Synthesis of Allylic Alcohols and their Application in Natural Products Synthesis

A Thesis
Submitted for the degree of
DOCTOR OF PHILOSOPHY
in Chemistry

By

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April 2014

To

My Grand Parents

Ram Reddy & Sheshamma

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STATEMENT

I hereby declare that the matter embodied in the thesis is the result of investigation carried out by me in the Dr. Reddy's Institute of Life Sciences, University of Hyderabad Campus, Hyderabad, India, under the supervision of **Prof. Javed Iqbal**.

In keeping with the general practice of reporting scientific observations, due acknowledgements have been made wherever the work described is based on the findings of other investigators. Any omission, which might have occurred by oversight or error, is regretted.

Narendar Reddy Gade

Dr. Reddy's Institute of Life Sciences
University of Hyderabad
April 2014

CERTIFICATE

This is to certify that the thesis entitled ***"Synthesis of Allylic Alcohols and their Application in Natural Products Synthesis"*** being submitted by ***Mr. Narendar Reddy Gade*** to University of Hyderabad for the award of Doctor of Philosophy in Chemistry has been carried out by him under my supervision and the same has not been submitted elsewhere for a degree. I am satisfied with that the thesis has reached to the standard fulfilling the requirements of the regulations relating to the nature of the degree.

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Narendar Reddy Gade

Dr. Reddy’s Institute of Life Scinecs
April 2014

Synopsis

This thesis entitled "Synthesis of Allylic Alcohols and their Application in Natural Products Synthesis" comprises five chapters.

Chapter 1

Review on the Synthesis of Allylic Alcohols or their Derivatives using Atom Economic Reactions

This chapter is a brief literature survey on synthesis of allylic alcohols or derivatives using atom economic reactions with a representative example on their application in natural product synthesis.

Chapter 2

A Stereoselective Formal Synthesis of Migrastatin Macrolide Core using Intramolecular Asymmetric Allylic C-H Oxidation.

Migrastatin **1** (Fig. 1) is a glutarimide side chain containing 14-member macrocylic natural product, isolated from a cultured broth of *Streptomyces* sp.Mk 929-43F$_1$ by Imoto and co-workers. Migrastatin analogues like macrolide **2** are even more potent than migrastatin and they bind to one of the actin binding sites on fascin to inhibit its activity consequently suppressing metastasis.

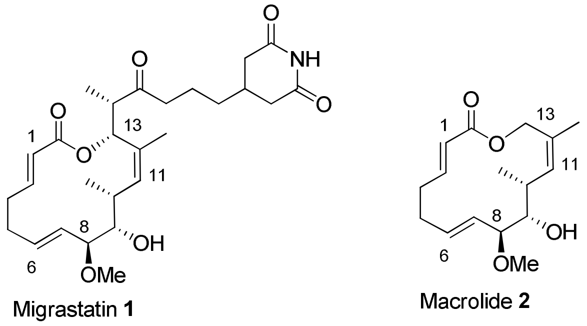
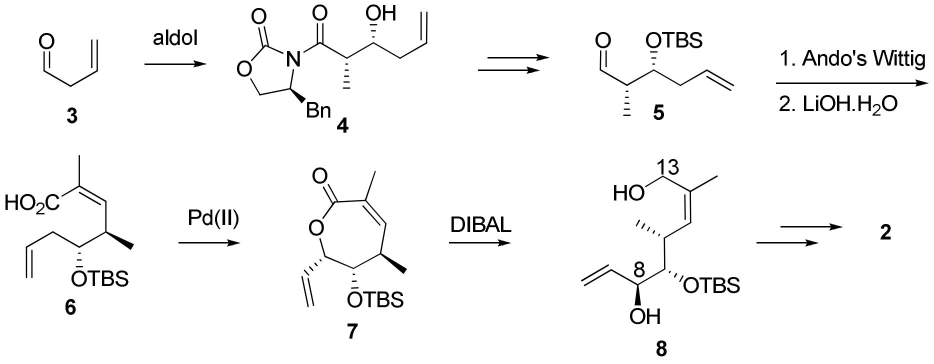


Figure 1. Migrastatin and macrolide.

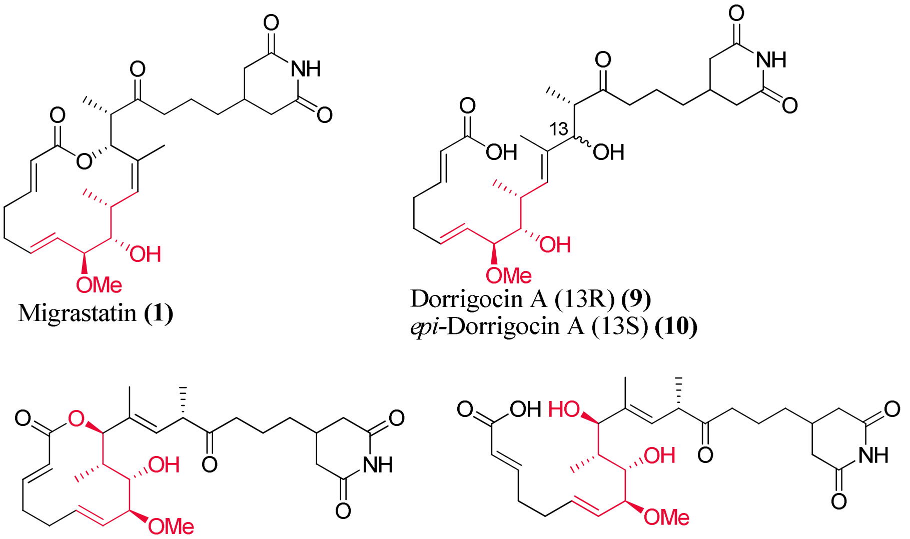
In our approach for the synthesis of macrolide core **2** of migrastatin, major focus is being given on generating the three contagious chiral centers (C8, C9, C10) and *Z*-olefin (C11- C12) in the key allylic alcohol intermediate **8**. Initially C9, C10 centers were built using aldol reaction, (C11-12) *Z*-olefin using Ando's Wittig protocol and finally C-8 chiral center was installed *via* a Pd(II) catalyzed stereoselective allylic C-H oxidation (Scheme 1).



Scheme 1

Chapter 3

Synthetic Studies towards a Unified Strategy for All Family Members of Migrastatin



Migrastatin **(1)**

Dorrigocin A (13R) **(9)**
epi-Dorrigocin A (13S) **(10)**

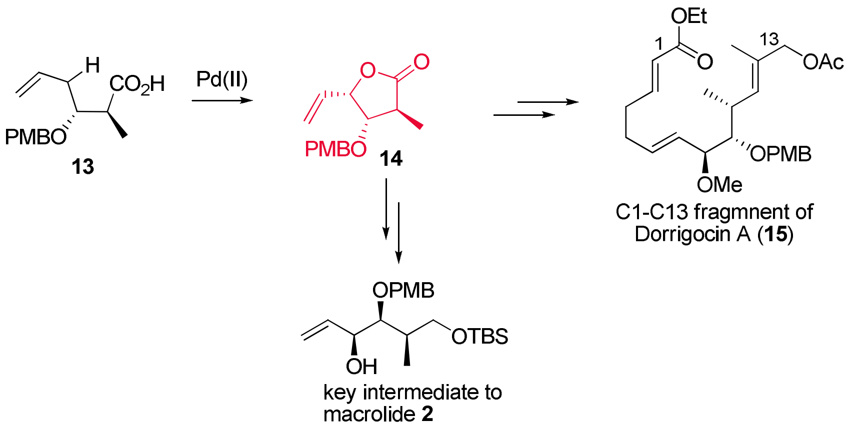
Isomigrastatin **(11)**

Dorrigocin B **(12)**

Figure 2. Migrastatin family members.

Dorrigocin A, epi-dorrigocin A, Isomigrastatin and Dorrigocin B are the members of migrastatin family of natural products (Fig. 2). All these compounds are potential cancer cell migration inhibitors. In this chapter we have demonstrated the synthesis of chiral trisubstituted butyrolactone **14** from **13** using Pd(II)-catalyzed asymmetric C-H oxidation. A common synthetic protocol was developed to convert the butyrolactone

14 to the key building blocks of Migrastatin, Isomigrastatin, and C1-C13 fragment of Dorrigocin A (scheme 2).



Scheme 2

Chapter 4

Design and Synthesis of Hybrid Molecules based on the Fragments Derived from Amphidinolide T1, Rhizoxin D and Migrastatin family

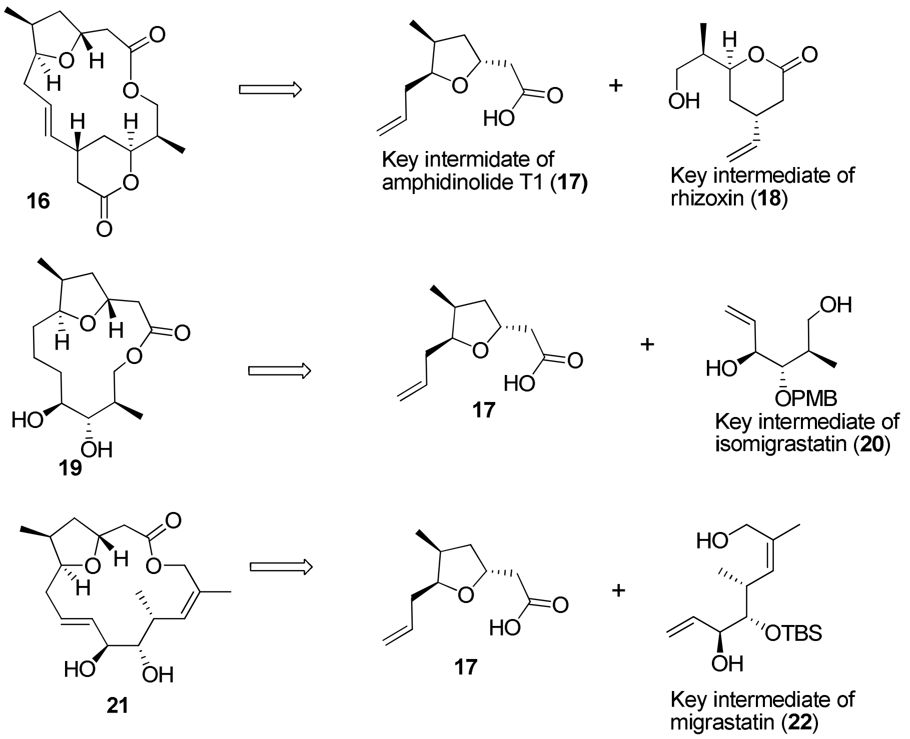
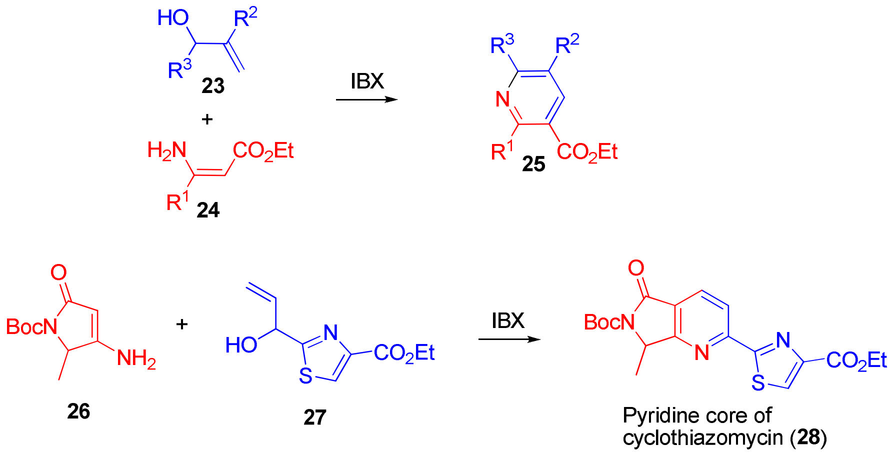


Figure 3. Designed hybrid molecules and their retrosynthesis

This chapter decribes our hypothesis, design and synthesis of hybrid molecules **16**, **19** and **21** as potential anticancer agents. The key fragments **20** and **22** synthesised earlier (chapter 2& 3) for accessing cyclic core of migrastatin and isomigrastatin were used to prepare the desinged hybrid molecules. The other key intermediate partner **17** and **18** for the hybrid molecules of interest were synthesized using known protocols developed earlier in our research group. A Steglich esterification followed by ring closing metathesis are the key reactions used in stitching the key fragments to access the hybrid molecules (Fig. 3).

Chapter 5

IBX Mediated Oxidative Annulation of Allylic Alcohols with Enamines: A Versatile Synthesis of Functionalized Pyridines and its Application to the Pyridine Core of Cyclothiazomycin



Scheme 3

This chapter describes the new IBX mediated domino oxidative annulation reaction of allylic alcohols **23** and enamines **24** to functionalized pyridines **25** and its application in the synthesis of pyridine core of cyclothiazomycin **28** (scheme 3)

List of Abbreviations

°C	degrees Celsius
^{13}C NMR	carbon- 13 nuclear magnetic resonance spectroscopy
^{1}H NMR	hydrogen- 1 nuclear magnetic resonance spectroscopy
Ac	acetyl
Ar	aryl
aq	aqueous
Bn	benzyl
Boc	tert-butoxycarbonyl
BQ	1,4-benzoquinone
BRSM	based on recovered starting material
Bu	butyl
Bz	benzoyl
Calcd	calculated
cm^{-1}	reciprocal centimeter
CAN	cerium(IV) ammonium nitrate
COSY	correlation spectroscopy
CSA	camphorsulfonic acid
d	doublet
d.r. (dr)	diastereomeric ratio
DBU	1,8-diazabicyclo[5.4.0-undec-7ene
DCE	1,2-dichloroethane
DCM	dichloromethane
DIBAL	diisobutylaluminum hydride
DIPEA	diisopropylethylamine
DMAP	4-(dimethylamino)pyridine

DMF	N,N-dimethylformamide
DMP	Dess-Martin periodinane
DMSO	dimethylsulfoxide
DTBMP	2,6-di-*tert*-butyl-4-methylpyridine
Et	ethyl
HRMS	high-resolution mass spectrometry
Hz	hertz
IBX	*o*-iodoxybenzoic acid
IC_{50}	inhibitory concentration 50%
g	gram
Imid	imidazole
IR	infrared spectroscopy
J	coupling constant in Hertz
m	multiplet
mg	milligram
M.S.	mass spectrometry
Me	methyl
mL	milliliter
mmol	millimole
NOE	Nuclear Overhauser Effect
Ph	phenyl
PMB	*p*-methoxybenzyl
Py	pyridine
RCM	Ring closing metathesis
Rf	retention factor
rt	room temperature
s	singlet

t	triptet
TBAF	tetra-*n*-butylammonium fluoride
TBS	*tert*-butyl-dimethyl silyl
TEA	triethylamine
THF	tetrahydrofuran
TMS	trimethyl silyl
δ	chemical shift in parts per million

CHAPTER 1

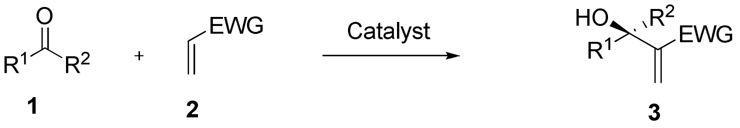
REVIEW ON THE SYNTHESIS OF ALLYLIC ALCOHOLS OR THEIR DERIVATIVES USING ATOM ECONOMIC REACTIONS

1.1. Introduction

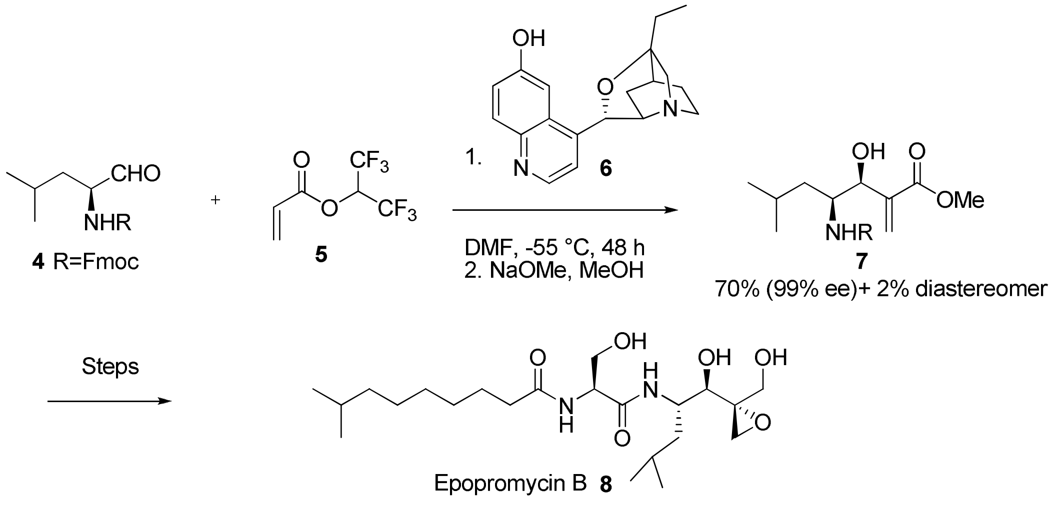
Allylic alcohols are important and versatile building blocks for organic synthesis.[1] There are several methods available for synthesizing allylic alcohols. However, very few methods afford these compounds in an atom-economical fashion. This chapter reviews the atom-economic reactions used thus far, for the synthesis of asymmetric allylic alcohols and/or their derivatives involved in natural product synthesis with a representative example for each one.

1.2. Morita-Baylis-Hillmann reaction

The Morita–Baylis–Hillman (MBH) reaction is one of the powerful atom-economic C-C bond-forming reactions.[2] This process involves coupling of an acceptor activated alkene **2** with a carbonyl electrophile **1** catalyzed mostly by tertiary amines or phosphines[3] Aldehydes and ketones have been widely used as electrophiles, thus allowing the formation of secondary and tertiary allylic alcohols **3** respectively (Scheme 1.1). Since all MBH reactions of carbonyl compounds generate allylic alcohols, it can be considered as a general method for their synthesis.



Scheme 1.1.

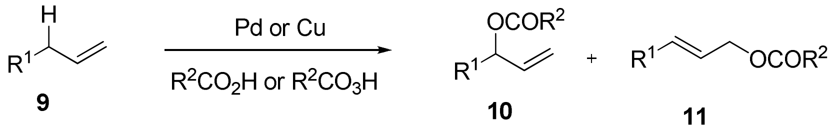


Scheme 1.2

S. Hatekayama and co-workers developed a highly enantio and stereo controlled route to **7,** the key precursor of the novel plant cell inhibitor epopromycin B **8**, by Baylis-Hillman reaction of N-Fmoc leucinal **4** catalyzed by a cinchona alkaloid **6** (Scheme 1.2).[4]

1.3. Allylic C-H oxidation reactions

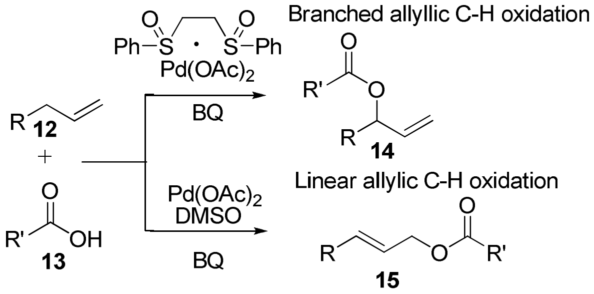
Allylic C-H Oxidation is a very attractive approach for accessing allylic alcohol derivatives from simple alkenes as no pre activation of the substrate would be required for the process. Simple alkenes **9** can be transformed to the corresponding allylic building blocks **10** or **11** in a single step (Scheme 1.3). Allylic C-H oxidation process is most economic when compared to classical allylic substitution reactions. Most of these processes are catalyzed either by palladium or copper.



Scheme 1.3

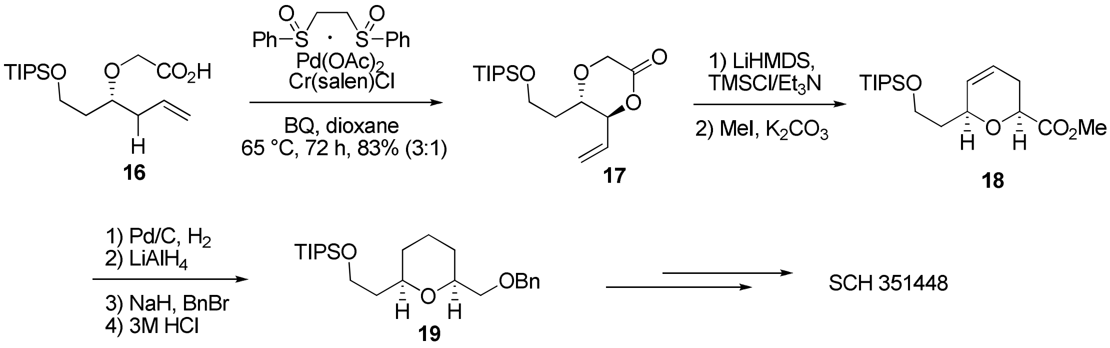
1.3.1. Palladium catalyzed allylic C-H oxidation[5]

White group has identified the appropriate conditions for preparing both branched allylic acetates and linear allylic acetates from terminal alkene **12** and carboxylic acid **13**. Linear (E)-allylic acetates **15** can be obtained using $Pd(OAc)_2$/DMSO/BQ (benzoquinone), whereas bis-sulfoxide/$Pd(OAc)_2$/BQ yields the branched allylic acetates **14** (Scheme 1.4).[6]



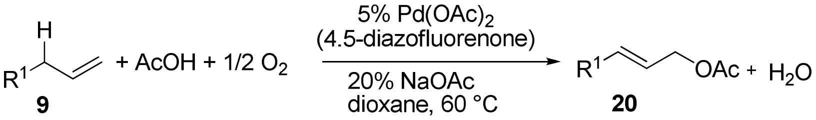
Scheme 1.4

Intramolecular variant of this reaction is applied in macrocyclization, also used in total synthesis of 6-deoxy erythronolide B.[7] An asymmetric version of both intermolecular and intramolecular reaction has also been developed by the same group using chiral Lewis acid promoters.[8] An intramolecular variant of this asymmetric reaction was also applied in the preparation of key intermediate **19** for the synthesis of SCH 351448 (Scheme 1.5).[8b]



Scheme 1.5

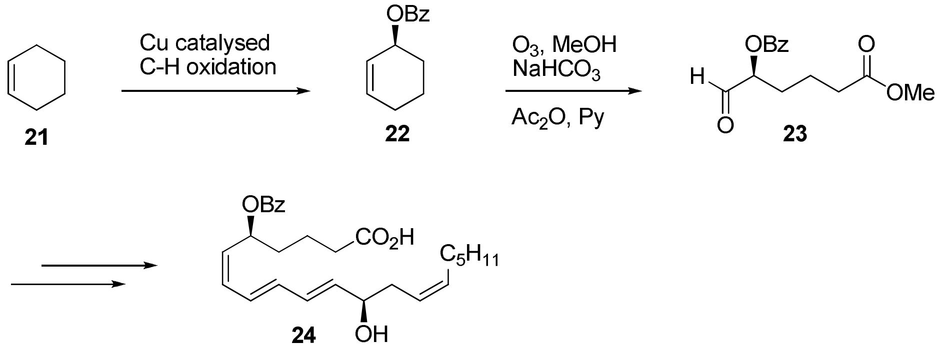
Even though allylic C-H oxidation has been an area with growing research interest in the recent past, these reactions are limited by the requirement of excess oxidant. However, S. S. Stahl *et al.* demonstrated the synthesis of linear allyl acetates using O_2 as the stoichiometric oxidant in Pd-catalyzed allylic C-H acetoxylation. Use of 4,5-diazafluorenone as an ancillary ligand for $Pd(OAc)_2$ enables the conversion of terminal alkenes to linear allylic acetoxylation products **20** in good yields and selectivity under 1 atm O_2 (Scheme 1.6).[5g]



Scheme 1.6

1.3.2. Copper catalyzed reactions (Kharasch–Sosnovsky reaction)

Allylic C-H oxidation using copper and cobalt with per esters were reported in late 1950s by Kharasch and Sosnovsky.[9] Some of the recent developments in the asymmetric allylic C-H oxidation of alkenes were reported by Pfaltz,[10] Andrus,[11] Singh,[12] Katsuki,[13] and Kim[14] groups but satisfactory enantiomeric excess was reported to be obtained only in the case of symmetric cyclic alkenes. Although this methodology was not directly used in total synthesis, it was applied in the synthesis of a formal intermediate **22** for the synthesis of leukotriene B4 (Scheme 1.7).[15]

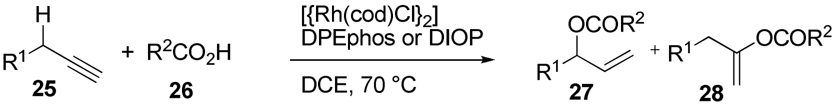


Scheme 1.7

1.4. Addition of O-nucleophiles to π systems

1.4.1. Redox-neutral coupling of alkynes

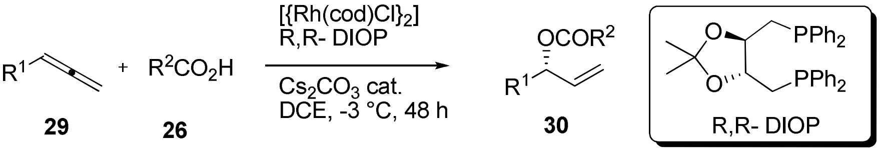
Breit and co-workers developed a remarkable methodology to synthesize branched allylic ester **27** starting from alkynes **25** and carboxylic acids **26**. Reaction employed a rhodium(I)/DPEphos catalyst and proceeds *via* a redox-neutral propargylic C-H activation (Scheme 1.8). An asymmetric version of this reaction also has been developed by the same group.[16]



Scheme 1.8

1.4.2. Enantioselective coupling reaction with allenes

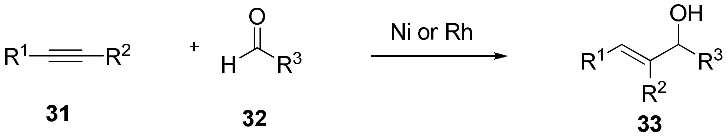
Breit and co-workers also applied the same conditions on allenes **29** to get branched allyl acetates **30** (Scheme 1.9).[17]



Scheme 1.9

1.5. Reductive coupling reactions

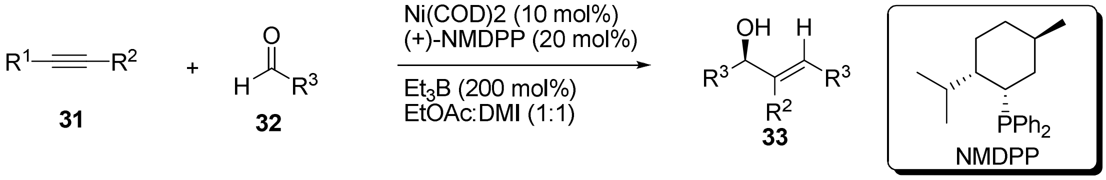
Allylic alcohols **33** can be accessed either by reductive coupling or alkylative reductive coupling reactions of alkynes **31** and aldehydes **32** (Scheme 1.10). After the pioneering work of Ojima *et al.*,[18] catalytic reductive coupling reactions using nickel and rhodium based catalysts have drawn considerable interest.



Scheme 1.10

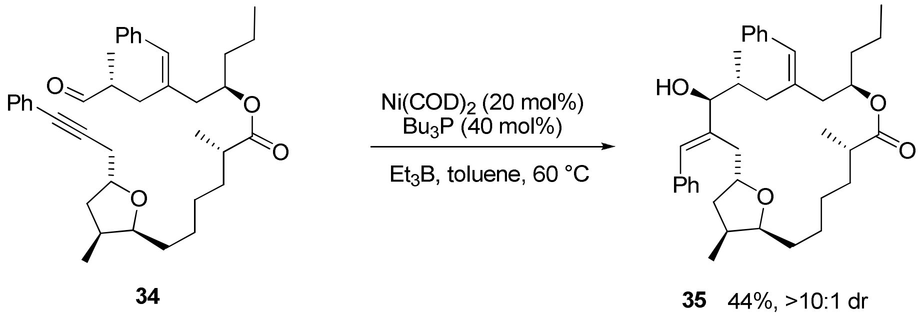
1.5.1. Nickel catalyzed reductive coupling reactions

Montgomery[19] and Jamison[20] have made significant contributions in this area that also included a few enantioselective processes. In 2003, Jamison and co-workers used phosphine as a chiral ligand for the asymmetric, regioselective nickel-catalyzed reductive coupling of alkynes and aldehydes. This protocol allows access to trisubstituted secondary allylic alcohols **33** with moderate to excellent enantiomeric excesses and excellent regioselectivity (Scheme 1.11).[20c]



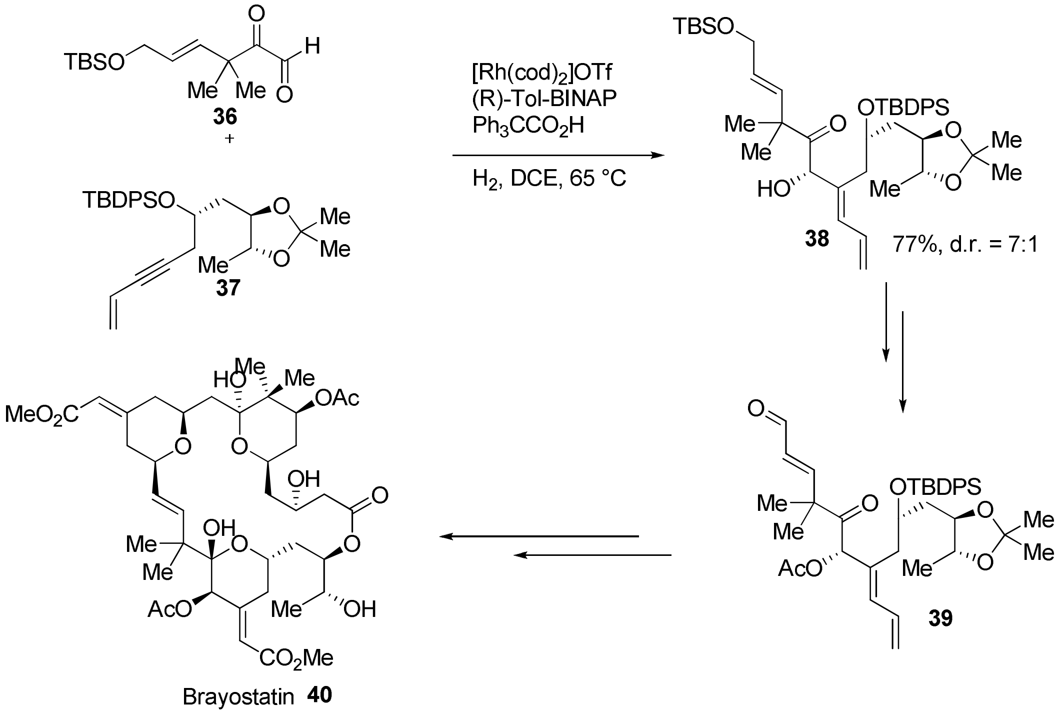
Scheme 1.11

However, a drawback of this method was the requirement of two equivalents of triethylborane as a terminal reductant. Jamison and co-workers used this methodology in macrocylzation step for the preparation of key intermediate **35** in total synthesis of amphidinolide T1 (Scheme 1.12).[21]



Scheme 1.12

1.5.2. Rhodium catalyzed reductive coupling reactions



Scheme 1.13

Krische and co-workers developed an interesting atom economic process for the reductive coupling under hydrogenation conditions. This rhodium catalyzed asymmetric reductive coupling reactions of 1,3-diynes,[22] 1,3-enynes,[23] and acetylene[24] with various carbonyl compounds (aldehydes, glyoxal, ethylglyoxylate, α-ketoesters) allows preparation of structurally diverse allylic alcohols. Cyclic allylic alcohols can be obtained in excellent enantiomeric excess using intramolecular variant of reductive coupling of acetylenic aldehydes under hydrogenation conditions.[25] The potential of this hydrogenative C-C coupling atom economic process has been demonstrated in the synthesis of bryostatin **40** (Scheme 1.13).[26]

1.6. Conclusions

This chapter reviewed the atom-economic reactions that are used for the synthesis of asymmetric allylic alcohols or their derivatives. Application of Pd(II) catalyzed allylic C-H oxidation for the preparation of key intermediates of migrastatin family members and their hybrid molecules will be discussed in the next 3 chapters.

1.7. References

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CHAPTER 2

A STEREOSELECTIVE FORMAL SYNTHESIS OF MIGRASTATIN MACROLIDE CORE USING INTRAMOLECULAR ASYMMETRIC ALLYLIC C-H OXIDATION.

Reference:

Narendar Reddy Gade and Javed Iqbal. *Tetrahedron Lett.* **2013**, *54*, 4225.

2.1. Introduction

Migrastatin **1** (Fig. 2.1) is a glutarimide side chain containing 14- member macrocylic natural product, isolated from a cultured broth of *Streptomyces* sp.Mk 929-43F$_1$ by Imoto and co-workers.[1] Since its isolation it has attracted lot of attention because its cell migration inhibition property. Danishefsky and co-workers have reported the first total synthesis of migrastatin,[2] followed by their diverted total synthesis approach showing that the simple analogues are more potent than the natural product (Fig. 2.1).[3-5,6b]

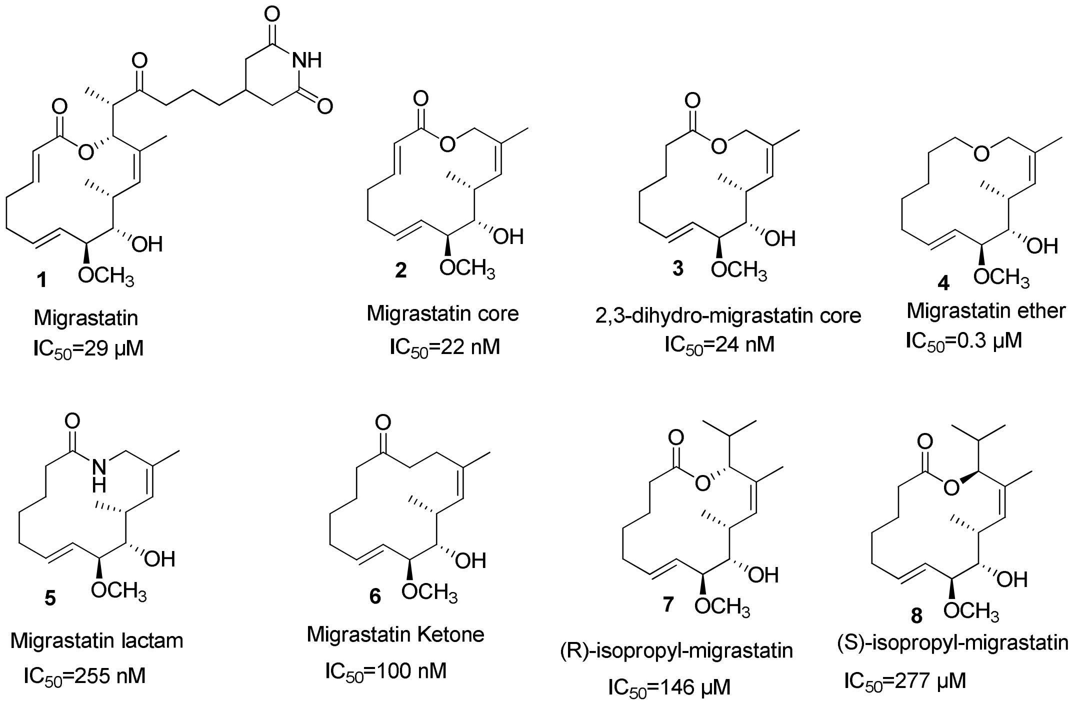


Figure 2.1. IC$_{50}$ values of migrastatin and its analogues towards 4T1 tumor cells

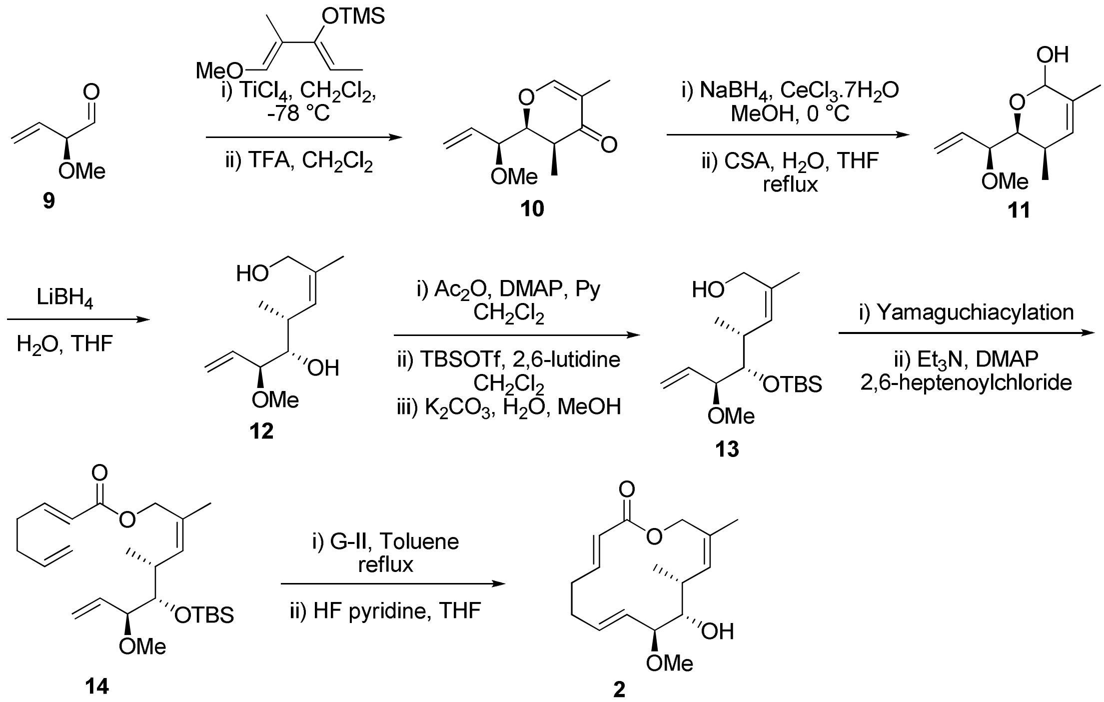
In 2005 Danishefsky *et al.* reported their initial studies on mechanism of action of migrastatin analogues[6a] and showed that migrastatin analogues block Rac activation, formation of lamellopodia, cell migration and their involvement in invasion step of the metastasis process.[6,7] In 2010, Chen and co-workers reported that migrastatin analogues bind to one of the actin binding sites on fascin to inhibit its activity (Fig. 2.2). Evidently actin cytoskeletal proteins such as fascin can be explored as new molecular targets for cancer treatment similar to tubulin.[8]

The presence of novel cyclic structure and promising biological activity associated with migrastatin and its analogues prompted us to explore a novel strategy for the synthesis of its macrolide core. This chapter covers the couple of previous approaches and our synthetic studies to the migrastatin macrolide core.

2.2. Previous approaches to migrastatin macrolide core

2.2.1. Danishefksy's approach

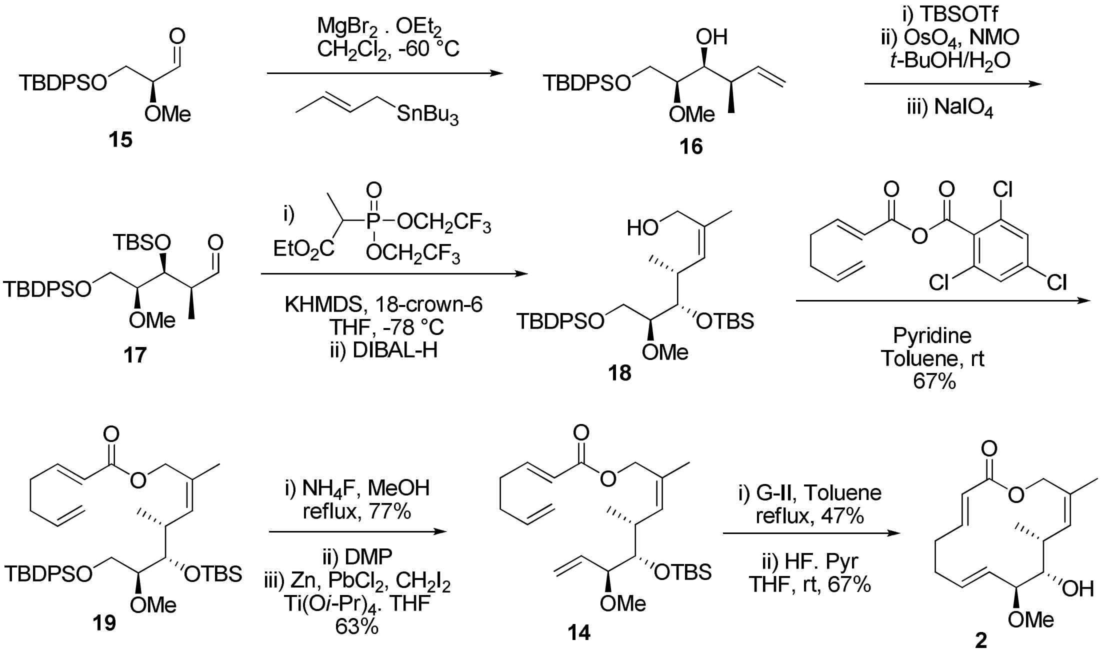
An important feature of Danishefksy's approach is the use of the chelation controlled Lewis acid catalyzed diene-aldehyde cyclocondensation (LACDAC) to build the three contiguous chiral centres C8, C9, and C10 including the C11-C12 (*Z*)-olefin (Scheme 2.1).[4] The synthesis commenced with chiral aldehyde **9** which can be prepared from readily available dimethyl 2,3-*O*-isopropylidene-l-tartrate in few steps. This sensitive aldehyde was used directly for the LACDAC sequence. Accordingly, under Lewis acidic conditions, the diene and aldehyde furnished the corresponding chelation controlled dihydropyrone product **10** which formed as a single diastereoisomer. The process also enabled proper presentation of the three contiguous stereo centers (C8, C9 and C10) of the macrolide. A few chemical transformations on dihydropyrone yielded the C7-C13 core fragment **13**, which is the key precursor required for the synthesis of migrastatin macrolide core and its analogues. Subsequently, the esterification of 2,6-hepta-dienoicacid with allylic alcohol **13** afforded **14**, which on ring closing metathesis afforded the macrocylic core 2.



Scheme 2.1

2.2.2. Cossy's approach

Cossy and co-workers have used RCM approach to macrocyclization similar to Danishefksy's method (Scheme 2.2).[9] Synthesis of allylic alcohol **18** started from chiral aldehyde **15**, which was obtained from readily available methyl-(*S*)-2,2-dimethyl-1,3-dioxolane-4-carboxylate. The chelation controlled diastereoselective crotylation on chiral aldehyde **15** yielded olefin **16** with three contigous chiral centres (C8, C9, and C10). The oxidative cleavage of olefin **16** afforded aldehyde **17**. Still–Gennari olefination on aldehyde **17** afforded the product with (*Z*) geometry at C11–C12 and the later on reduction afforded the corresponding allylic alcohol **18**. The esterification of allylic alcohol **18** with 2,6-hepta-dienoicacid afforded **19**, which upon TBDPS deprotection followed by oxidation gave diene **14**. Subsequent ring closing alkene metathesis on **14** followed by TBS deprotection afforded the macrocyclic core **2** of migrastatin.

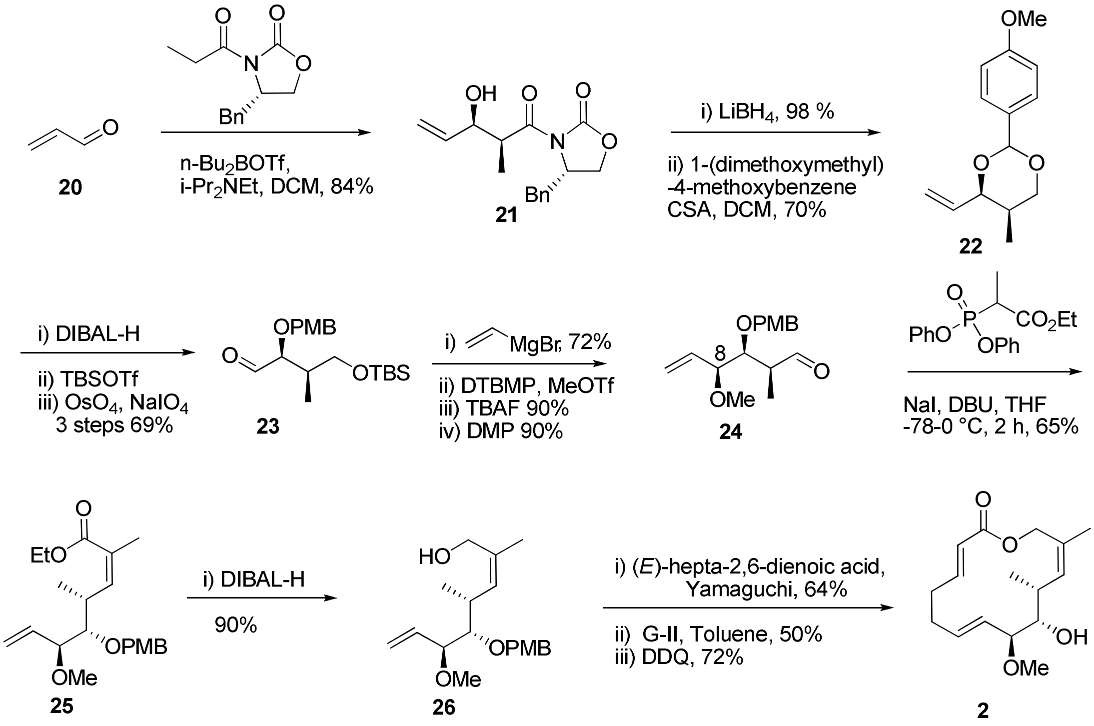


Scheme 2.2

2.2.3. Iqbal's approach

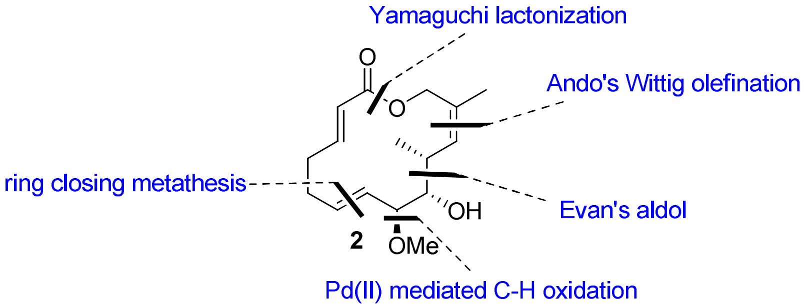
Iqbal's group has also used esterification and RCM as the key steps in synthesizing the macrolide core of migrastatin (Scheme 2.3).[10] However, the synthesis of allylic alcohol **26** followed a different approach from earlier ones. C8 center was generated using substrate controlled Lewis acid mediated stereoselective vinylation on aldehyde

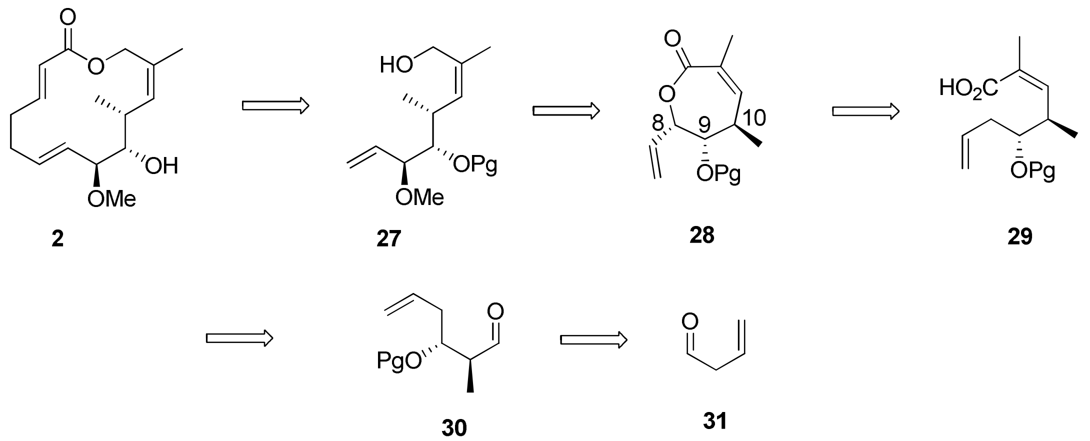
23. The C9, C10 centers were constructed initially using Evan's aldol reaction on acrolein **20** and the *Z*-olefin geometry on **25** at C11-C12 was achieved using Ando's Wittig reaction on aldehyde **24.**[11] The reduction of ester **25** to alcohol afforded the allylic alcohol **26**, which was converted to macrolide **2** by Yamaguchi lactonization followed by ring closing metathesis.



Scheme 2.3

2.3. Retrosynthesis of migrastatin macrolide core- The present approach



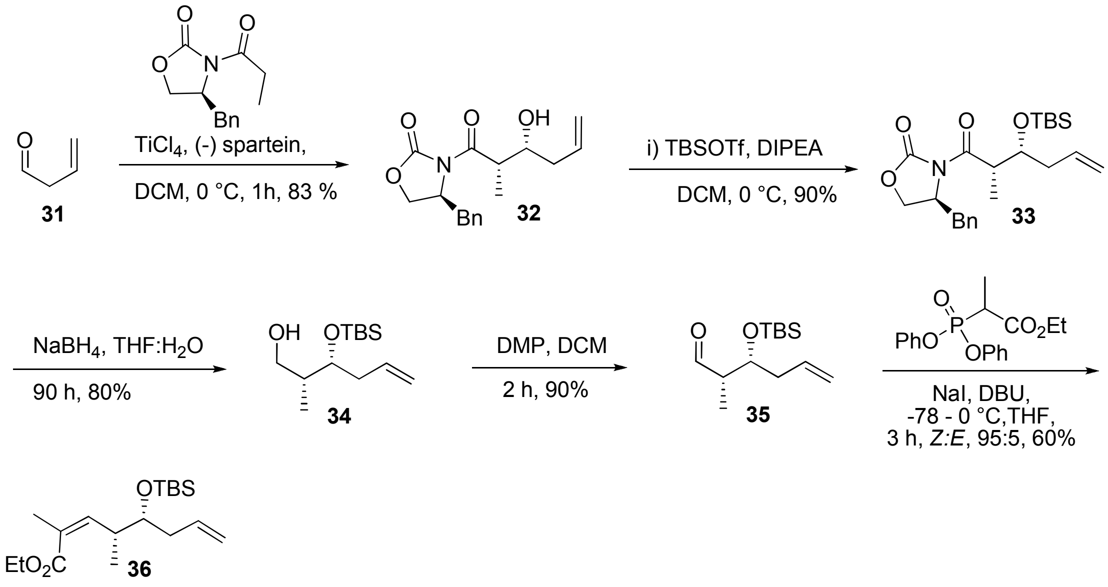


Scheme 2.4

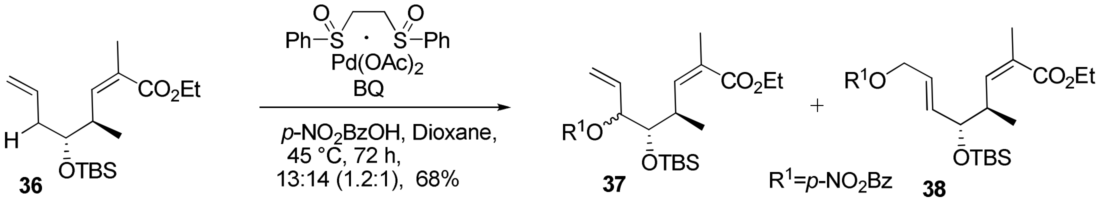
In the present approach, for the synthesis of macrolide core **2** of migrastatin, the major focus is being given on generating the three contagious chiral centers (C8, C9 and C10) and *Z*-olefin (C11-C12) for the key allylic alcohol intermediate **27**. We envisioned the installation of C9, C10 using aldol approach, C11-12 olefin geometry using Wittig protocol and finally introduction of C-8 chiral center *via* a Pd(II) catalyzed asymmetric C-H oxidation (Scheme 2.4).

2.4. Results & Discussion

According to our retrosynthetic plan, the C9, C10 centers were installed using titanium mediated Evans aldol reaction on 3-butenal **31** (Scheme 2.5).[12] The TBS protection of aldol adduct **32** was carried out using TBSOTf, followed by reduction gave the corresponding alcohol **34**. The C11-C12 olefin geometry (*Z*) was achieved following Ando's protocol using ethyl 2- (diphenylphosphono)acetate on aldehyde **35**. However, our initial efforts to promote intermolecular asymmetric allylic C-H oxidation on ester **36** with Pd(II) catalyst developed by White *et al.*[13] resulted in two regioisomers **37** and **38** in almost equal ratio (Scheme 2.6).

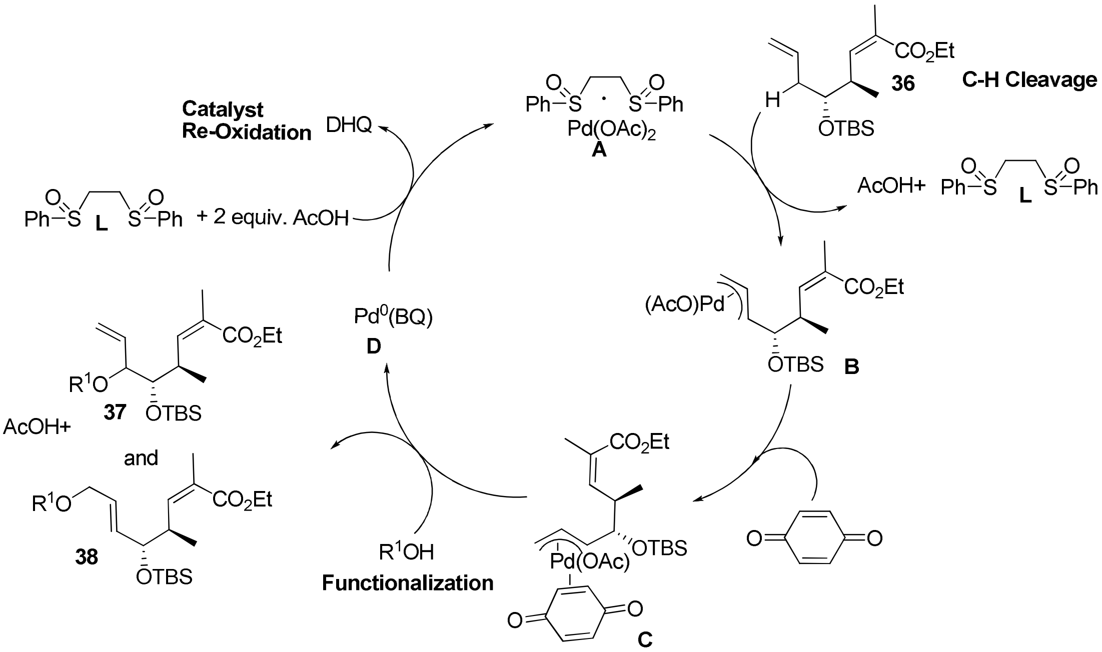


Scheme 2.5



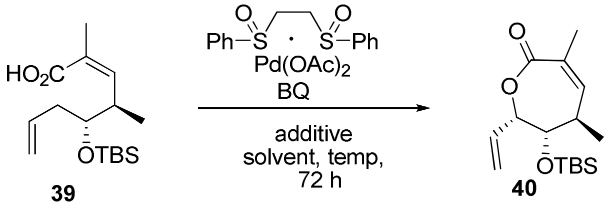
Shceme 2.6

The mechanistic rational for the formation of products can be explained *via* the first step involving electrophilic allylic C-H cleavage of the olefin via a L/Pd(OAc)$_2$ complex **A** to afford Pd-π–allyl intermediate (**B**). Under the reaction conditions, **(B)** reacts directly with BQ (present in high concentrations) to give (**C**) that is activated towards nucleophilic functionalization from any direction to give linear and branched products (Scheme 2.7).



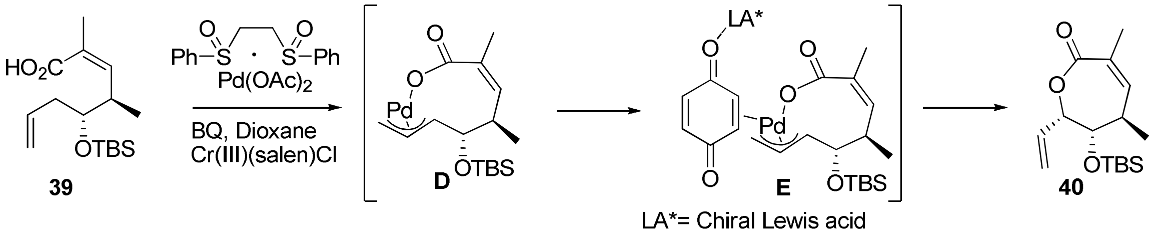
Scheme 2.7

Table 2.1. Summary of the Pd(II) catalyzed intramolecular C-H oxidation of acid **39**



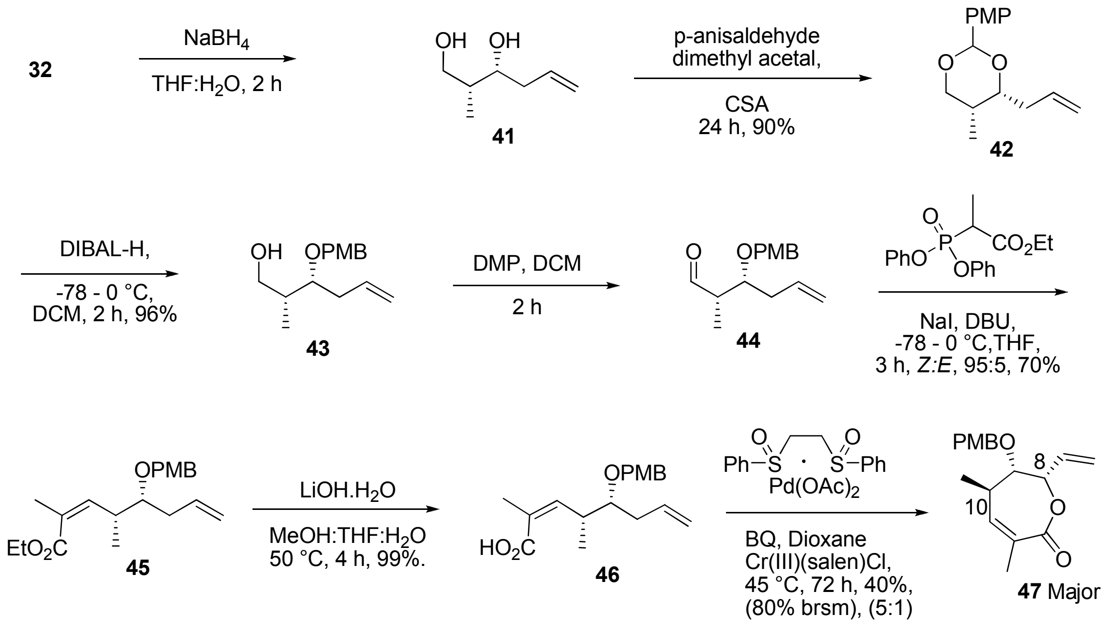
Solvent/additive	Temperature	Conversion	Isolated yield
CH_2Cl_2	45 °C	5 %	4 %
DCE	65-70 °C	5 %	-----
CH_2Cl_2	50 °C in sealed tube	5 %	-----
CH_2Cl_2/DIPEA	45 °C	40 %	20 %
CH_2Cl_2/Cr(III)salenCl	45 °C	50 %	35 %
Dioxane/Cr(III)salenCl	45 °C	50 %	40 %

We then shifted our focus to intramolecular C-H oxidation on the acid **39** derivable from ester **36** (Table 2.1). The acid **39** was subjected to macrocyclization conditions reported by White *et al.*[14] to give lactone **40** as a single diastereomer in low yields (<5%) (Table 2.1). A literature search guided us to attempt intramolecular C-H oxidation of **39** in the presence of chiral Lewis acid ((*R*,*R*)-Cr(III)salenCl) as promoter (Table 2.1).[15] Gratifyingly, White's oxidation on acid **39** under chiral Lewis acid promoter afforded the seven-member lactone **40** as single diastereomer in 40% yield (80% brsm) as an exclusive product. Mechanistically, the lactonization proceeds *via* a serial ligand catalysis mechanism (Scheme 2.7) by an additional coordination of oxophilic Lewis acid to carbonyl group of BQ which promotes inner sphere C-O bond formation from a template π–allylPd carboxylate intermediate **E** (Scheme 2.8).

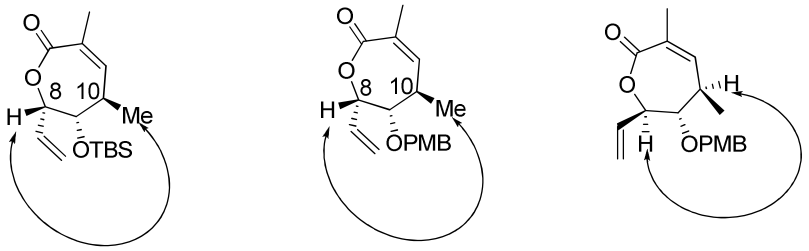


Scheme 2.8

We envisioned installing different functional group on **39** (on C9 hydroxyl adjacent to allylic C-H) to study its effect on intramolecular C-H oxidation. Accordingly, the corresponding PMB protected acid **46** was prepared from aldol adduct **32** in 6 steps (Scheme 2.9). The intramolecular C-H oxidation was carried out on acid **46**, which resulted decrease in desired diastereoselectivity (5:1). The stereochemistry of the C8 center in lactone **40** and **47** was established using NOESY experiments which showed a correlation between C8 proton and C10 methyl group (Fig. 2.3) which was further confirmed by elaboration of lactone **40** to a known compound **13** (Scheme 2.9).[5]



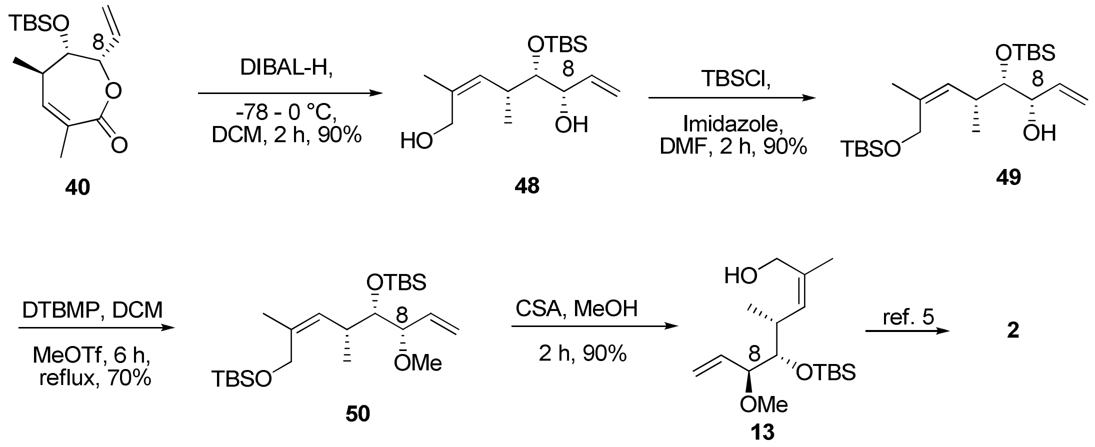
Scheme 2.9



40 **47 major** **47 minor**

Figure 2.3. Key NOE correlations

The key intermediate **13** was prepared from lactone **40** in four steps. Thus **40** was treated with DIBAL-H to afford diallylic alcohol **48** which upon selective protection of primary alcohol as silyl ether and secondary hydroxyl as methyl ether with MeOTf afforded the intermediate **50**. The primary hydroxyl on **50** was unmasked using CSA/MeOH to afford the intermediate **13.** The key intermediate 1**3** has already been used for the preparation of macrocycle **2** by our group[8] and others[5] and thus this approach constitutes a formal synthesis of macrolide core **2** of migrastatin (Scheme 2.10).



Scheme 2.10

2.5. Conclusions

In conclusion, we have successfully installed the C-8 chiral centre of migrastatin using Pd(II) catalyzed intramolecular asymmetric C-H oxidation leading to a stereoselective synthesis of migrastatin key intermediate **13** (C6-C13 fragment).

2.6. Experimental section

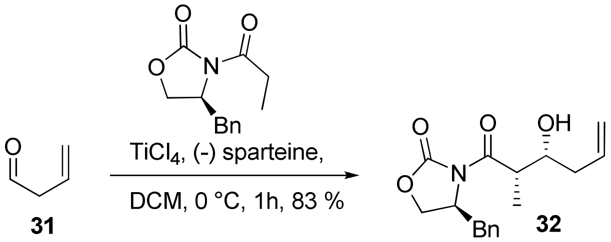
2.6.1. General experimental information for all the work presented in this thesis

Unless otherwise noted, all the reagents and intermediates were obtained commercially and used without purification. Column chromatography was carried out on silica gel using flash techniques (eluants are given in parentheses). Analytical thin-layer chromatography was performed on precoated silica gel F_{254} aluminum plates with visualization under UV light or by staining using either $KMnO_4$ spray reagent. ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ solution by using 400 and 100 MHz spectrometers (VARIAN 400 MR), respectively. Proton chemical shifts (δ) are relative to tetramethylsilane (TMS, $\delta = 0.00$) as internal standard and expressed in ppm. Spin multiplicities are given as s (singlet), d (doublet), t (triplet) and m (multiplet) as well as br (broad). Coupling constants (*J*) are given in hertz. Infrared spectra were recorded on a FT-IR spectrometer (FT/IR-4200, JASCO). Melting points were determined by using melting point apparatus (Buchi melting point B-540) and are uncorrected. MS spectra were obtained on a mass spectrometer (AGILENT 6430 triple quardrupole LC-MS). High resolution mass spectra were done on a Waters LCT premier XE instrument. Optical rotations were measured by using HORIBA high sensitive polarimeter SEPA-300.

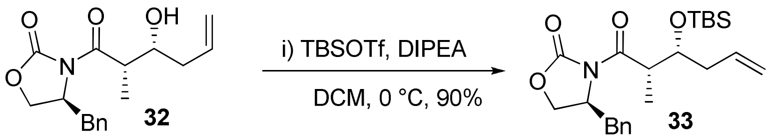
2.6.2. Materials

Evan's chiral auxiliary,[16] ethyl (diphenylphosphono)acetate,[17] and 3-butenal[18] were prepared according to the respective literature procedure. Analytical and spectral data of all those known compounds are exactly matching with the reported values.

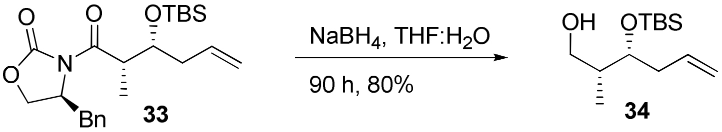
2.6.3. Experimental procedure, spectral and analytical data



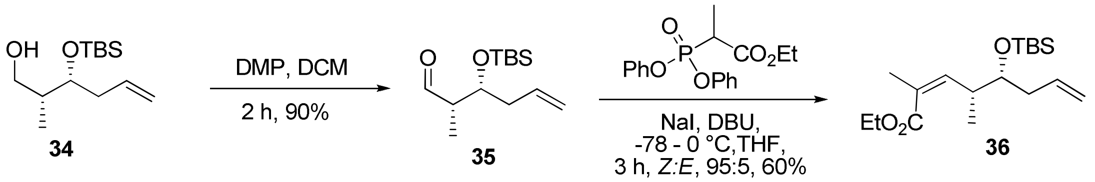
(*S*)-4-Benzyl-3-((2*S*, 3*R*)-3-hydroxy-2-methylhex-5-enoyl)oxazolidinon-2-one (32). A solution of Evan's auxiliary (2.66 g, 11.42 mmol) in dichloromethane (60 mL) was cooled to 0 °C. Titanium tetrachloride (1.3 mL, 11.99 mmol) was added drop wise and the solution was allowed to stir for 5 min. To the yellow slurry was added (-)-sparteine (6.6 mL, 28.5 mmol) drop wise. The dark red enolate was stirred for 20 min at 0 °C. To this, a solution of 3-butenal **31** (0.88 g, 12.56 mmol) in dichloromethane (5 mL) was added drop wise and the reaction mixture was stirred at 0 °C for 30 min. The reaction was quenched by the addition of saturated aqueous ammonium chloride solution and stirred at room temperature for 10 min. Reaction mixture was diluted with dichloromethane, washed successively with water and brine. The organic layer was dried over anhydrous Na_2SO_4 and rotary evaporated under reduced pressure. The residue was purified on silica gel (100-200 mesh) using 20% ethyl acetate in petroleum ether as eluent to afford **32** as colorless oil (2.87 g, d.r= 20:1, 83%). Rf = 0.30 (20% ethyl acetate in petroleum ether); $[\alpha]_D^{25}$ = +62.4 (c 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36-7.26 (m, 2H), 7.29-7.26 (m,1H), 7.22-7.19 (m, 2H), 5.89-5.78 (m, 1H), 5.18-5.10 (m, 2H), 4.73- 4.67 (m, 1H), 4.25-4.17 (m, 2H), 4.03-4.01(m, 1H), 3.85-3.79 (m, 1H), 3.26 (dd, *J* = 13.3, 3.4 Hz, 1H), 2.79 (dd, *J* = 13.2, 9.7 Hz, 2H), 2.38-2.22 (m, 2H), 1.28 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, CDCl3) δ 177.0, 152.8, 134.8, 134.3, 129.3, 128.8, 127.3, 117.7, 70.7, 66.0, 54.9, 41.6, 38.3, 37.6, 10.5; IR (Neat): 3509, 2925, 1779, 1694, 1386, 1210 cm^{-1}; MS(ES) m/z 304.0 (M+1); HRMS m/z found 304.1543, calcd for $C_{17}H_{22}NO_4$ 304.1549.



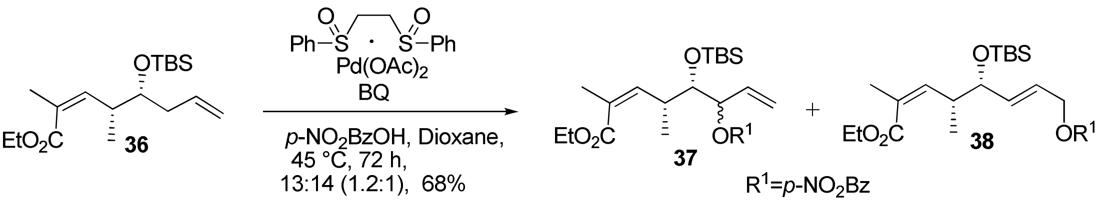
(*S*)-4-Benzyl-3-((2*S*,3*R*)-3-(*tert*-butyldimethylsilyloxy)-2-methylhex-5-enoyl)oxazolidin-2one (33): To an ice cooled solution of compound **32** (1.08 g, 3.56 mmol) in dichloromethane (10 mL) was added N-ethyldiisopropylamine (1.5 mL, 8.91 mmol) drop wise followed by *tert*-butyldimethylsilyltrifluoromethanesulfonate (1.2 mL, 5.35 mmol) and stirred at room temperature for 2 h. Reaction mixture was diluted with dichloromethane, washed successively with aqueous $NaHCO_3$ solution, water, and brine. The organic layer was dried over anhydrous Na_2SO_4 and rotary evaporated under reduced pressure. The residue was purified over silica gel (100-200 mesh) using 5% ethyl acetate in petroleum ether as eluent to afford **33** as a gummy material (1.34 g, 90%). Rf = 0.58 (10 % ethyl acetate in petroleum ether); $[\alpha]_D^{25}$ = +49.0 (c 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35-7.31 (m, 2H), 7.29-7.27 (m, 1H), 7.25-7.20 (m, 2H), 5.90-5.79 (m, 1H), 5.04-4.99 (m, 2H), 4.62-4.57 (m, 1H), 4.18-4.13 (m, 2H), 4.12-4.07 (m, 1H), 3.83 (dt, *J* = 12.8, 6.8 Hz, 1H), 3.27 (dd, *J* = 13.6, 3.2 Hz, 1H), 2.77 (dd, *J* = 13.4, 9.8 Hz, 2H), 2.32 (dt, *J* = 6.0, 1.6 Hz, 2H), 1.22 (d, *J* = 10.4 Hz, 3H), 0.89 (s, 9H), 0.06(s, 3H), 0.02 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.3, 152.9, 135.3, 134.7, 129.4, 128.9,127.3, 116.9, 72.2, 65.9, 55.6, 42.9, 40.6, 37.7, 25.7, 18.0, 12.4, -4.1, -4.8; IR (KBr) 2960, 2929, 2858, 1765, 1702, 1391, 1209 cm^{-1}; MS (ES) m/z 418.2 (M+1); HRMS m/z found 418.2419, calcd for $C_{23}H_{36}NO_4Si$ 418.2414.



(2R,3R)-3-(*tert*-butyldimethylsilyloxy)-2-methylhex-5-en-1-ol (**34**). To an ice cooled solution of compound **33** (4.55 g, 10.91 mmol) in THF (350 mL) was added a solution of sodium borohydride (8.25 g, 218.22 mmol) dissolved in cold water (115 mL) drop wise and stirred at room temperature for 90 h. The reaction was quenched by the addition of saturated ammonium chloride solution. The organic volatiles were removed in vacuo. The residue was diluted with ethyl acetate, washed successively with water and brine. The organic layer was dried over anhydrous Na_2SO_4 and rotary evaporated under reduced pressure. The residue was purified over silica gel (100-200 mesh) using 10% ethyl acetate in petroleum ether as eluent to afford **34** as colorless oil (2.13 g, 80%). Rf = 0.55 (10% ethyl acetate in petroleum ether); $[\alpha]_D^{25}$ = -5.6 (c 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.83-5.73 (m, 1H), 5.10-5.02 (m, 2H), 3.87-3.83 (m, 1H), 3.67 (t, *J* = 9.0 Hz, 1H), 3.55-3.50 (m, 1H), 2.38-2.34 (brs, 1H), 2.26(t, *J* = 1.1 Hz, 2H), 1.97-1.91 (m, 1H), 0.89 (s, 9H), 0.85 (d, *J* = 7.0 Hz, 3H), 0.08 (s, 3H), 0.07 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.4, 116.9, 74.7, 65.9, 39.5, 37.8, 25.8, 17.9, 11.4, -4.3, -4.7; IR (Neat): 3382, 3078, 2968, 2930, 2858, 1472, 1255, 1046 cm^{-1}; MS (ES): m/z 245.2 (M+1); HRMS: m/z found 245.1940, calcd for $C_{13}H_{29}O_2Si$ 245.1937.



(4*R*,5*R*,*Z*)-ethyl 5-(*tert*-butyldimethylsilyloxy)-2,4-dimethylocta-2,7-dienoate (36). To an ice cooled solution of compound **34** (0.35 g, 1.43 mmol) in CH_2Cl_2 (5 mL) and H_2O (0.1 mL) was added Dess-Martin periodinane (0.73 g, 1.72 mmol) and stirred at the same temperature for 2 h. Reaction mixture was diluted with additional CH_2Cl_2 and quenched with saturated sodium thiosulphate solution. To this saturated sodium bicarbonate solution was added and stirred at room temperature for 30 min. The organic layer was separated and was washed successively with water and brine, and dried over anhydrous Na_2SO_4, and rotary evaporated to afford the corresponding yellow colored crude aldehyde **35** (0.31g, 90% yield). A separate round bottomed flask was charged a solution of ethyl 2- (diphenylphosphono)acetate (0.535g, 1.60 mmol) in THF (3 mL) was treated with NaI (0.268 g, 1.79 mmol) and DBU (0.243 g, 1.60 mmol) at 0 °C and stirred for 10 min. After the mixture was cooled to -78 °C, above prepared aldehyde **35** (0.31g, 1.28 mmol) was added. After 10 min, the resulting mixture was warmed to 0 °C stirred for 2 h. The reaction was quenched with saturated NH_4Cl solution, followed by extracted with ethyl acetate. The extract was washed with brine and organic layer was dried over anhydrous Na_2SO_4 and rotary evaporated under reduced pressure. The residue was purified over silica gel (230-400 mesh) using 2% ethyl acetate in hexane to afford colorless liquid **36** (0.251g, 60%, *Z*:*E*, 95:5). Rf = 0.83 (10% ethyl acetate in hexane); $[\alpha]_D^{28}$= -35.2 (c 1.05, $CHCl_3$) ^1H NMR (400 MHz, $CDCl_3$) δ 5.86-5.72 (m, 2H), 5.06-4.98 (m, 2H), 4.18 (q, *J* = 7.1 Hz, 2H), 3.65 (dd, *J* = 11.1, 5.6 Hz, 1H), 3.26-3.14 (m, 1H), 2.31-2.15 (m, 2H), 1.90 (s, 3H), 1.27 (t, *J* = 7.1 Hz, 3H), 0.99-0.93 (d, *J* = 6.4 Hz, 3H), 0.89 (s, 9H), 0.03 (s, 3H), 0.003 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.0, 145.9, 135.0, 126.0, 116.6, 75.1, 60.0, 40.0, 37.6, 25.8, 20.8, 18.1, 14.2, -4.0, -4.6; IR (Neat): 3076, 2957, 1716, 1643, 1461, 1375, 1256, 1171, 1095, 1026 cm^{-1}; MS (ES): m/z 327.2 (M+1); HRMS: m/z found 327.2345, calcd for $C_{18}H_{35}O_3Si$ 327.2355.

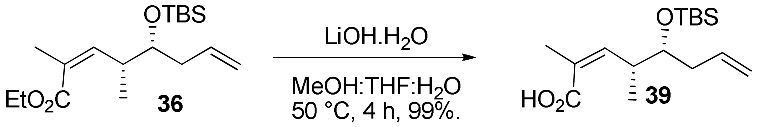


Intermolecular C—H Oxidation: To a stirred solution of 1,2-bis(phenylsulfinyl)ethane palladium (II) acetate (0.075 g, 0.153 mmol), 1,4-benzoquinone (0.33 g, 3.06 mmol), *p*-nitrobenzoic acid (0.384 mg, 2.3 mmol), in 1.3 mL 1,4- dioxane was added **36** (0.5 g, 1.53 mmol) in 10 mL Rb with stopper was stirred at 45 °C for 72 hrs. At this time, the black solution was cooled to room temperature and transferred in to a separatory funnel washing with CH_2Cl_2. A 5% K_2CO_3 solution was added and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 x 30 mL) and the combined organic layers were washed with a 5% K_2CO_3 solution (2 x 20 mL). The organic layer was then dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give yellow oil. residue was purified over silica gel (230-400 mesh) using 5% ethyl acetate in hexane to afford yellow colored gel (0.18 g of **37** and 0.15 g of **38**, 67% + 10% r.s.m)

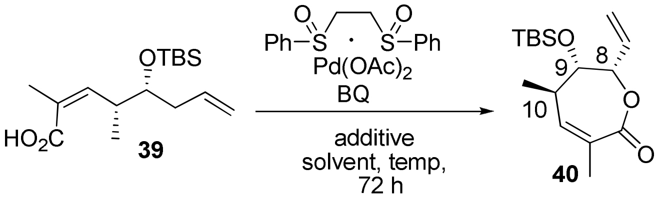
Compound (**37**). Rf = 0.6 (10% ethyl acetate in hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.32-8.23 (m, 4H), 6.08-5.98 (m, 1H), 5.85 (dd, *J* = 10.2, 1.44 Hz, 1H), 5.50 (dd, *J* = 7.0, 3.7 Hz, 1H), 5.36-5.3 (m, 2H), 4.19 (q, *J* = 7.1 Hz, 2H), 3.88 (dd, *J* = 6.3, 3.7 Hz, 1H), 3.47-3.36 (m, 1H), 1.93 (d, *J* = 1.4 Hz, 3H), 1.31-1.27 (t, *J* = 7.1 Hz, 3H), 1.07 (d, *J* = 6.7 Hz, 3H), 0.91-0.89 (s, 9H), 0.02 (s, 3 H), 0.01 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.7, 164.0, 150.5, 144.3, 135.8, 132.3, 130.8, 127.1, 123.5, 119.4, 79.0, 60.2, 36.6, 25.9, 20.8, 18.2, 15.9, 14.2, -3.8, -4.2; IR (Neat): 3085, 2957, 2931, 1723, 1646, 1531, 1462, 1348, 1270, 1220, 1105, 1028 cm^{-1}; MS (ES): m/z 492.2 (M+1); HRMS: m/z found 492.2414, calcd for $C_{25}H_{38}NO_7Si$ 492.2418.

Compound **(38)**. Rf = 0.5 (10% ethyl acetate in hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.31-8.27 (m, 2H), 8.22-8.18 (m, 2H), 5.87-5.84 (m, 1H), 5.81-5.77 (dd, *J* = 6.0,1.6 Hz 1H), 4.86-4.83 (m, 2H), 4.21-4.14 (m, 3H), 3.29-3.18 (m, 1H), 1.88 (d, *J* = 1.4 Hz, 3H), 1.31-1.27 (t, *J* = 7.0, 3H), 0.97 (d, *J* = 6.8 Hz, 3H), 0.91-0.88 (s, 9H), 0.003 (s, 3H), -0.02 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.9, 164.3, 145.3, 137.9, 135.6, 130.6, 126.7, 123.5, 123.4, 75.5, 65.8, 60.1, 39.3, 25.8, 20.7, 18.2, 14.4, 14.2, -4.2, -

4.9; IR (Neat): 3086, 2956, 2929, 2857, 1727, 1608, 1531, 1461, 1348, 1270, 1102, 1061 cm^{-1}; MS (ES): m/z 492.1 (M+1).

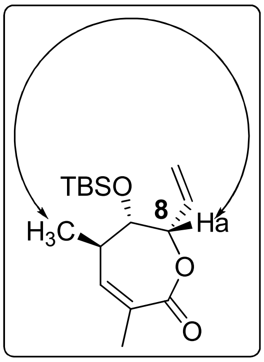


(4*R*,5*R*,*Z*)-5-(*tert*-butyldimethylsilyloxy)-2,4-dimethylocta-2,7-dienoic acid (39). To a solution of ester **36** (0.326 g, 1.0 mmol) in THF/MeOH/H_2O (18 mL, 2:1:1) was added LiOH. H_2O (63 mg, 1.5 mmol).The resultant mixture was stirred for 4 h at 55 °C then cooled to 0 °C and then acidified with 1M HCl and extracted five times with EtOAc. The combined organic extracts were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give **39** as pale yellow color crude acid (0.269 g, 90%). Rf = 0.45 (10% ethyl acetate in hexane); $[\alpha]_D^{28}$ = -38.9 (c 1.09, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.98 (dd, *J* = 10.2, 1.0 Hz, 1H), 5.84-5.04 (m, 1H), 5.07-5.0 (m, 2H), 3.68 (m, 1H), 3.39-3.27 (m, 1H), 2.33-2.16 (m, 2H), 1.93 (s, 3H), 0.98 (d, *J* = 6.7 Hz, 3H), 0.89 (s, 9H), 0.04 (s, 3H), 0.01 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.0, 149.3, 134.8, 125.2, 116.7, 75.2, 39.9, 37.9, 25.8, 20.7, 18.1, 14.2, -4.1, -4.6; IR (Neat): 3425, 2957, 2929, 2856, 1716, 1470, 1361, 1252, 1128, 1083, 1070 cm^{-1}; MS (ES): m/z 299.2 (M+1); HRMS: m/z found 299.2029, calcd for $C_{16}H_{31}O_3Si$ 299.2042.



Intramolecular C-H Oxidation: To solution of 1,2-bis(phenylsulfinyl)ethane palladium (II) acetate (0.051 g, 0.1 mmol, ((*R*,*R*)-Cr(salen)Cl) (0.063 g 0.1mmol) *p*-benzoquinone (0.216 g, 2.0 mmol) in 1,4- dioxane (3 mL) was added acid **39** (0.3 g, 1.0 mmol) in 10 mL flask with stopper was stirred at 45 °C for 72 h. The reaction was allowed to cool to room temperature and transferred to a separatory funnel with EtOAc (50 mL). The organic phase was washed with a saturated aqueous solution of sodium metabisulfite and brine. The organic layer was dried (Na_2SO_4), filtered and concentrated under reduced pressure. Residue was purified by flash chromatography eluting with 5% EtOAc in Hexane afforded the lactone as a single diastereomer as colorless liquid (0.119 g, 40% + 0.148 g s.m was recovered).

(5*R*,6*S*,7*S*)-6-(*tert*-butyldimethylsilyloxy)-3,5-dimethyl-7-vinyl-6,7-dihydrooxepin-2(5H)-one (**40**) Rf = 0.5 (10% ethyl acetate in hexane); $[\alpha]_D^{28}$= -67.8 (c 1.09, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 6.05-5.88 (m, 2H), 5.30 (dd, *J* = 26.6, 13.9 Hz, 2H), 4.73 (dd, *J* = 6.6, 1.2 Hz, 1H), 3.73 (dd, *J* = 7.9, 1.8 Hz, 1H), 2.58-2.48 (m, 1H), 1.97 (s, 3H), 1.18 (d, *J* = 7.0 Hz, 3H), 0.90 (s, 9H), 0.06 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.0, 140.4, 133.7, 129.7, 117.8, 81.9, 79.5, 40.1, 25.8, 20.1, 18.5, 18.1, -3.3, -4.1; IR (Neat): 3083, 2957, 2929, 2857, 1725, 1472, 1361, 1253, 1128, 1088, 1073 cm^{-1}; MS (ES): m/z 297.1 (M+1); HRMS: m/z found 297.1877 calcd for $C_{16}H_{29}O_3Si$ 297.1886.



The relative stereochemistry of **40** was established based on NOESY studies; NOEs between C10 methyl group (δ 1.18) and Ha (δ 4.73) clearly showing the trans of C8 vinyl group and C10 methyl group

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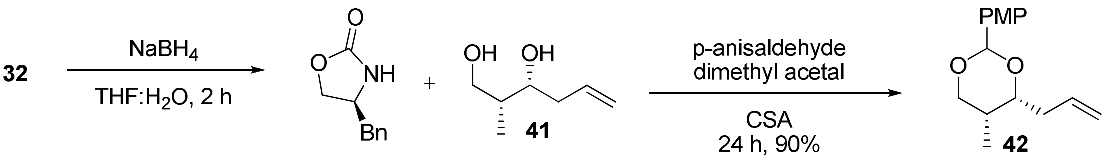
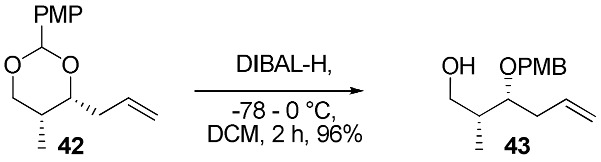
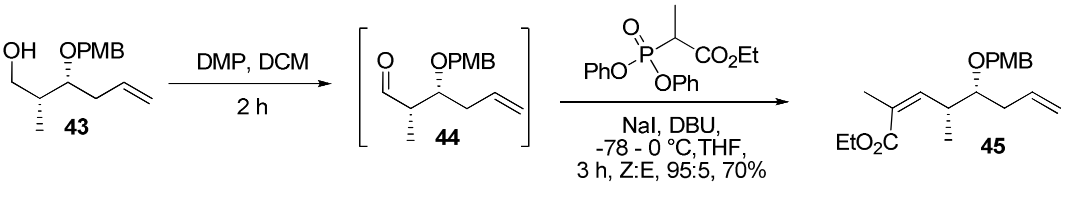


(4R,5R)-4-allyl-2-(4-methoxyphenyl)-5-methyl-1,3-dioxane (42): To a solution of **32** (0.303 g, 1 mmol) in 4:1 THF/H_2O (10 mL) added $NaBH_4$ (0.095 g, 2.5 mmol), the reaction was stirred at room temperature for 2 h. Reaction was quenched by the addition of 1N HCl (5 mL), and extracted with EtOAc (3 x 10 mL), dried (Na_2SO_4), and concentrated under reduced pressure, to give both diol **41** and oxazolidinone crude product which was without further purification (0.3 g) in 10 mL CH_2Cl_2 was added CSA (23 mg, 0.1 mmol, 10 mol %), and *p*-anisaldehyde dimethyl acetal (0.227 g, 1.25 mmol). The reaction was stirred at room temperature for 24 h, and quenched by the addition of saturated sodium bicarbonate solution. The layers were separated, and the aqueous phase was further extracted with CH_2Cl_2 (3 x 5 mL), dried (Na_2SO_4)

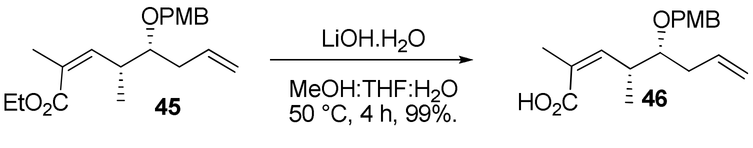
and concentrated under reduced pressure. Flash chromatography (2% EtOAc/Hexanes) provided the product **42** as clear oil (0.225 g, 90%). Rf = 0.65 (20% ethyl acetate in petroleum ether); $[\alpha]_D^{31}$ = +25.8 (c 2.1, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.42 (d, *J* = 8.4 Hz, 2H), 6.88 (d, *J* = 8.6 Hz, 2H), 5.88-5.74 (m, 1H), 5.45 (s, 1H), 5.11 (dd, *J* = 27.7, 13.6 Hz, 2H), 4.08-3.92 (m, 3H), 3.78 (s, 3H), 2.49-2.39 (m, 1H), 2.26-2.16 (m, 1H), 1.61-1.51 (m, 1H), 1.19 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.8, 134.0, 131.4, 127.3, 117.2, 113.6, 101.7, 79.2, 73.8, 55.2, 37.2, 31.1, 10.9; IR (Neat): 2963, 2838, 1616, 1517, 1462, 1441, 1395, 1356, 1338, 1301, 1212, 1160 cm^{-1}; MS (ES) m/z 271.1(M+Na).



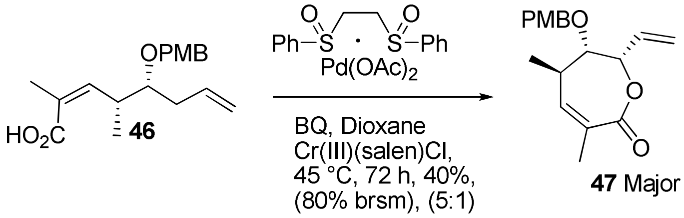
(2R,3R)-3-(4-methoxybenzyloxy)-2-methylhex-5-en-1-ol (43): To a solution of **42** (0.373 g, 1.5 mmol) in 10 mL CH_2Cl_2. The flask was cooled to -78 °C, and to this was added drop wise DIBAL-H (1M solution in hexane, 4.5 mL, 4.5 mmol). The reaction was warmed to room temperature after 2 h and quenched by the addition of a saturated aqueous solution of Rochelle's salt. After stirring 12 h, the layers were partitioned, and the aqueous layer further extracted with EtOAc (3 x 5 mL). The organic layer was dried (Na_2SO_4) and concentrated under reduced pressure. Flash chromatography (20% EtOAc/hexanes) provided **43** as clear oil (0.360 g, 96%). Rf = 0.25 (20% ethyl acetate in petroleum ether); $[\alpha]_D^{25}$ = -31.0 (c 1.5, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.26 (d, *J* = 8.4 Hz, 2H), 6.88 (d, *J* = 8.4 Hz, 2H), 5.89-5.75 (m, 1H), 5.09 (dd, *J* = 24.5, 13.6 Hz, 2H), 4.55 (d, *J* = 11.2 Hz, 1H), 4.45 (d, *J* = 11.2 Hz, 1H), 3.79 (s, 3H), 3.69-3.51 (m, 3H), 2.5-2.45 (m, 1H), 2.38-2.21 (m, 2H), 2.05-1.94 (m, 1H), 0.90 (t, *J* = 8.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.2, 135.2, 130.4, 129.4, 128.6, 116.9, 113.9, 113.8, 80.8, 71.3, 66.1, 55.2, 37.3, 35.0, 11.2; IR (Neat): 3404, 2932, 1735, 1639, 1612, 1586, 1513, 1463, 1441, 1352, 1301, 1170 cm^{-1}; MS (ES) m/z 273.1(M+Na).



(4R,5R,Z)-ethyl 5-(4-methoxybenzyloxy)-2,4-dimethylocta-2,7-dienoate (45): To an ice cooled solution of compound **43** (0.25 g, 1 mmol) in CH_2Cl_2 (10 mL) and H_2O (0.1 mL) was added Dess-Martin periodinane (0.53 g, 1.25 mmol) and stirred at the same temperature for 2 h. Reaction mixture was diluted with additional CH_2Cl_2 and quenched with saturated sodium thiosulphate solution. To this was added saturated sodium bicarbonate solution and stirred at room temperature for 30 min. The organic layer was separated and was washed successively with water and brine, and dried over anhydrous Na_2SO_4, and rotary evaporated to afford the corresponding yellow colored crude aldehyde **44** (0.24 g, 100% yield). A separate round bottomed flask was charged with a solution of ethyl (diphenylphosphono)acetate (0.420g, 1.25 mmol) in THF (3mL) was treated with NaI (0.208g, 1.5 mmol) and DBU (0.190 g, 1.25 mmol) at 0 °C for 10 min. After the mixture was cooled to -78 °C, above prepared aldehyde (0.24 g, 1 mmol) was added. After 10 min, the resulting mixture was warmed to 0 °C over 2 h. The reaction was quenched with saturated NH_4Cl solution, followed by extracted with ethyl acetate. The extract was washed with brine and organic layer was dried over anhydrous Na_2SO_4 and rotary evaporated under reduced pressure. The residue was purified over silica gel (230-400 mesh) using 7% ethyl acetate in hexane to afford **45** as color less liquid (0.232 g, 70%, Z:E, 95:5) Rf = 0.52 (10% ethyl acetate in hexane); $[\alpha]_D^{31}$ = -44.0 (c 2.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25 (d, *J* = 8.6 Hz, 3H), 6.86 (d, *J* = 8.6 Hz, 2H), 5.91-5.76 (m, 2H), 5.06 (t, *J* = 14.0 Hz, 2H), 4.51 (d, *J* = 11.2 Hz, 1H), 4.40 (d, *J* = 11.1 Hz, 1H), 4.18 (q, *J* = 7.1 Hz, 2H), 3.80 (s, 3H), 3.4-3.3 (m, 2H), 2.34-2.28 (m, 2H), 1.88 (s, 3H), 1.32-1.24 (m, 3H), 1.03 (d, *J* = 6.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.0, 159.0, 144.4, 135.2, 130.8, 129.3, 126.7, 116.7, 113.6, 81.9, 71.5, 60.1, 55.2, 36.8, 36.4, 20.9, 15.3, 14.2; IR (Neat): 3074, 2977, 2959, 1714, 1642, 1586, 1455, 1372, 1248, 1172, 1094, 1034 cm^{-1}; MS (ES) m/z 333.1(M+1).



(4R,5R,Z)-5-(4-methoxybenzyloxy)-2,4-dimethylocta-2,7-dienoic acid (**46**): To a solution of ester **45** (.180 g, 0.54 mmol) in THF/MeOH/H_2O (18 mL, 2:1:1) was added LiOH. H_2O (.045 mg, 1.08 mmol).The resultant mixture was stirred for 3 h at 50 °C and then acidified with 1M HCl and extracted with EtOAc (5x4 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated under reduced pressure to give the crude acid (.163 g, 99%). Rf: 0.26 (20% ethyl acetate in hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28-7.24 (m, 2H), 6.87 (d, *J* = 8.4 Hz, 2H) 5.91-5.79 (m, 2H), 5.15-5.02 (m, 2H), 4.49 (dd, *J* = 46.4, 11.0 Hz, 2H), 3.79 (s, 3H), 3.45-3.31 (m, 2H), 2.36-2.3 (m, 2H), 1.93 (s, 3H), 1.05 (d, *J* = 6.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.5, 159.2, 135.1, 130.0, 129.6, 128.6, 116.9, 113.7, 82.1, 71.8, 55.2, 37.3, 35.7, 20.8, 16.0; IR (Neat): 3425, 2959, 2931, 2869, 1689, 1640, 1512, 1458, 1301, 1248, 1174, 1077, 1034 cm^{-1}; MS (ES) m/z 303.2 (M-1).

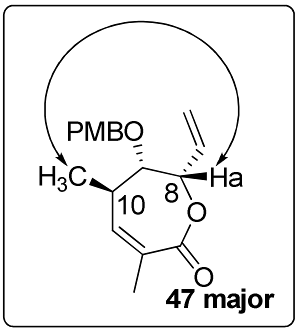


46

47 Major

Intramolecular C-H Oxidation: To a solution of 1,2-bis(phenylsulfinyl)ethane palladium (II) acetate 1 (0.025 g, 0.05 mmol), (1*R*,2*R*)-(-)-[1,2-cyclohexanediamine-*N*,*N'*-bis(3,5-di-tertbutylsalicylidine)] chromium(III) chloride ((*R*,*R*)-Cr(salen)Cl) (0.032 mg, 0.05 mmol, *p*-benzoquinone (0.1 g, 0.92 mmol) in 1.5 mL 1,4- dioxane added acid **46** (0.140 g, 0.46 mmol) in 5 mL round bottom flask with stopper, stirred at 45 °C in an oil bath for 72 h. The Rb was removed, allowed to cool to room temperature and transferred to a separatory funnel with ethyl acetate; organic phase was washed with a saturated aqueous solution of sodium meta-bisulfite (2 x 15 mL) and brine (2 x 15mL). The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by flash chromatography eluting with 10% EtOAc in hexane afforded the lactone as distereomeric mixture (0.055 g 40%, major: minor (5:1) +.07 g s.m recovered).

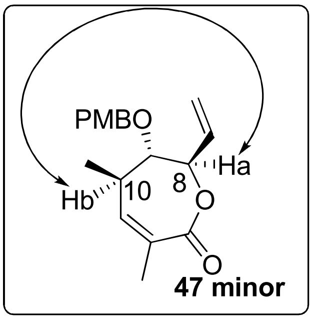
(5R,6S,7S)-6-(4-methoxybenzyloxy)-3,5-dimethyl-7-vinyl-6,7-dihydrooxepin-2(5H)-one (47 minor): Rf = 0.33 (20% ethyl acetate in hexane); $[\alpha]_D^{31}$= -70.0 (c 2.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25 (d, *J* = 9.4 Hz, 2H), 6.87 (d, *J* = 8.6 Hz, 2H), 6.19-6.06 (m, 1H), 5.92 (d, *J* = 4.2 Hz, 1H), 5.40 (dd, *J* = 48.1, 14.0 Hz, 2H), 4.84 (d, *J* = 3.4 Hz, 1H), 4.63 (d, *J* = 10.8 Hz, 1H), 4.42 (d, *J* = 10.8 Hz, 1H), 3.80 (s, 3H), 3.55 (dd, *J* = 9.1, 3.0 Hz, 1H), 2.74-2.63 (m, 1H), 1.97 (s, 3H), 1.18 (d, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.1, 159.3, 140.1, 133.0, 130.3, 129.8, 129.5, 117.9, 113.7, 85.9, 81.2, 73.1, 55.2, 37.2, 19.6, 17.9; IR (Neat): 3080, 2956, 2873, 1719, 1611, 1512, 1458, 1331, 1174, 1027 cm^{-1}; MS (ES): m/z 303.1 (M+1); HRMS: m/z found 303.1586, calcd for $C_{18}H_{23}O_4$ 303.1596.



47 major

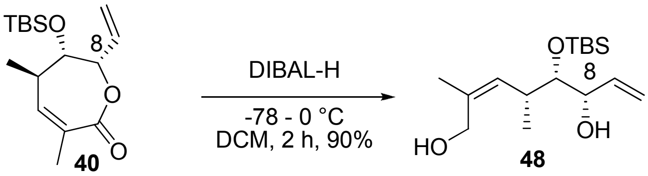
The relative stereochemistry of **47 major** was established based on NOESY studies; NOEs between C10 methyl group (δ 1.18) and Ha (δ 4.84) clearly showing the trans orientation of C8 vinyl group and C10 methyl group.

(5R,6S,7R)-6-(4-methoxybenzyloxy)-3,5-dimethyl-7-vinyl-6,7-dihydrooxepin-2(5H)-one (47 major) Rf = 0.4 (20% ethyl acetate in hexane); $[\alpha]_D^{31}$ = +36.0 (c 0.9, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23 (d, *J* = 8.4 Hz, 2H), 6.88 (d, *J* = 8.5 Hz, 2H), 6.28 (d, *J* = 7.8 Hz, 1H), 6.09-5.95 (m, 1H), 5.47 (d, *J* = 17.3 Hz, 1H), 5.30 (d, *J* = 10.7 Hz, 1H), 4.72 (t, *J* = 6.8 Hz, 1H), 4.47 (s, 2H), 3.82 (s, 3H), 3.44 (dd, *J* = 8.0, 3.7 Hz, 1H), 2.75-2.65 (m, 1H), 1.97 (s, 3H), 1.15 (d, *J* = 7.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.8, 159.4, 139.9, 134.0, 129.6, 129.4, 117.7, 113.8, 85.4, 80.3, 72.2, 55.2, 37.7, 20.0, 19.7; IR (Neat): 3074, 2956, 2924, 2870, 1722, 1612, 1512, 1458, 1330, 1248, 1117, 1066 cm^{-1}; MS (ES): m/z 303.1.



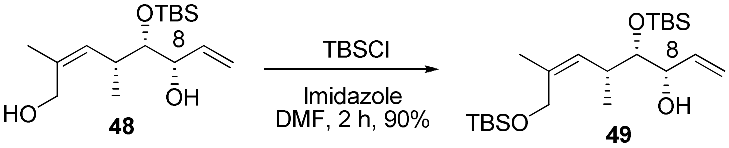
47 minor

The relative stereochemistry of **47 minor** was established based on NOESY studies; NOEs between Hb (δ 2.70) and Ha (δ 4.72) clearly showing the cis orientation of C8 vinyl group and C10 methyl group.

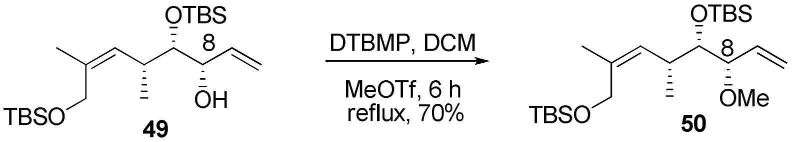


40 **48**

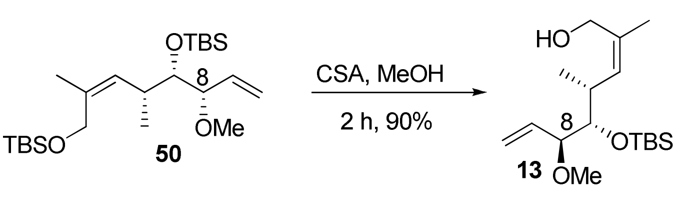
(4*R*,5*S*,6*S*,*Z*)-5-(*tert*-butyldimethylsilyloxy)-2,4-dimethylocta-2,7-diene-1,6-diol (48): To a stirred solution of lactone **40** (0.148 g, 0.5 mmol) in CH_2Cl_2 was added DIBAL-H (1M in THF, 2 mL) at -78 °C. After being stirred for 1h reaction temperature increased to 0 °C. After 1h, the reaction mixture was quenched with saturated aqueous potassium sodium tartarate. After the the addition reaction, mixture was warmed to room temperature and stirred for 1.5 h. Then the layers were separated, aqueous layer was extracted with EtOAc. Combined organic extracts was washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography eluting with 10% ethyl acetate in hexane to afford diol **48** as a colorless semi solid (0.135 g, 90%). Rf = 0.2 (10% ethyl acetate in hexane); $[\alpha]_D^{27}$= +18.0 (c 0.95, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 5.87-5.78 (m, 1H), 5.33-5.26 (m, 1H), 5.22-5.08 (m, 2H), 4.36-4.31 (m, 1H), 4.20-4.16 (m, 1H), 3.8-3.75 (m, 1H), 3.38 (dd, *J* = 8.2, 1.8 Hz, 1H), 2.83-2.76 (m, 1H), 1.83 (d, *J* = 1.2 Hz, 3H), 1.00 (d, *J* = 6.7 Hz, 3H), 0.92 (s, 9H), 0.09 (s, 3H), 0.05 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.4, 135.7, 130.6, 115.3, 79.4, 72.9, 61.6, 36.3, 26.1, 22.2, 18.3, 18.3, -3.1, -3.7; IR (Neat): 3365, 2956, 2982, 2857, 1643, 1456, 1253, 1128, 1088, 1073 cm^{-1}; MS (ES): m/z 301.2 (M+1); HRMS: m/z found 301.2210 calcd for $C_{16}H_{33}O_3Si$ 301.2199.



(3*S*,4*S*,5*R*,*Z*)-4,8-bis(*tert*-butyldimethylsilyloxy)-5,7-dimethylocta-1,6-dien-3-ol (49): To a stirred solution of diol **48** (0.08 g, 0.27 mmol) in 2 mL DMF, imidazole (0.036 g, 0.522 mmol) was added and stirred for 3 min, then the mixture was cooled to 0 °C .To the cooled solution TBSCl (0.081 g, 0.522 mmol) was added, stirred for 2 h at room temperature. Reaction mixture was quenched with saturated aqueous NH_4Cl; the aqueous layer was extracted with EtOAc. Combined organic layers was washed with brine and dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash column chromatography using eluent 1.5% EtOAc in hexane to afford **49** as colorless liquid (0.1 g, 90%). Rf = 0.5 (2% ethyl acetate in hexane); $[\alpha]_D^{25}$= -6.0 (c 0.85, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 5.92-5.80 (m, 1H), 5.30 (d, *J* = 17.2 Hz, 1H), 5.17 (d, *J* = 10.5 Hz, 1H), 5.08 (d, *J* = 10.1 Hz, 1H), 4.21-4.01 (m, 3H), 3.42-3.34 (m, 1H), 2.75-2.65 (m, 1H), 2.36 (d, *J* = 7.7 Hz, 1H), 1.74 (s, 3H), 0.96 (d, *J* = 6.7 Hz, 3H), 0.94-.88 (m, 18H), 0.09-.04 (m, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.1, 135.1, 129.7, 115.5, 79.0, 73.4, 61.9, 35.2, 29.6, 26.0, 25.8, 21.3, 18.3, 17.0, -3.7, -3.9, -5.3, -5.3; IR (Neat): 3365, 2956, 2982, 2857, 1643, 1456, 1253, 1128, 1088, 1073 cm^{-1}; MS (ES): m/z 415.3 (M+1); HRMS: m/z found 415.3073 calcd for $C_{22}H_{47}O_3Si_2$ 415.3064.



(8*R*,9*S*,*Z*)-9-((*S*)-1-methoxyallyl)-2,2,3,3,6,8,11,11,12,12-decamethyl-4,10-dioxa-3,11-disilatridec-6-ene (50): To a stirred solution of compound **49** (0.062 g, 0.15 mmol) in dry CH_2Cl_2 at room temperature were added 4-methyl-2,6-di-*tert*-butylpyridine (0.31 g, 1.51 mmol) and methyl triflate (0.12 g, 0.73 mmol) sequentially. The reaction mixture was stirred at 40 °C- for 6 h. Then reaction mixture was diluted with CH_2Cl_2 washed with 3N HCl solution, saturated $NaHCO_3$ solution followed by brine. Then the organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The resulting residue purified by column chromatography using 1% ethyl acetate in hexane to afford **50** as pale yellow liquid (0.044 g, 70%). Rf = 0.75 (2% ethyl acetate in hexane); $[\alpha]_D^{25}$= -6.2 (c 0.8, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 5.72-5.60 (m, 1H), 5.36-5.20 (m, 3H), 4.19-4.0 (m, 2H), 3.52-3.32 (m, 2H), 3.25 (s, 3H), 2.65-2.55 (m, 1H), 1.72 (s, 3H), 1.0-0.86 (br, 21H), 0.15-0.04 (br, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.4, 133.2, 131.4, 118.4, 86.1, 78.6, 61.9, 56.1, 33.8, 30.4, 29.6, 26.1, 25.9, 20.9, 18.5, 18.3, 14.1, -3.8, -4.8, -5.3; IR (Neat): 2957, 2930, 2853, 1472, 1460, 1250, 1127, 1080, 1028, 1006 cm^{-1}; MS (ES): m/z 446.3 ($M+NH_4$); HRMS: m/z found 446.3506 calcd for $C_{23}H_{52}NO_3Si_2$ 446.3486.



(4*R*,5*S*,6*S*,*Z*)-5-(*tert*-butyldimethylsilyloxy)-6-methoxy-2,4-dimethylocta-2,7-dien-1-ol (13):

To a stirred solution of compound **50** (0.04 g, 0.09 mmol) in MeOH 5 mL, CSA (0.002 g 0.005 mmol) was added and stirred at room temperature for 2 h. Then the reaction mixture was quenched with saturated $NaHCO_3$ solution, the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were dried on Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography using eluent 6% ethyl acetate in hexane to afford **13** as colorless liquid[5] (.025 g, 90%). Rf = 0.5 (10% ethyl acetate in hexane); $[\alpha]_D^{27}$= +4.4 (c 0.17, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.73-5.66 (m, 1H), 5.30-5.24 (m, 3H), 4.12 (dd, *J* = 11.8, 4.9 Hz, 1H), 4.00 (dd, *J* = 11.7 Hz, 6.5 Hz, 1H), 3.49-3-43(m, 2H), 3.23 (s, 3H), 2.69-2.66 (m, 1H), 1.78 (s, 3H), 1.68-1.65 (m, 1H), 0.91 (m, 12H), 0.06 (s, 3H), 0.04 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.1, 133.0, 118.5, 85.8, 78.2, 61.7, 56.1, 34.2, 26.1, 21.5, 18.4, 15.3, -3.8, -4.6; IR (Neat): 3352, 2956, 2930, 2857, 1472, 1462, 1250, 1127, 1081, 1028,1006 cm^{-1}; MS (ES): m/z 337.2 (M+Na).

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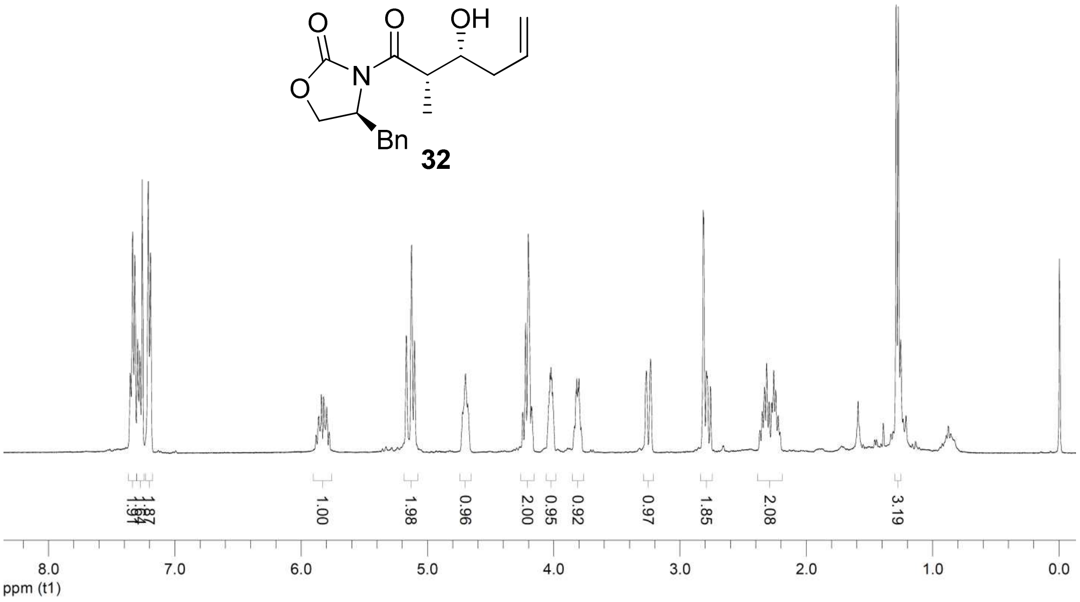
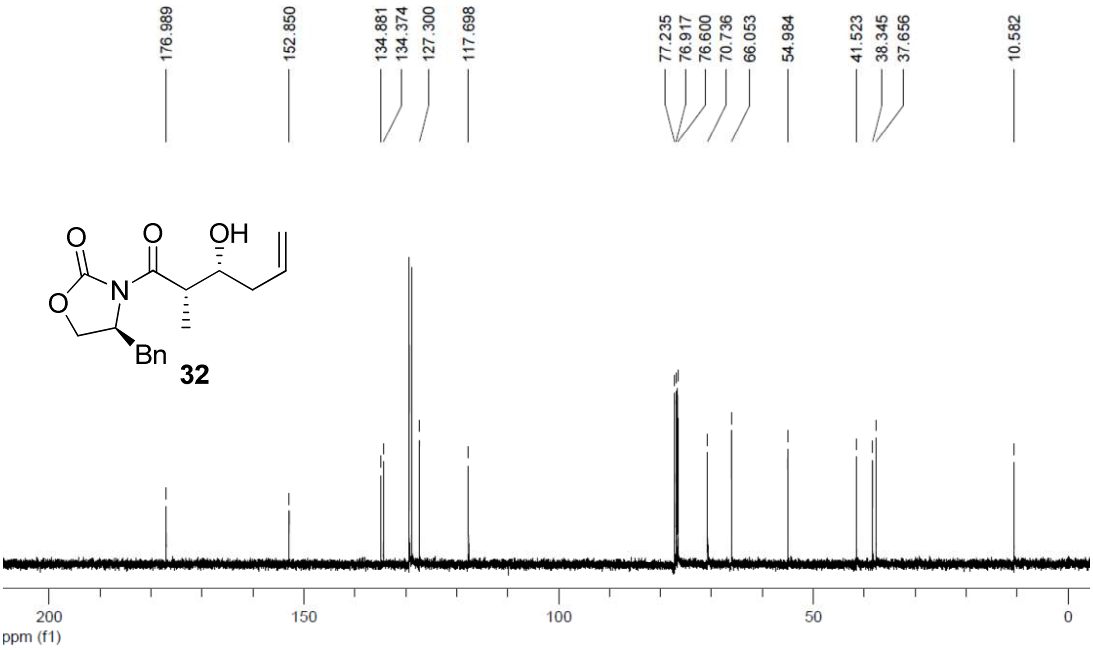
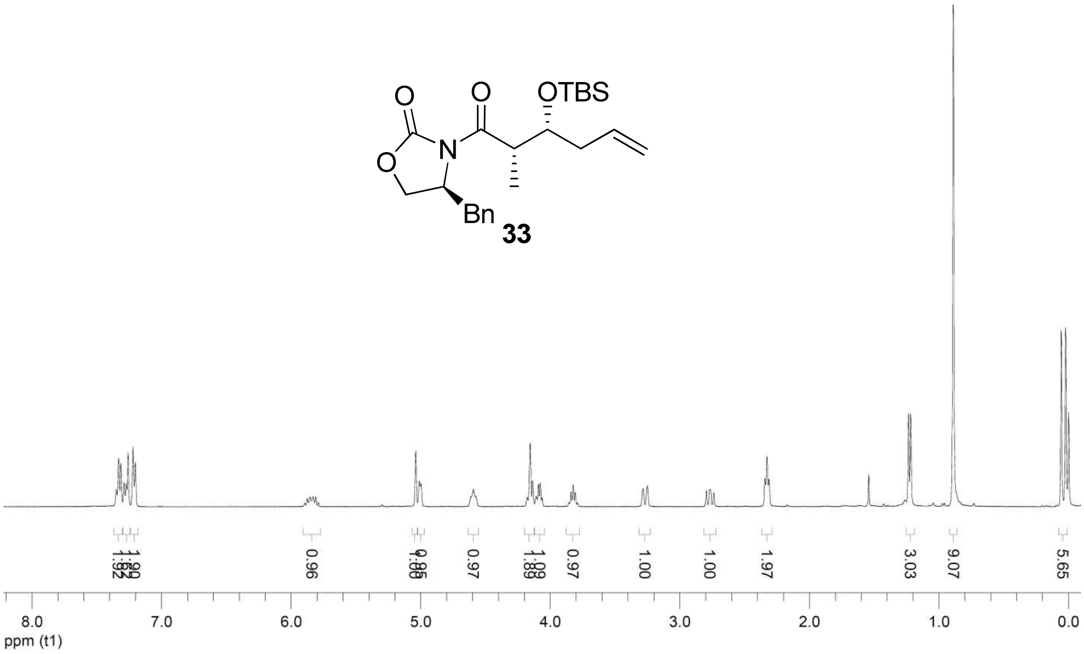
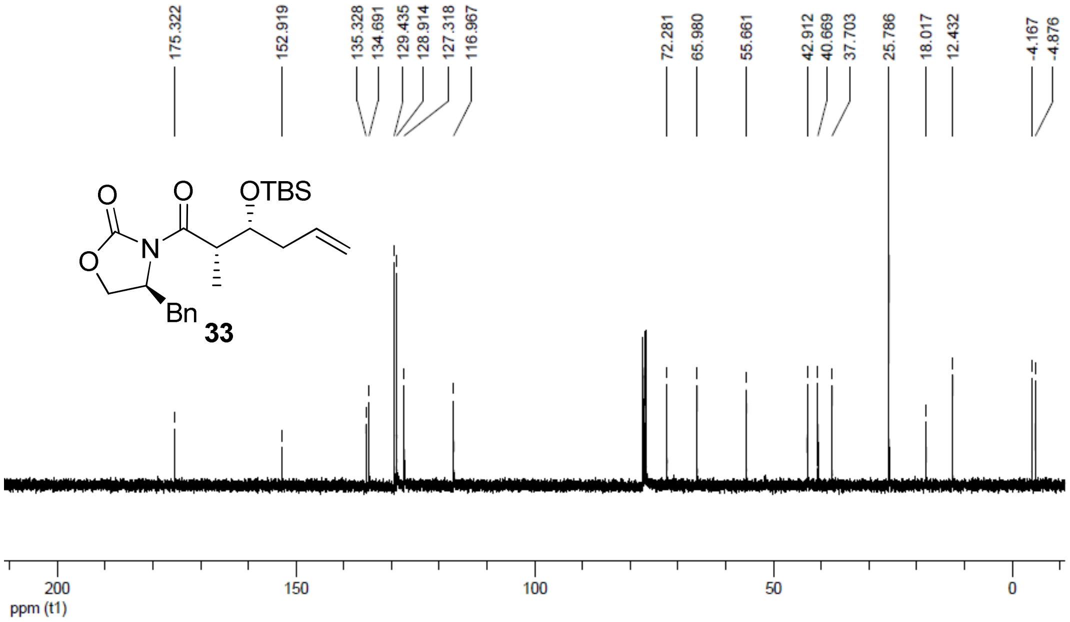
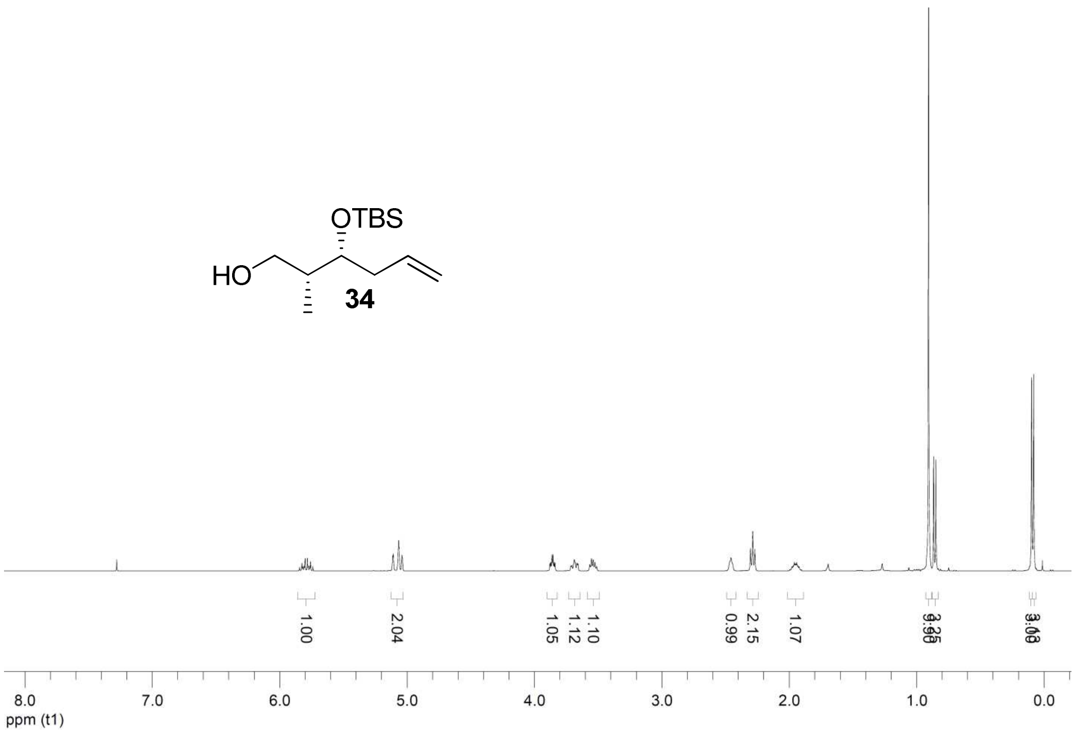
2.8. NMR spectra

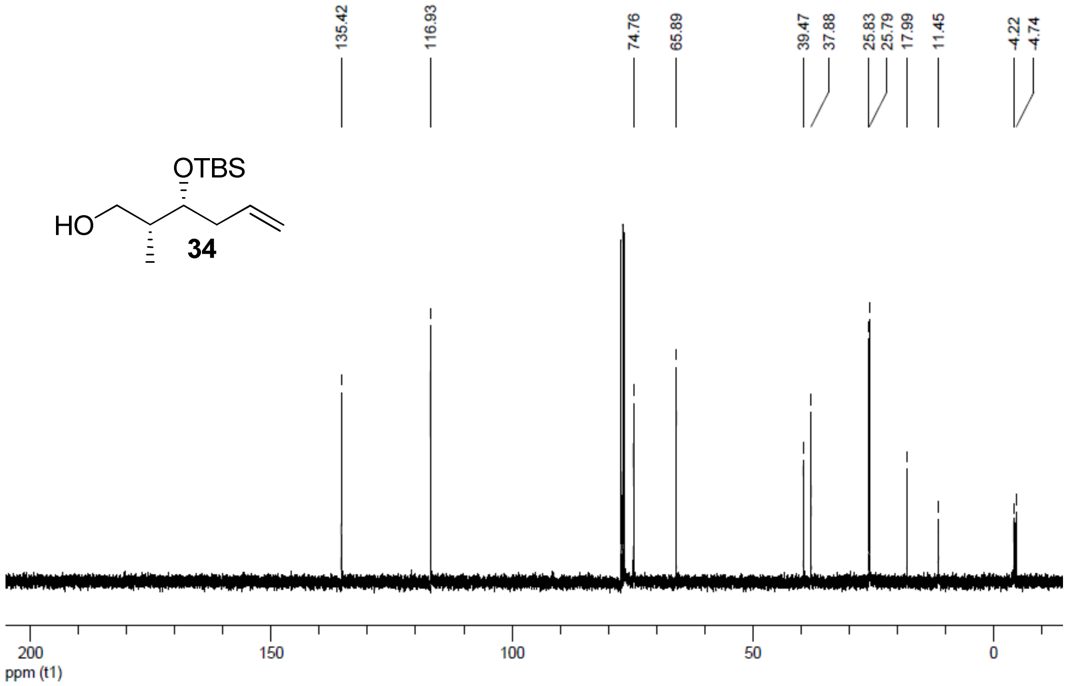


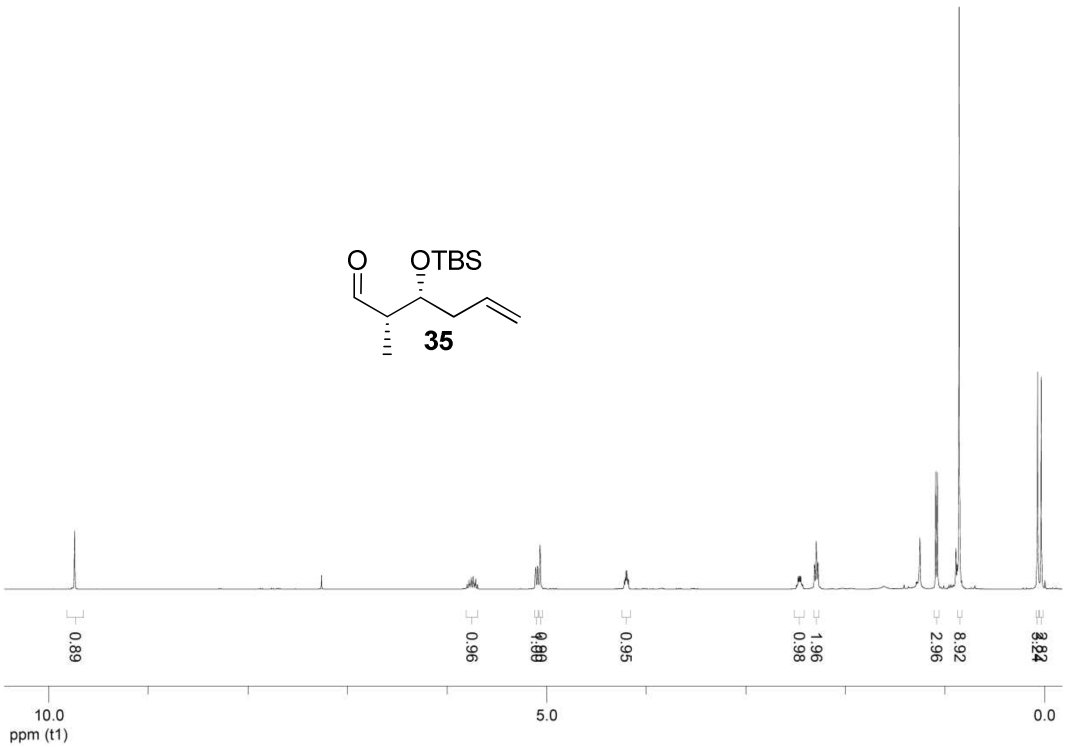


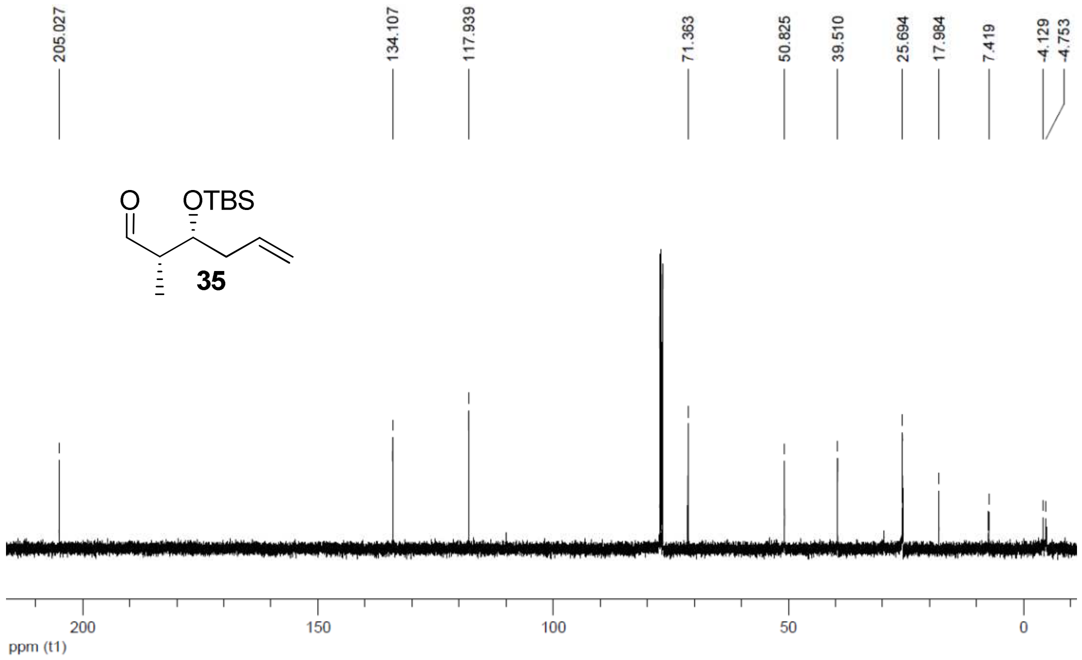

O
O
OTBS
N
O
Bn
33
0.96
0.97
0.97
1.00
1.00
1.97
3.03
9.07
5.65
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (t1)

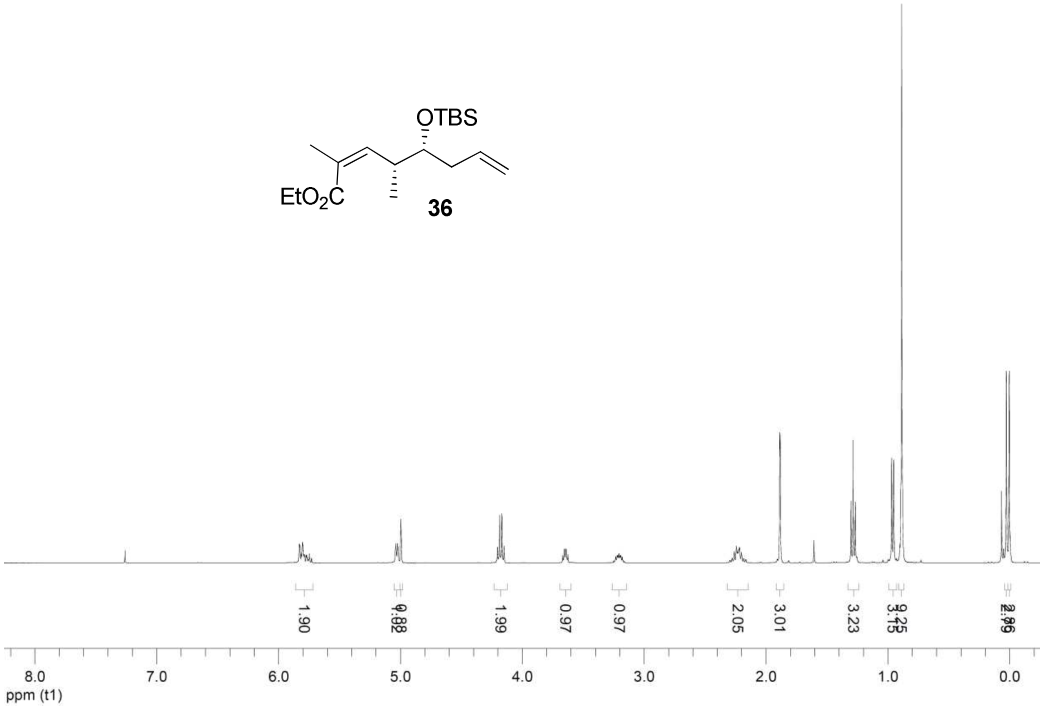

175.322
152.919
135.328
134.691
129.435
128.914
127.318
116.967
72.281
65.980
55.661
42.912
40.669
37.703
25.786
18.017
12.432
-4.167
-4.876
O
O
OTBS
N
O
Bn
33
200
150
100
50
0
ppm (t1)

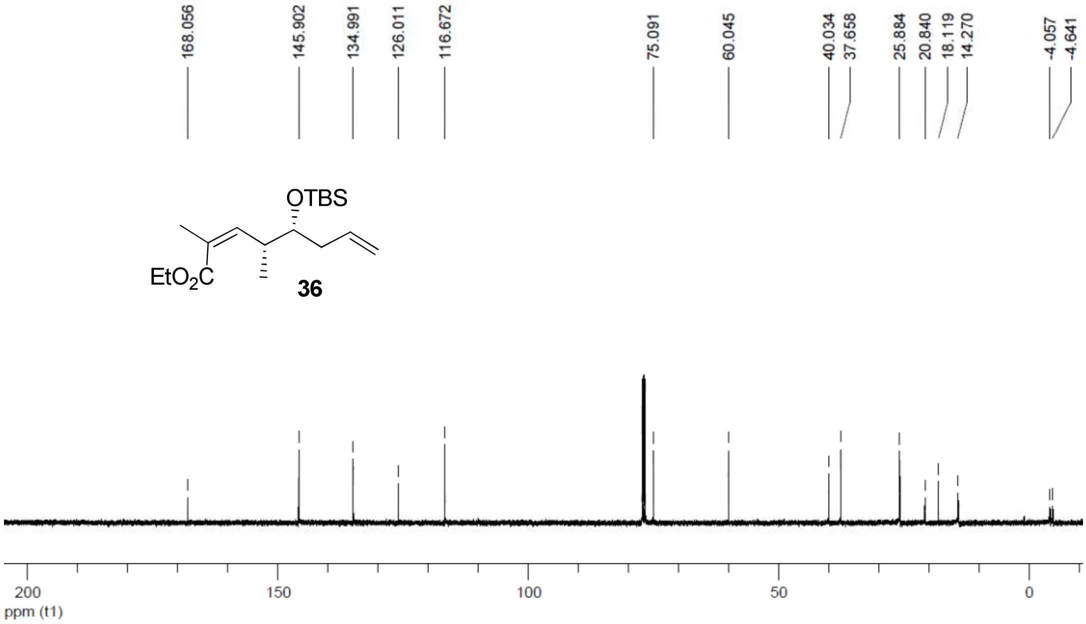

OTBS
HO
34
1.00
2.04
1.05
1.12
1.10
0.99
2.15
1.07
9.00
3.25
3.00
3.06
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (t1)

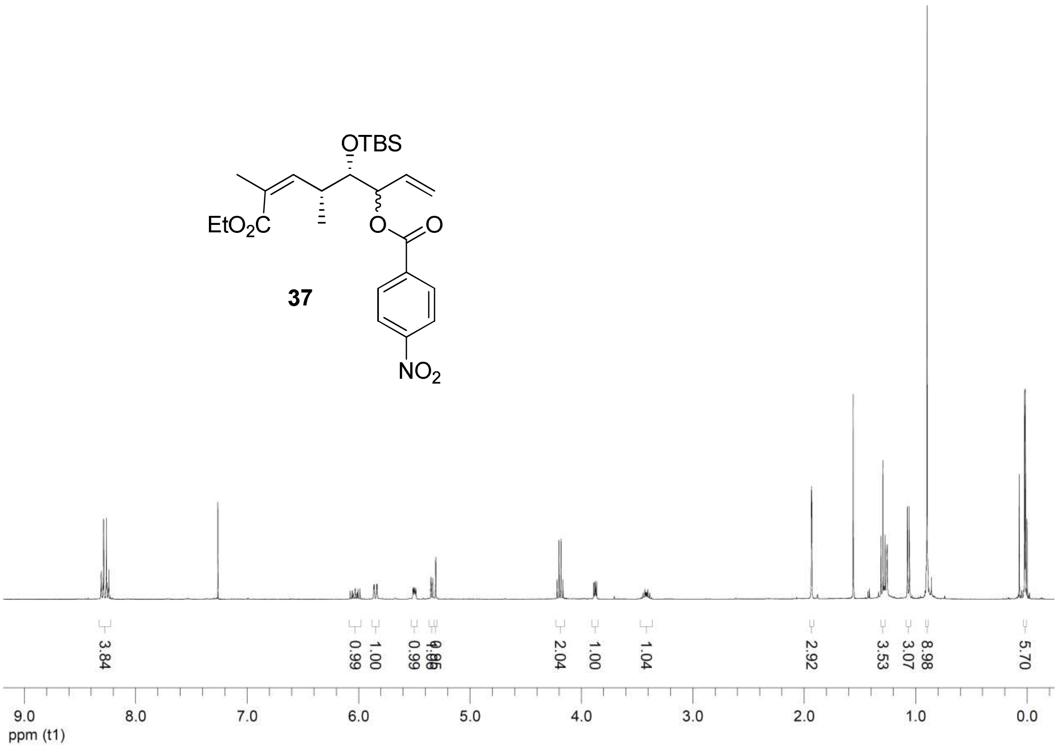

135.42
116.93
74.76
65.89
39.47
37.88
25.83
25.79
17.99
11.45
-4.22
-4.74
OTBS
HO
34
200
150
100
50
0
ppm (t1)

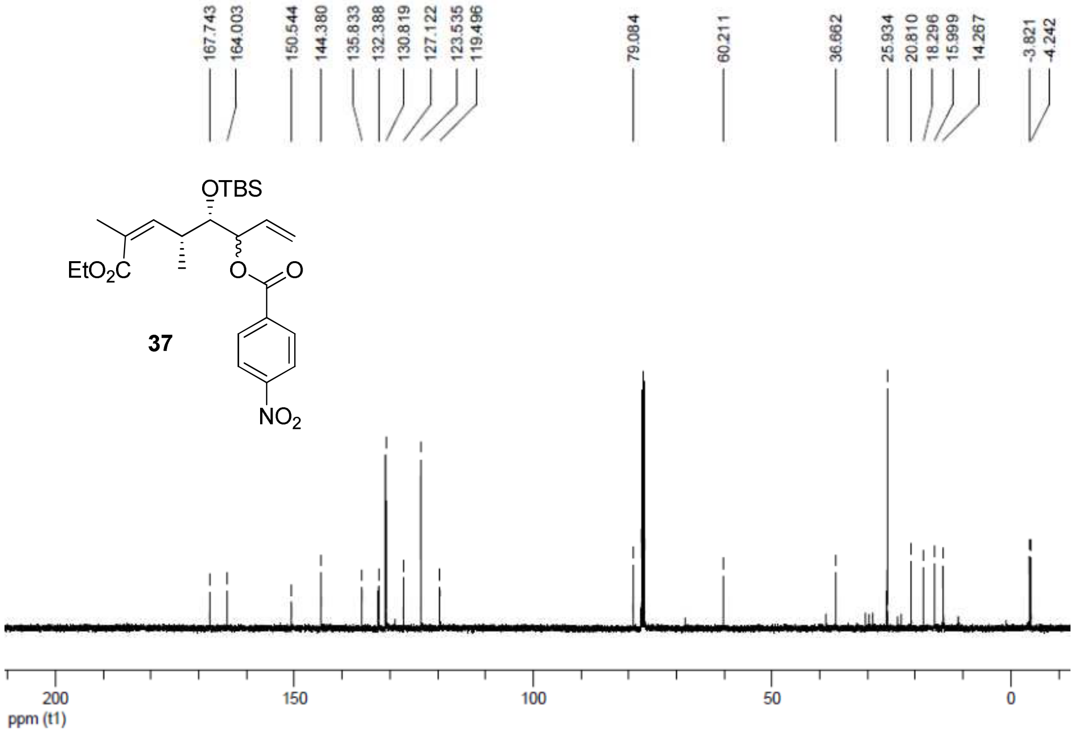

O
OTBS
35
0.89
0.96
0.95
0.98
1.96
2.96
8.92
10.0
ppm (t1)
5.0
0.0

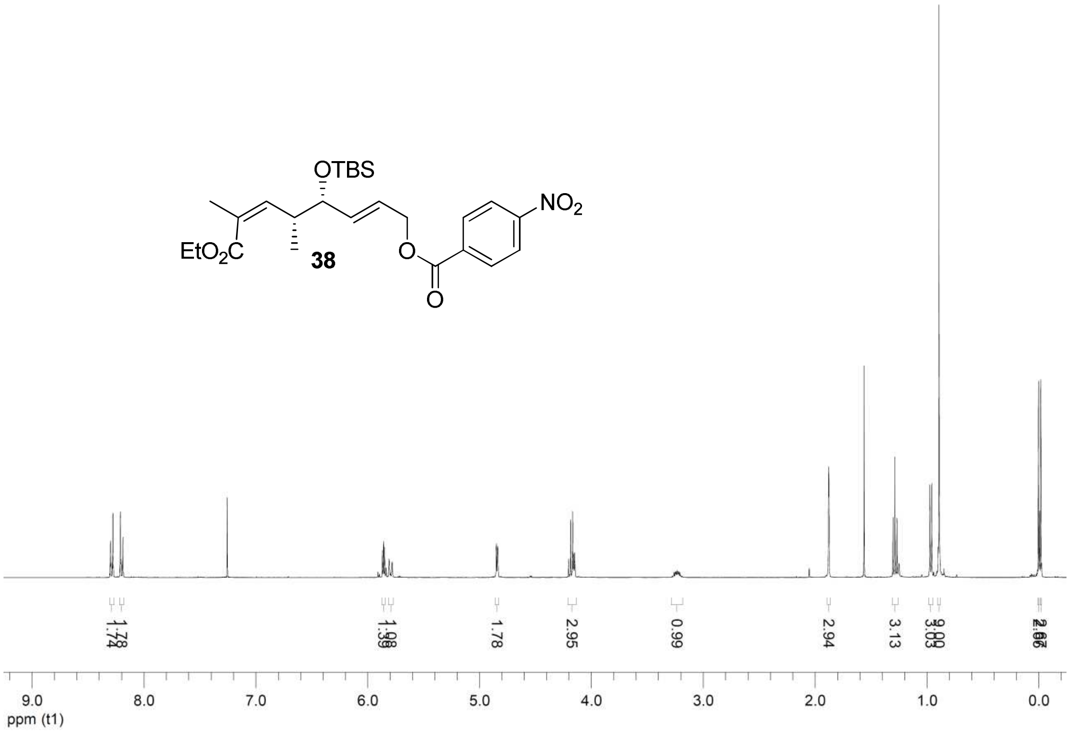

205.027
134.107
117.939
71.363
50.825
39.510
25.694
17.984
7.419
-4.129
-4.753
O
OTBS
35
200
150
100
50
0
ppm (t1)

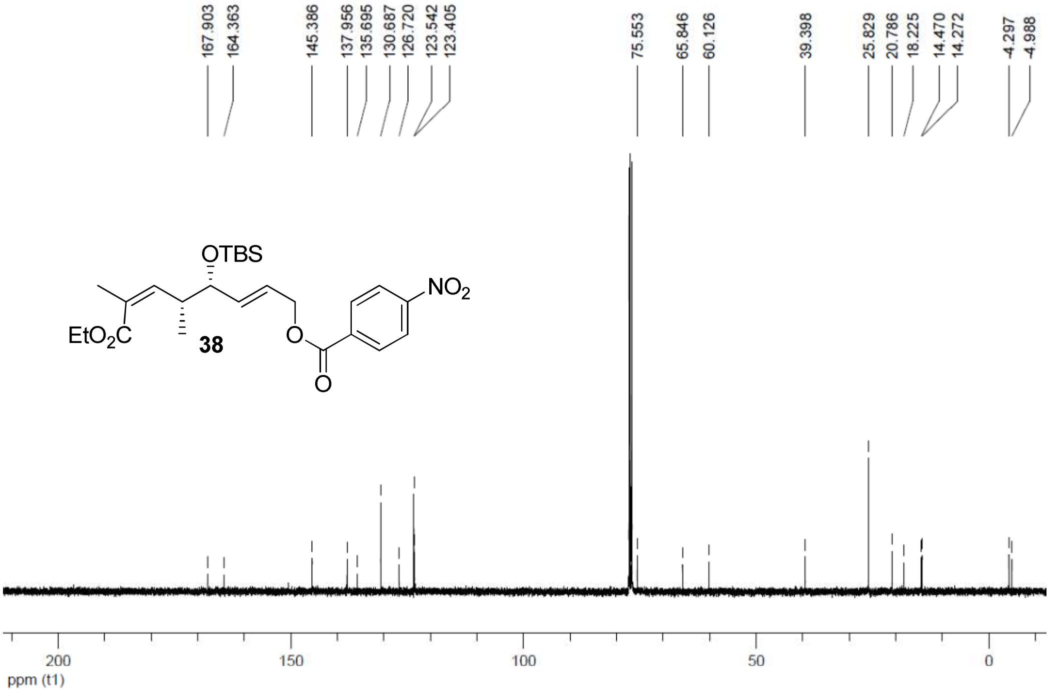

OTBS
EtO2C
36
1.90
1.99
0.97
0.97
2.05
3.01
3.23
3.15
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (t1)

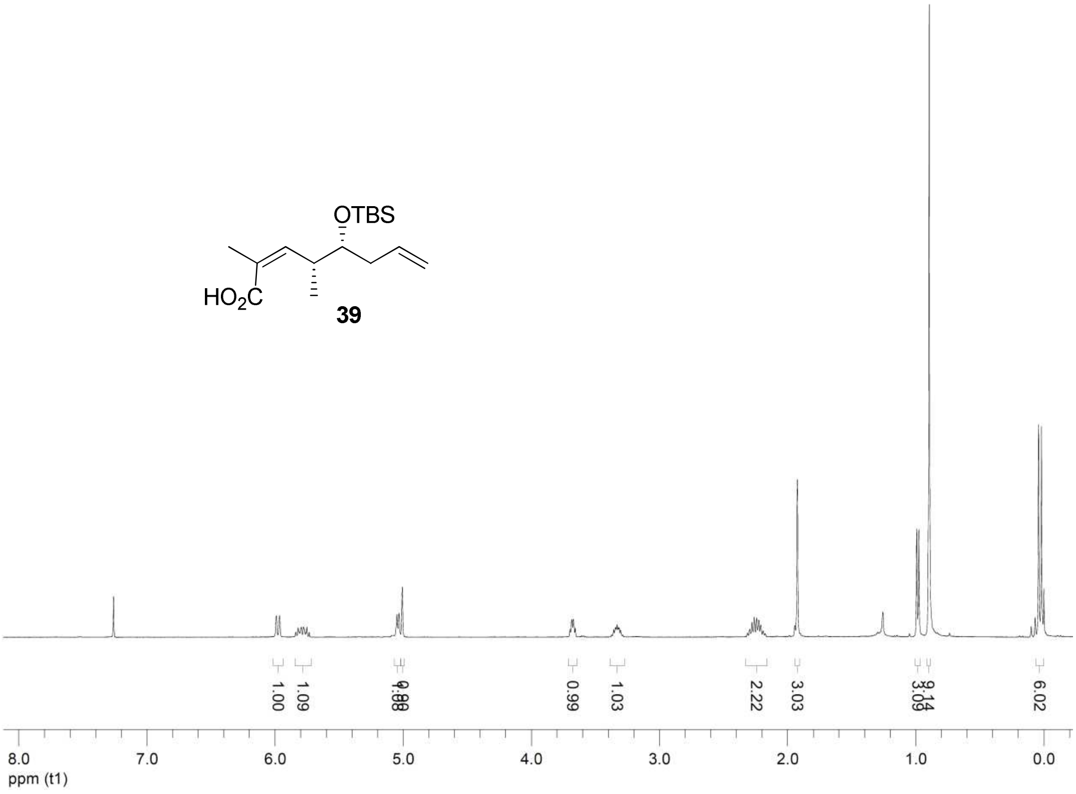

168.056
145.902
134.991
126.011
116.672
75.091
60.045
40.034
37.658
25.884
20.840
18.119
14.270
-4.057
-4.641
OTBS
EtO2C
36
200
150
100
50
0
ppm (t1)

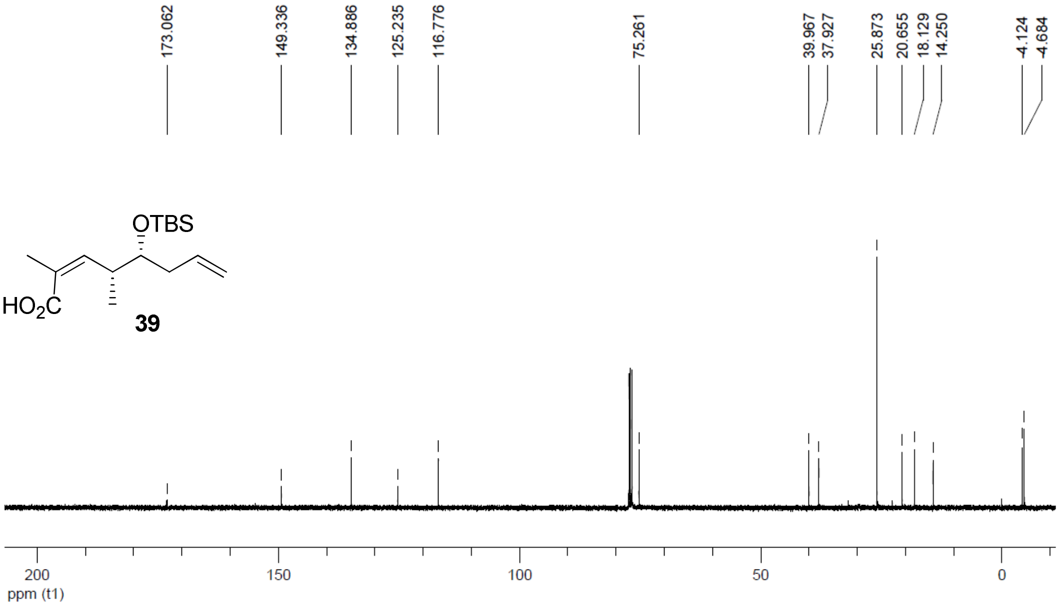

OTBS
EtO2C
O
O
37
NO2
3.84
0.99
1.00
0.99
1.06
0.95
2.04
1.00
1.04
2.92
3.53
3.07
8.98
5.70
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (t1)

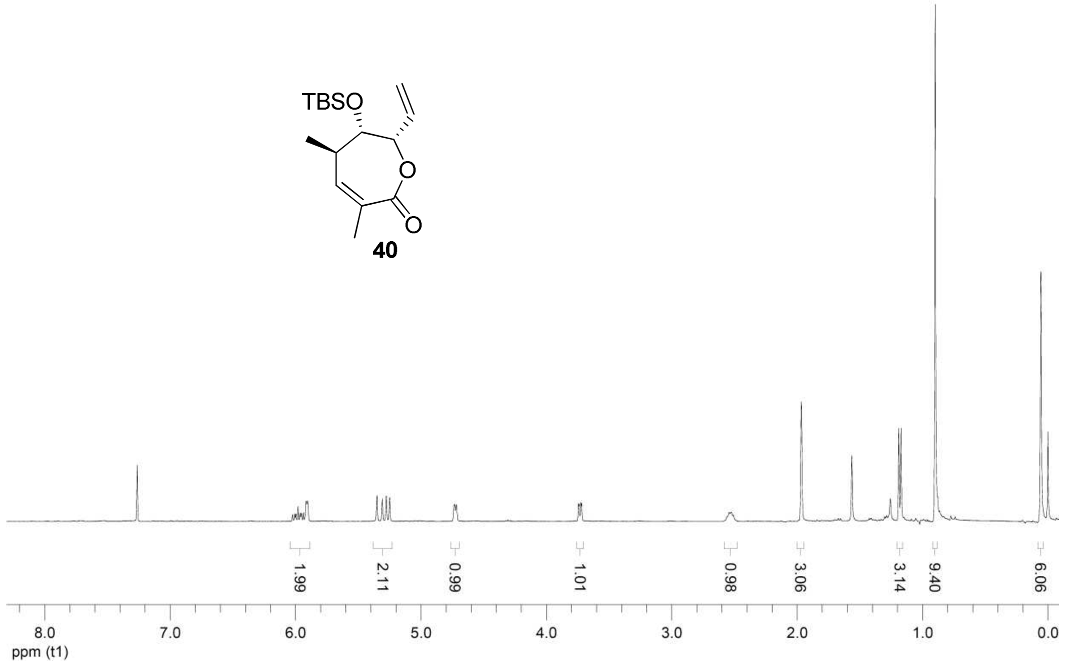

167.743
164.003
150.544
144.380
135.833
132.388
130.819
127.122
123.535
119.496
79.084
60.211
36.662
25.934
20.810
18.296
15.999
14.267
-3.821
-4.242
OTBS
EtO2C
O
O
37
NO2
200
150
100
50
0
ppm (t1)

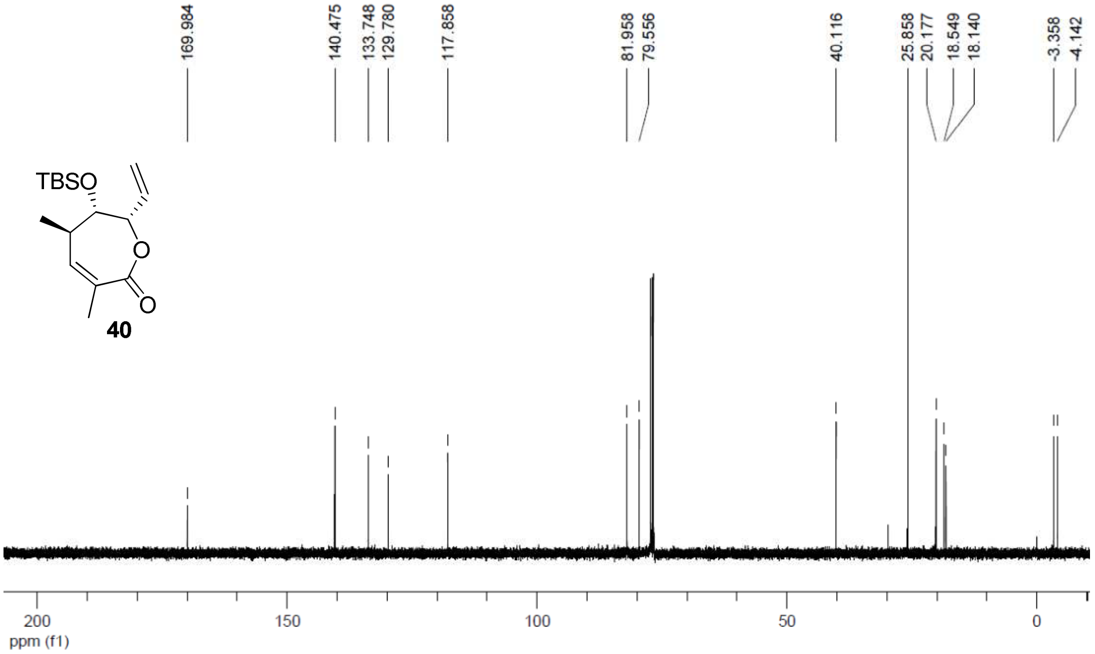

OTBS
NO2
EtO2C
38
O
O
1.74
1.78
1.98
1.98
1.78
2.95
0.99
2.94
3.13
3.03
9.00
6.06
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (t1)


167.903
164.363
145.386
137.956
135.695
130.687
126.720
123.542
123.405
75.553
65.846
60.126
39.398
25.829
20.786
18.225
14.470
14.272
-4.297
-4.988
OTBS
NO2
EtO2C
38
O
O
200
150
100
50
0
ppm (t1)

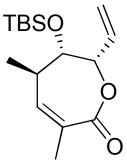

OTBS
HO2C
39
1.00
1.09
1.00
0.98
0.99
1.03
2.22
3.03
3.09
9.14
6.02
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (t1)

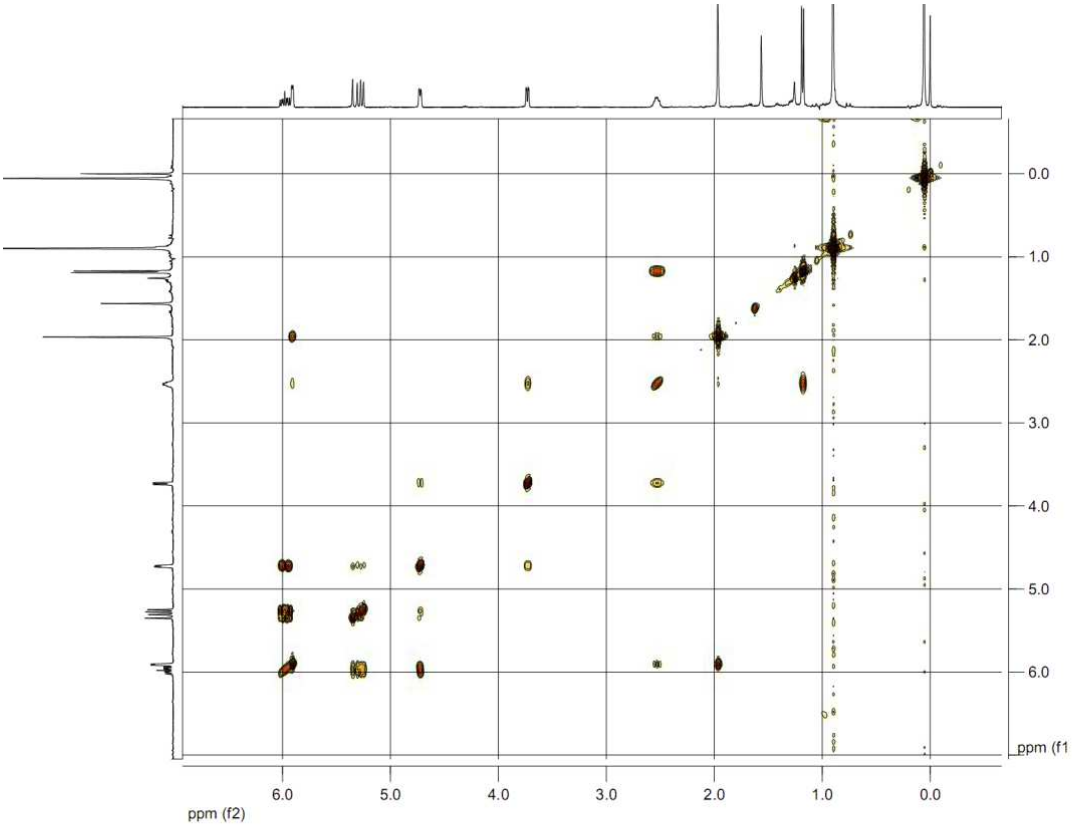

173.062
149.336
134.886
125.235
116.776
75.261
39.967
37.927
25.873
20.655
18.129
14.250
-4.124
-4.684
OTBS
HO2C
39
200
150
100
50
0
ppm (t1)


TBSO
O
O
40
1.99
2.11
0.99
1.01
0.98
3.06
3.14
9.40
6.06
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (t1)

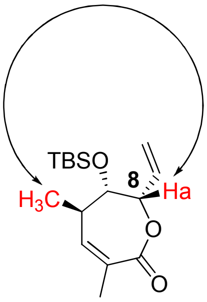

169.984
140.475
133.748
129.780
117.858
81.958
79.556
40.116
25.858
20.177
18.549
18.140
-3.358
-4.142
TBSO
O
O
40
200
150
100
50
0
ppm (f1)

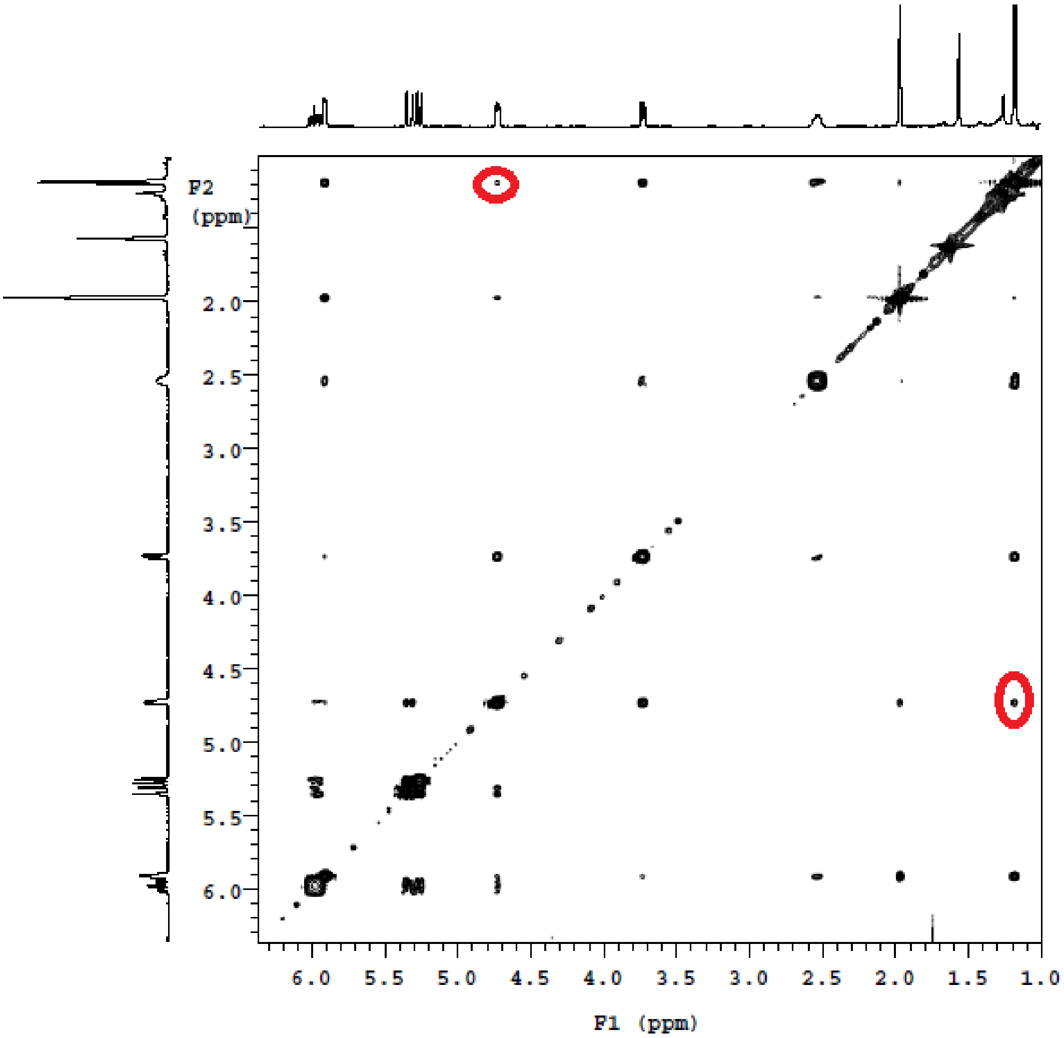
^{1}H-^{1}H COSY of compound 40

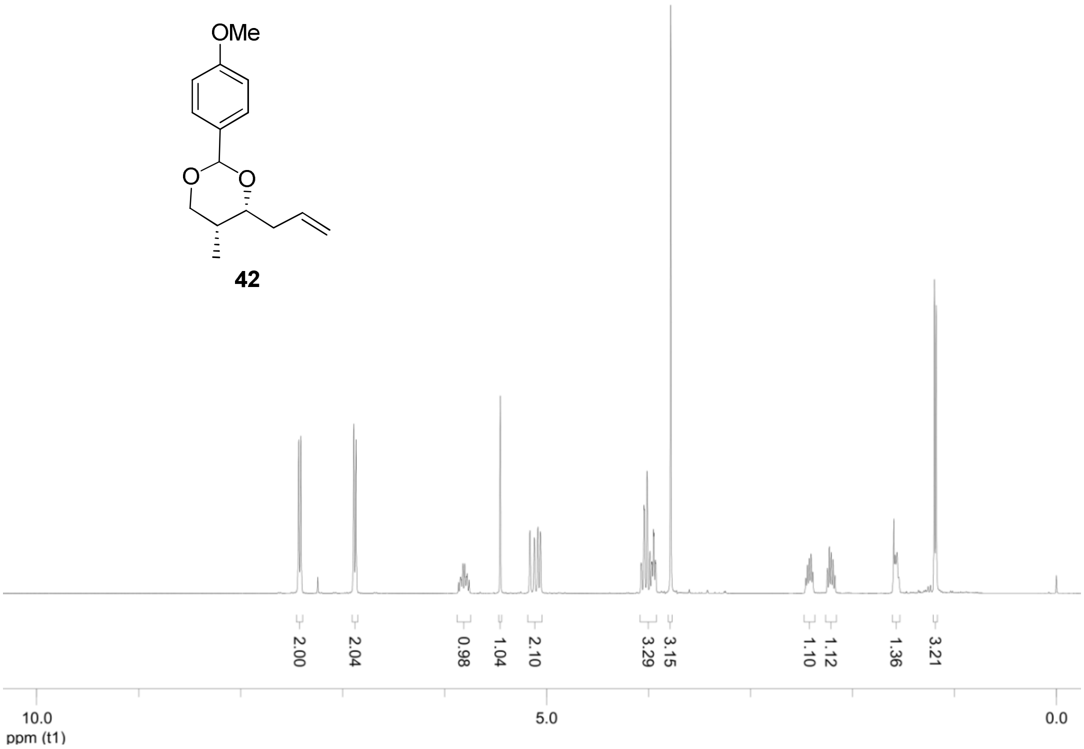




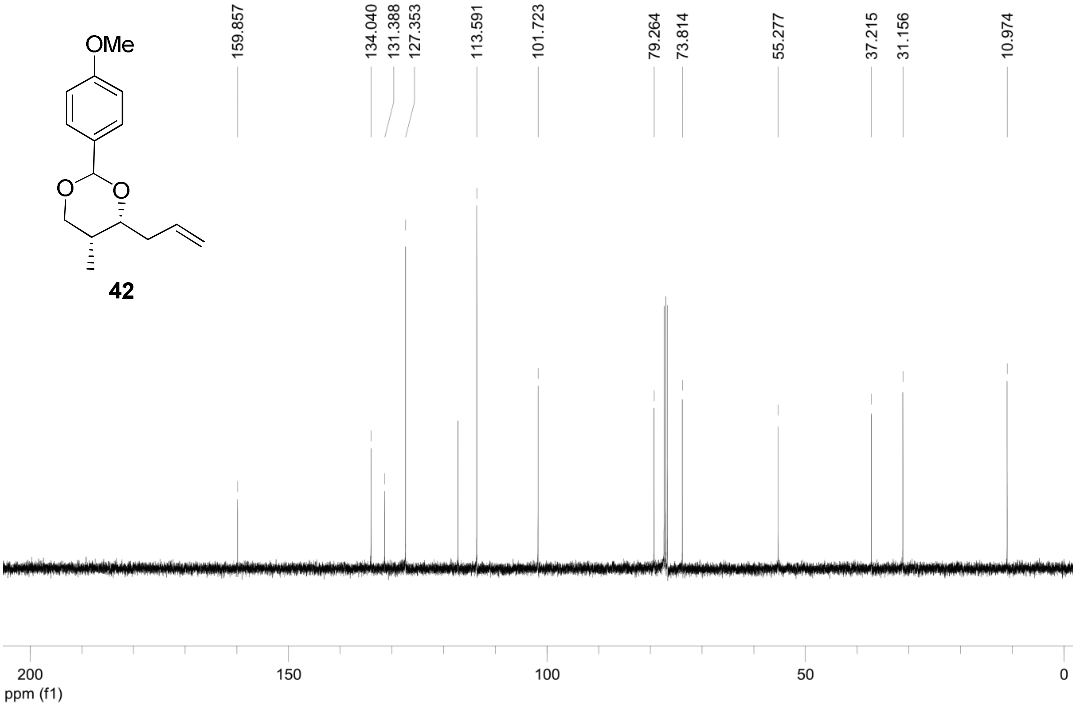
^{1}H-^{1}H NOESY of compound 40



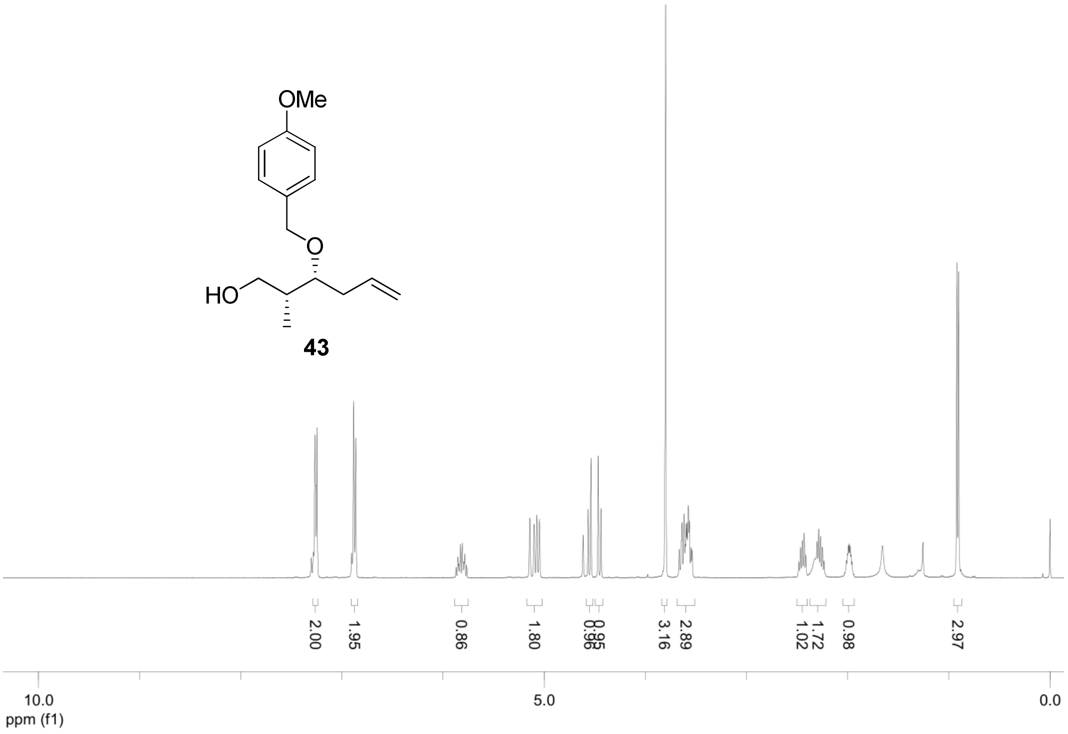


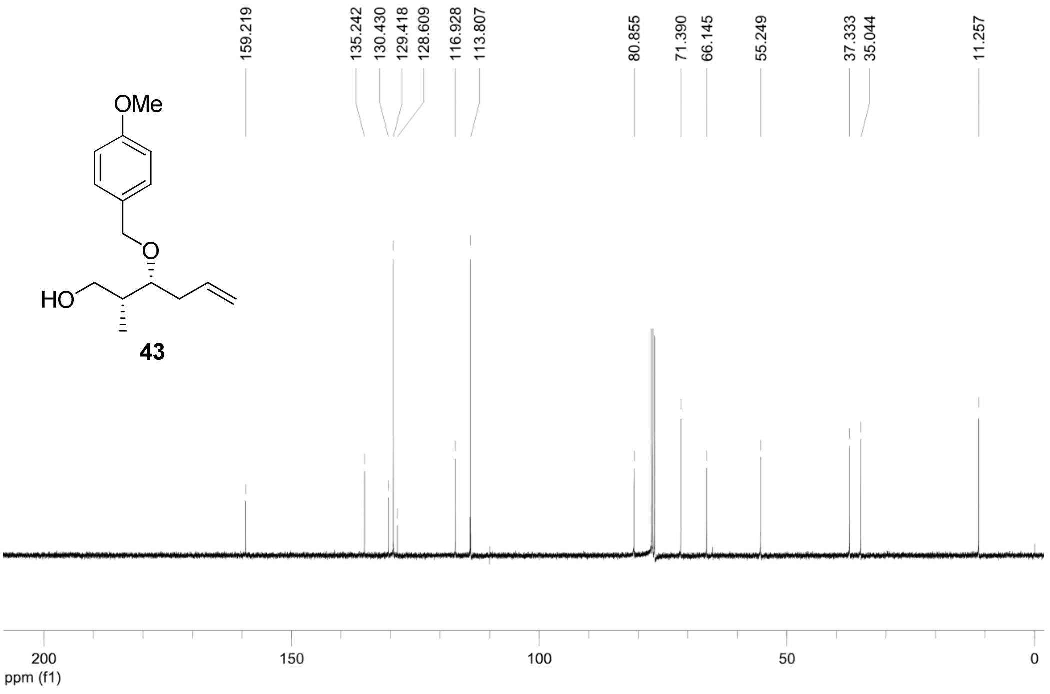

OMe
O
O
2.00
2.04
0.98
1.04
2.10
3.29
3.15
1.10
1.12
1.36
3.21
10.0
5.0
0.0
ppm (t1)

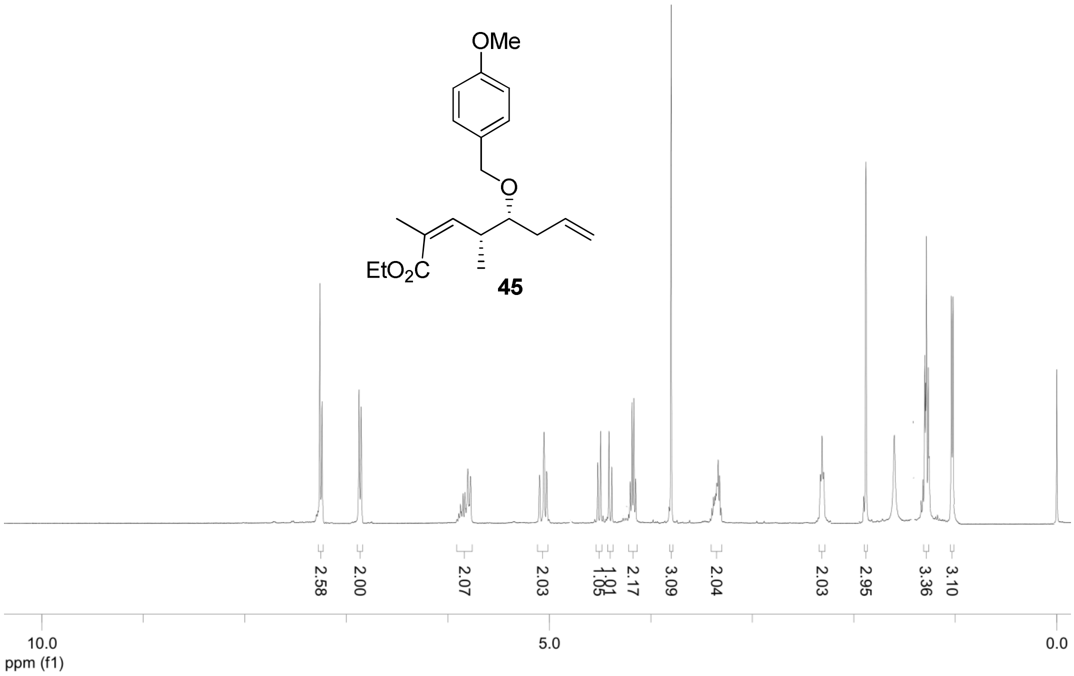
42

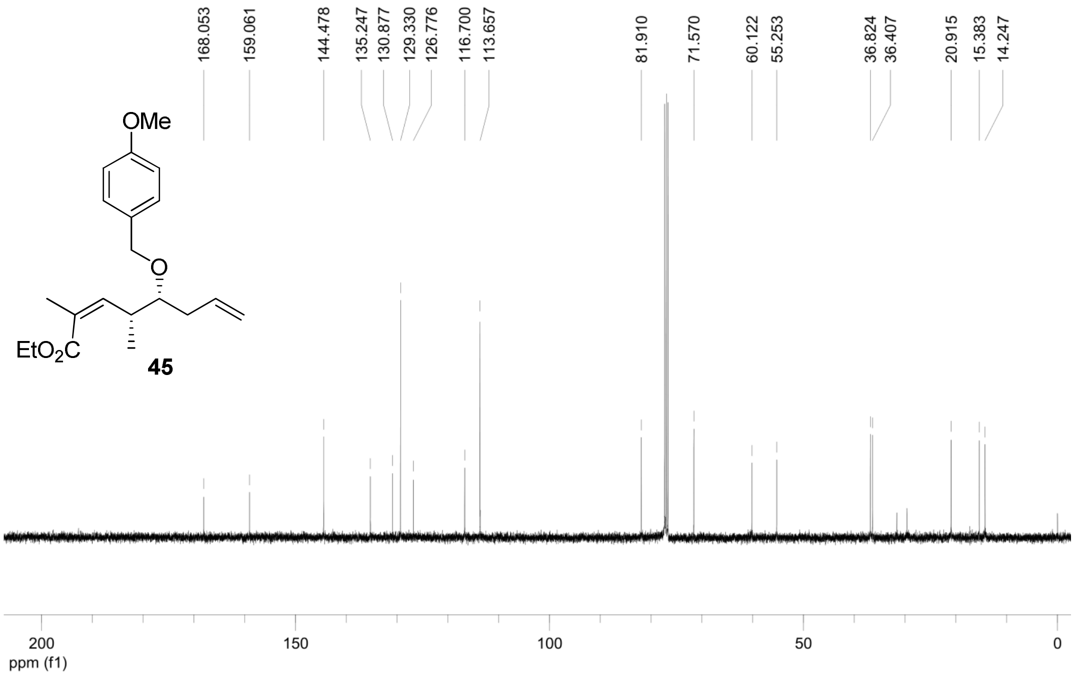

OMe
O
O
159.857
134.040
131.388
127.353
113.591
101.723
79.264
73.814
55.277
37.215
31.156
10.974
200
150
100
50
0
ppm (f1)

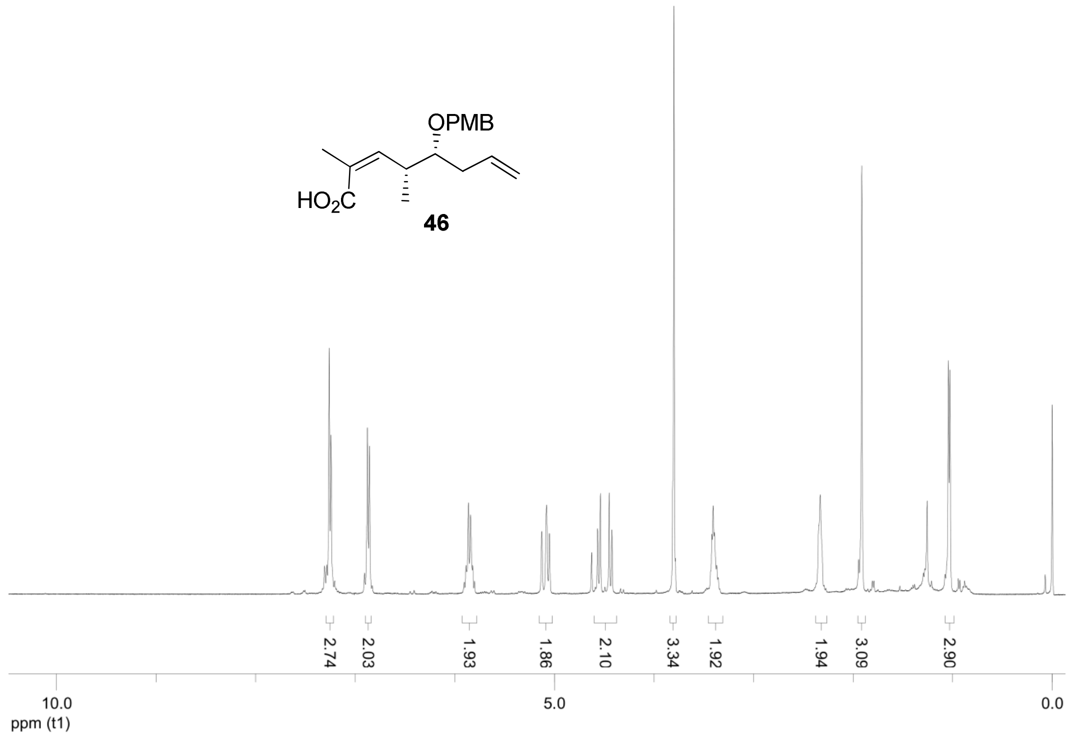
42

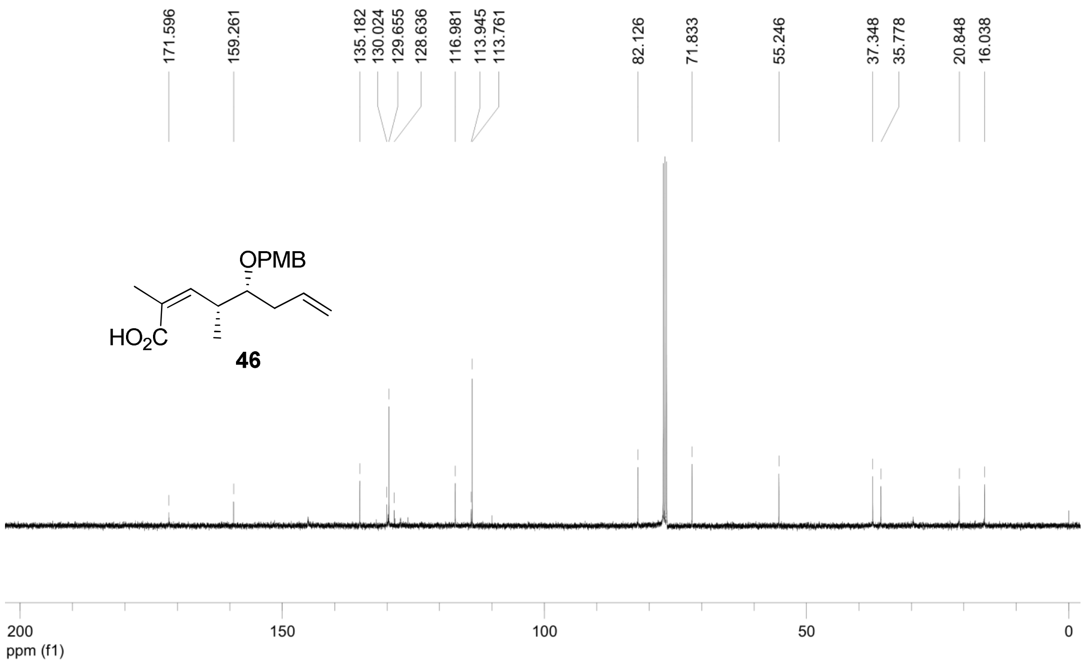

OMe
O
HO
43
2.00
1.95
0.86
1.80
0.96
0.95
3.16
2.89
1.02
1.72
0.98
2.97
10.0
ppm (f1)
5.0
0.0

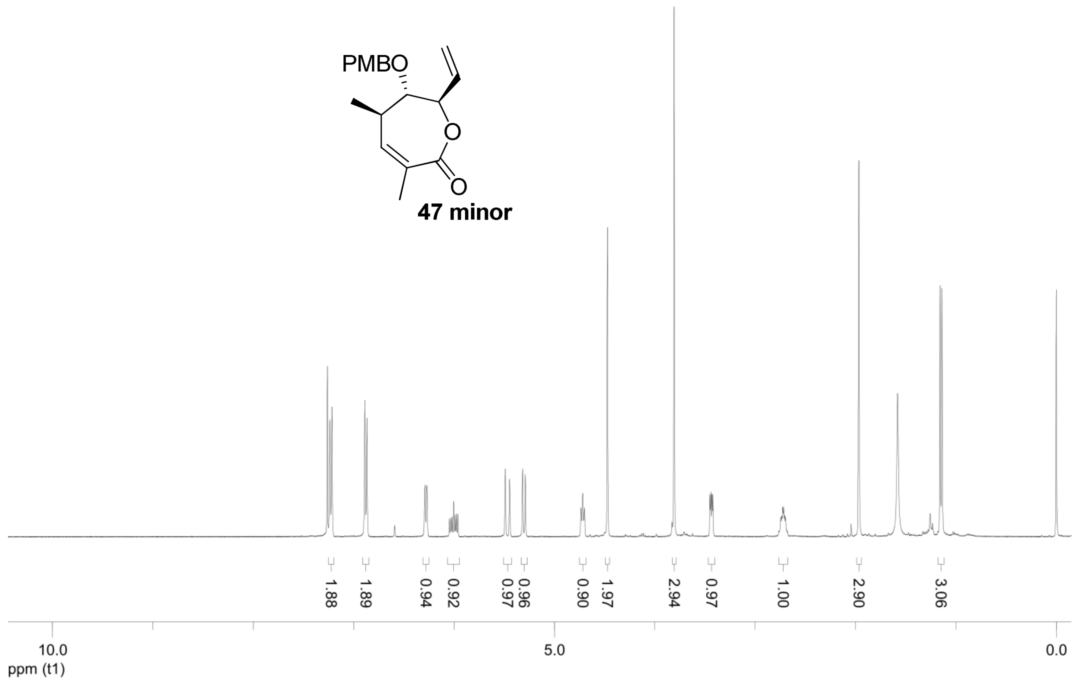

159.219
135.242
130.430
129.418
128.609
116.928
113.807
80.855
71.390
66.145
55.249
37.333
35.044
11.257
OMe
O
HO
43
200
ppm (f1)
150
100
50
0

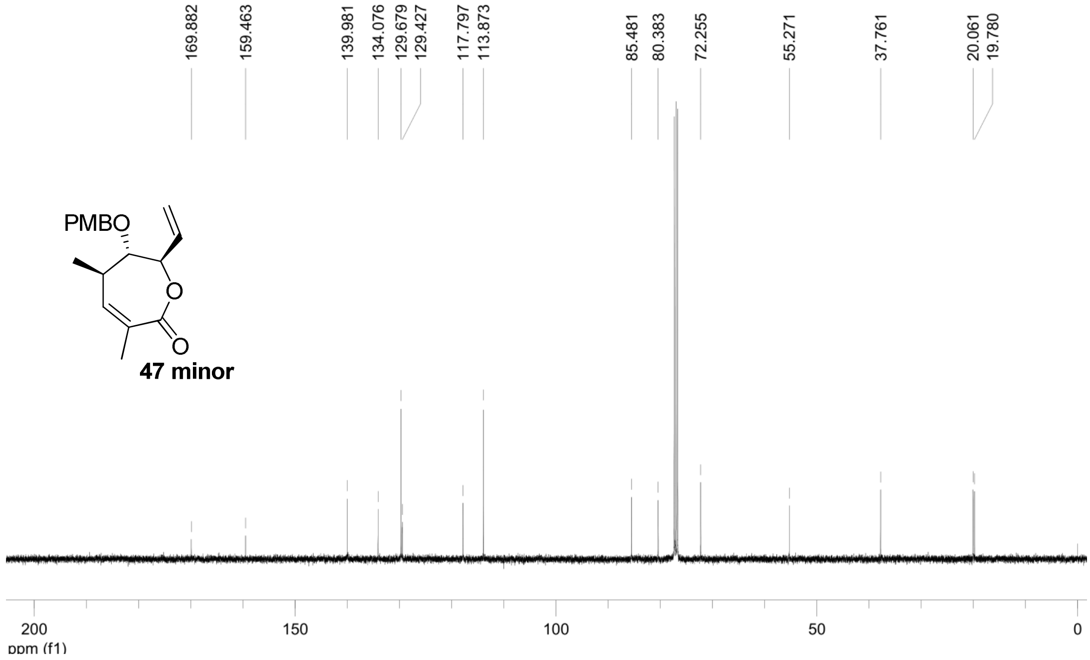

OMe
O
EtO2C
45
2.58
2.00
2.07
2.03
1.05
1.01
2.17
3.09
2.04
2.03
2.95
3.36
3.10
10.0
5.0
0.0
ppm (f1)

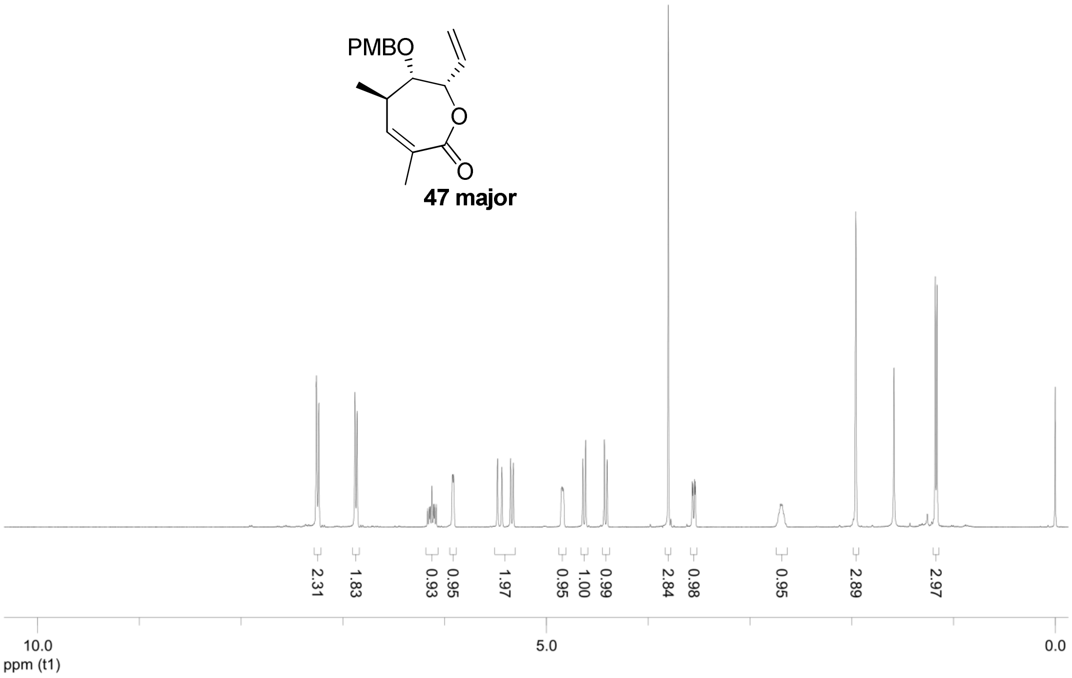

168.053
159.061
144.478
135.247
130.877
129.330
126.776
116.700
113.657
81.910
71.570
60.122
55.253
36.824
36.407
20.915
15.383
14.247
OMe
O
EtO2C
45
200
150
100
50
0
ppm (f1)

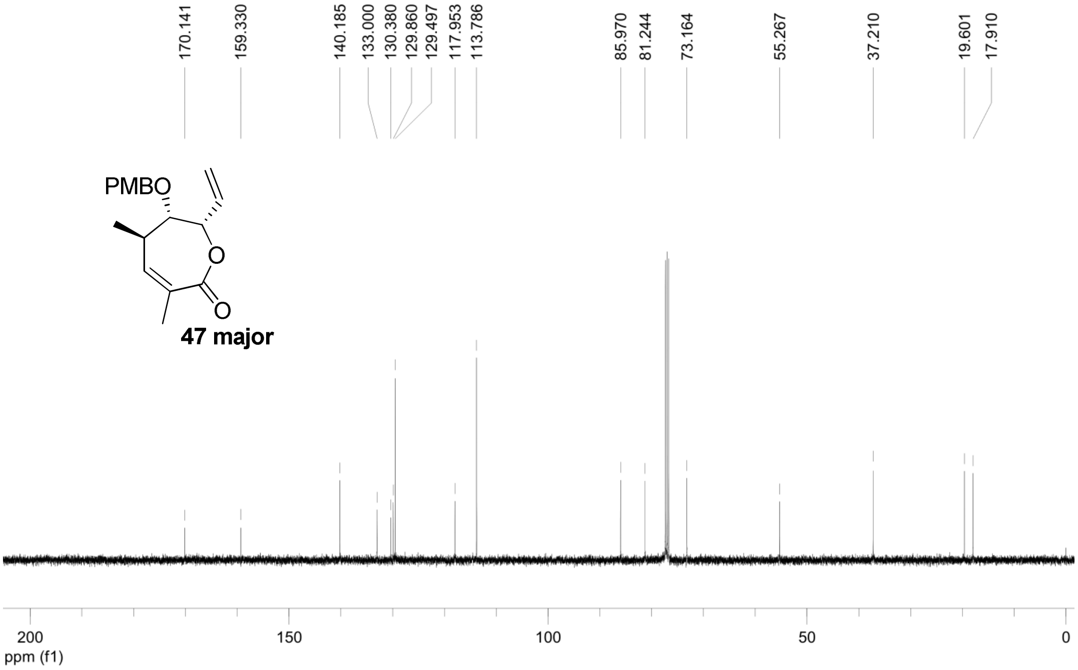

OPMB
HO2C
46
2.74
2.03
1.93
1.86
2.10
3.34
1.92
1.94
3.09
2.90
10.0
5.0
0.0
ppm (t1)


171.596
159.261
135.182
130.024
129.655
128.636
116.981
113.945
113.761
82.126
71.833
55.246
37.348
35.778
20.848
16.038
OPMB
HO2C
46
200
150
100
50
0
ppm (f1)

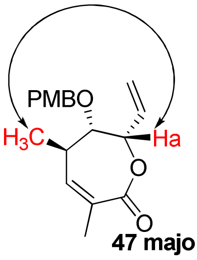

PMBO
O
O
47 minor
1.88
1.89
0.94
0.92
0.97
0.96
0.90
1.97
2.94
0.97
1.00
2.90
3.06
10.0
5.0
0.0
ppm (t1)


169.882
159.463
139.981
134.076
129.679
129.427
117.797
113.873
85.481
80.383
72.255
55.271
37.761
20.061
19.780
PMBO
O
O
47 minor
200
150
100
50
0
ppm (f1)

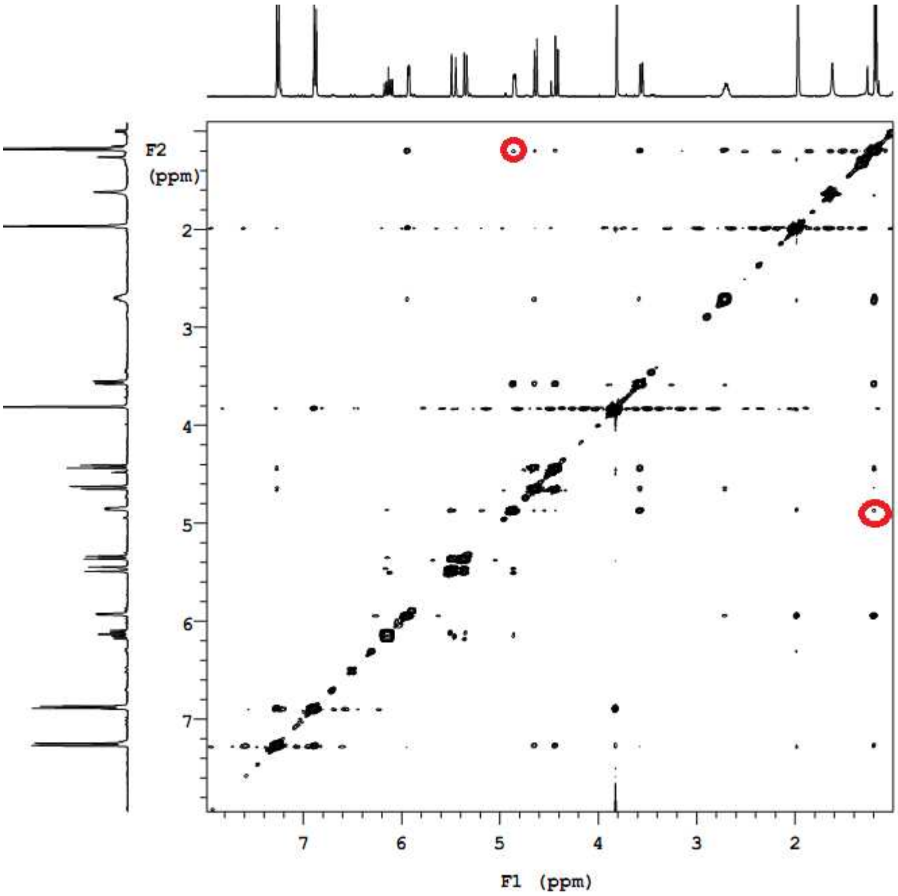

PMBO
O
O
47 major
2.31
1.83
0.93
0.95
1.97
0.95
1.00
0.99
2.84
0.98
0.95
2.89
2.97
10.0
ppm (t1)
5.0
0.0


170.141
159.330
140.185
133.000
130.380
129.860
129.497
117.953
113.786
85.970
81.244
73.164
55.267
37.210
19.601
17.910
PMBO
O
O
47 major
200
ppm (f1)
150
100
50
0

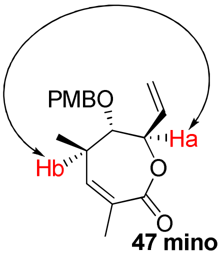
^{1}H-^{1}H NOESY of compound 47 major



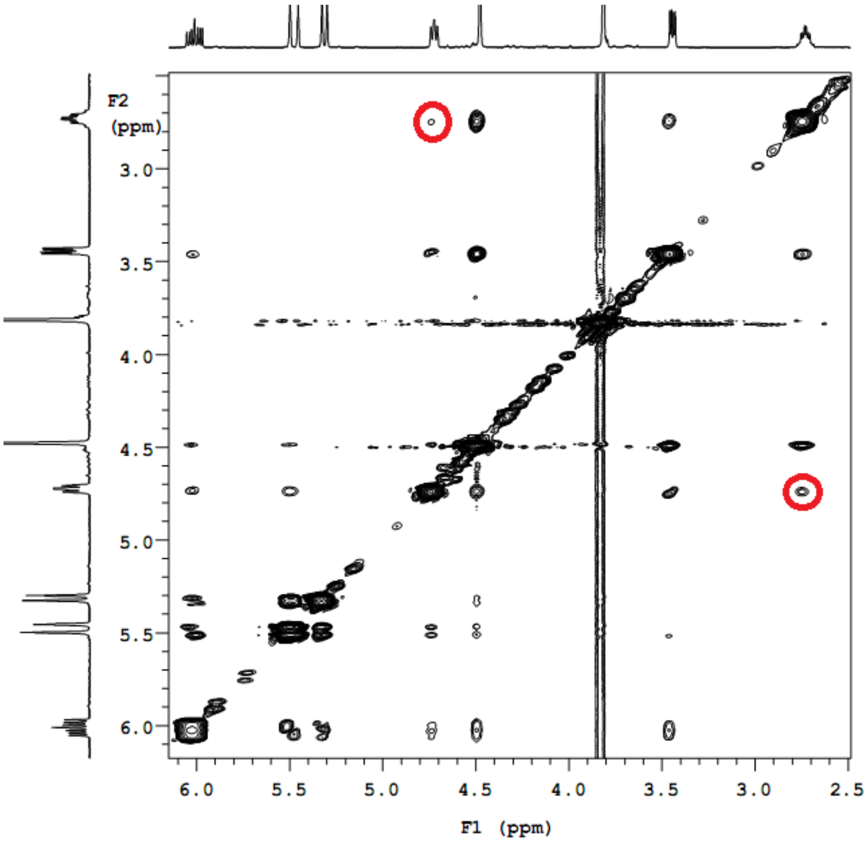
47 major



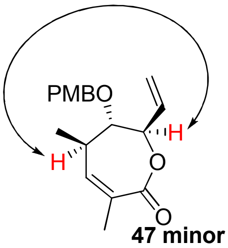
^{1}H-^{1}H NOESY of compound 47 minor



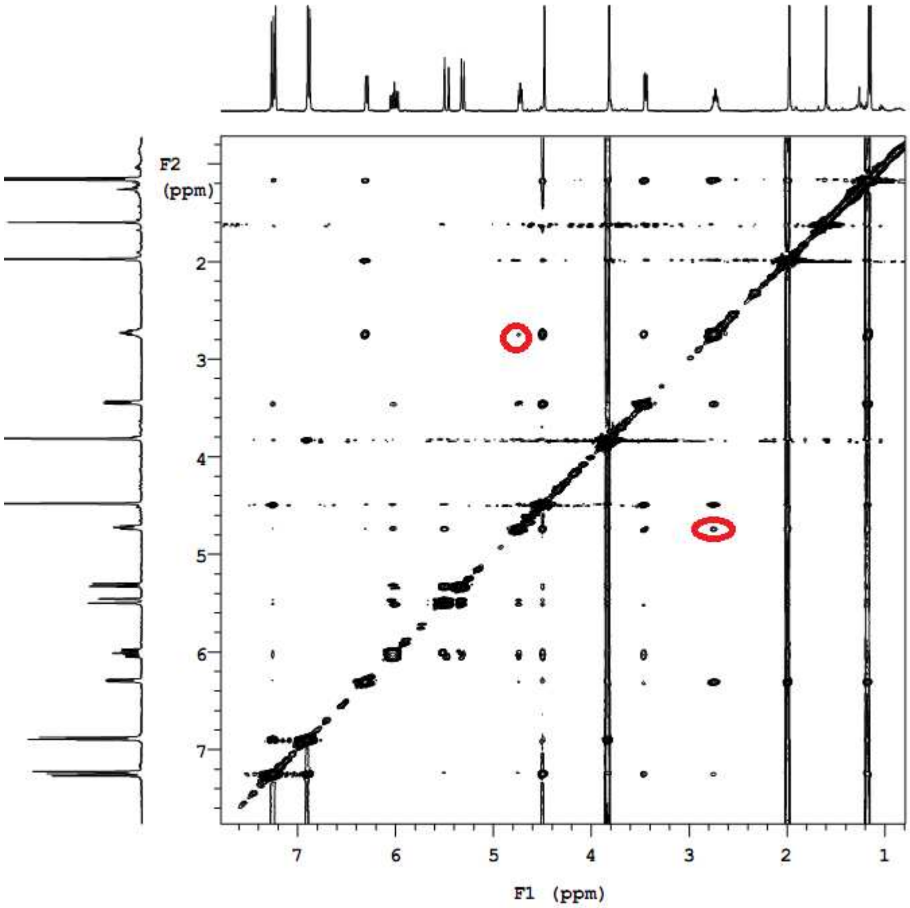
47 minor

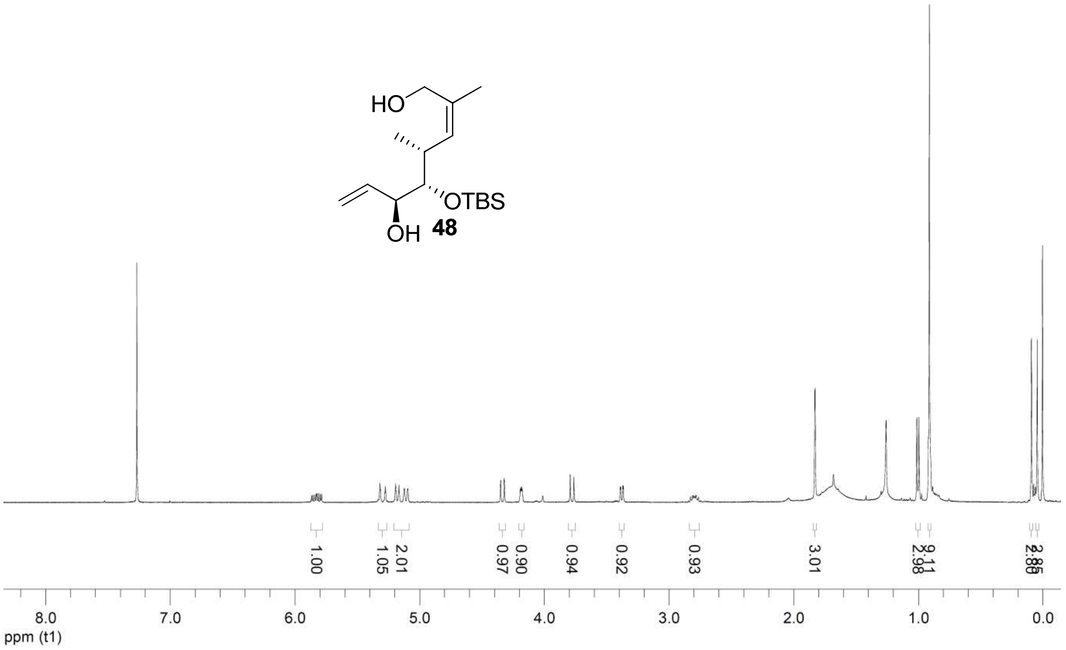


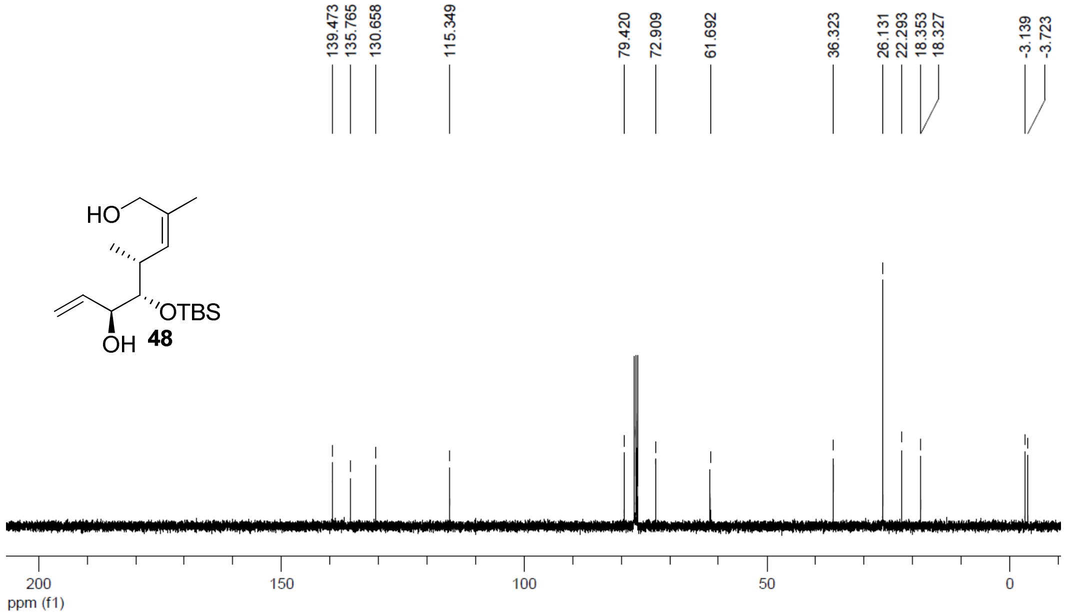
^{1}H-^{1}H NOESY of compound 47 minor

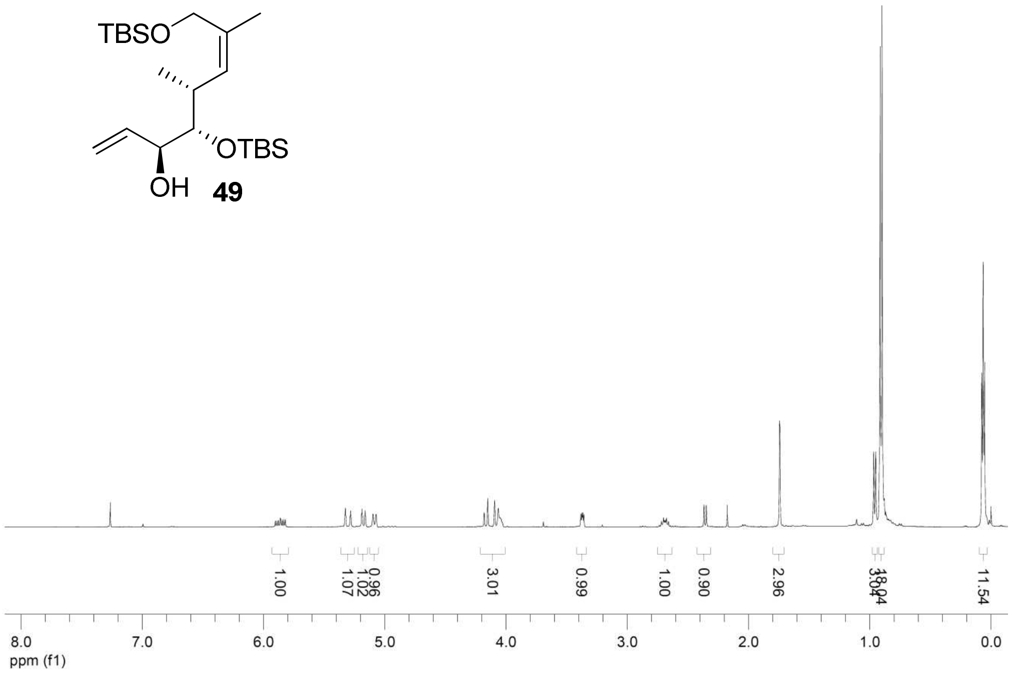


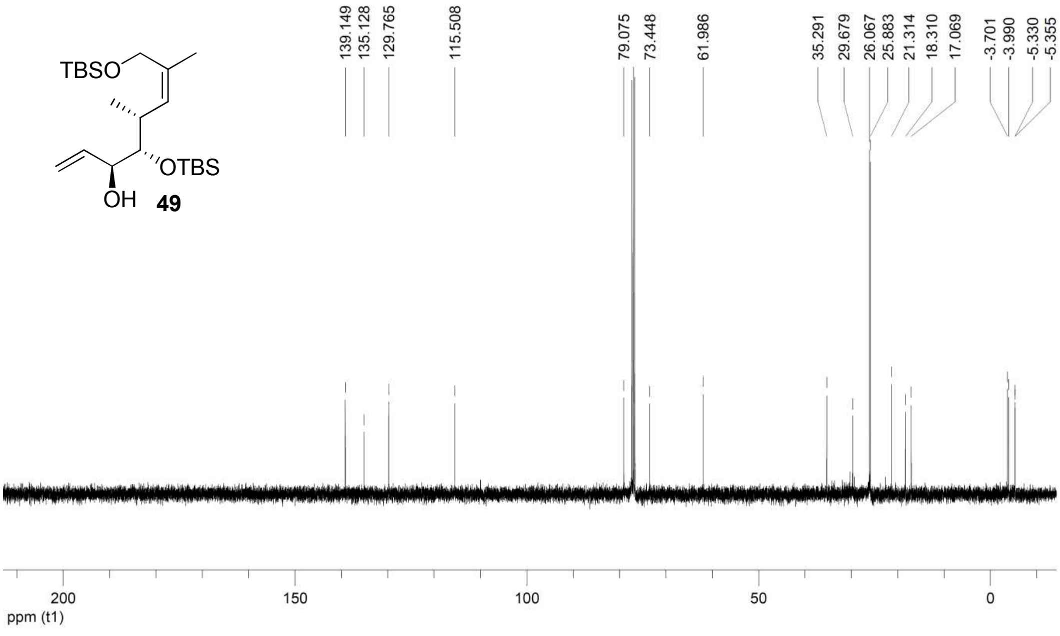
47 minor

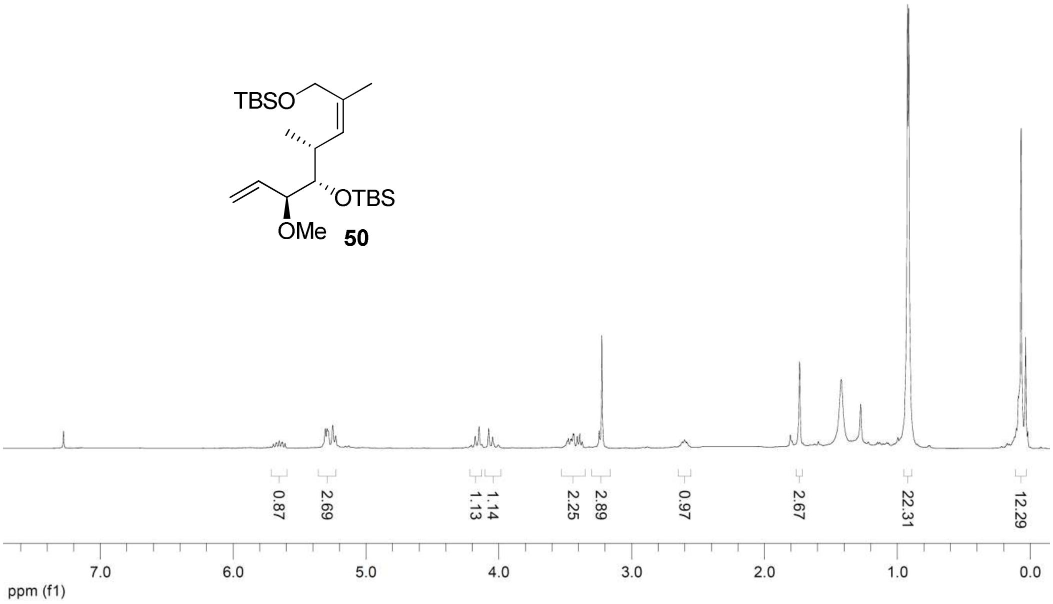


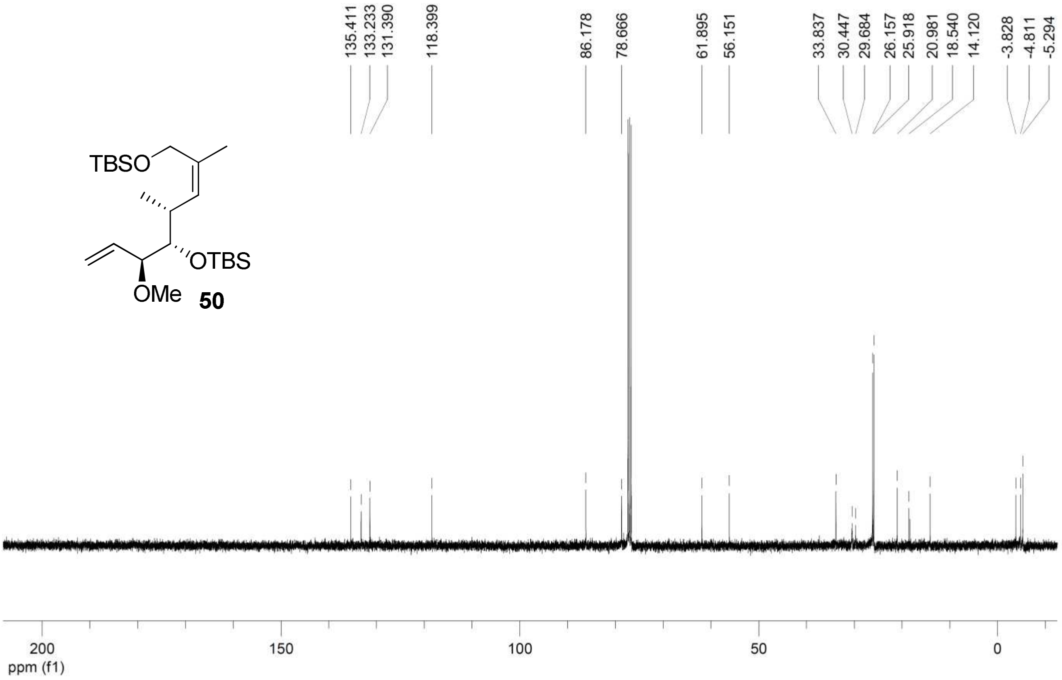

HO
OTBS
OH
48
1.00
1.05
2.01
0.97
0.90
0.94
0.92
0.93
3.01
2.98
9.11
2.85
2.80
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (t1)


139.473
135.765
130.658
115.349
79.420
72.909
61.692
36.323
26.131
22.293
18.353
18.327
-3.139
-3.723
HO
OTBS
OH
48
200
150
100
50
0
ppm (f1)


TBSO
OTBS
OH
49
1.00
1.07
1.02
0.96
3.01
0.99
1.00
0.90
2.96
3.04
18.04
11.54
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (f1)


139.149
135.128
129.765
115.508
79.075
73.448
61.986
35.291
29.679
26.067
25.883
21.314
18.310
17.069
-3.701
-3.990
-5.330
-5.355
TBSO
OTBS
OH
49
200
150
100
50
0
ppm (t1)


TBSO
OTBS
OMe
50
0.87
2.69
1.13
1.14
2.25
2.89
0.97
2.67
22.31
12.29
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (f1)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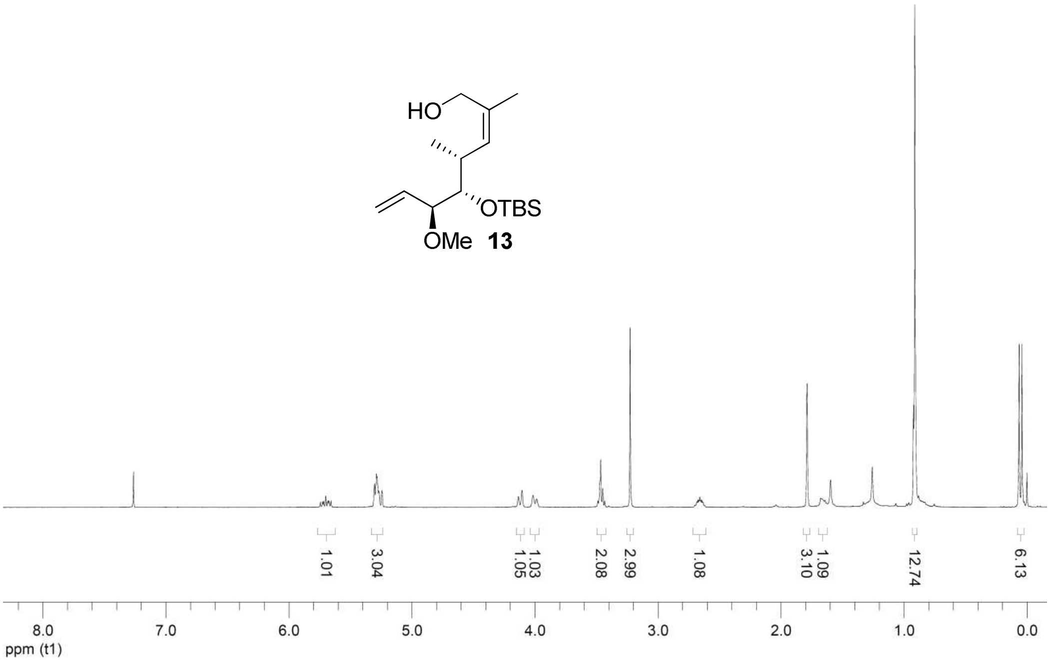
131.390
118.399
86.178
78.666
61.895
56.151
33.837
30.447
29.684
26.157
25.918
20.981
18.540
14.120
-3.828
-4.811
-5.294
TBSO
OTBS
OMe
50
200
150
100
50
0
ppm (f1)


HO
OTBS
OMe 13
1.01
3.04
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1.03
2.08
2.99
1.08
3.10
1.09
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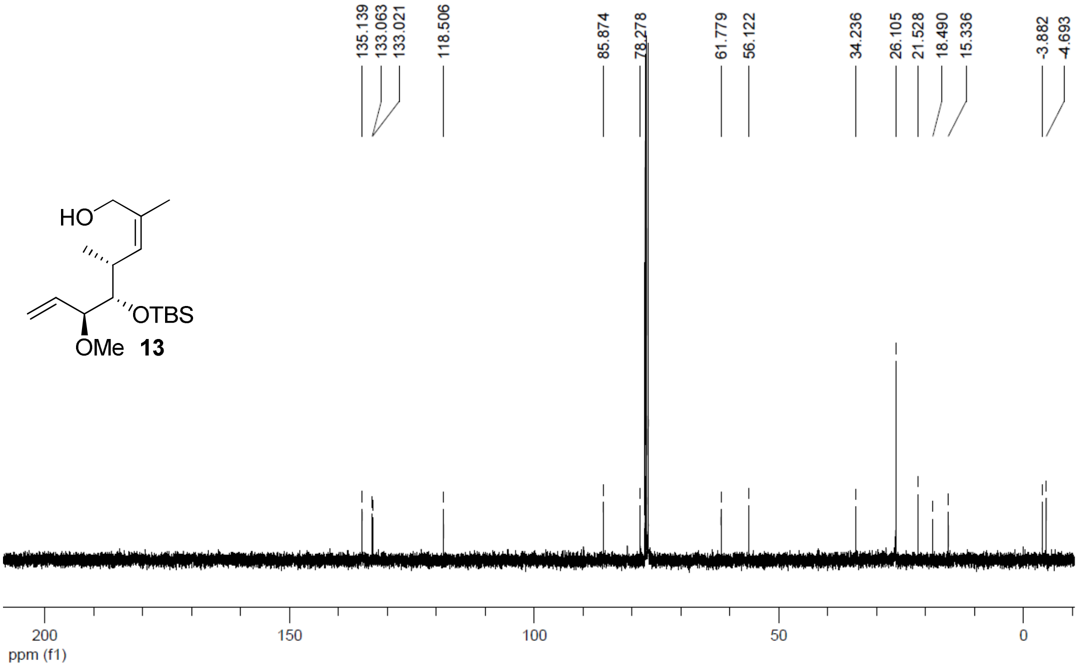
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78.278
61.779
56.122
34.236
26.105
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15.336
-3.882
-4.693
HO
OTBS
OMe 13
200
150
100
50
0
ppm (f1)

CHAPTER 3

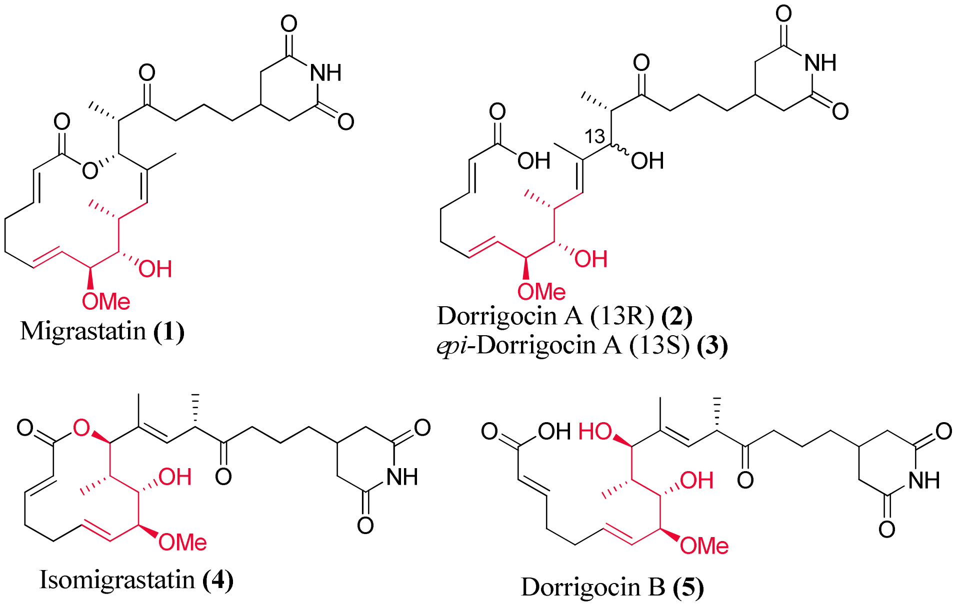
SYNTHETIC STUDIES TOWARDS A UNIFIED STRATEGY FOR ALL FAMILY MEMBERS OF MIGRASTATIN

Reference:

Narendar Reddy Gade and Javed Iqbal. *Manuscript submitted*

3.1. Introduction

Cancer metastasis, a major cause for cancerous deaths, has elicited keen interest among researchers to combat it using small molecule derived cell migration inhibitors. Migrastatin family of natural products (Fig. 3.1) are important class of molecules possessing cell migration inhibitory properties.[1] Structurally, migrastatin (**1**) is a 14-membered macrolide, while its related analogs, dorrigocin A (**2**) and 13-epi dorrigocin A (**3**) are acyclic variants with *E*-olefin geometry at C11-C12. Similarly, isomigrastatin (**4**) is a 12-memberd macrocycle and dorricoin B (**5**) is acyclic variant of isomigrastatin (Fig. 3.1). All these compounds possess a common C1-C10 skeleton. Danishefksy’s pioneering work on the synthesis of family of migrastatin and its analogues has shown the importance of this class and they have also demonstrated that analogous skeleletons present in these natural products could be derived by applying a diverted total synthesis approach.[2] Thus, the structural complexity and biological activity of migrastatin family prompted many scientific groups to work on the synthetic and biological aspects of these molecules.[3,4] In spite of several synthetic studies known for these natural products and their analogues, there still is a need to develop a common and commercially viable new strategies to access these pharmaceutically important class of molecules. This chapter deals with our synthetic efforts to access migrastatin analogues via an asymmetric C-H oxidation reaction as the key step.



Migrastatin (**1**)

Dorrigocin A (13R) (**2**)
epi-Dorrigocin A (13S) (**3**)

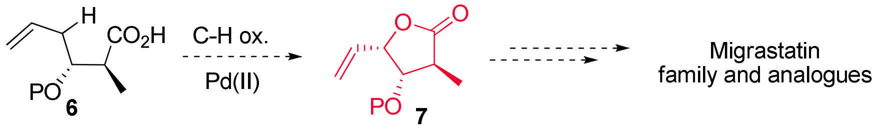
Isomigrastatin (**4**)

Dorrigocin B (**5**)

Figure 3.1. Migrastatin family members

3.2. Proposed synthetic plan

Based on the reported literature[2,3] and our previous studies,[3d-f] we envisioned that *β*-hydroxy-*γ*-butyrolactone **7** could be a common intermediate for accessing all the family members of migrastatin (Scheme 3.1). An extensive literature search revealed that the *β*-hydroxy-*γ*-butyrolactones are privileged substructures present in several biologically important natural products[5] or used as intermediates in natural product syntheis,[6] and many synthetic methodologies have been developed to access them.[7] The syntheses of 5-membered vinyl lactones using C-H oxidation methods have been reported,[8] however, stereoselective syntheses of *β*-hydroxy-*γ*-butyrolactones **7** is not known as yet. So, we envisioned that the allylic C-H oxidation of fragments like 2-methyl-3-hydroxy-hex-5-enoic acid **6** leading to **7** can serve as a versatile methodology for accessing the fully substituted chiral vinyl lactones (Scheme 3.1). It is noteworthy that lactone **7** is characterized by three important features; 1) presence of the alk-1-en-3,4-diol[9] system (numbering given based on olefin), 2) containing three contagious chiral centers (very common pattern present in tedanolides,[10a] amphidinolides,[10b] bafilomycins,[10c,d] thuggacins,[10e] and benzoquinone ansamycin antibiotics,[10f] etc.), and 3) most importantly presence of both terminal olefin and ester orthogonal functionalities, which can be used as handle to install the further functionalities required in natural products synthesis.



Scheme 3.1

3.3. Results & Discussion

In the current approach to *β*-hydroxy-*γ*-butyrolactones (Fig. 3.2, eq. 1), we have utilized a regio and stereoselective Pd(II)/sulfoxide-catalyzed allylic C-H oxidation reaction developed by White and co-workers for the synthesis of anti-1,4-dioxan-2-one from the homoallylic oxygenates (Fig. 3.2, eq. 2).[11] Accordingly, we prepared racemic 3-hydroxy-hex-5-enoic acid **10** (Scheme 3.2), from **9** which was derived from ethyl cyanoacetate **8** using Barbier reaction.[12] Thus, *β*-keto ester was reduced to the corresponding alcohol which upon PMB protection (PMBOC(=NH)CCl_3, CSA) followed by ester hydrolysis afforded the desired racemic acid **10**.[13] The acid **10** was subjected to White's oxidation conditions to afford a diastereomeric mixture (5:1) of lactone **11** in 60% yield. The relative stereo chemistry of the major diastereomer **11** was confirmed by conversion to the known compound **12.**[14]

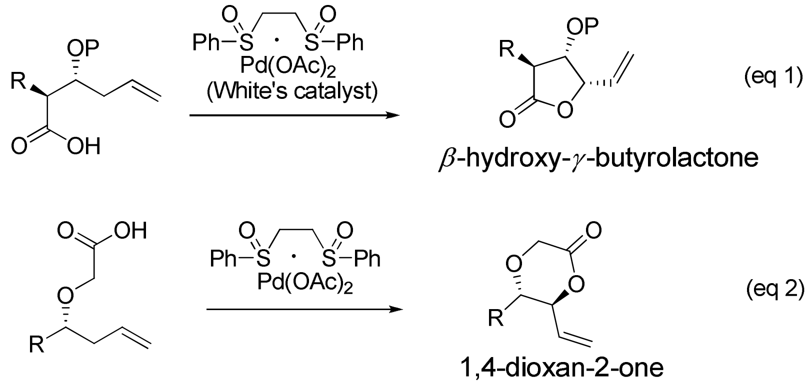
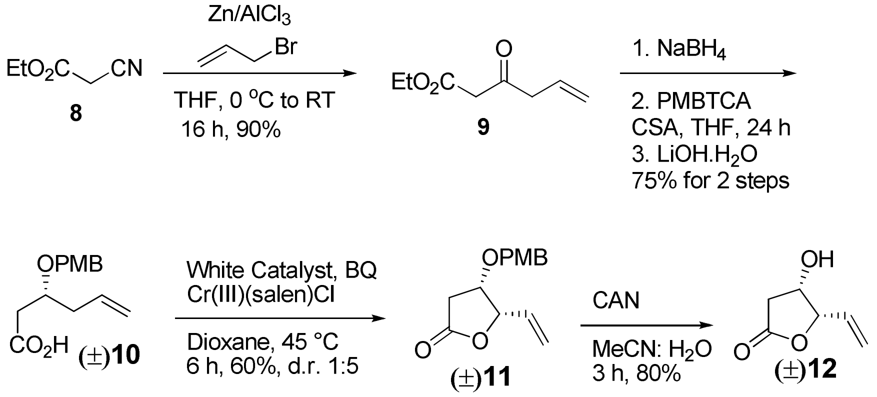


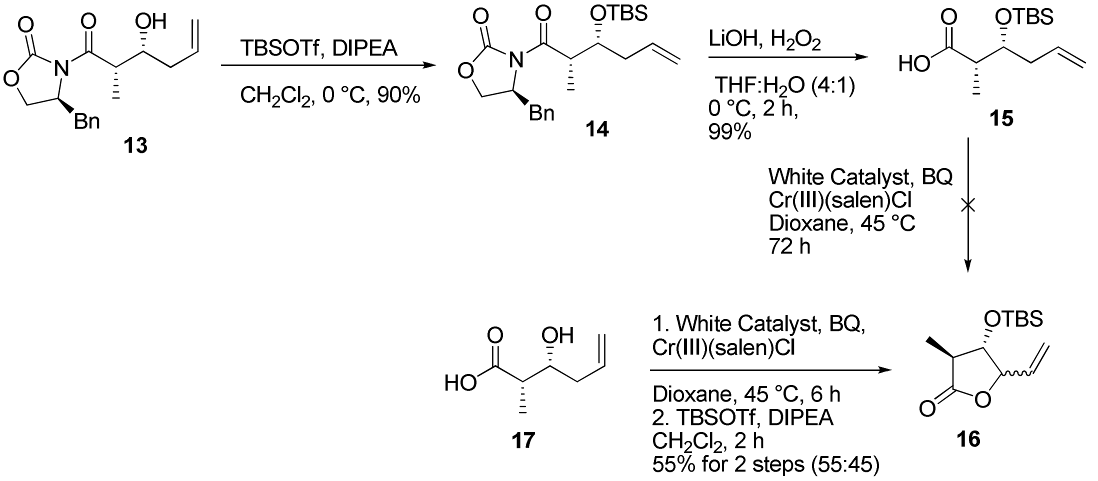
Figure 3.2. Application of White's oxidation in synthesis of vinyl lactones

A literature search revealed the versatility of lactone **12** which has been used in the synthesis of (+)-cardiobutanolide,[15] Hagen's gland lactones,[16] and the benzyl protected lactone like **11** was used in the synthesis of all brevicomins, styryllactones, cardiobutanolide, cardiobutanolide, and goniofufurone.[17] Also, the saturated lactone was used in the formal synthesis of (−)-isolaurepinnacin and (+)-rogioloxepane,[18] and the corresponding acid was used in the total synthesis of decarestrictine-D.[19]



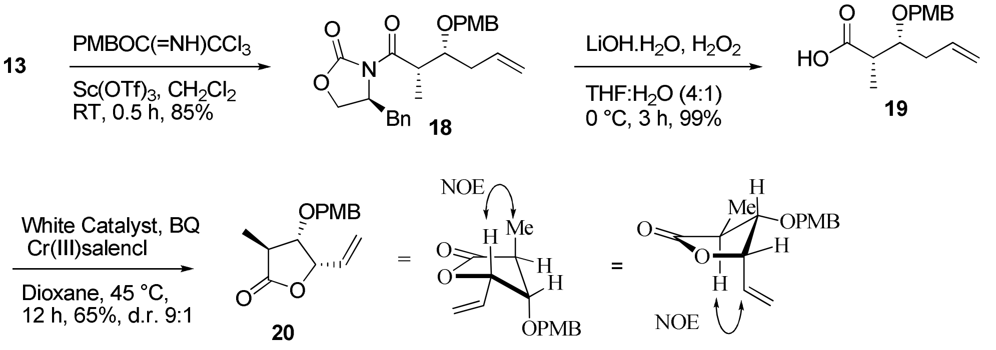
Scheme 3.2.

In order to access the trisubstituted asymmetric *β*-hydroxy-*γ*-butyrolactones (Scheme 3.3), we started from aldol adduct **13** followed by silyl protection gave **14**.[3f] Silyl ether **14** was subjected to hydrolysis to get the corresponding acid **15**, and later was subjected to White's oxidation, however, no desired product **16** was obtained and the starting materials remained largely intact even after 72 h. We then applied the White's reaction conditions (6 h) on acid **17** resulting in the lactone intermediate which was treated with TBSOTf to afford a separable diastereomeric mixture (55:45) of **16**.[20]



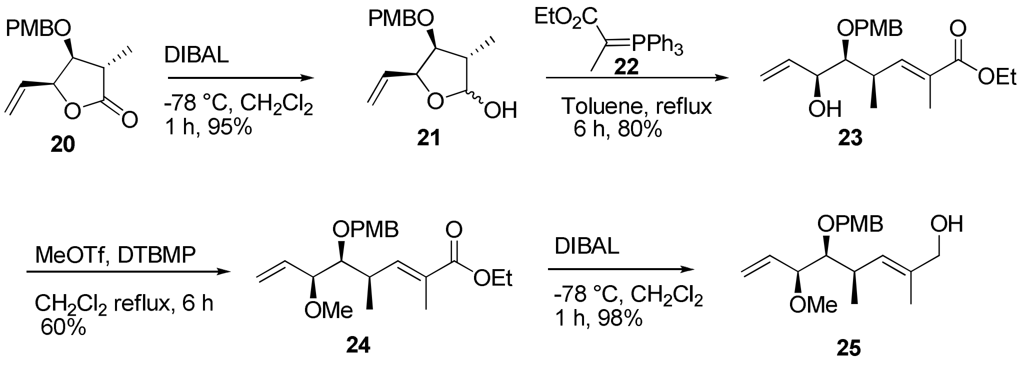
Scheme 3.3

In order to improve the poor diastereoselectivity, we envisioned creating a facial bias around the double bond during the White's oxidation reaction by protecting the hydroxyl group as PMB ether in acid **19** (Scheme 3.4). Thus, aldol adduct **13** was converted to PMB ether **18** (PMBOC(=NH)CCl_3, Sc$(OTf)_3$) which was hydrolyzed to give acid **19** in good yields. Gratifyingly, the White's oxidation on acid **19**, afforded the desired lactone **20** in 65% yield with good dia-stereoselectivity. The diastereomers were easily separated by flash chromatography leading to a ratio of 9:1. Relative stereochemistry of diastereomers was assigned using NOE studies (Scheme 3.4).

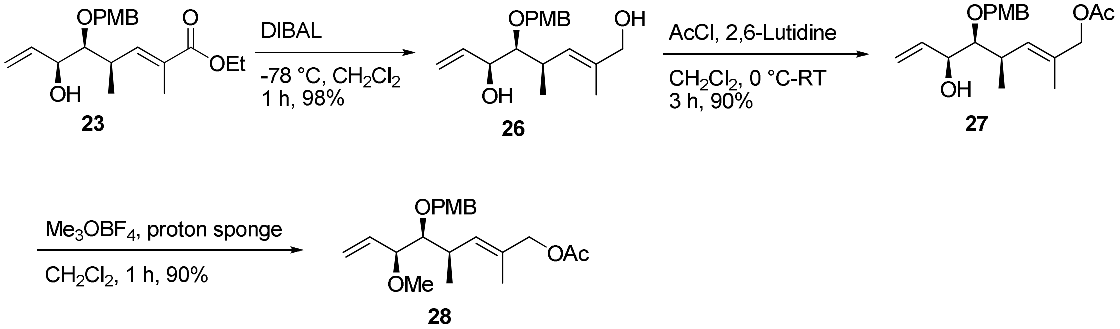


Scheme 3.4

Thus the valuable chiral lactone **20** in hand, we embarked upon the synthesis of C1-C13 fragment of dorrigocin A (Scheme 3.5), by first reducing (DIBAL) it to the corresponding lactol **21** and the reaction of resulting lactol with stabilized phosphorilidene **22** afforded the *E*-olefin **23** in good yields. Subsequently, the hydroxyl group in **23** was transformed to methyl ether **24** (MeOTf), and it was reduced to the desired corresponding allylic alcohol **25** having a C6-C13 fragment of dorrigocin A; also found in bafilomycin subclass of natural products (C12-C19 fragment).[21]



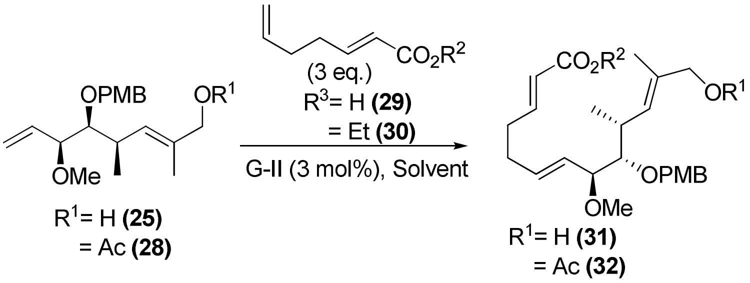
Scheme 3.5



Scheme 3.6

Our initial attempts on cross metathesis of **25** with olefin partner (*E*)-2,6-hept-denoic acid **29**[22] or the corresponding ester **30**[23] using Grubbs' second generation catalyst were not successful (Table 3.1, entry 1, 2), however, the corresponding acetyl protected compound **28** (synthesized from **23** in three steps; Scheme 3.6) underwent smooth cross metathesis reaction with the ethyl ester **30** affording the desired product **32** (Table 3.1, entry 3, 4) in moderate yields. The reaction proceeded slightly better in toluene as compared with dichloromethane as the reaction medium for the cross metathesis reaction. Thus, we have demonstrated that the C1-C13 fragment of dorrigocin A can be synthesized starting from the key lactone **20** via simple synthetic steps.

Table 3.1. Attempts at the olefin cross metathesis[a]

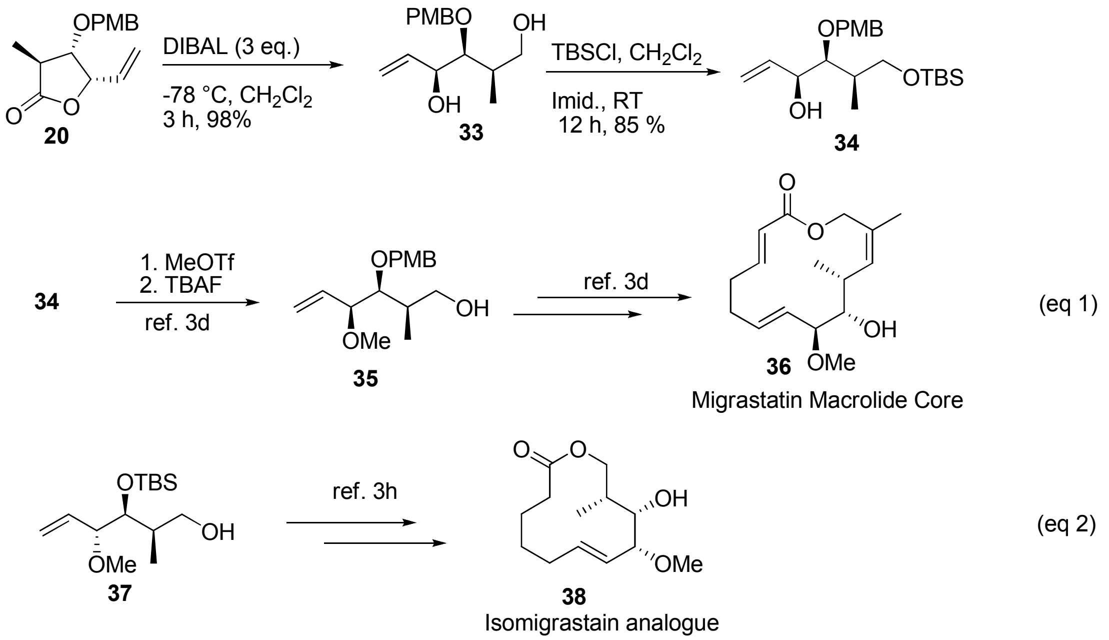


entry	R^1, R^2	solvent	time	Isolated yield
1[b]	H, H	CH_2Cl_2	4 h	-
2	H, Et	CH_2Cl_2	4 h	-
2	Ac, Et	CH_2Cl_2	2 h	15%
3	Ac, Et	Toluene	2 h	20%

[a]all reactions were carried out on 0.06 mmol scale at rt

[b]reaction conducted at 40 °C

Our attempts to access the migrastatin macrolide core **36** from lactone **20** (Scheme 3.7) via a Wittig olefination on the corresponding lactol **21** did not lead to the expected *Z*-olefin product[24] as it would have given direct access to the migrastatin key intermediate. So we resorted to a complete reduction of lactone **20**. Accordingly, lactone **22** was reduced to diol **33** using 3eq. DIBAL at -78 °C for 3 h in 98% yield. The primary alcohol in **33** was protected as silyl ether **34** which has already been converted earlier by our group to the macrolide core of migrastatin **36** (Scheme 3.7, eq. 1),[3d] A similar intermediate **37** was also used by Dias and co-workers in their synthesis of isomigrastatin analogues (Scheme 3.7, eq. 2).[3h] So the synthesis of **34** constitutes a formal synthesis of macrolide core of migrastatin and isomigrastatin analogues.



Scheme 3.7

3.4. Conclusions

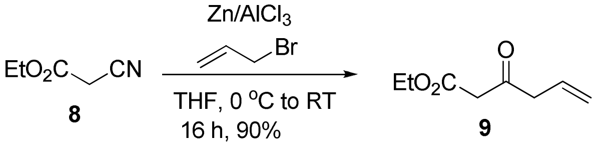
We have shown the synthesis of a versatile chiral trisubstituted butyrolactone **20** for the first time using Pd(II)/sulfoxide catalyzed asymmetric C-H oxidation. A common synthetic protocol was developed to convert the butyrolactone **20** to the key building blocks of migrastatin, isomigrastatin, and C1-C13 fragment of dorrigocin A.

3.5. Experimental section

3.5.1 Materials

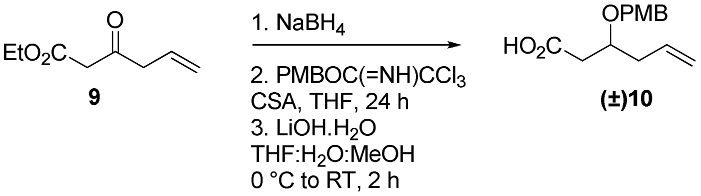
4-Methoxybenzyl-2,2,2-trichloroacetimidate (PMBTCA),[25] (*E*)-2,6-hept-denoic acid **29**,[22] ester **30**.[23] were prepared according to the respective literature procedure. Analytical and spectral data of all those known alkynes are exactly matching with the reported values. For preparation of aldol adduct **13** and silyl ether **14** (see chapter 2)

3.5.2. Experimental procedure, spectral and analytical data



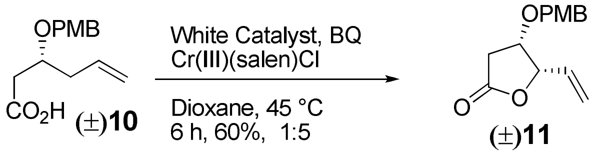
β-keto ester 9

To a suspension of zinc powder (1.31 g, 20 mmol) in anhydrous THF (10 mL), a solution of ethyl cyanoacetate **8** (0.565 g, 5 mmol) in anhydrous THF (30 mL) and allyl bromide (0.907 g, 7.5 mmol) were added under N_2 atmosphere. The mixture was cooled to 0 °C. Aluminum trichloride (0.266 g, 2 mmol) was dissolved in cold anhydrous THF and then slowly added to the reaction mixture. Then the reaction mixture allowed to warm to room temperature and stirred for 16 h. After the reaction was completed HCl (2M aqueous solution, 25 mL) was added, and the reaction mixture was stirred at room temperature for 5 min. The mixture was passed through a short silica gel column. The phases were separated, and the aqueous layer was extracted with ethyl acetate (3X25 mL). The combined organic layers were dried with sodium sulfate, and the solvent was removed under reduced pressure using a rotary evaporator. The product was **9**[26] yellow oil and was used without further purification (0.7 g, 90%). R_f = 0.5 (20% ethyl acetate in hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.98-5.85 (m, 1H), 5.27-5.15 (m, 2H), 4.21 (q, *J* = 7.2 Hz, 2H), 3.48 (s, 2H), 3.32 (d, *J* = 6.9 Hz, 2H), 1.29 (t, *J* = 7.2 Hz, 3H)



Acid 10:

To a solution of *β*-keto ester **9** (156 mg, 1 mmol) in methanol (5 mL) was added sodium borohydride (23.5 mg) at 0 °C and the mixture was stirred at the same temperature for 1 hour. The mixture was partitioned between 1N hydrochloric acid and ethyl acetate. The organic layer was separated, washed with water and brine, dried over sodium sulfate, and evaporated. The product was yellow oil (160 mg, crude). Crude oil was dissolved in solution of CSA (23 mg, 0.1 mmol) in CH_2Cl_2 (10 mL) and added 4-methoxybenzyl 2,2,2-trichloroacetimidate (562 mg, 2 mmol) stirred for 24 h. Reaction mixture was quenched by adding 5 mL saturated $NaHCO_3$ solution, and the aqueous layer was extracted with CH_2Cl_2 (3X5 mL). The combined organic layers were dried with sodium sulfate, and the solvent was removed under reduced pressure using a rotary evaporator. To a solution of PMB ether (208 mg) in THF/MeOH/H_2O (10 mL, 2:1:1) was added LiOH. H_2O (0.024 mg, 1.08 mmol) at 0 °C. The resultant mixture was stirred for 2 h at room temperature and then acidified with 1M HCl and extracted with EtOAc (5x4 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated under reduced pressure to give the acid **10**[27] (187 mg, for 3 steps 75%). R_f = 0.5 (25% ethyl acetate in hexane); ^1H NMR (400 MHz, $CDCl_3$) δ 7.30-7.21 (m, 2H), 6.88 (dd, *J* = 11.0, 5.2 Hz, 2H), 5.80 (m, 1H), 5.21-5.07 (m, 2H), 4.51 (m, 2H), 3.99-3.88 (m, 1H), 3.80 (s, 3H), 2.63-2.51 (m, 2H), 2.26-2.31 (m, 2H).

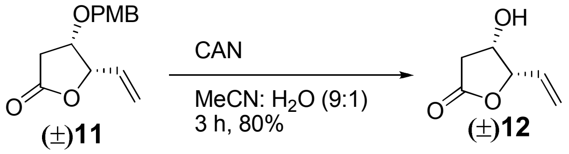


Lactone 11

To a solution of 1,2-bis(phenylsulfinyl)ethane palladium (II) acetate 1 (25 mg, 0.05 mmol), (1*R*,2*R*)-(-)-[1,2-cyclohexanediamine-*N*,*N*'-bis(3,5-di-tertbutylsalicylidine)] chromium(III) chloride ((*R*,*R*)-Cr(salen)Cl) (32 mg, 0.05

mmol, *p*-benzoquinone (108 mg, 1.0 mmol) in 1.5 mL 1,4- dioxane added acid **10** (125 mg, 0.5 mmol) in 5 mL round bottom flask with stopper, stirred at 45 ˚C in an oil bath for 6 h. The Rb was removed, allowed to cool to room temperature and transferred to a separatory funnel with ethyl acetate; organic phase was washed with a saturated aqueous solution of sodium meta-bisulfite (2 x 10 mL) and brine (2 x 10mL). The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by flash chromatography eluting with 10% EtOAc in hexane afforded the lactone **11** as distereomeric mixture (75 mg, 60 %, major: minor (5:1)). **Major isomer 11**, R_f = 0.25 (20% ethyl acetate in hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28-7.20 (m, 2H), 6.89 (d, *J* = 8.6 Hz, 2H), 5.86-5.78 (m, 1H), 5.40 (d, *J* = 17.2 Hz, 1H), 5.28 (d, *J* = 10.7 Hz, 1H), 4.97-4.90 (m, 1H), 4.50 (s, 2H), 4.08-4.02 (m, 1H), 3.81(s, 3H), 2.75-2.67 (m, 1H), 2.55 (dd, *J* = 17.8, 3.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.8, 159.5, 133.1, 129.4, 128.8, 117.9, 114.0, 84.6, 71.2, 55.3, 34.3; IR (Neat) 3082, 2955, 2922, 1770, 1611, 1512, 1247, 1019 cm^{-1}; MS (ES) m/z 249.2 (M+1).

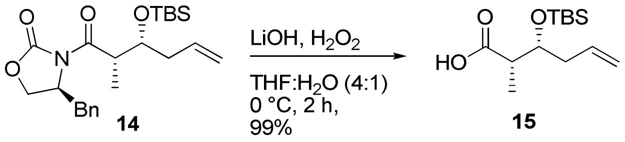
Minor isomer 11, R_f = 0.28 (20% ethyl acetate in hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.22 (d, *J* = 8.6 Hz, 2H), 6.88 (d, *J* = 8.6 Hz, 2H), 6.12-6.02 (m, 1H), 5.44 (dd, *J* = 22.1, 13.9 Hz, 2H), 4.92-4.86 (m, 1H), 4.47 (q, *J* = 11.6 Hz, 2H), 4.27 (q, *J* = 4.7 Hz, 1H), 3.81 (s, 3H), 2.66 (d, *J* = 4.6 Hz, 2H); IR (Neat) 3080, 2955, 2924, 1771, 1604, 1510, 1242, 1010 cm^{-1}; MS (ES) m/z 249.2 (M+1).



Lactone 12

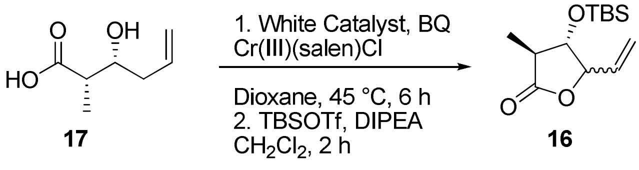
To a solution of the above compound **11** (25 mg, 0.01 mmol) in a mixture of CH_3CN/H_2O (9:1, 4 mL), was added CAN (109 mg, 0.02 mmol) at room temperature. After 1h of stirring, the reaction mixture was filtered and concentrated under reduced pressure. H_2O (5 mL) and CH_2Cl_2 (5 mL) were added, the organic phase was dried over Na_2SO_4 filtered and concentrated under *vacuo*. The residue was purified by column chromatography (1:1 EtOAc/Hexane), gave the lactone **12**[12] as colorless oil (11 mg, 80%). R_f = 0.2 (40% ethyl acetate in hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.95-5.82 (m, 1H), 5.50-5.42 (m, 1H), 5.37-5.32 (m, 1H), 4.88-4.80 (m, 1H), 4.44-

4.35 (m, 1H), 2.87-2.79 (s, 1H), 2.57-2.49 (m, 1H); IR (neat) 3446, 2934, 1770, 1639, 1430, 1413, 1333, 1309, 1203, 1158, 1080, 1015 cm^{-1}; MS (ES) m/z 129.2 (M+1).



Acid 15

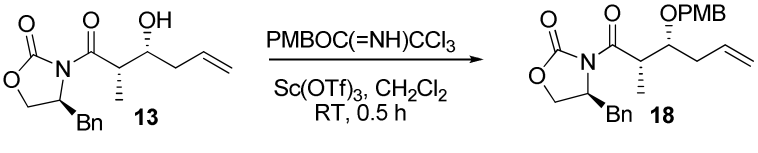
Silylether **14** (417 mg, 1.0 mmol) in 5 mL of four parts THF to one part distilled water is added to the flask, the solution was cooled to 0 °C in an ice/water bath. To the cooled, stirring solution added 4 equivalents of 30% hydrogen peroxide and a solution of lithium hydroxide (42 mg, 1mmol) in 2.0 mL distilled water via syringe. The reaction flask was kept in an ice bath and stirred for one hour. Then septum was then removed, and a solution of sodium sulfite (0.5 g) in 3 mL water was added. THF was removed on the rotary evaporator (careful of bumping with aqueous THF). The remaining solution (mostly aqueous) was extracted with dichloromethane (6 mLX3) to remove the free oxazolidinone. The aqueous layer containing the carboxylate salt of the desired product was cooled in an ice bath and brought to pH 1 with 6 N hydrochloric acid. The aqueous solution is then extracted with ethyl acetate (5 mLX4). The combined ethyl acetate layers were dried over anhydrous sodium sulfate, and then concentrated in *vacuo* and passed through shot pad of silica gel yielded pale yellow liquid **15** (256 mg, 99%). R_f = 0.3 (10 % ethyl acetate in petroleum ether); ^{1}H NMR (400 MHz, CDCl$_3$) δ 5.82-5.71 (m, 1H), 5.15-5.03 (m, 2H), 4.11 (dd, *J* = 10.8, 6.1 Hz, 1H), 2.66-2.51 (m, 1H), 2.28 (t, *J* = 6.7 Hz, 2H), 1.14 (d, *J* = 7.0 Hz, 3H), 0.87 (s, 9H), 0.06 (d, *J* = 10.8 Hz, 6H); IR (Neat) 3425, 3078, 2968, 2930, 2858, 1756, 1472, 1255, 1046 cm^{-1}; MS (ES) m/z 259.1 (M+1).



Lactone 16

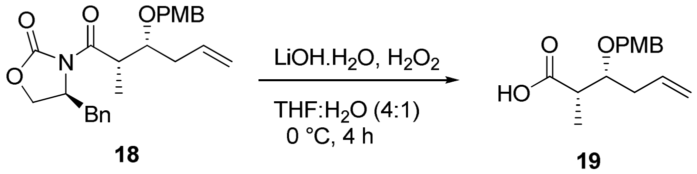
To a solution of 1,2-bis(phenylsulfinyl)ethane palladium (II) acetate 1 (10.5 mg, 0.02 mmol), (1*R*,2*R*)-(-)-[1,2-cyclohexanediamine-*N*,*N*'-bis(3,5-di-tertbutylsalicylidine)] chromium(III) chloride ((*R*,*R*)-Cr(salen)Cl) (12 mg, 0.02 mmol), *p*-benzoquinone (44 mg, 2.0 mmol) in 2.5 mL 1,4-dioxane added acid **17** (30 mg, 0.2 mmol) in 5 mL round bottom flask with stopper, stirred at 45 ˚C in an oil bath for 6 h. The Rb was removed, allowed to cool to room temperature and transferred to a separatory funnel with 10 mL ethyl acetate; organic phase was washed with a saturated aqueous solution of sodium meta-bisulfite (2 x 5 mL) and brine (2 x 5mL). The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. Crude material was dissolved in 5 mL of dichloromethane, DIPEA (0.2 mL) treated with TBSOTf (0.1 mL) at 0 °C for 2 h. After completion of reaction, mixture was washed with saturated sodium bicarbonate solution; aqueous layer was washed with dichloromethane (2X4 mL). Combined organic layers were dried on sodium sulfate and concentrated under *vacuo*. The residue was purified by flash chromatography using 2% EtOAc in hexane as eluent afforded the lactone **16** as distereomeric mixture (30 mg, 60 %, major: minor (55:45)). Relative stereochemistry of products was not assigned. Major isomer R_f = 0.7 (25 % ethyl acetate in petroleum ether); ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 6.01-5.92 (m, 1H), 5.38 (dd, *J* = 19.3, 13.9 Hz, 2H), 4.88-4.82 (m, 1H), 4.17-4.12 (m, 1H), 2.59-2.51 (m, 1H), 1.26 (d, *J* = 7.4 Hz, 3H), 0.89 (s, 9H), 0.08 (d, *J* = 4.1 Hz, 6H); IR (neat) 2956, 2931, 2858, 1788, 1462, 1388, 1254, 1135, 1004 cm^{-1}; MS (ES) m/z 257.2 (M+1).

minor isomer R_f = 0.75 (25 % ethyl acetate in petroleum ether); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.87-5.76 (m, 1H), 5.40 (dd, *J* = 40.1, 13.8 Hz, 2H), 4.44 (t, *J* = 7.0 Hz, 1H), 3.81-3.74 (m, 1H), 2.62-2.54 (m, 1H), 1.28 (d, *J* = 7.2 Hz, 3H), 0.89 (s, 9H), 0.07 (d, *J* = 13.2 Hz, 6H); MS (ES) m/z 257.2 (M+1).



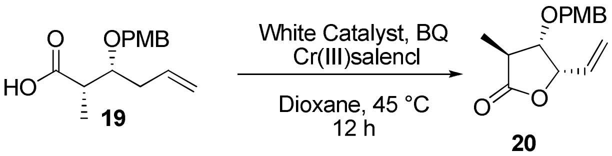
PMB ether 18

To a stirred solution of alcohol **13** (610 mg, 2 mmol) and PMBOC(=NH)CCl_3 (1.4 g, 5 mmol) in dry toluene (15 mL), $Sc(OTf)_3$ (30 mg, 0.06 mmol) was added at room temperature. The reaction was allowed to stir for 0.5 h, and then concentrated in *vacuo*. In order to precipitate trichloroacetamide, the residual oil was taken up in n-pentane/CH_2Cl_2 mixture (5/1, 50 mL) and filtered. The filtrate was concentrated and purified by flash chromatography (8% EtOAc in hexane) gave PMB ether **18** (721 mg, 85%) as a colorless gel. R_f = 0.67 (10 % ethyl acetate in petroleum ether); $[\alpha]_D^{27}$ +37.8 (c 1.15, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.34-7.24 (m, 5H), 7.19 (d, *J* = 7.2 Hz, 2H), 6.85 (d, *J* = 8.4 Hz, 2H), 5.94-5.80 (m, 1H), 5.13-5.04 (m, 2H), 4.56-4.39 (m, 3H), 4.09 (dd, *J* = 9.0, 0.9 Hz, 1H), 4.04-3.95 (m, 2H), 3.82-3.71 (m, 4H), 3.26 (dd, *J* = 13.4, 2.7 Hz, 1H), 2.73 (dd, *J* = 13.3, 9.7 Hz, 1H), 2.44-2.34 (m, 2H), 1.27 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.0, 159.1, 153.0, 135.3, 134.9, 130.5, 129.7, 129.4, 128.9, 127.3, 117.1, 113.6, 78.6, 71.6, 65.9, 55.6, 55.2, 41.4, 37.7, 36.7, 12.5; IR (neat) 3066, 2955, 2925, 2856, 1779, 1695, 1511, 1381, 1350, 1245, 1210, 1034 cm^{-1}; HRMS m/z found 424.2121, calcd for $C_{25}H_{30}NO_5$ 424.2124.



Acid 19

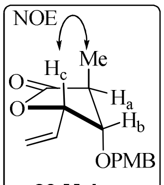
Acid **19** was prepared using previous procedure used for oxidative cleavage of **14** by taking **18** (425 mg, 1 mmol), yielded pale yellow oil (252 mg, 95%). R_f = 0.25 (20% ethyl acetate in petroleum ether); $[\alpha]_D^{27}$ -5.2 (c 1.04, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.28-7.21 (m, 2H), 6.86 (d, *J* = 8.6 Hz, 2H), 5.87-5.74 (m, 1H), 5.15-5.08 (m, 2H), 4.52 (dd, *J* = 30.3, 11.0 Hz, 2H), 3.84-3.76 (m, 4H), 2.75-2.66 (m, 1H), 2.45-2.26 (m, 2H), 1.20 (d, *J* = 7.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 179.6, 159.3, 133.9, 129.9, 129.5, 118.0, 113.8, 78.9, 71.9, 55.2, 42.5, 36.1, 11.2; IR (Neat) 3404, 2932, 1735, 1639, 1612, 1586, 1513, 1463, 1441, 1352, 1301, 1170 cm^{-1}; MS (ES) m/z 265.2 (M+1).



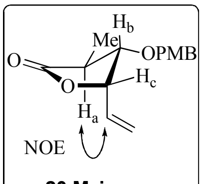
Lactone 20

Lactone **20** was prepared using previous procedure used for C-H oxidation reaction for **11** by taking acid **19** (200 mg, 0.76 mmol). After purification using flash column chromatography, yielded (130 mg, 65%, major: minor, 9:1). **Major isomer** R_f = 0.65

(20 % ethyl acetate in petroleum ether); $[\alpha]_D^{27}$ -72.1 (c 1.4, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.28-7.20 (m, 2H), 6.89 (d, *J* = 8.7 Hz, 2H), 6.05-5.97 (m, 1H), 5.42 (dd, *J* = 21.2, 13.9 Hz, 2H), 4.95 (t, *J* = 6.3 Hz, 1H), 4.55-4.45 (m, 2H), 3.98-3.92 (m, 1H), 3.81 (s, 3H), 2.75-2.67 (m, 1H), 1.26 (d, *J* = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.5, 159.5, 131.3, 129.4, 129.0, 119.6, 113.9, 81.5, 80.2, 71.9, 55.3, 39.6, 13.1; IR (neat) 3080, 2922, 2854, 1777, 1611, 1512, 1459, 1247, 1175, 1113, 1022 cm^{-1}; HRMS m/z found 263.1274, calcd for $C_{15}H_{19}O_4$ 263.1283.



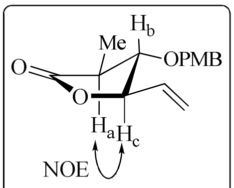
20 Major



20 Major

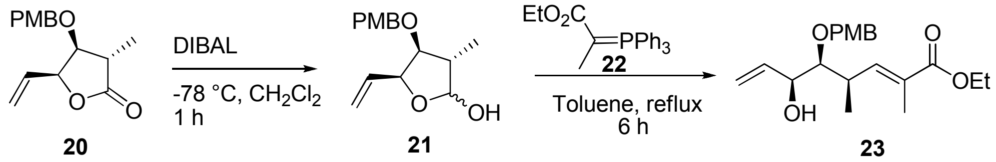
The relative stereochemistry of **20** major was established based on NOE studies; NOEs between methyl group (δ 1.26) and H_c (δ 4.95) clearly showing the trans orientation of vinyl group and methyl group. Another key NOE between H_a (δ 2.7) and vinylic group (δ 6.0) further confirmed the trans relationship of vinyl and methyl group.

Minor isomer R_f = 0.62 (20 % ethyl acetate in petroleum ether); ^1H NMR (400 MHz, $CDCl_3$) δ 7.23 (d, *J*= 8.5 Hz, 2H), 6.90 (d, *J* = 8.5 Hz, 2H), 5.94-5.83 (m, 1H), 5.49 (d, *J* = 17.2 Hz, 1H), 5.34 (d, *J* = 10.5 Hz, 1H), 4.68 (t, *J* = 6.4 Hz, 1H), 4.61-4.51 (m, 2H), 3.82 (s, 2H), 3.69 (t, *J* = 6.9 Hz, 1H), 2.76-2.67 (m, 1H), 1.29 (d, *J* = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.5, 159.5, 134.2, 129.4, 129.1, 119.2, 113.9, 85.0, 83.0, 72.3, 55.3, 42.1, 13.9; IR (neat) 3082, 2922, 2853, 1777, 1611, 1512, 1459, 1247, 1175, 1114, 1019 cm^{-1}; MS (ES) m/z 263.2 (M+1).



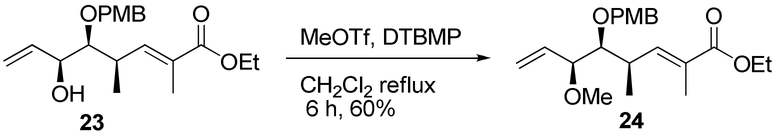
20 minor

The relative stereochemistry of **20** minor was established based on NOE studies; Key NOE between H_a (δ 2.72) and H_c (δ 4.68) confirmed the cis relationship of vinyl and methyl group



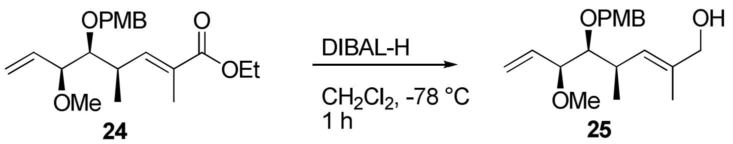
Alcohol 23

Diisobutylaluminum hydride (1.0 M) in cyclohexane (0.4 mL, 0.4 mmol) was added drop wise to a stirred solution of lactone **20** (100 mg, 0.38 mmol) in dry dichloromethane (5 mL) at -78 °C. The reaction mixture was stirred for 1 h at -78 °C under an atmosphere of nitrogen. The reaction was quenched with methanol and allowed to warm to bring it at room temperature. Saturated aqueous sodium/potassium tartrate solution (2 mL) was added and the resulting mixture was stirred for 4 h after which the product was extracted with EtOAc (2x5 mL). The combined organic extracts were dried over Na_2SO_4, concentrated in *vacuo*. The crude lactol **21** (100 mg, 98%) was directly used in next reaction without further purification. To the solution of lactol in 5 mL toluene triphenyl(1-[ethoxycarbonyl]ethylidene)phosphorane **22** (206 mg, 57 mmol) was added under N_2 atmosphere and the reaction refluxed for 6 h. After completion of reaction toluene was removed and the residue was purified by flash column chromatography yielded **23** as a colorless liquid (106 mg, 80%). R_f = 0.65 (20 % ethyl acetate in petroleum ether); $[\alpha]_D^{27}$ -1.0 (c 1.05, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29-7.22 (m, 2H), 6.88 (d, *J* = 8.63 Hz, 2H), 6.64 (dd, *J* = 10.3, 1.3 Hz, 1H), 5.97-5.89 (m, 1H), 5.37 (d, *J* = 17.2 Hz, 1H), 5.23 (d, *J* = 10.5 Hz, 1H), 4.55 (s, 2H), 4.19 (q, *J* = 7.1 Hz, 2H), 4.07-4.01 (m, 1H), 3.81 (s, 3H), 3.27-3.24 (m, 1H), 2.96-2.85 (m, 1H), 1.86 (d, *J* = 1.3 Hz, 3H), 1.30 (t, *J* = 7.1 Hz, 3H), 1.10 (d, *J* = 6.7 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.2, 159.4, 143.5, 138.8, 130.0, 129.7, 128.2, 116.0, 113.8, 84.8, 75.1, 72.9, 60.6, 55.3, 35.7, 15.8, 14.3, 12.6; IR (neat) 3491, 3080, 2979, 2962, 2932, 2875, 1707, 1613, 1513, 1462, 1249, 1175, 1033 cm^{-1}; HRMS m/z found 349.2001, calcd for $C_{20}H_{29}O_5$ 349.2015.



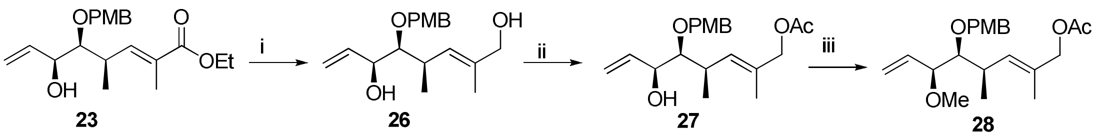
Ethyl ester 24

To a stirred solution of compound **23** (52 mg, 0.15 mmol) in dry CH_2Cl_2 at room temperature were added 4-methyl-2,6-di-*tert*-butylpyridine (310 mg, 1.51 mmol) and methyl triflate (120 mg, 0.73 mmol) sequentially. The reaction mixture was stirred at 40 °C for 6 h. Then reaction mixture was diluted with CH_2Cl_2 washed with 3N HCl solution, saturated $NaHCO_3$ solution followed by brine. Then the organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The resulting residue was purified by column chromatography using 5% ethyl acetate in hexane to afford **24** as pale yellow liquid (32 mg, 60%). R_f = 0.6 (10 % ethyl acetate in petroleum ether); $[\alpha]_D^{30}$ -17.0 (c 1.1, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.31-7.25 (m, 2H), 6.86 (d, *J* = 8.6 Hz, 2H), 6.67 (dd, *J* = 10.4, 1.3 Hz, 1H), 5.84-5.75 (m, 1H), 5.34-5.24 (m, 2H), 4.66 (d, *J* = 10.8 Hz, 1H), 4.49 (d, *J* = 10.8 Hz, 1H), 4.20 (q, *J* = 7.1 Hz, 2H), 3.80 (s, 3H), 3.52-3.51 (m, 1H), 3.30-3.22 (m, 4H), 2.97-2.85 (m, 1H), 1.85-1.82 (m, 3H), 1.31 (t, *J* = 7.1 Hz, 3H), 1.04 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.3, 159.1, 144.4, 135.8, 130.6, 129.8, 127.0, 118.4, 113.6, 84.6, 84.5, 75.0, 60.5, 56.6, 55.2, 35.3, 15.3, 14.3, 12.4; IR (neat) 3074 2978, 2931, 2876, 1708, 1611, 1512, 1462, 1250, 1123, 1017 cm^{-1}; HRMS m/z found 385.1987, calcd for $C_{21}H_{30}O_5Na$ ($M+Na^+$) 385.1990.



Allylic alcohol 25

To a stirred solution of ester **24** (91 mg, 0.25 mmol) in CH_2Cl_2 was added DIBAL-H (1M in THF, 0.5 mL) at -78 °C. After being stirred for 1h reaction temperature increased to 0 °C. After 1h, the reaction mixture was quenched with saturated aqueous potassium sodium tartarate solution. After the addition reaction, mixture was warmed to room temperature and stirred for 4 h. Then the layers were separated, aqueous layer was extracted with EtOAc. Combined organic extracts was washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography eluting with 10% ethyl acetate in hexane to afford allyl alcohol **25** as a colorless liquid (78 mg, 98%). R_f = 0.25 (25 % ethyl acetate in petroleum ether); $[\alpha]_D^{30}$ -28.0 (c 0.8, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27 (d, *J* = 8.6 Hz, 2H), 6.85 (d, *J* = 8.6 Hz, 2H), 5.86-5.74 (m, 1H), 5.27 (dd, *J* = 11.6, 4.4 Hz, 3H), 4.65 (d, *J* = 11.0 Hz, 1H), 4.49 (d, *J* = 11.0 Hz, 1H), 3.95 (s, 2H), 3.79 (s, 3H), 3.61 (dd, *J* = 7.7, 4.6 Hz, 1H), 3.23 (s, 3H), 3.18 (dd, *J* = 6.4, 4.7 Hz, 1H), 2.85-2.73 (m, 1H), 1.65 (s, 3H), 0.97 (t, *J* = 7.7 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.0, 136.1, 134.0, 131.0, 129.7, 129.1, 118.1, 113.5, 85.3, 84.6, 74.7, 68.8, 56.6, 55.2, 34.0, 29.7, 16.1, 13.7; IR (neat) 3383, 2919, 2881, 1609, 1512, 1463, 1247, 1118, 1077, 1037 cm^{-1}; HRMS m/z found 343.1876, calcd for $C_{20}H_{29}O_5$ $(M+Na^+)$ 343.1885.



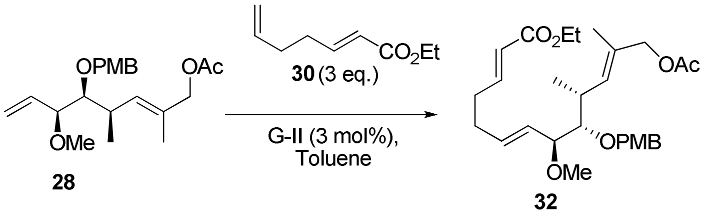
i) DIBAL, -78 °C, CH_2Cl_2, 1 h ii) Me_3OBF_4, proton sponge, CH_2Cl_2, 1 h iii) AcCl, 2,6-Lutidine, CH_2Cl_2, 0 °C-RT, 3 h

Acetylated allylic alcohol 28

Step i) Experiment was carried out using same experimental procedure as mentioned above for the reduction of ester **24**, Ester **23** (0.5 mmol) and taking 2 eq. of DIBAL-H yielded diallylic alcohol **26** was taken directly to next step without further purification (152 mg, 98%). R_f = 0.5 (50% ethyl acetate in petroleum ether); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29-7.22 (m, 2H), 6.88 (d, *J* = 8.5 Hz, 2H), 6.02-5.89 (m, 1H), 5.40-5.18 (m, 3H), 4.58-4.50 (m, 2H), 4.13-4.09 (m, 1H), 3.99 (s, 2H), 3.81 (s, 3H), 3.20-3.15 (m, 1H), 2.85-2.75 (m, 1H), 1.67 (s, 3H), 1.05 (d, *J* = 6.7 Hz, 3H); MS (ES) m/z 323.1 $(M+NH_3)$.

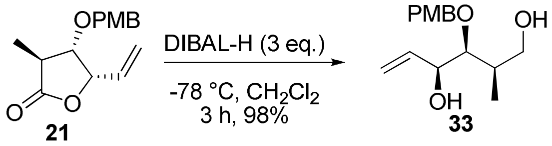
Step ii) To a solution of **26** (152 mg, 0.46 mmol) in 5 mL CH_2Cl_2, added 2,6-lutidine (64 mg (0.07 mL), 0.6 mmol). Then acetyl chloride (46 mg, 0.6 mmol) was added drop wise under N_2 at 0 °C. Upon the addition, the mixture was kept stirring for 3 hours, the reaction was quenched by adding saturated aqueous ammonium chloride solution. Then the layers were separated and aqueous layer was extracted with dichloromethane (3 mLx3). The combined organic layer was washed with brine and dried over anhydrous sodium sulfate, and concentrated gave **27** as a colorless oil used in next step without further purification (156 mg, 90%). ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.27- 7.24 (m, 2H), 6.88 (d, *J* = 8.6 Hz, 2H), 6.0-5.9 (m, 1H), 5.40-5.19 (m, 3H), 4.60-4.50 (m, 2H), 4.49-4.39 (m, 2H), 4.13-4.09 (m, 1H), 3.81 (s, 3H), 3.20-3.16 (m, 1H), 2.83-2.74 (m, 1H), 2.36 (d, *J* = 7.9 Hz, 1H), 2.07 (s, 3H), 1.68 (s, 3H), 1.04 (t, *J* = 6.4 Hz, 3H); MS (ES) m/z 365.2 (M+NH$_3$).

Step iii) To a stirred solution of allylic alcohol **27** (70 mg, 0.2 mmol) in 5 mL CH$_2$Cl$_2$ added proton sponge (171 mg, 0.8 mmol) and Me$_3$OBF$_4$ (120 mg, 0.8 mmol) at room temperature. After stirring 1 h, reaction mixture was quenched with saturated NaHCO$_3$ solution, aqueous layer was extracted with CH$_2$Cl$_2$. The combined organic layers were washed with brine and dried over anhydrous sodium sulfate, concentrated and then purified by column chromatography (7% EtOAc in Hexane) gave a colorless oil **28** (65 mg, 90%). R$_f$ = 0.25 (20 % ethyl acetate in petroleum ether); $[\alpha]_D^{25}$ -18.0 (c 0.5, CHCl$_3$); ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.27 (d, *J* = 8.0 Hz, 2H), 6.86 (d, *J* = 8.6 Hz, 2H), 5.87-5.74 (m, 1H), 5.38-5.24 (m, 3H), 4.66 (d, *J* = 10.9 Hz, 1H), 4.51-4.38 (m, 3H), 3.80 (s, 3H), 3.63-3.54 (m, 1H), 3.24 (s, 3H), 3.18 (dd, *J* = 6.6, 4.6 Hz, 1H), 2.85-2.75 (m, 1H), 2.06 (s, 3H), 1.66 (s, 3H), 0.99 (d, *J* = 6.7 Hz, 3H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 171.0, 159.1, 136.1, 132.6, 131.0, 129.6, 129.4, 118.1, 113.6, 85.3, 84.5, 74.9, 70.2, 56.6, 55.3, 34.3, 21.0, 15.9, 14.0; IR (neat) 3068, 2977, 2932, 1738, 1613, 1513, 1372, 1247, 1121, 1080 cm^{-1}; HRMS m/z found 385.1985, calcd for C$_{21}$H$_{30}$O$_5$ (M+Na$^+$) 385.1985.



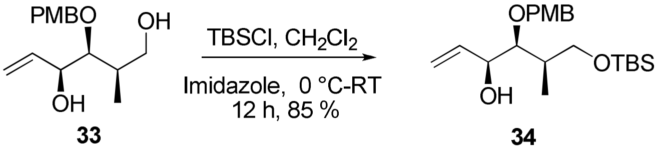
To the compound **28** (21 mg, 0.06 mmol), (*E*)-ethyl hepta-2,6-dienoate (36 mg, 0.18 mmol) was added in 0.5 mL toluene and Grubbs catalyst 2nd generation (1.5 mg, 3 mol%) at room temperature. After reaction mixture was stirred for 1h, solvent was removed in *vacuo* to give crude products. The residue was purified by flash column chromatography using (10% ethyl acetate in hexane) gave **32** as colorless oil (6 mg, 20%). R$_f$ = 0.30 (25 % ethyl acetate in petroleum ether); $[\alpha]_D^{25}$ +6.0 (c 0.25, CHCl$_3$); ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.28-7.26 (m, 2H), 7.00-6.92 (m, 1H), 6.87 (d, *J* = 8.7 Hz, 2H), 5.85 (dd, *J* = 14.7, 2.9 Hz, 1H), 5.70-5.61 (m, 1H), 5.50-5.40 (m, 1H), 5.34 (dd, *J* = 10.0, 1.0 Hz, 1H), 4.62 (d, *J* = 11.0 Hz, 1H), 4.54-4.40 (m, 3H), 4.21-4.16

(m, 2H), 3.81 (s, 3H), 3.55-3.51 (m, 1H), 3.20 (s, 3H), 3.17-3.17-3.12 (m, 1H), 2.85-2.76 (m, 1H), 2.34-2.23 (m, 4H), 2.07 (s, 3H), 1.66 (d, *J* = 1.1 Hz, 3H), 1.29-1.26 (m, 3H), 0.99 (d, *J* = 6.7 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.0, 166.5, 159.1, 148.0, 132.9, 132.7, 131.0, 129.7, 129.3, 129.1, 121.9, 113.6, 85.6, 83.8, 74.9, 70.2, 60.2, 56.3, 55.3, 34.4, 31.7, 30.7, 21.0, 15.9, 14.2, 14.0; IR (neat) 3068, 2978, 2929, 1735, 1721, 1655, 1512, 1370, 1248, 1078, 1033 cm^{-1}; HRMS m/z found 511.2666, calcd for $C_{28}H_{40}O_7$ (M+Na$^+$) 511.2666.



Diol 33

To a stirred solution of lactone **21** (65.5 mg, 0.25 mmol) in CH_2Cl_2 was added DIBAL (1M in THF, 0.75 mL) at -78 °C. After being stirred for 3 h reaction temperature increased to 0 °C. After 1h, the reaction mixture was quenched with saturated aqueous potassium sodium tartarate solution. After the addition reaction, mixture was warmed to room temperature and stirred for overnight. Then the layers were separated, aqueous layer was extracted with EtOAc. Combined organic extracts was washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography eluting with 40 % ethyl acetate in hexane to afford diol **33** as a colorless liquid (65 mg, 98%). R_f = 0.30 (40 % ethyl acetate in petroleum ether); $[\alpha]_D^{25}$ -2.5 (c 0.6, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27 (d, *J* = 8.6 Hz, 2H), 6.89 (d, *J* = 8.6 Hz, 2H), 5.98-5.87 (m, 1H), 5.35 (d, *J* = 17.2 Hz, 1H), 5.21 (d, *J* = 10.5 Hz, 1H), 4.61-4.52 (m, 2H), 4.26-4.21 (m, 1H), 3.81 (s, 3H), 3.72 (dd, *J* = 11.1, 3.9 Hz, 1H), 3.52 (dd, *J* = 11.0, 6.6 Hz, 1H), 3.44 (t, *J* = 4.8 Hz, 1H), 2.91-2.74 (brs, 1H), 2.03-1.95 (m, 1H), 0.98 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.3, 138.5, 130.2, 129.6, 116.2, 113.8, 82.7, 73.6, 72.2, 64.1, 55.3, 36.9, 12.3; IR (neat) 3423, 2919, 2881, 1612, 1513, 1463, 1247, 1118, 1077 cm^{-1}; HRMS m/z found 289.1410, calcd for $C_{15}H_{22}O_4$ (M+Na$^+$) 289.1410.



33 **34**

TBS Ether 34

To an ice cooled solution of compound **33** (50 mg, 0.19 mmol) in dichloromethane (4 mL) was added imidazole (25 mg, 0.38 mmol) *tert*-butyldimethylsilylchloride (36 mg, 0.23 mmol) and stirred at room temperature for 12 h. Reaction mixture was diluted with dichloromethane, washed water, and brine. The organic layer was dried over anhydrous Na_2SO_4 and rotary evaporated under reduced pressure. The residue was purified over silica gel (100-200 mesh) using 20% ethyl acetate in petroleum ether as eluent to afford **34** as a gummy material (61 mg, 85%). R_f = 0.30 (20 % ethyl acetate in petroleum ether); $[\alpha]_D^{25}$ -2.0 (c 0.6, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 (d, *J* = 8.1 Hz, 2H), 6.88 (d, *J* = 8.5 Hz, 2H), 5.95-5.85 (m, 1H), 5.36 (d, *J* = 17.2 Hz, 1H), 5.21 (d, *J* = 10.5 Hz, 1H), 4.63-4.53 (m, 2H), 4.21-4.14 (m, 1H), 3.81 (s, 3H), 3.66-3.60 (m, 1H), 3.58-3.48 (m, 2H), 3.01 (d, *J* = 4.3 Hz, 1H), 1.96-1.87 (m, 1H), 0.95-0.89 (m, 12H), 0.06 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.2, 138.2, 130.7, 129.4, 116.3, 113.8, 82.4, 74.2, 73.1, 65.1, 55.2, 37.5, 25.8, 18.2, 11.8, -5.4, -5.5; IR (neat) 3455, 2955, 2930, 2857, 1613, 1514, 1463, 1246, 1118, 1030 cm^{-1}; HRMS m/z found 403.2275, calcd for $C_{21}H_{36}O_4Si$ (M+Na$^+$) 403.2275.

3.6. References

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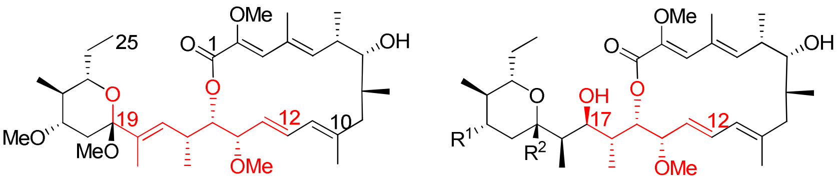

1. $R^1 = R^2 = OH$
2. $R^1 = OMe, R^2 = OH$
3. $R^1 = R^2 = OCH_3$

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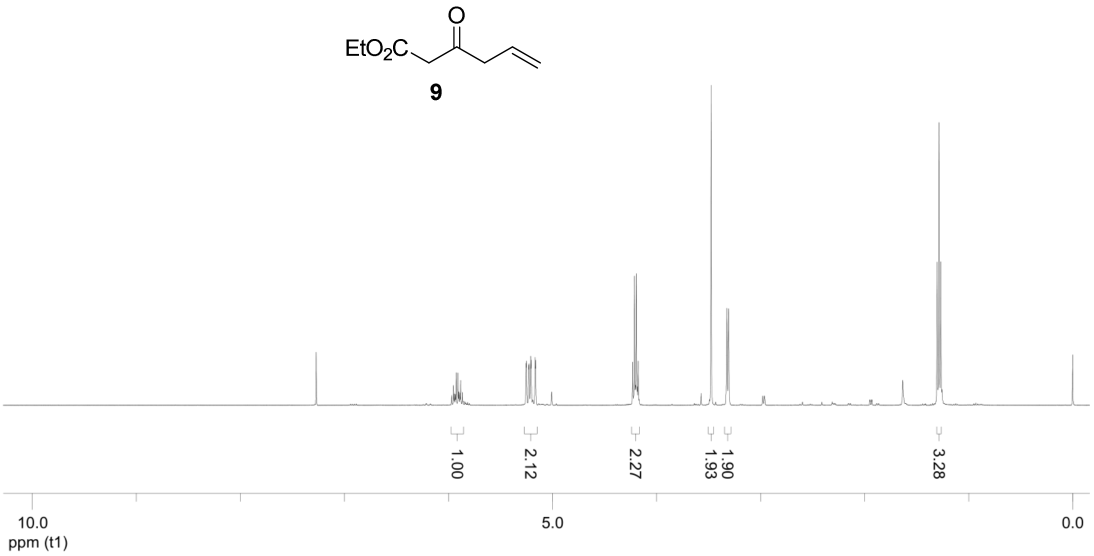
3.7. NMR spectra



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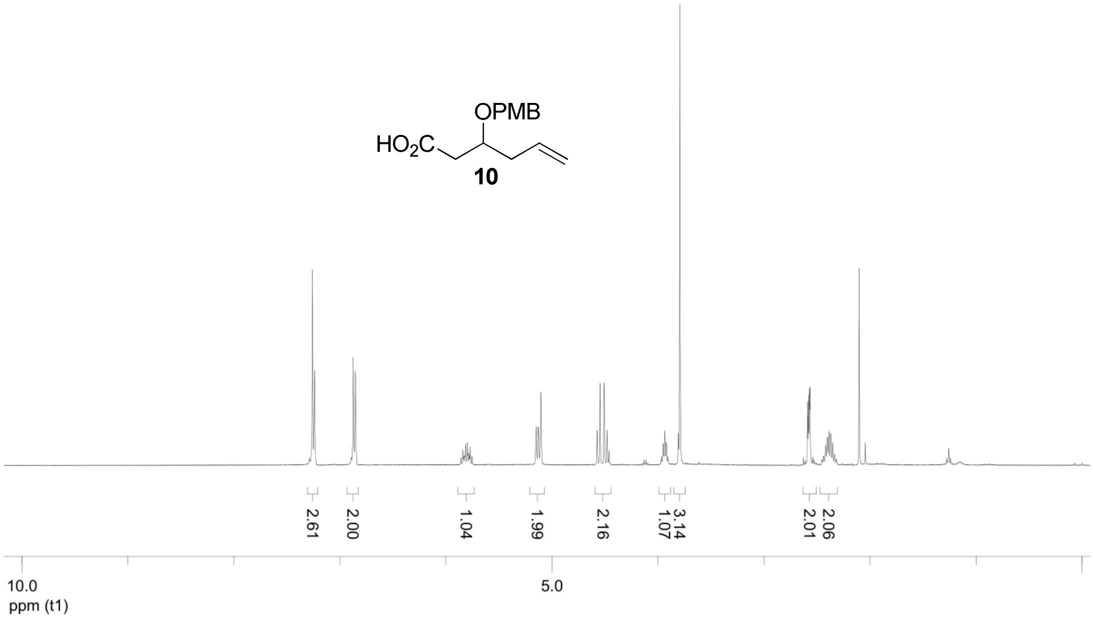

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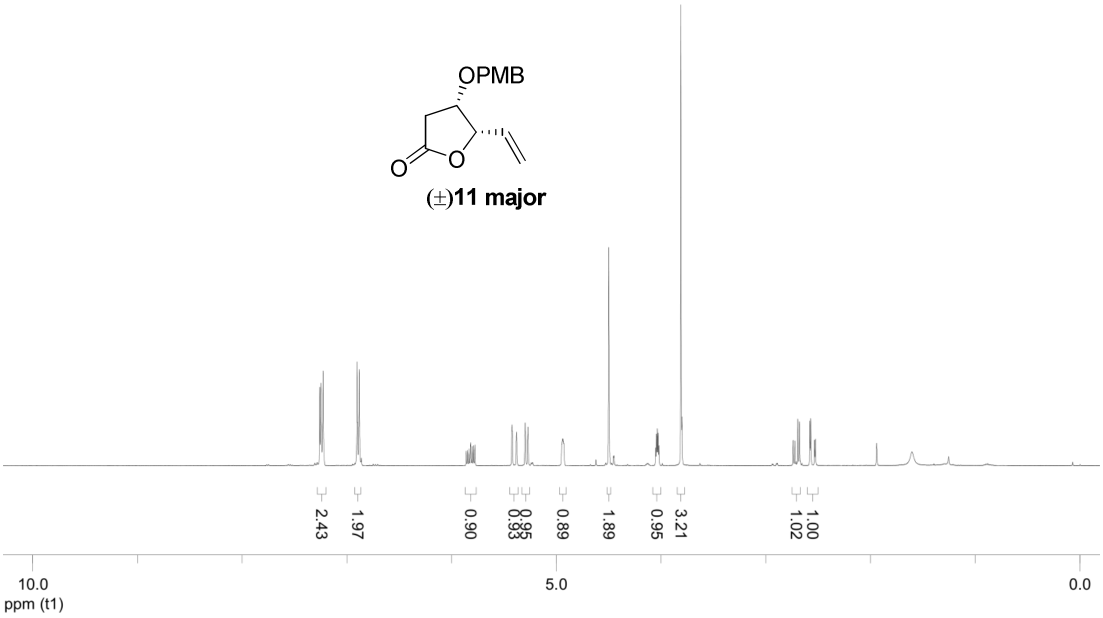

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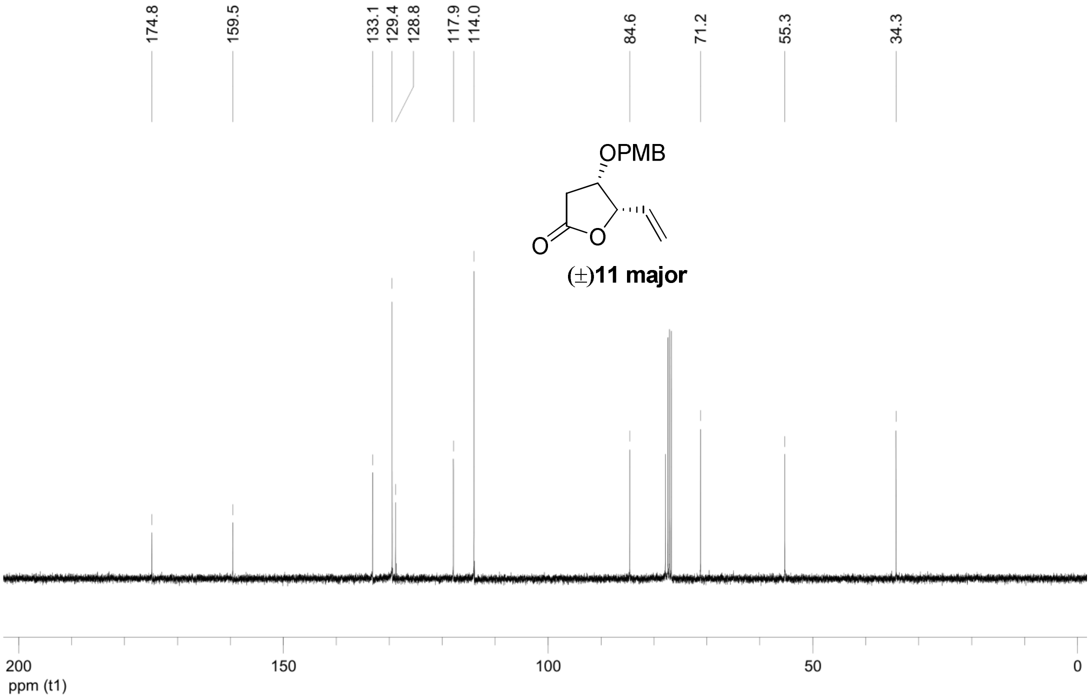

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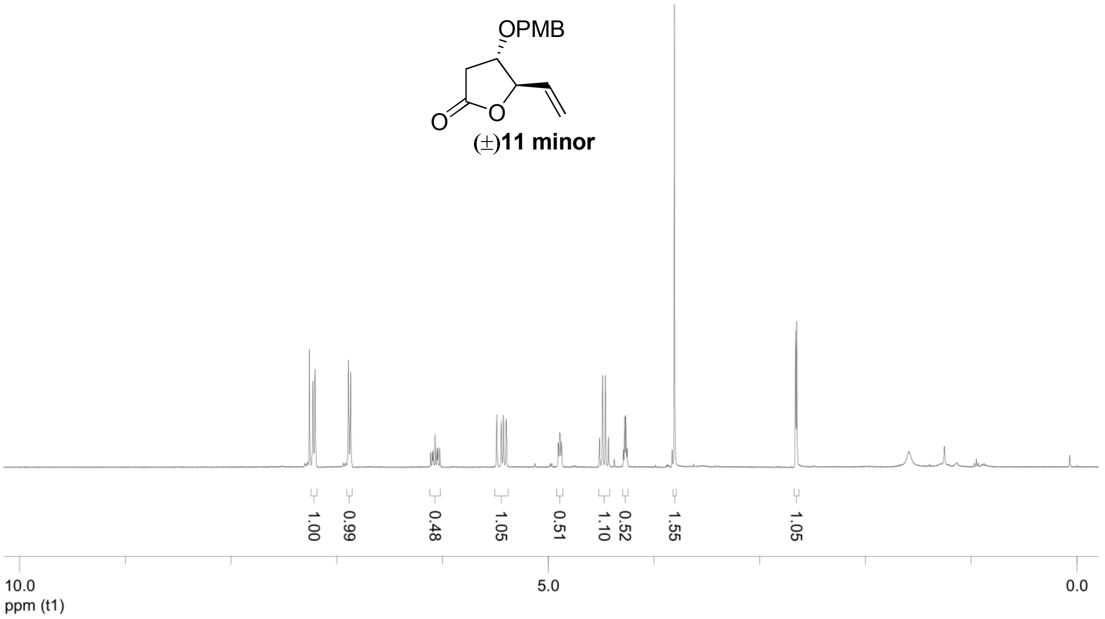
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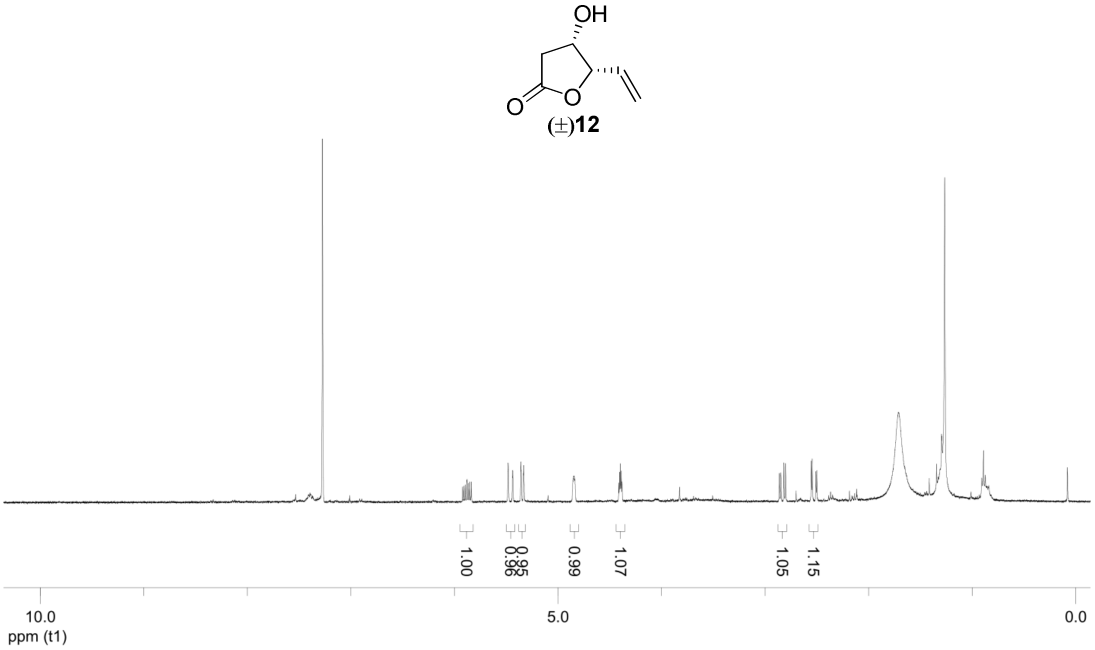
(±)**11 minor**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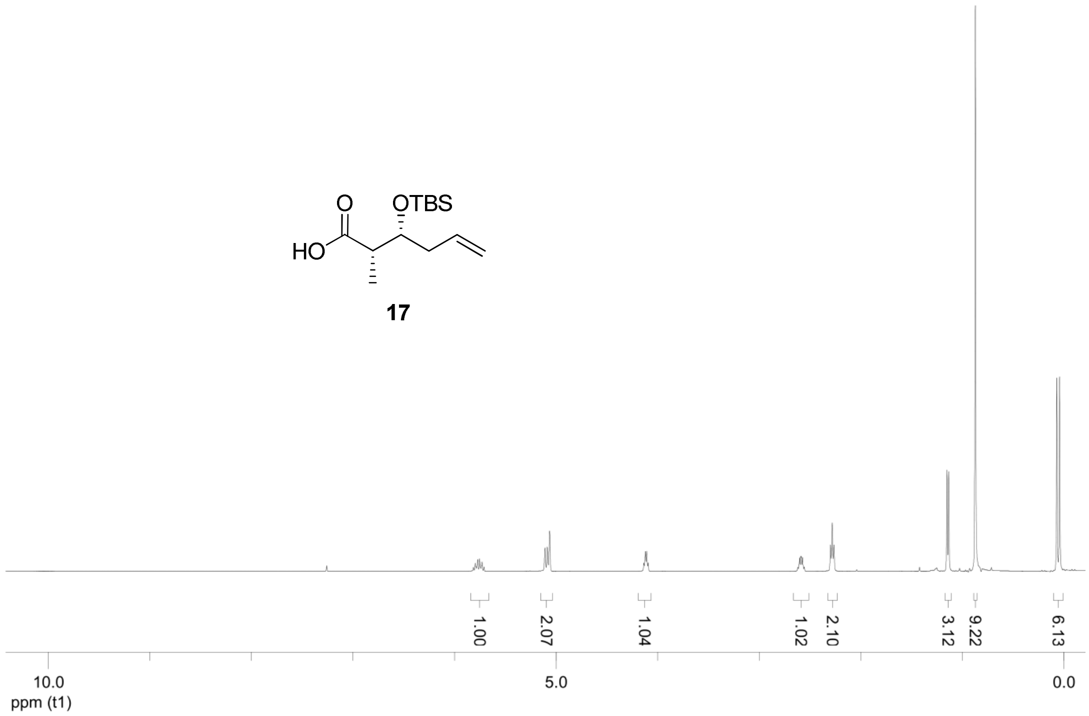
(±)**12**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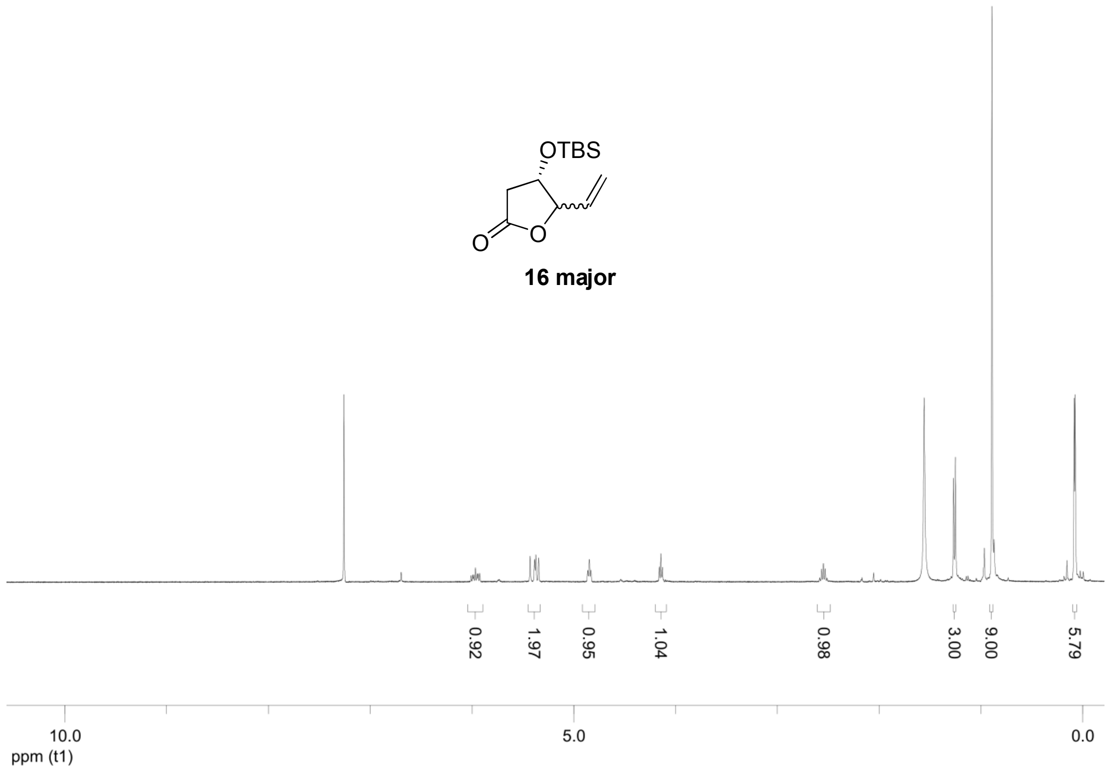
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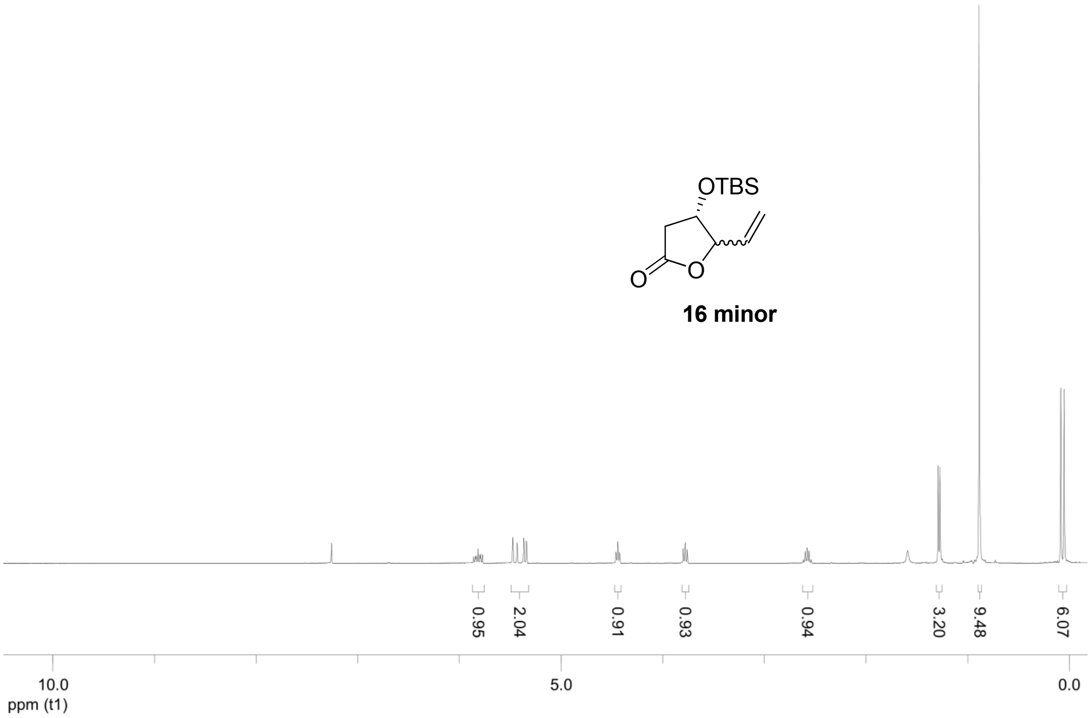
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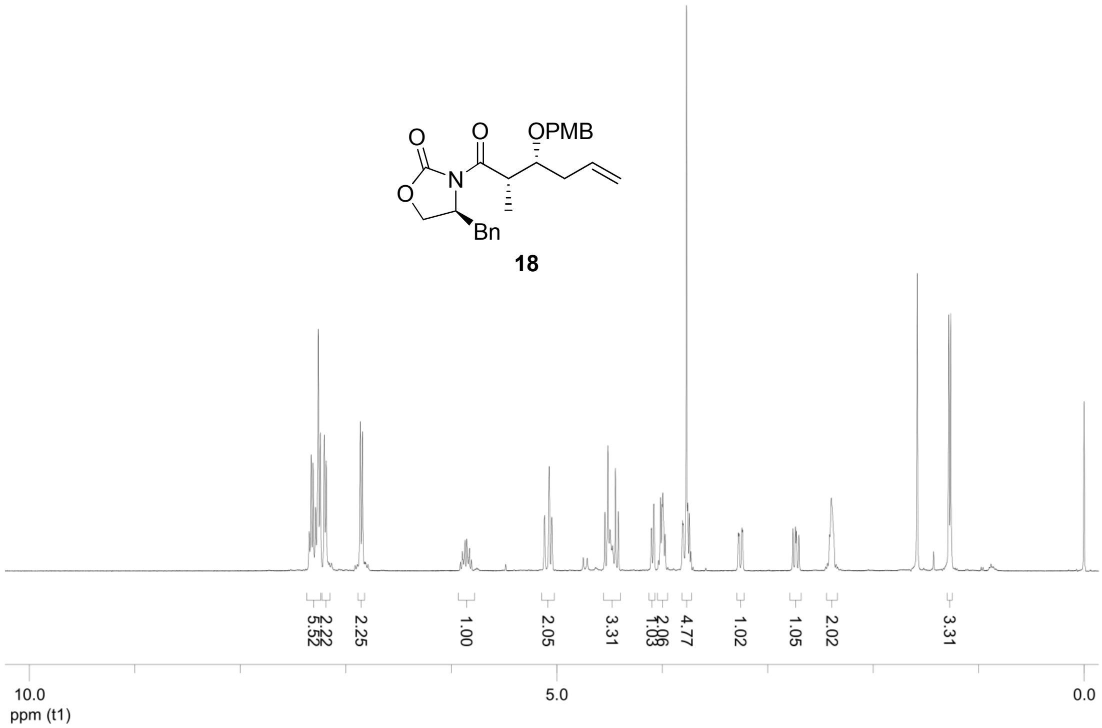
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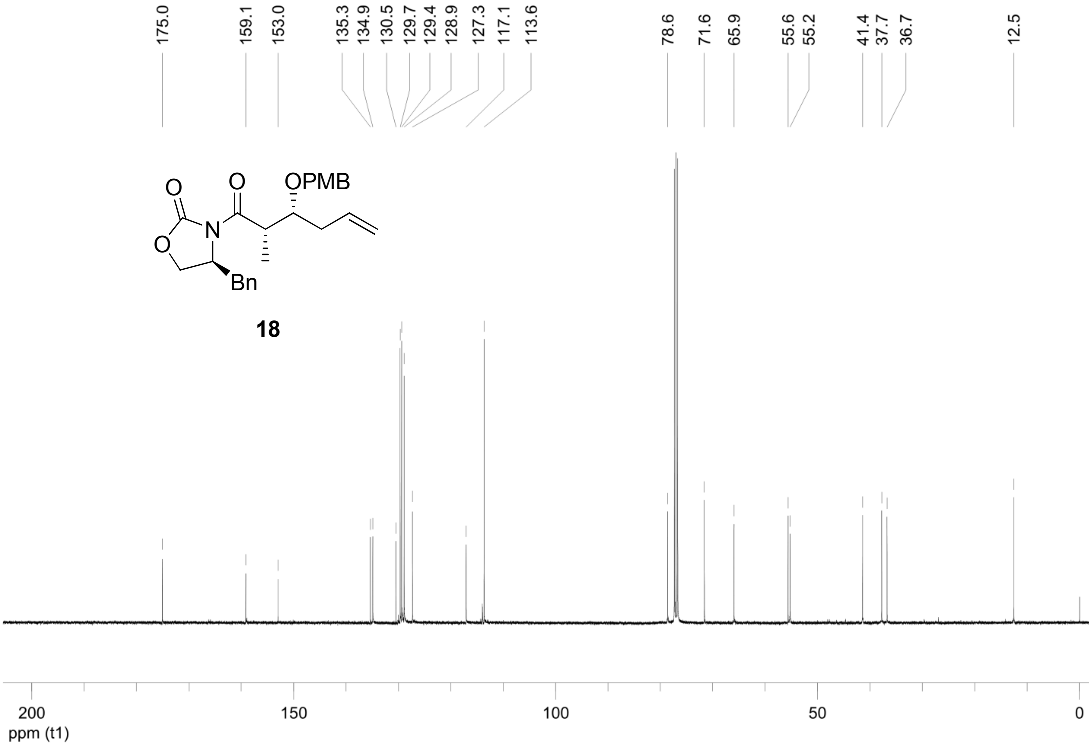
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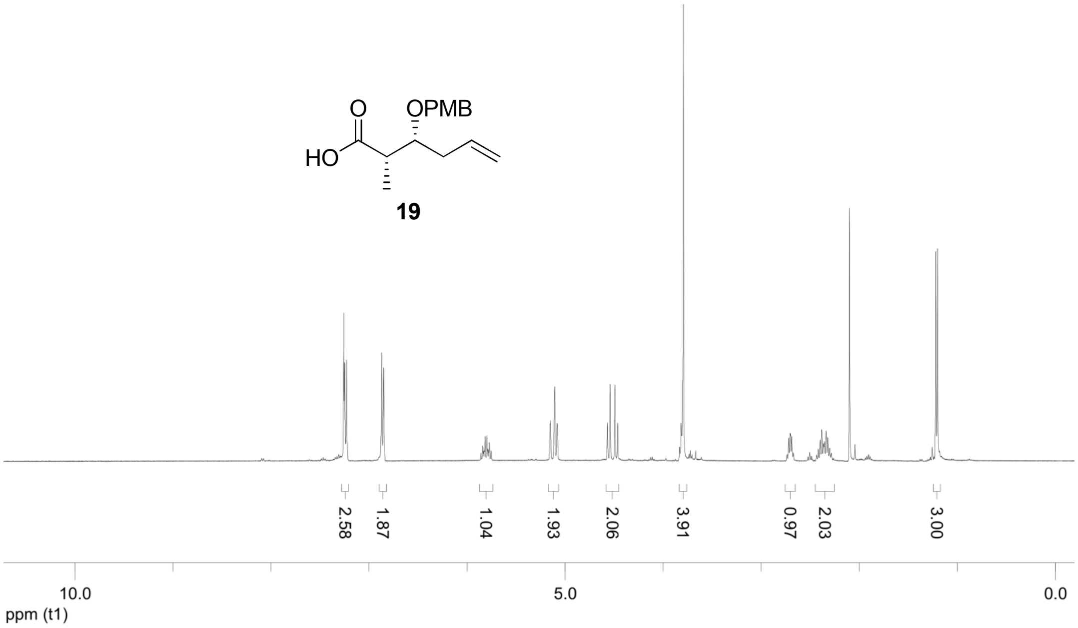
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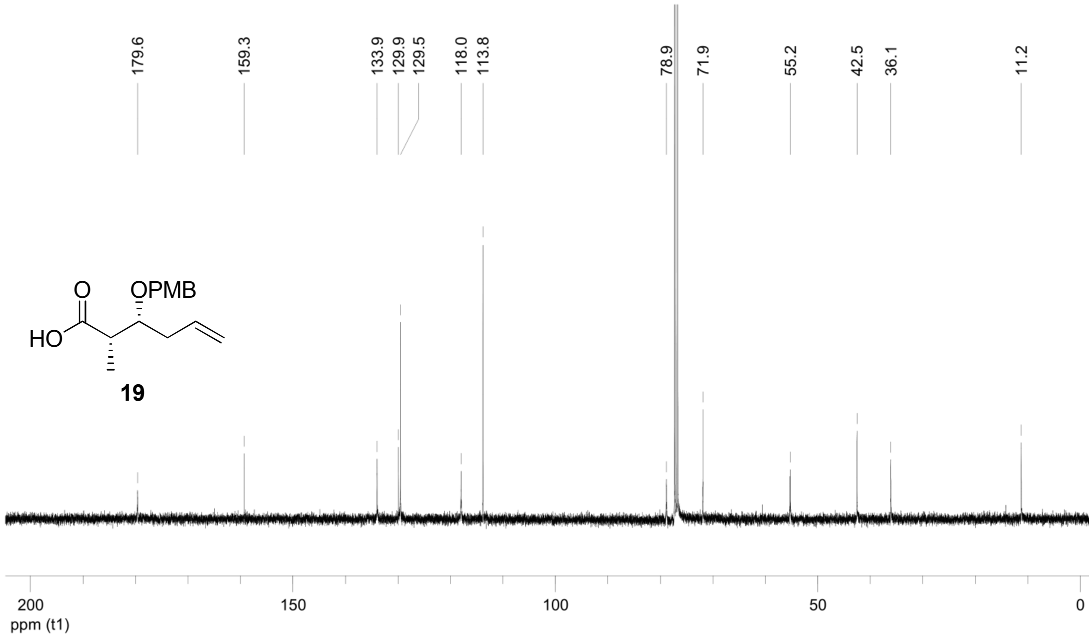
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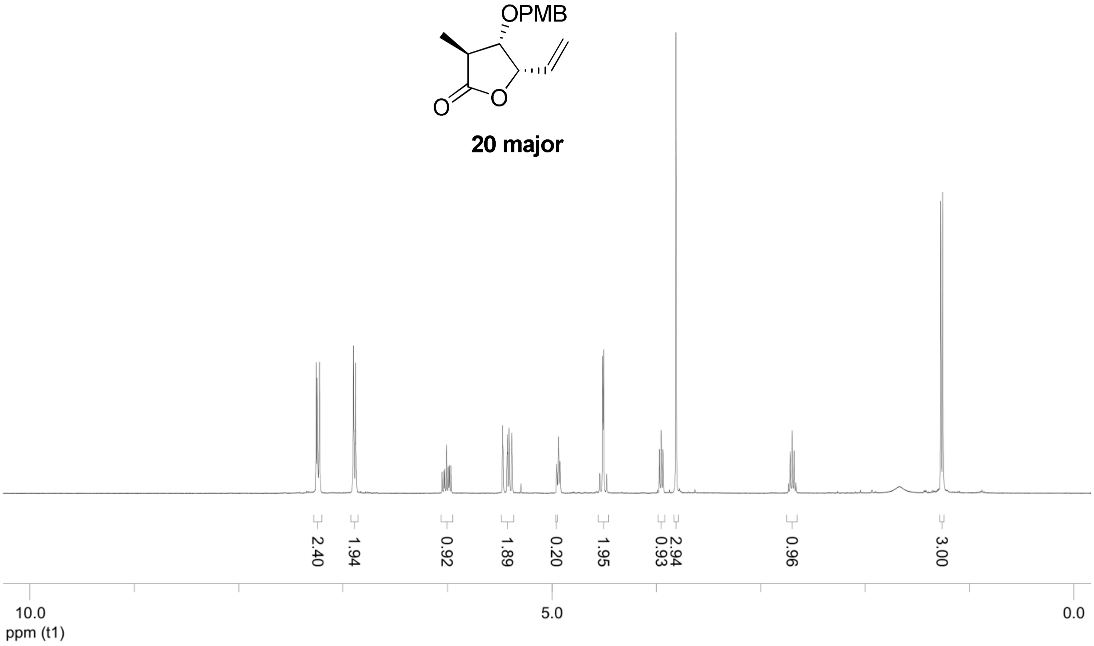
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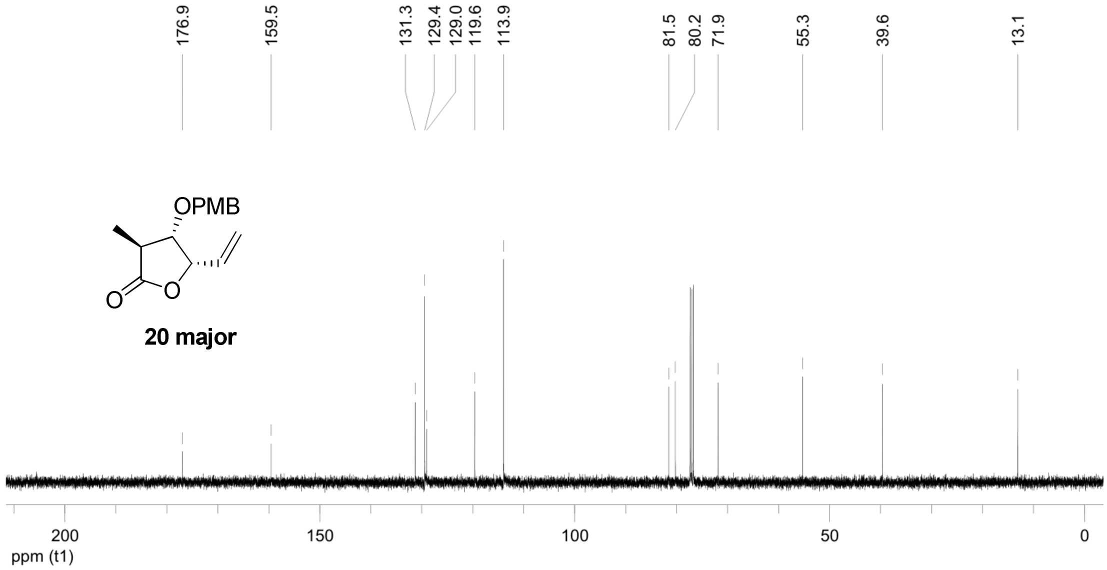

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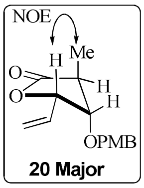

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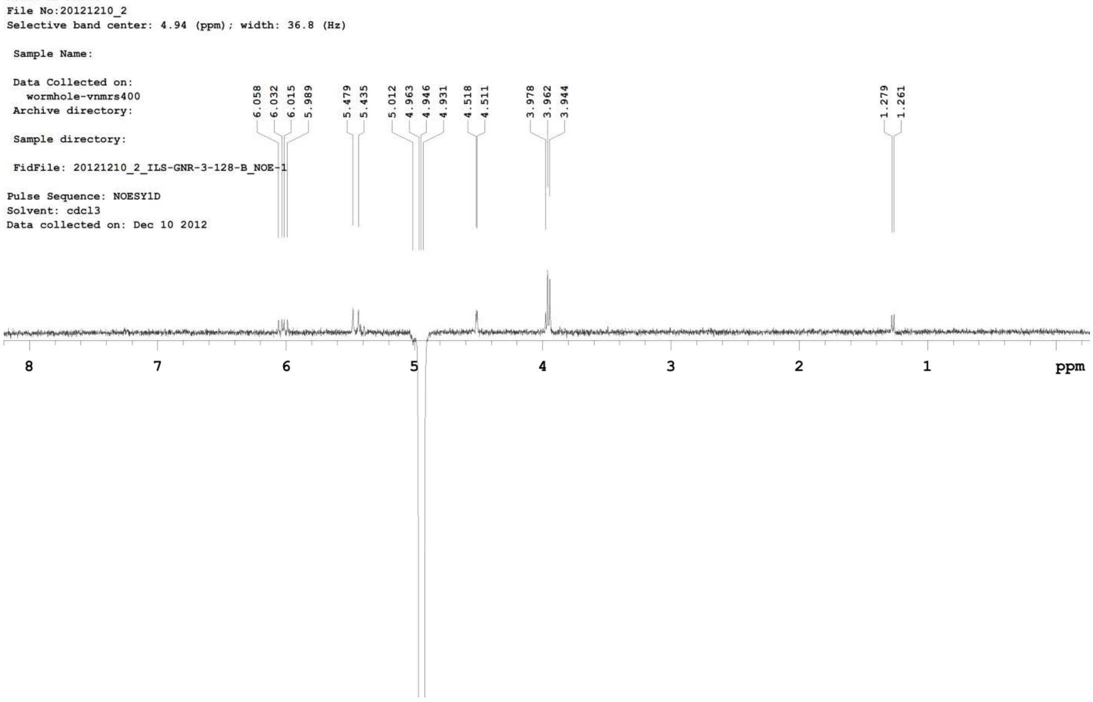
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Archive directory:

Sample directory:

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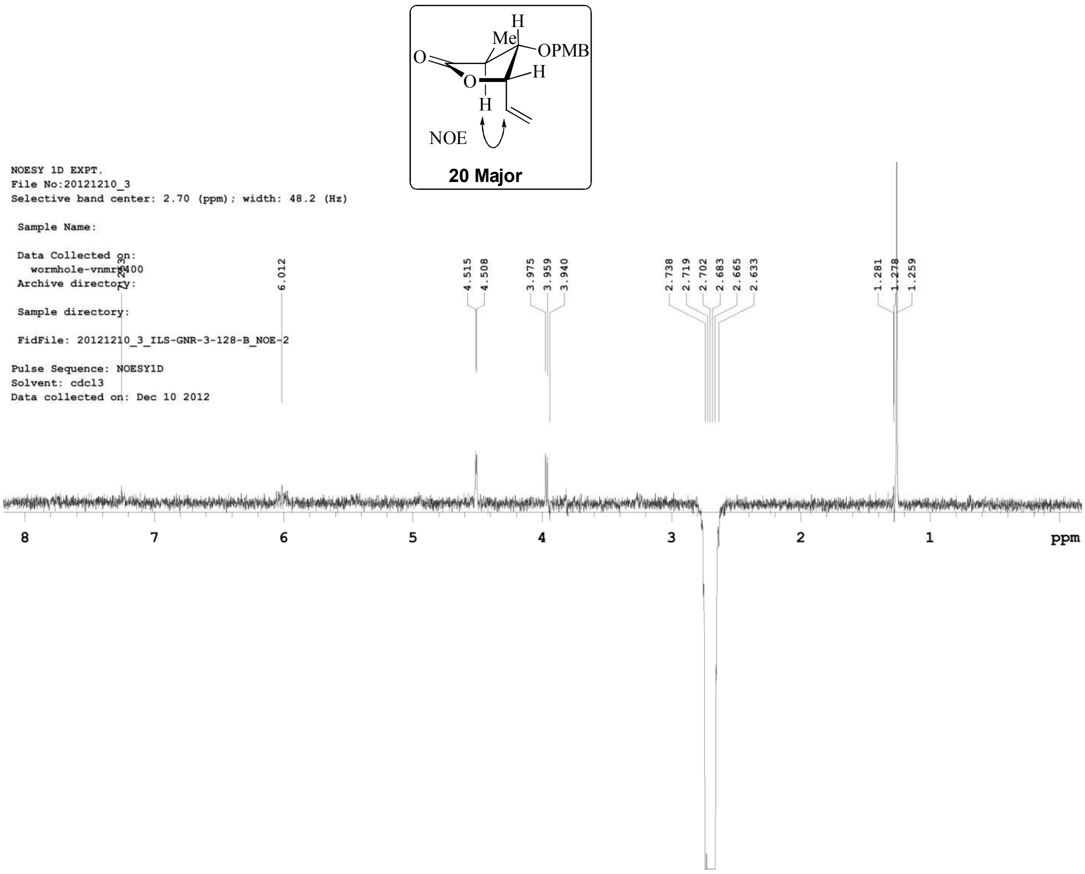
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O
H
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NOE
20 Major
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wormhole-vnmrs400
Archive directory:
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Solvent: cdcl3
Data collected on: Dec 10 2012
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4.508
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3.959
3.940
2.738
2.719
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7
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1
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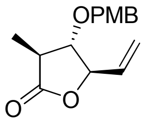

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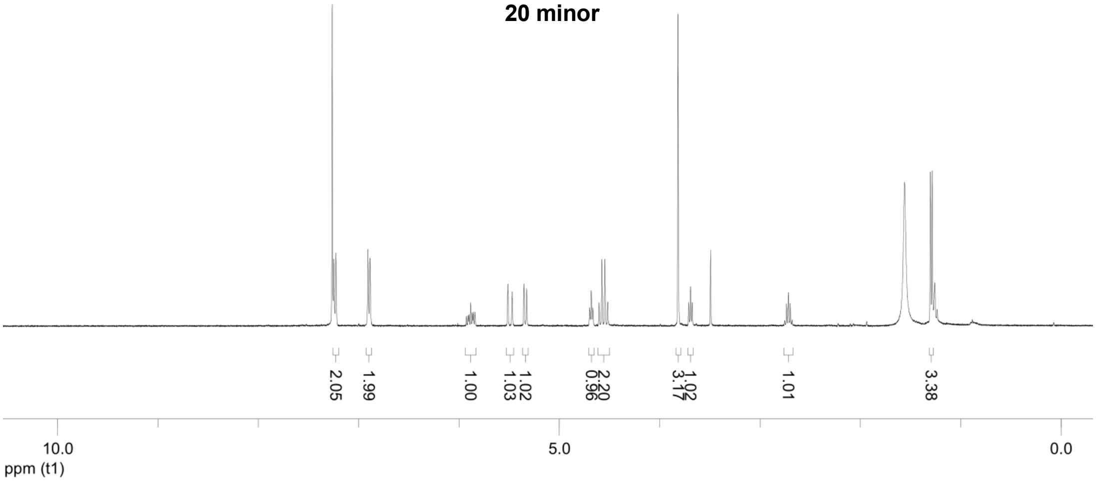
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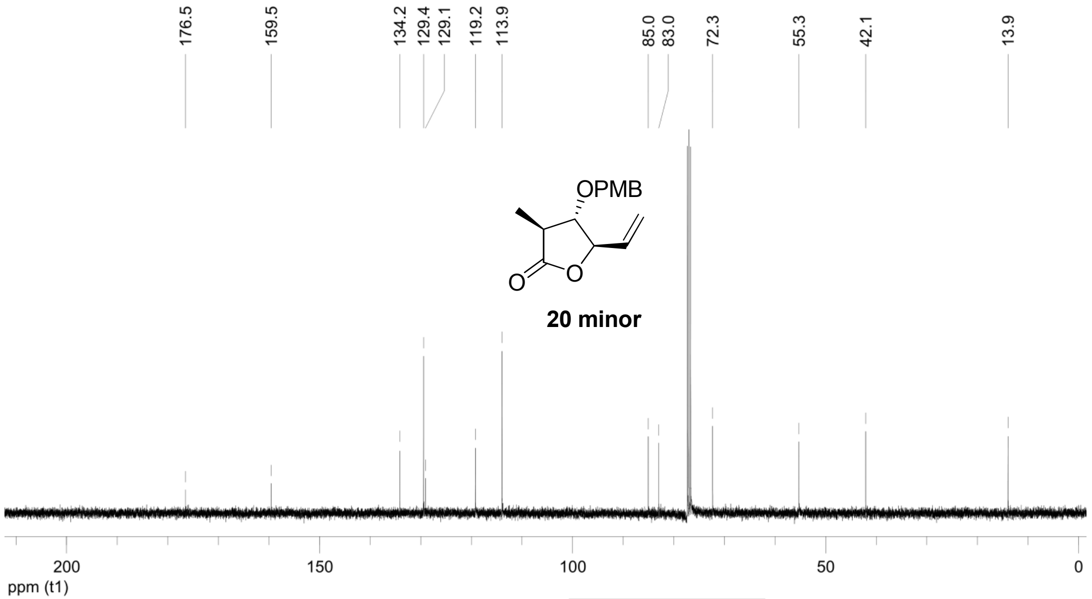

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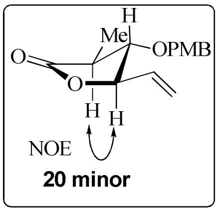

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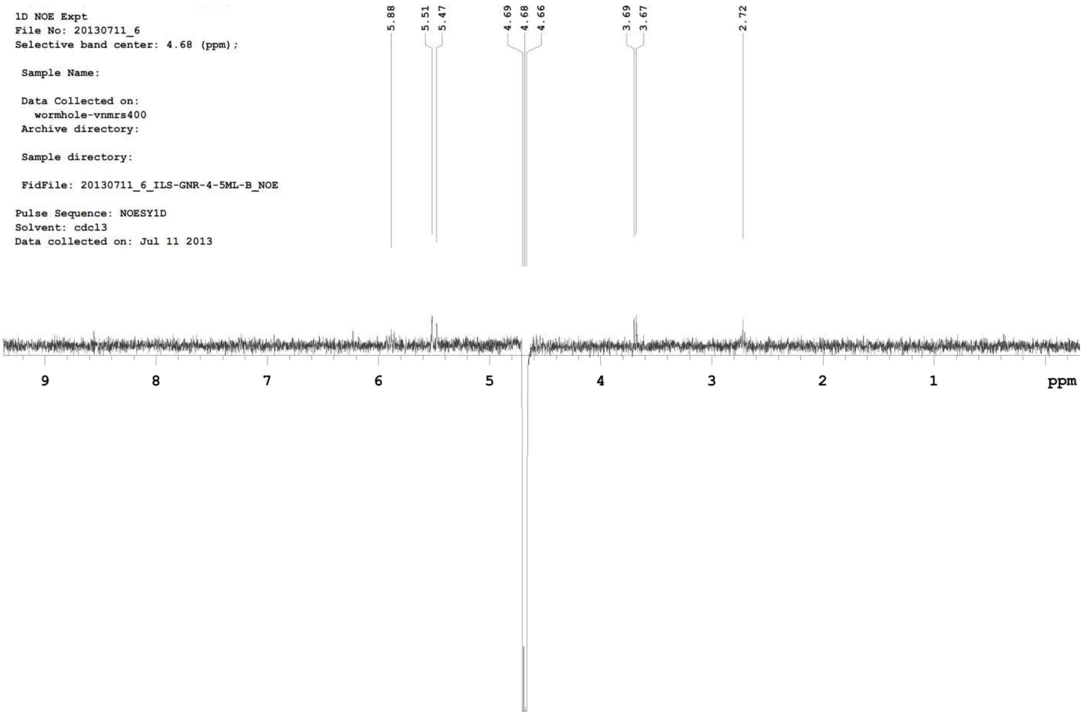

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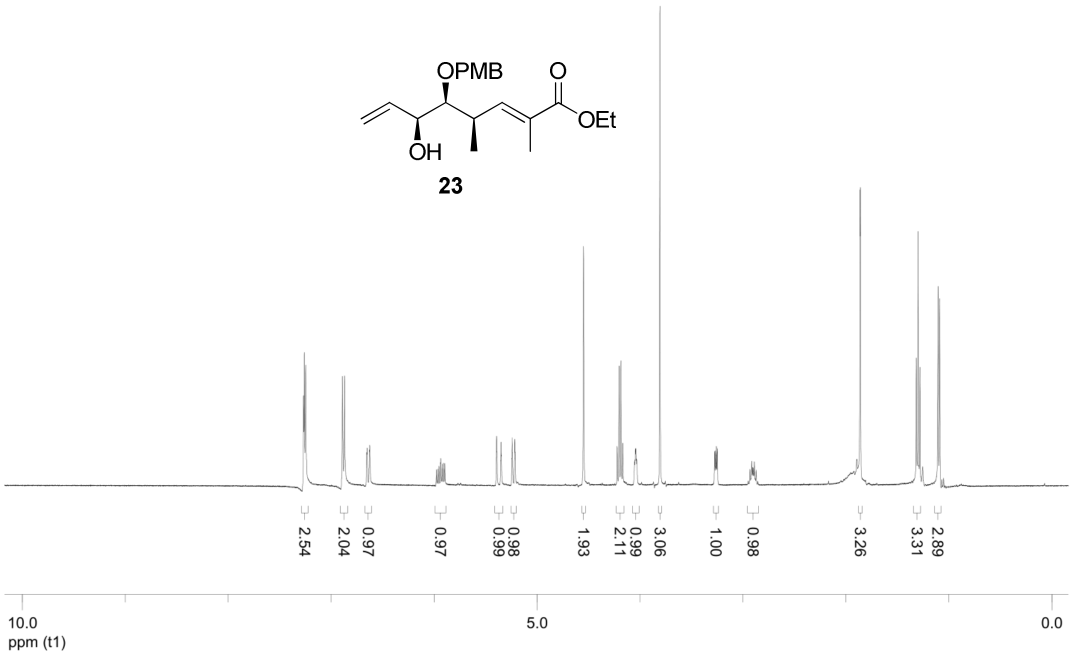
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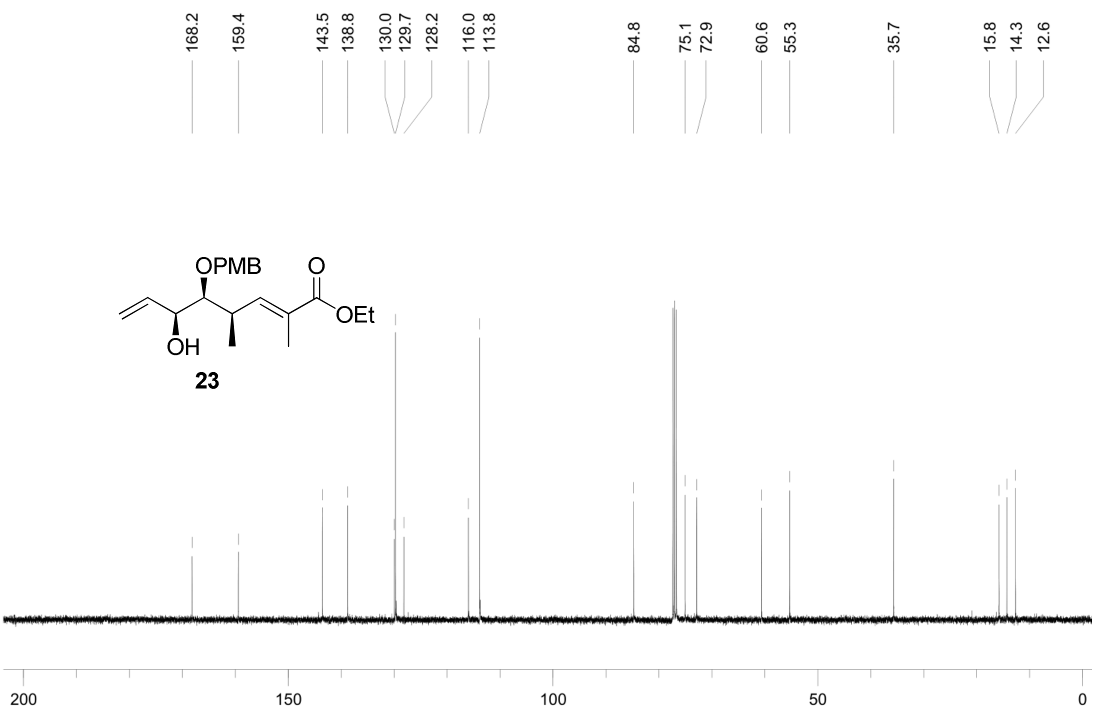
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55.3
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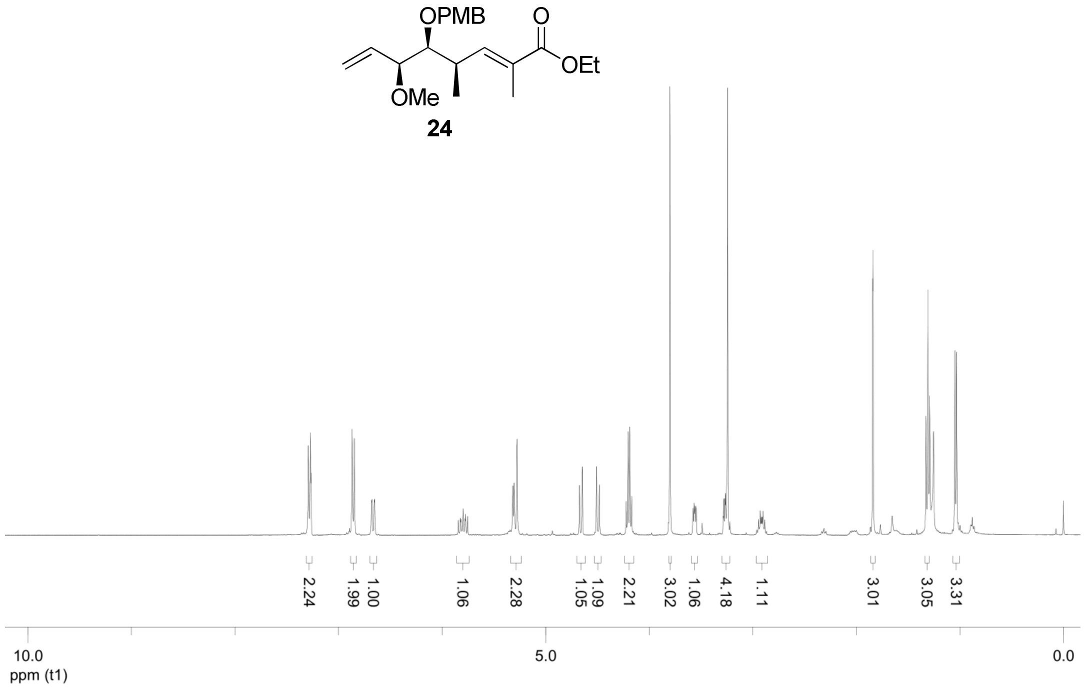
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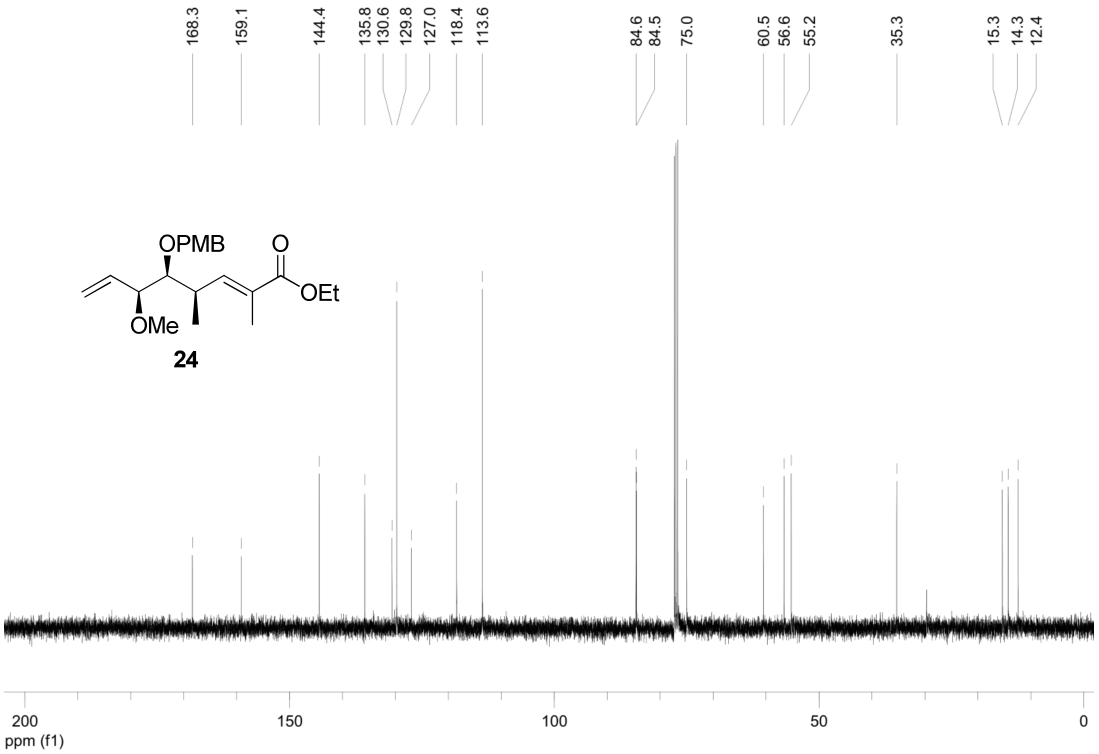
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12.4
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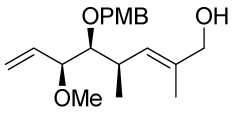
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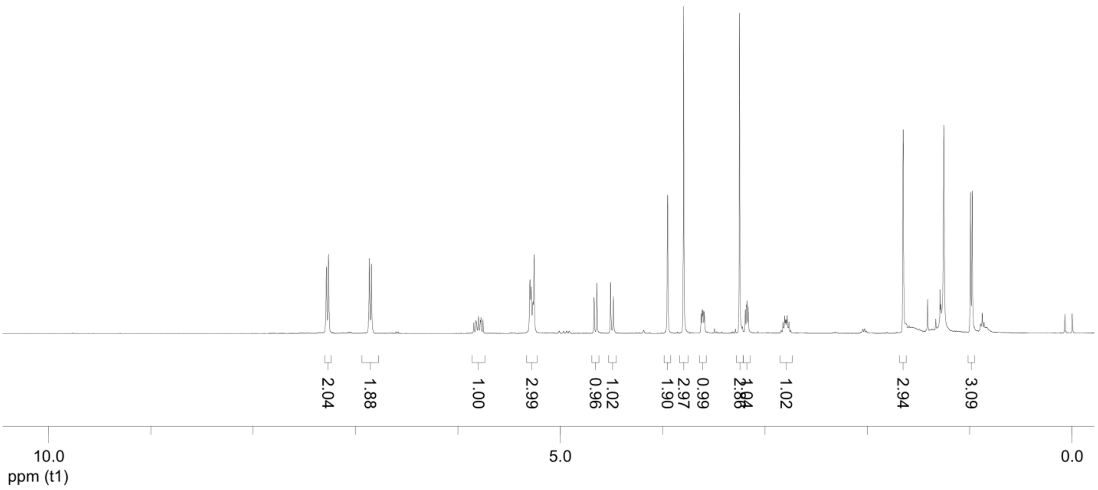
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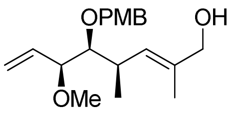
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OMe

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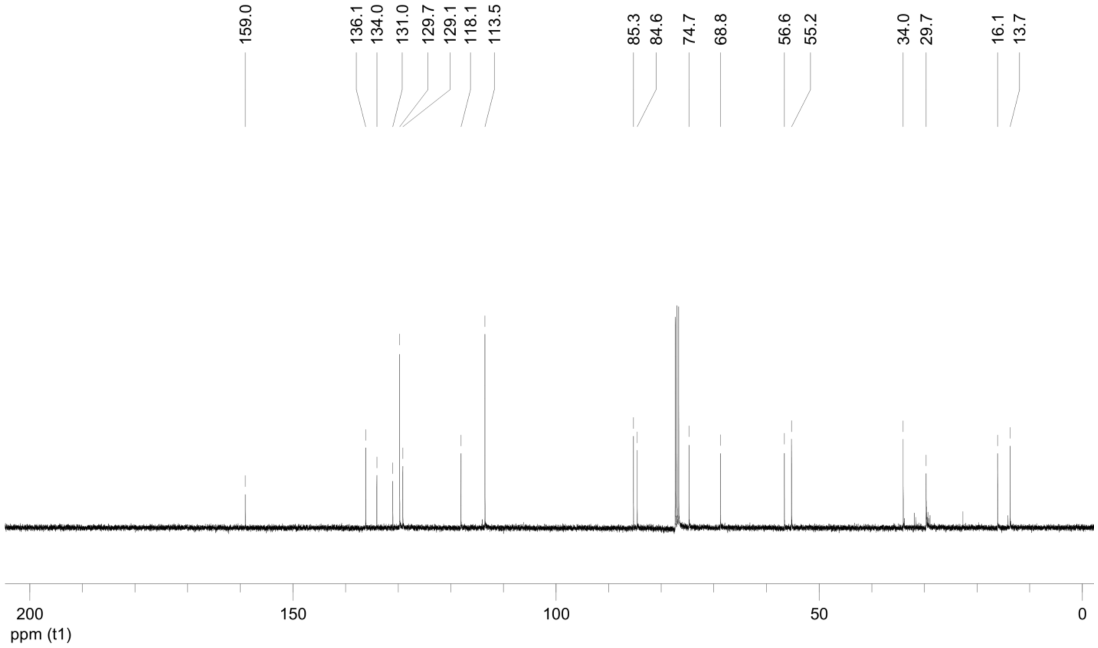
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55.2
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29.7
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13.7
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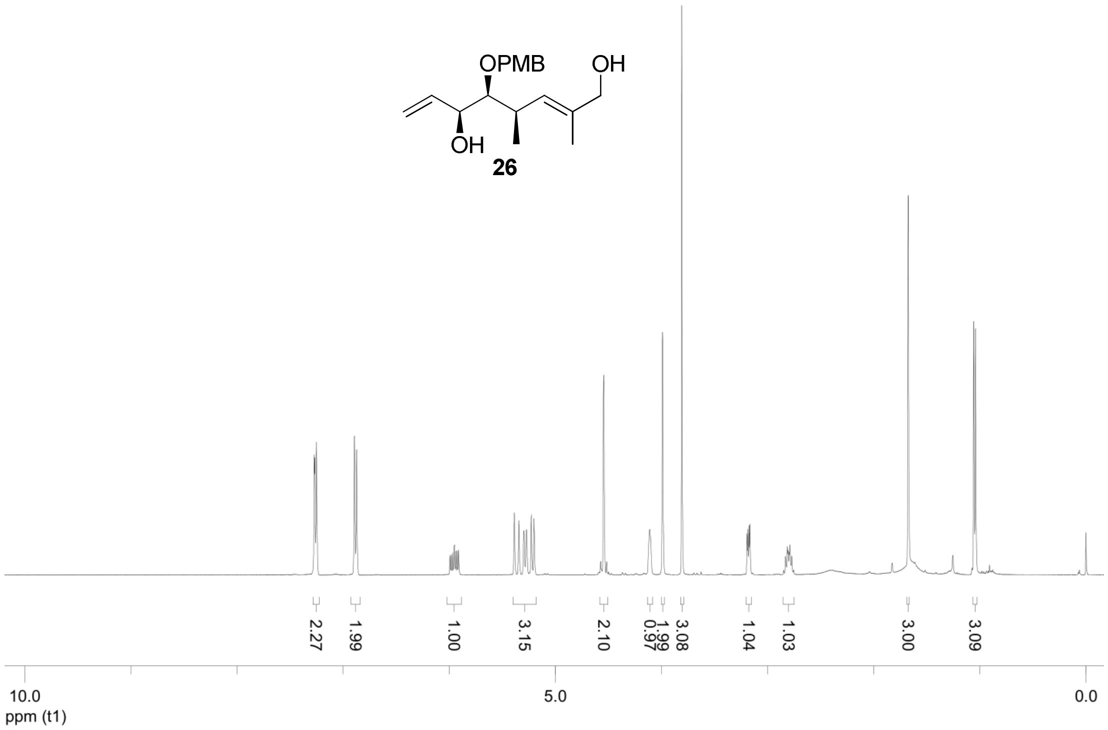
ppm (t1)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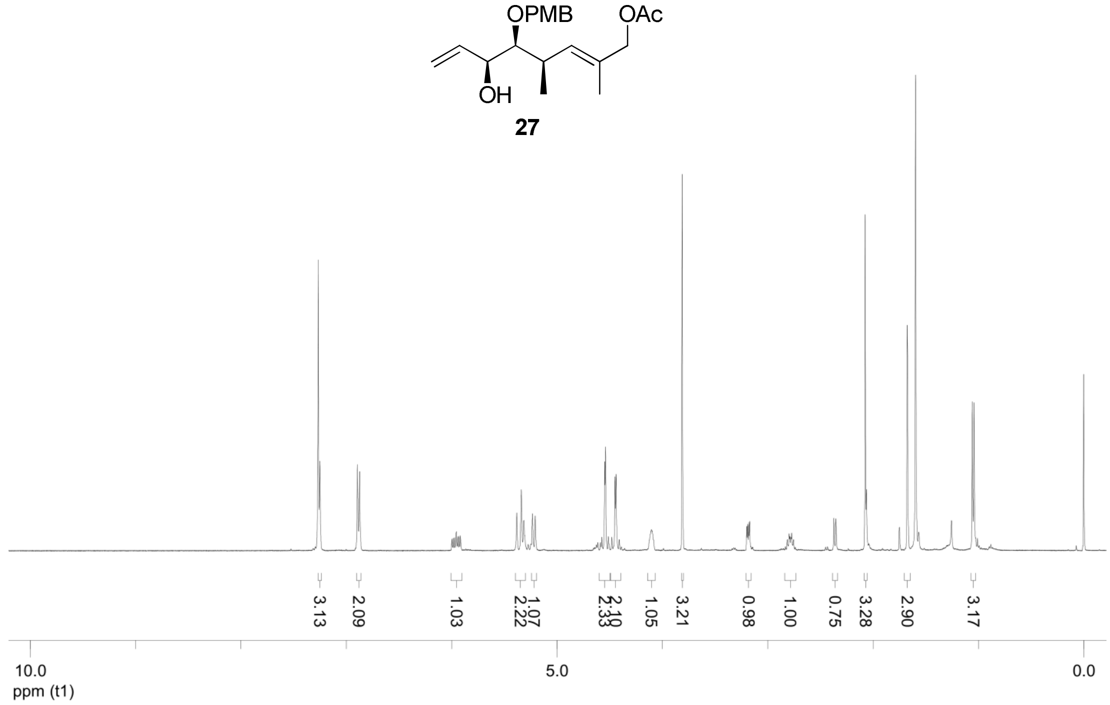
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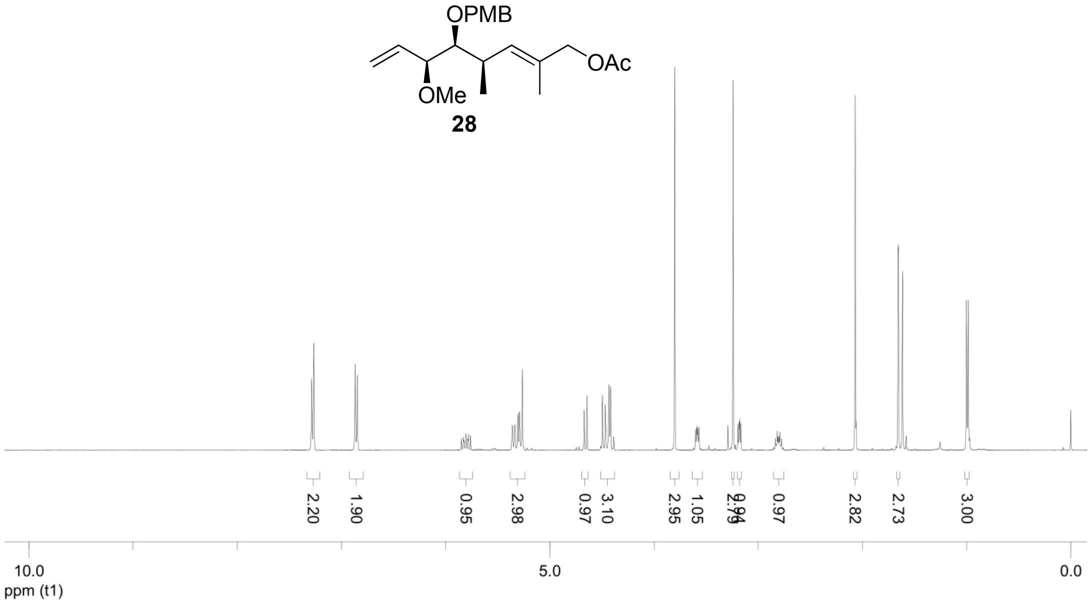
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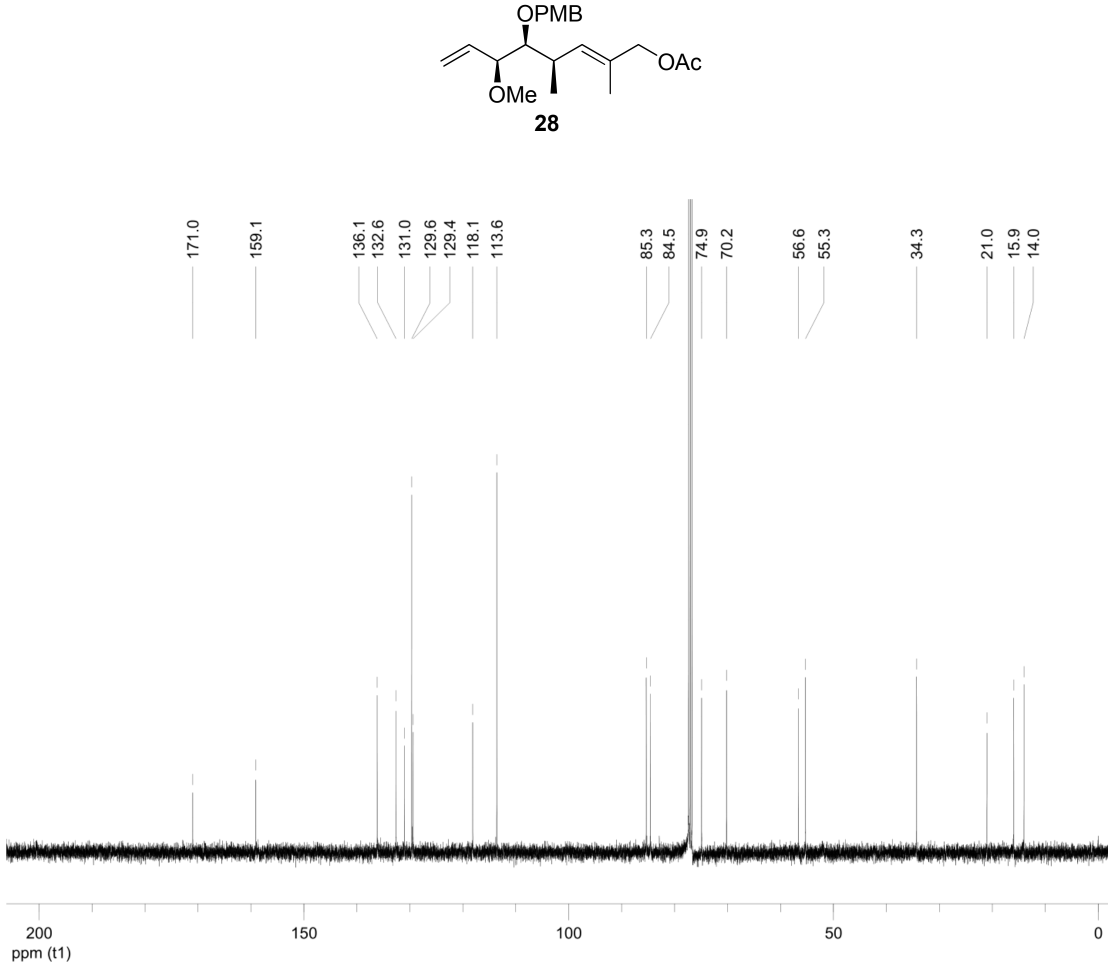
28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OMe
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131.0
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118.1
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85.3
84.5
74.9
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56.6
55.3
34.3
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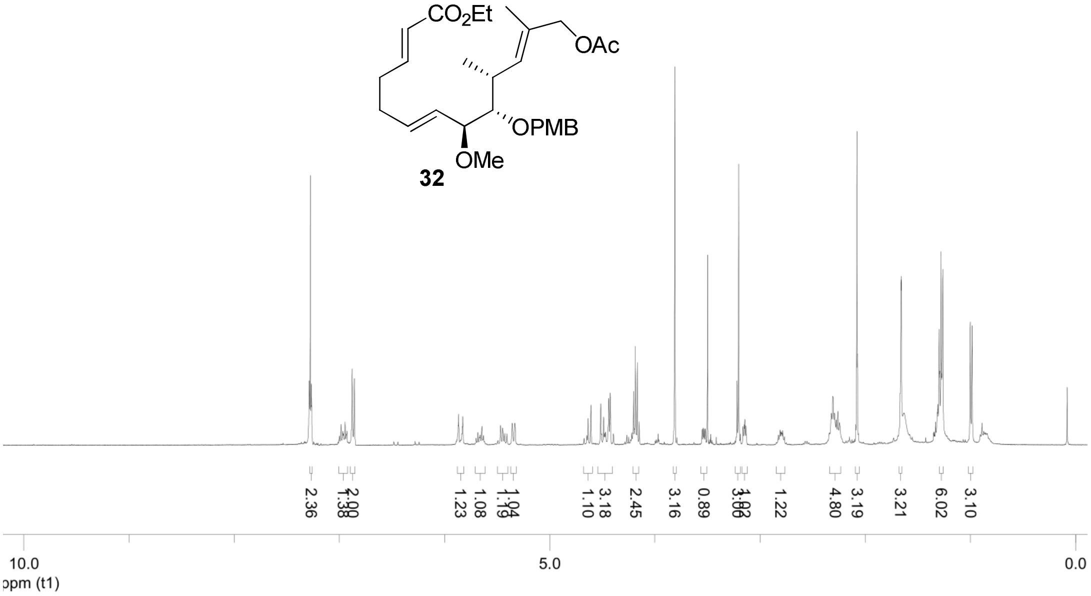
15.9
14.0
200
150
100
50
0
ppm (t1)

28



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OMe
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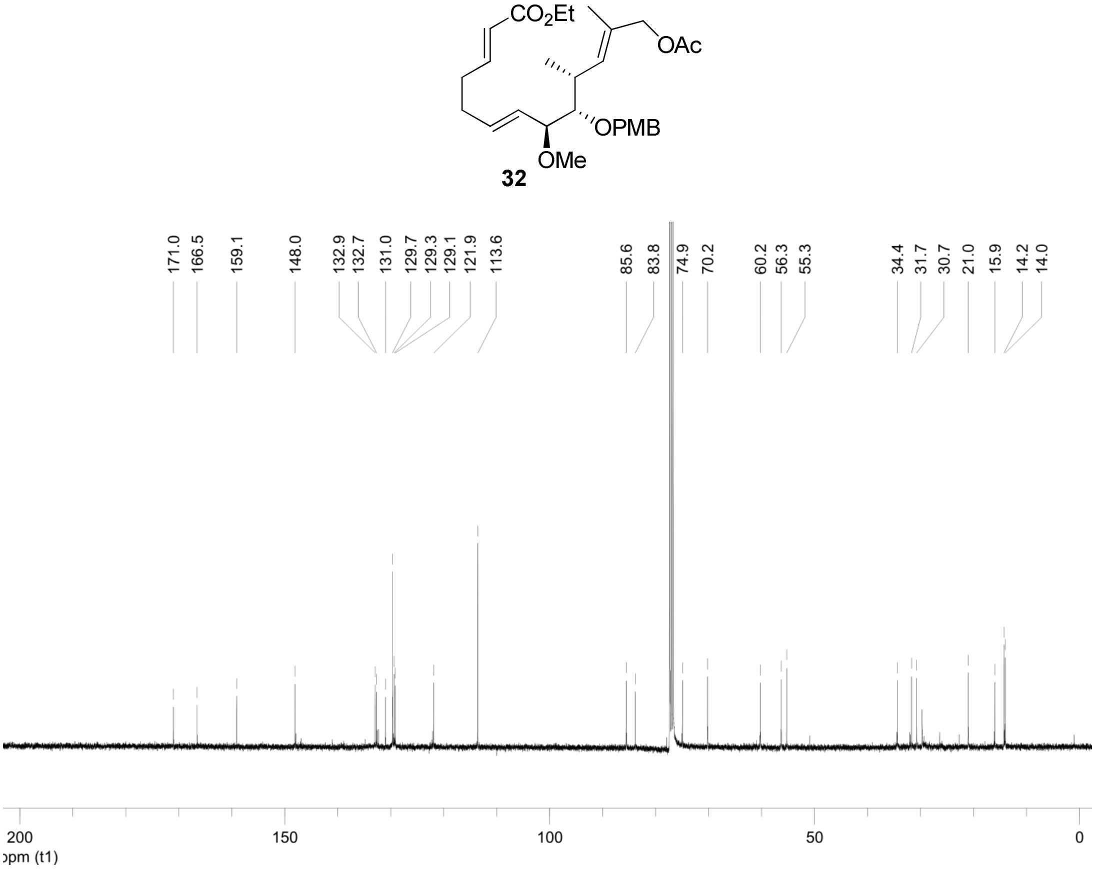
ppm (t1)



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60.2
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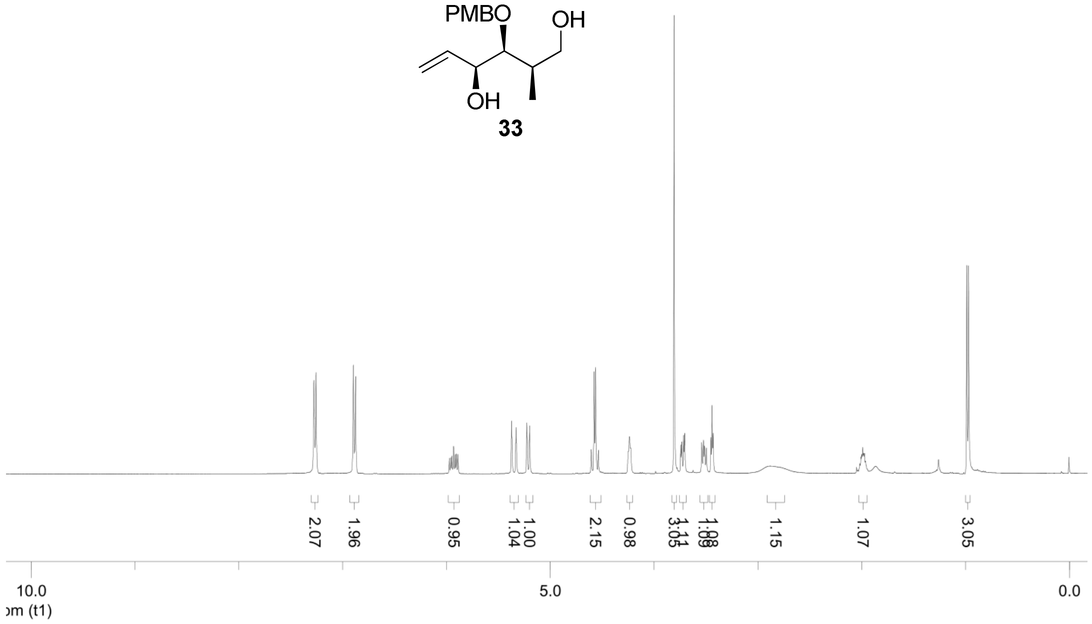
ppm (t1)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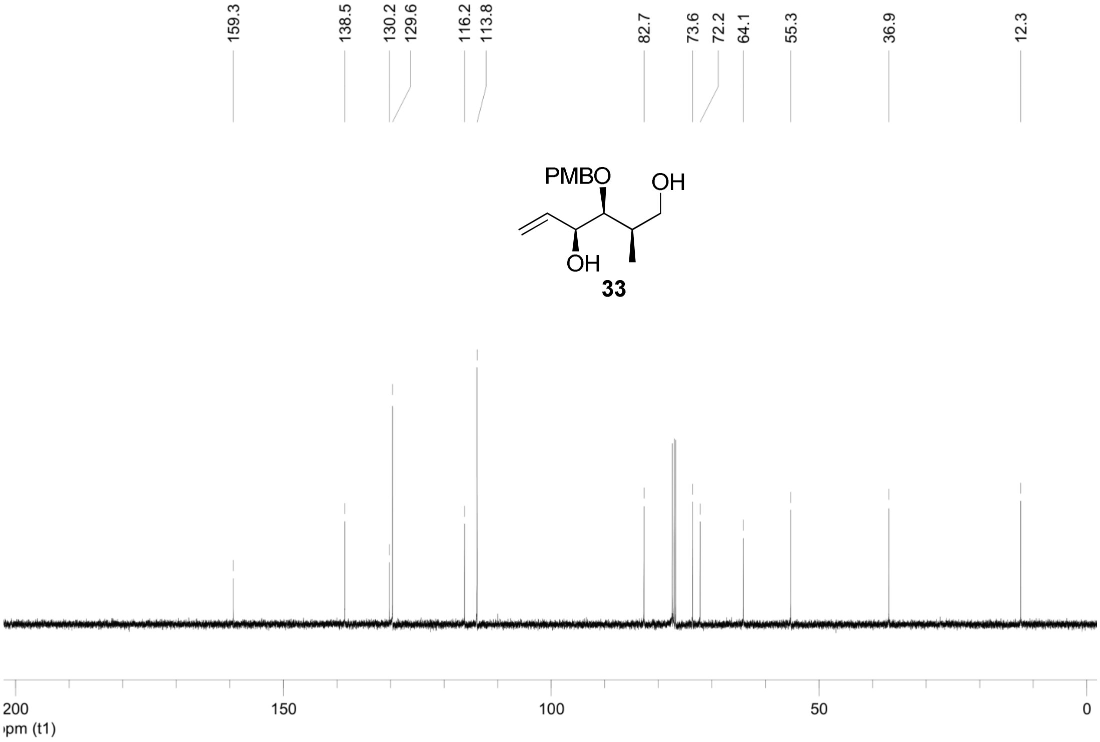
ppm (t1)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OH
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50
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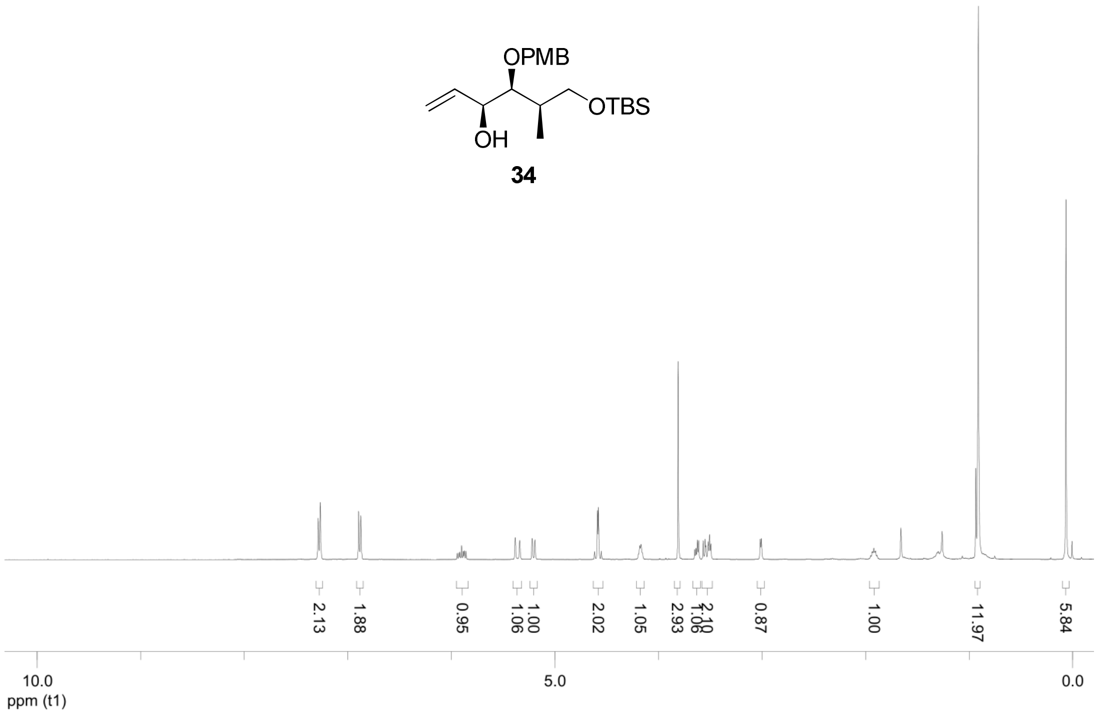
ppm (t1)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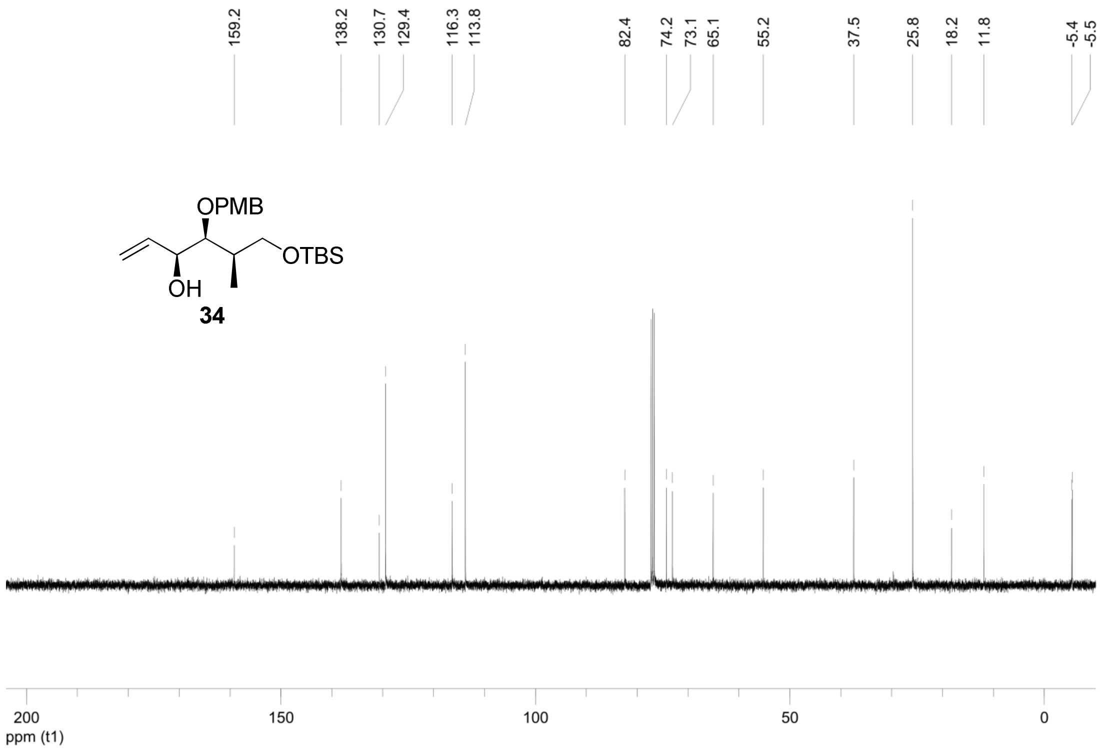
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25.8
18.2
11.8
-5.4
-5.5
OPMB
OTBS
OH
34
200
ppm (t1)
150
100
50
0

CHAPTER 4

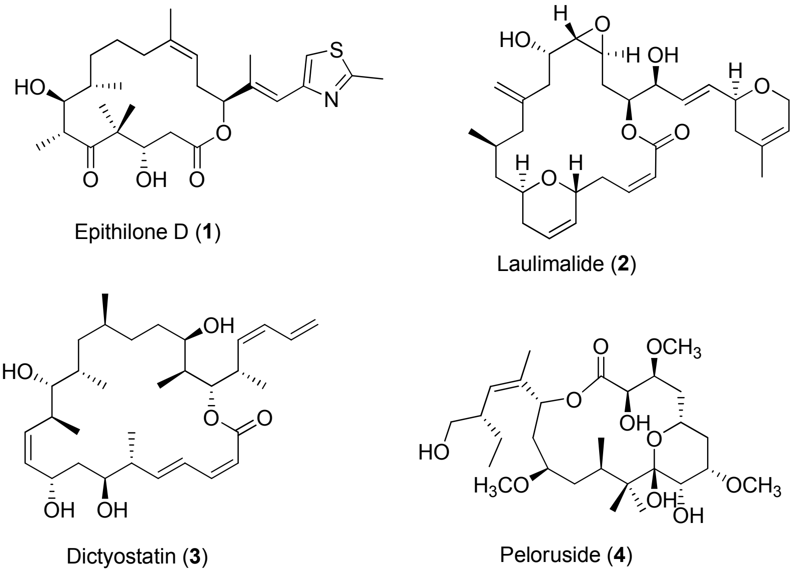
DESIGN AND SYNTHESIS OF HYBRID MOLECULES BASED ON THE FRAGMENTS DERIVED FROM AMPHIDINOLIDE T1, RHIZOXIN D AND MIGRASTATIN FAMILY

Reference:

Narendar Reddy Gade and Javed Iqbal. *Unpublished results*.

4.1. Introduction

Cancer is a most complicated disease and a global problem to be addressed. The basic problem associated with the cancer cells is uncontrolled growth, invasion and tumor metastasis.[1] Chemotherapy is one way of treating cancer with drugs that can destroy cancer cells. It interferes with cell division in various possible ways, e.g. with the duplication of DNA or the separation of newly formed chromosomes. Many natural products play a pivotal role in curing cancer by binding to the tubulin protein, so that they can interfere in microtubule dynamics,[2] which is essential for cell division. Many macrocylic natural products have been identified as anti cancer agents, e.g. epitholone D (**1**), laulimalide (**2**), dictyostatin (**3**) and peloruside (**4**) (Fig. 4.1).[3] It is generally observed that in cancer chemotherapy, cytotoxic molecules inhibit tumor cell proliferation and cause cell death. But cell migration (metastasis) is a major problem to be solved along with cell prolifiration. This chapter deals with our hypothesis, design and synthesis of hybrid molecules possening a dual property of cell growth inhibition and cell migration to address the challenge of motility and mobility in cancerous cells.



Epithilone D (**1**)

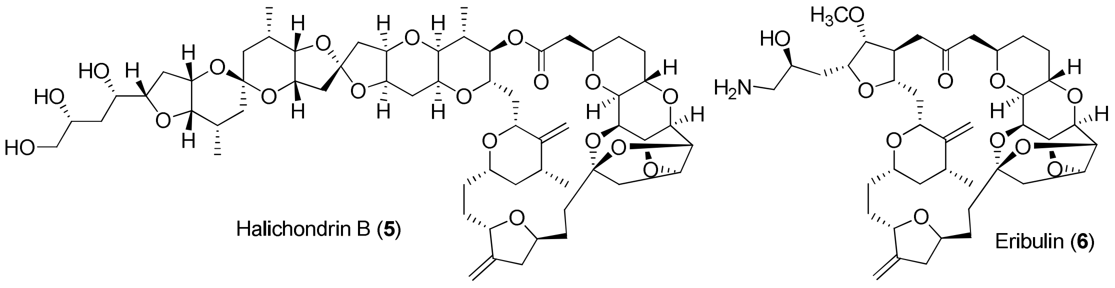
Laulimalide (**2**)

Dictyostatin (**3**)

Peloruside (**4**)

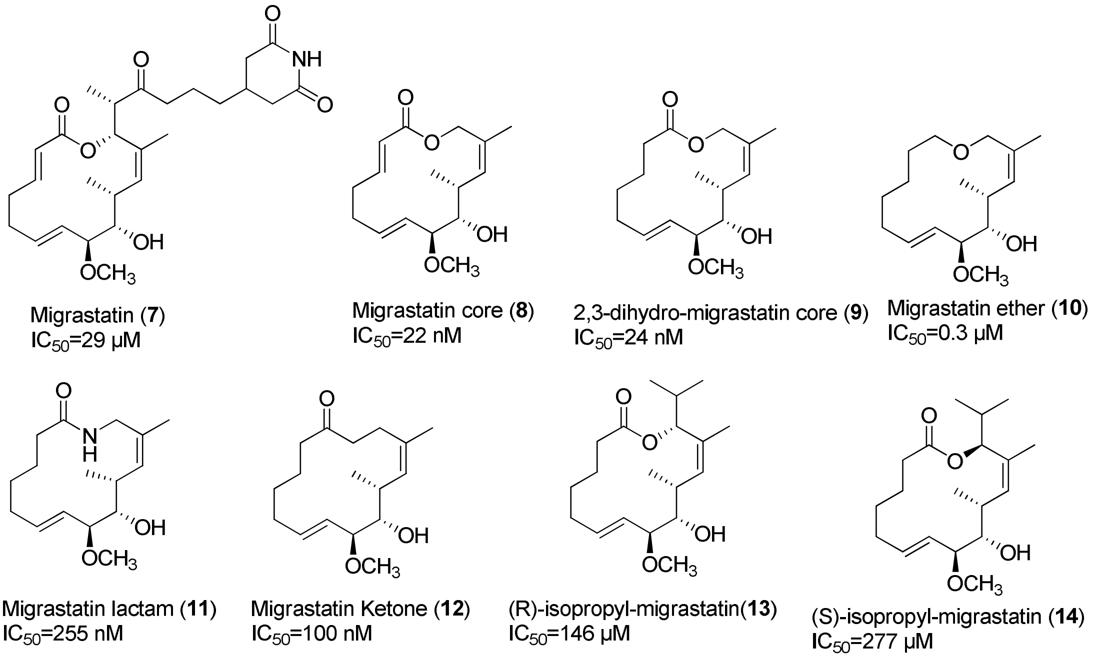
Figure 4.1. Macrolide natural products with anti cancer activity

Natural products often posses highly potent and selective bioactivity. But often they do not undergo evolutionary process to serve as human therapeutics but require structural fine tuning to obtatain the potency, selectivity, and pharmacokinetic properties desired in a clinically useful drug. Normally this fine tuning process involves the modification, removal, or introduction of functional groups and stereocenters or more drastic remodeling of the basic scaffold. Since the biosynthetic methods to obatin diveristy based on available pathways is limited in scope, synthetic chemistry can be used as a powerful tool to access the maximum number of modifications and structural diversity.[4]


Halichondrin B (**5**)

Eribulin (**6**)

Figure 4.2. Halichondrin B and eribulin


Migrastatin (**7**)
IC_{50}=29 μM

Migrastatin core (**8**)
IC_{50}=22 nM

2,3-dihydro-migrastatin core (**9**)
IC_{50}=24 nM

Migrastatin ether (**10**)
IC_{50}=0.3 μM

Migrastatin lactam (**11**)
IC_{50}=255 nM

Migrastatin Ketone (**12**)
IC_{50}=100 nM

(R)-isopropyl-migrastatin(**13**)
IC_{50}=146 μM

(S)-isopropyl-migrastatin (**14**)
IC_{50}=277 μM

Figure 4.3. IC_{50} values of migrastatin and its analogues towards 4T1 tumor cells

Diverted total synthesis apporach is often useful for the identfication of pharmacophores, which are the substurctural portions of the molecule possessing the required features for activity. The pharmacophore can be an advanced intermediate containing lesser complexity than the target natural product. The resulted pharmacophore sometimes may exhibit similar or better activity than the natural product. Halichondrin B (**5**) is a remarkable example, where the total synthesis studies led to find out the more potent pharmacophore eribulin (**6**) (Fig. 4.2), is currently marketed anti cancer drug.[5] Danishefsky's pioneering work in the area of diverted total synthesis has also shown that simpler analogues of migrastatin are more potent than the natural product (**7**) (Fig. 4.3).[6]

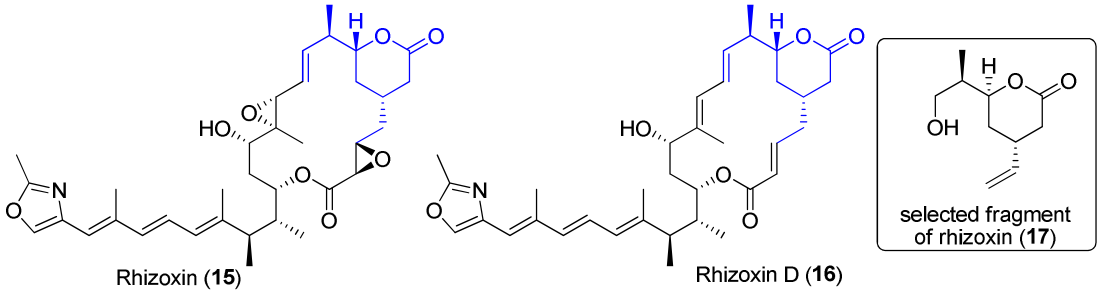


Figure 4.4. Rhizoxin family and selected fragment

Iwasaki and co-workers isolated a new class of macrolides in 1984 from the fungus *Rhizopus chinensis.*[7] Rhizoxin D (**16**) is believed to be the biogenetic precursor of rhizoxin (**15**) (Fig. 4.4) Shows potent *in vitro* cytotoxicity and *in vivo* anti-tumor activity through binding to *β*-tubulin, leading to cell death.

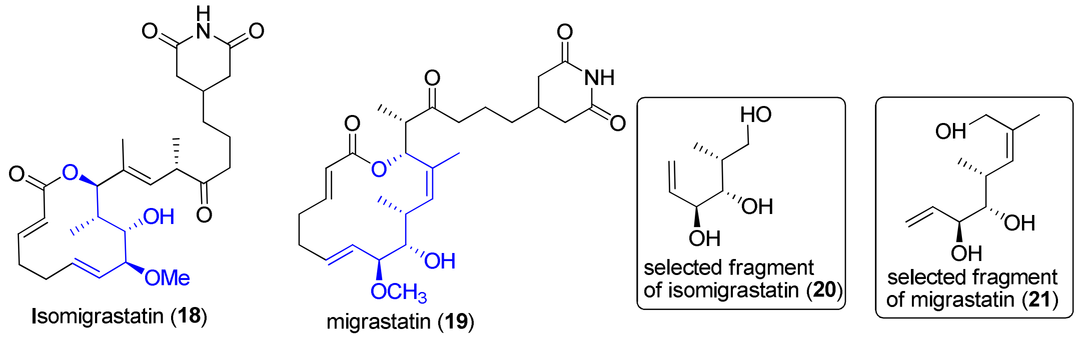


Figure 4.5. Migrastatin, isomigrastatin and selected fragments

Migrastatin (**19**) actually a shunt metabolite of isomigrastatin (**18**) (Fig. 4.5), produced by *Streptomyces* strains. Isomigrastatin transforms in to migrastatin by a strain relief driven [3,3]-sigmatropic rearrangement that does not need any enzyme catalysis.[8] Independent biochemical and biophysical studies have identified fascin as the primary target of migrastatin and congeners. Thus, fascin plays a pivotal role in regulating the assembly of the actin cytoskeleton and hence in cell motility and active cell movement.[9]

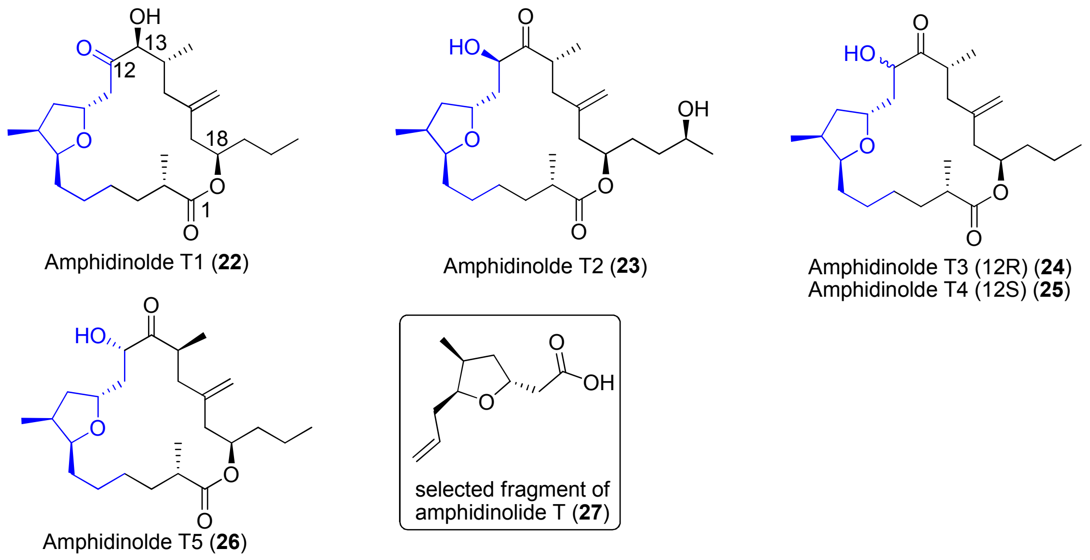


Figure. 4.6. Amphidinolide T family and selected fragment

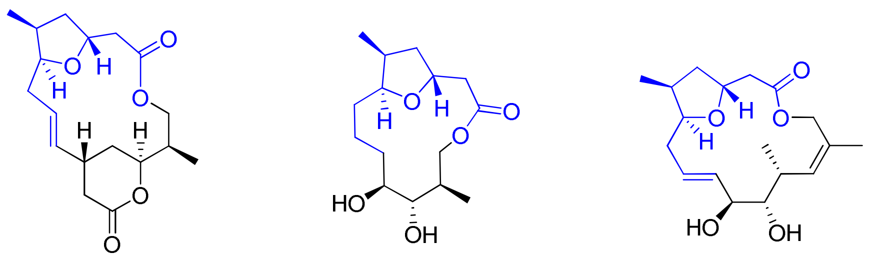
Amphidinolides have been isolated from marine dinoflagellates of the genus *Amphidinium sp.* amphidinolides T1–T5 (**22-26**) (Fig. 4.6) are somewhat less cytotoxic than some of the other amphidinolides but still possess activities with IC_{50} values from 7-18 µg/mL against murine leukemia cells and from 10-35 µg/mL against KB human epidermoid carcinoma cells.[10]

4.2. Design & Hypothesis

In light of information regarding anti cancer drugs, a single molecule with both properties of supression of tumor growth and control over the cell migration is an ideal solution to cancer. So we hypothesised that incorporating two pharmacophores in a single molecule may offer an opportunity to address the problem of cytotoxicity as well as cell migration.

Macrocyclic natural products have the profound pharmacological properties, diverse functionalities and stereo chemical complexity in a conformationally pre-organized ring structure attracting the attention of synthetic medicinal chemists.[11] Migrastatin (**19**) has proven to be an attractive molecule possessing impressive cell migration inhibition properties. Therefore, a designed molecule comprising of structural features present in migrastatin and a cytotoxic molecule promises to be a viable strategy to access hybrid new chemical entities possessing unique pharmacological properties of combating cell mobility and motility. This hypothesis is also based on the premise that the designed hybrid structures should be drug like and easily synthesizable. Thus, any design based on this assumption must incorporate only the “critical structural features” present in the parent natural products in order for the hybrid structure to be compliant with the requirement of drug-likeness and structural simplicity. Therefore, identification of the “critical structural features” in the parent natural products may be based on a pharmacophore like attribute inherent in the stereo-electronic architecture of the molecule. It is likely that the three-dimensional chiral backbone present in the macrocyclic part of migrastatin (**19**), amphidinolide T1 (**22**) and rhizoxin D (**16**) may have the stereo-electronic compatibility in order to bind with the target proteins responsible for the observed pharmacological behavior of these natural products. Thus, in the absence of any clear understanding on the pharmacophore responsible for the activitiy of these natural products, it was envisaged that by stitching together a combination of different fragments, derived from the chiral segment, present in the macrocycles, may provide a good starting point for the synthesis of hybrid molecules. Thus, hybrid molecules synthesized, by stitching fragments from different chiral segments of these natural products, may yield a class of new chemical entities possessing unique pharmacological properties and likely to act as a good probe to study cancer cell migration and motility. Accordingly, we have designed hybrid macrocyclic products by sticthing, via covalent bonds, few selceted fragments present in rhizoxin, migrastatin, isomigrastatin and amphidinolide T.

Thus, for the present studies, we have identified fragments **17** (Fig.4.4), **20** and **21** (Fig. 4.5) present in rhizoxin D, isomigrastatin and migrastatin respectively whereas the fragment **27** (Fig. 4.6) was identified from amphidinolides T1-T5. Accordingly, the hybrid structures **28**-**30** (Scheme 4.1) were designed based on the fragments **17**, **20**, **21** and **27**



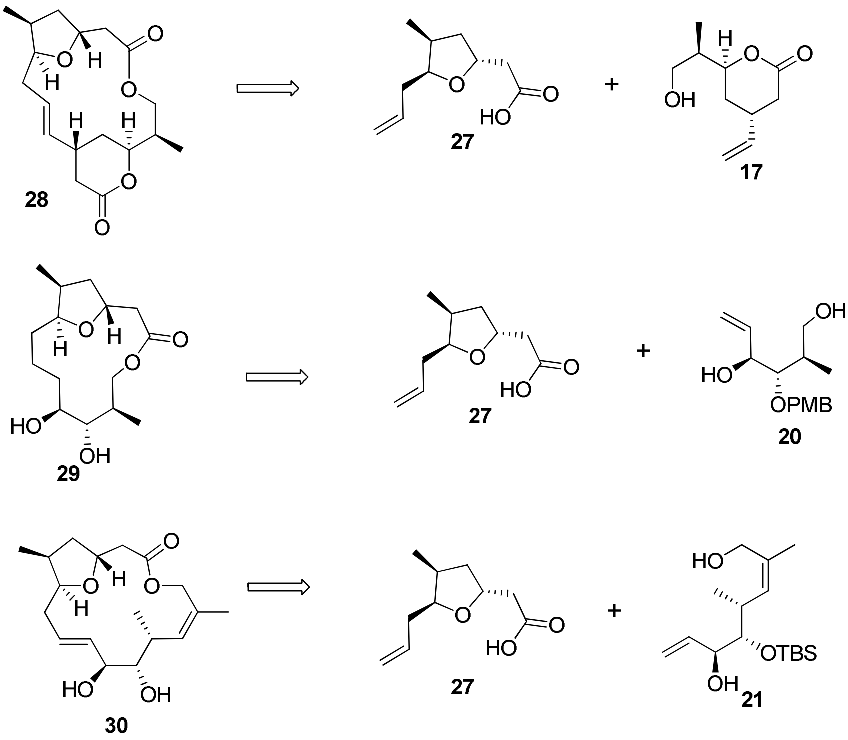
Amphdinolide T1-Rhizoxin hybrid (**28**)

Amphdinolide T1-Isomigrastatin hybrid (**29**)

Amphdinolide T1-Migrastatin hybrid (**30**)

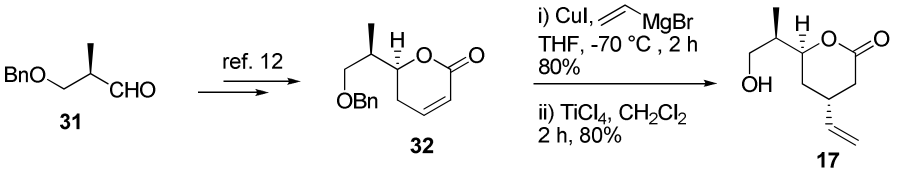
Scheme 4.1

4.3. Results & Discussions



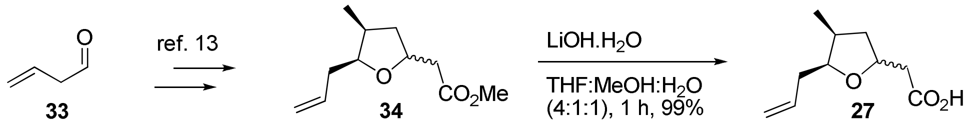
Scheme 4.2

To initiate the synthesis of hybrid molecules, as envisaged in the synthetic plan (Scheme 4.2), we prepared the required fragments as per the protocols developed in our laboratory. The fragments were then converted into designed hybrid macrolides by a standard procedure of esterification followed by the ring closing metathesis. Accordingly the δ-lactone **32** was synthesized from aldehyde **31** using the known protocol[12] in 4 steps. A stereoselective 1,4-addition of vinylmagnesium bromide followed by benzyl deprotection gave the desired alcohol **17** in good yields (Scheme 4.3).



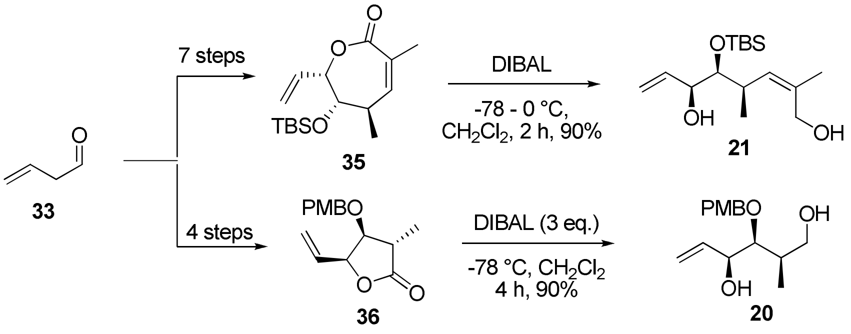
Scheme 4.3

The tetrahydrofuran moiety in amphidinolide T was prepared starting from 3-butenal **33** in 9 steps using literature protocol[13] which yielded the inseparable diastereomeric mixture (4:1) of acid **27** (Scheme 4.4).

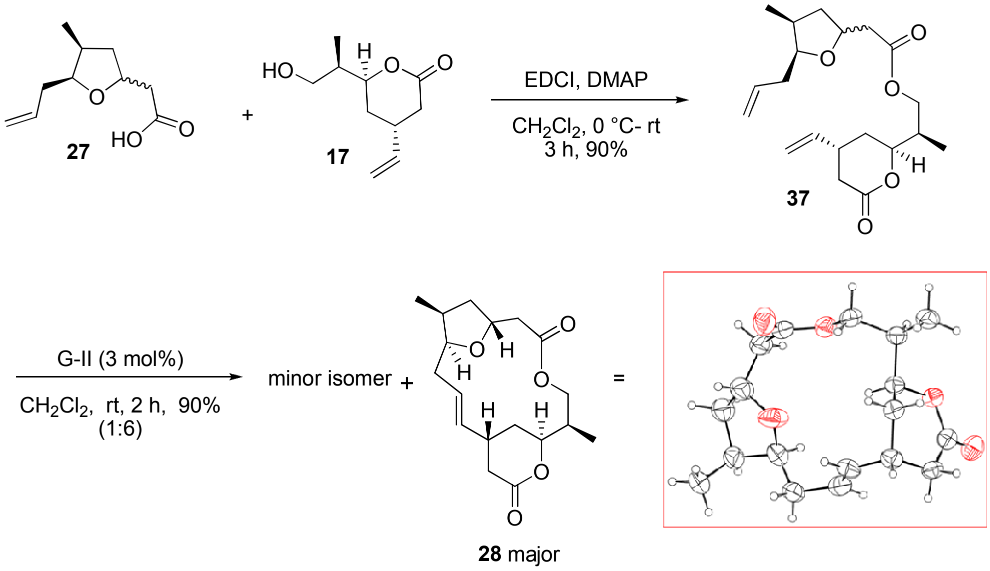


Scheme 4.4

The fragments **21** and **20** were prepared from 3–butenal **33** in 8 steps (for details see chaprter 2, page no. 24) and 5 steps (for details see chapter 3, page no. 73) respectively (Scheme 4.5).

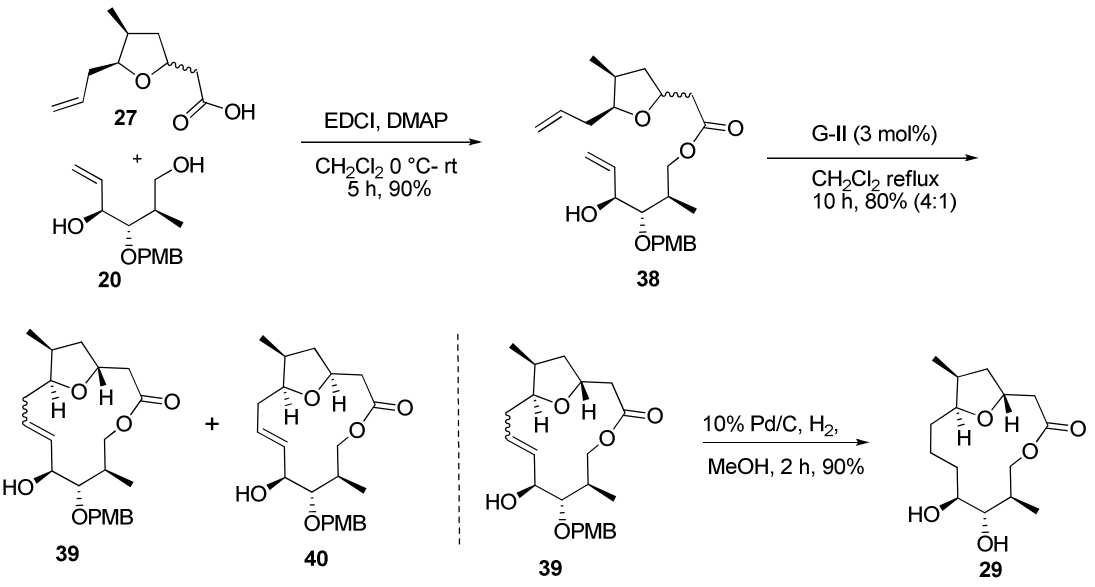


Scheme 4.5



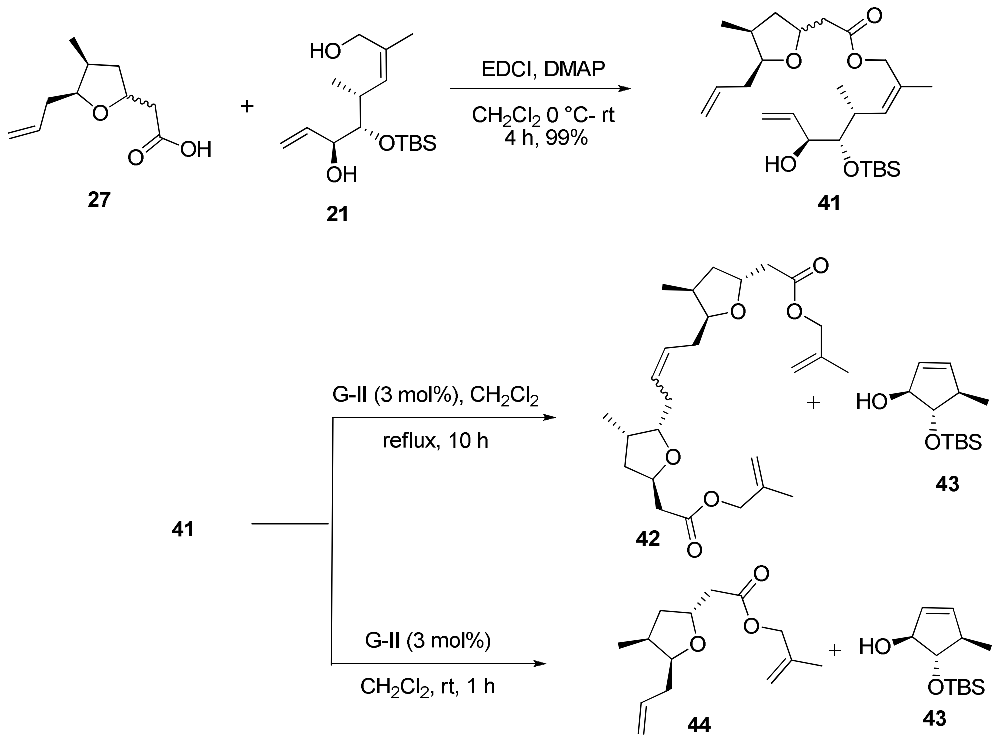
Scheme 4.6

After synthesizing the key fragments, the acid **27** was coupled with alcohol **17** using Steglich esterification (EDCI-DMAP) conditions to afford the corresponding ester **37** which was subjected to ring closing metathesis[14] leading to an inseparable mixture of diastereomers as colorless solid which after recrystallization yielded the major isomer **28** as colorless needles (Scheme 4.6). The structure of **28** was also confirmed by single crystal X-ray spectra. Similarly, the amphidinolide T1 and isomigrastatin hybrid synthesis was carried out by Steglich esterification followed by ring closing metathesis as the key steps, to afford a separable diastereomeric mixture (4:1) of hybrid **39** and **40**. The major diastereomer **39** was subjected to hydrogenation affording the desired hybrid **29** in very good yields (Scheme 4.7).



Scheme 4.7

However, our attempts to get migrastatin-amphidinolide T1 hybrid **30** (Scheme 4.8) by ring closing metathesis for longer duration (10 h) on **41** yielded a dimeric product **42** and cyclopentene derivative **43**. On the other hand, by subjecting **41** to ring closing metathesis reaction for a short duration (1 h) afforded the cyclopentene derivative **43** along with truncated product **44**. Thus, several attempts to access the desired hybrid molecule **30** by conducting ring closing metathesis following different reaction conditions resulted in a product mixture mainly comprised of **42**, **43** and **44** along with intractable polymeric material. It is, therefore, clear that the participation of the internal double bond with one of the terminal olefin dictates the course of the ring closing metathesis reaction on **41**. Studies are currently underway in our laboratory to access **30** by following different catalyst and conditions for ring closing metathesis reaction.



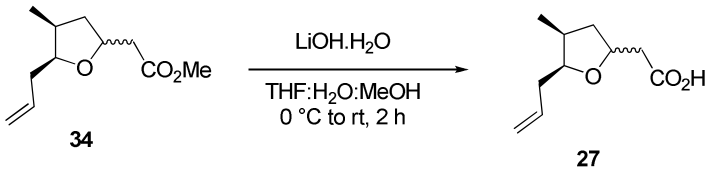
Scheme 4.8

4.4. Conclusions

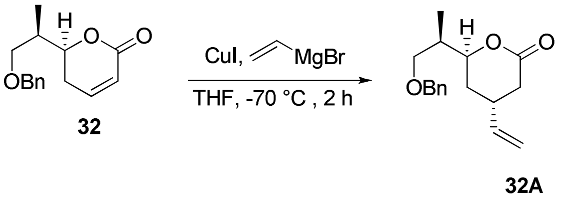
In conclusion, we have synthesized hybrid molecules **28** and **29** as probes to study the cancer cell mobility and mortality. These studies are inspired by natural products endowed with unique properties of cytotoxity (e.g., rhizoxin and amphidinolide) and cell migration inhibition (e.g., migrastatin family). The hybrid molecules have been synthesized by identifying certain pharmacophoric signatures in rhizoxin D, amphidinolide T and migrastatin family based on the assumption that structural features present in the hybrid molecules may represent the pharmacological behavior exhibited by the parent natural product thereby rendering unique dual properties of cytotoxicity and cell migration inhibition in the hybrid molecules **28** and **29**. Biological evaluation of these hybrid molecules is currently under progress in our laboratory.

4.5. Experimental section

4.5.1. Experimental procedure, spectral and analytical data

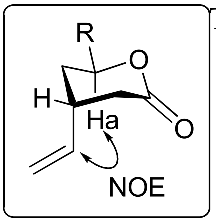


To a solution of methyl ester **34** (100.0 mg, 0.5 mmol) in THF/MeOH/H_2O (10 mL, 2:1:1) was added LiOH. H_2O (24.0 mg, 1.08 mmol) at 0 °C. The resultant mixture was stirred for 1 h at room temperature and then acidified with 1M HCl and extracted with EtOAc (3x4 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated under reduced pressure to give the acid **27** (92.0 mg, 99%). R_f = 0.2 (30% ethyl acetate in hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.91-5.75 (m, 1H), 5.18-5.08 (m, 2H), 4.55-4.46 (m, 1H), 4.27-4.19* (m, 0.28H), 4.02 (dd, *J* = 12.7, 6.3 Hz, 1H), 3.94* (dd, *J* = 13.6, 6.7 Hz, 0.28H), 2.74-2.57 (m, 1H), 2.51 (dd, *J* = 15.5, 5.6 Hz, 1H), 2.38-2.28 (m, 2H), 2.27-2.15 (m, 1H), 1.96-1.79 (m, 2H), 0.99 (t, *J* = 7.9 Hz, 3H); MS (ES) m/z 185.2 (M+1). Ratio of isomers is 4:1 (based on ^{1}H NMR). *corresponds to minor isomer.

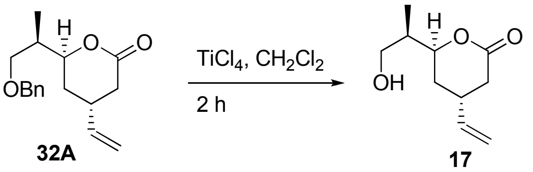


A stirred suspension of copper (I) iodide (10.0 mg, 0.05 mmol) in anhydrous THF (10 mL) was cooled to –78 °C under N_2 and treated with TMEDA (0.35 mL, 2.33 mmol). After 5 min, vinylmagnesium iodide (2.0 mL, 1 M in THF, 2.0 mmol) was added drop wise, and stirring was continued for 10 min. A solution of **30** (125.0 mg, 0.5 mmol) in anhydrous THF (5 mL) was added drop wise, and stirring was continued for 2 h. The reaction mixture was quenched with saturated NH_4Cl solution (10 mL), warmed to rt, and extracted with ether (3x15 mL). The combined extracts were washed with water and brine. The combined extracts were dried over Na_2SO_4, and the solvent was evaporated under reduced pressure to leave a residue that was purified by column chromatography on silica gel (elution with 40% of ethyl acetate in hexanes) to furnish **32A** as colorless oil (110.0 mg, 80%). R_f = 0.2 (30% ethyl acetate in hexane);

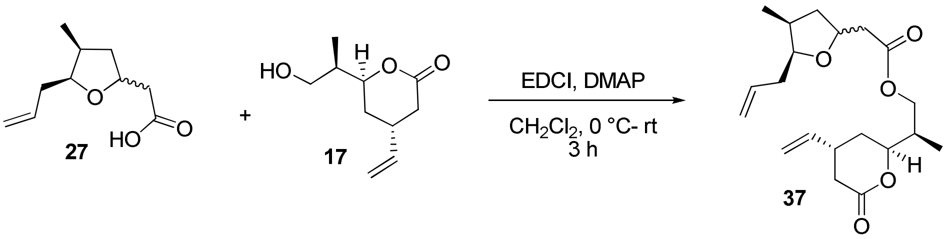
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40-7.26 (m, 5H), 5.88-5.78 (m, 1H), 5.12 (dd, *J* = 19.9, 13.8 Hz, 2H), 4.56-4.45 (m, 2H), 4.45-4.37 (m, 1H), 3.52 (d, *J* = 5.6 Hz, 2H), 2.81-2.71 (m, 1H), 2.62-2.47 (m, 2H), 2.17-2.08 (m, 1H), 1.95-1.85 (m, 1H), 1.76 (td, *J* = 14.1, 4.3 Hz, 1H), 1.00 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.9, 139.5, 138.3, 128.4, 127.6, 115.3, 78.1, 73.2, 71.2, 38.0, 34.1, 32.6, 29.8, 12.9; MS (ES) m/z 275.1(M+1).



The relative stereochemistry of **32A** was established based on NOESY studies; Key NOE between H_a (δ 4.49) and vinyl group (δ 5.83) confirmed the cis relationship of vinyl group and Ha

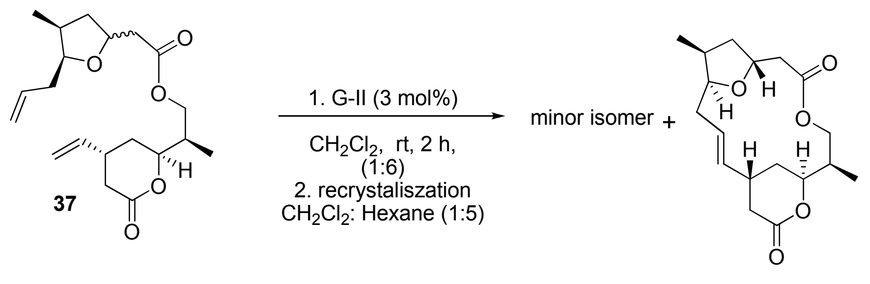


To a stirred solution of benzyl ether **32A** (28.0 mg, 0.1mmol) in dry dichloromethane (5 mL), $TiCl_4$ (0.05 mL) was added at room temperature. The reaction was allowed to stir for 2 h, and then quenched with saturated sodium bicarbonate solution (2 mL). Aqueous layer was extracted with dichloromethane (2x3 mL), combined organic layers were washed with brine and dried over Na_2SO_4. Solvent was removed under reduced pressure, the residue was purified by column chromatography using 40% ethyl acetate in hexane eluent gave **17** as colorless oil (15.0 mg, 80%). R_f = 0.2 (40% ethyl acetate in hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.90-5.72 (m, *J* = 20.7, 10.4, 6.2 Hz, 1H), 5.16-5.05 (m, 2H), 4.38-4.31 (m, 1H), 3.76-3.64 (m, 3H), 2.82-2.72 (m, 1H), 2.63-2.46 (m, 2H), 2.0.1.8 (m, 4H), 0.97 (d, *J* = 6.8 Hz, 3H) ; ^{13}C NMR (100 MHz, $CDCl_3$ δ 171.7, 139.4, 115.4, 79.2, 64.5, 40.1, 34.1, 32.6, 30.5, 12.9; MS (ES) m/z 185.1(M+1).

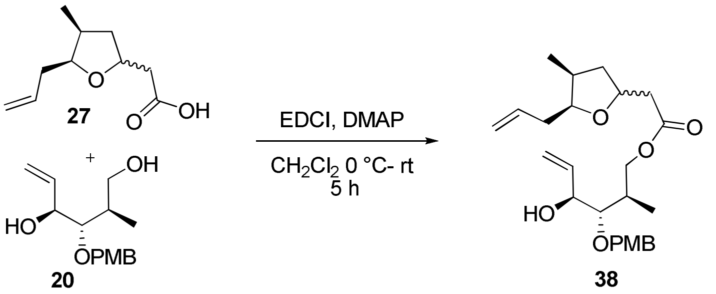


To a mixture of acid **27** (19.0 mg, 0.1 mmol), 4-(dimethylamino)pyridine (6.0 mg, 0.05 mmol) and N-(3-dimethylaminopropyl)-N′-ethylcarbodiimide hydrochloride

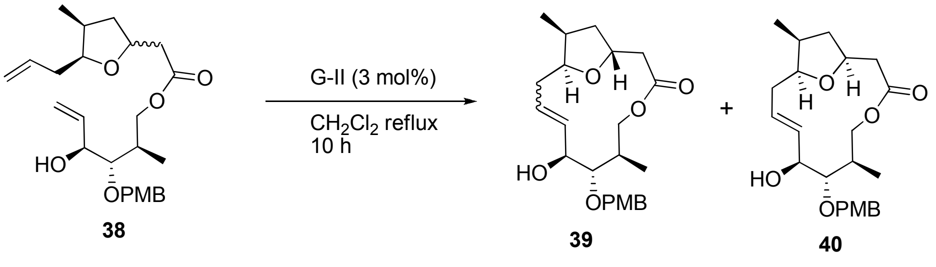
(28.0 mg, 0.15 mmol) at 0 °C a solution of alcohol **17** (19.0 mg, 0.1 mmol) in dichloromethane (1 mL) was added under N_2 via syringe. Reaction mixture was then stirred at room temperature for additional 3 h. A 50 % saturated solution of ammonium chloride (5 mL) was added to the yellow colored solution followed by dichloromethane (5 mL). The aqueous layer was extracted with dichloromethane (3×3 mL) and the organic layers were combined, dried over Na_2SO_4 and concentrated under reduced pressure. Purification by flash column chromatography (10% EtOAc in Hexane) gave the compound **37** as clear colorless oil (31.5 mg, 90%). R_f = 0.3 (20% ethyl acetate in hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 5.91-5.74 (m, 2H), 5.20-5.01 (m, 4H), 4.54-4.43 (m, 1H), 4.38-4.29 (m, 1H), 4.26-4.18 (m, 1H), 4.15-4.07 (m, 1H), 4.0- 3.96 (m, 1H), 2.85-2.10 (m, 12H), 1.96-1.74 (m, 4H), 1.69-1.48 (m, 3H), 1.05-0.94 (m, 7H); MS (ES) m/z 351.2(M+1).

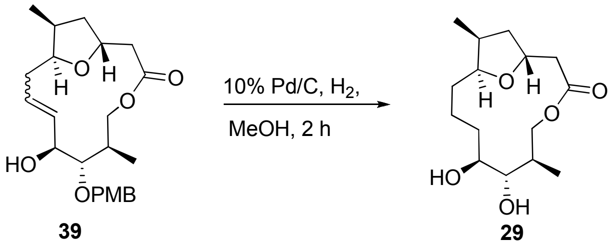


To a stirred solution of **37** (18.0 mg, 0.05 mmol) was dissolved in dichloromethane (25 mL). Grubbs 2nd generation catalyst (1.2 mg, 3 mol%) was added under N_2 and the reddish reaction mixture stirred 2 h at rt. The reaction mixture was then concentrated under reduced pressure. Purification by flash column chromatography (10% EtOAc in Hexane) gave the inseparable diastereomeric mixture of **28** as colorless solid (14.5 mg, 90%) (minor: major (1:6) based on LC-MS). Then the solid was subjected to recrystallization using 3 mL of dichloromethane: Hexane (1:5) turned major isomer as crystalline needles, and other isomer remained as white precipitate. Compound **28** Major: m.p: 100-103 °C; R_f = 0.25 (20% ethyl acetate in hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 5.56-5.49 (m, 1H), 5.42-5.32 (m, 1H), 4.83-4.77 (m, 1H), 4.41-4.30 (m, 1H), 4.07-3.96 (m, 2H), 3.93-3.87 (m, 1H), 2.92-2.85 (m, 1H), 2.75-2.59 (m, 2H), 2.47-2.40 (m, 2H), 2.37-2.29 (m, 2H), 2.11-2.02 (m, 2H), 1.84-1.74 (m, 2H), 1.70-1.60 (m, 3H), 0.96-91 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$ δ 172.0, 171.6, 134.2, 127.8, 79.3, 75.5, 73.2, 64.7, 42.1, 39.8, 36.1, 36.0, 33.4, 32.7, 30.9, 26.4, 14.5, 10.6; HRMS m/z found 345.1672, calcd for $C_{18}H_{26}NaO_5$ 345.1672.



Same procedure was used as mentioned above for preparation of **37** by taking **27** (25.0 mg, 0.14 mmol) and **20** (37.0 mg, 0.14 mmol) gave **38** as colorless liquid (55.0 mg, 90%, ratio of isomers is 4:1(based on ^{1}H NMR). R_f = 0.5 (25% ethyl acetate in hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32-7.25 (m, 2H), 6.93-87 (m, 2H), 5.95-5.75 (m, 2H), 5.39 (d, *J* = 17.2 Hz, 1H), 5.24 (d, *J* = 10.4 Hz, 1H), 5.16-5.01 (m, 2H), 4.59 (s, 2H), 4.55-4.52 (m, 1H), 4.26-4.15 (m, 1H), 4.15-4.04 (m, 2H), 3.98 (dd, *J* = 12.60, 6.44 Hz, 1H), 3.82 (s, 4H), 3.44 (dd, *J* = 5.79, 3.74 Hz, 1H), 2.74-2.58 (m, 1H), 2.55-2.42 (m, 1H), 2.38-2.25 (m, 2H), 2.24-2.10 (m, 4H), 1.93-1.78 (m, 2H), 1.02-0.94 (m, 6H); MS (ES) m/z 433.2(M+1).



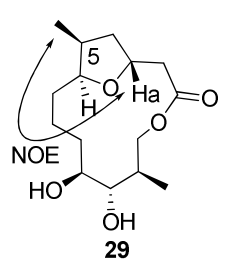


To a stirred solution of **38** (44.0 mg, 0.1 mmol) was dissolved in dichloromethane (50 mL). Grubbs 2nd generation catalyst (2.5 mg, 3 mol%) was added under N_2 and the reddish reaction mixture refluxed for 10 h. The reaction mixture was then concentrated under reduced pressure. Purification by flash column chromatography (15 % EtOAc in Hexane) gave colorless liquid **39** (26.0 mg) and **40** (6.5 mg).

To a solution of macrocycle **39** (21 mg, 0.05 mmol) in the methanol (3 mL), 10 % palladium on carbon (3.0 mg) was added and the suspension was stirred under an atmosphere of hydrogen (using a single balloon) for 2 h. The reaction mixture was then passed through a plug of celite and eluted with ethyl acetate (approx. 25 mL). The solvent was removed under reduced pressure. The residue was purified by column chromatography gave **29** as colorless solid (13.0 mg, 90%)

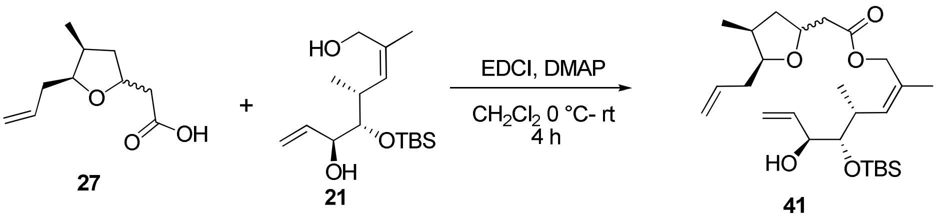
Compound **40**: R_f = 0.25 (20% ethyl acetate in hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29 (d, *J* = 8.6 Hz, 2H), 6.90 (d, *J* = 8.6 Hz, 2H), 5.65-5.56 (m, 1H), 5.38-5.28 (m, 1H), 4.78 (dd, *J* = 10.7, 2.9 Hz, 1H), 4.63(dd, *J* = 28.3, 10.7 Hz, 2H), 4.40-4.31 (m, 1H), 4.03 (m, 1H), 3.82 (s, 3H), 3.77 (t, *J* = 9.1 Hz, 1H), 3.55 (d, *J* = 9.5 Hz, 1H), 3.36 (t, *J* = 10.8 Hz, 1H), 2.60 (dd, *J* = 13.2, 3.1 Hz, 1H), 2.56-2.46 (m, 1H), 2.28-2.12 (m, 3H), 1.96-1.78 (m, 3H), 1.01 (d, *J* = 6.90 Hz, 3H), 0.94 (d, *J* = 7.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.9, 159.5, 132.7, 132.2, 130.1. 129.6, 114.0, 82.9, 78.9, 76.1, 75.1, 74.1, 67.9, 55.3, 43.1, 38.8, 37.1, 36.5, 35.6, 29.7, 13.4, 10.7; MS (ES) m/z 405.1(M+1).

Compound **29**: m.p.: 155-158 °C; R_f = 0.25 (50% ethyl acetate in hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.52-4-38 (m, 1H), 4.27 (dd, *J* = 11.2, 3.1 Hz, 1H), 4.05-3.97 (m, 1H), 3.95-3.83 (m, 2H), 3.65-3.57 (m, 1H), 2.69 (dd, *J* = 12.8, 4.8 Hz, 1H), 2.34 (dd, *J* = 12.8, 5.8 Hz, 1H), 2.30-2.18 (m, 4H), 2.09-2.00 (m, 1H), 1.82-1.36 (m, 9H), 0.99 (d, *J* = 7.0 Hz, 3H), 0.89 (d, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.8, 80.4, 73.8, 72.7, 70.2, 66.6, 40.3, 38.9, 37.2, 35.1, 31.0, 29.9, 20.0, 14.1, 12.0; HRMS m/z found 309.1672, calcd for $C_{15}H_{26}NaO_5$ 309.1672.

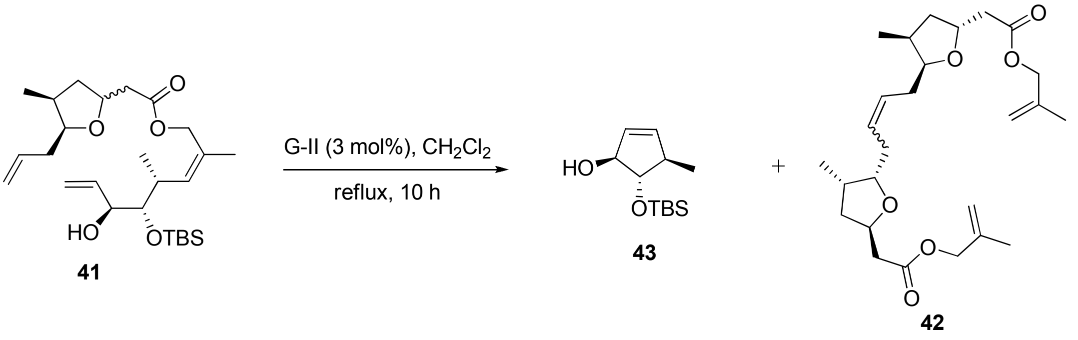


29

The relative stereochemistry of **29** was established based on NOESY studies; Key NOE between H_a (δ 4.45) and C5 methyl group (δ 0.89) confirmed the cis relationship of methyl group and Ha



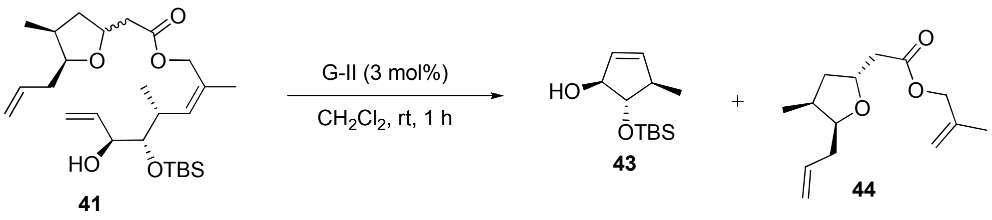
Same procedure was used as mentioned above for preparation of **37** by taking **27** (9.5 mg, 0.1 mmol) and **21** (15.0 mg, 0.1 mmol) gave **41** as clear colorless oil (23.0 mg, 99%, ratio of isomers is 4:1 (based on ^{1}H NMR). R_f = 0.4 (25% ethyl acetate in hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.91-5.74 (m, 3H), 5.34-5.25 (m, 3H), 5.20-5.01 (m, 4H), 4.68-4.43 (m, 4H), 4.08-4.02 (m,1H), 3.98-3.92 (m, 1H), 3.84* (d, J = 7.76 Hz, 0.25H), 3.39 (dd, J = 6.3, 3.4 Hz, 1H), 2.79-2.68 (m, 2H), 2.68-2.60 (m, 1H), 2.52-2.40 (m, 1H), 2.34-2.22 (m, 3H), 2.22-2.10 (m, 2H), 1.90-1.78 (m, 2H), 1.74 (s, 4H), 0.95 (dd, J = 10.8, 6.9 Hz, 8H), 0.93-0.89 (m, 12H), 0.06 (d, J = 8.6 Hz, 8H); MS (ES) m/z 467.1(M+1).



To a stirred solution of **41** (10.0 mg, 0.02 mmol) was dissolved in dichloromethane (25 mL). Grubbs 2nd generation catalyst (0.5 mg, 3 mol%) was added under N_2 and the reddish reaction mixture refluxed for 10 h. The reaction mixture was then concentrated under reduced pressure. Purification by flash column chromatography (8-20 % EtOAc in Hexane). Yields were not calculated

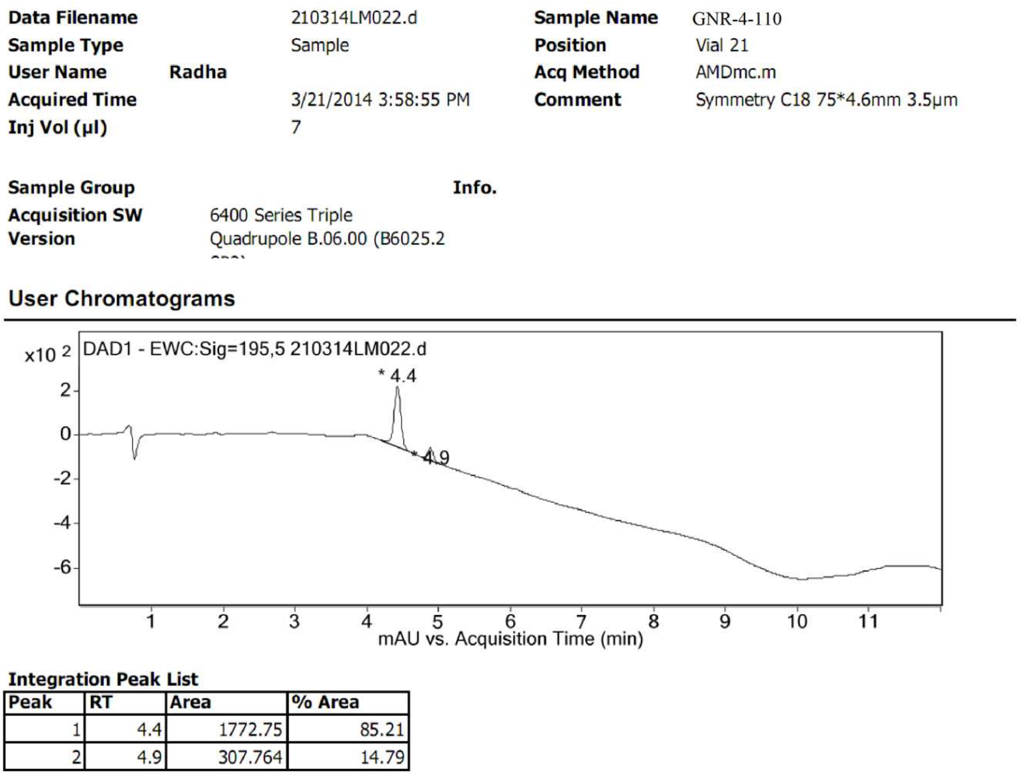
Compound **43**: R_f = 0.35 (10% ethyl acetate in hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.76-5.58 (m, 2H), 4.59-4.55 (m, 1H), 3.67 (t, J = 4.8 Hz, 1H), 2.55-2.46 (m, 1H), 1.10 (d, J = 7.1 Hz, 3H), 0.92 (s, 9H), 0.12 (d, J = 8.0 Hz, 6H); MS (ES) m/z 229.1(M+1).

Compound **42**: 5.54-5.42 (m, 2H), 4.95 (d, J = 23.6 Hz, 4H), 4.58-4.43 (m, 6H), 3.91 (d, J = 5.2 Hz, 2H), 2.66 (dd, J = 15.0, 6.8 Hz, 2H), 2.46 (dd, J = 15.0, 6.6 Hz, 2H), 2.35-2.06 (m, 8H), 1.91-1.77 (m, 4H), 1.75 (s, 6H), 0.94 (d, J = 7.2 Hz, 6H); MS (ES) m/z 446.1(M+1).



To a stirred solution of **41** (10.0 mg, 0.02 mmol) was dissolved in dichloromethane (25 mL). Grubbs 2nd generation catalyst (0.5 mg, 3 mol%) was added under N_2 and the reddish reaction mixture stirred for 1 h at room temperature. The reaction mixture was then concentrated under reduced pressure. Purification by flash column chromatography (5-8% EtOAc in Hexane). Yields were not calculated. Compound **44**: R_f = 0.5 (10% ethyl acetate in hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.88-5.72 (m, 1H), 5.14-4.90 (m, 4H), 4.57-4.45 (m, 3H), 4.01-3.92 (m, 1H), 3.89-3.83 (m, 1H), 2.72-2.62 (m, 1H), 2.79-2.72 (m, 1H), 2.52-2.46 (m, 1H), 2.34-2.12 (m, 4H), 1.88-1.80 (m, 2H), 1.76 (s, 3H), 0.95 (d, *J* = 7.2 Hz, 3H); MS (ES) m/z 239.1(M+1).

4.5.1.1. LC-MS report of 28 mixture



Data Filename	210314LM022.d	**Sample Name**	GNR-4-110
Sample Type	Sample	**Position**	Vial 21
User Name Radha		**Acq Method**	AMDmc.m
Acquired Time	3/21/2014 3:58:55 PM	**Comment**	Symmetry C18 75*4.6mm 3.5µm
Inj Vol (µl)	7		

Sample Group **Info.**
Acquisition SW 6400 Series Triple
Version Quadrupole B.06.00 (B6025.2

User Chromatograms

Integration Peak List

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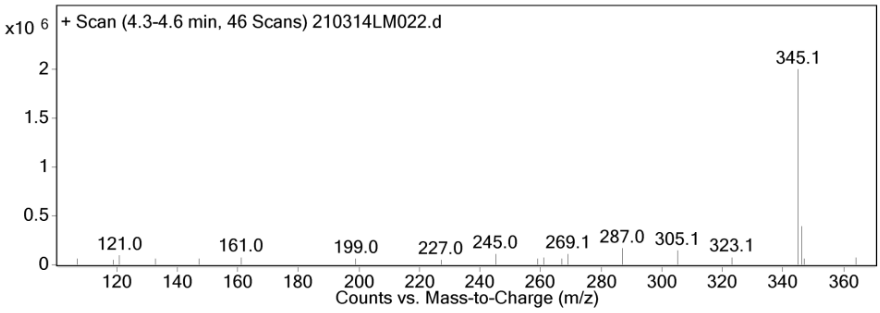

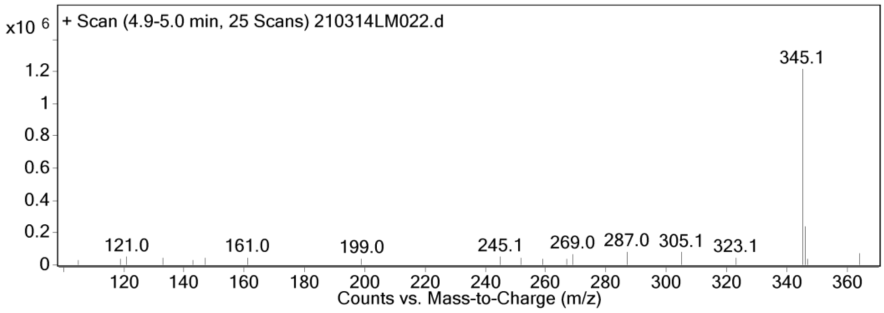

4.5.2. X-ray Crystallographic data

X-ray reflections on the compound **28 major** were collected on an Xcalibur Gemini EOS CCD diffractometer (Oxford Diffraction, Yarnton, UK) using Cu-Kα, radiation at 298K. Data reduction was performed using CrysAlisPro (version 1.171.33.55). OLEX2-1.0 and SHELX-TL 97[15] were used to solve and refine the reflections data. Non hydrogen atoms were refined anisotropically. All C–H atoms were fixed geometrically using HFIX command in SHELX-TL.[15] A check of the final CIF file using PLATON did not show any missed symmetry.

Table 5.1. Crystal data for **28 major**

Identification code	**28**
Formula	$C_{18}H_{26}O_5$
F_w	322.39
T (K)	298
λ (Å)	1.54184
Crystal system	Monoclinic
Space group	*C121*
a (Å)	16.0890 (14)
b (Å)	5.4322 (4)

c (Å)	20.0116 (17)
α (^{o})	90
β (^{o})	91.202 (8)
γ (^{o})	90
V (Å^{3})	1748.6 (3)
Z	4
ρ_{calcd} (Mg m^{-3})	1.225
μ (mm^{-1})	0.72
F (000)	696
Crystal Size (mm)	0.46 × 0.34 × 0.26
Reflections collected	3024
Unique reflections	2076
Completeness to 2θ (%)	69.99 (99.0)
T_{max}, T_{min}	0.8345, 0.7325
Parameters	211
GOF (F^2)	1.040
$R1$, $wR2$ [$I>2\sigma(I)$]	0.0469, 0.1219
$R1$, $wR2$ (all data)	0.0543, 0.1320
Largest diff. Peak and hole (e·Å^{-3})	0.274 and -0.169

4.6. References

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2. Microtubules (Eds.: Hyams, J. S.; Lloyd, C. W.) Willey- Liss, New York, **1994**. *K17*, 371.
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C. Dorn, K.-D. Wu, W. P. Tong, X.-Y. Huang, M. A. S. Moore, S. J. Danishefsky, *J. Am. Chem. Soc.* **2004,** *126*, 11326–11337*;* c) D. Shan, L. Chen, J. T. Njardarson, C. Gaul, X. Ma, S. J. Danishefsky, X.-Y. Huang, *Proc. Natl. Acad. Sci. USA* **2005,** *102*, 3772–3776*;* d) T. Oskarsson, P. Nagorny, I. J. Krauss, L. Perez, M. Mandal, G. Yang, O. Ouerfelli, D. Xiao, M. A. S. Moore, J. Massagué, S. J. Danishefsky*, J. Am. Chem. Soc.* **2010,** *132*, 3224–3228.

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10. a) Kobayashi, J.; Kubota, T. *J. Nat. Prod.* **2007,** *70*, 451-460. b) Kobayashi, J.; Endo, T.; Tsuda, M. *J. Org. Chem.* **2000,** *65*, 1349 Kobayashi, J.; Kubota, T.; Endo, T.; Tsuda, M. *J. Org. Chem.* **2001,** *66*, 134. c) Kobayashi, J.; Kubota, T.; Endo, T.; Tsuda, M.; Shiro, M. *Tetrahedron* **2001,** *57*, 6175
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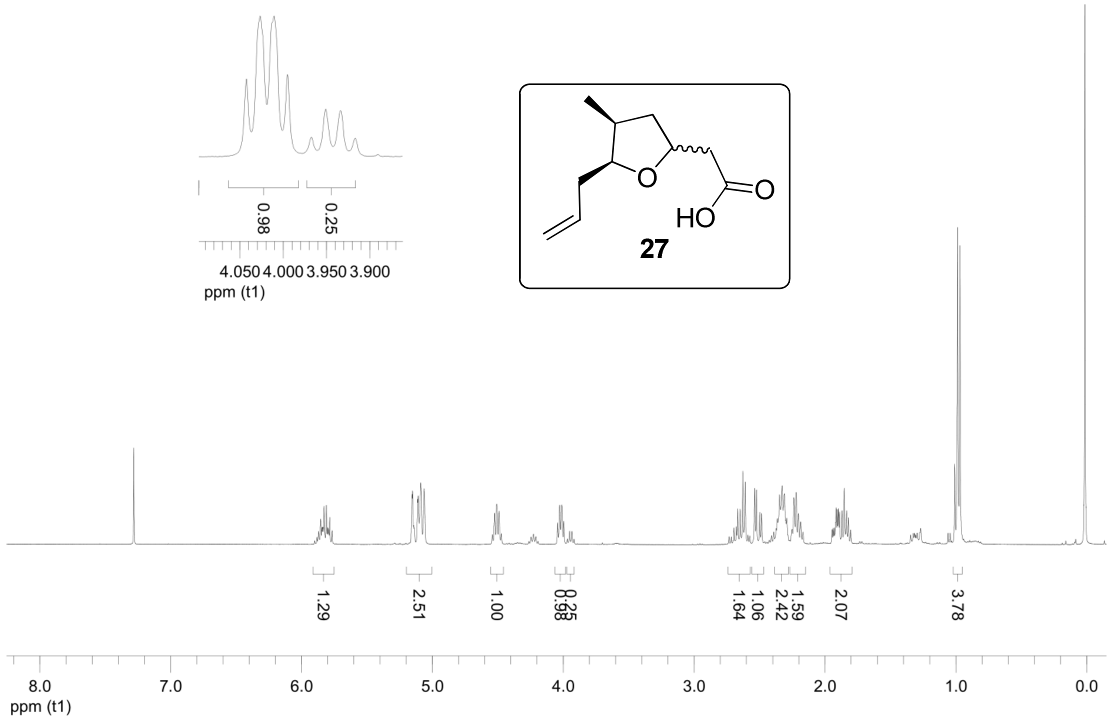
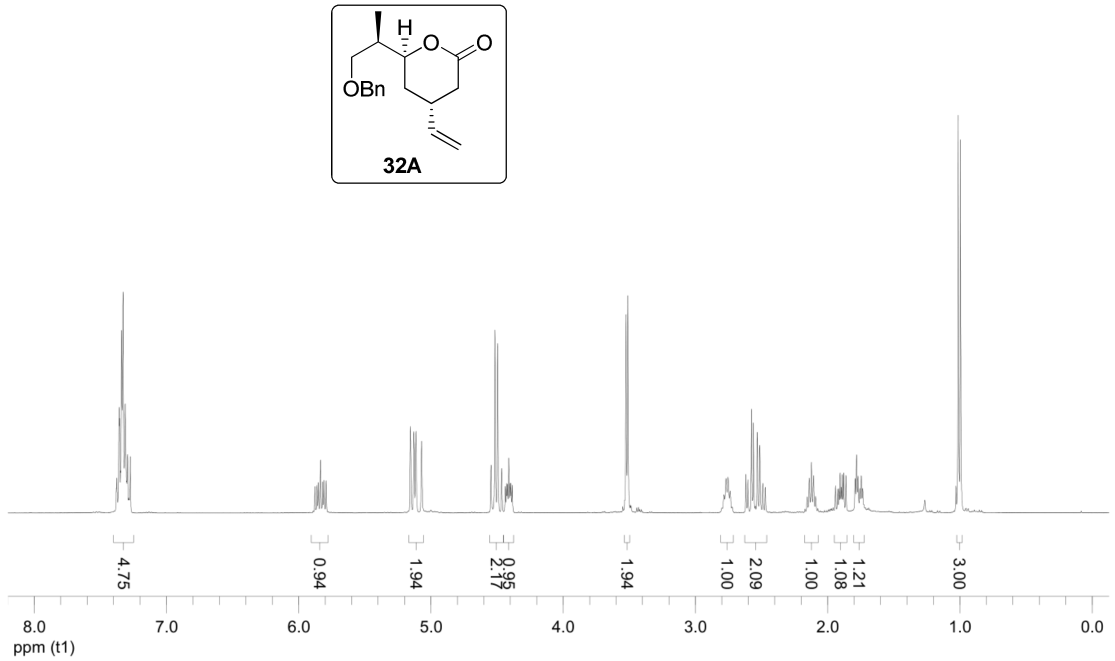
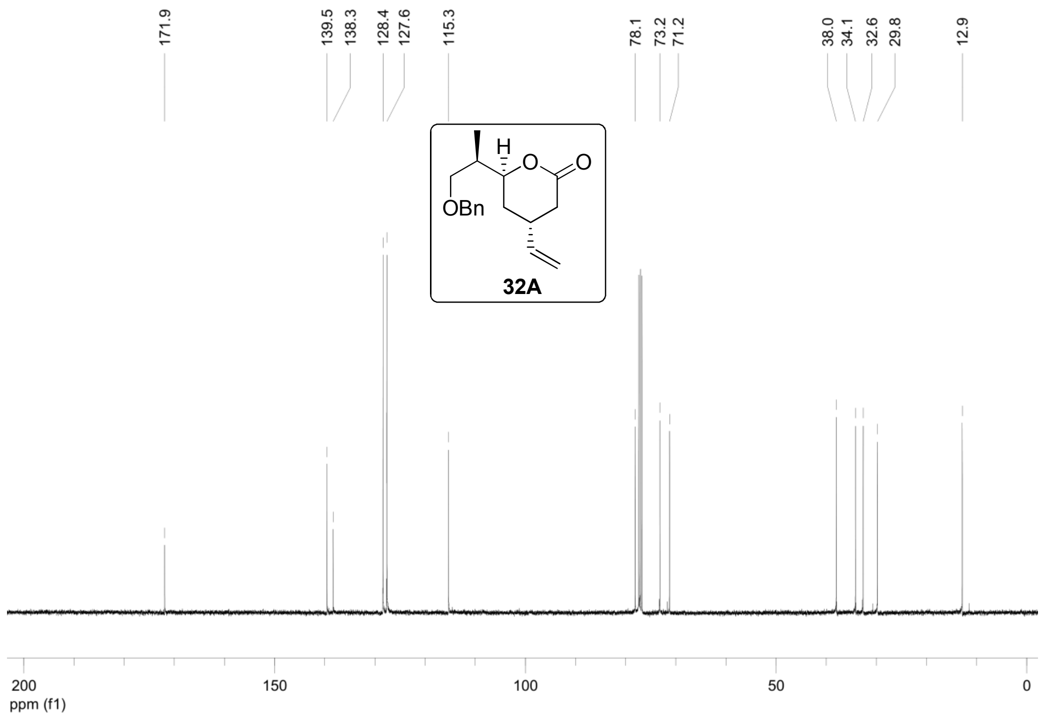
4.7. NMR spectra



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73.2
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12.9
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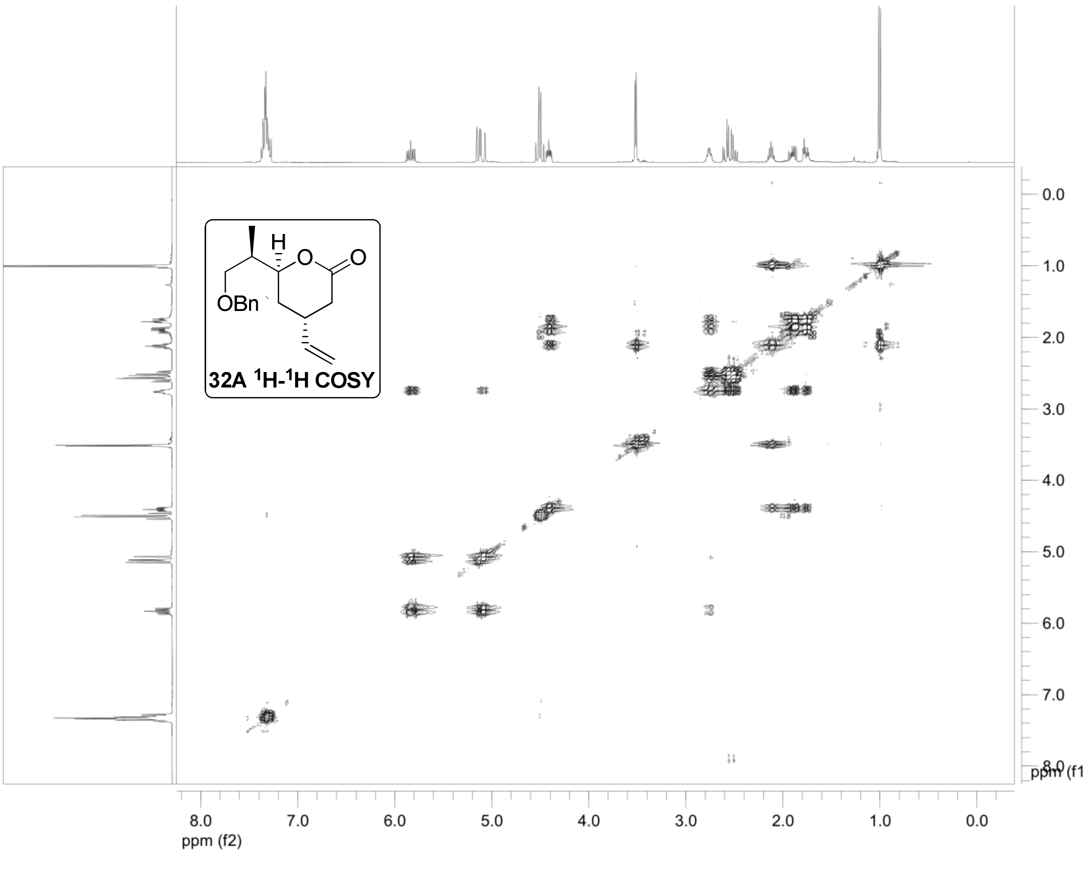
OBn
32A
200
150
100
50
0
ppm (f1)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O
OBn
32A ¹H-¹H COSY
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7.0
8.0
ppm (f1)
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7.0
6.0
5.0
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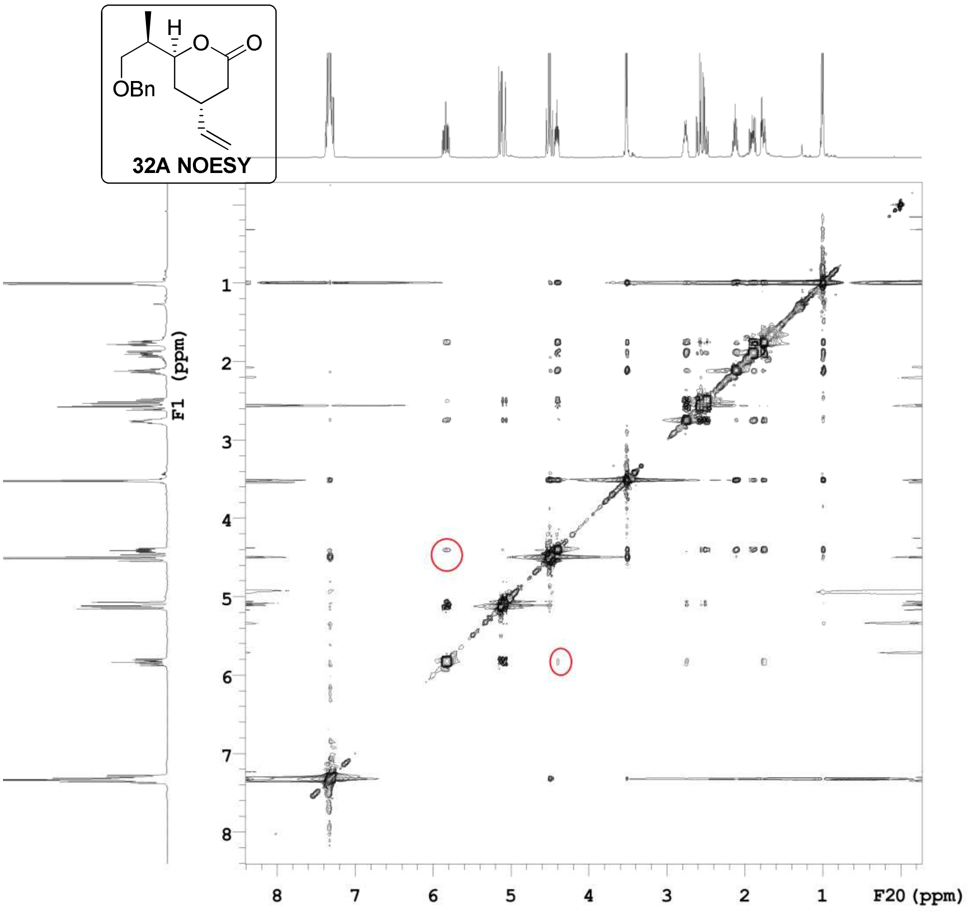
2.0
1.0
0.0
ppm (f2)



32A NOESY

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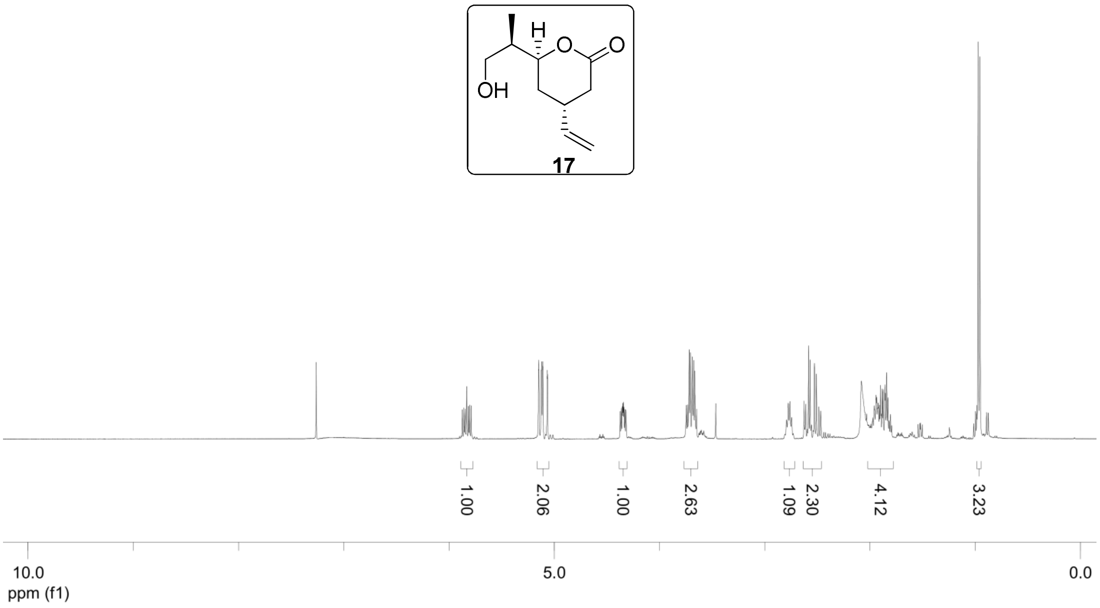
O
O
OBn
F1 (ppm)
1
2
3
4
5
6
7
8
F20 (ppm)



17

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O
OH
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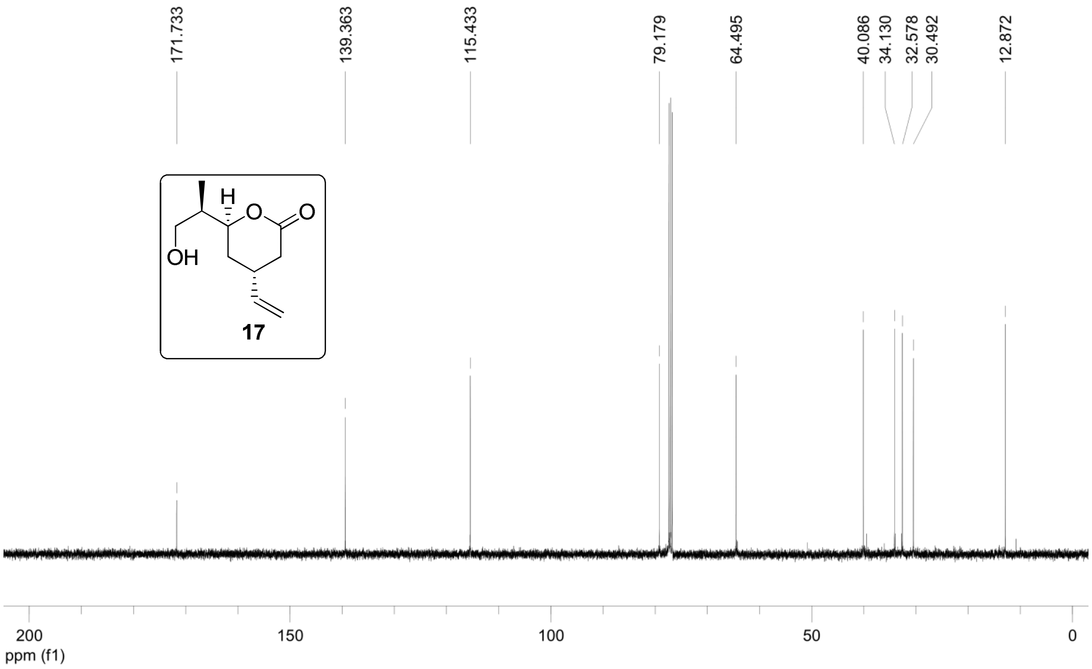
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17
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50
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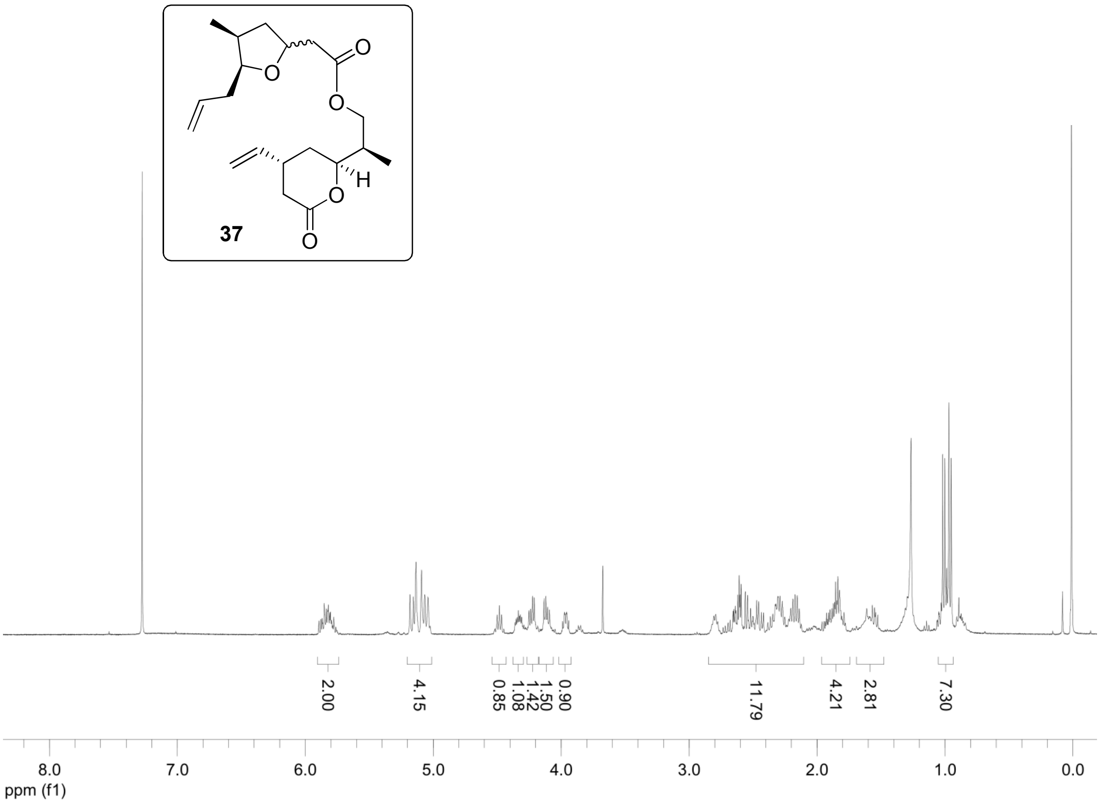
ppm (f1)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H
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0.90
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4.21
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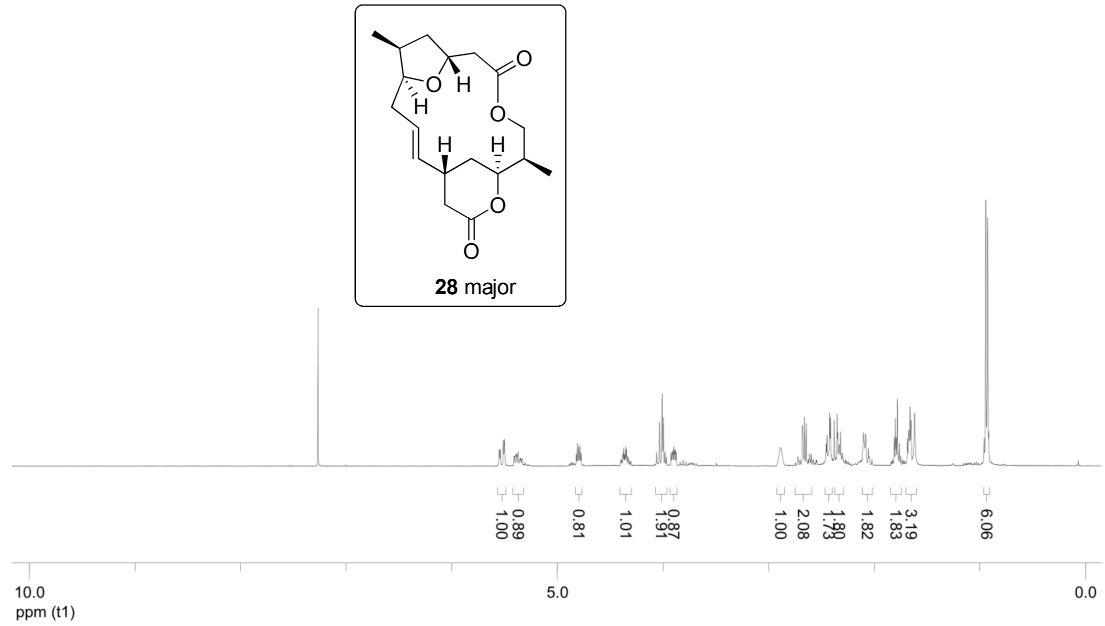
ppm (f1)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H
O
H
H
O
O
O
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1.01
1.91
0.87
1.00
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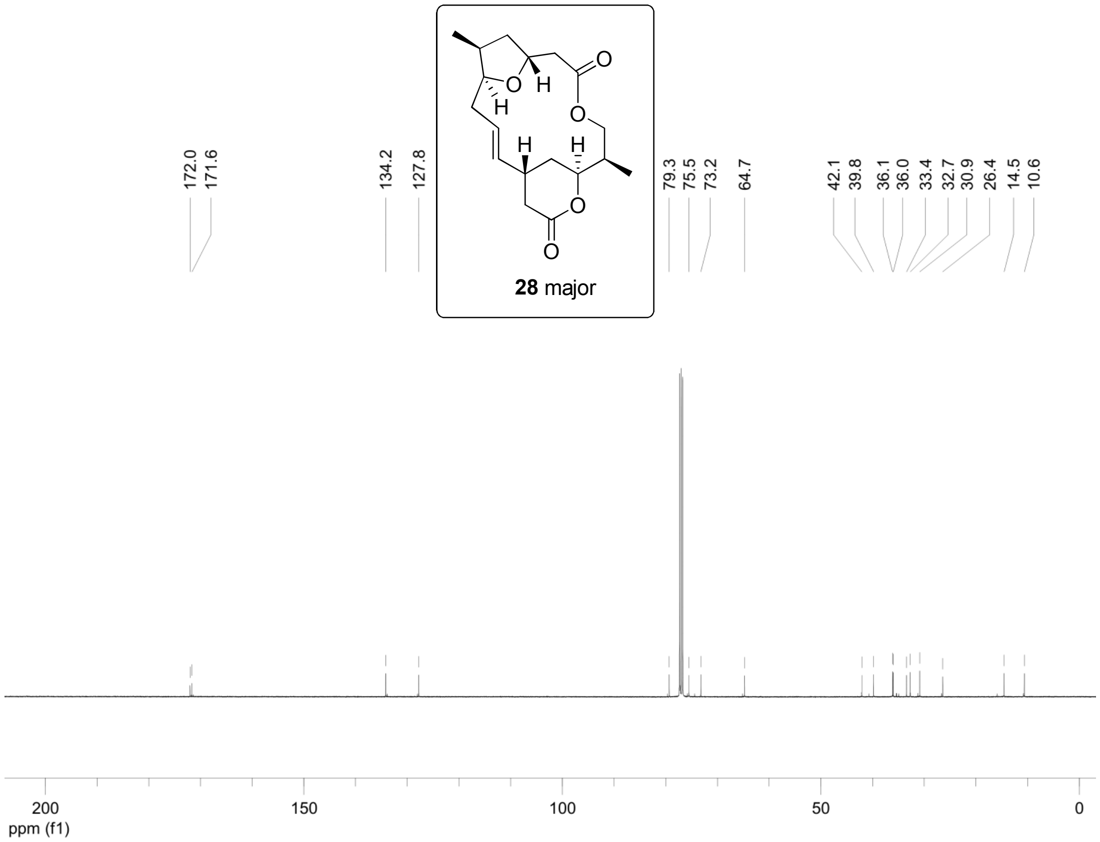
0.0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H
O
H
H
O
O
O
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171.6
134.2
127.8
79.3
75.5
73.2
64.7
42.1
39.8
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32.7
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10.6
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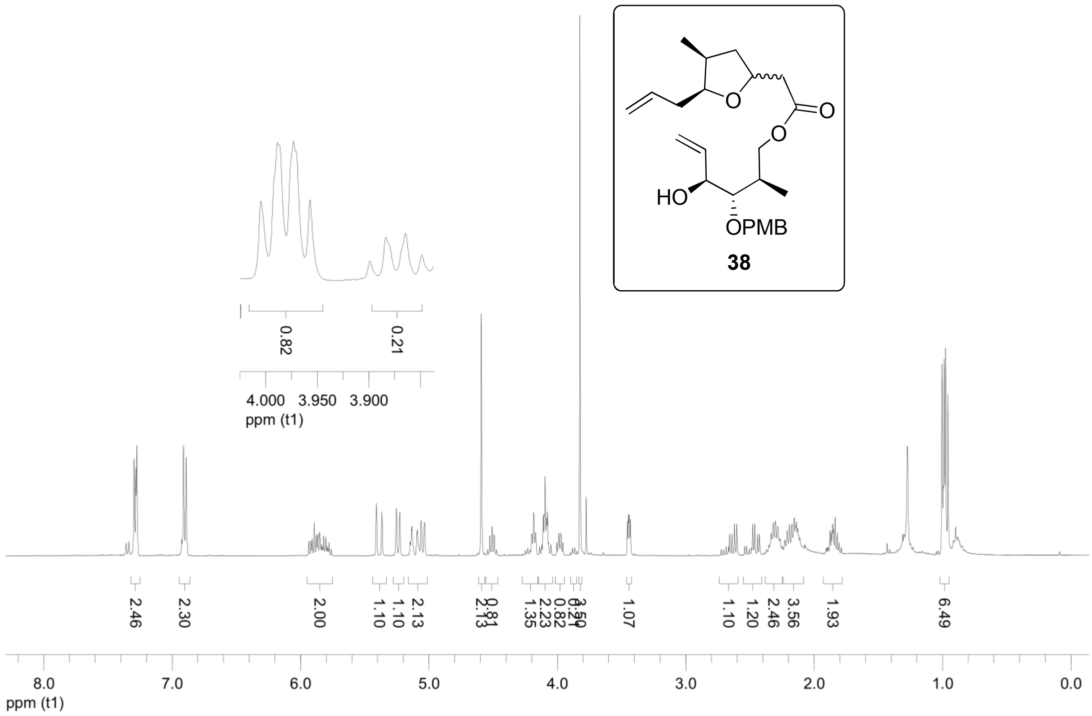
50
0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2.00
1.10
1.10
2.13
2.13
0.81
1.35
2.23
0.82
1.07
1.10
1.20
2.46
3.56
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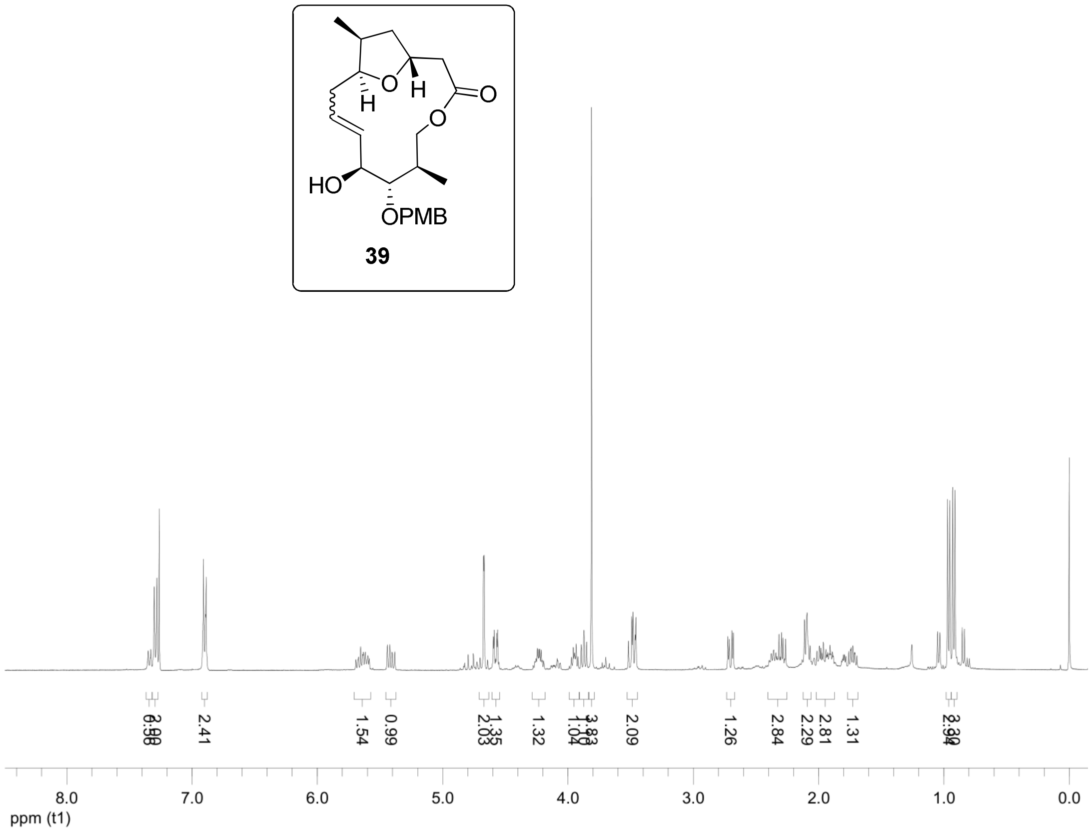
ppm (t1)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H
O
O
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1.35
1.32
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2.09
1.26
2.84
2.29
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2.0
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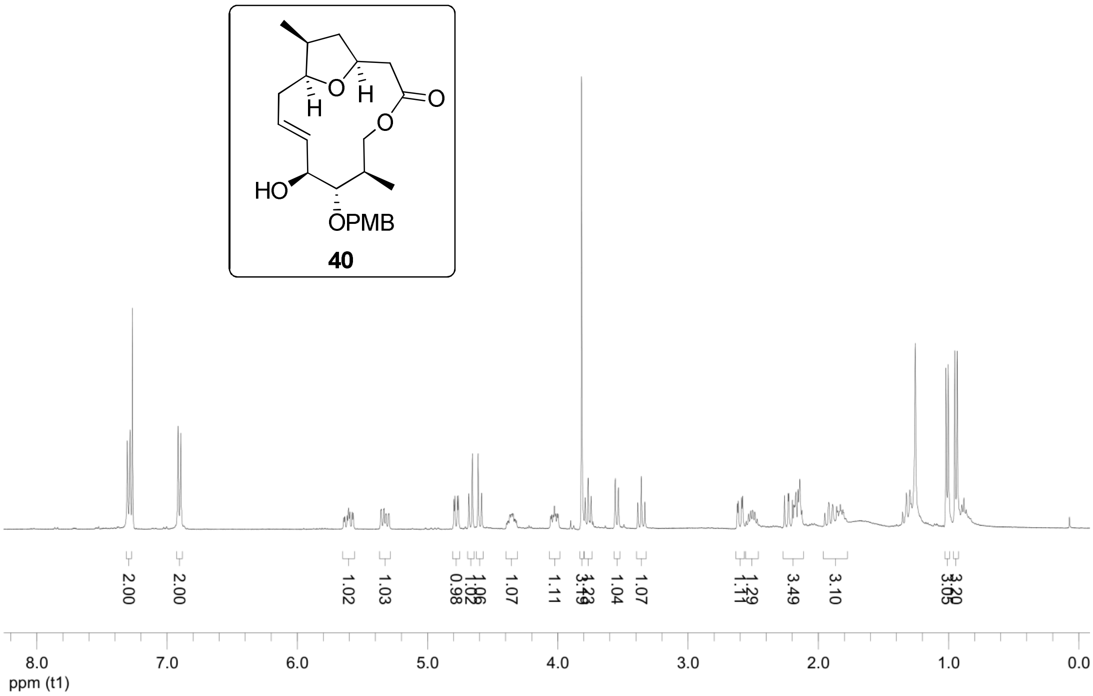
ppm (t1)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H
O
O
O
OPMB
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1.03
0.98
1.02
1.06
1.07
1.11
3.49
1.23
1.04
1.07
1.11
1.29
3.49
3.10
3.05
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7.0
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3.0
2.0
1.0
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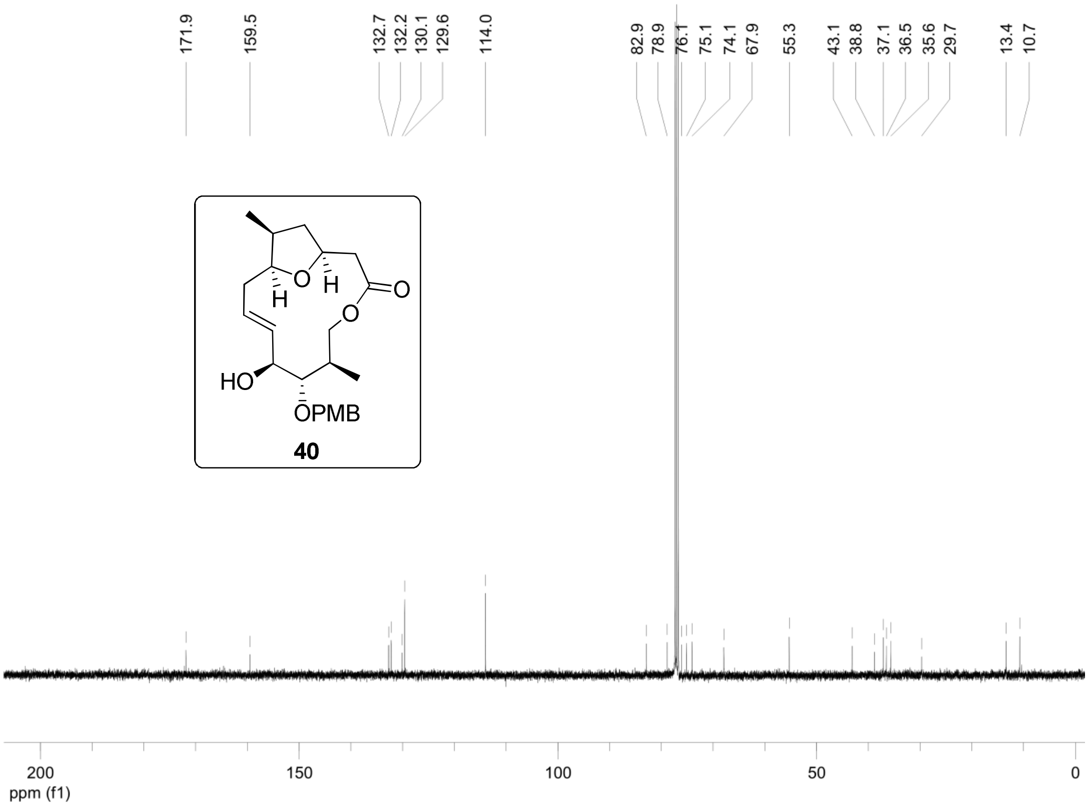
ppm (t1)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67.9
55.3
43.1
38.8
37.1
36.5
35.6
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H
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O
O
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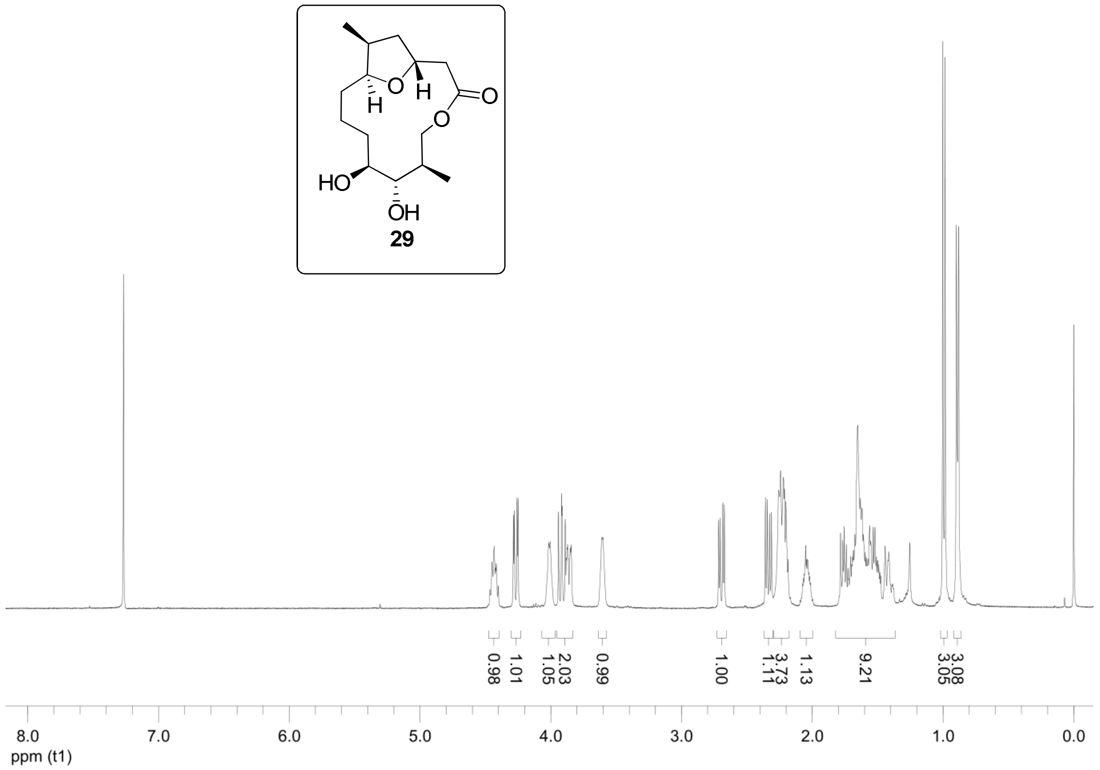
200
150
100
50
0
ppm (f1)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H
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O
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1.05
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0.99
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3.73
1.13
9.21
3.05
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6.0
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3.0
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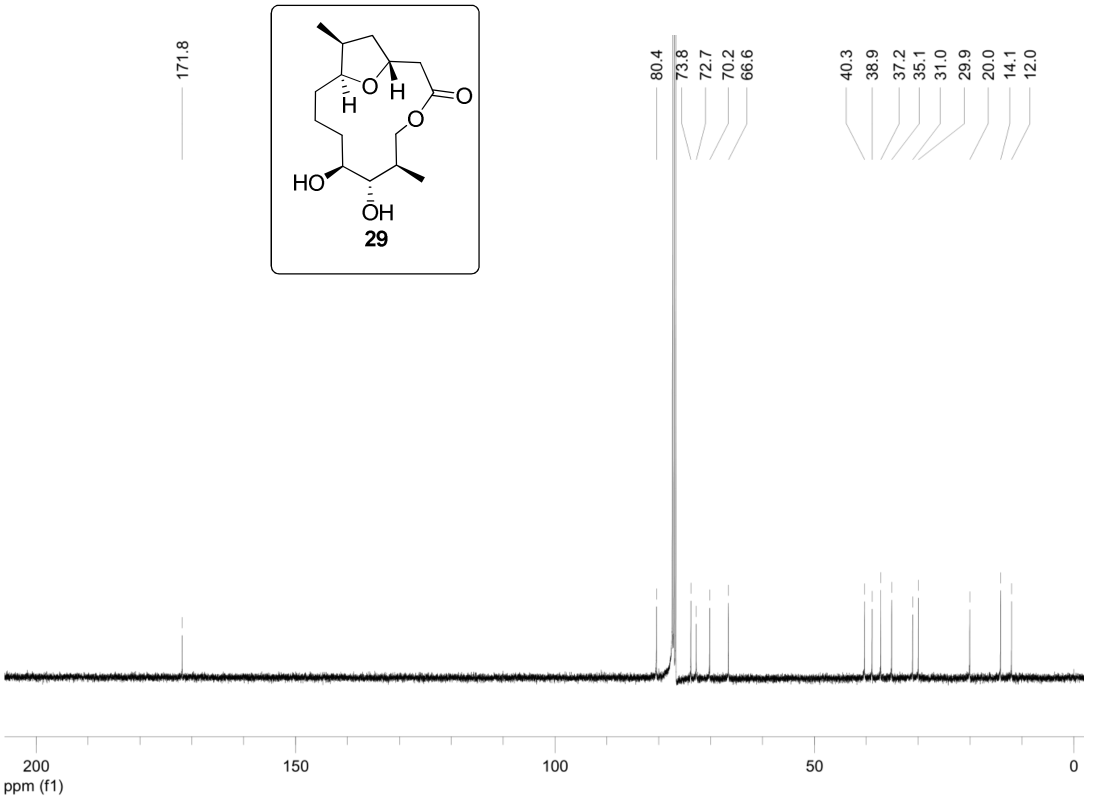
0.0
ppm (t1)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H
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O
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72.7
70.2
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37.2
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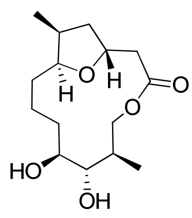
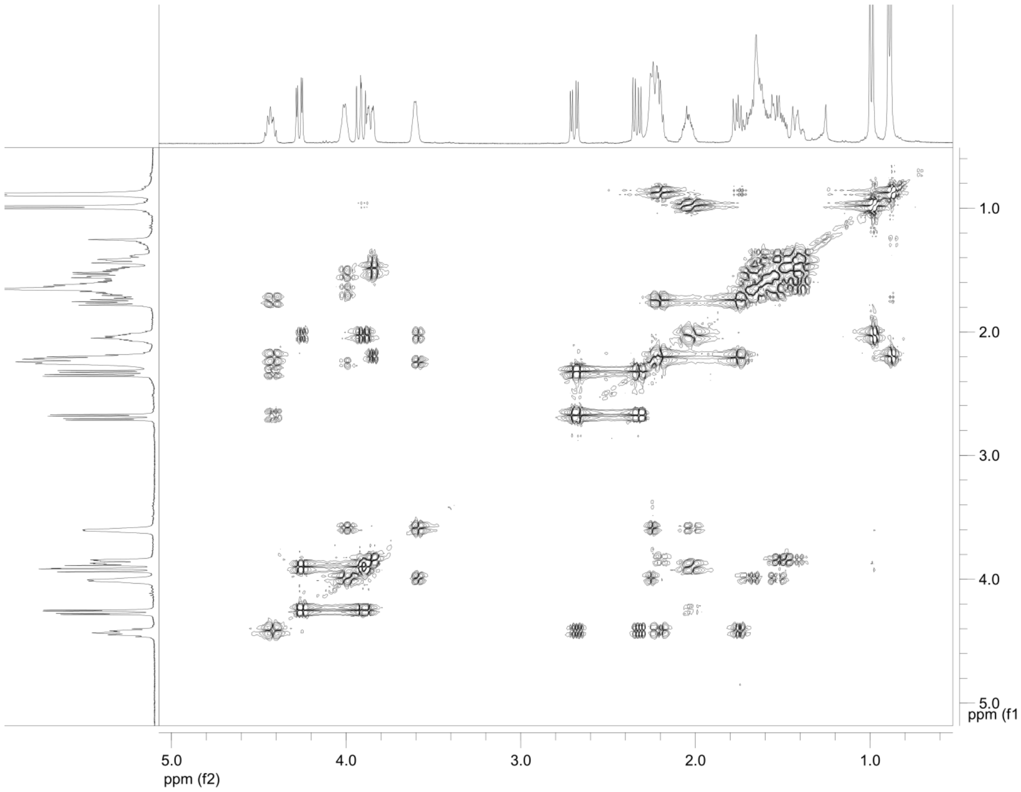
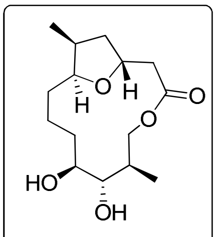
31.0
29.9
20.0
14.1
12.0
200
150
100
50
0
ppm (f1)

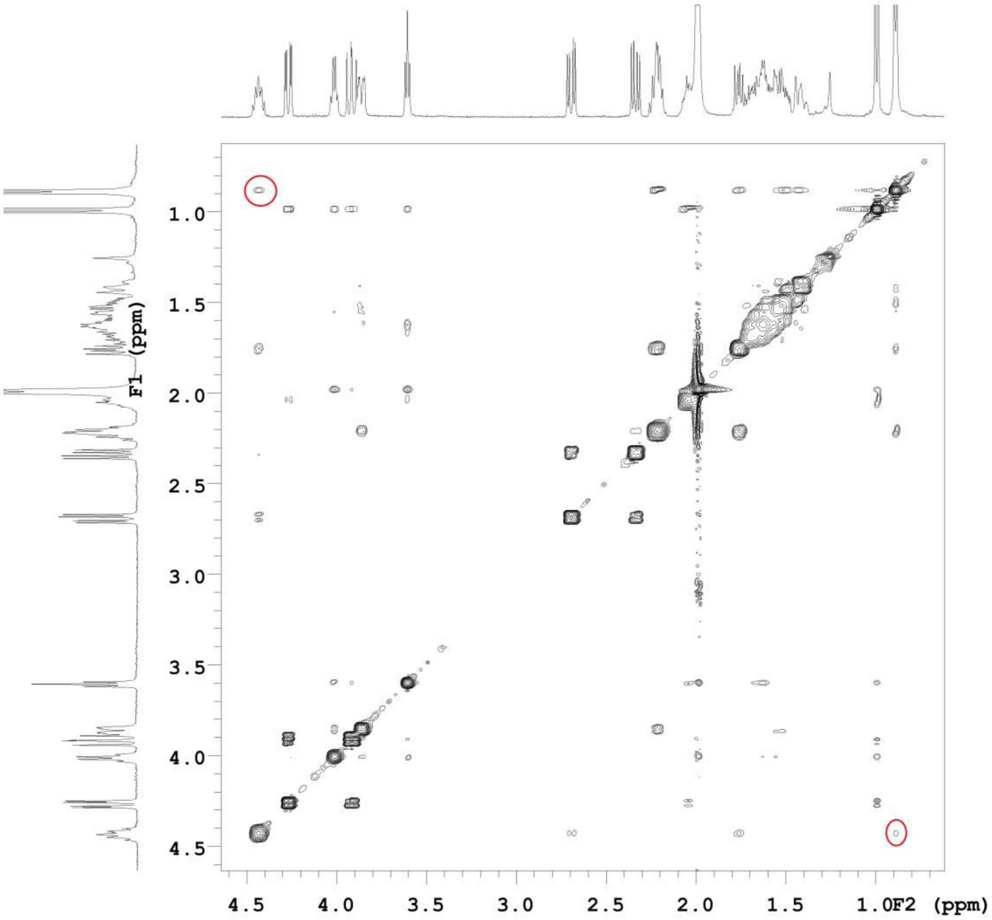


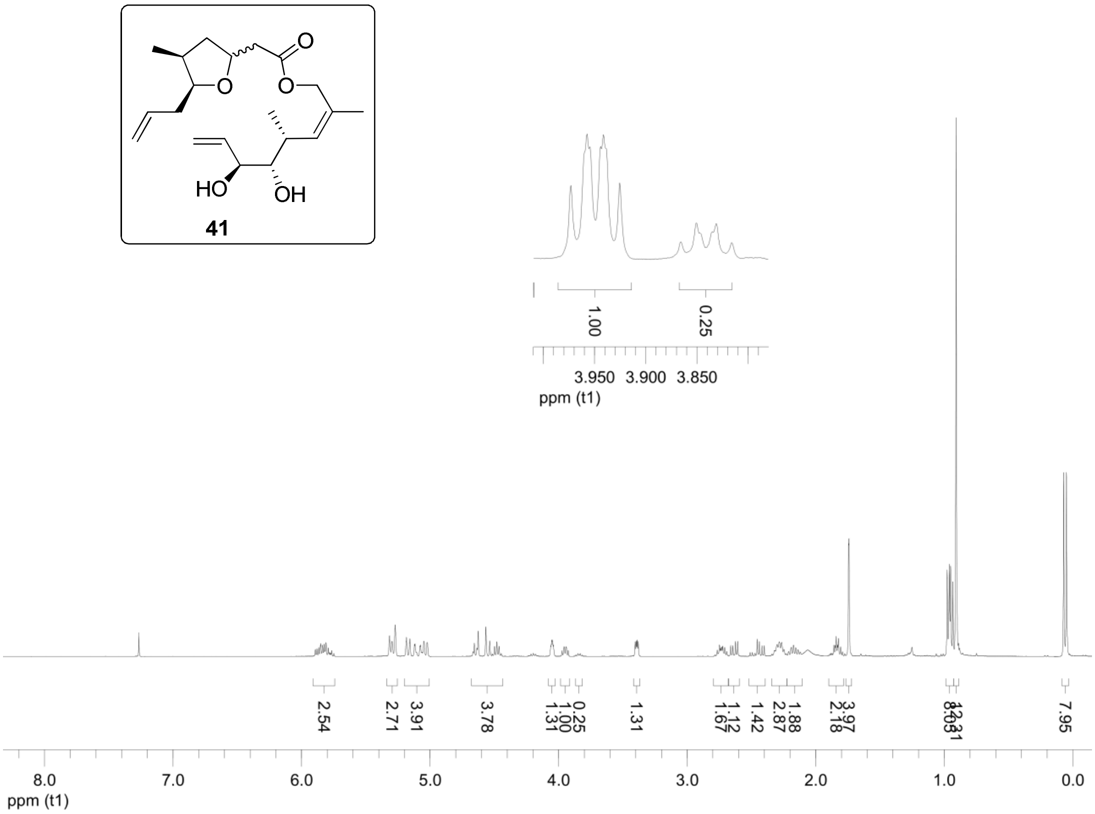
29 ^{1}H-^{1}H DQCOSY





29 NOESY





41

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3.950 3.900 3.850
ppm (t1)
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2.71
3.91
3.78
1.31
1.00
0.25
1.31
1.67
1.12
1.42
2.87
1.88
2.18
3.97
8.03
12.31
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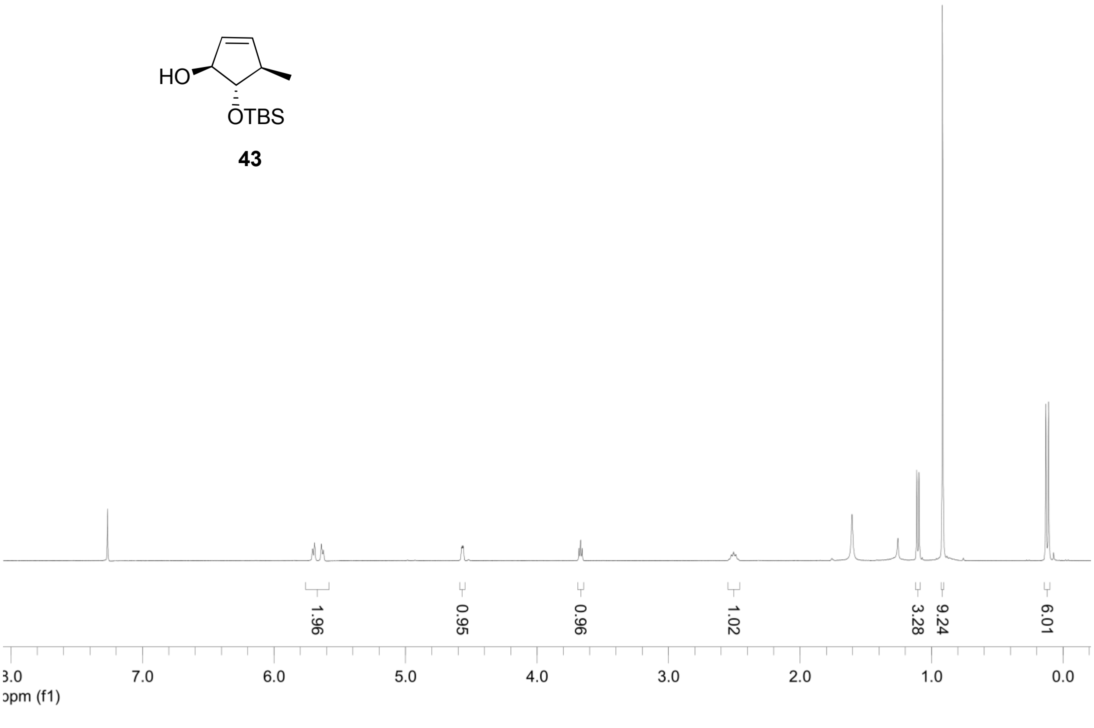

43

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3.28
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3.0
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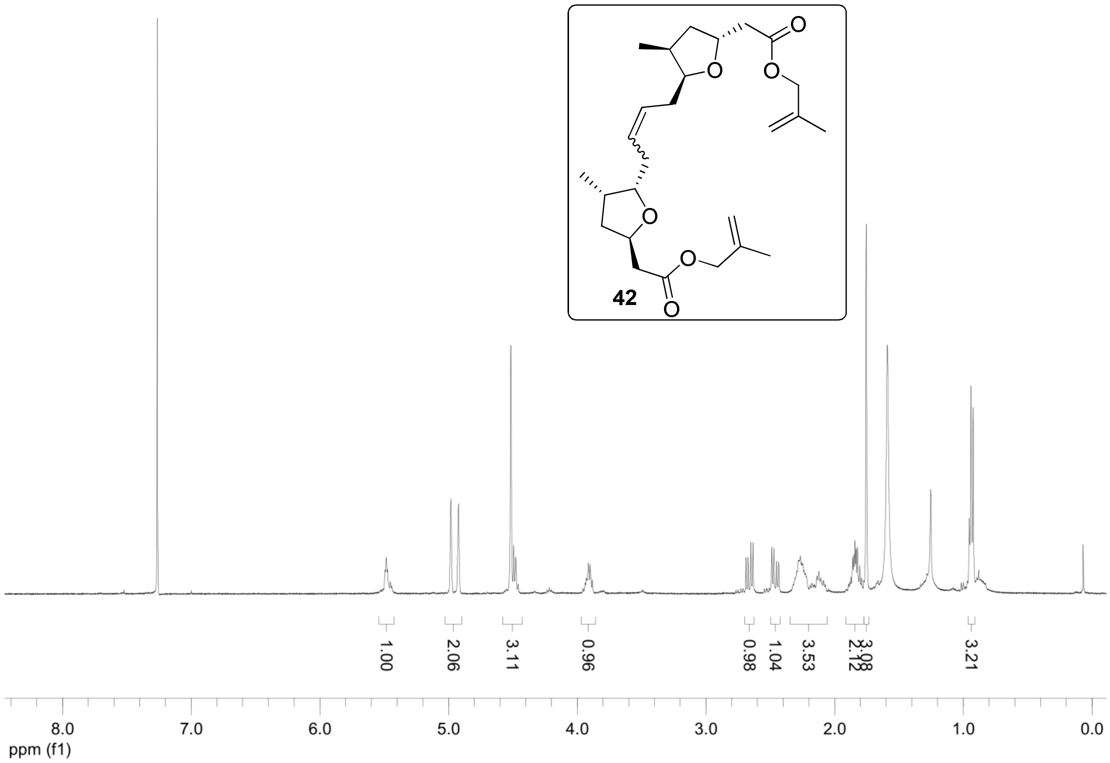
0.0
ppm (f1)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3.0
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1.0
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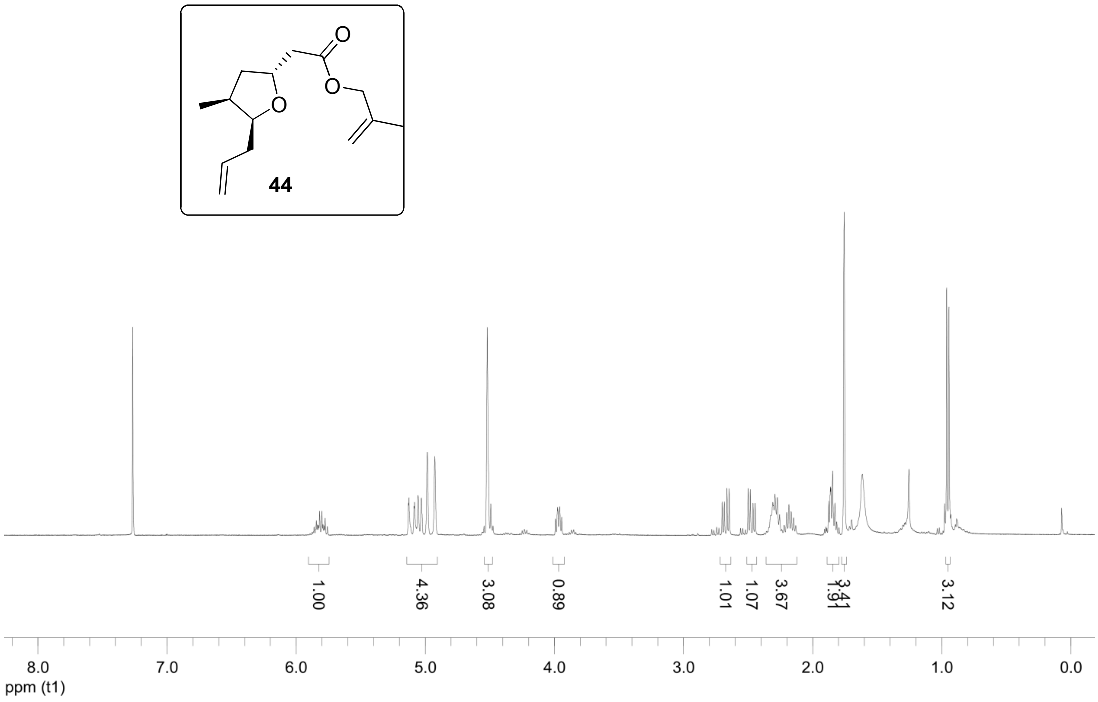
ppm (f1)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3.12
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (t1)

CHAPTER 5

IBX MEDIATED OXIDATIVE ANNULATION OF ALLYLIC ALCOHOLS WITH ENAMINES: A VERSATILE SYNTHESIS OF FUNCTIONALIZED PYRIDINES AND ITS APPLICATION TO THE PYRIDINE CORE OF CYCLOTHIAZOMYCIN

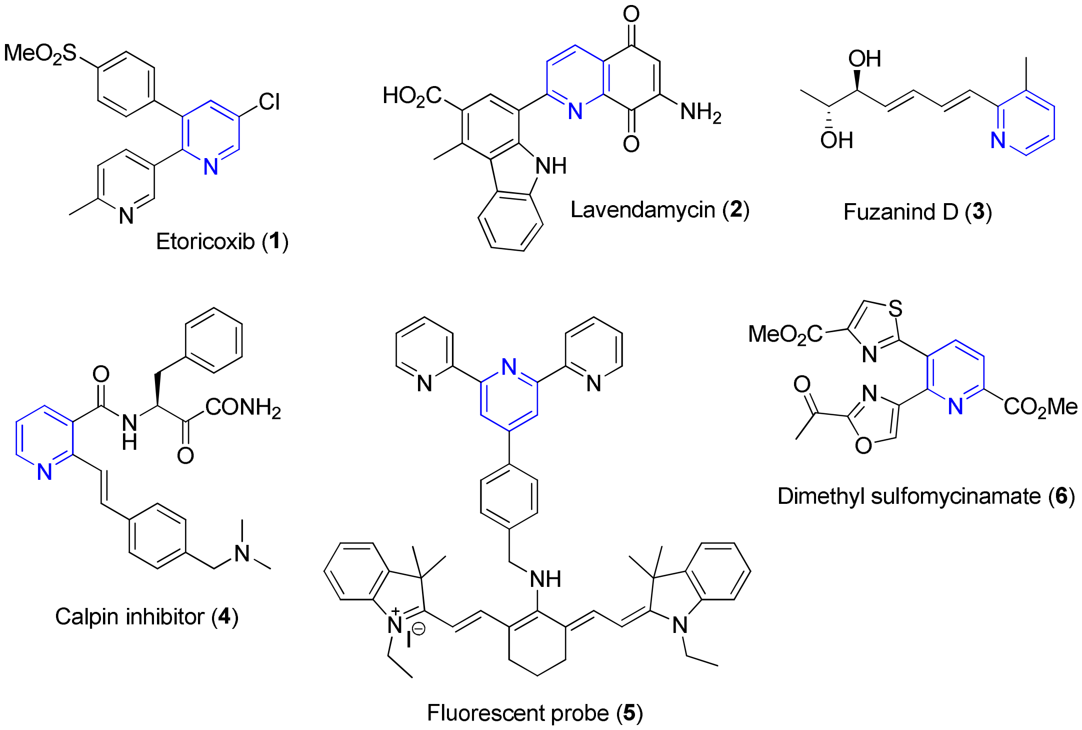
2013, *49*, 7926.

Reference:

Narendar Reddy Gade, Devendram V, Manojit Pal and Javed, Iqbal. *Chem. Commun.* **2013,** *49*, 7926.

5.1. Introduction

Pyridine is simple and important structural motif among the known *N*-heterocycles and is present in several natural products, pharmaceuticals and materials. It has received considerable attention from scientific community over the last century.[1]A few representative molecules bearing the pyridine skeleton are shown in (Fig. 5.1).



Etoricoxib (**1**)

Lavendamycin (**2**)

Fuzanind D (**3**)

Calpin inhibitor (**4**)

Fluorescent probe (**5**)

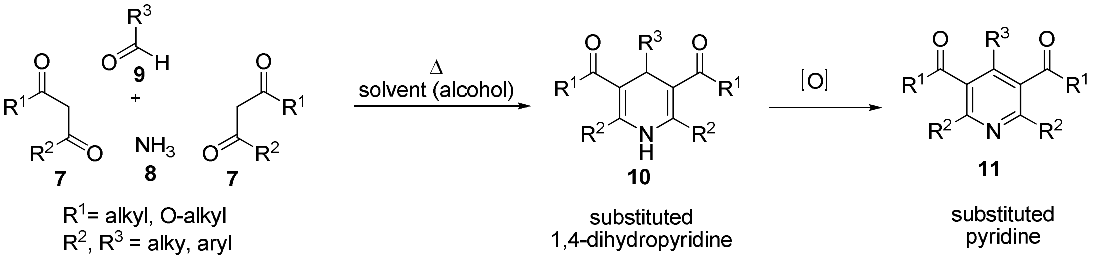
Dimethyl sulfomycinamate (**6**)

Figure 5.1. Few important pyridine derivatives

The pyridine nucleus containing drug molecules are very common such as etoricoxib (**1**) (MK-0663), a novel orally active agent that selectively inhibits cyclooxygenase-2 (COX-2).[2] Similarly, lavendamycin (**2**) is an antitumor antibiotic isolated from the fermentation broth of *Streptomyces lavendulae* in 1981.[3] Fuzanin D (**3**) is cytotoxic natural product isolated from the culture supernatant of *Kitasatospora* sp. IFM10917. Fuzanin D showed cytotoxicity against DLD-1cells (IC_{50}, ~ 40 µM) and moderate inhibition of Wnt signal transcription at 25 mM.[4] Calpin inhibitor (**4**) is potent and orally bioavailable water-soluble calpain inhibitor.[5] A near-neutral pH near-infrared fluorescent probe (**5**) used in imaging living HepG2 and HL-7702 cells for monitoring minor pH changes.[6] Dimethyl sulfomycinamate (**6**), an important molecule comprising of the oxazole−thiazole−pyridine product is generated in the methanolysis of the thiopeptide antibiotic sulfomycin.[7] As a result, there is considerable interest among synthetic chemists to develop several routes for the synthesis of pyridine derivatives. This chapter covers the earlier reports and our approach to the substituted pyridine derivatives starting from enamino esters or its analogues.

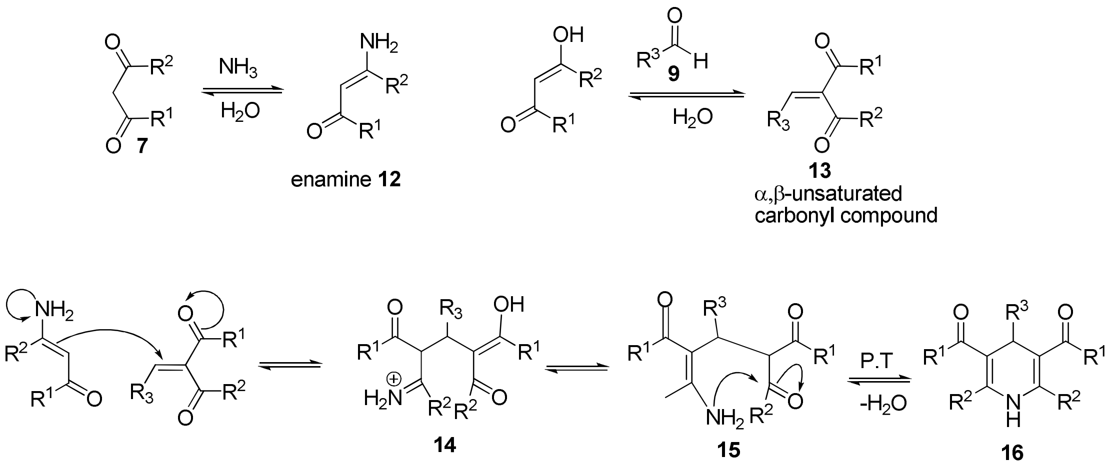
5.1.1 Precedents on synthesis of substituted pyridines

In 1882, Hantzsch prepared symmetrical dihydropyridine (Scheme 5.1) by condensing two moles of ethyl acetoacetate with one mole of acetaldehyde and ammonia.[8] The 1,4-dihydropyridine products thus formed are spontaneously oxidized to the corresponding substituted pyridines, however, in the case of stable dihydropyridines, the use of an oxidizing agent [e.g., HNO_2, HNO_3, $(NH_4)_2Ce(NO_3)_6$, MnO_2, $Cu(NO_3)_2$] is necessary.[9] Unsymmetrical dihydropyridines can be prepared using modified methods like 1) treating β-keto ester and a nitrogen source with α,β-unsaturated carbonyl compound (alkylidene), derived by condensation of one equivalent of a β-keto ester with an aldehyde of choice, 2) an α,β-unsaturated carbonyl compound (prepared from the condensation of active methylene compounds and aldehydes) is condensed with an enamine; [10] and 3) reaction of substituted 1,5-dicarbonyl compound with a nitrogen source (usually ammonium acetate-acetic acid).[11]



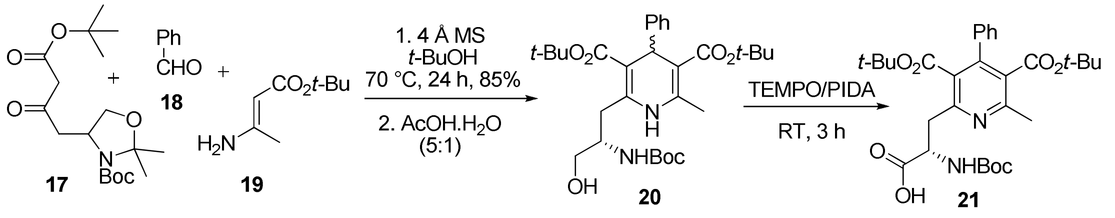
Scheme 5.1

The initial steps of the reaction involve a Knoevenagel condensation of the 1,3-dicarbonyl compound **7** with the aldehyde **9** to give α,β-unsaturated carbonyl compound **13** and a condensation of ammonia with another equivalent of the 1,3-dicarbonyl compound to give an enamine **12**. The rate determining step is the Michael addition of the enamine to the α,β-unsaturated carbonyl compound. Subsequently, the addition product **14** undergoes an intramolecular condensation of the amino and carbonyl groups to afford the desired substituted 1,4-dihydropyridine **16** (Scheme 5.2).



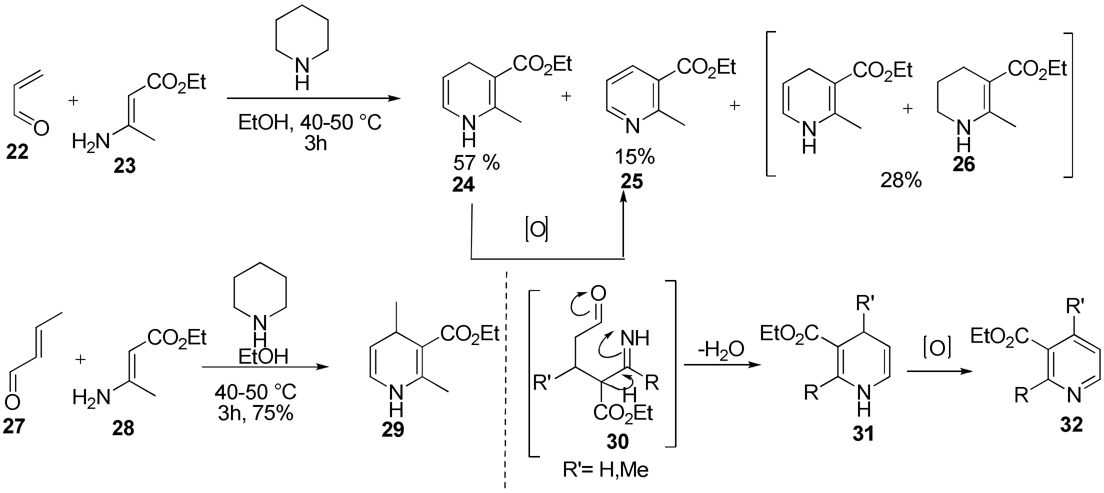
Scheme 5.2

Dondoni and co-workers applied this strategy to synthesize heterocyclic α-amino acids (Scheme 5.3).[12] Initially diastereomeric 1,4-dihydropyridines **20** was prepared by treating the enantiopure oxazolidinyl keto ester **17** which was condensed with benzaldehyde **18** and *tert*-butyl amino crotonate **19** in the presence of molecular sieves in 2-methyl-2-propanol.The removal of acetonide afforded the corresponding amino alcohol **20** which was oxidized to the desired 2-pyridyl α-alanine derivative **21**.



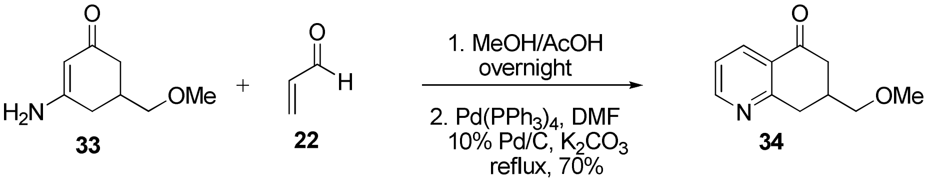
Scheme 5.3

Tsuda *et al.* reported a piperidine catalyzed reaction of acrolein or crotonaldehyde with ethyl *β*-aminocrotonate to synthesize pyridine or 1,4-dihydropyridine derivatives (Scheme 5.4).[13] A mechanistic rational for the formation of these pyridines could be explained by assuming that, acrolein may undergo Micheal addition with enamine leading to the intermediate **30** which on intramolecular cyclization gives dihydropyridine **31**. The dihydropyridine **31** converts to pyridine **32** under oxidation conditions.



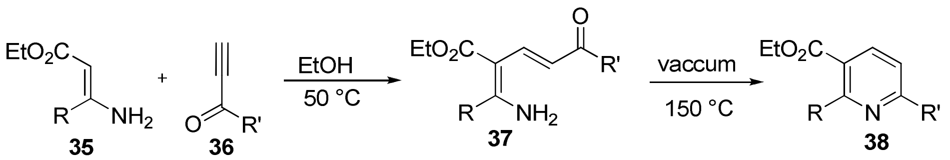
Scheme 5.4

Ravina and co-workers have used similar strategy to construct pyridine ring in synthesis of potent CNS agents **34** (Scheme 5.5)[14] by treating cyclic enaminone **33** with acrolein **32** in methanol followed by application of different oxidation conditions leading to the aromatic intermediate **34**.



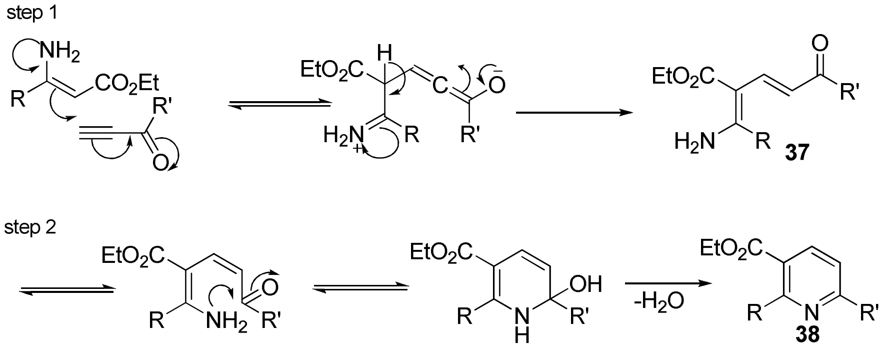
Scheme 5.5

Bohlmann and Rahtz have reported the two-step synthesis of trisubstituted pyridines by the reaction of enamines **35** and ethynyl ketones or aldehydes **36** (Scheme 5.6).[15]



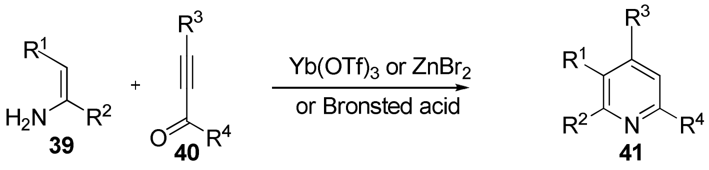
Scheme 5.6

The products formation can be explained by Michael addition of enamine **35** to unsaturated ketone or aldehyde **36** to give an aminodiene intermediate **37** that can be isolated and purified in high yield (Scheme 5.7). Intermediate **37** is kinetically stable and didn't undergo hetero annulation to give products due the *E*-geometery of the enone. However, *E/Z* iso-merization could be achieved by heating intermediate **37** to high temperatures (120–170 °C) leading to spontaneous cyclodehydration to give 2,3,6-trisubstituted pyridines **38**.

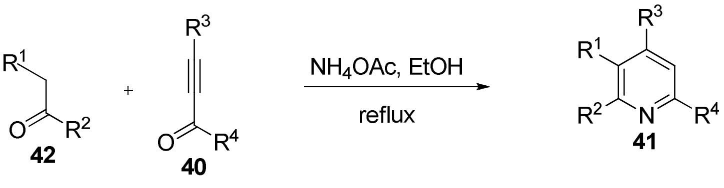


Scheme 5.7

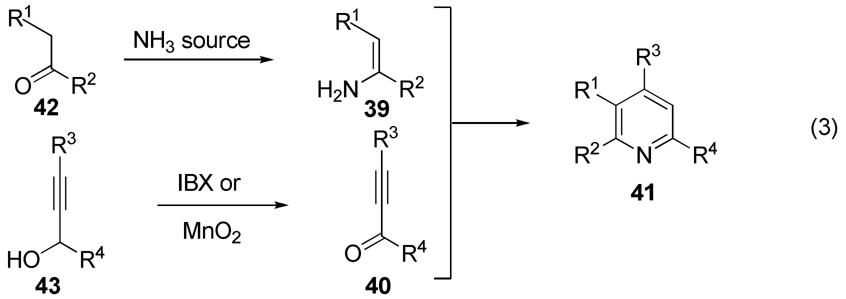
Bagley and his group have pioneered this reaction for a convenient one-pot method to substituted pyridines (Scheme 5.8).[16] They have achieved a one-pot synthesis of pyridines using Brønsted or Lewis acid promoted conjugate addition followed by double-bond isomerization of aminodiene to give intermediate which undergoes spontaneous cyclodehydration to pyridine (eq. 1). The presence of an acid also enabled the reaction to proceed at a lower temperature, which is a substantial improvement over existing methods by involving three component reactions between 1,3-dicarbonyl compounds, alkynones and ammonium acetate (eq. 2). They further improved the method by introducing domino approaches to this reaction via *in situ* preparation of enamine or alkynones (eq. 3).



(1)

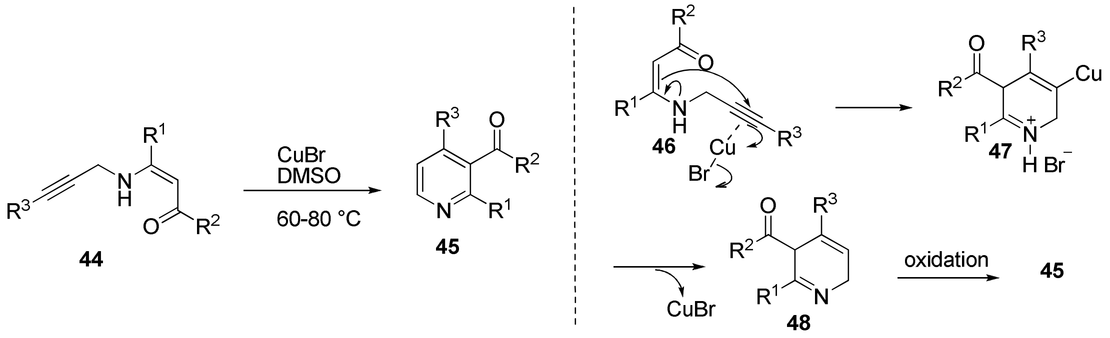


(2)



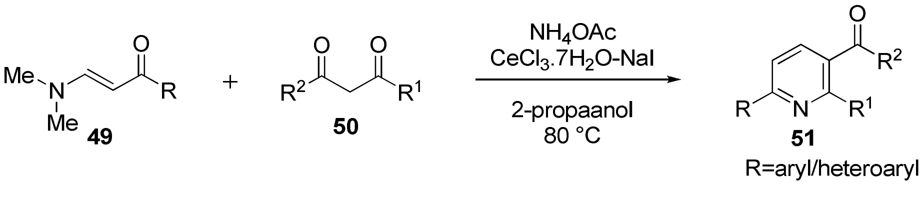
Scheme 5.8

In 2008, Cacchi and co-workers reported a transition metal catalyzed conversion of *N*-propargylic enaminones **44** to substituted pyridines **45** in one step (Scheme 5.9).[17] The pyridine ring formation from **44** can be explained by the coordination of the alkyne moiety with copper to give intermediate **46** and subsequent intramolecular nucleophilic attack of the carbon adjacent to the carbonyl carbon to the activated C-C triple bond in 6-endo-dig fashion leading to **47**. The intermediate **47** on protonation affords intermediate **48**, which on oxidation under the reaction conditions affords pyridine derivative **45**.



Scheme 5.9

In 2011, S. Kantaveri and co-workers developed a variant of Bohlmann-Rahtz reaction to substituted pyridines using *β*-N,N-dimethyl vinyl ketones **49**, 1,3-dicarbonyl compounds **50** and ammonium acetate in presence of catalytic $CeCl_3.7H_2O$-NaI, in isopropanol (Scheme 5.10).[18]

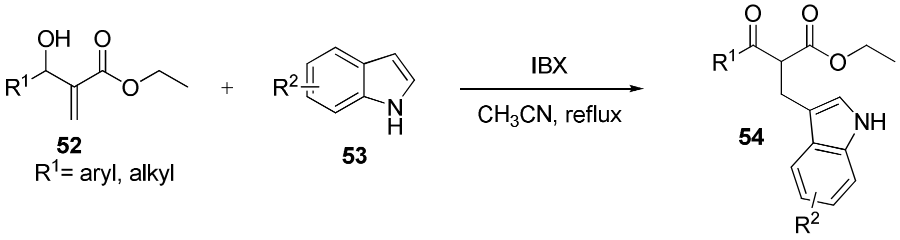


Scheme 5.10

Apart from the few known methods for pyridine synthesis most of methodologies often suffer from drawbacks like longer route, lower yields etc. Thus the synthesis of substituted pyridines offers challenges to design and develop simple and efficient strategies. Since the multiple transformations occur under the same conditions in a single pot, domino processes avoids the isolation of intermediates and further purification steps. Evidently, domino reactions provide suitable solutions and increase the efficiency of the synthetic methods.[19]

5.1.2. Background for oxidative annulation of readily accessible eanamine and allylic alcohols

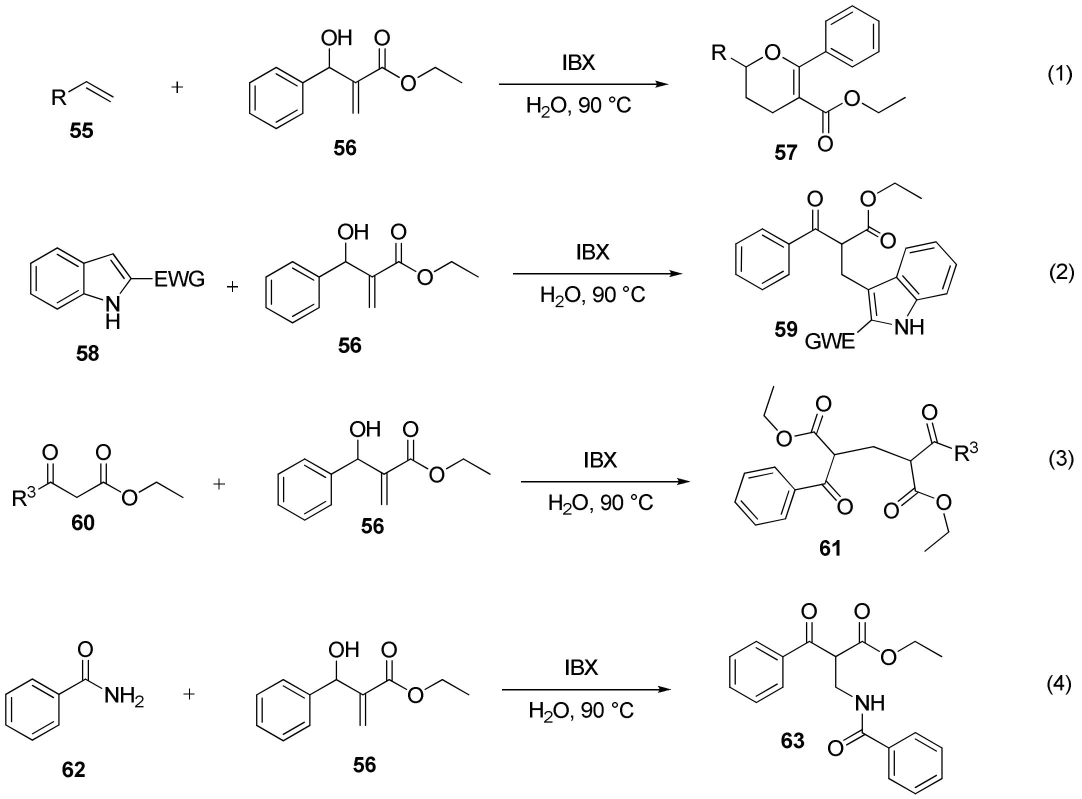
The oxidative annulation between eanamine and allylic alcohols is a direct and ideal process for the preparation of pyridines. These processes do not need the pre oxidized substrates, thereby enhancing the efficiency of the method.



Scheme 5.11

Yadav and co-workers have reported one such example of one-pot oxidative conjugate addition of Baylis–Hillman adducts with indoles, in the presence of 2-iodoxybenzoicacid (IBX) under neutral conditions to afford a new class of substituted indoles in good yields (Scheme 5.11).[20]

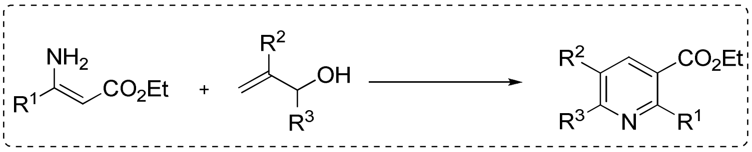
In 2010, Y. Gu *et al.* reported on one-pot oxidative oxo Diels–Alder reaction of Baylis–Hillman adducts with olefins (eq. 1), Michael reaction with β-dicarbonyl compounds (eq. 2) or less-reactive indoles (eq. 3) and aza-Michael reaction with benzamide (eq. 4) to develop an efficient route for synthetically important compounds (Scheme 5.12).[21]



Scheme 5.12

5.1.3. Challenges in the synthesis of pyridine derivatives

Though the annulation between enamine and unsaturated aldehydes or ketones provides pyridine derivatives with ease, a detailed survey of the literature reveals that the one-step synthesis of substituted pyridines from readily available enamines and stable allylic alcohols has so far remained elusive untill 2013 (Scheme 5.13).



Scheme 5.13

Therefore oxidative annulations of enamine and allylic alcohols to synthesize the pyridine derivatives is a considerable challenge.

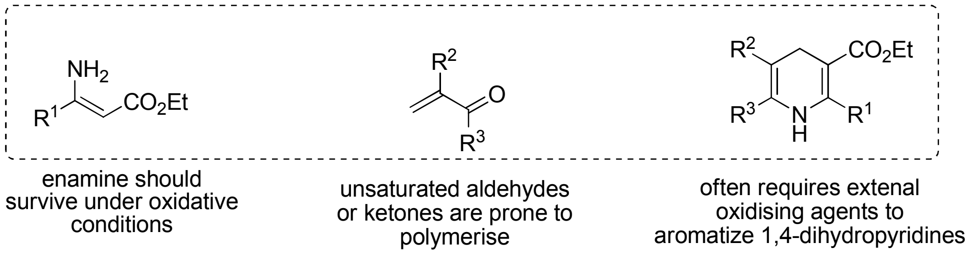


Figure 5.2. Cumulative challenges

The reactivity pattern of starting materials presents following challenges

1) Enamines should survive under oxidative conditions

2) Unsaturated carbonyl compounds are very much prone to polymerize

3) 1,4-dihydropyridines often requires external oxidizing agents to aromatize

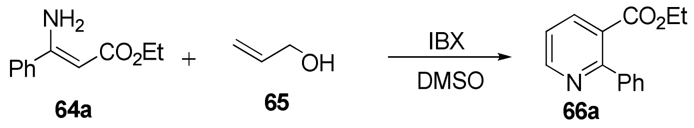
Based on these problems we envisioned that a domino reaction between *β*-enamino esters and allylic alcohols can afford substituted pyridines in the presence of suitable oxidising agent. Despite these cumulative challenges, we developed a one pot domino approach for substituted pyridine derivatives using IBX mediated oxidative annulation of readily accessible eanamines and allylic alcohols and the subsequent part of this chapter describes our attempts in this direction.

5.2. Results & Discussion

5.2.1. Initial results and optimization of reaction conditions

IBX (2-iodoxybenzoic acid), a versatile reagent,[22] have found wide applications in organic synthesis and was chosen as an oxidizing agent in our study. Initially, the reaction of (*E*)-ethyl 3-amino-3-phenylacrylate **64a** and allyl alcohol **65** was performed in DMSO to establish the optimized reaction conditions. After assessing various reaction conditions (Table 5.1) it was observed that the best result is obtained when the reaction is performed using enamine **64** (0.2 mmol), allyl alcohol **65** (2 equiv.) and IBX (1.2 equiv.) in DMSO (3 mL) at 70 °C for 3h to give the desired ethyl 2-phenylnicotinate **66a** in good yield (entry 3, Table 5.1). The reaction did not proceed in the absence of IBX indicating the key role played by the oxidant (entry 4, Table 5.1). The use of lower quantity of IBX (entry 5 and 6, Table 5.1) or alcohol **2** (entry 7, Table 5.1) decreased the product yield whereas increase in reaction temperature to 90 °C did not improve the yield of **66a** (entry 8, Table 5.1).

Table 5.1. Optimization of reaction conditions[a]



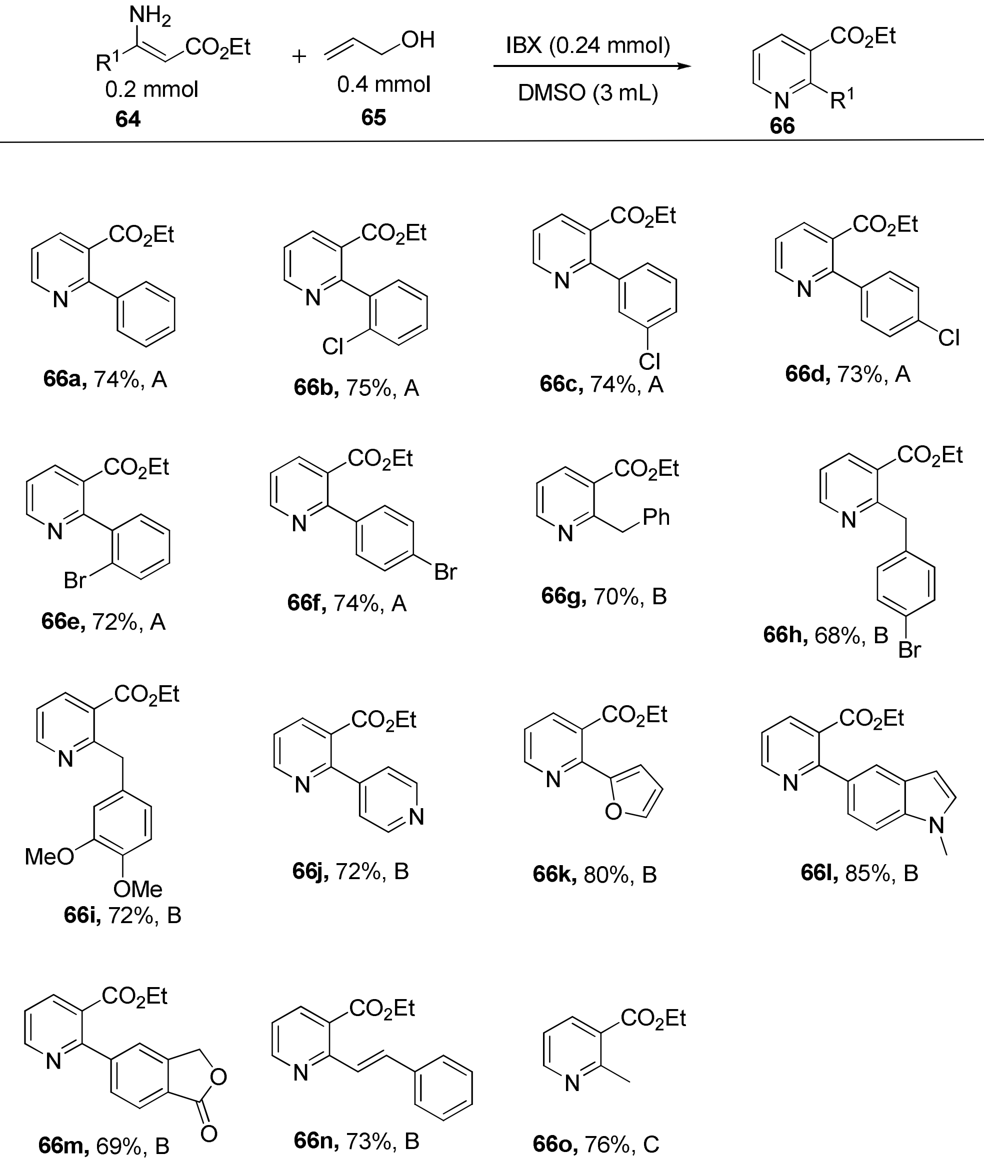
Entry	Temp (°C)	Time (**h**)	Yield[b] (%)
1	30	24 h	0
2	50	24 h	25
3	70	3 h	74
4	70	24 h	0[c]
5	70	10 h	10[d]
6	70	10 h	40[e]
7	70	10 h	50[f]
8	90	3 h	68

[a] All reactions were performed using the enamine **1a** (0.2 mmol), allyl alcohol **2** (2 equiv.) and IBX (1.2 equiv.) in DMSO (3 mL), [b] isolated yields, [c] The reaction was performed in the absence of IBX, [d] 0.05 equiv. IBX was used, [e] 0.5 equiv. of IBX was used, [f] 1.2 equiv. of allyl alcohol was used.

5.2.2. Scope of the reaction

With the optimized reaction conditions in hand we then examined the scope and generality of this method. Thus, a wide range of *β*-enamino esters (aryl/ hetero aryl/ benzyl/ cinnamyl/ aliphatic) were reacted with allyl alcohol in the presence of IBX to give various 2-substituted nicotinic acid derivatives (Table 5.2). All the reactions were performed either at 70 (**66a-66f**, Table 5.2) or 90 ºC (**66g-66n**, Table 5.2) except in one case (**66o**, Table 5.2). Notably, all the nicotinic acid derivatives synthesized (Table 5.2, entry **66a-66f**) can be converted to azafluorenones in a single step.[23] Azafluorenones, a common skeleton in many natural products and useful agents in medicinal chemistry, are generally accessed *via* multistep sequences using metal mediated reactions.[24]

Table 5.2. Synthesis of 2-substituted nicotinic acid[a]



66a, 74%, A

66b, 75%, A

66c, 74%, A

66d, 73%, A

66e, 72%, A

66f, 74%, A

66g, 70%, B

66h, 68%, B

66i, 72%, B

66j, 72%, B

66k, 80%, B

66l, 85%, B

66m, 69%, B

66n, 73%, B

66o, 76%, C

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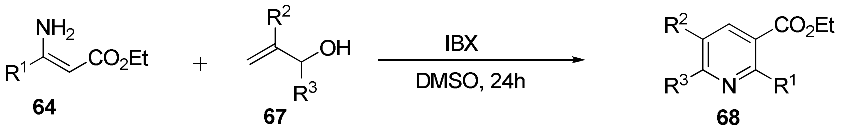
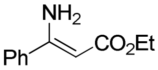
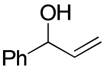
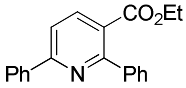
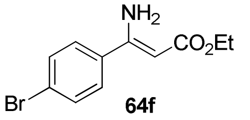
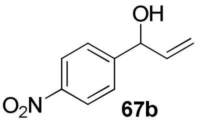
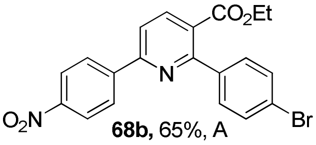
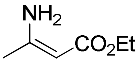
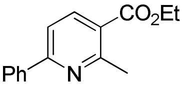
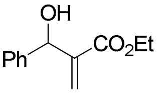
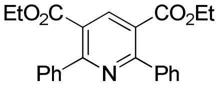
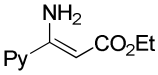
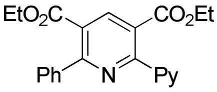
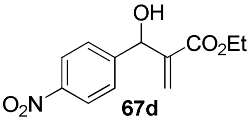
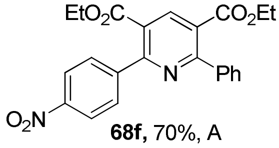
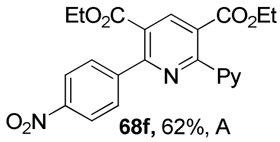
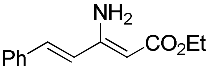
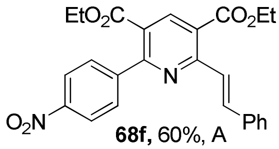
[a] Reaction conditions A: 70 °C, 3 h ; conditions B: 90 °C, 5 h; conditions C: 110 °C, 12 h

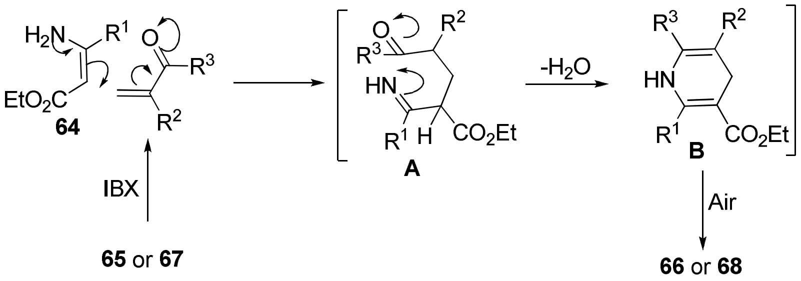
Table 5.3. Synthesis of substituted pyridines[a]



entry	enamine	allyl alcohol	product
1	 **64a**	 **67a**	 **68a,** 70%, A
2	 **64f**	 **67b**	 **68b,** 65%, A
3	 **64o**	**67a**	 **68c,** 72%, B
4	**64a**	 **67c**	 **68d,** 68%, A
5	 **64j**	**67c**	 **68e,** 60%, A
6	**64a**	 **67d**	 **68f,** 70%, A
7	**64j**	**67d**	 **68f,** 62%, A
8	 **64n**	**67d**	 **68f,** 60%, A

[a] Reaction conditions A: enamine (0.1 mmol), allylic alcohol (0.1 mmol), IBX (1.2 equiv.) in 3 mL DMSO at 30 °C; conditions B: enamine (0.1 mmol), allylic alcohol (0.1 mmol), IBX (1.2 equiv.) in 3 mL DMSO at 50 °C.

To expand the scope of this reaction further, we applied this methodology on substitted allylic alcohols. Thus various allyllic alcohols **67** were treated with *β*-enamino esters **64** in the presence of IBX to give the corresponding pyridines **68** in good yields (Table 5.3). Surprisingly *β*-enamino esters were smoothly converted to products even at 30 °C with subtstituted allylic alcohols. This method therefore provides a facile entry to unsymmetrical tetrasubstituted pyridines (Table 5.3, **68d-68f**) and seemed to have advantages over the traditional Hantzsch pyridine synthesis.[8,25] which affords symmetrical pyridines. However, the methodology was not successful in the preparation of 4-substituted pyridines from the corresponding allylic alcohols which appeared to be the limitation of this methodology.

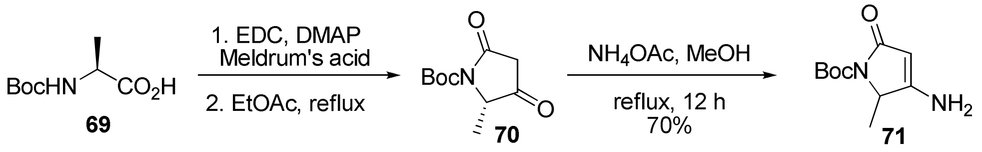


Scheme 5.14

Mechanistically, the reaction seems to proceed (Scheme 5.14) *via* (i) IBX mediated conversion [26] of the alcohol **65** or **67** to the corresponding carbonyl compound which upon (ii) Michael addition with *β*-enaminoester **64** followed by (iii) intra molecular cyclization gives **B** that (iv) aromatizes to **66** or **68** in the presence of air. [27]

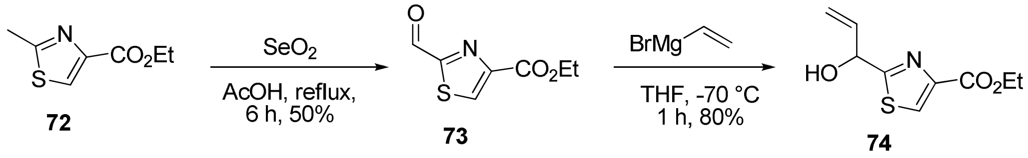
5.3. Application to pyridine core of cyclothiazomycin

The potential of this methodology was demonstrated in the synthesis of pyridine core of cyclothiazomycin[28] i.e. one of **76** structually distinct actinomycete thiopeptide antibiotics.[29] Many thiopeptides contains the 2,3,6-trisubstituted pyridine core and several groups have developed different synthetic routes to this moiety.[29] Our strategy was mainly based on bringing the corresponding cyclic enamine **71** and allylic alcohol **74** togather by applying the newly developed methodology. Thus, the required cyclic enamine **71** was prepared from *N*-Boc alanine in 3 steps (Scheme 5.15) and during the course of amination of *β*-keto amide **70**,[30] racemic enamine **71** was obtained.

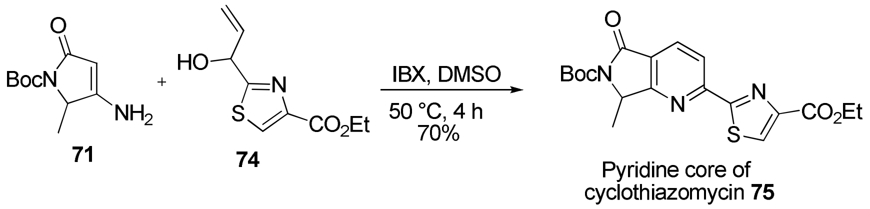


Scheme 5.15

The allylic alcohol **74** was prepared from ethyl 2-methylthiazole-4-carboxylate **72** in 2 steps (Scheme 5.16).[31] Gratifyingly, the critical annulation reaction was easily acheived by a IBX mediated oxidative annulation of allylic alcohol **74** and enamine **71** leading to the pyridine core of cyclothiazomycin **75** in good yields(Scheme 5.17).



Scheme 5.16



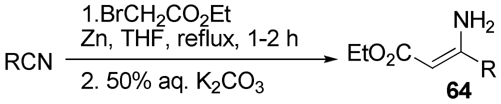
Scheme 5.17

5.4. Conclusions

In conclusion, a direct, one-pot and metal free synthesis of functionalized pyridines have been developed for the first time *via* the IBX mediated reaction of readily available *β*-enamino esters and allylic alcohols. This tandem method afforded 2-substituted nicotinic acids, tetra substituted unsymmetrical pyridines and precursors of azaflurenones in addition to the recemic pyridine core of cyclothiazomycin. The limitations and advantages of this methdology has been discussed. The methodology may find wide applications in the construction of pyridine based library of small molecules useful for medicinal uses or natural product synthesis.

5.5. Experimental section

5.5.1. Materials



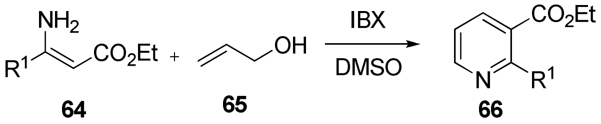
β-enamino esters **64** were synthesized based on the procedure given below: [32,33]

To activated zinc dust (1.31 g, 20 mmol) was added trimithylsilylchloride (3 drops) in anhydrous THF (10 mL). After 10 min of reflux, nitrile (10 mmol) was added all at once. While maintaining reflux temperature, ethyl bromoacetate (1.65 mL, 15 mmol in 5 mL THF) was added over 1h using addition funnel, and the reaction mixture was further heated at reflux for 1 h. After complete conversion of nitrile, the reaction mixture was cooled to room temperature and quenched with saturated aqueous K_2CO_3 at room temperature and extracted with ethyl acetate (3 x 30 mL). The combined organic layers was dried with anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography to get *β*-enamino ester.

β-keto amide **70**,[30] aldehyde **73,**[31] and IBX[34] were prepared according to the respective literature procedure. Analytical and spectral data of all those known compounds are exactly matching with the reported values.

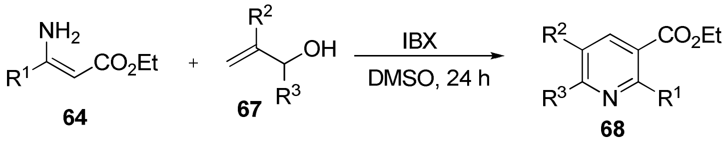
5.4.2. Experimental procedure, spectral and analytical data

General Procedure for Synthesis of 2–substituted nicotinic esters 66.



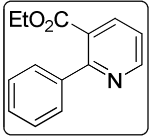
A mixture of *β*-enamino ester **64** (0.2 mmol), allyl alcohol **65** (2 equiv.) and IBX (1.2 equiv.) in DMSO (3 mL) was stirred at 70-110 ˚C for 3-12 h (see Table 5.2). After completion of the reaction (monitored by TLC), the mixture was cooled to room temperature, quenched with sat. $NaHCO_3$ solution (1.5 mL) and extracted with EtOAc (3 x 5 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated under low vacuum. The crude compound was purified by using flash chromatography (EtOAc/Hexane).

General procedure for the synthesis of substituted pyridines from substituted allylic alcohols.



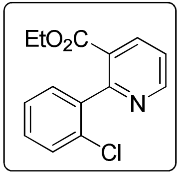
A mixture of *β*-enamino ester **64** (0.1 mmol), allyl alcohol **67** (1.1 equiv.) and IBX (1.2 equiv.) in DMSO (3 mL) was stirred at room temperature for 24h (see Table 5.3). After completion of the reaction (monitored by TLC), the mixture was quenched with sat. $NaHCO_3$ solution (1.5 mL) and extracted with EtOAc (3 x 4 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated under low vacuum. The crude compound was purified by using flash chromatography (EtOAc/Hexane).

Ethyl 2-phenylnicotinate (66a):



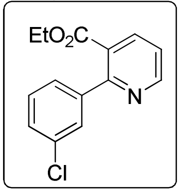
Yellow oil, R_f = 0.5 (20% EtOAc in hexane); ^{1}H NMR (400 MHz, *CDCl₃*) δ 8.77 (dd, *J* = 4.8, 1.7 Hz, 1H), 8.10 (dd, *J* = 7.8, 1.7 Hz, 1H), 7.57-7.52 (m, 2H), 7.47-7.40 (m, 3H), 7.34 (dd, *J* = 7.8, 4.8 Hz, 1H), 4.15 (q, *J* = 7.2 Hz, 2H), 1.04 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, *CDCl₃*) δ 168.1, 158.8, 151.1, 140.2, 137.8, 128.5, 128.5, 128.0, 127.40, 121.5, 61.4, 13.6; IR (cm^{-1}): 3053, 2982, 1721, 1565, 1433, 1368, 1053, 754; MS (ES mass) m/z: 228.1[M + 1].

Ethyl 2-(2-chlorophenyl)nicotinate (66b):



Dark yellow oil, R_f = 0.4 (10% EtOAc in hexane); ^{1}H NMR (400 MHz, *CDCl₃*) δ 8.82 (dd, *J* = 4.8, 1.7 Hz, 1H), 8.34 (dd, *J* = 7.9, 1.7 Hz, 1H), 7.47-7.32 (m, 5H), 4.15 (q, *J* = 7.1 Hz, 2H), 1.04 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, *CDCl₃*) δ 165.9, 157.4, 151.7, 139.9, 138.1, 132.2, 130.0, 129.3, 128.8, 127.3, 126.6, 122.5, 61.3, 13.4; IR (cm^{-1}): 3053, 2980, 1721, 1562, 1431, 1368, 1138, 1052, 774; MS (ES mass) m/z: 262.0 [M + 1].

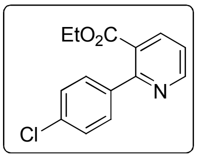
Ethyl 2-(3-chlorophenyl)nicotinate (66c):



Dark yellow oil, R_f = 0.35 (10% EtOAc in hexane); ^{1}H NMR (400 MHz, *CDCl₃*) δ 8.77 (dd, *J* = 4.8, 1.7 Hz, 1H), 8.14 (dd, *J* = 7.8, 1.7 Hz, 1H), 7.54 (s, 1H), 7.42-7.35 (m, 4H), 4.19 (q, *J* = 7.1 Hz, 2H), 1.10 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, *CDCl₃*) δ 167.5, 157.3, 151.2, 141.8, 138.0, 134.0, 129.2, 128.7, 128.6, 127.2, 126.7, 122.0, 61.6, 13.6;

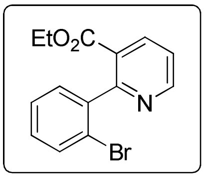
IR (cm^{-1}): 3053, 2982, 1723, 1585, 1433, 1368, 1050, 774; MS (ES mass) m/z: 262.1[M + 1].

Ethyl 2-(4-chlorophenyl)nicotinate (66d):



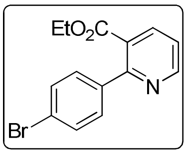
Brownish yellow gum, R_f = 0.45 (10% EtOAc in hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.76 (dd, *J* = 4.8, 1.6 Hz, 1H), 8.12 (dd, *J* = 7.8, 1.6 Hz, 1H), 7.48 (d, *J* = 8.5 Hz, 2H), 7.41 (d, *J* = 8.5 Hz, 2H), 7.35 (dd, *J* = 7.8, 4.8 Hz, 1H), 4.19 (q, *J* = 7.1 Hz, 2H), 1.11 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.6, 157.5, 151.1, 138.5, 137.9, 134.7, 129.9, 128.2, 127.1, 121.8, 61.5, 13.6; IR (cm^{-1}): 3052, 2981, 1724, 1584, 1434, 1282, 1136, 1051, 781; MS (ES mass) m/z: 262.1[M + 1].

Ethyl 2-(2-bromophenyl)nicotinate (66e):



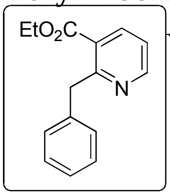
Pale yellow solid, m.p: 55-57 °C; R_f = 0.33 (10% EtOAc in hexane); ^{1}H NMR(400 MHz, $CDCl_3$) δ 8.82 (dd, *J* = 4.8, 1.7 Hz, 1H), 8.35 (dd, *J* = 7.9, 1.7 Hz, 1H), 7.61 (d, *J* = 7.9 Hz, 1H), 7.45-7.35 (m, 3H), 7.26 (dd, *J* = 6.7, 2.4 Hz, 1H), 4.2-4.07 (m, 2H), 1.03 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.9, 159.0, 151.7, 142.0, 138.3, 132.1, 129.9, 129.4, 127.1, 127.1, 122.6, 122.0, 61.3, 13.5; IR (cm^{-1}): 3052, 2982, 1722, 1585, 1430, 1388, 1060, 764; MS (ES mass) m/z: 306.0[M + 1].

Ethyl 2-(4-bromophenyl)nicotinate (66f):



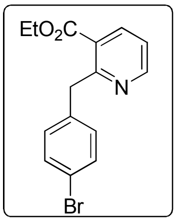
Pale yellow oil; R_f = 0.3 (10% EtOAc in hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.76 (dd, *J* = 4.8, 1.6 Hz, 1H), 8.13 (dd, *J* = 7.8, 1.6 Hz, 1H), 7.57 (d, *J* = 8.4 Hz, 2H), 7.41 (d, *J* = 8.4 Hz, 2H), 7.36 (dd, *J* = 7.8, 4.8 Hz, 1H), 4.19 (q, *J* = 7.1 Hz, 2H), 1.12 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.6, 157.7, 151.3, 139.1, 138.0, 131.2, 130.2, 127.1, 123.0, 121.8, 61.6, 13.7; IR (cm^{-1}): 3050, 2981, 1723, 1583, 1429, 1393, 1132, 1050, 768; MS (ES mass) m/z: 306.0[M + 1].

Ethyl 2-benzylnicotinate (66g):



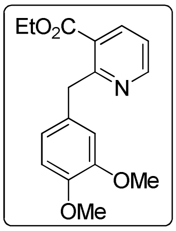
Yellow oil, R_f = 0.2 (10% EtOAc in hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.68 (dd, *J* = 4.7, 1.7 Hz, 1H), 8.16 (dd, *J* = 7.9, 1.7 Hz, 1H), 7.27-7.21 (m, 5H), 7.18-7.11 (m, 1H), 4.59 (s, 2H), 4.32 (q, *J* = 7.2 Hz, 2H), 1.33 (d, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.5, 161.1, 151.8, 139.6, 138.5, 128.9, 128.2, 126.1, 126.0, 121.2, 61.4, 42.3, 14.1; IR (cm^{-1}): 3053, 2982, 1721, 1565, 1433, 1368, 1052, 728; MS (ES mass) m/z: 242.1[M + 1].

Ethyl 2-(4-bromobenzyl)nicotinate (66h):



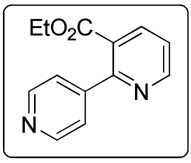
Pale yellow oil, R_f = 0.23 (10% EtOAc in hexane); ^{1}H NMR (400 MHz, *CDCl$_3$*) δ 8.68 (dd, *J* = 4.7, 1.6 Hz, 1H), 8.19 (dd, *J* = 7.9, 1.6 Hz, 1H), 7.36 (d, *J* = 8.4 Hz, 2H), 7.25 (dd, *J* = 7.7, 4.6 Hz, 1H), 7.15 (d, *J* = 8.3 Hz, 2H), 4.52 (s, 2H), 4.33 (q, *J* = 7.1 Hz, 2H), 1.34 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, *CDCl$_3$*) δ 166.3, 160.7, 152.0, 138.7, 138.6, 131.2, 130.7, 125.9, 121.4, 120.0, 61.4, 41.7, 14.1; IR (cm^{-1}): 3056, 2980, 1722, 1573, 1482, 1368, 1273, 1079, 762; MS (ES mass) m/z: 320.0[M + 1].

Ethyl 2-(3,4-dimethoxybenzyl)nicotinate (66i):



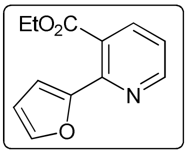
Yellow oil, R_f = 0.35 (20% EtOAc in hexane); ^{1}H NMR (400 MHz, *CDCl$_3$*) δ 8.68 (dd, *J* = 4.8, 1.7 Hz, 1H), 8.16 (dd, *J* = 7.9, 1.7 Hz, 1H), 7.23 (dd, *J* = 7.9, 4.8 Hz, 1H), 6.87 (s, 1H), 6.82-6.73 (m, 2H), 4.52 (s, 2H), 4.34 (q, *J* = 7.1 Hz, 2H), 3.82 (s, 6H), 1.35 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, *CDCl$_3$*) δ 166.5, 161.4, 151.8, 148.6, 147.3, 138.5, 132.2, 126.0, 121.1, 120.9, 112.4, 111.0, 61.4, 55.8, 55.7, 41.7, 14.1; IR (cm^{-1}): 3050, 2982, 1721, 1565, 1493, 1368, 1050, 1078, 754; MS (ES mass) m/z: 302.1[M + 1].

Ethyl 2,4'-bipyridine-3-carboxylate (66j):



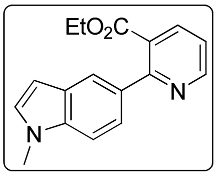
Brown oil, R_f = 0.2 (50% EtOAc in hexane); ^{1}H NMR (400 MHz, *CDCl$_3$*) δ 8.80 (dd, *J* = 4.6, 1.3 Hz, 1H), 8.68 (d, *J* = 5.5 Hz, 2H), 8.20 (dd, *J* = 7.9, 1.2 Hz, 1H), 7.43 (dd, *J* = 6.6, 2.5 Hz, 3H), 4.18 (q, *J* = 7.1 Hz, 2H), 1.08 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, *CDCl$_3$*) δ 166.9, 156.5, 151.5, 149.4, 147.9, 138.3, 127.1, 123.2, 122.8, 61.7, 13.5; IR (cm^{-1}): 3044, 2982, 1723, 1574, 1434, 1368, 1057, 777; MS (ES mass) m/z: 229.1[M + 1].

Ethyl 2-(furan-2-yl)nicotinate (66k):



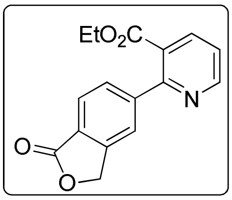
Dark brown oil, R_f = 0.5 (20% EtOAc in hexane); ^{1}H NMR (400 MHz, *CDCl$_3$*) δ 8.68 (dd, *J* = 4.8, 1.6 Hz, 1H), 7.89 (dd, *J* = 7.8, 1.7 Hz, 1H), 7.53 (d, *J* = 0.9 Hz, 1H), 7.24 (dd, *J* = 7.8, 4.8 Hz, 1H), 7.05 (d, *J* = 3.4 Hz, 1H), 6.54 (dd, *J* = 3.4, 1.7 Hz, 1H), 4.38 (q, *J* = 7.2 Hz, 2H), 1.31 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, *CDCl$_3$*) δ 168.2, 152.3, 150.7, 146.7, 143.7, 136.8, 126.0, 121.3, 111.9, 111.1, 61.7, 14.1; IR (cm^{-1}): 3128, 3047, 2982, 1728, 1584, 1487, 1287, 1052, 776; MS (ES mass) m/z: 218.1[M + 1].

Ethyl 2-(1-methyl-1H-indol-5-yl)nicotinate (66l):



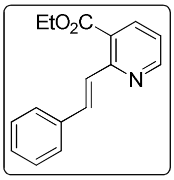
Yellow oil, R_f = 0.42 (20% EtOAc in hexane); ^{1}H NMR (400 MHz, *CDCl$_3$)* δ 8.77 (dd, *J* = 4.8, 1.7 Hz, 1H), 8.04 (dd, *J* = 7.8, 1.7 Hz, 1H), 7.84 (d, *J* =1.1 Hz, 1H), 7.46 (dd, *J* = 8.5, 1.6 Hz, 1H), 7.37 (d, *J* = 8.5 Hz, 1H), 7.32-7.27 (m, 1H), 7.08 (d, *J* = 3.1 Hz, 1H), 6.53 (t, *J* = 4.2 Hz, 1H), 4.16 (q, *J* = 7.1 Hz, 2H), 3.83 (s, 3H), 1.03 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, *CDCl$_3$)* δ ppm 159.6, 150.8, 137.5, 136.9, 131.3, 129.4, 128.4, 127.5, 122.5, 121.5, 120.5, 108.8, 101.7, 61.3, 32.9, 13.7; IR (cm^{-1}): 3100, 3044, 2970, 1721, 1574, 1430, 1368, 1285, 1093, 775; MS (ES mass) m/z: 281.2[M + 1].

Ethyl 2-(1-oxo-1,3-dihydroisobenzofuran-5-yl)nicotinate (66m):



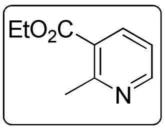
Colorless semisolid, R_f = 0.43 (50% EtOAc in hexane); ^{1}H NMR (400 MHz, *CDCl$_3$)* δ 8.81 (dd, *J* = 4.8, 1.6 Hz, 1H), 8.24 (dd, *J* = 7.9, 1.6 Hz, 1H), 7.97 (d, *J* = 7.9 Hz, 1H), 7.71 (s, 1H), 7.65-7.59 (m, 1H), 7.45 (dd, *J* = 7.9, 4.8 Hz, 1H), 5.38 (s, 2H), 4.21 (q, *J* = 7.14 Hz, 2H), 1.12 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, *CDCl$_3$)* δ 170.7, 166.9, 157.7, 151.5, 146.5, 146.3, 138.4, 129.9, 127.2, 125.6, 125.2, 122.6, 122.3, 69.6, 61.7, 13.7; IR (cm^{-1}): 3059, 2977, 1762, 1727, 1570, 1437, 1358, 1284, 1012, 771; MS (ES mass) m/z: 284.1[M + 1].

(E)-ethyl 2-styrylnicotinate (66n):



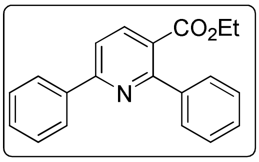
Yellow oil, R_f = 0.2 (10% EtOAc in hexane); ^{1}H NMR (400 MHz, *CDCl$_3$)* δ .75 (dd, *J* = 4.6, 1.7 Hz, 1H), 8.23 (dd, *J* = 7.9, 1.8 Hz, 1H), 8.18 (d, *J* = 15.7 Hz, 1H), 7.96 (d, *J* = 15.7 Hz, 1H), 7.67 (d, *J* = 7.2 Hz, 2H), 7.41 (t, *J* = 7.4 Hz, 2H), 7.34 (d, *J* = 7.3 Hz, 1H), 7.24 (dd, *J* = 7.9, 4.7 Hz, 1H), 4.46 (q, *J* = 7.1 Hz, 2H), 1.47 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, *CDCl$_3$)* δ 166.5, 155.2, 151.9, 138.7, 136.8, 135.9, 128.6, 128.5, 127.5, 125.0, 124.3, 121.3, 61.5, 14.3; IR (cm^{-1}): 3031, 2981, 1777, 1572, 1428, 1367, 1263, 1078, 775; MS (ES mass) m/z: 254.1[M + 1].

Ethyl 2-methylnicotinate (66o):



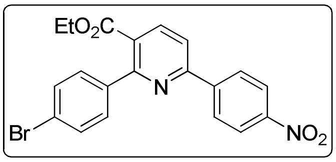
Colorless liquid, R_f = 0.5 (10% EtOAc in hexane); ^{1}H NMR (400 MHz, *CDCl$_3$)* δ 8.61 (dd, *J* = 4.8, 1.62 Hz, 1H), 8.19 (dd, *J* = 7.9, 1.7 Hz, 1H), 7.21 (dd, *J* = 7.9, 4.8 Hz, 1H), 4.39 (q, *J* = 7.2 Hz, 2H), 2.84 (s, 3H), 1.41 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, *CDCl$_3$)* δ 166.5, 159.7, 151.6, 138.4, 125.7, 120.9, 61.3, 24.7, 14.2 ; IR (cm^{-1}): 3020, 2979, 1724, 1572, 1461, 1368, 1293, 1138, 1084; MS (ES mass) m/z: 166.2[M + 1].

Ethyl 2,6-diphenylnicotinate (68a):



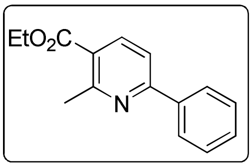
Yellow oil, R$_f$ = 0.2 (10% EtOAc in hexane); ^{1}H NMR (400 MHz, *CDCl$_3$)* δ 8.20-8.10 (m, 3H), 7.77 (d, *J* = 8.2 Hz, 1H), 7.64 (dd, *J* =7.4, 2.0 Hz, 2H), 7.52-7.41 (m, 6H), 4.18 (q, *J* = 7.1 Hz, 2H), 1.07 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, *CDCl$_3$)* δ 168.2, 158.7, 158.3, 140.4, 138.8, 138.2, 129.7, 128.8, 128.7, 128.5, 127.9, 127.2, 125.3, 117.8, 61.3, 13.6; IR (cm^{-1}): 3060, 3031, 2980, 1729, 1586, 1435, 1379, 1289,1180, 1052, 1017; MS (ES mass) m/z: 304.3[M + 1].

Ethyl 2-(4-bromophenyl)-6-(4-nitrophenyl)nicotinate (68b):



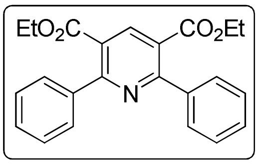
Colorless solid, m.p: 150-152 °C; R$_f$ = 0.3 (10% EtOAc in hexane); ^{1}H NMR (400 MHz, *CDCl$_3$)* δ 8.35 (d, *J* = 9.0 Hz, 2H), 8.31-8.25 (m, 3H), 7.87 (d, *J* = 8.1 Hz, 1H), 7.62 (d, *J* = 8.5 Hz, 2H), 7.52 (d, *J* = 8.5 Hz, 2H), 4.23 (q, *J* = 7.1 Hz, 2H), 1.16 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, *CDCl$_3$)* δ 167.4, 158.0, 155.9, 148.6, 143.7, 139.5, 138.8, 131.3, 130.4, 128.1, 126.5, 124.0, 123.4, 118.9, 114.0, 61.8, 13.8; IR (cm^{-1}): 3079, 2980, 2853, 1723, 1581, 1445, 1343, 1278, 1107, 1053; MS (ES mass) m/z: 427.1[M + 1].

Ethyl 2-methyl-6-phenylnicotinate (68c):



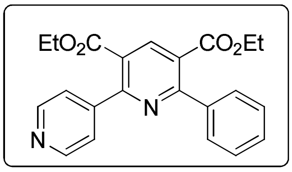
Colorless liquid, R$_f$ = 0.7 (10% EtOAc in hexane); ^{1}H NMR (400 MHz, *CDCl$_3$)* δ 8.27 (d, *J* = 8.2 Hz, 1H), 8.09-8.03 (m, 2H), 7.63 (d, *J* = 8.2 Hz, 1H), 7.52-7.43(m, 3H), 4.40 (q, *J* = 7.2 Hz, 2H), 2.92 (s, 3H), 1.42 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, *CDCl$_3$)* δ 166.6, 159.9, 159.0, 139.3, 138.5, 129.6, 128.8, 127.3, 123.6, 117.3, 61.1, 25.3, 14.3; IR (cm^{-1}): 3063, 2980, 2872, 1721, 1583, 1452, 1381, 1266, 1152, 1075; MS (ES mass) m/z: 242.2[M + 1].

Diethyl 2,6-diphenylpyridine-3,5-dicarboxylate (68d):



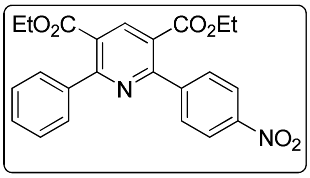
Colorless solid, m.p: 61-63 °C; R$_f$ = 0.7 (10% EtOAc in hexane); ^{1}H NMR (400 MHz, *CDCl$_3$)* δ 8.55 (s, 1H), 7.67-7.61 (m, 4H), 7.46-7.41 (m, 6H), 4.20 (q, *J* = 7.1 Hz, 4H), 1.10 (t, *J* = 7.1 Hz, 6H); ^{13}C NMR (100 MHz, *CDCl$_3$)* δ 167.4, 159.7, 140.3, 139.3, 129.1, 128.9, 128.0, 124.8, 61.6, 13.7; IR (cm^{-1}): 3059, 2981, 2872, 1725, 1590, 1447, 1365, 1251, 1105, 1030; MS (ES mass) m/z: 376.3[M + 1].

Diethyl 6-phenyl-2,4'-bipyridine-3,5-dicarboxylate (68e):



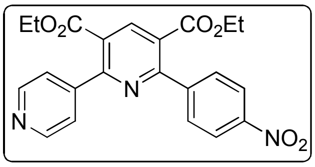
Color less solid, m.p: 63-65 °C; Rf = 0.2 (40% EtOAc in hexane); ^{1}H NMR (400 MHz, *CDCl$_3$)* δ 8.69 (d, J = 4.1 Hz, 2H), 8.61 (s, 1H), 7.63-7.58 (m, 2H), 7.50 (d, J = 5.7 Hz, 2H), 7.47-7.42 (m, 3H), 4.25-4.18 (m, 4H), 1.15-1.07 (m, 6H); ^{13}C NMR (100 MHz, *CDCl$_3$)* δ 167.1, 166.1, 160.2, 157.5, 149.4, 147.2, 140.7, 138.8, 129.5, 128.9, 128.2, 126.2, 124.7, 123.4, 62.0, 61.9, 13.7; IR (cm^{-1}): 3060, 3030, 2981, 2855, 1726, 1590, 1447, 1367, 1249, 1105, 1024; MS (ES mass) m/z: 377.3 [M + 1].

Diethyl 2-(4-nitrophenyl)-6-phenylpyridine-3,5-dicarboxylate (68f):



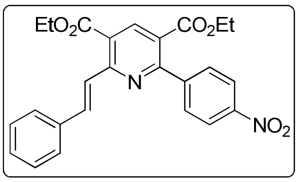
Pale Yellow solid, m.p: 88-90 °C; R$_f$ = 0.25 (10% EtOAc in hexane); ^{1}H NMR (400 MHz, *CDCl$_3$)* δ 8.65 (s, 1H), 8.31 (d, J = 8.8 Hz, 2H), 7.77 (d, J = 8.8 Hz, 2H), 7.67-7.58 (m, 2H), 7.50-7.43 (m, 3H), 4.3-4.2 (m, 4H), 1.18 (t, J = 7.1 Hz, 3H), 1.11 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, *CDCl$_3$)* δ 167.1, 166.0, 160.1, 157.9, 148.0, 145.7, 140.8, 138.7, 130.0, 129.6, 128.9, 128.2, 126.1, 124.5, 123.2, 62.0, 62.0, 13.8, 13.7; IR (cm^{-1}): 3031, 2981, 1720, 1570, 1428, 1379, 1249, 1105, 1017; MS (ES mass) m/z: 421.3[M + 1].

Diethyl 6-(4-nitrophenyl)-2,4'-bipyridine-3,5-dicarboxylate (68g):



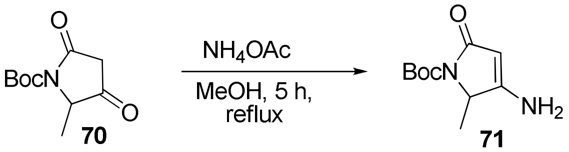
Yellow color solid, m.p: 89-91 °C; R$_f$ = 0.3 (50% EtOAc in hexane). ^{1}H NMR (400 MHz, *CDCl$_3$)* δ 8.76-8.70 (m, 3H), 8.32 (d, J = 8.6 Hz, 2H), 7.77 (d, J = 8.7 Hz, 2H), 7.50 (d, J = 5.6 Hz, 2H), 4.30-4.21 (m, 4H), 1.21-1.13 (m, 6H); ^{13}C NMR (100 MHz, *CDCl$_3$)* δ 165.8, 165.7, 158.3, 157.9, 149.6, 148.2, 146.6, 145.0, 141.2, 130.0, 126.0, 126.0, 123.3, 123.2, 62.3, 13.8, 13.6; IR (cm^{-1}): 3031, 2981, 1725, 1572, 1428, 1367, 1263, 1078; MS (ES mass) m/z: 422.3[M + 1].

(E)-diethyl 2-(4-nitrophenyl)-6-styrylpyridine-3,5-dicarboxylate (68h):



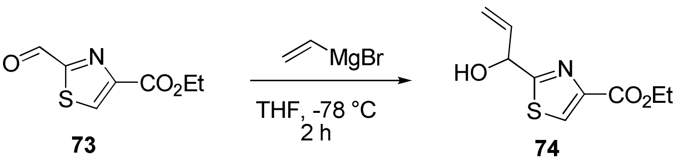
Pale yellow solid, m.p: 127-129 °C; R$_f$ = 0.3 (10% EtOAc in hexane). ^{1}H NMR (400 MHz, *CDCl$_3$)* δ 8.75 (s, 1H), 8.37-8.32 (m, 2H), 8.23 (d, J = 15.6 Hz, 1H), 8.09 (d, J = 15.6 Hz, 1H) 7.79 (d, J = 8.7 Hz, 2H), 7.65 (d, J = 7.0 Hz, 2H), 7.43-7.33 (m, 3H), 4.49 (q, J = 7.1 Hz, 2H), 4.23 (q, J = 7.1 Hz, 2H), 1.48 (t, J = 7.1 Hz, 3H), 1.16 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, *$CDCl_3$*) δ 166.1, 165.4, 158.6, 156.7, 148.0, 146.1, 141.9, 139.1, 136.2, 129.9, 129.3, 128.8, 127.9, 123.8, 123.2, 122.6, 62.0, 61.8, 14.3, 13.8; IR (cm^{-1}): 3050, 2981, 1719, 1573, 1448, 1347, 1236, 1089; MS (ES mass) m/z: 447.3[M + 1].

tert-Butyl 3-amino-2-methyl-5-oxo-2,5-dihydro-1H-pyrrole-1-carboxylate (71):



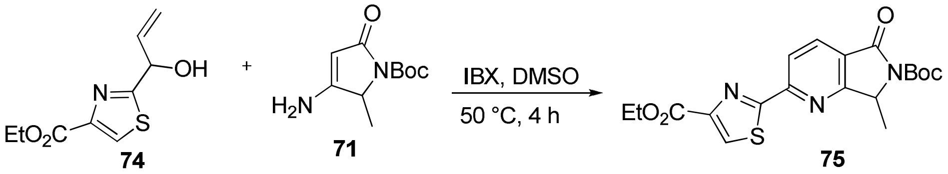
To a stirred solution of *tert*-butyl 2-methyl-3,5-dioxopyrrolidine-1-carboxylate **70**[31] (213 mg, 1 mmol) in dry MeOH (15 mL) was added NH_4OAc (385 mg, 5 mmol) under nitrogen. The mixture was heated to reflux and stirred overnight at the same temperature. After completion of the reaction the mixture was cooled to room temperature and evaporated under vacuo. The residue was dissolved in EtOAc (10 mL) and washed with saturated $NaHCO_3$ solution. The aqueous layer was further extracted with EtOAc (3 x 3 mL). The combined organic layers were collected, combined, washed with brine, dried over anhydrous Na_2SO_4, filtered and evaporated under *vacuo*. The residue was purified by flash chromatography using EtOAc to give the desired compound **71** (0.171 g, 80% yield) as a pale yellow solid; mp 88-90 °C; R_f = 0.2 (5% MeOH in DCM); ^{1}H NMR (400 MHz, *$CDCl_3$*) δ 5.26 (brs, 2H), 4.79 (s, 1H), 4.39 (q, *J* = 6.5 Hz, 1H), 1.52 (s, 9H), 1.50 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (100 MHz, *$CDCl_3$*) δ 171.1, 167.2, 149.5, 89.6, 81.8, 56.1, 28.2, 19.0; IR (cm^{-1}): 3345, 3271, 2981, 1745, 1672, 1597, 1349, 1255, 1159, 1086; MS (ES mass) m/z: 235.2[M + Na].

Ethyl 2-(1-hydroxyallyl)thiazole-4-carboxylate (74):



To a stirred solution of ethyl 2-formylthiazole-4-carboxylate **73**[32] (0.093 g, 0.05 mmol) in THF (5 mL) at -78 °C was added vinyl magnesium bromide (0.75 mL, 1.5 eq., 1M solution in THF). The mixture was stirred for 2 h and then quenched with saturated ammonium chloride solution. Aqueous layer was further extracted with EtOAc (3 x 5 mL). The organic layers were collected, combined, washed with brine, dried over anhydrous Na_2SO_4 and filtered. After removal of EtOAc under reduced pressure, the residue was purified by flash chromatography using 8% EtOAc in hexane to give the desired compound **74** (0.081 g, 76% yield) as a yellow color oil; R_f = 0.5 (20% EtOAc in hexane); ^{1}H NMR (400 MHz, *$CDCl_3$*) δ 8.15 (s, 1H), 6.22-6.08 (m, 1H), 5.60 (d, *J* = 5.6 Hz, 1H), 5.54 (d, *J* =17.1 Hz, 1H), 5.33 (d, *J* = 10.4 Hz, 1H), 4.41 (q, *J* = 7.1 Hz, 2H), 1.39 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, *$CDCl_3$*) δ 174.4, 161.3, 146.9, 137.1, 127.8, 117.3, 72.4, 61.5, 14.3. IR (cm^{-1}): 3450, 3113, 2981, 1723, 1589, 1482, 1368, 1215, 110, 1053; MS (ES mass) m/z: 214.2[M + 1].

Ethyl 2-(6-(tert-butoxycarbonyl)-7-methyl-5-oxo-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-2-yl)thiazole-4-carboxylate (75):



A mixture of enamine **74** (22 mg, 0.1 mmol), allyl alcohol **71** (23 mg, 0.1 mmol) and IBX (1.2 equiv.) in DMSO (2 mL) was stirred at 50 °C for 4h. After completion of the reaction (monitored by TLC), the mixture was quenched with sat. $NaHCO_3$ solution and extracted with EtOAc (3 x 3 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated under low vacuum. The crude compound was purified by flash chromatography using 30% EtOAc in Hexane to give the desired compound **75** (0.029 g, 70% yield) as a colorless solid; mp 161-163 °C; R_f = 0.3 (30% EtOAc in hexane); ^{1}H NMR (400 MHz, *$CDCl_3$*) δ 8.47 (d, *J* = 8.0 Hz, 1H), 8.34 (s, 1H), 8.27 (d, *J* = 8.0 Hz, 1H), 5.13 (q, *J* = 6.6 Hz, 1H), 4.47 (q, *J* = 7.1 Hz, 2H), 1.75 (d, *J* = 6.6 Hz, 3H), 1.63 (s, 9H), 1.45 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, *$CDCl_3$*) δ 168.2, 165.8, 164.2, 161.1, 154.9, 149.7, 148.8, 134.3, 130.5, 125.0, 120.4, 83.6, 61.6, 57.8, 28.1, 18.8, 14.3; IR (cm^{-1}): 2979, 2926, 2851, 1780, 1740, 1721, 1595, 1369, 1208, 1159, 1099, 1015; MS (ES mass) m/z: 404.3[M + 1].

5.6. References

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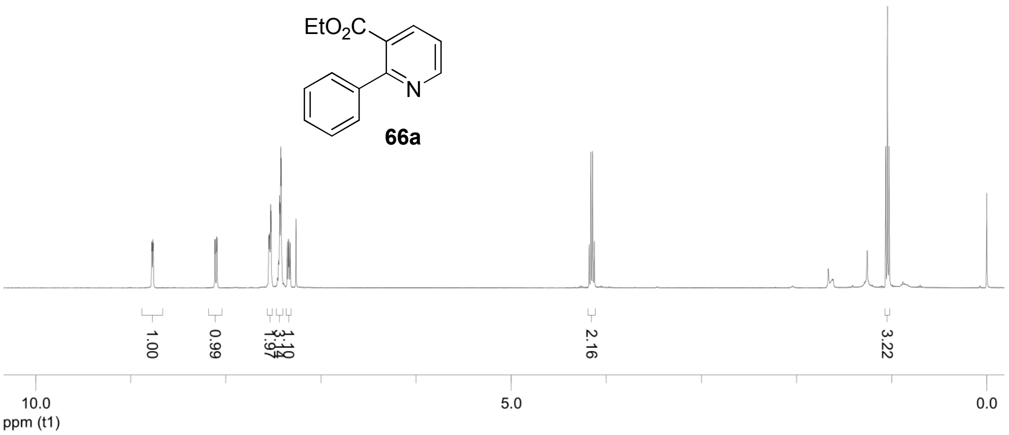
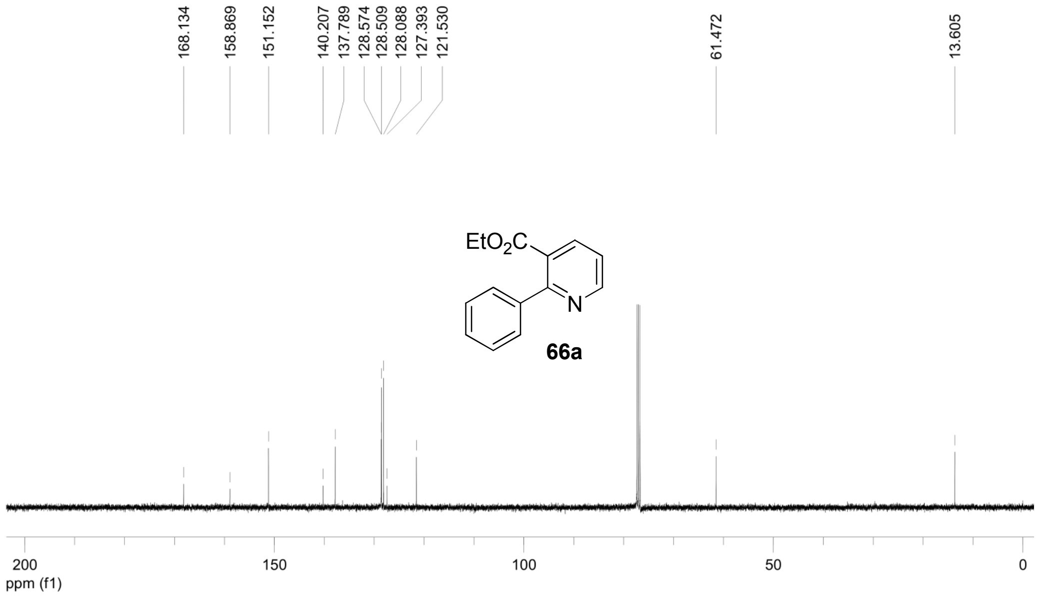
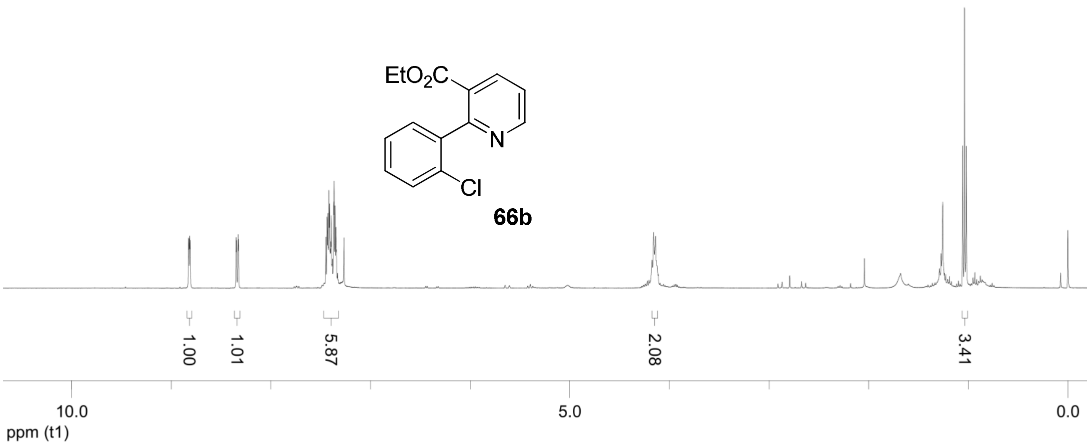
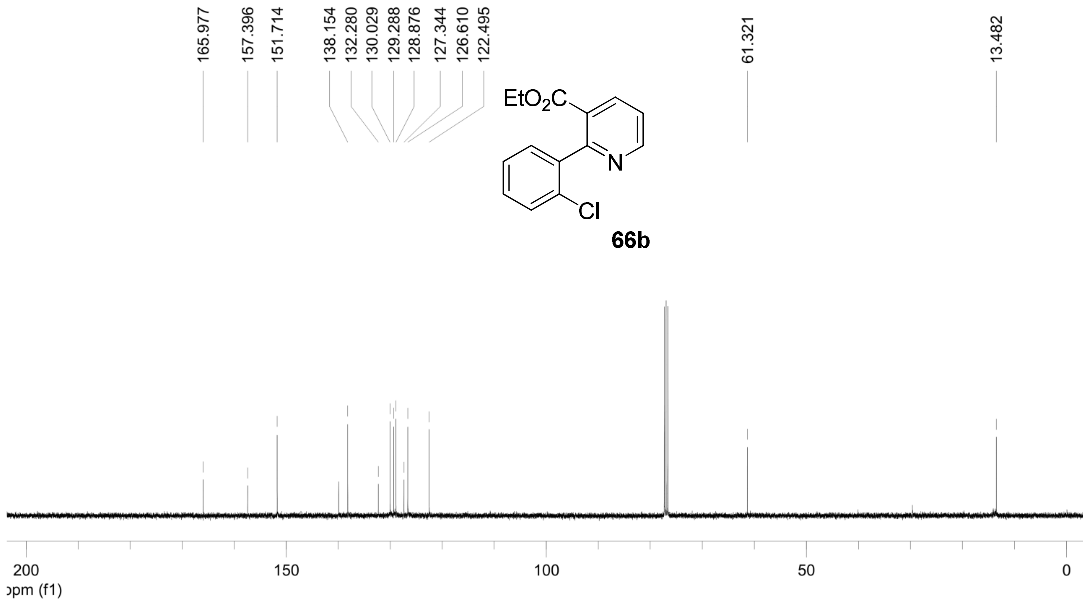
5.7. NMR Spectra





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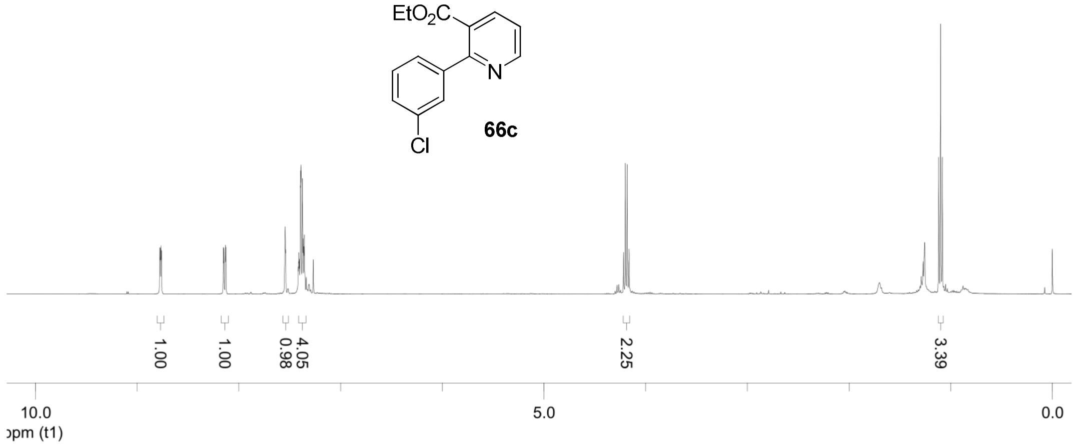
66b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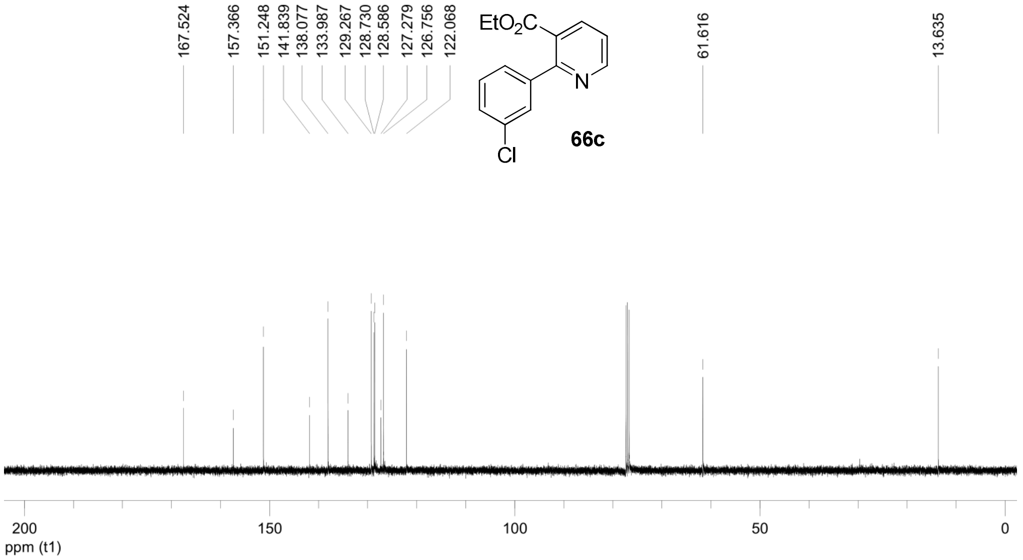
66c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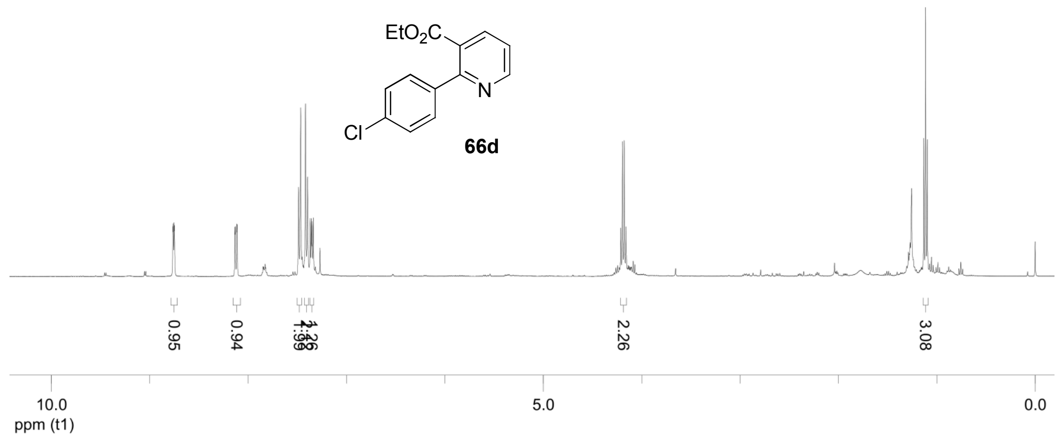
66c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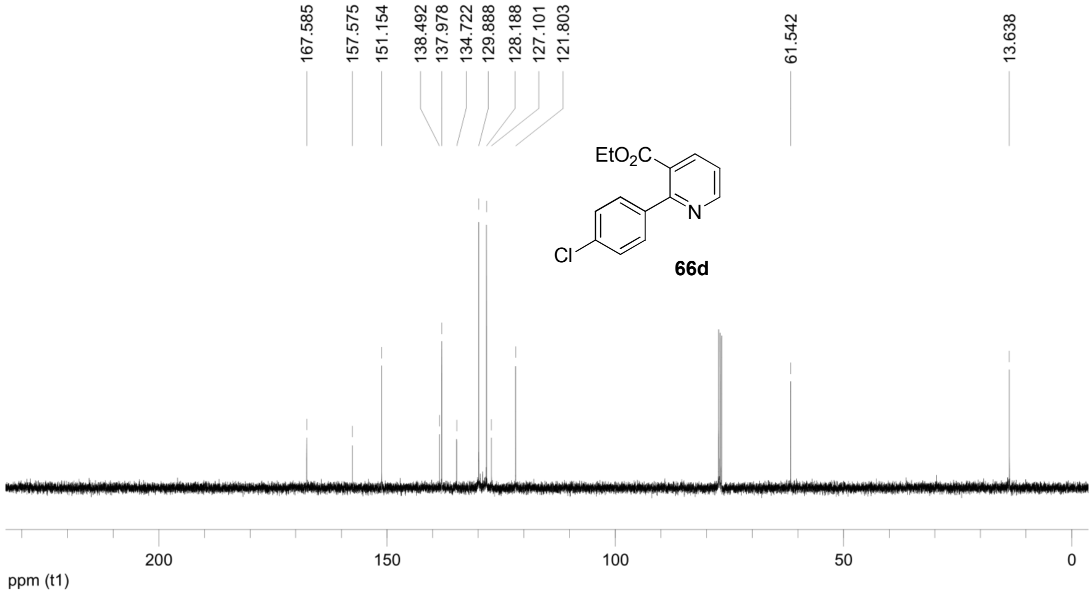
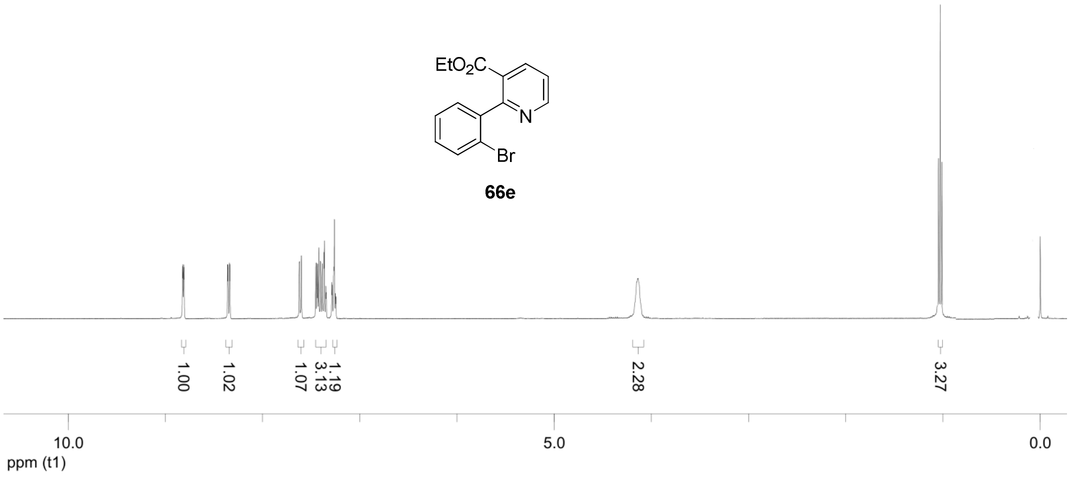
ppm (t1)

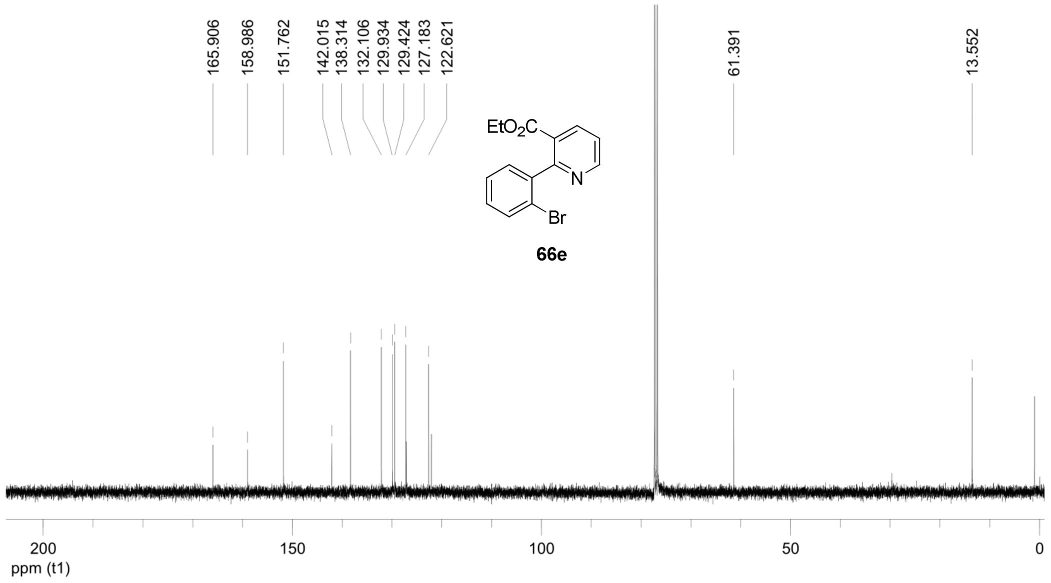
66d

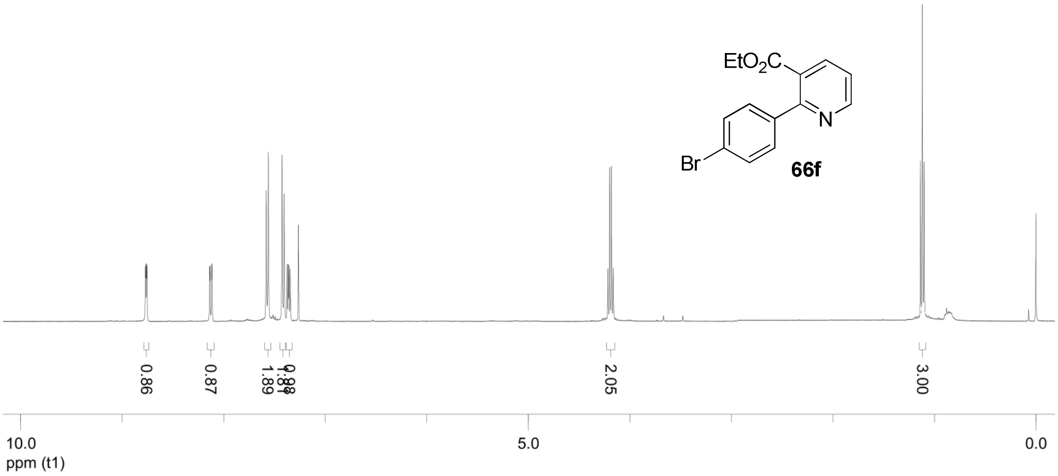

167.585
157.575
151.154
138.492
137.978
134.722
129.888
128.188
127.101
121.803
61.542
13.638
EtO2C
N
Cl
200
150
100
50
0
ppm (t1)

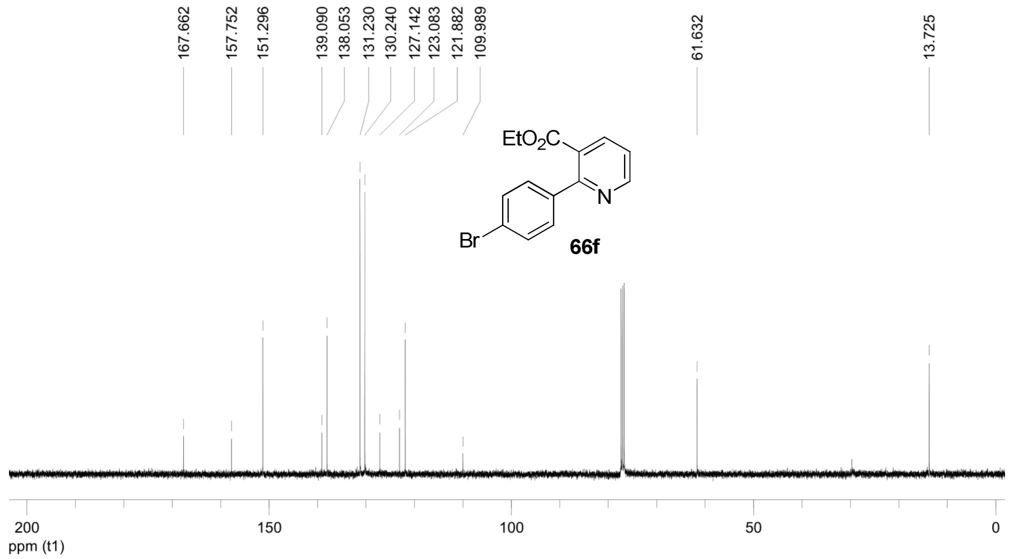
66d

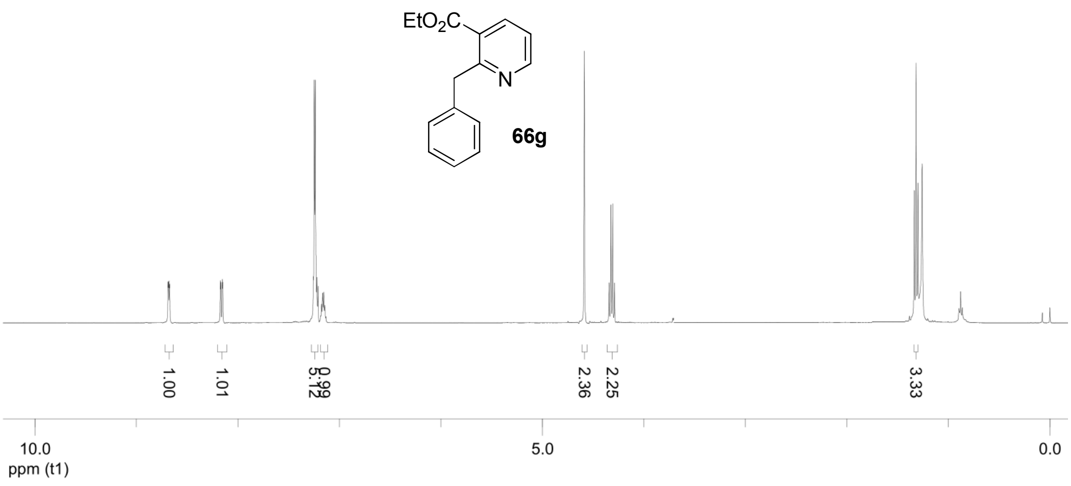

EtO2C
N
Br
1.00
1.02
1.07
3.13
1.19
2.28
3.27
10.0
5.0
0.0
ppm (t1)

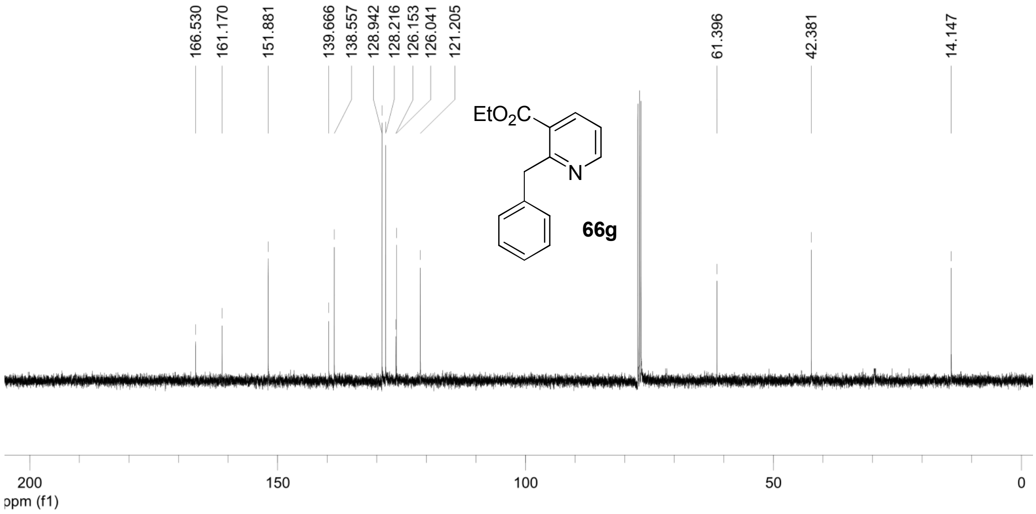
66e

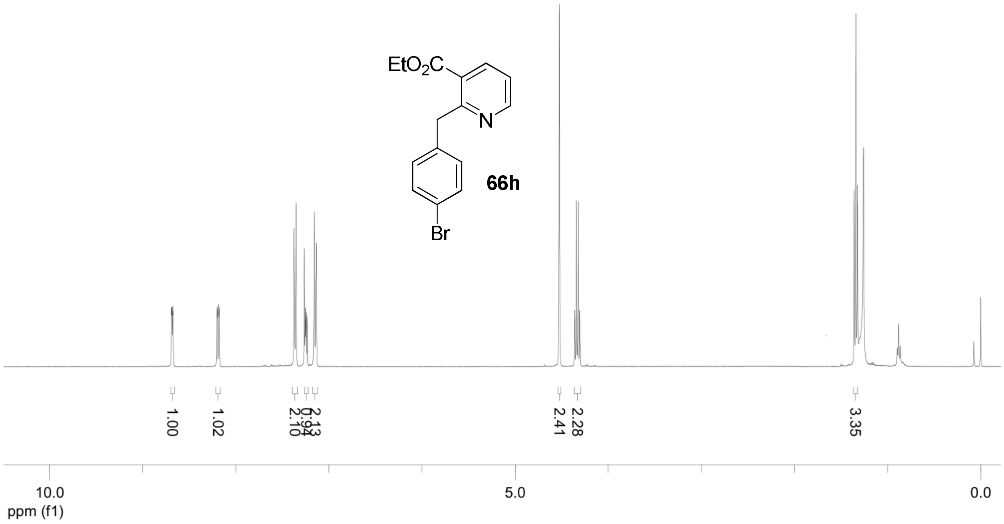

165.906
158.986
151.762
142.015
138.314
132.106
129.934
129.424
127.183
122.621
61.391
13.552
EtO_2C
N
Br
66e
200
150
100
50
0
ppm (t1)

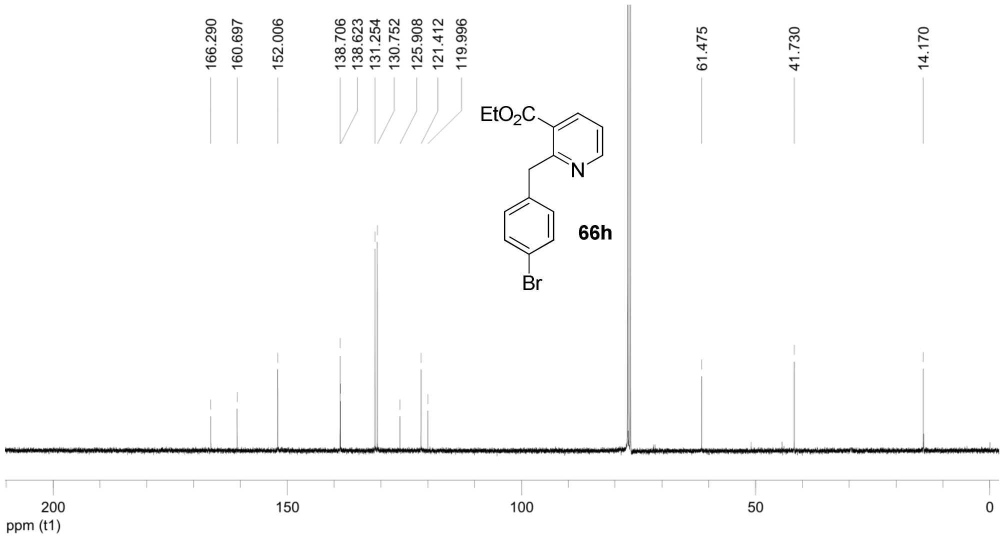

EtO_2C
N
Br
66f
0.86
0.87
1.89
1.81
0.88
2.05
3.00
10.0
5.0
0.0
ppm (t1)

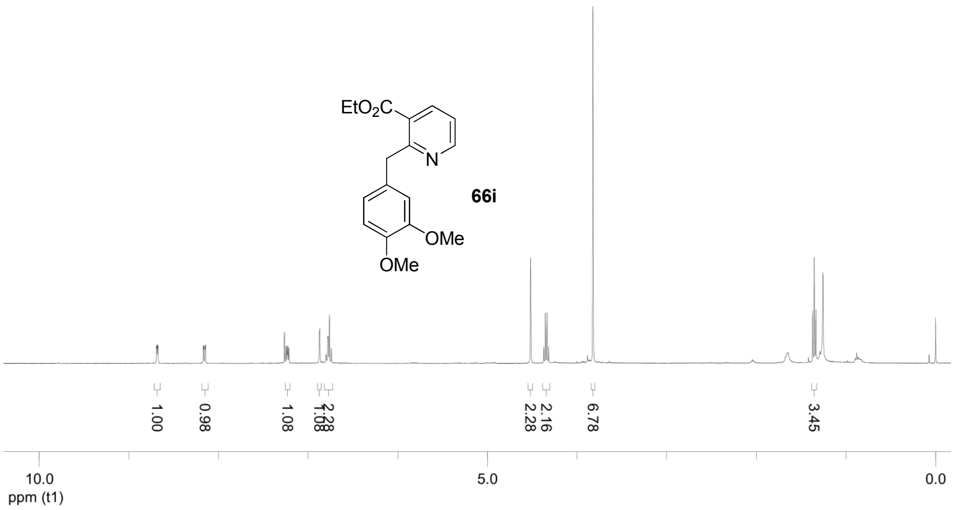

167.662
157.752
151.296
139.090
138.053
131.230
130.240
127.142
123.083
121.882
109.989
61.632
13.725
EtO_2C
N
Br
66f
200
150
100
50
0
ppm (t1)

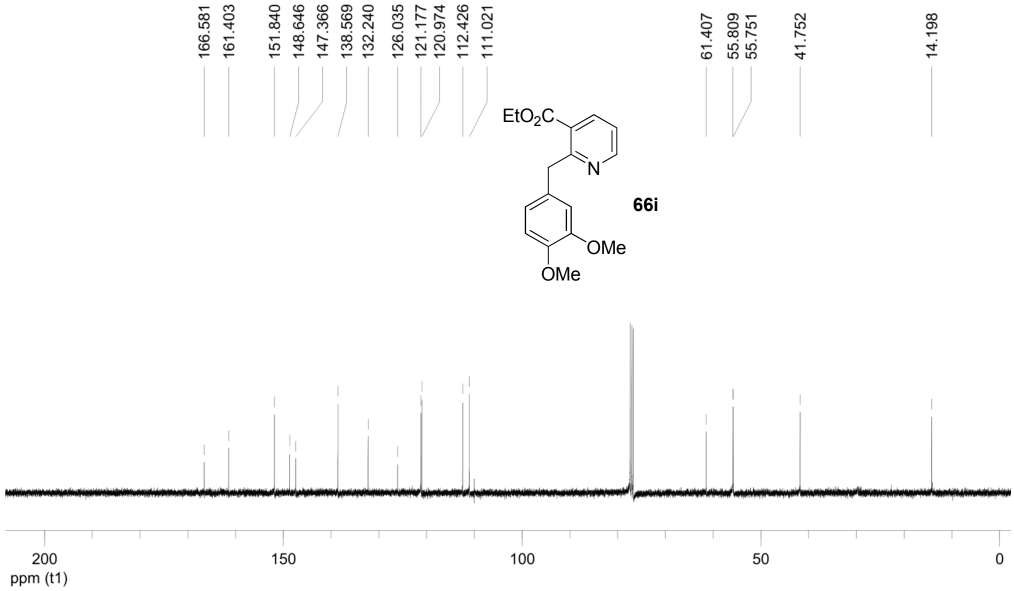

EtO2C
N
66g
1.00
1.01
5.12
0.99
2.36
2.25
3.33
10.0
ppm (t1)
5.0
0.0

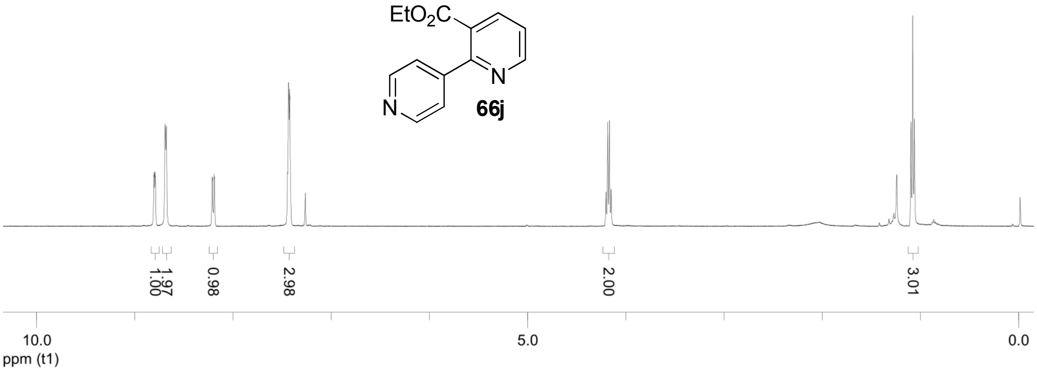

166.530
161.170
151.881
139.666
138.557
128.942
128.216
126.153
126.041
121.205
61.396
42.381
14.147
EtO2C
N
66g
200
ppm (f1)
150
100
50
0

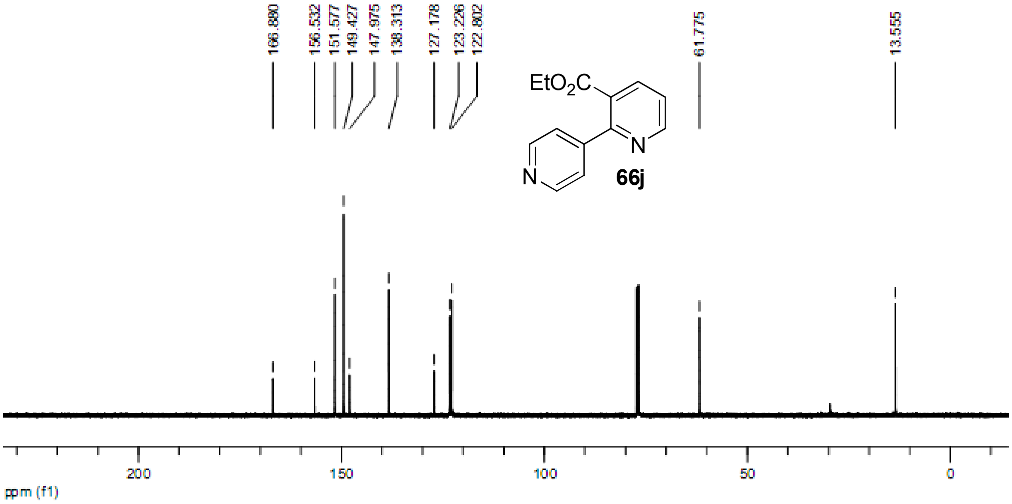

EtO2C
N
66h
Br
1.00
1.02
2.10
0.94
2.13
2.41
2.28
3.35
10.0
ppm (f1)
5.0
0.0

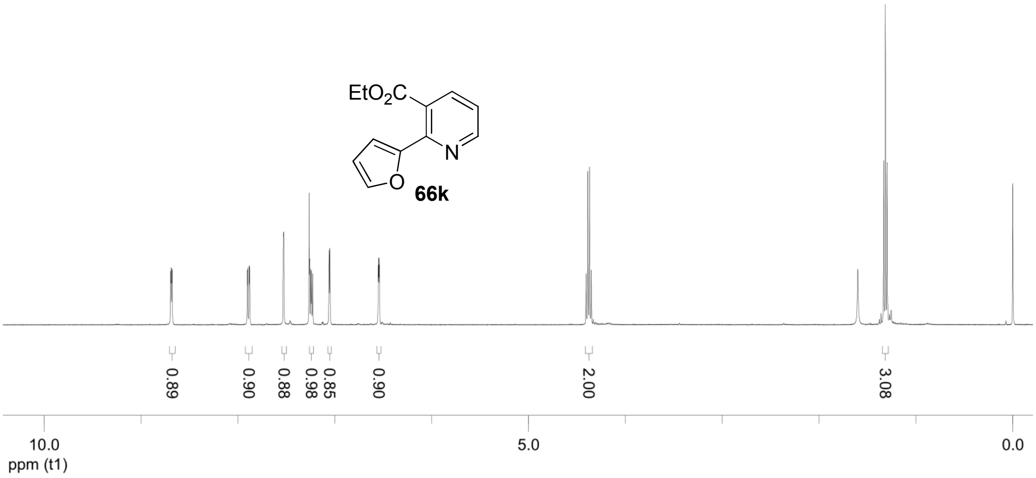

166.290
160.697
152.006
138.706
138.623
131.254
130.752
125.908
121.412
119.996
61.475
41.730
14.170
EtO2C
N
Br
66h
200
150
100
50
0
ppm (t1)

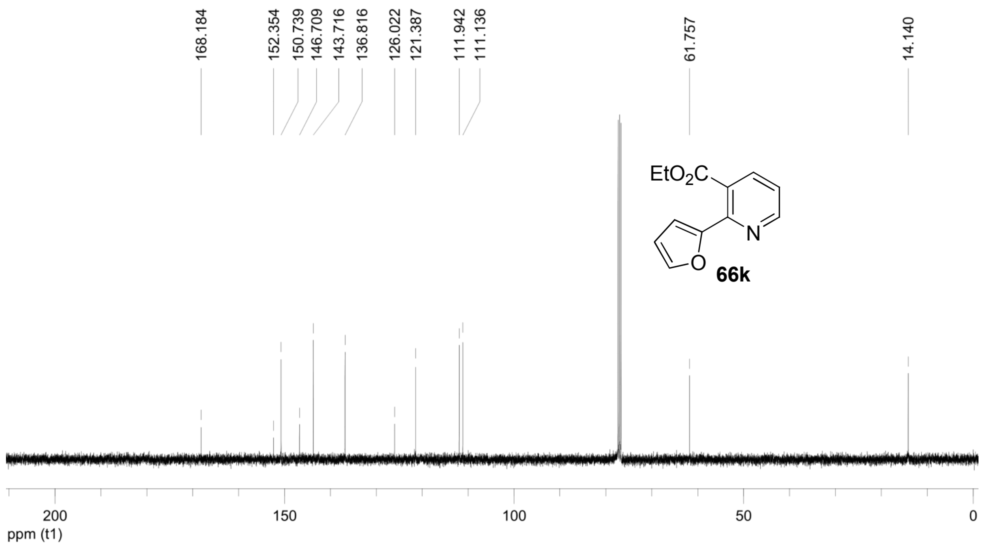

EtO2C
N
OMe
OMe
66i
1.00
0.98
1.08
1.08
2.28
2.28
2.16
6.78
3.45
10.0
5.0
0.0
ppm (t1)

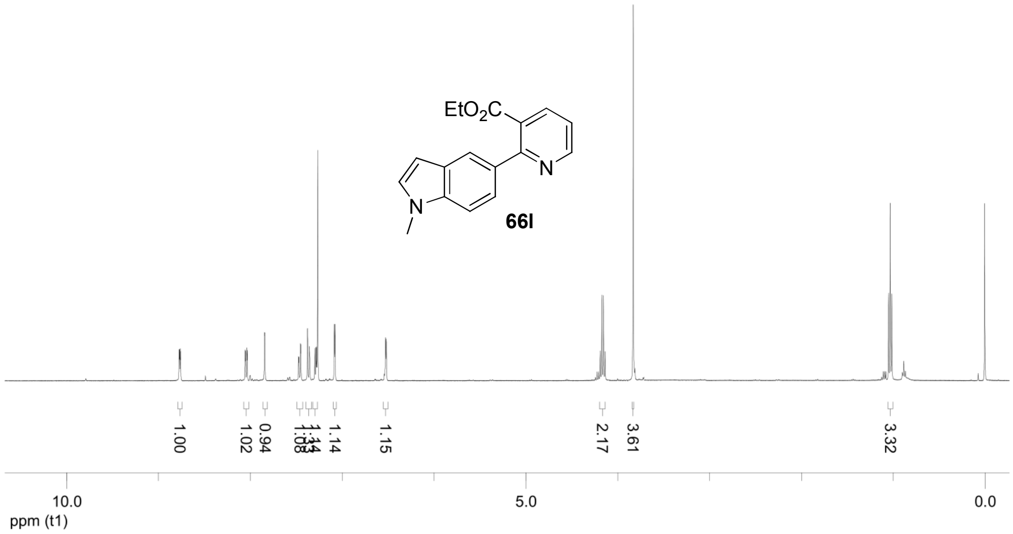

166.581
161.403
151.840
148.646
147.366
138.569
132.240
126.035
121.177
120.974
112.426
111.021
61.407
55.809
55.751
41.752
14.198
EtO2C
N
OMe
OMe
66i
200
150
100
50
0
ppm (t1)

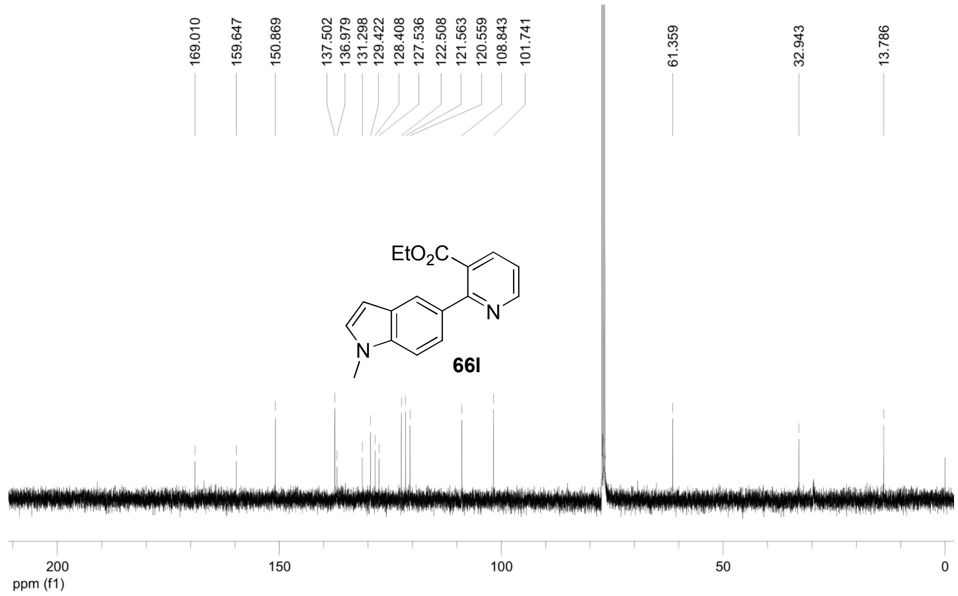

EtO2C
N
N
66j
1.00
1.97
0.98
2.98
2.00
3.01
10.0
5.0
0.0
ppm (t1)

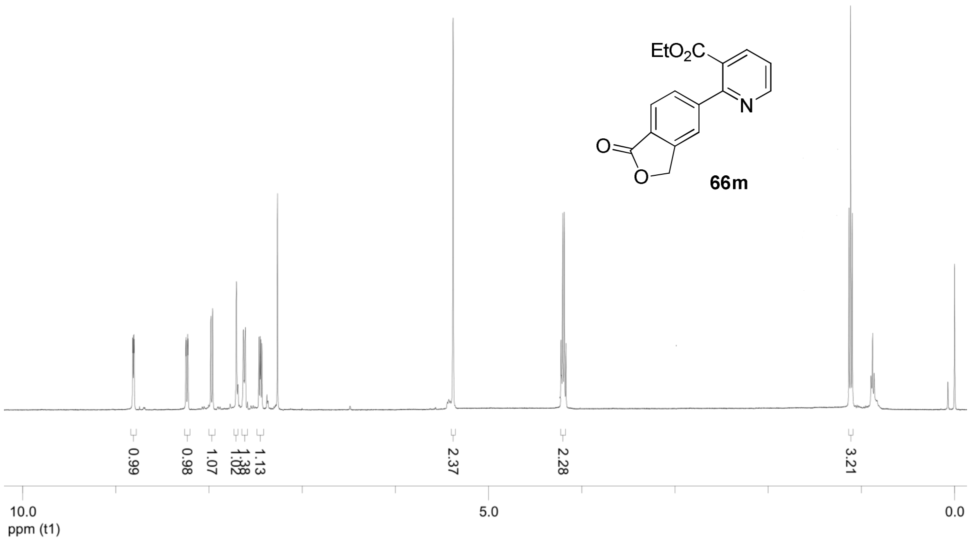

166.880
156.532
151.577
149.427
147.975
138.313
127.178
123.226
122.802
61.775
13.555
EtO2C
N
N
66j
200
150
100
50
0
ppm (f1)

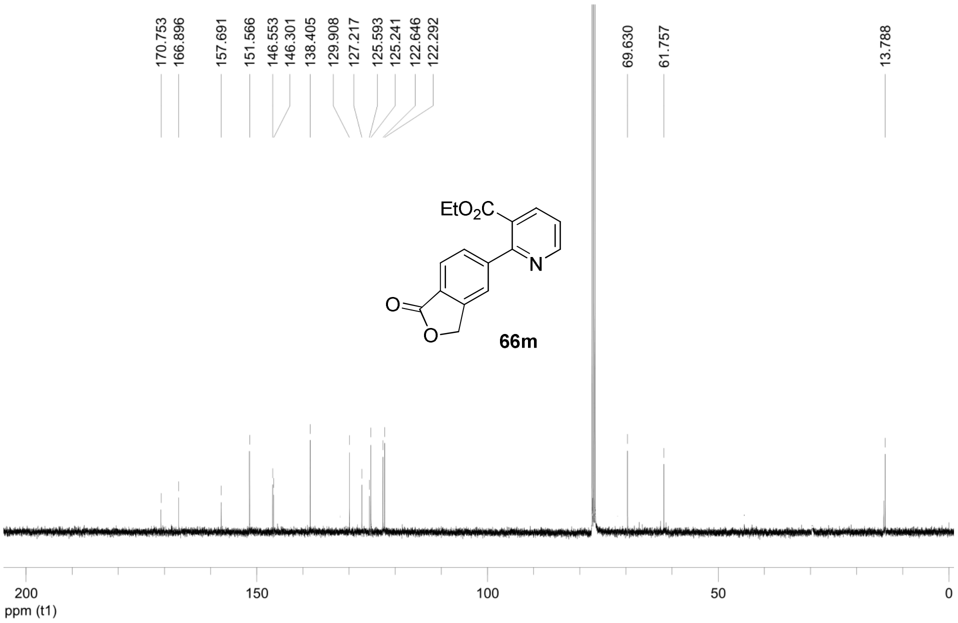

EtO2C
N
O
66k
0.89
0.90
0.88
0.98
0.85
0.90
2.00
3.08
10.0
5.0
0.0
ppm (t1)

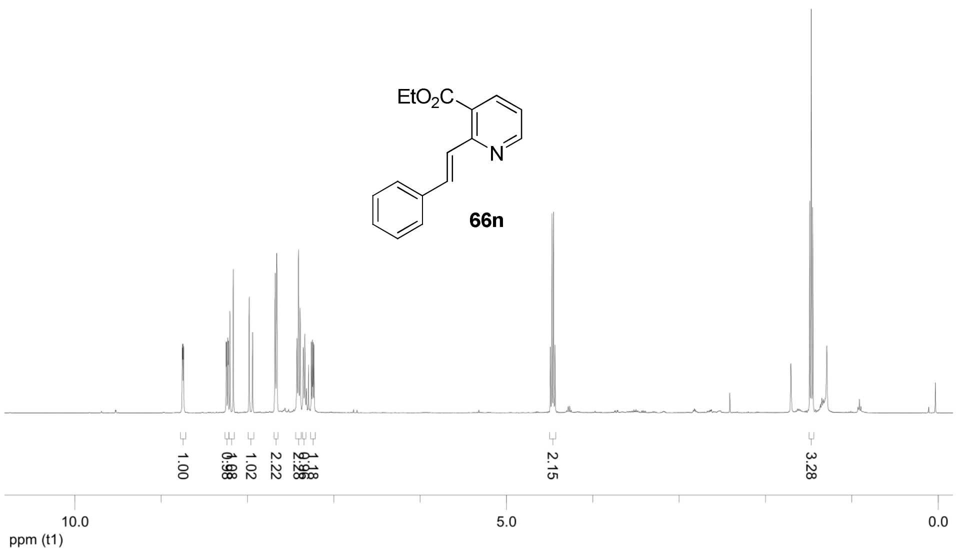

168.184
152.354
150.739
146.709
143.716
136.816
126.022
121.387
111.942
111.136
61.757
14.140
EtO$_2$C
N
O
66k
200
150
100
50
0
ppm (t1)

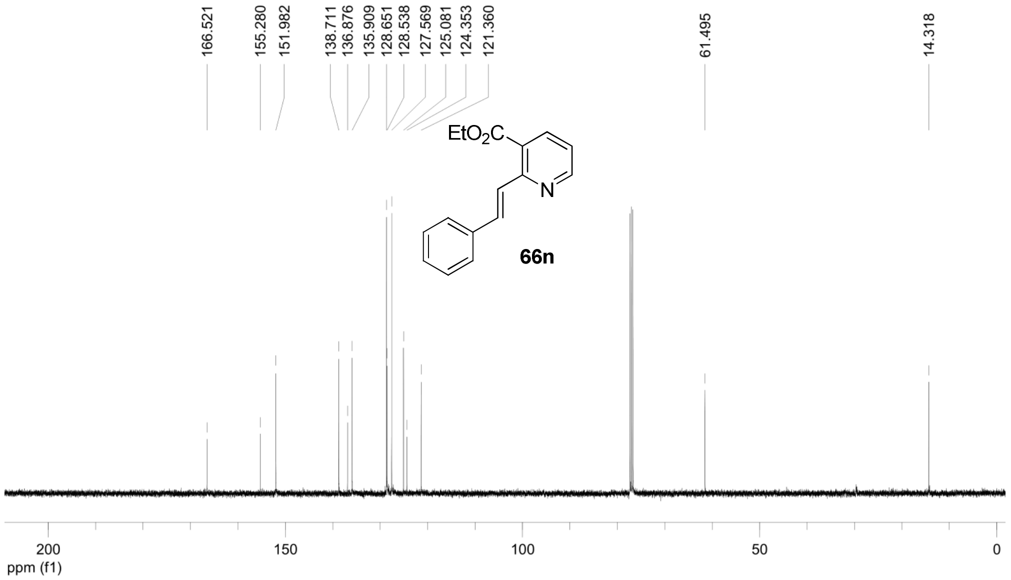

EtO$_2$C
N
N
66l
1.00
1.02
0.94
1.08
1.13
1.14
1.14
1.15
2.17
3.61
3.32
10.0
5.0
0.0
ppm (t1)


169.010
159.647
150.869
137.502
136.979
131.298
129.422
128.408
127.536
122.508
121.563
120.559
108.843
101.741
61.359
32.943
13.786
EtO$_2$C
N
N
66l
200
150
100
50
0
ppm (f1)

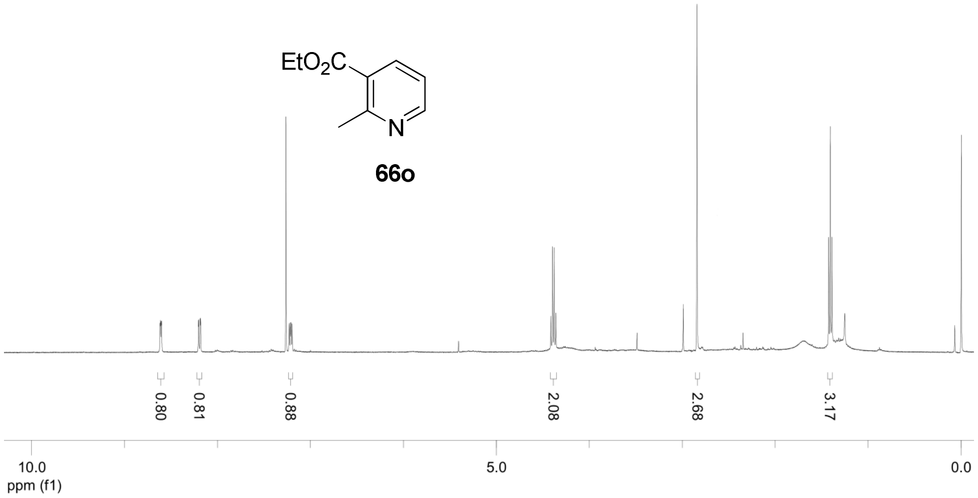

EtO2C
N
O
O
66m
0.99
0.98
1.07
1.02
1.38
1.13
2.37
2.28
3.21
10.0
ppm (t1)
5.0
0.0


170.753
166.896
157.691
151.566
146.553
146.301
138.405
129.908
127.217
125.593
125.241
122.646
122.292
69.630
61.757
13.788
EtO2C
N
O
O
66m
200
ppm (t1)
150
100
50
0

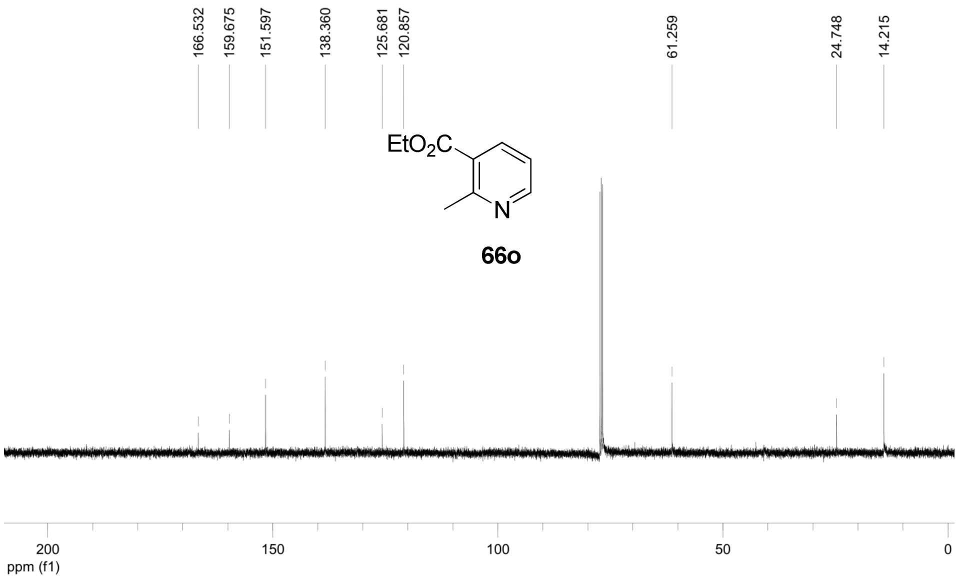

EtO2C
N
66n
1.00
0.98
1.08
1.02
2.22
2.28
0.96
1.18
2.15
3.28
10.0
ppm (t1)
5.0
0.0


166.521
155.280
151.982
138.711
136.876
135.909
128.651
128.538
127.569
125.081
124.353
121.360
61.495
14.318
EtO$_2$C
N
200
150
100
50
0
ppm (f1)

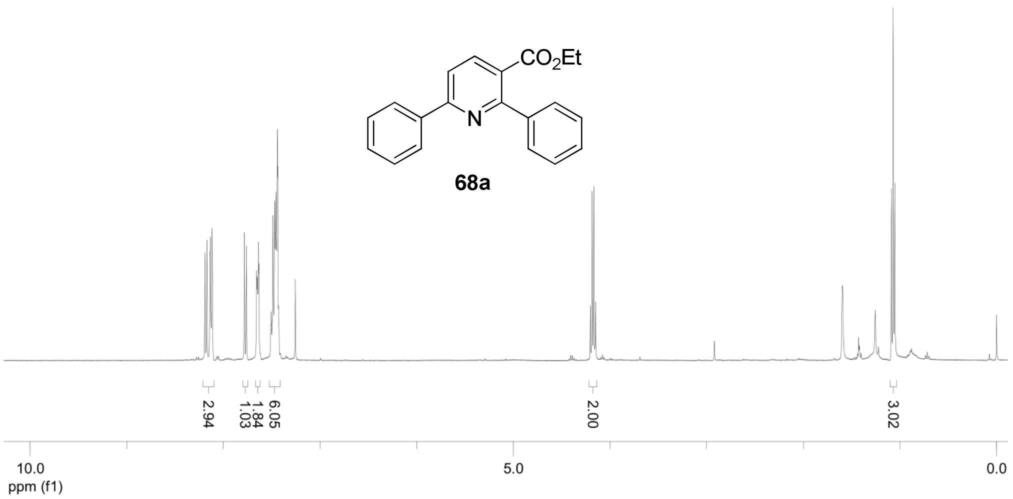
66n

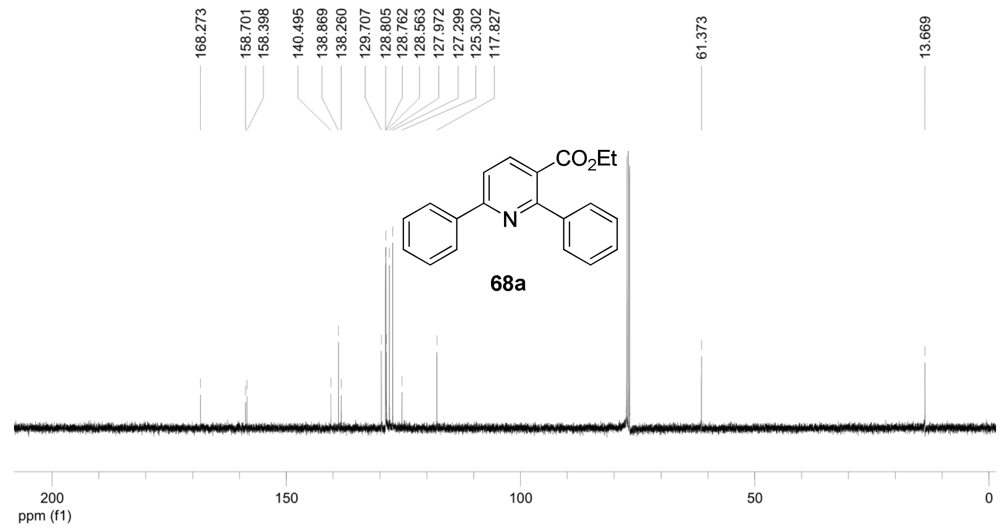

EtO$_2$C
N
0.80
0.81
0.88
2.08
2.68
3.17
10.0
5.0
0.0
ppm (f1)

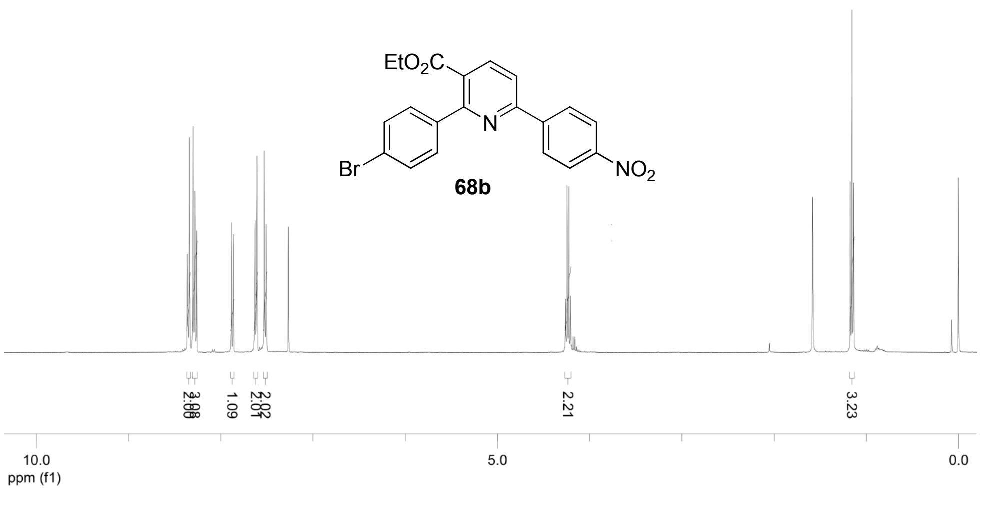
66o

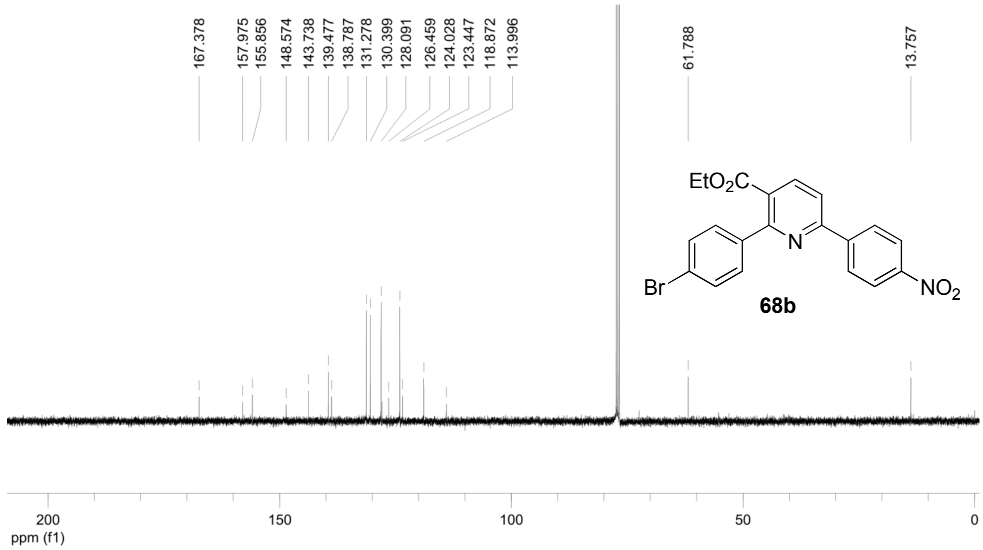

166.532
159.675
151.597
138.360
125.681
120.857
61.259
24.748
14.215
EtO$_2$C
N
200
150
100
50
0
ppm (f1)

66o


CO2Et
N
68a
2.94
1.03
1.84
6.05
2.00
3.02
10.0
ppm (f1)
5.0
0.0


168.273
158.701
158.398
140.495
138.869
138.260
129.707
128.805
128.762
128.563
127.972
127.299
125.302
117.827
61.373
13.669
CO2Et
N
68a
200
ppm (f1)
150
100
50
0

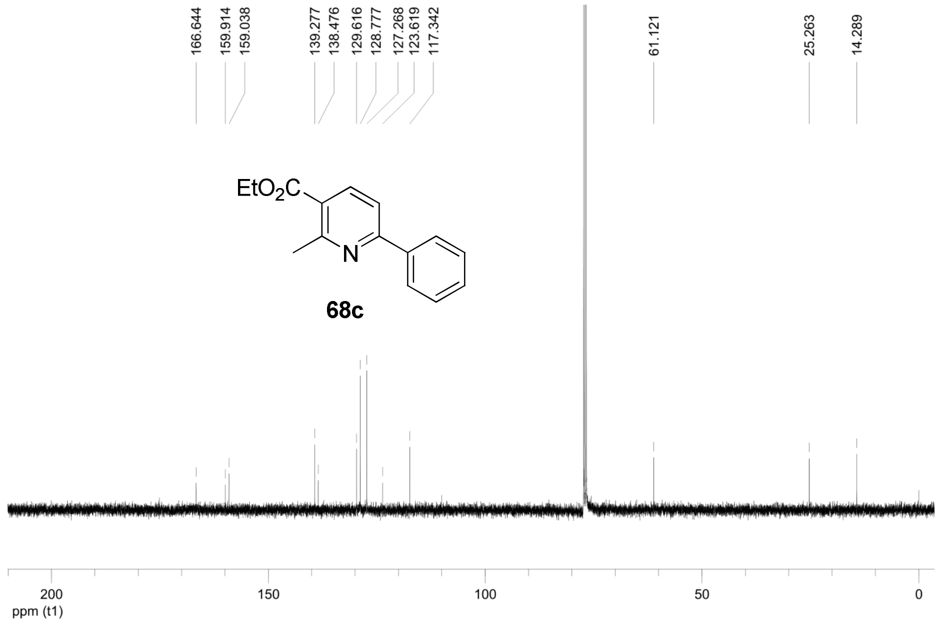

EtO2C
N
Br
NO2
68b
2.00
3.08
1.09
2.01
2.02
2.21
3.23
10.0
ppm (f1)
5.0
0.0


167.378
157.975
155.856
148.574
143.738
139.477
138.787
131.278
130.399
128.091
126.459
124.028
123.447
118.872
113.996
61.788
13.757
EtO2C
N
Br
NO2
200
150
100
50
0
ppm (f1)

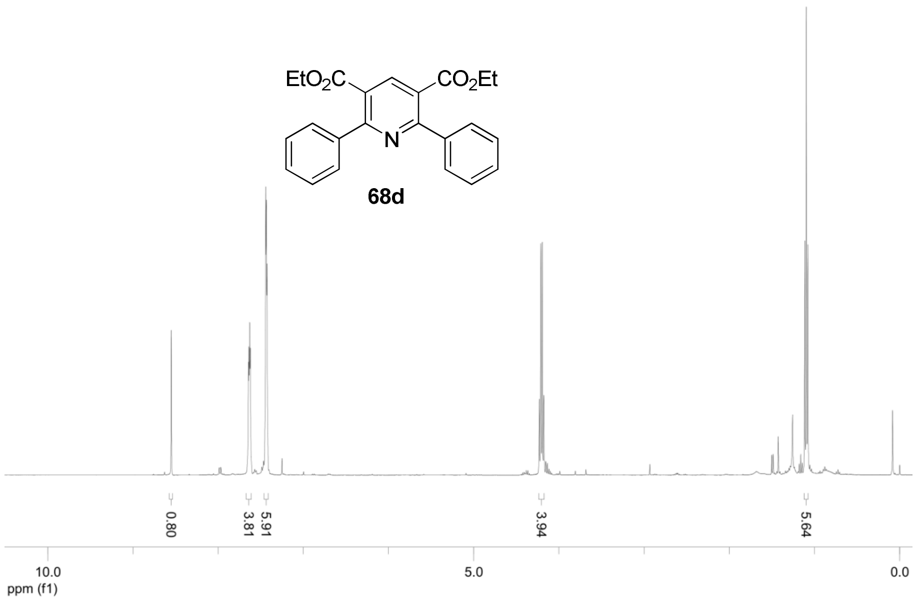
68b


EtO2C
N
1.05
2.17
1.13
3.17
2.22
3.00
3.28
10.0
5.0
0.0
ppm (t1)

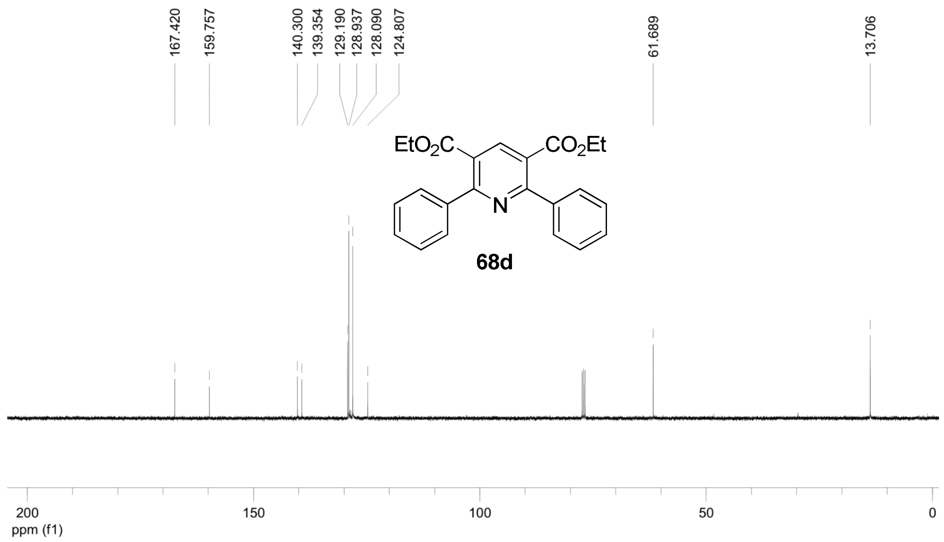
68c


166.644
159.914
159.038
139.277
138.476
129.616
128.777
127.268
123.619
117.342
61.121
25.263
14.289
EtO2C
N
200
150
100
50
0
ppm (t1)

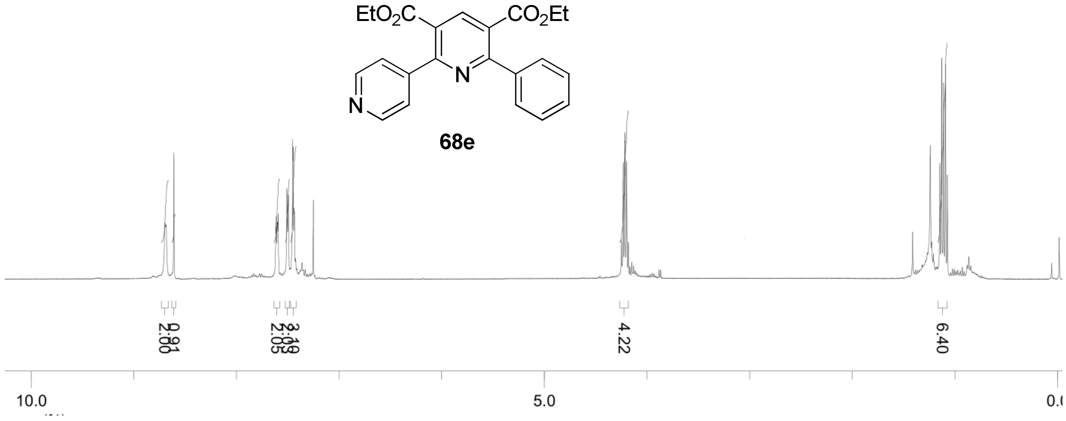
68c


EtO2C
CO2Et
N
0.80
3.81
5.91
3.94
5.64
10.0
5.0
0.0
ppm (f1)

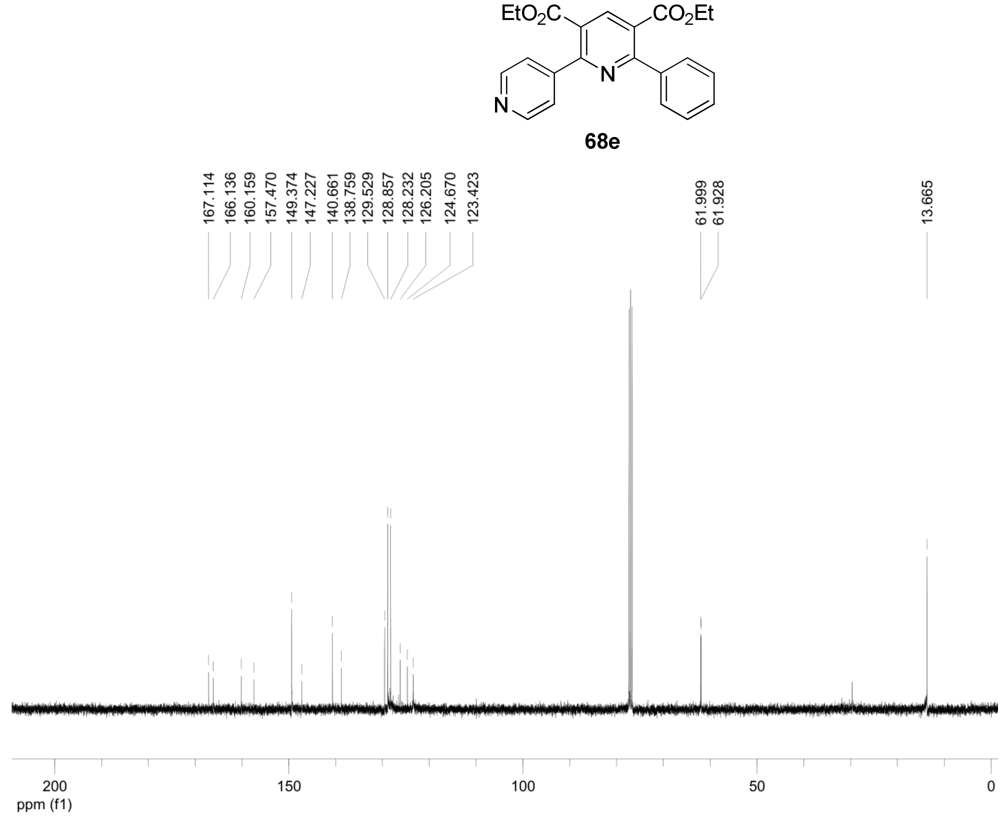
68d


167.420
159.757
140.300
139.354
129.190
128.937
128.090
124.807
61.689
13.706
EtO2C
CO2Et
N
200
150
100
50
0
ppm (f1)

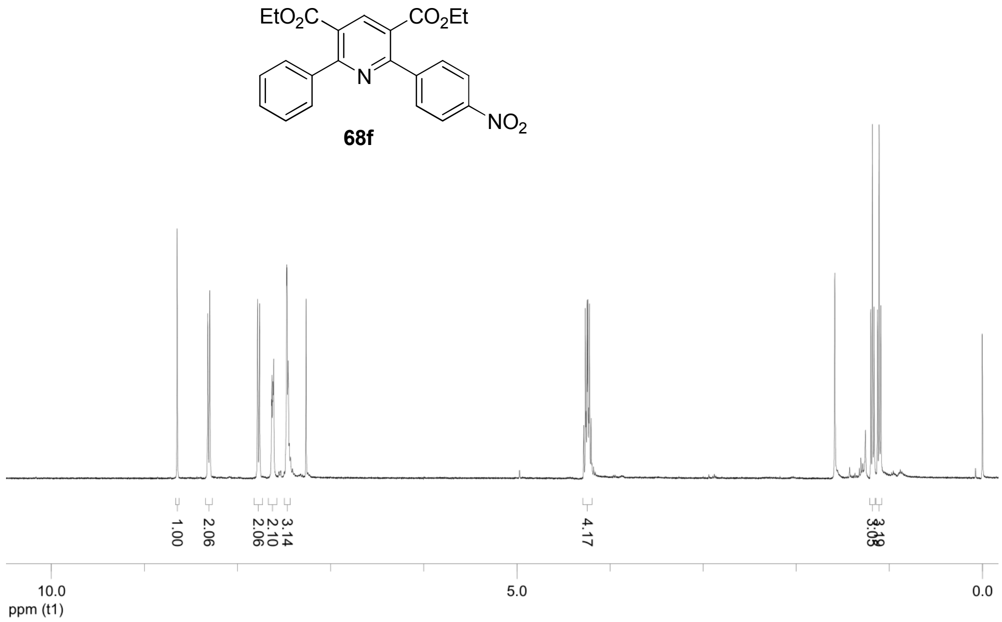
68d


EtO2C
CO2Et
N
N
2.00
0.91
2.05
2.03
3.19
4.22
6.40
10.0
5.0
0.0

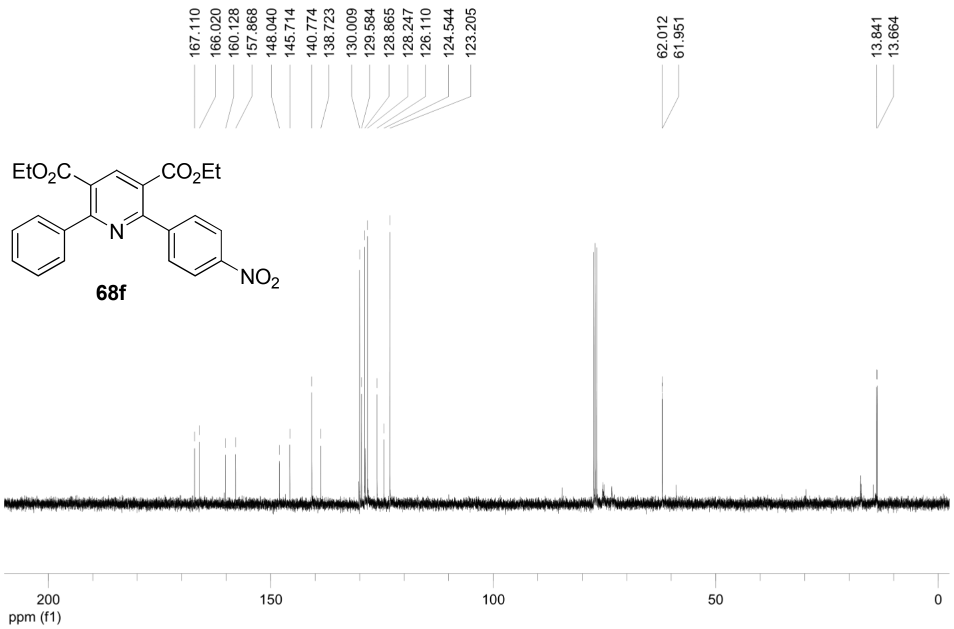
68e


EtO$_2$C
CO$_2$Et
N
N
167.114
166.136
160.159
157.470
149.374
147.227
140.661
138.759
129.529
128.857
128.232
126.205
124.670
123.423
61.999
61.928
13.665
200
150
100
50
0
ppm (f1)

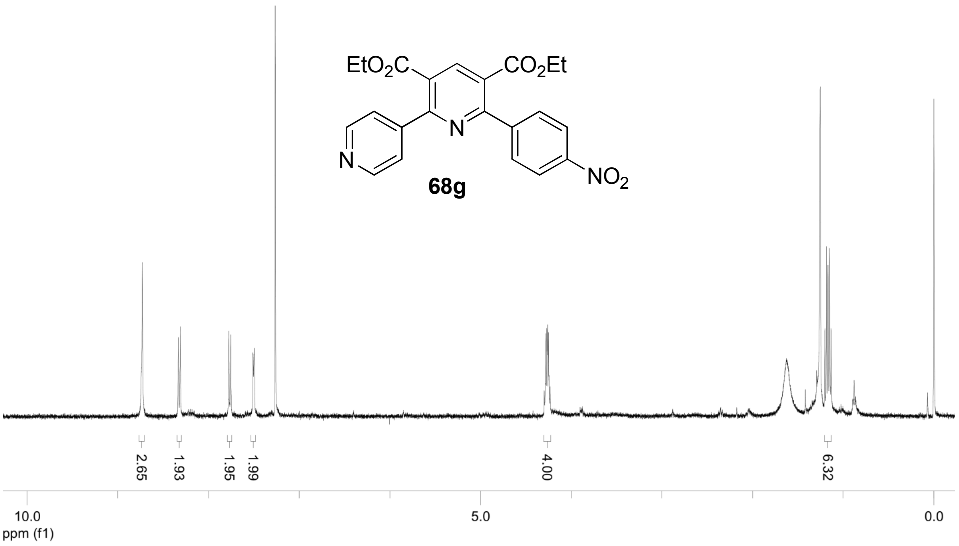
68e


EtO$_2$C
CO$_2$Et
N
NO$_2$
1.00
2.06
2.06
2.10
3.14
4.17
3.08
3.19
10.0
5.0
0.0
ppm (t1)

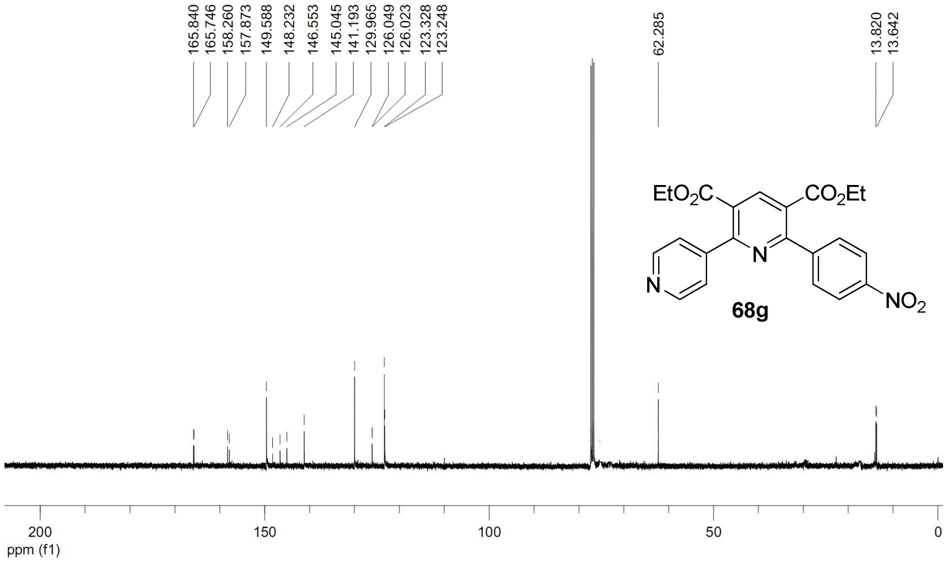
68f


167.110
166.020
160.128
157.868
148.040
145.714
140.774
138.723
130.009
129.584
128.865
128.247
126.110
124.544
123.205
62.012
61.951
13.841
13.664
EtO2C
CO2Et
N
NO2
200
150
100
50
0
ppm (f1)

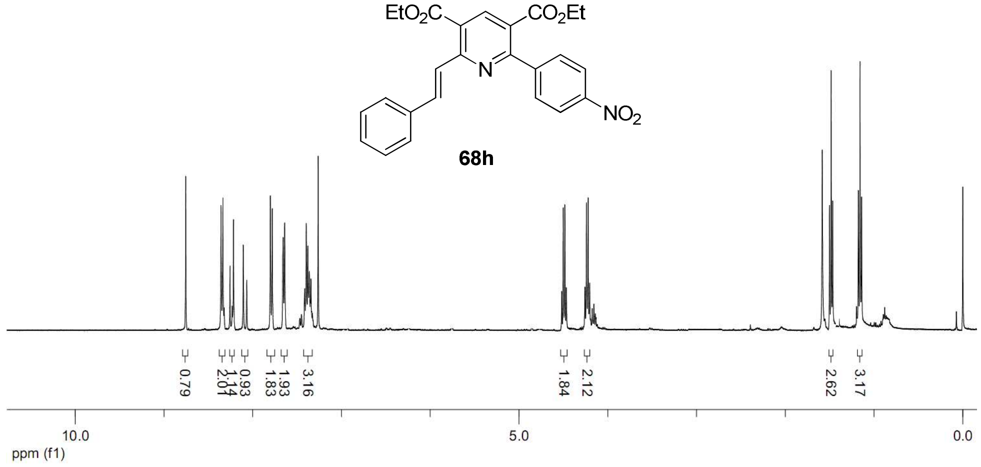
68f

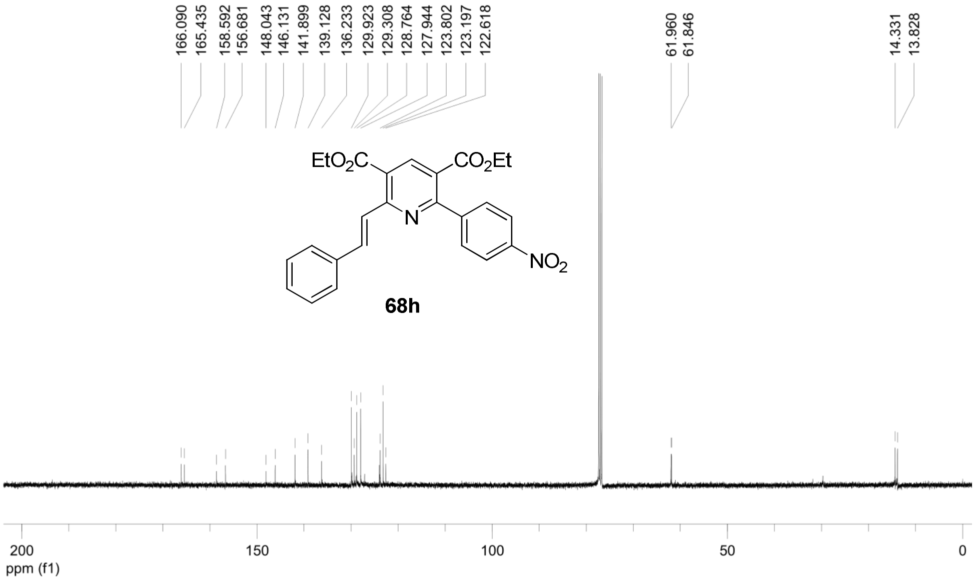

EtO2C
CO2Et
N
N
NO2
2.65
1.93
1.95
1.99
4.00
6.32
10.0
5.0
0.0
ppm (f1)

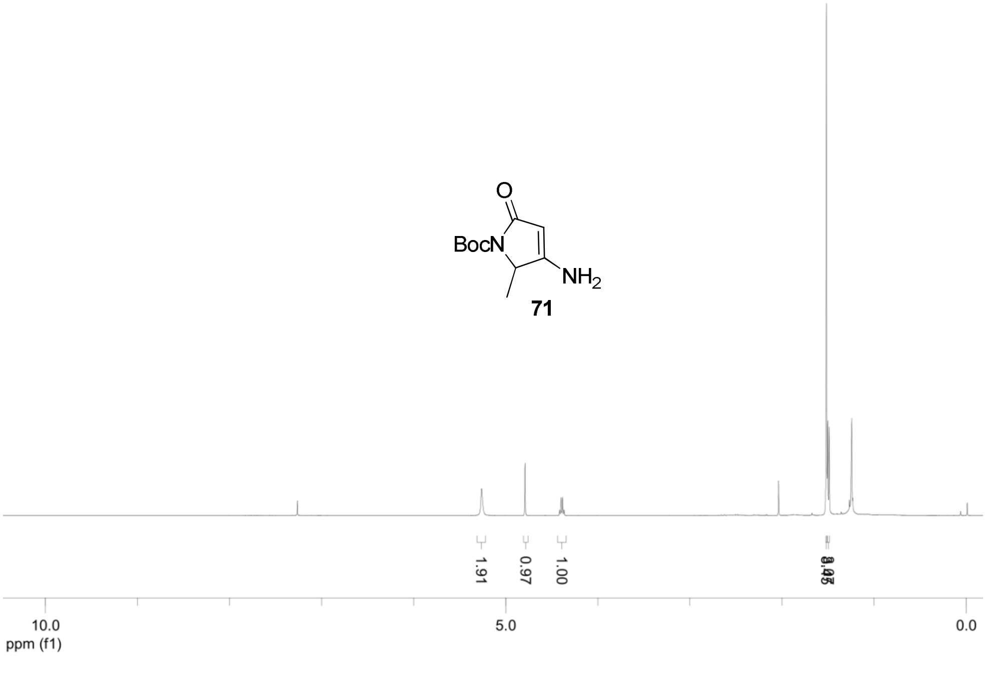
68g

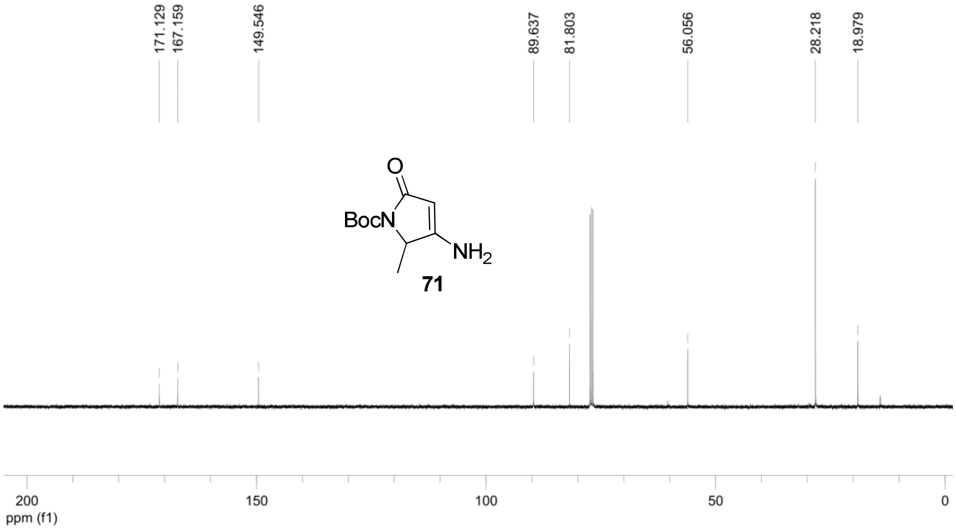

165.840
165.746
158.260
157.873
149.588
148.232
146.553
145.045
141.193
129.965
126.049
126.023
123.328
123.248
62.285
13.820
13.642
EtO2C
CO2Et
N
N
NO2
200
150
100
50
0
ppm (f1)

68g

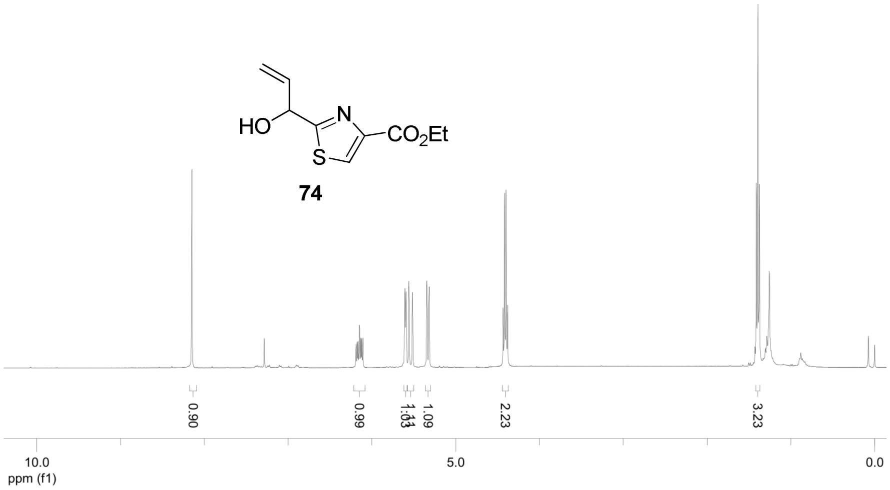

EtO$_2$C
CO$_2$Et
N
NO$_2$
68h
0.79
2.01
2.14
0.93
1.83
1.93
3.16
1.84
2.12
2.62
3.17
10.0
5.0
0.0
ppm (f1)


166.090
165.435
158.592
156.681
148.043
146.131
141.899
139.128
136.233
129.923
129.308
128.764
127.944
123.802
123.197
122.618
61.960
61.846
14.331
13.828
EtO$_2$C
CO$_2$Et
N
NO$_2$
68h
200
150
100
50
0
ppm (f1)

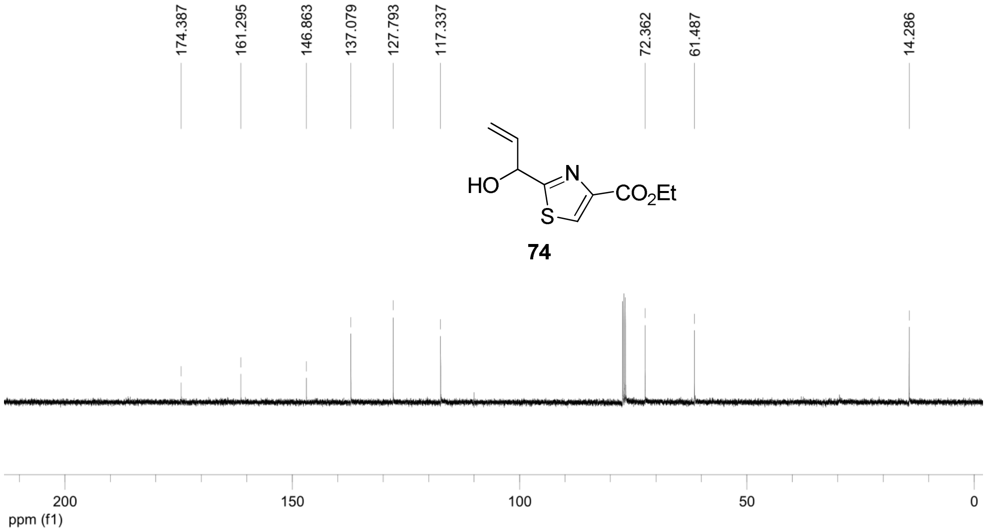

O
BocN
NH$_2$
71
1.91
0.97
1.00
10.0
5.0
0.0
ppm (f1)


171.129
167.159
149.546
89.637
81.803
56.056
28.218
18.979
O
BocN
NH2
200
150
100
50
0
ppm (f1)

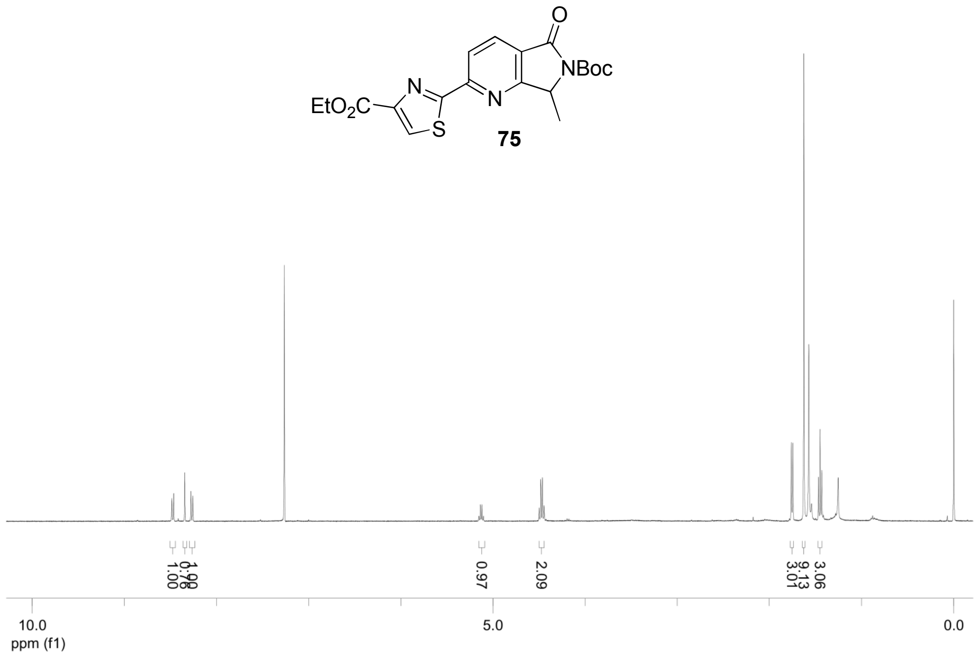
71


HO
N
S
CO2Et
0.90
0.99
1.01
1.03
1.09
2.23
3.23
10.0
5.0
0.0
ppm (f1)

74

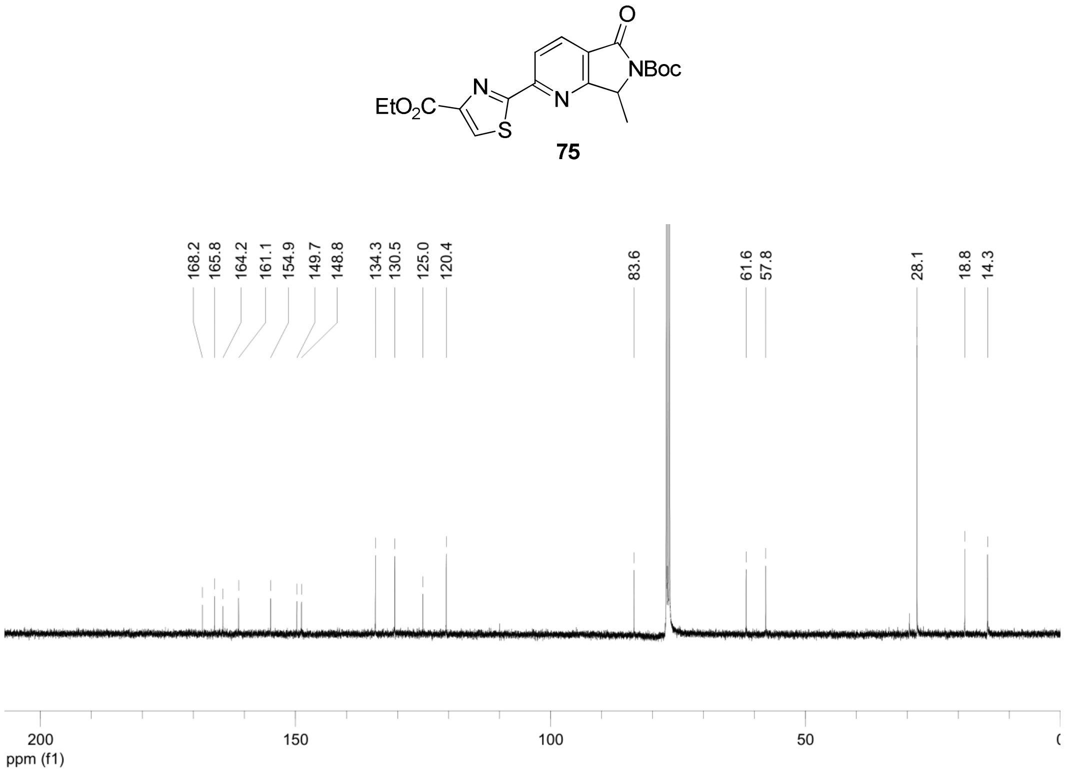

174.387
161.295
146.863
137.079
127.793
117.337
72.362
61.487
14.286
HO
N
S
CO2Et
200
150
100
50
0
ppm (f1)

74



75

EtO$_2$C
N
S
N
O
NBoc
1.00
0.96
1.00
0.97
2.09
3.01
9.13
3.06
10.0
5.0
0.0
ppm (f1)



75

EtO$_2$C
N
S
N
O
NBoc
168.2
165.8
164.2
161.1
154.9
149.7
148.8
134.3
130.5
125.0
120.4
83.6
61.6
57.8
28.1
18.8
14.3
200
150
100
50
ppm (f1)

Research Publications

1. Stereoselective formal synthesis of macrolide core of migrastatin using late stage C–H oxidation. **Narendar Reddy Gade,** Javed Iqbal. *Tetrahedron Lett.* **2013,** *54*, 4225-4227.
2. IBX mediated reaction of *β*-enamino esters with allylic alcohols: A one pot metal free domino approach to functionalized pyridines. **Narendar Reddy Gade,** V. Devendram, Manojit Pal, Javed Iqbal. *Chem. Commun.* **2013,** *49*, 7926.
3. A Common synthetic protocol for the cyclic and acyclic core of migrastatin, isomigrastatin and dorrigocin via chiral *β*-hydroxy-*γ*-butyrolactone intermediate. **Narendar Reddy Gade,** Javed Iqbal. *Manuscript Submitted*

Poster Presentations in Conferences and Symposiums

- **Narendar Reddy Gade**, Javed Iqbal*, Stereoselective Formal Synthesis of Macrolide Core of Migrastatin Using Late Stage C-H Oxidation
- Poster presentation at "***Chemistry and Chemical Biology of Natural Products (CCBNP-2012)***" held at Indian Institute of Chemical Technology, Hyderabad, India, on August, 2012.
- Poster presentation at "***Catalyst 2013, Dr. Reddy's Chemistry Conclave***", held at Dr. Reddy's Laboratories, Hyderabad, India on January, 2013.
- **Narendar Reddy Gade**, V. Devendram, Manojit Pal*, Javed Iqbal*, IBX mediated reaction of *β*-enamino esters with allylic alcohols: A one pot metal free domino approach to functionalized pyridines
- Poster presentation at "***International Conference on Chemical Biology (ICCB-2014)***" held at Indian Institute of Chemical Technology, Hyderabad, India, on February, 2014.
- **Narendar Reddy Gade** and Javed Iqbal*, Synthesis of Amphidinolide T1-Rhizoxin D and Amphidinolide T1-Isomigrastatiin hybrids and their cytotoxic activities**. (Best poster award)**
- Poster presentation at "***Nature Inspired Initiatives in Chemical Trends (NIICT-2014)***" held at Indian Institute of Chemical Technology, Hyderabad, India, on March, 2014.