Diastereoselective synthesis of β-Lactams and their applications

THESIS

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By

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Dedicated

To

My Late Father

National Chemical Laboratory
Division of Organic Chemistry (Synthesis)
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Dr. Ganesh Pandey
FNA, FNASc, FASc

CERTIFICATE

This is to certify that the work incorporated in the thesis entitled **"Diastereoselective synthesis of β-Lactams and their applications"** submitted by **Mr. Dharmendra Kumar Tiwari** was carried out by him under my supervision at the **National Chemical Laboratory, Pune.** Such material as obtained from other sources has been duly acknowledged in the thesis.

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DECLARATION

I hereby declare that the work presented in the thesis entitled **"Diastereoselective synthesis of β-Lactams and their applications"** submitted for Ph. D. degree to the University of Pune, has been carried out by me at **National Chemical Laboratory, Pune,** under the supervision of **Dr. Ganesh Pandey**. The work is original and has not been submitted in part or full by me for any degree or diploma to this or any other University.

Date: (Dharmendra Kumar Tiwari)

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Acknowledgements

In the first place I would like to express my sincere gratitude to Dr. Ganesh Pandey for his supervision, advice, and guidance from the very early stage of my research as well as giving me extraordinary experiences throughout the work. Above all and the most needed, he provided me unflinching encouragement and support in various ways. I thank him for the faith he has shown and the freedom he has given to explore my capabilities. This work would be highly impossible without him. I thank him for providing me the wonderful opportunity of being a part of his lab, which actually became my second home in the due course. Honestly it was only because of his trust in me, it has been possible for me to achieve my goal.

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Whatever I am and whatever I will be in future is because of the goodwill, unstinted support and blessings that I have received from my uncle Dr. R. K. Tiwari and elder brother G.D.Tiwari. Their kind cooperation and shower of love helped me in pursuing the PhD and no words are enough to acknowledge them. The deepest thanks from the bottom of my heart should be dedicated to all family members for enormous support in materializing this work into a reality. Words fail me to express my appreciation to my wife Ranjana whose dedication, love, and persistent confidence in me, has taken the load off my shoulders and it easy for me to focus on my work. I am equally indebted to my relatives for their constant support, trust and extra care.

Last but not least I thank my heavenly father for giving me religious potency, courage, guidance and commitment to do this work. He made it possible for things to happen. I am struggling to fight back my tears when writing these words. "The greatest regret that a child could have is an eternally lost opportunity of serving his or her parents with medicine and soup on their deathbed and not being present when they die" Love you babu ji from the bottom of my hearts…….without end

Dharmendra K. Tiwari

Contents

GENERAL REMARKS

1. All melting points (recorded on a Büchi melting point apparatus) are uncorrected and are recorded on the Celsius scale.
2. IR spectra were recorded as nujol mull or in chloroform, or neat on a Perkin-Elmer Infrared Spectrometer Model 599-B, Model 1600 FTIR and Shimadzu FTIR, using sodium chloride optics. IR bands are expressed in frequency (cm^{-1}).
3. Proton NMR spectra were recorded using tetramethylsilane as internal reference on Bruker AC-200, AV 200, MSL-300, AV400 and DRX-500 spectrometer. Chemical shifts were recorded in parts per million (δ, ppm). Abbreviations, *viz.*, s = singlet, d = doublet, t = triplet, dd = doublet of doublet, q = quartet, bs = broad singlet and m = multiplet have been used to describe the spectral data. $CDCl_3$ was used as the solvent unless otherwise mentioned.
4. ^{13}C NMR spectra were recorded on Bruker AC-200, AV 200, MSL-300, AV400 and DRX-500 instrument operating at 50.3 MHz, 75 MHz and 125.8 MHz respectively.
5. Elemental analyses (C, H, N, S) were obtained on a Carlo-Erba, 1100 automatic analyzer.
6. Optical rotations were measured on a JASCO-181 digital Polarimeter, JASCO P-1020 Polarimeter and ADP-220 Polarimeter using sodium D line (5893 Å). Concentration is expressed in g/ 100 ml.
7. EI Mass spectra were recorded on a Finnigan Mat-1020 Spectrometer with a direct inlet system or electron spray ionization method (EI).
8. Petroleum ether refers to the fraction boiling between 60-80 °C.
9. The progress of the reaction was monitored by analytical thin layer chromatography plates precoated with silica gel 60 F_{254} (Merck) and glass plates coated with silica gel F_{254}.
10. Silica Gel used for column chromatography was 60-120 mesh, 100-200 mesh or 230-400 mesh size.
11. ^{1}H NMR and ^{13}C NMR spectra of the representative compounds are attached at the end of the corresponding chapter. For all the samples containing methylene and quaternary carbons, DEPT spectrum was scanned after scanning ^{13}C NMR spectra and then the assignment of the peaks in ^{13}C NMR was done.

12. Solvents for column chromatography were distilled at their respective constant boiling points.
13. All the dry reactions were performed under an inert atmosphere of argon, using freshly distilled, degassed solvents.
14. Dichloromethane was dried over anhydrous P_2O_5 and stored over 4Å molecular sieves. THF was freshly distilled over sodium benzophenone ketyl. Triethyl amine was dried over potassium hydroxide.
15. All other solvents were dried following the procedures given in the book 'Purification of Laboratory Chemicals' by Armarego and Perrin (third edition).
16. Compounds have been named based on nomenclature provided by CS-ChemDraw software.

Abbreviations

Ac	Acetyl
AIBN	2,2'-Azobisisobutyronitrile [$(CH_3)_2C(CN)N=NC(CH_3)_2CN$]
Ar	Aryl
Bn	Benzyl
Boc	*t*-Butoxy carbonyl
CAN	Ceric ammonium nitrate
DCC	Dicyclohexylcarbodiimide
DCM	Dichloromethane
DEAD	Diethyl azodicarboxylate
DEPT	Distortionless enhancement by polarization transfer
DIBAL-H	Disiobutylaluminium hydride
DMAP	*N*,*N*'-Dimethylaminopyridine
DMF	*N*,*N*-Dimethylformamide
DMSO	Dimethyl sulfoxide
EDC	Dichloroethane or ethylene dichloride
Et	Ethyl
EtOAc	Ethyl acetate
EtOH	Ethyl alcohol
h	Hour(s)
Hz	Hertz
LAH	Lithium aluminium hydride
Me	Methyl
Ms	Methanesulfonyl
min	Minute
MP	Melting point
ORTEP	Oak Ridge Thermal Ellipsoid Plot Programme
Pet ether	Petroleum ether
Pd/C	Palladium carbon
PMP	*p*-Methoxyphenyl
PTSA or TSOH	*p*-Toluenesulfonic acid

Py	Pyridine
rt	Room temperature
TBDMS	*t*-Butyldimethylsilyl
TBDMSCl	*t*-Butyldimethylsilyl chloride
THF	Tetrahydrofuran
TLC	Thin layer chromatography
TMS	Trimethylsilyl
Ts	*p*-Toluenesulfonyl

Abstract of the thesis

Compound numbers in the abstract are different from those in the thesis

Thesis Abstract

Chapter-1: Introduction of Azetidin-2-one (*β*-lactam):

Azetidin-2-one (*β*-lactam), a four membered cyclic amide, is a part sub-structure of many biologically important antibiotics. Although, the first synthesis of *β*-lactam ring was reported way back in 1907 by Staudinger,[1] the actual worth of this ring was recognized after Fleming's landmark discovery of Penicillin in 1928[2]. The azetidin-2-one ring was identified as the key structural unit responsible for the antibiotic activity. *β*-lactam antibiotics have occupied a central role in the fight against pathogenic bacteria and the subsequent rise in quality of life for the world population as a whole.

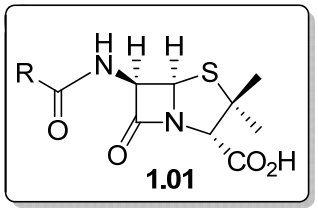


Figure 1. *Azetidin-2-one (Penicillin, β-Lactam ring)*

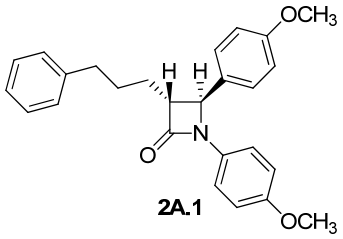
Besides their biological activities, *β*-lactams have gained importance as synthons in organic synthesis due to the possibility of selective ring cleavage of any one of the four single bonds. Therefore many organic chemists have been employed *β*-lactam as starting material in the preparation of substances of biological interest, including *α*-amino acids, *β*-amino acids, indolizidines, pyrrolizidines, eight-membered lactams, macrolides and complex natural products.

Chapter-2-Section A: Azetidin-2, 3-dione Synthon for Stereoselective Synthesis of *cis* and *trans* C-3-Alkyl/Aryl Azetidin-2-ones:

This section will describe the syntheses of various 3-alkyl/aryl azetidin-2ones, including cholesterol absorption inhibitor (SCH-48461).

3-phenyl propyl azetidine-2-one (cholesterol absorption inhibitor) has generated renewed interest in the synthesis of various 3-alkyl/aryl *β*-lactams. One such 3-alkyl β-lactam is SCH 48461 which exhibits a very strong cholesterol

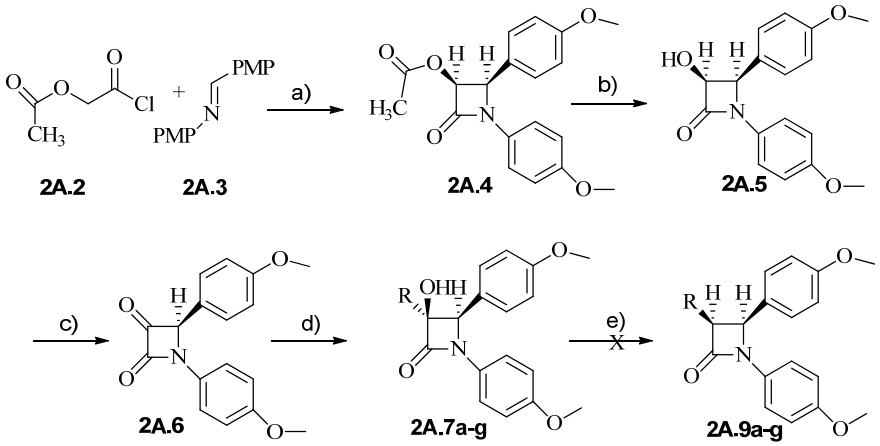
absorption inhibitory activity. Considering its medicinal value, we planned to devise a general route to 3-alkyl/aryl *β*-lactams along with the synthesis of SCH 48461.



2A.1

Figure 2. SCH 48461

freshly prepared acetoxy acetyl chloride **2A.2** was reacted with the imine **2A.3**, derived from *p*-anisaldehyde and *p*-anisidine, in the presence of Et_3N as a base, which gave *cis* 3-acetoxy azetidin-2-one **2A.4** in 62% yield.



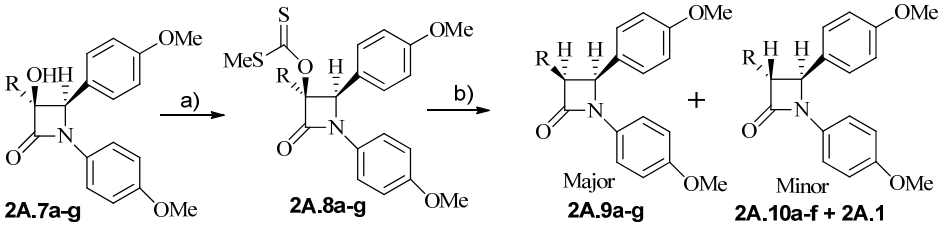
2A.2 2A.3 2A.4 2A.5 2A.6 2A.7a-g 2A.9a-g

Scheme-1 ***Reagents and conditions:*** *a) Et_3N, DCM, 0 °C-rt, 18 h, 62%; b) aq. $NaHCO_3$, Na_2CO_3, MeOH, rt, 18h, 85%; c) DMSO, P_2O_5, rt, 24h, 89%, d), RMgX, THF, 0 °C, 65%, e) EtSiH, BF_3:OEt, 0 °C-rt.*

In order to obtain 3-keto *β*-lactam **2A.6**, it was required to hydrolyze acetate moiety of **2A.5** first, before oxidation. In this context, **2A.4** was saponified using aq sodium bicarbonate in MeOH to obtain **2A.5** in 90% yield. Oxidation of **2A.5** was carried out by using anhydrous phosphorous pentoxide in dry dimethyl sulfoxide at room temperature to obtain the desired azetidin-2,3-dione **2A.6** in 89%.

Having synthesized the requisite azetidin-2,3-dione **2A.6,** we proceeded further with the synthesis of SCH 48461 (**2A.1)** by reacting it with alkyl / aryl Grignard reagent (Scheme-1) to obtain corresponding **2A.7a-g** in good to moderate

yields **(Table-1)**. The formation of a single diastereomer in this reaction suggests that the addition occurred exclusively from the opposite side of the C-4 to avoid steric congestion. Deoxygenation of **2A.7a-g** using triethylsilane in the presence of $BF_3{\cdot}OEt_2$ or trifluoroacetic acid to give target compound **2A.9a-g** remained unsuccessful (Scheme-1). Therefore, we decided to utilize Barton-McCombie protocol for this purpose as shown in Scheme 2. The required xanthate ester **2A.8a-g** for the Barton-McCombie deoxygenation reaction was obtained in 95% yield by the treatment of **2A.7a-g** with carbon disulfide followed by methylation in the presence of sodium hydride in THF (Scheme-2). **Table-1**



Scheme-2 ***Reagents and conditions****: a) NaH, CS_2, MeI, THF, 95%; b) t-BU_3SnH, AIBN, toluene, reflux, 6 h, 96%*

Table 1. *3-Alkyl/aryl-3-hydroxy-1,4-bis-(4-methoxyphenyl)azetidin-2-ones,* ***2A.7a-g*** *and xanthate esters* ***2A.8a-g***

Comp.	R	Yield (%)[a]	Mp (^oC)[b]	Comp.	R	Yield (%)[a]	Mp (^oC)
2A.7a	*n*-hexyl	68	oil	**2A.8a**	*n*-hexyl	89	Oil
7A.7b	n-pentyl	65	oil	**2A.8b**	n-pentyl	75	Oil
2A.7c	*n*-tetradecyl	68	oil	**2A.8c**	*n*-tetradecyl	96	Oil
2A.7d	*n*-decyl	72	oil	**2A.8d**	*n*-decyl	83	Oil
2A.7e	*n*-nonyl	66	oil	**2A.8e**	*n*-nonyl	97	Oil
2A.7f	phenyl	67	164-166	**2A.8f**	phenyl	92	176-178
2A.7g	3-phenylpropyl	57	oil	**2A8g**	3-phenylpropyl	95	Oil

[a] isolated yields. [b]m.p. of pure *cis* isomer

With the xanthate ester **2A.8a-g** in hand, we proceeded to reduce it by refluxing it with tributyltin hydride in the presence of catalytic amount of AIBN in toluene gave a mixture of *cis trans* isomers **2A.9a-g** and **2A.10a-f** + **2A.1** in (70:30)

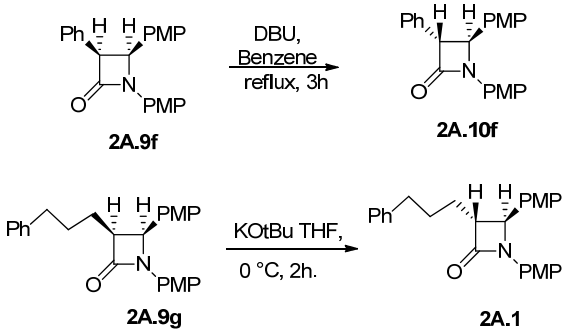
ratio (Table-2) The diastereomeric (*cis:trans*) mixture was confirmed by ^{1}H NMR spectrum.

Table-2-alkyl/3-aryl-azetidin-2-ones:

S. No.	Comp. (xanthate)	R	*cis:trans* (2A.9a-g, 2A.10a-f & 2A.01	Yield (%)[b]	Mp (^{o}C)
1.	**2A.8a**	*n*-hexyl	90:10	93	Oil
2.	**2A.8b**	*n*-pentyl	90:10	96	Oil
3.	**2A.8c**	*n*-tetradecyl	88:12	92	Oil
4.	**2A.8d**	*n*-decyl	88:12	90	Oil
5.	**2A.8e**	*n*-nonyl	94:6	90	Oil
6.	**2A.8f**	phenyl	95:5	92	144-146
7.	**2A.8g**	3-phenylpropyl	70:30	95	96-98

[a] ratios were determined by ^{1}H NMR. [b] isolated yields. [c] m.p. of pure *cis* isomer

Since the cholesterol absorption inhibition activity is mainly associated with *trans*-*β*-lactams, the base-catalyzed epimerization of *cis*- *β*-lactams were studied. In this perspective, **2A.9f** was refluxed in benzene in the presence of catalytic amount of DBU for 3 h. epimerization to form **2A.10f** (88% yield).



Scheme-3 *epimerization of **2A.9f** and **2A.9g***

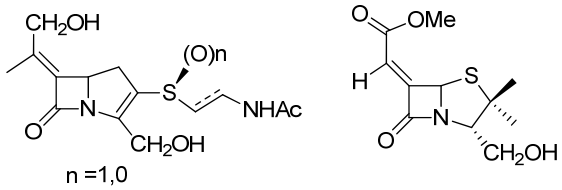
Similarly, **2A.9g** was also heated with DBU but to our surprise no epimerization could be observed in this case even after prolonged refluxing. Therefore, epimerization was attempted using potassium *tert*-butoxide in THF at 0 °C

and to our delight we observed the epimerization by recording the crude ^1H NMR spectrum (*trans:cis,* 84:16). Pure *trans*-isomer **2A.1** was obtained by recrystallization.

<u>Chapter -2 Section B:</u> Stereoselective synthesis of 3-alkylidene/alkylazetidin-2-ones from azetidin-2,3-diones:

This section will deals with syntheses of various 3-alkylidene/alkyl *β*-lactams from azetidin-2,3-diones.

α-alkylidine *β*-lactams are valuable synthetic intermediates which can serve not only for the introduction of side chain of the carbapenems, but also for the preparation of other useful biologically active molecules. 3-Alkylidene azetidin-2-one which has an *exo*-cyclic double bond on C-3 adjacent to the carbonyl carbon, making it more strained, has been shown to possess promising biological activity. For example, such structural frameworks are found as the part structures of the ene type of *β*-lactamase inhibitors such as asparenomycins (**2B.01)**[1], Ro 15-1903 (**2B.02)**[2] and in many related analogues. It has also been used in the synthesis of spiro *β*-lactams either by Diels alder condensation or 1,3 dipolar cycloaddition.

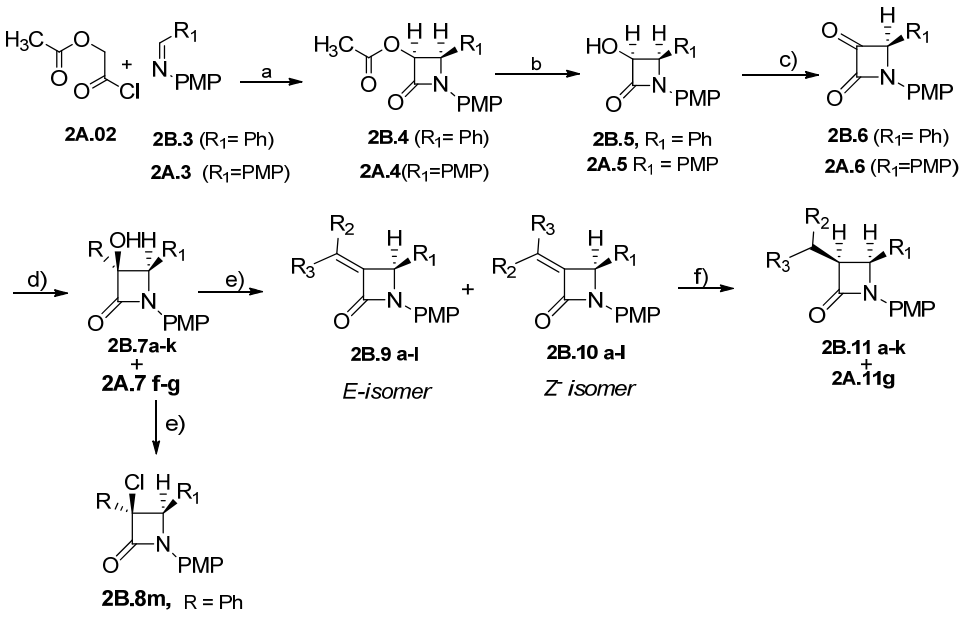


2B.01 **2B.02**

Figure 3. (*3-exo-alkylidine azetidin-2-ones)*

In view of all the aforementioned applications of 3-alkylidene *β*-lactams, we also became interested in devising a route for the synthesis of 3-alkylidene *β*-lactams, further enriching the repertoire of methods available for their synthesis. In addition, we were also interested in the synthetic manipulations of 3-alkylidene *β*-lactams to derive new chemical entities.

The key precursor 3-hydroxy alkyl/aryl azetidin-2-ones (**2B.7a-l** and **2A.7g**) were synthesized following the same procedure as discussed in previous section (**2A.7a-g)**.



Scheme-4. ***Reagents and conditions:*** *a) Et_3N, DCM, 0 °C-rt, 18 h, 65%; b) aq. $NaHCO_3$, Na_2CO_3, MeOH, rt, 18h, 85%; c) DMSO, P_2O_5, rt, 24h, 89 %, d), RMgX, THF, 0 °C, e) PPh_3, CCl_4, reflux, 6 h, 91%*

3-alkyl-3-hydroxyazetidin-2-one **2B.7a-l** and **2A.7g** on reaction with PPh_3 in refluxing CCl_4 did not give the expected 3-chloro-*β*-lactams (**2B.8a-l**). However, dehydration occurred and a mixture of *E* (**2B.9 a-l**) and Z-olefins (**2B.10 a-l**) were obtained in very good yield. *E* and Z isomers were separated by flash column chromatography. The structure of the major compound was established as the *E*-isomer (**2B.9 a-l**) on the basis of ^{1}H NMR spectrum.

Catalytic hydrogenation of a mixture of olefins **2B.9a-l** and **2B.10a-l** using Pd/C gave a mixture of (*cis/trans* 70:30). However *cis trans* selectivity was suppressed to (95:5) by using Pt/C 10% in ethyl acetate. In most of the cases only 3-5% *trans*-isomer was detected from the ^{1}H NMR spectrum.

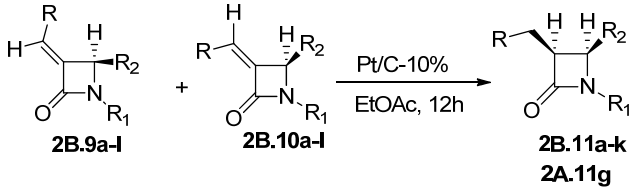


Table-1. 3-alkylidiene-azetidine-2ones *E* & *Z* isomers (**2B.9a-l & 2B.10 a-l**)

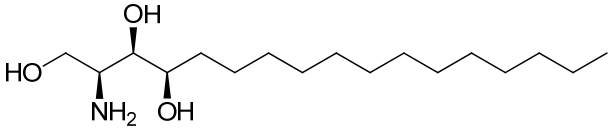
Comp. **2B.9a-l and 2B.10a-l**	R^1	R^2	R^3	Yield[a]	***E*:*Z*** **(2B.9a-l &2B.10a-l)**
a	PMP	*n*-propyl	H	90	72:28
b	Ph	*n*-propyl	H	90	71:29
c	PMP	*n*-heptyl	H	89	71:29
d	Ph	*n*-heptyl	H	88	66:34
e	PMP	*n*-hexyl	H	94	71:29
f	Ph	*n*-hexyl	H	89	69:31
g	PMP	ethyl	H	85	72:28
h	Ph	ethyl	H	86	69:31
i	PMP	Me	Me	71	--
j	Ph	Me	Me	70	--
k	PMP	2-phenylethyl	H	91	70:30
l	Ph	2-phenylethyl	H	89	70:30

[a] Total yield.

<u>Chapter-3:</u> Enantioselective total synthesis of D-*xylo*-phytosphingosine from substituted azetitidin-2-one:

This chapter deals with stereoselective synthesis of D-*xylo*-Phytosphingosine starting from D-mannitol derived β-lactam.

Sphingoshinse, and phytosphinoshines are long chain aliphatic compounds typically possessing a 2-amino-1,3-diol or 2-amino-1,3,4-triol functionality. They are the principle structural backbone of sphingolipids. Sphingolipids are involved in a number of cellular events including cell growth, adhesion differentiation and neutral

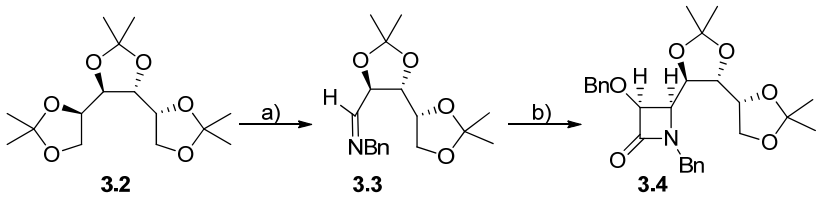


(2S,3R,4R)- D-Xylo-Phytosphingosine (3.1)

Figure-4

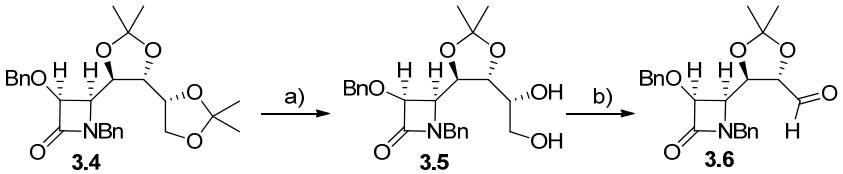
fungi, marine organisms, and even mammalian tissues. They have consist mainly of 18-carbon chain.

Synthesis of D-*xylo*-phytosphingosene begin with the synthesis of starting *β*-lactam **3.4** which was synthesized as a single diastereomer in 65% yield from D-mannitol triacetonide **3.2** in four steps.



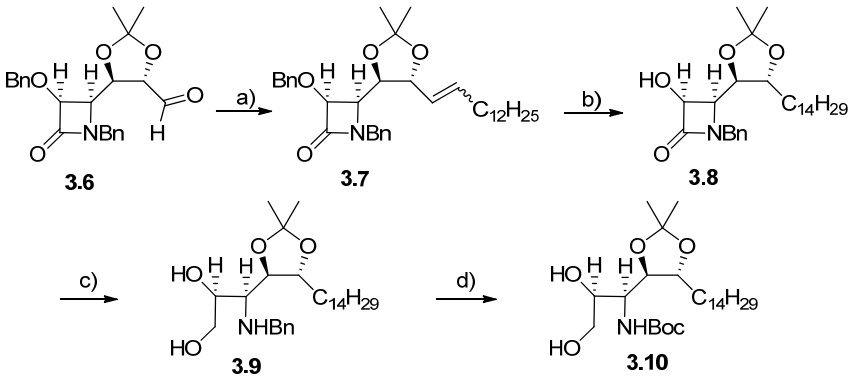
Scheme-5. ***Reagents and conditions:*** *a) (i) p-TSA, MeOH, 30 min, 80%, (ii) $NaIO_4$, DCM : H2O, 0 °C, 1 h, 90%; (iii) BnNH2, DCM, MS 4A°, rt 12 h, 95%, b) $BnCH_2COCl$, Et3N, DCM, -20 °C to rt 20 h, 70%*

The selective deprotection of one of the terminal acetonide group of **3.4** using acetic acid and water (3:1) at room temperature gave diol **3.5** with 90% yield. The sodium periodate mediated cleavage of **3.5** afforded the corresponding aldehyde **3.6** in 75% yield which was used as such for next step without any purification (Scheme 3.11).



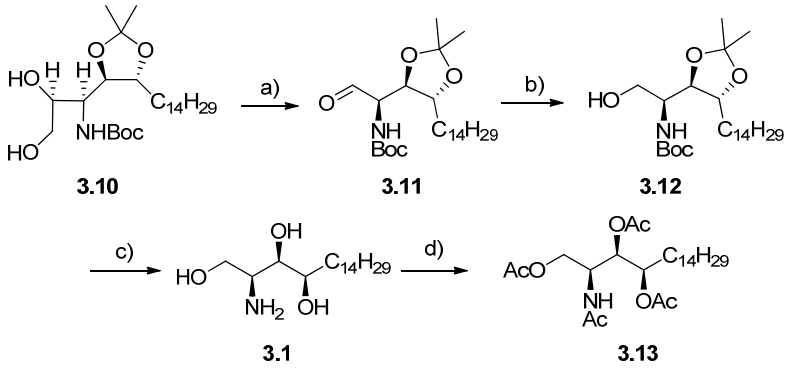
Scheme 6. ***Reagents and conditions:*** *a) Acetic acid, H_2O, (4:1), rt, 8 h, 90%; b) $NaIO_4$, MeOH, H_2O, rt,30 min, 75%.*

Wittig olefination of **3.6** with a 13-carbon ylide at 0 °C produced **3.7** in 70% yield as an inseparable *cis, trans* (55:45) mixture. The geometrical isomeric ratio was of no relevance to the planned synthetic sequence as the double bond was to be reduced in the immediate next step. Accordingly, **3.7** was reduced under transfer hydrogenation condition using ammonium formate and Pd/C 10% in methanol and obtained **3.8** in 80% yield. The reaction, as expected, proceeded with concomitant deprotection of the benzyl group. Treatment of **3.8** with lithium aluminium hydride in THF under reflux conditions gave vicinal diol **3.9.** *N*-Debenzylation of **3.9** by catalytic hydrogenation (Pd/C 10%) at atmospheric pressure of hydrogen followed by *N*-Boc protection in the same pot gave **3.10** in 93% yield over two steps.



Scheme-7. ***Reagents and conditions****: a) $PPh_3BrC_{13}H_{27}$, n-BuLi, dry THF, 0 °C, 1 h, 70%; b) $HCOONH_4$, Pd/C (10%), MeOH, reflux, 4 h; 80%; (c) LAH, dry THF, reflux, 4 h, 93%; (d) H_2, Pd/C (10%), MeOH, $(Boc)_2O$, rt 10 h, 93%.*

The oxidative cleavage of **3.10** using sodium periodate in ethanol/water (1:1) gave desired aldehyde **3.11** in more than 89% yield. Subsequent reduction of **3.12** with sodium borohydride in methanol produced **3.12** in quantitative yield.



Scheme-8. ***Reagents and conditions****: (a) $NaIO_4$, EtOH:H_2O (1:1) rt, 30 min, 89%; (b) $NaBH_4$, dry. MeOH, 0 °C to rt, 10 h; 92%; (c) TFA/H_2O (20:1), DCM, 0 °C, 3 h; (d) Ac_2O, dry Py, DMAP (cat) 91%.*

In order to obtain the target molecule, our next job remained the deprotection of acetonide and Boc group of **3.12** which was easily effected using a mixture of TFA/H_2O and obtained D-(*2S,3R,4R*)-2-amino-1,3,4 trihydroxyoctadecane (**3.1**). This compound was subsequently acetylated using Ac_2O, pyridine and catalytic amount of DMAP to give **3.13** in diastereomerically pure form. All the spectral data were in good agreement with reported one.

<u>Chapter 4:</u> Total synthesis of 3,7-di-*epi*-alexine 1-deoxy-6,8a-di-*epi*-castanospermine and 1,6,8a-tri-*epi*-castanospermine from D-mannitol derived *β*-lactam:

This chapter deals with total synthesis of 3,7-di-*epi*-alexine (**4.2**), 1-deoxy-6,8a-di-*epi*-castanospermine (**4.4**) and 1,6,8a-tri-*epi*-castanospermine (**4.6**) using *β*-lactam as a synthon.

Polyhydroxylated alkaloids such as alexine, epi-alexine castnaopsermine, and epi-castanospermin, their derivatives has attracted considerable interest in recent years due to their potent activity as glycosidase inhibitors. Further interest in this class of compounds has been generated by their wide range of pharmacological activity, including anti-viral, anti-HIV, anti-cancer, anti-feedant and immuneregulatory activity. Stereoisomers of polyhydroxylated pyrrolizidine and polyhydroxylated indolizidine have also been prepared and in some cases evaluated for inhibitory activity.

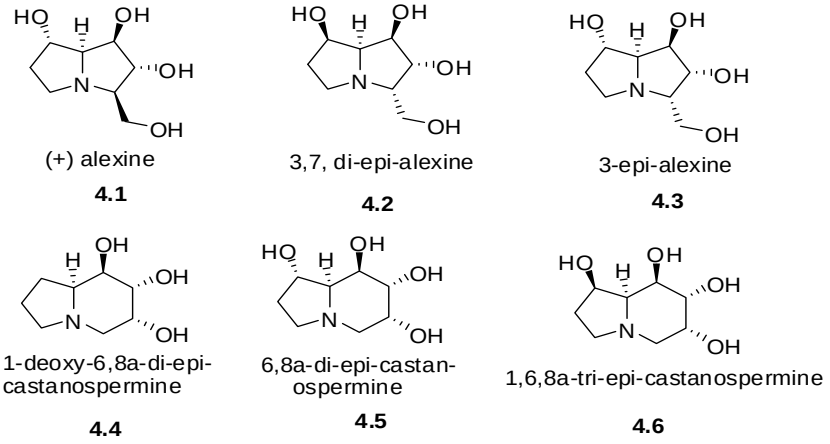
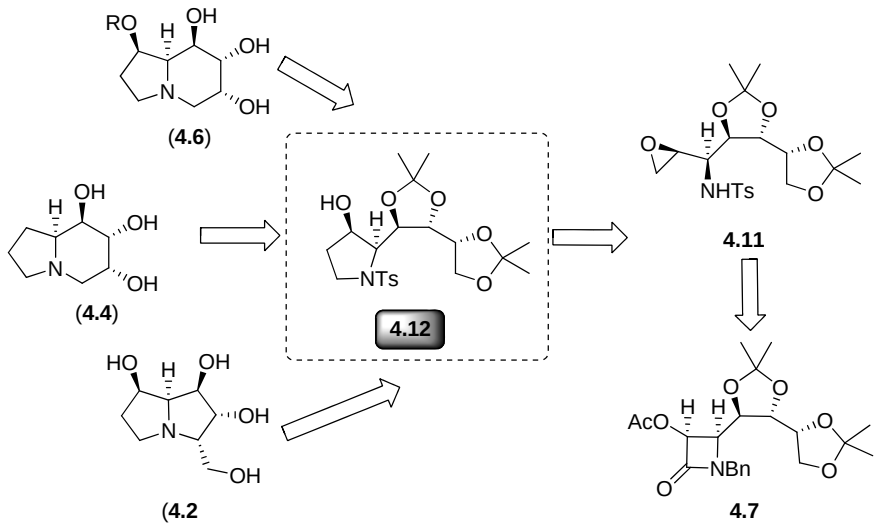


Figure 5.

Retrosynthetic analysis:

Considering the less explored significance of *β*-lactam as a synthon, we ventured into developing an entirely new and versatile strategy for the synthesis of polyhydroxylated indolizidine (**4.4** and **4.6**) and pyrrolizidine (**4.2**) alkaloids. It was visualized that the pyrrolidine derivative **4.12** can be easily synthesized from epoxy amine **4.11** by one carbon homologation followed by cyclization. The epoxy amine in

turn could be obtained from 3-acetoxy *β*-lactam **4.7**. Our key starting material **4.7** can be achieved in very good yield by [2+2]-cycloaddition of imine with suitable ketene.

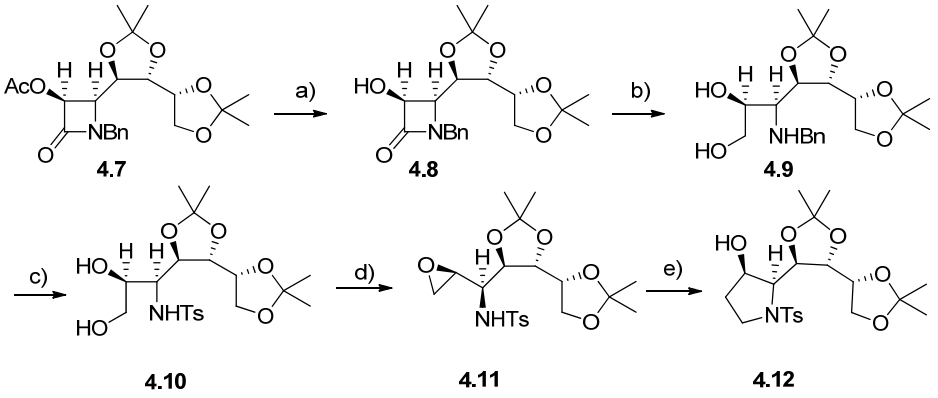


Scheme 4.5. *Retrosynthetic strategy*

Synthesis of (2*S*,3*R*)-2-((4R,4'*R*,5*R*)-2,2,2',2'-tetramethyl-4,4'-bi(1,3-dioxolan)-5-yl)-1-tosylpyrrolidin-3-ol (4.12):

Our synthetic effort towards precursor **4.12** began with the synthesis of 3-acetoxy *β*-lactam **4.7** using [2+2]- cycloaddition reaction of imine with a ketene generated *in situ* from acetoxy acetyl chloride in the presence of triethylamine gave **4.7** in 65% yield. The acetate group of **4.7** was saponified using aqueous sodium bicarbonate in MeOH, at room temp for 6 h to obtain **4.8** in excellent yield as a white solid. Compound **4.8** was converted into vicinal diol **4.9** in more than 88% yield by refluxing it with LAH in dry THF for 6-8 h.

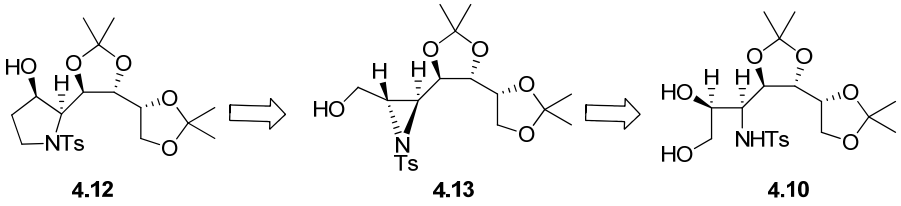
In order to get epoxide **4.11,** the N-benzyl group of **4.9** was deprotected under hydrogenation condition (Pd/C 10%) in ethyl acetate to get a polar amino diol. The primary amine was immediately tosylated using *p*-TsCl and *aq.* K_2CO_3 (1 *eq*) in DCM at room temperature for 4 h to obtain **4.10** in 91% yield. The transformation of **4.10** to **4.11** required selective tosylation of its primary hydroxyl group which was achieved (88%) using Martinell's (*n*-Bu_2SnO/*p*-TsCl/Et_3N/CH_2Cl_2) protocol and the resultant crude on stirring with K_2CO_3 in acetonitrile gave the desired epoxide **4.11** in 93% .



Sceheme-9. ***Regents and conditions: a)*** *aq. $NaHCO_3$, cat (Na_2CO_3, MeOH, 86%, c) $LiAlH_4$, THF, 0 °C , reflux 4-6 h, 89%, c) i) H_2/Pd-C-10%, EtOAc, 1atm, rt, 12 h, quant. (crude), ii) TsCl, K_2CO_3, DCM:H_2O (1:1), rt, 3 h, 91%, d) (i) TsCl, Et_3N, Bu_2SnO (cat), DCM, 0 °C-rt 2 h, 88%, (ii) b) K_2CO_3, CH_3CN, rt, 6 h, 93%, e) NaH, ,$(CH_3)_3SO^+I^-$,, dry DMSO, 85 °C 24 h, 40%.*

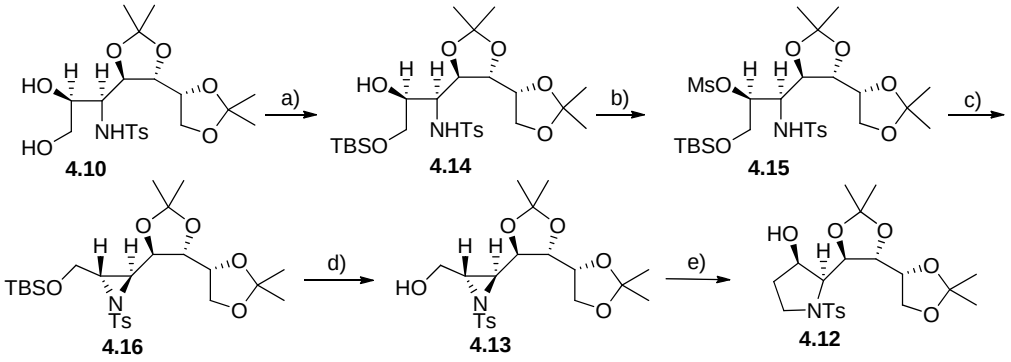
The epoxide **4.11** was then treated with trimethyl sulfoxonium iodide and NaH in dry DMSO and refluxed at 85 °C for 24 h, but a poor yield (40 %) of **4.12** was observed. However, changing solvents (THF or toluene) and reagents (*n*-BuLi/DMPU/THF/reflux) also did not help to us and we got up to 35% yield, which was not good as per expected.

Thus left with little choice, we changed our strategy and proposed to proceed *via* aza-Payne rearrangement of corresponding azeridinol **4.12** as shown in Scheme 10



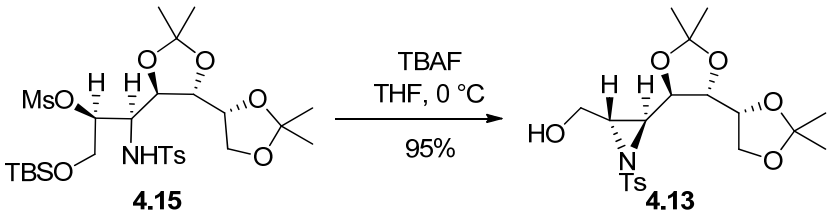
Scheme-10. *Revised retrosynthetic strategy*

The planned aziridinol **4.13** was synthesized from **4.10** by first selectively protecting the primary –OH moiety as TBS (TBSCl, imidazole, DCM, rt) and afterwards the secondary alcohol group was converted into O-Ms moiety (mesyl chloride and pyridine at room temperature) and obtained **4.15** in 88%.



Scheme-11. ***Reagents and conditions:*** *a) TBSDMSCl, Im, CH_2Cl_2 , rt, 1 h, 90%, b) MsCl, Et_3N, rt, 30 min, 87% ; c) n-BuLi, THF, - 78 °C, 2 h 50%; d) TBAF, THF, 65%; e)) NaH,$(CH_3)_3SO^+I^-$, dry DMSO, 85 °C 24 h, 70%.*

Further, mesylate **4.15** was on treatment with NaH in dry THF at 0 °C produced aziridine **4.16** in very low yield (20%). Several optimization attempts using different bases such as KH, *n*-BuLi, and *s*-BuLi also failed to improve the yield. The



Scheme-12.

lower yield may be due the steric hindrance of bulky TBS group. Therefore, it was visualized that replacing the –OTBS moiety with a less bulky group may help. To our delight, while deprotecting the –OTBS group using TBAF in dry THF at 0 °C, we obtained aziridinol **4.13** in 95 % yield (Scheme 4.10). Having Aziridinol **4.13** in hand, the next reaction *i.e.* aza-Payne rearrangement, was attempted by heating it in dry DMSO in the presence of NaH (8 *equiv*.) and trimethyl sulfoxonium iodide which resulted in desired hydroxy pyrrolidine **4.12** in 70% yield. The structure of **4.12** was further confirmed single X-ray -crystallography (Figure 6).

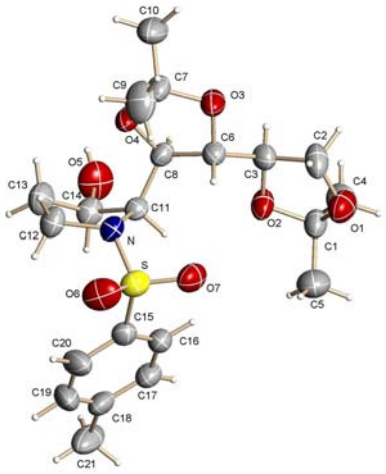


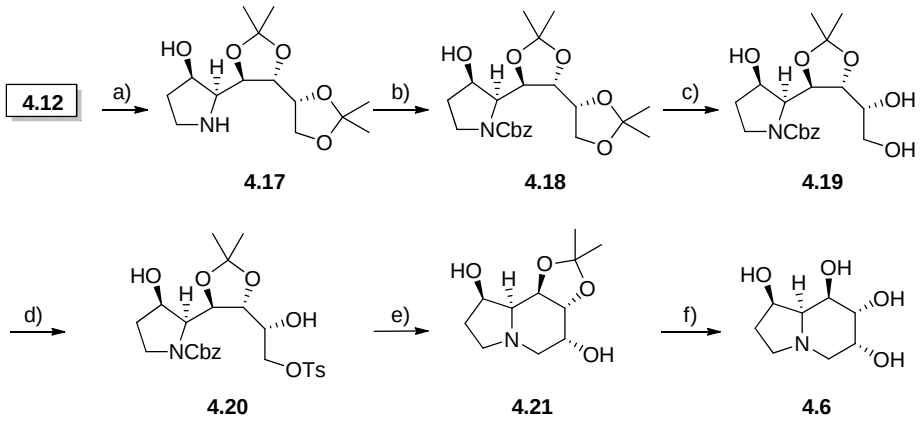
Fig-6-*ORTEP diagram of* ***4.12***

After successful synthesis of **4.12,** we moved on towards the synthesis of **4.6, 4.4** and **4.2** from this compound.

Synthesis of (1*R*,6*R*,7*R*,8*R*,8a*S*)-octahydroindolizine-1,6,7,8-tetraol (1,6,8a-tri-*epi*-castanospermine) 4.6:

Synthesis of 1,6,8a tri-*epi*-castanospermine began with the deprotection of tosyl group of **4.12** which was successfully achieved under Birch reaction condition (Na/Liq NH_3) in more than 90 % yield, at -78 °C in 45 min. The resultant free amine was immediately protected by Cbz group by using aq potassium carbonate in DCM to obtain **4.18** in 90% yield.

Since the transformation of **4.18** to corresponding **4.21** would require cyclization through the terminal hydroxyl group, terminal acetonide was first deprotected by refluxing it in $CH_3COOH/MeOH/H_2O$ (3:2:1) and the resultant primary –OH group was tosylated regioselectively to obtain **4.20** for better leaving ability.



Scheme-12. Reagents and conditions: *a) Na/Liq NH_3, -78 °C, 1 h; b) aq. K_2CO_3, CbzCl, CH_2Cl_2, 0 °C to rt, 30 min, 75% over two steps; c) $CH_3COOH/MeOH/H_2O$, (3:2:1), reflux, 5 h, 75%; d) Et_3N, TsCl, Bu_2SnO (cat), dry CH_2Cl_2, 0 °C, 2 h, 90%; e) H_2, Pd-C-10%, NaOAc, rt, 12 h; f) Dowex 50W-X8, THF-H_2O (3:1), reflux 12 h, 90% over two steps.*

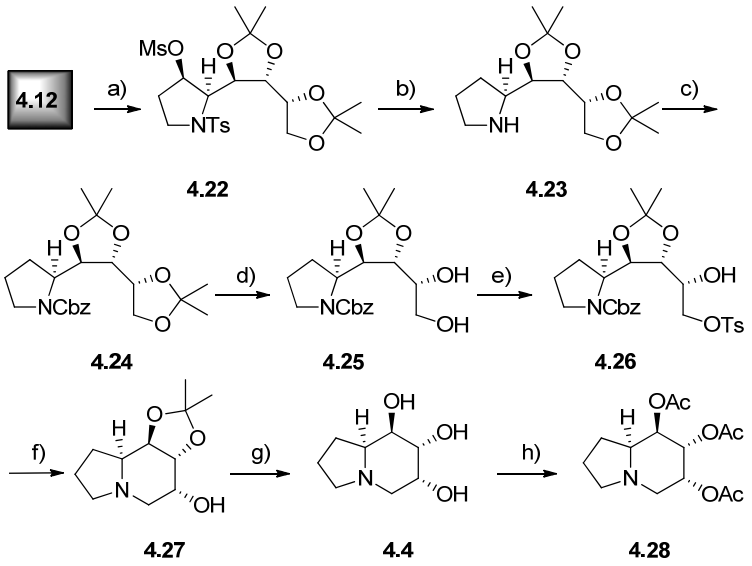
After having fully functionalized **4.20** in hand, our next concern was -NCbz deprotection followed by intramolecular cyclization and global deprotection to complete the total synthesis of 1,6,8a-tri-*epi*-castanoeprmine **4.6**. In this context, the deprotection of -NCbz group and intramolecular cyclization was carried in one pot by catalytic hydrogenation (Pd/C, 10%) in the presence of sodium acetate in dry MeOH

which gave **4.21** in 90% yield. The crude **4.21** on refluxing with acidic Dowex 50W-X8 in THF-H_2O (3:1) gave target molecule **4.6** in 85% yield.

Synthesis of (6*R*,7*R*,8*R*,8a*S*)-octahydroindolizine-6,7,8-triol-(1-deoxy-6,8a-di-*epi*-castanospermine 4.4):

After successfully completing the total synthesis of 1,6,8a-tri-*epi*-castanospermine **4.6**, we focused our effort on the synthesis of 1-deoxy-6,8a-di-*epi*-castanospermine **4.4** from the hydroxyl pyrrolidine **4.12** by following the steps as shown in Scheme 4.10 .

Towards our effort for deoxygenation of C3-OH of **4.70**, free hydroxyl moiety was first mesylated using mesylchloride in the presence of triethyl amine to obtain **4.22** in 85% yield.

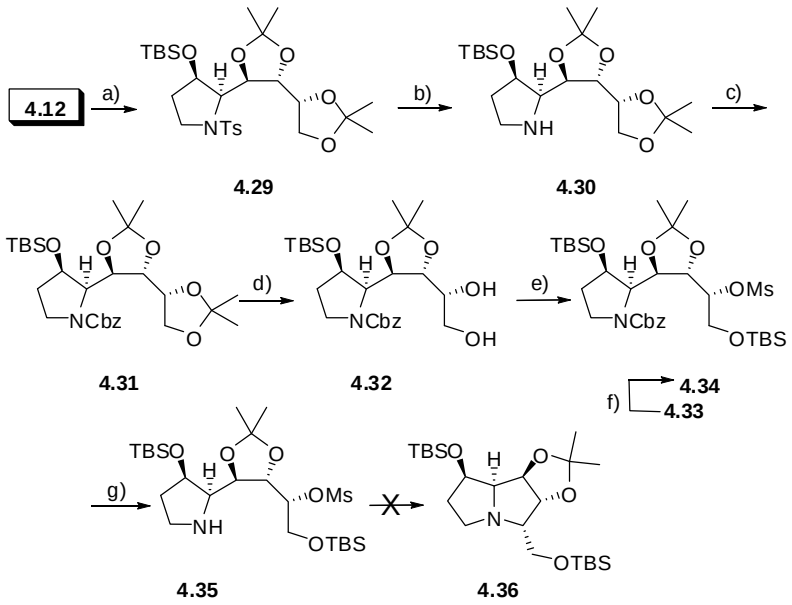


Scheme-13. Reagents and conditions: *MsCl, Et_3N, 0 °C, 1 h, 85%; b) LAH, reflux, 5 h,87%; c) aq K_2CO_3, CbzCl, 0 °C to rt, 1 h, 85% over two steps; d) $CH_3COOH/MeOH/H_2O$, (3:2:1), reflux, 5 h, 77%; e) Et_3N, TsCl, Bu_2SnO (cat), dry CH_2Cl_2, 0 °C, 2 h, 90%; f) H_2, Pd-C-10%, NaOAc, rt, 12 h, g) Dowex 50W-X8, THF-H_2O (3:1), reflux 12 h, 88% over two steps; h) Py, Ac_2O, rt 10 h, 90%.*

LAH reduction of **4.22** in dry THF under reflux condition, to our delight, produced **4.23** in 87% yield by effecting deoxygenation as well as *N*-detosylation in the same pot. As per our synthetic plan secondary amine of **4.23** was immediately protected by Cbz group to give **4.24 (**85% yield), Synthesis of 1-deoxy-6,8a di-*epi*-castanospermine (**4.4)** was achieved in four steps from the intermediate **4.24** by following the same reaction sequences as shown in previous Scheme 12.

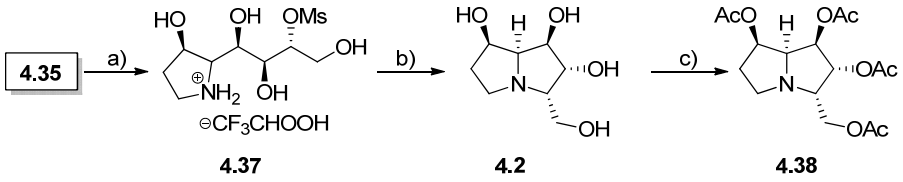
(1*R*,2*R*,3*S*,7*R*,7aS**)-3-(hydroxymethyl)-hexahydro-1H-pyrrolizine-1,2,7-triol (3,7-di-*epi*-alexine):**

We executed the synthesis of 3,7-di-*epi*-alexine **4.2**, as perceived through the retrosynthetic analysis (Scheme 4.5) by first protecting the free hydroxyl group of **4.12** was protected as -OTBS to give **4.29.** *N*-Detosylation under Birch reaction condition followed by Cbz protection gave **4.31** in 85% yield over two steps. The terminal aceotonide of **4.31** was selectively hydrolyzed under mild acidic condition using DOWEX 50 X8 to give diol **4.32** in quantitative yield**.** Selective TBS protection followed by mesylation gave **4.34** in 90% yield.



Scheme-14. ***Reagents and conditions:*** *a) TBSOTf, Et_3N, CH_2Cl_2, 0 °C to rt 2 h, 92%; b) Na/Liq NH_3, -78 °C, 1 h; c) aq. K_2CO_3, Cbz, CH_2Cl_2, 0 °C to rt, 1 h, 85% over two steps; d) Dowex 50W-X8, MeOH:$H_2$0, (9:1), 90%; e) TBSCl, Im, CH_2Cl_2, rt, 1 h, 90%; f) MsCl, Et_3N, THF, 0 °C, 30 min, 85%; g) H_2, Pd/C-10%, NaOAc, MeOH, rt 12 h, 90%.*

Cbz deprotection of **4.34,** gave uncyclized product, no spontaneous cyclization occurred. This failure may be due to presence of *trans* diol protected acetonide causing strain. Therefore all protecting group of **4.34** were removed by heating with 90% aq TFA and obtained **4.37,** was then treated with sodium acetate in MeOH to give desired product **4.2** in 89% yield. The compound **4.2** was further converted into its tetraacetate derivative for convenience in purification and characterizations.



Scheme-15. *Reagents and conditions: a) 90% aq TFA, rt, 5h; b) NaOAc, MeOH, rt, 10 h; c) Ac_2O, Py, DMAP (cat), rt, 12 h, 75% over three steps.*

CHAPTER 1

Introduction of Azetidin-2one (β-lactam)

1.1 A brief history of *β*-lactam:

Azetidin-2-one (*β*-lactam), a four membered cyclic amide, is a part sub-structure of many biologically important antibiotics. The unique structural features and chemotherapeutic properties of *β*-lactam continue to attract the attention of synthetic organic chemists owing to much of their pharmaceutical value and the variety they provide in terms of synthetic challenges. Although, the first synthesis of *β*-lactam ring was reported way back in 1907 by Staudinger,[1] the actual worth of this ring was recognized after Fleming's landmark discovery of Penicillin in 1928[2]. It was actually Prof. R. B. Woodward who first proposed the structure of Penicillin based on a *β*-lactam ring which was later confirmed and unambiguously proved by X-ray crystallography.[3]The azetidin-2-one ring was identified as the key structural unit responsible for the antibiotic activity.

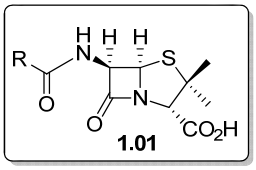


Figure 1.1. *Azetidin-2-one (Penicillin, β-Lactam ring)*

Until 1970, Penicillin and Cephalosporins[4] were the only examples of naturally occurring *β*-lactam antibiotics; the discovery of 7-a-methoxycephalosphorins[5] from *"Streptomyces"* in 1971 stimulated the search for novel antibiotics. The *β*-lactam antibiotics are now classified into several groups based on their structures (Figure 1.2)

Apart from above mentioned structural manifolds used as antibiotics, there are some other analogues which have also emerged as potent molecules in this category. For example, carbacephams,[6] the carbon analogues of cephalosporins are also being used as antibiotics. In fact, they have superior stability over cephalosporin. Lorabid (**1.11**) is the first molecule in this category to be approved for clinical use (Figure 1.3). Tricyclic *β*-lactam antibiotic (e. g. GV 104326) called trinems[7] (**1.12**), a new class of tricyclic carbapenems are known to be highly potent broad-spectrum antibacterial agent effective against gram-positive, gram-negative and anaerobic pathogenic bacteria.

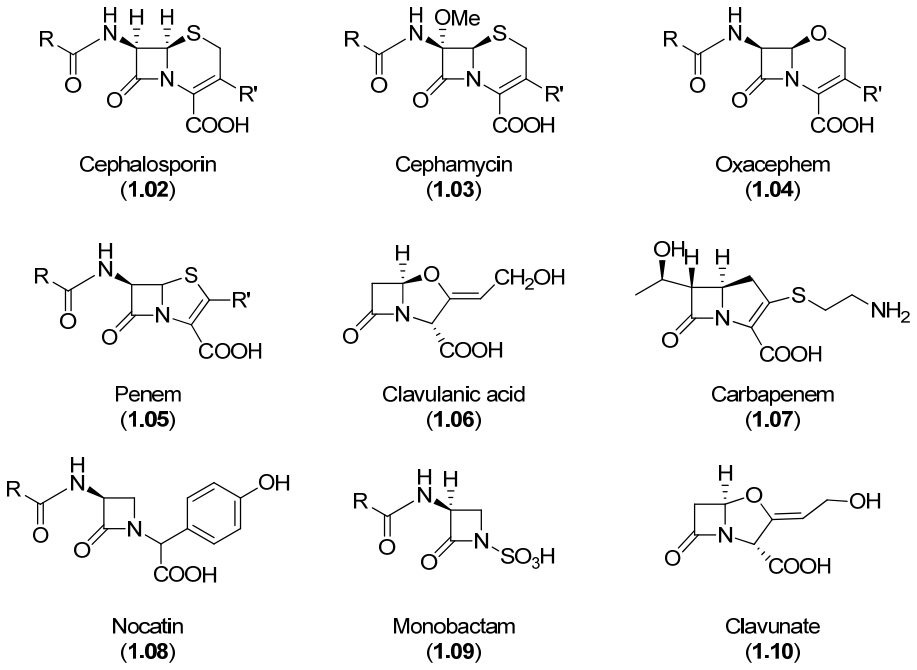


Figure 1.2. Classification of *β*-lactam antibiotics based on core structure

In 1995, a new class of compound (**1.13**) was also discovered[8] in which antibiotic property of *β*-lactams and antiviral property of nucleoside were incorporated together to afford dual properties to the drug. Kahagia *et al*.[9] reported another member of this class of *β*-lactams **1.14** in which steroidal and *β*-lactam units were coupled together *via* Ugi reaction.

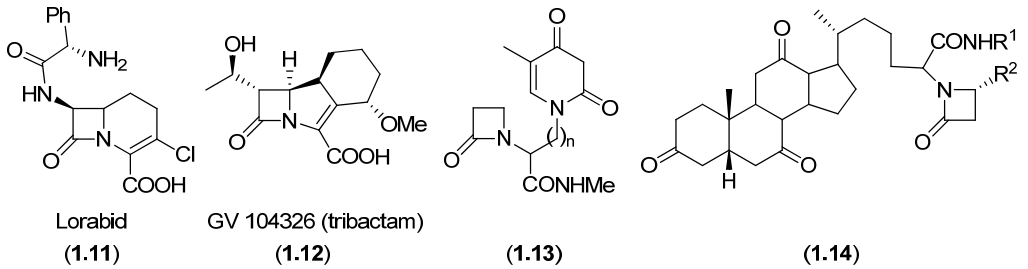
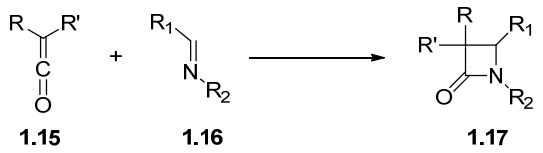


Figure 1.3. *Novel examples of biologically active molecules containing β-lactam*

1.2 General methods for the synthesis of the azetidin-2-one (*β*-lactam) ring system (Staudinger reaction):

Over the past few decades several methodologies have been developed to construct *β*-lactam ring *viz.,* hydroxamate cyclization[10], metalloester enolate-imine condensation[11], chromium carbene-imine reaction[12], isocyante-alkene cycloaddition[13],

and the ketene-imine cycloaddition (also known as Staudinger reaction)[1a]. However, the later method has provided useful and economical entries to the β -lactams, mainly due to the easy availability of both Schiff base and ketenes. This reaction utilizes the use of an acid chloride and an imine (Schiff base) in the presence of a tertiary amine (typically triethylamine). A ketene (**1.15**) is generated *in situ* from the β-elimination of the acid chloride in the presence of a tertiary amine which on [2+2]-cycloaddition reaction with an imine (**1.16**) results β-lactam ring efficiently with four possible diastereomers.



1.15 **1.16** **1.17**

Scheme 1.1. *Staudinger's (ketene-imine) reaction*

1.3 Asymmetric Induction in Staudinger reaction for the synthesis of β-lactams:

Asymmetric synthesis of β-lactams is an important area of research as their biological activity is closely related to their stereochemistry. Among the various methods available for the asymmetric synthesis of β-lactams, Staudinger reaction (ketene-imine cyclization) is the most widely used method due to its simplicity and versatility. Asymmetry can be induced in the Staudinger cycloaddition reaction by using chiral imine[14], chiral ketene [15]or chiral catalyst.[16,17]

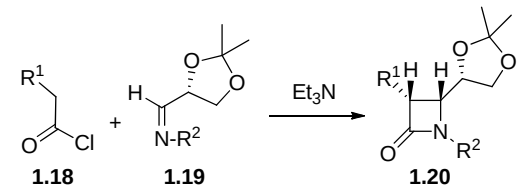
A brief summary of the methods using chiral imine, chiral ketene or chiral catalyst in Staudinger reaction is highlighted below.

1.4 Asymmetric Staudinger reaction using chiral imine:

The asymmetric induction in the reaction of achiral ketenes with chiral imines derived either from chiral aldehydes or chiral amines have been employed. In the later case, however, β-lactams are often produced, if at all, with low levels of diastereoselectivity.

Although, Staudinger reaction is known from more than 100 years, the first asymmetric Staudinger reaction[18] appeared only in 1983 by using D-mannitol derived imine **1.19** which gave corresponding β-lactam with complete diastereoselectivity.

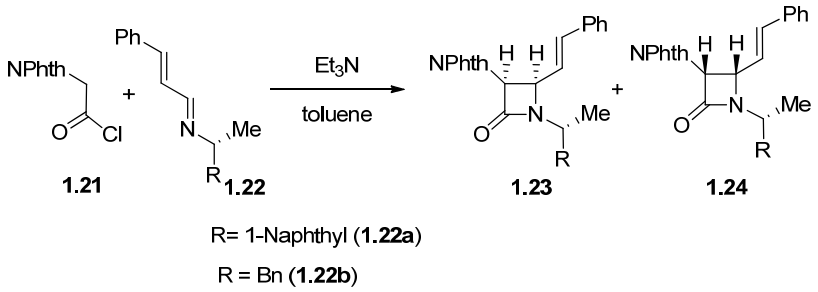
The high diastereoselectivity in this reaction is governed by chiral substituent present at α-position of Csp^2 atom of the imine (Scheme 1.2).



Scheme 1.2

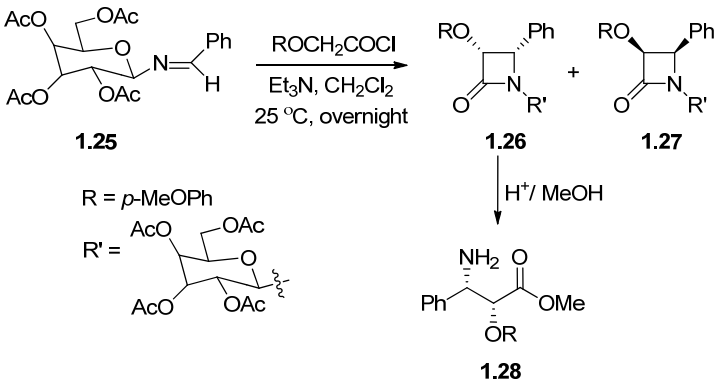
This observed high diastereoselectivity, opened door for many organic chemists to attempt diastereoselective Staudinger reaction utilizing carbohydrates and aminoacid derived imines. A few selected examples are described as follows:

George *et al.* illustrated the use of imines **1.22,** derived from both (*R*)-(1-naphthyl) ethylamine to obtain corresponding β-lactams **1.23** and **1.24 in** 82:18 ratio. The high diastereoselectivity is suggested due to the bulkiness of the naphthyl group.[19]



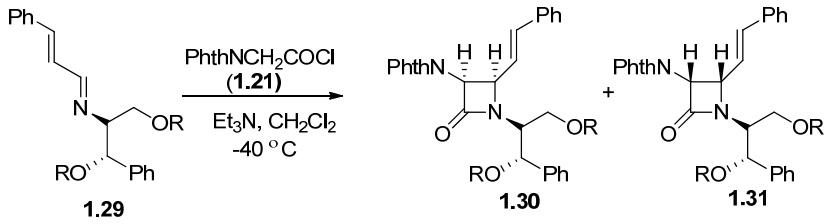
Scheme 1.3

The same group has further employed imine **1.25**, derived from 2,3,4,6-tetra-*O*-acetyl-β-D-galactose amine, and reported poor diastereoselectivity (*dr* 60:40). In this reaction, the α-anomer was found unreactive (Scheme-1.4)[20].



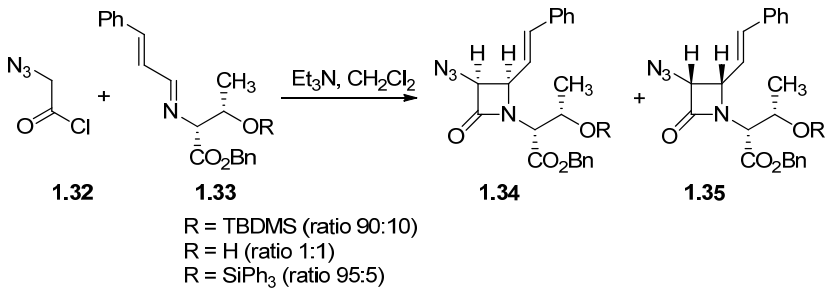
Scheme 1.4.

Gunda[21] has used **1.29,** derived from (1*S*, 2*S*)-2-amino-1-phenyl-1,3-propanediol and reported 2.5:1 diastereoselectivity (Scheme 1.5). The poor diastereoselectivity is due to the longer distance between the stereo directing group and the newly generated chiral center.



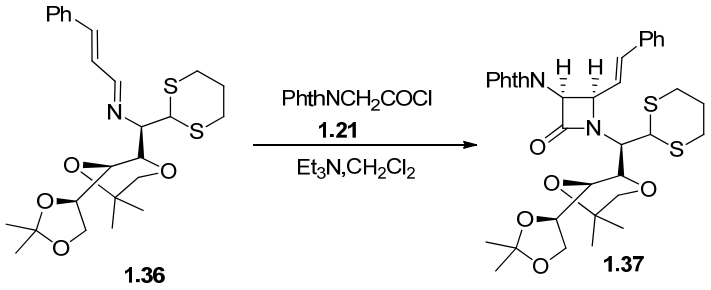
Scheme 1.5

The diastereoselectivity using D-threonine derived imine **1.33** was found to depend on the bulkiness of the protecting group on the hydroxyl moiety. For example, the more bulky group ($SiPh_3$) gave (95:5) whereas the less bulky group such hydrogen gave (1:1) diastereomeric ratio (Scheme 1.6).[22] The poor selectivity in the later case was explained by considering the strong hydrogen bonding between the ester carbonyl group and the *β* hydroxyl group giving the Schiff base an almost planar structure.



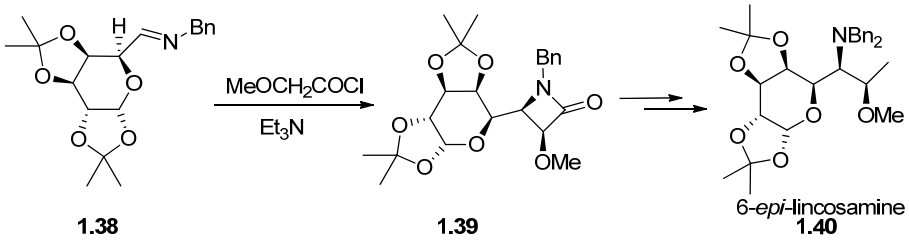
Scheme 1.6.

Imine **1.36,** derived from D-Glucosamine[23]and cinnamaldehyde, is reported give complete diastereoselectivity, producing *cis* β-lactam **1.37** in 82% yield (Scheme 1.7). The bulky substituents on both ketene as well as imine have influenced diastereoselectivity.



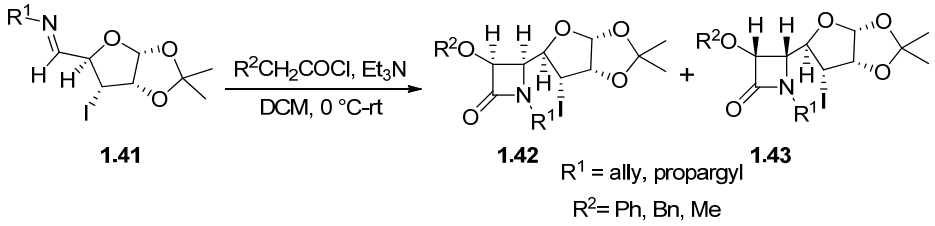
Scheme-1.7

Single *cis*-diastereomer **1.39** was obtained in 70% yield by the reaction of D-galactopyranose derived chiral imine **1.38** and methoxy-ketene (Scheme 1.8).[24]



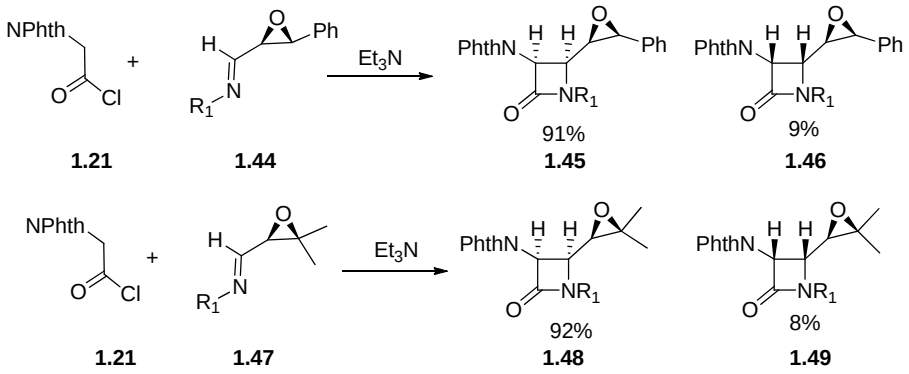
Scheme 1.8.

However, D-glucose derived imine **1.41** gave poor selectivity (1:1. The poor diastereoselectivity was implicated to the aliphatic chain in the amine (Scheme 1.9).[25]



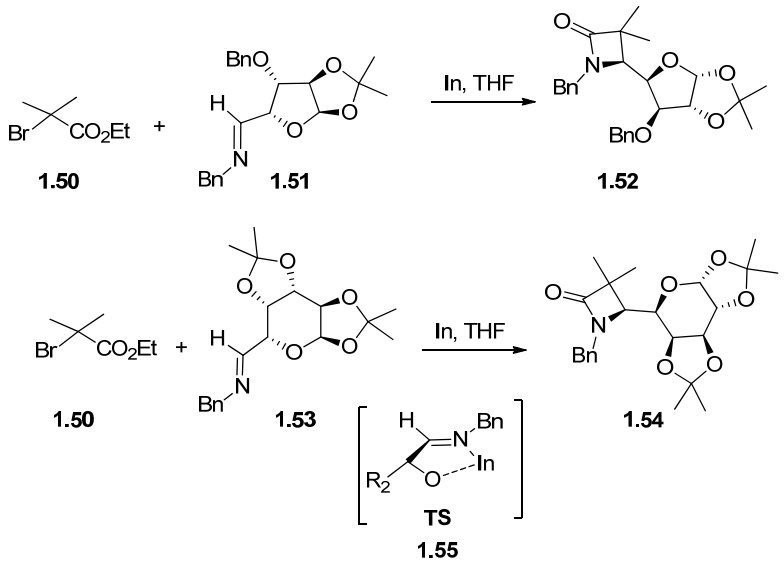
Scheme 1.9.

Evans *et al.* have reported high diastereoselectivity (91:9) using chiral epoxyimines (**1.48** & **1.52**) (Scheme 1.10).[26]



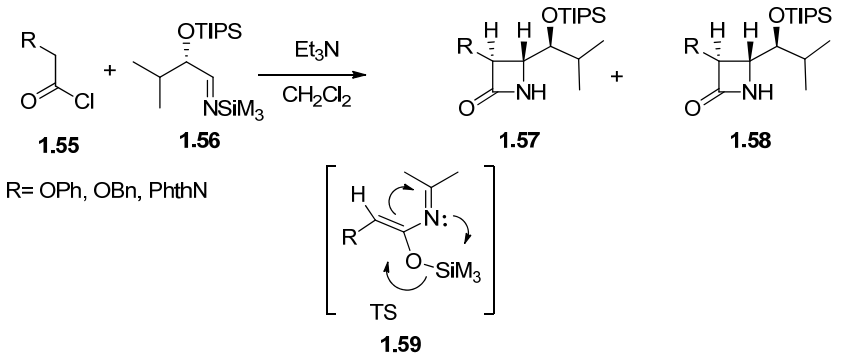
Scheme-1.10

Indium catalyzed highly diastereoselctive (98:2) synthesis of *β*-lactams, using imines **1.51** and **1.53,** was recently reported by Soengas *et al.*[27] in more than 70% yield. The high diastereoselectivity is explained due to the chelation of indium with the nitrogen and oxygen atoms of the imine as given in transition state (**1.55**) (Scheme 1.11).



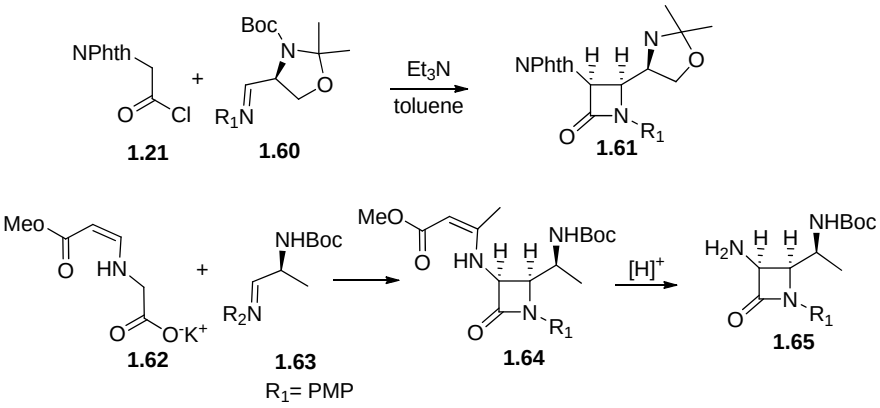
Scheme-1.11

Recently, Panunzio and co-workers have also reported *trans*- diastereoselectivity (85:15) in the formation of **1.57** involving transition state **1.59** as shown in Scheme-1.12.



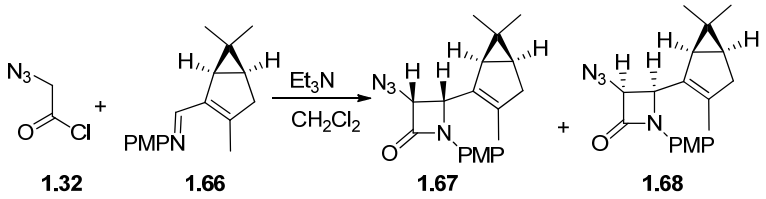
Scheme-1.12

Alternatively, the use of N-Boc-α-amino imines, readily obtainable from the α-amino aldehydes, is also known to form diastereomerically pure **1.61** in 85% yield. Likewise, the reaction of the Dane salt of glycine **1.62** with imine **1.63** also gives pure **1.64**. The origin of extremely high diastereoselectivity is implicated to the stereoelectronic effects of substituents at C3 (Scheme-1.13)[29]



Scheme-1.13

On the other hand, Bhaval *et al.* have reported that imine **1.66** gives a mixture of **1.67** and **1.68** in 86:14 diastereoselectivity (Scheme-1.14).[30]

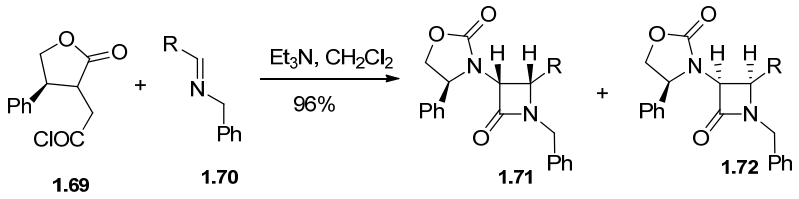


Scheme-1.14

1.5 Asymmetric Staudinger reaction using chiral ketene:

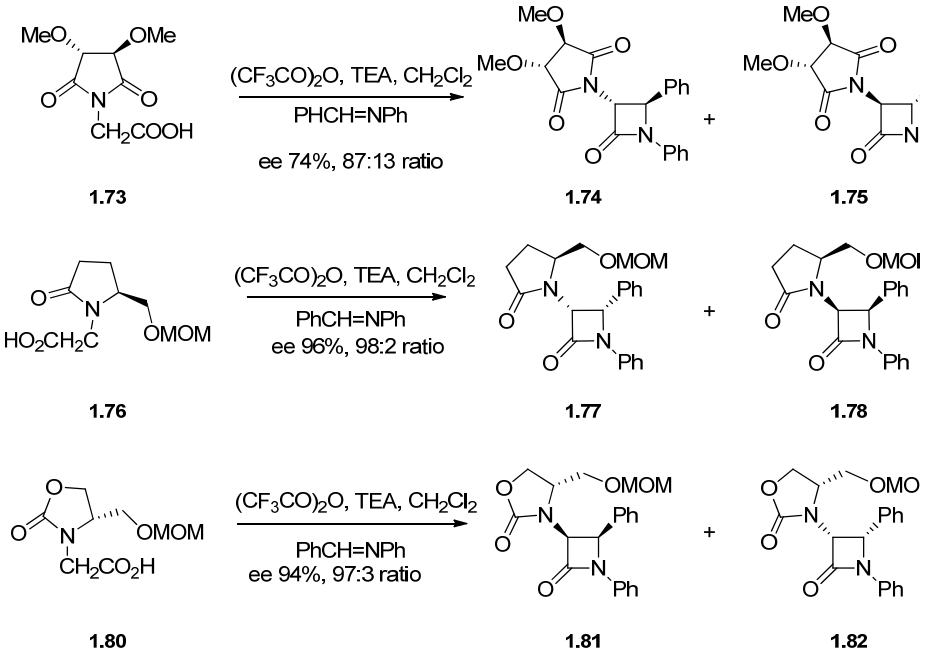
Various levels of diastereoselectivity in *β*-lactam formation using chiral ketene component have been reported. A brief review of this area is as follows:

The cycloaddition of Evans-Sjogren ketenes, generated from chiral oxazolidinyl acid chlorides **1.69** and triethylamine, with achiral imines **1.70** afforded *β*-lactams **1.71** and **1.72** in 96% diastereoselectivity and 90 % yield. (Scheme 1.15).[31]



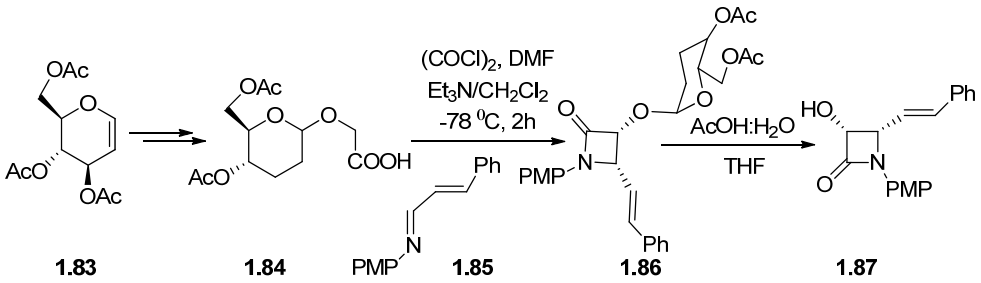
Scheme 1.15.

Similarly, high stereoselectivity is also reported in the reaction of chiral ketenes derived from **1.73, 1.76** and **1.80** as shown in Scheme 1.16.[32]



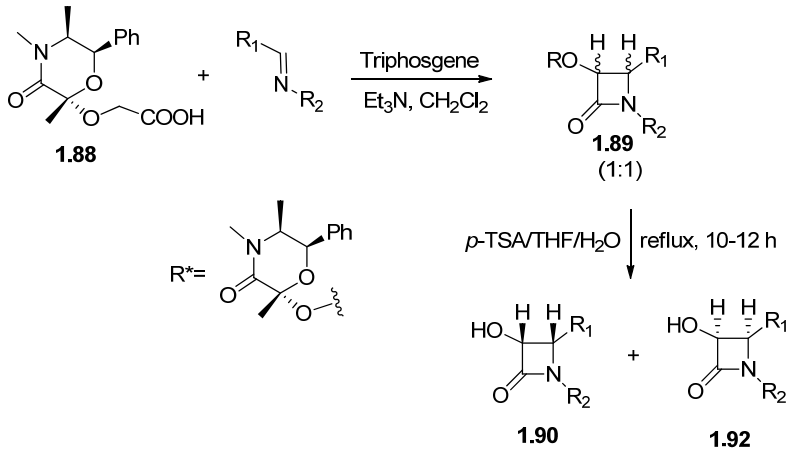
Scheme 1.16

However, tri-*O*-acetyl-D-glucal derived chiral ketene is found to give modest diastereoselectivity (70:30) (Scheme 1.17).[33]



Scheme 1.17.

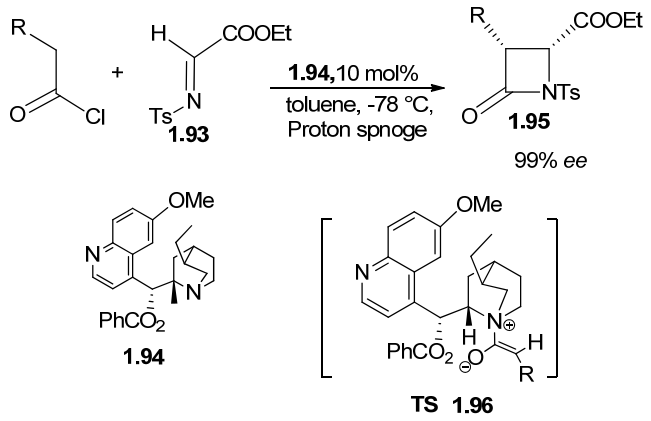
Ephedrine derived chiral ketene **1.88** has also been used[34] for asymmetric Staudinger reaction with various imines; however, no diastereoselectivity was observed (Scheme 1.18).



Scheme 1.18.

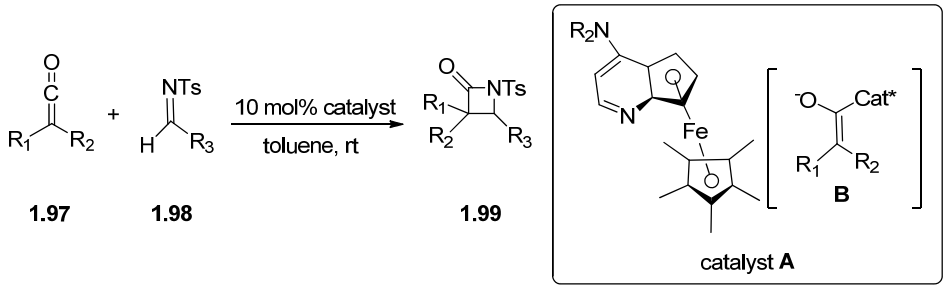
1.6 Asymmetric Staudinger using chrial catalyst:

Although, there are many attempts of inducing chirality in Staudinger reaction using both metal based catalysts and organo-catalysts. A wide range of induction has been noticed. Following are two examples in which maximum induction has been reported. Taggi *et al.* have employed benzoylquinine **1.194** and have reported high enantioselectivity (*ee* 99%),[35] however yield was only 36%. Mechanistically, zwitterionic **1.196** is proposed to be the intermediate where *re*-face is open for the imine to approach.



Scheme-1.19

Recently Hodous and Fu[36] have reported the use of a ferrocene based chiral catalyst (**A**) to obtain induction up to 98% *ee* (Scheme 1.19).



Scheme-1.20. *catalytic asymmetric Staudinger reaction*

1.7 Azetidine-2-ones, versatile building block for the stereoselective synthesis of alkloids, aminosugars, *α* and *β*-aminoacids, macroloids, and related alkaloids:

Besides their biological activities, *β*-lactams have gained importance as synthons in organic synthesis due to the possibility of selective ring cleavage of any one of the four single bonds (**Fig-1.4)**. However, the sequential or simultaneous fragmentation of two bonds of the 2-azetidinone ring has been seldom reported. The usefulness of these substrates for the preparation of substances of biological interest, including *α*-amino acids, *β*-amino acids, indolizidines, pyrrolizidines, eight-membered lactams, and complex natural products is well documented in literature[37,38].

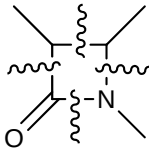
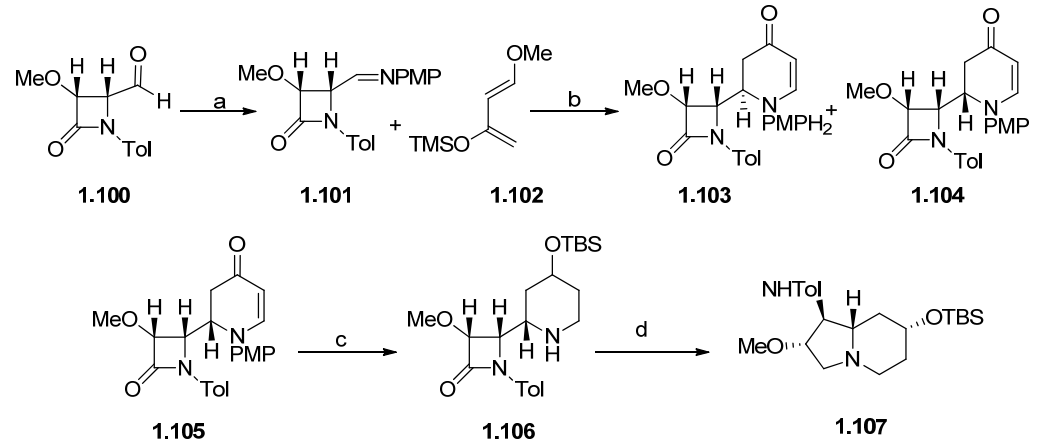


Figure 1.4 (Azetidinone ring)

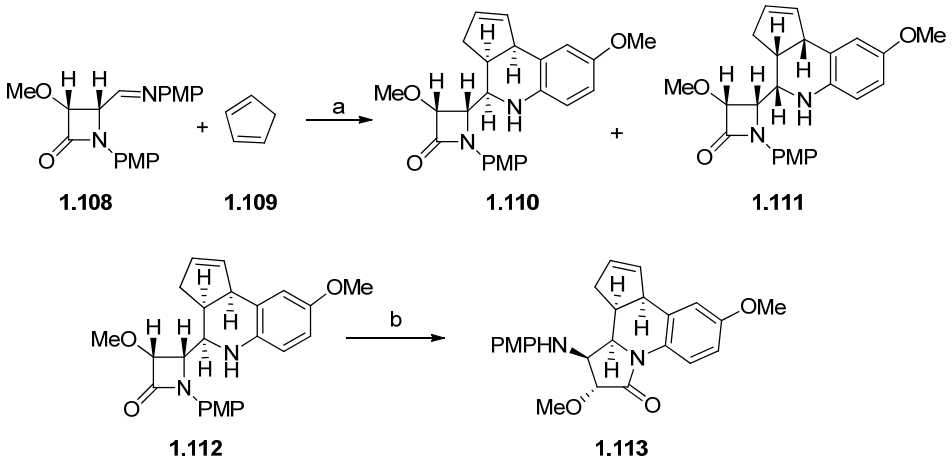
Organic chemists have successfully demonstrated the usefulness of the *β*-lactam nucleus in stereocontrolled synthesis of varied class of compounds through impressive variety of transformations carried out with this system. Few selected examples of *β*-lactam as a synthon is described as follows:

Alcaide *et al.* have synthesized various indolizidine systems **1.07** from **1.100** involving aza- Diels-ader cycloaddition reaction between 2-azetidinone-tethered imine **1.101** with Danishefsky's diene **1.102** as the key step (Scheme 1.21).[39]



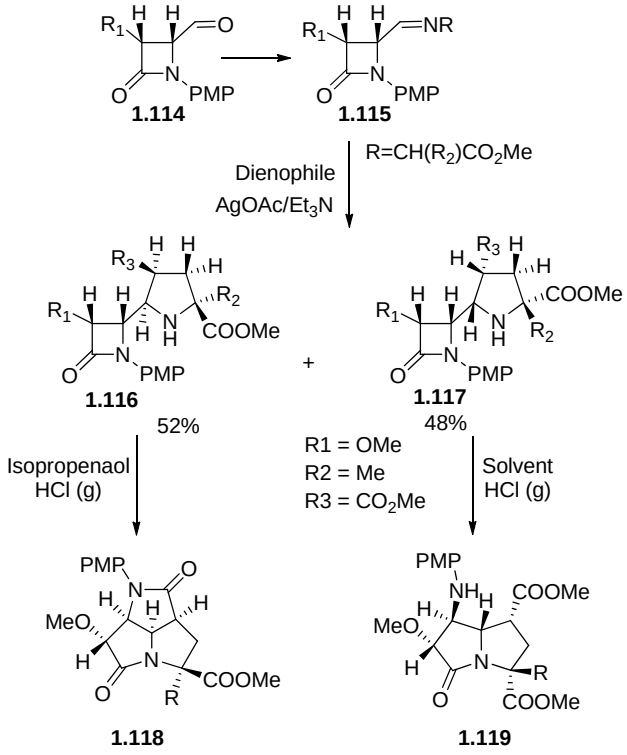
Scheme 1.21. ***Reagents and conditions:*** *a) P-*anisidine, $MgSO_4$, CH_2Cl_2; *b)* $ZnCl_2$, CH_3CN, *-20 °C, 95%; c) i) L- Selectride, ii)* $NaBH_4$, *iii) TBSCl, iv) CAN; d) NaOMe, MeOH, rt, 16 h.*

The same methodology has further been employed for the construction of tetracyclic indolizidine derivative **1.113** by using cyclopentadiene in the presence of indium. In this synthesis, the yield of the cycloaddition was very good (98%), however, diastereoselectivity was very poor (1:1). Scheme-1.22



Scheme 1.22. ***Reagents and conditions****: a) Incl*$_3$*, rt, 1 h; b) NaOMe, MeOH, rt, 16 h.*

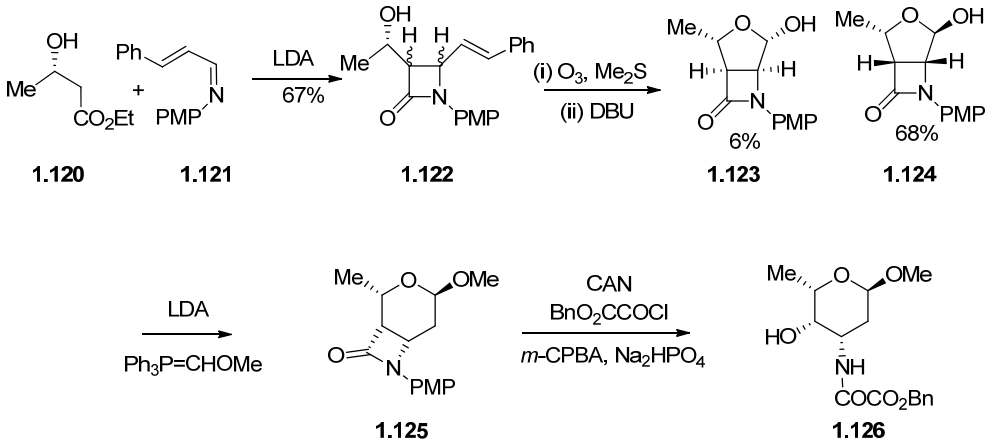
The same group have also described[40] the synthesis of complex pyrrolizidine alkaloids by 1,3-dipolar cycloaddition of an azomethine ylide, generated from **1.115,** with an appropriate dienophile (Scheme-1.23) as the key step.



Scheme 1.23

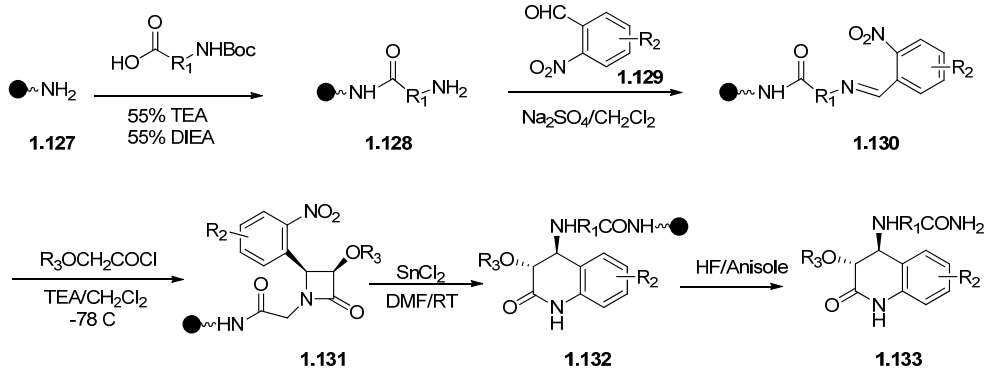
Hert *et al.*[41] have accomplished the enantioselective syntheses of aminosaccharides, analogs of daunosamine **1.126** using diastereomeric mixture of

1.22, obtained by the reaction of ester-enolate cycloaddition between **1.120** and **1.121**. This strategy involves the transformation of **1.125** to **1.126** followed by simple functional group transformations as shown **S**cheme 1.24.



Scheme 1.24.

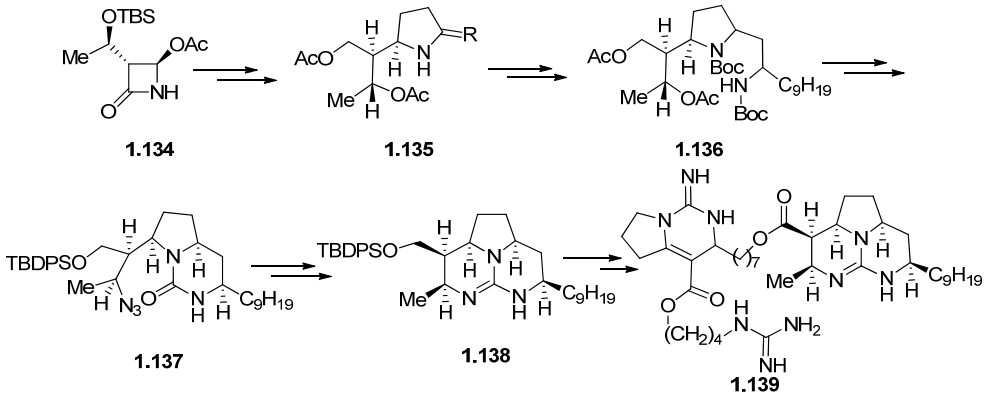
Synthesis of 3,4-dihydro-2(*1H*)- quinolinones **1.133** in 6 steps with 8% overall yield have been reported[42] through the Lewis acid mediated rearrangement of *β*-lactam intermideate **1.131** on solid phase.



Scheme 1.25 *Pei's approach*

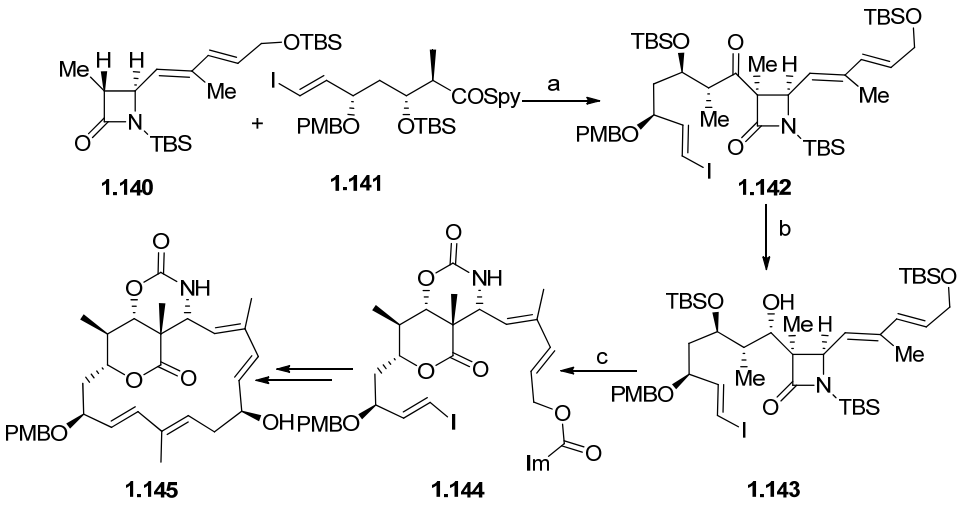
Gurjar *et al.*[43] have exploited commercially available *β*-lactam (**1.134**) as a building block for the synthesis of tricyclic guanidine segment **1.138** of batzelladine A (**1.139**) as shown in Scheme 1.26.

Batzelladine A-E was first isolated by a group of scientists at Smith-Kline Beecham from red Caribbean sponge of genus *Batzella*[44]. These natural products are well known for *anti*-HIV activity.



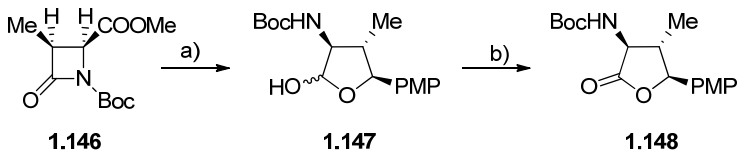
Scheme-1.26.

Another antitumor antibiotic lankacidin C [45] (a group of 17 membered macrocylic tetraenes) was synthesized from **1.140** via *β*-keto lactam **1.142** as shown in Scheme 1.27. The lankacidin show strong antimicrobial activity against a variety of gram-positive bacteria.



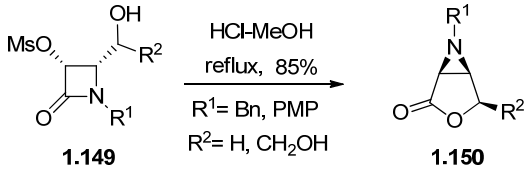
Scheme-1.27. ***Reagents and conditions****: a) LDA, THF, -78 °C, 85%; b) KEt$_3$BH, Et$_2$O, -78 °C, 85%; c) (i) Bu4NF, THF, rt, 2h, (ii) MsOH, rt, 2 h, (ii) Et$_3$N, CDI, DMAP, CH$_2$Cl$_2$, rt, 12 h 70%;*

Palomo *et al.*[46] have prepared **1.48,** part structure of nikkomycin, an antifungal agent**,** in enantiopure form from **1.46 (**Scheme 1.28) in three steps.



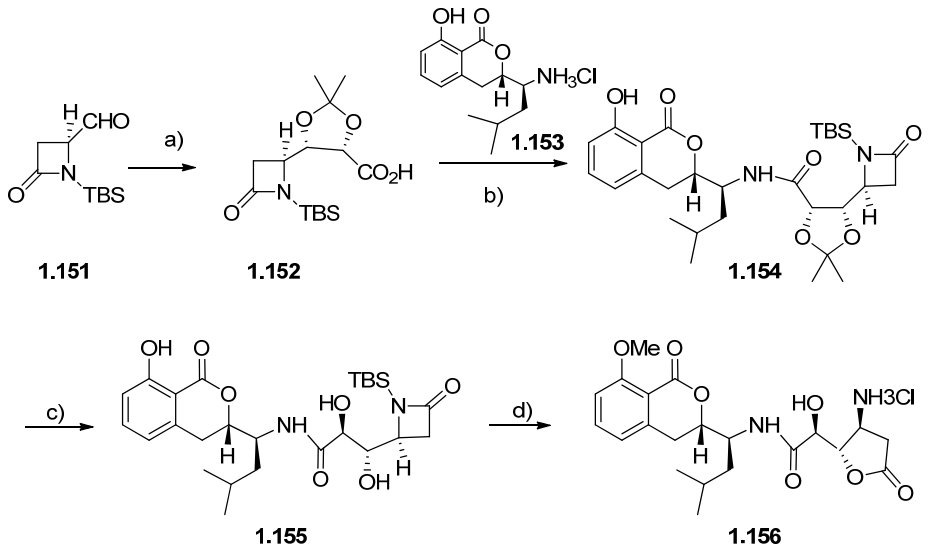
Scheme-1.28. ***Reagents and conditions:*** *(a) i) 4-MeOC$_5$H$_4$MgBr, THF, -40 °C, 1 h; ii) L-Selectride, THF, -78 °C, 1 h; (b) nicotinic acid, CrO$_3$, pyridine, toluene, rt, 4 h.*

Synthesis of 2,3 azeridineo-γ-lactones **1.150** have accomplished by Deshmukh *et al.* from 3-hydroxy- *β*-lactam by acid catalyzed tandem azetidinone ring opening followed by intramolecular azeridine ring formation via elimination of a mesylate group in more than 85% yield[47]. 2,3 azeridineo-γ-lactones are an important intermediate in the synthesis of 3,4-dihydroxy glutamic acids, an important excitatory neurotransmitter of the central nervous center.



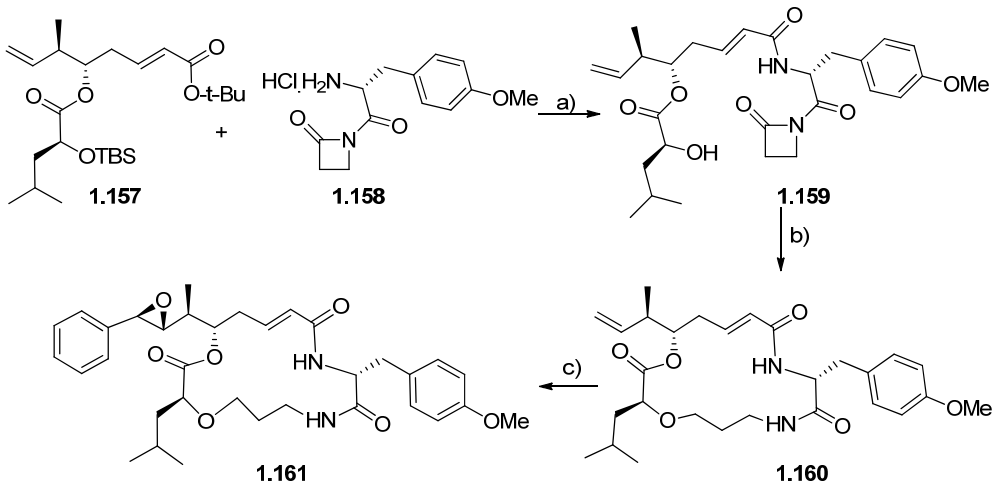
Scheme-1.29.

In another example, synthesis of amicoumacin C **1.156** have been reported from commercially available 4-formyl *β*-lactam **1.151** in seven steps employing *β*-lactam ring cleavage with sodium hydroxide followed by lactonization is the key step(Scheme 1.30).[48]



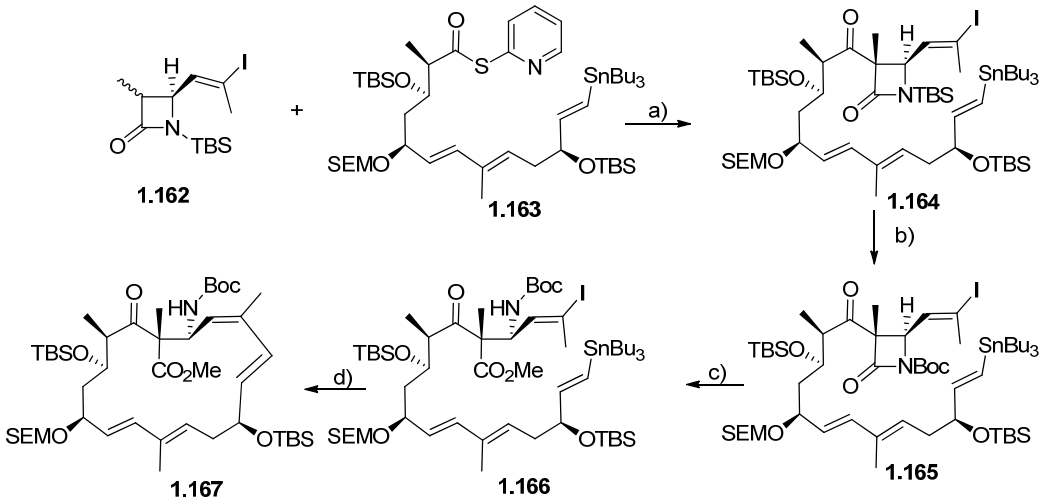
Scheme-1.30. ***Reagents and conditions:*** *(a) i) (F$_3$CCH$_2$O)$_2$P(O)CH$_2$CO$_2$Bn, K$_2$CO$_3$, 18-crown-6, toluene, 0 °C, 1 h; (ii) OsO$_4$, NMO, acetone-H$_2$O, rt, 3 days; (iii) Me$_2$C(OMe)$_2$, PTSA, CHCl$_3$, RT, 18 h; (iv) H$_2$, Pd-C, EtOH, rt, 18 h; (b) DCC, DMAP, CH$_2$Cl$_2$, rt, 18 h; (c) 1:1 aq HCl (3 M)-THF, rt, 6 h; (d) NaOH, pH 12, EtOH-H$_2$O, 18 h, then HCl (3 M), MeOH, 0 °C, 2 h.*

An efficient and concise approach to the synthesis of the macrolide core of cryptophycins **1.161** has been developed by Georg *et al.*.[49] Cyanide mediated ring opening of *β*-lactam **1.159** followed by cyclization to give **1.160** in 65% has been the key step in this synthesis. Cryptophycins are potent, tumor-selective tubulin-binding antimitotic agents with excellent activity against multidrug-resistant cancer cells.



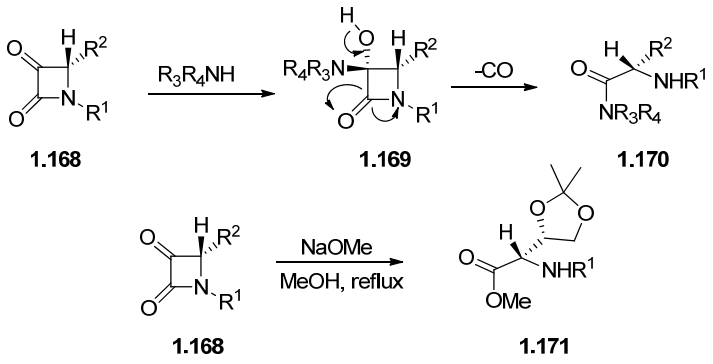
Scheme 1.31. ***Reagents and conditions:*** *(i) TFA, CH_2Cl_2, rt, 6 h; (ii) HBTU, DIEA, MeCN, rt, 1 h; (iii) $BF_3.Et_2O$, $CHCl_3$, rt, 1 h; (iv) Bu_4NCN, CH_2Cl_2, rt, 16 h; (v) PhI, $Pd(OAc)_2$, Et_3N, MeCN, 80 °C, 20 h; (vi) DMD, CH_2Cl_2-acetone, -30 °C, 24 h.*

Synthesis of 17-membered macrocycle tetraene **1.167** has been reported more recently[50] from **1.162** as shown in Scheme-1.32.



Scheme-1.32. ***Reagents and conditions:*** *a) LDA, THF, -78 °C; b) (i) KEt_3BH, Et_2O, -78 °C; (ii) Ac_2O, Et_3N, DMAP, CH_2Cl_2, rt; (iii) KF, MeOH, rt; (iv) Boc_2O, DMAP, MeCN; c) MeOH, KCN, DMF, rt; d) (i) TBAF, THF; (ii) $Pd_2(dba)_3$ (30 mol %), $AsPh_3$ (1.2 mol %), DMF, THF, rt.*

A very simple and short route for the synthesis of α-amino amides **1.170** in 95% yield and α -amino ester **1.171** in 94%, respectively, is also reported[51] from 3-keto *β*-lactams **1.168** as shown in Scheme-1.33.



Scheme-1.33.

1.8 Objective of the Thesis:

β-Lactam antibiotics have occupied a central role in the fight against pathogenic bacteria and are responsible for the subsequent rise in quality of life for the world population . Additional impetus for research efforts on *β*-lactam chemistry has been provided by the introduction of the *β*-lactams as synthon in organic synthesis. The use of *β*-lactam as synthon emerges due to the strain energy associated with the four member cyclic ring making it very vulnerable towards nucleophilic addition. Opening of the *β*-lactam nucleus can occur through cleavage of any of the single bonds of the four membered ring. The stereoselective synthesis of different sized heterocycles of biological significance has been accomplished using *β*-lactam as starting materials.

We got interested in using *β*-lactam as a synthon for the synthesis of biologically important products and took up the syntheses of cholesterol absorption inhibitor (CAI), 3-alkylidene aztitidin-2one (*β*-lactmase inhibitors), D-*xylo*-phytosphingosene, 3,7-di-*epi*-alexine, 1-deoxy-6,8a-di-*epi*-castanospermine, and 1,6,8a tri-*epi*-castanospermine, respectively. All our synthetic endeavors are described in detail in the following three chapters.

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CHAPTER 2 section-A

Azetidin-2,3-dione Synthon for Stereoselective Synthesis of *cis*- and *trans*-C-3-Alkyl/aryl Azetidin-2-ones

This work has been published in *Synthesis* **2006**, *01*, 115-122.

2A.1: Introduction

This section deals with the stereoselective synthesis of 3-alkyl/aryl azetidine-2-ones and SCH-48461, a cholesterol absorption inhibitor from azetidin-2,3-diones.

***Significance of SCH 48461(2A.01)*:** Cardiovascular diseases or coronary heart diseases (CHD) is one of the leading cause of death in both men and women in recent times across the globe.[1,2] Atherosclerosis remains a major cause of cardiovascular disease. High concentrations of total cholesterol, low density lipoprotein cholesterol and triglyceride and low levels of high density lipoprotein cholesterol are associated with increased risk of cardiovascular events making the identification and management of hyperlipedaemia in patients at the risk of future vascular events priority. CHD is mainly caused due to blockage of arteries carrying oxygen rich blood to the heart. This congestion takes place because of deposition of cholesterol on the inner walls of the arteries as a result arteries are narrowed, causing resistance to the flow of the blood towards heart leading pain in the chest (a condition called angina) and heart attacks.

"Absorption of cholesterol" is most accurately defined as the transfer of intraluminal cholesterol into intestinal or thoracic duct lymph. "Uptake of cholesterol" refers to entry of cholesterol into intestinal absorptive cells. According to these definitions, cholesterol absorption is a multistep process that is regulated by multiple genes.[3,4] There are three sources of intestinal cholesterol: the diet, the bile, and intestinal epithelial sloughing.

Cholesterol is a waxy steroid metabolite found in the cell membranes and transported in the blood plasma of all animals. It is essential component for healthy cells but if there is too much in the blood it can lead to coronary heart disease. Cholesterol is being transported in the blood stream by molecules called lipoproteins. Lipoproteins have cell targeting signals that direct the lipids they carry to certain tissues. For this reason there are several different types of lipoproteins within blood in order of increasing density but two of the main ones are low-density lipoproteins (LDL) and high-density lipoproteins (HDL). LDL also known as 'bad cholesterol' carries cholesterol from liver to the cell. HDL often termed as 'good cholesterol' carries the cholesterol from cells back to the liver where it broken down and thrown

out of the body. Those with higher levels of HDL-C seem to have fewer problems with cardiovascular diseases in comparison to those with low HDL-C cholesterol levels. In the people who have already attained high blood cholesterol levels, health check action becomes necessary and lifestyle changes such as weight control, smoking cessation, changing diet and exercising is suggested to be an useful tool.

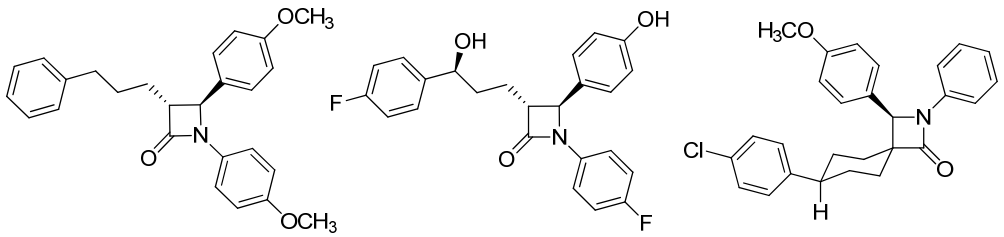
There are various kinds of treatments available for CHD. Medicines are generally prescribed. Aspirin, a familiar sight drug prevents blood clots from forming in our arteries and reduces risk of having heart attack. In addition, there are also drugs of the class; anti-coagulants which prevent blood clotting and clot busters but these have some serious side effects in case the patient has bleeding disorders.

Cholesterol lowering medicines called statins are also used against CHDs. They act by blocking the formation of cholesterol and increasing number of LDL receptors in liver which helps to remove LDL cholesterol from blood. The most frequently recommended medicines are β-blockers, ACE (angiotensin converting enzyme), diuretics, commonly called "water pills", sorbitate nitrate and anti-arrhythmic medicines.

The balance of cholesterol biosynthesis, intestinal absorption, transport, biliary clearance and excretion is complex and simultaneously regulated by various processes. Several clinical trials have demonstrated that reduction of plasma cholesterol levels decreases the risk of coronary artery disease. Although, current therapeutic options are effective in lowering cholesterol, clinical application is not optimized for many reasons. Many powerful drugs are available but these are often insufficient to meet the clinical demands for cholesterol-lowering therapy. Phytosterols and phytostanols have been partially effective by providing some inhibition of absorption of cholesterol. Compounds that specifically and more effectively block intestinal absorption of dietary and biliary cholesterol are still being pursued.

Cholesterol absorption inhibitors are relatively new class of compounds which function by preventing the uptake of cholesterol from the small intestine into the circulatory system. Among the compounds that have exhibited cholesterol absorption inhibitory activity, substituted azetidin-2-ones are most prominent class. Some of the important among this class are (-)-SCH 48461[5] **(2A.01),** ezetimibe (SCH 58235)[6]

(2A.02) and (+)-SCH 54016[7] **(2A.03)** (Figure 1). These compounds were first discovered at the Schering-Plough. In fact, a part of the name of these compounds 'SCH' derives itself from the word 'Schering'. They have displayed excellent cholesterol absorption inhibitory activity.



SCH 48461 (**2A.01**) ezetimibe **(2A.02)** SCH 54016 **(2A.03)**

Figure 2A.1. *SCH 48461 (**2A.01**), ezetimibe (**2A.02**) and SCH 54016 (**2A.03**)*

The mode of actions of these compounds is briefly described as follows:

There are two sources of cholesterol in the upper intestine; dietary (from food) and biliary (from bile). Dietary cholesterol, in the form of lipid emulsions combines with bile salts to form bile salt micelles from which cholesterol can be absorbed by the intestinal enterocyte. Once absorbed by the enterocyte, cholesterol is reassembled into large intestinal lipoproteins called chylomicrons. These chylomicrons are subsequently secreted into the lymphatics and circulated to the liver. These cholesterol particles are secreted by the liver into the blood as VLDL (very low density lipoproteins) particles, precursors to LDL. As a class, cholesterol absorption inhibitors block the uptake of micellar cholesterol, thereby, reducing the incorporation of cholesteryl esters into chylomicron particles. By reducing the cholesterol content in chylomicrons and chylomicron remnants, cholesterol absorption inhibitors effectively reduce the amount of cholesterol that is delivered back to the liver. The reduced delivery of cholesterol to the liver increases hepatic LDL receptor activity and thereby increases clearance of circulating LDL. The net result is a reduction in circulating LDL particles. Managing cholesterol at the site of absorption is an increasingly popular strategy being used against CHD and hence cholesterol absorption inhibitors like SCH 48461 (**2A.01**) are becoming valuable drug candidates.

(-)-SCH 48461 (**2A.01**) (Figure 2A.1) is a substituted azetidin-2-one with *trans* stereochemistry. Its chemical name is (3*R*,4*S*)-1,4-bis-(4-methoxy-phenyl)-3-(3-

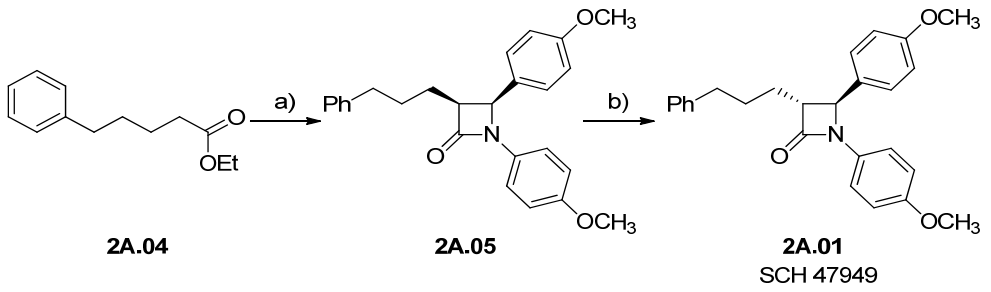
phenyl-propyl)-azetidin-2-one. Detailed studies of the effect of the SCH 48461 on cholesterol levels have been carried out and the compound has been evaluated for its effect on lipid parameters.[6b] The study has demonstrated a very clear clinical and statistical significance in cholesterol-lowering effect of SCH 48461 in patients with primary hypercholesterolemia.

2A.2: Background of the present work

Realizing the high medicinal importance of (-)-SCH 48461, we sought to synthesize this compound along with various analogues for further studies. It would be worth to give brief account of previous reports on this molecule before presenting our own approach.

There are many methods available in literature for the synthesis of (-)-SCH 48461, **2A.01** in racemic as well as enantiopure form[5,7-16] but few important methods are described below.

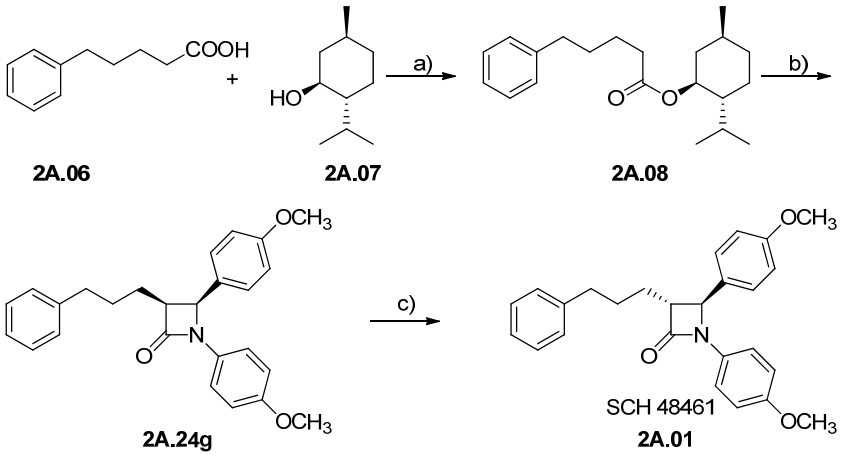
Burnett *et al.* have synthesized a series of such compounds using an ester-enolate and an imine cyclocondensation reaction to construct azitidinone ring in one step. The synthesis of a racemic SCH 48461 (**2A.01**) is described in Scheme 2A.01 [5]



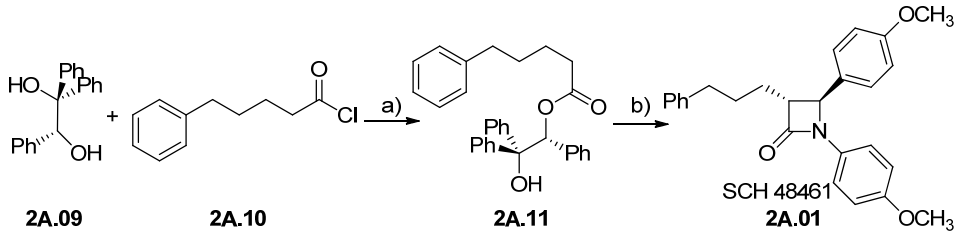
Scheme 2A.01. ***Reagents and conditions***: *a) i) LDA, THF, -78 °C, 54%; ii) PMP-N=CH-PMP, 65%; b) t-BuOK, THF, 0 °C, 90%.*

The same compound has also been resolved to obtain enantiomerically pure (-)-SCH 48461.

Another report also describes an enantioselective synthesis of (-)-SCH 48461[8] using menthyl ester of 5-phenylvaleric acid (**2A.08**) as a chiral starting material (Scheme 2A.02 and 2A.03).

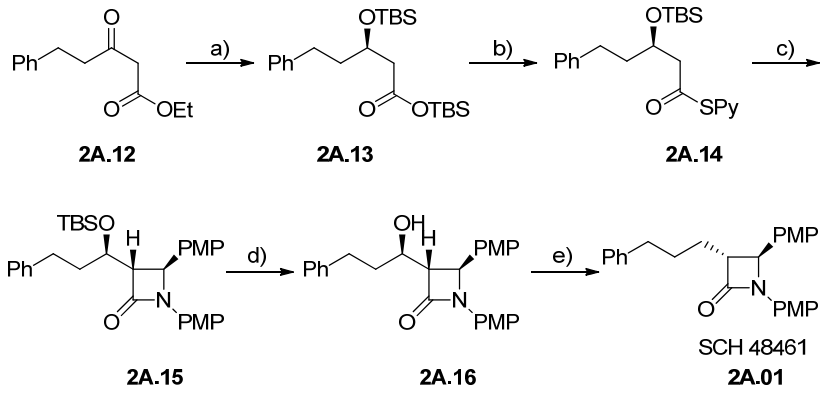


Scheme 2A.02. ***Reagents and conditions****: a) $(COCl)_2$, DCM,; 75% b) i) LDA, THF, -78 °C, ii) PMP-N=CH-PMP; 65% c) t-BuOK, THF, 0 °C, 90%.*



Scheme 2A.03. ***Reagents and conditions: a)*** *pyridine, DCM, 0 °C-rt, 2h, 55%; b) i) LDA, THF, -78 °C, ii) PMP-N=CH-PMP, 45%.*

Chiral pyridyl-thioester **2A.14,** obtained by enzymatic reduction of ethyl 5-phenyl-3-oxovalerate (**2A.12**) using Baker's yeast, have been utilized in the synthesis of SCH 48461 (Scheme 2A.04)[10] employing usual ester enolate-imine condensation reaction. The synthesis through this strategy utilized five steps with 12% over all yield.

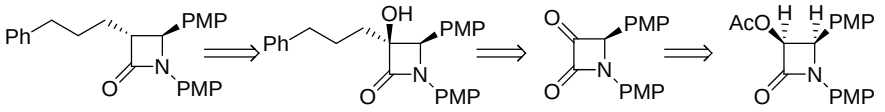


Scheme 2A.04. ***Reagents and conditions:*** *a) KOH, Baker's yeast, TBSCl; b) K_2CO_3, $(PyS)_2$; c) $TiCl_4$, Et_3N, PMP-N=CH-PMP; d) $Bu_4N^+F^-$; e) Thiocarbonyldiimidazole, Bu_3SnH.*

2A.3: Present work:

Considering the medicinal importance of the SCH 48461 **2A.01** as well as to explore the scope of developing cholesterol absorption inhibitor analogues, we have developed a simple strategy for synthesizing various 3-alkyl/aryl azetidin-2-ones employing Staudinger reaction as the key step from appropriately designed substrates.

Our retrosynthetic strategy for the synthesis of **2A.01** is shown in Scheme 2A.05, which is accessed from appropriately substituted 3-hydroxy azetidin-2-one **2A.22g**. This compound in turn can be obtained by the Grignard addition to a suitable azetidin-2,3-dione **2A.21,** easily obtainable from **2A.19** using Staudinger reaction**.**



Scheme 2A.05. *Our retrosynthetic approaches*

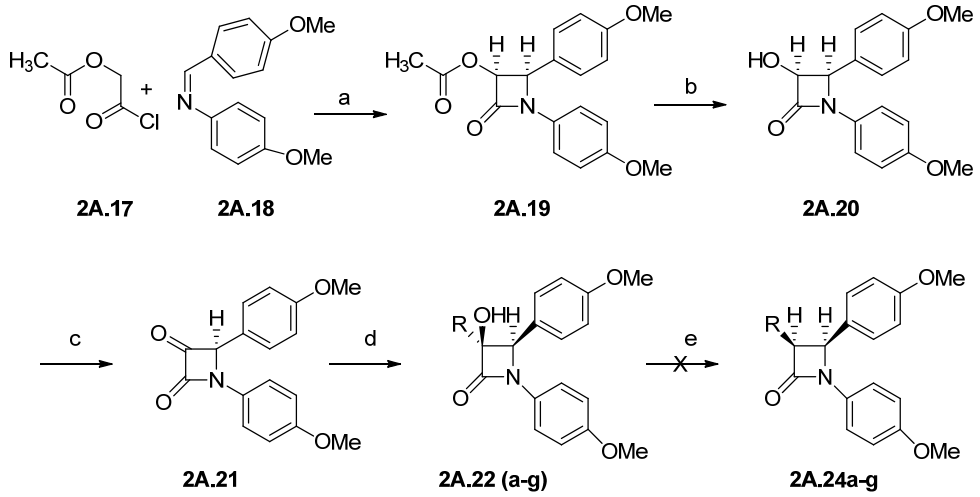
2A.4: Results and Discussion:

As per our synthetic plan, we started by synthesizing required azetidin-2,3-dione **2.20** at first, as shown in Scheme 2A.06.

Freshly prepared acetoxy acetyl chloride **2A.17** was reacted with the imine **2A.18**, derived from *p*-anisaldehyde and *p*-anisidine, in the presence of Et_3N as a base, which gave *cis*-3-acetoxy azetidin-2-one **2A.19** in 62% yield.

The IR spectrum of **2A.19** showed absorption band at 1753 cm^{-1}, characteristic of a β-lactam carbonyl group. The structure was further supported by ^1H NMR spectrum in which a singlet at δ 1.73 appeared for the methyl protons of the acetate group. The two PMP methyl protons appeared as a singlet at δ 3.74 and δ 3.80, respectively. The H3 and H4 of β-lactam ring appeared at δ 5.27 and δ 5.87 as doublets with the coupling constant (J = 5.1 Hz). Based on the coupling constant, *cis* configuration of β-lactam was assigned. The structure of **2A.19** was further confirmed by ^{13}C NMR Spectrum which displayed the carbonyl carbon of β-lactam ring at δ

161.0 and acetate carbonyl carbon at δ 169.2, respectively. The mass spectrum showed the base ion peak at *m/z* 342 corresponding to [M+1].



Scheme-2A.06. ***Reagents and Conditions****: Et_3N, DCM, 0 °C-rt, 18 h, b) aq. $NaHCO_3$, Na_2CO_3, MeOH, rt, 18h, c) DMSO, P_2O_5, rt, 24h, 89%,; d), RMgX, THF, 0 °C, e) EtSiH, BF_3:OEt, CH_3CN, 0 °C to rt.*

In order to obtain 3-keto-β-lactam **2A.21**, it was required to hydrolyze acetate moiety of **2A.19** at first before oxidation. In this context, **2A.19** was saponified using aq sodium bicarbonate in MeOH to obtain **21.20** in 90% yield. Usual Swern oxidation of **21.20,** however, was found to be very sluggish and the required 3-keto β-lactam **2A.21** was obtained only in poor yield (20%). This observation is possibly due the low solubility of 3-hydroxy β-lactam **2A.20** in DCM or THF. Ultimately, oxidation was carried out by using anhydrous phosphorous pentoxide in dry dimethyl sulfoxide at room temperature to obtain the desired azetidin-2,3-dione **2A.21** in 89%[11]. The success of the oxidation was confirmed by observing an absorption band corresponding to a keto carbonyl at 1809 cm^{-1}.

Having synthesized the requisite azetidin-2,3-dione **2A.21,** we proceeded further with the synthesis of SCH 48461 **2A.01** by reacting it with alkyl / aryl Grignard reagent (Scheme-2A.06) to obtain corresponding **2A.22a-g** in good to moderate yields **(Table 1)**. The formation of a single diastereoisomer in this reaction suggests that the addition occurred exclusively from the opposite side of the C-4 to avoid steric congestion.

The formation of **2A.22a-g** was confirmed by spectral analysis using IR, ^{1}H, and ^{13}C NMR. The complete characterization of one of the representative analogue **2A.22g** is described as follows:

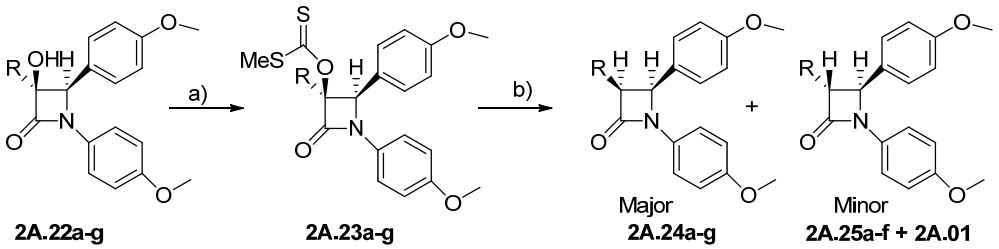
The IR spectrum of **2A.22g** displayed absorption bands at 3394 and 1730 cm^{-1} for hydroxyl and β-lactam carbonyl moieties, respectively. The ^{1}H NMR of **2A.22-g** showed six protons in aliphatic region between δ 1.9-2.55 as multiplets for three methylene groups. The ^{13}C NMR spectrum displayed two signals at δ 85.7 and δ 66.9 for C3 and C4 carbon, respectively. The assigned structure was further confirmed by the mass spectrum showing the molecular ion peak at *m/z* 418 corresponding to [M+1].

Comp.	R	Yield (%)[a]	Mp (^{o}C)	Comp.	R	Yield (%)[a]	Mp (^{o}C)
2A.22a	*n*-hexyl	68	oil	**2A.23a**	*n*-hexyl	89	Oil
2A.22b	n-pentyl	65	oil	**2A.23b**	n-pentyl	75	Oil
2A.22c	*n*-tetradecyl	68	oil	**2A.23c**	*n*-tetradecyl	96	Oil
2A.22d	*n*-decyl	72	oil	**2A.23d**	*n*-decyl	83	Oil
2A.22e	*n*-nonyl	66	oil	**2A.23e**	*n*-nonyl	97	Oil
2A.22f	phenyl	67	164-166	**2A.23f**	phenyl	92	176-178
2A.22g	3-phenylpropyl	57	oil	**2A.23g**	3-phenylpropyl	95	Oil

Table 1. *3-Alkyl/aryl-3-hydroxy-1,4-bis-(4-methoxyphenyl)azetidin-2-ones,* ***2A.09a-g*** *and xanthate esters* ***2A.10a-g***

It was envisioned that deoxygenation of **2A.22g** *via* ionic hydrogenolysis would give the target molecule **2A.01**, however**,** all our efforts using triethylsilane in the presence of $BF_3{\cdot}OEt_2$[12] or trifluoroacetic acid[13] remained unsuccessful. Even changing the solvent from dichloromethane to acetonitrile[14] did not help (Scheme-2A.06). Therefore, we decided to utilize Barton-McCombie protocol for this purpose as shown in Scheme 2A.07. The required xanthate ester **2A.23g** for the Barton-McCombie deoxygenation reaction was obtained in 95% yield by the treatment of **2A.22g** with carbon disulfide followed by methylation in the presence of sodium hydride in THF.

The formation of xanthate ester was confirmed by observing a singlet for three -S-CH_3 protons at δ 2.2, S-Me carbon at δ 19.2 and thiocarbonyl carbon (C=S) at δ 210.8 in the ^{1}H NMR and ^{13}C NMR spectra, respectively.



Scheme-2A.07. ***Reagents and conditions****: a) NaH, CS_2, MeI, THF, 0 °C, 3 h, b) n-Bu_3SnH, AIBN, toluene, reflux, 4 h.*

With the xanthate ester in hand, we proceeded for the reduction by refluxing it with tributyl tin hydride in the presence of catalytic amount of AIBN in toluene which gave expected **2A.24g** in 57% yield. The ^{1}H NMR suggested the product as a mixture of *cis* and *trans*-isomers (70:30) (**Table-2**). The major *cis*-isomer was easily isolated in pure form by column chromatography. The stereochemistry of the major isomer was established from the coupling constant of the azetidinone ring protons (J = 5.9 Hz for the *cis*-isomer **2A.24g)** and the minor isomer **2A.01** as the *trans* (J = 2.3 Hz). This synthetic protocol (Scheme 2A.07) was used for the synthesis of many C-3 substituted β-lactams (**Table-2**)

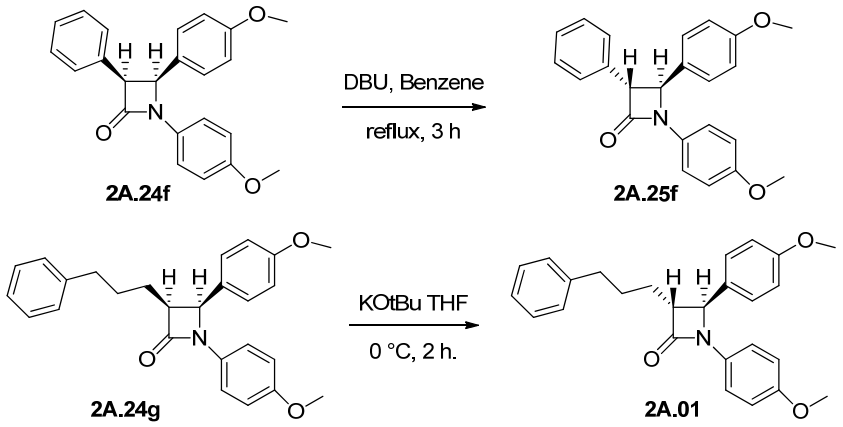
S. No.	Comp. (xanthate)	R	*cis:trans* (2A.24a-g, 2A.25a-f & 2A.01	Yield (%)[b]	Mp (^{o}C)
1.	**2A.23a**	*n*-hexyl	90:10	93	Oil
2.	**2A.23b**	*n*-pentyl	90:10	96	Oil
3.	**2A.23c**	*n*-tetradecyl	88:12	92	Oil
4.	**2A.23d**	*n*-decyl	88:12	90	Oil
5.	**2A.23e**	*n*-nonyl	94:6	90	Oil
6.	**2A.23f**	phenyl	95:5	92	144-146
7.	**2A.23g**	3-phenylpropyl	70:30	95	96-98

[a] ratios were determined by ^{1}H NMR. [b] isolated yields. [c] m.p. of pure *cis* isomer.

Table 2. *3-Alkyl/aryl-1,4-bis-(4-methoxyphenyl)azetidin-2-ones*

Since the cholesterol absorption inhibition activity is mainly associated with *trans*-*β*-lactams,[5] the base-catalyzed epimerization of *cis*-*β*-lactams were studied (Scheme 2A.09). In this context, **2A.24f** was refluxed in benzene in the presence of catalytic amount of DBU for 3 h. TLC comparison with the corresponding *cis* isomer as well as the ^{1}H NMR spectrum of the crude reaction mixture suggested the success of the epimerization to form **2A.25f** (88% yield). The pure **2A.25f** was easily obtained by single recrystallization of the crude from dichloromethane–petroleum ether.

Similarly, *cis*-1,4-bis-(4-methoxyphenyl)-3-(3-phenylpropyl)azetidin-2-one **2A.24g** was also heated with DBU, but to our surprise no epimerization could be observed in this case even after prolonged refluxing. Therefore, epimerization was attempted using potassium *tert*-butoxide in THF at 0 °C and delightful we observed the epimerization by recording the crude ^{1}H NMR (*trans:cis,* 84:16). Pure *trans*-isomer **2A.01** was obtained by recrystallization.



Scheme-2A.08. *Base mediated Isomerisations*

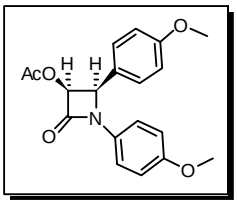
The epimerization of C3 center was confirmed by the ^{1}H NMR spectrum which displayed H-4 proton of the *β*-lactam ring at *δ* 4.56 as a doublet (*J* = 2.3 Hz).

2A.5: Conclusion:

In summary, azetidin-2,3-dione has been efficiently used for the syntheses of various 3-alkyl/aryl azetidin-2-ones. This synthesis demonstrates the use of *β*-lactam synthon for the synthesis of various analogues of cholesterol absorption inhibitors, which can be evaluated for biological activities.

2A.6 Experimental

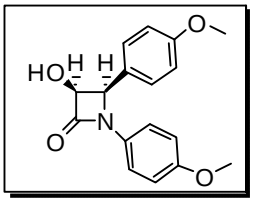
A typical experimental procedure for the synthesis of 3-Acetoxy-1,4-bis-(4-methoxy phenyl) azetidin-2-one (2A.19):



A solution of acetoxy acetyl chloride (4.83 mL, 45 mmol) in anhydrous dichloromethane (10 mL) was added slowly to a mixture of imine (7.23 gm, 30 mmol) and Et_3N (14.6 mL, 105 mmol) in dry dichloromethane (20 mL) at 0 °C. After completion of the addition, reaction mixture was allowed to warm up to room temperature and stirred for additional 18 hours. The reaction mixture was washed with water (3 × 50 mL), saturated $NaHCO_3$ (3 × 50 mL), and brine (50 mL). The organic layer was separated and dried over anhydrous sodium sulphate and concentrated under reduced pressure to get crude product, which was purified by column chromatography (silica gel 60-120 mesh) using pet ether-ethyl acetate (85:15 ratio) to afford pure 3-acetoxy-1,4-bis-(4-methoxy phenyl) azetidin-2-one as a white solid (62.21%).

mp 152-154 °C, **IR (ν_{max}, $CHCl_3$)**: 1753 cm^{-1}. **^{1}H NMR ($CDCl_3$, 200MHz)**: δ = 1.73 (s, 3H), 3.75 (s, 3H), 3.80 (s, 3H), 5.27 (d, *J* = 5.1 Hz 1H), 5.87 (d, *J* = 5.1 Hz, 1H), 6.77 (d, *J* = 9.00 Hz, 2H), 6.86 (d, *J* = 9.00 Hz, 1H), 7.22 (d, *J* = 9.0 Hz, 2 H), 7.25 (d, *J* = 8.5 Hz, 2H). **^{13}C NMR ($CDCl_3$, 50.3 MHz):** δ = 19.8, 55.1, 55.3; 61.0, 76.4, 113.8, 114.3, 118.7, 123.9, 129.2, 130.2, 156.4, 159.8, 161.3, 169.2. MS: *m/z* = 342 (M+1). Anal. Calcd. For $C_{19}H_{19}NO_5$: C, 66.85; H, 5.61; N, 4.10. Found: C, 66.93; H, 5.75; N, 4.08.

A typical experimental procedure for the synthesis of 3-hydroxy-1,4-bis(4-methoxy phenyl) azetidin-2-one (2A.20):

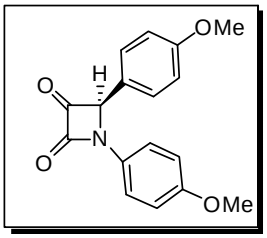


To a solution of 3-acetoxy *β*-lactam **2A.19** (8.35 g, 24.48 mmol) in methanol (70 mL) was added a saturated solution of sodium bicarbonate (35 mL) followed by catalytic amount of solid sodium carbonate. The reaction mixture was stirred at room temperature for 7 h. After the reaction was over (monitored by TLC) methanol was evaporated under reduced pressure and the resultant mass was diluted with dichloromethane. The organic layer was separated and the aqueous layer was washed

with DCM (2 × 10 mL). All the organic layers were collected, dried over anhydrous sodium sulphate and concentrated *in vacuo* to furnish the crude reaction mixture, which upon purification by silica gel column chromatography (60-120 mesh) using 30 % ethyl acetate-pet ether yielded **2A.20** as a pure white solid. 86%;

mp 146-149 °C, **IR (ν_{max}, $CHCl_3$):** 3353, 1708 cm^{-1}. **^{1}H NMR ($CDCl_3$, 200MHz):** δ = 2.15 (bs, 1H), 3.76 (s, 3H), 3.81 (s, 3H), 5.05 (d, *J* = 5.7 Hz, 1H), 5.13 (d, *J* = 5.7 Hz, 1H), 6.70 (d, *J* = 9.4 Hz, 2H), 6.84 (d, *J* = 8.6 Hz, 2H), 7.15 (d, *J* = 8.5 Hz, 2H), 7.24 (d, *J* = 9.4 Hz, 2H). **^{13}C NMR (DMSO d_6, 75.48 MHz):** δ = 55.0, 55.2, 61.7, 76.7, 113.6, 114.4, 118.2, 16.5, 129.3, 130.8, 155.5, 159.0, 166.40. **MS**: *m/z* = 300 (M+1). **Anal. Calcd. For $C_{17}H_{17}NO_4$:** C, 68.22; H, 5.73; N, 4.68. Found: C, 68.32; H, 5.80; N, 4.61.

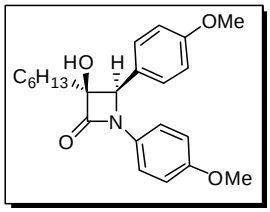
<u>A typical experimental procedure for the synthesis of 3,4-bis (4-methoxyphenyl) azetidin-2,3-dione (2A.21)</u>:



To an anhydrous P_2O_5 (0.980 mg, 3.5 mmol calculated for P_4O_{10}) was added dry dimethyl sulfoxide (15 mL) at room temperature. The suspension was stirred for five minutes at the same temperature and the corresponding 3-hydroxy *β*-lactam **2A.20** (1.5 g, 5 mmol) was added in one portion with vigorous stirring. The reaction mixture was stirred for 24 h. After the reaction was over, the mixture was gradually poured into cold aqueous $NaHCO_3$ (50 mL) and extracted with ethyl acetate. The organic layer was washed with brine (3 x 50 mL) and dried over sodium sulphate. Evaporation of the solvent under reduced pressure followed by column purification (60-120 mesh silica gel, 20% ethyl acetate-petroleum ether) provided the corresponding **2A.21** as a yellow solid (81%).

mp 144 °C. **IR (ν_{max}, $CHCl_3$):** 1832, 1809, 1753 cm^{-1}. **^{1}H NMR ($CDCl_3$, 200MHz):** δ = 3.79 (s, 3H), 3.80 (s, 3H), 5.52 (s, 1H), 6.90 (d, *J* = 9.00 Hz, 2H), 6.3 (d, *J* = 8.6 Hz, 2H), 7.25 (d, *J* = 8.6 Hz, 2H), 7.46 (d, *J* = 9.0 Hz, 2H). **^{13}C NMR ($CDCl_3$, 50.32 MHz):** δ = 55.3, 55.4, 74.4, 114.6, 114.8, 119.6, 123.5, 127.7, 129.8, 157.8, 160.1, 160.4, 191.2. **MS:** *m/z* = 298 (M+1). **Anal. Calcd. For $C_{17}H_{15}NO_4$:** C, 68.68; H, 5.08; N, 4.71. Found: C, 68.85; H, 5.13; N, 4.67.

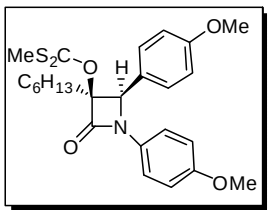
A typical experimental procedure for the synthesis of 3-hexyl-3-hydroxy-1,4-bis(4-methoxy phenyl) azetidin-2-one (2A.22a):



To a solution of dione **2A.21** (894 mg. 3 mmol) in dry ether (10 mL) was added a solution of n-hexyl magnesium bromide (3.9 mmol) in dry ether at 0 °C. The mixture was stirred for 2 hours at room temperature. Saturated aqueous NH_4Cl was added and the reaction mixture was extracted with ethyl acetate (3 x 15 mL). The combined organic layer was dried over anhydrous sodium sulphate and concentrated under reduced pressure. The residue was purified by flash column chromatography (230-400 mesh silica gel) using 15% ethyl acetate/petroleum ether to furnish **2A.22a,** 0.785 g (68%) thick oil.

IR (ν_{max}, $CHCl_3$): 3394, 1745, 1730 cm^{-1}. **^{1}H NMR ($CDCl_3$, 200MHz):** δ = 0.95 (t, *J* = 6.6 Hz, 3H), 1.30-1.40 (m, 8H), 1.85-2.05 (m, 2H), 3.77 (s, 3H), 3.82 (s, 3H), 4.91 (s, 1H), 6.77 (d, *J* = 9.0 Hz, 2H), 6.90 (d, *J* = 8.7 Hz, 2H), 7.19 (d, *J* = 8.8 Hz, 2H), 7.25 (d, *J* = 9.1 Hz, 2H). **^{13}C NMR ($CDCl_3$, 50.3 MHz):** δ = 14.0, 22.5, 23.5, 29.5, 31.6, 35.3, 55.2, 55.3, 66.8, 85.9, 114.3, 114.5, 118.8, 125.6, 128.4, 130.6, 156.2, 159.8, 168.0. **MS:** *m/z* = 384 (M+1). **Anal. Calcd. For $C_{23}H_{29}NO_4$:** C, 72.04; H, 7.62; N, 3.65. Found: C, 71.98; H, 7.46; N, 3.78.

A typical experimental procedure for the synthesis Dithiocarbonic acid *O*-[3-Hexyl-1,2-bis-(4-methoxy-phenyl)-4-oxo-azitidin-3-yl] ester *S*-methyl ester (2A.23a):

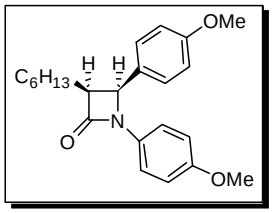


To a cooled suspension of NaH (0.024 g of 60% of NaH, 1.04 mmol) in anhydrous THF (5 mL) was added slowly the **2A.22a** (100 mg, 0.26 mmol). After completion of the addition the reaction mixture was stirred at room temperature for 30 minutes. It was again cooled to 0 °C followed by addition of a solution of CS_2 (0.047 mL, 0.78 mmol) in THF (5 mL). The reaction mixture was stirred for 1.5 hours at 0 °C. Methyl iodide (0.097 mL, 1.56 mmol) was added at the same temperature and the reaction mixture was stirred at room temperature for 3 hours. After completion of the reaction (TLC), saturated ammonium chloride (10 mL) was added and the most of the THF was removed *in vacuo*. The

residue was taken in dichloromethane and organic layer was washed with water, saturated brine and dried over sodium sulphate. The solvent was removed under reduced pressure to afford the crude product, which was purified by flash column chromatography (silica gel 230-400 mesh, ethyl acetate-petroleum ether 12%) to afford **2A.23a,** in 89% yield as colourless oil.

IR (ν_{max}, $CHCl_3$): 1758 cm^{-1}. **^{1}H NMR ($CDCl_3$, 200 MHz):** δ = 0.95 (t, *J* = 6.20 Hz, 3H), 1.30-1.40 (m, 8H), 1.85-2.05 (m, 2H), 2.32 (s, 3H), 3.77 (s, 3H), 3.81 (s, 3H), 5.19 (s, 1H), 6.77 (d, *J* = 9.1 Hz, 2H), 6.85 (d, *J* = 8.9 Hz, 2H), 7.25 (d, *J* = 8.9 Hz, 2H), 7.31 (d, *J* = 9.1Hz, 2H). **^{13}C NMR ($CDCl_3$, 50.3 MHz):** δ = 14.0, 19.2, 22.5, 23.4, 29.2, 31.4, 32.3, 55.2, 55.3, 66.9, 95.4, 113.7, 114.3, 119.0, 125.7, 129.5, 130.1, 155.4, 159.7, 162.7, 210.9. **MS:** *m/z* = 474 (M+1). **Anal. Calcd. For $C_{25}H_{31}NO_4S_2$:** C, 63.40; H, 6.59; N, 2.96; S, 13.54. Found: C, 63.55; H, 6.80; N, 3.01, S; 13.45.

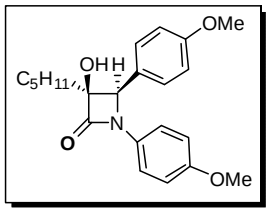
A typical experimental procedure for the synthesis of 3-Hexyl-1,4-bis(4-methoxy phenyl) azetidin-2-one (2A.24a):



A solution of tributyltin hydride (0.12 mL, 0.45 mmol) and AIBN (5 mg) in dry toluene (10 mL) was added drop wise to a solution of xanthate (150 mg, 0.3 mmol) in dry toluene (20 mL) under reflux condition. The reaction mixture was refluxed for 3 h under argon atmosphere. The solvent was concentrated in *vacuo* and the residue was purified by flash column chromatography (230-400 mesh silica gel) using (10%) ethyl acetate–petroleum ether to give **2A.24a** (107mg, 93%) as a thick oil.

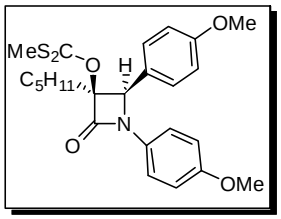
IR (ν_{max}, $CHCl_3$): 1741 cm^{-1}. **^{1}H NMR ($CDCl_3$, 200MHz):** δ 0.83 (t, *J* = 6.50 Hz, 3H), 1.10-1.19 (m, 8H), 1.25-1.35 (m, 2H), 3.40 (m, 1H), 3.74 (s, 3H), 3.81 (s, 3H), 5.10 (d, *J* = 5.60, 1H), 6.67 (d, *J* = 8.90 Hz, 2H), 6.75 (d, *J* = 8.70 Hz, 2H), 7.10 (d, *J* = 8.70 Hz, 2H), 7.25 (d, *J* = 8.90 Hz, 2H). **^{13}C NMR ($CDCl_3$, 50.3 MHz):** δ = 13.9, 22.3, 25.2, 27.1, 28.9, 31.3, 54.7, 55.2, 55.4, 57.9, 113.9, 114.2, 118.3, 126.9, 128.4, 131.3, 155.7, 159.4, 167.8. **MS**: *m/z* = 368 (M+1). **Anal.Calcd. for $C_{23}H_{29}NO_3$**: C, 75.17; H, 7.95; N, 3.81. Found: C, 75.29; H, 7.87; N, 3.75.

A typical experimental procedure for the synthesis of synthesis of 3-pentyl-3-hydroxy-1,4-bis(4-methoxy phenyl) azetidin-2-one (2A.22b):



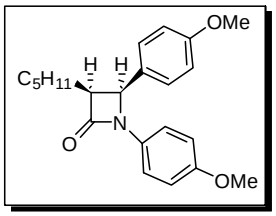
Isolated yield, 62%; thick oil; **IR (ν_{max}, $CHCl_3$):** 3338, 1751, 1716 cm^{-1}. **^{1}H NMR ($CDCl_3$, 200 MHz):** δ = 0.94 (t, *J* = 6.90 Hz, 3H), 1.30-1.40 (m, 6H), 1.92-2.09 (m, 2H), 3.76 (s, 3H), 3.81 (s, 3H), 4.98 (s, 1H), 6.81 (d, *J* = 9.1 Hz, 2H), 6.95 (d, *J* = 8.9 Hz, 2H), 7.23 (d, *J* = 8.9 Hz, 2H), 7.29 (d, *J* = 9.1 Hz, 2H). **^{13}C NMR ($CDCl_3$, 50.3 MHz):** δ = 13.9, 22.4, 23.2, 31.9, 35.3, 55.2, 55.4, 66.9, 86.0, 114.4, 114.6, 118.8, 125.8, 128.5, 130.7, 156.3, 159.9, 167.9. **MS:** ***m/z*** = 369 (M+1). **Anal. Calcd. For $C_{22}H_{27}NO_4$:** C, 71.52; H, 7.36; N, 3.79.Found: C, 71.89; H, 7.80; N, 3.71.

Synthesis of Dithiocarbonic acid *O*-[3-pentyl-1,2-bis-(4-methoxy-phenyl)-4-oxo-azitidin-3-yl] ester *S*-methy ester (2A.23b):



Isolated yield 87%; thick oil; **IR (ν_{max}, $CHCl_3$):** 1755 cm^{-1}. **^{1}H NMR ($CDCl_3$, 200 MHz):** δ = 0.91 (t, *J* = 6.6 Hz, 3H), 1.31-1.40 (m, 6H), 1.72-1.75 (m, 2H), 2.30 (s, 3H), 3.76 (s, 3H), 3.80 (s, 3H), 5.17 (s, 1H), 6.79 (d, *J* = 9.0 Hz, 2H), 6.84 (d, *J* = 8.8 Hz, 2H), 7.26 (d, *J* = 8.8 Hz, 2H), 7.29 (d, *J* = 8.9 Hz, 2H). **^{13}C NMR ($CDCl_3$, 75.48 MHz):** δ = 13.9, 19.2, 22.3, 23.1, 31.7, 32.0, 55.2, 55.4, 67.1, 95.5, 113.8, 114.4, 119.1, 125.8, 128.9, 130.2, 156.5, 159.8, 162.7, 210.6. **MS:** *m/z* = 459 (M+1). **Anal. Calcd. For $C_{24}H_{29}NO_4S_2$:** C, 72.72; H, 6.36; N, 3.05; S, 13.95. Found: C, 72.89; H, 6.50; N, 3.10; S, 14.05.

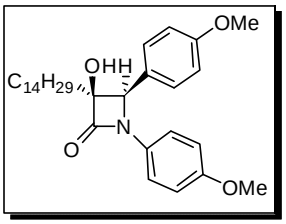
Synthesis of 3-pentyl-1,4-bis-(4-methoxyphenyl) azetidin-2-one (2A.24b):



Isolated yield, 96%; thick oil, **IR (ν_{max}, $CHCl_3$):** 1735 cm^{-1}. **^{1}H NMR ($CDCl_3$, 200MHz):** δ = 0.94 (t, *J* = 7.05 Hz, 3H), 1.12-1.27 (m, 6H), 1.31-1.39 (m, 2H), 3.50 (m, 1H), 3.75 (s, 3H), 3.81 (s, 3H), 5.11 (d, *J* = 5.7 Hz, 1H), 6.79 (d, *J* = 8.9 Hz, 2H), 6.90 (d, *J* = 8.6 Hz, 2H), 7.19 (d, *J* = 8.6 Hz, 2H), 7.25 (d, *J* = 8.9 Hz, 2H). **^{13}C NMR ($CDCl_3$, 75.48 MHz):** δ = 13.8, 22.1, 25.2, 26.8, 31.5, 54.7, 55.2, 55.3, 57.9, 113.9, 114.1, 118.3, 126.9, 128.8, 131.3, 155.7, 159.4,

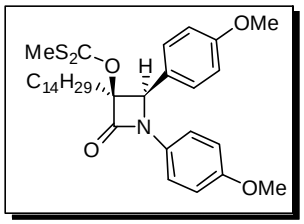
168. **MS:** *m/z* = 353 (M+1). **Anal. Calcd. For $C_{22}H_{27}NO_3$:** C, 74.76; H, 7.7; N, 3.96. Found: C, 74.66; H, 7.50; N, 3.81.

Synthesis of 3-tetradecyl-3-hydroxy-1,4-bis(4-methoxy phenyl) azetidin-2-one (2A.22c):



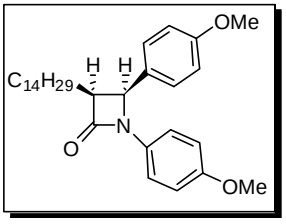
68%; thick oil; **IR (ν_{max}, $CHCl_3$):** 3400, 1737, 1731 cm^{-1}. **^{1}H NMR ($CDCl_3$, 200MHz):** δ = 0.89 (t, *J* = 6.80 Hz, 3H), 1.27 (m, 24H), 1.92-2.10, (m, 2H), 3.76 (s, 3H), 3.81 (s, 3H), 4.97 (s, 1H), 6.81 (d, *J* = 9.0 Hz, 2H), 6.95 (d, *J* = 8.6 Hz, 2H), 7.23 (d, *J* = 8.5 Hz, 2H), 7.29 (d, *J* = 9.1 Hz, 2H). **^{13}C NMR ($CDCl_3$, 75.48 MHz):** δ = 14.1, 22.6, 23.6, 29.4, 29.8, 31.86, 35.3, 55.2, 55.3, 66.8, 85.9, 114.2, 114.5, 118.8, 125.6, 128.3, 130.6, 156.2, 159.8, 168.0. **MS:** *m/z* = 496 (M+1). **Anal. Calcd. For $C_{31}H_{45}NO_4$:** C, 75.12; H, 8.07; N, 2.82. Found: C, 74.95; H, 8.12; N, 2.75.

Synthesis of Dithiocarbonic acid *O*-[3-tetradecyl-1,2-bis-(4-methoxyphenyl)-4-oxo-azitidin-3-yl] ester *S*-methyl ester (2A.23c):



Isolated yield, 96%; thick oil, **IR (ν_{max}, $CHCl_3$):** 1755 cm^{-1}. **^{1}H NMR ($CDCl_3$, 200 MHz):** δ = 0.89 (t, *J* = 6.70 Hz, 3H), 1.25 (m, 24H), 1.92-2.10 (m, 2H), 2.28 (s, 3H), 3.74 (s, 3H), 3.78 (s, 3H), 5.15 (s, 1H), 6.78 (d, *J* = 8.9 Hz, 2H), 6.82 (d, *J* = 8.7 Hz, 2H), 7.24 (d, *J* = 8.8 Hz, 2H), 7.28 (d, *J* = 8.7 Hz, 2H). **^{13}C NMR ($CDCl_3$, 75.48 MHz):** δ = 13.9, 14.1, 22.6, 23.4, 29.4, 29.3, 29.6, 31.8, 32.3, 55.1, 55.3, 66.9, 85.9, 113.7, 114.2, 118.9, 125.6, 128.3, 130.1, 156.4, 159.6, 168.6, **MS:** *m/z* = 586 (M+1). **Anal. Calcd. For $C_{33}H_{47}NO_4S_2$:** C, 67.66; H, 8.07; N, 2.39; S, 10.99. Found: C, 67.95; H, 8.95; N, 2.65; S, 10.85.

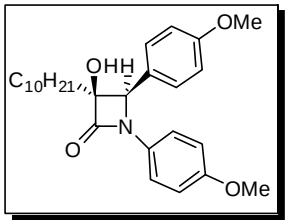
Synthesis of 3-tetradecyl-1,4-bis-(4-methoxyphenyl) azetidin-2-one (2A.24c):



Isolated yield 95%; thick oil, **IR (ν_{max}, $CHCl_3$):** 1745 cm^{-1}. **^{1}H NMR ($CDCl_3$, 200 MHz):** δ = 0.90 (t, *J* = 6.6 Hz, 3H), 1.27 (m, 26H), 3.50 (m, 1H), 3.76 (s, 3H), 3.81 (s, 3H), 5.11 (d, *J* = 5.9 Hz, 1H), 6.80 (d, *J* = 8.8 Hz, 2H), 6.90 (d, *J* = 8.8 Hz, 2H), 7.20 (d, *J* = 8.8 Hz, 2H), 7.25 (d, *J* = 8.7 Hz, 2H).

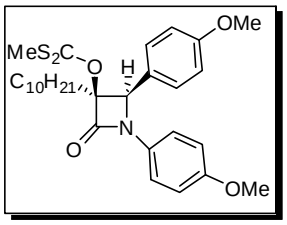
^{13}C NMR ($CDCl_3$, 75.48 MHz): δ = 14.1, 22.6, 25.2, 27.1, 29.3, 29.6, 31.8, 54.68, 55.1, 55.3, 57.9, 113.9, 114.2, 118.1, 118.4, 126.8, 128.3, 131.3, 155.6, 159.4, 167.7. **MS:** *m/z* = 480 (M+1). **Anal. Calcd. For $C_{31}H_{45}NO_3$:** C, 77.62; H, 9.45; N, 2.91. Found: C, 77.60; H, 9.32; N, 2.95.

Synthesis of 3-decyl-3-hydroxy-1,4-bis(4-methoxy phenyl) azetidin-2-one (2A.22d):



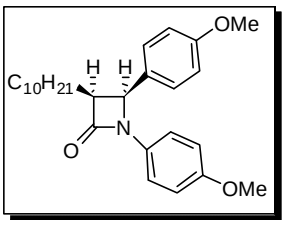
Isolated Yield 96%; thick oil, **IR (ν_{max}, $CHCl_3$):** 1731, 1745 cm^{-1}. **^{1}H NMR ($CDCl_3$, 200 MHz):** δ = 0.89 (t, *J* = 6.00 Hz, 3H), 1.27 (m, 16H), 1.89-2.05 (m, 2H), 3.76 (s, 3H), 3.81 (s, 3H), 4.97 (s, 1H), 6.80 (d, *J* = 9.0 Hz, 2H), 6.94 (d, *J* = 8.7 Hz, 2H), 7.22 (d, *J* = 8.7 Hz, 2H), 7.29 (d, *J* = 9.1 Hz, 2H). **^{13}C NMR ($CDCl_3$, 75.48 MHz):** δ = 14.0, 22.6, 23.6, 29.2, 29.4, 29.5, 29.8, 31.86, 35.4, 55.2, 55.4, 66.9, 86.1, 114.4, 114.6, 118.8, 125.8, 128.5, 130.8, 156.3, 160, 167.9. **MS:** *m/z* = 440 (M+1). **Anal. Calcd. For $C_{27}H_{37}NO_4$:** C, 73.72; H, 8.48; N, 3.18. Found: C, 73.95; H, 8.22; N, 3.20.

Synthesis of Dithiocarbonic acid *O*-[3-decyl-1,2-bis-(4-methoxyphenyl)-4-oxo-azitidin-3-yl] ester *S*-methyl ester (2A.23d):



Isolated yield 83%; thick oil, **IR (ν_{max}, $CHCl_3$):** 1755 cm^{-1}. **^{1}H NMR ($CDCl_3$, 200 MHz):** δ = 0.92 (t, *J* = 6.50 Hz, 3H), 1.29 (m, 18H), 2.32 (s, 3H), 3.77 (s, 3H), 3.82 (s, 3H), 5.19, (s, 1H), 6.81 (d, *J* = 9.0 Hz, 2H), 6.85 (d, *J* = 8.7 Hz, 2H), 7.30 (d, *J* = 8.7 Hz, 2H), 7.28 (d, *J* = 9.0 Hz, 2H). **^{13}C NMR ($CDCl_3$, 75.48 MHz):** δ = 14.1, 19.2, 22.6, 23.4, 29.2, 29.5, 31.8, 32.3, 55.1, 55.3, 66.9, 85.3, 113.7, 114.2, 118.8, 119, 125.6, 128.3, 130.1, 159.6, 162.6, 210.9. **MS:** *m/z* = 530 (M+1). **Anal. Calcd. For $C_{29}H_{39}NO_4S_2$:** C, 65.75; H, 7.42; N, 2.64. Found: C, 66.05; H, 7.22; N, 2.79; S, 12.10.

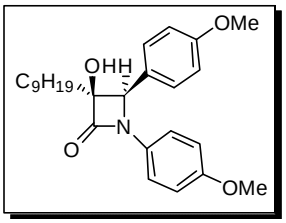
Synthesis of 3-decyl-1,4-bis-(4-methoxyphenyl) azetidin-2-one (2A.24d):



Isolated yield 90%; thick oil, **IR (ν_{max}, $CHCl_3$):** 1745 cm^{-1}. **^{1}H NMR ($CDCl_3$, 200 MHz):** δ = 0.93 (t, *J* = 6.7 Hz, 3H),

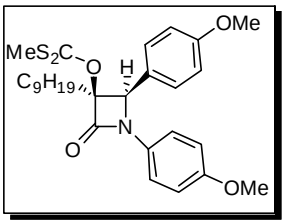
1.28 (m, 18H), 3.49-3.59 (m, 1H), 3.80 (s, 3H), 3.86 (s, 3H), 5.16 (d, *J* = 5.6 Hz, 1H), 6.84 (d, *J* = 9.0 Hz, 2H), 6.94 (d, *J* = 8.7 Hz, 2H), 7.24 (d, *J* = 8.8 Hz, 2H), 7.29 (d, *J* = 9.0 Hz, 2H).**^{13}C NMR ($CDCl_3$, 50 MHz):** δ = 14.0, 17.5, 22.6, 23.3, 27.1, 29.1, 29.2, 29.3, 31.8, 54.7, 55.1, 55.3, 57.9, 113.9, 114.1, 118.1, 126.8, 128.3, 131.3, 155.6, 159.3, 167.7. **MS**: *m/z* = 480 (M+1). **Anal. Calcd**. **For $C_{27}H_{37}NO_3$**: C, 76.56; H, 8.80; N, 3.30. Found: C, 76.60; H, 8.32; N, 2.95

Synthesis of 3-hydroxy-1,4-bis-(4-methoxyphenyl)-3-nonyl-azetidin-2-one (2A.22e):



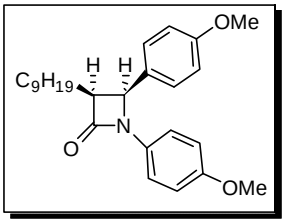
Isolated yield 76%; thick oil, **IR (ν_{max}, $CHCl_3$)**: 3394, 1726 cm^{-1}. **^{1}H NMR ($CDCl_3$, 200 MHz):** δ = 0.89 (t, *J* = 6.00 Hz, 3H), 1.28 (m, 14H), 1.89-2.15 (m, 2H), 2.55 (bs, 1H), 3.76 (s, 3H), 3.81 (s, 3H), 4.97 (s, 1H), 6.81 (d, *J* = 8.4 Hz, 2H), 6.94 (d, *J* = 7.6 Hz, 2H), 7.23 (d, *J* = 7.6 Hz, 2H), 7.29 (d, *J* = 8.5 Hz, 2H). **^{13}C NMR ($CDCl_3$, 75.48 MHz):** δ = 14.1, 22.6, 23.6, 29.2, 29.5, 29.8, 31.8, 35.3, 55.2, 55.4, 66.8, 85.8, 114.2, 114.5, 118.8, 125.6, 128.4, 130.6, 156.2, 159.8, 168.0. **MS:** *m/z* = 426 (M+1). **Anal. Calcd. For $C_{26}H_{35}NO_4$**: C, 73.38; H, 8.28; N, 3.29. Found: C, 73.56; H, 8.22; N, 3.20.

Synthesis of Dithiocarbonic acid *O*-[1,2-bis-(4-methoxyphenyl)-3-nonyl-4-oxo-azitidin-3-yl] ester *S*-methyl ester (2A.23e):



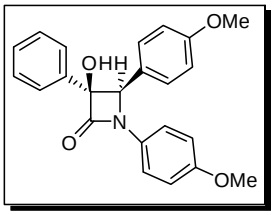
Isolated Yield 97%; thick oil, **IR (ν_{max}, $CHCl_3$):** 1755 cm^{-1}. **^{1}H NMR ($CDCl_3$, 200 MHz):** δ = 0.91 (t, *J* = 5.8 Hz, 3H), 1.29, (m, 16H), 2.31 (s, 3H), 3.77 (s, 3H), 3.81 (s, 3H), 5.18 (s, 1H), 6.81 (d, *J* = 8.4 Hz, 2H), 6.84 (d, *J* = 7.6 Hz, 2H), 7.23 (d, *J* = 7.6 Hz, 2H), 7.29 (d, *J* = 8.4 Hz, 2H). **^{13}C NMR ($CDCl_3$, 50 MHz):** δ = 14.0, 19.2, 22.6, 23.4, 29.2, 29.4, 29.6, 31.8, 32.6, 55.1, 55.3, 66.8, 95.3, 113.6, 114.2, 118.9, 125.6, 128.4, 130.6, 156.3, 159.6, 162.6, 210.9. **MS:** *m/z* = 516 (M+1). **Anal. Calcd. For $C_{28}H_{39}NO_4S_2$**: C, 65.21; H, 7.23; N, 2.71; S, 12.41. Found: C, 65.23; H, 7.36; N, 2.41; S, 11.87.

Synthesis of 1,4-bis-(4-methoxyphenyl)-3-nonyl-azetidin-2-one (2A.24e):



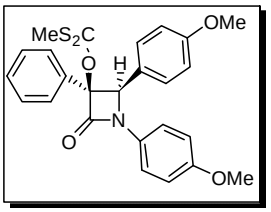
Yield 95%; thick oil; **IR (ν_{max}, $CHCl_3$):** 1745 cm^{-1}. **^{1}H NMR ($CDCl_3$, 200 MHz):** δ = 0.89 (t, *J* = 6.6 Hz, 3H), 1.28 (m, 18H), 3.47-3.54 (m, 1H), 3.76 (s, 3H), 3.82 (s, 3H), 5.12 (d, *J* = 5.8 Hz, 1H), 6.80 (d, *J* = 8.8 Hz, 2H), 6.90 (d, *J* = 8.8 Hz, 2H), 7.19 (d, *J* = 8.7 Hz, 2H), 7.26 (d, *J* = 8.7 Hz, 2H). **^{13}C NMR ($CDCl_3$, 75.48 MHz):** δ = 14.1, 22.6, 25.2, 27.2, 29.2, 29.2, 29.4, 31.8, 54.7, 55.2, 55.4, 57.9, 113.9, 114.2, 118.3, 118.4, 126.9, 128.4, 131.3, 155.7, 159.4, 167.8. **MS:** *m/z* = 410 (M+1). **Anal. Calcd. for $C_{26}H_{35}NO_3$:** C, 76.24; H, 8.61; N, 3.42. Found: C, 76.52; H, 8.32; N, 3.55.

A typical experimental procedure for the synthesis of 3-Hydroxy-1,4-bis-(4-methoxyphenyl)-3-phenyl-azetidin-2-one (2A.22f):



Isolated yield 67%; white solid, mp. 144-146 °C; **IR (ν_{max}, $CHCl_3$):** 3404, 1739 cm^{-1}. **^{1}H NMR ($CDCl_3$, 200 MHz):** δ = 2.74 (bs, 1H), 3.77 (s, 3H), 3.83 (s, 3H), 5.17 (s, 1H), 6.83 (d, *J* = 8.7 Hz, 2H), 6.94 (d, *J* = 8.6 Hz, 2H), 7.17-7.37 (m, 9H). **^{13}C NMR ($CDCl_3$, 75.48 MHz):** δ = 55.2, 55.4, 70.4, 86.6, 114.28, 114.4, 119.1, 124.9, 125.4, 128.4, 128.7, 130.2, 138.9, 156.4, 160.01, 166.5. **MS:** *m/z* = 376 (M +1). **Anal. Calcd. For $C_{23}H_{21}NO_4$**: C, 73.58; H, 5.64; N, 3.73. Found: C, 73.69; H, 5.62; N, 3.85.

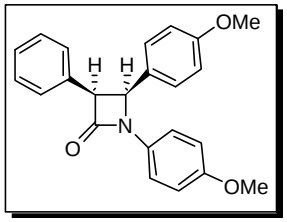
Synthesis of Dithiocarbonic acid *O*-[1,2-bis-(4-methoxyphenyl)-3-phenyl-4-oxo-azitidin-3-yl] ester *S*-methyl ester (2A.23f):



Isolated yield 92%; colourless liquid, **IR (ν_{max}, $CHCl_3$):** 1755 cm^{-1}. **^{1}H NMR ($CDCl_3$, 200MHz):** δ = 2.25 (s, 3H), 3.75 (s, 3H), 3.81 (s, 3H), 5.74 (s, 1H), 6.80 (d, *J* = 9.0 Hz, 2H), 6.88 (d, *J* = 8.6 Hz, 2H), 7.27-7.62 (m, 9H). **^{13}C NMR ($CDCl_3$, 75.48 MHz):** δ = 19.2, 55.2, 55.45, 66.7, 94.5, 113.8, 114.3, 118.9, 119.2, 124.9, 125.9, 128.6, 128.7, 129.3, 129.9, 130.4 134.3, 156.5, 159.9, 161.2, 209.9. **MS:**

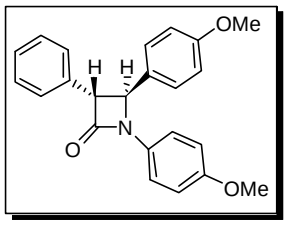
m/z = 466 (M^+ +1). **Anal. Calcd. For $C_{25}H_{23}NO_4S_2$**: C, 64.46; H, 4.98; N, 3.01, S, 13.77. Found: C, 64.69; H, 4.82; N, 3.05; S, 13.65.

Synthesis of (3S,4S)-1,4-bis(4-methoxyphenyl)-3-phenylazetidin-2-one (2A.24f):



IR (ν_{max}, $CHCl_3$): 1739 cm^{-1}. **^{1}H NMR ($CDCl_3$, 200MHz):** δ = 3.68 (s, 3H), 3.77 (s, 3H), 4.97 (d, *J* = 5.9 Hz, 1H), 5.39 (d, *J* = 5.8 Hz, 1H), 6.65 (d, *J* = 8.7 Hz, 2H), 6.82 (d, *J* = 9.0 Hz, 2H), 6.94-7.38 (m, 9H). **^{13}C NMR ($CDCl_3$, 75.48 MHz):** δ = 55.1, 55.6, 60.1, 90.3, 113.7, 114.4, 118.6, 126.5, 127.1, 128.1, 128.5, 128.9, 131.5, 132.6, 156.1, 159.3, 165.1. MS: *m/z* =360 (M +1). **Anal. Calcd. For $C_{23}H_{21}NO_3$**: C, 76.86; H, 5.89; N, 3.80. Found: C, 76.69; H, 5.82; N, 3.95.

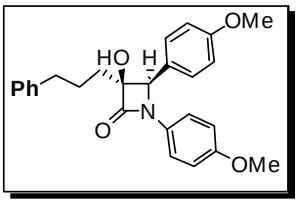
Synthesis of (3*R*,4*S*)-1,4-bis(4-methoxyphenyl)-3-phenylazetidin-2-one (2A.25f):



To a solution of **2A.24f** (0.025 g, 0.06 mmol) in dry benzene (7 mL), catalytic amount of DBU was added and the mixture was refluxed for 3 h. Benzene was removed by distillation under reduced pressure and the residue was diluted with CH_2Cl_2 (15 mL) and washed with 1N HCl solution (10 mL). The aqueous layer was extracted with CH_2Cl_2 (10 mL) and the combined organic layer dried over Na_2SO_4 and concentrated *in vacuo* to get a mixture of *cis*-and *trans*-azetidin-2-ones (0.021 g) in 12:88 ratio. The pure *trans*-azetidin-2-one **2A.25f** was obtained by recrystallization from dichloromethane-petroleum ether as a white crystalline solid.

Yield: 78%; mp 159-161 ^oC; **IR (ν_{max}, $CHCl_3$):** 1739 cm^{-1}. **^{1}H NMR ($CDCl_3$, 200 MHz):** δ = 3.67 (s, 3H), 3.73 (s, 3H), 4.16 (d, *J* = 2.4 Hz, 1H), 5.79 (d, *J* = 2.4 Hz, 1H), 6.73 (d, *J* = 9.0 Hz, 2H), 6.85 (d, *J* = 9.0 Hz, 2H), 6.94-7.38 (m, 9H). **^{13}C NMR ($CDCl_3$, 75.48 MHz):** δ = 55.1, 55.4, 60.1, 60.3, 113.7, 114.4, 118.5, 126.5, 127.0, 128.09, 128.4, 128.8, 131.4, 132.5, 156.1, 159.2, 165.1. **MS:** *m/z* =360 (M +1). **Anal. Calcd. for $C_{23}H_{21}NO_3$.**: C, 76.86; H, 5.89; N, 3.80; Found: C, 76.69; H, 5.82; N, 3.95.

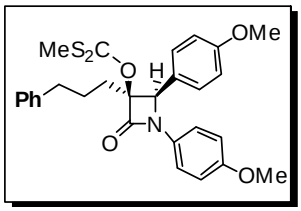
Synthesis of 3-hydroxy-1,4-bis-(4-methoxyphenyl)-3-(3-phenylpropyl)-azetidin-2-one (2A.22g):



To a solution of dione **2A.21** (594 mg, 2 mmol) in dry THF (10 mL) was added 3-phenyl propyl magnesium bromide (3 mmol) in dry THF at 0 °C. The reaction mixture was stirred for 6 hours at room temperature. Saturated aqueous NH_4Cl was added and the mixture was extracted with ethyl acetate (3 x 15 mL). The solvent was removed using rotary evaporator and the aqueous layer was extracted with ethyl acetate and the combined extracts were dried over anhydrous sodium sulphate and concentrated *in vacuo*. The residue was purified by flash column chromatography using 15% ethyl acetate/petroleum ether to furnish **2A.22g,** (0.48 g, 57%) as pale yellow oil.

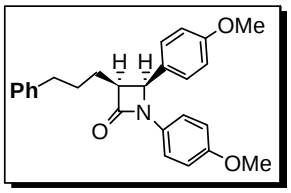
IR (ν_{max}, $CHCl_3$): 3384, 1747, 1731 cm^{-1}. **^{1}H NMR ($CDCl_3$, 200 MHz):** δ = 1.27 (t, *J* = 7.1 Hz, 2H), 2.05 (m, 2H), 2.72, (t, *J*= 6.5 Hz, 2H) 3.80 (s, 3H), 3.85 (s, 3H), 4.98 (s, 1H), 6.81 (d, *J* = 9.1 Hz, 2H), 6.94 (d, *J* = 8.6 Hz, 2H), 7.17-7.37, (m, 9H). **^{13}C NMR ($CDCl_3$, 75.48 MHz):** δ = 25.2, 34.9, 35.9, 55.2, 55.3, 67.0, 85.8, 114.3, 114.9, 118.9, 125.6, 125.7, 128.3, 128.5, 130.6, 141.8, 156.3, 159.9, 167.9. **MS:** *m/z* = 418 (M^+ +1). Anal. Calcd. for $C_{26}H_{27}NO_4$: C, 74.80; H, 6.52; N, 3.36. Found: C, 75.02; H, 6.32; N, 3.55.

Synthesis of Dithiocarbonic acid *O*-[1,2-bis-(4-methoxyphenyl)-3-(3-phenylpropyl)-4-oxo-azitidin-3-yl] ester *S*-methyl ester (2A.23g):



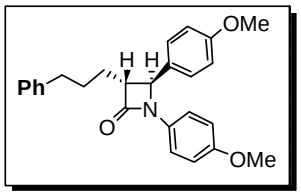
Isolated yield 95%; thick oil, **IR (ν_{max}, $CHCl_3$)** 1755 $cm.^{-1}$ **^{1}H NMR ($CDCl_3$, 200 MHz):** δ = 1.66-1.79 (m, 2H), 1.95-2.05 (m, 1H), 2.18 (s, 3H), 2.60 (t, *J* = 7.8Hz, 2H), 2.86-3.02 (m, 1H), 3.63 (s, 3H), 3.67 (s, 3H), 5.02 (s, 1H), 6.67 (d, *J* = 9.0 Hz, 2H), 6.71 (d, *J* = 8.8 Hz, 2H), 7.08-7.27 (m, 9H). **^{13}C NMR ($CDCl_3$, 75.48 MHz):** δ = 19.2, 24.9, 32.0, 35.5, 55.1, 55.3, 66.9, 95.1, 113.7, 114.2, 118.9, 125.5, 125.9, 128.3, 128.4, 130.5, 141.3, 156.4, 159.6, 162.4, 210.8. **MS:** *m/z* = 508 (M +1). **Anal. Calcd. For $C_{28}H_{29}NO_4S_2$**: C, 66.25; H, 5.76; N, 2.76; S, 12.63. Found: C, 66.42; H, 5.62; N, 2.85; S, 12.80.

Synthesis of (3*S*,4*S*)-1,4-bis(4-methoxyphenyl)-3-(3-phenylpropyl)azetidin-2-one (2A.24g):



Isolated yield 95%; thick oil, **IR (ν_{max}, $CHCl_3$):** 1741 cm^{-1}. **^{1}H NMR ($CDCl_3$, 200 MHz):** δ = 1.18-1.66 (m, 4H), 2.35-2.49 (m, 2H), 3.46-3.57 (m, 1H), 3.75 (s, 3H), 3.83 (s, 3H), 5.11 (d, *J* = 5.7, 1H), 6.78 (d, *J* = 8.9 Hz, 2H), 6.87 (d, *J* = 8.7 Hz, 2H), 7.0-7.27 (m, 9H). **^{13}C NMR ($CDCl_3$, 75.48 MHz):** δ = 24.9, 28.8, 35.6, 54.6, 55.2, 55.4, 57.9, 114.0, 114.2, 118.3, 125.6, 126.7, 128.2, 128.3, 131.2, 141.7, 155.7, 159.4, 167.4. **MS:** *m/z* = 402 (M +1). **Anal. Calcd. For $C_{28}H_{29}NO_4S_2$**: C, 66.25; H, 5.76; N, 2.76, S, 12.63. Found: C, 66.42; H, 5.62; N, 2.85 S, 12.56.

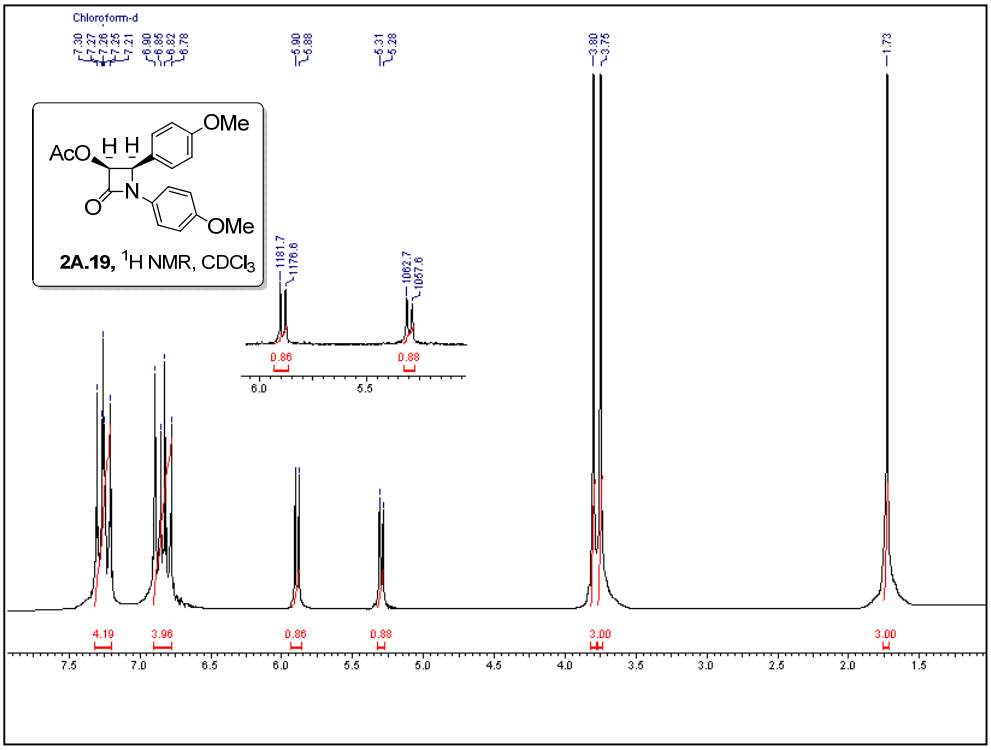
Synthesis of (3*R*,4*S*)-1,4-bis(4-methoxyphenyl)-3-(3-phenylpropyl)azetidin-2-one (2A.01):

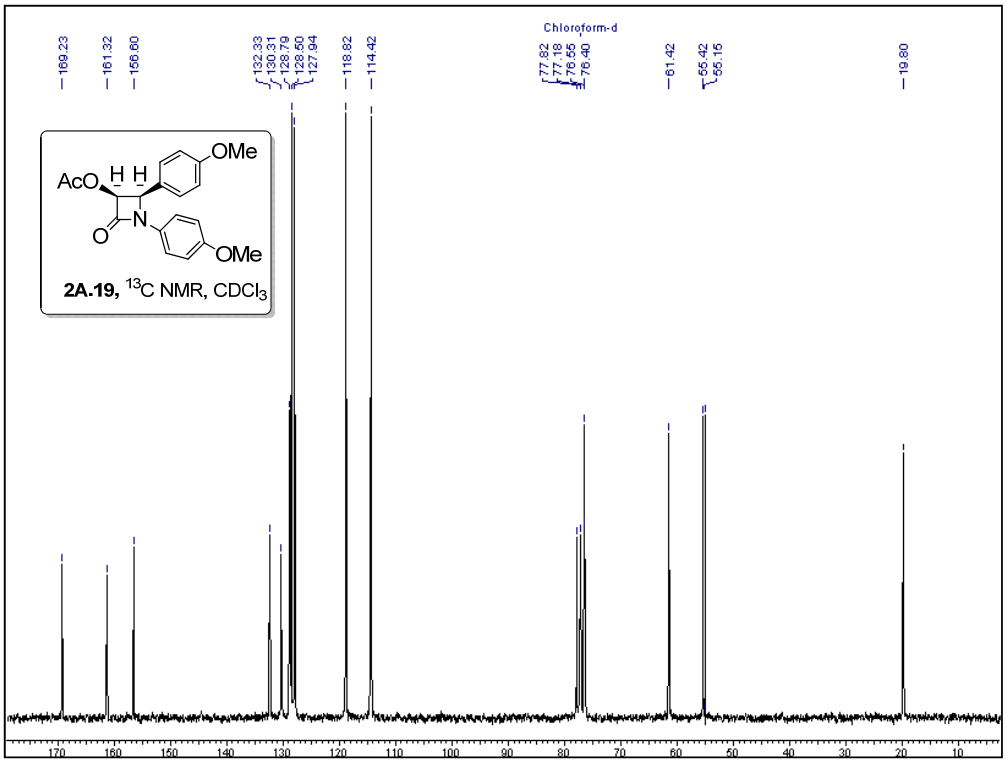


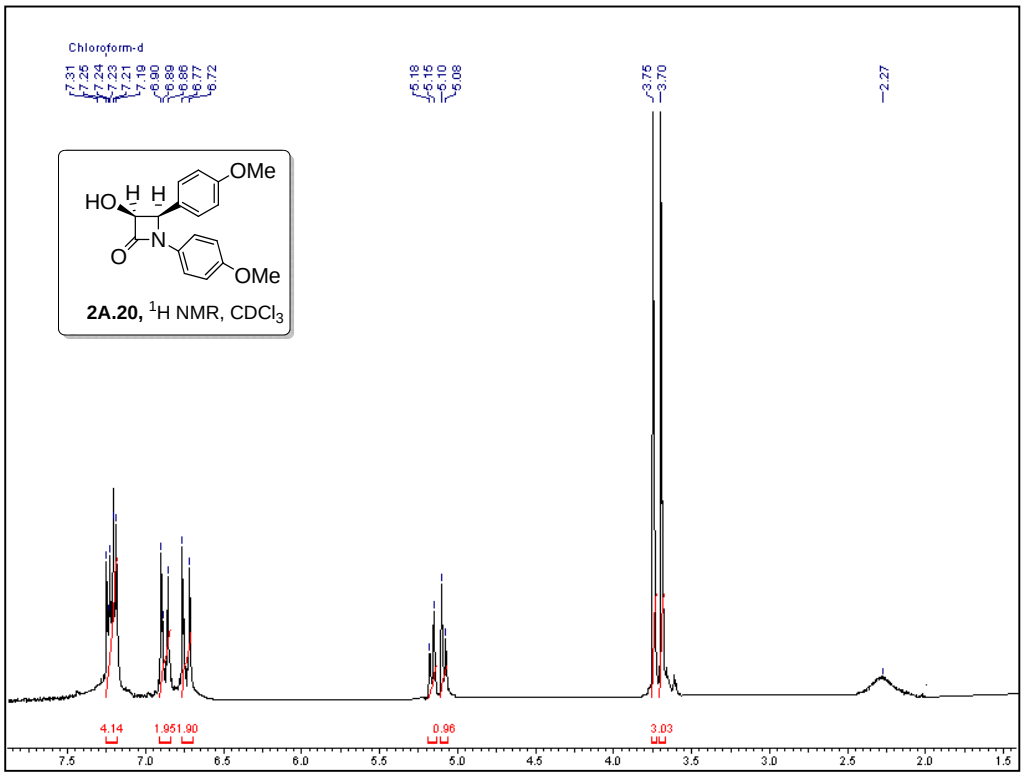
The *cis-trans* mixture of **2A.24g** (0.08 g, 0.20 mmol) was dissolved in dry THF (3 mL). Potassium tertiary butoxide (4 mg) was added and the mixture was stirred at 0 °C for 2 h. The reaction mixture was partitioned between 1N aqueous HCl (3 mL) and ether (7 mL). The aqueous layer was extracted with ether. The combined ether layer was dried over Na_2SO_4 and concentrated *in vacuo* to give (0.078 g) a mixture of *cis*-and *trans*-azetidin-2-ones (16:84). The pure *trans*-azetidin-2-one **2A.01** was isolated by recrystallization from dichloromethane-petroleum ether as white crystals.

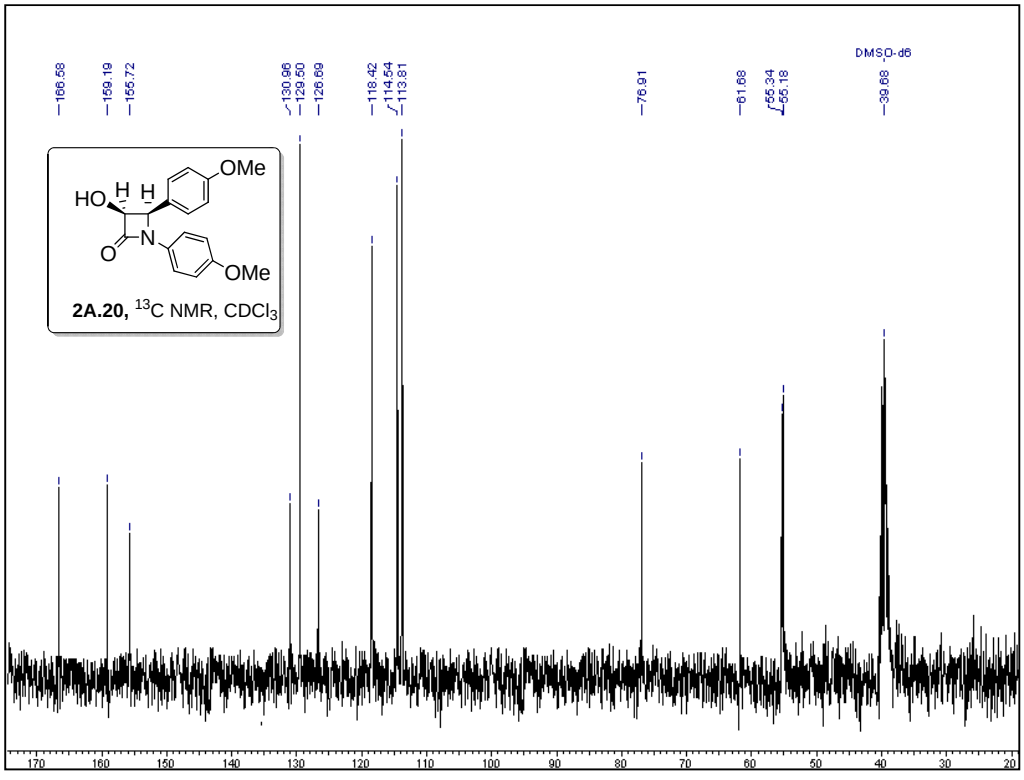
Isolated yield 70%; mp 96-98 ^oC, **IR (ν_{max}, $CHCl_3$):** 1741 cm^{-1}. **^{1}H NMR ($CDCl_3$, 200 MHz):** δ = 1.83-2.16 (m, 4H), 2.68 (t, *J* = 7.0, 2H), 3.07-3.15 (m, 1H), 3.77 (s, 3H), 3.83 (s, 3H), 4.60 (d, *J* = 2.3 Hz, 1H), 6.81 (d, *J* = 9.0 Hz, 2H), 6.88 (d, *J* = 9.0 Hz, 2H), 7.17-7.31 (m, 9H). **^{13}C NMR ($CDCl_3$, 75.48 MHz):** δ = 28.3, 28.9, 35.6, 55.2, 55.3, 60.4, 60.8, 114.2, 114.4, 118.8, 125.8, 127.1, 128.2, 128.3, 129.9, 131.2, 141.6, 155.8, 159.5, 167.2. **MS**: *m/z* = 402 (M +1). **Anal. Calcd. for $C_{26}H_{27}NO_3$**: C, 77.78; H, 6.78; N, 3.49. Found: C, 77.57; H, 6.62; N, 3.65.

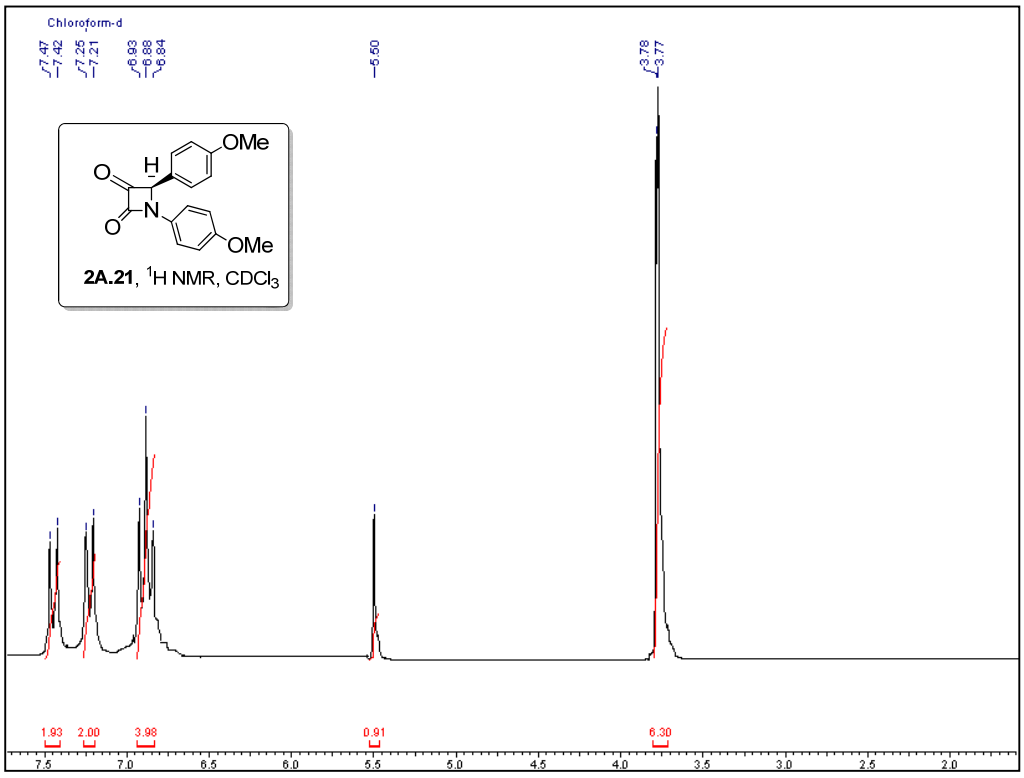
2A.7 Spectra

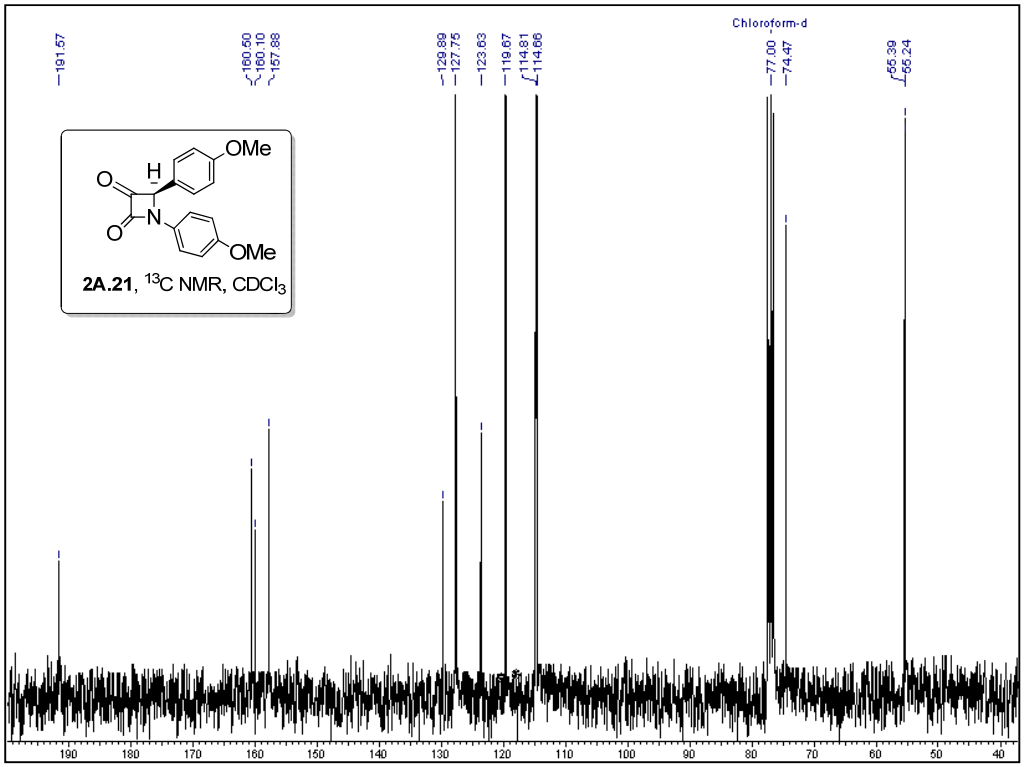

Chloroform-d
OMe
AcO
H H
N
O
OMe
2A.19, 1H NMR, CDCl3

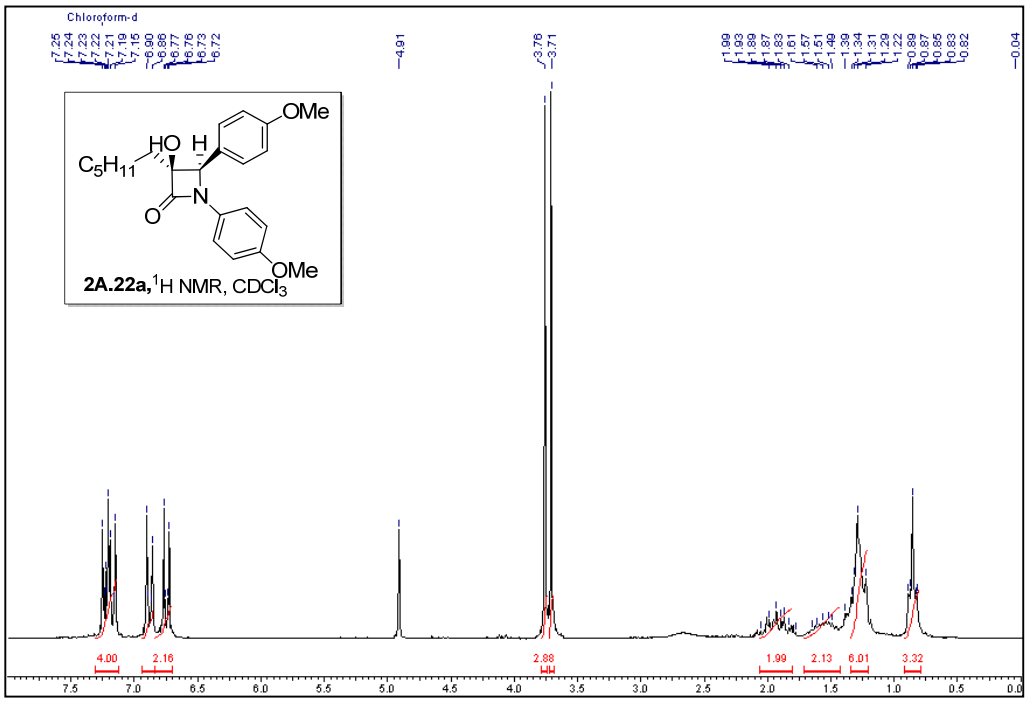

Chloroform-d
OMe
AcO
H H
N
O
OMe
2A.19, 13C NMR, CDCl3

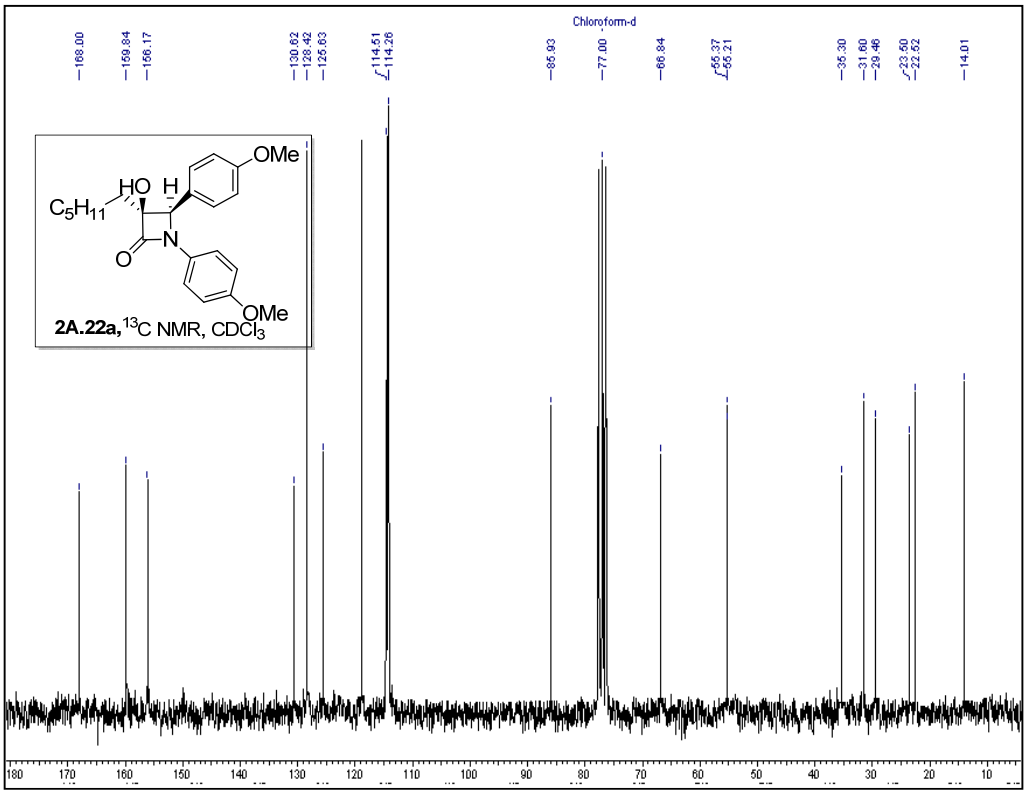

Chloroform-d
7.31
7.25
7.24
7.23
7.21
7.19
6.90
6.89
6.86
6.77
6.72
5.18
5.15
5.10
5.08
3.75
3.70
2.27
OMe
HO
H
H
N
O
OMe
2A.20, 1H NMR, CDCl3
4.14
1.95
1.90
0.96
3.03
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5

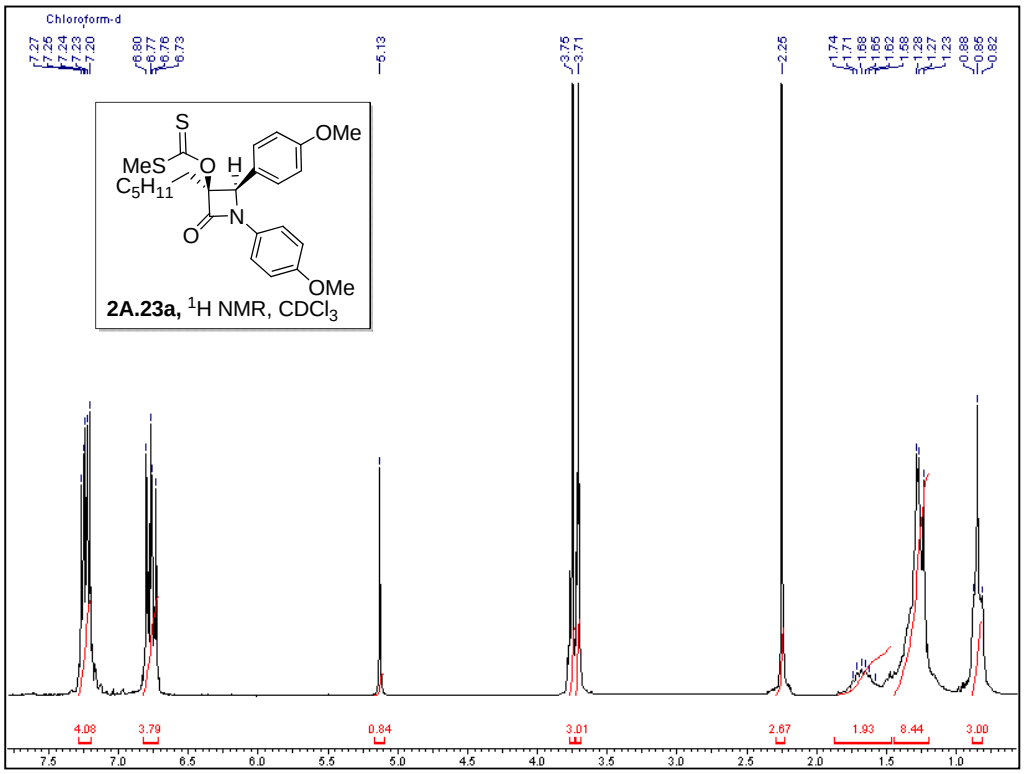

DMSO-d6
166.68
159.19
155.72
130.96
129.50
126.69
118.42
114.54
113.81
76.91
61.68
55.34
55.18
39.68
OMe
HO
H
H
N
O
OMe
2A.20, 13C NMR, CDCl3
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20

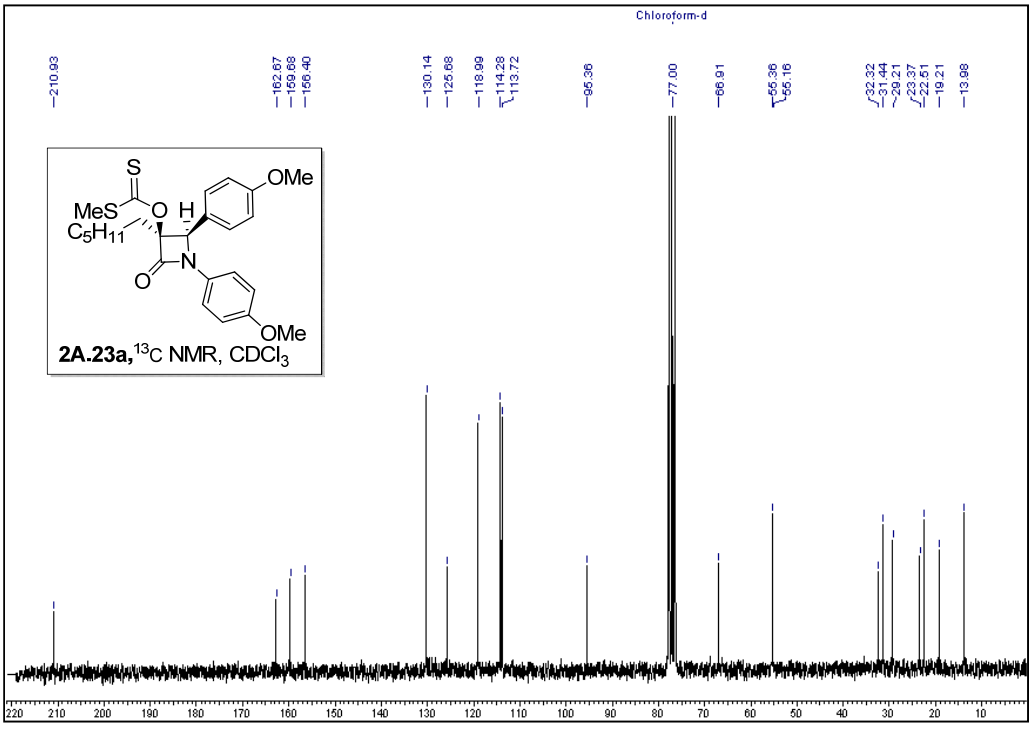

Chloroform-d
7.47
7.42
7.25
7.21
6.93
6.88
6.84
5.50
3.78
3.77
OMe
H
O
N
O
OMe
2A.21, 1H NMR, CDCl3
1.93
2.00
3.98
0.91
6.30
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0

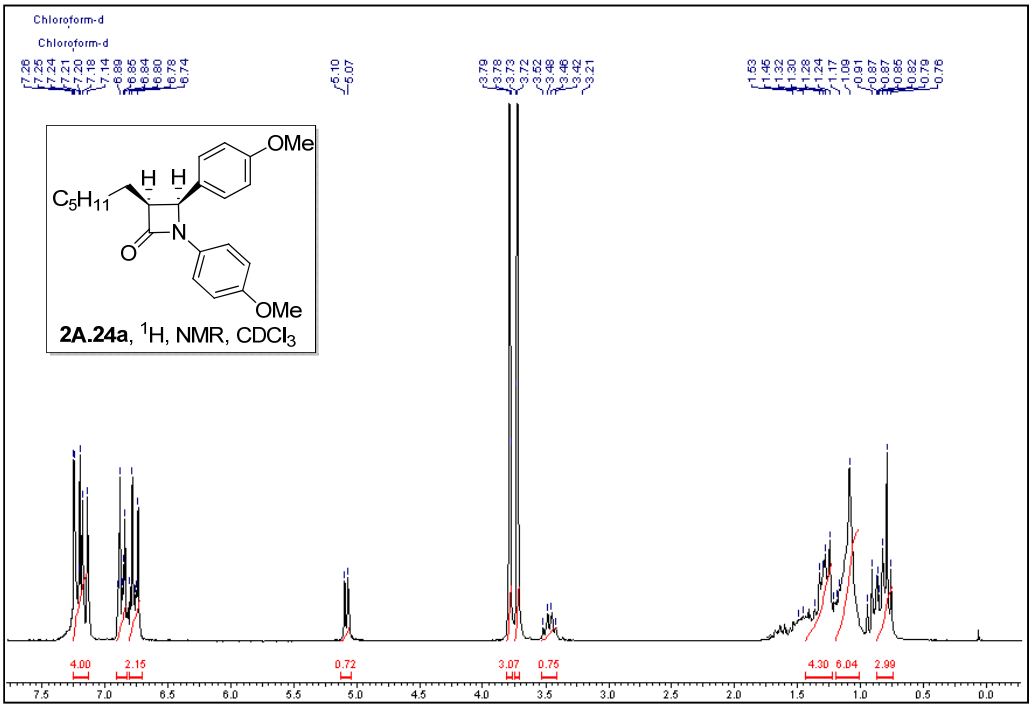

191.57
160.60
160.10
157.88
129.89
127.75
123.63
119.67
114.81
114.66
Chloroform-d
77.00
74.47
55.39
55.24
OMe
H
O
N
O
OMe
2A.21, 13C NMR, CDCl3
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40

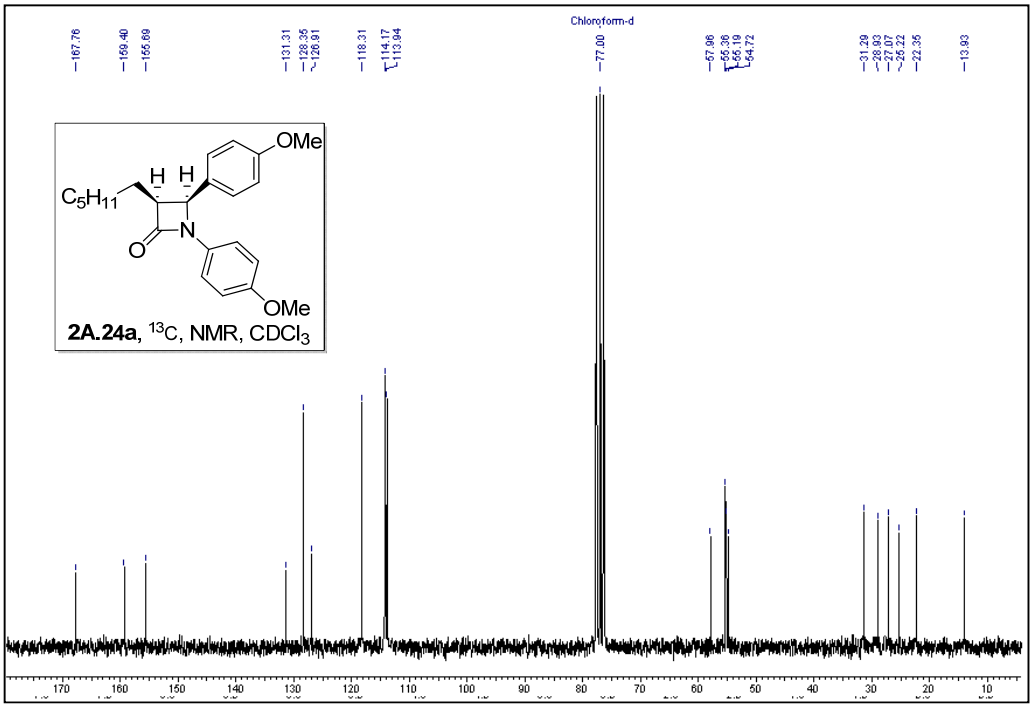

Chloroform-d
OMe
HO H
C_5H_{11}
N
O
OMe
2A.22a, ^{1}H NMR, $CDCl_3$

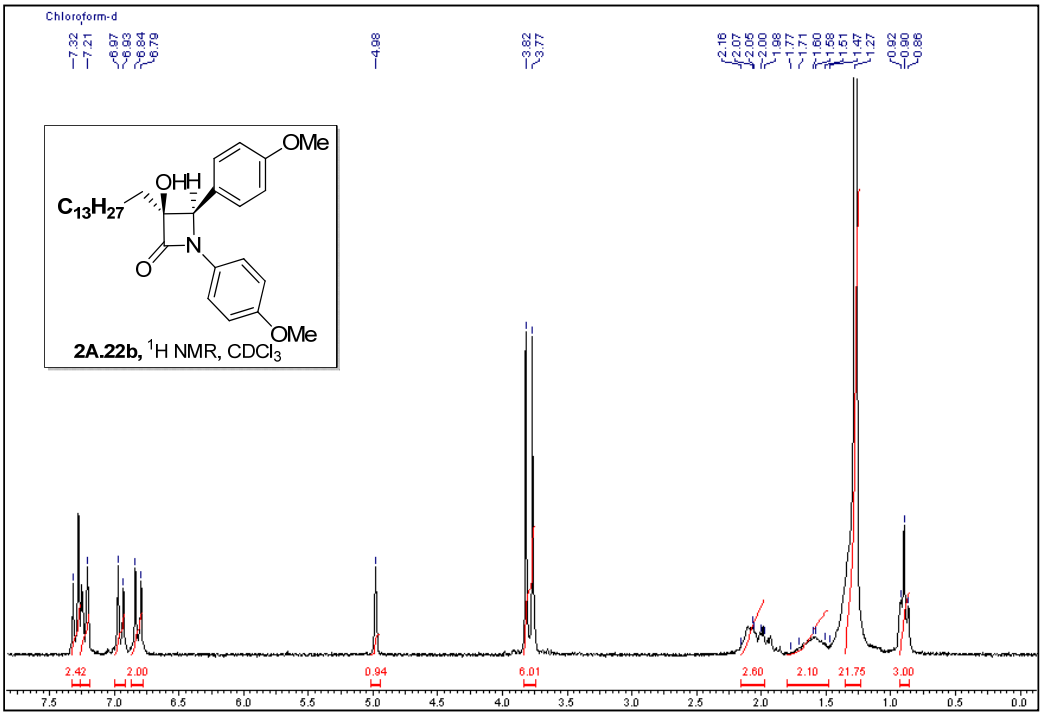

Chloroform-d
OMe
HO H
C_5H_{11}
N
O
OMe
2A.22a, ^{13}C NMR, $CDCl_3$

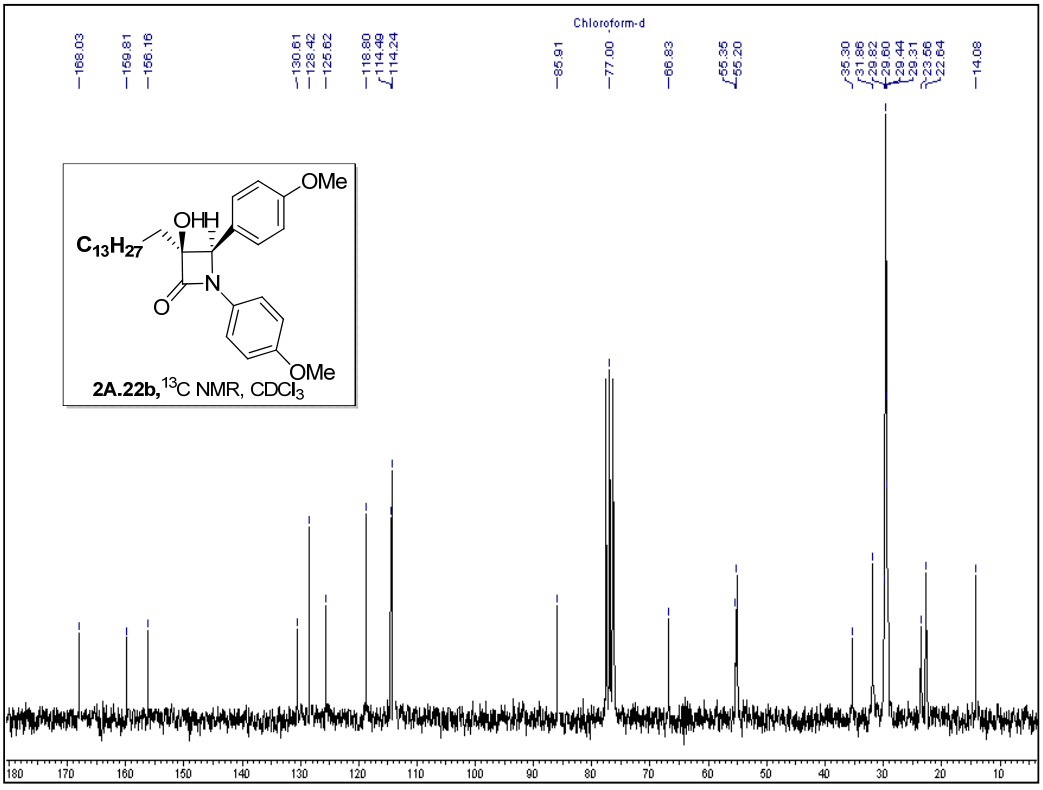

Chloroform-d
S
MeS
O
H
OMe
C_5H_{11}
N
O
OMe
2A.23a, ^{1}H NMR, $CDCl_3$

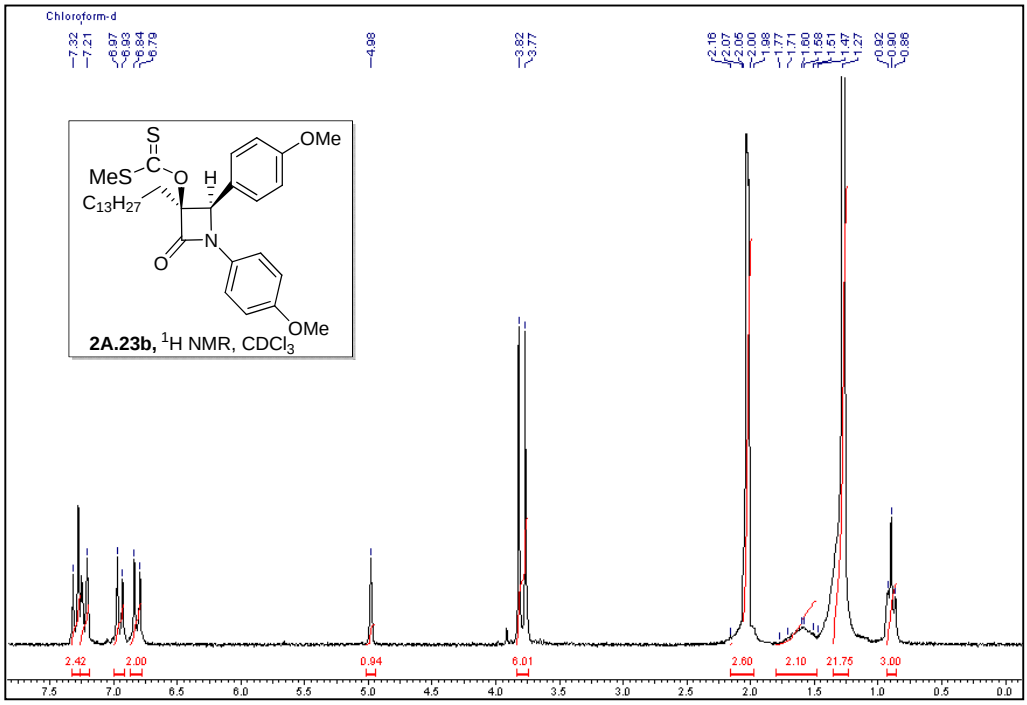

Chloroform-d
S
MeS
O
H
OMe
C_5H_{11}
N
O
OMe
2A.23a, ^{13}C NMR, $CDCl_3$

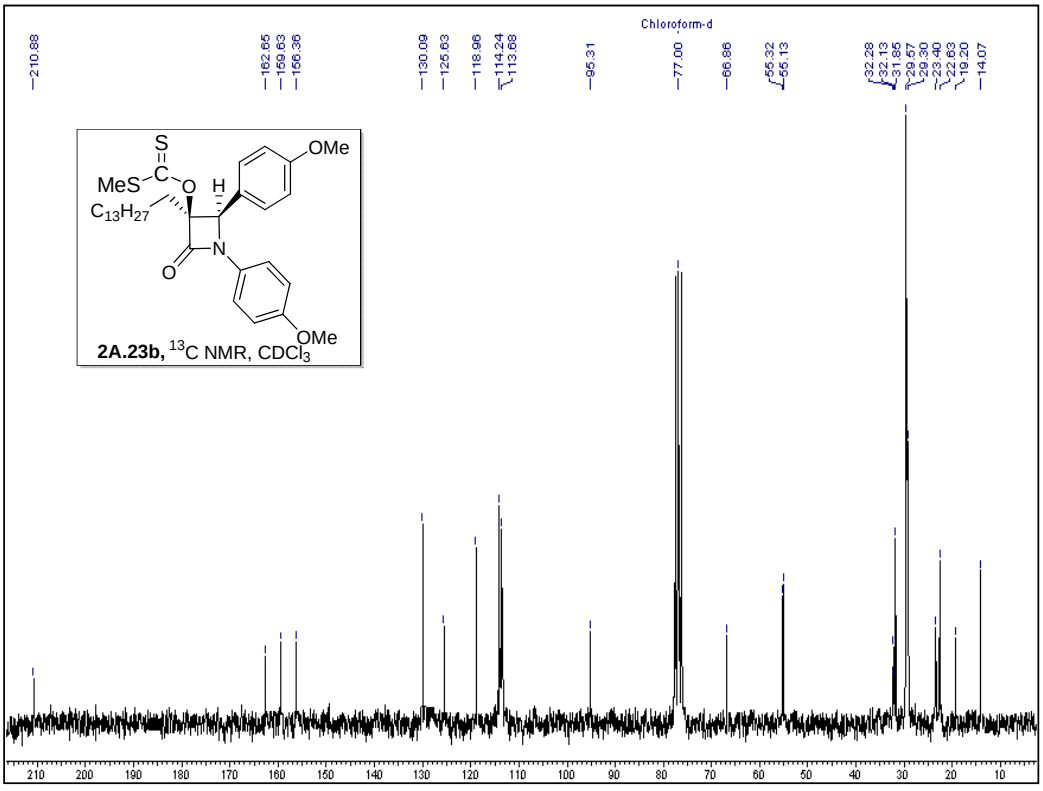

Chloroform-d
OMe
H H
C5H11
N
O
OMe
2A.24a, 1H, NMR, CDCl3

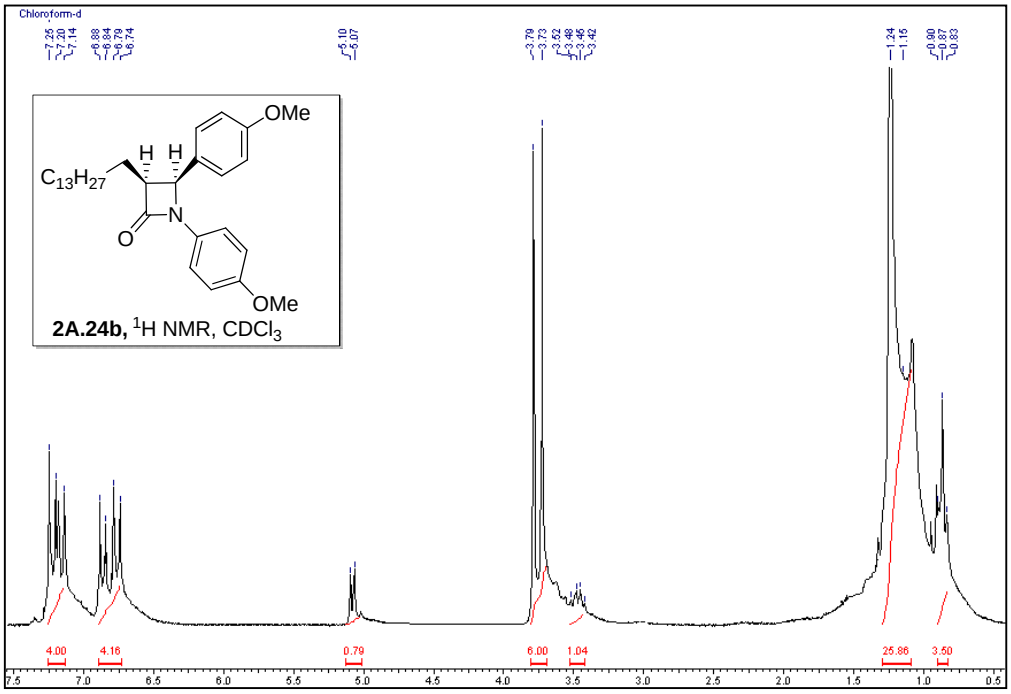

Chloroform-d
OMe
H H
C5H11
N
O
OMe
2A.24a, 13C, NMR, CDCl3

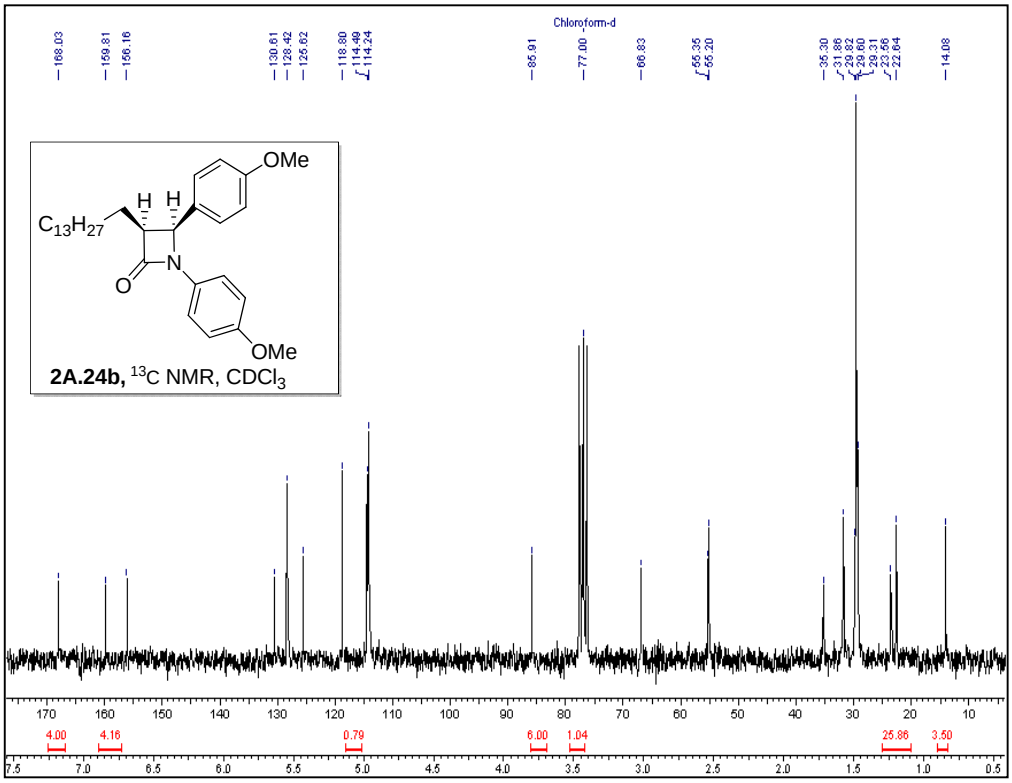

Chloroform-d
7.32
7.21
6.97
6.93
6.84
6.79
4.98
3.82
3.77
2.16
2.07
2.05
2.00
1.98
1.77
1.71
1.60
1.58
1.51
1.47
1.27
0.92
0.90
0.86
OMe
OHH
C13H27
N
O
OMe
2A.22b, 1H NMR, CDCl3
2.42
2.00
0.94
6.01
2.60
2.10
21.75
3.00

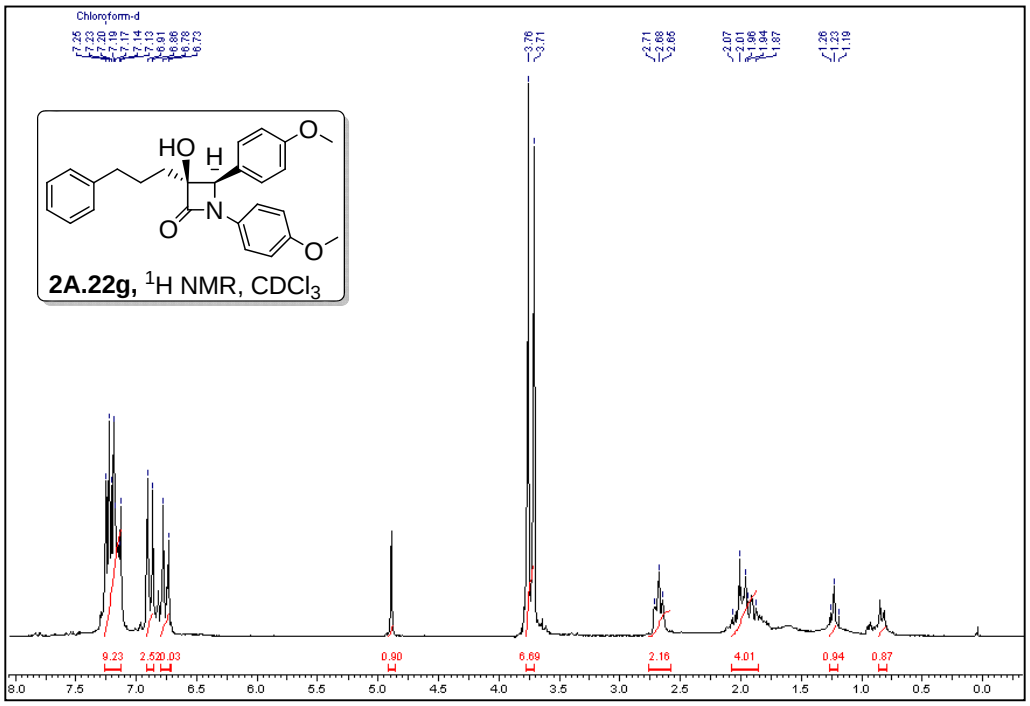

Chloroform-d
168.03
159.81
156.16
130.61
128.42
125.62
118.80
114.49
114.24
85.91
77.00
66.83
55.35
55.20
35.30
31.86
29.82
29.60
29.44
29.31
23.56
22.64
14.08
OMe
OHH
C13H27
N
O
OMe
2A.22b, 13C NMR, CDCl3

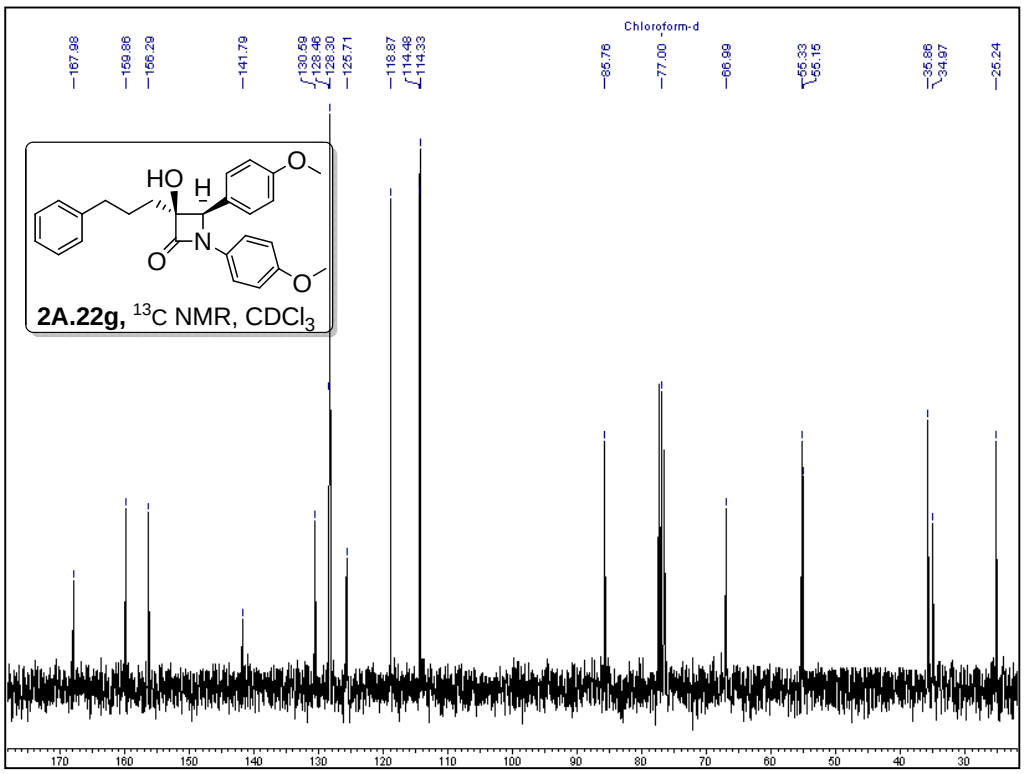

Chloroform-d
7.32
7.21
6.97
6.93
6.84
6.79
4.98
3.82
3.77
2.16
2.07
2.05
2.00
1.98
1.77
1.71
1.60
1.58
1.51
1.47
1.27
0.92
0.90
0.86
S
MeS
C
O
H
C13H27
N
O
OMe
OMe
2A.23b, 1H NMR, CDCl3
2.42
2.00
0.94
6.01
2.60
2.10
21.75
3.00
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

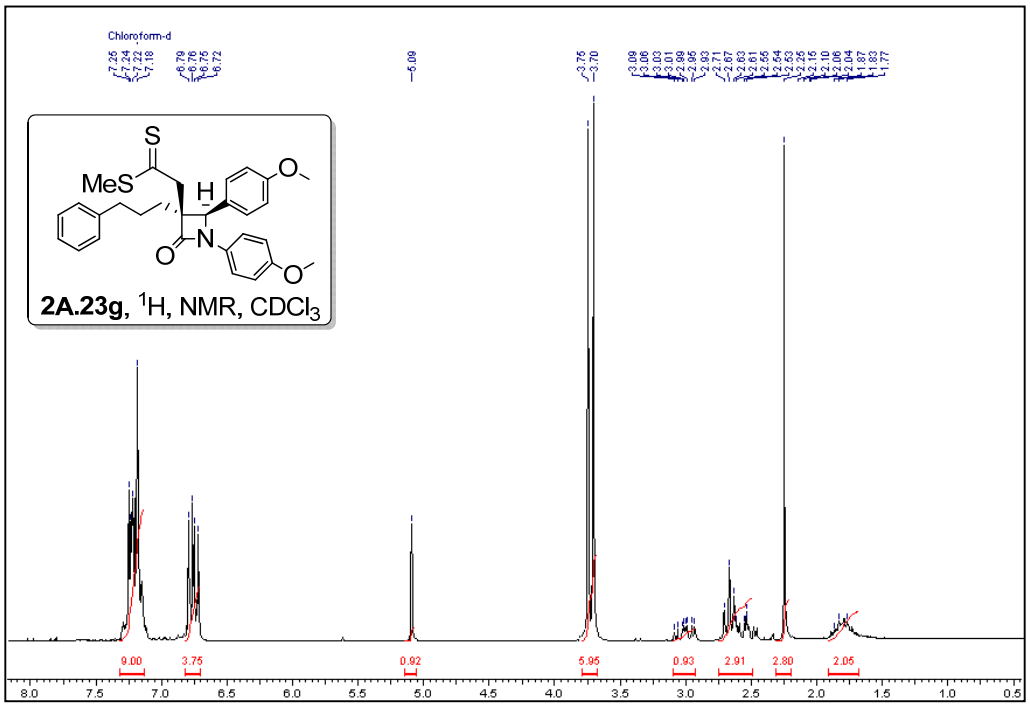

Chloroform-d
210.88
162.65
159.63
156.36
130.09
125.63
118.96
114.24
113.68
95.31
77.00
66.86
55.32
55.13
32.28
32.13
31.85
29.67
29.30
23.40
22.63
19.20
14.07
S
MeS
C
O
H
C13H27
N
O
OMe
OMe
2A.23b, 13C NMR, CDCl3
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10

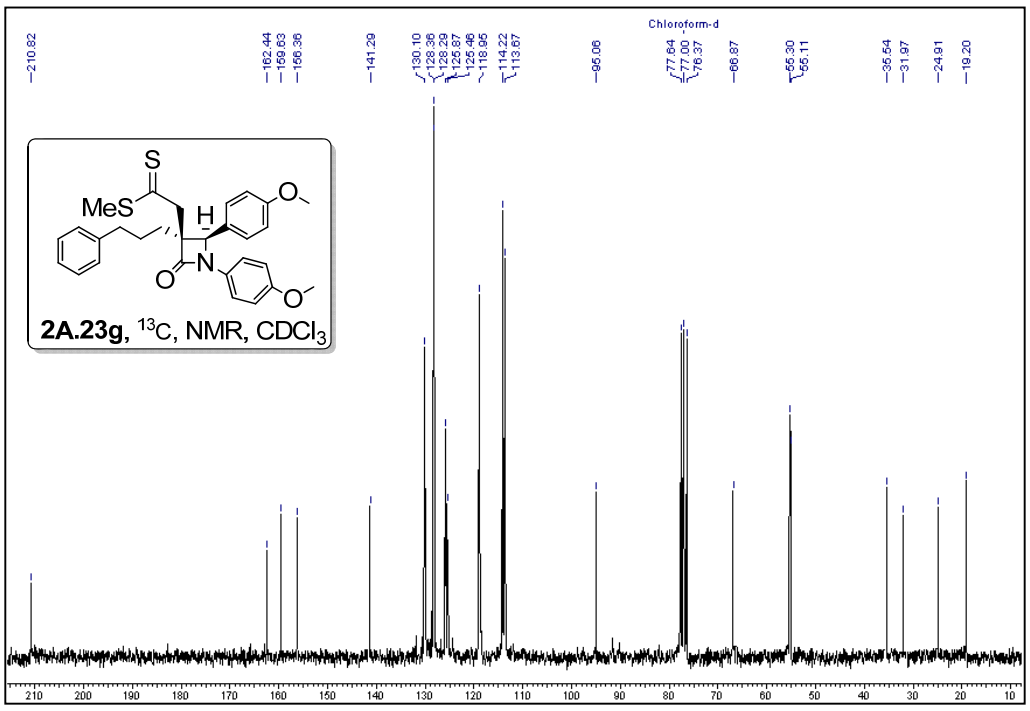

Chloroform-d
OMe
H H
$C_{13}H_{27}$
N
O
OMe
2A.24b, ^{1}H NMR, $CDCl_3$

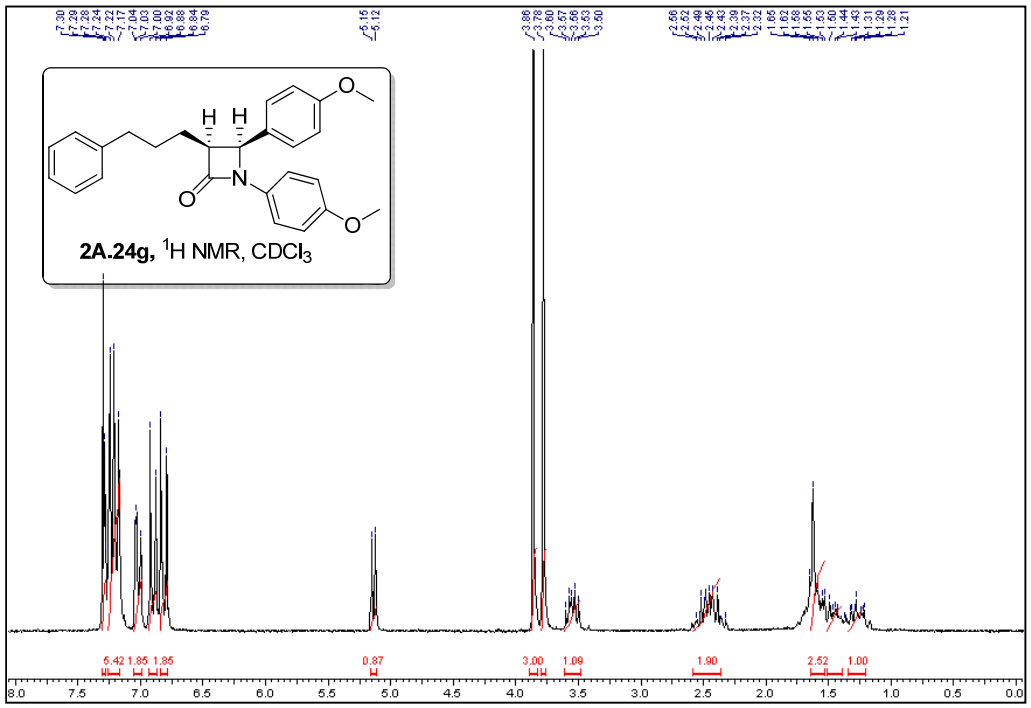

Chloroform-d
OMe
H H
$C_{13}H_{27}$
N
O
OMe
2A.24b, ^{13}C NMR, $CDCl_3$

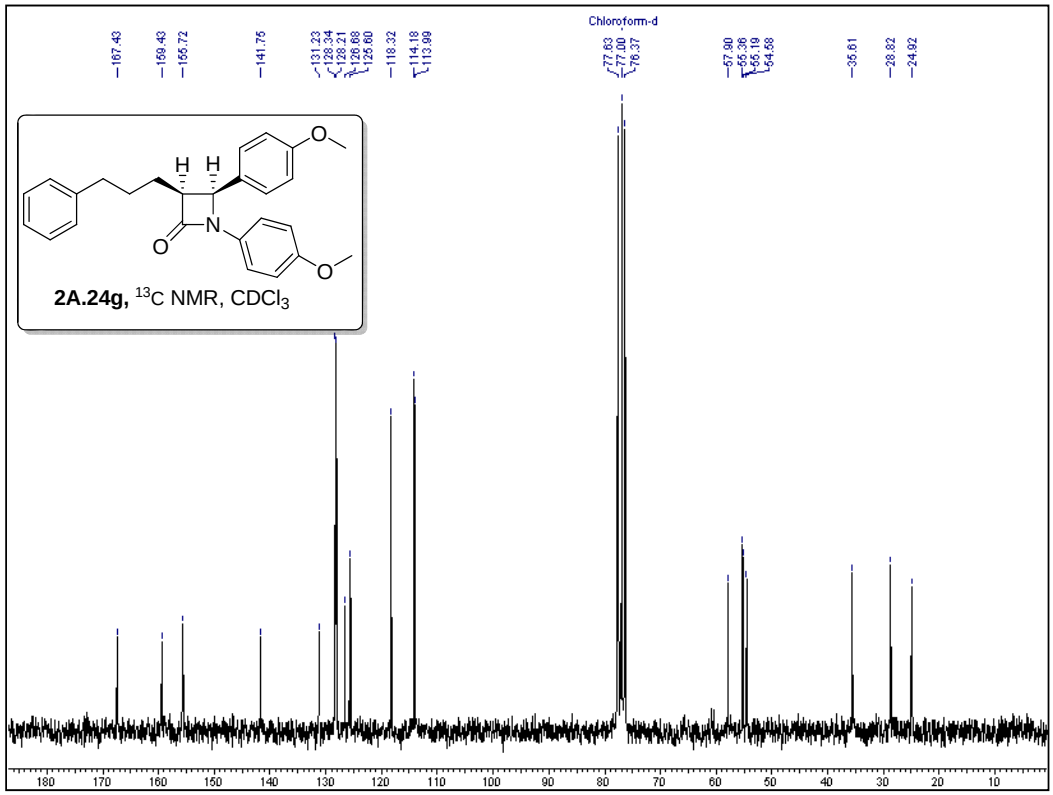

Chloroform-d
HO
H
O
N
O
O
2A.22g, ^{1}H NMR, CDCl$_3$

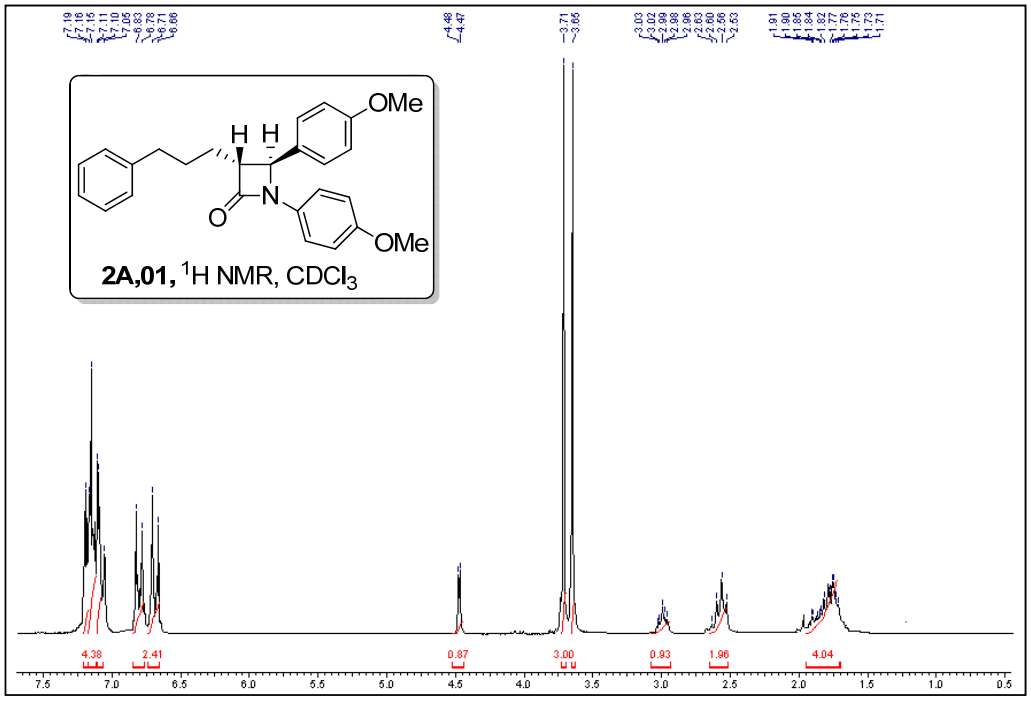

Chloroform-d
HO
H
O
N
O
O
2A.22g, ^{13}C NMR, CDCl$_3$

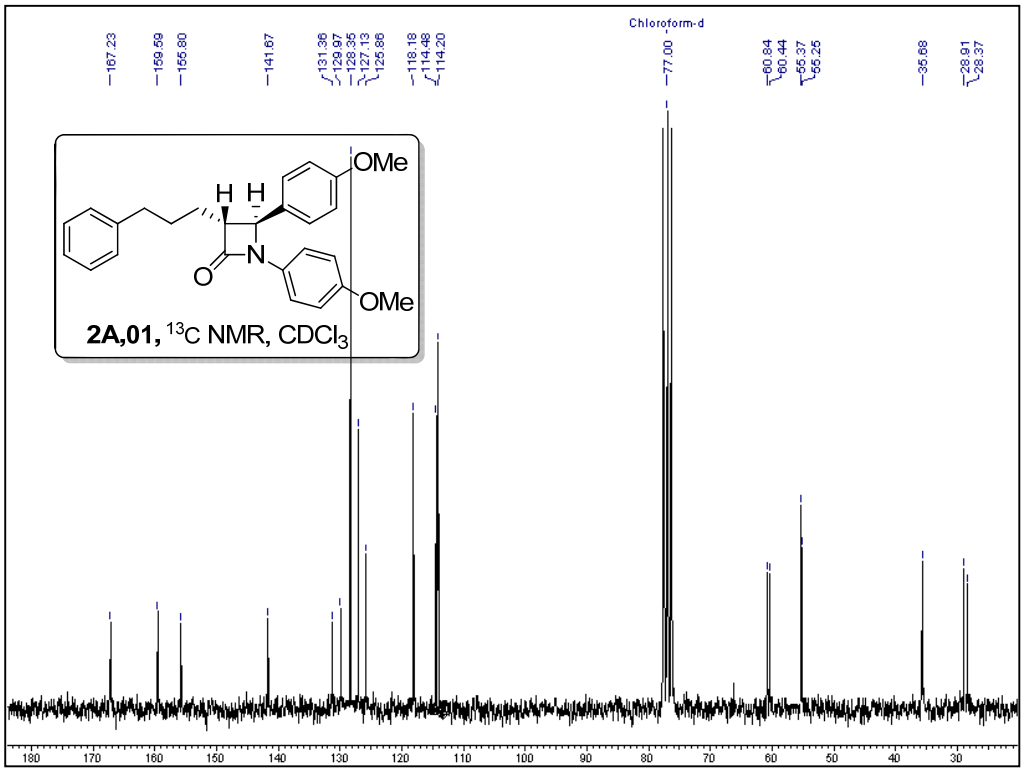

Chloroform-d
2A.23g, ^{1}H, NMR, CDCl$_3$


Chloroform-d
2A.23g, ^{13}C, NMR, CDCl$_3$


2A.24g, ^{1}H NMR, $CDCl_3$


Chloroform-d
2A.24g, ^{13}C NMR, $CDCl_3$


OMe
H H
N
O
OMe
2A,01, 1H NMR, CDCl3


Chloroform-d
OMe
H H
N
O
OMe
2A,01, 13C NMR, CDCl3

2A.8 References:

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CHAPTER 2 section-B

Stereoselective synthesis of 3-alkylidene/alkyl-azetidin-2-ones from azetidine-2,3-diones

This work has been published in *Tetrahedron* **2007**, *63*, 2524-2534.

2B.1: Introduction

It has been established that structural variations on the *β*-lactam ring have interesting and significant consequences in terms of their biological activities. 3-Alkylidene azetidin-2-ones, in which an *exo*-cyclic double bond on C-3 adjacent to the carbonyl carbon, making it more strained, have been shown to possess promising biological activities[4]. For example, such structural frameworks are found as the part structures of the ene type of *β*-lactamase inhibitors such as asparenomycins (**2B.01)**[1], Ro 15-1903 (**2B.02)**[2], 6-[(Z)-methoxymethylidene] penicillanic acid (**2B.03**)[3] and 6-(2'-pyridyl) methylene penem sulfone (**2B.04)**. *β*-Lactamase inhibitors are a special class of *β*-lactams which are used in tandem with *β*-lactam antibiotics and function in a way that enhances the efficacy of the antibiotics. Therefore, synthesis of novel 3-alkylidene *β*-lactams and subsequent testing of their activities has been an important area of research over the last few decades.

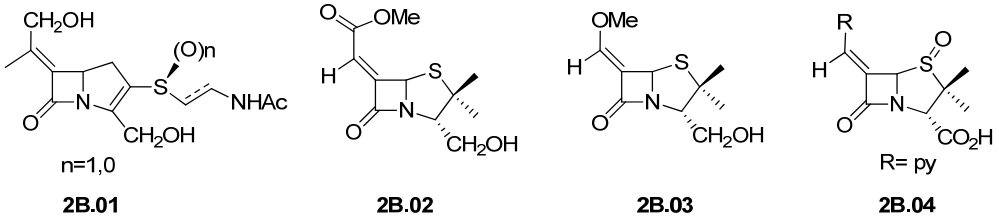
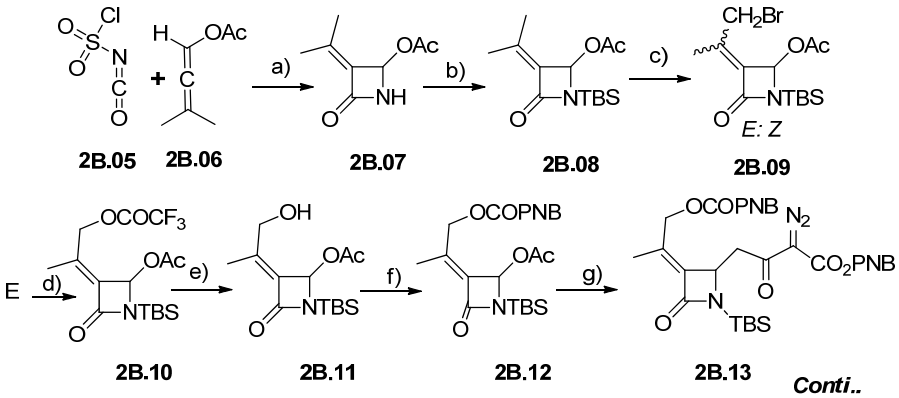
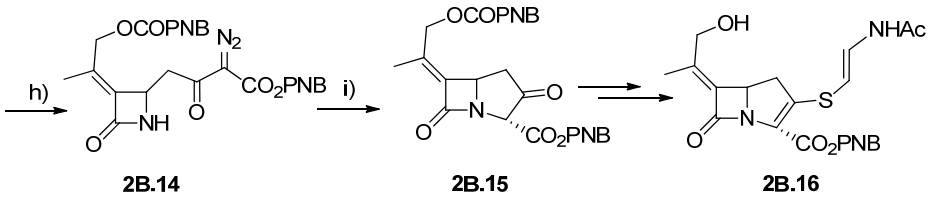


Figure 2B.1

Apart from the above mentioned biological applications, 3-alkylidene *β*-lactams have also been used as synthons for a variety of other useful products. In one such study, a substituted 3-alkylidene azetidin-2-one has been used as a synthon in the synthesis of asparenomycin C[5] as shown in Scheme 2B.1.

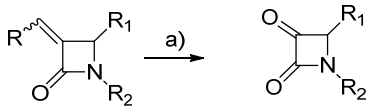




2B.14 **2B.15** **2B.16**

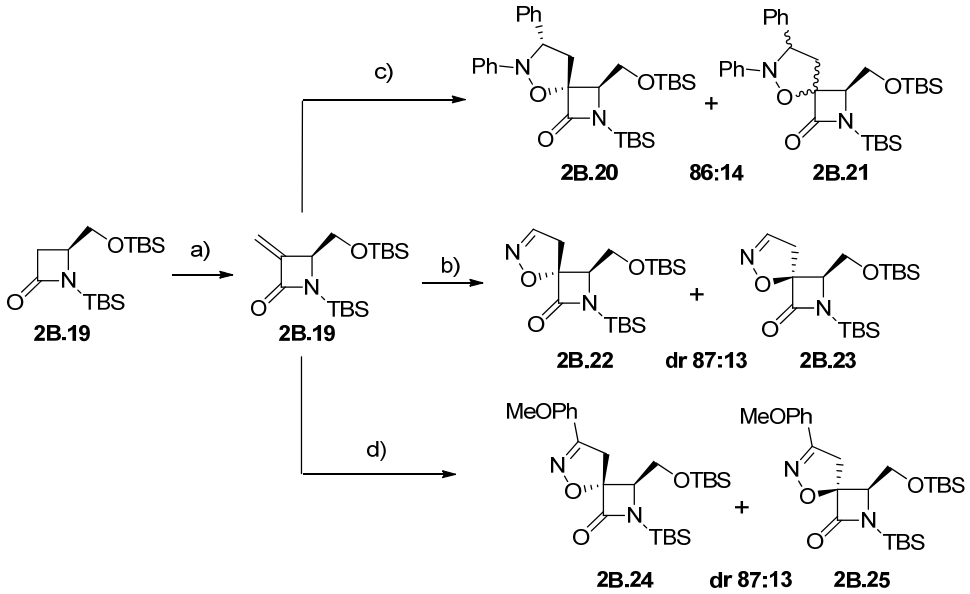
Scheme 2B.1. ***Reagents and conditions:*** *a), i) ether, -78° to -2 °C, 2h, ii) Na_2SO_3, K_2HPO_4, H_2O:ether (1:1), 0 °C to rt 2h, 23%, b) TBSCl, Et_3N, DMF, 0 °C, 2 h, 60%, c) NBS, AIBN (cat), CCl_4, reflux 30 min 78%, d) $AgCO_2CF_3$, benzene, reflux, 1 h, 90%. e) $KHCO_3$, MeOH:H_2O (4:1), rt, 30 min, 85%, f) p-nitrobenzylchloroformate, DMAP, DMF, rt, 30 min, 91%, g) Me_3SiOTf, p-nitrobenzyl-α-diazoacetoacetate, $ZnCl_2$, DCM, -78 °C to rt 1 h, 62%, h) 48% aq. HF, CH_3CN, 94%, i) $Rh_2(OAc)_4$, benzene, reflux, 20 min, 85%.*

Another application have also been demonstrated by Alcaide *et al.* in the synthesis of azetidin-2,3-diones[6, 8], a versatile synthetic intermediates of varied utility[7].



2B.17 **2B.18**

Scheme 2B.2. ***Reagents and conditions:*** *a) i) OsO_4 (cat), TMNO, acetone-water, rt and then 40% $NaHSO_3$; ii) $NaIO_4$, MeOH-water (9:1), rt.*



2B.20 **86:14** **2B.21**

2B.22 **dr 87:13** **2B.23**

2B.24 **dr 87:13** **2B.25**

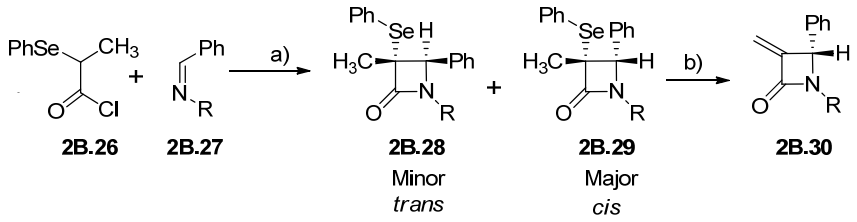
Scheme 2B.3. ***Reagents and conditions:*** *a) i) LDA, MeI, after 15 min PhSeBr, THF, -78 °C to rt 12 h, 46%; ii) H_2O_2, pyridine, CH_2Cl_2, 3 days, 73 %, b) CH_2N_2, ether, 0 °C, 6 h, c) 4-methoxy benzonitrile oxide, Et_3N, ether, rt 10 h, 95 %; d) diphenyl nitrone, toluene, reflux, 3 h, 40 %.*

Another synthetic exploitation of 3-alkylidine azetidin-2-dione may be found in Liebscher's[9] work where olefinic moiety has been used for various dipolar cycloaddition reactions to develop novel class of compounds (Scheme 2B.3) for biological evaluations.

2B.2 Background of the present work:

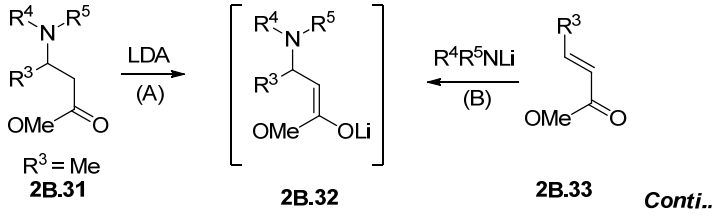
Owing to the above mentioned applications, synthesis of 3-alkylidene *β*-lactams has remained an important topic of research and has resulted in many publications on this topic. Some of the important contributions are highlighted as follows:

One of the earliest synthesis of 3-alkylidene *β*-lactams involved the Staudinger cycloaddition reaction of methyl-phenylseleno-ketene [10] with an imine followed by oxidative removal of the phenylselenyl moiety from **2B.28 & 2B.29** yielding the desired 3-alkylidene *β*-lactams (**2B.30.** 92%).

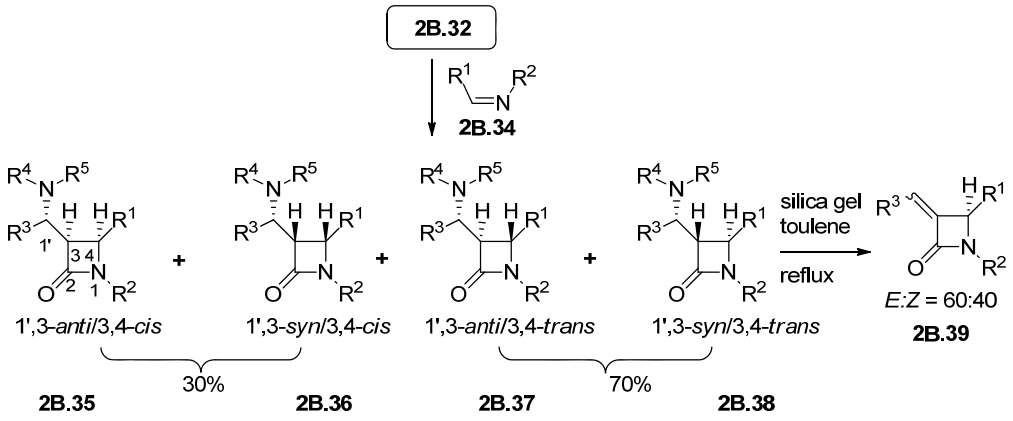


Scheme 2B.4. ***Reagents and conditions:*** *a) Et_3N, Benzene, rt, 2 h, 52%; b) H_2O_2, Py, 40 °C, 30 min, 92 %.*

Alcaide *et al.* have used *α*-[(dialkylamino) alkyl] *β*-lactams, *via* an appropriate ester enolate-imine condensation reaction followed by dehydroamination to afford *α*-alkylidene *β*-lactams in 62% yield.[8]

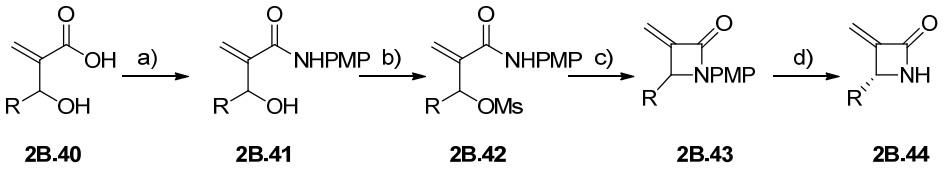


Conti..



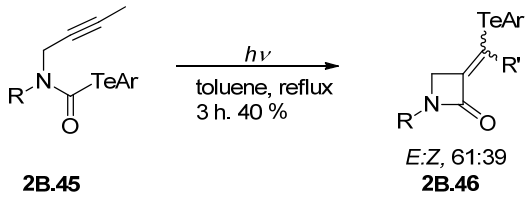
Scheme 2B.5

Enantiomerically pure (99% *ee*) *α*-methylene *β*-lactams are also synthesized[11] by lipase catalyzed kinetic resolution of **2B.43,** prepared in several steps from *α*-methylene *β*- hydroxy acids as shown in Scheme 2B.6.



Scheme 2B.6. ***Reagents and conditions:*** *a) p-anisidine, DCC, CH_2Cl_2, 0 °C, 2 h, 52%; b) MsCl, Et_3N, CH_2Cl_2, 0 °C, 79%; c) KO^{t}Bu, THF, 0 °C, 2 h, 71%, d) CAN, CH_3CN/H_2O, -15 °C, 1 h, 48 %.*

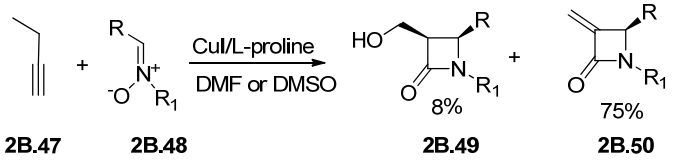
In a relatively recent report, Fujiwara *et al.*[12] have reported the synthesis of 3-alkylidene *β*-lactams **2B.46** (40%) by the irradiation of carbamotelluroates **2B.45** with visible light. This cyclization reaction involved group transfer radical reaction mainly proceeding with 4-*exo*-dig cyclization.



Scheme 2B.7

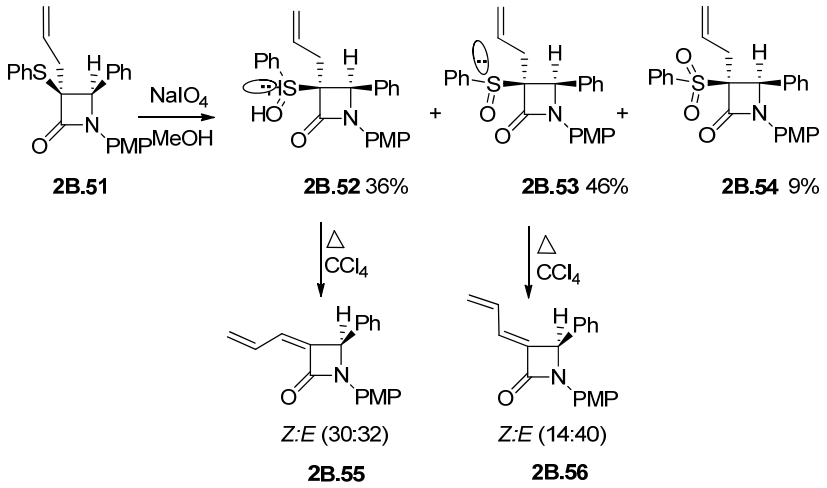
Basak *et al.*[13] have reported the synthesis of 3-*exo*-methylene *β*-lactams **2B.50** in a single step employing Cu(I) catalysed Kinugasa cycloaddition reaction between

propargyl alcohol **2B.47** and nitrones **2B.48** in the presence of L-proline. However, the enantiomeric purity obtained was very poor (15% ee).



Scheme 2B.8

3-Allylidene *β*-lactams **2B.55** and **2B.56** have recently been synthesized[14] by the oxidative removal of the thiophenyl moiety of *trans*-3-allyl-3-phenythio-*β*-lactams.



Scheme 2B.8

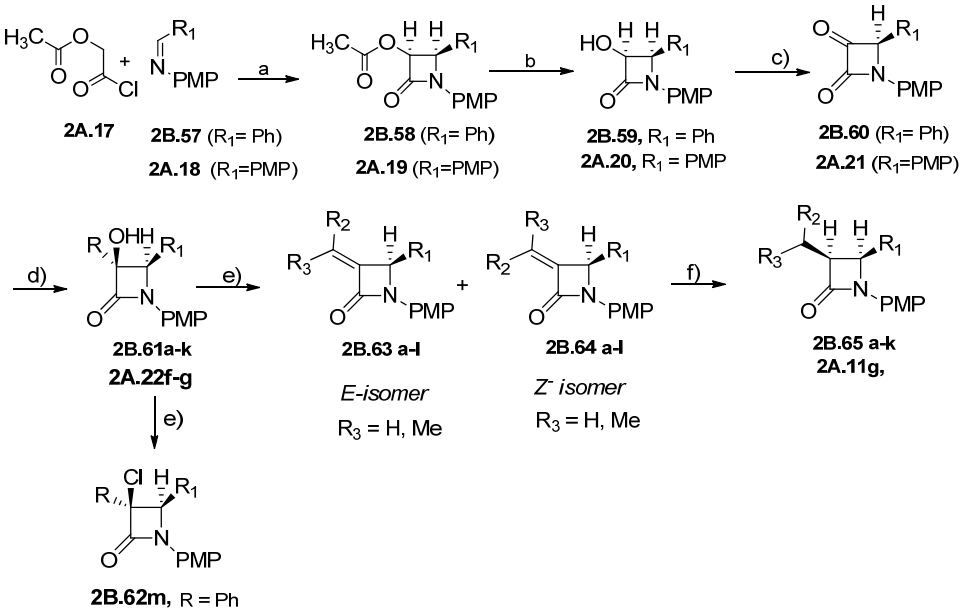
In view of all the aforementioned applications of 3-alkylidene *β*-lactams, we also became interested in devising a route for the synthesis of 3-alkylidene *β*-lactams, further enriching the repertoire of methods available for their synthesis. In addition, we were also interested in the synthetic manipulations of 3-alkylidene *β*-lactams to derive new chemical entities.

2B.3 Results and discussion:

The key precursor 3-hydroxy alkyl/aryl azetidin-2-ones (**2B.61a-k** and **2A.22 f & g**) were synthesized following the same procedure as discussed in previous section (**2A.19-2A.22**).

Compound **2B.61b** was taken as a representative analogue for characterization and spectral discussion

3-Butyl-3-hydroxy azetidin-2-one **2B.61b** on reaction with PPh_3 in refluxing CCl_4 did not give the expected 3-chloro *β*-lactam **2B.62b**, instead, we isolated the dehydration product as a geometrical mixture of *E*- and *Z*-olefins **2B.63b** and **2B.64b** in (91%) very good yield. The structure of the major product was established as *E*-isomer on the basis of ^{1}H NMR spectrum.



Scheme-2B.10. ***Reagents and conditions:*** *a) Et_3N, DCM, 0 °C-rt, 18 h,62%; b) aq. $NaHCO_3$, Na_2CO_3, MeOH, rt, 18h, 88%; c) DMSO, P_2O_5, rt, 24h, 90%; d), RMgX, THF, 0 °C,57%; e) PPh_3, CCl_4, reflux, 6 h, 91%; f) Pt/C, 10% ETOAc, 95%.*

The ^{1}H NMR of **2B.63b** displayed a triplet at δ 0.73 (J = 7.4 Hz), integrating for three protons and a multiplet at δ 1.26, integrating for two protons, which were assigned to the terminal methyl and a methylene protons attached to methyl group of side chain, respectively. The allylic methylenic protons appeared at δ 1.81-1.99 as a multiplet whereas the vinylic proton appeared at δ 6.23 (dt, J = 1.4, 7.6 Hz). Surprisingly, H4 of *β*-lactam ring appeared at δ 5.43 as a doublet with coupling constant J = 1.4 Hz, though, it was expected to be a singlet. This unexpected multiplicity may be due to long range coupling of H4 with one of the proton of the side chain. The ^{13}C NMR showed three signals at *δ* 13.5, 22.4, and 30.6 corresponding to terminal methyl, methylene and allylic methylenic carbons,

respectively. The C4 carbon appeared at δ 62.7 whereas C3 carbon of *β*-lactam ring appeared at δ 141.3. The vinylic carbon of side chain was noticed at δ 142. The structure of above product was further confirmed by *m/z* at 308 in the mass spectrum.

Entry No	Comp.	R	R^1	Yield[b]	Mp (°C)	
1.	**2B.61a**	*n*-butyl	PMP[a]	55	Thick oil	
2.	**2B.61b**	n-butyl	Ph	60	Thick oil	
3.	**2B.61c**	*n*-octyl	PMP	57	Thick oil	
4.	**2B.61d**	*n*-octyl	Ph	62	Thick oil	
5.	**2B.61e**	*n*-heptyl	PMP	62	Thick oil	
6.	**2B.61f**	*n*-heptyl	Ph	58	Thick oil	
7.	**2B.61g**	*n*-propyl	PMP	69	Thick oil	
8.	**2B.61h**	*n*-propyl	Ph	62	144-146	
9.	**2B.61i**	*iso*-propyl	PMP	49	Thick oil	
10.	**2B.61j**	*iso*-propyl	Ph	52	114-116	
11.	**2A.22g**	3-phenylpropyl	PMP	61	Thick oil	
12.	**2B.61k**	3-phenylpropyl	Ph	62	Thick oil	
13.	**2A.22f**	Ph	PMP	67	144-146	

[a] PMP = 4-Methoxyphenyl..

Table 2B.1. *3-alkyl-3-hydroxy azetidin-2-one*

Similarly, in the ^{1}H NMR spectrum of the *Z*-isomer (**2B.64b)**, the allylic methylenic protons appeared at δ 2.41-261 as a multiplet and vinylic protons at δ 5.56 (dt, *J* = 1.2, 7.9 Hz) as a doublet of triplet. Furthermore, H4 proton of the *β*-lactam ring was found resonating at δ 5.27 as a doublet with coupling constant (*J* = 1.2 Hz). The ^{13}C NMR displayed two carbon signals at δ 131.4 and 142.01 for vinylic and C3 carbon of the *β*-lactam, respectively. Mass spectrum showed base peak at *m/z* [308].

The downfield chemical shift of vinyl proton in *E* isomer (**2B.64b**, δ 6.23) compared to the corresponding *Z*-isomer (**2B.64b,** δ 5.56) may be due to an anisotropic deshielding effect of the *β*-lactam carbonyl group. A similar deshielding is also observed on the allylic methylene protons of *Z* isomer (**2B.64b**, δ 2.41-2.61, m, 2H; *E* isomer **2B.64b,** δ 1.81-1.99, 2H).

Comp. **2B.63 and 2B.64**	R^1	R^2	R^3	Yield[a]	***E*:*Z* (2B.63:2B.64)**
a	PMP	*n*-propyl	H	90	72:28
b	Ph	*n*-propyl	H	90	71:29
c	PMP	*n*-heptyl	H	89	71:29
d	Ph	*n*-heptyl	H	88	66:34
e	PMP	*n*-hexyl	H	94	71:29
f	Ph	*n*-hexyl	H	89	69:31
g	PMP	ethyl	H	85	72:28
h	Ph	ethyl	H	86	69:31
i	PMP	Me	Me	71	--
j	Ph	Me	Me	70	--
k	PMP	2-phenylethyl	H	91	70:30
l	Ph	2-phenylethyl	H	89	70:30

[a] Total yield. **Table 2**: 3-Alkylidene azetidin-2-ones **2B.63a-l** and **2B.64a-l**

The generality of the reaction was established by preparing several 3-alkylidine *β*-lactams as depicted in **Table-2**. Both the isomers were separated by column chromatography and in all cases *E*-isomer was found to be predominant geometrical isomer.

After having fully characterized 3-alkylidiene both (*E* & *Z*) isomers in hand, the next step was the reduction of double bond to prepare various 3-aklyl/aryl azetidin-2-one including cholesterol absorption inhibitor (**2A.24g**). We were expecting a single isomer from the catalytic hydrogenation of olefins **2B.63b** and **2B.64b** using Pd/C 10% in ethyl acetate. However, a partial isomerization of *cis β*-lactam to a more stable *trans* isomer was observed in (70:30) ratio. The isomerization phenomenon was considerably suppressed (*cis/trans* 97:3), when Pt/C catalyst was used, and a single major *cis β*-lactam **2B.65b** was obtained by the hydrogenation of *E/Z* mixture (**2B.63b** and **2B.64b**).

The formation of compound **2B.65b** was confirmed by spectroscopic techniques such as IR, ^{1}H NMR and ^{13}C NMR. The ^{1}H NMR spectrum of **2B.65b** displayed a signal at δ 0.72 (t, J = 6.9 Hz,), integrating for three protons, and a multiplet at δ 1.25-1.69, integrating for six protons, were assigned to methyl and three

methylene group of side chain, respectively. The H3 Proton of *β*-lactam ring resonated at δ 3.47 as a multiplet whereas H4 proton of *β*-lactam ring appeared at δ 5.11 as doublet with coupling constant *J* = 5.7 Hz. The higher coupling constant suggested that both the ring protons are in *cis* configuration to each other. In ^{13}C NMR spectrum, both the C3 and C4 carbon appeared at δ 55.3 and 54.7 respectively. Eventually, the structure was confirmed by mass spectrum showed a base ion peak at *m/z* 310 (M+1).

Comp.	R^1	R^2	R^3	Yield[a]	*Cis/trans*
2B.65 a	PMP	n-propyl	H	92	98:2
2B.65 b	Ph	n-propyl	H	95	96:4
2B.65 c	PMP	n-heptyl	H	94	97:3
2B.65 d	Ph	n-heptyl	H	91	97:3
2B.65 e	PMP	n-hexyl	H	94	97:3
2B.65 f	Ph	n-hexyl	H	95	98:2
2B.65 g	PMP	ethyl	H	97	96:4
2B.65 h	Ph	ehtyl	H	94	95:5
2B.65 i	PMP	Me	Me	92	95:5
2B.65 j	Ph	Me	Me	95	97:3
2A.11g	PMP	2-phenylethyl	H	94	97:3
2B.65 k	Ph	2-phenylethyl	H	95	96:4

[a] Isolated yields..

Table 2B.3: 3-Alkylazetidin-2-ones **9a-l**

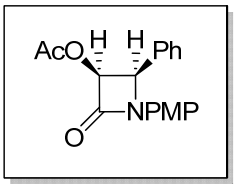
Similarly, various 3-alkyl/aryl -azetidin-2-ones were synthesized following the same protocol as shown in tabular form (Table 2B.3).

2B.4 Conclusion:

We have developed a simple and practical method for the synthesis of 3-alkylidene/alkyl azetidin-2-ones from azetidin-2,3-diones. One of the 3-alkyl azetidin-2-one **2A.11g** is well known as cholesterol absorption inhibitor. A mild and an efficient dehydration method has been shown using PPh_3/CCl_4 for 3-alkyl-3-hydroxyazetidin-2-ones.

2B.5 Experimental:

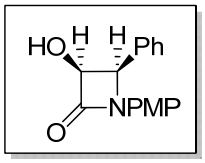
A typical experimental procedure for the synthesis of 3-Acetoxy-1-(4-methoxy phenyl)-4-phenyl-azetidin-2-one (2B.58):



A solution of acetoxy acetyl chloride **2A.17** (6.44 mL, 60 mmol) in anhydrous dichloromethane (20 mL) was added slowly to a mixture of imine **2B.57** (8.48 g, 40 mmol) and Et_3N (19.44 mL, 140 mmol) in anhydrous dichloromethane (40 mL) at 0 °C. After completion of the addition, reaction mixture was allowed to warm up to room temperature and stirred for additional 18 hours. The reaction mixture was washed with water (3 ×75 mL), saturated $NaHCO_3$ (3 × 75 mL), and brine (75 mL). The organic layer was separated and dried over anhydrous sodium sulphate and concentrated under reduced pressure to get crude product, which was purified by column chromatography (silica gel 60-120 mesh) using pet ether-ethyl acetate (83:17 ratio) to afford pure 3-Acetoxy-1-(4-methoxy phenyl)-4-phenyl-azetidin-2-one as a white solid.

Isolated yield 65%; white solid, mp 164-166 °C; **IR (ν_{max}, $CHCl_3$):** 1751 cm^{-1}; **^{1}HNMR (200MHz, $CDCl_3$):** δ 1.68 (s, 3H), 3.76 (s, 3H), 5.35 (d, *J* = 5.1 Hz, 1H), 5.95 (d, *J* = 5.1 Hz, 1H), 6.82 (d, *J* = 9.00 Hz, 2H), 7.28-7.35 (m, 7H); **^{13}C NMR ($CDCl_3$, 50.3 MHz):** δ 20.3, 55.9, 61.9, 76.3, 114.9, 119.3, 128.9, 129.3, 130.8, 132.8, 157.1, 161.8, 169.7; **MS** (*m/z*) = 312 (M+1). **Anal. Calcd**. For $C_{18}H_{17}NO_4$: C, 69.44; H, 5.50; N, 4.50. Found: C, 69.53; H, 5.45; N, 4.48;

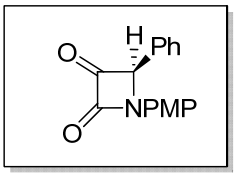
A typical experimental procedure for the synthesis of 3-Hydroxy-1-(4-methoxy-phenyl)-4-phenyl-azetidin-2-one (2B.59):



Following the similar experimental procedure as for compound **2A.20** in previous section.

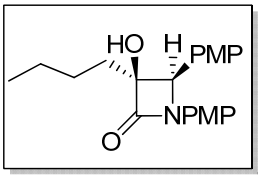
Isolated yield 88%; white solid, mp 215 °C; 0.5; **IR (ν_{max}, $CHCl_3$):** 3353, 1708 cm^{-1}; **^{1}H NMR (DMSO d_6, 200 MHz):** δ 3.76 (s, 3H), 4.50 (bs, 1H), 5.09 (d, *J* = 5.0 Hz), 5.12 (d, *J* = 5.0 Hz 1H), 6.71 (d, *J* = 9.1 Hz, 2H), 7.19-7.39 (m, 7H) **^{13}C NMR (DMSO-d_6, 50.3 MHz):**): δ 55.4, 62.1, 77.8, 114.6, 118.2, 127.9, 128.2, 128.4, 131.0, 135.1, 155.8, 166.40; **MS** (*m/z*) = 270 (M+1). **Anal. Calcd**. For $C_{16}H_{15}NO_3$: C, 71.36; H, 5.61; N, 5.20; Found: C, 71.32; H, 5.80; N, 5.08.

A typical experimental procedure for the synthesis of 1-(4-Methoxy-phenyl)-4-phenyl-azetidine-2,3-dione (2B.59): following the same experimental procedure as compound **2A.21.**



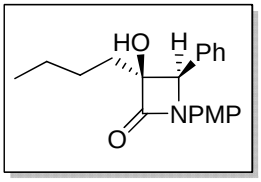
Yield 81%; yellow solid, mp 127 ^{o}C; **IR (ν_{max}, $CHCl_3$):** 1832, 1809, 1753 cm^{-1}; **^{1}H NMR ($CDCl_3$, 200 MHz):** δ 3.75 (s, 3H), 5.52 (s, 1H), 6.90 (d, *J* = 9.00 Hz, 2H), 7.24-7.38 (m, 7H); **^{13}C NMR ($CDCl_3$, 50.3 MHz):** δ 55.3, 74.4, 114.6, 114.8, 119.7, 123.5, 127.8, 129.9, 157.82, 160.44, 191.15; MS (*m/z*) = 268 (M+1); **Anal. Calcd**. For $C_{16}H_{13}NO_3$: C, 71.90; H, 4.90; N, 5.24; Found: C, 71.86; H, 5.11; N, 5.27.

synthesis of 3-Butyl-3-hydroxy-1,4-bis(4-methoxy-phenyl)-azetidin-2-one (2B.61a): Following the same experimental as for compound **2A.22g**.



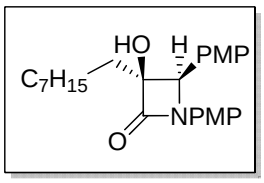
Yield, 55%; brownish oil; **IR (ν_{max}, $CHCl_3$):** 1728 cm^{-1}; **^{1}H NMR ($CDCl_3$, 200 MHz):** δ 0.96 (t, *J* = 6.9 Hz, 3H), 1.30-1.73 (m, 4H), 1.96-2.09 (m, 4H), 3.76 (s, 3H), 3.81 (s, 3H), 4.98 (s, 1H), 6.79 (d, *J* = 9.1 Hz, 2H), 6.82 (d, *J* = 8.7 Hz, 2H), 7.22 (d, *J* = 8.7 Hz, 2H), 7.29 (d, *J* = 8.9 Hz, 2H); **^{13}C NMR ($CDCl_3$, 50.3 MHz):** δ 13.9, 22.9, 25.6, 35.1, 55.2, 55.4, 66.9, 85.9, 114.3, 114.5, 118.8, 125.7, 128.4, 130.6, 156.2, 159.9, 168; **MS** (*m/z*) = 356 (M+1); **Anal. Calcd.** For $C_{21}H_{25}NO_4$: C, 70.96; H, 7.09; N, 3.94; Found: C, 70.98; H, 7.16; N, 3.89.

3-Butyl-3-hydroxy-1-(4-Methoxy-phenyl)-4-phenyl-azetidin-2-one (2B.61b):



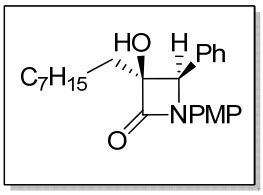
Yield 55%; thick oil; **IR (ν_{max}, $CHCl_3$):** 3388, 1737 cm^{-1}; **^{1}H NMR ($CDCl_3$, 200 MHz):** δ 0.83 (t, *J* = 6.9 Hz, 3H), 1.25-1.76 (m, 4H), 1.85-1.96 (m, 2H), 3.63 (s, 3H), 4.90 (s, 1H), 6.79 (d, *J* = 9.1 Hz, 2H), 7.22-7.37 (m, 7H); **^{13}C NMR ($CDCl_3$, 50.3 MHz):** δ 13.8, 22.9, 25.7, 35.1, 55.4, 66.9, 85.9, 114.3, 118.8, 127.2, 128.6, 129.1, 130.6, 134, 156.3, 167.9; **MS** (*m/z*) = 326 (M+1); **Anal. Calcd.** For $C_{20}H_{23}NO_3$: C, 73.82; H, 7.12; N, 4.30; Found: C, 73.98; H, 7.36; N, 3.98.

3-Octyl-3-hydroxy1,4-bis(4-methoxy-phenyl) azetidin-2-one (2B.61c):



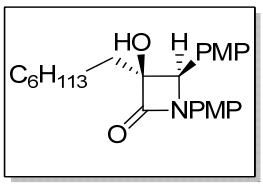
Yield 57%; thick oil; **IR (ν_{max}, $CHCl_3$):** 1747 cm^{-1}; **^{1}H NMR ($CDCl_3$, 200 MHz):** δ 0.92 (t, *J* = 6.4 Hz, 3H), 1.31-1.46 (m, 12H), 2.01-2.08 (m, 2H), 3.79 (s, 3H), 3.84 (s, 3H), 5.00 (s, 1H), 6.79 (d, *J* = 9.1 Hz, 2H), 6.97 (d, *J* = 8.9 Hz, 2H), 7.25 (d, *J* = 8.7 Hz, 2H), 7.26 (d, *J* = 9.0 Hz, 2H); **^{13}C NMR ($CDCl_3$, 50.3 MHz):** δ 14.0, 22.6, 25.23, 27.2, 29.3, 29.4, 31.8, 35.3, 55.2, 55.4, 66.9, 114.3, 114.5, 118.8, 125.7, 128.4, 130.7, 156.2, 159.8, 168.1; **MS** (*m/z*) = 412 (M+1); **Anal. Calcd.** For $C_{25}H_{33}NO4$: C, 72.96; H, 8.08; N, 3.40; Found: C, 72.87; H, 8.12; N, 3.55.

3-Octyl-3-hydroxy-1-(4-Methoxy-phenyl)-4-phenyl-azetidin-2-one (2B.61d):



Isolated yield, 62%; colourless oil; **IR (ν_{max}, $CHCl_3$):** 3384, 1730 cm^{-1}; **^{1}H NMR ($CDCl_3$, 200 MHz):** δ 0.91 (t, *J* = 6.7 Hz, 3H), 1.25-1.72 (m, 12H), 1.96-2.13 (m, 2H), 3.78 (s, 3H), 5.04 (s, 1H), 6.81 (d, *J* = 8.9 Hz, 2H), 7.28-7.45 (m, 7H); **^{13}C NMR ($CDCl_3$, 50.3 MHz):** δ 14.1, 22.7, 23.7, 25.8, 29.3, 29.9, 31.9, 35.6, 55.4, 66.4, 86.2, 114.4, 118.9, 127.2, 128.7, 129.1, 130.7, 134.1, 156.4, 168; **MS** (*m/z*) = 382 (M+1); **Anal. Calcd**. For $C_{24}H_{31}NO_3$: C, 75.56; H, 8.19; N, 3.67; Found: C, 75.62; H, 8.16; N, 3.75.

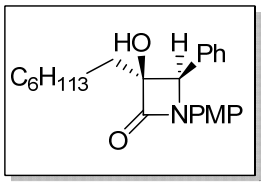
3-Heptyl-3-hydroxy-1,4-bis(4-methoxy-phenyl)-azetidin-2-one(2B.61e):



Yield 62%; colorless oil; **IR (ν_{max}, $CHCl_3$):** 3388, 1745, 1731 cm^{-1}; **^{1}H NMR ($CDCl_3$, 200 MHz):** δ 0.86 (t, *J* = 6.4 Hz, 3H), 1.20-1.54 (m, 10H), 1.89-2.02 (m, 2H), 3.73 (s, 3H), 3.78 (s, 3H), 4.94 (s, 1H), 6.76 (d, *J* = 9.1 Hz, 2H), 6.80 (d, *J* = 8.9 Hz, 2H), 7.23 (d, *J* = 8.6 Hz, 2H), 7.28 (d, *J* = 9.0 Hz, 2H); **^{13}C NMR ($CDCl_3$, 50.3 MHz):** δ 14.0, 22.5, 28.7, 29.2, 29.7, 31.5, 35.3, 55.2, 55.3, 66.7, 85.8, 114.3, 114.5, 118.1, 125.7, 128.5, 130.7, 156.2, 159.8, 168.2; **MS** (*m/z*) = 398 (M+1); **Anal. Calcd.** For $C_{24}H_{31}NO_4$: C, 72.52; H, 7.86; N, 3.52; Found: C, 72.78; H, 7.96; N, 3.68.

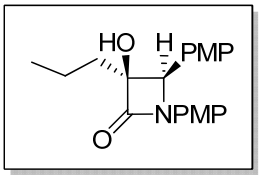
3-Heptyl-3-hydroxy-1-(4-Methoxy-phenyl)-4-phenyl-azetidin-2-one (2B.61f):

Yield 58%; thick oil; **IR (ν_{max}, $CHCl_3$):** 3390, 1747 cm^{-1}. **^{1}H NMR ($CDCl_3$, 200 MHz):** δ 0.89 (t, *J* = 6.8 Hz, 3H), 1.25-1.82 (m, 10H), 1.87-2.03 (m, 2H), 3.76 (s, 3H), 5.01 (s, 1H), 6.81 (d, *J* = 9.1 Hz, 2H), 7.27-7.39 (m, 7H); **^{13}C NMR ($CDCl_3$, 50.3 MHz):** δ 14.3, 22.9, 23.8, 29.3, 30.1, 31.9, 35.7, 55.6, 67.5, 86.4, 114.6, 119.1, 127.4, 129.3, 130.9, 134.3, 156.5, 168.1; **MS** (*m/z*) = 368 (M+1). **Anal. Calcd**. For $C_{23}H_{29}NO_3$: C, 75.17; H, 7.95; N, 3.81; Found: C, 75.26; H, 7.56; N, 3.76



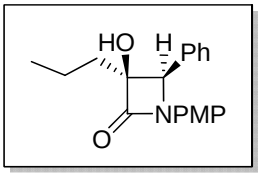
Synthesis of 3-Propyl-3-hydroxy-1,4-bis(4-methoxy-phenyl)-azetidin-2-one (2B.61g)::

Yield, 59%; thick oil; **IR (ν_{max}, $CHCl_3$):** 1739 cm^{-1}; **^{1}H NMR ($CDCl_3$, 200 MHz):** δ 0.98 (t, *J* =7.2 Hz, 3H), 1.53-1.62 (m, 2H), 1.90-1.98 (m, 2H), 3.72 (s, 3H), 3.77 (s, 3H), 4.94 (s, 1H), 6.75 (d, *J* = 9.1 Hz, 2H), 6.79 (d, *J* = 8.7 Hz, 2H), 7.21 (d, *J* = 8.7 Hz, 2H), 7.28 (d, *J* = 9.1 Hz, 2H); **^{13}C NMR ($CDCl_3$, 50.3 MHz):** δ 14.3, 17.1, 37.5, 55.2, 55.4, 66.9, 85.9, 114.3, 114.5, 118.8, 125.7, 128.4, 130.6, 156.2, 159.9, 167.9; **MS** (*m/z*) = 342 (M+1); **Anal. Calcd.** For $C_{20}H_{23}NO_4$: C, 70.36; H, 6.79; N, 4.10; Found: C, 70.18; H, 6.86; N, 3.98.



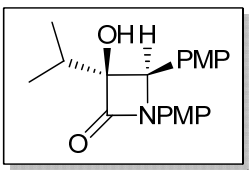
3-Propyl-3-hydroxy-1-(4-Methoxy-phenyl)-4-phenyl-azetidin-2-one (2B.61h):

Yield 62%; white solid, mp 144-146 °C; **IR (ν_{max}, $CHCl_3$):** 3461, 1739 cm^{-1}; **^{1}H NMR ($CDCl_3$, 200 MHz):** δ 1.03 (t, *J* = 6.5 Hz, 3H), 1.58-1.68 (m, 2H), 1.96-2.07 (m, 2H), 3.76 (s, 3H), 5.03 (s, 1H), 6.81 (d, *J* = 9.1 Hz, 2H), 7.14-7.31 (m, 7H); **^{13}C NMR ($CDCl_3$, 50.3 MHz):** δ 14.3, 17.1, 37.6, 55.4, 67.3, 86.2, 114.3, 118.8, 127.2, 128.6, 129, 130.6, 134, 156.3, 167.9; **MS** (*m/z*) = 312 (M+1); **Anal. Calcd.** For $C_{19}H_{21}NO_3$: C, 73.29; H, 6.80; N, 4.50; Found: C, 73.18; H, 6.76; N, 4.38.



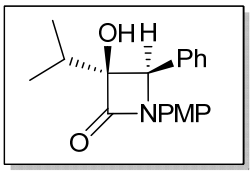
Synthesis of 3-Hydroxy-3-isopropyl-1,4-bis(4-methoxy-phenyl)-azetidin-2-one:

(2B.61i):



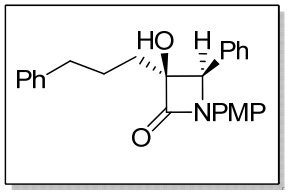
Yield, 49%; thick oil; **IR (ν_{max}, $CHCl_3$):** 3488, 1735 cm^{-1}; **^{1}H NMR ($CDCl_3$, 200 MHz):** δ 1.12 (d, *J* = 7.0 Hz, 3H), 1.20 (d, *J* = 6.9 Hz, 3H), 3.76 (s, 3H), 3.81 (s, 3H), 4.99 (s, 1H), 6.72 (d, *J* = 9.1 Hz, 2H), 6.81 (d, *J* = 8.9 Hz, 2H), 7.23 (d, *J* = 8.6 Hz, 2H), 7.30 (d, *J* = 9.2 Hz, 2H); **^{13}C NMR ($CDCl_3$, 50.3 MHz):** δ 16.7, 17.1, 33.2, 55.3, 55.5, 64.9, 88.8, 114.3, 114.5, 118.8, 125.7, 128.4, 130.6, 156.2, 159.9, 167.8; **MS** (*m/z*) = 342 (M+1); **Anal. Calcd.** For $C_{20}H_{23}NO_4$: C, 70.36; H, 6.79; N, 4.10; Found: C, 70.18; H, 6.86; N, 3.98.

3-Hydroxy-3-isopropyl-1-(4-methoxy-phenyl)-4-phenyl-azetidin-2-one (2B.61j):



Yield 51% white solid, mp 114-116 °C; **IR (ν_{max}, $CHCl_3$):** 3388, 1735 cm^{-1}. **^{1}H NMR ($CDCl_3$, 200 MHz):** δ 1.12 (d, *J* = 7.0 Hz, 3H), 1.20 (d, *J* = 6.9 Hz, 3H), 3.81 (s, 3H), 5.01 (s, 1H), 6.72 (d, *J* = 9.1 Hz, 2H), 7.19-7.56 (m, 7H); **^{13}C NMR ($CDCl_3$, 50.3 MHz):** δ 14.3, 17.1, 37.6, 55.4, 67.3, 86.2, 114.3, 118.8, 127.2, 128.6, 129, 130.6, 134, 156.3, 167.9; MS (*m/z*) = 312 (M+1); **Anal. Calcd.** For $C_{19}H_{21}NO_3$: C, 73.29; H, 6.80; N, 4.50; Found: C, 73.18; H, 6.76; N, 4.38.

3-Hydroxy-1-(4-methoxy-phenyl)-4-phenyl-3-(3-phenyl-propyl)-azetidin-2-one (2B.61k):

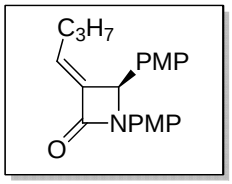


Yield 62%; thick oil; **IR (ν_{max}, $CHCl_3$):** 3369, 1747, 1731 cm^{-1}; **^{1}H NMR ($CDCl_3$, 200 MHz):** δ 1.81-2.01 (m, 4H), 2.67 (t, *J* = 7.1 Hz, 2H) 3.71 (s, 3H), 4.93 (s, 1H), 6.75 (d, *J* = 9.0 Hz, 2H), 7.18-7.40 (m, 12H); **^{13}C NMR ($CDCl_3$, 50.3 MHz):** δ 25.2, 35, 35.7, 55.2, 66.99, 85.76, 114.3, 118.8, 127.2, 128.6, 129, 130.6, 134, 156.3, 167.9; **MS** (*m/z*) = 388 (M +1); **Anal. Calcd.** For $C_{25}H_{25}NO_3$: C, 77.49; H, 6.50; N, 3.61; Found: C, 77.32; H, 6.52; N, 3.55.

General procedure for dehydration of 3-butyl-3-hydroxy-1,4-bis(4-methoxyphenyl) azetidin-2-ones : A solution of alcohol **2B.61a** (0.78 g, 2.19 mmol) and triphenylphosphine (1.14 g, 4.38 mmol) in anhydrous carbon tetrachloride (10 mL) was refluxed for 12 h. The reaction mixture was then filtered through a small pad of Celite and concentrated under reduced pressure to afford the crude product (0.67 g, 90%). The ^{1}H NMR of the crude product showed it to be a mixture of 3-alkylidene-*β*-

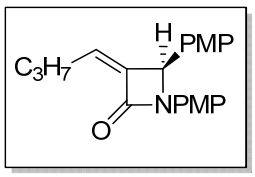
lactams **2B.63a** and **2B.64a** (*E* and Z isomers 72:28), which were separated by flash column chromatography (Pet ether/ethyl acetate 9:1).

***E*-1,4-Bis-(4-methoxy-phenyl)-3-butylidene-azetidine-2-one (2B.63a):**



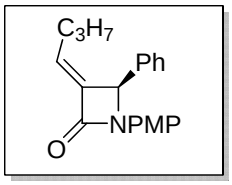
Yield 72%; white solid, mp 88-89 °C; **IR (ν_{max}, $CHCl_3$):** 1745, cm^{-1}; **^{1}H NMR ($CDCl_3$, 200 MHz):** δ 0.75 (t, *J* = 7.3 Hz, 3H), 1.24-1.37 (m, 2H), 1.86-1.99 (m, 2H), 3.77 (s, 3H), 3.84 (s, 3H), 5.38 (s, 1H), 6.25 (t, *J* = 7.7 Hz, 1H), 6.83 (d, *J* = 9.1 Hz, 2H), 6.93 (d, *J* = 8.7 Hz, 2H), 7.29 (d, *J* = 9.1 Hz, 2H), 7.40 (d, *J* = 8.7 Hz, 2H); **^{13}C NMR ($CDCl_3$, 50.3 MHz):** δ 13.4, 21.6, 29.6, 55.3, 55.4, 62.6, 114.3, 114.4, 118.1, 127.6, 128.3, 128.8, 131.4, 142.3, 155.8, 159.8, 161.3; **MS** (*m/z*) = 338 (M+1); **Anal. Calcd.** For $C_{21}H_{23}NO_3$: C, 74.75; H, 6.87; N, 4.15; Found: C, 74.68; H, 7.88; N, 4.29.

***Z*-1,4-Bis-(4-methoxy-phenyl)-3-butylidene-azetidine-2-one (2B.64a):**



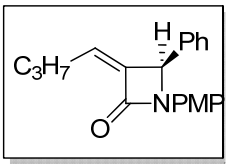
Yield 28%; yellow oil; **IR (ν_{max}, $CHCl_3$):** 1734, cm^{-1}; **^{1}H NMR ($CDCl_3$, 200 MHz):** δ 0.96 (t, *J* = 7.8 Hz, 3H), 1.40-1.58 (m, 2H), 2.44-2.66 (m, 2H), 3.76 (s, 3H), 3.82 (s, 3H), 5.20 (d, *J* = 1 Hz, 1H), 5.56 (dt, *J* = 1.0, 7.8 Hz, 1H), 6.82 (d, *J* = 9.1 Hz, 2H), 6.92 (d, *J* = 8.7 Hz, 2H), 7.28 (d, *J* = 9.1 Hz, 2H), 7.32 (d, *J* = 8.7 Hz, 2H); **^{13}C NMR ($CDCl_3$, 50.3 MHz):** δ 13.5, 22.4, 30.6, 55.2, 55.4, 62.5, 114.3, 114.4, 118.1, 128, 129.3, 131.3, 131.6, 142, 155.9, 159.7, 161.5; **MS** *m/z* = 338 (M+1); **Anal. Calcd.** For $C_{21}H_{23}NO_3$: C, 74.75; H, 6.87; N, 4.15; Found: C, 74.68; H, 7.88; N, 4.29.

***E*-1-(Methoxy-phenyl)-3-butylidene-4-phenyl-azetidine-2-one (2B.63b):**



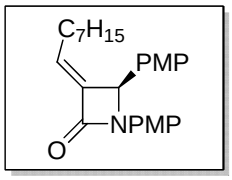
Yield 71%; white solid, mp 104-105 °C; **IR (ν_{max}, $CHCl_3$):** 1732 cm^{-1}; **^{1}H NMR ($CDCl_3$, 200 MHz):** δ 0.73 (t, *J* = 7.4 Hz, 3H), 1.26-1.33 (m, 2H), 1.81-1.99 (m, 2H), 3.78 (s, 3H), 5.43 (d, *J* = 1.4 Hz, 1H), 6.28 (dt, *J* = 1.4, 7.6 Hz, 1H), 6.73 (d, *J* = 9.1 Hz, 2H), 7.16-7.35 (m, 7H); **^{13}C NMR ($CDCl_3$, 50.3 MHz):** δ 13.5, 22.4, 30.6, 55.3, 62.7, 114.3, 118.1, 126.5, 127.8, 128.4, 131.5, 137.4, 141.6, 155.8, 161.3; MS (*m/z*) = 308 (M+1); **Anal. Calcd.** For $C_{20}H_{21}NO_2$: C, 78.15; H, 6.89; N, 4.56; Found: C, 78.41; H, 7.99; N, 4.78.

***Z*-1-(Methoxy-phenyl)-3-butylidene-4-phenyl-azetidine-2-one (2B.64b):**



Yield 29%, mp 106 °C; **IR (ν_{max}, $CHCl_3$):** 1735cm^{-1}; **^{1}H NMR ($CDCl_3$, 200 MHz):** δ 0.94 (t, *J* = 7.5 Hz, 3H), 1.41-1.52 (m, 2H), 2.41-2.64 (m, 2H), 3.75 (s, 3H), 5.27 (d, *J* = 1.2 Hz, 1H), 5.56 (dt, *J* = 1.2, 7.9 Hz, 1H), 6.79 (d, *J* = 9.1 Hz, 2H), 7.25-7.39 (m, 7H); **^{13}C NMR ($CDCl_3$, 50.3 MHz):** δ 13.3, 21.6, 29.8, 55.4, 63, 114.3, 118.2, 127.1, 128.6, 128.9, 131.4, 137, 142.1, 155.9, 161.2; **MS** (*m/z*) = 308 (M+1); **Anal. Calcd.** For $C_{20}H_{21}NO_2$: C, 78.15; H, 6.89; N, 4.56; Found: C, 78.41; H, 7.99; N, 4.78.

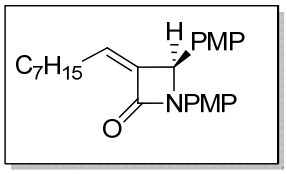
***E*-1,4-Bis-(4-methoxy-phenyl)-3-octylidene-azetidine-2-one(2B.63c):**



Yield 71%; colorless oil; **IR (ν_{max}, $CHCl_3$):** 1740, 1612 cm^{-1}; **^{1}H NMR ($CDCl_3$, 200 MHz):** δ 0.89 (t, *J* = 6.7 Hz, 3H), 1.13-1.28 (m, 10H), 1.87-2.01 (m, 2H), 3.77 (s, 3H), 3.83 (s, 3H), 5.37 (d, *J* = 1.2 Hz, 1H), 6.24 (dt, *J* = 1.2, 7.6 Hz, 1H), 6.81 (d, *J* = 9.1 Hz, 2H), 6.92 (d, *J* = 8.7 Hz, 2H), 7.31 (d, *J* = 9.1 Hz, 2H), 7.28 (d, *J* = 8.7 Hz, 2H); **^{13}C NMR ($CDCl_3$, 50.3 MHz):** δ 13.7, 22.2, 27.4, 28.0, 28.5, 31.3, 54.8, 55.0, 62.3, 114, 114.1, 117.8, 127.6, 128.3, 128.5, 131.1, 141.8, 155.5, 159.5, 161; **MS** (*m/z*) = 394 (M+1).

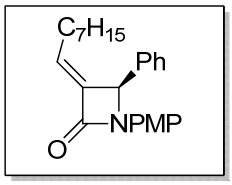
Anal. Calcd. For $C_{25}H_{31}NO_3$: C, 76.30; H, 7.94; N, 3.56 Found: C, 76.38; H, 7.96; N, 3.68.

***Z*- 1,4-Bis-(4-methoxy-phenyl)-3-octylidene-azetidine-2-one (2B.64c):**



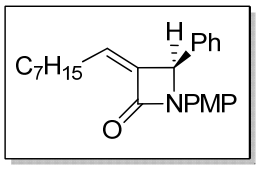
Yield 29%; colorless oil; **IR (ν_{max}, $CHCl_3$):** 1743, 1614 cm^{-1}; **^{1}H NMR ($CDCl_3$, 200 MHz):** δ 0.88 (t, *J* = 6.5 Hz, 3H), 1.14-1.62 (m, 10H), 2.48-2.62 (m, 2H), 3.75 (s, 3H), 3.80 (s, 3H), 5.22 (s, 1H), 5.54 (t, *J* = 7.9 Hz, 1H), 6.79 (d, *J* = 9.1 Hz, 2H), 6.89 (d, *J* = 8.7 Hz, 2H), 7.26 (d, *J* = 8.7 Hz, 2H), 7.28 (d, *J* = 9.0 Hz, 2H); **^{13}C NMR ($CDCl_3$, 50.3 MHz):** δ 14.0, 22.5, 28.6, 28.9, 29.1, 31.7, 55.1, 55.3, 62.3, 114.2, 118.1, 127.9, 129.3, 131.5, 141.7, 155.8, 159.7, 161.5; MS (*m/z*) = 394 (M+1); **Anal. Calcd.** For $C_{25}H_{31}NO_3$: C, 76.30; H, 7.94; N, 3.56%; Found: C, 76.38; H, 7.96; N, 3.68.

***E*-1-(Methoxy-phenyl)-3-octylidene-4-phenyl-azetidine-2-one (2B.63d):**



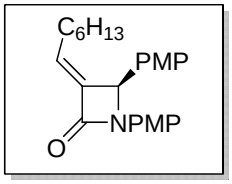
Yield 71%; white solid mp 74-76 °C; **IR (ν_{max}, $CHCl_3$):** 1731, 1616 cm^{-1}; **^{1}H NMR ($CDCl_3$, 200 MHz):** δ 0.79 (t, *J* = 6.8 Hz, 3H), 1.03-1.20 (m, 10H), 1.78-1.92 (m, 2H), 3.67 (s, 3H), 5.31 (d, *J* = 1.4 Hz 1H), 6.16 (dt, *J* = 1.4, 7.3 Hz, 1H), 6.76 (d, *J* = 8.9 Hz, 2H), 7.16-7.36 (m, 7H); **^{13}C NMR ($CDCl_3$, 50.3 MHz):** δ 13.7, 22.3, 27.5, 28.1, 28.5, 31.3, 55.1, 62.7, 114, 117.8, 126.7, 127.1, 127.8, 128.3, 128.7, 131.7, 141.6, 155.6, 161.9; **MS** (*m/z*) = 364 (M+1). **Anal. Calcd**. For $C_{24}H_{29}NO_2$: C, 79.30; H, 8.04; N, 3.86; Found: C, 79.41; H, 7.99; N, 3.72.

***Z*-1-(Methoxy-phenyl)-3-octylidene-4-phenyl-azetidine-2-one (2B.64d):**



Yield 29% colorless oil; **IR (ν_{max}, $CHCl_3$):** 1733, 1616 cm^{-1}; **^{1}H NMR ($CDCl_3$, 200 MHz):** δ 0.77 (t, *J* = 6.6 Hz, 3H), 1.17-1.57 (m, 10H), 2.34-2.56 (m, 2H), 3.66 (s, 3H), 5.17 (d, J = 1.0 Hz, 1H), 5.46 (dt, *J* = 1.0, 7.8 Hz, 1H), 6.70 (d, *J* = 8.9 Hz, 2H), 7.16-7.36 (m, 7H); **^{13}C NMR ($CDCl_3$, 50.3 MHz):** δ 13.8, 22.2, 27.4, 28.1, 28.5, 31.3, 55.2, 62.4, 114, 117.8, 127.6, 128.1, 128.5, 129.5, 131.1, 141.8, 155.5, 161; **MS** (*m/z*) = 364 (M+1); **Anal. Calcd**. For $C_{24}H_{29}NO_2$: C, 79.30; H, 8.04; N, 3.86; Found: C, 79.41; H, 7.99; N, 3.72.

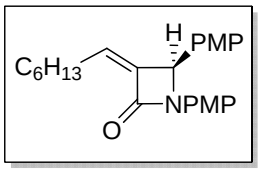
***E*-1,4-Bis-(4-methoxy-phenyl)-3-heptylidene-azetidine-2-one (2B.63e):**



Yield 71%; white solid, mp 65-66 °C; **IR (ν_{max}, $CHCl_3$):** 1737 cm^{-1}; **^{1}H NMR ($CDCl_3$, 200 MHz):** δ 0.86 (t, *J* = 6.7 Hz, 3H), 1.22-1.38 (m, 8H), 1.87-2.01 (m, 2H), 3.76 (s, 3H), 3.83 (s, 3H), 5.27 (d, *J* = 1.4 Hz, 1H), 6.24 (dt, *J* = 1.4, 7.6 Hz, 1H), 6.81 (d, *J* = 9.1 Hz, 2H), 6.92 (d, *J* = 8.7 Hz, 2H), 7.31 (d, *J* = 9.1 Hz, 2H), 7.38 (d, *J* = 8.7 Hz, 2H); **^{13}C NMR ($CDCl_3$, 50.3 MHz):** δ 13.9, 22.4, 27.7, 28.3, 28.5, 31.3, 55.1, 55.3, 62.6, 114.3, 118.1, 127.9, 128.30, 128.8, 131.4, 142.1, 155.8, 159.8, 161.3; **MS** (*m/z*) = 380 (M+1); **Anal. Calcd.** For $C_{24}H_{29}NO_3$: C, 75.96; H, 7.70; N, 3.69; Found: C, 75.88; H, 7.88 N, 3.68.

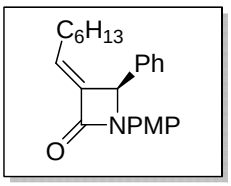
***Z*-1,4-Bis-(4-methoxy-phenyl)-3-heptylidene-azetidine-2-one(2B.64e):**

Yield 29%; white solid, mp 107-108 °C; **IR (ν_{max}, $CHCl_3$):** 1740 cm^{-1}; **^{1}H NMR ($CDCl_3$, 200 MHz):** δ 0.83 (t, *J* = 6.6 Hz, 3H), 1.19-1.39 (m, 8H), 2.46-2.57 (m, 2H), 3.70 (s, 3H), 3.76 (s, 3H), 5.17 (d, *J* = 1.4 Hz, 1H), 5.49 (dt, *J* = 1.0, 8.0 Hz, 1H), 6.72 (d, *J* = 9.1 Hz, 2H), 6.85 (d, *J* = 8.7 Hz, 2H), 7.34 (d, *J* = 9.1 Hz, 2H), 7.39 (d, *J* = 8.7 Hz, 2H); **^{13}C NMR ($CDCl_3$, 50.3 MHz):** δ 14, 22.5, 28.7, 28.2, 31.5, 55.2, 55.4, 62.4, 114.3, 114.4, 118.1, 128.1, 129.3, 131.6, 141.7, 155.8, 159.7, 161.5; MS (*m/z*) = 380 (M+1); **Anal. Calcd.** For $C_{24}H_{29}NO_3$: C, 75.96; H, 7.70; N, 3.69; Found: C, 75.88; H, 7.88 N, 3.68.



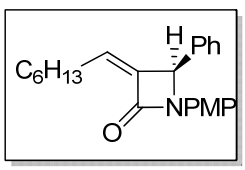
***E*-1-(Methoxy-phenyl)-3-heptylidene-4-phenyl-azetidine-2-one (2B.63f):**

Yield 69%, white solid mp 74 °C; **IR (ν_{max}, $CHCl_3$):** 1731, 1610 cm^{-1}; **^{1}H NMR ($CDCl_3$, 200 MHz):** δ 0.78 (t, *J* = 6.4 Hz, 3H), 1.14-1.65 (m, 8H), 2.34-2.53 (m, 2H), 3.66 (s, 3H), 5.17 (d, *J* = 1.2 Hz, 1H), 6.30 (dt, *J* = 1.2, 7.3 Hz, 1H), 6.70 (d, *J* = 9.1 Hz, 2H), 7.16-7.36 (m, 7H). **^{13}C NMR ($CDCl_3$, 50.3 MHz):** δ 13.7, 22.3, 28.4, 29.4, 31.3, 55.1, 62.5, 114.1, 117.8, 126.3, 128.2, 128.7, 131.6, 131.2, 141.1, 155.6, 161.1; **MS** (*m/z*) = 350 (M+1). **Anal. Calcd.** For $C_{23}H_{27}NO_2$: s C, 79.05; H, 7.79; N, 4.01; Found: C, 79.41; H, 7.99; N, 3.73.

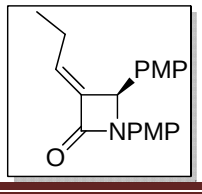


***Z*-1-(Methoxy-phenyl)-3-heptylidene-4-phenyl-azetidine-2-one (2B.64f)::**

Yield 31%; white solid, mp 68-70 °C; **IR (ν_{max}, $CHCl_3$):** 1731, 1610 cm^{-1}; **^{1}H NMR ($CDCl_3$, 200 MHz):** δ 0.78 (t, *J* = 6.4 Hz, 3H), 1.14-1.65 (m, 8H), 2.34-2.53 (m, 2H), 3.66 (s, 3H), 5.17 (d, *J* = 1.0 Hz, 1H), 5.46 (dt, *J* = 1.0, 7.9 Hz, 1H), 6.70 (d, *J* = 9.1 Hz, 2H), 7.16-7.36 (m, 7H). **^{13}C NMR ($CDCl_3$, 50.3 MHz):** δ 13.7, 22.3, 28.4, 29.4, 31.3, 55.1, 62.5, 114.1, 117.8, 126.3, 128.2, 128.7, 131.6, 131.2, 141.1, 155.6, 161.1; **MS** (*m/z*) = 350 (M+1). **Anal. Calcd**. For $C_{23}H_{27}NO_2$: C, 79.05; H, 7.79; N, 4.01; Found: C, 79.41; H, 7.99; N, 3.73.

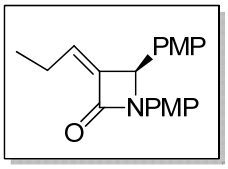


***E*-1,4-Bis-(4-methoxy-phenyl)-3-propyllidene-azetidine-2-one (2B.63g):**



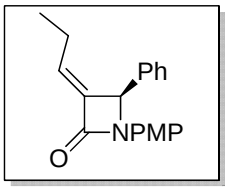
Yield 72%; white solid, mp 88-90 °C; **IR (ν_{max}, $CHCl_3$):** 1735, cm^{-1}; **^{1}H NMR ($CDCl_3$, 200 MHz):** δ 0.84 (t, *J* = 7.5 Hz, 3H), 1.67-2.05 (m, 2H), 3.74 (s, 3H), 3.81 (s, 3H), 5.36 (d, *J* = 1.4 Hz, 1H), 6.22 (dt, *J* = 1.4, 7.3 Hz, 1H), 6.78 (d, *J* = 9.1 Hz, 2H), 6.88 (d, *J* = 8.7 Hz, 2H), 7.25 (d, *J* = 9.1 Hz, 2H), 7.38 (d, *J* = 8.7 Hz, 2H); **^{13}C NMR ($CDCl_3$, 50.3 MHz):** δ 12.9, 21.3, 55.2, 55.3, 62.5, 114.2, 114.3, 118.1, 128.3, 128.8, 129.l, 131.4, 141.5, 155.8, 159.8, 161.4; **MS** (*m/z*) = 324 (M+1); **Anal. Calcd.** For $C_{20}H_{21}NO_3$: s C, 74.28; H, 6.55; N, 4.33; Found: C, 74.23; H, 7.68; N, 4.29.

***Z*-1,4-Bis-(4-methoxyphenyl)-3-propylideneazetidin-2-one (2B.64g):**



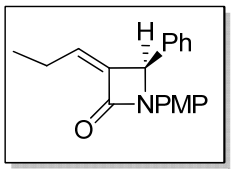
Yield 28%; white solid, mp 98–99 °C; **IR (ν_{max}, $CHCl_3$):** 1728, cm^{-1}; **^{1}H NMR ($CDCl_3$, 200 MHz):** δ 0.96 (t, *J* = 7.6 Hz, 3H), 2.40- 2.70 (m, 2H), 3.75 (s, 3H), 3.80 (s, 3H), 5.22 (d, *J* = 1.0 Hz, 1H), 5.54 (dt, *J* = 1.0, 7.7 Hz, 1H), 6.79 (d, *J* = 9.1 Hz, 2H), 6.89 (d, *J* = 8.7 Hz, 2H), 7.26 (d, *J* = 9.1 Hz, 2H), 7.29 (d, *J* = 8.7 Hz, 2H); **^{13}C NMR ($CDCl_3$, 50.3 MHz):** δ 13.8, 22.3, 55.2, 55.4, 62.3, 114.3, 114.4, 118.1, 127.9, 129.3, 131.6, 132.9, 141.2, 155.9, 159.8, 161.4; **MS** (m/z): 324 (M+1); **Anal. Calcd.** For $C_{20}H_{21}NO_3$: C, 74.28; H, 6.55; N, 4.33; Found: C, 74.23; H, 6.60; N, 4.37.

***E*-1-(Methoxy-phenyl)-3-propylidene-4-phenyl-azetidine-2-one (2B.63h):**



Yield 69%, white solid, mp 153-154 °C.; **IR (ν_{max}, $CHCl_3$):** 1733 cm^{-1}. **^{1}H NMR ($CDCl_3$, 200 MHz):** δ 0.82 (t, *J* = 7.4 Hz, 3H), 1.81-2.06 (m, 2H), 3.74 (s, 3H), 5.39 (d, *J* = 1.4 Hz, 1H), 6.21 (t, *J* = 1.4, 7.7 Hz, 1H), 6.79 (d, *J* = 9.1 Hz, 2H), 7.16-7.28 (m, 7H); **^{13}C NMR ($CDCl_3$, 50.3 MHz):** δ 12.9, 21.3, 55.3, 62.9, 114.3, 118.1, 127, 128.6, 128.9, 129.2, 131.4, 137, 141.4, 155.9, 161.3; **MS** (*m/z*) = 294 (M+1); **Anal. Calcd.** For $C_{19}H_{19}NO_2$: C, 77.79; H, 6.53; N, 4.77; Found: C, 79.67; H, 6.69; N, 4.85

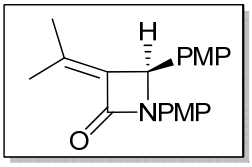
***Z*-1-(Methoxy-phenyl)-3-propylidene-4-phenyl-azetidine-2-one (2B.64h):**



Yield 31%, white solid mp 125-126°C; **IR (ν_{max}, $CHCl_3$):** 1739, 1610 cm^{-1}. ; **^{1}H NMR ($CDCl_3$, 200 MHz):** δ 0.96 (t, *J* = 7.2 Hz, 3H), 2.33-1.61 (m, 2H), 3.66 (s, 3H), 5.17 (d, *J* = 1.1 Hz, 1H), 5.46 (dt, *J* = 1.1, 8.1 Hz, 1H), 6.72 (d, *J* = 9.1 Hz, 2H),

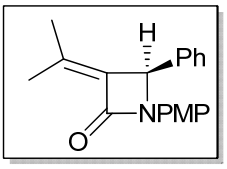
7.16-7.28 (m, 7H); **^{13}C NMR ($CDCl_3$, 50.3 MHz):** δ 13.8, 22.3, 55.4, 62.7, 114.3, 118.1, 126.5, 128.4, 128.9, 131.5, 133.1, 137,4, 140.9, 155.9, 161.3; **MS** (*m/z*) = 294 (M+1); **Anal. Calcd.** For $C_{19}H_{19}NO_2$: C, 77.79; H, 6.53; N, 4.77; Found: C, 79.67; H, 6.69; N, 4.85.

3-Isopropylidene-1,4-bis-(4-methoxy-phenyl)-azetidin-2-one (2B.63i):



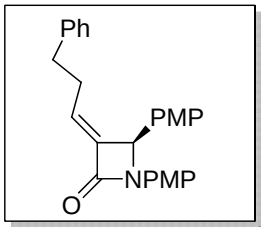
Yield, 91%; white solid, mp 146-147 °C; **IR (ν_{max}, $CHCl_3$):** 1731 cm^{-1}; **^{1}H NMR ($CDCl_3$, 200 MHz):** δ 1.54 (s, 3H), 2.11 (s, 3H), 3.73 (s, 3H), 3.80 (s, 3H), 5.22 (s, 1H), 6.76 (d, *J* = 9.1 Hz, 2H), 6.89 (d, *J* = 8.9 Hz, 2H), 7.25 (d, *J* = 9.0 Hz, 2H), 7.32 (d, *J* = 8.7 Hz, 2H); **^{13}C NMR ($CDCl_3$, 50.3 MHz):** δ 19.8, 20.2, 55.2, 55.4, 62.3, 114.3, 117.8, 128.4, 129.2, 131.8, 136.3, 137, 155.6, 159.6, 162; **MS** (*m/z*) = 324 (M+1). **Anal. Calcd.** For $C_{20}H_{21}NO_3$: C, 74.28; H, 6.55; N, 4.33; Found: C, 74.12; H, 6.65; N, 4.02.

3-Isopropylidene-1-(4-methoxy-phenyl)-4-phenyl-azetidin-2-one (2B.63j):



Yield 92%; white solid, mp 192-194 °C **IR (ν_{max}, $CHCl_3$):** 1735 cm^{-1}; **^{1}H NMR ($CDCl_3$, 200 MHz):** δ 1.55 (s, 3H), 2.12 (s, 3H), 3.73 (s, 3H), 5.28 (s, 1H), 6.78 (d, *J* = 9.1 Hz, 2H), 7.33-7.43 (m, 7H); **^{13}C NMR ($CDCl_3$, 50.3 MHz):** δ 16.7, 17.7, 55.4, 65.2, 114.3, 118.8, 127.2, 128.6, 129.1, 130.5, 131, 156.3, 162; **MS** (m/z): 294 (M+1); **Anal. Calcd.** For $C_{19}H_{19}NO_2$: C, 77.79; H, 6.53; N, 4.77; Found: C, 77.65; H, 6.65; N, 4.66

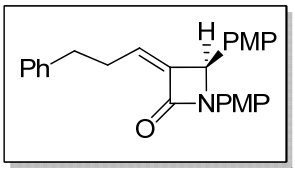
***E*-1,4-Bis-(4-methoxy-phenyl)-3-(3-phenyl-propylidene)-azetidine-2-one (2B.63k):**



Yield, 70%; white solid, mp 91-92 °C; **IR (ν_{max}, $CHCl_3$):** 1737 cm^{-1}; **^{1}H NMR ($CDCl_3$, 200 MHz):** δ 2.16-2.52 (m, 4H), 3.79 (s, 3H), 3.83 (s, 3H), 5.11 (s, 1H), 6.24 (t, *J* = 7.5 Hz, 1H), 6.79 (d, *J* = 9.1 Hz, 2H), 6.78 (d, *J* = 9.0 Hz, 2H), 6.89 (d, *J* = 8.7 Hz, 2H) 6.98-7.33 (m, 7H); **^{13}C NMR**

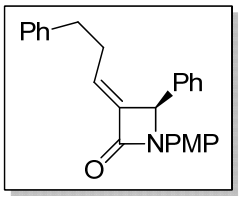
(CDCl$_3$, 50.3 MHz): δ 29.8, 34.6, 55.2, 55.4, 67.5, 114.3, 114.4, 118.2, 126.1, 126.3, 128.4, 128.7, 131.4, 140.6, 142.9, 155.9, 159.9, 161.1; **MS** (m/*z*) = 400 (M+1); **Anal. Calcd.** For $C_{26}H_{25}NO_3$: C, 78.17; H, 6.31; N, 3.51; Found: C, 78.02; H, 6.32; N, 3.85.

***Z*-1,4-Bis-(4-methoxy-phenyl)-3-(3-phenyl-propylidene)-azetidine-2-one (2B.64k):**



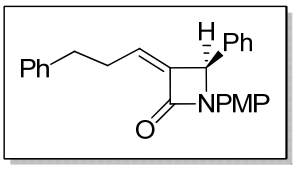
Yield, 30%; white solid, mp 103-105 °C; **IR (ν_{max}, CHCl$_3$):** 1733 cm^{-1}; **^{1}H NMR (CDCl$_3$, 200 MHz):** δ 2.71-2.94 (m, 4H), 3.73 (s, 3H), 3.79 (s, 3H), 5.18 (s, 1H), 5.51 (t, *J* = 7.5 Hz, 1H), 6.79 (d, *J* = 9.1 Hz, 2H), 6.82 (d, *J* = 8.6 Hz, 2H), 7.17-7.37 (m, 9H); **^{13}C NMR (CDCl$_3$, 50.3 MHz):** δ 29.2, 34.4, 55.1, 55.3, 67.8, 114.1, 114.3, 118.2, 126.1, 126.3, 128.4, 128.7, 131.4, 140.6, 142.9, 155.9, 159.9, 161.2; **MS** (m/*z*) = 400 (M+1). **Anal. Calcd.** For $C_{26}H_{25}NO_3$: C, 78.17; H, 6.31; N, 3.51; Found: C, 78.02; H, 6.32; N, 3.85.

***E*-1-(4-methoxy-phenyl)-4-phenyl-3-(3-phenyl-propylidene)-azetidin-2-one (2B.63l):**



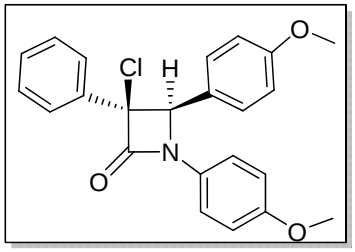
Yield 70%; white solid, mp 102-103 °C; **IR (ν_{max}, CHCl$_3$):** 1736 cm^{-1}; **^{1}H NMR (CDCl$_3$, 200 MHz):** δ 2.19-2.56 (m, 4H), 3.73 (s, 3H), 5.15 (s, 1H), 6.25 (t, *J* = 7.7 Hz, 1H) 6.78 (d, *J* = 9.1 Hz, 2H), 6.95 (d, *J* = 8.0 Hz, 2H) 7.21-7.38 (m, 10H); **^{13}C NMR (CDCl$_3$, 50.3 MHz):** δ 29.8, 34.6, 55.3, 62.8, 114.3, 118.1, 126.1, 126.5, 127.1, 128.4, 128.7, 131.3, 136.8, 140.5, 142.7, 155.9, 161; **MS** (*m/z*) = 370 (M +1); **Anal. Calcd.** For $C_{25}H_{23}NO_2$: C, 81.27; H, 6.27; N, 3.79; Found: C, 81.32; H, 6.38; N, 3.58.

***Z*-1-(4-methoxy-phenyl)-4-phenyl-3-(3-phenyl-propylidene)-azetidin-2-one (2B.64l):**



Yield 30%; white solid, mp 107-109 °C; **IR (ν_{max}, CHCl$_3$):** 1736 cm^{-1}; **^{1}H NMR (CDCl$_3$, 200 MHz):** δ 2.78-2.94 (m, 4H), 3.78 (s, 3H), 5.25 (s, 1H), 5.83 (t, *J* = 7.5 Hz, 1H) 6.83 (d, *J* = 8.9 Hz, 2H), 7.19-7.37 (m, 12H); **^{13}C NMR (CDCl$_3$, 50.3 MHz):** δ 29.9, 35.4, 55.4, 62.7, 114.3, 118.1, 126, 12.3, 128.3, 128.5, 130.3, 137.2, 140.6, 142.1, 155.9, 161.1; **MS** (*m/z*) = 370 (M +1). **Anal. Calcd.** For $C_{25}H_{23}NO_2$: C, 81.27; H, 6.27; N, 3.79; Found: C, 81.32; H, 6.38; N, 3.58.

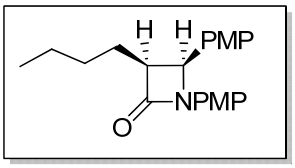
3-Chloro-1,4-bis-(4-methoxyphenyl)-3-phenylazetidin- 2-one (2B.62m):



Yield 92%; white solid, mp 58-60 °C, **IR (ν_{max}, $CHCl_3$):** 1757 cm^{-1}; **^{1}H NMR ($CDCl_3$, 200 MHz):** δ 3.70 (s, 3H), 3.76 (s, 3H), 5.50 (s, 1H), 6.65 (d, *J* = 8.8 Hz, 2H), 6.82 (d, *J* = 8.7 Hz, 2H), 7.12-7.34 (m, 9H); **^{13}C NMR ($CDCl_3$, 50.3 MHz):** δ 55.1, 55.4, 72.7, 113.9, 114.3, 119.3, 124.9, 125.1, 128.1, 128.6, 128.8, 130.2, 132, 156.6, 159.8, 161.7; **MS** (m/z): 394 (M+1), 395 (M+2). **Anal. Calcd.** For $C_{23}H_{20}ClNO_3$: C, 70.14; H, 5.12; Found, C, 70.17; H, 5.07.

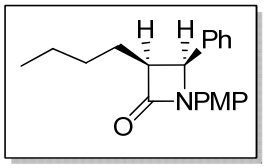
General procedure for the synthesis of 1,4-bis(4-methoxy-phenyl)- 3-Butyl-azetidin-2-one (2B.65a):

To a mixture of 3-alkylidene-*β*-lactams **2B.63a** and **2B.64a** (0.168 g, 0.5 mmol) in 15 mL of ethyl acetate was added a catalytic amount of 10% Pt/C (30 mg). Hydrogenation was carried out under atmospheric pressure for 12 h. The catalyst was filtered through a pad of Celite and the solvent was removed under reduced pressure to give compound **2B.65a** in very good yield.



Yield, 90%; White solid; mp 85-86 °C; **IR (ν_{max}, $CHCl_3$):** 3359, 1728 cm^{-1}; **^{1}H NMR ($CDCl_3$, 200 MHz):** δ 0.97 (t, *J* = 6.8 Hz, 3H), 1.12-1.50 (m, 6H), 3.47-3.57 (m, 1H), 3.74 (s, 3H), 3.80 (s, 3H), 5.11 (d, *J* = 5.6 Hz, 1H), 6.79 (d, *J* = 9.1 Hz, 2H), 6.82 (d, *J* = 8.7 Hz, 2H), 7.22 (d, *J* = 8.7 Hz, 2H), 7.29 (d, *J* = 8.9 Hz, 2H); **^{13}C NMR ($CDCl_3$, 50.3 MHz):** δ 13.9, 22.9, 25.6, 35.1, 55.2, 55.4, 66.9, 85.9, 114.3, 114.5, 118.8, 125.7, 128.4, 130.6, 156.2, 159.9, 168; **MS** (*m/z*) = 340 (M+1). **Anal. Calcd.** For $C_{21}H_{25}NO_4$: C, 74.31; H, 7.42; N, 4.13; Found: C, 74.27; H, 7.36; N, 4.02.

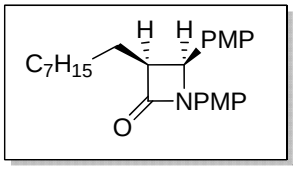
3-Butyl-1-(4-Methoxy-phenyl)-4-phenyl-azetidin-2-one (2B.65b):



Yield 95%; white solid, 89-90 °C; **IR (ν_{max}, $CHCl_3$):** 3388, 1737 cm^{-1}; **^{1}H NMR ($CDCl_3$, 200 MHz):** δ 0.72 (t, *J* = 6.9 Hz, 3H), 1.25-1.69 (m, 6H), 3.63 (s, 3H), 3.46-3.57 (m, 1H), 5.11 (d, *J* = 5.7 Hz, 1H), 6.73 (d, *J* = 9.0 Hz, 2H), 7.20-7.36 (m, 7H). **^{13}C NMR ($CDCl_3$, 50.3 MHz):** 13.4, 21.6, 29.6, 55.3, 55.4, 62.6,

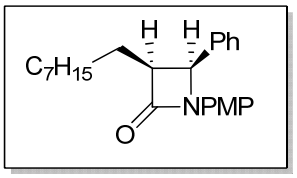
114.3, 114.4, 118.1, 127.6, 128.3, 128.8, 131.4, 142.3, 155.8, 159.8, 161.3; **MS** (m/z): 310 (M+1); **Anal. Calcd.** For $C_{20}H_{23}NO_2$: C, 77.64; H, 7.49; N, 4.53; Found: C, 77.50; H, 7.36; N, 4.45.

3-Octyl-1,4-bis(4-methoxy phenyl) azetidin-2-one (2B.65c):



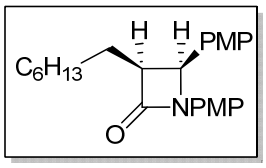
Yield 94%; thick oil; **IR (ν_{max}, $CHCl_3$):** 1745 cm^{-1}; **^{1}H NMR ($CDCl_3$, 200 MHz):** δ 0.86 (t, *J* = 6.7 Hz, 3H), 1.10-1.53 (m, 14H), 3.44-3.54 (m, 1H), 3.75 (s, 3H), 3.81 (s, 3H), 5.37 (d, *J* = 5.6 Hz, 1H), 6.79 (d, *J* = 9.0 Hz, 2H), 6.88 (d, *J* = 8.8 Hz, 2H), 7.19 (d, *J* = 8.7 Hz, 2H), 7.26 (d, *J* = 9.1 Hz, 2H); **^{13}C NMR ($CDCl_3$, 50.3 MHz):** δ 14.1, 22.6, 25.23, 27.2, 29.2, 29.3, 29.4, 31.8, 54.7, 55.2, 55.3, 57.9, 113.9, 114.2, 118.3, 118.4, 126.9, 128.4, 131.3, 155.7, 159.4, 167.7; **MS** (*m/z*) = 396 (M+1); **Anal. Calcd.** For $C_{25}H_{33}NO_3$: C, 75.91; H, 8.41; N, 3.54; Found: C, 75.57; H, 8.32; N, 3.55.

3-Octyl-1-(4-methoxy-phenyl)-4-phenyl-azetidin-2-one (2B.65d):



Yield 94%; thick oil; **IR (ν_{max}, $CHCl_3$):** 1747 cm^{-1}; **^{1}H NMR ($CDCl_3$, 200 MHz):** δ 0.78 (t, *J* = 7.00 Hz, 3H), 1.09-1.40 (m, 12H), 1.29-1.46 (m, 2H), 3.42-3.56 (m, 1H), 3.69 (s, 3H), 5.09 (d, *J* = 5.70 Hz, 1H), 6.73 (d, *J* = 9.1 Hz, 2H), 7.14-7.28 (m, 7H); **^{13}C NMR ($CDCl_3$, 50.3 MHz):** δ 13.9, 22.4, 25.2, 27.1, 28.7, 29.2, 29.4, 31.5, 54.7, 55.1, 55.3, 57.9, 113.9, 114.1, 118.3, 126.9, 131.3, 155.8, 167.7; **MS** (*m/z*) = 366 (M+1) **Anal. Calcd**. For $C_{24}H_{31}NO_2$: C, 78.87; H, 8.55; N, 3.83; [Found: C, 78.67; H, 8.19; N, 3.87.

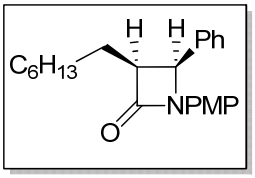
3-Heptyl-1,4-bis(4-methoxy-phenyl)azetidin-2-one (2B.65e)::



Yield 94%; **IR (ν_{max}, $CHCl_3$):** 1741 cm^{-1}; **^{1}H NMR ($CDCl_3$, 200 MHz):** δ 0.84 (t, *J* = 6.9 Hz, 3H), 1.11-1.53 (m, 12H), 3.44-3.47 (m, 1H), 3.75 (s, 3H), 3.81(s, 3H), 5.11 (d, *J* = 5.6 Hz, 1H), 6.77 (d, *J* = 9.1 Hz, 2H), 6.85 (d, *J* = 8.9 Hz, 2H), 7.19 (d, *J* = 8.9 Hz, 2H), 7.24 (d, *J* = 9.00 Hz, 2H); **^{13}C NMR ($CDCl_3$, 50.3 MHz):** δ 13.9, 22.4, 25.2, 27.1, 29.2, 31.5, 54.7, 55.1, 55.3, 57.9, 113.9,

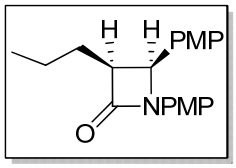
114.1, 118.3, 126.9, 128.3, 131.3, 155.7, 159.7, 167.7; MS (m/z): 382 (M+1); **Anal. Calcd**. For $C_{24}H_{31}NO_3$: C, 75.56; H, 8.19; N, 3.67, Found: C, 75.46; H, 8.34; N, 3.83.

3-Heptyl-1-(4-methoxyphenyl)-4-phenylazetidin- 2-one (2B.65f)::



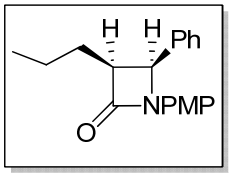
Yield 95%; white solid, mp 75-76 °C **IR (ν_{max}, $CHCl_3$):** 1739 cm^{-1}; **^{1}H NMR ($CDCl_3$, 200 MHz):** δ 0.89 (t, *J* = 6.8 Hz, 3H), 1.03-1.46 (m, 12H), 3.40–3.51 (m, 1H), 3.69 (s, 3H), 5.14 (d, *J* = 5.7 Hz, 1H), 6.81 (d, *J* = 9.1 Hz, 2H), 7.27–7.39 (m, 7H); **^{13}C NMR ($CDCl_3$, 50.3 MHz):** δ 14, 22.5, 25.3, 27.1, 28.8, 29.2, 31.6, 54.7, 55.4, 58.4, 114.3, 118.4, 127.2, 128.3, 128.6, 131.3, 135.2, 156.5, 168.2; **MS** (m/z): 352 (M+1); **Anal. Calcd**. For $C_{23}H_{29}NO_2$: C, 78.60; H, 8.32; N, 3.99; Found: C, 78.45; H, 8.13; N, 3.87.

3-Propyl-1,4-bis(4-methoxyphenyl)azetidin-2-one (2B.65g:



Yield 97%; white solid, mp 84–85 °C **IR (ν_{max}, $CHCl_3$):** 1737 cm^{-1}; **^{1}H NMR ($CDCl_3$, 200 MHz):** δ 0.77 (t, *J* = 6.5 Hz, 3H), 1.14-1.45 (m, 4H), 3.47-3.57 (m, 1H), 3.75 (s, 3H), 3.82 (s, 3H), 5.11 (d, *J* = 5.4 Hz, 1H), 6.80 (d, *J* = 9.00 Hz, 2H), 6.89 (d, *J* = 8.9 Hz, 2H), 7.22 (d, *J* = 8.9 Hz, 2H), 7.29 (d, *J* = 9.0 Hz, 2H); **^{13}C NMR ($CDCl_3$, 50.3 MHz):** δ 13.9, 20.5, 27.5, 54.5, 55.2, 55.4, 58, 113.9, 114.2, 118.3, 126.9, 127.1, 128.3, 131.3, 155.7, 159.4, 167.3; **MS** (m/z): 326 (M+1); **Anal. Calcd**. For $C_{20}H_{23}NO_3$: C, 73.82; H, 7.12; N, 4.30; Found: C, 73.76; H, 7.06; N, 4.25.

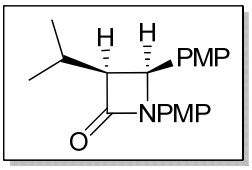
3-Propyl-1-(4-Methoxy-phenyl)-4-phenyl-azetidin-2-one (2B.65h):



Yield 94%; white solid, mp 111-112 °C; **IR (ν_{max}, $CHCl_3$):** 1739 cm^{-1}; **^{1}H NMR ($CDCl_3$, 200 MHz):** δ 0.75 (t, *J* = 6.58 Hz, 3H), 1.08- 1.46 (m, 4H), 3.51-3.61 (m, 1H), 3.75 (s, 3H), 5.16 (d, *J* = 5.7 Hz, 1H), 6.81 (d, *J* = 9.1 Hz, 2H), 7.14- 7.31 (m, 7H); **^{13}C NMR ($CDCl_3$, 50.3 MHz):** δ 13.8, 20.4, 27.9, 54.4, 55.3, 58.3, 114.2, 118.1, 118.3, 127.1, 128.1, 128.5, 131.3, 135.1, 155.4, 167.6; **MS** (m/z): 296 (M+1).

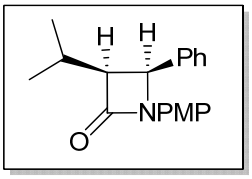
Anal. Calcd. For $C_{19}H_{21}NO_2$: C, 77.26; H, 7.17; N, 4.74; Found: C, 77.18; H, 7.06; 4.66.

1,4-bis(4-methoxy-phenyl)- 3-isopropyl azetidin-2-one (2B.65i):



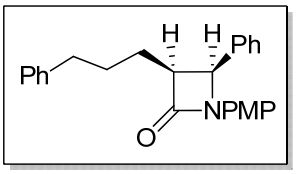
Yield 92%; white solid, mp 124-126 °C **IR (ν_{max}, $CHCl_3$):** 1731 cm^{-1}; **^{1}H NMR ($CDCl_3$, 200 MHz):** δ 0.49 (d, *J* = 6.3 Hz, 3H), 1.15 (d, *J* = 6.5 Hz, 3H) 1.52-1.79 (m, 1H), 3.17 (dd, *J* = 11.2 & 5.5 Hz, 1H), 3.73 (s, 3H), 3.80 (s, 3H), 5.06 (d, *J* = 5.5 1H), 6.74 (d, *J* = 9.1 Hz, 2H), 6.81 (d, *J* = 8.7 Hz, 2H), 7.23 (d, *J* = 8.6 Hz, 2H), 7.30 (d, *J* = 9.2 Hz, 2H); **^{13}C NMR ($CDCl_3$, 50.3 MHz):** δ 16.7, 17.1, 33.2, 55.3, 55.5, 64.9, 88.8, 114.3, 114.5, 118.8, 125.7, 128.4, 130.6, 156.2, 159.9, 167.8; **MS** (*m/z*) = 326 (M+1). **Anal. Calcd.** For $C_{20}H_{23}NO_3$: C, 73.82; H, 7.12; N, 4.30; Found: C, 73.79; H, 7.07; N, 4.27.

3-Isopropyl-1-(4-methoxyphenyl)-4-phenylazetidin- 2-one (2B.65j)::



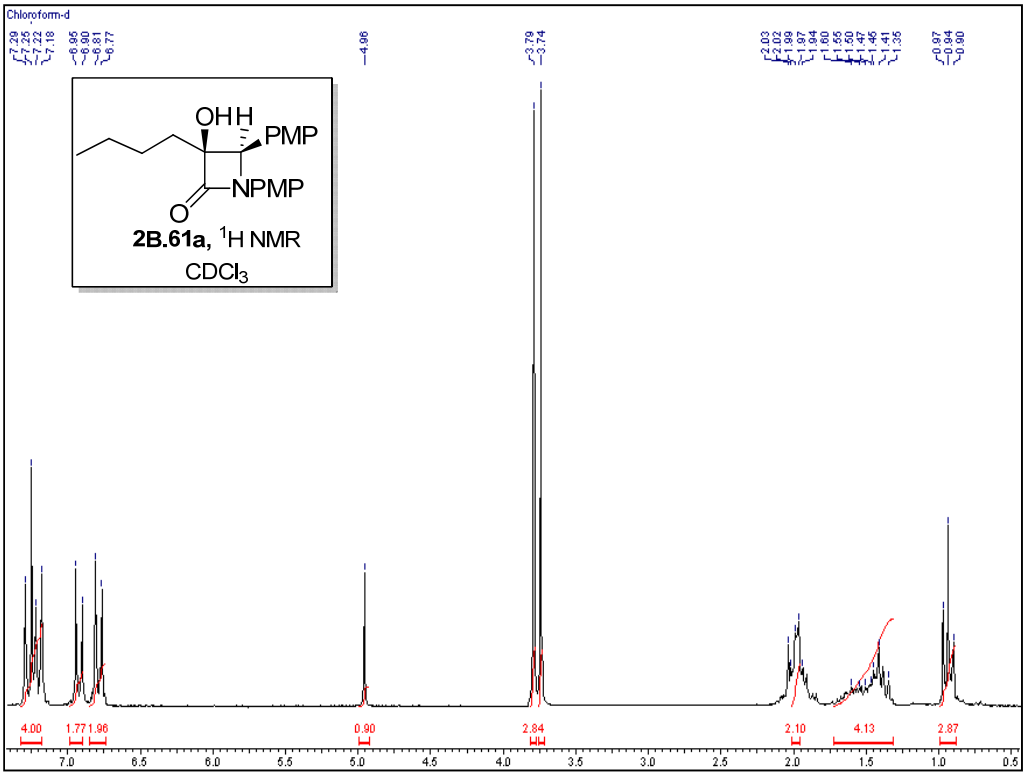
Yield 95%; white solid, mp 153-154 °C; **IR (ν_{max}, $CHCl_3$):** 1737 cm^{-1}; **^{1}H NMR ($CDCl_3$, 200 MHz):** δ 0.57 (d, *J* = 6.6 Hz, 3H), 1.12 (d, *J* = 6.7 Hz, 3H), 1.63–1.76 (m, 1H,), 3.17 (dd, *J* = 5.7, 11.2 Hz, 1H), 3.67 (s, 3H), 5.01 (d, *J* = 5.7 Hz, 1H), 6.74 (d, *J* = 9.0 Hz, 2H), 6.81-7.30 (m, 7H); **^{13}C NMR ($CDCl_3$, 50.3 MHz):** δ 20.4, 24.9, 25.4, 55.4, 58.7, 62, 114.2, 114.5, 127.3, 127.6, 128.4, 131.3, 159.7, 167.2; **MS** (m/z): 296 (M+1); **Anal. Calcd.** For $C_{19}H_{21}NO_2$: C, 77.26; H, 7.17; N, 4.74; Found: C, 77.21; H, 7.11; N, 4.76.

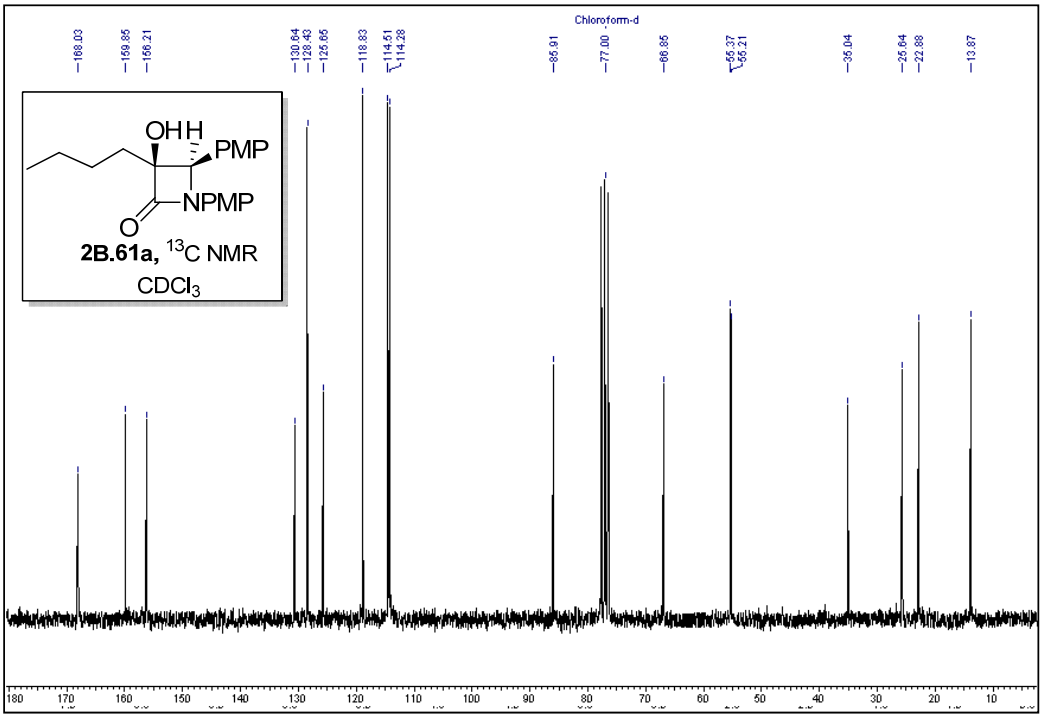
1-(4-methoxy-phenyl)-4-phenyl-3-(3-phenylpropyl)-azetidin-2-one (2B.65k):

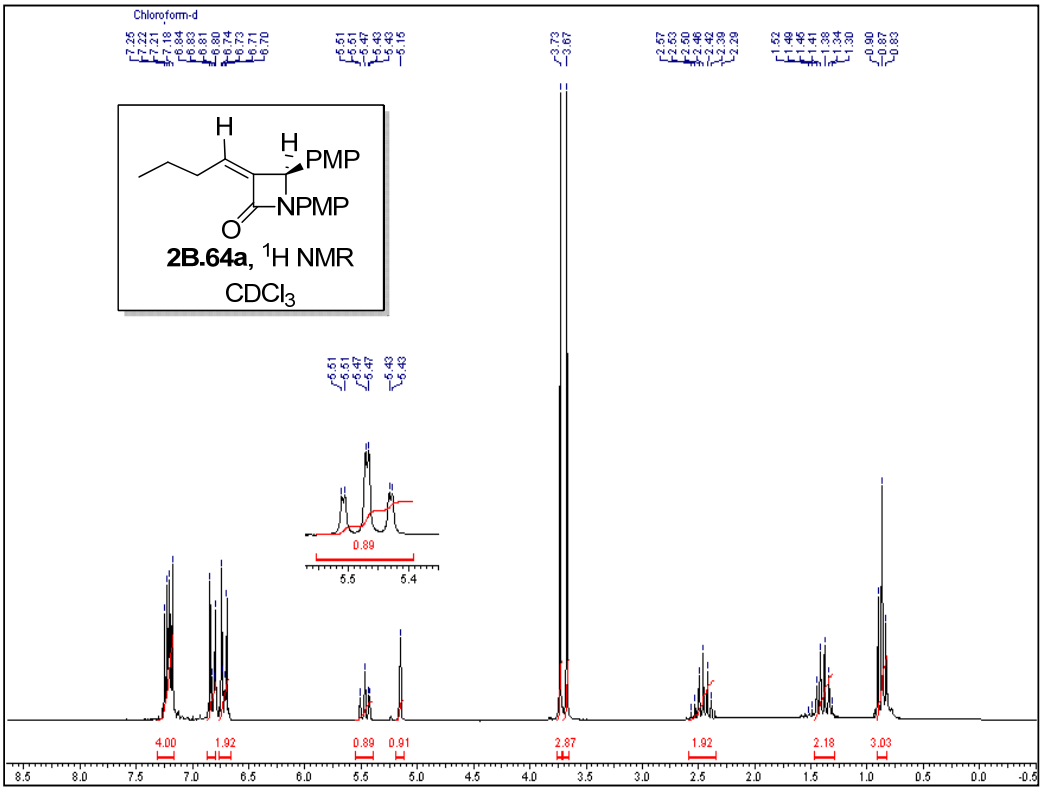


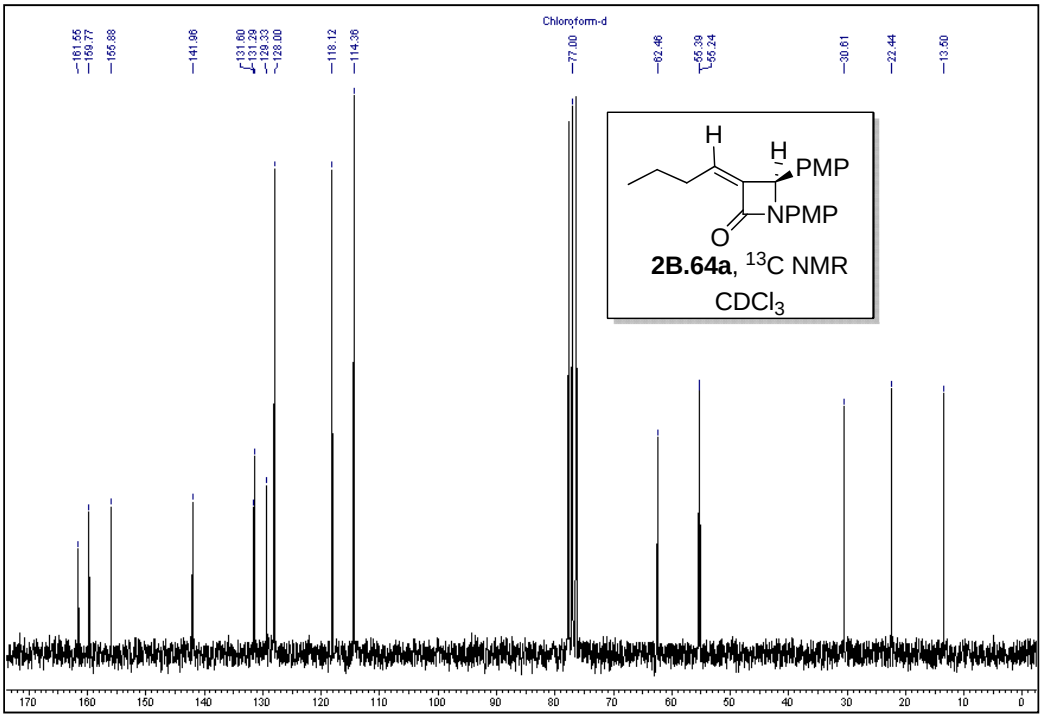
Yield, 95%; white solid, mp 115-117 °C; **IR (ν_{max}, $CHCl_3$):** 1739 cm^{-1}; **^{1}H NMR ($CDCl_3$, 200 MHz):** δ 1.21-1.62 (m, 4H), 2.36-2.45 (m, 2H), 3.49-3.60 (m, 1H), 3.74 (s, 3H), 5.15 (d, *J* = 5.8 Hz, 1H), 6.79 (d, *J* = 9.1 Hz, 2H), 6.97 (d, *J* = 8.9 Hz, 2H) 7.16-7.35 (m, 10H); **^{13}C NMR ($CDCl_3$, 50.3 MHz):** δ 24.7, 28.9, 35.7, 54.5, 55.3, 57.9, 114.0, 114.1, 118.3, 125.6, 126.6, 127.1, 128.2, 129.5, 131.2, 141.7, 159.4, 167.4; MS (m*/z*) = 372 (M+1); **Anal. Calcd.** For $C_{25}H_{25}NO_2$: C, 80.83; H, 6.78; N, 3.77; Found: C, 80.68; H, 6.69; N, 3.49.

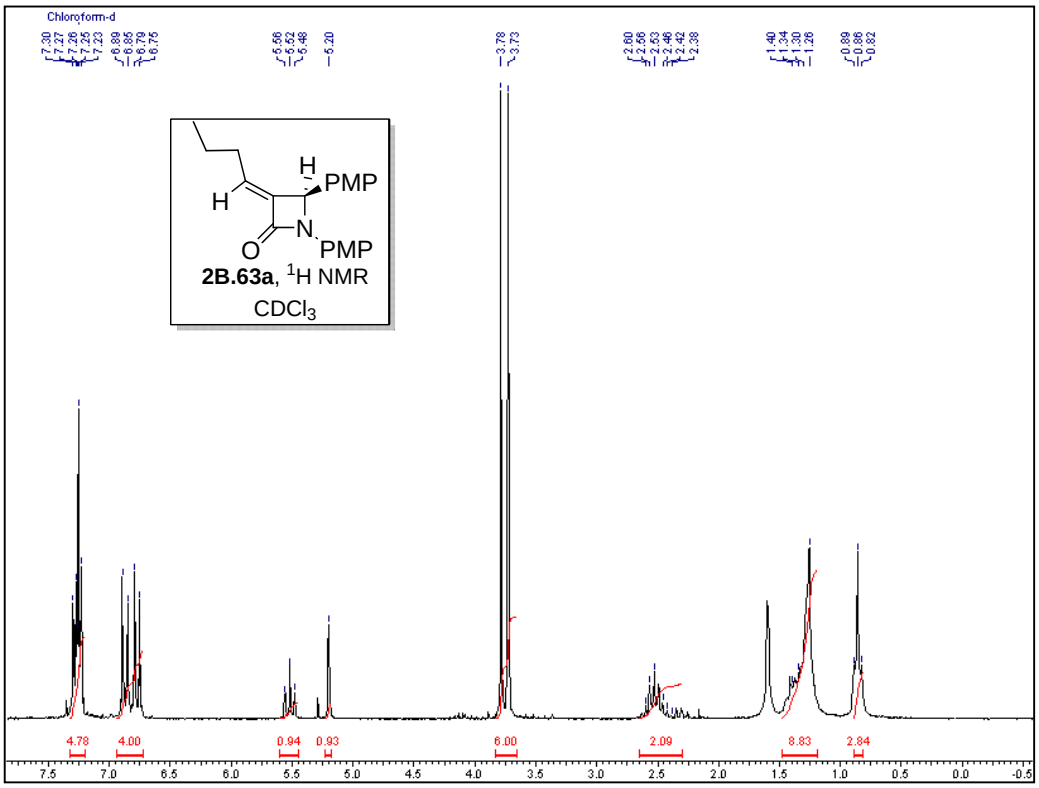
2B.6 Spectra

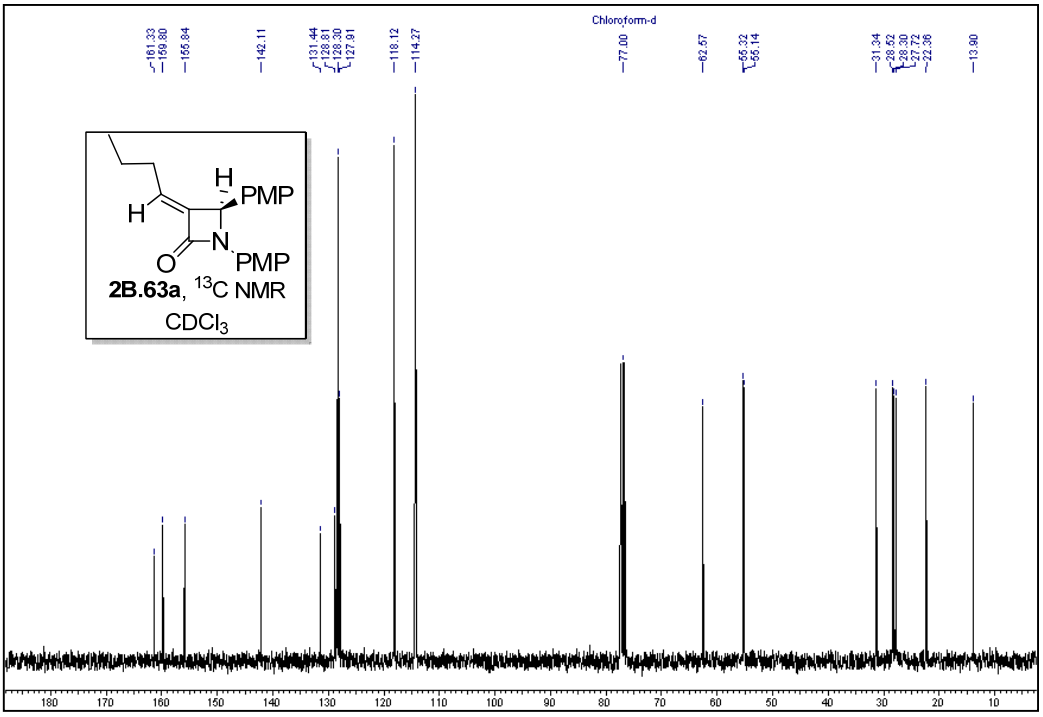

Chloroform-d
OH H
PMP
NPMP
O
2B.61a, ^{1}H NMR
$CDCl_3$

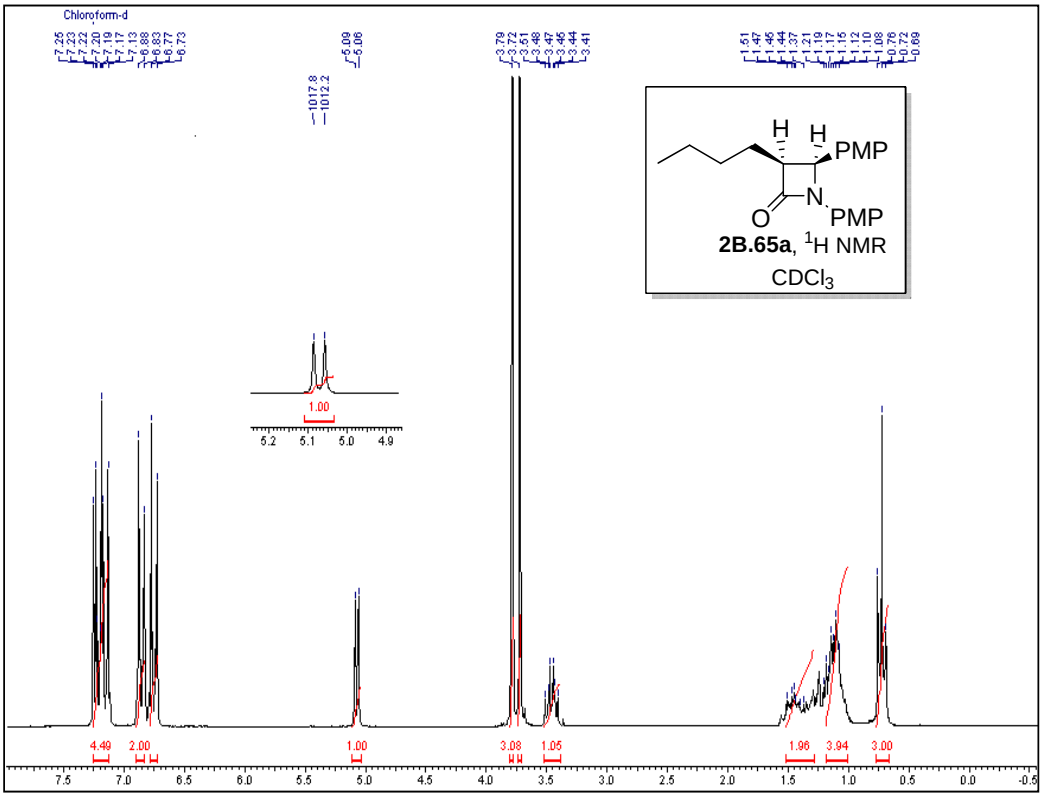

Chloroform-d
OH H
PMP
NPMP
O
2B.61a, ^{13}C NMR
$CDCl_3$

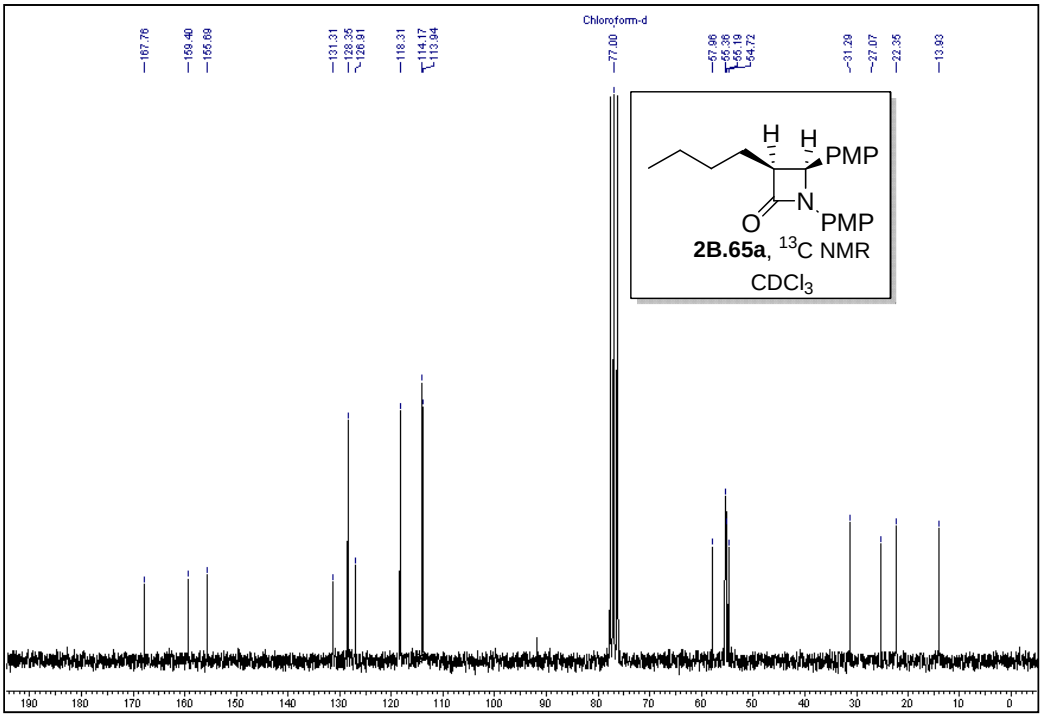

Chloroform-d
H
H
PMP
NPMP
O
2B.64a, 1H NMR
CDCl3

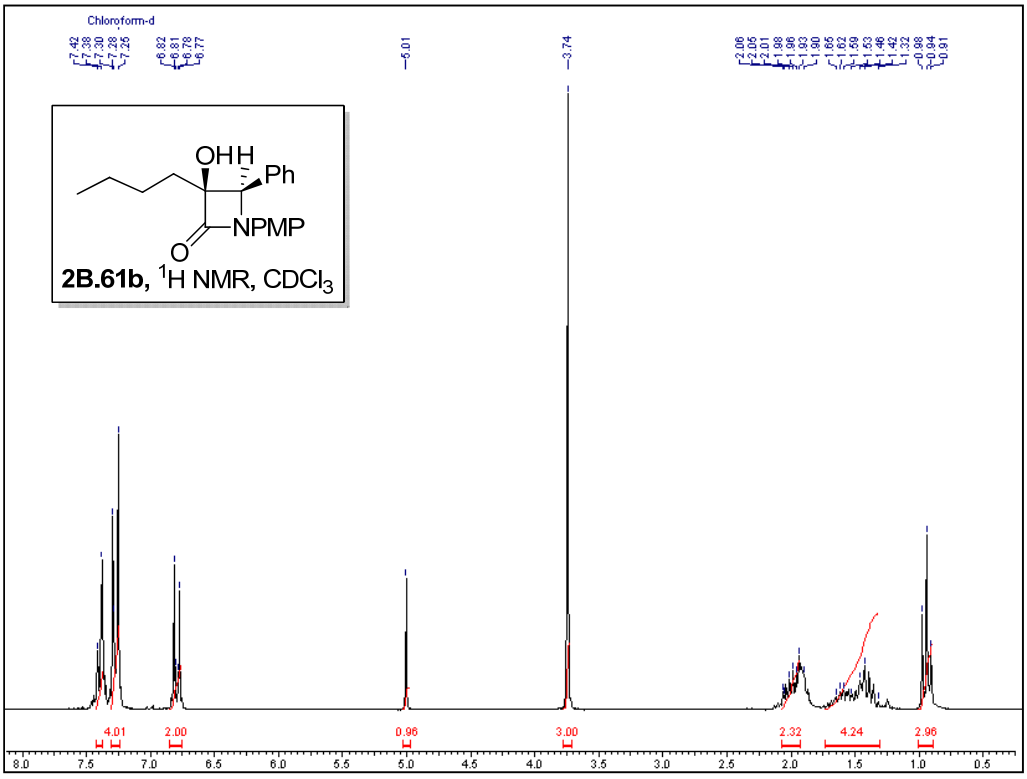

Chloroform-d
H
H
PMP
NPMP
O
2B.64a, 13C NMR
CDCl3

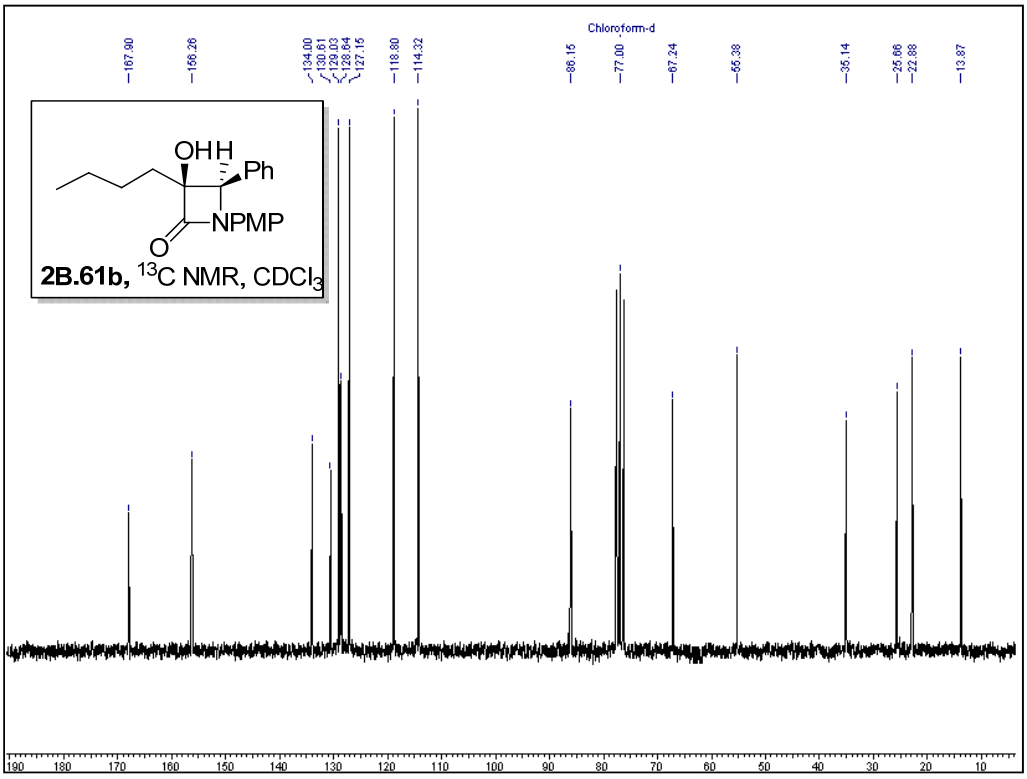

Chloroform-d
H
PMP
H
N
O
PMP
2B.63a, 1H NMR
CDCl3

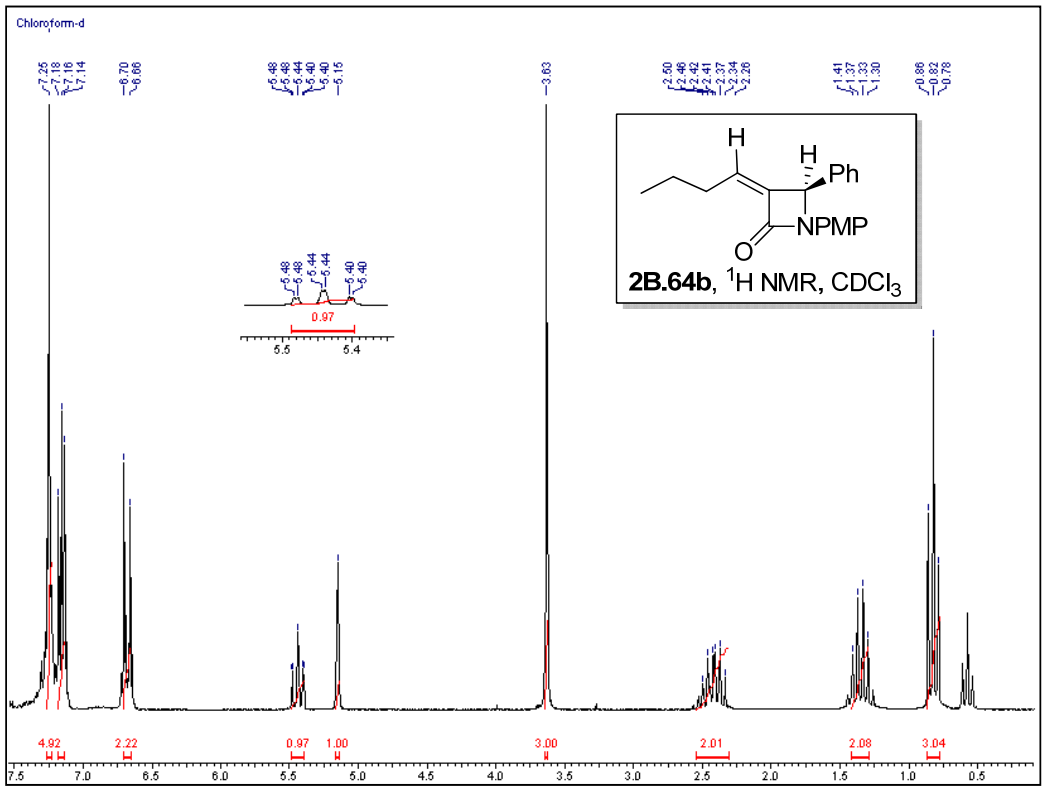

Chloroform-d
H
PMP
H
N
O
PMP
2B.63a, 13C NMR
CDCl3

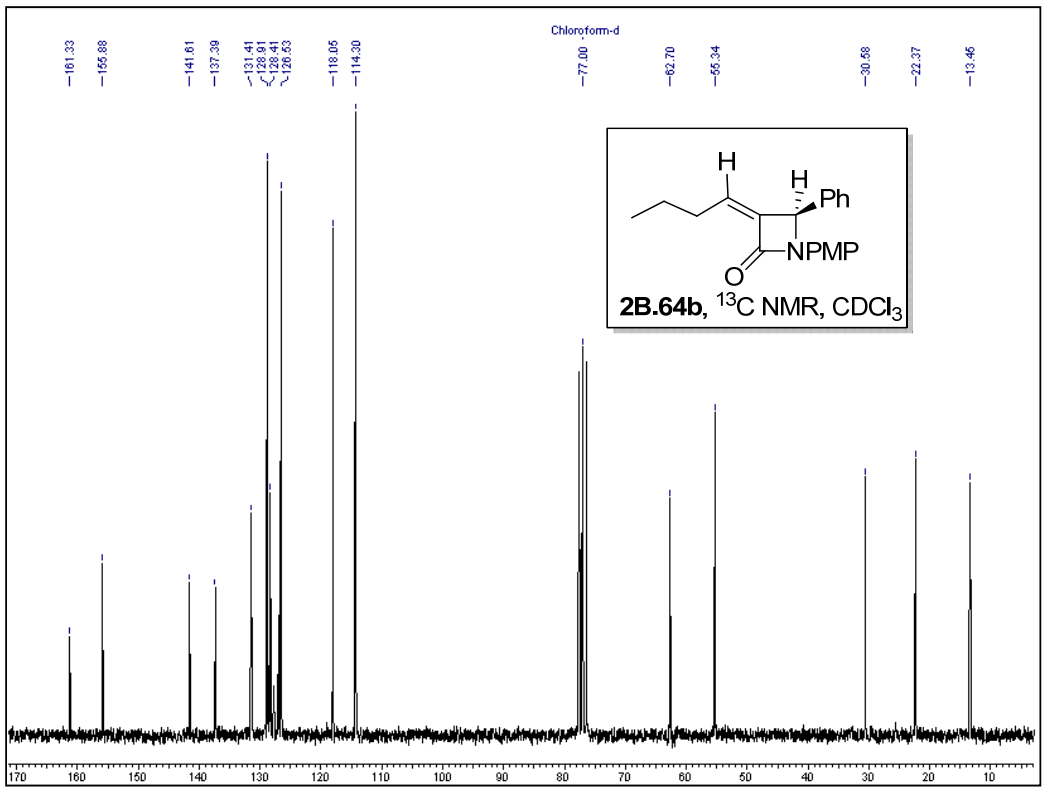

Chloroform-d
H
H
PMP
N
O
PMP
2B.65a, 1H NMR
CDCl3

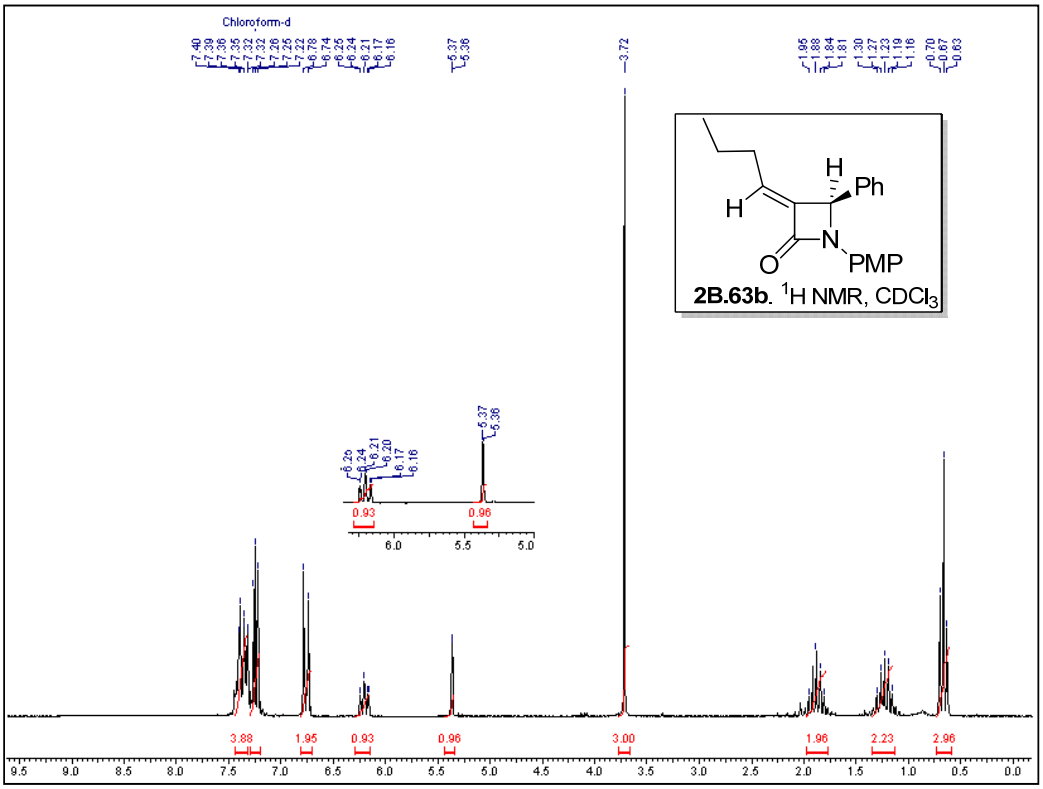

Chloroform-d
H
H
PMP
N
O
PMP
2B.65a, 13C NMR
CDCl3

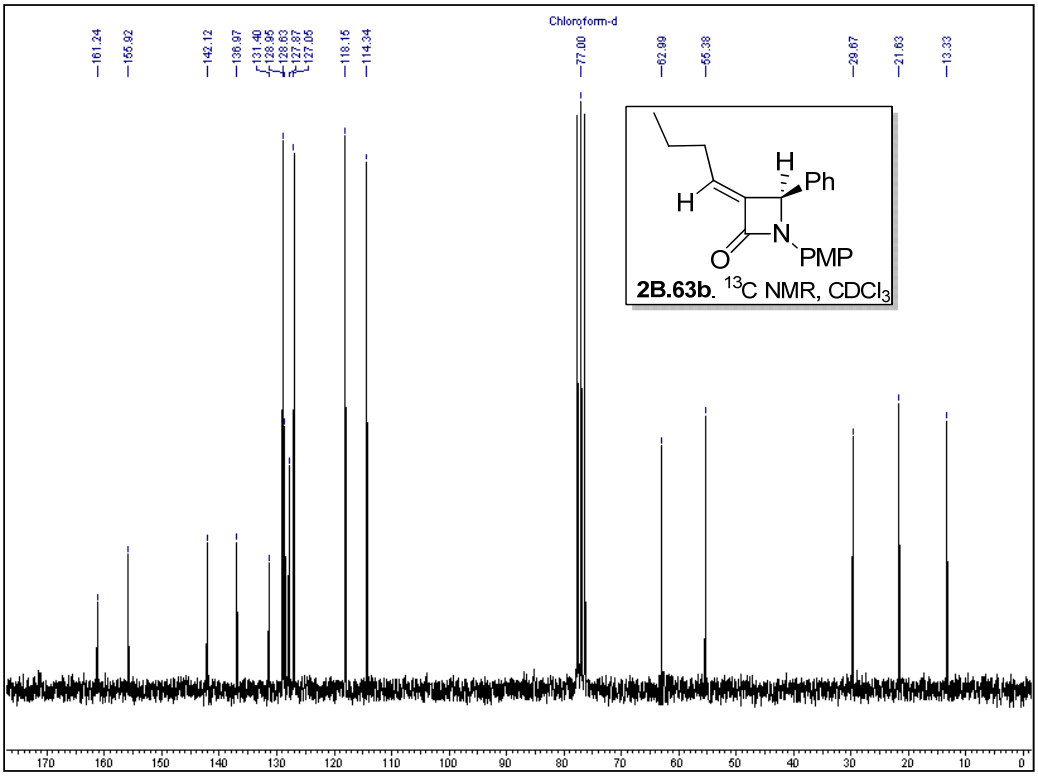

Chloroform-d
OH H
Ph
NPMP
O
2B.61b, ^{1}H NMR, $CDCl_3$

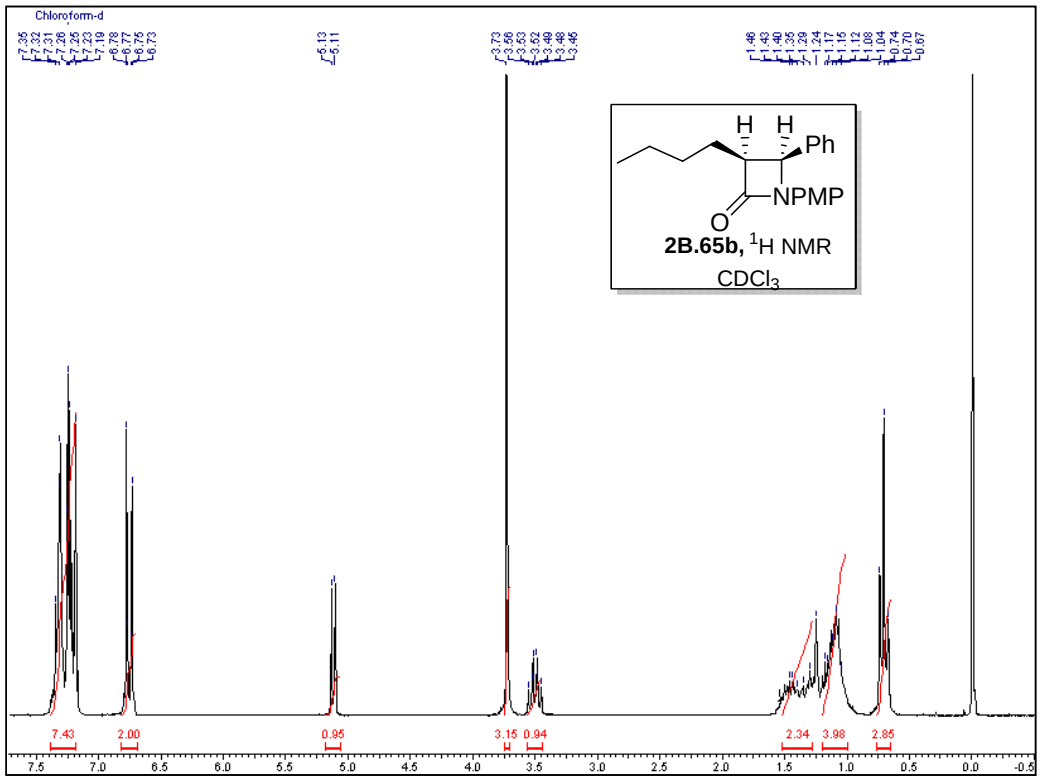

Chloroform-d
OH H
Ph
NPMP
O
2B.61b, ^{13}C NMR, $CDCl_3$

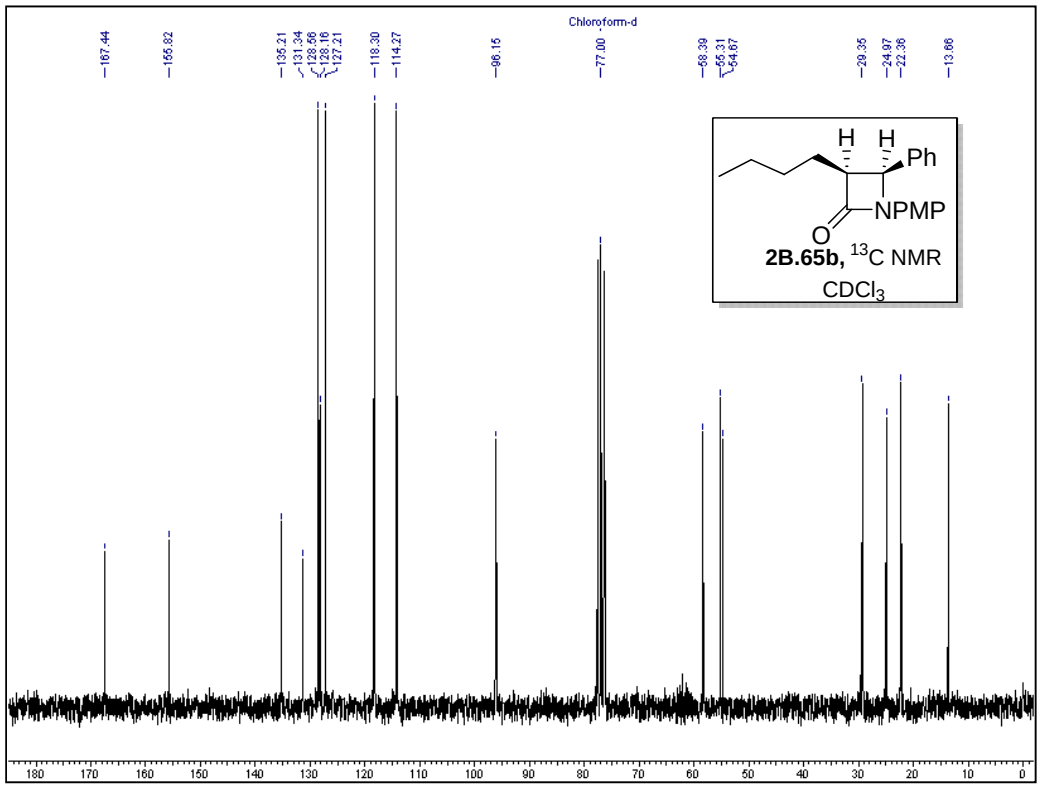

Chloroform-d
7.26
7.18
7.16
7.14
6.70
6.66
5.48
5.48
5.44
5.44
5.40
5.40
5.15
3.63
2.50
2.46
2.42
2.41
2.37
2.34
2.26
1.41
1.37
1.33
1.30
0.86
0.82
0.78
H
H
Ph
NPMP
O
2B.64b, 1H NMR, CDCl3
0.97
4.92
2.22
0.97
1.00
3.00
2.01
2.08
3.04

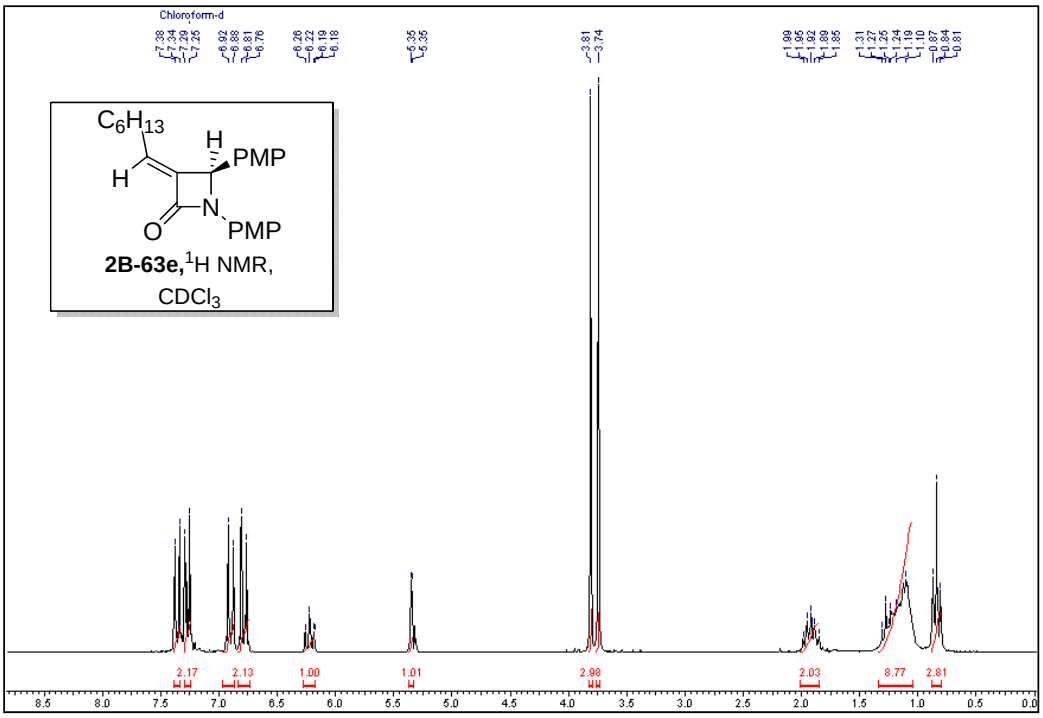

Chloroform-d
161.33
155.88
141.61
137.39
131.41
128.91
128.41
126.53
118.05
114.30
77.00
62.70
55.34
30.58
22.37
13.46
H
H
Ph
NPMP
O
2B.64b, 13C NMR, CDCl3

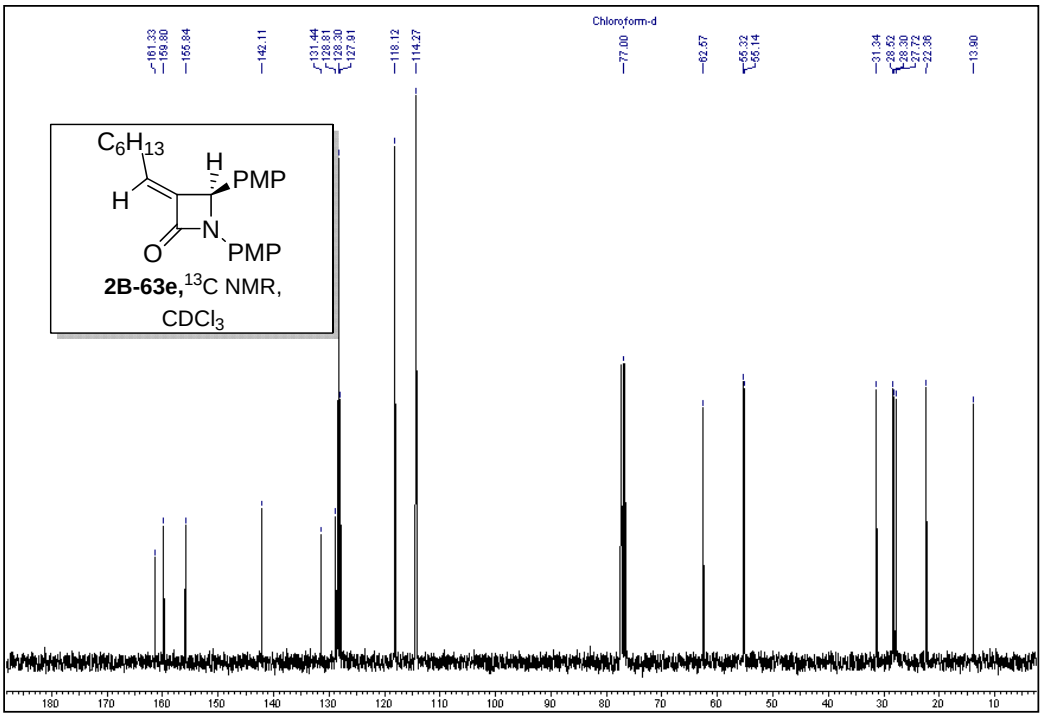

Chloroform-d
H
Ph
H
N
O
PMP
2B.63b. ^{1}H NMR, $CDCl_3$

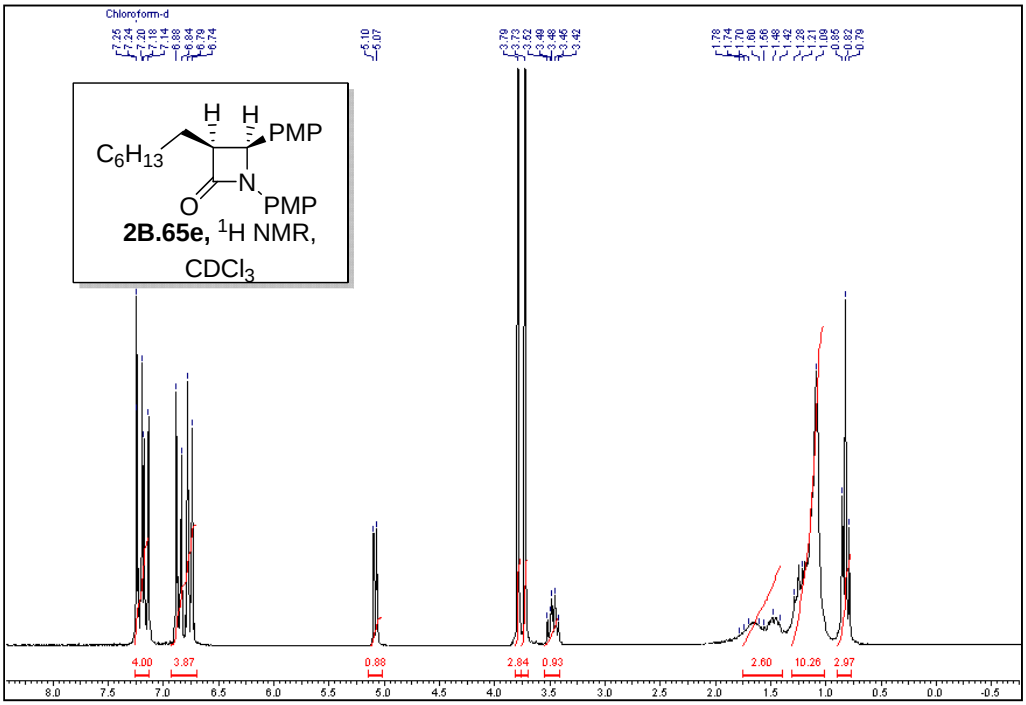

Chloroform-d
H
Ph
H
N
O
PMP
2B.63b. ^{13}C NMR, $CDCl_3$

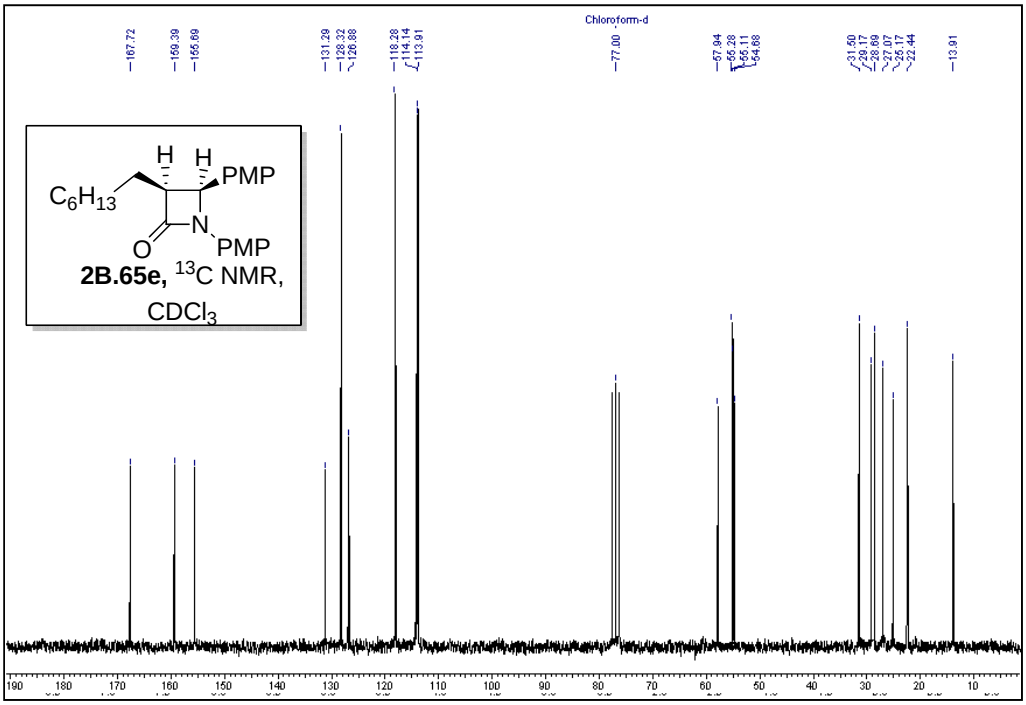

Chloroform-d
H H
Ph
NPMP
O
2B.65b, ^{1}H NMR
$CDCl_3$

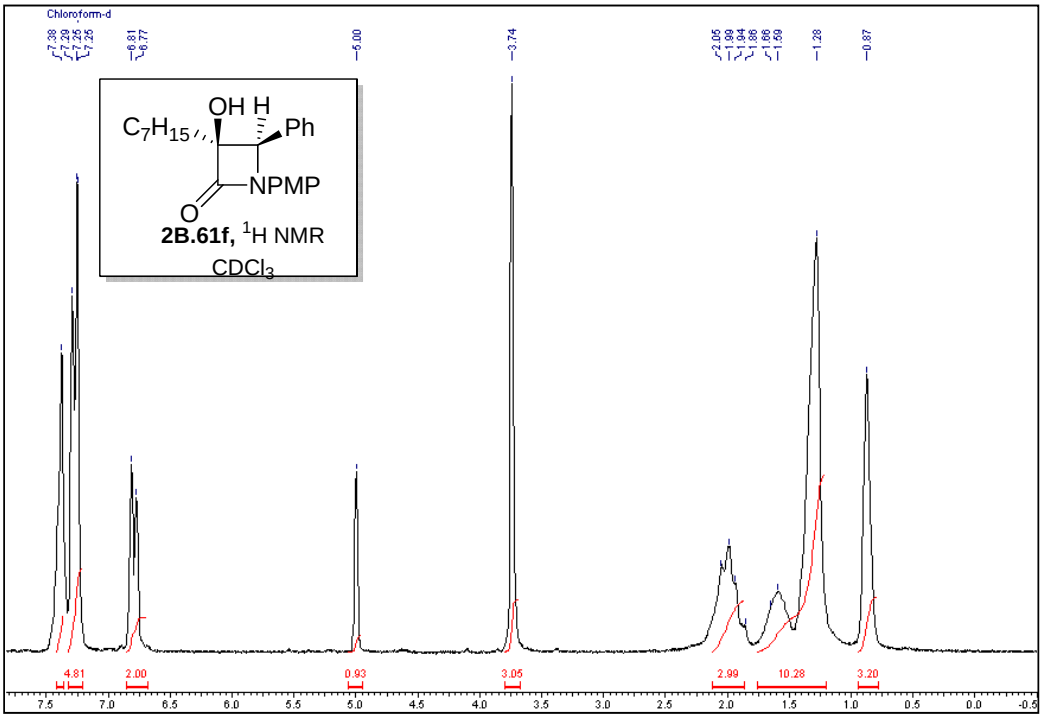

Chloroform-d
H H
Ph
NPMP
O
2B.65b, ^{13}C NMR
$CDCl_3$

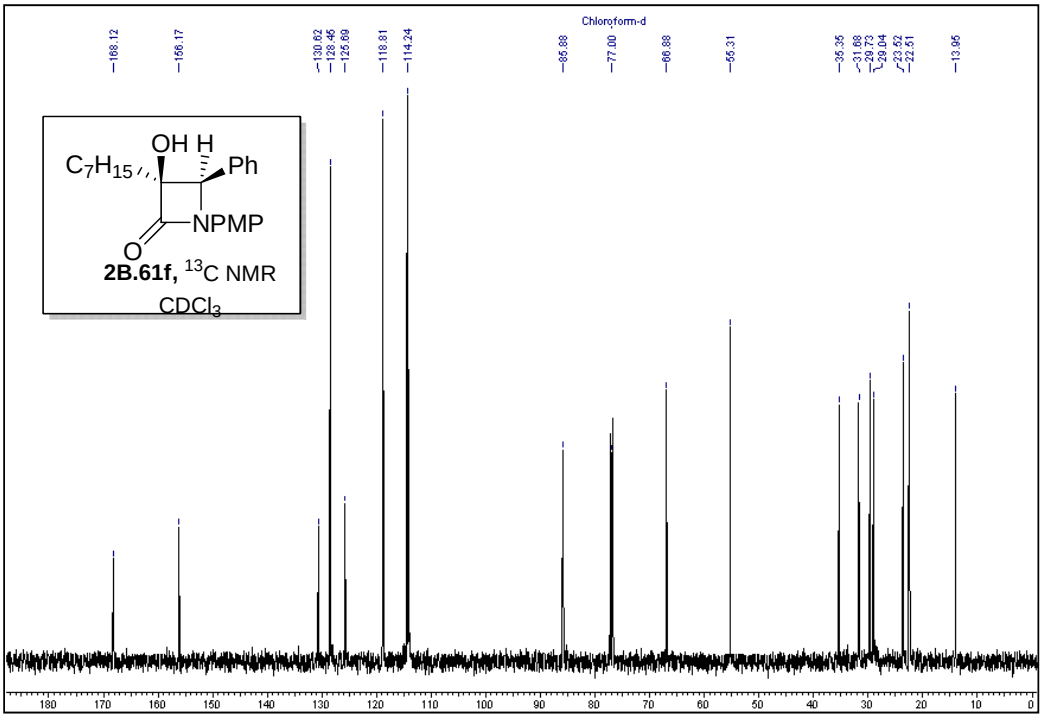

Chloroform-d
C6H13
H
PMP
H
N
O
PMP
2B-63e, 1H NMR,
CDCl3

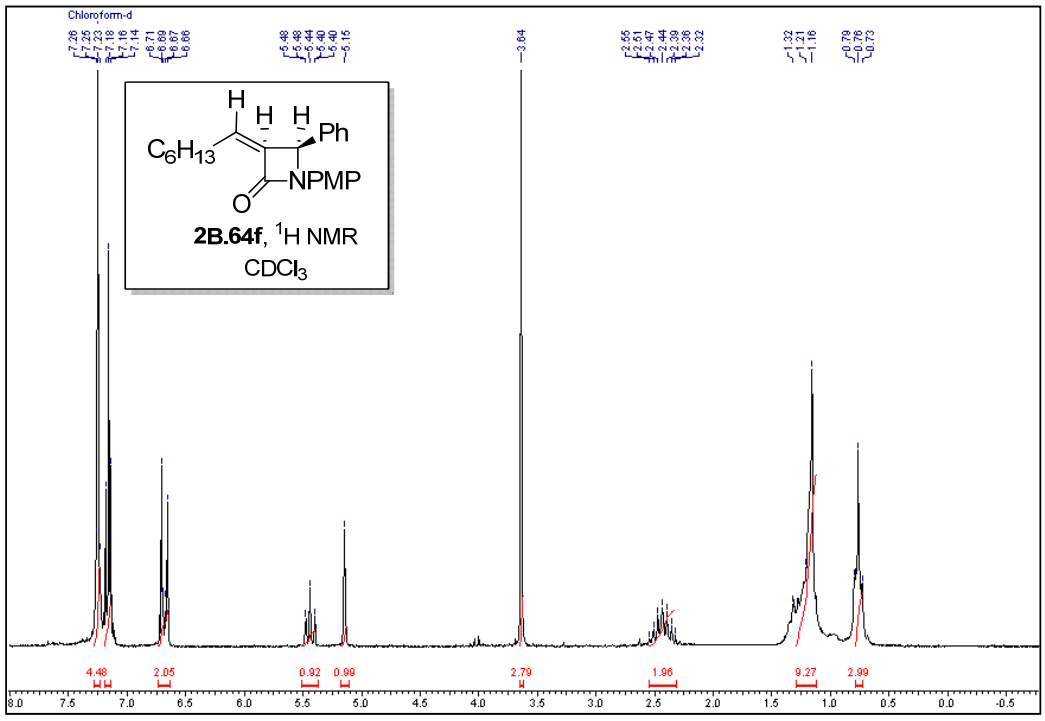

Chloroform-d
C6H13
H
PMP
H
N
O
PMP
2B-63e, 13C NMR,
CDCl3

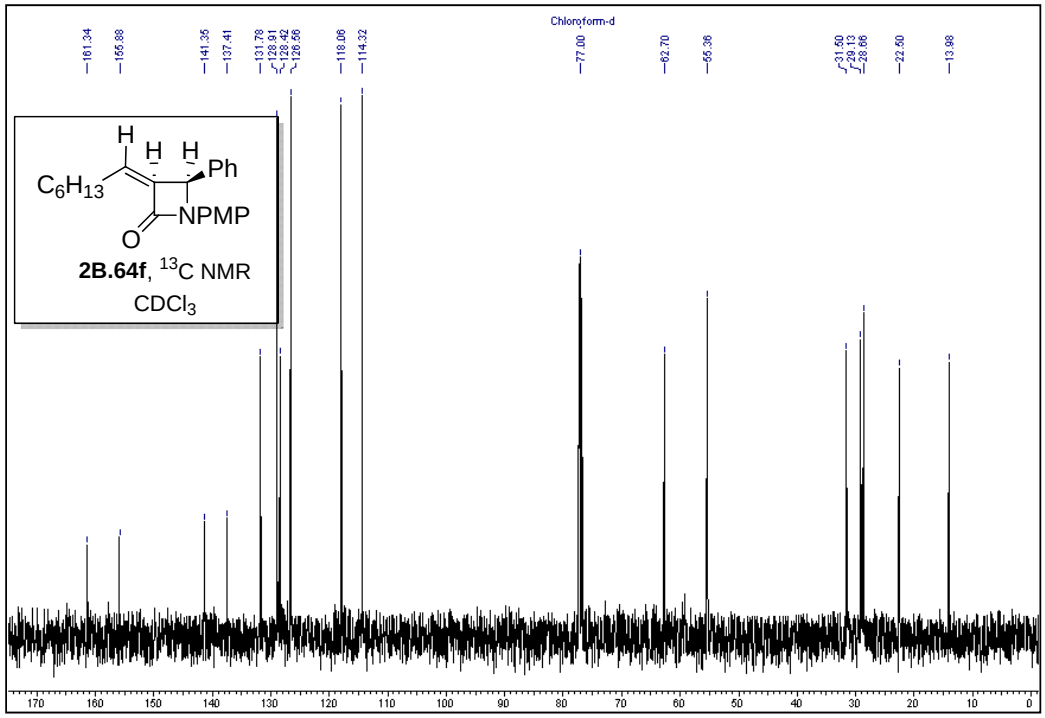

Chloroform-d
H
H
PMP
C6H13
N
O
PMP
2B.65e, 1H NMR,
CDCl3

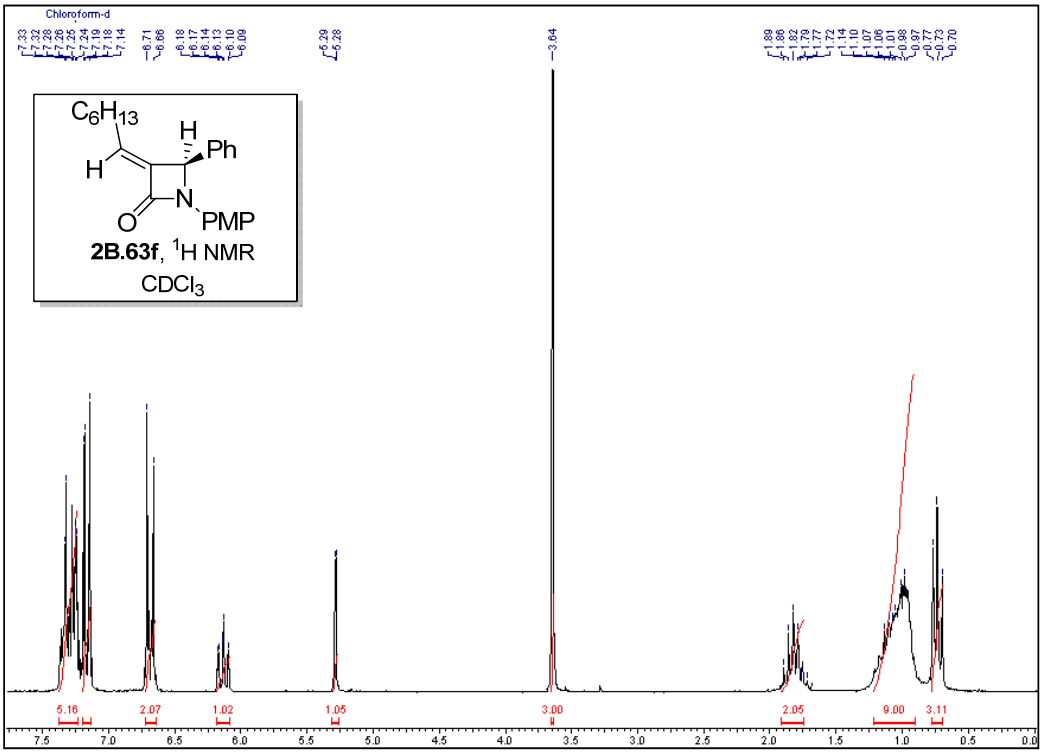

Chloroform-d
H
H
PMP
C6H13
N
O
PMP
2B.65e, 13C NMR,
CDCl3

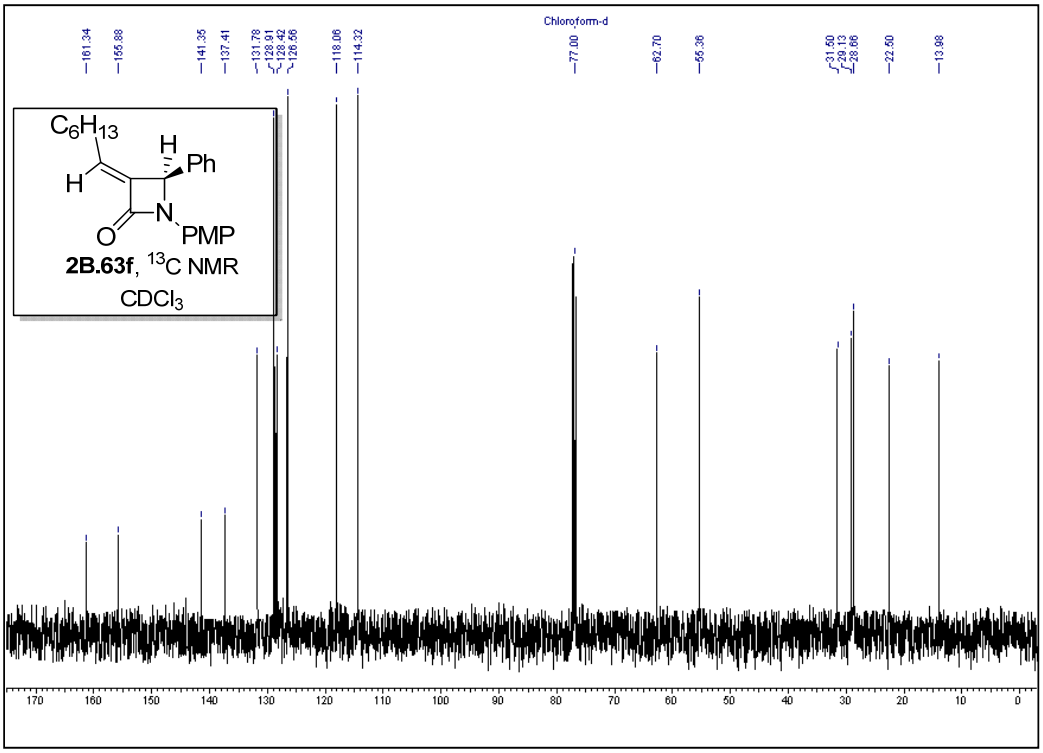

Chloroform-d
OH H
C7H15
Ph
NPMP
O
2B.61f, 1H NMR
CDCl3

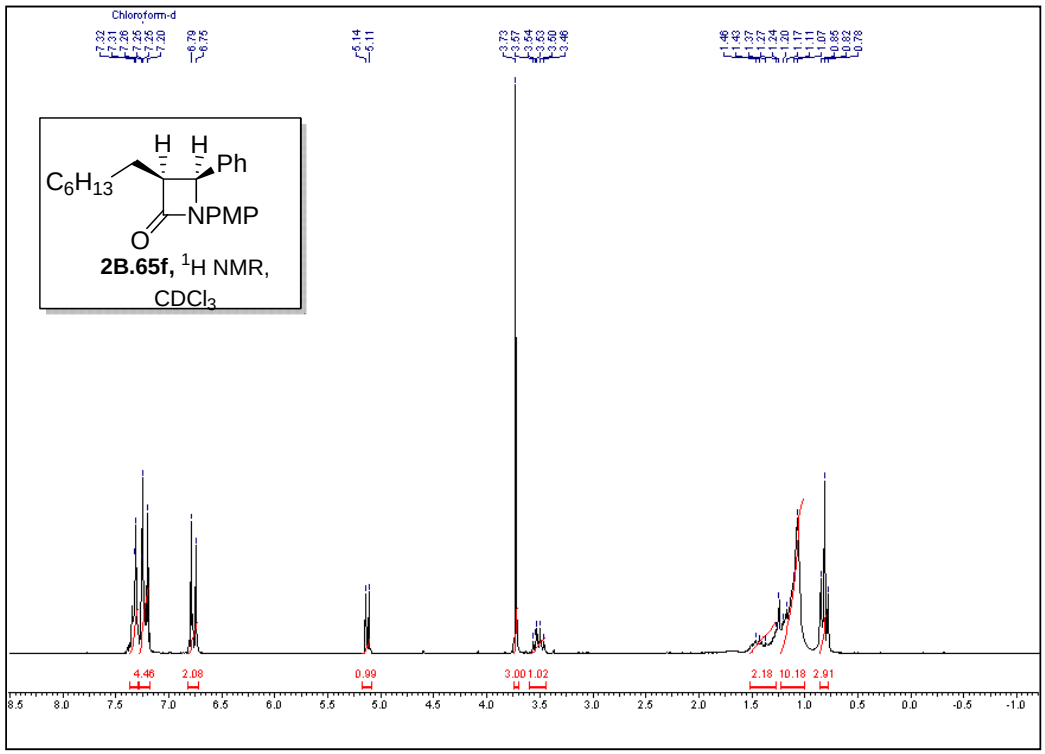

Chloroform-d
OH H
C7H15
Ph
NPMP
O
2B.61f, 13C NMR
CDCl3

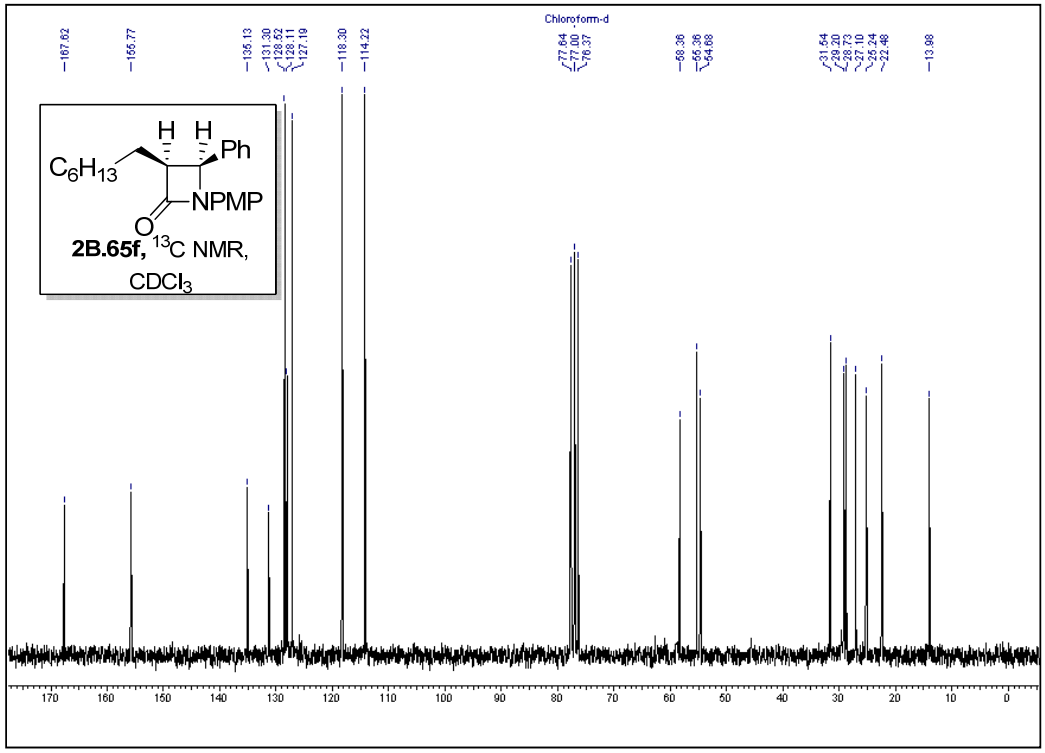

Chloroform-d
7.26
7.25
7.23
7.19
7.18
7.14
6.71
6.69
6.67
6.66
5.48
5.48
5.44
5.40
5.40
5.15
3.84
2.55
2.51
2.47
2.44
2.39
2.36
2.32
1.32
1.21
1.16
0.79
0.76
0.73
H
H
H
Ph
C6H13
NPMP
O
2B.64f, 1H NMR
CDCl3
4.48
2.05
0.92
0.99
2.79
1.96
9.27
2.99
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5


Chloroform-d
161.34
155.88
141.35
137.41
131.78
128.91
128.42
126.66
118.06
114.32
77.00
62.70
55.36
31.50
29.13
28.66
22.50
13.98
H
H
H
Ph
C6H13
NPMP
O
2B.64f, 13C NMR
CDCl3
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0


Chloroform-d
C6H13
H
Ph
H
N
O
PMP
2B.63f, 1H NMR
CDCl3


Chloroform-d
C6H13
H
Ph
H
N
O
PMP
2B.63f, 13C NMR
CDCl3


Chloroform-d
H H
Ph
C6H13
NPMP
O
2B.65f, 1H NMR,
CDCl3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O
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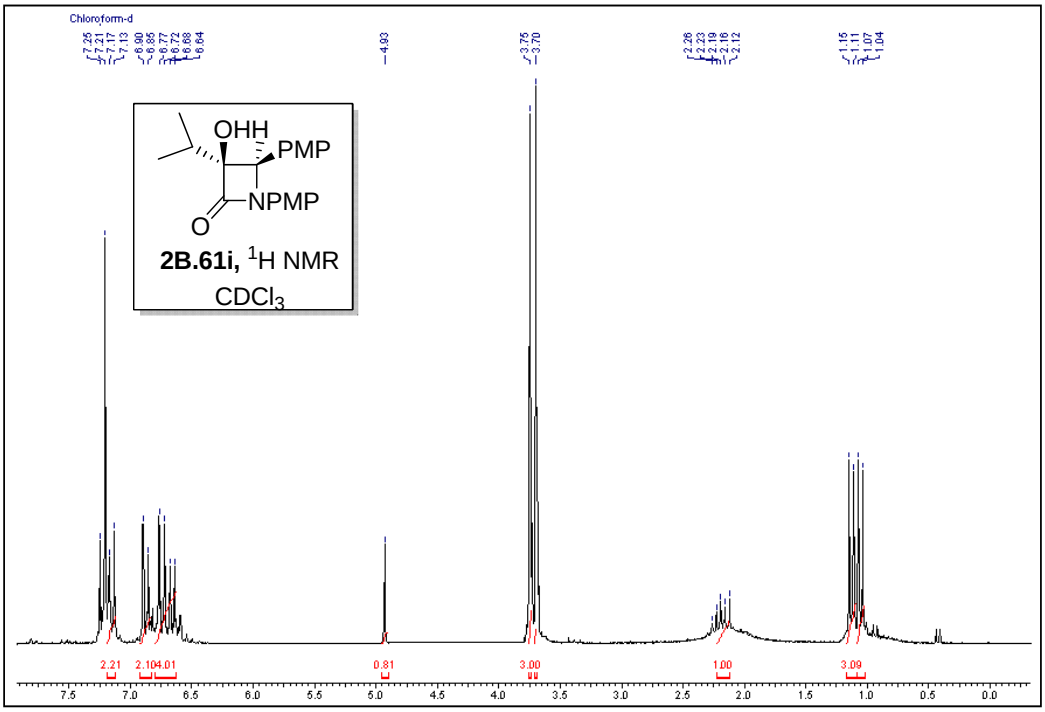
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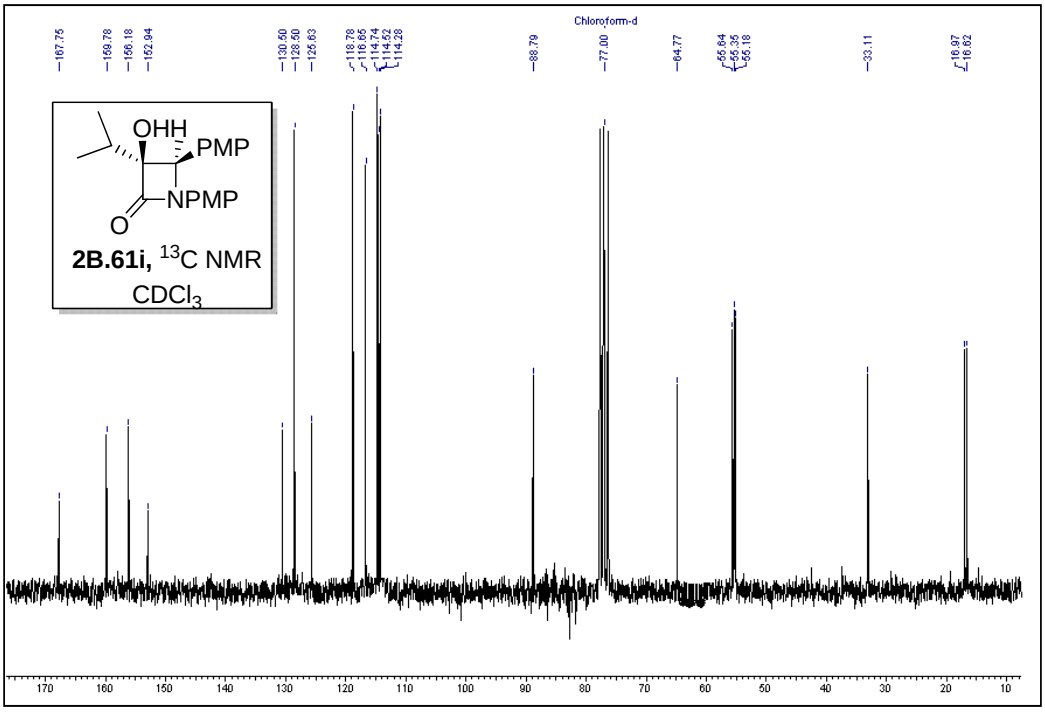
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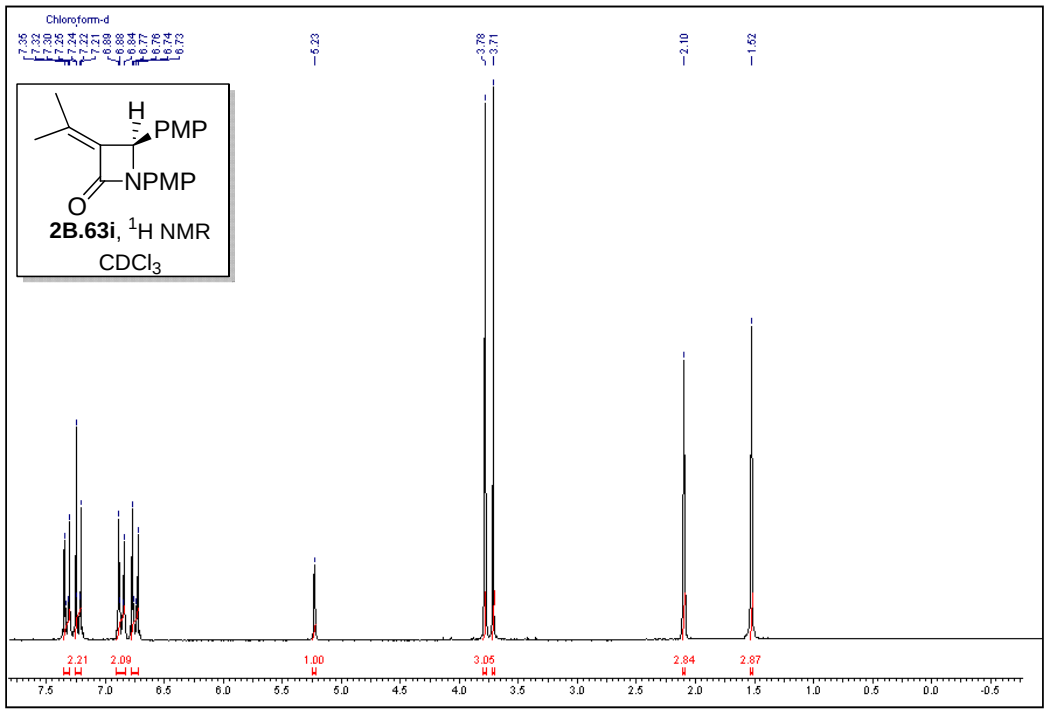
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6.74
6.73
5.23
3.78
3.71
2.10
1.52
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NPMP
O
2B.63i, 1H NMR
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1.00
3.05
2.84
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7.0
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6.0
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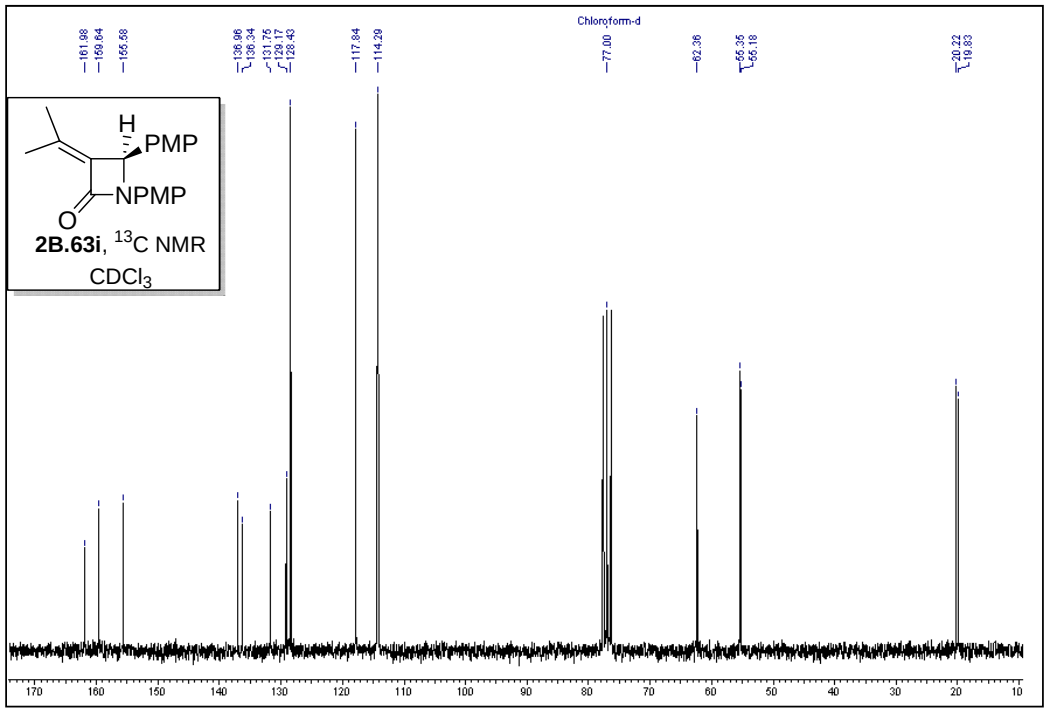
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130.17
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77.00
62.36
55.35
55.18
20.22
19.83
H
PMP
NPMP
O
2B.63i, 13C NMR
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70
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30
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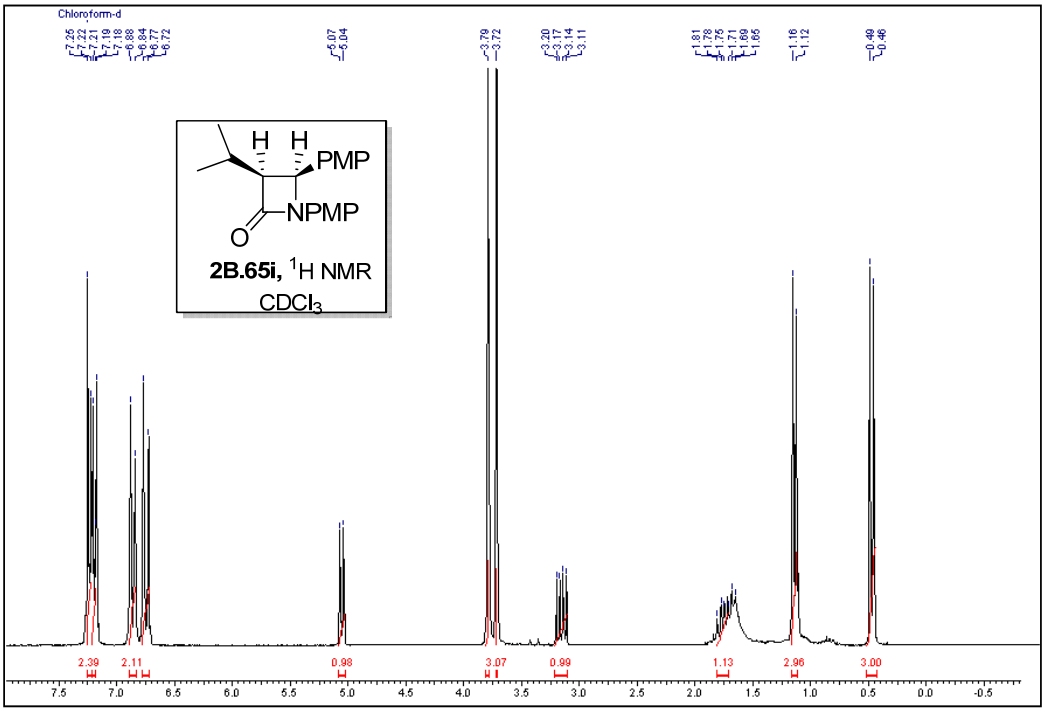
10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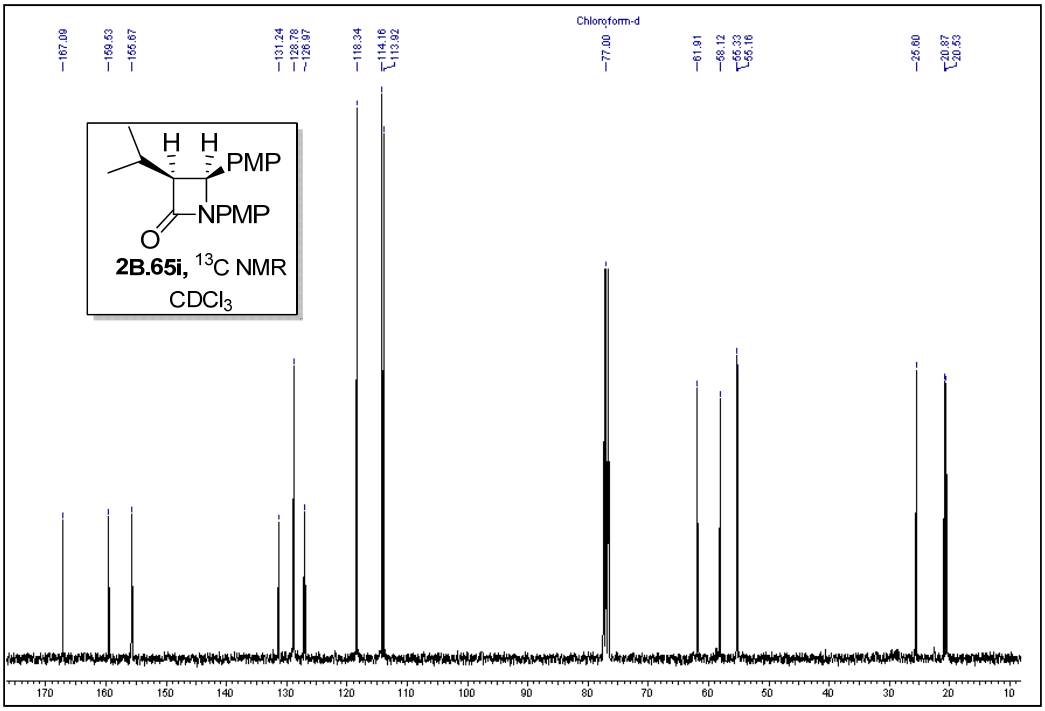
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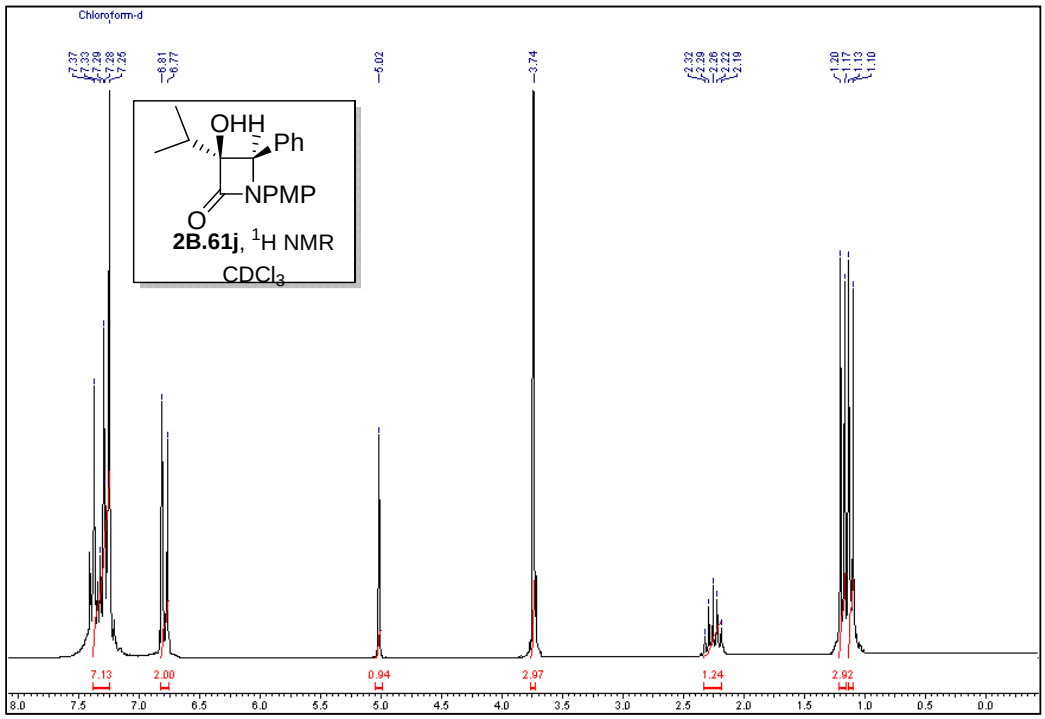
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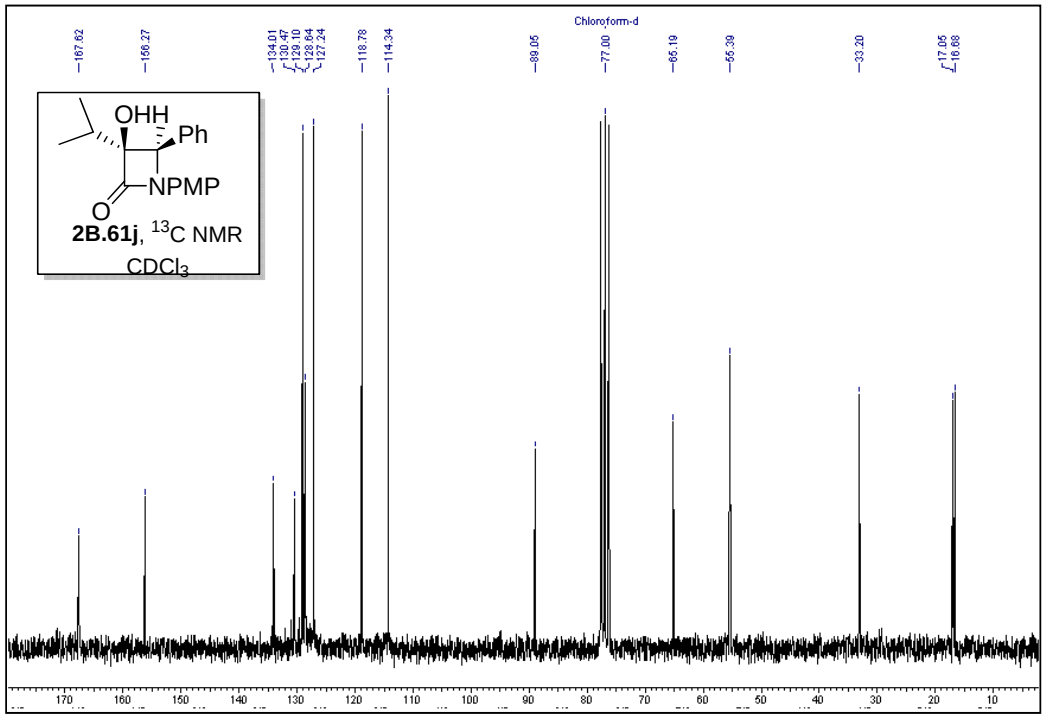
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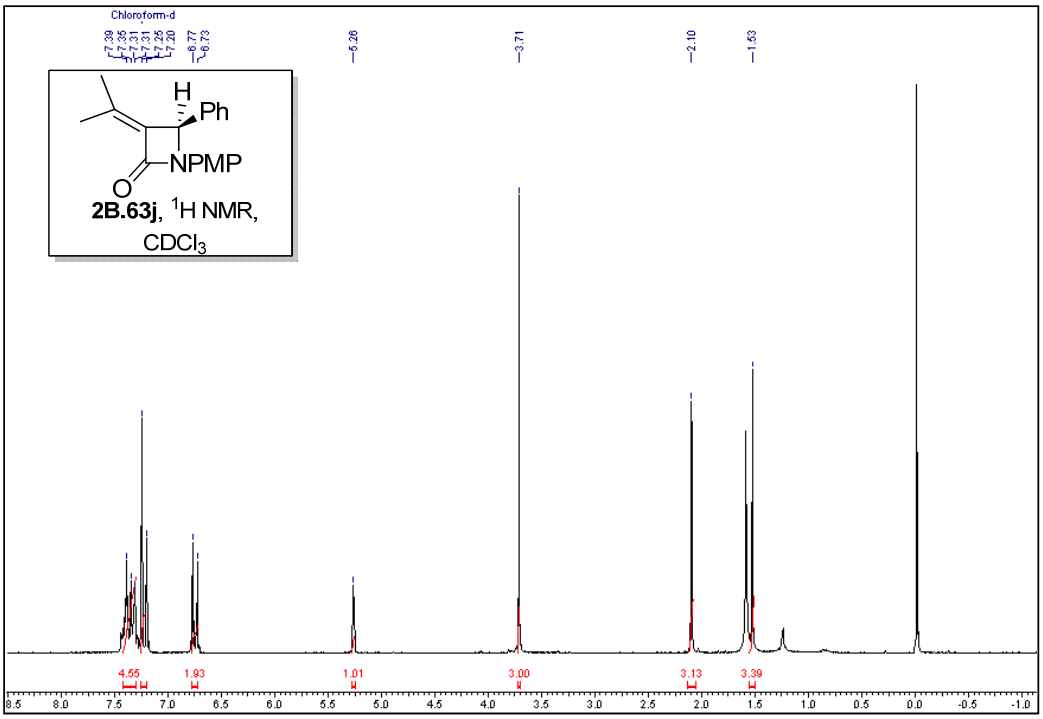
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6.73
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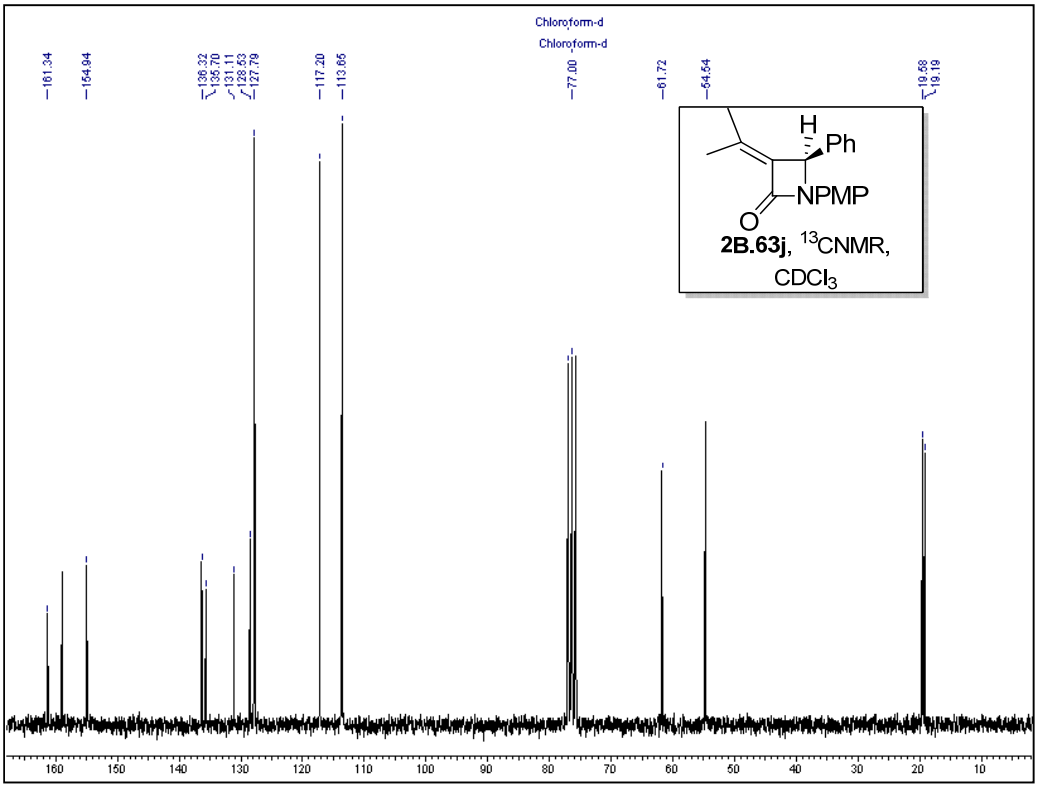
3.39


Chloroform-d
Chloroform-d
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O
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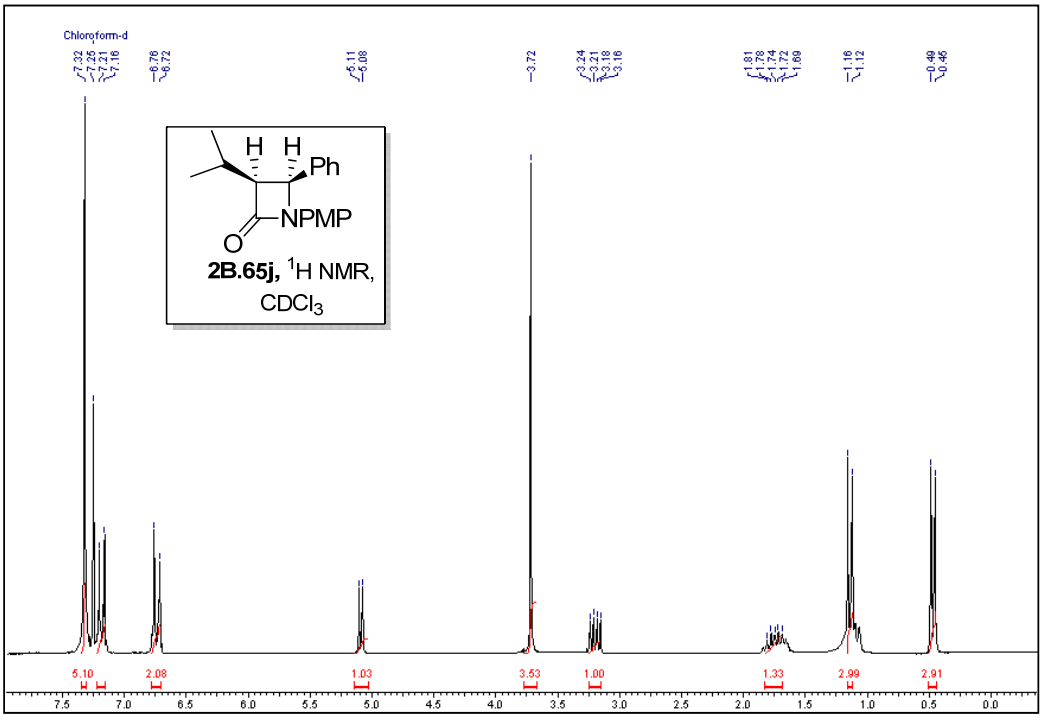
CDCl3


Chloroform-d
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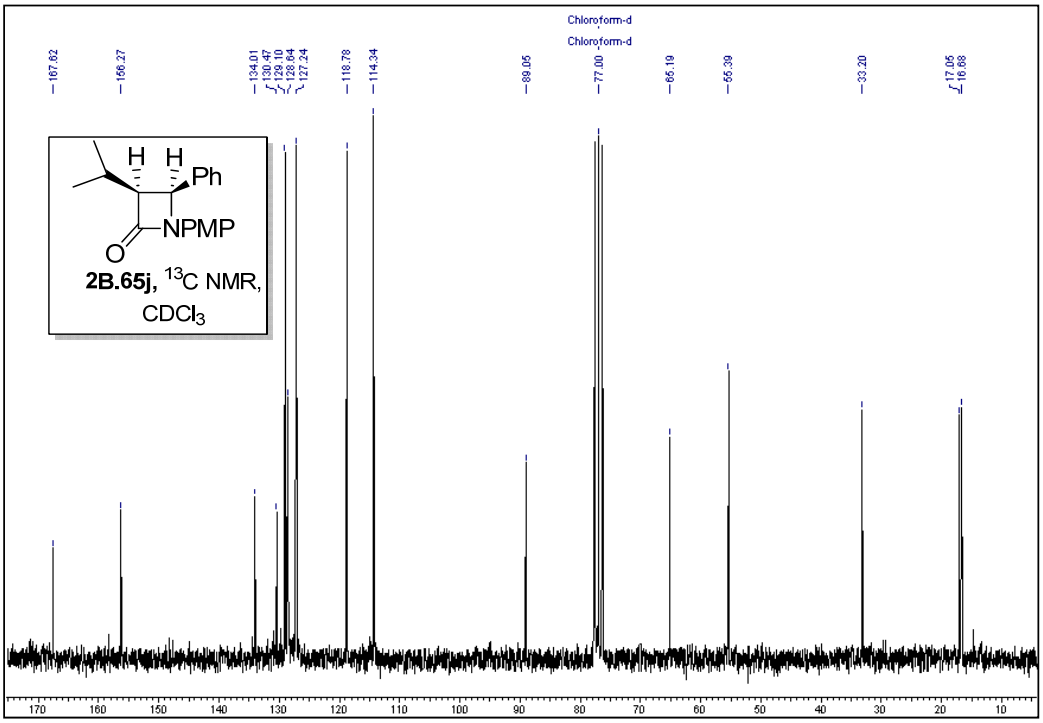
Ph
NPMP
O
2B.65j, ^{1}H NMR, $CDCl_3$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2B.7 References:

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CHAPTER-3
Enantioselective total synthesis of (2*S*,3*R*,4*R*)-*D*-*xylo*-phytosphingosene from substituted azetidin-2-one

This work has been published in *Tetrahedron* Letters **2009**, *50*, 3296-3298.

3.1: Introduction:

Sphingosines, dihydrosphingosines and phytosphingosines (Figure 3.1) constitute a group of related long-chain aliphatic 2- amino-1,3-diols, of which 2-amino-D-*erythro*-4-(*E*)-octadecene-1,3-diol (commonly called sphingosine **3.6**) occurs most frequently in animal glycosphingolipids.[1] Sphingosines are known inhibitors of protein kinase C and are major constituents of glycosphingolipids. This larger family of biomolecules is involved in a plethora of processes related to cell growth, differentiation, adhesion, and neuronal repair.[2]

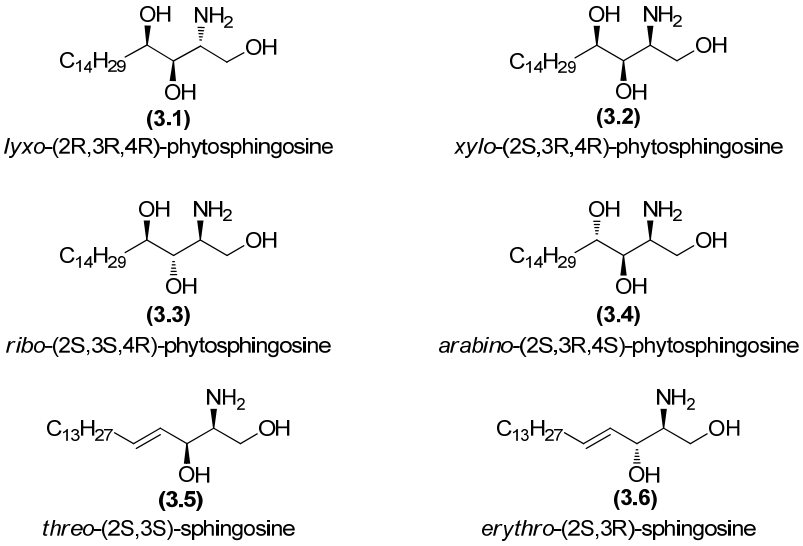
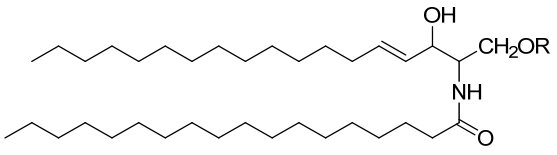


Figure 3.1. *Naturally occurring sphingosines, dihydrosphingosines and phytosphingosines*

Glycosphingolipids carry a hydrophobic ceramide **3.7** moiety and a hydrophilic extracellular oligosaccharide chain that protrudes from the membrane surface.[3,4] The ceramide portion consists of a long chain amino alcohol (sphingoid base) and an amide linked fatty acyl chain, e.g. stearoyl or palmitoyl. The saccharide moiety is represented by a single saccharide unit, as in the case of cerebrosides or di-saccharides as in the case of sulphatides and sometimes as linear or branched oligosaccharide chains as in the case of (iGB_3 or GM_3). The structural variation in fatty acids (*N*-acyl portion), sphingosines and carbohydrates results in a great variety of chemically distinct glycosphingolipids.[1] Glycosphingolipids are found in the cell membranes of all animal and many plant cells where they serve as identifying markers and regulate cellular recognition, growth and development.[5]



R = H, ceramide **(3.7)**
R = Phosphocholine, sphingamyeline **(3.8)**

Figgure 3.2. *Ceramide and sphingamyeline*

They are thought to function by anchoring the hydrophobic ceramide portion (Figure 3.3) in the plasma membrane, exposing the hydrophilic carbohydrate portion to the surrounding exterior which specifies the intended biological function.[6]

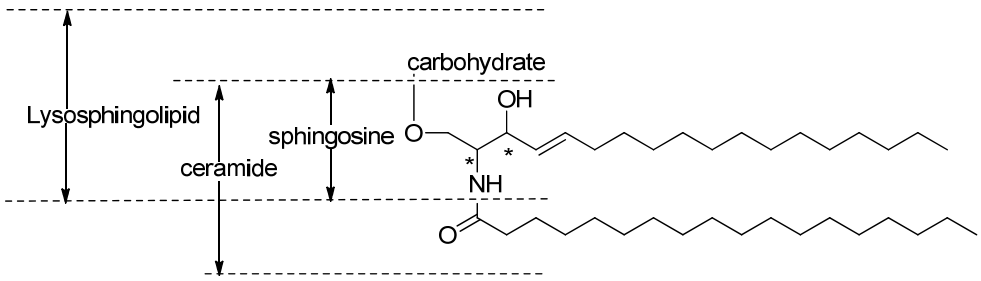


Figure 3.3 *Sphingolipid structure*

These compounds are involved in several biological functions such as (i) HIV binding to galactosyl ceramide receptor sites in cells lacking the principal CD4 cellular receptor,[7] (ii) being unambiguous links between specific sphingolipids and malignant tumors which enable them to be used as 'biological markers' for possible early detection of cancer,[5] and (iii) potent and reversible inhibition of protein kinase C by breakdown products of glycosphingolipids, e.g. sphingosine **3.6** and *lyso*-sphingolipids (Figure 3.3).

Dihydrosphingosine is an intermediate in the biosynthesis of sphingolipids such as ceramides **3.7**, sphengomyelin **3.8**, cerebrosides and gangliosides which play important role in cell regulation and signal transduction.[8] Dihydrosphingosine itself has been found to be an inhibitor of protein kinase C.[9]

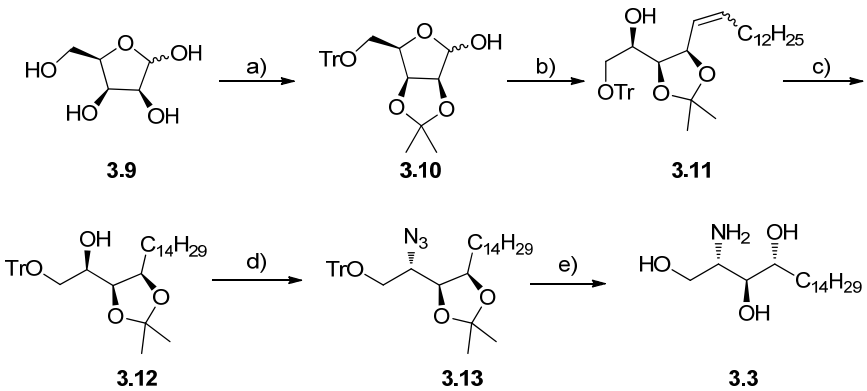
Phytosphingosines **3.1-3.4** (In Figure3.1**)** are characterized by the 2-amino-1,3,4-triol head group and are the most important naturally occurring sphingolipids prevalent in microorganisms, plants and many mammalian tissues such as brain, hair, intestine,[10] uterus,[11] liver,[12] skin,[13] kidney [14] and blood plasma[15]. They are also found

in human kidney cerebrosides and some cancer cell types[16]. They were first isolated from mushrooms in 1911[17] and its structure was elucidated by Oda[18] and Carter *et al*.[19] In addition to being base components of sphingolipids in membranes, phytosphingosines themselves are found to be bioactive lipids. For example, phytosphingosine **3.3** is a potential heat stress signal in yeast cells[20] and some of its derivatives exhibit important physiological activities. For example D-erythro-sphingosine **3.6** shows promising protein kinase inhibitory activity.[3, 21] It has also been established that various diastereomers of sphingosines exhibit different activities and metabolism.[22] which has resulted in an upsurge in amount of research devoted towards synthesis of its various diastereomers.[16, 23-25]

3.2 Background for the present work:

With this stimulating biological background and complicated availability of sphingosines, phytosphingosines and derivatives from natural sources, increasing demand for these compounds for biological testing has attracted a large number of synthetic chemists towards their synthesis.[25] This fact is reflected in a steep rise in the number of publications dealing with the synthesis of sphingosines.[23-25, 26] Phytosphingosines being popular synthetic targets, many synthetic routes have been reported using products of the chiral pool, mainly from carbohydrates and serine derivatives. They are being progressively replaced by asymmetric synthesis, particularly those based on catalytic reactions. A few interesting syntheses of phytosphingosines are described below.

Lin's approach:

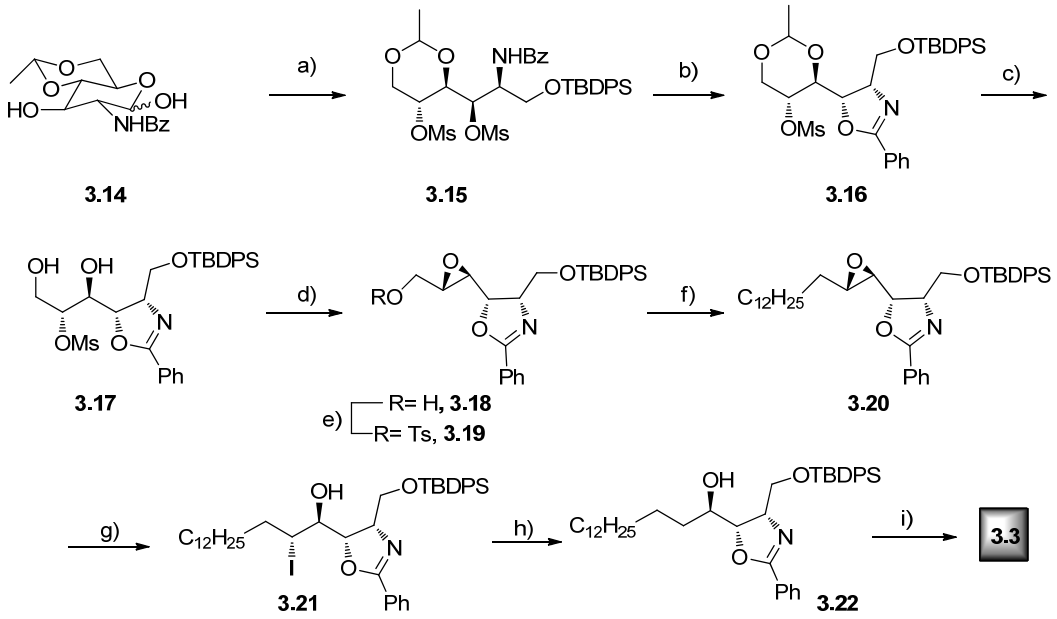


Scheme 3.1. ***Reagents and conditions****: a) i) 2,2-DMP, DMSO; ii) TrCl, py 76%,; b), $C_{13}H_{27}PPh_3Br$, LiHMDS, - 78 °C, 93%; c), $Pd(OH)_2$, H_2, EtOAc , 91% ; d) i) Tf_2O, Py, -60 °C, ii) TMGA, -60 °C, 73% two steps; e) i) HOAc, MeOH, 60 °C, ii) PPh_3, py, H_2O, 70%.*

Lin *et al.*[27] have devised a very short and efficient method for the synthesis of D-*ribo*-phytosphingosine **3.3** by using D-lyxose **3.9** as starting material. This method requires only six steps to give target the molecule in 28% overall yield (Scheme 3.1).

Murakami's approach:

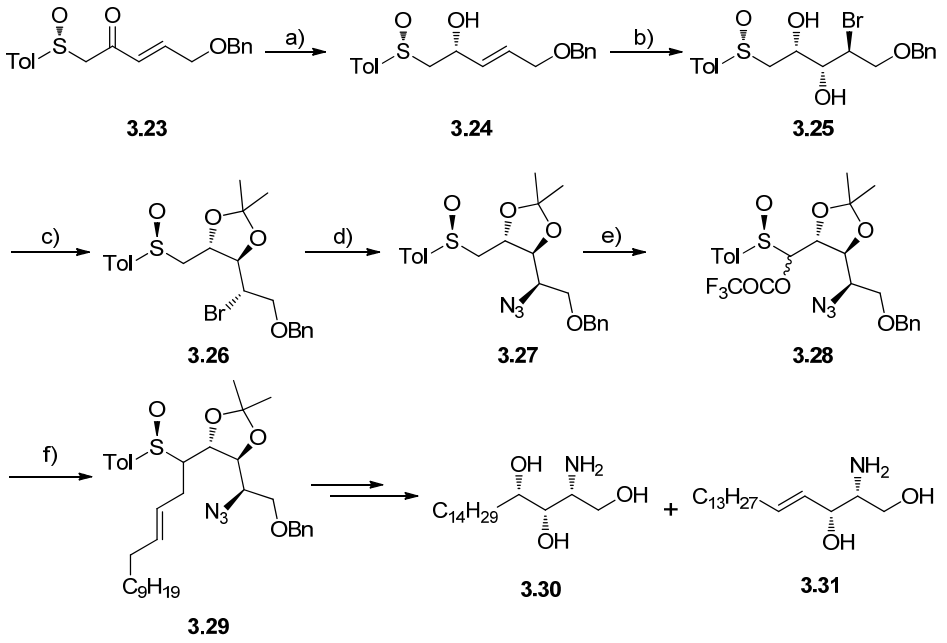
Murakami *et al.* have reported the synthesis of D-*ribo*-phytosphingosine **3.3** starting from D-glucosamine **3.14** [28] in eight steps (28.6% overall yield).



Scheme 3.2. ***Reagents and conditions:*** *a) i) $NaBH_4$, i-PrOH, H_2O, 0 °C, 1 h, 95%, ii) t-$BuPh_2Si$-Cl, pyridine, CH_2Cl_2, rt, 24 h then MsCl, Et_3N, CH_2Cl_2, 0 °C, 2 h; b) Pyridine, Et_3N, toluene, 110 °C, 24 h, 90%; c) $TiCl_4$, PhSH, CH_2Cl_2, 0 °C, 2 h, 83%; d) K_2CO_3, MeOH, 0 °C, 2 h; e) p-TsCl, DMAP, Et_3N, CH_2Cl_2, 0°C, 2 h, 88%, f) $C_{12}H_{25}MgBr$, CuBr, THF, -30 °C to 0 °C, 4 h, 84%. g) NaI, Me_3SiCl, H_2O, CH_3CN, 0 °C to 10 °C, 2 h; h) n-Bu_3SnH, AIBN, $PhCH_3$, 60 °C, 30 min, 88% i) i) 4N HCl, THF, rt, 24 h, ii) aq. NaOH, rt, iii) aq. NaOH, EtOH, 95 °C, 12 h, iv) Ac_2O, Et_3N, DMAP, CH_2Cl_2, 75%.*

Raghavan's approach:

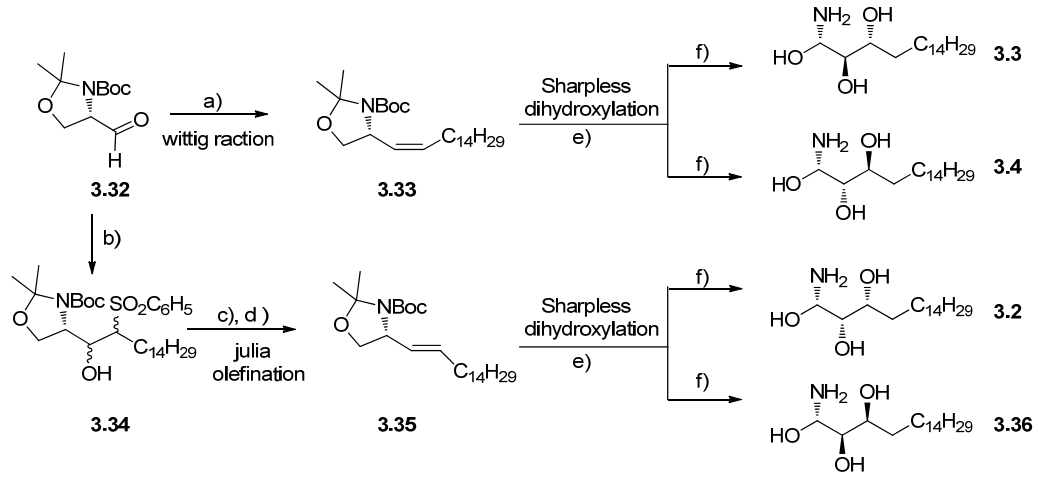
Stereoselective synthesis of *xylo*-(2*R*,3*S*,4*S*)-phytosphingosine and *threo*-(2*R*,3*R*)-C_{18}-sphingosine have been achieved[29] from the *β*-hydroxy-γ,δ-unsaturated sulfoxide **3.23** in nine steps with 17.8% overall yield.



Scheme 3.3. ***Reagents and conditions****: a) DIBAL-H, THF, -78 °C, 91 %; b) NBS, H_2O, toluene, rt, 88%; c) 2,2-DMP, acetone, CSA (cat) rt 86%); d) NaN_3, DMSO, 85 °C; e) TFA:H_2O, CH_2Cl_2, 0 °C; f) $C_{13}H_{26}$, $SnCl_4$, 0 °C, 65 %.*

Berova's approach:

A very short and general synthesis of the four diastereomeric phytosphingosines have been reported[30] from commercially available Garner's aldehyde **(3.32)** in excellent 25.2 overall yield.

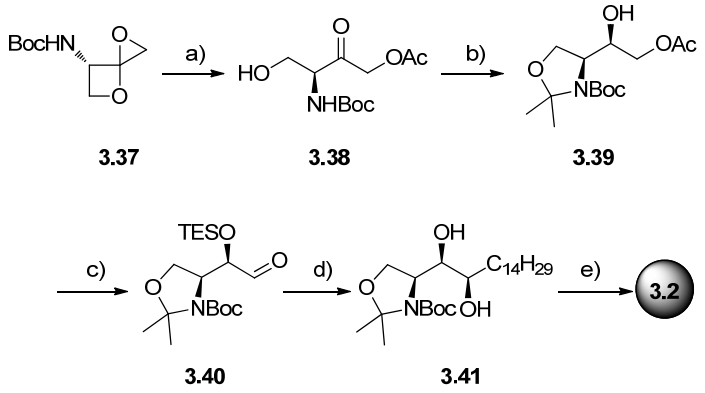


Shceme 3.4. ***Reogenrs and Conditions****: a) $[Ph_3PCH(CH_2)_{13}CH_3]^+Br^-$,n-BuLi, THF. -75 °C, 60%; b) $CH_3(CH_2)_{14}SO_2C_6H_5$. n-BuLi, THF, -75 °C, 67%; c) Ac_2O. pyridine, CH_2Cl_2, rt; d) Na(Hg), $NaHPO_4$,*

MeOH, -20 °C, 85% two steps; e) AD-mix-α or β, methanesulfonamide, t-BuOH-H_2O = 1:1, rt, 82-96%; f) TFA-H_2O=20:1, rt, 80-90 %.

Howell's aprpraoch:

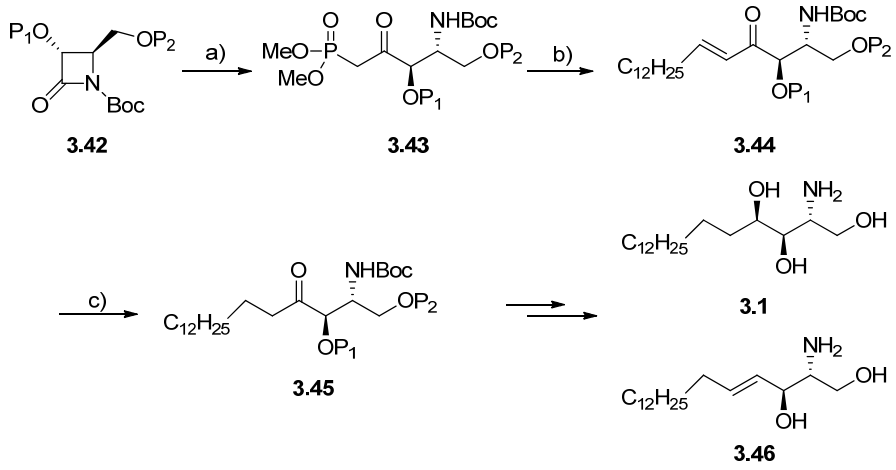
1,5-Dioxaspiro[3.2] hexanes **3.37** has been used[31] as a template for the synthesis of D-*xylo*-phytosphingosine and in 5 steps.[32].



Scheme 3.5. ***Reagents and conditions:*** *a) AcOH, CH_2Cl_2, rt, 96%; b) i) 2,2-DMP, CSA, CH_2Cl_2, 88% ii) $NaBH_4$, CH_2Cl_2 88%; c) i)TESOTf, py, CH_2Cl_2, 98%, ii) NaOMe, MeOH iii) Swern oxidation, 83%, d) i) $C_{14}H_{29}MgCl$, THF, ii)TBAF,THF,71 % over two steps.*

Pak's approach:

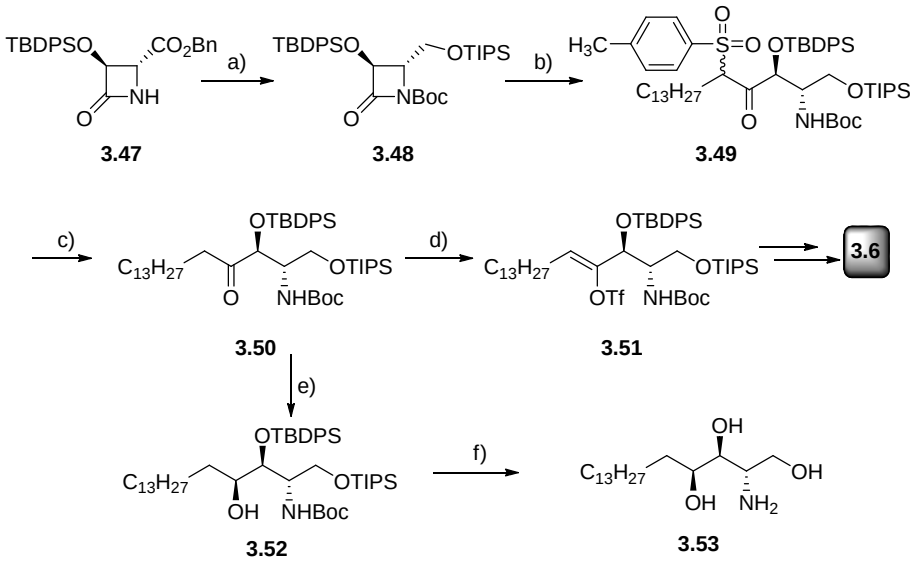
A formal synthesis of L-*erythro*-sphingosine **3.46** and D-*lyxo*-phytosphingosine **3.1** (Scheme 3.6) have been reported[33] using *β*-lactam **3.42** as a starting material.



Scheme 3.6. ***Reagents and conditions:*** *a) $CH_3P(O)OMe_2$ (2 equiv.), n-BuLi (2 equiv.), THF, - 78 °C; b) $CH_3(CH_2)_{11}CHO$, K_2CO_3, EtOH; c) H_2, 10% Pd/C, EtOAc.*

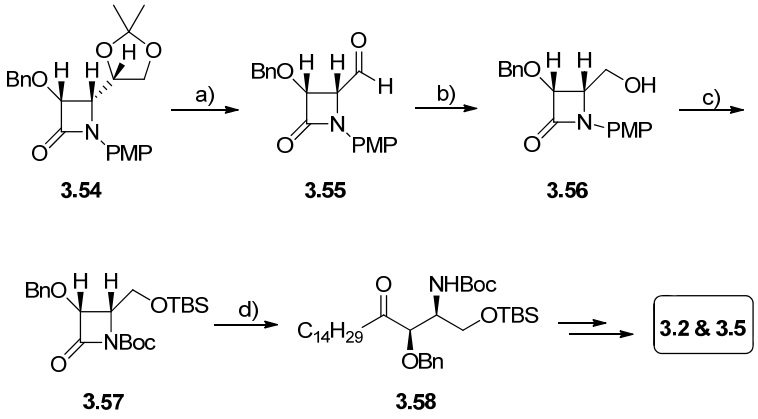
Shiozaki's approach:

Syntheses of ceramides and L-*lyxo*-phytosphingosine **3.51** and *erythro* (*2S,3R*)-sphingosine **3.6** have been accomplished from chiral *β*-lactam **3.47**, obtained from D-(−) tartaric acid,[34] in seven steps with 45% overall yield.



Scheme 3.7. ***Reagents and conditions*****:** *a) i) $NaBH_4$, EtOH, rt, 1 h, 73%; ii) TIPSCl, imidazole, DMF, rt 4h; iii) $(Boc)_2O$, Et_3N, DMAP, CH_2Cl_2, quantitative; b) n-$C_{13}H_{27}CH_2SO_2C_6H_4Me$, n-BuLi, -78 °C, THF, 1h 86%; c) lithium naphthalenide, THF, -78 °C, 20 min, 93%; d) $KN(SiM_3)_2$, THF, -78 °C, 1 h then $PhN(Tf)_2$, THF, -20 °C, 20 min, 99%; e) $LiEt_3BH$, THF, -78 °C; f) i) TBAF, THF, rt.; ii) 10% HCl, MeOH, rt; 82%.*

Deshmukh's approach:



Scheme 3.8. ***Reagents and conditions:*** *a) i) PTSA, H_2O, THF, reflux 24 h, 90%; ii), $NaIO_4$, acetone-H_2O, rt, 1 h, 92%; b) $NaBH_4$, MeOH, rt, 8h, 80%; c) i) CAN, CH_3CN-H_2O, rt 4h, 73%; ii) TBDMS-Cl,*

imidazole, DMF, 3 h, 82%; iii) $(Boc)_2O$, DMAP, DCM, rt, 5 h, 92%; d)$C_{14}H_{29}MgBr$, THF, -78 °C-40 °C, 1 h, 67 %.

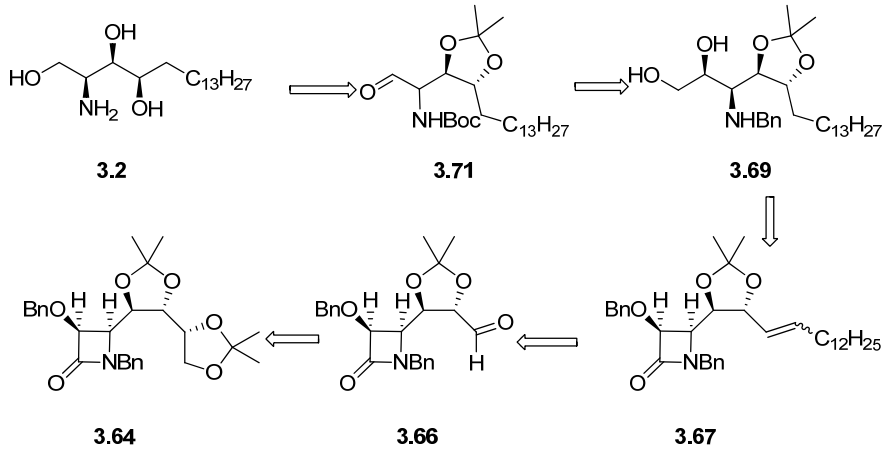
A stereoselective formal synthesis of *xylo*-(*2S,3R,4R*)-phytosphingosine **3.2** and *threo*-*2S,3R*)-sphingosine **3.5** have been achieved by Deshmukh's group[35] , starting from enantiopure 4-formyl-substituted *β*-lactam **3.54,** in seven steps.

3.3: Present work:

Sphingosines being popular synthetic targets, many synthetic routs have been reported. However, strategies originating using *β*-lactams as synthons are limited[33,34,35] While all above described strategies, represent attractive approach, the installation of the tetradecyl chain has not been easy and has often produced a mixture of different products.[36] Therefore, it was felt necessary to develop another route which introduces the long tetradecyl chain in sphingosines before the opening of the *β* -lactam ring. Toward this end, we have devised a synthetic route for D-*xylo*-phytosphingosine (**Scheme 3.9**), starting from *β*-lactam **3.64** derived from D-mannitol triacetonide.[37]

3.4 Retrosynthetic analysis:

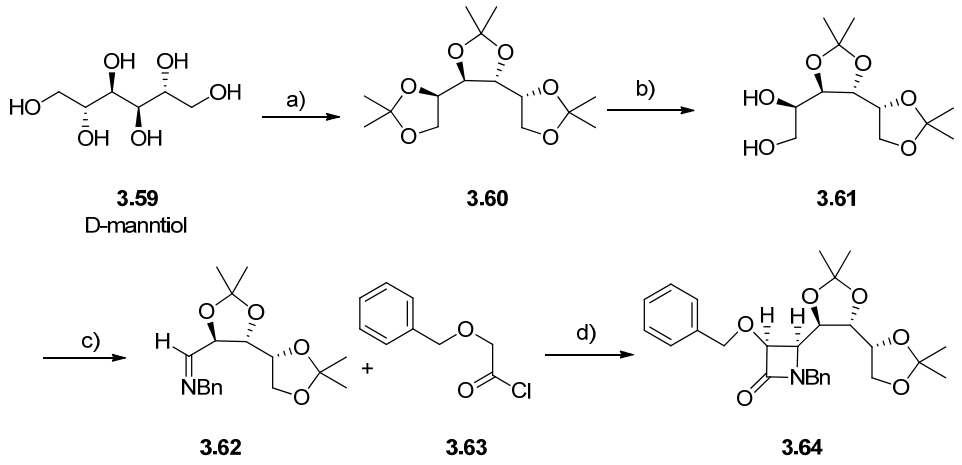
With our interest in utilizing *β*-lactam ring as a synthon for accessing biologically active compounds, it was visualized that the D-*xylo*-phytosphingosine could easily be accessed from **3.71** which in turn can come from vicinal diol **3.69**. The **3.69** can be synthesized from *β*-lactam **3.67,** derived from **3.64**.



Scheme 3.9. *Our Retrosynthetic strategy*

3.5 Results and discussion:

The synthesis of D-*xylo*-phytosphingosine commenced from the known optically pure, *cis* α-benzyloxy β-lactam **3.66**, easily synthesized in 70% yield from D-mannitol **3.59** using the reported protocol [37]**.** D-manntiol was converted to **3.60** by treating with *2,2*-dimethoxy-proapne in the presence of catalytic amount of *p*-TSA. Selective deprotection of one of the acetonide moiety of **3.60** using catalytic amount of *p*-TSA in methanol at room temperature furnished **3.61.** The oxidative cleavage of **3.61** by sodium periodate gave an aldehyde which on condensation with benzyl amine in the presence of $MgSO_4$ and molecular sieves ($4A^o$) yielded imine **3.62** in 90% yield. Imine **3.62** was subjected to Staudinger [2+2]-cycloadditon reaction with a ketene, generated *in situ* from benzyloxy acetyl chloride in the presence of triethyl amine, which gave lactam **3.64** in 70 % yield, (Scheme 3.10).

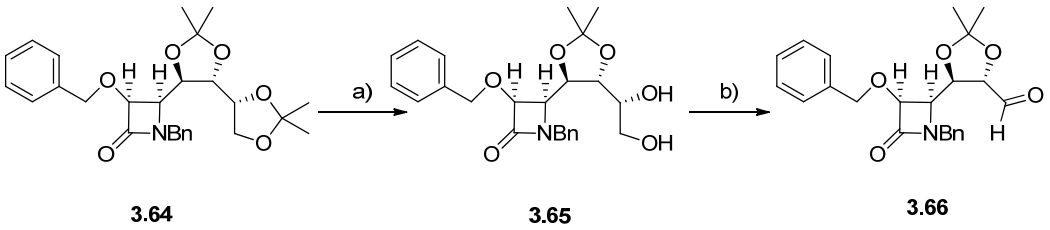


Scheme 3.10. ***Reagents and conditions:*** *a) 2,2-DMP, (cat) pTSA, acetone, rt, 36 h, 90%; b) (cat) pTSA, MeOH, rt, 30 min, 85%; c) i) $NaIO_4$, DCM:H_2O (4:1), 0 °C, 1 h, 87%; ii) Benzyl amine, $MgSO_4$, MS (4A°), DCM, 6 h, 90%; d) Et_3N, dry DCM, -20 °C to rt, 18 h, 70%.*

The IR spectrum of **3.64** showed a characteristic absorption band of β-lactam carbonyl at 1741 cm^{-1}. In ^1H NMR spectrum H_3 appeared at δ 4.65 as a doublet (J = 4.99 MHz) and H4 at δ 3.6 (dd, J= 5.1 Hz). Based on the coupling constant, it is suggested that both H_3 and H_4 are *cis* to each other. In the ^{13}C NMR spectrum C_3 and C_4 carbon of β-lactam ring appeared at δ 65.5 and δ 57.7, respectively and signals observed at δ 109.3 and 110.1 are assigned to quaternary carbon of acetonides.

The selective deprotection of one of the terminal acetonide group of **3.64** using acetic acid and water (3:1) at room temperature gave **3.65** in 90%. The sodium

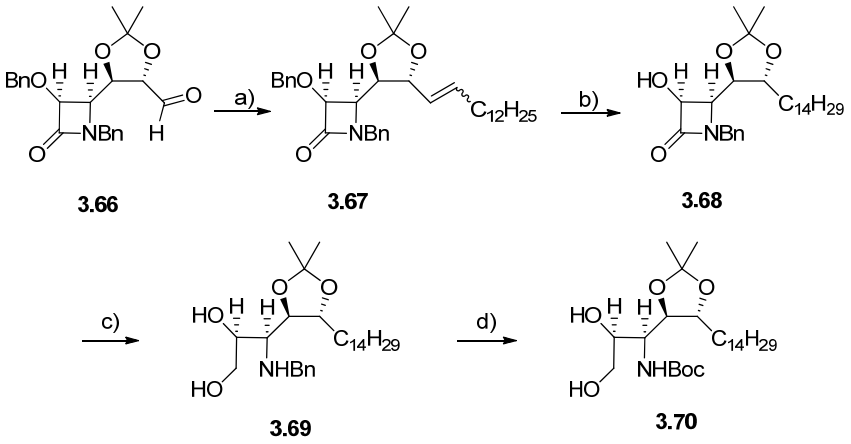
periodate mediated cleavage of **3.65** afforded corresponding aldehyde **3.66** in 75% yield which was used as such for next step without any purification (Scheme 3.11).



3.64 **3.65** **3.66**

Scheme 3.11. ***Reagents and conditions:*** *a) Acetic acid, H_2O, (4:1), rt, 8 h, 90%; b) $NaIO_4$, MeOH, H_2O, rt,30 min, 75%.*

Wittig olefination of **3.66** with a freshly prepared 13-carbon ylide at 0 °C produced **3.67** in 70% yield as a inseparable *cis, trans* (55:45) mixture. The distereomeric ratio was determined on the basis of ^{1}H NMR spectra of crude **3.67**. The geometrical isomeric ratio was of no relevance to the planned synthetic sequence as the double bond was to be reduced in the immediate next step. Accordingly, **3.67** was reduced using ammonium formate and Pd/C 10% in methanol and obtained **3.68** in 80% yield. The reaction, as expected proceeded with concomitant deprotection of the benzyl group. The IR spectrum of **3.68** showed a characteristic hydroxyl absorption band at 3331 cm^{-1} and the ^{1}H NMR showed 29 protons in aliphatic region indicating the presence of tetradecyl alkyl chain.



3.66 **3.67** **3.68**

3.69 **3.70**

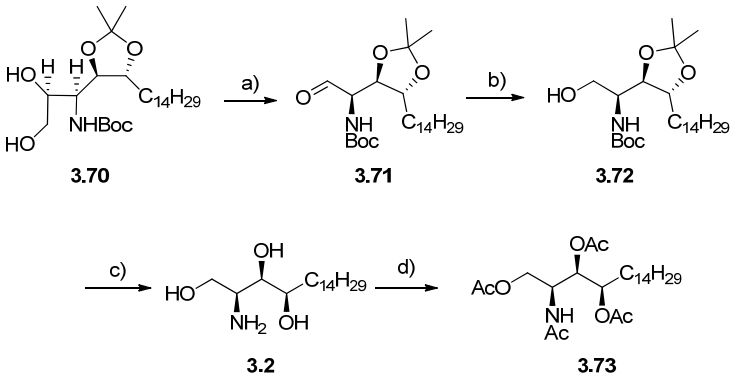
Scheme 3.12. ***Reagents and conditions****: a) $PPh_3BrC_{13}H_{27}$, n-BuLi, dry THF, 0 °C, 1 h, 70%; b) $HCOONH_4$, Pd/C (10%), MeOH, reflux, 4 h; 80%; (c) LAH, dry THF, reflux, 4 h, 93%; (d) H_2, Pd/C (10%), MeOH, $(Boc)_2O$, rt 10 h, 93%.*

Treatment of **3.68** with lithium aluminium hydride in THF under reflux conditions yielded **3.69**. The IR spectrum of **3.69** showed absence of β-lactam

carbonyl. The ^{1}H NMR spectrum displayed a multiplet at δ 3.61-3.64 integrating for one proton, corresponding to H3. The same proton had appeared as a doublet in **3.68** before reduction**.** The absence of carbonyl carbon in ^{13}C NMR spectrum confirmed the success of the above reaction. The ESI mass spectrum of this compound confirmed the structure of **3.69** with a base peak at m/z 478 (M+1).

N-Debenzylation of **3.69** by catalytic hydrogenation (Pd/C 10%) at atmospheric pressure of hydrogen followed by *N*-Boc protection in the same pot gave **3.70** in 93% yield. The IR spectrum of compound **3.70** showed Boc carbonyl absorption at 1695 cm^{-1}. The ^{1}H NMR spectrum of **3.70** displayed a sharp singlet at δ 1.44 integrating for nine protons, confirming the presence of Boc group in the product. The presence of Boc carbonyl carbon at δ 156.2 in ^{13}C NMR spectrum confirmed the above transformation.

The oxidative cleavage of **3.70** using sodium periodate in ethanol/water (1:1) gave desired aldehyde **(3.71)** in more than 89% yield. Subsequent reduction of **3.71** with sodium borohydride in methanol gave **3.72** in quantitative yield.



Scheme 3.13. ***Reagents and conditions****: (a) $NaIO_4$, EtOH:H_2O (1:1) rt, 30 min, 89%; (b) $NaBH_4$, dry. MeOH, 0 °C to rt, 10 h; 92%; (c) TFA/H_2O (20:1), DCM, 0 °C, 3 h; (d) Ac_2O, dry Py, DMAP (cat) 91%.*

In order to obtain the target molecule, our next job remained the deprotection of acetonide and Boc group of **3.72** which was easily effected using a mixture of TFA/H_2O and obtained D-(*2S,3R,4R*)-2-amino-1,3,4 trihydroxyoctadecane (**3.2**). This compound was subsequently acetylated using Ac_2O, pyridine and catalytic amount of DMAP to give **3.73** in diastereomerically pure form $\mathbf{[\alpha]_D^{27}}$**:** + 6.5 (c = 0.86, $CHCl_3$); {lit$\mathbf{[\alpha]_D^{27}}$**:** + 6.3 (c = 0.86, $CHCl_3$)}.[31] The IR spectrum of **3.73** exhibited

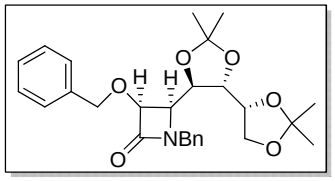
absorption band for amine at 3306 cm-^{1}, acetyl carbonyl at 1746 cm^{-1} and amide carbonyl 1667 cm^{-1}, respectively. The ^{1}H NMR displayed acetyl methyl protons at δ 2.00 (singlet, one methyl), 2.04 (singlet, two methyl) and 2.07 (singlet, one methyl), the chiral H, at 4.01 (multiplet, one proton), 4.51 (multiplet, one proton), 5.03 (doublet of doublet, *J*= 12.7, 6.8 Hz, one proton), 5.14 (doublet of doublet, *J* = 6.6, 4.3 Hz, one proton) and the amide proton at δ 5.77 (doublet with *J* = 9.5 Hz). The ^{13}C NMR spectrum displayed chiral carbons at δ 47.94, 62.90, and 71.90, respectively, whereas acetyl carbonyl appeared at δ 169.85, 170.13, and 170.56. The EIMS gave [M+1] peak at m/z 486. Spectral data and specific rotation were in good agreement with reported values.[31]

3.6 Conclusion:

In conclusion, we have established a short method for enantioselective total synthesis of (*2S,3R,4R*)-*D-xylo*-phytosphingosine starting from *β*-lactam derived from D-mannitol triacetonide in seven steps with 36% over all yield.

3.7 Experimental:

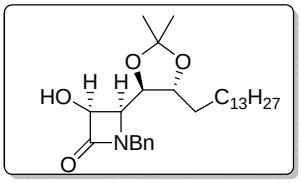
General procedure for the synthesis of (*3S,4R*)-1-benzyl-*3*-(benzyloxy)-*4*-(*4S,4′R,5R*)-2,2,2′,2′-tetramethyl-*4,4′*-bis(*1,3*-dioxolan)-5-yl)-azetidin-2-one (3.64):



A solution consisting of benzyloxy acetyl chloride (5.6 mL, 38 mmol) in dry dichloromethane (100 mL) was added dropwise to a stirred solution containing imine (9.6 g, 30 mmol) in dry triethyl amine (10.58 mL, 76 mmol) in dichloromethane (200 mL) at -20 °C. The reaction mixture was stirred overnight at room temperature, washed with saturated sodium bicarbonate solution (100 mL), brine (100 mL), dried and evaporated to give crude product which was purified by column chromatography over silicagel in 20% ethyl-acetate/petroleum ether gave white solid compound **3.64** in 65% yield.

65% Yield; **$[\alpha]_D^{27}$:** +12.5 (c= 1.2, $CHCl_3$)**:M.P.** 115 °C, IR, 3054, 2950, 1741, 1598, 1480, cm^{-1}; **^{1}H NMR ($CDCl_3$, 200 MHz):** δ = 1.21 (s, 3H), 1.28 (s, 3H), 1.37 (S, 6H), 3.69 (dd, *J* = 5.1, 6.8 Hz, 1H), 3.8 (m, 1H), 4.04 (d, *J* = 7.10 Hz, 1H), 4.10 (m, 3H), 4.15 (d, *J* = 14.8 Hz, 1H), 4.65 (d, *J* = 4.99 Hz, 1H), 4.70 (d, *J* = 11.4 Hz, 1H), 4.92, (d, *J* = 14.9 Hz, 1H), 4.98, (d, *J* = 11.4 Hz, 1H), 7.19-7.37 (m, 10H). **^{13}C NMR ($CDCl_3$, 50MHz):** δ = 25.22, 26.11, 27.00, 27.42, 45.02, 57.71, 65.53, 73.08, 75.60, 78.29, 79.13, 80.85, 109.30, 110.08, 127.66, 128.08, 128.19, 128.35, 128.45, 128.64, 135.52, 136.80, 167.44. **MS**: *m/z* = 468 (M+1). **Anal. Calcd**. For $C_{27}H_{33}NO_6$: C, 69.36; H, 7.11; N, 2.99. Found: C, 69.32, H, 7.15; N, 3.12.

General procedure for the synthesis of (*3S,4S*)-1-benzyl-4-((*4R,5R*)-2,2-dimethyl-5-tetradecyl-1,3-dioxolan-4-yl)-3-hydroxyazetidin-2-one (3.68) from aldehydes (3.68):



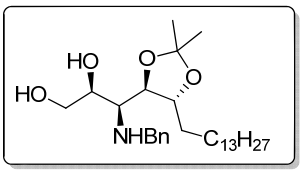
To a solution of *n*-tridecyl triphenyl phosphonium bromide (3.65 g, 6.9 mmol) in anhydrous THF (50 mL) at 0 °C, was added 2.0 M solution of *n*-butyl lithium (2.76 mL, 5.52 mmol).Solution colour changed from yellow to orange red was. The reaction mixture was stirred at this temperature for 45 min. A

solution of azetidin-2-one **3.66** (2.3 g, 5.8 mmol) in anhydrous THF (25 mL) was added dropwise at 0 °C to the reaction mixture and allowed to warm to room temperature. The reaction mixture was quenched with saturated solution of ammonium chloride (10 mL). Solvent was removed under reduced pressure and the residue was dissolved in ethyl acetate (20 mL), washed with water (15 mL), and with brine (15 mL) to afford the alkenes as an inseparable mixture of cis/trans isomers (55:44) isomers as confirmed by NMR spectrum. Compound **3.67** was filtered through a pad of silica gel to remove excess triphenylphosphine and it was used as such for the next step without further purification and characterization.

Compound **3.67** (2.5g, 4.5 mmol) was dissolved in anhydrous MeOH (15 mL) and to this mixture ammonium formate (2.82 g, 45 mmol) and Pd-C/10% was added. The reaction mixture was refluxed for 3-4 hrs. It was cooled to room temperature and passed through a pad of celite to give yellow oil as crude product. The crude product was purified by column chromatography with 15% ethylacetate-petroleum ether using 100-200 mesh silica gel to give the desired product as a white solid.

70% yield; **M.P**. 132 °C, $[\alpha]_D^{27}$: = + 18.5 (c =1.2, $CHCl_3$); **IR (ν_{max}, $CHCl_3$):** 1735, 3331 cm^{-1}; **^{1}H NMR ($CDCl_3$, 400MHz):** δ = 0.87 (t, *J* = 6.1 Hz, 3H), 1.24 (bs, 24 H) 1.37 (s, 3H), 1.40 (s, 3H), 1.42-1.63 (m, 2H), 3.63 (dd, *J* = 3.10, 4.65 Hz, 1H), 3.71-3.89 (m, 2H), 4.05 (d, *J* = 15.0 Hz, 1 H), 4.85-4.87 (m, 1H), 4.96 (d, *J* = 15.2 Hz, 1H), 7.19-7.34 (m, 5H). **^{13}C NMR ($CDCl_3$, 75MHz):** δ = 14.06, 22.65, 25.79, 27.32, 27.71, 29.32, 29.47, 29.42, 29.62, 28.62, 28.66, 31.89, 32.89, 45.44, 58.20, 78.85, 109.56, 109.56, 127.92, 128.32, 128.83, 134.99, 169.92. **MS**: *m/z* = 474 (M+1). **Anal. Calcd**. For $C_{29}H_{47}NO_4$: C, 73.53; H, 10.00; N, 2.96. Found: C, 75.42, H, 9.91; N, 3.12.

General procedure for the synthesis of (*2S,3S*)-3-(benzylamino)-3-((*4R,5R*)-2,2-dimethyl-5-tetradecyl-1,3 dioxolan-4-yl)propane-1,2-diol (3.69):

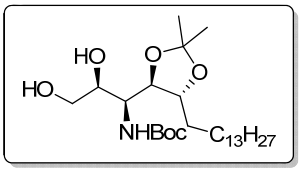


A solution of **3.68** (5 g, mmol) in dry THF (30 mL) was slowly added to a solution of lithium aluminum hydride (1.2 g, 31 mmol) in THF (100 mL) at 0 °C with stirring. The mixture was stirred at this temperature for 10 min, and further refluxed for 8 hrs. Excess LAH was decomposed by addition of aqueous

sodium sulfate to give white precipitate which was filtered off through sintered funnel. After filtration, the organic layer was dried over anhydrous Na_2SO_4 and was removed under reduced pressure to give pale yellow liquid. This was purified by column chromatography with 30% acetone-petroleum ether using 100-200 mesh silica gel. 70% yield; colourless oil.

$[\alpha]_D^{27}$: +7.8 (c = 1.5, $CHCl_3$)**: IR (ν_{max}, $CHCl_3$):** 1458, 3416 $cm.^{-1}$ **^{1}H NMR ($CDCl_3$, 400 MHz):** δ = 0.81 (t, *J* = 6.7 Hz, 3H), 1.19 (bs, 24 H) 1.35 (s, 3H), 1.39 (s, 3H), 1.43-1.48 (m, 2H), 2.74 (dd, *J* = 2.81, 5.1 Hz, 1H), 3.61-3.64 (m, 1H), 3.69 (dd, *J* = 3.70, 11.61 Hz, 2H), 3.73-3.76 (m, 2H), 3.84 (d, *J* = 13.68 Hz, 1H), 3.91 (d, *J* = 13.68 Hz, 1 H), 7.26-7.35 (m, 5H). **^{13}C NMR ($CDCl_3$, 75 MHz):** δ = 14.13, 22.70, 27.19, 27.40, 29.37, 29.61, 29.70, 31.93, 32.99, 53.91, 57.85, 63.63, 70.78, 78.19, 81.07, 108.47, 127.45, 128.35, 128.62, 139.70. **MS:** *m/z* = 478 (M+1). **Anal. Calcd**. For $C_{29}H_{51}NO_4$: C, 72.91; H, 10.76; N, 2.93. Found: C, 72.87, H, 10.91; N, 3.01.

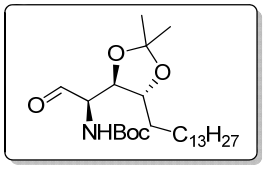
General procedure for the synthesis of *tert*-butyl-(*1S,2S*)-1-((*4R,5R*)-2,2-dimethyl-5-tetradecyl-1,3-dioxolan-4-yl)-2,3- dihydroxypropylcarbamate (3.70):



To a mixture of **3.69** (477 mg, 1 mmol) and 10% Pd/C (40 mg) was added methanol (6 mL) and di-*tert*-butyldicarbonate (0.24 mL, 1.0 mmol). The mixture was stirred at room temperature under an atmosphere of H_2 for 12 h. The resulting mixture was filtered through celite and the filtrate was concentrated. The residue was purified by flash chromatography on silica gel (eluent: ethyl acetate: petroleum ether = 20:80) to provide **3.70** (436 mg, 91%) as colourless liquid.

$[\alpha]_D^{27}$: +20.99 (c = 1.5, $CHCl_3$)**; IR (ν_{max}, $CHCl_3$):** 1695, 1712, 3441 $cm.^{-1}$ **^{1}H NMR ($CDCl_3$, 400 MHz):** δ = 0.86 (t, *J* = 5.9 Hz, 3H), 1.24 (bs, 24 H) 1.39 (s, 6H), 1.44 (s, 9H), 1.52-1.57 (m, 2H), 3.42 (dd, *J* = 7.4, 11.9 Hz, 1H), 3.63 (dd, *J* = 5.6 ,11.6, 1H), 3.75-3.86 (m, 3H), 3.91-3.93 (m, 1H), 5.12 (d, *J* = 10.2 Hz, 1H) **^{13}C NMR ($CDCl_3$, 75 MHz):** δ = 14.10, 22.67, 25.97, 26.80, 27.33, 28.25, 29.34, 29.47, 29.64, 29.68, 31.91, 32.35, 48.77, 62.38, 74.53, 76.74, 80.41, 82.83, 109.13, 157.05. **MS:** *m/z* = 488 (M+1). **Anal. Calcd**. For $C_{27}H_{53}NO_6$: C, 66.49; H, 10.95; N, 2.87. Found: C, 66.51, H, 10.90; N, 2.98.

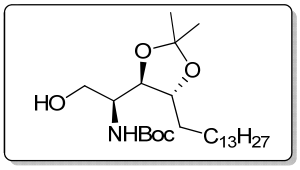
General procedure for the synthesis of *tert*-butyl-(*R*)-1-((*4R,5R*)-2,2-dimethyl-5-tetradecyl-1,3-dioxolan-4-yl)-2-oxoethylcarbamate (3.71):



Diol **3.70** (0.09 g, 0.184 mmol) was taken in a round-bottom flask and dissolved in 2 mL of a 1/1 mixture of EtOH/H_2O. $NaIO_4$ (0.039g, 0.184 mmol) was added portion wise and the reaction mixture was stirred for 2 h at room temperature. The white precipitate formed was filtered through sintered funnel. Ethanol was removed under reduced pressure and residue was extracted by dichloromethane (2×10 mL). The organic layer was dried over anhydrous sodium sulphate and solvent was removed to afford aldehyde **3.71** as colourless liquid in 89% yield.

$[\alpha]_D^{27}$: -0.34 (c = 1.5, $CHCl_3$), **IR (ν_{max}, $CHCl_3$):** 1710, 1722, 3450 $cm.^{-1}$ **^{1}H NMR ($CDCl_3$, 400 MHz):** δ = 0.86 (t, *J* = 5.8 Hz, 3H), 1.24 (bs, 24H) 1.36 (s, 6H), 1.45 (s, 9H), 1.57-1.64 (m, 2H), 3.78 (m, 1H), 4.14 (d, *J* = 8.3 Hz, 1H), 4.33 (d, *J* = 8.8 Hz, 1H), 5.28 (d, *J* = 8.8 Hz, 1H), 9.62 (s, 1 H). **^{13}C NMR ($CDCl_3$, 75 MHz):** δ = 14.10, 22.67, 26.03, 26.62, 27.21, 28.23, 29.34, 29.94, 29.57, 31.91, 32.38, 59.23, 80.49, 109.07, 155.93, 198.47. **MS:** *m/z* = 456 (M+1). **Anal. Calcd**. For $C_{26}H_{49}NO_5$: C, 68.53; H, 10.84; N, 3.07. Found: C, 68.51; H, 10.88; N, 2.99.

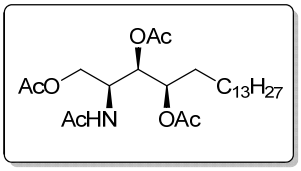
General procedure for the synthesis of *tert*-butyl-(S)-1-((*4R,5R*)-2,2-dimethyl-5-tetradecyl-1,3-dioxolan-4-yl)-2- hydroxyethylcarbamate (3.72):



To a cooled solution of aldehydes **3.71** (0.065 g, 0.143 mmol) in methanol (2 mL) at 0 °C was added $NaBH_4$ (0.011 g, 0.283 mmol) portion wise under argon atmosphere. The mixture was allowed to warm up to room temperature and stirred for 8 h. After completion of reaction (TLC), water (2 mL) was added carefully and the reaction mixture was further stirred for 1 h. Methanol was removed under reduced pressure and the residue was extracted with ethyl acetate (2 x 5 mL). The combined organic layer was washed with brine (15 mL) and dried over anhydrous Na_2SO_4. Removal of the solvent under reduced pressure gave crude product, which was purified by column chromatography using ethyl-acetate/petroleum ether (20:80) to afford alcohol **3.72** (0.064 g, 95%) as a colorless oil. 95% yield; colorless oil;

$[\alpha]_D^{27}$: + 15.53 (c = 1.5, $CHCl_3$); **IR (ν_{max}, $CHCl_3$):** 1705, 1720, 3446 $cm.^{-1}$ **^{1}H NMR ($CDCl_3$, 400 MHz):** δ = 0.86 (t, *J* = 6.8 Hz, 3H), 1.28 (bs, 24H) 1.38 (s, 6H), 1.44 (s, 9H), 1.54-1.64 (m, 2H), 3.68-3.78 (m, 5H), 5.12 (d, *J* = 8.5 Hz, 1H). **^{13}C NMR ($CDCl_3$, 75 MHz):** δ = 14.09, 22.67, 26.09, 26.78, 27.35, 28.32, 29.34, 29.51, 29.63, 29.66, 31.91, 32.44, 50.19, 65.36, 77.57, 81.82, 108.73, 156.73. **MS:** *m/z* = 458 (M+1). **Anal. Calcd**. For $C_{26}H_{49}NO_5$: C, 68.53; H, 10.84; N, 3.07. Found: C, 68.51; H, 10.88; N, 2.99.

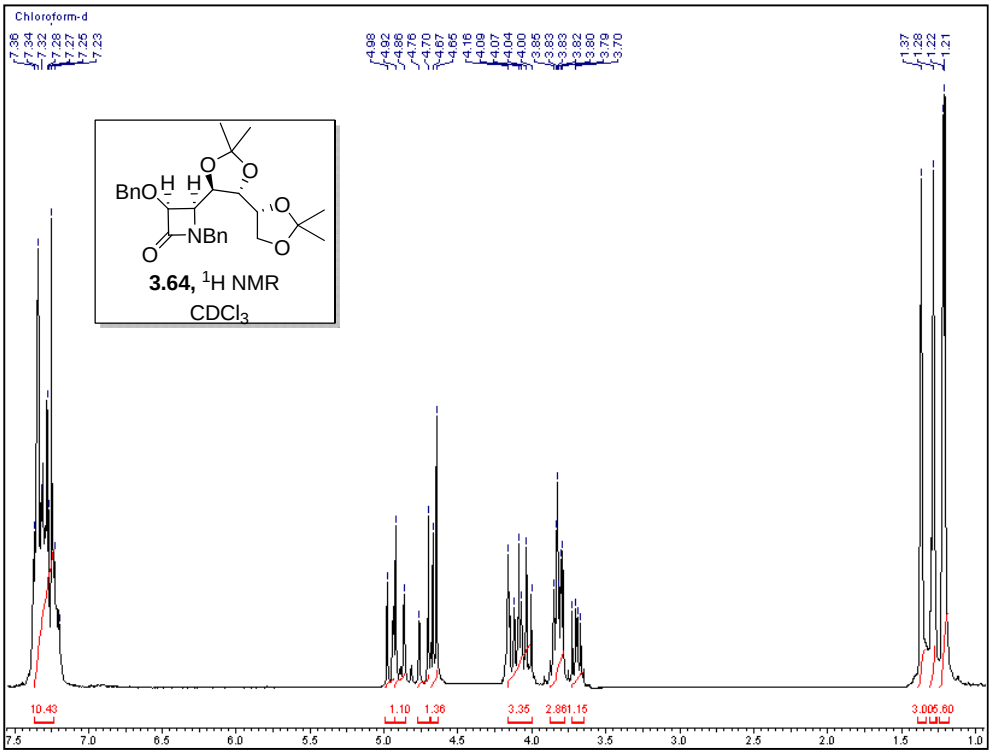
General procedure for the synthesis of (*2S,3R,4R*)-2-acetamido-1,3,4-triacetoxyoctadecane, (3.73):



To the protected amino alcohol (40 mg, 0.087 mmol) in DCM (0.4 mL), a 20:1 solution of TFA/H_2O (0.16 mL) was added and stirred at 0 °C for 3 h. The solvent was evaporated under reduced pressure and then azeotroped with benzene. The amino triol **3.2** was directly taken ahead to the next step without further purification. Pyridine (0.9 mL) and acetic anhydride (0.1 mL) were added to the reaction mixture. The resulting mixture was stirred overnight at rt, concentrated and the residue was chromatographed on silica gel using 30% EtOAc and petroleum ether.

M.p: 44–46 °C; **$[\alpha]_D^{27}$:** + 6.5 (c = 0.86, $CHCl_3$); **IR ($CHCl_3$)** 3306, 1746, 1663, 1372, 1226, 1046, 954 cm^{-1}, **^{1}H NMR (500 MHz, $CDCl_3$)** δ 5.77 (d, *J* = 9.5 Hz, 1H), 5.14 (dd, *J* = 6.6, 4.3 Hz, 1H), 5.03 (dd, *J* = 12.7, 6.8 Hz, 1H), 4.51 (m, 1H), 4.01 (m, 2H), 2.08 (s, 3H), 2.05 (s, 3H), 2.04 (s, 3H), 2.00 (s, 3H) 152–1.60 (m, 2H), 1.22 (bs, 24H), 0.86 (t, J = 6.4 Hz, 3H), **^{13}C NMR (75 MHz, $CDCl_3$):** 14.1, 20.6, 20.7, 23.2, 24.8, 29.2, 29.3, 29.7, 30.5, 31.9, 47.9, 62.9, 71.9, 72.2, 169.8, 170.1, 170.6. **MS** (m/z): 486 (M+1).

3.8 Spectra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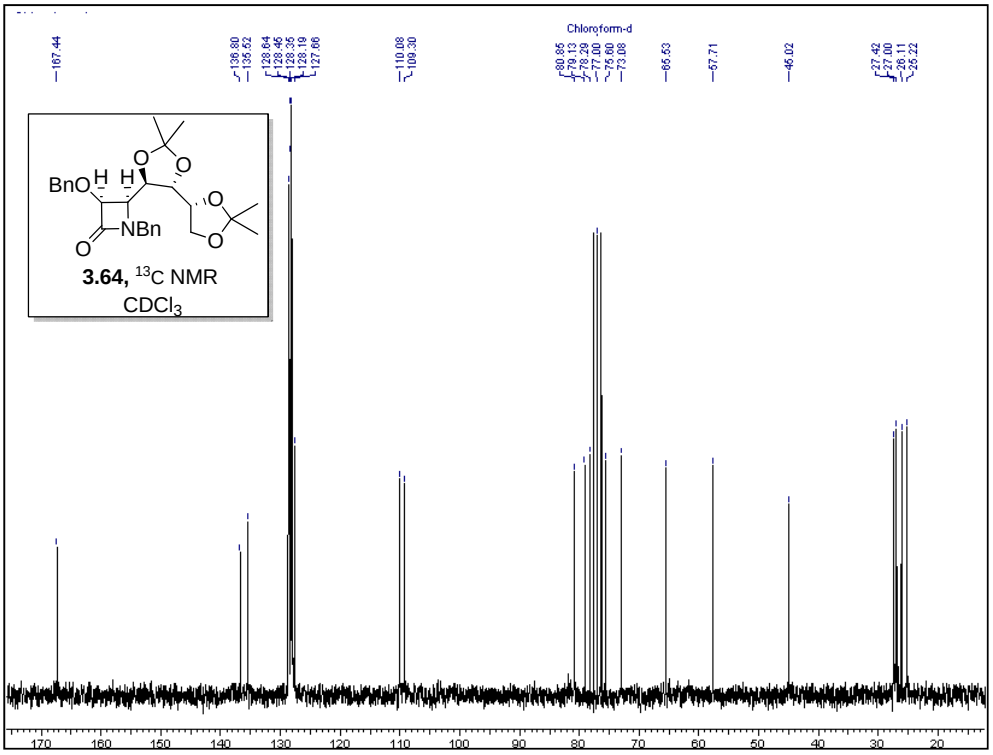
H
H
O
O
O
O
NBn
O
3.64, 1H NMR
CDCl3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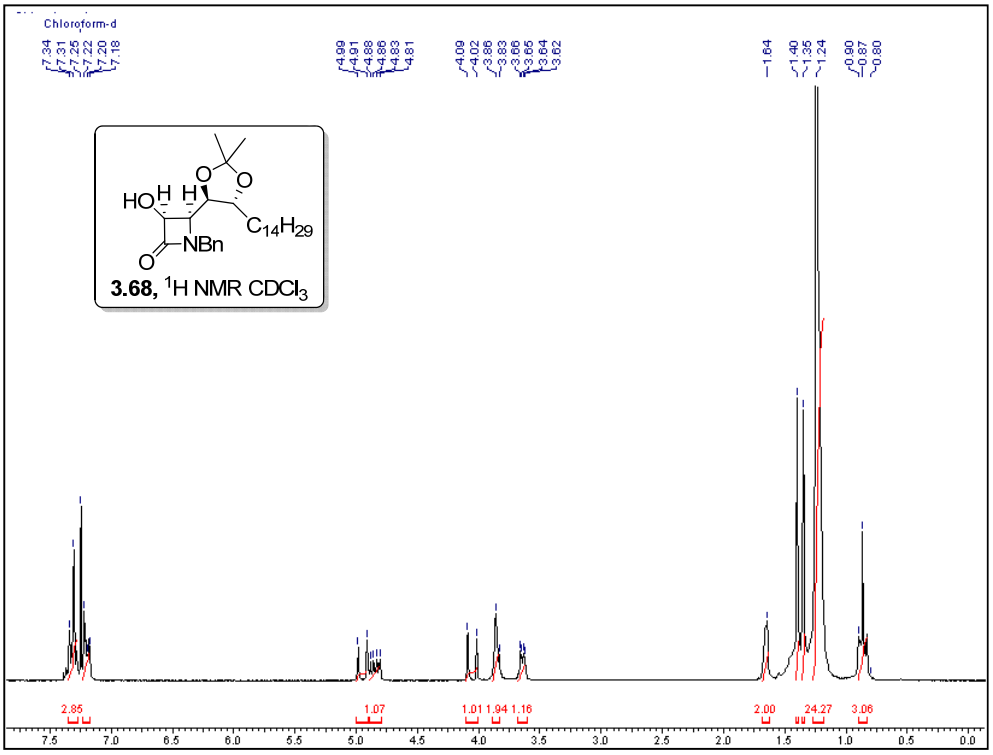
H
O
O
O
O
NBn
O
3.64, 13C NMR
CDCl3


Chloroform-d
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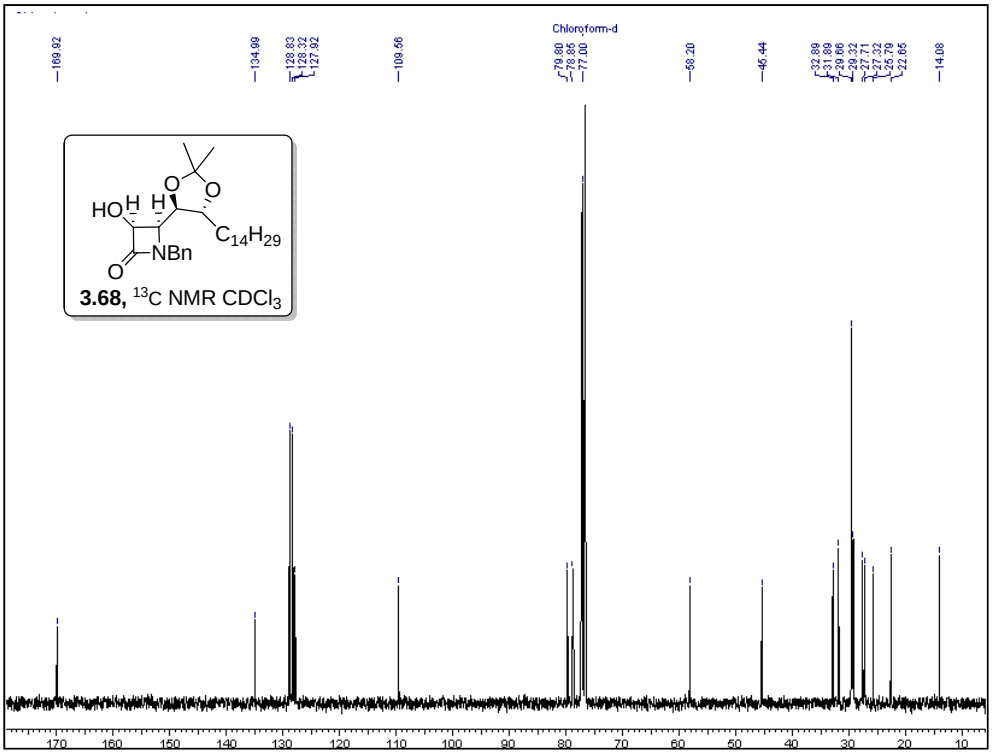
7.31
7.25
7.22
7.20
7.18
4.99
4.91
4.88
4.86
4.83
4.81
4.09
4.02
3.86
3.83
3.66
3.65
3.64
3.62
1.64
1.40
1.35
1.24
0.90
0.87
0.80
HO
H
H
O
O
C14H29
NBn
O
3.68, 1H NMR CDCl3
2.85
1.07
1.01
1.94
1.16
2.00
24.27
3.06
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0


Chloroform-d
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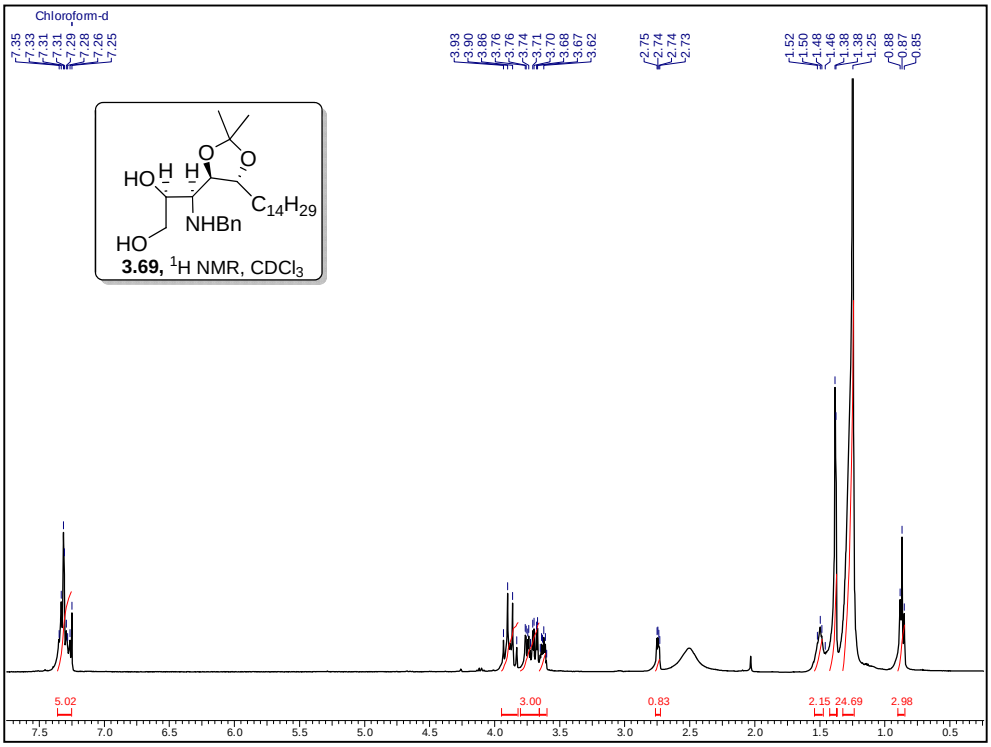
134.99
128.83
128.32
127.92
109.56
79.80
78.85
77.00
68.20
46.44
32.89
31.89
29.66
29.32
27.71
27.32
25.79
22.65
14.08
HO
H
H
O
O
C14H29
NBn
O
3.68, 13C NMR CDCl3
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10


Chloroform-d
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7.33
7.31
7.31
7.29
7.28
7.26
7.25
3.93
3.90
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3.76
3.76
3.74
3.71
3.70
3.68
3.67
3.62
2.75
2.74
2.74
2.73
1.52
1.50
1.48
1.46
1.38
1.38
1.25
0.88
0.87
0.85
HO
H
H
O
O
C14H29
NHBn
HO
3.69, 1H NMR, CDCl3
5.02
3.00
0.83
2.15
24.69
2.98
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
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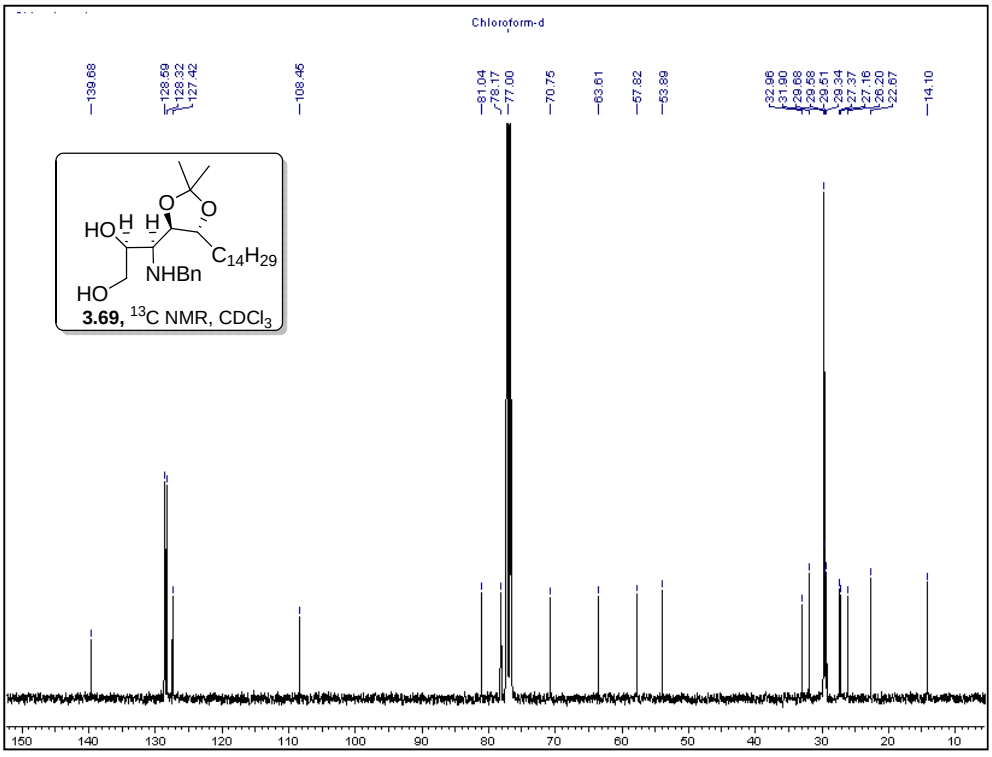
1.5
1.0
0.5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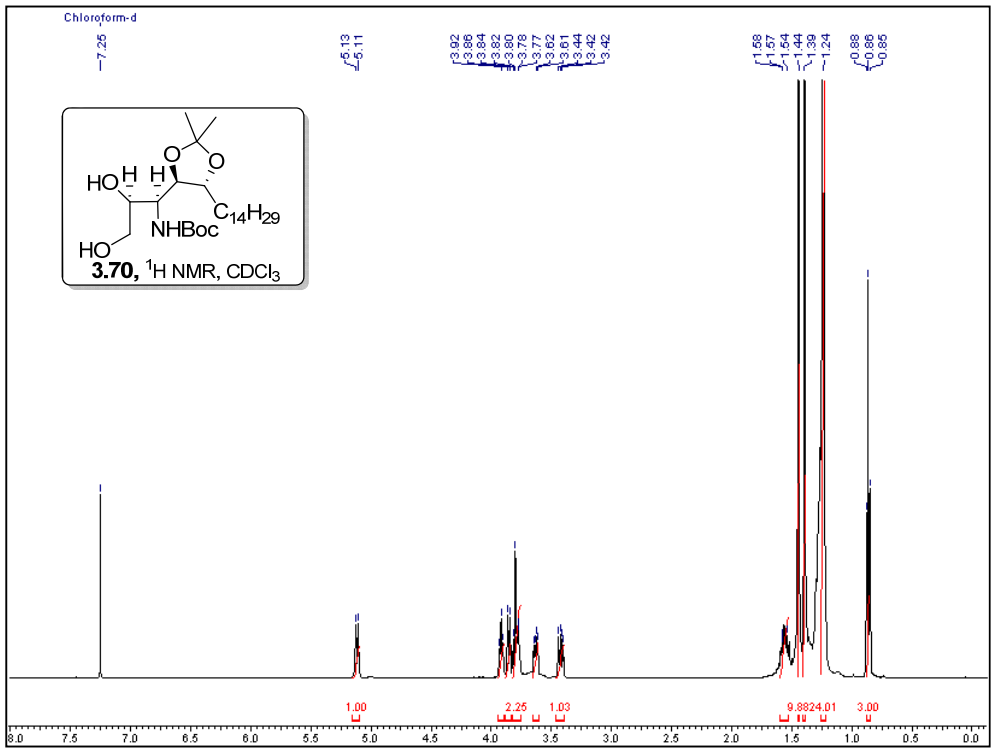
139.68
128.59
128.32
127.42
108.45
81.04
78.17
77.00
70.75
63.61
57.82
53.89
32.96
31.90
29.68
29.65
29.51
29.34
27.37
27.16
26.20
22.67
14.10
HO
H
H
O
O
C14H29
NHBn
HO
3.69, 13C NMR, CDCl3
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10


Chloroform-d
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5.13
5.11
3.92
3.86
3.84
3.82
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3.77
3.62
3.61
3.44
3.42
3.42
1.58
1.57
1.44
1.39
1.24
0.88
0.86
0.85
HO
H
H
O
O
C14H29
NHBoc
HO
3.70, 1H NMR, CDCl3
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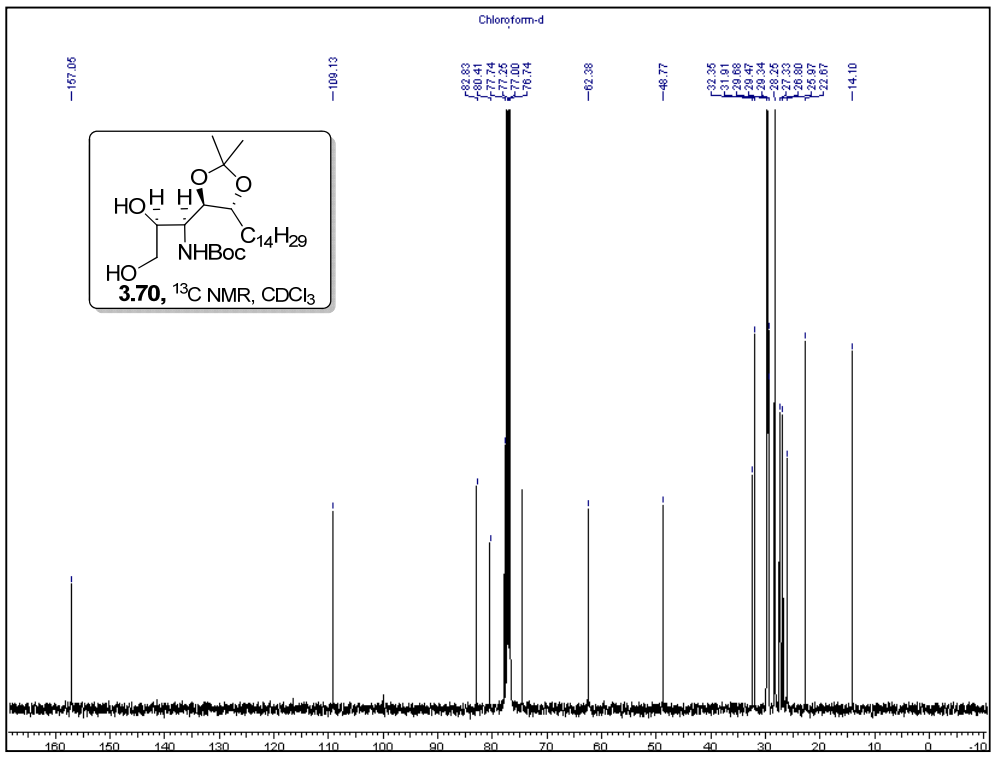
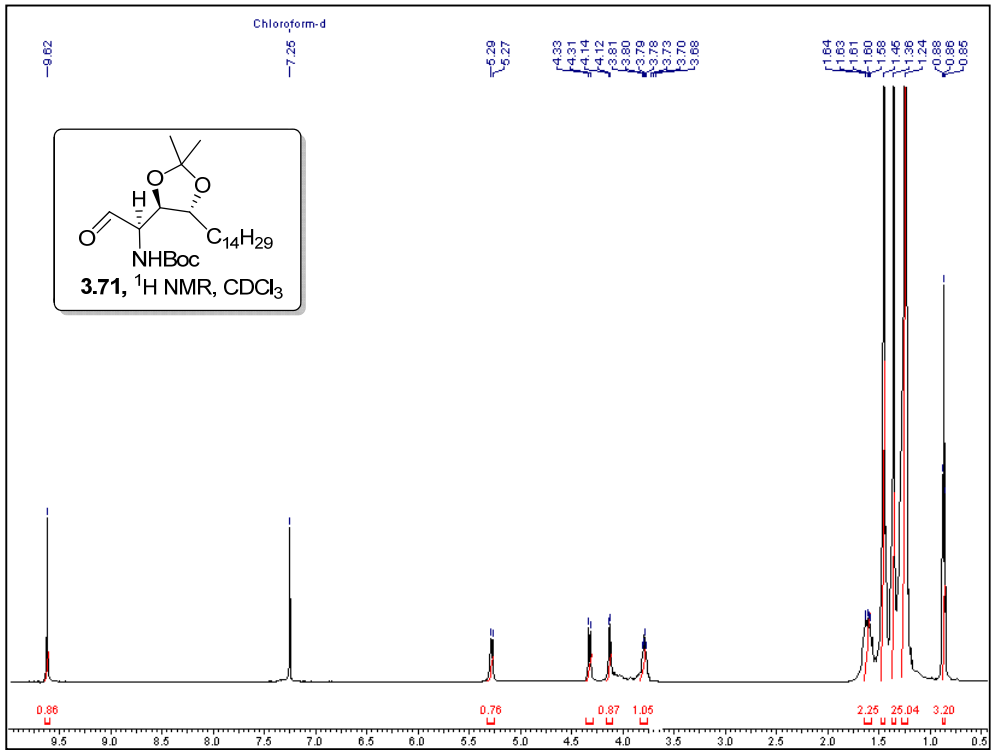
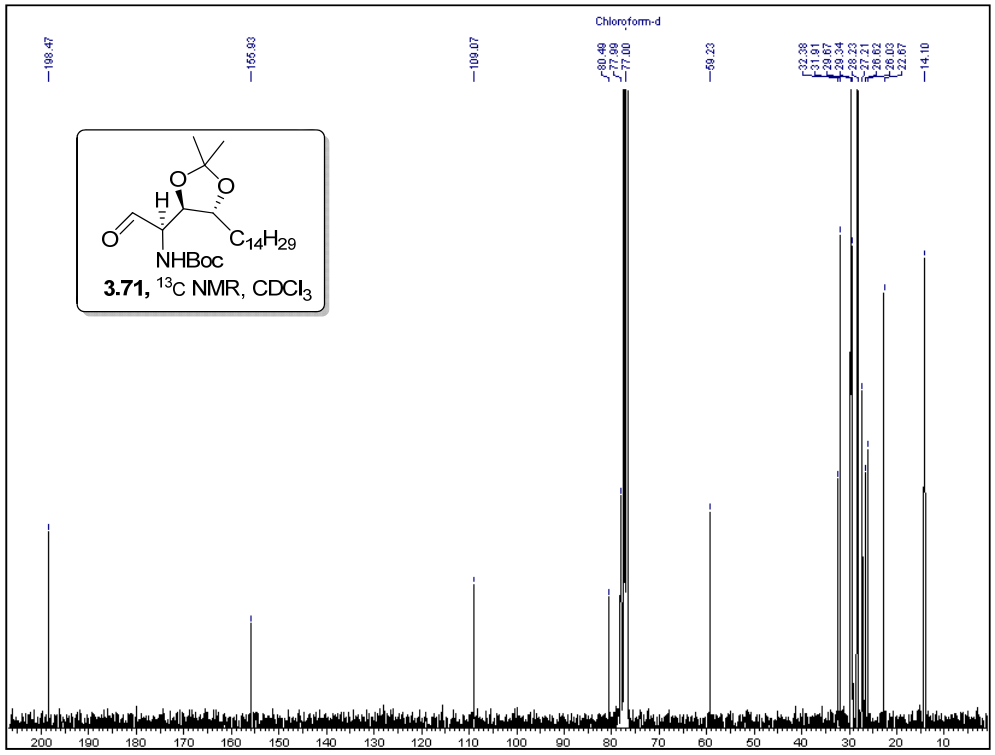
2.25
1.03
9.8824
4.01
3.00


Chloroform-d
157.05
109.13
82.83
80.41
77.74
77.25
77.00
76.74
62.38
48.77
32.35
31.91
29.68
29.47
29.34
28.25
27.33
26.80
25.97
22.67
14.10
HO
H
H
O
O
C14H29
NHBoc
HO
3.70, 13C NMR, CDCl3


Chloroform-d
9.62
7.25
5.29
5.27
4.33
4.31
4.14
4.12
3.81
3.80
3.79
3.78
3.73
3.70
3.68
1.64
1.63
1.61
1.60
1.58
1.46
1.36
1.24
0.88
0.86
0.85
O
O
H
O
C14H29
NHBoc
3.71, 1H NMR, CDCl3
0.86
0.76
0.87
1.05
2.25
25.04
3.20


Chloroform-d
198.47
155.93
109.07
80.49
77.99
77.00
69.23
32.38
31.91
29.67
29.34
28.23
27.21
26.62
26.03
22.67
14.10
O
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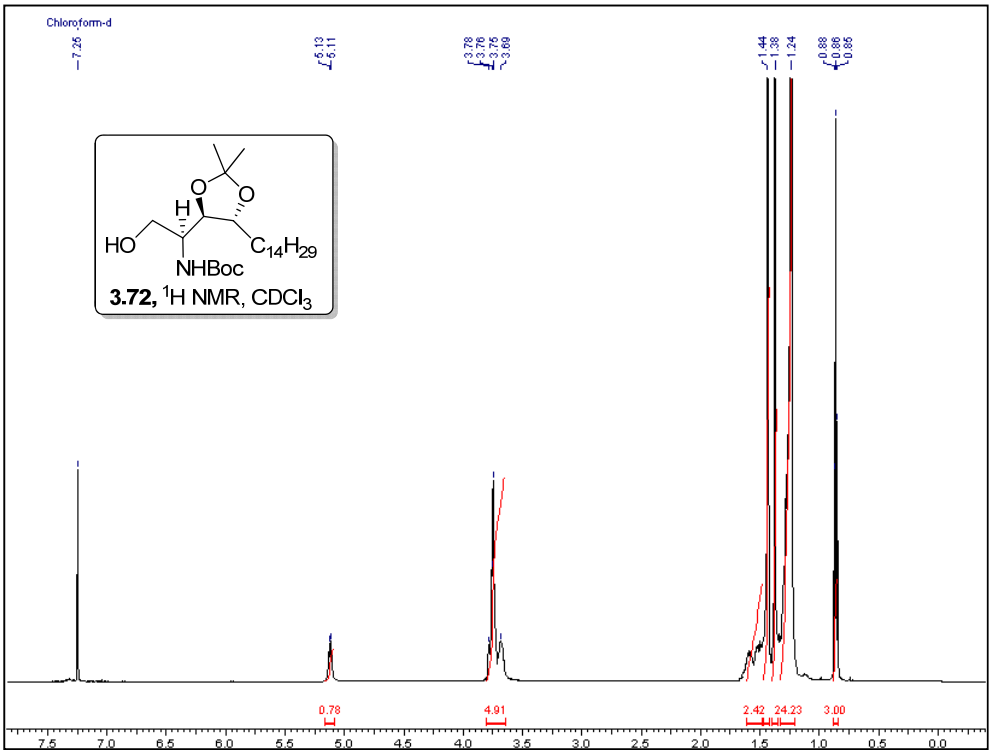
H
O
C14H29
NHBoc
3.71, 13C NMR, CDCl3


Chloroform-d
7.25
5.13
5.11
3.78
3.76
3.75
3.69
1.44
1.38
1.24
0.88
0.86
0.85
HO
O
O
H
NHBoc
C14H29
3.72, 1H NMR, CDCl3
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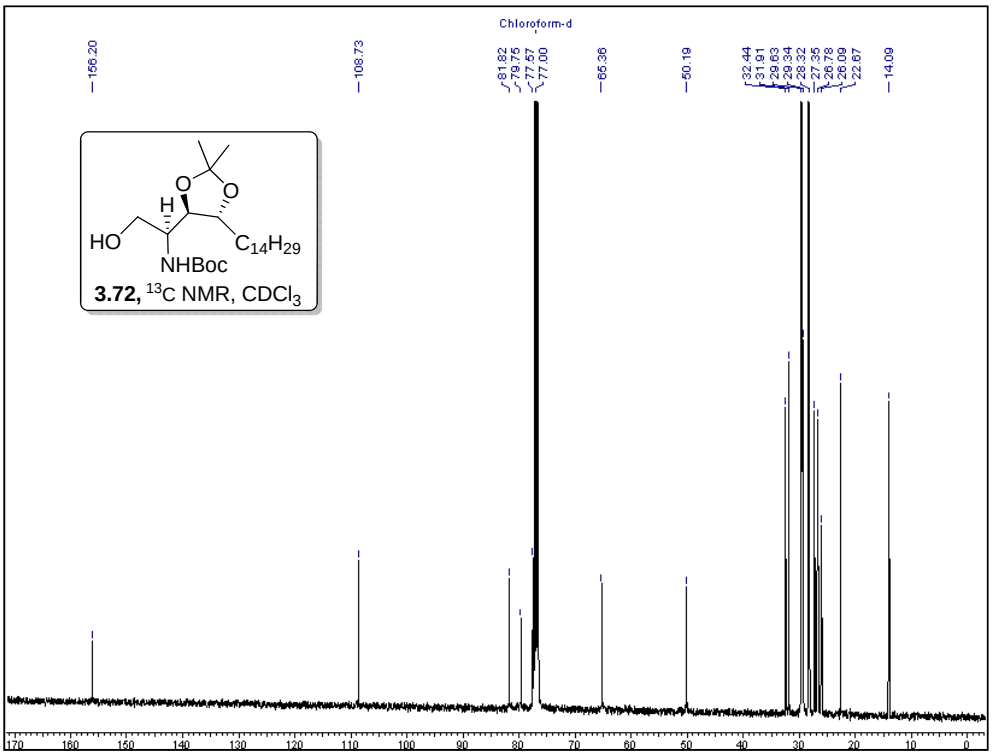
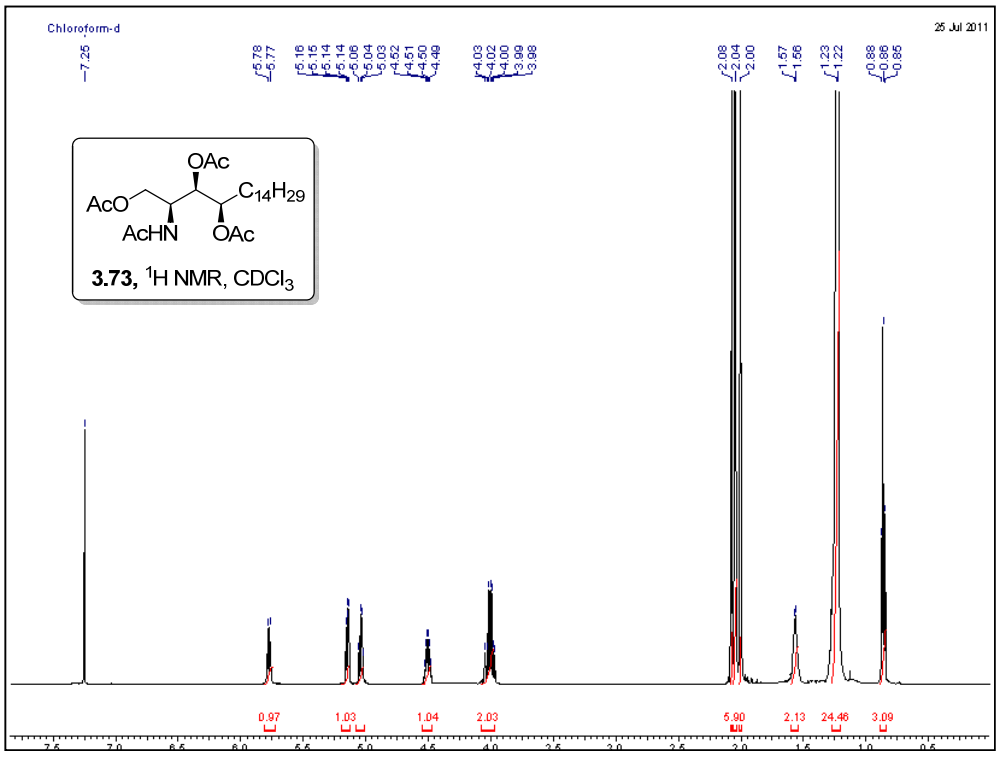
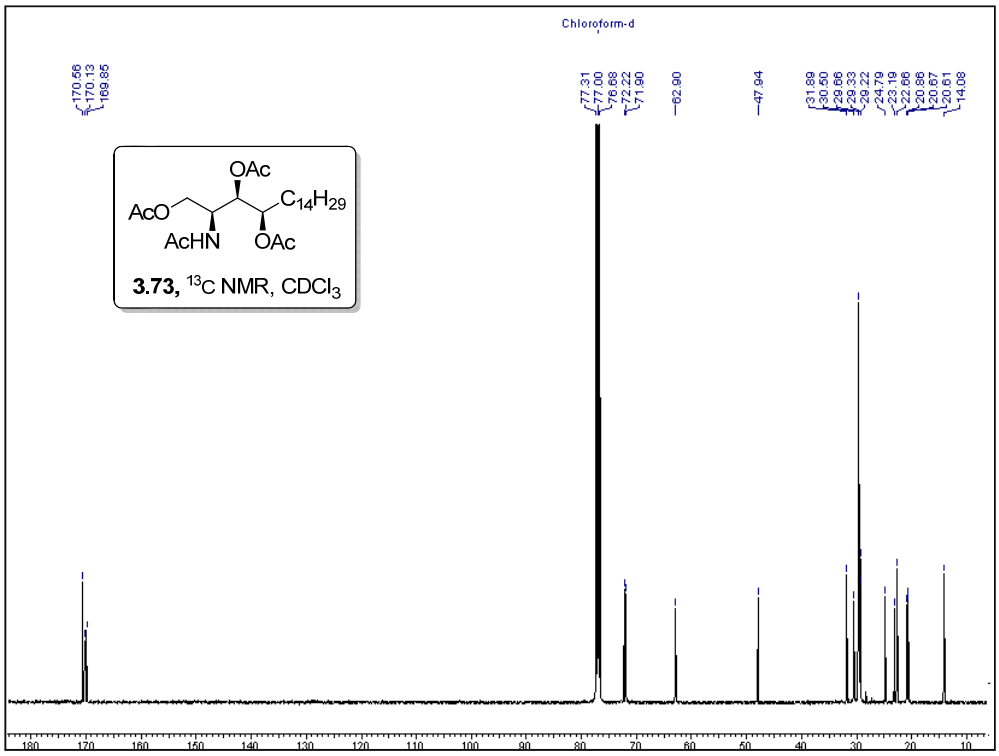
2.42
24.23
3.00


Chloroform-d
156.20
108.73
81.82
79.75
77.67
77.00
65.36
50.19
32.44
31.91
29.63
29.34
28.32
27.35
26.78
26.09
22.67
14.09
HO
O
O
H
NHBoc
C14H29
3.72, 13C NMR, CDCl3


Chloroform-d
25 Jul 2011
OAc
AcO
C14H29
AcHN
OAc
3.73, 1H NMR, CDCl3


Chloroform-d
OAc
AcO
C14H29
AcHN
OAc
3.73, 13C NMR, CDCl3

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CHAPTER-4

Total synthesis of 3,7-di-*epi*-alexine 1-deoxy-6,8a-di-*epi*-castanospermine and 1,6,8a-tri-*epi*-castanospermine from D-mannitol derived *β*-lactam:

4.1. Introduction:

Alkaloids are a group of naturally occurring biologically active organic molecules which mostly contain a basic nitrogen atom. Since, the present chapter is restricted to polyhydroxylated alkaloids; the description on this topic is only highlighted. A large number of polyhydroxylated alkaloids have been isolated from natural sources, mainly from plants and microorganisms. These alkaloids having nitrogen in the ring (commonly known as imino-sugars, aza-sugars or polyhydroxy piperidines, quinozilidine, pyrrolizidine and indolizidine) have become important tools in glycobiology due to their role as glycosidase inhibitors[1]. They have received a great deal of attention because of their therapeutic potentials in the treatment of cancer, viral infections including HIV, diabetes and other metabolic disorders.[1-3,3-6,] Amongst them polyhydroxy indolizidine, pyrrolizidine and their analogues have acquired significant attention due to their potential as drugs for treating a variety of complicated diseases.[1-6] One common characteristic of these compounds is that they possess bicyclic ring with single shared nitrogen. Representative examples of pyrrolizidines and indolizidine alkaloids include lycopsamine (**4.1**)[7], alexine (**4.2**)[8], castanospermine (**4.4**)[9] and swainsonine (**4.5**).[10]

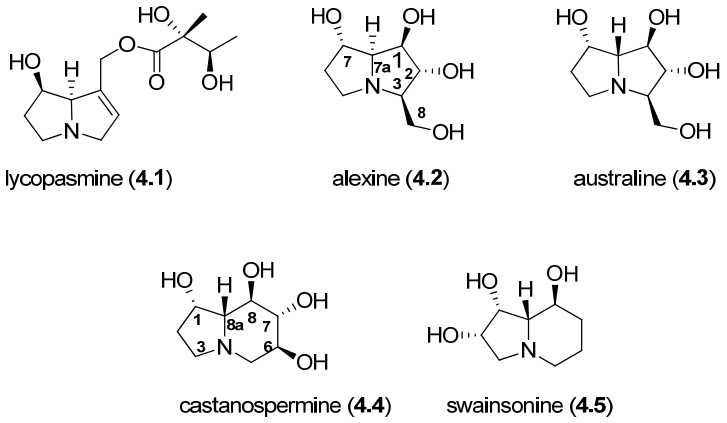


Figure 4.1 *Representative examples of pyrrolizidines and indolizidine alkaloids*

4.2 Castanospermine and their analogues:

1,6,7,8-Tetrahydroxyindolizidine, (castanospermine,**4.4**), isolated from the seeds of the Austalian legume *castanospermine australe*[9a] and dried pod of *Alexa leiopetala*[9b] is a potent and specific inhibitor of mammalian and plant α- and β-D-

glycosidases *in vitro*[9a,c] and *in vivo*[9d,e]. This molecule has exhibited potential for the treatment of diabetes, [11,12] obesity,[13] cancer[12,14,] and viral infections[15], including HIV-1[16] The inhibition of different types of cellular *α*- or *β*-glucosidases by castanospermine *in vivo* produces a wide range of biological effects suggesting wide ranging applications for this compound. A series of epimers and deoxy derivatives of castanospermine [17-19] (**Fig. 4.2**) have been synthesized to investigate the contribution of different chiral centers to the specificity and potency of inhibition for glycosidases.

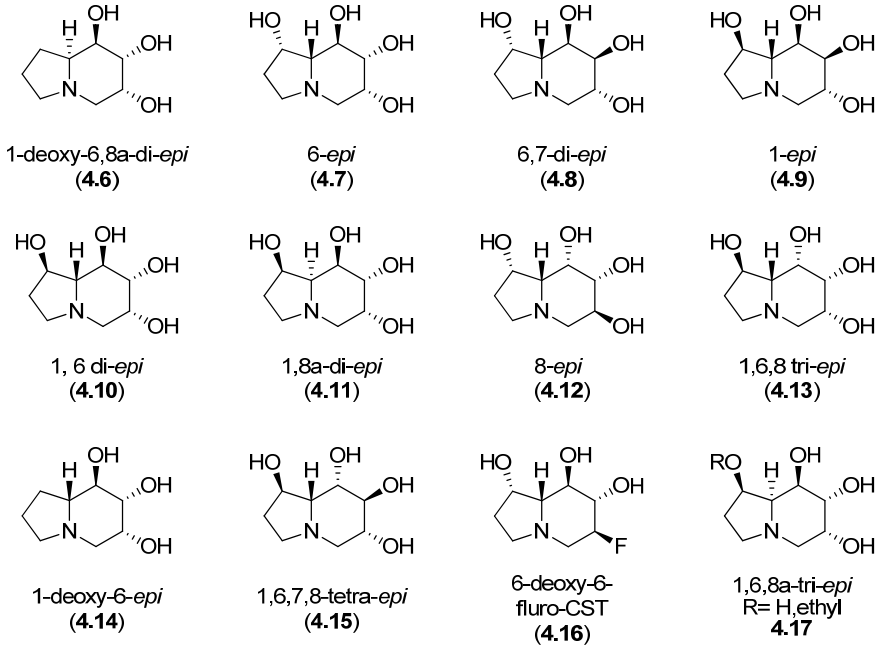


Figure 4.2. *Castanospermine and their analogues*

Castanospermine inhibits all forms of *α*- and *β*-D-glucosidases, but alteration to any of the five chiral centers in castanospermine changes its biological activities. For example, 6-*epi*-castanospermine (**4.7)** which is related to D-pyrranomannose does not inhibit lysosomal (acidic) *α*-mannosidase but is a good inhibitor of the cytosolic or neutral α-mannosidase. Conversely, 1-deoxy-6-*epi*-castanospermine (**4.14**) inhibits acidic *α*-mannosidase strongly but not the neutral *α*-mannosidase. 1-Deoxy-6,8a-*diepi*-castanospermine (**4.6)** which has four chiral centres identical to L-fucose is, however, a potent inhibitor of *α*-L-fucosidase (K_i 1.3 /μM). As a result, a nearly complete range of castanospermine analogues have been prepared and studied for their biological activities,[17,18,19] in which the stereochemistry of the five chiral centers have been inverted either individually or several at a time (**fig.4.2**). Derivatization of

the hydroxyl groups **4.17**[20] has also been studied in an effort to potentiate the selectivity of these compounds as anti-diabetics, antitumor, and *anti*-HIV agents.

4.3 Alexine and their analogues:

Another class of alkaloid alexine (**4.2)**, found in the same species of plants, was first isolated in 1988 from *Alexa leiopetala*[8a]. Alexines are polyhydroxylated pyrrolizidine alkaloids with a carbon substituent at C3 having five contiguous asymmetric carbons. They have been shown to posses interesting inhibitory activity towards glycosidase and show antiviral activity.

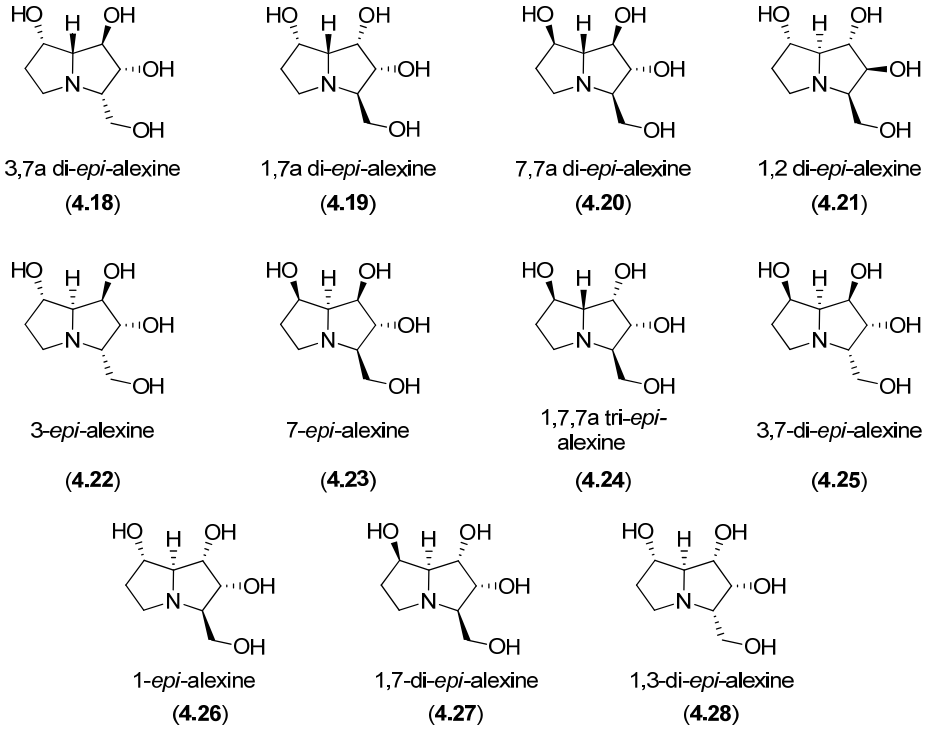


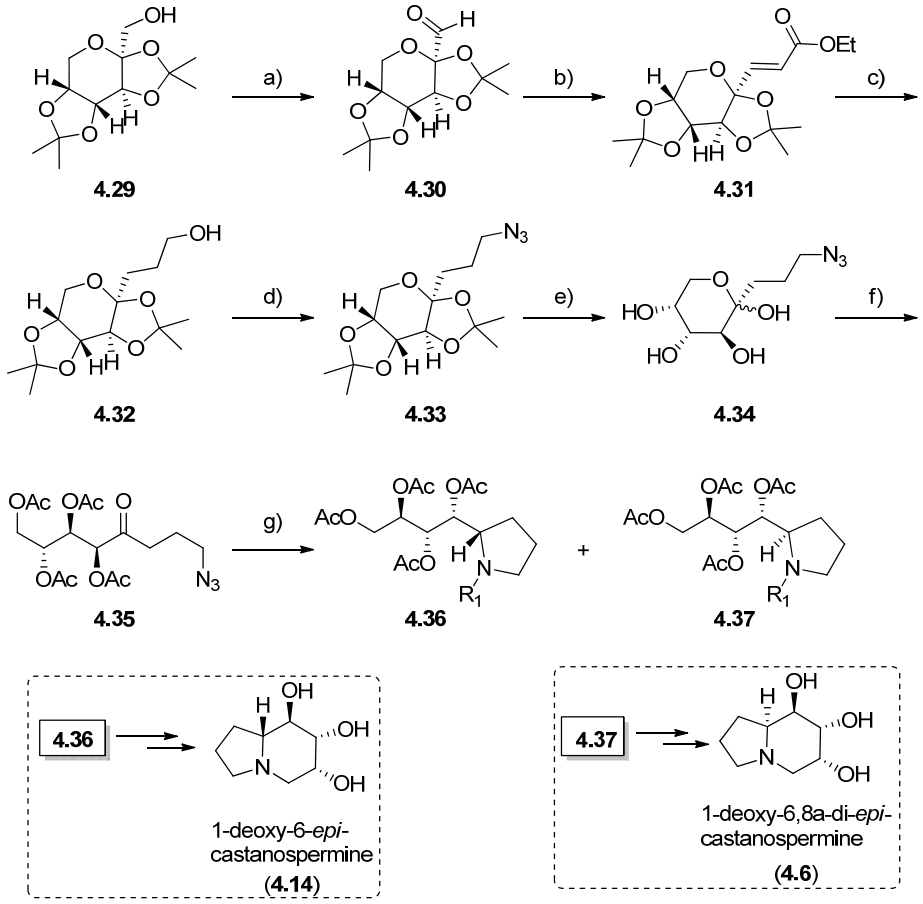
Figure 4.3. *Alexine and their analogues*

Since, glycosidases are involved in many vital biological processes and also believed to be implicated in human diseases such as diabetes, cancer, malaria, and viral infection[1-3], a plethora of research activities have been directed to find or prepare other stereoisomers and derivatives of alexine [21]. So far 13 stereoisomers of **4.2,** (out of 32 possible isomers) (**Fig-3)** are known from natural sources[8, 22] and syntheses.[23, 24]

4.4. Background of the present work:

In addition to their reflective biological activities, the castanospermine (**4.4**), alexine (**4.2)** and their representative analogues poses significant synthetic challenge. The critical element for any successful synthesis of these classes of alkaloids has been the construction of pyrrolizidine and indolizidine rings and stereoselective installation of substituents on each carbons of the ring. Although, the synthesis of **4.6** and **4.17** has been achieved previously by few groups, to the best of our knowledge, the synthesis of 3,7-*diepi*-alexine (**4.25**) has remained unattempted. In order to highlight the merits of our synthetic strategy towards this end, a brief account of few known important syntheses is described below:

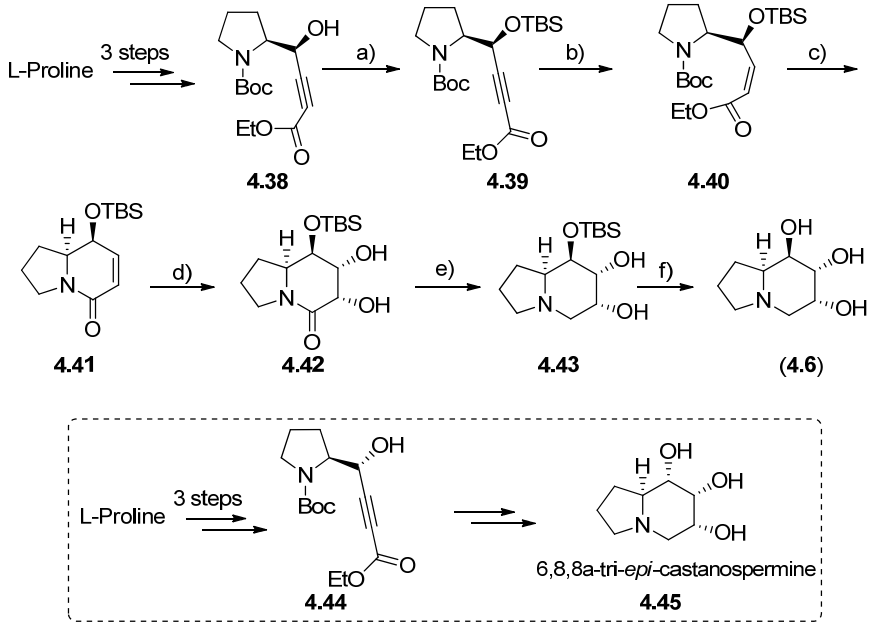
First synthesis of **4.6** was reported by Aamlid [25] *et al.* in 1990 through the sequences as depicted below in Scheme 4.1**.** This molecule was synthesized from commercially available D-fructopyranose (**4.29)** in eleven steps.



Scheme 4.1. ***Reagents and conditions:*** *a) CrO_3, py, CH_2Cl_2, rt, 80%, b) $Ph_3P^+Br^-CH_2COOEt$, CH_2Cl_2, rt, 60%, c) i) H_2/Pd/C-5%, EtOH, 98%, ii) LAH, dry ether, reflux 1 h, 57%, d) i) MsCl, Et_3N, CH_2Cl_2, 0 °C, 10 min; ii) NaN_3, DMF, 90 °C, 30 min, 76% over two steps, e) AcOH/H_2O, 105 °C, 5 h, 90 %, f)*

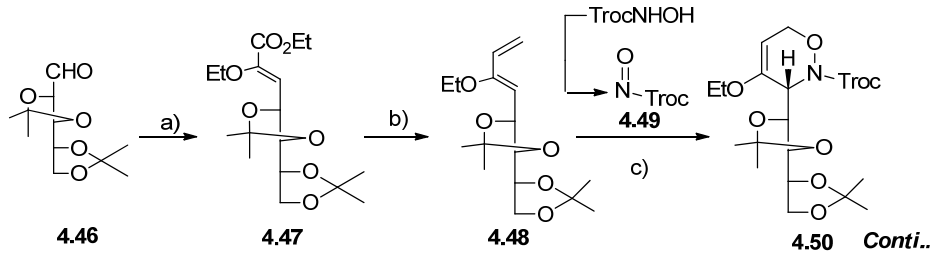
Ac_2O, py, rt, 12 h, 85 %., g) i) H_2/Pd-C-10%, EtOH, NaHCO3, rt, 5 h, 68%; ii) 1M, methanolic, NaOMe, MeOH, rt, 30 min, 86%.

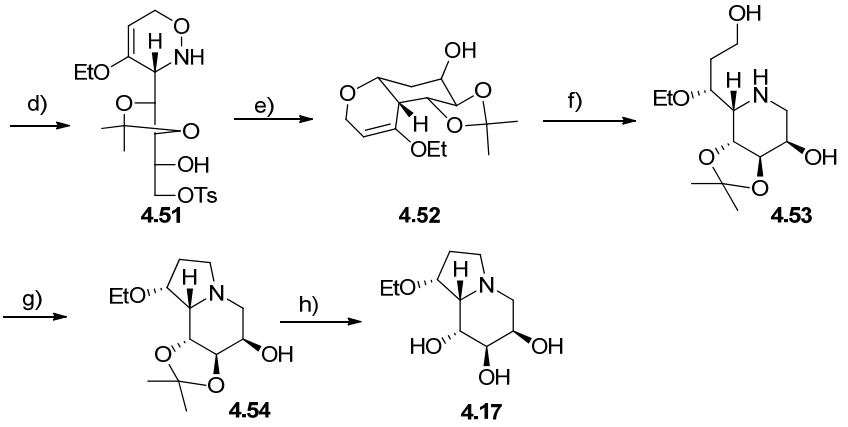
An elegant approach for the synthesis of **4.6** and **4.45** is also reported [26] involving intermediates **4.38** and **4.44**, readily available from *N* -Boc-L-proline in three and 6 steps, respectively, and in 31% overall yield.



Scheme 4.2. ***Reagents and conditions:*** *a) TBSCl, imidazole, CH_2Cl_2, rt, 12 h, 98%, b) H_2/Lindlar's catalyst, 1 atm., quionolene, MeOH, rt, 3d, 96 %, c), i) TFA, CH_2Cl_2, 0 °C, to rt, 1.5 h, ii), Et_3N, CH_2Cl_2, rt, 2d, 45%. d) OsO_4, NMO, acetone/H_2O (10:1), rt, 8h, 75%. e) i) $BH_3.Me_2S$/THF, rt, 4h, reflux, 1h ii) EtOH, reflux, 95% f) TBAF, 0 °C to rt 2 h, 90%.*

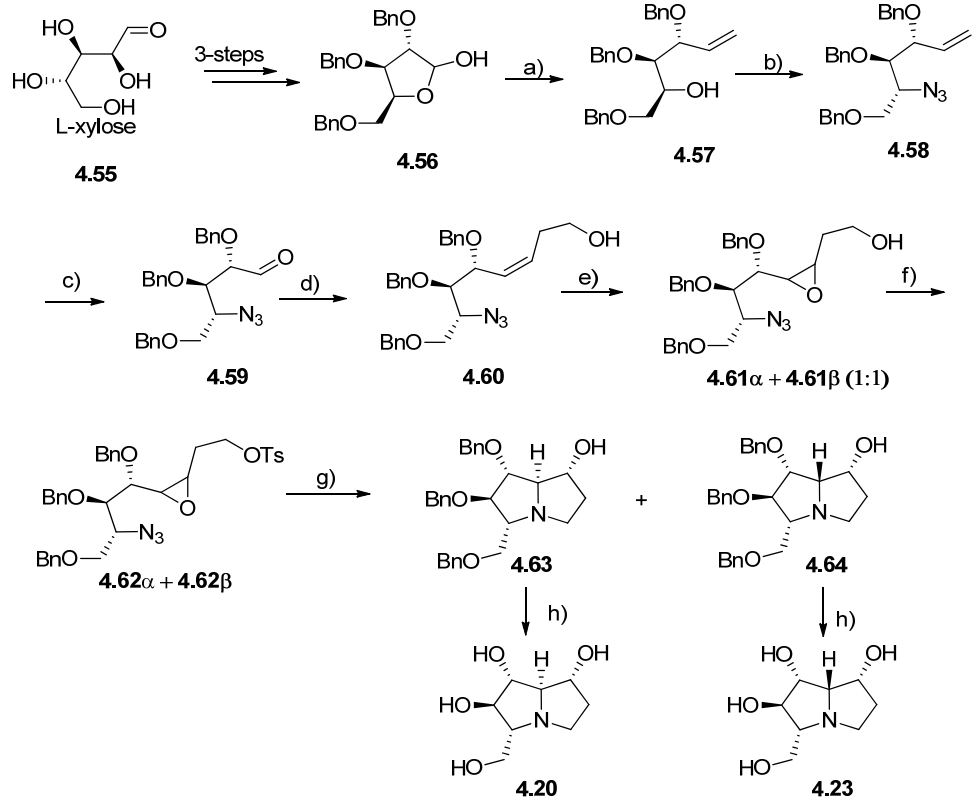
Grierson *et al.*[20] have synthesized 1,6,8a-*triepi*-castanospermine derivative in very good yield (Scheme 4.2) involving hetero Diels-Alder reaction of **4.48** with Troc-NO (**4.49**) generated *in situ* by periodate oxidation of TrocNHO as the key step.. The synthesis of **4.17** was accomplished in 10 steps from D-(-) arabinose and in 1.8% overall yield.





Scheme 4.3. ***Reagents and condtions:*** *a) $Ph_3P^+Br^-CH(OEt)COOEt$, n-BuLi, THF, 0 °C, 65%; b) i) LAH, THF, 0 °C; ii) MnO_2, PhH, reflux; iii) $Ph_3P{=}CH_2$, THF, n-BuLi, THF, 0 °C, 1 h, 71 % over 3-steps; c) $Et_4N^+IO_4^-$, CH_2Cl_2, 0 °C, 46%.; d) i) 80% aq. HOAc 65 °C; ii) Bu_2SnO, TsCl, Et_3N, CH_2Cl_2, 0 °C-rt; iii) Zn, HOAc, Et_3N, Heat, 1 h, 41 % over all yield; e) PhMe, NaOAc, reflux, 6 h, 42 % ; f) Ra-Ni, H_2 (100 atm), 20 °C, 48 h, quant; g) Ph_3P, DEAD, THF, 63%; h) aq. TFA, rt, 80%.*

A concise total synthesis of 7-*epi*-alexine (**4.23)** and 7,7a-di-*epi*-alexine (**4.20)** is also described[27] from commercially available L-xylose (**4.55**) in 10 steps and 8% overall yield.



Scheme 4.4. ***Reagents and conditions:*** *a) $Ph_3P^+CH_3Br^-$, n-BuLi, THF, -78 °C, b) Tf_2O, py, CH_2Cl_2, -40 °C 5 h, then $Bu_4N^+N_3^+$, PhH, 23 °C, 1 h; c) O_3, CH_2Cl_2/MeOH (6:1), Sudan III (0.1%), Me_2S, -78 °C to 23 °C, 3-5 h; d) $Ph_3P^+(CH_2)_3(OH)Br$, $KN(SiMe_3)_2$, THF, 0 °C, 1 h, 23 °C, 1h, Me_3SiCl, 0 °C, 10 min, add of* **4.59** *, - 78 °C, 1 h, 35%; e) m-CPBA, CH_2Cl_2, 0 °C to rt 24 h, 65%; f) p-TSCl, py, DMAP (cat), CH_2Cl_2, -15-0 °C, 77%; g) H_2/Pd-C-10%, Et_2O/EtOH (2:1), 1 atm, 15 h, filter add K_2CO_3, EtOH, reflux 20 h, 71%. h)) H_2/Pd-C-10%, EtOH, 1 atm, 87%.*

4.5. Present work:

In view of the biological activities associated with **4.2** and **4.4**, it is understandable that these alkaloids and their derivatives have remained popular synthetic targets. In particular, the ability to prepare alternative stereoisomers of these alkaloids is highly desirable since the biological activity of these compounds varies substantially with the stereochemistry of the substituents. Literature reports have revealed that most of the syntheses either begin with carbohydrates or amino acids. To the best of our knowledge the application of *β*-lactam for the synthesis of polyhydroxy indolizidine, pyrrolizidine and derivatives has remained unexplored.

In this section, we have discussed our efforts towards the total synthesis of naturally occurring 1,6,8a tri-*epi*-castanospermine (**4.17),** 1-deoxy-6,8a-di-*epi*-castanospermine (**4.6**) and 3,7-di-*epi*-alexine (**4.25).**

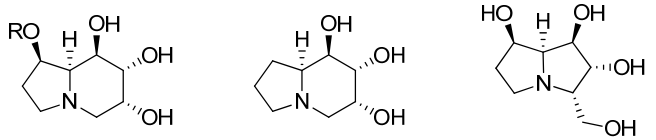
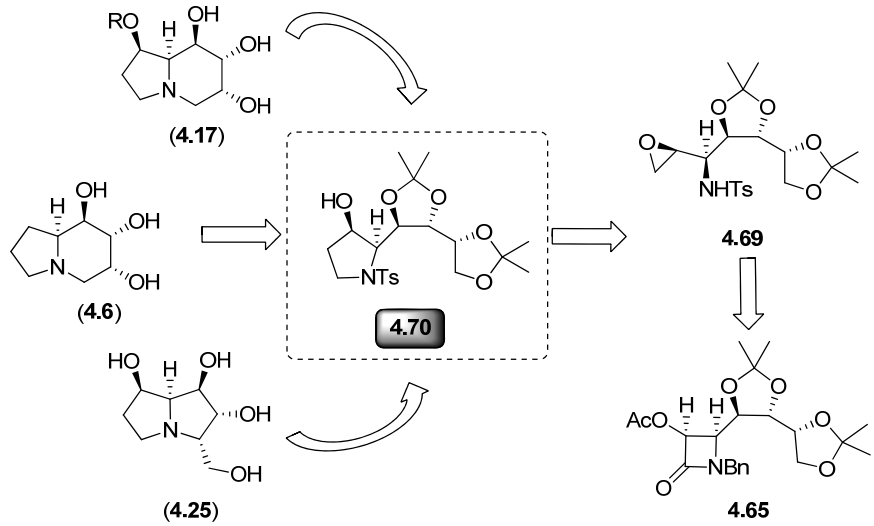


Figure 4.4.

4.6. Retrosynthetic analysis:

Considering the less explored significance of *β*-lactam as a synthon, we ventured into developing an entirely new and versatile strategy for the synthesis of polyhydroxylated 1-azabicyclo[4.3.0]nonane skeleton comprising of indolizidine (**4.17** and **4.6**) and 1-azabicyclo[3.3.0]nonane skeleton related to pyrrolizidine (**4.25**) alkaloids. The divergent synthetic approach has been envisioned towards the total synthesis of 1-deoxy-6,8a-di-*epi*-castanospermine (**4.6**), 1,6,8a-tri-*epi*-

castanospermine (**4.17**) and di-*epi*-alexine (**4.25**) from the common precursor **4.70** as depicted retrosynthetically in Scheme 4.5



Scheme 4.5. *Retrosynthetic strategy*

It was visualized that the pyrrolidine derivative **4.70** can be easily synthesized from epoxy amine **4.69** by one carbon homologation followed by cyclization. The epoxy amine in turn could be obtained from 3-acetoxy β-lactam **4.65**. Our key starting material **4.65** can be achieved in very good yield by [2+2]-cycloaddition of imine with suitable ketene.

4.7. Results and discussion:

We describe herein the results of our studies in detail towards the synthesis of polyhydroxy indolizidine and pyrrolizidine class of alkaloids.

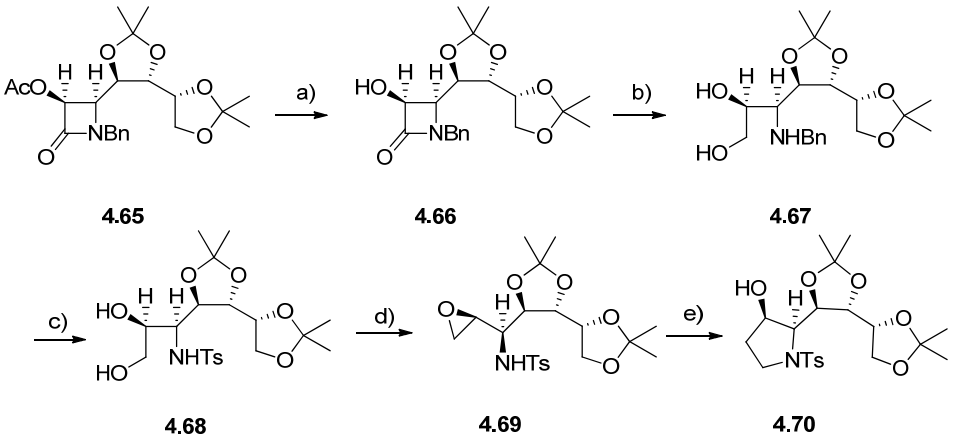
4.8. Synthesis of (2*S*,3*R*)-2-((4*S*,4'*R*,5*R*)-2,2,2',2'-tetramethyl-4,4'-bi(1,3-dioxolan)-5-yl)-1-tosylpyrrolidin-3-ol (4.70):

Our synthetic endeavor towards precursor **4.70** began with the synthesis of 3-acetoxy β-lactam **4.65** using [2+2]- cycloaddition reaction of imine **3.62** with a ketene generated *in situ* from acetoxy acetyl chloride in the presence of triethylamine The cycloadduct **4.65** was fully characterized by spectroscopic techniques.

Since the transformation of **4.65** to crucial precursor **4.70**, required the cleavage of N-C_1 bond of azetidine ring, acetate group was first removed by

saponification and reduced using LAH to obtain **4.67** (89%). The success of the cleavge was confirmed by the absence of the characteristic absorption band for the *β*-lactam carbonyl and appearance of a broad absorption band for -OH at 3430 cm^{-1}in the IR spectrum. The structure of **4.67** was further confirmed by ^{1}H and ^{13}C NMR spectra.

As subsequent conversion of **4.67** to **4.70** *via* cascade cyclization of **4.69** would require nucleophilic nitrogen, therefore, *N*-benzyl moiety of **4.67** was first removed by hydrogenation (Pd/C, 10%) and free amine was selectively tosylated using *p*-TSCl in aqueous potassium carbonate to obtain **4.68** in 91% yield. The support for the structure of **4.68** came by observing the methyl protons of tosyl group at δ 2.40 as a singlet in the ^{1}HNMR spectrum. The -NH proton coupled with adjacent hydrogen appeared as a doublet (J = 9.45 Hz) at δ 5.52. The methyl (tosyl) carbon appeared at δ 21.52 in the ^{13}C NMR. The ESI mass spectrum showed a base peak at *m/z* 447 (M+1).



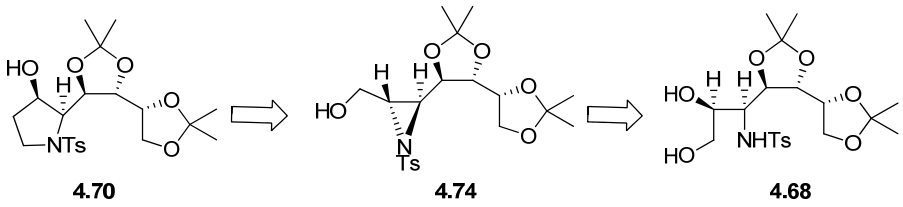
Sceheme 4.6. ***Regents and conditions: a****) aq. $NaHCO_3$, Na_2CO_3 (cat), MeOH, 86%, c) $LiAlH_4$, THF, 0 °C , reflux 4-6 h, 89%, c) i) H_2/Pd-C-10%, EtOAc, 1atm, rt, 12 h, quant. (crude), ii) TsCl, K_2CO_3, DCM:H_2O (1:1), rt, 3 h, 91%, d) (i) TsCl, Et_3N, Bu_2SnO (cat), DCM, 0 °C-rt 2 h, 88%, (ii) b) K_2CO_3, CH_3CN, rt, 6 h, 93%, e) NaH, $(CH_3)_2S^{+}OI^{-}$, dry DMSO, 85 °C 24 h, 40%.*

The transformation of **4.68** to **4.69** required selective tosylation of its primary hydroxyl group which was achieved (88%) using Martinell's (*n*-Bu_2SnO/*p*-$TsCl/Et_3N/CH_2Cl_2$) protocol and the resultant crude on stirring with K_2CO_3 in acetonitrile gave desired epoxide **4.69** in 93% . The ^{1}H NMR spectrum of **4.69** revealed two sets of doublet of doublet at δ 2.65 and δ 2.75 with the coupling

constants of J = 4.1 and 5.01 Hz which were assigned to the two diastereotopic methylene protons of the oxirane ring and another signal at 3.18 as a multiplet was assigned as methine carbon of oxirane. In the ^{13} C NMR, one of the methylene carbon of the epoxide **4.69** appeared at δ 43.02 whereas the methine carbon appeared at δ 51.54. The ESI mass spectrum exhibited a base peak at *m/z* 428 [M+1].

In order to transform **4.69** to desired pyrrolidine **4.70,** we had visualized a cascade type reaction by opening the epoxide ring with trimethyl sulfoxoinium ylide and its *in situ* cyclization with –NHTs group. Towards this end, **4.69** was reacted with the *in situ* generated ylide from trimethyl sulfoxonium iodide[28] using sodium hydride in dry DMSO. However, **4.70** was formed in poor yield (40 %). Our several attempt to improve the yield by using fresh reagent and use of different solvents[28b] such as THF or toluene remained unsuccessful. Furthermore, we also evaluated this reaction under Hodgson condition[29] (*n*-BuLi/DMPU/THF, reflux), but this effort also failed to improve the yield beyond 35%.

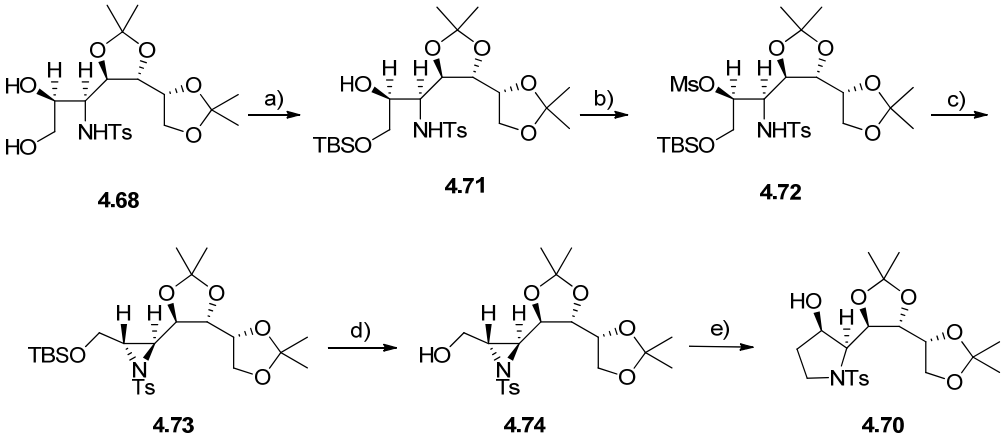
Thus left with little choice, we changed our strategy and proposed to proceed *via* aza-Payne rearrangement[30] of corresponding azeridinol **4.74** as shown in Scheme 4.8.



Scheme- 4.8. *Revised retrosynthetic strategy*

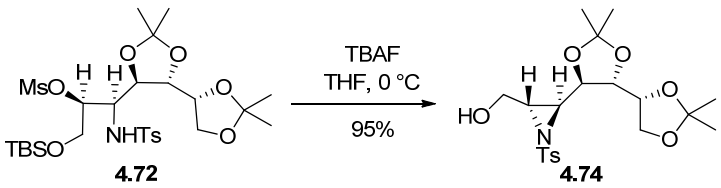
The planned aziridinol **4.74** was synthesized from **4.68** by first selectively protecting the primary –OH moiety as –OTBS (TBSCl, imidazole, DCM, rt) and afterwards the secondary alcohol group was converted into O-Ms moiety (mesyl chloride and pyridine at room temperature) and obtained **4.72** in 88%. The ^{1}H NMR of **4.72** showed characteristic signals of TBS and mesyl group at δ 0.04 and δ 0.88 and δ 2.99 as singlets, respectively. The structure was further confirmed by ^{13}C NMR which displayed four characteristic carbons of TBS group, at δ -5.64, δ -5.63, δ 18.11 (quaternary), δ 25.71 (three methyl), respectively, and methyl of mesyl at δ 38.21.

The ESI mass showed a base peak at *m/z* 638 [M+1] which further confirmed the structure.



Scheme 4.9. ***Reagents and conditions:*** *a) TBDMSCl, Im, CH_2Cl_2 , rt, 1 h, 90%, b) MsCl, Et_3N, rt, 30 min, 87% ; c) n-BuLi, THF, - 78 °C, 2 h 50%; d) TBAF, THF, 65%; e)) NaH, $(CH_3)_2S^+OI^-$, dry DMSO, 85 °C 24 h, 70%.*

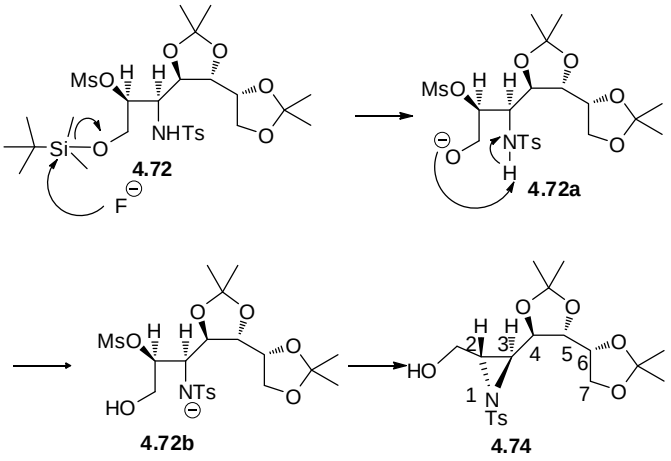
Further, mesylate **4.72** was on treatment with NaH in dry THF at 0 °C produced aziridine **4.73** in very low yield (20%). Several optimization attempts using different bases such as KH, *n*-BuLi, and *s*-BuLi also failed to improve the yield. The lower yield may be due the steric hindrance of bulky TBS group. Therefore, it was visualized that replacing the –OTBS moiety with a less bulky group may help. To our delight, while deprotecting the –OTBS group using TBAF in dry THF at 0 °C, we obtained aziridinol **4.74** in 95 % yield (Scheme 4.10).



Scheme 4.10. *One pot cascade reaction*

The structure of aziridinol **4.74** was established by IR, ^{1}H NMR and ^{13} C NMR specta. The IR spectrum of **4.74** showed an absorption band at 3450 cm^{-1} for the hydroxyl functionality. Disappearance of the protons of mesyl and TBS group in ^{1}H NMR and ^{13}C NMR suggested the success of the transformation. The H2 of aziridine ring appeared at δ 2.98 as a multiplet and H3 resonated at δ 3.06 (dd, J = 2.4, 5.6 Hz). The lower coupling constant between H2 and H3 suggested *trans* relationship

between these protons. Both the C2 and C3 carbon of aziridine ring appeared at δ 43.2 and δ 24.7, respectively. The ESI mass spectrum exhibited *m/z* 428 [M +1].



Scheme-4.11. Plausible mechanism of aziridinol **4.74** formation

Mechanistically, this reaction proceeds with an attack of fluoride ion on to the silicon atom, followed by exchange of proton from tosylamine to generate more stable nitrogen anion **4.72b** which undergoes cyclization by nucleophilic attack to the carbon containing mesylate producing aziridin-1-ol **4.74**.

Aziridinol **4.74** in hand, the next reaction *i.e.* aza-Payne rearrangement was attempted by heating it in dry DMSO in the presence of NaH (8 *equiv*.) and trimethyl sulfoxonium iodide (8 *equiv.*) which resulted desired hydroxy pyrrolidine **4.70** in 70% yield.

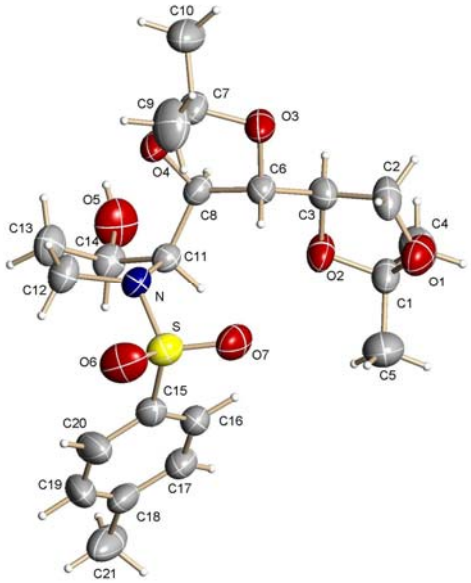


Figure 4.5. *ORTEP diagram of the molecule. Ellipsoids are drawn at 40% probability*

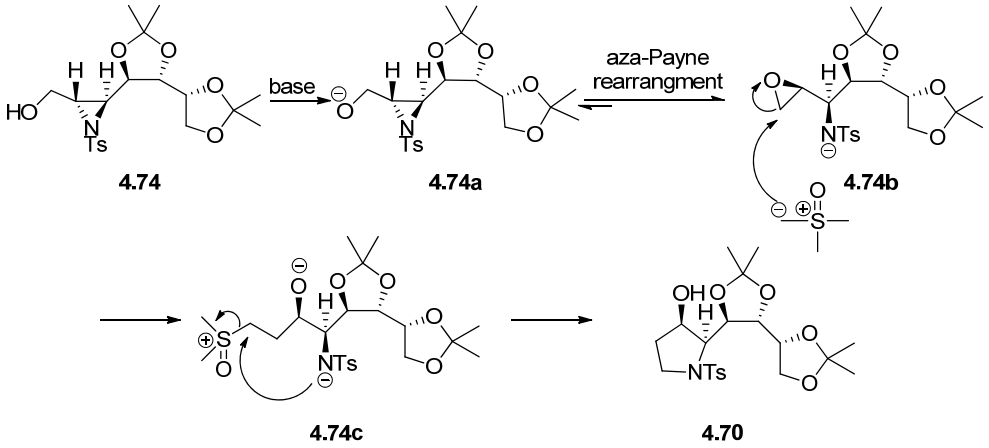
The IR spectrum of **4.70** showed a strong absorption band at 3389 cm^{-1} corresponding to hydroxyl functionality. In the ^1H NMR spectrum, a multiplet at δ 1.93

integrating for two protons were assigned to methylene group (NTs-CH_2CH_2). Another methylene protons attached to nitrogen appeared (NTs-CH_2CH_2) as two sets of multiplet at δ 3.45 and δ 3.67. In the ^{13}C NMR spectrum, two methylene groups of pyrrolizidine ring appeared at δ 33.6 and δ 47.1. Further, the success of the reaction was confirmed by ESI mass spectrum by observing *m/z* 464 [M+Na]. Since, at this stage establishment of relative stereochemistry between H3 and H4 on the basis coupling constant in the ^1H NMR was found difficult, therefore, we recrystallized it in DCM:pet- ether (1:10) for X-ray diffraction studies which confirmed its absolute conformation (Figure 4.5).

4.9 X-ray Crystal Structure Analysis for 4.70:

Crystal Data: Single crystals of the compound were grown by slow evaporation of the solution in dichloromethane and pet-ether. Colourless crystal of approximate size 0.23 x 0.09 x 0.02 mm, was used for data collection on *Bruker SMART APEX* CCD diffractometer using Mo K_α radiation with fine focus tube with 50kV and 30mA. C_{21} H_{31} N O_7 S, M = 441.53. Crystals belong to Orthorhombic, space group $P2_12_12_1$, a = 6.7501(5), b = b = 17.434(1) , c = c = 19.510(1) Å, V = 2296.1(3) $Å^3$, Z = 4, D_c = 1.277 g /cc, T = 293(2) K, 11648 reflections measured, 4023 unique, R value 0.0448, wR2 = 0.0997.. SHELX-97 (ShelxTL)[ref] was used for structure solution and full matrix least squares refinement on F^2. X-ray analysis revealed the relative configuration of the molecule as C3 (*R*), C6 (*R*), C8 (*R*), C11 (*S*) and C14 (*R),* respectively.

The mechanism of aza-Payne rearrangement is shown in Scheme 4.12. The key feature of this rearrangement is the equilibration of azeridin-1-ol **4.74a** towards the epoxyamine **4.74b** in an aprotic solvent**.** This situation may be due to greater ability of activated amine to stabilize negative charge (e.g. Scheme 4.8) under basic reaction condition and/or the greater thermodynamic stability of epoxy amine **4.74b** *vs* azeridinol **4.74**. Nucleophilic attack of sulfoxonium ylide to more stable epoxy amine gives *bis*-anion **4.74C** which upon 5-*exo-tet* ring closure produces desired pyrroldine **4.70**.



Scheme 4.12 mechanism of aza-Payne rearrangement

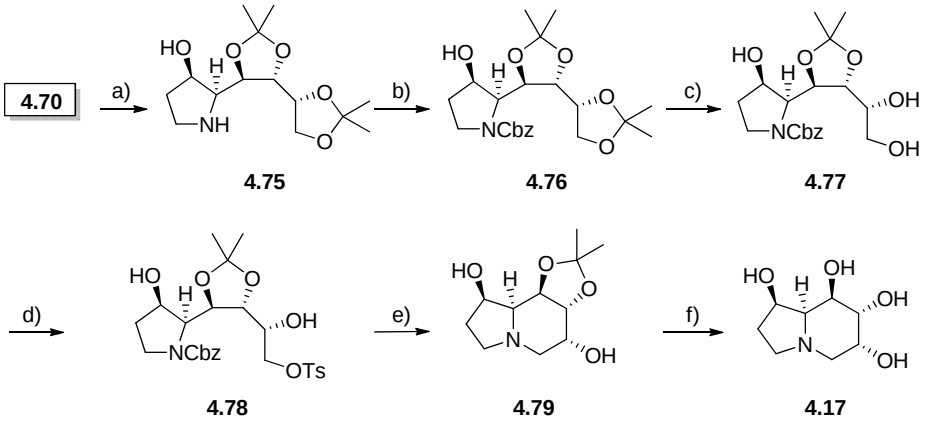
After successful synthesis of **4.70,** we moved on towards the synthesis of **4.6, 4.17** and **4.25** from this compound.

4.10. Synthesis of (1*R*,6*R*,7*R*,8*R*,8a*S*)-octahydroindolizine-1,6,7,8-tetraol (1,6,8a-tri-*epi*-castanospermine, 4.17):

In order to synthesize target molecule **4.17,** we first deprotected the tosyl moiety of **4.70** because it would be difficult to deprotect it at the later stage of the synthesis. N-Detosylation was successfully achieved under Birch reaction condition (Na/Liq NH_3) in 90% yield. The resultant free amine was immediately protected by Cbz group (**4.76,** 90%). Other methods such Na-Hg, Mg/MeOH, or Na/naphthalene for the detosyaltion were found either unsuccessful or less yielding. The success of this step was confirmed by observing a strong absorption band for amide carbonyl at 1699 cm^{-1}. The presence of N-Cbz group was also confirmed by ^1H NMR spectrum in which a multiplet at δ 7.34 integrating for five protons and a singlet at δ 5.13 integrating for two benzylic protons were observed. The ^{13}C NMR spectrum, displayed a signal at 156.02 cm^{-1} for Cbz carbonyl. ESI mass showed a base peak at *m/z* 422 [M+1].

Since the transformation of **4.77** to corresponding **4.79** would require cyclization through terminal hydroxyl group, terminal acetonide was first deprotected by refluxing it in $CH_3COOH/MeOH/H_2O$ (3:2:1) and the resultant primary –OH group was tosylated regioselectively to obtain **4.78** for better leaving ability. The formation of **4.78** was confirmed by ^1H and ^{13} C NMR analyses. The methyl proton of

tosyl group resonated at δ 2.41 in ^{1}H NMR whereas corresponding carbon signals appeared at δ 21.58 in ^{13}C NMR.



Scheme 4.13. Reagents and conditions: *a) Na/Liq NH_3, -78 °C, 1 h; b) aq. K_2CO_3, CbzCl, CH_2Cl_2, 0 °C to rt, 30 min, 75% over two steps; c) $CH_3COOH/MeOH/H_2O$, (3:2:1), reflux, 5 h, 75%; d) Et_3N, TsCl, Bu_2SnO (cat), dry CH_2Cl_2, 0 °C, 2 h, 90%; e) H_2, Pd-C-10%, NaOAc, rt, 12 h, f) Dowex 50W-X8, THF-H_2O (3:1), reflux 12 h, 90% over two steps.*

After having fully functionalized **4.78** in hand, our next concern was -NCbz deprotection followed by intramolecular cyclization and global deprotection to complete the total synthesis of 1,6,8a-tri-*epi*-castanoeprmine **4.17**. In this context, the deprotection of -NCbz group and intramolecular cyclization was carried in one pot by catalytic hydrogenation (Pd/C, 10%) in the presence of sodium acetate in dry MeOH which gave **4.79** in 90% yield. The crude **4.79** on refluxing with acidic Dowex 50W-X8 in THF-H_2O (3:1) gave target molecule **4.17** in 85% yield.

Compound **4.17** was fully characterized by IR, ^{1}H NMR, and ^{13}C NMR spectrum. In ^{1}H NMR spectrum**,** H1 appeared at δ 4.61 (ddd, *J* = 2.5, 4.8, 9.2 Hz), while H8 was found at δ 4.29 (dd, *J* = 1.6, 3.8 Hz) and the H6 resonated at δ 4.14 (ddd, *J* = 3.2, 4.7, 10.9 Hz). Two other signals appearing at δ 3.92 (dd, *J* = 3.5, 3.6 Hz) and δ 2.57 as multiplets were assigned to H7 and H8a, respectively. The ^{13}C NMR showed three methylene groups at δ 32.9 (C_2), 51.2 (C_3), and 51.9 (C_4). The five methine carbons appeared at δ 63.3 (C_{8a}), 65.0 (C_6), 69.3 (C8), 69.4 (C_1), and 71.9 (C_7). Finally the structure of **4.17** was confirmed by ESI mass spectrum by observing *m/z* 190 [M+1].

This tentatively assigned stereochemistry was further refined on the basis of extensive 2D-NMR studies of COSY and NOSEY ^{1}H NMR spectrum as shown in Figure 4.5.

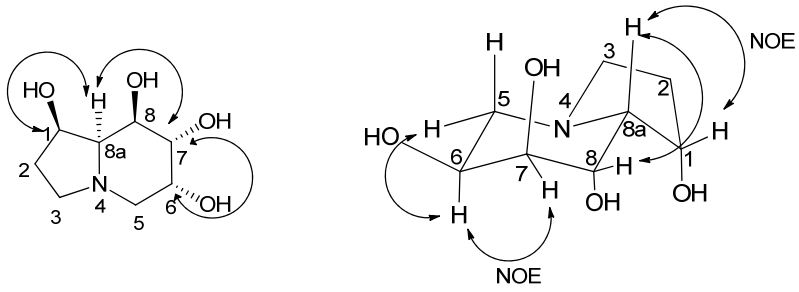


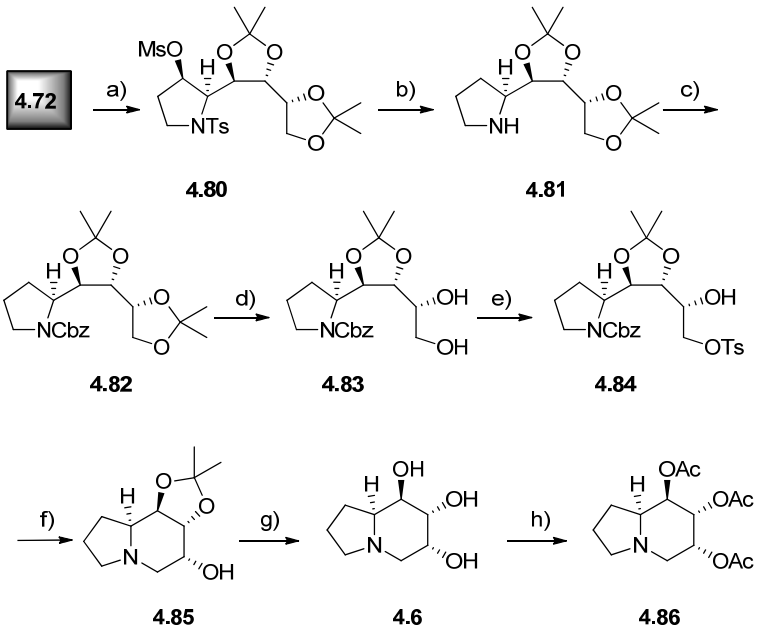
Figure 4.6. *Graphical summary of NOESY observed in* ***4.17***

The NOESY NMR spectrum showed a number of characteristic interactions; e.g. H8a showed a strong NOESY with H1 as well as H8, confirming their same spacial orientations. In another interaction, H6 showed relation with H7 and H5α indicating their *cis* orientation. Since, H7 didn't show any interaction with H8, it is suggested that they may be "*trans*" to each other.

4.11. Synthesis of (6*R*,7*R*,8*R*,8a*S*)-octahydroindolizine-6,7,8-triol-(1-deoxy-6,8a-di-*epi*-castanospermine 4.6):

After successfully completing the total synthesis of 1,6,8a-tri-*epi*-castanospermine **4.17**, we focused our effort on the synthesis of 1-deoxy-6,8a-diepi-castanospermine **4.6** from the hydroxyl pyrrolidine **4.70** by following the steps as shown in Scheme 4.10 .

Towards our effort for deoxygenation of C3-OH of **4.70**, free hydroxyl moiety was first mesylated using mesylchloride in the presence of triethyl amine to obtain **4.80** in 85% yield. The formation of **4.80** was confirmed by the appearance of a signal for methyl protons of mesyl group at δ 2.99 in the ^{1}H NMR spectrum and at 38.39 in ^{13}C NMR spectrum.



Scheme-4.14. Reagents and conditions: *MsCl, Et_3N, 0 °C, 1 h, 85%; b) LAH, reflux, 5 h,87%; c) aq K_2CO_3, CbzCl, 0 °C to rt, 1 h, 85% over two steps; d) $CH_3COOH/MeOH/H_2O$, (3:2:1), reflux, 5 h, 77%; e) Et_3N, TsCl, Bu_2SnO (cat), dry CH_2Cl_2, 0 °C, 2 h, 90%; f) H_2, Pd-C-10%, NaOAc, rt, 12 h, g) Dowex 50W-X8, THF-H_2O (3:1), reflux 12 h, 88% over two steps; h) Py, Ac_2O, rt 10 h, 90%.*

LAH reduction of **4.80** in dry THF under reflux condition, to our delight, produced **4.81** in 87% yield by effecting deoxygenation as well as *N*-detosylation in the same pot. As per our synthetic plan secondary amine of **4.81** was immediately protected by Cbz group to give **4.82 (**85% yield), characterized by ^{1}H and ^{13}C NMR spectra. The ^{1}H NMR spectrum showed benzylic protons at δ 5.13 (dd, *J* = 12.6 Hz, 2H) and aromatic protons as multilplet at δ 7.34. ESI mass at *m/z* 406 [M+1] further supported the transformation.

Synthesis of 1-deoxy-6,8a di-*epi*-castanospermine (**4.6)** was achieved in four steps from the intermediate **4.82** by following the same reaction sequences as shown in previous Scheme 4.9 from compound **4.76-4.17**.

The structural assignments of **4.6** were accomplished by ^{1}H NMR and ^{13}C NMR spectroscopy and the relative stereochemistry was ascertained from 2D COSY and NOESY correlation spectra (**Figure 4.6a** and **4.6b**).

In the ^{1}H NMR, the signals appearing at δ 4.20 (ddd, *J* = 3.2, 4.8, 10.5 Hz), δ 4.11 (dd, *J* = 3.4, 3.3 Hz), δ 3.90 (dd, *J* = 3.4, 1.8 Hz) and a multiplet at δ 2.73 were

assigned to 6- β-H, 7-β-H, 8-α-H and 8a-α-H, respectively. ^{13}C NMR showed three signals at 72.8, 70.3 and 67.5 corresponding to the three carbons attached to hydroxyl functionality. The other signals appearing at δ 62.9, δ 54.2, and δ 54.9 were assigned to (C_{8a}) C_3 and C_5 carbons, respectively. The most up field signals at δ 24.5 and δ 22.7 were assigned as C_1 and C_2 carbons, respectively.

NOSEY spectrum showed that H8 and H8a are close to one another in space s. In addition, comparison of the rotation of **4.6** with the literature value confirmed the absolute stereochemistry. {$[\alpha]^{25}_D$ = + 23.6 (0.90), MeOH: literature report[26] $[\alpha]^{25}_D$ = + 23.0 (MeOH)},

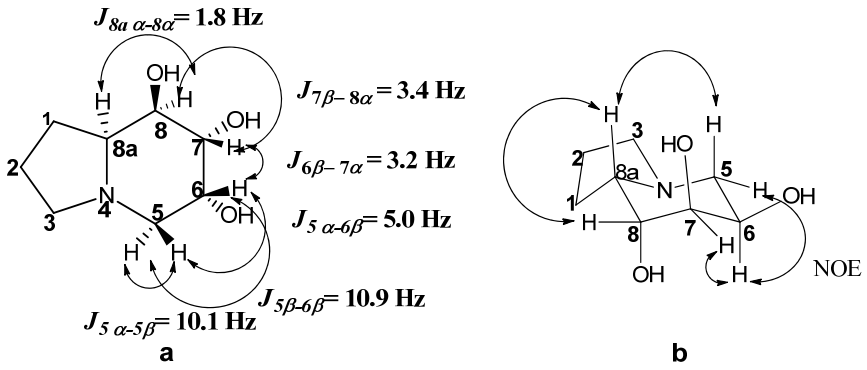


Figure 4.7 a) Meaningful coupling constants **b**) graphical summary of NOESY observed

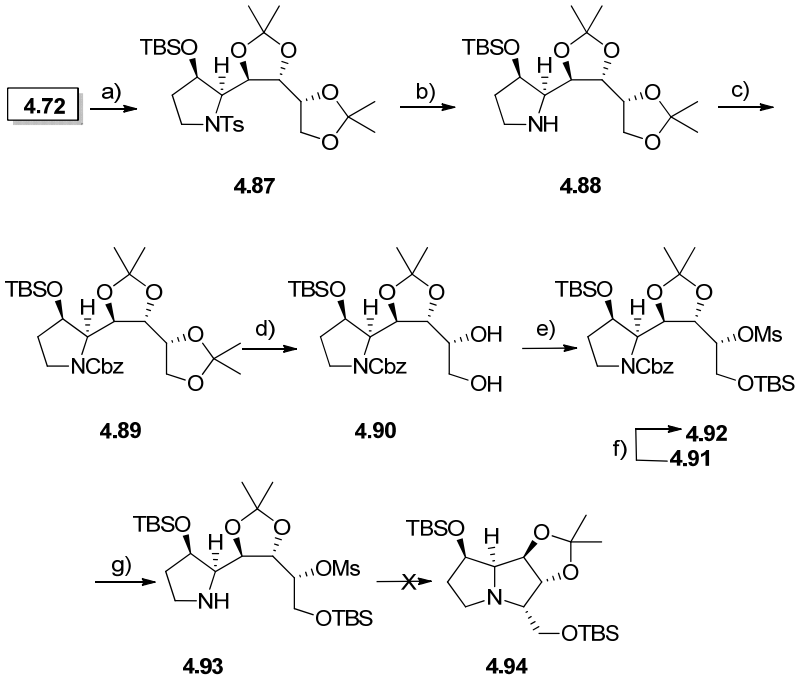
Since, the acetate derivative of **4.6** was reported by Aamid *et al*. in 1990[25] , we also converted our product into its triacetate derivative **4.86** using Ac_2O/Py and all spectral data and specific rotation of **4.86** matched excellently with the reported data.

4.12. (1*R*,2*R*,3*S*,7*R*,7aS)-3-(hydroxymethyl)-hexahydro-1H-pyrrolizine-1,2,7-triol (3,7-di-*epi*-alexine, 4.25):

We executed the synthesis of 3,7-di-*epi*-alexine **4.25**, as perceived through the retrosynthetic analysis (Scheme 4.5) by first protecting the free hydroxyl group of **4.70** as –OTBS ether (TBSOTf and Et_3N in dry DCM) derivative **4.87** (90 % yield). The characteristic signals of TBS group were observed in ^{1}H and ^{13}C NMR spectra. *N*-Detosylation under Birch reaction condition followed by Cbz protection gave **4.89** in 85% yield over two steps. The terminal acetonide of **4.89** was selectively hydrolyzed under mild acidic conditions using DOWEX 50 X8 to give diol **4.90** in quantitative yield**.** The ^{1}H and ^{13}C NMR spectrum revealed the disappearance of

acetonide confirming the formation of **4.90.** Selective TBS protection followed by mesylation produced **4.92** in 90% yield.

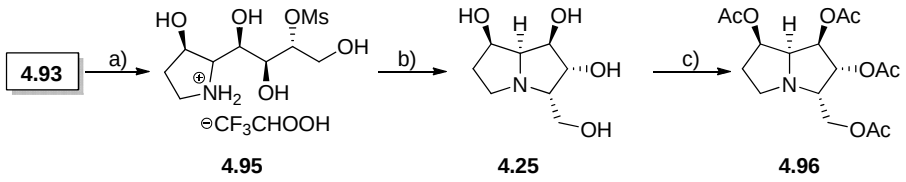
It was envisioned that Cbz deprotection of **4.92** under hydrogenation condition (H_2/Pd-C) in the presence of sodium acetate would give the desired cyclized product **4.94.** However, surprisingly we isolated uncyclized **4.93**. Further, we summarized that strong basic medium may effect the cyclization to produce **4.94.** Towards this end, several bases such as K_2CO_3, NaH and *n*-BuLi were evaluated but all attempts were found in vein.



Scheme-4.15. ***Reagents and conditions:*** *a) TBSOTf, Et_3N, CH_2Cl_2, 0 °C to rt 2 h, 92%; b) Na/Liq NH_3, -78 °C, 1 h; c) aq. K_2CO_3, Cbz, CH_2Cl_2, 0 °C to rt, 1 h, 85% over two steps; d) Dowex 50W-X8, MeOH:H_20, (9:1), 90%; e) TBSCl, Im, CH_2Cl_2, rt, 1 h, 90%; f) MsCl, Et_3N, THF, 0 °C, 30 min, 85%, g) H_2, Pd/C-10%, NaOAc, MeOH, rt 12 h, 90%.*

This failure may be due to the presence of *trans* diol protected acetonide causing strain and a sterically bulky TBS group at the adjacent carbon. Therefore, all the protecting groups of **4.93** were removed by heating with 90% aqueous trifluroacetic acid to free it from all steric restrictions and obtained **4.95**. Treatment of **4.95** with sodium acetate resulted in the clean cyclization and obtained desired 3,7-di-*epi*-alexine **4.25** in 89 % yield over the last two steps (based on crude product). Due to

high polarity of the product, it was purified after converting it to tetracetate derivative **4.96,** characterized by ^{1}H, ^{13}C and 2D NMR spectrum.



Scheme-4.16. *Reagents and conditions:90% aq TFA, 2 h; b) NaOAc, MeOH, rt 12 h; c) Ac2O, Py, DMAP (cat), rt 12 h, 75% yield over three steps.*

The ^{1}H NMR of **4.96** displayed three singlets at δ 2.03, 2.08, 2.09, integrating for three, six and three protons, respectively, which were assigned to four methyl of acetyl groups. While H7 appeared at δ 5.39 as a multiplet, H2 appeared at δ 5.51 (dd, J = 6.26, 7.54 Hz, 1H). The H1 resonated at δ 5.39 as a doublet of doublet with coupling constant 3.91 Hz and 8.27 Hz. The H8 and H8' were found at δ 4.01 and δ 3.86 as doublet of doublet with the coupling constant 5.74 and 11.10 Hz. The H7a appeared at δ 3.36 (dd, *J* = 5.92, 6.34 Hz, 1H), the higher coupling constant suggesting *cis* relationship between these protons. In the ^{13}C NMR spectrum three methylene carbons appeared at δ 29.7, 53.8 and 65.0 whereas four acetate carbonyl carbons appeared at δ 170.0, 170.1, 170.2, and 170.7. The ESI mass spectrum gave base peak at m/z 380 (M+Na). The stereochemistry of **4.96** was further defined on the basis of extensive study COSY and NOSEY ^{1}H NMR spectra. The NOSEY spectrum displayed strong interaction $H_{7a,}$ H_7 and H_1 confirming its same spacial arrangement.

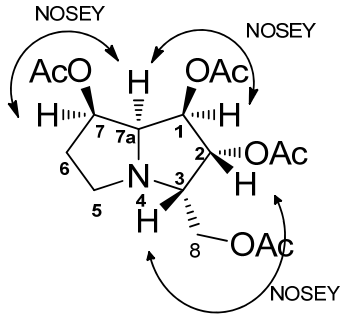


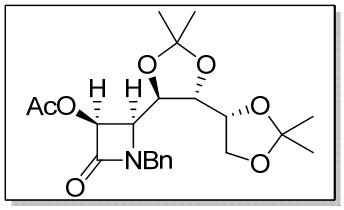
Fig-4.8, *NOSEY interaction in* ***4.96***

4.13. Conclusion:

In conclusion, we have demonstrated the utility of azetidin-2-one as a synthon for the synthesis of 1,6,8a-tri-*epi*-castanospermine (**4.17**), 1-dexoy-6,8a-di-*epi*-castanospermine (**4.6**) and 3,7-di-*epi*-alexine (**4.25**). In these syntheses, crucial step has been the synthesis of hydroxyl pyrrolidine (**4.70**) *via* an aza-Pyane rearrangement of corresponding **4.74**. The starting *β*-lactam was also made available easily in optically pure form from D-mannitol triacetonide.

4.13 Experimental:

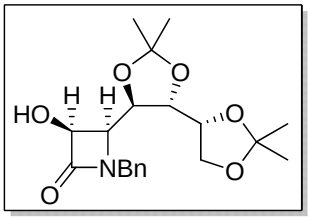
General procedure for the synthesis of 3-Acetoxy azetidin-2-one (4.65):



A solution of acetoxy acetyl chloride (11.2 mL, 10.3 mmol) in anhydrous dichloromethane (200 mL) was added to a precooled solution of imine (22 g, 6.8 mmol), anhydrous triethylamine (33.5 mL, 3.5 eq.) in anhydrous dichloromethane (400 mL) at -25 °C over a period of 1 h. The reaction mixture was allowed to warm to room temperature and stirred for 18 h. After completion of the reaction (TLC), the reaction mixture was diluted with dichloromethane and washed successively with water and brine. The organic layer was dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to get the crude product. The crude reaction mixture was purified using column chromatography (20% ethyl acetate-petroleum ether) to get pure compound as thick colourless oil.

Yield: 65%; colourless oil; $[\alpha]^{27}$: + 15.6 (c = 1.5, $CHCl_3$)**: IR (ν_{max}, $CHCl_3$):** 1770, $cm.^{-1}$ **^{1}H NMR ($CDCl_3$, 200 MHz):** δ = 1.11 (s, 3H), 1.1.8 (s, 3H), 1.29 (s, 6H), 2.05 (s, 3H), 3.48 (t, *J* = 7.12 Hz, 1H), 3.79-3.88 (m, 2H), 3.98-4.14 (m, 3H), 4.21-4.25 (m, 1H), 4.81 (d, *J* = 14.5 Hz, 1H) 5.89 (d, *J* = 4.88 Hz, 1H), 7.17-7.29 (m, 5H); **^{13}C NMR ($CDCl_3$, 50 MHz):** 20.74, 24.95, 26.27, 27.00, 27.29, 45.59, 57.21, 67.43, 73.61, 76.13, 78.56, 80.26, 109.64, 109.90, 127.81, 128.24, 128.76, 135.19, 165.26, 169.15; **MS:** *m/z* = 492 (M+1); **Anal. Calcd**. For $C_{22}H_{29}NO_7$: C, 62.99; H, 6.97; N, 3.34. Found: C, 62.87, H, 6.91; N, 3.31.

General procedure for the synthesis of 3-Hydroxy azetidin-2-one (4.66):

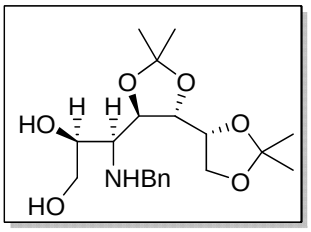


To a solution of 3-acetoxy *β*-lactam **4.65** (22 g, 47.7 mmol) in methanol (140 mL) was added a saturated aqueous solution of $NaHCO_3$ (70 mL) followed by solid Na_2CO_3 (cat). The reaction mixture was stirred at room temperature for 7 h. After the reaction was over (monitored by TLC), methanol and water was evaporated to dryness under reduced pressure and the resultant residue was dissolved in ethyl acetate and filtered through sintered funnel to remove sodium bicarbonate and sodium carbonate. The organic

layer was washed successively with water (50 mL) and brine (50 mL). The combined organic layer was dried over (Na_2SO_4) and the solvent was removed. The crude product was purified by column chromatography on silica gel (acetone- petroleum ether 2:8 as eluent) to get **4.66** as a white solid

Yield: 86%; mp 122-124 ^oC; **$[\alpha]_D^{27}$**: +9.5 (c = 1.2, $CHCl_3$)**: IR (ν_{max}, $CHCl_3$):** 1759, 3402 $cm.^{-1}$ **^{1}H NMR ($CDCl_3$, 500 MHz):** δ = 1.32 (s, 6H), 1.34 (s, 6H), 3.49 (dd, *J* = 6.72, 1.4 Hz, 1H), 3.88 (dd, *J* = 5.74, 8.80 Hz, 1H), 3.98-4.03 (m, 2H), 4.12-4.16 (m, 1H), 4.20 (d, *J* = 14.90 Hz, 1H), 4.75 (d, *J* = 14.70 Hz, 1H), 4.81 (d, *J* = 5.75 Hz, 1H), 7.30-7.31 (m, 5H). **^{13}C NMR ($CDCl_3$, 125 MHz):** 25.21, 26.37**,** 26.99, 27.11, 45.26, 76.80, 76.93, 79.79, 81.77, 110.04, 110.35, 128.57, 128.65, 135.81, 168.81. **MS:** *m/z* = 378 (M+1). **Anal. Calcd**. For $C_{20}H_{27}NO_6$: C, 63.64; H, 7.21; N, 3.71. Found: C, 63.77, H, 7.18; N, 3.65.

General procedure for the synthesis of (*2S, 3S*)-3-(benzylamino)-3-((*4S,4'R,5R*)-2,2,2'2'-tetramethyl-4,4'-bi(1,3-dioxolan)-5-yl)propane-1,2-diol (4.67):

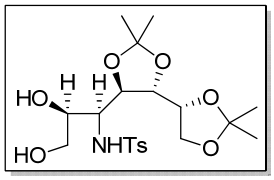


To a mixture of dry THF (100 mL) and $LiAlH_4$ (4.75g, 125 mmol) at 0 °C, a solution of 3- hydroxyl *β*-lactam **4.66** (18.8 g, 50 mmol) in dry THF (50 mL) was added drop wise over a period of 10 minutes. Ice bath was removed and reaction mixture was allowed to stir for 4-6 hrs under reflux condition, cooled to 0 °C again and subsequently quenched by saturated aqueous solution of sodium sulfate. White precipitate was filtered through sintered funnel, washed by ethyl acetate. Solvent was removed under reduced pressure to obtain colourless oil which was purified by column chromatography using (ethyl acetate-pet ether, 40%) on silica gel, to obtain vicinal diol **4.67** (17 g) as a colourless oil.

Yield: 89%; colourless oil; **$[\alpha]_D^{27}$:** -22 (c = 1.5, $CHCl_3$); **IR (ν_{max}, $CHCl_3$):** 1066, 1455, 3444 $cm.^{-1}$ **^{1}H NMR ($CDCl_3$, 400 MHz):** δ = 1.31 (s, 3H), 1.33 (s, 3H), 1.34, (s, 3H), 1.39 (s, 3H), 2.98 (dd, *J* = 3.5, 4.2 Hz, 1H), 3.67 (m, 2H), 3.74, (t, *J* = 4.20, 8.57 Hz, 1H), 3.83 (d, *J* = 12.89 Hz, 1H), 3.89 (d, *J* = 12.90 Hz, 1H), 3.94-4.02 (m, 3H), 4.11-4.18 (m, 2H), 7.30-7.32 (m, 5H); **^{13}C NMR ($CDCl_3$, 125 MHz):** 25.14, 26.34, 26.93, 27.04, 53.45, 58.82, 65.04, 68.10, 69.96, 77.15, 78.51, 80.44, 109.19,

109.95, 128.24, 128.50, 139.85. **MS:** *m/z* = 382 (M+1); **Anal. Calcd**. For $C_{20}H_{31}NO_6$: C, 62.97; H, 8.19; N, 3.67. Found: C, 63.12, H, 8.15; N, 3.61.

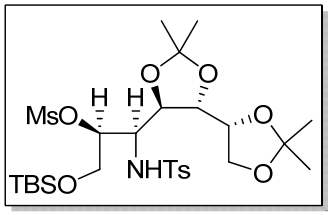
N-((1*S*,2*S*)-*2,3*-dihydroxy-1-((4*S*,4'*R*,5*R*)-2,2,2',2'-tetramethyl-4,4'-bi(1,3-dioxolan)-5- yl)-propyl)-4-methylbenzenesulfonamide (4.68):



To a mixture of **4.67** (16 g, 42 mmol) and 10 % Pd-C (1.6 g) was added ethyl acetate (80 mL). The mixture was stirred at room temperature and under an atmosphere of H_2 for 12 h. The mixture was filtered over celite and obatined primary amine as a colourless oil (12.2 g, 100%). The resultant amine was dissolved in DCM (40 mL) and an aqueous solution K_2CO_3 (6.36 in g, 46 mmol) in H_2O (40 mL) was added drop wise over a period of 10 min at room temperature. To the resultant solution, tosyl chloride (8.79 g, 46 mmol) was added portion wise under stirring. The reaction mixture was allowed to stir for an additional 3h, washed successively with water (20 mL) and brine (20 mL), dried over anhydrous sodium sulphate and concentrated to dryness. The crude product was chromatographed (50% ethyl acetate- petroleum ether) yielding 17.0 g of the desired product **4.68** in pure form.

Yield: 91%; white sticky solid; $[\alpha]_D^{27}$ -13.5 (c = 1.5, $CHCl_3$)**:** **IR (ν_{max}, $CHCl_3$):** 3450, 3293, 1599, 1066, 1160 $cm.^{-1}$ **^{1}H NMR ($CDCl_3$, 500 MHz):** δ = 1.23 (s, 3H), 1.28 (s, 3H), 1.36, (s, 3H), 1.45 (s, 3H), 2.42 (s, 3H), 2.62 (t, *J* = 6.97, 13.5 Hz, 1H), 2.74 (t, *J*= 6.97, 135.5 Hz, 1H), 3.62 (m, 2H), 3.66-3.70 (m, 2H), 3.75 (dd, *J* = 3.31, 7.70 Hz, 1H), 3.80-3.83 (m, 1H), 3.91 (dd, *J* = 2.21, 5.85 Hz, 1H), 3.99 (dd, *J* = 3.74, 7.26 Hz, 1H), 5.65 (d, *J* = 9.32 Hz, 1H), 7.3 (d, *J* = 8.5 Hz, 2H,) 7.76 (d, *J* = 8.5 Hz, 2H); **^{13}C NMR ($CDCl_3$, 125 MHz):** 21.52, 25.07, 26.08, 26.69, 26.79, 54.08, 62.91, 68.07, 71.11, 77.74, 80.48, 109.81, 110.14, 127.04, 129.71, 137.79, 143.77. **MS:** *m/z* = 446 (M+1). **Anal. Calcd**. For $C_{20}H_{31}NO_6$: C, 53.92; H, 7.01; N, 3.14. Found: C, 53.88, H, 7.75; N, 3.22.

General procedure for the synthesis of N-((1*S*,2*S*)-3-(*tert*-butyl dimethylsiloxy)-2-O-methanesulfonyl-1-((4*S*,4'*R*,5*R*)-2,2,2',2'-tetramethyl-4,4'-bi(1,3-dioxolan)-5-yl)-propyl)-4-methylbenzene -sulsulfonamide (4.72):

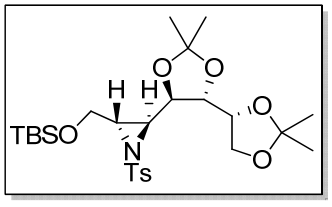


tert-Butyldimethylsilyl chloride (5.6 g, 37 mmol) was

added to a solution of diol **4.68** (15 g, 33 mmol) in dry pyridine (40 mL). The reaction mixture was stirred at room temperature for 5 h under the nitrogen atmosphere after which dichloromethane (200 mL) was added; the organic layer was washed with aqueous hydrochloric acid (200 mL, 1 M), sodium bicarbonate (50 mL) and brine (50 mL). The organic layer was dried over sodium sulfate and the solvent was removed in vacuo until a volume of 50 mL remained. Triethyl amine (6.88 mL, 49.5 mmol) and methanesulfonyl chloride (3.06 mL, 39.6 mmol) were added to the solution of crude silyl ether**.** The reaction mixture was stirred for 30 min at room temperature under nitrogen atmosphere, washed with aqueous hydrochloric acid (100 mL, 1M), sodium bicarbonate (50 mL) and brine (50 mL). The organic layer was dried (sodium sulfate) and the solvent removed to give a residue which was purified by column chromatography (ethyl acetate- petether 30%) to give the corresponding silyl mesylate **4.72** (15 g).

Yield: 71%; colourless oil; **$[\alpha]_D^{27}$:** +33 (c = 1.5, $CHCl_3$)**: IR (ν_{max}, $CHCl_3$):** 1599, 1372, 1160 $cm.^{-1}$ **^{1}H NMR ($CDCl_3$, 400 MHz):** δ = 0.04 (s, 6H), 0.88 (s, 9H), 1.30 (s, 3H), 1.32 (s, 3H), 1.38 (s, 3H), 1.43 (s, 3H), 2.41 (s, 3H), 2.99 (s, 3H), 3.50 (t, *J* = 8.09, 16.30 Hz, 1H), 3.63-3.66 (m, 1H), 3.70-3.73 (m, 2H), 3.92 (dt, *J* = 6.21, 8.09 Hz, 1H), 4.01-4.11 (m, 3H), 4.57-4.61 (m, 1H), 5.30 (d, *J* = 9.42 Hz, 1H), 7.30 (d, *J* = 8.72 Hz, 2H), 7.75 (*J* = 8.73 Hz, 1H). **^{13}C NMR ($CDCl_3$, 125 MHz):** -5.64, 18.11 21.43, 25.07, 25.71, 26.08, 26.82, 26.91, 30.85, 38.21, 52.09, 62.14, 68.01, 72.70, 77.76, 81.40, 109.83, 110.28, 127.01, 137.89, 143.65. **MS:** *m/z* = 637 (M+1). **Anal. Calcd**. For $C_{27}H_{46}NO_{10}S_2Si$: C, 50.92; H, 7.28; N, 2.20. Found: C, 50.89, H, 7.35; N, 2.26.

General procedure for the synthesis of (2*R*,3*R*)-2-((*tert*-butyldimethylsilyloxy)methyl-3-((4*S*,4'*R*,5*R*)-2,2,2',2'-tetramethyl-4,4'bi(1,3-dioxolan)-5-yl)-1-tosylazeridine (4.73):

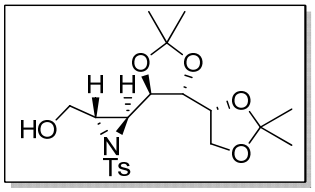


To a solution of mesylate **4.72** (2g, 3.13 mmol) in dry THF (30 mL) at -78 °C, *n*-BuLi (1.43 mL, 2.2 M) was added. The reaction mixture was stirred at this temperature for 2 h, quenched by the addition of saturated NH_4Cl (5 mL) and the reaction mixture allowed to reach room temperature. The aqueous phase was extracted with ethyl

acetate (3 x 30 mL) and the organic extracts were dried over sodium sulfate and solvent was removed under reduced pressure to give crude product which was purified by column chromatography using 100-200 mesh silica gel (20% ethyl acetate-pet ether) to yield **4.73** (0.9 g).

Yield: 53%; colourless oil; **$[\alpha]_D^{27}$:** -9.5 (c = 1.5, $CHCl_3$)**:** **IR (ν_{max}, $CHCl_3$):** 1602, 1381, 1070 $cm.^{-1}$ **^{1}H NMR ($CDCl_3$, 200 MHz):** δ = 0.07 (s, 6H), 0.79 (s, 9H), 1.30 (s, 3H), 1.33 (s, 6H), 1.45 (s, 3H), 2.41 (s, 3H), 2.98 (dd, *J* = 3.82, 7.27 Hz, 1H), 3.06 (m, 1H), 3.71 (dd, *J* = 11.60, 18.84 Hz, 1H), 3.83-3.93 (m, 3H), 3.97-4.06 (m, 2H), 4.14 (dd, *J* = 5.78, 7.83 Hz, 1H), 7.27 (d, *J* = 8.11 Hz, 2H), 7.85 (d, *J* = 8.20 Hz, 2H). **^{13}C NMR ($CDCl_3$, 100 MHz):** -5.56, -5.47, 18.27, 21.58, 25.30, 25.71, 25.80, 26.61, 26.67, 27.18, 43.53, 46.28, 60.47, 67.81, 76.91, 80.65, 109.86, 110.46, 128.30, 129.45, 135.03, 144.29. **MS:** *m/z* = 542 (M+1). **Anal. Calcd**. For $C_{26}H_{43}NO_7SSi$: C, 57.64; H, 8.00; N, 2.59. Found: C, 57.69, H, 7.96; N, 2.49.

General procedure for the synthesis of ((2*R*,3*R*)-3-((4*S*,4'*R*,5*R*)- 2,2,2',2'-tetramethyl-4,4'-bi(1,3-dioxolan)-5-yl)-1-tosylazeridin-2-yl)methanol (4.74):

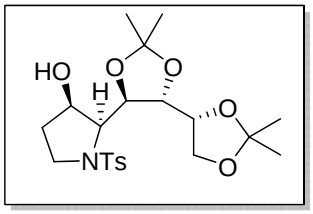


To a stirred solution of **4.73** (0.8 g, 1.47 mmol) in dry THF (20 mL) was added TBAF (1.47 mL of a 1M THF solution, 1.47 mmol) at 0 °C. The reaction mixture was stirred for 1h at the same temperature, quenched by adding few cubes of ice and extracted by ethyl acetate (3 x 15 mL). The organic layer was dried over sodium sulfate and solvent evaporated under reduced pressure. Purification of the crude by column chromatography on silica gel (ethyl acetate-pet ether 40%) afforded **4.74** (0.6 g).

Yield: 94%; colourless oil; **$[\alpha]_D^{27}$** +14.8 (c = 1.6, $CHCl_3$)**:** **IR (ν_{max}, $CHCl_3$):** 3393, 1598, 1372, 1091 $cm.^{-1}$ **^{1}H NMR ($CDCl_3$, 400 MHz):** δ = 1.25 (s, 3H), 1.27 (s, 3H), 1.33 (s, 3H), 1.44 (s, 3H), 2.43 (s, 3H), 2.94 (dd, *J* = 7.83, 15.82 Hz, 1H), 3.11-3.16 (m, 1H), 3.58 (dd, *J* = 8.32, 12.41 Hz, 1H), 3.82-3.86 (m, 2H), 3.93-3.97 (m, 2H), 4.13 (dd, *J* = 5.35, 8.24 Hz, 1H), 7.31 (d, *J* = 8.33 Hz, 2H), 7.83 (d, *J* = 8.30 Hz, 2H). **^{13}C NMR ($CDCl_3$, 100 MHz):** 21.62, 25.11, 26.53, 26.76, 25.86, 43.21, 45.73, 59.34, 67.94, 76.63, 76.87, 80.19, 110.27, 11047, 128.29, 129.48, 134.52, 144.65. **MS:** *m/z* =

428 (M+1). **Anal. Calcd**. For $C_{20}H_{29}NO_7S$: C, 56.19; H, 6.84; N, 3.28. Found: C, 56.29; H, 6.91; N, 3.35.

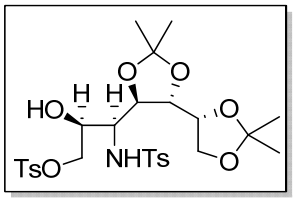
General procedure for the synthesis of (2*S*,3*R*)-2-((4*S*,4'*R*,5*R*)-2,2,2',2'-tetramethyl-4,4'-bi(1,3-dioxolan)-5-yl)-1- tosypyrrolidin3-ol (4.70):



NaH (60%, 1.1 g, 27.2 mmol), washed twice with pet ether, was placed in a flame dried flask and dry DMSO (30 mL) was added via syringe. Trimethyl sulfoxinium iodide (6.15 g, 27.2 mmol) was added in two portions at room temperature. After addition of trimethyl sulfoxinium iodide was complete, the reaction mixture was stirred for an additional 30 min until the bubbling of the milky white suspension ceased. The azeridinol **4.74** (1.5 g, 3.4 mmol) dissolved in dry DSMO (4 mL) was added drop wise, and the reaction mixture was stirred at room temperature for 4 h to complete the azapyene rearrangement. The reaction mixture was covered with aluminium foil and heated to 85 °C for 20 h. The dark brown mixture was cooled and diluted with 50 mL of water. The reaction mixture was extracted by ethyl acetate (5 x 50 mL). The organic layer was washed with aqueous sodium thiosulfate (50 mL) and brine (50 mL), dried over sodium sulfate. Solvent was removed under reduced pressure to yield a gave dark brown liquid on purification by column chromatography (40% ethyl acetate-pet ether) gave **4.70** as a white solid (1.1 g).

Yield: 70%; mp 151-153 ^oC; $[\alpha]^{27}_D$ = +9.8 (c = 0.6, $CHCl_3$)**: IR (ν_{max}, $CHCl_3$):** 3393, 1598, 1372, 1091 $cm.^{-1}$ **^{1}H NMR ($CDCl_3$, 200 MHz):** δ = 1.39 (s, 3H), 1.41 (s, 6H), 1.33 (s, 3H), 1.46 (s, 3H), 1.72-1.86 (m, 2H), 2.43 (s, 3H), 3.38 (ddd, *J* = 4.27, 7.28, 11.68 Hz, 1H), 3.54-3.64 (m, 1H), 3.81 (dd, *J* = 3.81, 5.83 Hz, 1H), 3.95-4.01 (m, 2H), 4.13-4.20 (m, 3H), 7.31 (d, *J* = 8.19 Hz, 2H), 7.75 (d, *J* = 8.19 Hz, 2H). **^{13}C NMR ($CDCl_3$, 50 MHz):** 21.52, 25.41, 26.53, 26.51, 26.71, 27.30, 33.57, 47.02, 60.92, 67.44, 73.15, 76.83, 78.49, 81.57, 109.68, 109.91, 127.81, 129.66, 133.65, 143.86. **MS:** *m/z* = 464 (M+Na). **Anal. Calcd**. For $C_{21}H_{31}NO_7S$: C, 57.12; H, 7.08; N, 3.17. Found: C, 57.18; H, 6.99; N, 3.33.

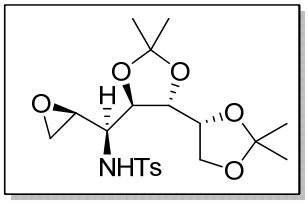
General procedure for the synthesis of (2S,3S)-2-hydroxy-3-(4-methylphenylsulfonamido)-3-((4S,4'R,5R)-2,2,2',2'-tetramethyl-4,4'-bi(1,3-dioxolan)-5-yl)-propym-4-methylbenzenesulfonate (4.68a):



To a solution of **4.68** (0.8 g, 1.79 mmol) in DCM (10 mL) were added *n*-Bu_2SnO (18 mg, 0.072 mmol), *p*-toluenesulfonyl chloride (0.37g, 1.96 mmol) and triethyl amine (0.35 mL, 1.96 mmol) at 0 °C. The reaction mixture was allowed to attain room temperature and was stirred for an additional 2 h. The reaction mixture was filtered through a small pad of celite and the filtrate was concentrated under reduced pressure to give crude product which was purified by column chromatography using (30% ethyl acetate-pet ether) to obtain **4.68a** (0.95 g).

Yield: 88%; sticky solid; **$[\alpha]_D^{27}$:** +27.3 (c = 1.5, $CHCl_3$); **IR (ν_{max}, $CHCl_3$):** 3445, 1597, 1379, $cm.^{-1}$ **^{1}H NMR ($CDCl_3$, 200 MHz):** δ = 1.21 (s, 3H), 1.24 (s, 6H), 1.29 (s, 3H), 1.36 (s, 3H), 2.16, (m, 1H), 2.41 (s, 3H), 2.45 (s, 3H), 3.47-3.75 (m, 3H), 3.86-3.96 (m, 2H), 4.02-4.12 (m, 3H), 5.63 (d, *J* = 9.57 Hz, 1H), 7.27 (d, *J* = 8.20 Hz, 2H), 7.35 (d, *J* = 8.20 Hz, 2H), 7.71 (d, *J* = 8.15 Hz, 2H), 7.76 (d, *J* = 8.14 Hz, 2H). **^{13}C NMR ($CDCl_3$, 50 MHz):** 21.53, 25.25, 26.05, 26.61, 26.77, 43.01, 50.11, 68.17, 76.47, 77.47, 77.72, 79.94, 109.54, 110.44, 126.93, 129.66, 138.16, 143.48. **MS:** *m/z* = 622 (M+Na). **Anal. Calcd**. For $C_{27}H_{37}NO_{10}S_2$: C, 54.07; H, 6.22; N, 2.34. Found: C, 54.11; H, 6.17; N, 2.33.

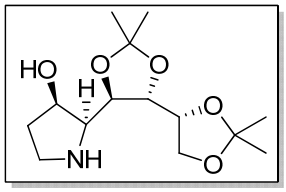
General procedure for the synthesis of 4-methyl-N-((S)-((S)-oxiran-2-yl)-((4*S*,4'*R*,5*R*)-2,2,2',2'-tetramethyl-4,4'-bi(1,3-dioxolan)-5-yl)-propym-4-methylbenzenesulfonmide (4.69):



Anhydrous K_2CO_3 (0.26 g, 1.87 mmol) was added at room temperature to a solution of **4.68a** (0.9 g, 1.5 mmol) in dry CH_3CN (15 mL) and it was stirred at same temperature for 6 h. The reaction mixture was passed through a pad of celite to remove excess K_2CO_3, filtrate was concentrated under reduced pressure to give crude product which was purified by column chromatography (ethyl acetate-pet ether 25%) to obtain **4.69** (0.6 g).

Yield: 93%; colourless oil; $[\alpha]^{27}_{D}$ = -5.65 (c = 0.5, $CHCl_3$); **IR (ν_{max}, $CHCl_3$):** 3449, 2987, 1629, 1372, $cm.^{-1}$ **^{1}H NMR ($CDCl_3$, 200 MHz):** δ = 1.23 (s, 3H), 1.34 (s, 3H), 1.39 (s, 3H), 1.49 (s, 3H), 2.65 (dd, *J* = 4.17, 5.11 Hz, 1H), 2.76 (dd, *J* = 2.63, 4.93 Hz, 1H), 3.19 (m, 1H), 3.60 (dd, *J* = 2.98, 7.75 Hz, 1H), 3.73-3.90 (m, 4H), 4.13 (dd, *J* = 5.78, 8.68 Hz, 1H), 5.79 (d, *J* = 9.79 Hz, 1H), 7.30 (d, *J* = 8.05 Hz, 2H), 7.75 (d, *J* = 8.10 Hz, 2H). **^{13}C NMR ($CDCl_3$, 50 MHz):** 21.46, 25.18, 26.00, 26.55, 26.71, 42.93, 50.03, 51.47, 68.09, 76.37, 77.65, 79.86, 109.47, 110.33, 128.86, 129.60, 138.10, 143.42. **MS:** *m/z* = 428 (M+1). **Anal. Calcd.** For $C_{20}H_{29}NO_7S$: C, 56.19; H, 6.84; N, 3.28. Found: C, 56.24; H, 6.79; N, 3.31.

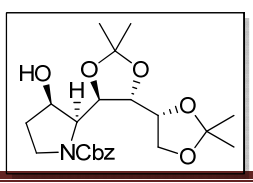
General procedure for the synthesis of (2*S*,3*R*)-2-((4*S*,4'*R*,5*R*)-2,2,2',2'-tetramethyl-4,4'-bi(1,3-dioxolan)-5-yl)-pyrrolidin-3-ol (4.75):



To a RB flask, fitted with cold finger condenser (acetone/solid CO_2), conatining **4.70** (0.3 g, 0.68 mmol) was introduced anhydrous ammonia (100 mL) at -20 0^C . Small pieces of sodium were added to the stirring solution until the solution became persistently dark blue. After 30 min, the reaction mixture was quenched by the addition of solid NH_4Cl, and allowed to stir until all ammonia had evaporated. The remaining solid was filtered through sintered funnel and washed with ethyl acetate three times. Evaporation of solvent under reduced pressure gave **4.75** (0.18 g). This was characterized without any purification.

Yield: 92%; colourless oil; $[\alpha]^{27}_{D}$ = +6.53 (c = 0.5, $CHCl_3$); **IR (ν_{max}, $CHCl_3$):** 3453, 2988, 1636, 1114, $cm.^{-1}$ **^{1}H NMR ($CDCl_3$, 200 MHz):** δ = 1.35 (s, 6H), 1.39 (s, 3H), 1.43 (s, 3H), 1.76-1.90 (m, 1H), 1.97-2.08 (m, 1H), 2.84-2.95 (m, 2H), 3.24 (dt, *J* = 7.84, 10.63 Hz, 1H), 3.84 (dd, *J* = 6.94, 8.46 Hz, 1H), 3.96 (dd, *J* = 5.37, 7.95 Hz, 1H), 4.01-4.13 (m, 2H), 4.16-4.27 (m, 3H). **^{13}C NMR ($CDCl_3$, 50 MHz):** 25.18, 26.20, 26.85, 26.99, 34.72, 44.30, 67.02, 68.26, 71.88, 77.39, 79.73, 80.50, 109.54, 110.18. **MS:** *m/z* = 289 (M+1). **Anal. Calcd.** For $C_{14}H_{25}NO_5$: C, 58.52; H, 8.77; N, 4.87. Found: C, 58.48; H, 8.73; N, 4.91.

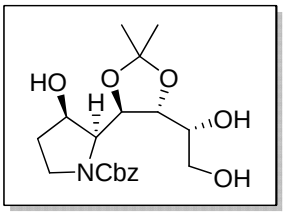
General procedure for the synthesis of (2*S*,3*R*)-benzyl-3-hydroxy-2-((4*S*,4'*R*,5*R*)-2,2,2',2'-tetramethyl-4,4'-bi-(1,3-dioxolan)-5-yl) pyrrolidine-1-carboxylate (4.76):



To a solution of **4.75** (0.861 g, 3 mmol) in CH_2Cl_2 (10 mL) was added aq K_2CO_3 (1.24 g, 9 mmol) and the mixture was cooled in an ice bath. To this stirring mixed-phase solution was added drop wise a solution of benzylchloroformate (0.85 mL, 6 mmol) in CH_2Cl_2 (5 mL), mixture allowed further to stir at r.t. for 30 min. The organic phase was washed with brine, and evaporated. The residue was chromatographed on silicagel (ethyl acetate-pet ether, 40%) to give **4.76** (1.15 g).

Yield: 90%; colourless oil; $[\alpha]^{27}_D$ = +3.88 (c = 0.5, $CHCl_3$); **IR (ν_{max}, $CHCl_3$):** 3453, 2986, 1699, 1412, $cm.^{-1}$ **^{1}H NMR ($CDCl_3$, 400 MHz):** δ = 1.30 (s, 3H), 1.34 (s, 6H), 1.37 (s, 3H), 1.96-2.08 (m, 1H), 2.17-2.25 (m, 1H), 2.38 (d, *J* = 8.51 Hz, 1H), 3.46 (dd, *J* = 7.84, 10.63 Hz, 1H), 3.84 (dd, *J* = 3.01, 9.44 Hz, 1H), 1.05-4.25 (m, 6H), 4.41, (dd, *J* = 7.82, 16.12 Hz, 1H), 5.13 (s, 2H), 7.34-7.35 (m, 5H) **^{13}C NMR ($CDCl_3$, 125 MHz):** 25.14, 26.07, 26.53, 27.22, 44.31, 58.87, 66.38, 67.08, 71.53, 76.82, 77.51, 109.28, 108.83, 128.03, 128.44, 136.47, 155.93. **MS:** *m/z* = 428 (M+1). **Anal. Calcd**. For $C_{22}H_{31}NO_7$: C, 62.69; H, 7.41; N, 3.32. Found: C, 62.72; H, 7.53; N, 3.41.

General procedure for the synthesis of (2*S*,3*R*)-benzyl-2-((4*R*,5*R*)-5-(*R*)-1,2-dihydroxyethyl)-2,2-dimethyl-1,3-dioxolan-4-yl)-3-hydroxypyrrolidine-1-carboxylate (4.77):

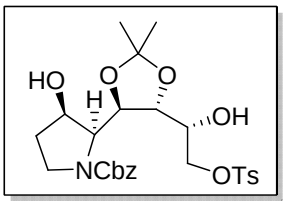


A solution of N-Cbz protected hydroxyl pyrrolidine **4.76** (1.28 g, 3 mmol) in a mixture of solvents containing methanol (3 mL), acetic acid (6 mL) and water (1 mL) was stirred at reflux temperature for 4 h under a nitrogen atmosphere. Solid sodium bicarbonate was added until all acetic acid was neutralized. The reaction mixture was extracted with ethyl acetate (100 mL), washed with water (50 mL), organic layer dried over sodium sulfate and evaporated. Purification of the residue by column chromatography (acetone-petether, 40%) gave **4.77** (0.85 g).

Yield: 75%; colourless oil; $[\alpha]^{27}_D$ = -13.56 (c = 1.5, $CHCl_3$); **IR (ν_{max}, $CHCl_3$):** 3417, 2985, 1682, 1417, $cm.^{-1}$ **^{1}H NMR ($CDCl_3$, 200 MHz):** δ = 1.30 (s, 3H), 1.38 (s, 3H), 2.04-2.32 (m, 2H), 2.45 (d, *J* = 10.30 Hz, 1H), 3.48 (dd, *J* = 7.84, 9.76 Hz, 2H), 3.59-3.72 (m, 2H), 3.79-3.88 (m, 1H), 4.21-4.31 (m, 2H), 4.35-4.47 (m, 2H), 5.13 (s,

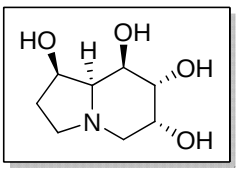
2H), 7.35 (bs, 5H) **^{13}C NMR ($CDCl_3$, 50 MHz):** 26.45, 27.09, 32.58, 44.12, 58.94, 65.01, 67.64, 71.58, 73.36, 75.75, 79.34, 108.80, 127.83, 128.22, 128.51, 136.07, 156.89. **MS:** *m/z* = 382 (M+1). **Anal. Calcd.** For $C_{19}H_{27}NO_7$: C, 59.83; H, 7.14; N, 3.67. Found: C, 59.75; H, 7.22; N, 3.59

General procedure for the synthesis of (2*S*,3*R*)-benzyl-3-hydroxy-2-((4*R*,5*R*)-5-(*R*)-1-hydroxy-2-(tosyloxy)ethyl)-2,2-dimethyl-1,3-dioxolan-4-yl)pyrrolidine-1-carboxylate (4.78):



Yield: 90%; white sticky solid; **$[\alpha]^{27}_D$** = +7.67 (c = 1.1, $CHCl_3$); **IR (ν_{max}, $CHCl_3$):** 3402, 2985, 1674, 1115, cm.$^{-1}$ **^{1}H NMR ($CDCl_3$, 200 MHz):** δ = 1.27 (s, 3H), 1.34 (s, 3H), 2.01-2.28 (m, 3H), 2.41 (s, 3H), 3.39-3.48 (m, 2H), 3.60 (dt, *J* = 3.27, 6.30 Hz, 1H), 3.83-3.86 (m, 1H), 4.10-4.20 (m, 4H), 4.34-4.47 (m, 1H), 5.06-5.21 (m, 2H), 7.29-7.36 (m, 7H), 7.84 (d, *J* = 8.5 Hz, 2H) **^{13}C NMR ($CDCl_3$, 50 MHz):** 21.58, 26.49, 27.01, 33.13, 43.94, 58.74, 67.84, 71.36, 71.93, 74.02, 80.19, 108.93, 128.05, 128.53, 129.67, 132.99, 136.12, 144.56, 156.86. **MS:** *m/z* = 536 (M+1). **Anal. Calcd.** For $C_{26}H_{33}NO_9S$: C, 58.30; H, 6.21; N, 2.62. Found: C, 58.27; H, 6.26; N, 2.57.

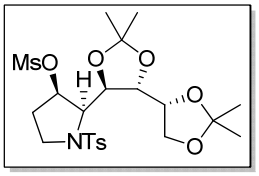
General procedure for the synthesis of (1*R*,6*R*,7*R*,8*R*,8a*S*)-octahydroindolizidine-1,6,7,8-tetraol-(1,6,8a-tri-epi-castanospermine (4.17) :



A mixture of **4.78** (0.1 g, 0.18 mmol), anhydrous sodium acetate (0.073 g, 0.9 mmol) and 10 % Pd/C (20 mg) in dry methanol (1.5 mL) was hydrogenated at atmospheric pressure for 10 h. The catalyst was filtered, methanol was evaporated and residue was dissolved in DCM. The organic layer was washed with water and brine, and dried over sodium sulfate. Solvent was removed and the crude product was refluxed over night with Dowex 50W-X8 (50 mg) in THF-H_2O (3:1). The reaction mixture was filtered and washed with MeOH. The remaining residue was eluted with 2N NH_3 solution. The NH_3 solution was evaporated to gave crude product which was purified by column chromatography (MeOH/EtOAc 10%) to obtain 1,6,8a tri-epi-castanospermine **4.17** (19 mg.)

Yield: 90%; colourless oil; $[\alpha]^{27}_{D}$ = −60.34 (c = 0.7, $CHCl_3$); **IR (ν_{max}, Neat):** 3434, 1403, 1265, cm.$^{-1}$ **^{1}H NMR (D_2O, 400 MHz):** δ = 1.69-1.82 (m, 1H), 2.35-2.57 (m, 3H), 3.07 (dd, *J* = 4.91, 10.6 Hz, 1H), 3.13 (t, *J* = 8.9, 17.24 Hz, 1H), 3.92 (t, *J* = 3.42, 7.21 Hz, 1H), 4.10-4.19 (m, 1H), 4.29 (dd, *J* = 1.64, 3.92 Hz, 1H), 4.57-4.64 (m, 1H). **^{13}C NMR ($CDCl_3$, 100 MHz):** 32.91, 51.25, 51.88, 63.25, 65.02, 69.25, 69.38, 71.94. **MS:** *m/z* = 190 (M+1). **Anal. Calcd**. For $C_8H_{15}NO_4$: C, 50.78; H, 7.99; N, 7.40. Found: C, 50.81; H, 7.95; N, 7.43.

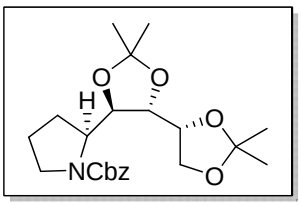
General procedure for the synthesis of (2*R*,3*R*)-2-((4*S*,4'*R*,5*R*)-2,2,2',2'-tetramethyl-4,4'-bi(1,3-dioxolan)-5-yl)-1-tosypyrrolidin3-yl methanesulfonate (4.80):



To a solution of **4.70** (0.5 g, 1.13 mmol) in dry DCM (4 mL) were added Et_3N (0.39 mL, 2.8 mmol) and methanesulfonyl chloride (0.13 mL, 1.7 mmol) at 0 °C. The reaction mixture was stirred for 30 min at r.t., and was subsequently quenched with sat. $NaHCO_3$ (5 mL). The reaction mixture was extracted with EtOAc (3 x 10 mL). The organic layer was concentrated and the residue was chromatographed on silica gel (EtOAc/petether 35%) to give **4.80** (0.54 g).

Yield: 91%; colourless oil; $[\alpha]^{27}_{D}$ = −13.13 (c 0.6, $CHCl_3$); **IR (ν_{max}, $CHCl_3$):** 1597, 1353, cm.$^{-1}$ **^{1}H NMR ($CDCl_3$, 200 MHz):** δ = 1.36 (s, 6H), 1.42 (s, 3H), 1.54 (s, 3H), 2.03-2.13 (m, 1H), 2.33-2.38 (m, 1H), 2.43 (s, 3H), 2.99 (s, 3H), 3.29 (dt, *J* = 8.46, 11.04 Hz, 1H), 3.51 (ddd, *J* = 2.89, 9.91, & 12.80 Hz, 1H), 3.97 (dd, *J* = 5.83, 7.54 Hz, 1H), 4.04-4.23 (m, 5H), 4.41-4.48 (m, 1H), 7.34 (d, *J* = 8.2 Hz, 2H), 7.67 (d, *J* = 8.19 Hz, 2H). **^{13}C NMR ($CDCl_3$, 100 MHz):** 21.56, 25.41, 26.14, 26.38, 27.34, 29.30, 31.51, 38.39, 45.70, 59.60, 67.22, 76.00, 76.94, 77.38, 109.76, 110.19, 127.25, 130.15, 134.52, 144.33. **MS:** *m/z* = 520 (M+1). **Anal. Calcd**. For $C_{22}H_{33}NO_9S_2$: C, 50.85; H, 6.40; N, 2.70. Found: C, 50.81; H, 6.55; N, 2.64.

General procedure for the synthesis of (*S*)-benzyl-2-((4*S*,4'*R*,5*R*)-2,2,2',2'-tetramethyl-4,4'-bi(1,3-dioxolan)-5-yl)-pyrrolidine-1-carboxylate (4.82):

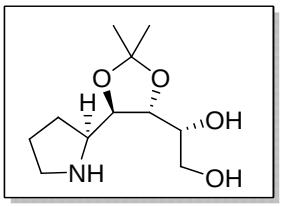


To a solution of **4.80** (0.5 g, 0.96 mmol) in dry THF (2 mL) was added a pre- cooled solution of LAH (0.18 g, 4.8

mmol) in THF (5 mL) and refluxed while stirring for 5 h. The reaction mixture was quenched with aq sodium sulfate, extracted with ethyl acetate (5 x 15 mL) and solvent removed under reduced pressure to give **4.81**. The crude **4.81** (0.26 g, 0.96 mmol) was dissolved in DCM (3 mL) containing an aq. solution of K_2CO_3 (0.4g, 2.89 mmol). CbzCl (0.2 mL, 1.4 mmol) was added to it at 0 °C. The reaction mixture was stirred at same temp for another 30 min. The organic layer was washed with water (1 x 5 mL) and brine (1 x 5 mL). Solvent was removed under reduced pressure and residue was purified by column chromatography (ethyl acetate- pet. ether 15%) to yield **4.82** (0.35 g).

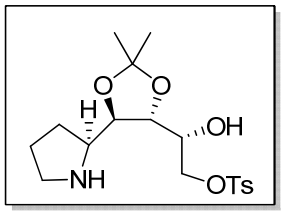
Yield: 89%; colourless oil; $[\alpha]^{27}_{D}$ = –12.96 (c = 1.3, $CHCl_3$); **IR (ν_{max}, $CHCl_3$):** 1597, 1353, $cm.^{-1}$ **^{1}H NMR ($CDCl_3$, 200 MHz):** δ = 1.31 (bs, 12H), 1.81-1.99 (m, 4H), 3.36-3.44 (m, 1H), 3.51-3.53 (m, 1H), 3.95-4.19 (m, 5H), 5.12 (d, *J* = 12.68 Hz, 1H), 5.13 (d, *J* = 12.68 Hz, 1H), 7.32-7.37 (m, 5H) **^{13}C NMR ($CDCl_3$, 100 MHz):** 25.28, 26.24, 26.70, 26.88, 27.15, 27.29, 47.42, 57.92, 66.87, 76.82, 77.24, 77.99, 81.99, 109.45, 109.52, 127.80, 127.89, 128.47, 136.90. **MS:** *m/z* = 406 (M+1). **Anal. Calcd**. For $C_{22}H_{31}NO_6$: C, 65.17; H, 7.71; N, 3.45. Found: C, 65.22; H, 7.61; N, 3.54.

Synthesis of (*S*)-benzyl-2-((4*R*,5*R*)-5-(*R*)-1,2-dihydroethyl)-2,2-dimethyl-1,3-dioxolan-4-yl)pyrrolidine-1-carboxylate: (4.83):



Yield: 72%; colourless oil; $[\alpha]^{27}_{D}$ = –31.52 (c = 1.25, $CHCl_3$); **IR (ν_{max}, $CHCl_3$):** 3418, 2934, 1674, 1417, $cm.^{-1}$ **^{1}H NMR ($CDCl_3$, 400 MHz):** δ = 1.27 (s, 3H), 1.34 (s, 3H), 1.80-1.84 (m, 2H), 2.15-2.24 (m, 1H), 3.41 (dt, *J* = 3.20, 11.21 Hz, 1H) 3.51-3.63 (m, 3H), 3.72-3.77 (m, 1H), 3.98 (dd, *J* = 1.7, 8.7 Hz, 1H), 4.26 (d, *J* = 7.2 Hz, 1H), 4.45 (d, *J* = 6.9 Hz, 1H), 5.12 (s, 2H), 7.34 (bs, 5H). **^{13}C NMR ($CDCl_3$, 100 MHz):** 24.11, 26.51, 26.92, 29.01, 47.00, 57.93, 65.43, 67.51, 73.22, 76.02, 83.92, 108.21, 127.78, 128.14, 128.50, 136.35, 157.00. **MS:** *m/z* = 366 (M+1). **Anal. Calcd**. For $C_{19}H_{27}NO_6$: C, 62.45; H, 7.45; N, 3.83. Found: C, 62.42; H, 7.53; N, 3.79.

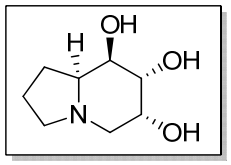
Synthesis of (*S*)-benzyl-2-((4*R*,5*R*)-5-((*R*)-1-hydroxy-2-(tosyloxy)ethyl-2,2-dimethyl-1,3-dioxolan-4-yl)-pyrrolidine-1-caboxylate (4.84): This compound was obtained by following the same experimental procedure as discussed for **4.84.**



Yield: 88%; colourless oil; $[\alpha]^{27}_{D}$ = ⁻11.44 (c 0.7, $CHCl_3$); **IR (ν_{max}, $CHCl_3$):** 3364, 2986, 1673, 1417, $cm.^{-1}$ **^{1}H NMR ($CDCl_3$, 400 MHz):** δ = 1.23 (s, 3H), 1.29 (s, 3H), 1.79-1.82 (m, 1H), 1.92-1.99 (m, 2H), 2.12-2.24 (m, 1H), 2.40 (s, 3H), 3.40 (dt, *J* = 2.91, 10.73 Hz, 1H) 3.51 (dd, *J* = 8.31, 18.15 Hz, 1H), 3.62 (t, *J* = 8.89, 18.2 Hz, 1H), 3.71 (t, *J* = 8.5, 17.63 Hz, 1H), 3.89 (dd, *J* = 1.70, 8.81 Hz, 1H), 4.06 (dd, *J* = 3.45, 10.17 Hz, 1H), 4.19-4.21 (m, 2H), 4.86 (d, *J* = 9.95 Hz, 1H) 5.10 (d, *J* = 12.65 Hz, 1H), 5.12 (d, *J* = 12.60 Hz, 1H) 7.29-7.37 (m, 7H), 7.83 (d, *J* = 8.5 Hz, 2H). **^{13}C NMR ($CDCl_3$, 100 MHz):** 21.60, 24.16, 26.52, 26.86, 28.76, 47.57, 57.81, 67.61, 71.49, 72.22, 74.26, 84.22, 108.30, 127.98, 128.09, 128.52, 129.65, 133.14, 136.45, 144.49, 156.91. **MS:** *m/z* = 520 (M+1). **Anal. Calcd**. For $C_{26}H_{33}NO_8S$: C, 60.10; H, 6.40; N, 2.70. Found: C, 60.22; H, 7.51; N, 2.76.

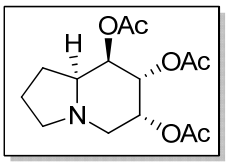
Synthesis of (6*R*,7*R*,8*R*,8a*S*)-octahydroindolizidine-6,7,8-triol(1-deoxy-6,8a-tri-*epi*-castanospermine, (4.6)

This compound was obtained by following the same procedure as discussed for 1,6,8a-tri-*epi*-castanospermine **4.17.**



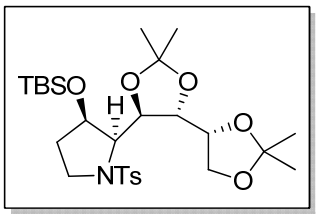
Yield: 86%; colourless oil; $[\alpha]_D^{27}$ +23.6 (c = 0.90, MeOH) ref{$[\alpha]_D^{27}$ = +23.5 (c = 0.90, MeOH)}; **IR (ν_{max}, $CHCl_3$):** 3336, 2956, 1673, 1081, $cm.^{-1}$ **^{1}H NMR (CD_3OD, 400 MHz):** δ = 1.68-1.87 (m, 4H), 2.24 (dd, *J* = 8.50, 16.70 Hz, 1H), 2.35 (t, *J* = 10.51, 21.17 Hz, 1H), 2.54 (m, 1H), 2.93 (dd, *J* = 5.11, 10.22 Hz, 1H), 3.01-3.06 (m, 1H), 3.77 (dd, *J* = 1.57, 3.35 Hz, 1H), 3.98 (t, *J* = 3.18, 6.50 Hz, 1H), 4.04 (m, 1H). **^{13}C NMR (CD_3OD, 100 MHz):** 21.22, 23.11, 52.76, 53.52, 61.59, 66.01, 68.89, 71.38. **MS:** *m/z* = 174 (M+1). **Anal. Calcd**. For $C_8H_{15}NO_3$: C, 55.47; H, 8.73; N, 8.09. Found: C, 55.39; H, 8.15; N, 8.13.

Synthesis of (6*R*,7*R*,8*R*,8a*S*)-octahydroindolizidine-6,7,8-triyl triacetate (4.86):
This compound was obtained by following the same experimental procedure as described for **3.73.**



Yield: 86%; colourless oil; $[\alpha]_D^{27}$ = −32.0 (c = 1.2, $CHCl_3$); **IR (ν_{max}, $CHCl_3$):** 2960,1743, 1223, cm.$^{-1}$ **^{1}H NMR (C_6D_6, 400 MHz):** δ = 1.35-1.40 (m, 4H), 1.57 (s, 3H), 1.68 (s, 3H), 1.70 (s, 3H), 1.90 (dd, *J* = 8.6, 16.90 Hz, 1H), 2.34-2.43 (m, 2H), 2.79 (dd, *J* = 2.5, 8.9 Hz, 1H), 2.97 (dd, *J* = 4.88, 9.90 Hz, 1H), 5.27 (dd, *J* = 2.2, 3.4 Hz, 1H), 5.57 (ddd, *J* = 3.30, 5.00 & 8.5 Hz, 1H), 5.69 (t, *J* = 2.9, 6.11 Hz, 1H). **^{13}C NMR (C_6D_6, 100 MHz):** 20.08, 20.32, 20.46, 21.68, 24.50, 50.42, 53.13, 60.54, 68.07, 68.53, 168.77, 169.35, 169.63. **MS:** *m/z* = 322 (M+Na). **Anal. Calcd**. For $C_{14}H_{21}NO_6$: C, 56.18; H, 7.07; N, 4.68. Found: C, 56.21; H, 7.14; N, 4.59.

General procedure for the synthesis of (2*R*,3*R*)-3-(tert-butyldimethylsilyloxy)-2-((4*S*,4'*R*,5*R*)-2,2,2',2'-tetramethyl-4,4'-bi(1,3-dioxolan)-5-yl)-1-tosylpyrrolidine: (4.87) :

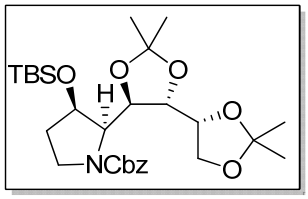


TBS-triflate (0.49 mL, 2.9 mmol) was added to a solution of **4.70** and triethyl amine (0.67 mL, 4.8 mmol) in dry DCM (10 mL) at 0 °C kept under nitrogen atmosphere. The reaction mixture was allowed to attain room temperature and stirred for 2-3 h. To the above reaction mixture, saturated solution of $NaHCO_3$ (5 mL) was added and extracted with DCM (2 x 10 mL). The organic layer was dried over sodium sulfate and solvent was removed under reduced pressure to furnish crude product which on purification by column chromatography (15% ethyl acetate-pet ether) gave **4.87** (0.973 g)

Yield: 86%; white crystalline; solid mp 132-134 °C; $[\alpha]_D^{27}$ = −11.65 (c = 0.6, $CHCl_3$); **IR (ν_{max}, $CHCl_3$):** 2986, 1609, 1251, cm.$^{-1}$ **^{1}H NMR ($CDCl_3$, 200 MHz):** δ = 0.09 (s, 6H), 0.79 (s, 9H), 1.35 (s, 6H), 1.42 (s, 3H), 1.54 (s, 3H), 1.73-1.84 (m, 1H), 1.93-2.13 (m, 1H), 2.42 (s, 3H), 3.25-3.36 (m, 2H), 3.45 (ddd, *J* = 2.06, 10.20, & 11.97 Hz, 1H), 3.83 (d, *J* = 7.3 Hz, 1H), 3.96 (d, *J* = 7.3 Hz, 1H), 3.99-4.08 (m, 1H), 4.20 (dd, *J* = 5.60, 7.67 Hz, 1H), 4.27-4.43 (m, 2H), 7.30 (d, *J* = 8.2 Hz, 2H), 7.67 (d, *J* = 8.2 Hz, 2H). **^{13}C NMR ($CDCl_3$, 50 MHz):** -5.31, -5.25, 18.14, 21.45, 25.54, 25.70, 26.38, 26.42, 27.29, 31.38, 46.31, 60.80, 68.39, 70.96, 76.74, 77.34, 109.38, 109.77, 127.25, 129.30, 135.17, 143.53. **MS:** *m/z* = 556 (M+1). **Anal. Calcd**. For $C_{27}H_{45}NO_7SSi$: C, 58.35; H, 8.16; N, 2.52. Found: C, 58.27; H, 8.13; N, 2.58.

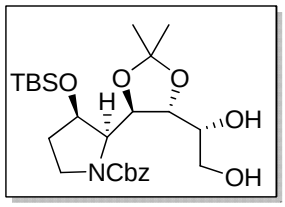
Synthesis of (2*R*,3*R*)-benzyl-3-(*tert*-butyldimethylsilyloxy)-2-((4*S*,4'*R*,5*R*)-2,2,2',2'-tetramethyl-4,4'-bi(1,3-dioxolan)-5-yl)pyrrolidine-1-carboxylate (4.89):

This compound was synthesized by following identical experimental conditions as described for **4.75-4.76**



Yield: 86%; colourless oil; $[\alpha]_D^{27}$ = -21.04 (c = 1.5, $CHCl_3$): **IR (ν_{max}, $CHCl_3$):** 2933, 1704, 1415, $cm.^{-1}$ **^{1}H NMR ($CDCl_3$, 200 MHz):** δ = 0.08 (s, 6H), 0.90 (s, 9H), 1.27 (s, 6H), 1.35 (s, 6H), 1.73-1.84 (m, 1H), 1.96-2.11 (m, 2H), 3.36 -3.46 (m, 2H), 3.94-4.15 (m, 4H), 4.27-4.34 (m, 3H), 5.01-5.25 (m, 2H), 7.33 (m, 5H). **^{13}C NMR ($CDCl_3$, 50 MHz):** -5.06, -4.94, 18.10, 25.39, 25.75, 26.34, 26.55, 27.25, 31.55, 44.23, 58.79, 67.23, 71.11, 76.91, 77.38, 77.50, 109.10, 109.40, 127.59, 128.50, 128.88, 136.87, 155.96. **MS:** *m/z* = 536 (M+1). **Anal. Calcd**. For $C_{28}H_{45}NO_7Si$: C, 62.77; H, 8.46; N, 2.61. Found: C, 62.73; H, 8.53; N, 2.55.

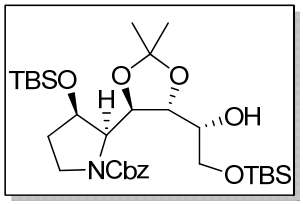
Synthesis of (2*R*,3*R*)-benzyl-3-(*tert*-butyldimethylsilyloxy)-2-((4*R*,5*R*)-5-((*R*)-1,2-dihydroxyethyl)-2,2-dimethyl-1,3-dioxolan-4-yl)pyrrolidine-1-carboxylate (4.90):



To a solution of **4.89** (0.6 g, 1.12 mmol) in 90% MeOH was added Dowex-50W-X8 resin (0.2 g). The reaction mixture was stirred for 18 h at room temperature, filtered and solvent was evaporated under reduced pressure. The crude residue was chromatographed on silica gel (ethyl acetate-pet ether 30%) to give **4.90** (0.5 g).

Yield: 91%; colourless oil; $[\alpha]_D^{27}$ = -63.82 (c = 1.5, $CHCl_3$); **IR (ν_{max}, $CHCl_3$):** 3421, 2957, 1672, 1265, $cm.^{-1}$ **^{1}H NMR ($CDCl_3$, 200 MHz):** δ = 0.06 (s, 6H), 0.89 (s, 9H), 1.28 (s, 3H), 1.33 (s, 3H), 1.93-2.07 (m, 1H), 2.16-2.39 (m, 1H), 3.40-3.48 (m, 2H), 3.56-3.81 (m, 3H), 4.00-4.23 (m, 3H), 4.32 (ddd, *J* = 7.67, 10.05 & 15.35 Hz, 1H), 5.12 (s, 2H), 7.34 (bs, 5H). **^{13}C NMR ($CDCl_3$, 50 MHz):** -4.96, -4.64, 17.93, 25.67, 26.71, 26.91, 31.76, 44.33, 58.88, 65.53, 67.49, 71.14, 72.72, 76.11, 78.77, 108.09, 127.84, 136.32, 156.73. **MS:** *m/z* = 496 (M+1). **Anal. Calcd**. For $C_{25}H_{41}NO_7Si$: C, 60.58; H, 8.34; N, 2.83. Found: C, 60.64; H, 8.29; N, 2.73.

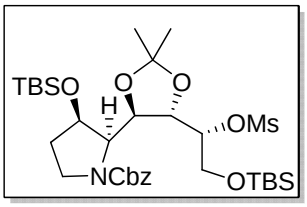
Synthesis of (2*R*,3*R*)-benzyl-3-(tert-butyldimethylsilyloxy)-2-((4*R*,5*R*)-5-((*R*)-2-(tert-butyldimethylsi-lyloxy)-1-hydroxyethyl)-1-hydroxyethyl)-2,2-dimethyl-1,3-dioxolan-4-yl)pyrrolidine-1-carboxylate (4.91) :



To a solution of **4.90** (0.53 g, 1.06 mmol) in CH_2Cl_2 (10 mL) were added imidazole (0.18 g, 2.78 mmol) and TBDMSCl (0.26 g, 1.70 mmol) at room temperature. After stirring the mixture for 45 min, sat. aq. $NaHCO_3$ solution (3 mL) was added and the mixture was extracted with CH_2Cl_2 (3 x 10 mL).The organic was concentrated and the residue was chromatographed on silica gel (ethyl acetate-pet ether 15%) to give **4.91** (0.57 g).

Yield: 88%; colourless oil; $[\alpha]_D^{27} = -47.02$ (c = 1.5, $CHCl_3$); **IR (ν_{max}, $CHCl_3$):** 3447, 2954, 1693, 1415, $cm.^{-1}$ **^{1}H NMR ($CDCl_3$, 500 MHz):** δ = 0.06 (s, 6H), 0.08 (s, 6H), 0.89 (s, 9H), 0.91 (s, 9H), 1.27 (s, 3H), 1.32 (s, 3H), 1.95-2.01 (m, 1H), 2.26 (quint, *J* = 10.15, 20.30 Hz, 1H), 3.41-3.45 (m, 2H), 3.50-3.55 (m, 2H), 3.71-3.78 (dd, *J* = 3.6, 12.42 Hz, 2H), 3.83 (d, *J* = 10.47 Hz, 1H), 3.95 (t, *J* = 9.01, 17.78 Hz, 1H), 4.08 (d, *J* = 9.01 Hz, 1H), 4.27-4.34 (m, 2H), 5.04 (d, *J* = 12.50 Hz, 1H), 5.18 (d, *J* = 12.50 Hz, 1H), 7.32-7.35 (m, 5H). **^{13}C NMR ($CDCl_3$, 50 MHz):** -5.45, -5.34, -4.90, -4.67, 17.97, 18.40, 25.72, 25.94, 26.62, 27.10, 31.82, 44.27, 59.00, 64.82, 67.00, 71.18, 73.86, 74.22, 79.51, 107.72, 127.75, 127.96, 128.45, 136.73, 156.24. **MS:** *m/z* = 610 (M+1). **Anal. Calcd**. For $C_{31}H_{55}NO_7Si_2$: C, 61.04; H, 9.09; N, 2.30. Found: C, 60.98; H, 9.16; N, 2.39.

General procedure for the synthesis of (2*R*,3*R*)-benzyl-2-((4*R*,5*S*)-5-((*R*)-1-mesyl-2-(*tert*-butyldimethylsilyloxy)ethyl)-2,2-dimethyl-1,3-dioxolan-4-yl)-3-(*tert*-butyldimethylsilylo-xy)pyrrolidine-1-carboxylate (4.92):

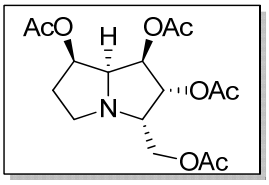


To a solution of **4.91** (0.5 g, 0.83 mmol) in dry THF (4 mL) were added Et_3N (0.25 mL, 1.83 mmol) and methanesulfonyl chloride (0.08 mL, 1.0 mmol) at 0 °C. The reaction mixture was stirred for 30 min at r.t. and was quenched by adding sat. aq $NaHCO_3$ solution (5 mL). The

organic layer was dried over sodium sulfate and concentrated under reduced pressure to give crude product which was purified by column chromatography (ethyl acetate-pet ether 10 %) to obtain **4.92** (0.52 g)

Yield: 93%; colourless oil; $[\alpha]_D^{27}$ = ⁻38.01 (c = 1.5, $CHCl_3$); **IR (ν_{max}, $CHCl_3$):** 2930, 1701, 1411, cm.$^{-1}$ **^{1}H NMR ($CDCl_3$, 500 MHz):** δ = 0.07 (s, 12H), 0.9 (s, 18H), 1.29 (s, 6H), 1.96-2.03 (m, 1H), 2.13-2.2 (m, 1H), 3.10 (s, 3H), 3.40-3.44 (m, 2H), 3.76-3.85 (m, 1H), 4.04 (dd, *J* = 2.84, 11.80 Hz, 1H), 4.11 (dd, *J* = 7.3, 18.11 Hz, 1H), 5.24 (dd, *J* = 6.00, 8.5 Hz, 1H), 4.31-4.35 (m, 1H), 4.48 (dd, *J* = 8.3, 18.11 Hz, 1H), 4.77-4.8 (m, 1H), 5.11 (s, 2H), 7.29-7.35 (m, 5H). **^{13}C NMR ($CDCl_3$, 50 MHz):** -5.42, -4.69, 17.94, 18.38, 25.73, 25.90, 26.07, 26.90, 31.94, 38.96, 44.36, 58.73, 63.39, 66.84, 70.93, 74.96, 76.65, 84.44, 109.01, 127.59, 128.44, 136.85, 456.09. **MS:** *m/z* = 688 (M+1). **Anal. Calcd**. For $C_{32}H_{57}NO_9SSi_2$: C, 55.86; H, 8.35; N, 2.04 Found: C, 55.88; H, 8.16; N, 2.14.

General procedure for the synthesis of (1*R*,2*R*,3*S*,7*R*,7a*S*)-3-(acetoxymethyl)hexahydro-1H-pyrrolizine-1,2,7-triyl-triacetate (3,7a-di-epi-alexine, 4.96):

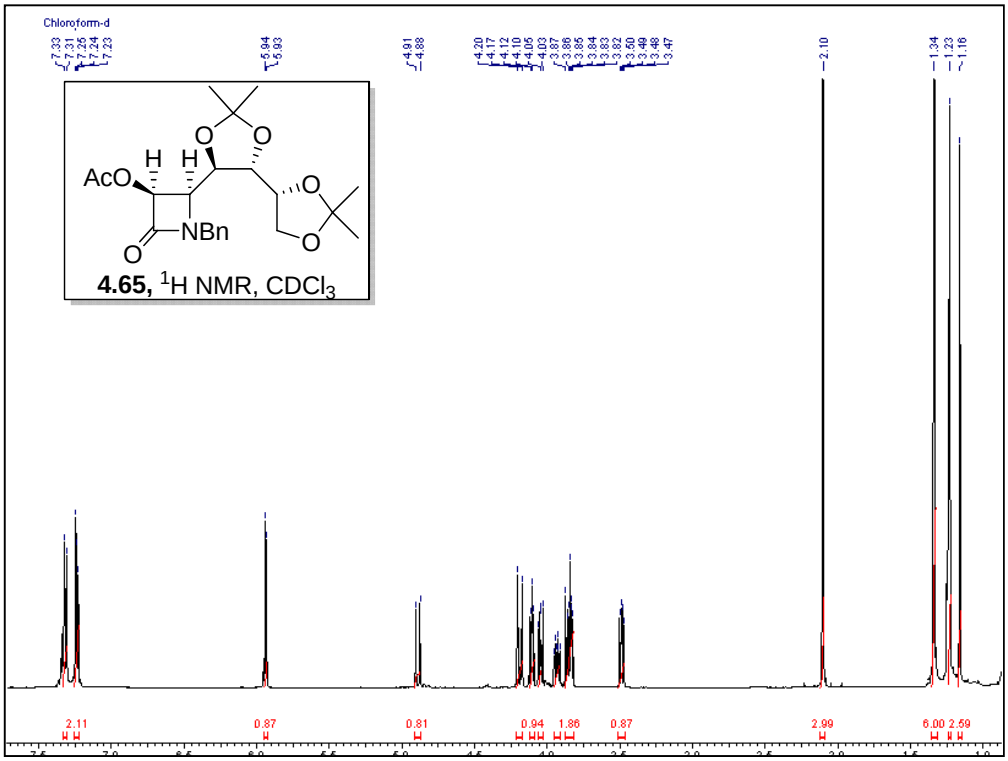


Compound **4.93** (0.064 g, 0.11 mmol) was stirred in a mixture of trifluroacetic acid (1.8) and water (0.2 mL) for 5 h at reflux temperature under nitrogen atmosphere. The solvent was evaporated to dryness to give crude **4.95** which was dissolved in methanol (2 mL). Sodium acetate (0.027 g, 0.33 mmol) was added to it and stirred over night at room temperature under nitrogen atmosphere. The solvent was removed in *vacuo,* residue stirred with a mixture of pyridine: Ac_2O (9:1) for 12 h. The reaction mixture was diluted with CH_2Cl_2 and organic layer was successively washed by water (2 x 10 mL) and 2N HCL (2 x 10 mL). The solvent was removed and residue purified by column chromatography (aceone-pet. ethe 40%) to give **4.96**.

Yield: 75 %; colourless oil; $[\alpha]_D^{27}$= +30.33 (c = 0.2, $CHCl_3$); **IR (ν_{max}, $CHCl_3$):** 2959, 1745, 1160, cm.$^{-1}$ **^{1}H NMR ($CDCl_3$, 500 MHz):** δ = 1.97-2.01 (m, 2H), 2.03 (s, 3H), 2.07 (s, 6H), 2.08 (s, 3H), 2.89-2.96 (m, 1H), 3.30-3.33 (m, 1H), 3.37 (dd, *J* = 5.75, 13.33 Hz, 1H), 3.86 (dd, *J* = 4.61, 6.57 Hz, 1H), 3.97 (dd, *J* = 5.80, 11.60 Hz, 1H), 4.09 (dd, *J* = 5.75, 1140 Hz, 1H), 5.33 (dd, *J* = 4.32, 8.64 Hz, 1H), 5.38 (t, *J* =

6.5, 12.81 Hz, 1H) 5.49 (dd, J = 6.39, 7.52 Hz, 1H); **^{13}C NMR ($CDCl_3$, 50 MHz):** 20.80, 20.84, 20.98, 21.43, 29.71, 32.72, 53.56, 64.95, 65.99, 75.28, 77.22, 169.95, 170.21, 170.70, 170.73. **MS:** *m/z* = 380 (M+Na). **Anal. Calcd**. For $C_{16}H_{23}NO_8$: C, 53.78; H, 6.49; N, 3.92 Found: C, 53.84; H, 6.43; N, 3.98.

4.14 Spectra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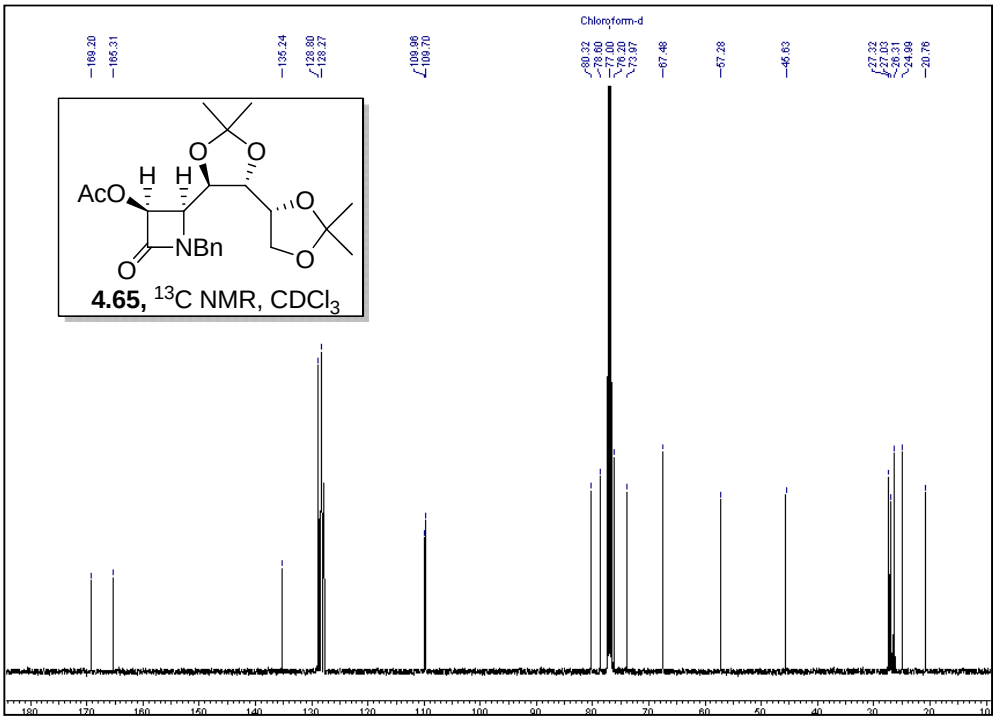
H
H
O
O
O
O
NBn
O
4.65, 1H NMR, CDCl3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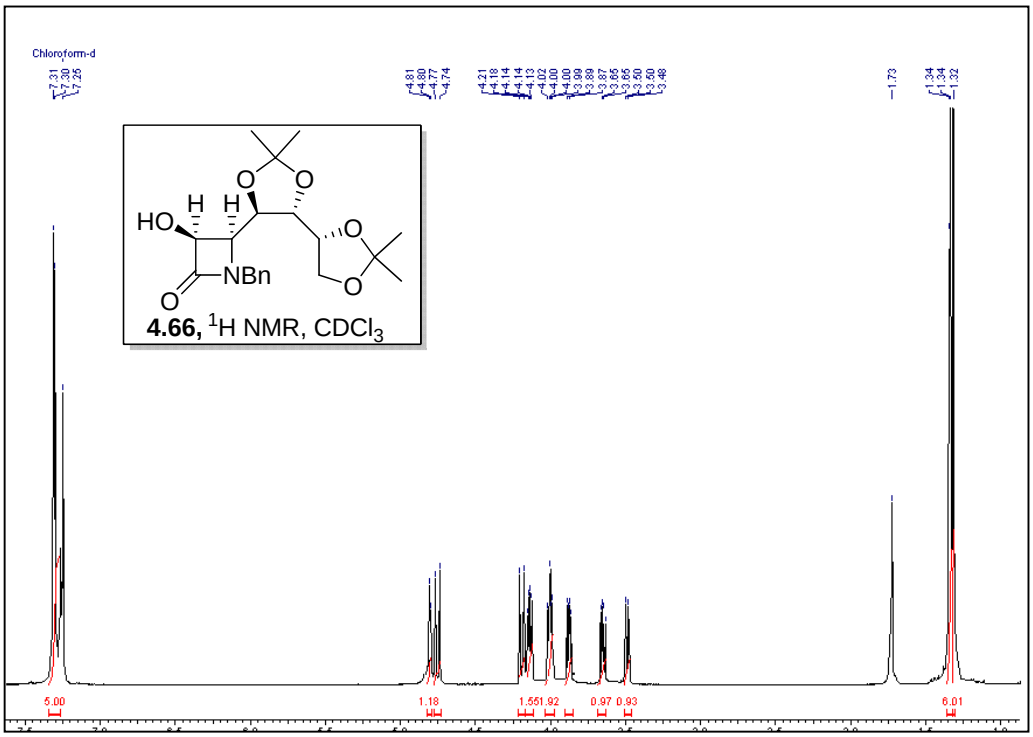
O
NBn
O
4.65, 13C NMR, CDCl3


Chloroform-d
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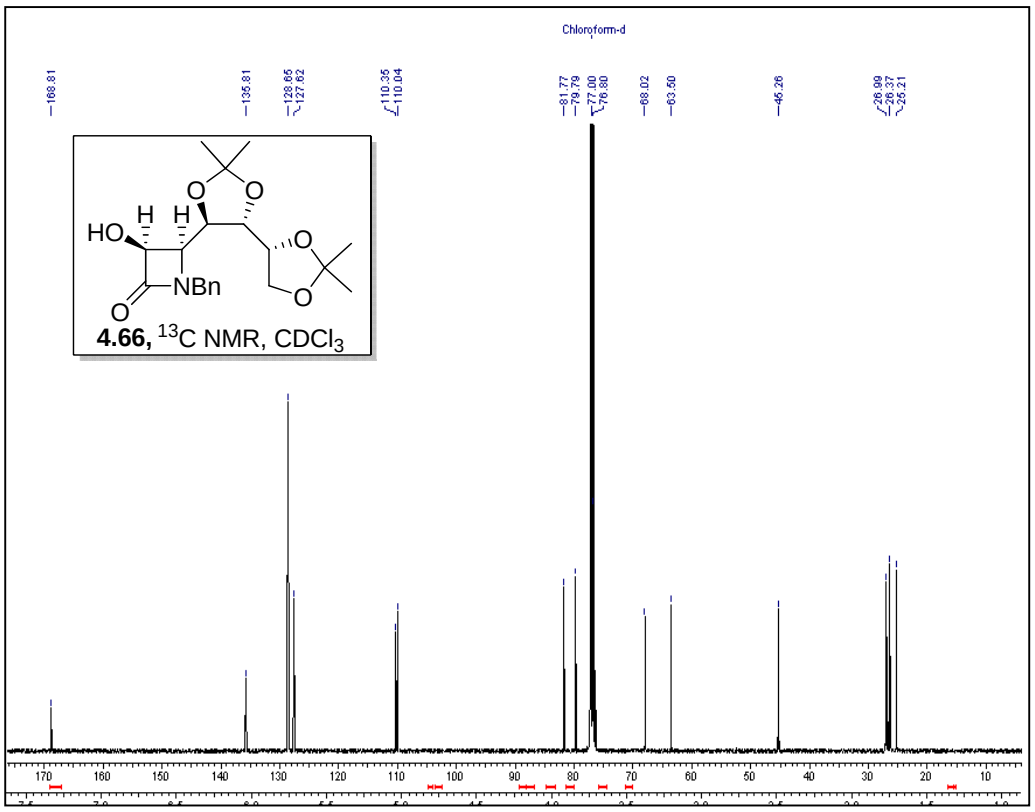
H
H
O
O
O
O
NBn
O
4.66, 1H NMR, CDCl3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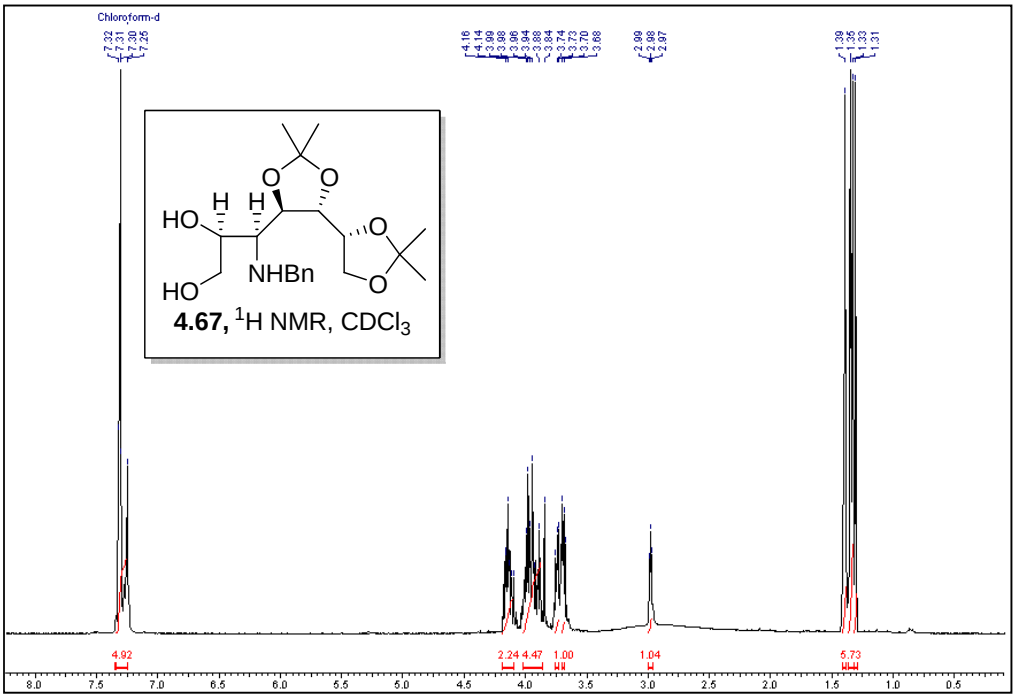
H
O
O
O
O
NBn
O
4.66, 13C NMR, CDCl3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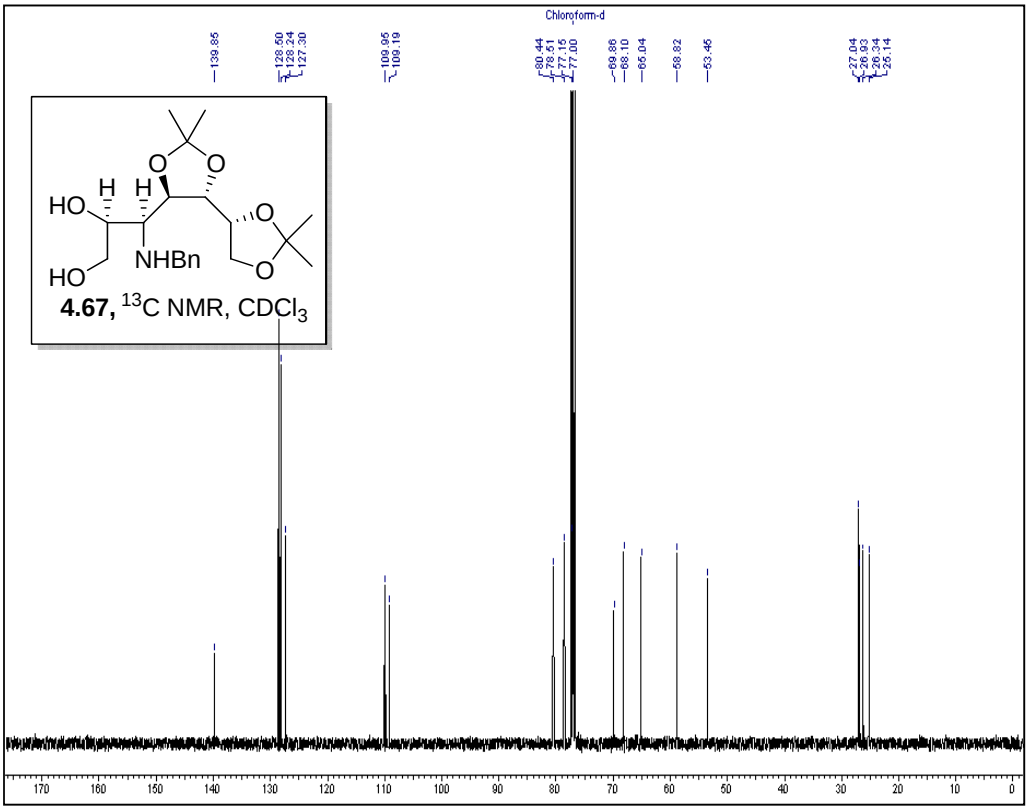
O
O
NHBn
HO
4.67, 1H NMR, CDCl3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O
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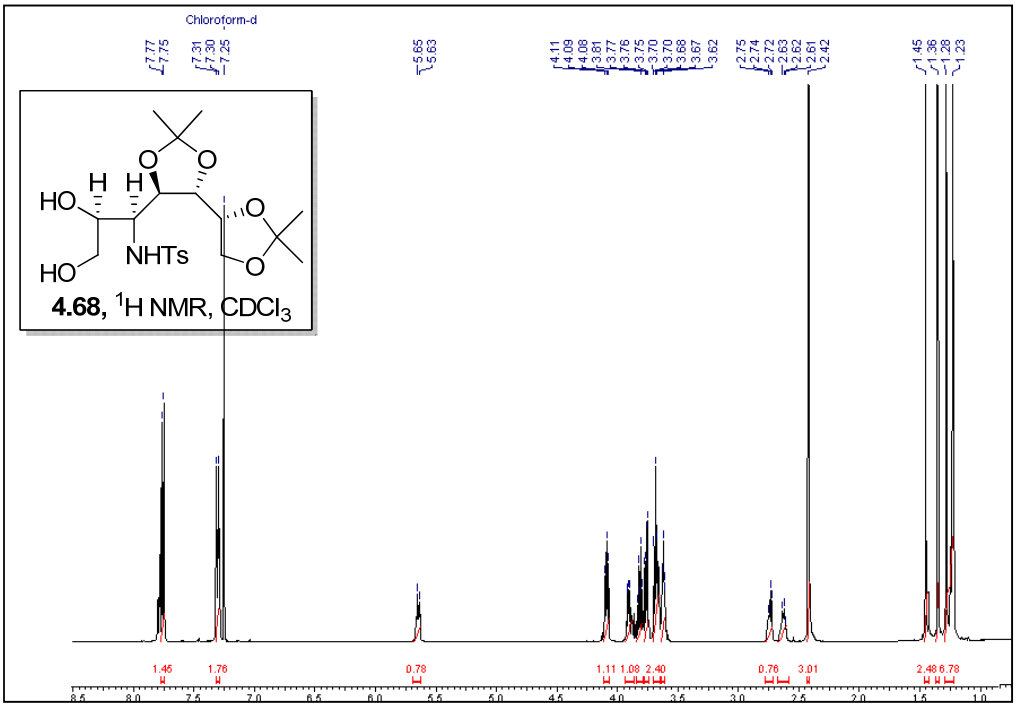
O
NHBn
HO
4.67, 13C NMR, CDCl3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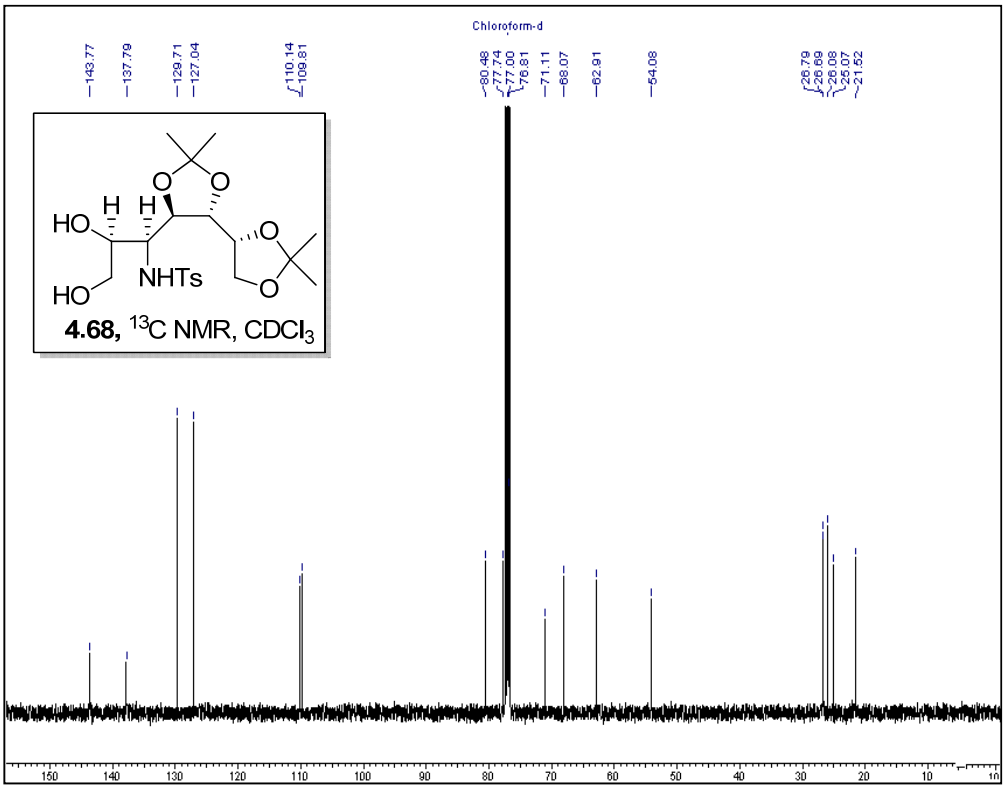
NHTs
4.68, ^{1}H NMR, $CDCl_3$


Chloroform-d
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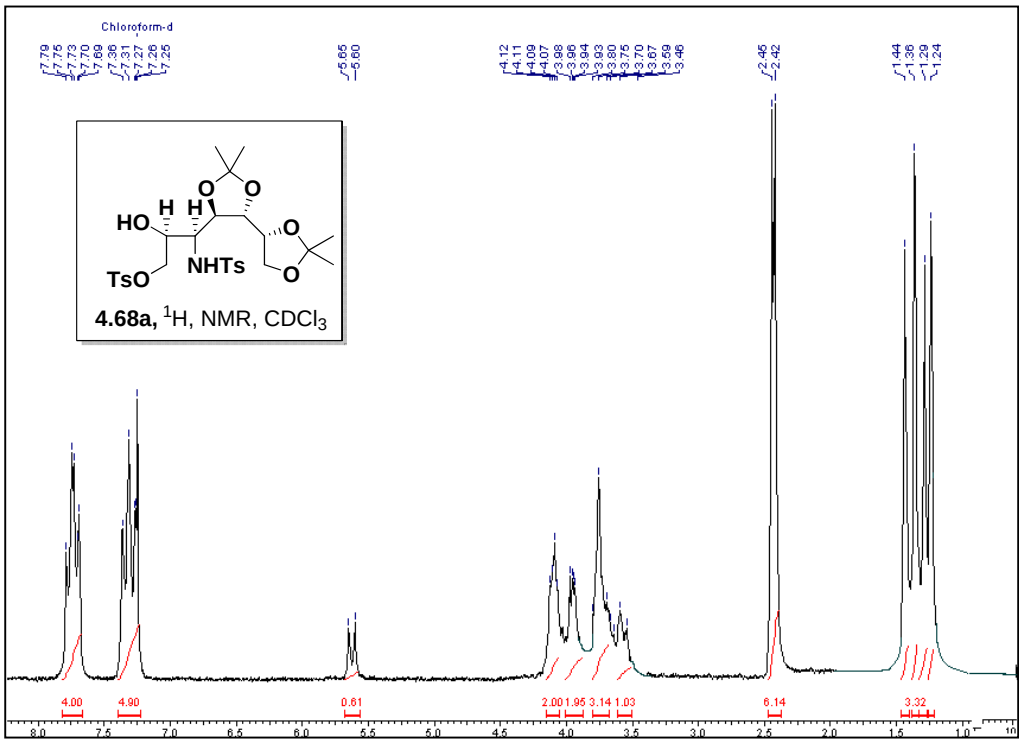
H
H
O
O
O
O
HO
NHTs
4.68, ^{13}C NMR, $CDCl_3$


Chloroform-d
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7.73
7.70
7.68
7.36
7.31
7.27
7.26
7.25
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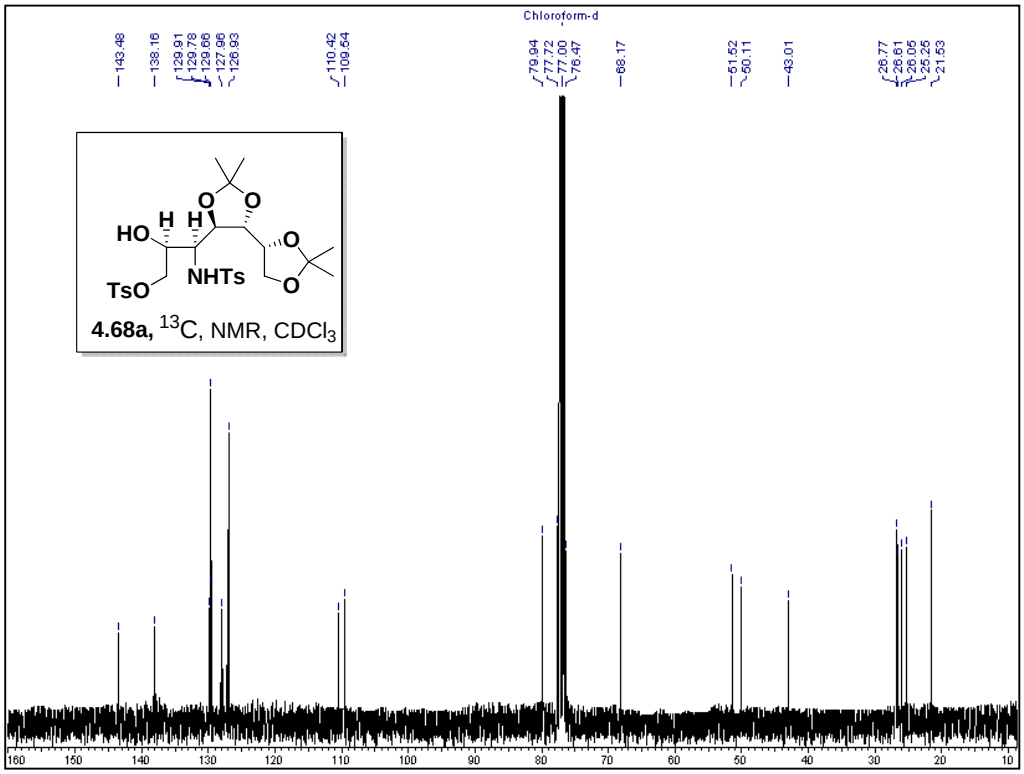
5.60
4.12
4.11
4.09
4.07
3.98
3.96
3.94
3.93
3.80
3.75
3.70
3.67
3.59
3.46
2.45
2.42
1.44
1.36
1.29
1.24
HO
H
H
O
O
O
O
NHTs
TsO
4.00
4.90
0.61
2.00
1.95
3.14
1.03
6.14
3.32
4.68a, 1H, NMR, CDCl3


Chloroform-d
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129.66
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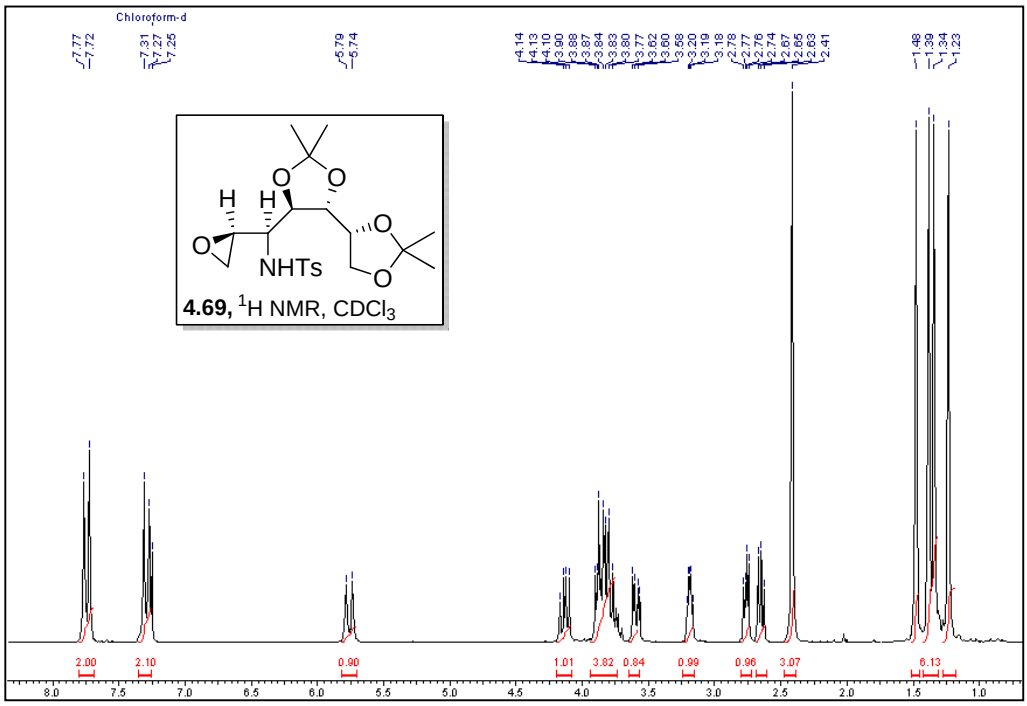
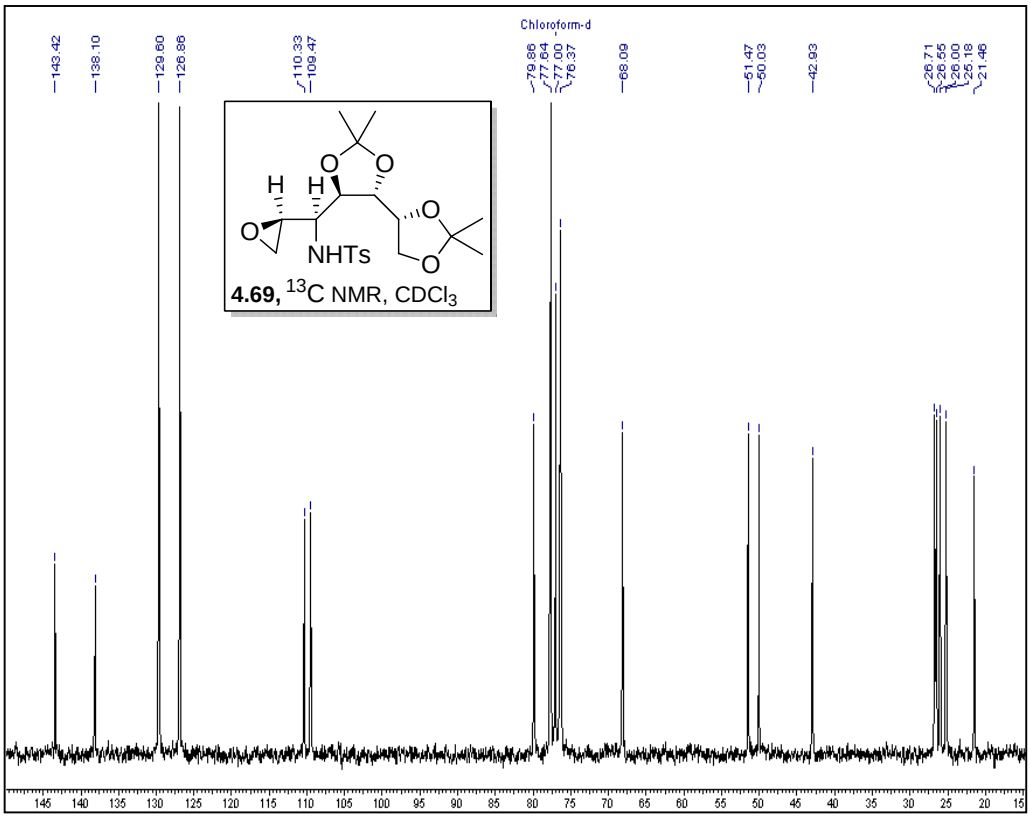
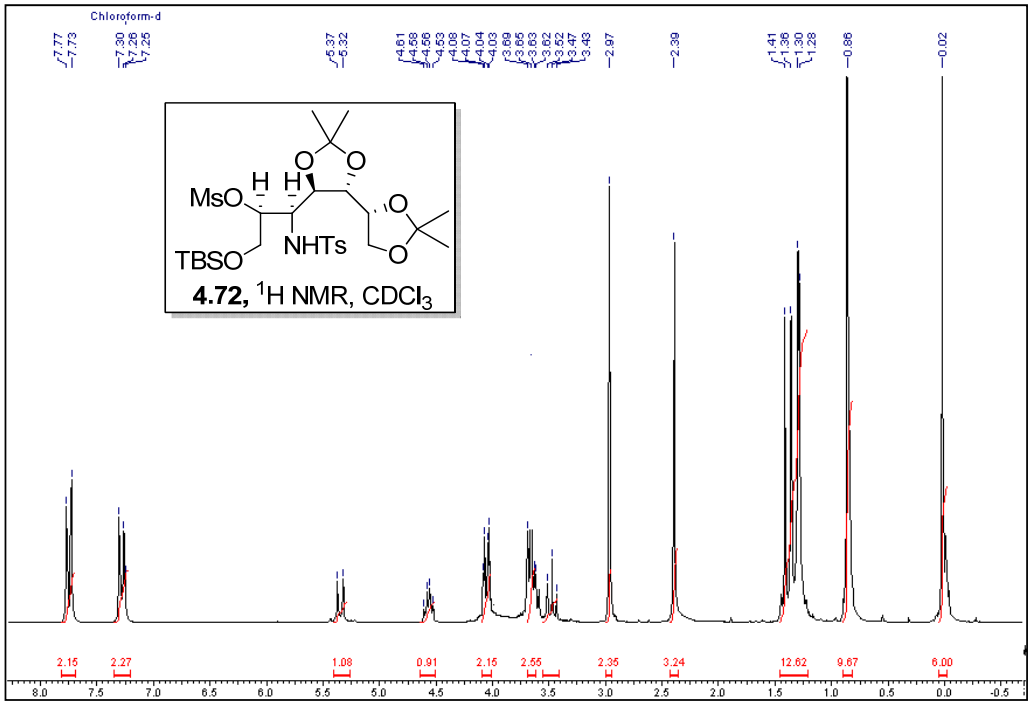
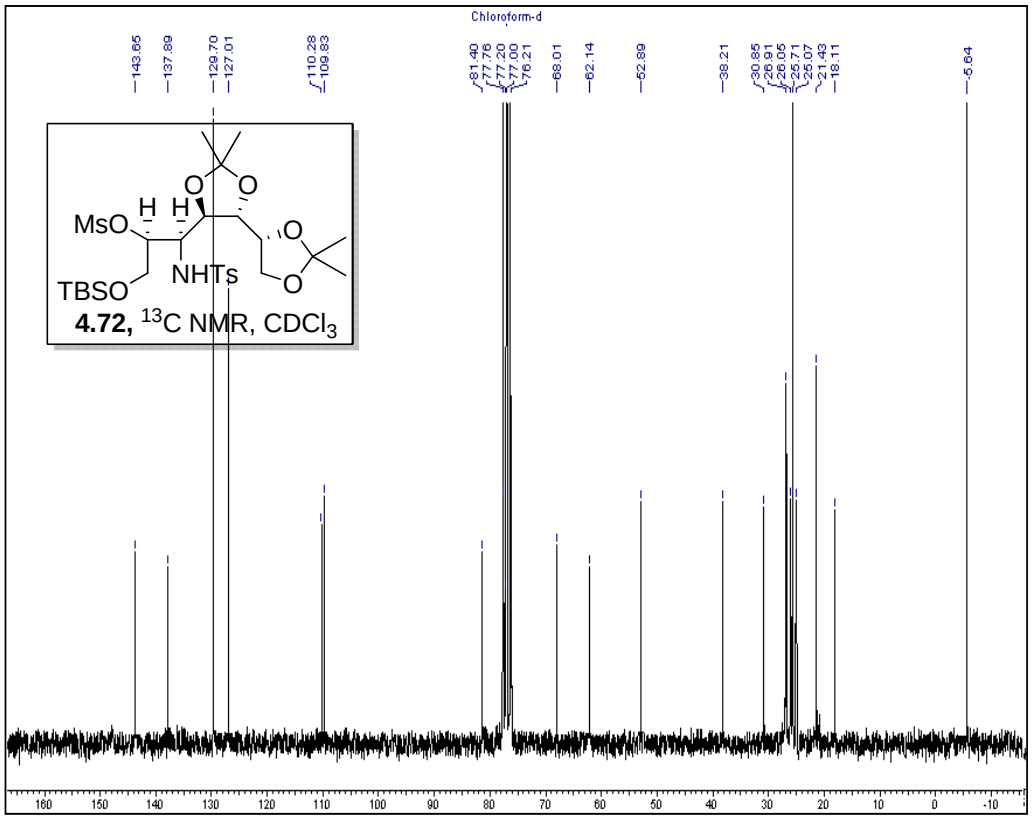
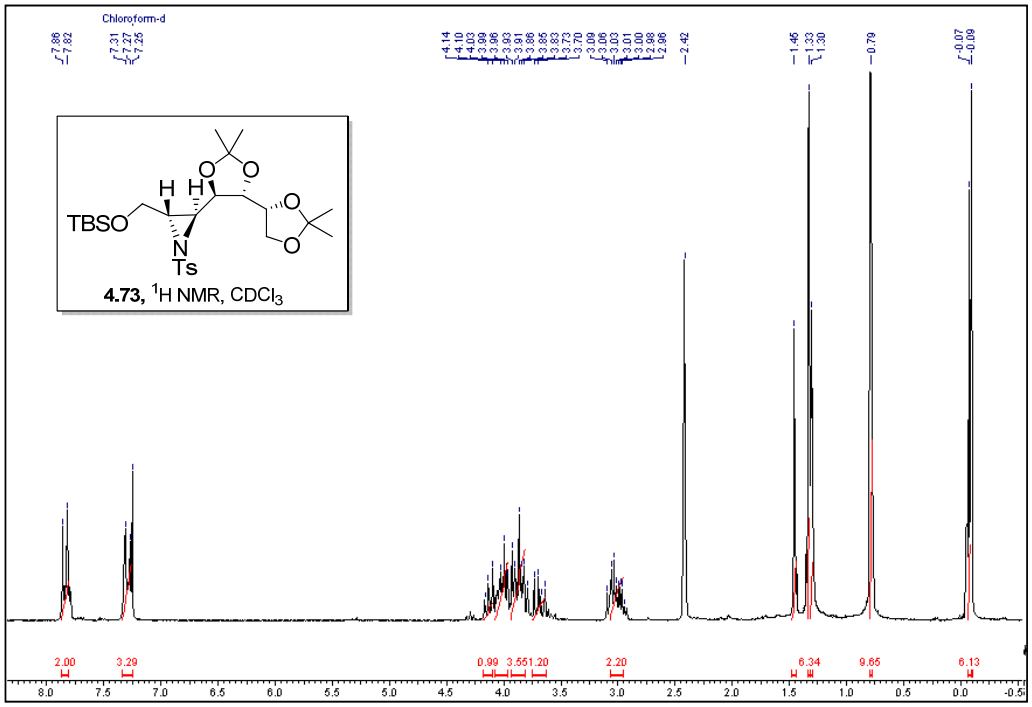
76.47
68.17
61.52
60.11
43.01
26.77
26.61
26.05
25.25
21.53
HO
H
H
O
O
O
O
NHTs
TsO
4.68a, 13C, NMR, CDCl3

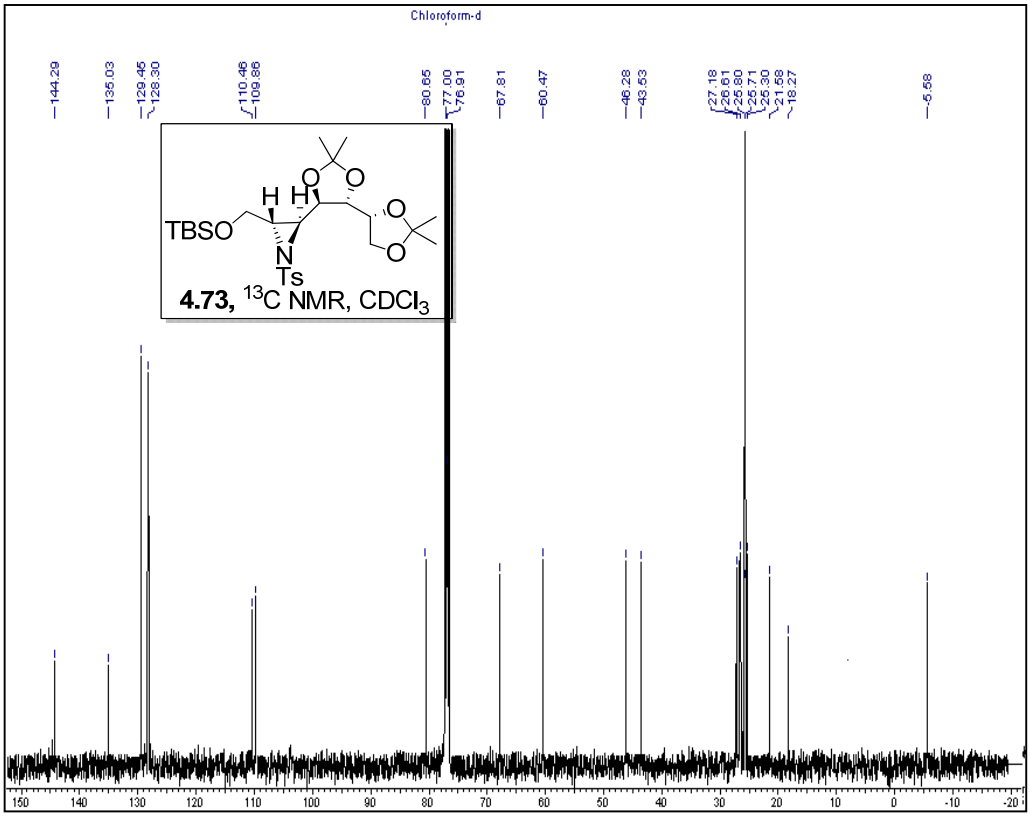

Chloroform-d
7.77
7.72
7.31
7.27
7.25
5.79
5.74
4.14
4.13
4.10
3.90
3.88
3.87
3.84
3.83
3.80
3.77
3.62
3.60
3.58
3.20
3.19
3.18
2.78
2.77
2.76
2.74
2.67
2.65
2.63
2.41
1.48
1.39
1.34
1.23
O
O
H
H
O
O
NHTs
O
4.69, 1H NMR, CDCl3
2.00
2.10
0.90
1.01
3.82
0.84
0.99
0.96
3.07
6.13
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0

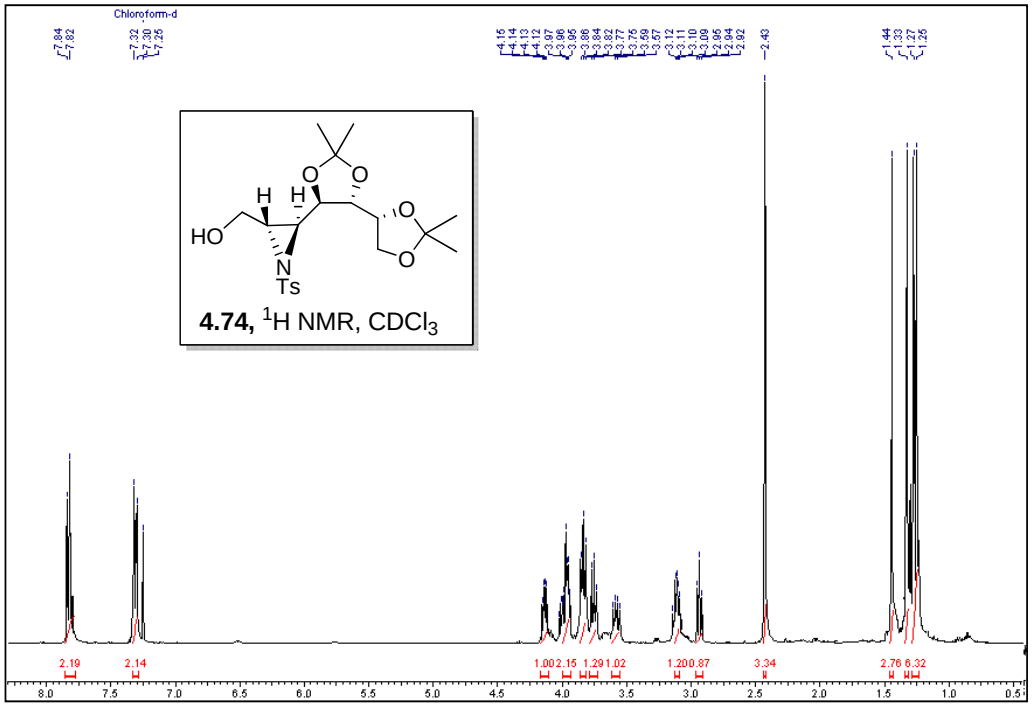

Chloroform-d
143.42
138.10
129.60
126.86
110.33
109.47
79.86
77.64
77.00
76.37
68.09
51.47
50.03
42.93
26.71
26.55
26.00
25.18
21.46
O
O
H
H
O
O
NHTs
O
4.69, 13C NMR, CDCl3
145
140
135
130
125
120
115
110
105
100
95
90
85
80
75
70
65
60
55
50
45
40
35
30
25
20
15

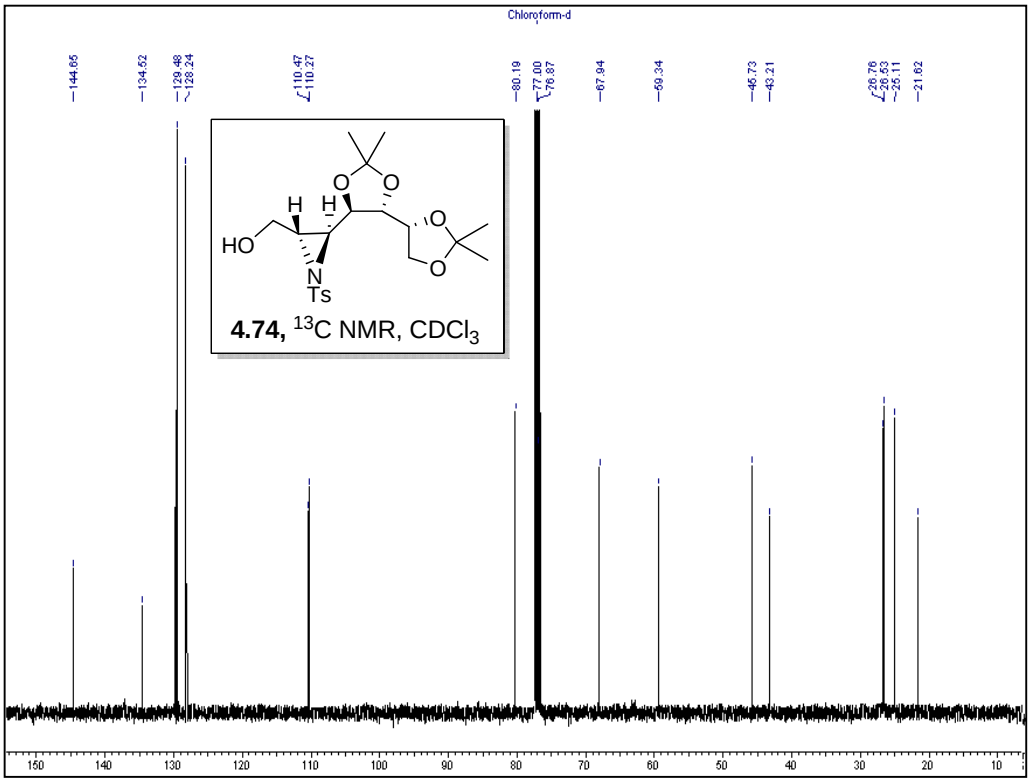

Chloroform-d
MsO
H
H
O
O
O
O
NHTs
TBSO
4.72, 1H NMR, CDCl3

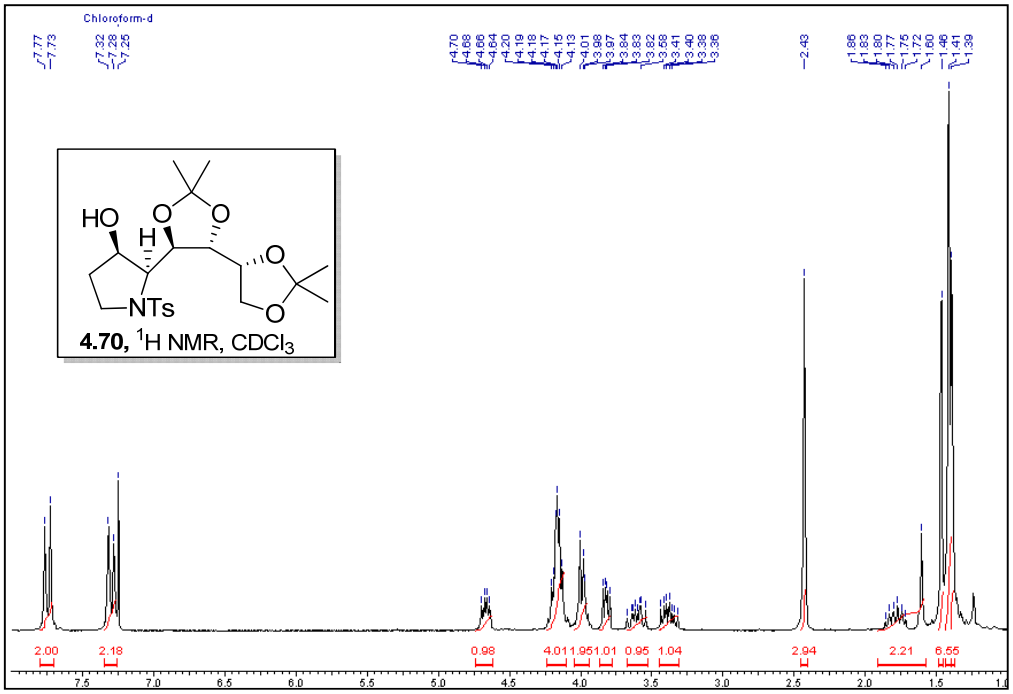

Chloroform-d
MsO
H
H
O
O
O
O
NHTs
TBSO
4.72, 13C NMR, CDCl3

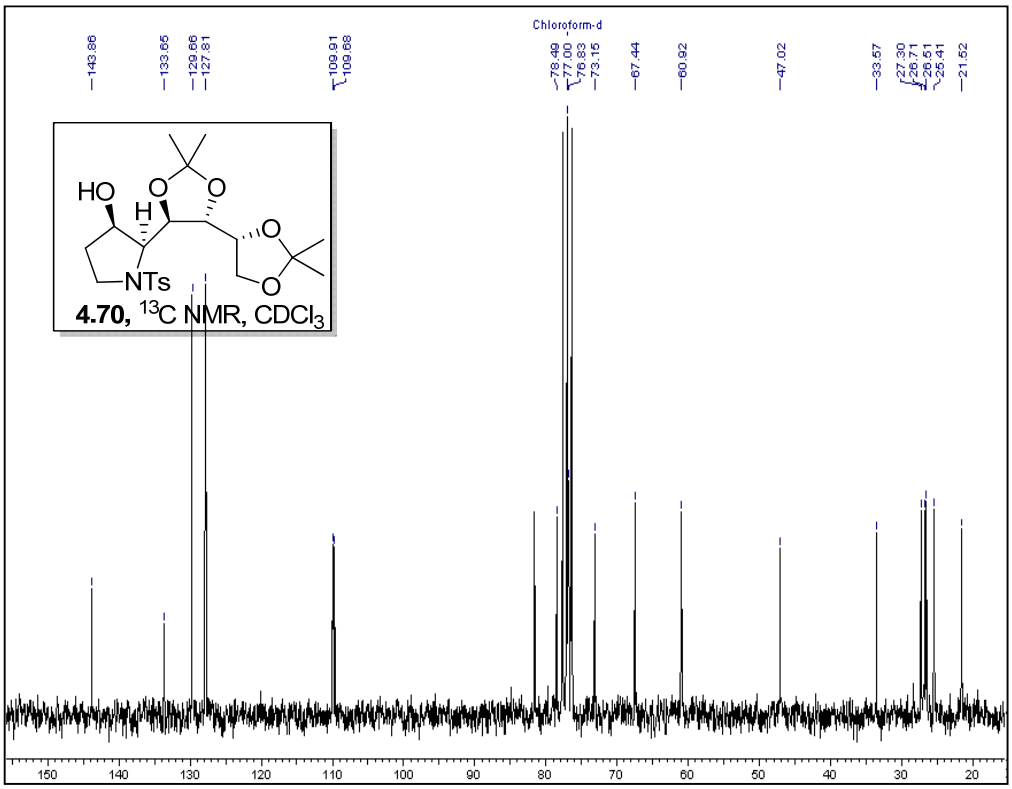

Chloroform-d
TBSO
H H
O
O
O
O
N
Ts
4.73, 1H NMR, CDCl3

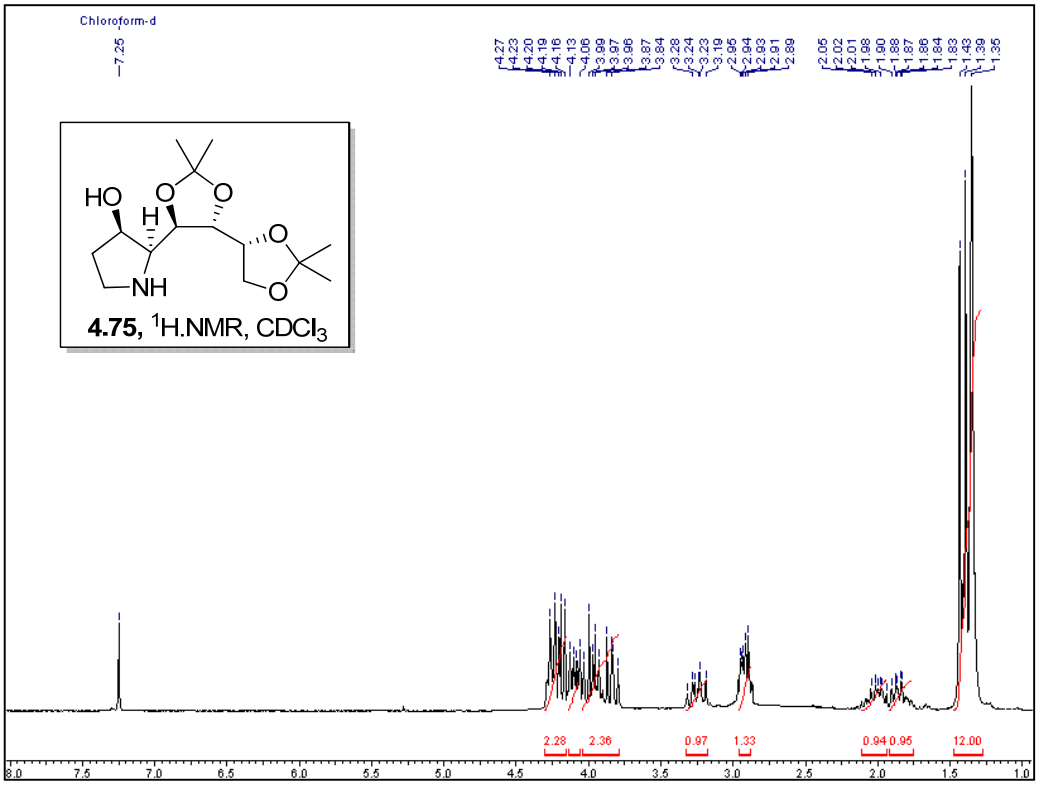

Chloroform-d
TBSO
H H
O
O
O
O
N
Ts
4.73, 13C NMR, CDCl3

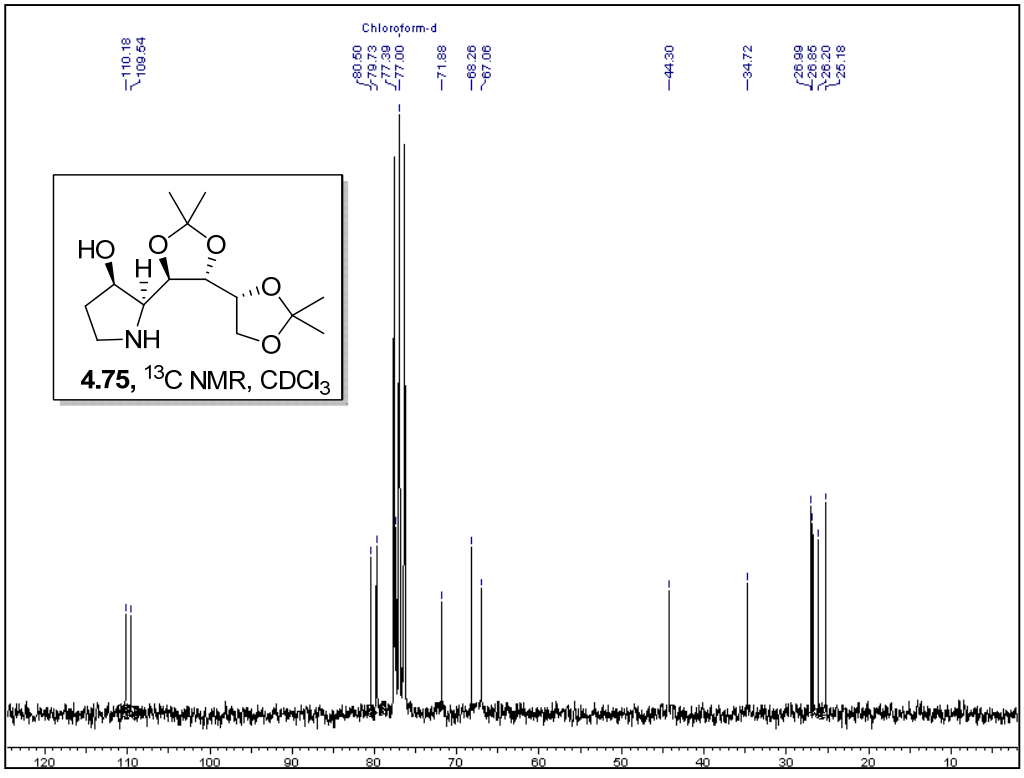

Chloroform-d
HO
H
H
O
O
O
O
N
Ts
4.74, 1H NMR, CDCl3

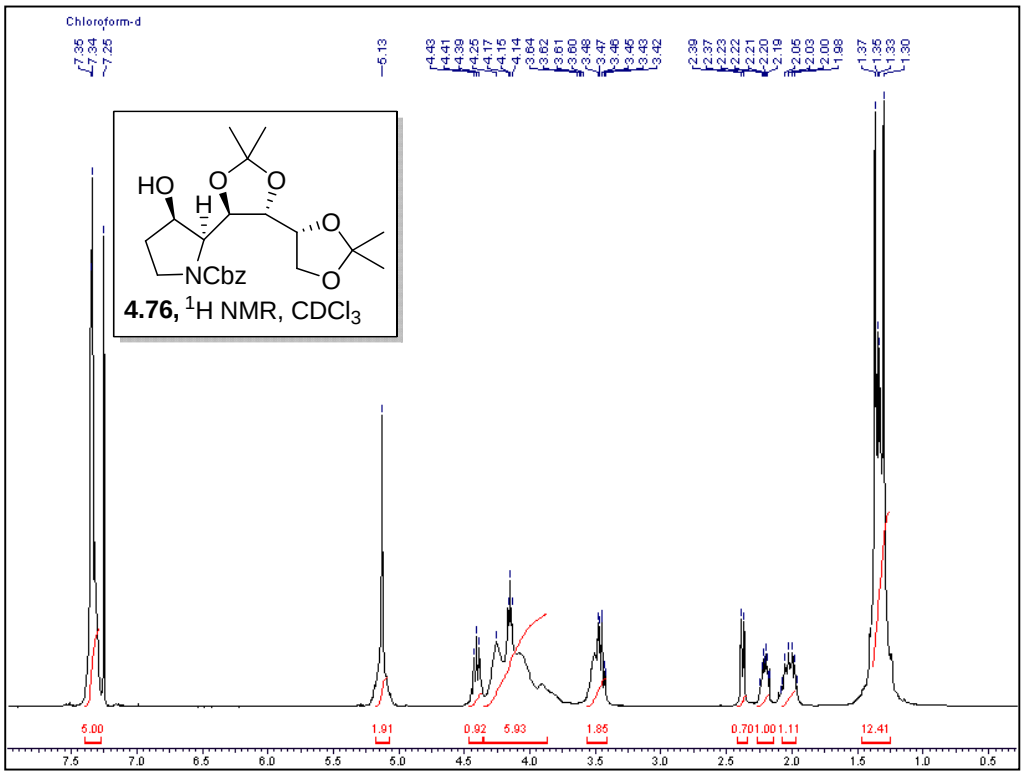

Chloroform-d
HO
H
H
O
O
O
O
N
Ts
4.74, 13C NMR, CDCl3

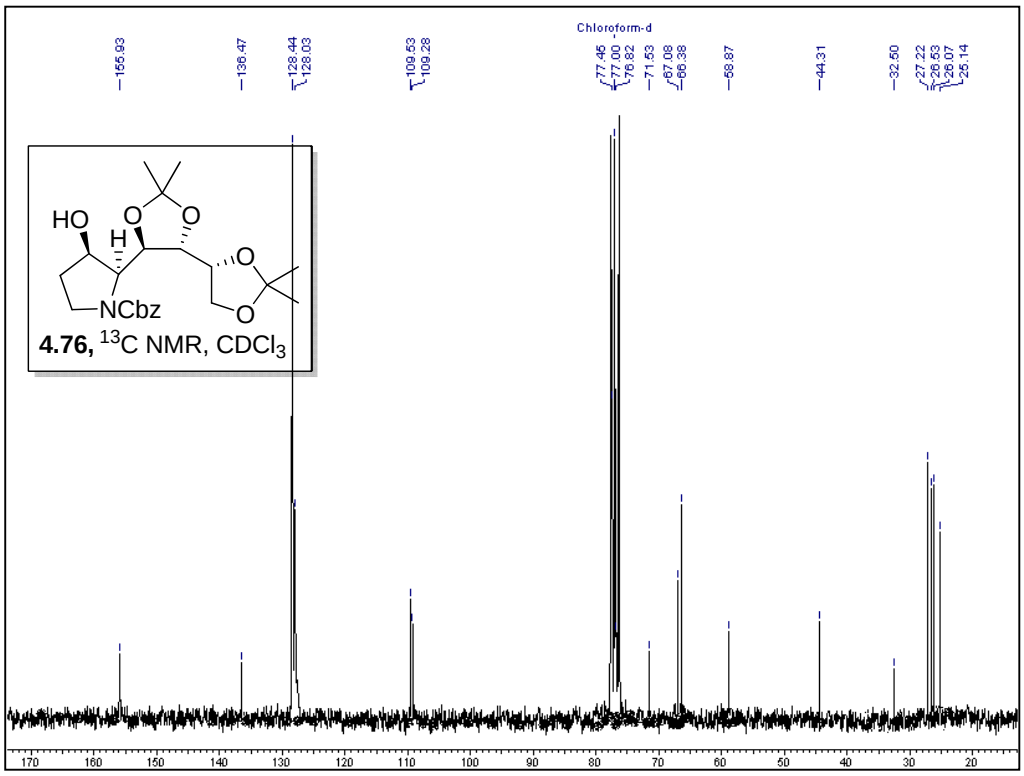

Chloroform-d
HO
O
O
H
O
O
NTs
4.70, 1H NMR, CDCl3

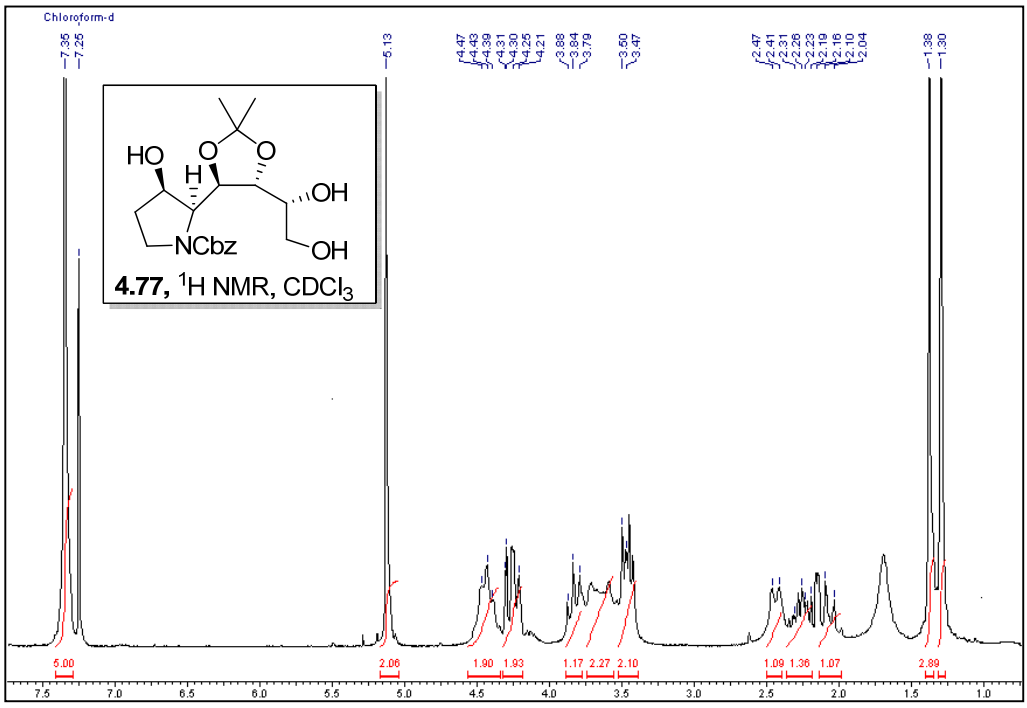

Chloroform-d
HO
O
O
H
O
O
NTs
4.70, 13C NMR, CDCl3

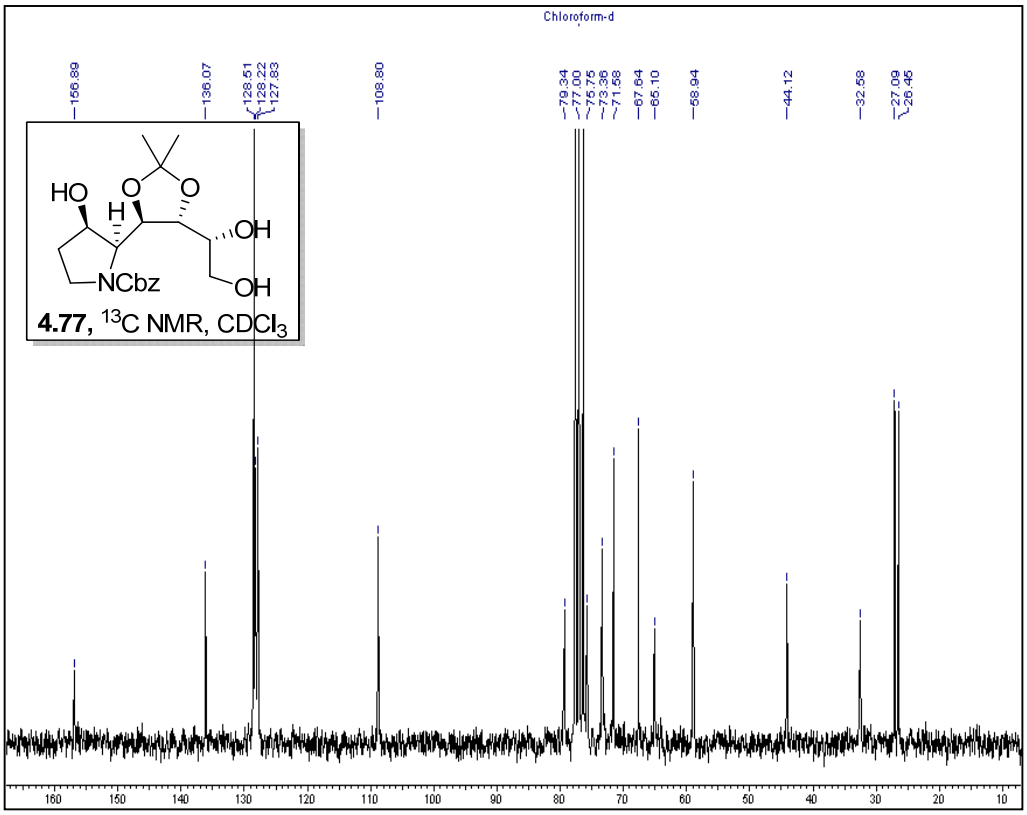

Chloroform-d
7.25
4.27
4.23
4.20
4.19
4.16
4.13
4.06
3.99
3.97
3.96
3.87
3.84
3.28
3.24
3.23
3.19
2.95
2.94
2.93
2.91
2.89
2.05
2.02
2.01
1.98
1.90
1.88
1.87
1.86
1.84
1.83
1.43
1.39
1.35
HO
O
O
H
O
NH
O
4.75, 1H.NMR, CDCl3
2.28
2.36
0.97
1.33
0.94
0.95
12.00
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0

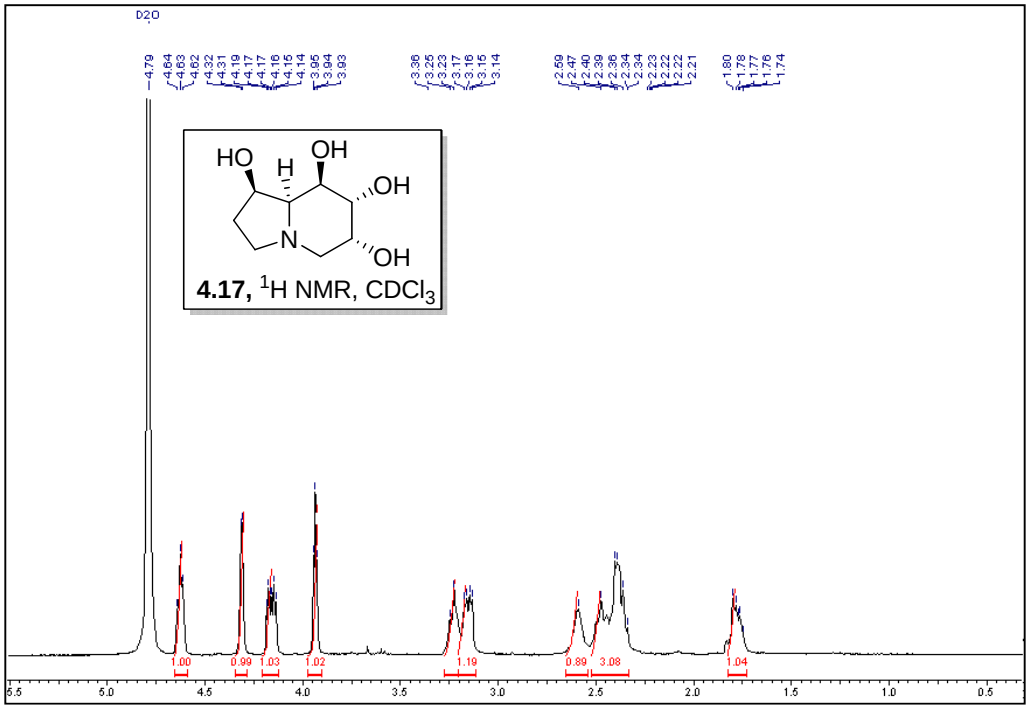

Chloroform-d
110.18
109.54
80.50
79.73
77.39
77.00
71.88
68.26
67.06
44.30
34.72
26.99
26.85
26.20
25.18
HO
O
O
H
O
NH
O
4.75, 13C NMR, CDCl3
120
110
100
90
80
70
60
50
40
30
20
10

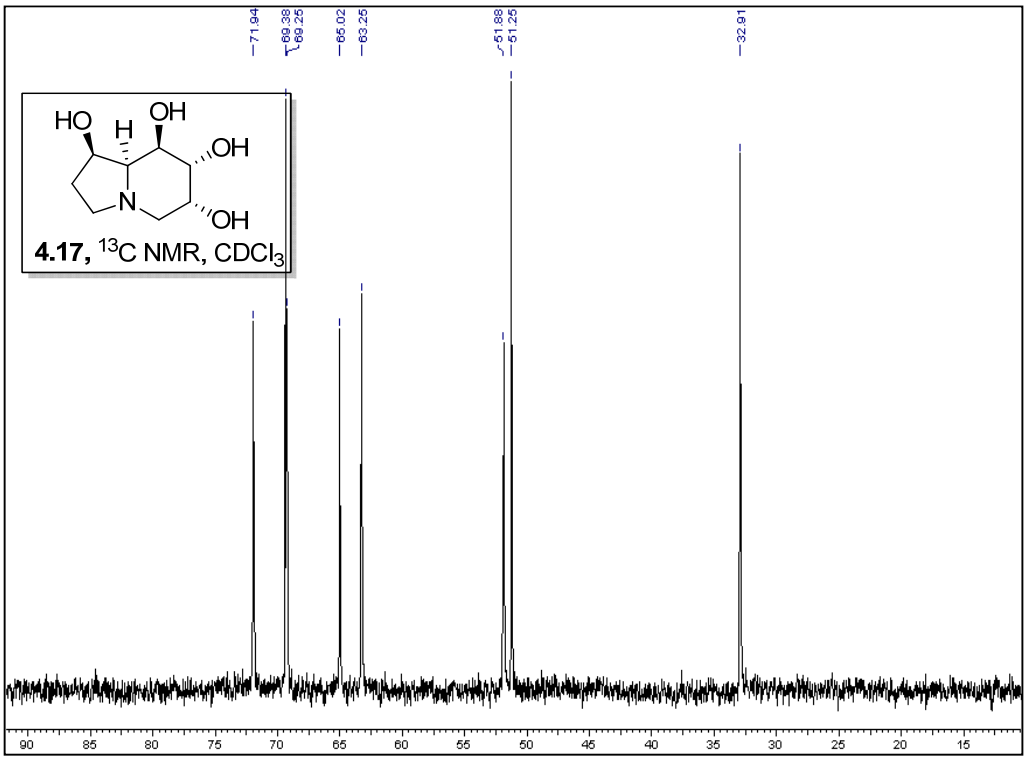

Chloroform-d
HO
H
O
O
O
O
NCbz
4.76, 1H NMR, CDCl3

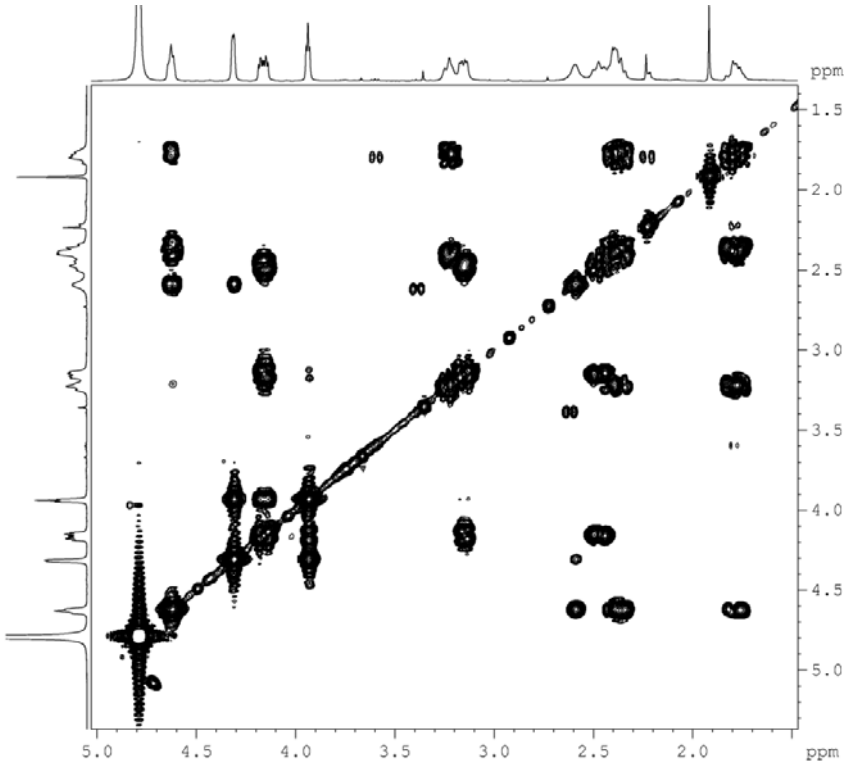

Chloroform-d
HO
H
O
O
O
O
NCbz
4.76, 13C NMR, CDCl3


Chloroform-d
HO
O
O
H
OH
NCbz
OH
4.77, 1H NMR, CDCl3

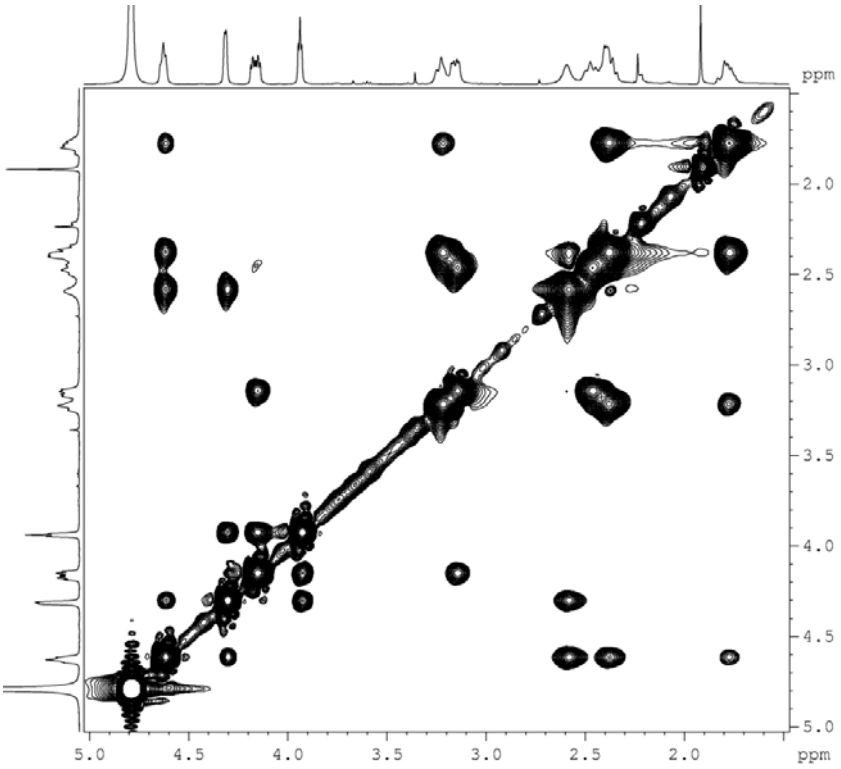

Chloroform-d
HO
O
O
H
OH
NCbz
OH
4.77, 13C NMR, CDCl3


D2O
4.79
4.64
4.63
4.62
4.32
4.31
4.19
4.17
4.17
4.16
4.15
4.14
3.95
3.94
3.93
3.36
3.25
3.23
3.17
3.16
3.15
3.14
2.59
2.47
2.40
2.39
2.36
2.34
2.23
2.22
2.22
2.21
1.80
1.78
1.77
1.76
1.74
HO
H
OH
OH
OH
N
4.17, 1H NMR, CDCl3
1.00
0.99
1.03
1.02
1.19
0.89
3.08
1.04
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5

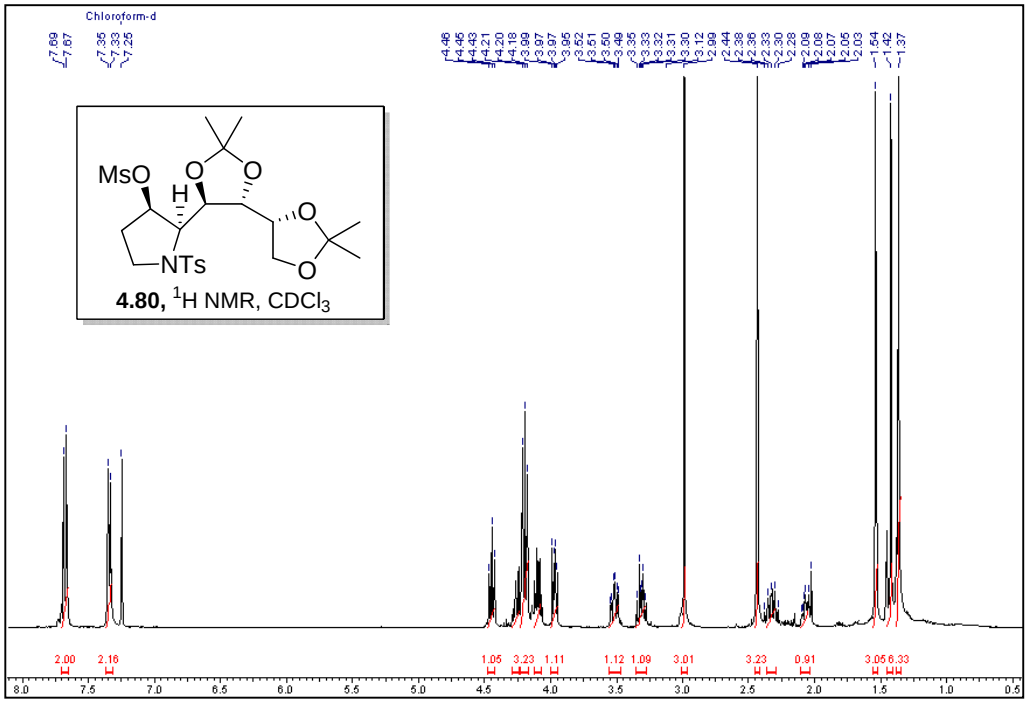

71.94
69.38
69.25
65.02
63.25
51.88
51.25
32.91
HO
H
OH
OH
OH
N
4.17, 13C NMR, CDCl3
90
85
80
75
70
65
60
55
50
45
40
35
30
25
20
15

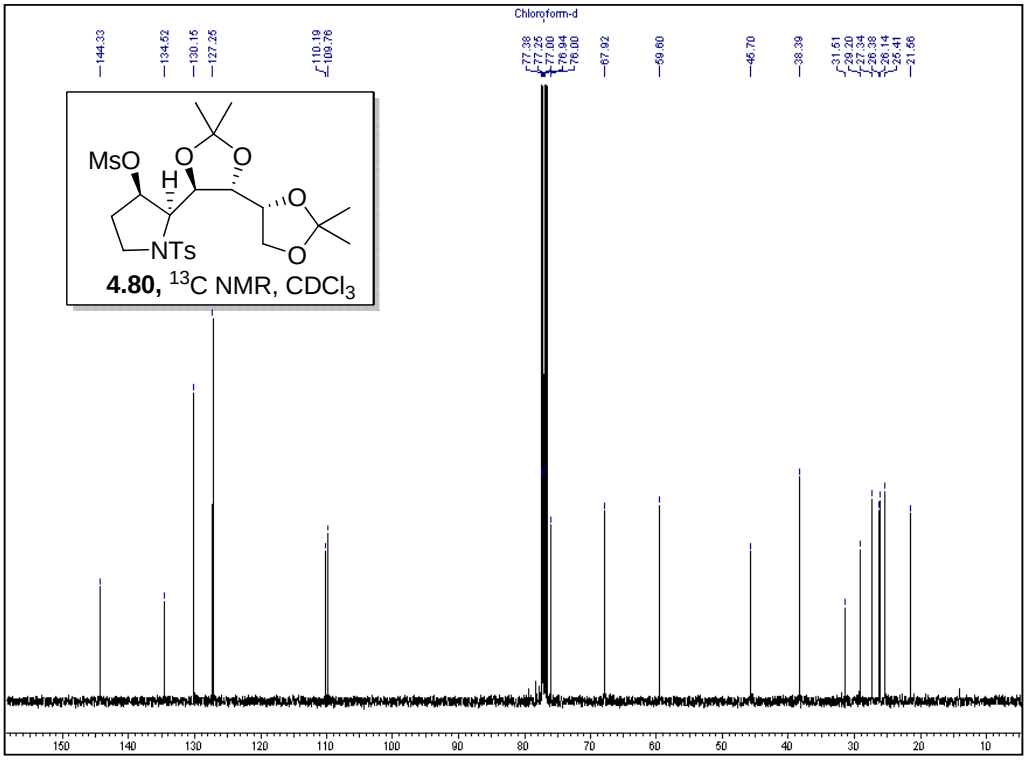


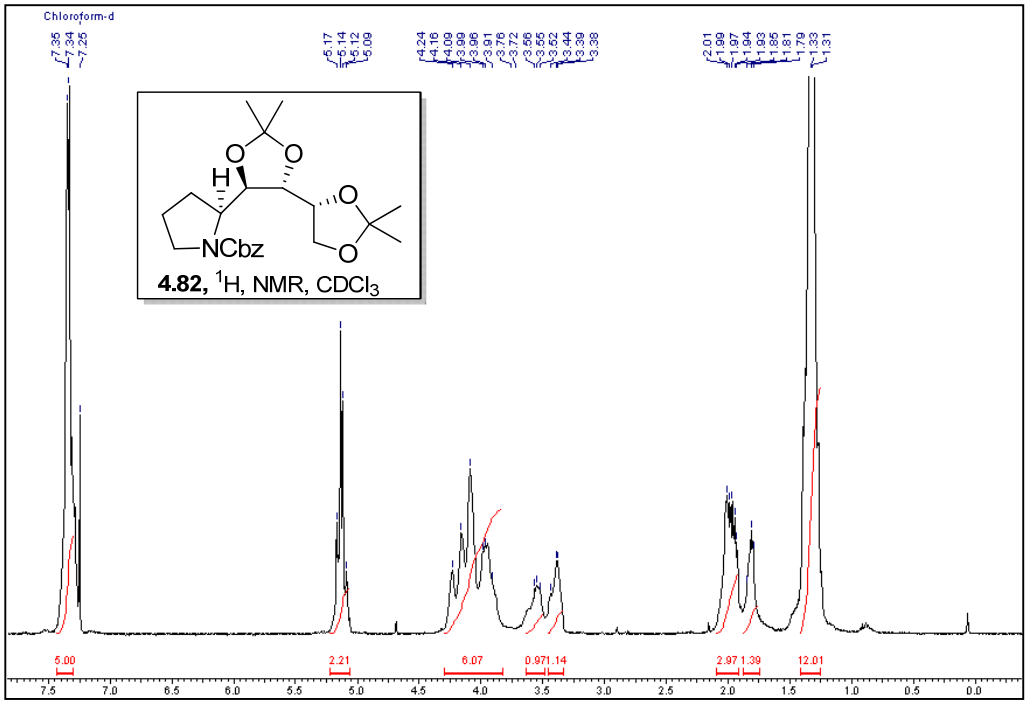
COSEY NMR Spectrum of **4.17**

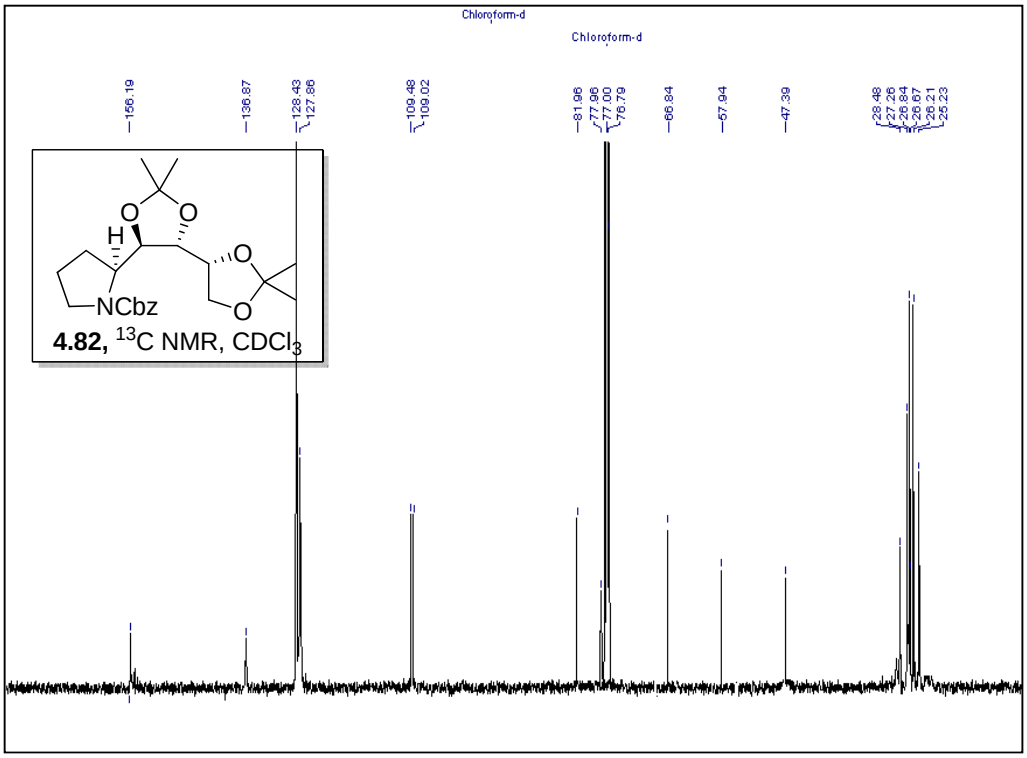


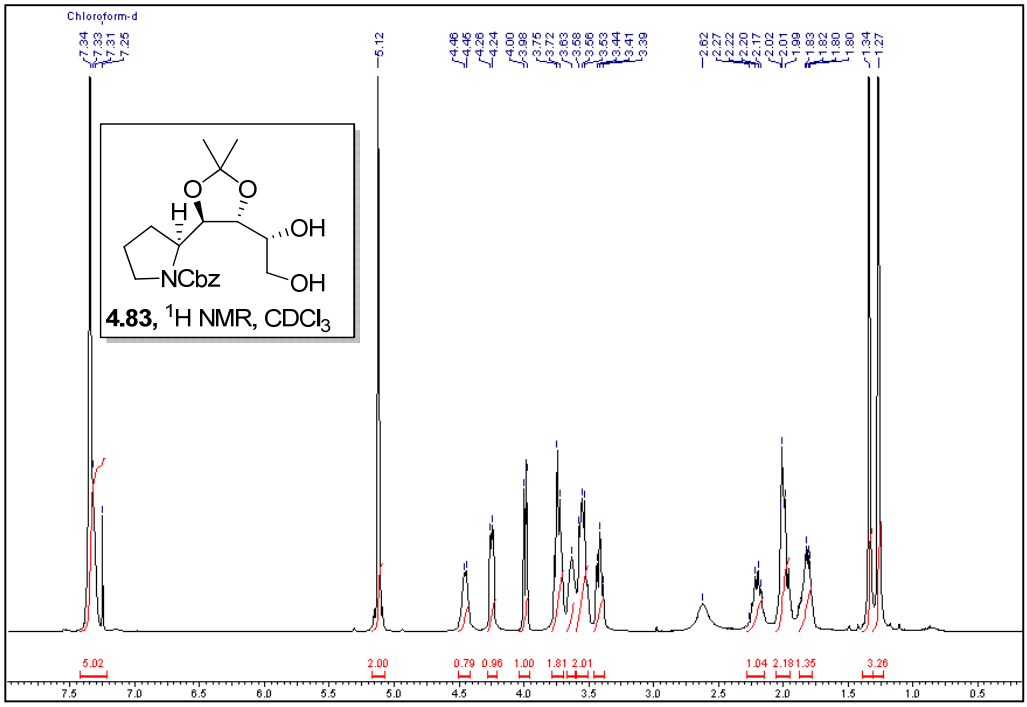
NOSEY NMR Spectrum of **4.17**

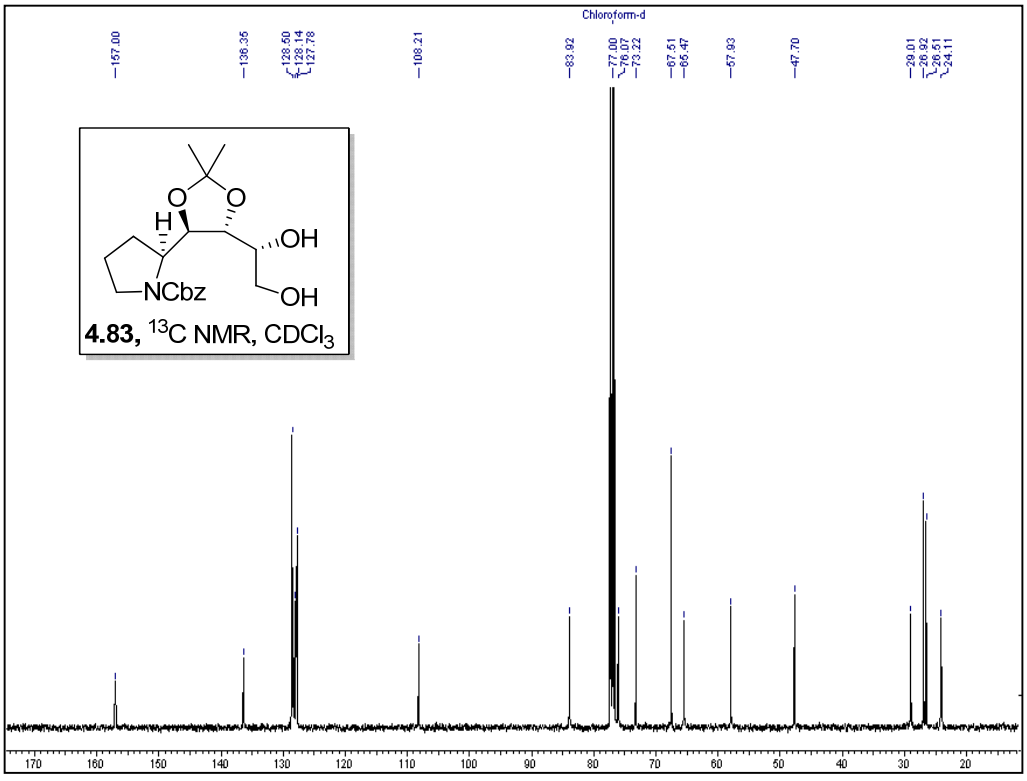

Chloroform-d
MsO
O
O
H
O
NTs
O
4.80, 1H NMR, CDCl3

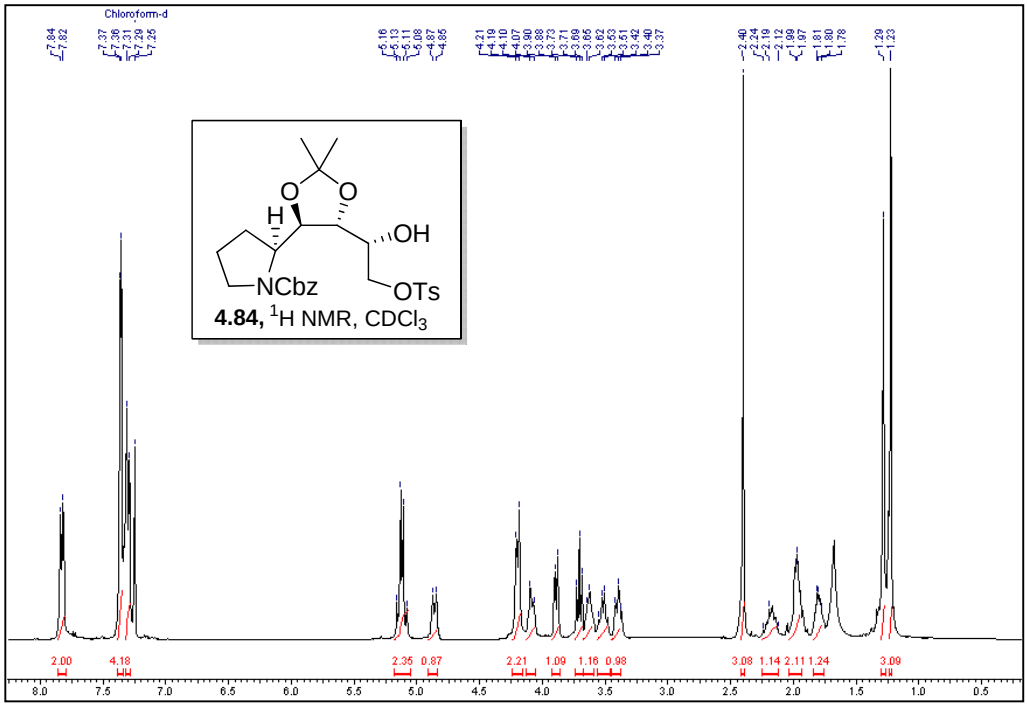

Chloroform-d
MsO
O
O
H
O
NTs
O
4.80, 13C NMR, CDCl3

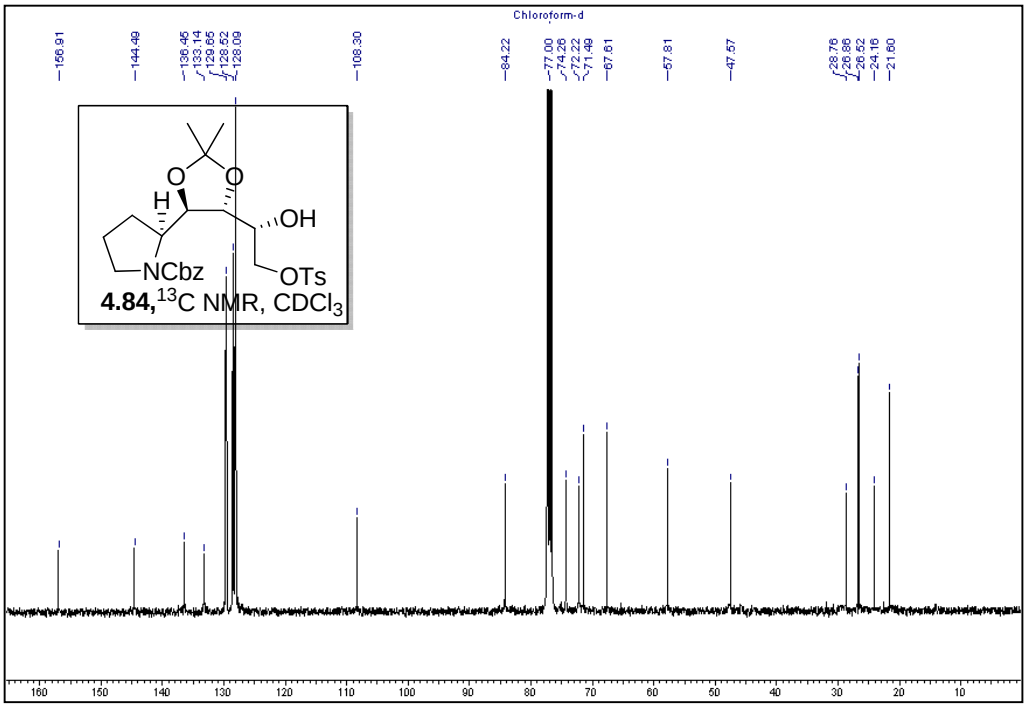

Chloroform-d
NCbz
4.82, 1H, NMR, CDCl3

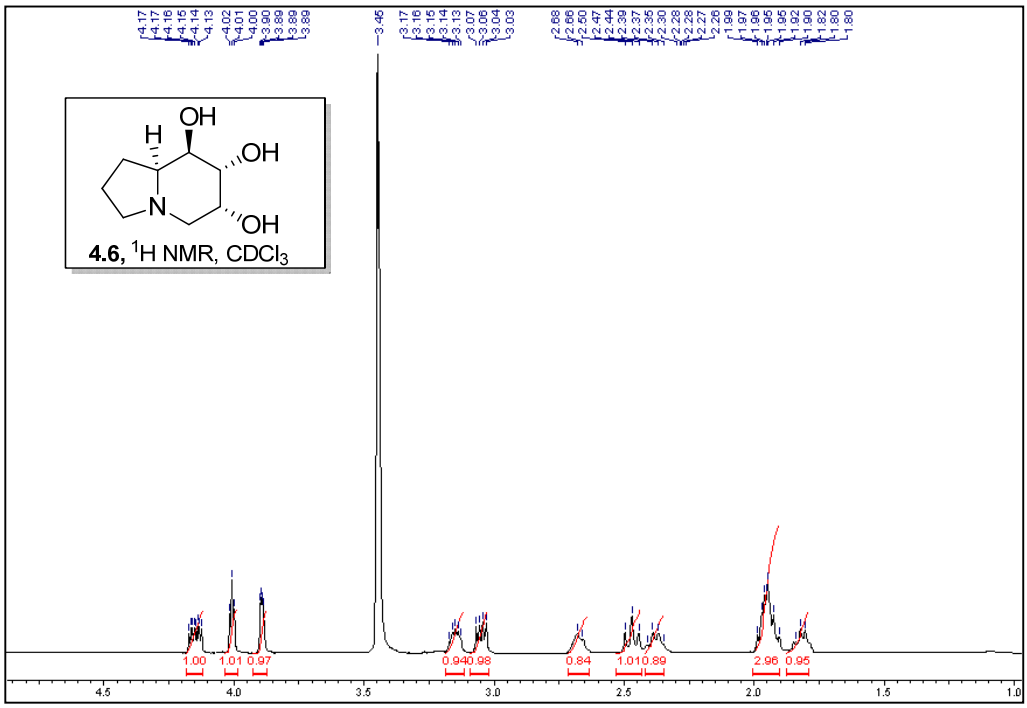

Chloroform-d
Chloroform-d
NCbz
4.82, 13C NMR, CDCl3

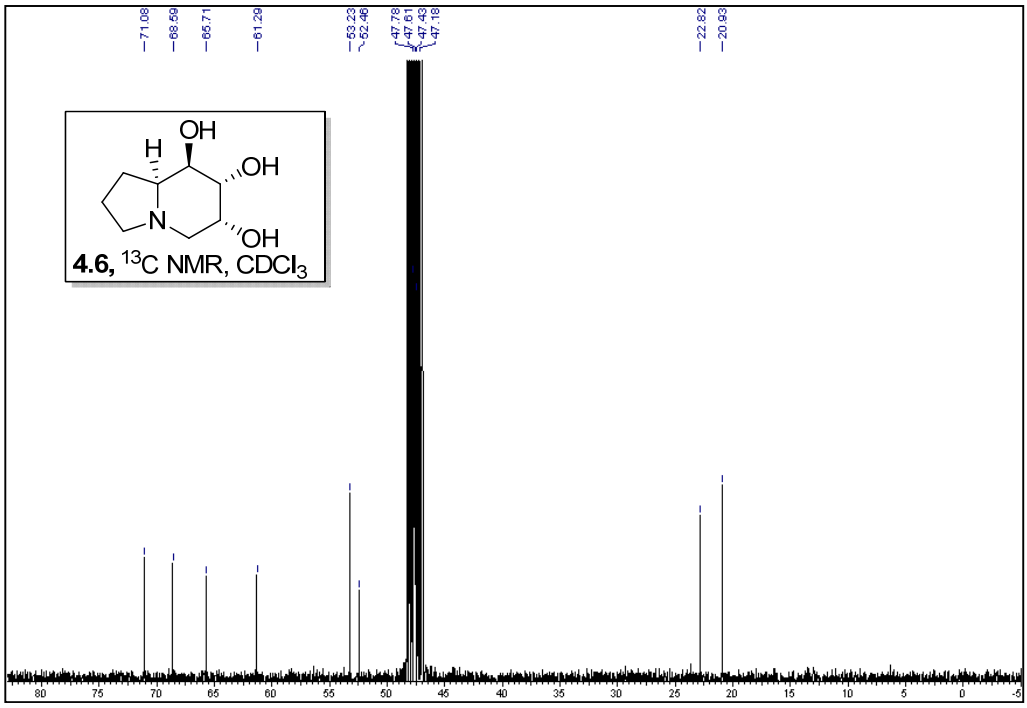

Chloroform-d
7.34
7.33
7.31
7.25
5.12
4.46
4.45
4.26
4.24
4.00
3.98
3.75
3.72
3.63
3.58
3.53
3.44
3.41
3.39
2.62
2.27
2.22
2.20
2.17
2.02
2.01
1.99
1.83
1.82
1.80
1.80
1.34
1.27
O
O
H
OH
NCbz
OH
4.83, 1H NMR, CDCl3
5.02
2.00
0.79
0.96
1.00
1.81
2.01
1.04
2.18
1.35
3.26
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5

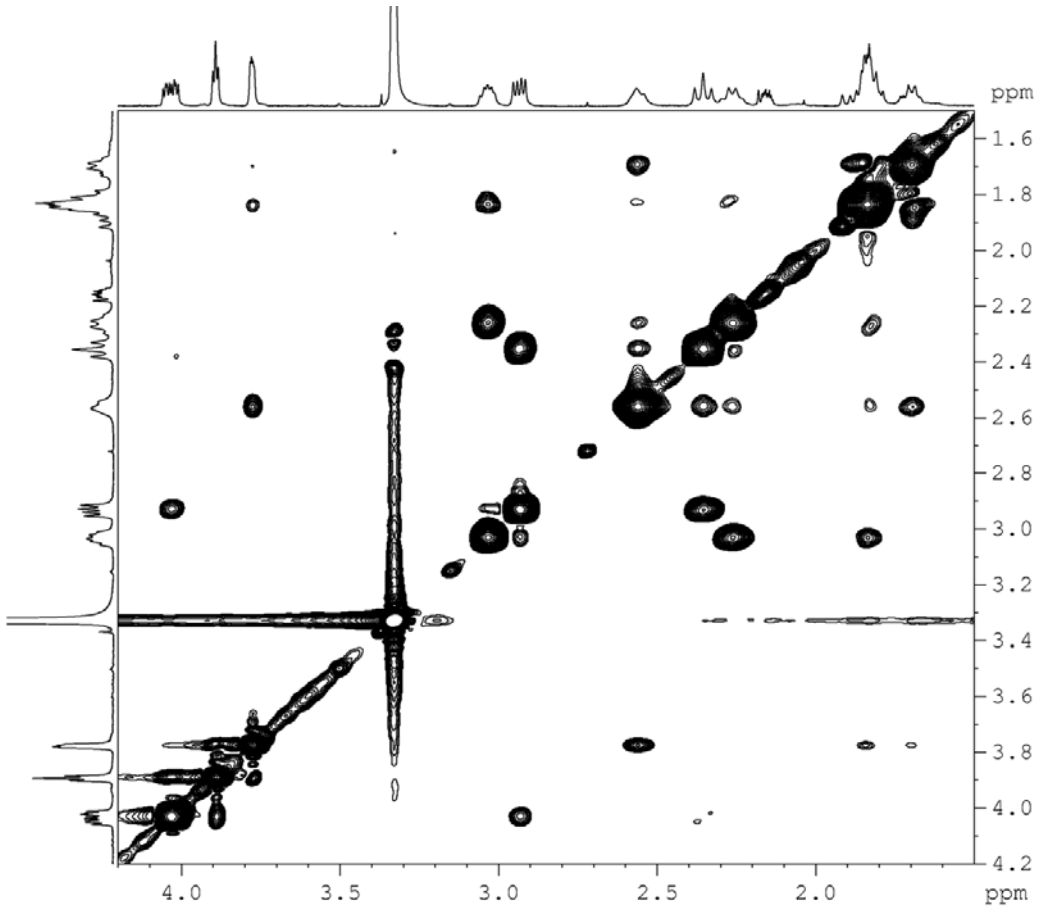

Chloroform-d
157.00
136.35
128.60
128.14
127.78
108.21
83.92
77.00
76.07
73.22
67.51
66.47
57.93
47.70
29.01
26.92
26.51
24.11
O
O
H
OH
NCbz
OH
4.83, 13C NMR, CDCl3
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20


Chloroform-d
O
O
H
OH
NCbz
OTs
4.84, 1H NMR, CDCl3

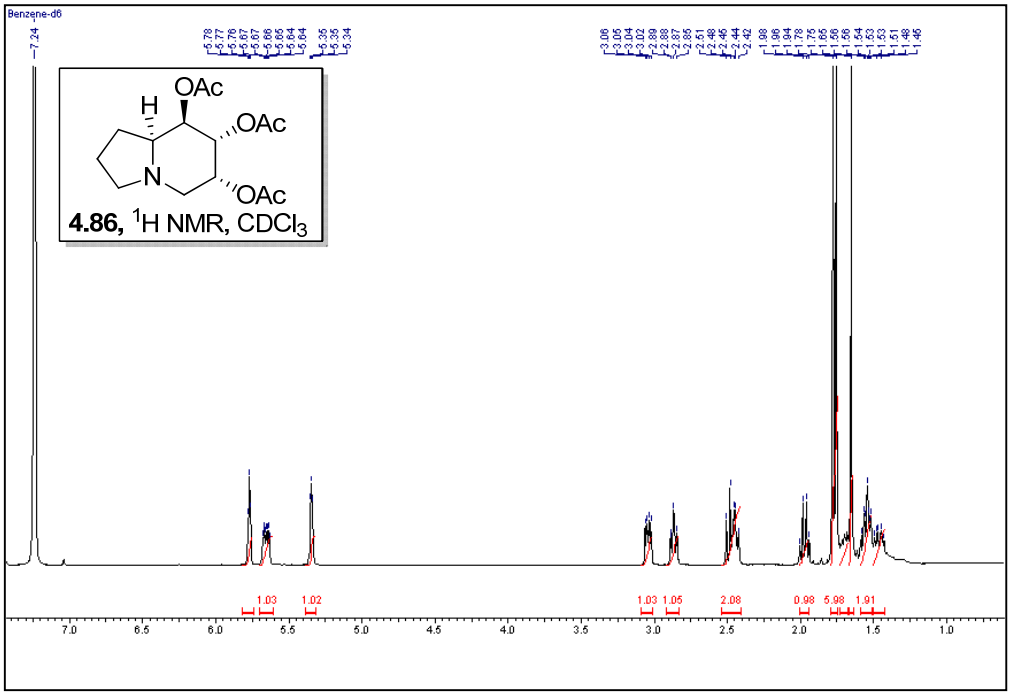

Chloroform-d
O
O
H
OH
NCbz
OTs
4.84,13C NMR, CDCl3

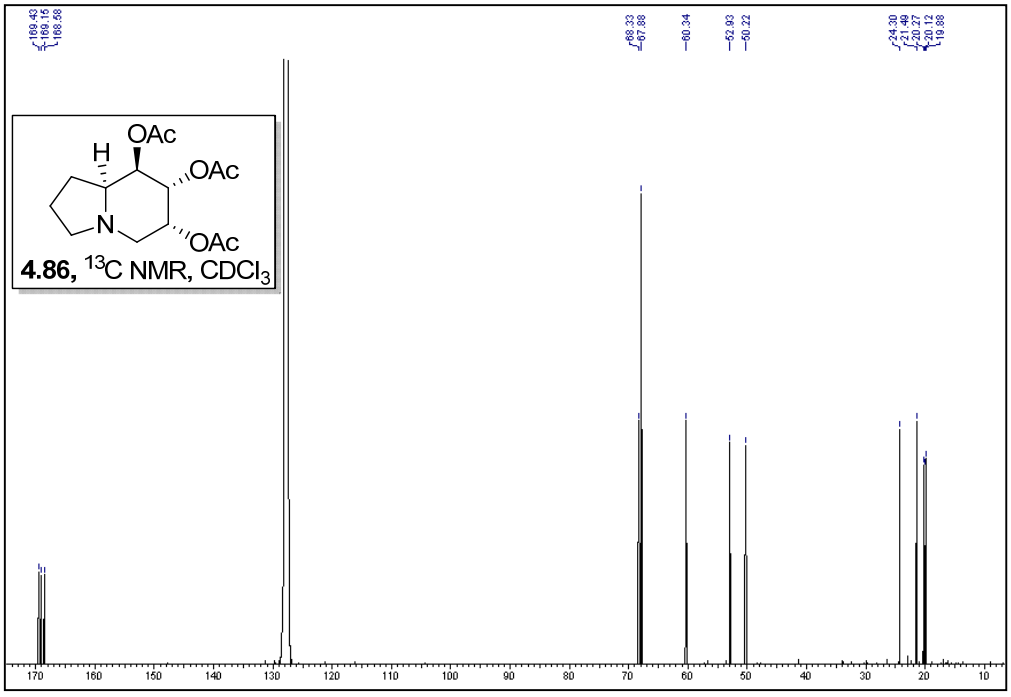

OH
H
OH
N
OH
4.6, 1H NMR, CDCl3

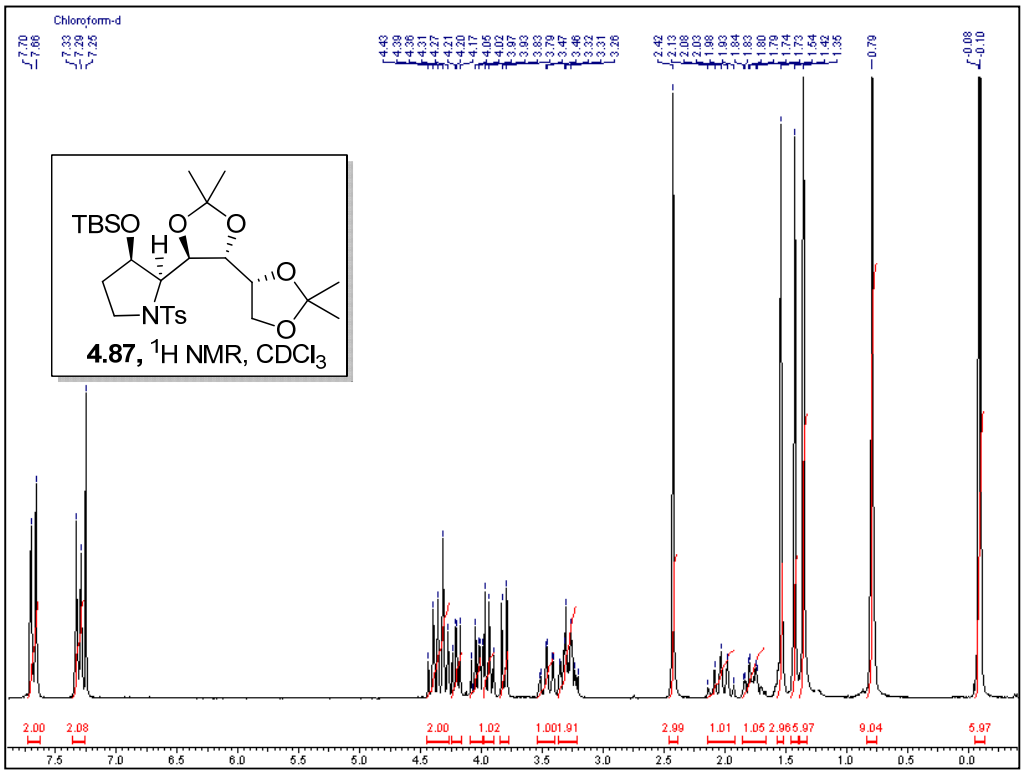

OH
H
OH
N
OH
4.6, 13C NMR, CDCl3

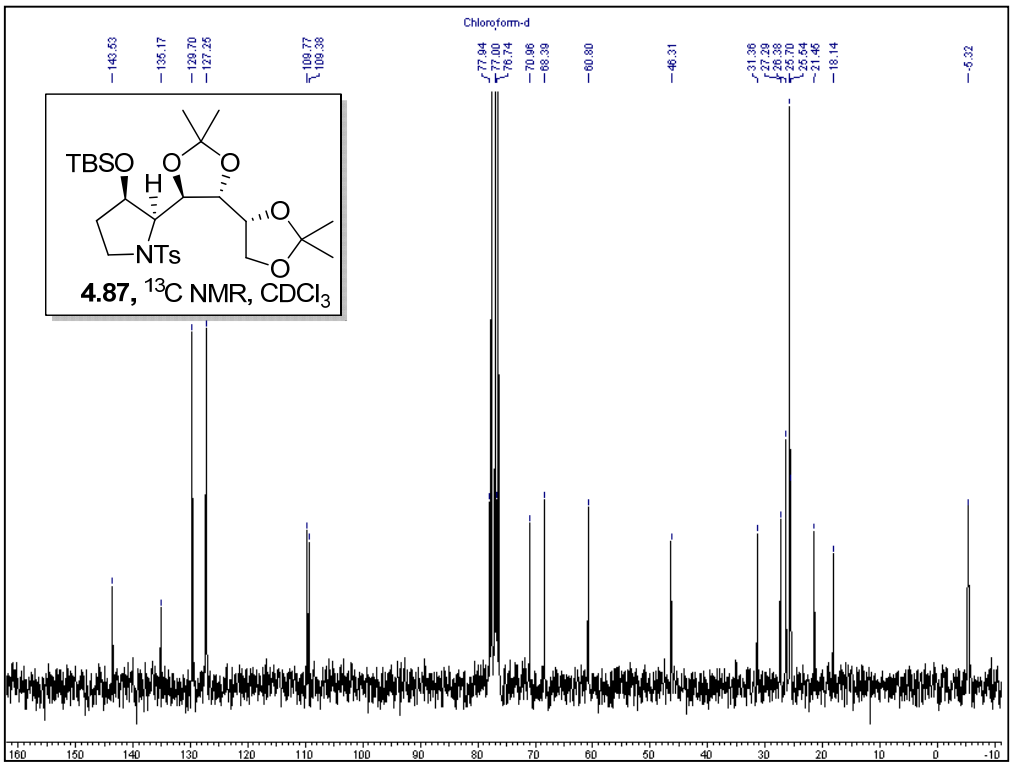


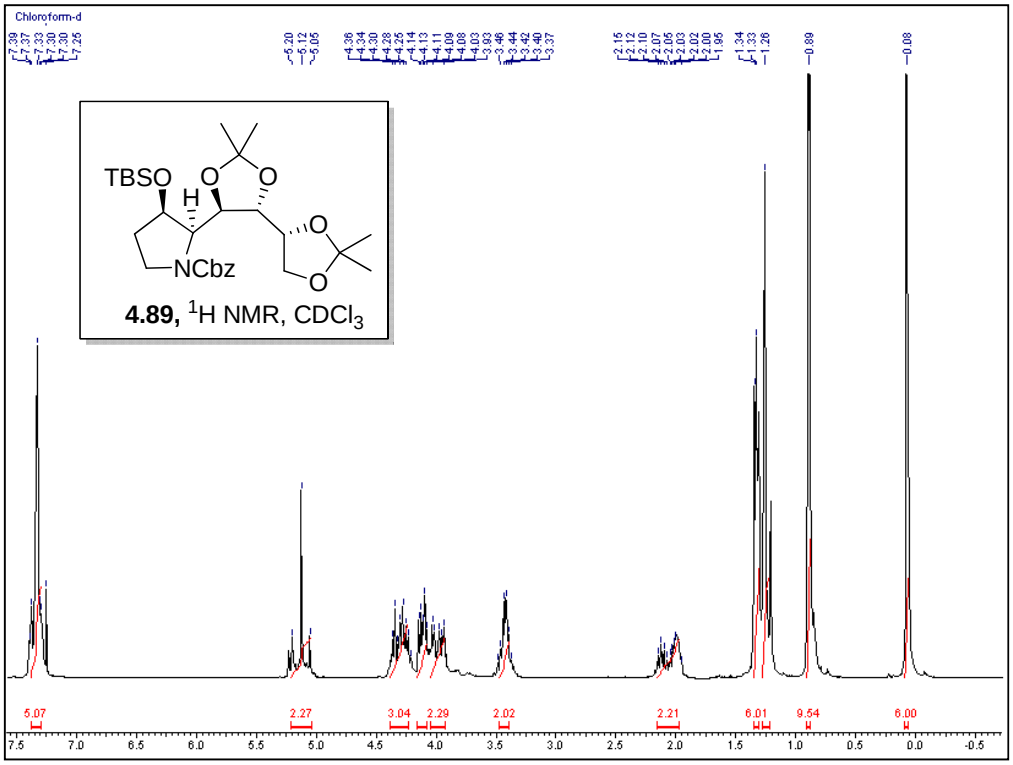
NOSEY NMR Spectrum of **4.6**

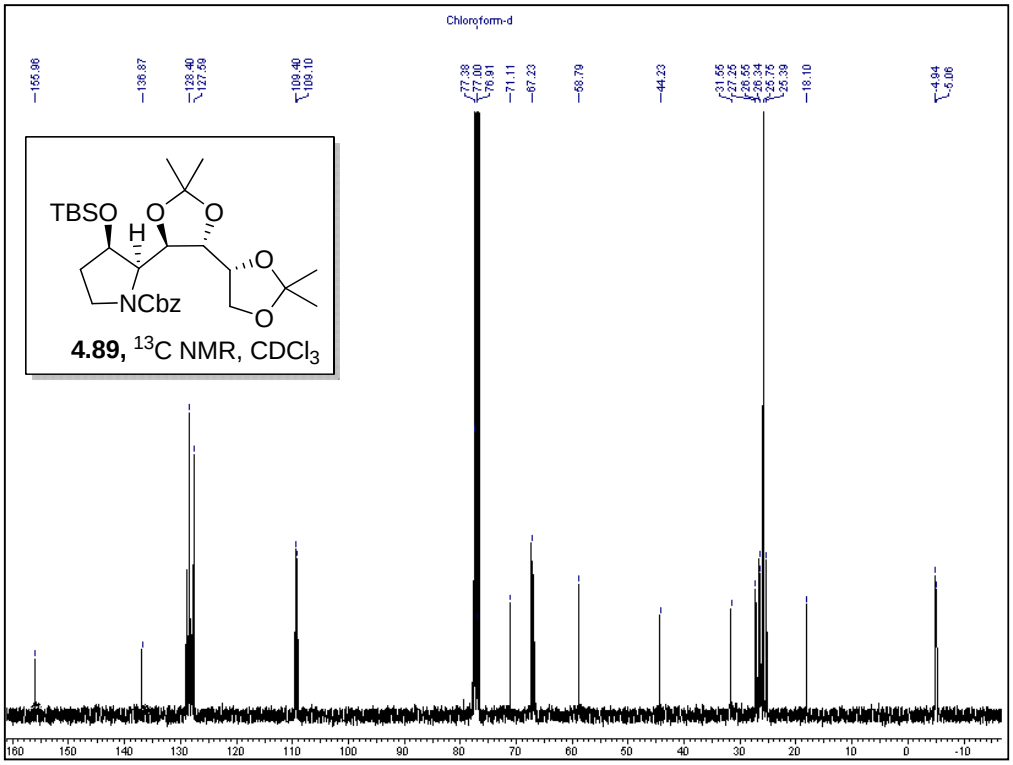

Benzene-d6
OAc
H
OAc
N
OAc
4.86, 1H NMR, CDCl3

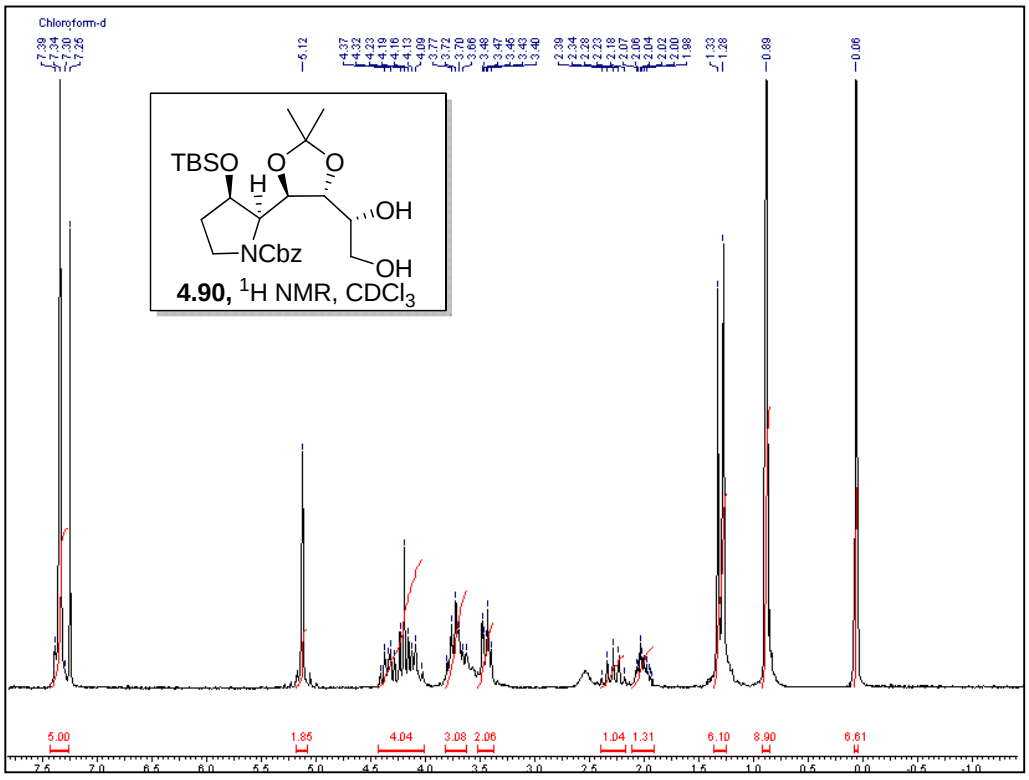

OAc
H
OAc
N
OAc
4.86, 13C NMR, CDCl3

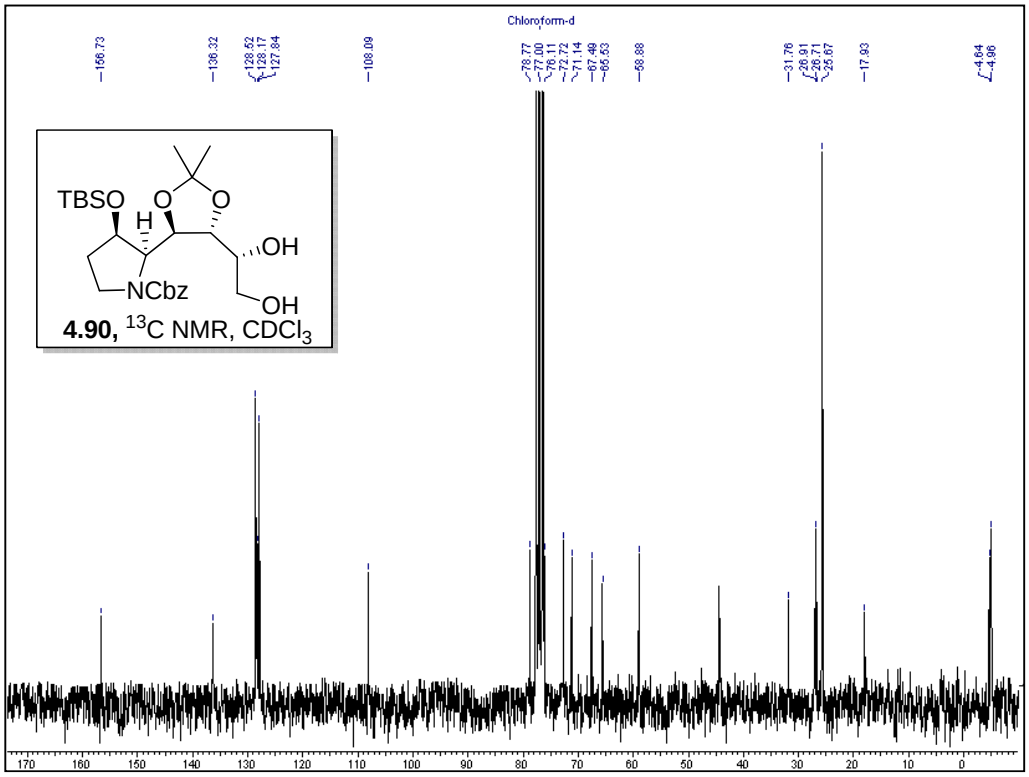

Chloroform-d
TBSO
O
O
H
O
NTs
O
4.87, 1H NMR, CDCl3


Chloroform-d
TBSO
O
O
H
O
NTs
O
4.87, 13C NMR, CDCl3


Chloroform-d
TBSO
H
O
O
O
O
NCbz
4.89, 1H NMR, CDCl3


Chloroform-d
TBSO
H
O
O
O
O
NCbz
4.89, 13C NMR, CDCl3


Chloroform-d
TBSO
O
O
H
OH
NCbz
OH
4.90, 1H NMR, CDCl3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O
H
OH
NCbz
OH
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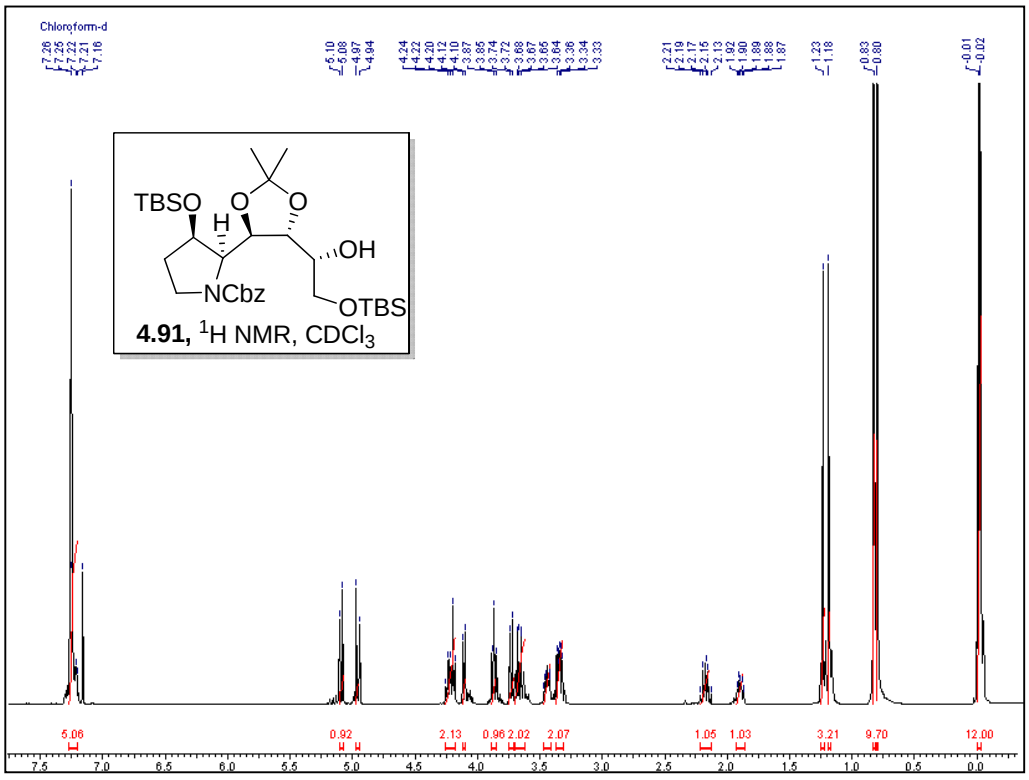
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O
O
H
OH
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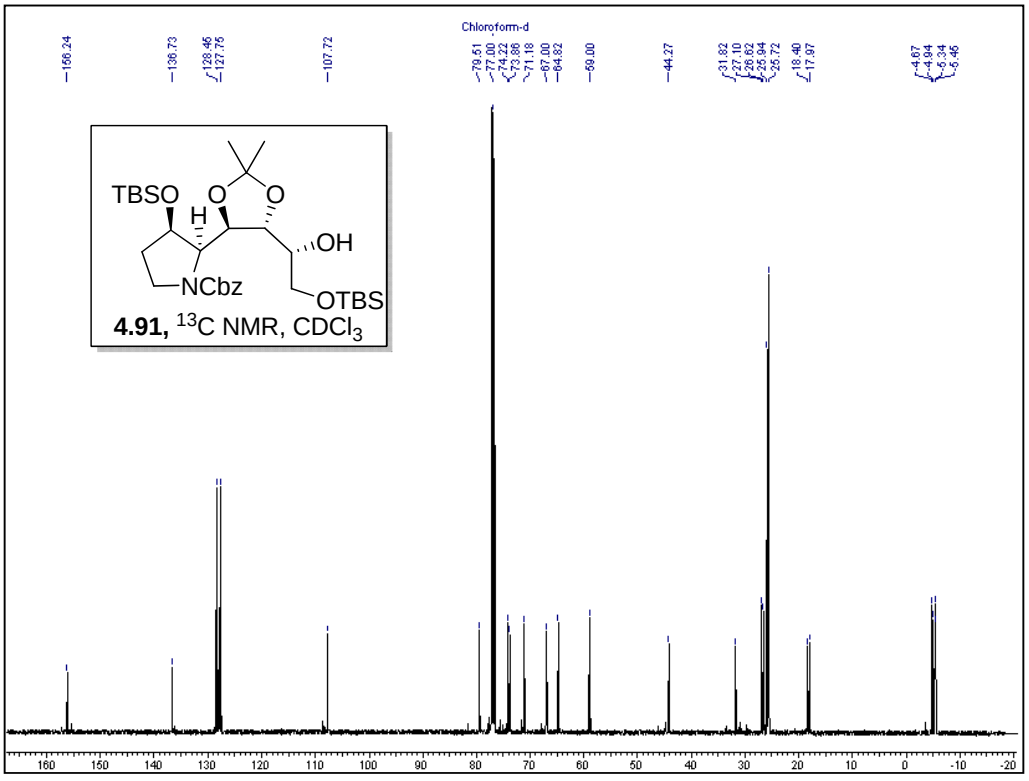
4.91, 1H NMR, CDCl3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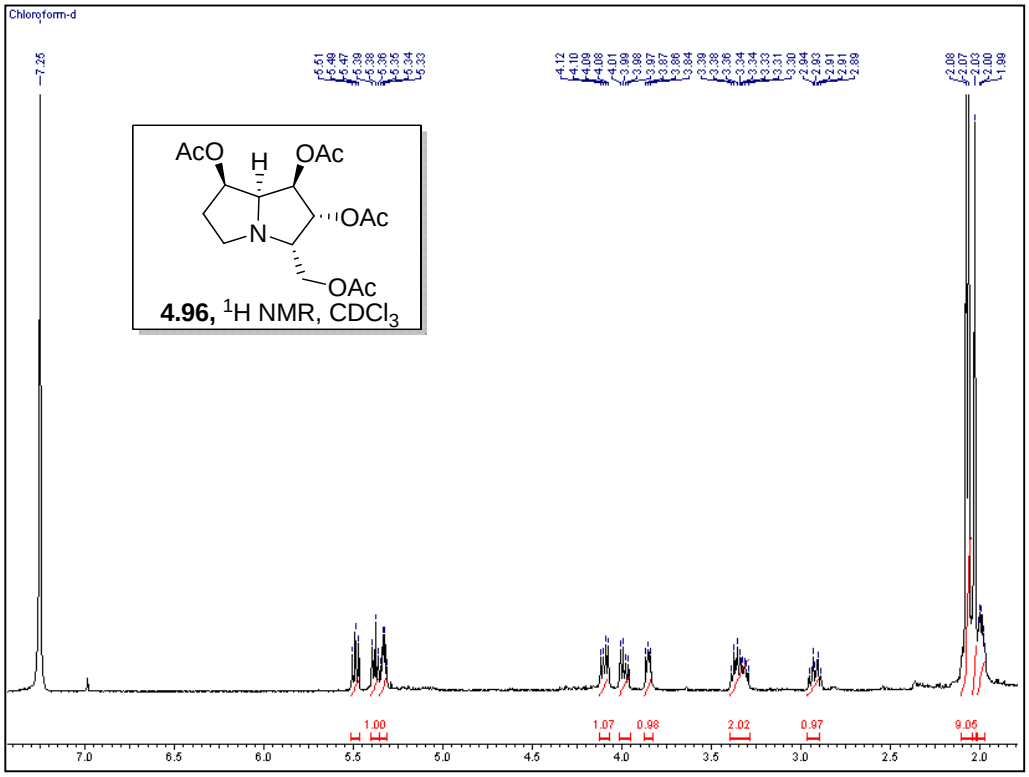
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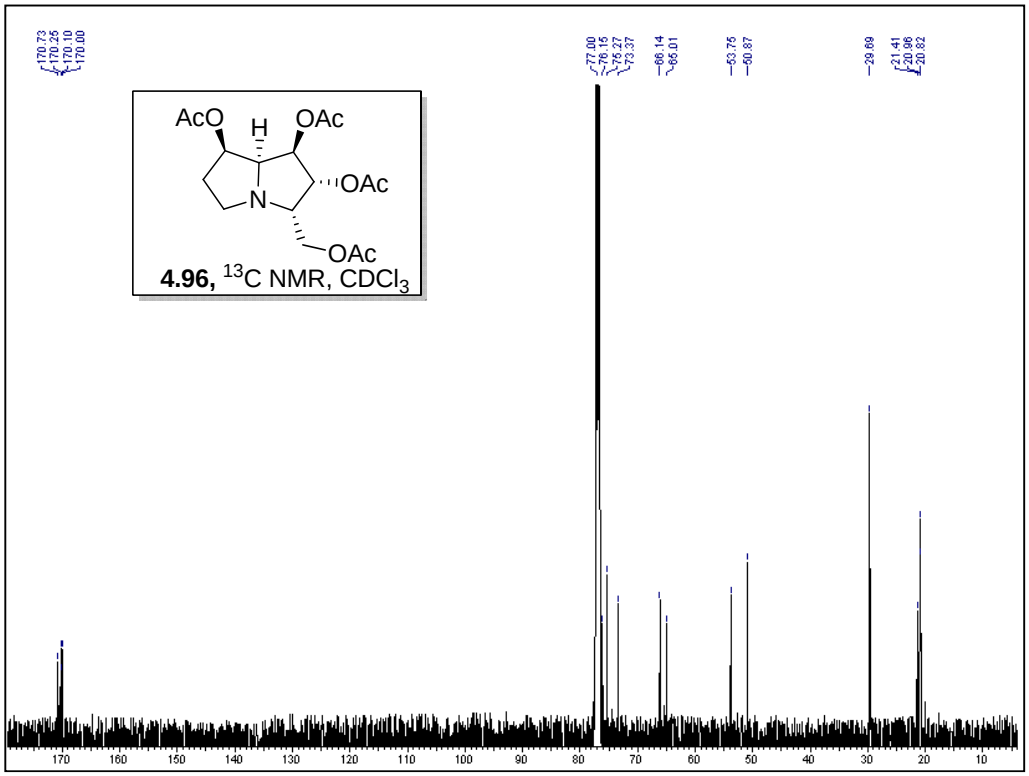
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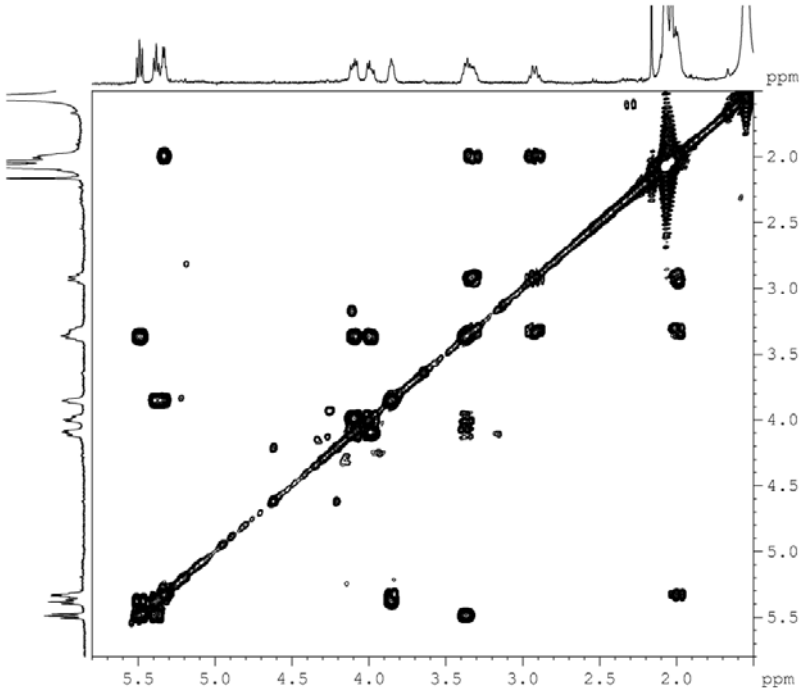
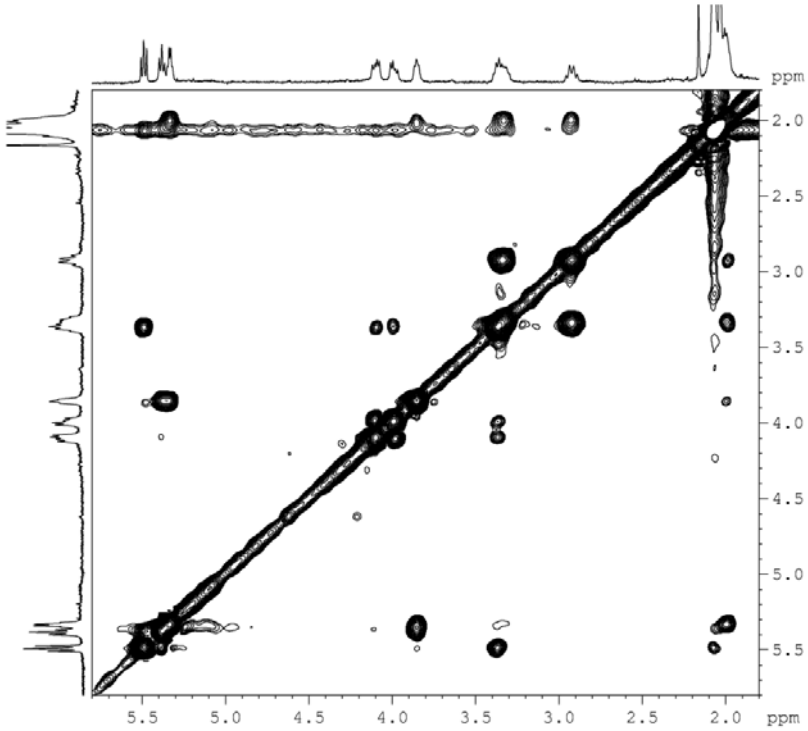


COSEY NMR Spectrum of **4.96**



NOSEY NMR Spectrum of **4.96**

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List of publications

1. Azetidin-2,3-dione Synthon for Stereoselective Synthesis of *cis*- and *trans*-C-3-Alkyl/Aryl Azetidin-2-ones.

Tiwari D.K.; Gumaste, V. K.; Deshmukh, A. R. A. S. *Synthesis* **2006**, *1*, 115-122

2. Stereoselective Synthesis of 3-alkylidene/alkyl-azetidin-2-ones from azetidin-2,3-diones.

Tiwari D. K.; Shaikh, A. Y.; Pavase, L.S.; Gumaste, V. K.; Deshmukh, A. R. A. S. *Tetrahedron* **2007,** *63***,** 2524-2534

3. Enantioselective Total Synthesis of (2*S*,3*R*,4*R*)-*D*-*xylo*-phytosphingosene From Substituted Azetidin-2-one.

Ganesh Pandey, **Tiwari D. K**.; *Tetrahedron* Letters **2009**, *50*, 3296-3298

4. Total Synthesis of 1-deoxy-6,8a-di-*epi*-castanospermine from D-mannitol derived *β*-lactam.

Ganesh Pandey, **Tiwari D.K**. (manuscript under preparation)

5. An Efficient Total Syntheses of 1,6,8a-tri-*epi*-castanospermine and 3,7-di-*epi*-alexine from poly-substituted *β*-lactam.

Ganesh Pandey, **Tiwari D.K**. (manuscript under preparation)

6. Azetidin-2-one a Synthon For The Enantioselective Total Synthesis of Trihydroxy and Pipacolic Acid 5-deoxy-mannojirimycin.

Ganesh Pandey, **Tiwari D.K**. (manuscript under preparation)

Erratum