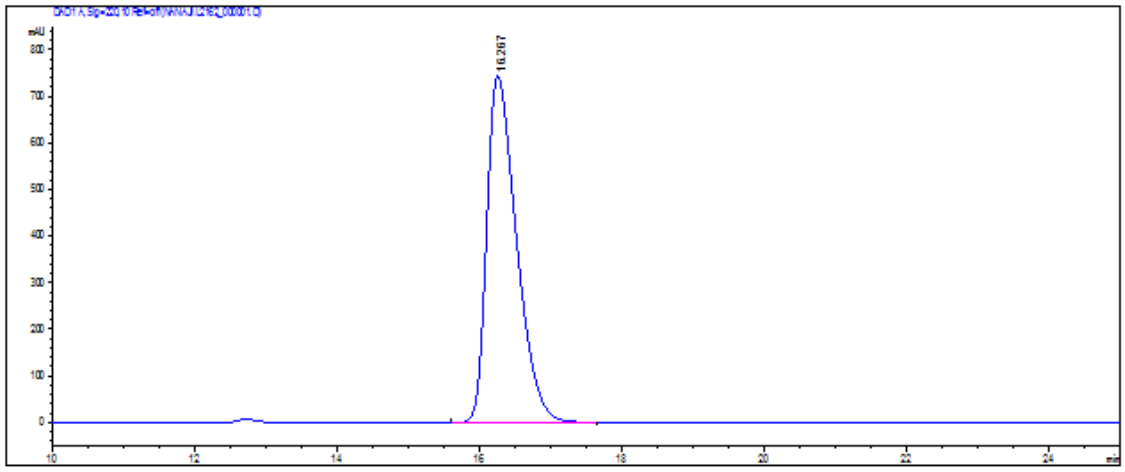


(+)-**133c** **Racemic** (Daicel CHIRALCEL OD-H, Hex: iPrOH-9:1, 0.5 mL/min, 220 nm)

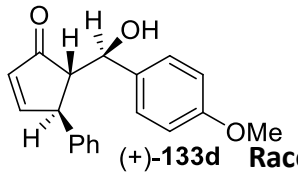


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	13.871	BB	0.3389	9760.70703	443.21783	49.3695
2	16.354	VB	0.4246	9771.88867	353.38275	49.4261
3	18.653	BB	0.5165	238.11638	6.22131	1.2044
Totals :				1.97707e4	802.82189	

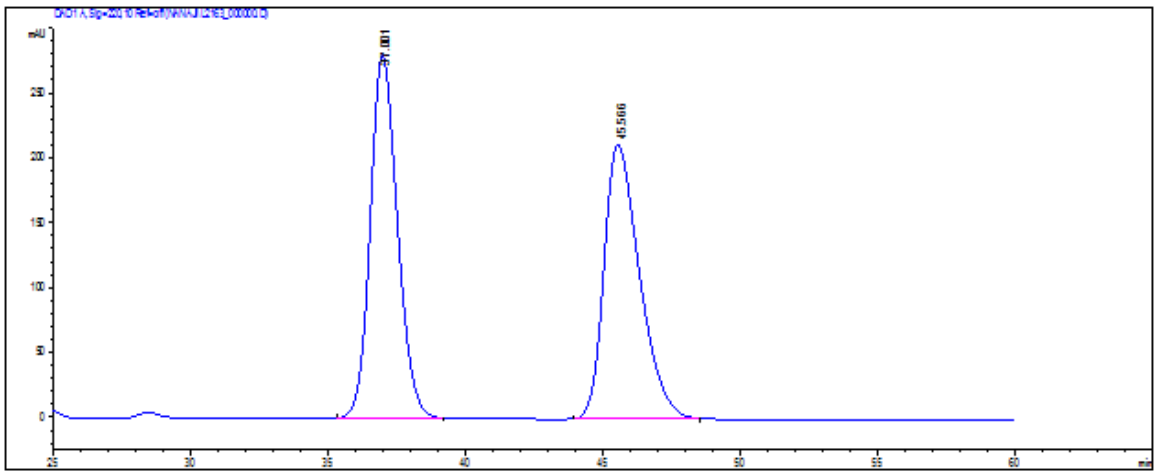
Pure



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	16.267	BB	0.4414	2.15171e4	744.00293	100.0000
Totals :				2.15171e4	744.00293	

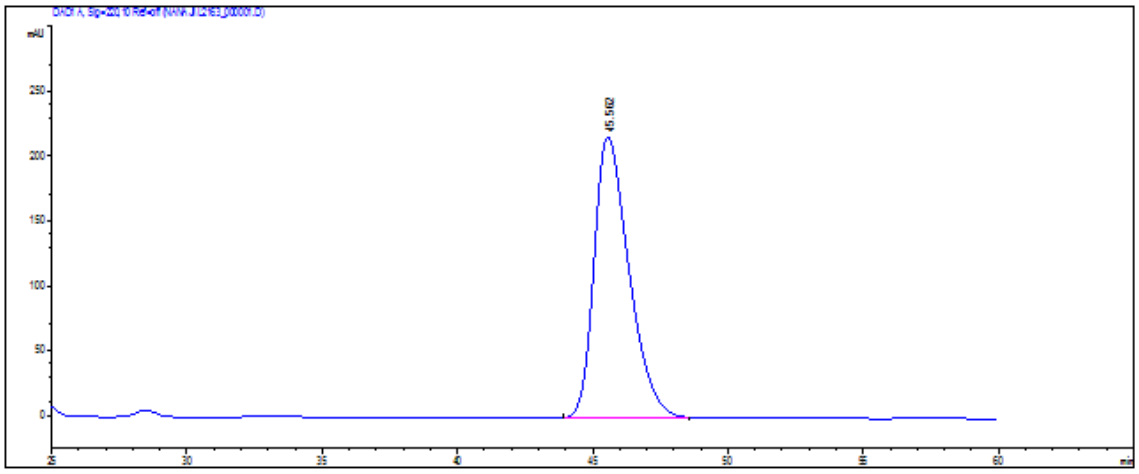


(+)-**133d** **Racemic** (Daicel CHIRALCEL OD-H, Hex: iPrOH-9:1, 0.5 mL/min, 220 nm)

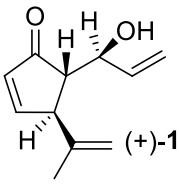


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	37.001	BB	1.0551	1.91694e4	279.18158	50.2680
2	45.566	BB	1.3402	1.89650e4	211.48711	49.7320
Totals :				3.81344e4	490.66869	

Pure

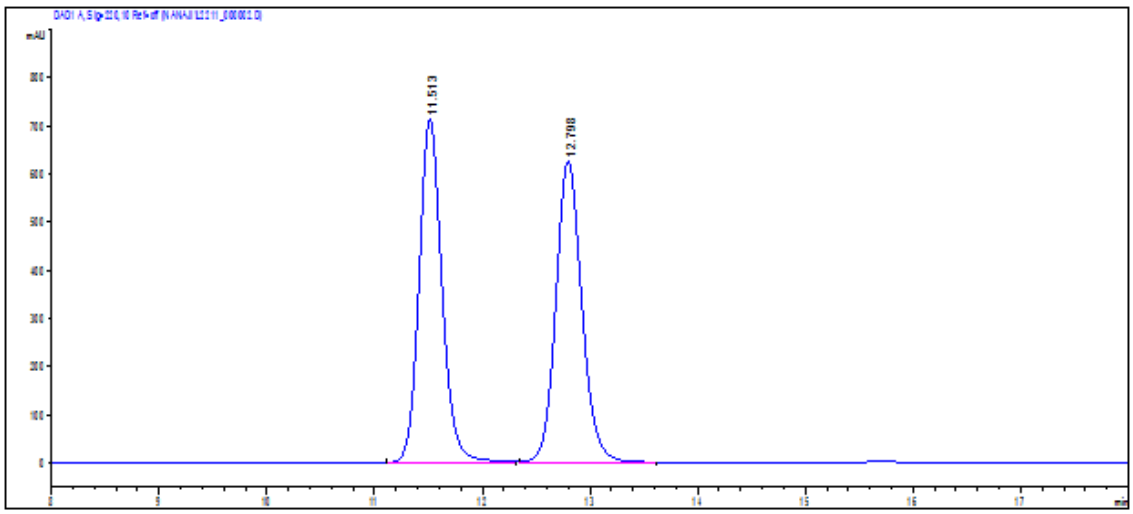


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	45.562	BB	1.3518	1.93902e4	216.71927	100.0000
Totals :				1.93902e4	216.71927	



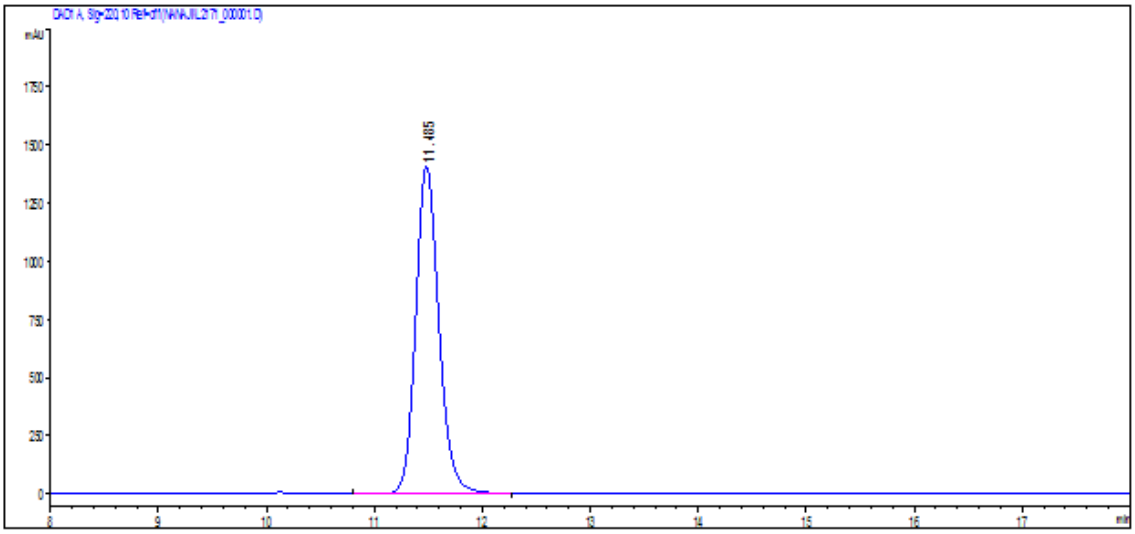
(+)-**133f**

Racemic (Daicel CHIRALCEL OD-H, Hex: iPrOH-9:1, 0.5 mL/min, 220 nm)

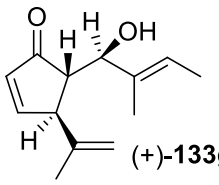


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	11.513	BB	0.2258	1.05228e4	714.52783	50.0456
2	12.798	BB	0.2576	1.05037e4	626.44678	49.9544
Totals :				2.10265e4	1340.97461	

Pure

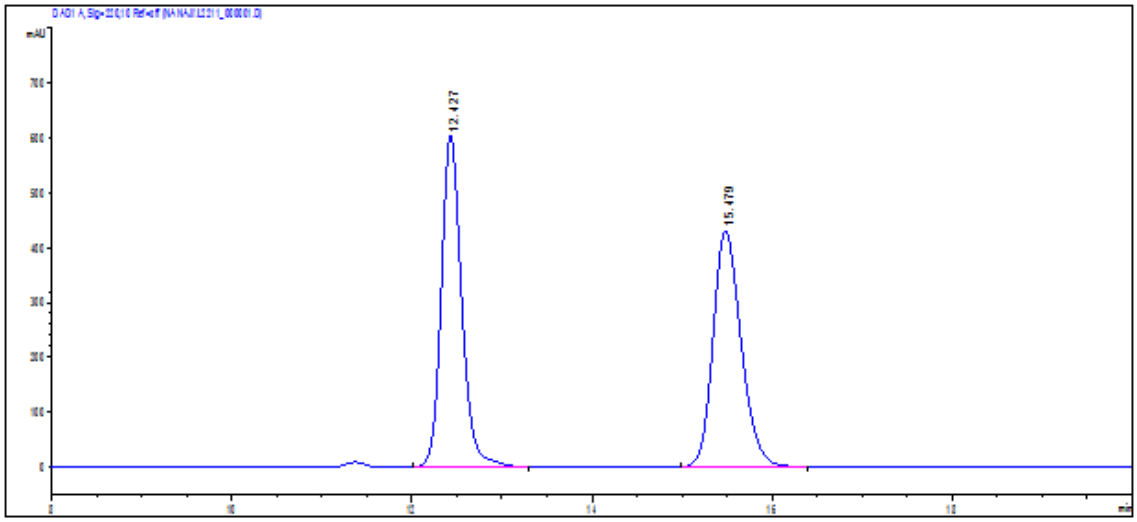


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	11.485	VB	0.2296	2.09386e4	1406.85852	100.0000
Totals :				2.09386e4	1406.85852	



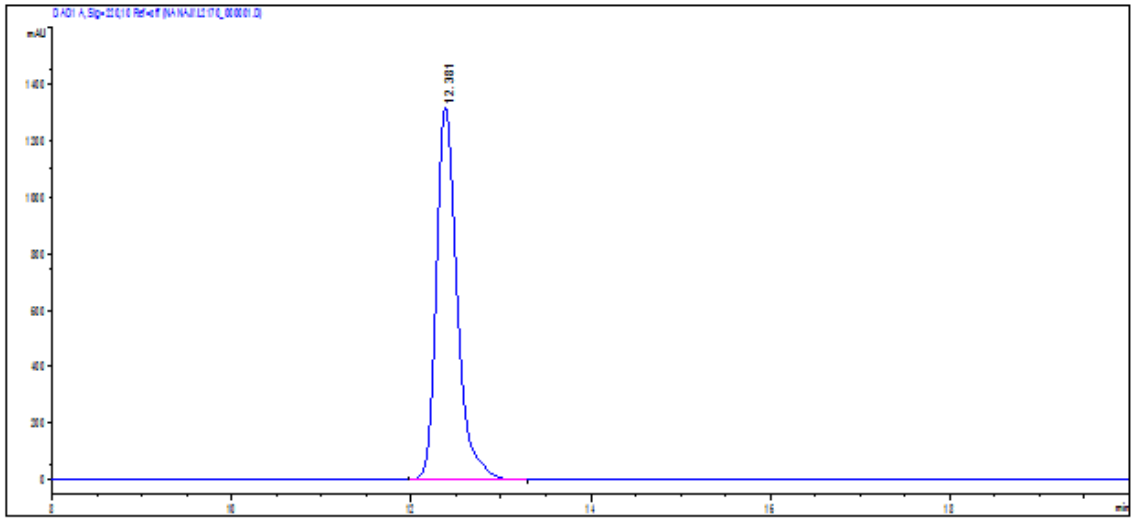
(+)-**133g**

Racemic (Daicel CHIRALCEL OD-H, Hex: iPrOH-9:1, 0.5 mL/min, 220 nm)

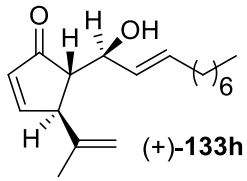


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	12.427	BB	0.2390	9467.62305	603.64832	50.3922
2	15.479	BB	0.3344	9320.26563	430.74310	49.6078
Totals :				1.87879e4	1034.39142	

Pure

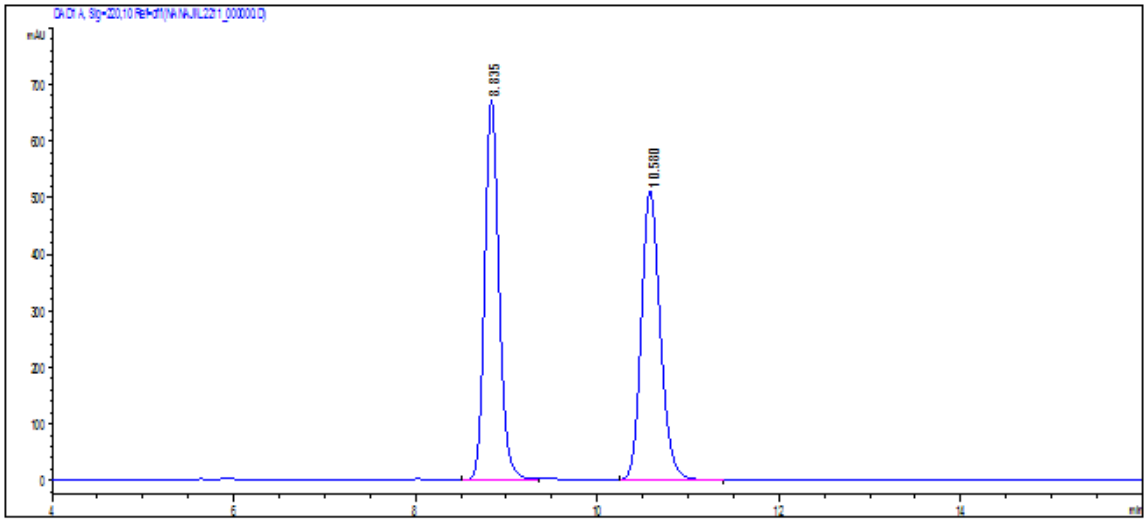


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	12.381	BB	0.2450	2.11340e4	1318.22864	100.0000
Totals :				2.11340e4	1318.22864	



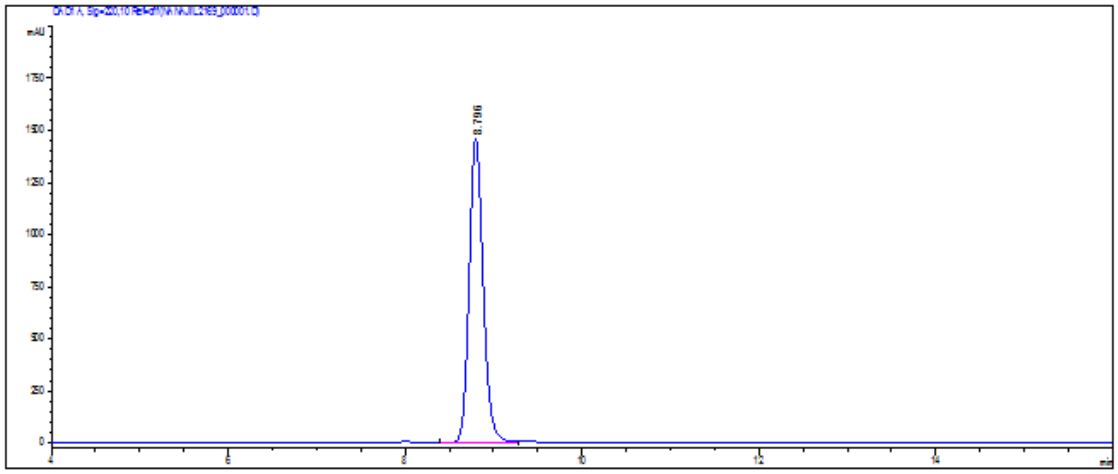
(+)-**133h**

Racemic (Daicel CHIRALCEL OD-H, Hex: iPrOH-9:1, 0.5 mL/min, 220 nm)

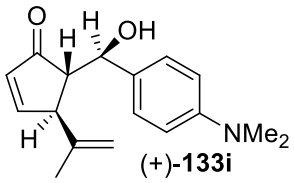


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	8.835	BV	0.1681	7372.73145	671.32239	49.8038
2	10.580	BB	0.2238	7430.82373	510.52188	50.1962
Totals :				1.48036e4	1181.84427	

Pure

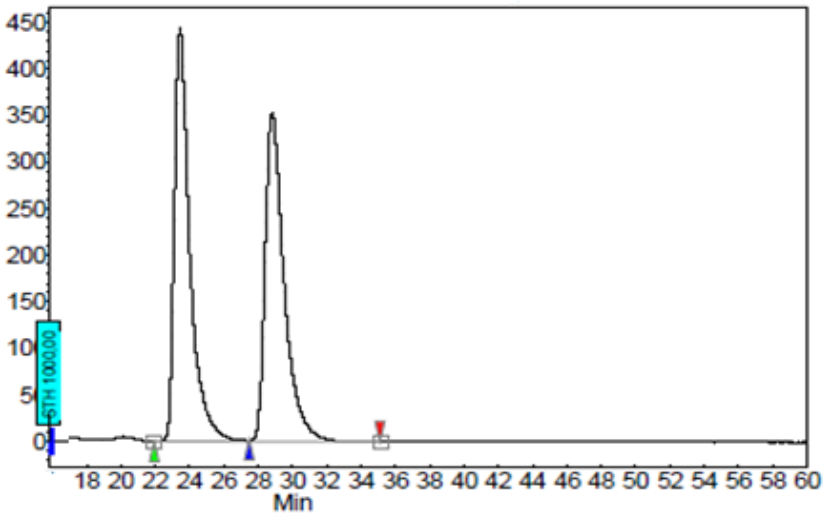


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	8.796	VV	0.1709	1.61348e4	1460.01709	100.0000
Totals:				1.61348e4	1460.01709	



(+)-**133i**

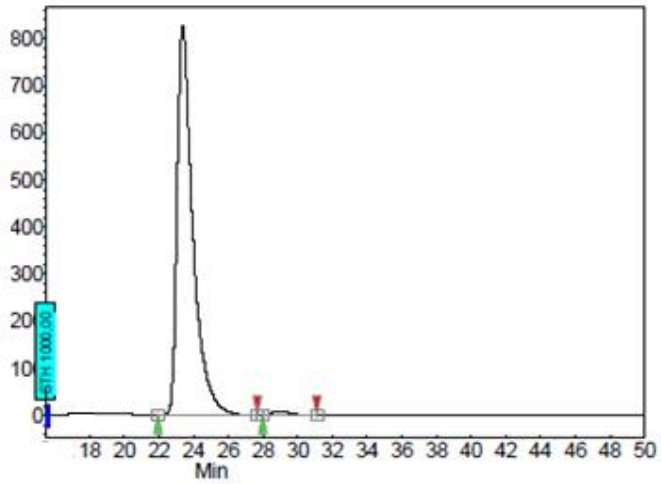
Racemic (Phenomenex Lux Cellulose-2, n-Hep: iPrOH-1:1, 0.5 mL/min, 254 nm)



Peak Results :

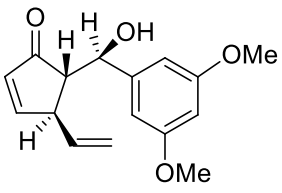
Index	Name	Time [Min]	Quantity [% Area]	Height [mAU]	Area [mAU.Min]	Area % [%]
1	UNKNOWN	23,44	50,44	444,7	463,8	50,445
2	UNKNOWN	28,82	49,56	354,1	455,6	49,555
Total			100,00	798,8	919,5	100,000

Pure



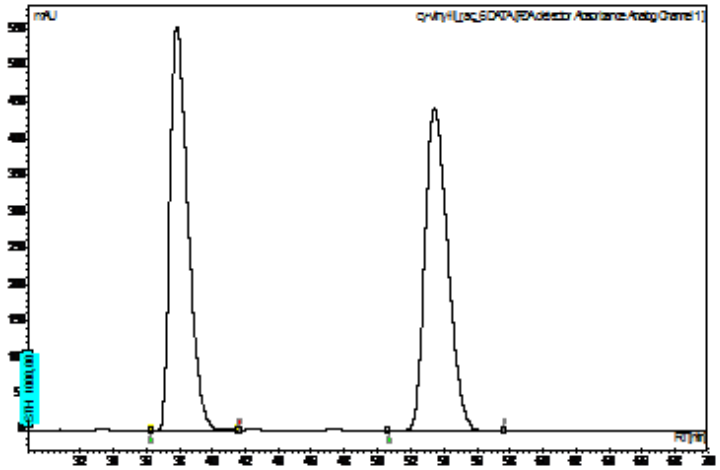
Peak Results :

Index	Name	Time [Min]	Quantity [% Area]	Height [mAU]	Area [mAU.Min]	Area % [%]
1	UNKNOWN	23,37	99,09	827,0	871,2	99,085
2	UNKNOWN	28,95	0,91	7,2	8,0	0,915
Total			100,00	834,2	879,3	100,000



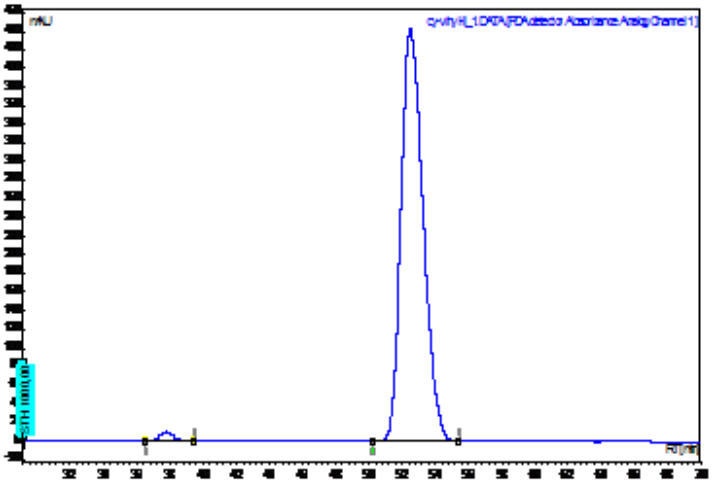
(+)-**133k**

Racemic (Chiralpak AS-H, n-Hep: iPrOH-7:3, 0.5 mL/min, 215 nm)

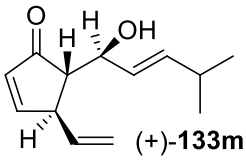


#	Name	Time [Min]		Quantity [% Area]		Height
[mAU]		Area [mAU.Min]		Area % [%]		
1	UNKNOWN	37,85	49,81	554,4	706,0	49,812
2	UNKNOWN	53,44	50,19	443,5	711,3	50,188
	Total	100,00	997,8	1417,3	100,000	

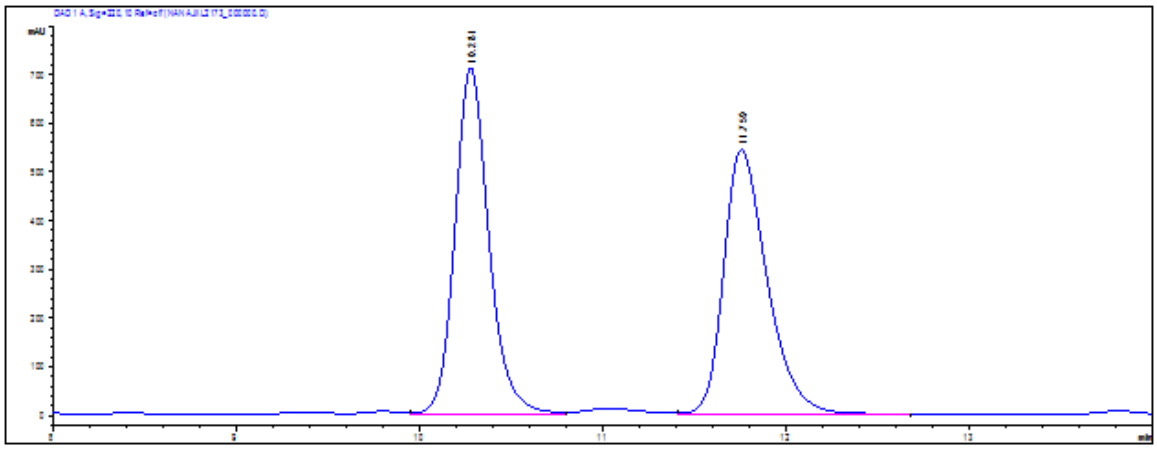
Pure



#	Name	Time [Min]		Quantity [% Area]		Height
[mAU]		Area [mAU.Min]		Area % [%]		
1	UNKNOWN	37,78	1,54	10,0	10,7	1,541
2	UNKNOWN	52,50	98,46	441,9	684,0	98,459
Total	100,00	451,9	694,7	100,000		

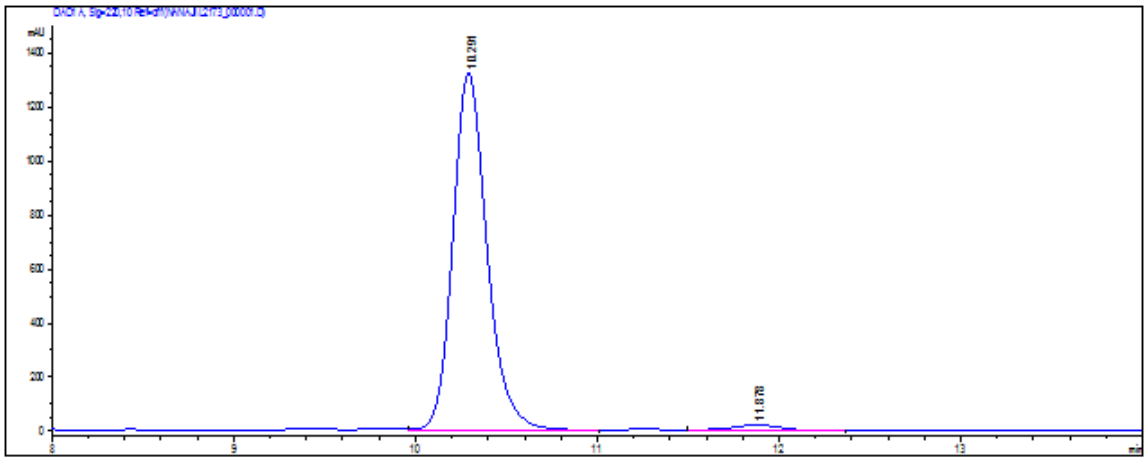


(+)-**133m** **Racemic** (Daicel CHIRALCEL OD-H, Hex: iPrOH-9:1, 0.5 mL/min, 220 nm)

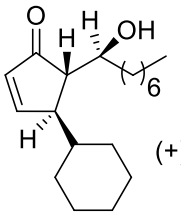


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	10.281	VV	0.1967	9210.60352	712.91986	50.6279
2	11.759	VB	0.2505	8982.14063	544.43036	49.3721
Totals :				1.81927e4	1257.35022	

Pure

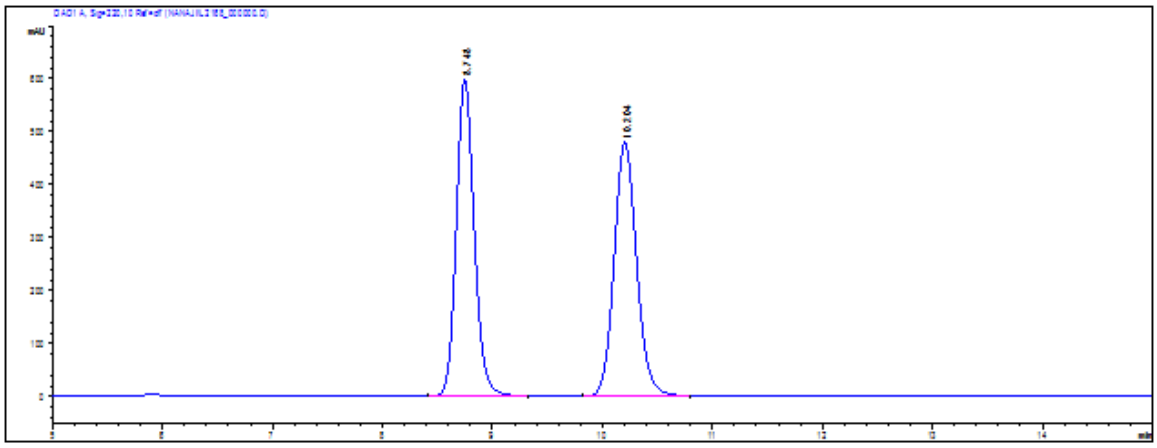


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	10.291	VB	0.2013	1.74345e4	1326.84680	97.5320
2	11.878	VB	0.2892	441.18079	22.45942	2.4680
Totals :				1.78757e4	1349.30622	



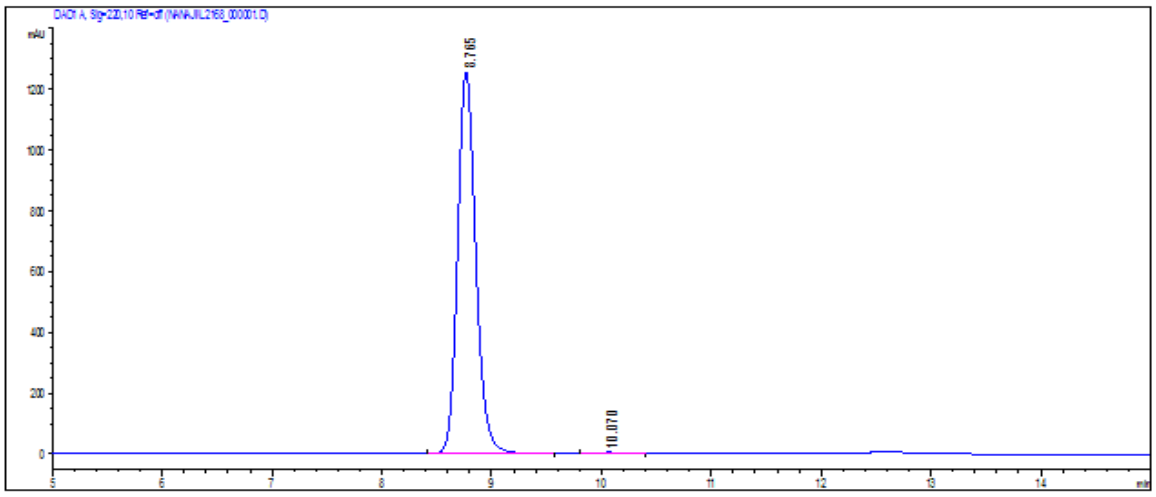
(+)-**133n**

Racemic (Daicel CHIRALCEL OD-H, Hex: iPrOH-9:1, 0.5 mL/min, 220 nm)

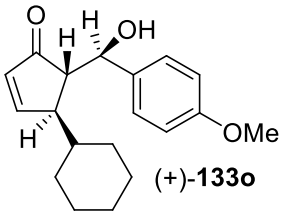


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	8.748	BB	0.1746	6796.20410	597.86981	49.7955
2	10.204	BV	0.2187	6852.02930	479.49533	50.2045
Totals :				1.36482e4	1077.36514	

Pure

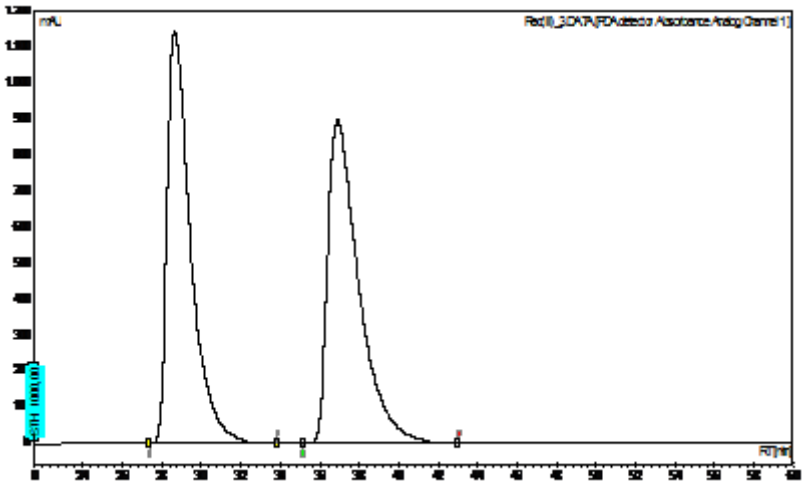


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	8.765	VB	0.1764	1.44741e4	1256.32727	99.4524
2	10.070	BV	0.2340	79.69231	5.16510	0.5476
Totals :				1.45538e4	1261.4923	



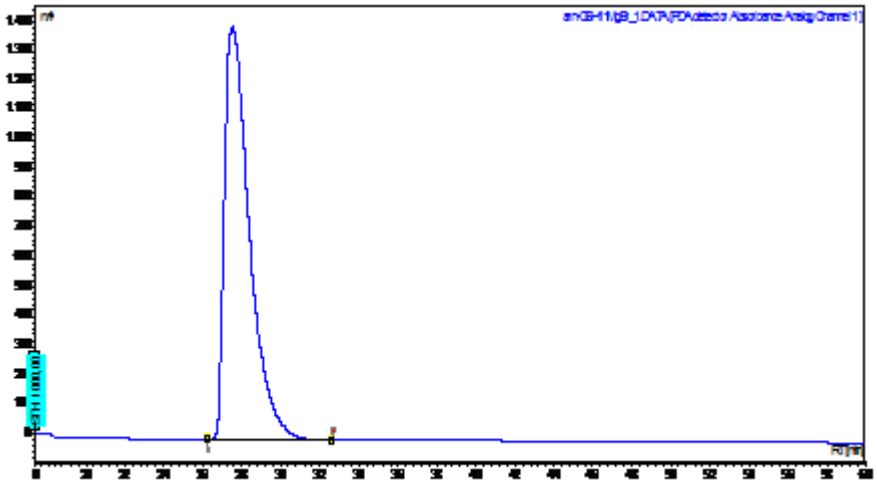
(+)-**133o**

Racemic (Phenomenex Lux Cellulose-2, n-Hep: iPrOH-7:3, 0.5 mL/min, 215 nm)

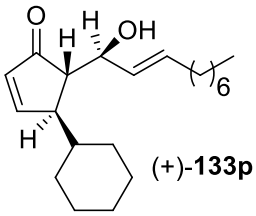


#	Name	Time [Min]		Quantity [% Area]		Height
[mAU]		Area [mAU.Min]		Area % [%]		
1	UNKNOWN	28,67	49,16	1144,9	1582,4	49,165
2	UNKNOWN	36,90	50,84	898,0	1636,1	50,835
Total			100,00	2042,9	3218,5	100,000

Pure

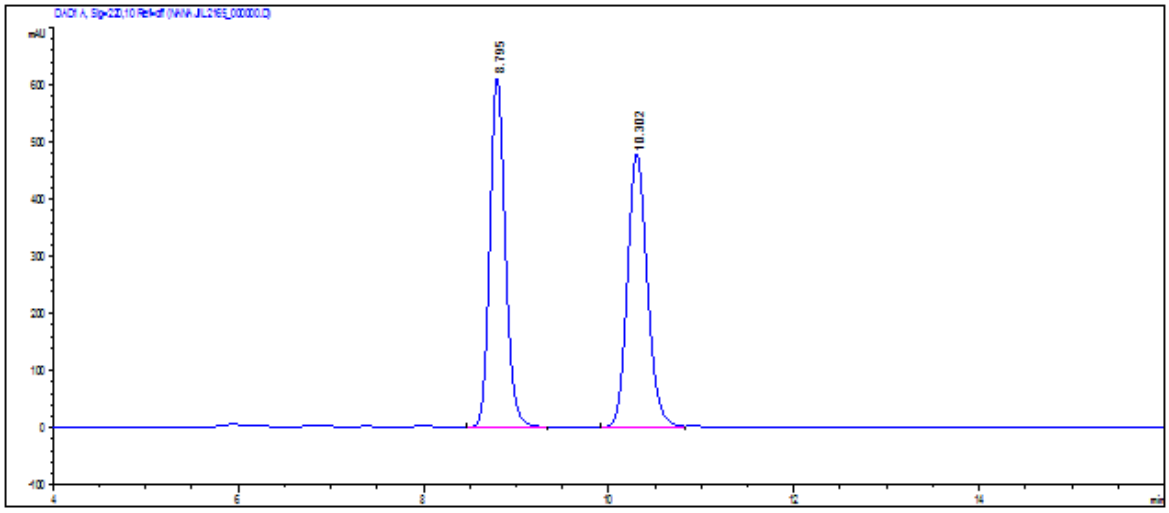


#	Name	Time [Min]		Quantity [% Area]		Height
[mAU]		Area [mAU.Min]		Area % [%]		
1	UNKNOWN	27,51	100,00	1400,6	2075,5	100,000
	Total	100,00	1400,6	2075,5	100,000	



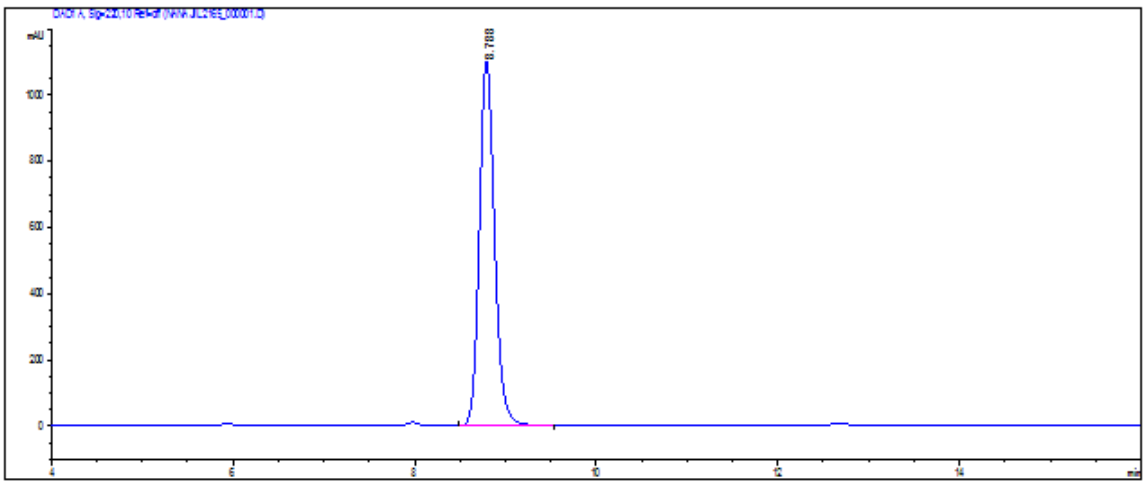
(+)-**133p**

Racemic (Daicel CHIRALCEL OD-H, Hex: iPrOH-9:1, 0.5 mL/min, 220 nm)

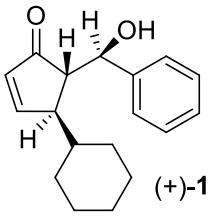


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	8.795	VB	0.1794	7092.45117	611.27081	49.7676
2	10.302	VV	0.2306	7158.68506	478.45273	50.2324
Totals :				1.42511e4	1089.72354	

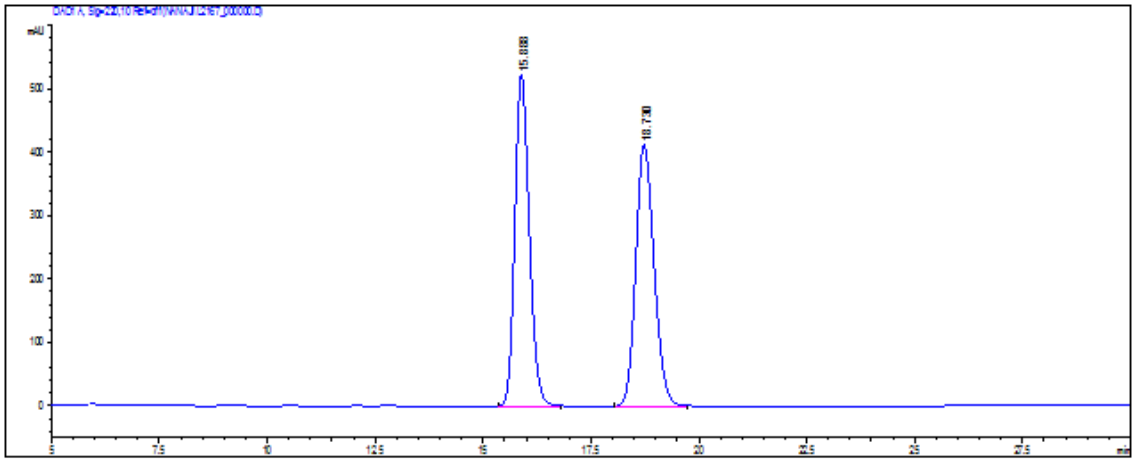
Pure



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	8.788	BB	0.1799	1.28671e4	1104.21106	100.0000
Totals :				1.28671e4	1104.21106	

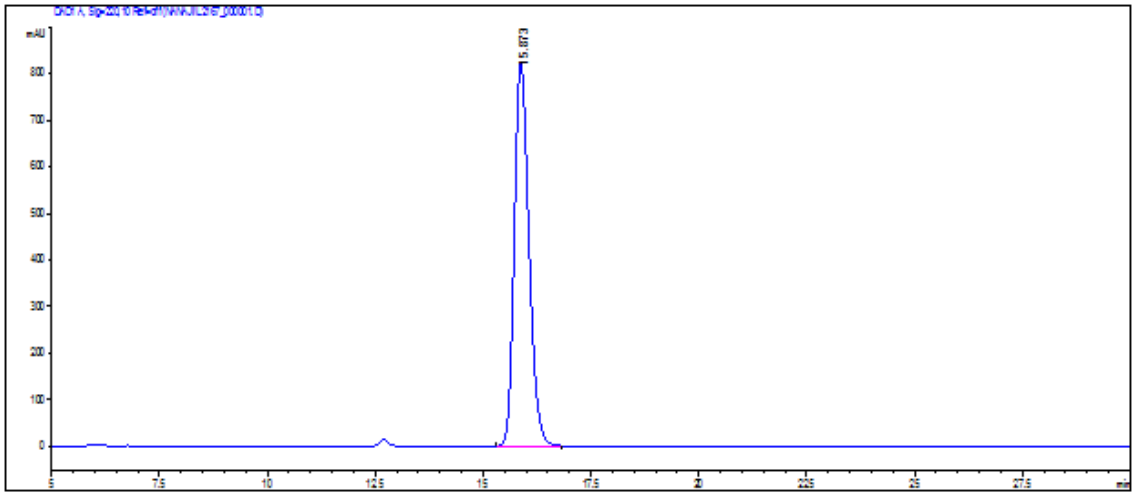


(+)-**133r** **Racemic** (Daicel CHIRALCEL OD-H, Hex: iPrOH-9:1, 0.5 mL/min, 220 nm)

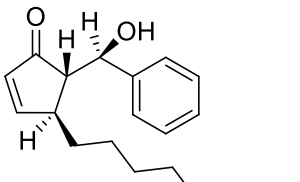


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	15.888	BB	0.3596	1.21483e4	521.80676	49.9664
2	18.730	BB	0.4566	1.21646e4	411.81943	50.0336
Totals :				2.43129e4	933.62619	

Pure

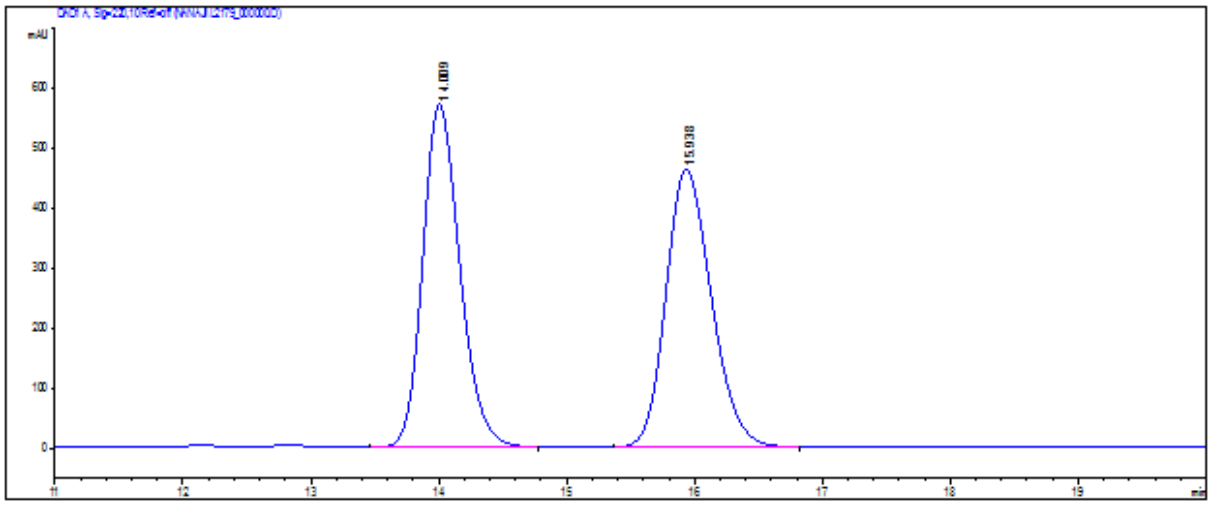


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	15.873	BB	0.3658	1.94189e4	821.36072	100.0000
Totals :				1.94189e4	821.36072	



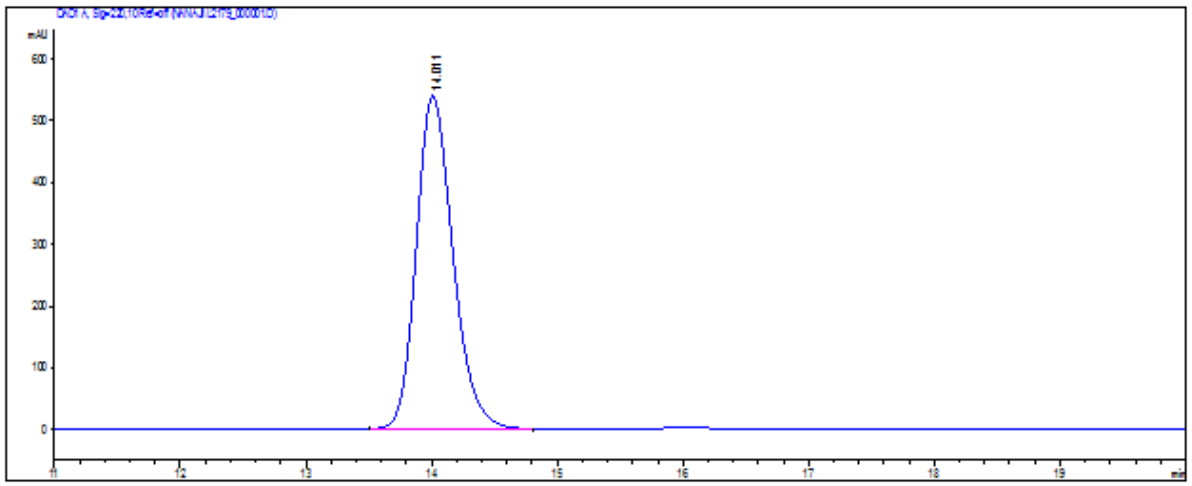
(+)-**133s**

Racemic (Daicel CHIRALCEL OD-H, Hex: iPrOH-9:1, 0.5 mL/min, 220 nm)

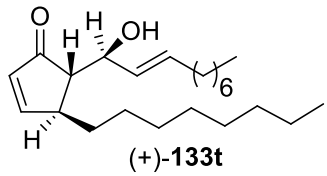


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	14.009	BB	0.3094	1.15398e4	571.83917	50.1461
2	15.938	BB	0.3829	1.14726e4	463.29245	49.8539
Totals :				2.30124e4	1035.13162	

Pure

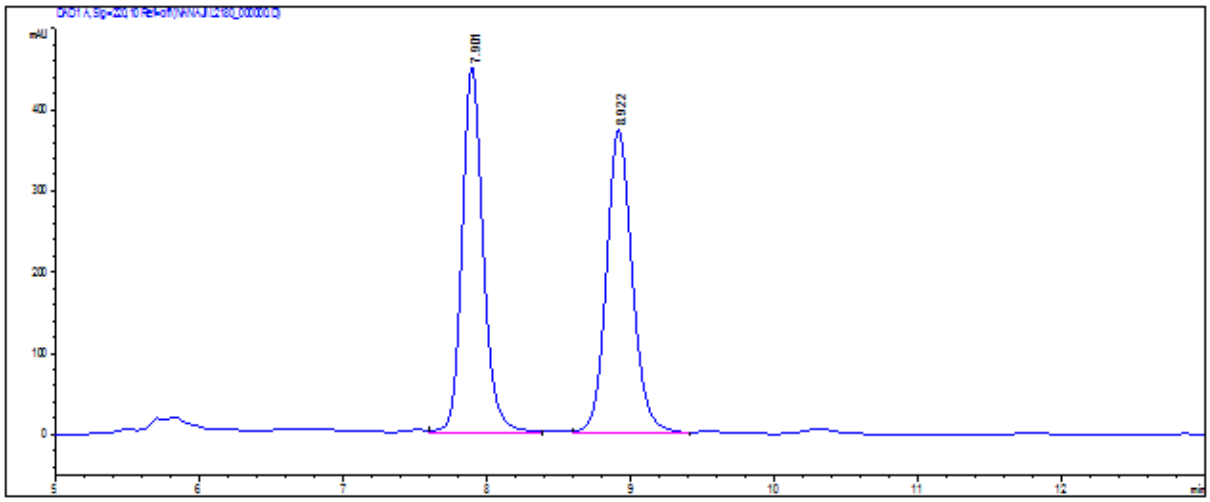


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	14.011	BB	0.3103	1.09369e4	539.99188	100.0000
Totals :				1.09369e4	539.99188	



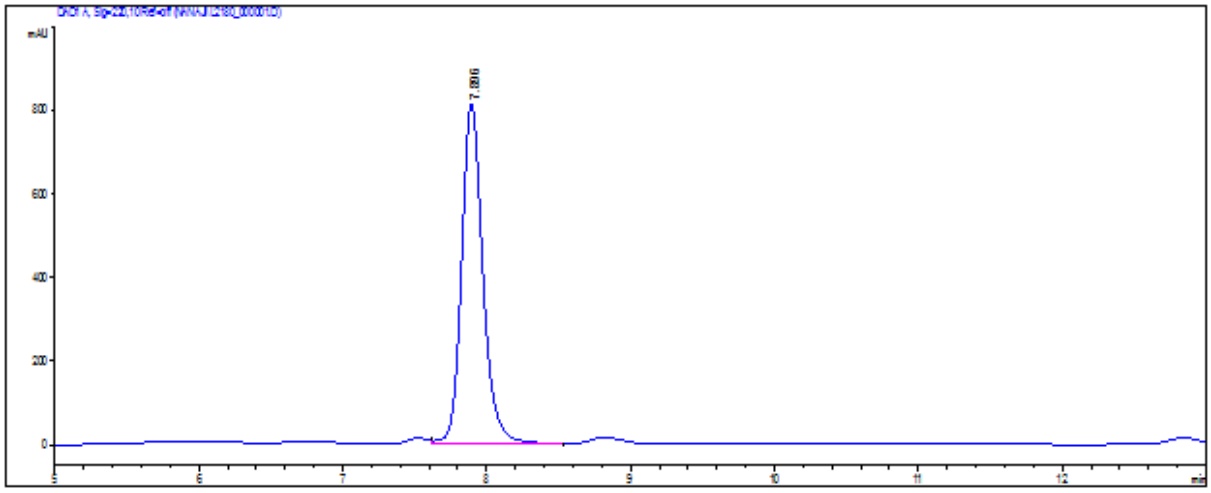
(+)-**133t**

Racemic (Daicel CHIRALCEL OD-H, Hex: iPrOH-9:1, 0.5 mL/min, 220 nm)

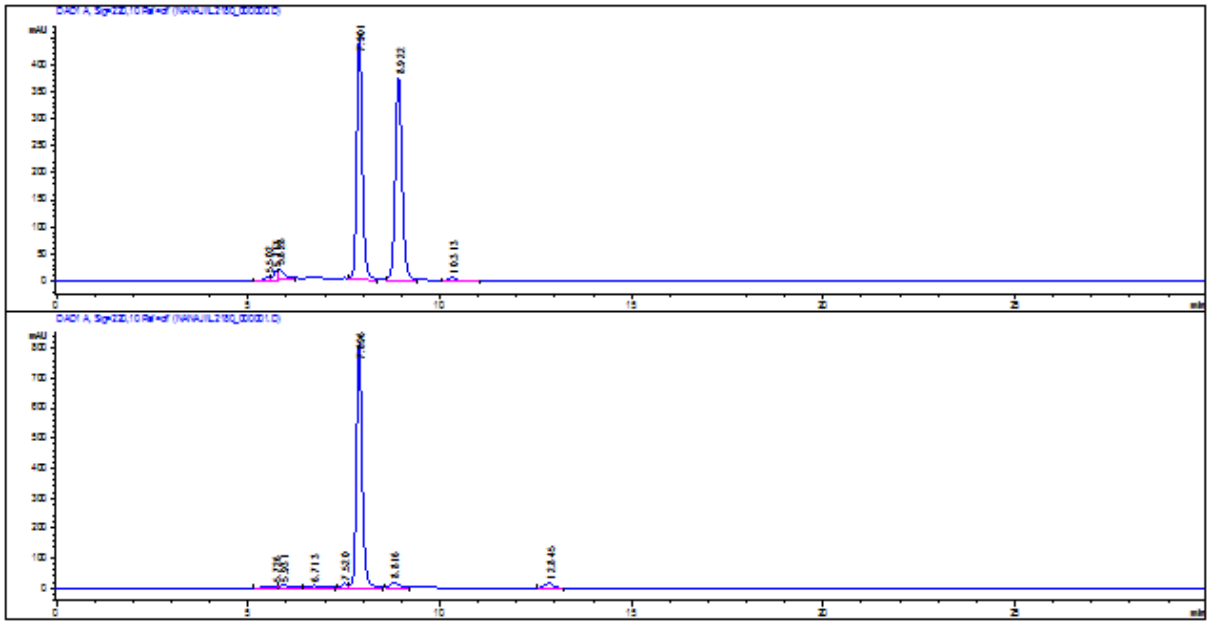


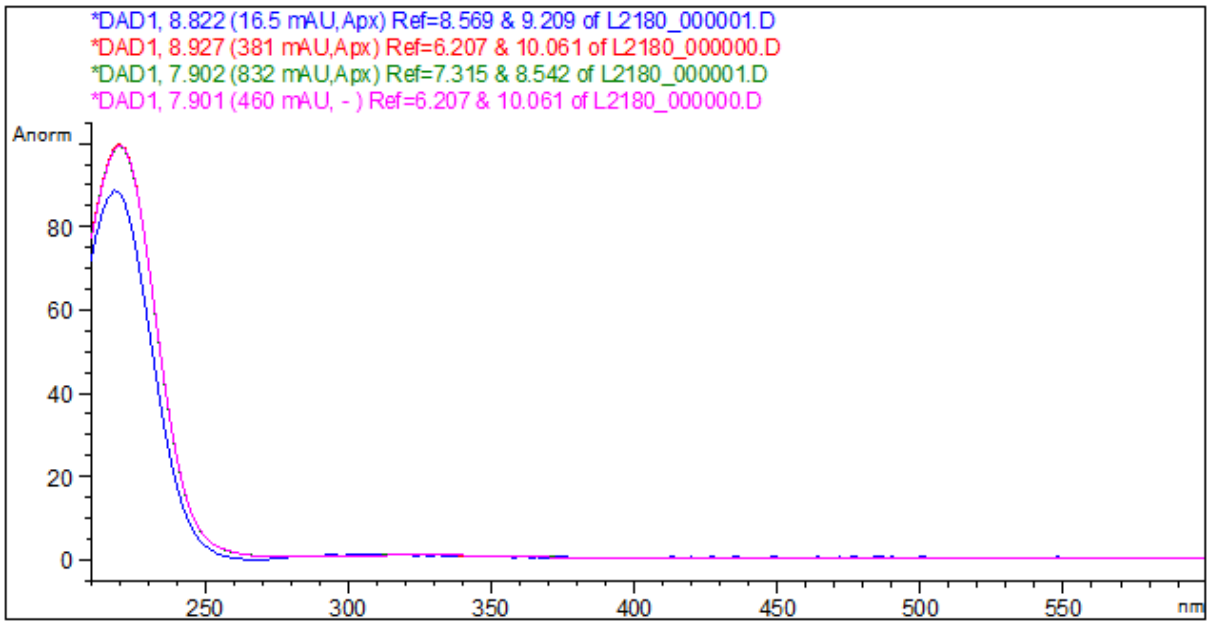
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	7.901	VV	0.1567	4571.86377	449.38071	49.4026
2	8.922	VV	0.1924	4682.43164	373.02985	50.5974
Totals :				9254.29541	822.41055	

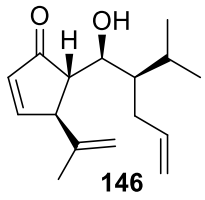
Pure



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	7.896	VB	0.1584	8418.02637	815.66779	100.0000
Totals :				8418.02637	815.6677	




*DAD1, 8.822 (16.5 mAU,Apx) Ref=8.569 & 9.209 of L2180_000001.D
*DAD1, 8.927 (381 mAU,Apx) Ref=6.207 & 10.061 of L2180_000000.D
*DAD1, 7.902 (832 mAU,Apx) Ref=7.315 & 8.542 of L2180_000001.D
*DAD1, 7.901 (460 mAU, -) Ref=6.207 & 10.061 of L2180_000000.D
Anorm
80
60
40
20
0
250
300
350
400
450
500
550
nm



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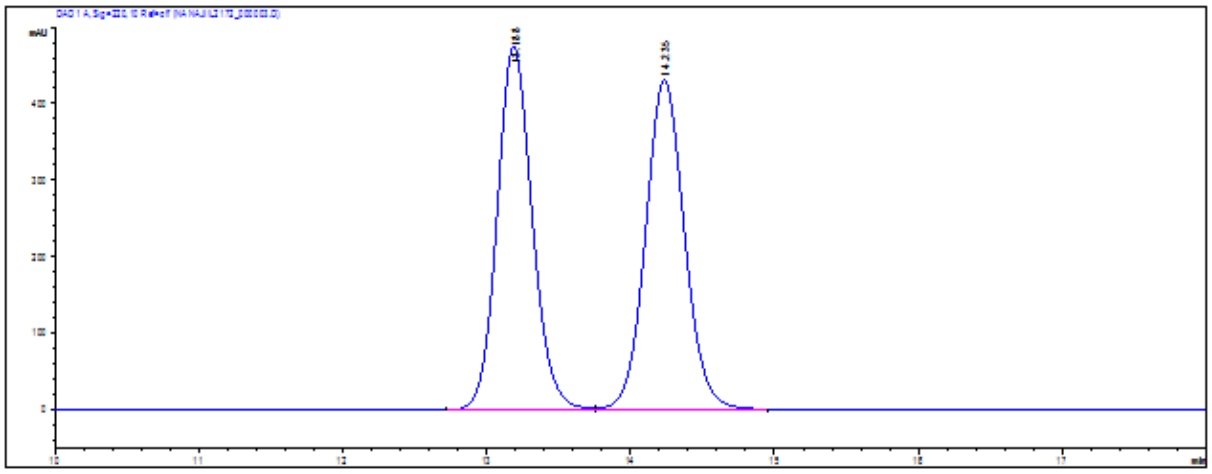
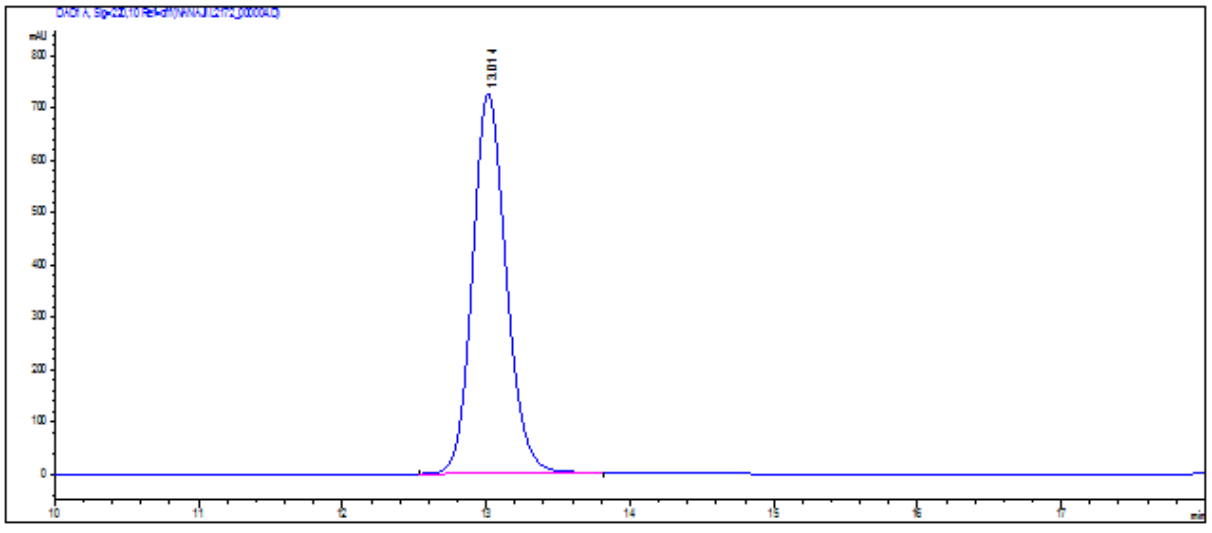
Racemic (Daicel CHIRALCEL OD-H, Hex: iPrOH-9:1, 0.5 mL/min, 220 nm)

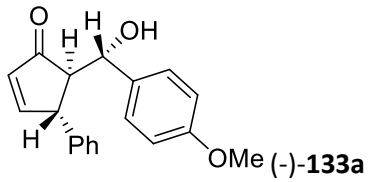


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	13.188	BV	0.261	8066.14697	476.19882	49.8447
2	14.235	VB	0.2916	8116.41406	431.12695	50.1553
Totals :				1.61826e4	907.32578	

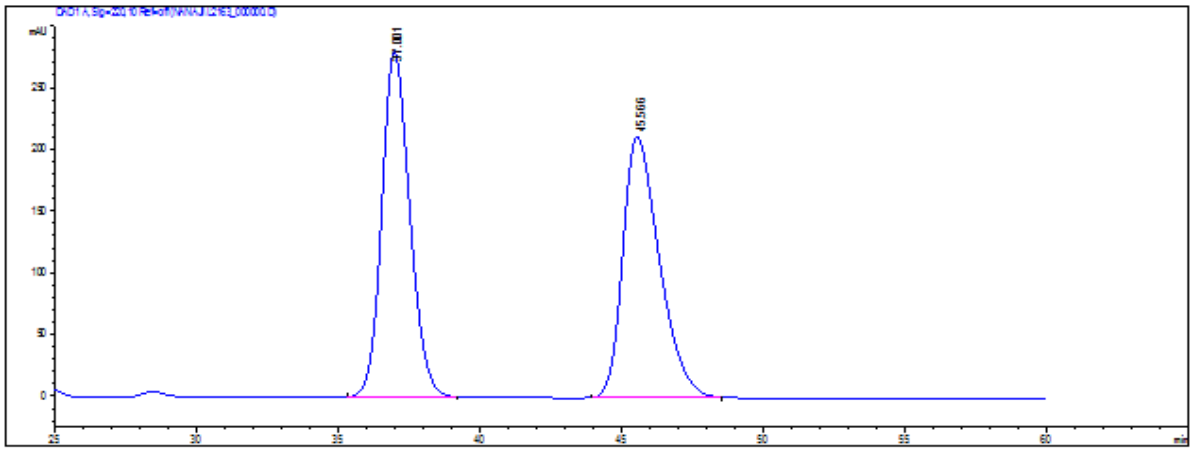
Pure



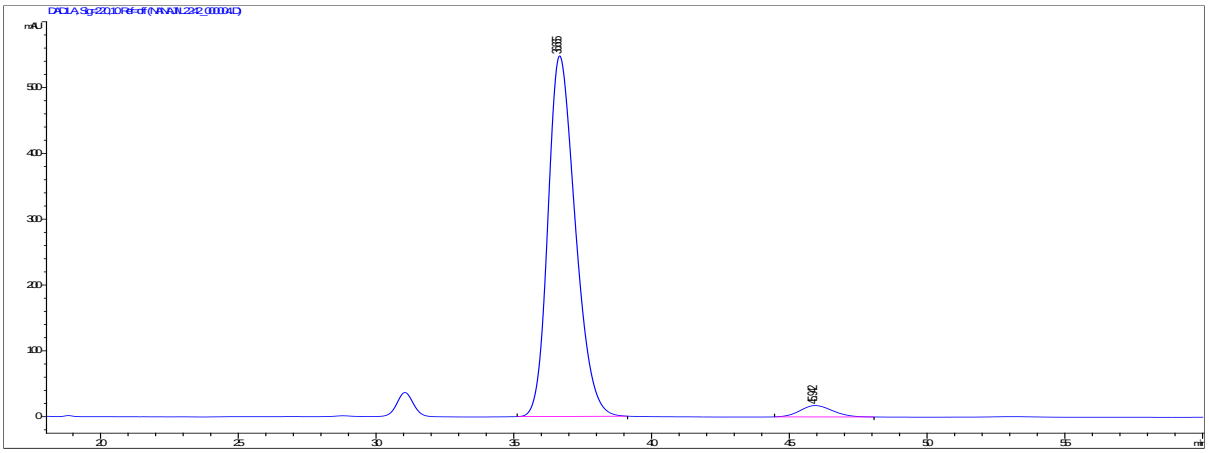
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	13.014	BB	0.2496	1.18239e4	727.64905	100.0000
Totals :				1.18239e4	727.64905	



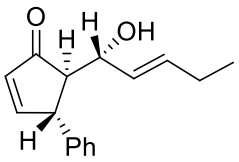
(-)-**133a**



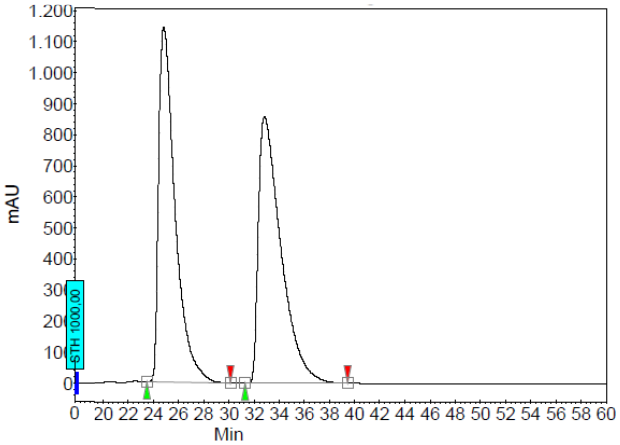
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	37.001	BB	1.0551	1.91694e4	279.18158	50.2680
2	45.566	BB	1.3402	1.89650e4	211.48711	49.7320
Totals :				3.81344e4	490.66869	



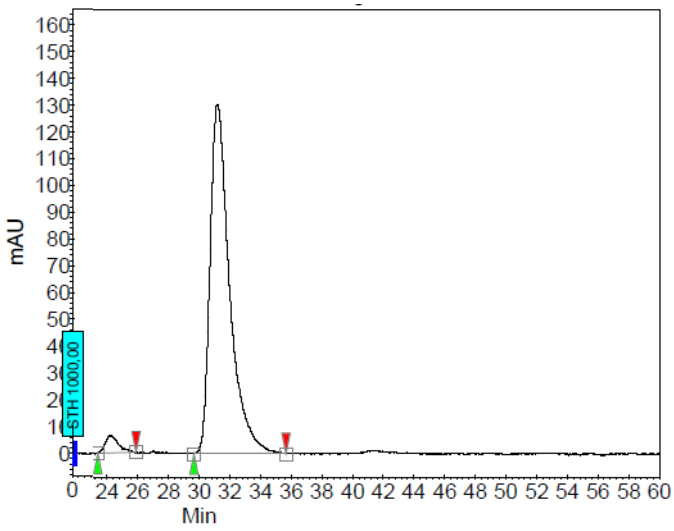
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	36.665	BB	1.0582	3.77625e4	547.85675	96.3837
2	45.942	BB	1.0578	1416.82507	17.25836	3.6163
Totals :				3.91793e4	565.11511	



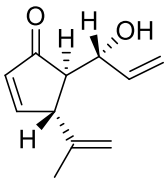
(-)-**133c**



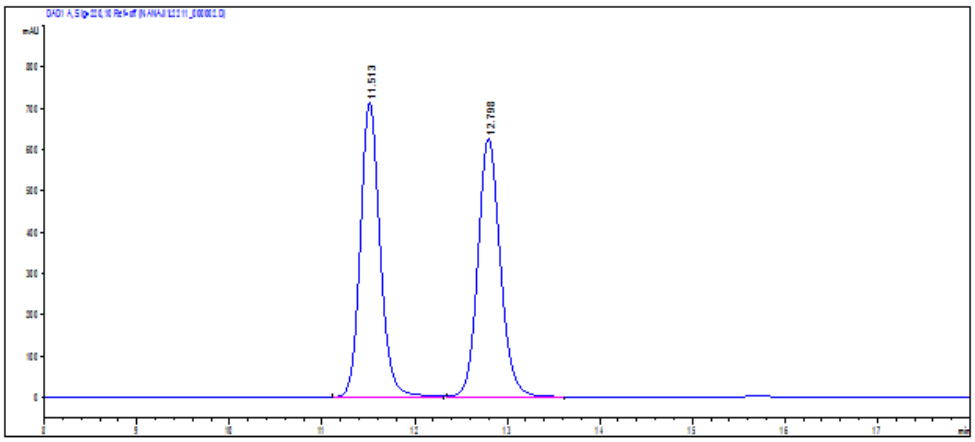
Index	Name	Time [Min]	Quantity [% Area]	Height [mAU]	Area [mAU.Min]	Area % [%]
1	UNKNOWN	24,82	49,18	1145,5	1728,6	49,177
2	UNKNOWN	32,83	50,82	860,7	1786,4	50,823
Total			100,00	2006,1	3515,0	100,000



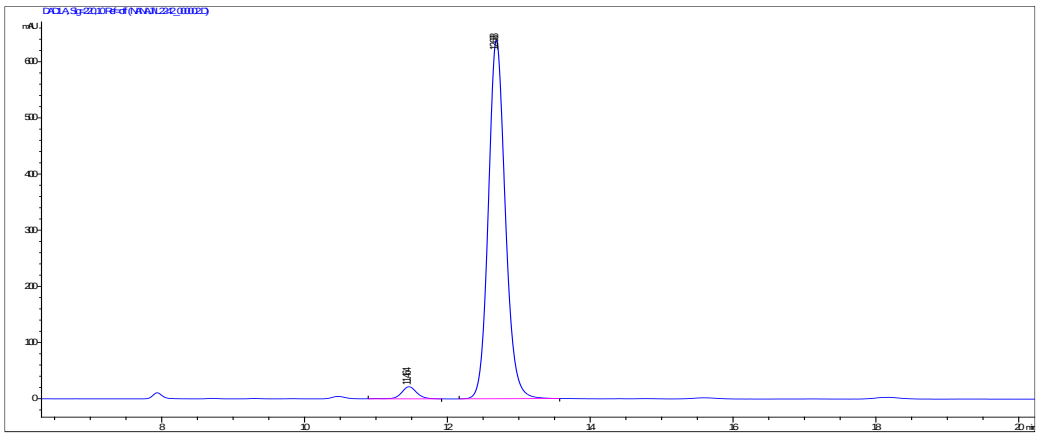
Index	Name	Time [Min]	Quantity [% Area]	Height [mAU]	Area [mAU.Min]	Area % [%]
1	UNKNOWN	24,19	3,18	6,4	6,3	3,180
2	UNKNOWN	31,20	96,82	130,3	193,1	96,820
Total			100,00	136,7	199,5	100,000



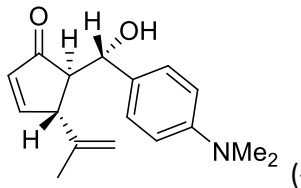
(-)-**133d**



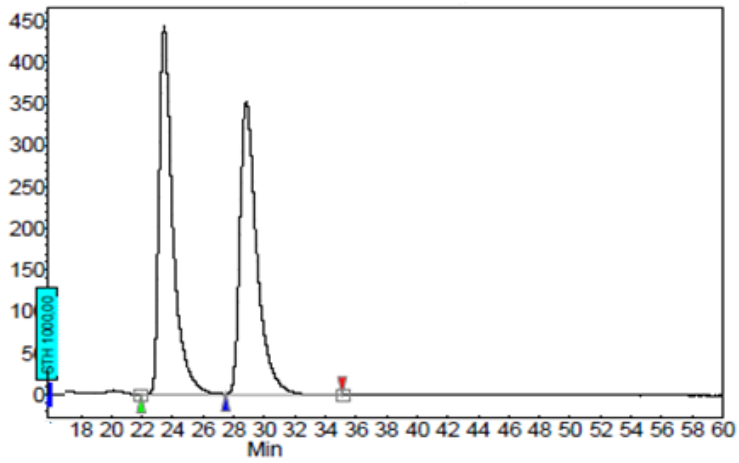
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	11.513	BB	0.2258	1.05228e4	714.52783	50.0456
2	12.798	BB	0.2576	1.05037e4	626.44678	49.9544
Totals :				2.10265e4	1340.97461	



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	11.464	BB	0.2259	322.78360	21.65867	2.9755
2	12.688	BB	0.2521	1.05252e4	639.23163	97.0245
Totals :				1.08480e4	660.89030	

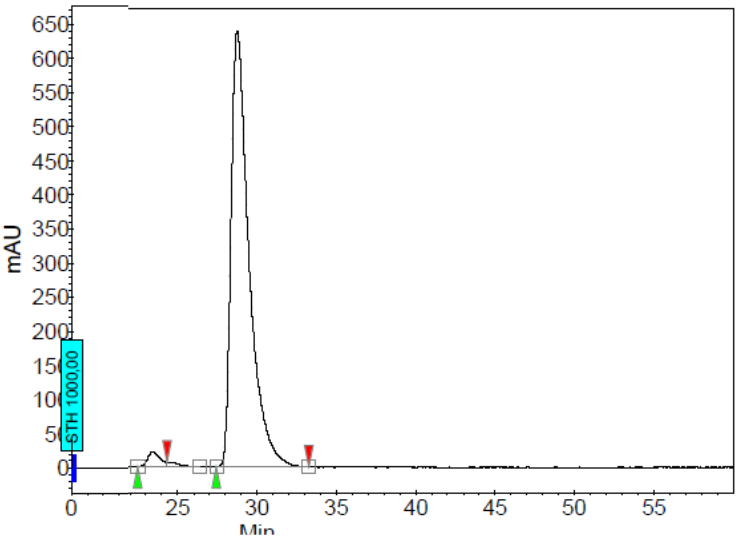


(-)-**133g**



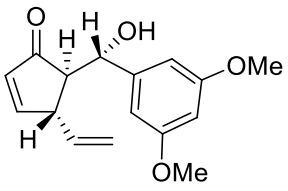
Peak Results :

Index	Name	Time [Min]	Quantity [% Area]	Height [mAU]	Area [mAU.Min]	Area % [%]
1	UNKNOWN	23,44	50,44	444,7	463,8	50,445
2	UNKNOWN	28,82	49,56	354,1	455,6	49,555
Total			100,00	798,8	919,5	100,000

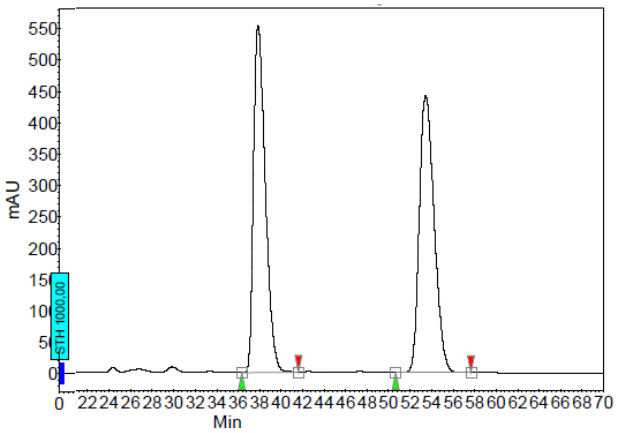


Peak Results :

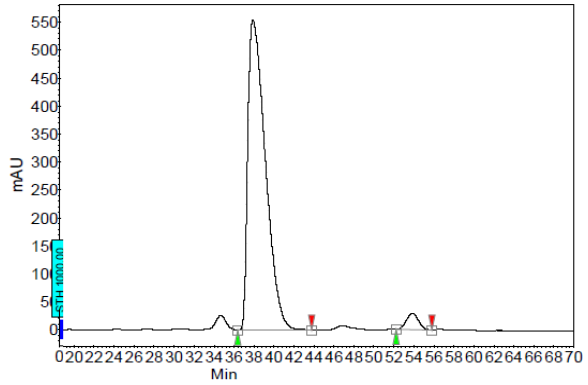
Index	Name	Time [Min]	Quantity [% Area]	Height [mAU]	Area [mAU.Min]	Area % [%]
1	UNKNOWN	23,45	2,38	22,3	20,7	2,382
2	UNKNOWN	28,76	97,62	643,6	846,6	97,618
Total			100,00	665,9	867,2	100,000



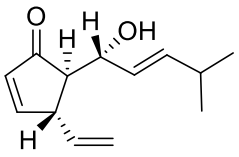
(-)-**133h**



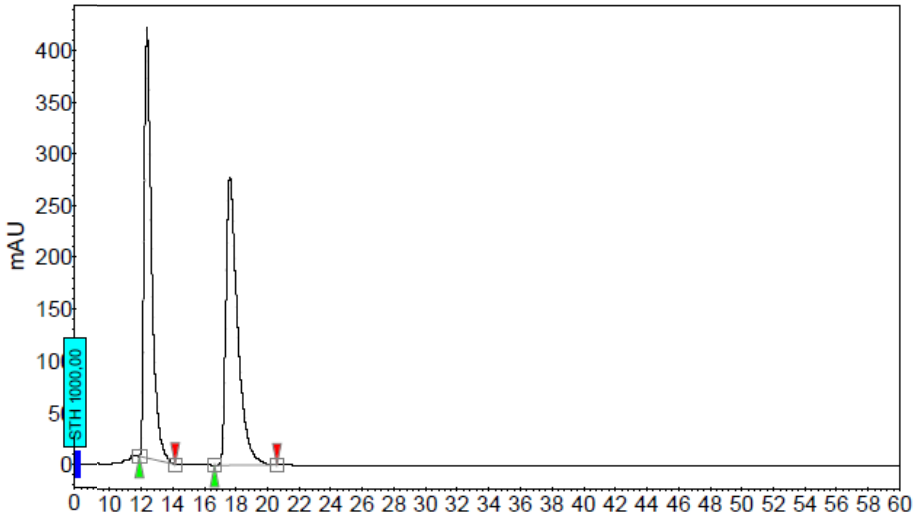
Index	Name	Time [Min]	Quantity [% Area]	Height [mAU]	Area [mAU.Min]	Area % [%]
1	UNKNOWN	37,85	49,81	554,4	706,0	49,812
2	UNKNOWN	53,44	50,19	443,5	711,3	50,188
Total			100,00	997,8	1417,3	100,000



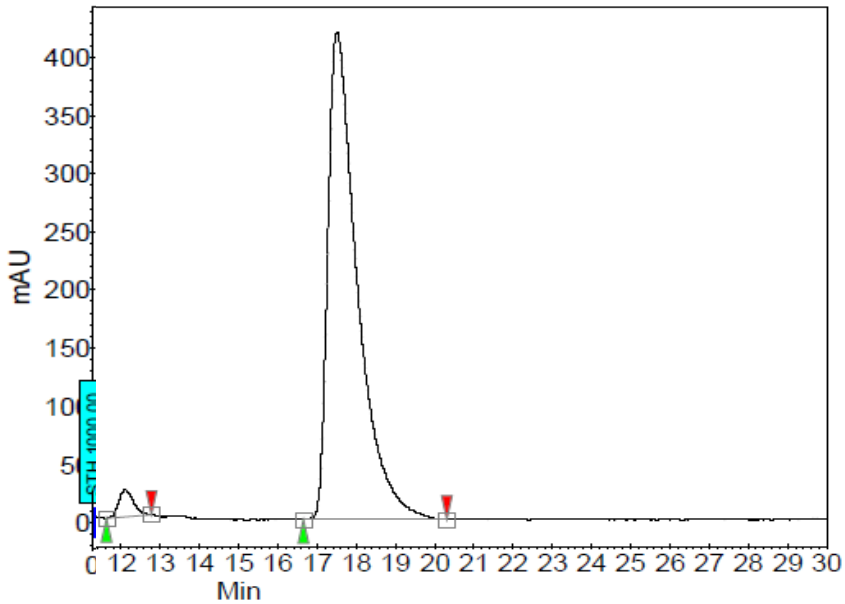
Index	Name	Time [Min]	Quantity [% Area]	Height [mAU]	Area [mAU.Min]	Area % [%]
1	UNKNOWN	37,90	96,48	697,2	1423,9	96,482
2	UNKNOWN	53,85	3,52	36,9	51,9	3,518
Total			100,00	734,0	1475,8	100,000



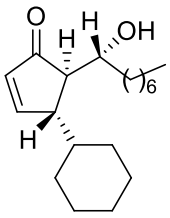
(-)-**133j**



Index	Name	Time [Min]	Quantity [% Area]	Height [mAU]	Area [mAU.Min]	Area % [%]
2	UNKNOWN	12,38	48,90	415,0	226,1	48,897
1	UNKNOWN	17,62	51,10	277,8	236,3	51,103
Total			100,00	692,7	462,5	100,000



Index	Name	Time [Min]	Quantity [% Area]	Height [mAU]	Area [mAU.Min]	Area % [%]
1	UNKNOWN	12,11	2,68	17,8	7,7	2,677
2	UNKNOWN	17,51	97,32	321,8	278,9	97,323
Total			100,00	339,6	286,6	100,000



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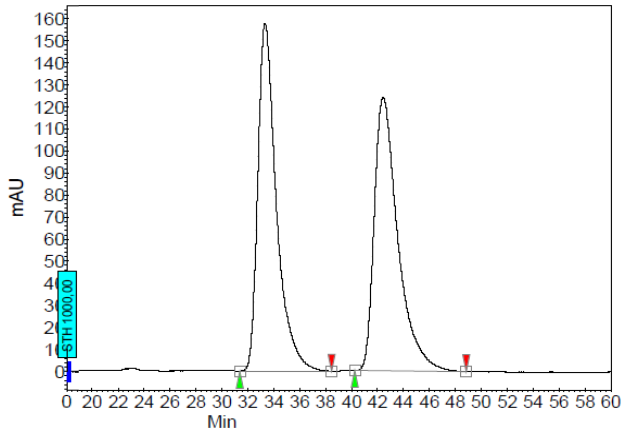
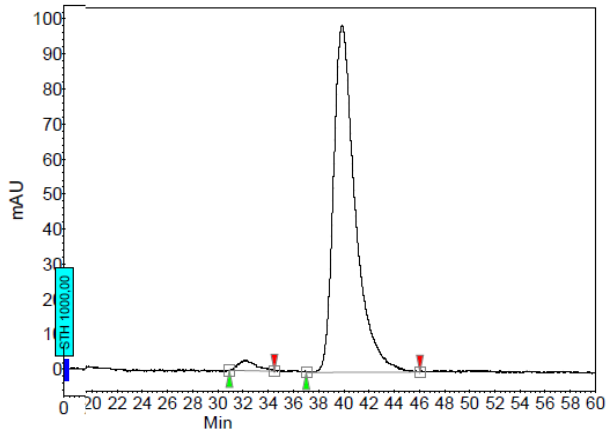
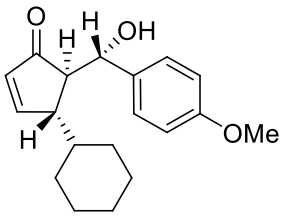


Index	Name	Time [Min]	Quantity [% Area]	Height [mAU]	Area [mAU.Min]	Area % [%]
1	UNKNOWN	33,33	50,13	149,8	249,4	50,127
2	UNKNOWN	42,44	49,87	117,7	248,1	49,873
Total			100,00	267,5	497,5	100,000



Index	Name	Time [Min]	Quantity [% Area]	Height [mAU]	Area [mAU.Min]	Area % [%]
2	UNKNOWN	32,29	2,42	3,1	5,0	2,418
1	UNKNOWN	39,86	97,58	100,9	202,2	97,582
Total			100,00	104,0	207,2	100,000



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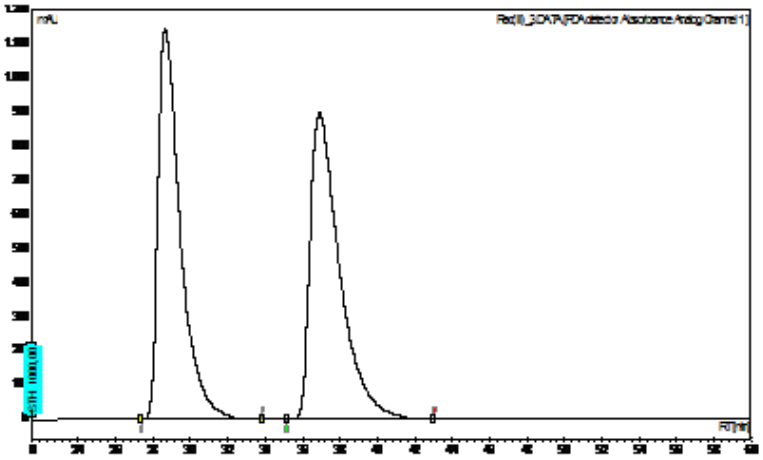
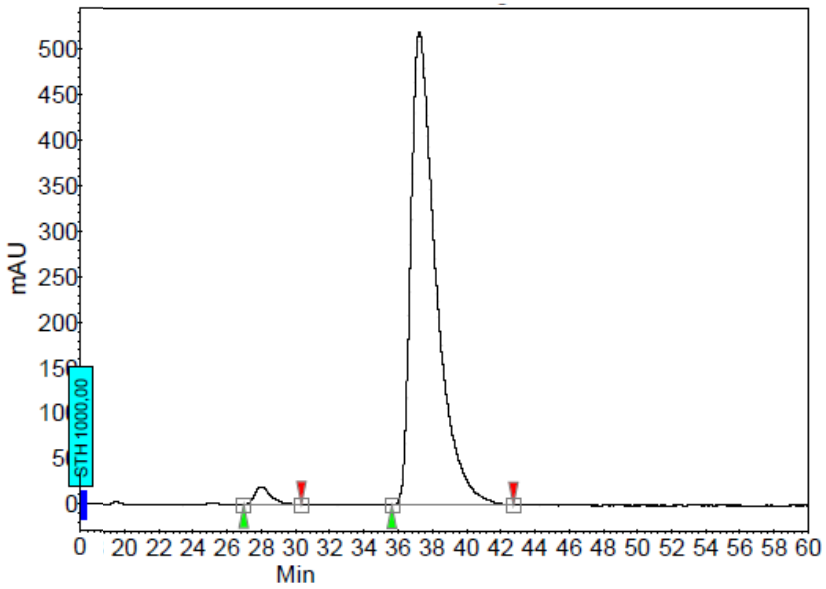
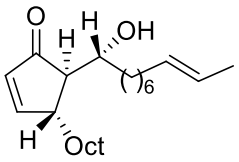


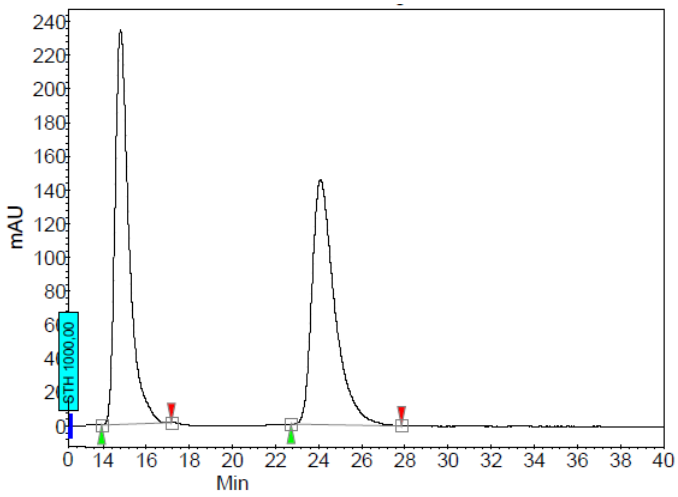
Index	Name	Time [Min]	Quantity [% Area]	Height [mAU]	Area [mAU.Min]	Area % [%]
1	UNKNOWN	28,67	49,16	1144,9	1582,4	49,165
2	UNKNOWN	36,90	50,84	898,0	1636,1	50,835
Total			100,00	2042,9	3218,5	100,000



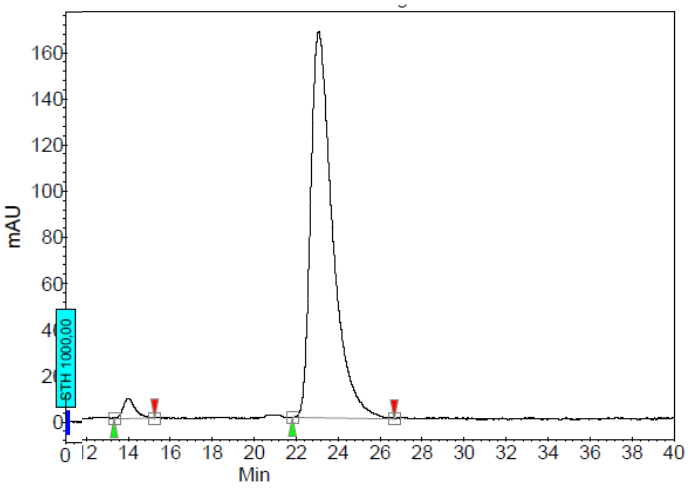
Index	Name	Time [Min]	Quantity [% Area]	Height [mAU]	Area [mAU.Min]	Area % [%]
1	UNKNOWN	27,98	2,44	19,9	22,1	2,435
2	UNKNOWN	37,25	97,56	519,7	887,2	97,565
Total			100,00	539,6	909,3	100,000



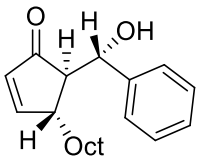
(-)-**133n**



Index	Name	Time [Min]	Quantity [% Area]	Height [mAU]	Area [mAU.Min]	Area % [%]
1	UNKNOWN	14,81	49,92	234,0	176,3	49,923
2	UNKNOWN	24,09	50,08	145,1	176,9	50,077
Total			100,00	379,1	353,2	100,000



Index	Name	Time [Min]	Quantity [% Area]	Height [mAU]	Area [mAU.Min]	Area % [%]
1	UNKNOWN	13,97	2,84	8,7	5,9	2,836
2	UNKNOWN	23,08	97,16	168,6	202,6	97,164
Total			100,00	177,2	208,5	100,000



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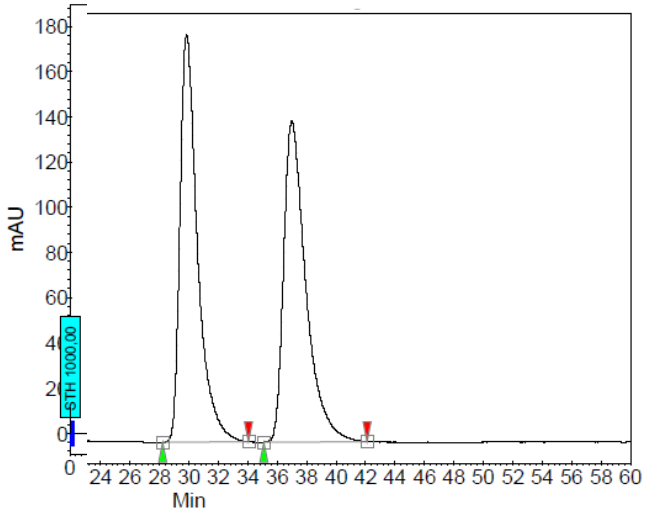
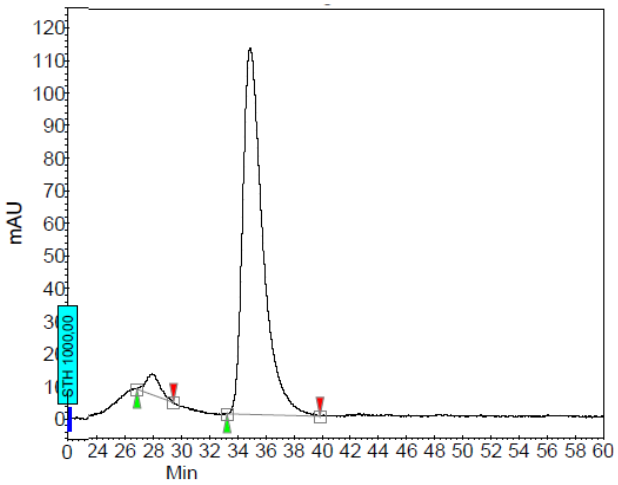


Index	Name	Time [Min]	Quantity [% Area]	Height [mAU]	Area [mAU.Min]	Area % [%]
1	UNKNOWN	29,85	50,02	180,5	247,6	50,018
2	UNKNOWN	37,00	49,98	141,9	247,4	49,982
Total			100,00	322,4	494,9	100,000



Index	Name	Time [Min]	Quantity [% Area]	Height [mAU]	Area [mAU.Min]	Area % [%]
1	UNKNOWN	28,00	3,83	6,5	7,4	3,827
2	UNKNOWN	34,90	96,17	113,2	186,0	96,173
Total			100,00	119,7	193,4	100,000

3. X-Ray structure of *epoxy*-Orientalol-F 197:

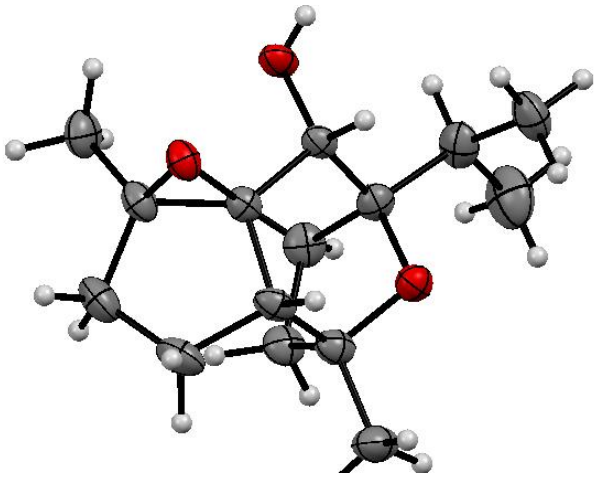


Table 1. Crystal data and structure refinement for **197**.

Identification code	l274
Empirical formula	$C_{15}H_{24}O_3$
Formula weight	252.34
Temperature/K	123.01(10)
Crystal system	orthorhombic
Space group	$P2_12_12_1$
a/Å	6.08287(12)
b/Å	9.5429(2)
c/Å	24.1276(6)
α/°	90
β/°	90
γ/°	90
Volume/Å^3	1400.56(5)

Z	4
ρ_{calc}g/cm^3	1.197
μ/mm^{-1}	0.650
F(000)	552.0
Crystal size/mm^3	0.1731 × 0.1344 × 0.1244
Radiation	CuKα (λ = 1.54184)
2Θ range for data collection/°	7.32 to 147.52
Index ranges	-7 ≤ h ≤ 6, -11 ≤ k ≤ 7, -29 ≤ l ≤ 26
Reflections collected	6079
Independent reflections	2648 [R_{int} = 0.0205, R_{sigma} = 0.0214]
Data/restraints/parameters	2648/0/166
Goodness-of-fit on F^2	1.079
Final R indexes [I>=2σ (I)]	R_1 = 0.0374, wR_2 = 0.1038
Final R indexes [all data]	R_1 = 0.0399, wR_2 = 0.1061
Largest diff. peak/hole / e Å^{-3}	0.39/-0.23
Flack parameter	0.0(2)

Table 2. Fractional Atomic Coordinates (×10^4) and Equivalent Isotropic Displacement Parameters (Å^2×10^3) for l274. U_{eq} is defined as 1/3 of of the trace of the orthogonalised U_{IJ} tensor.

Atom	***x***	***y***	***z***	**U(eq)**
O1	-278.0(19)	4268.7(12)	807.3(5)	29.3(3)
O2	2033.9(19)	3132.9(12)	2133.9(5)	30.4(3)
O3	259.0(18)	5948.4(12)	2393.8(5)	28.6(3)
C1	1217(3)	3494.9(17)	1154.6(7)	28.0(4)
C2	3507(3)	4114.7(19)	1022.5(7)	33.0(5)

C3	2985(3)	5545.8(19)	756.5(7)	33.6(5)
C4	474(3)	5697.3(18)	821.1(7)	29.4(4)
C5	-212(3)	6302.8(16)	1385.1(7)	28.0(4)
C6	771(2)	5410.1(16)	1842.7(6)	24.3(4)
C7	629(3)	3841.8(16)	1761.8(6)	24.4(4)
C8	927(3)	1922.0(19)	1030.4(8)	37.1(5)
C9	-1454(3)	1454.4(19)	1107.8(9)	43.4(6)
C10	1689(5)	1511(3)	458(1)	60.1(8)
C11	-615(3)	6464(2)	343.1(8)	41.2(5)
C12	570(4)	7811.2(18)	1520.0(8)	38.9(5)
C13	2556(3)	7680.8(19)	1907.6(8)	39.0(5)
C14	2441(3)	6220.6(17)	2150.5(7)	30.0(4)
C15	4359(3)	5689(2)	2473.9(8)	37.9(5)

Table 3. Anisotropic Displacement Parameters ($Å^2 \times 10^3$) for l274. The Anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U_{11}+2hka^*b^*U_{12}+\ldots]$.

Atom	**U_{11}**	**U_{22}**	**U_{33}**	**U_{23}**	**U_{13}**	**U_{12}**
O1	25.5(5)	29.8(6)	32.5(6)	2.1(4)	-2.3(4)	1.6(5)
O2	25.4(6)	25.6(5)	40.2(6)	10.0(5)	-5.9(5)	0.2(5)
O3	23.4(5)	28.0(6)	34.4(6)	-3.4(4)	4.5(4)	-3.1(5)
C1	23.1(7)	27.6(8)	33.2(8)	0.5(6)	-2.1(6)	4.2(6)
C2	23.1(7)	37.2(9)	38.6(8)	-2.6(7)	4.3(6)	5.0(7)
C3	25.5(8)	39.1(9)	36.1(8)	3.6(7)	5.4(6)	-1.4(7)
C4	23.9(7)	29.9(8)	34.4(8)	6.9(6)	1.4(6)	0.0(7)
C5	23.0(7)	22.9(7)	38.0(8)	7.3(6)	3.0(6)	3.9(6)
C6	19.8(7)	23.6(7)	29.5(7)	1.1(6)	2.5(6)	1.3(6)
C7	19.6(7)	21.2(7)	32.4(7)	3.4(6)	-1.3(6)	1.9(6)

C8	35.6(9)	29.5(8)	46.2(10)	-8.0(7)	-6.0(8)	8.3(7)
C9	43.1(10)	25.2(8)	61.9(12)	-6.6(8)	-2.9(9)	-2.8(8)
C10	65.4(14)	54.6(13)	60.4(13)	-24.0(11)	12.3(12)	-2.5(12)
C11	38.1(9)	44.3(10)	41.3(9)	16.1(8)	-4.5(8)	-2.4(9)
C12	45.5(10)	23.1(8)	48.1(10)	5.4(7)	8.5(9)	1.3(8)
C13	39.8(9)	27.7(8)	49.6(10)	-1.9(7)	8.8(8)	-9.1(8)
C14	24.7(7)	27.2(8)	38.1(8)	-1.5(6)	5.7(7)	-4.4(6)
C15	23.5(8)	43.7(10)	46.4(10)	-2.3(8)	-3.0(7)	-5.8(7)

Table 4. Bond Lengths for l274.

Atom	**Atom**	**Length/Å**	**Atom**	**Atom**	**Length/Å**
O1	C1	1.440(2)	C4	C11	1.518(3)
O1	C4	1.438(2)	C5	C6	1.517(2)
O2	C7	1.412(2)	C5	C12	1.551(2)
O3	C6	1.4591(19)	C6	C7	1.512(2)
O3	C14	1.474(2)	C6	C14	1.477(2)
C1	C2	1.547(3)	C8	C9	1.527(3)
C1	C7	1.544(2)	C8	C10	1.509(3)
C1	C8	1.541(2)	C12	C13	1.533(3)
C2	C3	1.542(3)	C13	C14	1.513(2)
C3	C4	1.542(3)	C14	C15	1.492(3)
C4	C5	1.536(2)			

Table 5 Bond Angles for l274.

Atom	**Atom**	**Atom**	**Angle/˚**	**Atom**	**Atom**	**Atom**	**Angle/˚**
C1	O1	C4	105.76(12)	O3	C6	C7	117.00(12)

C6	O3	C14	60.46(9)	O3	C6	C14	60.28(10)
O1	C1	C2	104.64(13)	C5	C6	C7	116.06(12)
O1	C1	C7	107.21(13)	C5	C6	C14	110.05(13)
O1	C1	C8	108.30(14)	C7	C6	C14	128.51(13)
C2	C1	C7	108.80(14)	O2	C7	C1	111.12(13)
C2	C1	C8	115.83(15)	O2	C7	C6	110.95(12)
C7	C1	C8	111.53(14)	C1	C7	C6	108.76(12)
C1	C2	C3	103.83(14)	C1	C8	C9	111.69(15)
C2	C3	C4	104.18(14)	C1	C8	C10	113.34(17)
O1	C4	C3	102.93(13)	C9	C8	C10	109.11(18)
O1	C4	C5	106.90(13)	C5	C12	C13	107.13(15)
O1	C4	C11	107.49(14)	C12	C13	C14	105.94(15)
C3	C4	C5	113.19(14)	O3	C14	C6	59.26(10)
C3	C4	C11	113.62(14)	O3	C14	C13	110.98(14)
C5	C4	C11	111.91(14)	O3	C14	C15	115.83(14)
C4	C5	C6	109.05(13)	C6	C14	C13	108.62(14)
C4	C5	C12	116.86(15)	C6	C14	C15	128.50(15)
C6	C5	C12	104.33(14)	C13	C14	C15	118.64(15)
O3	C6	C5	112.42(12)				

Table 6. Hydrogen Bonds for l274.

D	**H**	**A**	**d(D-H)/Å**	**d(H-A)/Å**	**d(D-A)/Å**	**D-H-A/°**
C2	H2A	O2	0.9900	2.5700	2.979(2)	105.00
O2	H2O	O3[1]	0.76(3)	1.99(3)	2.7549(16)	177(3)
C15	H15C	O2[2]	0.9800	2.3900	3.339(2)	164.00

[1]-X,-1/2+Y,1/2-Z; [2]1-X,1/2+Y,1/2-Z

Table 7. Torsion Angles for l274.

A	B	C	D	Angle/˚	A	B	C	D	Angle/˚
O1	C1	C2	C3	19.31(16)	C5	C6	C7	O2	165.72(13)
O1	C1	C7	O2	-179.50(12)	C5	C6	C7	C1	43.20(18)
O1	C1	C7	C6	-57.09(17)	C5	C6	C14	O3	105.01(13)
O1	C1	C8	C9	-55.95(19)	C5	C6	C14	C13	1.17(18)
O1	C1	C8	C10	67.8(2)	C5	C6	C14	C15	-154.93(17)
O1	C4	C5	C6	57.59(17)	C5	C12	C13	C14	-19.1(2)
O1	C4	C5	C12	175.52(15)	C6	O3	C14	C13	99.77(15)
O3	C6	C7	O2	-57.76(17)	C6	O3	C14	C15	-121.12(16)
O3	C6	C7	C1	179.72(12)	C6	C5	C12	C13	19.46(19)
O3	C6	C14	C13	-103.84(15)	C7	C1	C2	C3	-95.01(15)
O3	C6	C14	C15	100.06(19)	C7	C1	C8	C9	61.8(2)
C1	O1	C4	C3	43.94(15)	C7	C1	C8	C10	-174.49(18)
C1	O1	C4	C5	-75.54(16)	C7	C6	C14	O3	-102.35(17)
C1	O1	C4	C11	164.16(14)	C7	C6	C14	C13	153.81(15)
C1	C2	C3	C4	6.38(17)	C7	C6	C14	C15	-2.3(3)
C2	C1	C7	O2	-66.87(17)	C8	C1	C2	C3	138.45(15)
C2	C1	C7	C6	55.55(17)	C8	C1	C7	O2	62.10(18)
C2	C1	C8	C9	-173.07(15)	C8	C1	C7	C6	-175.48(14)
C2	C1	C8	C10	-49.3(2)	C11	C4	C5	C6	175.02(14)
C2	C3	C4	O1	-29.91(16)	C11	C4	C5	C12	-67.1(2)
C2	C3	C4	C5	85.10(16)	C12	C5	C6	O3	52.35(17)
C2	C3	C4	C11	-145.81(15)	C12	C5	C6	C7	-169.19(14)
C3	C4	C5	C6	-55.03(18)	C12	C5	C6	C14	-12.79(18)
C3	C4	C5	C12	62.9(2)	C12	C13	C14	O3	-52.17(18)
C4	O1	C1	C2	-40.05(16)	C12	C13	C14	C6	11.18(19)
C4	O1	C1	C7	75.39(15)	C12	C13	C14	C15	170.00(16)

C4	O1	C1	C8	-164.15(13)	C14	O3	C6	C5	-101.05(14)
C4	C5	C6	O3	177.91(12)	C14	O3	C6	C7	120.91(15)
C4	C5	C6	C7	-43.63(18)	C14	C6	C7	O2	14.5(2)
C4	C5	C6	C14	112.77(15)	C14	C6	C7	C1	-108.07(18)
C4	C5	C12	C13	-101.01(18)					

Table 8. Hydrogen Atom Coordinates (Å×10^4) and Isotropic Displacement Parameters (Å^2×10^3) for l274.

Atom	***x***	***y***	***z***	**U(eq)**
H2A	4387	4232	1365	40
H2B	4323	3506	762	40
H2O	1430(40)	2530(30)	2275(9)	37
H3A	3413	5557	361	40
H3B	3764	6311	952	40
H5	-1851	6268	1415	34
H7	-917	3537	1834	29
H8	1843	1392	1303	44
H9A	-2403	1976	853	52
H9B	-1913	1638	1490	52
H9C	-1574	449	1030	52
H10A	3245	1754	415	72
H10B	818	2014	180	72
H10C	1499	499	408	72
H11A	-342	5953	-3	49
H11B	-4	7411	314	49
H11C	-2202	6521	409	49
H12A	991	8307	1176	47

H12B	-622	8345	1703	47
H13A	3942	7810	1699	47
H13B	2484	8395	2205	47
H15A	5329	5151	2229	45
H15B	3836	5084	2775	45
H15C	5172	6482	2630	45

Experimental

Single crystals of $C_{15}H_{24}O_3$ [I274] were []. A suitable crystal was selected and [] on a SuperNova, Single source at offset), Atlas diffractometer. The crystal was kept at 123.01(10) K during data collection. Using Olex2 [1], the structure was solved with the [2] structure solution program using and refined with the [3] refinement package using minimisation.

1. Dolomanov, O.V., Bourhis, L.J., Gildea, R.J, Howard, J.A.K. & Puschmann, H. (2009), J. Appl. Cryst. 42, 339-341.
2.
3.

Crystal structure determination of [I274]

Crystal Data for $C_{15}H_{24}O_3$ (*M* =252.34 g/mol): orthorhombic, space group $P2_12_12_1$ (no. 19), *a* = 6.08287(12) Å, *b* = 9.5429(2) Å, *c* = 24.1276(6) Å, *V* = 1400.56(5) Å^3, *Z* = 4, *T* = 123.01(10) K, μ(CuKα) = 0.650 mm^{-1}, *Dcalc* = 1.197 g/cm^3, 6079 reflections measured (7.32° ≤ 2Θ ≤ 147.52°), 2648 unique (R_{int} = 0.0205, R_{sigma} = 0.0214) which were used in all calculations. The final R_1 was 0.0374 (I>2σ(I)) and wR_2 was 0.1061 (all data).

Refinement model description

Number of restraints - 0, number of constraints - ?.

Details:

1. Others
Fixed Uiso: H2A(0.04) H2B(0.04) H2O(0.037) H3A(0.04) H3B(0.04) H5(0.034)

H7(0.029) H8(0.044) H9A(0.052) H9B(0.052) H9C(0.052) H10A(0.072) H10B(0.072) H10C(0.072) H11A(0.049) H11B(0.049) H11C(0.049) H12A(0.047) H12B(0.047) H13A(0.047) H13B(0.047) H15A(0.045) H15B(0.045) H15C(0.045)

Fixed X: H2A(0.4387) H2B(0.4323) H3A(0.3413) H3B(0.3764) H5(-0.1851) H7(-0.0917) H8(0.1843) H9A(-0.2403) H9B(-0.1913) H9C(-0.1574) H10A(0.3245) H10B(0.0818) H10C(0.1499) H11A(-0.0342) H11B(-0.0004) H11C(-0.2202) H12A(0.0991) H12B(-0.0622) H13A(0.3942) H13B(0.2484) H15A(0.5329) H15B(0.3836) H15C(0.5172)

Fixed Y: H2A(0.4232) H2B(0.3506) H3A(0.5557) H3B(0.6311) H5(0.6268) H7(0.3537) H8(0.1392) H9A(0.1976) H9B(0.1638) H9C(0.0449) H10A(0.1754) H10B(0.2014) H10C(0.0499) H11A(0.5953) H11B(0.7411) H11C(0.6521) H12A(0.8307) H12B(0.8345) H13A(0.781) H13B(0.8395) H15A(0.5151) H15B(0.5084) H15C(0.6482)

Fixed Z: H2A(0.1365) H2B(0.0762) H3A(0.0361) H3B(0.0952) H5(0.1415) H7(0.1834) H8(0.1303) H9A(0.0853) H9B(0.149) H9C(0.103) H10A(0.0415) H10B(0.018) H10C(0.0408) H11A(-0.0003) H11B(0.0314) H11C(0.0409) H12A(0.1176) H12B(0.1703) H13A(0.1699) H13B(0.2205) H15A(0.2229) H15B(0.2775) H15C(0.263)

This report has been created with Olex2, compiled on 2014.06.27 svn.r2953 for OlexSys. Please let us know if there are any errors or if you would like to have additional features.

4. Curriculum Vitae

Personal data:

Name:	Nanaji Arisetti
Date of birth:	01.07.1987 in Andhra Pradesh, India
Marital status:	Unmarried
Nationality:	Indian

Education:

2011-2015	**PhD thesis** at the University of Regensburg under supervision Of Prof. Dr. Oliver Reiser, as a fellow of DAAD
2009-2011	**Junior Research Fellow** (JRF) at the Indian Institute of Chemical Technology (IICT), Hyderabad : Organic transformations by using nano-sized Metal oxides (Baeyer-Villiger oxidation Reactions)
2007-2009	**Master of Science** at the Andhra University, Visakhapatnam, India Bioinorganic Chemistry
2004-2007	**Bachelor of Science** at the Andhra University,Visakhapatnam, India Chemistry, Botany, Zoology (CBZ)

Languages:

Telugu (Native)

English

German

Professional references:

Prof. Dr. Oliver Reiser

University of Regensburg

Institute of Organic Chemistry

Universitätsstr 31

D-93053 Regensburg

Germany

Phone: +49-941-9434631

E-mail: oliver.reiser@chemie.uni-regensburg.de

5. List of Publications:

1. Nanaji Arisetti, Oliver Reiser, Traceless stereoinduction for the enantiopure synthesis of substituted-2-cyclopentenones. *Org. Lett*. **2015**, *17*, 94-97.

2. A novel, economic and eco friendly process for bulk synthesis of single phase titanium dioxide nanoparticles and its biocompatibility evaluation. Devi Gangadharam Sarala, Prakasham Reddy shetty, Kennadey Packiyanathan Kavin, Raveendranath Kancham, **Nanaji Arisetti**. *Indian Pat. Appl*. (2011) IN 2011DEO2768 A 20130322.

3. Nanaji Arisetti, Oliver Reiser, Total synthesis of (+)-Orientalol-F and formal synthesis of Englerin-A. *Manuscript Submitted*.

6. Poster Presentation and Scientific Meetings:

1 Participated in **"Indian Science Congress (ISCA)"** held at, Andhra University, India on 1st to 7th January 2008.

2 National Symposium on **"Current Development in Organic Chemistry"** held at Department of Chemistry (Organic Divison) Andhra University, India on 12th & 14th Dec- 2008.

3 Participated in **"International Symposium on Analytical Chemistry"** at Andhra University, India during November 2-7, 2008.

4 Participated in **"INDO-NIMS Workshop on Advanced Materials"** held at Indian Institute of Chemical Technology (IICT, India) Dec-22-23rd, 2009.

5 Participated in **12th CRSI National symposium** held at IICT organized by Chemical Research Society of India (CRSI) during February 2-5, 2010.

6 Participated in **Heidelberg Forum of Molecular Catalysis** (HFMC), held at Heidelberg University, Germany 2013 (Poster presentation).

7 Participated in **GDCh-Wissenschaftsforum Chemie**, held at Darmstadt University, Germany, Oct-01-04, 2013 (Poster presentation).

8 Participated in **4th INDIGO PhD research conference**, held at University of Regensburg, Germany Oct 6-10, 2013.

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Declaration

Herewith I declare that I have made this existing work single-handedly. I have only used the stated utilities.

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Nanaji Arisetti