"Total Syntheses of (+)-Cylindricine C, D, E and (-)-Lepadiformine A by Development of a Non-Biogenetic Tandem Rearrangement"

A THESIS
SUBMITTED FOR THE DEGREE OF
DOCTOR OF PHILOSOPHY
(IN CHEMISTRY)

TO

SAVITRIBAI PHULE PUNE UNIVERSITY

BY

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(Research Guide)

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Dedicated To

Chemistry Lab

DECLARATION

I hereby declare that the work presented in the thesis entitled "**Total Syntheses of (+)-Cylindricine C, D, E and (–)-Lepadiformine A by Development of a Non-Biogenetic Tandem Rearrangement**" submitted for Ph. D Degree to the University of Pune, has been carried out at CSIR-National Chemical Laboratory, Pune under the supervision of **Prof. Ganesh Pandey**. This work is original and has not been submitted in part or full, for any degree or diploma of this or any other university/Institute.

Date: **(Janakiram V)**

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For initiating my research carrier

……..***Janakiram Vaitla***

Contents

List of Abbreviations

aq	Aquoes	NMR	Nuclear magnetic resonance
bp	Boiling point	nOe	Nuclear Overhauser effect/enhancement
Bn	Benzyl	NOESY	Nuclear Overhauser Enhancement Spectroscopy
Boc	*t*-Butoxycarbonyl	*p*-TSA	*p*-Toluenesufonic acid
DCM	Dichloromethane	py	Pyridine
DEPT	Distortionless enhancement by polarization transfer	rt	Room temperature
DMF	N,N-dimethyl formamide	TBS	t-Butyl dimethyl silyl
DMSO	Dimethyl sulfoxide	TBDPS	t-Butyldiphenyl silyl
COSY	Correlated spectroscopy	TEA	Triethyl amine
g	Gram	TFA	Trifluoroacetic acid
HRMS	High Resolution Mass Spectra	THF	Tetrahydrofuran
h	Hour	TLC	Thin layer chromatography
Hz	Hertz	TMS	Trimethyl silyl
M	Molarity (molar)	HSQC	Heteronuclear Single Quantum Coherence
mg	milligram	HMBC	Heteronuclear Multiple-Bond Correlation
min	minute(s)	GC	Gas Chromatography
mL	Millilitre	IBX	o-iodoxybenzoic acid
mmol	millimole	LDA	Lithium diisopropylamide
mp	Melting Point	PPTS	Pyridinium para-toluene sulfonate
DIBAL-H	Diisobutylaluminium hydride	*m*-CPBA	3-chloro peroxybenzoincacid
ESI	Electron spray ionization	Ac	acetyl
MsCl	Methane sulfonyl chloride	Ar	aryl
TsCl	*p*-Toluene sulfonyl chloride	n-Buli	n-Butyl lithium

General Remarks

- All the solvents were purified according to the literature procedure.[1]
- Column chromatographic separations were carried out by gradient elution with suitable combination of two solvents and silica gel (60-120 mesh / 100-200 mesh / 230-400 mesh) obtained from S. D. Fine Chemical Co. India or SRL India
- Reactions were monitored by thin layer chromatography (TLC, 0.25 mm E. Merck silica gel plates, 60 F_{254}) and visualized by using UV light, ethanolic solution of phosphomolybdic acid (PMA), iodine, ninhydrin and $KMnO_4$ solution.
- Dry tetrahydrofuran (THF) and diethyl ether (Et_2O) were obtained by passing commercially available pre-dried, oxygen-free formulations through activated alumina columns and dried by distillation over sodium/benzophenone. Toluene and benzene were distilled over calcium hydride and stored over 4Å molecular sieves. Pyridine and triethylamine (Et_3N) were distilled over potassium hydroxide.
- All commercial reagents were obtained from Sigma-Aldrich Chemical Co. and S. D. Fine Chemical Co., Spectrochem, LOBA, Alfa-aeser, HIMEDIA, acros chemicals, Merck India.
- IR spectra were recorded on a Perkin-Elmer FT-IR Spectrometer.
- ^1H NMR spectra were recorded on BRUKER AC-200, BRUKER 400 UltraShield and BRUKER 800 ULTRASHIELD PLUS instruments using Deuterated chloroform as standard. Chemical shifts are reported in *ppm*. ^{13}C NMR spectra were recorded on BRUKER 400 UltraShield and BRUKER 800 ULTRASHIELD PLUS instruments operating at 101MHz and 201MHz respectively. ^{13}C NMR chemical shifts are reported in ppm relative to the central line of $CDCl_3$ ($\delta = 77.12$).
- Electro spray ionization (ESI) mass spectrometry (MS) experiments were performed on Agilent Technologies 6530 Accurate-Mass Q-TOF LC/MS.
- Optical rotations were measured on a Digipol 781 M6U Automatic Polarimeter.
- HPLC were performed on Agilent Technologies 1260 Infinity.
- **Numbering of compounds, Schemes, Tables, Referencing and Figures for each chapter and in abstract are independent.**

1) Perrin, D.D.; Armarego, W. L. F. Purification of Laboratory chemicals, 4th ed., Butterworth Heinemann, **1999**

Research Student: Janakiram V

Research Guide: Prof. Ganesh Pandey

Title of Thesis: Total Syntheses of (+)-Cylindricine C, D, E, and (-)- Lepadiformine A by Development of a Non-Biogenetic Tandem Rearrangement

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Thesis Abstract

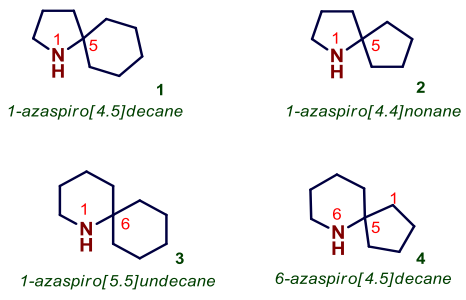
The present dissertation is divided into three chapters. Chapter one deals with the overview of 1-azaspiro tricyclic marine alkaloids and developing our own strategy for the generation of 1-aza quaternary scaffolds by selective bond cleavage of bridgehead substituted 7-azabicyclo[2.2.1]heptane. Chapter two presents introduction and synthetic reports of cylindricine class of alkaloids and our approach for the construction of (+)-cylindricine C-E. Chapter three illustrates the literature reports for the synthesis of lepadiformine class alkaloids as well as our synthetic approach for the construction of (–)-lepadiformine A.

Chapter 1:- Chiral Aza-Quaternary Scaffolds by Selective Bond Cleavage of Bridgehead Substituted 7-Azabicyclo[2.2.1]heptane

This section describes reported strategies for the synthesis of these structural frameworks in asymmetric fashion and outline of our strategy for constructing these structural frameworks by selective bond cleavages of bridgehead substituted 7-azabicyclo[2.2.1]heptanes.

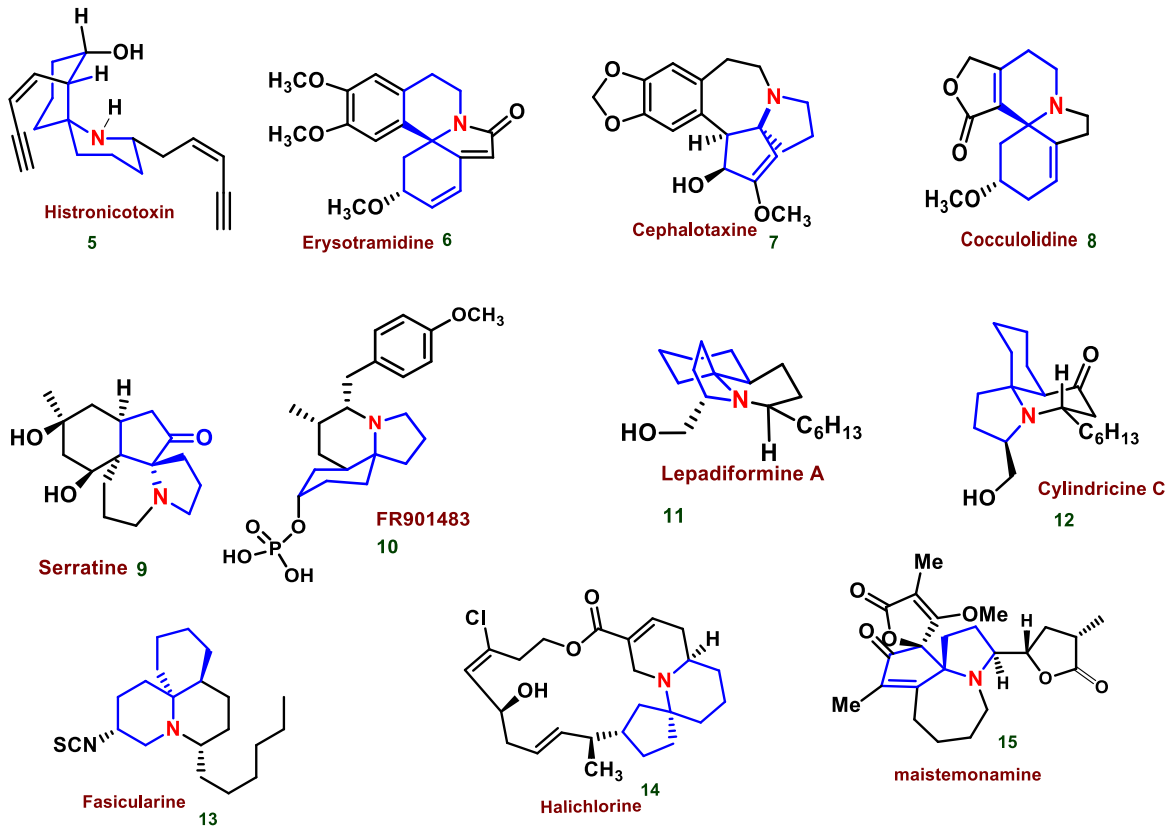
Bicyclic frameworks containing two rings fused by a spiro ring possessing a nitrogen atom adjacent to the ring junction are called as '1-azaspirocyclanes'.

Figure 1: Nomenclature of azaspirocyclanes



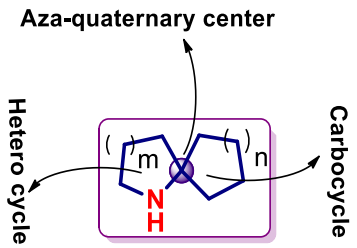
Azaspirocyclane scaffolds are common core of many alkaloids viz. histrionicotoxin, cephalotaxine, halichlorine,pinnaic acid, TAN1251A, FR901483 and members of the cylindricine family of alkaloids, fasicularin, lepadiformine and erythrina alkaloids.

Figure 2: Alkaloids that contain 1-azaspirocycle motifs



The common 1-azaspirocyclic ring system present in these natural products are characterised by 1-azaspiro[4.5]decane, 1-azaspiro[5.5]undecane, 1-azaspiro[4.4]nonane and 6-azaspiro[4.5] decane structural motifs (Figure 3).

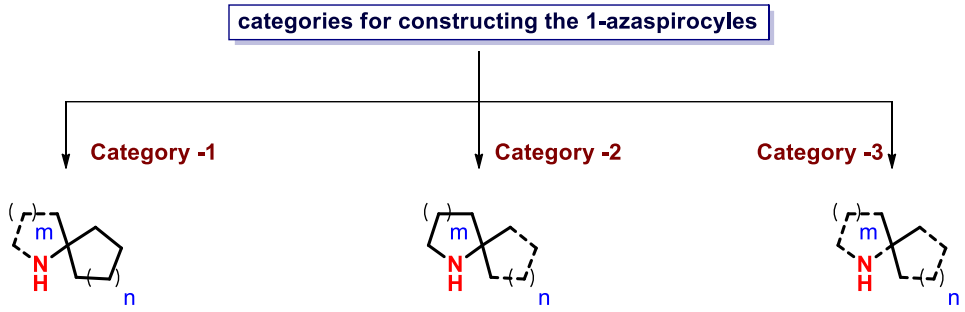
Figure 3: Structural challenges of azaspirocyclane



The construction of these structural frameworks in asymmetric fashion is summarised into three general categories as shown in Figure. 4. While first category employs construction of the aza-quaternary centre followed by heterocyclization/ a-ring (path-a), second category involves construction of the aza-quaternary centre followed by carbocyclization /b-ring (path-b). These two approaches have employed two-step

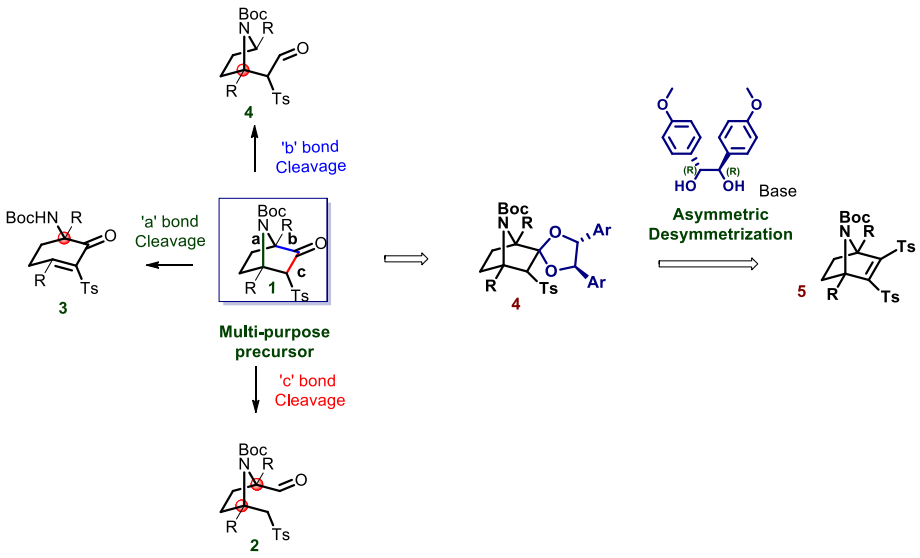
processes involving construction of the aza-quaternary carbon and the spiro-cyclic ring system separately and subsequently joining them together. However, the third category utilizes the construction of the aza-quaternary centre followed by spirocyclization to form either a or b-ring (either heterocycle or carbocycle) in one step (path-c) (Fig. 4).

Figure 4: Classification of reported strategies for azaspirocyclane scaffolds in asymmetric fashion



This Chapter also includes our strategy of constructing 1-azaquaternarycyclanes by selective bond dissociations of the structural framework **1,** designed by considering its ring strain as shown in Scheme 1.

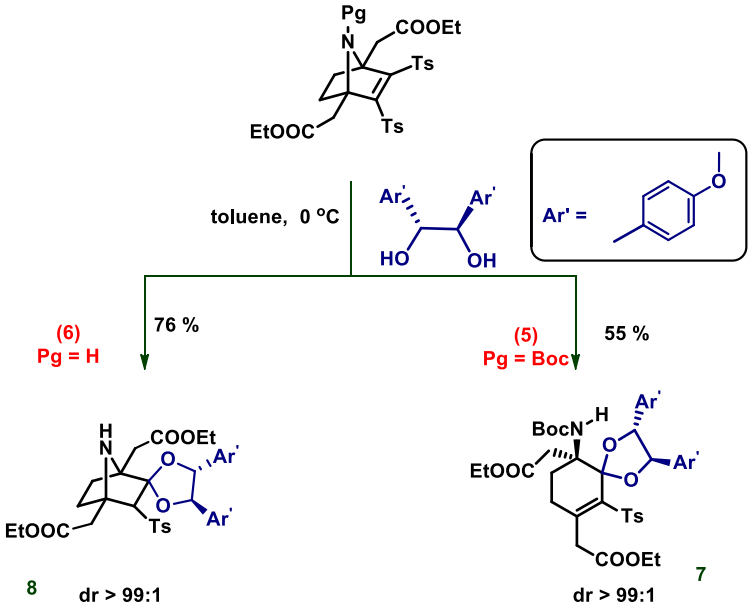
Scheme 1: Selective bond dissociation of 1



Synthesis of **1** is achieved by the asymmetric desymmetrization of *meso*-**5** using (*R*,*R*)-hydroanisoin (Scheme 1).

During the study of desymmetrization, N-Boc group was found to determine the formation of either **7** or **6** as shown in Scheme 2.

Scheme 2: Asymmetric desymmetrization

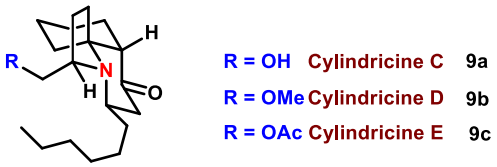


Chapter 2:- Stereoselective Total Synthesis of Cylindricine Class of Alkaloids:

This chapter describes an overview of cylindricine family of alkaloids and our approach for the synthesis of cylindricine C, D, E.

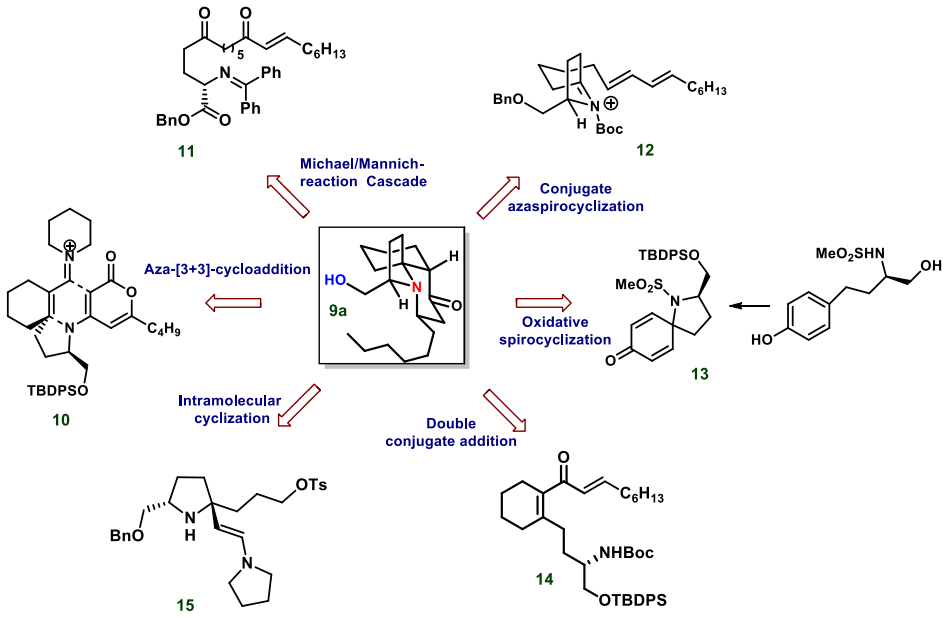
Cylindricine C- D (**9a-c**) belongs to the family of marine ascidian alkaloids and possesses perhydropyrrolo[2,1-*j*]quinolone framework. Cylindricines are known to exhibit bioactivity against brine shrimp larvae in a bioassay. Among this class of alkaloids, **9a** represents an intriguing target for synthetic chemists due to unusual tricyclic structural framework containing four stereo centers including one aza-quaternary center.

Figure 5: Cylindricine class of alkaloids



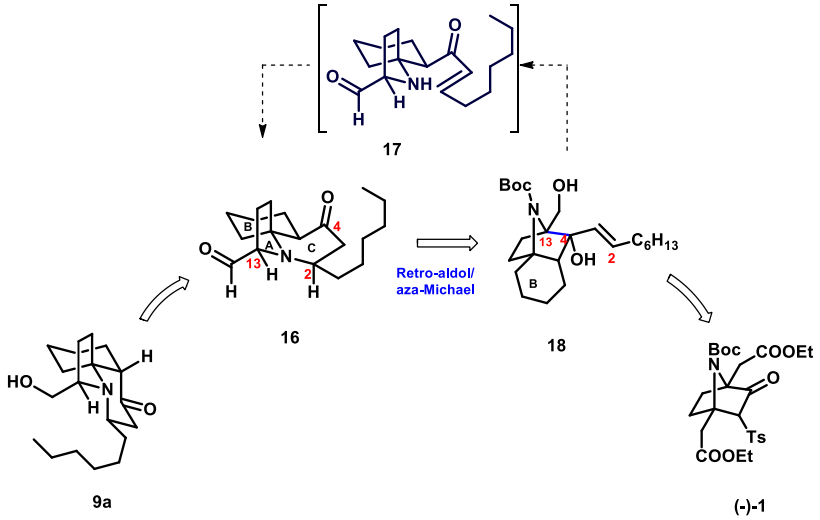
Although, there are few elegant approaches are known in the literature, majority of the reports involves chiral pool approaches. The important strategies can be summarized as shown in figure 6.

Figure 6: Summary of literature reports



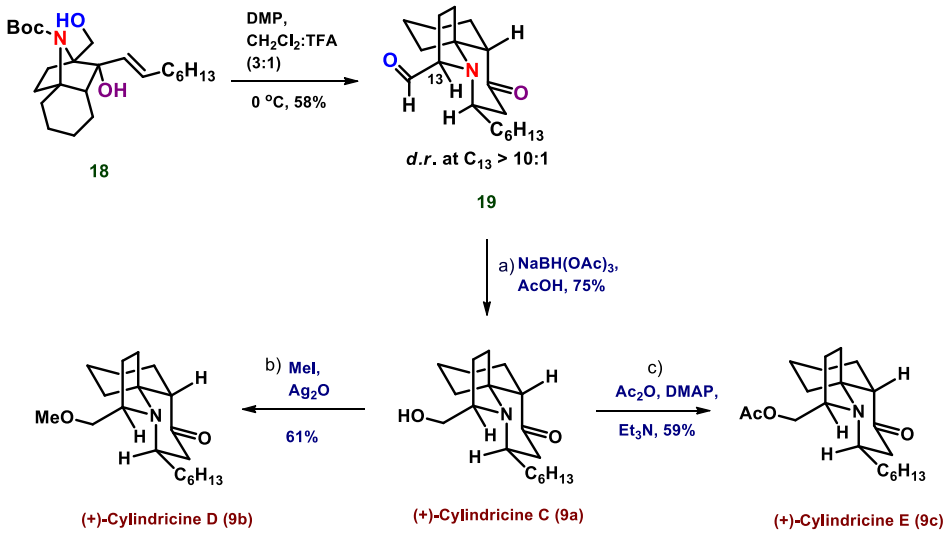
However, since the absolute configuration of natural alkaloid is still unknown, it was felt necessary to develop a different route which can deliver both enantiomers of cylindricines. In this context, an innovative cascade rearrangement (Retro-aldol/Aza-Michael) approach was devised to synthesize **9** as shown in Scheme 3.

Scheme 3: Retrosynthetic analysis of 9a



As per our design, DMP oxidation of **18** in the presence of TFA was found to give **19** with excellent diastereoselectivity (Scheme 4) which was converted to cylindricine C-E by following simple functional group transformations.

Scheme 4: Cascade rearrangement of 18 for syntheses of 9

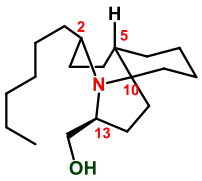


The plausible mechanism for the cascade reaction is also presented.

Chapter 3:- Stereoselective Total Synthesis of Lepadiformine A:

This chapter describes an overview of Lepadiformine family of alkaloids along with our approach for the synthesis of (–)-Lepadiformine A (**24**).

Figure 7: Lepadiformine A (24)

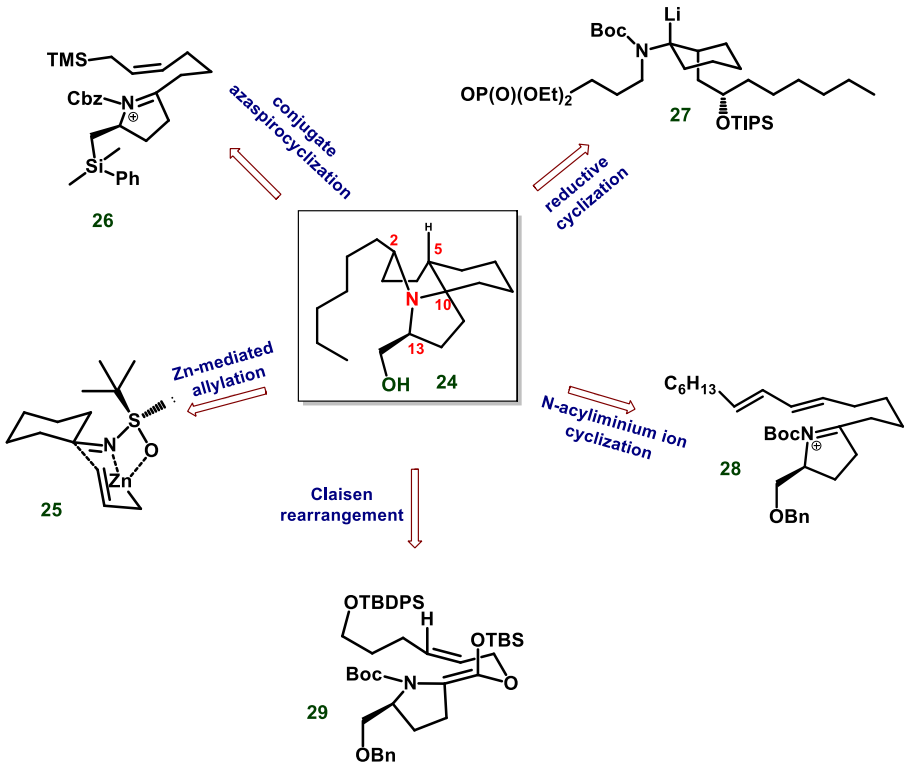


(24)

Lepadformine was isolated from the extracts of the marine tunicate *Clavelina lepadiformis* which exhibited inhibitory effects on the inward rectifying potassium current which causes bradycardia, an effect seen in antiarrhythmic agents.

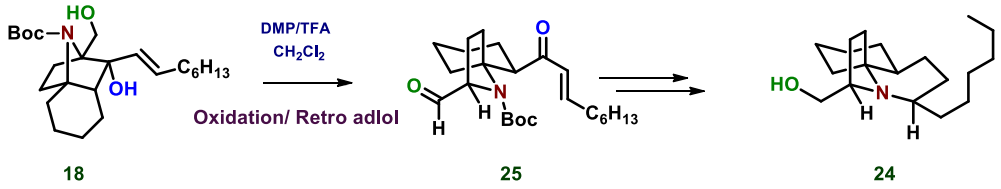
The reported strategies for the synthesis of **24** are summarized in fig **8**.

Figure 8: Summary of literature reports for 24



We accomplished the total synthesis of 24 in 6 steps from **18** by interrupting the cascade sequence at **25** to stop C_5 epimerization as shown in Scheme 5.

Scheme 5: Total Synthesis of (–)-Lepadiformine A



Chapter 1:-

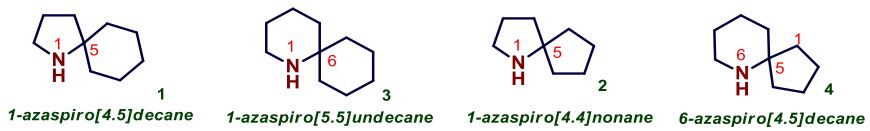
“Chiral Aza-Quaternary Scaffolds by Selective Bond Cleavage of Bridgehead Substituted 7-Azabicyclo[2.2.1]heptane”

Section –1.1 : An overview of 1-azaspirocyclanes

Introduction to 1-azaspirocyclanes:

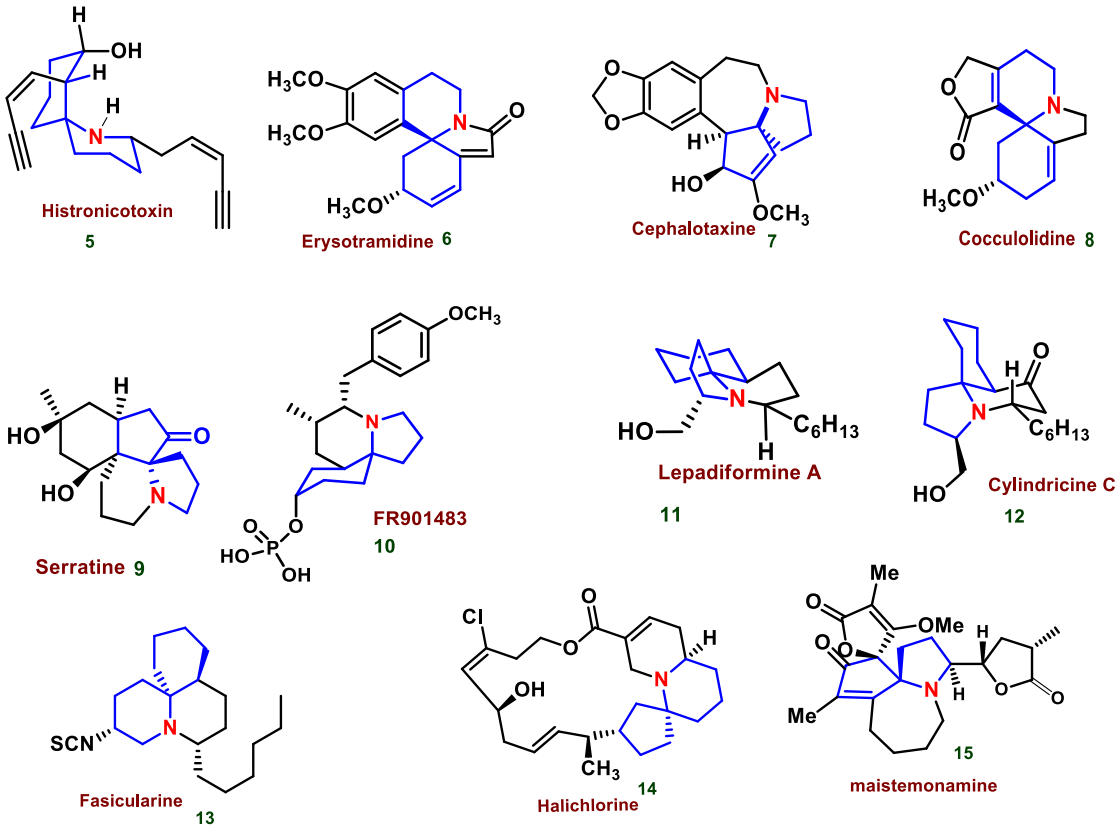
Bicyclic frameworks containing two rings fused by a spiro ring possessing a nitrogen atom adjacent to the ring junction is called as '1-azaspirocyclanes'.[1]

Figure 1: 1-azaspirocyclane framework



Azaspirocyclane scaffolds are common core of many alkaloids viz. histrionicotoxin,[2] cephalotaxine,[3] halichlorine,[4] pinnaic acid,[5] TAN1251A,[6] FR901483[7] and members of the cylindricine family of alkaloids,[8] fasicularin,[9] lepadiformine[10] and erythrina[11] alkaloids.

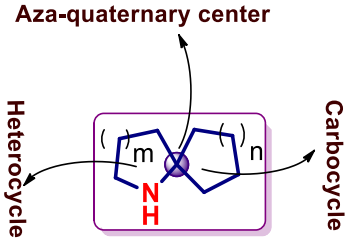
Figure 2: Alkaloids that contain 1-azaspirocycle motifs



Section –1.2 : Synthetic approaches for the 1-azaspiro framework:

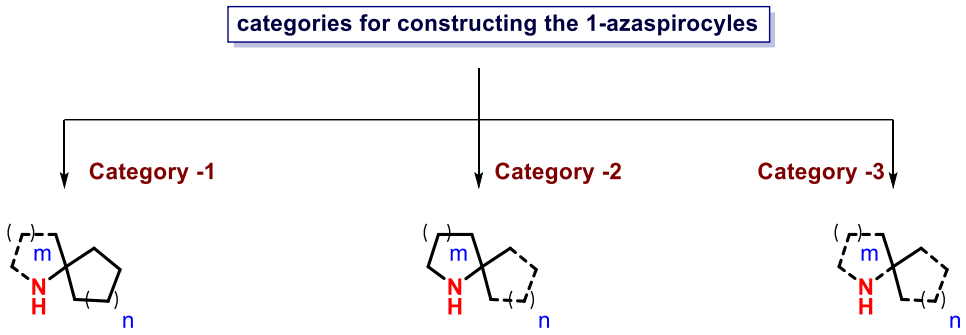
The common 1-azaspirocyclic ring system present in natural products are characterised by 1-azaspiro[4.5]decane, 1-azaspiro[5.5]undecane, 1-azaspiro[4.4]nonane and 6-azaspiro[4.5] decane structural motifs. There are two main challenges for constructing these 1-azaspirocyclic motifs; a) construction of the aza-quaternary center bearing nitrogen atom at the spirocyclic ring junction and b) construction of fused carbocyclic / heterocyclic ring system (Figure 3).

Figure 3: Structural challenges of azaspirocyclane



A number of methods have been described for the construction of these ring systems[1, 2] and strategies known for the synthesis of these structural frameworks in asymmetric fashion can be divided into three general categories as shown in Figure. 4. While first category employs construction of the aza-quaternary centre followed by heterocyclization/ a-ring cyclization, second category involves construction of the aza-quaternary centre followed by carbocyclization /b-ring cyclization. These two approaches employ two-step processes involving construction of the aza-quaternary carbon and the spiro-cyclic ring system separately and subsequently joining them together. However, the third category utilizes the construction of the aza-quaternary centre followed by spirocyclization to form either a or b-ring (either heterocycle or carbocycle) in one step (Fig. 4).

Figure 4: Classification of reported strategies for azaspirocyclane scaffolds in asymmetric fashion

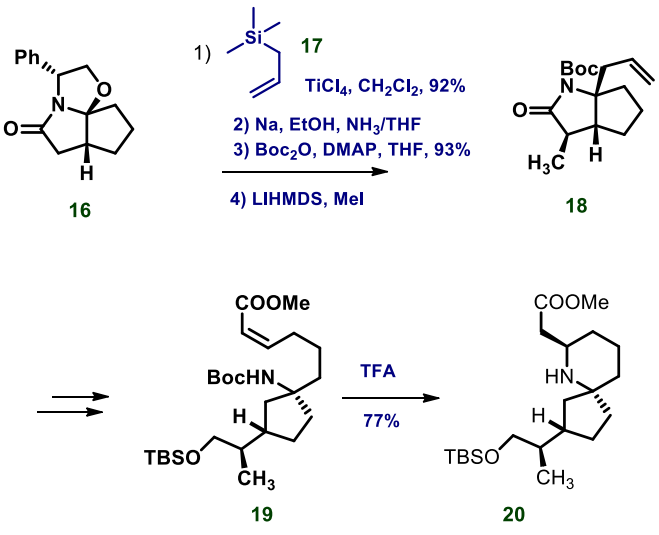


(Category – I) –Construction of the aza-quaternary centre followed by heterocyclizations (A-ring):-

Danishefsky's approach: - {*Angew. Chem., Int. Ed.* **1999**, *38*, 3542} [12]

The key feature of this approach involves addition of allyl trimethyl silane to a masked iminium ion for generating aza-quaternary centre **18** which on subsequent

Scheme 1:- Danishefsky's approach for 1-azaspirocyclane 20

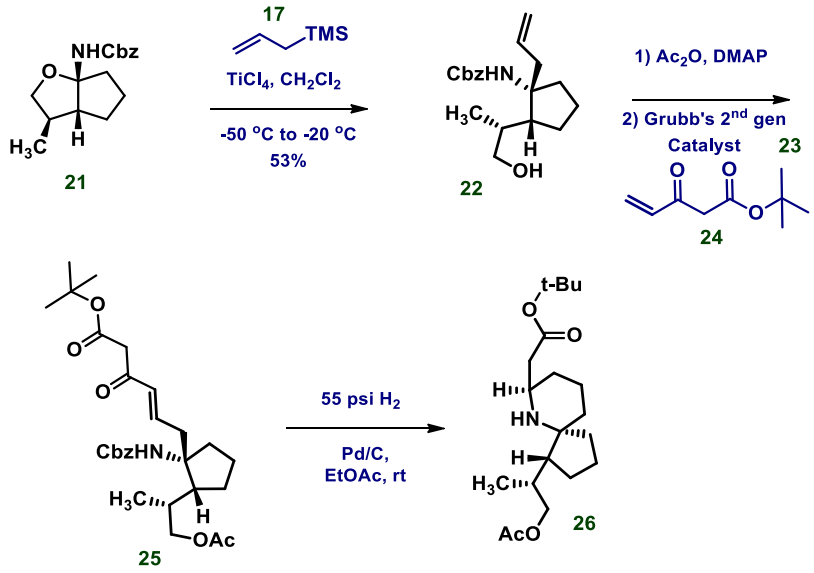


heterocyclization using intramolecular aza-Michael addition reaction affords azaspirocyclane ring system **20** as shown in Scheme 1.

Heathcock's approach:- { *Proc. Natl. Acad. Sci. U.S.A.***2004**, *101*, 12079}[13]

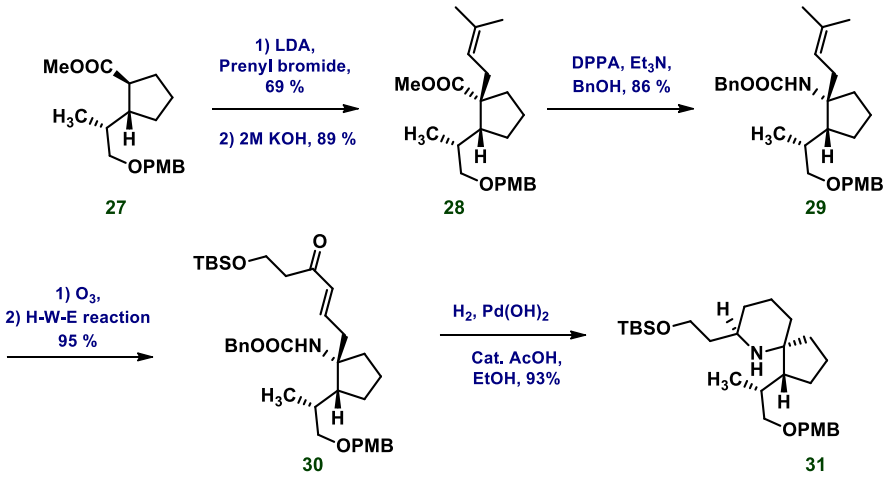
This group [13] have utilized similar strategy for generating aza-quaternary centre **22**, however, heterocyclization in this case is achieved by intramolecular reductive amination to obtain **26** as shown in Scheme 2.

Scheme 2:- Heathcock's approach for 1-azaspirocyclane 26



Arimoto's approach: - {*Tetrahedron Lett*. **1999**, *40*, 3583.}[14]

Scheme 3 :- Arimoto's approach for 1-azaspirocyclane 31

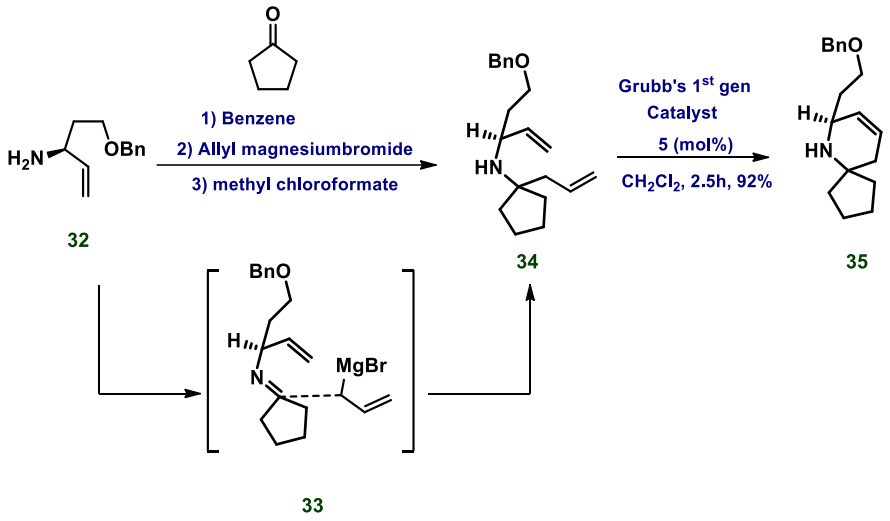


Arimoto *et al.* [14] utilized Curtius rearrangement from **28** for constructing aza-quaternary centre **29** which on heterocyclization by reductive amination affords azaspirocyclane ring system **31** as shown in Scheme 3.

Wright's approach :-{ *Org. Lett*. **2000**, *2*, 1847.} [15]

In this approach, 1-azaquaternary centre is constructed by the addition of allyl magnesium bromide to an imine **33** followed Grubbs cross metathesis for heterocyclization to obtain **35** as shown in Scheme 4.

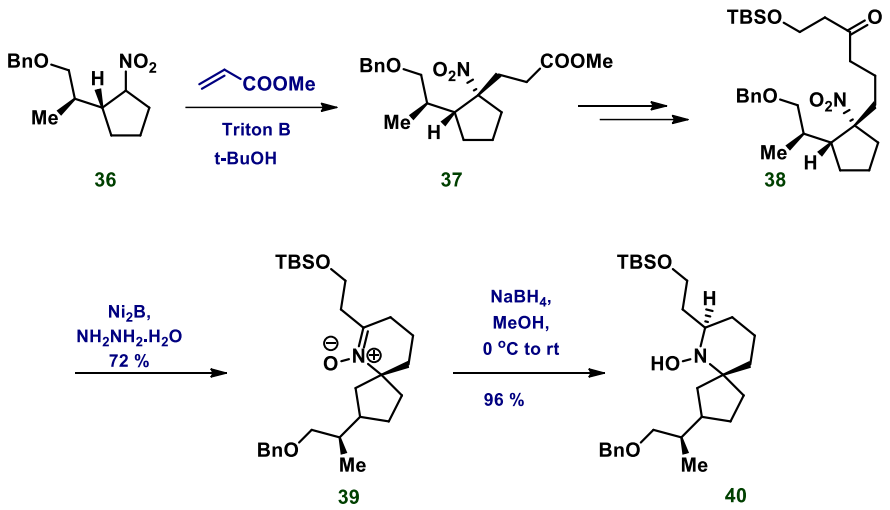
Scheme 4:- Wright's approach for 1-azaspirocyclane 35



Zhao's route :-{ *J. Org. Chem*. **2005**, *70*, 4954.} [15]

Zhao's route [16] for synthesizing 6-azaspiro[4.5]decane ring system involved conjugate addition of the corresponding carbanion of **36** to methyl acrylate in order to generate 1-azaquaternary centre **37** which by following simple functional group transformations produced **40** as a pure diastereomer (Scheme 5).

Scheme 5:- Zhao's approach for 1-azaspirocyclane 40

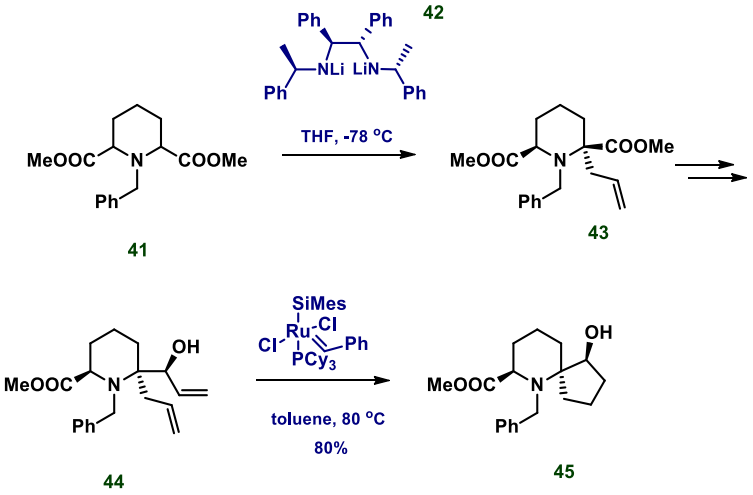


(Category – II) Construction of aza-quaternary centre followed by carbocyclization (B-ring):-

Simpkin's route:- { *Synlett* **2004**, 2295.}[17]

An alkylative desymmetrization [17a], employing a chiral base, was used in this strategy to generate aza-quateranary centre **43** (*de* = 69 %) which on carbocyclization employing cross metathesis of **44** gave **45, a** halichlorine framework (Scheme 6).

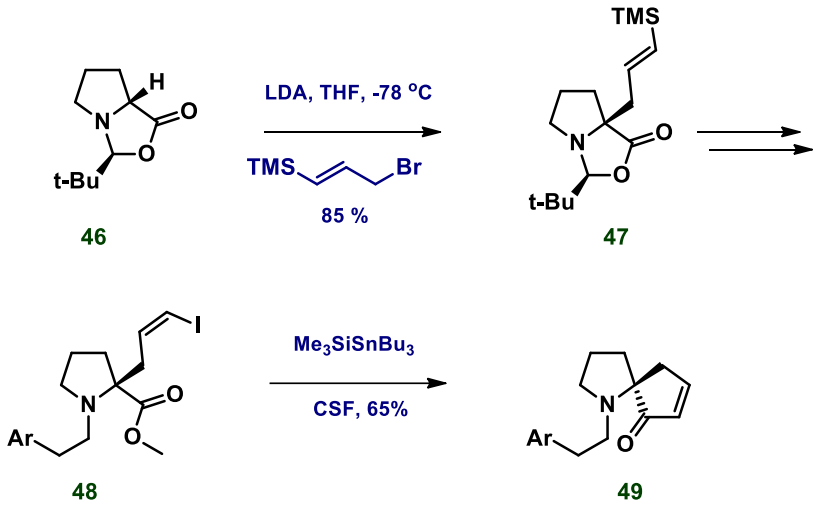
Scheme 6:- Simpkin's approach for 1-azaspirocyclane 45



Mori's route:-{ *J. Org. Chem.* **1995**, *60*, 115.} [18]

1-Azaspiro[4,4]nonane skeleton[18] related to cephalotaxine skeleton **49**, was synthesized by the allylation of **46** followed by carbocyclisation as shown in Scheme-7.

Scheme 7:- Mori's approach for 1-azaspirocyclane 49

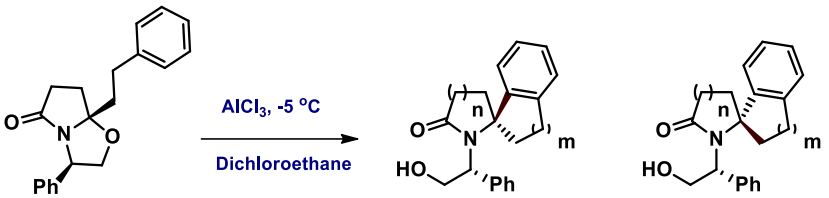


(Category– III) : Construction of the aza-quaernary centre and spirocycle in the same step:-

Vernon's route:- {*Tetrahedron Lett.* **1994**, 35, 7115.} [19a]

Vernon's group[19] utilized intramolecular cyclization of an in situ generated iminium ion with arene nucleophiles to produce 1-azaspirocycle **51** and **52**, respectively. The diastereomeric ratio of azaspirocyclization depended on the ring size formed. For example, when aza spirocyclane [5, 5] fused bicyclic framework is formed, the major diastereomer would be **51** whereas it would be **52** for azaspirocyclane [5, 6] fused bicyclic framework**.**

Scheme 8:- Vernon's approach for 1-azaspirocyclane 51 and 52



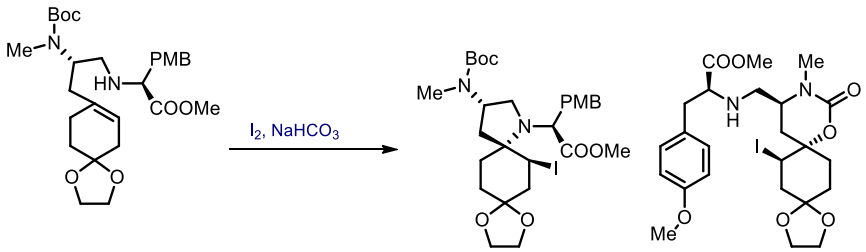
50 51 52

	diastereomeric ratio	
	51	52
a) n=1, m=1	3.6	1
a) n=1, m=2	1	3.9

Bonjoch's route:- {*Tetrahedron Lett.* **2003**, *44*, 8387.} [20]

Bonjoch'group attempted [20] an iodonium ion spirocyclization of **53** to produce 1-azaspirocyclane **54,** however, it was formed only as a minor product (Scheme 9). The major product **55** resulted from the interception of the putative halonium ion species with the carbonyl atom of the *t*-butylcarbamate of **53.**

Scheme 9:- Bonjoch's approach for 1-azaspirocyclane 54

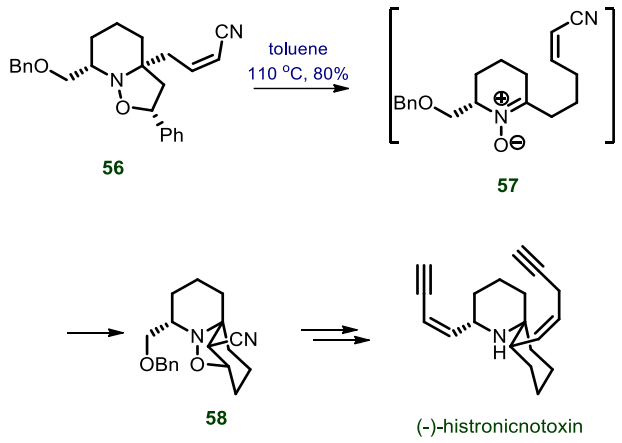


53 54 55

Holmes's approach:- {*J. Am. Chem. Soc.* **1999**, *121*, 4900.} [21a]

Although, efforts were made to achieve 1-azasprocyclane skeleton by [3+2]-Nitrone–alkene cycloadditions[21a], it remained unsuccessful due the formation of an undesired regioisomer as the major product. However, Holmes group [21b] succeeded in carrying out an intramolecular [3+2]-cycloaddition with an in situ generated nitrone **57.**

Scheme 10:- Holme's approach for 1-azaspirocyclane 58

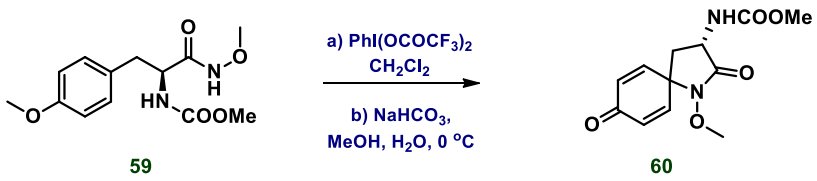


The use of an unsaturated nitrile was crucial to ensure the appropriate regiochemical outcome of **58**.

Wardrop's approach:- { *Org. Lett.* **2001**, *3*, 1053.} [22a]

Wardrop's group [22] studied oxidative azaspirocyclization of **59** using hypervalent iodine reagent PIFA for the formation of azaspirocyclane **60** (Scheme 11). This approach has been used to generate key intermediates in the synthesis of FR901483 and (K)-TAN 1251A.

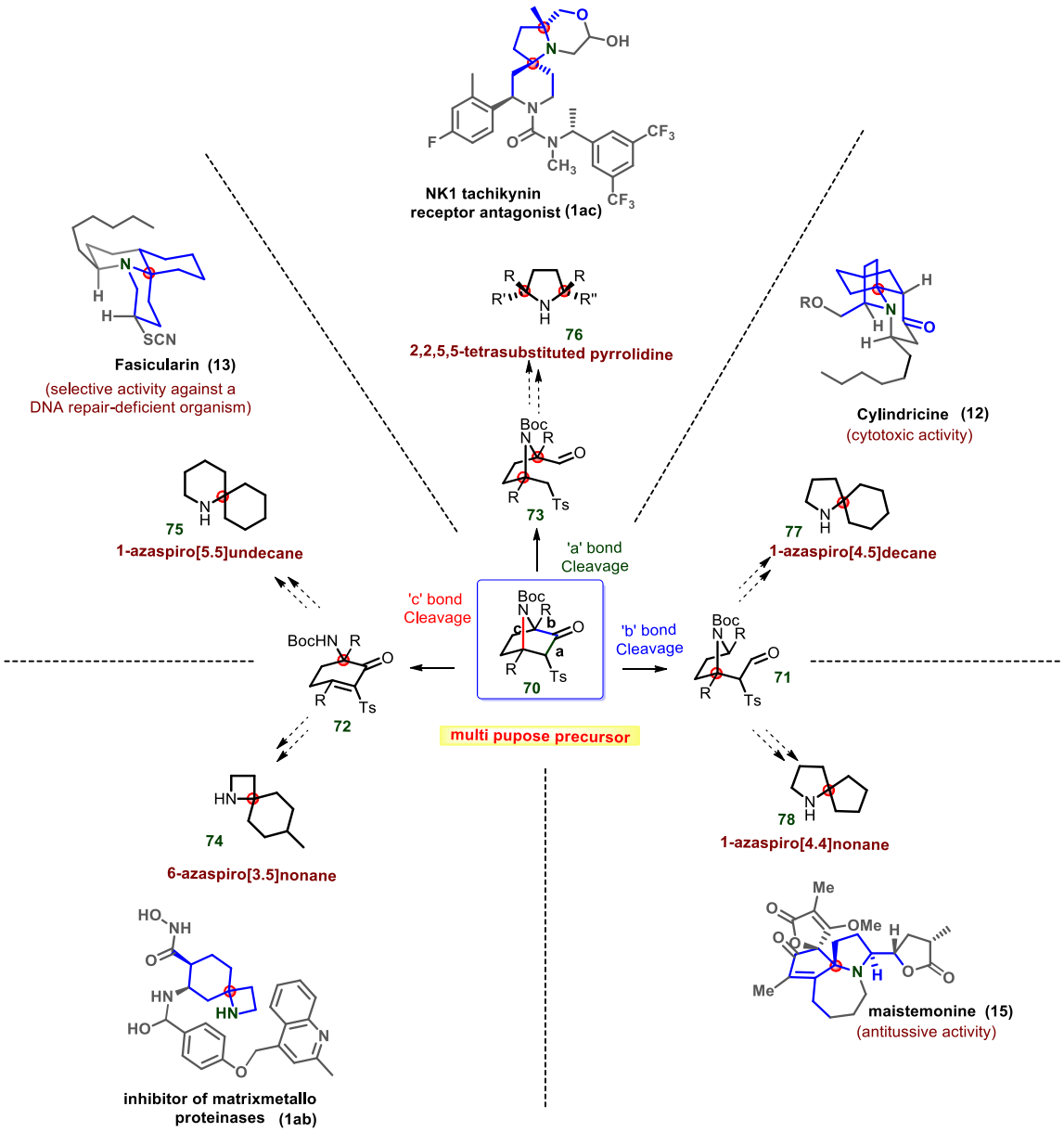
Scheme 11:- Wardrop's approach for 1-azaspirocyclane



Section –1.3: Developing a new concept of constructing 1-aza quaternary scaffolds by Selective bond cleavage of Bridgehead substituted 7-azabicyclo[2.2.1]heptane.

Considering the importance of 1-azaspirocyclanes in natural product synthesis[1,2] and drug developments[28] we were interested in synthesizing these spirocyclic frameworks by a conceptually different approach.

Scheme 12:- Possible diversification of bridged bicyclic precursor into various 1-azaspirocyclane scaffolds



Although, above mentioned strategies for the construction of 1-azaspirocyclanes in chiral fashion are interesting, efficiency and enatioselectivity still remains a challenge. Moreover, these strategies are also restricted for the construction of a particular type of framework only. [12-21a]

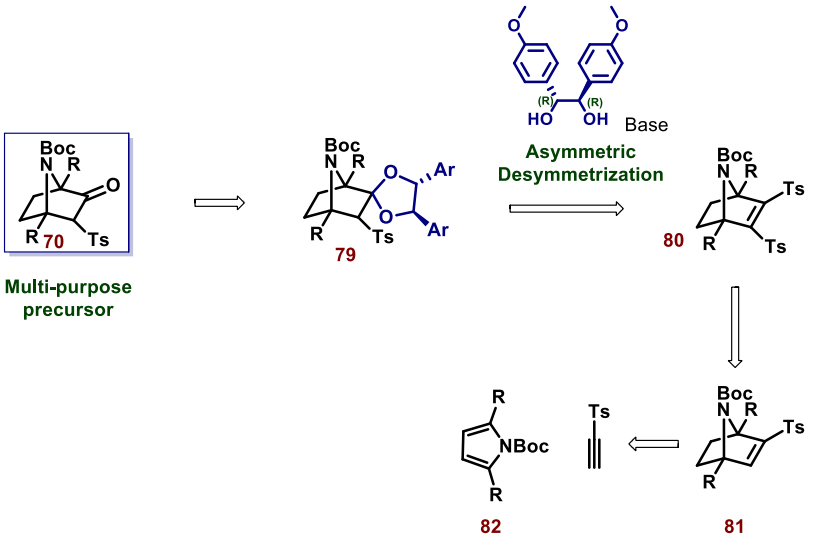
To address the synthetic challenges in the context of synthesizing structurally diverse 1-azaspirocyclane frameworks belonging to different classes of bioactive alkaloids (**12, 13, 15, 1ab, 1ac**), we sought to design a precursor which can expeditiously establish these privileged functionalized structural scaffolds embedded with challenging 1-aza quaternary stereo centers. To find a solution to this challenging problem, we hypothesized a structural framework **70** which is endowed with privileged functionality required to meet the challenge of synthesizing various chiral 1- azaquaternary scaffolds. This structural framework was selected considering its ring strain for carrying out selective bond dissociations which upon simple chemical transformation would provide rapid access to various 1-azaspirocyclane scaffolds. For example, 1-azaspiro[3.5]nonane **74** and 1-azaspiro[5.5]undecane **75** could be obtained via 'a' bond (C-N bond) fragmentation whereas cleavage of 'b' bond can lead to 1-azaspiro[4.4]nonane **77** and 1-azaspiro[4.5]decane **78** frameworks, respectively.

Similarly, by cleaving 'c' bond would lead to 1-azaspiro[4.5]decane framework containing 2,2,5,5-tetrasubstituted pyrrolidine **76** as a central motif.

It may be emphasized that there is no synthetic strategy which offers densely functionalized chiral pyrrolidine moiety, a key structural component of NK1 tachikynin receptor antagonist **1ac**.[28] During the selection of **70**, care was taken in the beginning itself that for 'a' bond fragmentation,[29] N-Boc group would be required to act as a nucleofugal moiety whereas for 'c' bond scission,[30] phenylsulfonyl group would assist as a nucleofugal group. However, for 'b' bond fragmentation a nucleofugal group adjacent to the keto functionality would be required and another bridgehead substituent can be used for cyclization to produce corresponding 1-azaspirocyclanes.

The key precursor **70** can be obtained by asymmetric desymmetrization[23] of *meso*-**80** using (*R*,*R*)-hydroanisoin[24] (Scheme-14). Importantly, this asymmetric desymmetrization protocol produces two chiral 1-azaquaternary centres in a single operation which cannot be possible using traditional approaches.[25]

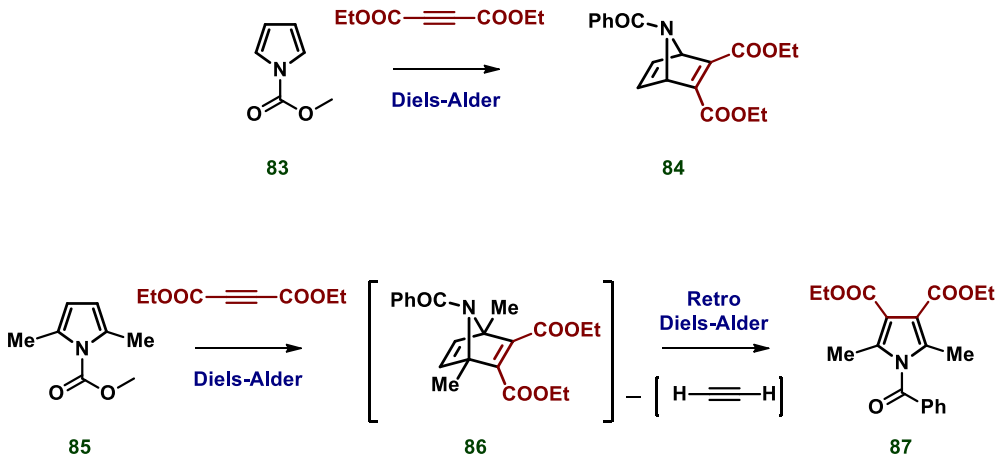
Scheme 14:- Retrosynthesis of 70



Results and discussion:-

Our initial study focused on the synthesis of **81** by following the general strategy of [4+2]-cycloaddition reaction between N-protected pyrroles and dienophiles for the synthesis of the 7-azabicyclo[2.2.1]heptane scaffolds.[33, 41]

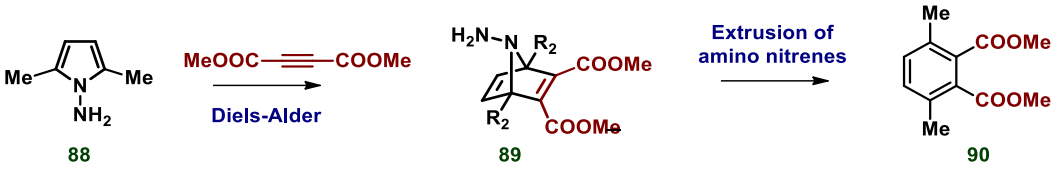
Scheme 15:- Diels-Alder reaction of pyrroles with dimethyl acetylenedicarboxylate



However, reaction of 2,5-symmetrically disubstituted pyrrole **85** with dimethyl acetylenedicarboxylate at 150 °C produced only **87** which was explained to have

formed by subsequent retro Diels-Alder reaction of the corresponding cycloadduct **86** with the loss of acetylene[42].

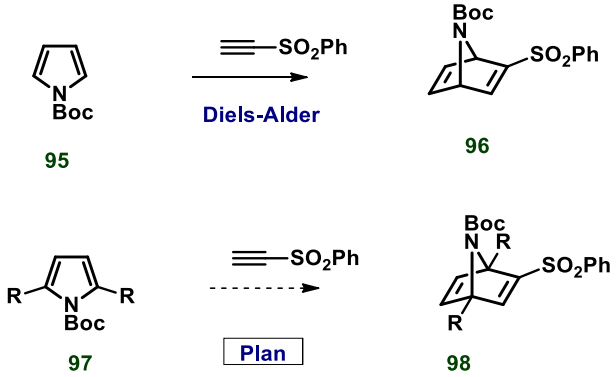
Scheme 15:- Diels-Alder reaction of 88 with dimethyl acetylenedicarboxylate



Similar observation was also made[43] during attempted cycloaddition of the 1-(alkylamino) pyrrole **88** with dimethyl acetylenedicarboxylate producing **90** in 68% yield. The reaction was proposed to involve **89** followed by facile aminonitrenes extrusion.

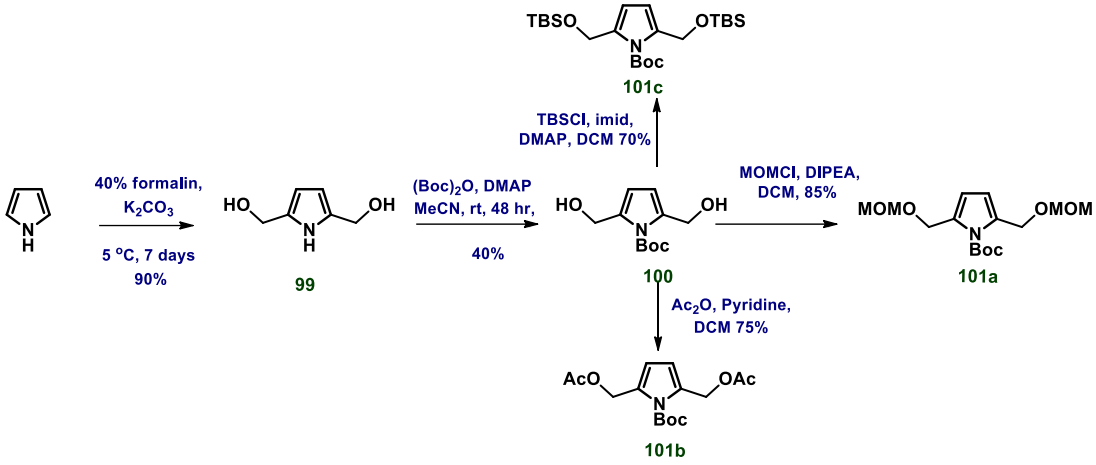
Generally, the failure to isolate the Diels-Alder cycloadducts with substituted pyrrole derivatives[42b] has been attributed to their thermal instability and their susceptibility to rearrange in basic or acidic media and even when exposed to light. Furthermore, stability of pyrrole Diels-Alder cycloadducts are also known to depend on the dienophiles. With this concept in mind, we planned to obtain **98** by the cycloaddition of **97** with the phenyl sulfonyl acetylene as the dienophile. It may be appropriate to mention here our own success[24] in this regard by successful Diels-Alder cycloaddition between **95** with phenylsulfonyl acetylene to obtain **96 (**Scheme-16**)**.

Scheme 16:- Diels-Alder reaction of pyrroles with phenyl sulfonyl acetylenes



Thus, substituted pyrroles **(101a-101c)** were obtained by following the sequence as outlined in Scheme-17.

Scheme 17:- Preparation of 2,5-disubstituted pyrrole for cycloaddition



However, when cycloaddition of these pyrroles (**101a-c**) were carried out with phenyl sulfonyl acetylene under identical experimental condition as reported earlier[24], surprisingly, not even a trace amount of corresponding cycloadducts **98a-c** was not detected. This reaction was further attempted using different Lewis acid but without any success. This failure led us to assume that cycloaddition probably requires significant activation of dienophile to overcome this cycloaddition problem. Therefore, cycloaddition was attempted with bromosubstituted dienophiles (entry No. 5 and 6) but this reaction was also unsuccessful.

Scheme 18:- Attempted cycloaddition with symmetrically substituted pyrroles with phenyl sulfonyl acetylene

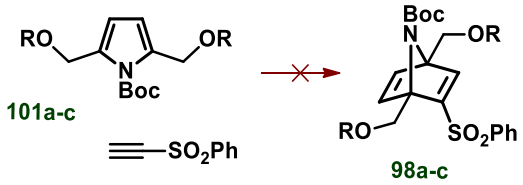


Table 1:- Screening of conditions for cycloadduct 97

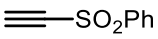
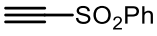
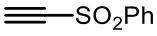
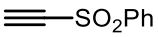
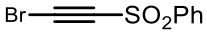
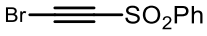
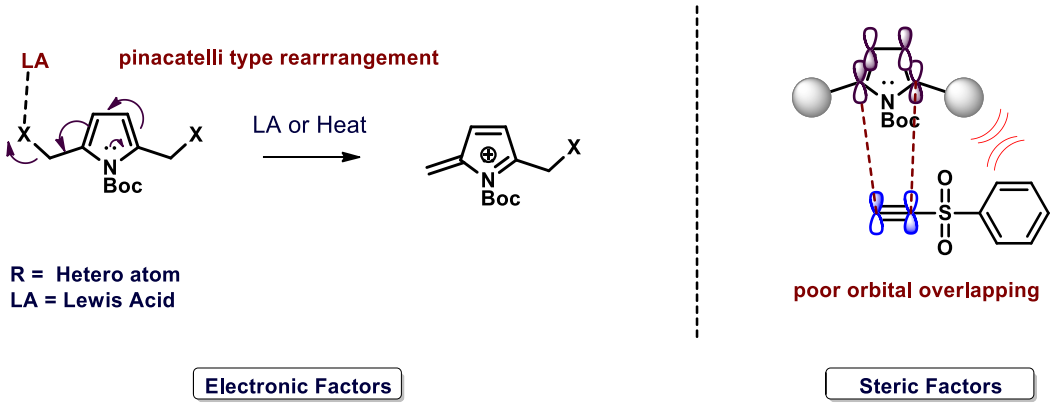
Sl.No	Electrophile	Conditions	Temp	Inference
1		neat	80 °C	Decompostion of **101**
2		$AlCl_3$, DCM	0 °C	Decompostion of **101**
3		$BF_3.OEt_2$	0 °C	Decompostion of **101**
4		Nitromethane as solvent	80 °C	no reaction
5		Toulene	70 °C	Decompostion of **101**
6		CS_2 as solvent	80 °C	No reaction

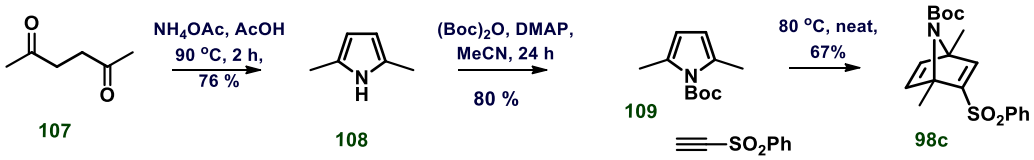
Figure 5:- Factors affecting at Diels-Alder reaction



At this stage, we surmised that the reason for **101** not undergoing Diels-Alder reaction is possibly due to the combined effect of both steric as well as electronic factors [42] as shown in Fig.5

To support this argument, a cycloaddition reaction of 2,5-dimethyl N-Boc pyrrole (**109**) was carried out with phenylsulfonyl acetylene which gave **98c** in 67 % yield. The preparation and cycloaddition of **109** is shown in Scheme 20.

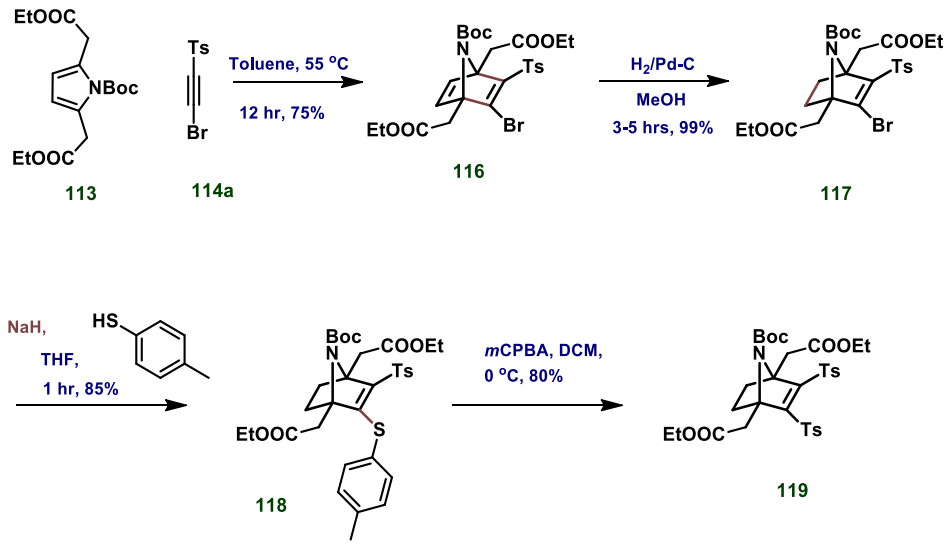
Scheme 20:- Model study of Diels-Alder reaction of 2,5- dimethyl pyrrole



This result encouraged us to utilize suitably substituted **113** for Diels-Alder cycloaddition reaction with **114a** to prepare **70** in optically pure form through a desymmetrization protocol.

The synthesis commenced from **113** which can be prepared via Paal-Knorr reacton of **111**[37, 38]. Cycloaddition of **113** with **114a** was carried out by heating both together in toluene at 55 °C which afforded **116** in 75% yield (Scheme 21).

Scheme 21:- Preparation of *meso* - 119



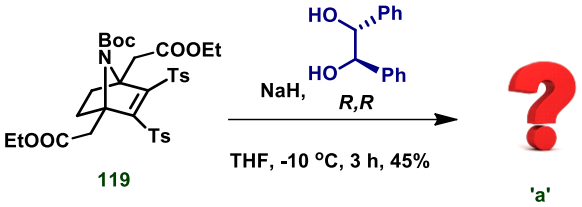
Cycloadduct **116** was characterised by observing olefinic protons at {6.94 (d, *J* = 5.4 Hz, 1H), 6.90 (d, *J* = 5.4 Hz, 1H), respectively.

in ^{1}H NMR and corresponding bridgehead carbons in the ^{13}C NMR at 60.79, 60.61 ppm.Hydrogenation of **116** (Pd/C, 10 %, 1 atm.), gave **117** in quantitative yield (99%). Nucleophilic substitution of bromo moiety in **117** with 4-methyl thiophenol sodium salt afforded **118** in 85% yield which on oxidation using *m*-CPBA produced *meso*-**119** in 80 % yield. The structure of **118** was confirmed by detailed ^{1}H NMR and ^{13}C NMR spectroscopy.

Desymmetrization of *meso*-119:-

As per our planned strategy of obtaining **70** in optically pure form, we proceeded further with the desymmetrization of **119** by reacting it with the sodium salt of chiral benzoin [sodium hydride (2.1 mmol), hydrobenzoin (2.1 mmol), toluene (0.1 M)] which gave compound **'a'** in 45% yield.

Scheme 22:- Desymmetrization of *meso* - 119

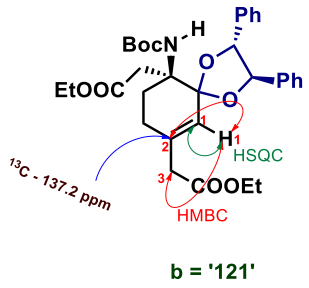


Highly complex NMR data (both ^{1}H and ^{13}C NMR) made it difficult to completely characterise[39] this product. HPLC analyses (column: Atlantis C18, mobile phase: {MeOH: Water} = (90:10)), however, indicated it to be a single compound. The complexity observed in the NMR spectra was, thus, implicated to the presence of the rotamers linked to N-Boc group. Our attempted N-Boc deprotection (TFA, CH_2Cl_2, r.t.) also deprotected chiral acetal moiety. Therefore, to solve this problem **'a'** was first subjected to desulfonylation by reacting with sodium amalgam under boric acid buffer medium[44] which yielded compound '**b**' in 55% (Scheme 22).

^{1}H NMR (800 MHz, $CDCl_3$) indicated two sets of protons for each indicating it to be a mixture of rotamers. The aromatic protons appeared in four bunches at δ = 7.31 (m, 1H), 7.27 – 7.22 (m, 1H), 7.14 – 7.08 (m, 3H), 6.90 – 6.78 (m, 5H) corresponding to two phenyl groups of hydrobenzoin. Proton appearing at 5.86 – 5.67 (m, 1H) may be characterised to an olefinic proton. Proton appearing at 5.10 (br, 1H), which was D_2O exchangeable, corresponds to –NH proton. Two protons appearing between 4.91 – 4.66 (m, 2H) corresponds to benzylic protons of hydrobenzoin moiety. Protons at 4.27 – 3.99 (m, 4H) corresponds to esters (-OCH_2).

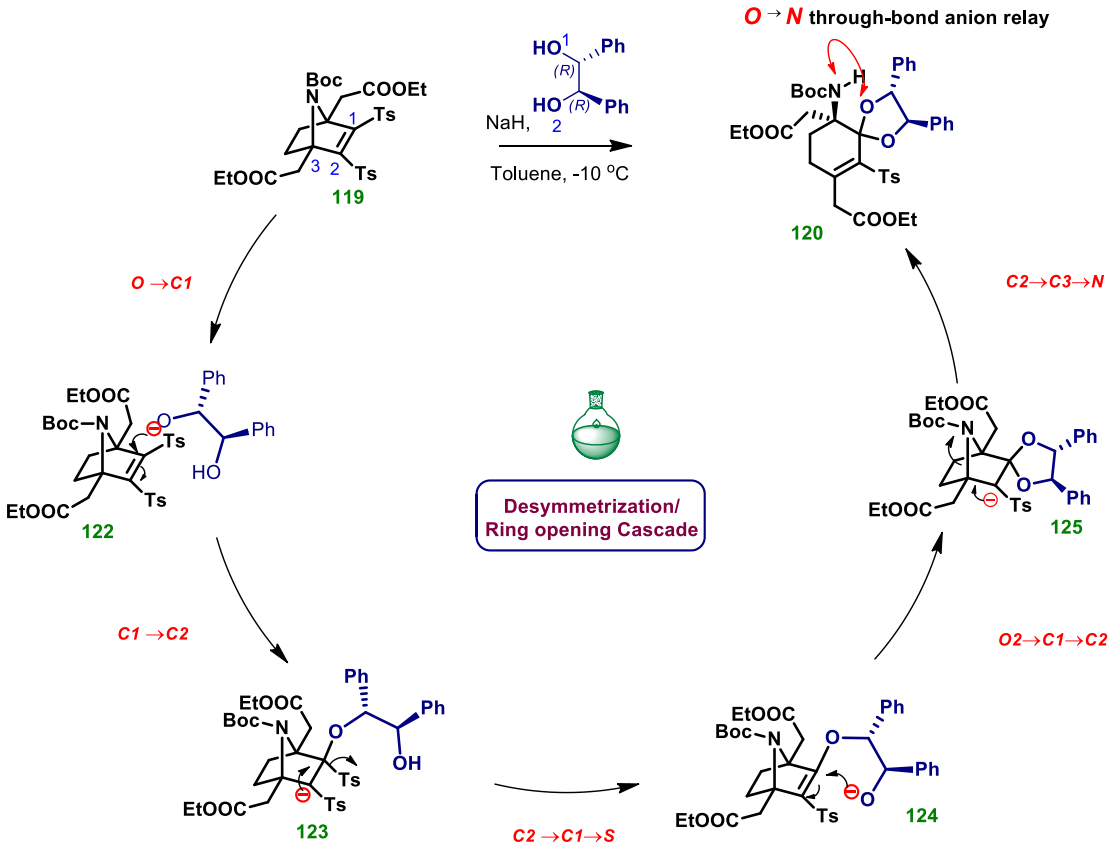
^{13}C NMR of compound '**b**' shows one signal of quaternary carbons in aliphatic region (δ 60.31 ppm) and another quaternary carbon signal in the olefinic region (δ 137.6 ppm). HSQC cross peak (δ 5.86 and δ 130.2) gave characteristic peak corresponding to olefinic C_1 to H_1 correlation. In HMBC spectra cross peak appearing at δ 5.86 and δ 137.2 shows correlation of C_2 to H_1 and another cross peak appearing at δ 5.86 and δ 55.28 shows correlation of H_1 to C_3. HRMS indicated molecular ion peak $[M + Na]^+$ peak at 602.2718 corresponding to $C_{33}H_{41}NNaO_8^+$. Optical rotation of **"b"** was recorded as $[\alpha]_D^{22}$ = +22.3° (*c* = 1.2, $CHCl_3$). Therefore, based on detailed NMR and HRMS data '**b**' was assigned structure **121** as shown in figure 6.

Figure 6:- 2D NMR analysis of 121



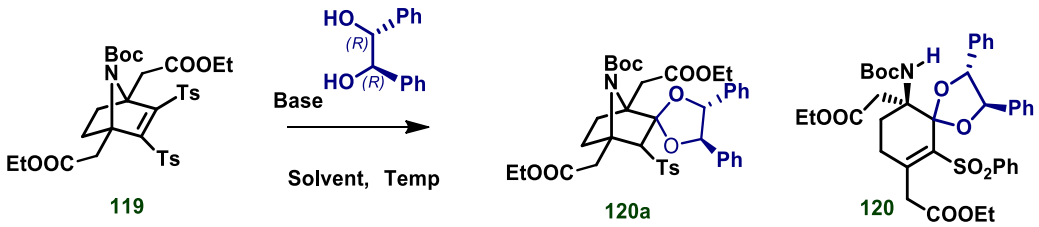
The postulated mechanism for the formation of **'a = 120'** is shown in Scheme 23.

Scheme 23:- Plausible mechanism of desymmetrization/ ring opening cascade



Since our objective was to obtain desymmetrized product **120a** in order to study the selective bond cleavage reaction, we attempted various reaction conditions to obtain **120a** and results are shown in Table 2.

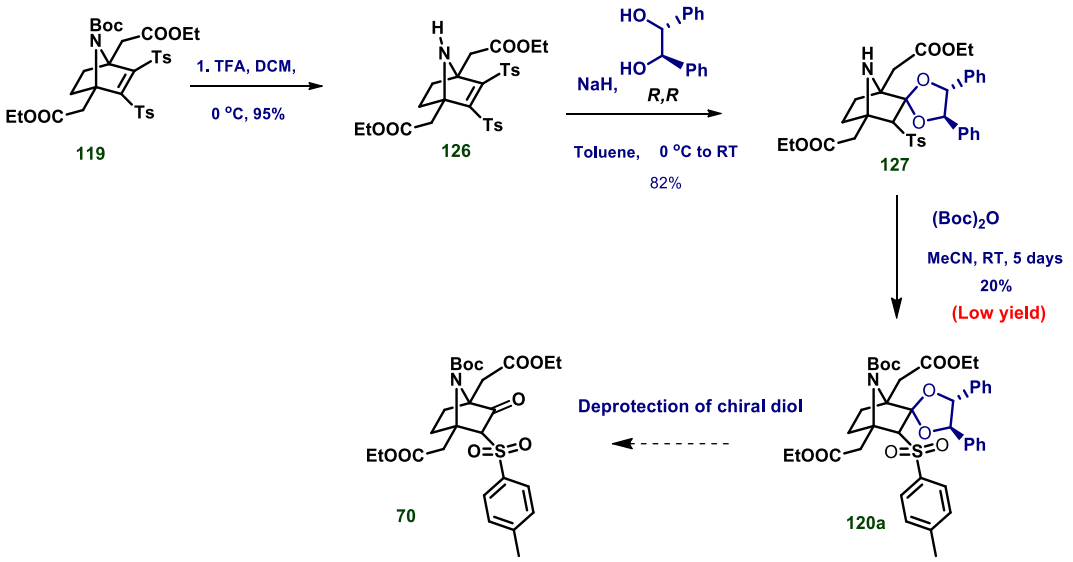
Table -2: Screening the conditions in desymmetrization reaction.



Sl.N	Base	Solvent	Temp (°C)	120a	120
1	NaH	THF	0		35%
2	NaH	THF	-78		30%+ (60% of **117** recovered)
3	NaH	Toluene	0		70%
4	KH	THF	-78	10%	30%
5	KH	Toluene	-78	8%	52%
6	n-BuLi	THF	0,-78		45 % + (25% of **117** recovered)
7	NaH	THF	rt		30%
8	NaH	Cyclopentyl methyl ether	0		42%
9	NaH	Ether	0, -78		Not detected
10	n-BuLi	Ether	0		40%

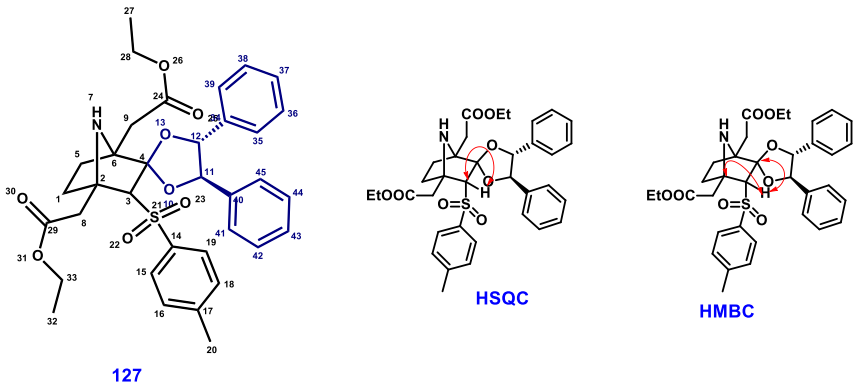
After exhaustive experimentation, we realized that N-Boc group in *meso*-**119** may be responsible for ring opening reaction during desymmetrization. Therefore, we carried out desymmetrization of N-Boc deprotected **126** under the identical reaction condition as described above for the reaction depicted in Scheme 21 which produced **127** in 82 % yield.

Scheme 24:- Modified desymmetrization



HPLC analysis [(coloumn: Atlantis C18, mobile phase: {MeOH: Water} = (90:10)] indicated this to be a pure single compound.

Figure 7:- Spectral analysis of 127



In ^{1}H NMR spectrum, protons appearing at δ 7.75 (d, J = 8.0 Hz, 2H) were assigned to H_{19} and H_{15}. Protons appearing at (δ 7.45 (d, J = 6.5 Hz, 2H)) were assigned to H_{16} and H_{18}. The aromatic protons of hydrobenzoin part appeared in two bunches at (δ 7.34, m, 5H) and (δ 7.28, m, 5H), respectively. Protons appearing at δ 5.15 (d, J = 9.0 Hz, 1H) and δ 4.92 (d, J = 9.0 Hz, 1H) corresponds to two benzylic protons (H_{11} and H_{12}). Proton appearing at δ 4.38 (s, 1H) corresponded to H_3 confirming the formation

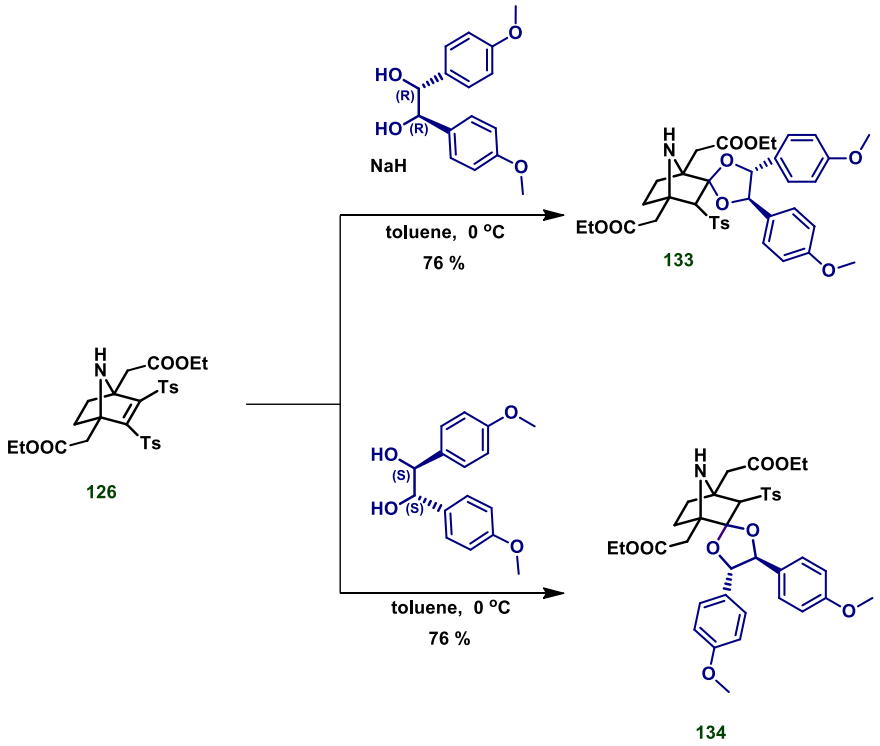
of **127**. Four bunches of multiplets at δ 4.16 (m, 1H), δ 4.11 (m, 1H), δ 3.99 (m, 1H) and δ 3.94 (m, 1H) corresponds to (-OCH_2) protons of two esters. A broad singlet at δ 3.60 (br, 1H) corresponded to –NH proton. Two doublets appearing at δ 3.08 (d, *J* = 14.5 Hz, 2H) and δ 2.87 (d, *J* = 15.0 Hz, 2H) corresponded to H_8-(2H) and H_9-(2H). Another two triplets appearing at δ 1.25 (t, *J* = 7.5 Hz, 3H) and δ 1.15 (t, *J* = 7.5 Hz, 3H) were assigned to H_{32}-(3H) and H_{27}-(3H), respectively.

In ^{13}C NMR and DEPT spectra, characteristic bridgehead quaternary carbons C_2 and C_6 appeared at δ 69.06 and δ 65.10, respectively. Further support to the structural assignments of **127** came from HSQC cross peak correlation between H_3 (δ 4.38 and C_3 (at δ 75.2). Similarly, in HMBC, showed correlation between H_3 (δ 4.38) with C6 (δ 65.10) and C_4 (δ 114.88). HRMS gave molecular ion peak $[M + Na]^+$ at 656.2290 corresponding to $C_{35}H_{39}NNaO_8S^+$. Optical rotation of **127** was recorded as $[\alpha]_D^{22}$ = +24.3° (*c* = 1.2, $CHCl_3$).

With this success in hand, we turned our attention towards preparing desired compound **70** (Scheme 24) by N-Boc protection followed by removal of the acetal moiety. However, our various attempts to affect N-Boc protection from **127** remained ineffective**.** This unexpected observation led us to reason out that ester groups of **127** may be forming intramolecular H-bonding with –NH group making it difficult for Boc anhydride to approach for reaction.

Therefore, we selected (*R, R)*-hydroanisoin for desymmetrization considering its easy removal. Usual reaction of *meso*-**126** with (*R,R*)- hydroanisoin under identical reaction conditions {sodium hydride (2.1 mmol), hydrobenzoin (2.1 mmol), toluene (0.1 M)} as mentioned above provided **133** (76 %) as a single diastereomers. Reaction with (*S,S*)-hydroanisoin gave expected opposite diastereomer **134** (Scheme 25)**.**

Scheme 25:- Modified desymmetrization of *meso* - 126



The plausible mechanism for desymmetrization is depicted in Scheme 26.

Scheme 26: Plausible mechanism of desymmetrization

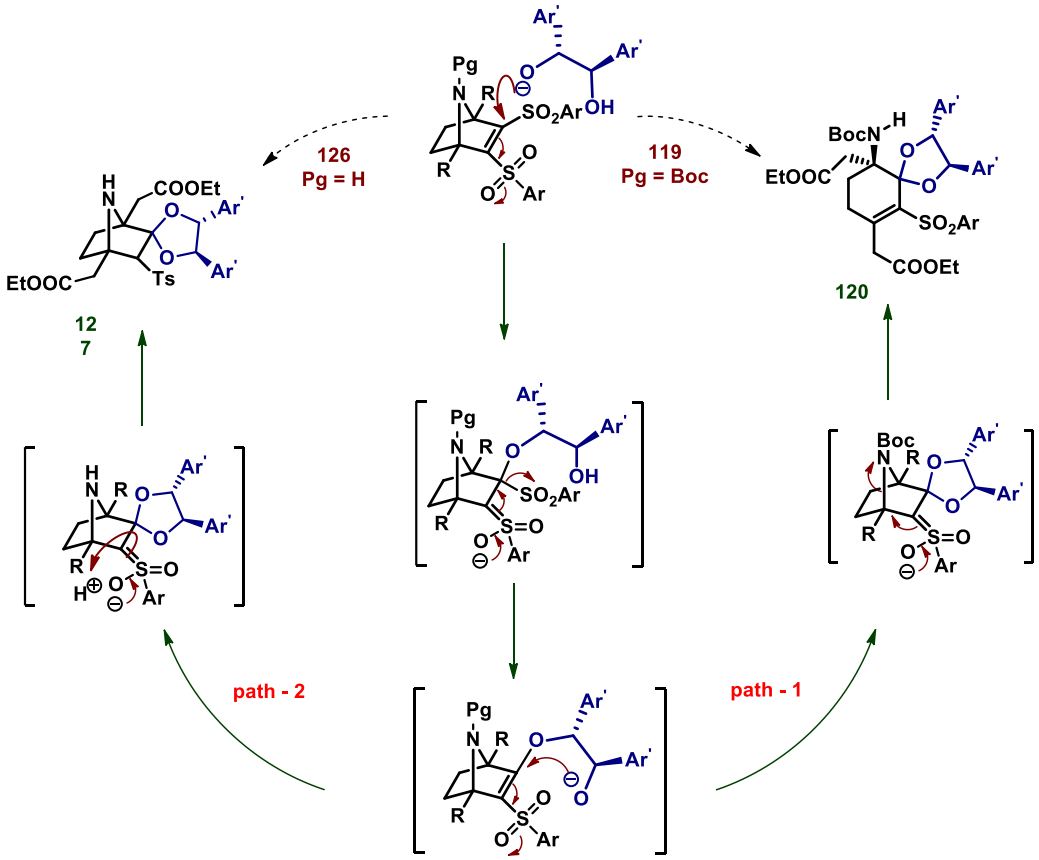
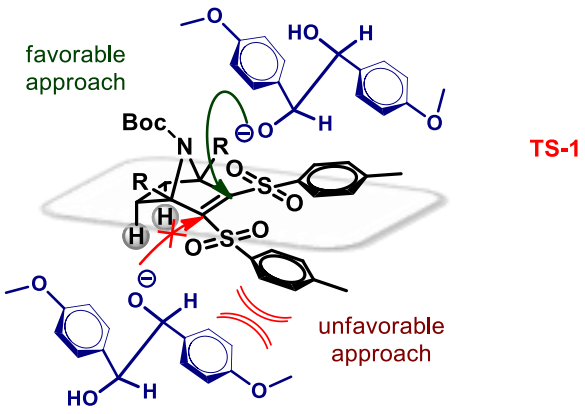
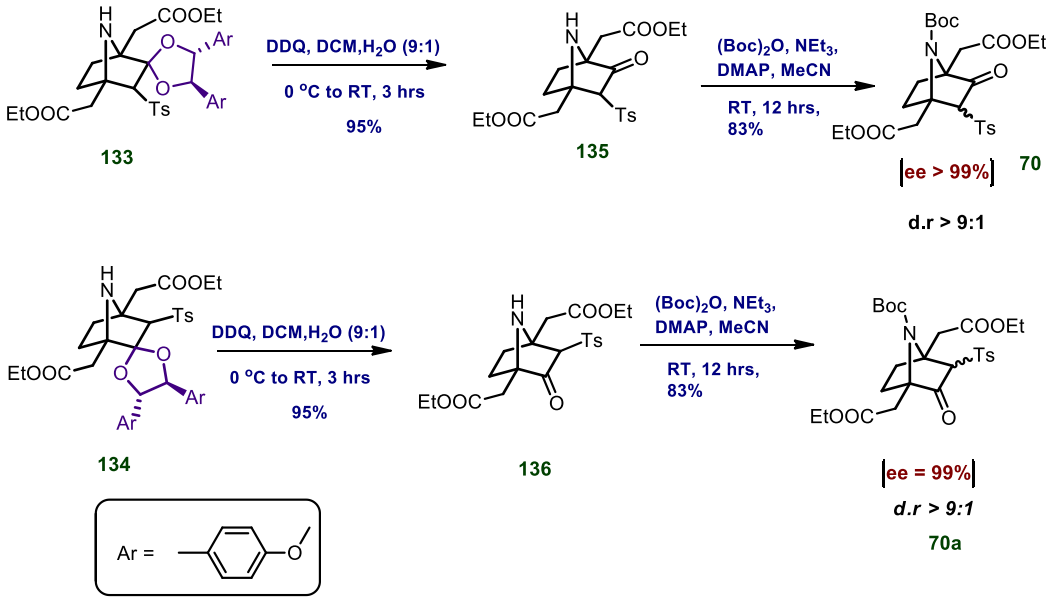


Figure 7: Transition state for diastereoselectivity at desymmetrization



From the results, it is obvious that desymmetrization of **119** follows path-1 to yield **120** whereas **126** follow path-2 to produce **127**. It may be worthy of mention that conformational geometry of 7-azabicyclic framework and stearic hindrance between phenyl groups of hydroanisoin and phenylsulfonyl group probably governs the diastereoselectivity as depicted above implicating transition state (TS-1, figure 7).[24b] It would also be appropriate here to refer to our previous study where temperature was used as a switch for diastereoselctivity whereas present result suggests that N-Boc group could be used to tune the structural isomerism.

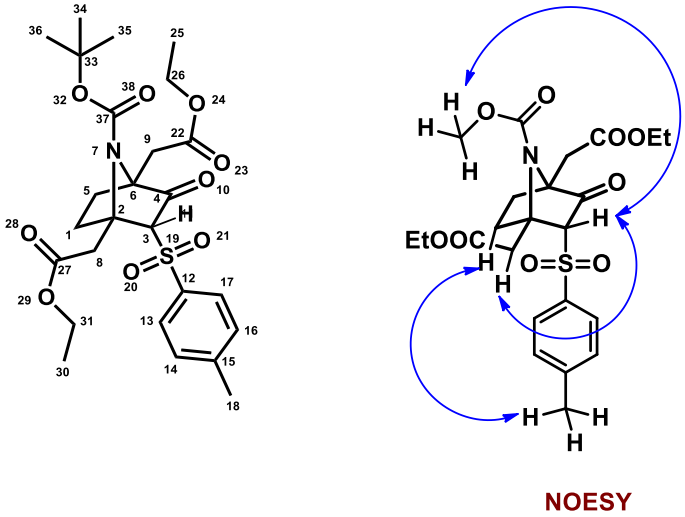
Scheme 27:- Preparation of 70 and 70a from desymmetrized 134



Removal of the chiral ketal moiety from **133** (1 mmol) by stirring with DDQ (3 mmol) in DCM: H_2O (9:1) for 3 h afforded **135** in 95 % yield.

^{13}C NMR of crude **135** showed a signal at δ 202.92 corresponding to a keto functionality confirming the success of the ketal deprotection. N-Boc protection (Boc anhydride, NEt_3, MeCN) of **135** furnished **70** in 83% yield in 9:1 diastereomeric ratio.

Figure - 8:- Spectral analysis of 70



After separation of major diastereomer by column chromatography (72%), its chiral purity (>99 %) was ascertained by chiral HPLC (chromasil–ODH, mobile phase (n-hexane: iso- propyl alcohol= 70:30) analysis.

Aromatic protons of *p*-tosyl group in ^1H NMR spectrum appeared in a AB pattern at δ 7.84 (d, *J* = 8.3 Hz, 2H) and δ 7.34 (d, *J* = 8.0 Hz, 2H), respectively. The doublet appearing at δ 5.56 (d, *J* = 1.9 Hz, 1H) corresponded to H3 while two distinct $–OCH_2$ protons of the ester groups appeared at δ 4.17 (qd, *J* = 7.1, 2.8 Hz, 2H), δ 4.01 (qd, *J* = 7.1, 2.8 Hz, 2H), respectively. Two methylene protons belonging to H_8 and H_9 appeared at δ 3.63 (d, *J* = 17.7 Hz, 2H) and at δ 3.44 (d, *J* = 17.7 Hz, 2H), respectively. Methyl protons of N- Boc group appeared as a singlet at δ 1.33 (s, 9H). Other remaining protons corresponding to C_{30}-3H and C_{25}-3H appeared at δ 1.27 (t, *J* = 7.1 Hz, 3H), δ 1.15 (t, *J* = 7.1 Hz, 3H), respectively.

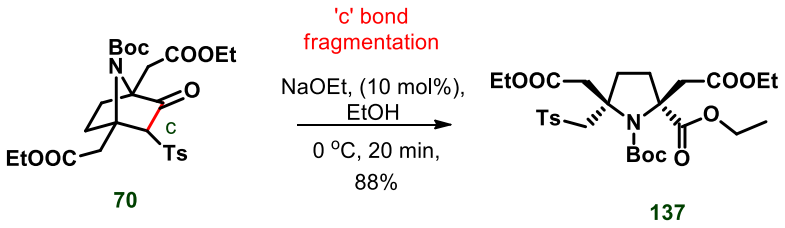
In ^{13}C NMR spectrum, two bridgehead carbons (C_5 and C_2) appeared at δ 60.62, δ 60.49, respectively. The *endo*-orientation of *p*-tosyl group is suggested based on the observed correlation between H_3 (δ 5.56) and methyls (δ 1.33) of Boc group in the NOESY spectrum. HRMS indicated molecular ion peak $[M + Na]^+$ peak 560.1924 corresponding to $C_{26}H_{35}NNaO_9S^+$. Optical rotation of **70** was found to be $[\alpha]_D^{22}$ = -27.6° (c = 0.9, $CHCl_3$). Identical reactions with **134** also gave **70a** (*ee* = >99%, $[\alpha]_D^{22}$ = +27.1° (c = 1.0, $CHCl_3$).

Section –1.4: Selective Bond fragmentation of 70

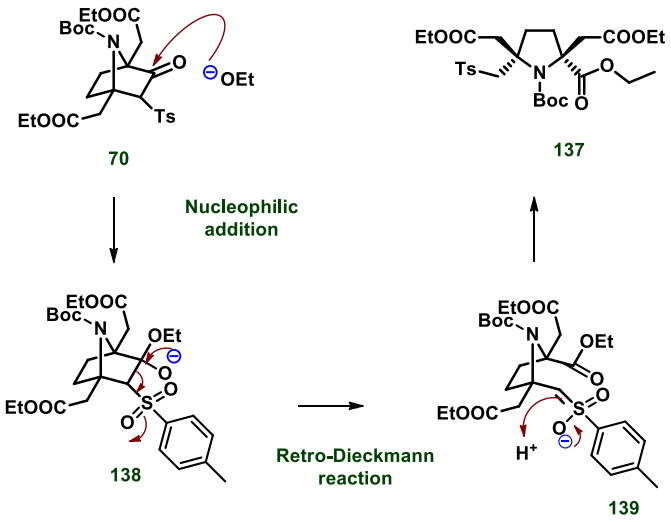
"*c*" bond cleavage of 70 :

Having secured scalable route to **70**, we turned our attention towards establishing its selective bond dissociation chemistry. As planned in Scheme 9, selective bond dissociation of **70** can give corresponding aza-quaternary scaffolds which can produce chiral azaspirocyclanes belonging to various family of alkaloids.

Scheme 28:- '*c*' bond dissociation of bicyclic precursor 70



To realize our proposed transformation, at first, '*c*' bond fragmentation was carried out by treating **70** with sodium ethoxide (10 mol %) in ethanol which afforded **137** in 88 % yield. Cleavage mechanism for this reaction is shown to involve two steps as shown in Scheme 29. Product **137** was characterized by detailed spectroscopic analyses. In the ^1H NMR spectrum, protons related to *p*-tosyl group appeared in AB pattern at δ 7.62 (d, *J* = 8.3 Hz, 2H) and δ 7.36 (d, *J* = 8.3 Hz, 2H), respectively. Six protons appearing at δ 4.16 – 4.09 (m, 6H) corresponds to three ($-OCH_2$) groups. Four bunches of methylene protons, belonging to ester methylenes, appeared doublet each at δ 3.64 (d, *J* = 17.6 Hz, 1H), δ 3.37 (d, *J* = 17.7 Hz, 1H), δ 3.33 (d, *J* = 17.3 Hz, 1H), δ 3.23 (d, *J* = 17.7 Hz, 1H) and at 3.10 (d, *J* = 17.7 Hz, 1H), and δ 2.71 (d, *J* = 17.7 Hz, 1H).

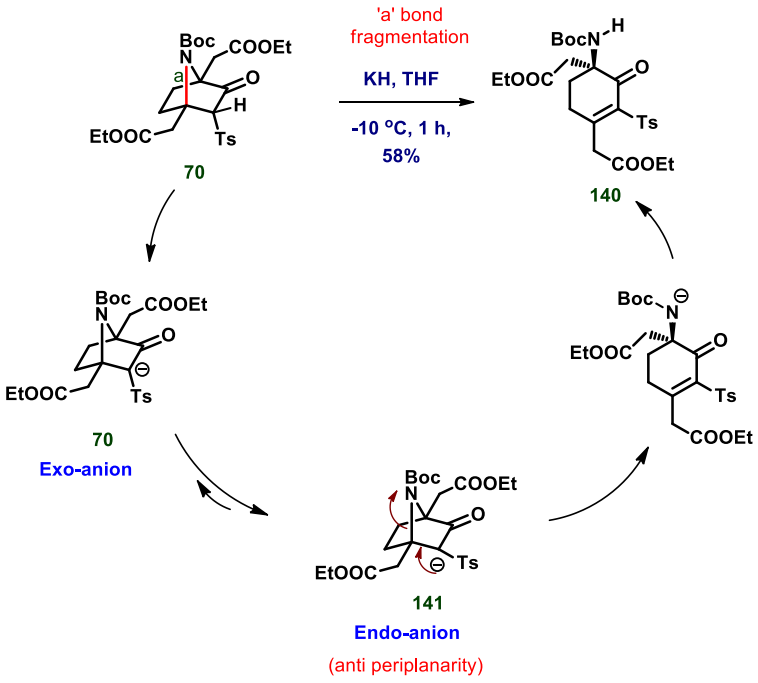


Scheme 29:- Plausible mechanism for '*c*' bond cleavage.

Two other methylene protons, belonging to pyrrolidine moiety appeared at δ 1.66 (d, *J* = 13.1Hz, 4H). Protons related to N-Boc methyls appeared at δ 0.88-1.05 (m, 9H). In ^{13}C NMR, carbon appearing at δ 70.91 corresponding to C_9, providing crucial information for '*c*' bond cleavage.

"*a*" bond cleavage of 70 :

Scheme 30:- '*a*' bond dissociation of bicyclic precursor 70



After successful cleavage of '*c*' bond in **70**, we carried out 'a' bond cleavage by reacting it with potassium hydride (2 mmol) at -78 °C in THF which furnished **140** in 58 % yield.

It may be noted that cyclohexylamine derivatives related to **140** structural frameworks forms core scaffold of many natural products as well as drug derivatives (Scheme 30).

The structural assignment of **140** was made by detailed spectroscopic analysis. For example, in ^{1}H NMR spectrum, protons related to *p*-tosyl group appeared at δ 7.89 (d, *J* = 8.3 Hz, 2H) and at δ 7.36 (d, *J* = 8.0 Hz, 2H), respectively. Methylene protons belonging to (-OCH_2) groups were characterized at δ 4.24 – 4.08 (m, 4H). Ester methylene protons adjacent to aza-quaternary centre, appeared at δ 3.85-3.62 (m, 1H), δ 3.48 (d, *J* = 17.6 Hz, 1H) and protons appearing at δ 3.11 (d, *J* = 17.7 Hz, 2H) were assigned to two protons corresponding to methylene protons of other ester part. Methyl groups of N-Boc group as well as ester methyls merged together and appeared at δ 0.88-1.31 (m, 14H).

In ^{13}C NMR spectrum, carbon signal at δ 145.67 was assigned to C_6 which gave crucial information of 'a' bond cleavage whereas other aza-quaternary carbon signal appeared at δ 60.97.

Conclusion:-

In summary, We have developed conceptually different approach for the synthesis of bridgehead quaternary 7-azabicycloheptane[2.2.1]template in chiral fashion using asymmetric desymmetrization protocol. Conceptual exploitation of ring strain of this aza-bicyclic ring system is utilized for selective bond dissociation reaction to obtain various aza-quaternary scaffolds which presents core structures of many biologically active natural products and drugs. An unprecedented protecting group effect for tuning the structural isomerism during the desymmetrization is also observed.

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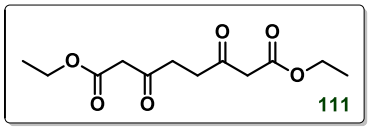
Section 1.6 : Experimental section

Methyl 2-[2-(MethoxycarbonyI)-3-oxocyclopent-l-enyl]acetate (111):



A three necked 5 L round bottom flask was charged with magnesium (25 g, 1.05 mol) in dry tetrahydrofuran (400 mL) and stirred. To this suspension, slow addition of isopropyl bromide (123 g, 1 mol) in dry tetrahydrofuran (400 mL) at -10 °C generated isopropyl magnesium bromide. After 2 h, the reaction mixture was diluted with THF (2 L) and potassium ethyl malonate (178 g, 1 mol) was added over a period of 30 min. The slurry was heated until gas evolution ceased and allowed to warm up to room temperature. Succinyl chloride (38.3 g, 0.25 mol) was added drop wise over a period of 20 min and stirring was continued for 18 h. The reaction mixture was quenched with a solution of sulfuric acid (70 mL) in ice water (700 mL). The organic layer was separated and the residual aqueous phase was extracted with ethyl acetate (3 X 200 mL). These extracts and the organic layer were combined, washed with saturated sodium bicarbonate solution and brine and dried over sodium sulphate. Evaporation of the solvents afforded **111** as an oil (49 g, 76.5% yield)

TLC: - R_f =0.5 (EtOAc:Hexane = 1:3, UV, ninhydrin, $KMnO_4$)

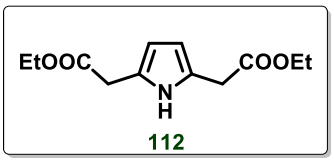
IR (film): ν_{max} = 1740, 1701cm^{-1}

^{1}H NMR (800 MHz, $CDCl_3$): δ = 4.19 (q, *J* = 7.09, 4H), 3.48 (s, 4H), 2.85 (s, 4H), 1.26 (t, *J* = 7.09, 6H)

^{13}C NMR (201 MHz, $CDCl_3$): δ = 201.2, 167.1, 61.6, 49.4, 36.5, 14.2

HRMS:- $[M + Na]^+$ calcd for $C_{12}H_{18}O_6Na^+$ 281.0996, found 281.1002.

Diethyl 2, 2'-(1H-pyrrole-2,5-diyl)diacetate (112):-



112

In a 1L round bottom flask diethyl 3,6-dioxooctanedioate (**111)** (25.8 g, 100.0 mmol) and ammonium acetate (30.8 g, 400.0 mmol) were mixed together by stirring. The mixture was heated at 85 °C for 1 h while stirring and acetic acid (100 mL) was added to the stirring suspension. After 3 h of stirring, a brown colour thick solution appeared which was diluted by adding dichloromethane (1000 mL) and distilled water (1000 mL) and organic layer was separated. The residual aqueous phase was extracted with dichloromethane (500 mL x 2) and the combined extracts were dried over Na_2SO_4. The drying agent was filtered off and the filtrate evaporated in vacuo to yield **112** as a brown solid (21.9 g, 91%).

TLC: - R_f =0.4 (EtOAc:Hexane = 1:3, UV, ninhydrin, $KMnO_4$)

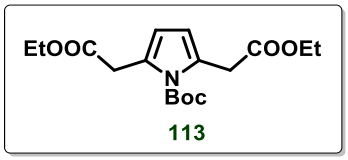
IR (film): ν_{max} = 3373, 3180, 3107, 2982, 2937, 1733, 1591, 1506, 1445, 1404, 1369, 1030, 768.cm^{-1}

^{1}H NMR (800 MHz, $CDCl_3$): δ = 9.04 (s, 1H), 5.91 (d, *J* = 2.72, 2H), 4.18 (q, *J* = 7.15 4H), 3.62 (s, 4H), 1.28 (t, *J* = 7.10, 6H)

^{13}C NMR (201 MHz, $CDCl_3$): δ = 171.2, 123.5, 107.4, 61.1, 33.5, 14.2.

HRMS:- $[M + Na]^+$ calcd for $C_{12}H_{17}NNaO_4^+$ 262.1050, found 262.1052.

Diethyl 2,2'-(1-(*t*ert-Butoxycarbonyl)-1H-pyrrole-2,5-diyl)diacetate (113):-



113

To a stirred solution of **112** (23.9 g, 0.1 mol) in dry acetonitrile (100 mL) was added DMAP (1.2 g, 0.01 mol) and Boc_2O (26 g, 0.12 mol) at room temperature. Evolution of gas commenced and after 0.5 h, the colour of the reaction mixture turned dark red. The stirring at room temperature for 48 h, the solvent was evaporated under vacuum and the residue was subjected to flash column chromatography using EtOAc/hexane (1:4) under reduced pressure to obtain **113** as an yellow oil (20.0 g, 79%).

TLC: - R_f =0.4 (EtOAc:Hexane = 1:4, UV, ninhydrin, $KMnO_4$)

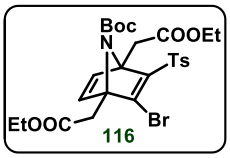
IR (film): ν_{max} = 3373, 3180, 3107, 2982, 2937, 1721, 1732, 1591, 1506, 1445, 1404, 1369, 1030, 768.cm^{-1}

^{1}H NMR (800 MHz, $CDCl_3$): δ = 5.97 (s, 2H), 4.13 (q, *J* = 7.15 4H), 3.83 (s, 4H), 1.52 (s, 9H), 1.24 (t, *J* = 7.10, 6H)

^{13}C NMR (201 MHz, $CDCl_3$): δ = 171.01, 171.0, 149.91, 128.31, 112.59, 84.4, 60.75, 35.91, 27.83, 27.74.

HRMS:- $[M + Na]^+$ calcd for $C_{17}H_{25}NNaO_6^+$ 362.1574, found 362.1572.

Diethyl 2,2'-((1R,4R)-2-bromo-7-(*tert*-Butoxycarbonyl)-3-tosyl-7-azabicyclo [2.2.1] hepta -2,5-diene-1,4-diyl)diacetate (116):-



116

To a stirred suspension of **113** (25.9 g, 0.1 mol) in toluene (60 mL) was added **114a**, (33.9 g, 0.1 mol) at 55 °C. The resultant mixture was stirred at that temperature for 12 h. The solvent was evaporated under vacuum and the residue was subjected to flash column chromatography using EtOAc/hexane (1:4) as an eluent to give resultant cycloadduct (46 g, 77%) as a yellow oil.

TLC: - R_f =0.3 (EtOAc:Hexane = 1:3, UV, ninhydrin, $KMnO_4$)

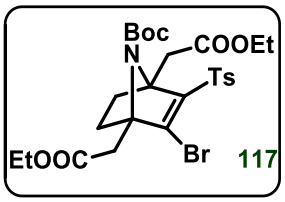
IR (film): ν_{max} = 2982, 2256, 1735, 1324, 1155, 909, 734 cm^{-1}

^{1}H NMR (800 MHz, $CDCl_3$): δ = 7.75 (d, *J* = 8.2 Hz, 2H), 7.32 (d, *J* = 8.0 Hz, 2H), 6.94 (d, *J* = 5.4 Hz, 1H), 6.90 (d, *J* = 5.4 Hz, 1H), 4.19 - 4.06 (m, 4H), 3.61 (d, *J* = 16.8 Hz, 1H), 3.54 (d, *J* = 16.8 Hz, 1H), 3.45 (s, *J* = 16.8 Hz, 1H), 3.39 (d, *J* = 16.8 Hz, 1H), 2.42 (s, 3H), 1.30 (s, 9H), 1.22 (td, *J* = 7.1, 3.5 Hz, 6H).

^{13}C NMR (201 MHz, $CDCl_3$): δ = 169.38, 169.23, 154.29, 153.66, 152.10, 145.52, 145.21, 141.26, 136.81, 129.97, 127.69, 82.82, 79.68, 60.79, 60.61, 35.23, 35.12, 27.92, 21.73, 14.16, 14.13. HRMS (*m/z*):

HRMS:- $[M + Na]^+$ calcd for $C_{26}H_{32}BrNNaO_8S^+$ 620.0924, found 620.0913.

Diethyl 2,2'-(2-bromo-7-(*tert*-Butoxycarbonyl)-3-tosyl-7-azabicyclo[2.2.1]hepta-2,5-diene-1,4-diyl)diacetate (117):-



The resultant **116** (5 g, 8.36 mmol) was dissolved in methanol (50 mL) and was evacuated. The flask was refilled with argon (two cycles), Pd/C (10 wt%, 0.515 g, 0.484 g atom) was added to the flask, flushed with hydrogen gas (2 cycles) and stirred. Reaction progress was monitored by TLC. After complete conversion (3 h), reaction mixture was passed through celite pad, and pad was washed with ethyl acetate (3x50 mL). The solvent was evaporated under vacuum and the residue was subjected to flash column chromatography using EtOAc/hexane (1:4) as eluent to give **117** (4.9 g, 98%).

TLC:- R_f =0.33 (EtOAc:Hexane = 1:4, Ninhydrin).

IR (film): ν_{max} = 2982, 2255, 1736, 1699, 1371, 910, 732 cm^{-1}

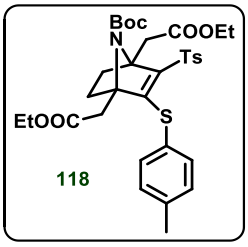
^{1}H NMR (800 MHz, $CDCl_3$) δ = 7.83 (d, *J* = 8.3 Hz, 2H), 7.31 (d, *J* = 8.0 Hz, 3H), 4.14 - 4.06 (m, 2H), 4.05 -3.96 (m, 2H), 3.56 (d, *J* = 17.8 Hz, 1H), 3.44 (d, *J* =

17.8 Hz, 1H), 3.29 (d, *J* = 17.4 Hz, 1H), 3.23 (d, *J* = 17.4 Hz, 1H), 2.40 (s, 3H), 2.25 - 2.21 (ddd, 1H), 2.13 -2.08 (ddd, 2H), 1.48 (ddd, *J* = 11.9, 8.9, 3.5 Hz, 2H), 1.34 (ddd, *J* = 12.4, 8.9, 3.8 Hz, 2H), 1.24 (s, 9H), 1.19 (td, *J* = 7.2 Hz, 6H).

^{13}C NMR (201 MHz, $CDCl_3$) δ = 169.52, 169.06, 152.90, 145.09, 144.07, 140.47, 138.16, 129.95, 129.93, 127.82, 81.89, 73.80, 72.92, 60.67, 60.42, 36.57, 35.85, 33.05, 30.37, 28.01, 21.82, 14.21, 14.17.

HRMS (*m/z*): $[M + Na]^+$ calcd for $C_{26}H_{34}BrNNaO_8S^+$ 622.1081, found 622.1076.

Diethyl2,2'-((1S,4S)-7-(tert-butoxycarbonyl)-2-(p-tolylthio)-3-tosyl-7-azabicyclo [2.2.1]hept- 2-ene-1,4-diyl)diacetate (118):-



To an ice cooled suspension of NaH (2.34 g, 58.4 mmol, 60% suspension in mineral oil) in anhydrous THF (60 mL) was added drop wise a solution of 4-methyl thiophenol (6.0 g, 48.66 mmol) dissolved in anhydrous THF (120 mL). After complete addition, the reaction mixture was stirred at room temperature for additional 15 min. A solution of **117** (29.1 g, 48.66 mmol) dissolved in anhydrous THF (120 mL) was added drop wise into the flask while stirring at 0 °C. The reaction mixture was further allowed to stir at room temperature for additional 1 h. Completion of the reaction was monitored by TLC and after complete disappearance of **117**, the reaction mixture was quenched with brine (100 mL). The mixture was extracted with EtOAc (2 x 200 mL) and the combined organic layers were dried over Na_2SO_4, filtrated and concentrated in *vacuo*. The residue was purified by flash chromatography (hexane:EtOAc = 4:1) affording **118** (25.89 g, 89%).

TLC:- R_f =0.3 (EtOAc:Hexane = 1:4, Ninhydrin).

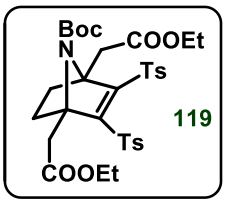
IR (film): ν_{max} = 2980, 2254, 1741, 1704, 1323, 1152, 1033,732 cm^{-1}

^{1}H NMR (800 MHz, $CDCl_3$) δ = 7.95 (d, *J* = 8.2 Hz, 1H), 7.29 (d, *J* = 8.1 Hz, 1H), 7.04 (d, *J* = 8.1 Hz, 1H), 7.01 (d, *J* = 8.1 Hz, 1H), 4.20 - 4.11 (m, 1H), 4.02 - 3.94 (m, 1H), 3.65 (d, *J* = 17.6 Hz, 1H), 3.60 (d, *J* = 17.6 Hz, 1H), 2.90 (d, *J* = 17.2 Hz, 1H), 2.74 (d, *J* = 17.2 Hz, 2H), 2.45 (s, 0H), 2.41 (s, 2H), 2.31 (s, 2H), 1.62 (ddd, 1H), 1.37 (ddd, 1H), 1.27 (t, *J* = 7.1 Hz, 3H), 1.24 (s, 9H), 1.14 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (201 MHz, $CDCl_3$) δ = 170.12, 169.67, 154.00, 150.20, 144.75, 139.09, 138.57, 131.67, 130.25, 129.71, 128.56, 128.21, 81.56, 75.53, 72.86, 60.47, 60.40, 36.38, 36.31, 32.84, 30.74, 28.00, 27.10, 21.83, 21.36, 14.37, 14.21.

HRMS (*m/z*): $[M + Na]^+$ calcd for $C_{33}H_{41}NNaO_8S_2^+$ 666.2166, found 666.2150.

Diethyl 2,2'-(7-(tert-butoxycarbonyl)-2,3-ditosyl-7-azabicyclo[2.2.1]hept-2-ene-1,4-diyl)diacetate (119):-



119

To an ice-cooled solution of **118** (25 g, 40.27 mmol) in CH_2Cl_2 (250 mL) was added a solution of *m*-CPBA (29.634 g, 120.81 mmol) in CH_2Cl_2 (250 mL) drop wise. After complete addition, the reaction mixture was allowed to stir at the same temperature for 3 h and finally at room temperature for another 1 h. Silica gel was added to the reaction mixture to absorb the crude product and purified by silica gel column chromatography using ethyl acetate: hexane (1:3 – 1:2) which gave **119** (24.1 g, 92%) as a white foam.

TLC:- R_f = 0.4 (EtOAc:Hexane = 1:2, Ninhydrin).

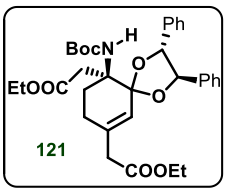
IR (film): ν_{max} = 2982, 2256, 1738, 1596, 1339, 1323, 1157, 910,733 cm^{-1}

^{1}H NMR (800 MHz, $CDCl_3$) δ = 7.95 (d, *J* = 8.3 Hz, 4H), 7.32 (d, *J* = 8.2 Hz, 4H), 4.11 - 4.04 (m, 4H), 3.54 (d, *J* = 17.4 Hz, 2H), 3.44 (d, *J* = 17.4 Hz, 2H), 2.47 (d, *J* = 8.1 Hz, 2H), 2.42 (s, 6H), 1.51 (d, *J* = 8.1 Hz, 2H), 1.21 (t, *J* = 7.1 Hz, 6H), 1.19 (s, 9H).

^{13}C NMR (201 MHz, $CDCl_3$) δ = 169.72, 154.63, 153.71, 145.39, 138.32, 129.86, 128.43, 82.31, 73.78, 60.57, 36.42, 31.22, 27.79, 27.03, 21.88, 14.25.

HRMS (*m/z*): $[M + Na]^+$ calcd for $C_{33}H_{41}NNaO_{10}S_2^+$ 698.2064, found 698.2059.

Diethyl 2,2'-((2R,3R,6S)-6-((*tert*-butoxycarbonyl)amino)-2,3-diphenyl-1,4-dioxaspiro [4.5]dec-9-ene-6,9-diyl)diacetate (121) :-



To an ice-cooled anhydrous toluene (3 mL) solution containing suspension of NaH (0.17 g, 4.33 mmol, 60% suspension in mineral oil) was added drop wise a solution of (+)-hydrobenzoin[4] (0.451 g, 2.11 mmol) dissolved in anhydrous toluene (6 mL). After complete addition, the reaction mixture was allowed to stir at room temperature for 0.5 h and cooled to 0 °C. A solution of **119** (1.36 g, 2.11 mmol) dissolved in anhydrous toluene (8 mL) was added drop wise into the flask while stirring at -10 °C. The reaction mixture was further allowed to stir at the same temperature for an additional 3.5 h. After complete disappearance of **119**, the reaction was quenched at the same temperature by drop wise addition of methanol (2 mL). The mixture was extracted with EtOAc (2x 20 mL) and the combined organic layers were dried over Na_2SO_4, filtered and concentrated in *vacuo*. The residue was purified by flash chromatography (hexanes:EtOAc = 3:1) affording **120** (0.540 g, 55%)[5]

To a stirring solution of boric acid (0.463 g, 7.5 mmol) in anhydrous methanol (2 mL), **120** (0.54 g, 0.75 mmol) dissolved in methanol (7 mL) was added. The reaction mixture was cooled to 0 °C and sodium amalgam (2.0 g, 7%) was added portion wise

(30 min) while stirring at the same temperature. The reaction mixture was allowed to stir for an additional 3 h at 0 °C. The progress of reaction was monitored by TLC and after the completion of the reaction; water (1 mL) was added drop wise. The solution was warmed to room temperature and extracted with ethyl acetate. The combined organic layer was washed with brine and dried over Na_2SO_4. Solvent was evaporated under reduced pressure and purified by column chromatography affording desulfonylated cyclohexylamine **121** (0.286 g, 53%).

TLC:- R_f = 0.6 (EtOAc:Hexane = 1:4, PMA).

IR (film): ν_{max} = 2981, 2254, 1739, 1704, 1321, 1052, 1021,921,732 cm^{-1}

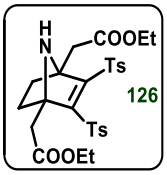
1H NMR (800 MHz, $CDCl_3$) (mixture of rotamers) 1H NMR (800 MHz, $CDCl_3$) δ = 7.31 (d, *J* = 8.2, 1H), 7.27 – 7.22 (m, 1H), 7.14 – 7.08 (m, 2H), 6.90 – 6.78 (m, 4H), 5.86 – 5.67 (m, 1H), 5.10 (d, *J*=18.1, 1H), 4.91 – 4.66 (m, 2H), 4.27 – 3.99 (m, 4H), 3.86 – 3.71 (m, 6H), 3.18 – 2.68 (m, 5H), 2.34 – 2.07 (m, 3H), 1.43 (d, *J* = 7.8, 9H), 1.32 – 1.17 (m, 6H).

^{13}C NMR (201 MHz, $CDCl_3$) δ = 171.28, 170.61, 170.57, 160.00, 159.90, 159.64, 159.62, 155.19, 137.63, 128.86, 128.78, 128.00, 127.84, 113.98, 113.95, 113.93, 113.89, 106.86, 106.74, 85.33, 84.84, 84.55, 60.84, 60.82, 60.43, 60.31, 55.28, 55.26, 55.23, 42.64, 42.60, 34.69, 31.62, 28.51, 28.48, 28.41, 26.34, 22.68, 14.29, 14.25, 14.16.

HRMS (*m/z*): $[M + Na]^+$ calcd for $C_{33}H_{41}NNaO_8^+$ 602.2724, found 602.2718.

$[\alpha]_D^{22}$ = +22.3° (*c* = 1.2, $CHCl_3$).

Diethyl 2,2'-(2,3-ditosyl-7-azabicyclo[2.2.1]hept-2-ene-1,4-diyl)diacetate (126):-



To a solution of trifluoroacetic acid (25 mL) in dichloromethane (100 mL) was added slowly at 0 °C to a solution of **119** (15 g, 22.22 mmol) in CH_2Cl_2 (100 mL) and the reaction was allowed to warm to room temperature and stirred for 2.5 h. The reaction mixture was quenched with saturated sodium carbonate solution (100 mL) and extracted with dichloromethane (2 × 200 mL). The organic layers were combined, dried over sodium sulphate and concentrated in *vacuo* to afford corresponding **126** (12.1 g, 95%).

TLC:- R_f = 0.4 (EtOAc:Hexane = 1:1, Ninhydrin).

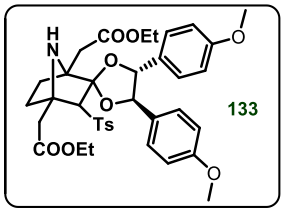
IR (film): ν_{max} = 3441, 3055, 2986, 2305, 1776, 1730, 1265, 1155, 1033,740, 705 cm^{-1}

^{1}H NMR (800 MHz, $CDCl_3$) δ = 7.91 (d, *J* = 8.2 Hz, 4H), 7.30 (d, *J* = 8.1 Hz, 4H), 4.70 (s, 1H), 3.98 (q, *J* = 7.1 Hz, 4H), 3.60 (d, *J* = 17.9 Hz, 2H), 2.70 (d, *J* = 17.9 Hz, 2H), 2.41 (s, 6H), 1.75 (d, *J* = 7.4 Hz, 2H), 1.33 (d, *J* = 7.6 Hz, 2H), 1.19 (t, *J* = 7.2 Hz, 6H).

^{13}C NMR (201 MHz, $CDCl_3$) δ = 170.71, 155.33, 145.03, 137.79, 129.55, 128.37, 72.49, 60.68, 37.46, 32.63, 21.63, 13.95.

HRMS (*m/z*): $[M + Na]^+$ calcd for $C_{28}H_{33}NNaO_8S_2^+$ 598.1540, found 598.1527.

Diethyl 2,2'-((1*S*,3*R*,4*S*,4'*R*,5'*R*)-4',5'-bis(4-methoxyphenyl)-3-tosyl-7-azaspiro [bicycle [2.2.1]heptane-2,2'-[1,3]dioxolane]-1,4-diyl)diacetate (133):-



To an ice-cooled anhydrous toluene (30 mL) solution containing suspension of NaH (3.21 g, 80.86 mmol, 60% suspension in mineral oil) was added drop wise a solution of (*R*,*R*)-hydroanisoin (8.871 g, 32.34 mmol) dissolved in anhydrous toluene

(60 mL). After complete addition, the reaction mixture was allowed to stir at room temperature for 0.5 h and then cooled to –10 °C. A solution of **126** (15.5 g, 26.95 mmol) dissolved in anhydrous toluene (80 mL) was added drop wise into the flask while stirring at -10 °C. The reaction mixture was further allowed to stir at the same temperature for an additional 3.5 h. After complete disappearance of amine, the reaction was quenched at the same temperature with drop wise addition of methanol (10 mL). The mixture was extracted with EtOAc (2x 200 mL) and the combined organic layers were dried over Na_2SO_4, filtered and concentrated in *vacuo*. The residue was purified by flash chromatography (hexane:EtOAc = 3:1 – 2:1) affording **133** (14.17 g, 76%).

TLC:- R_f =0.4 (EtOAc:Hexane = 1:2, Ninhydrin).

IR (film): ν_{max} = 3440, 3019, 2400, 1727, 1614, 1516, 1422, 1215,928, 771 cm^{-1}

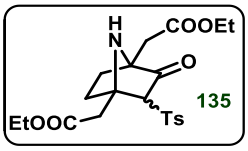
^{1}H NMR (800 MHz, $CDCl_3$) δ = 7.78 (d, *J* = 8.0 Hz, 2H), 7.43 (d, *J* = 8.0 Hz, 2H), 7.31 (d, *J* = 8.0 Hz, 2H), 7.28 (d, *J* = 8.6 Hz, 2H), 6.89 (d, *J* = 8.3 Hz, 2H), 6.84 (dd, *J* = 8.7, 1.3 Hz, 2H), 5.13 (d, *J* = 9.2 Hz, 1H), 4.86 (d, *J* = 9.2 Hz, 1H), 4.36 (d, *J* = 1.9 Hz, 1H), 4.18 (dd, *J* = 10.8, 7.2 Hz, 1H), 4.15 - 4.10 (m, 1H), 4.04 - 4.00 (m, 1H), 3.97 (d, *J* = 7.1 Hz, 1H), 3.83 (d, *J* = 1.7 Hz, 3H), 3.78 (d, *J* = 1.6 Hz, 3H), 3.09(d, *J* = 14.8 Hz, 1H), 2.86 (d, *J* = 14.8 Hz, 1H), 2.61 (t, *J* = 9.1 Hz, 1H), 2.47 (s, 3H), 2.43 (m, 1H), 2.22 (d, *J* = 17.7 Hz, 1H), 1.92 - 1.83 (m, 2H), 1.70 (bs, 1H), 1.40 (q, *J* = 11.9 Hz, 1H), 1.27 (t, *J* = 7.1 Hz, 3H), 1.18 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (201 MHz, $CDCl_3$) δ = 171.05, 170.88, 160.02, 159.65, 144.93, 138.08, 130.10, 129.22, 129.13, 128.81, 126.76, 126.63, 115.31, 114.01, 113.69, 86.26, 83.51, 76.51, 69.18, 65.18, 60.89, 60.62, 55.43, 55.36, 37.43, 35.64, 30.69, 27.94, 21.85, 14.38, 14.23.

HRMS (*m/z*): $[M + Na]^+$ calcd for $C_{37}H_{43}NNaO_{10}S^+$ 716.2500, found 716.2502.

$[\alpha]_D^{22}$ = +29.9° (*c* = 1.0, $CHCl_3$).

Diethyl 2,2'-((1*S*,4*S*)-2-oxo-3-tosyl-7-azabicyclo[2.2.1]heptane-1,4-diyl) diacetate (135) :-



To a stirring solution of **133** (5 g, 7.215 mmol) in CH_2Cl_2/H_2O (100 mL, 20:1) was added DDQ (4.54 g, 21.645 mmol, 3 equiv). The resulting mixture was stirred for 3 h at rt. The mixture was poured into saturated aqueous $NaHCO_3$ solution and was further diluted with CH_2Cl_2. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2 x 10 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The residue was filtered through a Celite pad. The plug was washed with CH_2Cl_2 (200 mL). The solvents were removed under reduced pressure to give the crude product **135** mixture as a brown oil. This crude product was taken directly to the next step without further purification (2.58 g, 82%). For analytical purpose small amount of **135** was purified by flash column chromatography (CH_2Cl_2: MeOH = 15:1).

TLC:- R_f = 0.3 (CH_2Cl_2: MeOH = 15:1, Ninhydrin).

IR (film): ν_{max} = 3438, 3021, 2067, 1640, 1379, 1215, 1043, 752, 668 cm^{-1}

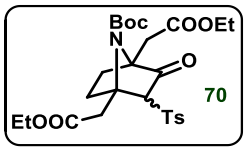
^{1}H NMR (800 MHz, $CDCl_3$) δ = 7.80 (d, *J* = 8.2 Hz, 2H), 7.33 (d, *J* = 8.0 Hz, 2H), 4.63 (d, *J* = 2.1 Hz, 1H), 4.17 (q, *J* = 7.1 Hz, 2H), 4.03 (qd, *J* = 7.1, 1.1 Hz, 2H), 3.56 (d, *J* = 17.4 Hz, 1H), 2.97 (d, *J* = 17.8 Hz, 1H), 2.75 (d, *J* = 17.4 Hz, 1H), 2.65 - 2.58 (m, 1H), 2.41 (s, 3H), 1.83 - 1.74 (m, 2H), 1.67 (tdd, *J* = 12.2, 5.5, 2.2 Hz, 1H), 1.26 (t, *J* = 7.1 Hz, 3H), 1.16 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (201 MHz, $CDCl_3$) δ = 202.92, 171.58, 170.69, 145.17, 137.12, 129.83, 128.78, 73.45, 70.20, 65.41, 61.10, 61.05, 38.01, 33.99, 31.04, 29.18, 21.75, 14.25, 14.08

HRMS (*m/z*): $[M + Na]^+$ calcd for $C_{21}H_{27}NNaO_7S^+$ 460.1400, found 460.1406.

$[\alpha]_D^{22}$ = - 12.6° (*c* = 1.1, $CHCl_3$).

Diethyl 2,2'-((1*S*,4*S*)-7-(*tert*-Butoxycarbonyl)-2-oxo-3-tosyl-7-azabicyclo[2.2.1] heptane -1,4-diyl)diacetate (70):-



To a stirring solution of **135** (2.58 g, 5.9 mmol) in CH_2Cl_2 (30 mL) was added Et_3N (2.5 mL, 17.7 mmol) at 0 ^oC. To this cooled solution, Boc anhydride (1.5 mL, 7.08 mmol) in 10 mL CH_2Cl_2 was added drop wise. The mixture was allowed to stir at rt overnight. The solvent was removed under reduced pressure to give crude product as a yellow oil which was purified by flash chromatography (hexanes:EtOAc = 5:1-4:1) affording **70** (0.252 g, *exo* isomer 76%) and (2.49 g, *endo* isomer 8%).

TLC:- R_f =0.5 (EtOAc:Hexane = 1:4, Ninhydrin).

IR (film): ν_{max} = 2982, 2934, 2256, 1771, 1733, 1701, 1463, 1394, 1318, 1149, 909, 732 cm^{-1}

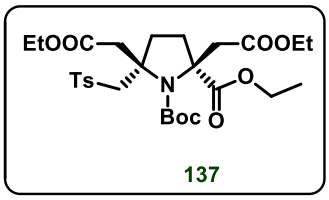
^{1}H NMR (800 MHz, $CDCl_3$) δ = 7.84 (d, *J* = 8.3 Hz, 2H), 7.34 (d, *J* = 8.0 Hz, 2H), 5.56 (d, *J* = 1.9 Hz, 1H), 4.17 (qd, *J* = 7.1, 2.8 Hz, 2H), 4.09 - 3.98 (m, 2H), 3.63 (d, *J* = 17.7 Hz, 1H), 3.44 (d, *J* = 17.7 Hz, 1H), 3.10 (q, *J* = 17.6, 2H), 2.66 (ddd, *J* = 12.9, 9.1, 3.9 Hz, 1H), 2.41 (s, 3H), 2.17 (td, *J* = 12.6, 3.9 Hz, 1H), 1.90 (tdd, *J* = 12.4, 5.4, 2.1 Hz, 1H), 1.82 (ddd, *J* = 13.1, 9.0, 5.4 Hz, 1H), 1.33 (s, 9H), 1.27 (t, *J* = 7.1 Hz, 3H), 1.15 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (201 MHz, $CDCl_3$) δ = 198.81, 170.76, 169.14, 152.71, 145.32, 137.23, 129.84, 128.88, 82.13, 71.87, 71.82, 68.26, 60.62, 60.49, 36.46, 34.31, 32.08, 29.56, 28.04, 21.77, 14.16, 14.02.

HRMS (*m/z*): $[M + Na]^+$ calcd for $C_{26}H_{35}NNaO_9S^+$ 560.1925, found 560.1924.

$[\alpha]_D^{22}$ = -27.6° (*c* = 0.9, $CHCl_3$).

(2S,5R)-1-*tert*-Butyl 2-ethyl 2,5-bis(2-ethoxy-2-oxoethyl)-5-(tosylmethyl)pyrrolidine-1,2-dicarboxylate (137):-



137

To a stirring solution of **70** (100 mg, 0.18 mmol) in ethanol (3 mL) at 0 °C, was added sodium ethoxide (50 mg , 0.74 mmol). The resultant dark colored solution was stirred for 20 min at 0 °C and 1M HCl (~2 mL) was added carefully to quench excess of sodium ethoxide. The reaction mixture solidified after approx. 5 min and was diluted with EtOAc (5 mL) and water (5 mL). The resulting layers were separated and the aq. layer extracted with EtOAc (5 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, filtrated and conc. in vacuo to give viscous oil. Purification by flash chromatography (hexane:EtOAc = gradient 1:1 - 1:2 – 0:1) afforded **137** (96 mg, 88 %) as a stable white foam.

TLC:- R_f =0.4 (EtOAc:Hexane = 1:4, Ninhydrin).

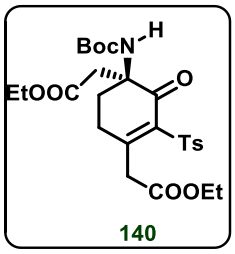
IR (film): ν_{max} = 2985, 2932, 2256, 1782, 1733, 1702, 1463, 1394, 1318, 1149, 900, 732 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.62 (d, *J* = 8.3 Hz, 2H), 7.36 (d, *J* = 8.0 Hz, 2H), 4.56 (d, *J* = 1.9 Hz, 1H), 4.14 (qd, *J* = 7.1, 2.8 Hz, 6H), 3.64 (d, *J* = 17.6 Hz, 1H), 3.37 (d, *J* = 17.7 Hz, 1H), 3.33 (d, *J* = 17.3 Hz, 1H), 3.23 (d, *J* = 17.7 Hz, 1H) 3.10, 2.71 (d, *J* = 17.7 Hz, 1H) 1.66 (d, *J* = 13.1Hz, 4H), 0.88-1.05 (m, 11H)

^{13}C NMR (101 MHz, $CDCl_3$) δ = 170.53, 170.47, 170.25, 152.04, 145.10, 130.40, 130.29, 128.85, 128.03, 127.82, 82.32, 74.58, 70.91, 63.18, 62.37, 60.83, 60.76, 60.68, 41.44, 41.37, 28.64, 28.56, 28.49, 21.94, 14.53, 14.47, 14.24.

HRMS (*m/z*): $[M + Na]^+$ calcd for $C_{28}H_{41}NNaO_{10}S^+$ 606.2343, found 606.2340. $[\alpha]_D^{22}$ = -32.6° (*c* = 1.0, $CHCl_3$).

(*S*)-diethyl 2,2'-(4-((*tert*-Butoxycarbonyl)amino)-3-oxo-2-tosylcyclohex-1-ene-1, 4-diyl)diacetate (140):-



140

To a stirring solution of **70** (100 mg, 0.18 mmol) in THF (5 mL) at -10 °C, was added potassium hydride (25 mg, 0.62 mmol). The dark brown colored solution was stirred for 2 h at -10 °C and ice flakes were added carefully to quench excess of potassium hydride. The flask was removed from the cooling bath and diluted with EtOAc (10 mL) and water (10 mL). The, layers were separated and the aq. layer extracted with EtOAc (5x3 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and conc. in vacuo to give viscous oil. Purification by flash chromatography (hexane:EtOAc = gradient 1:1 - 1:2 – 0:1) afforded **140** (58 mg, 58 %) as a stable yellow color foam.

TLC:- R_f =0.5 (EtOAc:Hexane = 1:4, Ninhydrin).

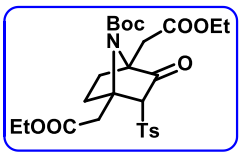
IR (film): ν_{max} = 2982, 2936, 2257, 1780, 1743, 1702, 1465, 1394, 1319, 1119, 918, 733 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.89 (d, *J* = 8.3 Hz, 2H), 7.36 (d, *J* = 8.0 Hz, 2H), 4.24 – 4.08 (m, 4H), 3.85-3.62 (m, 1H), 3.48 (d, *J* = 17.6 Hz, 1H), 3.11 (d, *J* = 17.7 Hz, 2H), 2.33 (s, 3H), 2.23 (t, *J* = 17.7 Hz, 1H) 1.53 (d, *J* = 13.1Hz, 2H), 0.88-1.31 (m, 14H)

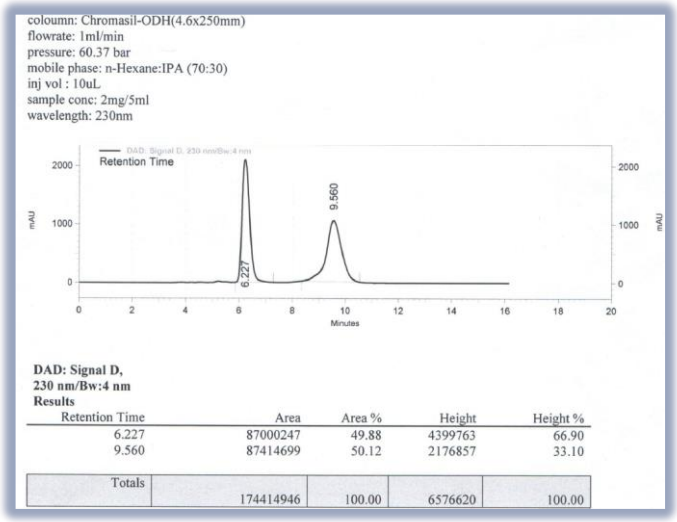
^{13}C NMR (101 MHz, $CDCl_3$): 199.16, 171.12, 169.51, 145.67, 137.58, 130.19, 129.23, 82.50, 60.97, 60.84, 36.81, 34.65, 32.42, 29.89, 28.39, 22.11, 14.59, 14.53, 14.39.

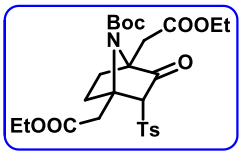
HRMS (*m/z*): $[M + Na]^+$ calcd for $C_{26}H_{35}NNaO_9S^+$ 560.1925, found 560.1920. $[\alpha]_D^{22}$ = +19.6° (*c* = 1.0, $CHCl_3$).

HPLC data:-

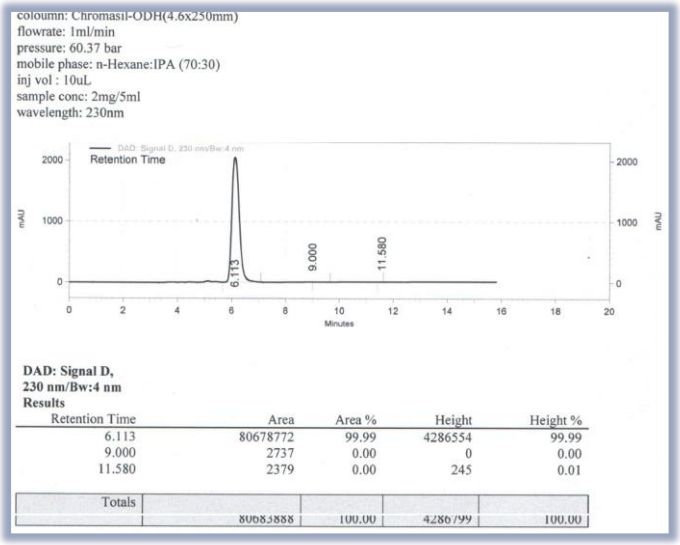


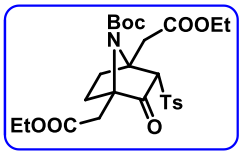
Racemic compound (70)



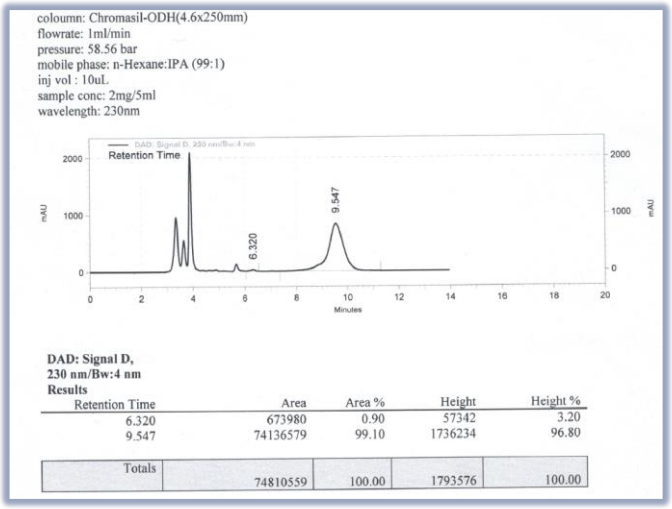


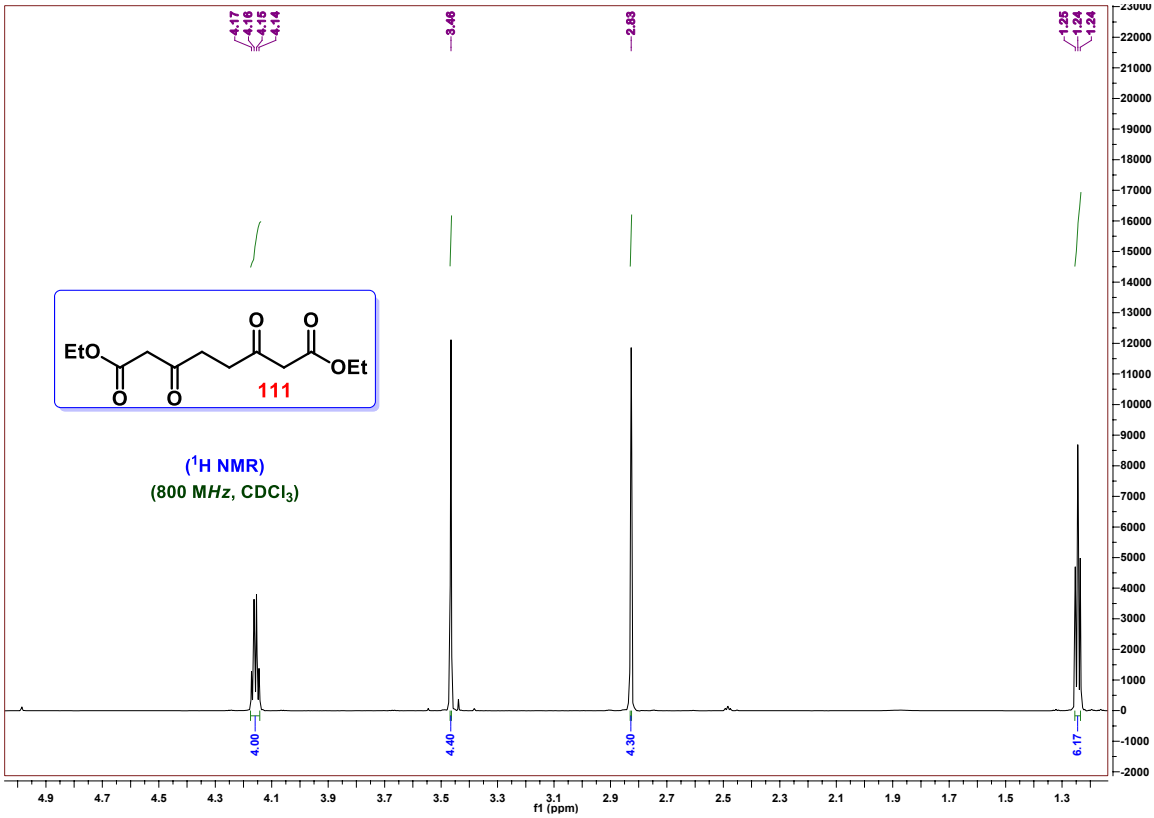
(+)-**70**

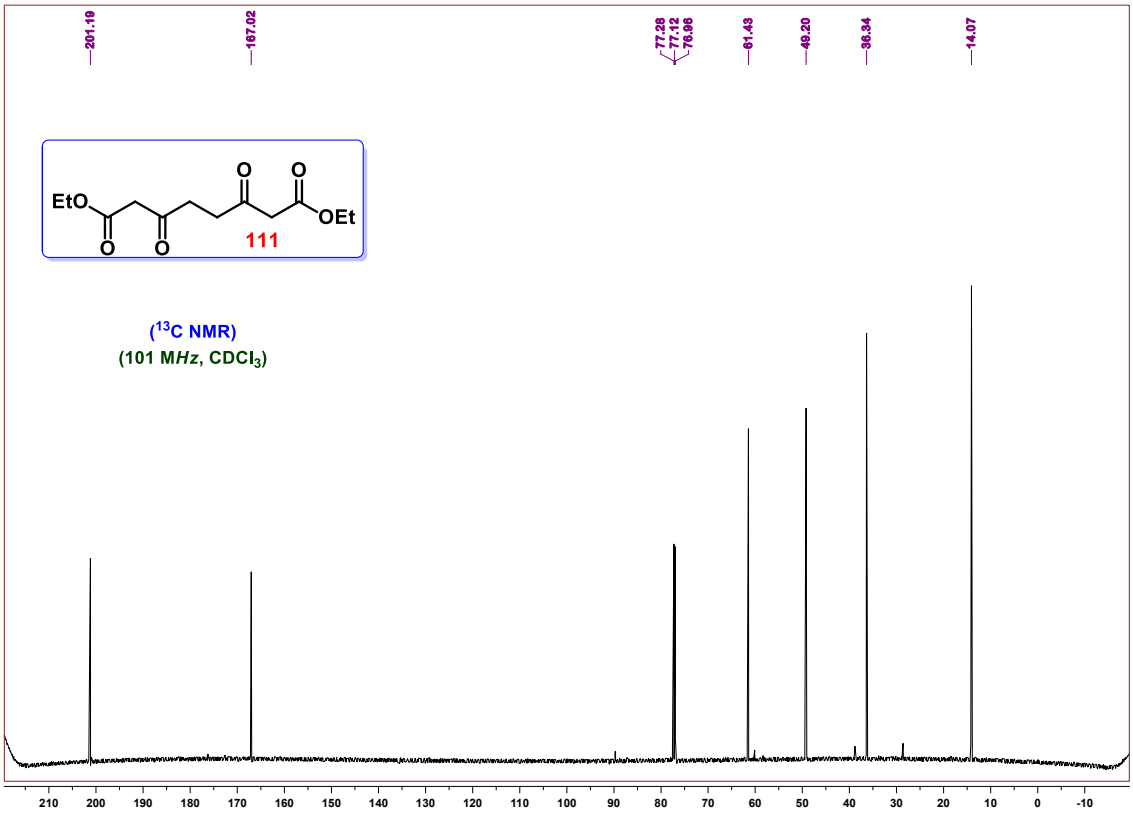


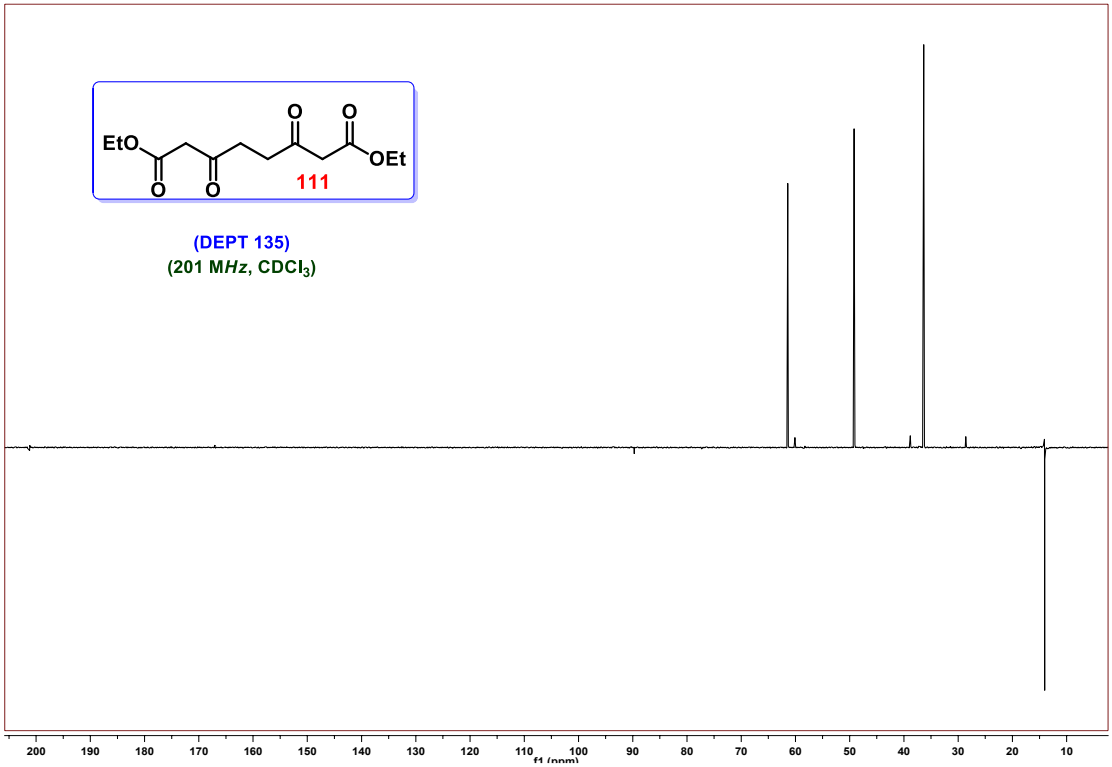


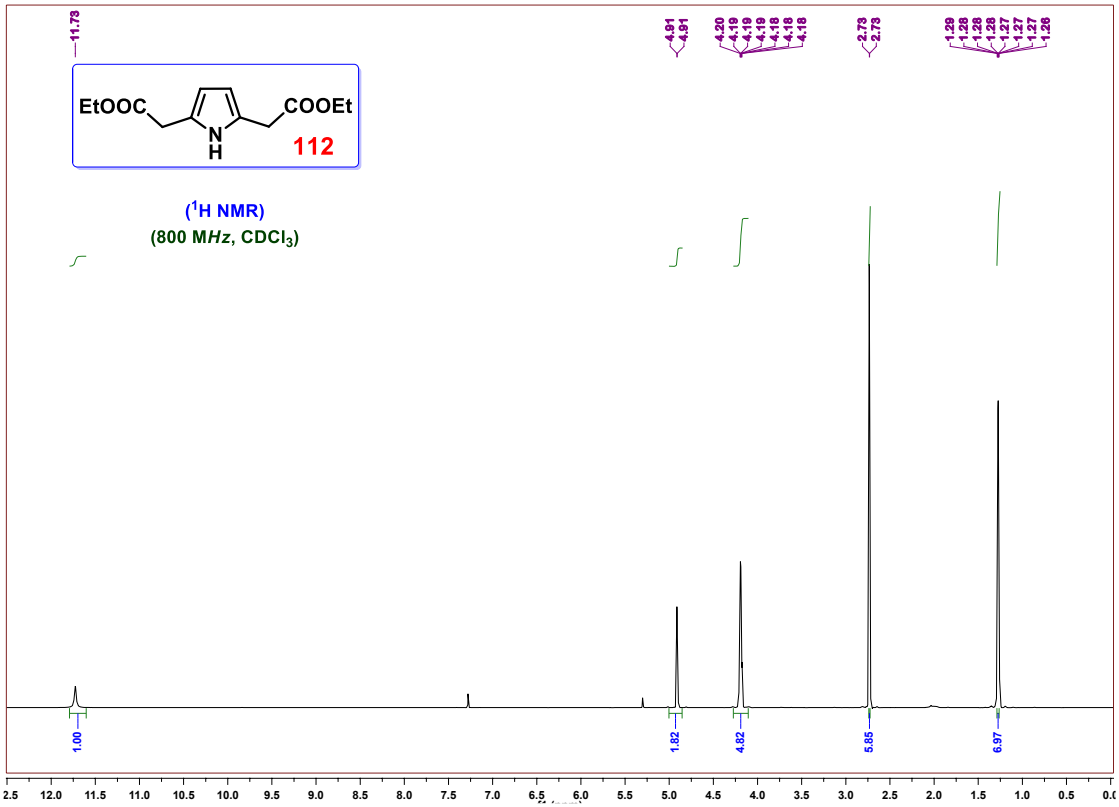
(-)-**70**

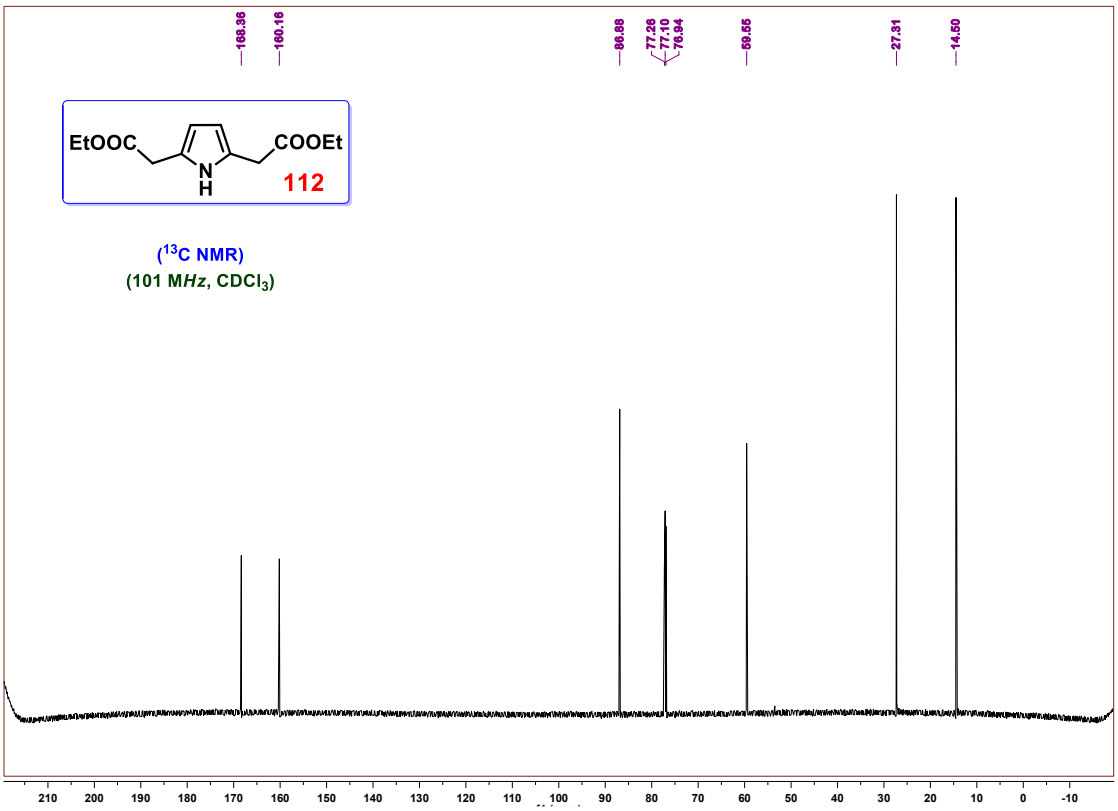


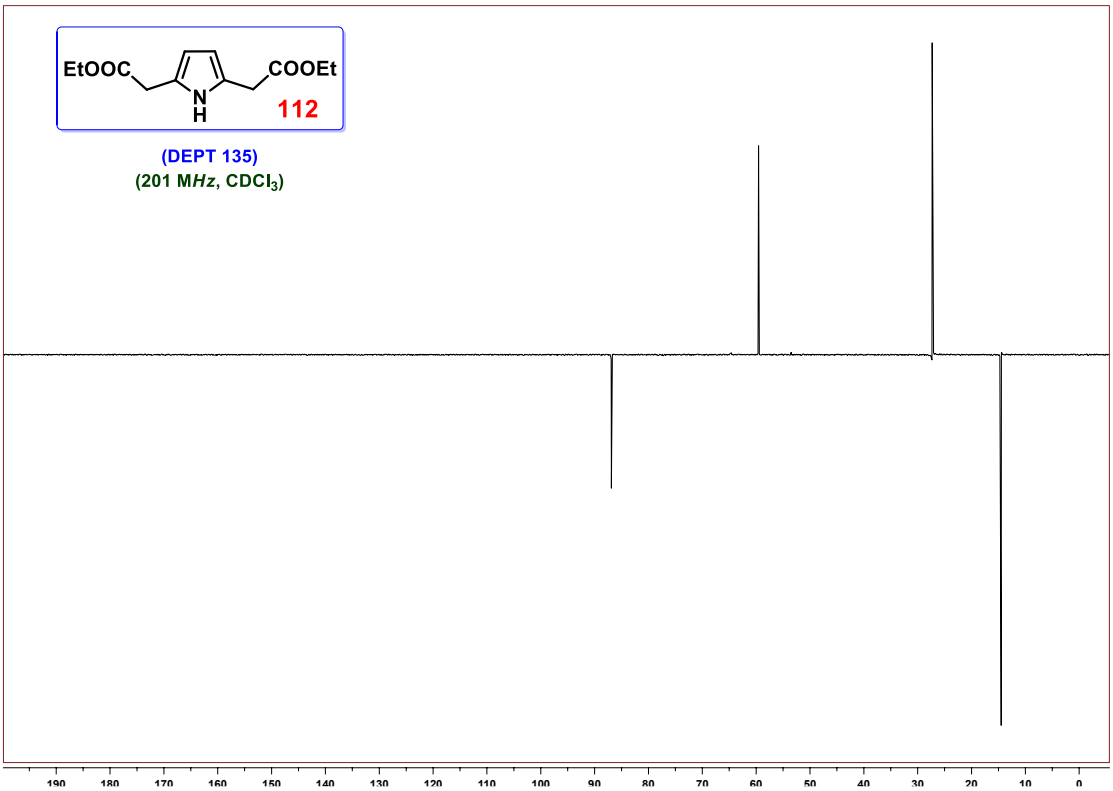

4.17
4.16
4.15
4.14
3.46
2.83
1.25
1.24
1.24
EtO
OEt
111
(1H NMR)
(800 MHz, CDCl3)
4.00
4.40
4.30
6.17
f1 (ppm)

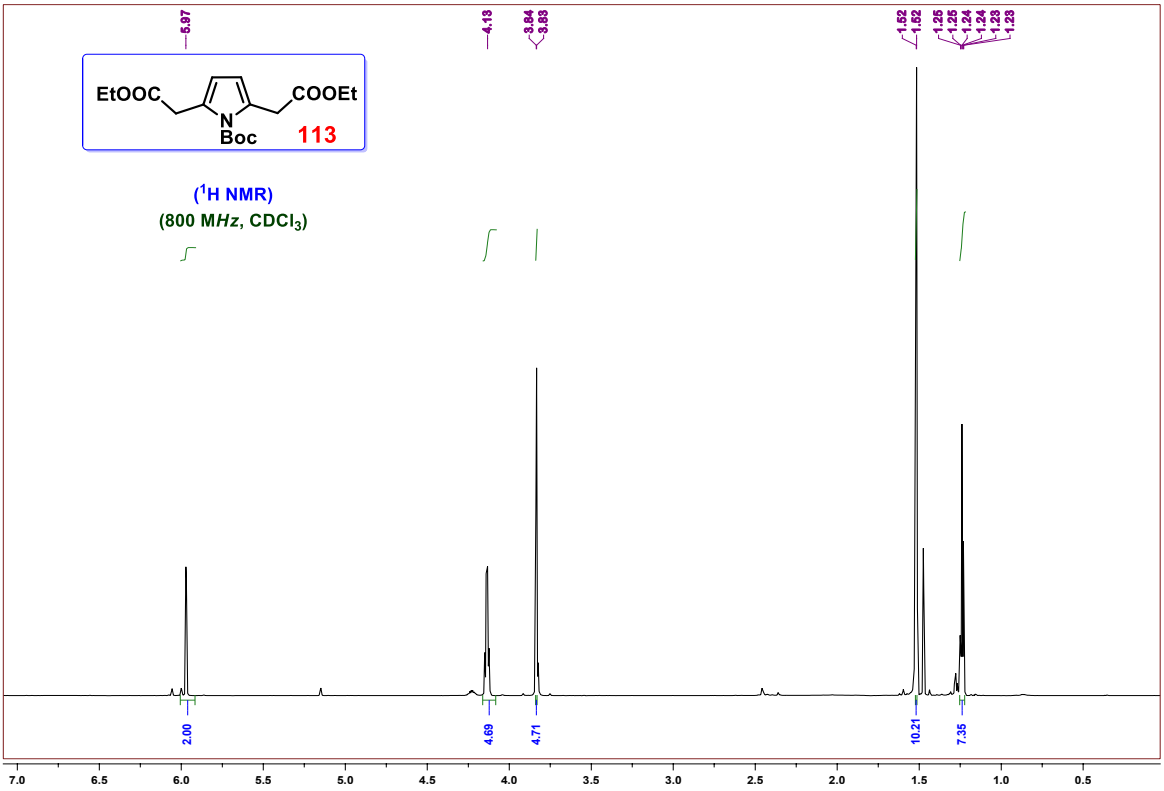

201.19
167.02
77.28
77.12
76.96
61.43
49.20
36.34
14.07
EtO
OEt
111
(13C NMR)
(101 MHz, CDCl3)

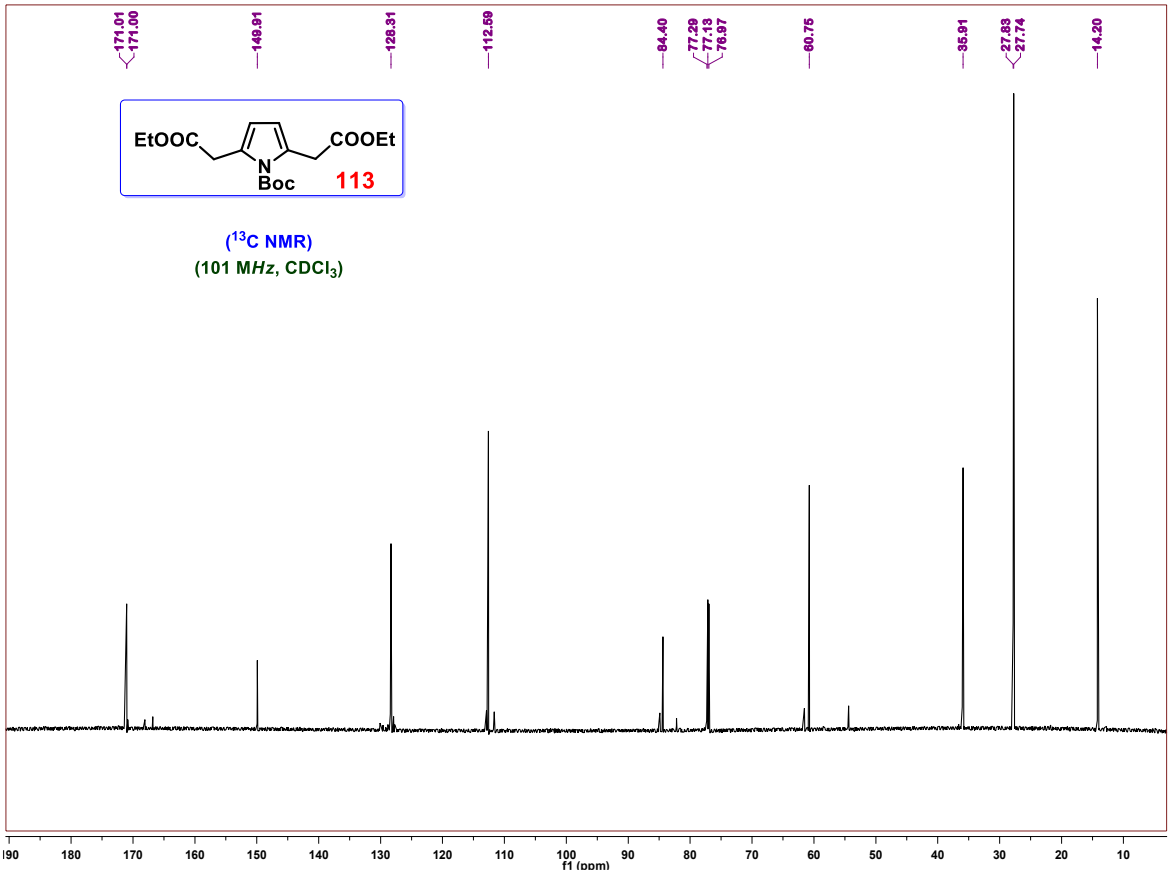

EtO
O
O
O
O
OEt
111
(DEPT 135)
(201 MHz, CDCl3)
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
f1 (ppm)

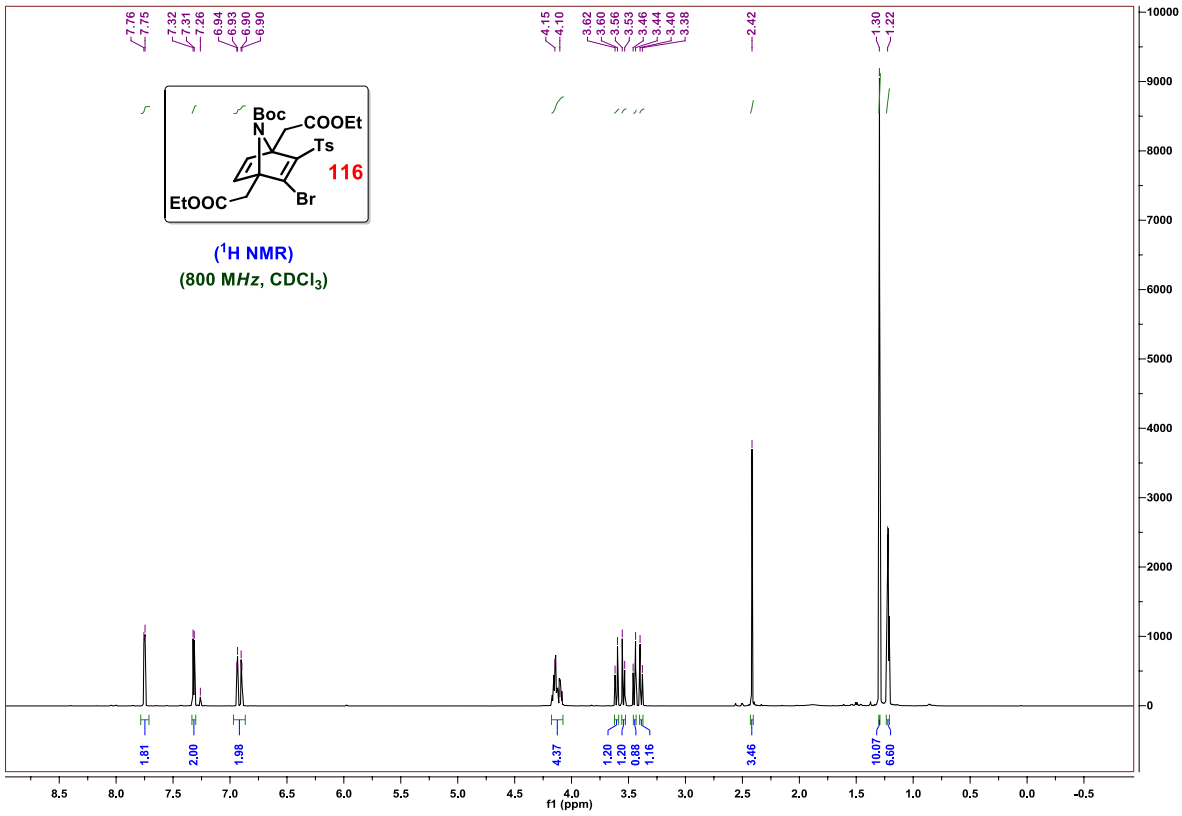

11.78
4.91
4.91
4.20
4.19
4.19
4.19
4.18
4.18
4.18
2.73
2.73
1.29
1.28
1.28
1.28
1.27
1.27
1.27
1.26
EtOOC
COOEt
N
H
112
(1H NMR)
(800 MHz, CDCl3)
1.00
1.82
4.82
5.85
6.97
2.5 12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5


166.36
160.16
86.88
77.26
77.10
76.94
69.55
27.31
14.50
EtOOC
COOEt
N
H
112
(13C NMR)
(101 MHz, CDCl3)
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10

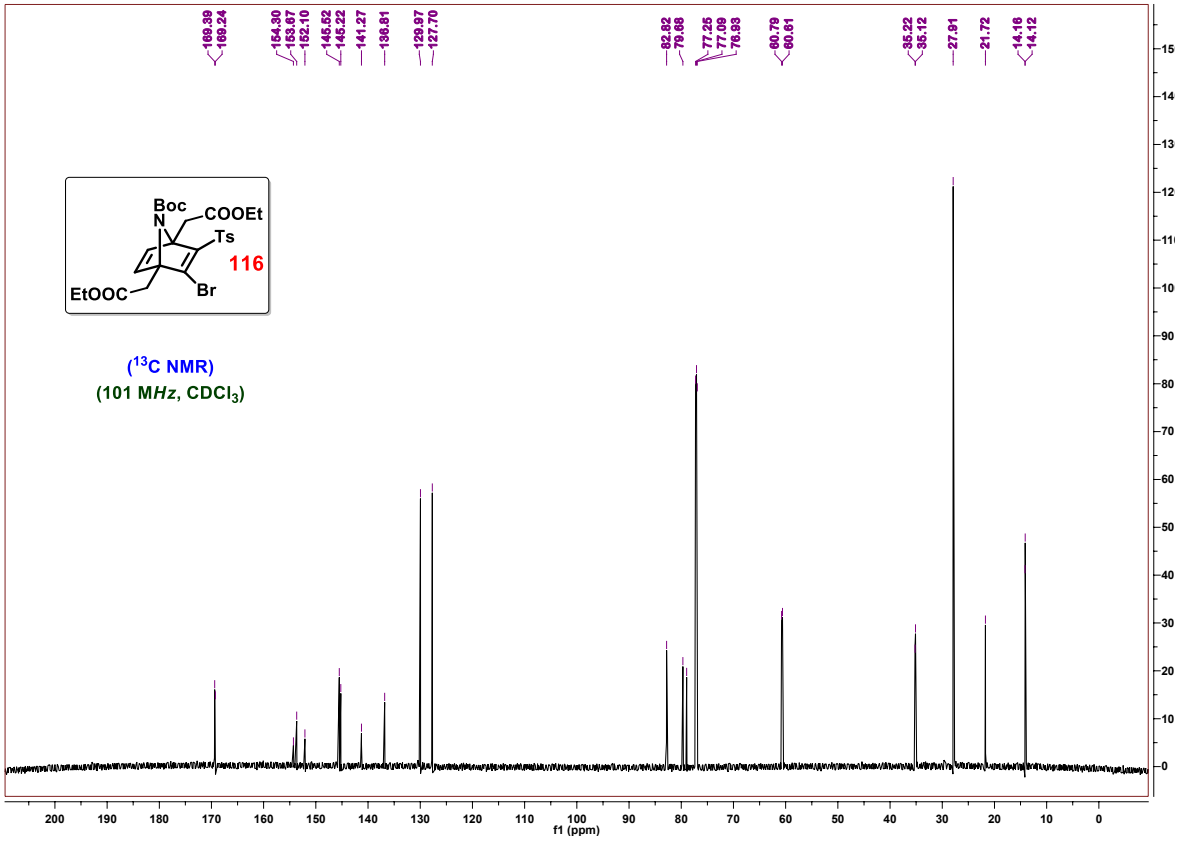

EtOOC
COOEt
N
H
112
(DEPT 135)
(201 MHz, CDCl3)
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0


EtOOC
COOEt
N
Boc
113
(1H NMR)
(800 MHz, CDCl3)
5.97
4.13
3.84
3.83
1.52
1.52
1.25
1.25
1.24
1.24
1.23
1.23
2.00
4.69
4.71
10.21
7.35
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5

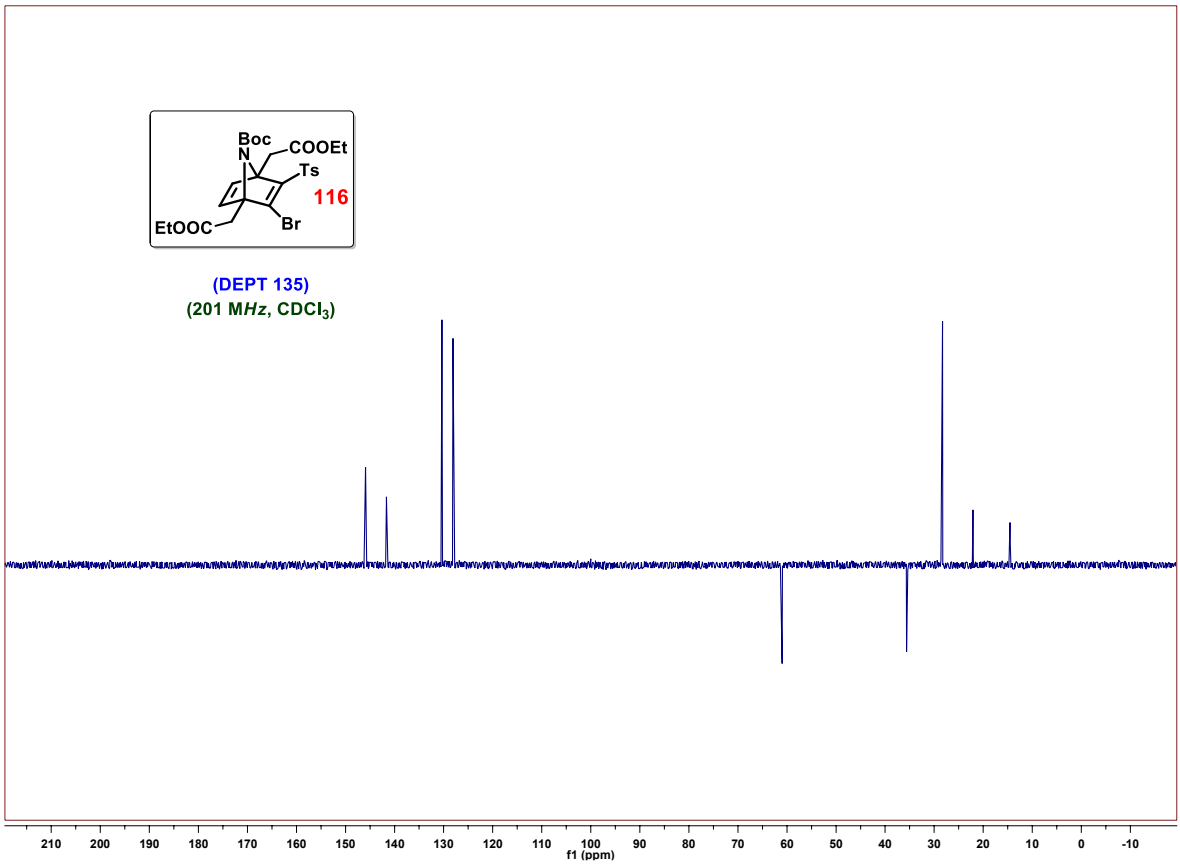

EtOOC
COOEt
N
Boc
113
(13C NMR)
(101 MHz, CDCl3)
171.01
171.00
149.91
128.31
112.59
84.40
77.29
77.13
76.97
60.75
35.91
27.83
27.74
14.20
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)

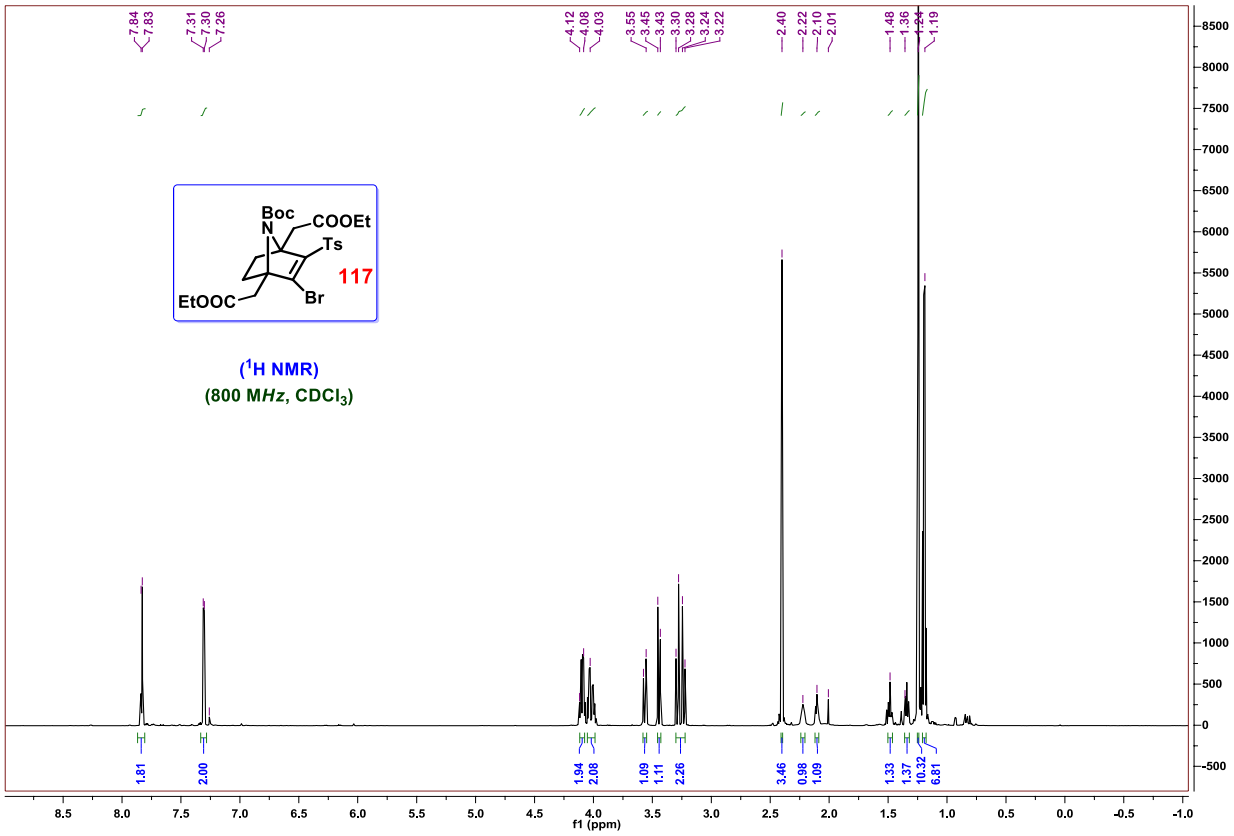


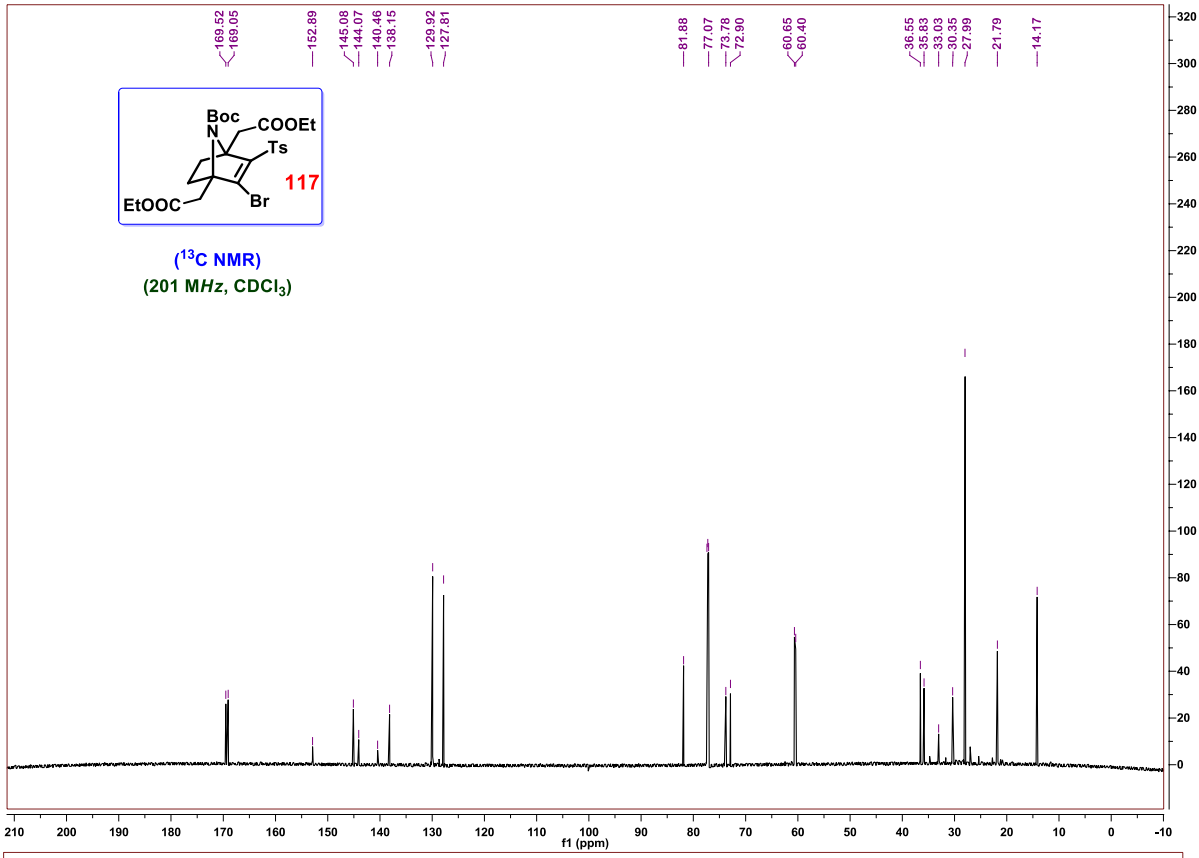
(^{1}H NMR)
(800 M*Hz*, $CDCl_3$)



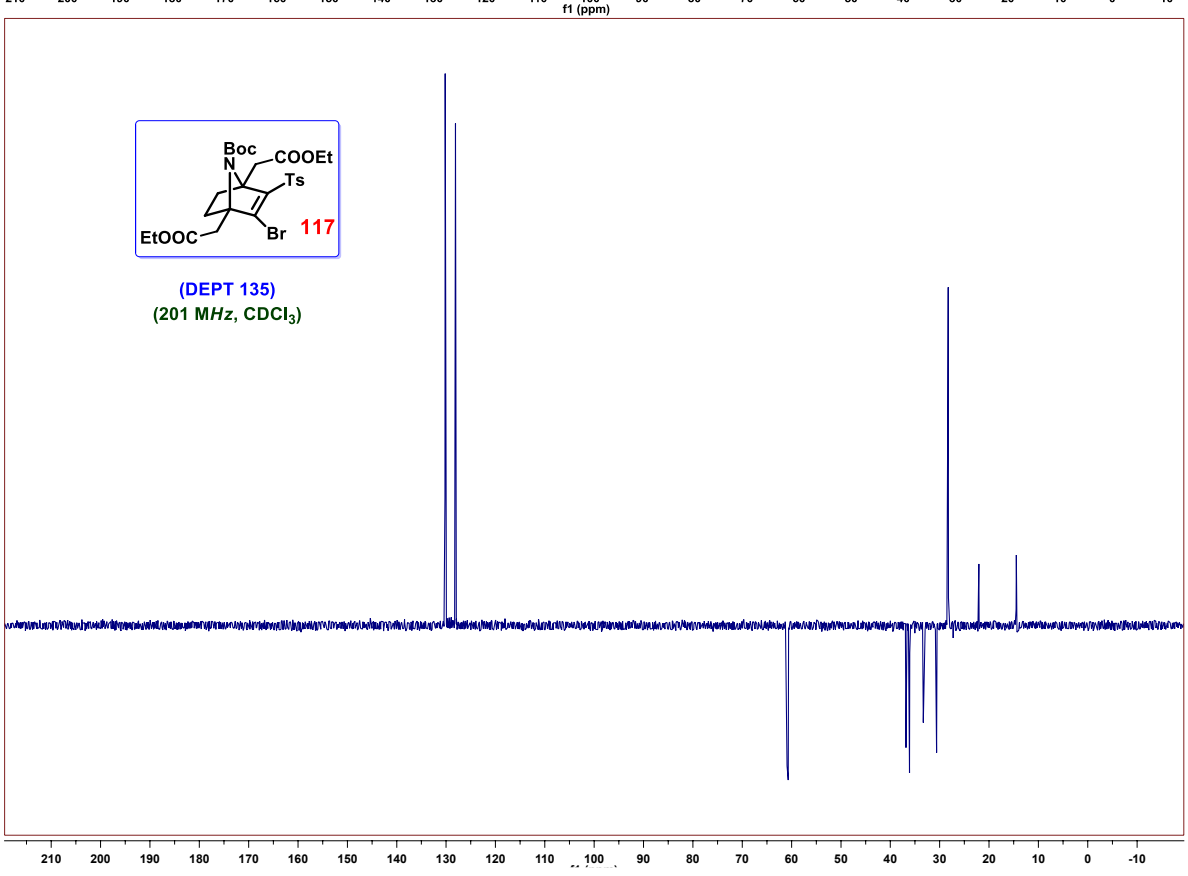
(^{13}C NMR)
(101 M*Hz*, $CDCl_3$)


Boc
N
COOEt
Ts
116
EtOOC
Br
(DEPT 135)
(201 MHz, CDCl3)
f1 (ppm)

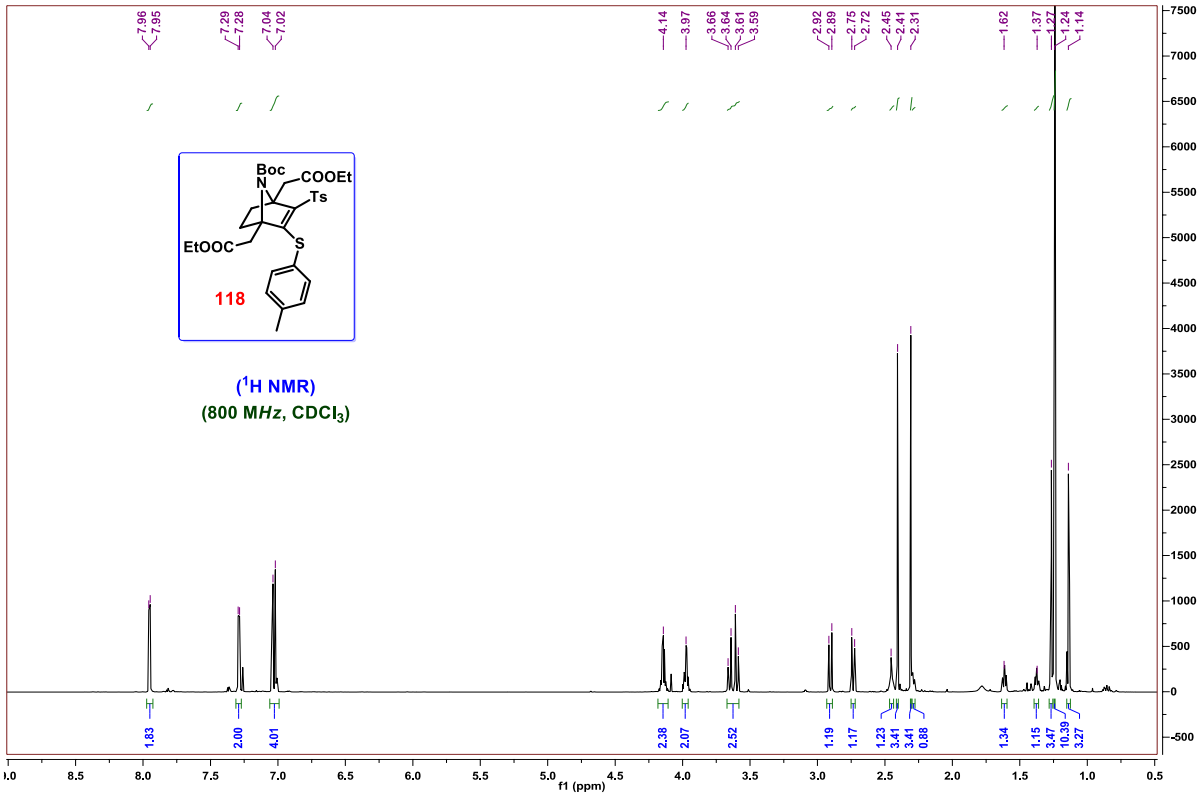

Boc
N
COOEt
Ts
117
EtOOC
Br
(1H NMR)
(800 MHz, CDCl3)
f1 (ppm)

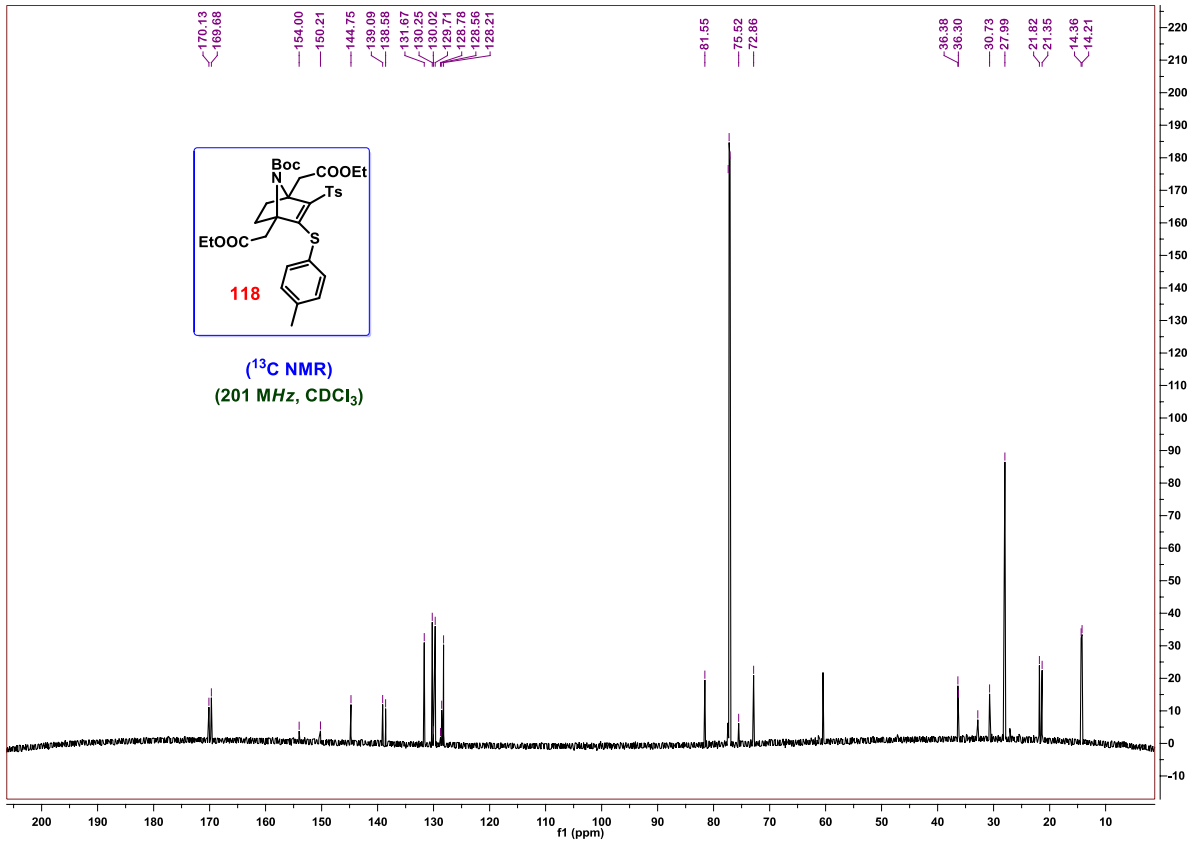


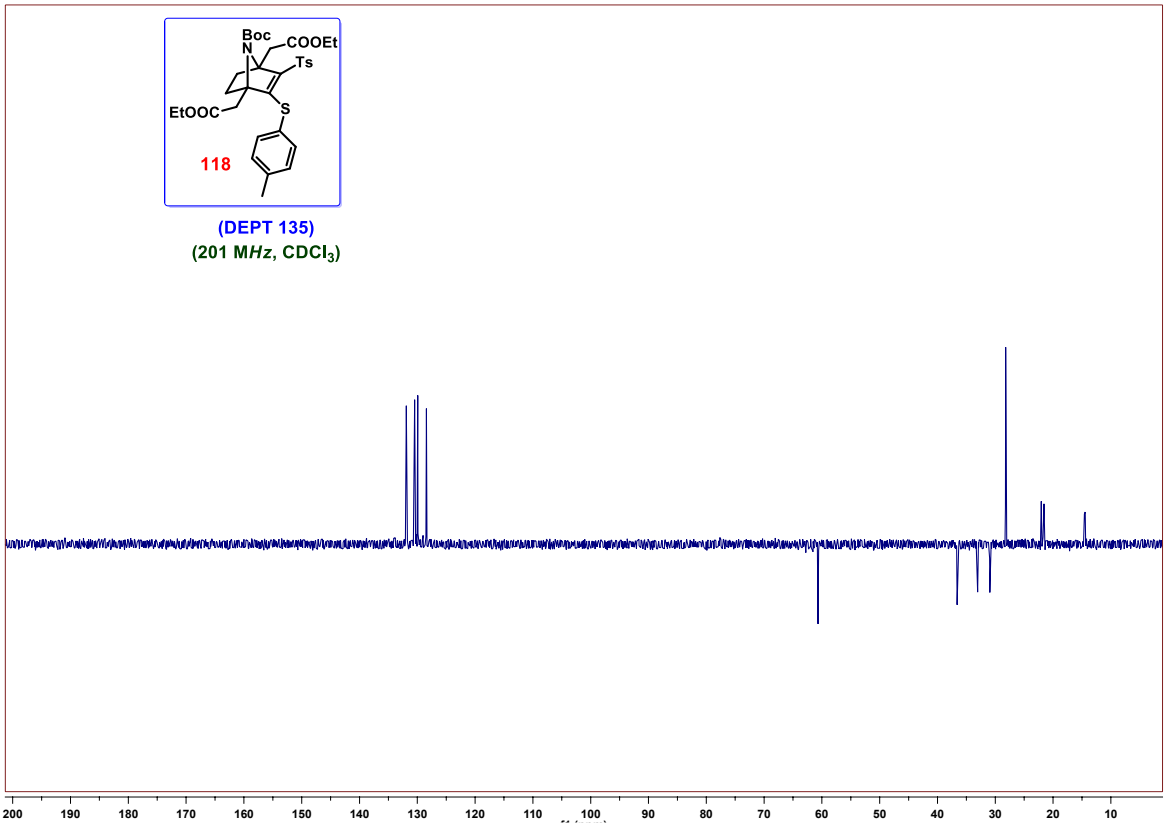
(^{13}C NMR)
(201 M*Hz*, $CDCl_3$)

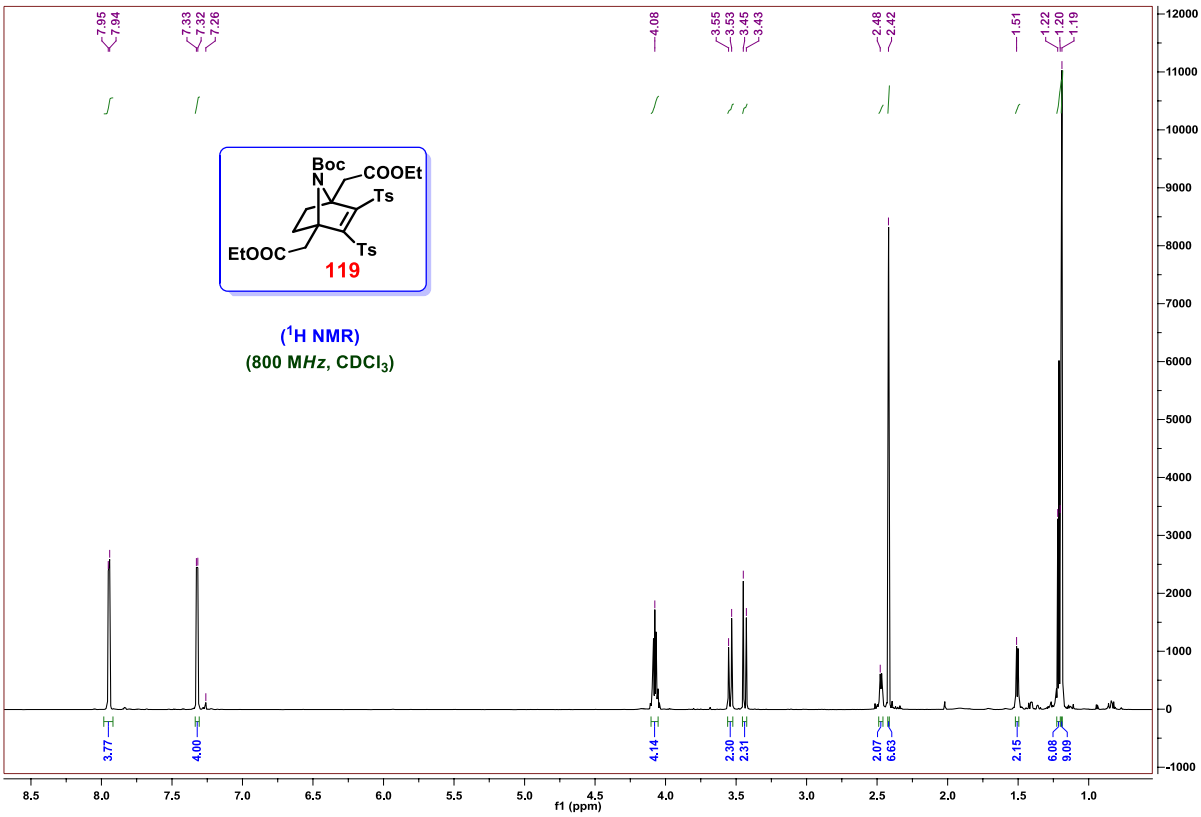


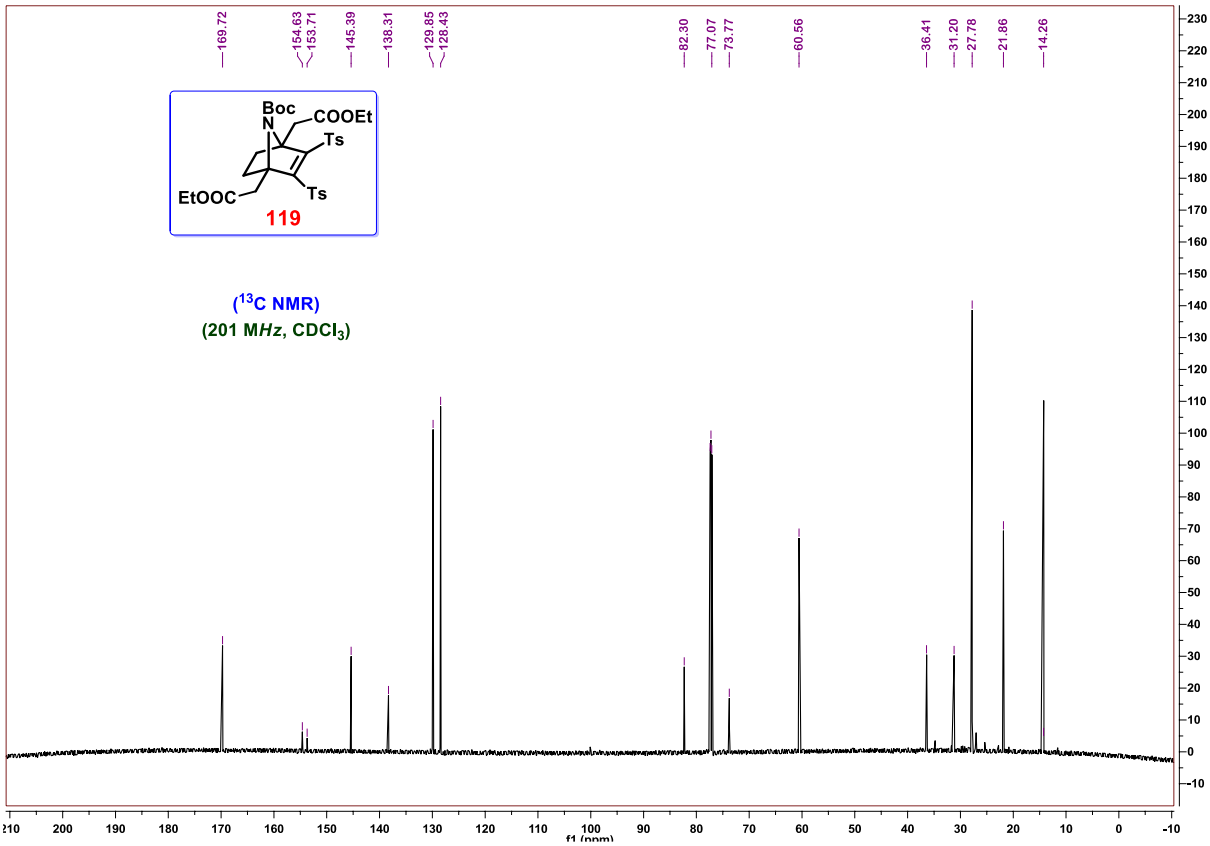
(DEPT 135)
(201 M*Hz*, $CDCl_3$)

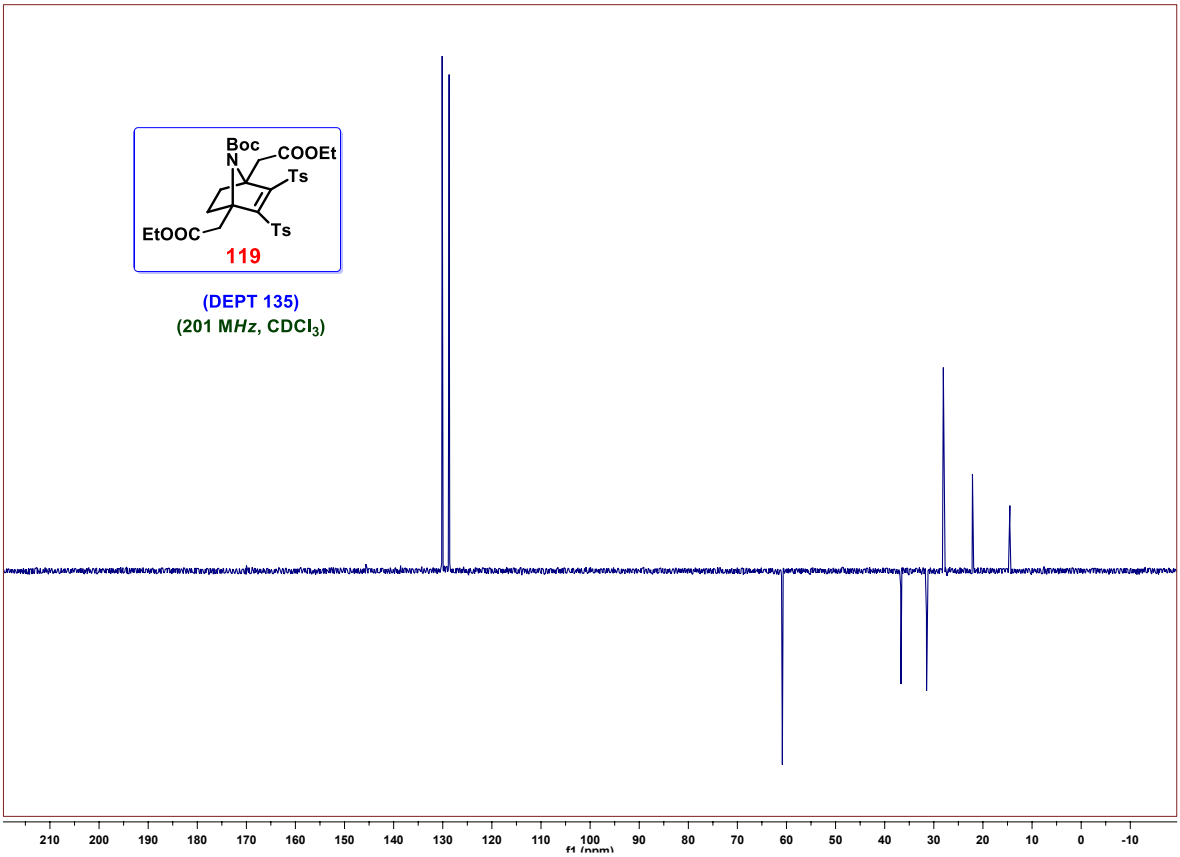

Boc
N
COOEt
Ts
EtOOC
S
118
(1H NMR)
(800 MHz, CDCl3)
f1 (ppm)

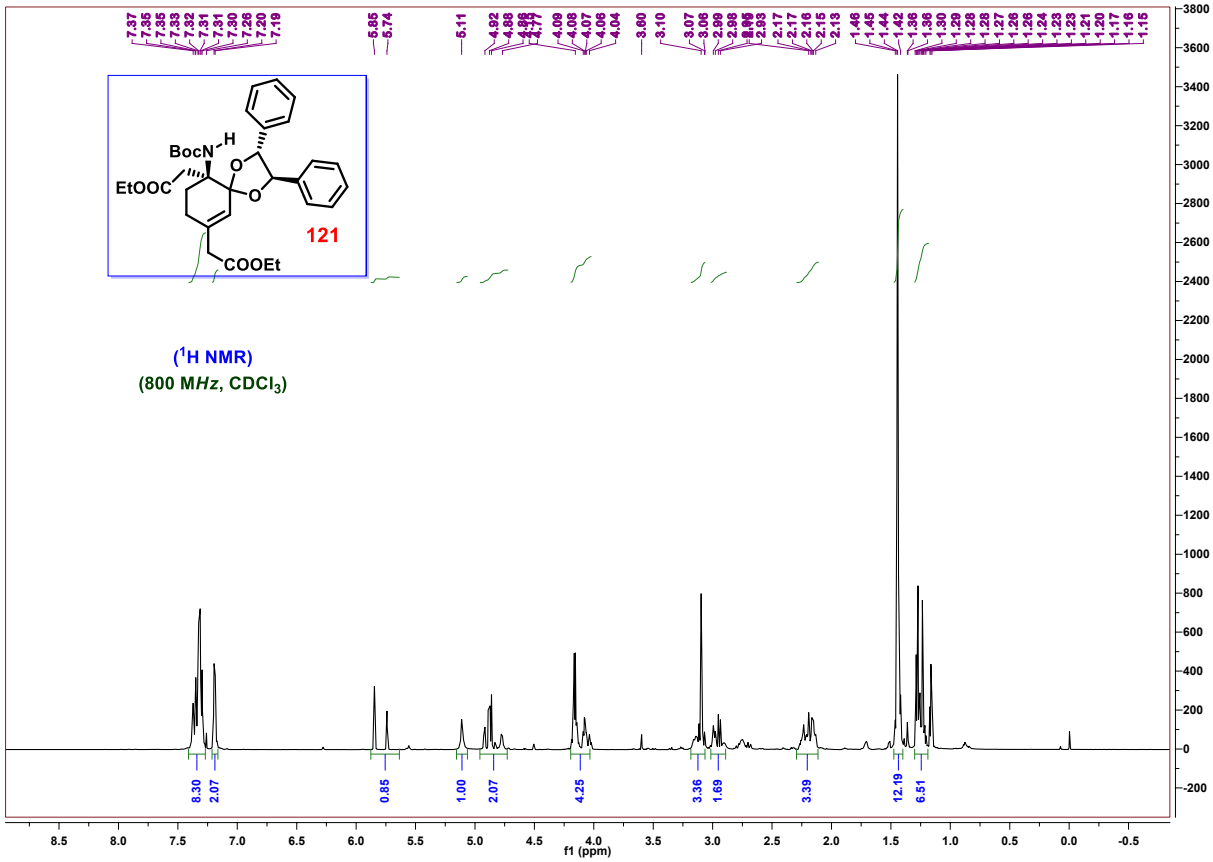

Boc
N
COOEt
Ts
EtOOC
S
118
(13C NMR)
(201 MHz, CDCl3)
f1 (ppm)

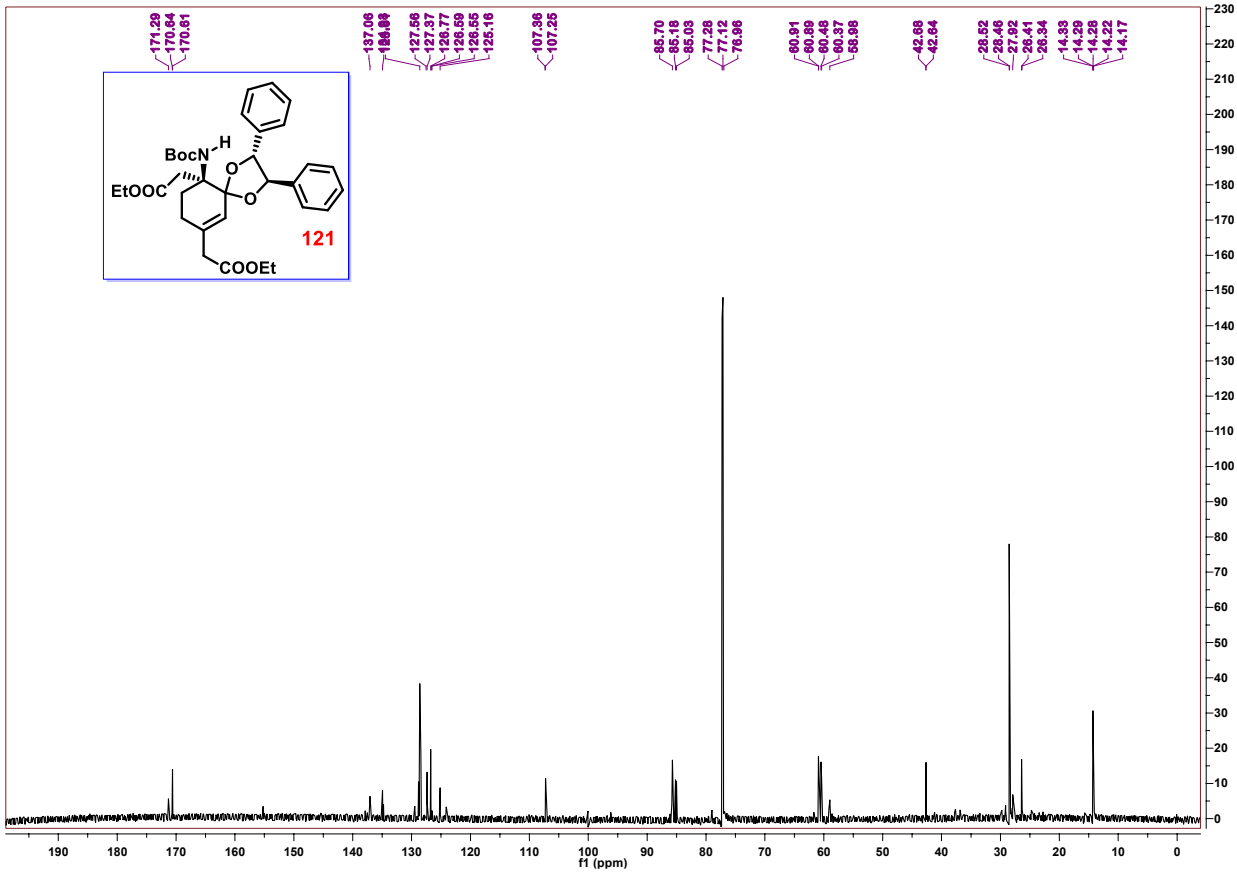

Boc
N
COOEt
Ts
EtOOC
S
118
(DEPT 135)
(201 MHz, CDCl3)

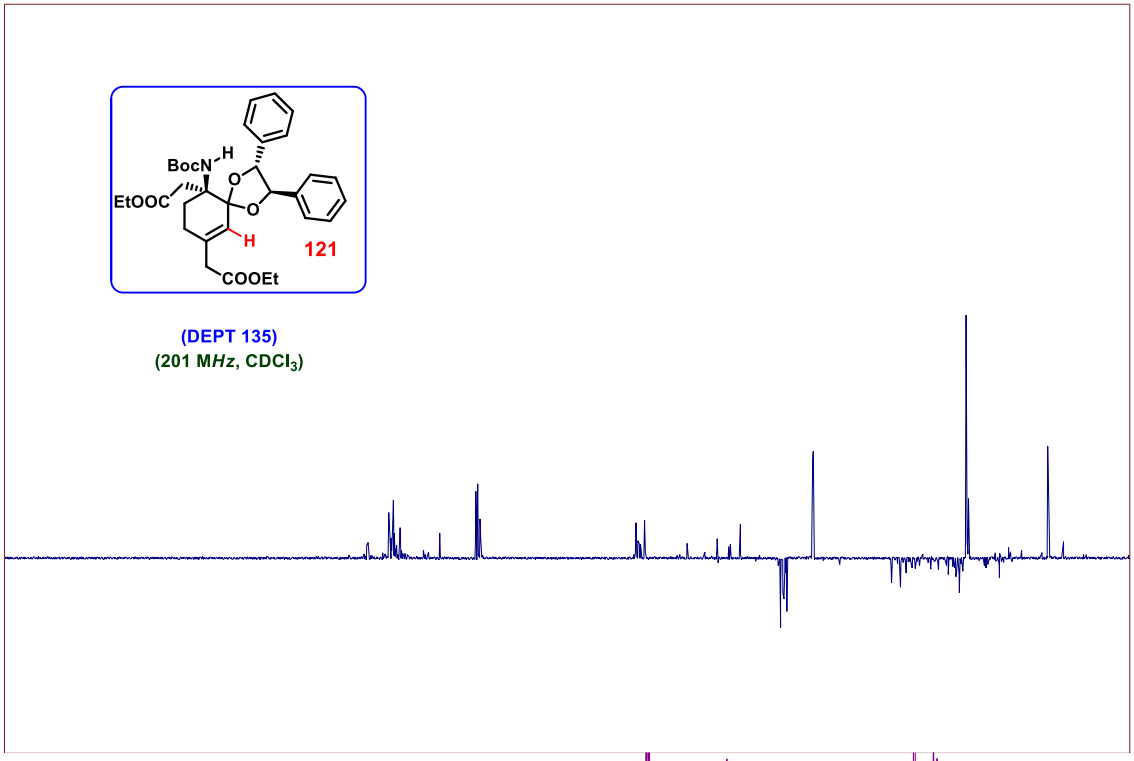

Boc
N
COOEt
Ts
EtOOC
Ts
119
(1H NMR)
(800 MHz, CDCl3)
f1 (ppm)

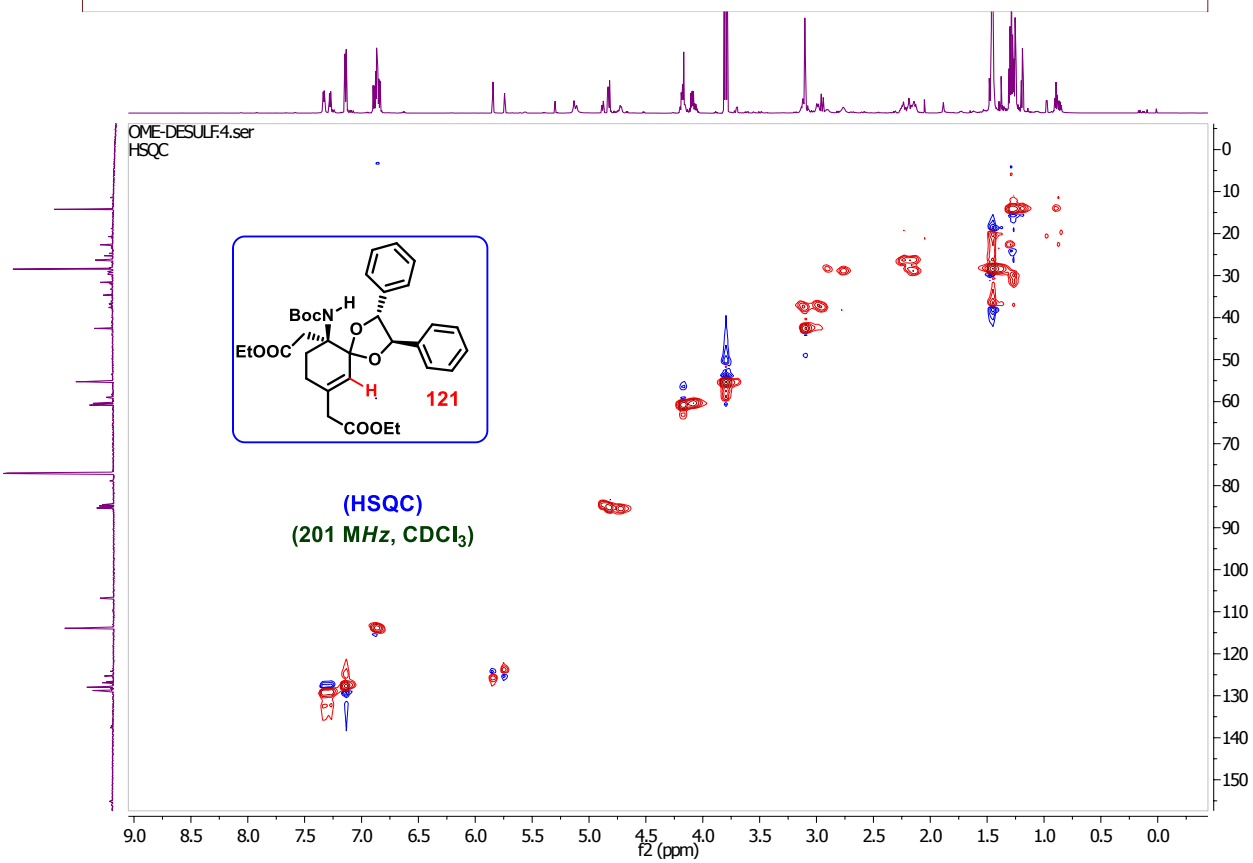

169.72
154.63
153.71
145.39
138.31
129.85
128.43
82.30
77.07
73.77
60.56
36.41
31.20
27.78
21.86
14.26
Boc
N
COOEt
Ts
EtOOC
Ts
119
(13C NMR)
(201 MHz, CDCl3)
f1 (ppm)

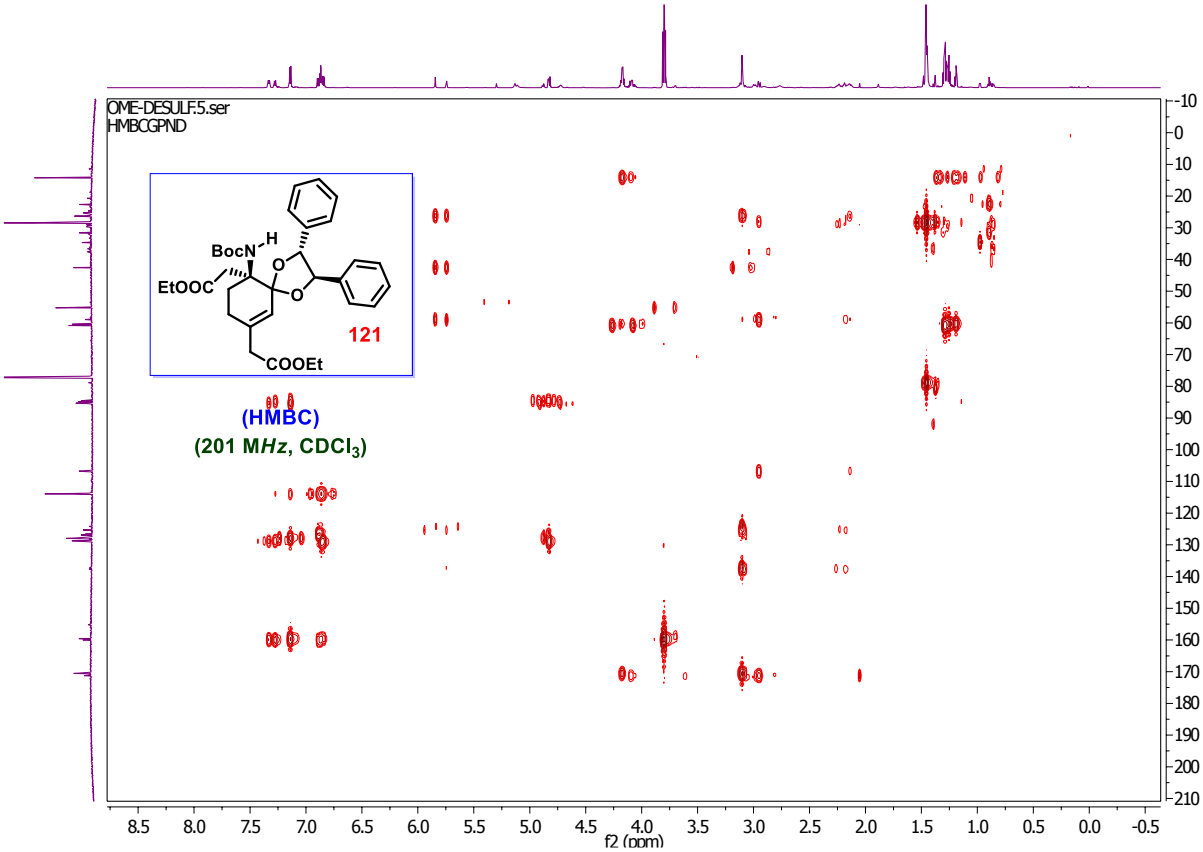

Boc
N
COOEt
Ts
EtOOC
Ts
119
(DEPT 135)
(201 MHz, CDCl3)
f1 (ppm)


BocN
H
EtOOC
COOEt
121
(1H NMR)
(800 MHz, CDCl3)
f1 (ppm)


BocN
H
EtOOC
COOEt
121
f1 (ppm)

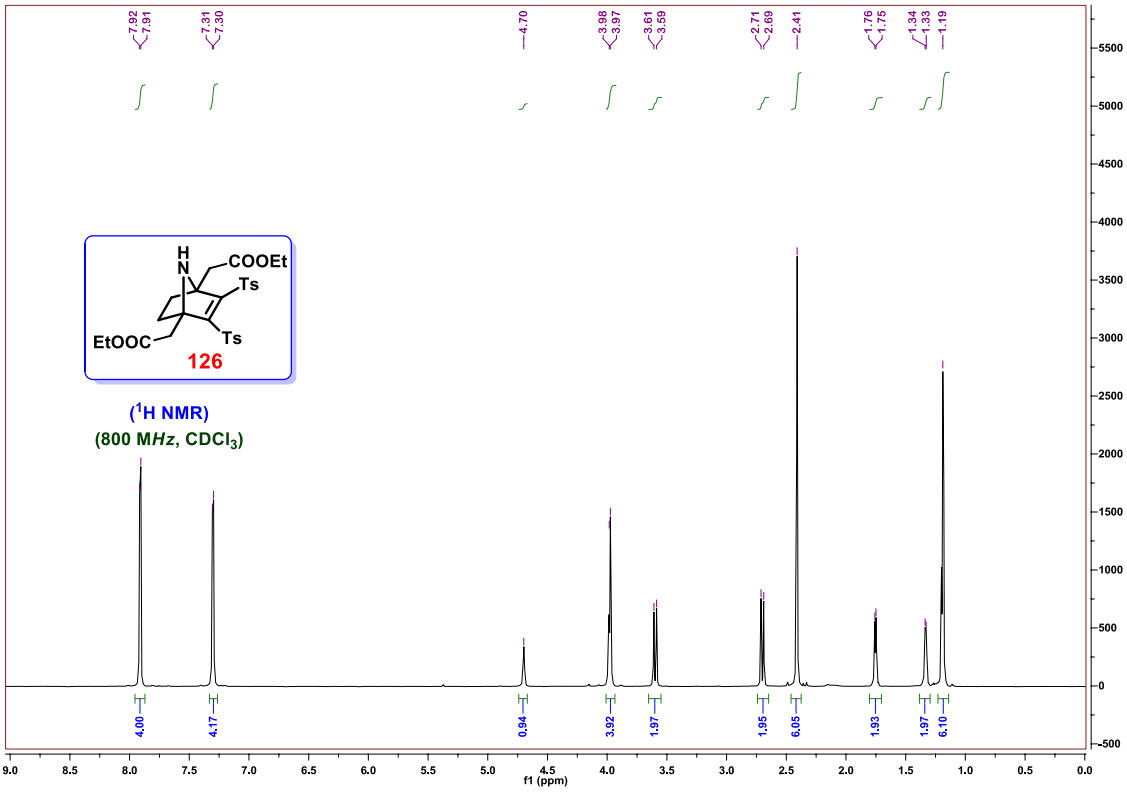

BocN
H
O
O
EtOOC
H
121
COOEt
(DEPT 135)
(201 MHz, CDCl3)


OME-DESULF-4.ser
HSQC
BocN
H
O
O
EtOOC
H
121
COOEt
(HSQC)
(201 MHz, CDCl3)
f2 (ppm)



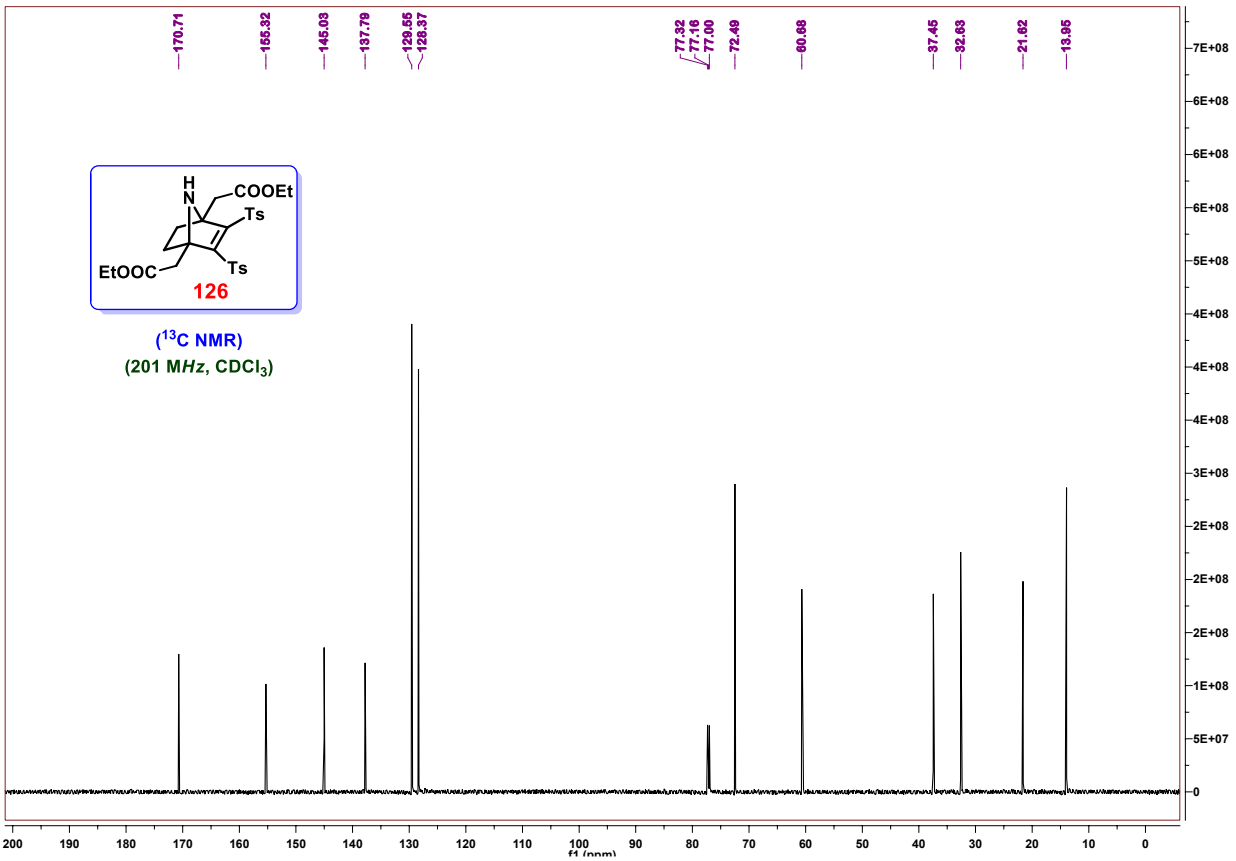
(HMBC)

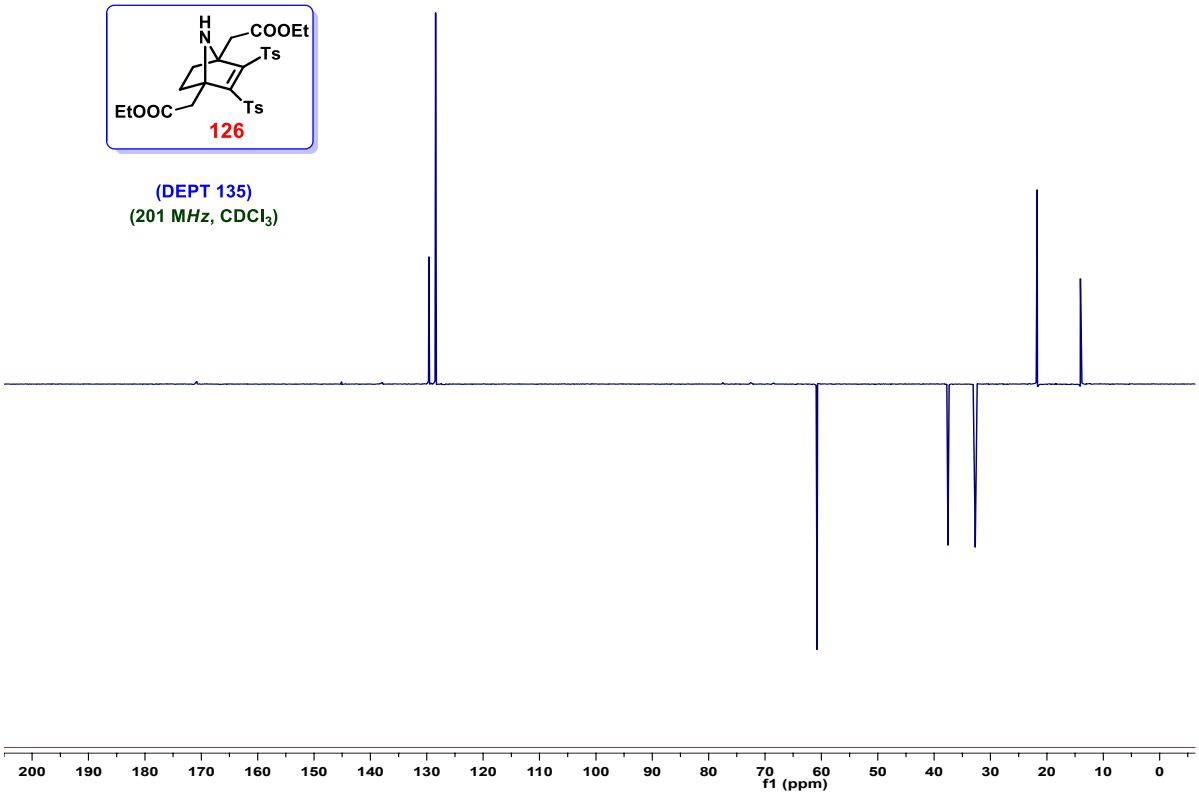
(201 M*Hz*, $CDCl_3$)

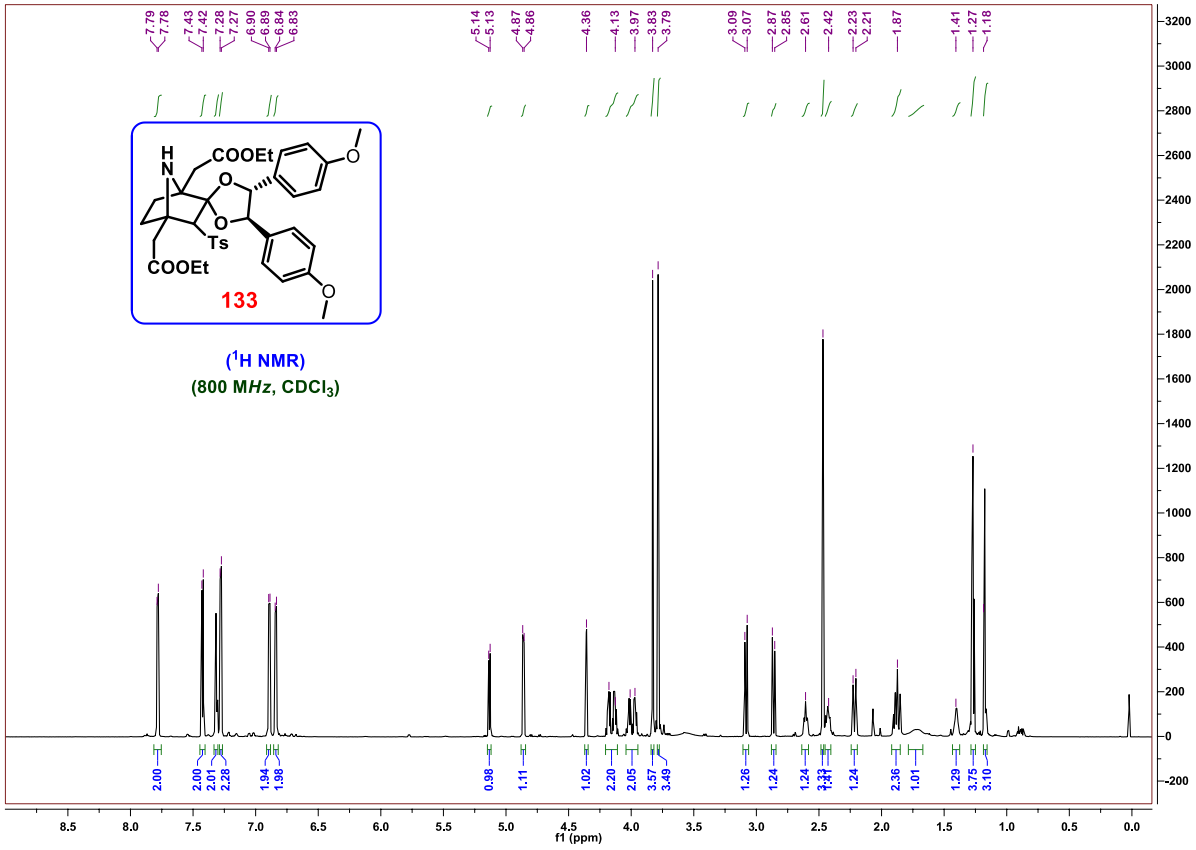


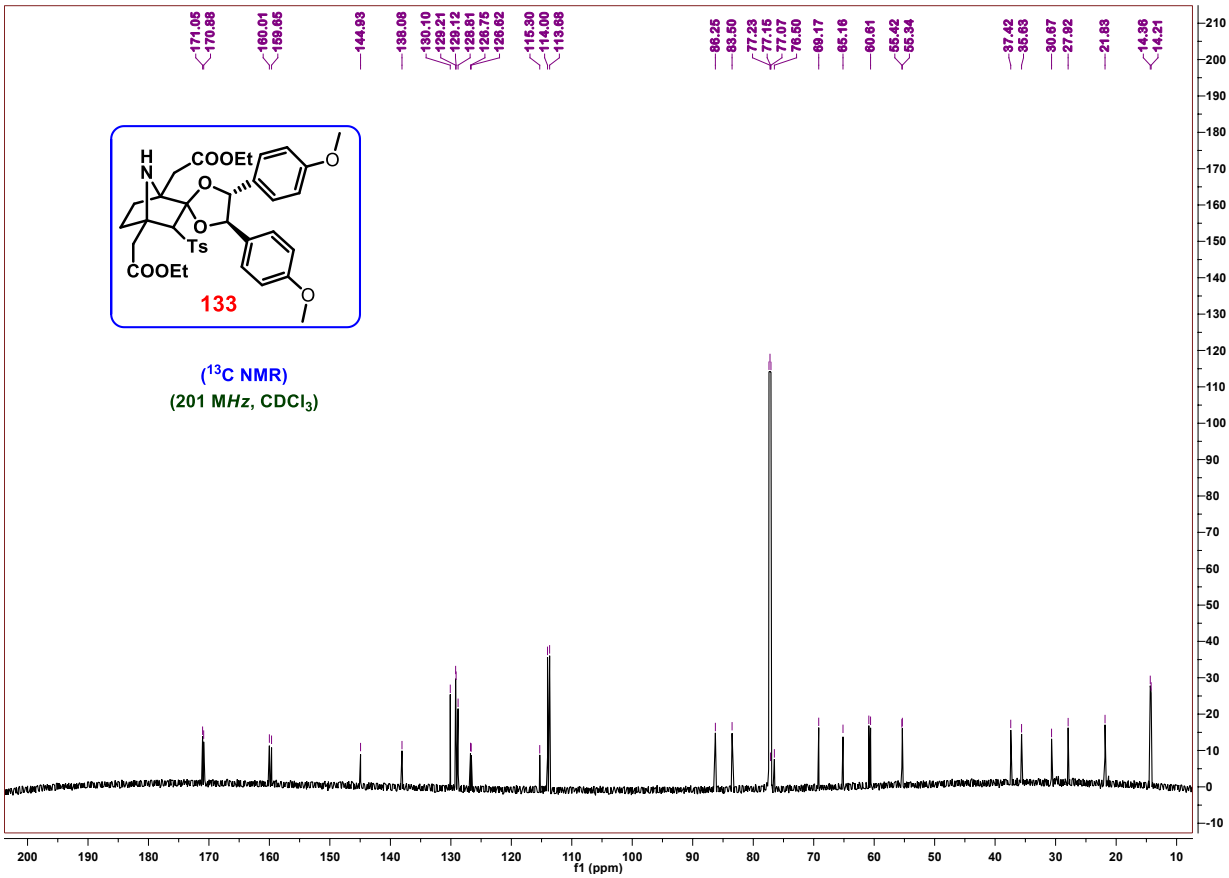
(^{1}H NMR)

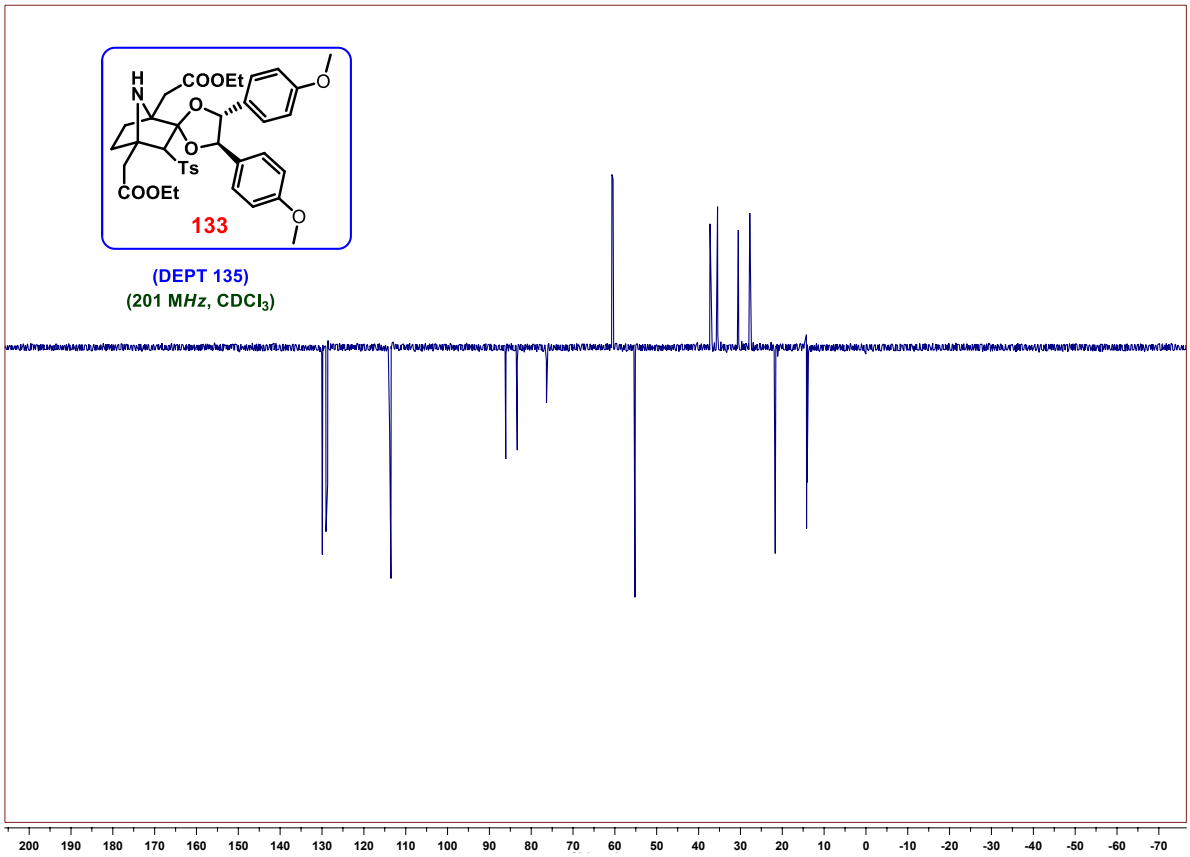
(800 M*Hz*, $CDCl_3$)

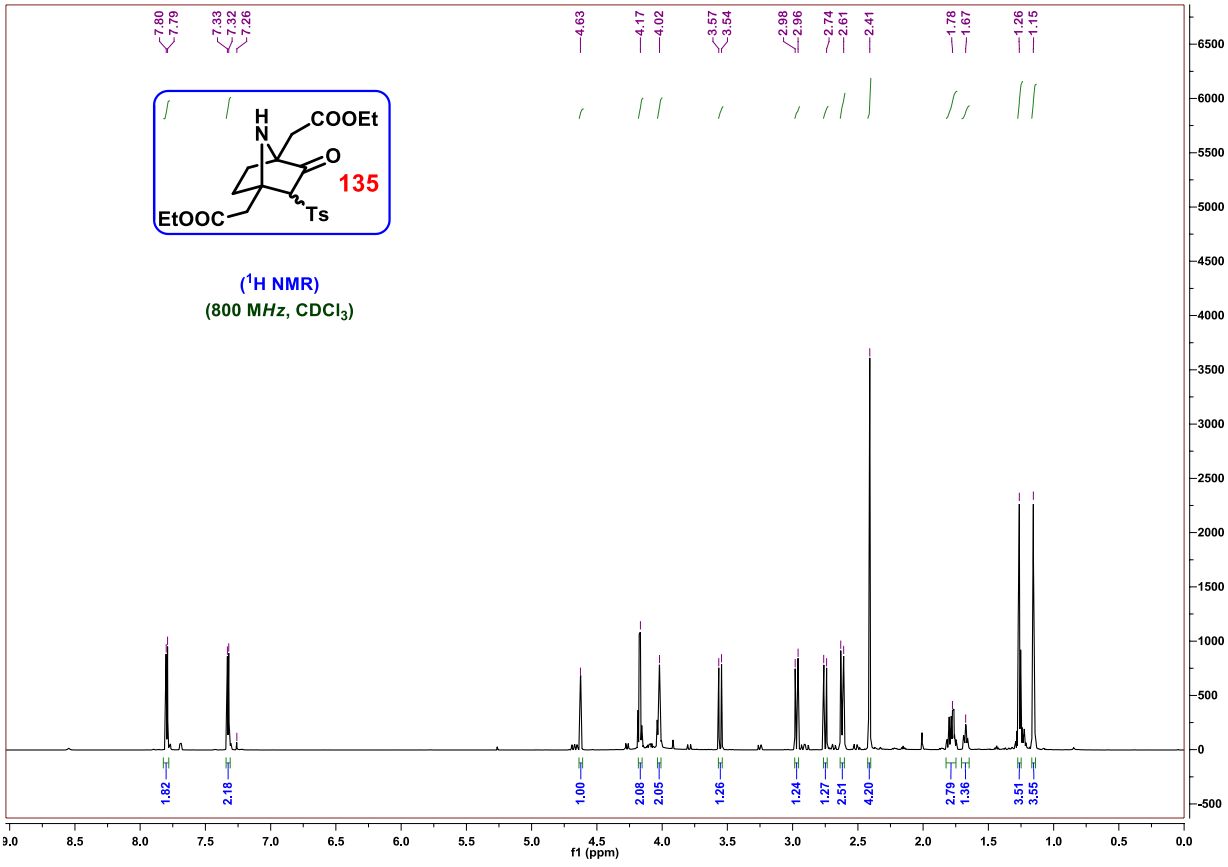

170.71
165.32
145.03
137.79
129.55
128.37
77.32
77.16
77.00
72.49
60.68
37.45
32.63
21.62
13.95
H
N
COOEt
Ts
EtOOC
Ts
126
(13C NMR)
(201 MHz, CDCl3)
7E+08
6E+08
6E+08
6E+08
5E+08
4E+08
4E+08
4E+08
3E+08
2E+08
2E+08
2E+08
1E+08
5E+07
0
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

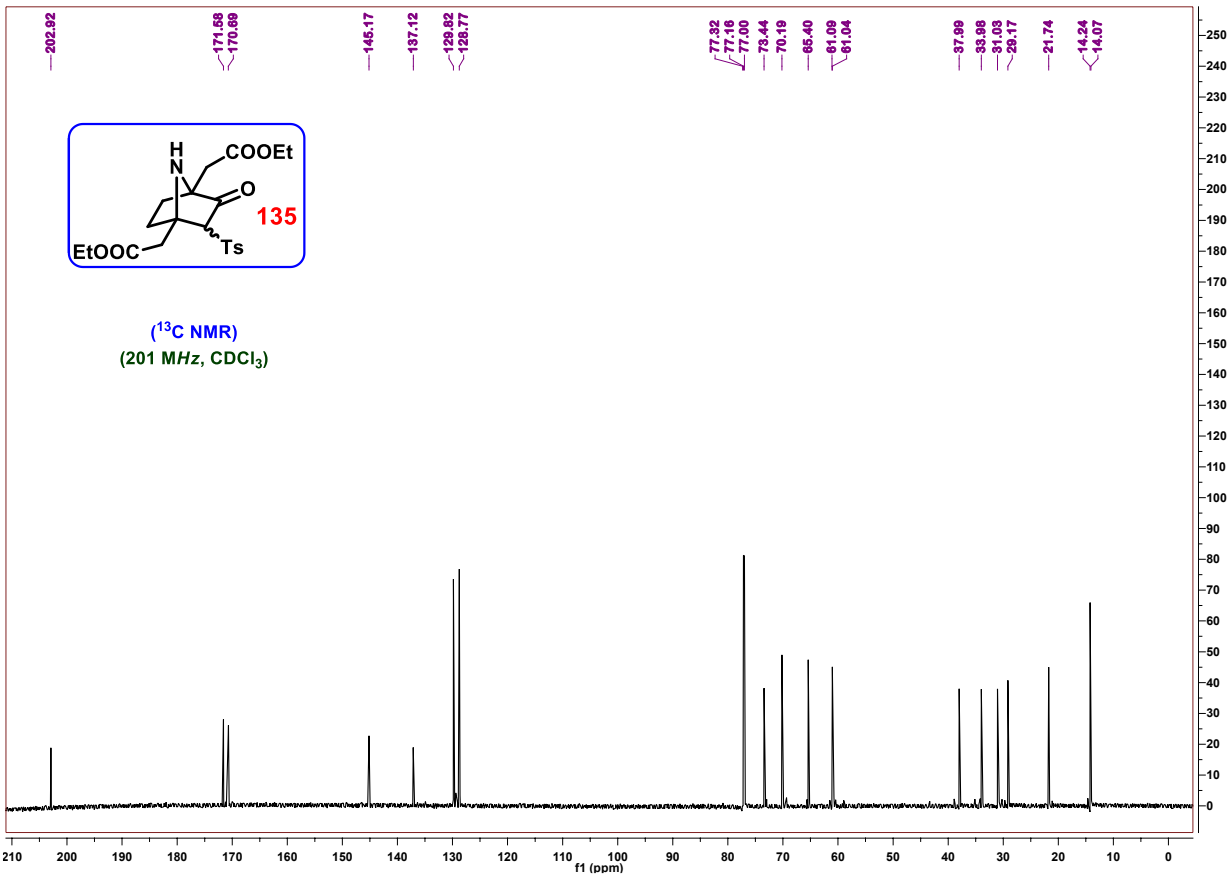

H
N
COOEt
Ts
EtOOC
Ts
126
(DEPT 135)
(201 MHz, CDCl3)
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

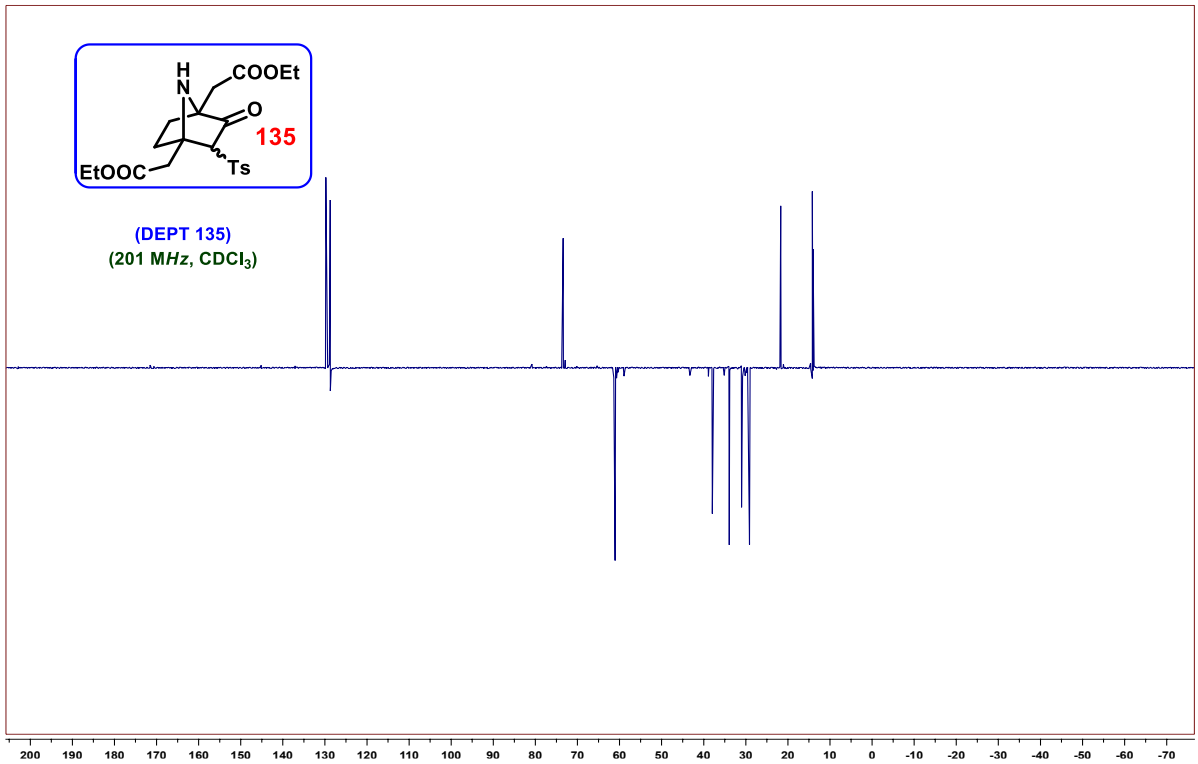

7.79
7.78
7.43
7.42
7.28
7.27
6.90
6.89
6.84
6.83
5.14
5.13
4.87
4.86
4.36
4.13
3.97
3.83
3.79
3.09
3.07
2.87
2.85
2.61
2.42
2.23
2.21
1.87
1.41
1.27
1.18
H
N
COOEt
O
O
Ts
COOEt
O
133
(1H NMR)
(800 MHz, CDCl3)
2.00
2.00
2.01
2.28
1.94
1.98
0.98
1.11
1.02
2.20
2.05
3.57
3.49
1.26
1.24
1.24
3.33
1.24
2.36
1.01
1.29
3.75
3.10
f1 (ppm)

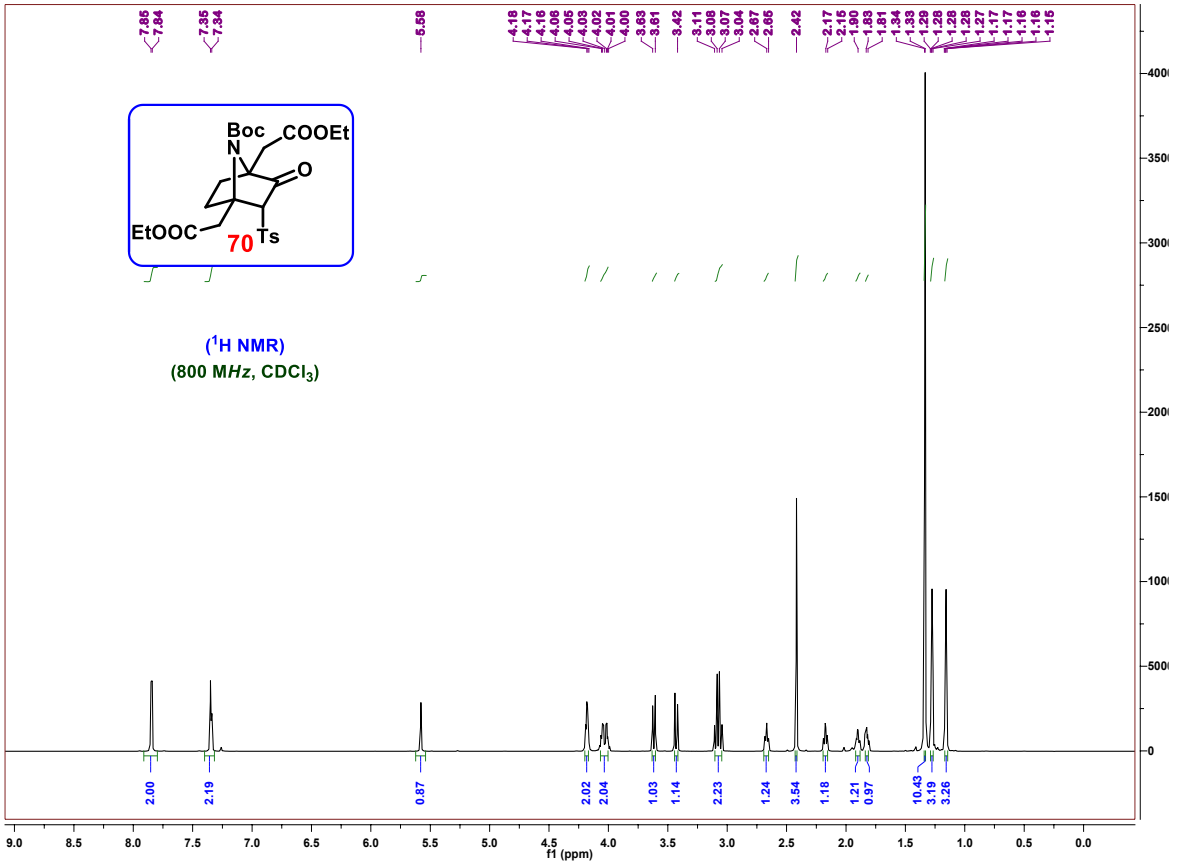

171.05
170.88
160.01
159.65
144.93
138.06
130.10
129.21
129.12
128.81
126.75
126.62
115.30
114.00
113.68
96.25
83.50
77.23
77.15
77.07
76.50
69.17
65.16
60.61
55.42
55.34
37.42
35.63
30.67
27.92
21.83
14.36
14.21
H
N
COOEt
O
O
Ts
COOEt
O
133
(13C NMR)
(201 MHz, CDCl3)
f1 (ppm)

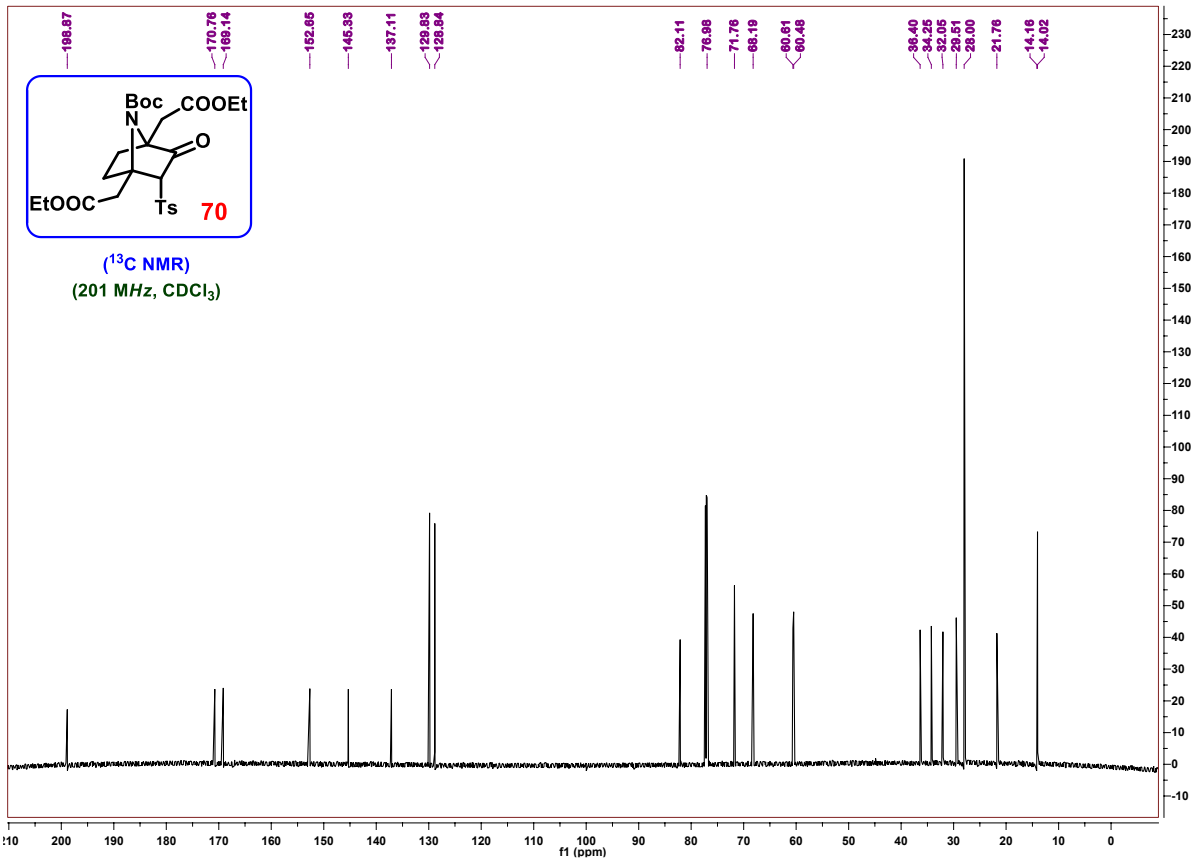

H
N
COOEt
O
O
Ts
COOEt
O
O
133
(DEPT 135)
(201 MHz, CDCl3)
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20 -30 -40 -50 -60 -70

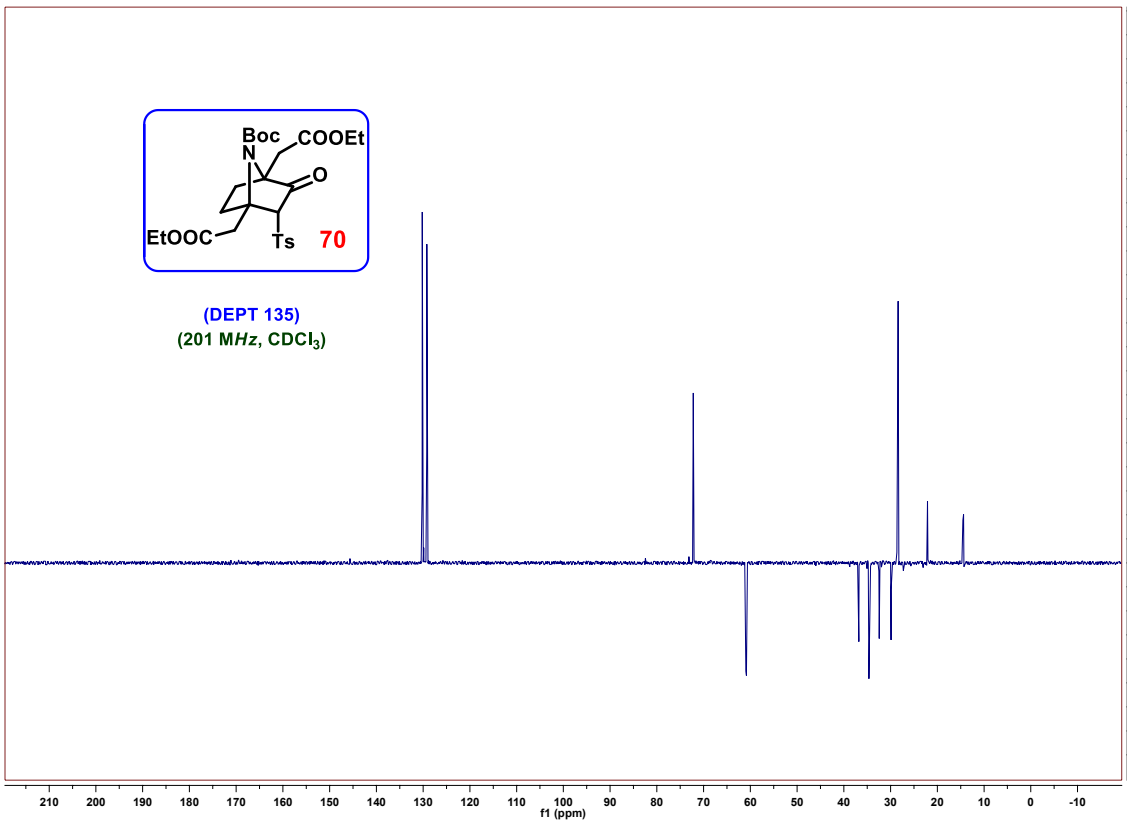

7.80
7.79
7.33
7.32
7.26
4.63
4.17
4.02
3.57
3.54
2.98
2.96
2.74
2.61
2.41
1.78
1.67
1.26
1.15
H
N
COOEt
O
135
EtOOC
Ts
(1H NMR)
(800 MHz, CDCl3)
1.82
2.18
1.00
2.08
2.05
1.26
1.24
1.27
2.51
4.20
2.79
1.36
3.51
3.55
f1 (ppm)

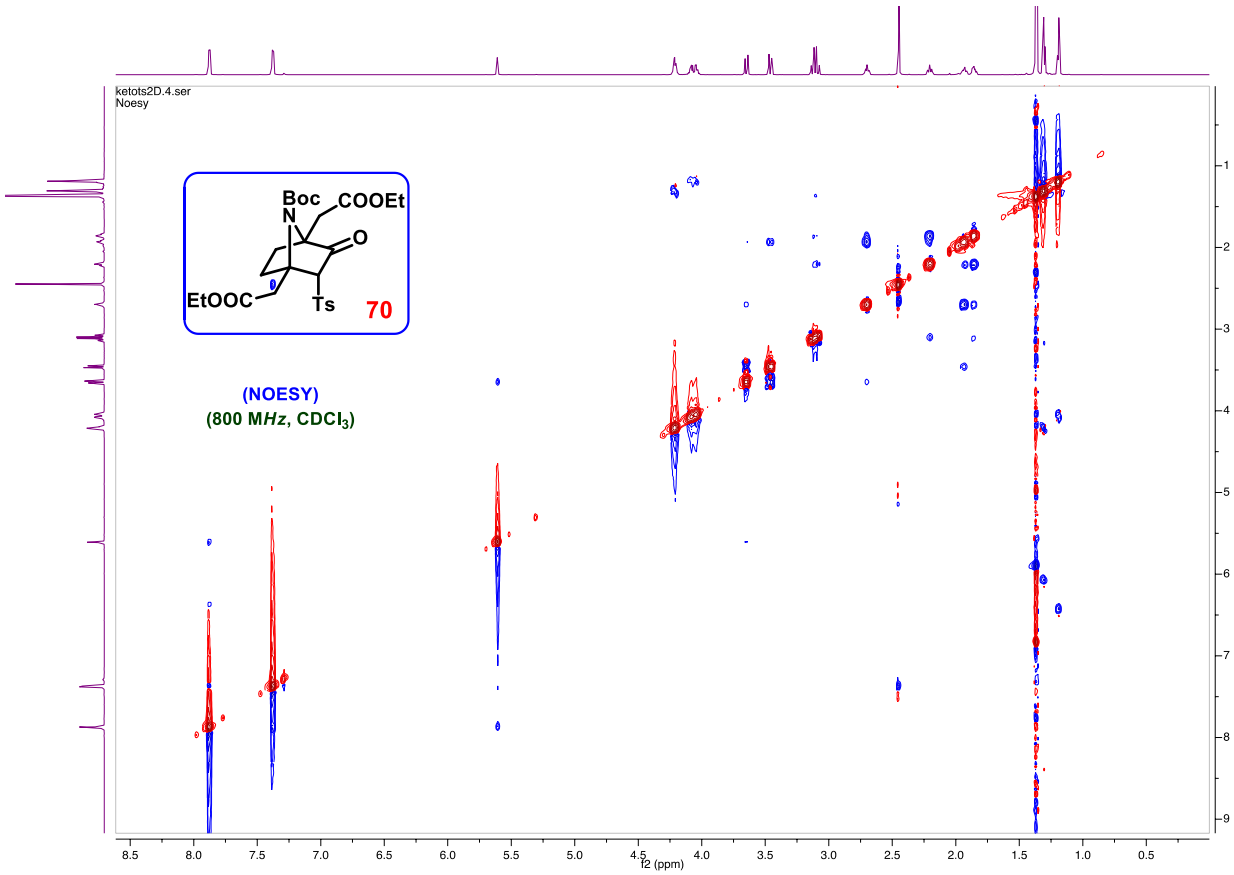

202.92
171.58
170.69
145.17
137.12
129.82
128.77
77.32
77.16
77.00
73.44
70.19
65.40
61.09
61.04
37.99
33.98
31.03
29.17
21.74
14.24
14.07
H
N
COOEt
O
135
EtOOC
Ts
(13C NMR)
(201 MHz, CDCl3)
f1 (ppm)

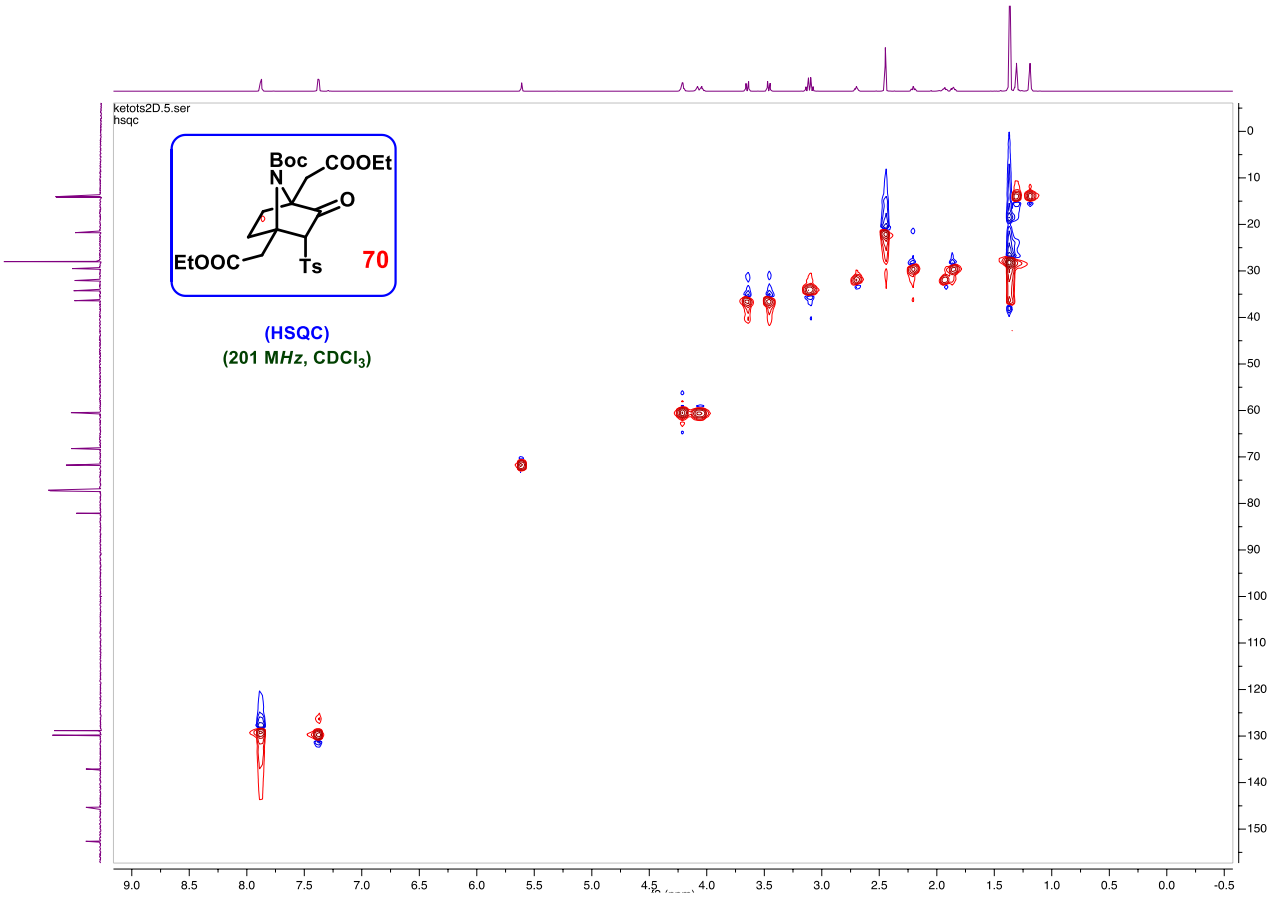

H
N
COOEt
O
135
EtOOC
Ts
(DEPT 135)
(201 MHz, CDCl3)

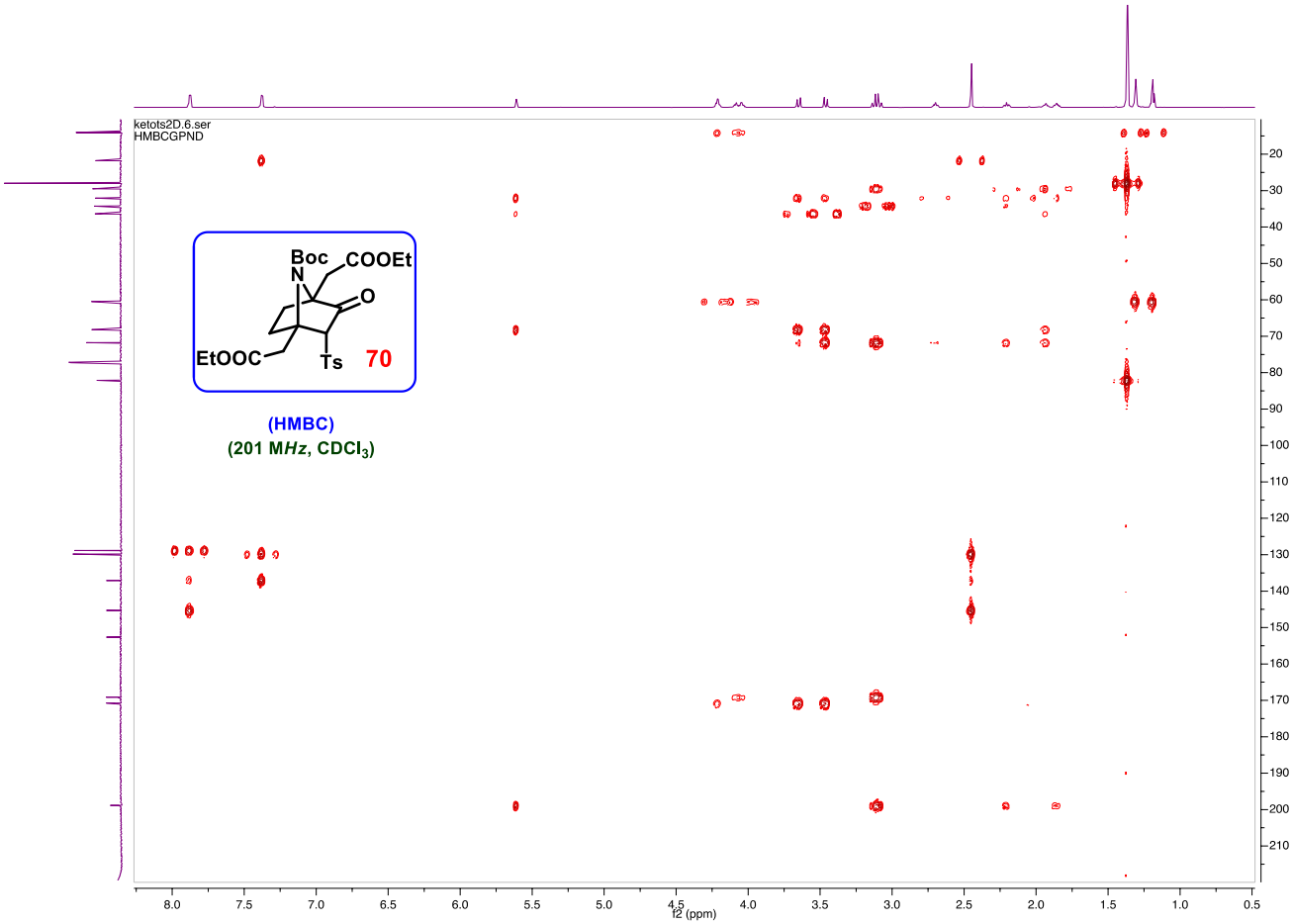

Boc
COOEt
N
O
EtOOC
Ts
70
(1H NMR)
(800 MHz, CDCl3)
f1 (ppm)

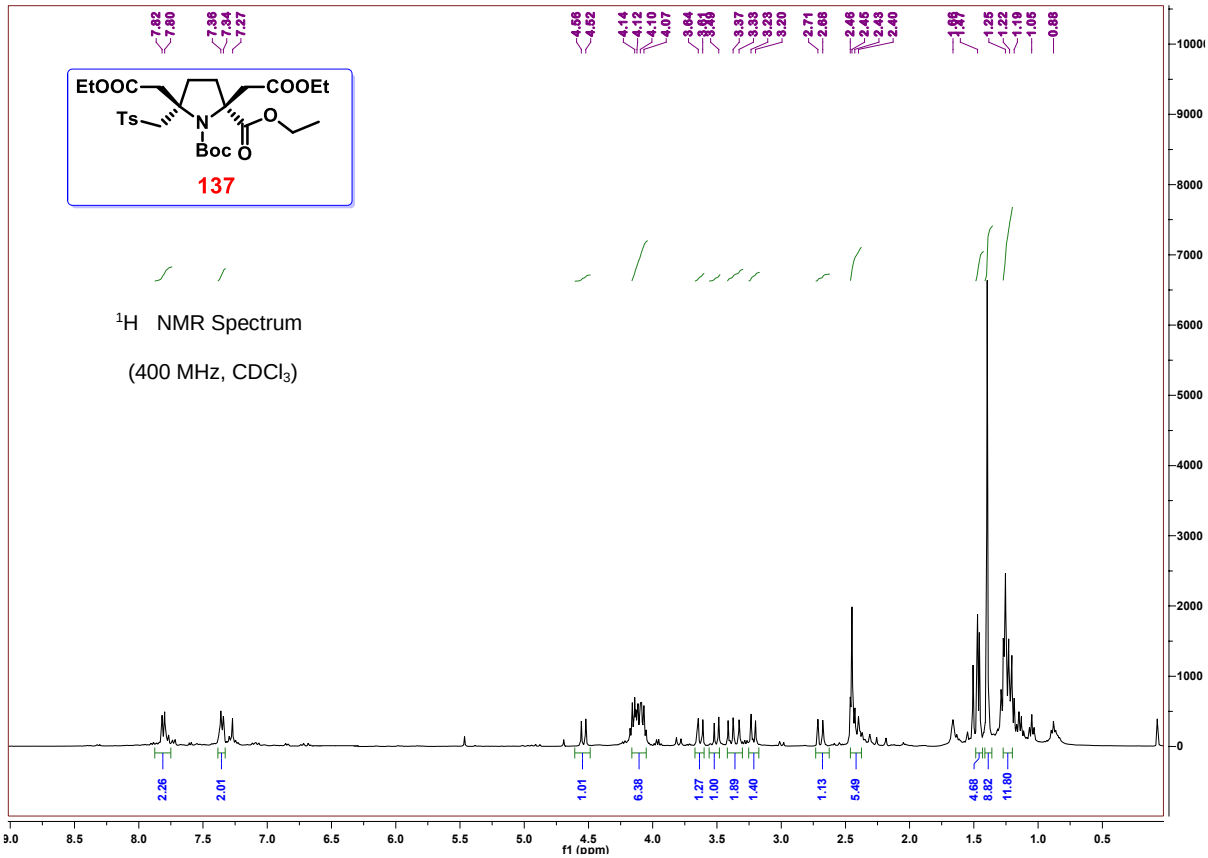

Boc
COOEt
N
O
EtOOC
Ts
70
(13C NMR)
(201 MHz, CDCl3)
f1 (ppm)

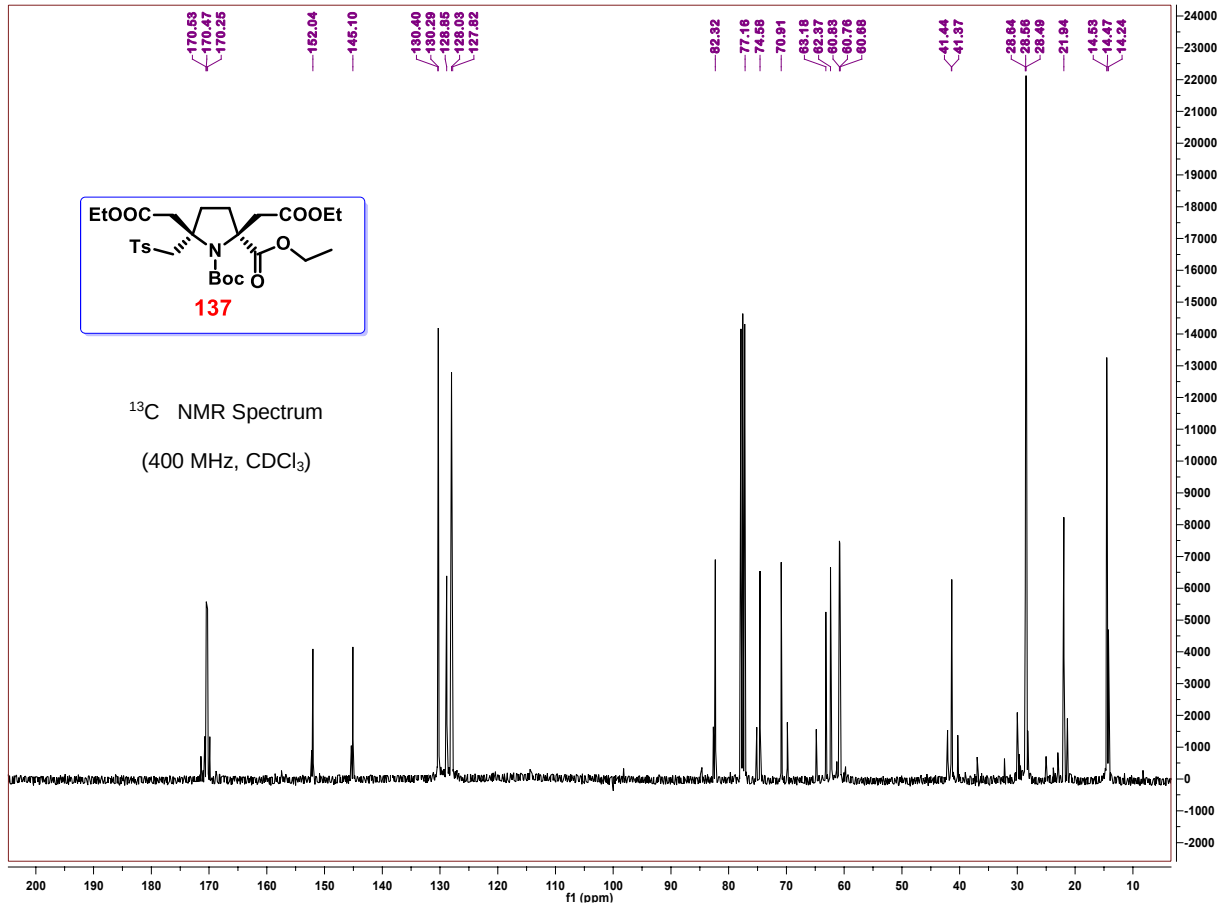

Boc
COOEt
N
O
EtOOC
Ts
70
(DEPT 135)
(201 MHz, CDCl3)
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

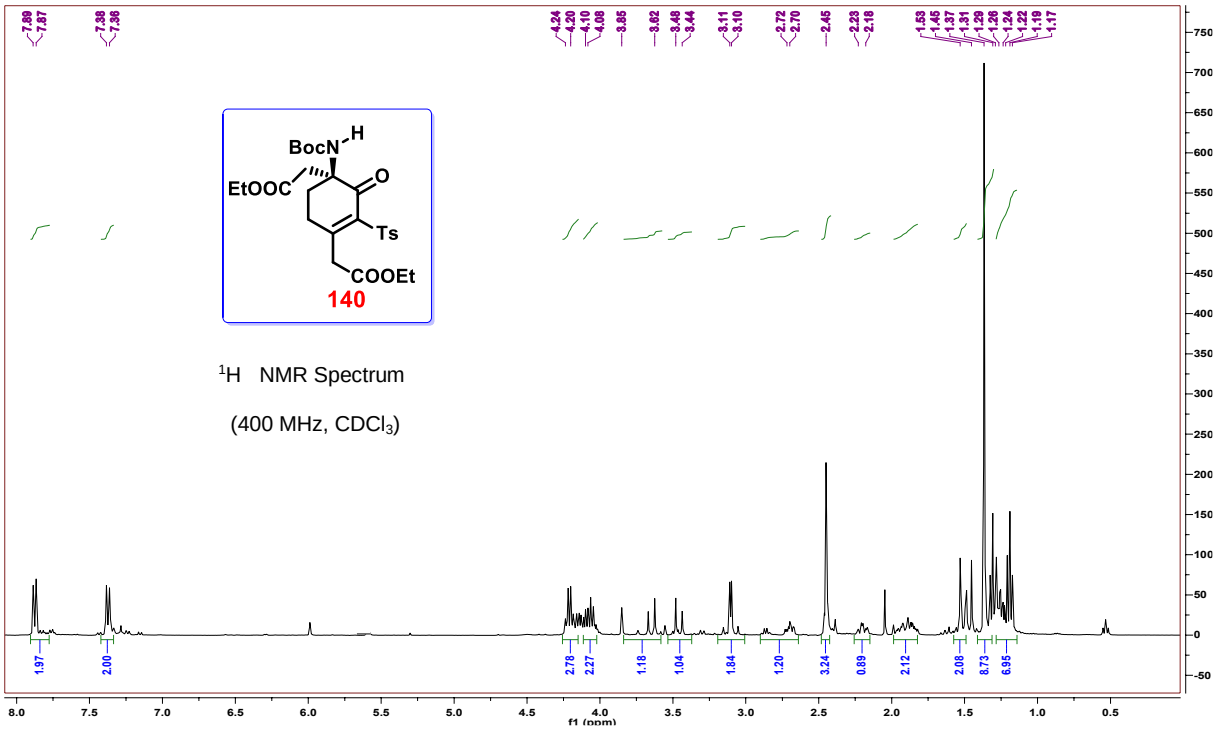

ketots2D.4.ser
Noesy
Boc
COOEt
N
O
EtOOC
Ts
70
(NOESY)
(800 MHz, CDCl3)
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f2 (ppm)
1 2 3 4 5 6 7 8 9


ketots2D.5.ser
hsqc
Boc
COOEt
N
O
EtOOC
Ts
70
(HSQC)
(201 MHz, CDCl3)


ketots2D.6.ser
HMBCGPND
Boc
COOEt
N
O
EtOOC
Ts
70
(HMBC)
(201 MHz, CDCl3)
f2 (ppm)

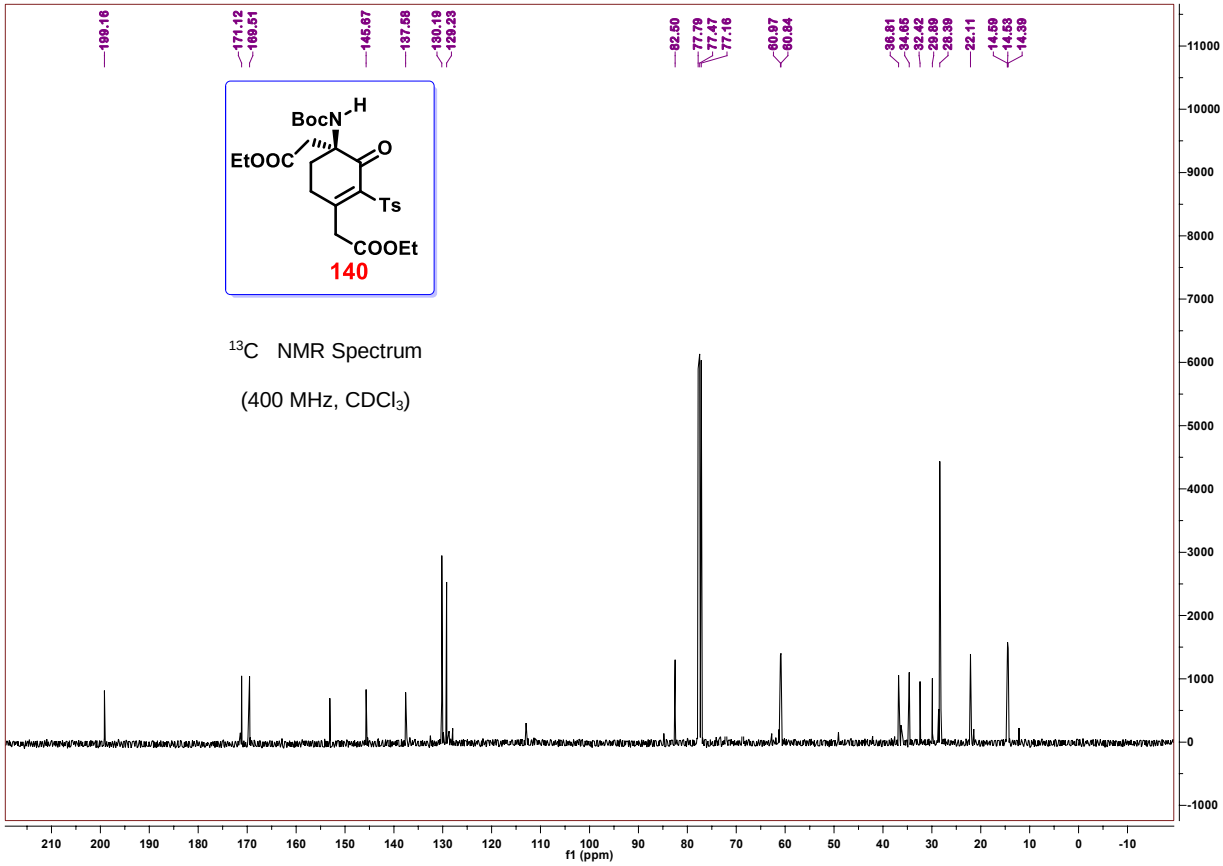

EtOOC
COOEt
Ts
N
Boc
O
137
^{1}H NMR Spectrum
(400 MHz, $CDCl_3$)
f1 (ppm)


EtOOC
COOEt
Ts
N
Boc
O
137
^{13}C NMR Spectrum
(400 MHz, $CDCl_3$)
f1 (ppm)



^{1}H NMR Spectrum

(400 MHz, $CDCl_3$)



^{13}C NMR Spectrum

(400 MHz, $CDCl_3$)

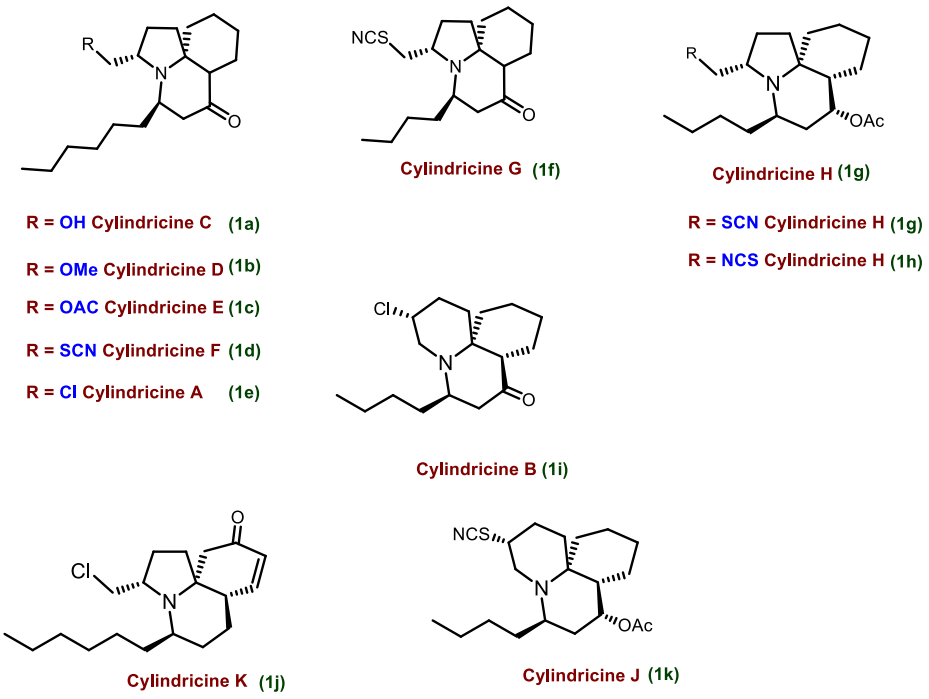
Chapter 2:-

“*Stereoselective Total Synthesis of Cylindricine Class of Alkaloids*”

Section -2.1: Introduction to cylindricine family of alkaloids

Marine ascidians, known as *Clavelina* is made up of a wide variety of colored sea squirts that have produced a plethora of natural products including the cylindricine and lepadiformine family of alkaloids. *Clavelina cylindrica* is the source of the cylindricine family of alkaloids consisting of 11 tricyclic alkaloids (Figure 1), isolated off the coast of Tasmania, in yields ranging between 0.0002-0.009 %. Biosynthetic pathways and natural function of these alkaloids are still unknown. A modest cytotoxity[4-6] is reported from a mixture of cylindricines A and B (equilibrium mixture 3:2) on a brine shrimp assay. Cytotoxicity observed from these alkaloids is believed to arise from DNA cleavage at guanine site due to alkylation involving strained aziridinium intermediate (**1l**)[1-3] as shown in Scheme 1.

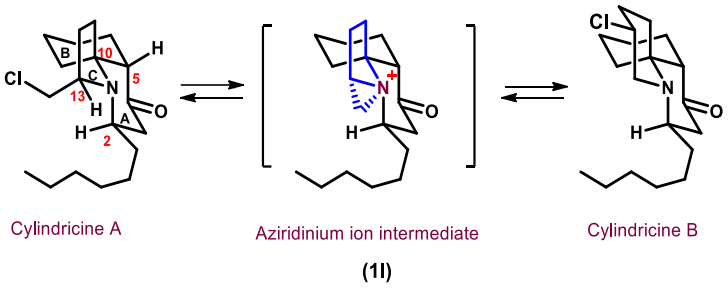
Figure 1:- Classification of Cylindricine family of alkaloids



The absolute configuration of the natural enantiomer still remains unknown as no optical rotation was taken at the time of isolation of these molecules, perhaps due to insufficient amount of isolated compounds. In spite of moderate biological activity exhibited by this class of alkaloids, synthesis of Cylindricines have become intriguing

targets for organic chemists[7] due to complex tricyclic 1-azaspirocyclane structures which poses a formidable synthetic challenge.

Scheme 1: Inter conversion of Cylindricine A and B



(1l)

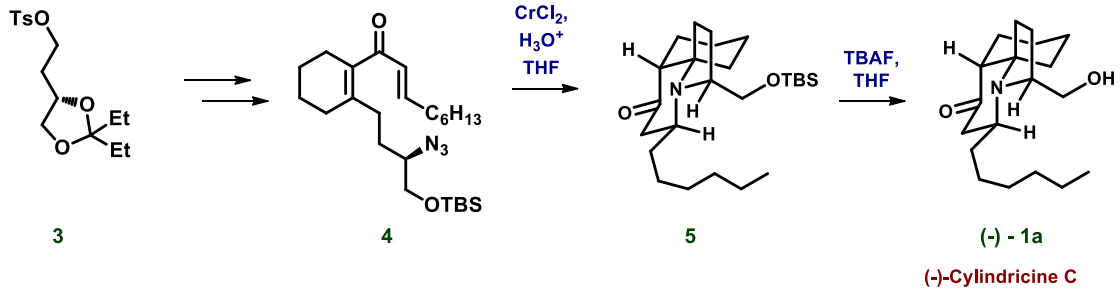
Section -2.2: Reported synthetic strategies for the Cylindricine C

Several synthetic approaches have been developed to synthesize Cyclindricine C both in racemic as well as in optically active form. However, only synthesis of **1** in optically active form will be discussed to keep the discussion to a finite perspective.

Molander's Approach: (*J. Org. Chem*. **1999**, *64*, 5183)[35]

First asymmetric synthesis of **1** was accomplished in 1999 in 11 steps and 12 % yield (Scheme 2) utilizing an intramolecular double conjugate addition of an in situ generated amine functionality from **4** as a key step shown in Scheme 2.

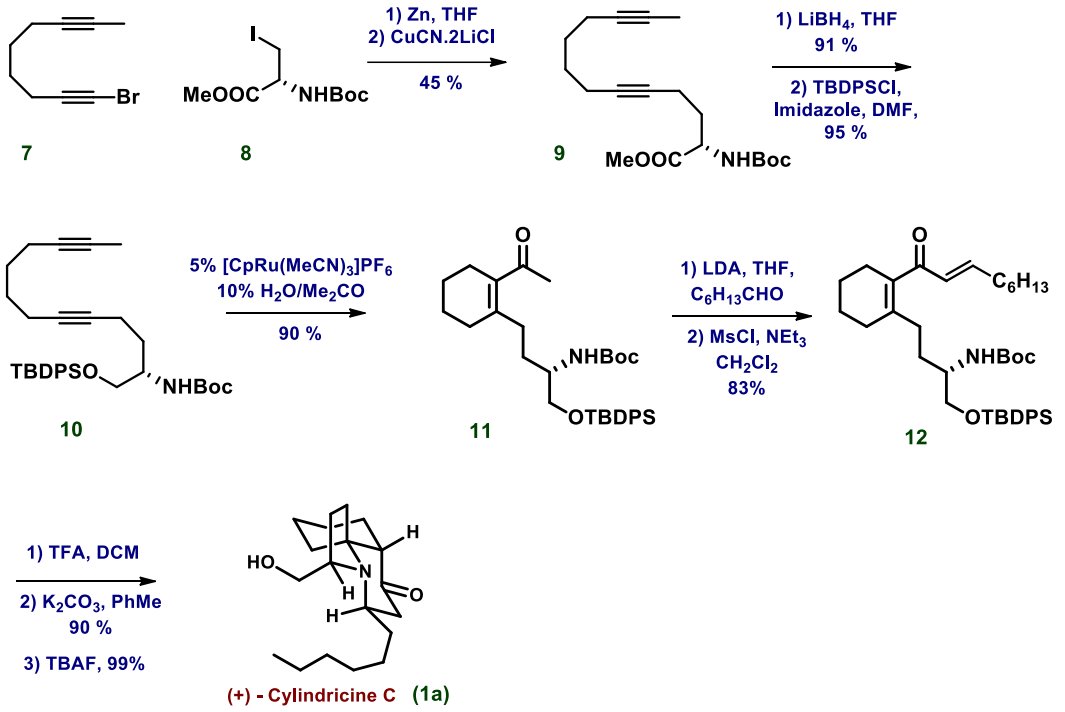
Scheme 2:- Molander's Synthesis of (–)-Cylindricine C



Trost's synthesis of (+)- cylindricine C: (*Org. Lett*. **2003**, *5*, 4599.)[28]

Trost and coworkers also used an intramolecular double conjugate addition strategy, similar to Molander, from **12** to obtain **1a** (Scheme 3). Precursor **12** was obtained by hydrative diyne cylization of **10** followed by subsequent steps as shown in Scheme 3 (9 steps and 12 % yield).

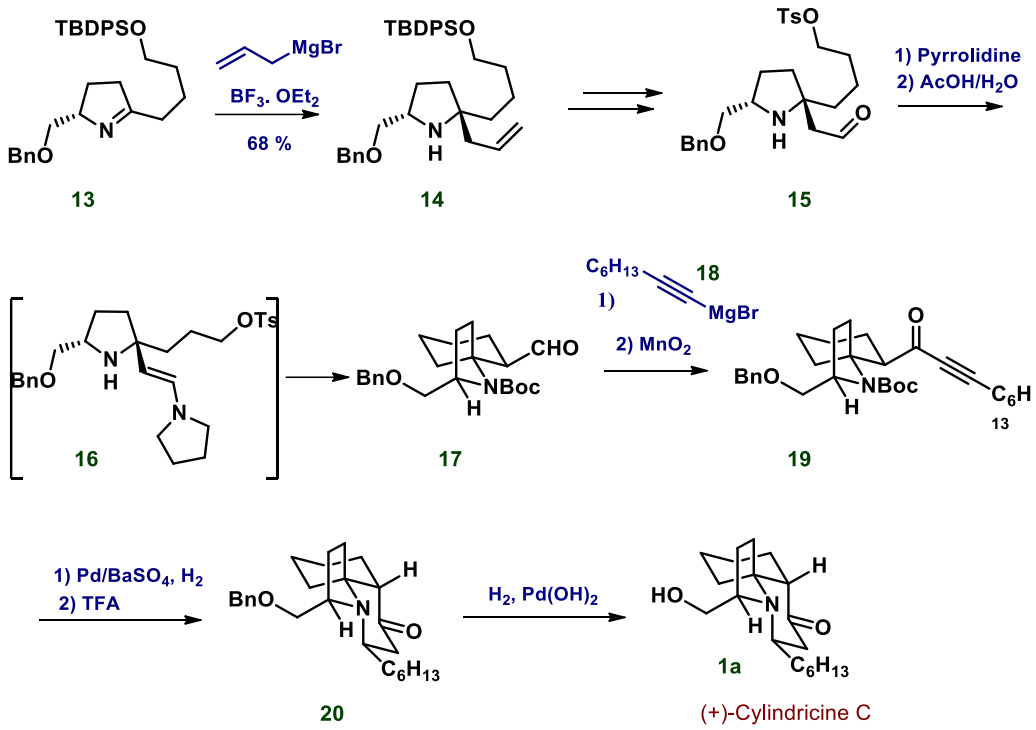
Scheme 3: Trost's Synthesis of (+)-Cylindricine C



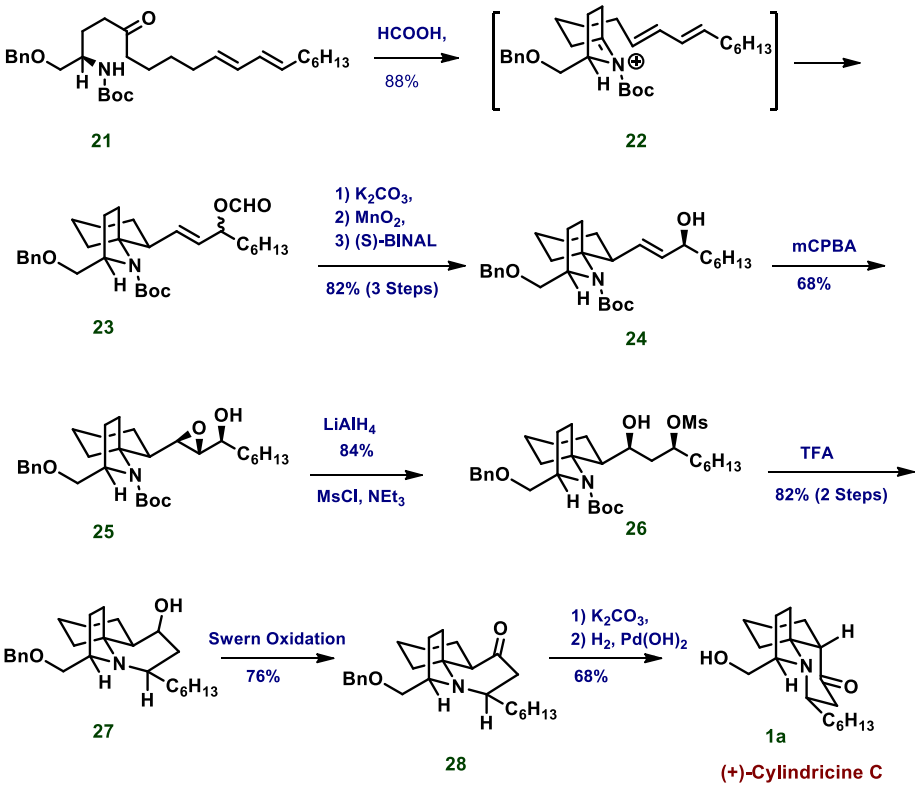
Kibayashi's synthesis of (+)-cylindricine C: (*Tetrahedron Lett.* **2004**, *45*, 5921)[10] (*J. Am. Chem. Soc*. **2005**, *127*, 1473.) [11]

Kibayashi and coworkers accomplished the synthesis of **1a** in 14 steps and 9 % yield (Scheme 4) utilizing intramolecular cyclization of an in situ generated enamine moiety from **16** to construct spirobicyclic skeleton **17** which by following simple steps as shown in Scheme 4 delivered **1a**. The key precursor **14** was obtained by the allyl Grignard addition on **13**.

Scheme 4: Kibayashi's Synthesis of (+)-Cylindricine C



Scheme 5: Kibayashi's Second Synthesis of (+)-Cylindricine C

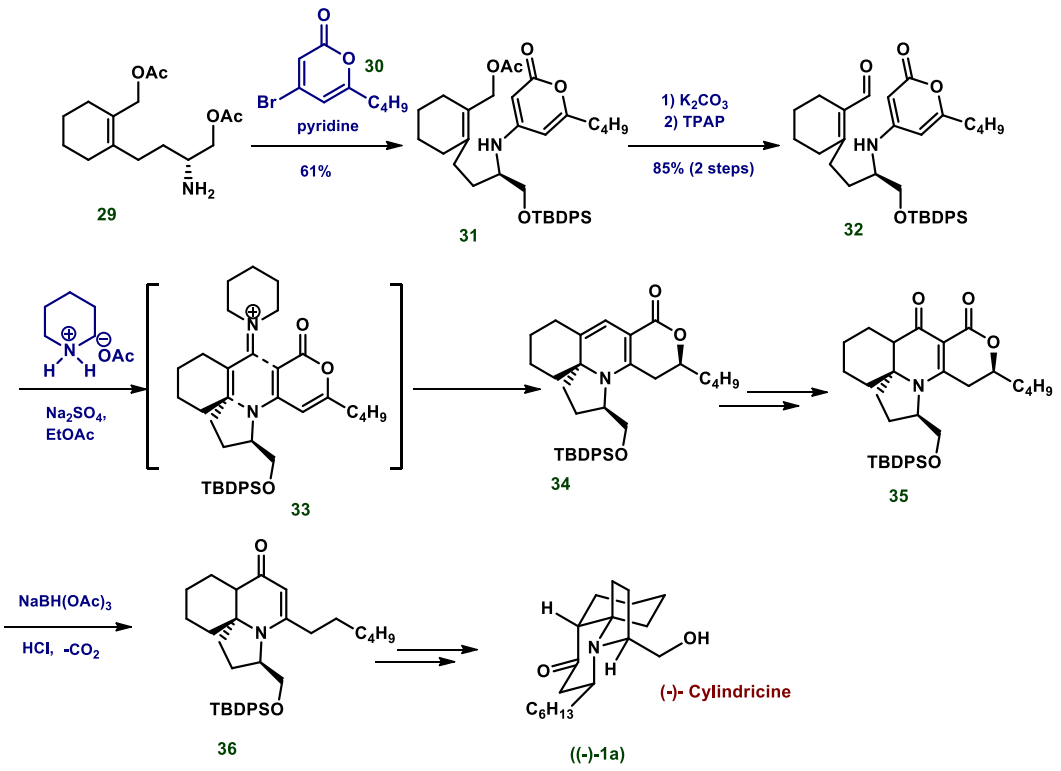


Subsequently, the same group also reported another strategy to obtain **1a** in 12 steps and 12 % overall yield utilizing an intramolecular conjugate azaspirocyclization of **22** as the key step to obtain bicyclic framework **23.** Further functional group transformations followed by intramolecular SN^2 substitution of mesylate group in **26** gave tricyclic framework **27** as shown in Scheme-5**.**

Hsung's [3+3] Annulation Approach to (-)-Cylindricine C: (*Org. Lett.* **2006**, *8*, 777.) [13]

This group has utilized[13] an intramolecualr aza-[3+3]-cycloaddition of **33** to obtain core azaspirocyclane framework **34** and further transformations (9 steps) gave **1a** (total 22 steps, 5% overall yield) (Scheme 6).

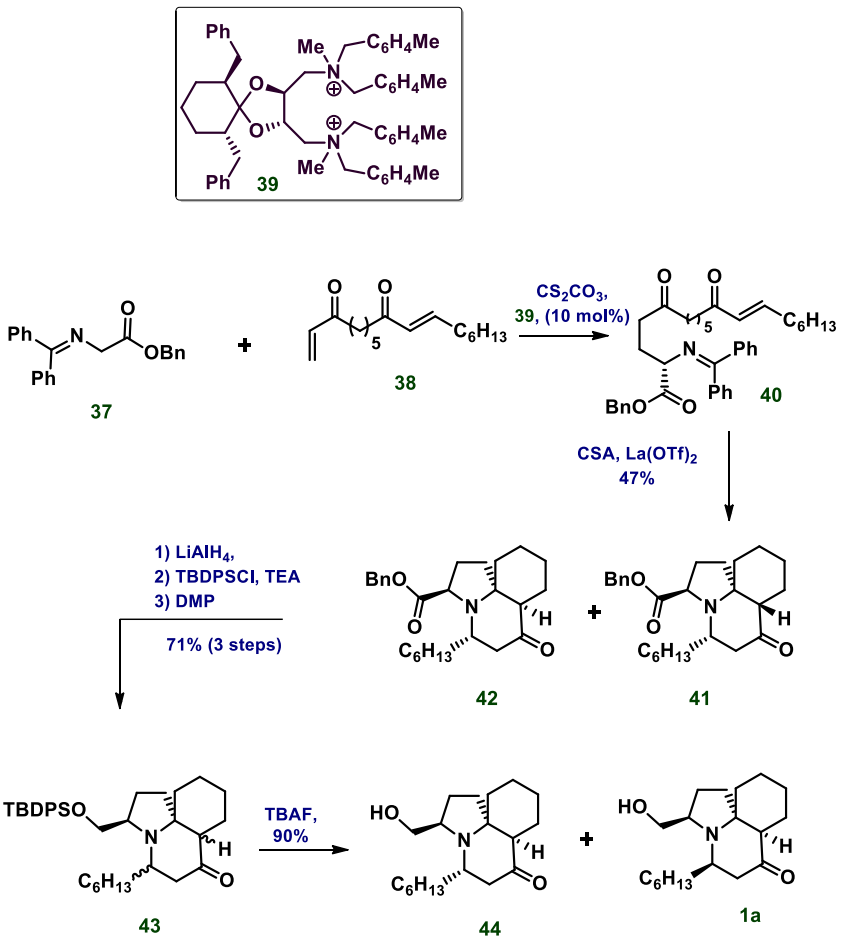
Scheme 6: Hsung's [3+3] Annulation Approach to (-)-Cylindricine C



Shibasaki's Approach: - (*Angew. Chem. Intl. Ed.* **2006**, *45*, 4635.) [14]

A short synthesis (6 steps) of **1a** is reported by Shibasaki's group by employing a cascade sequence of Michael/Mannich-reaction to obtain a key azaspirocyclane skeleton efficiently (Scheme 7). This group used chiral ammonium salt **39** as a phase transfer catalyst for chiral induction during Michael reaction.

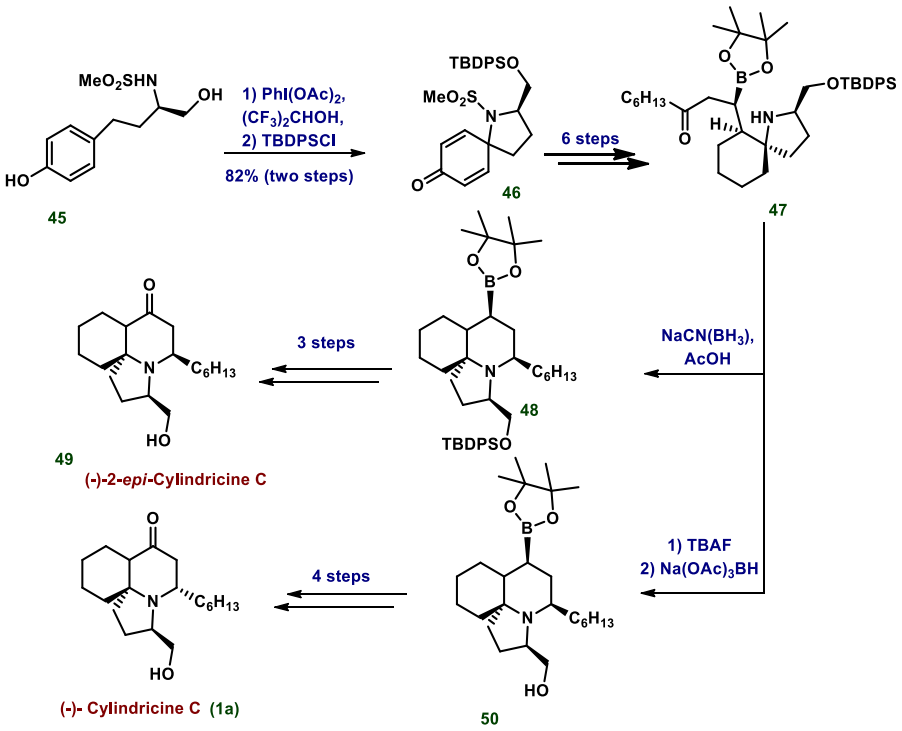
Scheme 7: Shibasaki's Organocatalysis approach to (-)-Cylindricine C and (–)-2-*epi*-Cylindricine C



Ciufolini's Approach: (*Angew. Chem., Intl. Ed.* **2005**, *43*, 4336) [15]

A conceptually different approach for the synthesis of **1a** and its unnatural analogue **49** is reported by Ciufolini and co-workers. Starting with an oxidative spirocyclization of **45** in the presence of iodosobenzene diacetate afforded **46** which on further reactions (6 steps) provided **47**, a common precursor for both **1a** and **49** (18 steps and 15 % overall yield) as shown in Scheme 9.

Scheme 9: Ciufolini's Oxidative Spirocyclization Approach to (-)-Cylindricine C and (–)-2-*epi*-cylindricine C



Section -2.3: Total synthesis of (+)-Cylindricine C, D, E.

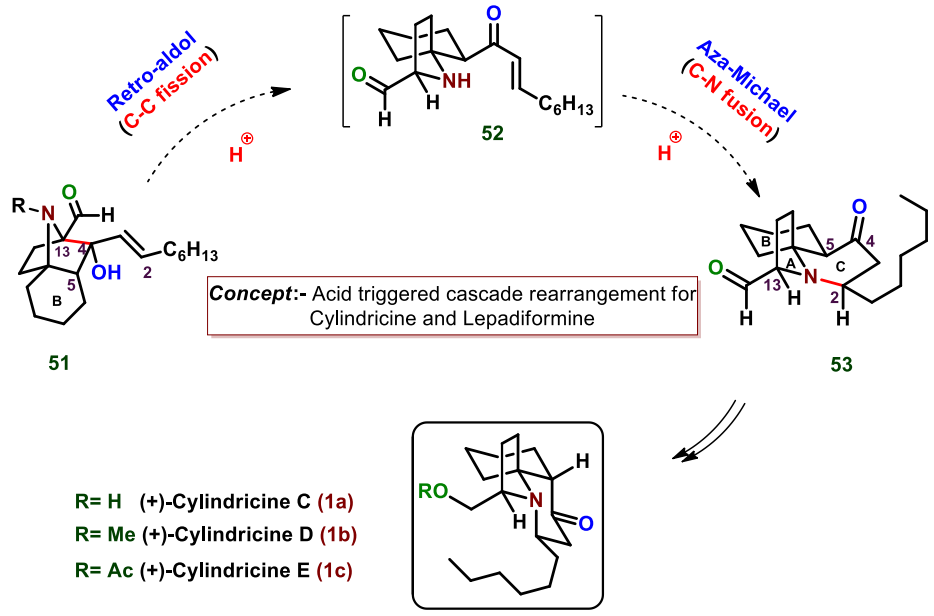
Objective of the present study:-

From above introductory remarks, it is clear that known strategies in the context of synthesizing cylindricines can either give (+)-**1** or (-)-**1** as all of them are based on chiral pool approach**.** However, since the absolute configuration of natural alkaloid is still unknown, it was felt necessary to develop a conceptually different route which can deliver both enantiomers of cylindricines. In this context, we have devised an innovative cascade rearrangement approach to synthesize **1** which is described as follows:

For the synthesis of the key perhydropyrrole[2,1-*j*] quinolone framework **53,** we envisaged a novel cascade transformation[16] from a bridged tricyclic precursor **51**[17] via an acid mediated retro-aldol fragmentation / aza-Michael addition reaction as shown

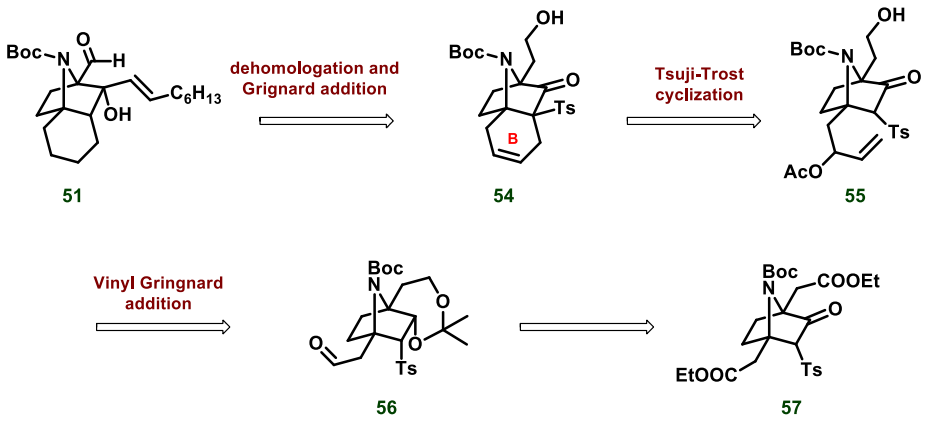
in Scheme 10. This framework was proposed to be diversified into **1a-1c** by selective reduction of aldehydic functionality followed by epimerization.

Scheme 10: Proposed cascade rearrangement for 1a, 1b, 1c



Retro Synthetic analysis:

Scheme 11: Retrosynthesis of 51

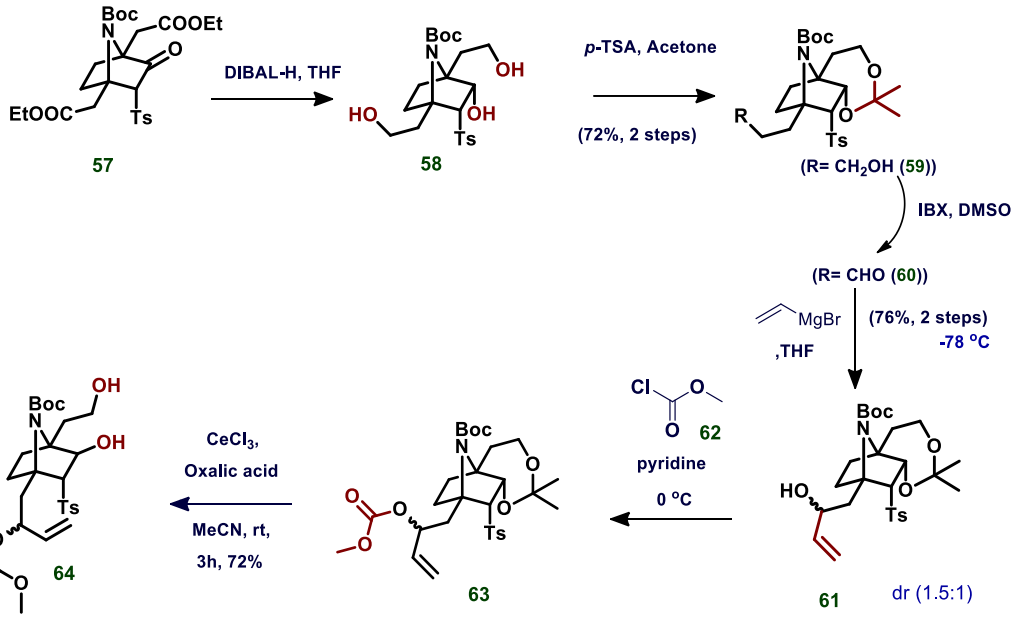


Compound **54** for the construction of key cascade precursor **51**, was envisaged to be synthesized by an intramolecular Tsuji-Trost reaction of compound **55** which can in turn be prepared via a vinyl grignard addition on **56** followed by esterification. A simple functional group transformation could be utilized for obtaining **56** from compound **57**.

Having designed above schematic route, we commenced our synthesis by synthesizing **58** by reduction[12] of **57** (9.34 mmol) with DIBAL-H (45.0 mmol, [DIBAL-H: 1M concentration in hexane] in THF (60 ml)) at –20 °C. Molecular ion peak $[M+Na]^+$ in HRMS at 478.1864 supported the formation of **58**. Further confirmation to the structure of **58** came by observing –OH group (3340 cm^{-1}) in the IR spectrum. Although, we proceeded with the next step with crude **58** a small amount was purified for spectral details.

1,4-Diol moiety of crude **58** (8.67 mmol) was protected by stirring with 2,2-dimethoxypropane (10.4 mmol) in CH_2Cl_2 in presence of catalytic amount of *p*-TSA (0.86 mmol) to obtain **59** (80% yield over two steps).

Scheme 12: Synthesis towards pivotal precursor of Tsuji-Trost reaction



Structural support for the formation of **59** came by observing two methyl protons at δ 0.34, (s, 3H) and δ 1.21, (s, 3H) as well as a quaternary carbon at (δ 101.93) in the ^1H NMR and ^{13}C NMR spectrum, respectively. Further support to the structure came from a molecular ion peak $[M+Na]^+$ at 518.2181 in HRMS. Optical rotation of **59** was found as $[\alpha]_D^{22}$ = -29.1°(c = 0.50, $CHCl_3$).

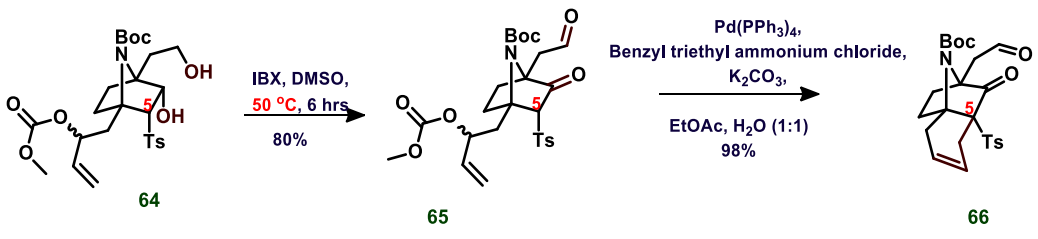
IBX oxidation (23.0 mmol, DMSO, 60 mL, 2 h, rt) of the primary alcohol moiety of **59** (23.0 mmol) gave **60** quantitatively which on reacting with vinyl magnesium bromide

(1M concentration in THF, 14.2 mmol, THF, 0 °C), however, gave a complex reaction mixture, possibly, due to 7-azabicyclo[2.2.1]heptane ring opening.[19] After surveying various conditions for vinyl Grignard addition, it was found that slow addition of the Grignard reagent (10 mL/h) in a mixture of toluene: THF (1:5) at −78 °C gave **61** (76 % yield, *d.r* = 1:1.5) (Scheme 12). We proceeded to the next step without separating the diastereomers. Methyl carbamate protection of **61** (3.36 mmol) using methyl chloroformate (7.72 mmol,) in the presence of pyridine (7.72 mmol) in CH_2Cl_2 at 0 °C afforded **63** in 84% yield. Crude **63** (2.88 mmol) on reacting with ceric chloride (3.36 mmol)[20] in presence of catalytic amount of oxalic acid (0.68 mmol) in acetonitrile at rt yielded **64** in 72% yield.

Structural assignment of **64** was made by detailed spectral analyses. For example, three alkenes protons appeared at δ 5.82 (ddd, J = 16.9, 10.5, 6.2 Hz, 1H), δ 5.30 - 5.20 (m, 1H), δ 5.13 (d, J = 10.1 Hz, 1H), respectively in ^{1}H NMR spectrum. A doublet of a triplet appearing at 4.95 (td, J = 7.1 Hz, 1H) was assigned to the proton attached with the ether moiety. Proton attached to tosyl functionality appeared at δ 3.93 (dd, J = 10.2, 4.7 Hz, 1H). In ^{13}C NMR spectrum, two carbony carbons appeared at δ 156.30 (Boc group) and at δ 155.20 (allyl carbonate), respectively. Carbon bearing tosyl functionality appeared at δ 67.27. Molecular ion peak $[M + Na]^+$ in HRMS was observed at 562.2077confirming the structure of **64**. Optical rotation for **64** was estimated to be $[\alpha]_D^{22}$ = -6.1° (c = 0.8, $CHCl_3$).

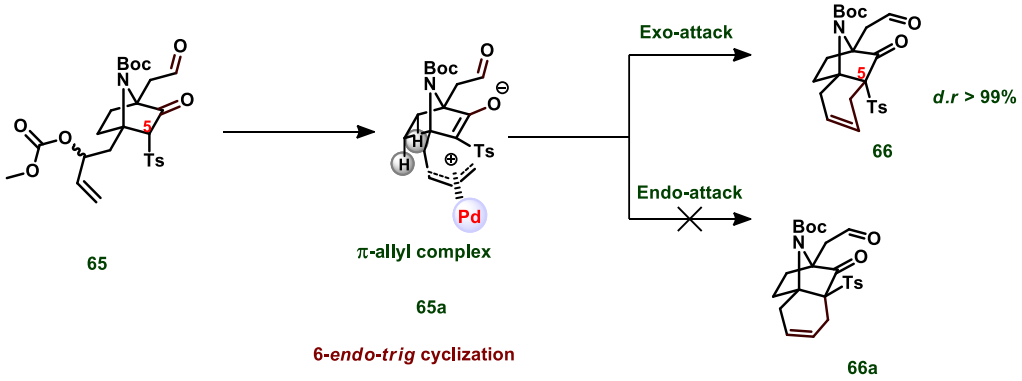
In order to transform **64** to **65,** a two-step protocol was utilized as shown in Scheme-13. First, -OH groups of **64** were oxidized by stirring with IBX (2.5 mmol)/DMSO, 10 mL, 6 h) at 50 °C to afford **65** in 80 % yield which upon Tsuji-Trost cyclization [21] using $Pd(PPh_3)_4$ (0.018 mmol) as a catalyst , benzyltriethyl ammonium chloride as a phase transfer catalyst (0.037 mmol) and K_2CO_3 as a base (1.11 mmol) in water : ethyl acetate (1:1) mixture gave **66** quantitatively.

Scheme 13: Synthesis of 66 by Tsuji-Trost reaction



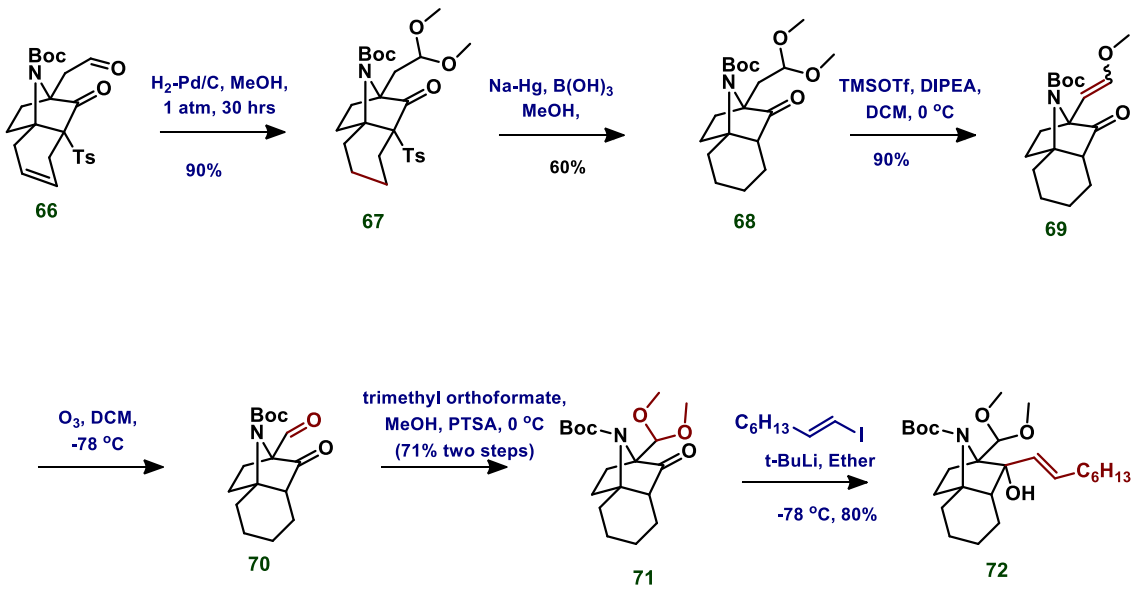
Formation of **66** was confirmed by observing two protons in the olefinic region in the ^{1}HNMR spectrum at δ 5.92 (ddd, J = 10.4, 4.8, 2.5 Hz, 1H), δ 5.51 (ddd, J = 10.0, 4.9, 2.2 Hz, 1H)) respectively. A carbon signal in ^{13}C NMR at δ 81.76 also confirmed the formation of a newly generated quaternary carbon C-5. Molecular ion peak $[M + Na]^{+}$ at 482.1608 confirmed the structure of **66.** Optical rotation for **66** was found to be $[\alpha]_{D}^{22}$ = -31.8° (c = 1.0, $CHCl_3$).

Scheme 14: Selectivity at C-5 position of in Tsuji-Trost reaction of 65



Emerging stereoselectivity at C-5, during Tsuji-Trost 6-*endo-trig* cyclization[22] is explained by considering *exo*-face attack of π-allyl complex to avoid steric repulsion with *endo*-oriented protons of bicyclic framework **65** (Scheme 14).

Scheme-15: Synthesis of 72



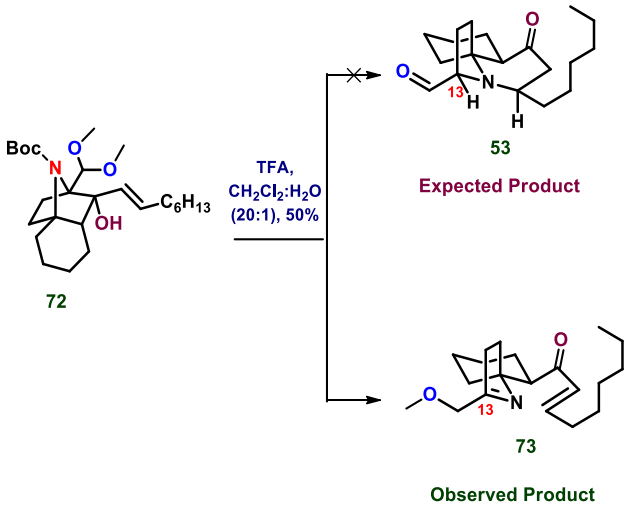
Having efficiently assembled **66**, our next target was to prepare **72,** the designed precursor for cascade rearrangement. Towards this end, **66** (1.09 mmol) was hydrogenated (H_2-Pd/C (0.048 mmol, MeOH) at 1 atm to afford **67** in 90% yield. Although, disappearance of corresponding olefinic protons in ^{1}HNMR spectra, were expected from this reaction, appearance of two sets of protons as multiplets, integrating three each at δ 3.31 - 3.27 (m, 3H) and δ 3.19 - 3.16 (m, 3H) were surprising. Furthermore, carbon signal related to the aldehydic moiety at δ 202 was also found missing. HRMS provided molecular ion peak $[M + Na]^+$ at 530.2180. Thus, based on these results it was inferred that during hydrogenation reaction, aldehydic moiety got protected as an acetal. [23] Although, this result was unexpected, it turned out to be fortuitous outcome which safeguarded the aldehyde moiety during subsequent desulfonylaton step. [24] Stirring of crude **67** (1 mmol) with Na-Hg (7%, 5 mmol), $B(OH)_3$ (1.5 mmol) in MeOH at 0 °C → rt, 3-5 h [25] afforded **68** in (60 % yield in two steps). Formation of **68** is suggested by the absence of aromatic protons in ^{1}H NMR spectrum which was further confirmed by HRMS (molecular ion peak $[M + Na]^+$ at 376.2092). Optical rotation was found to be $[\alpha]_D^{22}$ = +14.6° (*c* = 1.1, $CHCl_3$).

Moving towards our target, **68** (0.66 mmol) was treated with trimethyl silyl triflate (0.73 mmol) in CH_2Cl_2 at 0 °C in the presence of Huing's base (DIPEA) (0.8 mmol)[26] to obtain **69** which was used without purification in the next step. One carbon truncation of crude **69** by ozonolysis (O_3, CH_2Cl_2, -78 °C, PPh_3) [30] afforded **70** which on immediate acetal protection (trimethyl orthoformate (1.2 mmol), MeOH, *p*TSA (0.05 mmol), 0 °C) furnished **71** (71% over two steps). Reaction of **71** with (*E*)-1-octenyl lithium furnished **72** in 80 % yield (Scheme 13). Formation of **72** was suggested by observing olefinic protons at δ 5.52 (dt, *J* = 15.6, 6.5 Hz, 1H) and δ 5.46 (d, *J* = 15.6 Hz, 1H), respectively, in the ^{1}H NMR spectrum.

Section -2.4: Development of a Tandem rearrangement:

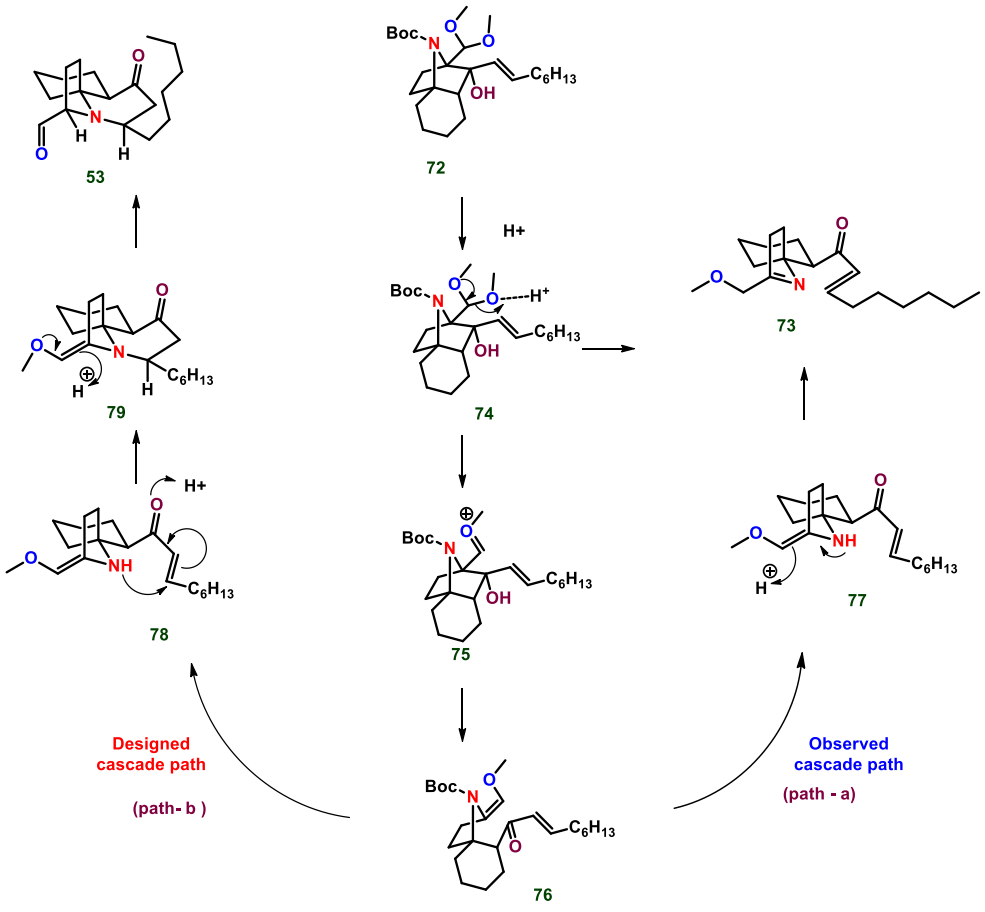
Having assembled trigger **72** for cascade rearrangement, it was envisaged that under an acidic condition acetal moiety of **72** would undergo deprotection producing a free aldehydic moiety which on rearrangement would give perhydropyrrolo[2,1-*j*]quinolone framework **53** . However, unfortunately, stirring of **72** in CH_2Cl_2: H_2O (20:1) containing TFA (3 mmol) produced unexpectedly **73** (50 % yield) (Scheme 10).

Scheme 16: Cascade reaction of 72



Formation of **53** was ruled out as in ^{1}H NMR spectrum of the product, two olefinic protons still appeared at δ 5.86, (d, J =15.5, 1H) and δ 6.12, (d, J =15.5, 1H), respectively

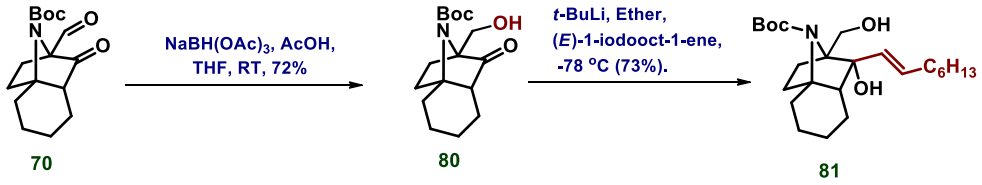
Scheme 17: Plausible cascade pathway for the formation of 73



. Moreover, protons corresponding to an aldehyde moiety were also found absent, instead, a appearance of a methylene proton at δ 3.54, (m, 2H, -CH_2-O-) and –OMe at (δ 3.14, s, 3H) indicated the formation of **73.**

This observation led us to speculate that **77** possibly underwent enamine tautomerization [28, 29] much faster than enol ether hydrolysis (Scheme 17). Therefore, to overcome this inherent enamine tautomerization problem at the intermediate stage, we sought to prepare an alternative precursor **81** (Scheme 18).

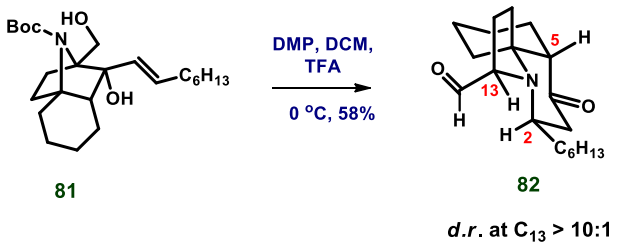
Scheme 18: Preparation of a modified cascade precursor 81



70 80 81

In this context, selective reduction of 7**0** (0.563 mmol) by $NaBH(OAc)_3$ (2.26 mmol) in AcOH:THF (1:10), rt, 16 h) was carried out to obtain **80** in 72 % yield which on reacting with (*E*)-1-octenyl lithium at -78 °C afforded **81.** Formation of **81** was supported by observing characteristic olefinic protons in the ^{1}HNMR spectrum at δ 5.52 (d, J = 15.6, 1H), δ 5.46 (d, J = 15.6 Hz, 1H), respectively**.**

Scheme 19: Cascade reaction of 81



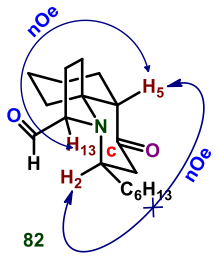
81 82

d.r. at C_{13} > 10:1

Believed to have right precursor in hand, we proceeded with its oxidation (DMP (0.14 mmol) in TFA:CH_2Cl_2 (1:3)) at 0 °C to obtain **47** in 58 % yield (*dr* = 10:1). The structure of **82** was fully established by detailed NMR spectral analyses and stereochemistry was established by NOESY analyses.

In ^{1}H NMR spectrum, aldehydic proton appeared as a singlet at δ 9.26 (d, J = 4.7 Hz, 1H) whereas protons of H_{13}, H_2 and H_5 appeared at δ 3.70 - 3.66 (m, 1H), 3.45 (ddd, J = 11.2, 6.7, 4.7 Hz, 1H), δ 2.73 - 2.70 (m, 1H), respectively. In ^{13}C NMR, carbon signal appearing at δ 212.21 corresponded to aldehyde carbon and another signal at δ 204.61 corresponded to keto carbon. Further support to the structural assignment of **82** was obtained by analysing HSQC cross peaks where correlation was found between H_{13} (δ 3.70)- C_{13} (δ 67.43), H_2 (δ 3.45)-C_2 (δ 68.89) and H_5 (δ 2.74)-C5 (δ 53.94) respectively.

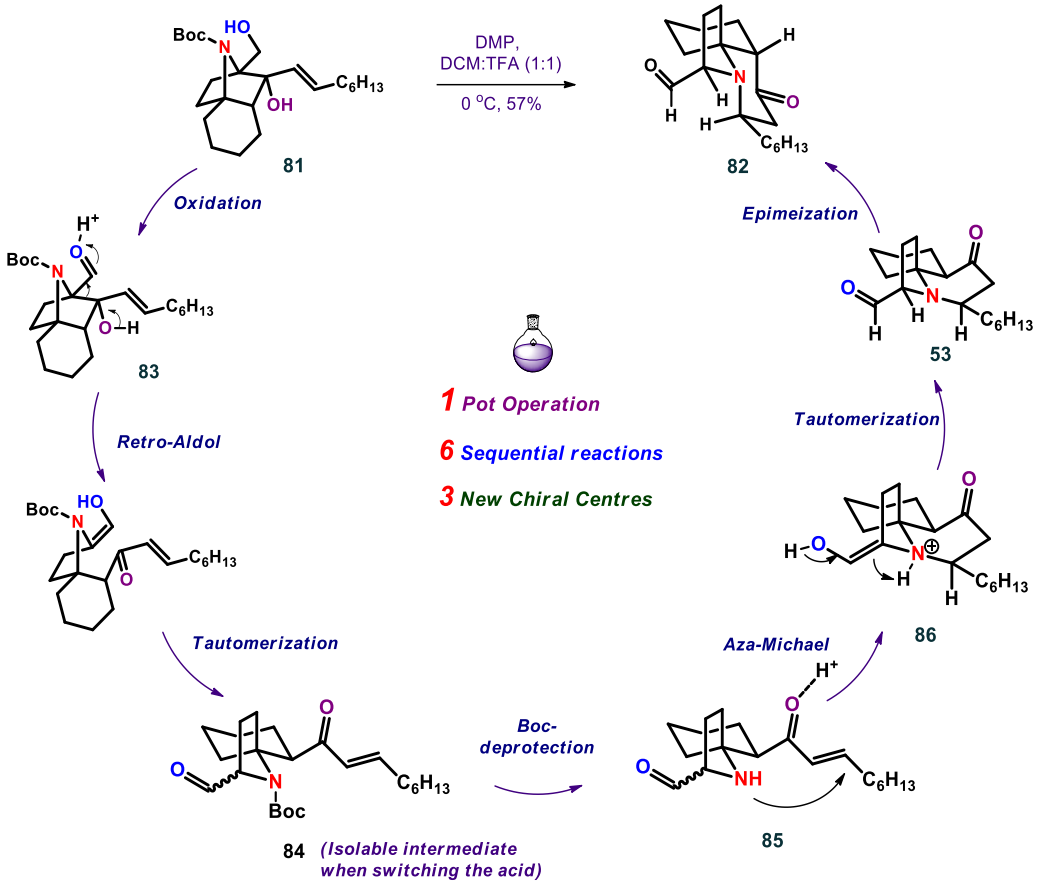
Figure 2: NOESY correlation of product 82



NOESY (Figure 2) spectrum also indicated coupling between H_{13} (δ 3.70) – H_{15} (δ 2.74) and no coupling between H_5 (δ 2.74)- H_2 (δ 3.45) suggesting '*c*' ring to be in chair conformation. The plausible mechanism for this transformation is depicted in Scheme 20.

Based on these observations, it appears that oxidation of **81** produces **83** which being highly unstable undergoes concomitant retro-aldol fragmentation under acidic condition furnishing **84**. Strong acidic condition of the medium (TFA) further affected the N-Boc deprotection which on intramolecular aza-Michael addition reaction produced **53**. Facial protonation of **86** produced required C_{13} selectivity.[33] Origin of C_{13} selectivity in **82** is further proved by the ^{1}H NMR analysis by comparing the C_{13} selectivity of **84**. Due to the lack of facial protonation selectivity at C_{13} was obtained in 6:1 ratio. However, in **82,** there is a possibility of facial protonation (Scheme 20) in **86** during the tandem rearrangement leads to excellent diastreoselectivity (10:1). Selectivity at C_2 position is possibly governed by the C_{10} aza-quaternary centre and equatorial substitution at on cyclohexane ring at C_5 in **85.**

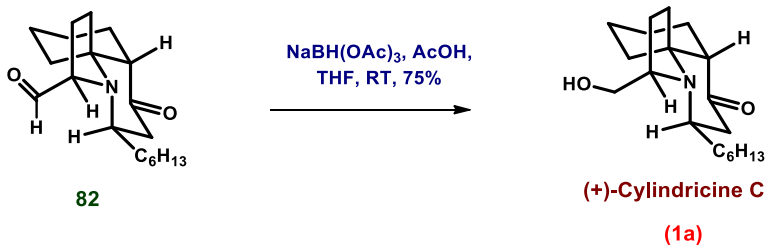
Scheme 20: Plausible mechanism of cascade rearrangement of 81



Initially, we expected tandem process could be stopped[27, 31] at **53**. However, it seems from the NOESY of **82** (Figure 2) that it underwent epimerization to produce thermodynamically more stable intermediate **82**. With this result in hand, forwarded this intermediate **82** to complete the synthesis of cylindricine class of alkaloids. Overall, this tandem transformation involved six sequential reactions generating three new chiral centres with required configuration in one pot.

Total synthesis of Cylindricine C (1a):

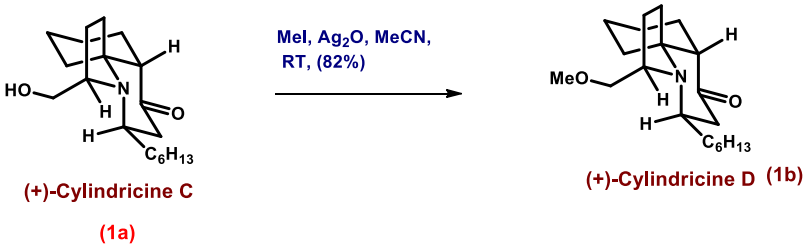
Scheme 21: Synthesis of (+)-(1a)



Compound **82** (0.081 mmol) on selective reduction with $NaBH(OAc)_3$, [(0.324 mmol) AcOH:THF, (1:3), rt, 16 h)] furnished **1a** in 75% yield. Structure of **1a** was confirmed by detailed NMR analysis (800 MHz, $CDCl_3$) and comparing the optical rotation $[\alpha]_D^{22}$ = +60.2° (*c* = 0.50, $CHCl_3$) with the reported values. [27,34]

Total synthesis of Cylindricine D (1b):

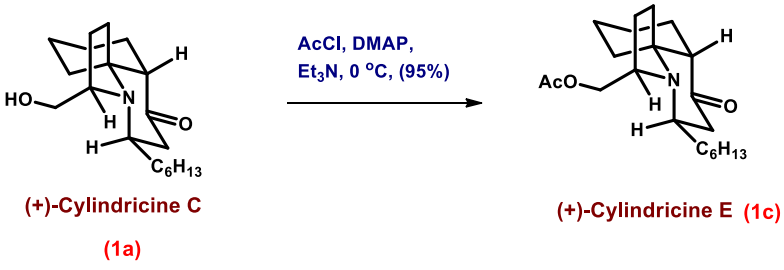
Scheme 22: Synthesis of (+)-(1b)



O-Methylation of **1a** (0.054 mmol) with methyl iodide (1.8 mmol) in presence of silver oxide (0.072 mmol) in acetonitrile (stirring for 2 days) gave **1b** in 82% yield. Optical rotation of the cylindricine D was found $[\alpha]_D^{22}$ = +21.3° (*c* = 0.1, $CHCl_3$).[27]

Total synthesis of Cylindricine E (1c):

Scheme 23: Synthesis of (+)-(1c)



Treating **1a** (0.04 mmol) with acetic anhydride (0.588 mmol) in triethyl amine (0.6 mmol) DMAP (0.014 mmol) in CH_2Cl_2 gave (+)-**1c** in 95% yield. Optical rotation was found $[\alpha]_D^{22}$ = +28.3 (*c* = 0.15, $CHCl_3$). HRMS gave molecular ion peak $[M + H]^+$ at 350.2695**.**

Section -2.4: Summary

*In summary, we have developed a strategy for the synthesis of cylindricne C, D, E alkaloids. Suitable precursor **81** was designed from **57** to initiate a cascade sequence to accomplish the planned targets. Since the absolute configuration of natural cylindricine is unknown till date, availability of both (-)-**57** and (+)-5**8** provides an opportunity to obtain both enantiomers of **1a, 1b, 1c**. Additional features of the study includes late stage oxidation/retro-aldol/aza-Michael cascade sequence generating three new chiral centres in required configuration, Biphasic intramolecular Tsuji-Trost reaction is applied for 'b' ring cyclization.*

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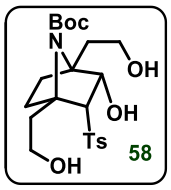
Experimental Section:

(1S,2S,3R,4S)-tert-butyl 2-hydroxy-1,4-bis(2-hydroxyethyl)-3-tosyl-7-azabicyclo[2.2.1]heptane-7-carboxylate (58):-



To a stirring solution of **57** (5 g, 9.34 mmol) in THF (60 mL), cooled to –78 °C, was added DIBAL-H (8 mL, 45 mmol) drop wise over 5 min. The colourless solution was stirred for 2 h at 0 °C and MeOH (~2 mL) was added carefully to quench excess DIBAL-H. The flask was removed from the cooling bath and a solution of Na,K-tartrate (sat., 50 mL) was added slowly. The reaction mixture solidified after approx. 5 min and was diluted with EtOAc (100 mL) and water (20 mL). The resulting mixture was vigorously stirred for 90 min at rt, the layers were separated and the aq. layer extracted with EtOAc/ether (1:1, 40 mL). The combined org. layers were washed with brine, dried over Na_2SO_4, filtrated and conc. in vacuo to give a viscous oil. Purification by flash chromatography (hexane:EtOAc = gradient 1:1 - 1:2 – 0:1) afforded **58** (3.6 g, 72%) as a stable white foam.

TLC:- R_f =0.3 (ethyl acetate = 100%, Ninhydrin).

IR (film): ν_{max} = 3340, 2980, 2254, 1687, 1369, 1314, 1142, 1079, 907, 647 cm^{-1}.

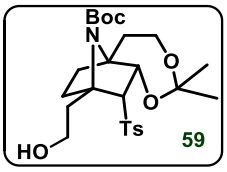
1H NMR (800 MHz, $CDCl_3$) δ = 7.81 (d, *J* = 8.2 Hz, 2H), 7.32 (d, *J* = 8.1 Hz, 2H), 4.90 (d, *J* = 7.4 Hz, 1H), 3.98 (t, *J* = 8.2 Hz, 1H), 3.90 (dd, *J* = 11.6 Hz, 0H), 3.80 (dq, *J* = 15.8, 5.7 Hz, 2H), 3.74 (dt, *J* = 10.6, 5.1 Hz, 1H), 3.68 (ddd, *J* = 11.5, 8.7, 4.0 Hz, 1H), 3.48 (s, 1H), 2.87 (s, 1H), 2.45 - 2.55 (m, 2H), 2.41 (s, 3H), 2.29 - 2.19 (m, 4H), 1.80 (tdd, *J* = 12.9, 5.6, 2.3 Hz, 1H), 1.60 (tdd, *J* = 12.8, 4.1, 1.8 Hz, 1H), 1.40 (s, 9H).

^{13}C NMR (201 MHz, $CDCl_3$) δ = 155.75, 145.07, 137.94, 129.87, 128.35, 81.92, 73.19, 72.50, 72.32, 66.40, 59.40, 59.17, 36.47, 35.99, 30.16, 28.30, 25.42, 21.74.

HRMS (*m/z*): $[M + Na]^+$ calcd for $C_{22}H_{33}NNaO_7S^+$ 478.1870, found 478.1864.

$[\alpha]_D^{22}$ = -12.8° (*c* = 0.50, $CHCl_3$).

(5a*S*,8*S*,9*R*,9a*S*)-*tert*-Butyl 8-(2-hydroxybut-3-en-1-yl)-2,2-dimethyl-9-tosyl hexahydro -4H-5a,8-epiminobenzo[d][1,3]dioxepine-10-carboxylate (59):-



To a solution of **58** (7.9 g, 17.34 mmol) in acetone (150 mL) was added Na_2SO_4 (5.0 g) and *p*-TsOH-H_2O (0.14 g, 0.86 mmol, 0.05 equiv.) at rt. The flask was immersed in a preheated oil bath (50 °C) and stirred at this temperature until TLC indicated complete consumption of the starting material and cleavage of the dioxane functionality (approx. 1 h). The mixture was allowed to cool to rt and concentrated in *vacuo*. Ether (100 mL) and $NaHCO_3$ (sat., 60 mL) were added to the residue, the layers were separated and aq. layer extracted with ether (50mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated in vacuo to produce a milky emulsion. The remaining water was removed by azeotropic distillation with toluene (20 mL) to furnish **59** as yellow oil (8.1 g, 98%). This material was pure enough to be used without further purification for the next step. However, a small amount was purified by flash chromatography (hexanes:EtOAc = 3:1 – 2:1) to get an analytically pure sample.

TLC:- R_f =0.3 (EtOAc:Hexane = 1:2, Ninhydrin).

IR (film): ν_{max} = 3454, 2985, 2936, 2881, 1706, 1695, 1596, 1365, 1293, 1144, 824, 664 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.76 (d, *J* = 8.2 Hz, 2H), 7.31 (d, *J* = 8.0 Hz, 2H), 4.52 (dd, *J* = 10.5, 2.1 Hz, 1H), 4.07 - 3.91 (m, 2H), 3.54 (dd, *J* = 7.1, 3.1 Hz, 2H), 3.04 (s, 1H), 2.93 - 2.76 (m, 2H), 2.70 - 2.56 (m, 2H), 2.42 (s, 3H), 2.18 - 2.08 (m,

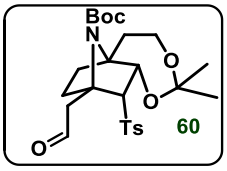
2H), 1.69 (dddd, *J* = 12.6, 8.8, 6.8, 3.6 Hz, 1H), 1.43 (s, 9H), 1.21 (s, 3H), 0.34 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ = 155.10, 144.39, 139.11, 129.51, 128.57, 101.99, 81.49, 73.83, 71.64, 69.91, 62.56, 60.32, 58.47, 53.57, 37.55, 35.20, 34.86, 28.46, 28.39, 26.64, 24.48, 22.90, 21.70.

HRMS (*m/z*): $[M + Na]^+$ calcd for $C_{25}H_{37}NNaO_7S^+$ 518.2183, found 518.2181.

$[\alpha]_D^{22}$ = -29.1°(c = 0.50, $CHCl_3$).

(5aS,8S,9R,9aS)-*tert*-Butyl2,2-dimethyl-8-(2-oxoethyl)-9-tosylhexahydro-4H-5a,8-epiminobenzo[d][1,3]dioxepine-10-carboxylate (60):-



59 (8.1 g) was dissolved in DMSO (60 mL). To this solution was added IBX (6.42 g, 23.0 mmol) at 22 °C. The reaction mixture was stirred at that temperature for 2 h, and quenched with saturated aq. $NaHCO_3$ (100 mL). The resultant mixture was extracted with EtOAc (300 mL), washed with water followed by brine solution (200 mL). The combined organic phases were dried over anhydrous Na_2SO_4. The solvent was evaporated under vacuum, to obtain a colourless foam **60** (7.6 g, 89%).

TLC:- R_f =0.5 (EtOAc:Hexane = 1:3, Ninhydrin).

IR (film): ν_{max} = 2961, 2941, 2881, 2732, 1701, 1728, 1596, 1458, 1210, 1139, 819 cm^{-1}.

^{1}H NMR (800 MHz, $CDCl_3$) δ = 9.83 (d, *J* = 1.1 Hz, 1H), 7.74 (d, *J* = 8.2 Hz, 2H), 7.31 (d, J = 7.9 Hz, 2H), 4.70 (dd, *J* = 10.6, 2.1 Hz, 1H), 3.99 (dd, *J* = 10.6, 1.9 Hz, 1H), 3.64 - 3.49 (m, 4H), 2.90 (ddd, *J* = 12.3, 9.1, 2.8 Hz, 1H), 2.68 (ddd, *J* = 12.3, 9.1, 6.7 Hz, 1H), 2.42 (s, 3H), 2.30 (ddd, *J* = 14.4, 11.3, 4.7 Hz, 1H), 2.04 (dd, *J* =

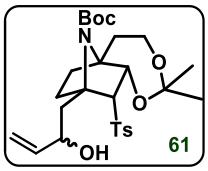
14.8, 2.3 Hz, 1H), 1.69 (tdd, *J* = 12.4, 6.6, 2.1 Hz, 1H), 1.44 (ddt, *J* = 12.4, 10.2, 2.5 Hz, 1H), 1.40 (s, 9H), 1.23 (s, 3H), 0.42 (s, 3H).

^{13}C NMR (201 MHz, $CDCl_3$) δ = 199.94, 154.03, 144.51, 138.78, 129.52, 128.58, 102.01, 81.29, 71.61, 69.78, 69.56, 63.24, 58.49, 45.95, 37.12, 33.82, 28.41, 27.07, 24.50, 23.11, 21.71.

HRMS (*m/z*): $[M + Na]^+$ calcd for $C_{25}H_{35}NNaO_7S^+$ 516.2026, found 516.2018.

$[\alpha]_D^{22}$ = -31.4° (*c* = 0.50, $CHCl_3$).

(5a*S*,8*S*,9*R*,9a*S*)-*tert*-Butyl 8-(2-hydroxybut-3-en-1-yl)-2,2-dimethyl-9-tosylhexahydro -4H-5a,8-epiminobenzo[d][1,3]dioxepine-10-carboxylate (61):-



A commercial 1M solution of vinyl magnesium bromide in THF (14.2 mL, 14.2 mmol) was cooled to –78 °C to which a solution of **60** (6.0 g, 12.1 mmol) in dry THF was added dropwise. Stirring was continued at room temperature for 2 h. The resulting mixture was cooled to 0 °C and quenched with a saturated aqueous solution of NH_4Cl. The aqueous mixture was extracted several times with ethyl acetate. The collected organic phases were dried over anhydrous Na_2SO_4 and evaporated to dryness under reduced pressure, and purified by column chromatography affording two diastereomers of **61** as 1.5:1 ratio (5.6 g, 84%). This material was used as such for the next step. A small sample major diastereomer was further purified by flash chromatography (hexanes:EtOAc = 3:1 – 2:1) to get an analytically pure sample.

TLC:- R_f =0.4 (EtOAc:Hexane = 1:2, Ninhydrin).

IR (film): ν_{max} = 3366, 2980, 2946, 2250, 1658, 1390, 1369, 1314, 1146, 907, 731 cm^{-1}.

^{1}H NMR (800 MHz, $CDCl_3$) δ = 7.76 (d, *J* = 8.2 Hz, 2H), 7.31 (d, *J* = 8.0 Hz, 2H), 6.00 (ddd, *J* = 17.2, 10.4, 4.8 Hz, 1H), 5.37 (dt, *J* = 17.1, 1.7 Hz, 1H), 5.11 (dd, *J* =

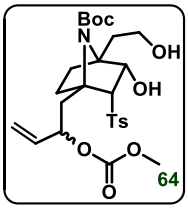
10.4, 1.6 Hz, 1H), 4.81 (d, *J* = 8.9 Hz, 0H), 4.63 - 4.59 (m, 1H), 4.41 (dd, *J* = 10.6, 2.0 Hz, 1H), 3.95 (dd, *J* = 10.5, 1.9 Hz, 1H), 3.56 (dt, *J* = 7.9, 2.1 Hz, 2H), 2.94 (ddd, *J* = 12.3, 9.1, 2.7 Hz, 1H), 2.68 (dd, *J* = 15.8, 11.0 Hz, 1H), 2.63 (ddd, *J* = 12.2, 9.0, 6.9 Hz, 1H), 2.55 (dd, *J* = 15.7, 3.5 Hz, 1H), 2.42 (s, 3H), 2.13 - 2.04 (m, 1H), 1.71 (s, 1H), 1.67 (tdd, *J* = 12.6, 6.9, 2.1 Hz, 1H), 1.43 (s, 9H), 1.22 (s, 3H), 0.36 (s, 3H).

^{13}C NMR (201 MHz, $CDCl_3$) δ = 155.35, 144.48, 142.19, 138.94, 129.48, 128.70, 113.46, 102.01, 82.16, 73.22, 71.73, 69.56, 69.25, 61.81, 58.33, 38.59, 37.63, 36.11, 28.48, 25.94, 24.47, 22.91, 21.71

HRMS (*m/z*): $[M + Na]^+$ calcd for $C_{27}H_{39}NNaO_7S^+$ 544.2339, found 544.2331.

$[\alpha]_D^{22}$ = -26.3° (*c* = 0.50, $CHCl_3$).

(1*S*,2*S*,3*R*,4*S*)-*tert*-Butyl2-hydroxy-1-(2-hydroxyethyl)-4-(2-(methoxycarbonyl)oxy) but-3-en-1-yl)-3-tosyl-7-azabicyclo[2.2.1]heptane-7-carboxylate (64) :-



To a stirred solution of methyl chloroformate (0.92 mL, 12.0 mmol) was added a solution of **61** (1.7 g, 3.36 mmol) and pyridine (0.96 mL, 12.0 mmol) in CH_2Cl_2 (20 mL) at 0 °C. The cooling bath was removed and the mixture was stirred for additional 2 h at room temperature. The solution was diluted with saturated aqueous NaCl (20 mL) and the layers were separated. The aqueous layer was extracted with Et_2O (3 x 10 mL) and the combined organic fractions were washed with saturated aqueous $NaHCO_3$ (10 mL), dried (Na_2SO_4) and concentrated under reduced pressure to provide the desired allylic carbonate as colorless oil **63** (1.71 g). This product was used for the next step without purification.

To a stirred suspension of $CeCl_3$-$7H_2O$ (1.25 g, 3.36 mmol) and oxalic acid (0.06 g, 0.68 mmol) was added a solution of **63** (1.667 g, 2.88 mmol) in MeCN (50 mL) at rt and the resulting milky mixture was stirred for 2 h open to air. The reaction was

quenched with aq. $NaHCO_3$ (sat., 20 mL) and extracted with CH_2Cl_2 (2 x 40 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by flash chromatography through silica (hexanes:EtOAc = 1:1 – 1:2 – 0:1) affording **64** (1.0 g, 88%) as a white foam.

TLC:- R_f =0.3 (EtOAc:Hexane = 2:1, Ninhydrin).

IR (film): ν_{max} = 3454, 2972, 2930, 2254, 1742, 1679, 1650, 1276, 1142, 907 cm^{-1}.

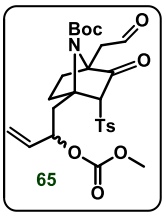
^{1}H NMR (800 MHz, $CDCl_3$) δ = 7.82 (d, *J* = 8.0 Hz, 2H), 7.34 (d, *J* = 7.9 Hz, 2H), 5.82 (ddd, *J* = 16.9, 10.5, 6.2 Hz, 1H), 5.30 - 5.20 (m, 1H), 5.13 (d, *J* = 10.1 Hz, 1H), 4.95 (t, *J* = 7.1 Hz, 1H), 3.93 (dd, *J* = 10.2, 4.7 Hz, 1H), 3.81 - 3.76 (m, 2H), 3.74 (s, 3H), 3.73 - 3.69 (m, 1H), 3.31 (s, 1H), 2.65 - 2.58 (m, 2H), 2.49 (ddd, *J* = 13.5, 9.5, 4.1 Hz, 1H), 2.43 (s, 4H), 2.25 (ddd, *J* = 14.4, 9.5, 4.6 Hz, 1H), 2.19 (tdt, *J* = 14.4, 8.6, 4.9 Hz, 2H), 1.94 (tdd, *J* = 13.1, 5.6, 2.2 Hz, 1H), 1.57 (ddd, *J* = 14.7, 8.5, 3.2 Hz, 1H), 1.41 (s, 9H).

^{13}C NMR (201 MHz, $CDCl_3$) δ = 156.30, 155.20, 145.19, 137.92, 136.53, 129.97, 128.37, 116.41, 81.80, 76.32, 74.41, 73.00, 71.65, 67.27, 59.28, 54.78, 38.07, 37.01, 32.02, 29.76, 29.71, 28.62, 28.37, 28.27, 25.05, 21.76.

HRMS (*m/z*): $[M + Na]^+$ calcd for $C_{26}H_{37}NNaO_9S^+$ 562.2081, found 562.2077.

$[\alpha]_D^{22}$ = -6.1° (*c* = 0.8, $CHCl_3$).

(1*S*,2*R*,4*S*)-*tert*-Butyl 1-(2-((methoxycarbonyl)oxy)but-3-en-1-yl)-3-oxo-4-(2-oxoethyl) -2-tosyl-7-azabicyclo[2.2.1]heptane-7-carboxylate (65):-



To a solution of **64** (1.0 g, 1.85 mmol) in DMSO (20 mL) was added IBX (0.84 g, 3.00 mmol) and resulting suspension was immersed in an oil bath set to 50 °C and stirred vigorously open to the atmosphere. After 6 h (TLC monitoring), the reaction was cooled to room temperature and filtered through a celite pad. The filter cake was washed with 3 × 10 mL of ethyl acetate and the combined filtrates were concentrated and the residue was purified by flash chromatography through silica gel (hexane:EtOAc = 4:1) affording **65** (0.8 g, 81%) as a gummy solid.

TLC:- R_f =0.6 (EtOAc:Hexane = 1:3, Ninhydrin).

IR (film): ν_{max} = 2972, 2929, 2253, 1742, 1701, 1679, 1649, 1276, 1142, 913 cm^{-1}.

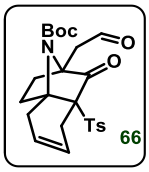
^{1}H NMR (800 MHz, $CDCl_3$) δ = 9.63 (d, *J* = 1.7 Hz, 1H), 7.88 (dd, J = 8.3, 2.1 Hz, 2H), 7.39 (d, *J* = 8.0 Hz, 2H), 5.97 (ddd, *J* = 15.1, 10.5, 6.2 Hz, 1H), 5.53 - 5.49 (m, 1H), 5.38 (dd, *J* = 17.3, 1.5 Hz, 1H), 5.24 (dd, *J* = 10.6, 1.5 Hz, 1H), 4.41 (d, *J* = 2.1 Hz, 1H), 3.76 (d, *J* = 2.0 Hz, 3H), 3.16 (dd, *J* = 15.5, 9.1 Hz, 1H), 3.11- 2.99 (m, 2H), 2.93 (dd, *J* = 15.5, 3.0 Hz, 1H), 2.68 (ddd, *J* = 13.0, 9.2, 3.7 Hz, 1H), 2.46 (s, 3H), 2.09 (tdd, *J* = 12.8, 5.4, 2.2 Hz, 1H), 2.03 (td, *J* = 12.6, 3.6 Hz, 1H), 1.96 -1.90 (m, 1H), 1.40 (d, *J* = 2.2 Hz, 9H).

^{13}C NMR (201 MHz, $CDCl_3$) δ = 198.39, 197.40, 155.45, 154.82, 145.80, 137.02, 136.16, 130.03, 129.17, 117.44, 83.42, 75.93, 73.51, 72.72, 71.33, 54.96, 53.60, 42.70, 36.99, 30.11, 29.89, 28.19, 21.91, 1.16.

HRMS (*m/z*): $[M + Na]^+$ calcd for $C_{26}H_{33}NNaO_9S^+$ 558.1768, found 558.1774.

$[\alpha]_D^{22}$ = -11.4 (*c* = 1.3, $CHCl_3$).

(2*S*,8a*S*)-*tert*-Butyl 1-oxo-2-(2-oxoethyl)-8a-tosyl-2,3,4,5,8,8a-hexahydro-1H-2,4a-epiminonaphthalene-9-carboxylate (66):-



To a stirred solution of **65** (0.2 g, 0.372 mmol), benzyl triethyl ammonium chloride (9 mg, 0.037 mmol) and tetrakis(triphenylphosphine)palladium(0) (0.021 g, 0.018 mmol) in ethyl acetate (3 mL) at 0 °C, was added a solution of K_2CO_3 (0.15 g, 1.12 mmol) dissolved in distilled water (3 mL). Biphasic reaction mixture was stirred at rt for 2 h. Two layers were separated and aqueous layer was extracted with ethyl acetate (3 x 10 mL) and the combined organic fractions were washed with brine solution (10 mL), dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by flash chromatography (hexanes:EtOAc = 4:1) to give **66** as a white foam (0.17 g, 99%).

TLC:- R_f =0.6 (EtOAc:Hexane = 1:3, Ninhydrin).

IR (film): ν_{max} = 2979, 2932, 2255, 1765, 1726, 1689, 1596, 1458, 1392, 1147, 909 cm^{-1}.

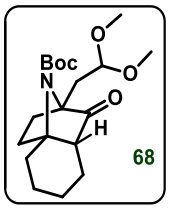
^{1}H NMR (800 MHz, $CDCl_3$) δ = 9.63 (s, 1H), 7.89 (dd, *J* = 8.3, 2.0 Hz, 2H), 7.36 (dd, *J* = 8.3, 2.0 Hz, 2H), 5.92 (ddd, *J* = 10.4, 4.8, 2.5 Hz, 1H), 5.51 (ddt, *J* = 10.0, 4.9, 2.2 Hz, 1H), 3.38 (d, *J* = 18.0 Hz, 1H), 3.30 (ddd, *J* = 18.9, 4.8, 2.3 Hz, 1H), 3.16 (dd, *J* = 18.0, 1.7 Hz, 1H), 3.01 (dt, *J* = 19.0, 2.8 Hz, 1H), 2.90 (tdd, *J* = 9.0, 7.2, 6.3, 3.1 Hz, 1H), 2.62 (dd, *J* = 19.8, 3.1 Hz, 1H), 2.45 (d, *J* = 2.6 Hz, 3H), 2.13 - 2.07 (m, 1H), 2.06 - 1.97 (m, 2H), 1.36 (d, *J* = 3.0 Hz, 9H).

^{13}C NMR (201 MHz, $CDCl_3$) δ = 203.00, 196.97, 196.95, 152.61, 145.55, 141.73, 134.49, 130.03, 129.61, 127.94, 118.62, 81.76, 74.17, 70.71, 69.36, 42.53, 33.11, 30.08, 29.05, 28.52, 28.06, 21.73.

HRMS (*m/z*): $[M + Na]^+$ calcd for $C_{24}H_{29}NNaO_6S^+$ 482.1608, found 482.1609.

$[\alpha]_D^{22}$ = -31.8° (*c* = 1.0, $CHCl_3$).

(2*S*,4a*R*)-*tert*-Butyl2-(2,2-dimethoxyethyl)-1-oxooctahydro-1H-2,4a-epiminonaphthalene-9-carboxylate (68):-



Solution of **66** (0.5 g, 1.09 mmol) in methanol (15 mL) was placed in a two neck round bottom flask was first evacuated and refilled with argon. After following two cycles of this sequence, Pd/C 10 wt% (0.05 g, 0.048 mmol) was added and flushed with hydrogen gas (2 cycles) and stirred. Reaction progress was monitored by TLC. After complete conversion (3 h), reaction mixture was passed through celite pad. The celite plug was washed with ethyl acetate (3 x 20 mL). Solvent was evaporated under vaccum and crude product **67** as such was advanced for the next step.

To a stirring solution of boric acid (0.46 g, 7.5 mmol) in anhydrous methanol (2 mL), **67** (0.5 g, 1.0 mmol) dissolved in methanol (10 mL) was added. The reaction mixture was cooled to 0 °C and sodium amalgam (2.0 g, 7%) was added portion wise (30 min) while stirring at the same temperature. The reaction mixture was allowed to stir for an additional 3 h at 0 °C. The progress of reaction was monitored by TLC and after the completion of the reaction; water (1 mL) was added drop wise. The solution was warmed to room temperature and was extracted with ethyl acetate. The combined organic layer was washed with brine and dried over Na_2SO_4. Solvent was evaporated under reduced pressure and purified by column chromatography to afford **68** (0.27 g, 71%)**.**

TLC:- R_f =0.5 (EtOAc:Hexane = 1:3, Ninhydrin).

IR (film): ν_{max} = 3055, 2980, 2934, 2309, 1755, 1700, 1448, 1264, 1159, 1113, 739 cm^{-1}.

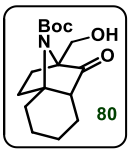
^{1}H NMR (800 MHz, $CDCl_3$) δ = 4.66 (dt, *J* = 8.8, 2.4 Hz, 1H), 3.31 - 3.27 (m, 3H), 3.19 - 3.16 (m, 3H), 2.54 - 2.45 (m, 2H), 2.29 (dt, *J* = 13.9, 2.3 Hz, 1H), 2.20 - 2.14 (m, 1H), 2.08 (tdd, *J* = 13.3, 4.1, 1.9 Hz, 1H), 2.01 - 1.91 (m, 2H), 1.80 (tdd, *J* = 12.4, 5.4, 2.2 Hz, 1H), 1.77 - 1.72 (m, 2H), 1.51 (tq, *J* = 11.7, 1.9 Hz, 1H), 1.45 (s, 9H), 1.42 - 1.39 (m, 1H), 1.31 - 1.05 (m, 3H).

^{13}C NMR (201 MHz, $CDCl_3$) δ = 212.80, 156.34, 102.62, 80.83, 74.78, 68.92, 57.40, 52.86, 52.66, 34.11, 32.72, 31.87, 28.38, 27.88, 25.02, 23.04, 21.87.

HRMS (*m/z*): $[M + Na]^+$ calcd for $C_{19}H_{31}NNaO_5^+$ 376.2094, found 376.2092.

$[\alpha]_D^{22}$ = +14.6° (*c* = 1.1, $CHCl_3$).

(2*S*,4a*R*)-*tert*-Butyl 2-(hydroxymethyl)-1-oxooctahydro-1H-2,4a-epimino naphthalene-9-carboxylate (80):-



To an ice cooled solution of **68** (0.23 g, 0.66 mmol), DIPEA (0.14 mL, 0.8 mmol,) in CH_2C1_2 (4 mL), was added a solution of TMSOTf (0.13 mL, 0.73 mmol, 1.1 equiv) in CH_2C1_2 (2 mL) drop wise via a syringe. The pale yellow solution was allowed to warm to ambient temperature for 2 h. The reaction was quenched by the addition of aqueous NaOH solution (2.1 mL of a 1.0 N solution). The resulting mixture was vigorously stirred for 1 min, the layers were separated and the aq. layer was extracted with ether (40 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, filtrated and conc. in *vacuo* to give a viscous oil **69** which was forwarded to the next step without further purification.

A solution of **69** (0.2 g, 0.62 mmol) in CH_2C1_2 (80 mL) was treated with $NaHCO_3$ (0.01 g) and cooled to -78 °C. Ozone was bubbled through the solution at -78 °C until a deep blue colour persisted. The ozone-generator was turned off and excess ozone was removed by bubbling the solution with O_2 for 5 min followed by argon for 15 min. To the resulting colourless solution was added PPh_3 (0.45 g, 1.72 mmol) in CH_2C1_2 (10 mL) and the reaction was allowed to warm to rt over 1 h. The solution was washed with phosphate buffer (pH 7, 0.1 M, 10 mL) and the aq. layer was extracted with CH_2C1_2 (50 mL). The combined organic layers were dried over Na_2SO_4, filtrated and concentrated in *vacuo* to afford **70** as colourless foam.

$NaBH(OAc)_3$ (0.48 g, 2.26 mmol) and acetic acid (0.3 mL) were added to the **70** (0.16 g, 0.56 mmol) in THF (30 mL) at 0 °C. The cooling bath was removed and the resulting mixture was stirred for 90 min at rt. Excess reducing agent was quenched with water (10 mL) and the resulting mixture was diluted with aq. $NaHCO_3$ (sat., 50 mL). The emulsion was extracted with CH_2C1_2 (2 x 50 mL) and the combined organic layers were dried over Na_2SO_4, filtrated and concentrated in *vacuo*. The residue was purified by flash chromatography (hexanes:EtOAc = 3:1 – 2:1) to afford **80** (0.141 g, 51%) over three steps), as a colourless oil.

TLC:- R_f =0.3 (EtOAc:Hexane = 1:2, Ninhydrin).

IR (film): ν_{max} = 3439, 2869, 2979, 2941, 2253, 1757, 1671, 1393, 1252, 1150, 908 cm^{-1}.

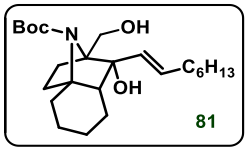
^{1}H NMR (800 MHz, $CDCl_3$) δ = 4.24 (s, 1H), 4.15 (dt, *J* = 13.2, 2.1 Hz, 1H), 4.07 - 4.01 (m, 1H), 2.35 (dt, *J* = 13.1, 3.4 Hz, 1H), 2.21 - 2.15 (m, 1H), 2.11 (tt, *J* = 12.3, 4.5 Hz, 2H), 2.06 (ddd, *J* = 12.9, 9.0, 5.0 Hz, 1H), 2.04 - 2.00 (m, 1H), 1.83 - 1.75 (m, 3H), 1.56 (dtdd, *J* = 20.5, 10.0, 8.6, 4.3 Hz, 2H), 1.47 (s, 9H), 1.37 (ddd, *J* = 12.9, 9.0, 4.4 Hz, 1H), 1.30 (tt, *J* = 10.3, 2.4 Hz, 1H), 1.26 - 1.21 (m, 2H).

^{13}C NMR (201 MHz, $CDCl_3$) δ = 211.79, 155.29, 81.61, 77.76, 68.28, 59.02, 58.81, 58.17, 55.01, 35.81, 33.82, 30.11, 28.51, 28.40, 28.03, 27.82, 26.06, 25.17, 24.47, 24.07, 23.08, 22.76, 22.33.

HRMS (*m/z*): $[M + Na]^+$ calcd for $C_{16}H_{25}NNaO_4^+$ 318.1676, found 318.1670.

$[\alpha]_D^{22}$ = +18.7° (*c* = 1.5, $CHCl_3$).

(2*S*,4a*R*)-*tert*-Butyl 1-hydroxy-2-(hydroxymethyl)-1-((E)-oct-1-en-1-yl) octahydro-1H-2,4a-epiminonaphthalene-9-carboxylate (81):-



To a solution of *t*-BuLi (0.35 mL, 1.9M) in ether (0.2 mL) was introduced through cannula drop wise solution of (*E*)- 1-iodooct-1-ene (0.09 g, 0.37 mmol) in 0.5 mL ether and cooled to –78 °C. The solution was stirred at -78 °C for 1 h and the solution of **81** (0.100 g, 0.338 mmol) in ether (1 mL) at -78 °C was added and stirred for 2h. The reaction was quenched with sat aq. $NaHCO_3$ at -78 °C and slowly warmed up to rt. The aqueous portion was extracted with ether (3 x 5 mL) and organic phases were combined, washed with sat aq NaCl, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (10% ethyl acetate : 90 %z hexane) to provide **82** (0.1 g, 73%).

TLC:- R_f =0.5 (EtOAc:Hexane = 1:4, Ninhydrin).

IR (film): ν_{max} = 3392, 2927, 2856, 1661, 1366, 1252, 1153, 1086, 979 cm^{-1}.

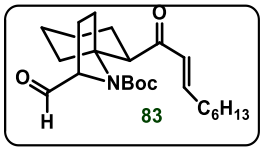
^{1}H NMR (800 MHz, $CDCl_3$) δ = 5.52 (dt, *J* = 15.6, 6.5 Hz, 1H), 5.46 (d, J = 15.6 Hz, 1H), 4.28 (dd, *J* = 11.9, 8.4 Hz, 0H), 4.05 (d, *J* = 13.1 Hz, 1H), 3.44 (dd, J = 13.9, 6.3 Hz, 1H), 2.17 (dt, *J* = 12.9, 3.4 Hz, 1H), 2.09 (ddd, *J* = 12.5, 9.2, 5.6 Hz, 1H), 2.05 - 1.98 (m, 4H), 1.93 (td, *J* = 13.1, 4.1 Hz, 1H), 1.88 (td, *J* = 12.5, 5.5 Hz, 1H), 1.78 (dt, *J* = 13.2, 3.1 Hz, 1H), 1.70 - 1.65 (m, 1H), 1.53 (ddd, *J* = 12.8, 3.9, 1.8 Hz, 1H), 1.45 (s, 9H), 1.42 (s, 2H), 1.36 - 1.31 (m, 3H), 1.31 - 1.30 (m, 1H), 1.29 - 1.24 (m, 5H), 1.20 (tt, *J* = 13.1, 3.9 Hz, 1H), 0.87 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (201 MHz, $CDCl_3$) δ = 156.11,134.68, 127.11, 80.46, 77.84, 76.33, 69.44, 61.19, 55.35, 51.22, 40.19, 35.09, 32.20, 31.80, 29.83, 29.52, 28.97, 28.72, 28.62, 27.09, 25.69, 23.26, 22.75, 21.04, 14.22.

HRMS (*m/z*): $[M + Na]^+$ calcd for $C_{24}H_{41}NNaO_4^+$ 430.2928, found 430.2917.

$[\alpha]_D^{22}$ = +12.1° (*c* = 0.50, $CHCl_3$).

(2*S*,5*S*,6*R*)-*tert*-Butyl 2-formyl-6-((E)-non-2-enoyl)-1-azaspiro[4.5]decane-1-carboxylate (83):-



To an ice cold solution of **81** (0.05 g, 0.12 mmol) in CH_2Cl_2 (1 mL) was added acetic acid (7 µl, 0.12 mmol) in CH_2Cl_2 (1 mL) at 0 °C. To this was added Dess-Martin periodinane (0.07 g, 0.15 mmol) and the resultant turbid mixture was stirred for 0.5 h at the same temperature. The solution was diluted with saturated aqueous NaCl (20 mL) and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 x 5 mL) and the combined organic fractions were washed with saturated aqueous $NaHCO_3$ (10 mL), dried (Na_2SO_4) and concentrated under reduced pressure. The crude residue was purified by flash chromatography eluting with ethyl acetate:hexane (1:4) to provide **83** (0.04 g, 87%) as an inseparable mixture of diastereomers.

TLC:- R_f =0.5 (EtOAc:Hexane = 1:5, Ninhydrin, $KMnO_4$).

IR (film): ν_{max} = 2932, 2857, 1751, 1705, 1391, 1448, 1040, 762 cm^{-1}.

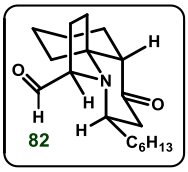
^{1}H NMR (800 MHz, $CDCl_3$) δ = 9.46 (d, *J* = 1.9 Hz, 0.11H), 9.38 (d, *J* = 2.5 Hz, 0.78 H), 6.86 (dt, *J* = 15.5, 7.0 Hz, 1H), 6.14 (ddt, *J* = 15.1, 12.1, 1.5 Hz, 1H), 4.03 -3.95 (m, 2H), 2.64 (td, *J* = 12.9, 4.3 Hz, 1H), 2.47 (ddd, *J* = 13.2, 8.0, 5.3 Hz, 1H), 2.19 - 2.11 (m, 3H), 1.79 (dq, *J* = 13.1, 8.5 Hz, 1H), 1.74 - 1.70 (m, 1H), 1.70 - 1.66 (m, 3H), 1.63 - 1.59 (m, 1H), 1.57 (s, 2H), 1.41 (s, 9H), 1.32 - 1.23 (m, 12H), 0.87 (t, *J* = 6.9 Hz, 3H).

^{13}C NMR (201 MHz, $CDCl_3$) δ = 203.61, 200.18, 152.96, 147.34, 130.39, 80.72, 68.31, 67.49, 50.45, 36.87, 32.64, 31.73, 30.83, 29.12, 28.72, 28.45, 26.99, 24.62, 23.94, 23.92, 22.67, 14.18.

HRMS (*m/z*): $[M + H]^+$ calcd for $C_{24}H_{39}NNaO_4^+$ 428.2771, found 428.2767.

$[\alpha]_D^{22}$ = -98.9° (*c* = 0.7, $CHCl_3$).

(3*S*,5*R*,7a*S*,11a*S*)-5-hexyl-7-oxodecahydro-1H-pyrrolo[2,1-*j*]quinoline-3-carbaldehyde (82) :-



To an ice cold solution of **81** (0.05 g, 0.12 mmol) in CH_2Cl_2 (1 mL) was added Dess-Martin periodinane (0.07 g, 0.15 mmol). This turbid mixture was stirred for 0.5 h at the same temperature. To this suspension was added trifluoro acetic acid (0.5 mL) in CH_2Cl_2 (0.5 mL). Reaction mixture was stirred at the same temperature for another 2 h. The solution was diluted with saturated aqueous NaCl (20 mL) and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 x 5 mL) and the combined organic fractions were washed with saturated aqueous $NaHCO_3$ (10 mL), dried (Na_2SO_4) and concentrated under reduced pressure. The crude residue was purified by flash chromatography eluting with ethyl acetate:hexane (1:3) to provide **82** (0.02 g, 58%) as an inseparable mixture of diastereomers.

TLC:- R_f =0.5 (EtOAc:Hexane = 1:4, Ninhydrin, $KMnO_4$).

IR (film): ν_{max} = 2930, 2857, 1761, 1705, 1390, 1448, 1040, 762 cm^{-1}.

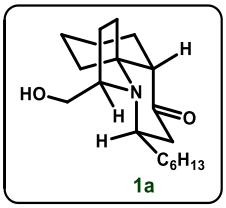
^{1}H NMR (800 MHz, $CDCl_3$) δ = 9.49 (d, *J* = 4.8 Hz, 0H), 9.26 (d, *J* = 4.7 Hz, 1H), 3.70 - 3.66 (m, 1H), 3.45 (ddd, *J* = 11.2, 6.7, 4.7 Hz, 1H), 2.73 - 2.70 (m, 1H), 2.27 (d, *J* = 0.9 Hz, 1H), 1.99 (dd, *J* = 12.6, 6.6 Hz, 1H), 1.93 (dq, J = 10.4, 2.4 Hz, 1H), 1.83 (dt, *J* = 13.1, 6.9 Hz, 1H), 1.79 - 1.76 (m, 1H), 1.75 - 1.71 (m, 1H), 1.65 - 1.60 (m, 3H), 1.59 - 1.55 (m, 1H), 1.37 (ddt, *J* = 16.1, 9.9, 3.0 Hz, 2H), 1.29 - 1.21 (m, 19H), 1.11 (tdd, J = 12.9, 6.9, 1.7 Hz, 1H), 0.87 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (201 MHz, $CDCl_3$) δ = 212.21, 204.61, 68.89, 67.43, 55.24, 53.94, 41.91, 39.62, 33.82, 31.82, 31.44, 29.84, 29.20, 26.90, 24.90, 24.51, 24.46, 24.31, 22.69, 22.64, 14.18, 1.16.

HRMS (*m/z*): $[M + H]^+$ calcd for $C_{19}H_{32}NO_2^+$ 306.2428, found 306.2420.

[α]$_D^{22}$ = -47.3° (*c* = 0.30, $CHCl_3$).

Synthesis of Cylindricine C (1a):-



1a

To a stirred solution of **82** (0.025 g, 0.08 mmol) in THF (1 mL) was added $NaBH(OAc)_3$ (0.07 g, 0.33 mmol) and acetic acid (0.1 mL) in THF (1 mL) at 0 °C. The cooling bath was removed and the resulting mixture was stirred for 90 min at rt. Excess reducing agent was quenched with water (1 mL) and the resulting mixture was diluted with aq. $NaHCO_3$ (sat., 5 mL). The emulsion was extracted with CH_2Cl_2 (2 x 5 mL) and the combined organic layers were dried over Na_2SO_4, filtrated and concentrated in vacuo. The residue was purified by flash chromatography (silica, hexanes:EtOAc = 3:1 - 2:1) to give **1a** (0.02 g, 75%) as a pale yellow oil.

TLC:- R_f =0.3 (EtOAc:Hexane = 1:3, Ninhydrin, PMA).

IR (film): ν_{max} = 3436, 2932, 2857, 1705, 1448, 1040 cm^{-1}.

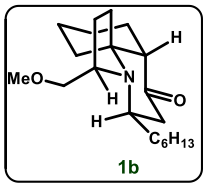
^{1}H NMR (800 MHz, $CDCl_3$) δ = 3.52 (q, *J* = 8.4, 6.0 Hz, 2H), 3.41 (d, *J* = 9.8 Hz, 1H), 3.30 - 3.22 (m, 1H), 2.89 (s, 1H), 2.32 - 2.26 (m, 2H), 2.24 - 2.16 (m, 3H), 2.10 (dd, *J* = 12.4, 7.9 Hz, 1H), 1.81 (dd, *J* = 13.3, 8.3 Hz, 1H), 1.70 - 1.59 (m, 4H), 1.47 (dd, *J* = 12.7, 7.8 Hz, 1H), 1.34 (td, J = 12.3, 11.1, 6.6 Hz, 4H), 1.30 - 1.21 (m, 7H), 0.86 (t, *J* = 7.0 Hz, 3H).

^{13}C NMR (201 MHz, $CDCl_3$) δ = 210.56, 70.70, 66.39, 56.54, 55.34, 50.26, 42.53, 36.42, 35.91, 35.21, 31.71, 29.30, 28.71, 27.12, 24.28, 22.74, 22.58, 21.87, 14.05.

HRMS (*m/z*): $[M + H]^+$ calcd for $C_{19}H_{34}NO_2^+$ 308.2584, found 308.2583.

[α]$_D^{22}$ = +60.2° (*c* = 0.50, $CHCl_3$).

Synthesis of Cylindricine D (1b):-



1b

To a solution of **1a** (0.016 g, 0.05 mmol) in CH_3CN (0.5 mL) was added Ag_2O (0.17 g, 0.72 mmol) and MeI (0.11 mL, 1.8 mmol) at rt. The solution was stirred at rt for 48 h and filtered through celite to remove the excess Ag_2O. The filtrate was concentrated under reduced pressure and the residue was purified by flash column chromatography on silica gel (6% EtOAc: 93% n-hexane) to provide **1b** as a pale yellow oil in 61 % yield (0.01 g, 61%).

TLC:- R_f =0.4 (EtOAc:Hexane = 1:4, Ninhydrin, PMA).

IR (film): ν_{max} = 2930, 2863, 1709, 1451, 1331, 1195, 1116, 910, 773 cm^{-1}.

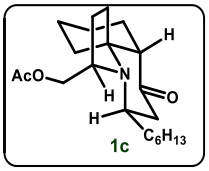
^{1}H NMR (800 MHz, $CDCl_3$) δ = 3.41 (dt, *J* = 12.3, 6.1 Hz, 1H), 3.36 (s, 4H), 3.23 - 3.17 (m, 1H), 3.04 (t, *J* = 9.0 Hz, 1H), 2.28 - 2.17 (m, 5H), 2.11 - 2.07 (m, 1H), 2.06 - 2.02 (m, 1H), 1.85 (dd, *J* = 13.1, 7.6 Hz, 1H), 1.71 (tt, *J* = 9.7, 4.9 Hz, 1H), 1.68 - 1.64 (m, 1H), 1.64 - 1.60 (m, 1H), 1.57 (dt, *J* = 12.8, 6.5 Hz, 1H), 1.47 - 1.44 (m, 1H), 1.41 (dtd, *J* = 13.6, 9.1, 4.3 Hz, 1H), 1.35 - 1.31 (m, 3H), 1.27 (ddt, *J* = 18.0, 12.4, 5.8 Hz, 8H), 0.87 (t, *J* = 7.0 Hz, 3H).

^{13}C NMR (201 MHz, $CDCl_3$) δ = 211.46, 78.32, 59.23, 55.64, 55.58, 51.06, 43.00, 36.04, 35.34, 35.08, 31.91, 29.44, 27.22, 26.83, 24.57, 23.06, 22.05, 14.19.

HRMS (*m/z*): $[M + H]^+$ calcd for $C_{20}H_{36}NO_2^+$ 322.2741, found 322.2738.

$[\alpha]_D^{22}$ = +21.3° (*c* = 0.1, $CHCl_3$).

Synthesis of Cylindricine E (1c):-



To a solution of **1a** (0.013 g, 0.04 mmol) in CH_2Cl_2 (1 mL) was added Et_3N (0.1 mL, 0.6 mmol), DMAP (12 g, 14.4mol %) and acetic anhydride (55 µL, 0.588 mmol) at –10 °C. The solution was stirred at rt for 2 h and quenched with H_2O at -10 °C. The aqueous fraction was extracted with CH_2Cl_2 (3 x 3mL) and the organic phases were combined, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (5% EtOAc: 95 % hexane) to provide **1c** in 59% yield (0.012 g, 59%).

TLC:- R_f =0.6 (EtOAc:Hexane = 1:6, Ninhydrin, PMA).

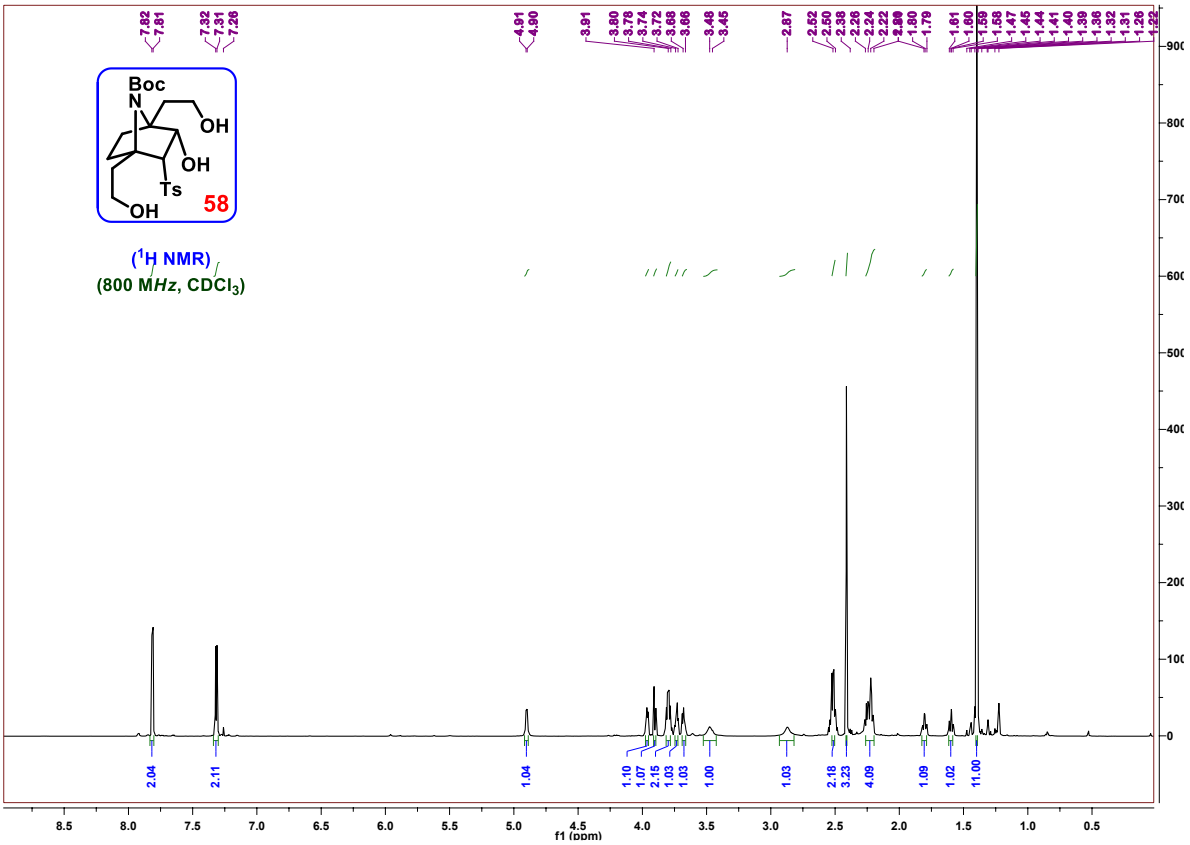
IR (film): ν_{max} = 2934, 2861, 1743, 1707, 1448, 1381, 1227, 1023, 910, 781 cm^{-1}.

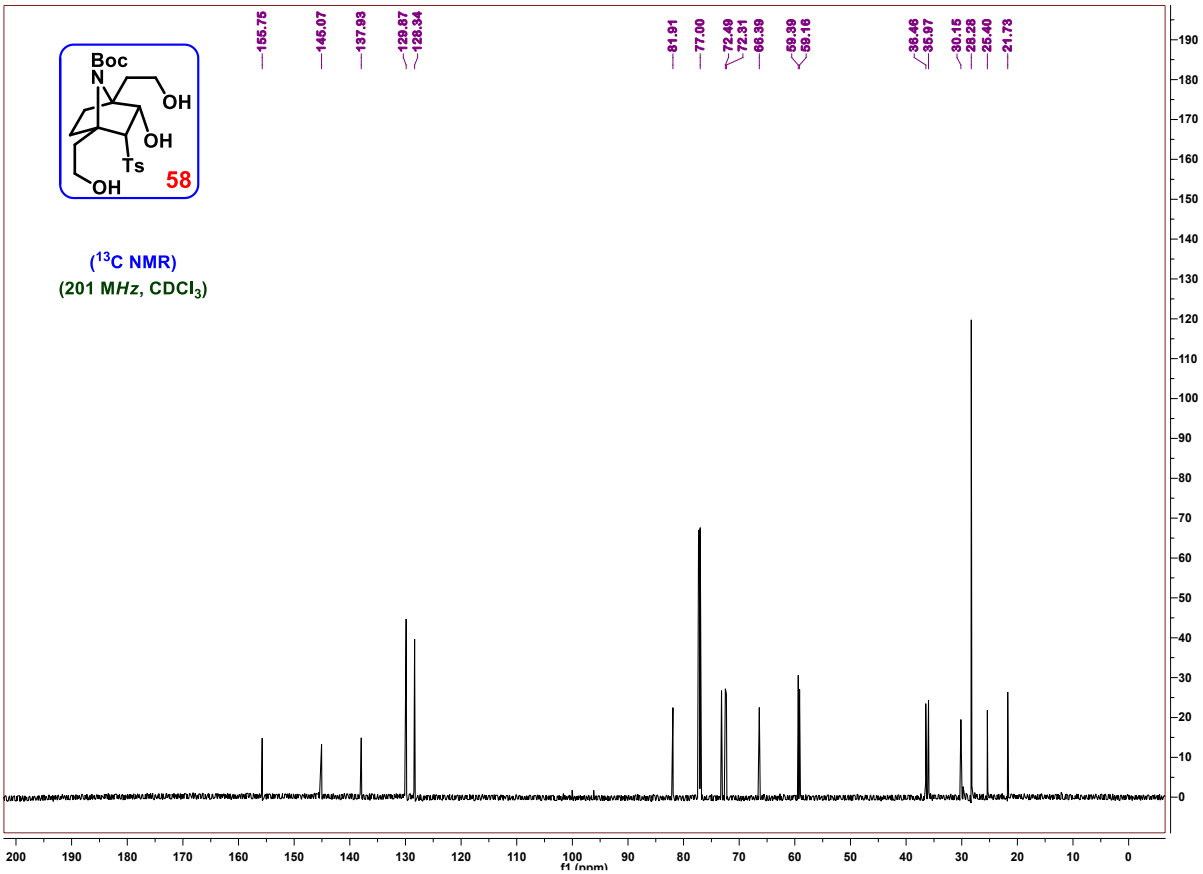
^{1}H NMR (800 MHz, $CDCl_3$) δ = 4.10 (dd, *J* = 10.7, 3.2 Hz, 1H), 3.66 (dd, *J* = 10.7, 8.9 Hz, 1H), 3.49 (td, *J* = 9.0, 3.0 Hz, 1H), 3.20 (tt, *J* = 9.5, 5.0 Hz, 1H), 2.26 - 2.18 (m, 4H), 2.12 - 2.01 (m, 5H), 1.81 - 1.72 (m, 2H), 1.64 (dt, *J* = 16.9, 7.3 Hz, 2H), 1.57 (td, *J* = 12.6, 3.5 Hz, 1H), 1.45 (dddd, *J* = 17.8, 13.2, 9.4, 4.7 Hz, 2H), 1.35 - 1.21 (m, 12H), 0.86 (t, *J* = 7.0 Hz, 3H).

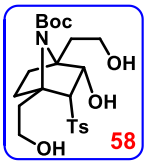
^{13}C NMR (201 MHz, $CDCl_3$) δ = 211.18, 171.20, 70.11, 68.70, 55.36, 54.63, 51.16, 43.03, 36.10, 35.07, 35.05, 31.90, 29.38, 27.22, 26.56, 24.53, 23.06, 22.68, 22.01, 21.15, 14.17.

HRMS (*m/z*): $[M + H]^+$ calcd for $C_{21}H_{36}NO_3^+$ 350.2690, found 350.2695.

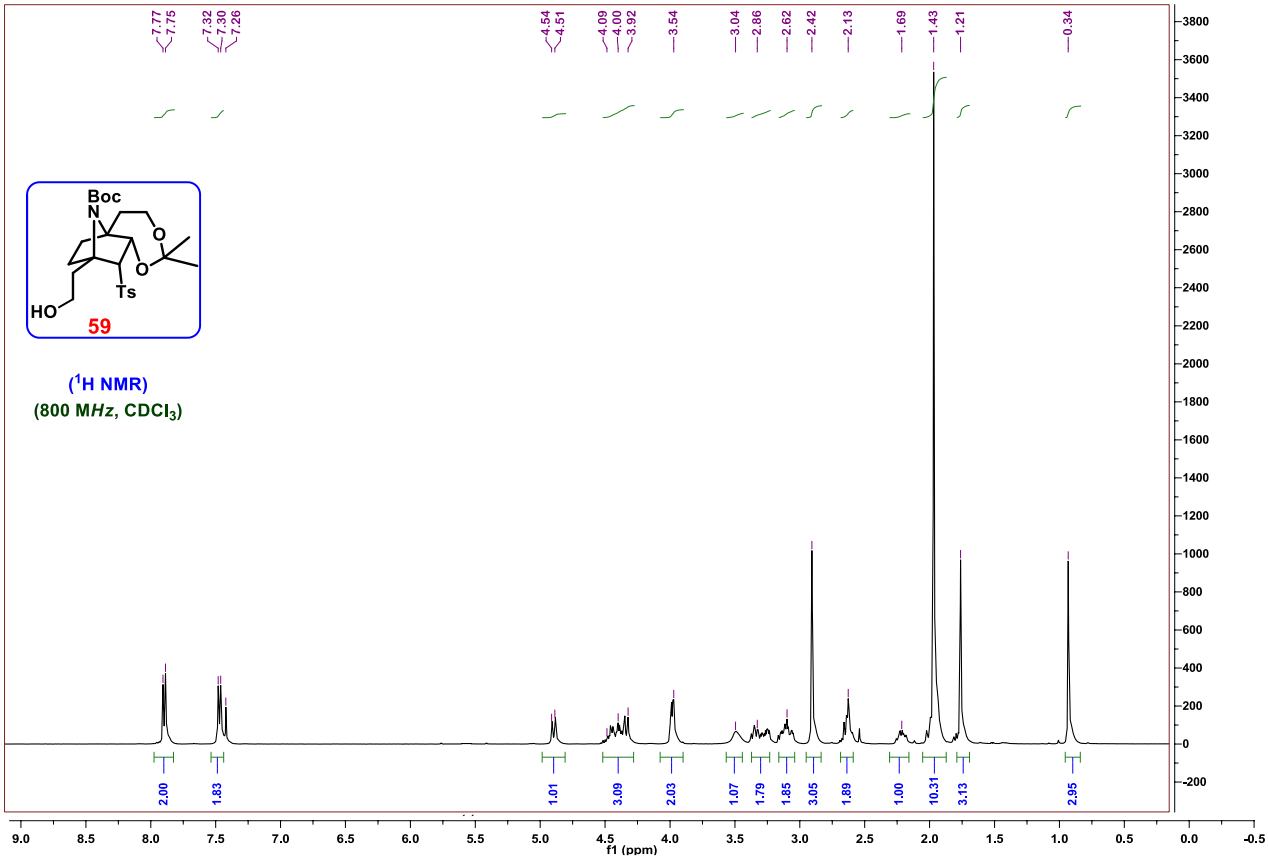
$[\alpha]_D^{22}$ = +28.3 (*c* = 0.15, $CHCl_3$).


Boc
N
OH
OH
Ts
OH
58
(1H NMR)
(800 MHz, CDCl3)
f1 (DDM)

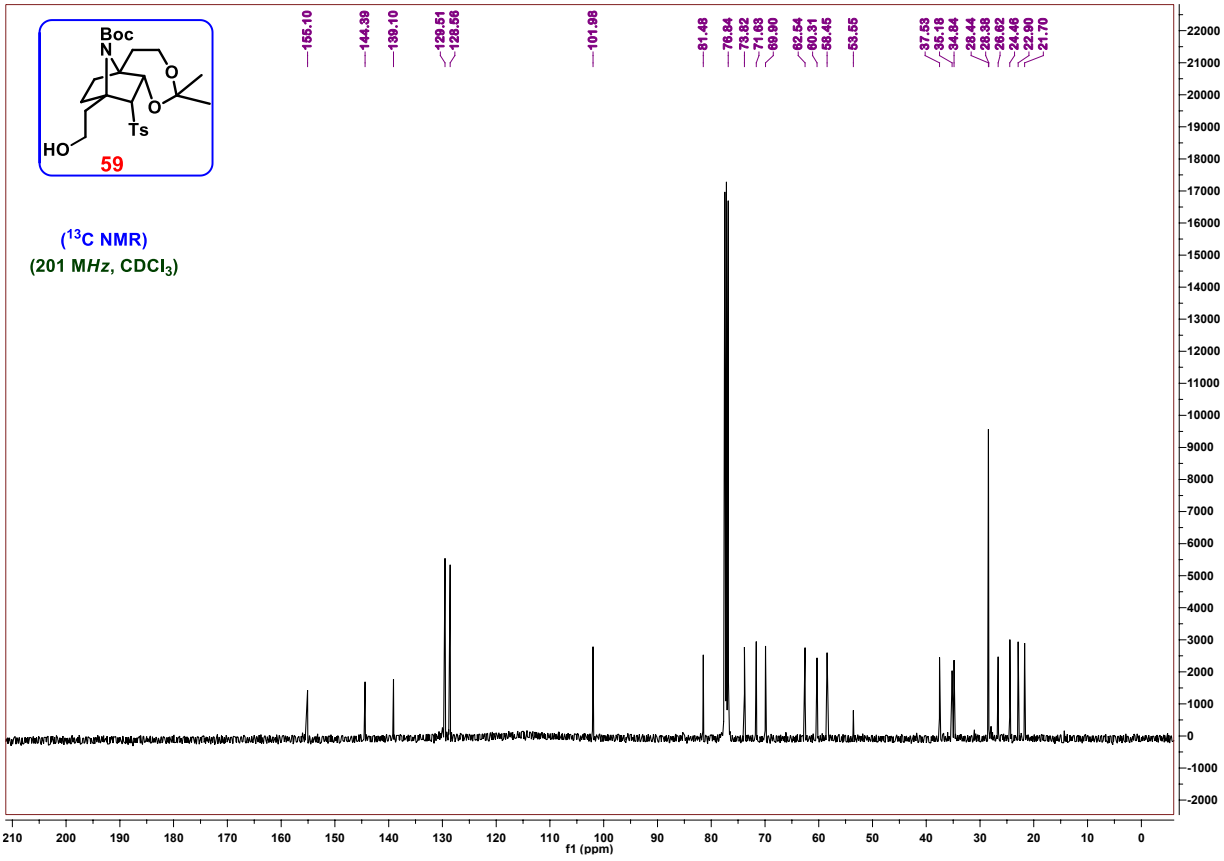

Boc
N
OH
OH
Ts
OH
58
(13C NMR)
(201 MHz, CDCl3)
f1 (ppm)



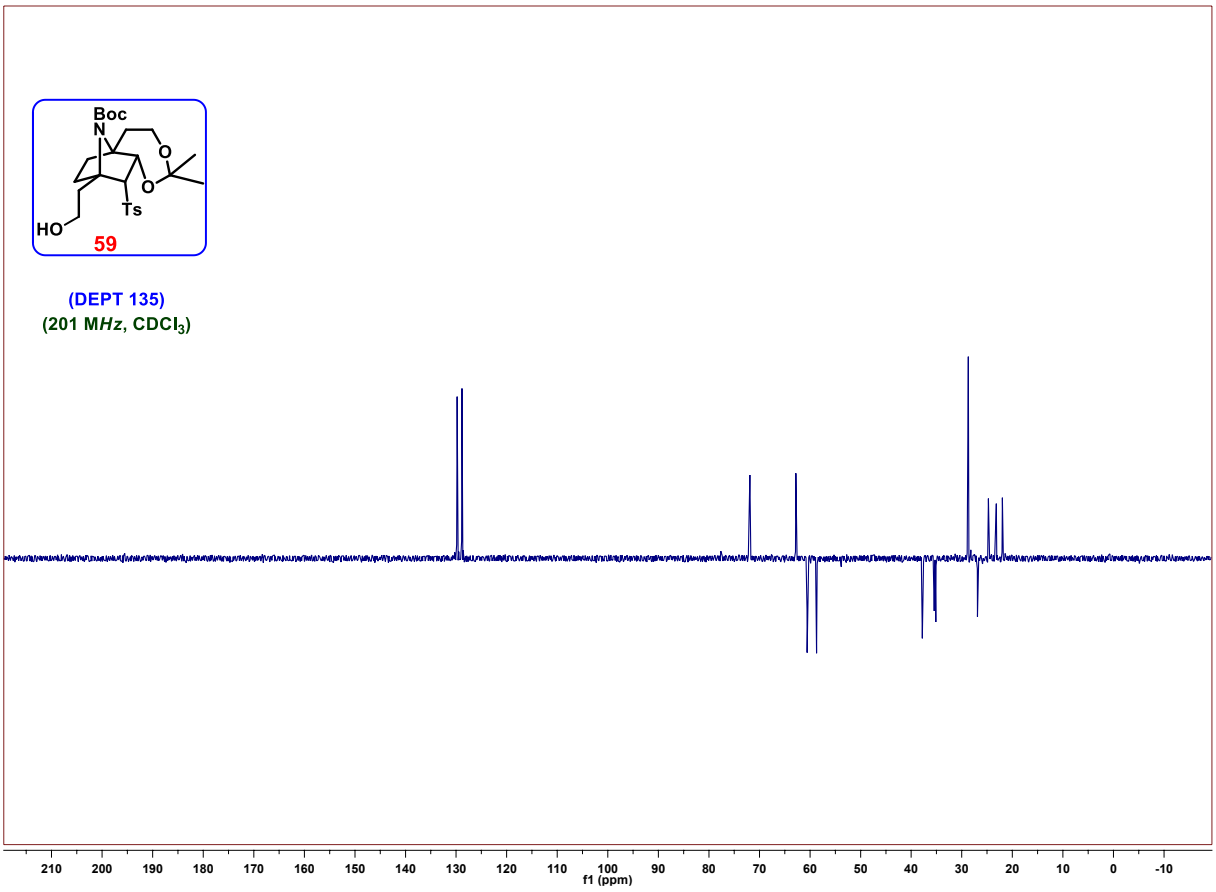
(DEPT 135)
(201 MHz, $CDCl_3$)



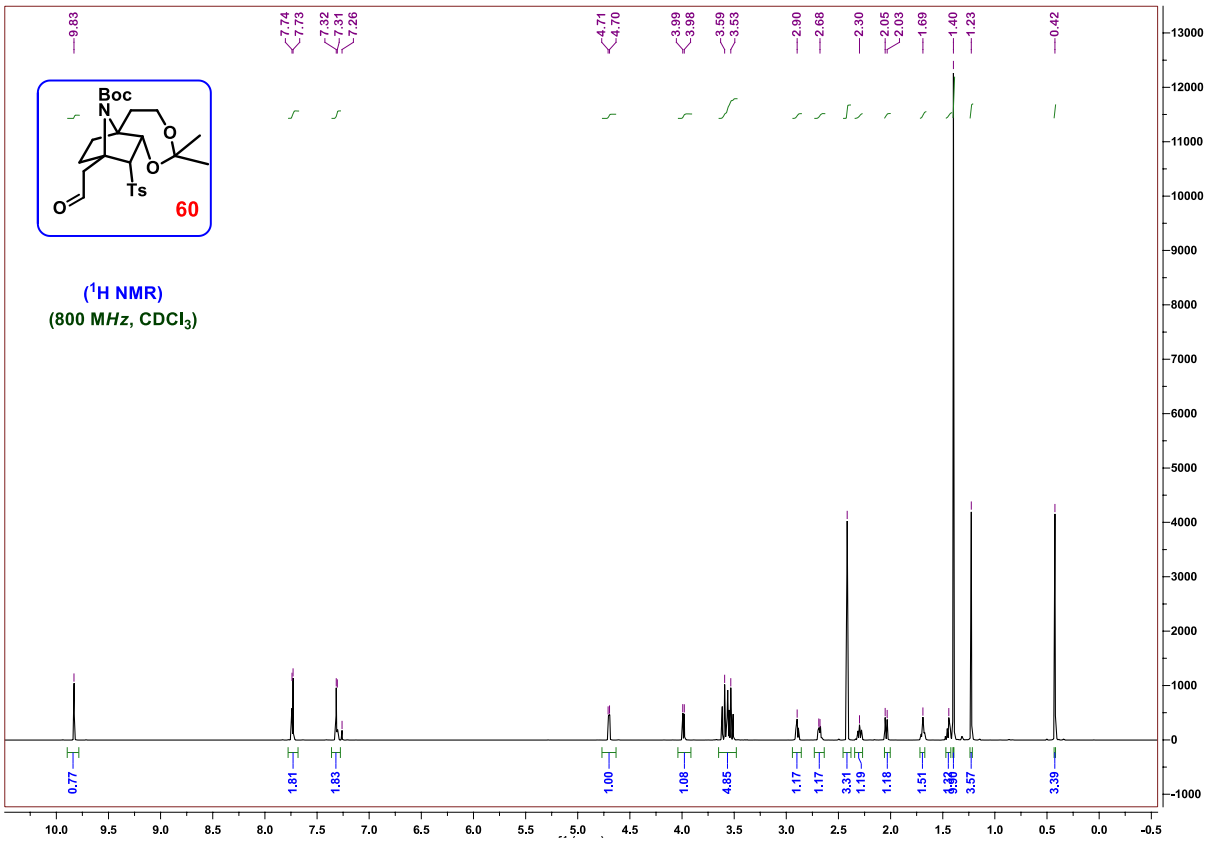
(1H NMR)
(800 MHz, $CDCl_3$)

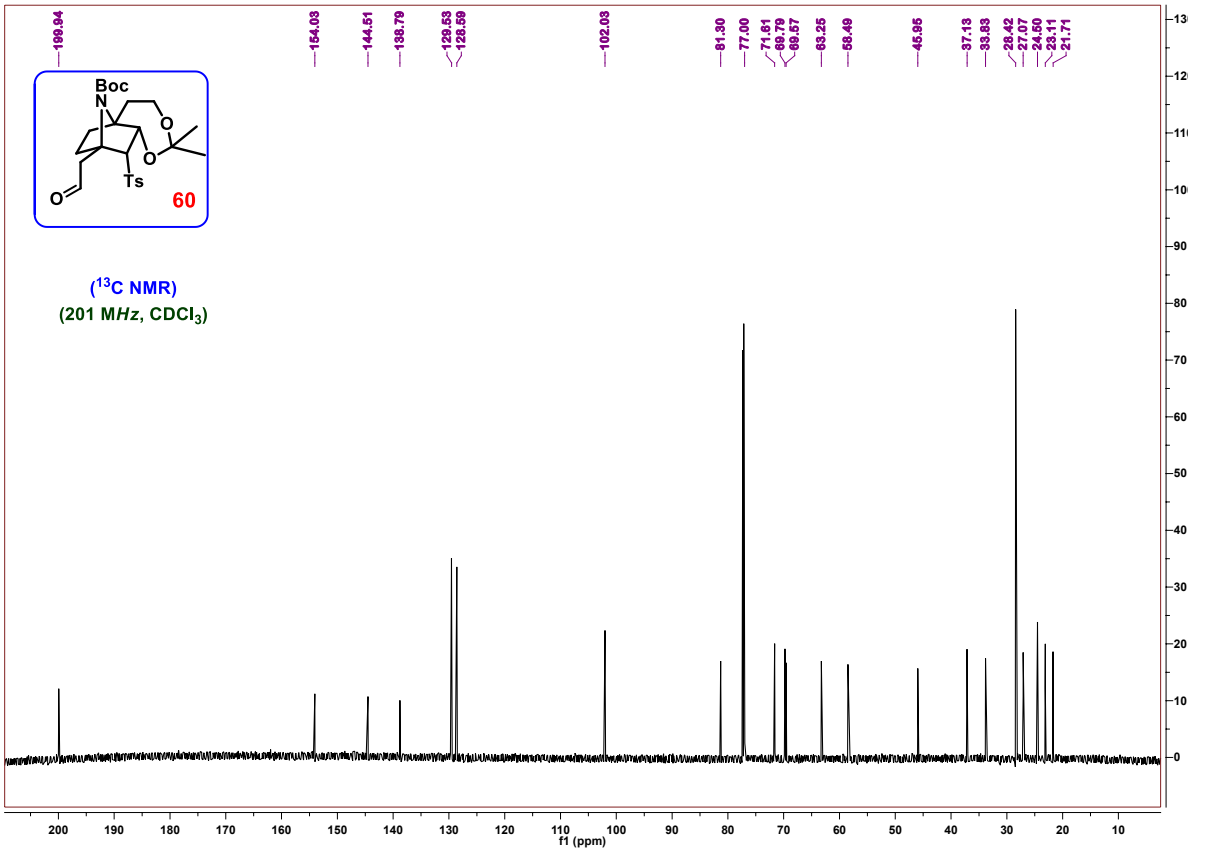


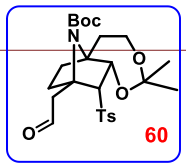
(^{13}C NMR)
(201 M*Hz*, $CDCl_3$)



(DEPT 135)
(201 M*Hz*, $CDCl_3$)

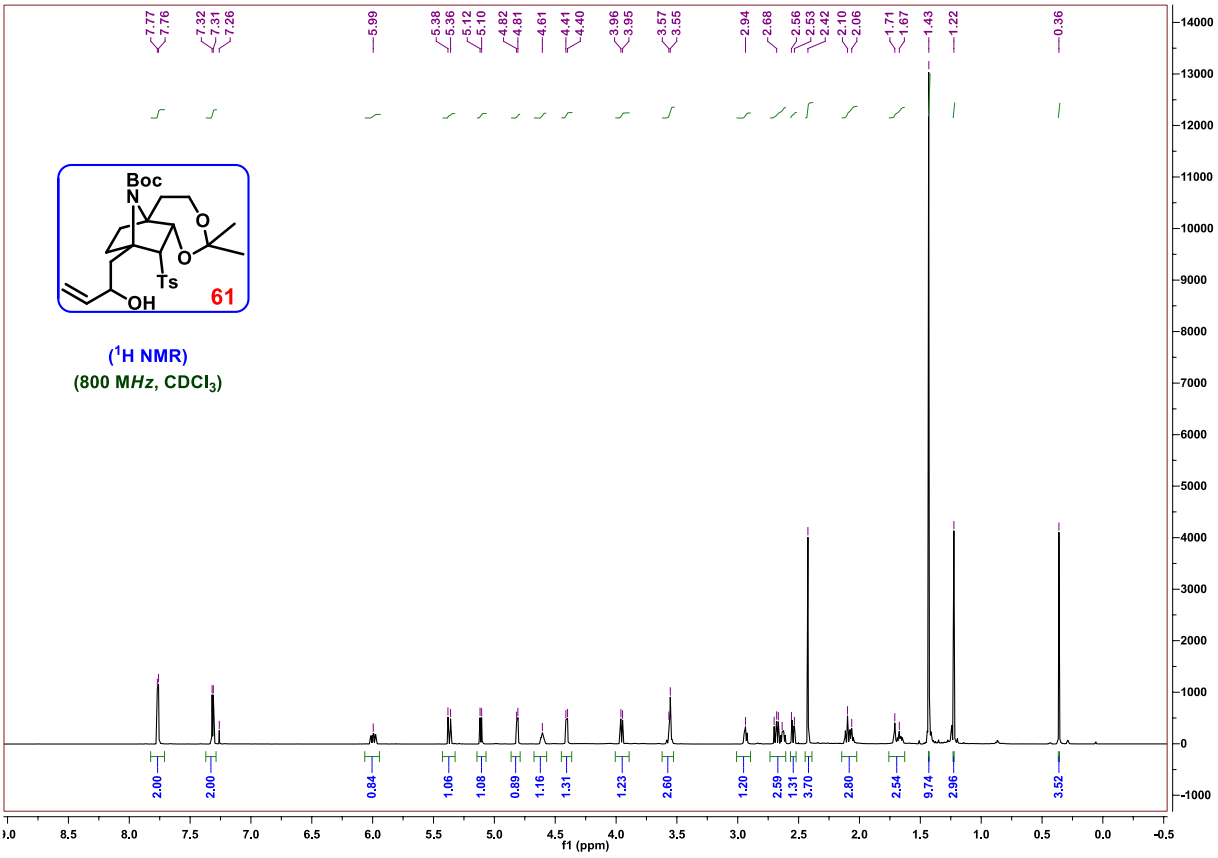

9.83
7.74
7.73
7.32
7.31
7.26
4.71
4.70
3.99
3.98
3.59
3.53
2.90
2.68
2.30
2.05
2.03
1.69
1.40
1.23
0.42
Boc
N
O
O
Ts
O
60
(1H NMR)
(800 MHz, CDCl3)
0.77
1.81
1.83
1.00
1.08
4.85
1.17
1.17
3.31
1.19
1.18
1.51
3.57
3.39

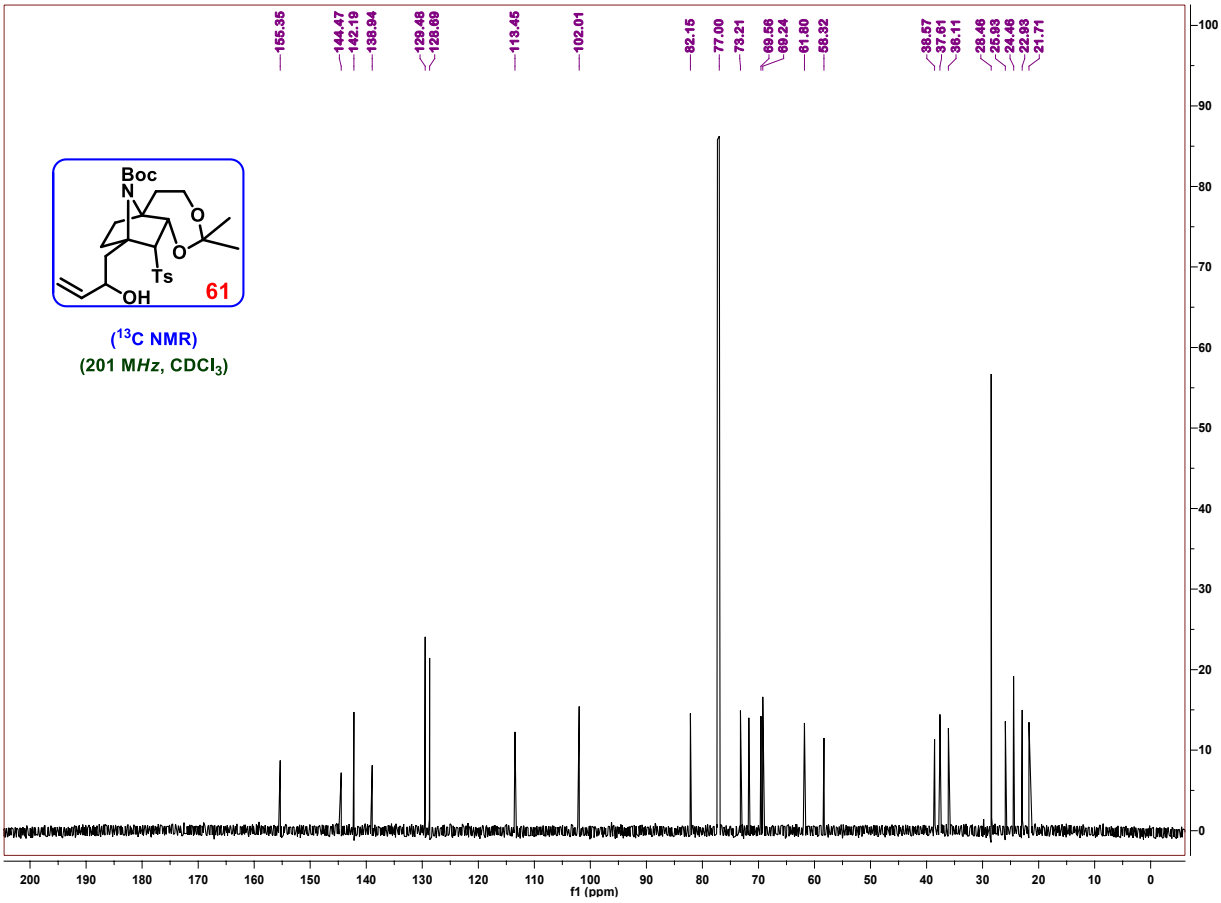

199.94
154.03
144.51
138.79
129.53
128.59
102.03
81.30
77.00
71.61
69.79
69.57
63.25
58.49
45.95
37.13
33.83
28.42
27.07
24.50
23.11
21.71
Boc
N
O
O
Ts
O
60
(13C NMR)
(201 MHz, CDCl3)
f1 (ppm)



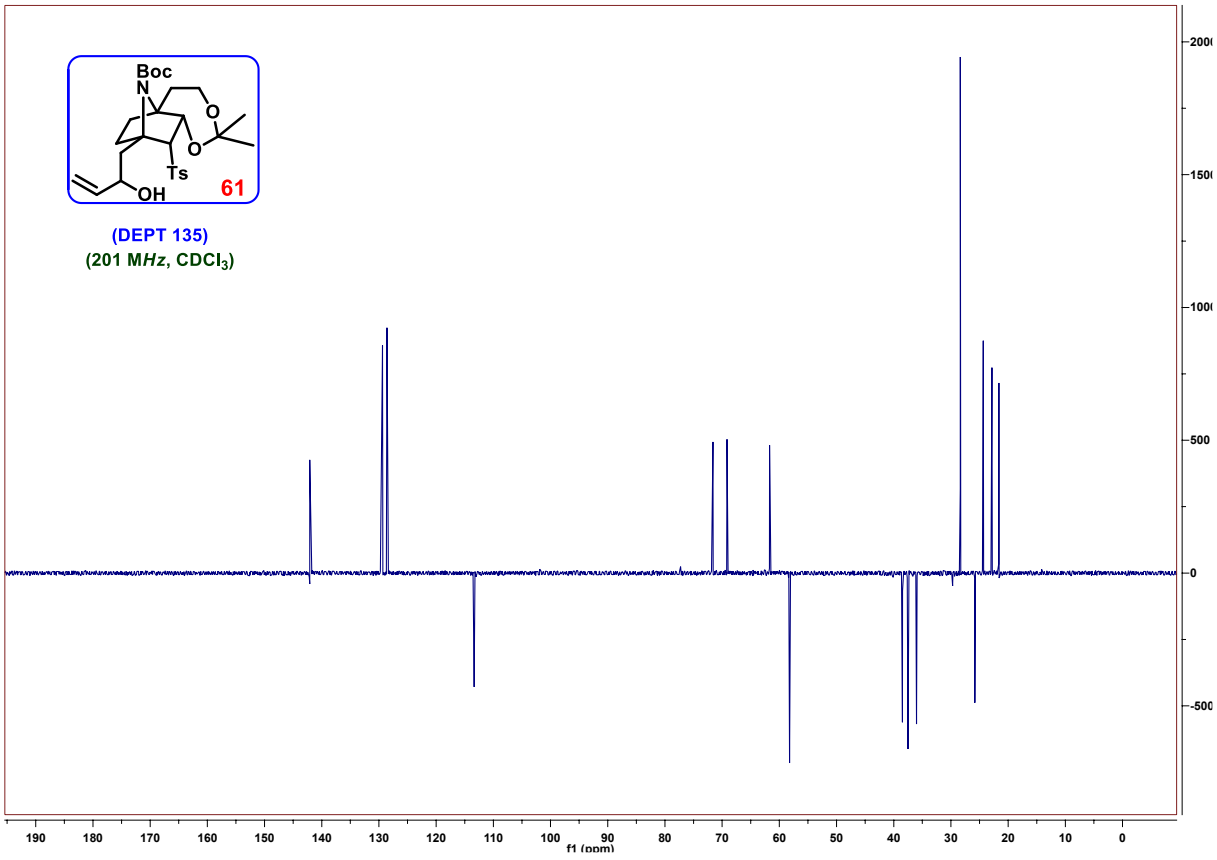
(DEPT 135)
(201 M*Hz*, $CDCl_3$)

(^{1}H NMR)
(800 M*Hz*, $CDCl_3$)

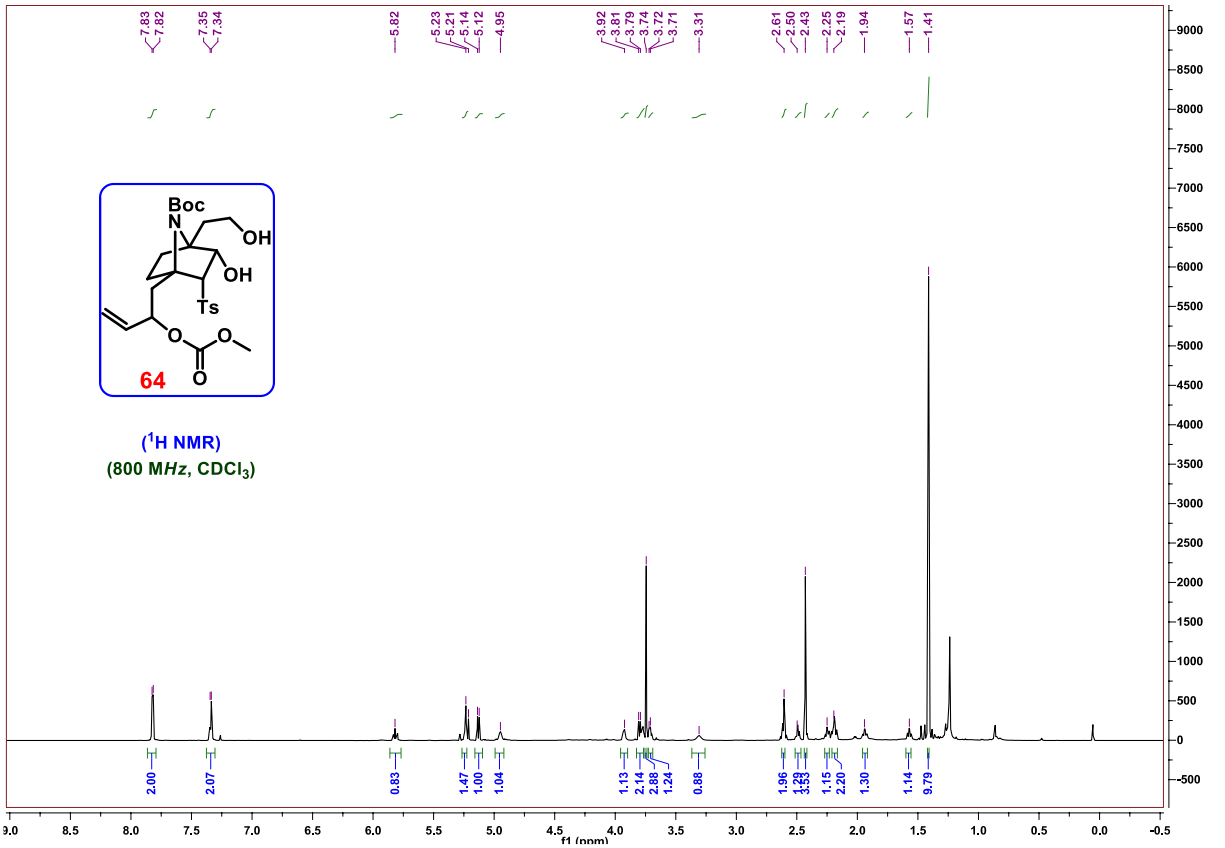




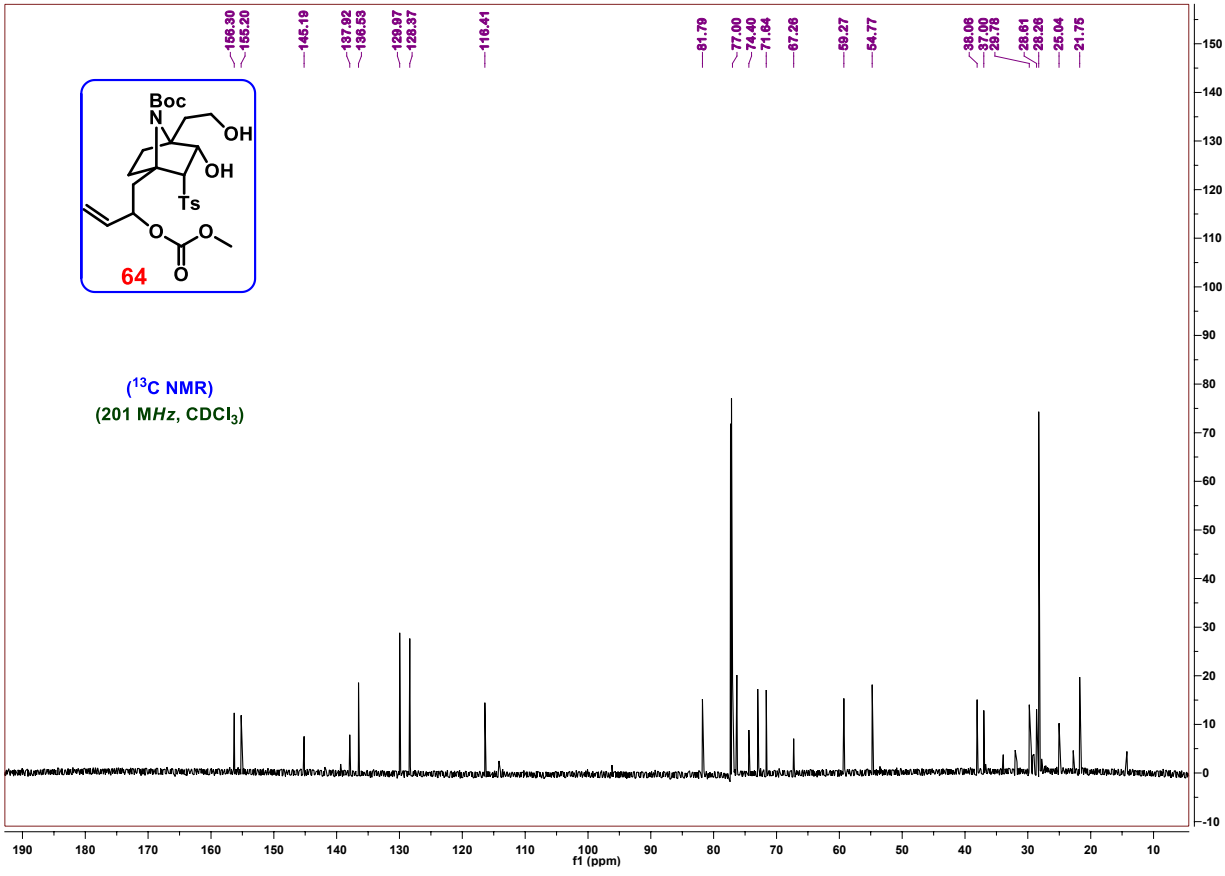
(^{13}C NMR)
(201 M*Hz*, $CDCl_3$)



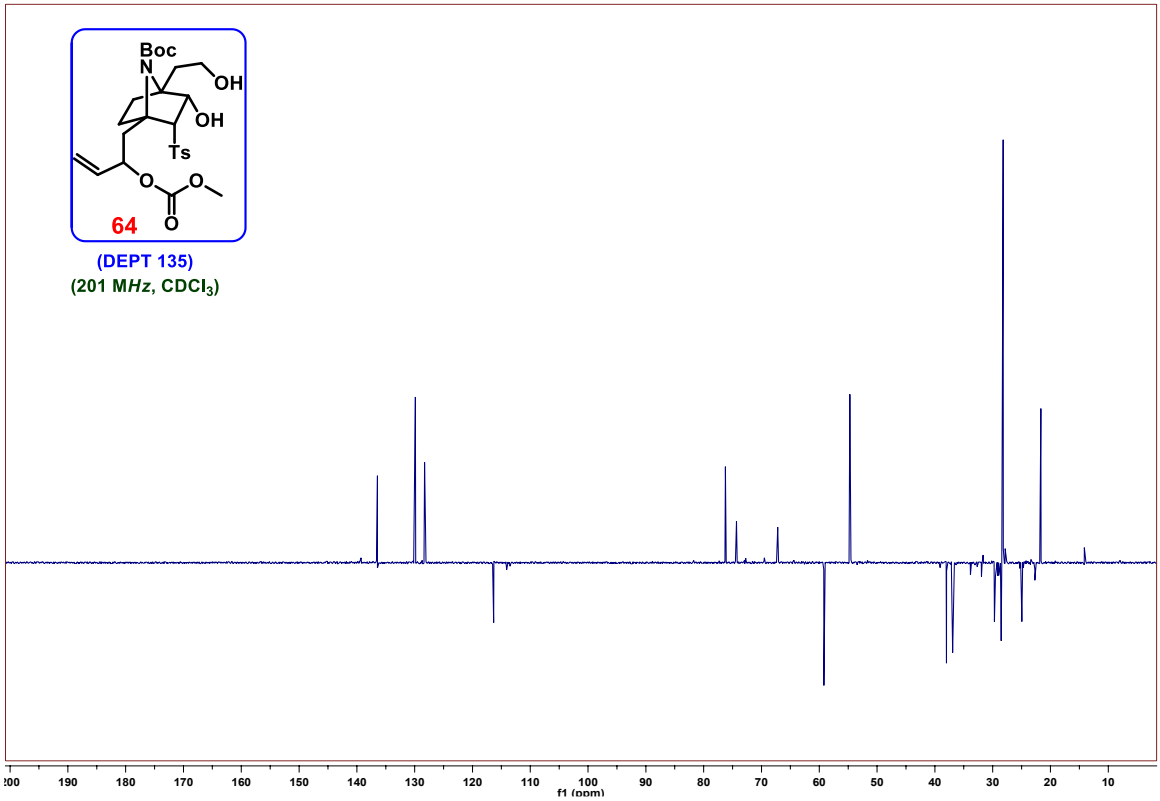
(DEPT 135)
(201 M*Hz*, $CDCl_3$)

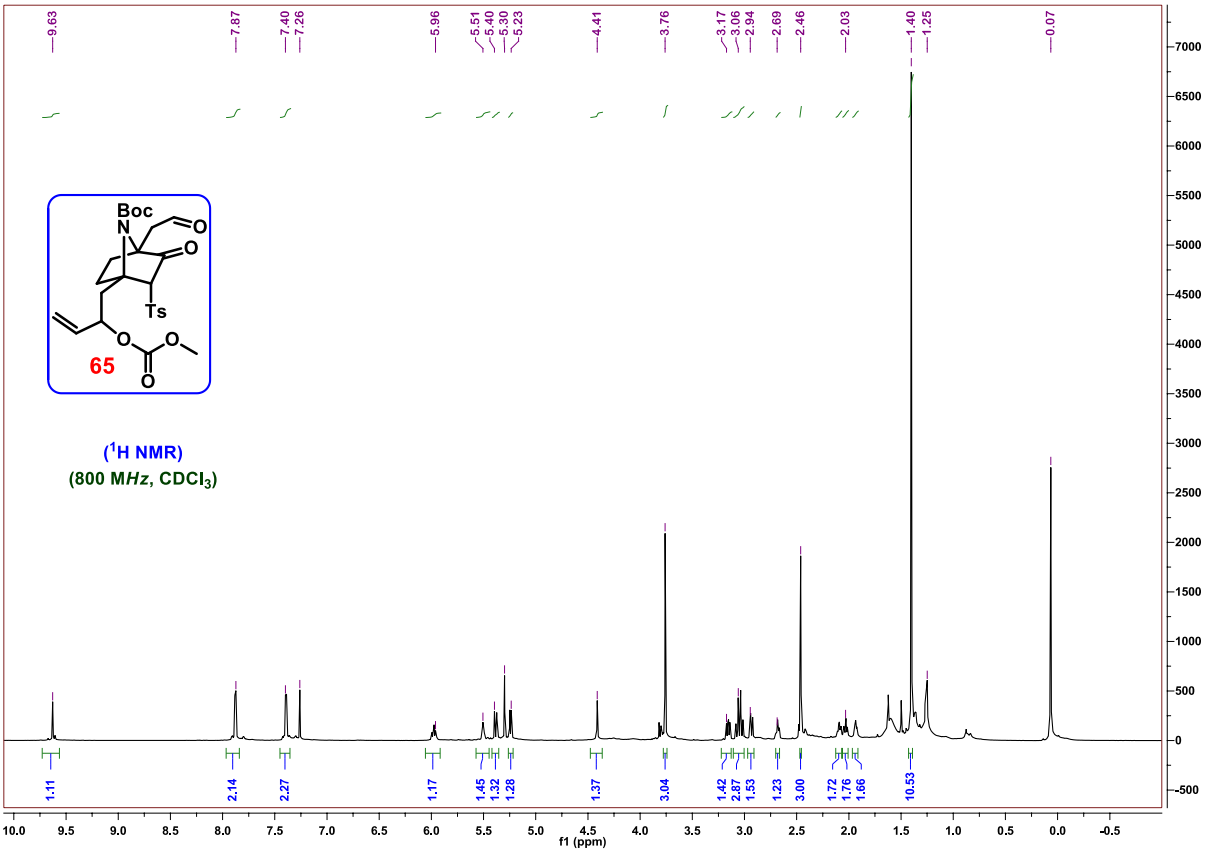


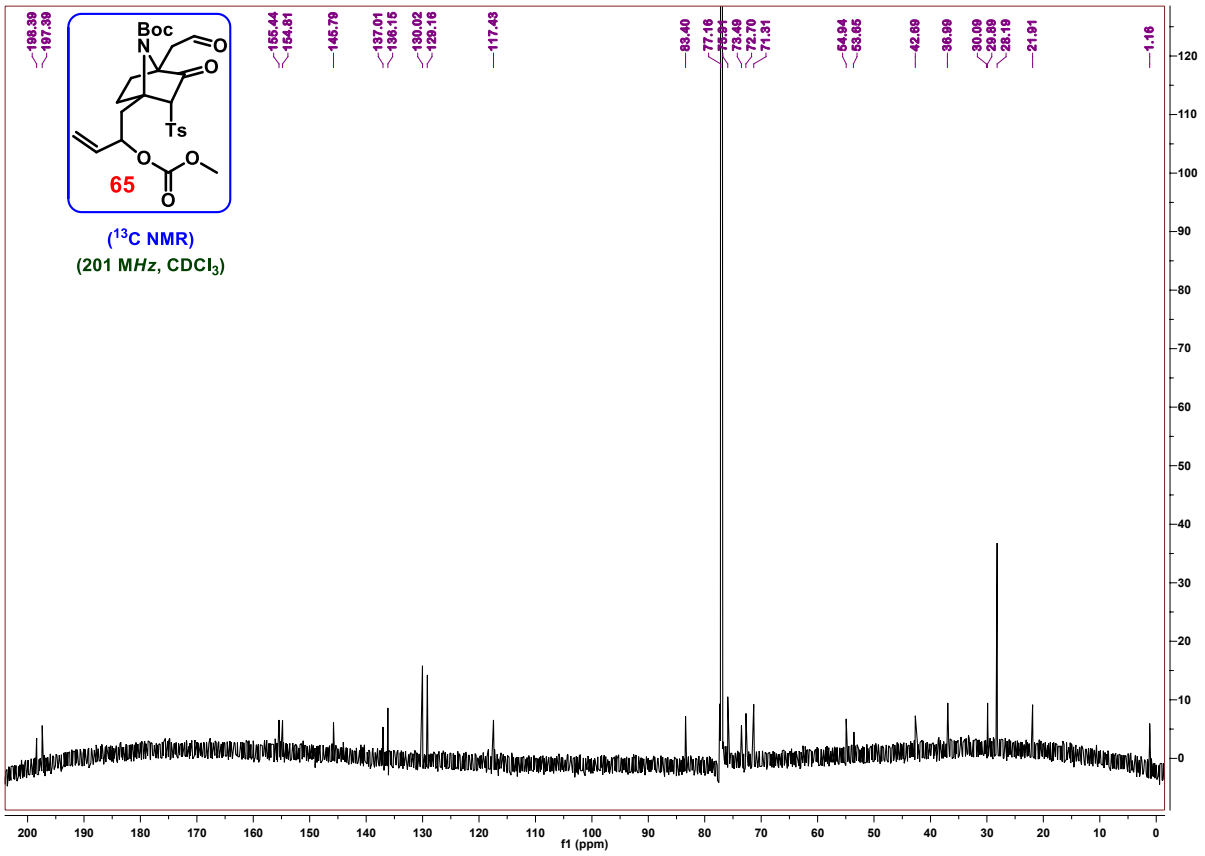
(^{1}H NMR)
(800 M*Hz*, $CDCl_3$)



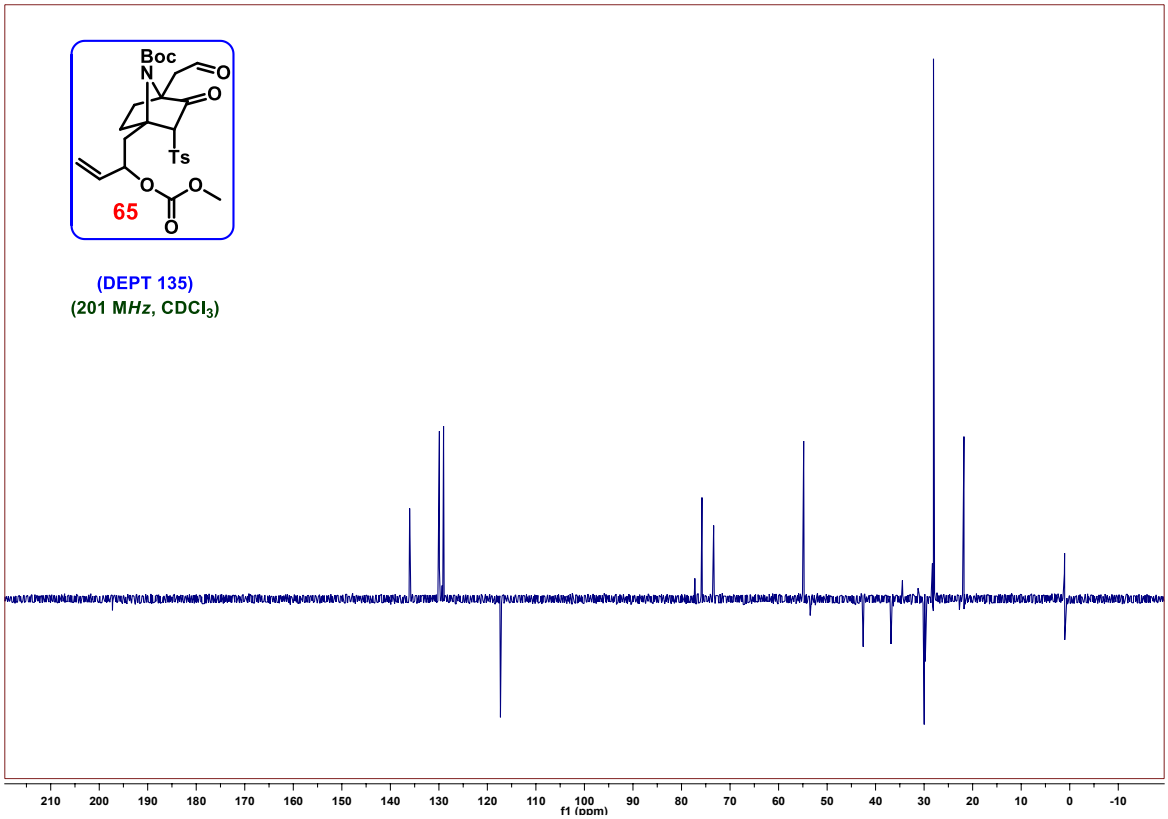
(^{13}C NMR)
(201 M*Hz*, $CDCl_3$)


Boc
N
OH
OH
Ts
O
O
O
64
(DEPT 135)
(201 MHz, CDCl3)
f1 (ppm)

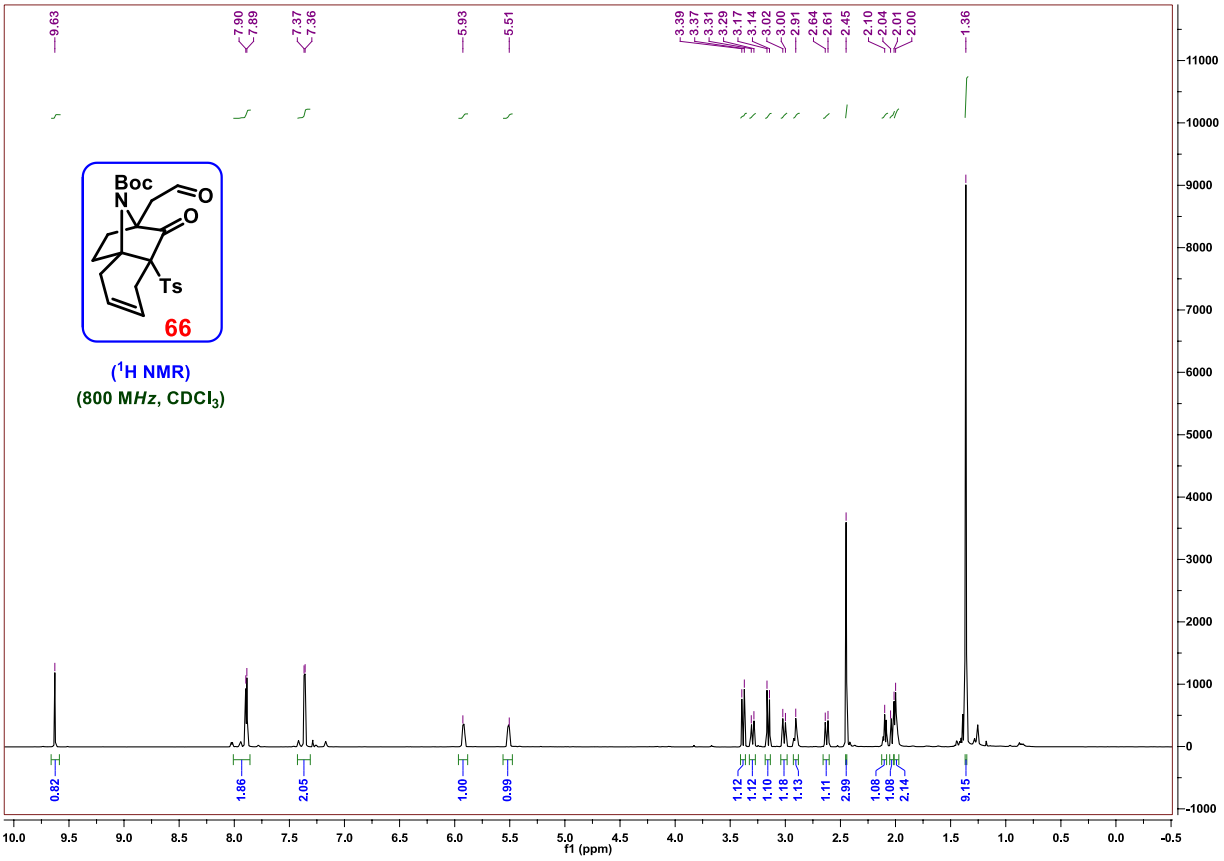

9.63
7.87
7.40
7.26
5.96
5.51
5.40
5.30
5.23
4.41
3.76
3.17
3.06
2.94
2.69
2.46
2.03
1.40
1.25
0.07
Boc
N
O
O
Ts
O
O
O
65
(1H NMR)
(800 MHz, CDCl3)
1.11
2.14
2.27
1.17
1.45
1.32
1.28
1.37
3.04
1.42
2.87
1.53
1.23
3.00
1.72
1.76
1.66
10.53
f1 (ppm)

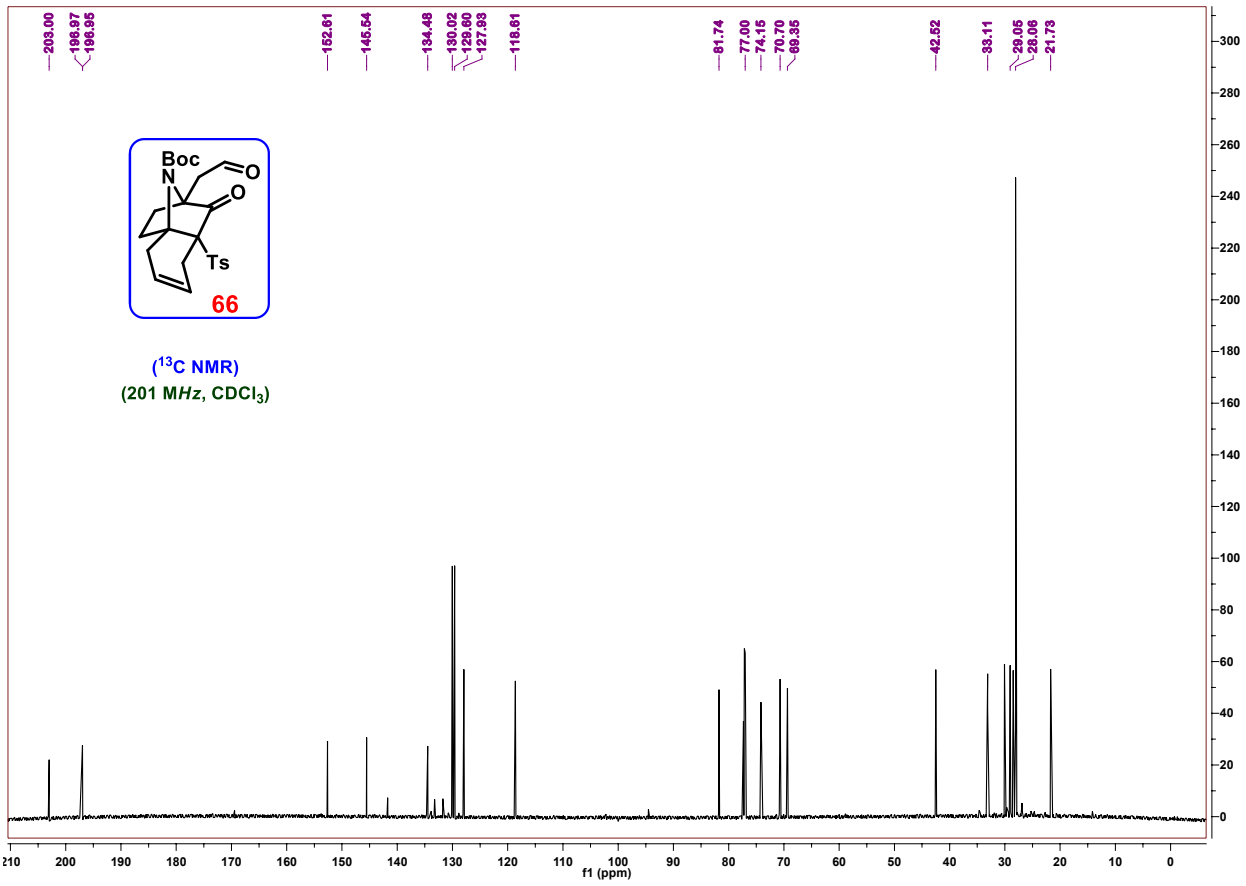


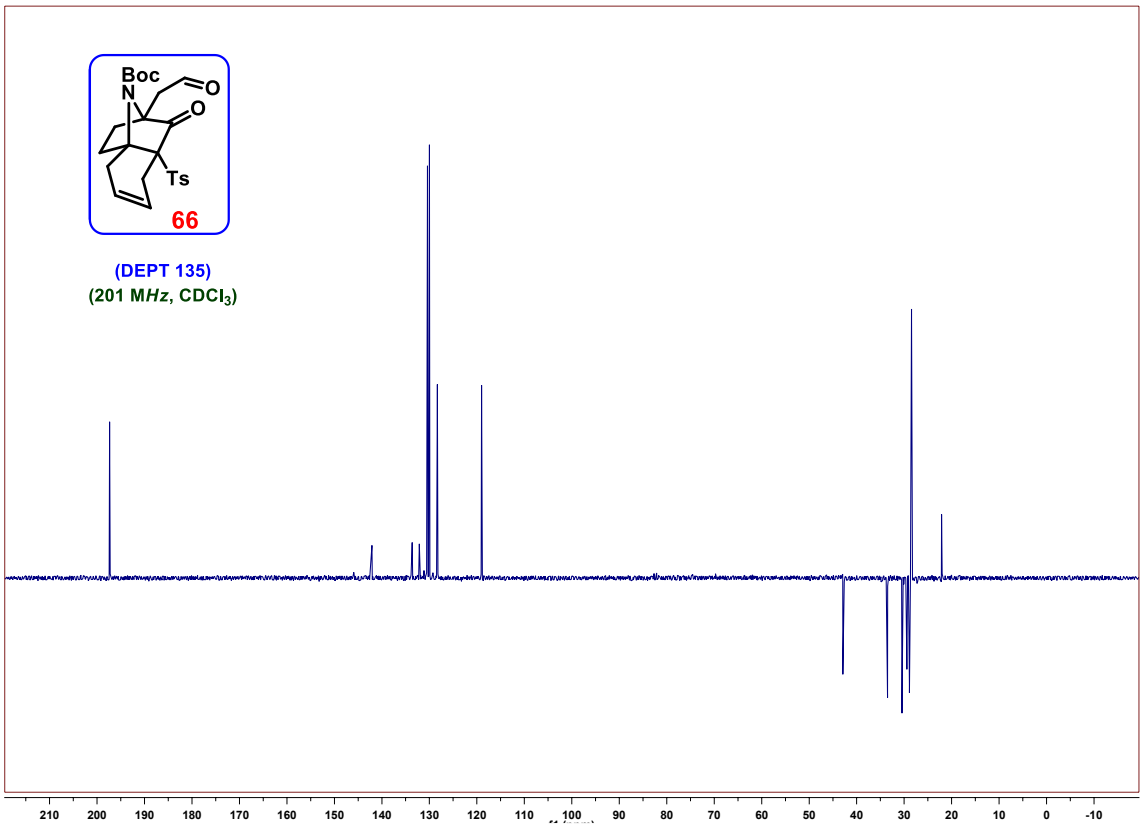
(^{13}C NMR)
(201 M*Hz*, $CDCl_3$)

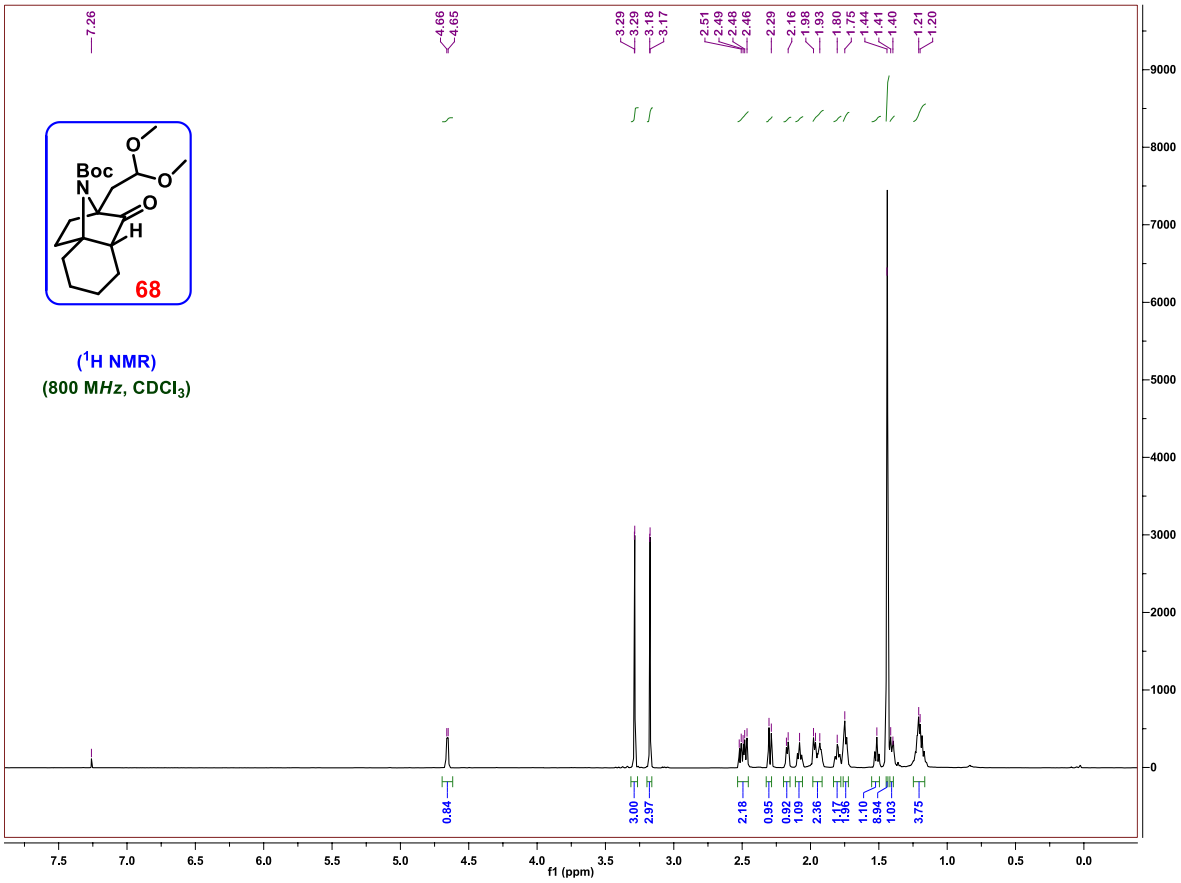


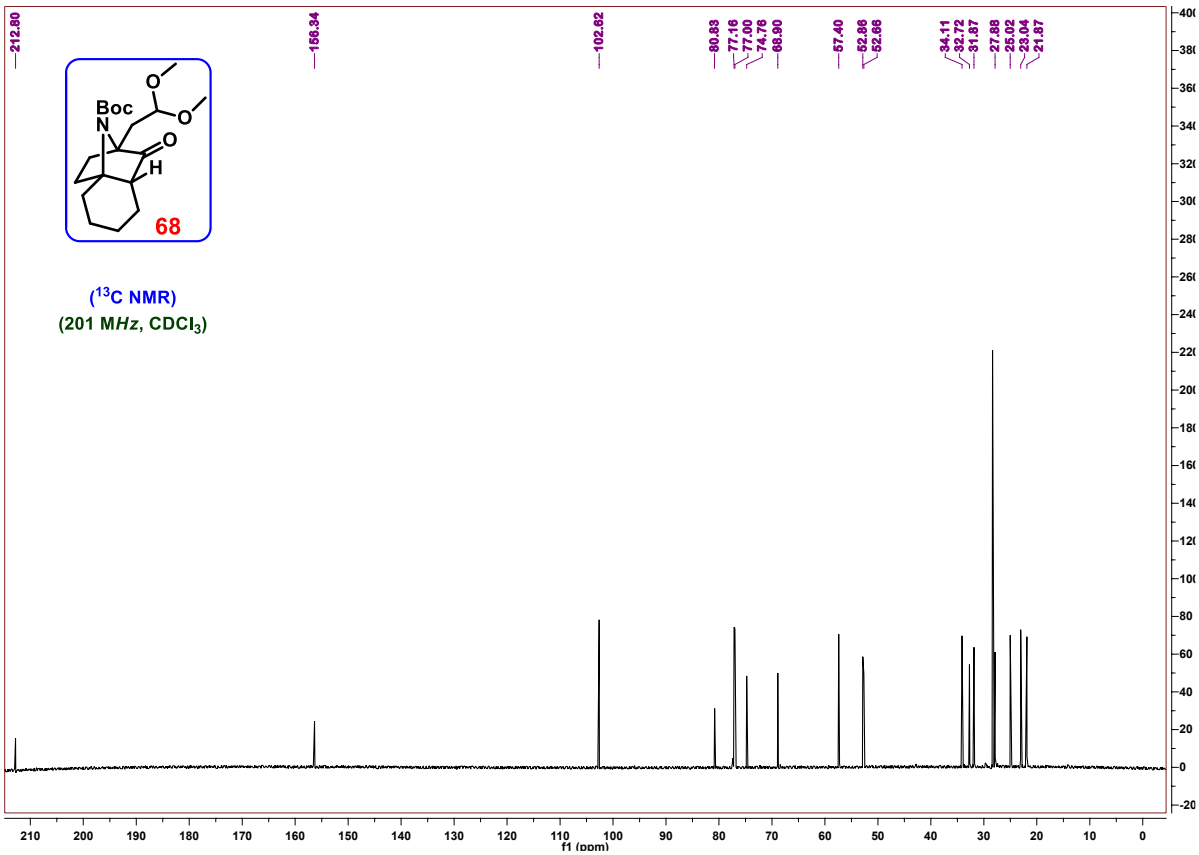
(DEPT 135)
(201 M*Hz*, $CDCl_3$)

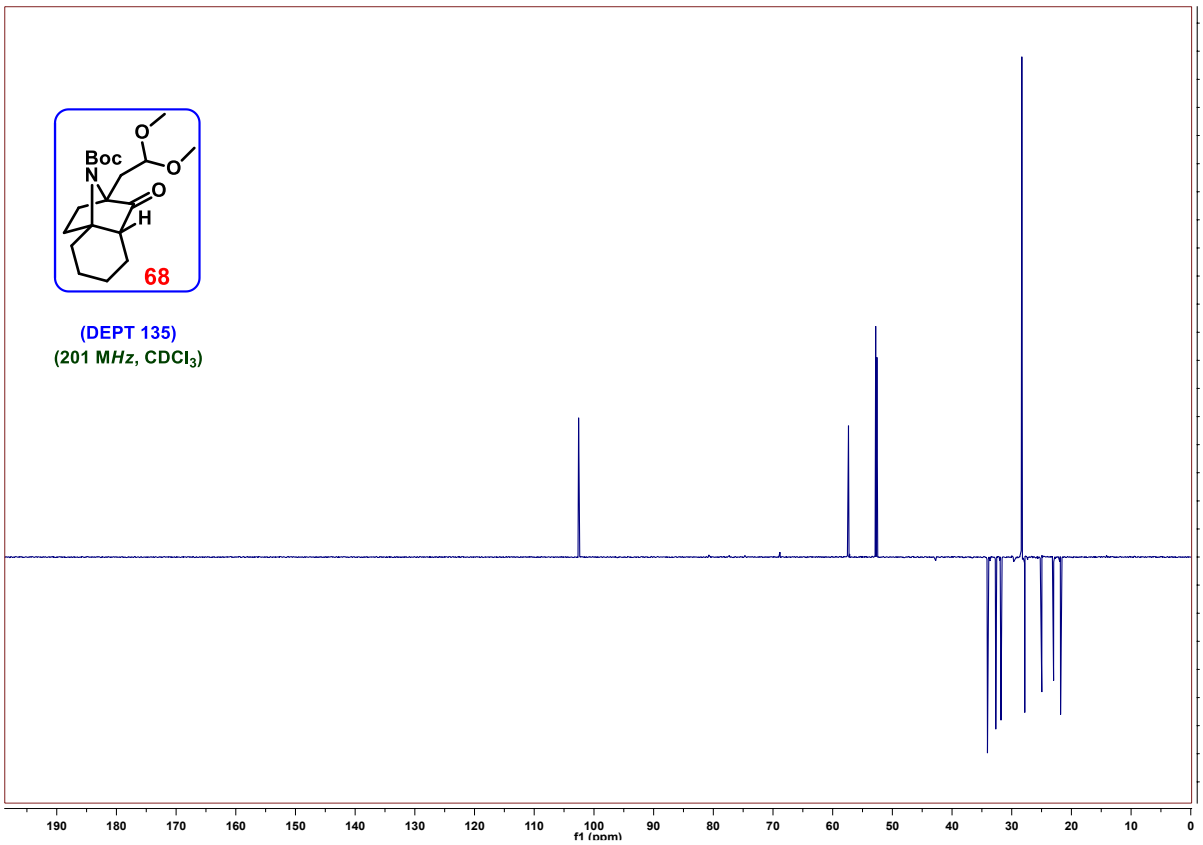

9.63
7.90
7.89
7.37
7.36
5.93
5.51
3.39
3.37
3.31
3.29
3.17
3.14
3.02
3.00
2.91
2.64
2.61
2.45
2.10
2.04
2.01
2.00
1.36
Boc
N
O
O
Ts
66
(1H NMR)
(800 MHz, CDCl3)
0.82
1.86
2.05
1.00
0.99
1.12
1.12
1.10
1.18
1.13
1.11
2.99
1.08
1.08
2.14
9.15
f1 (ppm)

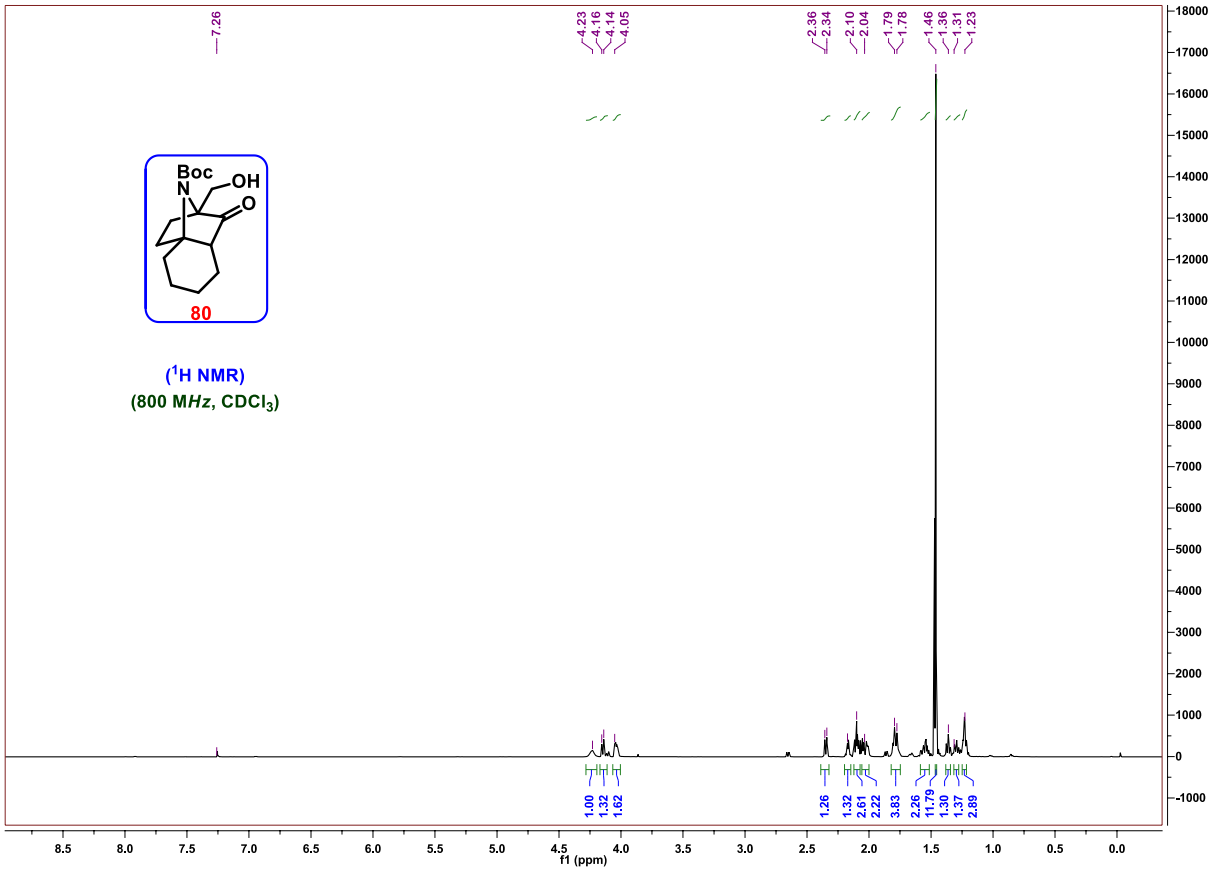

203.00
196.97
196.85
152.61
145.54
134.48
130.02
129.80
127.93
118.61
81.74
77.00
74.15
70.70
69.35
42.52
33.11
29.05
28.06
21.73
Boc
N
O
O
Ts
66
(13C NMR)
(201 MHz, CDCl3)
f1 (ppm)


Boc
N
O
O
Ts
66
(DEPT 135)
(201 MHz, CDCl3)
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10

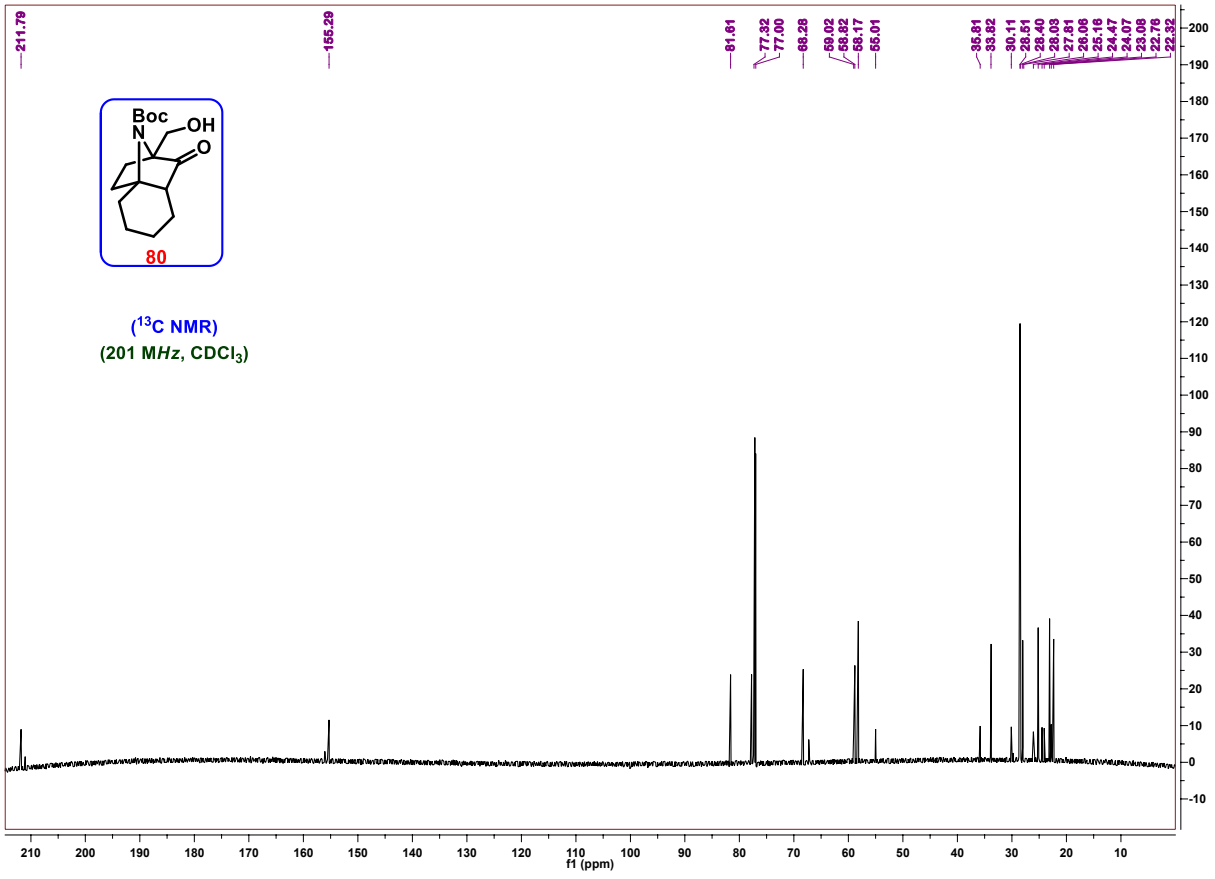

7.26
4.66
4.65
3.29
3.29
3.18
3.17
2.51
2.49
2.48
2.46
2.29
2.16
1.98
1.93
1.80
1.75
1.44
1.41
1.40
1.21
1.20
Boc
N
O
O
O
H
68
(1H NMR)
(800 MHz, CDCl3)
0.84
3.00
2.97
2.18
0.95
0.92
1.09
2.36
1.17
1.96
1.10
8.94
1.03
3.75
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)


212.80
156.34
102.62
80.83
77.16
77.00
74.76
68.90
67.40
62.86
62.66
34.11
32.72
31.87
27.88
25.02
23.04
21.87
Boc
N
O
O
O
H
68
(13C NMR)
(201 MHz, CDCl3)
f1 (ppm)

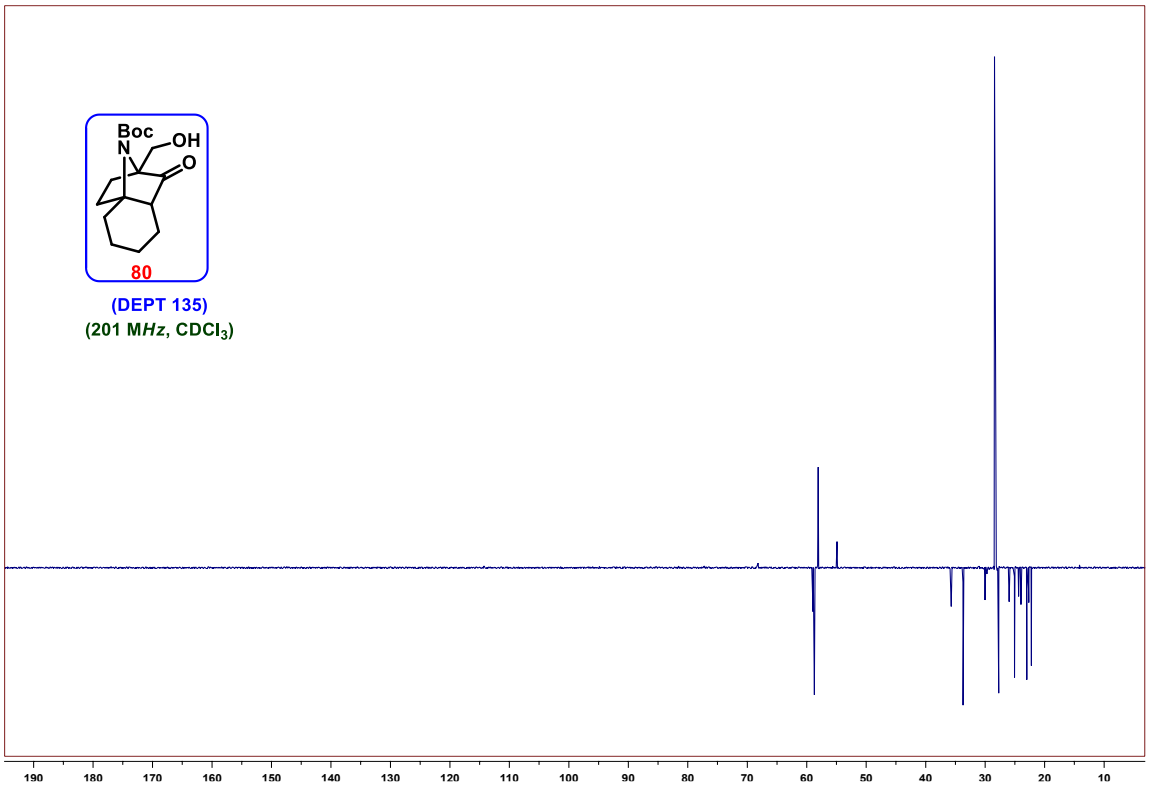

Boc
N
O
O
O
H
68
(DEPT 135)
(201 MHz, CDCl3)
f1 (ppm)

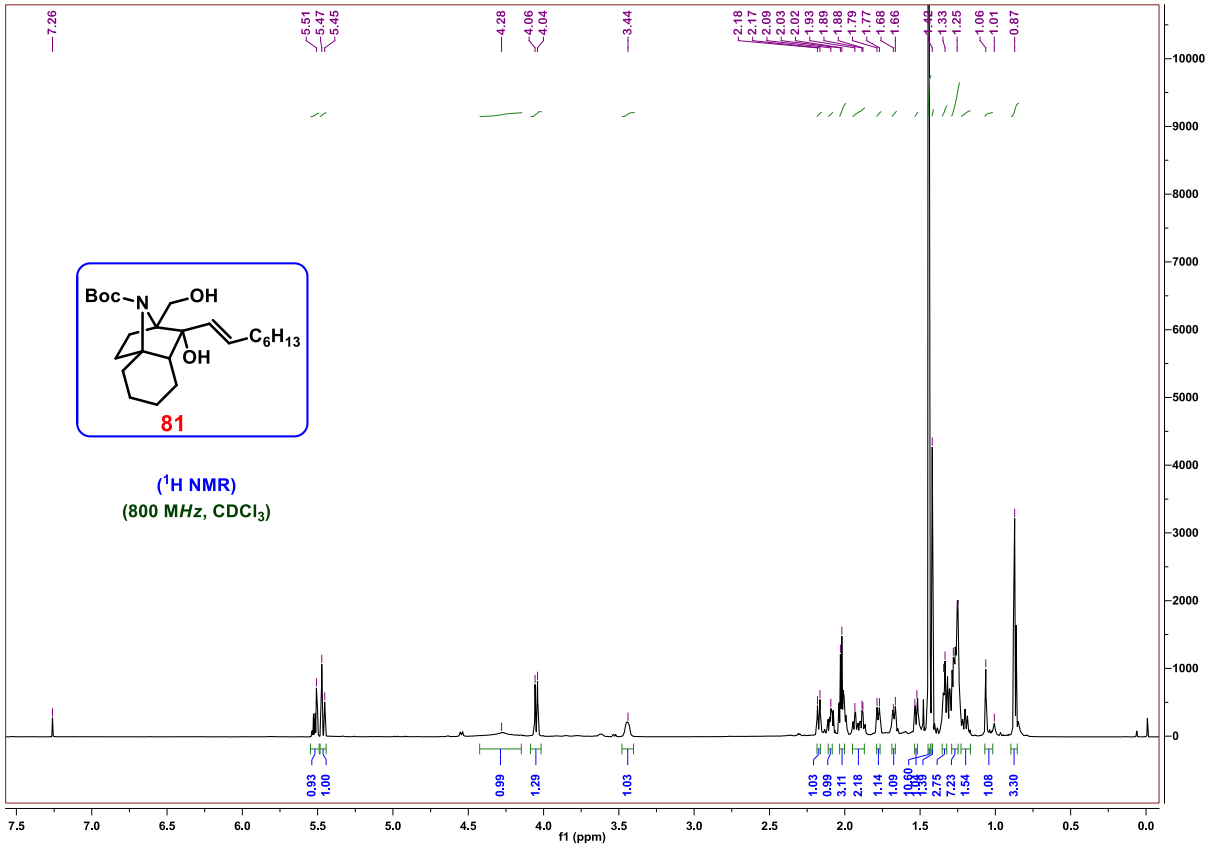


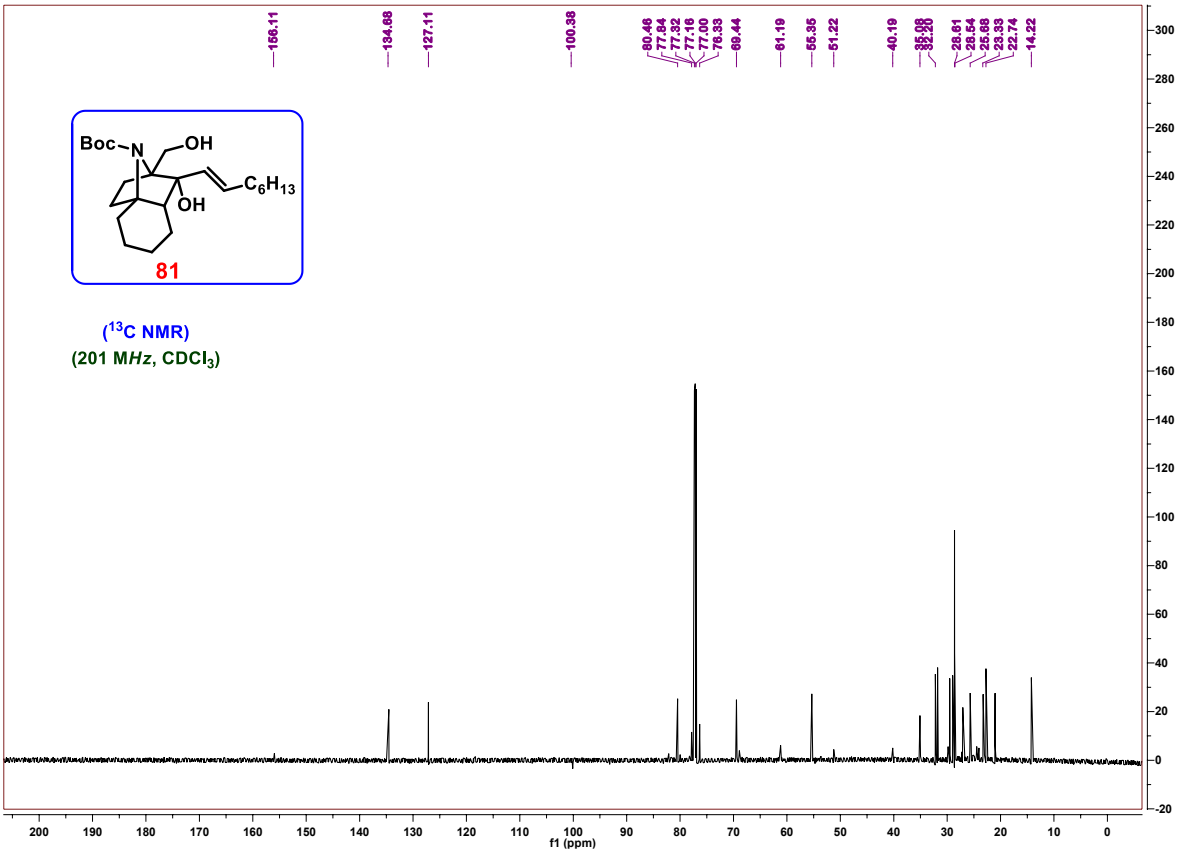
(^{1}H NMR)
(800 M*Hz*, $CDCl_3$)

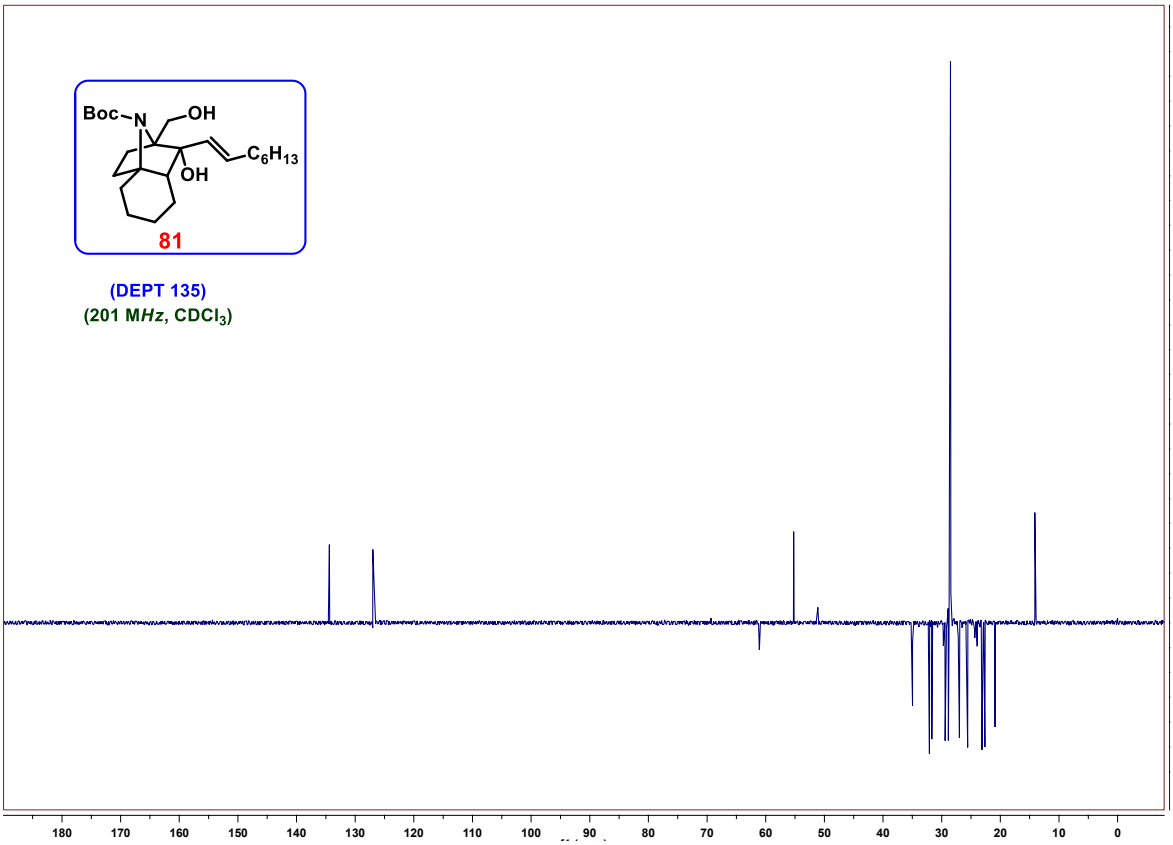


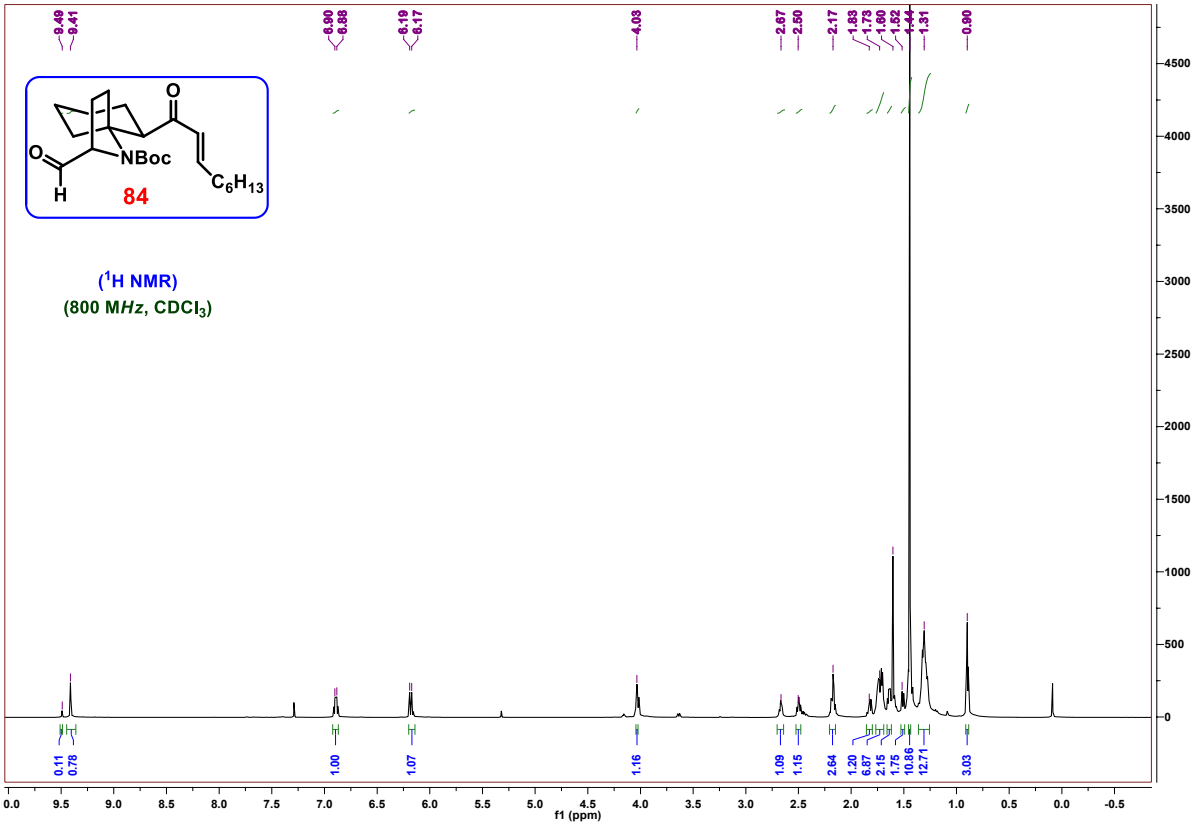
(^{13}C NMR)
(201 M*Hz*, $CDCl_3$)

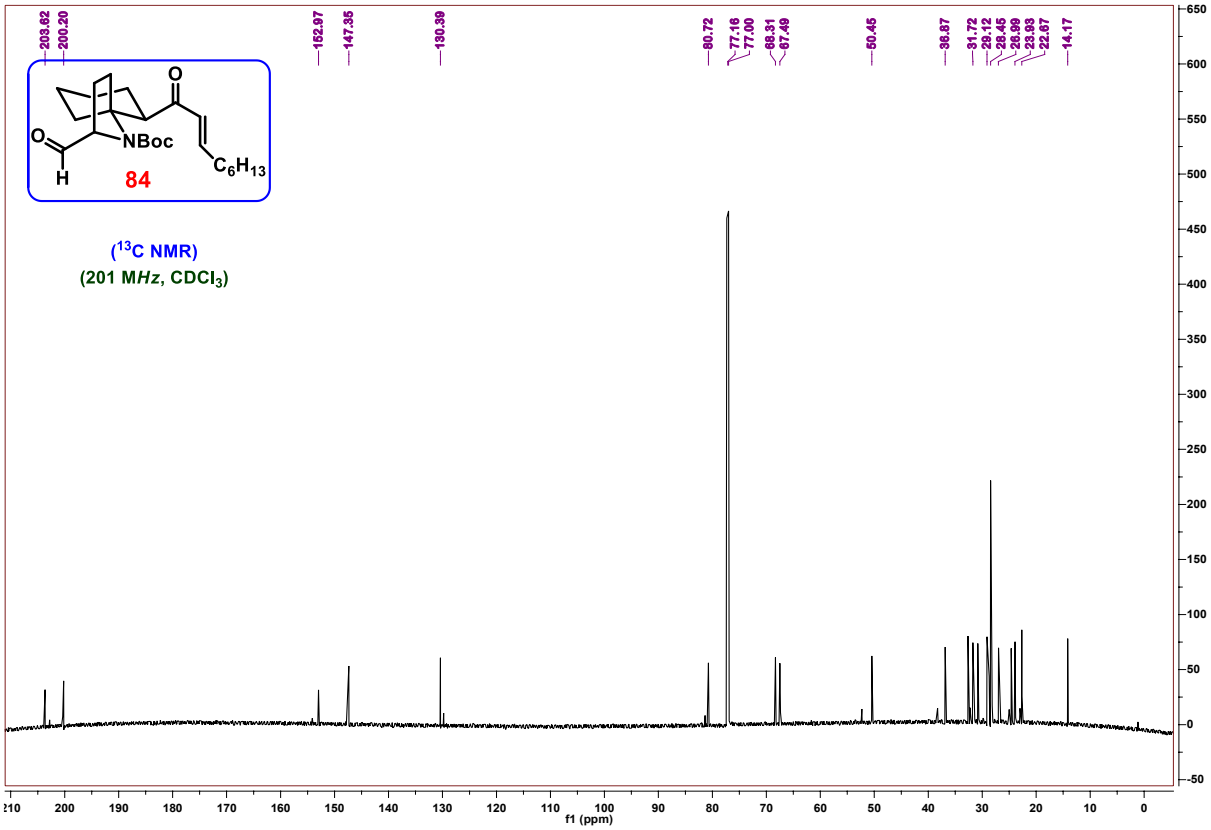

Boc
N
OH
O
80
(DEPT 135)
(201 MHz, CDCl3)
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10

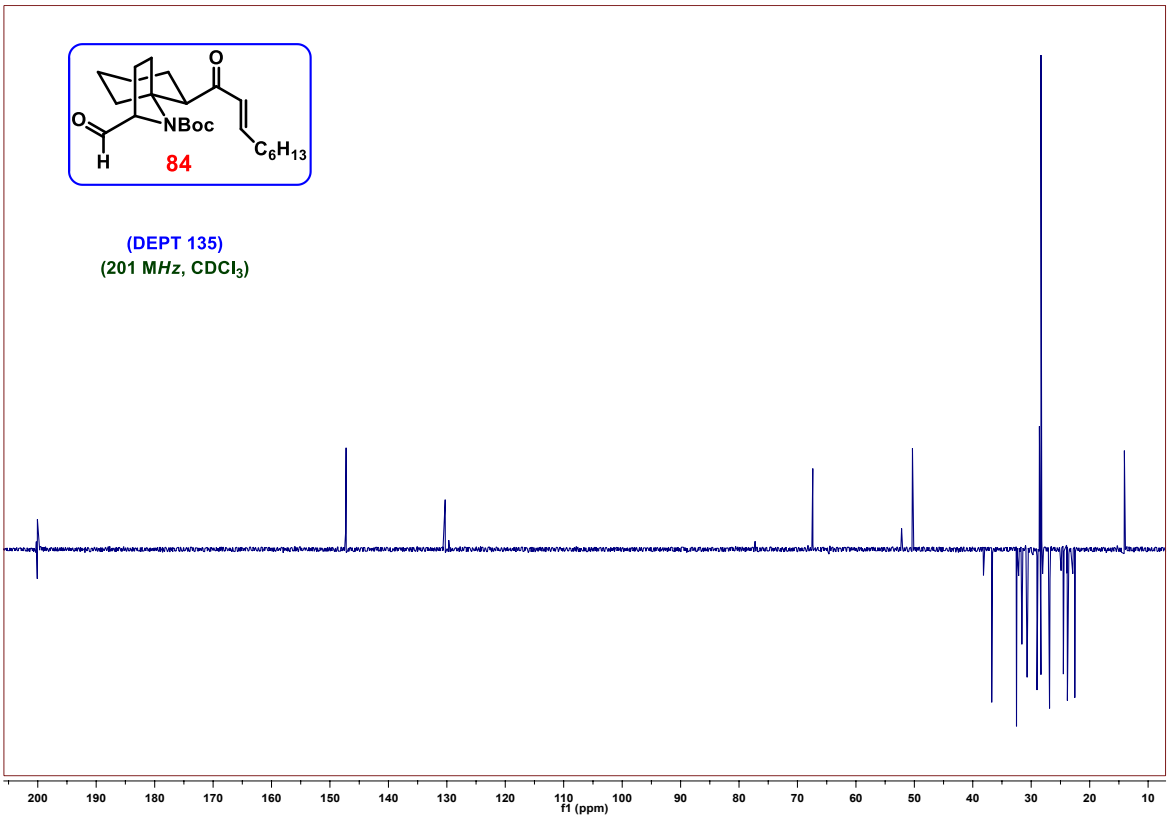

7.26
5.51 5.47 5.45
4.28 4.06 4.04
3.44
2.18 2.17 2.09 2.03 2.02 1.93 1.89 1.88 1.79 1.77 1.68 1.66
1.42 1.33 1.25 1.06 1.01 0.87
Boc
N
OH
OH
C6H13
81
(1H NMR)
(800 MHz, CDCl3)
0.93 1.00 0.99 1.29 1.03 1.03 0.99 3.11 2.18 1.14 1.09 10.60 2.75 2.23 1.54 1.08 3.30
f1 (ppm)

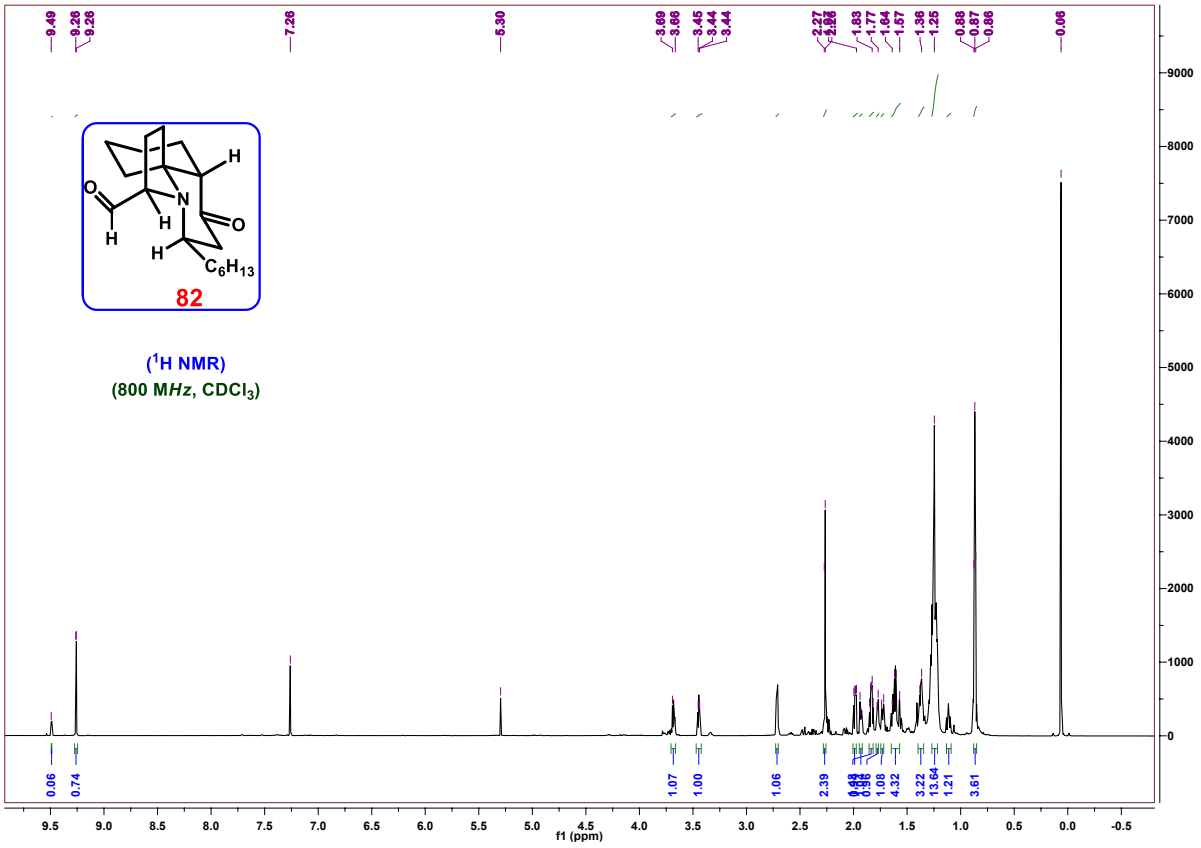

156.11
134.68
127.11
100.38
80.46
77.84
77.32
77.16
77.00
76.33
69.44
61.19
55.35
51.22
40.19
35.08
32.20
28.61
28.54
25.88
23.33
22.74
14.22
Boc
N
OH
OH
C_6H_{13}
81
(^{13}C NMR)
(201 M*Hz*, $CDCl_3$)
f1 (ppm)

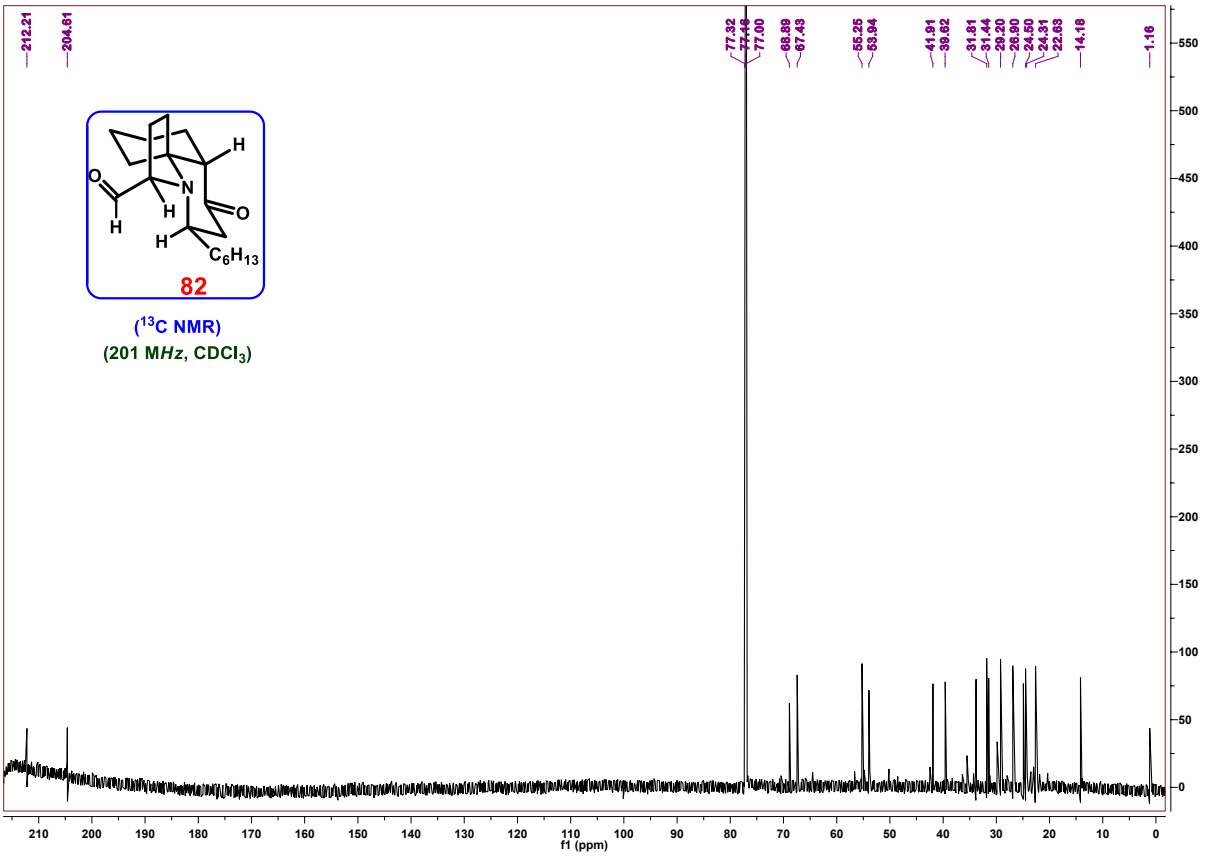

Boc
N
OH
OH
C_6H_{13}
81
(DEPT 135)
(201 M*Hz*, $CDCl_3$)

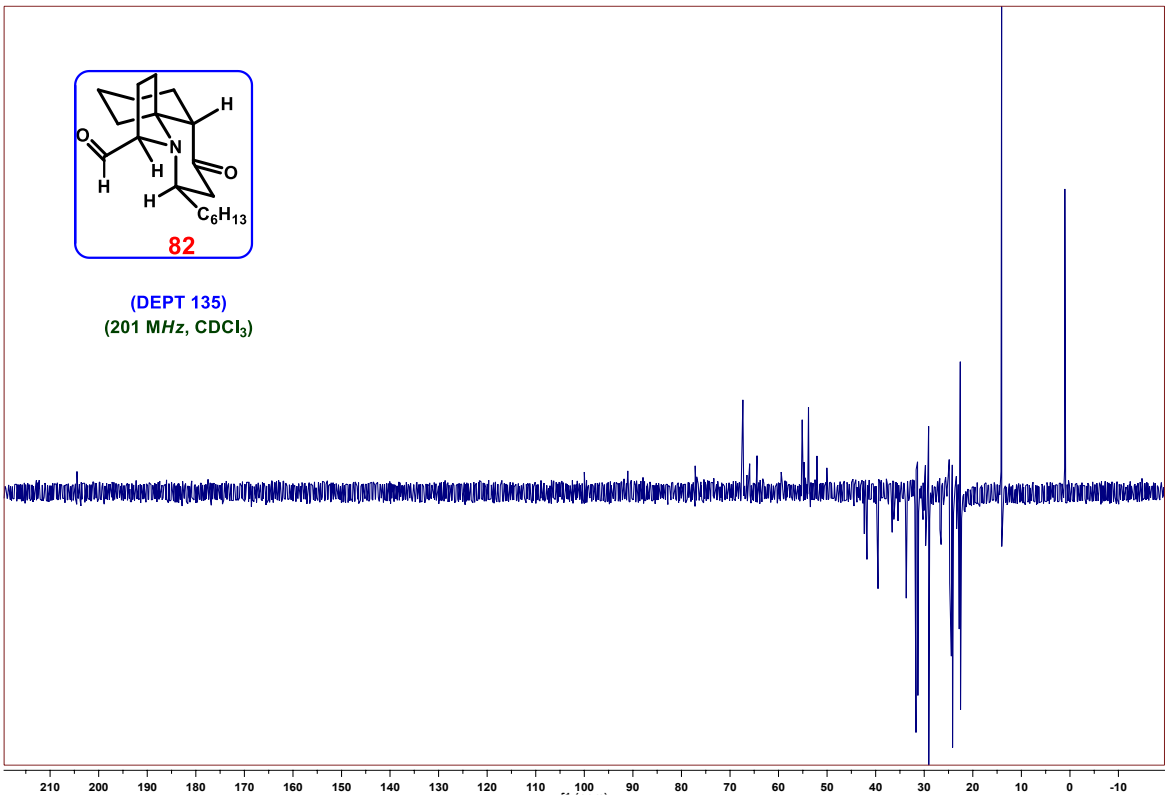

8.49
8.41
6.90
6.88
6.19
6.17
4.03
2.67
2.50
2.17
1.83
1.73
1.60
1.52
1.44
1.31
0.90
NBoc
C_6H_{13}
84
(^{1}H NMR)
(800 MHz, $CDCl_3$)
0.11
0.78
1.00
1.07
1.16
1.09
1.15
2.64
1.20
6.87
2.15
1.75
10.86
12.71
3.03
f1 (ppm)

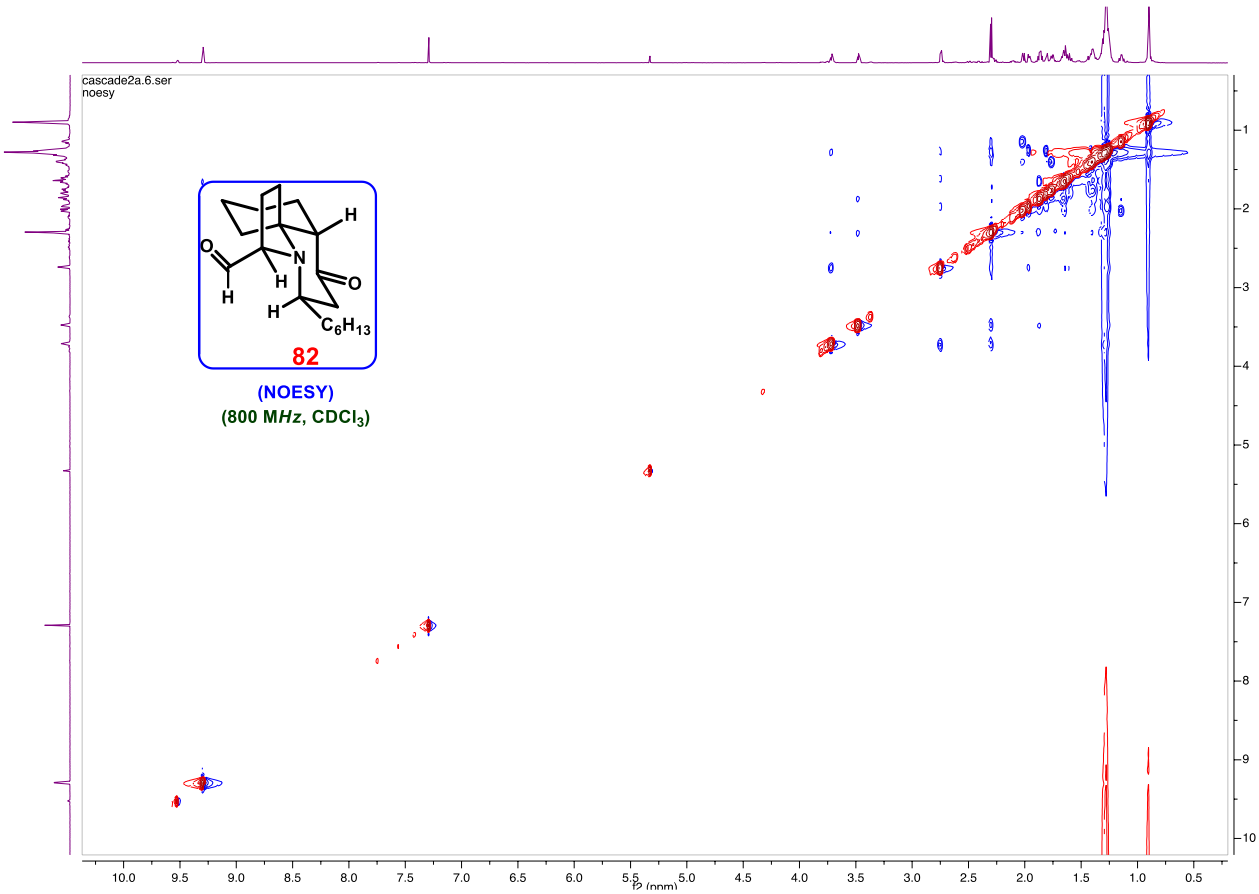

203.62
200.20
152.97
147.35
130.39
80.72
77.16
77.00
69.31
67.49
50.45
38.67
31.72
29.12
28.45
28.09
23.93
22.67
14.17
NBoc
C_6H_{13}
84
(^{13}C NMR)
(201 MHz, $CDCl_3$)
f1 (ppm)


O
NBoc
O
H
C_6H_{13}
84
(DEPT 135)
(201 MHz, $CDCl_3$)
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
f1 (ppm)

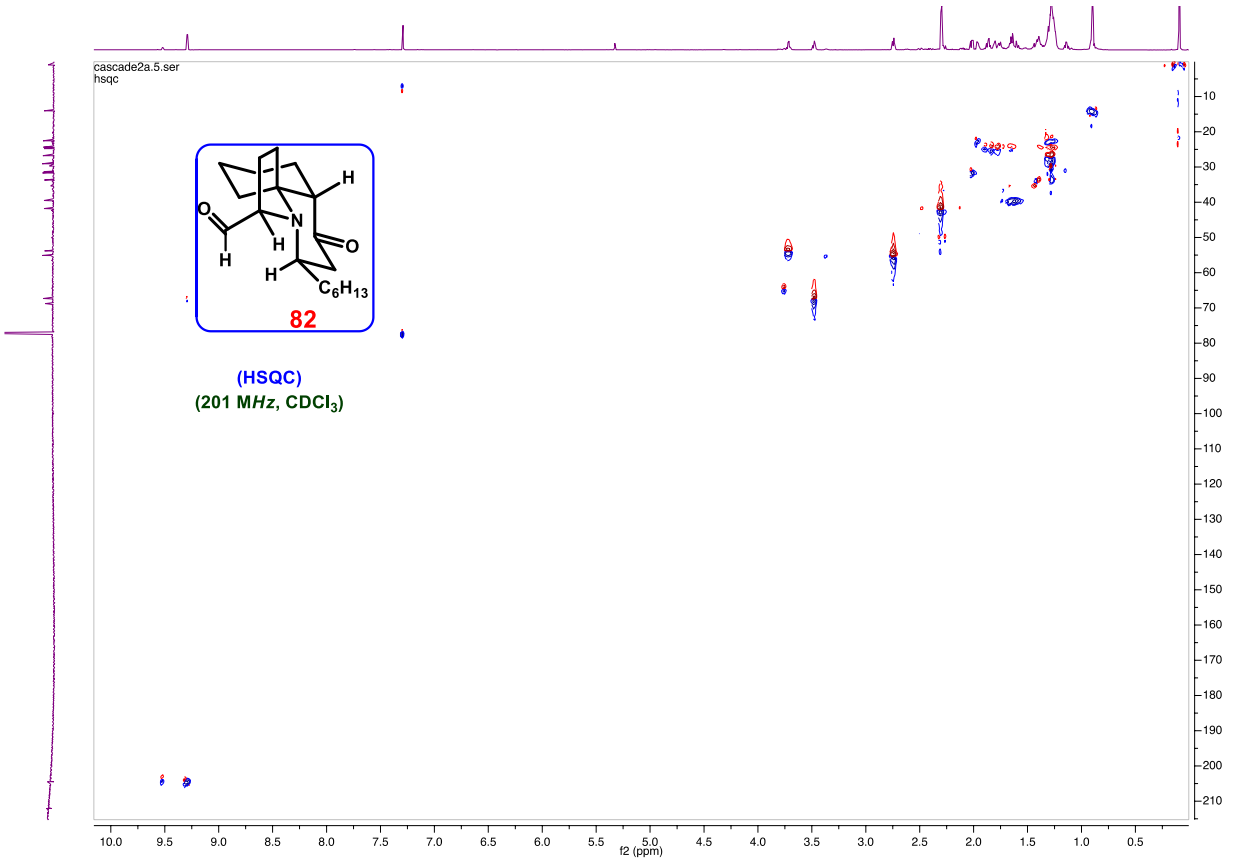

9.49
9.26
9.26
7.26
5.30
3.69
3.66
3.45
3.44
3.44
2.27
1.83
1.77
1.64
1.57
1.36
1.25
0.88
0.87
0.86
0.06
H
O
N
H
O
H
H
C_6H_{13}
82
(^{1}H NMR)
(800 MHz, $CDCl_3$)
0.06
0.74
1.07
1.00
1.06
2.39
1.08
4.32
3.22
13.64
1.21
3.61
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)
9000
8000
7000
6000
5000
4000
3000
2000
1000
0


212.21
204.61
77.32
77.16
77.00
68.89
67.43
55.25
53.94
41.91
39.62
31.81
31.44
29.20
26.90
24.50
24.31
22.63
14.18
1.16
O
H
N
H
H
O
H
C6H13
82
(13C NMR)
(201 MHz, CDCl3)
f1 (ppm)

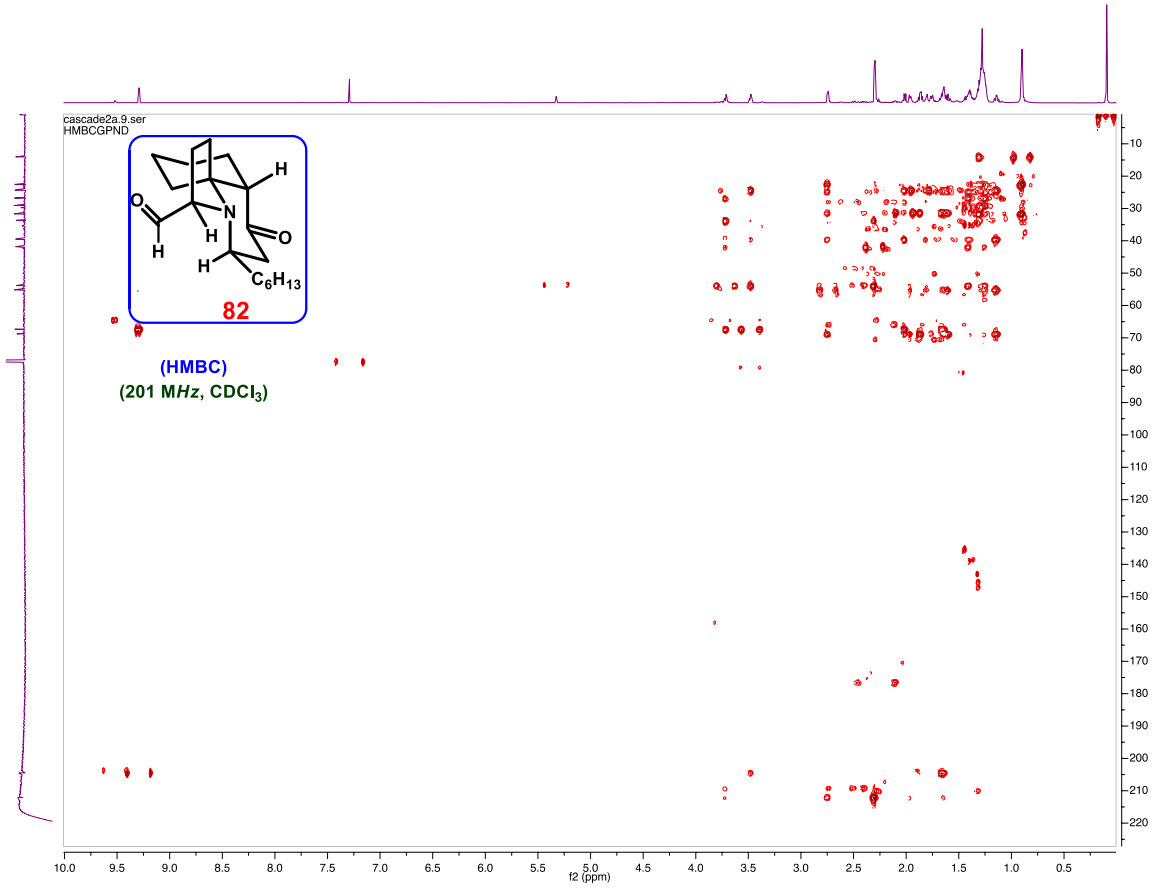

O
H
N
H
H
O
H
C6H13
82
(DEPT 135)
(201 MHz, CDCl3)

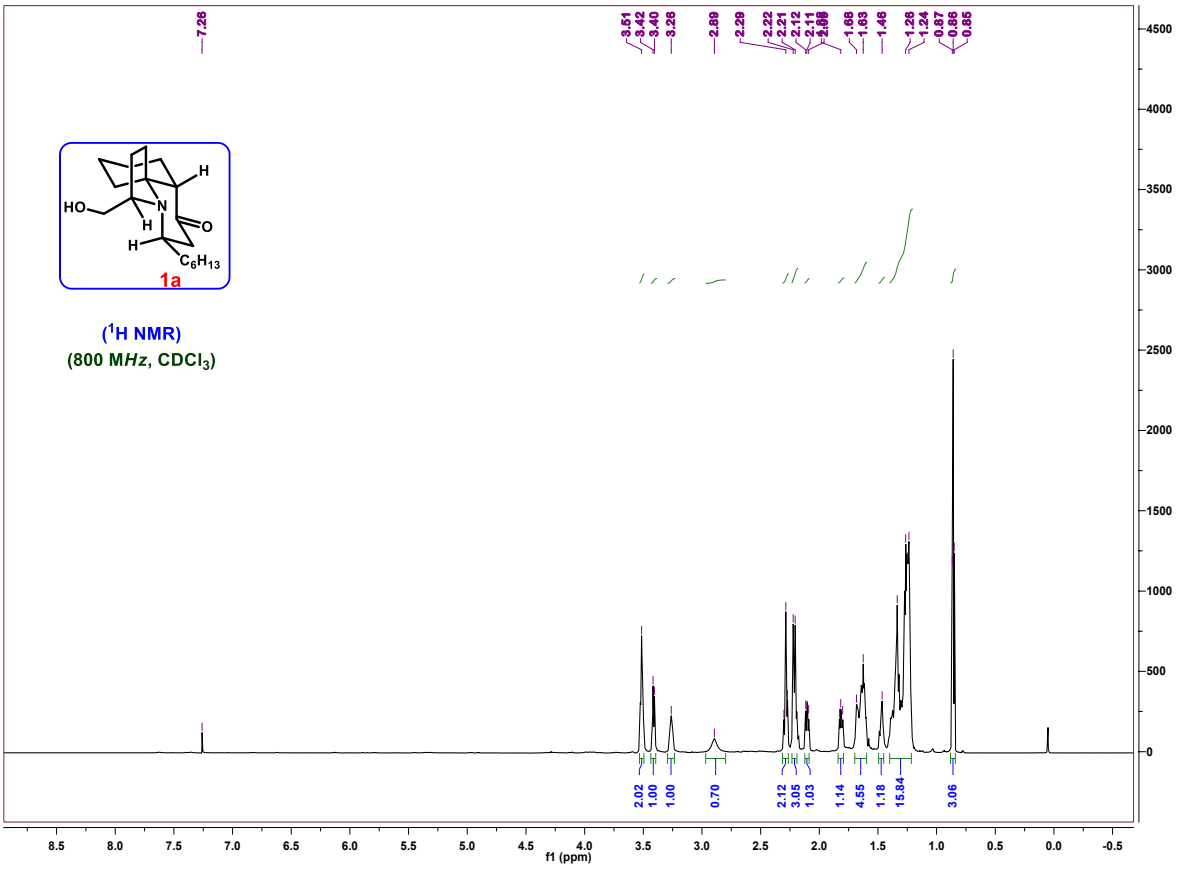


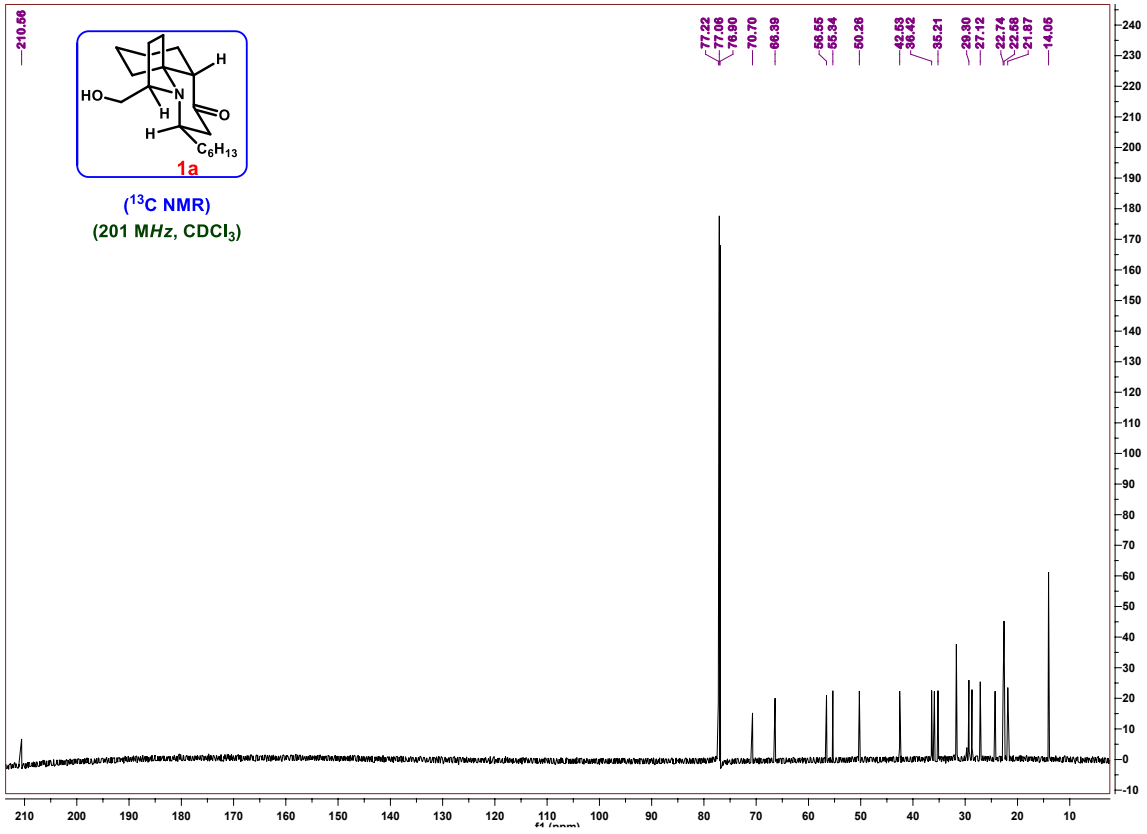
(NOESY)
(800 MHz, $CDCl_3$)



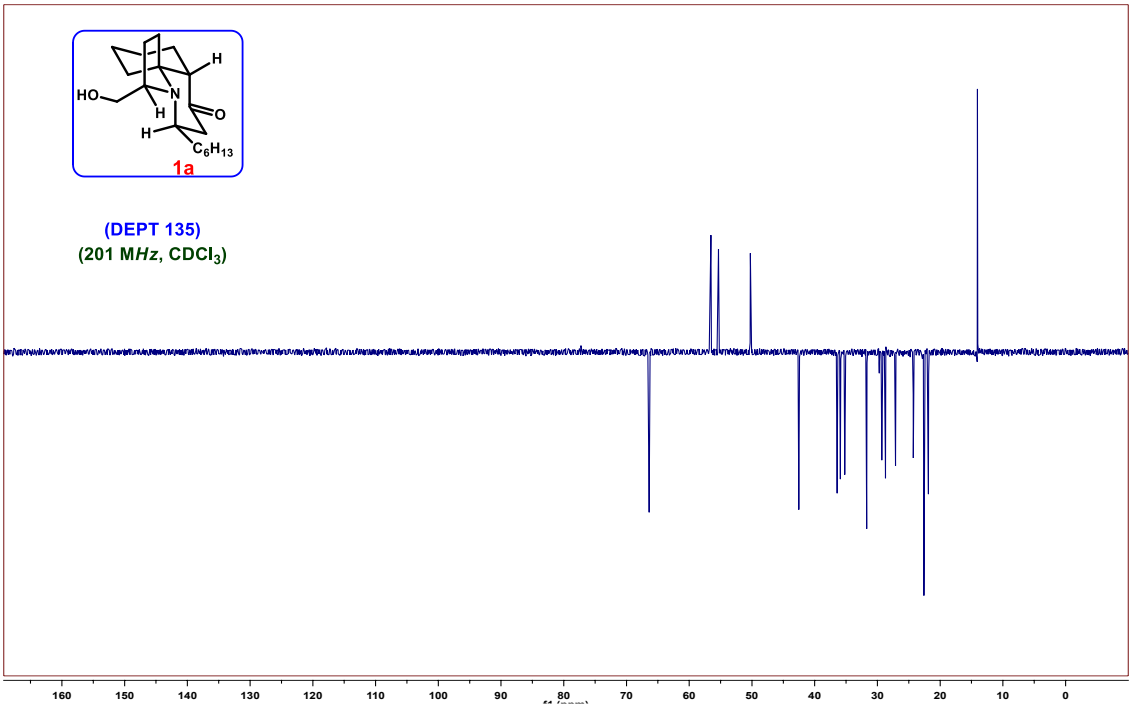
(HSQC)
(201 MHz, $CDCl_3$)


cascade2a.9.ser
HMBCGPND
82
(HMBC)
(201 MHz, CDCl3)
f2 (ppm)

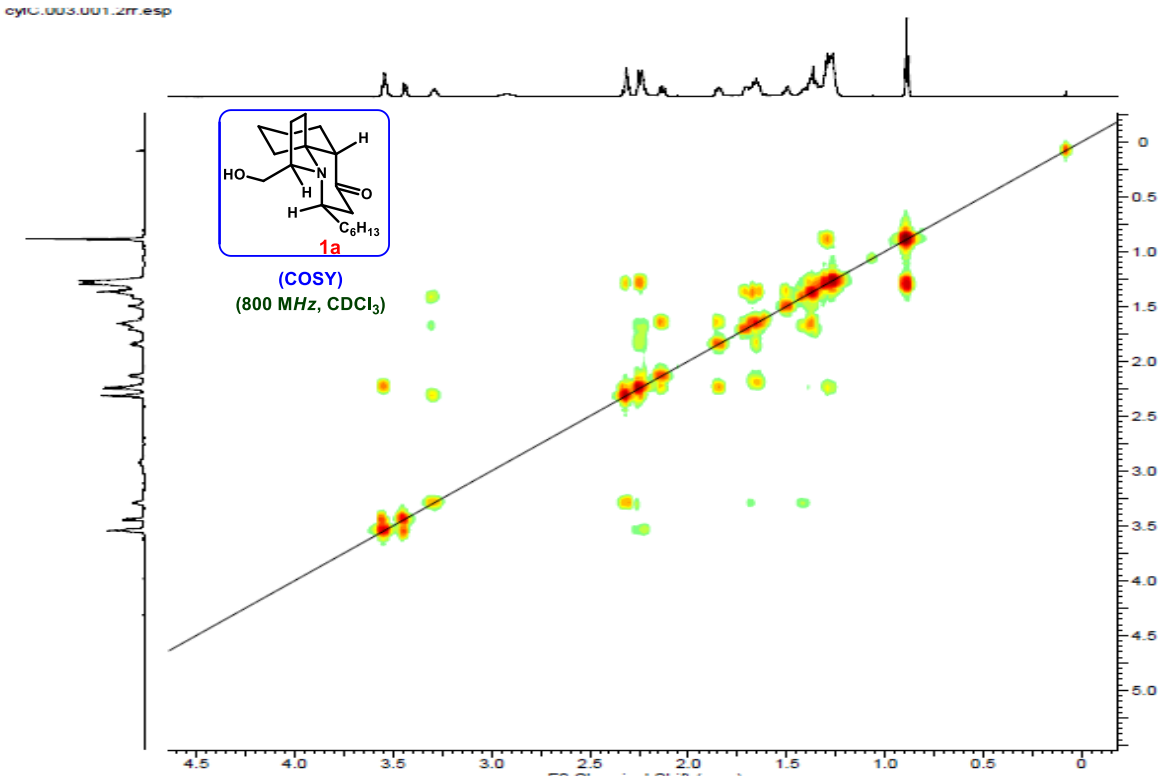

1a
(1H NMR)
(800 MHz, CDCl3)
f1 (ppm)

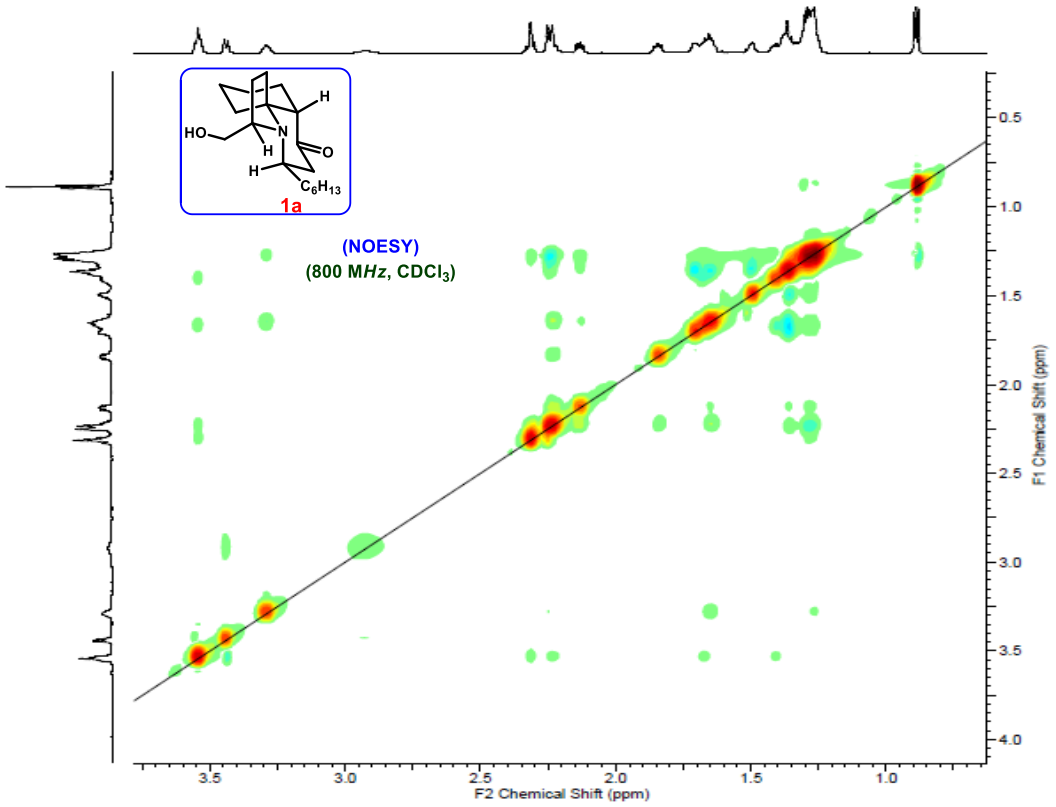


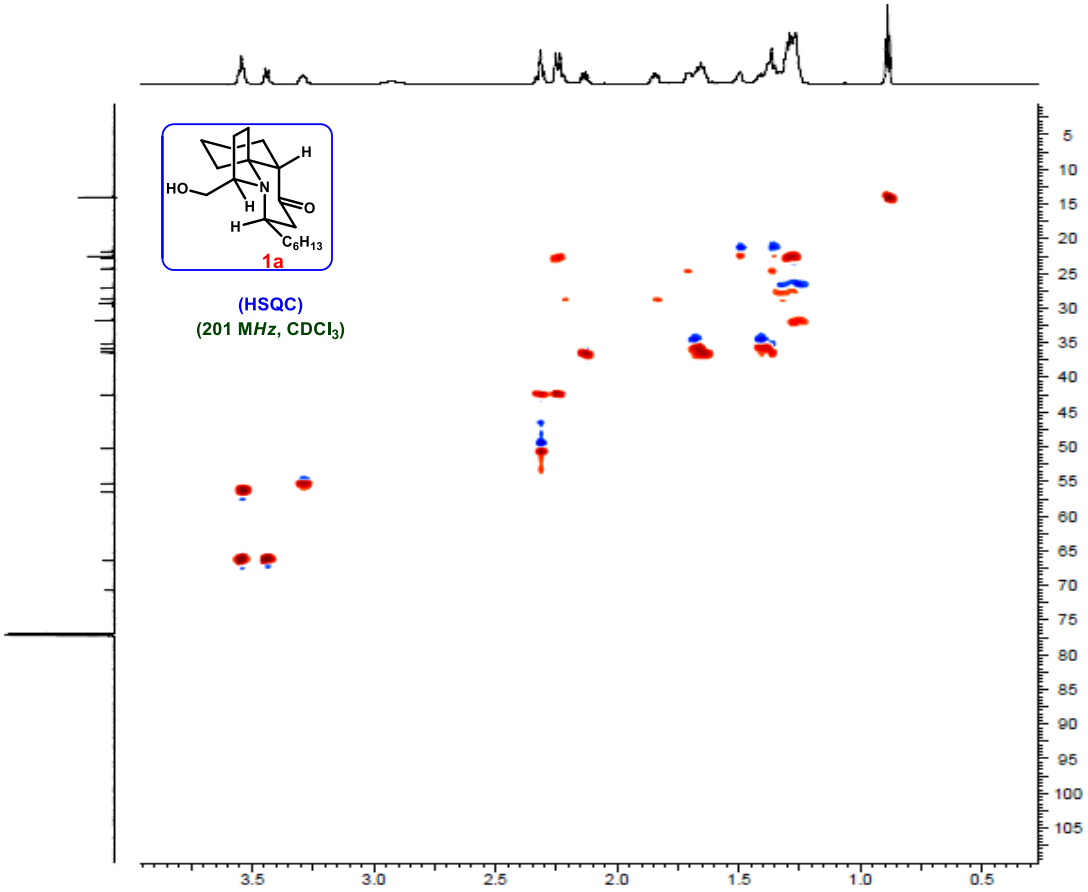
(^{13}C NMR)
(201 M*Hz*, $CDCl_3$)

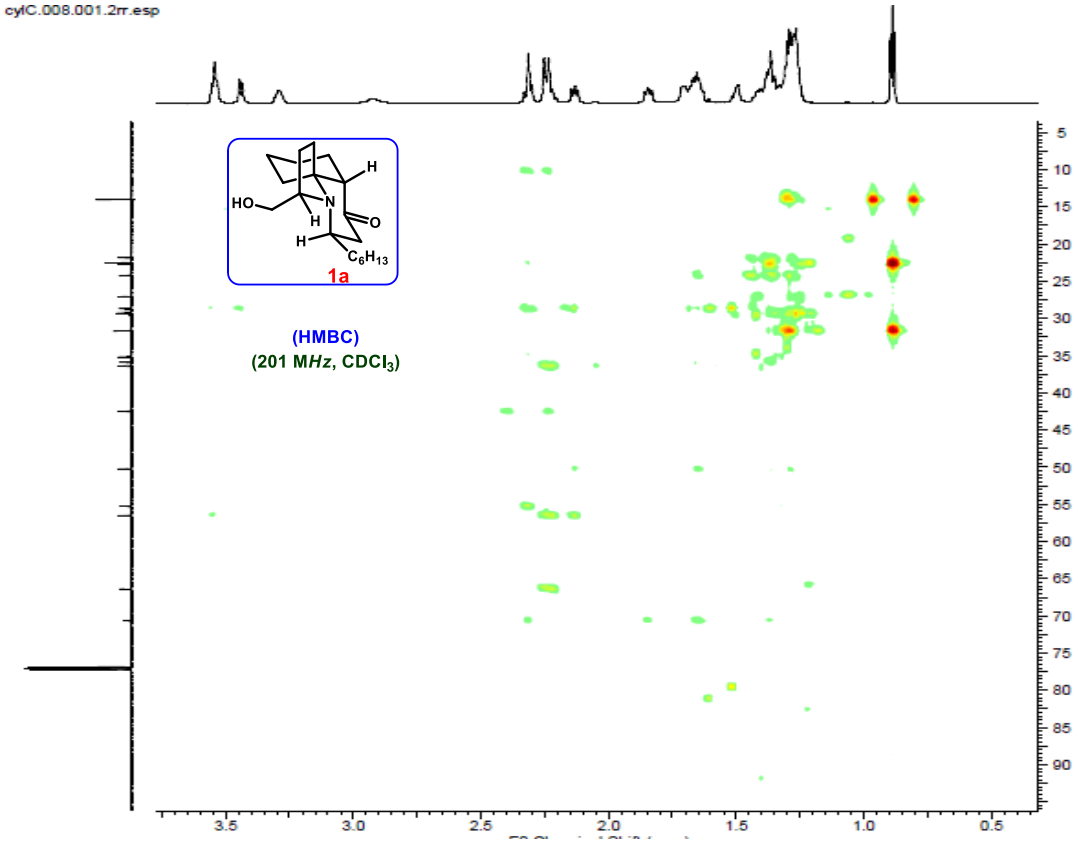


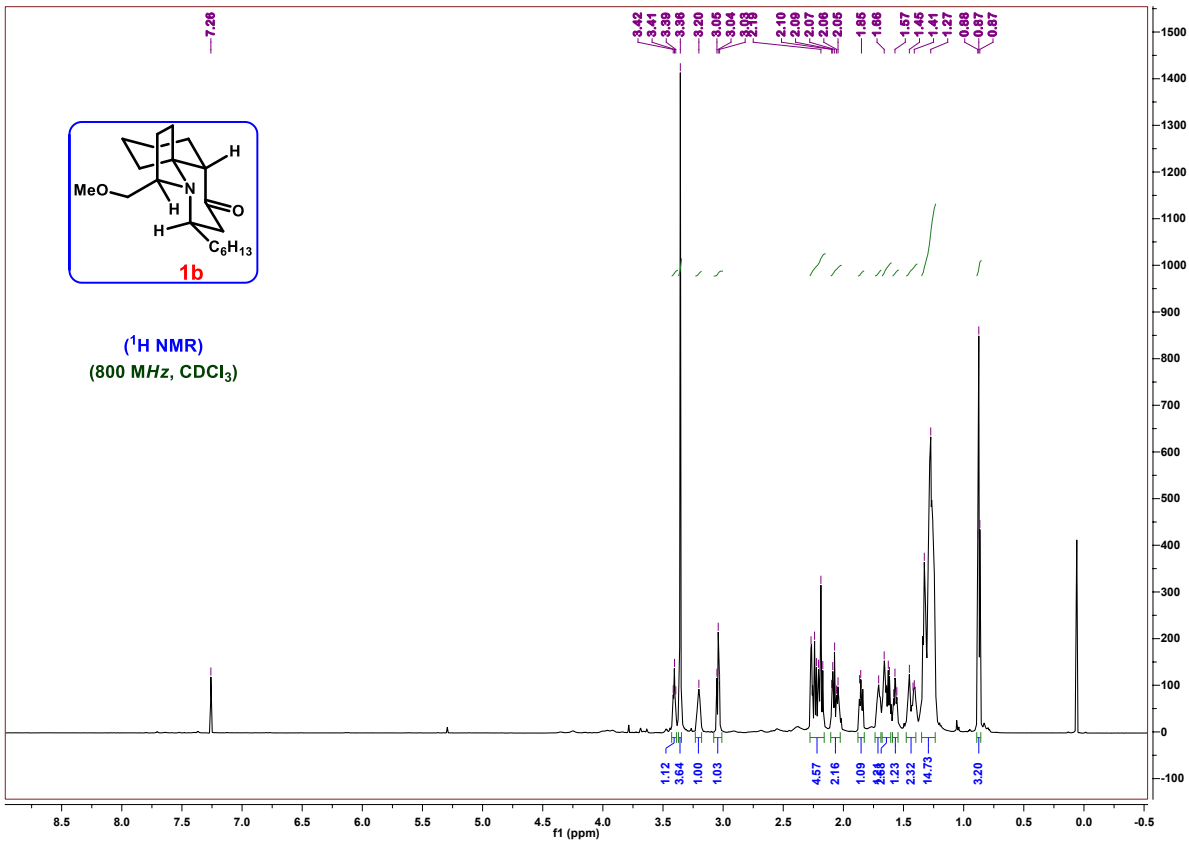
(DEPT 135)
(201 M*Hz*, $CDCl_3$)

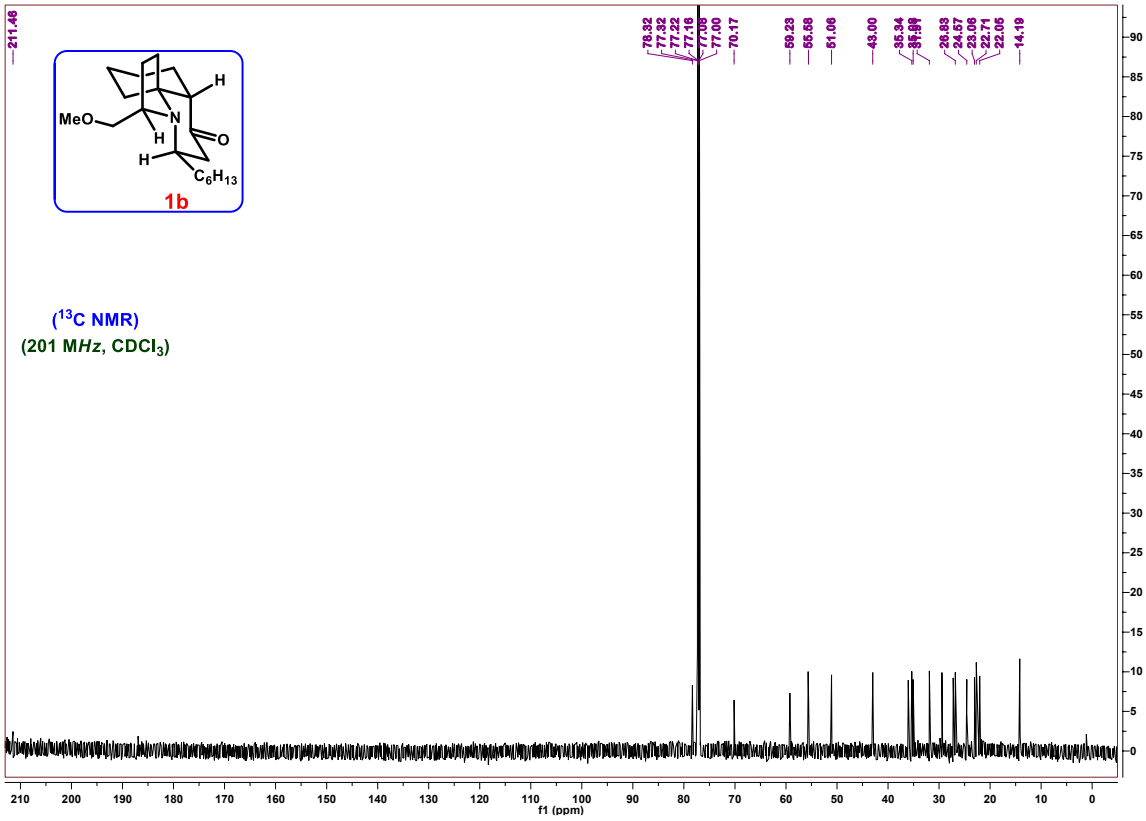

HO
N
H
H
O
C_6H_{13}
1a
(COSY)
(800 MHz, $CDCl_3$)

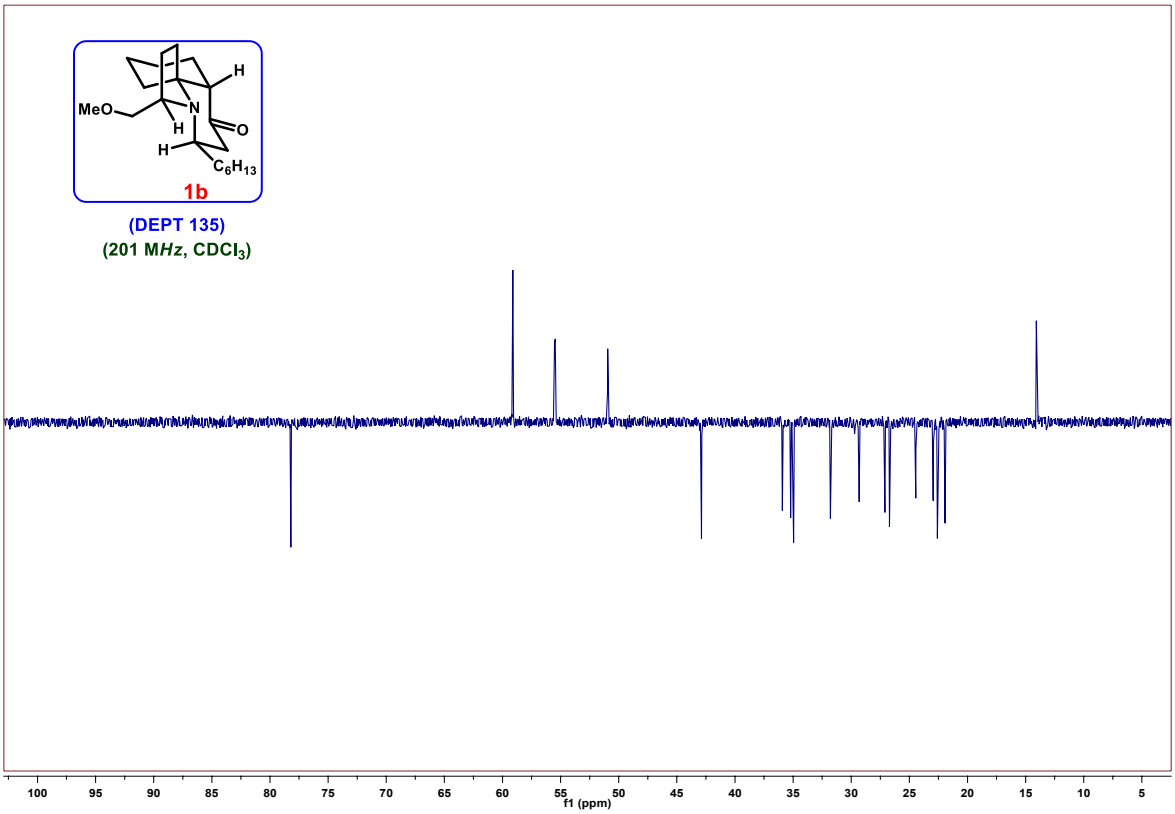

HO
N
H
H
O
C_6H_{13}
1a
(NOESY)
(800 MHz, $CDCl_3$)
F2 Chemical Shift (ppm)
F1 Chemical Shift (ppm)

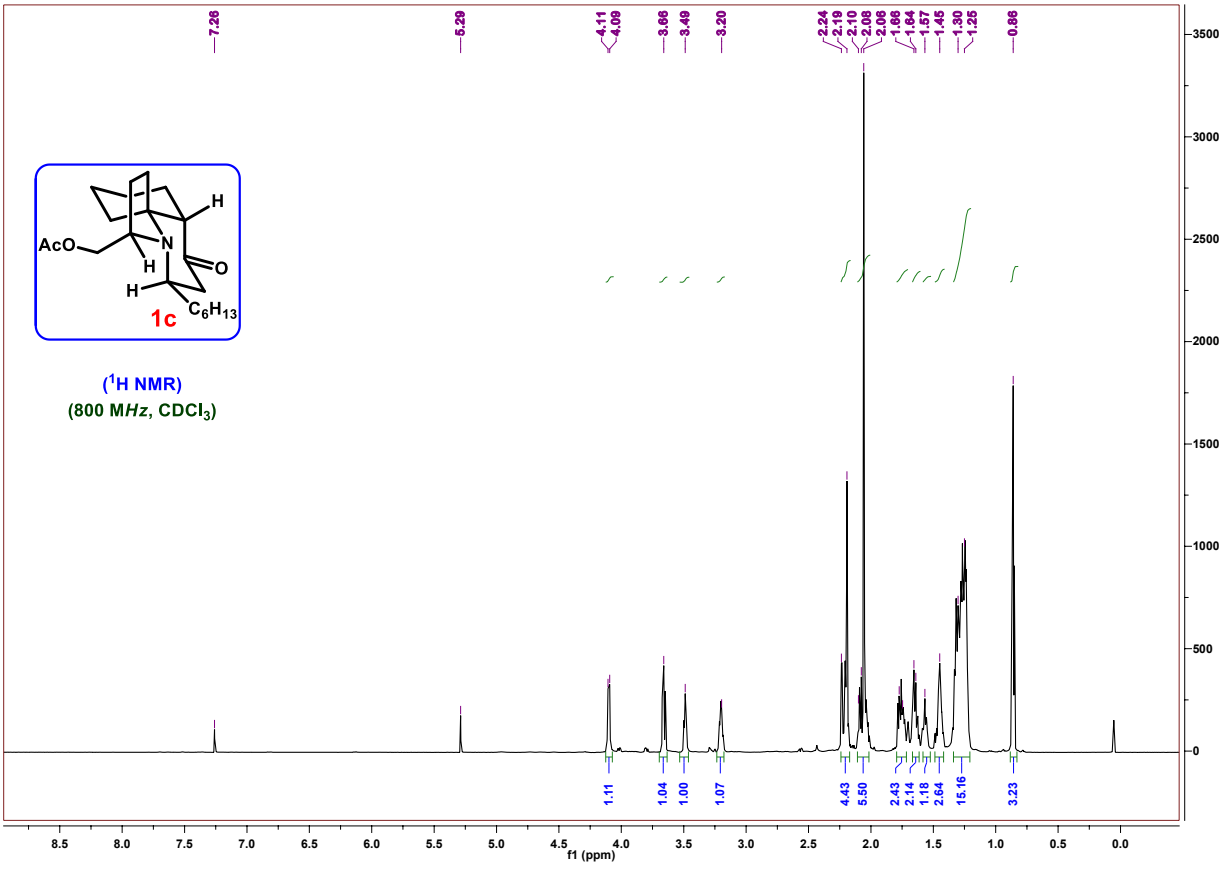

HO
H
N
H
H
O
C_6H_{13}
1a
(HSQC)
(201 MHz, $CDCl_3$)
5
10
15
20
25
30
35
40
45
50
55
60
65
70
75
80
85
90
95
100
105
3.5
3.0
2.5
2.0
1.5
1.0
0.5

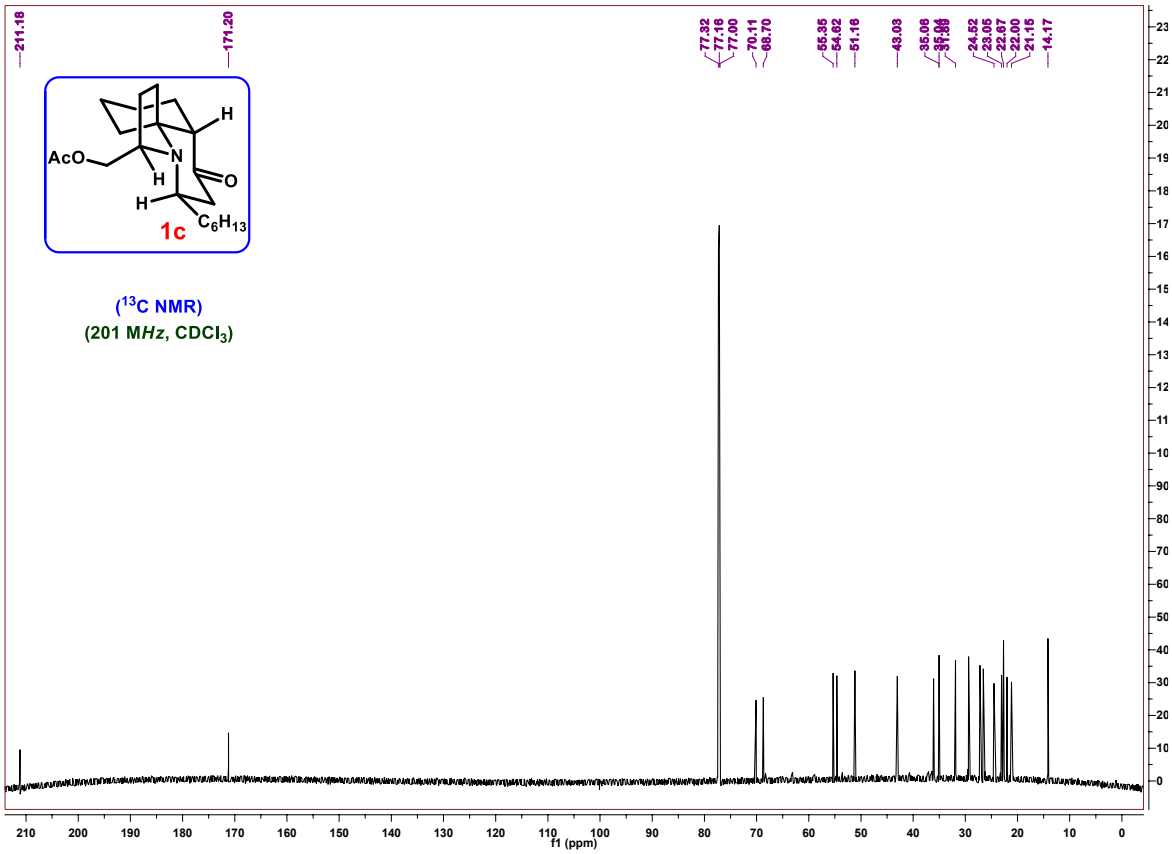

cylC.008.001.2rr.esp
HO
H
N
H
H
O
C_6H_{13}
1a
(HMBC)
(201 MHz, $CDCl_3$)
5
10
15
20
25
30
35
40
45
50
55
60
65
70
75
80
85
90
3.5
3.0
2.5
2.0
1.5
1.0
0.5


7.26
3.42
3.41
3.39
3.36
3.20
3.05
3.04
2.10
2.09
2.07
2.06
2.05
1.85
1.66
1.57
1.45
1.41
1.27
0.88
0.87
0.87
MeO
N
H
H
O
C_6H_{13}
1b
(^{1}H NMR)
(800 M*Hz*, $CDCl_3$)
1.12
3.64
1.00
1.03
4.57
2.16
1.09
1.23
2.32
14.73
3.20
f1 (ppm)

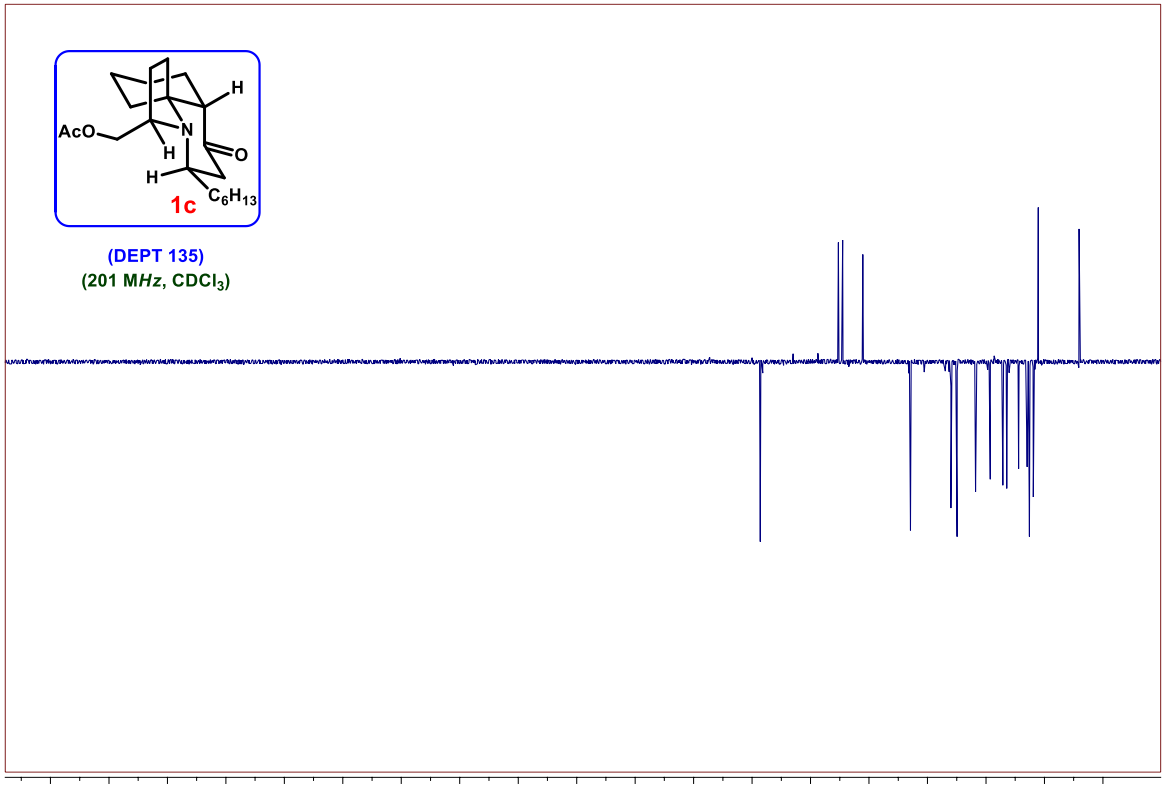

211.46
76.32
77.32
77.22
77.16
77.08
77.00
70.17
59.23
55.58
51.06
43.00
35.34
28.83
24.57
23.06
22.71
22.05
14.19
MeO
N
H
H
O
C_6H_{13}
1b
(^{13}C NMR)
(201 M*Hz*, $CDCl_3$)
f1 (ppm)


MeO
N
H
H
O
H
C_6H_{13}
1b
(DEPT 135)
(201 MHz, $CDCl_3$)
f1 (ppm)


7.26
5.29
4.11
4.09
3.66
3.49
3.20
2.24
2.19
2.10
2.08
2.06
1.66
1.64
1.57
1.45
1.30
1.25
0.86
AcO
N
H
H
O
H
C_6H_{13}
1c
(^{1}H NMR)
(800 MHz, $CDCl_3$)
1.11
1.04
1.00
1.07
4.43
5.50
2.43
2.14
1.18
2.64
15.16
3.23
f1 (ppm)



(^{13}C NMR)
(201 M*Hz*, $CDCl_3$)



(DEPT 135)
(201 M*Hz*, $CDCl_3$)

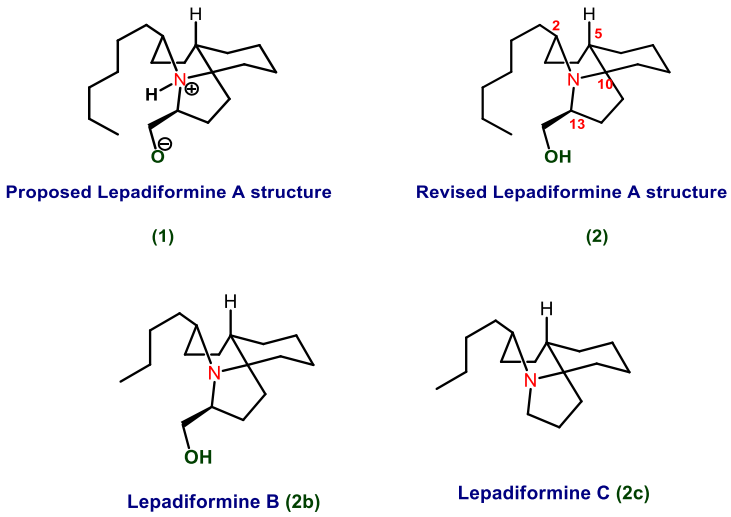
Chapter 3:-

“*Stereoselective Total Synthesis of Lepadiformine A*.”

Section -3.1: Introduction of Lepadiformine family of alkaloids.

Lepadiformine, isolated from the extracts of the marine tunicate *Clavelina lepadiformis* by Biard et al.,[1-3] was originally proposed to possess an unusual zwitterionic amino alcohol structure **1** (Figure 1) based on extensive NMR experiments. However, later Kibayashi's group corrected its structure as **2** by a racemic total synthesis.[4] Since, absolute stereochemistry of **2** was not established, Weinreb's et al. assigned its absolute configuration as 2*R*, 5*S*, 10*S*, and 13*S*[5b] (Figure 1) by synthesis. Subsequently two other alkaloids belonging to same class **2b-2c** were also isolated from *Clavelina lepadiformis* off the coast of Tunisia and *Clavelina moluccensis* off the coast of Djibouti,[2] respectively.

Figure 1: Classification of Lepadiformine family of alkaloids



Alkaloids **2** and **2b** have shown inhibitory effects on the inward rectifying potassium current which causes bradycardia, an effect seen in antiarrhythmic agents.[2, 3] It was also shown that **2** exhibits moderate in *vitro* activity against HT29 (IC_{50} = 0.75 *µg/mL*), KB (IC_{50} = 9.20 *µg/mL*), P388 (IC_{50} = 3.10 *µg/mL*), and NSCLC-N6 (IC_{50} = 6.10 *µg/mL*) cells. Recent studies show that **2** is also very active in the cardiovascular system in *vivo* and indicates that it may have antiarrhythmic properties.[3]

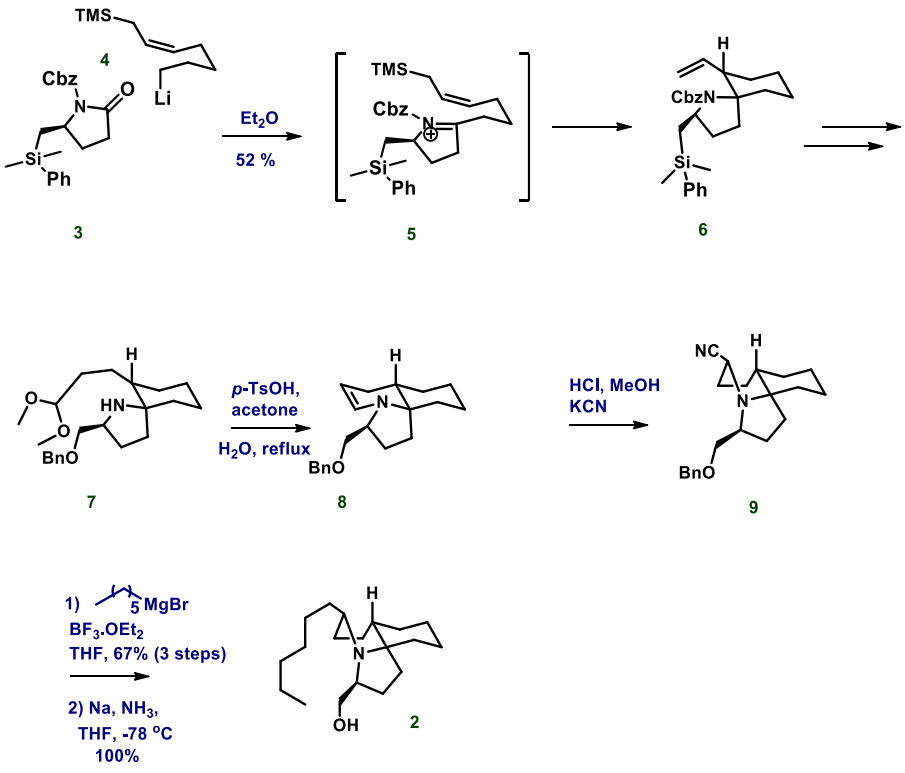
Section -3.2: Synthetic reports of Lepadiformine (2).

Several synthetic approaches have been developed to synthesize cyclindricine C both in racemic as well as in optically active form. However, only synthesis of **2** in optically active form will be discussed to keep the discussion to a finite perspective.

Weinreb 's total synthesis of (–)-Lepadiformine (2): [(a) *J. Org. Chem.* **2002**, *67*, 4337. (b) *Org. Lett.* **2001**, *3*, 3507.][5]

First asymmetric total synthesis of **2** was reported by an intramolecular cyclization of in situ generated N-acyliminium ion **5** with allyl silane to generate aza-spirocycle **6** as a key step [5b] (Scheme 1).

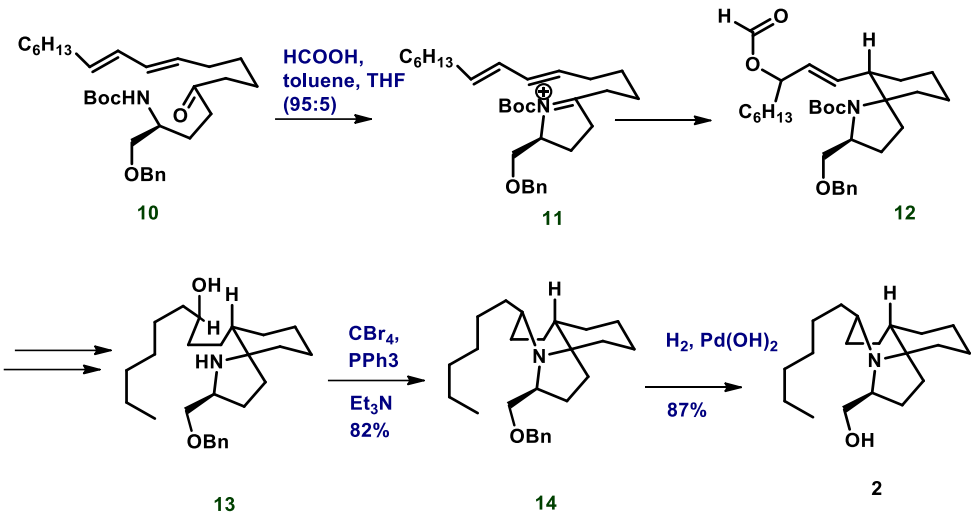
Scheme 1: Weinreb's total synthesis of (–)- Lepadiformine



Subsequent steps as shown in Scheme 1 produced **2** in total 15 steps and 13% yield.

Kibayashi approach: *(Angew. Chem. Int. Ed.* **2002**, 41, 3017.) [6, 7a]

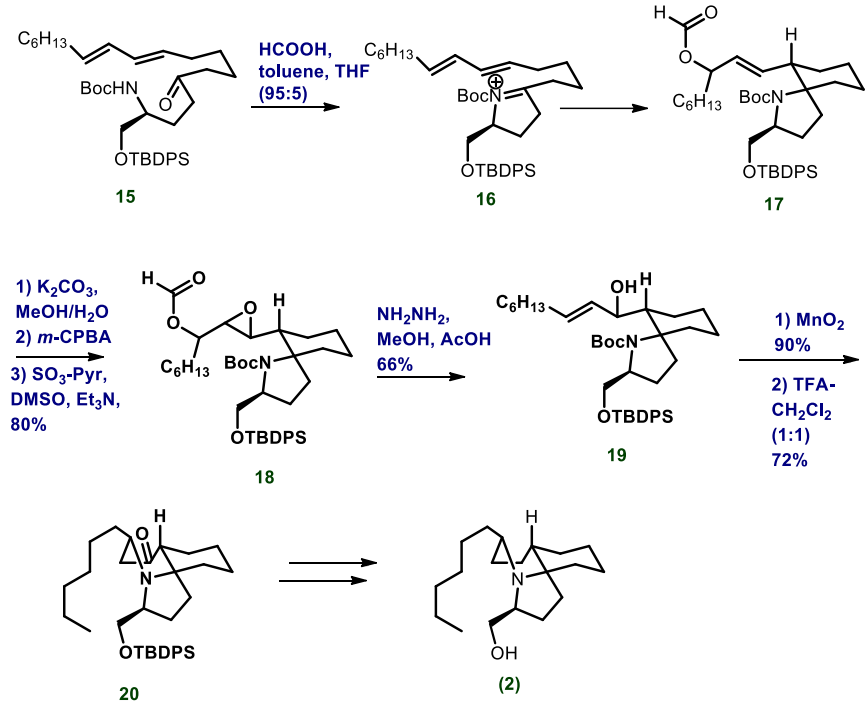
Scheme 2: Kibayashi's total synthesis of (–)- Lepadiformine



The key step in this synthesis employed formic acid-induced intramolecular conjugate azaspirocyclization of **11** to obtain 1-azaspirocyclane framework **12** which was diversified to cylindricine, lapdiformine and fasicularine alkaloids [7a] as shown in Scheme 2.

Hsung's approach to (–)-Lepadiformine :- (*Org. Lett.* **2004**, 6, 3989.)[8a, b]

Scheme 3: Hsung's total synthesis of (–)- Lepadiformine

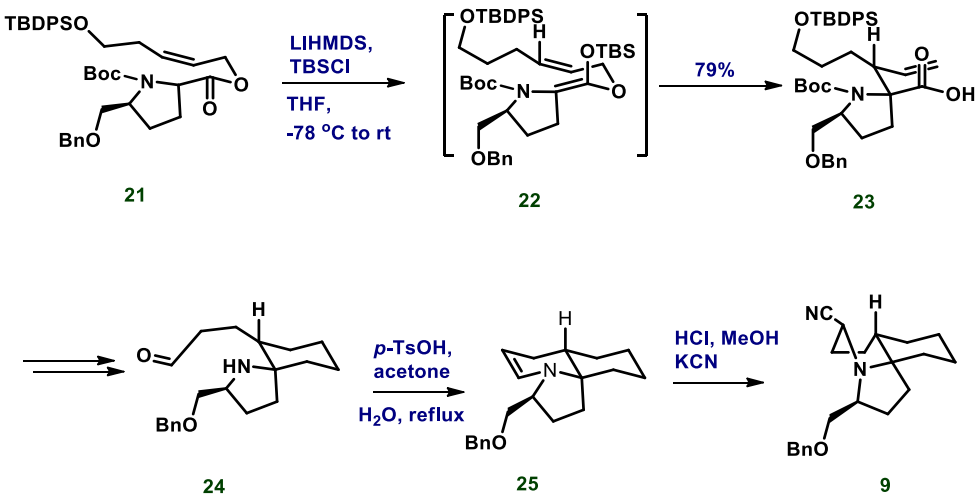


Identical strategy, as shown in Scheme 2, has been utilized for azaspirocyclization reaction [8a, b] by these authors to construct **17.** Further transformation of **17** → **19** via Wharton rearrangement[8c, d] of epoxide **18** was used as a key step in the synthesis. Oxidation of **18** followed by intramolecular Mannich reaction to build intricate tricyclic framework **20** to complete the total synthesis of **2** (Scheme 3).

Kim's formal synthesis of (–)-Lepadiformine: *(Org. Lett*. **2006**, *8*, 745.)[9]

A formal synthesis [9] of (–)-**2** (Scheme 4) was achieved (15 steps) by synthesizing Weinreb's nitrile[5] intermediate **9** by the Claisen- rearrangement of **22** to furnish **23** which was forwarded for further transformations as shown in Scheme 4.

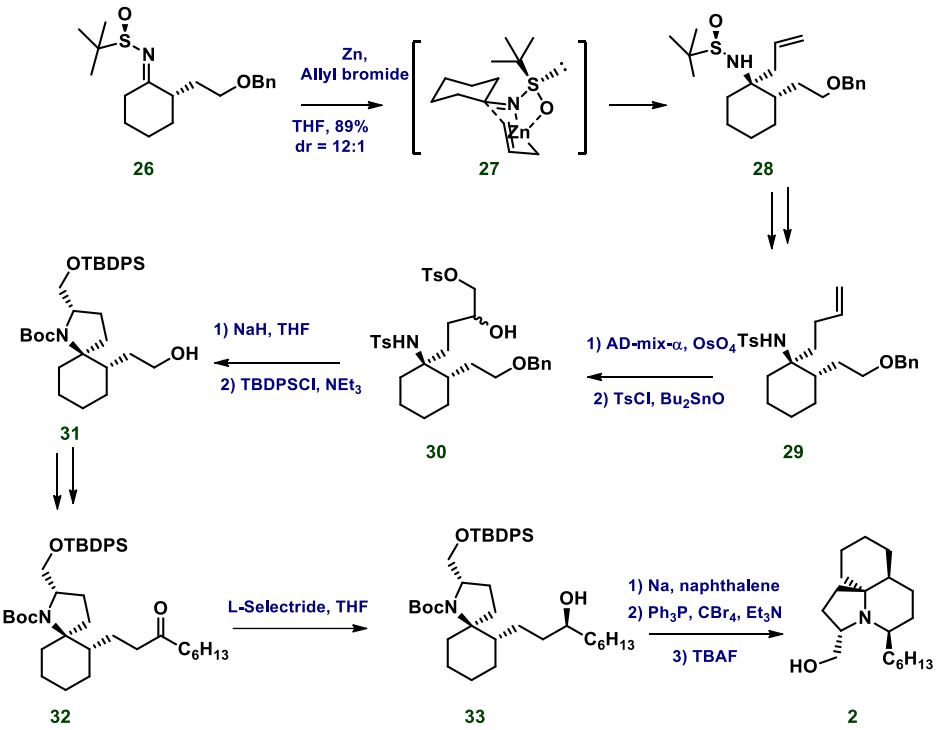
Scheme 4: Kim's formal synthesis of (–)- Lepadiformine



Zhao's synthesis of (–)-Lepadiformine: *(Eur. J. Org. Chem*. **2010**, 1660.)[10]

This group accomplished the synthesis of **2** in 20 steps involving Zn-mediated allylation of chiral aliphatic *N-tert*butyl sulfinyl ketimine (**26)** to construct the key precursor **28** which by following a series of reactions as shown in Scheme 5 delivered **2** in 5 % overall yield. By using intermediate **32**, this group has also accomplished the synthesis of fasicularin.

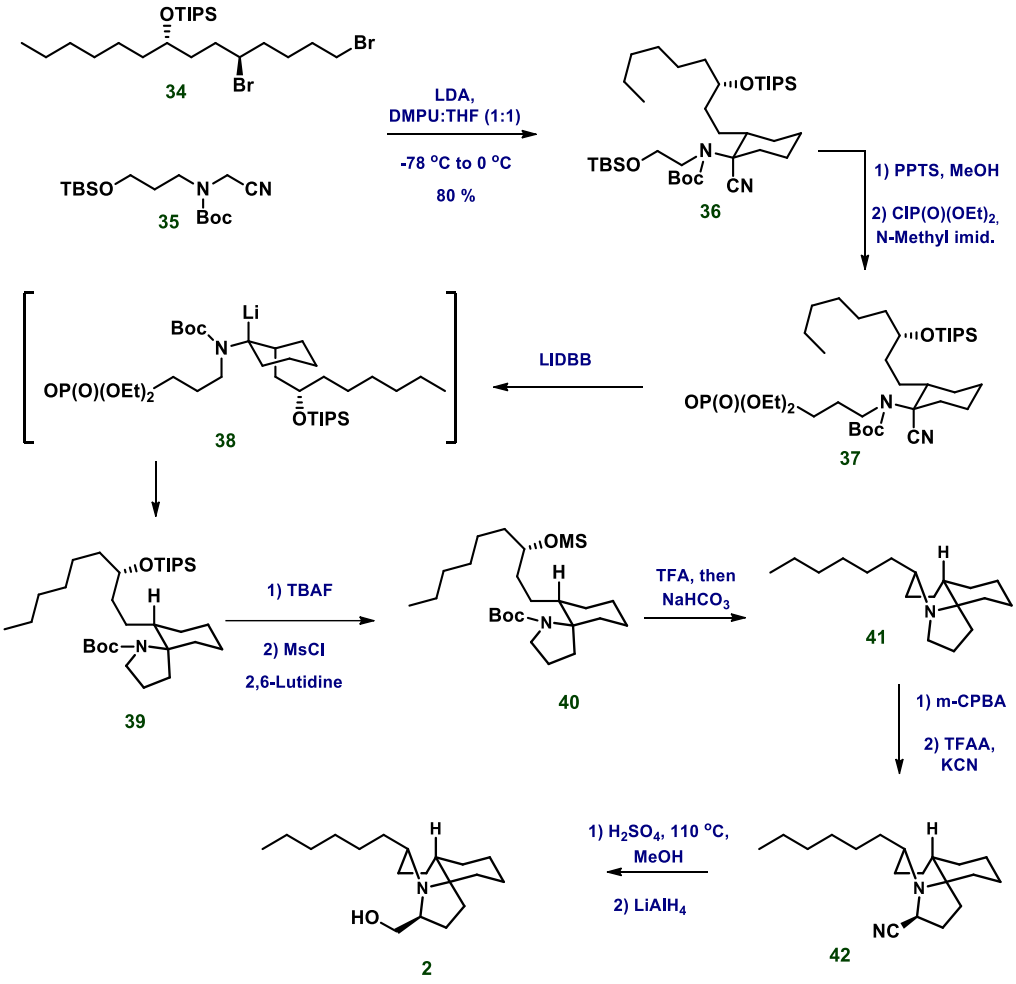
Scheme 5: Zhao's total synthesis of (–)- Lepadiformine



Rychnovsky's approach: (*J. Org. Chem.* **2012**, *77*, 3390.)[11a]

Rychnovsky and co-workers used reductive cyclization of **38** to obtain 1-azaspirocyclane framework **39** which was transformed further to 41, as an advanced precursor, to carry out Polonovski–Potier[11b] reaction to obtain **42** for synthesizing **2b-2c** as shown in Scheme 6.

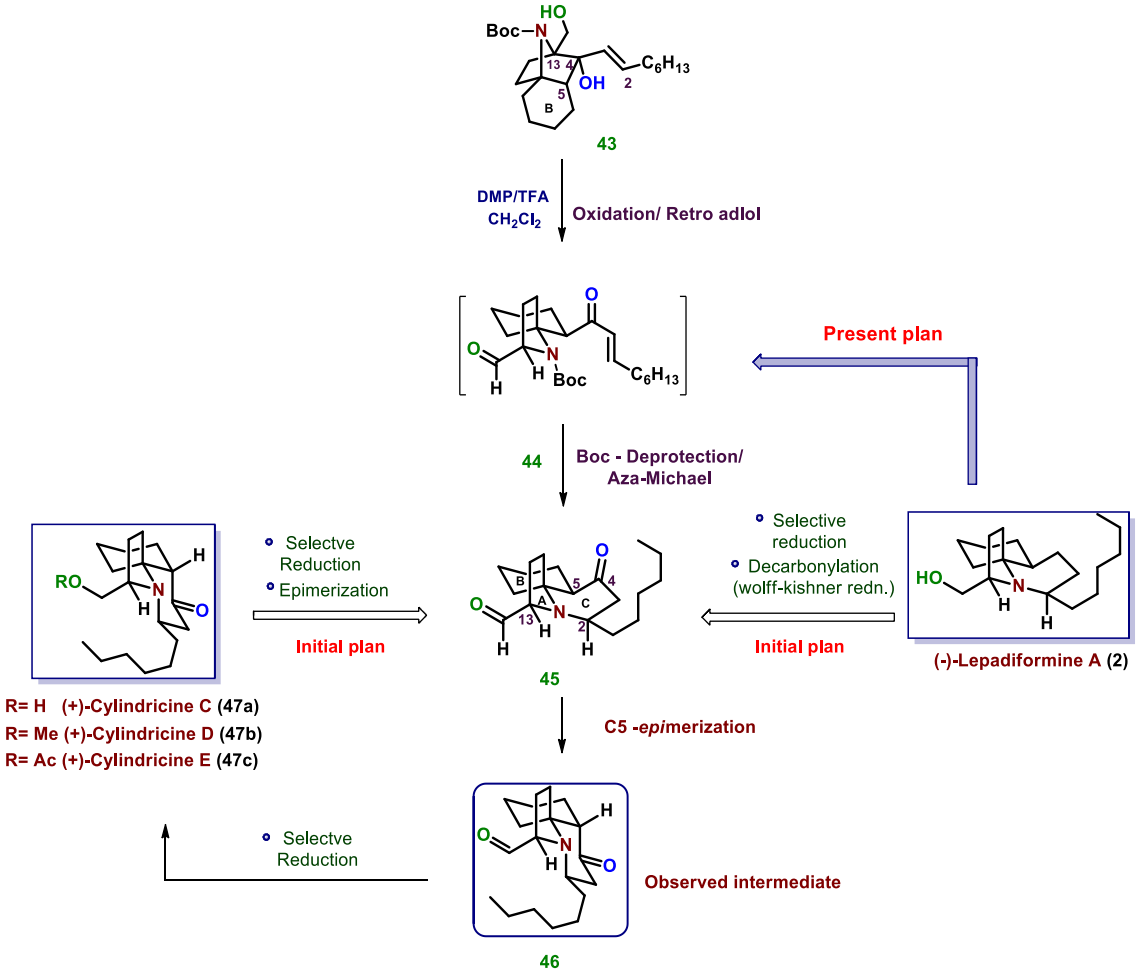
Scheme 6: Rychnovsky 's total synthesis of (–)- Lepadiformine



Section -3.3: Total synthesis of (–)-Lepadiformine A (2):

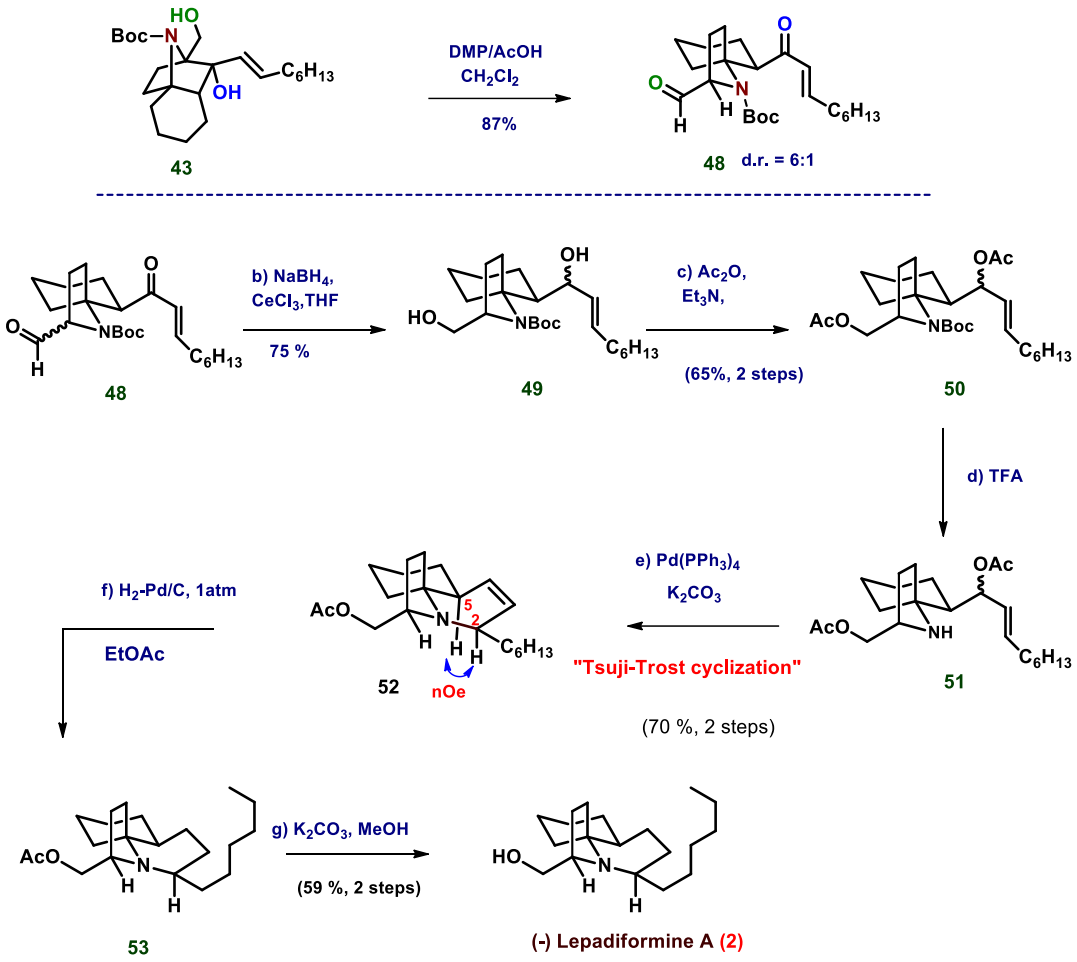
It was planned at the design stage of the synthesis (Scheme 7) that cascade rearrangement of **43** would stop at **45** which will be diversified in to both **47** by epimerization at C_5 as well as to **2** by selective reduction followed by decarbonylation, respectively. However, present reaction indicated that cascade did not terminate at **45** instead led to C_5 epimerization producing **46**. This observation suggested that rearrangement of **46** is governed by energetically more favorable chair-chair conformation of **46** rather than the chair-boat conformation of **45**.

Scheme 7: Modified design plan for the synthesis of Lepadiformine A



After successfully accomplishing the total synthesis of **47a-c**, as described in the preceding chapter, we proceeded to complete the total synthesis of **2** by interrupting the cascade sequence at **44** to stop C_5 epimerization. To interrupt cascade sequence in order to stop C5 epimerization, we envisaged to carry out reaction in acetic acid, instead of TFA, which may not deprotect N-Boc functionality at the rearrangement step. To test this proposition, **43** (0.12 mmol) was subjected to Dess-Martin periodinane oxidation (DMP (0.14 mmol) in AcOH (0.12 mmol) in CH_2Cl_2 which furnished **48** (*d.r.* 6:1) in 87% yield) (Scheme 7). Success of the rearrangement to form **48** was confirmed by observing α, β-unsaturated carbonyl moiety at 1751 cm $^{-1}$ in the IR spectrum. In order to proceed further towards completing the synthesis of the target, **48** (Scheme 8) was reduced by $NaBH_4$ (0.65 mmol) in the presence of $CeCl_3.7H_2O$ (0.216 mmol) to afford **49** in 75% yield.

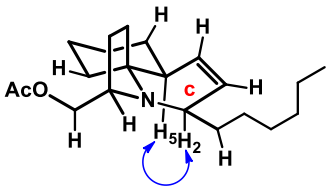
Scheme 8: Total synthesis of Lepadiformine A (2)



Absence of both aldehydic as well as α, β-unsaturated carbonyl moiety band in the IR spectrum confirmed the reduction. Hydroxyl groups of **49** (0.13 mmol) were acetylated by stirring with acetic anhydride (0.59 mmol) in presence of Et_3N (0.6 mmol) and DMAP (0.013 mmol) to obtain **50** in 95% yield. N-Boc deprotection of **50** (trifluoroacetic acid, CH_2Cl_2, at 0 °C) gave free amine **51 (**95 %) which without purification was subjected to Tsuji-Trost cyclization using $Pd(PPh_3)_4$, (0.005 mmol) benzyltriethyl ammonium chloiride (0.01 mmol), potassium carbonate (0.3 mmol) in water:ethyl acetate (1:1) which gave **52** in 71% yield. Structural confirmation to the formation of **52** was made by observing olefinic protons at δ5.98 (dt, J=7.9, 3.5, 1H)

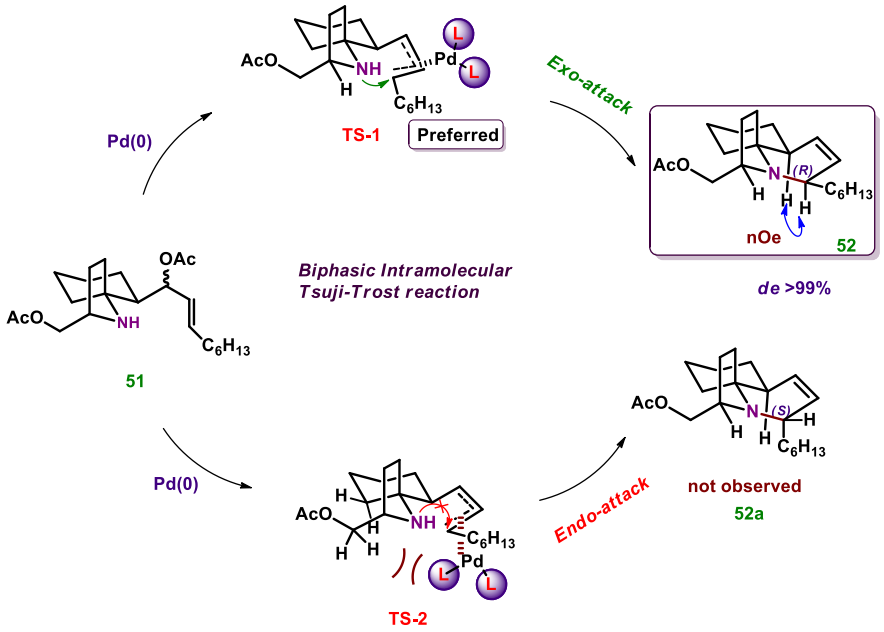
and 5.83 - 5.73 (m, 1H), respectively in the ^{1}H NMR spectrum which was further supported by the molecular ion peak $[M+H]^{+}$ at 334.2737. Stereochemistry between H2-H5 was established by observing NOESY correlation which also confirmed boat conformation for 'c' ring.

Figure 2: NOESY correlation of product 52.



52

Scheme 9: Selectivity at C2-position in Tsuji-Trost cyclization



Formation of **52** as a pure diastereomer with required stereochemistry at C2 position is supported through a more favourable TS-1 as shown in Scheme 9. The synthesis of (–)-**2** was completed by the hydrogenation of **52** ((Pd/C (10 wt %) -H_2, 1 atm) in EtOAc

(Scheme 8) followed by deacetylation (stirring with K_2CO_3, (1.5 mmol) MeOH, 67% yield). The spectral data of **2** {$[\alpha]_D^{22}$ = -15.1° (*c* = 0.4, $CHCl_3$)**}** completely matched with the values reported earlier.[12]

Section -3.4: Conclusion

In summary, we have developed a strategy for the synthesis of (–)-Lepadiformine A by utilizing oxidation/retro-aldol fragmentation cascade. Additional feature of this strategy includes mild reaction conditions and selective intramolecular Tsuji-Trost reaction for 'c' ring cyclization.

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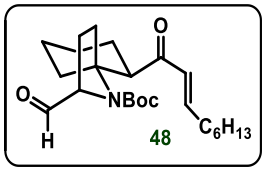
(2*S*,5*S*,6*R*)-*tert*-Butyl 2-formyl-6-((E)-non-2-enoyl)-1-azaspiro[4.5]decane-1-carboxylate (48):-



To an ice cold solution of **43** (0.050 g, 0.123 mmol) in CH_2Cl_2 (1 mL) was added acetic acid (7 µl, 0.123 mmol) in CH_2Cl_2 (1 mL). To this reaction mixture was added Dess-Martin periodinane (0.063 g, 0.147) and resultant turbid mixture was stirred for 0.5 h at the same temperature. The mixture was diluted with saturated aqueous NaCl (20 mL) and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 x 5 mL) and the combined organic fractions were washed with saturated aqueous $NaHCO_3$ (10 mL), dried (Na_2SO_4) and concentrated under reduced pressure. The crude residue was purified by flash chromatography eluting with ethyl acetate:hexane (1:4) to provide **48** (0.043 g, 87%) as an inseparable mixture of diastereomers.

TLC:- R_f =0.5 (EtOAc:Hexane = 1:5, Ninhydrin, $KMnO_4$).

IR (film): νmax = 2932, 2857, 1751, 1705, 1391, 1448, 1040, 762 cm^{-1}

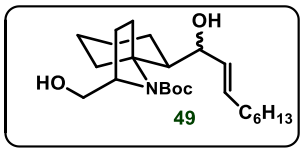
^{1}H NMR (800 MHz, $CDCl_3$) δ = 9.46 (d, *J* = 1.9 Hz, 0.11H), 9.38 (d, *J* = 2.5 Hz, 0.78 H), 6.86 (dt, *J* = 15.5, 7.0 Hz, 1H), 6.14 (ddt, *J* = 15.1, 12.1, 1.5 Hz, 1H), 4.03 -3.95 (m, 2H), 2.64 (td, *J* = 12.9, 4.3 Hz, 1H), 2.47 (ddd, *J* = 13.2, 8.0, 5.3 Hz, 1H), 2.19 - 2.11 (m, 3H), 1.79 (dq, *J* = 13.1, 8.5 Hz, 1H), 1.74 - 1.70 (m, 1H), 1.70 - 1.66 (m, 3H), 1.63 - 1.59 (m, 1H), 1.57 (s, 2H), 1.41 (s, 9H), 1.32 - 1.23 (m, 12H), 0.87 (t, *J* = 6.9 Hz, 3H).

^{13}C NMR (201 MHz, $CDCl_3$) δ = 203.61, 200.18, 152.96, 147.34, 130.39, 80.72, 68.31, 67.49, 50.45, 36.87, 32.64, 31.73, 30.83, 29.12, 28.72, 28.45, 26.99, 24.62, 23.94, 23.92, 22.67, 14.18.

HRMS (*m/z*): $[M + H]^+$ calcd for $C_{24}H_{39}NNaO_4^+$ 428.2771, found 428.2767.

$[\alpha]_D^{22}$ = -98.9° (*c* = 0.7, $CHCl_3$).

(2*S*, 5S, 6R)-*tert*-Butyl 2-(hydroxymethyl)-6-((E)-1-hydroxynon-2-en-1-yl)-1-azaspiro [4.5]decane-1-carboxylate (49):-



49

To a cold solution of **48** (0.067 g, 0.166 mmol) and $CeCl_3 \cdot 7H_2O$ (0.080 g, 0.216 mmol) in MeOH (1.5 mL), $NaBH_4$ (0.0246 g, 0.65 mmol) was added and the solution was stirred at room temperature for 1 h. A saturated aqueous solution of NaCl (1 mL) was added and the mixture was extracted with CH_2Cl_2 (3 x 5 mL). The combined organic phases were dried (anhydrous Na_2SO_4) and concentrated in vacuo. The crude residue was purified by flash chromatography eluting with ethyl acetate:hexane (1:1 - 1:0) to provide **49** (0.051 g, 75%) as a colourless oil,

TLC:- R_f =0.4 (EtOAc 100%, Ninhydrin, PMA).

IR (film): νmax = 2961, 2941, 2881, 2732, 1701, 1728, 1596, 1458, 1210, 1139, 819 cm^{-1}

^{1}H NMR (800 MHz, $CDCl_3$) (mixture of rotamers) δ = 5.44 (ddt, *J* = 37.9, 18.1, 9.2 Hz, 2H), 4.25 (t, *J* = 10.0 Hz, 0.39H), 4.08 - 3.94 (m, 1.56H), 3.89 (t, *J* = 6.6 Hz, 0.36H), 3.58 (q, *J* = 13.4, 11.7 Hz, 1H), 3.52 (d, *J* = 10.7 Hz, 0.52H), 3.45 (t, *J* = 8.6 Hz, 1H), 3.34 (t, *J* = 9.3 Hz, 0.36H), 3.09 - 3.02 (m, 0.55H), 2.55 (tt, *J* = 13.7, 6.1 Hz, 0.4H), 2.28 (dt, *J* = 13.2, 9.7 Hz, 1H), 2.13 - 1.97 (m, 1H), 1.78 (qd, *J* = 12.3, 5.8 Hz, 1H), 1.71 - 1.59 (m, 6H), 1.50 (s, 6H), 1.45 (d, *J* = 4.5 Hz, 4H), 1.26 (dq, *J* = 18.8, 11.5, 9.0 Hz, 11H), 0.86 (t, *J* = 6.9 Hz, 3H),

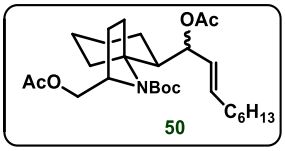
^{13}C NMR (201 MHz, $CDCl_3$) (mixture of rotamers) δ = 156.51, 156.39, 153.08, 152.97, 134.14, 133.98, 133.86, 133.39, 132.26, 132.14, 131.84, 96.17, 80.81, 80.70, 79.39, 79.34, 73.60, 73.18, 72.90, 72.70, 68.74, 68.62, 68.55, 68.12, 67.92, 65.23,

62.65, 62.59, 61.32, 61.19, 43.87, 43.62, 42.19, 41.89, 38.58, 38.49, 38.21, 37.57, 37.49, 37.44, 31.92, 31.90, 31.85, 31.47, 30.28, 30.02, 29.77, 29.36, 29.31, 29.29, 28.70, 28.67, 28.62, 28.43, 26.37, 26.26, 25.53, 25.43, 25.39, 25.14, 25.08, 24.22, 24.12, 22.72, 22.68.

HRMS (*m/z*): $[M + Na]^+$ calcd for $C_{24}H_{43}NNaO_4^+$ 432.3084, found 432.3081.

$[\alpha]_D^{22}$ = -61.7° (*c* = 0.50, $CHCl_3$).

(2*S*,5*S*,6*R*)-*tert*-Butyl 2-(acetoxymethyl)-6-((E)-1-acetoxynon-2-en-1-yl)-1-azaspiro [4.5]decane-1-carboxylate (50) :



To a solution of **49** (0.051 g, 0.124 mmol) in CH_2Cl_2 (1 mL), kept at -10 °C, was added Et_3N (0.1 mL, 0.6 mmol), DMAP (0.0012 g, 14.4 mol %) and acetic anhydride (55 µL, 0.588 mmol). The solution was stirred at rt for 2 h and quenched with H_2O at -10 °C. The aqueous fraction was extracted with CH_2Cl_2 (3 x 3mL) and the organic phases were combined, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel provide a pale yellow oil **50**, (0.06 g, 90%).

TLC:- R_f =0.6 (EtOAc:Hexane = 1:6, Ninhydrin, PMA).

IR (film): νmax = 2933, 2861, 1756, 1743, 1709, 1447, 1381, 1227, 1021, 910, 776 cm^{-1}

^{1}H NMR (800 MHz, $CDCl_3$) (mixture of rotamers) δ = 5.44 (td, *J* = 15.7, 15.2, 8.8 Hz, 1H), 5.34 - 5.26 (m, 1H), 5.11 (p, *J* = 7.4 Hz, 1H), 4.04 (ddd, *J* = 13.4, 10.7, 3.1 Hz, 0.68H), 4.00 - 3.95 (m, 1H), 3.88 (dtd, *J* = 19.6, 10.7, 9.1, 6.5 Hz, 1H), 3.30 (q, *J* = 9.9 Hz, 1H), 2.98 (d, *J* = 9.6 Hz, 0.18H), 2.52 (dddd, *J* = 13.0, 10.1, 6.5, 3.3 Hz,

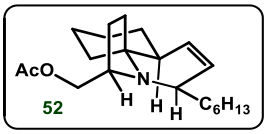
0.8H), 2.27 (d, *J* = 13.7 Hz, 0.19H), 2.09 (dd, *J* = 20.4, 11.8 Hz, 1H), 2.03 (d, *J* = 2.3 Hz, 2H), 2.00 (dt, *J* = 7.1, 4.0 Hz, 4H), 1.73 - 1.53 (m, 7H), 1.47 (s, 2H), 1.43 (d, *J* = 2.5 Hz, 7H), 1.28 - 1.19 (m, 12H), 0.84 (t, *J* = 6.9 Hz, 3H).

^{13}C NMR (201 MHz, $CDCl_3$) (mixture of rotamers) δ = 170.91, 170.85, 170.40, 170.36, 153.63, 152.91, 152.79, 135.57, 135.45, 134.82, 129.66, 129.52, 129.27, 129.22, 79.94, 79.88, 79.27, 79.11, 75.26, 75.22, 75.06, 74.66, 68.64, 68.33, 67.71, 67.56, 65.30, 65.08, 64.77, 64.66, 58.35, 58.28, 58.22, 58.07, 44.01, 43.86, 42.37, 42.23, 39.03, 38.04, 38.01, 34.63, 34.53, 34.50, 32.62, 32.55, 31.84, 31.77, 31.75, 31.46, 31.35, 30.11, 30.09, 29.87, 29.85, 29.16, 29.06, 28.67, 28.65, 28.62, 28.57, 28.52, 26.25, 26.10, 25.62, 25.53, 25.47, 25.22, 25.15, 25.10, 25.01, 24.17, 24.08, 24.06, 22.66, 22.63, 22.61, 21.45, 21.41, 21.35, 21.08, 21.04, 14.11.

HRMS (*m/z*): $[M + Na]^+$ calcd for $C_{28}H_{47}NNaO_6^+$ 516.3296, found 516.3299.

$[\alpha]_D^{22}$ = -76.8° (*c* = 1.5, $CHCl_3$).

((3*S*,5*R*,7a*S*,11a*S*)-5-hexyl-2,3,5,7a,8,9,10,11-octahydro-1H-pyrrolo[2,1-j]quinolin-3-yl)methyl acetate (52):



52

A solution of trifluoroacetic acid (0.04 mL, 0.537) in dichloromethane (0.5 mL) at 0 °C was added slowly a solution of **50** (0.053 g, 0.1 mmol) in CH_2Cl_2 (1 mL) and the reaction was allowed to warm to room temperature and stirred for 2 h. The reaction mixture was quenched with saturated sodium carbonate solution (5 mL) and extracted with dichloromethane (2 × 5 mL). The organic solvents were combined, dried over sodium sulphate and concentrated in *vacuo* to afford **51** (0.040 g, 95%) which was forwarded further without purification.

To a stirred solution of **51** (0.040 g, 0.1 mmol), benzyltriethyl ammonium chloride (0.003 g, 0.01 mmol) and tetrakis(triphenylphosphine)palladium(0) (0.006 g, 0.005 mmol) in ethyl acetate (0.8 mL) at 0 °C was added a solution of K_2CO_3 (0.042 g, 0.3

mmol) dissolved in distilled water (0.8 mL). Biphasic reaction mixture was stirred at rt for 2 h. Two layers were separated and aqueous layer was extracted with ethyl acetate (3 x 2 mL) and combined organic fractions were washed with brine solution (2 mL), dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by flash chromatography (silica gel, hexanes:EtOAc = 3:1) to obtain **52** (0.024 g, 71%) as an yellow oil.

TLC:- R_f =0.5 (EtOAc:Hexane = 1:2, Ninhydrin, PMA, $KMnO_4$).

IR (film): νmax = 2933, 2861, 1704, 1696, 1438, 1371, 1227, 1023, 910, 796 cm^{-1}

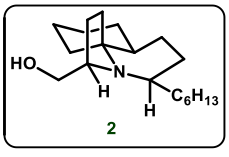
^{1}H NMR (800 MHz, $CDCl_3$) δ = 5.98 (dt, *J*=7.9, 3.5, 1H), 5.83 - 5.73 (m, 1H), 4.25 (dd, *J*=10.7, 3.8, 1H), 3.71 (dd, *J*=10.6, 7.9, 1H), 3.15 (dq, *J*=14.0, 6.6, 4.9, 2H), 2.03 (s, 3H), 1.89 (dd, *J*=12.7, 3.5, 1H), 1.83 - 1.81 (m, 1H), 1.74 (dt, *J*=12.9, 7.3, 2H), 1.71 - 1.64 (m, 3H), 1.58 (ddd, *J*=28.1, 13.8, 7.8, 3H), 1.40 (qd, *J*=12.6, 10.4, 4.1, 4H), 1.32 (dd, *J*=10.4, 4.8, 2H), 1.29 -1.23 (m, 12H), 0.87 (t, *J*=6.9, 3H).

^{13}C NMR (201 MHz, $CDCl_3$) δ = 171.18, 136.07, 134.82, 70.95, 70.42, 60.21, 56.47, 44.44, 39.10, 32.51, 31.94, 29.78, 29.59, 29.35, 28.33, 28.26, 27.89, 26.10, 24.65, 22.68, 21.11, 14.16.

HRMS (*m/z*): $[M + H]^+$ calcd for $C_{21}H_{36}NO_2^+$ 334.2741, found 334.2737.

$[\alpha]_D^{22}$ = -15.5° (*c* = 1.5, $CHCl_3$).

Synthesis of (–)-Lepadiformine (2):-



2

Compound **52** (0.022 g, 0.06 mmol) was dissolved in ethyl acetate (1.5 mL) and the flask was evacuated vacuum, argon gas was introduced to the flask and the process was repeated for two cycles. Pd/C 10 wt% (0.005 g) was added to the flask and flushed with

hydrogen gas (2 cycles) and stirred. Reaction progress was monitored by TLC. After complete conversion (3 h) reaction mixture was passed through a celite pad. Solvent was evaporated under vacuum to provide **53** (0.018 g, 95%) as pale yellow oil which was used as such for the next step.

To a solution of **53** (0.018 g, 0.05 mmol) in a mixture of MeOH (1 mL) and H_2O (1 drop) at 0 °C was added K_2CO_3 (0.032 g, 1.5 mmol) and stirred for 1 h. 2 mL of water was added and reaction mixture extracted with CH_2Cl_2 (3x5 mL), dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel ($CHCl_3$: MeOH: aq. NH_3 (97:2:1) to provide **2** (0.010 g, 67%).

TLC:- R_f =0.3 ($CHCl_3$:MeOH:aq NH_3 = 97:2:1, Ninhydrin).

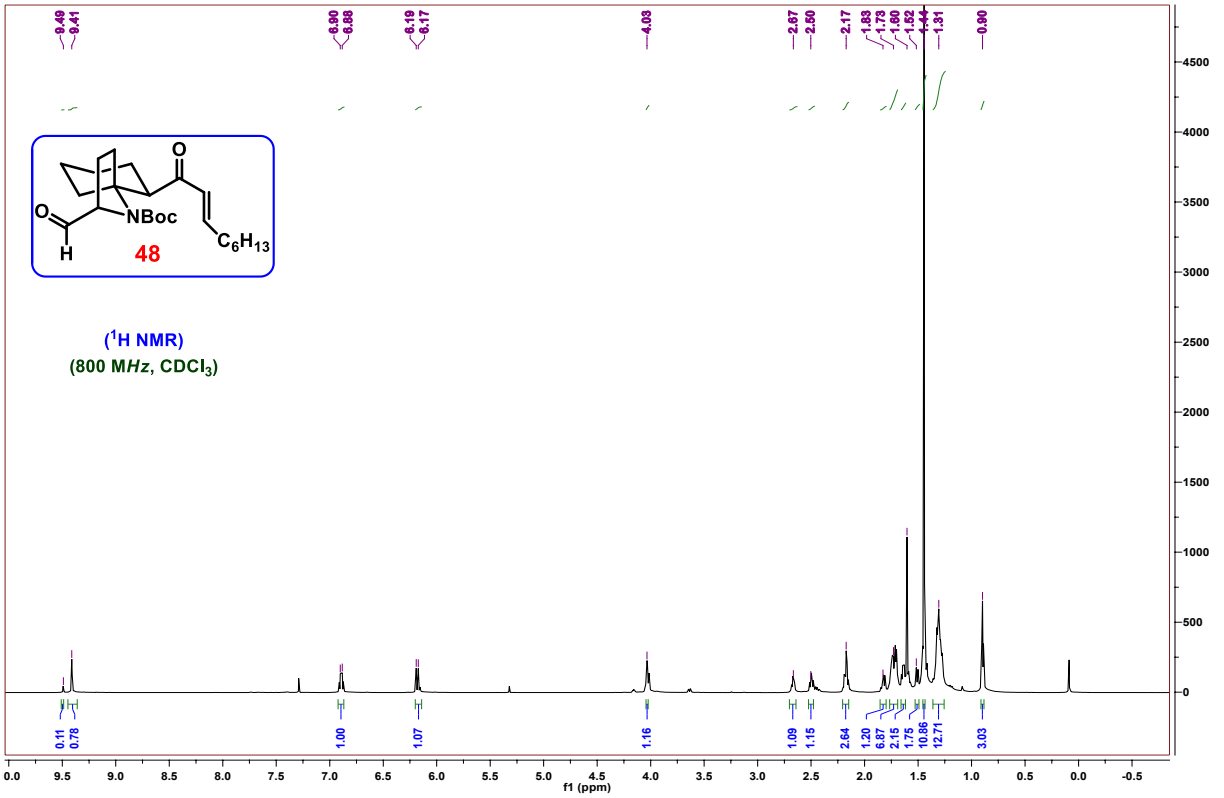
IR (film): νmax = 3401, 2919, 2853, 1463, 1081, 786 cm^{-1}

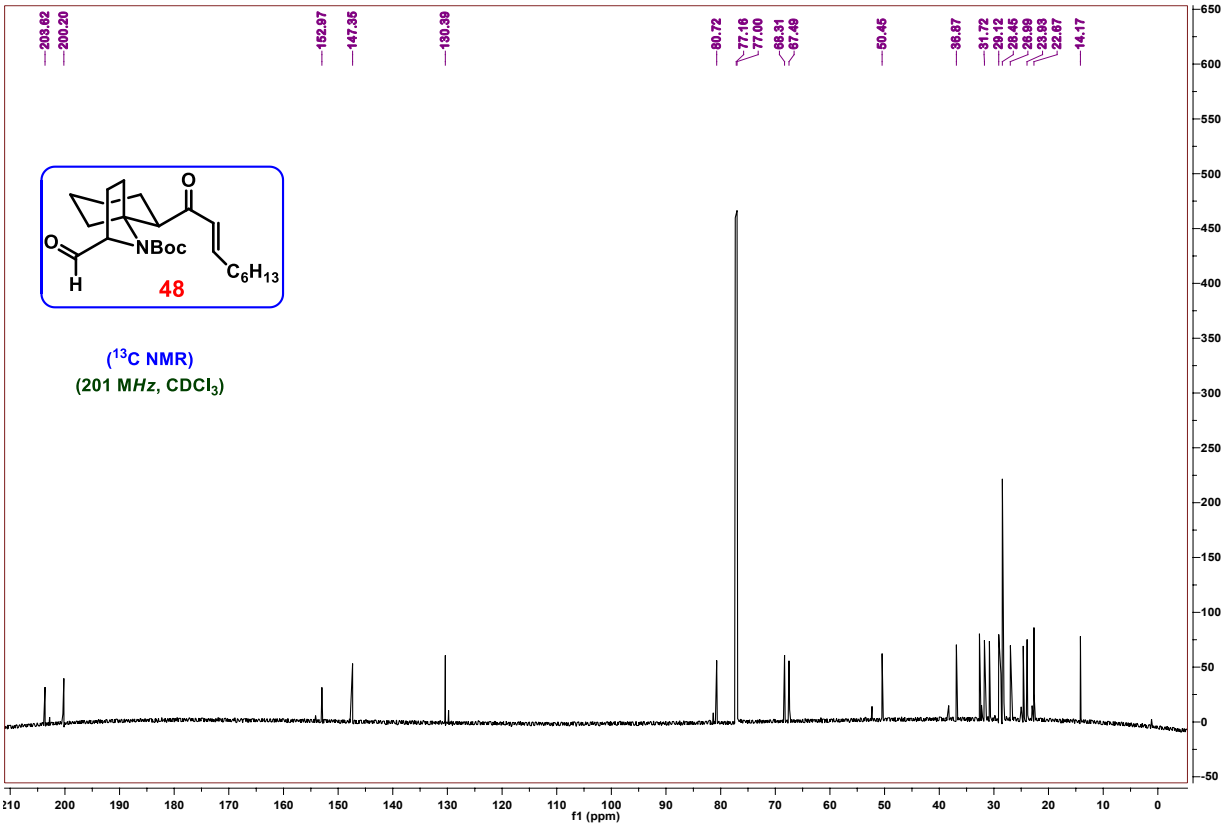
^{1}H NMR (400 MHz, $CDCl_3$) δ 3.40 (m, 1H), 3.35 (m, 1H), 3.25 (dd, J = 9.5, 9.5 Hz, 1H), 3.17 (m, 1H), 1.81-1.46 (m, 13H), 1.37-1.14 (m, 14H), 1.06-0.98 (m, 1H), 0.88 (t, J = 7.0 Hz, 3H)

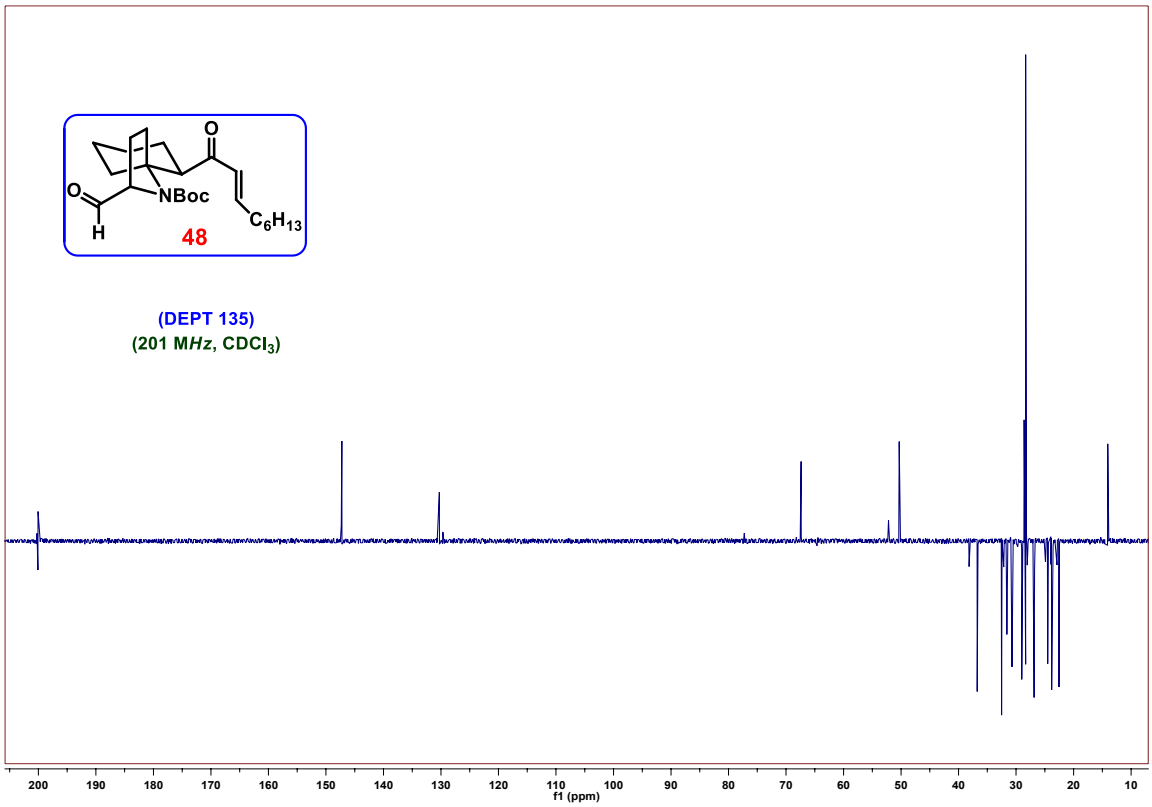
^{13}C NMR (101 MHz, $CDCl_3$) δ 77.00, 67.22, 62.27, 58.29, 53.19, 40.20, 38.29, 29.61, 27.66, 27.59, 26.33, 24.29, 23.26, 22.63, 14.11

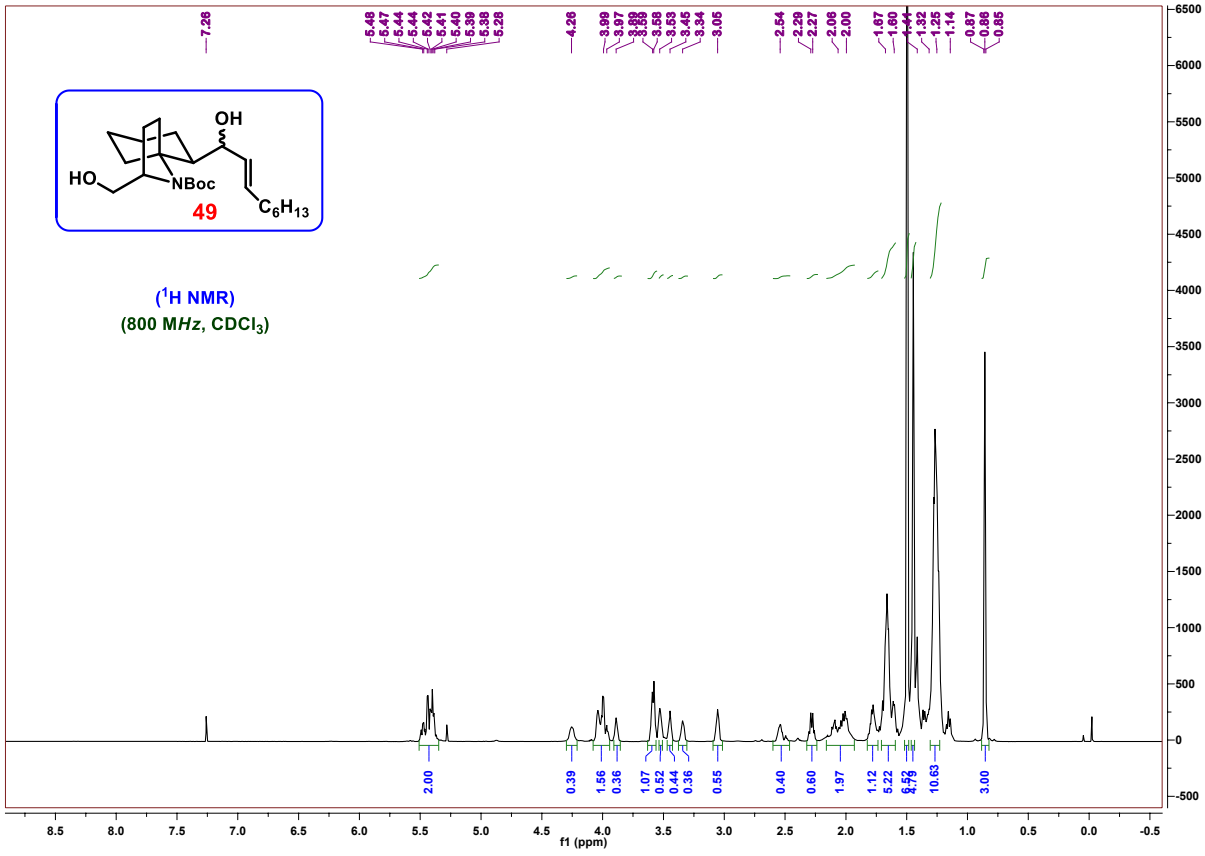
HRMS (*m/z*): $[M + H]^+$ calcd for $C_{19}H_{36}NO^+$ 294.2791, found 294.2790.

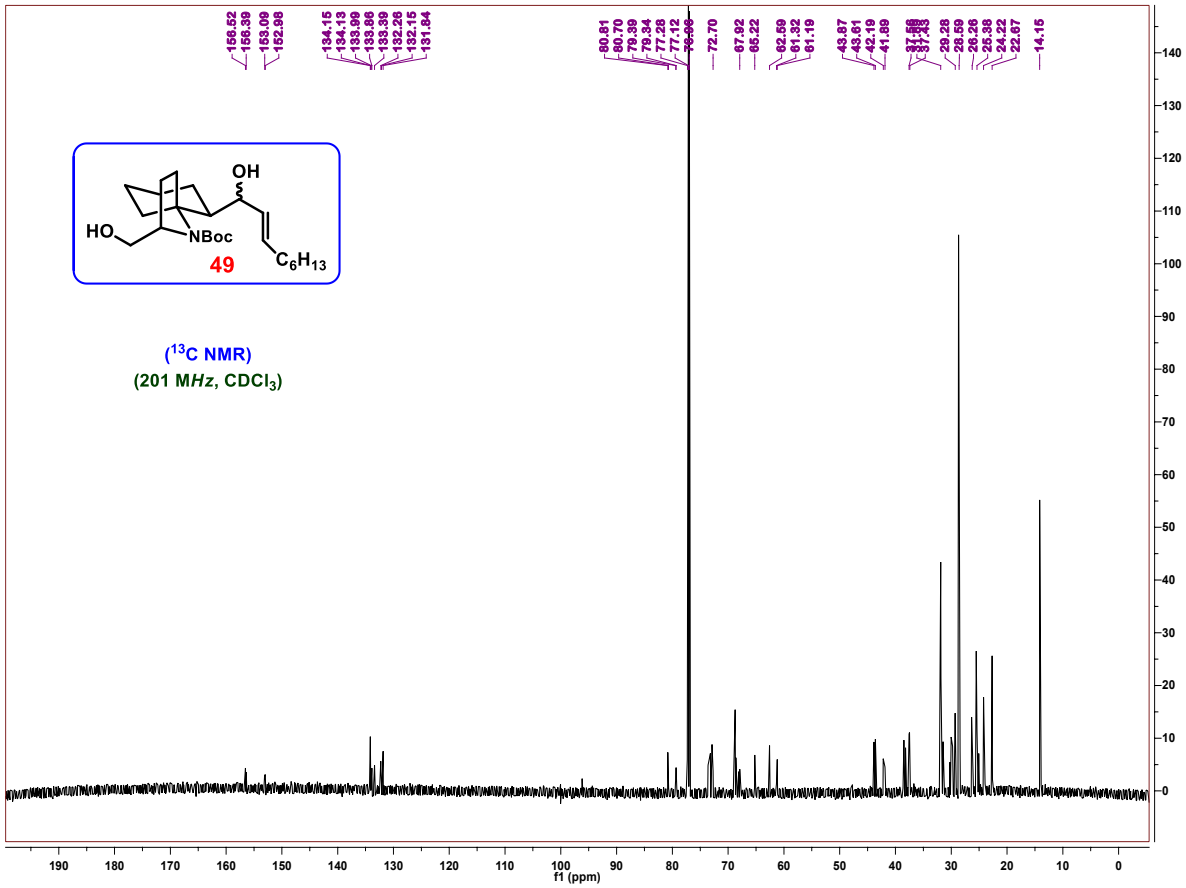
$[\alpha]_D^{22}$ = -15.1 (c = 0.41, $CHCl_3$).


9.49
9.41
6.90
6.88
6.19
6.17
4.03
2.67
2.50
2.17
1.83
1.73
1.60
1.52
1.44
1.31
0.90
O
NBoc
O
H
C6H13
48
(1H NMR)
(800 MHz, CDCl3)
0.11
0.78
1.00
1.07
1.16
1.09
1.15
2.64
1.20
6.87
2.15
1.75
10.86
12.71
3.03
f1 (ppm)

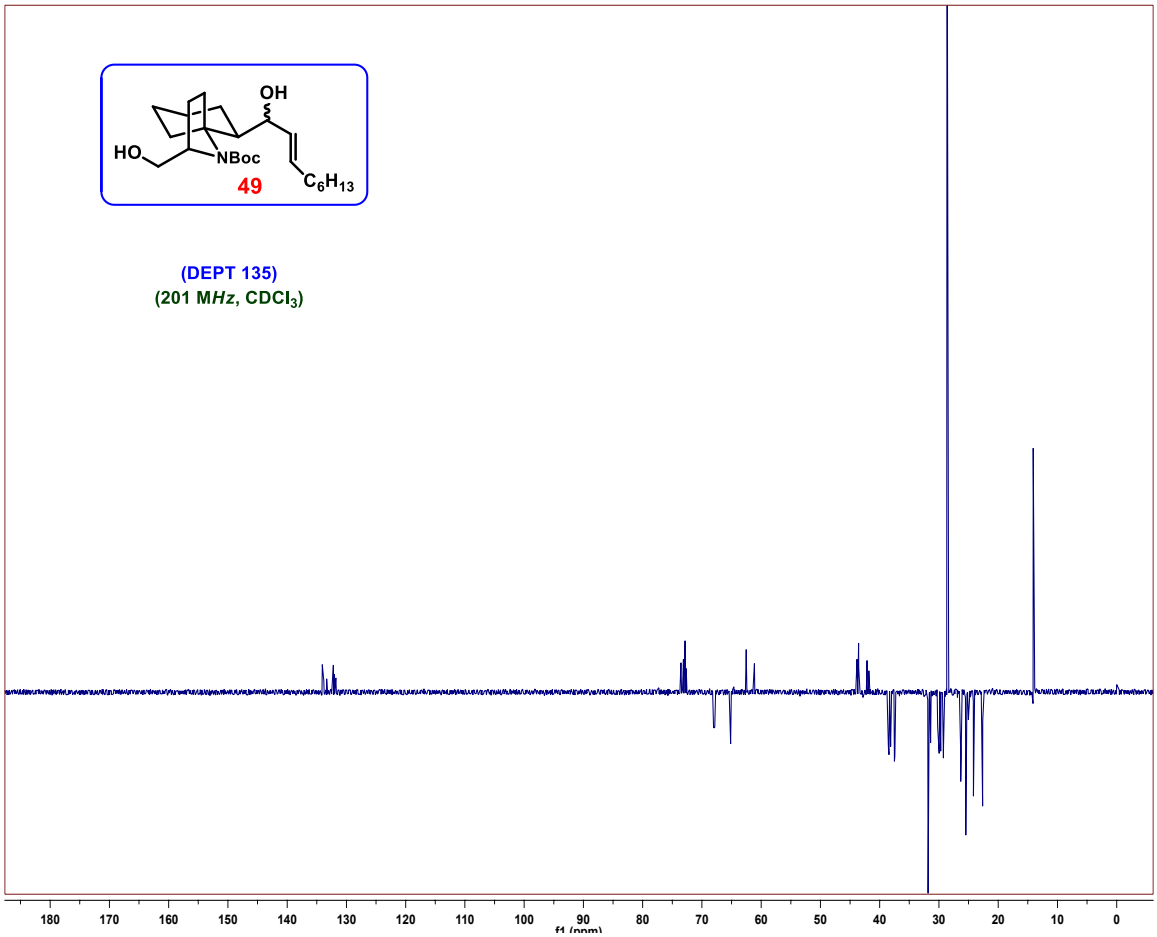

203.62
200.20
152.97
147.35
130.39
80.72
77.16
77.00
68.31
67.49
50.45
36.87
31.72
29.12
28.45
28.99
23.93
22.67
14.17
O
NBoc
O
H
C6H13
48
(13C NMR)
(201 MHz, CDCl3)
f1 (ppm)


O
O
NBoc
H
C_6H_{13}
48
(DEPT 135)
(201 MHz, $CDCl_3$)
f1 (ppm)

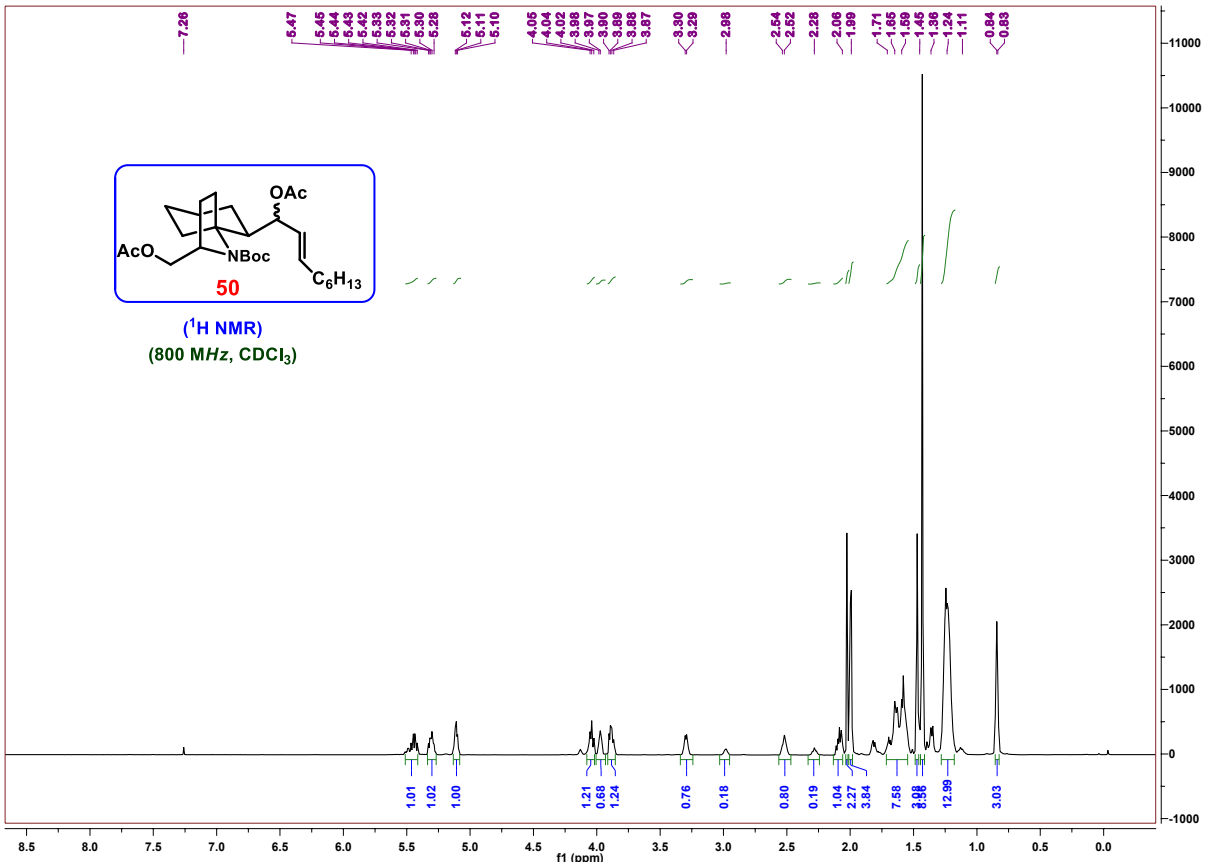

OH
HO
NBoc
C_6H_{13}
49
(^{1}H NMR)
(800 MHz, $CDCl_3$)
f1 (ppm)

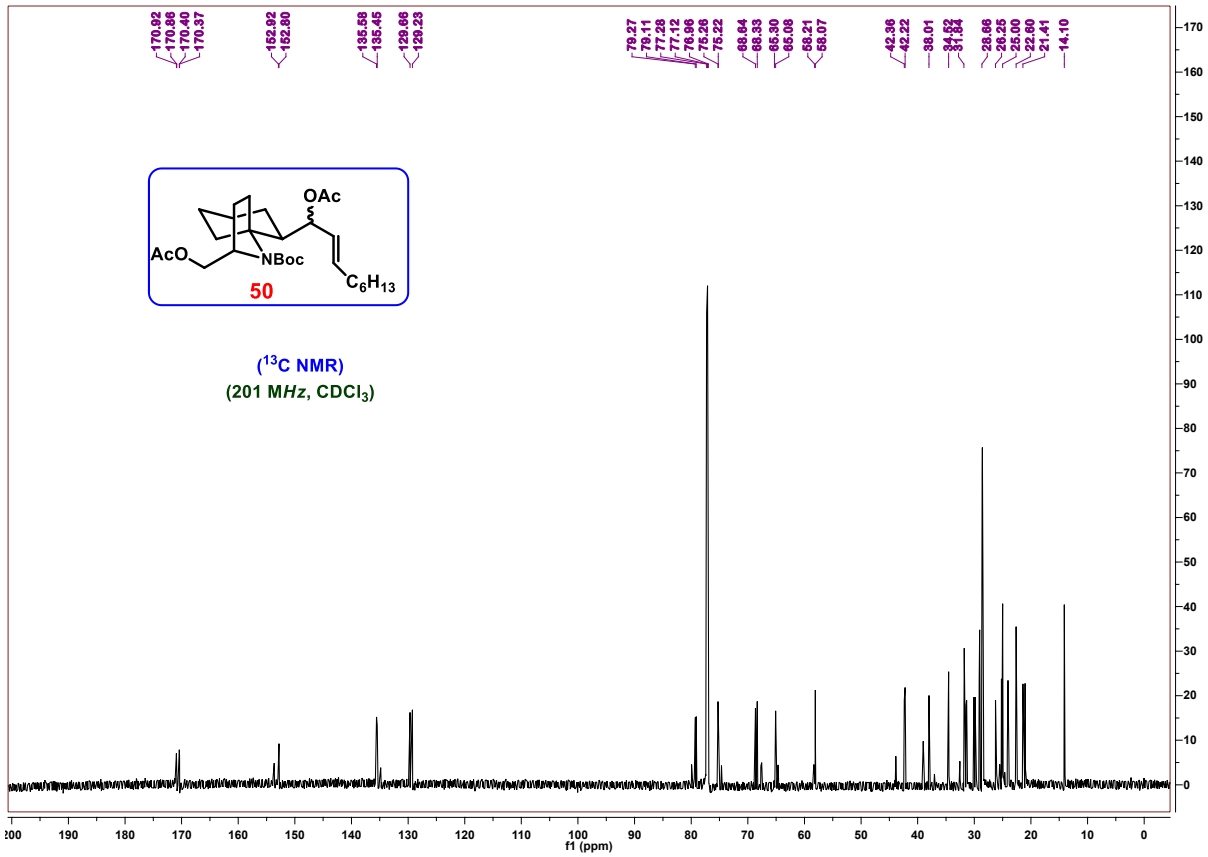


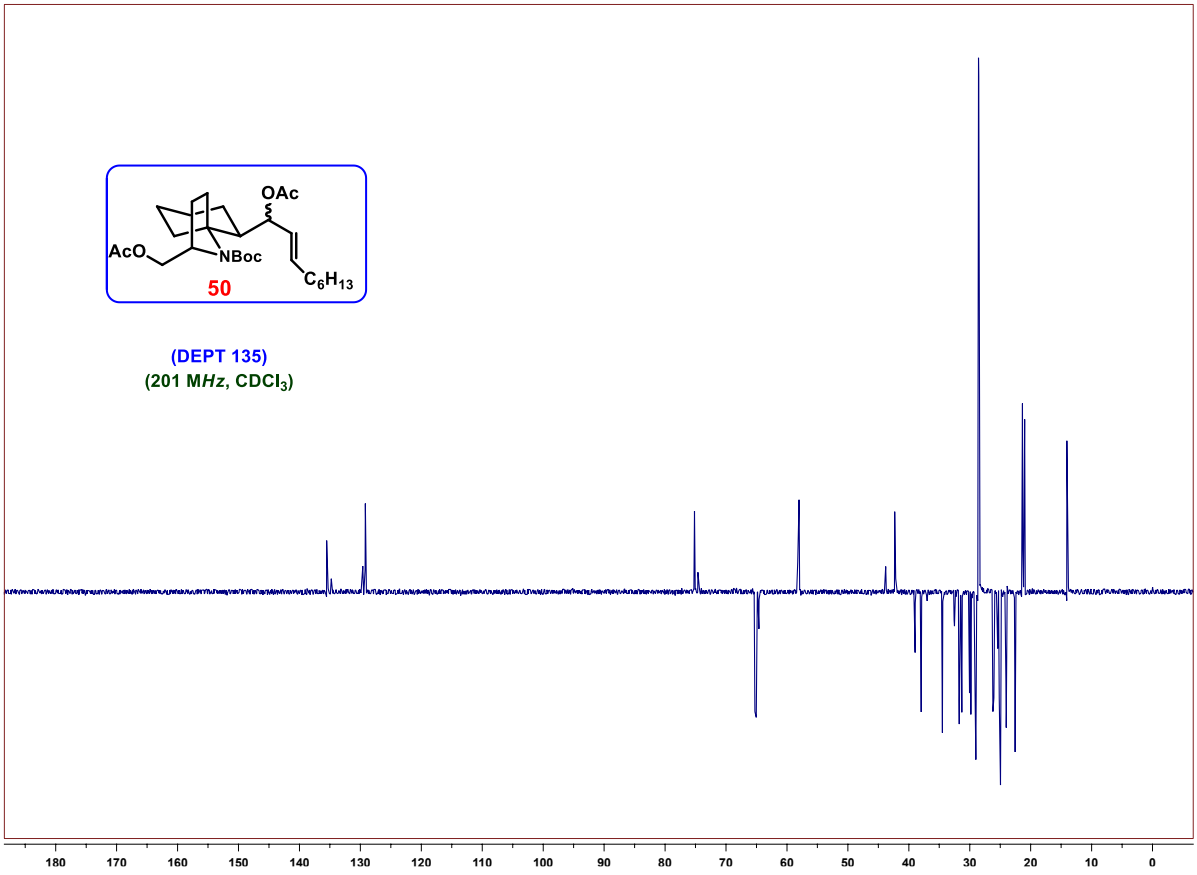
(^{13}C NMR)
(201 M*Hz*, $CDCl_3$)

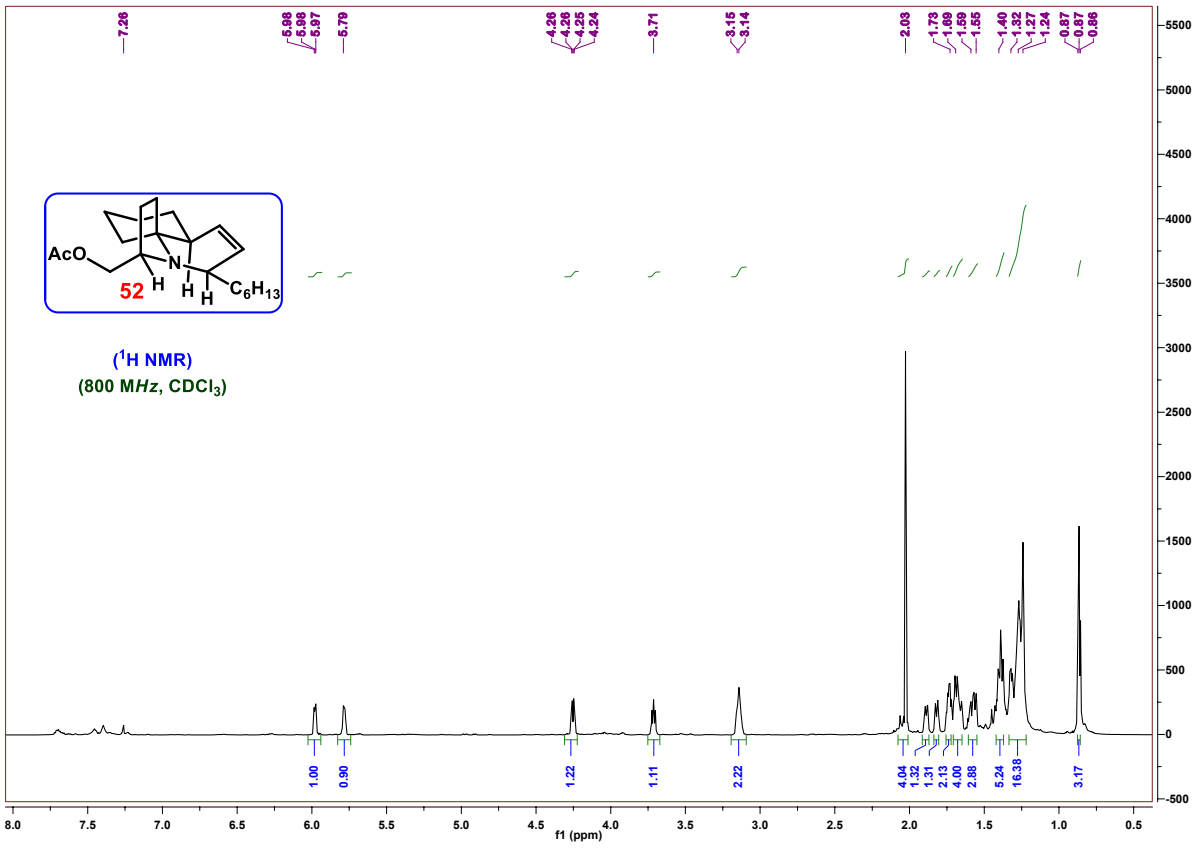


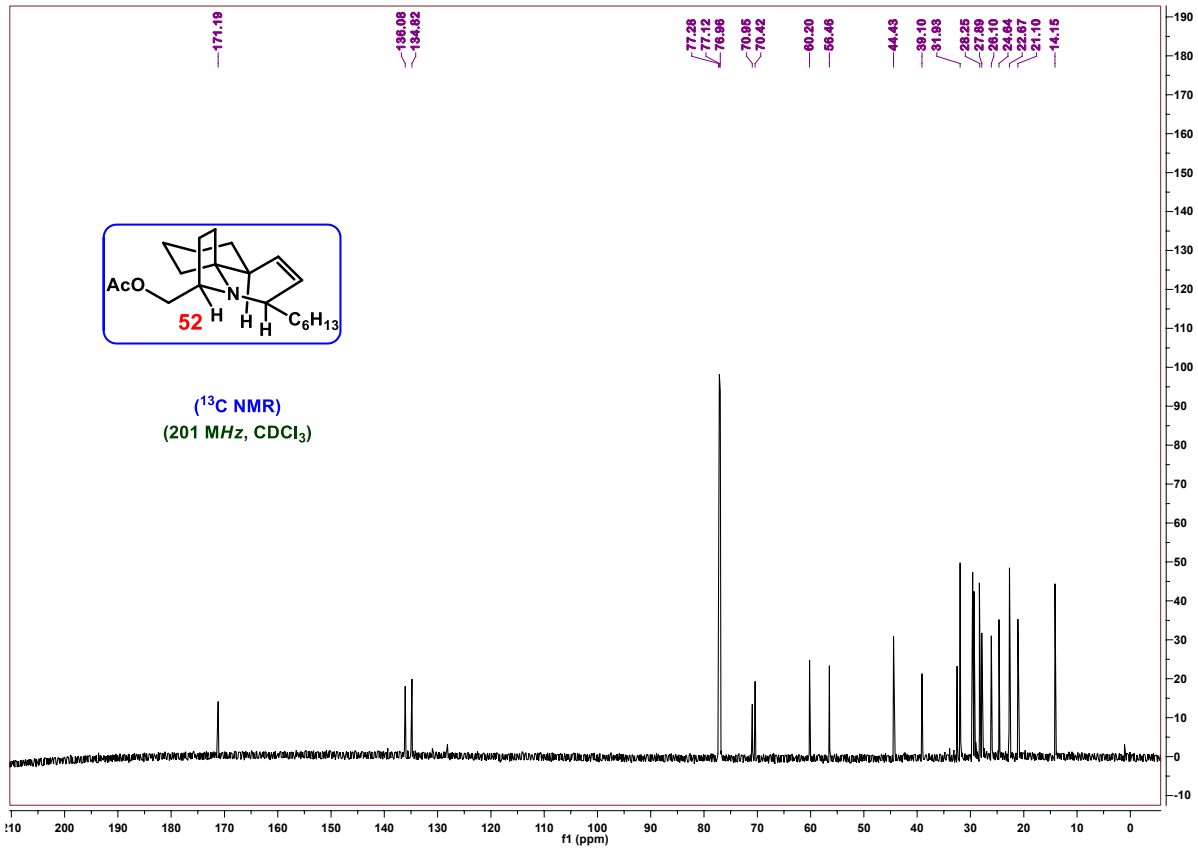
(DEPT 135)
(201 M*Hz*, $CDCl_3$)


OAc
AcO
NBoc
C_6H_{13}
50
(^{1}H NMR)
(800 MHz, $CDCl_3$)
f1 (ppm)

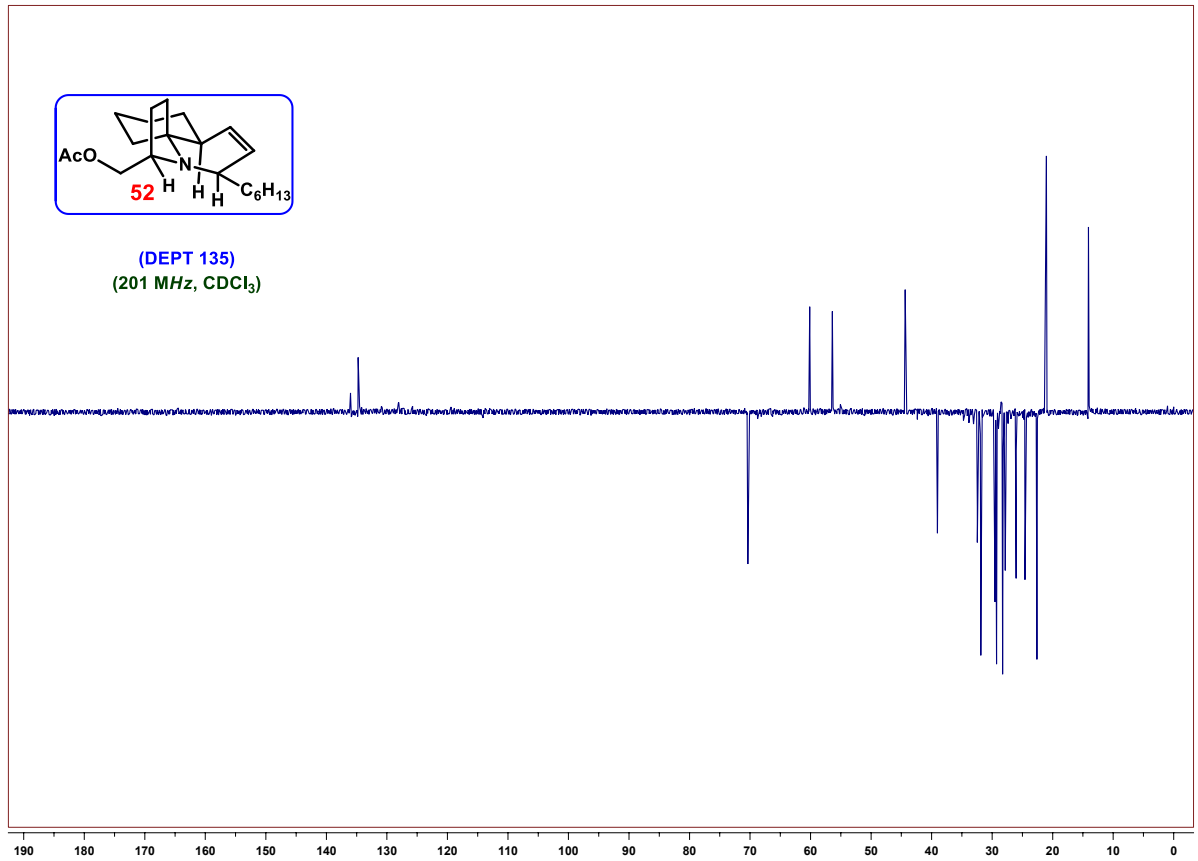

OAc
AcO
NBoc
C_6H_{13}
50
(^{13}C NMR)
(201 MHz, $CDCl_3$)
f1 (ppm)


OAc
AcO
NBoc
C_6H_{13}
50
(DEPT 135)
(201 MHz, $CDCl_3$)
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0

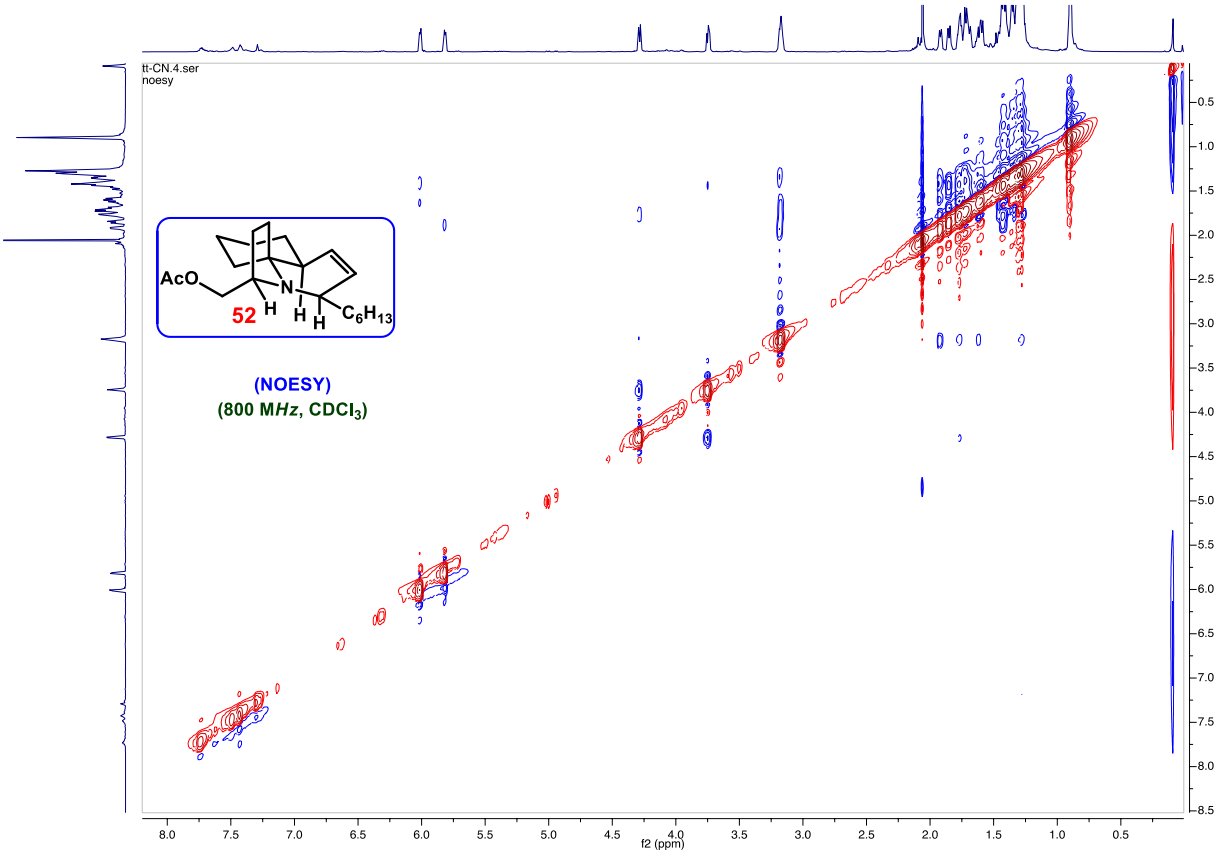

7.26
5.98 5.98 5.97
5.79
4.26 4.26 4.25 4.24
3.71
3.15 3.14
2.03
1.73 1.69 1.59 1.55
1.40 1.32 1.27 1.24
0.87 0.87 0.86
AcO
N
H
H
H
C_6H_{13}
52
(^{1}H NMR)
(800 MHz, $CDCl_3$)
1.00 0.90 1.22 1.11 2.22 4.04 1.32 1.31 2.13 4.00 2.88 5.24 16.38 3.17
f1 (ppm)

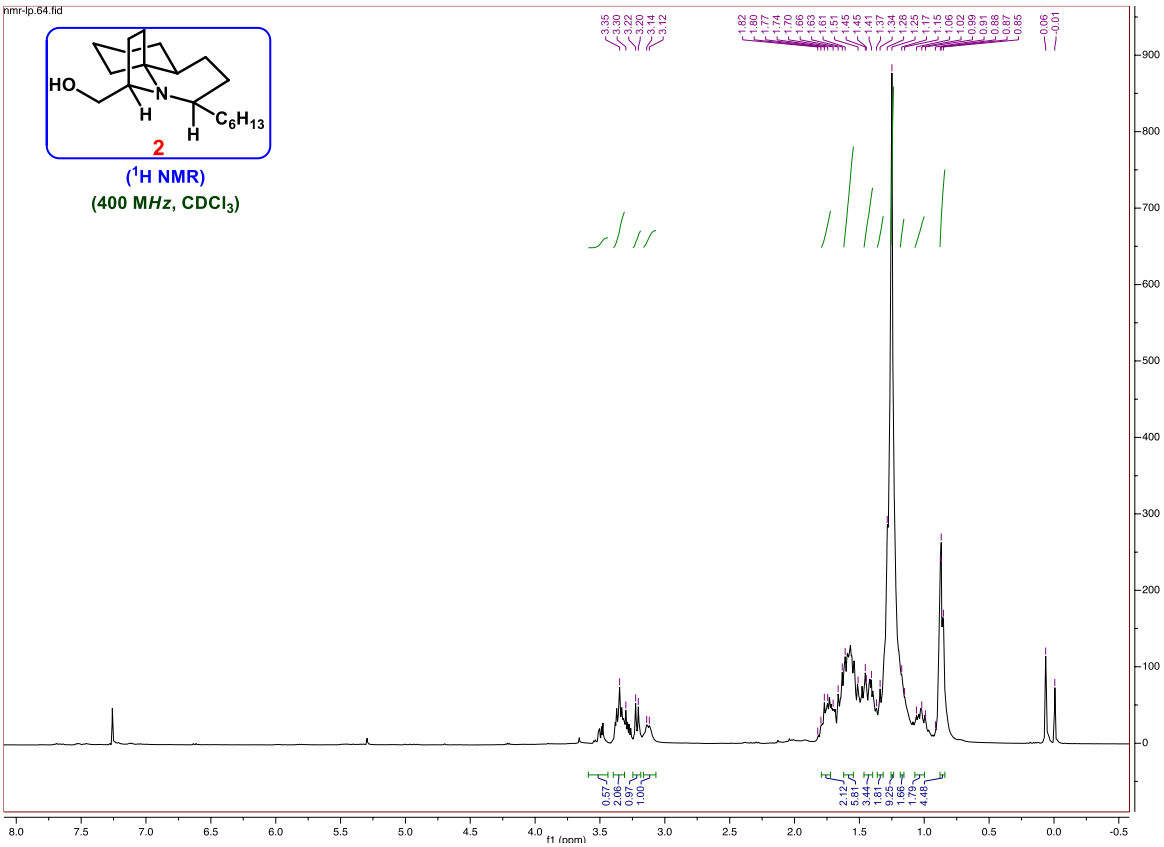


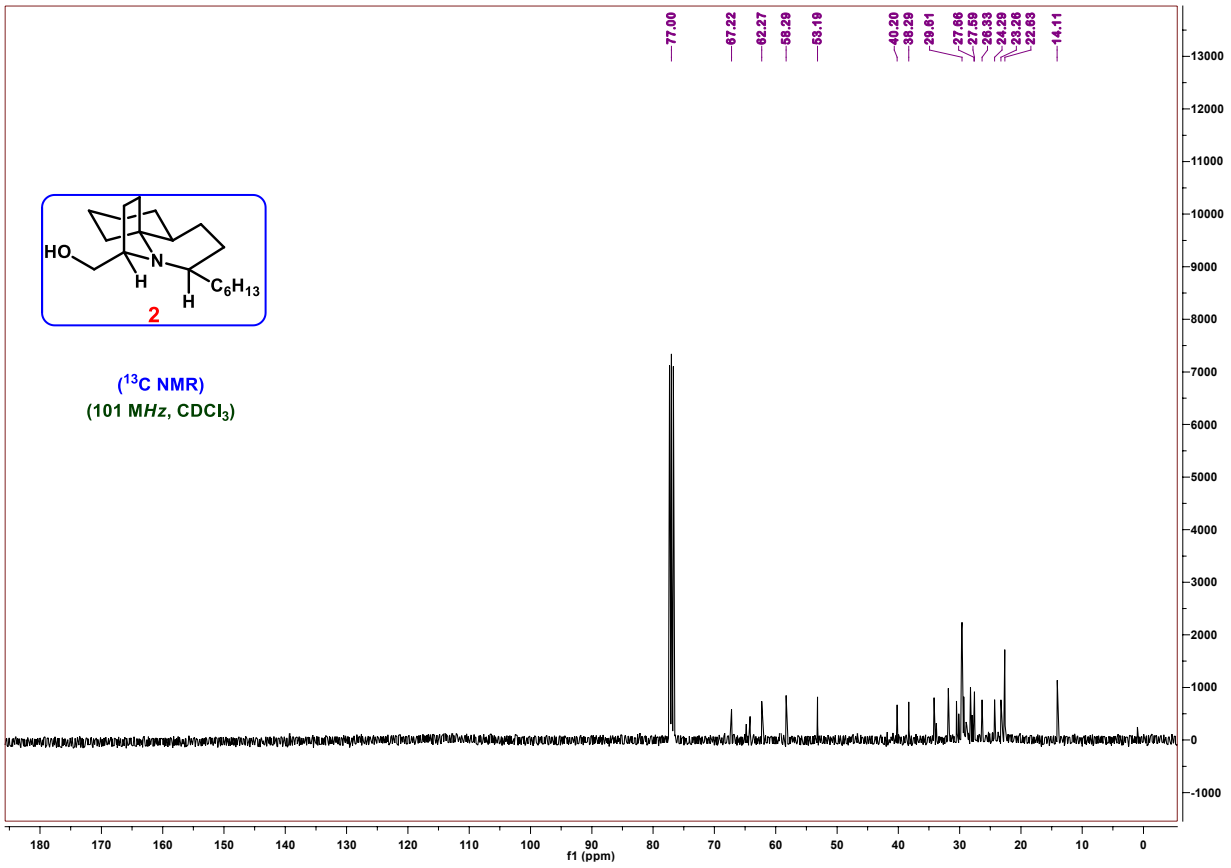
(^{13}C NMR)
(201 M*Hz*, $CDCl_3$)



(DEPT 135)
(201 M*Hz*, $CDCl_3$)


tt-CN.4.ser
noesy
AcO
N
H
H
H
C6H13
52
(NOESY)
(800 MHz, CDCl3)
f2 (ppm)


nmr-lp.64.fid
HO
N
H
H
C6H13
2
(1H NMR)
(400 MHz, CDCl3)
f1 (ppm)


77.00
67.22
62.27
58.29
53.19
40.20
38.29
29.61
27.66
27.59
26.33
24.29
23.26
22.83
14.11
HO
N
H
H
C_6H_{13}
2
(^{13}C NMR)
(101 M*Hz*, $CDCl_3$)
f1 (ppm)

1) "Aza-Quaternary Scaffolds from Selective Bond Cleavage of Bridgehead Substituted 7-azabicyclo[2.2.1]heptane: Total Synthesis of (+)-Cylindricine C-E and (-)-Lepadiformine A"

   Ganesh Pandey and **Vaitla Janakiram** (Accepted in *Chem. Eur. J*)

2) "Simmons smith/Julia type fragmentation of β-ketosulfones to α,β-unsaturated ketones."

   Ganesh Pandey and **Vaitla Janakiram** (to be communicated)