APPROACHES TOWARDS THE SYHTHESIS OF POLYHYDROXYLATED ALKALOIDS AND TETRAHYDROPYRANS USING CARBOHYDRATE SCAFFOLDS; CHEMICAL TRANSFORMATIONS OF ABUNDANT NATURAL PRODUCTS AND CHEMICAL EXAMINATION OF *Polyalthia longifolia* var. *pendula* FOR BIOACTIVE MOLECULES

A THESIS

Submitted to the

SAVITRIBAI PHULE PUNE UNIVERSITY

For the degree of

DOCTOR OF PHILOSOPHY

in

CHEMISTRY

by

HEMENDER R. CHAND

Research Supervisor

DR. ASISH KUMAR BHATTACHARYA

DIVISION OF ORGANIC CHEMISTRY

CSIR-NATIONAL CHEMICAL LABORATORY

PUNE 411008, INDIA

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DEDICATED

TO

MY PARENTS

AND

TEACHERS

राष्ट्रीय रासायनिक प्रयोगशाला
(वैज्ञानिक तथा औद्योगिक अनुसंधान परिषद)
डॉ. होमी भाभा रोड, पुणे - 411 008. भारत
NATIONAL CHEMICAL LABORATORY
(Council of Scientific & Industrial Research)
Dr. Homi Bhabha Road, Pune - 411008. India

CERTIFICATE

This is to certify that the work incorporated in the thesis entitled "*Approaches Towards the Synthesis of Polyhydroxylated Alkaloids and Tetrahydropyrans Using Carbohydrate Scaffolds; Chemical Transformations of Abundant Natural Products and Chemical Examination of Polyalthia longifolia var. pendula for Bioactive Molecules*" which is being submitted to the *Savitribai Phule Pune University* for the award of *Doctor of Philosophy* in *Chemistry* by ***Mr. Hemender R. Chand*** was carried out by him under my supervision at the CSIR-National Chemical Laboratory, Pune. Such material as has been obtained from other sources has been duly acknowledged in the thesis.

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CANDIDATE'S DECLARATION

I hereby declare that the thesis entitled "*Approaches Towards the Synthesis of Polyhydroxylated Alkaloids and Tetrahydropyrans using Carbohydrate Scaffolds; Chemical Transformations of Abundant Natural Products and Chemical Examination of Polyalthia longifolia var. pendula for Bioactive Molecules*" submitted by me for the degree of *Doctor of Philosophy* in *Chemistry* to the *Savitribai Phule Pune University* is the record of work carried out by me during the period *November, 2009 to September, 2015* and has not been submitted by me for a degree to any other University or Institution. This work was carried out at Division of Organic Chemistry, CSIR-National Chemical Laboratory, Pune, India.

Hemender R. Chand **July 2016**
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Hemender R. Chand

CONTENTS

GENERAL REMARKS

- Independent reference and compound numbering have been employed for each chapter as well as sections of the chapters.
- All the solvents used were purified using the known literature procedures.
- Petroleum ether used in the experiments was of 60-80 °C boiling range.
- Column chromatographic separations were carried out by gradient elution using silica gel (100-200 mesh/230-400 mesh) with light petroleum ether-ethyl acetate mixture, unless otherwise mentioned.
- TLC was performed on E-Merck pre-coated silica gel 60 F254 plates and the spots were rendered visible by exposing to UV light, iodine, charring or staining with ninhydrin, *p*-anisaldehyde solutions in ethanol.
- All the melting points reported are uncorrected and were recorded using Buchi Melting Point apparatus B-540.
- IR spectra were recorded on Shimadzu FTIR instrument, for solid either as nujol mull or in chloroform solution and neat in case of liquid compounds.
- NMR spectra were recorded on Bruker ACF 200 and AV200 (200.13 MHz for ^{1}H NMR and 50.03 MHz for ^{13}C NMR), MSL 300 (300.13 MHz for ^{1}H NMR and 75.03 MHz for ^{13}C NMR), AV 400 (400.13 MHz for ^{1}H NMR and 100.03 MHz for ^{13}C NMR) and DRX 500 (500.13 MHz for ^{1}H NMR and 125.03 MHz for ^{13}C NMR) spectrometers. Chemical shifts (δ) reported are referred to internal reference tetramethylsilane (TMS). The following abbreviations were used: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, bs = broad singlet, dd = doublet of doublet, dt = doublet of triplet and ddd = doublet of doublet of doublet. Mass spectra were recorded on LC-MS/MS-TOF API QSTAR PULSAR spectrometer, samples introduced by infusion method using Electrosprey Ionization Technique.
- Optical rotations were obtained on Bellingham & Stanley ADP-220 Polarimeter. Specific rotations $[\alpha]_D$ are reported in deg/dm, and the concentration (c) is given in g/100 mL in the specific solvent.
- All the compounds previously known in the literature were characterized by comparison of their R_f values on TLC, IR and NMR spectra.

- Starting materials were obtained from commercial sources or prepared using known procedures.
- Compounds have been named based on nomenclature provided by Chem Bio Draw Ultra 13.0 software.
- Flash chromatography were carried out by **Combi*Flash*®$\mathbf{R_f}$ *200i*** Teledyne Isco instrument using UV/ELSD detector and appropriate solvent system mentioned in the procedure.

ABBREVIATIONS

Ac	Acetyl
ACE	Angiotensin-converting Enzyme
AcOH	Acetic acid
Ac_2O	Acetic anhydride
AIBN	Azobisisobutyronitrile
AIDS	Acquired Immunodeficiency Syndrome
Anhyd.	Anhydrous
Aq.	Aqueous
BAIB	Bis-acetoxy Iodo Benzene
$BF_3.Et_2O$	Boron trifluoride-diethyletherate
$BH_3.DMS$	Borane-dimethyl sulfide complex
Boc	*tert*-Butoxycarbonyl
$(Boc)_2O$	Boc anhydride
Bn	Benzyl
$^{n}BuLi$	*n*-Butyl-lithium
$^{t}BuLi$	*tert*-Butyl-lithium
Bu_3SnH	Tributyltinhydride
CAN	Ceric Ammonium Nitrate
Cbz	Benzyloxycarbonyl
COSY	Correlation spectroscopy
d	Day/s
DBU	1,8- diaza-bicyclo[5.4.0]undec-7-ene
DCFH-DA	2′,7′-dichlorofluorescein diacetate
DCM	Dichloromethane
DCC	N,N'-Dicyclohexylcarbodiimide
DEAD	Diethyl Azodicarboxylate
DEPT	Distortionless Enhancement by Polarization Transfer
DHP	Dihydropyran
DHR	Dihydrorhodamine
$(DHQ)_2AQN$	Hydroquinine anthraquinone-1,4-diyl diether
$(DHQD)_2AQN$	Hydroquinidine (anthraquinone-1,4-diyl) diether
DIBAL	Diisobutylaluminium Hydride
DIPEA	N,N-Diisopropylethylamine
DMAP	4-(Dimethylamino)pyridine
DMF	Dimethylformamide
DMSO	Dimethyl Sulphoxide
DNA	Deoxyribose Nucleic Acid
EBA	Ethyl Bromo Acetate
EtOH	Ethanol
EtOAc	Ethyl acetate
Et_3N	Triethylamine
h	Hour(s)
HIV	Human Immunodeficiency Virus
HMBC	Heteronuclear Multiple Bond Coherence
HMDS	Hexamethyl disilazide
HMPA	Hexamethylphosphoric triamide
HOBT	Hydroxybenzotriazole

HPLC	High Performance Liquid Chromatography
HRMS	High Resolution Mass Spectrometry
HSQC	Heteronuclear Single Quantum Coherence
Hz	Hertz
IR	Infra Red
LAH	Lithium Aluminum Hydride
LC-MS	Liquid Chromatography-Mass Spectrometry
LDA	Lithium diisopropyl amide
LHMDS	Lithium hexamethyl disilazide
*m*CPBA	*m*-Chloroperoxybenzoic acid
MeCN	Acetonitrile
MeOH	Methanol
MIC	Minimum Inhibitory Concentration
min.	Minute(s)
mL	Millilitre(s)
μM	Micromolar
mmol	Millimole(s)
Mp	Melting Point
MS	Mass Spectrum
MS 4Å	Molecular Sieves (4Å)
MsCl	Mesyl Chloride
NCIM	National Collection of Industrial Microorganisms
NMMO	N-Methylmorpholine N-oxide
NMR	Nuclear Magnetic Resonance
ORTEP	Oak Ridge Thermal Ellipsoid Plot
Pd/C	Palladium on charcoal
$Pd(OAc)_2$	Palladium acetate
p-TSA	*para*-toluene sulphonic acid
PMP	*p*-Methoxyphenyl
*p*TSA	*p*-Toluenesulfonic acid
*p*TsCl	*p*-Toluenesulfonyl chloride
Py	Pyridine
R	Rectus
RBC	Red Blood Corpuscle
RNA	Ribonucleic Acid
ROS	Reactive Oxygen Species
S	Sinister
SAR	Structure Activity Relationship
SiO_2	Silica
Sm	Starting material
rt	Room Temperature
TBAB	Tetrabutylammonium bromide
TBAI	Tetrabutylammonium Iodide
TBAF	Tetra-n-butylammonium fluoride
TCCA	Trichloroisocyanuric Acid
TEA	Triethylamine
TEMPO	(2,2,6,6-Tetra methyl piperidin-1-yl) oxyl free radical
TFA	Trifluoroacetic acid
TFAA	Trifluoroacetic anhydride

Tf_2O	Triflic anhydride
THF	Tetrahydrofuran
TLC	Thin Layer Chromatography
TMEDA	Tetramethyl ethylenediamine
TMSCl	Trimethylsilylchloride
TMSCN	Trimethylsilylcyanide
TMSOTf	Trimethylsilyl trifloromethanesulfonate
TPAP	Tetra n-propyl ammonium perruthenate
WHO	World Health Organization

Abstract

The thesis entitled ñApproaches Towards the Synthesis of Polyhydroxylated Alkaloids and Tetrahydropyrans using Carbohydrate Scaffolds; Chemical Transformations of Abundant Natural Products and Chemical Examination of *Polyalthia longifolia* var. *pendula* for Bioactive Moleculesò consists of four chapters.

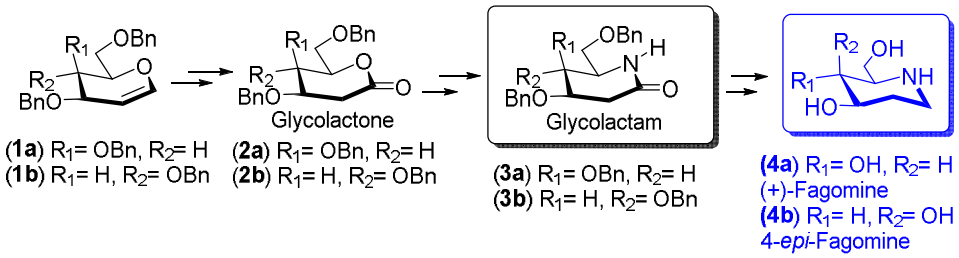
Chapter 1: **Approaches Towards the Synthesis of Polyhydroxylated Alkaloids using Carbohydrate scaffolds**.

This chapter is divided into two sections.

Section A: Approaches Towards the Synthesis of Fagomine, 4-*epi*-Fagomine, Nojirimycin and 2-Deoxynojirimycin

This chapter provides a short introduction to polyhydroxylated alkaloids. And also reviews the reported synthesis of fagomine, 4-*epi*-fagomine, nojirimycin, deoxynojirimycin and pipecolic acid using carbohydrate building blocks and also from non-carbohydrate precursors.

Sugars are readily available and one of the richest source of raw material available from chiral pool for the synthesis of a number of diverse and complex molecules. We have utilized *D*-glycals (**1a**/**b**) as starting material, which is converted to glycolactone (**2a**/**b**) and which in turn is transformed to glycolactam (**3a**/**b**) from which fagomine (**4a**), 4-*epi*-fagomine (**4b**) are readily synthesized (Scheme 1).

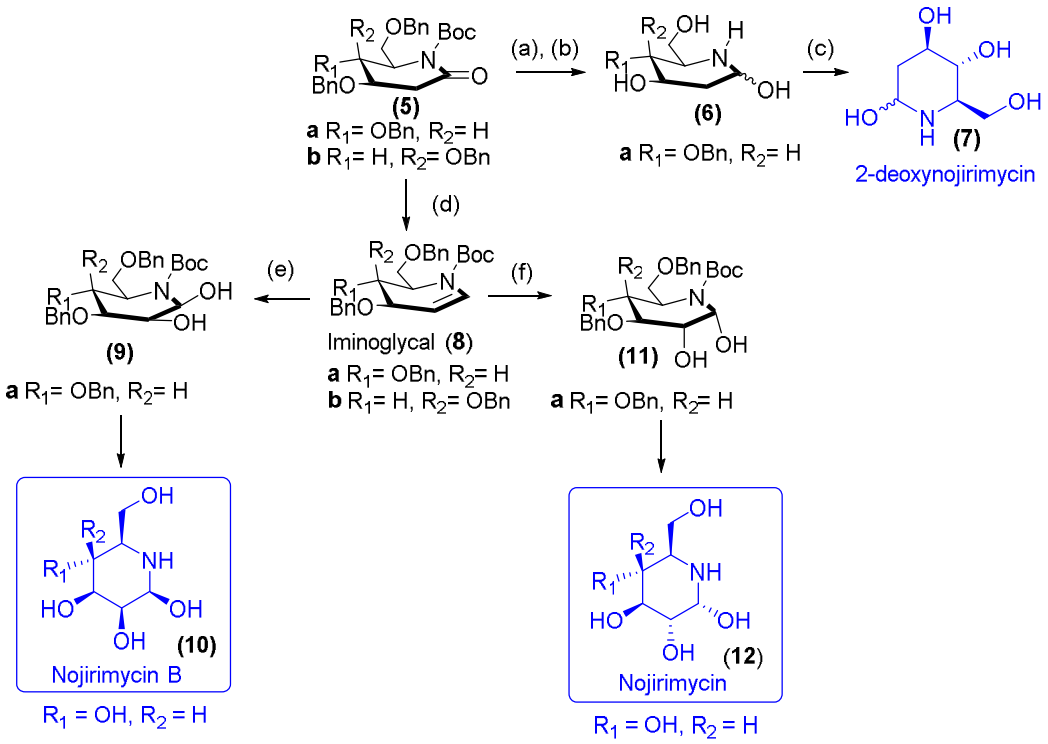


Scheme 1. Synthesis of (+)-fagomine and 4-*epi*-fagomine.

Approach Towards the Synthesis of Nojirimycin and 2-Deoxynojirimycin

Nojirimycin and its derivatives are well known for their glycosidase inhibitory activities. Further utilizing the synthesized glycolactam (**3a**/**b**) for the synthesis of piperidine alkaloids by protecting the nitrogen and partial reduction of amide carbonyl in one case and partial reduction of amide carbonyl followed by elimination of OH

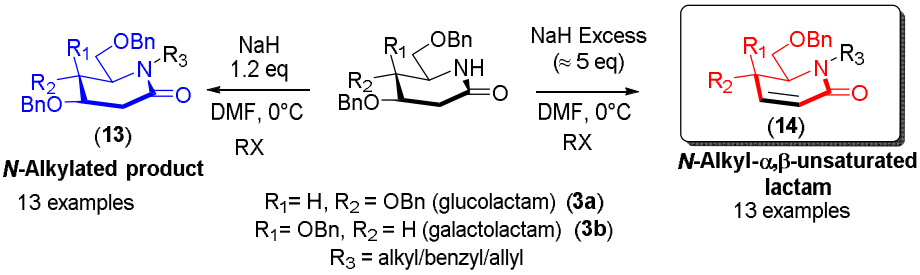
group to induce a double bond *i.e.* to generate an iminoglycal (**8a/b**) by utilizing super hydride as reducing agent selectively C_1-C_2 position has been functionalized. Dihydroxylation of iminoglycal (**8a/b**) provided the desired nojirimycin B (**10**) and nojirimycin (**12**). The partial reduction provided the desired 2-deoxynojirimycin (**7**) (Scheme 2). [1]



Scheme 2. Synthesis of nojirimycin (**12**) and nojirimycin B (**10**). *Reagents and conditions;* (a) (i) Superhydride, toluene, -76 °C 1h; (ii) NH_4Cl, -76 °C to rt; (b) Aq. HCl, MeOH, 70 °C; (c) H_2, Pd-C (10%), AcOH; (d) (i) Superhydride, toluene, -70 °C, 30 min; (ii) TFAA, DIPEA, DMAP (cat), -70 °C to rt, 2h; (e) $(DHQD)_2AQN$, $K_3Fe(CN)_6$, K_2CO_3, $K_2OsO_2(OH)_4$, $CH_3SO_2NH_2$, *t*-butyl alcohol : H_2O (1:1) 0 °C for 66 h; (f) $(DHQ)_2AQN$, $K_3Fe(CN)_6$, K_2CO_3, $K_2OsO_2(OH)_4$, $CH_3SO_2NH_2$, *t*-butyl alcohol : H_2O (1:1) 0 °C for 66 h.

Section B: Novel Synthetic Methodology and its Applications in the Synthesis of Piperidine Alkaloids

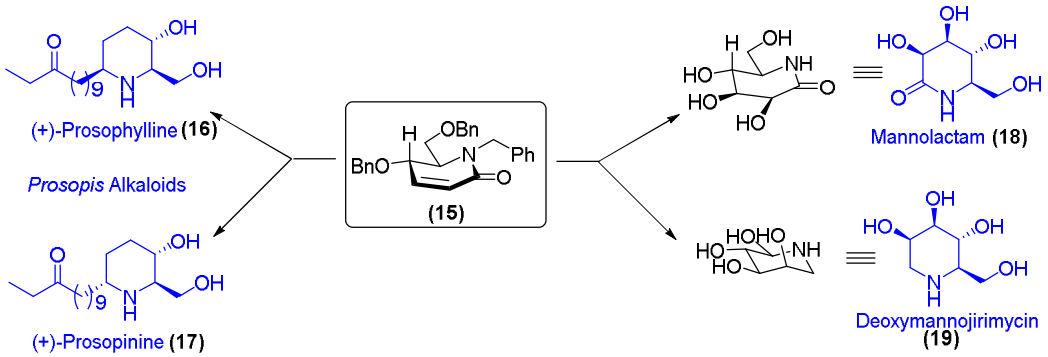
We have developed an efficient methodolgy for the regioselective *N*-alkylation and regioselective *N*-alkyl-Ŭ,ß-unsaturated glycolactam formation (Scheme 3).



Scheme 3. Regioselective *N*-alkylation and regioselective *N*-alkyl-Ŭ, ɓ-unsaturated lactam formation.

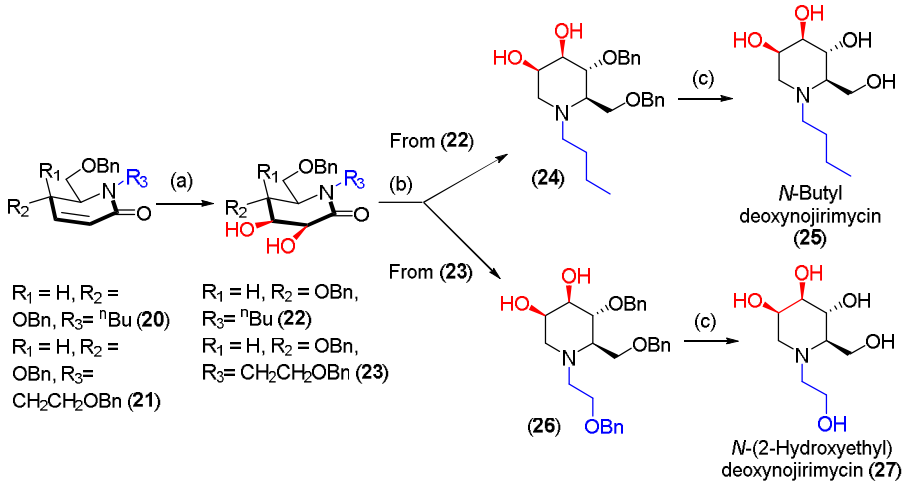
Applications of the Developed Methodology for the Synthesis of Piperidine Alkaloids

Application 1: Formal synthesis of Mannolactam, Deoxymannojirimycin, (+)-Prosophylline and (+)-Prosopinine



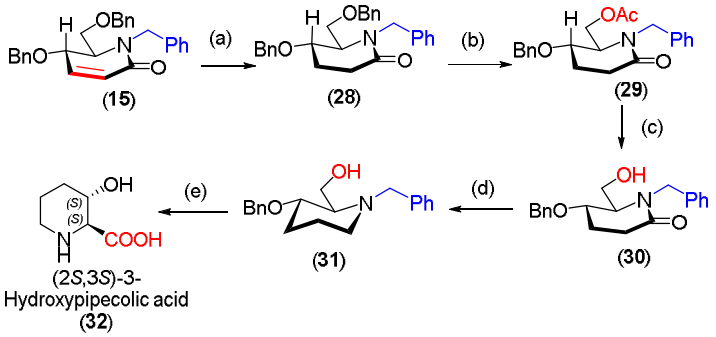
Scheme 4. Formal synthesis of mannolactam, deoxymannojirimycin, (+)-prosophylline and (+)-prosopinine.

Application 2: Formal Synthesis of *N*-Alkyl-1-deoxymannojirimycin derivatives



Scheme 5. Formal synthesis of *N*-alkyl-1-deoxynojirimycin derivatives (**25**) and (**27**). *Reagents and conditions*; (a) $RuCl_3$, $NaIO_4$, CH_3CN:H_2O (6:1), 0-5 °C, 35 min; (b) BH_3.DMS THF, 0 °C, rt, reflux (Table 3); (c) 1 atm H_2, Pd/C, MeOH (Ref: 2a)

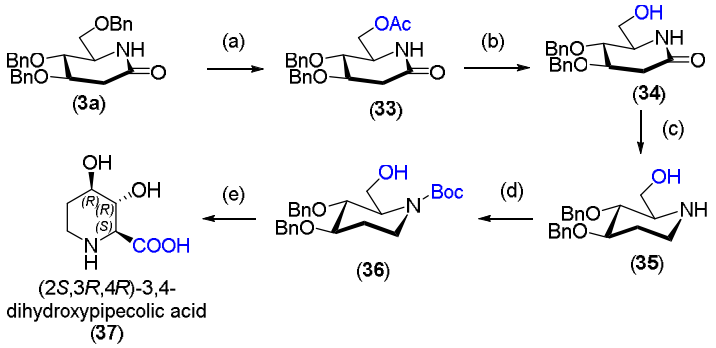
Application 3: Formal Synthesis of (2*S*,3*S*)-3-Hydroxypipecolic acid



Scheme 6. Formal synthesis of (2*S*,3*S*)-3-hydroxypipecolic acid (**32**). *Reagents and conditions:* (a) $NiCl_2.6H_2O$, $NaBH_4$, MeOH, 0 °C to rt, 2.5h; (b) Ac_2O, H_2SO_4 in AcOH; (c) NaOMe in MeOH; (d) BH_3.DMS THF, 0 °C, rt, reflux.; (e) Ref: 2b.

We have successfully utilized our developed methodology *i.e.* *N*-alkyl-Ŭ,ɓ-unsaturated glycolactam for the synthesis of key intermediates (which on carrying out general transformations by reported procedure[2] will furnish the final target molecule) for the formal synthesis of (+)-prosophylline (**16**), (+)-prosopinine (**17**), mannolactam (**18**), deoxymannojirimycin (**19**), *N*-alkyldeoxnojirimycin derivatives (**25**), and (**27**), and (2*S*,3*S*)-3-hydroxypipecolic acid (**32**).

Formal Synthesis of (2*S*,3*R*,4*R*)-3,4-Dihydroxypipecolic acid



Scheme 7. Formal synthesis of (2*S*,3*R*,4*R*)-3,4-dihydroxypipecolic acid (**37**). *Reagents and conditions;* (a) Ac_2O, H_2SO_4 in AcOH; (b) NaOMe in MeOH; (c)

BH_3.DMS THF, 0 °C, rt, reflux.; (d) Boc_2O, Et_3N, DMAP, DCM, 0 °C- rt; (e) Ref: 2c,d.

Similar to the formal synthesis of (2*S*,3*S*)-3-hydroxypipecolic acid (**32**), the formal synthesis of (2*S*,3*R*,4*R*)-3,4-Dihydroxypipecolic acid (**37**) was also undertaken.

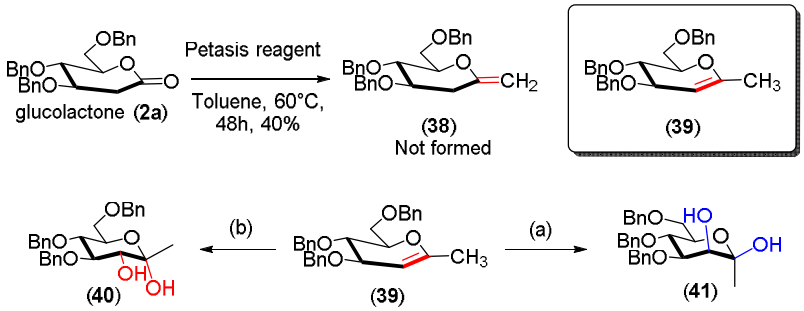
Chapter 2: Approaches Towards the Synthesis of Tetrahydropyrans Using Carbohydrate Scaffolds

Utility of Carbohydrate Scaffolds for the Synthesis of Bioactive Natural Products; Tetrahydropyrans

This chapter gives an introduction to bioactive polyhydroxylated tetrahydropyrans, and also provides an Introduction to DAH and kamusol. A short literature survey of the reported synthesis of DAH and kamusol is described.

Approaches Towards the Synthesis of Kamusol and DAH

We first tried the synthesis of DAH and kamusol by cyanation strategy however the reaction failed to furnish the titled molecule. We then explored the methylenation strategy (Scheme 8).



Scheme 8. Methylenation using Petasis reagent and its application. *Reagents and conditions*. (a) $(DHQD)_2AQN$, $K_3Fe(CN)_6$, K_2CO_3, $K_2OsO_2(OH)_4$, $CH_3SO_2NH_2$, *t*-butyl alcohol : H_2O (1:1) 0 °C for 44 h, 93 %; (b) $(DHQ)_2AQN$, $K_3Fe(CN)_6$, K_2CO_3, $K_2OsO_2(OH)_4$, $CH_3SO_2NH_2$, *t*-butyl alcohol : H_2O (1:1) 0 °C for 44 h, 88 %.

By using Petasis reagent the reaction failed to provide the target molecule (**38**) of interest however the dihydroxylated product (**40**) formed the core structure of biologically active molecules like tofogliflozin (**42**) and papulacandins A-E (**43**) (Fig.1).

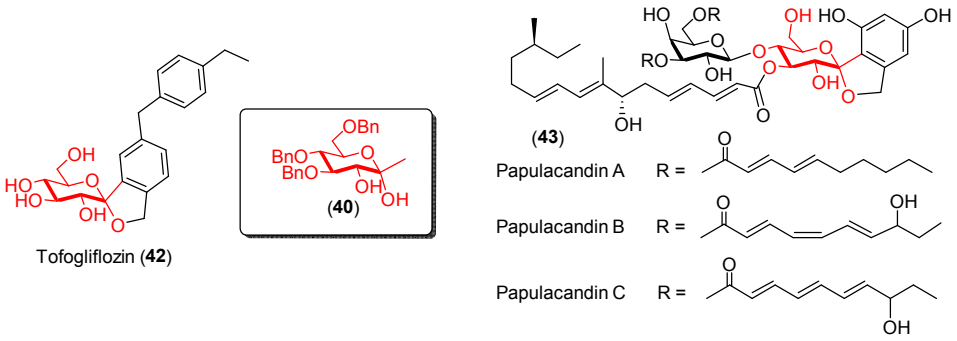
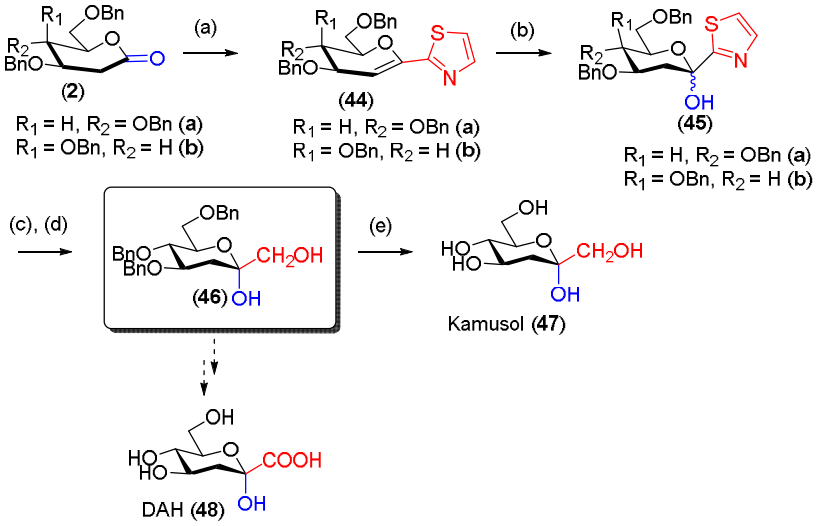


Figure 1. Representative structures of tofogliflozin (**42**) and papulacandins A-E (**43**) and their core structure (**40**).

Finally we could achieve the synthesis of benzyl protected kamusol (**46**) by using the masked carbonyl strategy[3a-g] (Scheme 9).

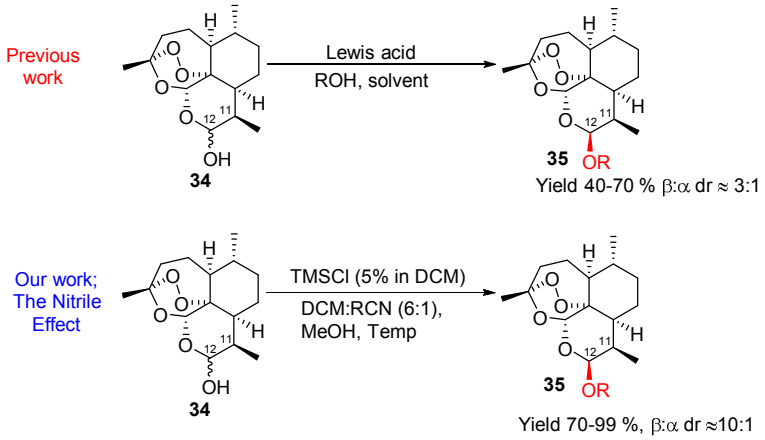


Scheme 9. Synthesis DAH (**48**) and kamusol (**47**). *Reagents and conditions*. (a) 2-Bromo thiazole, ^{n}BuLi, Ac_2O, -78 °C to rt, THF, 50%; (b) THF, H_2O, c.HCl.(cat), 64%; (c) (i) Methyltriflate $NaBH_4$, 0 °C, $HgCl_2$, CH_3CN:H_2O (10:1), (ii) $NaBH_4$ MeOH, 42% yield in 2 steps; (d) $NaBH_4$, $CeCl_3$, MeOH; (e) Ref: 3h.

Chapter 3: **Chemical Transformations of Abundant Natural Products; Diastereoselective Synthesis of β-Arteether Derivatives of Artemisinin**

Diastereoselective Synthesis of β-Ether Derivatives of Artemisinin

Malaria continues to be a threatening disease to major population of the world. A number of antimalarial drugs have been developed so far but still are ineffective in complete cure of the disease. Artemisinin and its derivatives are used in artemisinin combination therapy (ACT) for the effective treatment of malaria with minimum side effects. It has been reported that the ɓ-ether derivatives of artemisinin exhibits higher antimalarial activity in comparison to their Ŭ-ether derivatives. Hence it becomes necessary to stereoselectively synthesize ɓ-ether derivatives of artemisinin. After verifying number of reaction conditions *viz.* temp, reagent, solvent, and stoichiometric quantities of the solvent, we have developed an optimum reaction condition for the diastereoselective synthesis of ɓ-arteether derivatives of artemisinin in high yield and high dr. (Scheme 10).[4]

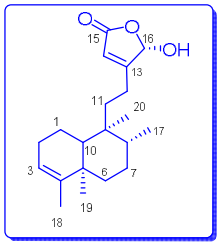


Scheme 10. Stereoselective synthesis of C-12ɓ ether derivatives of dihydrortemisinin.

Chapter 4: **Chemical Examination of *Polyalthia longifolia* var. *pendula* for Bioactive Molecules**

Natural products have been an indispensible source for bioactive molecules. A number of drugs even today continue to rely on natural product sources. It becomes necessary to explore new molecules for their diverse biological activities.

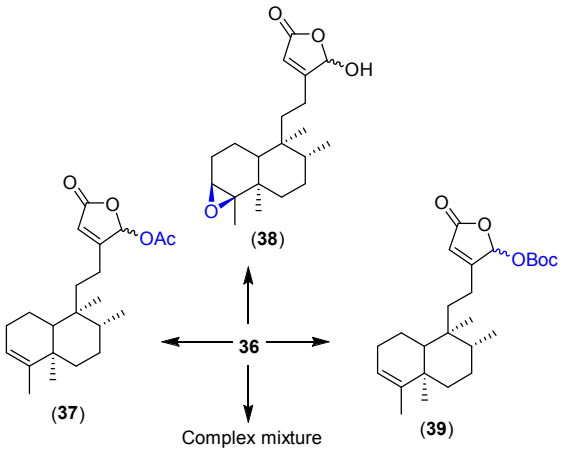
We have isolated a diterpene (**36**) which was identified as 16α-hydroxycleroda-3,13(14)*Z*-dien-15,16-olide from the methanolic extract of the leaves of *P. longifolia* var. *pendula*.[5] The isolated diterpene (**36**) was screened for antifungal activity against a number of fungal strains.



Clerodane diterpene (36)

Figure 2. Isolation of clerodane diterpene (**36**) from leaves (1.4% overall yield)

In order to devise the structure-activity-relationship (SAR) derivatives (**37-39**) were synthesized (Scheme 11). From the initial structure-activity-relationship (SAR) studies from the assay of synthesized derivatives (**37-39**) it was clear that the double bond between C3-C4 and the free hydroxyl group at C16 are crucial for the antifungal activity of the diterpene (**36**).



Scheme 11. Preparation of derivatives of diterpene (**36**).

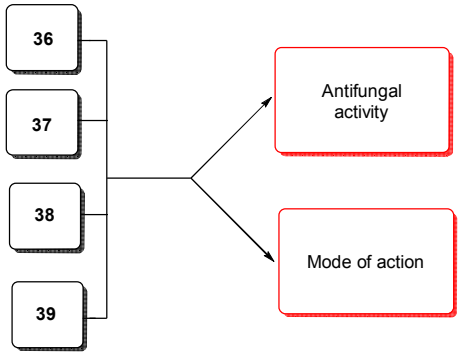


Figure 3. SAR studies of the clerodane diterpene (**36**) and their derivatives (**37-39**) for their antifungal activity and the probable mode of action.

We have devised the mode of action of the diterpene (**36**), and is due to compromised cell membrane permeability. Further, intracellular ROS generation by the diterpene (**36**) was confirmed by using DCFH-DA and DHR123 staining of *C. albicans* NCIM3557 cells, suggests mechanism of antifungal activity of the diterpene (**36**). It is presumed that our studies on this molecule could be further utilized for target-based approach to explore its therapeutic potentials.

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4. (a) Novel process for the synthesis of an antimalarial drug. Bhattacharya, A. K.; Chand, H. R. **Indian Patent Filed 3079/DEL/2014, 29.10.2014**; (b) Chand, H. R.; Bhattacharya, A. K. *Asian J. Org. Chem*. **2015**, *5*, 201.
5. (a) Bhattacharya, A. K.; Chand, H. R.; John, J.; Deshpande, M. V. *Eur. J. Med. Chem.* **2015,** *94*, 1; (b) Process for isolation of diterpene from *Polyalthia longifolia*. Bhattacharya, A. K.; Chand, H. R.; Deshpande, M. V. **Indian Patent No.** 2114/DEL/2014, 25.07.2014.

Chapter 1

Approaches Towards the Synthesis of Polyhydroxylated Alkaloids using Carbohydrate Scaffolds

Section A

Approaches Towards the Synthesis of Fagomine, 4-*epi*-Fagomine, Nojirimycin and 2-Deoxynojirimycin

1.1 Approaches Towards the Synthesis of Fagomine, 4-*epi*-Fagomine, Nojirimycin and 2-Deoxynojirimycin

1.1.1 Approaches Towards the Synthesis of Fagomine and 4-*epi*-Fagomine

1.1.1.1 An Introduction to Polyhydroxylated Alkaloids

Plants, animals and micro-organisms have innumerable polyhydroxylated alkaloids. These are of considerable interest as potential therapeutic agents. They can also serve as tools used to understand biological recognition processes and hence their synthesis and biological activity studies are increasingly becoming important. Because of close similarity in chemical structures with sugars, these alkaloids can be considered as analogues of monosaccharides in which the ring oxygen has been replaced by nitrogen. They are monocyclic and bicyclic polyhydroxylated derivatives of the following ring systems: **pyrrolidine**, **piperidine**, **pyrrolizidine** (two fused pyrrolidines with N at the bridgehead), octahydroindolizine or **indolizidine** (fused piperidine and pyrrolidine) and **nortropane** (Fig.1). [1]

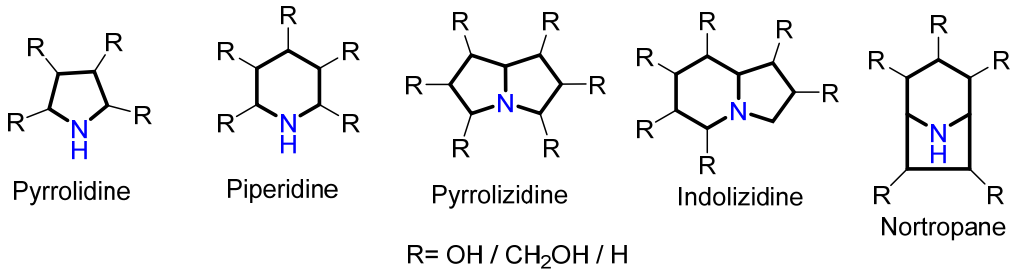


Figure 1. Some common classes of alkaloids found in nature.

Occurrence of polyhydroxylated alkaloids: Polyhydroxylated alkaloids are generally distributed in species of Streptomyces, Leguminosae, Solanaceae and Convolvulaceae families.

Therapeutic potential of polyhydroxylated alkaloids: Polyhydroxylated alkaloids have shown diverse biological activities such as anti-cancer, anti-diabetic, immune stimulants, anti-viral, treatment of glycosphingolipid lysosomal storage diseases, treatment of infectious agents and associated complications.[1]

Piperidine alkaloids exhibit stereoselectivity in biological activity because of their biological and chemical diversity (Fig. 2) in terms of structural information, similar to that of small sugars (hexose-pyranose).

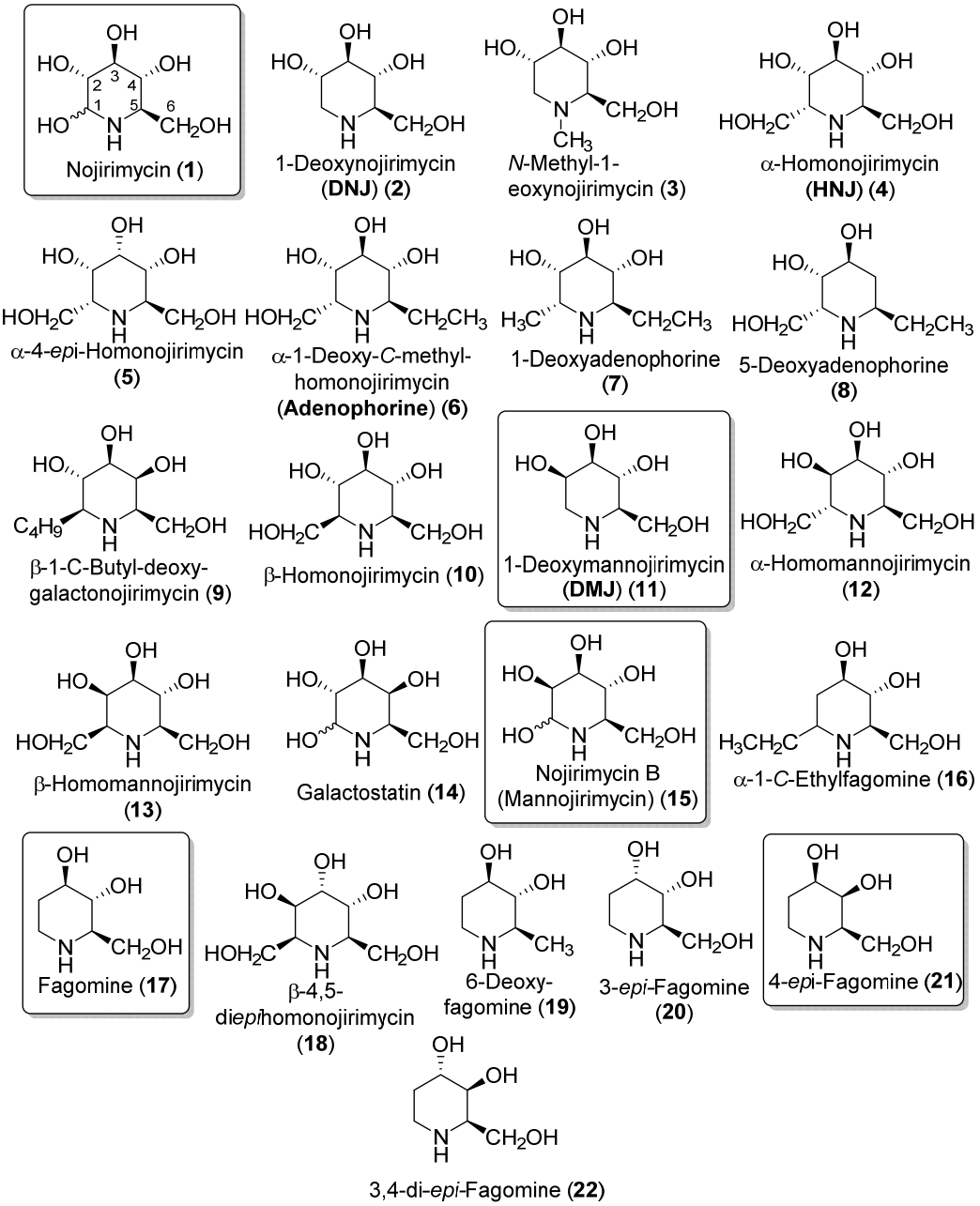


Figure 2. Some common piperidine alkaloids of therapeutic value.

Nojirimycin (**1**) (Fig. 2) was the first natural polyhydroxylated piperidine alkaloid to be isolated from a *Streptomyces* filtrate in 1966 by Inouye *et al*.[2] Systematically, these alkaloids have been described in the literature as derivatives of the parent heterocyclic compounds or sugars. 1-**d**eoxy**n**o**j**irimycin (**2**) (Fig. 2) (2*S*-hydroxymethyl-3*R*,4*R*,5*S*-trihydroxy-piperidine or 1,5-dideoxy-1,5-imino-*D*-glucitol is well known as **DNJ**. Similarly following the trivial system 1-deoxy piperidine analogue of mannose has been given the trivial name of 1-**d**eoxy**m**anno**j**irimycin (**11**) in short **DMJ** (Fig. 2). Henceforth the numbering and nomenclature used most frequently for particular compounds and their common names/abbreviations will be used in this chapter.

1.1.1.2 An Introduction to Fagomine and 4-*epi*-Fagomine

1,2-Dideoxy-iminosugars exemplify a small, but an essential class of glycosidase inhibitors.[3] One of the members of this family, fagomine (**17**), was isolated from the seeds of Japanese buckwheat *Fagopyrum esculentum austral* Moench[4] and also from the seeds of *Castanospermum austral*[5] (Leguminosae). Recently, isomers of fagomine such as (**22**) and (**20**) are shown to be present in the leaves and roots of the legume *Xanthocersis zambesiaca*.[6] It has been reported to have a potent antihyperglycemic effect in streptozocin-induced diabetic mice and in potentiation of glucose-induced insulin secretion.[7] Recently it has been found that 4-*epi*-fagomine (**21**) (Fig. 3) behaves as a potent glycosidase inhibitor, particularly for mammalian α-glucosidase and β-galactosidase, as well as for lysosomal α-galactosidase A in Fabry lymphoblasts.[8]

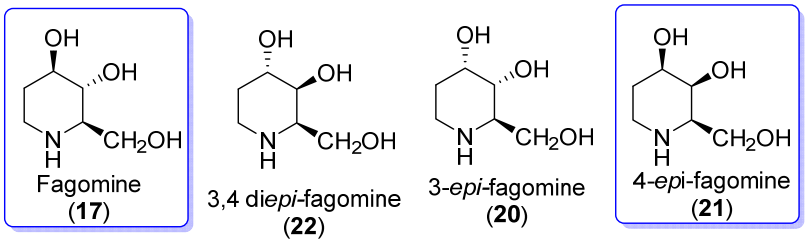


Figure 3. Fagomine and its congeners.

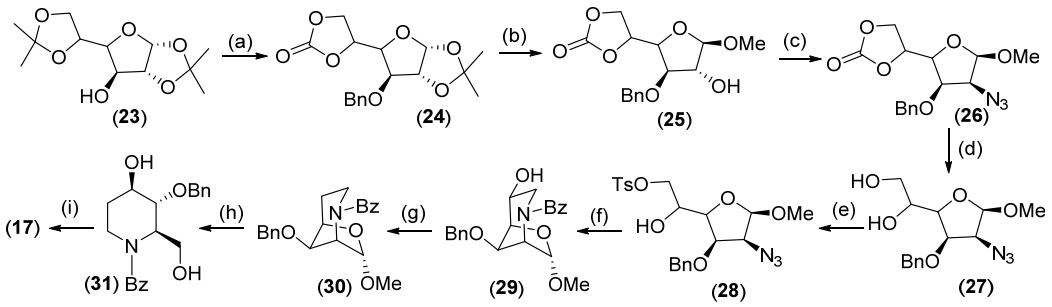
1.1.1.3 Reported Synthesis of Fagomine, 4-*epi*-Fagomine, Nojirimycin, Deoxynojirimycin and Pipecolic acid

Extensive literature survey of fagomine and 4-*epi*-fagomine indicates that, its synthesis involves use of either carbohydrate building blocks or from non-carbohydrate precursors. This section describes some selected synthesis of fagomine and 4-*epi*-fagomine.

1.1.1.3.1 Use of Carbohydrate Building Blocks

Fleet *et al.*[9] (*Tetrahedron Lett.* **1985**, *26*, 1469)

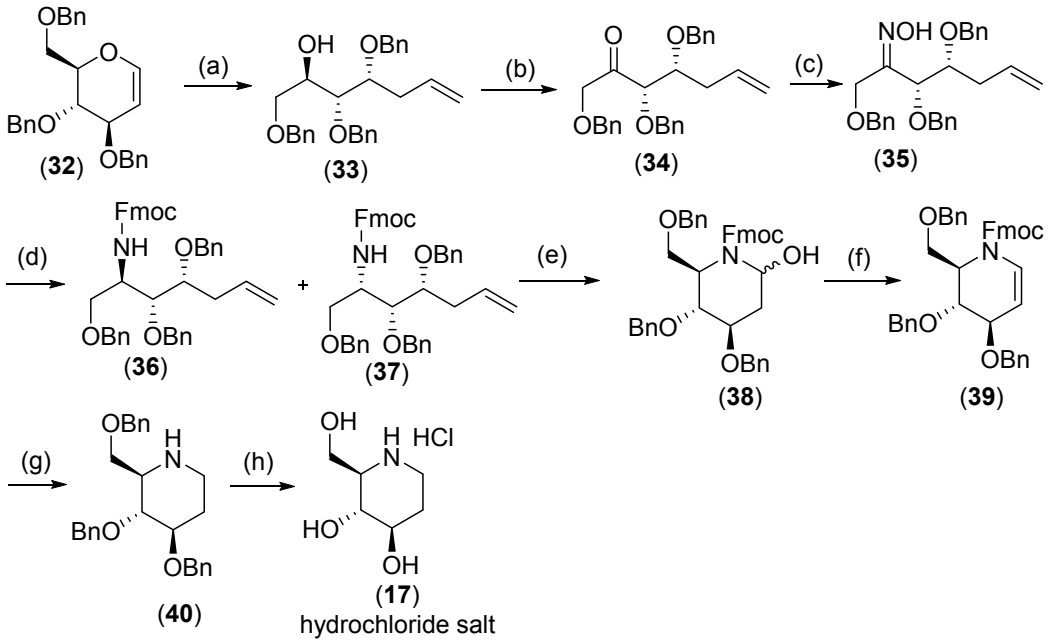
Fleet *et al.* accomplished the total synthesis of fagomine from diacetonide glucose using reductive cyclization as the key step (Scheme 1).



Scheme 1. *Reagents and conditions:* (a) (i) $PhCH_2Br$; (ii) 0.5% HCl in MeOH, room temp, 12 h; then $(MeO)_2CO$, NaOMe, reflux (b) Dowex 50W-X8 resin (H^+ form), MeOH, reflux; (c) Triflic anhydride, pyridine, CH_2Cl_2, -20 ^oC, 20 min; then NaN_3, DMF, 50 °C, 2 d; (d) MeOH with a trace of NaOMe, room temp. (e) p-Toluene sulphonyl chloride, pyridine, room temp, 6 h; (f) (i) Pd/H_2, EtOH, 30 min; then NaOAc, EtOH, 50 °C; (ii) $PhCH_2OCOCl$, ether, H_2O, $NaHCO_3$ (g) (i) Triflic anhydride, pyridine, -20 ^oC; then $LiBHEt_3$, THF; (ii) $PhCH_2OCOCl$, ether, H_2O containing $NaHCO_3$; (h) CF_3COOH: H_2O (1:1), room temp, 1 h; then $NaBH_4$ in EtOH - H_2O; (i) $Pd(OH)_2$, H_2, EtOH.

Désiré *et al*.[10] (*Synlett* **2001**, 1329).

J. Désiré *et al.* reported total synthesis of (+)-fagomine from tri-*O*-benzyl-D-glucal by utilizing reductive cyclization as the key step with tri-*O*-benzyl-D-glucal (**32**) as sm (Scheme 2)**.**



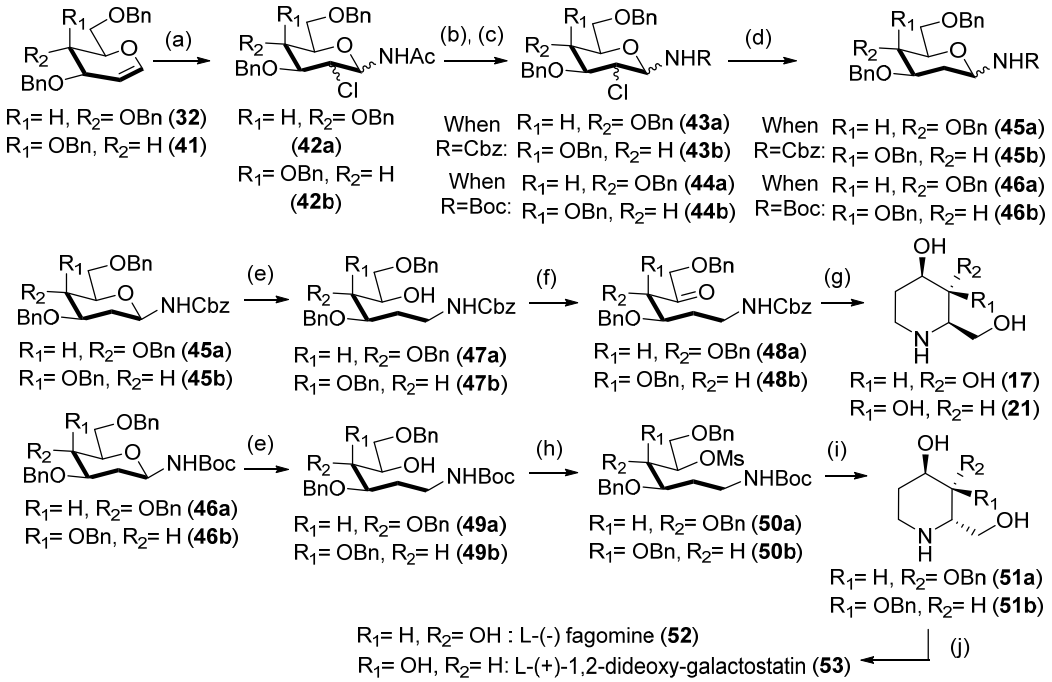
Scheme 2. *Reagents and conditions:* (a) Ref 11; (b) TPAP, NMO, DCM, 4A^{o} sieves, 83%; (c) NH_2OH, HCl, Py, EtOH, 60 ^{o}C, 98%: (d) (i) LAH, Et_2O; (ii) FmocCl, K_2CO_3, THF/H_2O, 0 ^{o}C, 57%; (e) O_3, DCM, -78 ^{o}C, PPh_3, 87%; (f) $(COCl)_2$, DCM, DMF, 95%; (g) H_2, Pd/C, morpholine, EtOH, 70%; (h) H_2, Pd/C, EtOH, HCl, 85%.

Vankar *et al.*[12] (*Eur. J. Org. Chem.* **2009**, 160).

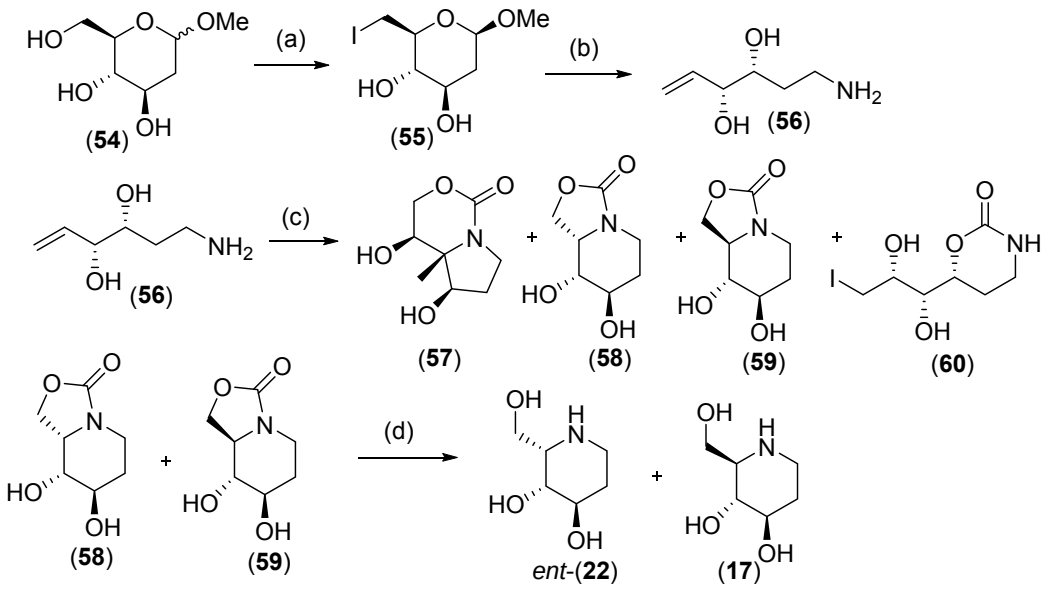
Vankar *et al* have reported an efficient and stereo divergent synthesis of D and L-fagomine and 1, 2-dideoxy-galactostatin and its congeners (Scheme 3) by using chloro amidation of glycals[13] and also by azidation of glycals.[14] Chloro amidation of glycals [13] resulted in compound (**42a**) and (**42**b). By carrying out synthetic transformation (**17**), (**21**), (**52**) and (**53**) are synthesized.

Stoker and Timmer, *et al.* [15] (*J. Org. Chem.* **2013**, *78*, 9791).

Stoker and Timmer, *et al.* have devised a protecting-group-free synthetic strategy, utilizing I_2-mediated carbamate annulations strategy (Scheme 4) to furnish the desired product *ent*-(**22**) and (**17**).



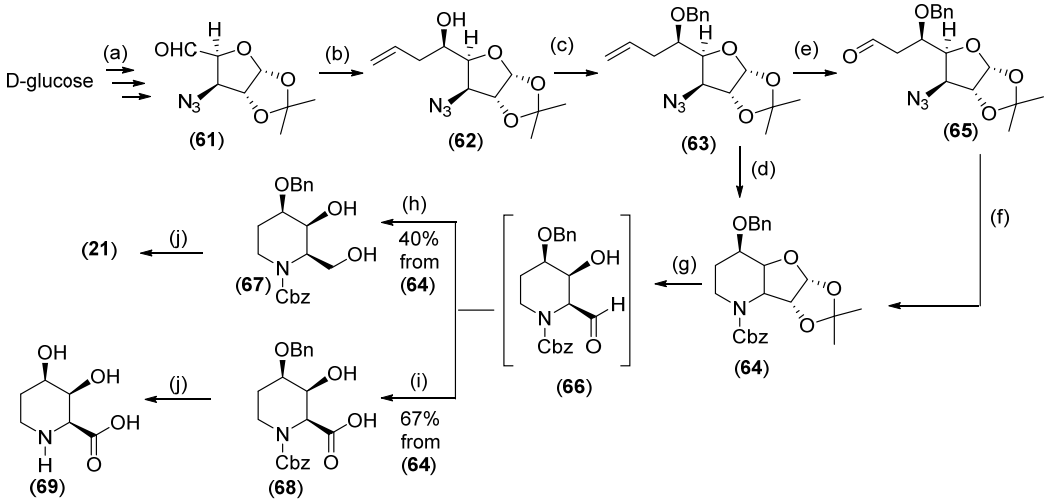
Scheme 3. *Reagents and conditions: (a) Ref 13;* (b) 0.7N HCl. 50-60 °C, 7-10h; (c) Sat. $NaHCO_3$, Boc_2O or CbzCl, EtOAc, rt, 3-5h; (d) Bu_3SnCl, $NaBH_3CN$, AIBN, ^{t}BuOH, reflux; (e) LAH, THF, 2h; (f) PCC, DCM, 4 Å Mol. sieves, 2h; (g) 10 % Pd/C, MeOH, H_2 atm, 50 psi, 10h; (h) MsCl, DCM, Et_3N, DMAP, 2h; (i) (i) TFA/DCM, 1h; (ii) K_2CO_3, CH_3CN, 50 °C, 10h; (j) $Pd(OH)_2$, MeOH, H_2 atm, 50 psi, 24h.



Scheme 4. *Reagents and conditions:* (a) I_2, PPh_3, Imid. THF, 75 °C, 64%; (b) Zn, NH_4OAc, NH_3, $NaCNBH_3$, EtOH, reflux, 86 %; (c) I_2 (3 × 1.5 equiv added over 22 days), $NaHCO_3$ (sat.), rt; (d) NaOH, EtOH, reflux, 2h quant.

Chattopadhyay *et al.*[16] (*J. Org. Chem.* **2013**, *78*, 7406).

One-pot three-step protocol involving a Staudinger reaction, reductive amination, and benzyloxy carbonyl protection is the key step successfully utilized for the synthesis of 4-*epi*-fagomine (**21**) and dihydroxypipecholic acid (**69**) (Scheme 5).



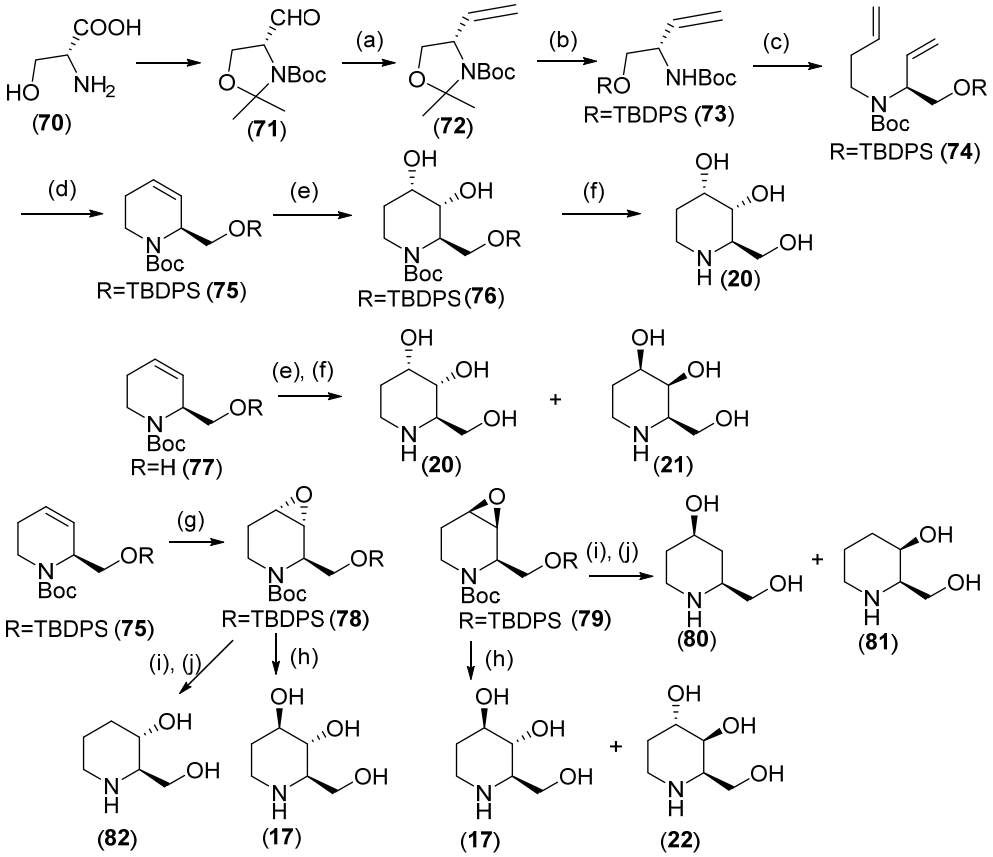
Scheme 5. *Reagents and conditions:* (a) Ref 17; (b) Allyl bromide, Zn, THF, 0 to 20°C, and 7 h. (c) BnBr, NaH, THF, 0 to 25 °C, and 4 h. (d) (i) O_3, CH_2Cl_2, -78 °C,

then PPh_3, -78 to 25 °C, 12 h; (ii) $NaBH_3CN$, MeOH, and AcOH (cat.); (iii) CbzCl, $NaHCO_3$, MeOH, 0 to 25 °C, and 4 h. (e) O_3, CH_2Cl_2, -78 °C, then Me_2S, -78 to 25 °C, and 24 h. (f) (i) PPh_3, MeOH, 0 to 25 °C, and 1 h; (ii) $NaBH_3CN$, MeOH, AcOH (cat.), 0 °C, and 2 h, then 25 °C, and 8 h; (iii) CbzCl, $NaHCO_3$, MeOH, 0 to 25 °C, and 6 h. (g) (i) TFA-H_2O (3:2), 0 °C, and 1 h; (ii) $NaIO_4$, acetone-water (4:1), 0 °C, and 30 min. (h) $NaBH_4$, MeOH-H_2O (9:1), 0 °C, and 20 min. (i) NaH_2PO_4, $NaClO_2$, 30% H_2O_2, CH_3CN, 0 to 25 °C, and 7 h. (j) H_2 (80 psi), 10% Pd/C, MeOH, 25 °C, and 12 h.

1.1.1.3.2 Use of Non-carbohydrate Precursors

Takahata *et al.* [18] (*J. Org. Chem.* **2003**, *68*, 3603).

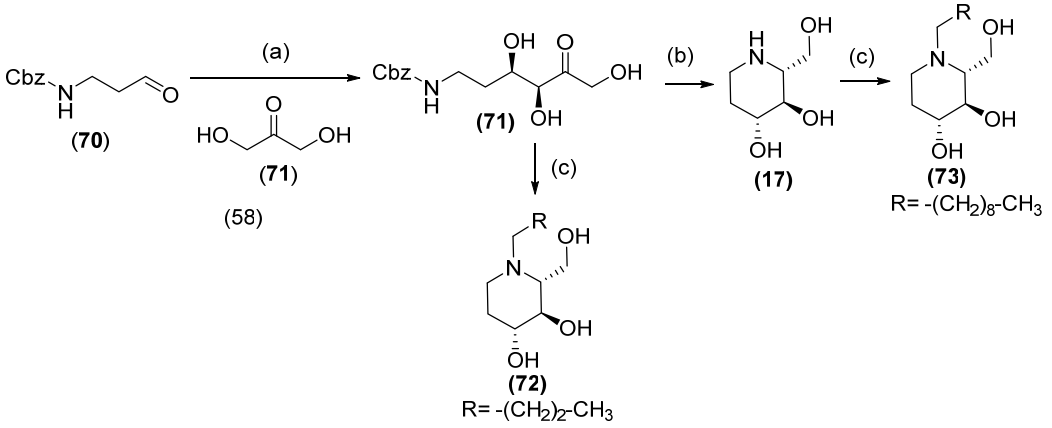
Takahata *et al.* reported fagomine and its isomers by employing ring closing metathesis as the key step. Synthesis started from Garner aldehyde (**71**) (Scheme 6) (derived from D-serine (**70**))



Scheme 6. *Reagents and conditions:* (a) $Ph_3P^+CH_3I^-$, $NaN(TMS)_2$, THF; (b) (i) p-TsOH.H2O, MeOH; (ii) TBDPSCl, DMAP, imidazole, CH_2Cl_2; (c) (i) CF_3COOH, CH_2Cl_2; (ii) 4-bromo-1-butene, K_2CO_3, CH_3CN ; (iii) $(Boc)_2O$, Et_3N, THF; (d) Grubb's catalyst, CH_2Cl_2; (e) cat. $K_2OsO_4.2H_2O$, NMO, H_2O, acetone; (f) 10% HCl, 1,4-dioxane; (g) Oxone, CF_3COCH_3, $NaHCO_3$, aq Na_2.EDTA, CH_3CN; (h) H_2SO_4, 1,4-dioxane, H_2O; (i) Super hydride in THF; (j) HCl, 1,4-dioxane, dowex , 1× 2 (OH^- form).

Castillo *et al* [19] (*Org. Lett.* **2006,** *8*, 6067)

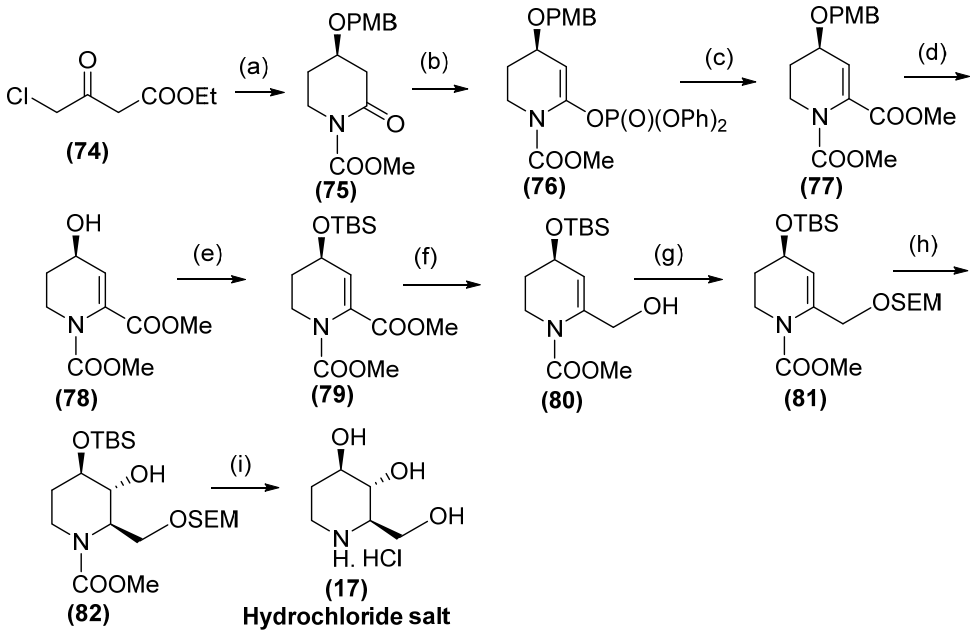
Castillo *et al.* reported total synthesis of D-fagomine and its *N*-allylated derivatives by employing D-fructose-6-phosphate aldolase (FSA) as the key step. 3-Aminopropanal (**70**) was prepared by known literature procedure.[20] The FSA-catalyzed aldol addition of DHA (**71**) with 3-aminopropanal (**70**), furnished (**71**) which was then converted to *D*-Fagomine (**17**) by synthetic transformations (Scheme 7).



Scheme 7. *Reagents and conditions:* (a) FSA, DMF, buffer; (b) H_2, Pd/C, EtOH/H_2O; (c) RCHO, H_2, Pd/C, EtOH/H_2O.

Bartali *et al* [21] (*Synlett* **2009**, 913)

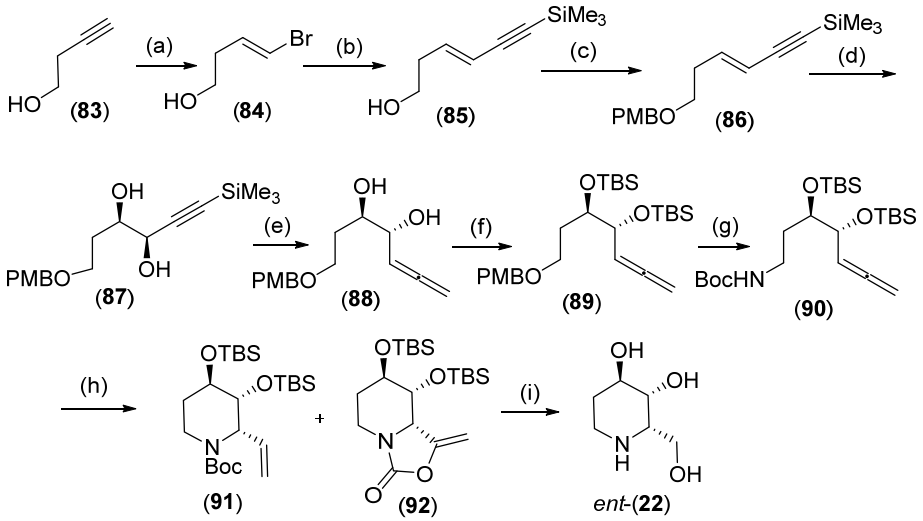
Bartali *et al.* accomplished total synthesis of fagomine by employing stereoselective hydroboration oxidation of enamine double bond as the key step. Keto compound (**74**) was transformed into enantiomerically pure *N*-protected lactams (**75**) by reported methodology[22] which was later converted to hydrochloride salt of D-fagomine (**17**) (Scheme 8).



Scheme 8. *Reagents and conditions:* (a) Ref 22; (b) (i) KHMDS, THF, -78 ^{o}C; (ii) $(PhO)_2POCl$, THF, -78 ^{o}C, 85%; (c) $Pd(OAc)_2$, Ph_3P, CO, MeOH, TEA, DMF, 50 ^{o}C, 95%; (d) DDQ, DCM/H_2O, 81%; (e) TBSCl, imidazole, DMF, 40 ^{o}C, 91%; (f) DIBAL-H, DCM, -78 ^{o}C, 73%; (g) (i) SEMCl, DIPEA, DCM, 76%; (h) (i) BH_3.THF, -78 ^{o}C- 0 ^{o}C; (ii) Me_3NO, THF, 65 ^{o}C, 70%; (i) 2N HCl, reflux, 100%.

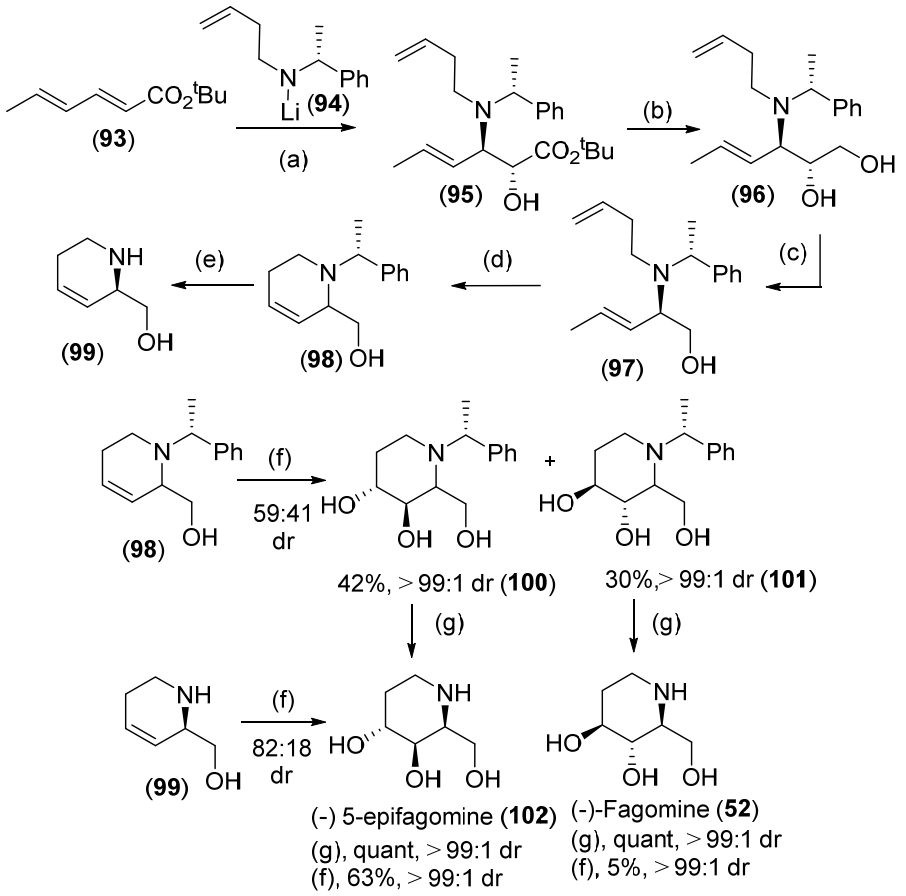
Bates *et al* [23] (*Tetrahedron Lett.* **2011**, *52*, 2969)

Bates *et al.* reported total synthesis of 3,4-di-*epi*-fagomine *ent*-(**22**) *via* gold catalyzed cyclization (Scheme 9). as the key step.



Scheme 9. *Reagents and conditions: (*a) (i) NBS, $AgNO_3$; (ii) $AlCl_3$, LAH, 66%; (b) $CHCSiMe_3$, $(Ph_3P)_2PdCl_2$, TEA, THF, 70%; (c) $MeOC_6H_4OH$, PPh_3, DIAD, 63%; (d) AD-mix-β, $MeSO_2NH_2$, *t*-BuOH/H_2O, 86%; (e) (i) MeOH, K_2CO_3;(ii) $(CH_2O)n$, Cy_2NH, CuBr, 75%; (f) (i) TBSOTf, 2,6-lutidine, 86%; (g) (i) $Ce(NH_4)_2(NO_3)_6$, py., aq. MeCN, 81%; (ii) MsCl, TEA; (iii) NaN_3, 66%; (iv) PPh_3, H_2O; (v) Boc_2O, i-PrNEt; (h) Ph_3PAuCl, $CaCO_3$, $AgSbF_6$, 85%;(i) (i) O_3, $NaBH_4$; (ii) HCl, MeOH, dioxane; (iii) Amberlyst, 53% (over three steps).

Davies *et al*.[24] (*Tetrahedron* **2015**, *71*, 7170; *J. Org. Chem*. **2014**, *79*, 10932).
Diastereoselective *syn*- and *anti*-dihydroxylations of enantiopure tetrahydropyridine is the key step used by Davies *et al*. (Scheme 10).



Scheme 10. *Reagents and conditions:* (a) THF, -78 °C, then (-)-CSO, -78 °C to rt; (b) LAH, THF, -78 °C to rt; (c) $NaIO_4$ EtOH/H_2O, 20 min then $NaBH_4$, 0 °C to rt; (d)

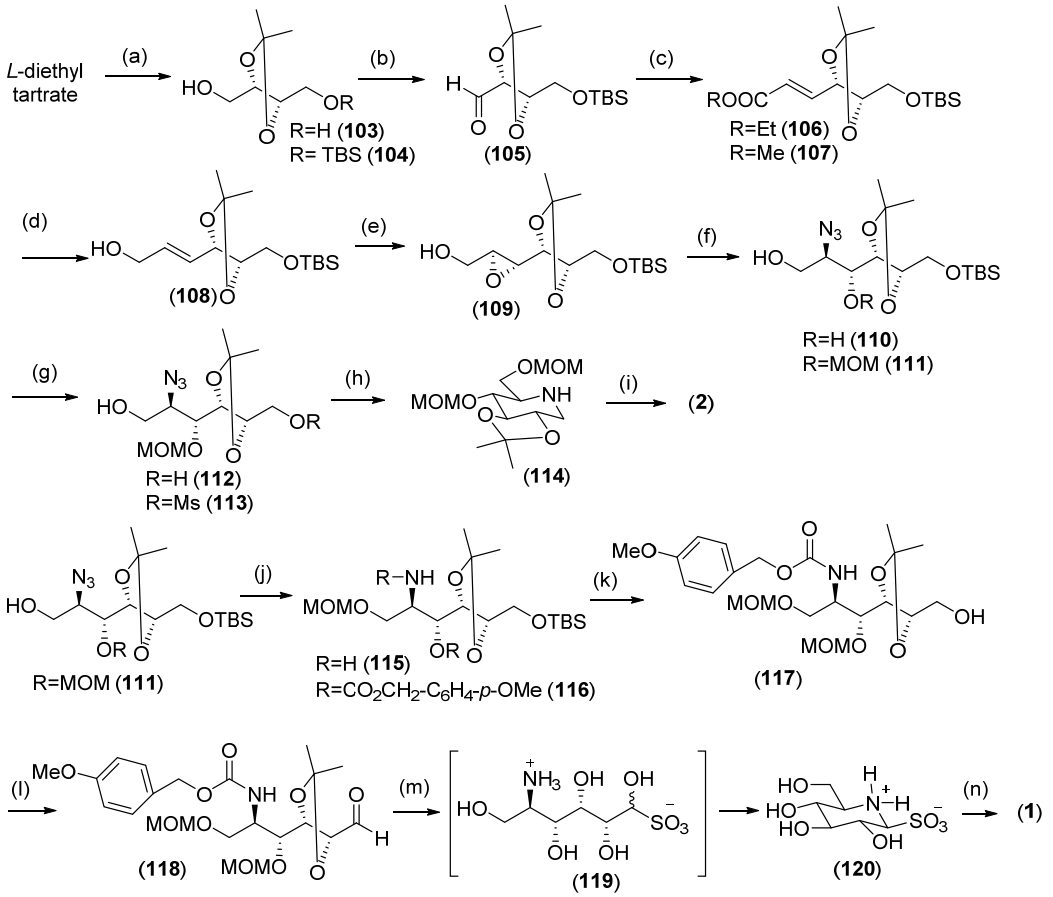
Grubbs II, DCM, 35 °C, 48h; (e) 6.0 M aq. HCl reflux; (f) *m*-CPBA, aq HBF_4, DCM, rt; (g) $Pd(OH)_2/C$, H_2 (1 atm), MeOH, rt, 12h.

1.1.1.4 Literature Survey: Reported Synthesis of Nojirimycin, Deoxynojirimycin and Pipecolic Acid

Although nojirimycin is very active glycosidase inhibitor, it has been observed that the deoxy derivatives are much more stable than nojirimycin and moreover the deoxy derivatives show broad range of activity than nojirimycin. This derivative has become a model compound in this area of research. Hence synthetic chemists have focused their attention for synthesis of deoxynojirimycin. Analogous to fagomine and 4-*epi*-fagomine, synthesis of nojirimycin, deoxynojirimycin and pipecholic acids involves use of either carbohydrate building blocks or from non-carbohydrate precursors but here they are clubbed together for simplicity. Some selected reported synthesis of nojirimycin, deoxynojirimycin and pipecholic acids are described below.

Kibayashi *et al.*[25] (*J. Org. Chem*. **1987**, *52*, 3337).

An efficient chiral total synthesis of (+)-nojirimycin (**1**) and (+)-1-deoxynojirimycin (**2**) has been achieved in optically pure form from the common intermediate derived from the non-sugar chiral pool *viz.* L-tartrate (Scheme 11).

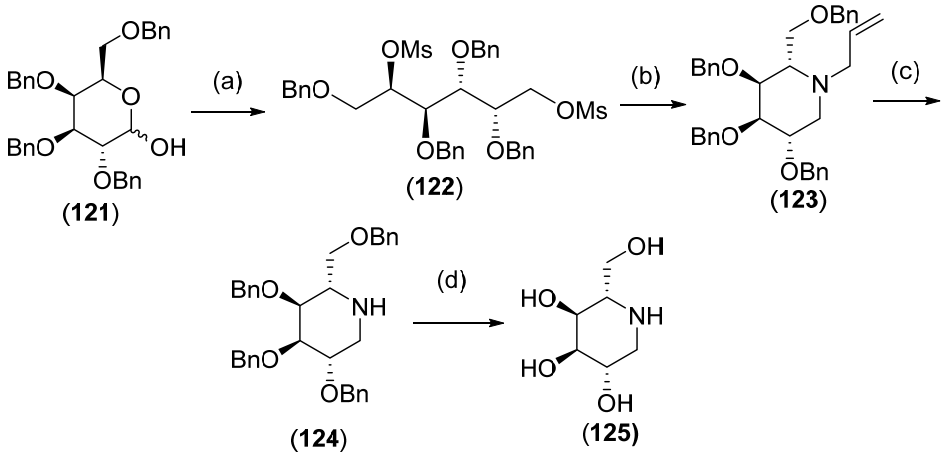


Scheme 11. *Reagents and conditions:* (a) TBSCl, NaH, 99.7% ; (b) DMSO, Oxalyl chloride, Et_3N -78 °C to rt. 85%; (c) Trimethylphosphonoacetate,95%; (d) DIBAL-H,THF, 81%; (e) Sharpless asymmetric epoxidation conditions, 78%; (f) (i) NaN3, DME, 75% (ii) MOMCl, DCM, (g) (i) $^{n}Bu_4NF$, THF;(ii) MsCl, DCM 89%;(h) (i) $Pd(OH)_2/C$, H_2 (1 atm), MeOH, rt, 12;(ii) MeOH, reflux 92%; (i) HCl/H_2O 90%; (j)(i) Pd/C, H_2 (1 atm), MeOH, rt, 14h;(ii) $COClCH_2$-C_6H_4-p-OMe, DCM; (k) $^{n}Bu_4NF$, THF; (l) DMSO, Oxalyl chloride, Et_3N, -78 °C to rt. 85%; (m) aq. H_2SO_4, 63h, 60%; (n) Dowex 1-X2 (OH^-) resin,92% yield.

Wennekes *et al* [26] (*J. Med. Chem.* **2010,** *53*, 689)

Wennekes *et al.* accomplished synthesis of *galacto*-1-DNJ, *altro*-1-DNJ and their derivatives utilizing *N*-allylation as the key step. 2,3,4,6-Tetra-*O*-benzyl-D-glucopyranose (**121**) (Scheme 12) was derived by known literature protocol.[27] Compound (**121**) was converted to di-mesyl derivative (**122**), also by known literature

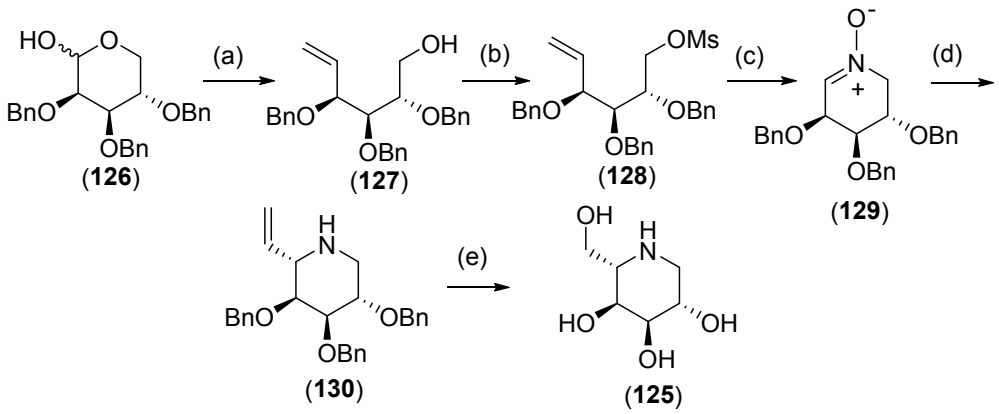
protocol.[28]



Scheme 12. *Reagents and conditions:* (a) Ref 27, 28; (b) Allylamine, reflux, 20 h, 82% over two steps; (c) (i) ^{t}BuOK, DMSO, 100 °C, 30 min; (ii) 1 M aq. HCl, 15 min, 73%; (d) BCl_3, CH_2Cl_2, 0 °C, 20 h.

Chan *et al.* [29] (*Eur. J. Org. Chem.* **2010**, 5555)

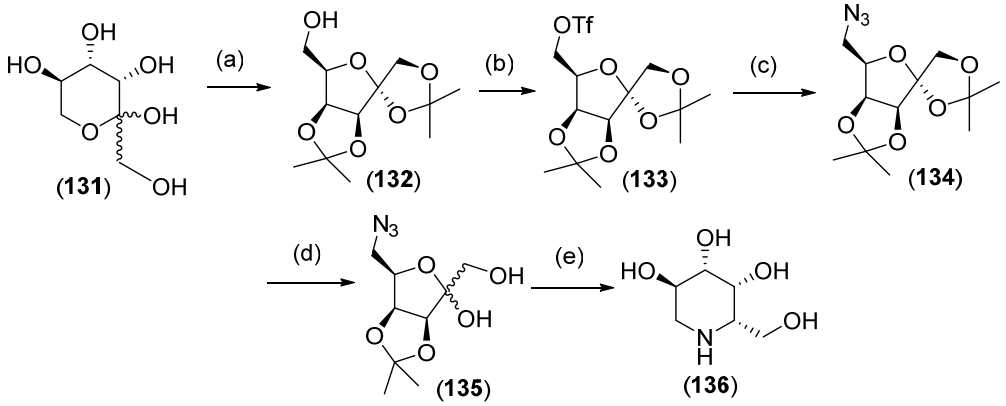
Chan *et al.* accomplished L-*altro*-1-DNJ employing diastereoselective nucleophilic addition of Grignard reagent on cyclic nitrone as the key step (Scheme 13).



Scheme 13. *Reagents and conditions:* (a) $MePPh_3Br$, ^{n}BuLi, THF, –78 °C to room temp.; (b) MsCl, Et_3N, DCM; (c) (i) O_3, MeOH/DCM, –78 °C, then DMS; (ii) $H_2NOH{\cdot}HCl$, $NaHCO_3$, MeOH, reflux; (d) (i) VinylMgBr, THF, 0 °C; (ii) Excess Zn, AcOH, room temp.; (e) (i) $(Boc)_2O$, Et_3N, DCM; (ii) O_3, MeOH/DCM, –78 °C, then DMS; (iii) $NaBH_4$, MeOH, 10% HCl (aq.), MeOH, 70 °C; (iv) H_2, $Pd(OH)_2/C$, 10% HCl (aq.)/MeOH, room temp.

Jenkinson *et al.* [30] (*Org. Lett.* **2011**, *13*, 4064)

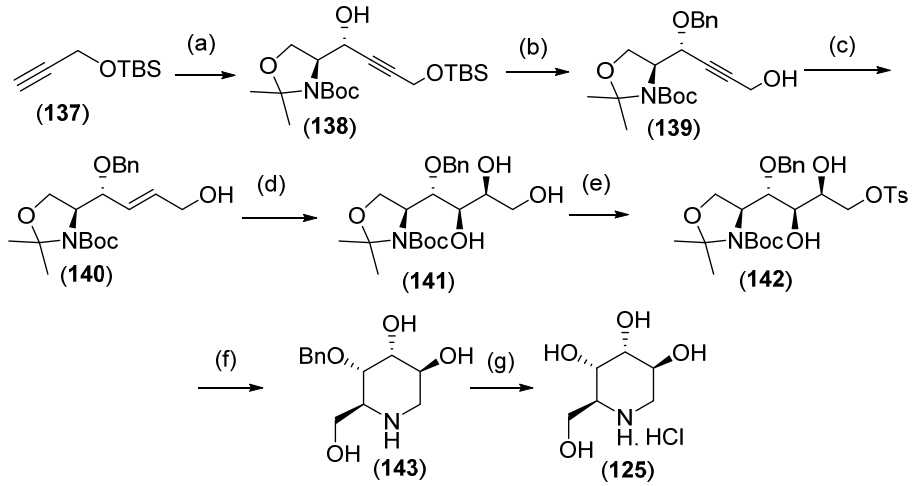
Jenkinson *et al.* reported total synthesis of both enantiomers of *galacto*-1-DNJ from D and L-tagotase employing reductive cyclization as the key step (Scheme 14).



Scheme 14. *Reagents and conditions:* (a) Acetone, $CuSO_4$, H_2SO_4, rt, 18 h, 79%; (b) Tf_2O, py., DCM, -30 ^oC to 10 ^oC, 3h; (c) NaN_3, DMF, rt, 18 h, 93% (over two steps); (d) Dowex, 1,4-dioxane, H_2O, rt, 3 d, 86%; (e) H_2, Pd/C, EtOH/H_2O, rt, 18 h, 97%.

Karjalainen *et al.*[31] (*Org. Bio. Chem.* **2011**, *9*, 1231)

Karjalainen *et al.* reported total synthesis of *altro*-1-DNJ using Garner aldehyde as the chiral template (Scheme 15).

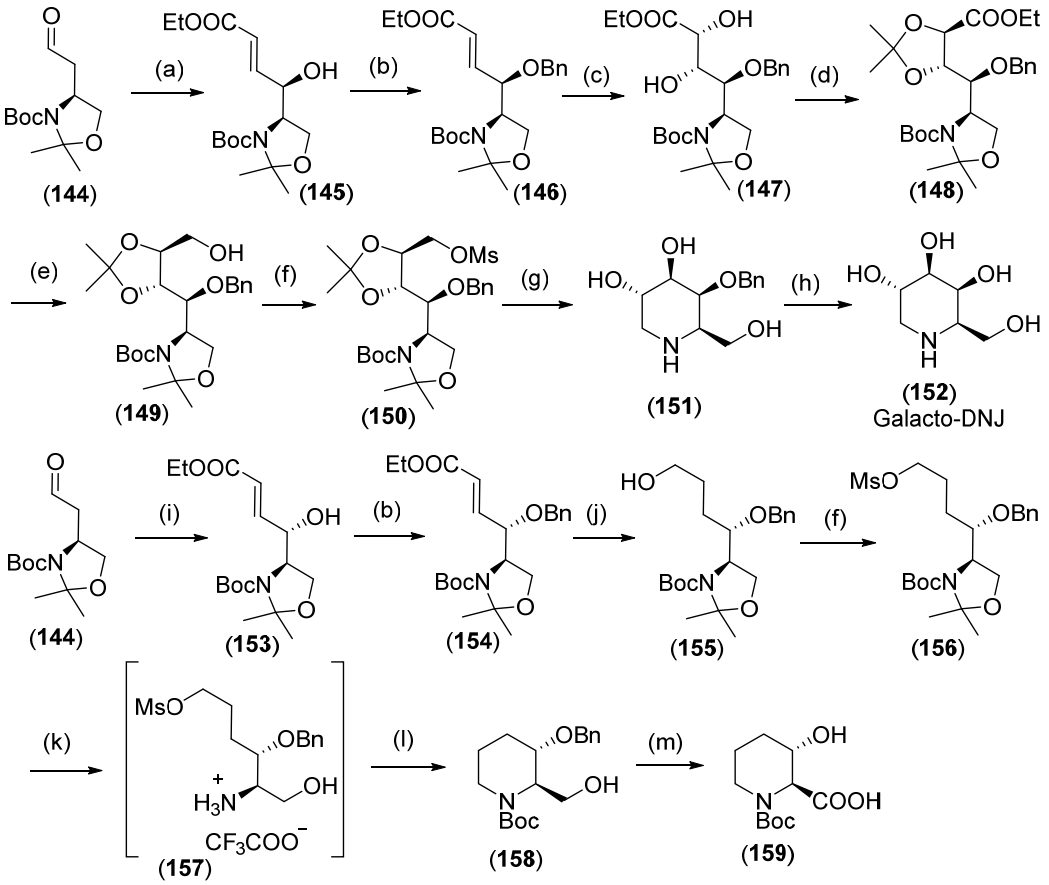


Scheme 15. *Reagents and conditions: (*a) ^{n}BuLi, THF, Garner aldehyde -78 ^oC; (b) BnBr, NaH, KI, DMF, 0 ^oC, (ii) NH_3.HF. HF, MeOH, rt, 95%; (c) Red Al, 0 ^oC, THF; (d) OsO_4, NMO, citric acid, acetone : H_2O (8:2), 81%, dr 6:1; (e) TsCl, N-methyl

imidazole, DCM, 0 ^{o}C, 76%, (f) HCl, MeOH, 50 ^{o}C, (ii) $CaCO_3$, MeOH, 0 ^{o}C, 68%; (g) Pd/C, MeOH, H_2, HCl.

Ramapanicker *et al*. [32] (*J. Org. Chem*. **2015,** *80*, 4776).

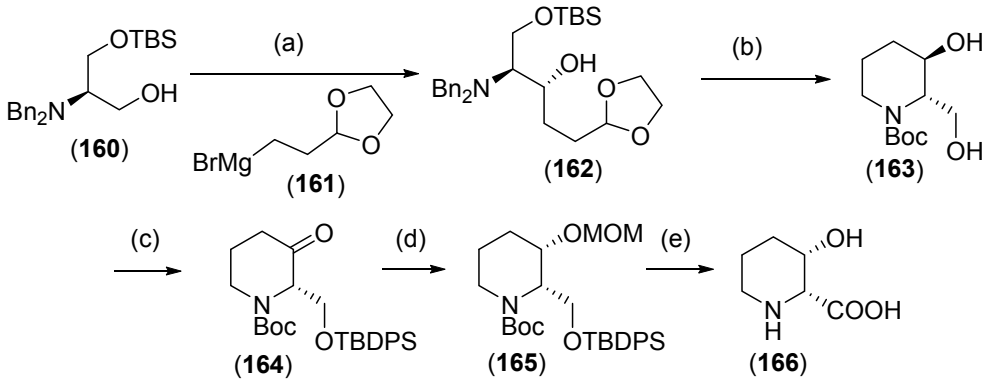
Use of proline catalyzed asymmetric α-aminoxylation of a higher homologue of Garner's aldehyde, derived from *L*-aspartic acid, is reported by Ramapanicker *et al*. This method is also used for a highly diastereoselective synthesis of the *N*-Boc derivative of (2*S*,3*S*)-3-hydroxypipecolic acid (Scheme 16).



Scheme 16. *Reagents and conditions:* (a) (i) D-proline, PhNO, -78 °C; (ii) $Ph_3P{=}CHCO_2Et$; (iii) $Cu(OAc)_2$; (b) BnBr, NaH, TBAI, DMF, 0 °C; (c) acetone water, rt, OsO_4, NMO; (d) pTSA, DMP, toluene, heat; (e) LAH, THF, rt (f) Et_3N, MsCl, DMAP, DCM, 0 °C, (g) (i) HCl, MeOH, rt (ii) K_2CO_3, MeOH; (h) Pd/C, MeOH, H_2; (i) (i) L-proline, PhNO, -78 °C; (ii) $Ph_3P{=}CHCO_2Et$; (iii) $Cu(OAc)_2$; (j) $LiBH_4$, THF; (k) TFA in DCM; (l) MeOH, K_2CO_3, Boc_2O; (m) (i) Jones Oxid., (ii) Pd/C EtOH.

Zhu *et al.*[33] (*Tetrahedron Lett*. **2000**, *41*, 7033).

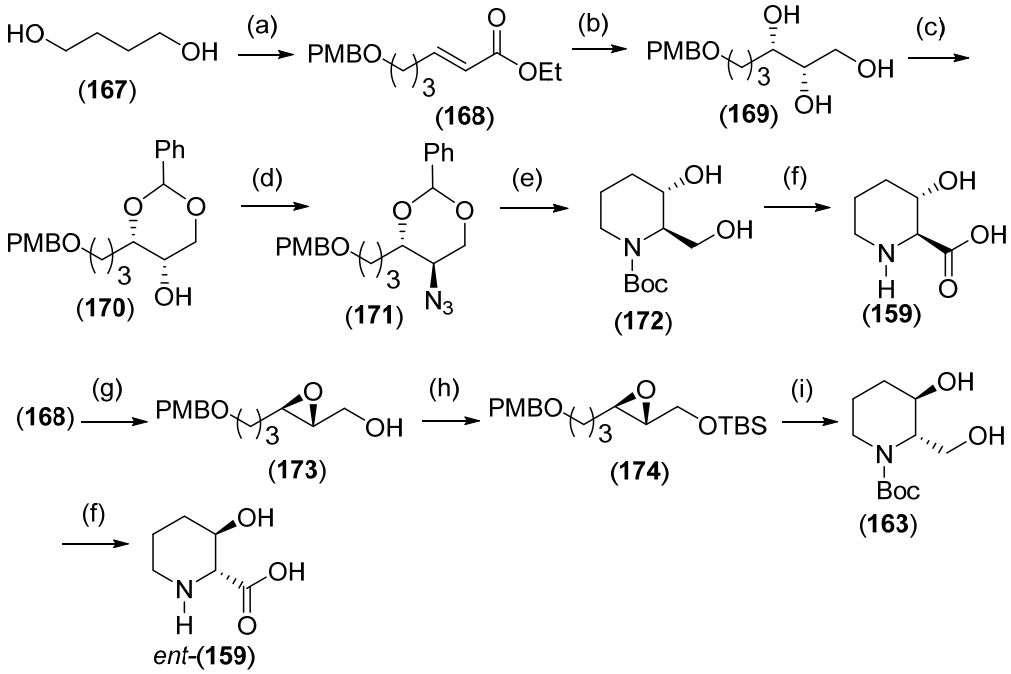
Zhu *et al*. synthesized (2*R*,3*S*)-3-hydroxypipecolic acid *ent*-**1** starting from amino alcohol (**160**) derived from *L*-serine (Scheme 17).



Scheme 17. *Reagents and conditions:* (a) Swern oxidation; (b) (i) H_2, Pd/C, 3N HCl; (ii) $(Boc)_2O$, 1N NaOH; (c) (i) TBDPSCl, Im., DMF; (ii) Swern oxidation; (d) (i) $NaBH_4$, MeOH, 88%; (ii) MOMCl, DIPEA, 92%; (e) (i) HF, Py; (ii) CrO_3/H_2SO_4; (iii) 6N HCl.

Pradeep Kumar *et al.*[34] (*J. Org. Chem*. **2005**, *70*, 360).

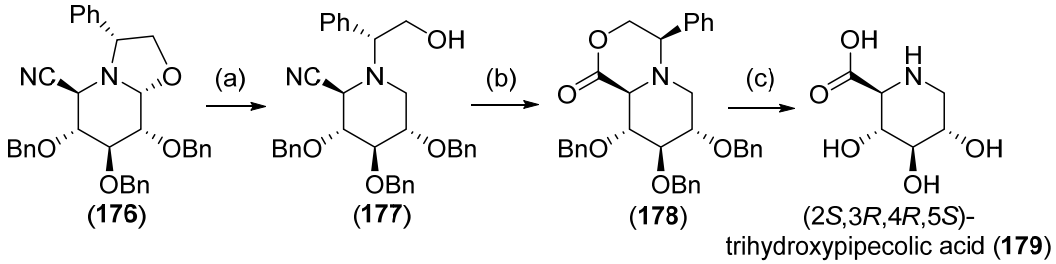
Pradeep Kumar *et al*. (Scheme 18) achieved formal synthesis of (**159**) starting from butan-1,4-diol.



Scheme 18. *Reagents and conditions:* (a) (i) NaH, PMB-Br; (ii) PCC, Ph_3PCHCO_2Et; (b) (i) DIBAL-H, DCM; (ii) K_2CO_3, K_3FeCN_6, $CH_3SO_2NH_2$, OsO_4, $(DHQ)_2PHAL$; (c) $C_6H_5CH(OMe)_2$,CH_2Cl_2, TsOH; (d) (i) MsCl, Et_3N; (ii) NaN_3, DMF; (e) DDQ, CH_2Cl_2, H_2O; (ii) MsCl, Et_3N, DMAP; (iii) H_2 / 10% Pd-C, MeOH then Boc_2O; (f) ref Zhu et al (Tetrahedron Lett. **2000**, 41, 7033) ; (g) (i) DIBAL-H, DCM; (ii) $Ti(i\text{-}OPr)_4$, (-)-DIPT, TBHP, CH_2Cl_2; (h) (i) TBDMSCl, Et_3N; (ii) DDQ, CH_2Cl_2, H_2O; (iii) MsCl, Et_3N, DMAP; (i) (i) NaN_3, DMF; (ii) Ph_3P, THF/H_2O, then Boc_2O, NaOH.

Lallemand and Husson *et al.*[35] (*Tetrahedron: Asymmetry* **2007,** *18*, 1585).

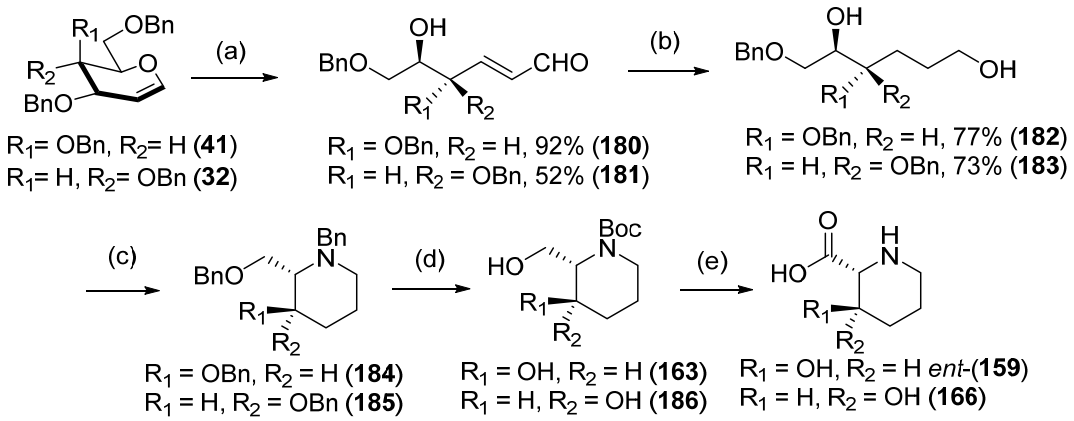
Lallemand and Husson *et al* have reported a novel four step synthesis of enantiomerically pure (2*S*,3*R*,4*R*,5*S*)-trihydroxypipecolic acid with readily available starting materials, *i.e*. condensation products of (*R*)-(-)-phenylglycinol with a mesotrihydroxylated glutaraldehyde (Scheme 19).



Scheme 19. *Reagents and conditions:* (a) $Et_3SiH/TiCl_4$, DCM; (b) K_2CO_3, acetone, $TiCl_4$; (c) H_2, $Pd(OH)_2/C$, EtOH, 4 bars.

Vankar *et al.*[36] (*J. Org. Chem.* **2010**, *75*, 4608).

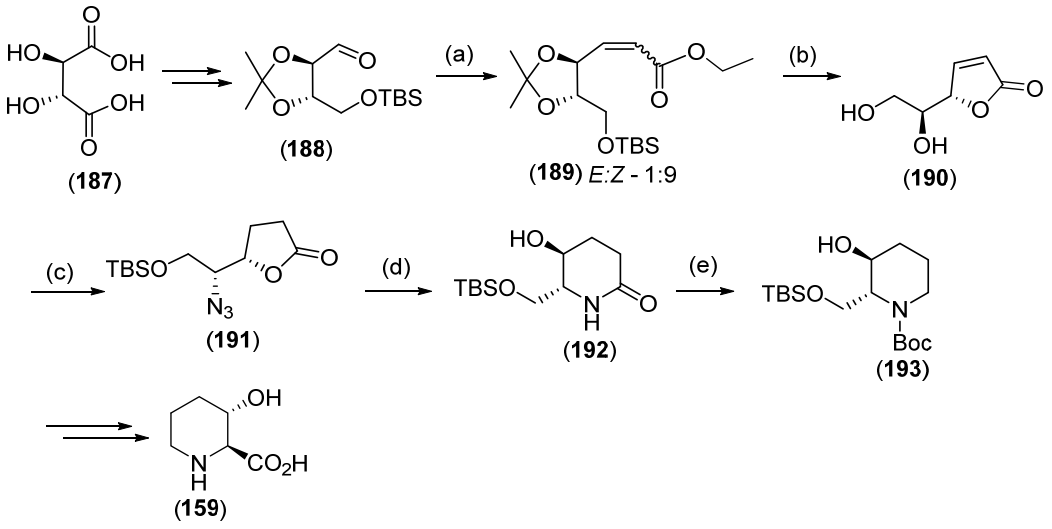
Vankar *et al*. (Scheme 20) completed formal synthesis of pipecolic acid along with deoxoprosophylline starting from *D*-glycal by taking advantage of Perlin hydrolysis, chemoselective saturation of olefins and reductive amination as the key steps. By synthetic transformations and then by following the reported procedure of Ferreira *et al*.[37] it was converted into the corresponding pipecolic acid.



Scheme 20. *Reagents and conditions:* (a) Perlin hydrolysis; (b) (i) $NaBH_4$, $CeCl_3.7H_2O$; (ii) H_2, Pd/C; (c) (i) MsCl, Et_3N; (ii) $BnNH_2$; (d) (i) H_2, $Pd(OH)_2$; (ii) Boc_2O; (e) Ref: 37.

Chavan *et al.*[38] (*Tetrahedron: Asymmetry* **2011**, *22*, 587).

Synthetic strategy for (2*S*,3*S*)-3-hydroxypipecolic acid (**159**) (Scheme 21) was reported by Chavan and co-workers using Mitsunobu reaction and kinetically controlled butenolide formation as the key steps.



Scheme 21. *Reagents and conditions*: (a) Ph_3PCHCO_2Et, MeOH, -50 °C, 70%; (b) PTSA, MeOH, 82%; (c) (i) H_2, Pd/C, MeOH; (ii) TBSCl, Im, DCM; (iii) HN_3, DEAD, PPh_3, THF; (d) (i) H_2, Pd/C, MeOH; (ii) Cat. NaOMe, MeOH, reflux; (e) BH_3.DMS, THF, then $(Boc)_2O$, Et_3N.

1.1.1.5 Present work: Objective and Rationale

Our own interest in synthesizing bio-active compounds, prompted us to devise for an efficient synthetic strategy for piperidine alkaloids *viz*. fagomine and 4-*epi*-fagomine. So far, most of the reported synthesis of fagomine and 4-*epi*-fagomine suffers from some drawbacks such as (i) requiring hazardous reagents, (ii) long reaction steps (iii) poor yields of products (iv) expensive reagents and catalysts and (v) complex reaction procedures difficult to handle. In order to overcome the above shortcomings we intented to synthesize fagomine and 4-*epi*-fagomine in an efficient and easy way. Sugars are readily available and one of the richest source of raw material as a chiral pool for the synthesis of a number of diverse and complex molecules. Some of the structural features shared by iminosugars and carbohydrates have made them ideal starting materials. The main challenges of this strategy are:

1. Differentiation of the hydroxyl groups of an open carbohydrate-derived intermediate.
2. Conversion of one of them into an amino group or precursor.
3. Intramolecular cyclization of the open intermediate, a crucial step determining the efficiency and viability of the syntheses.

We envisioned that *D*-glycals could be efficiently utilized for the synthesis of piperidine alkaloids as depicted in Fig. 4.

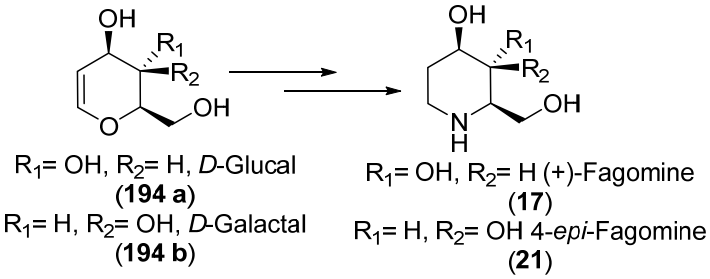
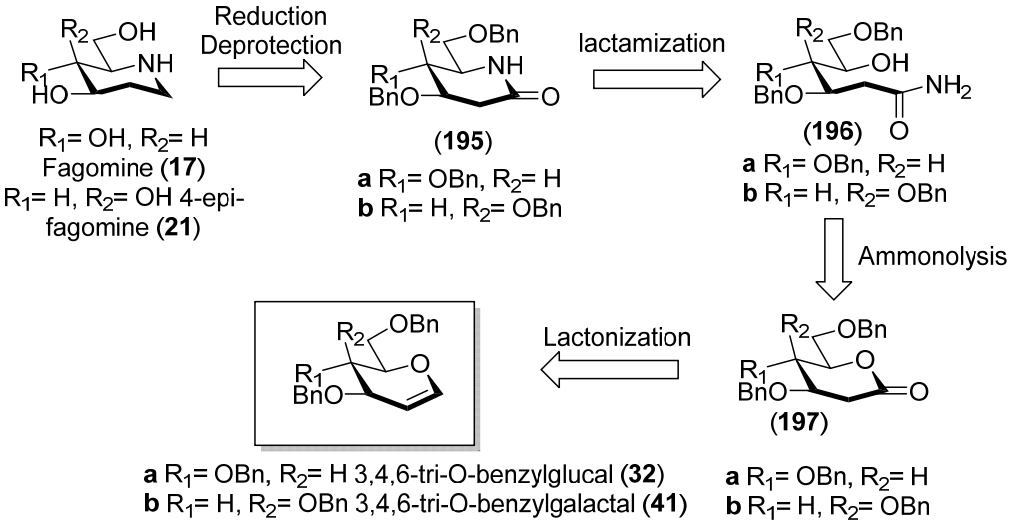


Figure 4. Blue print for the synthesis of fagomine and 4-*epi*-fagomine.

1.1.1.6 Results and Discussion

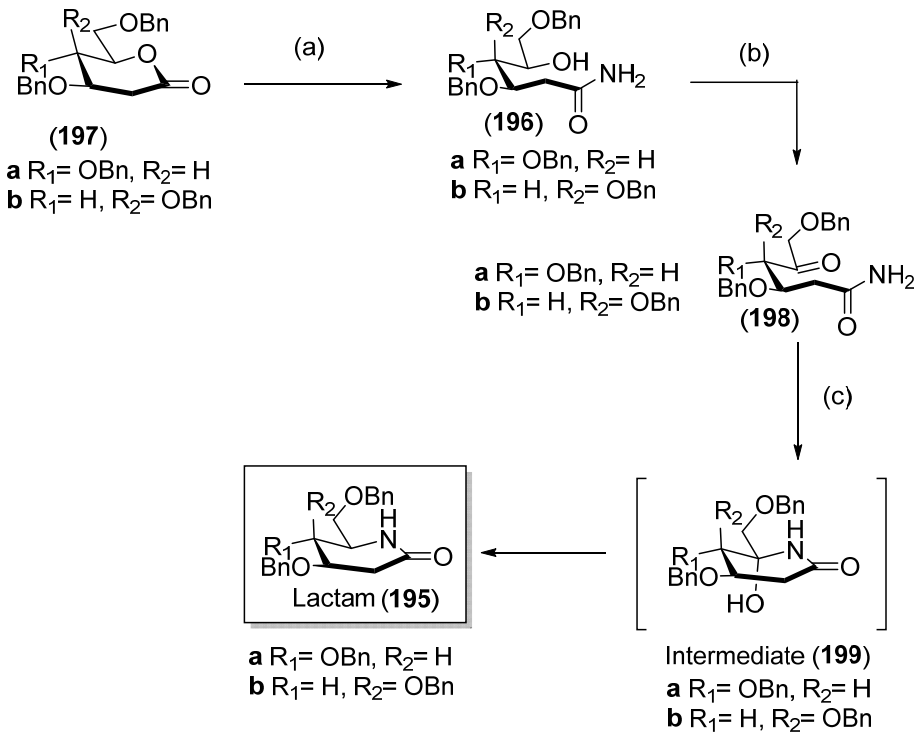
Due to diverse biological activities, we have devised a retrosynthetic plan for the synthesis of fagomine and 4-*epi*-fagomine (Scheme 22) starting from easily available D-glucal and D-galactal.



Scheme 22. Retrosynthetic plan for the synthesis of fagomine (**17**) and 4-*epi*-fagomine (**21**).

Fagomine (**17**) and 4-*epi*-fagomine (**21**) could be obtained by lactamization of δ-hydroxy amides (**196a/b**). δ-hydroxy amides (**196a/b**) in turn can be obtained by ammonolysis of lactones (**197a/b**), which in turn can be accessed from readily available tri-*O*-benzyl-D-glucal (**32**) or tri-*O*-benzyl-D-galactal (**41**) respectively (Scheme 22).

Glycals (**194a/b**) were readily converted into the corresponding lactones (**197a/b**) via acid catalyzed hydration of glycals (**194a/b**) and then oxidation of lactol to lactone (**197a/b**) by following the known literature protocol.[39] We thought that by using Pandit's method[40] we could open the lactone (**197a/b**) with 7N methanolic ammonia. Hence, treatment of lactones (**197a/b**) with 7N methanolic ammonia (ammonolysis) furnished the ring opened compounds δ-hydroxy amides (**196a**) in 82% and 96% (**196b**) from lactones (**197a**) and (**197b**) respectively.



Scheme 23. *Reagents and conditions:* (a) NH_3 in CH_3OH (7N soln.), (6h, 82%) (**196a**) (11h, 96 %) (**196b**); (b) AC_2O/DMSO, (23h, 59%) (**198a**), (26h, 64%) (**198b**); (c) HCOOH/$NaBH_3CN$, CH_3CN reflux, (4.5h, 59%) (**195a**), (4.5h, 59%) (**195b**).

The IR spectrum of both (**196a**) and (**196b**) displays strong band at 1653 cm^{-1} and at 3473 and 3375 cm^{-1} indicates presence of -$CONH_2$ amide group. The ^1H NMR spectrum of compound (**196a**) showed one of the *H*-2 proton at δ 2.65-2.56 as a multiplet and the other *H*-2 proton was observed as a multiplet at 2.55-2.45 these protons were present at α position to carbonyl group. A broad singlet at δ 5.65 for one proton was assigned for NH. And the other NH proton was observed as a broad singlet at 5.22, were assigned by D_2O exchange studies. Compound (**196a**) in ^{13}C NMR spectrum showed peaks at δ 173.5 corresponding to the carbonyl (C-1) and 37.2 corresponding to CH_2 at (C-2) this also confirms the formation of δ-hydroxy amide (**196a**). The HRMS spectrum showed the desired peak at *m/z* 472.2088 $[C_{27}H_{31}NO_5Na]$ $(M+Na)^+$. The galactolactone (**197b**) on following the same reaction conditions furnished δ-hydroxy amides (**196b**) in 96% and which was characterized by its IR and NMR spectral data (Scheme 23).

Subjecting δ-hydroxy amides (**196a/b**) to Albright Goldmann oxidation condition *i.e.* Ac_2O and DMSO at rt furnished the desired δ-keto amides (**198a/b**) were obtained were used as such for the next step without any further purification. The crude of (**198a/b**) was then treated with formic acid, and followed by $NaBH_3CN$, to furnish the desired lactams (**195a/b**). This step being a very crucial step of **intramolecular reductive amination,** which involves condensation of amine with the ketone to furnish the cyclized product. Formic acid complexes with the ketone carbonyl and increases its electrophilicity to facilitate the attack of amine, the iminium ion (**200**) formed *in situ* after dehydration from (**199a/b**) (which is also assisted by formic acid) undergoes $NaBH_3CN$ reduction to form the desired lactams (**195a/b**) (Scheme 23).

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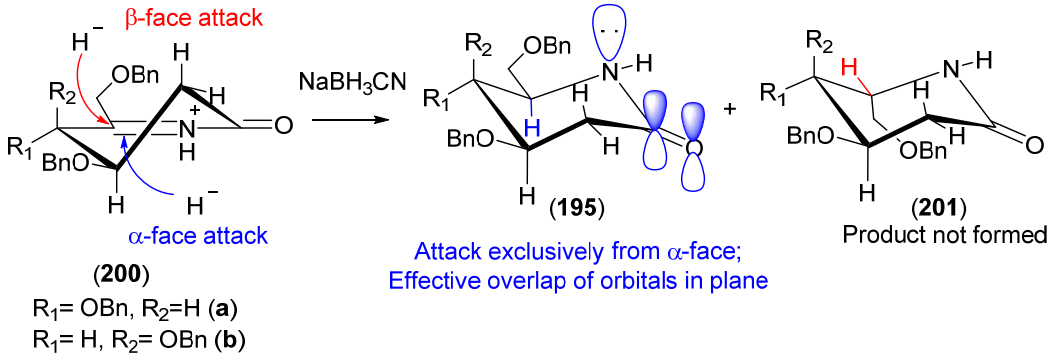
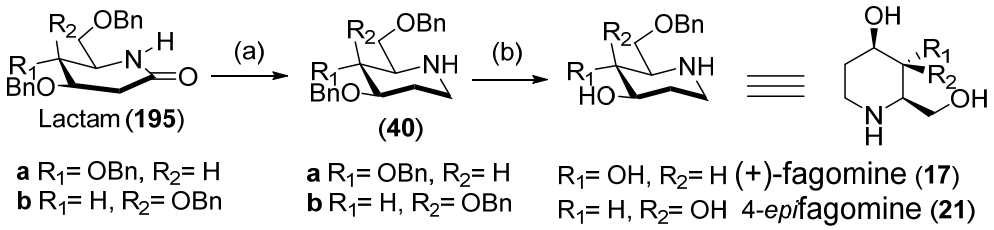


Figure 5. Stereochemical course of reduction of lactams.

It is noteworthy here to describe the stereochemical course of reduction of the lactams. Initially in the presence of formic acid nucleophilic attack of amide nitrogen on the carbonyl ketone furnishes hydroxy lactam substrates (**199a/b**). Acid catalyzed dehydration of the hydroxy lactam substrates (**199a/b**) produces acyliminium ion (**200a/b**). The mechanism of reductive amination step presumably involves a hydride donation by the $NaBH_3CN$ reagent to the acyliminium ion (**200a/b**). Hydride can approach from α-face of the ring or from the β-face of the ring depending on the predominance of stereoelectronic or steric factor. In this case the reduction is governed by the stereoelectronically controlled transition states. The hydride approaches the α-face of the ring, thus generating that configuration of the developing nitrogen electron-pair, which allows the most effective overlap with the orbitals of the lactam carbonyl. Steric factors also govern the course of reaction, where the attack of

hydride from β-face of the ring is possible, which will lead to mixture of products (**195a/b**) and (**201a/b**),[40] but as the products (**201a/b**) were not isolated, we assume that stereoelectronic factors operate in the transition state of the reaction with only α-face attack (Fig. 5).

The IR spectrum of (**195a**) showed band at 1666 cm^{-1} and 3396 cm^{-1} for -CO and amide –NH group. The ^{1}H NMR spectrum of compound (**195a**) showed one proton at δ 2.79 as a doublet of doublet with coupling constants J = 5.3, 17.2 Hz and other proton as doublet of doublet at 2.48 with coupling constant J = 7.6, 17.4 Hz indicates both protons were present at α position to carbonyl group of amide. Moreover a broad singlet for one proton at δ 6.33 could be NH, was assigned by D_2O exchange studies. Similarly the ^{13}C NMR spectrum of compound (**195a**) exhibited δ 169.8 corresponds to carbonyl (C-1) and 35.1 corresponds to CH_2 at (C-2) also confirms formation of glucolactam (**195a**). There are in all 14 sites of unsaturation present in the product (**195a/b**). 13 Sites of unsaturation being already present in the starting material (**198a/b**) (12 from benzenoid system and 1 from carbonyl) increase in unsaturation by 1 unit in the product (**195a/b**) can be accounted for the ring formation which was also in accordance to the observation of peak in HRMS spectrum at *m/z* 432.2169 $[C_{27}H_{30}NO_4]$ $(M+H)^+$. Similarly, from δ-hydroxy amides (**196b**) in two steps following the same reaction conditions galactolactam (**195b**) was isolated in 59% and characterized by its spectral data.



Scheme 24. *Reagents and conditions:* (a) LAH / THF reflux, (4h, 49%) (**202a**), (2 h, 41%) (**202b**). (b) Ref .10 (H_2, Pd/C, EtOH, HCl, 85%)

Reduction of lactam carbonyl (**195a/b**) will furnish the desired benzyl protected fagomine and 4-*epi*-fagomine. Hence the corresponding reaction in THF and LAH as reducing agent was carried out with slow addition of LAH as reducing agent at 0 °C

and then stirring at rt for 1h and finally refluxed for around 4h yielded benzyl protected fagomine in 49% and benzyl protected 4-*epi*-fagomine in 41% respectively from the corresponding glycolactams (**195a/b**) (Scheme 24).

The product thus obtained was characterized by its spectral data; The IR spectrum of compound (**195a**) showed only NH stretching frequency at 3151 cm^{-1} and absence of CO frequency. The ^{1}H NMR spectrum of compound (**195a**) showed δ 2.34 as a broad singlet integrating for one proton and was assigned for NH by D_2O exchange studies. Protons present α to amine group are deshielded and observed at δ 3.10-3.05 as ddd for one proton with coupling constants of J = 1.8, 2.3, 12.6 Hz, which was assigned as H-1_a. The signal at δ 2.62-2.56 showed a doublet of a triplet for one proton with J = 12.6, 2.3 Hz, which was assigned as H-1_b. A proton with unit integration at δ 2.76-2.71 was observed as a multiplet and was assigned to H-5. Similarly ^{13}C NMR spectrum of compound (**195a**) showed δ 43.6 corresponding to (C-1) and no signal for CO group was observed. Reduction in sites of unsaturation from 14 in starting material (**195a/b**) to 13 in the product (**14**) and (**21**) is also reflected in HRMS spectrum with the desired peak at *m/z* 418.2378 $[C_{27}H_{31}NO_3]$ $(M+H)^+$. Following the same reaction conditions benzyl protected 4-*epi*-fagomine was also synthesized and characterized by its IR and NMR spectral data.

Finally following the reported procedure by Désiré *et al*.[10] deprotection can be carried out to furnish fagomine (**14**) and 4-*epi*-fagomine (**21**) respectively in 12% and 5% yields, respectively from the corresponding glycolactams (**195a/b**).

1.1.2 Approach Towards the Synthesis of Nojirimycin and 2-Deoxynojirimycin

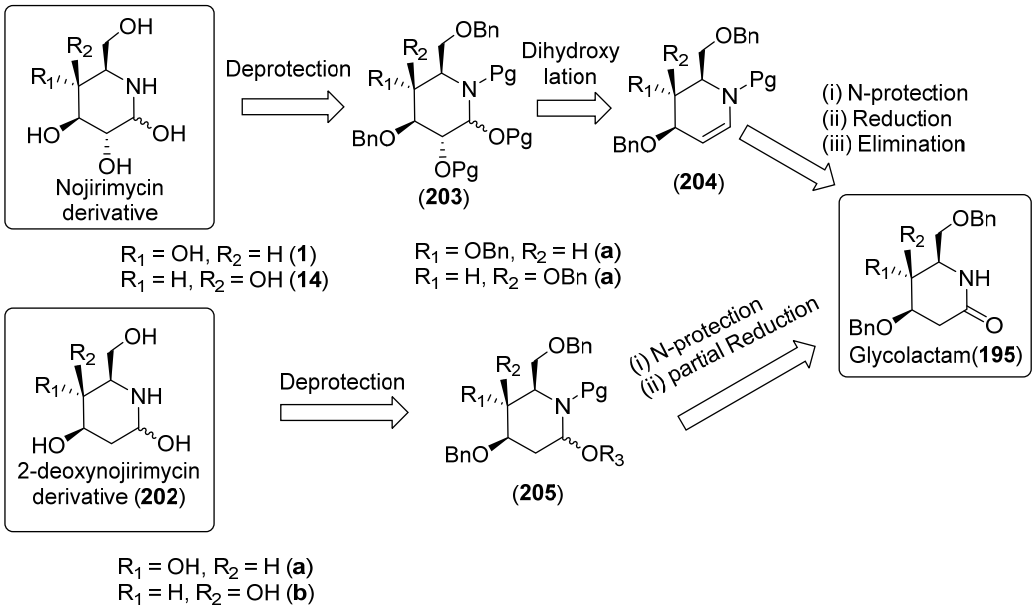
1.1.2.1. Present work: Objective and Rationale

Reported synthesis of nojirimycin (**1**), its derivatives deoxynojirimycin (**2**, **11**, **14**) has been discussed in Section **1.1.3**. Fascinated by the biological activities and their amazing diversity, prompted us to undertake the synthesis of these piperidine

alkaloids. We presumed that glycolactams (**195a/b**) can be utilized to synthesize the biologically important piperidine alkaloids such as nojirimycin and its analogue.

1.1.2.2 Results and Discussion

We visualized that *N*-protected glycolactam (**204**) which can be readily obtained in 3 steps from glycolactam (**195**) *i.e*., (i) *N*-protection, (ii) reduction of carbonyl and finally (iii) elimination. Dihydroxylation of (**204**) will furnish protected nojirimycin derivative which on deprotection will give the desired nojirimycin (**1**) and galactostatin (**14**). Similarly 2-deoxynojirimycin (**202a/b**) can be synthesized from **(205a/b**) by deprotection, **(205a/b**) in turn can be obtained from glycolactam (**195**) by *N*-protection followed by partial reduction of lactam carbonyl (Scheme 25).

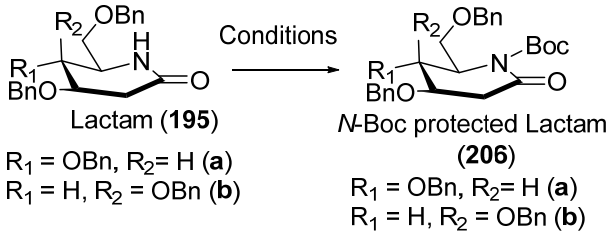


Scheme 25. Retrosynthetic plan for the synthesis of nojirimycin (**1**), its analogues and 2-deoxynojirimycin (**202**).

In order to achieve the synthesis of nojirimycin (**1**) and 2-deoxynojirimycin (**202**), we first tried to protect the nitrogen with Boc group by following the reaction condition in Table 1. Initially we tried with well known conditions[41] such as Boc_2O, py, DMAP at rt but it lead to the recovery of starting material. Thereafter we changed the base to $NaHCO_3$ and the reduction was carried out in binary solvent system H_2O-THF with

Boc_2O at rt; however the starting material was recovered. Then changing the solvent to CH_3CN also could not furnish the desired product. Finally when the reaction was carried out with Boc_2O in presence of triethylamine catalyzed by DMAP in DCM as solvent at 0 °C followed by rt[42] lead to the formation of Boc-protected glycolactams (**206a/b**) in good yields.

Table 1. Attempt for *N*-protection of lactam.

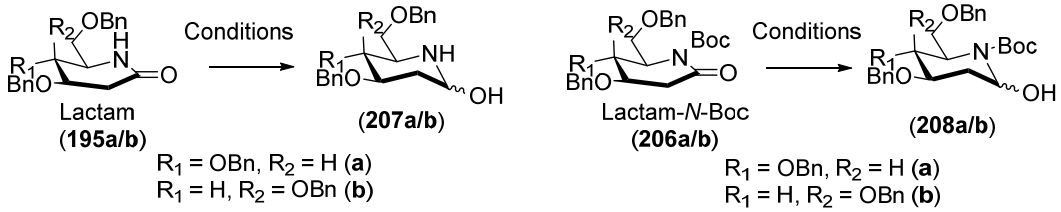


Entry	Reagents and condition	Remark
1	Boc_2O, Py, DMAP, rt	Sm recovered
2	Boc_2O, $NaHCO_3$, H_2O -THF, rt	Sm recovered
3	Boc_2O, CH_3CN , NEt_3, DMAP (cat)	Sm recovered
4	Boc_2O, DCM, NEt_3, DMAP (cat), 0 °C then rt	**95 % Glucolactam (206a)** **79 % Galactolactam (206b)**

The formation of *N*-Boc protected lactams (**206a/b**) was confirmed by their NMR spectra (**206a/b**). The ^1H NMR spectrum of compound (**206a**) showed the disappearance of NH protons and appearance of corresponding Boc protons (9H) at δ 1.48 ppm unambiguously confirmed the formation of (**206a**). The ^{13}C NMR spectrum of compound (**206a**) exhibited the two carbonyl groups at δ 169.6, 152.2, also -CH_3 of Boc at 28.0 supports the formation of *N*-Boc protected lactams (**206a**). The galactolactam (**195b**) on following the same reaction conditions furnished *N*-Boc protected lactams (**206b**) in 79% and which was characterized by its IR and NMR spectral data.

Our idea was then to partially reduce the lactams (**195a/b**) carbonyl group and also to bring the dehydration of the lactamol group. In order to proceed for that we started with lactams (**195a/b**) and treated with $NaBH_4$ in MeOH following the reported procedure[43] carried out on similar type of substrates. However in all the cases even with Lactam-*N*-Boc (**206a/b**) and also under varying conditions and solvents desired product was not formed and starting material (sm) was recovered as it is (Table 2).

Table 2. Conditions for partial reduction of lactams (**195a/b**) and lactam-*N*-Boc (**206a/b**).



Entry	Reagents and condition	Remark
1	$NaBH_4$, MeOH, 0 °C	Sm recovered
2	$NaBH_4$, MeOH, 0 °C , then rt	Sm recovered
3	$NaBH_4$, THF-MeOH, 0 °C, then rt	Sm recovered
4	$NaBH_4$, THF-MeOH, rt	Sm recovered

Sm = Starting material

During our literature survey for the synthesis of fagomine, 4-*epi*-fagomine and nojirimycin, we learned that so far Super hydride or $LiBHEt_3$ have been used mainly for three purposes (i) regioselective epoxide ring opening[18,44] (ii) reduction of ester to alcohols[45] and (iii) knocking off OH with hydride, by means of converting OH into good leaving group like triflate -OTf.[9] There are hardly any references for the use of super hydride in the reduction of amide carbonyl and (which have been utilized in the synthesis of piperidine alkaloids). On the extensive literature search, we came across only three references using super hydride for the reduction of carbonyl group, however these were not on iminosugar substrate.[46] As delineated in our retro synthetic

scheme (Scheme 25) in partial reduction of amide carbonyl followed by elimination of OH group to induce a double bond *i.e.* to generate an iminoglycal (**204a/b**), we thought of utilizing super hydride here to introduce the double bond. Super hydride has a dual role. *i.e*., reduction of carbonyl group and / or elimination of OH to form the double bond. We could achieve the synthesis of both partially reduced lactam carbonyl *i.e.* lactamol (**208a/b**) as well as the reductive dehydrated product iminoglycal (**204a/b**) in good yields (Scheme 26) in one pot with just slight variation in the reaction conditions

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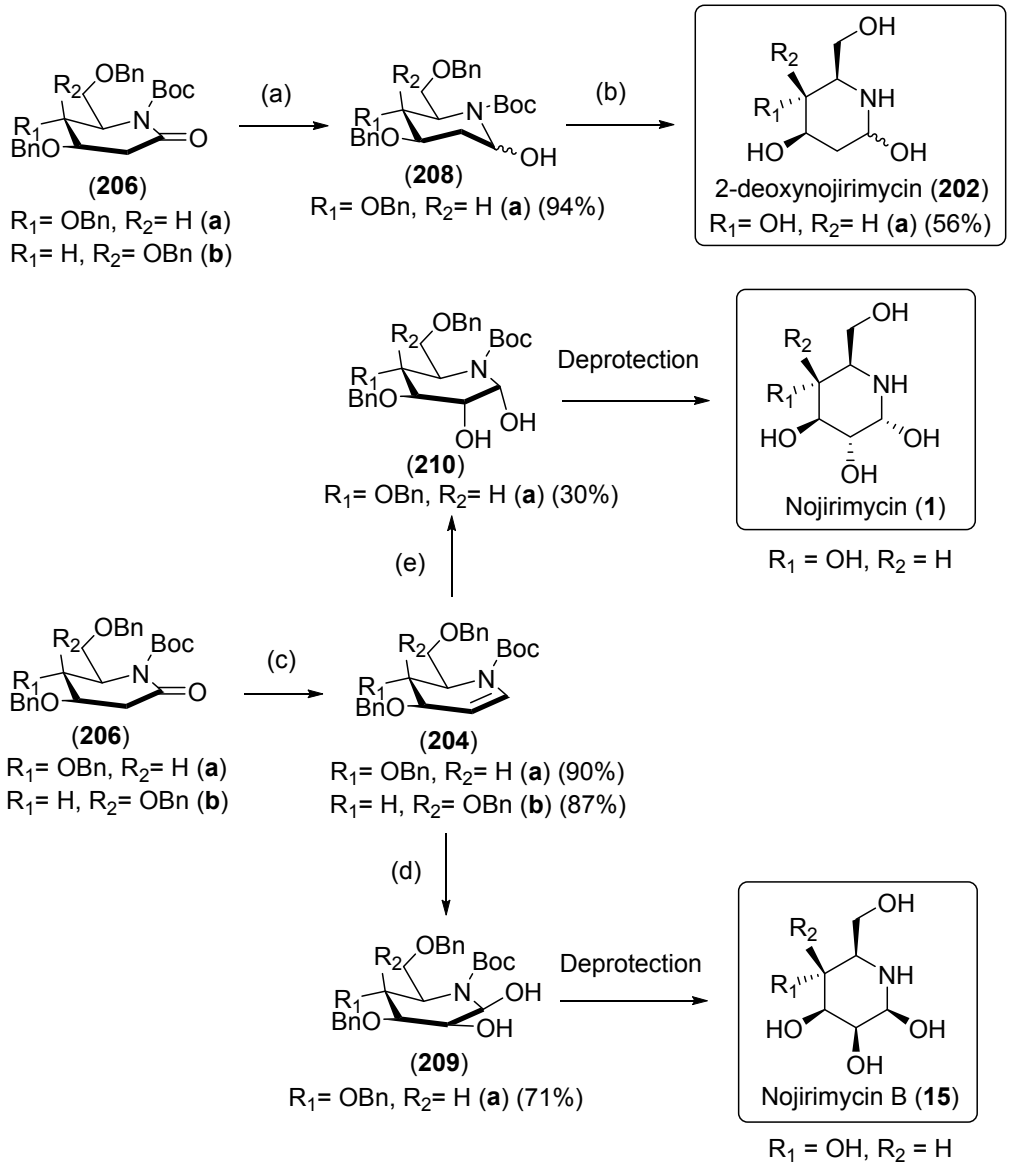


Scheme 26. *Reagents and conditions;* (a) (i) Superhydride, toluene, -76 °C 1h; (ii) NH_4Cl, -76 °C to rt; (b) (i) aq. HCl, MeOH, 70 °C; (ii) H_2, Pd-C (10%), AcOH; (c) (i)

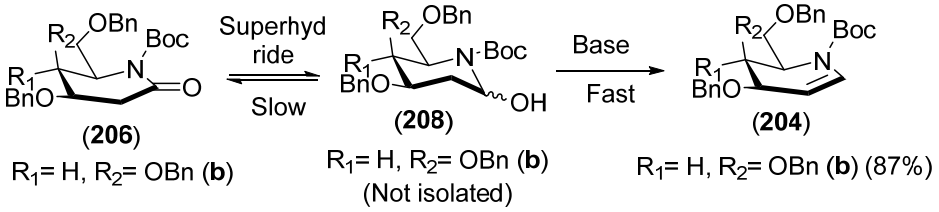
Superhydride, toluene, -70 °C, 30 min; (ii) TFAA, DIPEA, DMAP (cat), -70 °C to rt, 2h; (d) $(DHQD)_2AQN$ (5 mol%), $K_3Fe(CN)_6$, K_2CO_3, $K_2OsO_2(OH)_4$ (5.59 mol%) $CH_3SO_2NH_2$, *t*-butyl alcohol : H_2O (1:1) 0 °C for 66 h; (e) $(DHQ)_2AQN$ (5 mol%), $K_3Fe(CN)_6$, K_2CO_3, $K_2OsO_2(OH)_4$ (5.59 mol%) $CH_3SO_2NH_2$, *t*-butyl alcohol : H_2O (1:1) 0 °C for 66 h.

Lactam-*N*-Boc (**206a/b**) was treated with superhydride in toluene[46a,b] at -76 °C for 1h and then with NH_4Cl at -76 °C to rt (6h) furnished the desired lactamol (**208a**) in 94% yield which was analyzed by spectral data; The IR spectrum of compound (**208a**) showed strong bands at 3740 cm^{-1} corresponding to OH stretch and 1692 cm^{-1} for CO group of Boc. The ^1H NMR spectrum of compound (**208a**) exhibited δ 5.64 brs which was assigned as *H*1 protons, which is deshielded due to -OH and also by *N* atom. The ^{13}C NMR spectrum of compound (**208a**) exhibited the disappearance of lactam carbonyl peak which was present in starting material (**206a/b**) which indicates reduction happened exclusively at lactam carbonyl only, as the CO group of Boc was observed intact at 156.7 ppm. The HRMS spectrum of compound (**208a**) showed increment in mass by 2 units with respect to starting material *viz. m/z* 556.2670 $[C_{32}H_{39}NO_6Na]$ $(M+Na)^+$ also concludes the formation of lactamol (**208a**). However when galacatolactam-*N*-Boc (**206b**) was treated with superhydride under similar reaction conditions, desired product galactolactamol could not be obtained (Scheme 26).

Treatment of compound. (**208a**) by known rection methods *viz.* aq. HCl, MeOH, 70 °C and then hydrogenolysis with H_2, Pd-C (10%) in AcOH will furnish the desired product, 2-deoxynojirimycin (**202**).

In order to generate the key intermediate iminoglycal (**204a/b**), Lactam-*N*-Boc (**206a/b**) was treated with superhydride, in toluene at -70 °C for 30 min followed by addition of TFAA and base DIPEA in presence of DMAP (cat.) then raising the temp of the reaction from -70 °C to rt,[46a,c] complete consumption of starting material was in 2h. Both the products (**204a**) and (**204b**) were obtained in 90% and 87%, respectively from (**206a**) and (**206b**) (Scheme 26).

It is very interesting to note that lactamol (**208b**), which could not be isolated, might have formed in the absence of base, may be in equilibrium with starting material. Product (**208b**) may be formed very slowly and gets reversibly converted to sm (**206b**). However on addition of base the formed galactolactamol product (**208b**) undergoes rapid elimination of water molecule leading to formation of (**204b**). Hence lactamol (**208b**) could not be isolated in the previous conditions in the absence of base but the more stable product (**206b**) could be isolated under this condition in the presence of base (Scheme 27). In case of glucolactamol (**208a**) product being stable is formed irreversibly and hence was isolated easily, both the steps in this case *viz.* attack of hydride and then dehydration by base are fast.



Scheme 27. Plausible pathway for the conversion of galactolactam-*N*-Boc (**206b**) to iminogalactal (**204b**).

The formed iminoglycal (**204a/b**) was characterized as below; The IR spectrum of compound (**204a**) showed bands at 3426 cm^{-1} and 1645 cm^{-1} for alkenyl CH stretch and C=C stretch. The ^{1}H NMR spectrum of compound (**204a**) showed δ 7.11-6.93 multiplet integrating for one proton and δ 5.10-4.90 multiplet for one proton, which were assigned to the olefinic protons. The ^{13}C NMR spectrum of compound (**204a**) showed δ 101.5 and was assigned to the β-carbon (*C*-2). The other olefinic α-carbon (*C*-1) signal is merged with the aromatic carbons which appears in the range 128.6-126.6 ppm. A closer look at the ^{13}C NMR spectrum of compound (**204a**) revealed that product was a mixture of two compounds, possibly due to the presence of Boc group which attains different conformation, once in the plane of piperidine ring and in other times out of the plane of piperidine ring. Finally by HRMS spectrum desired peak at *m/z* 538.2564 $[C_{32}H_{37}NO_5Na]$ $(M+Na)^+$ supported the formation of product (**204a**). The galactolactam-*N*-Boc (**206b**) on following the same reaction conditions furnished

iminogalactal (**204b**) in 87% and which was characterized by its IR and NMR spectral data.

By synthesizing this iminoglycal (**204a/b**) we have functionalized the *C-1* and *C-2* position of iminosugar, which can grant access to synthesis of various other biologically active molecules. As per our retrosynthetic plan, dihydroxylation of iminoglycal can afford nojirimycin and nojirimycin B (mannojirimycin). Following the very well established condition for dihydroxylation[47a] of (**204a/b**) with commercially available AD-mix α and AD-mix β both in *t*-butyl alcohol : H_2O (1:1) 0 °C for 4d, resulted in complete recovery of sm. It is reported in literature that strong chelating ligands and methanesulfonamide accelerated the dihydroxylation reaction which prompted us to try this condition by using $(DHQD)_2AQN$ and $(DHQ)_2AQN$.[47b,48] However the dihydroxylation reaction was complete in 66h. By treating Iminoglycal (**204a**) with $(DHQD)_2AQN$ (5 mol%), with $K_3Fe(CN)_6$ as oxidant and K_2CO_3 as base, $K_2OsO_2(OH)_4$ (5.59 mol%) $CH_3SO_2NH_2$ as an additive in *t*-butyl alcohol:H_2O (1:1) °C for 66h, furnished the protected derivative of nojirimycin B (**209**). Which can be readily converted to nojirimycin B (**15**) by following the known methods of Boc deprotection and dehydrogenation as reported in synthesis of nojirimycin and deoxynojirimycin discussed in Section **1.1.3**. Similarly by treating iminoglycal (**204a**) with $(DHQ)_2AQN$ (5 mol%), with $K_3Fe(CN)_6$, K_2CO_3, $K_2OsO_2(OH)_4$ (5.59 mol%) $CH_3SO_2NH_2$ in *t*-butyl alcohol : H_2O (1:1) °C for 66 h, furnished the protected derivative of nojirimycin (**210**). This can also be readily converted to nojirimycin (**1**) by following the known literature methods of Boc deprotection and dehydrogenation as discussed in Section **1.1.3**.

All the attempts to dihydroxylate iminoglycal (**204b**) by following the same reaction conditions as that for iminoglucal (**204a**) with $(DHQD)_2AQN$ as well as $(DHQ)_2AQN$ did not furnish the desired product. Probably we could reason that, the axial OBn group at C-4 in case of iminogalactal (**204b**) blocks the approach of Osmium from β-face and α-face is blocked by Boc group, as it is already occupied by it (Boc group adopts position trans to C-4 OBn group to minimize steric interaction). The situation is different in iminoglycal (**204a**) where the OBn group at C-4 is in equatorial position doesn't hinders approach of Osmium from either of the facial attack, also Boc group

maintains more stable equatorial position in the plane of the ring without hampering the dihydroxylation process.

The IR spectrum of the derivative of nojirimycin B (**209**) showed strong bands at 3442 cm^{-1} and 1691 cm^{-1} indicating the presence of OH and CO group. The ^{1}H NMR spectrum of compound (**209**) showed a multiplet at δ 5.69-5.56 integrating for one proton and was assigned to *H*-1 proton, as it is deshielded by OH and *N* atom. The broad singlet observed for one proton each at δ 2.74 and 1.79 indicated the presence of two OH protons. The ^{13}C NMR spectrum of compound (**209**) showed signals in the range δ 81.7- 77.0 ppm, indicated the carbon attached to OH group *i.e*., C-1 and C-2. The HRMS spectrum of (**209**) exhibited the mass peak at *m/z* 572.2621 $[C_{32}H_{39}NO_7Na^+]$ $(M+Na)^+$ supported the formation of dihydroxylated product (**209**). The iminoglycal (**204a**) on following the same reaction conditions but using $(DHQ)_2AQN$ furnished The derivative of nojirimycin (**210**) in 30% and which was characterized by its IR, HRMS and NMR spectral data.

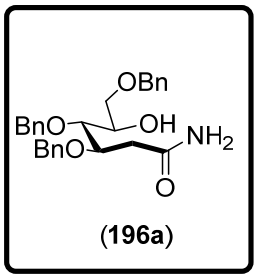
There are reported procedures[18,10] where Boc deprotection is obtained in quantitative yields[18] and debenzylation are obtained in yields of 85%[10] utilizing assumption for final deprotection (Boc deprotection and debenzylation) starting from glucolactam (**195a**) 2-deoxynojirimycin (**202**) is obtained in 76%. And in 22% starting from lactone (**197a**). Similarly nojirimycin (**1**) is synthesized in 22% from glucolactam (**195a**) and in 6% starting from lactone (**197a**). Likewise nojirimycin B or mannojirimycin (**15**) is synthesized in 52% from glucolactam (**195a**) and in 15% starting from lactone (**197a**).

1.1.3 Conclusions

We have successfully synthesized fagomine (**17**) and 4-*epi*-fagomine (**21**) from glucolactone (**197a**) and galactolactone (**197b**) respectively. We have synthesized iminoglycal and functionalized the *C-1* and *C-2* position of iminosugar, which can serve as an handle for the synthesis of various other biologically active molecules. Also formal synthesis of nojirimycin (**1**), nojirimycin B (**15**) and 2-deoxy nojirimycin (**202**) has been achieved.

1.1.4 Experimental

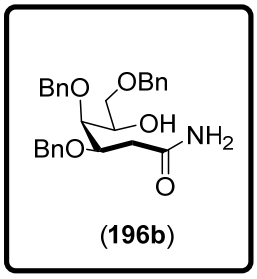
Procedure for the synthesis δ-hydroxy amides / (3*R*,4*R*)-3,4,6-Tris(benzyloxy)-5-hydroxyhexanamide (196a) : Gluconolactone **(197a)** (1.393 g, 2.32 mmol) was dissolved in methanolic ammonia soln. (7N, 22 mL) and was stirred at room temperature for 1.5h. After completion of the reaction (TLC), reaction mixture was concentrated in vacuo followed by purification by SiO_2 column chromatography (EtOAc-petroleum ether, 6:4) to afford **(196a)** (859 mg, 82%) as colorless solid; mp 74-76 °C. R_f 0.26 (EtOAc-petroleum ether, 1:1); $[\alpha]^{20}_D$ +14.27 (*c* 1.43, $CHCl_3$); IR ($CHCl_3$): υ_{max} 3473, 3374, 3201, 3012, 2869, 1673, 1615, 1404, 1216, 1072, 1028, 908, 747, 698, 667 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, assignment by COSY, HSQC and HMBC experiments): δ_H 7.38-7.22 (m, 15H, Ar*H*), 5.65 (bs, 1H, N*H*), 5.22 (bs, 1H, N*H*), 4.62 (s, 2H, Ph-C*H*$_2$), 4.59 - 4.48 (m, 4H, Ph-C*H*$_2$), 4.31-4.23 (m, 1H, H-3), 3.95 (bs, 1H, H-5), 3.68-3.61 (m, 3H, H-4, H-6), 3.06 (bs, 1H, O*H*), 2.65-2.56 (m, 1H, H-2), 2.55-2.45 (m, 1H, H-2); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 173.5 (C-1) 138.0, 137.8, 137.6 (Ar), 128.5, 128.4, 128.3, 128.0, 127.8 (Ar), 78.1 (C-4), 76.7 (C-3), 73.5 (-O*C*H$_2$Ph), 73.3 (2C, C-6,-O*C*H$_2$Ph), 71.1 (-O*C*H$_2$Ph), 70.8 (C-5), 37.2 (C-2); ESI-MS: *m/z* 450.2240 $(M+H)^+$; HRMS: *m/z* calcd for $C_{27}H_{31}NO_5Na$ 472.2094, found 472.2087.



(**196a**)

Procedure for the synthesis δ-hydroxy amides / (3*R*,4*S*)-3,4,6-tris(benzyloxy)-5-hydroxyhexanamide (196b)

Galactonolactone **(197b)** (2.0 g, 4.65 mmol) was dissolved in methanolic ammonia soln. (7N, 25 mL) and stirred at room temperature for 1.5h under nitrogen atmosphere. After completion of the reaction (TLC), reaction mixture was concentrated in vacuo to furnish a crude which was purified by SiO_2 column chromatography (EtOAc-petroleum ether, 1:1) to afford (**196b**) (1.997 g, 96%) as yellowish gum. R_f 0.19 (EtOAc-petroleum ether, 1:1); $[\alpha]^{20}_D$+2.92 (*c* 1.2, $CHCl_3$); IR ($CHCl_3$): υ_{max} 3660, 3372,3019, 2872, 1736, 1454, 1216, 1101, 1064, 908, 755, 698, 668 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$, assignment by COSY, HSQC and

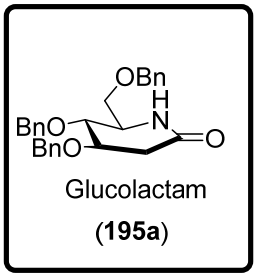


(**196b**)

HMBC experiments, D_2O exchange): δ_H 7.33-7.25 (m, 15H, Ar*H*), 6.00 (bs, 1H, N*H*), 5.51 (bs, 1H, N*H*), 4.79-4.48 (m, 6H, PhCH_2), 4.18-4.10 (m, 1H, H-3), 3.95 (bs, 1H, H-4), 3.76-3.72 (m, 1H, H-5), 3.60-3.44 (m, 2H, H-6), 2.83 (bs, 1H, O*H*), 2.68-2.47 (m, 2H, H-2); ^{13}C NMR (50 MHz, $CDCl_3$): δ_C 173.6 (C-1), 137.8, 137.7 (Ar), 128.6, 128.5, 128.1, 128.0, 127.9 (Ar), 78.8 (C-4), 77.3 (C-3), 74.1, 73.5, 73.0, 71.1 (Ph*C*H_2, C-6), 69.9 (C-5), 37.7 (C-2); ESI-MS: *m/z* 450.4348 $(M+H)^+$, 472.4115 $(M+Na)^+$, 487.5341 $(M+K)^+$; HRMS: *m/z* calcd for $C_{27}H_{31}NO_5Na$ 472.2094, found 472.2088.

Procedure for the synthesis of glucolactam / (5*R*,6*R*)-4,5-Bis(benzyloxy)-6-(benzyloxymethyl)piperidin-2-one (195a):

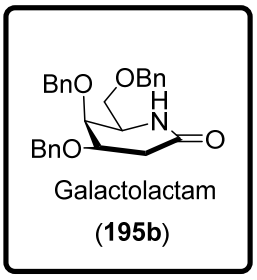
Compound (**196a**) (582 mg, 1.302 mmol) was dissolved in CH_3CN (20 mL) and HCOOH (3.8 mL) was added to the reaction mixture followed by $NaBH_3CN$ (177 mg, 2 eqs.) and the reaction mixture was refluxed at 85 °C for 4.5 h. The reaction mixture was then cooled in an ice-bath and was quenched by adding aq. HCl solution (0.1 N, 30 mL). After stirring for another 15 minutes, EtOAc (50 mL) and then saturated aq. $NaHCO_3$ solutions (50 mL) were added to it. The water layer was separated and extracted with EtOAc (2 x 25 mL), the combined organic fractions were pooled and then washed with brine (1 x 30 mL) and dried (anhyd. Na_2SO_4). After concentration in vacuo, the resulting crude was purified by SiO_2 column chromatography (EtOAc-petroleum ether, 4:6) to afford a white solid which on crystallization (EtOAc-petroleum ether) furnished **(195a)** as colorless needles (329 mg, 59%); mp 73-75 °C; R_f 0.32 (EtOAc-petroleum ether, 1:1); $[\alpha]^{20}_D$+16.78 (*c*1.02, $CHCl_3$); IR ($CHCl_3$): υ_{max} 3396, 3019, 2868, 1666, 1455, 1215, 1100, 755, 699, 669 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$):δ_H 7.37-7.23 (m, 15H, Ar*H*), 6.33 (bs, 1H, N*H*), 4.79 (d, *J* = 11.5 Hz, 1H, PhCH_2), 4.66-4.60 (m, 1H, PhCH_2), 4.60-4.50 (m, 2H, PhCH_2), 4.45 (s, 2H, PhCH_2), 3.88 (dt, *J* = 5.3, 7.2 Hz, 1H, H-6), 3.64-3.49 (m, 3H, H-6, H-3, H-4), 3.42-3.33 (m, 1H, H-5), 2.79 (dd, *J* = 5.3, 17.2 Hz, 1H), 2.48 (dd, *J* = 7.6, 17.4 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$):δ_C 169.8 (q, C-1, C=O), 137.7, 137.6, 137.4 (Ar),128.5, 128.0, 128.0, 127.9, 127.9, 127.8, 127.8, 127.7, 127.5 (*C*H, Ar), 75.7 (C-



Glucolactam
(**195a**)

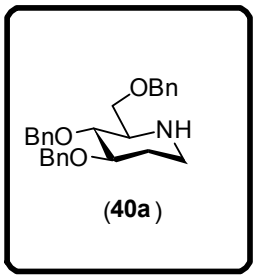
4), 75.5 (C-3), 73.6, 73.3, 71.6 (-*C*H_2Ph), 71.0 (d, C-6), 54.9 (C-5), 35.1 (C-2); ESI-MS: *m/z* 432.7864 $(M+H)^+$, 454.5697 $(M+Na)^+$, 470.7429 $(M+K)^+$; HRMS:*m/z* calcd for $C_{27}H_{30}NO_4$ 432.2169, found 432.2166.

Procedure for the synthesis of galactolactam / (5*S*,6*R*)-4,5-Bis(benzyloxy)-6-(benzyloxymethyl)piperidin-2-one (195b):



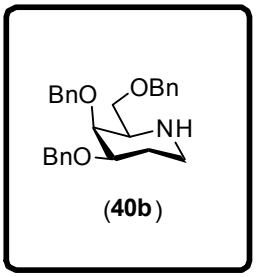
Following the same procedure as for the synthesis of (**195b**) the crude on SiO_2 column chromatography (EtOAc-petroleum ether, 4:6) afforded a colorless semi-solid **5b** (250 mg 59%); R_f 0.21 (EtOAc-petroleum ether); $[\alpha]^{20}_D$+29.43 (c1.1, $CHCl_3$); IR ($CHCl_3$): υ_{max} 3395, 3017, 2926, 1663, 1454, 1216, 1114, 756, 698, 668 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ_H 7.40-7.25 (m, 15H, Ar*H*), 6.06 (bs, 1H, N*H*) 4.97-4.39 (m, 6H, PhCH_2), 4.00 (bs, 1H, H-4), 3.89-3.79 (ddd, 1H, *J* = 10.6, 6.3, 1.6 Hz, H-5), 3.59-3.48 (m, 3H, H-6, H-3), 2.91-2.63 (m, 2H, H-2); ^{13}C NMR (50 MHz, $CDCl_3$): δ_C 170.2 (C-1), 138.1, 137.7, 137.4 (Ar), 128.6, 128.6, 128.4, 128.0, 128.0, 127.9, 127.8, 127.5 (Ar), 75.6 (C-4), 73.9, 73.6, 71.7 (C- 3), 70.9, 70.6 (Ph*C*H_2, C-6), 54.9 (C-5), 33.7 (C-2); ESI-MS: *m/z* 432.3909 $(M+H)^+$, 454.3993 $(M+Na)^+$, 470.3436 $(M+K)^+$; HRMS: *m/z* calcd for $C_{27}H_{29}NO_4$ 432.2169, found 432.2170.

Preparation of tri-*o*-benzyl fagomine / (2*R*,3*R*,4*R*)-3,4-Bis(benzyloxy)-2-(benzyloxymethyl)piperidine (40a): To a solution of (**195a/b**) (256 mg, 0.594 mmol) in THF (15 mL), LAH (68 mg, 3 eqs.) was added. The reaction mixture was stirred for 4h at 70°C under nitrogen atmosphere. The mixture was then brought to room temperature and poured into a mixture of diethyl ether and ice water (1:1, 100 mL). After stirring for 15 minutes, 0.5 M aq. NaOH (75 mL) was added and the mixture was stirred for another 10 minutes. The water layer was then separated and extracted with diethyl ether (3 x 50 mL), the organic fractions were pooled, washed with brine and finally dried (anhyd. Na_2SO_4) and concentrated in vacuo. The crude product was purified by SiO_2 column chromatography (EtOAc-petroleum ether, 1:1) to afford (**40a)** (120 mg, 49%) as a yellow syrup; R_f 0.12 (EtOAc-petroleum ether, 1:1); $[\alpha]^{20}_D$ +21.76 (*c* 1.1, $CHCl_3$); IR ($CHCl_3$):υ_{max} 3151, 3017, 2922, 1398, 1220, 1099, 772, 669, 615cm^{-1}; ^1H NMR (400



MHz, $CDCl_3$): δ_H7.37-7.22 (m, 15H, Ar*H*), 4.98-4.47 (m, 6H, PhCH_2), 3.71 (dd, 1H, *J* = 2.5, 9.0 Hz, H-6_a), 3.60-3.47 (m, 2H, H-6_b, H-3), 3.32 (t, 1H, *J* = 9.0 Hz, H-4), 3.09-2.99 (ddd, 1H, *J* = 1.8, 2.3, 12.6 Hz, H-1_a), 2.70 (ddd, m, *J* = 2.5, 6.3, 9.3 Hz, 1H, H-5), 2.55 (dt, 1H, *J* = 12.6, 2.3 Hz, H-1_b), 2.30 (bs, 1H, NH), 2.18-2.08 (m, 1H, H-2_a), 1.55-1. 41 (m, 1H, H-2_b); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 138.8, 138.7, 138.2 (Ar), 128.4, 128.4, 128.4, 128.1, 127.9, 127.7, 127.7, 127.6, 127.6 (Ar), 82.5 (C-3), 80.8 (C-4), 75.2, 73.4, 71.5 (Ph*C*H_2), 70.7 (C-6), 60.1 (C-5), 43.6 (C-1), 32.1 (C-2); ESI-MS: *m/z* 418.4191 $(M+H)^+$; HRMS: *m/z* calcd for $C_{27}H_{31}NO_3$ 418.2377, found 418.2378.

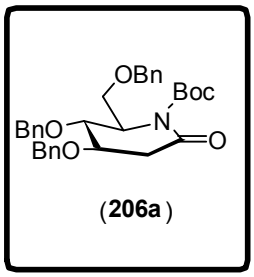
Preparation of tri-*o*-benzyl 4-*epi*-fagomine / (2*R*,3*S*,4*R*)-3,4-Bis(benzyloxy)-2-(benzyloxymethyl)piperidine (40b):



(**40b**)

To a solution of (**195b**) (242 mg, 0.58 mmol) in THF (15 mL), LAH (65 mg, 3 eq.) was added. The reaction mixture was stirred for 2h at 70 ^oC under nitrogen atmosphere. The reaction mixture was then brought to room temperature and poured into a mixture of diethyl ether and ice water (1:1, 100 mL). After stirring for 15 minutes, aq. NaOH (0.5 M, 75 mL) was added and the reaction mixture was stirred for another 10 minutes. The water layer was then separated and extracted with diethyl ether (3 x 50 mL), the organic fractions were pooled and washed with brine (1 x 30 mL) and dried (anhyd. Na_2SO_4). After concentration in vacuo, the reaction mixture was purified by SiO_2 column chromatography (EtOAc-petroleum ether, 1:1) to afford (**40b**) (95 mg, 41%) as a yellow syrup; R_f0.12 (EtOAc-petroleum ether); $[\alpha]^{20}_D$ -4.07 (*c* 1.0, $CHCl_3$); IR ($CHCl_3$): υ_{max} 3302, 3089, 3066, 3019, 2929, 1455, 1365, 1216, 1088, 751, 699, 669 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.39-7.24 (m, 15H, Ar*H*), 4.94-4.39 (m, 6H, PhCH_2), 3.93 (bs, 1H, H-4), 3.56-3.49 (m,1H, H-6_a), 3.49-3.42 (m,1H, H-3), 3.42-3.37 (t, 1H, *J* = 8.5, 7.8 Hz, H-6_b), 3.27 (1H, bs, N*H*), 3.16-3.04 (dd, 1H, *J* = 13.3, 2.0 Hz, H-1_a), 2.78 (t, 1H, *J* = 6.8 Hz, H-5), 2.57 (dt, 1H, *J* = 12.8, 3.0 Hz, H-1_b), 2.02-1.87 (m, 1H, H-2_a), 1.79 (dd, 1H, *J* = 12.4, 2.2 Hz, H-2_b); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 139.1, 138.7, 138.0 (Ar), 128.4, 128.3, 128.2, 128.1, 127.9, 127.8, 127.7, 127.6, 127.5, 127.3, (Ar), 79.6 (C-3), 74.0, 73.4, , 73.3 (C-4), 70.3 C-6), 70.1 (Ph*C*H_2), 58.7 (C-5), 44.1 (C-1), 27.6 (C-2); ESI-MS: *m/z* 418.0585 $(M+H)^+$; HRMS: *m/z* calcd for $C_{27}H_{32}NO_3$ 418.2377, found 418.2377.

Preparation of *tert*-butyl (*2R*,*3R*,*4S*)-3,4-bis(benzyloxy)-2-((benzyloxy)methyl)-6-oxopiperidine-1-carboxylate (206a):

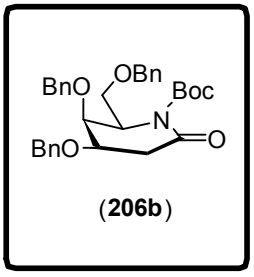


(**206a**)

Glycolactam (**195a**) (150mg, 0.35 mmol) was dissolved in DCM (10 mL), Et_3N (48.8 μL, 0.35 mmol) was added and cooled to 0°C, then Boc_2O (152 mg, 0.70 mmol) was added followed by DMAP (43 mg, 0.35 mmol) and stirred at 25°C till completion of the reaction (TLC). The reaction mixture was evaporated to dryness and subjected to SiO_2 column chromatography (EtOAC-Et_3N-petroleum ether, 5:2:93) to afford (**206a**) (175 mg, 95%) as an oily syrup; R_f 0.76 (EtOAc-petroleum ether, 1:1); $[\alpha]^{25}_D$-49.53 (*c* 1.12, $CHCl_3$); IR ($CHCl_3$): υ_{max} 3021, 2978, 2402, 2360, 1767, 1718, 1511, 1220, 1034, 789, 734, 670 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ_H 7.37-7.13 (m, 15H, Ar*H*), 4.65 (s, 2H), 4.55 (s, 2H), 4.51 (brs, 1H), 4.45 (s, 2H), 4.07-3.98 (m, 1H), 3.95-3.78 (m, 1H), 3.67 (dd, *J* = 6.9, 9.3 Hz, 1H), 3.53 (dd, *J* = 4.1, 9.3 Hz, 1H), 2.86 (dd, *J* = 4.9, 16.8 Hz, 1H), 2.64 (dd, *J* = 8.9, 16.5 Hz, 1H), 1.48 (s, 9H); ^{13}C NMR (50 MHz, $CDCl_3$): δ_C 169.6, 152.1, 137.8, 137.7, 128.5, 128.4, 128.0, 127.9, 127.8, 127.7, 127.6, 127.4, 83.3, 75.5, 73.2, 72.2, 71.6, 70.3, 59.0, 37.6, 28.0; ESI-MS: *m/z* 554.23 $(M+Na)^+$; HRMS: *m/z* calcd for $C_{32}H_{37}NO_6Na$ 554.2513 $(M+Na)^+$, found 554.2513.

Preparation of *tert*-butyl (*2R*,*3S*,*4S*)-3,4-Bis(benzyloxy)-2-((benzyloxy)methyl)-6-oxopiperidine-1-carboxylate (206b):

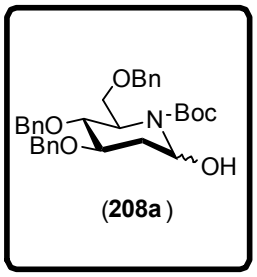
Similarly (**206b**) was obtained from (**195b**) by following above-mentioned procedure. The crude reaction mixture was purified by SiO_2 column chromatography (EtOAC-Et_3N-petroleum ether, 5:2:93) to afford (**206b**) as an oily syrup (143 mg, 79%); R_f 0.57 (EtOAc-petroleum ether, 1:1); $[\alpha]^{25}_D$+1.16 (*c* 1.14, $CHCl_3$); IR ($CHCl_3$): υ_{max} 3014, 2362, 1741, 1707, 1657, 1516, 1265, 1033, 812, 759, 674 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ_H 7.34-7.24 (m, 15H), 4.86-4.46 (m, 6H), 4.40-4.30 (m, 1H), 4.16-4.13 (m, 1H), 3.92-3.85 (m, 2H), 3.77-3.69 (m,1H), 3.02-2.89 (dd, 1H, *J* = 17.2, 9.2 Hz), 2.77-2.66 (dd, 1H, *J* = 17.2, 5.7 Hz), 1.45 (s, 9H); ^{13}C NMR (50 MHz, $CDCl_3$): δ_C 168.6, 152.5, 138.1, 138.0, 137.8,



(**206b**)

128.5, 128.4, 128.0, 127.7, 127.5, 83.7, 73.7, 73.5, 73.3, 73.1, 71.4, 68.9, 57.1, 37.0, 27.8; ESI-MS: *m/z* 554.27 $(M+Na)^+$; HRMS: *m/z* calcd for $C_{32}H_{37}NO_6Na$ 554.2513 $(M+Na)^+$, found 554.2521.

Preparation of *tert*-butyl (*2R,3R*)-3,4-bis(benzyloxy)-2-((benzyloxy)methyl)-6-hydroxypiperidine-1-carboxylate (208a):

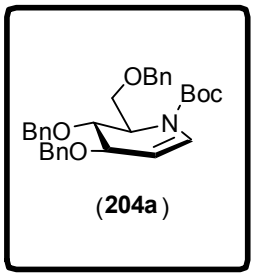


(**208a**)

N-Boc protected lactam (**206a**) (100 mg, 0.188 mmol) was dissolved in dry toluene (5.0 mL) and cooled to -76°C under inert atmosphere, and superhydride (1.0 M in THF) (0.21 mL, 1.12 eq) was added slowly drop wise over a period of 10 min, and stirred at -76°C for 1 h. Saturated NH_4Cl soln (4.0 mL) was added and stirred further for 1.5 h at -76°C, and then temp was raised to room temperature and stirred at room temperature for 10h. Reaction mixture was then treated with 10% Na_2CO_3 soln (4.0 mL) and DCM (10 mL) was added to the reaction mixture. The organic layer was separated, and the aq. layer was extracted with DCM (3 x 5 mL). All the organic layers were pooled together, dried (anhyd. Na_2SO_4), concentrated in vacuo and finally purified by SiO_2 column chromatography (EtOAC-Et_3N-petroleum ether, 5:1:44) to afford (**208a**) as a viscous oil (94 mg, 94%); R_f 0.38 (EtOAc-petroleum ether, 3:7); $[\alpha]^{25}_D$-47.44 (*c*1.21, $CHCl_3$); IR ($CHCl_3$): υ_{max} 3741, 3019, 2362, 2334, 1692, 1531, 1216, 757, 695, 672 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ_H 7.30-7.25 (m, 15H), 5.64 (brs, 1H), 4.71-4.48 (m, 6H), 4.05-4.01 (m, 2H), 3.85-3.68 (m, 2H), 3.62-3.50 (m, 1H), 2.26-2.15 (m, 1H), 2.04-1.90 (m, 1H), 1.69 (brs, 1H), 1.46 (s, 9H); ^{13}C NMR (50 MHz, $CDCl_3$): δ_C 156.7, 138.2, 138.1, 137.5, 128.5, 128.4, 128.0, 127.7, 127.7, 127.5, 80.8, 77.3, 74.8, 73.2, 72.9, 71.7, 71.5, 30.9, 28.4; ESI-MS: *m/z* 556.27 $(M+Na)^+$; HRMS: *m/z* calcd for $C_{32}H_{39}NO_6Na$ 556.2670, found 556.2670.

Preparation of *tert*-butyl (2*R*,3*R*)-3,4-bis(benzyloxy)-2-((benzyloxy)methyl)-3,4-dihydropyridine-1(2*H*)-carboxylate (204a):

N-Boc protected lactams (**206a**) (136 mg, 0.26 mmol) was dissolved in dry toluene (3 mL) and cooled to -70°C under inert atmosphere, and superhydride (1.0 M in THF) was added slowly drop wise over a period of 10 min, and stirred at -70°C for 30 min. TFAA (0.31 mL, 2.2 mmol) was added followed by addition of DIPEA (1.5 mmol) and catalytic amount of DMAP.

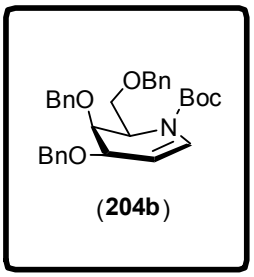


(**204a**)

Temperature is then raised from -70°C to room temperature in 8h and stirred further for 3h at 25°C. Water was added (10 mL), organic layer was separated, washed with water (2x 10 mL), dried (anhyd. Na_2SO_4), concentrated in vacuo and purified by SiO_2 column chromatography (EtOAC-Et_3N-petroleum ether, 3:2:95) to afford (**204a**) as a viscous oil (119 mg, 90%); R_f 0.57 (EtOAc-petroleum ether, 1:1); $[\alpha]^{25}_D$-97.97 (*c*1.10, $CHCl_3$); IR ($CHCl_3$): υ_{max} 3739, 3426, 2362, 2334, 1645, 1547, 1365, 924, 800, 699 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ_H 7.35-7.24 (m, 15H), 7.11-6.93 (m, 1H), 5.10-4.90 (m, 1H), 4.74-4.56 (m, 3H), 4.52-4.39 (m, 4H), 4.19-4.13 (m, 1H), 3.86-3.57 (m, 3H), 1.54-1.49 (m, 9H); ^{13}C NMR (125 MHz, $CDCl_3$, mixture of isomers): δ_C 152.3, 138.8, 138.6, 138.3, 138.0, 128.6, 128.5, 128.4, 128.2, 127.7, 127.4, 127.3, 126.9, 126.6, 101.5, 81.5, 81.4, 77.9, 77.8, 75.6, 75.1, 73.1, 72.9, 72.9, 72.8, 72.7, 71.9, 71.5, 71.2, 71.1, 70.9, 70.7, 70.4, 70.2, 68.4, 66.9, 66.8, 66.5, 66.0, 28.2, 28.1, 27.9; ESI-MS: *m/z* 538.27 $(M+Na)^+$; HRMS: *m/z* calcd for $C_{32}H_{37}NO_5Na$ 538.2564, found 538.2564.

Preparation of *tert*-butyl (*2R,3S*)-3,4-bis(benzyloxy)-2-((benzyloxy)methyl)-3,4-dihydropyridine-1(2H)-carboxylate (204b):

Similarly (**204b**) was obtained from (**206b**) (283 mg, 0.533 mmol) by following the same procedure described above as a pale yellow viscous oil (238 mg, 87%) after purification by SiO_2 column chromatography (EtOAC-Et_3N-petroleum ether, 3:2:95); R_f 0.57 (EtOAc-petroleum ether, 1:1); $[\alpha]^{25}_D$-56.21 (*c* 1.13, $CHCl_3$); IR ($CHCl_3$): υ_{max} 3740, 3620, 2362, 2334, 1647, 1547, 1367, 921, 821, 678 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ_H 8.29 (m, 1H), 7.35-7.22 (m, 15H), 4.89-4.77 (m, 2H), 4.70-4.61 (m, 3H), 4.52-4.29 (m, 2H), 3.99-3.95 (m, 2H), 3.85-3.73 (m, 1H), 3.64-3.44 (m, 1H), 1.48-1.46 (m, 9H); ^{13}C NMR (50 MHz, $CDCl_3$): δ_C 150.9, 138.8, 138.3, 137.5, 128.6, 128.5, 128.2, 128.1, 128.1, 127.7,

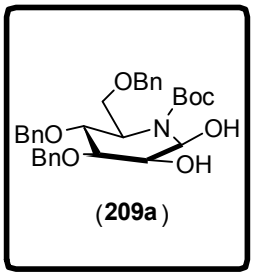


(**204b**)

127.7, 127.6, 127.5, 127.4, 110.5, 75.6, 75.1, 72.9, 71.6, 68.5, 67.7, 63.8, 62.8, 58.0, 27.7; ESI-MS: *m/z* 538.08 $(M+Na)^+$; HRMS: *m/z* calcd for $C_{32}H_{37}NO_5Na$ 538.2564, found 538.2565.

Preparation of *tert*-Butyl (*2R,3R,5S,6S*)-3,4-bis(benzyloxy)-2-((benzyloxy)methyl)-5,6-dihydroxypiperidine-1-carboxylate (209a):

$(DHQD)_2AQN$ (4.16 mg, 0.00485 mmol, 5 mol%), $K_3Fe(CN)_6$ (96 mg, 0.291 mmol, 3 eq), K_2CO_3 (93.7 mg, 0.679 mmol, 70 eq), and $K_2OsO_2(OH)_4$ (2 mg, 0.00543 mmol, 5.59 mol%) were dissolved in *tert*-butyl alcohol and water (5 ml each) at room temperature. $CH_3SO_2NH_2$ (18.43 mg, 0.194 mmol, 2.0 eq) was added. The solution was cooled to 0 °C and Boc-iminoglycal (**204a**) was added (50 mg, 0.097 mmol). The mixture was stirred at 0 °C for 60h. In the work up Na_2SO_3 (200 mg) was slowly added and the suspension was warmed to room temperature with vigorous stirring. Ethyl acetate was added and the aq. layer was further extracted with EtOAc (2x5 ml), the combined organic layers were washed with 2M NaOH (20 ml). The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo, which on preparative TLC separation (20% EtOAc-Pet ether) furnished (**209a**) (38 mg, 71%), R_f 0.23 (EtOAc-petroleum ether, 7:3); $[\alpha]^{25}_D$ -18.79 (*c* 1.15% , $CHCl_3$); υ_{max} $(CHCl_3)/cm^{-1}$, 667; δ_H (200 MHz, $CDCl_3$) 7.39-7.24 (m, 15H), 5.69-5.56 (m, 1H), 4.69-4.48 (m, 6H), 4.19-4.08 (m, 1H), 3.99-3.93 (m, 1H), 3.87-3.85 (m, 2H), 3.78-3.69 (m, 1H) , 3.63-3.55 (m, 1H), 2.74 (brs, 1H), 1.79 (brs, 1H), 1.53-1.47 (m, 9H); δ_C (50 MHz, $CDCl_3$) 155.4, 138.2, 137.9, 137.7, 128.6, 128.5, 128.4, 128.4, 128.4, 128.3, 128.2, 128.1, 128.0, 127.9, 127.9, 127.7, 127.5, 81.2, 81.1, 73.0, 72.8, 71.8, 71.6, 71.5, 70.0, 65.7, 28.3; ESI-MS: *m/z* 572.27 $(M+Na)^+$; HRMS: *m/z* calcd for $C_{32}H_{39}NO_7Na^+$ 572.2619, found 572.2621.

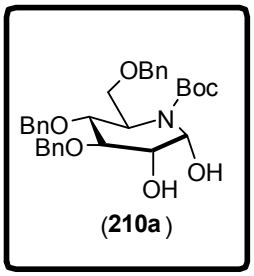


(**209a**)

Preparation of *tert*-Butyl (*2R,3R,5R,6R*)-3,4-bis(benzyloxy)-2-((benzyloxy)methyl)-5,6-dihydroxypiperidine-1-carboxylate (210a):

$(DHQ)_2AQN$ (5.0 mg, 0.0058 mmol, 5 mol%), $K_3Fe(CN)_6$ (118 mg, 0.358 mmol, 3 eq), K_2CO_3 (114 mg, 0.826 mmol, 70 eq), and $K_2OsO_2(OH)_4$ (2.5 mg, 0.0068 mmol, 5.59 mol%) were dissolved in *t*-butyl alcohol and water (6 ml each) at room temperature. $CH_3SO_2NH_2$ (23 mg, 0.242 mmol, 2.0 eq) was added. The solution was

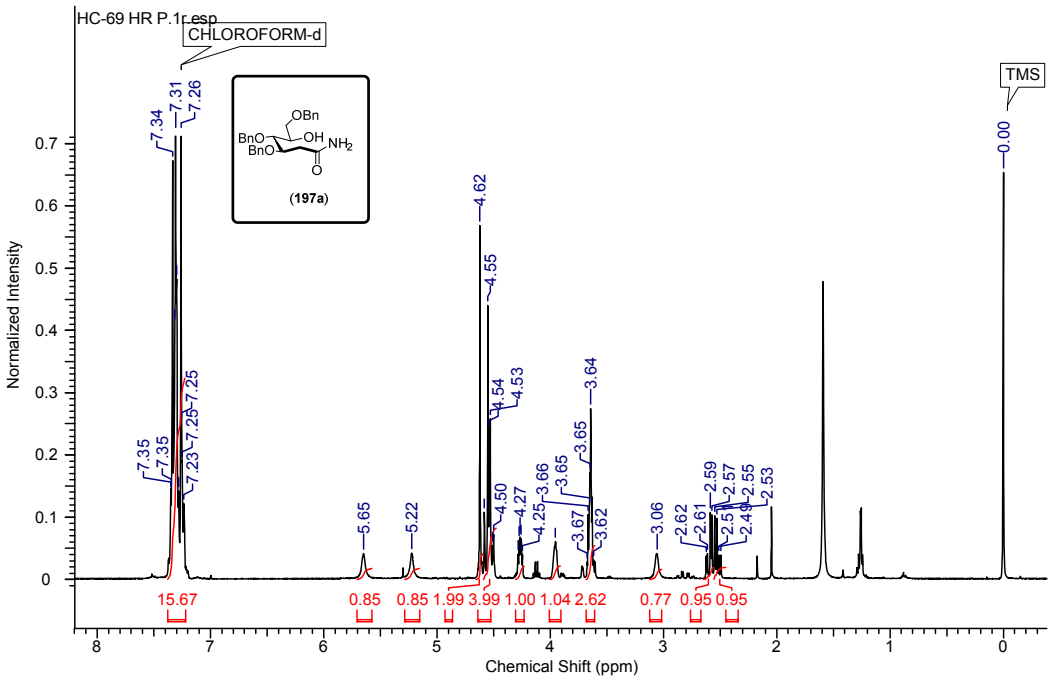
cooled to 0 °C and Boc-iminoglycal (**204a**) was added (61 mg, 0.118 mmol). The mixture was stirred at 0 °C for 66h. In the work up, Na_2SO_3 (200 mg) was slowly added and the suspension was warmed to room temperature with vigorous stirring. EtOAc was added and the aq layer was further extracted with ethyl acetate (2x5 ml), the combined organic layers were washed with 2M NaOH (20 ml). The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo, which on preparative TLC separation (EtOAc-petroleum ether, 7:3) furnished (**210a**) (20 mg, 30%), R_f 0.21 (EtOAc-petroleum ether, 7:3); $[\alpha]^{25}_D$ -13.33 (*c* 1.1%, $CHCl_3$); υ_{max} ($CHCl_3$)/cm^{-1} 3443, 3064, 2927, 2859, 2362, 2334, 1690, 1499, 1368, 1086, 757, 699, 669; δ_H (200 MHz, $CDCl_3$) 7.35-7.26 (m, 15H), 5.65-5.52 (m, 1H), 4.70-4.41 (m, 6H), 4.24-4.04 (m, 1H), 3.95-3.89 (m, 1H), 3.85-3.80 (m, 1H), 3.75-3.63 (m, 2H), 3.58-3.45 (m, 1H), 2.68 (brs, 1H), 1.68 (brs, 1H), 1.48-1.40 (m, 9H); δ_C (50 MHz, $CDCl_3$) 154.0, 138.0, 137.4, 137.3, 128.6, 128.5, 128.4, 128.4, 128.2, 128.2, 128.1, 128.0, 127.9, 127.8, 127.7, 127.5, 87.9, 81.3, 78.5, 77.3, 73.3, 73.0, 72.9, 72.4, 64.2, 61.3, 28.3; ESI-MS: *m/z* 572.26 $(M+Na)^+$; HRMS: *m/z* calcd for $C_{32}H_{39}NO_7Na^+$ 572.2619, found 572.2619.



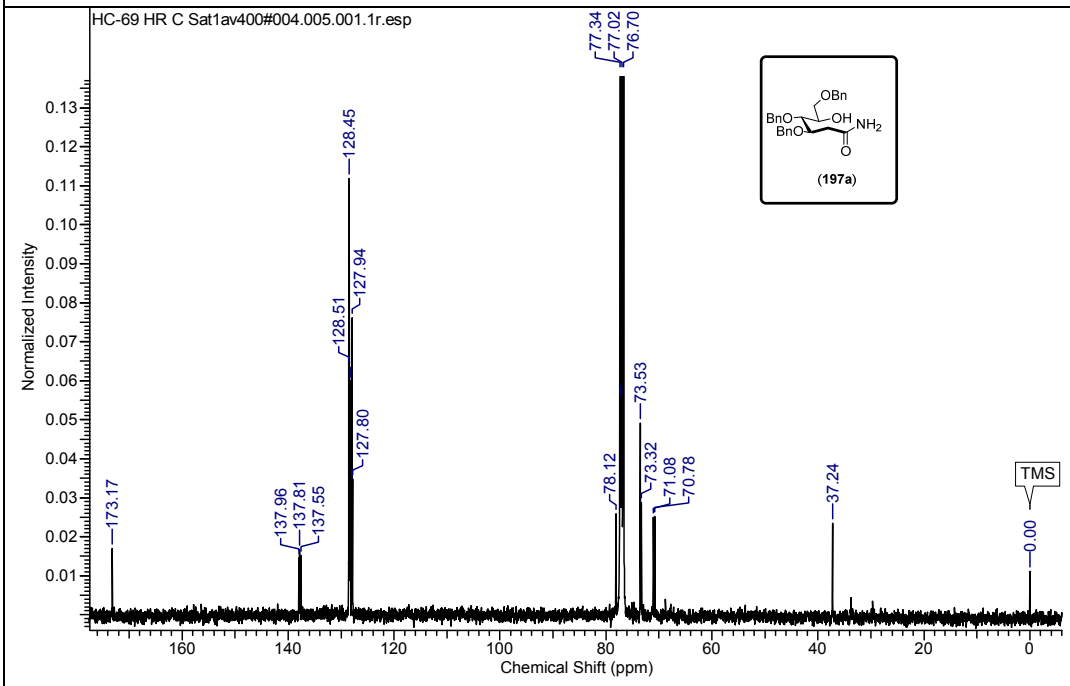
(**210a**)

1.1.5 Spectra

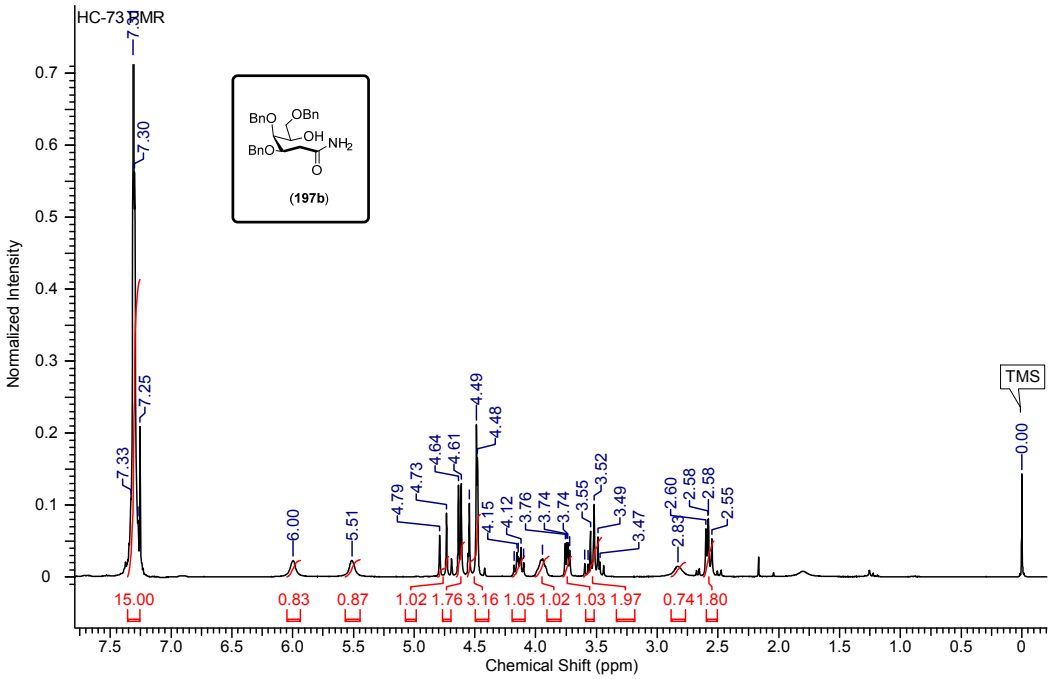
^{1}H NMR (400 MHz, $CDCl_3$) of (**197a**)



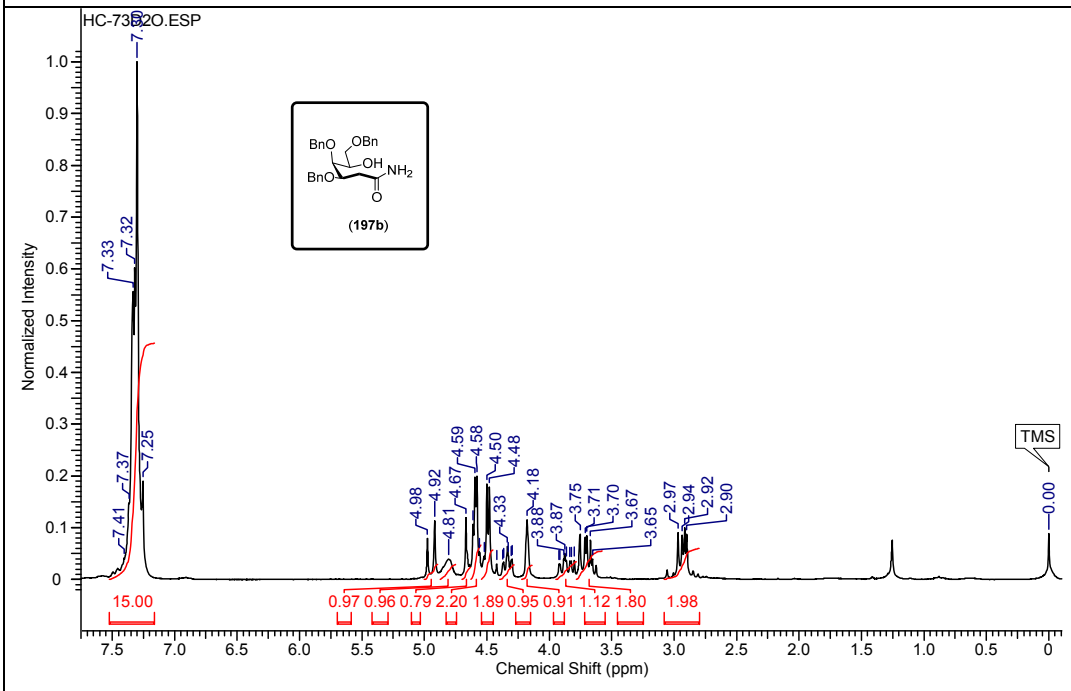
^{13}C NMR (100 MHz, $CDCl_3$) of (**197a**)



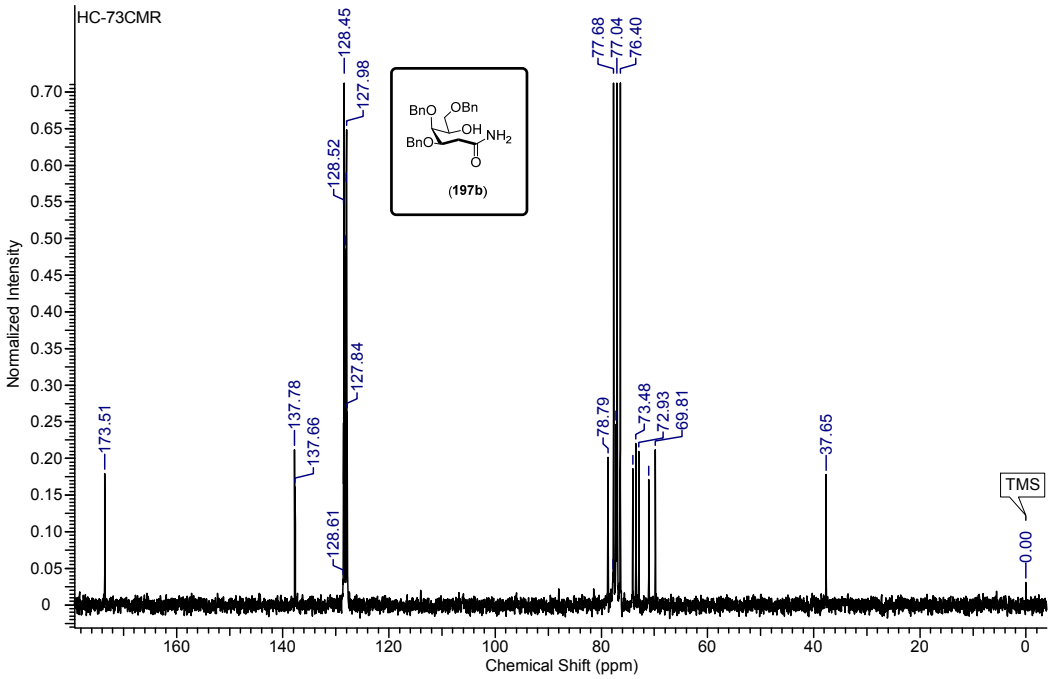
^{1}H NMR (200 MHz, $CDCl_3$) of (**197b**)



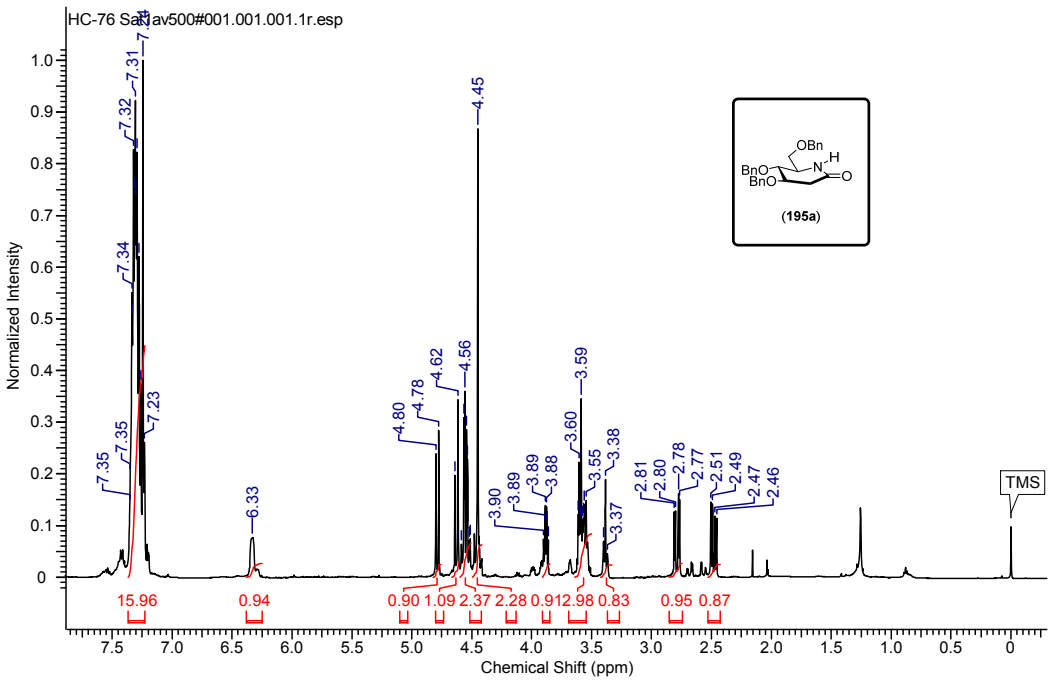
^{1}H NMR (100 MHz, $CDCl_3$) of (**197b**) D_2O exchange study



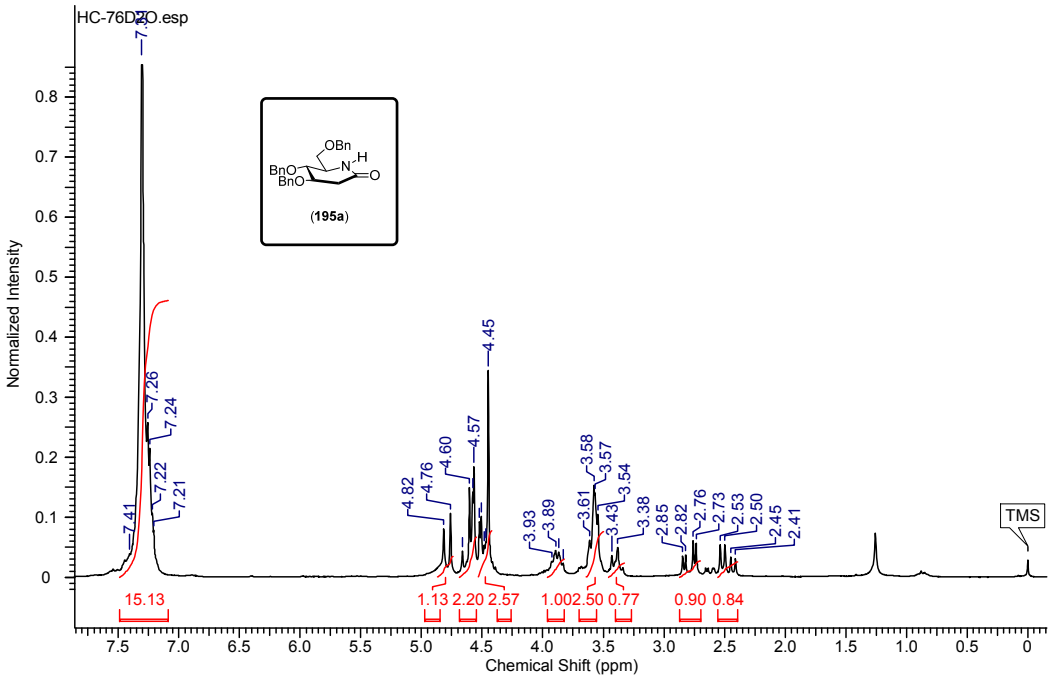
^{13}C NMR (50 MHz, $CDCl_3$) of (**197b**)



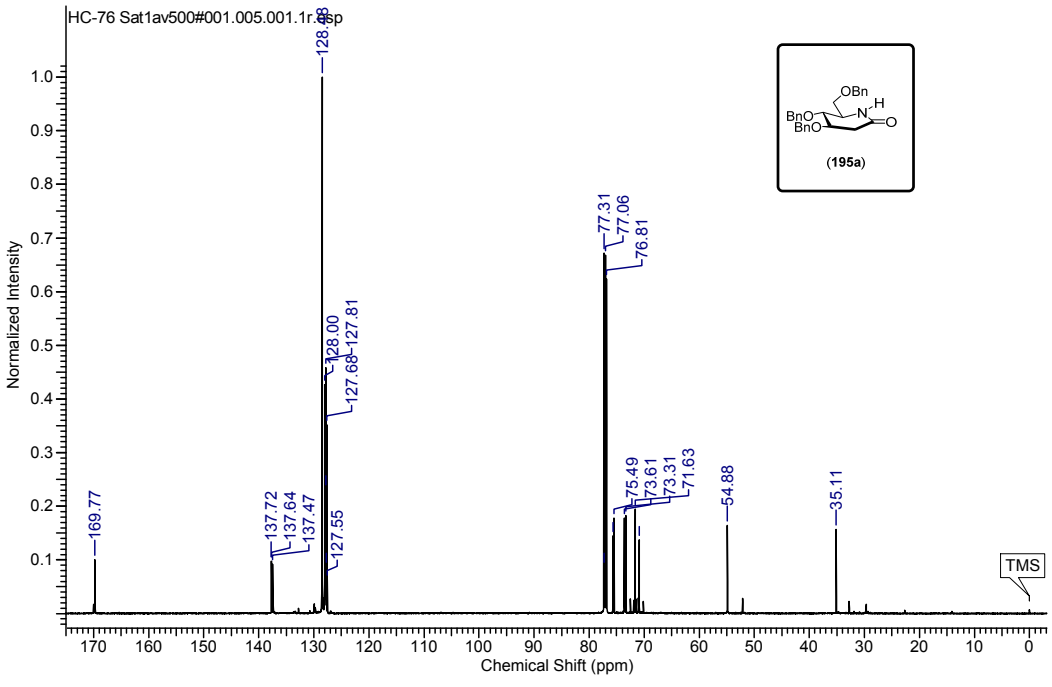
^{1}H NMR (500 MHz, $CDCl_3$) of (**195a**)



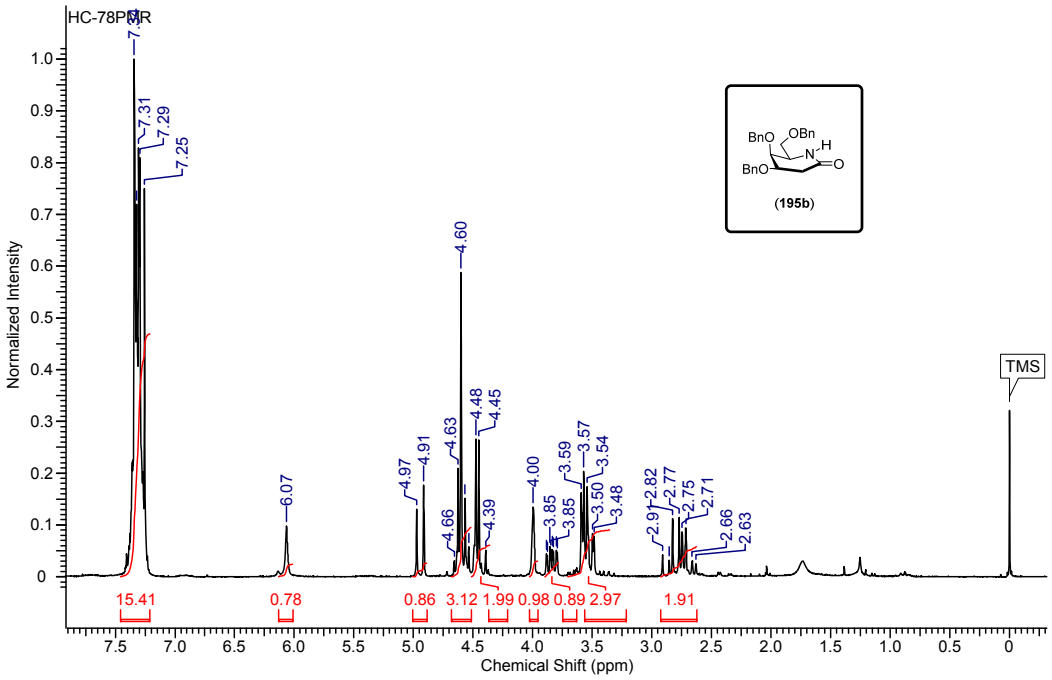
^{1}H NMR (200 MHz, $CDCl_3$) of (**195a**) D_2O exchange study



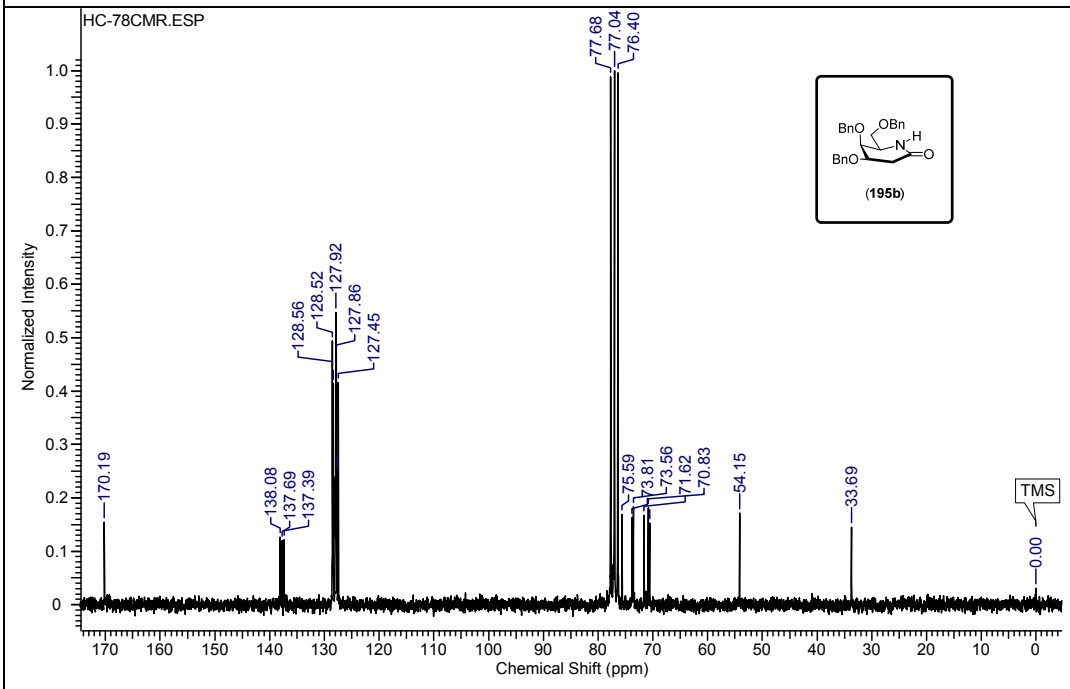
^{13}C NMR (125 MHz, $CDCl_3$) of (**195a**)



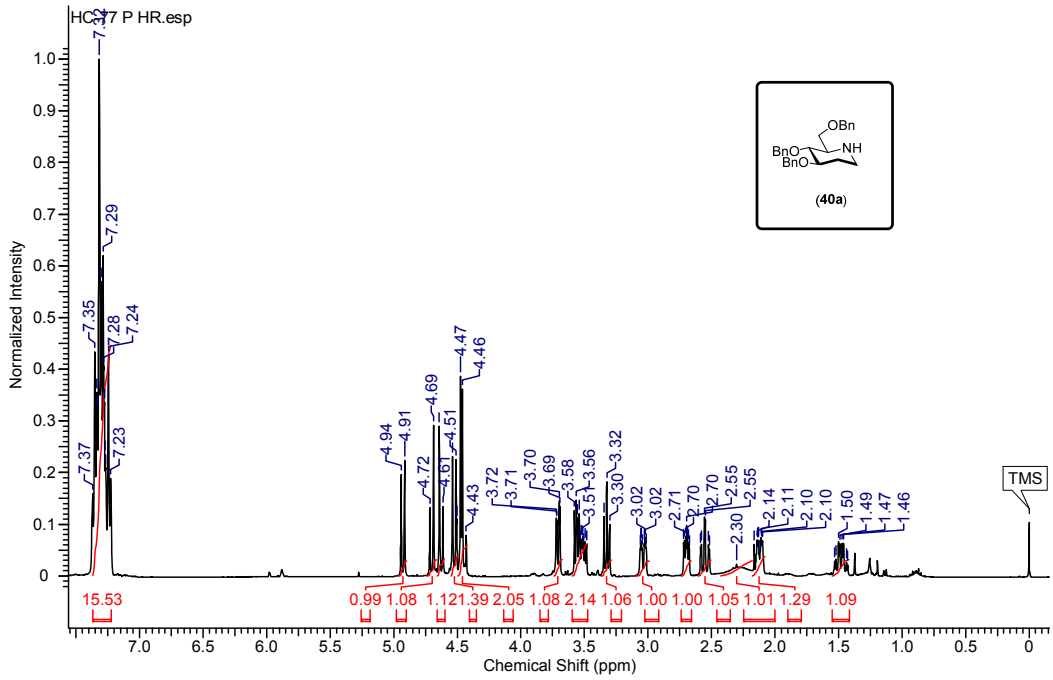
^{1}H NMR (200 MHz, $CDCl_3$) of (**195b**)



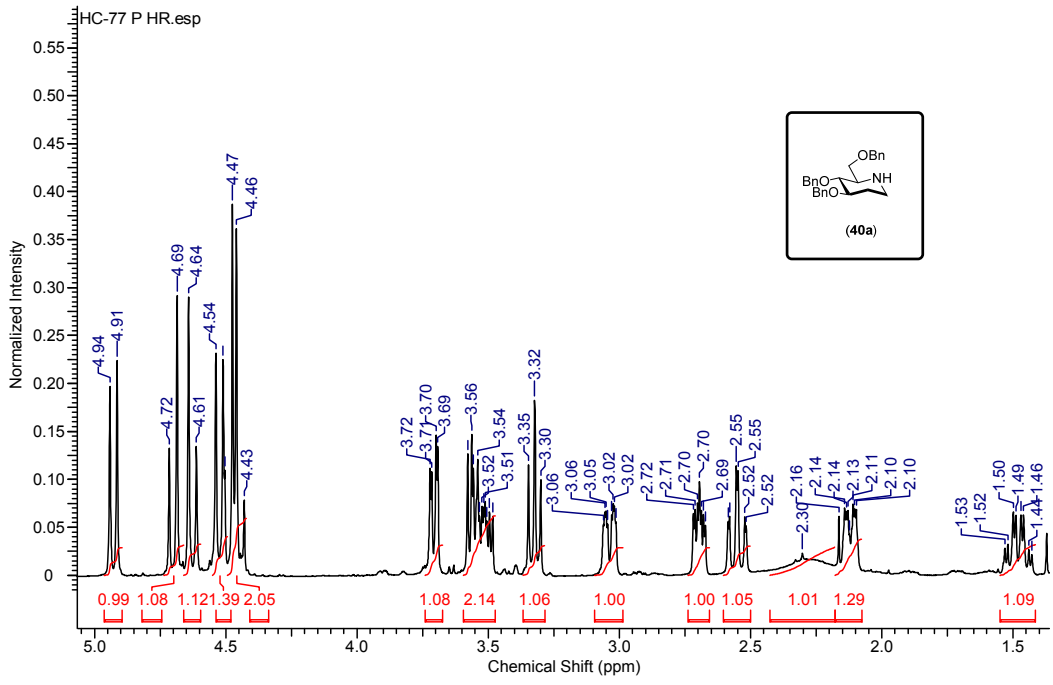
^{13}C NMR (50 MHz, $CDCl_3$) of (**195b**)



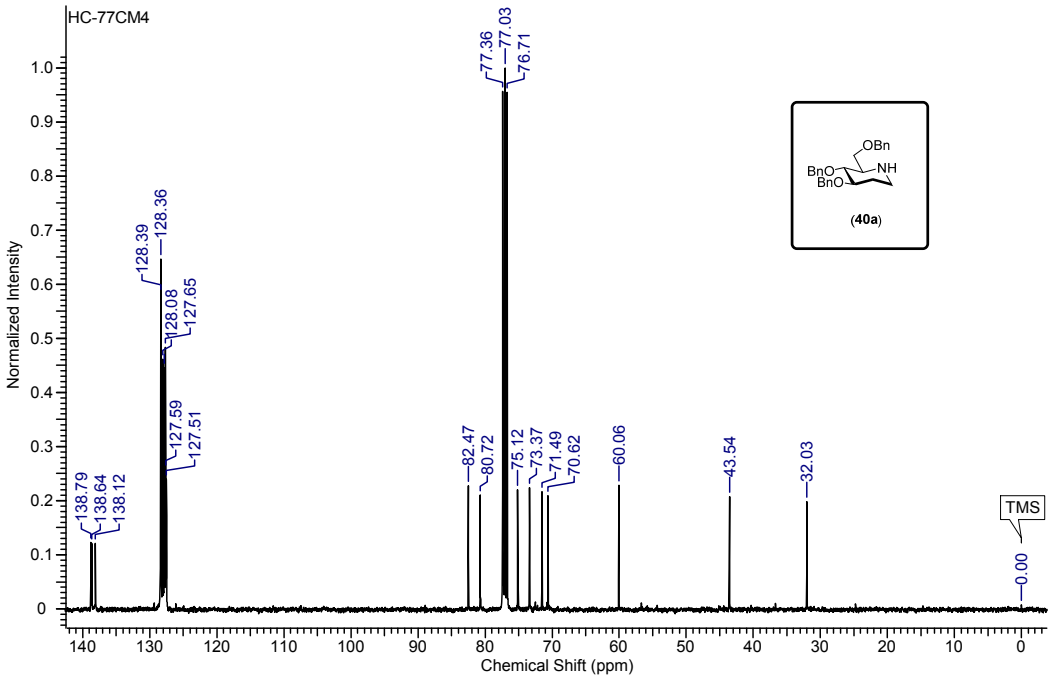
^{1}H NMR (400 MHz, $CDCl_3$) of (**40a**)



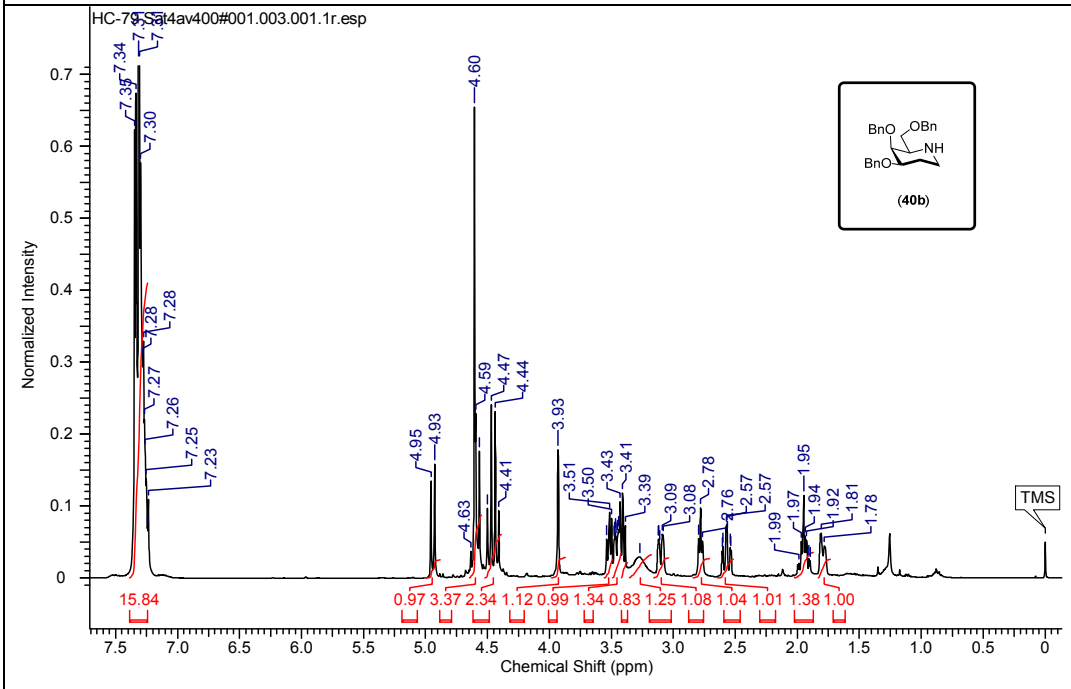
^{1}H NMR (400 MHz, $CDCl_3$) of (**40a**) Offset 5-1 ppm



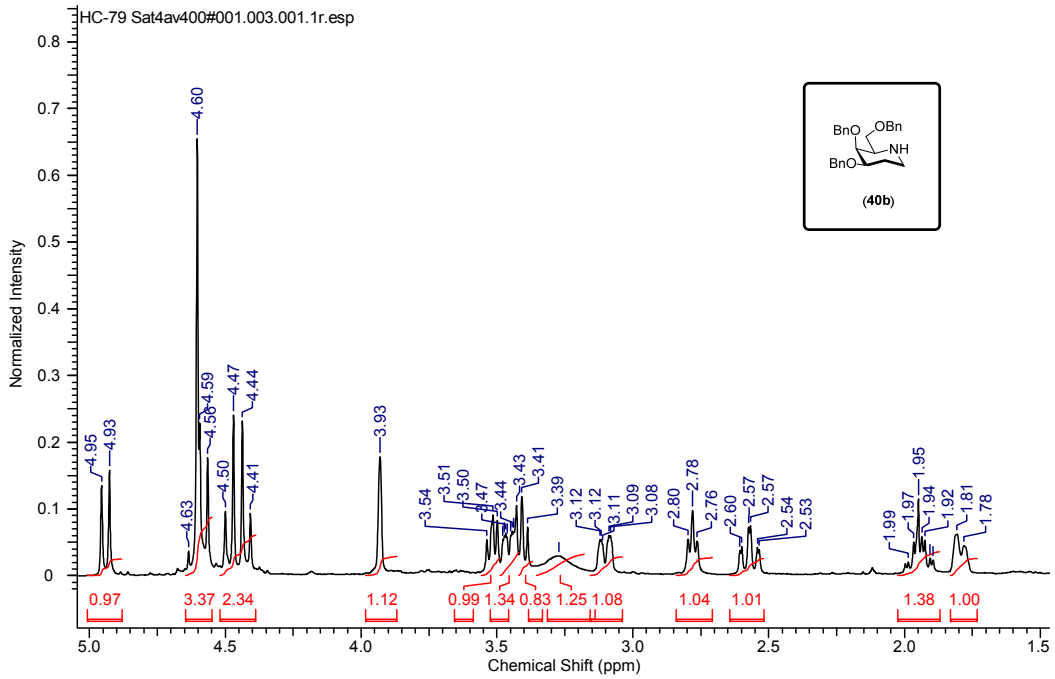
^{13}C NMR (100 MHz, $CDCl_3$) of (**40a**)



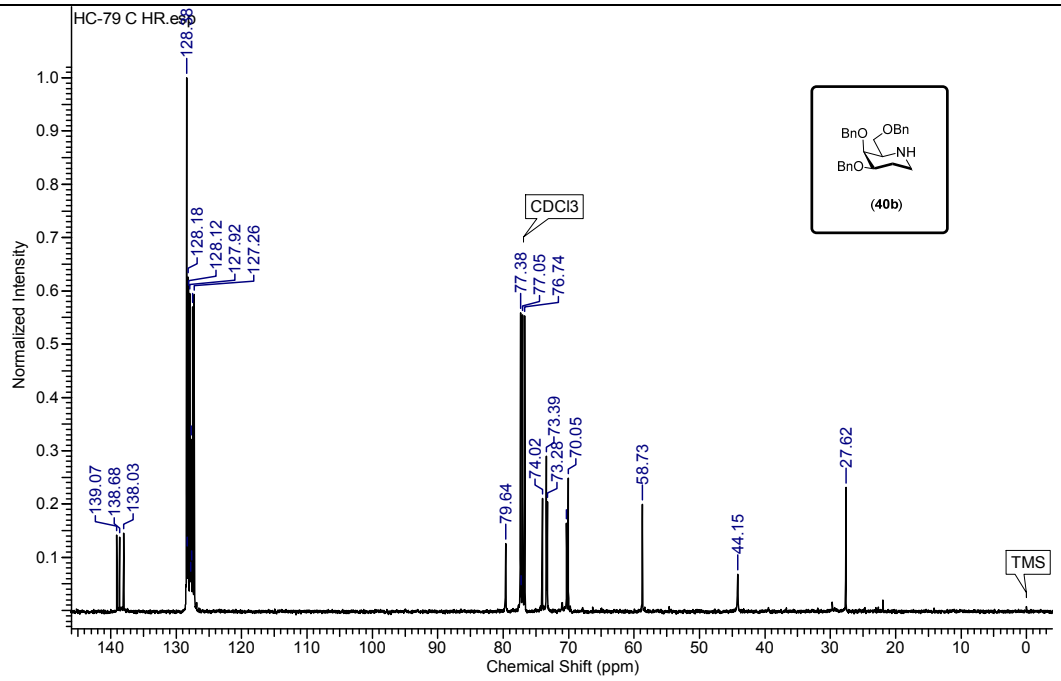
^{1}H NMR (400 MHz, $CDCl_3$) of (**40b**)



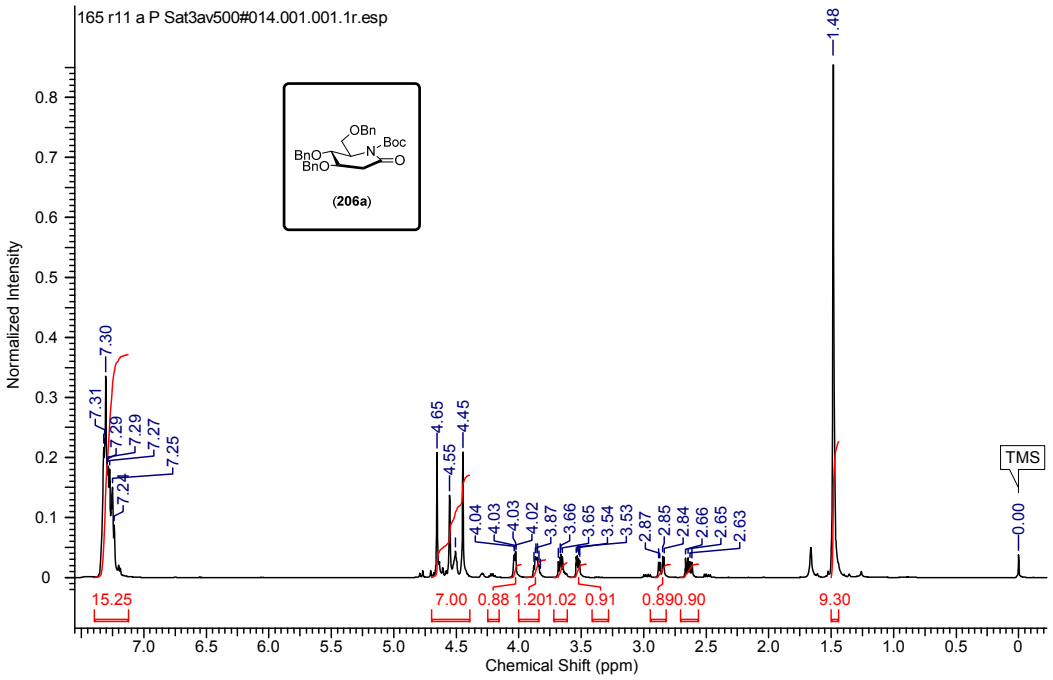
^{1}H NMR (400 MHz, $CDCl_3$) of (**40b**) Offset 5-1.5 ppm



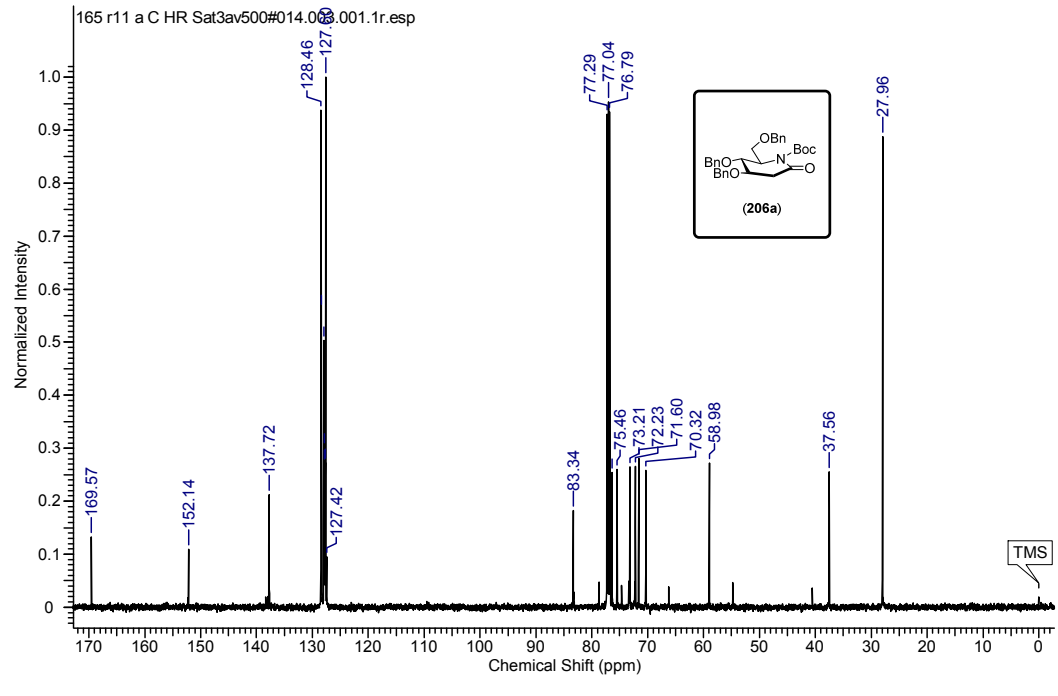
^{13}C NMR (100 MHz, $CDCl_3$) of (**40b**)



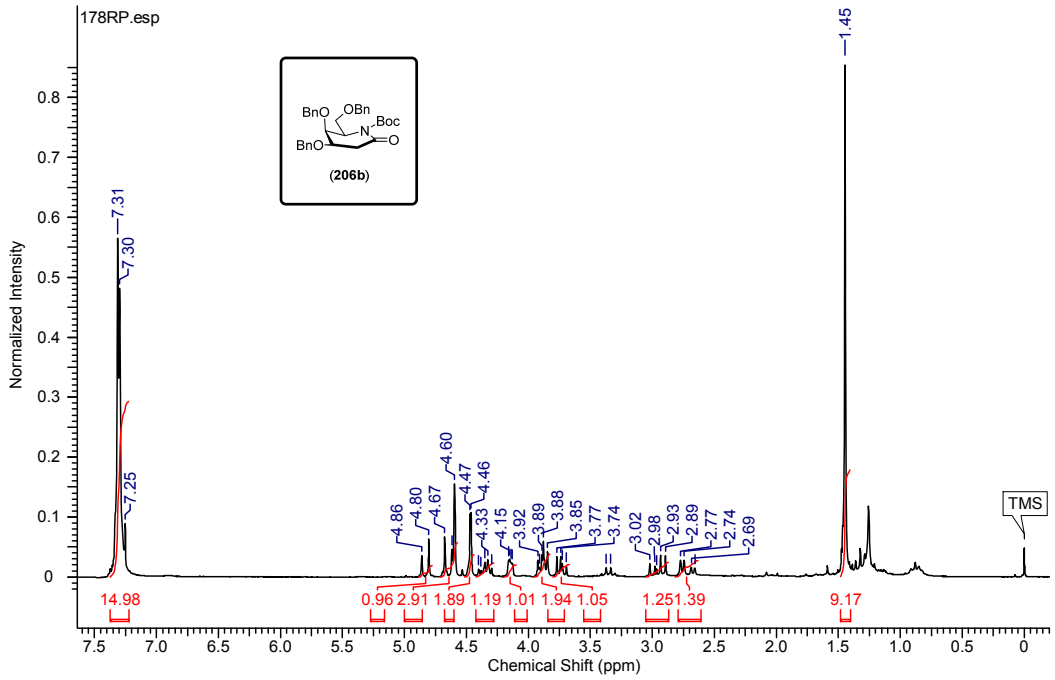
^{1}H NMR (500 MHz, $CDCl_3$) of (**206a**)



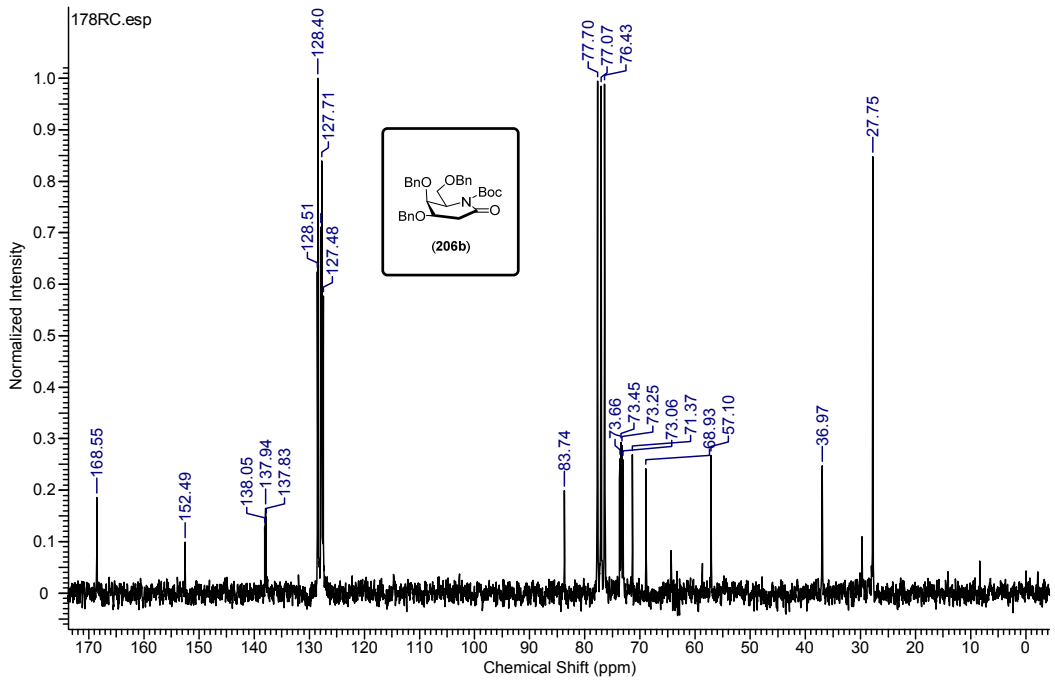
^{13}C NMR (125 MHz, $CDCl_3$) of (**206a**)



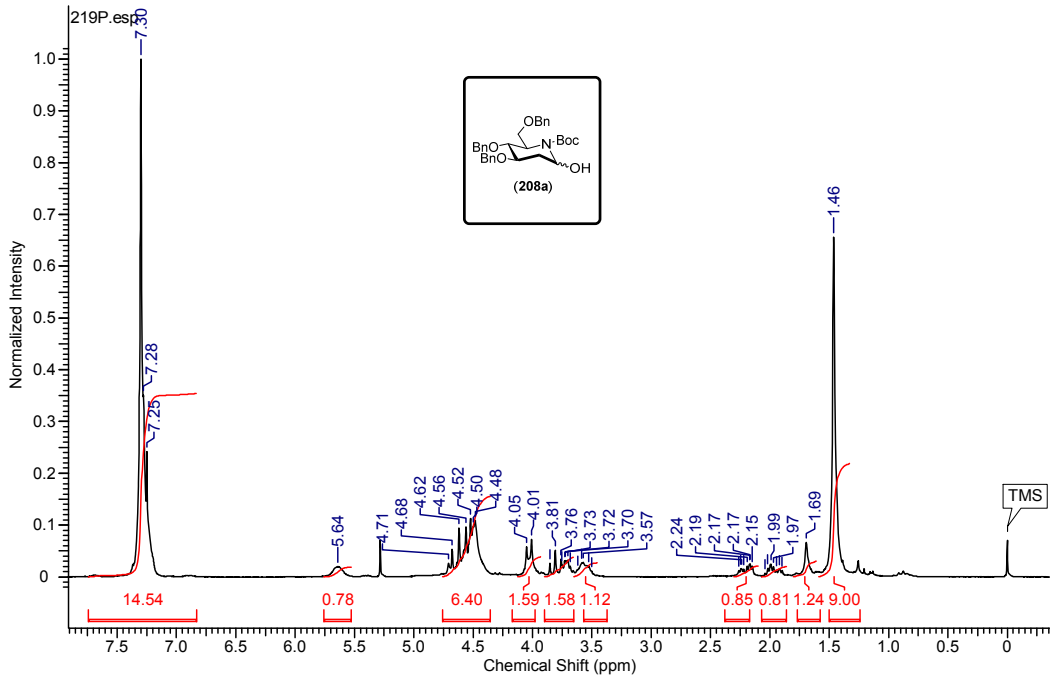
^{1}H NMR (200 MHz, $CDCl_3$) of (**206b**)



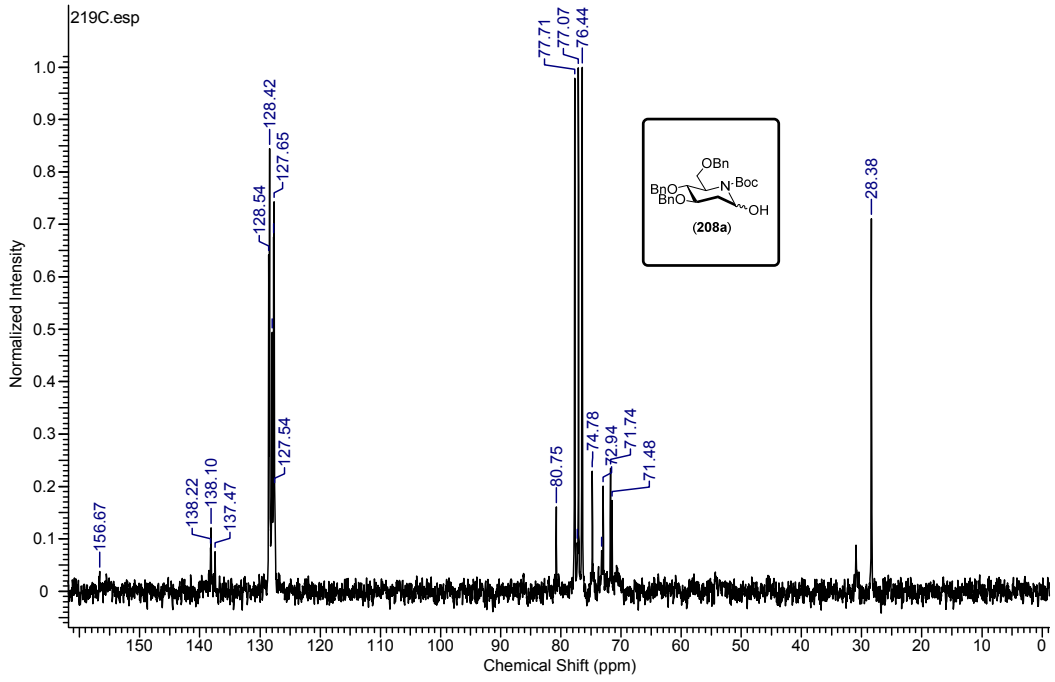
^{13}C NMR (50 MHz, $CDCl_3$) of (**206b**)



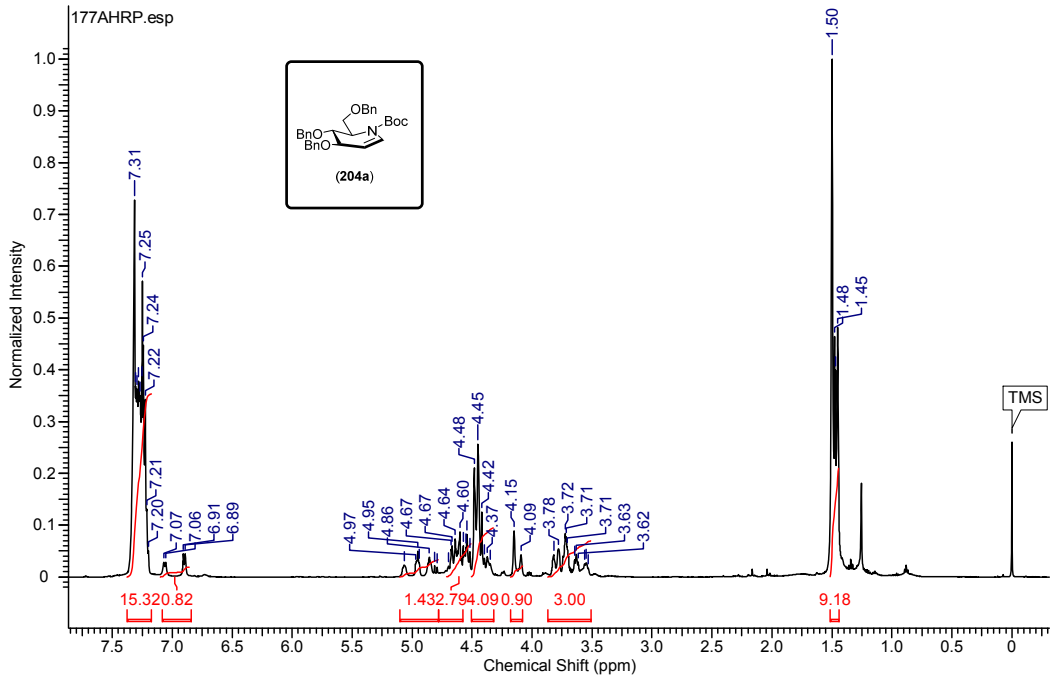
^{1}H NMR (200 MHz, $CDCl_3$) of (**208a**)



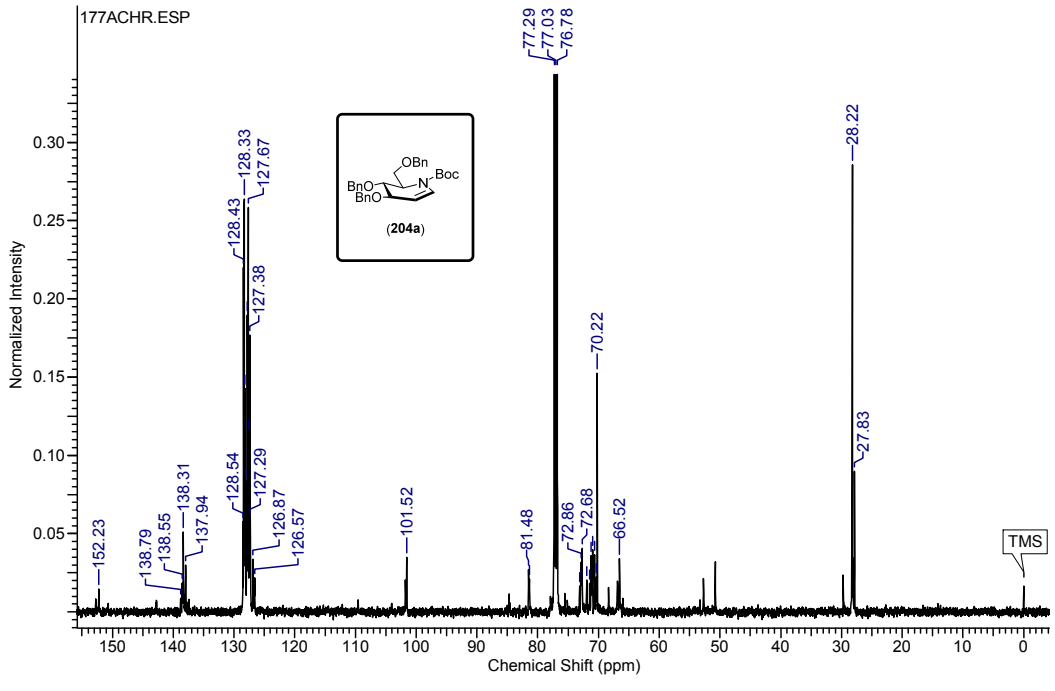
^{13}C NMR (50 MHz, $CDCl_3$) of (**208a**)



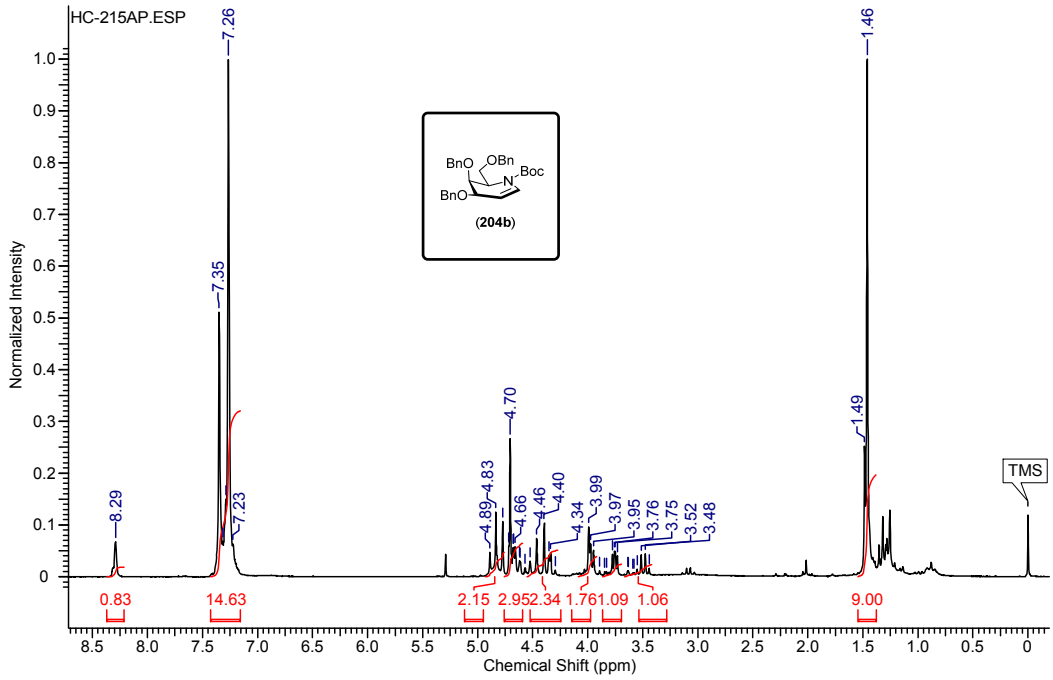
^{1}H NMR (500 MHz, $CDCl_3$) of (**204a**)



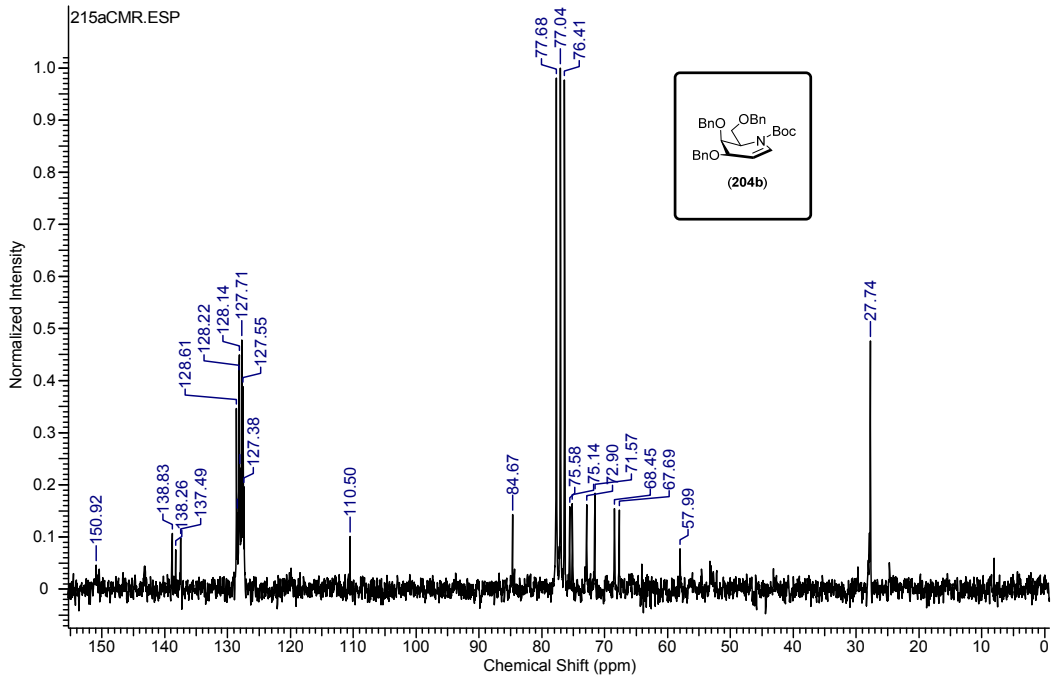
^{13}C NMR (125 MHz, $CDCl_3$) of (**204a**)



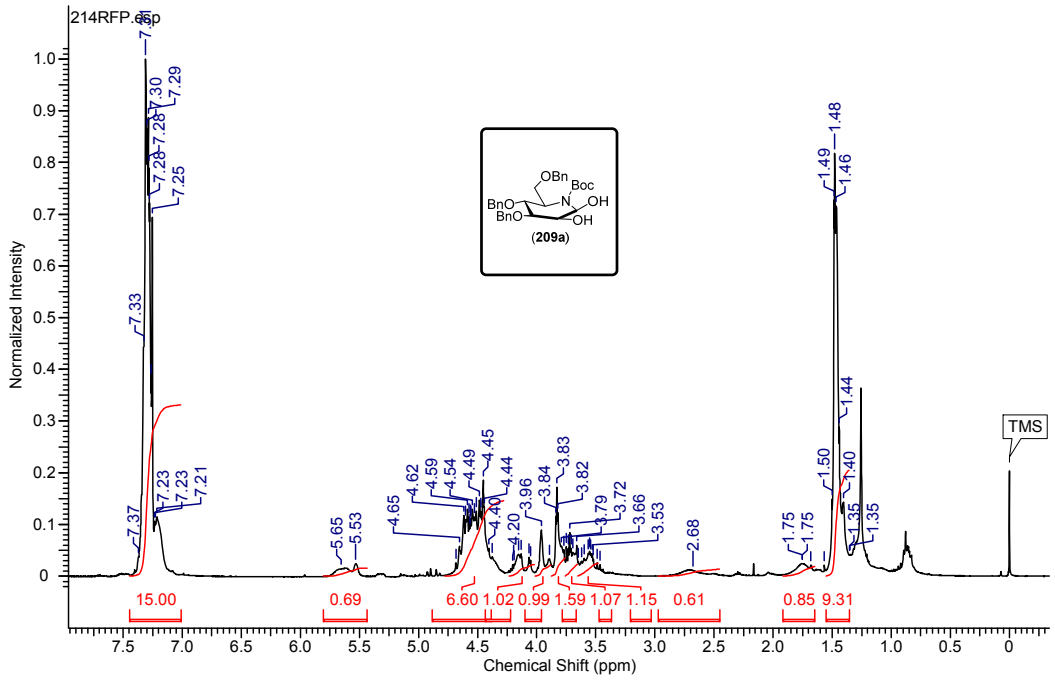
^{1}H NMR (200 MHz, $CDCl_3$) of (**204b**)



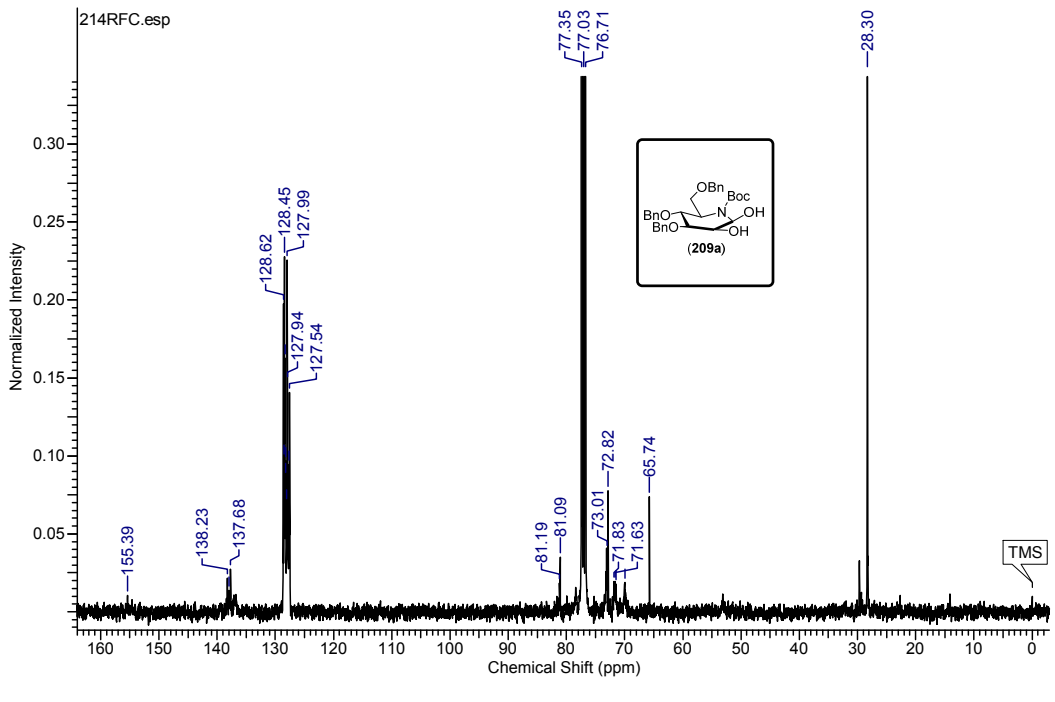
^{13}C NMR (50 MHz, $CDCl_3$) of (**204b**)



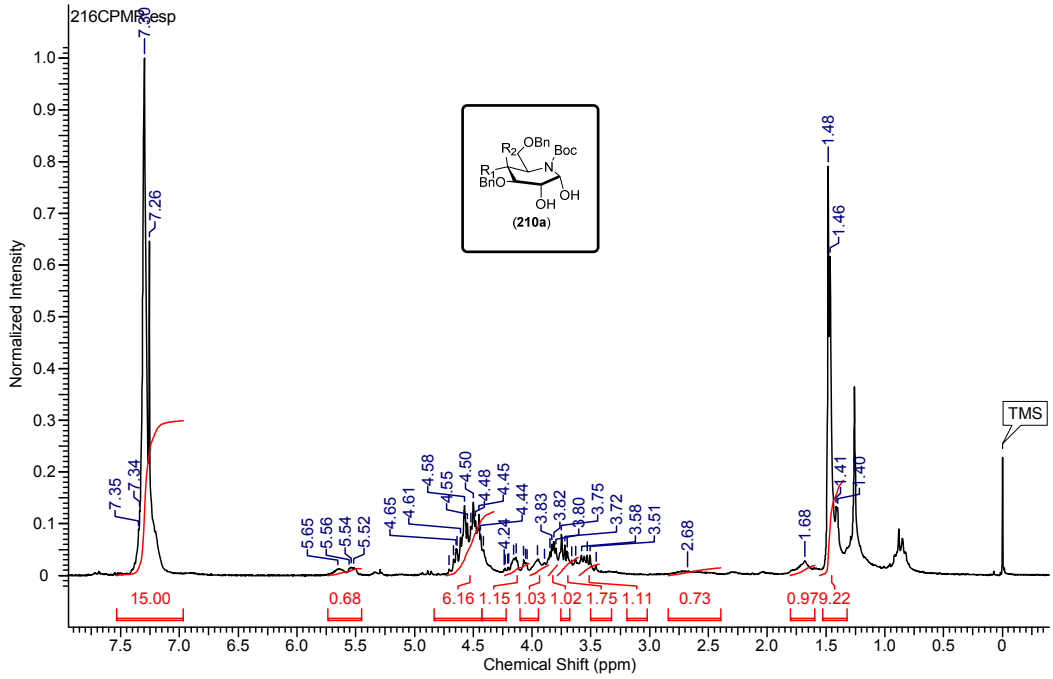
^{1}H NMR (400 MHz, $CDCl_3$) of (**209a**)



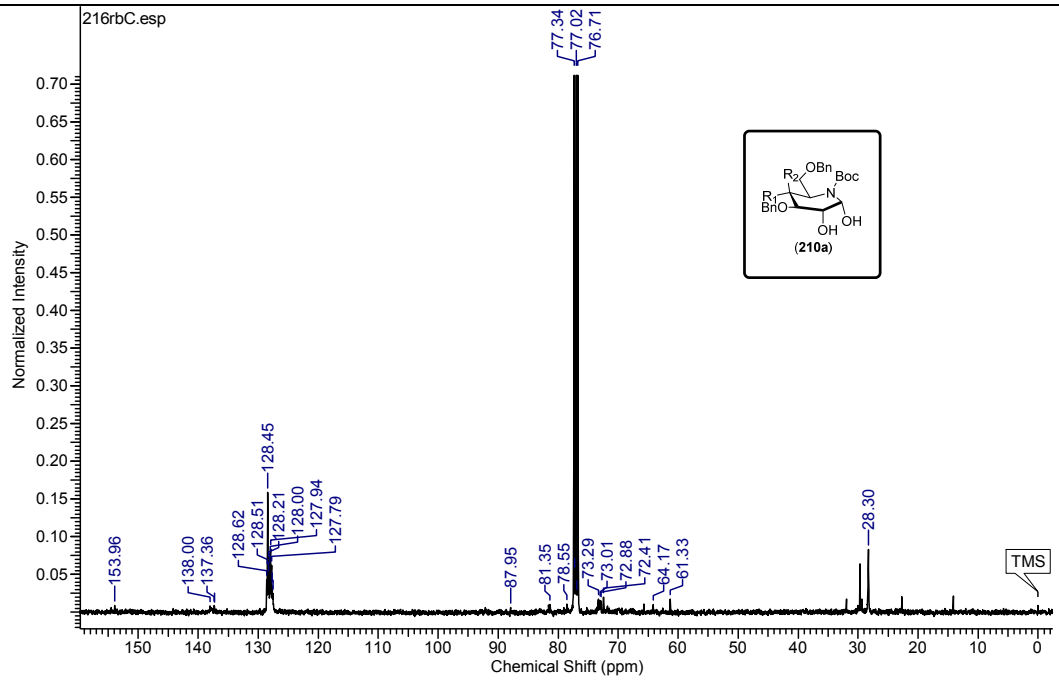
^{13}C NMR (100 MHz, $CDCl_3$) of (**209a**)



^{1}H NMR (400 MHz, $CDCl_3$) of (**210a**)



^{13}C NMR (100 MHz, $CDCl_3$) of (**210a**)



1.1.6 References

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Chapter 1

Approaches Towards the Synthesis of Polyhydroxylated Alkaloids using Carbohydrate Scaffolds

Section B

Novel Synthetic Methodology and its Applications in the Synthesis of Piperidine Alkaloids

1.2 Novel Synthetic Methodology and its Applications in the Synthesis of Piperidine Alkaloids.

1.2.1 Introduction

Immense research interest is focused on the chemistry and biology of naturally occurring azasugars due to their significant and selective inhibition of various glycosidases,[1] a peculiarity of their structural simulation as well as ability to mimic the glycosidase oxocarbenium-ion transition state.[2] Deoxymannojirimycin **DMJ** (**1**) is a specific inhibitor of Golgi mannosidase-I, responsible to block the conversion of mannose to complex oligosaccharides. DMJ is also well-known to inhibit α-L-fucosidase and possess α-D-glucosidase activity.[3] Its corresponding lactum D-mannolactam (**2**) inhibits both α-D-mannosidase and α-D-glucosidase.[4] With the successful launch of clinically proven, synthetically modified azasugar based drugs such as **Zavesca®** *viz.* *N*-butyldeoxynojirimycin (**3**) (for the control of **Gaucher's disease**) and **Glyset®** *viz.* *N*-hydroxyethyldeoxynojirimycin (**4**) (**type-II diabetes mellitus**, for non-insulin dependent diabetes) (Fig. 1) has further allured for research in this area.[5]

The occurrence of natural piperidine alkaloids with long aliphatic appendages, such as the prosopis (**5**) and (**6**) and cassia alkaloids (**9, 10, 11 and 12**),[6] have gained increasing attention as therapeutic agents due to the variety of pharmacological properties they exhibit. The prosopis alkaloids (**5**) and (**6**), encompasses a number of physiologically important structural features.[7] At one end of the molecule is the polar head group with a configuration of hydroxyl substituents similar to that found in (**1**) and (**2**), while a lipophilic tail portion resembles that of the membrane lipid sphingosine (**15**). Similar mixtures of alkyl chain "tail" and carbohydrate "head" structural features are found in other molecules like (**7**), (**8**), (**13**) (**14**) and (**15**). In each of these molecules, the alkyl chain serves to (i) facilitate transfer across membranes, (ii) anchor the active compound in the membrane with the polar portion protruding and (iii) interact with the hydrophobic portion of the enzymes to which

these compounds bind. Compounds (**7**) and (**8**) share close structural similarity with that of (**3**) and (**4**) but with just a change in stereochemistry at C-2 (Fig. 1).

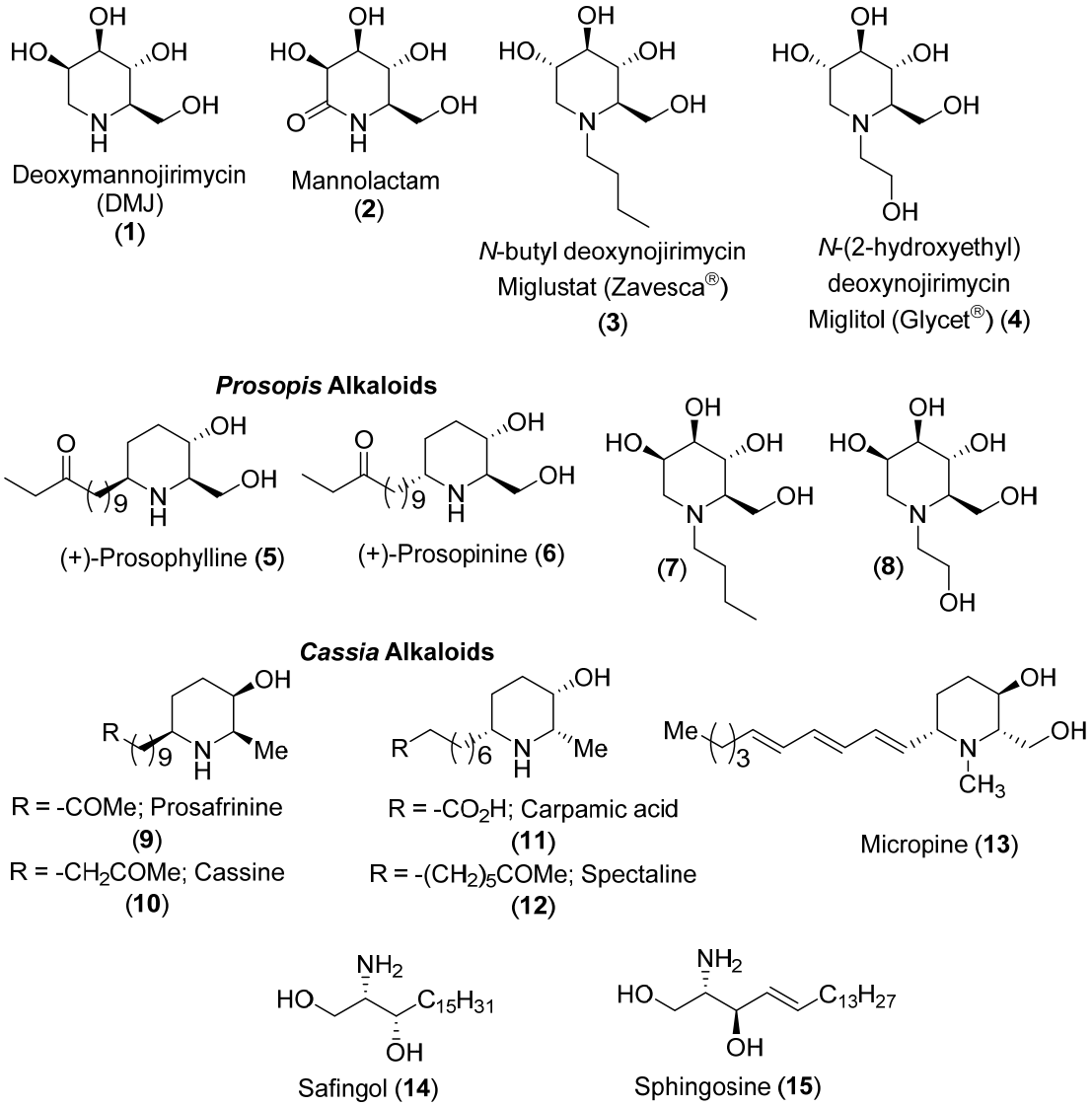


Figure 1. Representative examples of azasugars (**1-13**) and other bioactive molecules (**14**) and (**15**).

1.2.2 Present Work

In case of azasugars one of the structural motifs that is prevalent and imparts bioactivity is the 3-hydroxypiperidine unit, which is present in a number of pharmaceutically relevant small molecules. Due to their interesting biological properties, stereoselective synthesis of 3-hydroxypiperidines has been an important research area of concern. Several diastereoselective total synthesis have been reported in which chirality was mostly introduced by using chiral pool approach or with the help of stoichiometric chiral auxiliaries.[8] It has been observed that *N*-alkyl derivatives of piperidine alkaloids have wide pharmacological applications when compared with that of unalkylated precursor. Hence it becomes necessary to introduce a side chain alkyl moiety in the piperidine alkaloids.

1.2.3 Results and Discussion

Regioselective *N*-Alkylation

An amide has three sites for alkylation, *N*, *O* and α-*C* leading to the formation of *N*-alkylated, *O*-alkylated or α-*C* alkylated product. Proper selection of reaction conditions such as solvent, base, electrophile and temperature can furnish the desired regioselective alkylated product (Fig. 2).

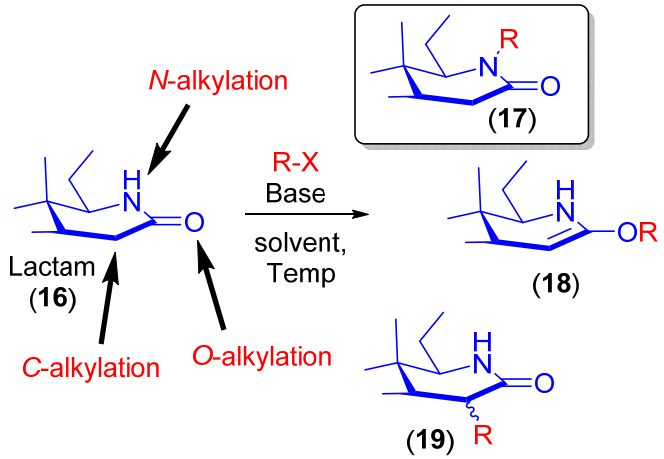
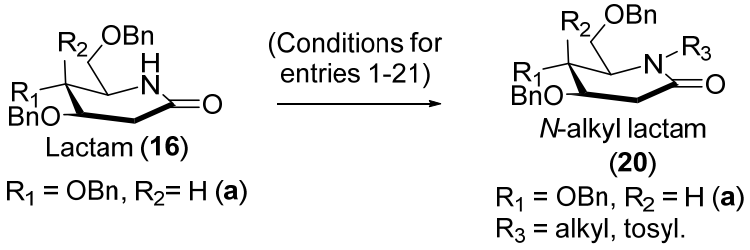


Figure 2. Regioselective sites for alkylation of amide.

In the previous Section **1.1.2.2**, we witnessed the *N*-Boc protection condition *viz*. Boc_2O, DCM, NEt_3, DMAP (cat), and temperature ranging from 0 °C then rt to furnish the product in excellent yields (Fig. 3) which may be utilized here for *N*-alkylation of lactam to furnish the desired product (**20**) as given in Scheme 1 under various reaction conditions (Table 1).



Scheme 1. *N*-protection of glucolactam (**16a**).

Table 1. Conditions for *N*-alkylation of glycolactam (**16**).

Entry	Sm	Reaction condition	Product
1	**(16a)**	^{n}BuI, TEA, DMAP (cat), DCM, 0 °C then rt	-
2	**(16a)**	^{n}BuOTs, TEA, DMAP (cat), DCM, 0 °C then rt	-
3	**(16a)**	^{n}BuI, DMAP (cat), Neat, 0 °C then rt	-
4	**(16a)**	TsCl, TEA, DMAP (cat), DCM, 0 °C then rt	-
5	**(16a)**	^{n}BuI, NaH, DCM, 0 °C - rt	-
6	**(16a)**	^{n}BuI, TEA, DMAP (cat), THF, 0 °C then rt	-
7	**(16a)**	^{n}BuBr, NaH, TBAI, THF, rt	-
8	**(16a)**	^{n}BuOTs, NaH, TBAI, THF, 0 °C then rt	-
9	**(16a)**	TsCl, NaH, THF, rt	
10	**(16a)**	^{n}BuI, TEA, DMAP (cat), THF, 0 °C then rt	-
11	**(16a)**	^{n}BuOTs, NaH, TBAI, THF, 0 °C then rt	-
12	**(16a)**	K_2CO_3, TBAB, ^{n}BuBr , neat	-
13	**(16a)**	^{n}BuLi, TMEDA, ^{n}BuI, THF, -20 °C	-
14	**(16a)**	^{n}BuLi, TMEDA,Ethylbromoacetate, THF, -20 °C	-
15	**(16a)**	^{t}BuLi, -78 °C, ^{n}BuBr	-

Cont.

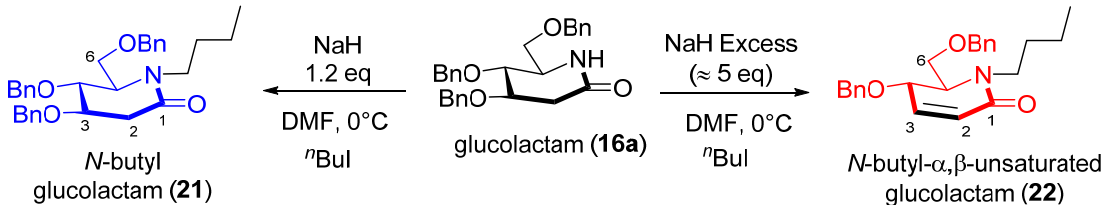
Entry	Sm	Reaction condition	Product
16	*N*-Chlorolactam of **(16a)**	^{t}BuLi, -78 °C, ^{n}BuBr	**(16a)**
17	**(16a)**	^{n}BuOH, Montmorillonite KSF, 1,4-dioxane reflux 100 °C	-
18	**(16a)**	^{n}BuI, K_2CO_3, DMF, rt	-
19	**(16a)**	^{n}BuBr, Cs_2CO_3, DMF, 70-75 °C	-
20	**(16a)**	^{n}BuBr, NaH, DMSO, 10 °C- rt	-
21	**(16a)**	**^{n}BuI, NaH (1.2eq), DMF, 0 °C**	***N*-butyl prod (20a)**

Initially the reaction was carried out in DCM with ^{n}BuI, TEA, DMAP (cat) at 0 °C then rt, however the desired product could not be obtained (Entry 1). Changing the alkyl halide with ^{n}BuOTs as alkylating agent and following the same reaction conditions, no reaction took place and starting material was recovered (Entry 2). Excess of alkyl halide under neat conditions with catalytic DMAP could not furnish the desired product (Entry 3). Similar to conditions in Entry 1 but using TsCl, *N*-tosylated product was also not observed (Entry 4). Switching base *i.e.* using NaH (60% dispersed in mineral oil) was also ineffective (Entry 5). We then wished to see the reaction course in THF with ^{n}BuI as alkylating agent, TEA as a base and DMAP (cat), at 0 °C followed by stirring at rt however, this condition was also not effective (Entry 6). Changing the base and using additive TBAI, which is known to accelerate the reaction and following the reported reaction condition[9a] ^{n}BuBr, NaH as a base in presence of TBAI in THF at rt did not yield the desired product (Entry 7). Then using ^{n}BuOTs[9b] as an alkylating agent instead of ^{n}BuBr also did not yield the desired product (Entry 8). An attempt to tosylate using tosyl chloride with NaH as a base in THF at rt did not furnish the desired product (Entry 9). Carrying out the reaction in THF and with TEA as a base and ^{n}BuI, alkylating agent and catalytic DMAP at 0 °C then stirring at rt, resulted in complete recovery of starting material (Entry 10). Then following the condition, ^{n}BuOTs as an alkyalting agent, NaH as a base in presence of TBAI in THF, 0 °C then rt (Entry 11) also resulted in complete recovery of starting material. We tried the reaction under neat condition[9c] using K_2CO_3 as base in presence

of TBAB, with ^{n}BuBr as an alkylating agent (Entry 12) but still the reaction need not proceed. We then wished to change the base with ^{n}BuLi and following the condition[9d] as mentioned in (Entry 13) TMEDA, ^{n}BuI as an alkylating agent in THF at -20 °C this also could not furnish the desired product. It is well known that α-haloesters like EBA (ethyl bromoacetate) are reactive and the α-halo group can be readily displaced by nucleophilic terminals such as *N*- or *O*- and the resultant product can later be functionalized at the ester moiety, this prompted us to use ^{n}BuLi, TMEDA in presence of EBA as an alkylating agent in THF at -20 °C, however this condition was also not effective (Entry 14). With none of the reactions working with ^{n}BuLi as base we opined to use stronger base ^{t}BuLi, (Entry 15) however in this case also desired product could not be obtained at -78 °C. Then we thought of using the metal halide exchange reaction to facilitate the attack on alkyl bromide by converting first the lactams into its *N*-chloro derivative which can be synthesized by using TCCA by following the known procedure.[9e] Treatment of *N*-chloro lactam with ^{t}BuLi at -78 °C followed by reaction with ^{n}BuBr and after aqueous work up yielded the dechlorinated lactam (**16a**) (Entry 16). Solid acid catalysts at elevated temp have been widely used for alkylation,[9f] following the condition, we used ^{n}BuOH as an alkylating agent in presence of Montmorillonite KSF in 1,4-dioxane and refluxing the reaction mixture at 100 °C, however the desired product was not obtained (Entry 17). We then had a choice to carry out the reaction in polar solvents *viz.* DMSO or DMF. When the reaction was carried out by treatment with ^{n}BuI in presence of K_2CO_3 in DMF at rt no product formation was observed (Entry 18). Use of more basic carbonate[9g] *i.e.* Cs_2CO_3 in presence of ^{n}BuBr in DMF at 70-75 °C was also ineffective (Entry 19). Also use of DMSO and NaH and ^{n}BuBr at 10 °C and stirring at rt. did not yield the desired product (Entry 20). Finally the formation of the desired product *N*-butyl glucolactam (**20a**) was achieved by carrying out the reaction with ^{n}BuI and NaH (1.2eq) in DMF at 0 °C (Entry 21) which was characterized by its spectral data; IR spectrum of compound (**20a**) showed band at 1641 cm^{-1} for amide carbonyl. The ^{1}H NMR spectrum of compound (**20a**) displayed a multiplet for one proton at δ 3.57 and a doublet of doublet of doublet with coupling constant J = 5.3, 8.9, 13.6 Hz integrating for one proton at δ 2.89, which were assigned as the protons α to Nitrogen

present in the alkyl side chain. A doublet of doublet at δ 2.78 having coupling constant J = 4.9, 16.8 Hz for one proton and a doublet of doublet at δ 2.50 with J = 7.3, 16.8 Hz integrating for one proton, respectively are the protons α to the carbonyl carbon group of amide group. Also the protons at δ 1.57-1.40 (*m*, 2H), 1.34-1.27 (*m*, 2H), 0.88 (*t*, J = 7.2 Hz, 3H) indicate incorporation of ^{n}Bu side chain in the molecule. The ^{13}C NMR spectrum of compound (**20a**) displayed δ 168.1 indicates (*C* 1) the carbonyl group and δ 45.0 is (*C*'1) the carbon α to Nitrogen present in the alkyl side chain whereas δ 35.1 is (*C* 2) carbon α to the carbonyl of amide group similarly the signals at δ 29.5, 20.1 and 13.9 are the signals due to the other three (*C*'2, *C*'3 and *C*'4) carbons present in the ^{n}Bu side chain. The HRMS spectrum exhibited the desired mass peak at 488.2792 $[C_{31}H_{38}NO_4]$ $(M+H)^+$.

Having established a method (^{n}BuI, NaH, DMF, 0 °C) for the regioselective *N*-alkylation of glucolactam, we wished to study the role of NaH has on the course of reaction. When glucolactam (**16a**) was reacted with ^{n}BuI in DMF with 1.2 eq. of NaH at 0 °C (Scheme 2) *N*-butylglucolactam (**21**) was obtained in 60% yield. However, when the concentration of NaH was increased to ≥ 5 eq. an interesting product (**22**) was formed.



N-butyl glucolactam (**21**)

glucolactam (**16a**)

N-butyl-α,β-unsaturated glucolactam (**22**)

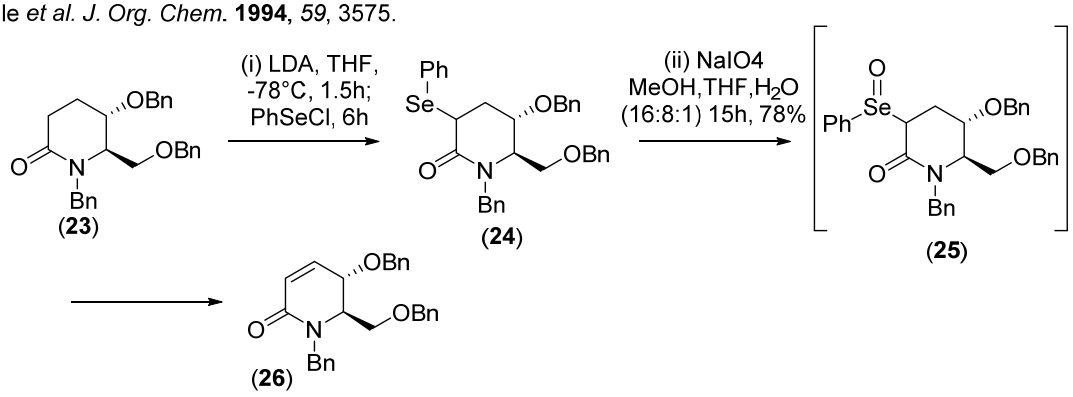
Scheme 2. Formation of *N*-butyl lactam (**21**) and *N*-butyl-α,β-unsaturated lactam (**22**) from glucolactam (**16a**).

The IR spectrum of compound (**22**) showed bands at 1664 and 1611 cm^{-1} for carbonyl group and double bond functionality respectively. The ^{1}H NMR spectrum of compound (**22**) showed a multiplet for ten protons at δ 7.40-7.24, presence of 10 protons instead of 15 indicated loss of one phenyl group. A ddd at δ 6.42 with coupling constant J = 1.5, 5.6, 9.7 Hz, integrating for one proton and a doublet with J = 9.7 Hz for one proton at δ 6.06 were assigned for the olefinic protons *H*-3 and *H*-2 respectively. The ^{13}C NMR spectrum of compound (**22**) exhibited δ 162.2 which was

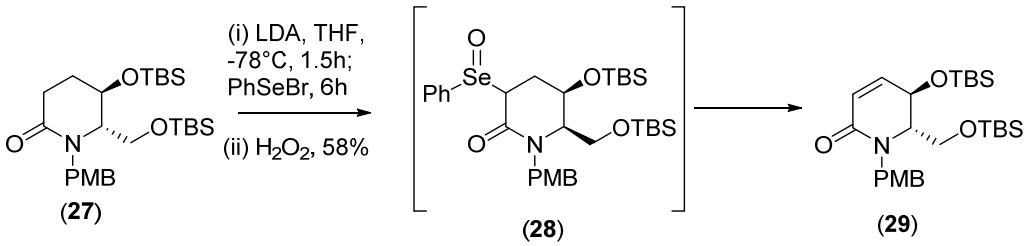
assigned for the carbonyl carbon group and δ 134.1, 128.6 indicated the presence of newly formed double bond. Also the HRMS spectrum showed the desired mass peak at *m/z* 380.2217 $[C_{24}H_{30}NO_3]$ $(M+H)^+$. The spectral data of the product so formed suggested that *N*-alkylation has taken place with the elimination of OBn group at *C*-3 position leading to the formation of *N*-butyl-α,β-unsaturated glucolactam (**22**).

On our extensive literature search for the synthesis of *N*-alkylated-α,β-unsaturated glycolactams we could not find any previous report. We came across three previous reports however not exactly related to our work.

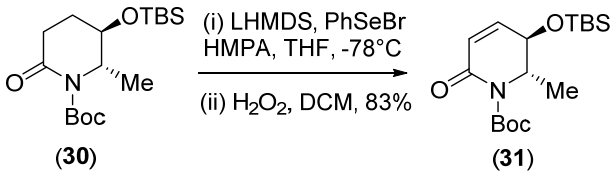
Stille *et al. J. Org. Chem.* **1994**, *59*, 3575.



Huang *et al. Tetrahedron* **2006**, *62*, 190.



Huang *et al. J. Org. Chem.* **2010**, *75*, 4230.



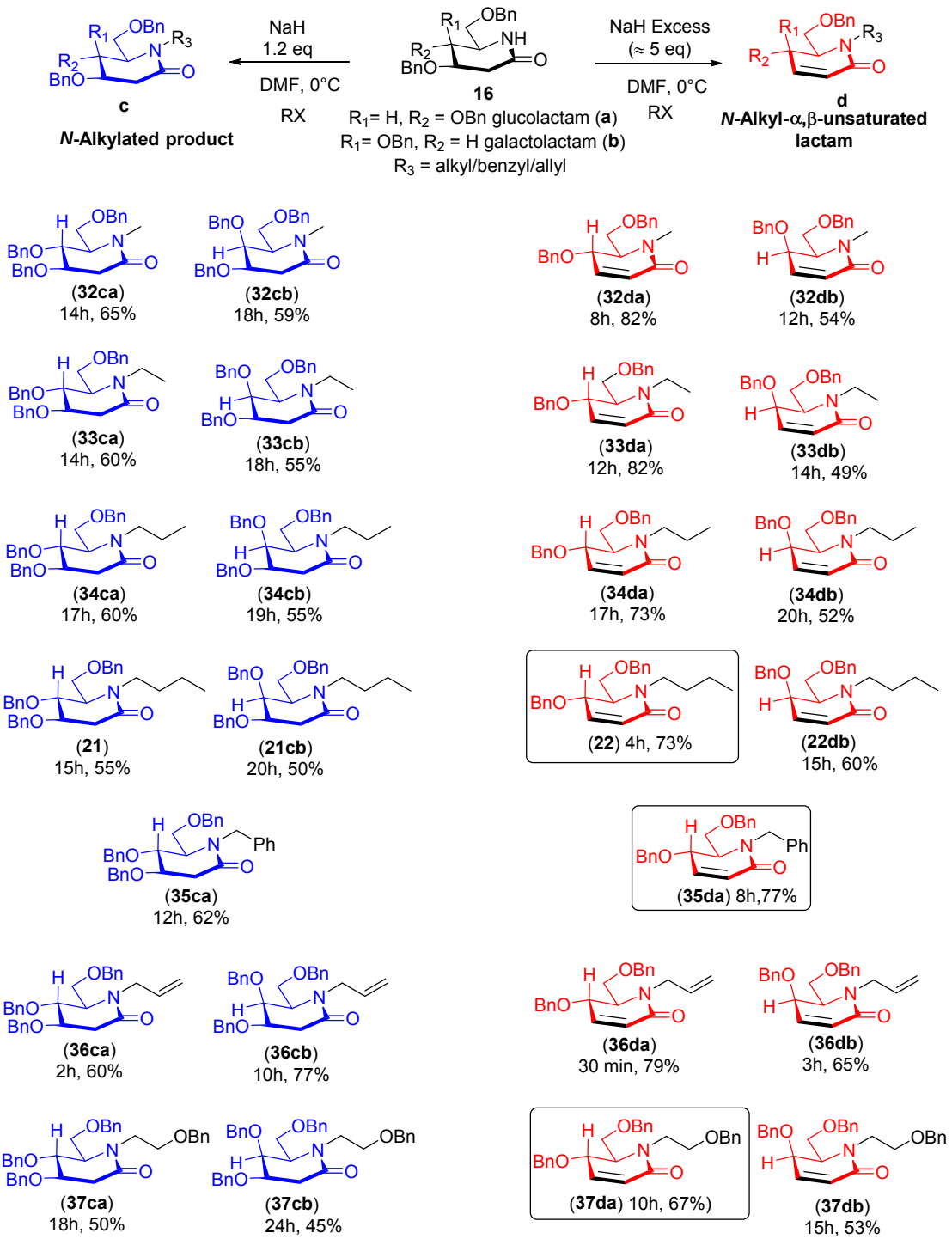
Scheme 3. Reported strategy for the synthesis of α,β-unsaturated lactams.

The first report by Stille *et al.*[10a] described the two step synthesis of unsaturated lactams by reacting *N*-benzyl lactams with PhSeCl and LDA in THF at -78 °C to

furnish α-selenylated product (**24**) which undergoes oxidation of Selenium with $NaIO_4$ (**25**) followed by elimination to furnish α,β-unsaturated lactam (**26**) in 78% yield (Scheme 3). Other two methods by Huang *et al.*[10b,c] had utilized the synthetic methodology developed by Stille *et al.*[10a] with different protecting groups for nitrogen.

The reported methods do suffer from some drawbacks such as (i) use of toxic selenium reagents (ii) use of strong base *viz.* LDA, LHMDS or DBU (iii) oxidants like $NaIO_4$ or H_2O_2 and moreover low yields of the product over two steps. Further, most of the reported methods use *N*-protected lactams as starting material.

Having established an excellent reaction condition for *N*-alkylation and simultaneous *N*-alkylation and debenzylation of glucolactams with 1.2 eq. and ≥ 5 eq. of NaH, respectively, we wished to generalize this reaction by reacting diverse alkyl bromides or iodides with gluco/galactolactams. The results are summarized in (Scheme 4). In general all the reactions of alkyl, benzyl, allylic halides (iodides or bromides) with gluco/galactolactams went smoothly. In case of alkyl halides, it was observed that primary halides reacted well as compared to secondary alkyl halides. When the reaction of isopropyl bromide was carried out by reacting it with glucolactam (**16a**), trace amount of product was formed. However, the quantity of the product was insufficient to fully characterize it. Henceforth we used only primary alkyl halides for all the reactions. It was interesting to note that in the *N*-alkylated glycolactam product (**c**) as well as in the *N*-alkylated-α,β-unsaturated glycolactam (**d**) chiral center is generated at Nitrogen. However, in almost all products (Scheme 4) only one product in which the alkyl group is either above the plane of the ring or below the plane of the ring *i.e* β(*N*-R) or α(*N*-R) is obtained. But in few representative examples (**32cb**), (**32db**) and (**37db**), a mixture of product **β(*N*-R) + α(*N*-R)** was obtained in almost equal ratio. We could separate both these diastereomers of compounds (**32cb**), (**32db**) and (**37db**) by flash chromatography. However, we could not assign the stereochemistry at the nitrogen centre by their NMR spectra *i.e*. which one is β- and which is α-isomer. Hence, NMR data of one isomer of these compounds is given in the experimental section.



Scheme 4. Regioselective *N*-alkylation and regioselective *N*-alkyl-α, β-unsaturated lactam formation.

Table 2. Reaction conditions for stereoselective *N*-alkylation of glycolactam (**16**).

Entry	Sm	Reaction condition	Product
1	(**16a**)	NaH (2.5 eq), ^{n}BuI (4.1 eq), $K_2S_2O_8$ (2.1 eq)	(**21**) (25%), (**22**) (23%), 22h
2	(**16a**)	NaH (2.5 eq), ICH_2CH_2OBn (4.1 eq), $K_2S_2O_8$ (2.1 eq)	(**37ca**) (25%), sm (60%), 3d
3	(**16a**)	NaH (2.5 eq), ^{n}BuI (4.1 eq), $K_2S_2O_8$ (4.1 eq)	(**21**) (31%), sm (20%), 33h
4	(**16a**)	NaH (2.5 eq), ^{n}PrBr (4.1 eq), NaI (4.1 eq), $K_2S_2O_8$ (2 eq)	(**34ca**) (20%), sm (25%), 22h
5	(**16a**)	NaH (2.5 eq), ^{n}PrI (4.1 eq), NaI (4.1 eq), $K_2S_2O_8$ (2 eq)	(**34ca**) (15%), sm (25%)
6	(**16a**)	NaH (excess), ^{n}PrBr (12.4 eq), NaI (12.4 eq), $K_2S_2O_8$ (8 eq)	(**34da**) (50%), 50h
7	(**16b**)	NaH (2.5 eq), EtBr (4.1 eq), $AgNO_3$ (4.1 eq)	Sm recovered, 3d
8	(**16b**)	NaH (2.5 eq), ^{n}PrBr (4.1 eq), $AgNO_3$ (4.1 eq)	Sm recovered, 3d
9	(**16b**)	NaH (2.5 eq), AllylBr (4.1 eq), $AgNO_3$ (2.1 eq)	(**36cb**) (17%), sm (54%), 11h
10	(**16b**)	NaH (2.5 eq), MeI (4.1 eq), $K_2S_2O_8$ (2.1 eq)	(**32cb**) (49%), 18 h
11	(**16b**)	NaH (7.5 eq), ^{n}BuI (12.4 eq), $K_2S_2O_8$ (6.6 eq)	(**21cb**) (30%), sm (20%), 69h
12	(**16b**)	NaH (7.5 eq), ^{n}EtBr (12.4 eq), NaI (12.4 eq), $K_2S_2O_8$ (6.6 eq)	(**33cb**) (13%), sm (20%), 69h
13	(**16b**)	NaH (2.5 eq), ^{n}PrBr (12.4 eq), NaI (12.4 eq), $K_2S_2O_8$ (8 eq)	(**34cb**) (22%), sm (15%), 5d
14	(**16b**)	NaH (excess), ^{n}PrBr (12.4 eq), NaI (12.4 eq), $K_2S_2O_8$ (4.1 eq)	(**34db**) (50%), 20h

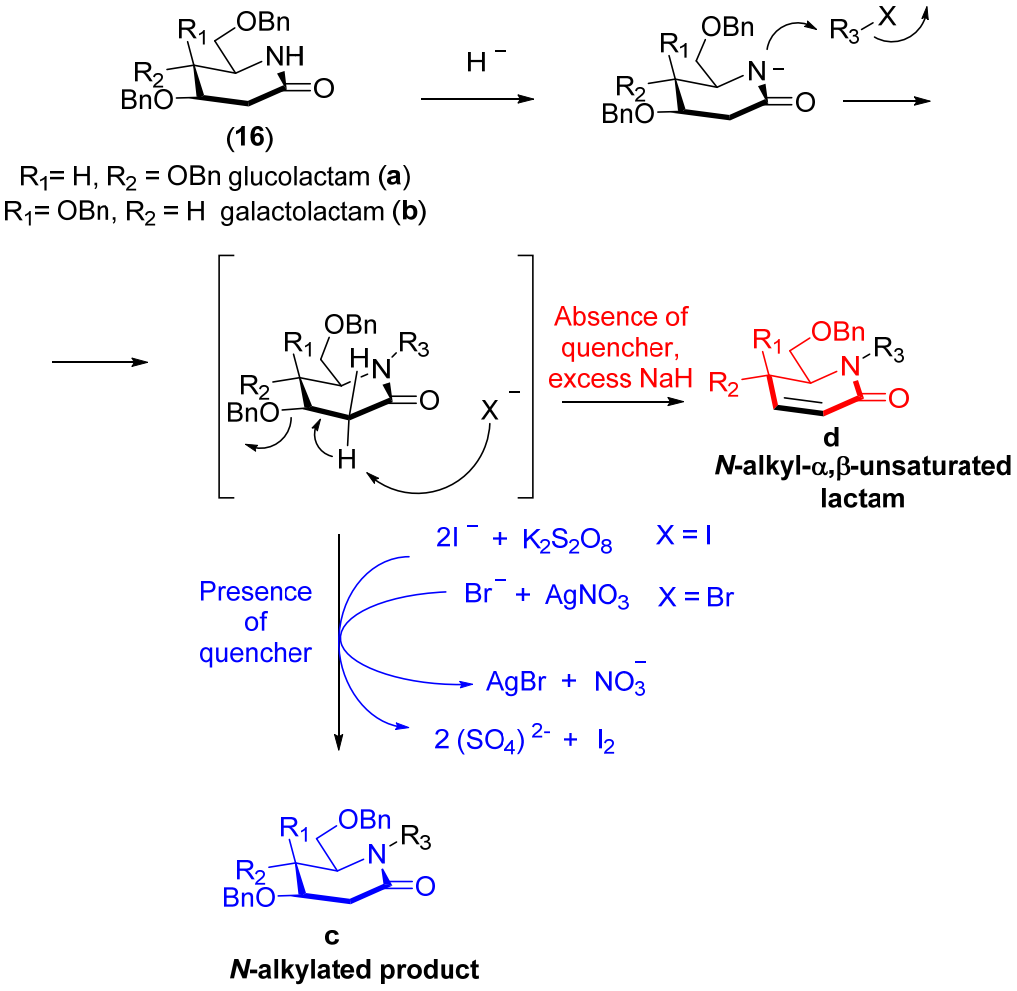
sm: starting material

We then decided to study the quantity of NaH required to catalyze this reaction *i.e.* elimination of benzyl group to form the *N*-alkyl-α,β-unsaturated lactams (**d**), we carried out a series of reactions by changing the reaction conditions. Glucolactam

(**16a**) on treatment with NaH (2.5 eq), ^{n}BuI (4.1 eq) and $K_2S_2O_8$ (2.1 eq) gave a mixture of *N*-butyl (**21**) as well as *N*-butyl-α,β-unsaturated lactam (**22**) in 25% and 23%, respectively in 22h (Entry 1, Table 2). However on changing the alkyl group with ICH_2CH_2OBn (4.1 eq) and reacting (**16a**) with NaH (2.5 eq) and $K_2S_2O_8$ (2.1 eq) furnished only the *N*-alkyl product (**37ca**) (25%), with recovery of starting material (60%), however reaction was sluggish ***i.e***. took 3d (Entry 2, Table 2). Carrying out the reaction with ^{n}BuI (4.1 eq) and (**16a**) with increased concentration of iodide quencher $K_2S_2O_8$ (4.1 eq) and NaH (2.5 eq) furnished only the *N*-butyl product (**21**) (31%) and starting material (20%) and the reaction was complete in 33h (Entry 3, Table 2). This can be compared with the observation of Entry 1 where mixtures of products were obtained with $K_2S_2O_8$ (2.1 eq). Alkyl bromides are somewhat less reactive than alkyl iodides, hence we thought they can be converted *in situ* to their iodide (Finkelstein reaction) by adding NaI which in turn should accelerate the rate of reaction. On treatment of (**16a**) with NaH (2.5 eq), ^{n}PrBr (4.1 eq), NaI (4.1 eq), $K_2S_2O_8$ (2 eq) gave exclusively *N*-propyl product (**34ca**) (20%), with recovery of starting material (25%) in 22h (Entry 4, Table 2). Carrying out the reaction with (**16a**) and NaH (2.5 eq), ^{n}PrI (4.1 eq), NaI (4.1 eq) and $K_2S_2O_8$ (2 eq) had no appreciable effect on the yield as well as on the rate of reaction (Entry 5, Table 2). We then thought NaH in excess should accelerate the rate of reaction and also increased the concentration of alkylbromide, NaI and quencher $K_2S_2O_8$. When (**16a**) was treated with excess of NaH, ^{n}PrBr (12.4 eq), NaI (12.4 eq) and $K_2S_2O_8$ (8 eq) (Entry 6, Table 2) only the *N*-propyl debenzylated product (**34da**) was formed (50%) in 50h. It may be noted here that *N*-alkyl debenzylated products are formed at faster rate in excess NaH but here in presence of $K_2S_2O_8$ it took longer reaction time. For alkyliodides, $K_2S_2O_8$ served as a good quencher so, we thought that for alkylbromides $AgNO_3$ can perform the same role. Reaction of galactolactam (**16b**) with NaH (2.5 eq), EtBr (4.1 eq) and $AgNO_3$ (4.1 eq) for 3 days led to complete recovery of starting material (Entry 7, Table 2). Similarly complete recovery of starting material was observed when NaH (2.5 eq), ^{n}PrBr (4.1 eq), $AgNO_3$ (4.1 eq) were used (Entry 8, Table 2). This failure of reaction could be due to less reactivity of alkylbromides and sluggish nature of galactolactam as a substrate. However the reaction worked with reactive allyl bromide. When (**16b**)

was treated with NaH (2.5 eq), allylbromide (4.1 eq) and $AgNO_3$ (2.1 eq), it furnished only the *N*-allyl product (**36cb**) (17%) with recovery of starting material (54%) in 11h (Entry 9, Table 2). Alkyliodides react well and faster than the alkylbromides which is evident from the reaction of (**16b**) with NaH (2.5 eq), MeI (4.1 eq), $K_2S_2O_8$ (2.1 eq) to furnish exclusively *N*-methyl product (**32cb**) (49%) in18h (Entry 10, Table 2). The reaction took longer time when ^{n}BuI (12.4 eq) was used (Entry 11, Table 2), but *N*-alkyl-α,β-unsaturated lactam was not formed even with excess NaH when the reaction was carried out with NaH (7.5 eq), ^{n}BuI (12.4 eq) and $K_2S_2O_8$ (6.6 eq). The only product formed was (**21cb**) (30%) with recovery of starting material (20%) in 69h. Low reactivity of alkylbromides prompted us to use NaI *in situ* to study the rate of the reaction. Hence when (**16b**) was treated with excess of NaH (7.5 eq), ^{n}EtBr (12.4 eq), NaI (12.4 eq) and $K_2S_2O_8$ (6.6 eq) only *N*-ethyl product (**33cb**) (13%), starting material (20%), in 69h was observed (Entry 12, Table 2). However on lowering the concentration of NaH (2.5 eq) and carrying the reaction with (**16b**) and), ^{n}PrBr (12.4 eq), NaI (12.4 eq) and $K_2S_2O_8$ (8 eq), *N*-propyl product (**34cb**) (22%) was formed with starting material (15%) but the reaction took long time for completion 5d (Entry 13, Table 2). However reaction of (**16b**) with excess of NaH but with low concentration of $K_2S_2O_8$ (4.1 eq) furnished the *N*-propyl debenzylated product (**34db**) (50%) in 20h. Here in this case the quencher was in low concentration and elimination of benzyl group was facilitated by excess of NaH and also by NaI (12.4 eq).

From the above set of observations we could conclude that *N*-alkylation occurs first followed by debenzylation. If the ratio of alkyliodide and $K_2S_2O_8$ is 2:1 then *N*-alklation is preferred, if NaH is in excess and reaction is carried in absence of iodide quencher $K_2S_2O_8$, *N*-alkyl-α,β-unsaturated lactam formation is favored. For alkylbromides the favourable condition for *N*-alklation is alkylbromide and $AgNO_3$ in (1:1) ratio. However, when NaI is added in that case maintaining the ratio of NaI and $K_2S_2O_8$ in 2:1 furnishes *N*-alkyl lactams. Lower concentration of $K_2S_2O_8$ favours *N*-alkyl-α,β-unsaturated lactam formation. Based on the above results a postulated mechanism for *N*-alkylation and *N*-alkyl-α,β-unsaturated lactam formation has been delineated in Scheme 5.



Scheme 5. Plausible mechanism for regioselective *N*-alkylation and regioselective *N*-alkyl-α,β-unsaturated lactam formation.

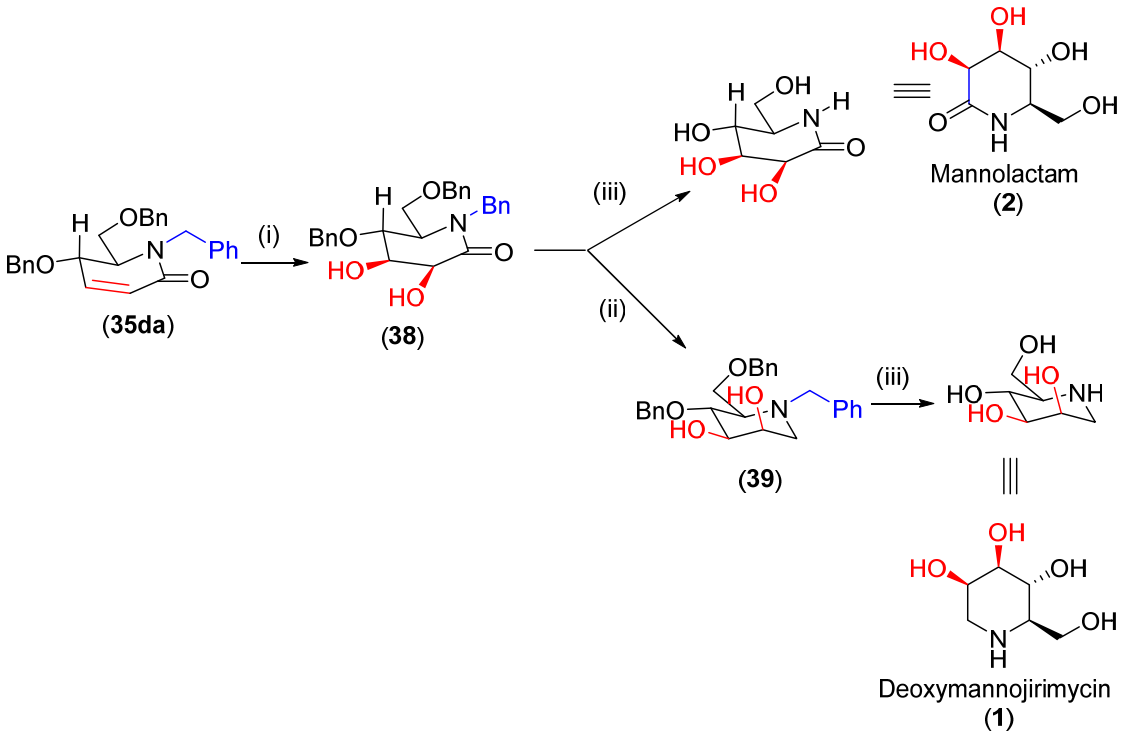
Hydride from NaH abstracts the acidic NH proton of the lactam (**16**) to generate amide anion which is delocalized with carbonyl carbon. The nitrogen anion then attacks the alkyl halide to undergo *N*-alkylation. However due to the presence of halide anion in vicinity in polar solvent, the halide in absence of any quencher abstracts the proton α to the carbonyl carbon group and causes elimination of β-benzyl group. No other benzyl groups underwent elimination as the driving force here is the conjugation assisted by the carbonyl group with the double bond in the product (**d**). In presence of either $K_2S_2O_8$ or $AgNO_3$, the halide is quenched (to iodine or precipitated as AgBr), hence no longer available for abstraction of the protons α to the carbonyl group and thereby furnishing *N*-alkyl lactam (Scheme 5). It is evident from the

postulated mechanism, that for quenching iodide, alkyl iodide and $K_2S_2O_8$ should be in the ratio of (2:1) and for quenching bromide, alkyl bromide and $AgNO_3$ should be in the ratio of (1:1) for *N*-alkylation.

1.2.4 Applications of the Developed Methodology for the Synthesis of Piperidine Alkaloids

1.2.4.1 Formal Synthesis of Mannolactam, Deoxymannojirimycin, (+)-Prosophylline and (+)-Prosopinine

Some of the previously reported synthesis of mannolactam (**2**) and deoxymannojirimycin (**1**) are described in **1.1.1.4.** Our developed methodology can be utilized in the synthesis of mannolactam and deoxymannojirimycin. In the previous Section (**1.2.3**) we have functionalized the *C*2-*C*3 position of the lactam, which can be used as a key intermediate in the synthesis of a number of piperidine alkaloids. Here (**35da**) has been used for the synthesis of the title compounds. (Scheme 6).

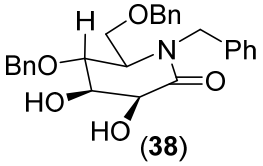
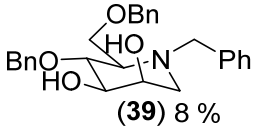
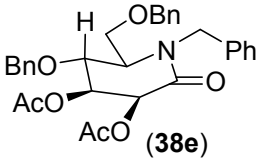
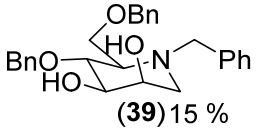
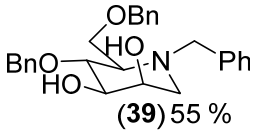


Scheme 6. *Reagents and conditions*; (i) $RuCl_3$, $NaIO_4$, CH_3CN:H_2O (6:1), 0-5 °C, 35 min; (ii) BH_3.DMS THF, 0 °C, rt, reflux (Table 3); (iii) 1 atm H_2, Pd/C, MeOH (Ref: 10a)

We envisioned that compound (**35da**) could be dihydroxylated streroselectively in *syn* fashion by following the Flash dihydroxylation condition[12] ($RuCl_3$, $NaIO_4$, CH_3CN:H_2O (6:1), 0-5 °C). The reaction was complete in 35 min and the product (**38**) was obtained 43% yield. The IR spectrum of compound (**38**) showed broad peak at 3443 cm^{-1} for OH groups, 1641cm^{-1} for carbonyl group. The ^1H NMR spectrum of compound (**38**) showed multiplet integrating for ten protons at δ 7.39-7.25 which were assigned for OBn group. A multiplet at δ 7.21-7.04 integrating for five protons were assigned for Bn group attached to *nitrogen*. A doublet at δ 5.27 with coupling constant of J = 15.4 Hz integrating for one proton was assigned to the corresponding *H*-2 proton. A signal at δ 3.96 (t, J = 2.9 Hz, 2H) was for one OH merged with other protons and a broad singlet at δ 3.08 integrating for one proton was assigned to the corresponding OH (determined by D_2O exchange experiment). Compound (**38**) in ^{13}C NMR spectrum showed δ 171.2 for carbonyl carbon, 68.9 and 68.1 were signals from

*C*3 and *C*2 carbons respectively. The HRMS spectrum of compound (**38**) showed desired mass at *m/z* 470.1937 $[C_{27}H_{29}NO_5Na]$ $(M+Na)^+$.

Table 3. Reduction conditions of various lactam substrates.

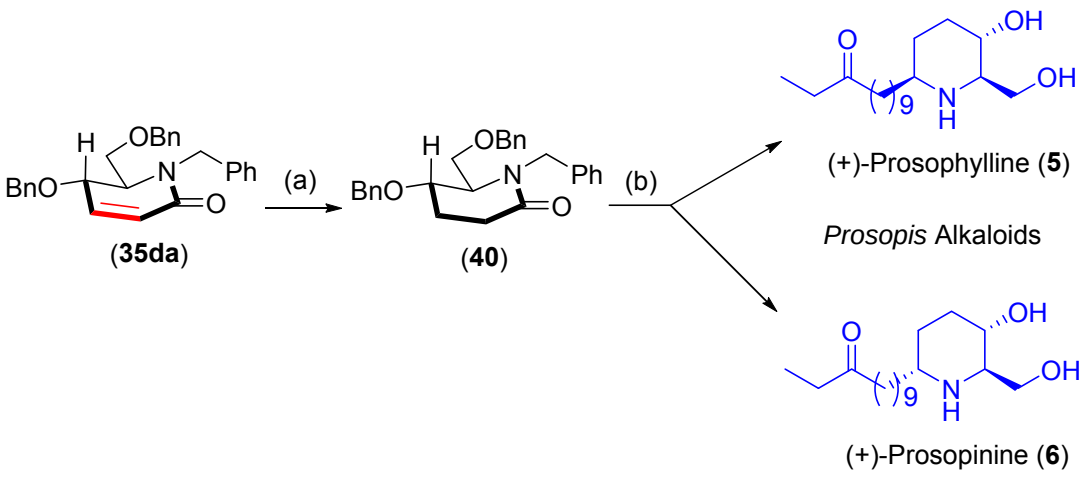
Entry	Substrate	Reagents and Conditions	Product
1	 (**38**)	LAH (excess), THF, 0 °C - rt, reflux	 (**39**) 8 %
2	 (**38e**)	(i) Tf_2O, DCM, 0-5 °C (ii) $NaBH_4$, THF, rt	SM recovered
3	(**38**)	DIBAL-H (10 eq), THF, -72 °C	 (**39**) 15 %
4	(**38**)	BH_3.THF, THF, 0 °C - rt, reflux	SM recovered
5	(**38**)	**BH_3.DMS (20 eq), THF, 0 °C - rt, reflux**	 (**39**) 55 %

Compound (**38**) on treating with 10 eq of LAH[13a] in THF, 0 °C and then stirring at rt followed by reflux gave the desired product (**39**), but in poor yield 6%, (Entry 1, Table 3). Xiang *et al.*[13b] have reported a reduction method in which the amide carbonyl is converted into -OTf by using Tf_2O and then reduced with $NaBH_4$, however under this condition di-*O*-acetate protected glucolactam (**38e**) failed to give the desired product (Entry 2, Table 3). When the reaction was carried out with (**38**) in DIBAL-H[13c] (3 eq) in THF at -72 °C the desired product (**39**) was obtained in only 15 % yield (Entry 9, Table 3). Following the reduction procedure with (**38**) using BH_3.THF, THF, 0 °C then stirring at rt followed by reflux for 6h resulted in complete recovery of starting material (Entry 4, Table 3). Borane DMS has been used extensively in the reduction of the carbonyl group and also carbonyl of the amide

group. When (**38**) was reacted under this condition[13d,e] BH_3.DMS (20 eq), THF at 0 °C then stirring at rt followed by reflux (6h) the desired product (**39**) was obtained in 55% (Entry 5, Table 3).

The IR spectrum of compound (**39**) showed OH stretching frequency at 3408 cm^{-1}, (absence of CO frequency).The ^1H NMR spectrum of compound (**39**) showed multiplet for fifteen protons at δ 7.39-7.27 for all the three phenyl rings. A doublet for one proton at δ 3.29 with J = 13.2 was assigned to *H*-1a. A doublet of doublet at δ 2.93 with coupling constant J = 3.2, 12.2 Hz for one proton was assigned for *H*-1b. A broad singlet at δ 2.58 integrating for one proton was due to *H*'-1a, similarly δ 2.39 (d, J = 8.3 Hz, 1H) was the signal due to *H*'-1b. The *H*-5 proton appeared at δ 2.23 (d, J = 12.5 Hz, 1H). The ^{13}C NMR spectrum of compound (**39**) showed δ 56.7, 54.7 indicated two CH_2 groups adjacent to nitrogen, absence of carbonyl carbon signal indicated reduction reaction at the lactam carbonyl. The HRMS spectrum of compound (**39**) showed desired mass peak at *m/z* 434.2327 $[C_{27}H_{32}NO_4]$ $(M+H)^+$.

Finally hydrogenolysis of (**39**) by following the reported procedure by Stille *et al.*[10a] can furnish deoxynojirimycin (**1**). Similarly hydrogenolysis of (**38**) can furnish mannolactam (**2**).



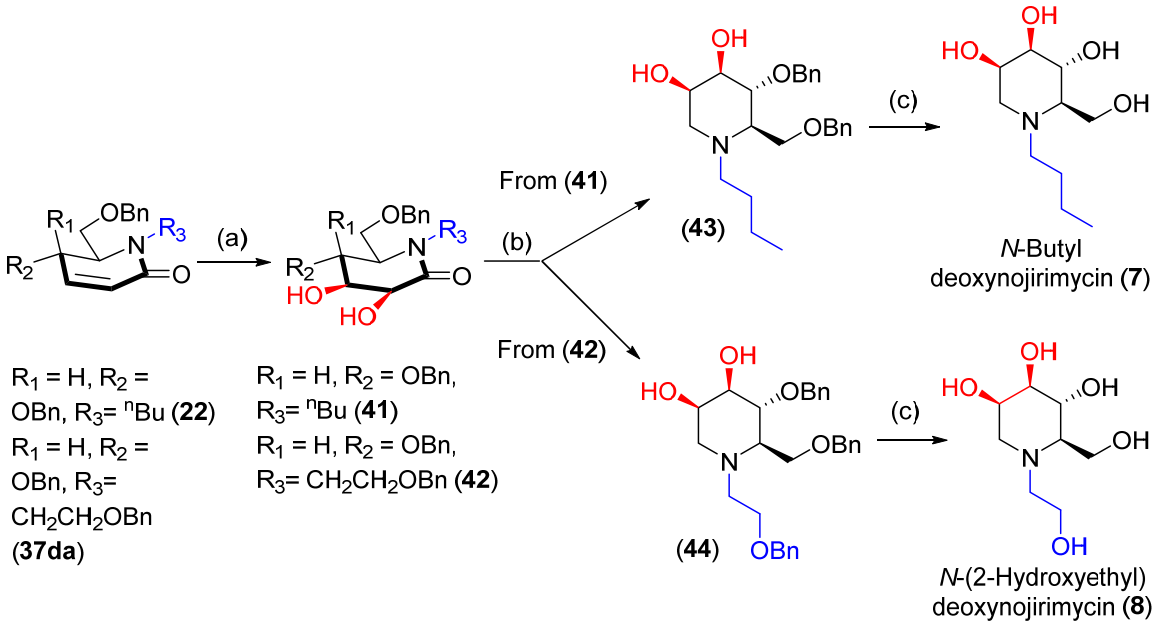
Scheme 7. *Reagents and conditions*; (a) $NiCl_2.6H_2O$, $NaBH_4$, MeOH, 0 °C to rt, 2.5h; (b) Ref: 10a, 11a-c.

One more application of our developed methodology utilizing compound (**35da**) was in the formal synthesis of *Prosopis* alkaloids, (+)-prosophylline (**5**) and (+)-prosopinine (**6**). Reduction of the unsaturated double bond using nickel boride generated *in situ* by the reaction of $NiCl_2.6H_2O$ and $NaBH_4$ in MeOH at 0 °C to rt[14] furnished the desired key intermediate (**40**) in 66 % yield (Scheme 7). Compound (**40**) in IR spectrum showed 1642 cm^{-1} for carbonyl group stretch (no double bond stretching frequency was observed). The ^1H NMR spectrum of compound (**40**) showed multiplet for 15 protons at δ 7.40-7.10 for the three phenyl groups from Bn. The multiplet integrating for one proton at δ 2.78-2.63 and a multiplet at δ 2.49-2.35 integrating for one proton was assigned for *H*-2 protons. Similarly two protons at δ 2.09-1.93 were observed as a multiplet was due to *H*-3 protons. The chemical shifts of *H*-2 and *H*-3 protons indicate the reduction of double bond. The ^{13}C NMR spectrum of compound (**40**) showed δ 170.3, for carbonyl carbon, 27.4 and 22.4 for *C*3 and *C*2 carbons, respectively. The HRMS spectrum of compound (**40**) showed desired peak at *m/z* 416.2217 $[C_{27}H_{30}NO_3]$ $(M+H)^+$.

(+)-Prosophylline (**5**) and (+)-prosopinine (**6**) can be readily synthesized from key intermediate (**40**) by following the reported literature methods[10a,11a-c]

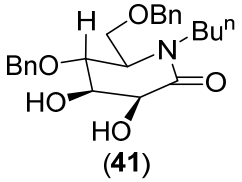
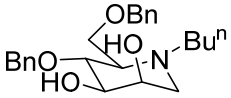
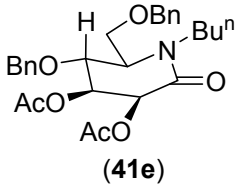
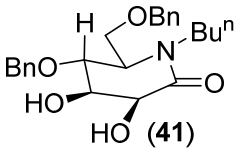
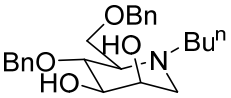
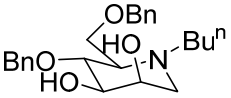
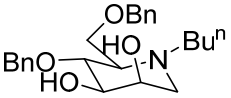
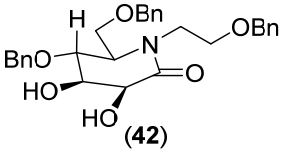
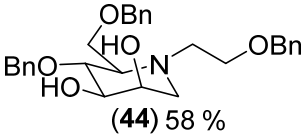
1.2.4.2 Formal Synthesis of *N*-Alkyl-1-deoxymannojirimycin Derivatives

We decided to apply our developed methodology (described in Section **1.2.3**) for the synthesis of *N*-alkyl-1-deoxynojirimycin derivatives, as drugs such as **Zavesca®** *viz.* *N*-butyldeoxynojirimycin (**3**) and **Glyset®** *viz.* *N*-hydroxyethyldeoxynojirimycin (**4**) which show antidiabetic activity (Section **1.2.1**). Our developed methodology can also be utilized for the synthesis of compounds (**7**) and (**8**). Compounds (**22**) and (**37da**) on flash dihydroxylation furnished (**41**) and (**42**) in 46% and 57% yield respectively (Scheme 8). Compounds (**41**) and (**42**) have a close resemblance with compound (**29**) (Section **1.2.4.1)**, and were characterized by its spectral data. A number of reducing agents were tried for the reduction of the lactam carbonyl. Various reducing agents were screened for the complete reduction of lactam carbonyl to methylene group however only BH_3.DMS gave the desired product in better yields (55-60%) as described in Table 4. Compound (**41**) and (**42**) on reduction with Borane Dimethylsulfide furnished compounds (**43**) and (**44**) respectively (Scheme 8).



Scheme 8. Formal synthesis of *N*-alkyl-1-deoxynojirimycin derivatives (**7**) and (**8**). *Reagents and conditions;* (a) $RuCl_3$, $NaIO_4$, CH_3CN:H_2O (6:1), 0-5 °C, 35 min; (b) BH_3.DMS THF, 0 °C, rt, reflux; (c) H_2, Pd/C MeOH (Ref: 10a).

Table 4. Reduction conditions of various lactam substrates.

Entry	Substrate	Reagents and Conditions	Product
1	 (**41**)	LAH, Et_2O, 0 °C - rt	SM recovered
2	(**41**)	LAH, Et_2O, rt	SM recovered
3	(**41**)	LAH (5eq), THF, 0 °C - rt	 (**43**) 10 %
4	(**41**)	Et_3Al (0.6 M Heptane), Alane N,N-dimethylethyl amine complex sol (0.5 M Toluene) THF	SM recovered
5	 (**41e**)	LAH (8 eq), THF, 0 °C - rt, reflux	 (**41**)
6	(**41**)	DIBAL-H (10 eq), THF, -72 °C	 (**43**) 20 %
7	(**41**)	Red-Al, THF, 0 °C - rt	 (**43**) 20 %
8	(**41**)	**BH_3.DMS (20 eq), THF, 0 °C - rt, reflux**	 **(43)** 60 %
9	 (**42**)	**BH_3.DMS (20 eq), THF, 0 °C - rt, reflux**	 (**44**) 58 %

A number of papers have been published reporting the reduction of lactam carbonyl group using LAH in Et_2O at 0 °C- rt,[13a] however this did not work with our substrate (Entry 1, Table 3). Reduction of (**41**) with LAH at rt also failed to yield the desired product (Entry 2, Table 3). On changing the solvent from Et_2O to THF product (**43**) was formed but in very low yield (10 %) (Entry 3, Table 4). Strong Lewis acids are known to complex the oxygen of carbonyl group and increase the electrophilicity of the carbonyl group and make it susceptible for the attack of nucleophile at carbonyl carbon. Hence using Et_3Al (0.6 M heptane) in presence of alane *N*,*N*-dimethylethyl amine complex sol (0.5 M toluene) in THF[13f] could not furnish the desired product (Entry 4, Table 4). Carrying out the reaction with di-*O*-acetate protected lactam (**41e**) and LAH (8 eq) in THF at 0 °C - rt and then refluxing for 12h (Entry 5, Table 4) resulted in deacetylated product with lactam carbonyl group intact (**41**). When the reaction was carried out with (**41**) in DIBAL-H (10 eq), THF at -72 °C[13d] the desired product (**43**) was obtained in 20 % yield (Entry 6, Table 4). Red-Al[13g] (sodium bis (2-methoxyethoxy) aluminum hydride solution), has been used as a good source of hydride for reduction, however following the above procedure using (**41**) furnished (**43**) in only 20% yield (Entry 7, Table 4). We thought of utilizing Borane-DMS reduction procedure which we had earlier used for the reduction of compound (**38**). Following the similar reaction conditions[13d.e] using (**41**) in presence of BH_3.DMS (20 eq) in THF at 0 °C - rt and then refluxing for 6h furnished (**43**) in 60% yield (Entry 8, Table 4). Furthermore reaction of (**42**) under identical conditions furnished the desired product (**44**) in 58% (Entry 9, Table 4).

Compound (**43**) in IR spectrum showed bands at 3384, 3066, 3014 cm^{-1}, and band for CO group was absent. The ^1H NMR spectrum of compound (**43**) showed δ 3.28-3.18 (m, 1H), 2.94 (brs, 1H), 2.80 (brs, 1H), 2.70 (d, *J* = 10.4 Hz, 1H), 2.66-2.59 (m, 1H), 1.57-1.42 (m, 2H), 1.31-1.27 (m, 1H), 1.23-1.16 (m, 1H), 0.87 (t, *J* = 7.3 Hz, 3H) are the signals for protons due to *H*-1, *H*-5, *H*'-1, *H*'-2, *H*'-3 and *H*'-4, respectively. The ^{13}C NMR spectrum of compound (**43**) showed δ 63.7, 54.7, 52.8, 25.8, 20.2 and 13.8, which are signals due to *C*6, *C*1, *C*'1, *C*'2, *C*'3 and *C*'4, respectively. The HRMS

spectrum of compound (**43**) showed desired peak at m/z 400.2482 [$C_{24}H_{34}NO_4$] $(M+H)^+$.

Compound (**44**) in IR spectrum showed bands at 3396, 3018, 2927, 2857 cm^{-1}, and band for CO group was absent. The ^1H NMR spectrum of compound (**44**) showed δ 4.88 (d, *J* = 11.3 Hz, 1H), 4.53-4.38 (m, 6H), 3.84 (brs, 1H), 3.77-3.69 (m, 2H), 3.61-3.50 (m, 4H), 3.15 - 3.04 (m, 2H), 2.91 (td, *J* = 5.4, 14.3 Hz, 1H), 2.62 (d, *J* = 12.2 Hz, 1H) and 2.45 (d, *J* = 8.5 Hz, 2 H); The ^{13}C NMR spectrum of compound (**44**) showed δ 56.1 and 51.5, which are signals due to *C*1 and *C*'1, respectively. The HRMS spectrum of compound (**44**) showed the desired mass peak at *m/z* 478.2587 [$C_{29}H_{36}NO_5$] $(M+H)^+$.

1.2.4.3 Formal Synthesis of (2*S*,3*S*)-3-Hydroxypipecolic Acid

3-Hydroxypipecolic acid derivatives form the skeleton backbone of a wide variety of naturally occurring alkaloids[15]and drugs[16] (Fig. 3). It is well known that sugars and amino acid form the fundamental building blocks in nature. The core structure of this hybrid molecule is an excellent union of sugar framework and amino acid functionality which rejoices its important place in a special class of compounds called sugar amino acids (**Saa**).[17] This non-proteinogenic unnatural amino acids displays a wide range of bioactivities such as enzyme inhibitors,[18] immunosupressants,[19] anticancer,[20] NMDA antagonists[21] and anti-HIV[22] agents. These are useful building blocks for the preparation of peptides and peptide mimetics.[23] Thus, the above influential points make it an attractive synthetic target. Synthesis of pipecolic acid has already been discussed in Section **1.1.1.4**.

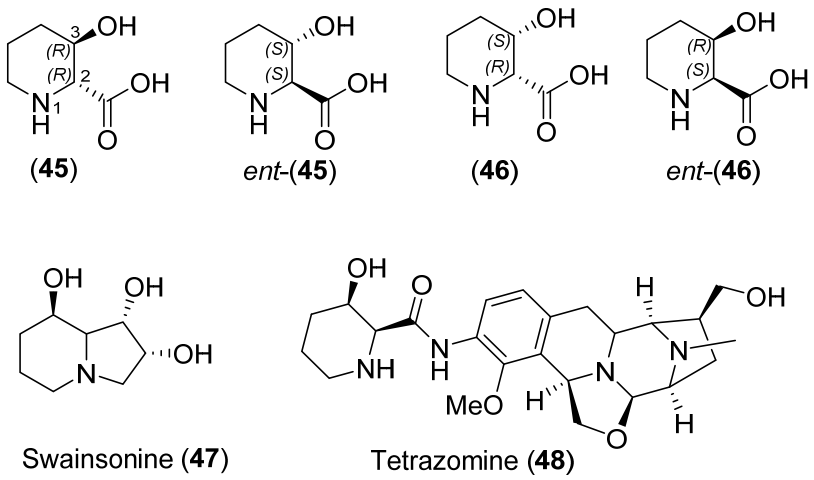
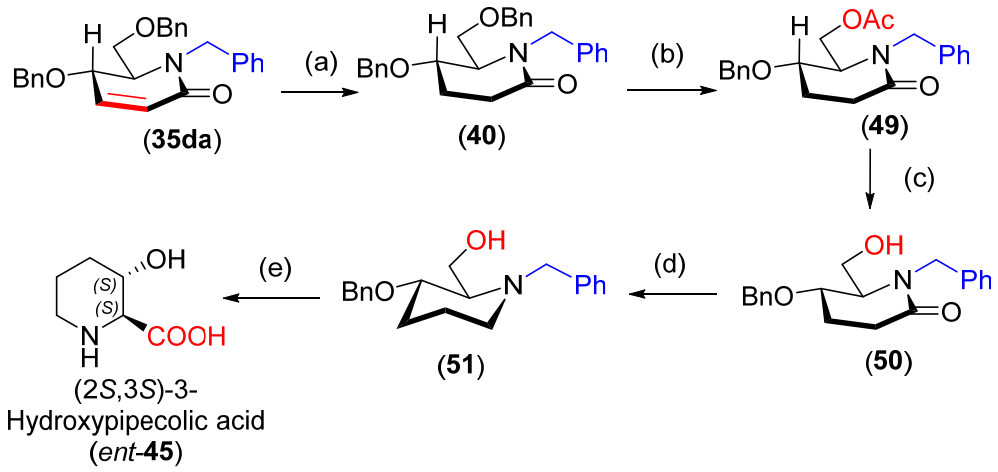


Figure 3. Privileged structures of 3-hydroxypipecolic acid (**45**, *ent*-**45**, **46**, *ent*-**46**) and its biologically important derivatives (**47** and **48**).

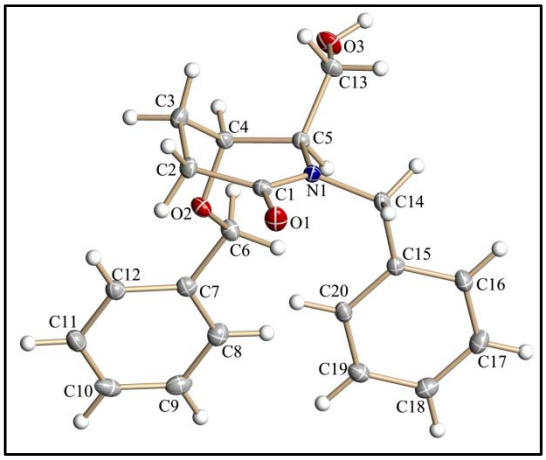
Our developed one pot alkylation and debenzylation strategy was utilized for the synthesis of (2*S*,3*S*)-3-hydroxy pipecolic acid (*ent*-**45**). Using compound (**35da**) as starting material and reduction of the unsaturated double bond using nickel boride[13] furnished the desired product (**40**) in 66% yield (Scheme 9). Regioselective deprotection[24] of primary OBn in presence of secondary OBn was carried and the free primary OH was *in situ* protected as its acetate.

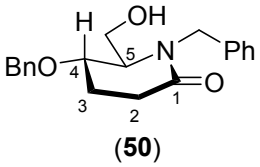


Scheme 9. Formal synthesis (2*S*,3*S*)-3-hydroxypipecolic acid. *Reagents and conditions:* (a) $NiCl_2.6H_2O$, $NaBH_4$, MeOH, 0 °C to rt, 2.5h; (b) Ac_2O, H_2SO_4 in AcOH; (c) NaOMe in MeOH; (d) BH_3.DMS THF, 0 °C, rt, reflux.; (e) Ref: 25.

Thus, compound (**40**) was first treated with Ac_2O in presence of catalytic H_2SO_4 in AcOH at rt to furnish the acetate derivative (**49**). The IR spectrum of compound (**49**) showed bands at 1723, 1667 cm^{-1} corresponding to the CO groups of ester and an amide respectively. The ^1H NMR spectrum of compound (**49**) showed a singlet at δ 2.01 integrating for three protons indicating the presence of CH_3 groups from acetate functionality. A triplet of doublet integrating for one proton at δ 2.73 with coupling constant *J* = 9.2, 17.9 Hz and a triplet of doublet integrating for one proton at δ 2.46 are the *H*-2 protons. A multiplet at δ 2.09 - 2.03 for one proton was assigned for *H*-3 proton. Compound (**49**) in ^{13}C NMR spectrum showed δ 170.4 and 170.1 which are the signals corresponding to the CO carbon of ester and an amide respectively. δ 27.3, 22.2 and 20.8 are the signals indicating presence of -CH_3 group from acetate functionality, *C*-3, *C*-2 carbons, respectively. HRMS spectra of compound (**49**) showed the desired mass peak at *m/z* 390.1674 $[C_{22}H_{25}NO_4Na]$ $(M+Na)^+$.

Compound (**49**) on Zemplén deacetylation condition gave (**50**). The IR spectrum of compound (**50**) showed 3355 and 1619 cm^{-1}strong stretching frequency for OH and amide CO group respectively. The ^1H NMR spectrum of compound (**50**) showed a doublet of a doublet of doublet with coupling constants of *J* = 6.8, 10.5, 17.9 Hz integrating for one proton at δ 2.66 and a multiplet for one proton was observed at δ 2.43-2.32 were assigned the signals for *H*-2 proton. The multiplet for one proton each at δ 2.24-2.12 and δ 2.05-1.90 are due to *H*-3 protons. The ^{13}C NMR spectrum of compound (**50**) exhibited the carbonyl carbon at δ 171.2 ppm. Peaks at δ 27.5, 22.7 were assigned for *C*-3 and *C*-2 carbons, respectively. HRMS spectrum of the deacetylated product (**50**) showed the desired mass peak at *m/z* 326.1749 $[C_{20}H_{24}NO_3]$ $(M+H)^+$. Formation of compound (**50**) was proved by its single crystal X-ray analysis (Fig. 4)





(**50**)

Figure 4. ORTEP diagram of compound (**50**).

The reduction of lactam carbonyl group of (**50**) was achieved by following the BH_3.DMS reduction protocol to furnish the product (**51**). The IR spectrum of compound (**51**) showed strong stretching band for OH at 3424 cm^{-1} and the stretching band corresponding to CO group of amide was absent. The ^{1}H NMR spectrum of compound (**51**) showed a broad singlet integrating for one proton at δ 2.57 for OH proton. The multiplet for one proton at δ 2.47-2.37, a multiplet integrating for two protons at δ 2.22-2.06 and a multiplet for one proton observed at δ 1.79-1.63 are the signals corresponding to two *H*-1, one *H*-3a and one *H*-2a protons. Similarly δ 1.48 - 1.31 (m, 2H) are the signals for one *H*-3b and one *H*-2b protons. The ^{13}C NMR spectrum of compound (**51**) showed no signal for carbonyl carbon. The signals at δ 50.5, 28.8 and 21.1 ppm corresponds to *C*-1, *C*-3, and *C*-2, respectively. Reduction in mass by 14 unit from the obtained mol formula from HRMS mass peak *m/z* 312.1958 $[C_{20}H_{25}NO_2]$ $(M+H)^+$, also confirmed the reduction of CO group. Finally, (*ent*-**45**) could be synthesized from compound (**51**) by following the reaction conditions which was reported by Zhu *et al*.[25]

1.2.4.4 Formal Synthesis (2*S*,3*R*,4*R*)-3,4-Dihydroxypipecolic Acid

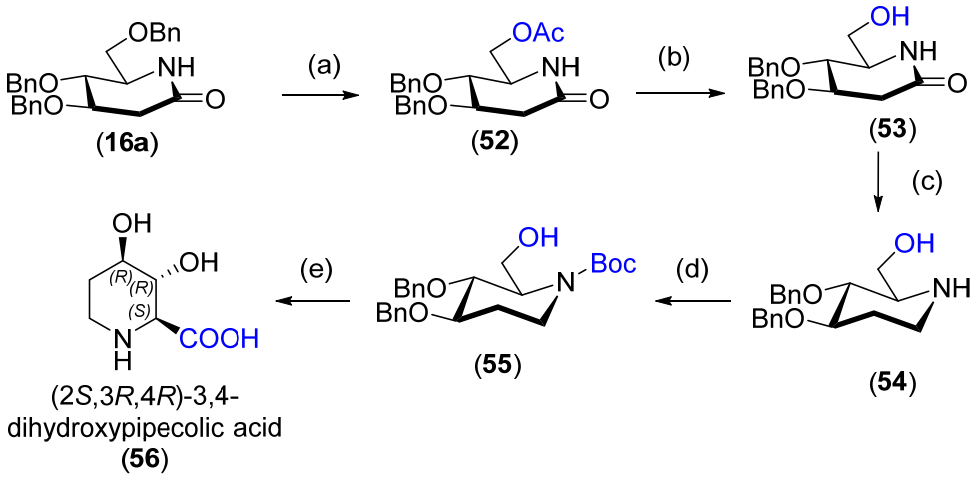
3,4-Dihydroxypipecolic acid (**56**) also shows a number of promising biological activities similar to 3-hydroxypipecolic acid (**45**, *ent*-**45**, **46**, *ent*-**46**). Its synthesis is also important to study the detailed structure-activity-relationship (SAR) of this molecule as enzyme inhibitors.

We thought 3,4-dihydroxypipecolic acid (**56**) can be synthesized from the lactam (**16a**). In order to achieve that, lactam (**16a**) (Scheme 10) by regioselective deprotection[24] and subsequently protecting the primary OH as acetate to furnish compound (**52**). Compound (**52**) was used as such for the next step subjected without purification. Compound (**52**) on deacetylation furnished compound (**53**). The reduction of the lactam carbonyl of (**53**) was carried out by using BH_3.DMS reduction procedure to furnish product (**54**). The IR spectra of (**54**) showed broad peak for OH group at 3363 cm^{-1} and 3088 cm^{-1} for NH group. The ^{1}H NMR spectrum of compound (**51**) exhibited a multiplet integrating for one proton each at δ 2.24-2.08 and δ 2.08-1.91 corresponding to *H*-3 protons. The two *H*-2 protons are mixed in the signals δ 3.62-3.41 (m, 2H) and 3.15-3.03 (m, 1H). One protons which appears as a broad singlet at δ 2.85 was possibly due to the labile NH or OH proton. The ^{13}C NMR spectrum of compound (**51**) showed δ at 42.6 and 29.4 corresponding to signals for *C*-5 and *C*-6, respectively. The HRMS spectrum of compound (**51**) exhibited the desired mass peak at *m/z* 328.1907 $[C_{20}H_{26}NO_3]$ $(M+H)^+$.

The imine nitrogen in product (**54**) was protected with Boc_2O in presence of Et_3N, and catalytic DMAP in DCM to furnish the Boc protected compound (**55**). Compound (**55**) in IR spectrum showed broad peaks for OH group at 3443 and 1667 cm^{-1} for CO stretch of the Boc group. The ^{1}H NMR spectrum of compound (**55**) showed singlet integrating for nine protons at δ 1.45 corresponding to the ^{t}Bu of Boc group. Similarly in ^{13}C NMR spectrum of compound (**55**) showed δ 156.1 indicates presence of carbonyl group of Boc and the three CH_3 groups are observed at 24.8 ppm confirming

the incorporation of Boc group. The HRMS spectrum of compound (**55**) showed the desired peak at *m/z* 450.2250 [$C_{25}H_{33}NO_5Na$] $(M+Na)^+$.

The product (**55**) could be readily converted into the desired (2*S*,3*R*,4*R*)-3,4-dihydroxypipecolic acid (**56**) by following the reported procedure *viz. pri*-OH oxidation, followed by benzyl and Boc deprotection.[25,26]



Scheme 10. Formal synthesis of (2*S*,3*R*,4*R*)-3,4-dihydroxypipecolic acid. *Reagents and conditions;* (a) Ac_2O, H_2SO_4 in AcOH; (b) NaOMe in MeOH; (c) BH_3.DMS THF, 0 °C, rt, reflux.; (d) Boc_2O, Et_3N, DMAP, DCM, 0 °C- rt; (e) Ref: 26.

1.2.5 Conclusion

The results obtained in chapter1 (Section A and Section B) has been summarized in Fig. 5. We have synthesized glycolactam from glycolactone, and efficiently converted them to fagomine and *epi*-fagomine respectively using chiral pool approach. We have successfully synthesized nojirimycin, nojirimycin B and 2-deoxynojirimycin from glycolactam.[27] We have developed an efficient methodolgy for the regioselective *N*-alkylation and regioselective *N*-alkyl-α,β-unsaturated glycolactam formation. A postulated mechanism of formation of *N*-alkyl-α,β-unsaturated glycolactam has been proposed. We have successfully utilized our developed methodology *i.e.* *N*-alkyl-α,β-unsaturated glycolactam for the synthesis of key intermediates which can lead to the

formal synthesis of *N*-alkyldeoxnojirimycin derivatives, deoxymannojirimycin, mannolactam (+)-prosophylline (+)-prosopinine and *N*-butyl deoxynojirimycin. We have also successfully synthesized key intermediates utilized in the formal synthesis of (2*S*,3*S*)-3-hydroxy pipecolic acid and (2*S*,3*R*,4*R*)-3,4-dihydroxpipecolic acid.

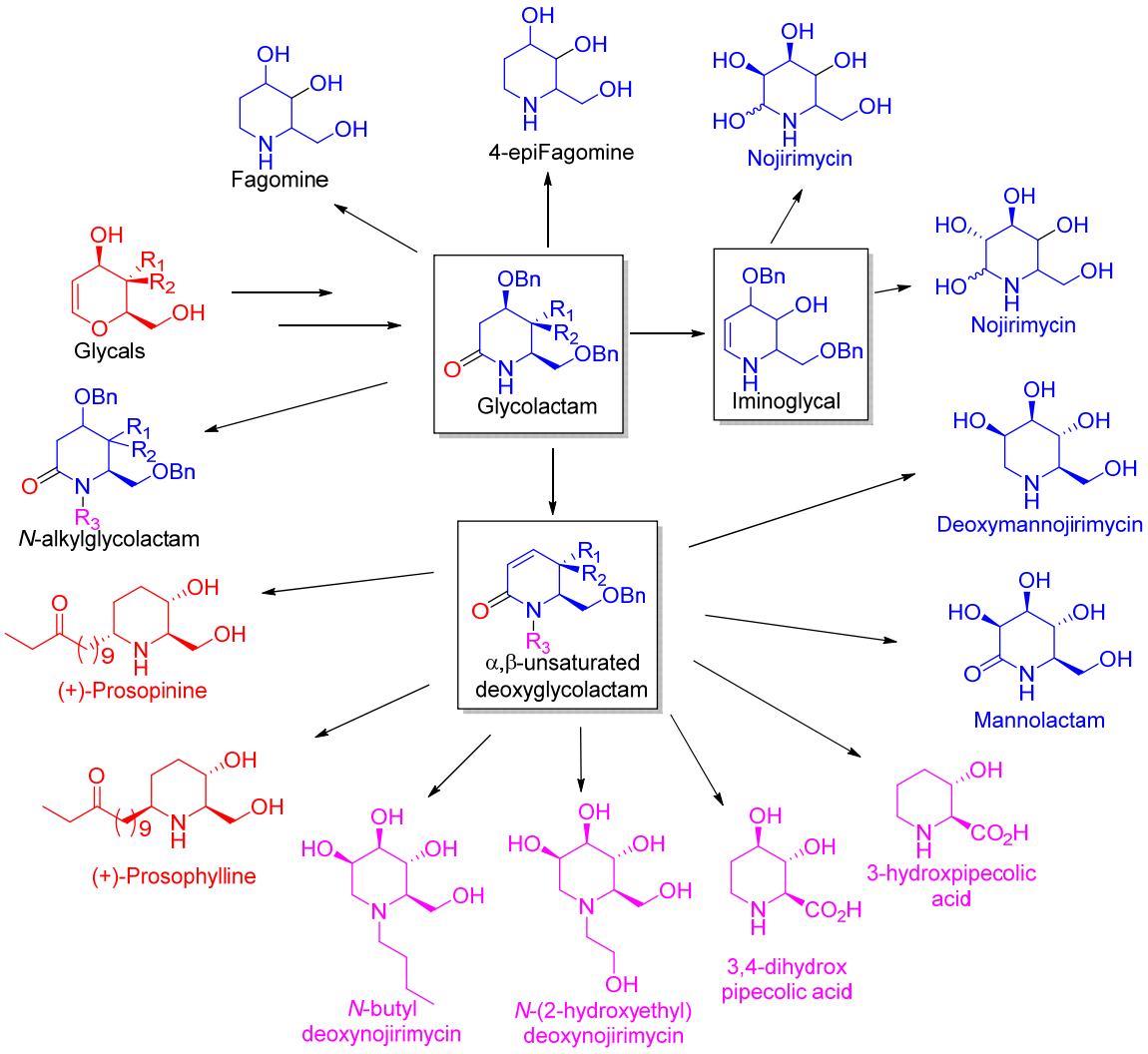


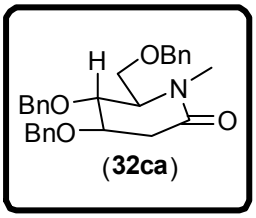
Figure 5. Privileged structures of molecules which could be synthesized by our approach.

1.2.6 Experimental

General procedure for the synthesis of *N*-alkylated product (**32ca**, **32cb**, **33ca**, **33cb**, **34 ca**, **34cb**, **21**, **21cb**, **35ca**, **35cb**, **36ca**, **36cb**, **37ca** and **37cb**)

To a solution of glycolactam (50 mg, 0.12 mmol) in 8 ml DMF at 0 °C was added NaH (60% dispersion in oil, 3.4 mg, 1.2 eq) and stirred at 0 °C for 10 min. Alkyl halide RX (2 eq) was added and stirred at 0 °C till complete consumption of starting material with periodic TLC check. Ethyl acetate (10 ml) was added followed by drop wise addition of cold sat. NH_4Cl solution with vigorous stirring. The aq. layer was extracted with ethyl acetate (4x10 ml), dried, concentrated and residual nonvolatile solvent was removed by co-distillation with toluene under reduced pressure with water bath temperature not exceeding 50°C, and crude was then subjected to flash chromatography.

Compound (**32ca**): (4*R*,5*R*,6*R*)-4,5-bis(benzyloxy)-6-((benzyloxy)methyl)-1-methylpiperidin-2-one.

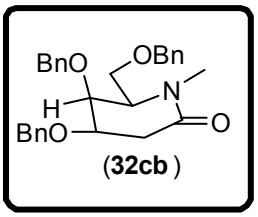


(**32ca**)

Colorless oil, $C_{28}H_{31}NO_4$, R_f 0.40 (EtOAc-petroleum ether, 1:1); 14h. Flash chromatography elution with 20-25 % EtOAc-petroleum ether, yield 65%; $[\alpha]^{25}_D$ +10.60 (*c* 0.73 $CHCl_3$); IR ($CHCl_3$): υ_{max} 3394, 3089, 3065, 3029, 3006, 2954, 2924, 2865, 1723, 1642, 1454, 1264, 1099, 1074, 754, 698cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 7.35 - 7.24 (m, 15H), 4.73 (d, *J* = 11.7 Hz, 1H), 4.62 - 4.54 (m, 2H), 4.53 - 4.44 (m, 1H), 4.42 (s, 2H), 3.93 (dd, *J* = 3.8, 6.2 Hz, 1H), 3.89 - 3.80 (m, 1H), 3.67 (dd, *J* = 5.5, 9.7 Hz, 1H), 3.52 (ddd, *J* = 4.0, 9.4, 17.1 Hz, 2H), 2.92 (s, 3H), 2.79 (dd, *J* = 4.8, 17.0 Hz, 1H), 2.50 (dd, *J* = 7.1, 16.9 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C = 168.4, 137.9, 137.8, 134.4, 128.5, 127.9, 127.9, 127.8, 127.7, 127.6, 127.6, 75.5, 75.2, 73.2, 72.9, 71.4, 68.5, 62.9, 34.8, 33.3; ESI-MS: *m/z* 468.14 $(M+Na)^+$; HRMS: *m/z* calcd for $C_{28}H_{32}NO_4$ 446.2326, found 446.2325.

Compound (**32cb**): (4*R*,5*S*,6*R*)-4,5-bis(benzyloxy)-6-((benzyloxy)methyl)-1-methylpiperidin-2-one.

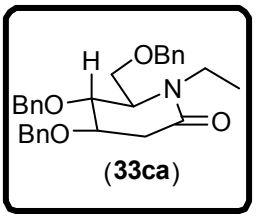
Colorless oil, $C_{28}H_{31}NO_4$, 18h, R_f 0.421 (EtOAc-petroleum ether, 1:1); $[\alpha]^{25}_D$ +12.43 (*c* 0.83, $CHCl_3$); Flash chromatography elution with 10-25 % EtOAc-petroleum ether, β (*N*-CH_3) + α (*N*-CH_3) yield 59 % (β+α); IR ($CHCl_3$): υ_{max} 3402, 3087, 3065, 3008, 2920, 2854, 1724, 1640, 1453, 1213, 1102, 1027, 756, 698, 667 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$, ^1H NMR data of one isomer) δ_H = 7.40-7.23 (m, 15H), 4.78 (d, J = 11.6 Hz, 1H), 4.65-4.56 (m, 3H), 4.47 (s, 2H), 4.0 -4.03 (m, 1H), 3.98 (dd, J = 4.3, 9.8 Hz, 1H), 3.88 (ddd, J = 1.7, 5.2, 6.9 Hz, 1 H), 3.79 (dd, J = 6.1, 10.1 Hz, 1H), 3.70 - 3.65 (m, 1H), 2.99 (s, 3H), 2.88 - 2.78 (m, 1H), 2.61 (dd, J = 5.0, 17.2 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$, ^{13}C NMR data of one isomer) δ_C = 167.9, 138.0, 137.9, 128.5, 128.4, 128.4, 127.8, 127.8, 127.7, 127.6, 127.4, 74.3, 73.8, 73.4, 72.8, 71.3, 71.1, 60.8, 35.3, 33.3;ESI-MS: *m/z* 468.03 $(M+Na)^+$; HRMS: *m/z* calcd for $C_{28}H_{31}NO_4Na$ 468.2145, found 468.2142.



(**32cb**)

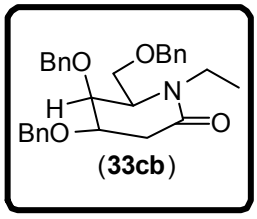
Compound (**33ca**): (4*R*,5*R*,6*R*)-4,5-bis(benzyloxy)-6-((benzyloxy)methyl)-1-ethylpiperidin-2-one.

Colorless oil, $C_{29}H_{33}NO_4$,14h, R_f 0.53 (EtOAc-petroleum ether, 1:1); Flash chromatography elution with 15-25 % EtOAc-petroleum ether, yield 60%; $[\alpha]^{25}_D$ -10.84 (*c* 1.11, $CHCl_3$); IR ($CHCl_3$): υ_{max} 3400, 3088, 3065, 3009, 2921, 2853, 1724, 1640, 1455, 1216, 1102, 1027, 756, 698, 667 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ_H = 7.38-7.22 (m, 15H), 4.71-4.63 (m, 1H), 4.63-4.53 (m, 2H), 4.53-4.46 (m, 1H), 4.43 (s, 2H), 3.97-3.91 (m, 1H), 3.87-3.74 (m, 2H), 3.73-3.65 (m, 1H), 3.63-3.57 (m, 1H), 3.55 (dd,J = 4.0, 9.2 Hz, 1H), 3.06 (qd, J = 13.7, 7.0 Hz, 1H), 2.78 (dd, J = 5.0, 16.9 Hz, 1H), 2.50 (dd, J = 6.9, 16.9 Hz, 1H), 1.10 (t, J = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C = 168.0, 137.9, 137.9, 137.7, 128.5, 127.9, 127.8, 127.8, 127.7, 127.6, 75.5, 75.4, 73.3, 72.4, 71.3, 69.2, 60.4, 40.4, 35.0, 12.7; ESI-MS: *m/z* 482.26.16 $(M+Na)^+$; HRMS: *m/z* calcd for $C_{29}H_{33}NO_4Na$ 482.2302, found 482.2299.



(**33ca**)

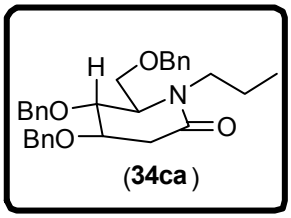
Compound (**33cb**): (4*R*,5*S*,6*R*)-4,5-bis(benzyloxy)-6-((benzyloxy)methyl)-1-ethylpiperidin-2-one.



(**33cb**)

Colorless oil, $C_{29}H_{33}NO_4$, 18h, R_f = 0.49 (EtOAc-petroleum ether, 7:3); Flash chromatography elution with 20-35 % EtOAc-petroleum ether, yield 55%; $[\alpha]^{25}_D$ +6.23 (*c* 0.68, $CHCl_3$); IR ($CHCl_3$): υ_{max} 3401, 3088, 3064, 3008, 2921, 2854, 1724, 1641, 1455, 1215, 1102, 1028, 756, 698, 667 cm^{-1};; ^1H NMR (500 MHz,$CDCl_3$) δ_H = 7.36-7.27 (m, 15H), 4.77 (d, J = 11.6 Hz, 1H), 4.65-4.56 (m, 3H), 4.48 (s, 2H), 4.04 - 3.98 (m, 2H), 3.86 (t, J = 5.3 Hz, 1H), 3.80 - 3.69 (m, 3H), 3.33 (qd, J = 7.0, 13.7 Hz, 1H), 2.81 (dd, J = 6.4, 17.4 Hz, 1H), 2.60 (dd, J = 5.2, 17.4 Hz, 1H), 1.09 (t, J = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, CDCl3) δ_C = 167.5, 138.1, 138.0, 137.9, 128.4, 127.8, 127.8, 127.7, 127.7, 127.6, 127.4, 74.6, 73.6, 73.4, 72.7, 71.4, 71.4, 58.6, 40.5, 35.7, 12.8; ESI-MS: *m/z* 482.24 $(M+Na)^+$; HRMS: *m/z* calcd for $C_{29}H_{34}NO_4$ 460.2482, found 460.2481.

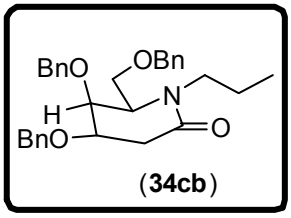
Compound (**34ca**): (4*R*,5*R*,6*R*)-4,5-bis(benzyloxy)-6-((benzyloxy)methyl)-1-propyl piperidine-2-one.



(**34ca**)

Colorless oil, $C_{30}H_{35}NO_4$, 17h, R_f 0.7 (EtOAc-petroleum ether, 1:1); $[\alpha]^{25}_D$ -7.94 (*c* 0.85 $CHCl_3$); Flash chromatography elution with 10-25 % EtOAc-petroleum ether, yield 60%; IR ($CHCl_3$): υ_{max}3401, 3086, 3065, 3008, 2921, 2853, 1724, 1640, 1456, 1215, 1102, 1027, 756, 698, 667 cm^{-1}; ^1H NMR (400MHz, $CDCl_3$) δ_H = 7.38-7.26 (m, 15H), 4.72-4.64 (m, 1H), 4.64-4.48 (m, 3H), 4.48-4.39 (m, 2H), 3.95 (dd, J = 3.2, 5.6 Hz, 1H), 3.90-3.75 (m, 2H), 3.71-3.64 (m, 1H), 3.64-3.58 (m, 1H), 3.56-3.50 (m, 1H), 2.92-2.84 (m, 1H), 2.84-2.73 (m, 1H), 2.55-2.46 (m, 1H), 1.62-1.54 (m, 2H), 0.87 (d, J = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C = 168.3, 137.9, 137.9, 137.7, 128.5, 127.8, 127.8, 127.7, 127.5, 75.7, 75.5, 73.3, 72.4, 71.3, 69.1, 60.5, 46.9, 35.0, 20.6, 11.2; ESI-MS: *m/z* 474.1 $(M+H)^+$; HRMS: *m/z* calcd for $C_{30}H_{35}NO_4$ 474.2639 found 474.2641.

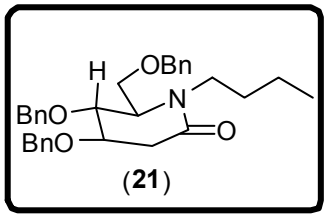
Compound (**34cb**): (4*R*,5*S*,6*R*)-4,5-bis(benzyloxy)-6-((benzyloxy)methyl)-1-propylpiperidin-2-one



(**34cb**)

Colorless oil, $C_{30}H_{35}NO_4$, 19h, R_f 0.47 (EtOAc-petroleum ether, 7:3); $[\alpha]^{25}_D$ +3.11 (*c* 1.2, $CHCl_3$); Flash chromatography elution with 20-30 % EtOAc-petroleum ether, yield 55%; IR ($CHCl_3$):υ_{max} 3400, 3088, 3065, 3009, 2922, 2855, 1724, 1640, 1456, 1218, 1102, 1027, 756, 698, 667 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ_H = 7.42 - 7.19 (m, 16H), 4.76 (d, J = 11.6 Hz, 1H), 4.66 - 4.55 (m, 3H), 4.52 - 4.41 (m, 2H), 4.06 - 3.96 (m, 2H), 3.87 (t, J = 4.9 Hz, 1H), 3.80 - 3.67 (m, 3H), 3.21 - 3.12 (m, 1H), 2.81 (dd, J = 17.4, 6.4 Hz, 1H), 2.61 (dd, J = 17.4, 4.9, Hz 1H), 1.67 - 1.53 (m, 2H), 0.83 (t, J = 7.5 Hz, 3H); ^{13}C NMR (125MHz, $CDCl_3$) δ_C = 167.6, 138.1, 138.0, 137.9, 128.4, 127.8, 127.7, 127.7, 127.7, 127.6, 127.4, 74.6, 73.6, 73.3, 72.6, 71.5, 71.4, 58.7, 47.1, 35.7, 20.5, 11.3; ESI-MS: *m/z* 474.2 $(M+Na)^+$; HRMS: *m/z* calcd for $C_{30}H_{35}NO_4Na$ 474.2639, found 474.2638.

Compound (**21**): (4*R*,5*R*,6*R*)-4,5-bis(benzyloxy)-6-((benzyloxy)methyl)-1-butylpiperidin-2-one.

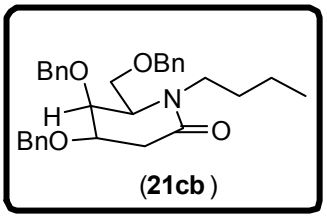


(**21**)

Colorless oil, $C_{31}H_{37}NO_4$, 15h, R_f 0.53 (EtOAc-petroleum ether, 1:1); Flash chromatography elution with 10-20 % EtOAc-petroleum ether, yield 55%; $[\alpha]^{25}_D$ -18.5 (*c* 1.34, $CHCl_3$); IR ($CHCl_3$): υ_{max} 3396, 3088, 3064, 3030, 3007, 2958, 2929, 2869, 1723, 1641, 1454, 1266, 1099, 1074, 754, 698 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ_H = 7.38 - 7.20 (m, 15H), 4.71 - 4.64 (m, 1H), 4.62 - 4.53 (m, 2H), 4.53 - 4.46 (m, 1H), 4.46 - 4.38 (m, 2H), 3.95 (dd, J = 3.2, 5.0 Hz, 1H), 3.87 - 3.78 (m, 2H), 3.71 - 3.63 (m, 1H), 3.62 - 3.57 (m, 1H), 3.53 (dd, J = 4.0, 9.5 Hz, 1H), 2.89 (ddd, J = 5.3, 8.9, 13.6 Hz, 1H), 2.78 (dd, J = 4.9, 16.8 Hz, 1H), 2.50 (dd, J = 7.3, 16.8 Hz, 1H), 1.57 - 1.40 (m, 2H), 1.34 - 1.27 (m, 2H), 0.88 (t, J = 7.2 Hz, 3H); ^{13}C NMR (125MHz, $CDCl_3$) δ_C = 168.1, 138.0, 137.9, 137.7, 128.5,

127.8, 127.8, 127.7, 127.6, 127.6, 75.8, 75.6, 73.3, 72.4, 71.3, 69.1, 60.5, 45.0, 35.1, 29.5, 20.1, 13.9; ESI-MS: *m/z* 510.13 $(M+Na)^+$; HRMS: *m/z* calcd for $C_{31}H_{38}NO_4$ 488.2795, found 488.2792.

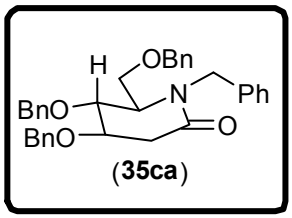
Compound (**21cb**): (4*R*,5*S*,6*R*)-4,5-bis(benzyloxy)-6-((benzyloxy)methyl)-1-butylpiperidin-2-one.



(**21cb**)

Colorless oil, $C_{31}H_{37}NO_4$, 20h, R_f 0.56 (EtOAc-petroleum ether, 7:3); Flash chromatography elution with 20-35% EtOAc-petroleum ether, yield 50%; $[\alpha]^{25}_D$ +3.03 (*c* 0.86, $CHCl_3$); IR ($CHCl_3$): υ_{max} 3395, 3088, 3063, 3029, 3006, 2957, 2928, 2868, 1721, 1640, 1454, 1263, 1097, 1074, 754, 697 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ_H = 7.35 - 7.26 (m, 15H), 4.76 (d, J = 11.6 Hz, 1H), 4.64 - 4.56 (m, 3H), 4.51 - 4.45 (m, 2H), 4.02 (dd,J = 3.4, 9.5 Hz, 1H), 3.99 (dd, J = 1.7, 4.4 Hz, 1H), 3.89 - 3.85 (m, 1H), 3.80 - 3.72 (m, 3H), 3.22 - 3.14 (m, 1H), 2.81 (dd, J = 6.1, 17.4 Hz, 1H), 2.61 (dd, J = 5.2, 17.4 Hz, 1H), 1.58 - 1.50 (m, 1H), 1.44 - 1.36 (m, 1H), 1.31 - 1.26 (m, 2H), 0.88 (t, J = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$)δ_C = 167.6, 138.1, 138.0, 138.0, 128.4, 127.8, 127.7, 127.6, 127.6, 127.4, 74.6, 73.6, 73.3, 72.6, 71.4, 71.4, 58.7, 45.3, 35.8, 29.4, 20.2, 13.9;ESI-MS: *m/z* 510.35 $(M+Na)^+$; HRMS: *m/z* calcd for $C_{31}H_{37}NO_4Na$510.2615, found 510.2613.

Compound (**35ca**): (4R,5R,6R)-1-benzyl-4,5-bis(benzyloxy)-6-((benzyloxy)methyl)piperidin-2-one.

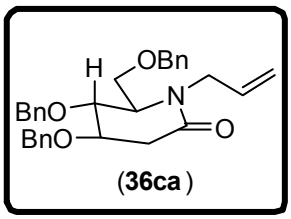


(**35ca**)

Colorless oil, $C_{34}H_{35}NO_4$, 12h, R_f 0.7 (EtOAc-petroleum ether, 7:3); Flash chromatography: Elution with 15-25 % EtOAc-petroleum ether, yield 42%; $[\alpha]^{25}_D$ -7.56 (*c* 1.33 $CHCl_3$); IR ($CHCl_3$): ν_{max} 3444, 3088, 3065, 3030, 2925, 2855, 1643, 1453, 1248, 1099, 756, 698, 666 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ_H =

7.35 - 7.13 (m, 20H), 5.32 (d, *J* = 15.4 Hz, 1H), 4.66 - 4.55 (m, 1H), 4.54 - 4.44 (m, 2H), 4.41 - 4.32 (m, 3H), 4.10 (d, *J* = 15.2 Hz, 1H), 3.95 - 3.91 (m, 1H), 3.88 (q, *J* = 5.5 Hz, 1H), 3.69 - 3.64 (m, 1H), 3.62 - 3.58 (m, 1H), 3.58 - 3.53 (m, 1H), 2.91 (dd, *J* = 5.1, 17.1 Hz, 1H), 2.63 (dd, *J* = 6.4, 17.1 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ_C = 168.5, 137.8, 137.8, 137.7, 137.1, 128.6, 128.5, 128.5, 128.4, 128.4, 127.9, 127.8, 127.8, 127.8, 127.7, 127.7, 127.5, 127.5, 127.2, 75.3, 75.2, 73.2, 72.1, 71.4, 69.1, 58.9, 47.7, 35.0; ESI-MS: *m/z* 544.28 $(M+Na)^+$; HRMS: *m/z* calcd for $C_{34}H_{35}NO_4Na$ 544.2458, found 544.2458.

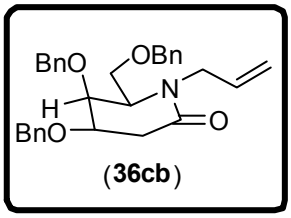
Compound (**36ca**): (4*R*,5*R*,6*R*)-1-allyl-4,5-bis(benzyloxy)-6-((benzyloxy)methyl)piperidin-2-one.



(**36ca**)

Colorless oil, 2h, R_f 0.59 (EtOAc-petroleum ether, 1:1); Flash chromatography elution with 20-25% EtOAc-petroleum ether, yield 60%; $[\alpha]^{25}_D$ - 2.72 (*c* 0.71 $CHCl_3$); IR ($CHCl_3$): ν_{max} 3446, 3086, 3064, 3030, 3007, 2922, 2855,1650,1456,1259, 1206, 1099, 1028, 739, 699 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ_H = 7.43 - 7.25 (m, 15H), 5.89 - 5.61 (m, 1H), 5.24 - 5.12 (m, 1H), 5.12 - 5.06 (m, 1H), 4.75 - 4.44 (m, 6H), 4.41 (s, 2H), 4.02 - 3.93 (m, 1H), 3.92 - 3.79 (m, 1H), 3.73 - 3.48 (m, 4H), 2.82 (dd, *J* = 5.0, 17.0 Hz, 1H), 2.54 (dd, *J* = 6.6, 17.1 Hz, 1H);^{13}C NMR (100MHz, $CDCl_3$) δ_C = 168.3, 137.9, 137.9, 137.8, 133.3, 128.5, 128.0, 127.9, 127.8, 127.6, 117.2, 75.4, 73.2, 72.5, 71.4, 68.9, 59.8, 47.4, 35.0; ESI-MS: *m/z* 494.25 $(M+Na)^+$;HRMS: *m/z* calcd for $C_{30}H_{33}NO_4Na$ 494.2302, found 494.2296.

Compound (**36cb**): (4*R*,5*S*,6*R*)-1-allyl-4,5-bis(benzyloxy)-6-((benzyloxy)methyl)piperidin-2-one.

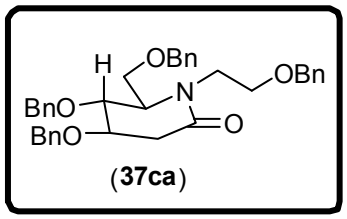


(**36cb**)

Colorless oil, $C_{30}H_{33}NO_4$,10h, R_f 0.45 (EtOAc-petroleum ether, 7:3); Flash chromatography elution with 10-20% EtOAc-petroleum ether, 71%; $[\alpha]^{25}_D$ +20.73 (*c* 1.27, $CHCl_3$); IR ($CHCl_3$): ν_{max} 3445, 3086, 3063, 3032, 3006, 2924, 2852, 1650, 1456, 1257, 1204,

1097, 1028, 739, 699 cm^{-1}; ^1H NMR (400MHz ,$CDCl_3$) δ_H = 7.36 - 7.23 (m, 15H), 5.80 - 5.67 (m, 1H), 5.16 - 5.03 (m, 2H), 4.76 (d, *J* = 11.7 Hz, 1H), 4.68 - 4.54 (m, 3H), 4.48 - 4.38 (m, 3H), 4.06 - 3.91 (m, 2H), 3.91 - 3.72 (m, 4H), 2.85 (dd, *J* = 6.5, 17.5 Hz, 1H), 2.63 (dd, *J* = 5.1, 17.6 Hz, 1H); ^{13}C NMR (100MHz, $CDCl_3$) δ_C = 167.7, 138.1, 138.0, 138.0, 133.1, 128.4, 127.8, 127.7, 127.7, 127.6, 127.4, 116.9,74.5, 73.8, 73.3, 72.7, 71.4, 71.1, 58.3, 47.3, 35.6; ESI-MS: *m/z* 494.27 $(M+Na)^+$; HRMS: *m/z* calcd for $C_{30}H_{34}NO_4$ 472.2482, found 472.2482.

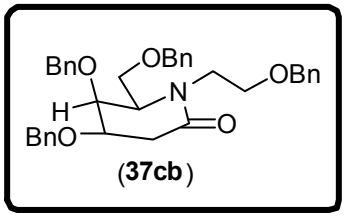
Compound (**37ca**): (4*R*,5*R*,6*R*)-4,5-bis(benzyloxy)-1-(2-(benzyloxy)ethyl)-6-((benzyloxy)methyl) piperidin-2-one.



(**37ca**)

Colorless oil, $C_{36}H_{39}NO_5$,18h, R_f 0.47 (EtOAc-petroleum ether, 1:1); Flash chromatography elution with 20-25 % EtOAc-petroleum ether, yield 50%; $[\alpha]^{25}_D$ -12.45 (*c* 0.79 $CHCl_3$); IR ($CHCl_3$): ν_{max} 3409, 3087, 2922, 2857, 2360, 1722, 1647, 1454, 1365, 1271, 1100, 1028, 738, 698 cm^{-1}. ^1H NMR (500MHz ,$CDCl_3$) δ_H = 7.33 - 7.22 (m, 20H), 4.64 - 4.60 (m, 1H), 4.59 - 4.53 (m, 2H), 4.51 - 4.46 (m, 1H), 4.44 (d, J = 3.7 Hz, 2H), 4.39 (s, 2H), 3.99 - 3.92 (m, 2H), 3.88 - 3.81 (m, 2H), 3.70 (dd, *J* = 6.3, 9.9 Hz, 1H), 3.67 - 3.63 (m, 1H), 3.60 (td, *J* = 5.0, 10.2 Hz, 2H), 3.32 (ddd, J = 5.2, 7.3, 14.0 Hz, 1H), 2.79 (dd, J = 5.2, 16.8 Hz, 1H), 2.52 (dd, J = 6.9, 16.9 Hz, 1H); ^{13}C NMR (125MHz, $CDCl_3$) δ_C = 168.6, 138.2, 138.0, 137.9, 137.8, 128.4, 128.4, 128.3, 127.8, 127.7, 127.6, 127.5, 75.5, 75.4, 73.2, 73.1, 72.1, 71.3, 69.2, 68.6, 61.4, 45.5, 35.1;ESI-MS: *m/z* 588.2 $(M+Na)^+$; HRMS: *m/z* calcd for $C_{36}H_{40}NO_5$ 566.2901, found 566.2900.

Compound (**37cb**): (4*R*,5*S*,6*R*)-4,5-bis(benzyloxy)-1-(2-(benzyloxy)ethyl)-6-((benzyloxy)methyl)piperidin-2-one.



(**37cb**)

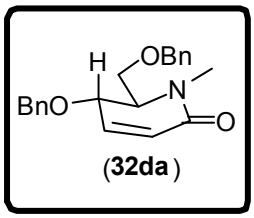
Colorless oil, $C_{36}H_{39}NO_5$, 24h, R_f 0.62 (EtOAc-petroleum ether, 7:3); Flash chromatography elution with 20-35% EtOAc-petroleum ether, 45%; $[\alpha]^{25}_D$ +13.78 (*c* 0.81, $CHCl_3$); IR ($CHCl_3$):

νmax 3408, 3087, 2924, 2857, 2360, 1722, 1646, 1455, 1365, 1270, 1100, 1025, 738, 698 cm-1; ^{1}H NMR (500MHz , $CDCl_3$) δH = 7.32 - 7.25 (m, 20H), 4.64 - 4.54 (m, 4H), 4.48 - 4.34 (m, 5H), 4.07 - 4.00 (m, 1H), 3.99-3.94 (m, 2H), 3.89 - 3.84 (m, 2H), 3.72 - 3.65 (m, 1H), 3.62 - 3.50 (m, 2H), 2.78 (dd, J = 17.5, 5.6 Hz, 1H), 2.60 (dd, J = 17.5 Hz, 5.3, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δC = 168.0, 138.4, 138.2, 138.1, 138.1, 128.4, 128.4, 127.7, 127.7, 127.6, 127.5, 127.4, 74.8, 73.6, 73.2, 72.9, 72.4, 71.8, 71.6, 68.3, 59.6, 45.4, 36.0; ESI-MS: m/z 588.68 (M+Na)+; HRMS: m/z calcd for $C_{36}H_{39}NO_5Na$ 588.2720, found 588.2722.

General procedure for the synthesis of *N*-alkyl-α,β-unsaturated glycolactam (32da, 32db, 33da, 33db, 34 da, 34db, 22, 22db, 35da, 35db, 36da, 36db, 37da, 37db)

To a solution of glycolactam (50 mg, 0.12 mmol) in 8 ml DMF at 0°C was added NaH (60% dispersion in oil, 15 mg, 5.3 eq) and stirred at 0°C for 10 min. Alkyl halide RX (2-5 eq) was added and stirred at 0°C till complete consumption of starting material with periodic TLC check. Ethyl acetate (10 ml) was added followed by cold sat. NH_4Cl solution dropwise with vigorous stirring. The aq layer was extracted with ethyl acetate (4x10 ml), dried, concentrated and residual nonvolatile solvent was removed by co-distillation with toluene under reduced pressure with water bath temperature not exceeding 50 °C, crude was then subjected to flash chromatography.

Compound (**32da**): (5*S*,6*R*)-5-(benzyloxy)-6-((benzyloxy)methyl)-1-methyl-5,6-dihydropyridin-2(1H)-one.

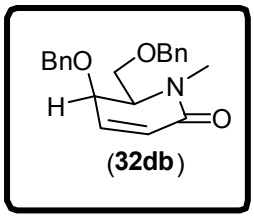


(**32da**)

Colorless oil, $C_{21}H_{23}NO_3$, 8h, R_f 0.45 (EtOAc-petroleum ether, 1:1); Flash chromatography elution with 15-25 % EtOAc-petroleum ether, yield 82%; $[\alpha]^{25}_{D}$ + 179.1280 (*c* 1.0, $CHCl_3$); IR ($CHCl_3$): νmax 3384, 3016, 2961, 2931, 2871, 2361, 1721, 1664, 1611, 1454, 1269, 1216, 1069, 768, 712, 668 cm-1; ^{1}H NMR (500MHz , $CDCl_3$) δH 7.37 - 7.24 (m, 10H), 6.42 (ddd, J=9.7, 5.5, 0.9 Hz, 1H),

6.07 (d, J = 10.1 Hz, 1H), 4.58 (s, 2H), 4.50 (d, J = 11.9 Hz, 1H), 4.44 (d, J = 11.9 Hz, 1H), 4.13 (dd, J = 0.9, 5.5 Hz, 1H), 3.79 - 3.74 (m, 1H), 3.53 (dd, J = 4.9, 9.5 Hz, 1H), 3.31 (t, J = 9.2 Hz, 1H), 3.01 (s, 3H); ^{13}C NMR (125MHz, $CDCl_3$) δC 162.5, 137.8, 137.4, 134.4, 128.5, 128.5, 128.0, 128.0, 127.9, 127.8, 127.6, 73.4, 70.4, 68.6, 67.9, 62.0, 34.0; ESI-MS: m/z 360.09 (M+Na)+; HRMS: m/z calcd for $C_{21}H_{24}NO_3Na$ 338.1751, found 338.1749.

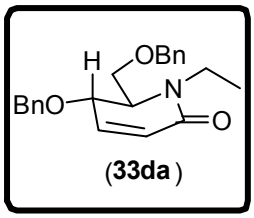
Compound (**32db**): (5*R*,6*R*)-5-(benzyloxy)-6-((benzyloxy)methyl)-1-methyl-5,6-dihydropyridin-2(1H)-one.



(**32db**)

Colorless oil, $C_{21}H_{23}NO_3$,12h, R_f 0.47 (EtOAc-petroleum ether, 1:1); Flash chromatography elution with 10-20 % EtOAc-petroleum ether, β (*N*-CH_3) + α (*N*-CH_3) yield 54% (β+α) ; $[\alpha]^{25}_D$ +65.32 (*c* 1.06, $CHCl_3$); IR ($CHCl_3$): ν_{max} 3383, 3015, 2961, 2931, 2873, 2361, 1720, 1663, 1611, 1454, 1269, 1216, 1069, 768, 712, 668 cm^{-1}; 34 h , ^{1}H NMR (400MHz, $CDCl_3$, ^{1}H NMR data of one isomer) δ_H = 7.40 - 7.24 (*m*, 10H), 6.38 (*d*, *J* = 10.1 Hz, 1H), 5.83 (*dd*, *J* = 10.1, 2.4 Hz, 1H), 4.65 (*dd*, *J* = 2.3, 3.5 Hz, 1H), 4.63 - 4.54 (*m*, 2H), 4.54 - 4.44 (*m*, 2H), 3.94 - 3.87 (*m*, 1H), 3.84 - 3.75 (*m*, 2H), 3.11 (*s*, 3H); ^{13}C NMR (100MHz, $CDCl_3$, ^{13}C NMR data of one isomer) δ_C = 163.5, 140.0, 138.0, 137.2, 128.6, 128.4, 128.1, 127.7, 127.5, 124.5, 73.6, 72.9, 71.6, 68.8, 61.1, 35.4; ESI-MS: *m/z* 360.01 $(M+Na)^+$; HRMS: *m/z* calcd for $C_{21}H_{23}NO_3$ 338.1751, found 338.1747.

Compound (**33da**): (5*S*,6*R*)-5-(benzyloxy)-6-((benzyloxy)methyl)-1-ethyl-5,6-dihydropyridin-2(1H)-one.



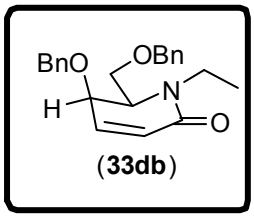
(**33da**)

Colorless oil, $C_{22}H_{25}NO_3$, 12h, R_f 0.32 (EtOAc-petroleum ether, 1:1); Flash chromatography elution with 20-25 % EtOAc-petroleum ether, yield 70%; $[\alpha]^{25}_D$ +140.63 (*c* 0.89, $CHCl_3$); IR ($CHCl_3$): ν_{max} 3446, 3064, 3006, 2925, 2855, 1668, 1611, 1471, 1455, 1217, 1090, 1070, 1027, 755, 699 cm^{-1}; ^{1}H NMR (500MHz, $CDCl_3$) δ_H = 7.38 - 7.25 (m, 10H), 6.41 (dd, J = 5.8, 8.9 Hz, 1H), 6.07 (d, J = 9.8 Hz, 1H),

4.65 - 4.54 (m, 2H), 4.52 - 4.41 (m, 2H), 4.13 (d, J = 5.2 Hz, 1H), 4.05 - 3.95 (m, 1H), 3.82 (dd, J = 4.4, 8.7 Hz, 1H), 3.50 (dd, J = 4.6, 9.5 Hz, 1H), 3.32 (t, J = 9.3 Hz, 1H), 2.89 (qd, J = 7.0, 13.7 Hz, 1H), 1.16 (t, J = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C = 161.9, 137.9, 137.5, 134.2, 128.6, 128.5, 128.5, 128.0, 127.9, 127.7, 127.6, 73.4, 70.4, 68.4, 59.0, 40.7, 12.9;ESI-MS: *m/z* 374.11 $(M+Na)^+$; HRMS: *m/z* calcd for $C_{22}H_{26}NO_3$ 352.1907, found 352.1906.

Compound (**33db**): (5*R*,6*R*)-5-(benzyloxy)-6-((benzyloxy)methyl)-1-ethyl-5,6-dihydropyridin-2(1H)-one.

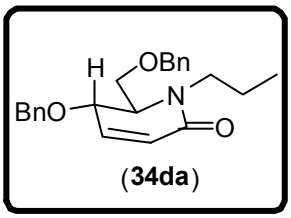
Colorless oil, $C_{22}H_{25}NO_3$, 14h, R_f 0.57 (EtOAc-petroleum ether, 7:3); Flash chromatography elution with 10-20 % EtOAc-petroleum ether, 49%; $[\alpha]^{25}_D$ +32.66 (*c* 1.0, $CHCl_3$); IR ($CHCl_3$): ν_{max} 3446, 3063, 3006, 2924, 2853, 1668, 1611, 1473, 1453, 1214, 1089, 1070, 1028, 755, 699 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H = 7.50 - 7.26 (m, 10H), 6.39 (d, J = 9.9 Hz, 1H), 5.85 (dd, J = 2.3, 9.9 Hz, 1H), 4.69 - 4.64 (m, 1H), 4.64 - 4.58 (m, 2H), 4.56 - 4.47 (m, 2H), 4.09 (qd, J = 7.2, 13.9 Hz, 1H), 3.95 (dd, J = 9.5, 3.1 Hz, 1H), 3.90 - 3.83 (m, 1H), 3.81 - 3.73 (m, 1 H), 3.12 (qd, J = 13.9, 6.9 Hz, 1H), 1.18 (*t*, *J* = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C = 162.8, 140.0, 138.0, 137.2, 128.6, 128.4, 128.1, 127.8, 127.7, 127.5, 124.7, 73.7, 73.6, 71.6, 69.0, 58.0, 41.7, 13.8; ESI-MS: *m/z* 374.03 $(M+Na)^+$; HRMS: *m/z* calcd for $C_{22}H_{26}NO_3$ 352.1907, found 352.1904.



(**33db**)

Compound (**34da**): (5*S*,6*R*)-5-(benzyloxy)-6-((benzyloxy)methyl)-1-propyl-5,6-dihydropyridin-2(1H)-one.

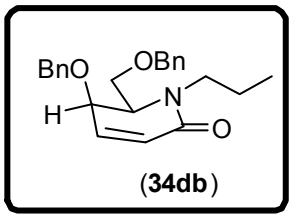
Colorless oil, $C_{23}H_{27}NO_3$,17h, R_f 0.46 (EtOAc-petroleum ether, 7:3); Flash chromatography elution with 10-20 % EtOAc-petroleum ether, yield 73%; $[\alpha]^{25}_D$ +130.42 (*c* 1.05, $CHCl_3$); IR ($CHCl_3$): ν_{max} 3384, 3015, 2963, 2930, 2870, 2361, 1721, 1664, 1611, 1452, 1269, 1216, 1069, 768, 712, 668 cm^{-1}; ^{1}H NMR (500MHz, $CDCl_3$) δ_H 7.36 - 7.26 (m, 10H), 6.41 (ddd, J = 9.7, 5.6, 1.2, Hz, 1H), 6.06



(**34da**)

(d, J = 9.8 Hz, 1H), 4.62 (d, J = 11.9 Hz, 1H), 4.57 (d, J = 11.9 Hz, 1H), 4.49 (d, J = 11.9 Hz, 1H), 4.44 (d, J = 11.9 Hz, 1H), 4.13 - 4.10 (m, 1H), 3.97 (td, J = 7.6, 13.4 Hz, 1H), 3.82 (dd, J = 4.6, 9.2 Hz, 1H), 3.49 (dd, J = 4.7, 9.6 Hz, 1H), 3.31 (t, J = 9.5 Hz, 1H), 2.73 (td, J = 6.9, 13.7 Hz, 1H), 1.59 (sxt, J = 7.3 Hz, 2H), 0.92 (t, J = 7.3 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C 162.2, 137.9, 137.5, 134.1, 128.5, 128.5, 128.0, 127.9, 127.7, 127.6, 73.4, 70.5, 68.5, 68.2, 59.1, 47.3, 21.1, 11.2; ESI-MS: *m/z* 388.2 $(M+H)^+$; HRMS: *m/z* calcd for $C_{23}H_{28}NO_3$ 366.2064, found 366.2063.

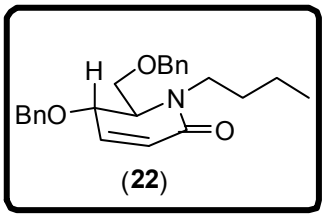
Compound (**34db**): (5*R*,6*R*)-5-(benzyloxy)-6-((benzyloxy)methyl)-1-propyl-5,6-dihydropyridin-2(1H)-one.



(**34db**)

Colorless oil, $C_{23}H_{27}NO_3$, 20h, R_f 0.63 (EtOAc-petroleum ether, 7:3); Flash chromatography elution with 20-35% EtOAc-petroleum ether, yield 52%; $[\alpha]^{25}_D$ +29.37 (*c* 1.05 $CHCl_3$); IR ($CHCl_3$): ν_{max} 3402, 3083, 3066, 3006, 2923, 2854, 1724, 1640, 145, 1216, 1103, 1027, 756, 698, 667 cm^{-1}; ^{1}H NMR (500MHz, $CDCl_3$) δ_H = 7.39 - 7.24 (m, 10H), 6.35 (d, J = 10.1 Hz, 1H), 5.81 (dd, J = 2.4, 10.1 Hz, 1H), 4.65 - 4.54 (m, 3H), 4.52 - 4.44 (m, 2H), 4.04 (td, J = 7.3, 14.0 Hz, 1H), 3.91 (dd, J = 3.4, 9.8 Hz, 1H), 3.84 - 3.77 (m, 1H), 3.77 - 3.70 (m, 1H), 2.98 - 2.89 (m, 1H), 1.62 - 1.52 (m, 2H), 0.89 (t, J = 7.3 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C = 163.0, 140.0, 138.0, 137.2, 128.6, 128.4, 128.1, 127.8, 127.7, 127.5, 124.7, 73.6, 73.5, 71.6, 69.0, 58.5, 48.5, 21.7, 11.3;ESI-MS: *m/z* 366.2 $(M+H)^+$; HRMS: *m/z* calcd for $C_{23}H_{28}NO_3$ 366.2064, found 366.2062.

Compound (**22**): (5*S*,6*R*)-5-(benzyloxy)-6-((benzyloxy)methyl)-1-butyl-5,6-dihydropyridin-2(1H)-one.



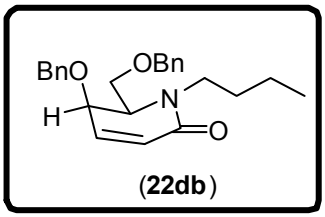
(**22**)

Colorless oil, $C_{24}H_{29}NO_3$, 4h, R_f 0.41 (EtOAc-petroleum ether, 1:1); Flash chromatography elution with 20-35% EtOAc-petroleum ether, yield 73%; $[\alpha]^{25}_D$ +133.4359 (*c* 1.17 $CHCl_3$); IR ($CHCl_3$): ν_{max} 3384, 3017, 2962, 2931, 2872, 2361, 1721, 1664, 1611, 1452, 1269, 1216, 1069, 768, 712, 668 cm^{-1}; ^{1}H NMR

(500MHz, $CDCl_3$) δ_H = 7.40 - 7.24 (m, 10H), 6.42 (ddd, *J* = 1.5, 5.6, 9.7 Hz, 1H), 6.06 (d, *J* = 9.7 Hz, 1H), 4.65 - 4.35 (m, 4H), 4.18 - 4.05 (m, 1H), 4.05 - 3.91 (m, 1H), 3.82 (tdd, *J* = 1.3, 4.6, 9.4 Hz, 1H), 3.50 (dd, *J* = 4.7, 9.5 Hz, 1H), 3.30 (t, *J* = 9.5 Hz, 1H), 2.75 (td, *J* = 6.8, 13.5 Hz, 1H), 1.60 - 1.44 (m, 2H), 1.42 - 1.29 (m, 2H), 0.94 - 0.84 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C = 162.2, 137.9, 137.5, 134.1, 128.6, 128.6, 128.0, 127.9, 127.8, 127.7, 73.4, 70.5, 68.6, 68.2, 59.1, 45.5, 30.1, 20.0, 14.0; ESI-MS: *m/z* 402.09 $(M+Na)^+$;HRMS: *m/z* calcd for $C_{24}H_{30}NO_3$ 380.2220, found 380.2217.

Compound (**22db**): (5*R*,6*R*)-5-(benzyloxy)-6-((benzyloxy)methyl)-1-butyl-5,6-dihydropyridin-2(1H)-one.

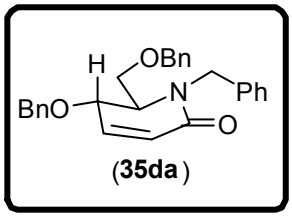
Colorless oil, $C_{24}H_{29}NO_3$,15h, R_f 0.47 (EtOAc-petroleum ether, 1:1); Flash chromatography elution with 10-20 % EtOAc-petroleum ether, yield 60%; $[\alpha]^{25}_D$ +36.23 (*c* 1.10, $CHCl_3$); IR ($CHCl_3$): ν_{max} 3382, 3016, 2961, 2931, 2872, 2361, 1720, 1665, 1612, 1451, 1268, 1215, 1068, 767, 714, 665 cm^{-1};



(**22db**)

^{1}H NMR (500 MHz, $CDCl_3$) δ_H 7.40-7.23 (m, 10H), 6.35 (d, J = 10.1 Hz, 1H), 5.81 (dd, J = 10.1, 2.4 Hz, 1H), 4.65-4.61 (m, 1H), 4.61-4.55 (m, 2H), 4.52-4.44 (m, 2H), 4.11-4.03 (m, 1H), 3.91 (dd, J = 9.6, 3.2 Hz, 1H), 3.83 - 3.77 (m, 1H), 3.76 - 3.71 (m, 1H), 3.01 - 2.92 (m, 1H), 1.52 (quin, J = 7.5 Hz, 2H), 1.33 - 1.28 (m, 2H), 0.91 (t, J = 7.3 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C 163.0, 140.0, 138.0, 137.2, 128.6, 128.4, 128.1, 127.8, 127.7, 127.5, 124.7, 73.6, 73.5, 71.6, 69.0, 58.4, 46.6, 30.7, 20.1, 13.9;ESI-MS: *m/z* 402.11 $(M+Na)^+$; HRMS: *m/z* calcd for $C_{24}H_{30}NO_3$ 380.2220, found 380.2220.

Compound (**35da**): (5*S*,6*R*)-1-benzyl-5-(benzyloxy)-6-((benzyloxy)methyl)-5,6-dihydropyridin-2(1H)-one.



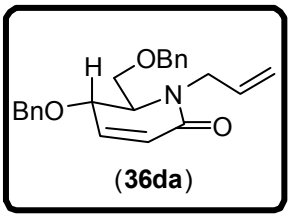
(**35da**)

Colorless oil, $C_{27}H_{27}NO_3$, 8h, R_f 0.62 (EtOAc-petroleum ether, 7:3); Flash chromatography elution with 10-15% EtOAc-petroleum ether, yield 77%; $[\alpha]^{25}_D$ +173.41 (*c* 1.4,

$CHCl_3$); IR ($CHCl_3$): ν_{max} 3064, 3030, 3007, 2923, 2860, 1721, 1668, 1612, 1495, 1452, 1266, 1094, 754, 699cm^{-1}; ^1H NMR (500MHz, $CDCl_3$) δ_H 7.38 - 7.22 (m, 13H), 7.13 (brs., 2H), 6.48 - 6.45 (m, 1H), 6.16 (d, *J* = 9.5 Hz, 1H), 5.38 (d, J = 15.3 Hz, 1H), 4.44 (d, J = 11.9 Hz, 1H), 4.40 (d, J = 11.9 Hz, 1H), 4.32 (d, J = 11.6 Hz, 1H), 4.28 (d, J = 11.6 Hz, 1H), 4.13 - 4.05 (m, 1H), 4.00 (d, J = 15.3 Hz, 1H), 3.83 (brs., 1H), 3.48 (dd, J = 3.8, 8.7 Hz, 1H), 3.34 (t, J = 9.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C 162.5, 137.6, 137.5, 137.0, 134.8, 128.6, 128.5, 128.4, 128.1, 128.1, 128.0, 127.8, 127.6, 127.4, 73.3, 70.2, 68.6, 68.1, 57.4, 48.1;ESI-MS: *m/z* 436.07 $(M+Na)^+$; HRMS: *m/z* calcd for $C_{27}H_{27}NO_3Na$ 436.1883, found 436.1880.

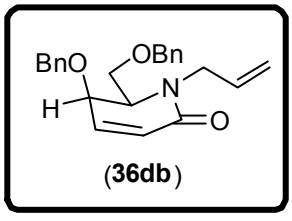
Compound (**36da**): (5S,6R)-1-allyl-5-(benzyloxy)-6-((benzyloxy)methyl)-5,6-dihydropyridin-2(1H)-one.

Colorless oil, $C_{23}H_{25}NO_3$, 30min, R_f 0.41 (EtOAc-petroleum ether, 1:1); Flash chromatography elution with 20-35 % EtOAc-petroleum ether, yield 77%; $[\alpha]^{25}_D$ +160.41 (*c* 1.22 $CHCl_3$); IR ($CHCl_3$): ν_{max} 3445, 3065, 3012, 2923, 2855, 2361, 2340, 1721, 1668, 1613, 1417, 1217, 1109, 1068, 757, 699 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ_H = 7.40 - 7.21 (m, 10H), 6.44 (ddd, *J* = 1.5, 5.6, 9.8 Hz, 1H), 6.09 (d, *J* = 9.9 Hz, 1H), 5.90 - 5.66 (m, 1H), 5.37 - 5.21 (m, 1H), 5.16 (dd, *J* = 1.3, 10.1 Hz, 1H), 4.72 - 4.62 (m, 1H), 4.61 - 4.52 (m, 2H), 4.51 - 4.42 (m, 2H), 4.13 (dd, *J* = 1.4, 5.6 Hz, 1H), 3.88 (tdd, *J* = 1.4, 4.8, 9.1 Hz, 1H), 3.59 - 3.42 (m, 2H), 3.39 - 3.24 (m, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ_C = 162.1, 137.8, 137.5, 134.6, 133.0, 128.5, 128.1, 127.9, 127.9, 127.6, 117.6, 77.7, 77.1, 76.4, 73.3, 70.4, 68.7, 68.2, 58.2, 47.7;ESI-MS: *m/z* 386.04 $(M+Na)^+$;HRMS: *m/z* calcd for $C_{23}H_{25}NO_3Na$ 386.1727, found 386.1722.



(**36da**)

Compound (**36db**): (5*R*,6*R*)-1-allyl-5-(benzyloxy)-6-((benzyloxy)methyl)-5,6-dihydropyridin-2(1H)-one.



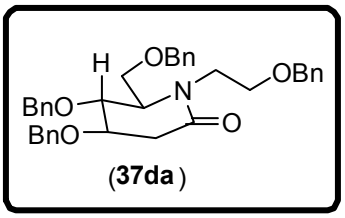
(**36db**)

Colorless oil, $C_{23}H_{24}NO_3$, 3h, R_f 0.58 (EtOAc-petroleum ether, 1:1); Flash chromatography elution with 10-20 %

EtOAc-petroleum ether, yield 79%; $[\alpha]^{25}_{D}$ +54.89 (*c* 1.15, $CHCl_3$); IR ($CHCl_3$): ν_{max} 3444, 3065, 3013, 2923, 2855, 2362, 2341, 1721, 1668, 1613, 1417, 1215, 1106, 1068, 757, 699 cm^{-1}; ^1H NMR (500MHz, $CDCl_3$) δ_H = 7.40 - 7.19 (*m*, 10H), 6.38 (d, J = 10.1 Hz, 1H), 5.85 (dd, J = 10.1, 2.4 Hz, 1H), 5.78 (dddd, J = 4.3, 7.2, 10.2, 17.1 Hz, 1H), 5.23 - 5.11 (m, 2H), 4.87 - 4.76 (m, 1H), 4.65 - 4.52 (m, 3H), 4.52 - 4.42 (m, 2H), 3.93 - 3.83 (m, 2H), 3.82 - 3.74 (m, 1H), 3.59 (dd, *J* = 7.3, 15.6 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C = 162.8, 140.4, 138.0, 137.1, 133.8, 128.6, 128.4, 128.1, 127.8, 127.7, 127.5, 124.4, 117.2, 73.5, 73.3, 71.7, 68.8, 57.0, 48.5;ESI-MS: *m/z* 386.07 $(M+Na)^+$; HRMS: *m/z* calcd for $C_{23}H_{25}NO_3$ 364.1907, found 364.1903.

Compound (**37da**): (5*S*,6*R*)-5-(benzyloxy)-1-(2-(benzyloxy)ethyl)-6-((benzyloxy) methyl)-5,6-dihydropyridin-2(1H)-one.

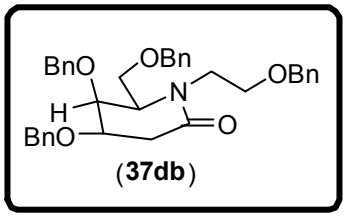
Colorless oil, $C_{29}H_{31}NO_4$, 10h, R_f 0.31 (EtOAc-petroleum ether, 1:1); Flash chromatography elution with 35-40 % EtOAc-petroleum ether, yield 67%; $[\alpha]^{25}_{D}$ +107.59 (*c* 1.17, $CHCl_3$); IR ($CHCl_3$): ν_{max} 3062, 3030, 3006, 2924 ,2860, 1669, 1614, 1495, 1456, 1360, 1204, 1101, 1028, 820, 739, 699 cm^{-1};



(**37da**)

^1H NMR (500 MHz, $CDCl_3$) δ_H = 7.39 - 7.16 (m, 15H), 6.43 (dd, *J* = 6.6, 9.6 Hz, 1H), 6.07 (d, *J* = 9.8 Hz, 1H), 4.59 - 4.35 (m, 6H), 4.17 - 4.00 (m, 3H), 3.74 - 3.61 (m, 2H), 3.58 (dd, *J* = 4.7, 9.6 Hz, 1H), 3.35 - 3.18 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C = 162.5, 138.1, 137.9, 137.6, 134.8, 128.4, 128.4, 128.3, 128.1, 127.8, 127.8, 127.8, 127.7, 127.6, 127.6, 73.3, 73.2, 70.1, 69.1, 68.4, 68.2, 60.0, 46.2;ESI-MS: *m/z* 480.16 $(M+Na)^+$;HRMS: *m/z* calcd for $C_{29}H_{31}NO_4Na$ 480.2145, found 480.2141.

Compound (**37db**): (5*R*,6*R*)-5-(benzyloxy)-1-(2-(benzyloxy)ethyl)-6-((benzyloxy) methyl)-5,6-dihydropyridin-2(1H)-one.



(**37db**)

Colorless oil, $C_{29}H_{31}NO_4$, 15h, R_f 0.47 (EtOAc-petroleum ether, 7:3); Flash chromatography elution with 20-35 % EtOAc-petroleum ether, β (*N*-$(CH_2)_2$-OBn) + α (*N*-$(CH_2)_2$-OBn) yield (β+α) 53%; $[\alpha]^{25}_{D}$ +52.44 (*c* 0.97 $CHCl_3$); IR ($CHCl_3$): ν_{max}3061,

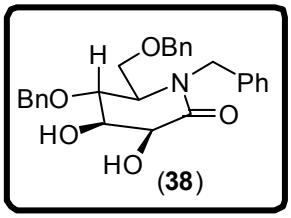
3029, 3003, 2924, 2861, 1668, 1613, 1497, 1455, 1362, 1208, 1102, 1026, 820, 739, 699 cm^{-1}; ^1H NMR (500MHz, $CDCl_3$, ^1H NMR data of one isomer) δ_H = 7.35 - 7.20 (m, 15H), 6.35 (d, *J* = 10.1 Hz, 1H), 5.81 (dd, *J* = 2.4, 10.1 Hz, 1H), 4.63 - 4.57 (m, 1H), 4.52 - 4.43 (m, 5H), 4.36 - 4.28 (m, 2H), 4.12 (brs., 1H), 3.84 (dd, J = 3.2, 9.9 Hz, 1H), 3.76 (t, J = 9.2 Hz, 1H), 3.69 - 3.61 (m, 2H), 3.29 (ddd, J = 4.3, 9.2, 14.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$, ^{13}C NMR data of one isomer) δ_C = 163.1, 140.9, 138.4, 138.1, 137.3, 128.5, 128.4, 128.0, 127.7, 127.6, 127.6, 127.5, 124.2, 73.6, 73.5, 73.3, 71.5, 69.6, 68.9, 59.3, 47.0; ESI-MS: *m/z* 480.11 $(M+Na)^+$; HRMS: *m/z* calcd for $C_{29}H_{31}NO_4Na$ 480.2145, found 480.2141.

General procedure for dihydroxylation; synthesis of (38/41/42);

To a vigorously stirred solution of compound (**35da/22/37da**) (46.5 mg, 0.113 mmol) in CH_3CN (1.2 ml) at 0-5°C was added a solution of $RuCl_3.3H_2O$ (15 ul, 0.1 M aq 0.105 eq) and $NaIO_4$ (48 mg, 0.226 mmol, 2 eq) in distilled water (0.2 ml). The mixture was stirred for 35 min by complete consumption of starting material (TLC). The suspension was then filtered through a thin pad of silica gel, which was washed with ethyl acetate (20 ml). Concentration of the filtrate and flash chromatography gave the diol.

Compound **(38)**: (3*S*,4*R*,5*R*,6*R*)-1-benzyl-5-(benzyloxy)-6-((benzyloxy)methyl)-3,4-dihydroxypiperidin-2-one.

Colorless oil, $C_{27}H_{29}NO_5$, 35 min, R_f 0.6 (EtOAc-petroleum ether, 7:3); Flash chromatography elution with 20-25% EtOAc-petroleum ether, yield 43% $[\alpha]^{25}_D$ +12.96 (*c* 1.6 $CHCl_3$); IR ($CHCl_3$): ν_{max} 3443, 3066, 3018, 2926, 2401, 2361, 1722, 1641, 1453, 1215, 1075, 1029, 757, 699, 669 cm^{-1};; ^1H NMR (400MHz, $CDCl_3$) δ_H = 7.39 - 7.25 (m, 10H), 7.21 - 7.04 (m, 5H), 5.27 (d, *J* = 15.4 Hz, 1H), 4.51 - 4.39 (m, 5H), 4.38 - 4.29 (m, 2H), 3.96 (t, *J* = 2.9 Hz, 2H), 3.78 - 3.70 (m, 2H), 3.66 (s, 1H), 3.08 (br. s., 1H); ^{13}C NMR (100MHz, $CDCl_3$) δ = ^{13}C NMR (100MHz , $CDCl_3$) δ_C = 171.2, 137.4, 137.2, 136.8, 128.6, 128.5, 128.5, 128.0, 127.9, 127.8, 127.3, 75.2,

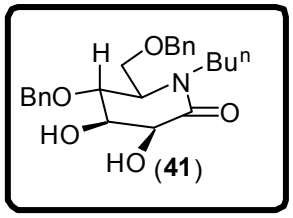


(**38**)

73.2, 71.6, 69.5, 68.9, 68.1, 59.0, 47.6; ESI-MS: *m/z* 448.2 $(M+H)^+$; HRMS: *m/z* calcd for $C_{27}H_{29}NO_5Na$ 470.1938 found 470.1937.

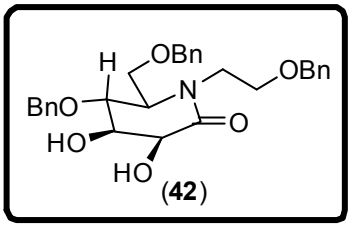
Compound **(41)**: (3*S*,4*R*,5*R*,6*R*)-5-(benzyloxy)-6-((benzyloxy)methyl)-1-butyl-3,4-dihydroxy-piperidin-2-one.

Pale yellow oil, $C_{24}H_{31}NO_5$, 45 min, R_f 0.3 (EtOAc-petroleum ether, 1:1); Flash chromatography elution with 15-25% EtOAc-petroleum ether, yield 46%; $[\alpha]^{25}_D$ -0.89 (*c* 0.75, $CHCl_3$); IR ($CHCl_3$): ν_{max} 3411, 3066, 3016, 2959, 2928, 2858, 1724, 1638, 1494, 1367, 1300, 1216, 1028, 757, 698, 667 cm^{-1}; ^1H NMR (400MHz, $CDCl_3$) δ_H 7.40 - 7.21 (m, 10H), 4.65 - 4.59 (m, 2H), 4.51 - 4.45 (m, 2H), 4.30 (dd, J = 10.3, 3.2 Hz, 2H), 4.00 (brs., 1H), 3.93 - 3.75 (m, 3H), 3.74 - 3.68 (m, 1H), 3.68 - 3.60 (m, 1H), 3.12 - 3.00 (m, 1H), 2.86 (brs, 1H), 1.58 - 1.43 (m, 2H), 1.33 - 1.27 (m, 2H), 0.88 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100MHz, $CDCl_3$) δ_C 170.5, 137.5, 137.4, 128.5, 128.0, 127.9, 127.8, 75.0, 73.3, 71.8, 69.5, 68.6, 67.8, 60.1, 44.8, 29.6, 20.0, 13.8;ESI-MS: *m/z* 436.11 $(M+Na)^+$; HRMS: *m/z* calcd for $C_{24}H_{31}NO_5Na$ 436.2094, found 436.2088.



Compound **(42)**: (3*S*,4*R*,5*R*,6*R*)-5-(benzyloxy)-1-(2-(benzyloxy)ethyl)-6-((benzyloxy) methyl)-3,4-dihydroxypiperidin-2-one.

Pale yellow oil, $C_{29}H_{33}NO_6$, 55 min, R_f 0.37 (EtOAc-petroleum ether, 7:3); Flash chromatography elution with 30-40 % EtOAc-petroleum ether, yield 57%; $[\alpha]^{25}_D$ +17.25 (*c* 1.07, $CHCl_3$); IR ($CHCl_3$): ν_{max} 3410, 3066, 3015, 2922, 2853, 1723, 1640, 1495, 1454, 1365, 1216, 1028, 757, 698, 667 cm^{-1}; ^1H NMR (400MHz ,) δ_H = 7.35 - 7.24 (m, 15H), 4.61 - 4.51 (m, 2H), 4.51 - 4.41 (m, 4H), 4.31 (s, 2H), 4.02 (td, J = 14.2, 4.5 Hz, 1H), 3.93 (brs, 1H), 3.87 (d, J = 6.6 Hz, 3H), 3.77 - 3.70 (m, 1H), 3.68 - 3.56 (m, 2H), 3.51 - 3.42 (m, 1H), 2.85 (brs, 1H), 1.61 (brs, 1H);^{13}C NMR (100 MHz, $CDCl_3$) δ_C = 170.9, 138.1, 137.5, 137.4, 128.5, 128.4, 128.0, 127.9, 127.8, 127.8, 127.6, 127.6, 75.3, 73.2, 71.6,

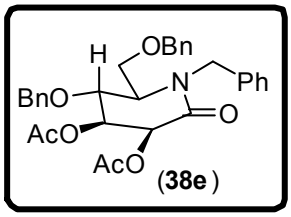


69.1, 68.8, 68.2, 68.0, 60.3, 44.7; ESI-MS: *m/z* 514.2 $(M+Na)^+$; HRMS: *m/z* calcd for $C_{29}H_{33}NO_6Na$ 514.2200, found 514.2198.

General procedure for acetylation of diols; Synthesis of (38e/ 41e).

To a stirred solution of (**38/ 41**) 75 mg was added Ac2O under N2 atmosphere and stirred at rt for overnight. On completion of the reaction al the contents were evaporated in vacuo and subjected to flash column chromatography.

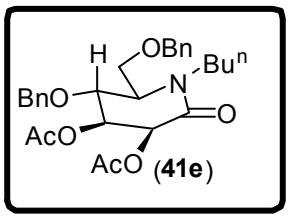
Compound of (**38e**): (3*S*,4*S*,5*R*,6*R*)-1-benzyl-5-(benzyloxy)-6-((benzyloxy)methyl)-2-oxopiperidine-3,4-diyl diacetate.



(**38e**)

Colorless oil, $C_{31}H_{33}NO_7$, 10h, R_f 0.61 (EtOAc-petroleum ether, 1:1); Flash chromatography elution with 20-25% EtOAc-petroleum ether, yield 99% $[\alpha]^{25}_D$ +14.35 (*c* 1.05 $CHCl_3$); IR ($CHCl_3$): υ_{max} 3447, 3066, 3019, 2928, 2859, 2361, 2340, 1751, 1662, 1496, 1452, 1218, 1076, 1030, 757, 699, 668 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ_H = 7.38 - 7.11 (m, 15H), 5.81 (d, *J* = 3.7 Hz, 1H), 5.50 (t, *J* = 3.8 Hz, 1H), 5.26 (d, *J* = 15.4 Hz, 1H), 4.59 (d, *J* = 11.7 Hz, 1H), 4.45 (d, *J* = 11.5 Hz, 1H), 4.41 - 4.24 (m, 3H), 3.94 (t, *J* = 3.8 Hz, 1H), 3.73 - 3.63 (m, 1H), 3.60 - 3.50 (m, 2H), 2.16 (s, 3H), 1.98 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C = 169.9, 169.7, 165.8, 137.3, 136.9, 136.8, 128.7, 128.6, 128.5, 128.1, 128.0, 127.9, 127.4, 127.4, 73.2, 72.8, 71.8, 69.9, 68.3, 67.2, 58.8, 47.4, 20.8, 20.7; ESI-MS: *m/z* 554.1 $(M+Na)^+$; HRMS: *m/z* calcd $C_{31}H_{34}NO_7$ 532.2330 found 532.2327

Compound of (**41e**): (3*S*,4*S*,5*R*,6*R*)-5-(benzyloxy)-6-((benzyloxy)methyl)-1-butyl-2-oxopiperidine-3,4-diyl diacetate.



(**41e**)

Colorless oil, $C_{28}H_{35}NO_7$, 8 h , R_f 0.48 (EtOAc-petroleum ether, 1:1); Flash chromatography elution with 10-20% EtOAc-petroleum ether, yield 97%; $[\alpha]^{25}_D$ -14.49 (*c* 0.9, $CHCl_3$); IR ($CHCl_3$): υ_{max} 3447, 3066, 3020, 2928, 2859, 2361, 2340, 1751, 1663, 1218, 1076, 1028, 757, 699 668 cm^{-1}; ^1H NMR (400MHz,

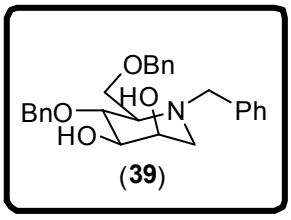
$CDCl_3$) δ_H 7.38 - 7.19 (*m*, 10H), 5.68 (d, *J* = 3.7 Hz, 1H), 5.49 - 5.40 (m, 1H), 4.77 - 4.64 (m, 1H), 4.61 (d, *J* = 12.0 Hz, 1H), 4.50 - 4.31 (m, 2H), 4.04 - 3.91 (m, 1H), 3.82 - 3.72 (m, 1H), 3.70 - 3.62 (m, 1H), 3.59 (d, *J* = 5.6 Hz, 2H), 3.04 (dt, *J* = 4.8, 9.1 Hz, 1H), 2.15 - 2.05 (m, 3H), 1.97 - 1.82 (m, 3H), 1.58 - 1.43 (m, 2H), 1.33 - 1.26 (m, 2H), 0.91 - 0.84 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 169.8, 169.6, 165.0, 137.3, 137.0, 128.5, 128.1, 128.0, 127.8, 73.3, 72.6, 72.0, 69.5, 68.5, 67.0, 60.0, 45.0, 29.6, 20.7, 20.7, 20.0, 13.8; ESI-MS: *m/z* 520.21 $(M+Na)^+$; HRMS: *m/z* calcd for $C_{28}H_{35}NO_7Na$ 520.2306, found 520.2303.

General procedure for reduction of lactams carbonyl using BH_3·SMe_2; Synthesis of (39/ 43/ 44).

To an ice-cold solution of lactams (**38/41/42**) (0.16 mmol) in dry THF (5 mL) was added BH_3·SMe_2 (1.7 mL, 3.28 mmol 2.0 M in THF) dropwise under argon, and the reaction mixture was kept at room temperature for 8h, followed by reflux for 4h. The excess of reducing agent was quenched by slow addition of EtOH (5 mL). After evaporation of the solvent, the residue was dissolved in EtOH (10 mL) and heated at reflux for 2h. The cooled mixture was then evaporated and subjected to flash chromatography.

Compound (**39**): (3*R*, 4*R*, 5*R*, 6*R*)-1-benzyl-5-(benzyloxy)-6-((benzyloxy)methyl) piperidine-3,4-diol.

Pale yellow oil, $C_{27}H_{31}NO_4$, R_f 0.51 (MeOH-DCM, 1:9); Flash chromatography elution with 0-5 % MeOH-DCM, yield 55%. $[\alpha]^{25}_D$ -10.61 (*c* 1.1 $CHCl_3$); IR ($CHCl_3$): ν_{max} 3408, 3064, 3011, 2926, 2856, 2361, 2340, 1657, 1453, 1216, 1104, 1074, 756, 699, 667 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 7.39 - 7.27 (m, 15H), 4.91 (d, *J* = 11.0 Hz, 1H), 4.56 (d, *J* = 11.0 Hz, 1H), 4.46 (s, 2H), 4.18 (d, *J* = 13.2 Hz, 1H), 3.89 - 3.72 (m, 3H), 3.66 (t, *J* = 8.4 Hz, 2H), 3.57 (d, *J* = 8.3 Hz, 1H), 3.29 (d, *J* = 13.2 Hz, 1H), 2.93 (dd, *J* = 3.2, 12.2 Hz, 1H), 2.58 (br. s., 1H), 2.39 (d, *J* = 8.3 Hz, 1H), 2.23 (d, *J* = 12.5 Hz, 1H); ^{13}C NMR (100MHz, $CDCl_3$) δ_C = 138.5, 138.3,

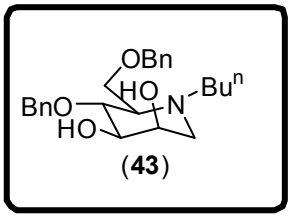


(**39**)

137.8, 129.1, 128.5, 128.1, 127.9, 127.7, 127.3, 78.3, 75.9, 74.7, 73.3, 68.1, 66.7, 64.8, 56.7, 54.7;ESI-MS: *m/z* 434.2 $(M+H)^+$; HRMS: *m/z* calcd for $C_{27}H_{32}NO_4$ 434.2326, found 434.2327.

Compound (**43**): (3*R*, 4*R*, 5*R* ,6*R*)-5-(benzyloxy)-6-((benzyloxy)methyl)-1-butyl piperidine-3,4-diol.

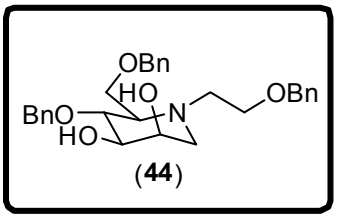
Pale yellow oil, $C_{24}H_{33}NO_4$, R_f 0.46 (MeOH-DCM, 1:9); Flash chromatography elution with 0-4 % MeOH-DCM, yield 60%; $[\alpha]^{25}_D$ -14.73 (*c* 0.7 $CHCl_3$); IR ($CHCl_3$): ν_{max} 3384, 3066, 3014, 2961, 2931, 2873, 1641, 1496, 1454, 1216, 1076, 1028, 757 cm^{-1}; ^1H NMR (500MHz, $CDCl_3$) δ_H = 7.40 - 7.21 (m, 10H), 4.93 (d, *J* = 11.0 Hz, 1H), 4.58 - 4.41 (m, 3H), 4.02 (br. s., 1H), 3.91 - 3.80 (m, 1H), 3.80 - 3.58 (m, 3H), 3.47 - 3.28 (m, 2H), 3.28 - 3.18 (m, 1H), 2.94 (br. s., 1H), 2.80 (br. s., 1H), 2.70 (d, *J* = 10.4 Hz, 1H), 2.66 - 2.59 (m, 1H), 1.57 - 1.42 (m, 2H), 1.31 - 1.27 (m, 1H), 1.23 - 1.16 (m, 1H), 0.87 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C= 138.1, 137.3, 128.5, 128.5, 128.2, 128.1, 128.0, 127.8, 75.0, 73.3, 67.3, 65.6, 63.7, 54.7, 52.8, 25.8, 20.2, 13.8; ESI-MS: *m/z* 400.1 $(M+H)^+$; HRMS: *m/z* calcd for $C_{24}H_{34}NO_4$ 400.2482, found 400.2482.



(**43**)

Compound (**44**): (3*R*, 4*R*, 5*R*,6*R*)-5-(benzyloxy)-1-(2-(benzyloxy)ethyl)-6-(benzyloxy) methyl) piperidine-3,4-diol.

Pale yellow oil, $C_{29}H_{35}NO_5$, R_f 0.54 (MeOH-DCM, 1:9); Flash chromatography elution with 0-4 % MeOH-DCM, yield 58%; $[\alpha]^{25}_D$ -4.85 (*c* 0.76 $CHCl_3$); IR ($CHCl_3$): ν_{max} 3396, 3018, 2927, 2857, 1641, 1497, 1216, 1072, 758 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ_H = 7.38 - 7.26 (m, 15H), 4.88 (d, *J* = 11.3 Hz, 1H), 4.53 - 4.38 (m, 6H), 3.84 (br. s., 1H), 3.77 - 3.69 (m, 2H), 3.61 - 3.50 (m, 4H), 3.15 - 3.04 (m, 2H), 2.91 (td, *J* = 5.4, 14.3 Hz, 1H), 2.62 (d, *J* = 12.2 Hz, 1H), 2.45 (d, *J* = 8.5 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C = 138.4, 138.1, 137.7, 128.6, 128.5, 128.5, 128.1, 128.1, 127.9, 127.9, 127.7, 127.7, 78.1, 76.0, 74.8, 73.3,

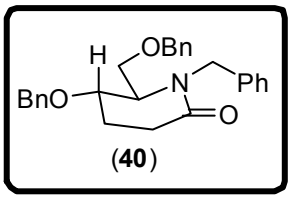


(**44**)

73.2, 68.3, 67.2, 66.4, 64.0, 56.1, 51.5; ESI-MS: *m/z* 500.2 $(M+Na)^+$;HRMS: *m/z* calcd for $C_{29}H_{36}NO_5$478.2588, found 478.2587.

Synthesis of compound (40): (5S,6R)-1-benzyl-5-(benzyloxy)-6-((benzyloxy)methyl) piperidin-2-one.

A solution of (**35da**) (37mg, 0.089 mmol) in methanol (3 ml) was cooled to 0 °C and treated with $NiCl_2.6H_2O$ (16mg, 0.066 mmol). The resulting mixture was stirred at the same temperature for 15 min before the addition of $NaBH_4$ (2.6 mg, 0.066 mmol). After 30 min, further portion of $NaBH_4$ (2.6 mg, 0.066 mmol) was added, and the reaction was allowed to stir for additional 10 min at 20°C. The reaction was quenched with a saturated solution of NH_4Cl (5 ml) and extracted with CH_2Cl_2 (3x10 ml). The combined extracts were dried ($MgSO_4$) and concentrated under vacuum. Flash column chromatography (silica gel, 20-30% EtOAc in hexanes) afforded as a colourless oil $C_{27}H_{29}NO_3$ (24 mg, 66% yield). 2.5 h, *Rf* = 0.61 (silica gel, ethyl acetate/hexanes, 7:3). Flash chromatography elution with 20-25% EtOAc-petroleum ether yield 66%; $[\alpha]^{25}_D$ +49.11 (*c* 1.08 $CHCl_3$); IR ($CHCl_3$): υ_{max} 3443, 3087, 3066, 3031, 2965, 2854, 1642, 1455, 1248, 1096, 756, 698, 666 cm^{-1}; ^1H NMR (400MHz, $CDCl_3$) δ_H = 7.40 - 7.10 (m, 15 H), 5.36 (d, *J* = 15.2 Hz, 1H), 4.48 - 4.34 (m, 3H), 4.33 - 4.24 (m, 1H), 4.00 (d, *J* = 15.2 Hz, 1H), 3.91 - 3.82 (m, 1H), 3.66 (td, *J* = 3.1, 6.7 Hz, 1H), 3.55 (dd, *J* = 4.0, 9.9 Hz, 1H), 3.42 (dd, *J* = 7.1, 10.0 Hz, 1H), 2.78 - 2.63 (m, 1H), 2.49 - 2.35 (m, 1H), 2.09 - 1.93 (m, 2H); ^{13}C NMR (101MHz, $CDCl_3$) δ_C = 170.3, 138.1, 137.6, 137.2, 128.5, 128.5, 128.3, 127.9, 127.8, 127.6, 127.6, 127.3, 127.2, 73.3, 72.0, 70.1, 69.4, 58.6, 48.0, 27.4, 22.4; ESI-MS: *m/z* 416.3 $(M+H)^+$; HRMS: *m/z* calcd for $C_{27}H_{30}NO_3$ 416.2220 found 416.2217.

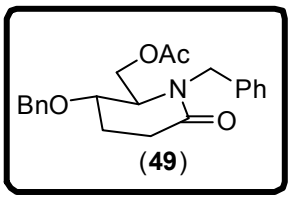


(**40**)

Synthesis of compound (49): To a stirred solution of (**40**) (95 mg, 0.23mmol) dissolved in 5 mL Ac_2O was added 1.5 ml of c H_2SO_4 in AcOH (2% sol.in AcOH) and the solution was stirred at rt for 20h. On completion of the reaction all the contents were evaporated by co-distillation with toluene. And to the residue was

added NaOAc and TEA and the contents evaporated to dryness and directly subjected to further purification.

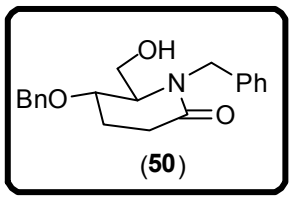
Pale yellow oil, $C_{22}H_{25}NO_4$, 20h, R_f 0.38 (EtOAc-petroleum ether, 7:3); Flash chromatography elution with 30-40% EtOAc-petroleum ether, yield 86%; $[\alpha]^{25}_D$ +70.03 (*c* 1.05 $CHCl_3$); IR ($CHCl_3$): υ_{max} 3443, 3066, 3014, 2928, 2361, 2340, 1723, 1667, 1496, 1454, 1278, 1069, 758, 698, 668 cm^{-1}; ^1H NMR (500MHz, $CDCl_3$) δ_H = 7.34 - 7.23 (m, 8H), 7.18 (d, *J* = 7.0 Hz, 2H), 5.46 (d, *J* = 15.3 Hz, 1H), 4.37 (d, *J* = 11.9 Hz, 1H), 4.30 (d, *J* = 11.9 Hz, 1H), 4.18 (dd, *J* = 3.8, 11.7 Hz, 1H), 4.08 (dd, *J* = 7.2, 11.7 Hz, 1H), 3.99 (d, *J* = 15.3 Hz, 1H), 3.74 (q, *J* = 3.3 Hz, 1H), 3.67 (td, *J* = 3.3, 6.9 Hz, 1H), 2.73 (td, *J* = 9.2, 17.9 Hz, 1H), 2.46 (td, *J* = 5.1, 17.9 Hz, 1H), 2.09 - 2.03 (m, 2H), 2.01 (s, 3H); ^{13}C NMR (125MHz, $CDCl_3$) δ_C = 170.4, 170.1, 137.7, 136.9, 128.6, 128.4, 127.9, 127.7, 127.4, 127.4, 77.3, 77.1, 76.8, 71.4, 70.1, 62.7, 57.5, 47.8, 27.3, 22.2, 20.8; ESI-MS: *m/z* 390.1 $(M+Na)^+$; HRMS: *m/z* calcd for $C_{22}H_{25}NO_4Na$ 390.1676, found 390.1674.



(**49**)

Synthesis of compound (**50**): To a stirred solution of (**49**) (mg, mmol) in MeOH was added NaOMe (mg, mmol) and the solution was stirred at rt for 3h. On completion of the reaction all the contents were evaporated by co-distillation with toluene. And to the residue was added NaOAc and TEA and the contents evaporated to dryness and directly subjected to further purification.

Colorless solid, M.p 102-104 °C, $C_{20}H_{23}NO_4$, 3h, R_f 0.53 (DCM-MeOH, 9:1); Flash chromatography elution with 0-4% DCM-MeOH, yield 86%; $[\alpha]^{25}_D$ +80.8 (*c* 1.25 $CHCl_3$); IR ($CHCl_3$): υ_{max} 3355, 3064, 3008, 2927, 1619, 1476, 1216, 1083, 759 cm^{-1}; ^1H NMR (400MHz, $CDCl_3$) δ_H = 7.36 - 7.12 (m, 10H), 5.36 (d, *J* = 15.2 Hz, 1H), 4.39 (d, *J* = 11.2 Hz, 1H), 4.31 (d, *J* = 11.7 Hz, 1H), 4.05 (d, *J* = 15.2 Hz, 1H), 3.89 - 3.80 (m, 1H), 3.71 (dd, *J* = 5.9, 11.7 Hz, 1H), 3.62 (d, *J* = 11.7 Hz, 1H), 3.51 (br. s., 1H), 3.46 (br. s., 1H), 2.66 (ddd, *J* = 6.8, 10.5, 17.9 Hz, 1H), 2.43 - 2.32 (m, 1H), 2.24 - 2.12 (m, 1H), 2.05 - 1.90 (m, 1H); ^{13}C NMR (100MHz, $CDCl_3$) δ_C =

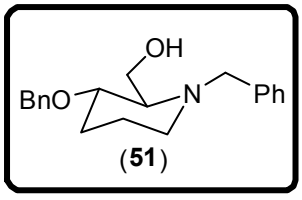


(**50**)

171.2, 138.1, 137.0, 128.6, 128.3, 127.6, 127.3, 72.6, 70.1, 61.2, 60.5, 47.7, 27.5, 22.7; ESI-MS: *m/z* 348.1 $(M+Na)^+$; HRMS: *m/z* calcd $C_{20}H_{24}NO_3$ 326.1751 found 326.1749.

XRD Single crystal X-ray crystallography confirmed that the relative stereochemistry of C-4-OBn and hydroxymethyl groups were *cis* to each other.

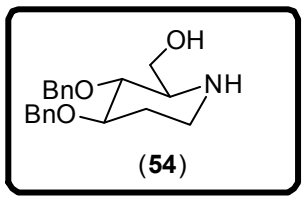
Synthesis of compound (**51**): Starting with compound (**50**) and by following the general procedure for reduction of lactam carbonyl using $BH_3{\cdot}SMe_2$ furnished compound (**51**)



(**51**)

Colorless oil, $C_{20}H_{24}NO_2$, 14h, R_f 0.57 (EtOAc-petroleum ether, 7:3); Flash chromatography elution with 30-40% EtOAc-petroleum ether, yield 62%; $[\alpha]^{25}_D$ +15.33 (*c* 0.75 $CHCl_3$); IR ($CHCl_3$): υ_{max} 3424, 3015, 2933, 1216, 760 cm^{-1}; ^1H NMR (400MHz, $CDCl_3$) δ_H = 7.41 - 7.19 (m, 10H), 4.66 (d, *J* = 11.6 Hz, 1H), 4.53 (d, *J* = 11.0 Hz, 1H), 4.13 (d, *J* = 13.4 Hz, 1H), 4.00 - 3.82 (m, 2H), 3.59 - 3.47 (m, 1H), 3.40 (d, *J* = 13.4 Hz, 1H), 2.84 (d, *J* = 12.2 Hz, 1H), 2.57 (br. s., 1H), 2.47 - 2.37 (m, 1H), 2.22 - 2.06 (m, 2H), 1.79 - 1.63 (m, 1H), 1.48 - 1.31 (m, 2H); ^{13}C NMR (100MHz, $CDCl_3$) δ_C = 138.5, 128.9, 128.4, 128.4, 127.8, 127.7, 127.1, 74.9, 71.2, 65.7, 58.4, 57.8, 50.5, 28.8, 21.1; ESI-MS: *m/z* 312.2 $(M+H)^+$; HRMS: *m/z* calcd $C_{20}H_{25}NO_2$ 312.1958 found 312.1958.

Synthesis of compound (**54**): To a stirred solution of (**16a**) (300 mg, 0.7mmol) dissolved in 10 mL Ac_2O was added 3.5 ml of cH_2SO_4 in AcOH (2% sol.in AcOH) and the solution was stirred at rt for 20h. On completion of the reaction all the contents were evaporated by co-distillation with toluene. And to the residue was added NaOAc and TEA and the contents evaporated to dryness and directly utilized for the next step. To the crude was added 0.14 M solution of NaOMe (37 mg) in MeOH (5mL) and the solution was stirred at rt for 3h. On completion of the reaction all the contents were evaporated by co-distillation with toluene. And to the residue was added NaOAc and TEA and the contents evaporated



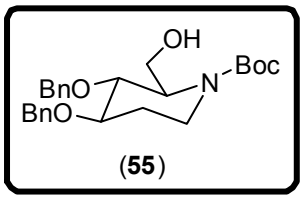
(**54**)

to dryness and then dissolved in EtOAc and the organic layer washed with sat. NH_4Cl and brine and dried over Sodium sulfate and evaporated in vacuo. The crude obtained was then subjected to the general procedure for reduction of lactam carbonyl using $BH_3 \cdot SMe_2$, furnished compound (**54**)

Colorless oil, $C_{20}H_{25}NO_3$, R_f 0.62 (MeOH-DCM, 1:4); Flash chromatography elution with 0-5 % MeOH-DCM, yield 79%; $[\alpha]^{25}_D$ +1.93 (*c 0*.91 $CHCl_3$); IR ($CHCl_3$): υ_{max} 3363, 3088, 3064, 2924, 2853, 1657,1455, 1402, 1216, 1102, 1028, 755, 699 cm^{-1}; ^1H NMR (400MHz, $CDCl_3$) δ_H = 7.41 - 7.25 (m, 10 H), 4.90 (d, *J* = 11.0 Hz, 1H), 4.72 - 4.43 (m, 4H), 4.17 - 3.88 (m, 2H), 3.79 (td, *J* = 5.4, 11.2 Hz, 1H), 3.75 - 3.62 (m, 1H), 3.62 - 3.41 (m, 2H), 3.15 - 3.03 (m, 1H), 2.85 (br. s., 1H), 2.24 - 2.08 (m, 1H), 2.08 - 1.91 (m, 1H); ^{13}C NMR (100MHz, $CDCl_3$) δ_C = 138.5, 138.3, 128.6, 128.5, 128.2, 127.9, 127.7, 127.1, 80.9, 78.9, 75.2, 71.7, 61.3, 61.0, 42.6, 29.4; ESI-MS: *m/z* 328.1 $(M+H)^+$; HRMS: *m/z* calcd for $C_{20}H_{26}NO_3$ 328.1907, found 328.1907.

Synthesis of compound (**55**): By following the general procedure for Boc protection as was done in previous Section compound (**55**) was synthesized

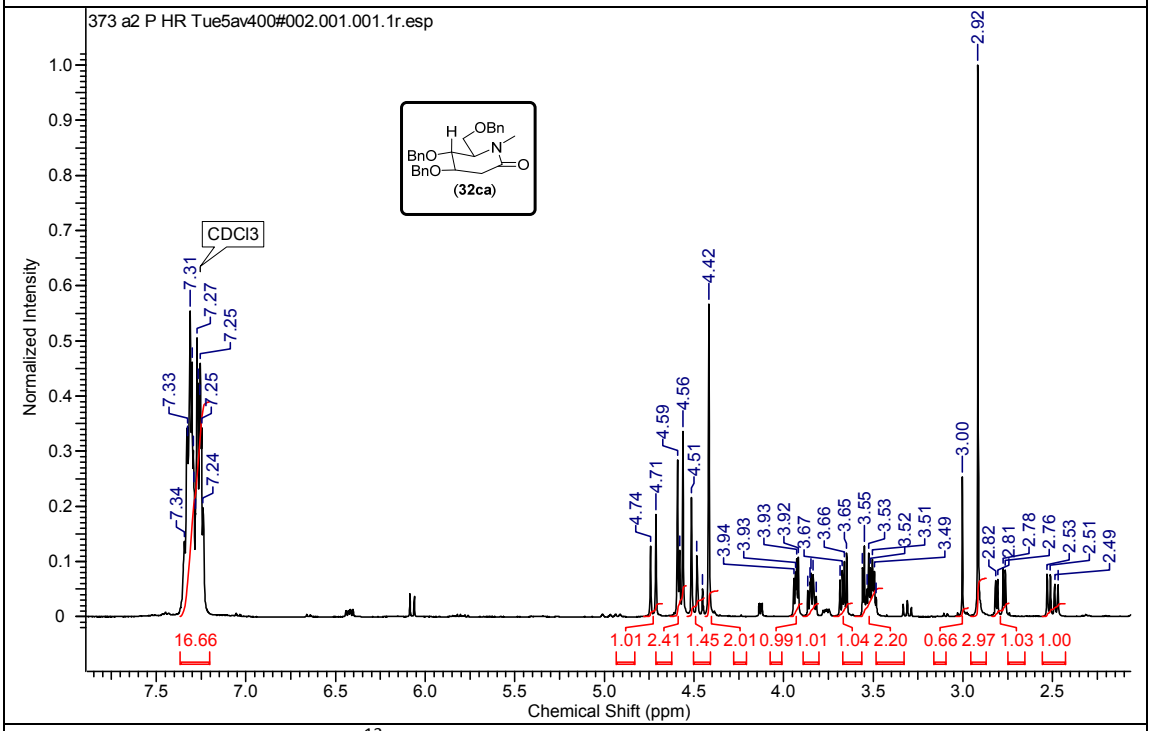
Colorless oil, $C_{25}H_{33}NO_5$, 2d, R_f 0.6 (EtOAc-petroleum ether, 1:1); Flash chromatography elution with 20-25% EtOAc-petroleum ether, yield 37%; $[\alpha]^{25}_D$ -57.241 (*c* 0.85 $CHCl_3$); IR ($CHCl_3$): υ_{max} 3443, 3066, 3014, 2928, 2361, 2340, 1723, 1667, 1496, 1454, 1278, 1069, 758, 698, 668 cm^{-1}; ^1H NMR (500MHz, $CDCl_3$) δ_H = 7.39 - 7.22 (m, 10H), 4.67 (d, *J* = 11.8 Hz, 1H), 4.59 - 4.54 (m, 1H), 4.48 (d, *J* = 11.8 Hz, 3H), 3.99 - 3.91 (m, 1H), 3.91 - 3.81 (m, 1H), 3.76 (dd, *J* = 5.3, 11.4 Hz, 1 H), 3.74 - 3.69 (m, 1H), 3.58 (br. s., 1H), 3.25 (t, *J* = 12.4 Hz, 1H), 2.54 (br. s., 1H), 2.02 - 1.93 (m, 1H), 1.74 - 1.65 (m, 1H), 1.45 (s, 9H); ^{13}C NMR (125MHz, $CDCl_3$) δ_C = 156.1, 138.1, 137.8, 128.6, 128.4, 127.9, 127.7, 127.6, 127.5, 80.0, 73.8, 71.3, 71.3, 61.8, 55.4, 29.7, 28.4, 24.8; ESI-MS: *m/z* 328.2 $[(M\text{-Boc})+H]^+$; HRMS: *m/z* calcd for $C_{25}H_{33}NO_5Na$ 450.2251, found 450.2250.



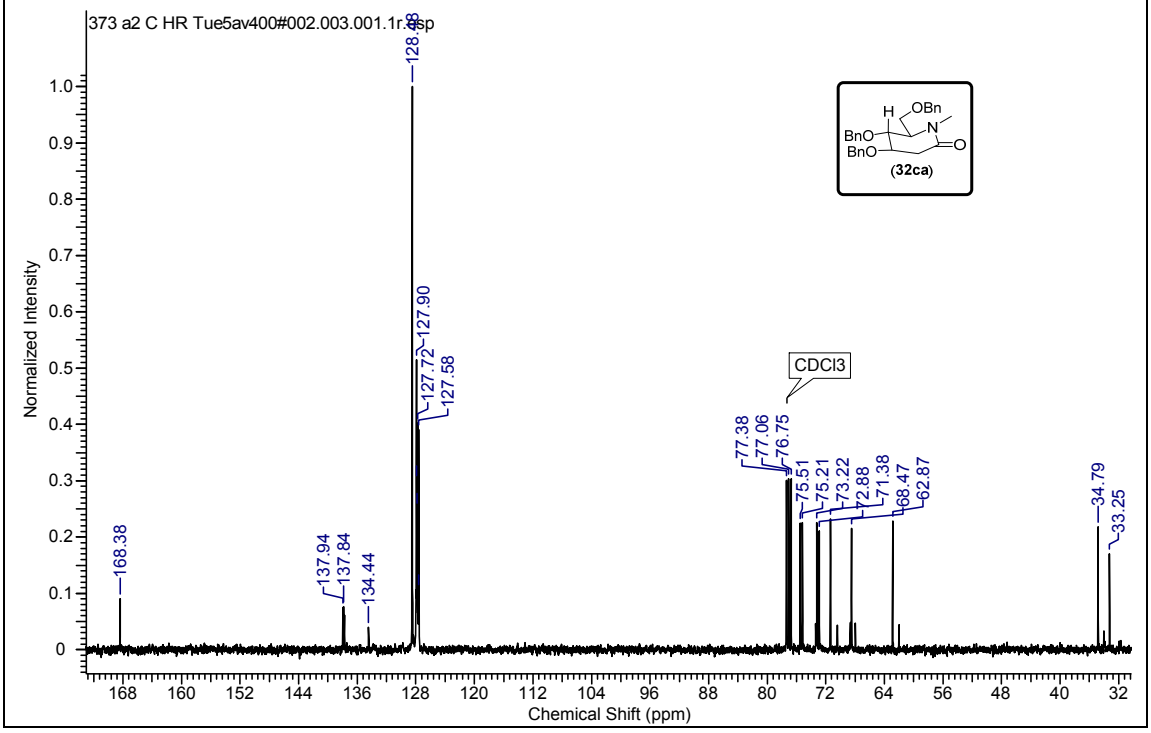
(**55**)

1.2.7 Spectra

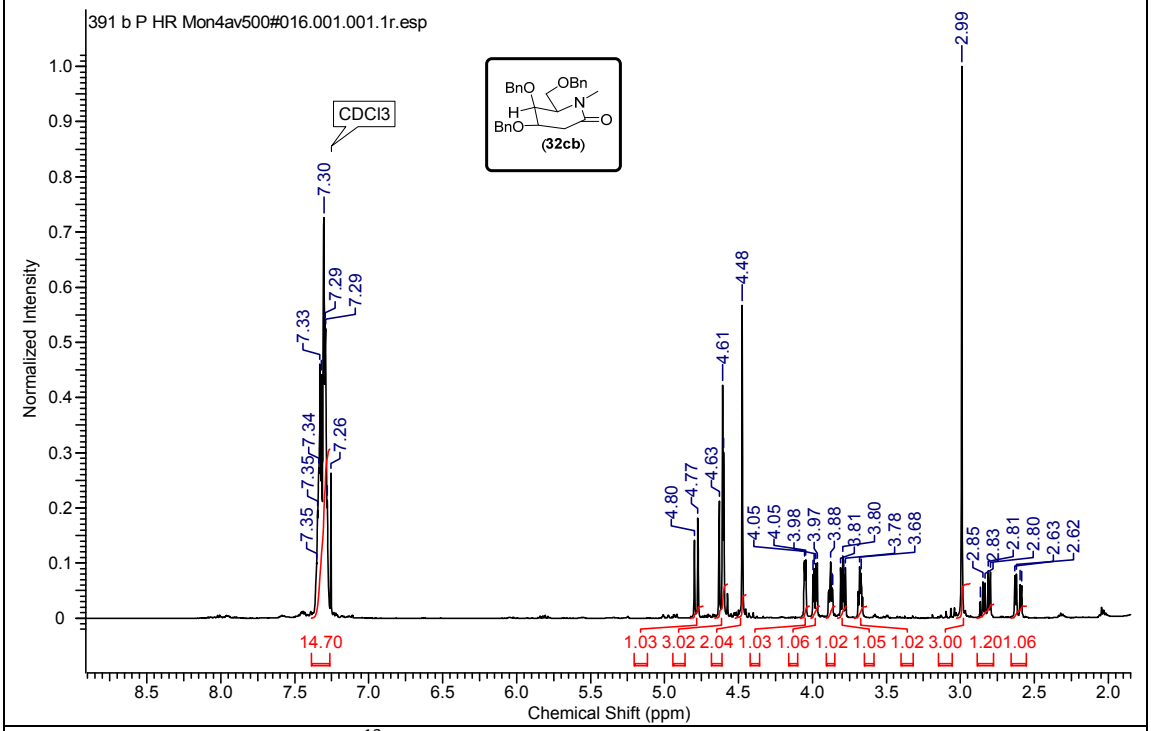
^{1}H NMR (400 MHz, $CDCl_3$) of (**32ca**)



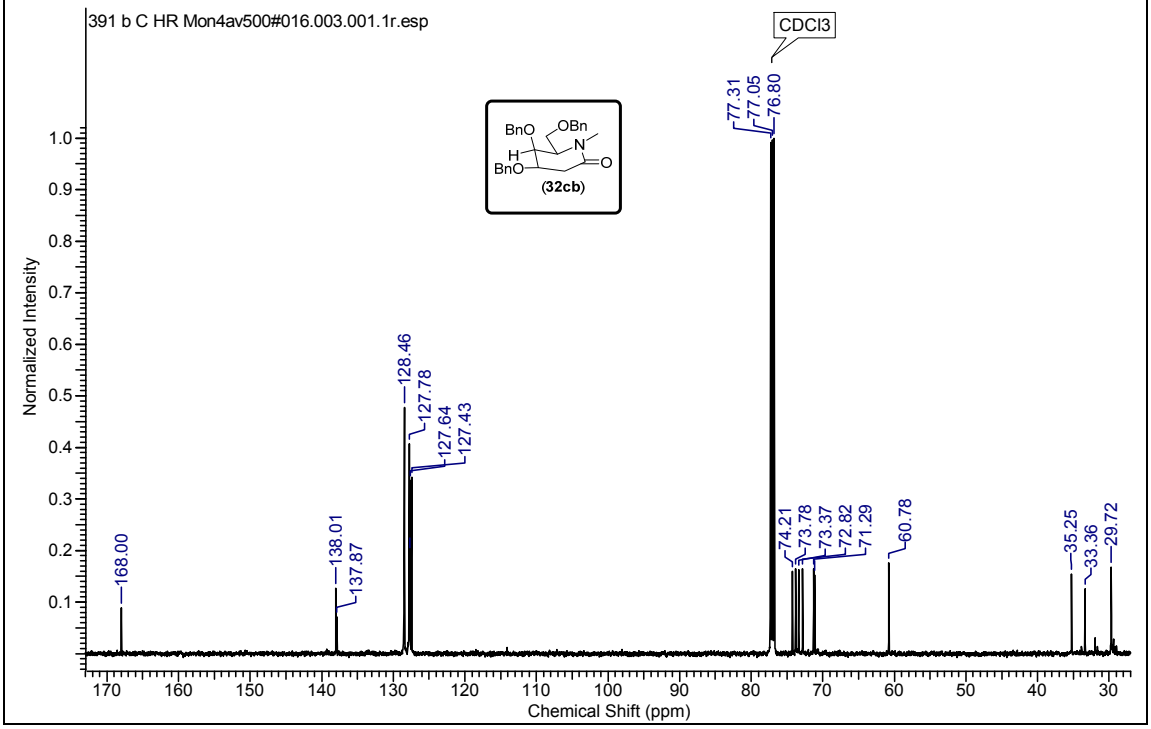
^{13}C NMR (100 MHz, $CDCl_3$) of (**32ca**)



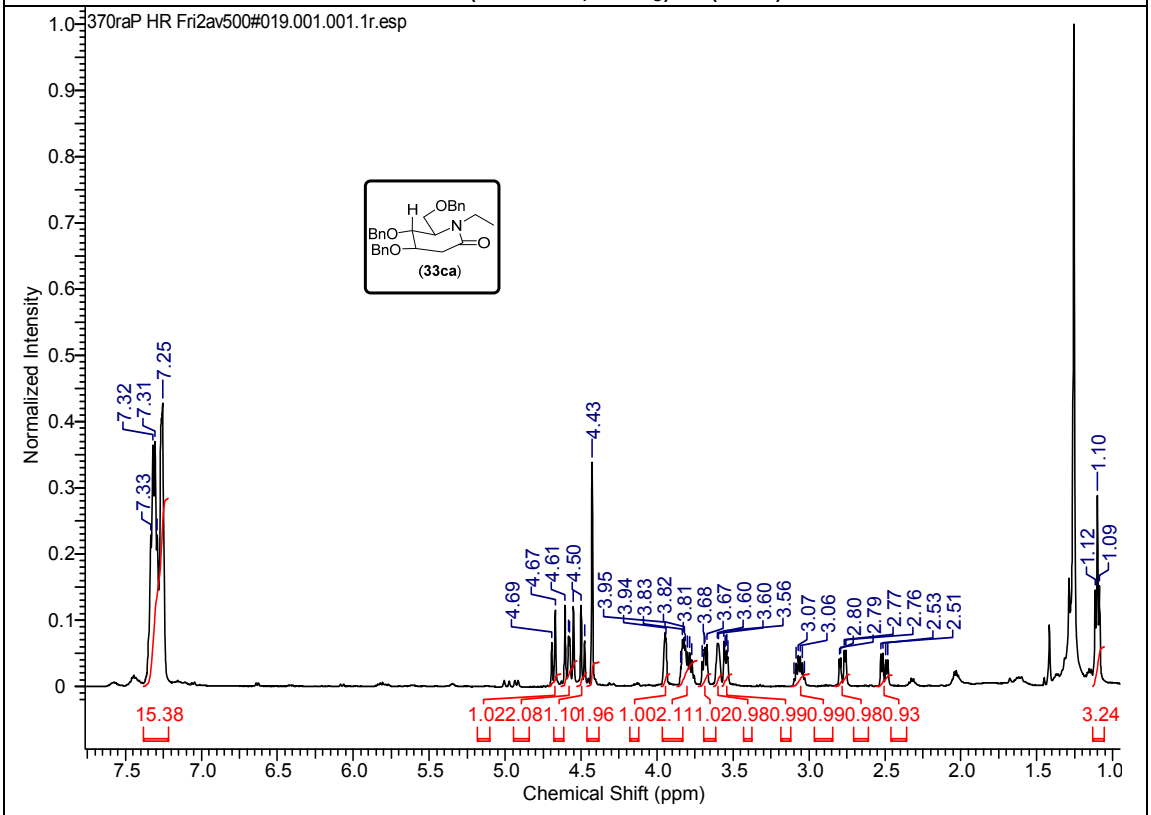
^{1}H NMR (500 MHz, $CDCl_3$) of (**32cb**)



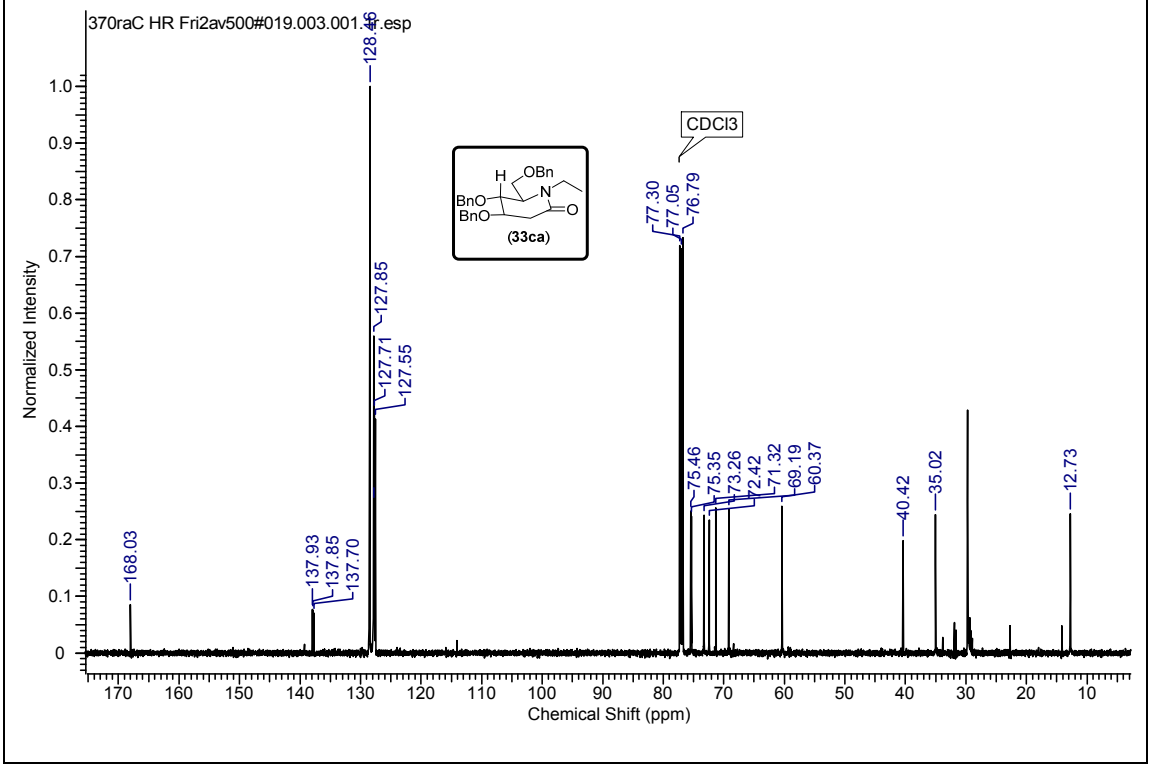
^{13}C NMR (125 MHz, $CDCl_3$) of (**32cb**)



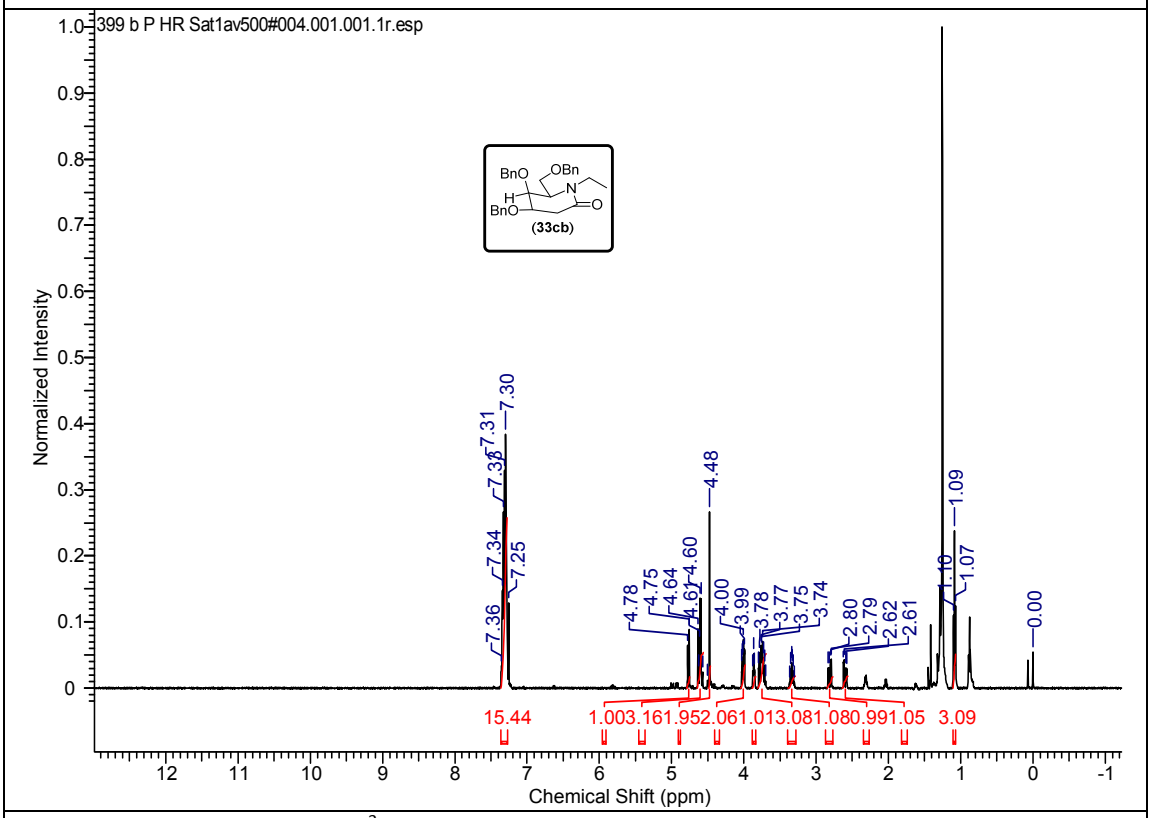
^{1}H NMR (500 MHz, $CDCl_3$) of (**33ca**)



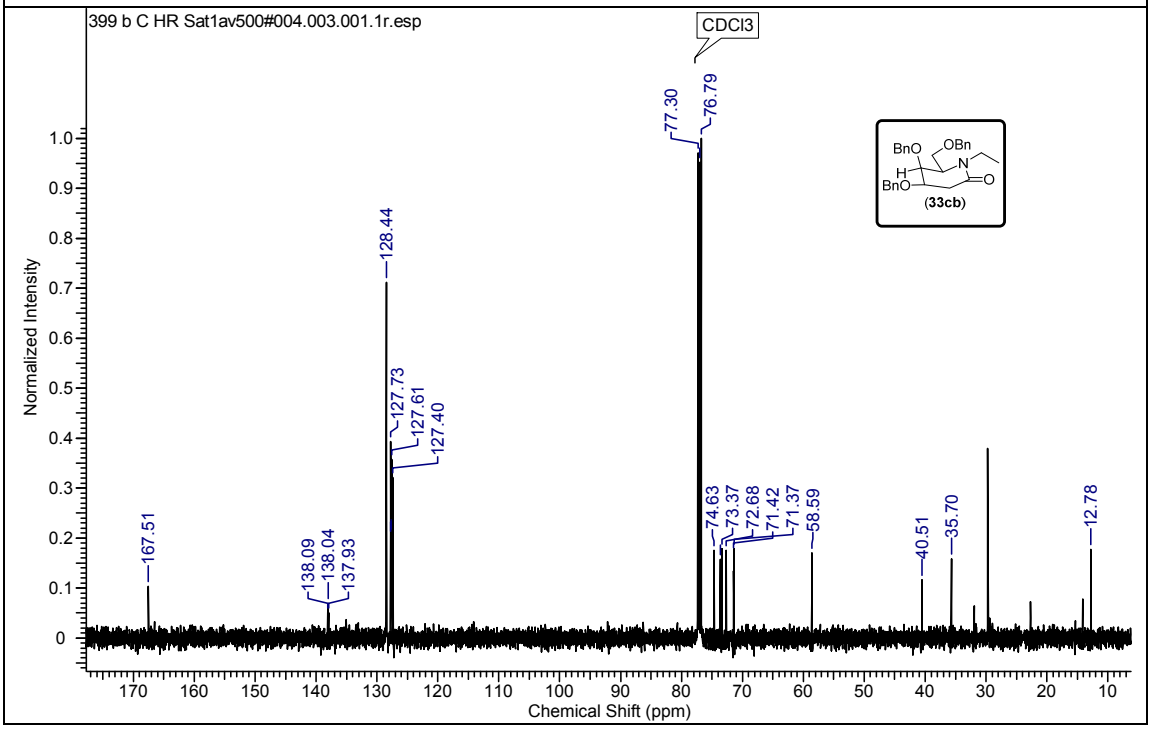
^{13}C NMR (125 MHz, $CDCl_3$) of (**33ca**)



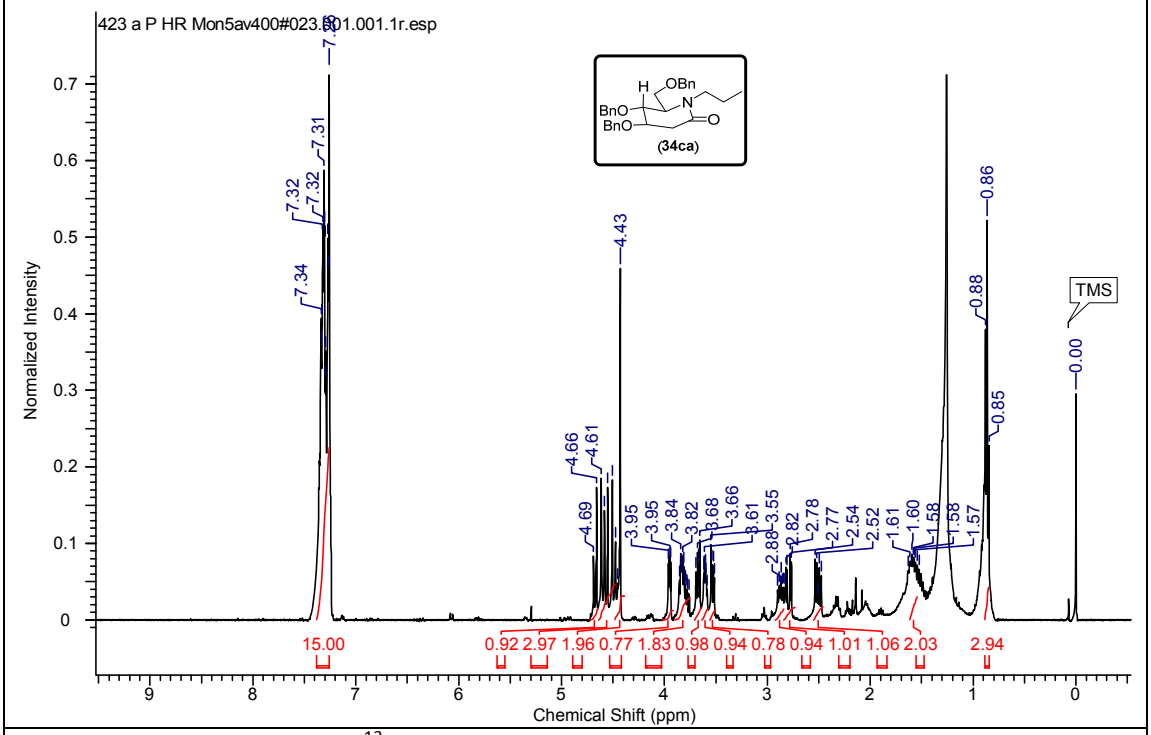
^{1}H NMR (500 MHz, $CDCl_3$) of (**33cb**)



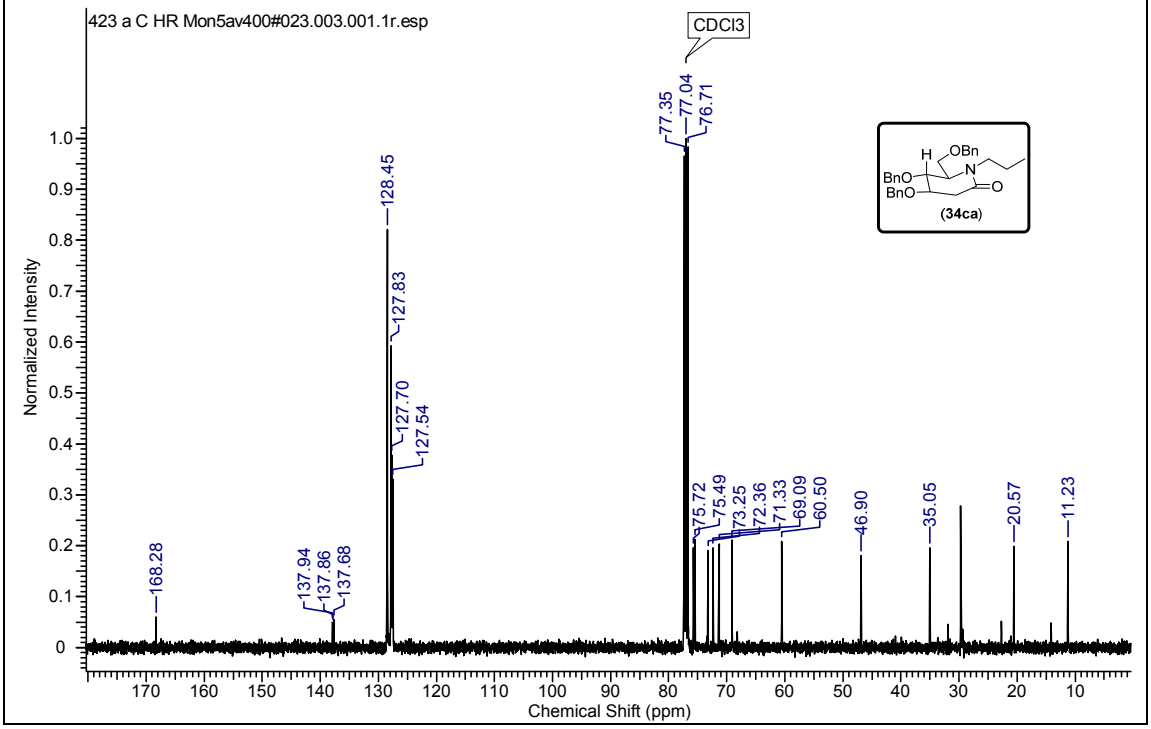
^{3}C NMR (125 MHz, $CDCl_3$) of (**33cb**)



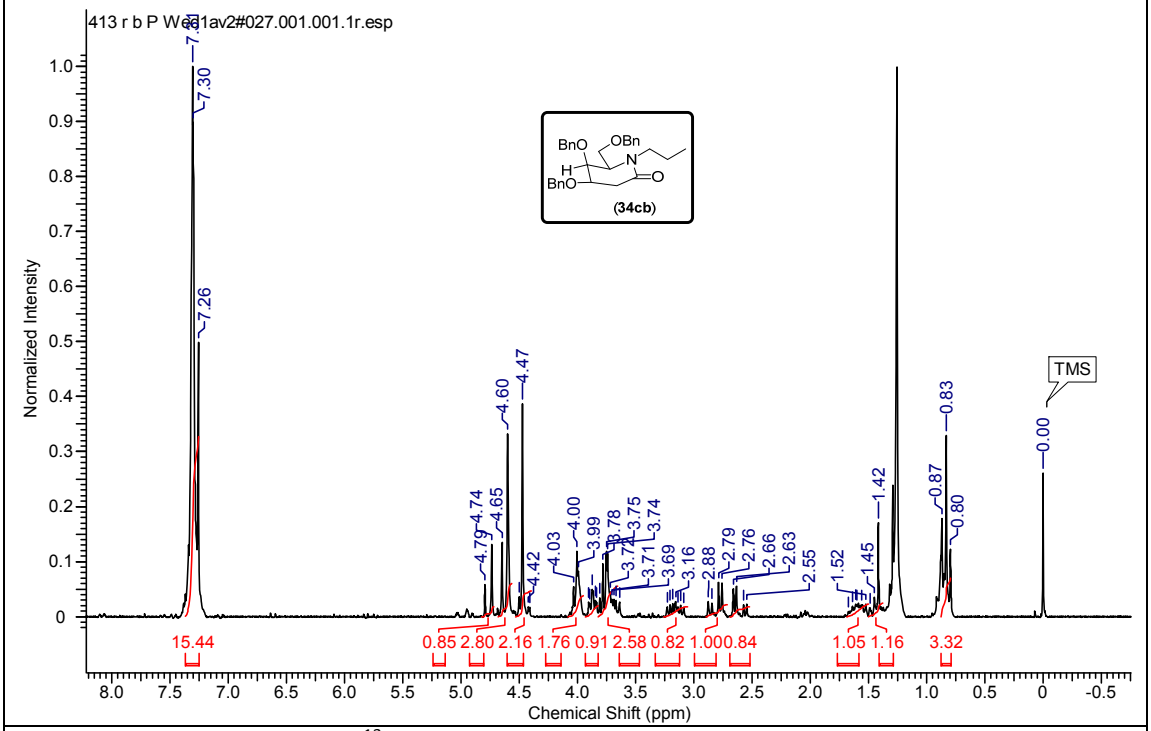
^{1}H NMR (400 MHz, $CDCl_3$) of (**34ca**)



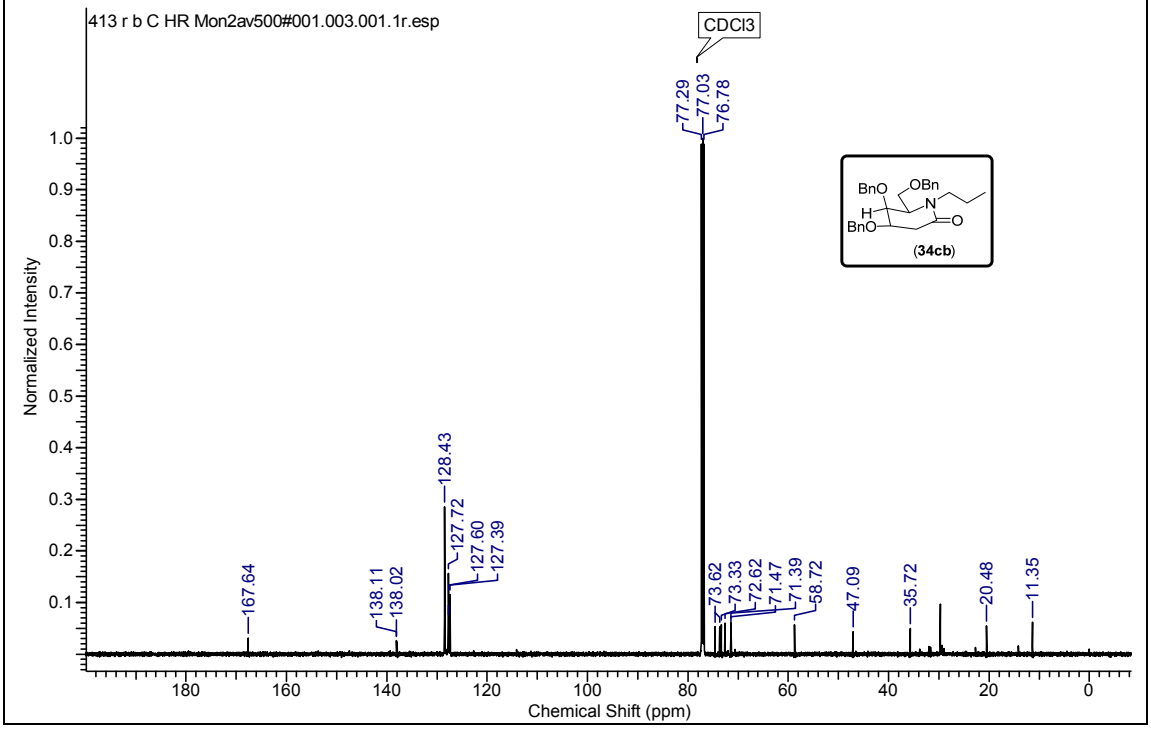
^{13}C NMR (100 MHz, $CDCl_3$) of (**34ca**)



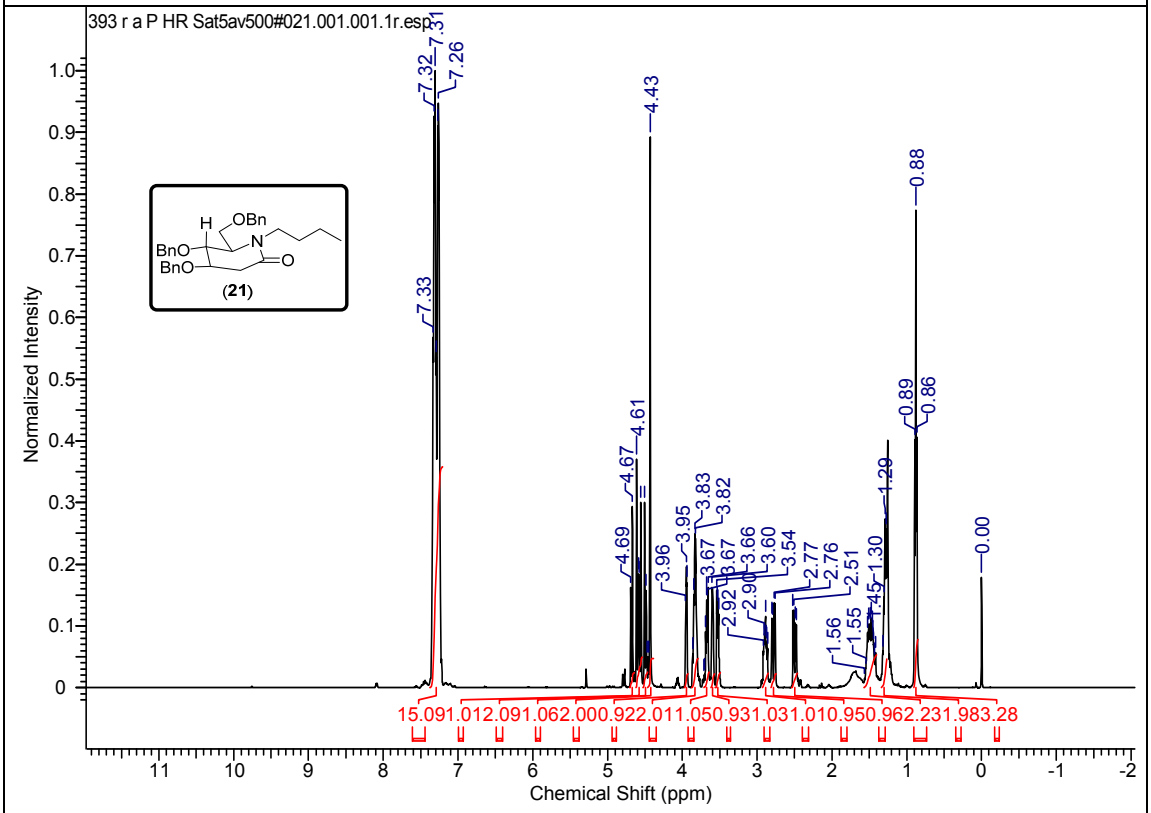
^{1}H NMR (400 MHz, $CDCl_3$) of (**34cb**)



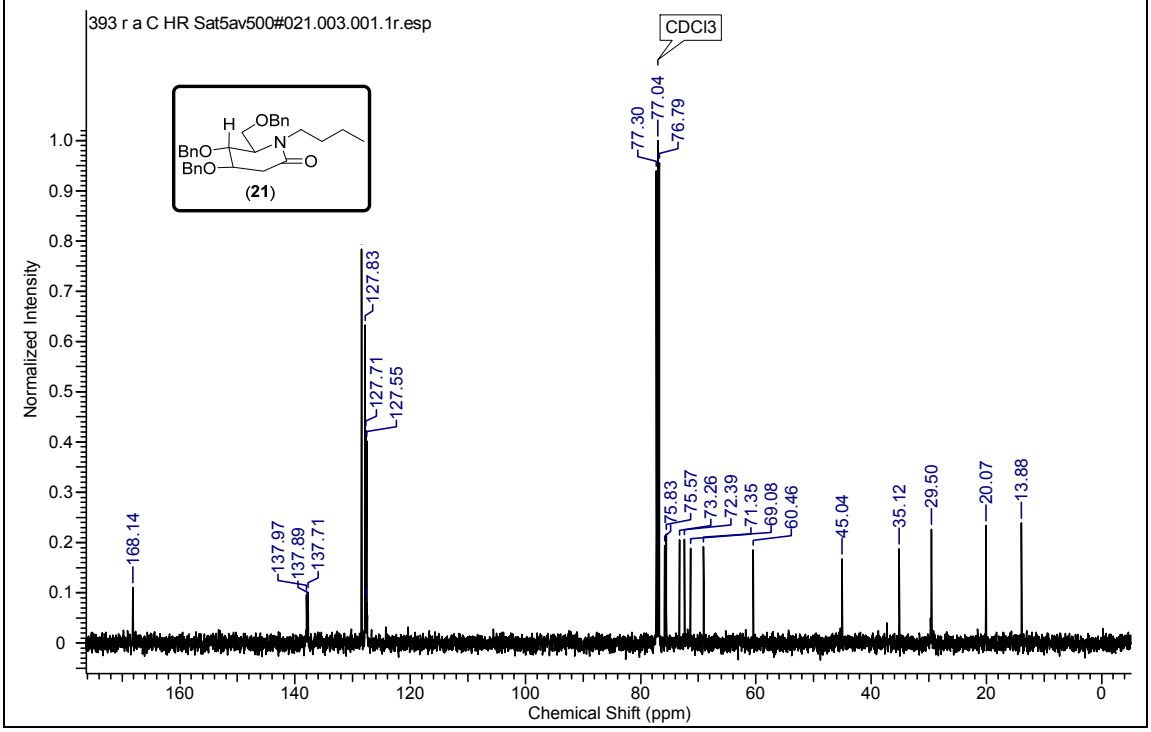
^{13}C NMR (100 MHz, $CDCl_3$) of (**34cb**)



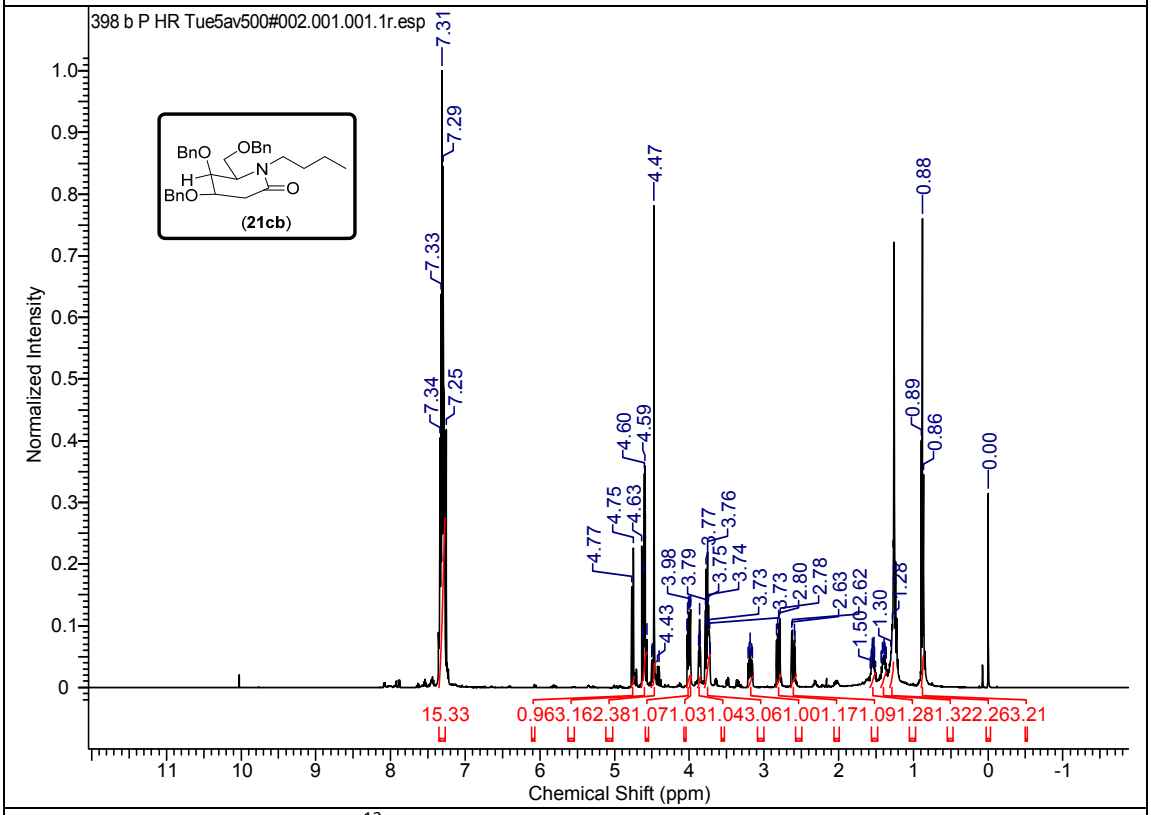
^{1}H NMR (400 MHz, $CDCl_3$) of (**21**)



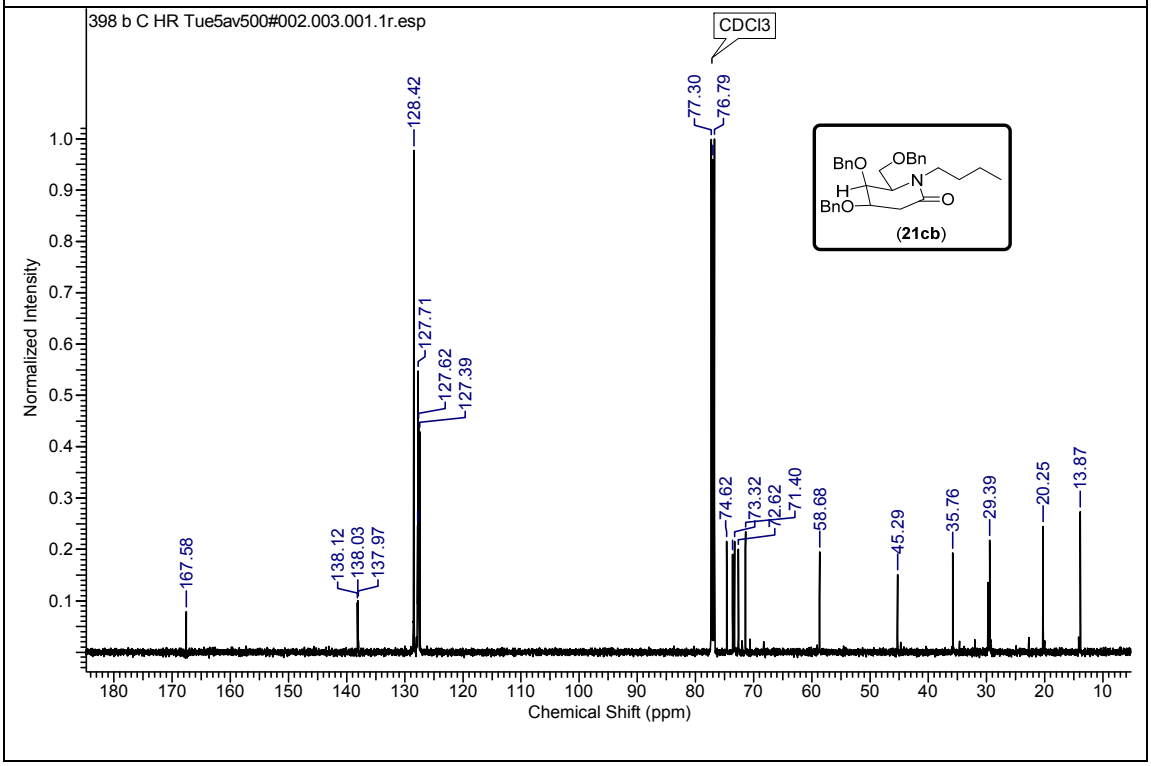
^{13}C NMR (100 MHz, $CDCl_3$) of (**21**)



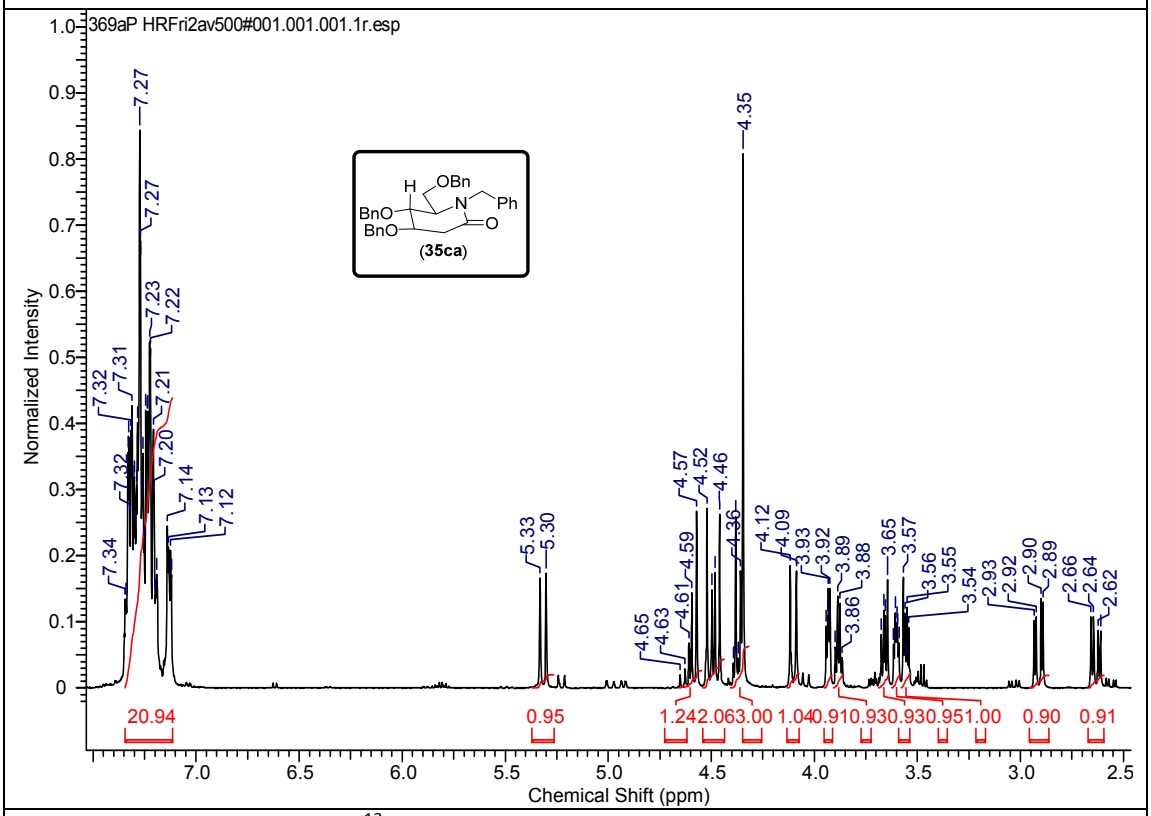
^{1}H NMR (500 MHz, $CDCl_3$) of (**21cb**)



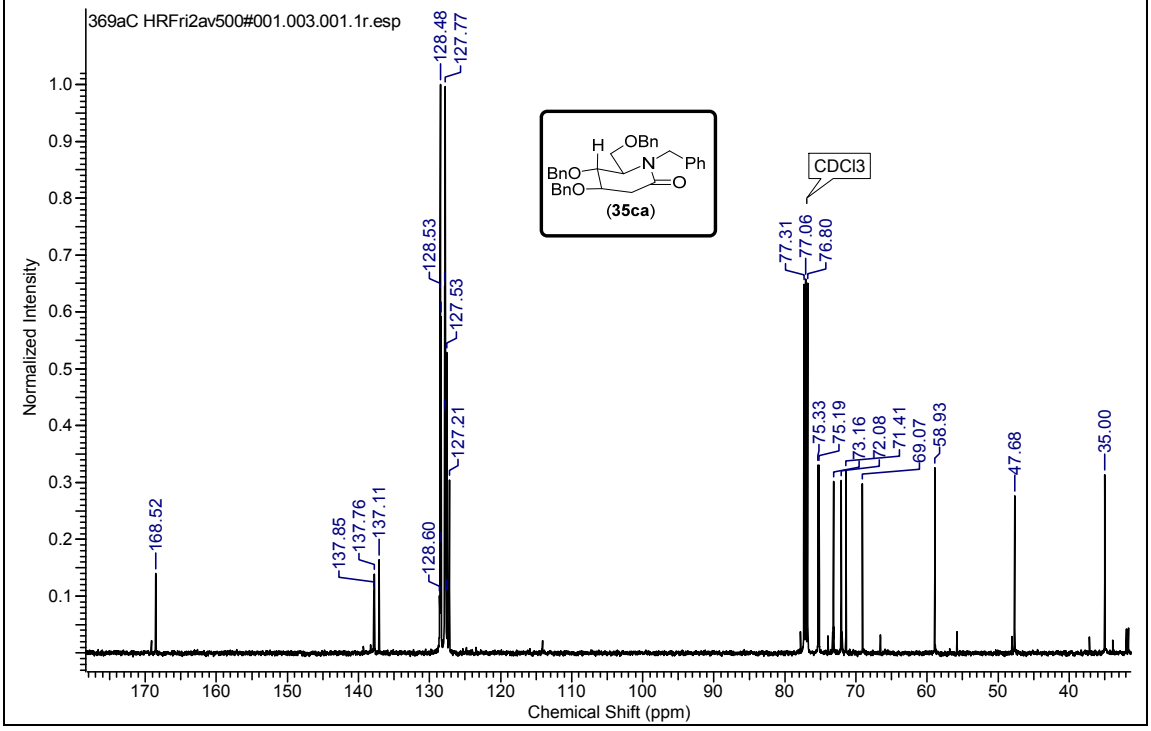
^{13}C NMR (125 MHz, $CDCl_3$) of (**21cb**)



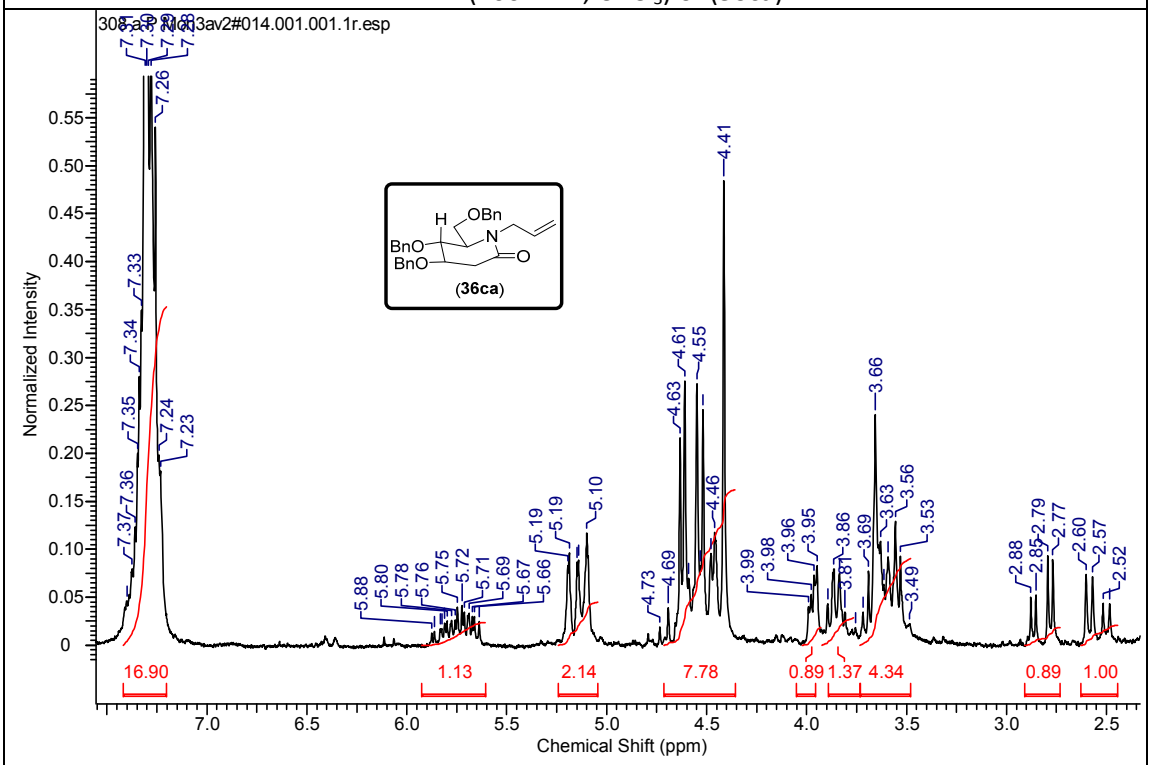
^{1}H NMR (500 MHz, $CDCl_3$) of (**35ca**)



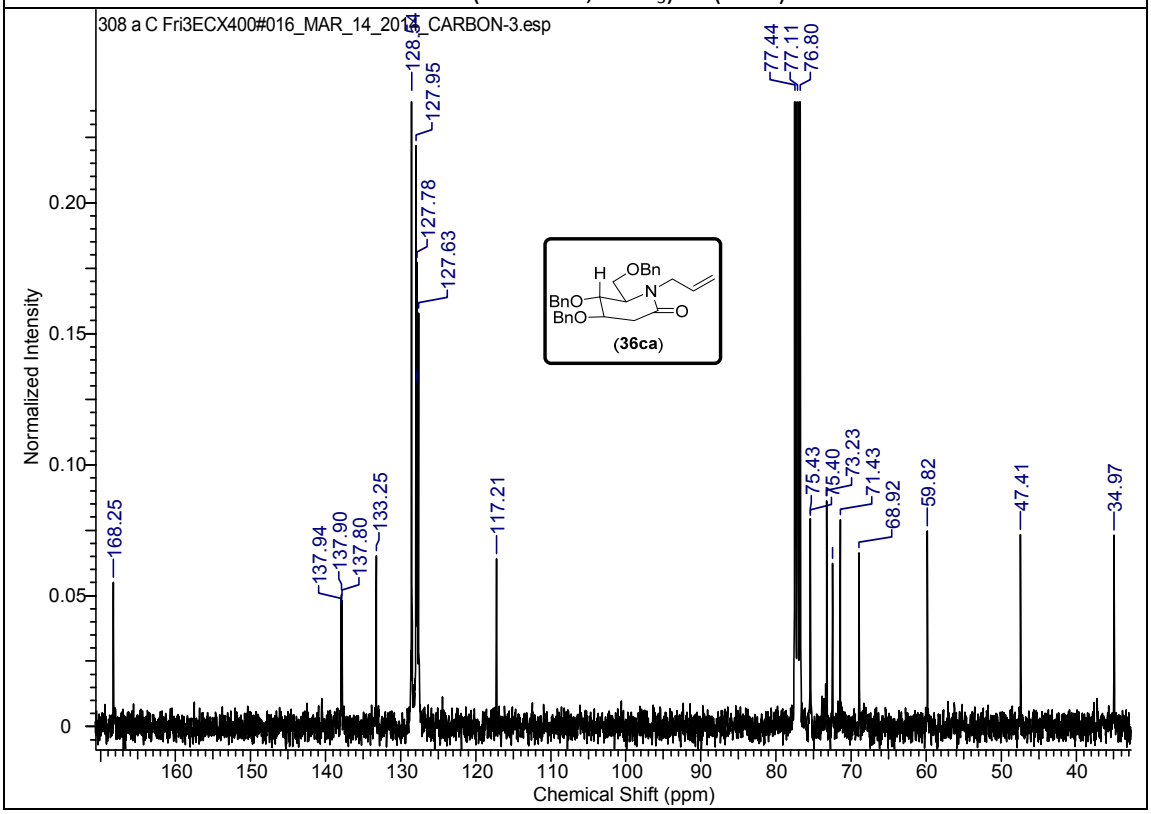
^{13}C NMR (125 MHz, $CDCl_3$) of (**35ca**)



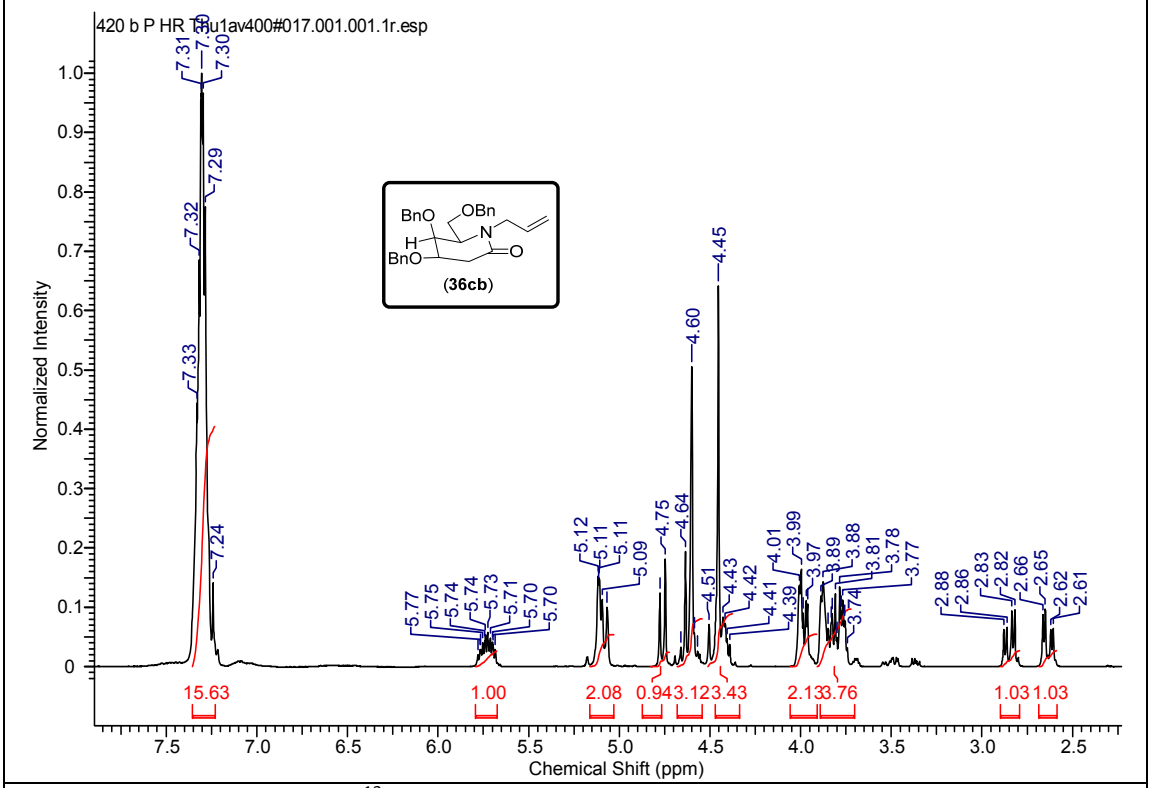
^{1}H NMR (400 MHz, $CDCl_3$) of (**36ca**)



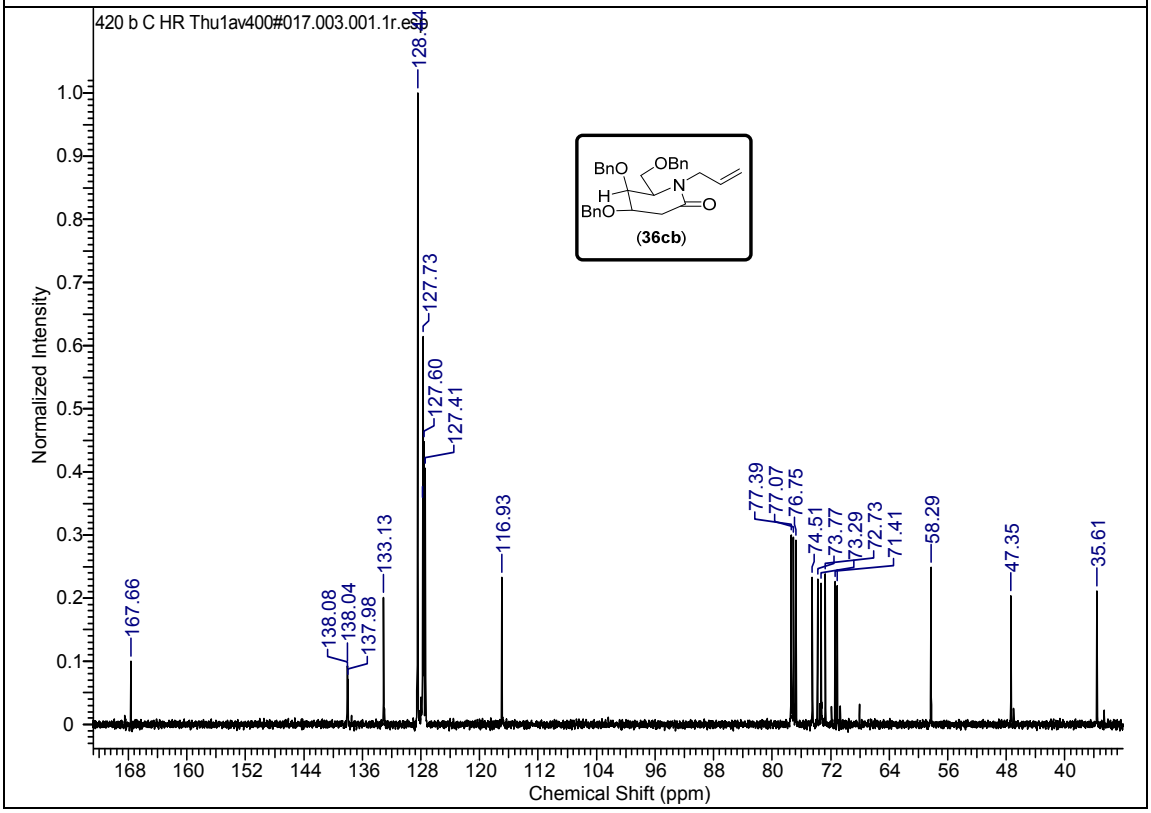
^{13}C NMR (100 MHz, $CDCl_3$) of (**36ca**)



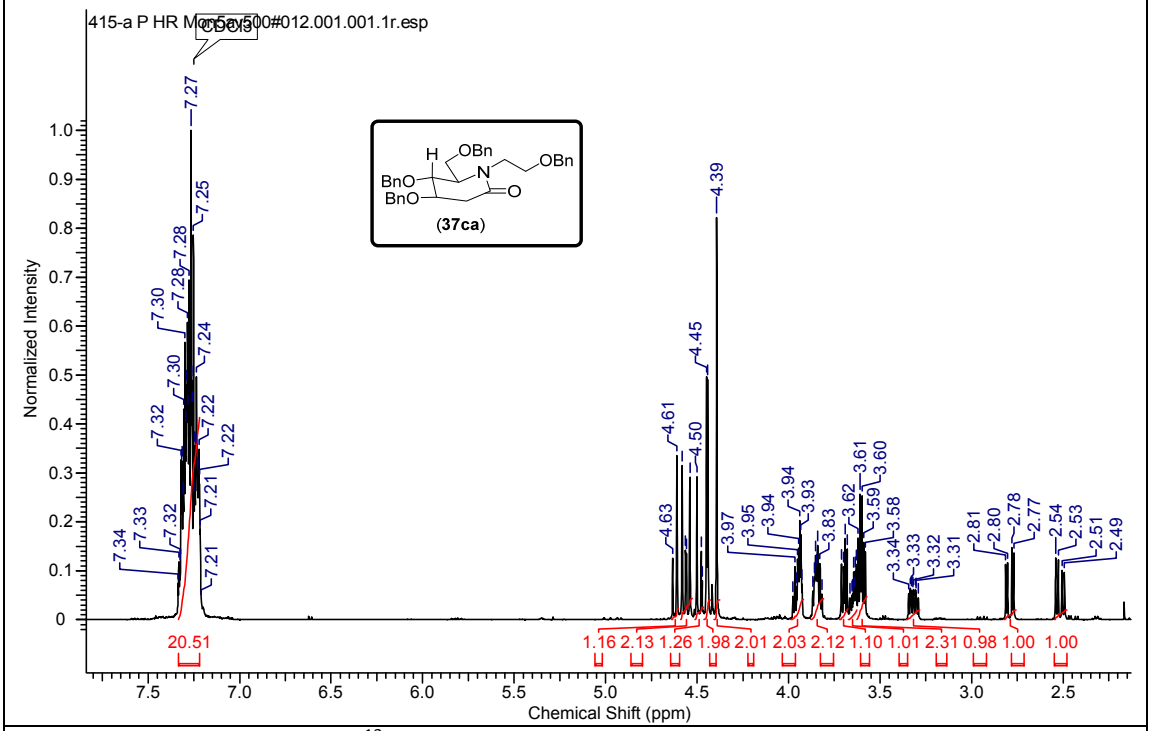
^{1}H NMR (400 MHz, $CDCl_3$) of (**36cb**)



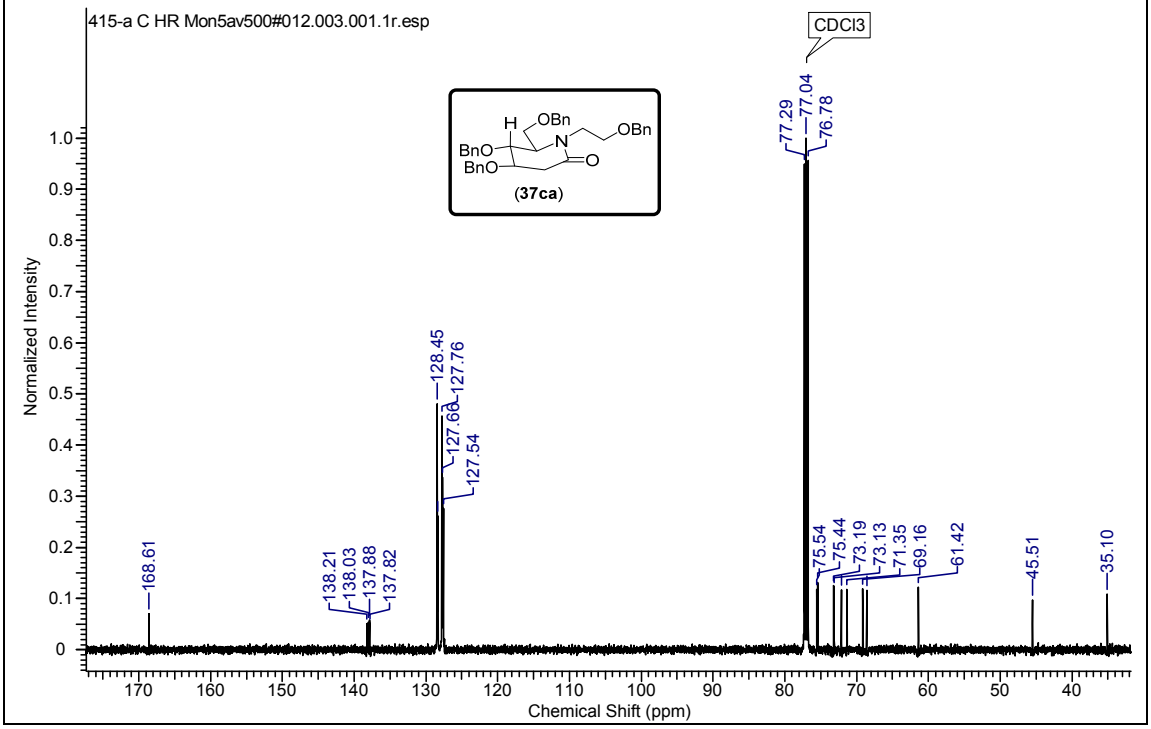
^{13}C NMR (100 MHz, $CDCl_3$) of (**36cb**)



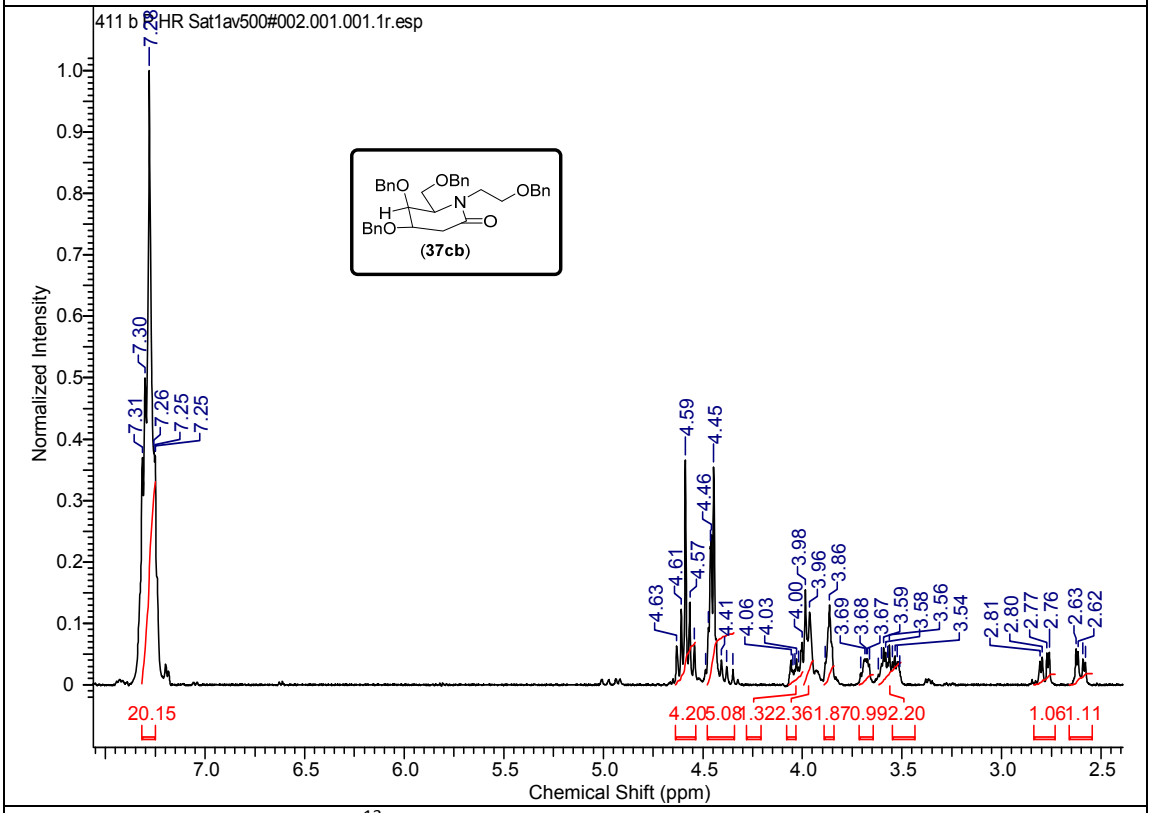
^{1}H NMR (500 MHz, $CDCl_3$) of (**37ca**)



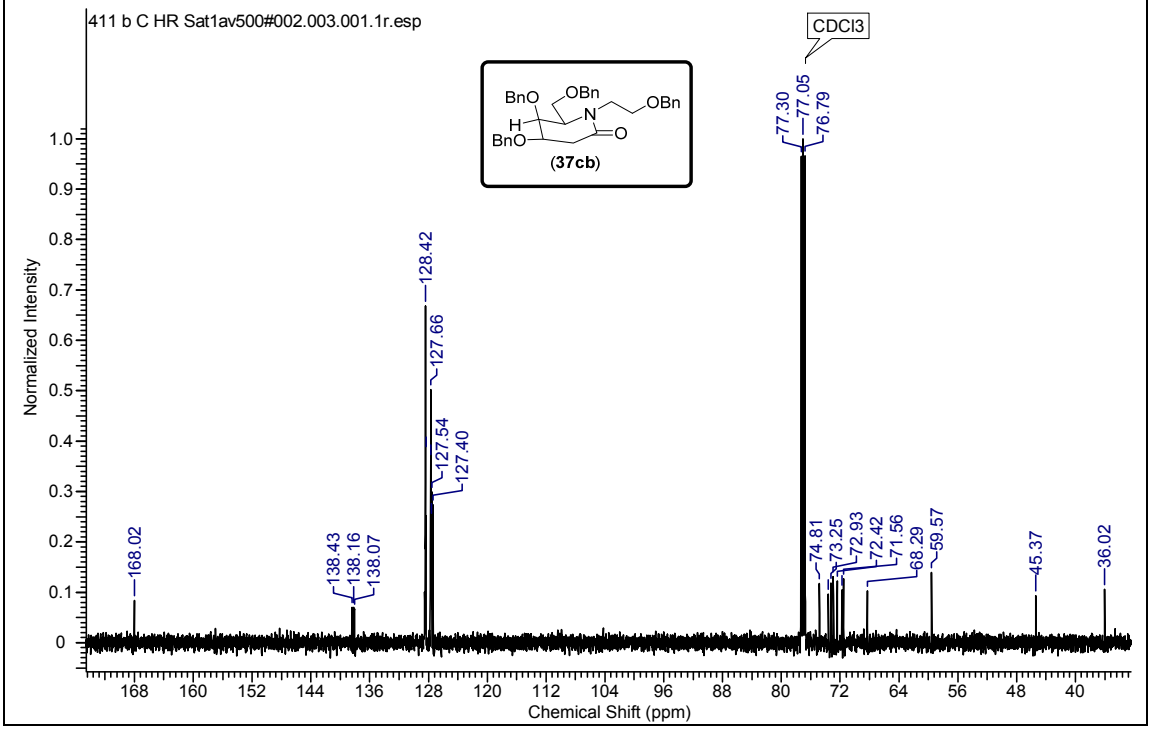
^{13}C NMR (125 MHz, $CDCl_3$) of (**37ca**)



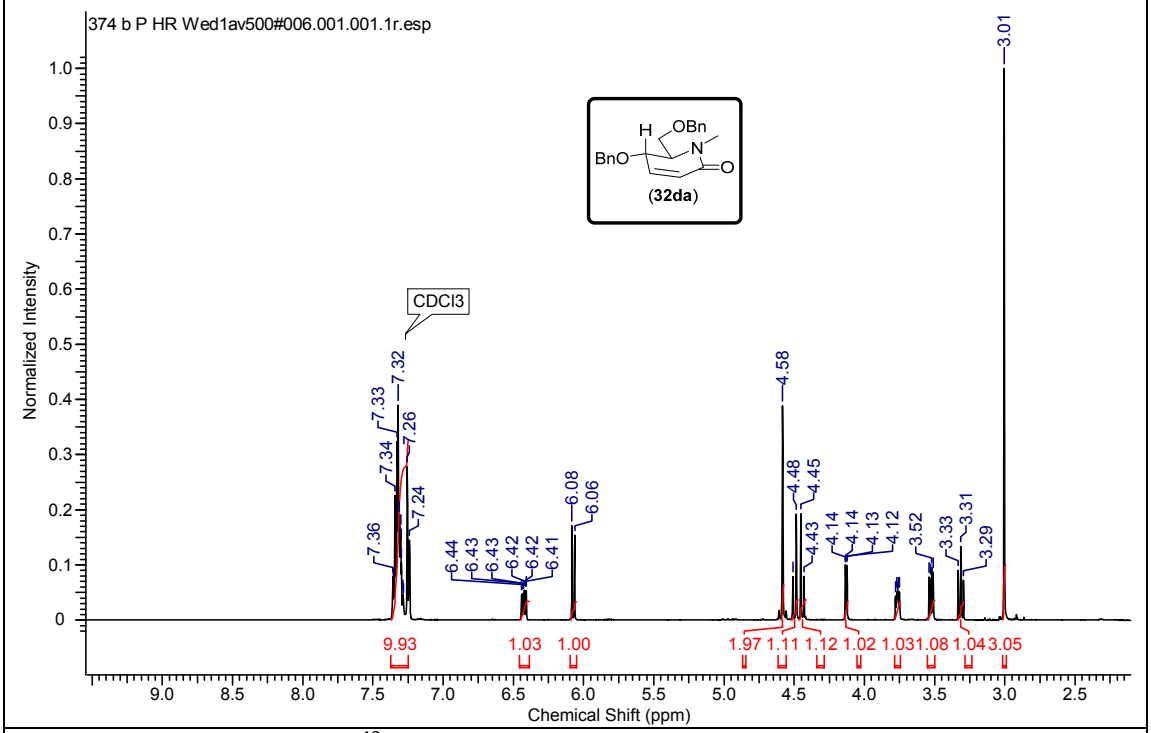
^{1}H NMR (500 MHz, $CDCl_3$) of (**37cb**)



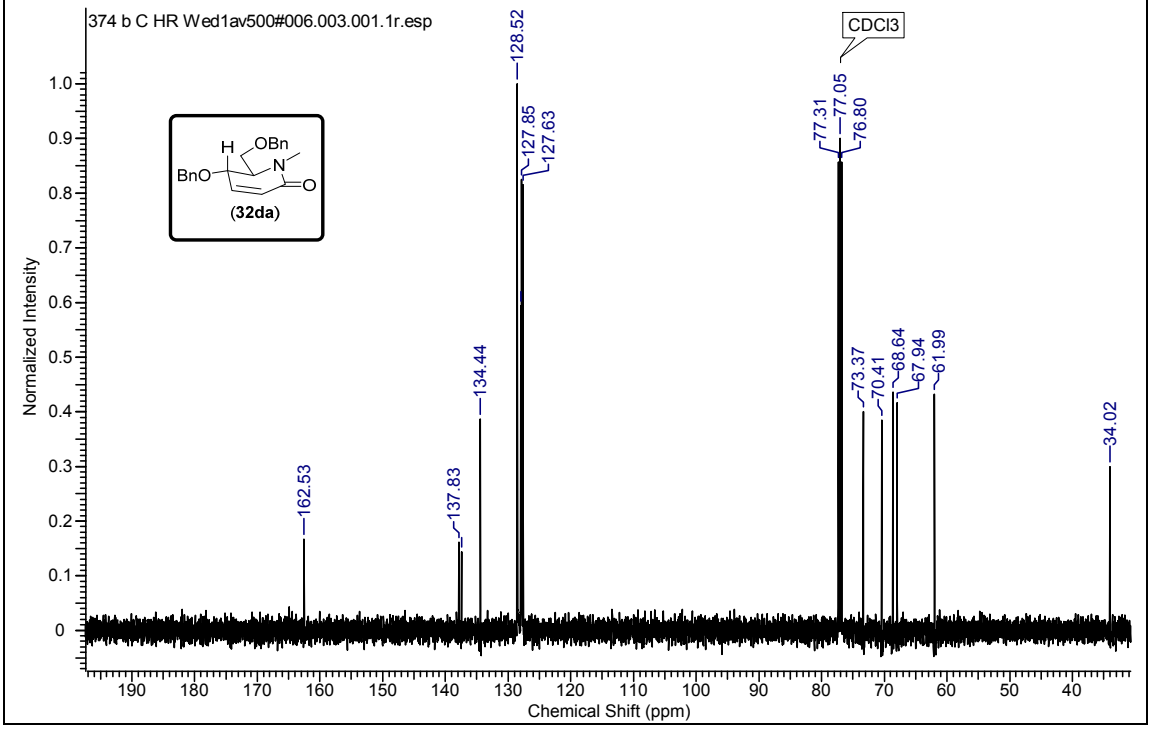
^{13}C NMR (125 MHz, $CDCl_3$) of (**37cb**)



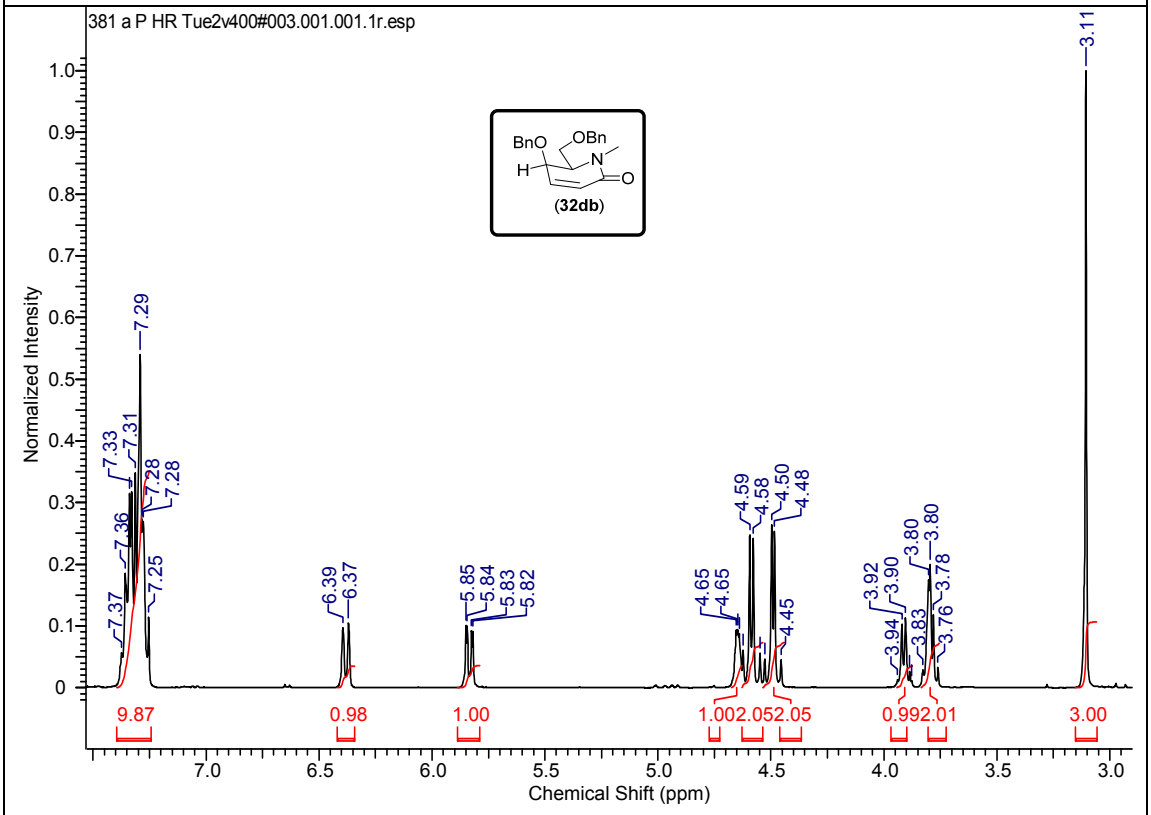
^{1}H NMR (400 MHz, $CDCl_3$) of (**32da**)



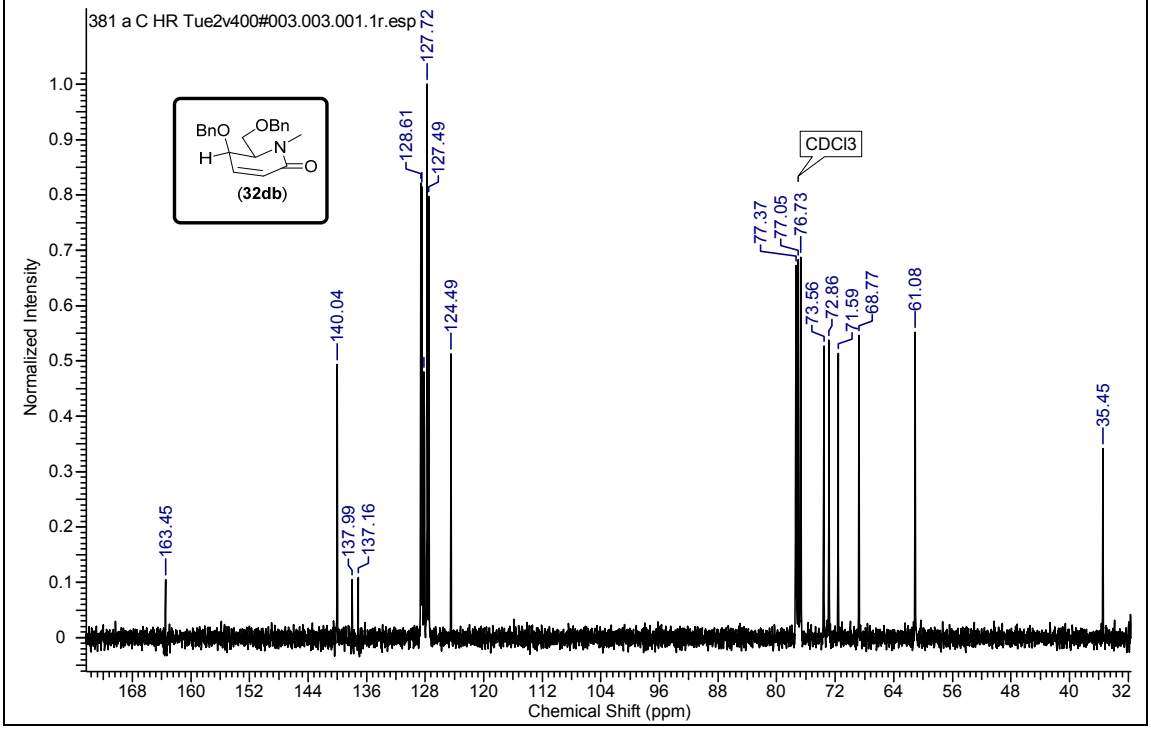
^{13}C NMR (125 MHz, $CDCl_3$) of (**32da**)



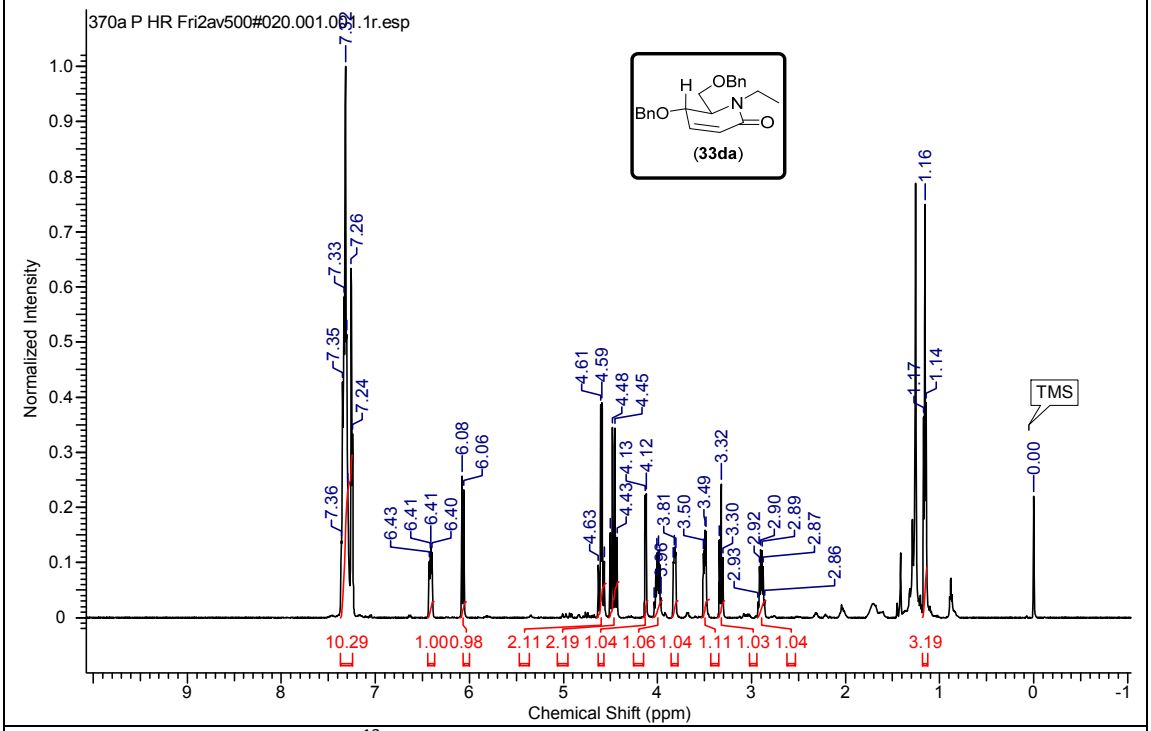
^{1}H NMR (500 MHz, $CDCl_3$) of (**32db**)



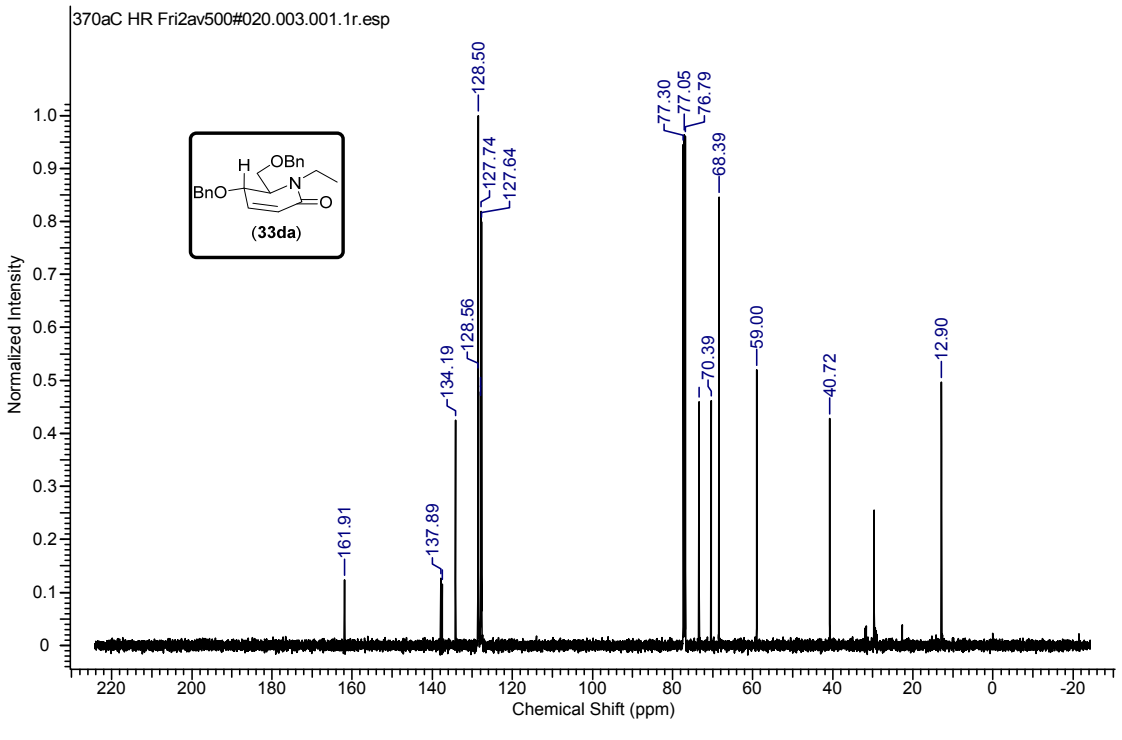
^{13}C NMR (125 MHz, $CDCl_3$) of (**32db**)



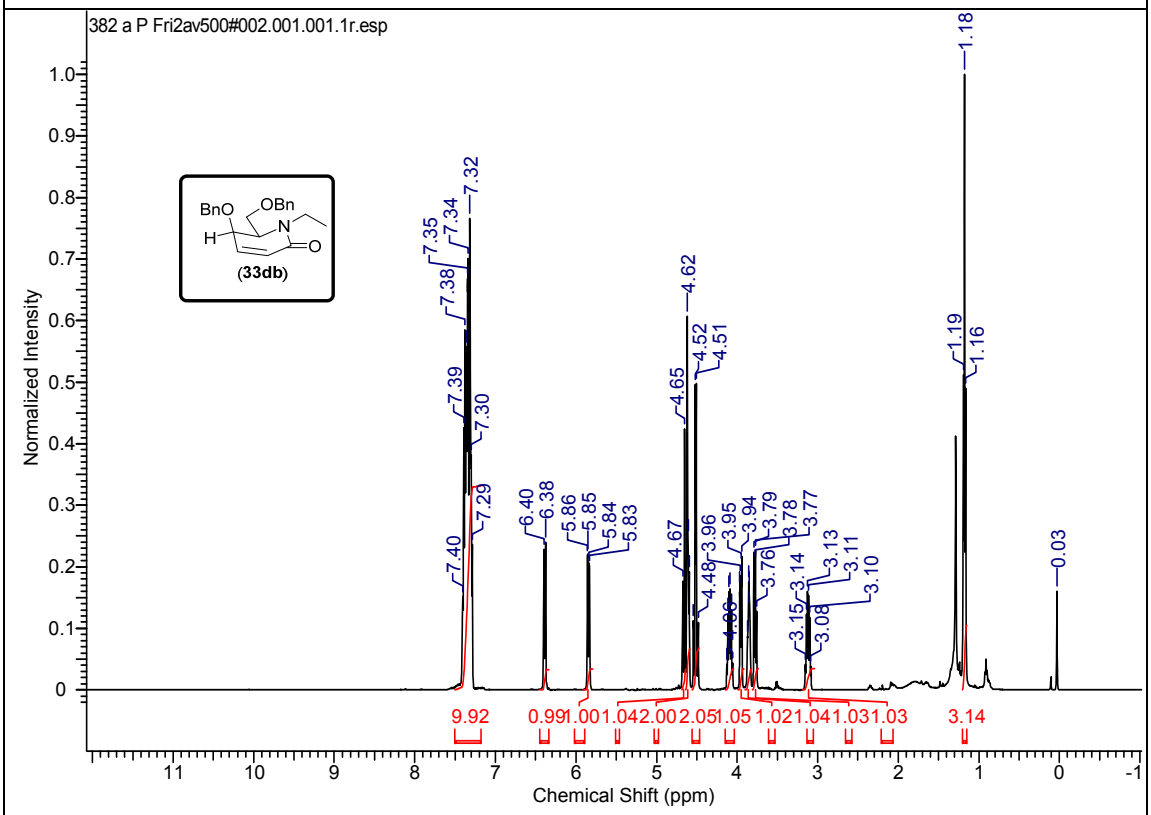
^{1}H NMR (500 MHz, $CDCl_3$) of (**33da**)



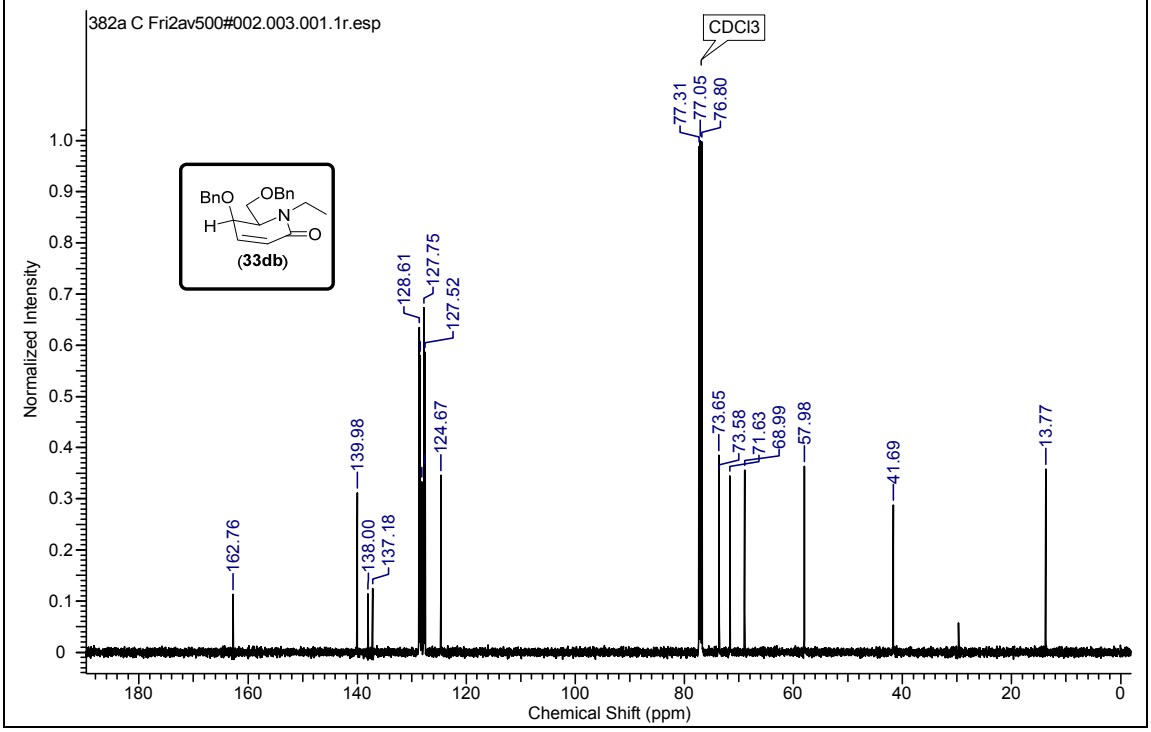
^{13}C NMR (125 MHz, $CDCl_3$) of (**33da**)



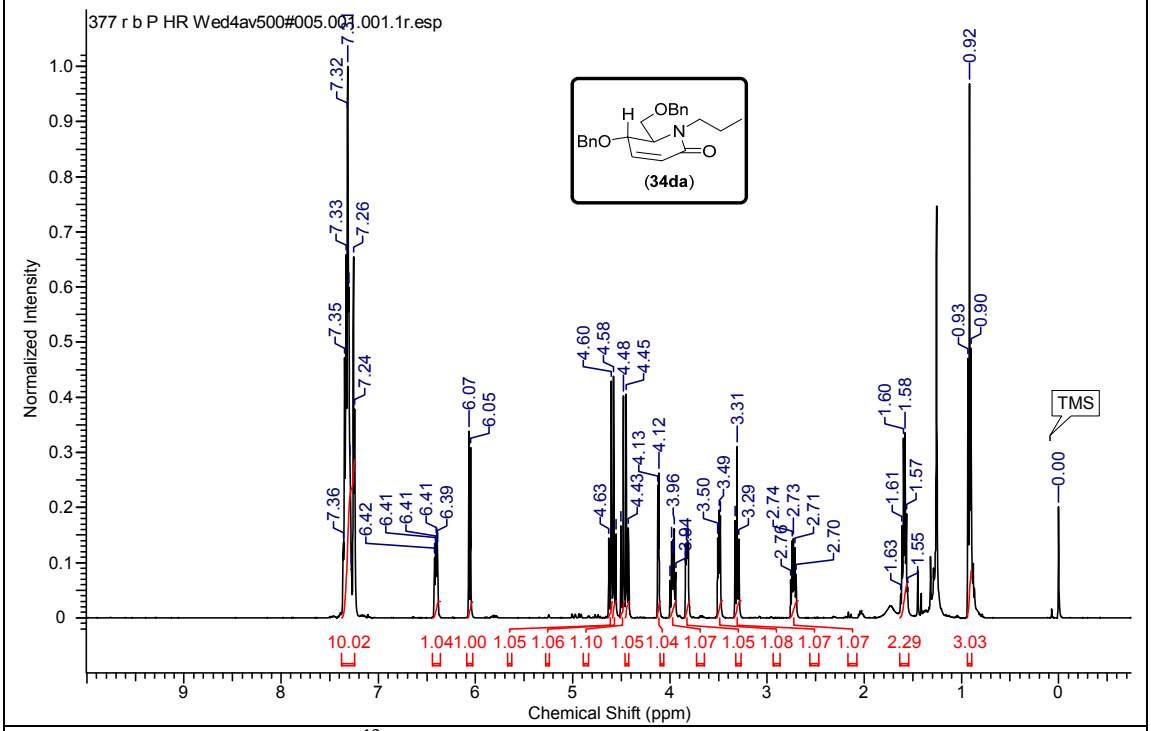
^{1}H NMR (500 MHz, $CDCl_3$) of (**33db**)



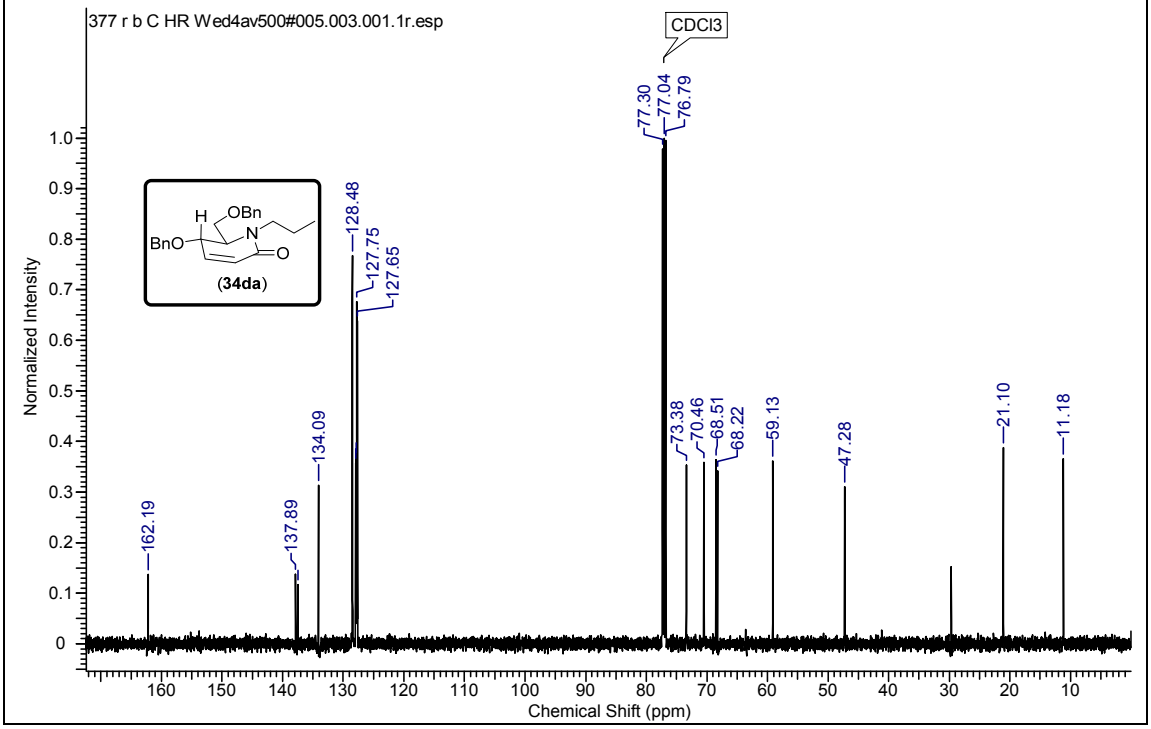
^{13}C NMR (125 MHz, $CDCl_3$) of (**33db**)



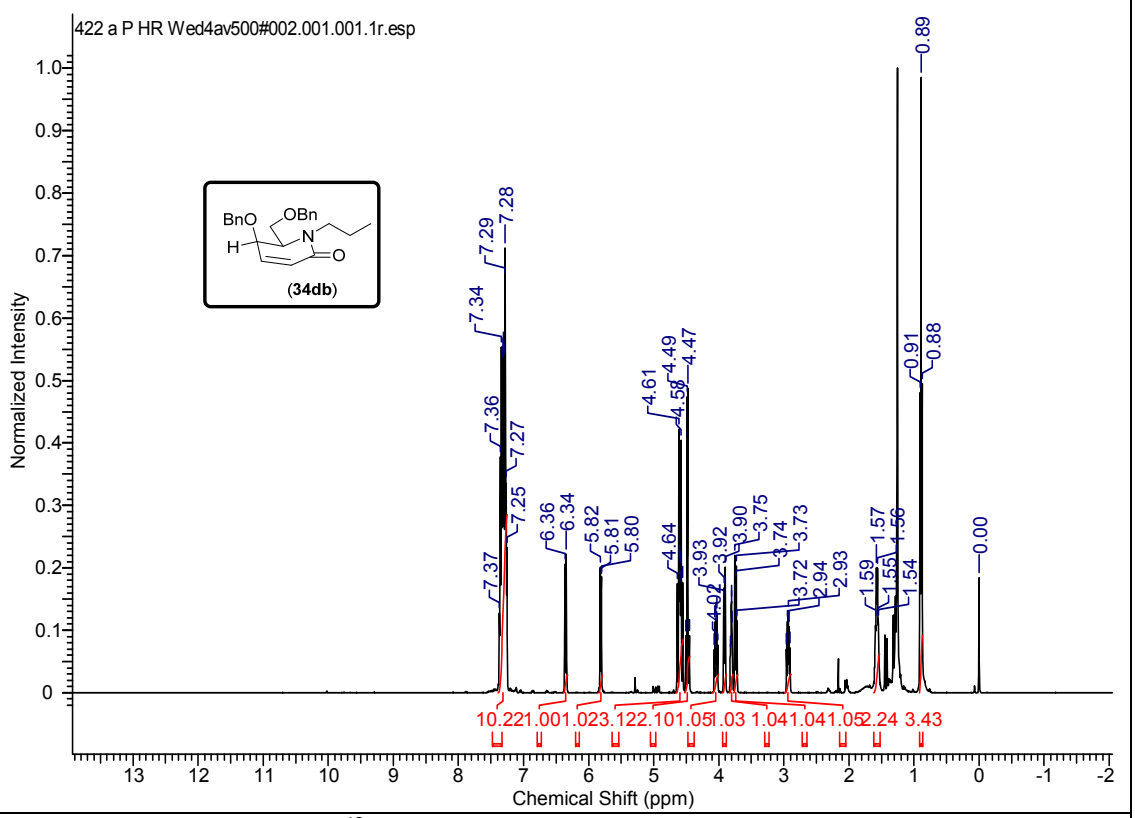
^{1}H NMR (500 MHz, $CDCl_3$) of (**34da**)



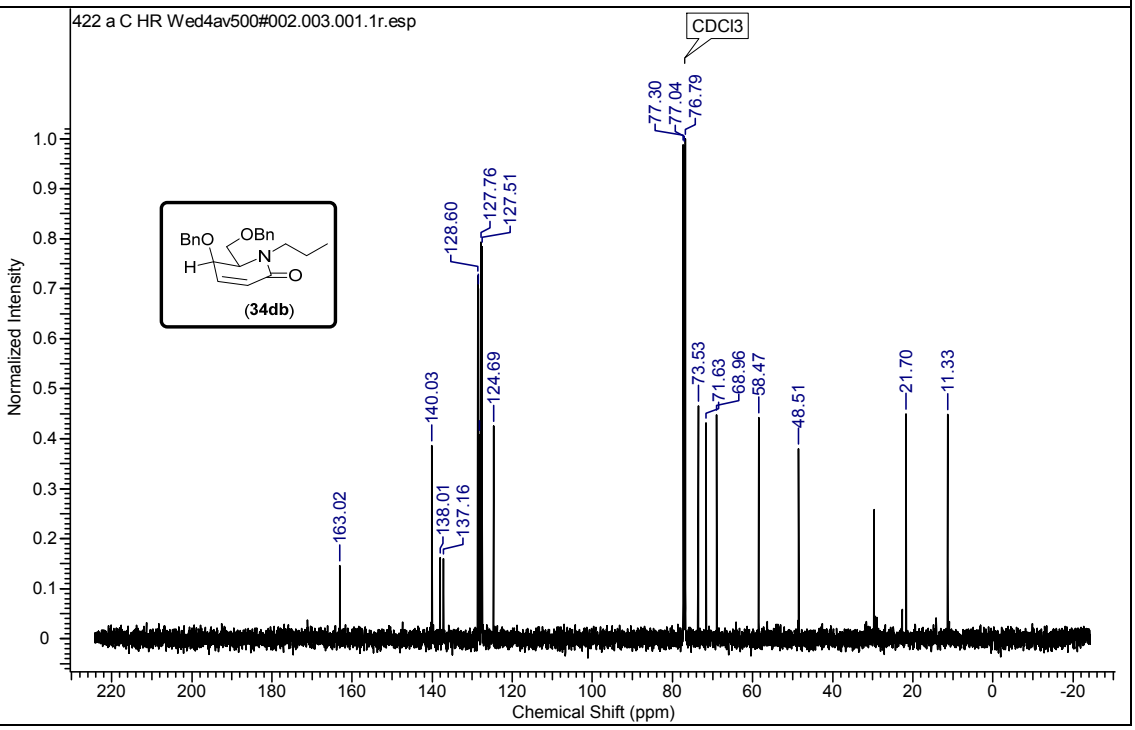
^{13}C NMR (125 MHz, $CDCl_3$) of (**34da**)



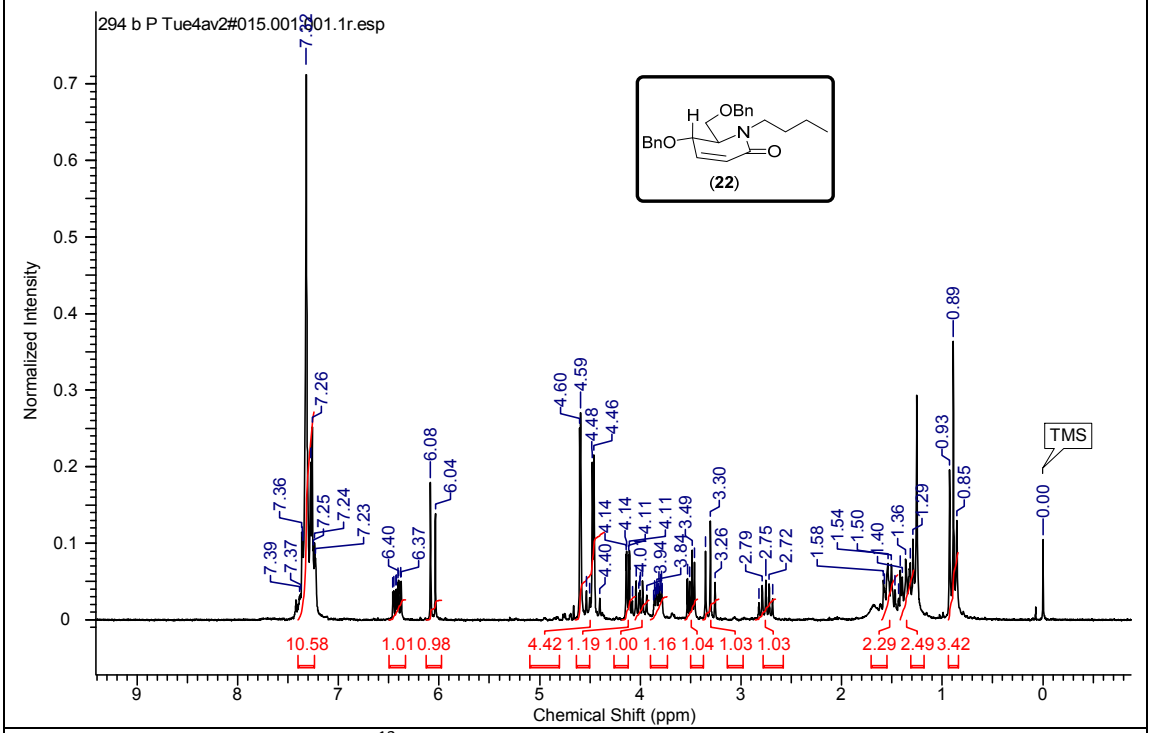
^{1}H NMR (500 MHz, $CDCl_3$) of (**34db**)



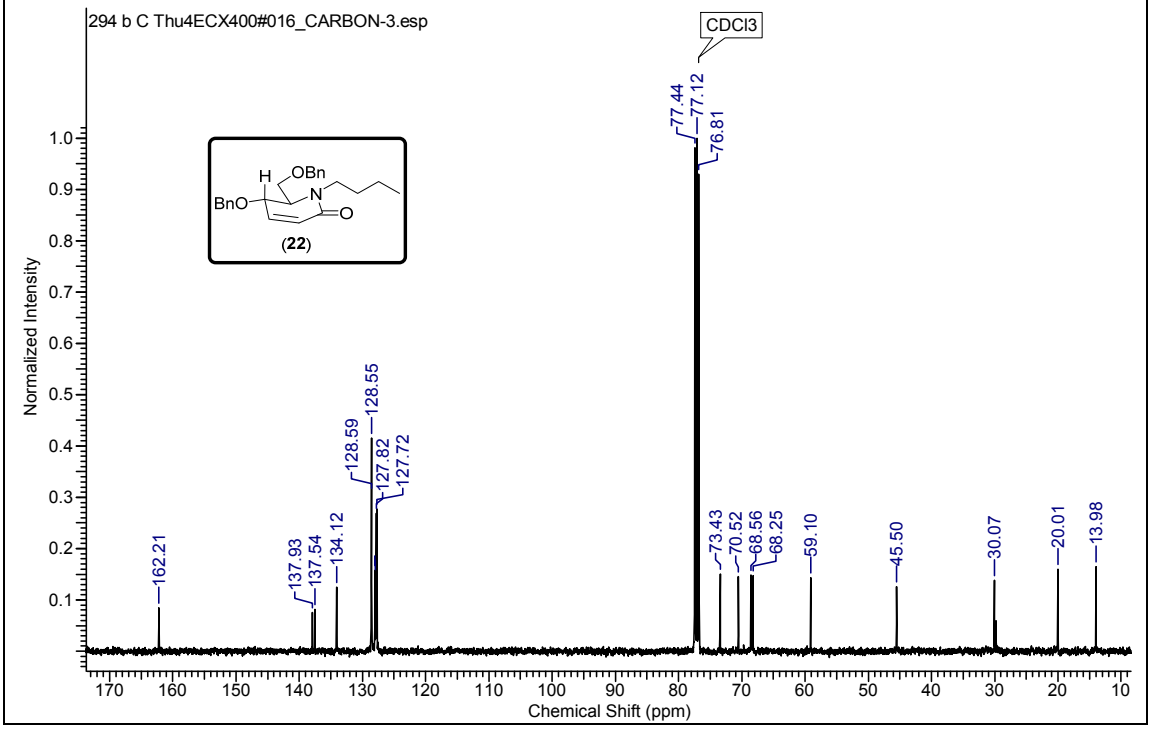
^{13}C NMR (125 MHz, $CDCl_3$) of (**34db**)



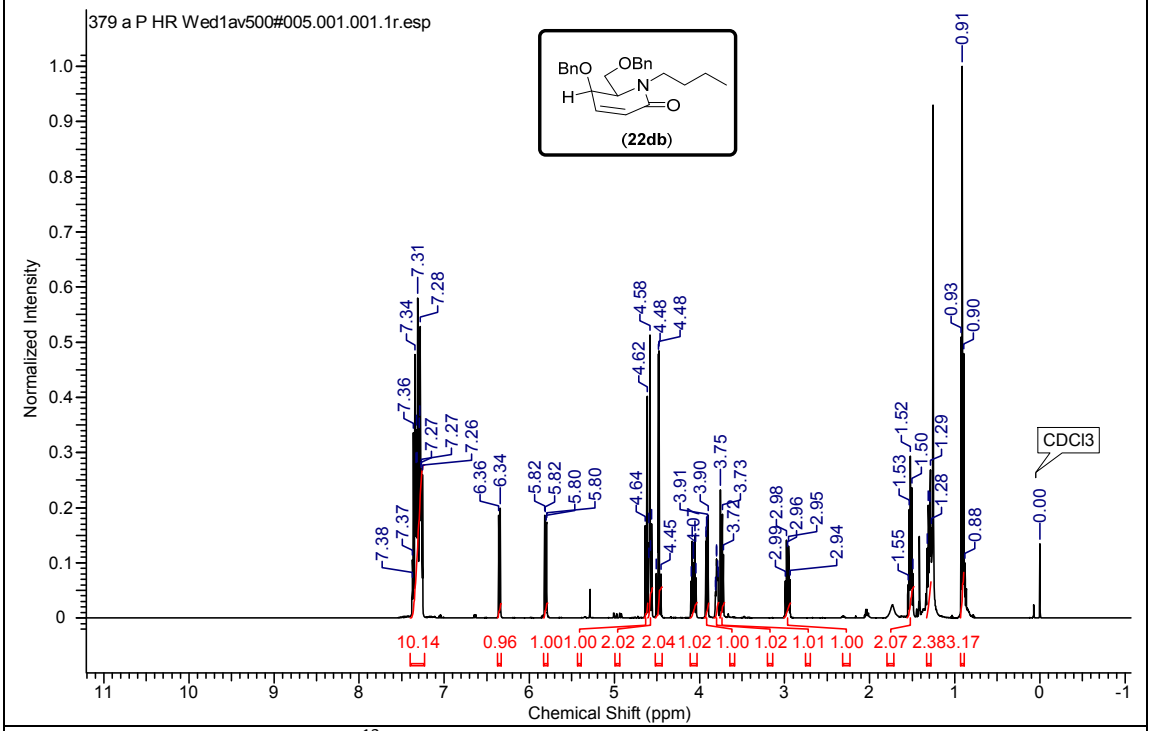
^{1}H NMR (200 MHz, $CDCl_3$) of (**22**)



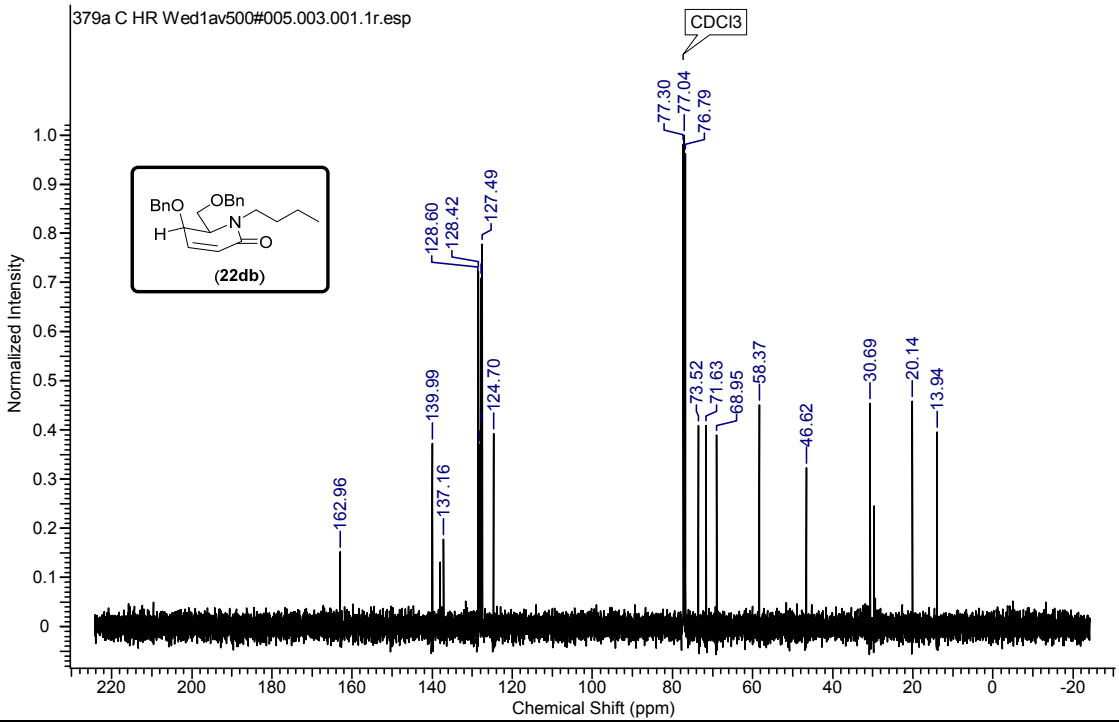
^{13}C NMR (100 MHz, $CDCl_3$) of (**22**)



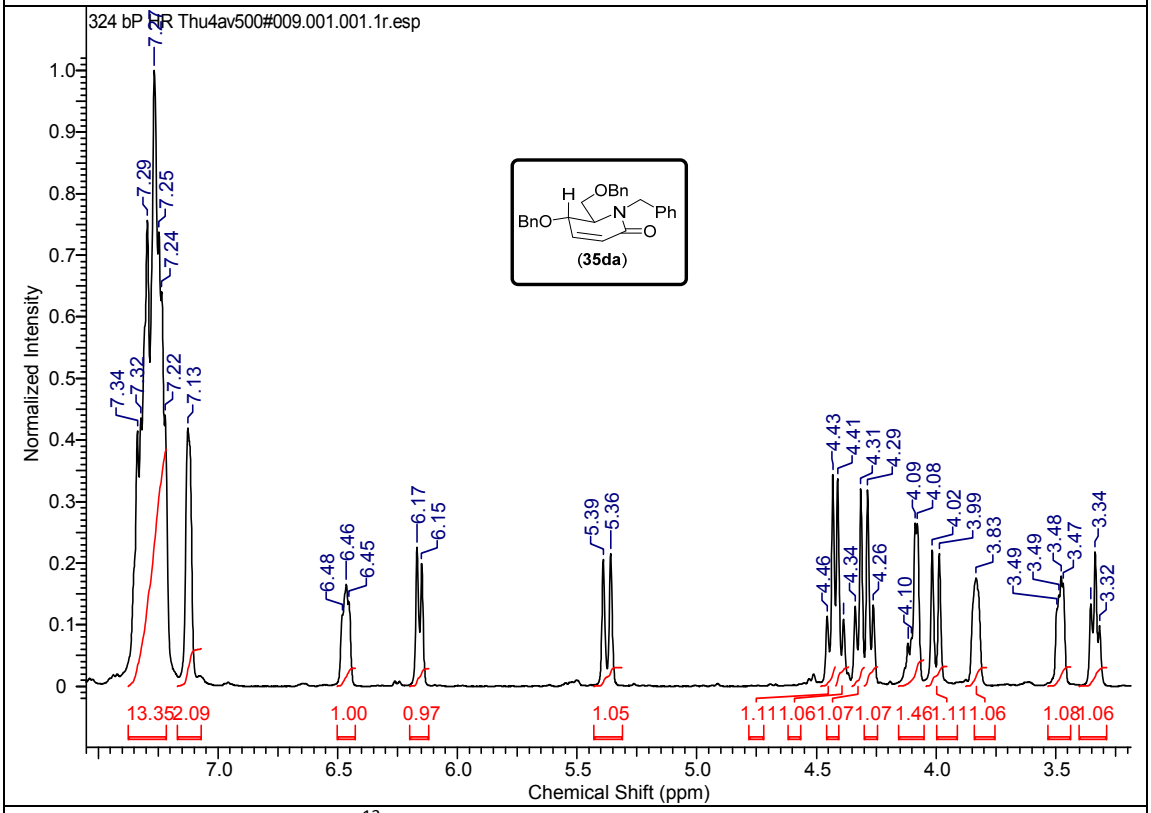
^{1}H NMR (500 MHz, $CDCl_3$) of (**22db**)



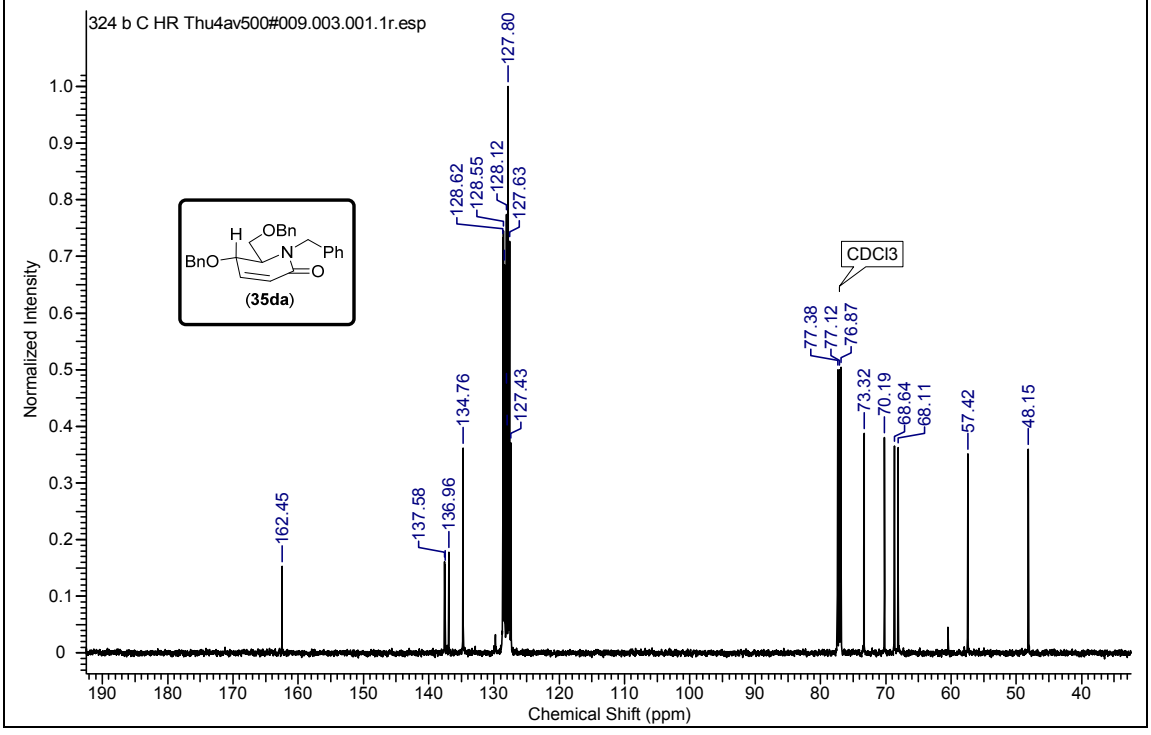
^{13}C NMR (125 MHz, $CDCl_3$) of (**22db**)



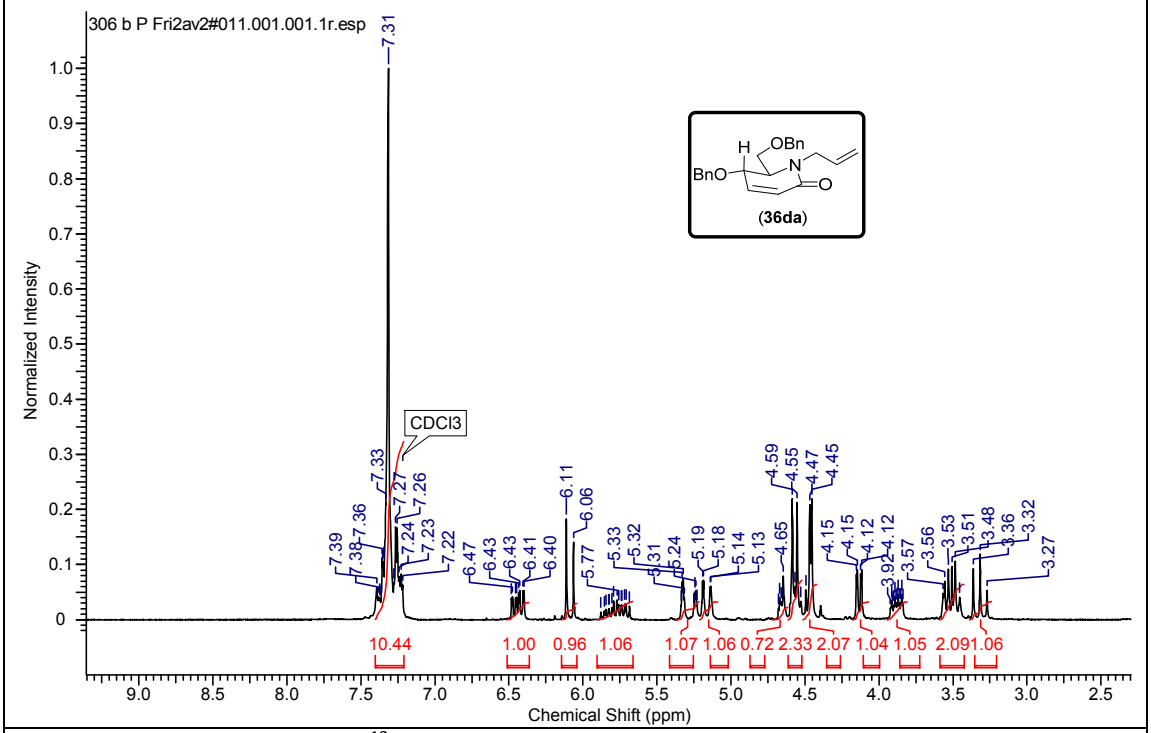
^{1}H NMR (500 MHz, $CDCl_3$) of (**35da**)



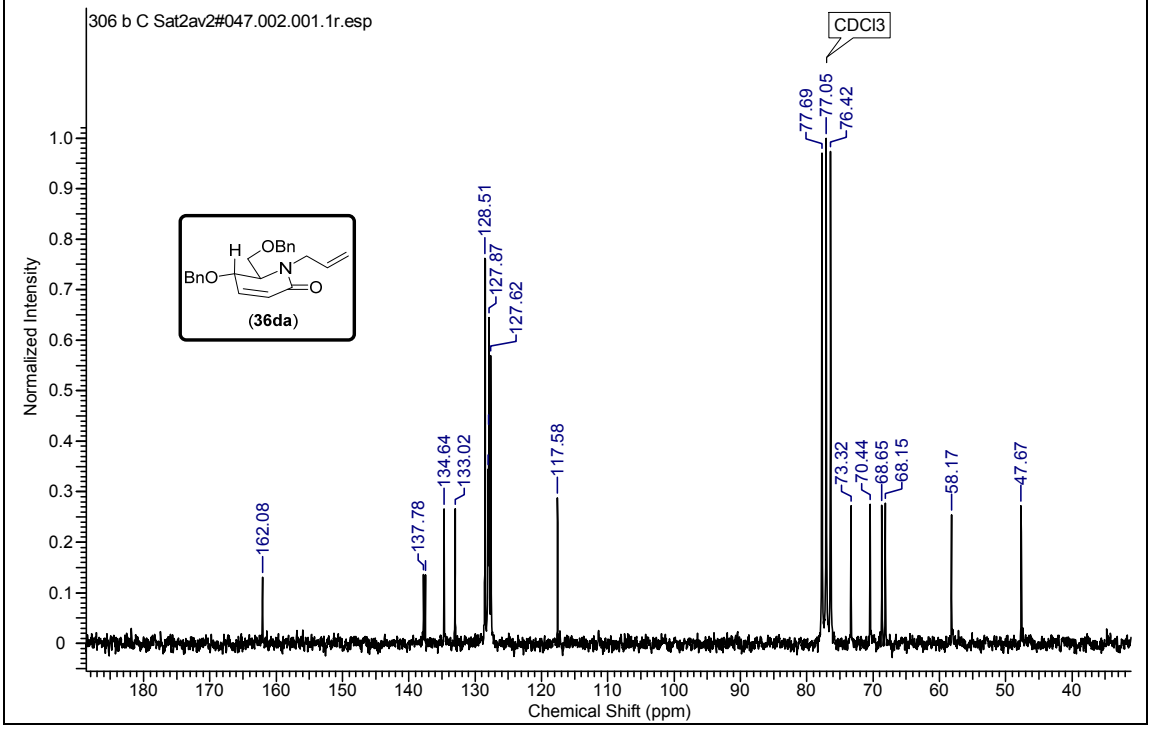
^{13}C NMR (125 MHz, $CDCl_3$) of (**35da**)



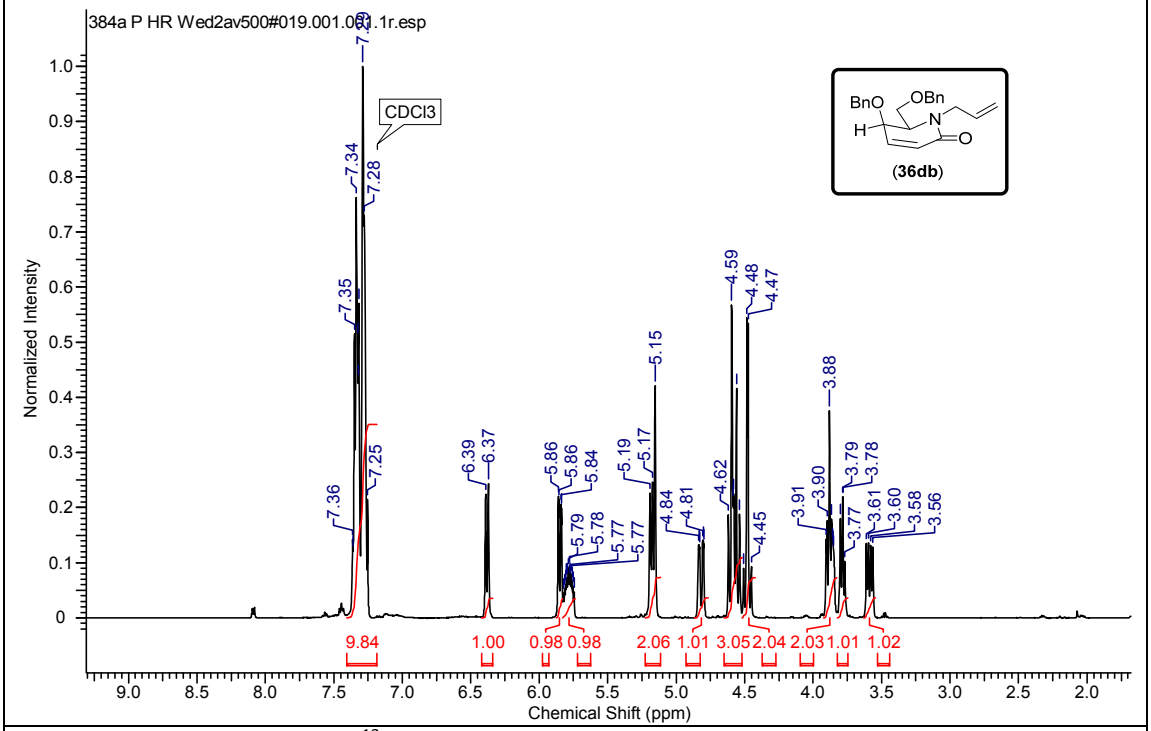
^{1}H NMR (200 MHz, $CDCl_3$) of (**36da**)



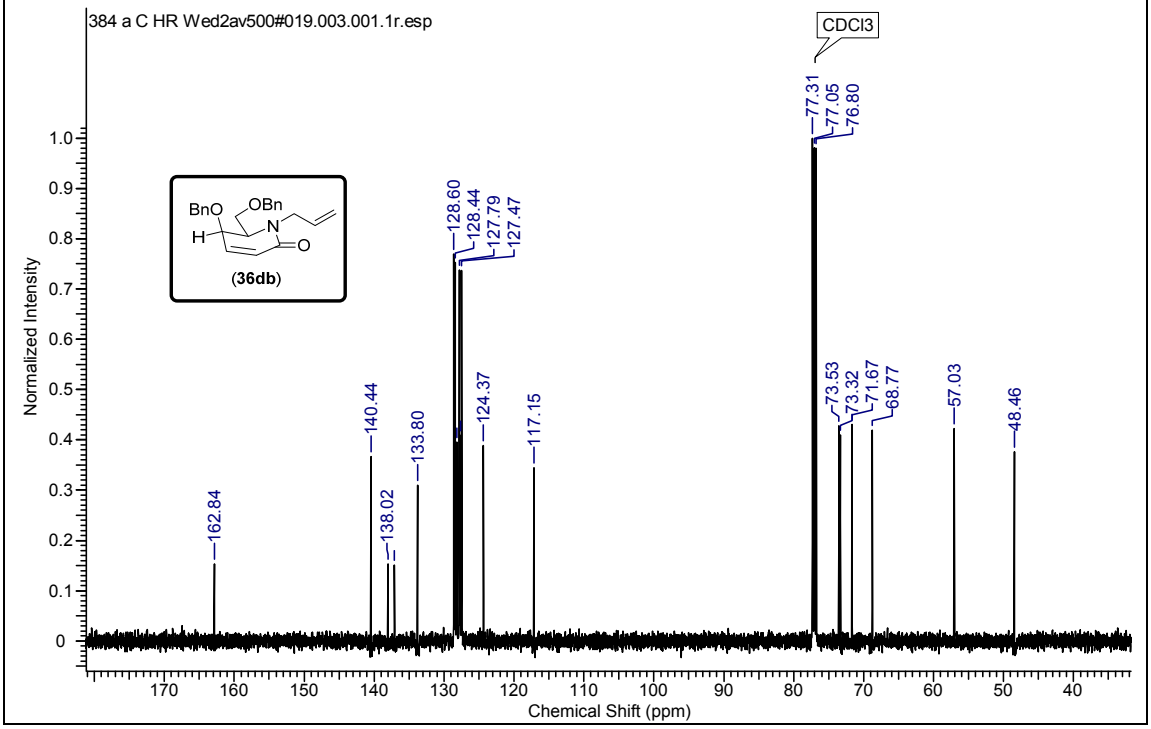
^{13}C NMR (50 MHz, $CDCl_3$) of (**36da**)



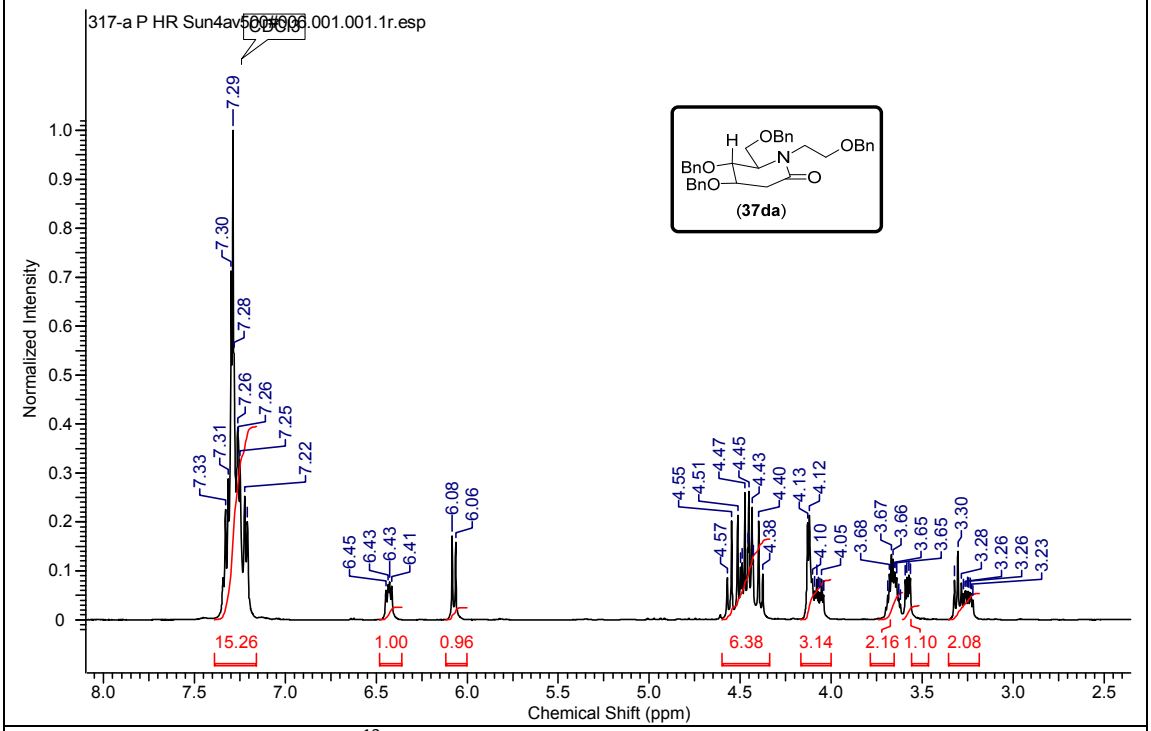
^{1}H NMR (500 MHz, $CDCl_3$) of (**36db**)



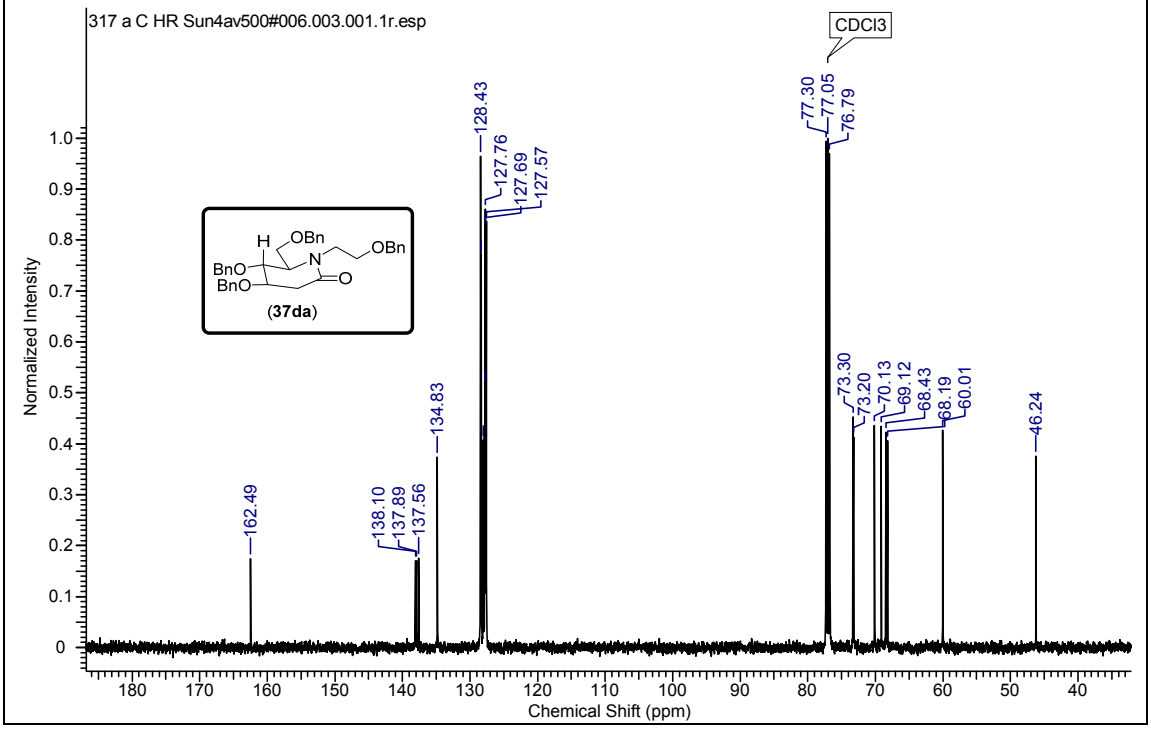
^{13}C NMR (125 MHz, $CDCl_3$) of (**36db**)



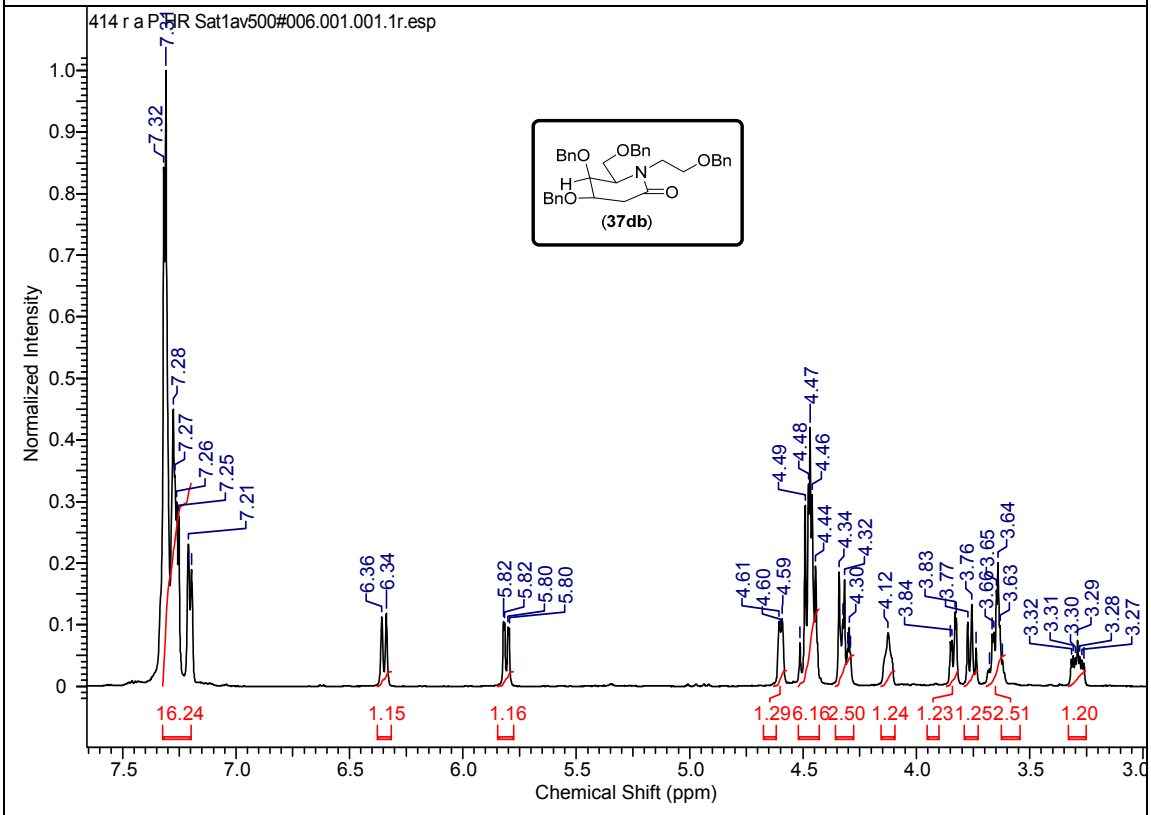
^{1}H NMR (500 MHz, $CDCl_3$) of (**37da**)



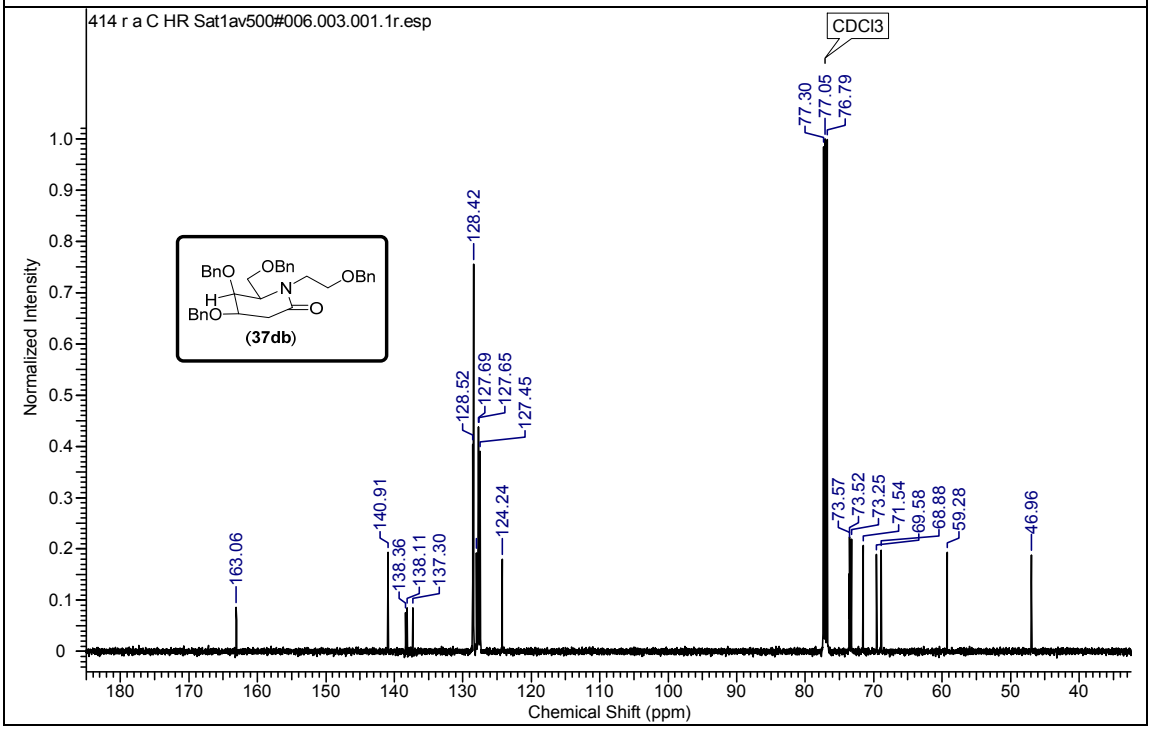
^{13}C NMR (125 MHz, $CDCl_3$) of (**37da**)



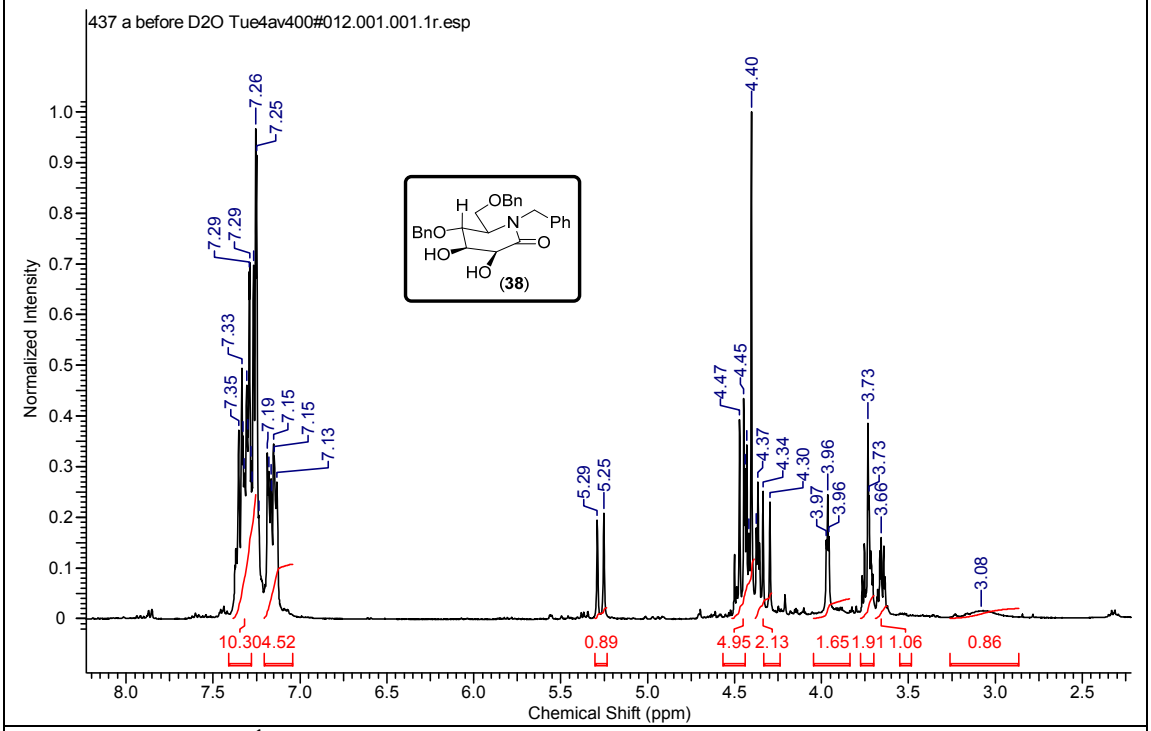
^{1}H NMR (400 MHz, $CDCl_3$) of (**37db**)



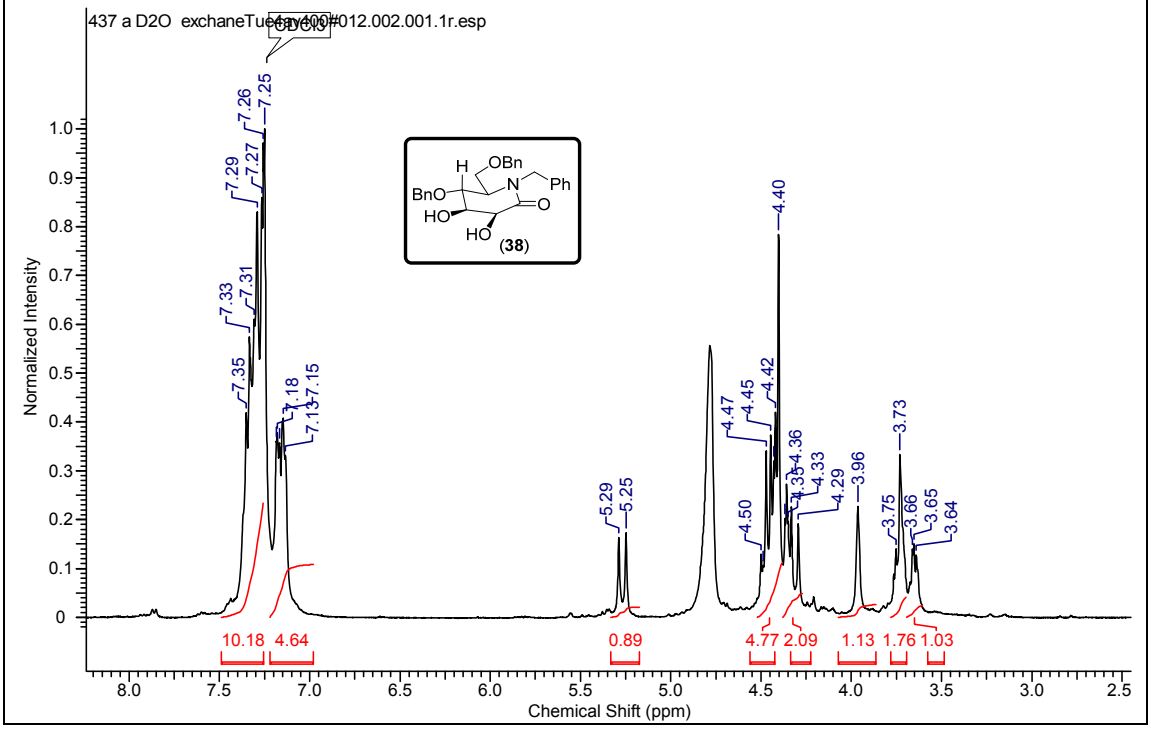
^{13}C NMR (100 MHz, $CDCl_3$) of (**37db**)



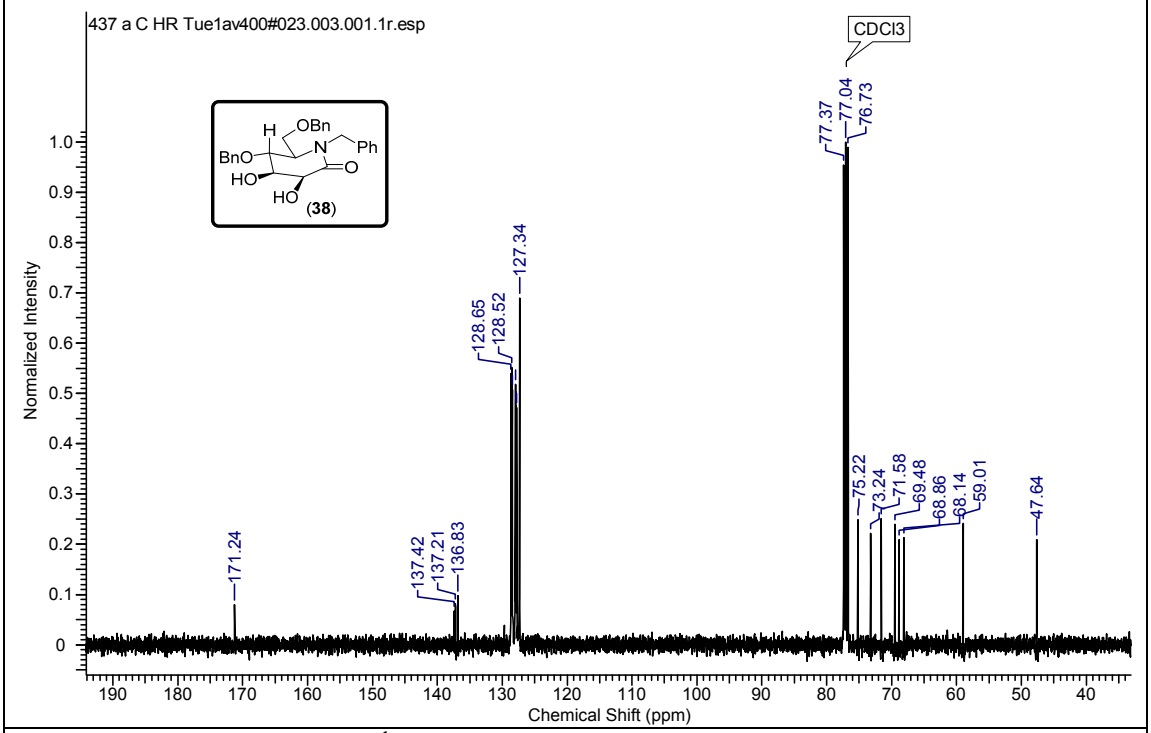
^{1}H NMR (400 MHz, $CDCl_3$) of (**38**)



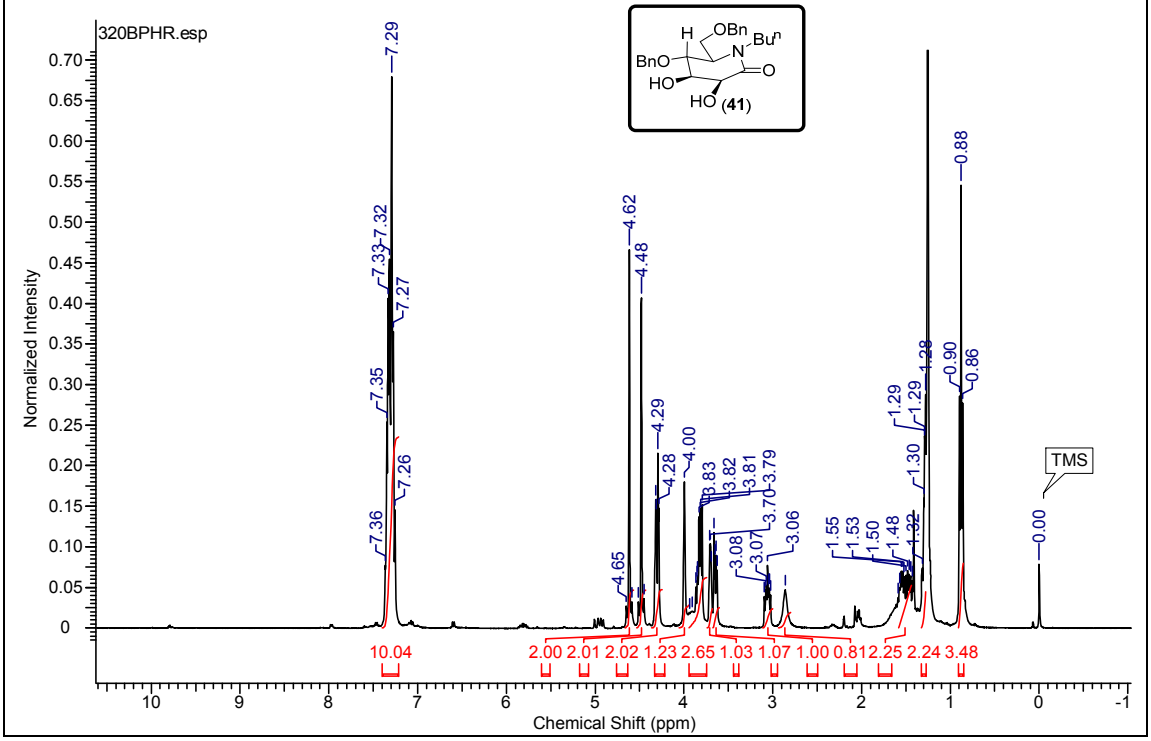
^{1}H NMR (400 MHz, $CDCl_3$) of (**38**). D_2O exchange study



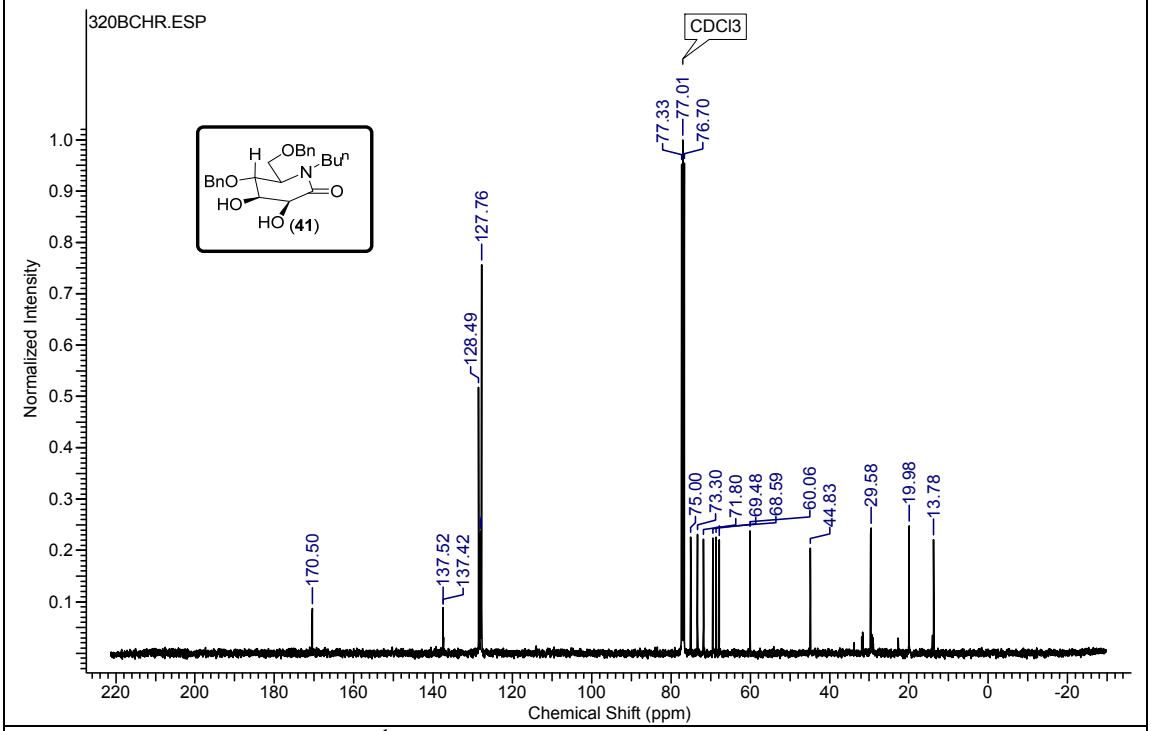
^{13}C NMR (100 MHz, $CDCl_3$) of (**38**)



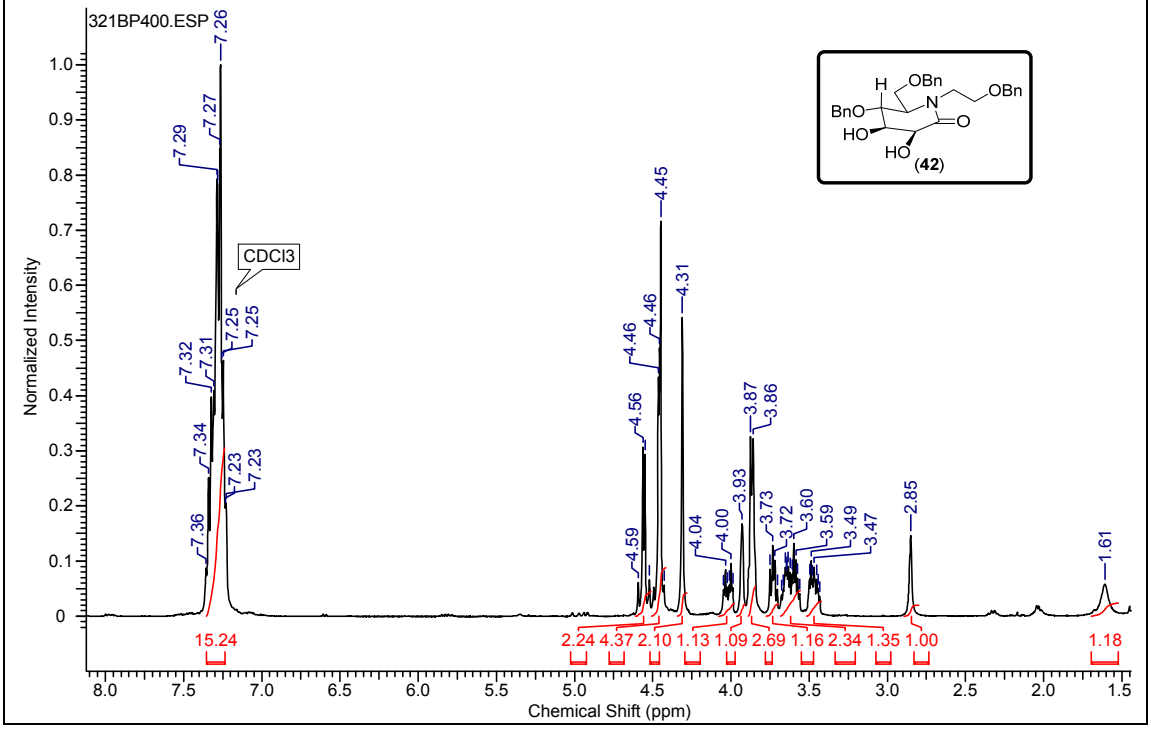
^{1}H NMR (400 MHz, $CDCl_3$) of (**41**)



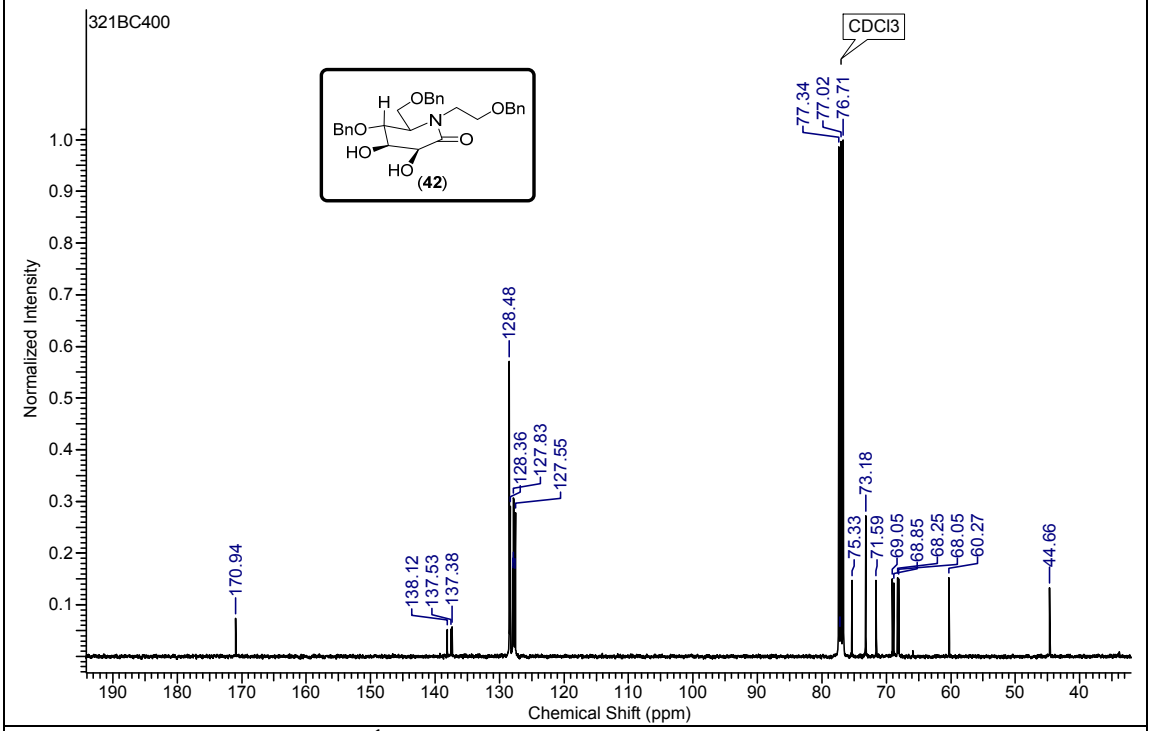
^{13}C NMR (100 MHz, $CDCl_3$) of (**41**)



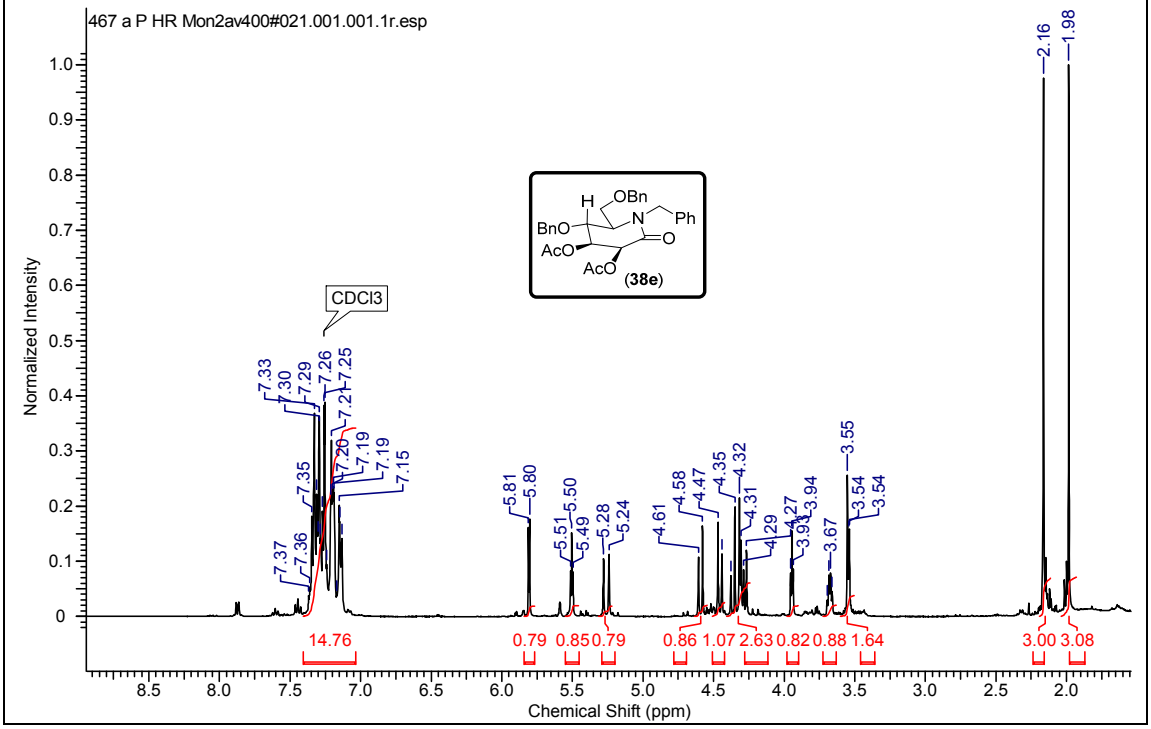
^{1}H NMR (400 MHz, $CDCl_3$) of (**42**)



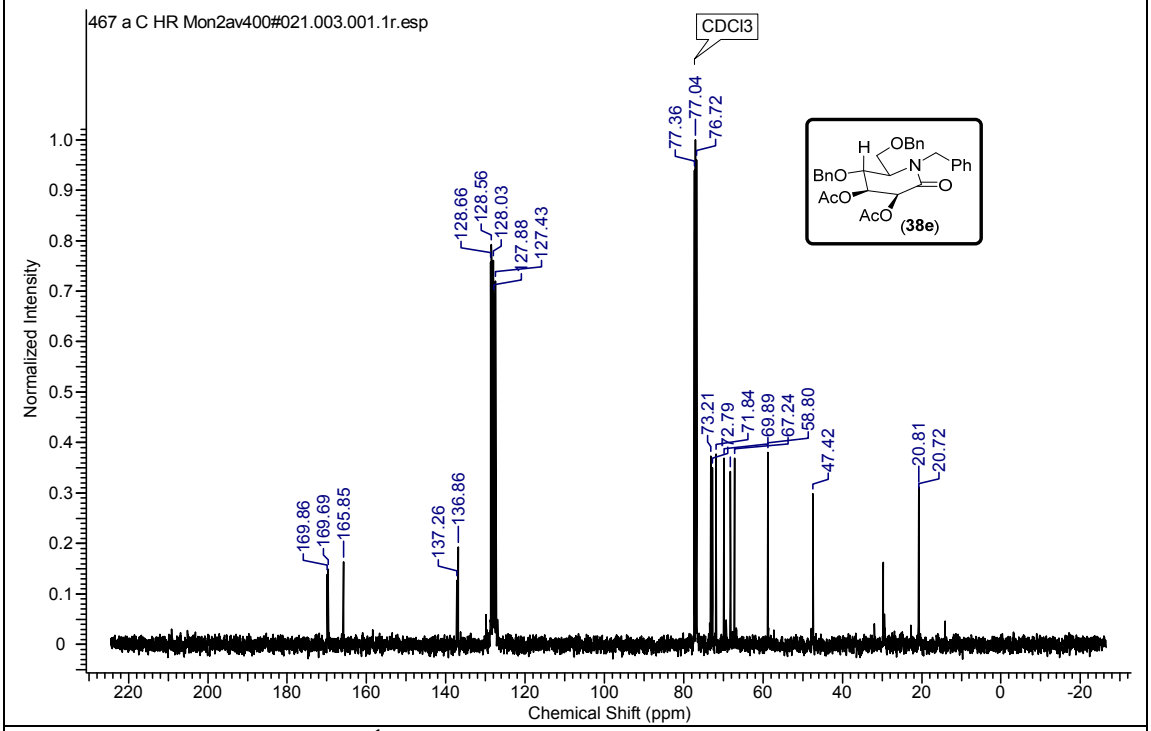
^{13}C NMR (100 MHz, $CDCl_3$) of (**42**)



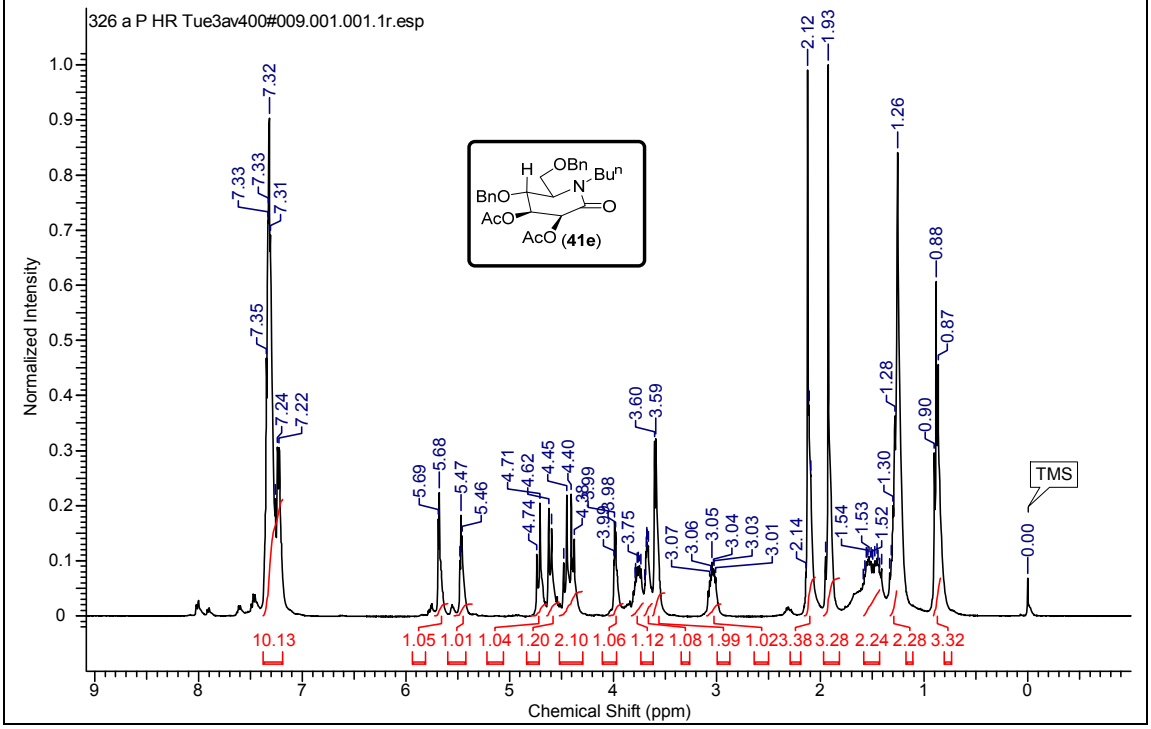
^{1}H NMR (400 MHz, $CDCl_3$) of (**38e**)



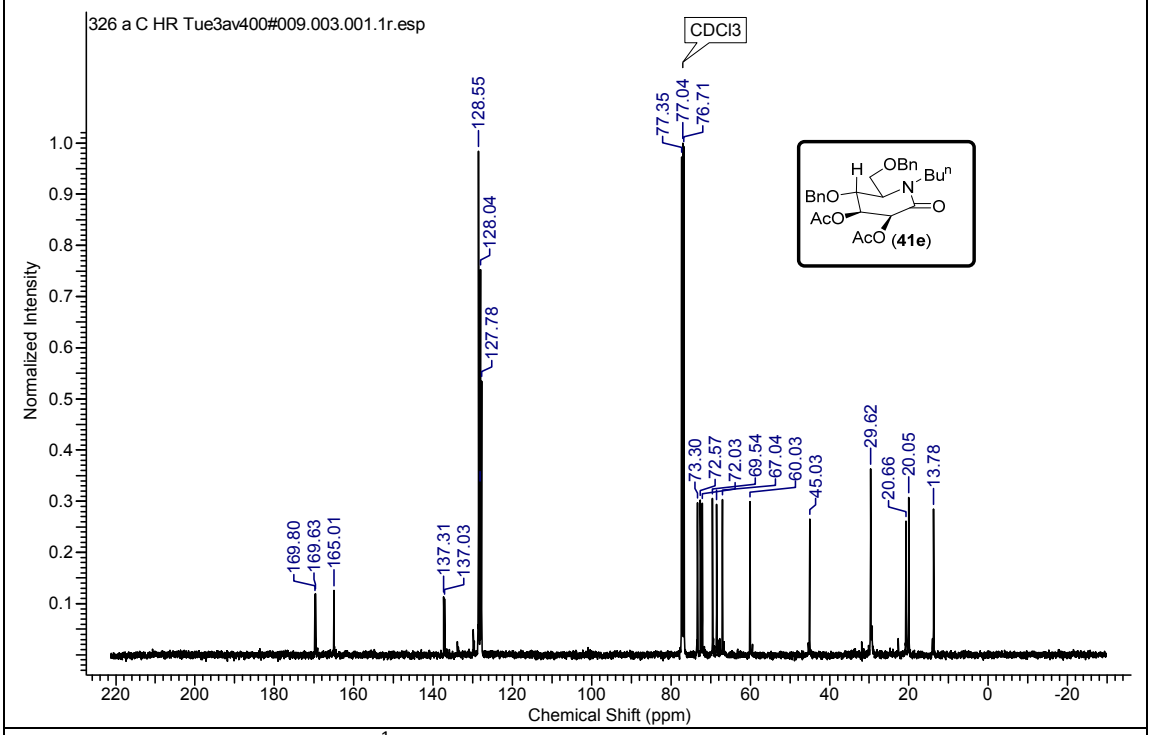
^{13}C NMR (100 MHz, $CDCl_3$) of (**38e**)



^{1}H NMR (400 MHz, $CDCl_3$) of (**41e**)



^{13}C NMR (100 MHz, $CDCl_3$) of (**41e**)



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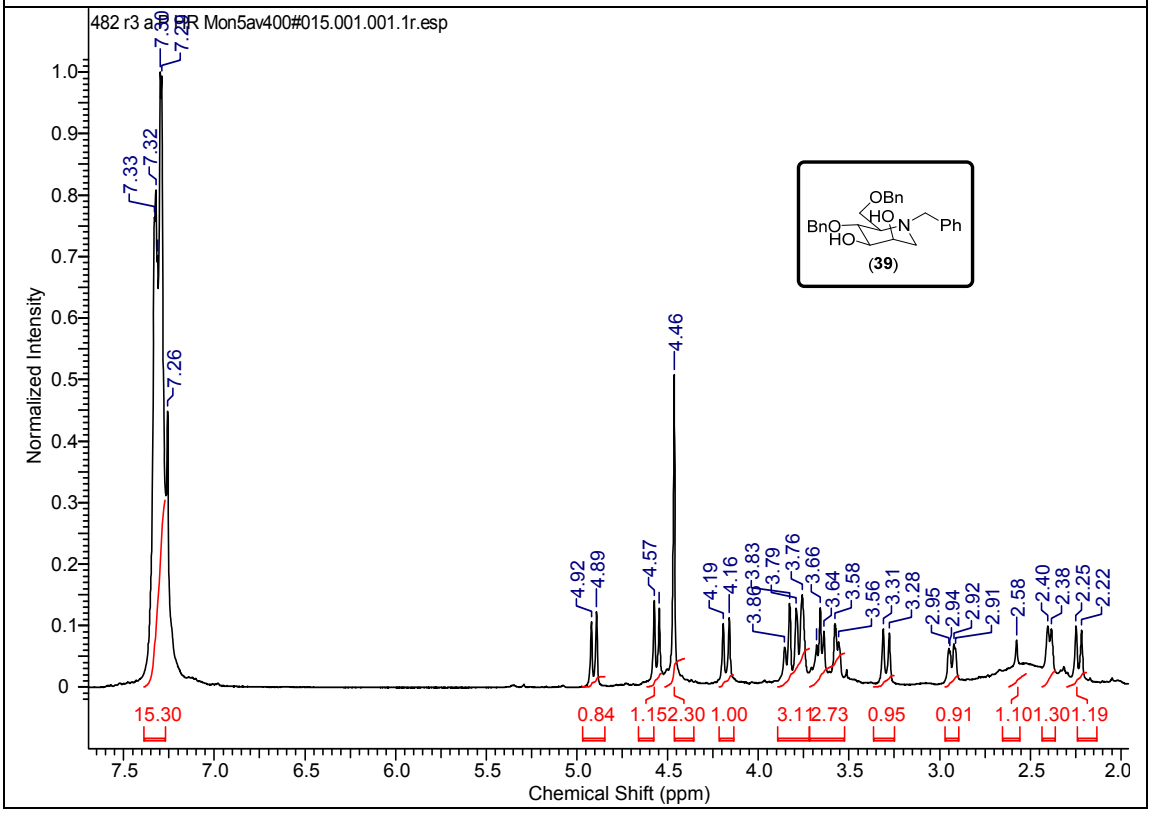

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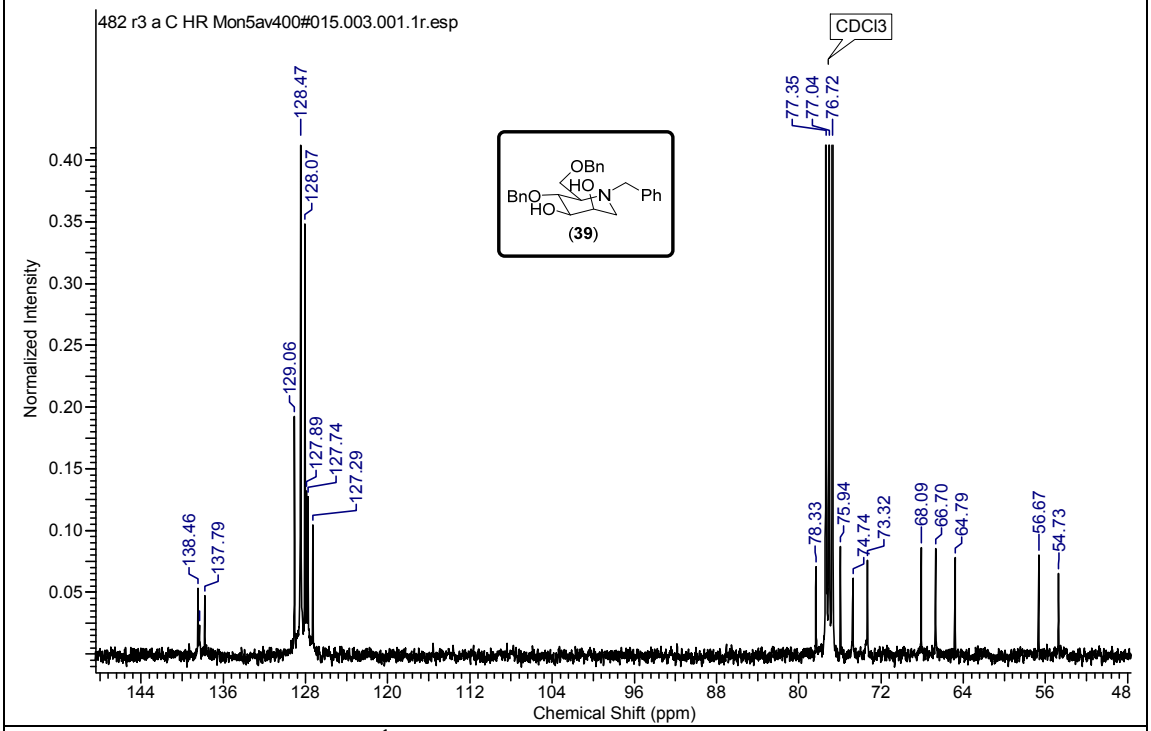
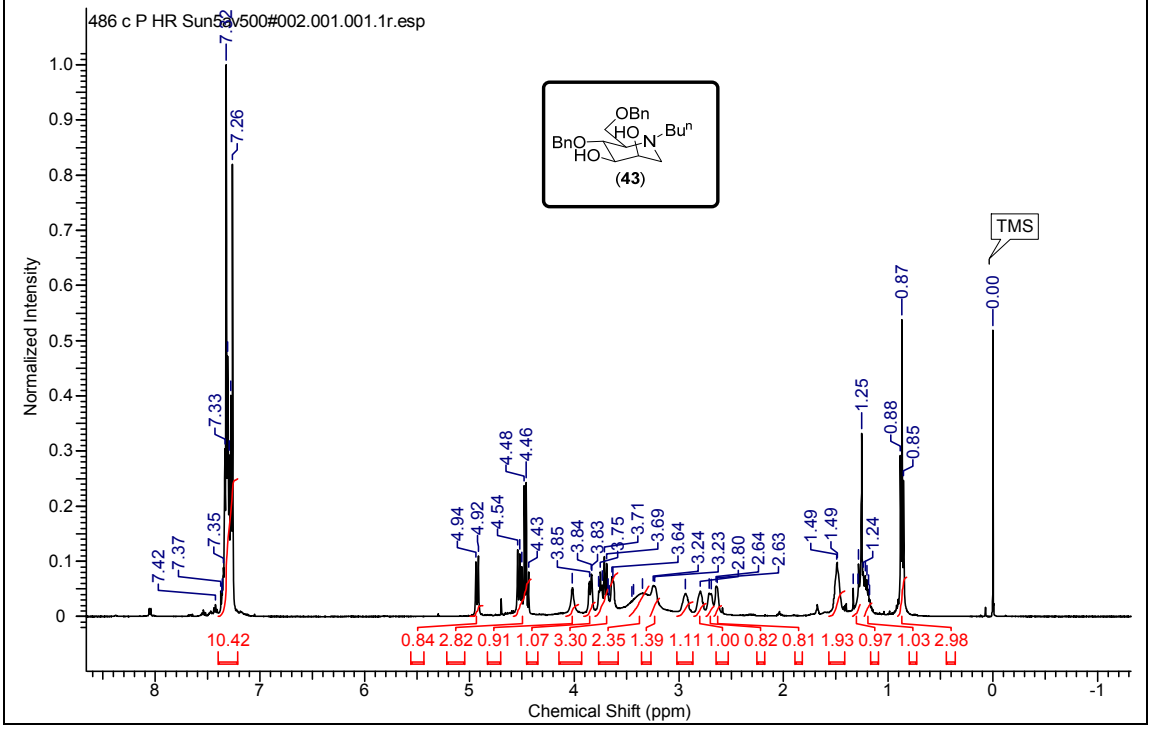


^{1}H NMR (500 MHz, $CDCl_3$) of (**43**)



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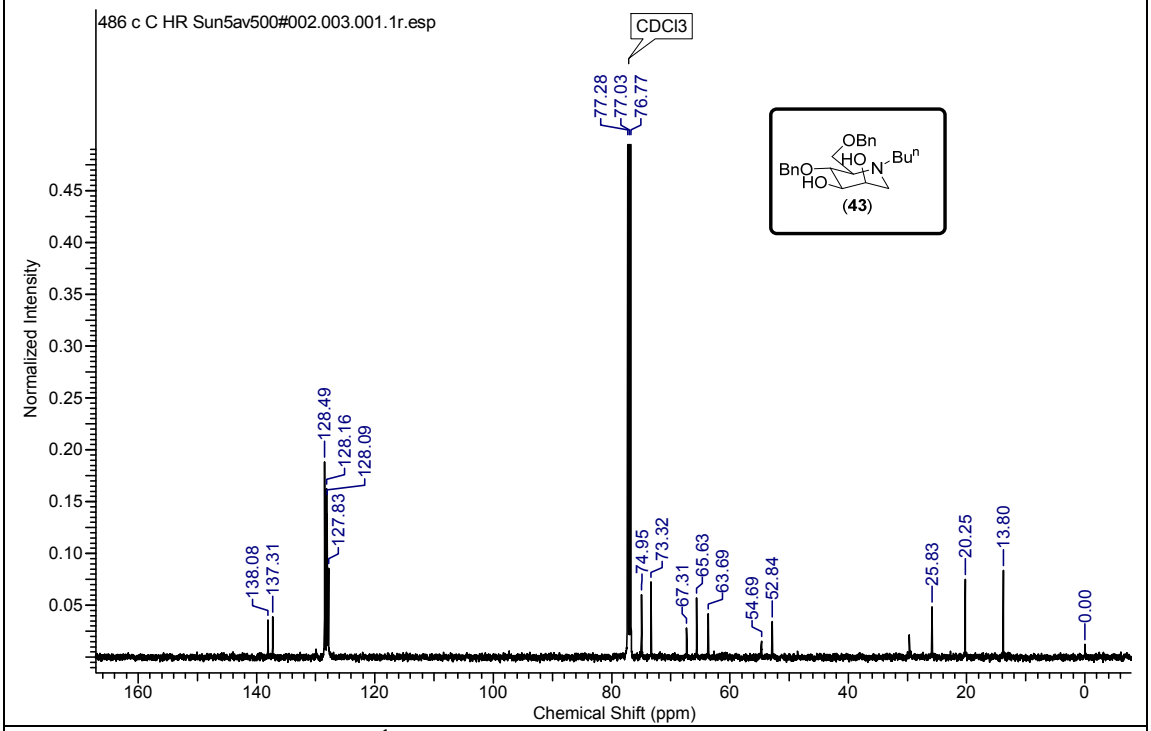

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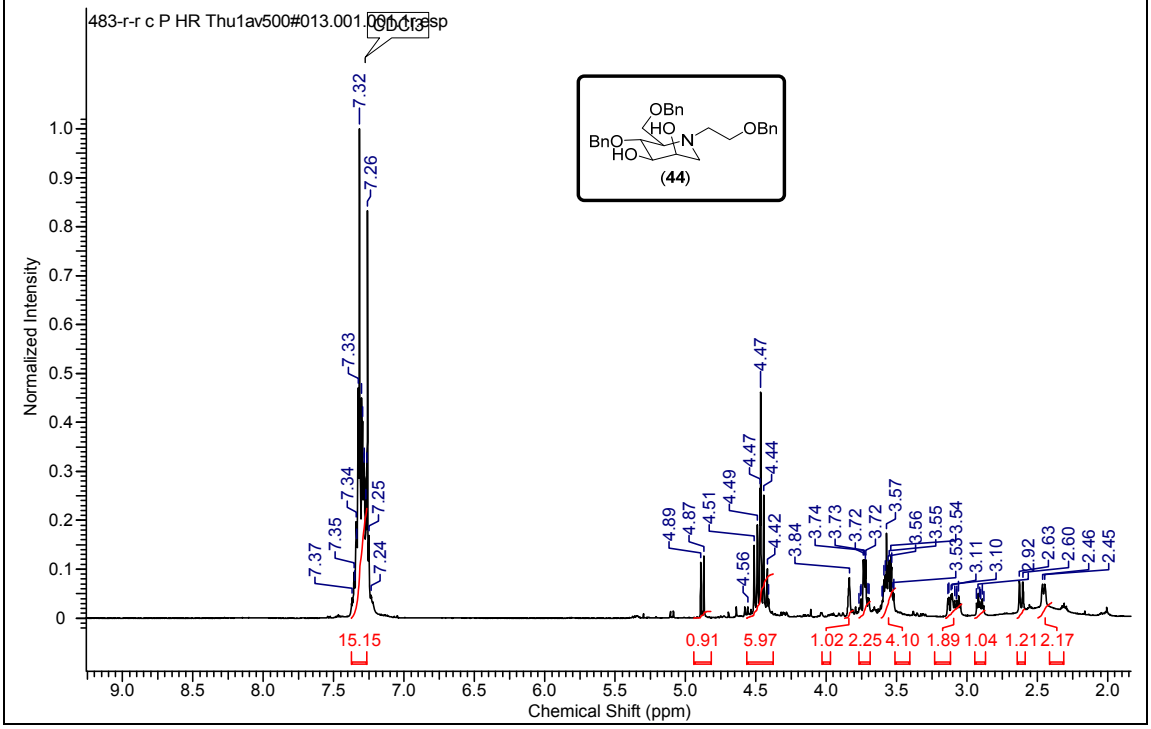

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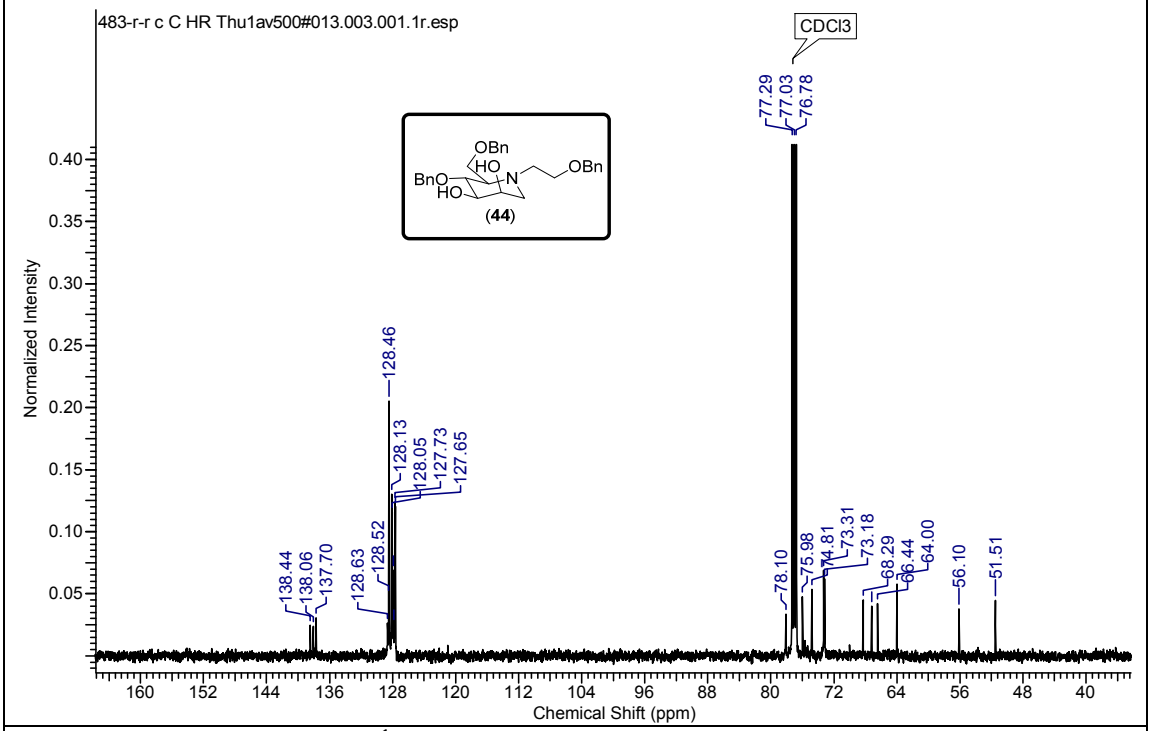
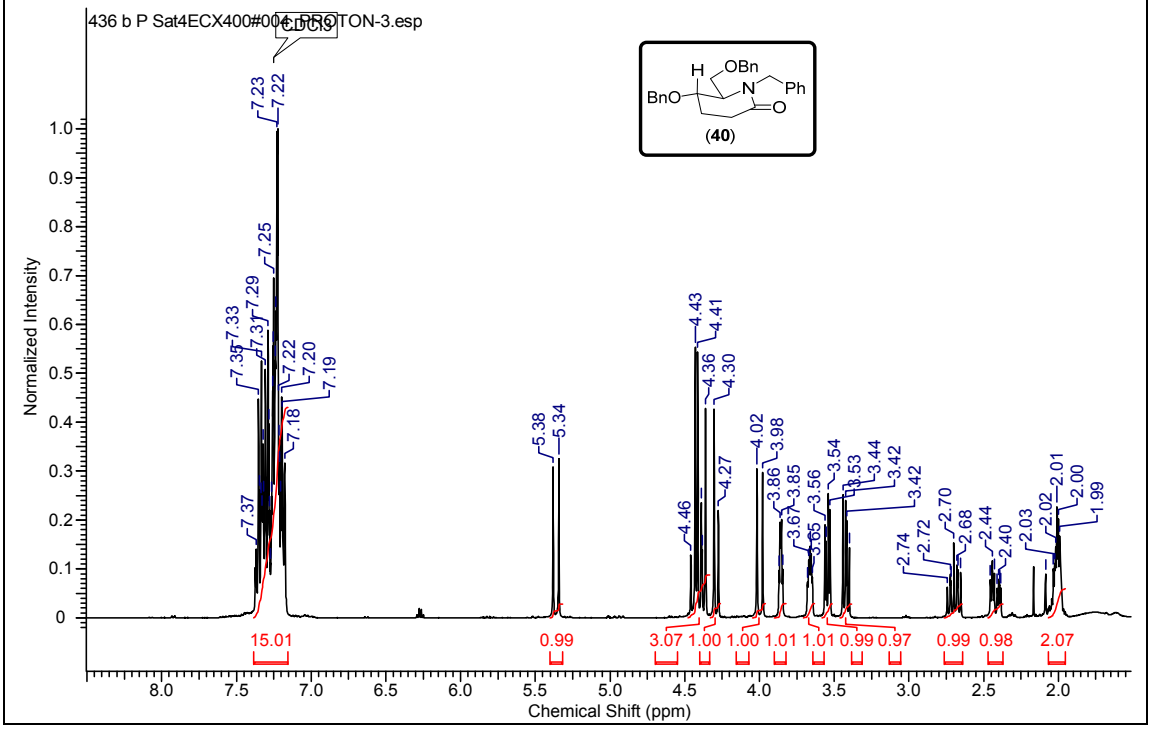
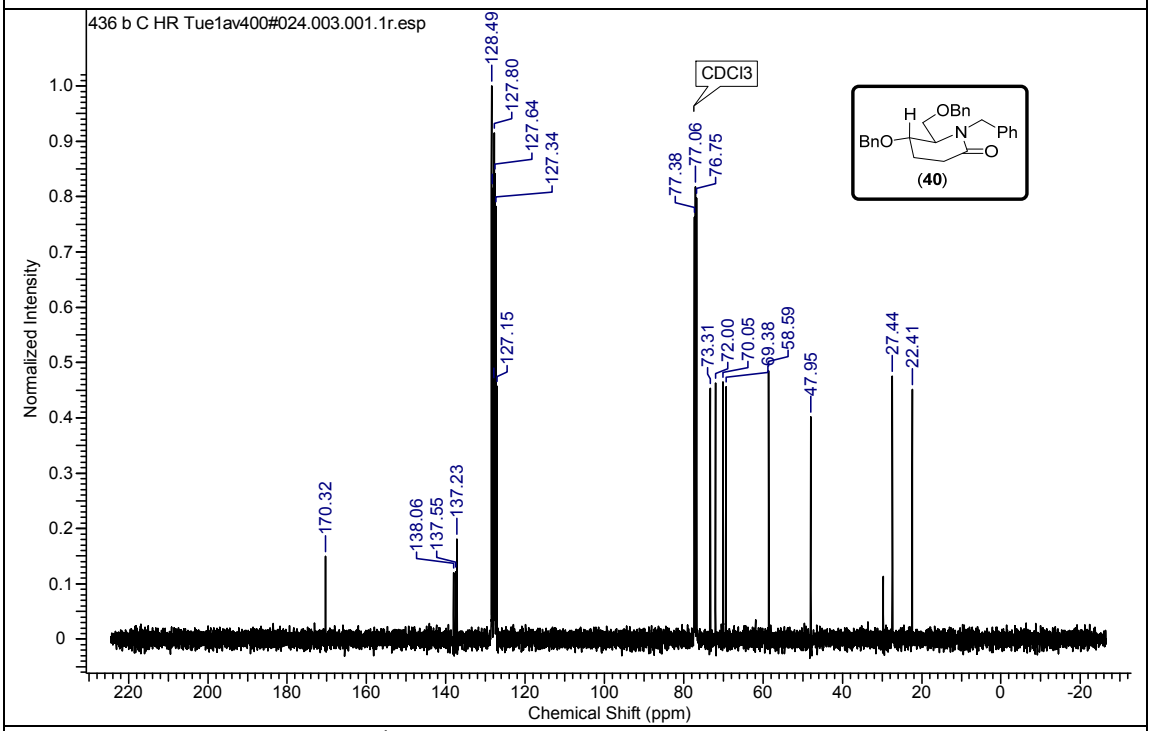


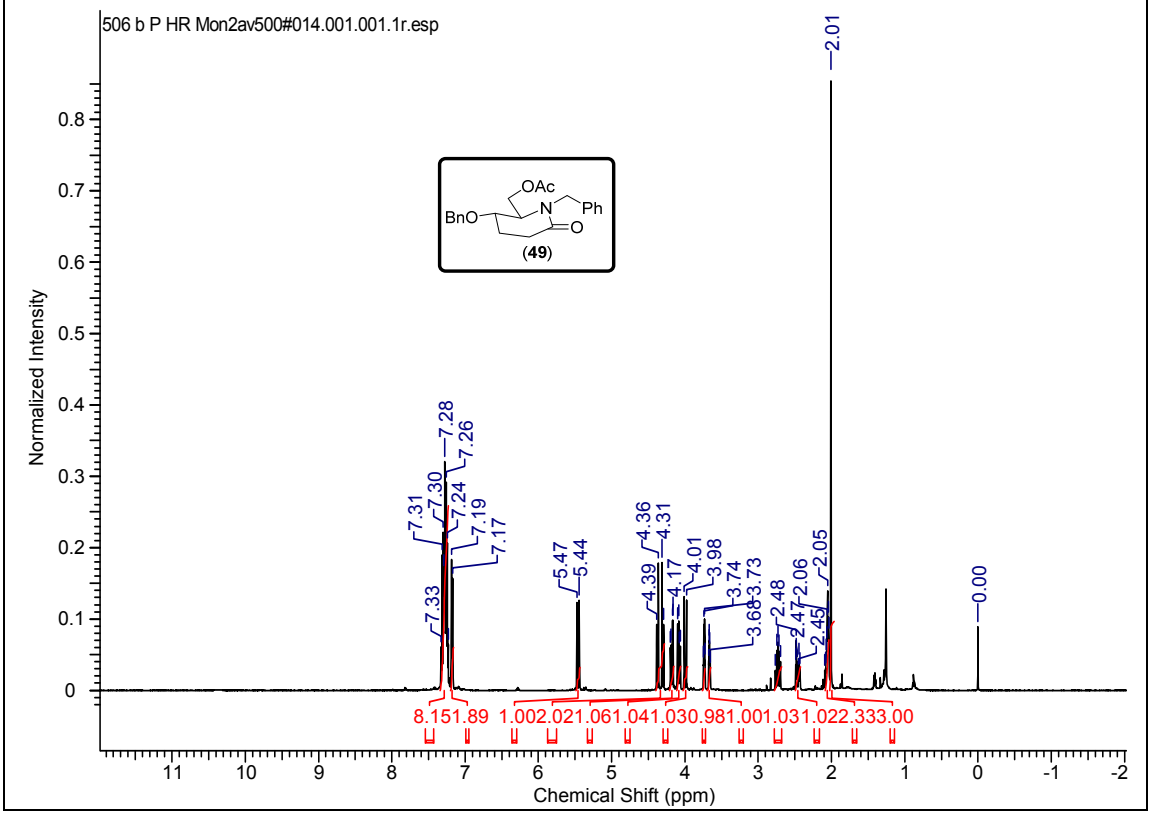
^{1}H NMR (400 MHz, $CDCl_3$) of (**40**)



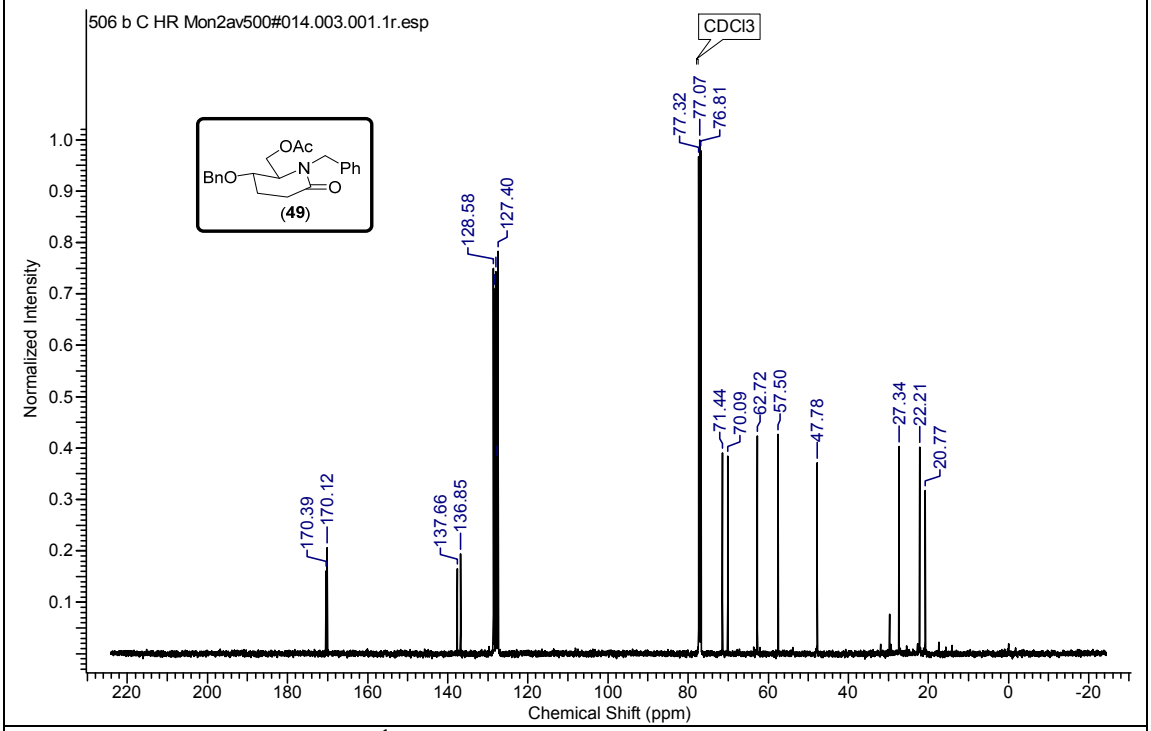
^{13}C NMR (100 MHz, $CDCl_3$) of (**40**)



^{1}H NMR (500 MHz, $CDCl_3$) of (**49**)



^{13}C NMR (125 MHz, $CDCl_3$) of (**49**)



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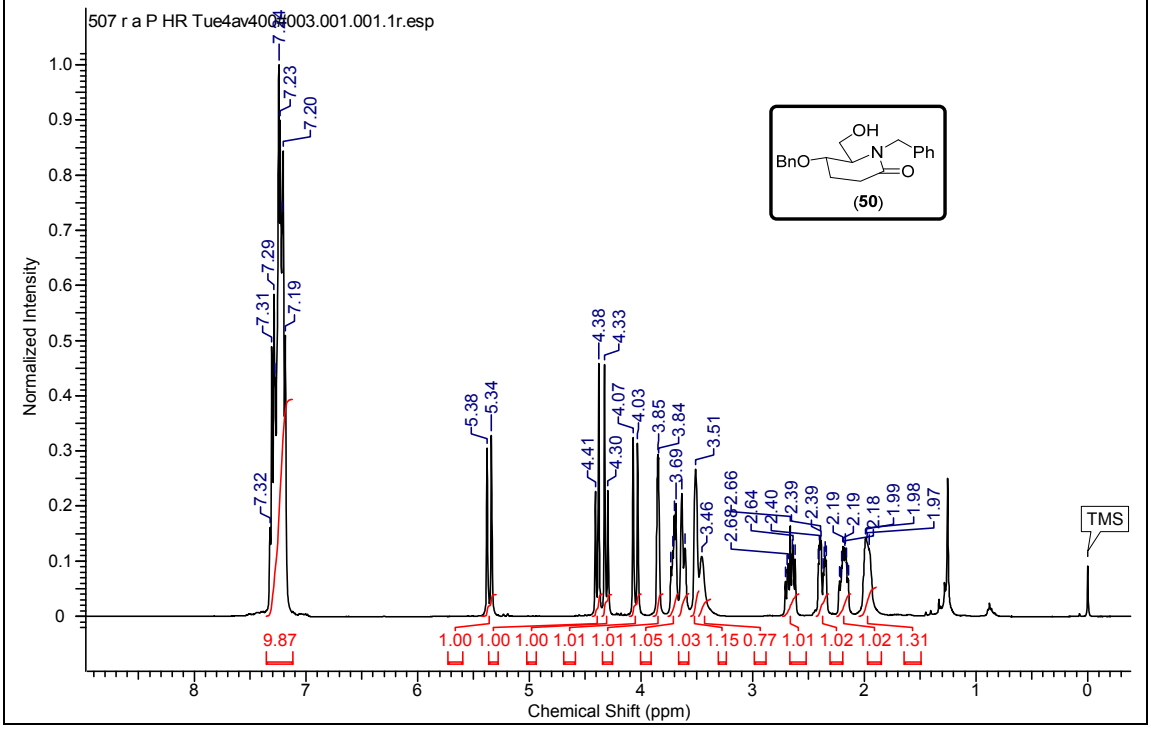
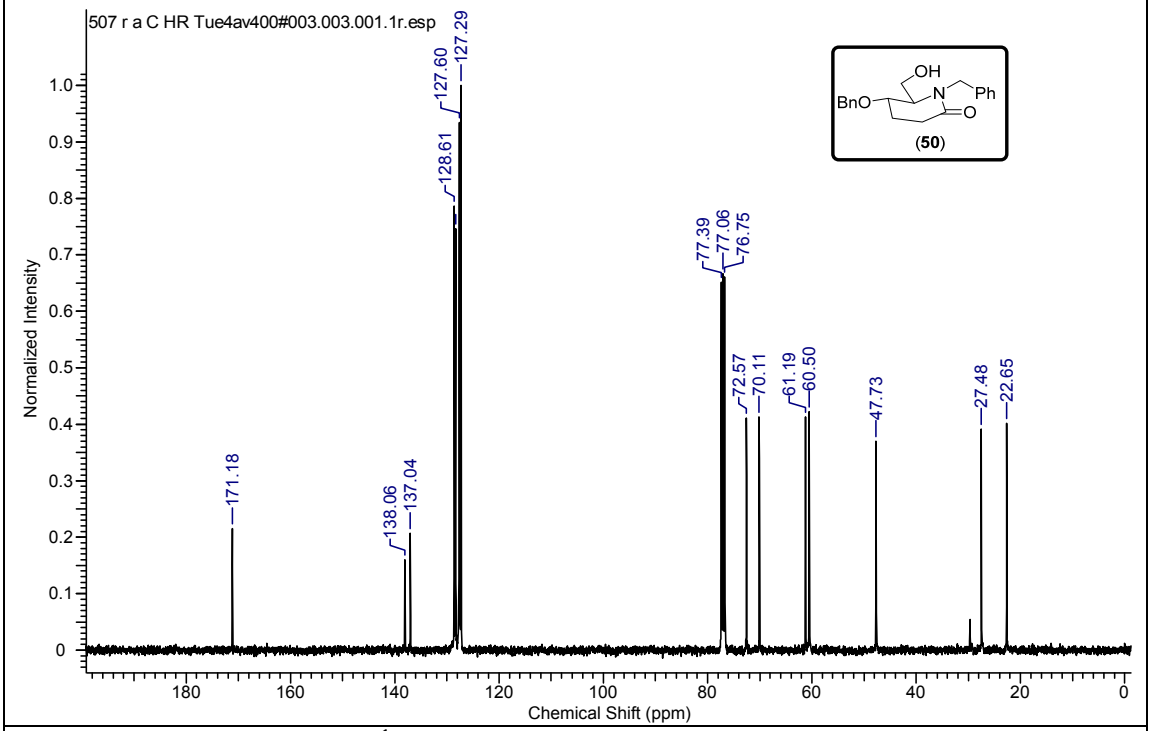
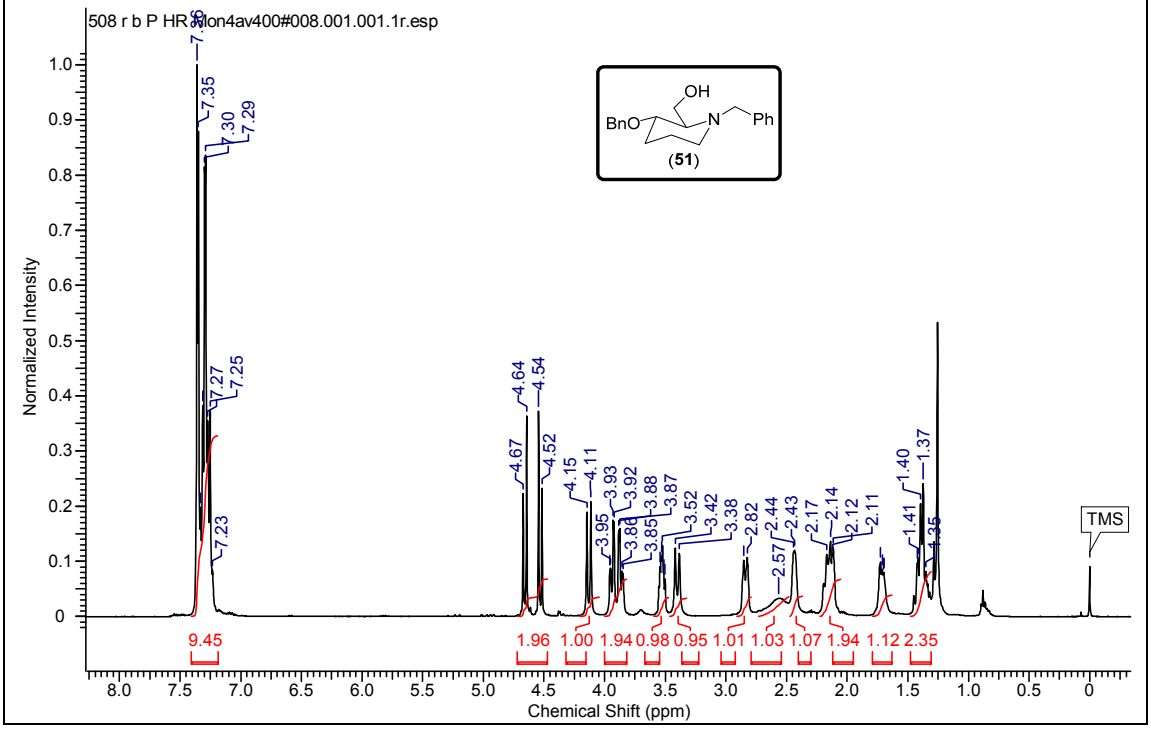


^{13}C NMR (100 MHz, $CDCl_3$) of (**50**)



^{1}H NMR (400 MHz, $CDCl_3$) of (**51**)



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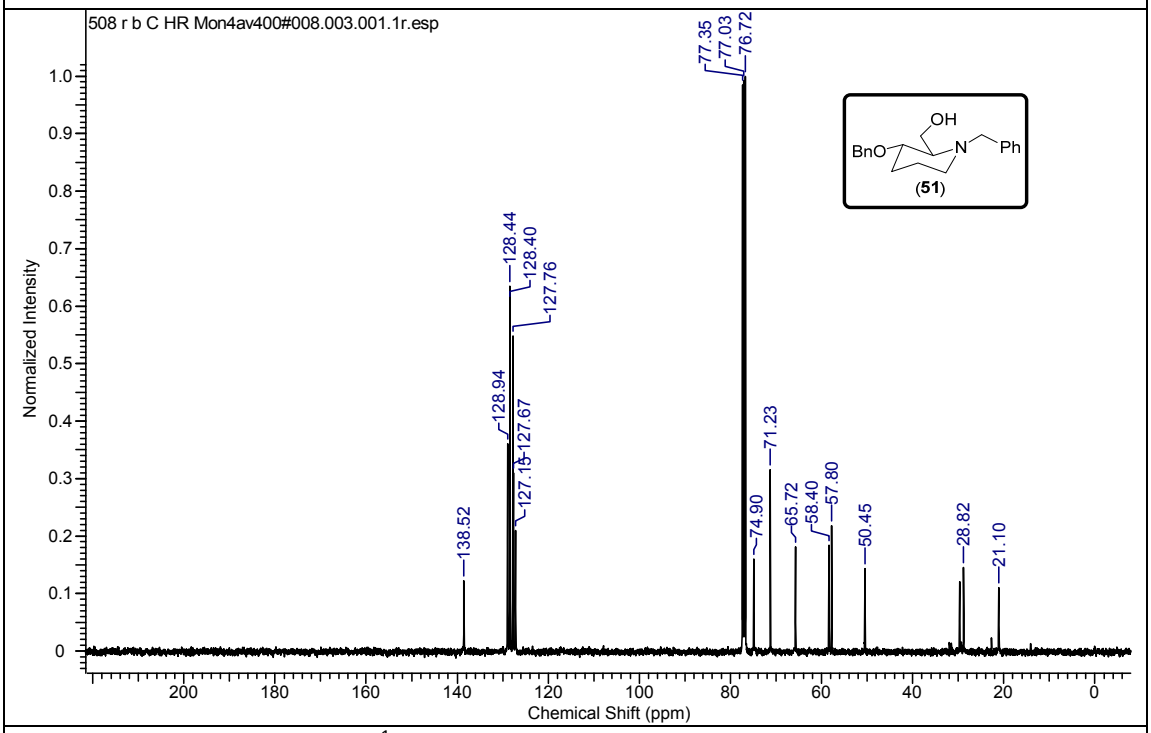
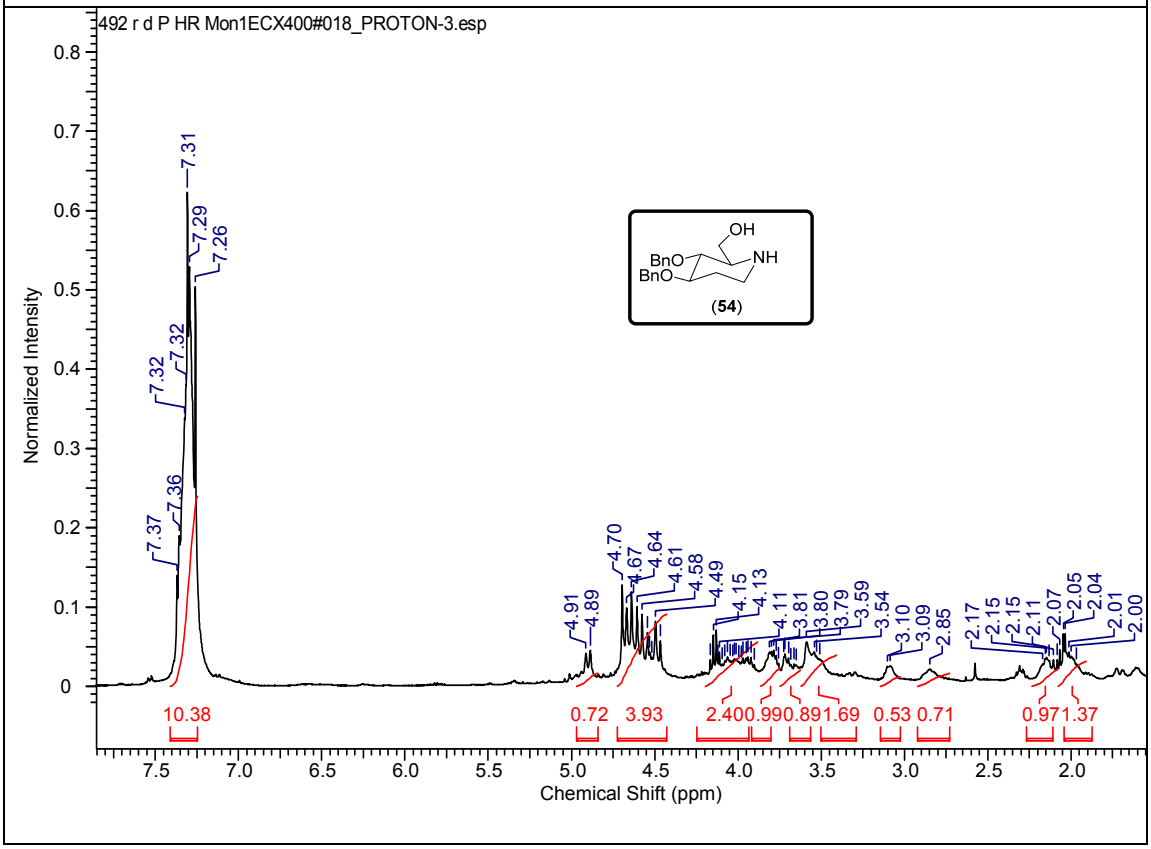
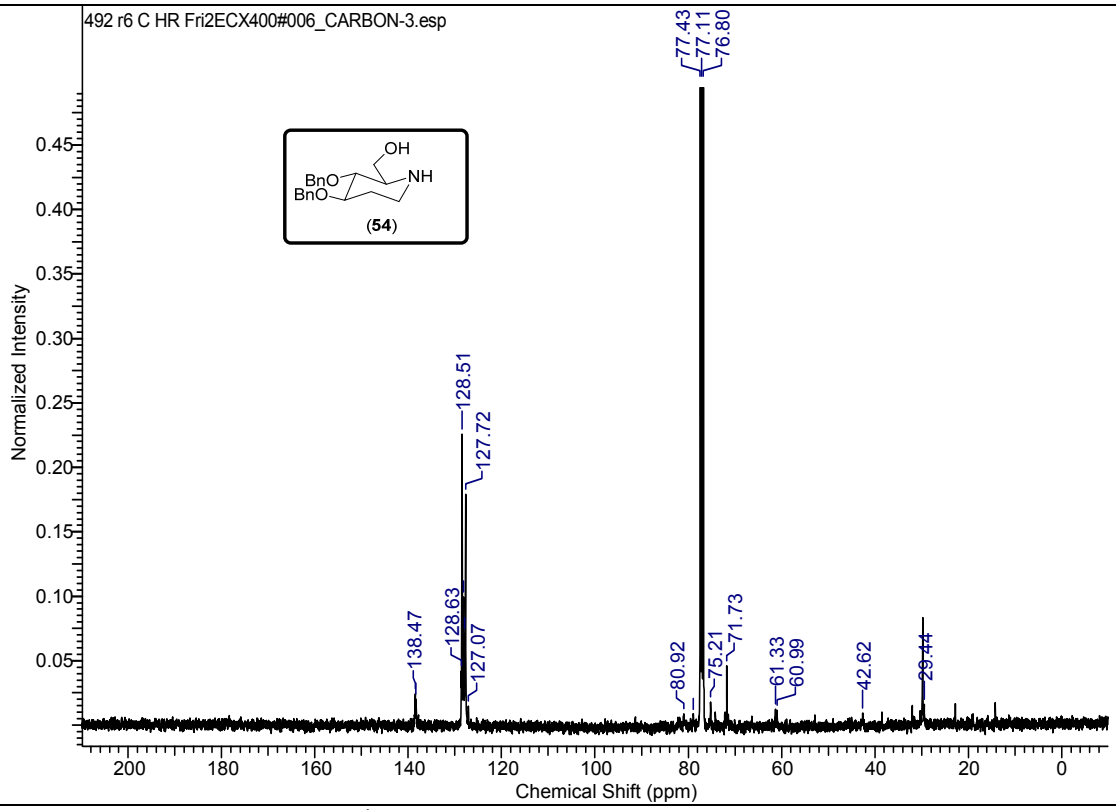


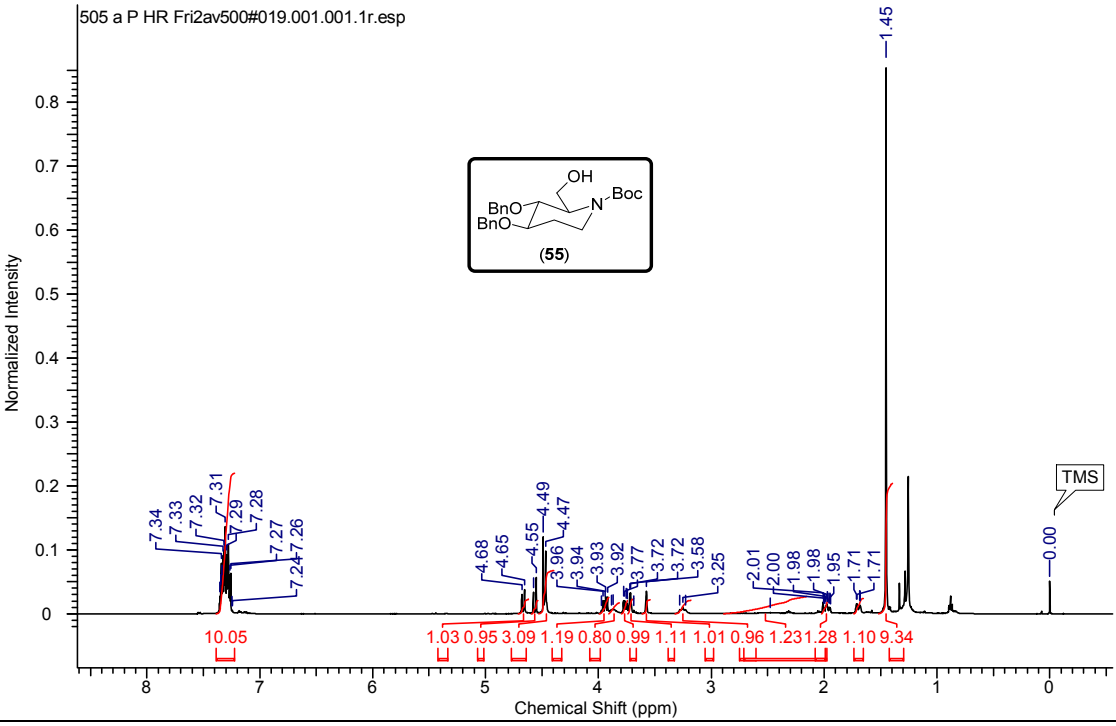
^{1}H NMR (400 MHz, $CDCl_3$) of (**54**)



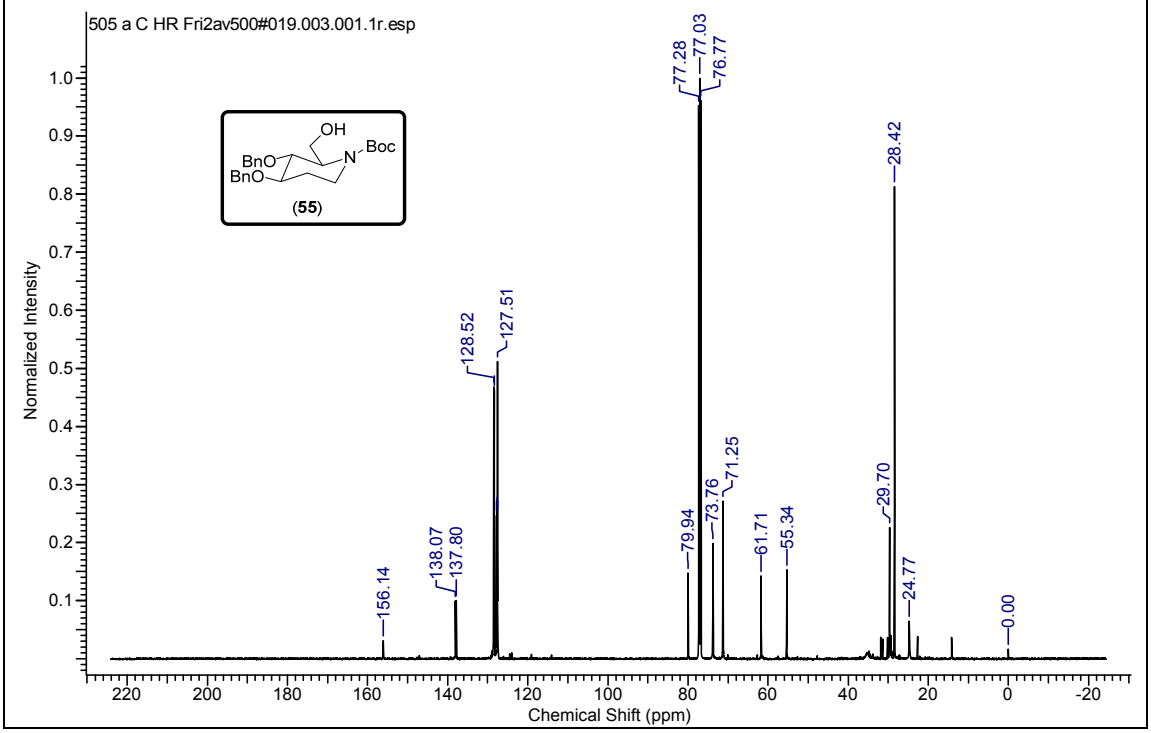
^{13}C NMR (100 MHz, $CDCl_3$) of (**54**)



^{1}H NMR (500 MHz, $CDCl_3$) of (**55**)



^{13}C NMR (125 MHz, $CDCl_3$) of (**55**)



Single crystal analysis and ORTEP Diagram :

Table 4. Crystal data and structure refinement for (**50**).

Identification code	HC507_R	
Empirical formula	$C_{20}H_{23}NO_3$	
Formula weight	325.39	
Temperature	100(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P 21	
Unit cell dimensions	a = 9.1116(5) Å	α= 90°.
	b = 7.9894(4) Å	β= 92.981(2)°.
	c = 11.4329(6) Å	γ = 90°.
Volume	831.15(8) Å^3	
Z	2	
Density (calculated)	1.300 Mg/m^3	
Absorption coefficient	0.087 mm^{-1}	

F(000)	348
Crystal size	0.360 x 0.220 x 0.180 mm^3
Theta range for data collection	1.784 to 32.711°.
Index ranges	-13<=h<=10, -9<=k<=11, -17<=l<=17
Reflections collected	10176
Independent reflections	4800 [R(int) = 0.0360]
Completeness to theta = 25.242°	99.9 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.985 and 0.969
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	4800 / 1 / 218
Goodness-of-fit on F^2	1.029
Final R indices [I>2sigma(I)]	R1 = 0.0463, wR2 = 0.0951
R indices (all data)	R1 = 0.0546, wR2 = 0.1001
Absolute structure parameter	-1.2(6)
Extinction coefficient	n/a
Largest diff. peak and hole	0.318 and -0.253 $e.Å^{-3}$

1.2.8 References

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Chapter 2

Approaches Towards the Synthesis of Tetrahydropyrans Using Carbohydrate Scaffolds

2.1 Utility of Carbohydrate Scaffolds for the Synthesis of Bioactive Natural Products; Tetrahydropyrans

2.1.2 Approaches Towards the Synthesis of Kamusol and DAH

2.1.1.1 An Introduction to Bioactive Polyhydroxylated Tetrahydropyrans

Polyhydroxylated tetrahydropyrans form an ubiquitous motif of several sugar acids.[1] Sugar acids comprises of monosaccharides bearing a carboxyl functional group.[2] Sugar acids have been categorized in four major classes and these are:

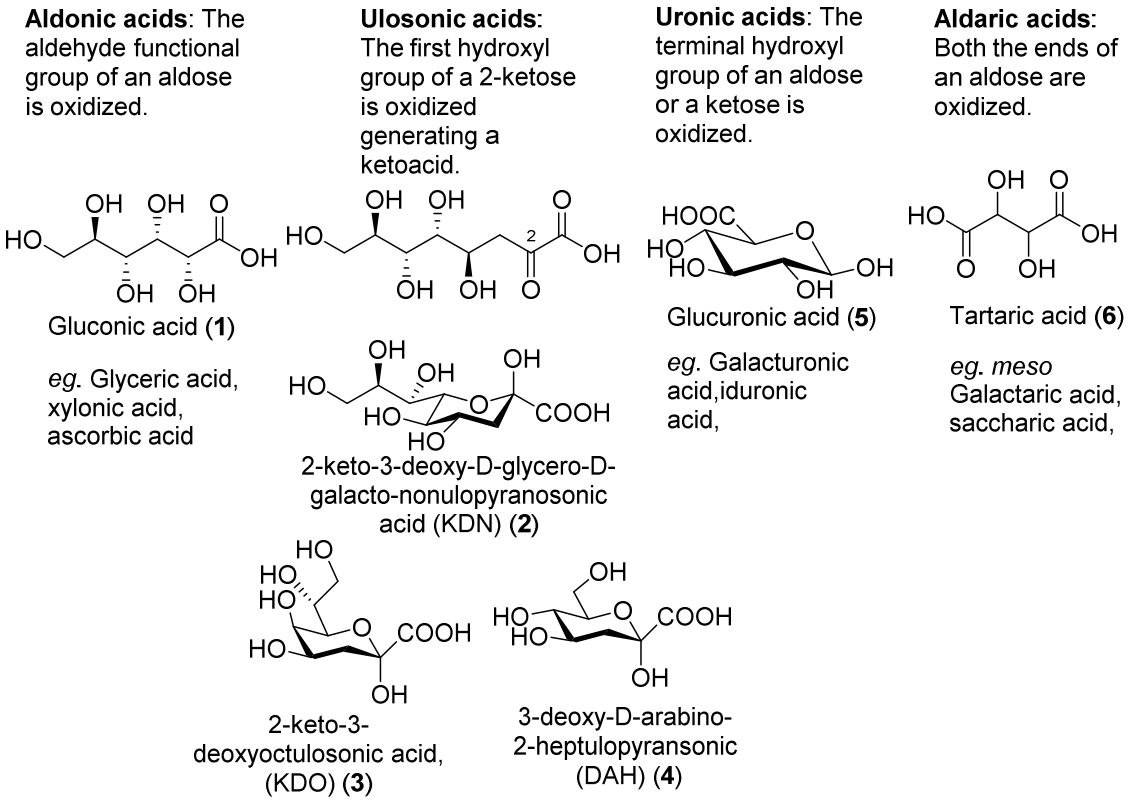


Figure 1. Some sugar acids classes and their representative examples.

Sugars belonging to **Aldonic acids** are being used in day to day life and has many applications in the food, detergent, cosmetics and pharmaceutical industries. To mention a

few, gluconic acid (**1**) is widely used in removing calcareous and rust deposits from metals or other surfaces.[3] It is also used for chelating metals, its derivatives have the ability to scavenge free radicals and are used in protecting skin from harmful UV radiation.[4]

Ulosonic acids possess important biological functions. The most common ulosonic acids are *N*-acetylneuraminic acid (**NANA**) well known as sialic acid, 2-keto-3-deoxy-*D*-glycero-*D*-galacto-nonulopyranosonic acid (**KDN**) (**2**) and 2-keto-3-deoxy-*D*-manno-octulosonic acid (**KDO**) (**3**). They form an essential part of many glycoconjugates, which are placed at the non-reducing ends of oligosaccharide chains. Glycoproteins containing NANA, are involved in cell interactions with other cells, microorganisms, toxins and antibodies.[5] The characteristic features that govern the role of ulosonic acids are (i) their size (ii) negative charge and (iii) their occurrence as the terminal residue on cell surface glycoconjugates. Widely used anti-influenza drugs (Oseltamivir and Zanamivir) are sialic acid analogs and are responsible for the inhibition of viral enzyme neuraminidase.[6] C-glycosides of ulosonic acids are of particular interest for their potential pharmaceutical applications. These are expected to have both improved enzymatic hydrolytic stability and an exoanomeric conformation similar to the corresponding *O*-glycosides.[7] KDO is an essential component of the outer membrane lipopolysaccharide (LPS) of gram-negative bacteria where it forms the link between the lipid A and polysaccharide components of the LPS. Incorporation of KDO is highly likely to be a vital step in the growth of gram-negative bacteria. KDO acts as inhibitor for the bacterial cell wall assembly process.[8-10]

Glucuronic acid, a sugar belonging to the **uronic acids** class plays a vital role in the detoxification of aromatic acids by binding with them when glycine is no longer available to perform the same function due to its consumption.[11]

Aldaric acids, are the diacids of sugars. These find their application as an important building blocks[12] for the synthesis of bioactive molecules and are also utilized in polymer, detergent and pharmaceutical industries.

2.1.1.2 An Introduction to DAH and Kamusol

Shikimic acid is utilized in the biosynthesis of a number of aromatic amino acids *viz.* phenylalanine, tyrosine, and tryptophan in plants and microorganisms.[13] 3-Deoxy-*D*-*arabino*-2-heptulosonate-7-phosphate (**DAHP**) (**7**) is the first metabolic intermediate in this pathway. DAHP is formed by the condensation of *D*-erythrose-4-phosphate and phosphoenolpyruvate in a reaction catalyzed by DAHP synthase.[14] Exquisite inhibiting activities of DAHP (**7**) analogues towards dehydroquinate synthase have inspired chemists to devise enzymatic and chemical syntheses of its precursor, **DAH** (**4**). DAH (**4**) also has utility as a potential herbicide.

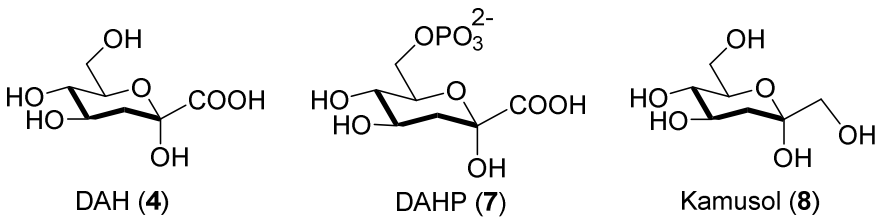


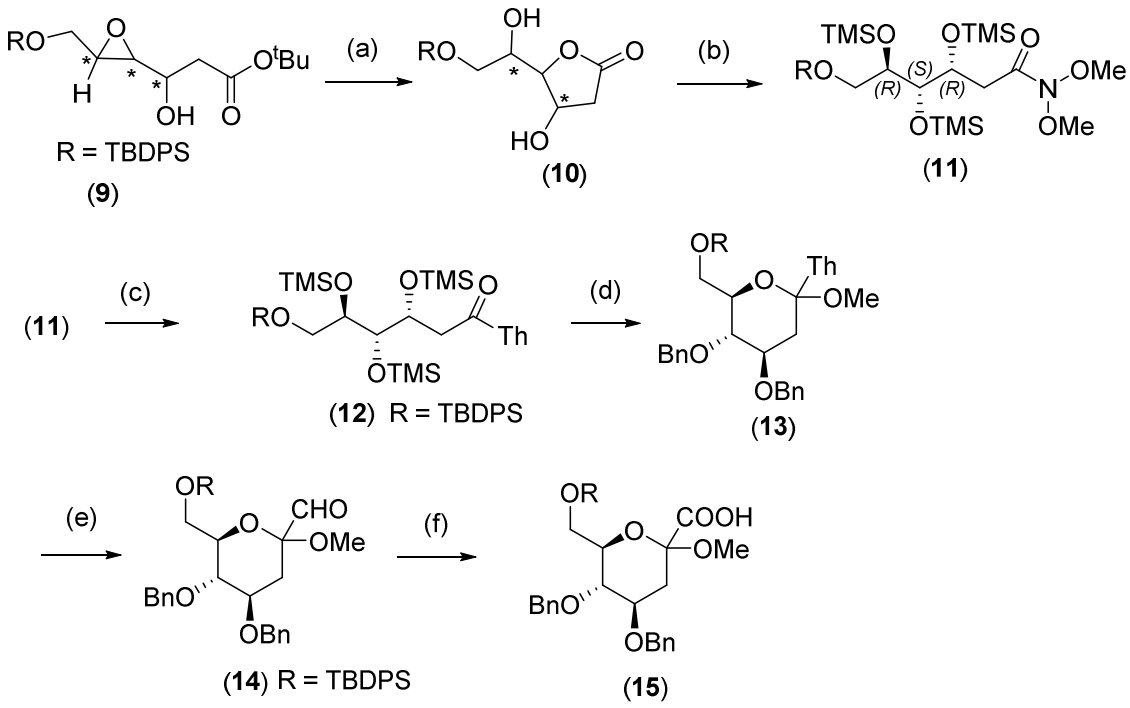
Figure 1. Representative structures of DAH (**4**), DAHP (**7**) and kamusol (**8**).

2.1.1.3 Reported Synthesis of DAH and Kamusol

Some of the reported synthesis of DAH (**4**) and kamusol (**8**) are described in short:

Gorrichon *et al.*[15a] (*J. Org. Chem.* **1995,** *60*, 7343).

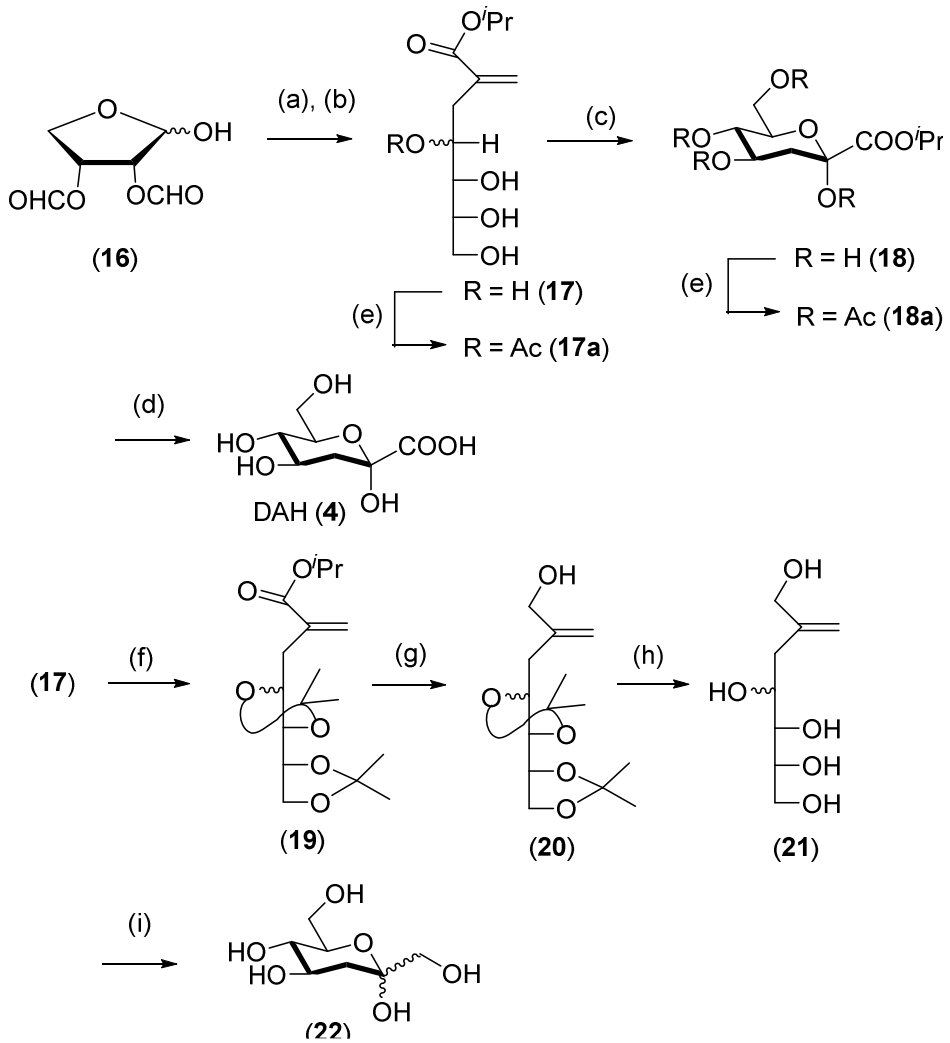
They have used non-carbohydrate precursor, chiral γ,δ-epoxy-β-hydroxyester and DAH (**4**) was synthesized in 6 steps in overall 19 % yield by following well known synthetic transformations (Scheme 1).



Scheme 1. *Reagents and conditions*. (a) Zn/TMSCl/CH_2Cl_2/rt, 96%; (b) MeNHOMe.HCl/$Al(Me)_3$/CH_2Cl_2/0 °C→rt, then Me_3SiCl/HMDS/pyridine, 79%; (c) thiazole/^nBuLi/Et_2O/-78 °C→rt, 87%; (d) PTSA/MeOH/ 50 °C, then BnBr/NaH/$^nBu_4NI$/THF/0 °C→rt, 70%; (e) MeOTf/molecular sieves, 4 Å/CH_3CN/rt, then $NaBH_4$/MeOH/0 °C, then CuO/$CuCl_2$/CH_3CN/H_2O/rt, 69%; (f) NaOH/$AgNO_3$/H_2O/ THF, 79%.

Schmid *et al.* [15b] (*Monatshefte für Chemie* **1996,** *127*, 1045).

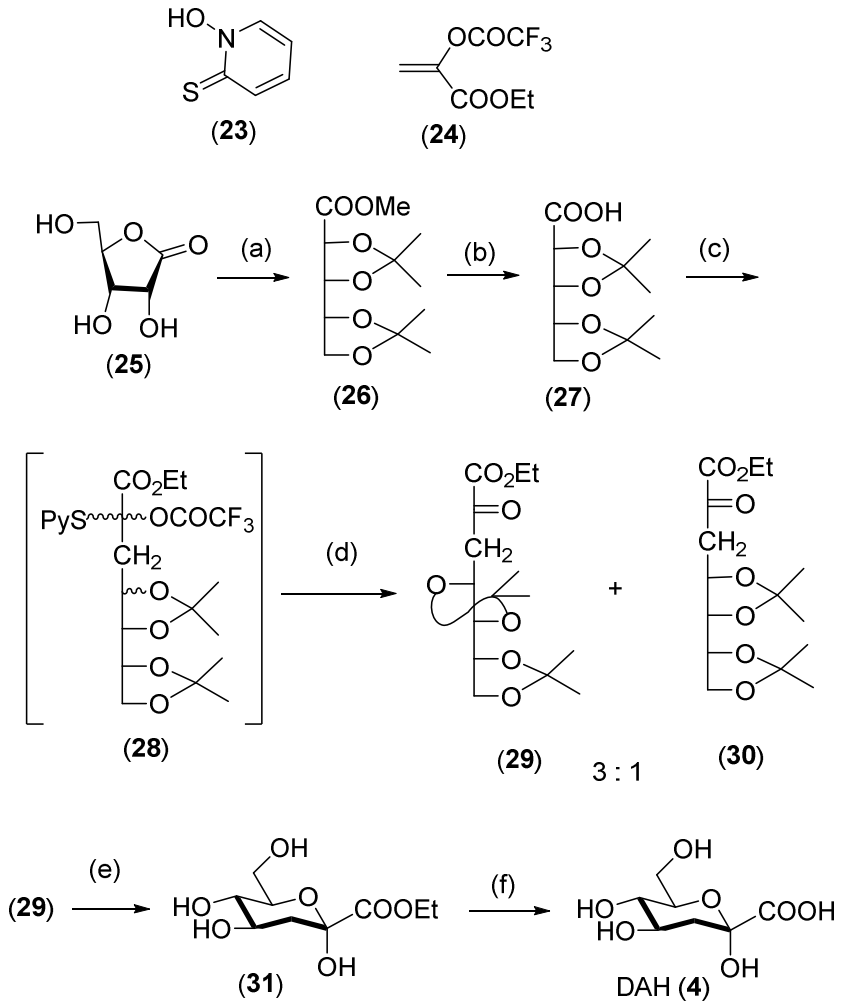
Schmid. *et al.* have synthesized both DAH (**4**) and kamusol (**8**) from 2,3-di-*O*-formyl-D-erythrose derivative and using indium mediated allylation as a key step (Scheme 2).



Scheme 2. *Reagents and conditions*. (a) Dowex 50W, H^+; (b) isopropyl-2-(bromomethyl)acrylate, indium metal, ultrasound; (c) O_3, -78 °C, Ph_3P; (d) NaOH, then H^+; (e) Ac_2O, pyridine, DMAP; (f) Acetone, $(CH_3)_2C(OCH_3)_2$, H^+; (g) DIBAH; (h) Dowex 50W, H+; (i) O_3, -78 °C, Ph_3P.

Barton *et al.*[15c] (*Tetrahedron Lett*. **1997**, *38*, 367).

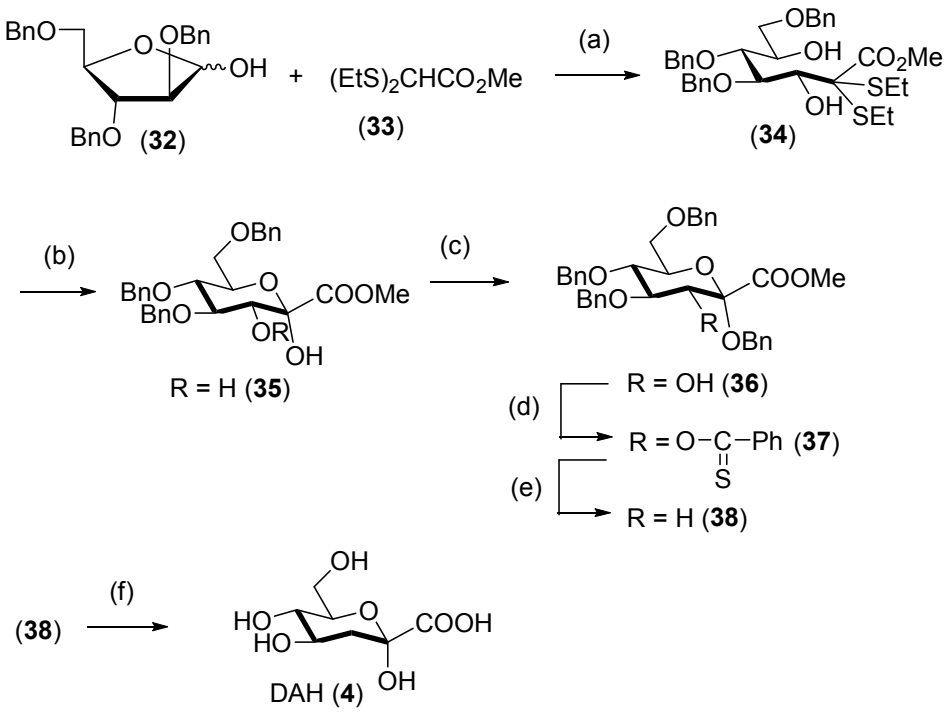
Acyl derivatives of *N*-hydroxy-2-thiopyridone (**23**) (Barton esters) had been employed as a source of radical, along with 2-(trifluoroacetoxy)acrylate (**24**) as a radical trap for the synthesis of α-keto acids (**23**). Starting material is *D*-ribonolactone and DAH (**4**) obtained in overall 46% yield (Scheme 3).



Scheme 3. *Reagents and conditions*. (a) $Me_2C(OMe)_2$, *p*-TsOH (cat.), rt, 48h, 85%; (b) NaOH (aq.), rt, 1.5h, 90%; (c) (i) (**23**)/DCC/CH_2Cl_2, 0 °C, 2h; (ii) (**24**), *hv*, 0 °C, 2.5h; (d) $NaHCO_3$ (aq.), rt, 3h, 60%; (e) Dowex-50W (H^+), H_2O/EtOH (2:1), rt, 100%; (f) Dowex-50W (H^+), D_2O, rt, quantitative.

Schmidt *et al.*[15d] (*Eur. J. Org. Chem.* **2002**, 57).

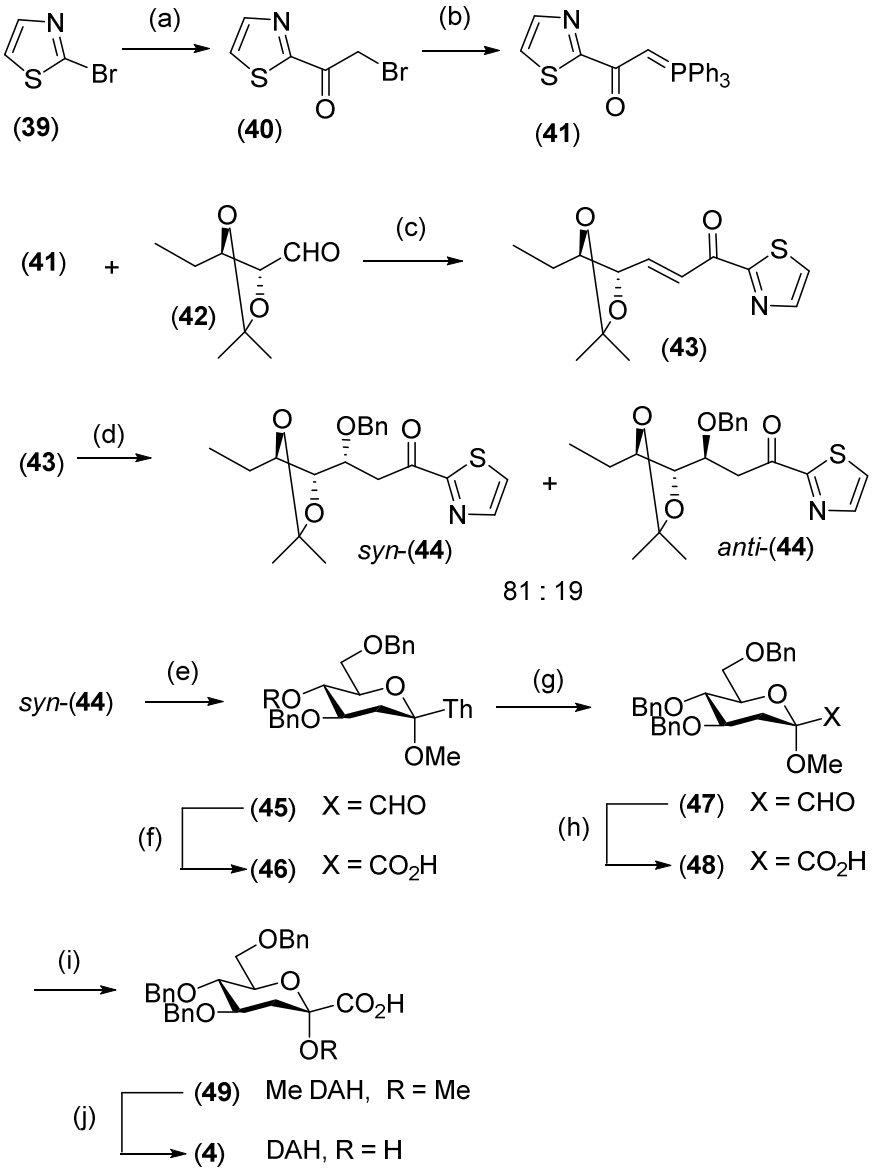
Two carbon chain elongation of 2,3,5-tri-*O*-benzyl-D-arabinose by means of diethylmercaptal of methyl glyoxylate was used as the key step by Schmidt and coworkers. Mercaptal cleavage followed by general synthetic transformation furnished DAH (**4**) in 27% overall yield (Scheme 4).



Scheme 4. *Reagents and conditions*. (a) (**33**), LDA, $MgBr_2$, THF, 79%; (b) NIS, acetone, 72%; (c) BnBr, NaH, DMF; MeOH, NaOMe, 78%; (d) $PhC(Cl)=NMe_2Cl$, pyridine, CH_2Cl_2, H_2S, 96%; (e) Bu_3SnH, AIBN, toluene; 64%; (f) Pd/C, H_2 (4 bar), 0.1 M NaOH, quant.

Dondoni *et al.*[15e] (*J. Am. Chem. Soc*. **1994**, *116*, 3324).

Dondoni and co-workers have utilized thiazole group, which is a formyl equivalent for the introduction of (2-thiazolylcarbonyl) methylene group, *i.e.* a masked pyruvate unit, in sugar-derived aldehydes. The strategy involved Wittig olefination with a thiazole-armed carbonyl ylide and conjugate addition of the benzyl oxide anion to the resultant *E*-α,β-enone (Scheme 5).



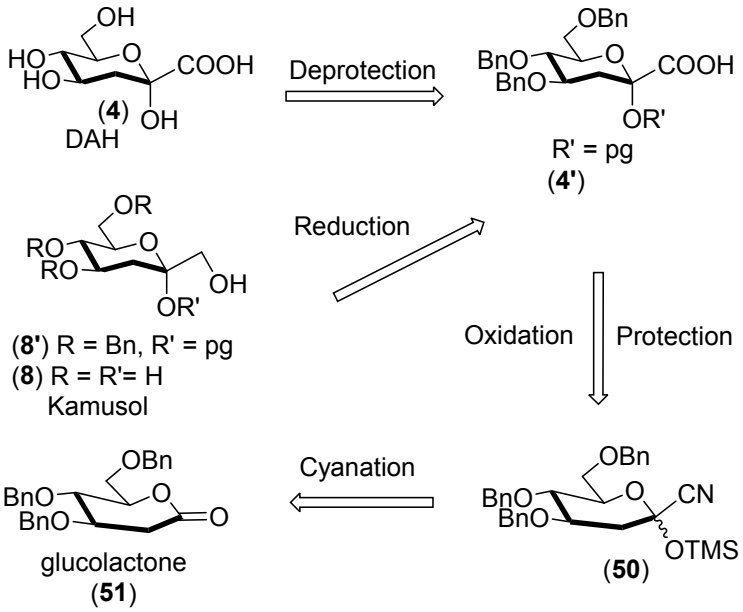
Scheme 5. *Reagents and conditions*. (a) (i) ^{n}BuLi, (ii) $BrCH_2CO_2Et$, 45%; (b) (i) PPh_3, 95%; (ii) NaOH, 100%; (c) $CHCl_3$, rt, 36h, 83%; (d) BnONa, 80%; (e) HCl/MeOH, 90%; (f) BnBr, NaH, 80%; (g) TfOMe, then $NaBH_4$, then $CuCl_2$-CuO-H_2O; (h) Ag_2O; (i) H_2-Pd/C; (j) AcOH-H_2O.

2.1.1.4 Present Work

Kamusol (**8**) (3-deoxy-*D*-arabino-2-heptulose) has been an interesting molecule for synthetic organic chemists and various approaches have been developed for its synthesis. Intrigued by unique structural features, we wished to develop a short and efficient synthesis of DAH (**4**) and kamusol (**8**) from cheap and readily available tri-*O*-benzyl glucal from cheap and readily available tri-*O*-benzylglucal using chiral pool strategy.

2.1.1.5 Results and Discussions

The proposed retrosynthetic route for the synthesis of DAH (**4**) and kamusol (**8**) is delineated in Scheme 6.



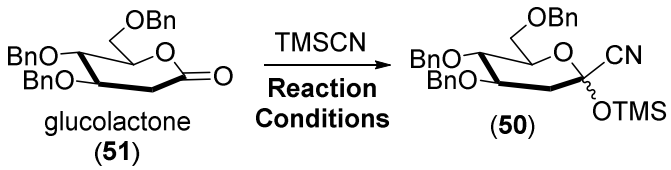
Scheme 6. *Retrosynthesis plan 1*; Cyanation strategy.

We opined that DAH (**4**) can be obtained by the global deprotection of protecting groups from (**4'**), which in turn can be obtained by oxidation of the cyano group and protection of the OH group with a suitable protecting group. Cyanation of the the synthesized

lactone (**51**) shall furnish the desired compound (**50**). Kamusol (**8**) can be readily obtained by the reduction of (**4'**).

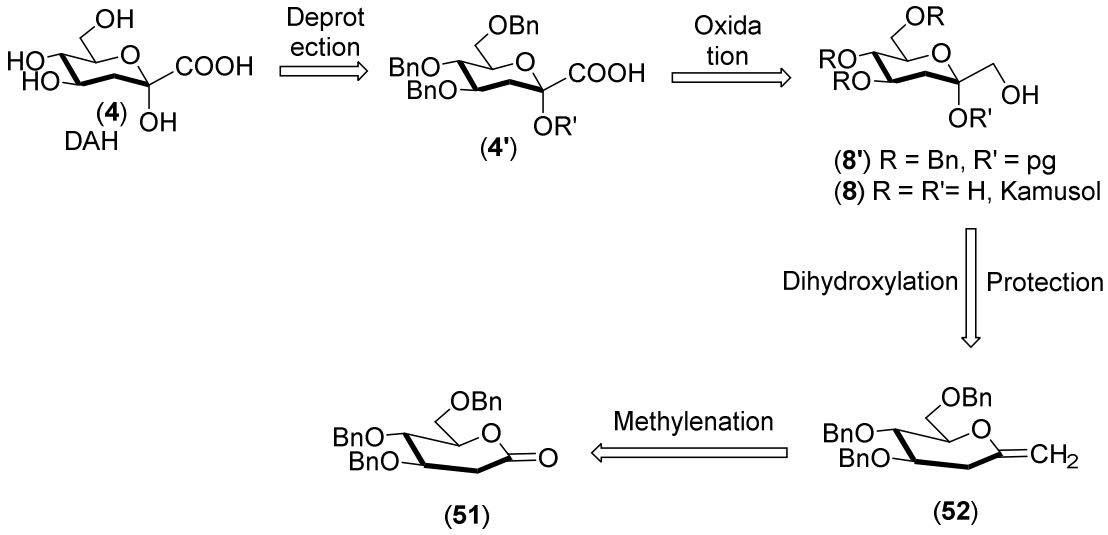
Cyanide is a good source of nucleophile and can be readily converted into carboxylic acid, hence we carried out the cyanation of lactone (**51**) with TMSCN utilizing various Lewis acids.[16a] When the reaction was carried out using $TiCl_4$ at -70 °C, starting material was recovered as it is (Entry 1, Table 1). On using $BF_3.OEt_2$ and following the similar reaction conditions as in the previous case also resulted in the complete recovery of the starting material (Entry 2, Table 1). Also on using triethyl aluminium in THF at -70 °C, starting material was recovered as it is as no reaction had taken place (Entry 3, Table 1). Ji *et al.*[16d] have demonstrated the use of alkali salt of L-proline to be an efficient and practical catalyst for the cyanosilylation of a wide variety of simple and functionalized carbonyl compounds. We wished to use L-proline in presence of *R,R*-salen Mn(II) chloride cat (15 mol %)[16c] for the diasterofacial addition of cyano group to lactone, but the reaction failed with complete recovery of the starting material (Entry 4, Table 1).[16b-d]

Table 1. Lewis acid catalyzed addition of TMSCN to glucolactone (**51**).



Entry	Reagents and condition	Solvent, Temperature	Remark
1	$TiCl_4$	DCM, -70 ˚C	Sm recovered
2	$BF_3.OEt_2$	DCM, -70 ˚C	Sm recovered
3	Et_3Al (0.6 M in Heptane)	THF, -70 ˚C	Sm recovered
4	*R,R*-Salen Mn(II) chloride cat (15 mol %), L-Proline (15 mol %)	Toluene, -70 ˚C	Sm recovered

Failure of cyanide attack on lactone to furnish the desired product again made us to modify the retrosynthetic plan for the synthesis of DAH (**4**) and kamusol (**8**) (**Modified retrosynthesis 2,** Scheme 7).



Scheme 7. *Retrosynthesis plan 2*; Methylenation strategy.

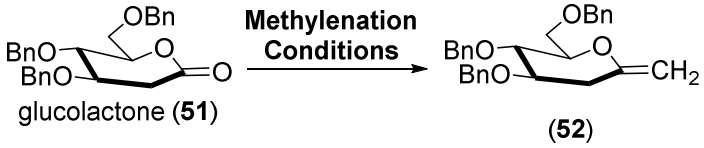
We thought DAH (**4**) can be obtained by the global deprotection of (**4'**), which in turn can be obtained by oxidation of the primary -OH group. Kamusol (**8**) can be synthesized form dihydroxylation of the methylenated compound (**52**), which in turn can be obtained by methylenation of the lactone (**51**).

Various reagents for methylenation of lactone (**51**) were explored to obtain (**52**) as shown in **Table 2**.

We first tried with Lombardo's regent[17a-c], which is a reagent generated in situ by reacting Zn/CH_2Br_2 $TiCl_4$ in DCM, but under this condition no reaction occurred (Entry 1, Table 2). Modified Lombardo's reagent,[17d] are also known for methylenation of esters and however by following the modified conditions (Entry 2, Table 2) did not furnish the desired product. Tebbe olefination with Tebbe reagent[18] is well known for methylenation of ester carbonyl group and we tried it under different reaction conditions. First reaction of (51) with Tebbe reagent (obtained from Sigma-Aldrich) (Entry 3-6 Table 2) could not

give the desired product. Methylenation activity is diminished if there is a time gap between the preparation of the reagent and its use,[18d] so we decided to use freshly prepared reagent rather than using commercial reagent. Tebbe reagent was prepared (Titanocene dichloride+Me_3Al) by known method[18b] and used immediately by following various reaction conditions (Entry 7-10 Table 2), but this also didn't furnish the desired product.

Table 2. Methylenation conditions for lactone (**51**)**.**



glucolactone (**51**) (**52**)

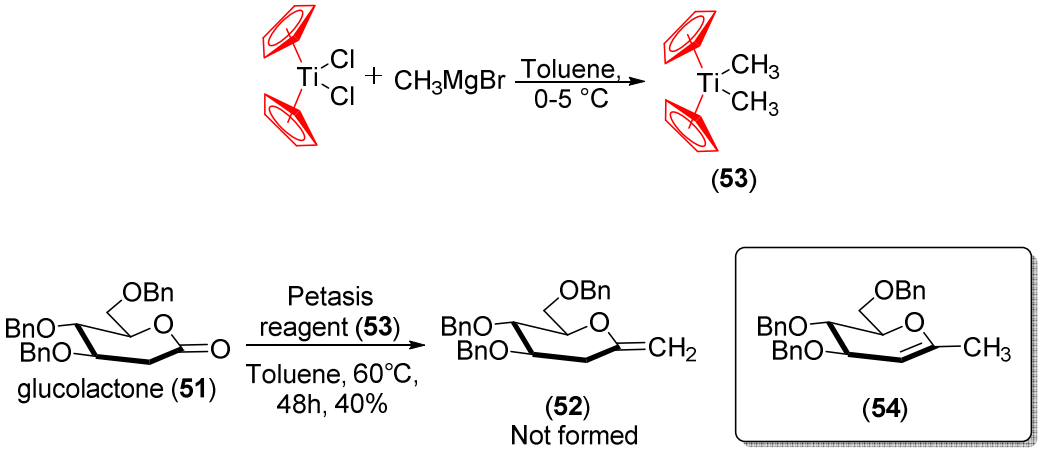
Entry	Reagents	Condition	Remark
1	Lombardo's Reagent	Zn/ CH_2Br_2 $TiCl_4$, DCM, 20 ^oC	Sm recovered
2	Modified Lombardo's	Zn/ CH_2Br_2 $TiCl_4$, $PbCl_2$,TMEDA, TH, 20 ^oC	Sm recovered
3	Tebbe (Commercial)	Tol : THF (1:4), -78 ^oC	Sm recovered
4	-do-	Tol : THF (1:4), -40 ^oC	Sm recovered
5	-do-	Tol : THF (1:4), -20 ^oC to rt	Sm recovered
6	-do-	Tol : THF (1:4), 0 ^oC to rt	Sm recovered
7	Tebbe (Freshly Prepared) Titanocene dichloride + Me_3Al	Tol : THF(1:4), -78 ^oC	Sm recovered
8	-do-	Tol : THF (1:4), -40 ^oC	Sm recovered

Cont…

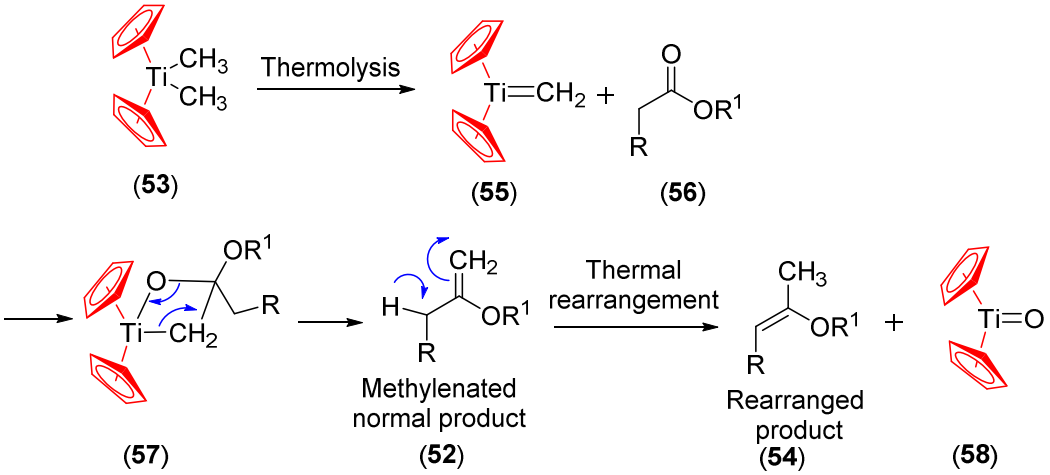
Entry	Reagents	Condition	Remark
9	-do-	Tol : THF (1:4), -20 ^{o}C to rt	Sm recovered
10	-do-	Tol : THF (1:4), 0 ^{o}C to rt	Sm recovered

We then turned our attention towards Petasis reagent which is known to readily methylenate carbonyl groups, which was synthesized from titanocene dichloride and MeMgBr by following the reagent preparation conditions (Scheme 8).[19]

The reaction product so obtained from the reaction of Petasis reagent with the glucolactone (**51**) was not the expected methylenic compound (**52**) as evident by its ^{1}H NMR and ^{13}C NMR spectra. Instead a rearrangement has taken place with the migration of double bond leading to the formation of compound (54)



Scheme 8. Methylenation using Petasis reagent.



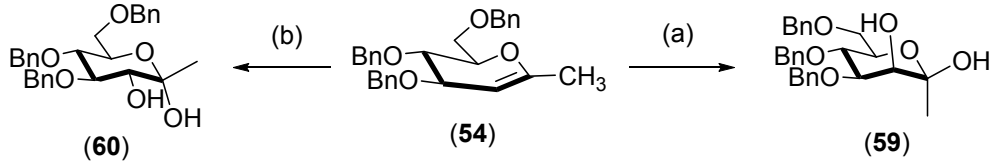
Scheme 9. Plausible mechanism of methylenation using Petasis reagent.

The plausible mechanism of the methylenation is delineated in Scheme 9. The mechanism is somewhat similar to the Tebbe olefination[18b,20] where rapid thermolysis of (**53**) occurs to form a carbene, which immediately reacts with the carbonyl group to form an oxetane (**57**). Decomposition of the oxetane (**57**) occurs to furnish the normal methylenated product (**52**). However, we observed a rearranged product (**54**) which is immediately formed due to reorganisation of the proton under thermal condition. During our approach for the synthesis of DAH (**4**) and kamusol (**8**) we came across one reference Thiem *et al*.[21] where in Petasis reagent is reported to give the desired methylenation product (**52**). However under identical conditions we could get only the rearranged product (**54**).

Compound (**54**) in IR showed band at 3015 cm^{-1} for the olefinic double bond. The ^{1}H NMR spectrum of compound (**54**) showed a peak at δ 1.81 (s, 3H) corresponding to the methyl group at C-1. The proton attached to the double bond at C-2 is embedded along with the signals of the benzyl CH_2 protons. The ^{13}C NMR spectrum of compound (**54**) showed δ 152.9, 95.6 and 19.8 ppm corresponding to the signals of the olefinic double bond carbons C-1, C-2 and CH_3, respectively. Also the HRMS spectrum furnished the desired mass peak at *m/z* 453.2036 $[C_{28}H_{30}O_4Na]$ $(M+Na)^+$.

We thought we could utilize compound (**54**) for the synthesis of some molecules having pyran moeity, which could later be screened for their biological activity.

In order to proceed further, we carried out dihydroxylation reaction of (**54**) using $(DHQD)_2AQN$ and $(DHQ)_2AQN$ in *t*-butyl alcohol and water (Scheme 10).



(**60**) (**54**) (**59**)

Scheme 10. Application of compound (**54**) for the synthesis of pyran analogues. *Reagents and conditions*. (a) $(DHQD)_2AQN$ (5 mol%), $K_3Fe(CN)_6$, K_2CO_3, $K_2OsO_2(OH)_4$ (5.59 mol%) $CH_3SO_2NH_2$, *t*-butyl alcohol : H_2O (1:1) 0 °C for 44 h, 93 %; (b) $(DHQ)_2AQN$ (5 mol%), $K_3Fe(CN)_6$, K_2CO_3, $K_2OsO_2(OH)_4$ (5.59 mol%) $CH_3SO_2NH_2$, *t*-butyl alcohol : H_2O (1:1) 0 °C for 44 h, 88 %.

Compound (**59**) in IR spectrum showed strong stretching band at 3447 cm^{-1} for two OH groups. The ^1H NMR spectrum of compound (**59**) exhibited broad singlet integrating for one proton at δ 2.84 and another broad singlet for one proton at δ 2.24 corresponding to the two OH protons which were confirmed by D_2O exchange study. A singlet for three protons at δ 1.50 was assigned for the CH_3 group. The ^{13}C NMR spectrum of compound (**59**) showed δ 97.2 and 26.2 ppm are the signals assigned for the anomeric carbon and CH_3 group, respectively. Also the HRMS spectrum showed desired peak at *m/z* 487.2091 $[C_{28}H_{32}O_6Na]$ $(M+Na)^+$.

Similarly using dihydroxylation reaction condition using $(DHQ)_2AQN$ furnished compound (**60**) which in IR spectrum showed strong stretching band at 3422 cm^{-1} for two OH groups. The ^1H NMR spectrum of compound (**60**) showed signals at δ 2.82 (brs, 1H), 2.24 (brs, 1H) and 1.50 (s, 3H) corresponding to the presence of two OH protons (confirmed by D_2O exchange) and CH_3 group, respectively. The ^{13}C NMR spectrum of compound (**60**) signals at δ 97.2 and 26.3 ppm were assigned for the anomeric carbon and CH_3 group, respectively. Also, the HRMS spectrum gave the desired peak at *m/z* 487.2091 $[C_{28}H_{32}O_6Na]$ $(M+Na)^+$.

One of the product obtained (**60**) after the dihydroxylation reaction of (**54**) was the core structure present in the tofogliflozin (**61**) which is a highly selective SGLT2 inhibitor[21-22]

used as an antidiabetic drug[23] and papulacandins A-E (**62**) are naturally occurring antifungal agents[24] (Fig. 2).

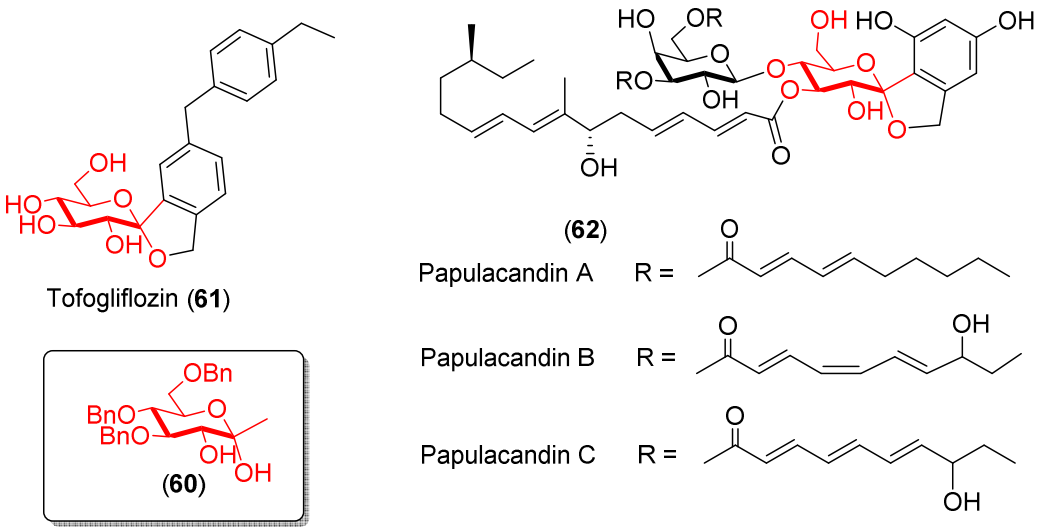
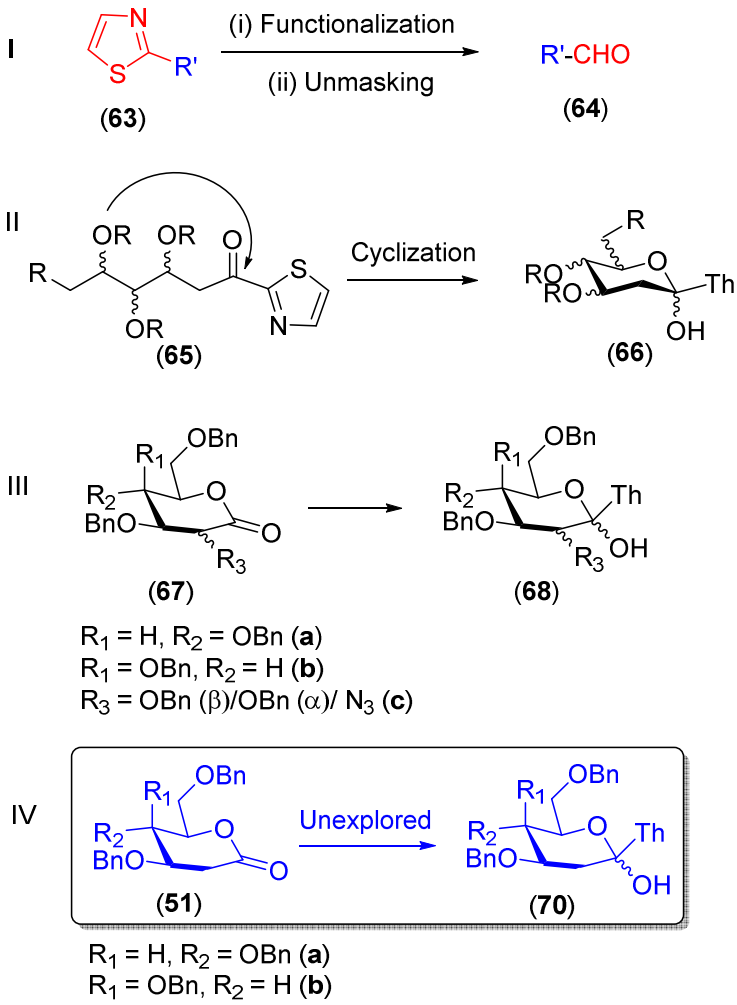


Figure 2. Representative structures of tofogliflozin (**61**) and papulacandins A-E (**62**) and their core structure (**60**).

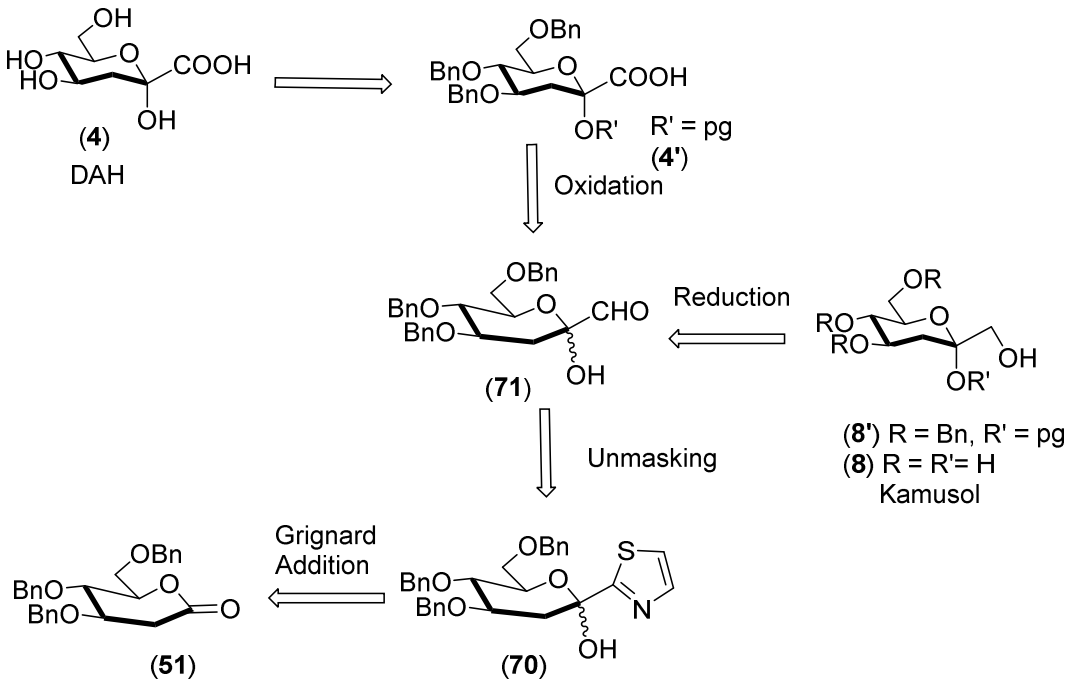
Since the methylenation strategy which we wished to use for the synthesis of DAH (**4**) and kamusol (**8**) turned out to be reported by Thiem *et al.*[25] (we had missed this reference due to our oversight), we didn't wish to proceed further using this approach.

Dondoni and co-workers[26a-c,e-j] have developed an excellent method to introduce the formyl group using the umpolung strategy with thiazole group[26a,b] (equation I, Scheme 11). Since 1990 thiazoles have been extensively used on a variety of substrates. On extensive literature search we found that thiazoles are used before the ring cyclization (5/6 membered) step[15e] (equation II, Scheme 11) otherwise they are used at C-2 substitiuted lactones[26c] (equation III, Scheme 11) but they have not been used on deoxy sugar lactones (equation IV, Scheme 11).[26d-g]



Scheme 11. Thiazole strategy exploited till date and its potential

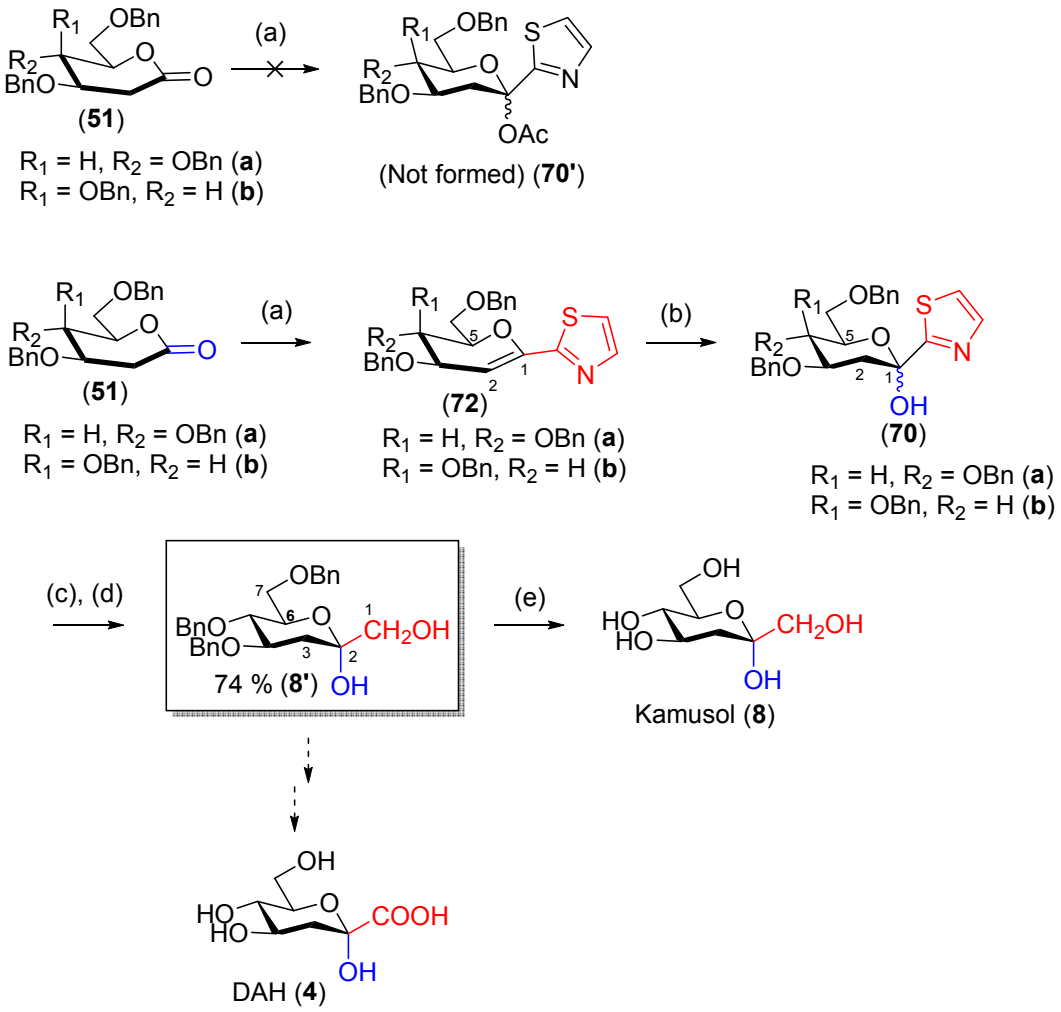
Extensive uses of thiazoles have been reported along with a number of sugar derived lactone substrates, but why they have not been utilized on 2-deoxy lactone substrates? Gave us an impetus to find out the reason. We were excited to use thiazoles on our 2-deoxy lactone substrates (**51a/b**) and hence we changed our retrosynthetic plan employing thiazole as delineated in Scheme 12.



Scheme 12. Retrosynthesis plan 2 (Masked carbonyl approach).

The desired carboxylic acid group in DAH (**4**) can be obtained by oxidation of aldehyde, (**71**) and also kamusol (**8**) can be obtained by the reduction of aldehyde (**71**) to furnish kamusol (**8**). The aldehyde (**71**) which serves as a common precursor for both DAH (**4**) and kamusol (**8**) can be obtained from 2-bromo thiazole and ^{n}BuLi which generates aryl lithium, which in turn attacks the lactone (**51**) to give addition product (**71**) (Scheme 12).

The reaction of lactone (**51a/b**) with 2-lithio-thiazole generated in situ by means of 2-bromo thiazole and ^{n}BuLi proceeded with complete consumption of starting material, however instead of the desired product *i.e.* acetate derivative (**70'**), product (**72a/b**) was obtained due to elimination of the acetate group (Scheme 13). The ^{1}H NMR spectrum of compound (**70a**) exhibited a doublet at δ 6.13 (J = 3.2 Hz) integrating for one proton corresponding to C-2 olefinic proton. The ^{13}C NMR spectrum of compound (**70a**) showed signals at δ 147.1 and 98.2 corresponding to the C-1 and C-2 olefinic carbons.The HRMS spectrum gave the desired mass peak which was observed at *m/z* 500.1890 [$C_{30}H_{30}NO_4S$] $(M+H)^+$. In the similar way, compound (**72b**) was obtained from lactone (**51b**) in 42% yield, which was also characterized by its spectral data.

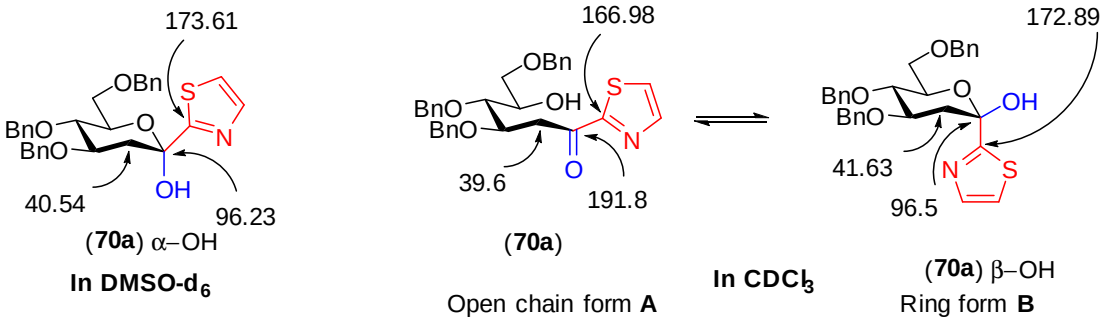


Scheme 13. Synthesis DAH (**4**) and kamusol (**8**); *Reagents and conditions*. (a) 2-Bromo thiazole, ^{n}BuLi, Ac_2O, -78 °C to rt, THF, 50%; (b) THF, H_2O, c.HCl.(cat), 64%; (c) (i) Methyltriflate $NaBH_4$, 0 °C, $HgCl_2$, CH_3CN:H_2O (10:1), (ii) $NaBH_4$ MeOH, 42% yield in 2 steps; (d) $NaBH_4$, $CeCl_3$, MeOH; (e) Ref 25.

Compound (**72a/b**) was then subjected to acid catalyzed hydration reaction to furnish the product (**70a/b**). IR spectrum of (**70a**) showed strong band at 3408 cm^{-1} indicated the presence of OH group. The ^{1}H NMR spectrum of compound (**70a**) in DMSO-d_6 showed a doublet of a doublet at δ 2.73 with J = 4.4, 12.7 Hz, for one proton and a triplet at δ 1.76 with J = 12.0 Hz for one proton which were assigned to the two protons present at C-2. The ^{13}C NMR spectrum of compound (**70a**) in DMSO-d_6 showed signals at δ 173.6, 96.2, 40.6 which were assigned to the quaternary thazolyl C-2', C-1 and C-2, respectively. The

HRMS spectrum showed the desired mass peak at *m/z* 540.1815 $[C_{30}H_{31}O_5NSNa]$ $(M+Na)^+$.

It is pertinent to mention here that when the ^1H NMR spectrum of compound (**70a**) was recorded in $CDCl_3$, almost two sets of signals were observed which were not distinguishable. However, the ^{13}C NMR spectrum in $CDCl_3$ was more prominent suggested that (**70a**) was existing in two forms **A** (open chain form) and **B** (ring form) in the solvent $CDCl_3$. The two sets of signals of ^{13}C NMR could be assigned as delineated in Scheme 14. However compound (**70a**) was crystalline solid (recrystallized from EtOAc-petroleum having melting point 102-104 °C) and therefore we could perform its single crystal X-ray analysis. The X-ray structure is concomitant with the solution state structure (DMSO-d_6) Fig. 3.



Scheme 14. Stereochemical entity of compound (**70a**) with ^{13}C NMR assignment.

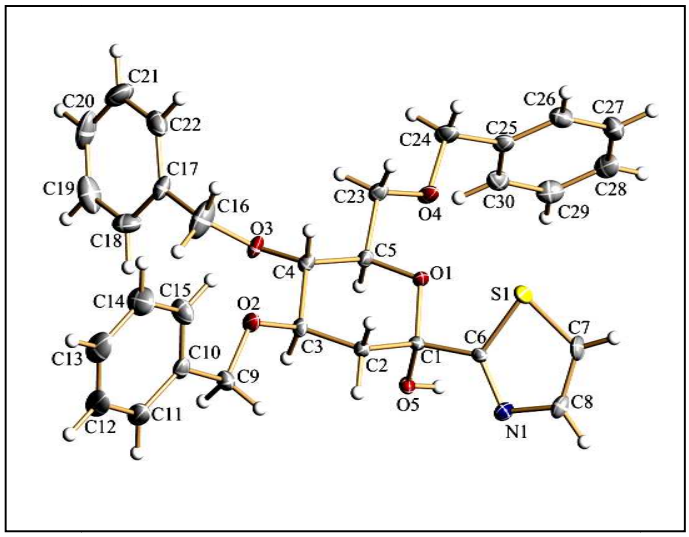
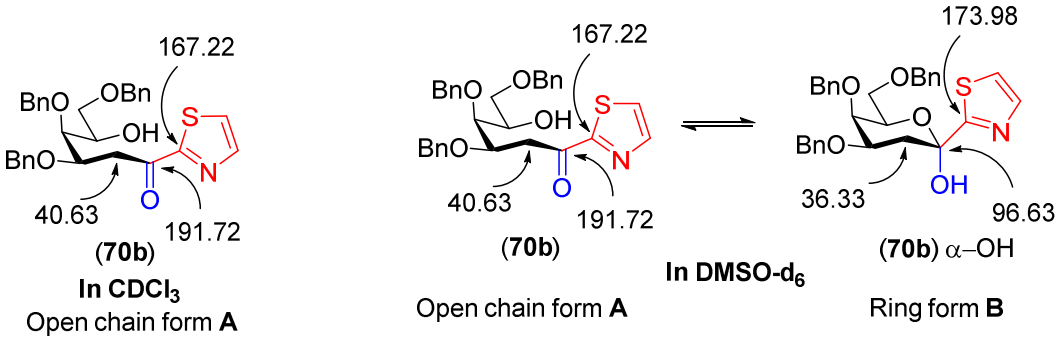


Figure 3. ORTEP diagram of compound (**70a**).

Similarly, compound (**72b**) on hydration furnished compound (**70b**) in 34% yield which was characterized by spectral data. It is interesting to note here that the compound (**70b**) was found to be in its keto form *i.e.* open chain form **A** when the NMR spectrum was recorded in $CDCl_3$ unlike compound (**70a**) which existed in **A** and **B** form. However, when the NMR spectrum was recorded in DMSO-d6 it revealed that compound (**70b**) existed in **A** and **B** form (Scheme 15).



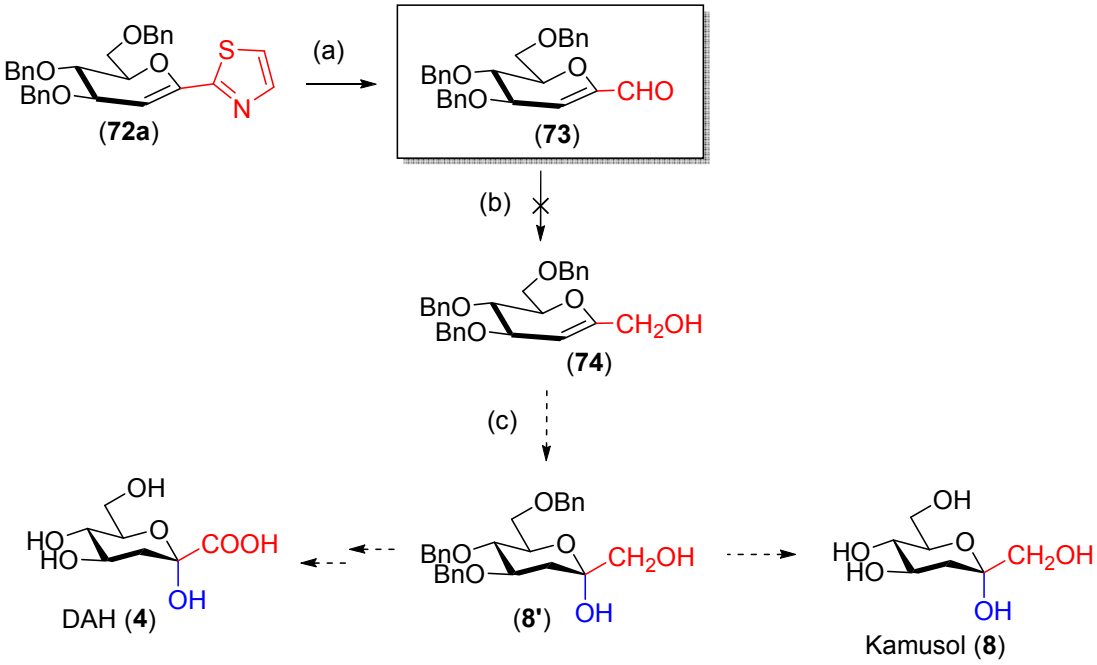
Scheme 15. Stereochemical entity of compound (**70b**) with ^{13}C NMR assignment.

Utilizing compound (**70b**), unmasking of the carbonyl group was carried out by using methyltriflate, $NaBH_4$ at 0 °C in presence of $HgCl_2$ in binary solvent system CH_3CN:H_2O (10:1) by following the reported procedure, and without isolating an aldehyde the crude was directly subjected to $NaBH_4$ reduction, which yielded benzyl protected kamusol (**8'**) in 42% in 2 steps.

Compound (**8'**) in IR spectrum showed strong band at 3383 cm^{-1} for two OH groups. The ^1H NMR spectrum of compound (**8'**) in DMSO-d_6 showed one proton at δ 5.63 with integration of 1 unit as a broad singlet which was assigned to the OH proton, The triplet at 3.29 ppm with a coupling constant of J = 6.6 Hz for 2 protons were assigned for the protons at C-1. A doublet of a doublet at δ 2.19 with coupling constants of J = 4.6, 12.5 Hz for one proton and a triplet at δ 1.44 with coupling constant of J = 11.7 Hz (for one proton) were assigned for the protons at C-3. The ^{13}C NMR spectrum of compound (**8'**) in DMSO-d_6 showed signals at δ 97.0, 67.6 and 35.9 which were for the signals corresponding to the C-2, C-1 and C-3 carbons, respectively. The HRMS spectrum of

compound (**8'**) showed mass peak at *m/z* 487.2091 [$C_{28}H_{32}O_6Na$] $(M+Na)^+$. By following the known methods[25] of benzyl deprotection, kamusol (**8**) can be readily synthesized.

We wished to use the masked carbonyl compound (**72**) for the synthesis of kamusol (**8**) by another method (Scheme 16). In order to achieve that we first unmasked the carbonyl group from compound (**72**) by following the reported procedure to furnish the α,β-unsaturated aldehyde (**73**). IR spectrum of compound (**73**) showed bands at 3017 and 1641 cm^{-1} indicated the presence of C=C bond and aldehyde carbonyl group, respectively. The ^1H NMR spectrum of compound (**73**) exhibited a singlet at δ 9.21 integrating for one proton and a doublet at δ 5.83 (J = 2.9 Hz, 1H) which were assigned to the aldehydic and olefinic protons at C-3, respectively. The ^{13}C NMR spectrum of compound (**73**) showed peaks at δ 186.2 and 151.6 were the signals for aldehyde carbonyl carbon and olefinic carbon at C-2. This also supported the formation of α,β-unsaturated aldehydes (**73**). The HRMS spectrum of compound (**73**) exhibited the mass peak at 467.1829 [$C_{28}H_{28}O_5Na$] $(M+Na)^+$.

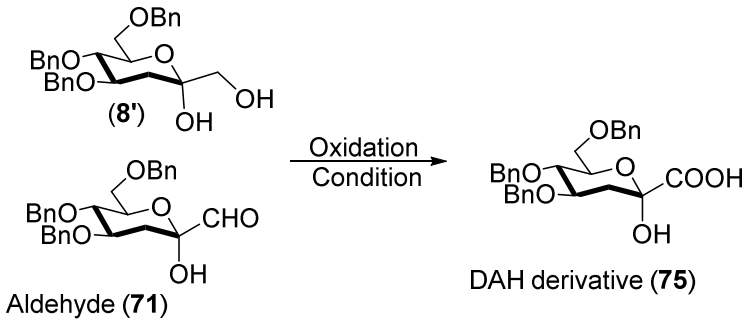


Scheme 16. Synthesis DAH (**4**) and kamusol (**8**); *Reagents and conditions*. (a) (i) Methyltriflate, $NaBH_4$, 0 °C, $HgCl_2$, CH_3CN:H_2O (10:1); (ii) $NaBH_4$ MeOH, 42% yield in 2 steps; (b) $NaBH_4$, $CeCl_3$, MeOH; (c) $Hg(OAc)_2$, $NaBH_4$, THF, H_2O.

We thought we could reduce the aldehyde to alcohol and then regioselctive acid catalyzed hydration can be carried out at the double bond by using mercuration-demercuration strategy. For that purpose, we tried to reduce the carbonyl group of aldehyde to alcohol (**74**) by using $NaBH_4$. However on reduction the desired product was not obtained and a complex reaction mixture was obtained which was not studied further.

We then turned our attention towards protected kamusol derivative (**8'**) and its precursor aldehyde (**71**) which can be utilized under oxidation condition to furnish the DAH (**4**) derivative (**75**). Various oxidizing agents were used under different reaction conditions as delineated in Table 3.

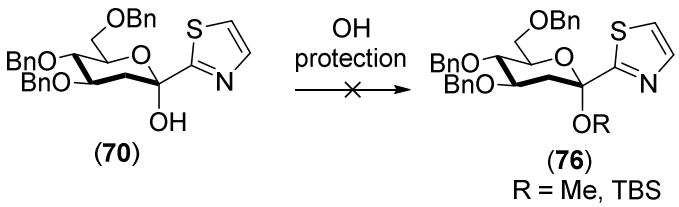
Table 3. Oxidizing agents for the synthesis of DAH (**4**).



Entry	Substrate	Reagents and Condition	Product
1	(**71**)	$NaClO_2$, *t*-BuOH, NaH_2PO_4, 2-methyl-2-butene	Sm recovered
2	(**71**)	PDC, DMF, 4 Å MS	Sm recovered
3	(**8'**)	TEMPO, $PhI(OAc)_2$, (ACN, H_2O)	Sm recovered
4	(**71**)	$AgNO_3$, H_2O_2	Sm recovered
5	(**8'**)	Jones Oxidation	Sm recovered
6	(**71**)	Jones Oxidation	Sm recovered

7	(**71**)	$KMnO_4$, Py : H_2O (1: 1)	rt	Sm recovered

All the attempts to oxidize either substrate (**8'**) or (**71**) with a number of oxidizing agents were unsuccessful (Table 3). So we thought oxidation can be carried out by protecting first the tertiary OH group at the earlier stage *viz.* before unmasking step on compound (**70**) (Scheme 17). We tried to protect the OH with TBS group using TBSCl in presence of NaH as a base in DMF,[27a] and then we tried to protect the OH with methyl group by using MeI, with NaH as a base in DMF,[27b] solvent and also by diazomethane generated in situ using $TMSCHN_2$ and HBF_4 (aq.) in DCM,[27c] solvent (Scheme 17), however no OH protection was observed and starting material was recovered back in each reactions.



Scheme 17. Protection of the alcohol of compound (**70**). *Reagents and conditions*: (i) TBSCl, NaH, DMF or (ii) MeI, NaH, DMF or (iii) $TMSCHN_2$, HBF_4 (aq.), DCM.

2.1.1.6 Conclusion

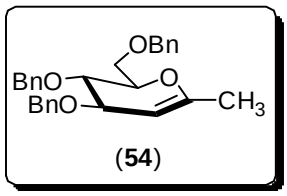
We have successfully synthesized kamusol derivative (**8'**) using chiral pool approach. We have also synthesized two pyrans (**59**) and (**60**) utilizing dihydroxylation reaction on C-1 methyl glucal substrate (**54**). We have achieved the synthesis of compound (**60**) which is a structurally important motif present in tofogliflozin (**61**) and papulacandins A-E (**62**). We have studied the existence and interconversion of various conformers of compound (**70a/b**) in different solvents and confirmed the structure of compound (**70a**) by single crystal X-ray analysis.

2.1.1.7 Experimental

Synthesis of reagents: Tebbe reagent and Petasis reagents were synthsiszed by following the reported procedures.[18,19]

Synthesis of compound (**54**).

Lactone (**51a**) (1.0 mmol) was dissolved in dry toluene (5 mL) and Petasis reagent was added (2.2 mmol). Reaction mixture was heated to 60 °C for 48 h. After completion, the solvent was removed in vacuo, and the residue was purified by flash chromatography. 26% yield; R_f 0.47 (EtOAc-petroleum ether, 3:17); Flash chromatography elution with EtOAc-petroleum ether, 1:19; $[\alpha]_D^{28}$ +43.60 (*c* 0.86, $CHCl_3$); IR ($CHCl_3$) 3015, 2927, 1723, 1216, 1078, 768 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ = 7.40 - 7.18 (m, 15H), 4.89 - 4.75 (m, 1H), 4.72 - 4.44 (m, 6H), 4.11 (dt, *J* = 4.3, 7.9 Hz, 2H), 3.96 - 3.71 (m, 3H), 1.81 (s, 3H); ^{13}C NMR (50MHz , $CDCl_3$) δ = 152.9, 138.6, 138.3, 128.4, 128.0, 127.9, 127.8, 127.6, 95.6, 76.8, 76.1, 74.1, 73.4, 70.3, 68.7, 19.8; ESI-MS: *m/z* 453.15 $(M+Na)^+$; HRMS: *m/z* calcd for $C_{28}H_{30}O_4Na$ 453.2036 $(M+Na)^+$, found 453.2036.

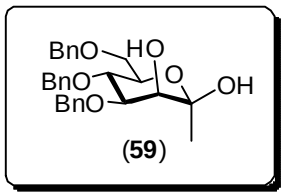


(**54**)

Representative procedure for synthesis of compounds (**59**) **and** (**60**).

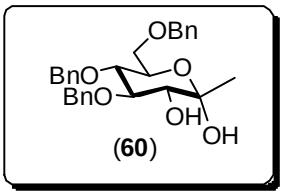
The general procedure followed for dihydroxylation was similar to that in **section 1.1.4**

Compound (**59**) 93% yield; 2d; R_f 0.35 (EtOAc-petroleum ether, 1:1); Flash chromatography elution with EtOAc-petroleum ether, 7:13; $[\alpha]_D^{28}$ +66.83 (*c* 0.98, $CHCl_3$); IR ($CHCl_3$) 3447, 3018, 1216, 1082, 770 cm^{-1}; ^1H NMR (400MHz, $CDCl_3$) δ = 7.51 - 7.26 (m, 12H), 7.24 - 6.98 (m, 3H), 4.96 - 4.74 (m, 3H), 4.67 - 4.43 (m, 3H), 3.99 (td, *J* = 3.3, 9.9 Hz, 1H), 3.81 - 3.61 (m, 3 H), 3.61 - 3.48 (m, 1H), 3.41 (d, *J* = 8.5 Hz, 1H), 2.84 (brs., 1H), 2.24 (brs., 1H), 1.50 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 138.7, 138.2, 138.1, 128.6, 128.4, 128.0, 127.9, 127.8, 127.7, 127.7, 97.2, 83.6, 78.2, 76.0, 75.3,



(**59**)

74.8, 73.4, 71.5, 69.0, 26.2; ESI-MS: *m/z* 487.10 $(M+Na)^+$; HRMS: *m/z* calcd for $C_{28}H_{32}O_6Na$ 487.2091 $(M+Na)^+$, found 487.2093.

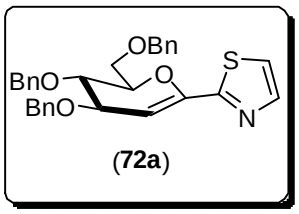


(**60**)

Compound (**60**) 88% yield; 2d; R_f 0.38 (EtOAc-petroleum ether, 1:1); Flash chromatography elution with EtOAc-petroleum ether, 7:13; $[\alpha]_D^{28}$ +55.91 (*c* 0.93, $CHCl_3$); IR ($CHCl_3$) 3422, 3015, 1216, 1084, 758 cm^{-1}; ^1H NMR (400MHz, $CDCl_3$) δ = 7.49 - 7.26 (m, 12H), 7.24 - 6.95 (m, 3H), 4.98 - 4.75 (m, 3H), 4.64 - 4.48 (m, 3H), 3.99 (d, *J* = 9.8 Hz, 1H), 3.83 - 3.62 (m, 3H), 3.62 - 3.51 (m, 1H), 3.41 (d, *J* = 9.2 Hz, 1H), 2.82 (brs., 1H), 2.24 (brs., 1H), 1.50 (s, 3H); ^{13}C NMR (100MHz, $CDCl_3$) δ = 138.7, 138.2, 138.1, 128.6, 128.4, 128.4, 128.0, 127.9, 127.8, 127.7, 127.7, 97.2, 83.6, 78.2, 76.0, 75.3, 74.8, 73.4, 71.5, 69.0, 26.2; ESI-MS: *m/z* 487.08 $(M+Na)^+$; HRMS: *m/z* calcd for $C_{28}H_{32}O_6Na$ 487.2091 $(M+Na)^+$, found 487.2092.

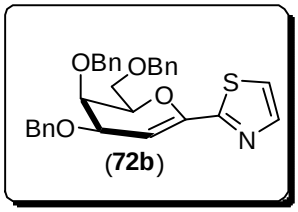
Synthesis of compound (**72a/b**)

To a stirred solution of 2-bromotiazole (1.1 mmol, 90 µl) in dry Et_2O (1 ml) under argon atmosphere at -78 °C was added dropwise ^{n}BuLi (1.6 M in hexane, 7.1 mmol, 0.67 ml) and stirred for 30 min at -78 °C. Lactone (**51a**) (0.7 mmol, 303 mg) in THF (5 ml) was added dropwise and stirred for 30 min. Temperature was then increased to -65 °C and stirring continued for 30 min. Ac_2O (2.5 eq.) was then added slowly and stirred for 30 min at -65 °C. Reactio mixture was then warmed to rt and reaction contents were diluted with DCM (10 ml) and poured into a phosphate buffer solution (0.1 M, 50 ml) of pH 7 and extracted with DCM (4 X 25 ml). The organic layer was dried and concentrated to furnish crude which was purified with flash chromatography to obtain (**72a**), 50% yield; R_f 0.46 (EtOAc-petroleum ether, 3:7); Flash chromatography elution with EtOAc-petroleum ether, 7:13; $[\alpha]_D^{28}$-14.3 (*c* 0.7, $CHCl_3$); IR ($CHCl_3$) 3407, 3066, 2924, 1726, 1687, 1216, 1097, 757 cm^{-1}; ^1H NMR (200MHz, $CDCl_3$) δ = 7.82 (d, *J* = 3.2 Hz, 1H), 7.49 - 7.23 (m, 16H), 6.13 (d, *J* = 3.2 Hz, 1H), 4.95 - 4.52 (m, 6H), 4.44 - 4.25 (m, 2H), 4.11 - 3.78 (m, 3H); ^{13}C NMR (50MHz, $CDCl_3$) δ = 163.2, 147.1, 143.5, 138.2, 138.1, 128.5, 128.0, 127.9, 127.8, 127.7, 119.8,



(**72a**)

98.2, 78.2, 75.5, 74.2, 73.8, 73.5, 70.6, 68.2.; ESI-MS: *m/z* 522.15 $(M+Na)^+$; HRMS: *m/z* calcd for $C_{30}H_{30}NO_4S$ 500.1890 $(M+H)^+$, found 500.1891.



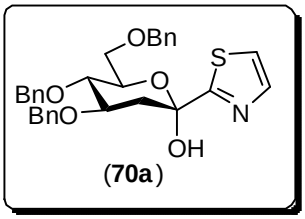
(**72b**)

Similarly following the similar reaction condition starting with (**51b**) product (**72b**) was obtained in 42% yield; R_f 0.46 (EtOAc-petroleum ether, 3:7); Flash chromatography elution with EtOAc-petroleum ether, 7:13; $[\alpha]_D^{28}$+9.4 (*c* 0.9, $CHCl_3$); IR ($CHCl_3$) 3407, 3066, 2924, 1726, 1687, 1216, 1097, 757 cm^{-1}; ^1H NMR (200MHz, $CDCl_3$) δ = 7.80 (d, *J* = 3.2 Hz, 1H), 7.39 - 7.25 (m, 15H), 6.10 (dd, *J* = 0.9, 3.2 Hz, 1H), 5.00 - 4.83 (m, 1H), 4.83 - 4.72 (m, 1H), 4.72 - 4.59 (m, 2H), 4.57 - 4.30 (m, 4H), 4.05 (t, *J* = 2.7 Hz, 1H), 3.96 - 3.74 (m, 2H); ^{13}C NMR (50MHz, $CDCl_3$) δ = 163.3, 146.6, 143.4, 138.3, 138.1, 128.4, 128.4, 128.2, 127.8, 127.7, 127.7, 127.6, 119.5, 98.5, 77.1, 73.5, 73.4, 71.2, 71.0, 68.1; ESI-MS: *m/z* 500.0 $(M+H)^+$; HRMS: *m/z* calcd for $C_{30}H_{30}NO_4S$ 500.1890 $(M+H)^+$, found 500.1892.

Synthesis of compound (**70a/b**)

Compound (**72a/b**) (600 mg, 1.2 mmol) was dissolved in THF (10 ml), H_2O (0.5 ml) and cooled in an ice bath. cHCl (0.1 ml) was then added slowly and stirring continued at 0 °C for 10 min and then at rt, with periodic tlc monitor. After complete consumption of the sm, 50 ml EtOAc was added and EtOAc layer was washed with sat $NaHCO_3$ (3 X 30 ml). Organic layers were dried evaporated and subjected to flash chromatography to furnish Compound (**70a/b**)

Compound (**70a**) crystalline solid mp 102-104 °C; 64% yield; R_f 0.20 (EtOAc-petroleum ether, 3:7); Flash chromatography elution with EtOAc-petroleum ether, 1:4; $[\alpha]_D^{30}$-1.5 (*c* 1.0, $CHCl_3$) ; IR ($CHCl_3$) 3408, 3012, 2924, 1604, 1270, 1097, 756 cm^{-1}; ESI-MS: *m/z* 540.0 $(M+Na)^+$;



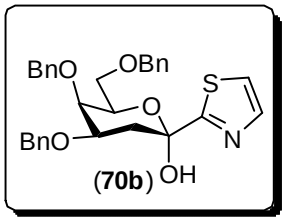
(**70a**)

^1H NMR (400MHz, DMSO-d_6) δ = 7.78 (d, *J* = 3.4 Hz, 1H), 7.69 (d, *J* = 2.9 Hz, 1 H), 7.41 - 7.23 (m, 15H), 4.85 (d, *J* = 11.2 Hz, 1H), 4.68 (d, *J* = 11.7 Hz, 1H), 4.64 - 4.43 (m, 5 H), 4.14 - 3.93 (m, 2H), 3.80 - 3.64 (m, 2H), 3.52 (t, *J* = 9.5 Hz, 1H), 2.73 (dd, *J* = 4.4, 12.7 Hz, 1H), 1.76 (t, *J* = 12.0 Hz, 1H); ^{13}C NMR (100MHz, DMSO-d_6) δ = 173.6, 142.7,

139.2, 139.0, 138.9, 128.7, 128.7, 128.2, 128.1, 128.1, 128.0, 127.9, 127.9, 127.8, 121.0, 96.2, 78.3, 77.7, 74.5, 72.7, 72.7, 70.7, 69.4, 40.6.

^{1}H NMR (400MHz, $CDCl_3$) δ = 7.96 (d, *J* = 2.9 Hz, 1H), 7.69 (d, *J* = 2.9 Hz, 1H), 7.62 (d, *J* = 2.9 Hz, 1H), 7.39 - 7.28 (m, 15H), 7.23 - 7.15 (m, 3H), 4.98 - 4.91 (m, 1H), 4.77 - 4.47 (m, 10H), 4.28 - 4.16 (m, 2H), 4.07 (dd, *J* = 3.4, 7.8 Hz, 1H), 3.84 - 3.71 (m, 3H), 3.71 - 3.58 (m, 3H), 3.55 - 3.43 (m, 1H), 2.77 (dd, *J* = 4.9, 12.7 Hz, 1H), 1.89 (t, *J* = 12.0 Hz, 1H); ^{13}C NMR (100MHz, $CDCl_3$) δ = 191.8, 172.9, 144.7, 141.9, 138.5, 138.4, 138.1, 137.8, 137.6, 128.4, 128.4, 128.3, 128.2, 128.0, 127.9, 127.8, 127.7, 127.6, 127.6, 127.5, 126.3, 120.4, 96.5, 78.4, 78.2, 77.9, 77.5, 77.4, 77.1, 76.7, 75.6, 75.5, 75.3, 75.0, 74.1, 73.7, 73.5, 73.4, 73.3, 73.2, 73.0, 71.7, 71.2, 70.9, 70.6, 69.3, 69.2, 41.6, 39.6;HRMS: *m/z* calcd for $C_{30}H_{31}O_5NSNa$ 540.1815 $(M+Na)^+$, found 540.1817.

Compound (**70b**) 34% yield; R_f 0.46 (EtOAc-petroleum ether, 1:1); Flash chromatography elution with EtOAc-petroleum ether, 3:17 to 1:4; $[\alpha]_D^{30}$-1.5 (*c* 1.0, $CHCl_3$) ; IR ($CHCl_3$) 3408, 3015, 2926, 1686,1216,1097,757 cm^{-1}; ESI-MS: *m/z* 540.0 $(M+Na)^+$; HRMS: *m/z* calcd for $C_{30}H_{31}O_5NSNa$ 540.1815 $(M+Na)^+$, found 540.1816.



(**70b**)

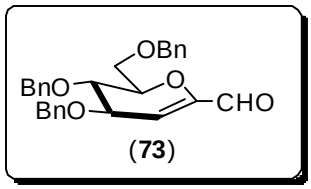
^{1}H NMR (200MHz, $CDCl_3$) δ = 7.94 (d, *J* = 3.0 Hz, 1H), 7.61 (d, *J* = 3.0 Hz, 1H), 7.36 - 7.17 (m, 15H), 4.87 - 4.72 (m, 1H), 4.71 - 4.40 (m, 6H), 4.09 - 3.91 (m, 1 H), 3.81 (dd, *J* = 3.1, 4.5 Hz, 1H), 3.71 - 3.43 (m, 4H), 2.93 (br. s., 1H); ^{13}C NMR (50MHz, $CDCl_3$) δ = 191.7, 167.2, 144.7, 137.9, 128.4, 128.4, 128.2, 128.1, 127.9, 127.7, 127.3, 126.3, 79.4, 76.4, 73.9, 73.4, 72.7, 71.1, 70.1, 40.7.

^{1}H NMR (400MHz, DMSO-d_6) δ = 8.18 (d, *J* = 2.4 Hz, 1 H), 8.12 (d, *J* = 2.4 Hz, 1 H), 7.96 (d, *J* = 7.9 Hz, 1 H), 7.74 (d, *J* = 3.1 Hz, 1 H), 7.65 (d, *J* = 3.1 Hz, 1 H), 7.56 - 7.40 (m, 1 H), 7.40 - 7.11 (m, 18 H), 7.00 (br. s., 1 H), 4.85 - 4.75 (m, 1 H), 4.71 - 4.65 (m, 1 H), 4.64 - 4.40 (m, 6 H), 4.32 - 4.13 (m, 1 H), 4.07 (d, *J* = 11.6 Hz, 1 H), 4.00 (br. s., 1 H), 3.88 (br. s., 1 H), 3.83 - 3.75 (m, 1 H), 3.75 - 3.47 (m, 4 H), 2.41 - 2.27 (m, 1 H), 2.27 - 2.09 (m, 1 H); ^{13}C NMR (100MHz, DMSO-d6) δ = 192.4, 174.0, 167.3, 145.5, 142.5, 139.5, 139.3, 139.1, 138.9, 138.8, 138.7, 133.3, 129.7, 129.0, 128.7, 128.7, 128.6, 128.5,

128.4, 128.3, 128.2, 128.1, 128.1, 128.0, 127.9, 127.8, 127.7, 120.8, 96.6, 80.4, 77.0, 75.2, 74.6, 74.2, 74.1, 73.4, 72.8, 72.3, 71.8, 71.8, 71.7, 69.9, 69.8, 69.6, 40.9, 36.3

Procedure for unmasking of the carbonyl group

Thiazole masked carbonyl compound (**70**/**72**) (500 mg, 0.21 mmol, 1 eq.) was dissolved in CH_3CN (4 ml) and 4 Å MS (0.5g) were added followed by methyltriflate (55 μL, 0.5 mmol, 2.3 eq.) and stirred vigorously for 15 min. All the contents were concentrated to dryness to obtain crude methyltiazolium salt which was dissolved in 4 ml MeOH and cooled to 0 °C and $NaBH_4$ (4.3 eq.) were added to it. Reaction mixture was then warmed to rt and stirred for 15 min. Acetone (4.5 ml) was used to quench excess $NaBH_4$. All the contents were filtered over the celite bed and concentrated. The reduced product was then dissolved in CH_3CN (4 ml) and $HgCl_2$ (80 mg) was added and then H_2O (0.23 ml), reaction mixture was then stirred for 15 min at rt. The crude product was again filtered through celite bed and concentrated, dissolved in DCM (20 ml) and the org layer was washed with 20 % aq. KI sol. (3 X 20 ml), the with brine, H_2O. Organic layer was dried, concentrated and purified with flash chromatography.

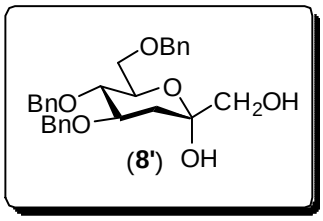


(**73**)

Compound (**73**) 83% yield; R_f 0.46 (EtOAc-petroleum ether, 3:7); Flash chromatography elution with EtOAc-petroleum ether, 3:17; $[\alpha]_D^{28}$ -13 (*c* 1.0, $CHCl_3$); IR ($CHCl_3$): υ_{max} 3017, 2924, 2864, 1702, 1641, 1216, 1097, 754, 495 cm^{-1}; ^1H NMR (200MHz, $CDCl_3$) δ_H = 9.21 (s, 1H), 7.51 - 7.09 (m, 15H), 5.83 (d, *J* = 2.9 Hz, 1H), 4.91 - 4.48 (m, 6H), 4.37 (dd, *J* = 2.8, 6.3 Hz, 1H), 4.25 - 4.13 (m, 1H), 4.10 - 3.96 (m, 1H), 3.86 (d, *J* = 3.5 Hz, 2H); ^{13}C NMR (50MHz, $CDCl_3$) δ_C = 186.2, 151.6, 137.9, 137.9, 137.7, 128.6, 128.5, 128.4, 128.0, 128.0, 127.9, 127.7, 117.1, 77.7, 75.7, 74.1, 73.6, 73.6, 71.6, 67.7; ESI-MS: *m/z* 467.17$(M+Na)^+$; HRMS: *m/z* calcd for $C_{28}H_{28}O_5Na$ 467.1829 $(M+Na)^+$, found 467.1829.

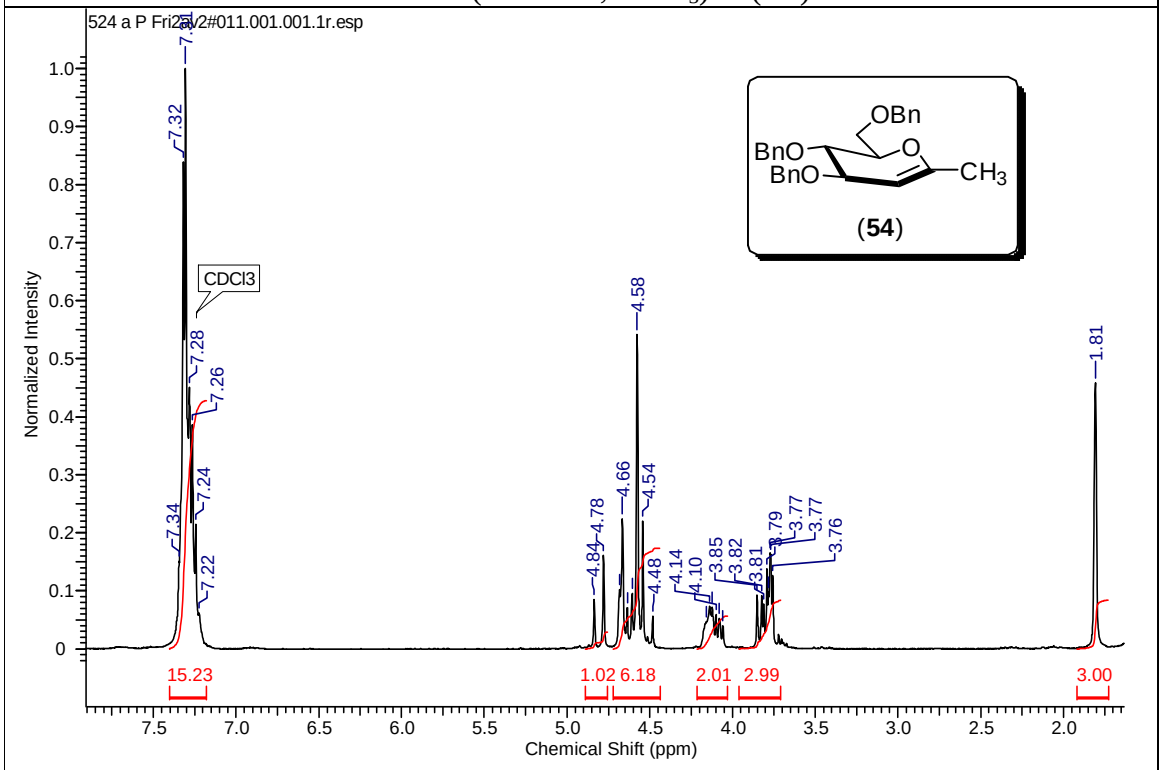
Synthesis of compound (**8'**)

To the crude (obtained after unmasking of the carbonyl group) in MeOH at 0 °C was added portionwise $NaBH_4$ (4 eq.) at regular intervals and with occasional tlc check. On complete consumption of the sm, solution was cooled and neutralised with 50% AcOh in MeOH till slightly acidic (pH = 6). All the contents were evaported to dryness and subjected to flash chromatography to furnish (**8'**) 74% yield; R_f 0.25 (EtOAc-petroleum ether, 1:1); Flash chromatography elution with EtOAc-petroleum ether, 7:13; $[\alpha]_D^{28}$ +41.5 (*c* 1, $CHCl_3$); IR ($CHCl_3$) 3383, 1216, 1074, 1025, 755 cm^{-1}; ^1H NMR (400MHz, DMSO-d_6) δ = 7.39 - 7.25 (m, 13 H), 7.20 (d, *J* = 6.4 Hz, 2 H), 5.63 (s, 1 H), 4.85 - 4.74 (m, 2 H), 4.71 - 4.59 (m, 1 H), 4.58 - 4.40 (m, 4 H), 3.93 - 3.85 (m, 1 H), 3.82 (dd, *J* = 2.9, 9.8 Hz, 1 H), 3.69 - 3.52 (m, 2 H), 3.29 (t, *J* = 6.6 Hz, 2 H), 2.19 (dd, *J* = 4.6, 12.5 Hz, 1 H), 1.44 (t, *J* = 11.7 Hz, 1 H); ^{13}C NMR (100 MHz ,DMSO-d_6) δ = 138.9, 138.7, 138.4, 128.2, 128.2, 128.2, 127.8, 127.6, 127.4, 127.4, 127.3, 97.0, 78.5, 77.6, 73.9, 72.3, 71.1, 70.1, 69.4, 67.6, 35.9; ESI-MS: *m/z* 487.22 $(M+Na)^+$ HRMS: *m/z* calcd for $C_{28}H_{32}O_6Na$ 487.2091 $(M+Na)^+$, found 487.2053.

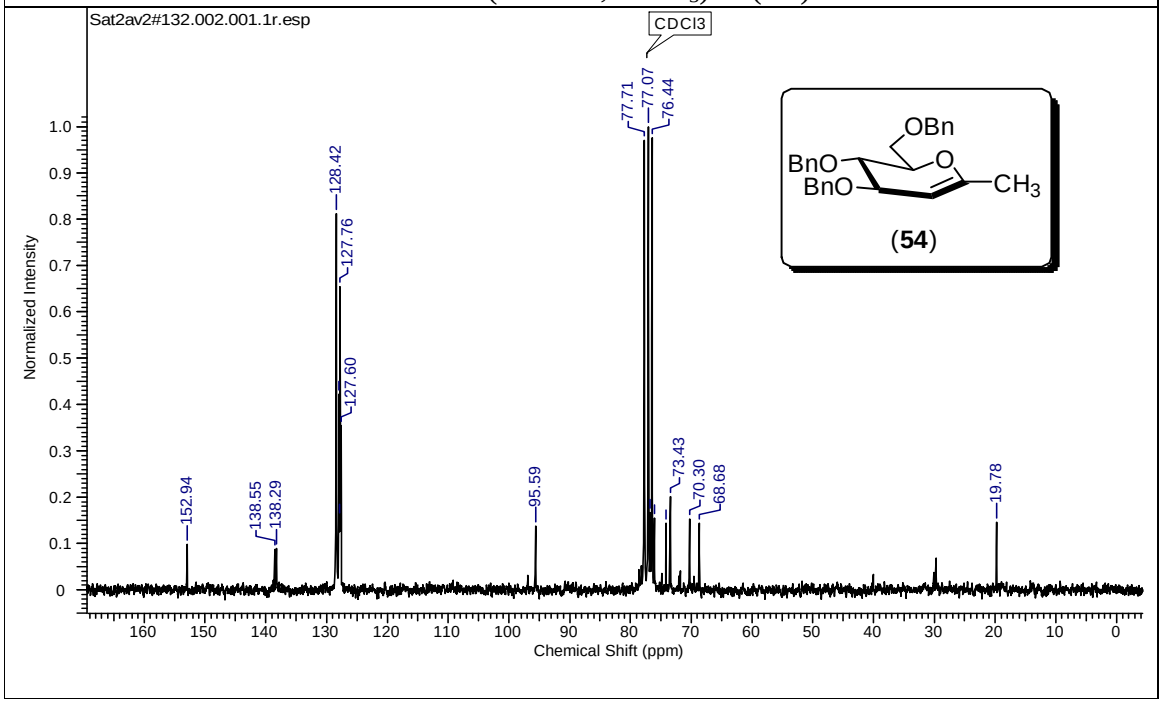


2.1.1.8 Spectra

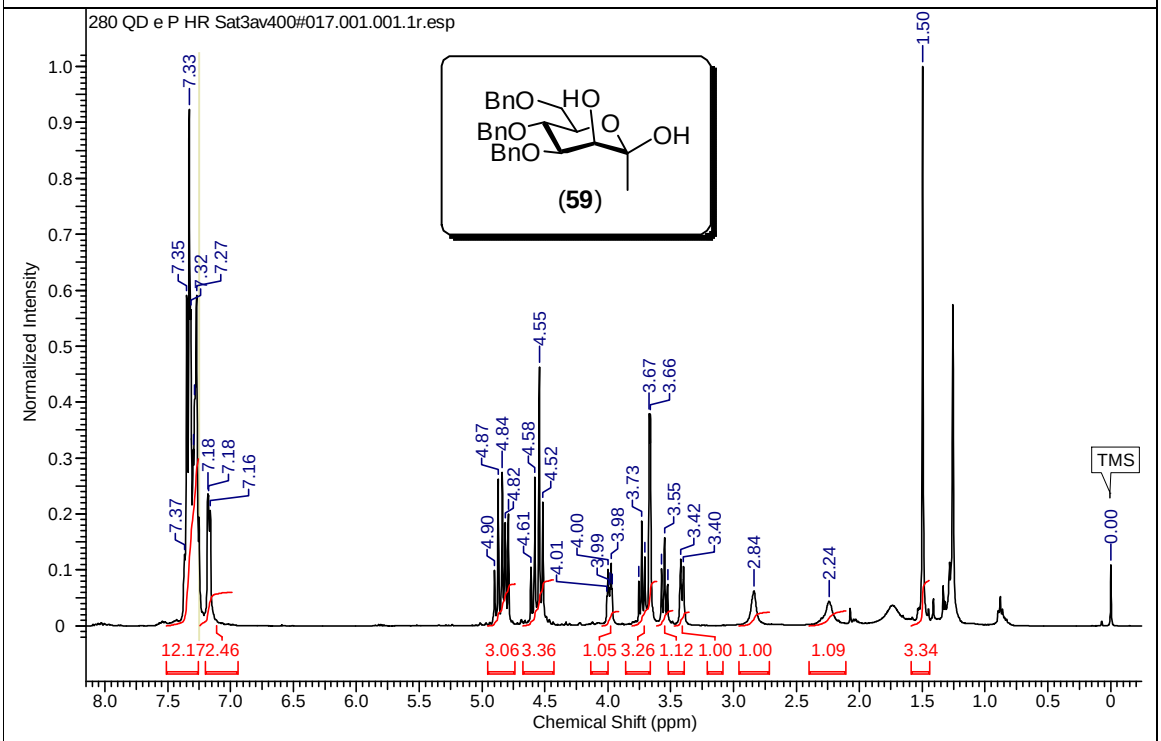
^{1}H NMR (200 MHz, $CDCl_3$) of (**54**)



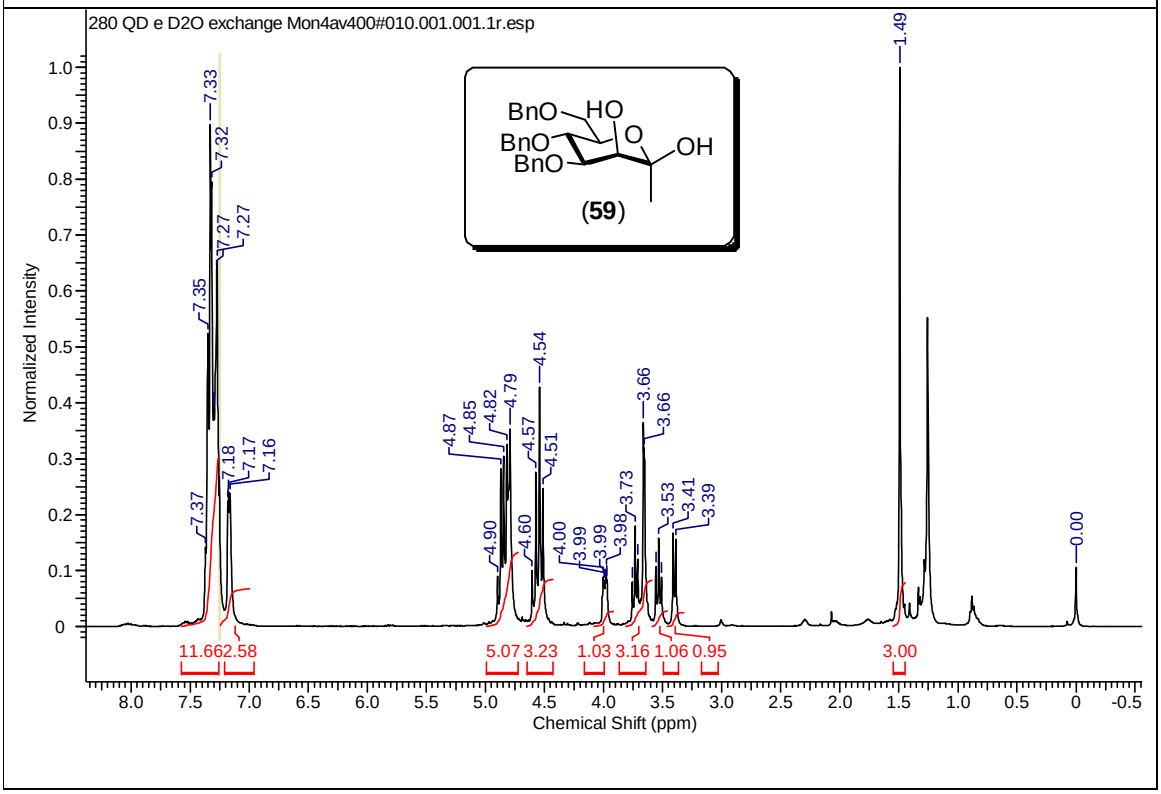
^{13}C NMR (50 MHz, $CDCl_3$) of (**54**)



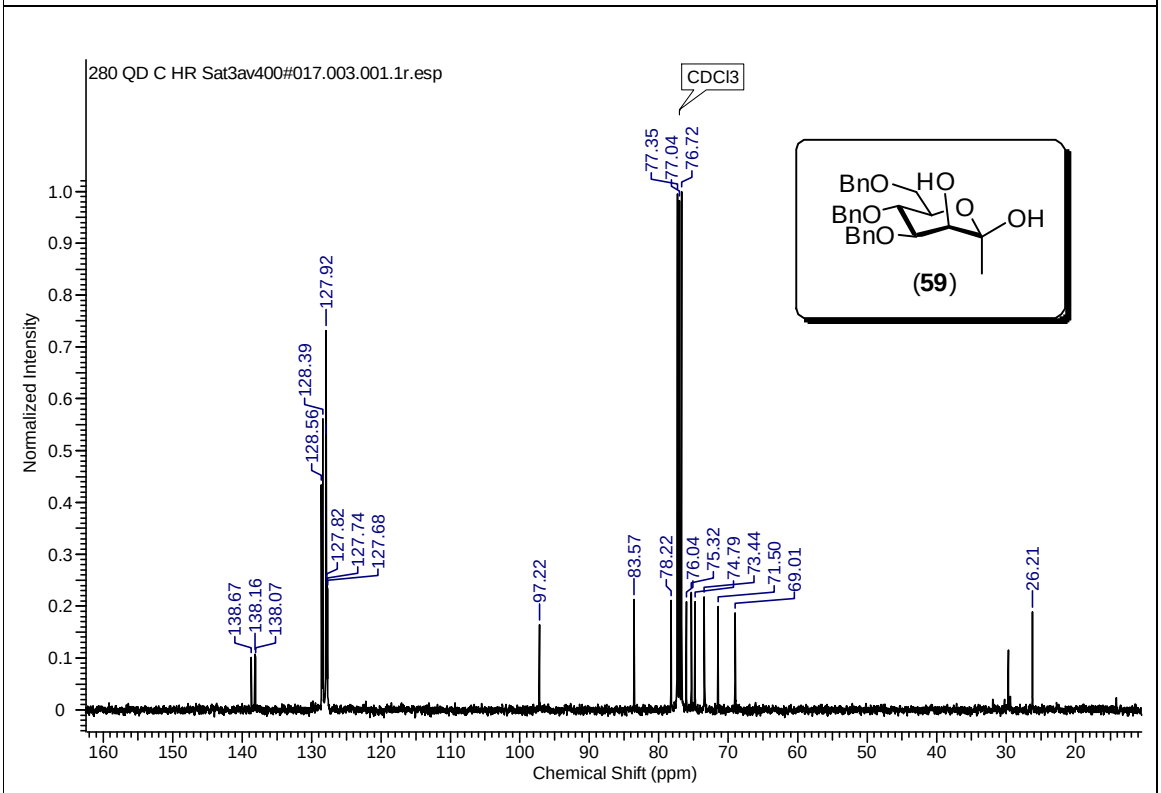
^{1}H NMR (400 MHz, $CDCl_3$) of (**59**)



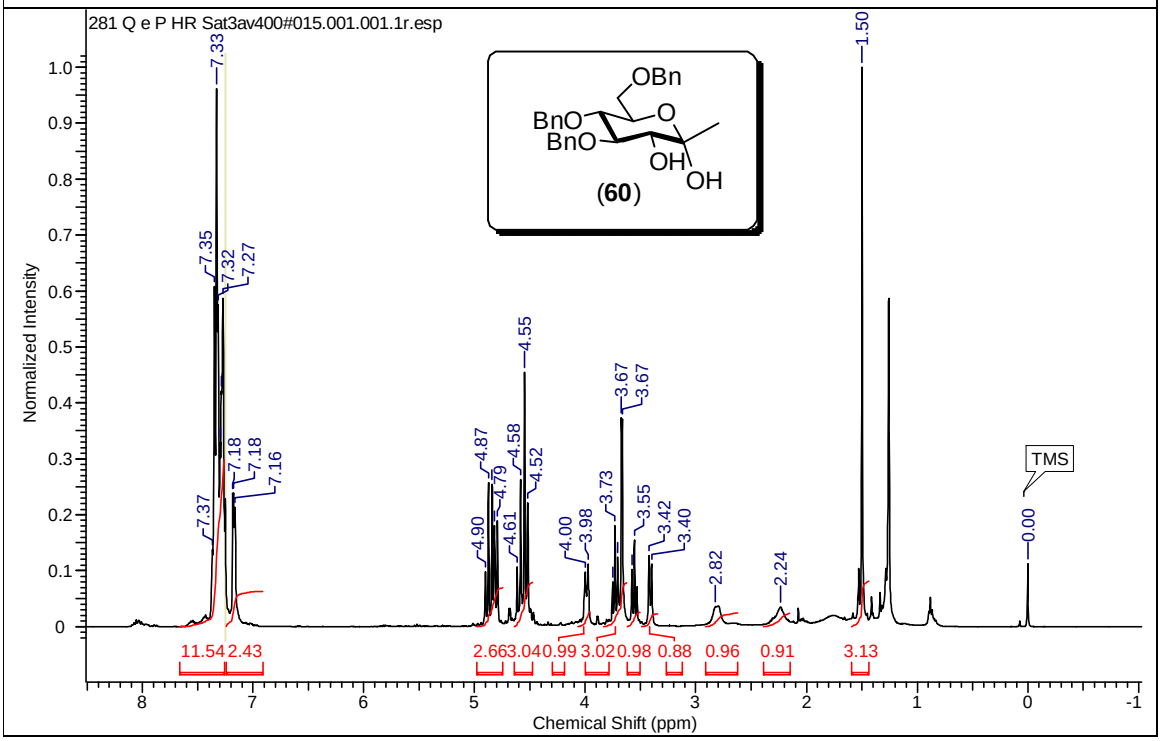
^{1}H NMR (400 MHz, $CDCl_3$) of (**59**) D_2O exchange



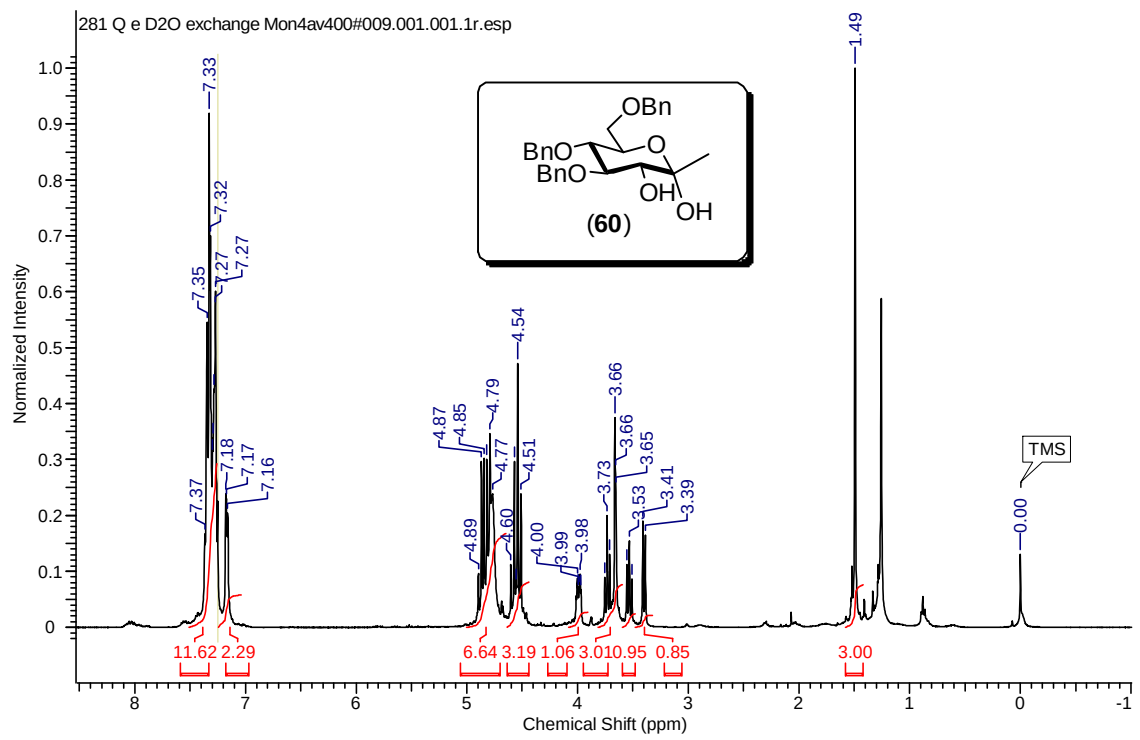
^{13}C NMR (100 MHz, $CDCl_3$) of (**59**)



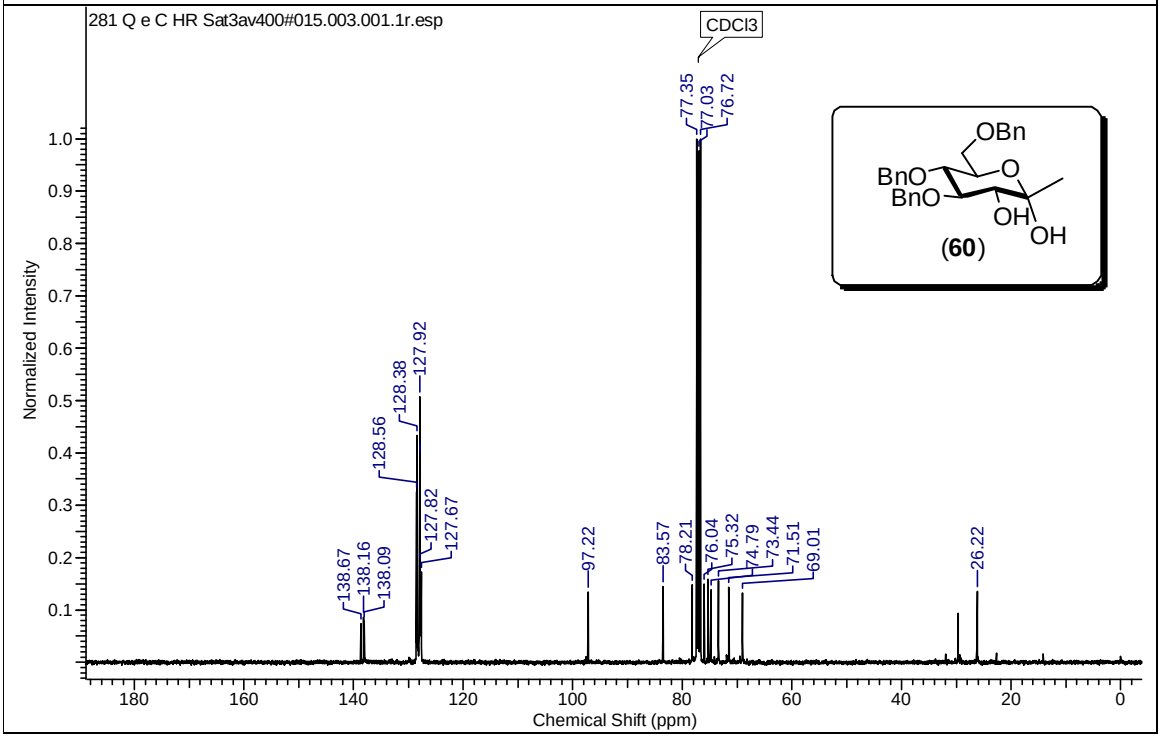
^{1}H NMR (400 MHz, $CDCl_3$) of (**60**)



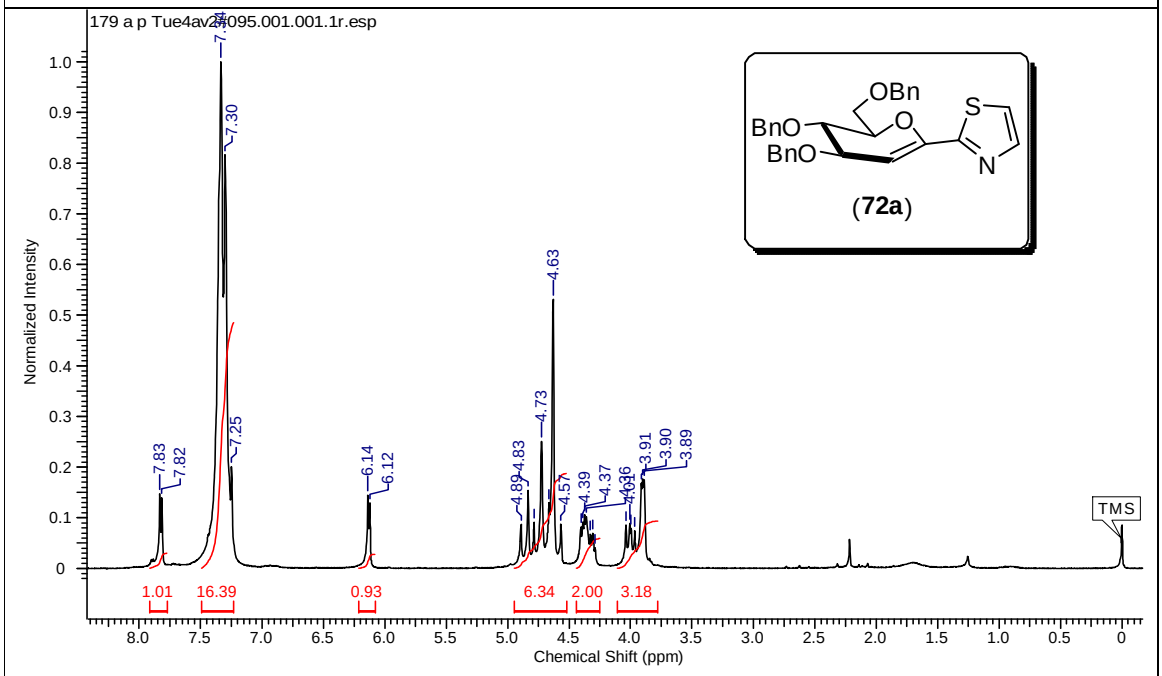
^{1}H NMR (400 MHz, $CDCl_3$) of (**60**) D_2O exchange



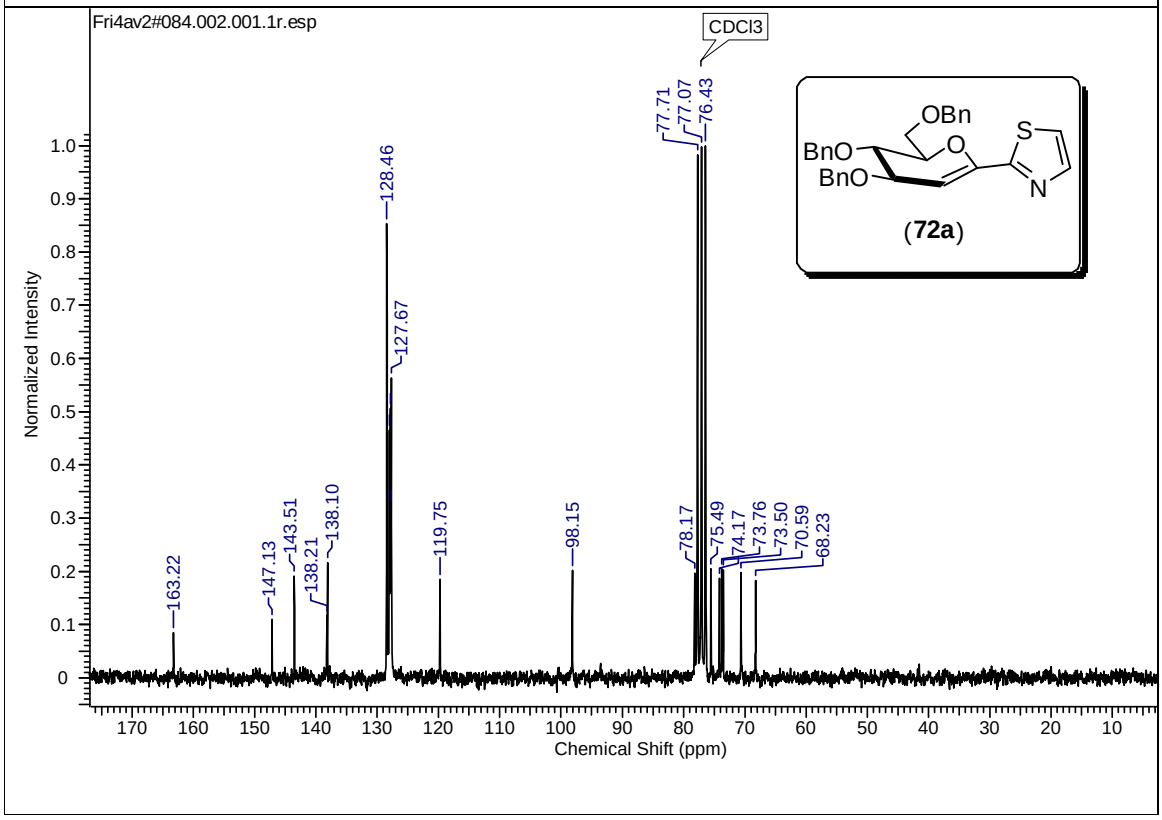
^{13}C NMR (50 MHz, $CDCl_3$) of (**60**)



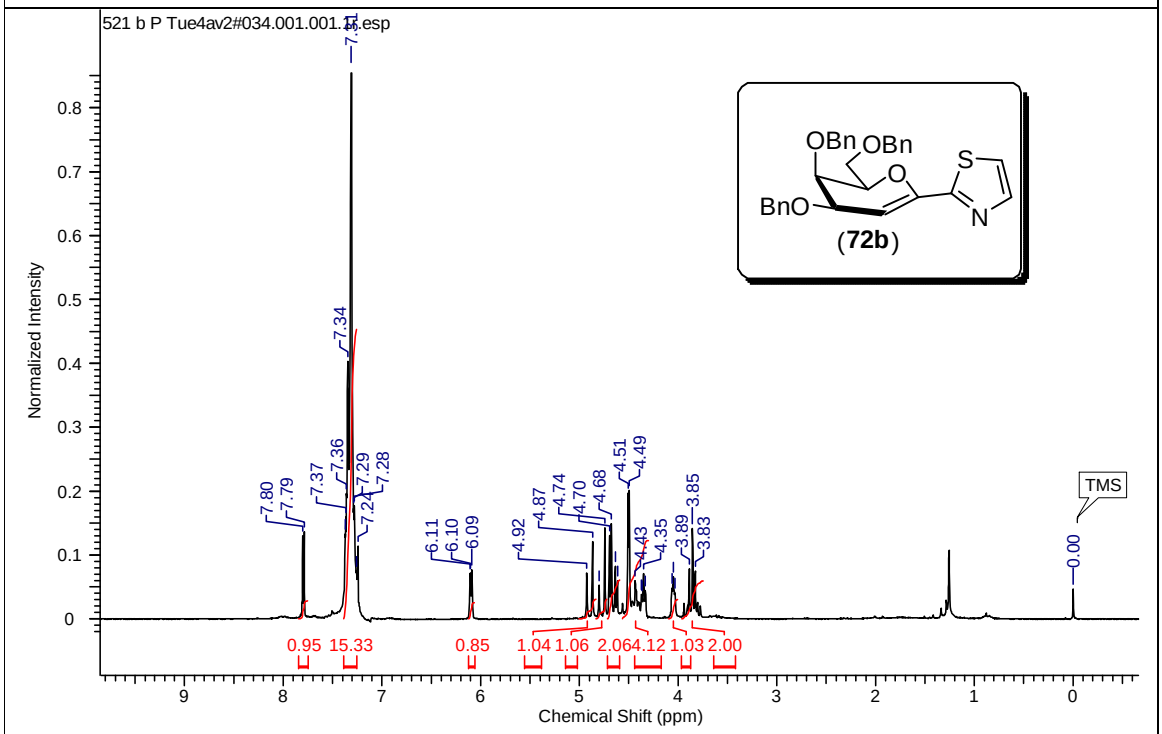
^{1}H NMR (200 MHz, $CDCl_3$) of (**72a**)



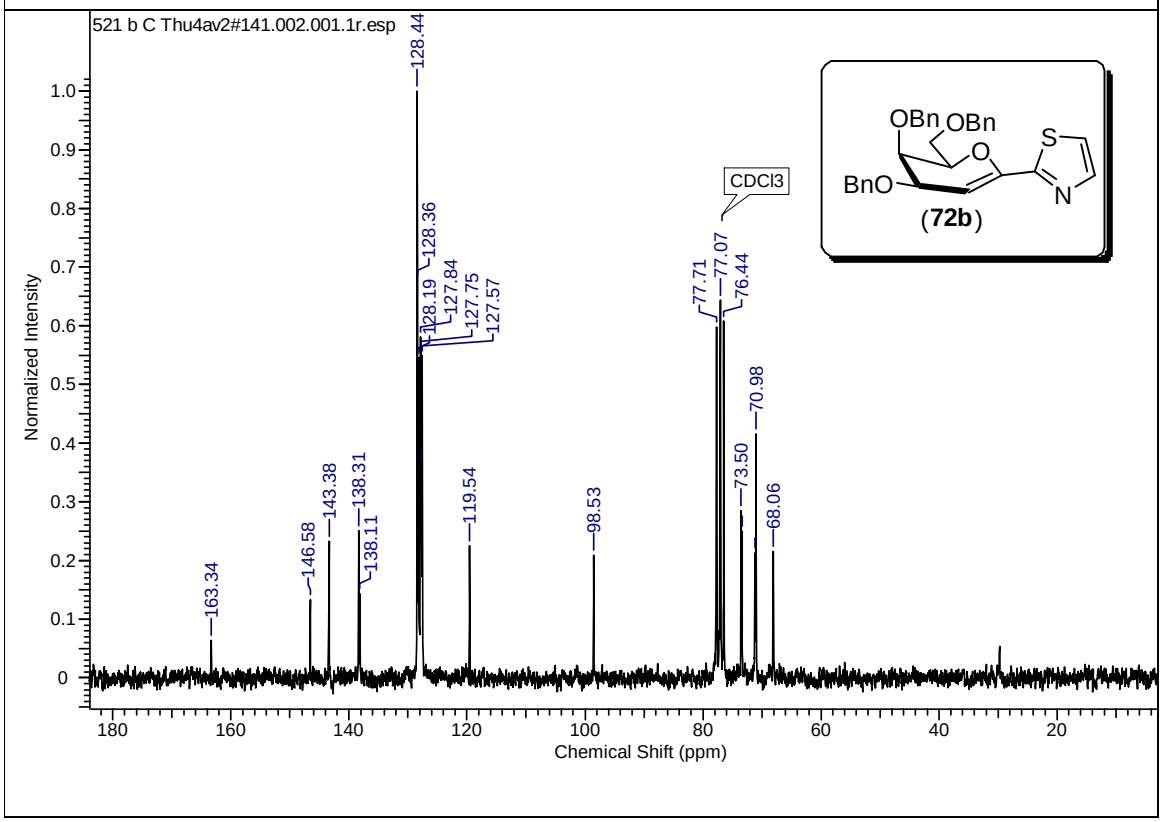
^{13}C NMR (50 MHz, $CDCl_3$) of (**72a**)



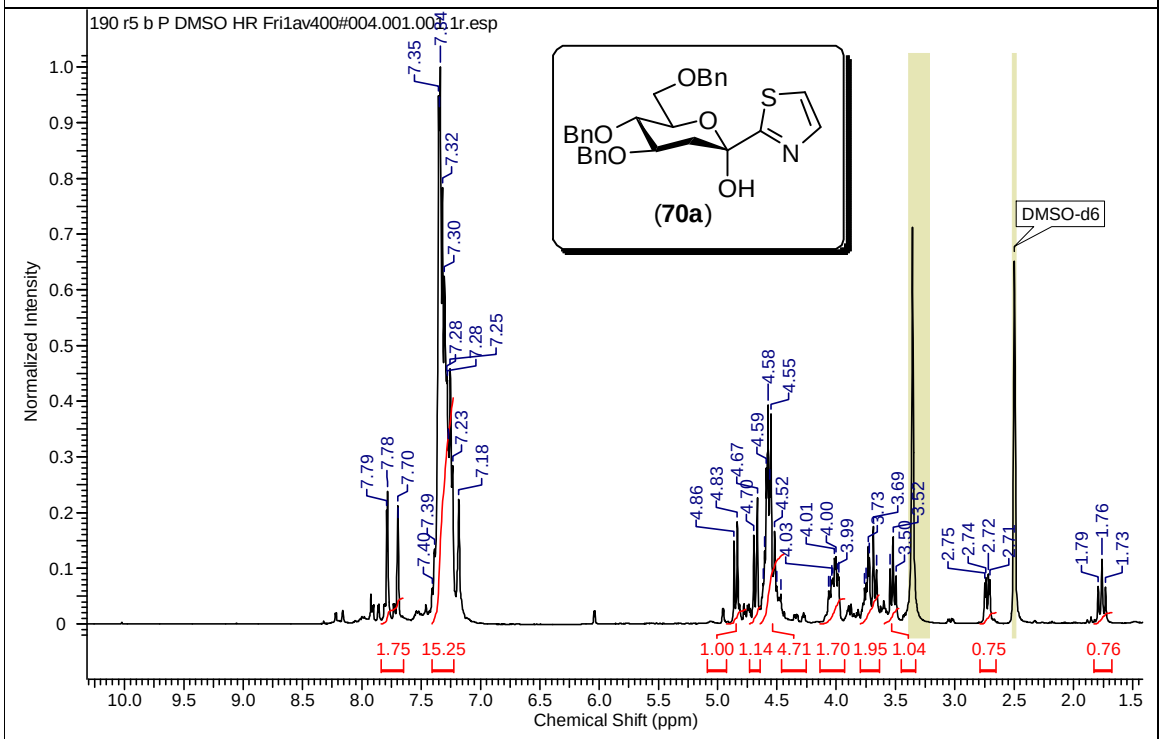
^{1}H NMR (200 MHz, $CDCl_3$) of (**72b**)



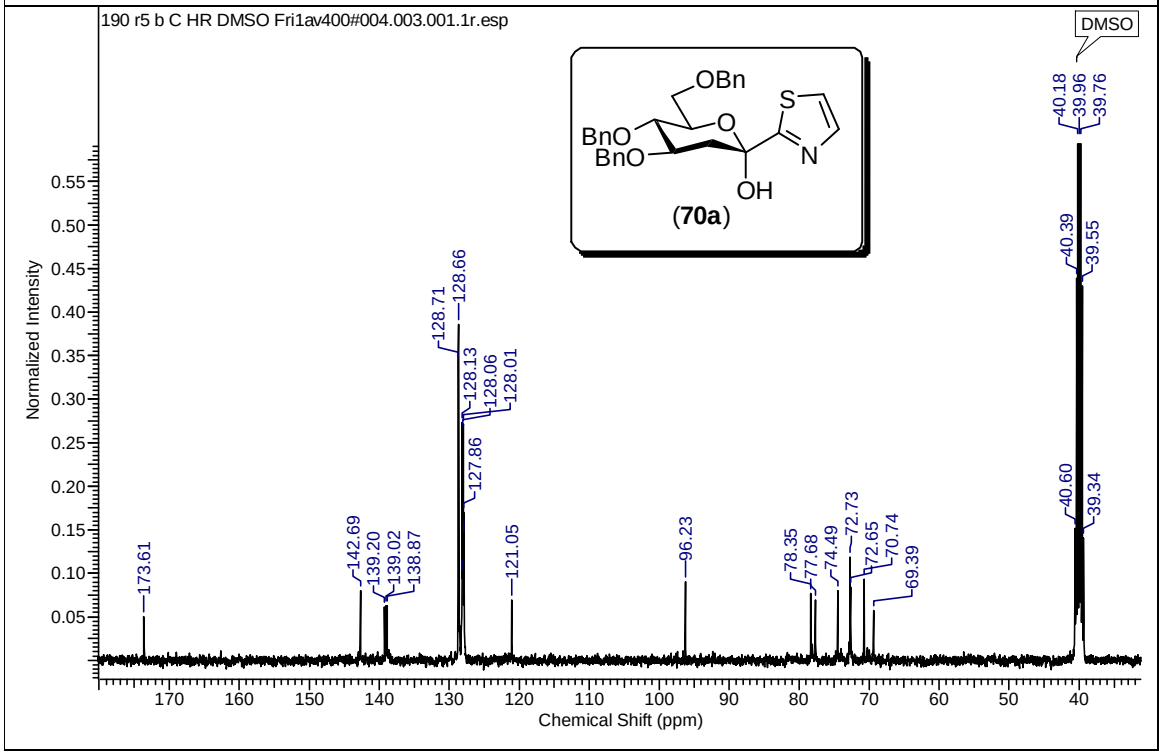
^{13}C NMR (200 MHz, $CDCl_3$) of (**72b**)



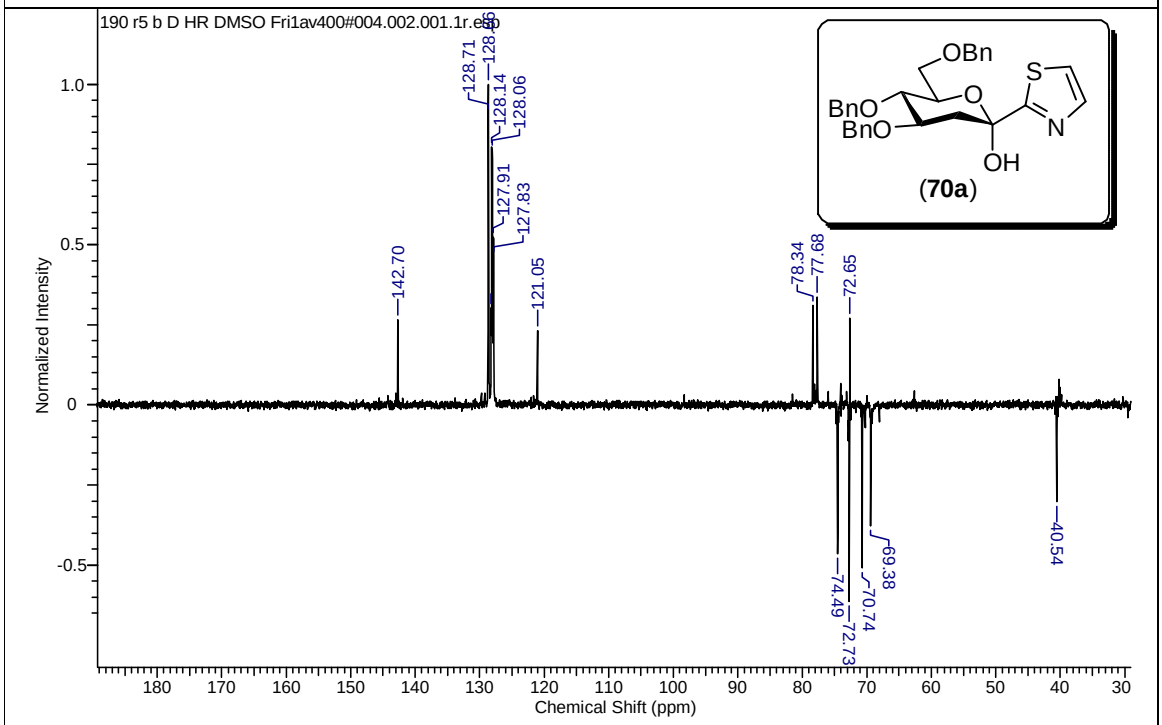
^{1}H NMR (400 MHz, DMSO-d_6) of (**70a**)



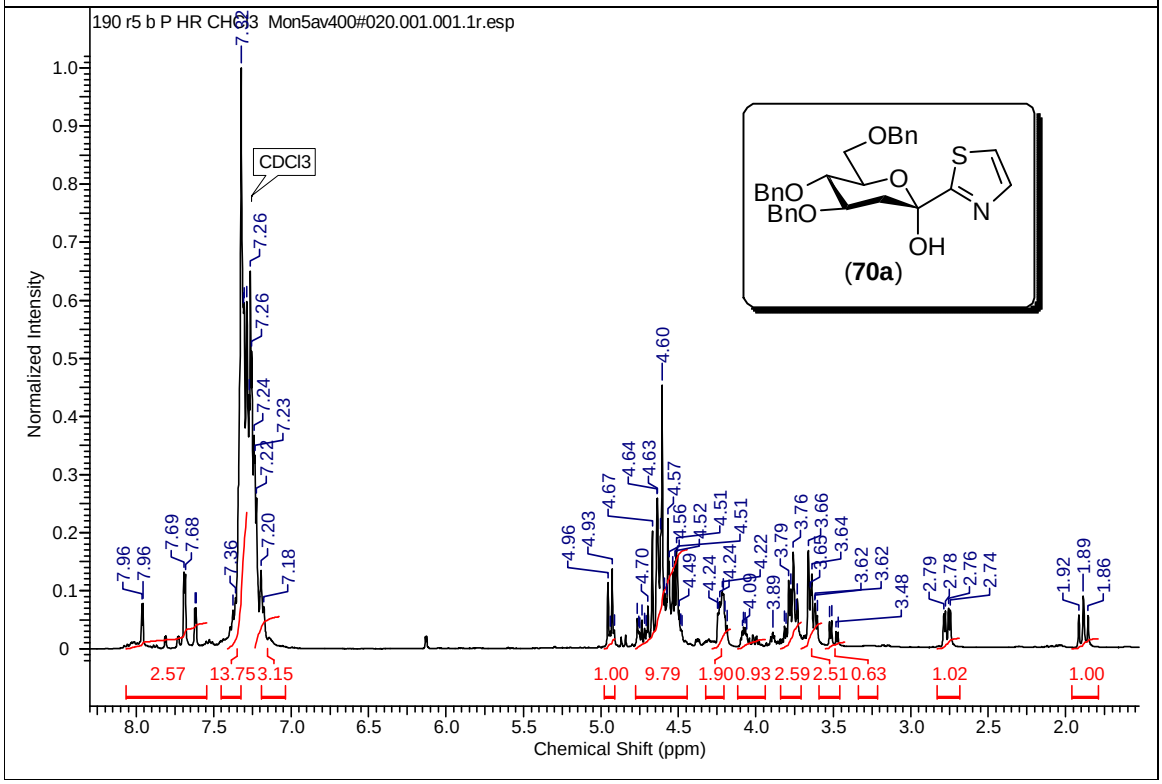
^{13}C NMR (100 MHz, DMSO-d_6) of (**70a**)



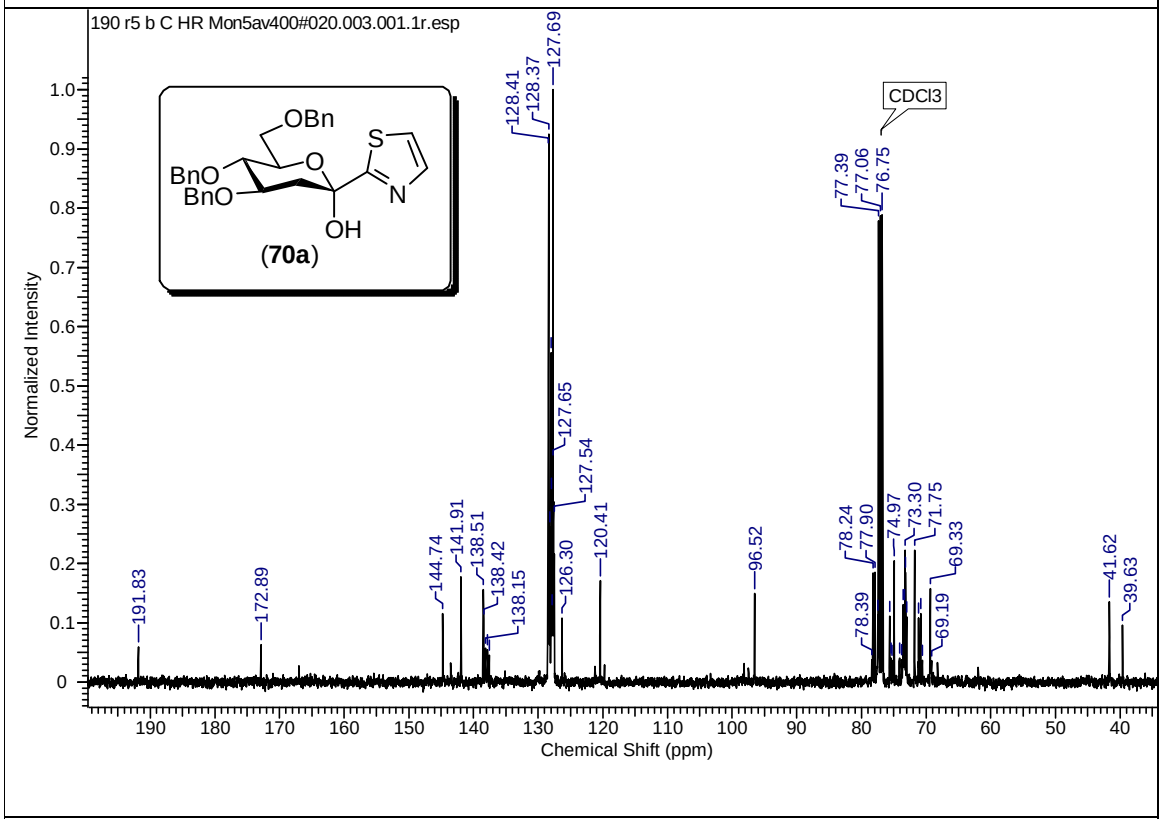
DEPT (100 MHz, DMSO-d_6) of (**70a**)



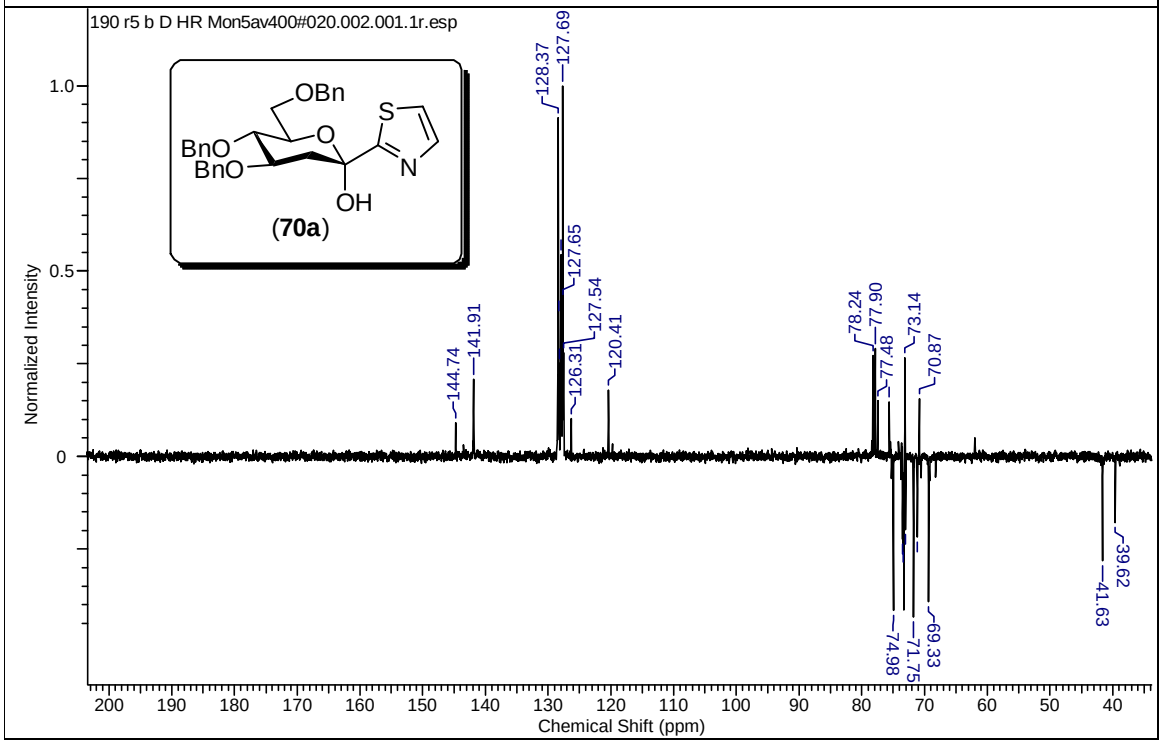
^{1}H NMR (400 MHz, $CDCl_3$) of (**70a**)



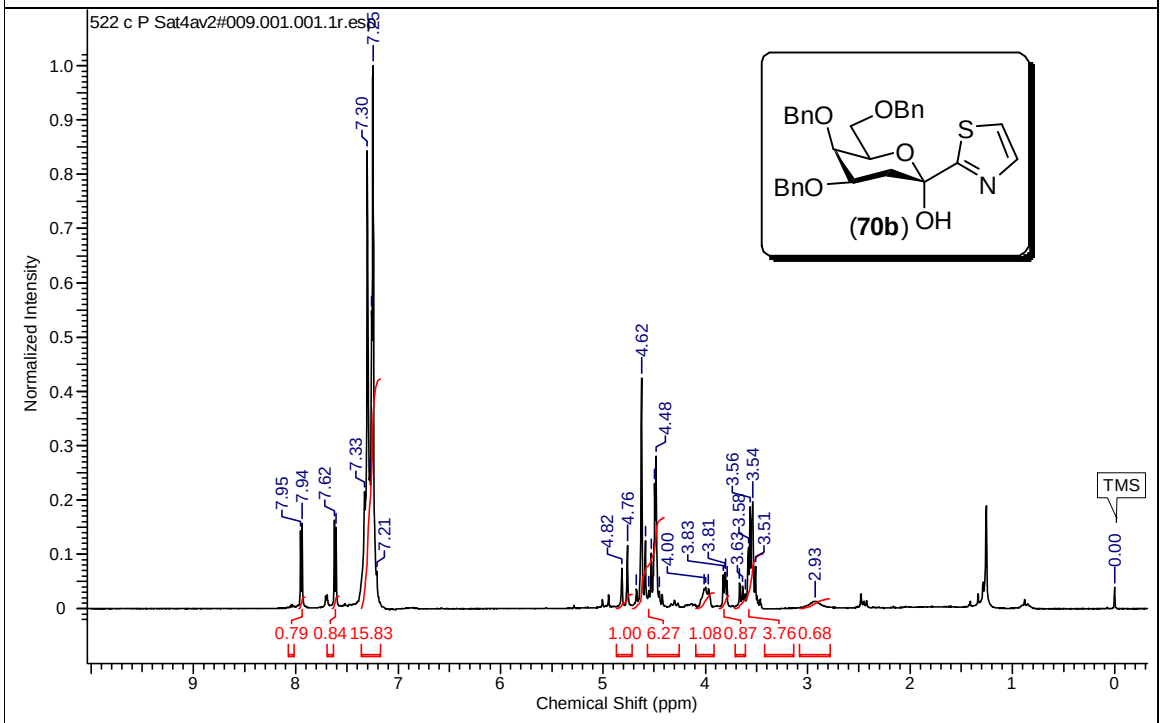
^{13}C NMR (100 MHz, $CDCl_3$) of (**70a**)



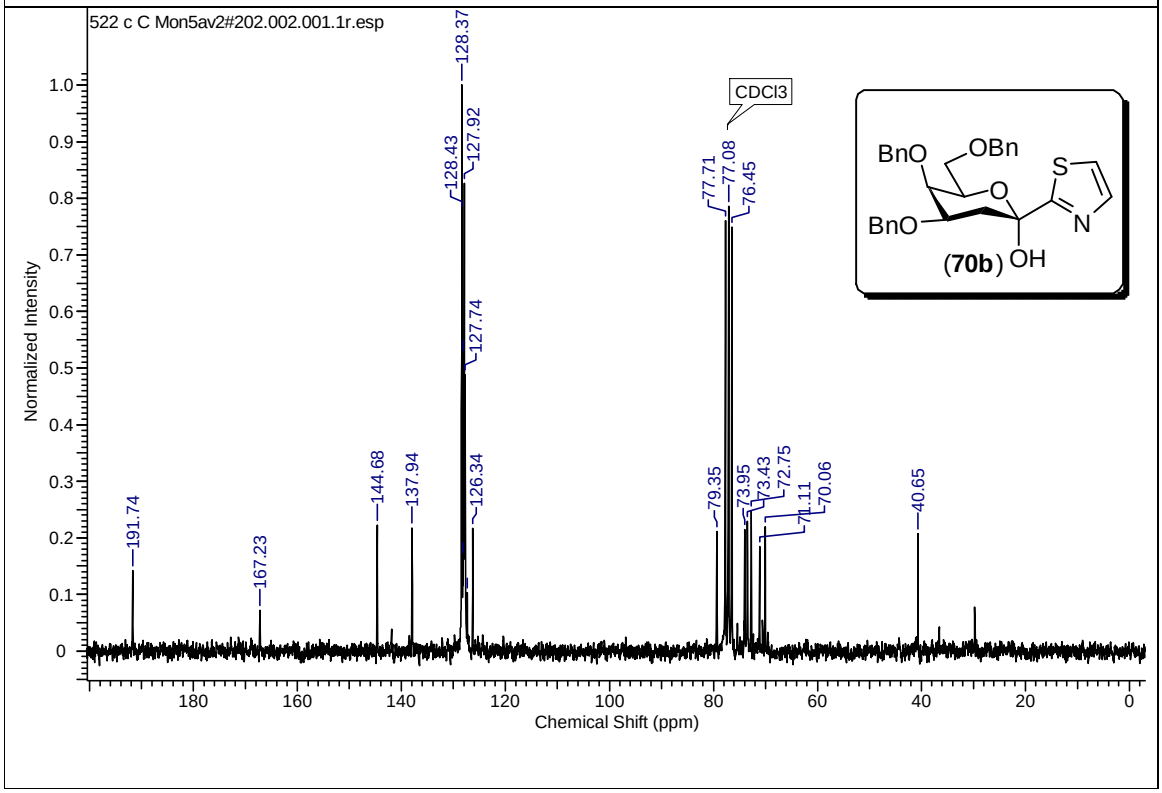
DEPT (100 MHz, $CDCl_3$) of (**70a**)



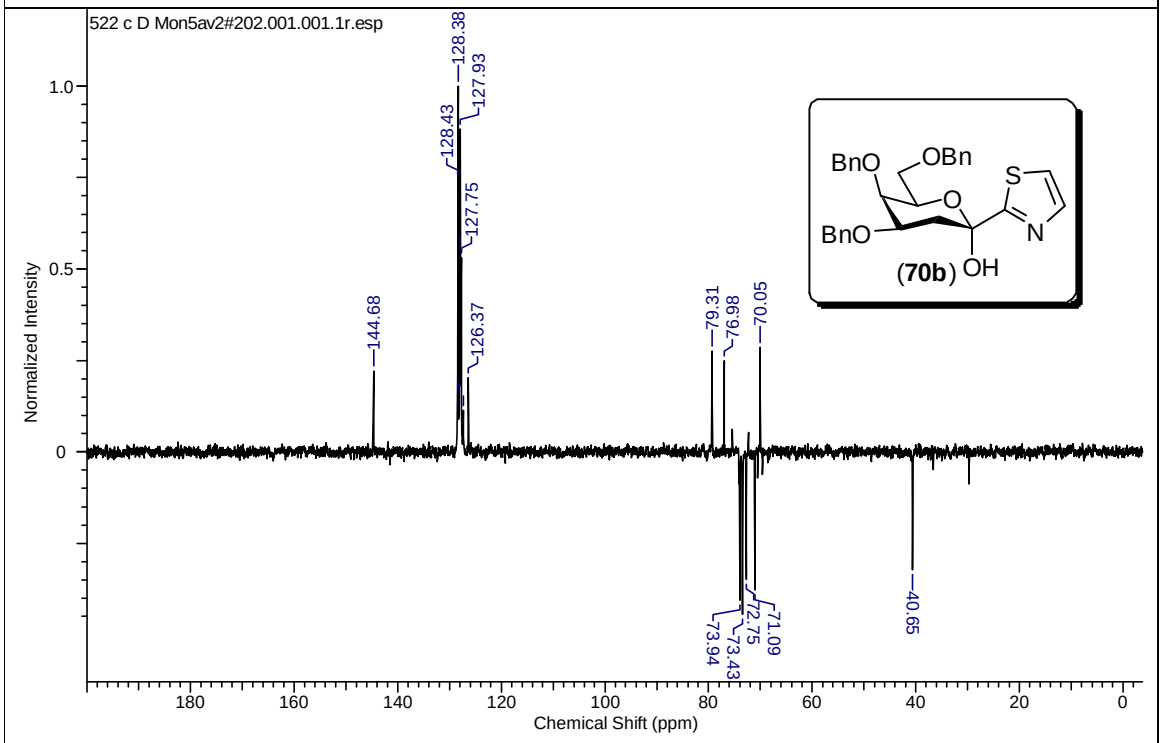
^{1}H NMR (200 MHz, $CDCl_3$) of (**70b**)



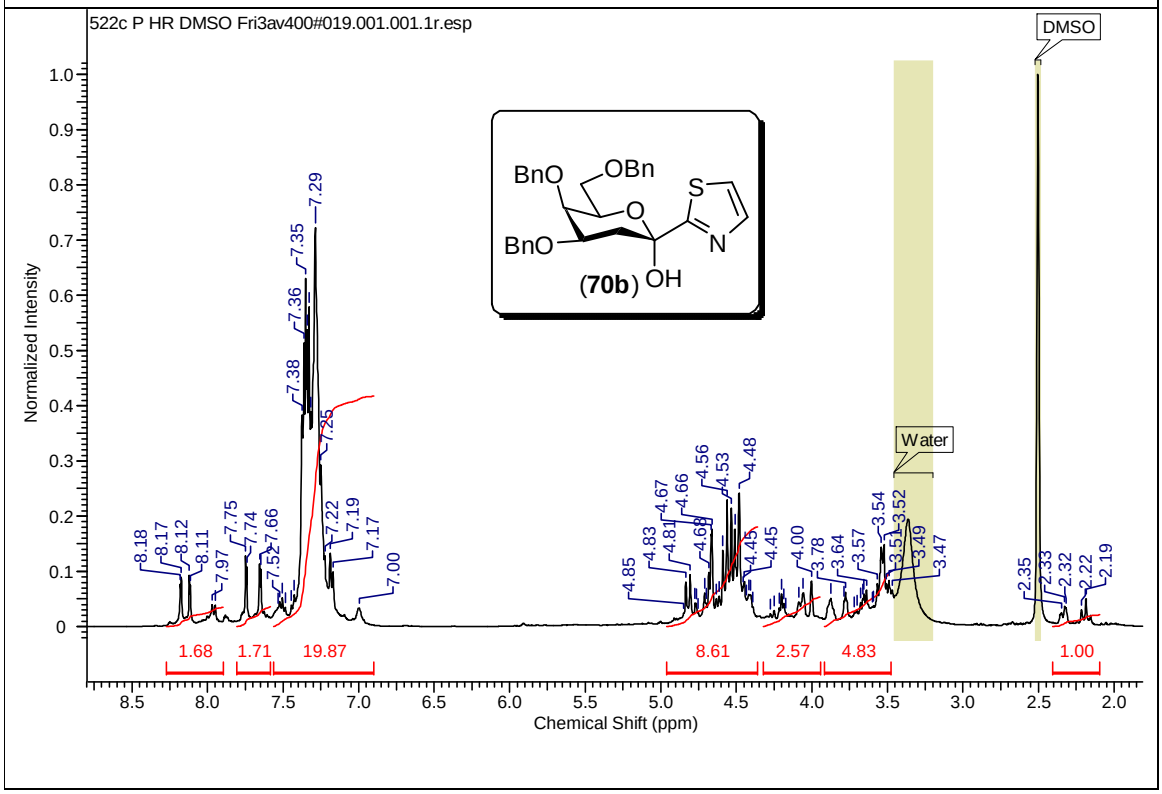
^{13}C NMR (50 MHz, $CDCl_3$) of (**70b**)



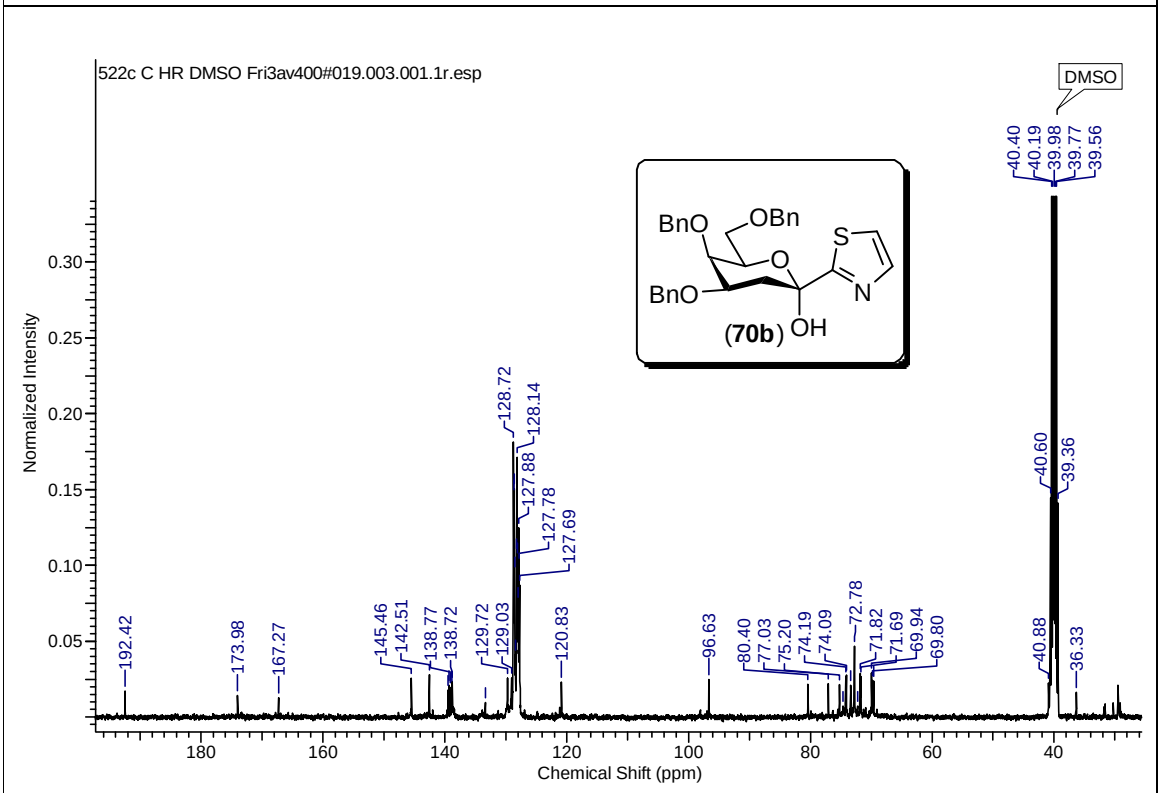
DEPT (50 MHz, DMSO-d6) of (**70b**)



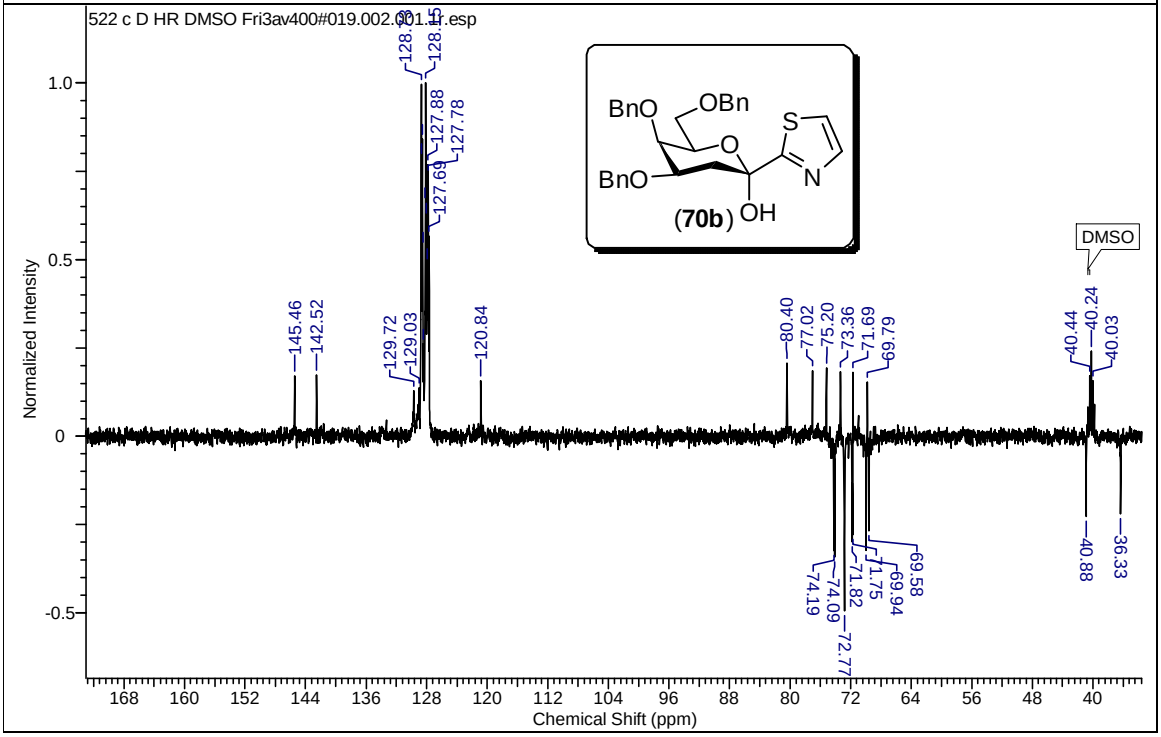
^{1}H NMR (400 MHz, DMSO-d6) of (**70b**)



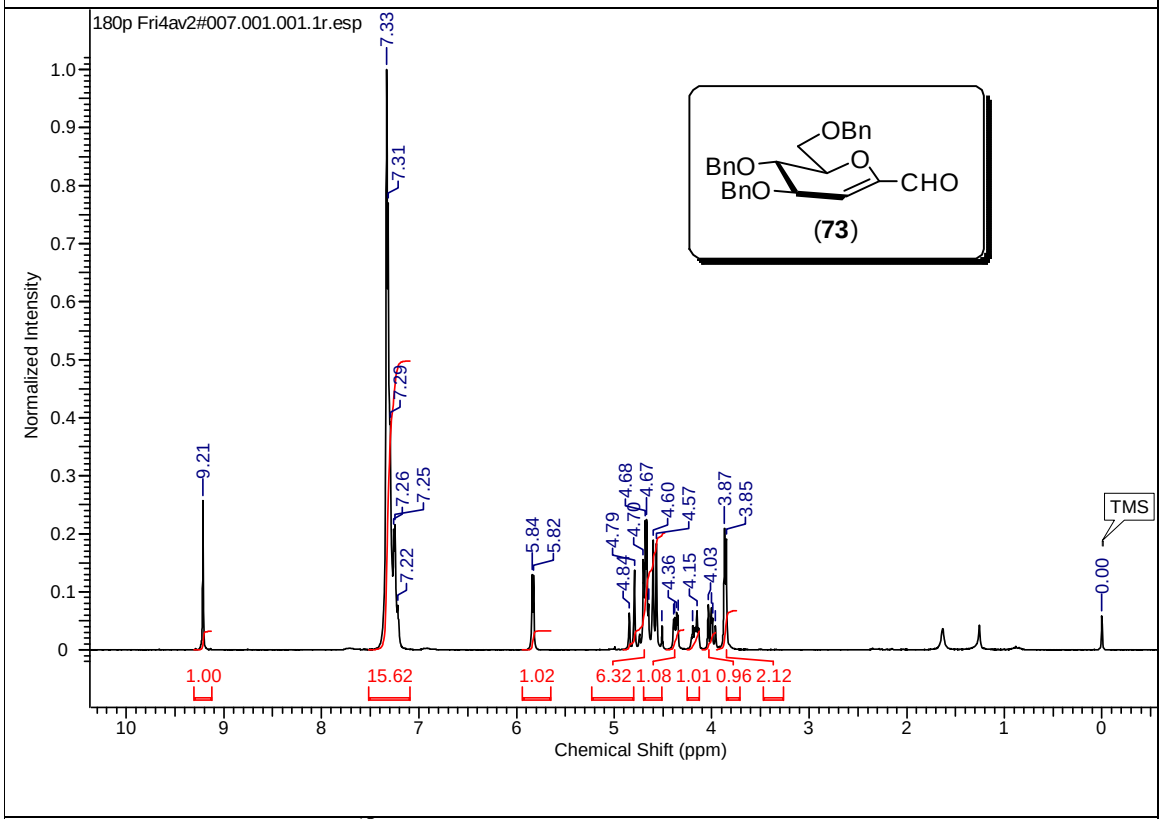
^{13}C NMR (400 MHz, DMSO-d6) of (**70b**)



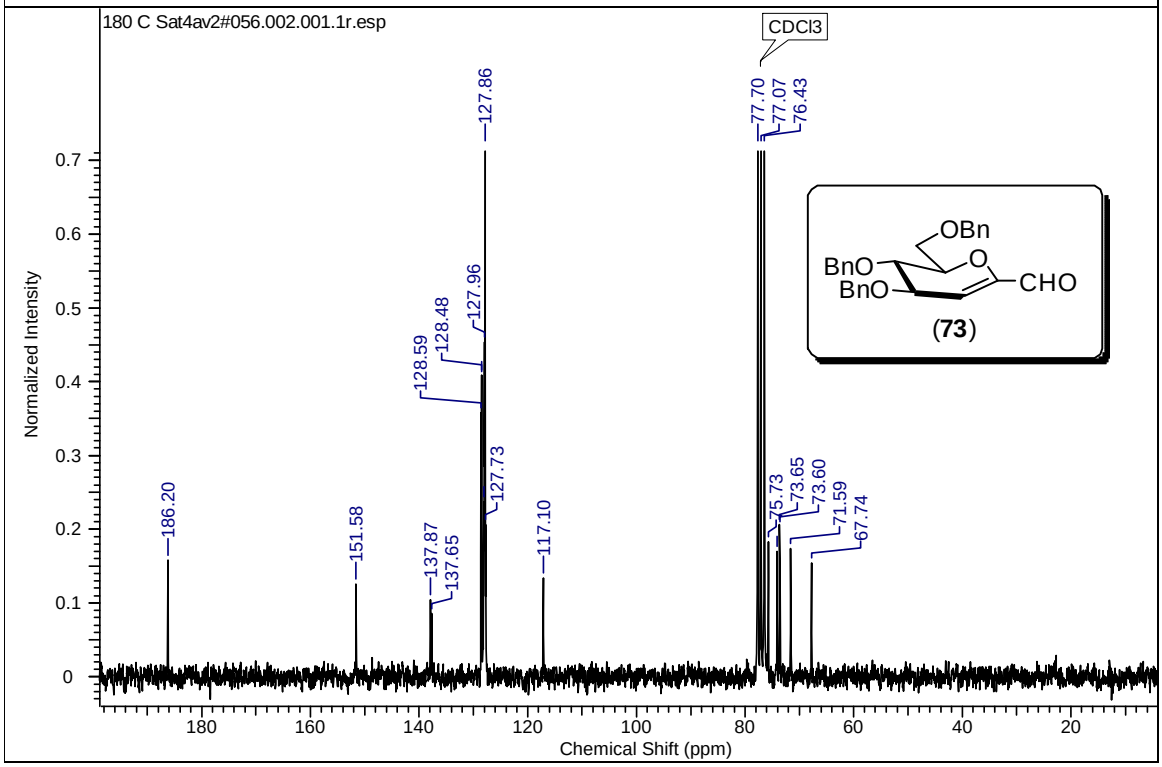
DEPT (400 MHz, DMSO-d6) of (**70b**)



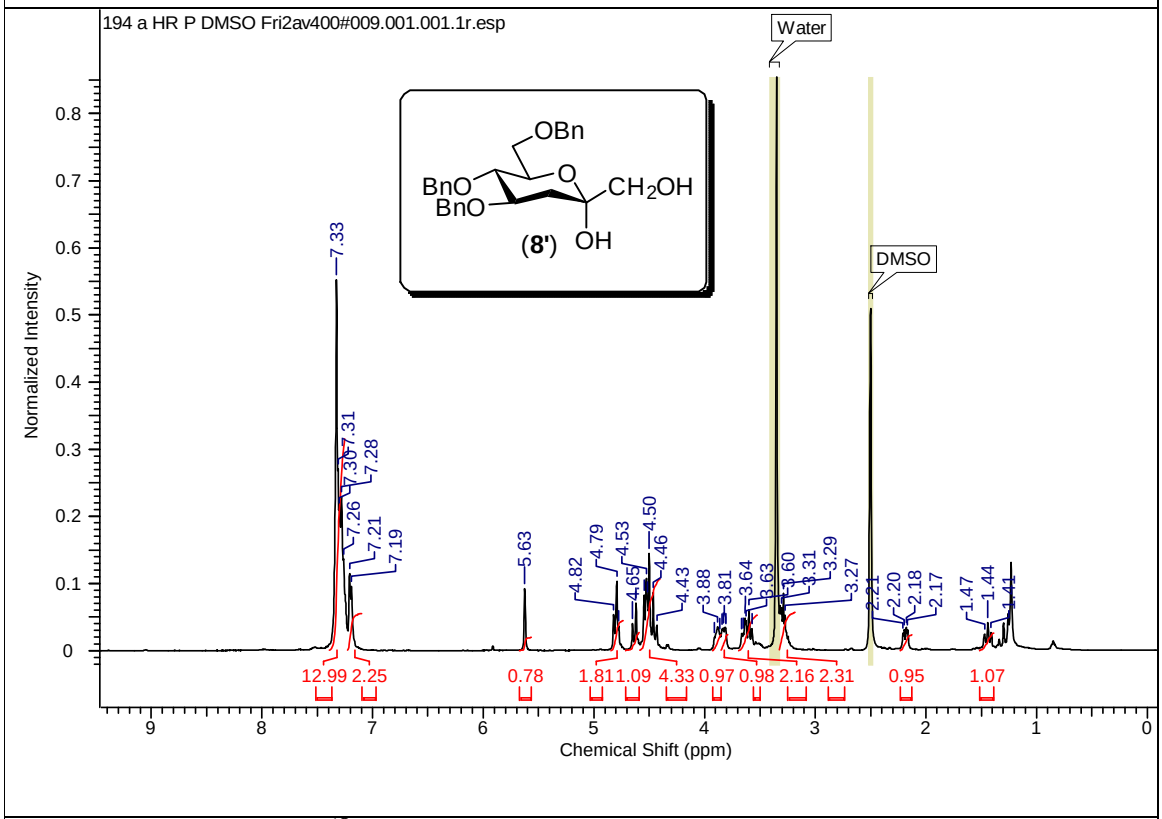
^{1}H NMR (200 MHz, $CDCl_3$) of (**73**)



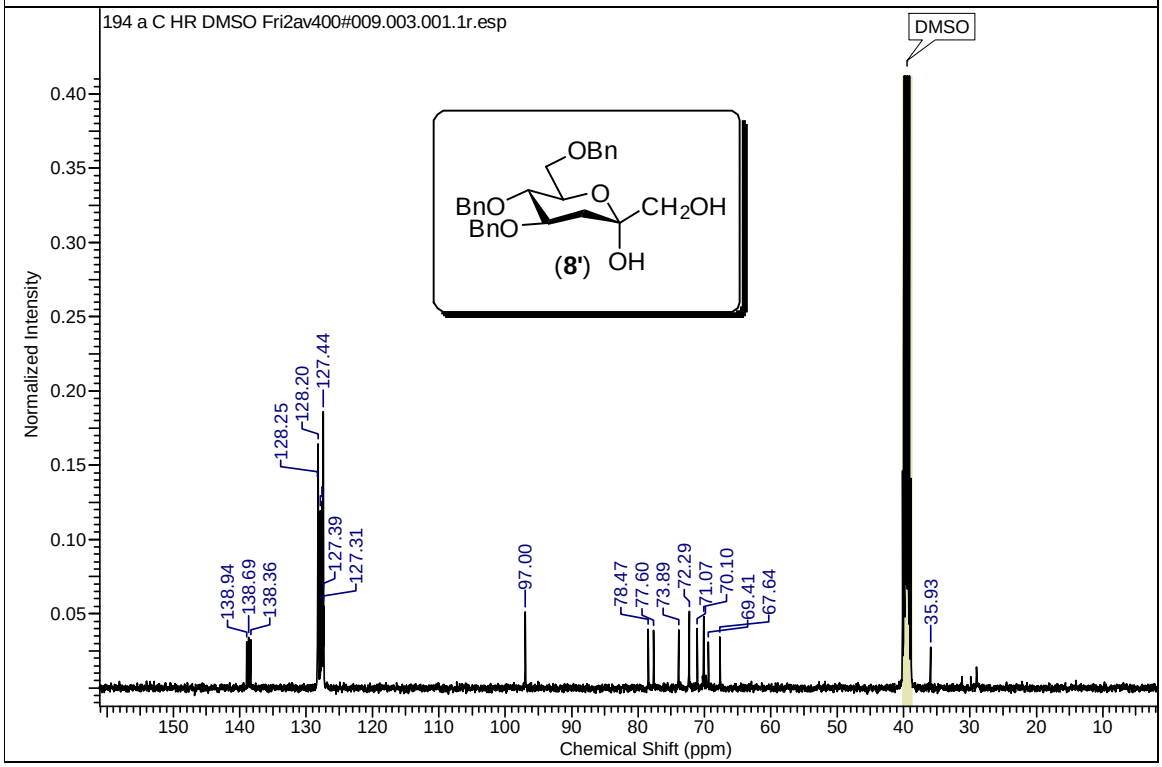
^{13}C NMR (50 MHz, $CDCl_3$) of (**73**)



^{1}H NMR (400 MHz, DMSO-d_6) of (**8'**)



^{13}C NMR (100 MHz, DMSO-d_6) of (**8'**)



Single crystal analysis and ORTEP Diagram :

Table 4. Crystal data and structure refinement for (**70a**).

Identification code	HC_19_R_0m	
Empirical formula	C_{30} H_{31} N O_5 S	
Formula weight	517.62	
Temperature	150(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	C 2	
Unit cell dimensions	a = 22.368(6) Å	α= 90°.
	b = 6.2362(17) Å	β= 119.491(4)°.
	c = 22.045(6) Å	γ = 90°.
Volume	2676.7(13) $Å^3$	
Z	4	
Density (calculated)	1.284 Mg/m^3	
Absorption coefficient	0.161 mm^{-1}	
F(000)	1096	
Crystal size	0.390 x 0.310 x 0.260 mm^3	
Theta range for data collection	2.092 to 24.998°.	
Index ranges	-26<=h<=26, -7<=k<=7, -26<=l<=26	
Reflections collected	13981	
Independent reflections	4726 [R(int) = 0.0365]	
Completeness to theta = 25.242°	97.5 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.959 and 0.940	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	4726 / 13 / 335	
Goodness-of-fit on F^2	1.035	
Final R indices [I>2sigma(I)]	R1 = 0.0400, wR2 = 0.0836	
R indices (all data)	R1 = 0.0468, wR2 = 0.0871	
Absolute structure parameter	0.03(4)	
Extinction coefficient	n/a	
Largest diff. peak and hole	0.462 and -0.416 e.$Å^{-3}$	

2.1.1.9 References

1. Robyt, J.F., *Essentials of carbohydrate chemistry*. **1998.** *Springer.ISBN 0-387-94951-8.*
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Chapter 3

Chemical Transformations of Abundant Natural Products; Diastereoselective Synthesis of β-Ether Derivatives of Artemisinin

3.1 Diastereoselective Synthesis of β-Ether Derivatives of Artemisinin

3.1.1 Introduction

Malaria is the most common of the parasitic diseases caused by protozoan parasites of the genus *Plasmodium*, but in humans, there are four species *P. falciparum*, *vivax*, *malariae* and *ovale* that are responsible for the spread of the disease in around 96 countries.[1,2] In the year 2014 alone, more than 214 million people were diagnosed with malaria, leading to 438 000 deaths worldwide. From India 1102 205 confirmed cases with 561 deaths in the year 2014 were reported.[3] Excessive usage of insecticides has resulted in the development of resistance by the vector mosquitoes and also plasmodium parasites have developed substantial immunity against the most widely used antimalarial agents, such as quinine and chloroquine. This has created a pressing demand for the search of new antimalarials.[4,1a]

Ayurveda (Indian traditional system of medicine) extensively describes remedy for the cure of many diseases utilizing substances from natural sources of which plants form the major source. One of the earliest natural compounds that highlight the value of natural products in the fight against malaria is quinine (**1**), isolated from the Cinchona bark. It also served as a template for the development of structurally simpler analogues such as chloroquine (**2**), primaquine (**3**), mepacrine (**4**) and mefloquine (**5**) as effective antimalarials. Recently some compounds to name a few pyrimethamine (**6**), proguanil (**7**), sulphadoxine (**8**), pamaquine (**9**), tefnoquine (**10**), mefloquine (**11**), atovaquine (**12**) and artemisinin (**13**) have emerged as a paramount source of antimalarial drugs (Figure 1).[3,5]

Chloroquine was once the most effective drug for the treatment of malaria, but resistance has been developed in the parasite against this drug.[6] *P. falciparum* has developed resistance to all of our available drugs; therefore it is an overwhelming cause of serious disease and death. The development of resistance to mainstay drugs like chloroquine, and controlled use of new artemisinin analogs have created an urgent need to discover new antimalarial agents.

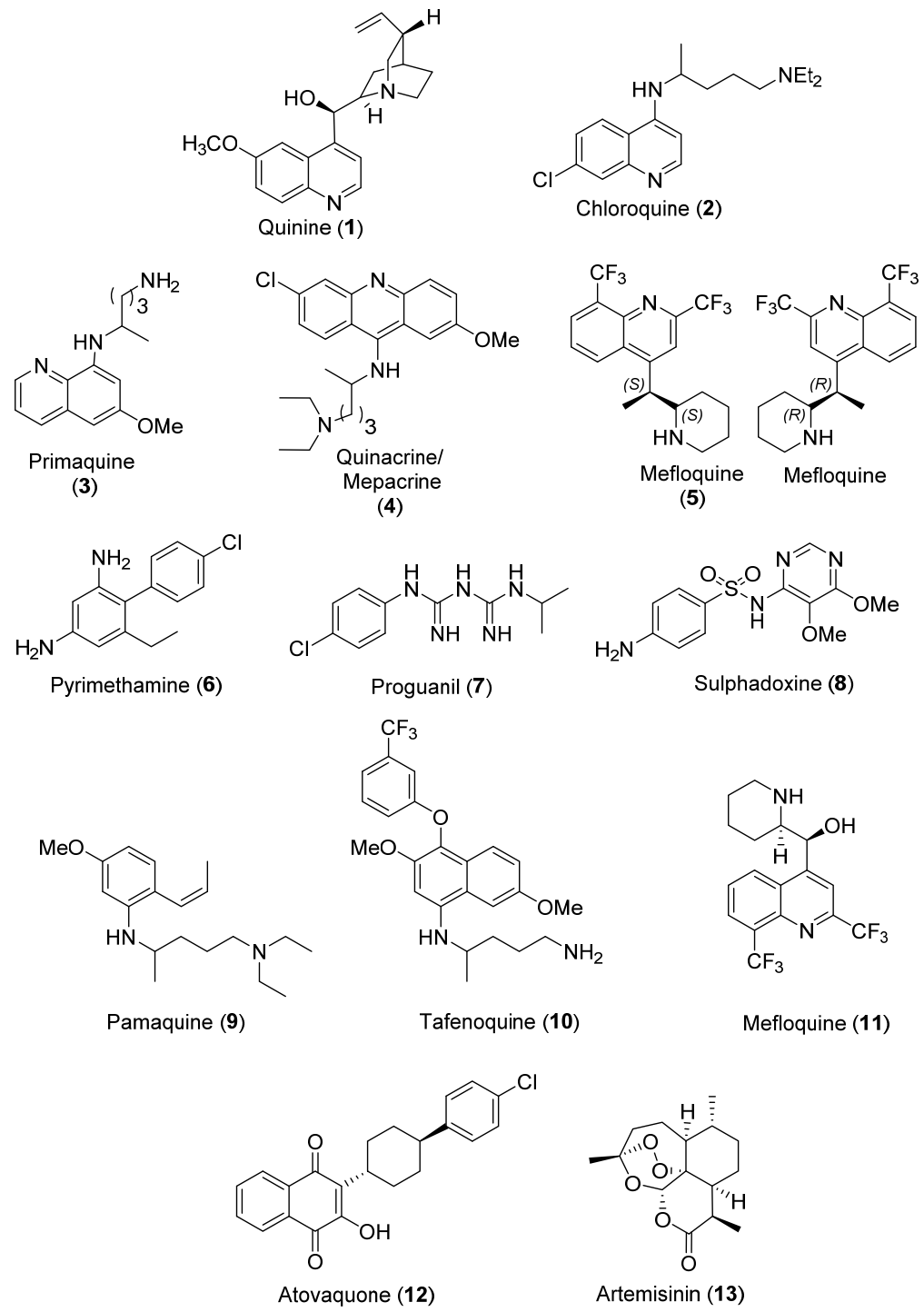


Figure 1. Structures of selected anti-malarial drugs.

Artemisinin

The plant *Artemisia annua* (Family: *Asteraceae*) also known as sweet wormwood, sweet annie, sweet sagewort, annual mugwort or annual wormwood

(Chinese qinghao). It is well known and has its origin in traditional Chinese system of medicine and is being used as a cure for fever and malaria for over 2000 years.[7]

The sui generis structural feature of sesquiterpene lactone is the endoperoxide having all the five oxygen atoms on the same side of the molecule. Devoid of the nitrogen containing heterocyclic ring system, a distinct feature of conventional antimalarial drugs artemisinin belongs to **amorphane** sub-group of **cadinenes** (Fig. 2). The maximum yield of artemisinin (**13**) in the plant *Artemisia annua* is 0.1%. The two biogenetic precursors of artemisinin (**13**), arteannuin B (**14**) and artemisinic acid (**15**) are present in the plant *A. annua* (Fig. 2).[7]

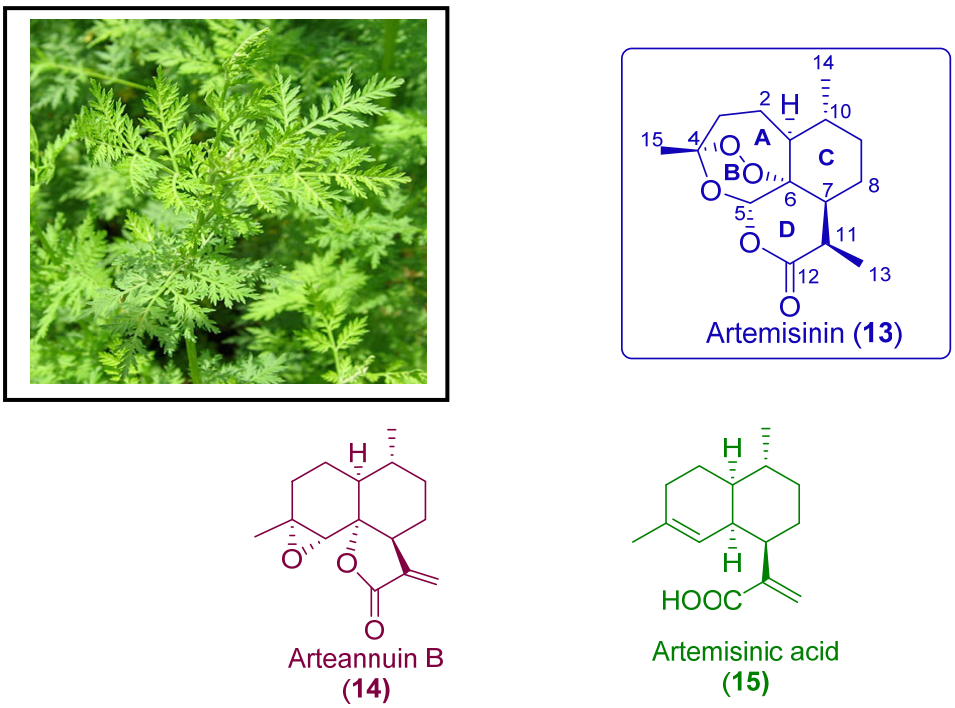


Figure 2. *A. annua* and its important chemical constituents, artemisinin (**13**), arteannuin B (**14**) and artemisinic acid (**15**).

In comparison to conventional antimalarial drugs such as chloroquine, quinine etc., artemisinin (**13**) has superior plasmodial and blood schizontocidal activity with an additional advantage of no side effects.[8] However, some factors that hampers its direct and wide usage are (i) its poor solubility either in oil or water,[9] (ii) the high rate of parasite recrudescence after treatment[10a] and (iii) its short-plasma half life (3–5h) and its poor oral activity.[10b] This has persuaded researchers to plan and synthesize various derivatives which can overcome some of these flaws. For her work on

development of artemisinin as an antimalarial drug, Chinese scientist Prof. Tu, Youyou, was awarded the 2015 Nobel Prize in medicine jointly shared with Prof. Campbell William C. and Prof. Ōmura Satoshi.[11]

Artemisinin (**13**), a natural sesquiterpene lactone endoperoxide and subsequent development of its oil-soluble derivatives, for example, artemether (**17**, **19**), arteether (**18**, **20**) and water-soluble artelinate (**21**) and artesunate (**22**) has resulted in efficient treatment of malaria and cerebral malaria (Fig. 3)[12-17].

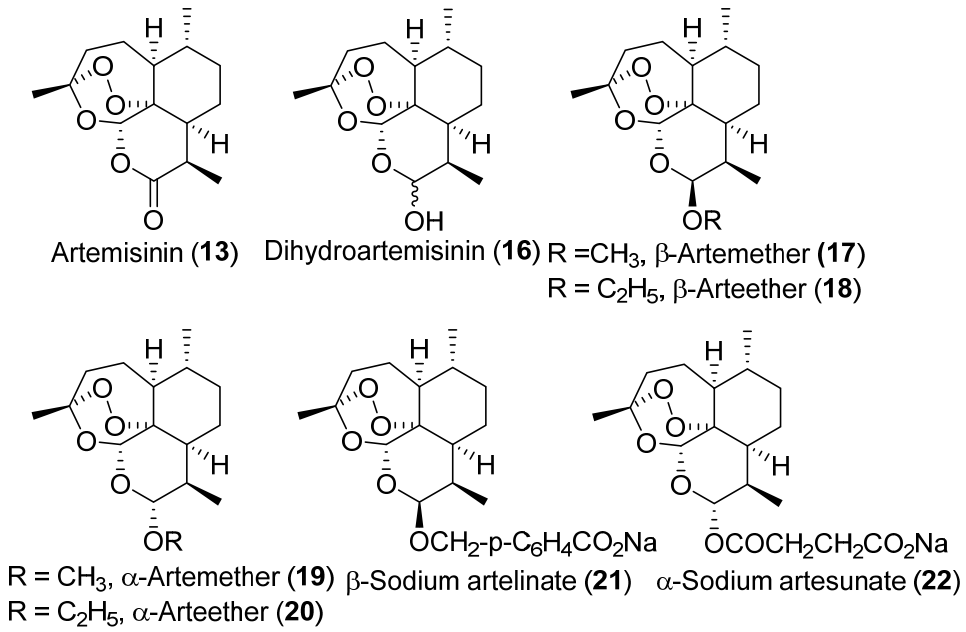


Figure 3. Artemisinin (**13**) and its oil- and water-soluble derivatives.

When the antimalarial activity of β-ether derivatives and α-ether derivatives are compared, it is observed that the former (**17** and **18**) is having higher activity than the later (**19** and **20**; Table 1).[17a] Also, β-ether derivatives (**17** and **18**) are solids in contrast to their α-derivatives (**19** and **20**) which are oily in nature, thus they can be easily purified by crystallization[17a] from the respective crude reaction mixture. The benefit of this technique is that it can be easily performed on a pilot-plant production scale without the need of expensive column chromatography; this in turn could help to lower the production costs of this life-saving antimalarial drug. Hence, we believed that a stereoselective synthesis of β-ether derivatives of (**16**) would be highly desirable considering the above indispensable points.

Table 1. Reported antimalarial activities[17a] of dihydroartemisinin (**16**) and its ether derivatives (**17–20**).

Entry	Compound	*Plasmodium falciparum* clones	
		W-2 Indochina (IC_{50} nM)	D-6 Sierra Leone (IC_{50} nM)
1	Dihydroartemisinin (**16**)	1.79	1.83
2	12β-artemether (**17**)	3.34	4.49
3	12α-artemether (**19**)	3.42	3.70
4	12β-arteether (**18**)	2.94	4.07
5	12α-arteether (**20**)	3.07	4.18

3.1.2 Present Work

Search for efficient glycosylation.

There is a great deal of structural as well as chemical reactivity similarity between the lactol, dihydroartemisinin (**16**) and the anomeric hydroxyl of pyranose sugar.[18–21] There are various methods available for efficient glycosylation such as (**A**) Fisher-Helferich method, (**B**) Koenigs-Knorr method and methods closely related to the Koenigs-Knorr which utilizes the exchange of the anomeric oxygen atom for fluorine, alkylthio or arylthio leaving group, (**C**) anomeric *O*-alkylation method and (**D**) Schmidt's trichloroacetimidate and few other methods[23] (Fig. 4). All the methods other than Schmidt's glycosidation suffers from either one or more drawbacks. Schmidt's glycosidation[22-24] is an exquisite tool for *O*-glycoside bond forming strategy which utilizes trichloroacetimidate as a glycosyl donor to afford stereoselective synthesis of glycosylated product. *O*-Glycosyl trichloroacetimidates are having a number of advantages such as, ease of formation, reactivity, high product yields as well as high levels of anomeric stereocontrol and wide applicability with various sugars having diverse protecting groups.[24a] We wished to apply Schmidt's glycosidation strategy for the stereoselective synthesis of C-12β-ether derivatives of (**16**).

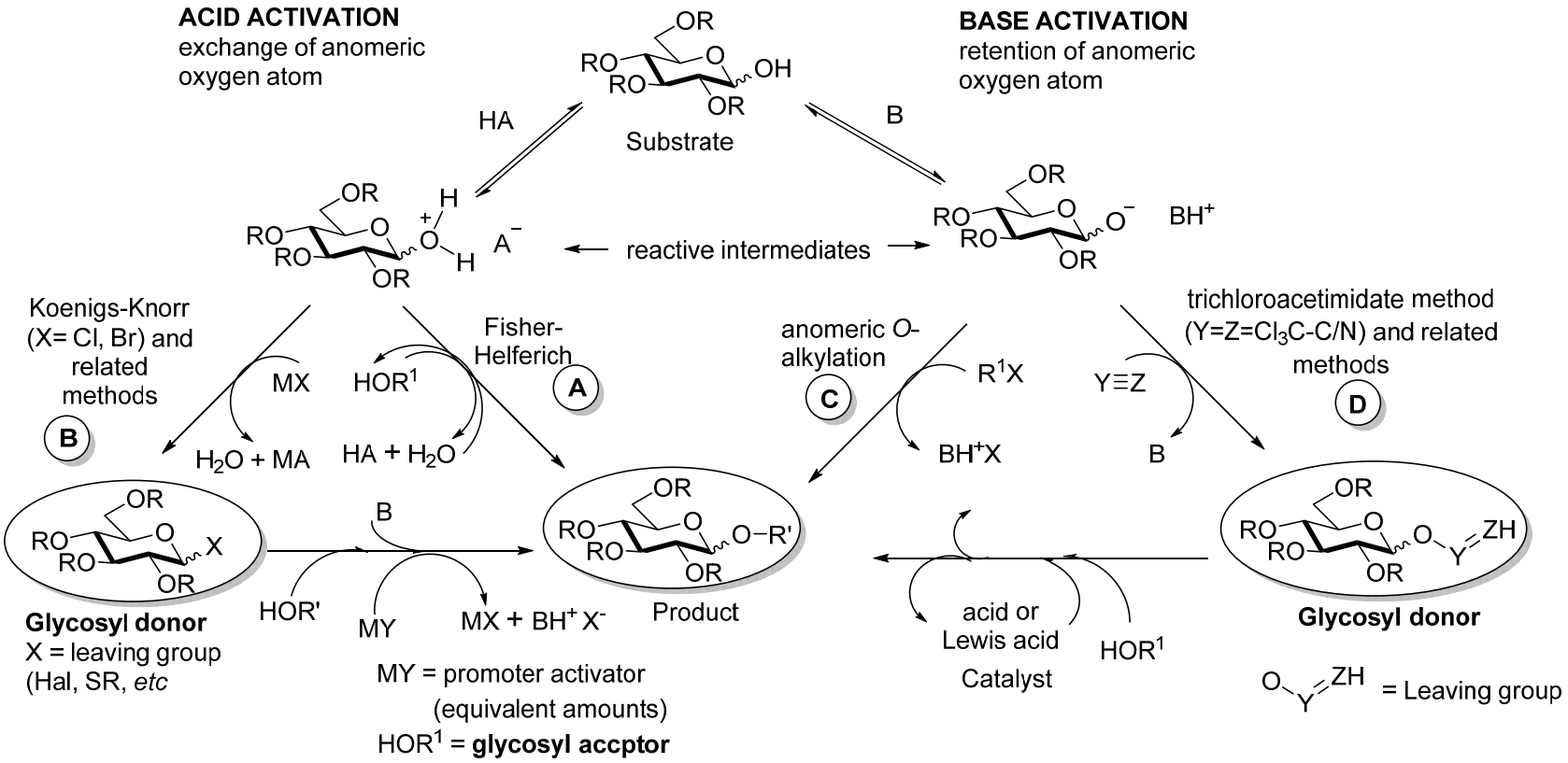


Figure 4. Various *O*-glycoside bond forming reactions.

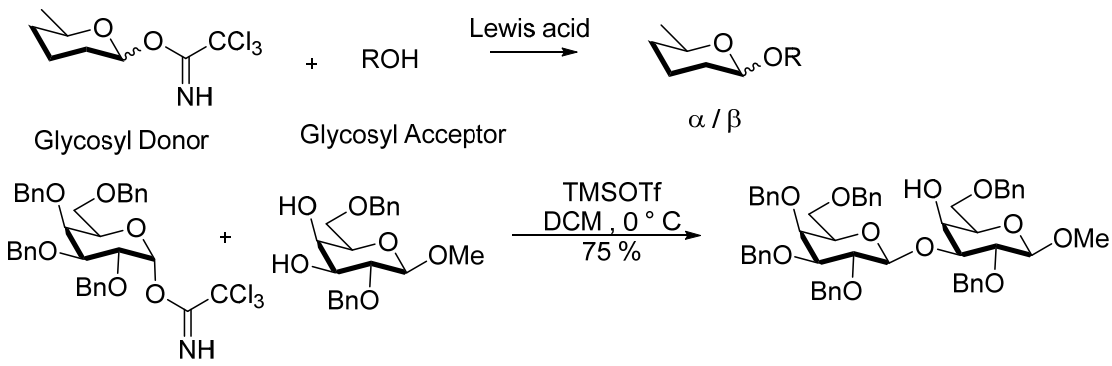
Utilization of Elegant Glycosylation; Schmidt's Trichloroacetimidate

Schmidt's trichloroacetimidate has been reported to act as glycosyl donor and in the presence of nucleophile leads to the formation of glycoside linkage depending on the condition under which it is generated α/β glycoside.

Imidates: are stable adducts, which are less sensitive to hydrolysis. With different bases (K_2CO_3, $CaCO_3$, NaH, DBU, or others) trichloroacetimidates can be isolated, often in pure form and in high yields.

β-Trichloroacetimidates (*kinetic control*) can be selectively prepared with K_2CO_3 as base.

α-Trichloroacetimidates (*thermodynamic control*) synthesized by base NaH, $CsCO_3$ or KOH with phase transfer catalyst.



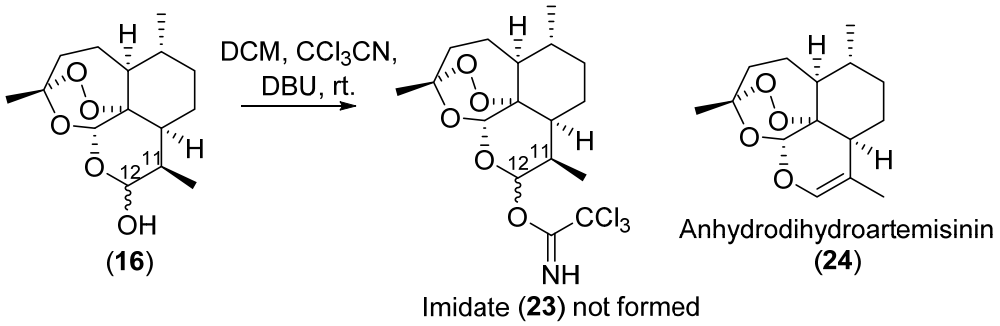
Scheme 1. Schmidt's glycosylation utilizing glycosyl donor and glycosyl acceptor.

3.1.3 Results and Discussion

Stereoselective Synthesis of C-12 Substituted Artemisinin Ether Derivatives

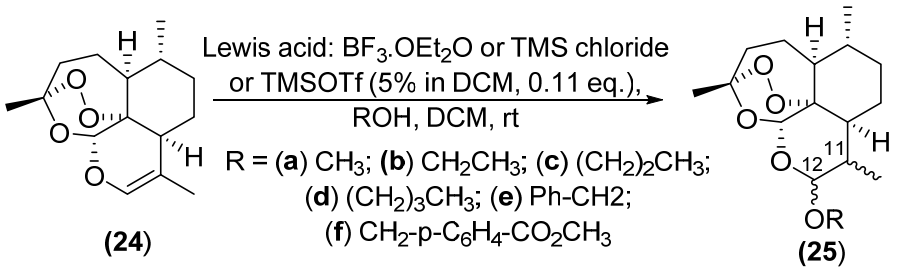
In an attempt to prepare trichloroacetimidate derivative (**23**), compound (**16**) was dissolved in CH_2Cl_2 and treated with CCl_3CN and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) at room temperature (Scheme 2). This reaction yielded a solid product (m.p. 95-97.8 °C). The ^1H and ^{13}C NMR spectra revealed formation of another product rather than the expected imidate (**23**). A peak at δ 6.19 ppm (d, J = 1.53 Hz, 1H) and two peaks at δ 135.0 and 108.1 ppm corresponding to methine and a quaternary

carbon in the ^{1}H and ^{13}C NMR spectra, respectively were observed. The HRMS (ESI) spectrum of the product contained a peak at *m/z* 289.1407 ($C_{15}H_{22}O_4Na$). These spectral data indicated that enol ether (**24**) had formed. We were expecting imidate (**23**) to be formed in the above-mentioned reaction conditions, however, we obtained instead anhydrodihydroartemisinin (an enol ether, **24**)[25] as a major product.



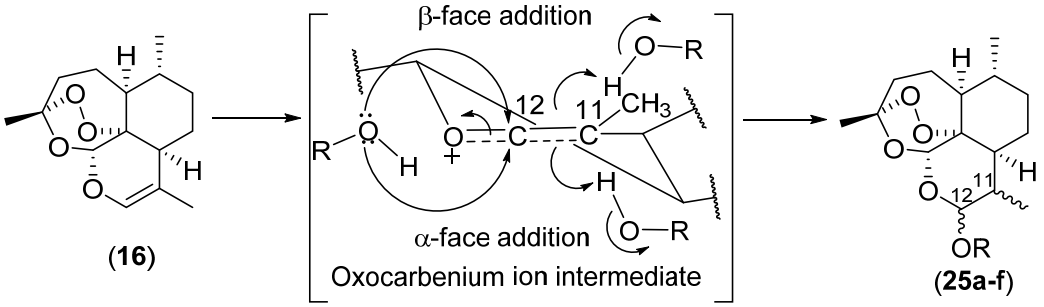
Scheme 2. Synthesis of anhydrodihydroartemisinin (**24**).

There are few reports for etherification of (**16**) using the trichloroacetimidate-based method.[19b] However, our attempt to activate (**16**) in this way resulted in elimination product to give enol ether (**24**). It is important to mention here literature reports of the formation of compound (**24**) as a by product[25a,b] in the Lewis-acid-catalyzed etherification of (**16**), however, we obtained compound (**24**) from a base-catalyzed reaction. Similar results were experienced by Ziffer *et al*.[21] earlier when he tried to form ether derivatives by triphenylphosphine hydrobromide-catalyzed electrophilic addition of alcohols to the C-11, 12 double bond of compound (**24**), however, mixtures of C-11- and C-12-epimerized products[26] were obtained. With (**24**) as a major product, we tried to explore the stereoselective addition of alcohols to the enol ether by reacting it with various Lewis acids (5% $BF_3{\cdot}Et_2O$/TMSCl/TMSOTf in CH_2Cl_2) in CH_2Cl_2 at room temperature (Scheme 3). In all cases however, (**25**) was obtained as a complex mixture of C-11- and C-12-epimerized products in different diastereomeric ratios, which could not be separated by chromatographic techniques.



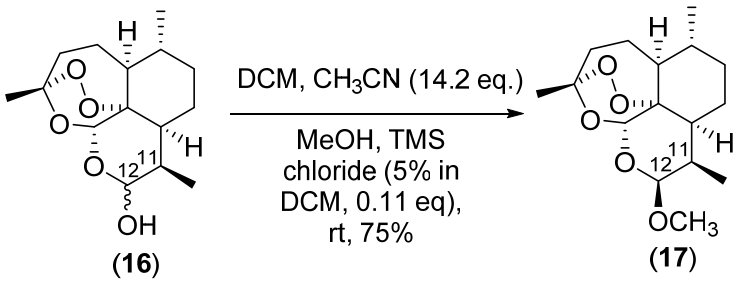
Scheme 3. Synthesis of *epi*-dihydroartemisinin ethers (**25a-f**).

A plausible mechanism for the formation of C-11- and C-12-epimerized products is described in Scheme 4. It is inferred that the lone pair of electrons of alcohol could easily attack the C- 12 position and addition of the proton at C-11 can take place from either the *re* face and/or the *si* face, thereby furnishing C-11- and C-12-epimerized ether derivatives.



Scheme 4. Plausible mechanism for formation of *epi*-dihydroartemisinin ethers (**25a-f**).

As the nitrilium-nitrile effect on stereoselective glycosylations as well as yield is well established,[27] we tried to explore the same with (**16**)**.** In an initial experiment, we studied acetal formation from compound (**16**) with MeOH in the presence of acetonitrile (14.2 equiv) in CH_2Cl_2 at room temperature (Scheme 5). The catalyst screening (Table 2) of this reaction condition revealed that TMSCl (5% in CH_2Cl_2, 0.11 equiv) furnished artemether (**17**) with the most favourable d.r. (75:16).



Scheme 5. Synthesis of β-artemether (**17**).

We could estimate the formation of β-artemether (**17**, δ 4.69 ppm, J = 3.4 Hz, 1H) and β-arteether (**17**, δ 4.80 ppm, J = 3.4 Hz, 1 H) on the basis of their respective coupling constants and chemical shift values (Fig. 5).[28] Although, there are few methods for the analysis of artemisinin and its derivatives such as, using HPLC-RI method, HPLC-ELSD and gradient HPLC-UV method.[29a-c] However there were certain limitations (adequate sample preparation/treatment, detector sensitivity, gradient elution, complex solvent system) in using the reported methods and they turned out to be complicated for analysis. This inspired us to modify the HPLC-UV method to overcome the limitations and to exploit it for its wide application for the analysis of C-12-artemisinin ethers.[29a-c] Fig. 6 describes the quantitative estimation of products β-artemether (**17**) and β-arteether (**18**) synthesized at 0 °C in acetonitrile as reaction medium. Using TMSCl as a catalyst, next we carried out temperature screening for the etherification of compound (**16**) (Table 3)

Table 2. Screening of Lewis acids: dihydroartemisinin (**16**), MeOH, Lewis acid catalyst, acetonitrile (14.2 equiv), CH_2Cl_2, RT.

Entry	**Lewis acid**	**Time (h)**	**Yield (%)[a]** **β : α**
1	BF_3OEt_2(10 mol%)	4	59 : 32
2	TMSOTf (5 % in DCM, 0.11 eq)	6	56 : 36
3	**TMSCl** (5 % in DCM, 0.11 eq)	**2**	**75 : 16**

Table 3. Optimizing the temperature conditions using acetonitrile as reaction medium.

Entry	Alcohol	Temp	Time	Yield[a]/Ratio (β:α)
1	CH_3OH	-78 ºC	-	-
2	CH_3OH	-40 ºC	-	-
3	**CH_3OH**	**0 ºC**	**3h**	**93% (5:1)**
4	CH_3OH	25 ºC	30min	90% (3:2)
5	EtOH	0 ºC	4h	89% (6:1)

[a] Overall isolated yield.

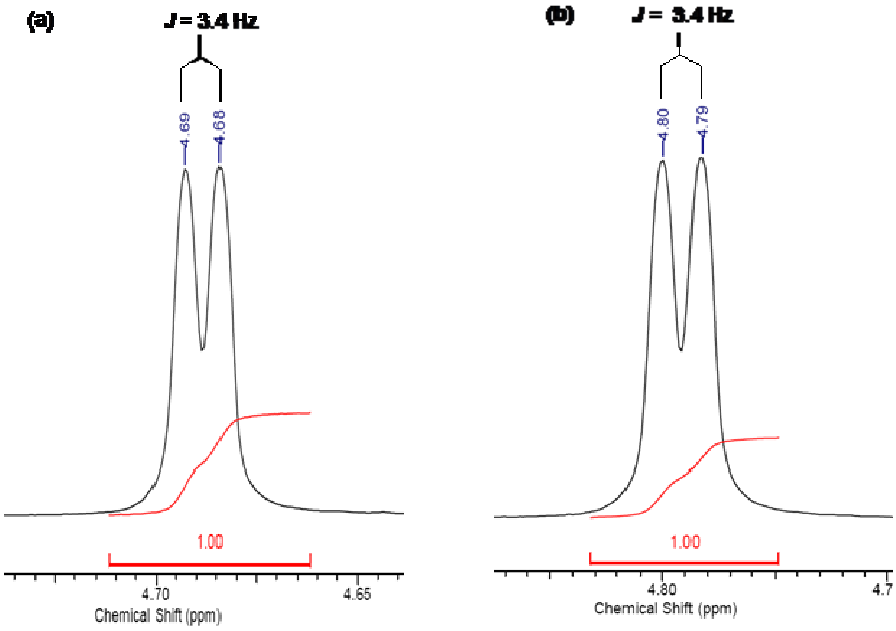
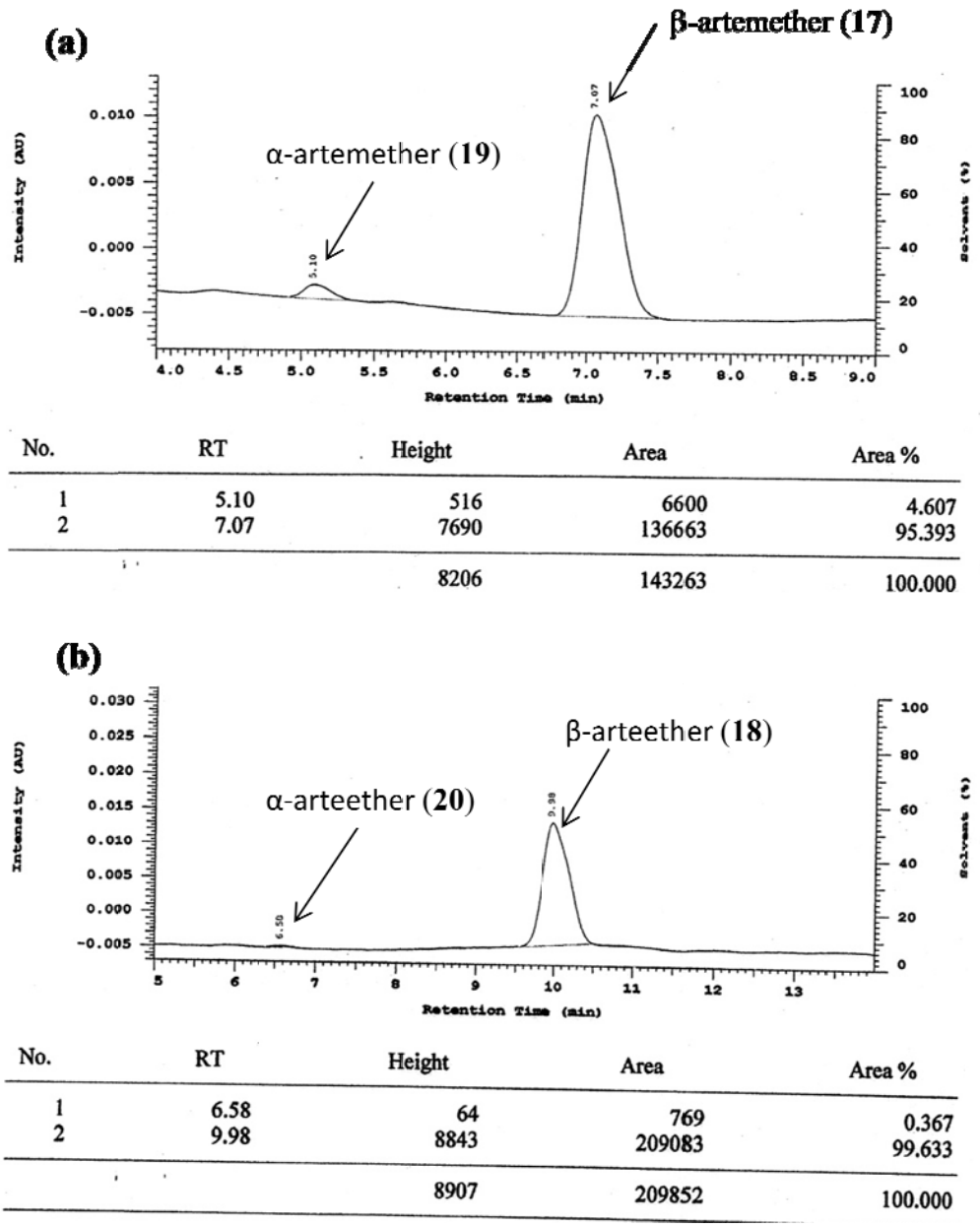


Figure 5. Coupling constant values of (a) β-artemether (**17**); (b) β-arteether (**18**).



No.	RT	Height	Area	Area %
1	5.10	516	6600	4.607
2	7.07	7690	136663	95.393
		8206	143263	100.000

No.	RT	Height	Area	Area %
1	6.58	64	769	0.367
2	9.98	8843	209083	99.633
		8907	209852	100.000

Figure 6. HPLC separation of ethers synthesized at 0 °C in acetonitrile as reaction medium: (a) artemether (**17** and **19**); (b) arteether (**18** and **20**).

We observed that synthesis of artemether (**17**) was complete in 3h at 0 ºC with a 93% yield (d.r.=5:1; Table 3, entry 3). We wished to explore the use of nitriles as reaction media (to study both steric and electronic effects; Table 4) at 0 ºC for the etherification of compound (**16**) with MeOH, therefore we performed the reaction in several nitriles and found that CH_3CN was the best as the reaction could be accomplished in 3h with 93% yield (d.r.=5:1; Table 4, entry 1). Interestingly,

trichloroacetonitrile (Table 4, entry 6) was found to be comparable to acetonitrile as a reaction medium with respect to diastereoselectivity (d.r.=5:1) however, completion of the reaction took a longer time.

Table 4. Optimizing different nitriles as reaction medium

Entry	Nitrile	Temp	Time	Yield[a]/Ratio (β:α)
1	**CH_3CN**	**0 ºC**	**3h**	**93% (5:1)**
2	EtCN	0 ºC	15h	82% (4:1)
3	BnCN	0 ºC	1d	15%[b]
4	*t*-BuCN	0-5 ºC	3d	55%[b]
5	*o*-Tolunitrile	0 ºC	3d	60%[b]
6	**CCl_3CN**	**0 ºC**	**4h**	**90% (5:1)**

[a] Overall isolated yield. [b] Ratio not determined.

After exhaustive screening of nitrile, temperature, catalyst; using the optimized reaction conditions, that is, 0 ºC with CH_3CN as solvent and TMSCl as Lewis acid catalyst, (henceforth termed as method I) etherification of compound (**16**) with various alcohols was achieved (Table 5). Overall, artemether (**17**) arteether (**18**) (Table 5, entries 1 and 2, respectively) were obtained in good yields and good diastereomeric ratios. It was unfortunate that, artelinic acid ester (Table 5, entry 10) was obtained in only 50% yield (d.r.=10:1) after 12h. Good yields and diastereoselectivities of the β-ether derivatives were witnessed using method-I, however our intrusiveness and inclination to further advance the reaction condition, provoked us to explore more optimal reaction conditions, such as reactions at room temperature and short reaction times with high yield, as well as high diastereomeric ratio. Since the solubility of compound **(16)** in CH_2Cl_2 at room temperature and at low temperatures, is higher than in nitriles, we re-examined the role of CH_2Cl_2 and CH_3CN/CCl_3CN in various

combinations as reaction media, and in different temperature conditions (Table 6). From the observations, we were elated to see that when the reaction was carried out at room temperature with CH_2Cl_2 and CCl_3CN (6:1), artemether (**17**) was formed in 93% yield with a d.r. of 10:1 and the reaction was complete in short time within 20 min (Table 6, entry 14). It is remarkable to mention here that when CH_2Cl_2 alone was used as a reaction medium (Table 6, entry 1), no reaction occurred, which clearly signifies the effect of the nitrile on the course of the reaction.

With one more condition built *viz.* CH_2Cl_2/CCl_3CN (6:1) as the solvent, room temperature, with TMSCl as a catalyst (henceforth called as method-II, Table 7) we aspired to establish these conditions by carrying out etherification with various alcohols, and the results are summarized in Table 7. The antimalarial drugs, pure (**17**) and (**18**) were obtained in 88% isolated yields, with a d.r. of 10:1 and 11:1, respectively[29d] (Table 7, entries 1 and 2). Yields and diastereoselectivity trends were not convincing in the case of methyl 4-hydroxymethylbenzoate (artelinic acid ester; Table 7, entry 10), the reaction was sluggish, resulting in a low yield of the β - derivative and low d.r. (70% and 6.5:1, respectively).

We assumed that stereoselective synthesis of β-ether derivatives of (**16**) proceeds via a SN^2 mechanism. A plausible mechanism is shown in Scheme 6. Mechanistically, trichloroacetonitrile is more electron-withdrawing compared to acetonitrile. The hydroxyl group at C-12 in compound (**16**) in solution exists in both α and β-epimers, which undergo slow equilibration.[30] (**16**) behaves as a glycosyl donor and the pyran oxygen atom forms a hydrogen bond with the alcohol (glycosyl acceptor). The Lewis acid, TMSCl, and trichloroacetonitrile forms a complex with the anomeric hydroxyl group placed in an equatorial position, hence α-face addition of the alcohol becomes sterically disfavored. Thus, the lone pair of electrons on the glycosyl acceptor attacks the C-12 position from the β-face resulting in the stereoselective formation of β-ether derivatives of (**16**).[31] The fast reaction rate in trichloroacetonitrile at room temperature could be attributed to the presence of the electron- withdrawing chloro groups.

Table 5. Screening of various alcohols using acetonitrile as reaction medium, at 0 ºC.

Entry	Alcohol	Time	Product yield (% by HPLC)		**(Compd. Code) Yield %[a]**
			12β	12α	
1	**CH_3OH**	**3h**	**95.4**	**4.6**	**(17) 93**
2	**EtOH**	**4h**	**99.6**	**0.37**	**(18) 89**
3	*n*-PrOH	4h	87.6	12.4	(**26**) 96
4	*n*-BuOH	4h	92.9	7.1	(**27**) 88
5	*n*-Pentyl alcohol	13h	89.1	10.9	(**28**) 83
6	Cyclopentyl alcohol	13h	n.d.	n.d.	(**29**) 49
7	*n*-Hexyl alcohol	13h	84.9	15.1	(**30**) 87
8	Cyclohexyl alcohol	1d	83.4	16.6	(**31**) 45
9	Benzyl alcohol	12h	88.6	11.4	(**32**) 70
10	*p*-CH_3CO_2-C_6H_4-CH_2OH	12h	90.2	9.8	(**33**) 50

[a] Isolated yield. n.d.: Not determined.

Table 6. Optimization of reaction conditions for the synthesis of artemether **(16)** using combination of CH_2Cl_2 and a nitrile.

Entry	**Solvent system (x:y)**	**Temp.**	**Time**	**Yield (%)**	**Ratio (β:α)**
1	DCM	0 ºC	-	-	-
2	DCM:CH_3CN (24:1)	0 ºC	16h	10% completion	-

Cont.

Entry	Solvent system (x:y)	Temp.	Time	Yield (%)	Ratio (β:α)
3	DCM:CH_3CN (1:1)	0 ºC	16h	30% completion	-
4	DCM:CH_3CN (1:3)	0 ºC	30min	80	-
5	DCM:CH_3CN (1:24)	0 ºC	4h	72	5:1[a]
6	DCM:CCl_3CN (24:1)	rt	3h	75	5:1[a]
7	DCM:CCl_3CN (6:1)	0-5 ºC to rt	4h	80	5:1[a]
8	DCM:CCl_3CN (6:1)	Addition at 0-5 ºC then immediately brought to rt	30 min	89	5:1[a]
9	DCM:CCl_3CN (6:1)	0-5 ºC for 10 min then at rt	45 min	88	4:1[a]
10	DCM:CCl_3CN (6:1)	Reflux	30 min	72	2:1[a]
11	DCM:CCl_3CN (6:1)	10 ºC	5h	81	4:1[a]
12	DCM:CCl_3CN (6:1)	16 ºC	3.5h	83	5:1[a]
13	DCM:CCl_3CN (6:1)	20 ºC	2.5h	89	7:1[a]
14	**DCM:CCl_3CN (6:1)**	**rt**	**20**	**93**	**10:1[b]**

[a] Overall isolated yield. [b] Ratio not determined.

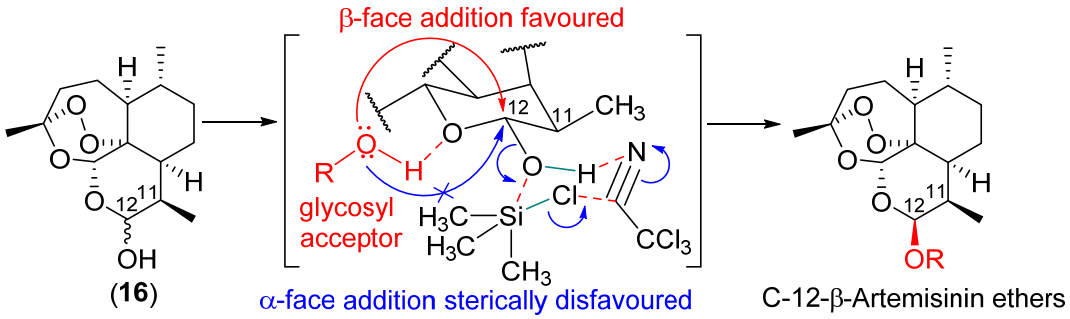
In the case of acetonitrile as solvent at 0 ºC (Table 5), it is presumed that the reaction follows the same mechanism as that if trichloroacetonitrile is used. However, the longer reaction time in acetonitrile compared to trichloroacetonitrile at room

temperature might be due to the absence of electron withdrawing groups. The high diastereoselectivity in the case of acetonitrile at 0 ºC compared to trichloroacetonitrile at room temperature is presumably due to the low temperature.[22b,32]

Table 7. Stereoselective Synthesis of Various C-12β-substituted Ether Derivatives Using DCM: CCl_3CN (6:1) as Solvent System.

Entry	ROH	Time (min)	Product yield (% by HPLC)		Isolated yield (%)
			12β	**12α**	
1	Methanol	20	90.8	9.2	(**17**) 88
2	Ethanol	20	91.7	8.33	(**18**) 88
3	*n*-Propyl alcohol	20	94.5	5.5	(**26**) 90
4	*n*-Butyl alcohol	20	97.7	2.3	(**27**) 91
5	*n*-Pentyl alcohol	30	95.9	4.1	(**28**) 90
6	*n*-Hexyl alcohol	30	n.d.	n.d.	(**30**) 80
7	Cyclohexyl alcohol	30	n.d.	n.d.	(**31**) 56
8	*p*-CH_3CO_2-C_6H_4-CH_2OH	60	86.8	13.2	(**33**) 70

n.d.: Not determined.



Scheme 6. Plausible mechanism for diastereofacial addition of alcohols to dihydroartemisinin (**16**).

In short Fig. 7 describes our entire present work on diastereoselective synthesis of β-artemisinin ether derivatives.

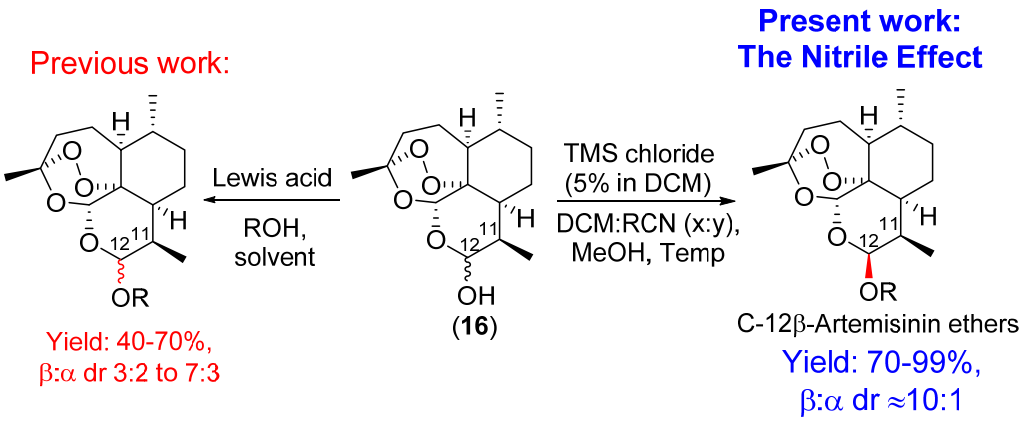


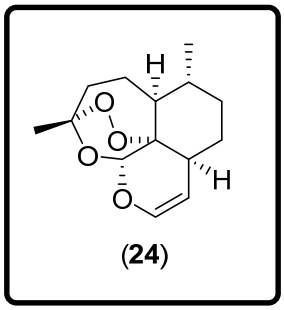
Figure 7. Diastereoselective synthesis of β-artemisinin ether derivatives.[33]

3.1.4 Conclusions

In conclusion, we have established two methods for a stereoselective synthesis of C-12β-ether derivatives of dihydroartemisinin (**16**) by performing the reaction either in acetonitrile or in a CH_2Cl_2/CCl_3CN mixture (6:1) at 0 °C or room temperature, respectively, in high yield and high diastereoselectivity. The mechanism for the diastereofacial addition of a glycosyl acceptor to (**16**) in CCl_3CN with TMSCl as activator has been explained. We expect that our stereoselective synthesis will find utility in the pharmaceutical industry to make this life-saving drug available at an affordable price to a large population affected with malaria.

3.1.5 Experimental

Procedure for the synthesis of anhydrodihydroartemisinin (24): To a stirred solution of dihydroartemisinin (**16**) (1.0 g, 3.5 mmol), in dry DCM (30 ml) was added DBU (0.66 ml, 4.45 mmol, 1.3 eq.) and CCl_3CN (4.4 ml, 43.8 mmol, 12.5 eq.) and stirred at rt till the completion of reaction (TLC). The reaction mixture was evaporated to dryness under reduced pressureand subjected to flash chromatography using RediSep™ (silica gel, 12g) with a gradient of 5-10% EtOAc-pet ether to yield pure product (**24**) as a colorless solid, 75% yield). $C_{15}H_{22}O_4$, Colorless solid mp 95-97 ºC [lit.[30] 96-98 ºC]; R_f 0.62 (EtOAc-petroleum ether,1:4); $[\alpha]_D^{25}$ = +157.33 (c = 1.07, $CHCl_3$); IR ($CHCl_3$) υ_{max}3021, 2929, 2868, 1687, 1449, 1215, 1002, 763cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.19 (d, J = 1.53 Hz, 1H), 5.54 (s, 1H), 2.44-2.37 (m, 1H), 2.08-2.02 (m, 2H), 1.95-1.89 (m, 1H), 1.73-1.69 (m, 1H), 1.67-1.64 (m, 1H), 1.59-1.55 (m, 4H), 1.48-1.41 (m, 5H), 1.21-1.15 (m, 1H), 1.14-1. 06 (m, 1H), 0.98 (d, J = 6.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 135.0, 108.1, 104.5, 89.7, 79.0, 51.5, 44.5, 37.5, 36.2, 34.1, 30.0, 25.9, 24.4, 20.3, 16.2; ESI-MS: 289.14 $(M+Na)^+$; HRMS (ESI): *m/z* calcd for $C_{15}H_{22}O_4Na$ 289.1410, found 289.1407.

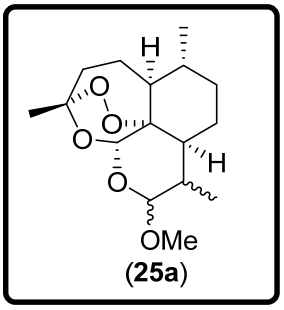


(**24**)

Synthesis of epimers (25a-f): To a stirred solution of anhydrodihydroartemisinin (**24**) (100 mg, 0.38 mmol) in dry DCM (3.0 mL) was added CCl_3CN (0.5 mL, 5.0 mmol, 14.2 eq.), appropriate alcohol (0.5 mL) and CTMS (5% in DCM, 1.0 mL, 0.039 mmol, 0.11 eq.) were added and the reaction mixture was stirred at room temperature. After completion of the reaction (TLC), the reaction mixture was filtered over celite and the filtrate evaporated in vaccuo. Purification of the residue by flash chromatography using RediSep™ (silica gel, 12g) using a gradient of 5-10% EtOAc-pet ether yielded the mixture of epimers (**25a-f**), respectively. The spectral data of major pair of diastereomers (less polar) are reported.

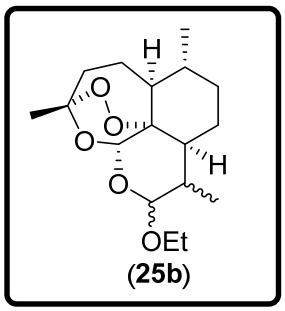
C-12-methyl ether (25a) [NMR chemical shifts of the major epimers]**:** $C_{16}H_{26}O_5$, Colorless semi-solid; R_f 0.5 (EtOAc- petroleum ether, 1:4); ^{1}H NMR (200 MHz, $CDCl_3$) δ 5.45 (s, 1H), 4.87 (d, J = 4.6 Hz, 1H), 3.50 (s, 3H), 2.46-2.24 (m, 1H), 2.08-

2.05 (m, 1H), 2.01-1.85 (m, 2H), 1.79-1.75 (m. 1H), 1.69-1.61 (m, 3H), 1.57-1.51 (m, 2H), 1.45-1.40 (m, 6H), 1.33-1.25 (m, 3H), 1.22-1.19 (m, 4H), 0.96-0.89 (m, 6H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 104.2, 104.1, 103.4, 103.1, 88.8, 87.8, 81.5, 81. 1, 56.1, 56.0, 52.5, 51.9, 46.4, 44.5, 39.6, 37.4, 37.2, 36.5, 36.4, 34.6, 34.4, 31.6, 30.9, 29.7, 26.2, 26.0, 24.7, 24.5, 20.4, 20.1, 19.6, 13.0; HRMS (ESI): *m/z* calcd for $C_{16}H_{26}O_5Na$ 321.1672, found 321.1675.



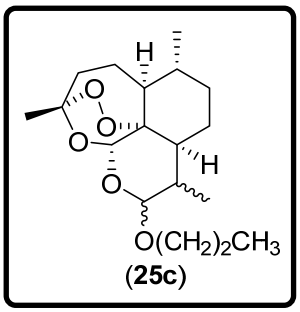
(25a)

C-12-ethyl ether (25b) [NMR chemical shifts of the major epimers]**:** $C_{17}H_{28}O_5$, Colorless semi-solid; R_f 0.30 (EtOAc-petroleum ether, 1:9); ^{1}H NMR (200 MHz, $CDCl_3$) δ 5.46 (s, 1H), 5.00 (d, J = 5.31 Hz, 1H), 3.92 (m, 1H), 3.57 (m, 1H), 2.31 (m, 1H), 2.39-2.33 (m, 1H), 2.07-1.93 (m, 1H), 1.88-0.76 (m, 1H), 1.68-1.51 (m, 4H), 1.42 (s, 3H), 1.30-1.15 (m, 7H), 0.96-0.92 (m, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 104.1, 103.0, 102.4, 101.7, 89.2, 87.9, 81.7, 81.2, 77.7, 77.0, 76.4, 64.2, 63.8, 52.6, 51.8, 46.6, 44.5, 40.0, 37.5, 37.3, 36.5, 34.7, 34.4, 31.6, 30.9, 26.2, 26.0, 24.7, 24.5, 20.4, 20.1, 19.5, 15.2, 13.0; ESI-MS: 335.06 $(M+Na)^+$; HRMS (ESI): *m/z* calcd for $C_{17}H_{28}O_5Na$ 335.1829, found 335.1832.



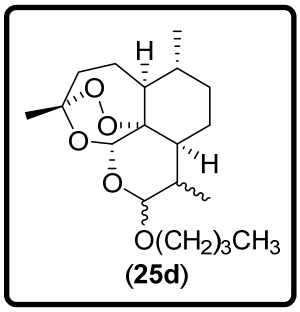
(25b)

C-12-^{n}propyl ether (25c) [NMR chemical shifts of the major epimers]**:** $C_{18}H_{30}O_5$, Colorless oil; R_f 0.21 (EtOAc-petroleum ether, 5:95); ^{1}H NMR (200 MHz, $CDCl_3$) δ 5.45 (s, 1H), 4.97 (d, J = 4.8 Hz, 1H), 3.89-3.70 (m, 1H), 3.51-3.32 (m, 1H), 2.62 (m, 1H), 2.45-2.30 (m, 1H), 2.09-1.98 (m, 1H), 1.95-1.76 (m, 3H), 1.67-1.49 (m, 5H), 1.44 (m, 4H), 1.30-1.21 (m, 2H), 0.97-0.89 (m, 9H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 104.0, 103.0, 102.8, 101.9, 98.8, 92.0, 89.0, 87.9, 81.6, 81.2, 71.1, 70.4, 70.1, 52.6, 51.9, 46.5, 44.5, 39.7, 38.9, 37.5, 37.3, 36.5, 36.4, 34.7, 34.5, 31.6, 31.0, 26.2, 26.0, 25.9, 24.7, 24.5, 23.0, 22.9, 22.8, 20.4, 20.1, 19.6, 13.0, 10.9, 10.7; HRMS (ESI): *m/z* calcd for $C_{18}H_{30}O_5Na$ 349.1985, found 349.1987.



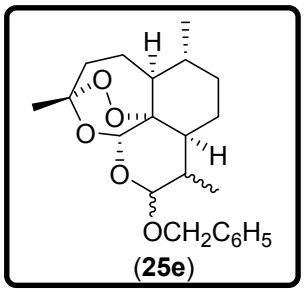
(25c)

C-12-^{n}butyl ether (25d) [NMR chemical shifts of the major epimers]**:** $C_{19}H_{32}O_5$, Colorless oil; R_f 0.21 (EtOAc-petroleum ether, 1:19); ^{1}H NMR (200 MHz, $CDCl_3$) δ 5.45 (s, 1H), 4.97 (d, J = 4.9 Hz, 1H), 3.93-3.82 (m, 1H), 3.54-3.43 (m, 1H), 2.39-2.23 (m, 1H), 2.08-1.86 (m, 3H), 1.79-1.69 (m, 1H), 1.67-1.51 (m, 7H), 1.48-1.46 (m, 1H), 1.44 (m, 2H), 1.42-1.41 (m, 4H) 1.38-1.36 (m, 2H), 1.35-1.33 (m, 1H), 1.30-1.25 (m, 2H), 1.19 (d, J= 7.2 Hz, 3H), 0.96-0.88 (m, 9H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 104.0, 103.0, 102.8, 102.0, 89.0, 87.9, 81.6, 81.2, 68.6, 68.2, 52.6, 51.9, 46.5, 44.5, 39.8, 37.5, 37.3, 36.5, 34.7, 34.5, 31.8, 31.6, 30.9, 26.2, 26.0, 24.7, 24.4, 20.4, 20.1, 19.5, 19.4, 14.0, 13.0; ESI-MS: 363.29 $(M+Na)^+$; HRMS (ESI): *m/z* calcd for $C_{19}H_{32}O_5Na$ 363.2142, found 363.2135.



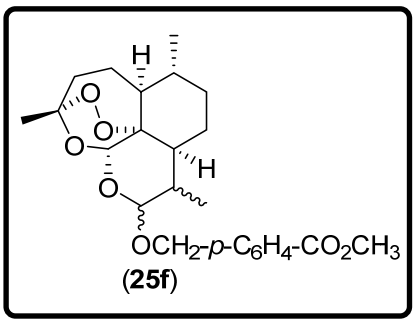
(25d)

C-12-benzyl ether (25e) [NMR chemical shifts of the major epimers]**:** $C_{22}H_{30}O_5$, Colorless oil; R_f 0.25 (EtOAc-petroleum ether, 1:19); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.32 (m, 5H), 5.47 (s, 1H) 4.92 (d, J = 3.5 Hz, 1H), 4.91 (d, J = 12.4 Hz, 1H), 4.52 (d, J = 12.4 Hz, 1H), 2.68 (m, 1H), 2.46-2.31 (m, 1H), 2.10-1.78 (m, 5H), 1.68-1.58 (m, 2H), 1.55-1.52 (m, 1H), 1.46-1.44 (m, 4H), 1.31-1.21 (m, 4H), 0.97-0.93 (m, 6H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 138.4, 128.3, 127.4, 127.2, 104.2, 103.1, 102.2, 101.5, 89.1, 88.1, 81.7, 81.2, 70.2, 69.8, 52.6, 51.9, 46.5, 44.4, 39.7, 37.4, 36.4, 34.6, 31.0, 29.7, 26.2, 24.7, 24.5, 20.4, 19.6, 13.1; ESI-MS: 397.16 $(M+Na)^+$; HRMS: *m/z* calcd. For $C_{22}H_{30}O_5Na$ 397.1985, found 397.1982.



(25e)

Methyl *p*-[(12-dihydroartemisinoxy)methyl] benzoate (25f) [NMR chemical shifts of the major epimers]**:** $C_{24}H_{32}O_7$, Colorless oil; R_f 0.34 (EtOAc-petroleum ether, 1:4); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 (d, J = 8.2 Hz, 1H), 7.38 (d, J = 2.0 Hz, 1H), 5.47 (s, 1H), 4.96 (d, J = 13.1 Hz, 1H), 4.92 (d, J = 3.4 Hz, 1H), 4.58 (d, J = 13.1 Hz, 1H), 3.91 (s, 3H), 2.69 (m, 1H), 2.41-2.35 (m, 1H), 2.06-2.02 (m, 1H), 1.91-1.85 (m, 1H), 1.83-1.80 (m, 2H), 1.65-1.61 (m, 1H), 1.53-1.43 (m, 6H), 1.34-1.24 (m, 4H), 0.97 (d, J = 7.3 Hz,



(25f)

3H), 0.95 (d, J = 6.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.0, 143.7, 143.4, 129.7, 129.2, 127.3, 126.8, 104.2, 103.2, 102.4, 101.6, 89.2, 88.1, 81.6, 81.1, 77.4, 77.2, 77.0, 76.7, 69.5, 69.2, 52.5, 52.1, 51.8, 46.5, 44.3, 39.7, 37.4, 37.3, 36.5, 36.4, 34.6, 34.4, 31.6, 30.9, 26.2, 26.0, 24.7, 24.5, 20.3, 20.1, 19.5, 13.1; ESI-MS: 455.13 $(M+Na)^+$; HRMS (ESI): *m/z* calcd for $C_{24}H_{32}O_7Na$ 455.2040, found 455.2043.

General procedures for the synthesis of artemisinin ethers:

Method-I:

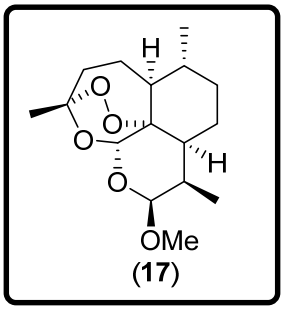
Dihydroartemisinin (**16**) (50 mg, 0.18 mmol) was dissolved in dry acetonitrile (4.0 mL) at rt and the solution cooled to 0 ^oC, appropriate alcohol (0.25 mL) and CTMS (2.5-3.0 μL, 0.0198 mmol, 0.11 eq.) were added and the reaction mixture was stirred at 0 ^oC. After completion of the reaction (TLC), the reaction mixture was filtered over celite and the filtrate evaporated in vaccuo. Purification of the residue by flash chromatography using RediSep™ (silica gel, 12g) and a gradient of 5-10% EtOAc-pet ether yielded the pure products.

Method-II:

To a stirred solution of dihydroartemisinin (**16**) (100 mg, 0.35 mmol) in dry DCM (3.0 mL), CCl_3CN (0.5 mL, 5.0 mmol, 14.2 eq.), appropriate alcohol (0.5 mL) and CTMS (5% in DCM, 1.0 mL, 0.039 mmol, 0.11 eq.) were added and the reaction mixture was stirred at room temperature. After completion of the reaction (TLC), the reaction mixture was filtered over celite and the filtrate evaporated in vaccuo. Purification of the residue by flash chromatography using RediSep™ (silica gel, 12g) and a gradient of 5-10% EtOAc-pet ether furnished the pure products.

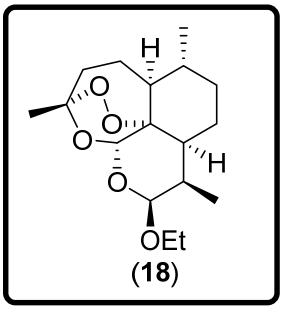
Corresponding C-12α ether derivatives (**19, 20, 26**α, **33**α) were synthesized following literature procedure [17] for comparison of their spectral data and for HPLC.

C-12β-methyl ether (17): $C_{16}H_{26}O_5$, Colorless solid, mp 87-89 ºC; R_f 0.5 (EtOAc-petroleum ether, 1:4); $[\alpha]_D^{26}$ = +156.09 (c = 1.26, $CHCl_3$); IR ($CHCl_3$) υ_{max} 2928, 2865, 1378, 1217, 1045, 1024, 762 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.39 (s, 1H), 4.69 (d, J = 3.4 Hz, 1H), 3.43 (s, 3H), 2.63 (m, 1H), 2.37 (m, 1H), 2.07-2.01 (m, 1H), 1.88 (m, 1H), 1.80-1.73 (m, 2H), 1.66-1.60 (m, 1H), 1.55-1.48 (m, 1H), 1.47-1.42 (m, 4H), 1.38-1.31 (m, 1H), 1.27-1.23 (m, 2H), 0.96 (d, J = 6.4 Hz, 3H), 0.91 (d, J = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 104.1, 103.4, 87.8, 81.1, 55.9, 52.6, 44.5, 37.4, 36.4, 34.6, 30.9, 26.2, 24.7, 24.5, 20.3, 12.9; ESI-MS: 321.05 $(M+Na)^+$; HRMS (ESI): *m/z* calcd for $C_{16}H_{26}O_5Na$ 321.1672, found 321.1673.



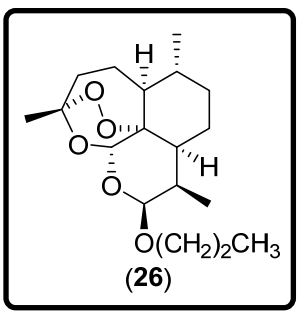
(**17**)

C-12β-ethyl ether (18): $C_{17}H_{28}O_5$, Colorless solid, mp 81-83 ºC [lit.[17] 80-82 ºC]; R_f 0.53 (EtOAc-petroleum ether, 1:4); $[\alpha]_D^{26}$ = +151.8 (c = 0.91, $CHCl_3$) [reported [17] $[\alpha]_D^{26}$ = +154.5 (c =1.0, $CHCl_3$)]; IR ($CHCl_3$) υ_{max} 2927, 2884, 1378, 1217, 1024, 875, 767cm^{-1}; ^1H NMR(400 MHz, $CDCl_3$) δ 5.41 (s, 1H), 4.80 (d, J = 3.4 Hz, 1H), 3.90-3.83 (m, 1H), 3.50-3.43 (m, 1H), 2.61 (m, 1H), 2.41-2.33 (m, 1H), 2.06-2.00 (m, 1H), 1.91-1.85 (m, 1H), 1.83-1.71 (m, 2H), 1.66-1.60 (m, 2H), 1.53-1.42 (m, 5H), 1.27-1.25 (m, 2H), 1.18 (t, J = 7.1 Hz, 3H), 0.95 (d, J = 6.4 Hz, 3H), 0.90 (d, J = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 104.1, 103.4, 87.8, 81.1, 63.8, 52.6, 44.5, 37.4, 36.5, 34.7, 30.9, 26.2, 24.7, 24.5, 20.4, 15.2, 13.0; ESI-MS: 335.13 $(M+Na)^+$; HRMS (ESI): *m/z* calcd for $C_{17}H_{28}O_5Na$ 335.1829, found 335.1827.



(**18**)

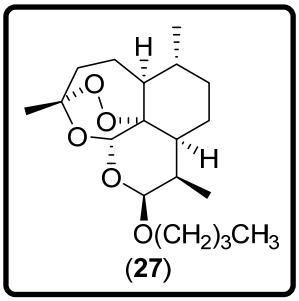
C-12β-^{n}propyl ether (26): $C_{18}H_{30}O_5$, Colorless oil; R_f 0.53 (EtOAc-petroleum ether, 1:4); $[\alpha]_D^{26}$ = +153.51 (c = 1.21, $CHCl_3$); IR ($CHCl_3$) υ_{max} 2954, 2930, 2874, 1218, 1105, 1002, 1018, 763 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 5.40 (s, 1H), 4.79 (d, J = 3.3 Hz, 1H), 3.85-3.73 (m, 1H), 3.40-3.29 (m, 1H), 2.62 (m, 1H), 2.45-2.30 (m, 1H), 2.09-1.98 (m, 1H), 1.95-1.76 (m, 3H), 1.67-1.49 (m, 5H), 1.44 (m, 4H), 1.30-1.21 (m, 2H), 0.97-0.89 (m, 9H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 104.0,



(**26**)

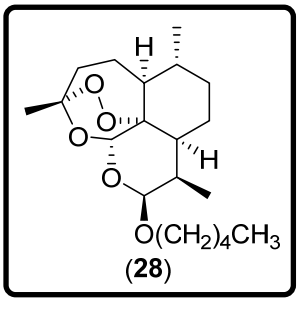
101.9, 87.9, 81.2, 70.1, 52.6, 44.5, 37.5, 36.5, 34.7, 31.0, 26.2, 24.7, 24.5, 23.0, 20.4, 13.0, 10.9; ESI-MS: 349.06 $(M+Na)^+$; HRMS (ESI): *m/z* calcd for $C_{18}H_{30}O_5Na$ 349.1985, found 349.1987.

C-12β-^{n}butyl ether (27): $C_{19}H_{32}O_5$, Colorless oil; R_f 0.61 (EtOAc-petroleum ether, 1:4); $[\alpha]_D^{26}$ = +143.1 (c = 0.94, $CHCl_3$); IR ($CHCl_3$) υ_{max} 2951, 2873, 1374, 1218, 1023, 764 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 5.39 (s, 1H), 4.78 (d, *J* = 3.3 Hz, 1H), 3.90-3.78 (m, 1H), 3.42-3.31 (m, 1H), 2.61 (m, 1H), 2.45-2.30 (m, 1H), 2.09-1.98 (m, 1H), 1.95-1.85 (m, 1H), 1.81-1.73 (m, 1H), 1.69-1.58 (m, 3H), 1.55-1.48 (m, 3H), 1.44-1.42 (m, 4H) 1.39-1.34 (m, 2H), 1.31-1.19 (m, 2H), 0.97-0.88 (m, 9H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 104.0, 102.0, 87.9, 81.2, 68.2, 52.6, 44.5, 37.5, 36.5, 34.7, 31.9, 31.0, 26.2, 24.7, 24.5, 20.4, 19.5, 13.9, 13.0; ESI-MS: 363.20 $(M+Na)^+$; HRMS (ESI): *m/z* calcd for $C_{19}H_{32}O_5Na$ 363.2142, found 363.2135.



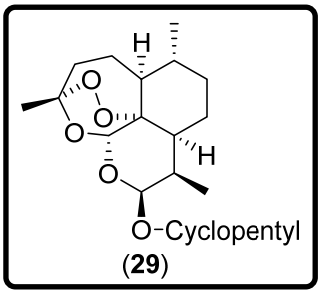
(**27**)

C-12β-^{n}pentyl ether (28): $C_{20}H_{34}O_5$, Colorless oil; R_f 0.66 (EtOAc-petroleum ether, 1:4); $[\alpha]_D^{26}$ = +137.65 (c = 1.07, $CHCl_3$); IR ($CHCl_3$) υ_{max} 2930, 2866, 1374, 1218, 1008, 763 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 5.40 (s, 1H), 4.78 (d, *J* = 3.3 Hz, 1H), 3.88-3.77 (m, 1H), 3.42-3.30 (m, 1H), 2.61 (m, 1H), 2.45-2.30 (m, 1H), 2.09-1.98 (m, 1H), 1.93-1.80 (m, 2H), 1.78-1.74 (m, 1H), 1.71-1.64 (m, 1H), 1.63-1.48 (m, 4H), 1.44-1.42 (m, 4H) 1.35-1.24 (m, 6H), 0.97-0.88 (m, 9H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 104.0, 102.0, 87.9, 81.2, 68.5, 52.6, 44.5, 37.5, 36.5, 34.7, 31.0, 29.4, 28.5, 26.2, 24.7, 24.5, 22.4, 20.4, 14.1, 13.0; ESI-MS: 377.20 $(M+Na)^+$; HRMS (ESI): *m/z* calcd for $C_{20}H_{34}O_5Na$ 377.2298, found 377.2295.



(**28**)

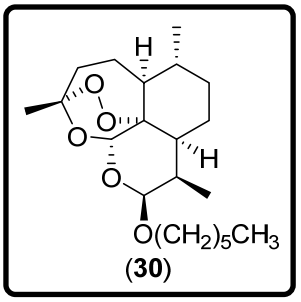
C-12β-cyclopentyl ether (29): $C_{20}H_{32}O_5$, Colorless solid, mp 55.2-57.2 ºC; R_f 0.60 (EtOAc-petroleum ether, 1:4); $[\alpha]_D^{26}$ = +150.0 (c = 1.13, $CHCl_3$); IR ($CHCl_3$) υmax 2955, 2870, 1450, 1217, 999, 763 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 5.42 (s, 1H), 4.84 (d, *J* = 3.5 Hz, 1H), 4.31 (m, 1H), 2.60 (m, 1H), 2.45-2.29 (m, 1H), 2.09-1.98



(**29**)

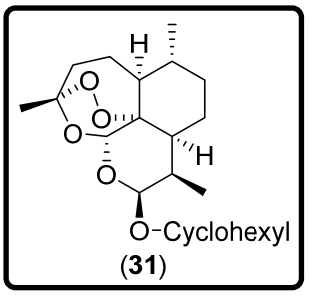
(m, 1H), 1.95-1.79 (m, 2H), 1.76-1.52 (m, 14H), 1.44-1.42 (m, 4H), 0.95 (d, J = 6.0 Hz, 3H), 0.86 (d, J = 7.3 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 104.0, 100.2, 88.1, 81.2, 78.6, 52.7, 44.6, 37.5, 36.5, 34.8, 33.6, 31.6, 30.7, 26.3, 24.7, 24.4, 23.6, 23.2, 20.4, 13.0; ESI-MS: 375.09 $(M+Na)^+$; HRMS (ESI): *m/z* calcd. for $C_{20}H_{32}O_5Na$ 375.2142 found 375.2138.

C-12β-^{n}hexyl ether (30): $C_{21}H_{36}O_5$, Colorless oil; R_f 0.60 (EtOAc-petroleum ether, 1:4); $[\alpha]_D^{26}$ = +127.2 (c = 1.18, $CHCl_3$); IR ($CHCl_3$) υ_{max} 2930, 2866, 1375, 1218, 1015, 766 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 5.40 (s, 1H), 4.78 (d, J = 3.3 Hz, 1H), 3.88-3.77 (m, 1H), 3.42-3.31 (m, 1H), 2.61 (m, 1H), 2.45-2.30 (m, 1H), 2.09-1.98 (m, 1H), 1.95-1.80 (m, 2H), 1.78-1.74 (m, 1H), 1.69-1.64 (m, 1H), 1.62-1.59 (m, 1H), 1.55-1.48 (m, 2H), 1.44-1.42 (m, 4H), 1.39-1.24 (m, 9H), 0.97-0.85 (m, 9H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 104.0, 102.0, 87.9, 81.2, 68.5, 52.6, 44.5, 37.5, 36.5, 34.7, 31.6, 31.0, 29.6, 26.2, 25.9, 24.7, 24.5, 22.6, 20.4, 14.0, 13.0; ESI-MS: 391.19 $(M+Na)^+$; HRMS (ESI): *m/z* calcd for $C_{21}H_{36}O_5Na$ 391.2455, found 391.2454.



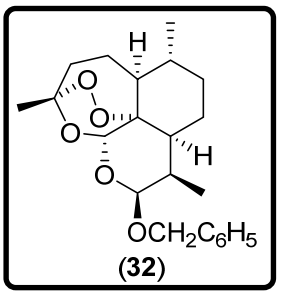
(**30**)

C-12β-cyclohexyl ether (31): $C_{21}H_{34}O_5$, Colorless oil; R_f 0.56 (EtOAc-petroleum ether, 1:4); $[\alpha]_D^{26}$ = +149.71 (c = 1.16, $CHCl_3$); IR ($CHCl_3$) υ_{max} 2933, 2863, 1452, 1374, 1217, 1001, 765 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 5.45 (s, 1H), 4.92 (d, J = 3.1 Hz, 1H), 3.71 (m, 1H), 2.60 (m, 1H), 2.40-2.34 (m, 1H), 2.05-2.01 (m, 1H), 1.91-1.82 (m, 3H), 1.76-1.72 (m, 2H), 1.67-1.61 (m, 4H), 1.52-1.40 (m, 7H), 1.37-1.21 (m, 6H), 0.96 (d, J = 6.4 Hz, 3H), 0.89 (d, J = 7.3 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 104.0, 99.8, 88.1, 81.3, 74.4, 52.7, 44.6, 37.5, 36.5, 34.7, 33.7, 31.1, 30.9, 26.3, 25.8, 24.7, 24.6, 23.9, 23.5, 20.4, 13.2; ESI-MS: 389.21 $(M+Na)^+$; HRMS (ESI): *m/z* calcd for $C_{21}H_{34}O_5Na$ 389.2298, found 389.2291.



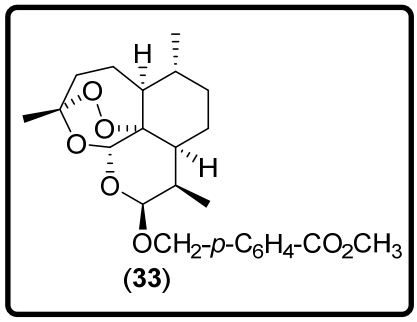
(**31**)

C-12β-benzyl ether (32): $C_{22}H_{30}O_5$, Colorless oil; R_f 0.38 (EtOAc-petroleum ether, 1:4); $[\alpha]_D^{26}$ = +134.89 (c = 0.95, $CHCl_3$); IR ($CHCl_3$) υ_{max} 2929, 2873, 1455, 1373, 1218, 1016, 765 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.32 (m, 5H), 5.47 (s, 1H) 4.92 (d, J = 3.5 Hz, 1H), 4.91 (d, J = 12.4 Hz, 1H), 4.52 (d, J = 12.4 Hz, 1H), 2.68 (m, 1H), 2.46-2.31 (m, 1H), 2.10-1.99 (m, 1H), 1.92-1.78 (m, 3H), 1.66-1.56 (m, 2H), 1.54-1.52 (m, 1H), 1.46 (m, 4H), 1.31-1.22 (m, 2H), 0.95 (d, J = 7.6 Hz, 3H), 0.94 (d, J = 5.4 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 138.4, 128.3, 127.4, 127.2, 104.2, 101.5, 88.1, 81.2, 69.8, 52.6, 44.5, 37.4, 36.5, 34.7, 31.0, 26.2, 24.7, 24.5, 20.4, 13.1; ESI-MS: 397.16 $(M+Na)^+$; HRMS: *m/z* calcd. for $C_{22}H_{30}O_5Na$ 397.1985, found 397.1982.



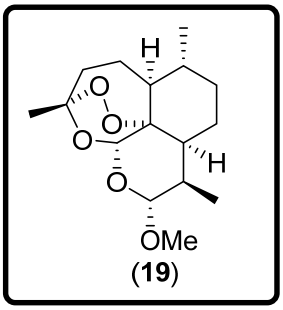
(32)

β-Methyl-*p*-[(12-dihydroartemisinoxy)methyl] benzoate (33): $C_{24}H_{32}O_7$, Colorless oil; R_f 0.31 (EtOAc-petroleum ether, 1:4); $[\alpha]_D^{26}$ = +104.28 (c = 1.35, $CHCl_3$); IR ($CHCl_3$) υ_{max} 2964, 2874, 1732, 1377, 1129, 1107, 1021, 767cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.01 (d, J = 8.2 Hz, 1H), 7.38 (d, J = 8.2 Hz, 1H), 5.45 (s, 1H), 4.96 (d, J = 13.1 Hz, 1H), 4.92 (d, J = 3.4 Hz, 1H), 4.58 (d, J = 13.1 Hz, 1H), 3.91 (s, 3H), 2.69 (m, 1H), 2.41-2.35 (m, 1H), 2.06-2.02 (m, 1H), 1.91-1.85 (m, 1H), 1.83-1.80 (m, 2H), 1.65-1.61 (m, 1H), 1.53-1.43 (m, 6H), 1.34-1.24 (m, 4H), 0.97 (d, J = 7.3 Hz, 3H), 0.95 (d, J = 6.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.0, 143.7, 129.7, 129.2, 126.9, 104.2, 101.6, 88.1, 81.1, 69.2, 52.6, 52.1, 44.4, 37.4, 36.4, 34.6, 30.9, 26.2, 24.7, 24.5, 20.3, 13.1; ESI-MS: 455.28 $(M+Na)^+$; HRMS (ESI): *m/z* calcd for $C_{24}H_{32}O_7Na$ 455.2040, found 455.2036.



(33)

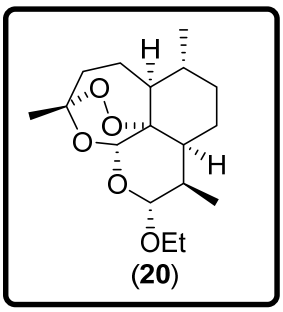
C-12α-methyl ether (19): $C_{16}H_{26}O_5$, Colorless oil; R_f 0.37 (EtOAc-petroleum ether, 1:4); IR ($CHCl_3$) υ_{max} 2925, 2860, 1372, 1215, 1050, 1024, 756 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 5.35 (s, 1H), 4.36 (d, J = 9.2 Hz, 1H), 3.52 (s, 3H), 2.50-2.28 (m, 2H), 2.11-1.96 (m, 1H), 1.78-1.63 (m, 3H),



(19)

1.59 (d, *J* = 3.5 Hz, 1H), 1.53 (d, *J* = 4.2 Hz, 1H), 1.51-1.44 (m, 4H), 1.41-1.35 (m, 1H), 1.34-1.27 (m, 2H), 0.96 (d, *J* = 5.8 Hz, 3H), 0.88 (d, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 104.3, 101.2, 91.3, 80.4, 56.4, 51.6, 45.4, 37.4, 36.4, 34.3, 32.5, 26.1, 24.7, 22.2, 20.3, 12.6; ESI-MS: 321.05 $(M+Na)^+$; HRMS (ESI): *m/z* calcd for $C_{16}H_{26}O_5Na$ 321.1672, found 321.1673.

C-12α-ethyl ether (20): $C_{17}H_{28}O_5$, Colorless oil; R_f 0.4 (EtOAc-petroleum ether, 1:4); $[\alpha]_D^{25}$ = -2.6 (c = 1.0, $CHCl_3$) [lit.[30] $[\alpha]_D^{25}$= -2.6 (c = 1.0, $CHCl_3$)]; IR ($CHCl_3$) υ_{max} 2928, 2862, 1365, 1218, 1021, 863, 761cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 5.34 (s, 1H), 4.44 (d, *J* = 9.2 Hz, 1H), 4.01 (qd, *J* = 7.1, 9.6 Hz, 1H), 3.60-3.41 (m, 1H), 2.48-2.29 (m, 2H), 2.11-1.95 (m, 1H), 1.95-1.78 (m, 2H), 1.76-1.49 (m, 4H), 1.45 (s, 3H), 1.37-1.27 (m, 3H), 1.20-1.16 (m, 3H), 0.96 (d, *J* = 5.8 Hz, 3H), 0.88 (d, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 104.3, 99.9, 91.3, 80.4, 64.5, 51.7, 45.4, 37.4, 36.4, 34.3, 32.6, 26.2, 24.8, 22.3, 20.4, 15.2, 12.7; HRMS (ESI): *m/z* calcd for $C_{17}H_{28}O_5Na$ 335.1829, found 335.1830.



(**20**)

3.1.6 HPLC Methods:

In our method, pure compounds were analyzed first to get the retention times of the respective compounds β-ether and α-ether respectively. Then, using the same condition crude samples synthesized by either method-I / or method-II were injected and matching the retention times and integrating the peaks elucidated the percent purity of artemisinin ether derivates.

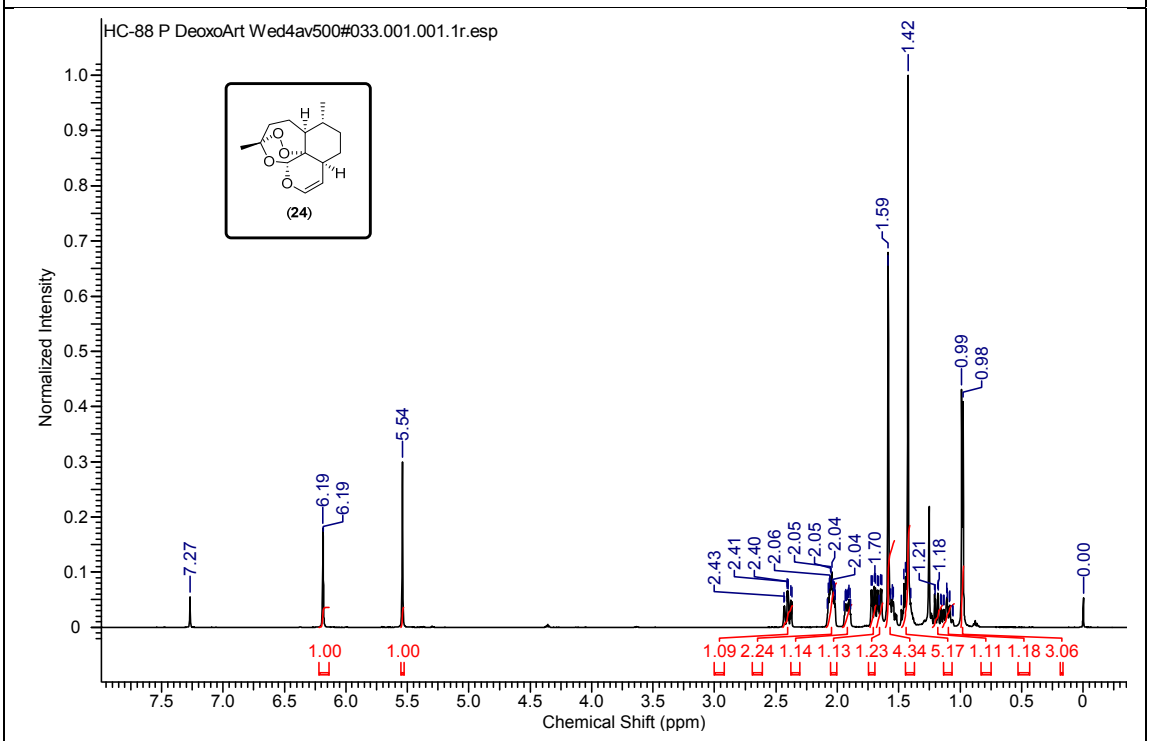
Wavelength 215 nm, flowrate 1ml min^{-1} (960 *psi*) sample concentration in the range of 0.5 mg to 1.2 mg in 0.5 to 1.2 ml, injection volume 10-20 µl.

Table 8. HPLC conditions for C-12-artemisinin ethers.

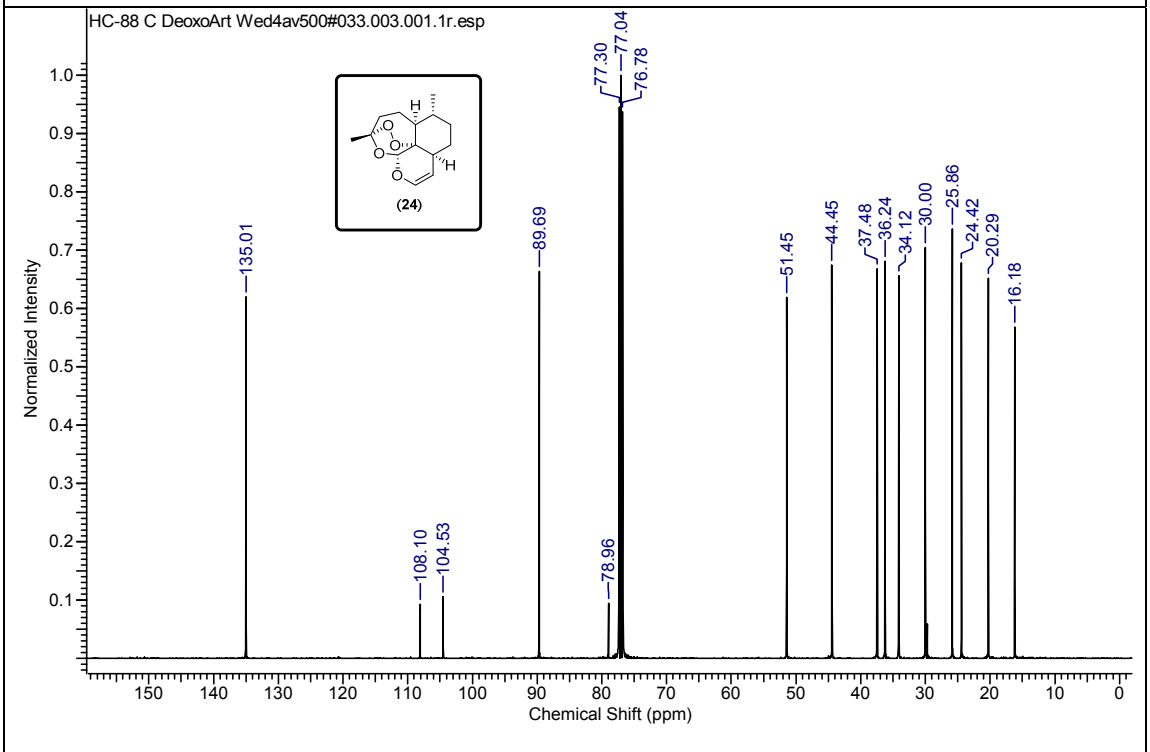
Entry	**Comp**	**Column**	**Mobile phase $CH_3CN:H_2O$**
1	C-12β/C-12α-methyl ether	KROMASIL C-18	75:25
2	C-12β/C-12α-ethyl ether	KROMASIL C-18	75:25
3	C-12β/C-12α-propyl ether	KROMASIL C-18	85:15
4	C-12β/C-12α-butyl ether	KROMASIL C-18	85:15
5	C-12β/C-12α-pentyl ether	KROMASIL C-18	90:10
6	C-12β/C-12α-cyclopentyl ether	KROMASIL C-18	90:10
7	C-12β/C-12α-hexyl ether	KROMASIL C-18	90:10
8	C-12β/C-12α-cyclohexyl ether	KROMASIL C-18	90:10
9	C-12β/C-12α-benzyl ether	KROMASIL C-8	80:20
10	C-12β/C-12α-methylartelinate ether	KROMASIL C-8	80:20

3.1.7 Spectra

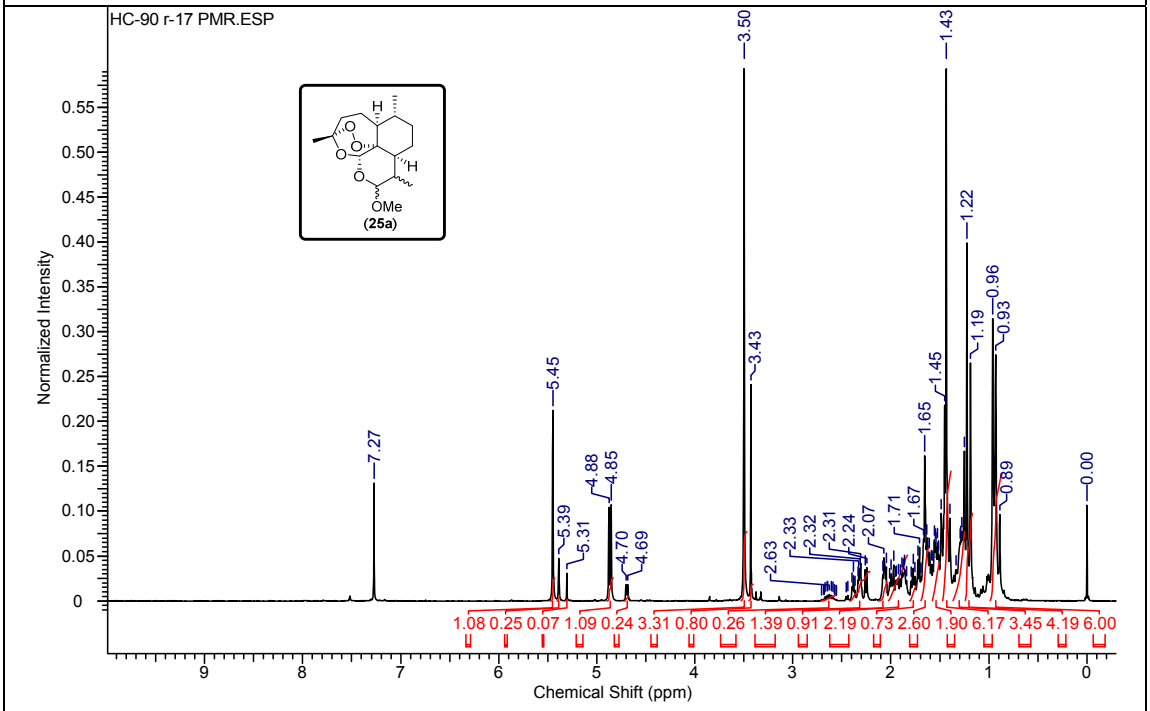
^{1}H NMR (500 MHz, $CDCl_3$) of (**24**)



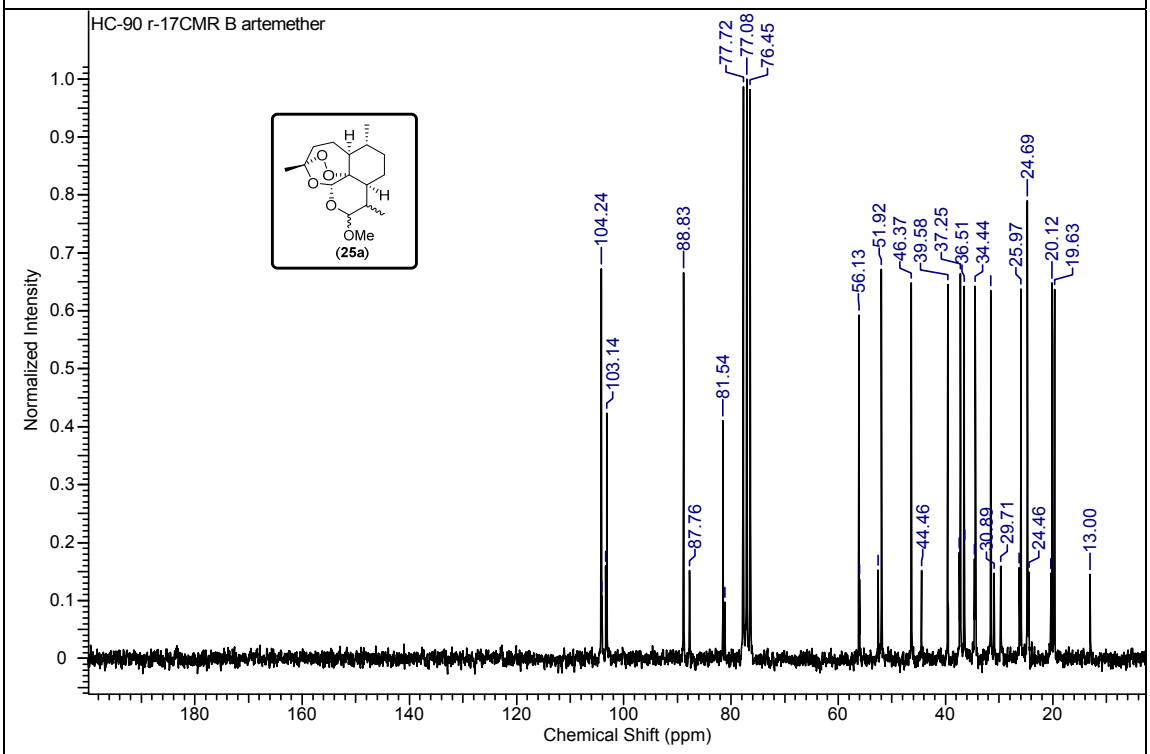
^{13}C NMR (125 MHz, $CDCl_3$) of (**24**)



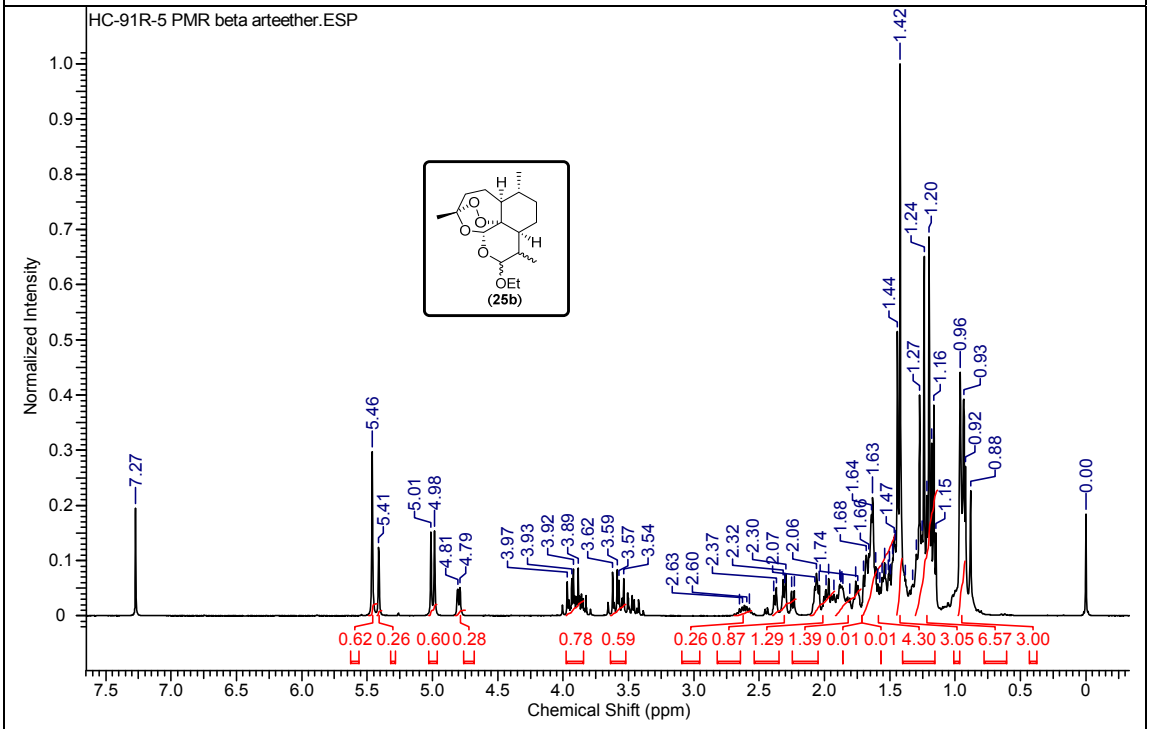
^{1}H NMR (200 MHz, $CDCl_3$) of (**25a**)



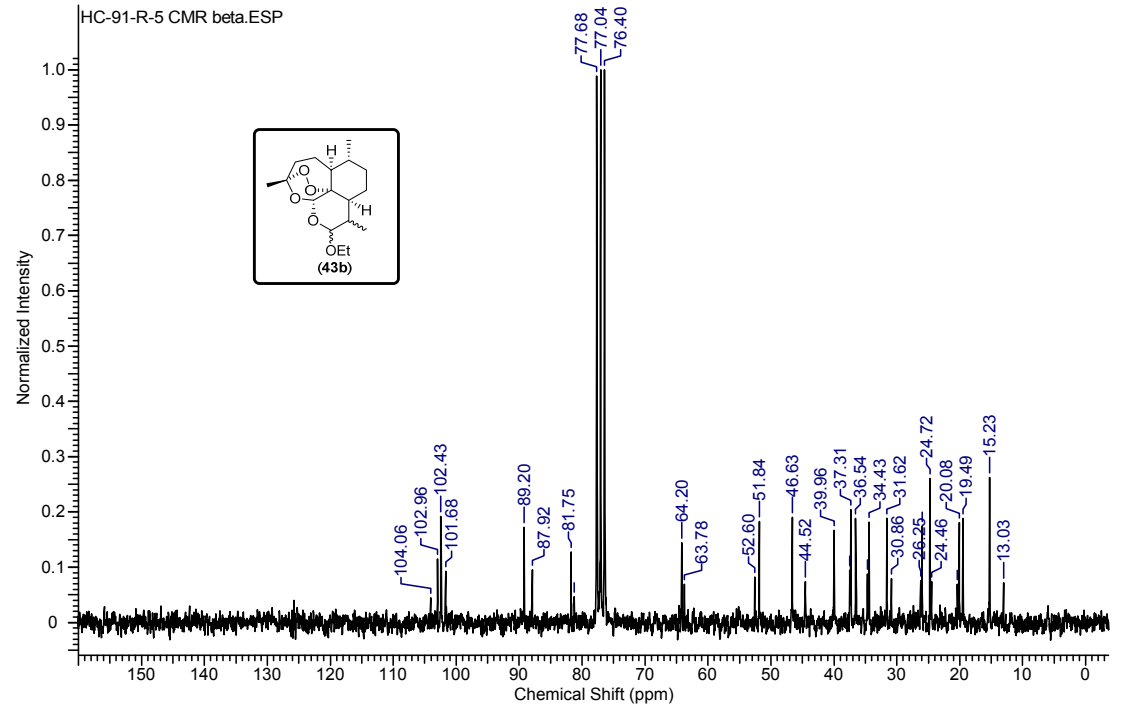
^{13}C NMR (50 MHz, $CDCl_3$) of (**25a**)



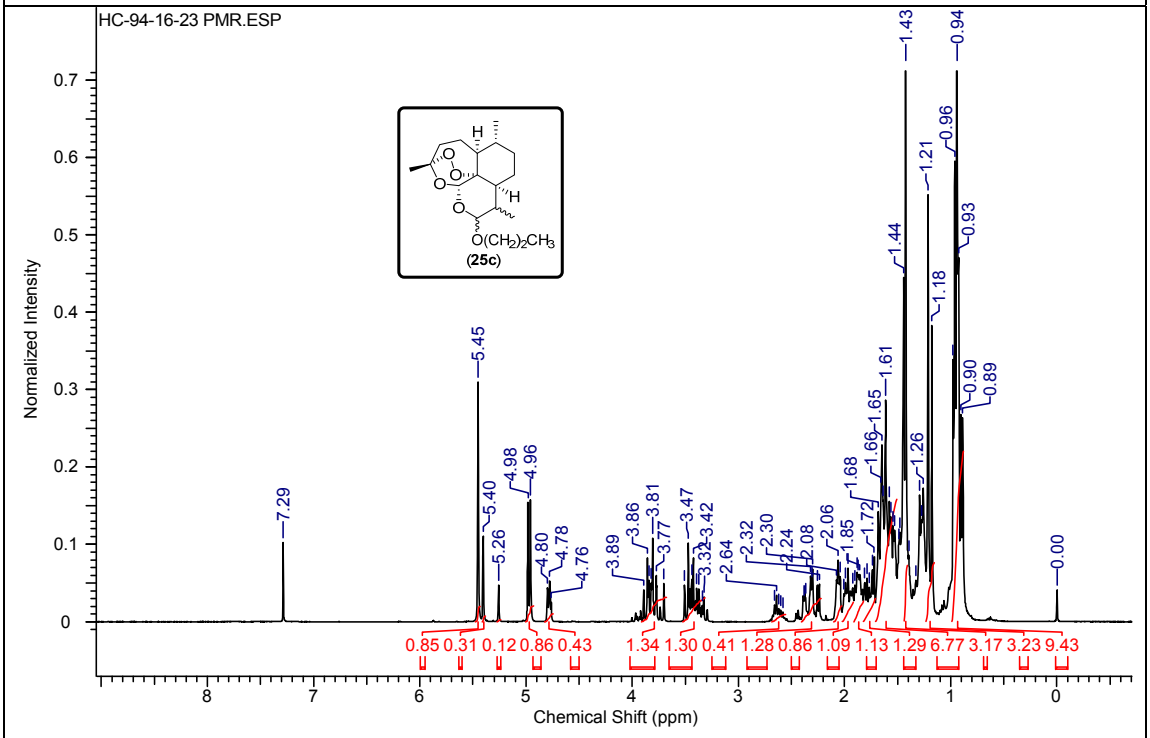
^{1}H NMR (200 MHz, $CDCl_3$) of (**25b**)



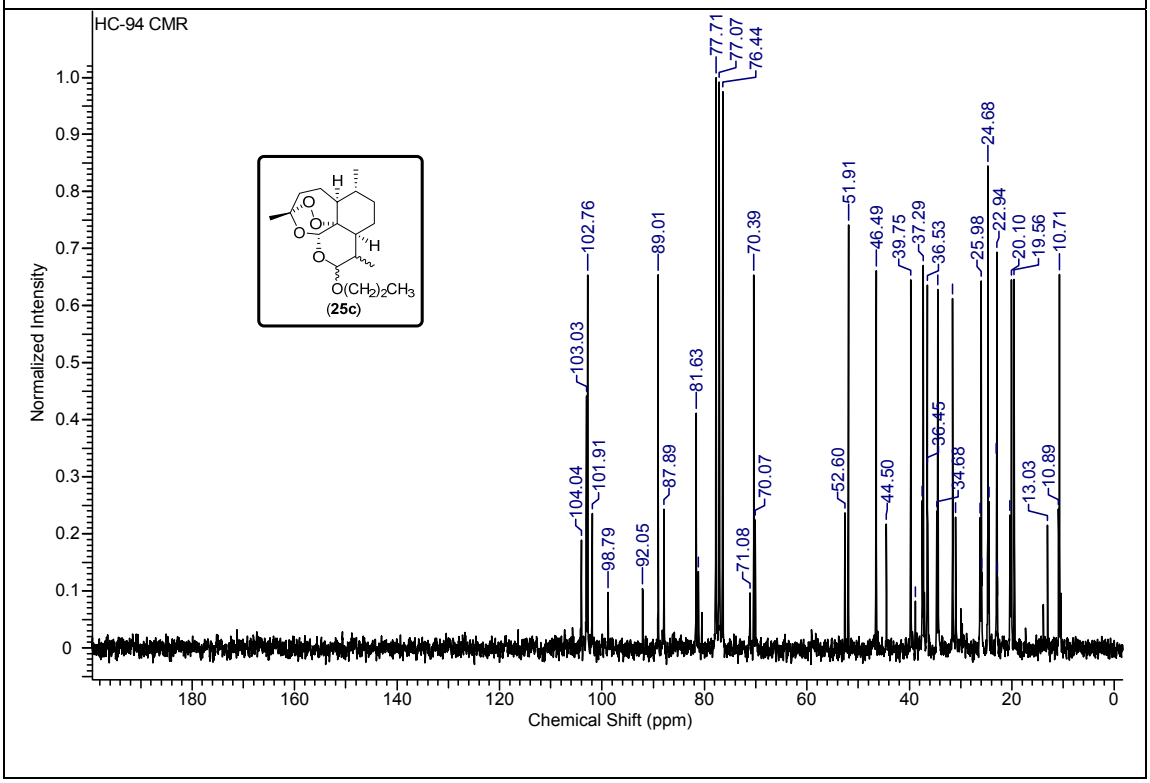
^{13}C NMR (50 MHz, $CDCl_3$) of (**25b**)



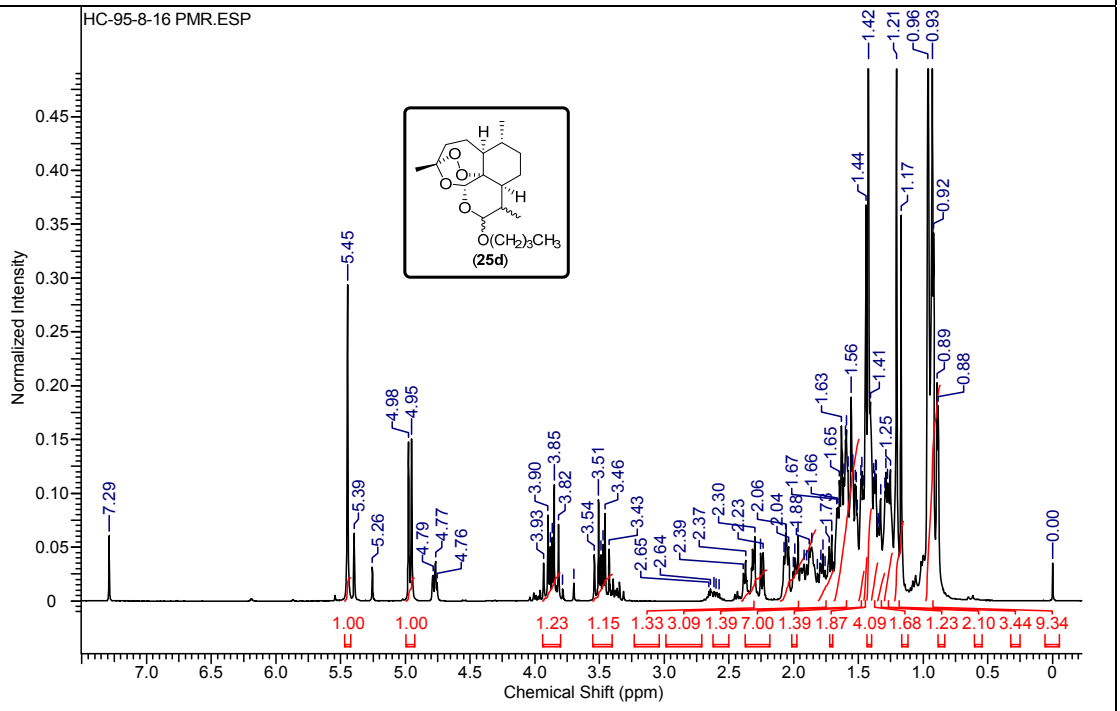
^{1}H NMR (200 MHz, $CDCl_3$) of (**25c**)



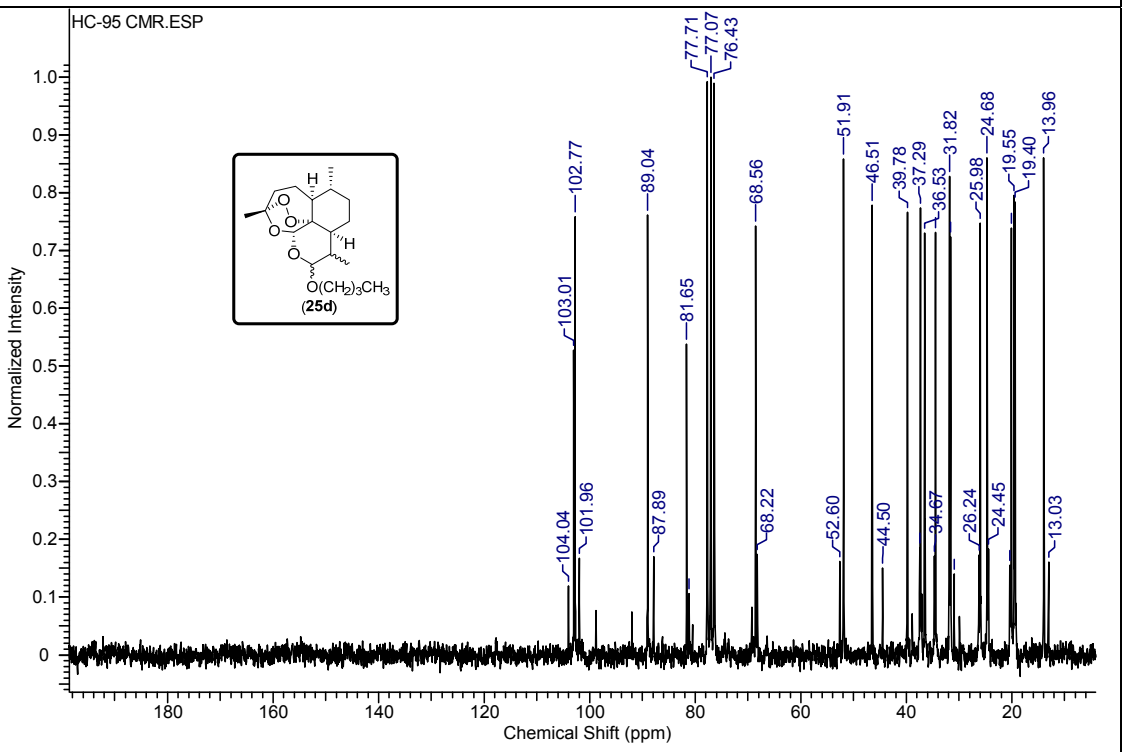
^{13}C NMR (50 MHz, $CDCl_3$) of (**25c**)



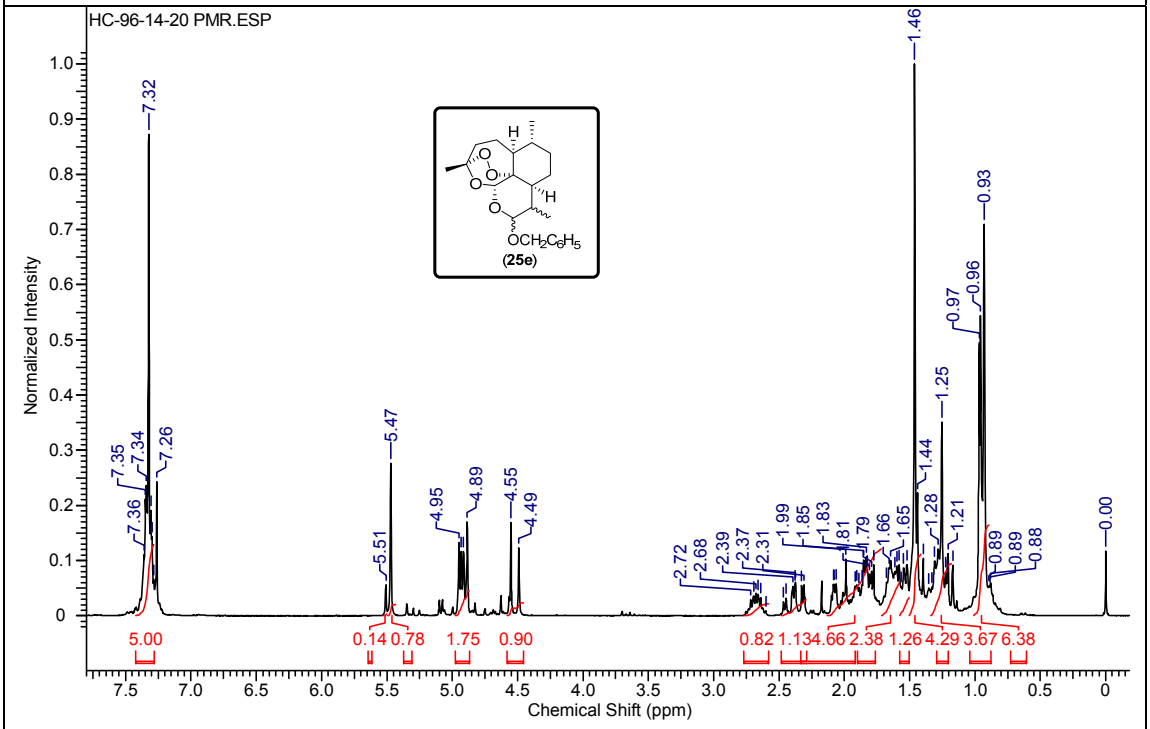
^{1}H NMR (200 MHz, $CDCl_3$) of (**25d**)



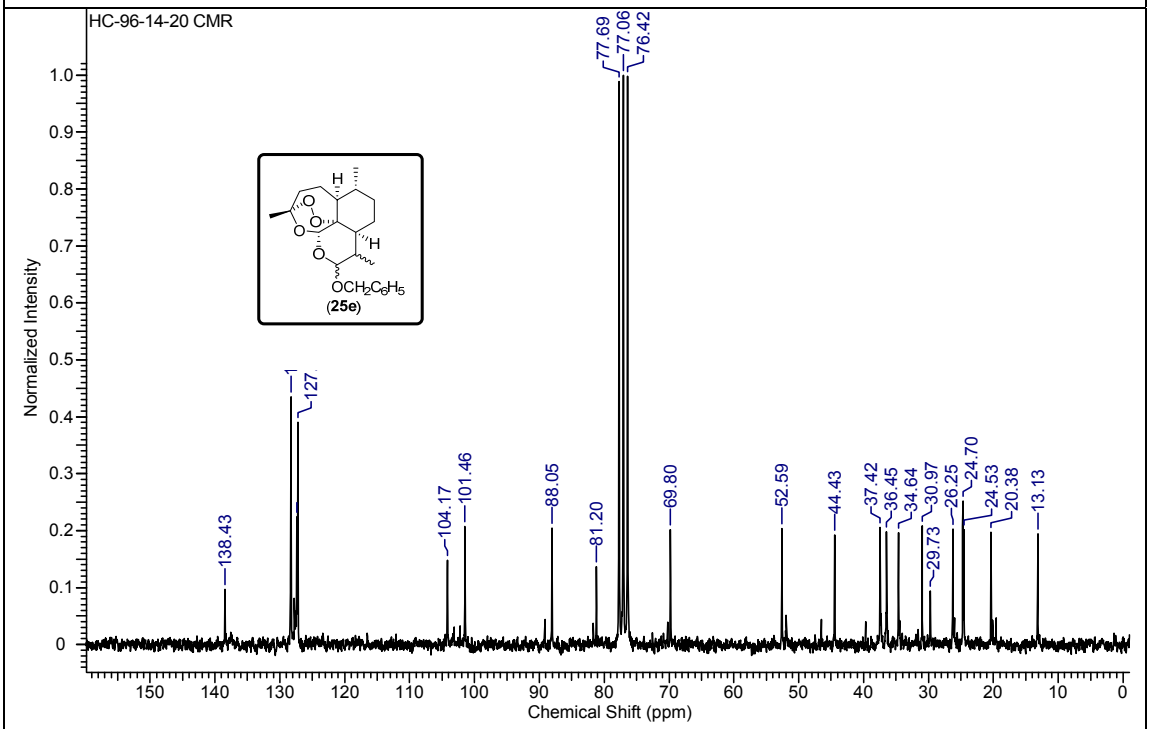
^{13}C NMR (50 MHz, $CDCl_3$) of (**25d**)



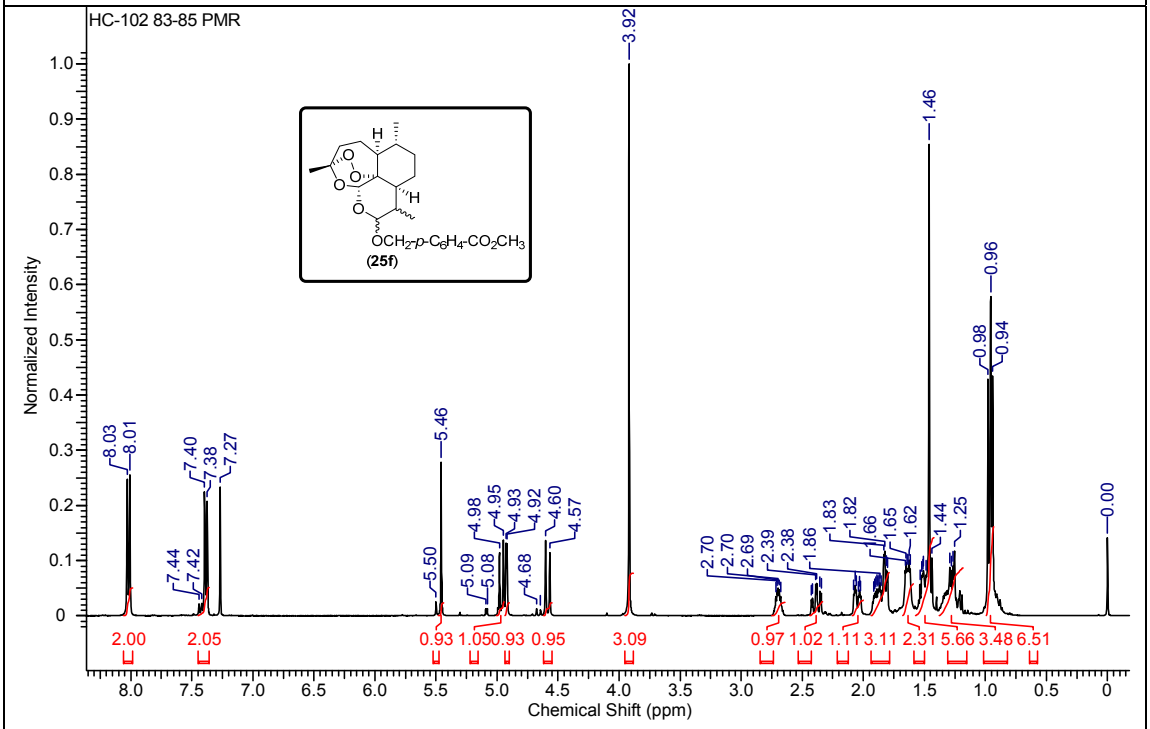
^{1}H NMR (200 MHz, $CDCl_3$) of (**25e**)



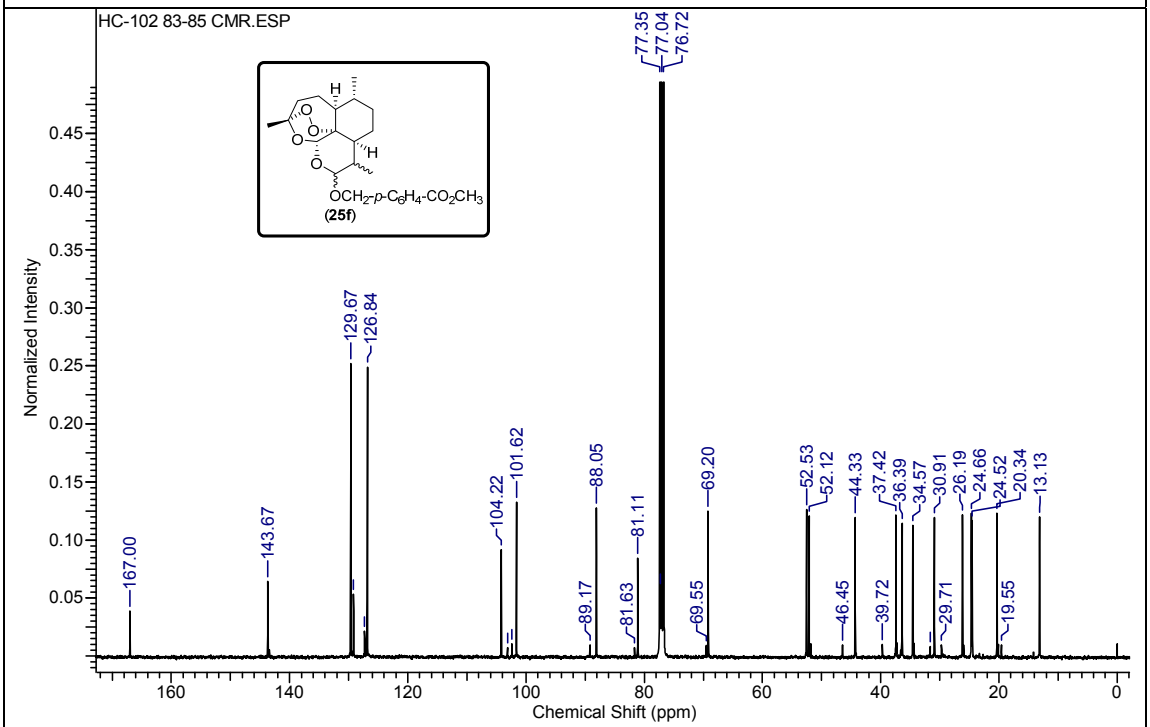
^{13}C NMR (50 MHz, $CDCl_3$) of (**25e**)



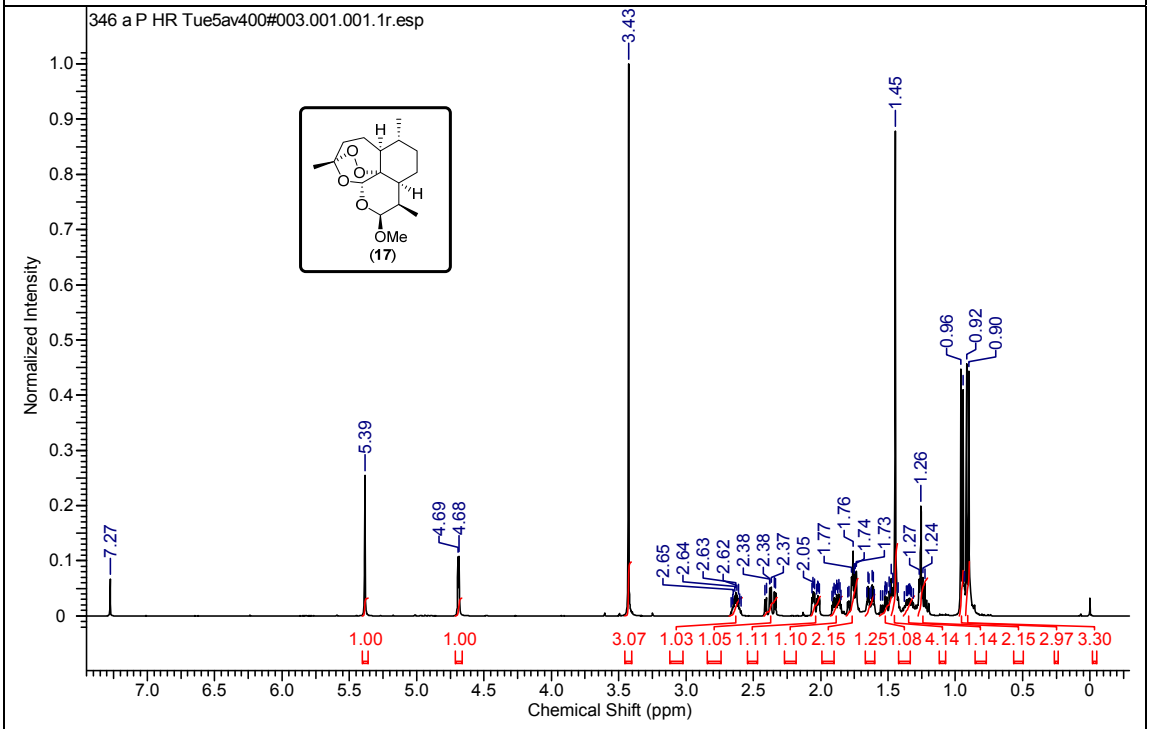
^{1}H NMR (400 MHz, $CDCl_3$) of (**25f**)



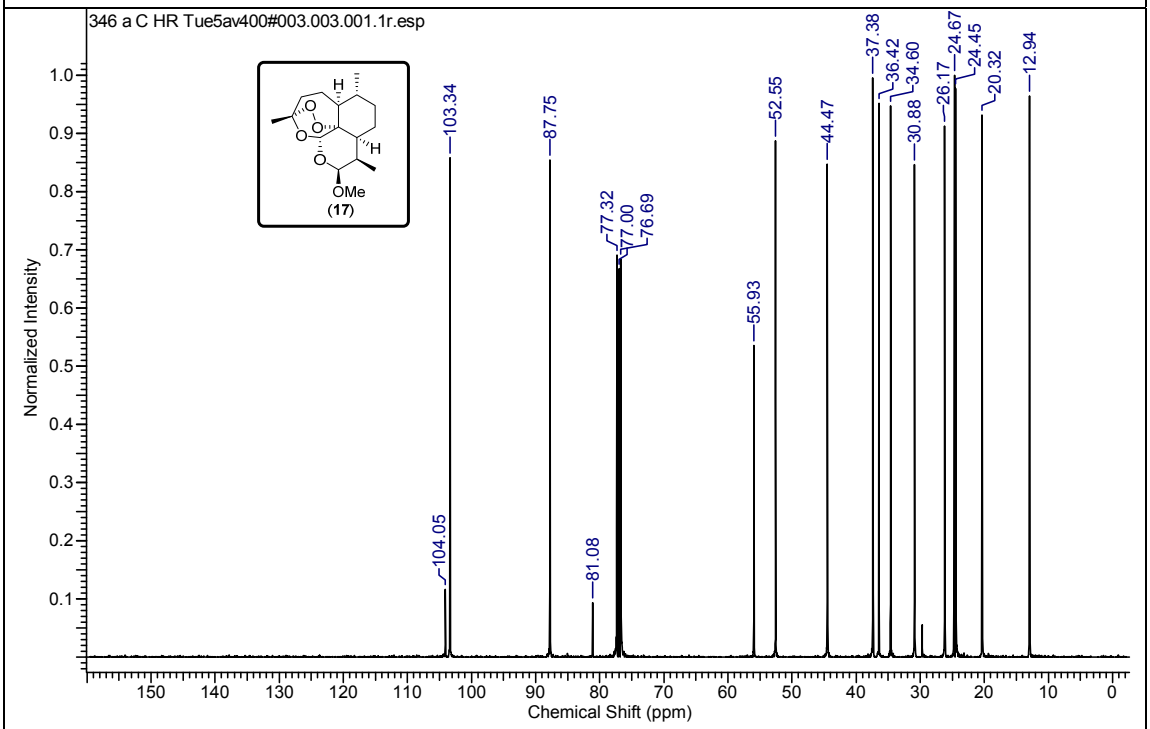
^{13}C NMR (100 MHz, $CDCl_3$) of (**25f**)



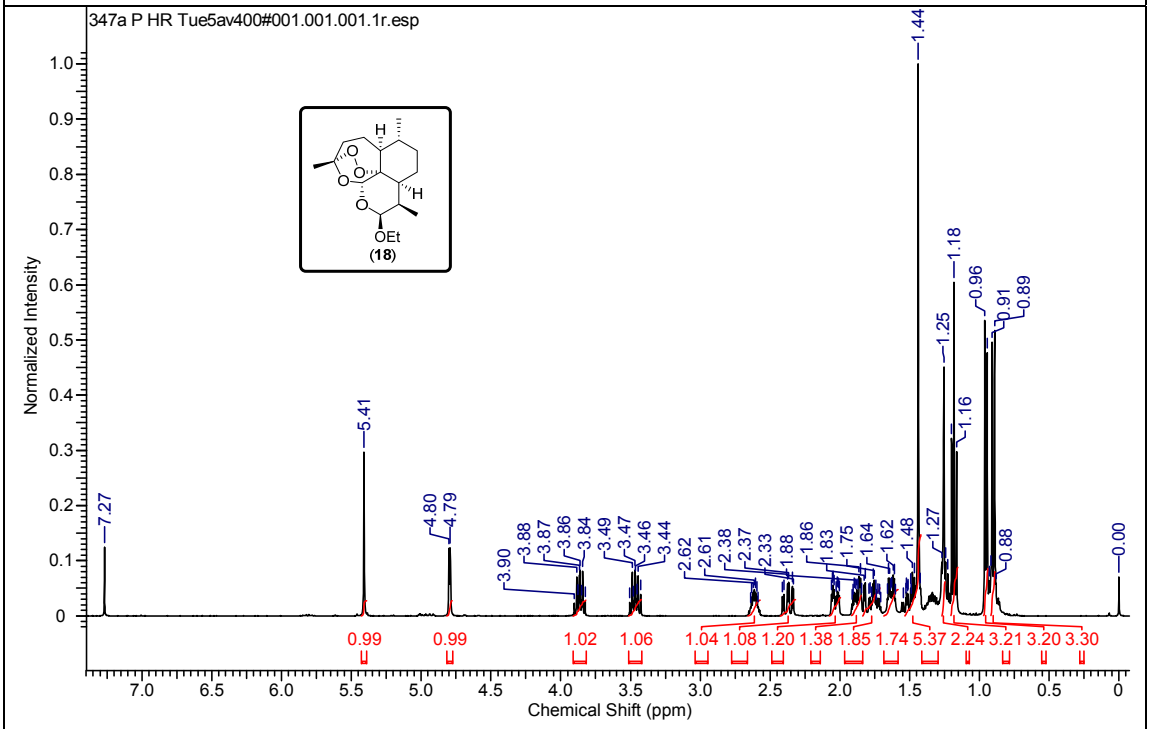
^{1}H NMR (400 MHz, $CDCl_3$) of (**17**)



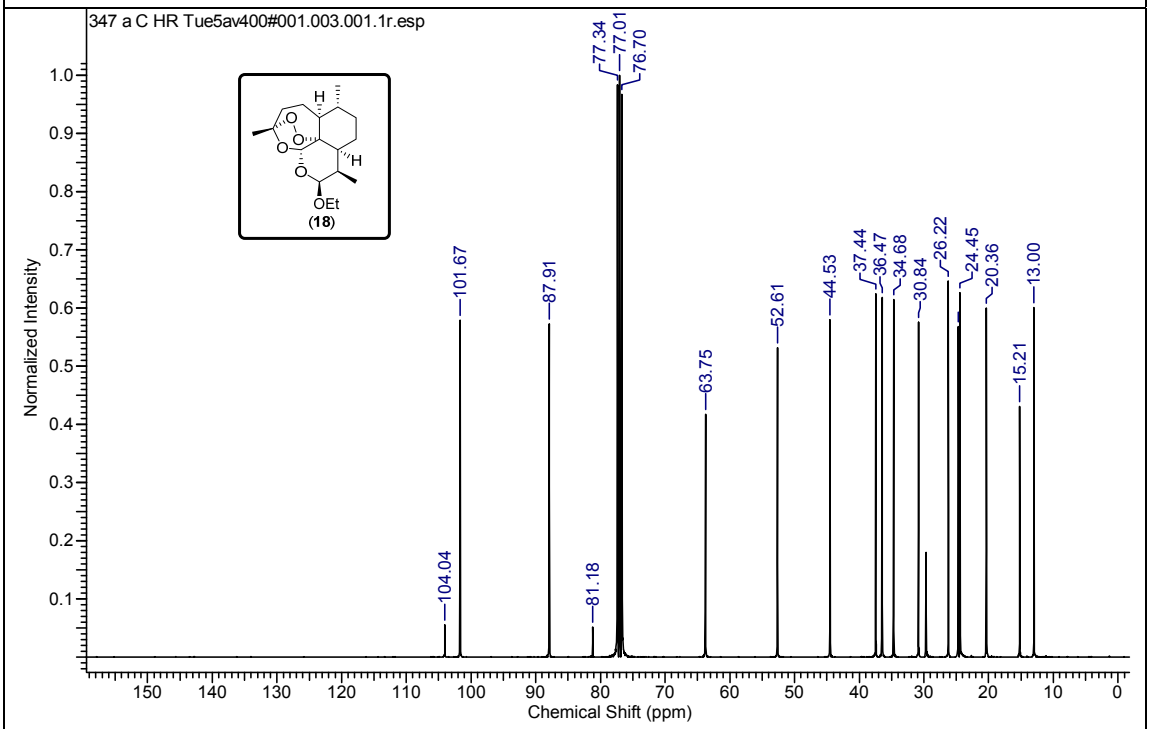
^{13}C NMR (100 MHz, $CDCl_3$) of (**17**)



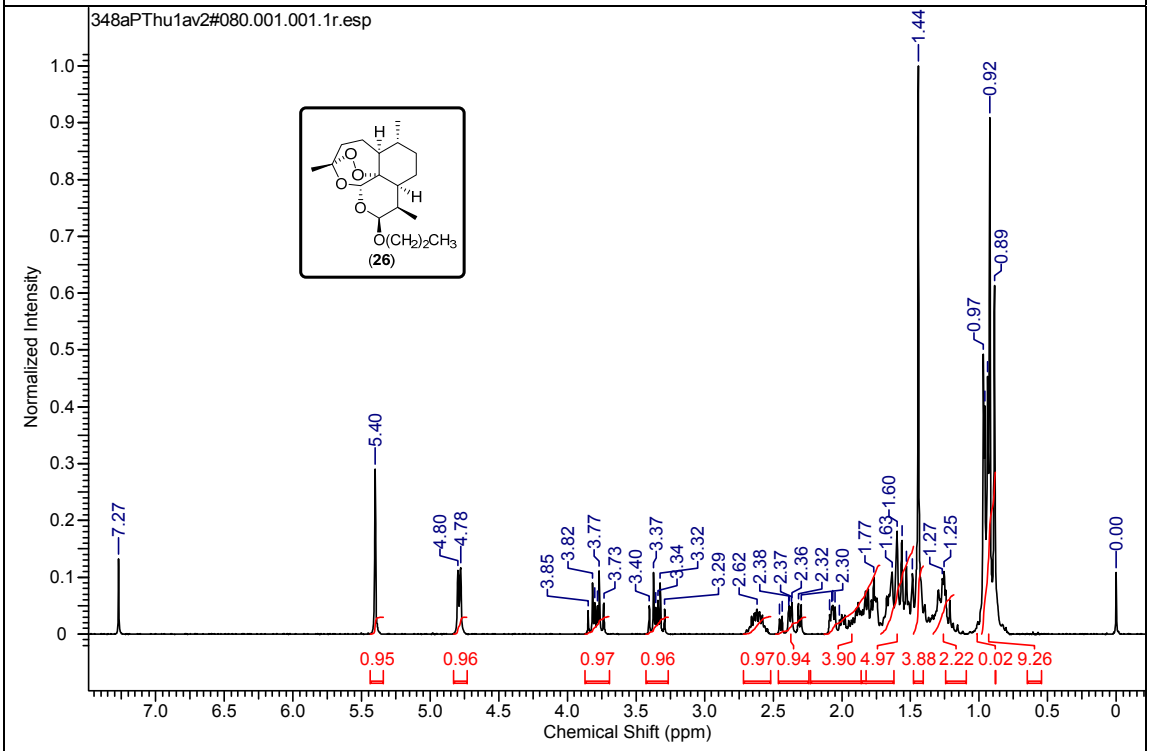
^{1}H NMR (400 MHz, $CDCl_3$) of (**18**)



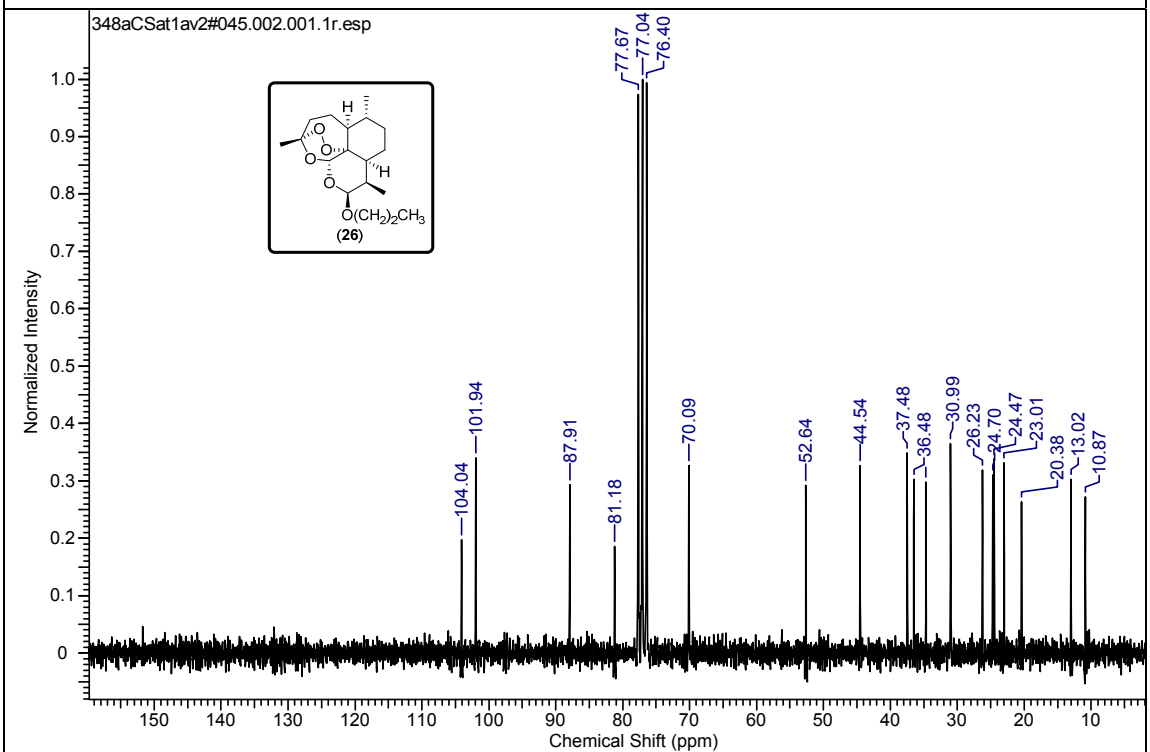
^{13}C NMR (100 MHz, $CDCl_3$) of (**18**)



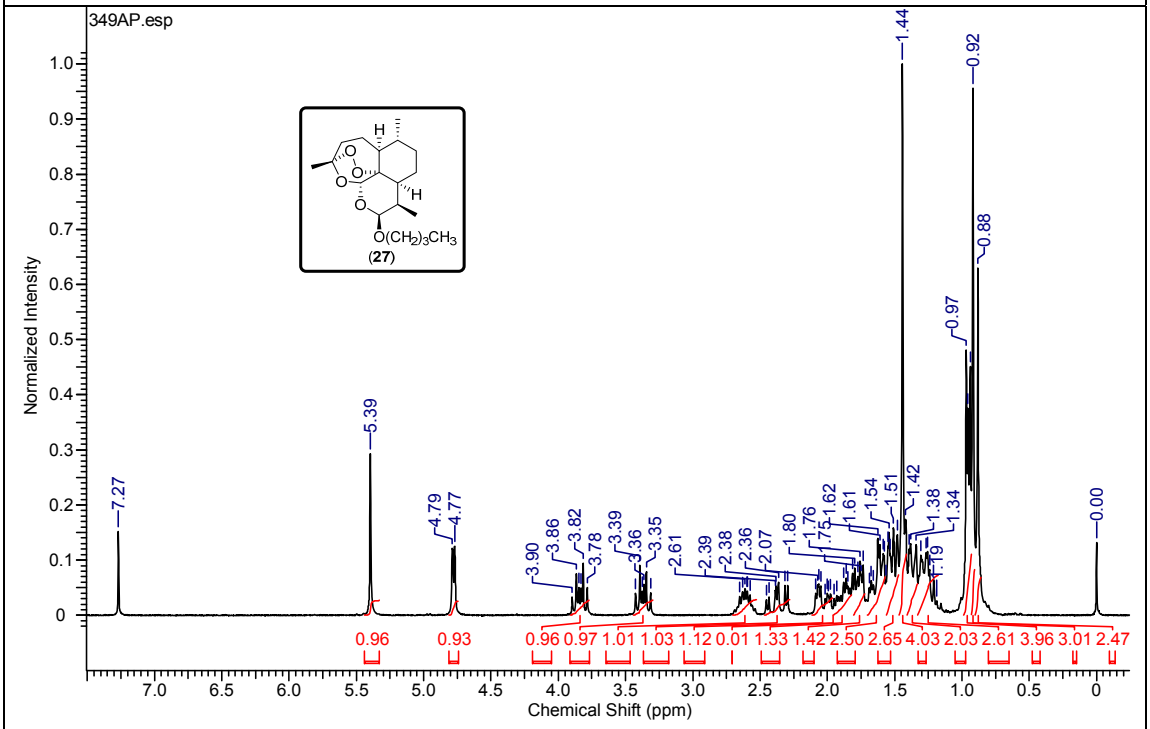
^{1}H NMR (200 MHz, $CDCl_3$) of (**26**)



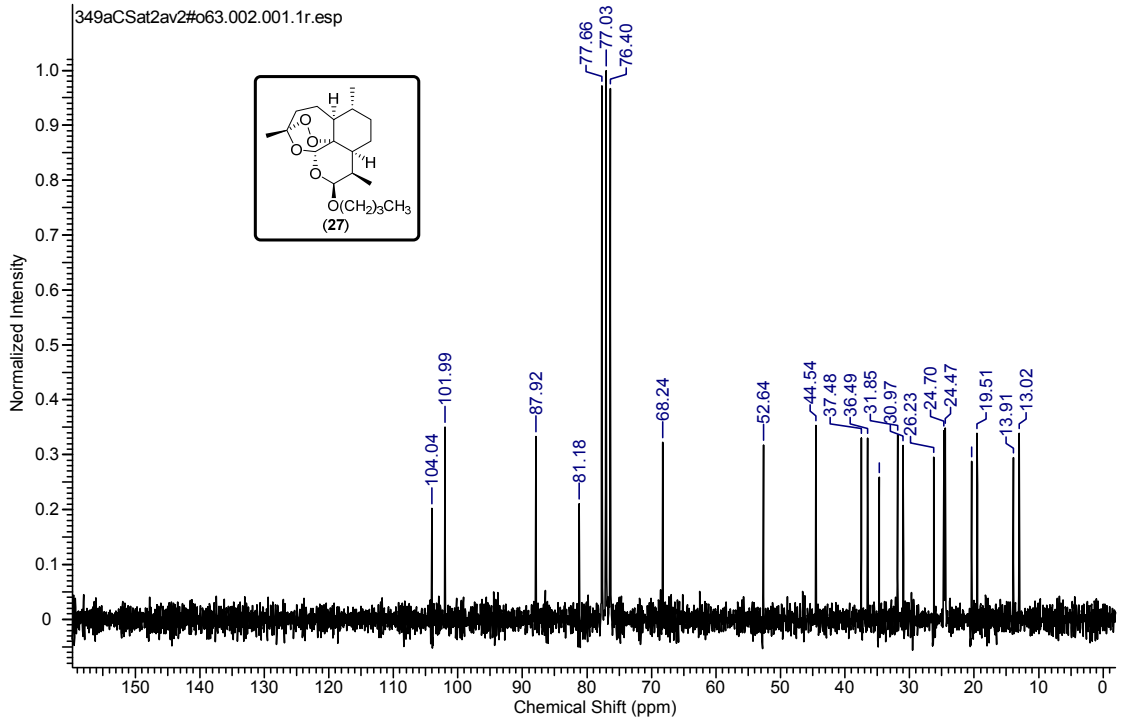
^{13}C NMR (100 MHz, $CDCl_3$) of (**26**)



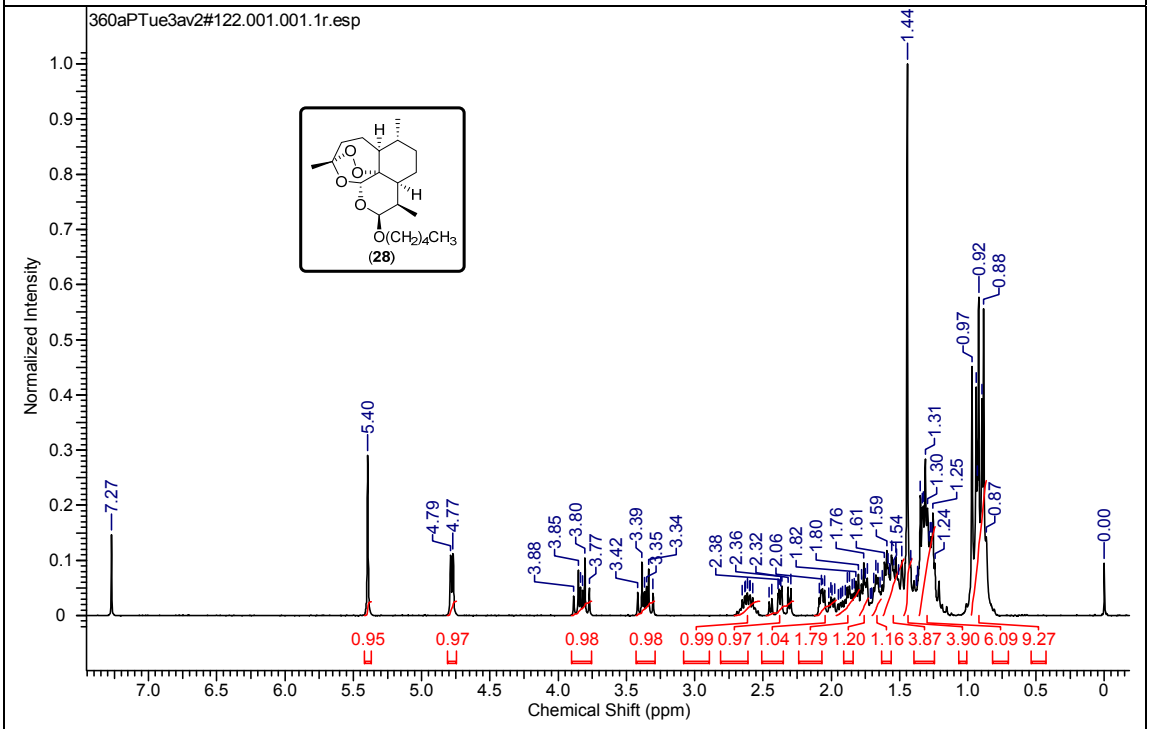
^{1}H NMR (200 MHz, $CDCl_3$) of (**27**)



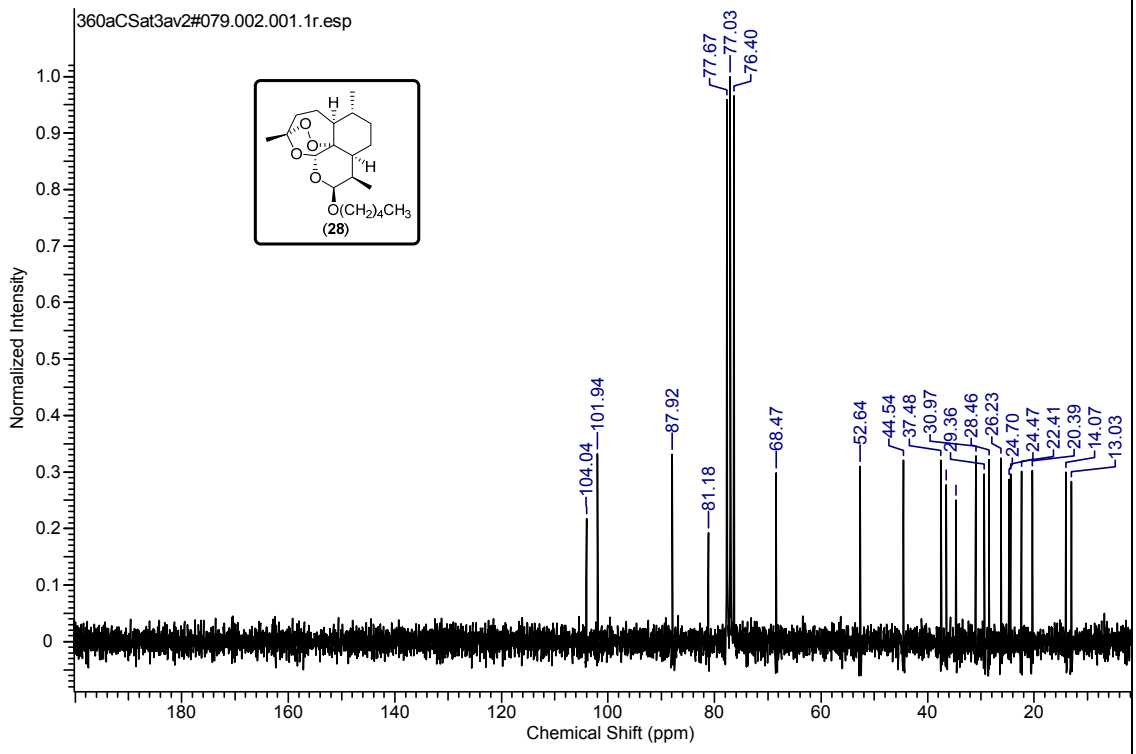
^{13}C NMR (50 MHz, $CDCl_3$) of (**27**)



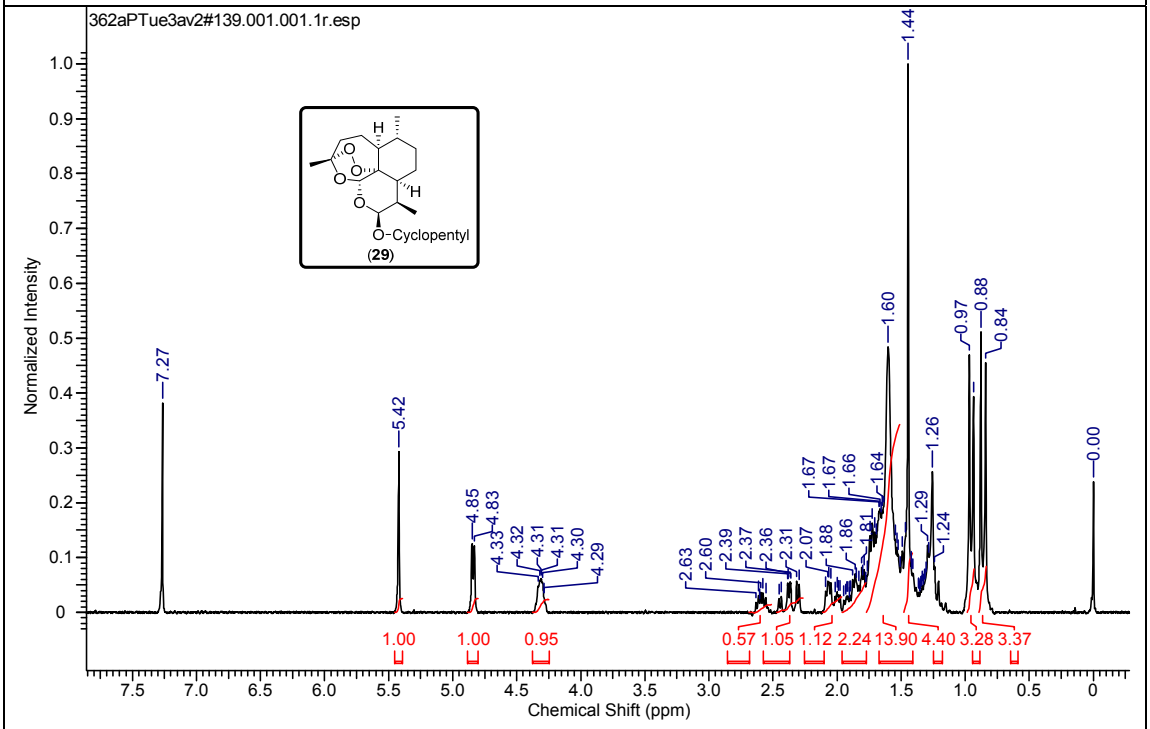
^{1}H NMR (200 MHz, $CDCl_3$) of (**28**)



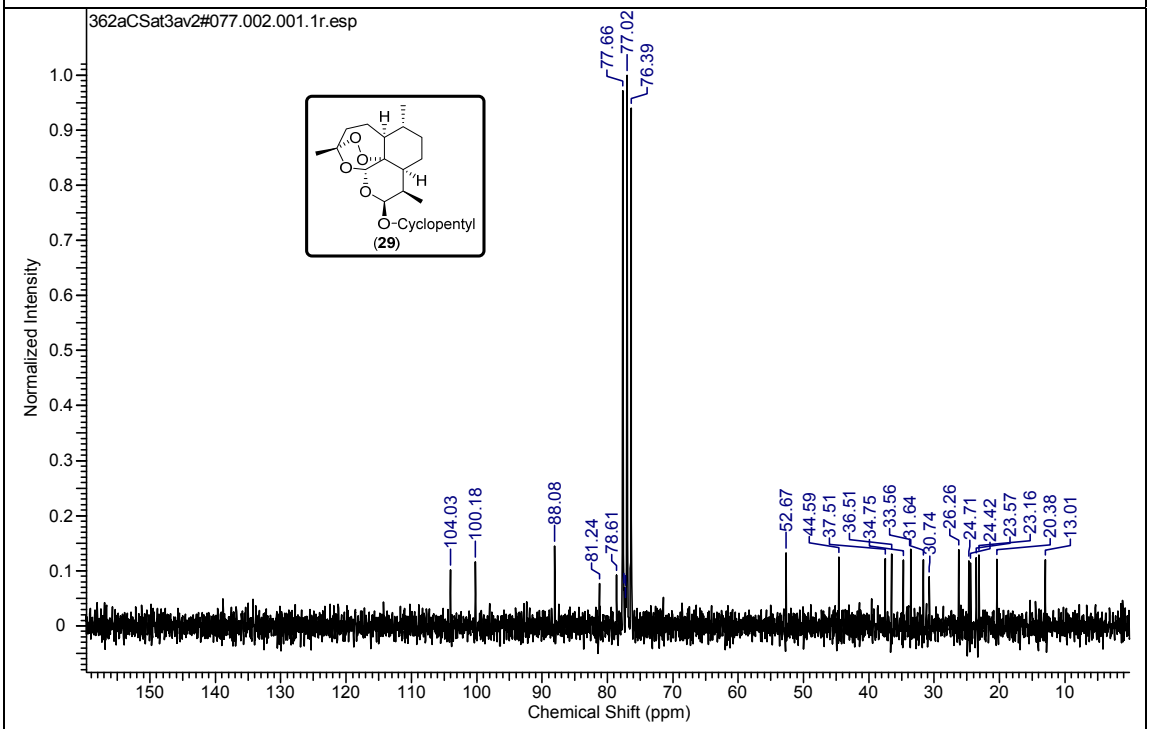
^{13}C NMR (50 MHz, $CDCl_3$) of (**28**)



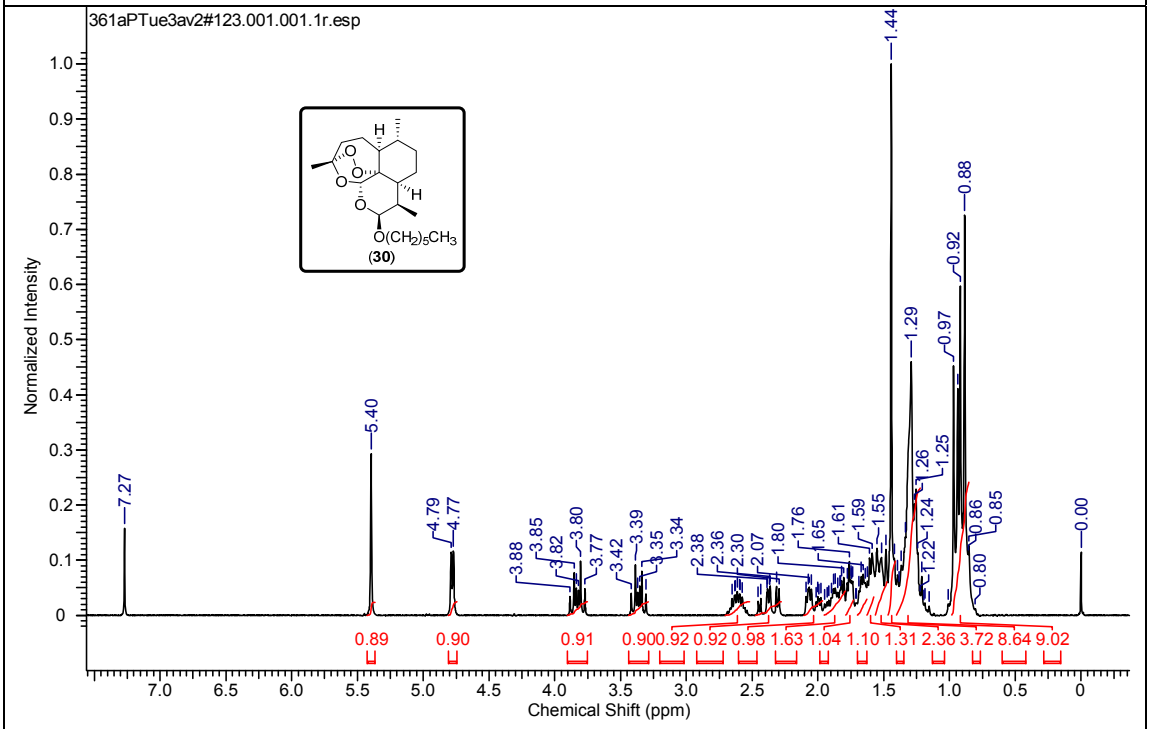
^{1}H NMR (200 MHz, $CDCl_3$) of (**29**)



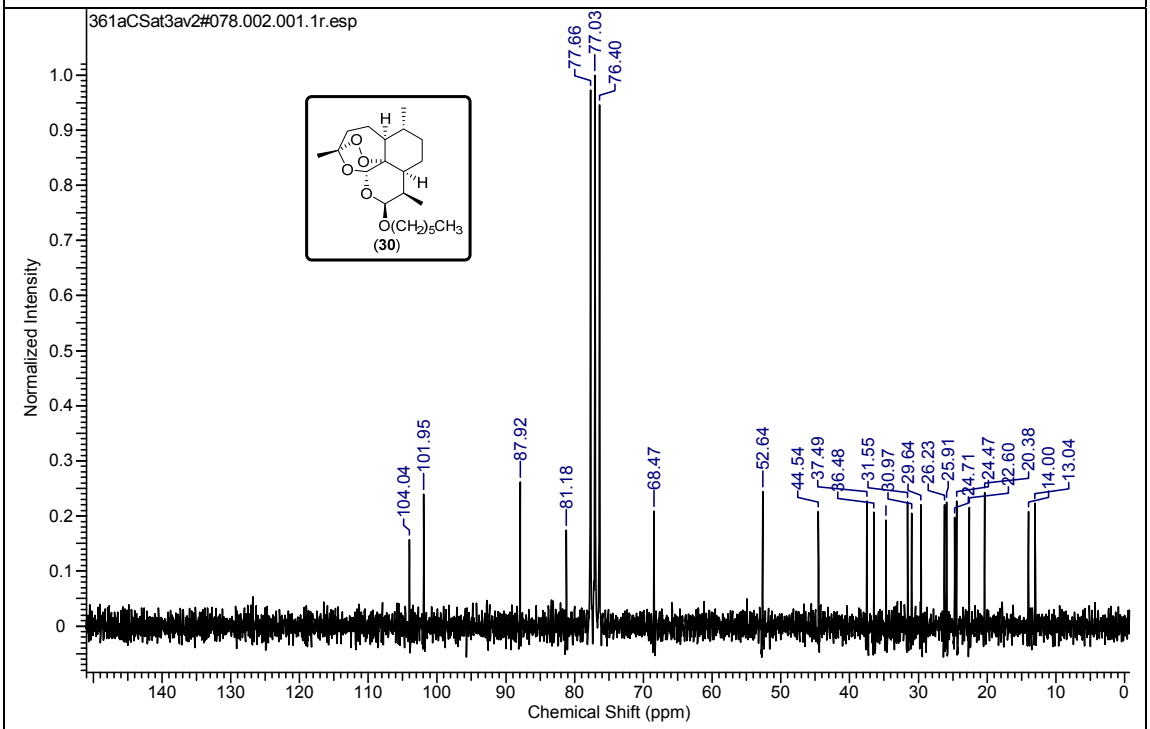
^{13}C NMR (50 MHz, $CDCl_3$) of (**29**)



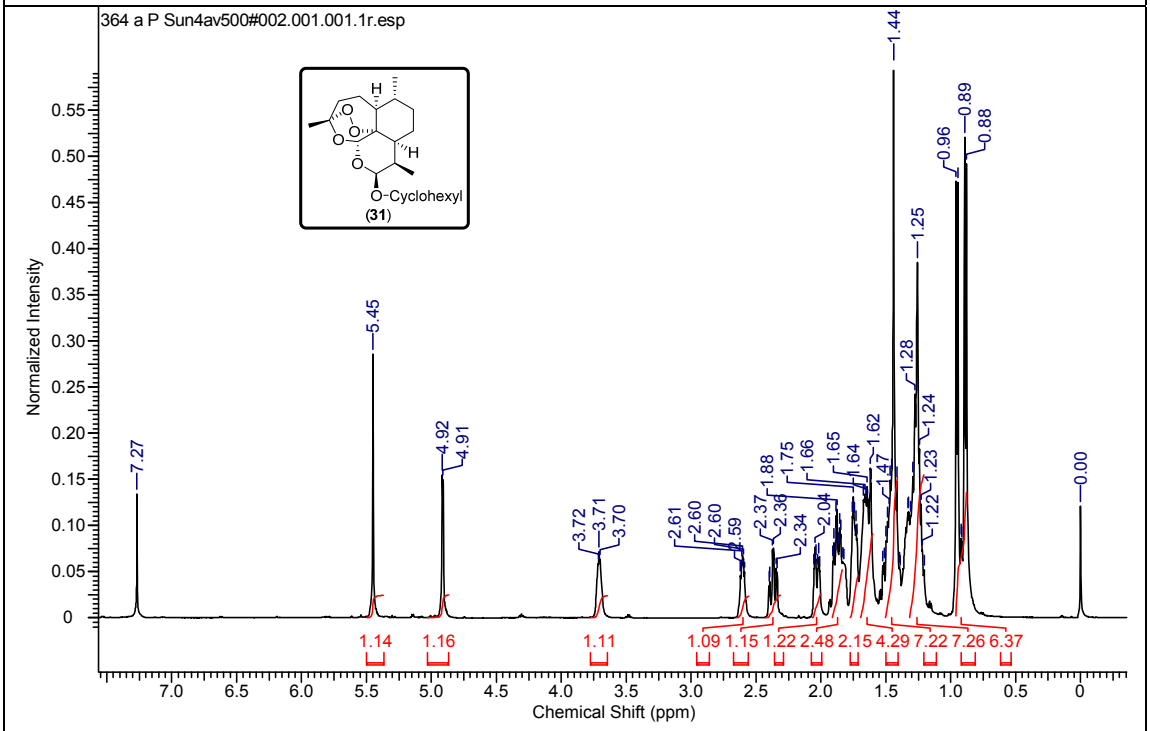
^{1}H NMR (200 MHz, $CDCl_3$) of (**30**)



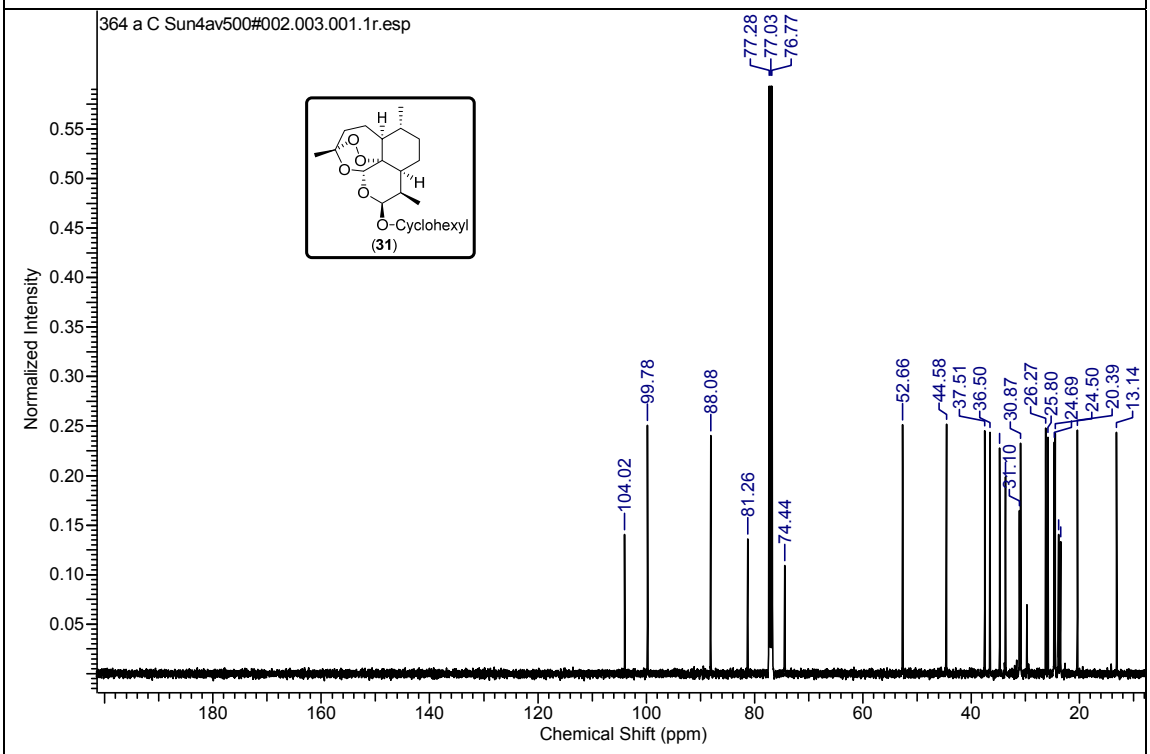
^{13}C NMR (50 MHz, $CDCl_3$) of (**30**)



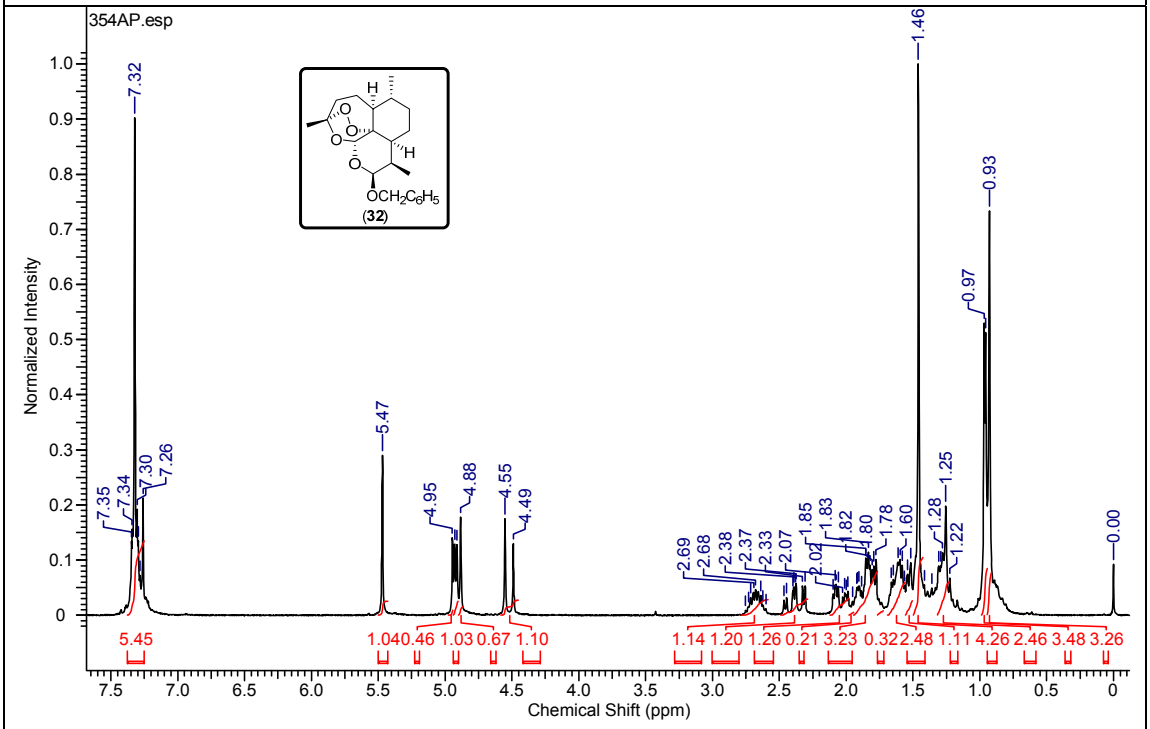
^{1}H NMR (500 MHz, $CDCl_3$) of (**31**)



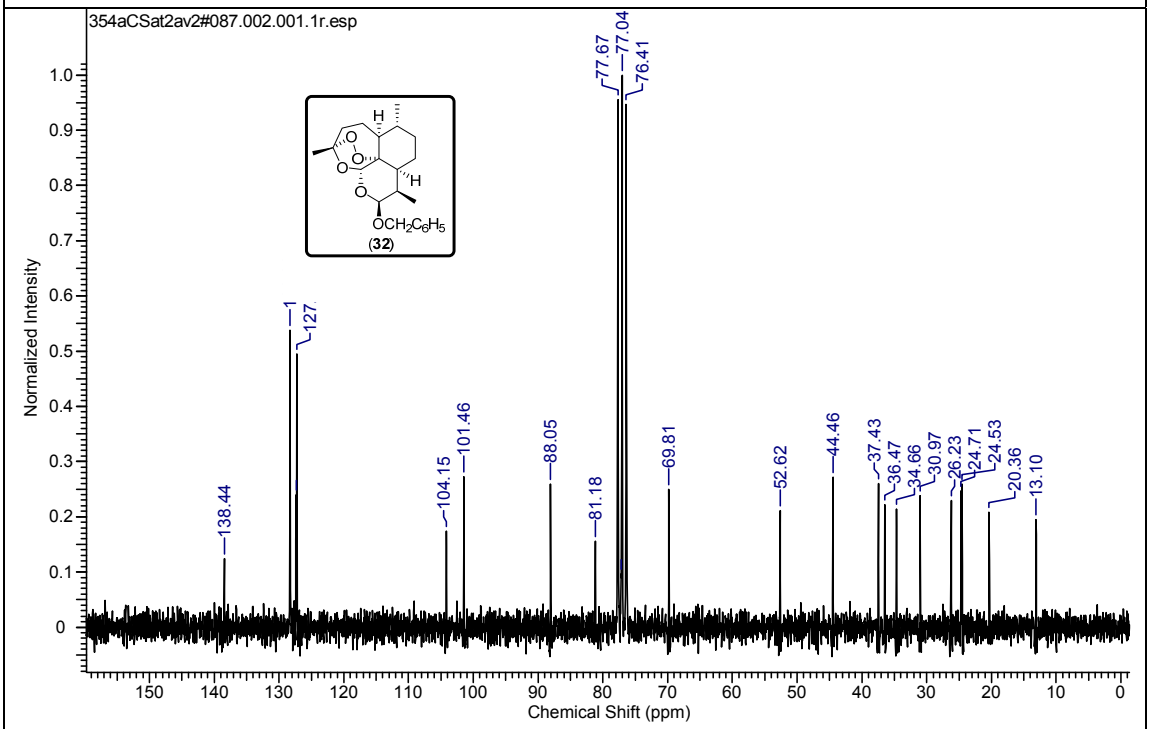
^{13}C NMR (125 MHz, $CDCl_3$) of (**31**)



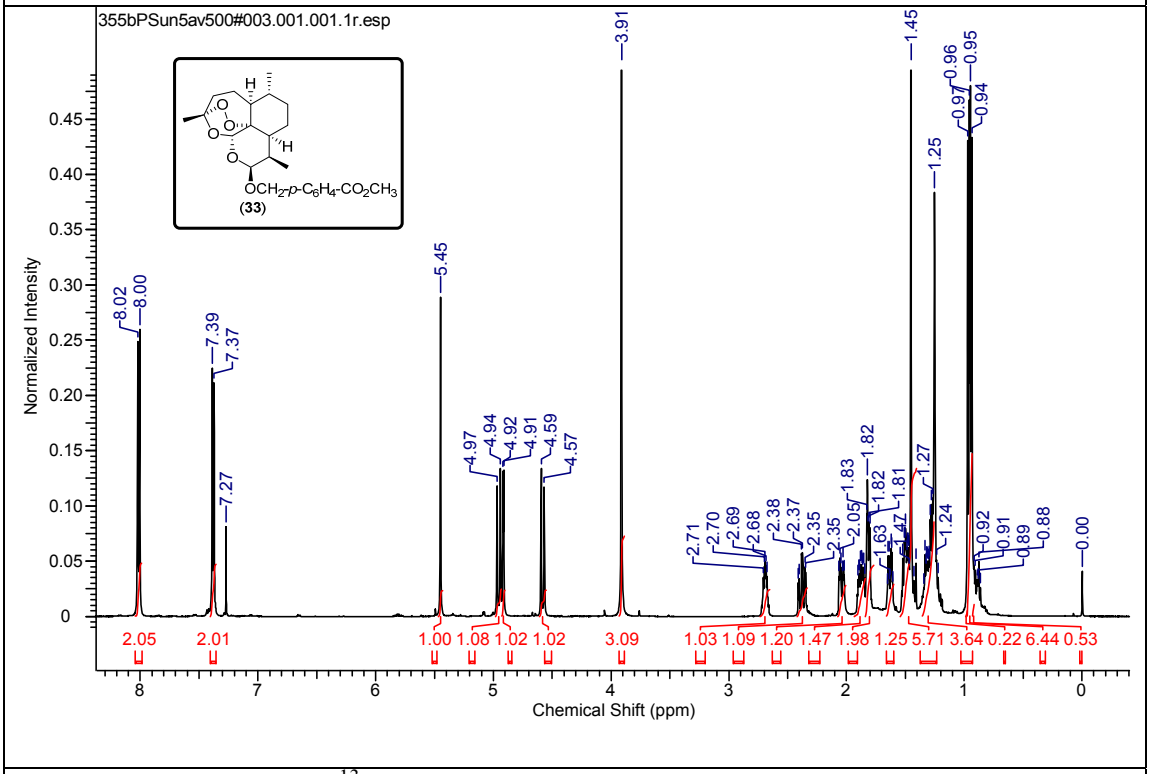
^{1}H NMR (200 MHz, $CDCl_3$) of (**32**)



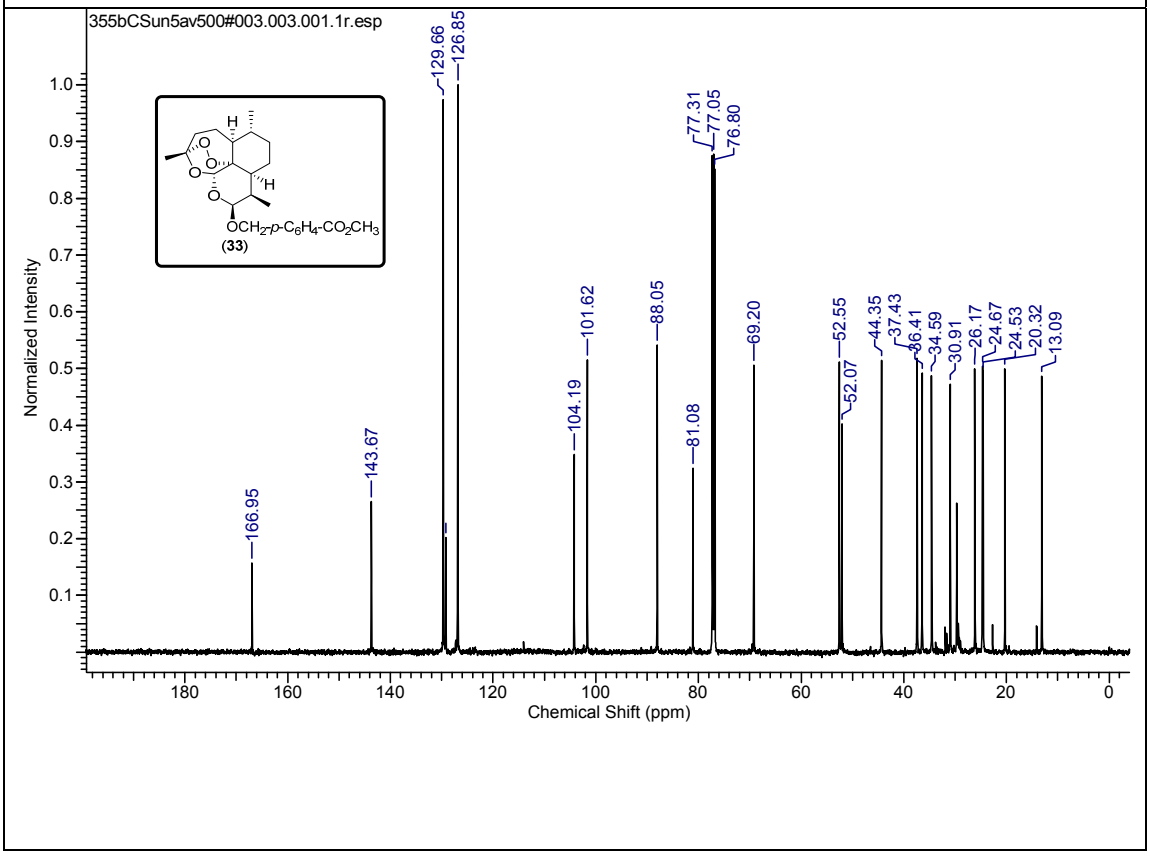
^{13}C NMR (50 MHz, $CDCl_3$) of (**32**)



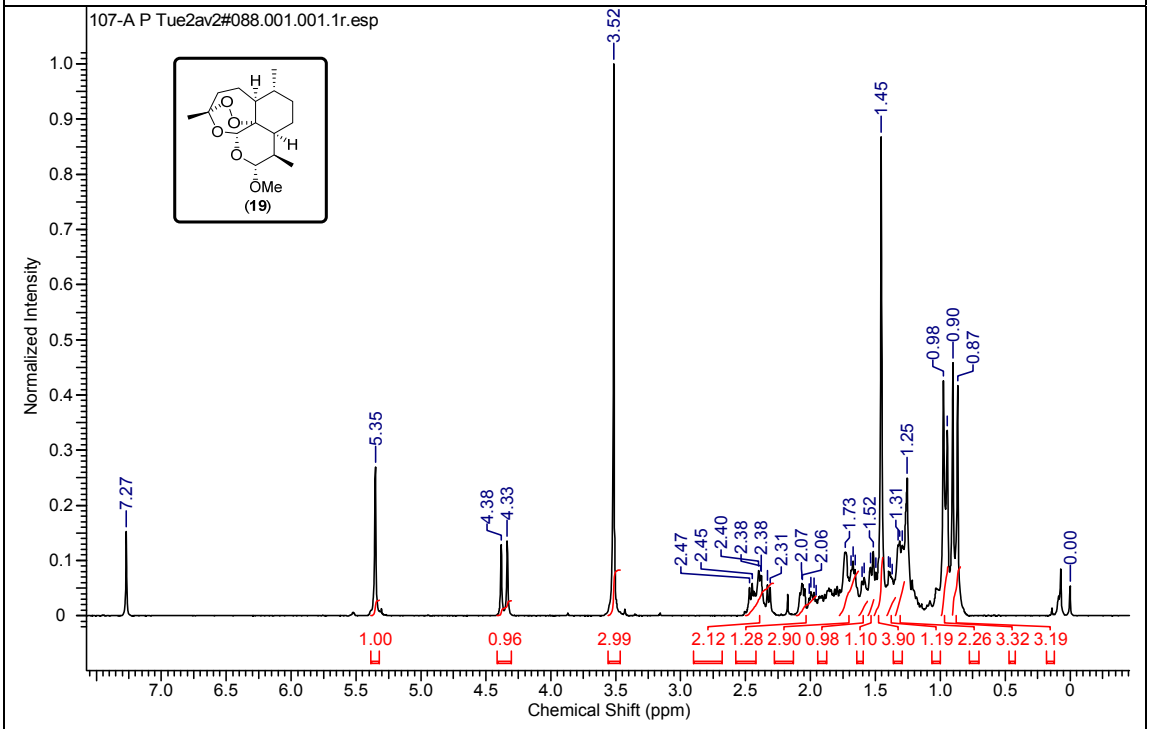
^{1}H NMR (500 MHz, $CDCl_3$) of (**33**)



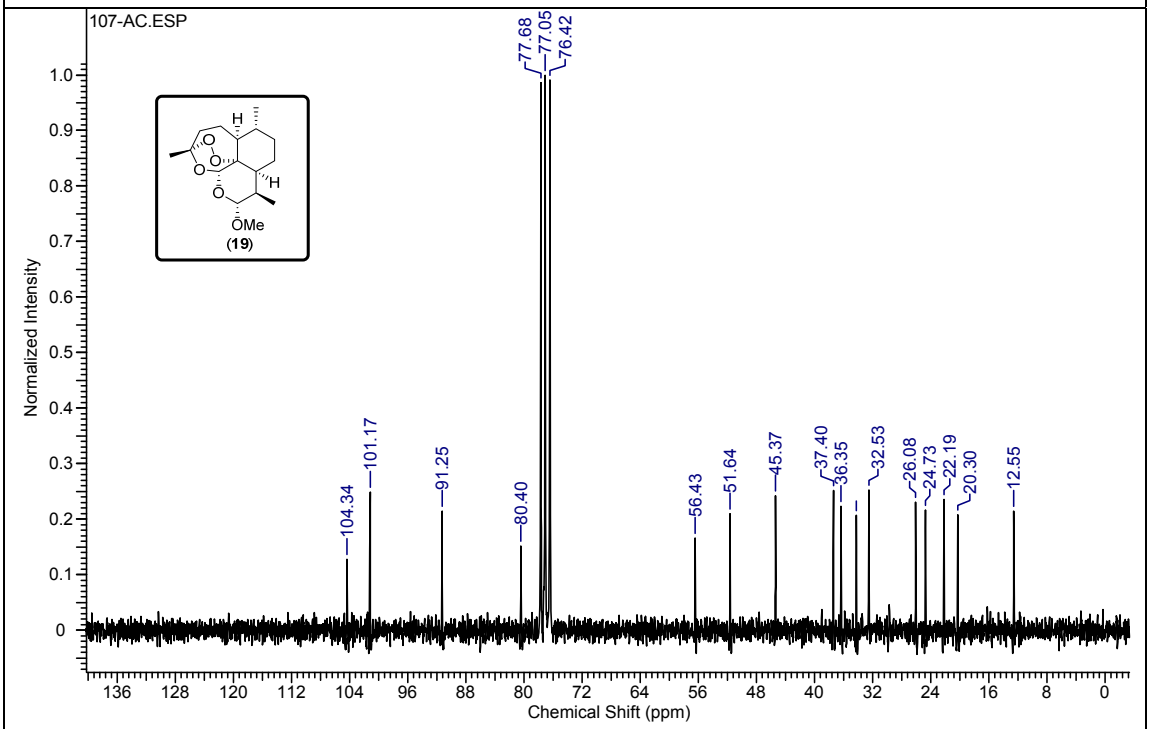
^{13}C NMR (125 MHz, $CDCl_3$) of (**33**)



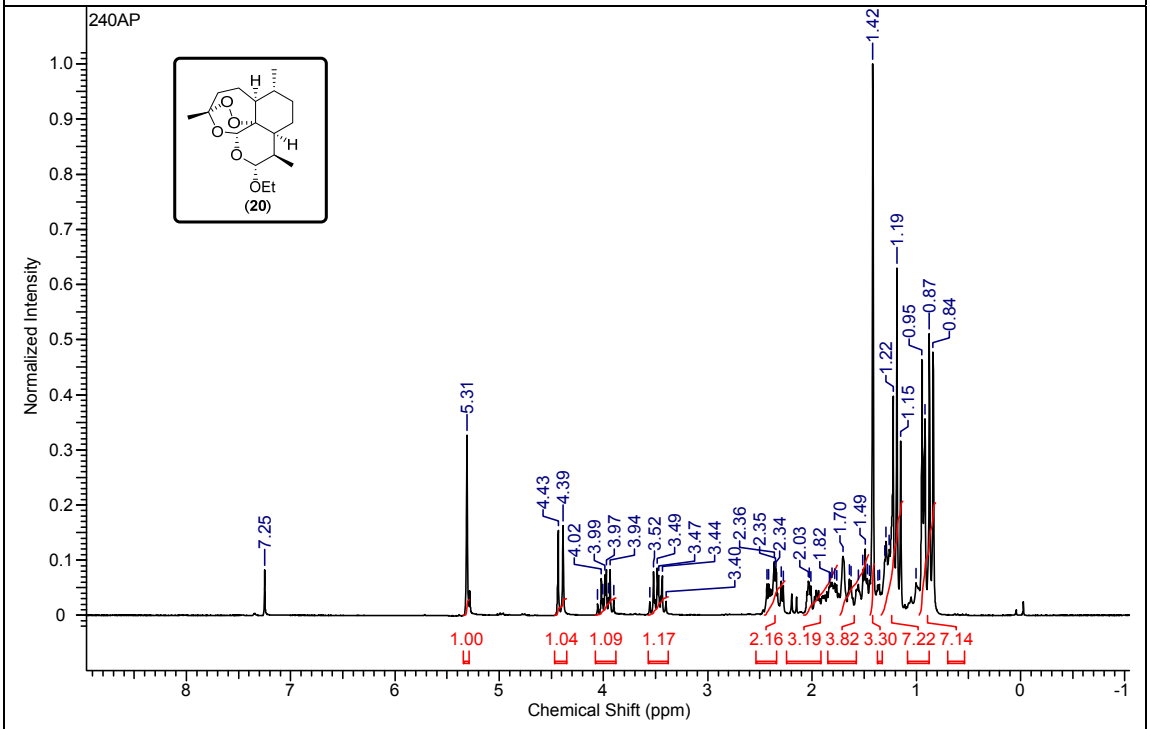
^{1}H NMR (200 MHz, $CDCl_3$) of (**19**)



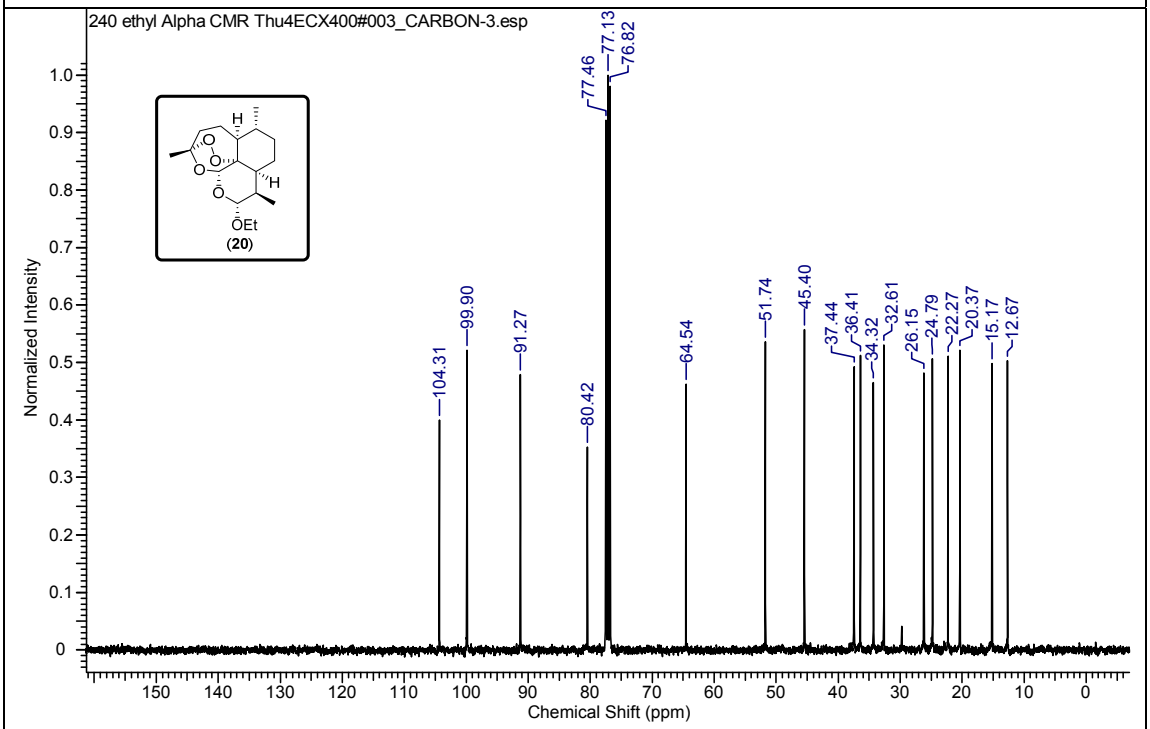
^{13}C NMR (50 MHz, $CDCl_3$) of (**19**)



^{1}H NMR (200 MHz, $CDCl_3$) of (**20**)

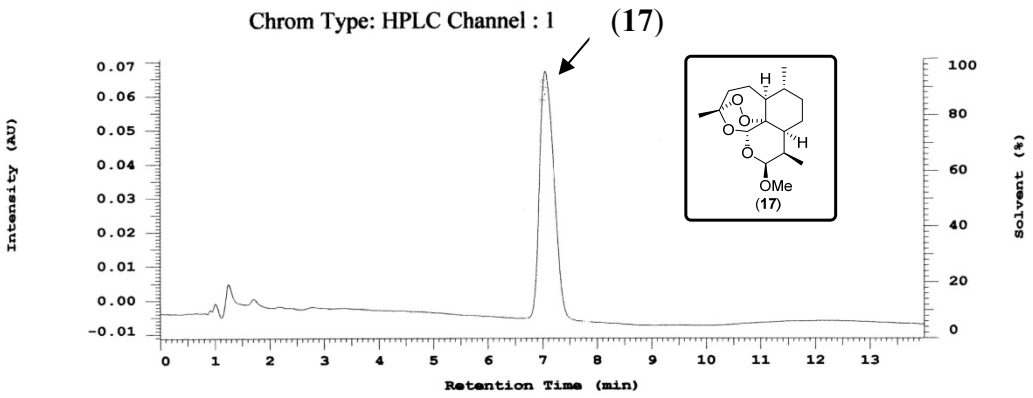


^{13}C NMR (100 MHz, $CDCl_3$) of (**20**)



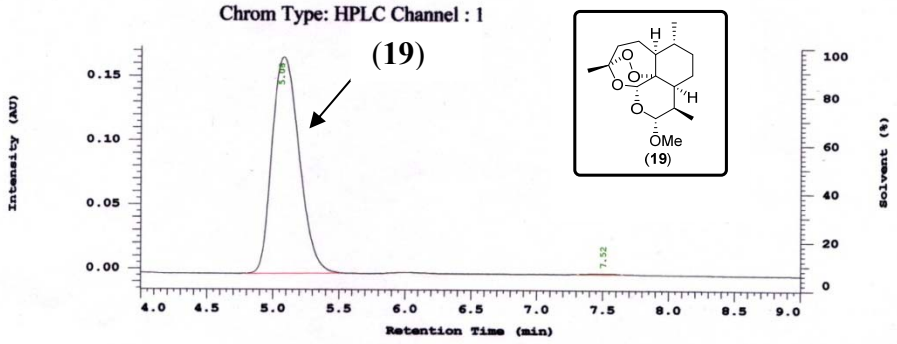
3.1.8 HPLC Chromatograms

C-12β-methyl ether (17)



No.	RT	Height	Area	Area %
1	7.05	36379	672635	100.000
		36379	672635	100.000

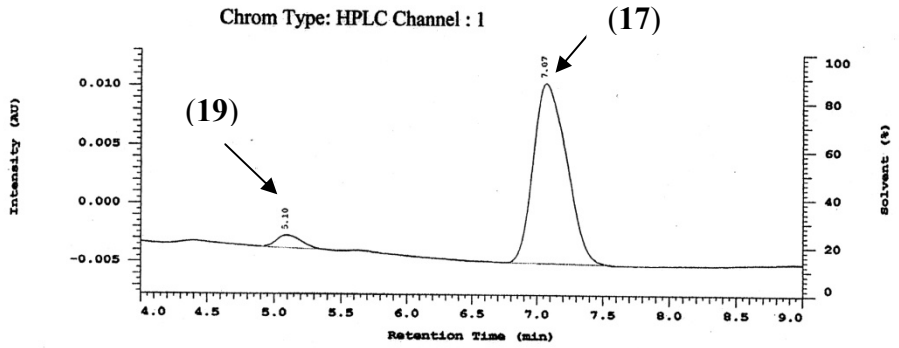
C-12α-methyl ether (19)



No.	RT	Height	Area	Area %
1	5.08	84075	1205969	99.798
2	7.52	206	2442	0.202
		84281	1208411	100.000

HPLC of crude mixture (17 and 19) synthesized

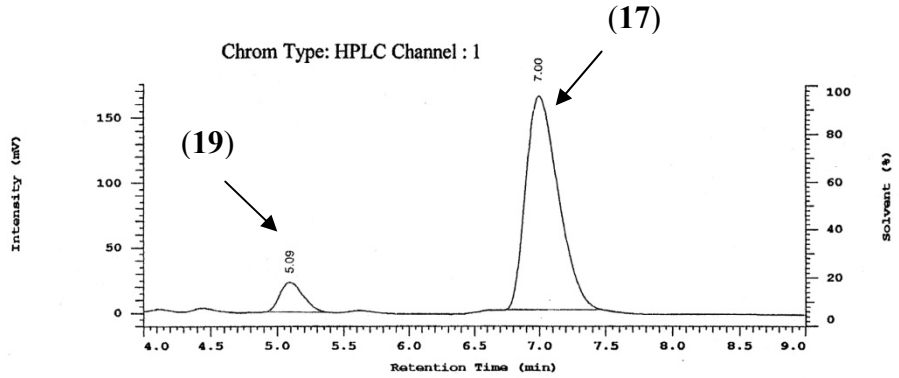
by Method I (CH_3CN at 0 °C)



No.	RT	Height	Area	Area %
1	5.10	516	6600	4.607
2	7.07	7690	136663	95.393
		8206	143263	100.000

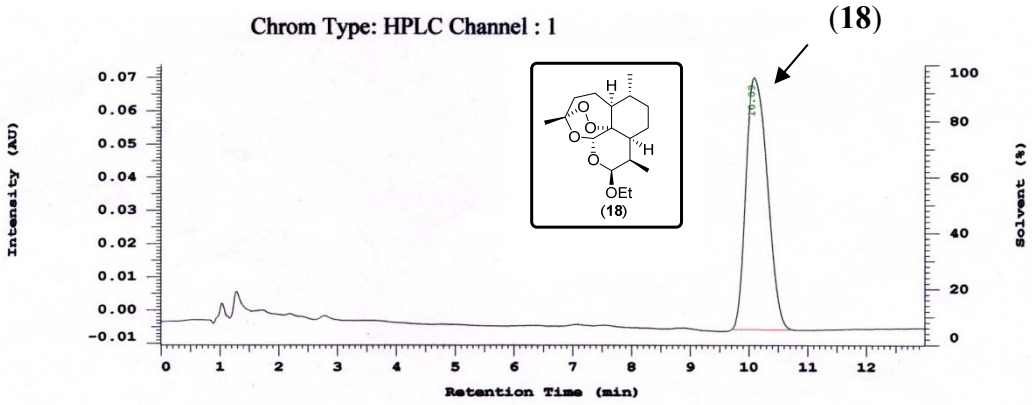
HPLC of crude mixture (17 and 19) synthesized

by Method II (CCl_3CN at rt)



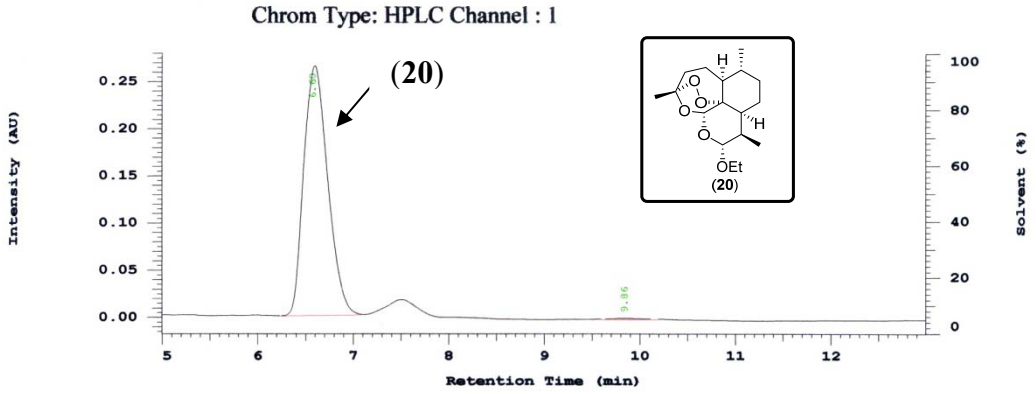
No.	RT	Height	Area	Area %
1	5.09	23180	285629	9.174
2	7.00	164249	2827737	90.826
		187429	3113366	100.000

C-12β-ethyl ether (18)



No.	RT	Height	Area	Area %
1	10.09	37821	967376	100.000
		37821	967376	100.000

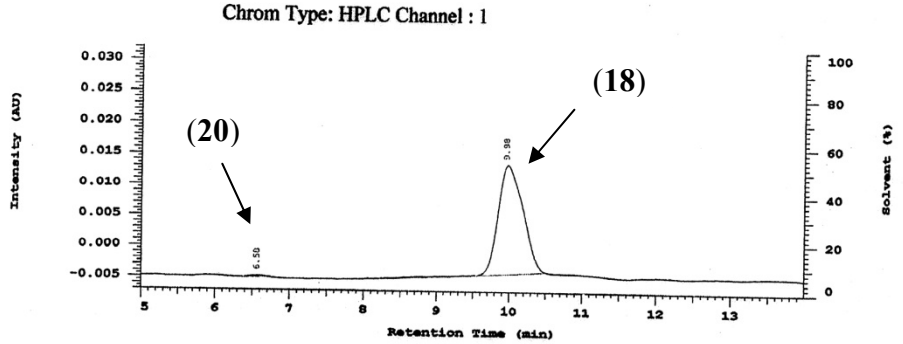
C-12α-ethyl ether (20)



No.	RT	Height	Area	Area %
1	6.60	132148	2321539	99.690
2	9.86	345	7218	0.310
		132493	2328757	100.000

HPLC of crude mixture (18 and 20) synthesized

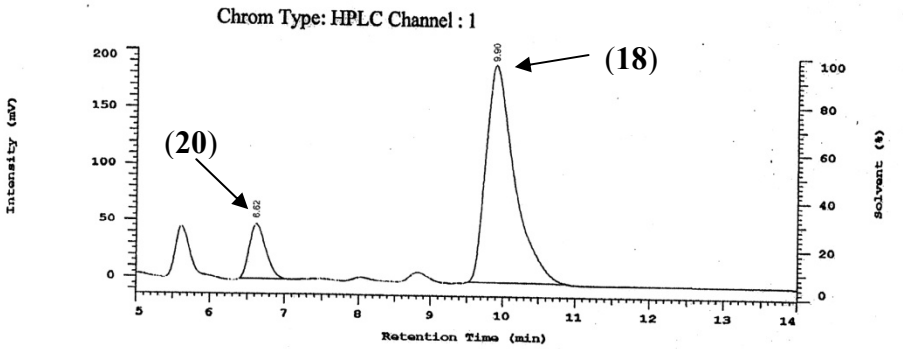
by Method I (CH_3CN at 0 °C)



No.	RT	Height	Area	Area %
1	6.58	64	769	0.367
2	9.98	8843	209083	99.633
		8907	209852	100.000

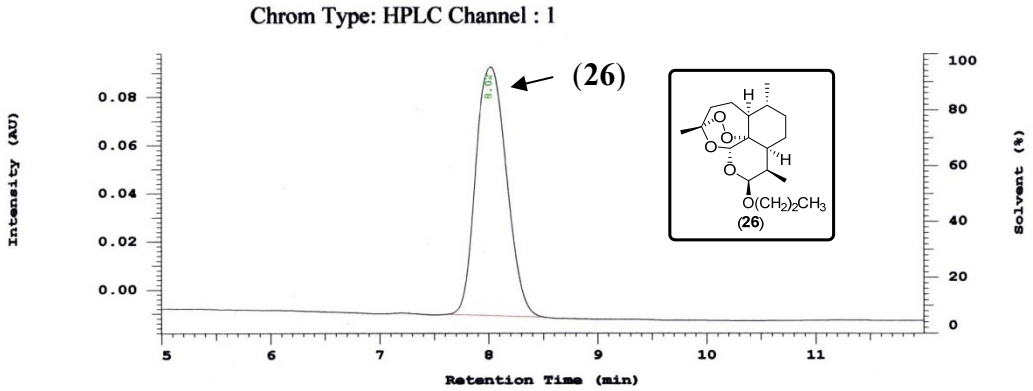
HPLC of crude mixture (18 and 20) synthesized

by Method II (CCl_3CN at rt)



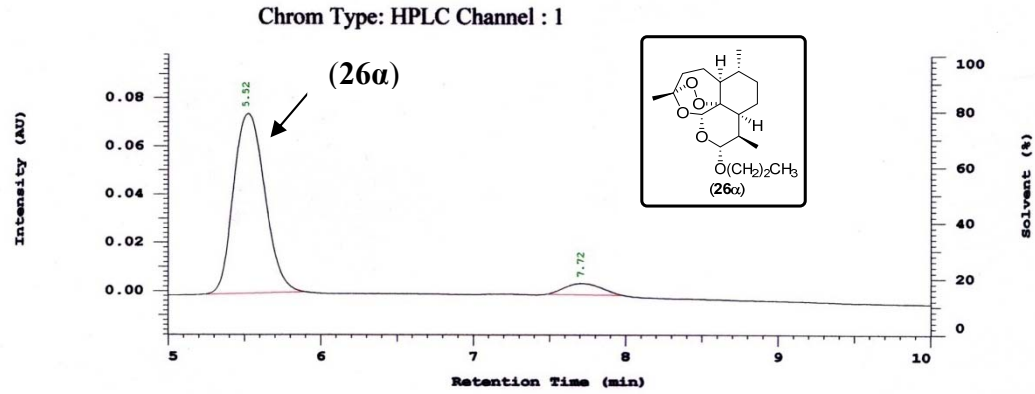
No.	RT	Height	Area	Area %
1	6.62	46990	699667	11.660
2	9.90	191918	5300832	88.340
		238908	6000499	100.000

C-12β-^{n}propyl ether (26)



No.	RT	Height	Area	Area %
1	8.02	51435	1013036	100.000
		51435	1013036	100.000

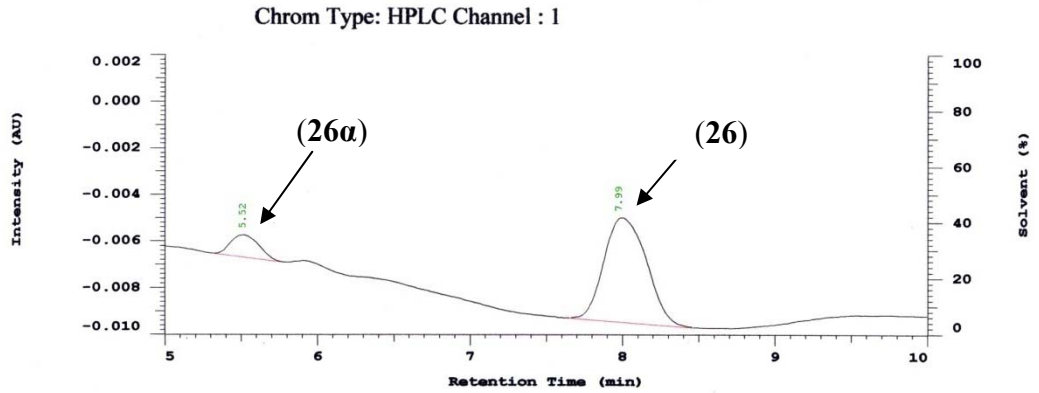
C-12α-^{n}propyl ether (26α)



No.	RT	Height	Area	Area %
1	5.52	37203	531186	93.475
2	7.72	2242	37077	6.525
		39445	568263	100.000

HPLC of crude mixture (26and 26α) synthesized

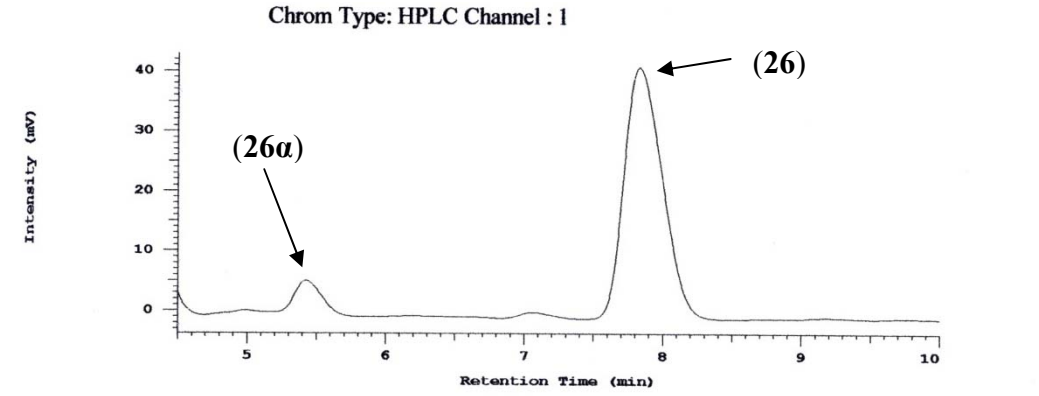
by Method I (CH_3CN at 0 °C)



No.	RT	Height	Area	Area %
1	5.52	472	6096	12.364
2	7.99	2227	43215	87.636
		2699	49311	100.000

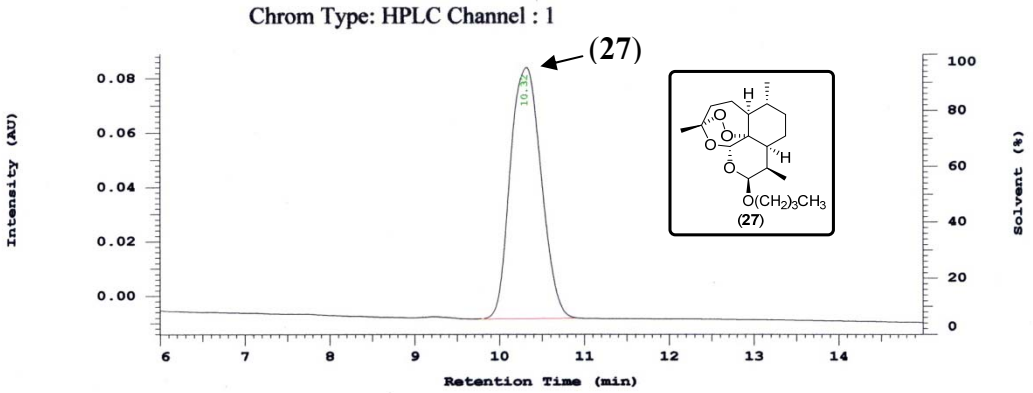
HPLC of crude mixture (26 and 26α) synthesized

by Method II (CCl_3CN at rt)



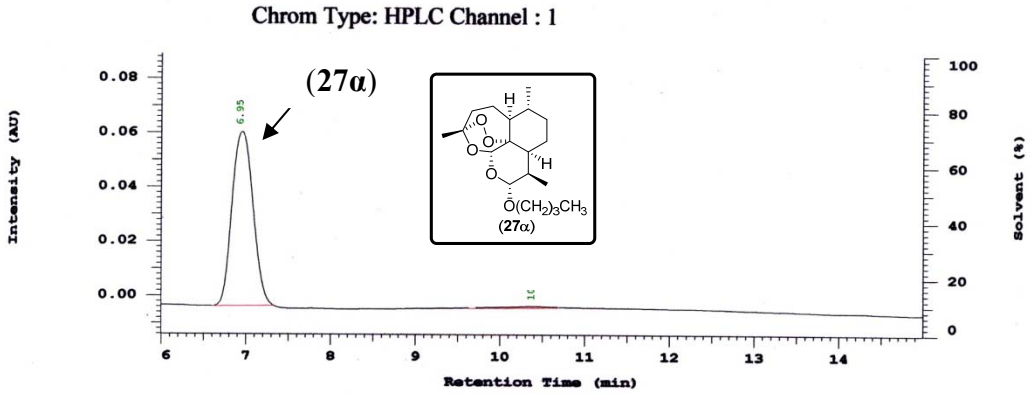
No.	RT	Height	Area	Area %
1	5.43	4322	45025	5.492
2	7.83	41487	774859	94.508
		45809	819884	100.000

C-12β-^{n}butyl ether (27)



No.	RT	Height	Area	Area %
1	10.32	46068	1159406	100.000
		46068	1159406	100.000

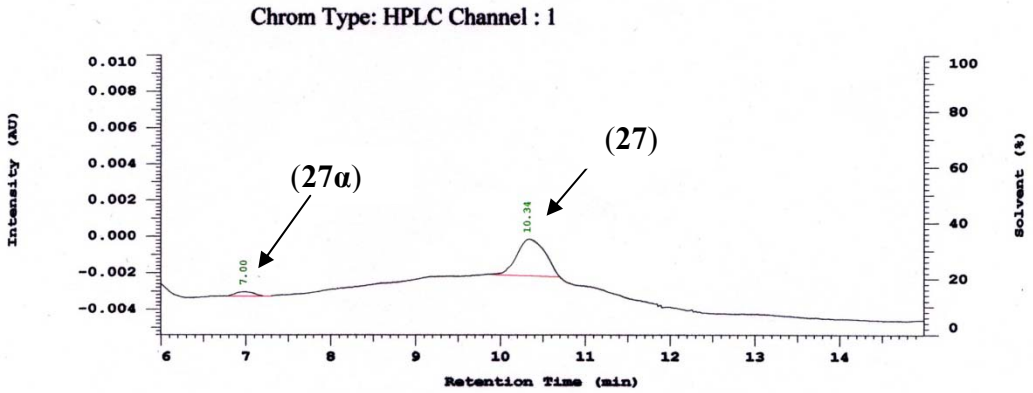
C-12α-^{n}butyl ether (27α)



No.	RT	Height	Area	Area %
1	6.95	32008	551283	99.025
2	10.39	165	5425	0.975
		32173	556708	100.000

HPLC of crude mixture (27 and 27α) synthesized

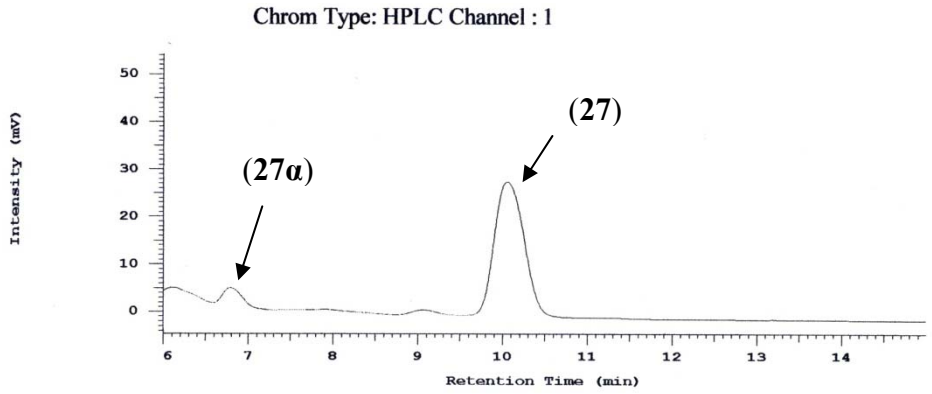
by Method I (CH_3CN at 0 °C)



No.	RT	Height	Area	Area %
1	7.00	119	1710	7.058
2	10.34	988	22517	92.942
		1107	24227	100.000

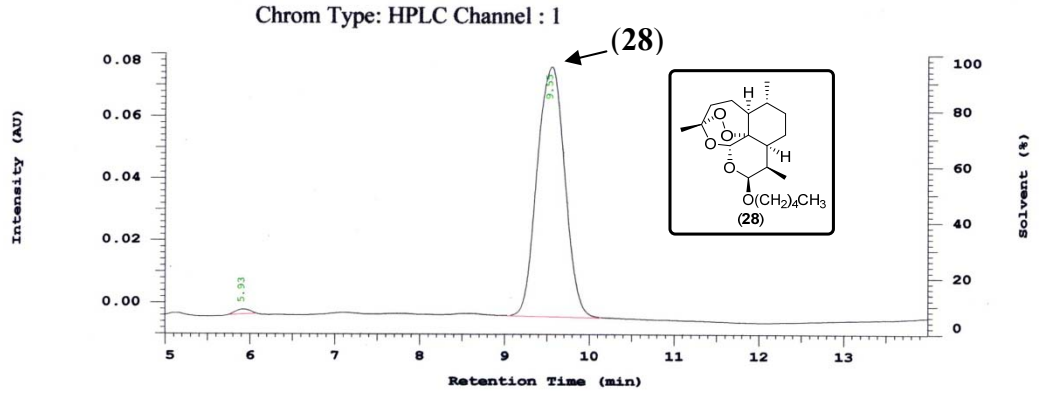
HPLC of crude mixture (27 and 27α) synthesized

by Method II (CCl_3CN at rt)



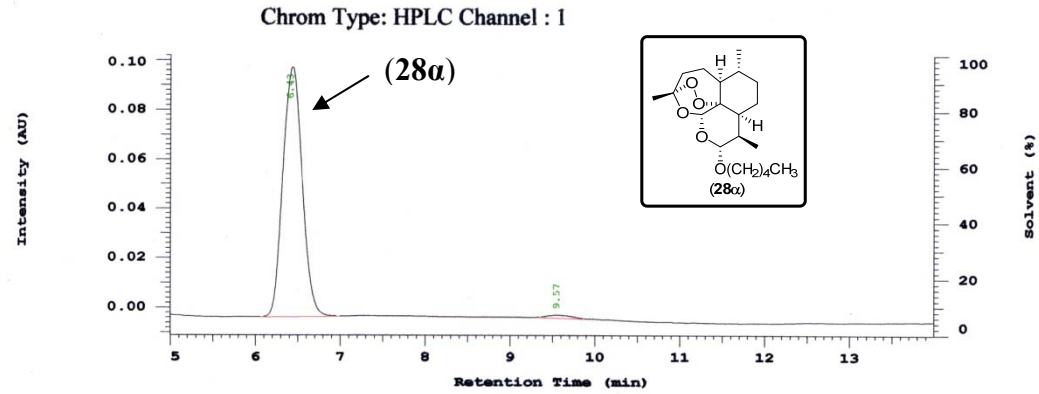
No.	RT	Height	Area	Area %
1	6.79	1729	15554	2.316
2	10.05	27709	656113	97.684
		29438	671667	100.000

C-12β-^{n}pentyl ether (28)



No.	RT	Height	Area	Area %
1	5.93	744	8444	0.923
2	9.55	40114	906619	99.077
		40858	915063	100.000

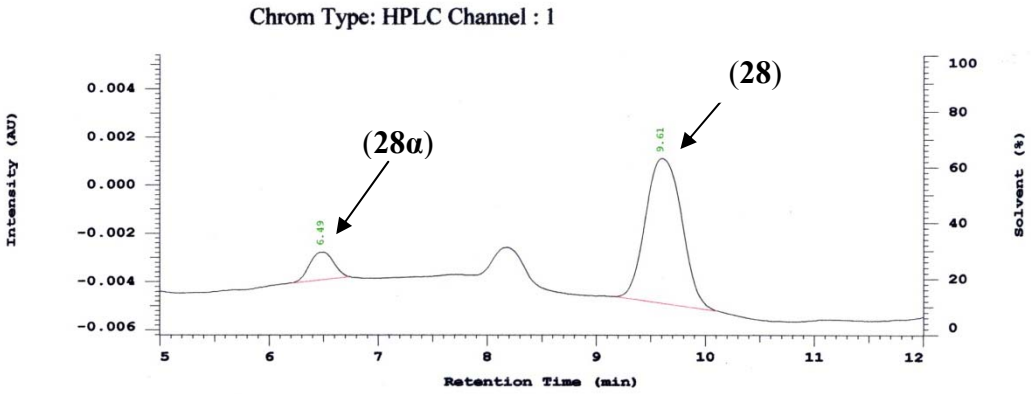
C-12α-^{n}pentyl ether (28α)



No.	RT	Height	Area	Area %
1	6.43	50363	795889	98.762
2	9.57	530	9974	1.238
		50893	805863	100.000

HPLC of crude mixture (28 and 28α) synthesized

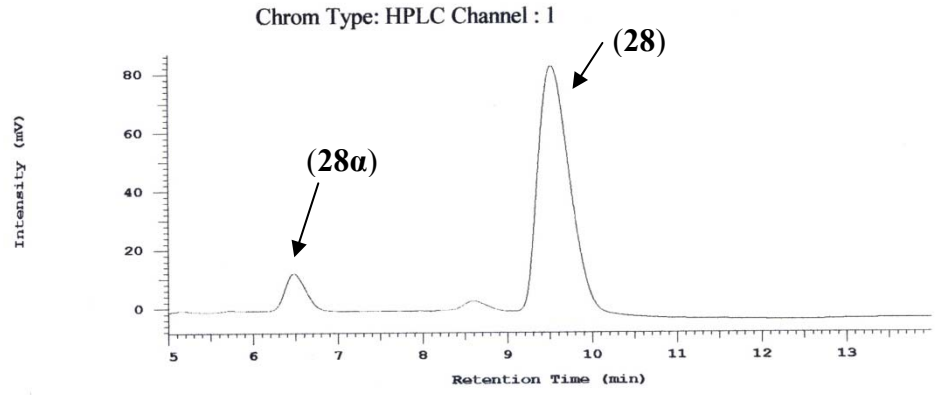
by Method I (CH_3CN at 0 °C)



No.	RT	Height	Area	Area %
1	6.49	560	8457	10.923
2	9.61	2994	68967	89.077
		3554	77424	100.000

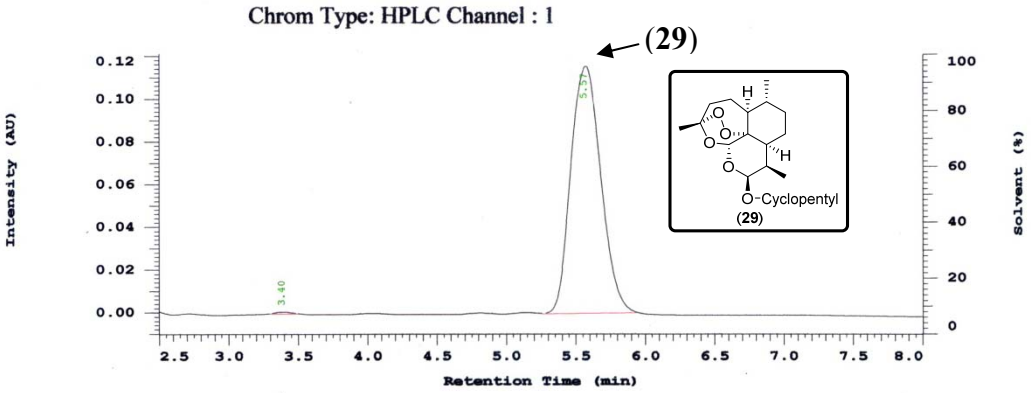
HPLC of crude mixture (28 and 28α) synthesized

by Method II (CCl_3CN at rt)



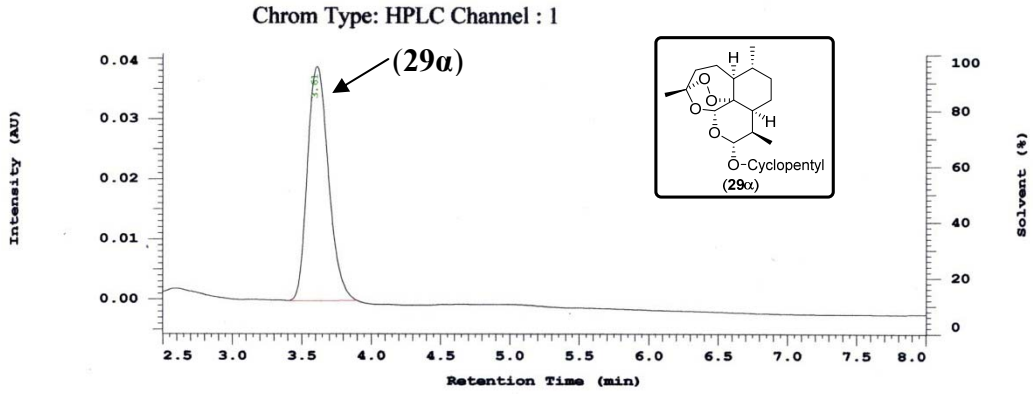
No.	RT	Height	Area	Area %
1	6.48	8050	90530	4.076
2	9.52	83622	2130733	95.924
		91672	2221263	100.000

C-12β-cyclopentyl ether (29)



No.	RT	Height	Area	Area %
1	3.40	408	2896	0.332
2	5.57	57663	869641	99.668
		58071	872537	100.000

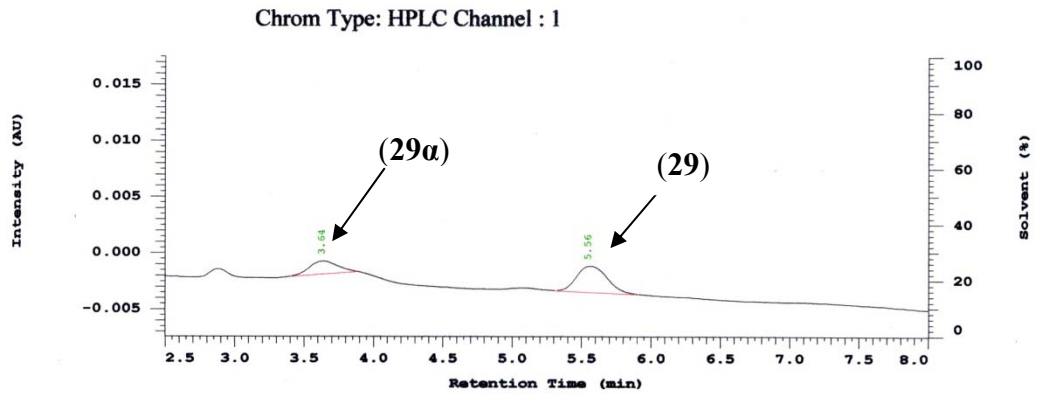
C-12α-cyclopentyl ether (29α)



No.	RT	Height	Area	Area %
1	3.61	19421	206582	100.000
		19421	206582	100.000

HPLC of crude mixture (29 and 29α) synthesized

by Method I (CH_3CN at 0 °C)

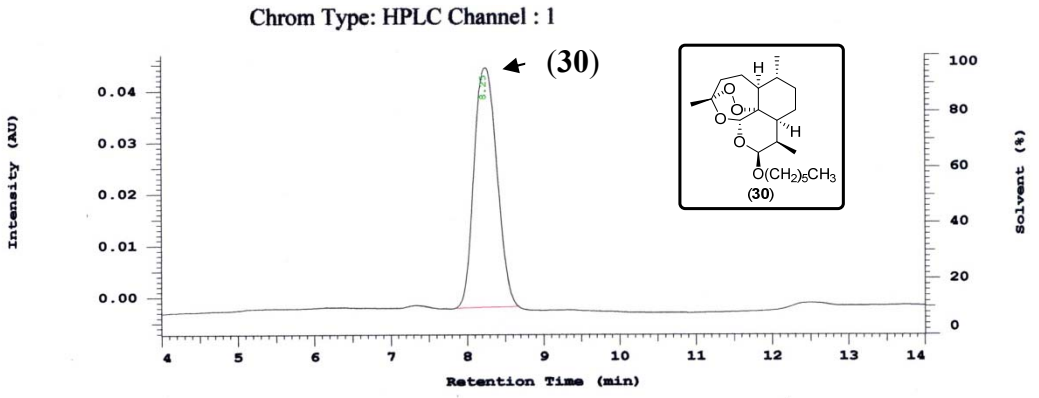


No.	RT	Height	Area	Area %
1	3.64	556	7748	30.804
2	5.56	1150	17404	69.196
		1706	25152	100.000

HPLC of crude mixture (29and 29α) synthesized

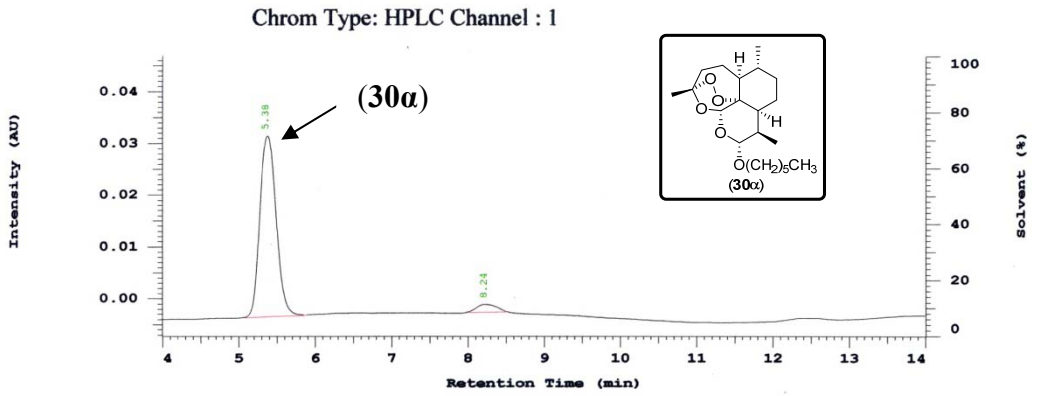
by Method II (CCl_3CN at rt): n.d.

C-12β-^{n}hexyl ether (30)



No.	RT	Height	Area	Area %
1	8.25	23091	485226	100.000
		23091	485226	100.000

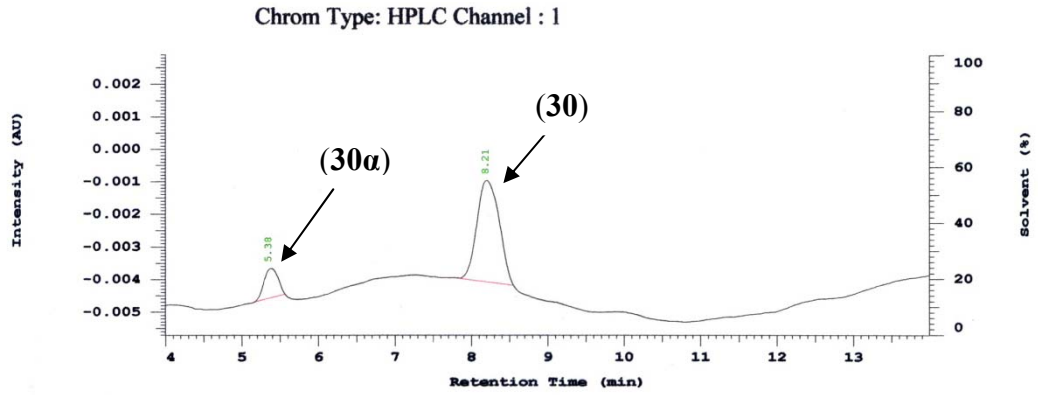
C-12α-^{n}hexyl ether (30α)



No.	RT	Height	Area	Area %
1	5.38	17416	257530	95.306
2	8.24	711	12684	4.694
		18127	270214	100.000

HPLC of crude mixture (30 and 30α) synthesized

by Method I (CH_3CN at 0 ^{o}C)

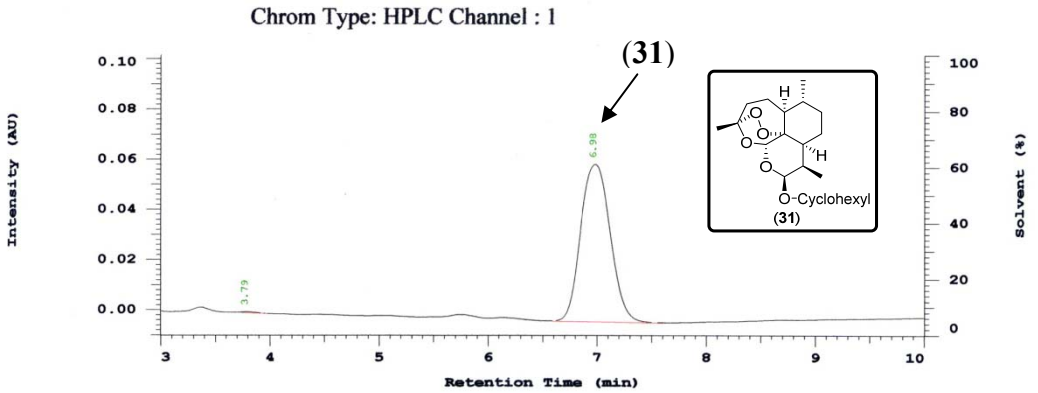


No.	RT	Height	Area	Area %
1	5.38	441	5554	15.087
2	8.21	1547	31263	84.913
		1988	36817	100.000

HPLC of crude mixture (30 and 30α) synthesized

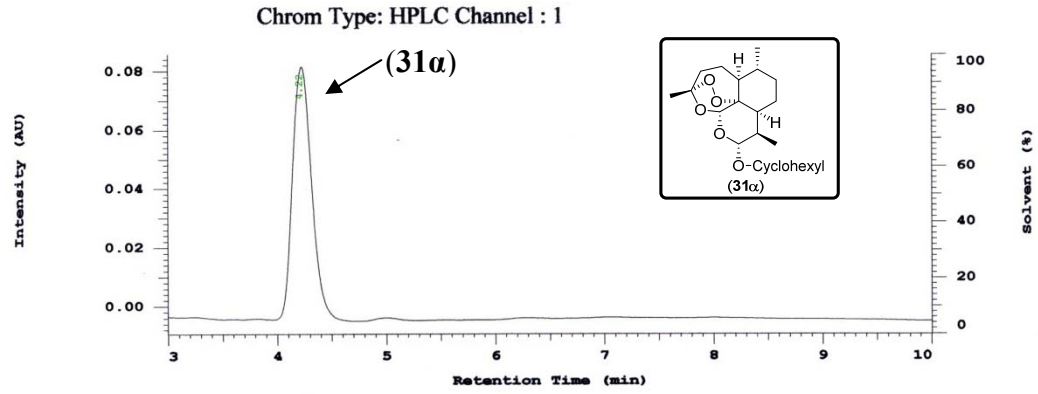
by Method II (CCl_3CN at rt): n.d.

C-12β-cyclohexyl ether (31)



No.	RT	Height	Area	Area %
1	3.79	129	1187	0.202
2	6.98	31262	587261	99.798
		31391	588448	100.000

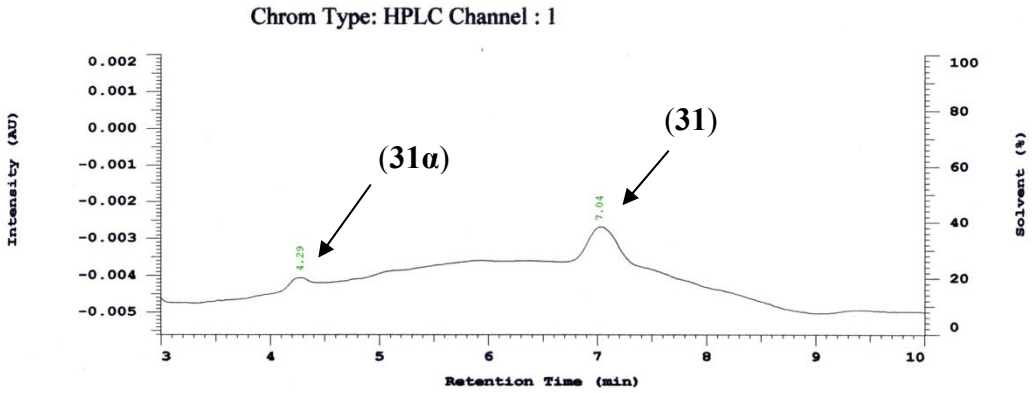
C-12α-cyclohexyl ether (31α)



No.	RT	Height	Area	Area %
1	4.22	42919	522036	100.000
		42919	522036	100.000

HPLC of crude mixture (31 and 31α) synthesized

by Method I (CH_3CN at 0 °C)

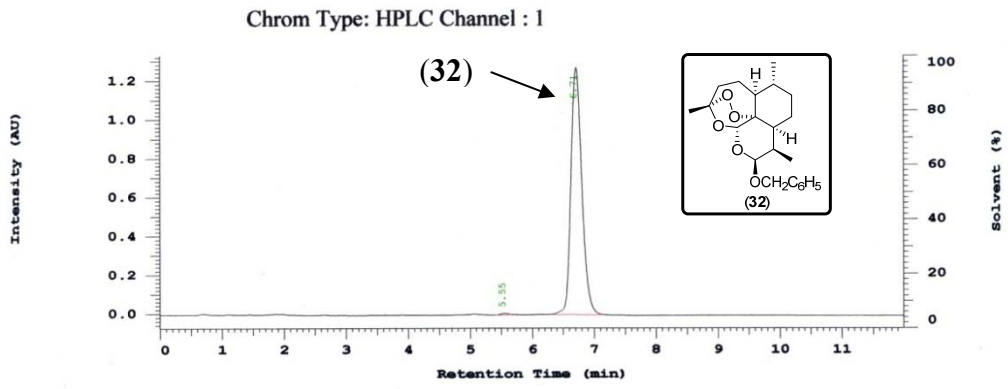


No.	RT	Height	Area	Area %
1	4.29	131	1652	16.639
2	7.04	477	8279	83.361
		608	9931	100.000

HPLC of crude mixture (31 and 31α) synthesized

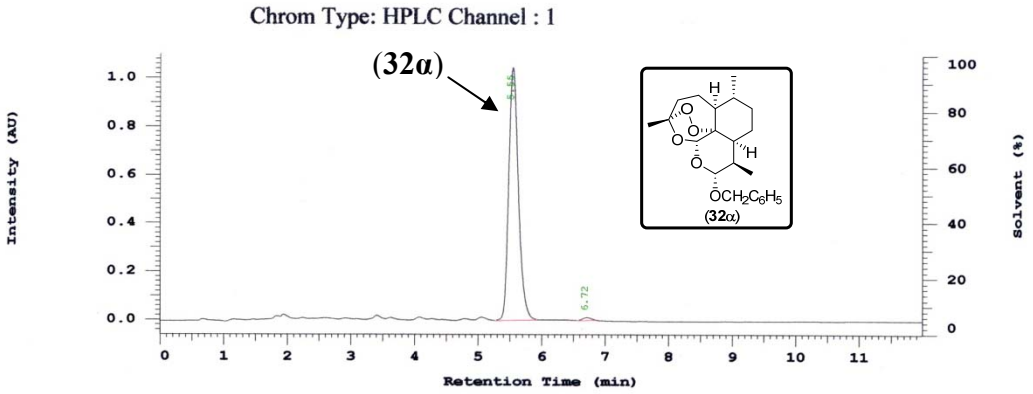
by Method II (CCl_3CN at rt): n.d.

C-12β-benzyl ether (32)



No.	RT	Height	Area	Area %
1	5.55	2918	21185	0.275
2	6.71	634095	7694930	99.725
		637013	7716115	100.000

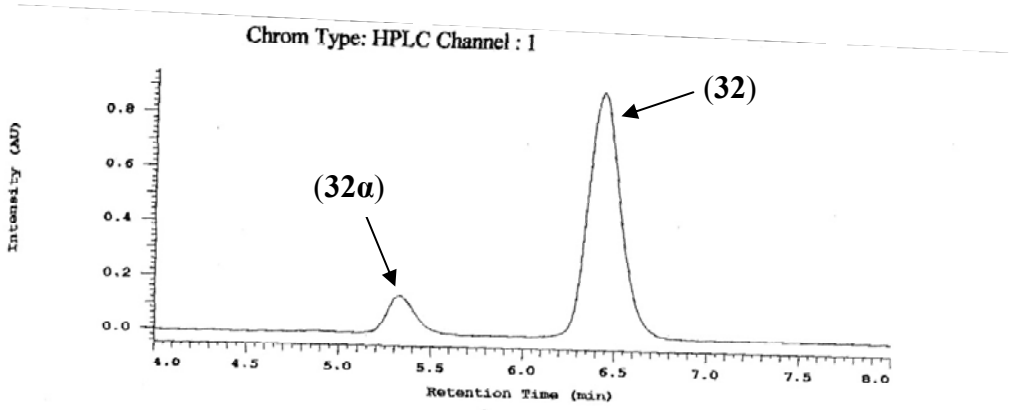
C-12α-benzyl ether (32α)



No.	RT	Height	Area	Area %
1	5.55	522159	5469077	99.128
2	6.72	5521	48096	0.872
		527680	5517173	100.000

HPLC of crude mixture (32 and 32α) synthesized

by Method I (CH_3CN at 0 °C)

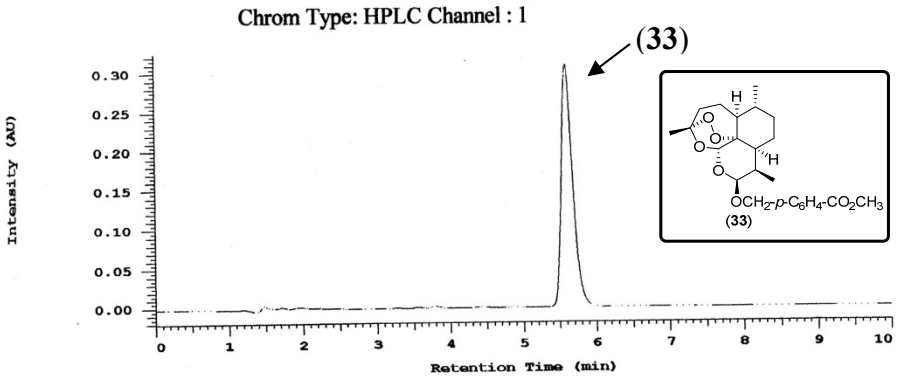


No.	RT	Height	Area	Area %
1	5.33	69319	706894	11.447
2	6.43	449118	5468388	88.553
		518437	6175282	100.000

HPLC of crude mixture (32 and 32α) synthesized

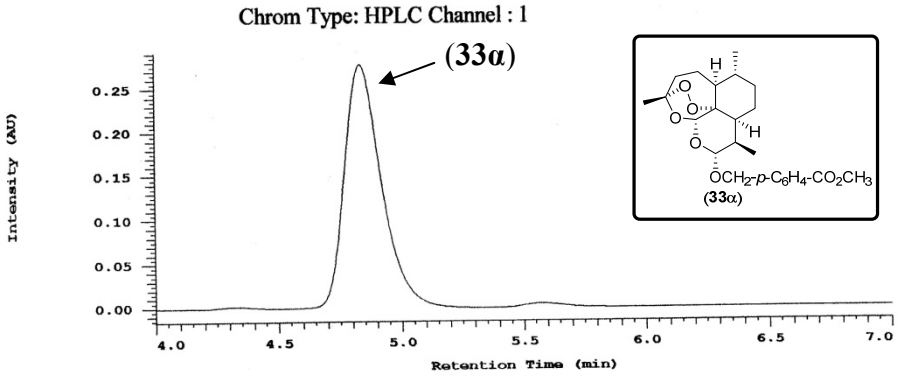
by Method II (CCl_3CN at rt): n.d.

β-Methyl-*p*-[(12-dihydroartemisinoxy)methyl] benzoate (33)



No.	RT	Height	Area	Area %
1	5.59	154003	1647320	100.000
		154003	1647320	100.000

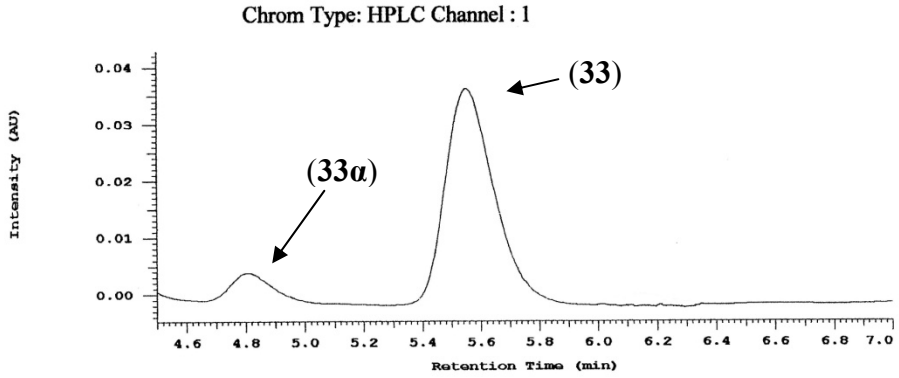
α-Methyl-*p*-[(12-dihydroartemisinoxy)methyl] benzoate (33α)



No.	RT	Height	Area	Area %
1	4.84	137738	1408919	100.000
		137738	1408919	100.000

HPLC of crude mixture (33 and 33α) synthesized

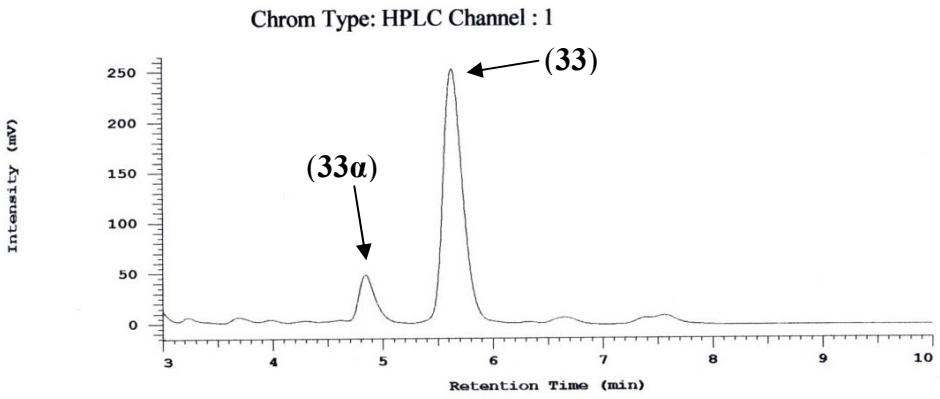
by Method I (CH_3CN at 0 °C)



No.	RT	Height	Area	Area %
1	4.81	2500	23827	9.795
2	5.55	19032	219428	90.205
		21532	243255	100.000

HPLC of crude mixture (33 and 33α) synthesized

by Method II (CCl_3CN at rt)



No.	RT	Height	Area	Area %
1	4.84	45985	466938	13.216
2	5.63	250912	3066320	86.784
		296897	3533258	100.000

3.1.9 References

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31. One may think that at the time of formation of ether derivative 1 equivalent of water formed can bring the hydrolysis imidoyl chloride and generate HCl. The generated HCl can then catalyze the reaction. However, this possibility is ruled out as the provious reports by Boehm *et al.* suggest that HCl-catalyzed etherification of (**34**) in acetonitrile furnished the product in the diastereomeric mixtures (β/α, 59:41). As we got the product in high diastereomeric ratio and yield, HCl participation can be readily ignored mixtures, see: Boehm, M.; Fuenfschilling, P. C.; Krieger, M.; Kuesters, E.; Struber, F. *Org. Process Res. Dev*. **2007**, *11*, 336.

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Chapter 4

Chemical Examination of *Polyalthia longifolia* var. *pendula* for Bioactive Molecules

4.1 Clerodane Diterpene as Antifungal Agents

4.1.1 Introduction to Natural Products as Drugs

Any chemical compound or substance produced by a living organism-which is found in nature is called **natural product**.[1-3] Moreover any substance produced by life also forms natural products.[4,5] Natural products have opened new doors for organic chemists for their semi synthesis or total synthesis by providing challenging synthetic targets. The term natural product is also applicable to cosmetics, dietary supplements, and foods produced from natural sources without added artificial ingredients.[6]

Concerning organic chemistry, natural products is better described as an purified organic compounds isolated from natural sources that are obtained by means of primary or secondary metabolism pathways.[7] Where as in medicinal chemistry field, natural product is limited only to secondary metabolites.[8,9] Unlike primary metabolites which have intrinsic role and important for survival, secondary metabolites have extrinsic role and are not very crucial for survival but they have a leading role in the organisms that produce them for evolutionary advantage. Natural products are usually derived from plants, animals, micro organisms or from marine organisms.

Traditional medicinal practices form the backbone of today's current modern medicine. Traditional medicine after subsequent modification in clinical, pharmacological and chemical studies has emerged as modern medicine. Probably the most famous and well known example to date would be the synthesis of the anti-inflammatory agent, acetylsalicylic acid (aspirin, nonsteroidal anti-inflammatory drug, NSAID) derived from the natural product, salicin isolated from the bark of the willow tree *Salix alba* L (Fig. 1). Investigation of *Papaver somniferum* L. (opium poppy) resulted in the isolation of several alkaloids including morphine, which is an analgesic opioid and is one of the most potent pain relievers. For thousands of years macro and micro fungi have been part of human life and have been used as food (*e.g.* mushrooms), in preparation of alcoholic beverages (*e.g.* yeasts) and medication in traditional medicine. In past few decades with advancement in microbiology their uses have extended to enzymes, biological control, antibiotics and other pharmacologically active products. It is noteworthy that one of the most famous natural product

discoveries is that of penicillin, which is obtained from the fungus, *Penicillium notatum* discovered by Fleming in 1929. Penicillin G today is a well known antibiotic in medicine. Mevastatin used as a hypolipidemic agent (cholesterol lowering agent), belongs to statins class and isolated from *Penicillium cetrinum*. Similar to mevastatin, atorvastatin is another drug which shares the common use. Colchicine used to treat gout is a toxic natural product and extracted from plants of genus *Colchicum*.[11] Teprotide is a nonapeptide, an angiotensin converting enzyme inhibitor (ACE inhibitor), which inhibits the conversion of angiotensin I to angiotensin II. It has been isolated from the snake *Bothrops jararaca*.[12] It is used as an antihypertension agent. Many ACE inhibitors have been developed since past few years but Captopril emerged as the first antihypertension drug. Paclitaxel, isolated from the bark of *Taxus brevifolia* (Pacific Yew tree) is an anti cancer (antineoplastic or cytotoxic) chemotherapy drug[10] and even today it is isolated from its natural source. It is being most widely used as a breast cancer drug (Fig. 1).

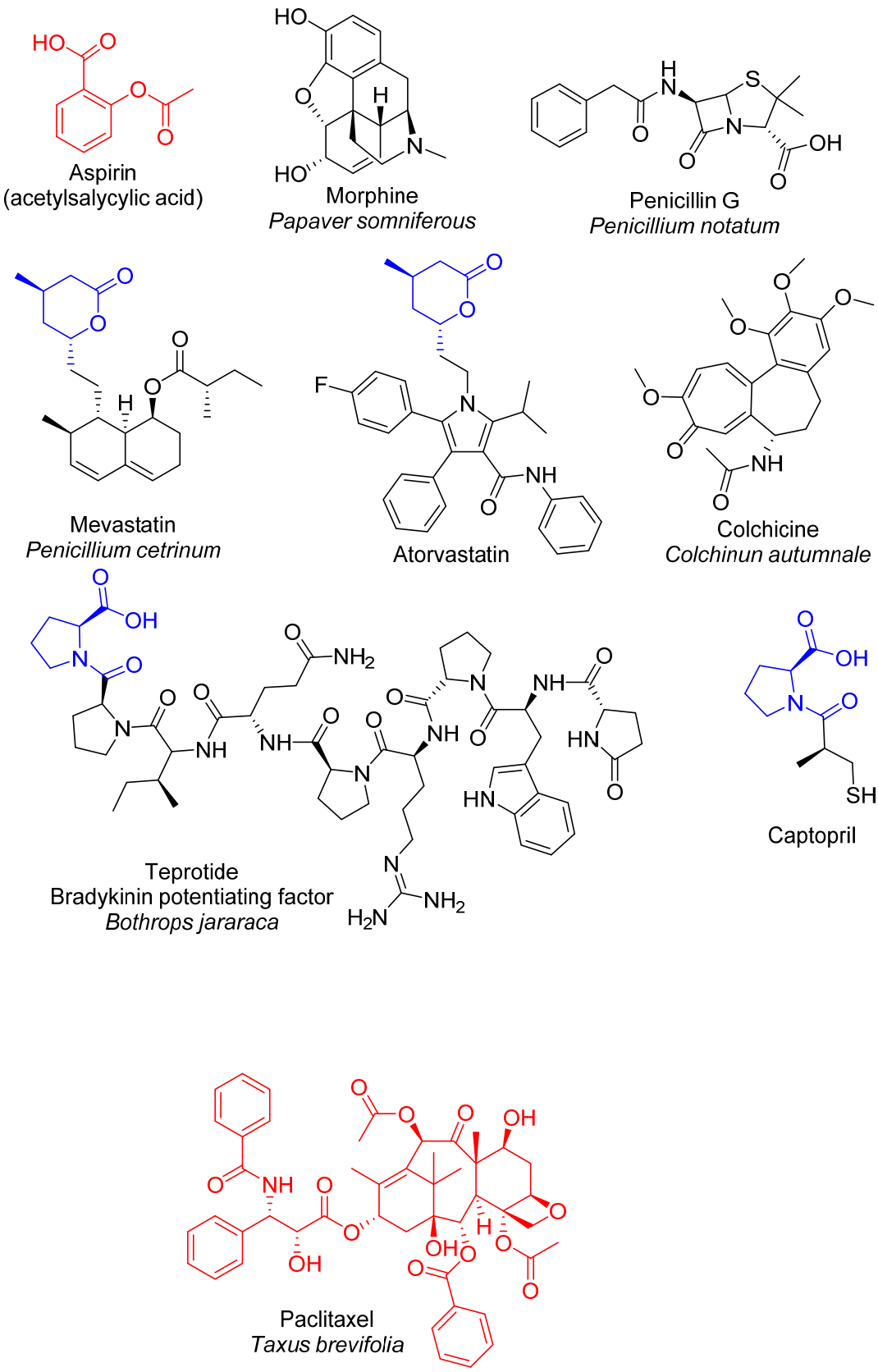


Figure 1. Few representative examples of drugs based on natural products.[10-12]

4.1.2 Introduction to *Polyalthia longifolia* var. *pendula*:

Polyalthia is the Greek word for poly, meaning much or many and althia from àltheo, meaning to cure. The genus *Polyalthia* (Annonaceae) has been credited with seventy species out of which only seven are indigenous to India. *Polyalthia longifolia* var. *pendula* Linn. is popularly known as "ulta Ashok" in India and widely grown in the gardens of tropical and subtropical Asia as an evergreen ornamental tree (Fig. 2).[13]

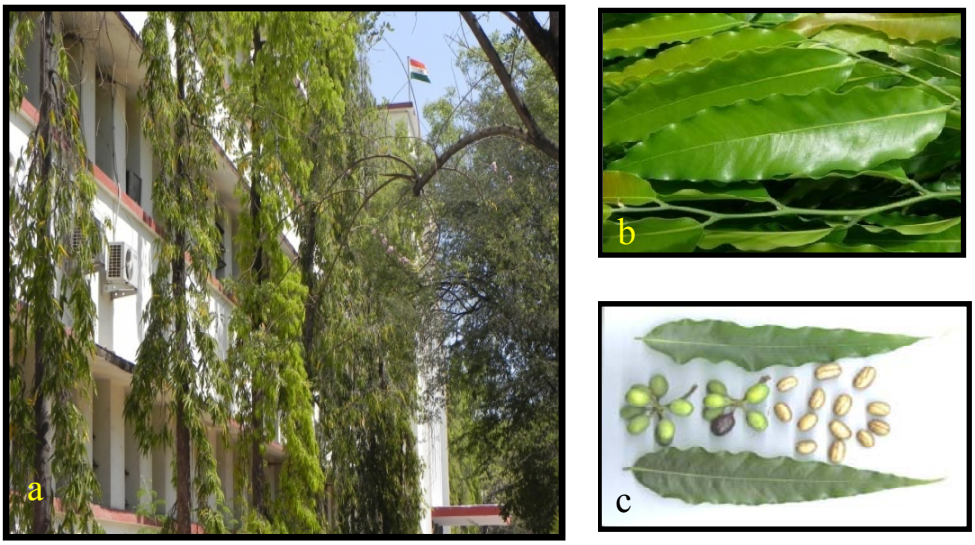


Figure 2. (a) An aerial view of *P. Longifolia* at CSIR-NCL, Pune. (b) Leaves and (c) Leaves and seeds.

Medicinal importance of *Polyalthia longifolia* var.*pendula*

This plant has been reported to be widely used in traditional system of medicine for the treatment of hypertension, fever, diabetes, helminthiasis and skin diseases.[14]

4.1.3 Chemical Constituents of *Polyalthia longifolia* var. *pendula*

The chemical examination of *P. longifolia* var. *pendula* has resulted in the isolation of several classes of compounds such as diterpenes, including clerodane, triterpenes and aporphine alkaloids and these have been investigated for various biological activities.[3-8] This section gives a short insight to the isolated compounds from *P. longifolia.*

Diterpenes *viz.* **labdane** and **clerodane** dominate the major chemical constituents in *P. longifolia* (Fig. 3).

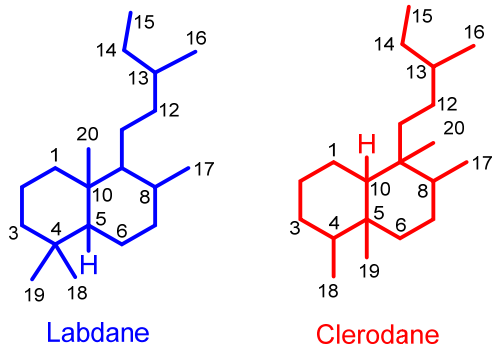


Figure 3. Major diterpene skeleton: labdane and clerodane found in *P. longifolia.*

Diterpene compounds (**1-4**) were isolated by Lee *et al.*[15] from the methanol extract of the stems of *P. longifolia* var. *pendula*. Hara *et al.*[16] reported *ent*-halimane diterpenes compounds (**5-10**) from the hexane extract of stem bark of *P. longifolia* (Fig. 4).

Alkaloids belonging to aporphine and azafluorene also form the essential part of chemical constituents of *P. longifolia.* Isolation of cytotoxic aporphine alkaloids liriodenine (**11**), and two aporphine alkaloids noroliveroline (**12**), and oliveroline-β-*N*-oxide (**13**) were reported by Wu *et al.*[17] They also reported bio-inactive azafluorene alkaloids darienine (**14**), polyfothine (**16**) isooncodine (**17**) along with (**15**), (**18**) and (**19**) from stem and stem barks of *P. longifolia* (Fig. 5).

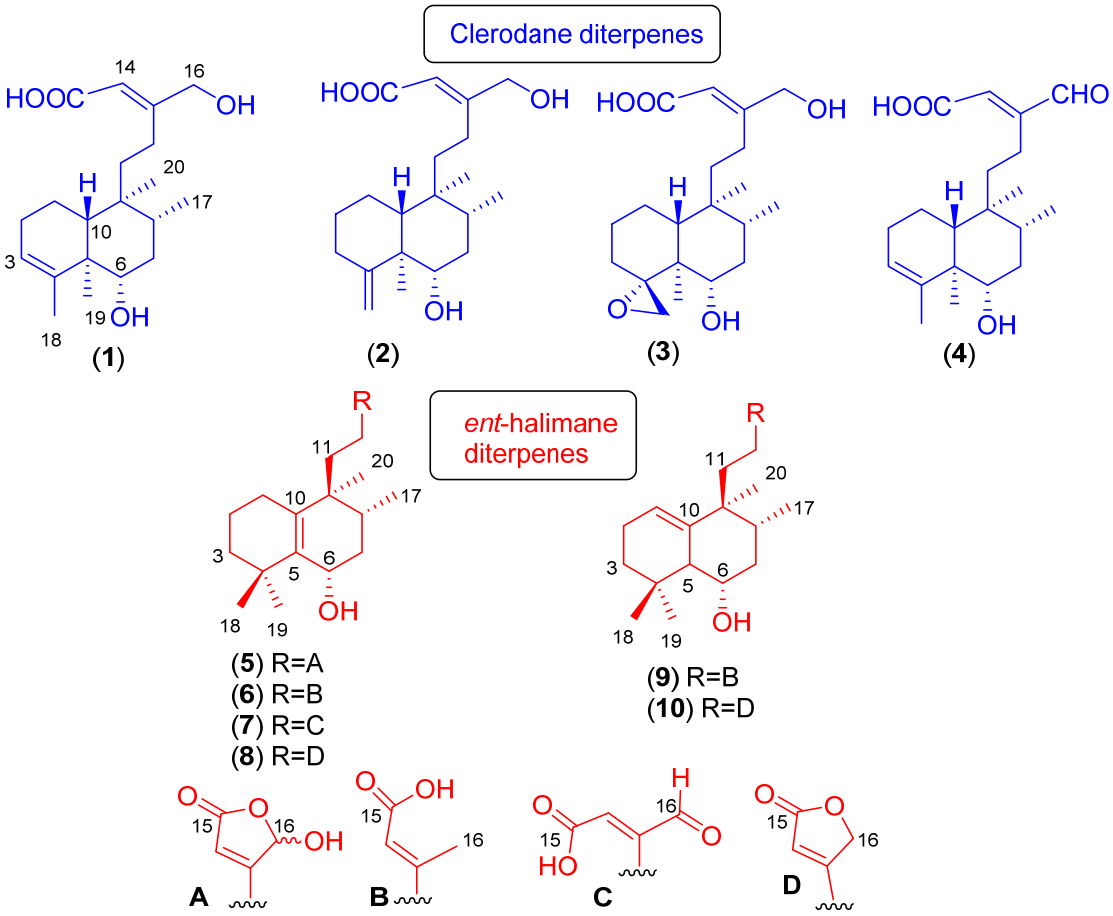


Figure 4. Major clerodane diterpenes and *ent*-halimane diterpenes from *P. longifolia*.

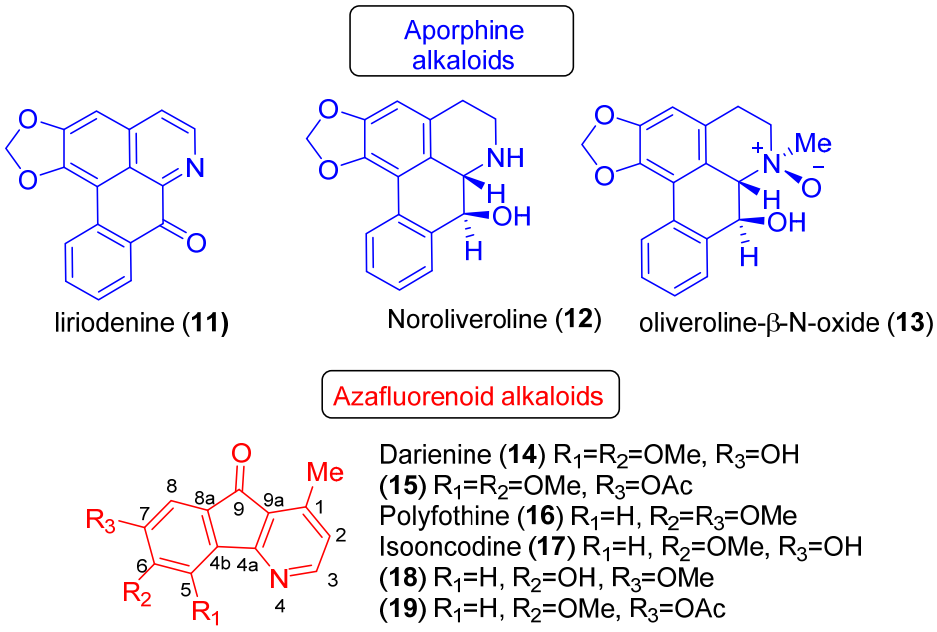


Figure 5. Alkaloids (aporphine and azafluorene) from *P. longifolia*.

Clerodane acids derivatives are commonly found in the fruits of *P. longifolia.* Wu *et al.*[18] have reported isolation of three new clerodane diterpenes, (4→2)-*abeo*-cleroda-2,13*E*-dien-2,14-dioic acid (**20**), (4→2)-*abeo*-2,13-diformyl-cleroda-2,13*E*-dien-14-oic acid (**22**) and 16(*R*&*S*)- methoxycleroda-4(18),13-dien-15,16-olide (**23**) from the unripe fruit of *P. longifolia* var. *pendula.*

Similarly three new diterpenes, polylongifoliaic A (**25**), polylongifoliaons A (**26**) and B (**27**) were isolated from the unripe fruits of *P. longifolia* by Wu *et al.*[19] (Fig. 6).

Some other compounds isolated from *P. longifolia.* are kolavanic acid,[20] lanuginosine, oxostephanine,[21] (-)-8-oxopolyalthianine, α-amyrin, β-amyrin, querctin and its glycoside, (+)-isoboldine, (-)-asimilobine, hordenine, anonaine,[22] (+) norlirioferine, (-) stepholidine,[23] altholactone[24] and proanthocyanidin.[25,26]

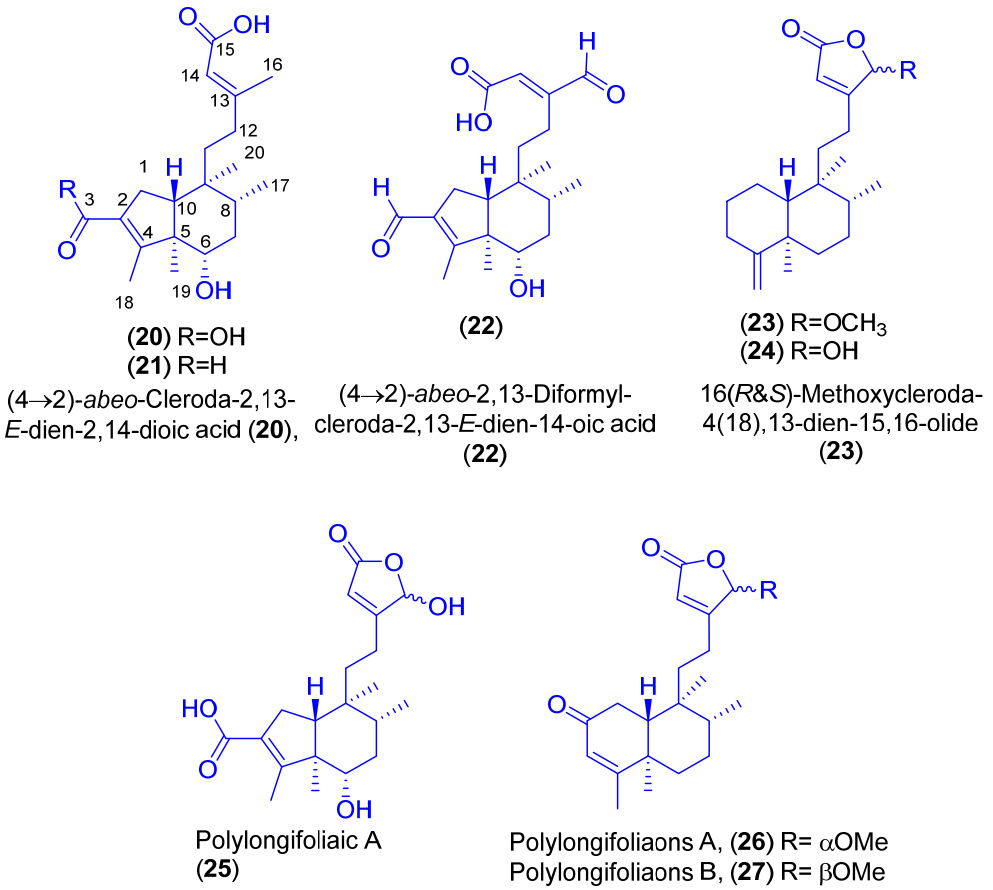


Figure 6. Clerodane acids derivatives and other compounds from fruits of *P. longifolia.*

4.1.4 Antifungal Agents

4.1.4.1 Introduction

Even today natural product constituents serve as the remedy for many illnesses, for good health and are preferred to the synthetic one. The biggest boon which natural product shares in having its curative properties is that they have minimum side effects.

Since past few decades, development of resistance in several species of fungi to available drugs/fungicides has resulted in considerable increase in medical expenditure.[27] It is estimated that greater than 75 % of all the fungal infections are caused by the *Candida* species *viz*. *Candida albicans*, *C. tropicalis*, *C. glabrata* and *C. parapsilosis* in humans.

4.1.4.2 Antifungal Agents: Chemical Entity

Extensive research on the development of new antifungal agents has been carried out but only some have completed clinical trials and are being used as drugs and few more molecules are undergoing clinical trials at present. Currently the drugs available for the treatment of fungal infections could be broadly classified into five classes of compounds, which include **azoles** (**28-33**), **fluoro pyrimidines** (**34**), **allyl amines** (**35**), **echinocandins** and **polyenes**[28,29a] (Fig. 7, 8 and 9).[28e,f] Echinocandins[29b-h] and polyenes[29i,j] are of natural origin and the rest of the classes of antifungals are of synthetic origin. Apart from these **sordarins**[28f,29k] which are not used very commonly and **griseofulvin** are also antifungal compounds. None of the antifungal agent alone can give fully satisfactory and 100% desired effect. Use of an antifungal agent is limited by one or more factors to mention a few of them are, (i) pathogens becoming resistant to drugs, (ii) the interaction of the drugs with the host cells instead of the pathogens, (iii) side effects associated with the drugs, and (iv) poor bioavailability of the drug.

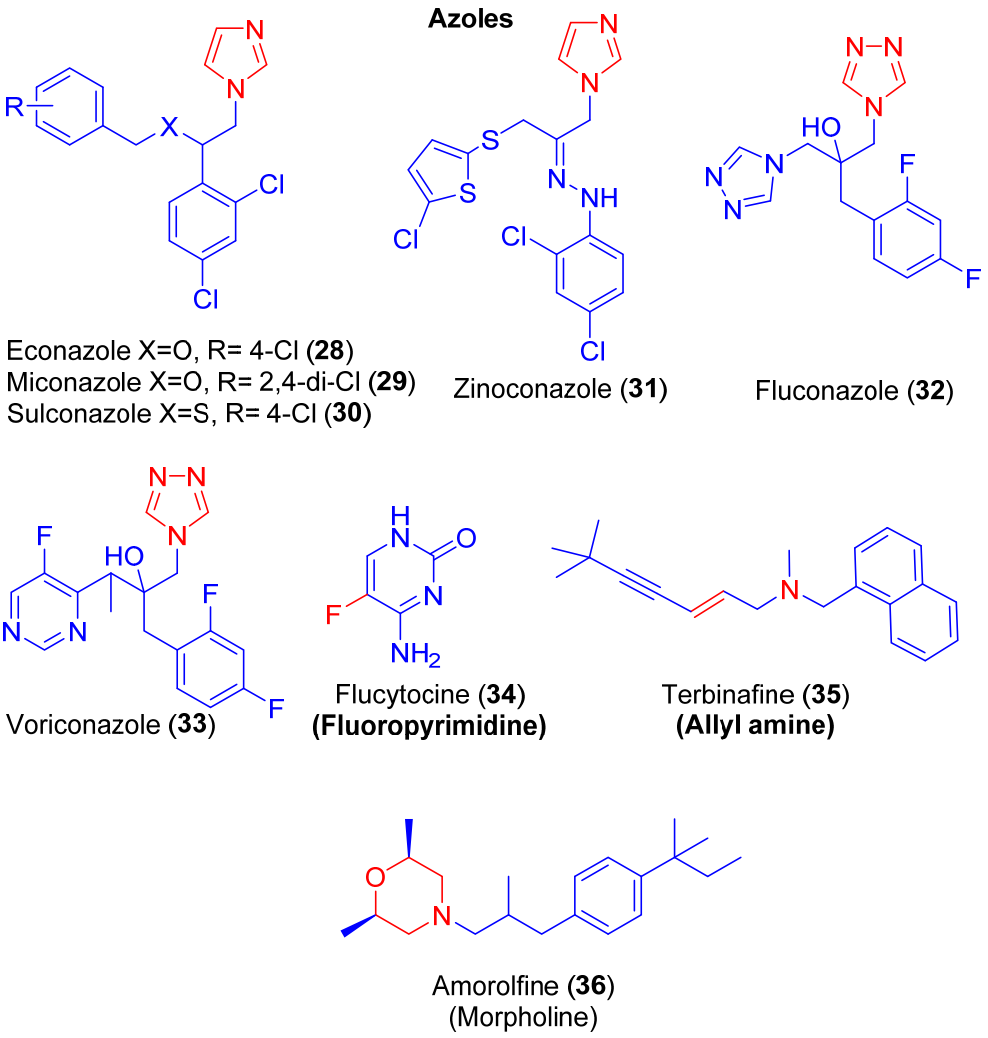
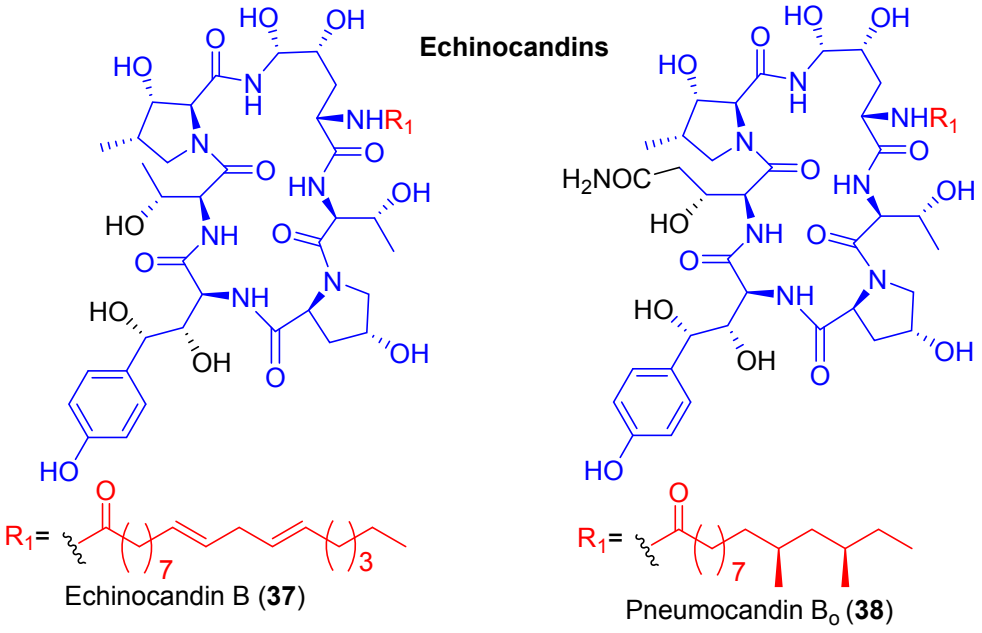


Figure 7. Some antifungal drugs from azole, fluoropyrimidine, allyl amine and morpholine classes.



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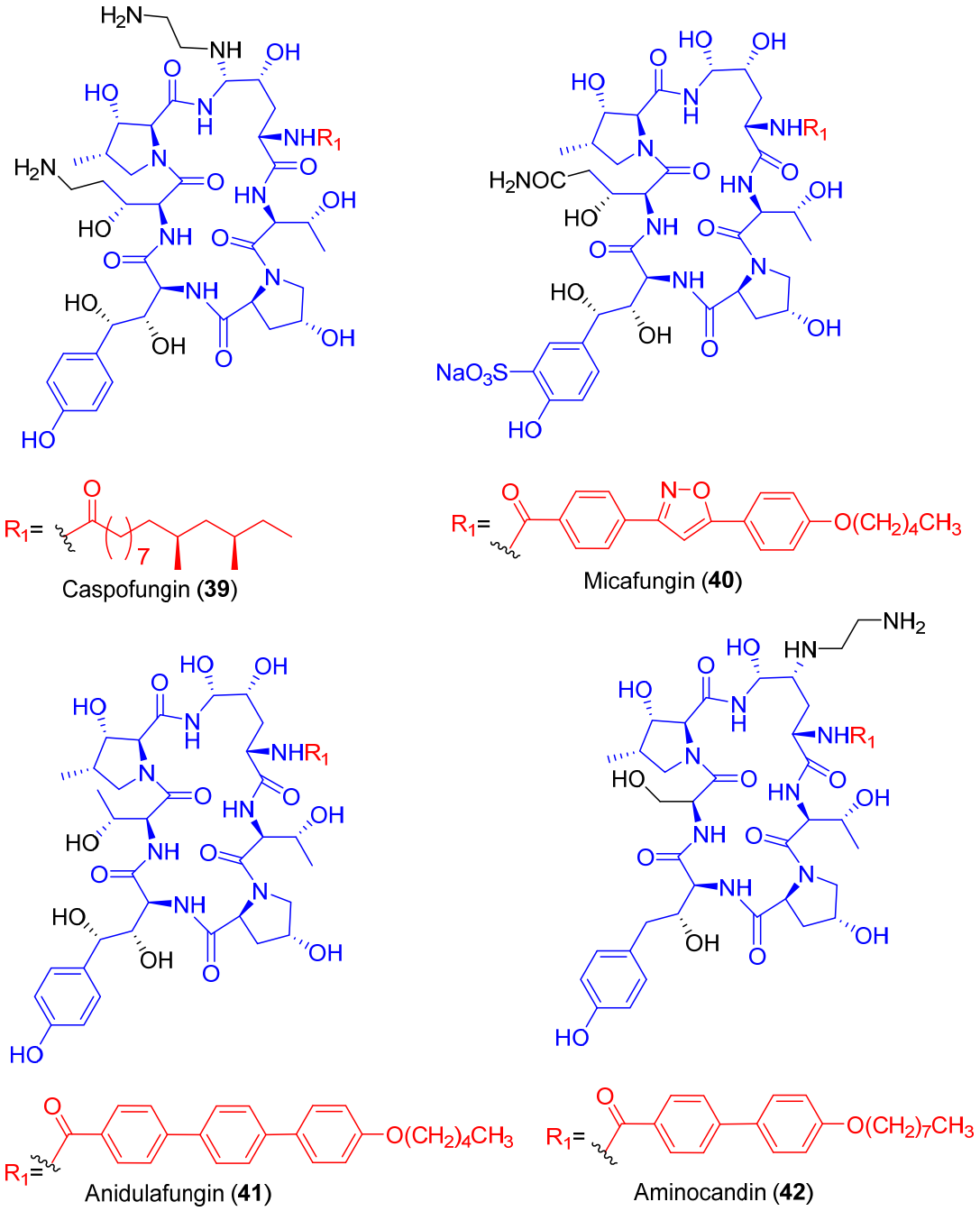


Figure 8. Structures of two natural echinocandins (**37** and **38**) and four clinically available semi-synthetic echinocandins (**39-42**).

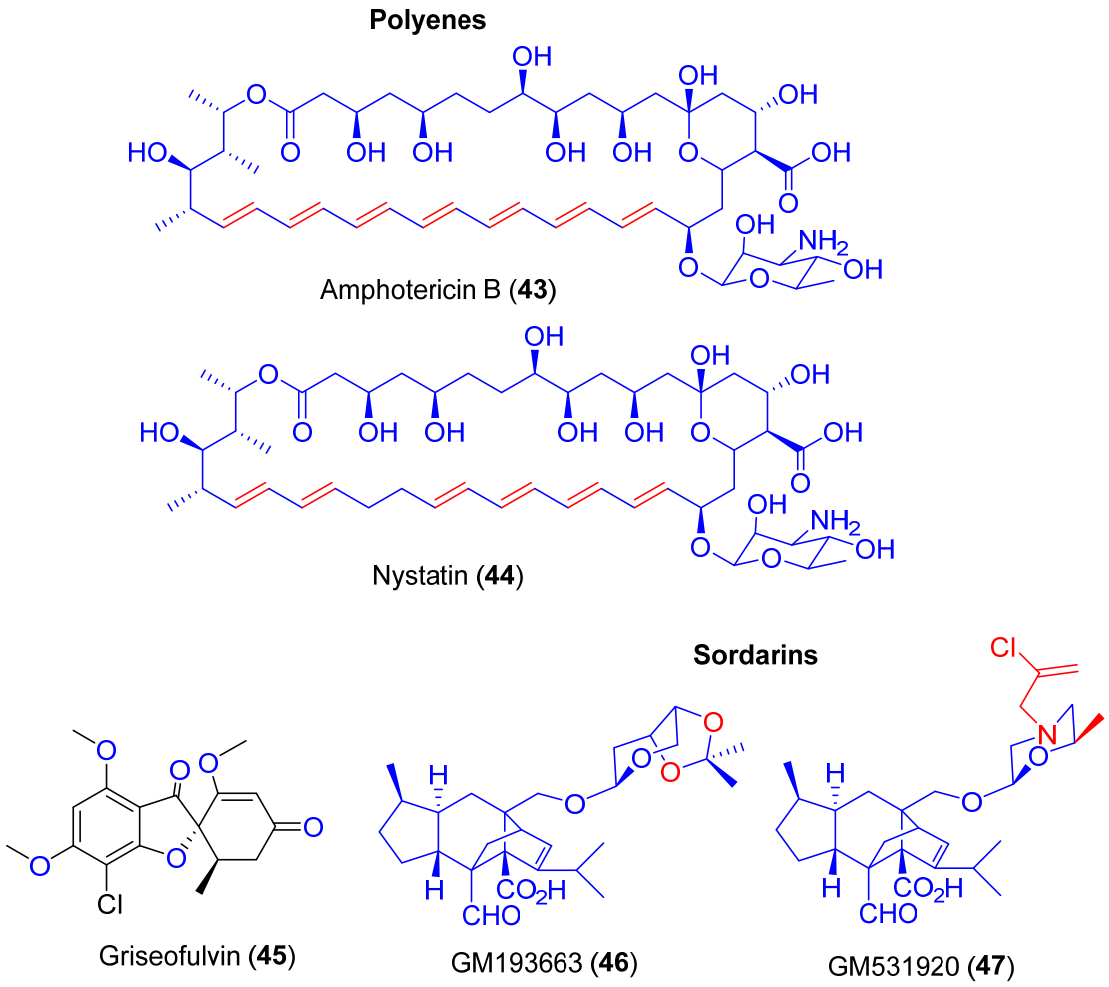


Figure 9. Polyenes class antifungals; amphotericin (**43**) and nystatin (**44**); griseofulvin (**45**), sordarins class GM193663 (**46**) and GM531920 (**47**).

In recent times, several classes of compounds have been isolated from various species of plants, which are reported to possess antifungal activities.[30,31] However, these could not be developed into useful antifungal drugs, as some or other drawbacks were associated with these molecules. Hence, there is an urgent need to develop new naturally occurring antifungal agents having target specificity, broad-spectrum activity and different mechanism of action than the existing drugs.

4.1.4.3 Targets, Mechanisms of Antifungal Action: Bio-chemical Entity

Because of the varied species of pathogens present in nature and its ability to affect the host, a number of classes of antifungal had been developed. An antifungal drug of a particular class may not be as effective as that of an antifungal drug of other class since the mode of action varies from class to class. Basically the target can be (i) **fungal cell wall**, (ii) **sterol synthesis** at the endoplastic reticulum, (iii) **Protein synthesis**, (iv) **DNA and RNA** synthesis, (v) **Microtubule assembly**. Fig. 10 summarizes targets of antifungal agents used in medical applications. From Fig. 10 it is clear that although a considerable diversity of antifungal targets already exists, however in terms of numbers of classes of agents that can be used to treat life threatening mycoses, the targets are still relying, directly or indirectly, on the cell membrane and also on the fungal membrane sterol, ergosterol, and its biosynthesis. So, there is an indispensable need for the development of drugs for targets other than cell membrane as day by day pathogens are becoming resistant to the available drugs.

Azoles (Fig. 7) account for the largest class of antifungal agents in therapeutic application. They act by inhibiting 14α-demethylation of lanosterol formed in the biosynthetic pathway.[30a] It disturbs the enzyme responsible in cell wall synthesis (Fig. 10).[30b]

Flucytosine (**34**) (5-fluorocytosine; Fig. 7) is responsible for conversion to 5-fluorouracil within target cells. Fluorouracil gets inserted into RNA, which are also responsible for chain propagation (translation step) can no longer continue to perform propagation ultimately result in chain termination, and it inhibits DNA synthesis (Fig. 10). Flucytosine is limited to pathogenic yeasts (*Candida* species *viz*. *C. neoformans*).[30c]

Allylamines and **morpholines**; the ergosterol biosynthetic pathway forms a prevalent target for these two classes of antifungal agent. The allylamines, markedly terbinafine (Fig. 7), inhibit squalene epoxidase, an initial step in the pathway, with fungicidal action in susceptible species. Its effect is observed in filamentous fungi and few pathogenic yeasts. Amorolfine belonging to phenylmorpholine class, influence the two targets late in the ergosterol pathway: Erg24p, the Δ^{14} reductase enzyme, and Erg2p, the Δ^{8}-Δ^{7} isomerase enzyme (Fig. 10).

The **echinocandins** are fungal secondary metabolites (Fig. 8) comprising a

cyclic hexapeptide core with a lipid side-chain responsible for antifungal activity. The target for the echinocandins is the complex of proteins responsible for synthesis of cell wall **β-1,3 glucan polysaccharides** (Fig. 10). The exact details of the mode of action of echinocandins is still uncertain, mainly because a membrane-associated protein complex is involved,[30d,e] but it is assumed that echinocandins are possibly involved in glucan synthesis and its inhibition. This represents the first novel target in 20 years of antifungal drug discovery in terms of clinically useful drugs.

Amphotericin B (**43**) (Fig. 9) an antifungal from polyene class can be administered systemically to treat visceral infection. It acts in a different way in comparison to other antifungal class agents. It doesn't causes any inhibition of an enzyme, but it binds to ergosterol, the principal sterol in fungal membranes, which ultimately results in upsetting membrane function to the point of causing outgoing of cellular contents (Fig. 10). There is a greater ease for binding of amphotericin to ergosterol this criteria imparts more selectivity of antifungal amphotericin B.[30f] Amphotericin B on binding with fungal sterol orients in such a way that the bound molecule with its hydrophilic edge remains unbalanced relative to the larger hydrophobic portion of the complex. Eventually the outcome is creating stress within the membrane and finally rupture of the cell membrane. Amphotericin B can be applied on a broad spectrum of fungal species. Despite considerable toxicity problems and its selective mode of action, this molecule still remains a choice in its clinical application.

Amphotericin B is toxic to mammalian cells, causing **nephrotoxicity**. In order to reduce nephrotoxicity, it is delivered slowly by formulating in lipid form like encapsulated in liposomes or in ribbon-like or disc-like lipid complexes.[30g] Based on these lines, antifungal polyene nystatin (**44**) is also being administered in a liposomal formulation for systemic use.

The exact mode of action of **griseofulvin** (**45**) (Fig. 9) is not clear yet however, possibly it interferes with microtubule assembly[30h] (Fig. 10). Selectivity being moderate towards the pathogens, liver toxicity is reported as side effect for this drug. This has applications in use against dermatophyte fungi-causes of ringworm and athlete's foot.[30i]

Sordarins are not so developed for medicinal applications (Fig. 9), it has its bright side in the fact that, these have new mechanism of action (Fig. 10). They are

responsible in inhibition of protein synthesis by arresting the function of **fungal translation Elongation Factor 2** (**EF2**).[30j]

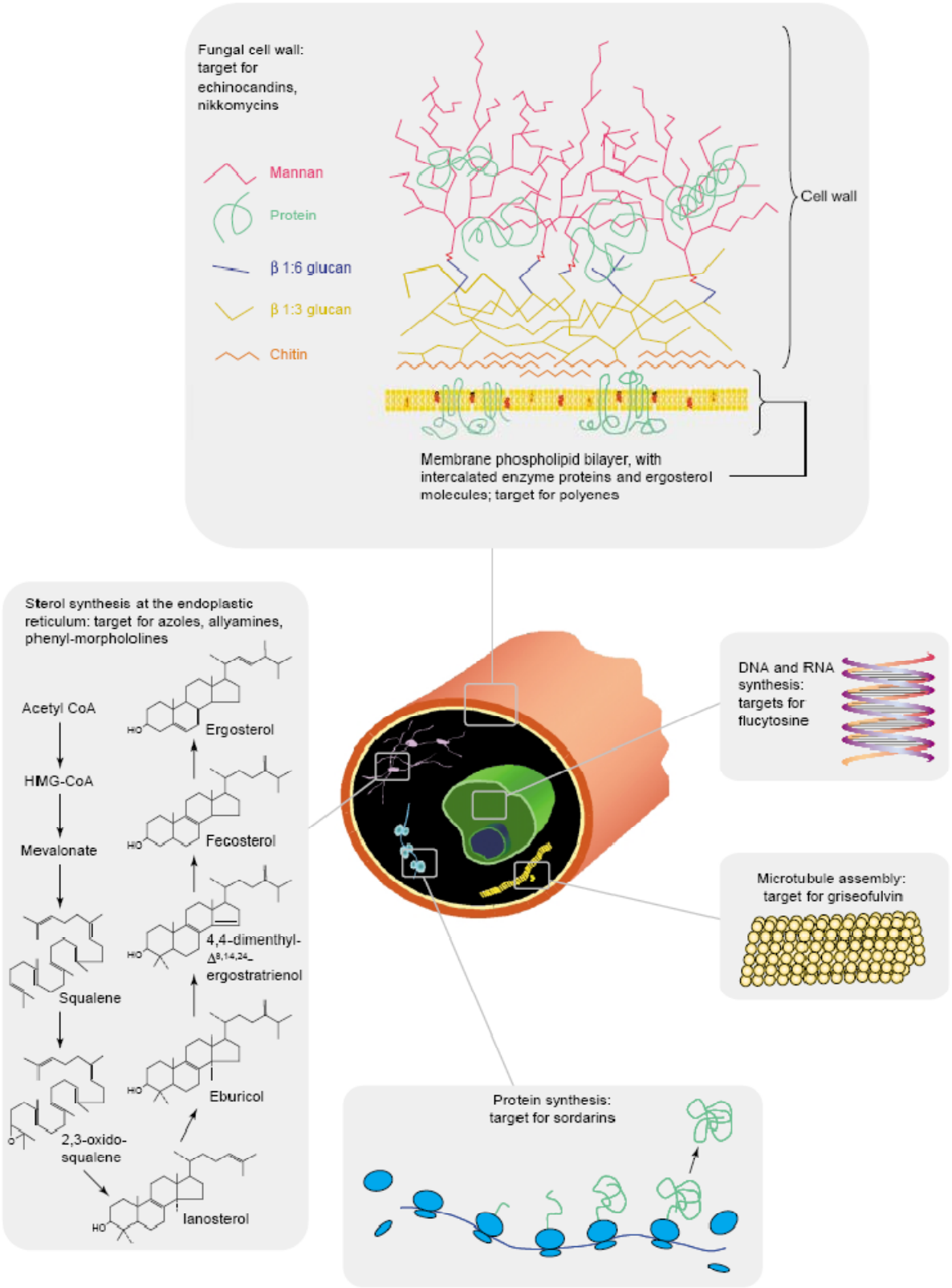


Figure 10. Targets of antifungal agents used in medical applications (or those in early/ late clinical trial stage of drug discovery).

4.1.5 Present work

Natural source remains an immortal and biggest source for isolation of new molecules, a number of classes of compounds have been extracted from diverse plants, which are known to have antifungal activities[31]. However, due to certain constraints all of them could not be utilized into useful antifungal drugs. Hence, there is pressing need to develop new naturally occurring antifungal agents which will overcome all the shortcomings, so as to enjoy the status of a widely acceptable drug. With this aim, this section details isolation of naturally occurring antifungal agents from the plant, *Polyalthia longifolia* var. *pendul*a.

4.1.6 Results and Discussion

As described in Section (**1.1.3**) The genus *Polyalthia* (Annonaceae) shares a very important place in traditional system of medicine due to a number of curative propeties such as for the treatment of hypertension, fever, diabetes, helminthiasis and skin diseases.[32] Several classes of compounds such as diterpenes, including clerodane and triterpenes and aporphine alkaloids have been isolated and investigated for various biological activities.[33] from the plant species *P. longifolia* var. *pendula.*

In continuation of our interest[34] in isolation of naturally occurring bioactive secondary metabolites, a systematic chemical examination of *P. longifolia* var. *pendula* for its antifungal constituents was initiated. The crude methanolic extract was subjected to flash chromatography which resulted in 6 sub-fractions (**A-F**). On assaying all the six fractions for their antifungal properties against a screen of fungal strains, an active fraction (fraction **B**) was obtained exhibiting promising activities. Further, endeavor in isolation of active secondary metabolites from fraction **B** by automated flash chromatography using RediSep® column (SiO_2, 2x12 g, stacked) resulted in the isolation of a pure compound **clerodane diterpene** (Fig. 11), which was identified as 16α-hydroxycleroda-3,13(14)*Z*-dien-15,16-olide (**48**) (Fig. 12) on the basis of its spectral data.[33d] There are three reports for total synthesis of diterpene (**48**) in the literature.[35] The isolated pure compound (**48**) was assayed against five human pathogens such as *Candida albicans* NCIM3557, *C. glabrata* NCIM3237, *Cryptococus neoformans* NCIM3542, *Aspergilus fumigatus* NCIM902, *A. niger*

NCIM628, *C. albicans* NCIM3471 (non-pathogenic), phytopathogen, *Fusarium oxysporum* NCIM1043 and a saprophyte, *Neurospora crassa* NCIM870 (Table 1). The diterpene (**48**) showed MIC_{90} values of 50.3, 100.6 and 201.2 μM against *C. albicans* NCIM3557, *C. neoformans* NCIM3542 and *N. crassa* NCIM870, respectively. Just to mention for the sake of comparison of the activity of diterpene (**48**), the standard antifungal drugs fluconazole and amphotericin B exhibited MIC_{90} values of 32 and 2 μg/mL against *C. albicans* NCIM3557, respectively,[36] suggesting analogues/derivatives of diterpene (**48**) could be developed as antifungal drug in future.

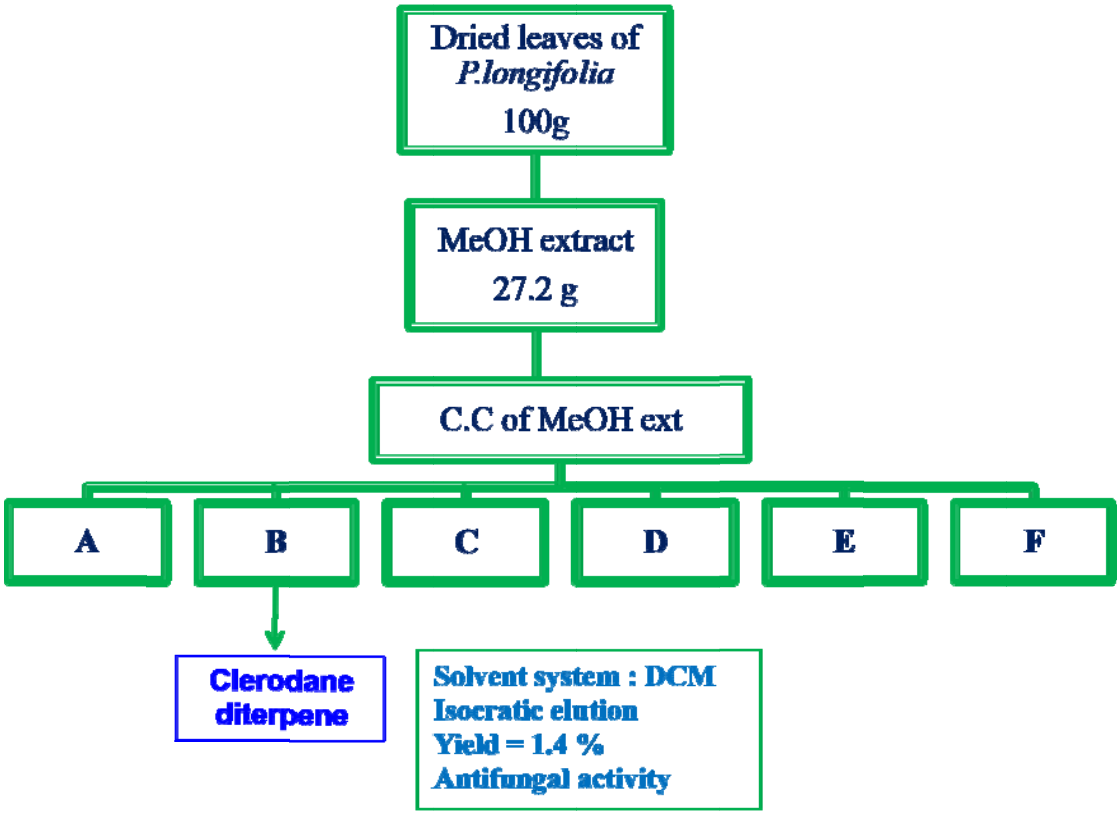
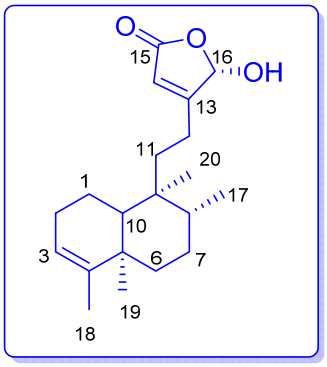


Figure 11. Isolation of clerodane diterpene from *P. longifolia.*



Clerodane diterpene (48)

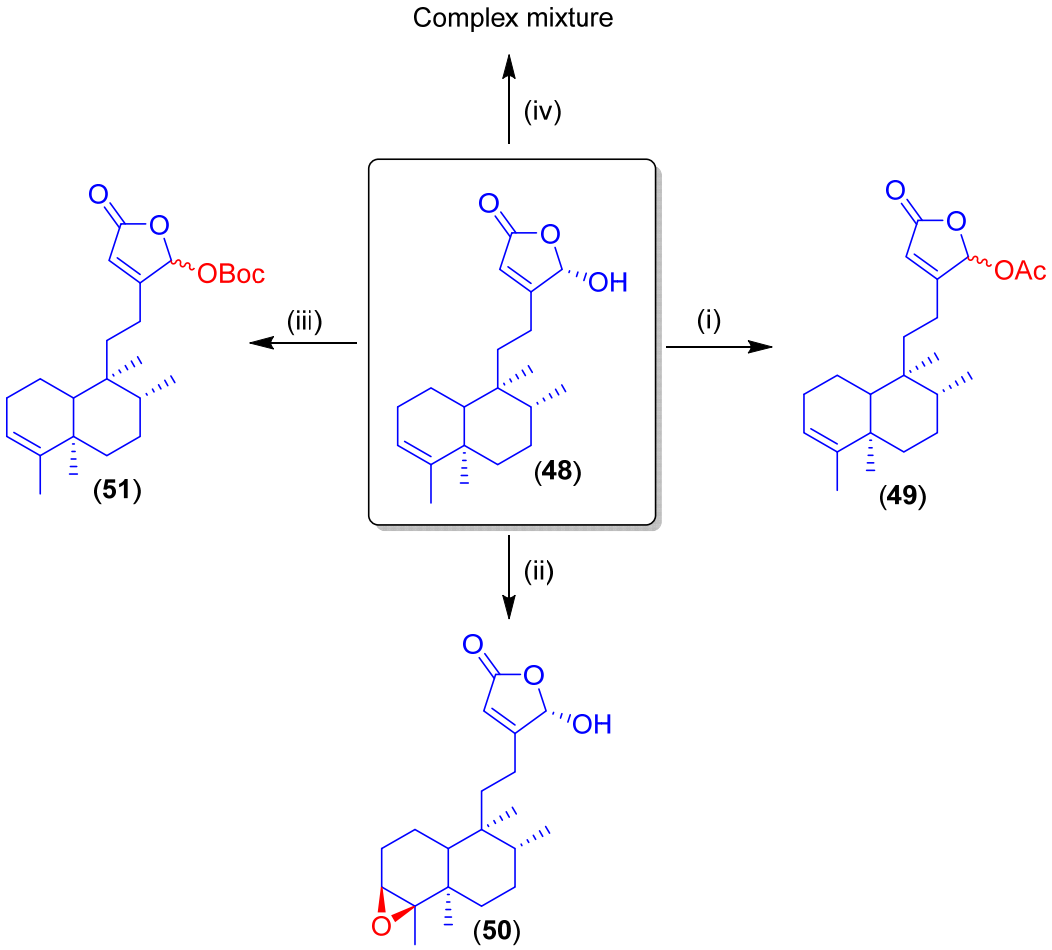
Figure 12. Structure of clerodane diterpene (**48**), 16α-hydroxycleroda-3,13(14)*Z*-dien-15,16-olide.

Table 1. MIC_{90} values of compound (**48**).

Strains	(μM)
C. albicans NCIM3557	50.3
C. albicans NCIM3471	805.0
C. glabrata NCIM3237	805.0
Cryptococcus neoformans NCIM3542	100.6
Aspergillus fumigatus NCIM902	805.0
A. niger NCIM628	805.0
Fusarium oxysporum NCIM1043	805.0
Neurospora crassa NCIM870	201.2

In order to study the structure-activity-relationship (SAR) and to acquire information on pharmacophores responsible for the antifungal activities of the secondary metabolite (**48**), we initiated some analogue synthesis of compound (**48**) (Scheme 1). Acetylation of compound (**48**) with Ac_2O and pyridine yielded the desired acetate (**49**), colourless solid, m.p. 134-136 °C. However, it was found to be a mixture of acetate isomers formed due to epimerization[37] at C-16 as evident from its ^1H and ^{13}C NMR spectra. When epoxidation of compound (**48**) was carried out with *m*-CPBA in DCM, epoxide (**50**) was obtained as a viscous oil, $[\alpha]^{27}_D$ -24.43 (*c* 0.95, $CHCl_3$). The Boc derivative (**51**) of compound (**48**) was synthesized by the reaction of Boc_2O in presence of TEA and catalytic amount of DMAP in DCM. However, the ^1H and ^{13}C NMR spectra of compound (**51**) indicated that it exists as a mixture of isomers

due to the epimerization[37] at C-16. When we tried to reduce the double bond at C3-C4 and also C13-C14 by hydrogenation using 10% Pd in Ethyl acetate the desired product was not obtained even on prolong reaction time *viz*. 5d. However, the tlc pattern revealed a complex mixture which was difficult to separate and identify even on repetitive flash chromatography. The three semi-synthetic derivatives (**49-51**) of the diterpene (**48**) were assayed against all the test organisms. MIC_{90} values >600 µM were observed for all the three synthesized derivatives (**49-51**) against all the strains. From the preliminary structure-activity-relationship (SAR) studies from the assay of synthesized derivatives (**49-51**) it can be estimated that the double bond between C3-C4 and the free hydroxyl group at C16 is an essential requirement for the antifungal activity of the diterpene (**48**). However, the complete SAR remains to be concluded with the synthesis of some more derivatives/analogues of (**48**).



Scheme 1. Preparation of derivatives of (**48**). *Reagents and conditions*: (i) Py, Ac_2O, rt, 24h; (ii) *m*CPBA, DCM, 1.5h; (iii) Boc_2O, TEA, DMAP (cat), DCM, 0 °C, 2h; (iv) 10% Pd /C, H_2 (1 atm), EtOAc, rt, 5d.

Moreover, it was necessary to assess the natural product (**48**) and its semi-synthetic derivatives (**49-51**) for their **haemolytic potential** on red blood cells (RBCs).[38] The compounds (**48-51**) were incubated with **RBC**s and release of haemoglobin due to the RBC lysis was measured (Fig. 13). It is noteworthy to mention here that at the tested concentrations closer to the MIC of *C. albicans* (NCIM3557), none of the compounds displayed any significant haemolysis. The red blood cell haemolysis was found to be less than 15% for all the compounds (**48-51**) when tested at highest concentration, *i.e*. 1200 μM.

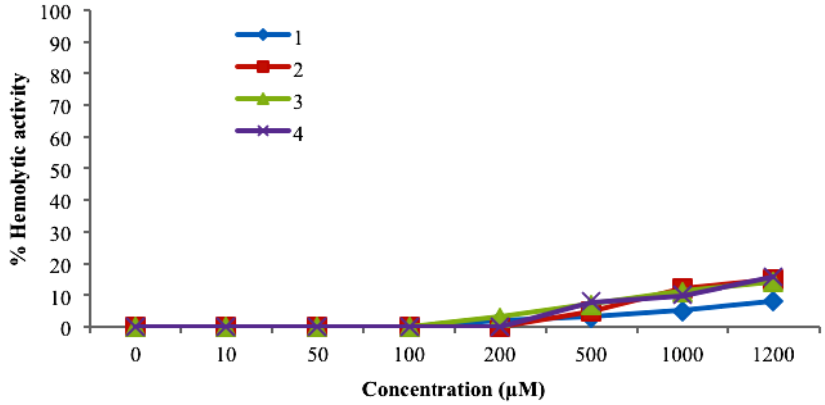


Figure 13. Haemolytic activity of compounds (**48-51**).

Dimorphism is an environmentally regulated 'reversible' process, by which certain fungi can switch between **yeast (Y)** and **hyphal (H)** stages. This condition of 'reversibility' is widely applicable for many dimorphic fungi, but not all. It is unique property of the opportunistic animal pathogen *Candida albicans*, whose cells can change their morphology back and forth according to environmental fluctuation. Esentially, for *C. albicans*, the ability to undergo morphological change is an imperative factor for pathogenicity.[39] Hence, in order to deduce the effect of the compounds on (Y) and hyphal (H) stages, all the compounds (**48-51**) were tested for their **Y to H transition inhibition**. It was very interesting to note that all the tested compounds inhibited Y-H transition in *C. albicans* NCIM3557 at much lower concentration than their MIC_{90} values (Table 2).

Propidium iodide (PI) has been used extensively as a nucleic acid staining **fluorescent dye**[40a] due to its excellent membrane impermeablility. PI penetrates inside the cells with compromised permeability only and it readily binds to the double stranded nucleic acids and ultimately produces a red fluorescence when excited at 480 nm. We have utilized **epifluorescence microscopy** to study the uptake of PI by

Candida cells in the presence of the natural diterpene (**48**) at two concentrations, 50.3 μM and 100.6 μM (Fig. 14). In order to elaborate further the uptake of PI, confocal microscopy was undertaken at three different concentrations, 25.2 μM, 50.3 μM (MIC_{90}) and 100.6 μM (Fig. 15).[40b]

Table 2. Effect of compounds on yeast-hypha (Y-H) transition in *Candida albicans* NCIM3557.

Compound	Inhibition of 50% germ tube formation in *C. albicans* (μM)
(**48**)	25.14
(**49**)	177.80
(**50**)	191.60
(**51**)	153.10

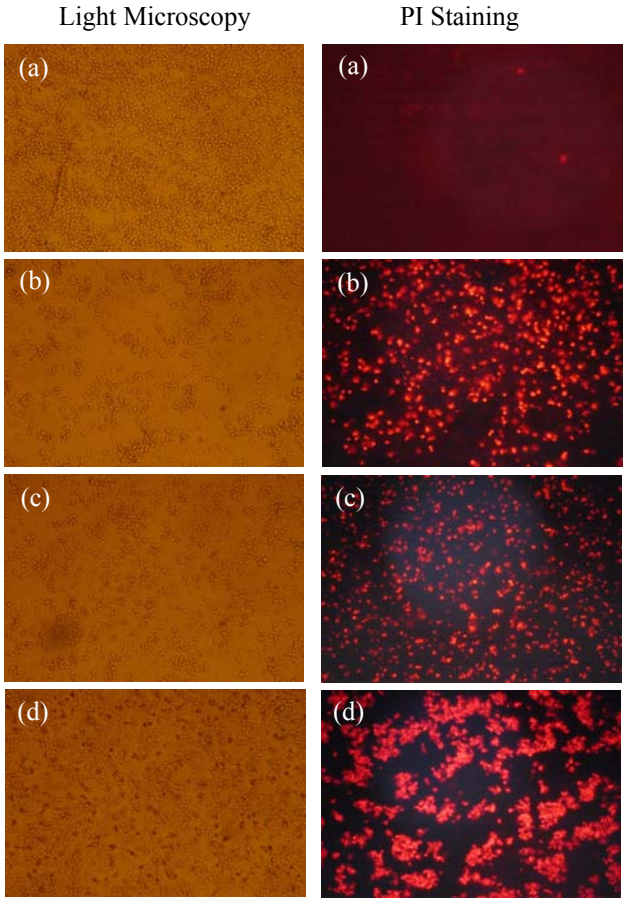


Figure 14. Fluorescence microscope images of membrane permeabilization by propidium iodide (PI) uptake: (a) Untreated control (in absence of compound **48**); (b)

positive control (heat-killed); (c) *C. albicans* (NCIM3557) cells in presence of compound (**48**) (50.3 μM); (d) *C. albicans* (NCIM3557) cells in presence of compound (**48**) (100.6 μM).

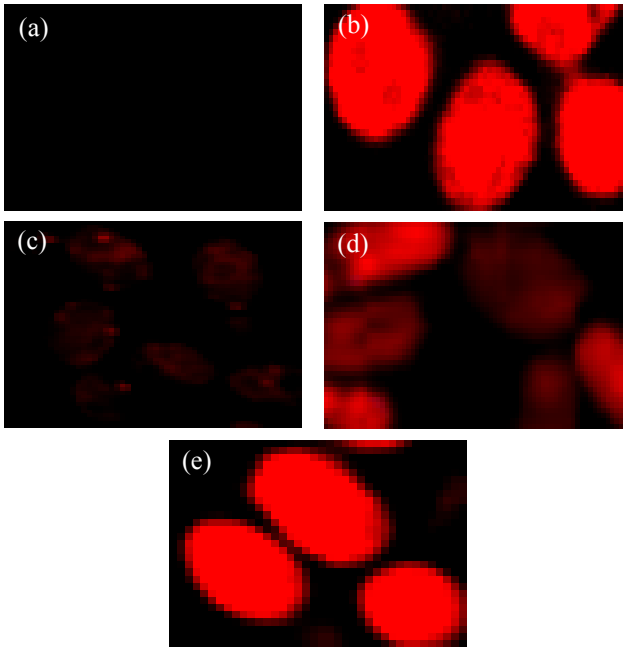


Figure 15. Confocal laser scanning microscopy (CLSM) images of membrane permeabilization by propidium iodide (PI) uptake: (a) Untreated control (in absence of compound **48**); (b) positive control (heat-killed); (c) *C. albicans* (NCIM3557) cells in presence of compound (**48**) (25.2 μM); (d) *C. albicans* (NCIM3557) cells in presence of compound (**48**) (50.3 μM); (e) *C. albicans* (NCIM3557) cells in presence of compound (**48**) (100.6 μM).

The generation of **reactive oxygen species** (ROS) by compound (**48**) was studied so as to verify the antifungal mechanism of the isolated natural diterpene (**48**), It is evident that the generation of reactive oxygen species (ROS) is considered to be associated with apoptosis (a programmed cell death) and necrosis. Two staining reagents have been employed *viz*. DHR123 (dihydrorhodamine)[41] (Fig. 16) DCFH-DA staining[42] (Fig. 17) for the investigating the ROS generation by diterpene (**48**). On incubation of *C. albicans* NCIM3557 cells with different concentrations of of diterpene (**48**) (50.3, 100.6 and 201.2 μM) followed by treatment with DHR123 for 30 min. Fluorescence was captured at 525 nm which was due to the oxidation of the dye DHR123. With the increase in concentration of compound (**48**), the relative

fluorescence increased which means that generation of intracellular ROS had taken place. The cells without the compound were considered as negative control whereas cells with H_2O_2 were treated as positive control.

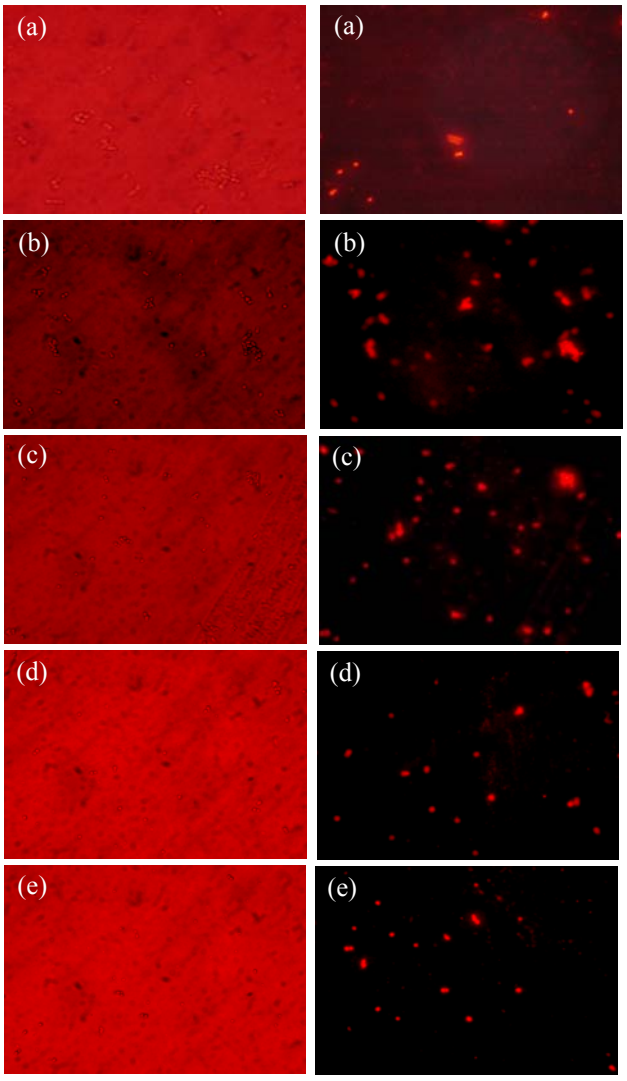


Figure 16. Determination of ROS levels by DHR123 (dihydrorhodamine) staining in the presence of different concentrations of the diterpene (**48**) in *C. albicans* (NCIM3557) cells by epifluorescence microscopy: (a) Control (in absence of compound **48**); (b) positive control with H_2O_2; (c) compound (**48**) (50.3 µM); (d) compound (**48**) (100.6 µM); (e) compound (**48**) (201.2 µM).

Similarly, for executing the DCFH-DA the *C. albicans* NCIM3557 cells were incubated along with diterpene (**48**) at different concentrations (25.2 µM, 50.3 µM and 100.6 µM). Epifluorescence microscope using I3 filter was used to analyze the

fluoresence in the cells resulting from oxidation of dye DCFH-DA. Fluorescence was clearly witnessed at all the three concentrations of the cells treated with diterpene (**48**) (25.2 µM, 50.3 µM and 100.6 µM). As the concentration of the compound increased the relative fluorescence also increased substantially, illustrating the production of intracellular ROS. Cells without the compound were considered as the negative control (Fig. 17).

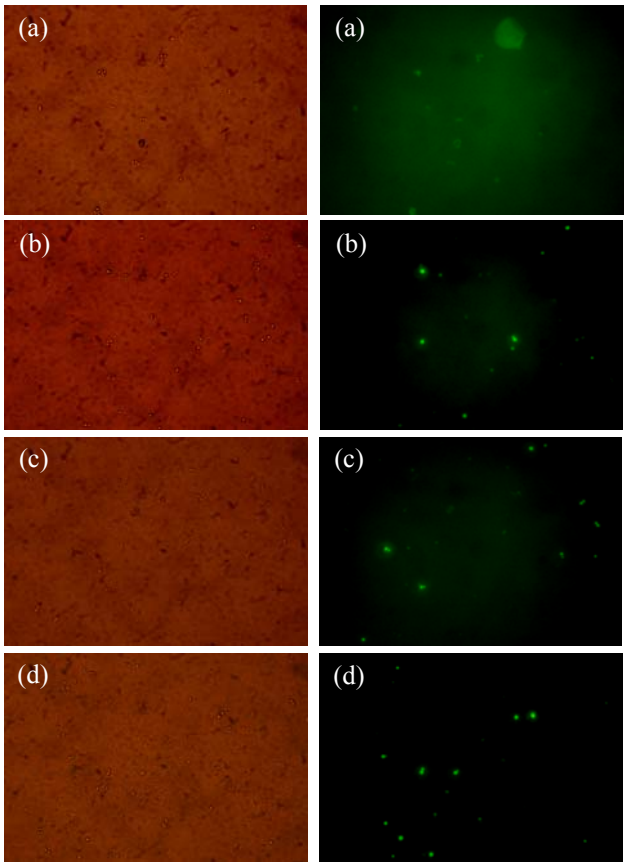


Figure 17. Determination of ROS levels by DCFH-DA staining in the presence of different concentrations of the diterpene (**48**) in *C. albicans* (NCIM3557) cells by epifluorescence microscopy: (a) Control (in absence of compound **48**); (b) compound (**48**) (25.2 µM); (c) compound (**48**) (50.3 µM); (d) compound (**48**) (100.6 µM).

4.1.7 Conclusions

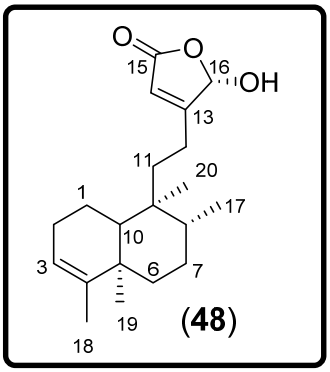
We have successfully isolated a diterpene (**48**) and identified as 16α-hydroxycleroda-3,13(14)*Z*-dien-15,16-olide without following solvent-solvent extraction protocols, from the methanolic extract of the leaves of *P. longifolia* var. *pendula*.[43]. MIC_{90} values of the diterpene (**48**) with different concentration of 50.3, 100.6 and 201.2 μM against *C. albicans* NCIM3557, *C. neoformans* NCIM3542 and *N. crassa* NCIM870, respectively, indicate the compound to be an active antifungal agent. From the preliminary structure-activity-relationship (SAR) studies from the assay of synthesized derivatives (**49-51**) it can be estimated that the double bond between C3-C4 and the free hydroxyl group at C16 is an essential requirement for the antifungal activity of the diterpene (**48**). Moreover, we have proved that the mode of action of diterpene (**48**) in *C. albicans* is due to compromised cell membrane permeability probably due to disruption of cell wall structures. We have also verified its broad spectrum fungicidal activity by screening diterpene (**48**) with a number of fungal strains. All the synthesized derivatives (**48-51**) exhibit less than 15% haemolysis of red blood cells and also inhibited Y-H transition in a dimorphic *C. albicans* at much lower concentration than their MIC_{90} values. The probable mechanism of the antifungal activity exhibited by the diterpene (**48**) is the generation of ROS which was evaluated with DCFH-DA and DHR123 staining of *C. albicans* NCIM3557 cells. We envisage that the diterpene (**48**) can be further elaborated in detail for target-based approach to explore its therapeutic potentials.

4.1.8 Experimental

Plant material: Plant leaves were collected from the garden maintained at CSIR-NCL, Pune during the month of June, 2010.

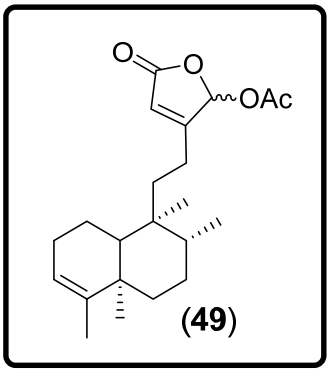
Extraction and isolation: Air-dried and grounded leaves (100 g) of *Polyalthia longifolia* var. *pendula* were extracted with MeOH (5 x 1.0 L) at room temperature for five days. After completion of the extraction, the solvent was evaporated under reduced pressure to afford the MeOH extract (27.2 g). A portion of the MeOH extract (5.2 g) was fractionated on SiO_2 (200 g, 230-400 mesh) column eluting with DCM: MeOH (0→20%) to furnish 6 sub-fractions (**A**-**F**). The compound (**48**) was present in DCM: MeOH (99:1) fraction (fraction **B**). The fraction **B** (1.250 g) was flash chromatographed on CombiFlash Companion, Isco Teledyne Inc., USA using RediSep® column (SiO_2, 2x12 g, stacked together) and isocratic elution was done with DCM to furnish the pure compound (**21**) (270 mg) with 1.4% overall yield.

Clerodane diterpene : 16α-hydroxycleroda-3,13(14)Z-dien-15,16-olide (**48**): R_f 0.36 (MeOH-DCM, 9:1); $[\alpha]^{27}_D$ -42.57 (*c* 1.49, MeOH); υ_{max} ($CHCl_3$)/cm^{-1} 3376, 2930, 1748, 1650, 1459, 1386, 1130, 948, 755; δ_H (400 MHz, $CDCl_3$) 6.07 (s, 1H), 5.85 (s, 1H), 5.20 (brs, 1H), 2.37-2.20 (m, 2H), 2.10-2.01 (m, 2H), 1.76-1.65 (m, 2H), 1.60 (s, 3H), 1.57-1.43 (m, 6H), 1.37-1.19 (m, 5H), 1.02 (s, 3H), 0.83 (d, *J* = 6.5 Hz, 3H), 0.79 (s, 3H); δ_C (100 MHz, $CDCl_3$) 171.7, 170.6, 144.3, 120.4, 117.1, 99.9, 46.5, 38.7, 38.2, 36.7, 36.3, 34.8, 27.4, 26.8, 21.4, 20.0, 18.3, 18.2, 18.0, 16.0; ESI-MS *m/z* 341.1985 $(M+Na)^+$; HRMS (ESI) calcd for $C_{20}H_{30}O_3Na$ 341.2087, found 341.2089.



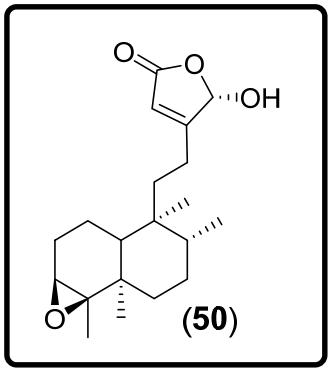
Preparation of acetate derivative (**49**): To a solution of compound (**48**) (21 mg, 0.066 mmol) in pyridine (0.3 mL), Ac_2O (0.6 mL) was added and left at ambient temp for overnight. Toluene (3 x 5 mL) was then added to remove pyridine and Ac_2O by co-distillation on rotary evaporator under reduced pressure. Crude product on

complete dryness followed by flash chromatography on RediSep® column (SiO_2, 12g) eluting with DCM (isocratic) afforded compound (**49**) as a colourless solid (20 mg, 84%), which was a mixture of acetate isomers due to epimerization at C-16 [11]. M.p. 134-136 °C; R_f 0.39 (MeOH-DCM, 1:9); $[\alpha]^{27}_D$ -19.56 (*c* 0.9, $CHCl_3$); υ_{max} ($CHCl_3$)/cm^{-1} 3752, 2967, 2927, 1757, 1649, 1454, 1379, 1212, 1053, 982, 756; δ_H (200 MHz, $CDCl_3$) 6.84 (s, 1H), 5.94 (s, 1H), 5.19 (brs, 1H), 2.38-2.22 (m, 1H), 2.18-2.14 (m, 4H), 2.11-1.93 (m, 2H), 1.77-1.64 (m, 2H), 1.60 (m, 5H), 1.53-1.39 (m, 6H), 1.01 (s, 3H), 0.82 (t, *J* = 3.0 Hz, 3H), 0.77 (s, 3H); δ_C (100 MHz, $CDCl_3$) 170.0, 169.2, 168.2, 168.1, 144.5, 144.5, 120.3, 118.2, 118.1, 93.9, 93.9, 46.6, 46.6, 38.7, 38.2, 36.7, 36.4, 35.0, 34.9, 27.4, 26.9, 26.9, 21.3, 21.2, 20.8, 20.0, 18.4, 18.3, 18.1, 16.1, 16.0; ESI-MS *m/z* 383.01 $(M+Na)^+$; HRMS (ESI) calcd for $C_{22}H_{32}O_4Na$ 383.2193, found 383.2191.



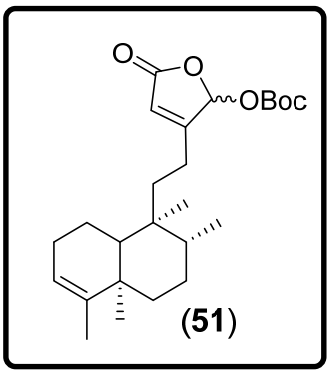
(**49**)

Preparation of epoxide (**50**): To a stirred solution of compound (**48**) (43 mg, 0.135 mmol) in DCM (4 mL) cooled in ice-water bath, was added *m*-CPBA (33 mg, 0.189 mmol, 1.4 eq.). After stirring for 1.5 h, DCM (10 mL) was added and the organic layer was separated, washed with aq. 10% KI solution (2 x 20 mL), followed by 10 % $Na_2S_2O_3$ solution (2 x 20 mL), 10 % $NaHCO_3$, (2 x 20 mL) solution and then finally with H_2O (2 x 20 mL). The organic layer was then dried (anhydrous Na_2SO_4), evaporated in vaccuo, which on flash chromatography on (RediSep® SiO_2 column, 12g) eluting with 2% MeOH-DCM (isocratic) furnished compound (**50**) as a viscous oil (25 mg, 45%). R_f 0.57 (MeOH-DCM, 1:9); $[\alpha]^{27}_D$ -24.43 (*c* 0.95, $CHCl_3$); υ_{max} ($CHCl_3$)/cm^{-1} 3369, 2926, 2857, 1752, 1648, 1577, 1560, 1458, 1141, 951, 757; δ_H (200 MHz, $CDCl_3$) 6.00 (s, 1H), 5.82 (s, 1H), 2.94 (m, 1H), 2.41-2.18 (m, 2H), 1.94-1.86 (m, 2H), 1.74-1.57 (m, 4H), 1.46-1.37 (m, 5H), 1.53-1.37 (m, 5H), 1.01 (s, 3H), 0.80 (3H), 0.73 (s, 3H); δ_C (100 MHz, $CDCl_3$) 171.8, 170.8, 117.0, 99.4, 67.0, 61.4, 47.9, 39.2, 38.5, 37.9, 36.1, 34.6, 26.8, 21.5, 21.4, 21.4, 18.3, 17.7, 16.3, 16.0; ESI-MS *m/z* 357.08 $(M+Na)^+$; HRMS (ESI) calcd for $C_{20}H_{30}O_4Na$ 357.2036, found 357.2034.



(**50**)

Preparation of Boc derivative (**51**): Compound (**48**) (31 mg, 0.097 mmol) was dissolved in DCM (4 mL) and cooled in ice-water bath, Boc_2O (80 mg, 0.37 mmol, 3.7 eq.) was then added followed by TEA (10 μL, 0.074 mmol) and catalytic amount of DMAP (2 mg, 0.016 mmol) and reaction mixture was stirred for 2h. After completion of the reaction (TLC), the reaction mixture was then evaporated in vaccuo and directly subjected to flash chromatography (RediSep® SiO_2 column, 12g) eluting with EtOAc: petroleum ether (1: 19) to furnish the pure compound (**51**) which was obtained as a viscous oil (33 mg, 80%) and found to be an inseparable mixture of C-16 epimers.[11] R_f 0.62 (DCM); $[\alpha]^{27}_D$ -27.15 (*c* 1.0, $CHCl_3$); υ_{max} ($CHCl_3$)/cm^{-1} 3683, 3618, 3440, 3020, 2928, 2856, 2400, 1799, 1765, 1649, 1458, 1373, 1256, 1216, 757, 669; δ_H (500 MHz, $CDCl_3$) 6.66 (d, *J* = 8.2 Hz, 1H), 5.93 (s, 1H), 5.20 (s, 1H), 2.37-2.27 (m, 2H), 2.25-2.21 (m, 1H), 2.12-1.98 (m, 5H), 1.75-1.64 (m, 4H), 1.59 (m, 4H), 1.54-1.53 (m, 9H), 1.50-1.44 (m, 9H), 1.01 (s, 3H), 0.81 (m, 3H), 0.77 (s, 3H); δ_C (125 MHz, $CDCl_3$) 169.8, 167.6, 167.5, 151.5, 144.5, 144.4, 120.4, 120.3, 118.2, 118.1, 104.4, 96.4, 84.8, 84.7, 46.5, 46.5, 38.7, 38.7, 38.2, 36.7, 36.4, 36.3, 34.9, 34.8, 31.9, 29.6, 29.4, 29.3, 27.6, 27.3, 26.8, 26.8, 21.3, 21.2, 19.9, 18.3, 18.2, 18.0, 16.0, 15.9; ESI-MS *m/z* 441.08 $(M+Na)^+$; HRMS (ESI) calcd for $C_{25}H_{38}O_5Na$ 441.2611, found 441.2612.



(**51**)

Reduction of diterpene (**48**): Compound (**48**) (18 mg, 0.056 mmol) was dissolved in EtOAc (3 mL) and Pd-C (10%, 9 mg) was added to the reaction mixture. Stirring was continued at rt under an atmosphere of hydrogen for 5d. After 5d, the catalyst was filtered off over a celite bed and the reaction mixture was then evaporated in vaccuo. The reaction mixture showed a complex TLC pattern (30% EtOAc-PE), which could not be further purified using flash chromatography (RediSep® SiO_2 column, 4g) eluting with petroleum ether: EtOAc (0→30, gradient).

4.1.9 Antifungal Assays

Fungi growth conditions: Human and plant pathogenic fungal strains, *Candida albicans* NCIM3557, *C. albicans* NCIM3471, *C. glabrata* NCIM3237, *Cryptococcus neoformans* NCIM3542, *Aspergillus niger* NCIM628, *A. fumigatus* NCIM902, *Fusarium oxysporum* NCIM1043 and a saprophyte model, *Neurospora crassa* NCIM870 were obtained from National Collection of Industrial Microorganisms (NCIM), CSIR-National Chemical Laboratory, Pune, India. The human pathogenic fungal strains were maintained on slants of YPG agar (yeast extract, 0.3%; peptone, 0.5%; glucose, 1.0%; agar, 2.0%) and the plant pathogenic fungi were maintained on potato dextrose agar (2% PDA) slants at 28°C and sub-cultured every 15 days. During experimentation, the fungal strains were grown in YPG broth.

Minimum inhibitory concentration (MIC) determination: The purified final compounds were evaluated for antifungal susceptibility testing by microbroth dilution method according to the recommendations of the CLSI.[44] Appropriate amount of test compounds were dissolved in DMSO to get 100X final strength. The stock was then diluted 1:40 in YPG medium and 200 µL from this was added to the first row of a 96-well microtiter plate. The compound was serially diluted two fold in successive wells to get a range of 4-512 µg/mL. Fungal yeast cells (~$2x10^4$ cfu/mL, spores for phytopathogens), freshly grown in YPG broth in logarithmic phase, were suspended in the medium and inoculated (100 µL) in the wells of the plate. The microtiter plates were incubated for 24-48h, and the absorbance was measured at 600 nm by using microtiter plate reader to measure the cell growth. The MIC was defined as the lowest concentration required for >90% inhibition of growth with respect to the growth in control and IC_{50} was the concentration at which 50% growth inhibition was observed.

Membrane integrity assay: Propidium iodide (PI) staining was used for checking integrity of fungal plasma membrane following treatment with diterpene (**48**). *Candida albicans* NCIM3557 cells were harvested at the logarithmic phase and 1×10^6 cells/mL were added in phosphate buffer saline (PBS, 0.1 mM, pH 7.2), containing inhibitor. The tubes were incubated at 37°C for 2h. Cells were separated by centrifugation and washed with PBS. Cells were then incubated with 3 µM of PI for 10 min, harvested by centrifugation, washed (using PBS) and suspended in PBS. PI

stained cells were counted using epifluorescence microscope (Leitz Laborlux, Germany). A filter set, N 2.1 filter block with excitation filter BP 515-560 and emission filter LP 580 were used.

Confocal microscopy: The effect of compound (**48**) on membrane integrity of fungal cell was confirmed by confocal microscopy using PI.[40b] The *C. albicans* (NCIM3557) cells (~1 × 106 CFU/ml) growing in log phase were suspended in an RPMI-1640 medium containing diterpene (**21**) at its MICs (50.3 μM) and PI (3 μM). The mixture was incubated at 37°C for 2h at 180 rpm. The cells were harvested by centrifugation and resuspended in PBS (pH 7.4). The cells were observed under confocal microscope with a wavelength N560 nm for PI. All images were captured at 400X magnification.

Cellular toxicity assay: The cellular toxicity of compounds was determined by red blood cells (RBC) lysis assay [38]. In brief, the RBCs of sheep blood were washed with 2-3 times with PBS (pH 7.0) and finally RBCs were resuspended in PBS so as to obtain the 4% solution. Then, 1000 μL of PBS containing the appropriate concentration of test compound was mixed with 1000 μL of 4% RBC suspension and incubated at 37°C for 2 h. No haemolysis and 100% haemolysis were observed in PBS and 0.1% Triton-X 100, respectively. The reaction mixture was centrifuged at 2,000 rpm for 5 min and the absorbances of supernatant were read at 545 nm. Percent haemolysis was calculated as: =[(A540 in the test - A540 in PBS)/(A540 in 0.1% Triton-X 100 - A540 in PBS) X 100. All experiments were done in triplicate and the average values were given as percent haemolysis.

Measurement of reactive oxygen species (ROS) production: Fluorescence based assays such as 2′,7′-dichlorofluorescein diacetate (DCFH-DA) and dihydrorhodamine123 (DHR123) staining were used to monitor the generation of reactive oxygen species (ROS) in *Candida albicans* cells after incubation with the diterpene (**48**). The cell-permeant dye DCFH-DA and DHR123 are oxidized by ascorbic acid, peroxinitrite and hydroxyl radicals (OH•) to yield the fluorescent molecule 2′,7′-dichlorofluorescein and rhodamine123.

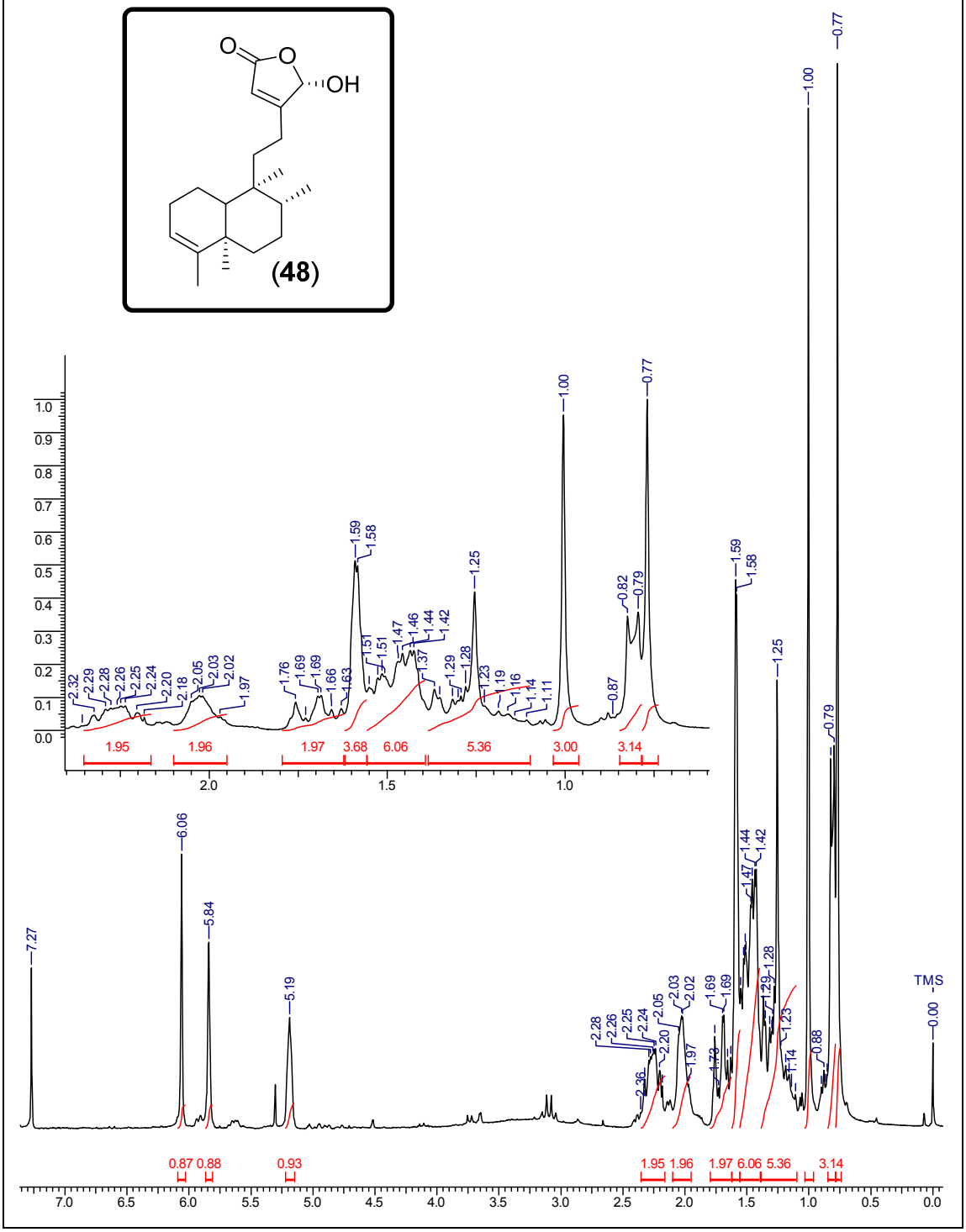
DHR123 (dihydrorhodamine) staining:[41] Dihydrorhodamine123 is the reduced form of rhodamine123, commonly used as a fluorescent mitochondrial dye.

Dihydrorhodamine123 itself is nonfluorescent, but it readily enters cells and gets oxidized by reactive oxygen species (ROS) to fluorescent rhodamine123 that accumulates in mitochondrial membranes. The DHR123 staining was carried out according to the reported procedure.[41] 1×10^{6} cells of *Candida albicans* NCIM3557 were inoculated in YPG broth containing different concentrations of inhibitor and incubated at 37°C for 200 min. After completion of incubation, cells were harvested by centrifugation and washed with PBS. 5 μg/mL DHR123 was added (from a 2.5 mg/mL stock solution in ethanol) to the cells, suspended in PBS and tubes were further incubated for 30 min. Cells were separated by centrifugation. Cell pellet was washed and resuspended in PBS. Cells were observed for fluorescence with excitation and emission wavelengths of 480 nm and 525 nm respectively.

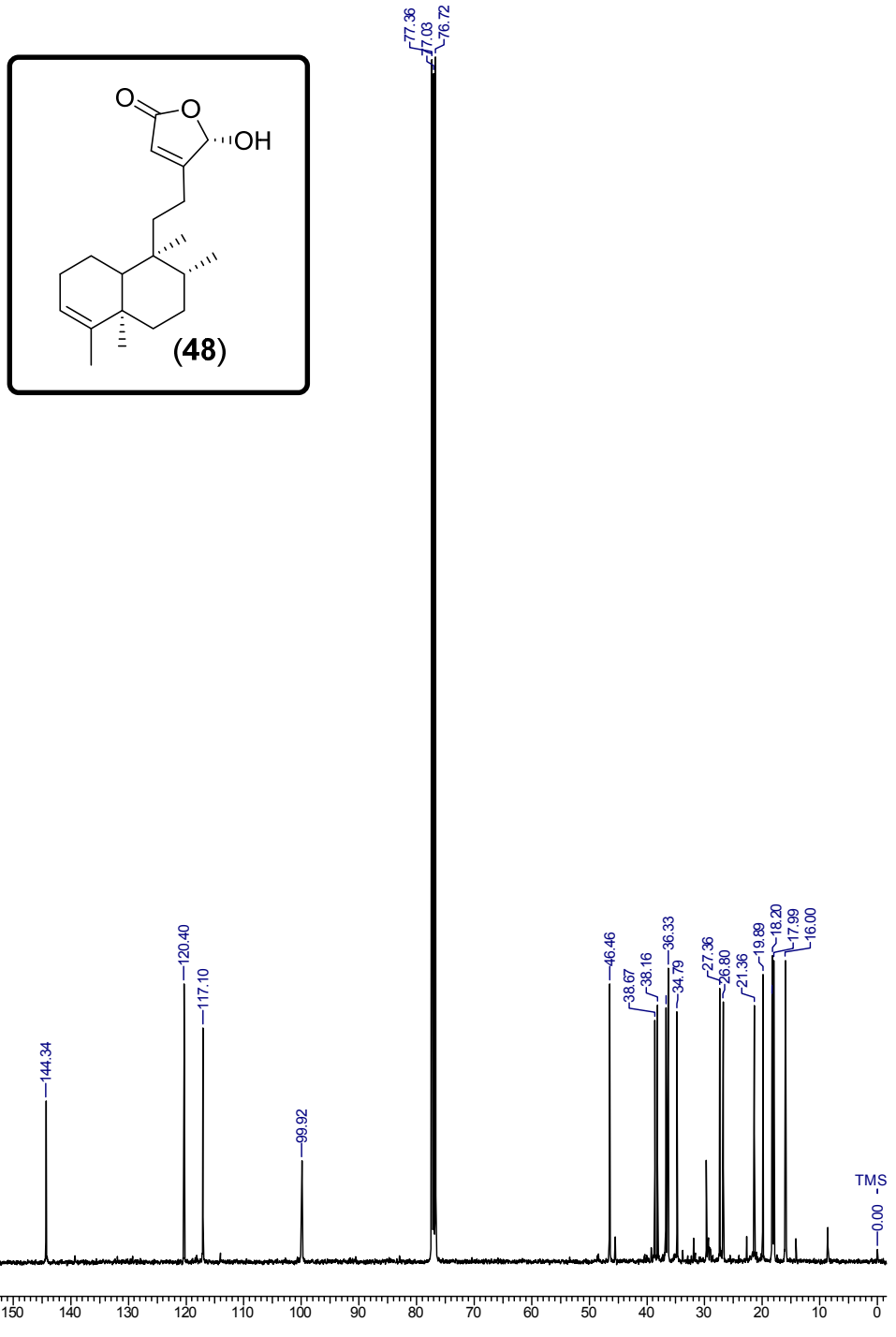
DCFH-DA staining [42]: Amount of ROS generated was measured by fluorometric assay with DCFH-DA. $1x10^{7}$ cells of *C. albicans* NCIM3557 were inoculated in PBS containing compound and incubated at 37°C for 60 min. After completion of incubation, 10 μM of DCFH-DA was added and incubated for 2h. Cells were separated by centrifugation. Cell pellet was washed with PBS and resuspended in PBS. The fluorescence intensities (excitation 485 nm and emission 538 nm, respectively) of the resuspended cells were measured with a spectrofluorometer.

4.1.10 Spectra

^{1}H NMR (400 MHz, $CDCl_3$) of clerodane diterpene (**48**)

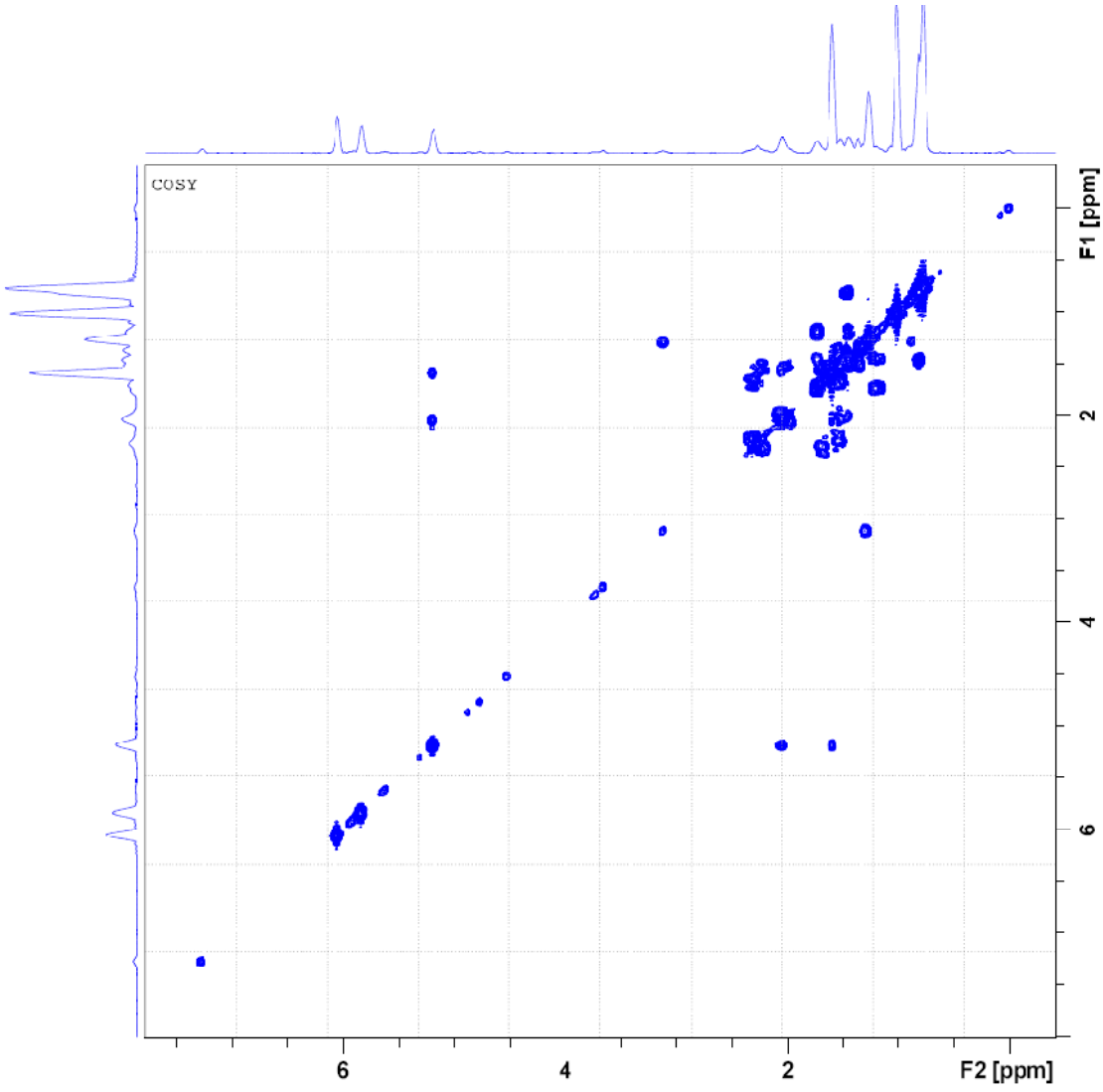


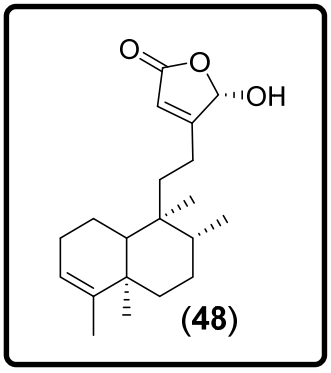
^{13}C NMR (100 MHz, $CDCl_3$) of clerodane diterpene (**48**)



Clerodane diterpene (**48**)

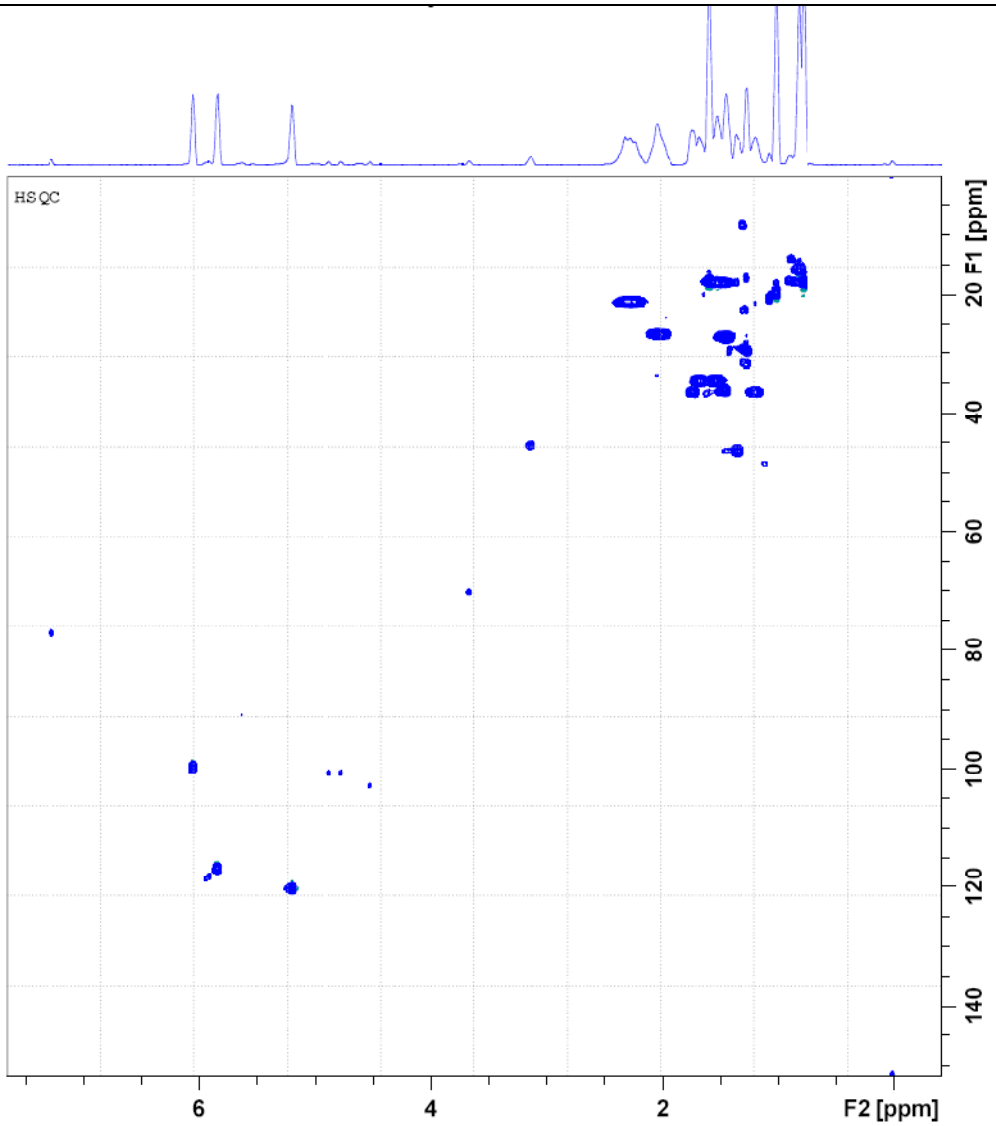
: ^{1}H-^{1}H COSY

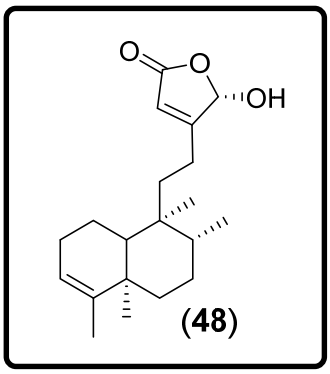




Clerodane diterpene (**48**)**:**

HSQC

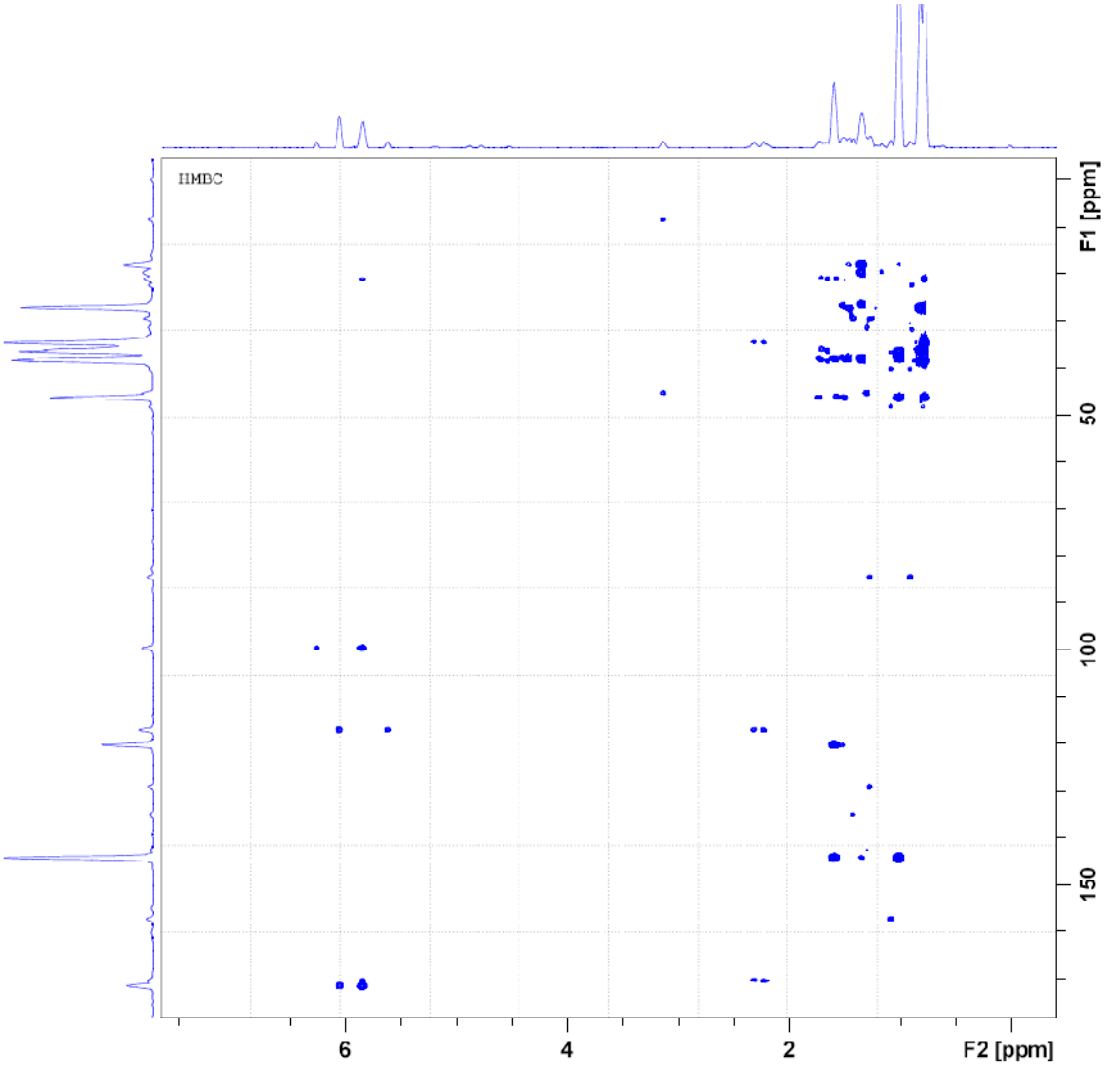


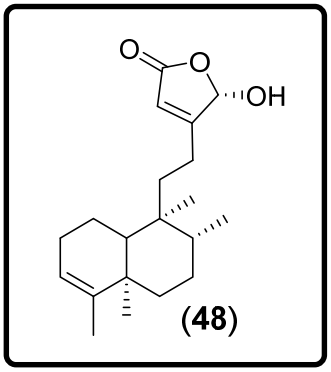


(**48**)

Clerodane diterpene (**48**)**:**

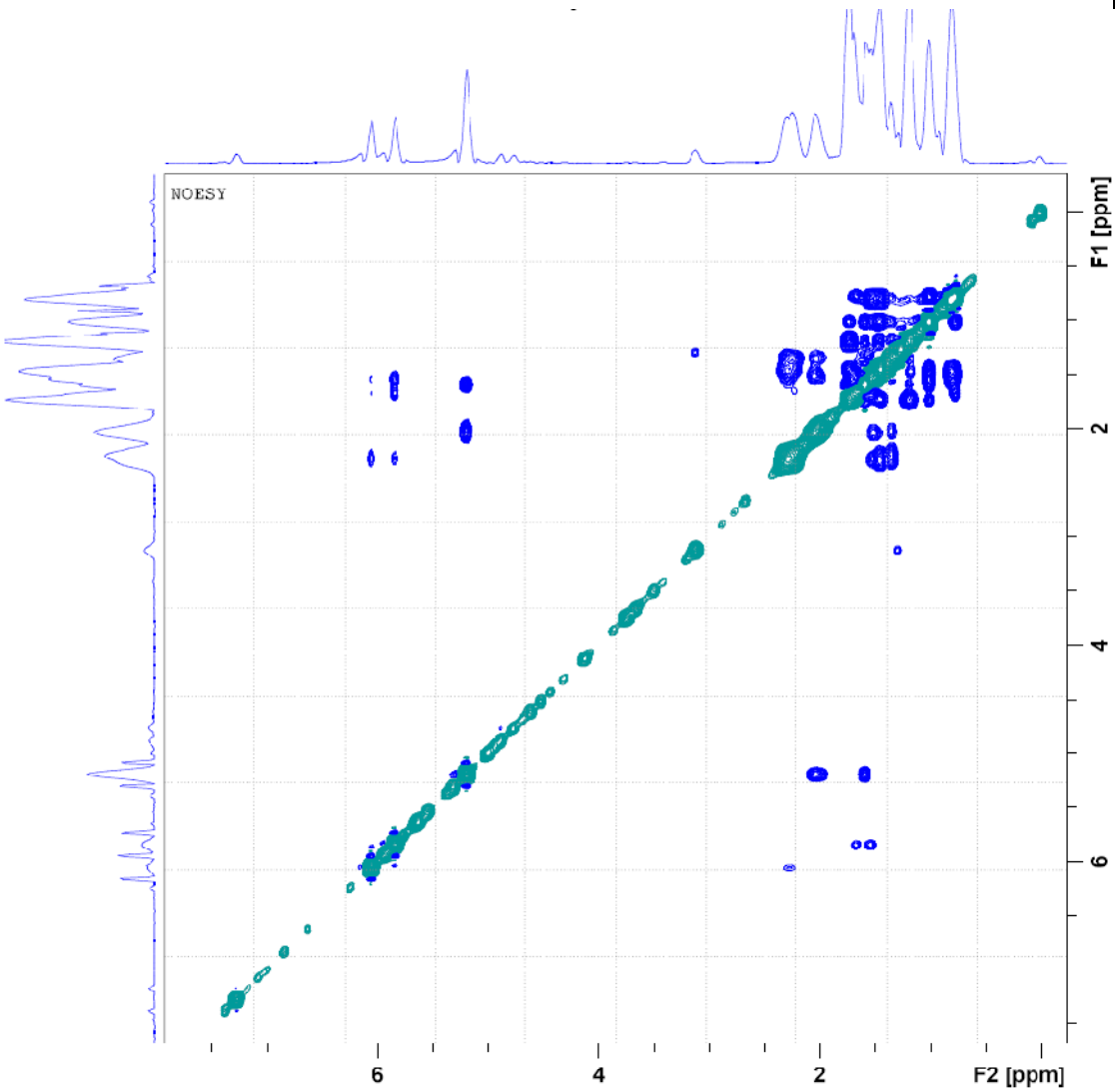
HMBC

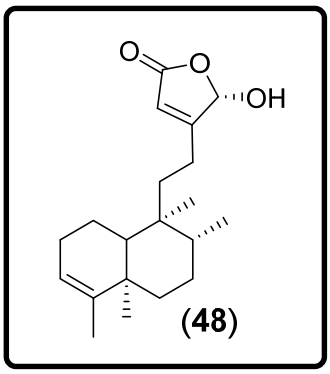




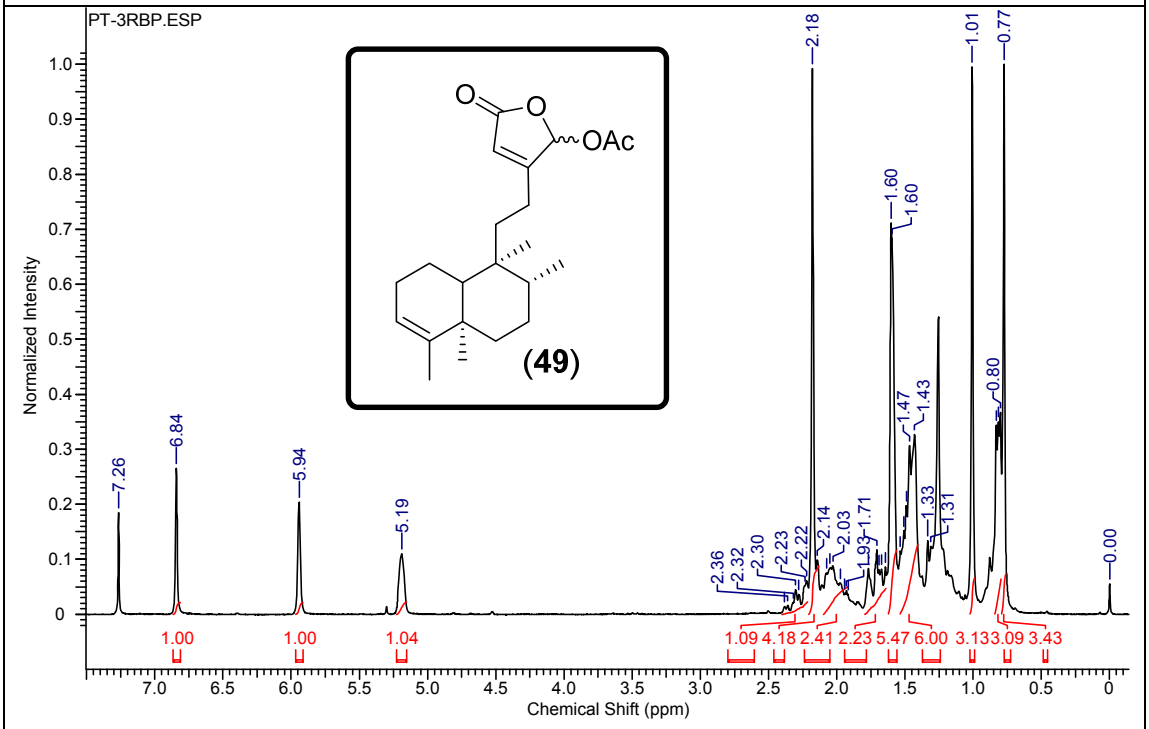
Clerodane diterpene (**48**)**:**

NOESY

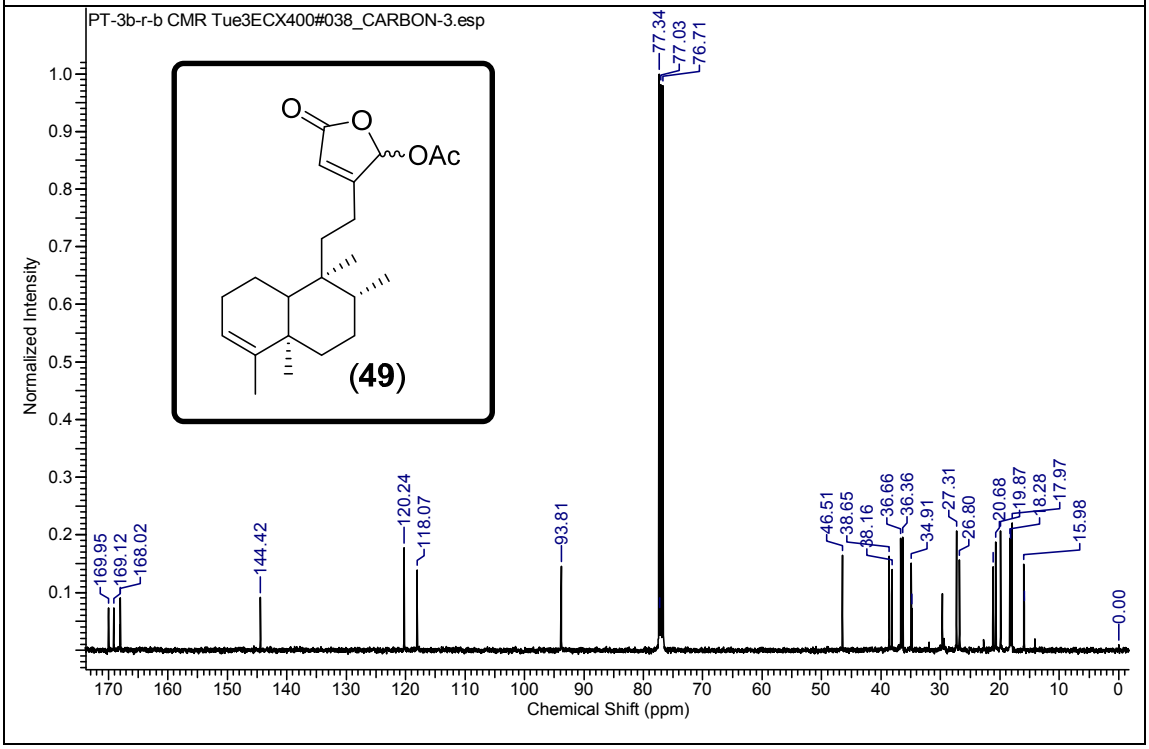




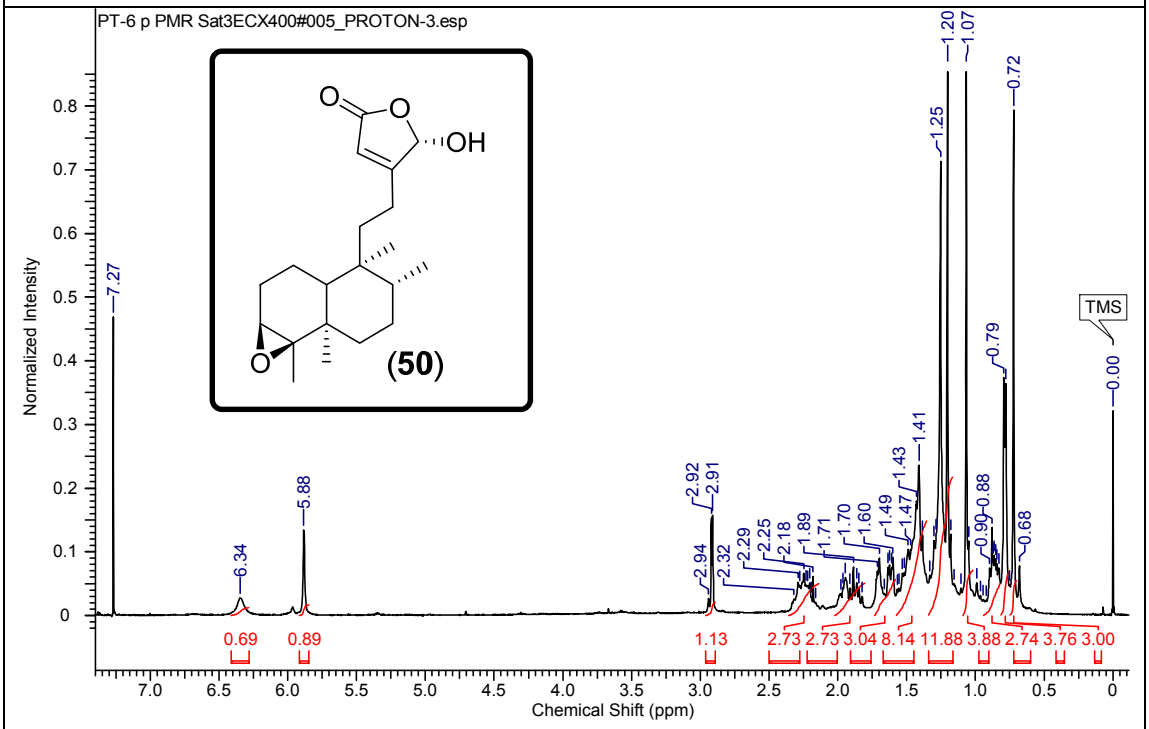
^{1}H NMR (200 MHz, $CDCl_3$) of (**49**)



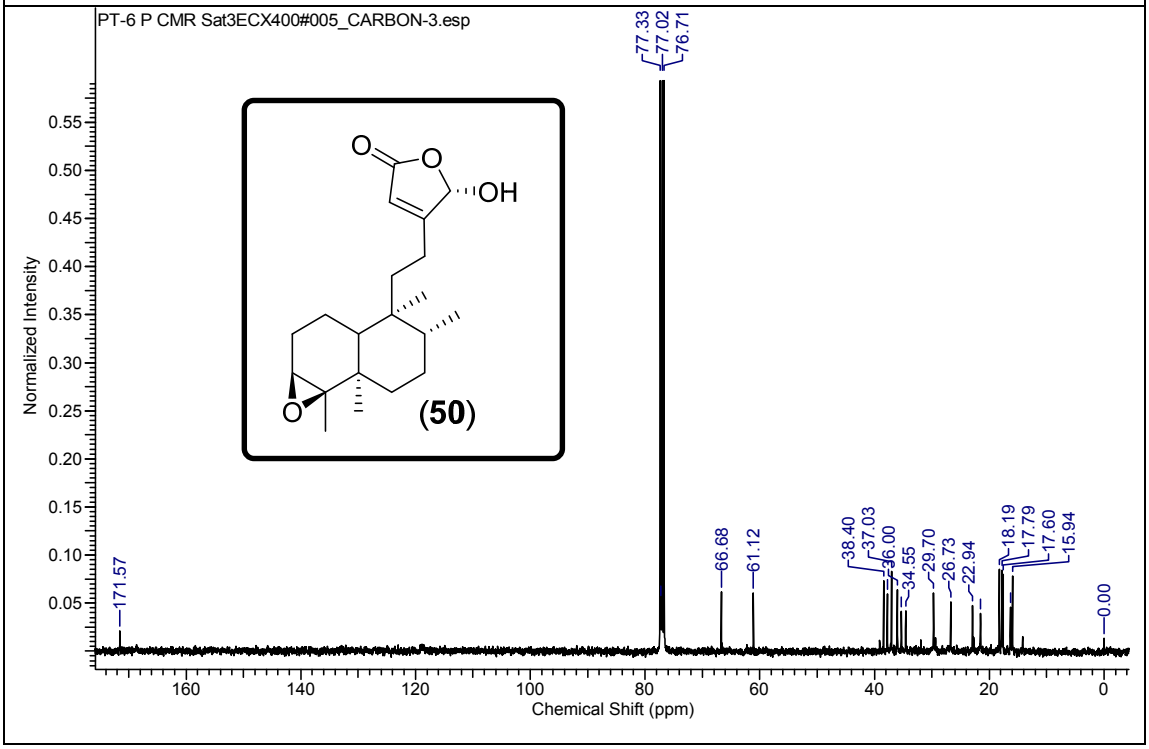
^{13}C NMR (100 MHz, $CDCl_3$) of (**49**)



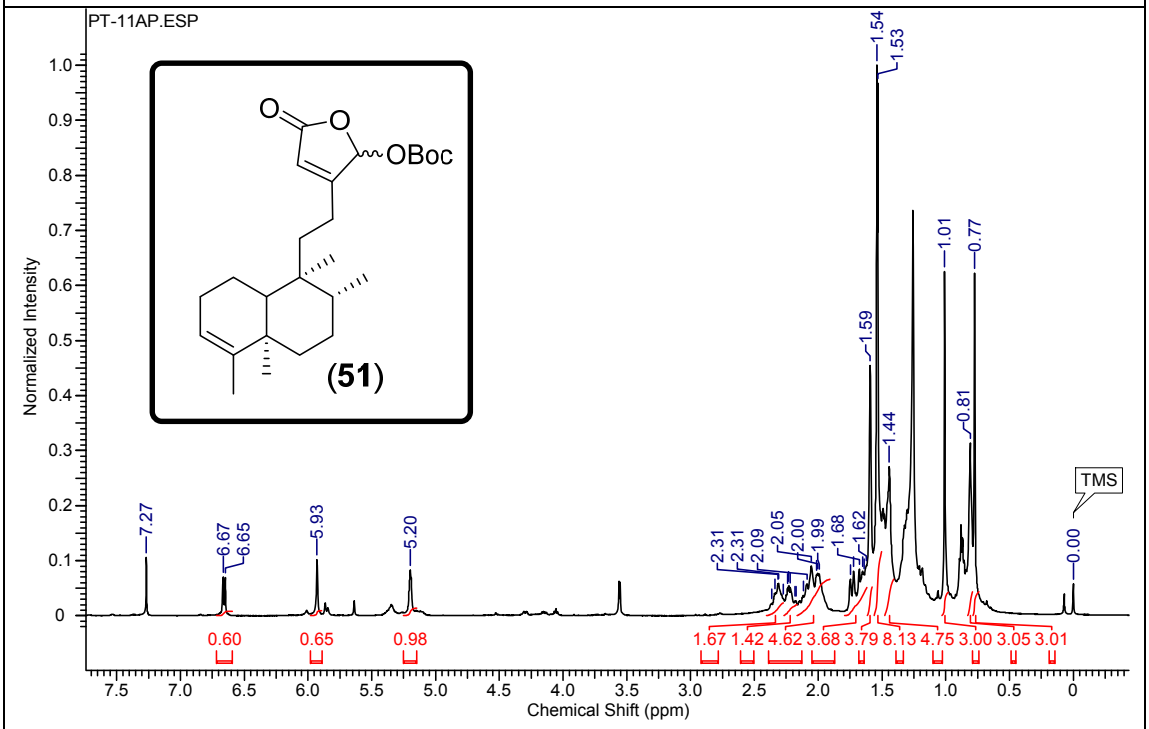
^{1}H NMR (400 MHz, $CDCl_3$) of (**50**)



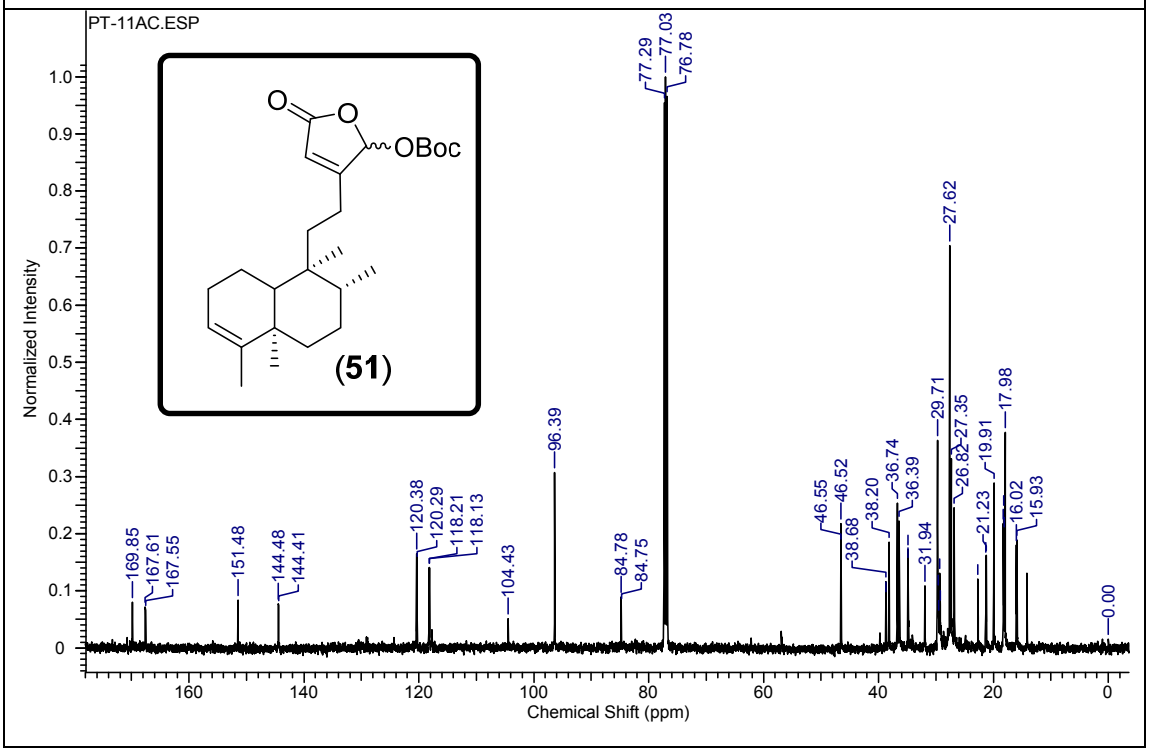
^{13}C NMR (100 MHz, $CDCl_3$) of (**50**)



^{1}H NMR (500 MHz, $CDCl_3$) of (**51**)



^{13}C NMR (125 MHz, $CDCl_3$) of (**51**)



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5. Novel Synthetic Methodology for the Synthesis of *N*-Alkyl-α,β-Unsaturated Glycolactam and its Applications in the Synthesis of Piperidine Alkaloids; Formal Synthesis of Mannolactam, Deoxymannojirimycin, (+)-Prosophylline, (+)-Prosopinine, (2*S*,3*S*)-3-Hydroxypipecolic Acid and *N*-Alkyl-1-deoxymannojirimycin Derivatives. Chand, H. R.; Bhattacharya, A. K. (manuscript under preparation).
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Patents

1 A Process for Synthesis of Piperidine Alkaloids. Bhattacharya, A. K.; Chand, H. R. **PCT Int**. Appl. (**2015**), **WO 2015170339 A1 20151112**.

2 Novel process for the synthesis of an antimalarial drug. Bhattacharya, A. K.; Chand, H. R. **Indian Patent Filed 3079/DEL/2014, 29.10.2014**.

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Symposia and Presentations

1. Participated in Indo-Korean (INSA-KOSEF) Symposium in Organic Chemistry, CSIR-NCL, Jan. 12-13, 2009.
2. Participated in "Indo-French Conference in Organic Synthesis" CSIR-NCL, Pune, Dec. 7-9, 2011.
3. Oral presentation at VIIth J-NOST, IISER Mohali, Dec. 15-18, 2011.
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5. Poster presented on National Science Day at CSIR-NCL, Feb, 2011.
6. Participated in International Symposium in Carbohydrate Chemistry IISc Bengaluru, Jan. 2014.
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8. Poster presented on National Science Day at CSIR-NCL, Feb. 2015.

Erratum

Erratum

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