Synthetic Studies Toward Schulzeines B and C, (*S*)-(+) and (*R*)-(–)-Plakolide A

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

TO

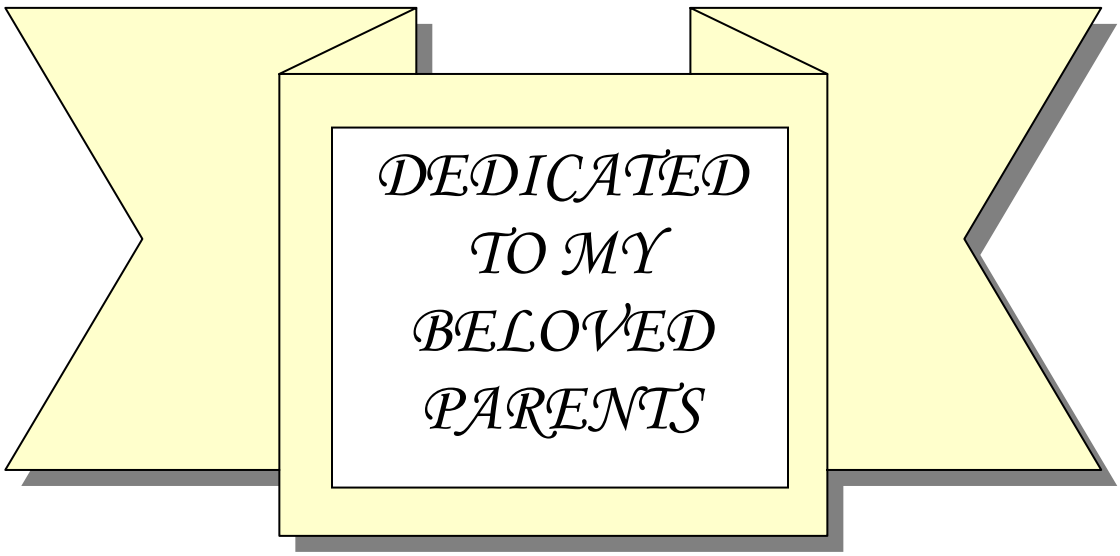
KALYANI UNIVERSITY

BY

CHINMOY PRAMANIK

ORGANIC CHEMISTRY: TECHNOLOGY
NATIONAL CHEMICAL LABORATORY
PUNE-411 008

OCTOBER 2007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TO MY
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PARENTS

DECLARATION

This research work embodied in this thesis has been carried out at National Chemical Laboratory, Pune under the supervision of Dr. M. K. Gurjar, Deputy Director, and Head, Division of Organic Chemistry: Technology, National Chemical Laboratory, Pune – 411 008. This work is original and has not been submitted part or full, for any degree or diploma of this or any other University.

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CERTIFICATE

The research work presented in thesis entitled "**Synthetic studies toward Schulzeines B and C, (*S*)-(+) and (*R*)-(–)-Plakolide A**" has been carried out under my supervision and is a bonafide work of **Mr. Chinmoy Pramanik**. This work is original and has not been submitted for any other degree or diploma of this or any other University.

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October 2007

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Research Guide

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Chinmoy Pramanik

ABBREVIATIONS

AcOH	-	Acetic acid
Ac_2O	-	Acetic anhydride
Bn	-	Benzyl
BnBr	-	Benzyl bromide
$BH_3 \cdot Me_2S$	-	Boron dimethyl sulfide complex
Boc	-	*tert*-Butoxy carbonyl
$(Boc)_2O$	-	Di-*tert*-butyl dicarbonate
BuLi	-	Butyl Lithium
DCM	-	Dichloromethane
DIBAL	-	Diisobutylaluminiumhydride
DMP	-	Dess–Martin periodinane
DMP	-	2,2-Dimethoxypropane
DMF	-	*N, N'*-Dimethylformamide
DMAP	-	*N,N'*-Dimethylaminopyridine
DMSO	-	Dimethyl sulfoxide
EtOH	-	Ethanol
Et	-	Ethyl
Et_2O	-	Diethyl ether
EtOAc	-	Ethyl acetate
Et_3N	-	Triethylamine
Im	-	Imidazole
MeOH	-	Methanol
Me	-	Methyl
MeI	-	Methyl iodide
$NaBH_4$	-	Sodiumborohydride
NaH	-	Sodium hydride
NOE	-	Neuclear Overhauser Effect
Ph	-	Phenyl

Py	-	Pyridine
PDC	-	Pyridiniumdichromate
p-TSA	-	*para*-Toluenesulfonic acid
RCM	-	Ring closing metathesis
TBAI	-	Tetra-*n*-butylammonium iodide
TBAF	-	Tetra-*n*-butylammonium fluoride
TBDMSCl	-	*tert*-Butyldimethyl chlorosilane
TBDMS	-	*tert*-Butyldimethyl silyl
TBDPSCl	-	*tert*-Butyldiphenyl chlorosilane
TBDPS	-	*tert*-Butyldiphenyl silyl
TBS-OTf	-	*tert*-Butyldimethyl silyl trifflate
THF	-	Tetrahydrofuran
TPP	-	Triphenylphosphine
TsCl	-	*p*-Toluenesulphonyl chloride

GENERAL REMARKS

❋ ^{1}H NMR spectra were recorded on AC-200 MHz, MSL-300 MHz, and DRX-500 MHz spectrometer using tetramethylsilane (TMS) as an internal standard. Chemical shifts have been expressed in ppm units downfield from TMS.

❋ ^{13}C NMR spectra were recorded on AC-50 MHz, MSL-75 MHz, and DRX-125 MHz spectrometer

❋ ESI Mass spectra were recorded on Finngan MAT-1020 spectrometer at 70 *eV* using a direct inlet system.

❋ The X-Ray Crystal data were collected on Bruker SMART APEX CCD diffractometer using Mo K radiation with fine focus tube with 50 kV and 30 mA.

❋ Infrared spectra were scanned on Shimadzu IR 470 and Perkin-Elmer 683 or 1310 spectrometers with sodium chloride optics and are measured in cm^{-1}.

❋ Optical rotations were measured with a JASCO DIP 370 digital polarimeter.

❋ Melting points were recorded on Buchi 535 melting point apparatus and are uncorrected.

❋ All reactions are monitored by Thin Layer chromatography (TLC) carried out on 0.25 mm E-Merck silica gel plates (60F-254) with UV light, I_2 and anisaldehyde in ethanol as development reagents.

❋ All solvents and reagents were purified and dried by according to procedures given in Vogel's Text Book of Practical Organic Chemistry. All reactions were carried out under nitrogen or argon atmosphere with dry, freshly distilled solvents under anhydrous conditions unless otherwise specified. Yields refer to chromatographically and spectroscopically homogeneous materials unless otherwise stated.

❋ All evaporations were carried out under reduced pressure on Buchi rotary evaporator below 42 °C.

❋ Silica gel (60–120) used for column chromatography was purchased from ACME Chemical Company, Mumbai, India.

❋ Independent numbering of compounds, schemes, tables & figures have been employed for Abstract, introduction and Present Work of each Chapter.

CONTENTS

Abstract

The thesis entitled **"Synthetic studies toward Schulzeines B and C, (*S*)-(+) and (*R*)-(–)-Plakolide A"** consists of two chapters and each chapter is further sub-divided into following sections: Introduction, Present work, Experimental, Spectroscopic data and References. Chapter I describes total syntheses of schulzeines B and C while Chapter II involves total syntheses of (*S*)-(+) and (*R*)-(–)-Plakolide A.

Chapter I: *Total Syntheses of Schulzeines B and C*

Schulzeines A (**1**), B (**2**) and C (**3**) were isolated from hydrophilic extract of Marine sponge *Penares Schulzei* (Figure 1).

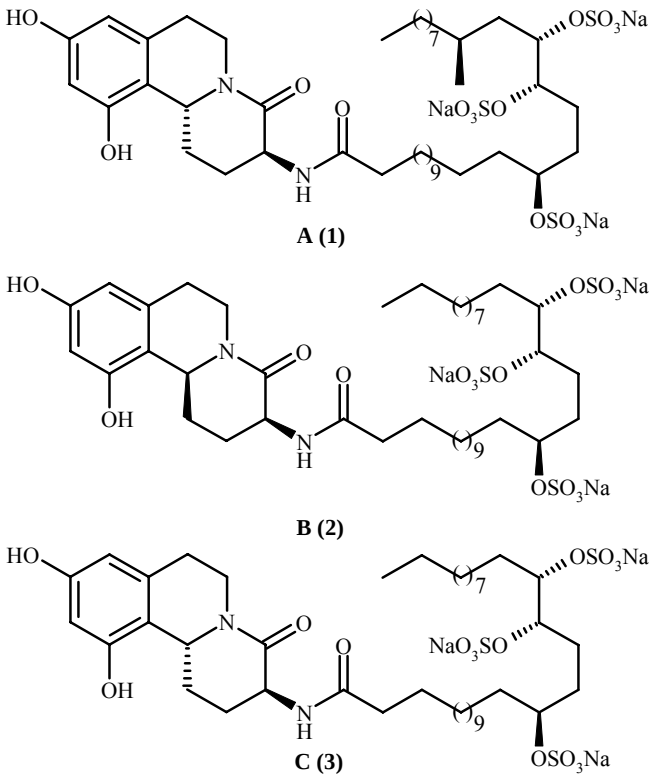
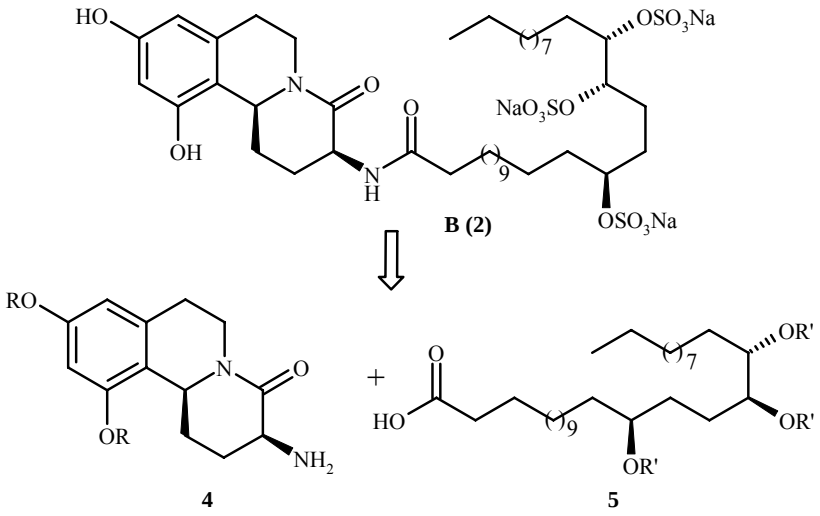


Figure 1. *Structure of schulzeines A, B and C.*

These are α-Glucosidase inhibitors with IC_{50} values of 48-170 nM desulfated schulzeines still retain activity. Schulzeines encompass the tetrahydroisoquinoline constellations and are characterized by a fused γ-lactam ring **4** and a C28 sulfated fatty acid side chain **5** linked via an amide bond (Scheme 1).

Scheme 1

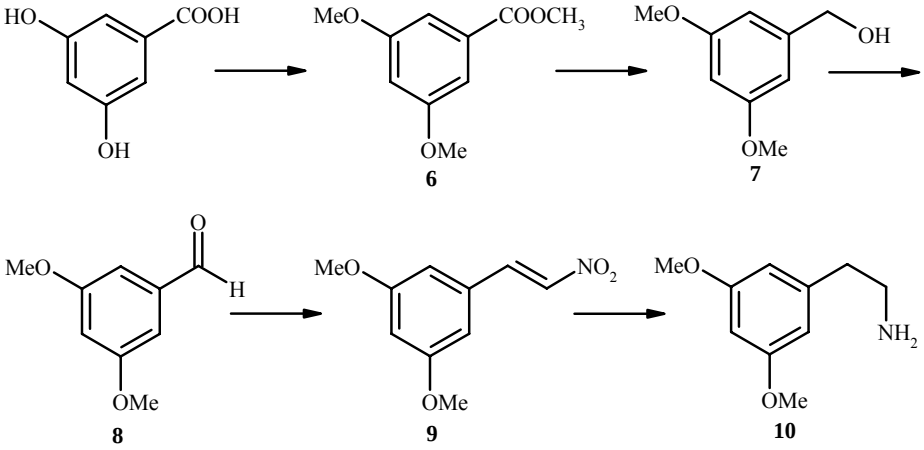


The structural complexity and interesting biological activity of these natural products drew our attention to undertake their total syntheses.

Our initial experimental approach was aimed to develop a general synthetic pathway to the desulfated schulzeines. The key step of our strategy for the construction of the tricyclic core was Bischler-Napieralski cyclization/reduction sequence

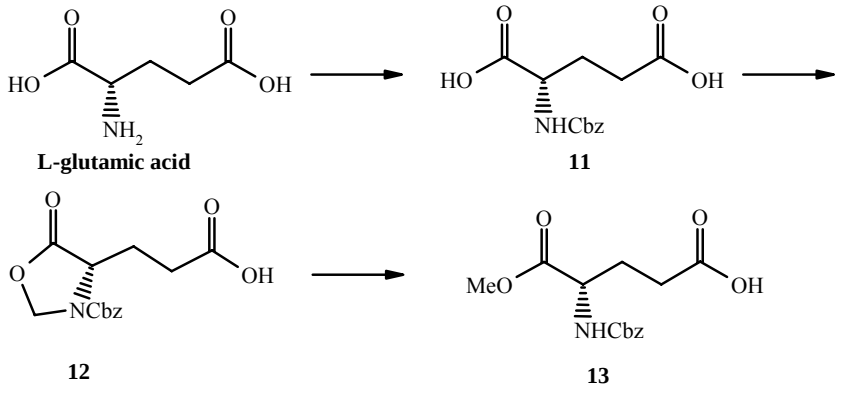
Accordingly, we chose 3,5-dimethoxyphenethylamine (**10**) and glutamic acid derivative **13** as starting materials. The amine **10** was obtained from 3,5-dihydroxybenzoic acid by following sequence of reaction i.e. excessive methylation, $LiAlH_4$ reduction, oxidation, nitro aldol with nitro methane and final reduction (Scheme 2).

Scheme 2



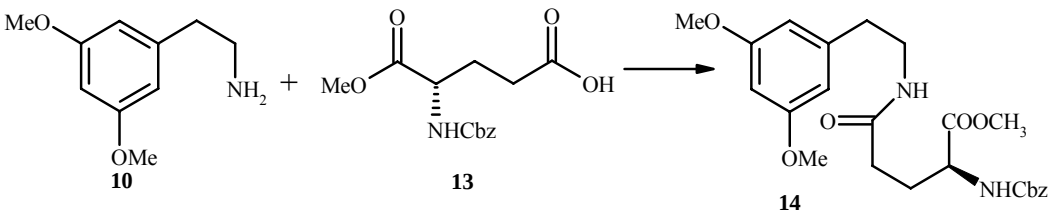
In a parallel procedure α-carboxylic acid group of L-N-Cbz-glutamic acid (**11**) was protected as its methyl ester through oxazoline formation followed by opening with $NaOCH_3$ to afford the required acid **13** (Scheme 3).

Scheme 3



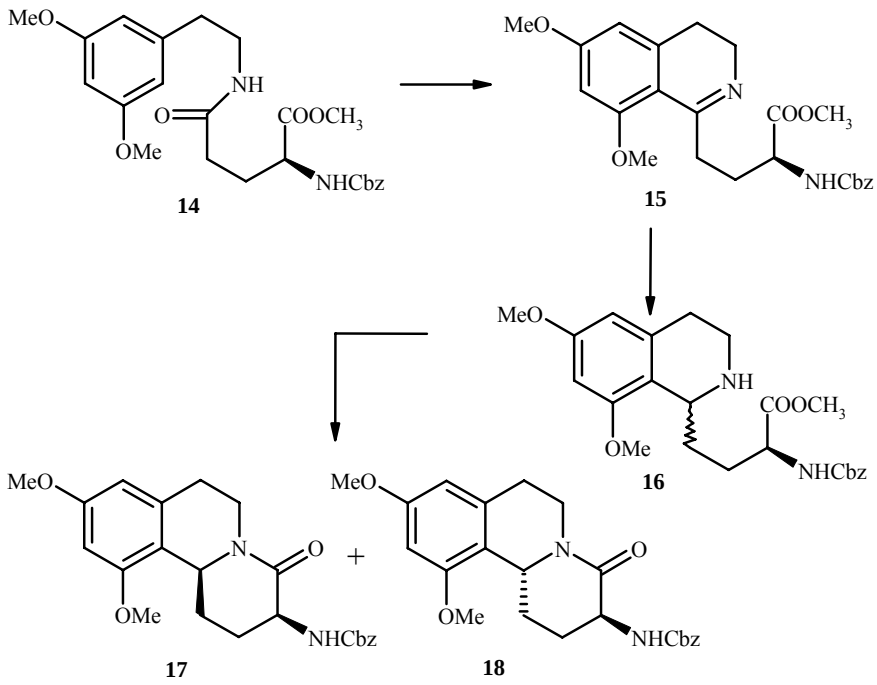
Amide **14** was obtained by coupling of amine **10** with glutamic acid derivative **13** using EDC as coupling reagent (Scheme 4).

Scheme 4

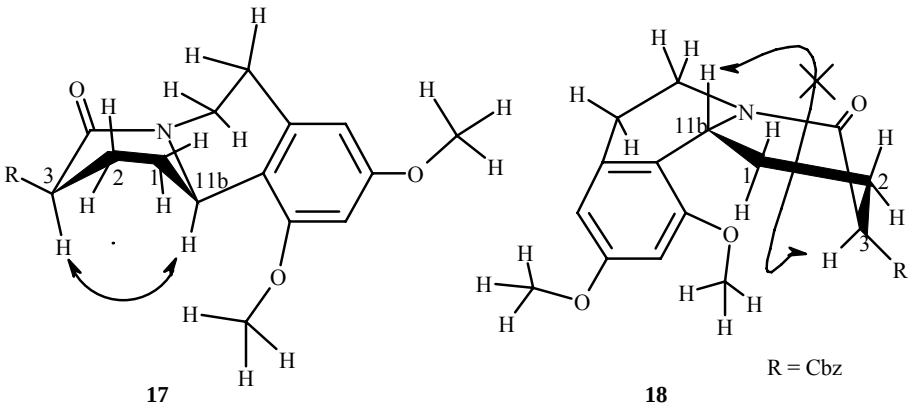


Our strategy, to the tetrahydroisoquinoline part involved Bischler-Napieralski cyclization of amide **14** to 2,3-dihydroisoquinoline **16**. The reduction of imine using $NaCNBH_3$ and subsequent cyclization of the resulting intermediate provide 1,2,3,4-tetrahydroisoquinoline **17**/**18** with 2:3 diatereomeric ratio (Scheme 5). The products were easily separated by silica gel column chromatography.

Scheme 5



The stereochemistry at C-11b position was confirmed by 2D NMR studies. In NOESY spectrum of **17** showed strong correlation between H-3 and H-11b confirmed its cis geometry whereas no such interaction in case of **18** (Figure 2).

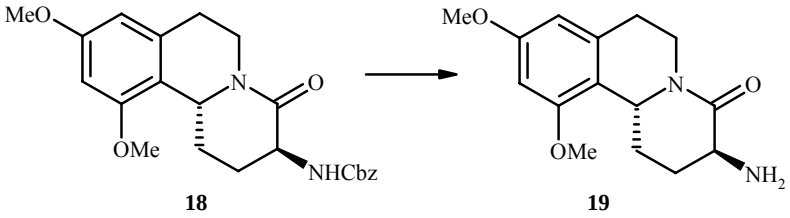


17 **18**

Figure 2

Compound **18** exposured on hydrogenolysis condition with Pd/C under hydrogen atmosphere furnished free amine **19** quantitatively (Scheme 6).

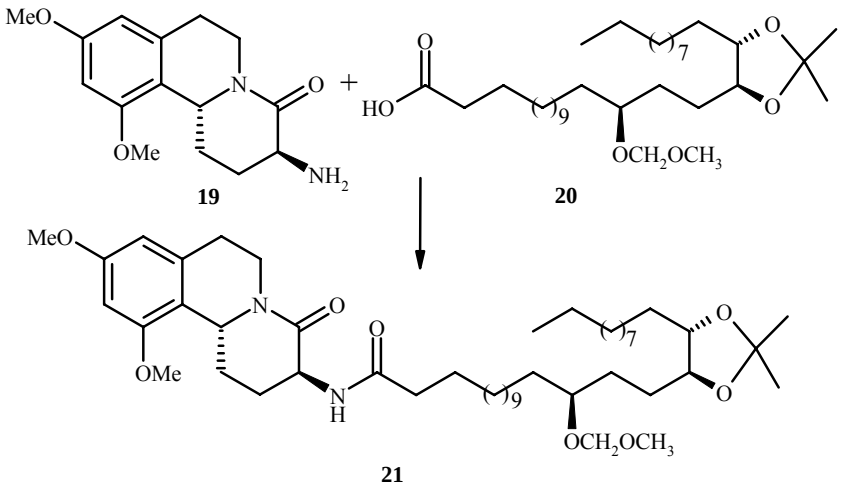
Scheme 6



18 **19**

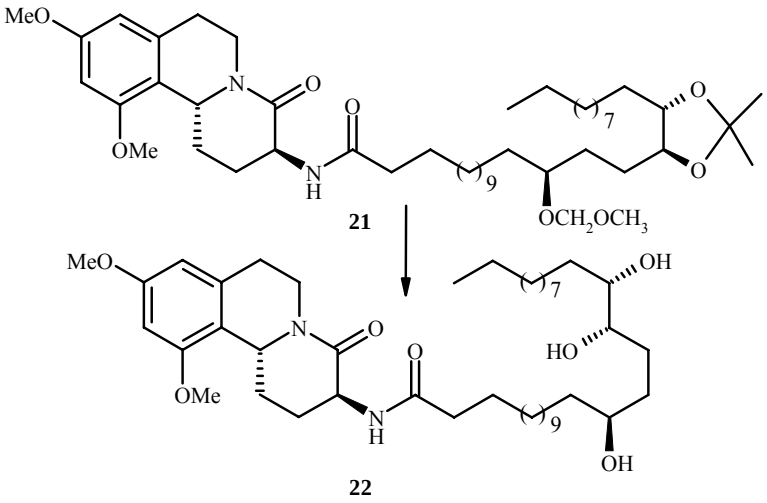
The suitable protected C28 fatty acid part **20** was made separately in our group. Having both the subunits in hand, we turned to couple them together applying the EDC-HOBt protocol to furnish amide **21** (Scheme 7).

Scheme 7



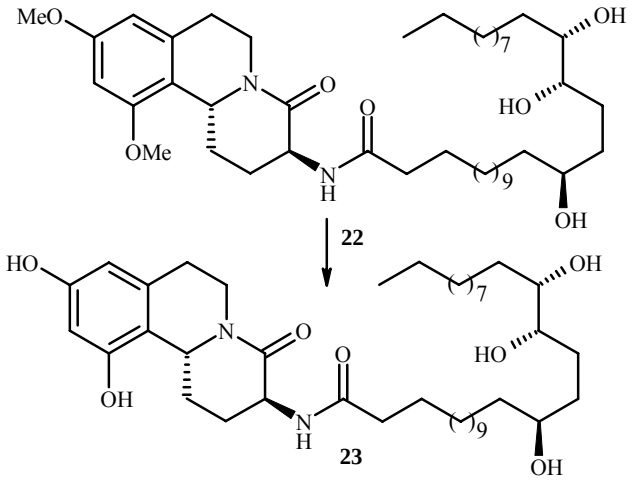
Attempt at deprotection of mom and acetonide by the use various literature procedure/reagents were not fruitful giving a complex mixture of products. The use of TMSI in methylene chloride at 0 ^{o}C was found to be the most effective, giving triol **22** albeit the yield was not satisfactory (Scheme 8).

Scheme 8



Next our attempt was the deprotection of methyl to make desulfated-schulzeine B; we tried various methods for deprotection, but finally remained unsuccessful (Scheme 9).

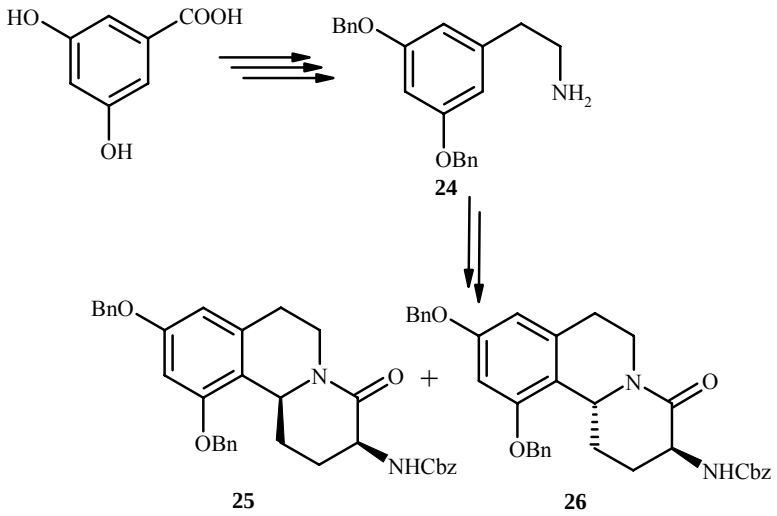
Scheme 9



This result necessitated devising a new approach to the schulzeines. We therefore decided to look at other protecting groups that might be removed under neutral condition. We made benzyl ether in place of methyl ether for the phenolic hydroxyl protection.

Accordingly, 3,5-dihydroxy benzoic acid was converted into amide **25**/**26** with good overall yield via a similar sequence of reactions as in case of **17**/**18** (Scheme 10).

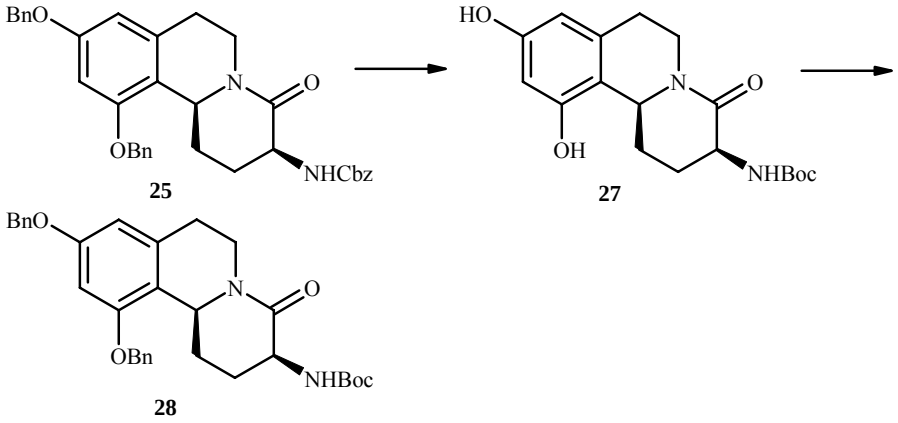
Scheme 10



The relative stereochemistry at C-11b position of **25**/**26** was confirmed by 2D NMR studies as in case of **17**/**18**.

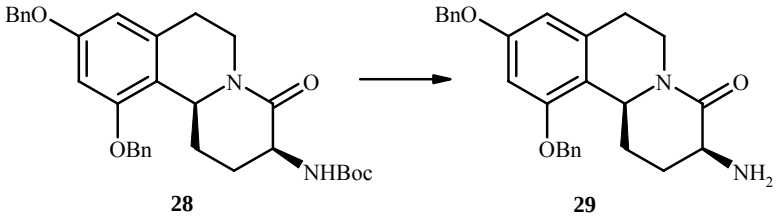
On simple protecting group manipulation compound **25** gave rise to **28** (Scheme 11).

Scheme 11



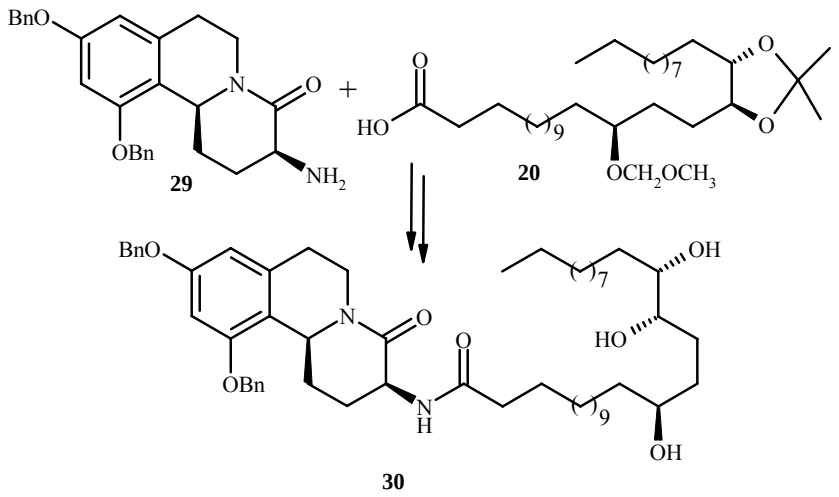
Compound **28** on subjecting to 3 N HCl in ethyl acetate at rt. for 3 h resulted in Boc deprotection to afford the free amine **29** (Scheme 12).

Scheme 12



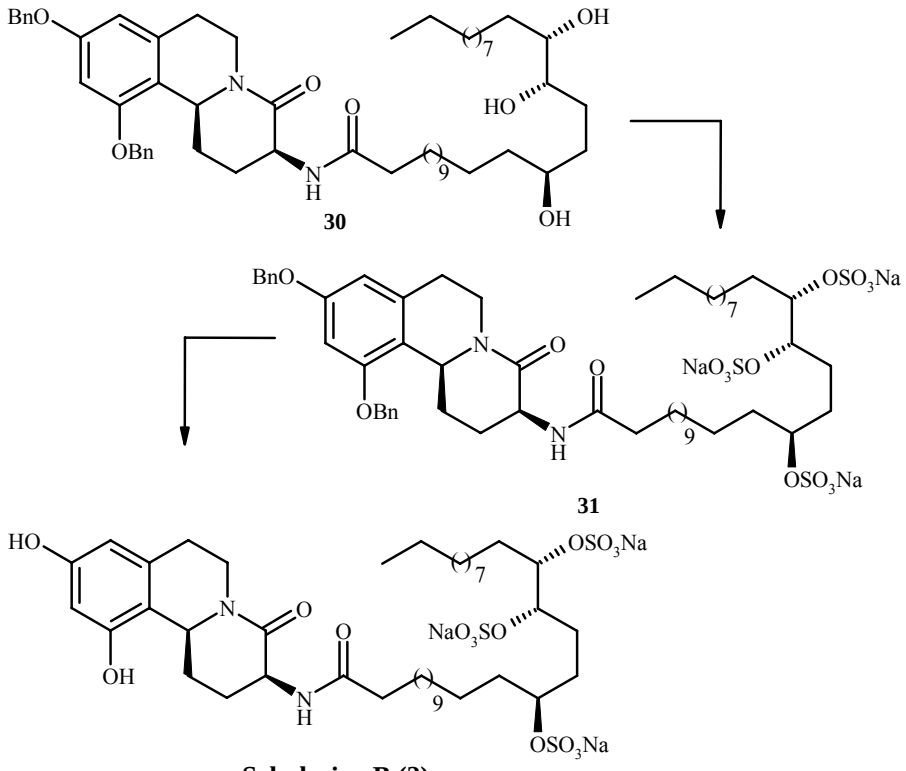
The amine **29** was converted to the triol **30** following the same procedure as in case of **22** (Scheme 13).

Scheme 13



Transformation of triol **26** to **27** was readily effected using SO_3.Py complex in dry DMF at room temperature. Finally removal of benzyl group in **27** furnished schulzeine B (**2**) with good overall yield (Scheme 14). The synthetic schulzeines B (2) displayed ^{1}H and ^{13}C NMR spectroscopic data which were indistinguishable from those obtained for naturally derived material.

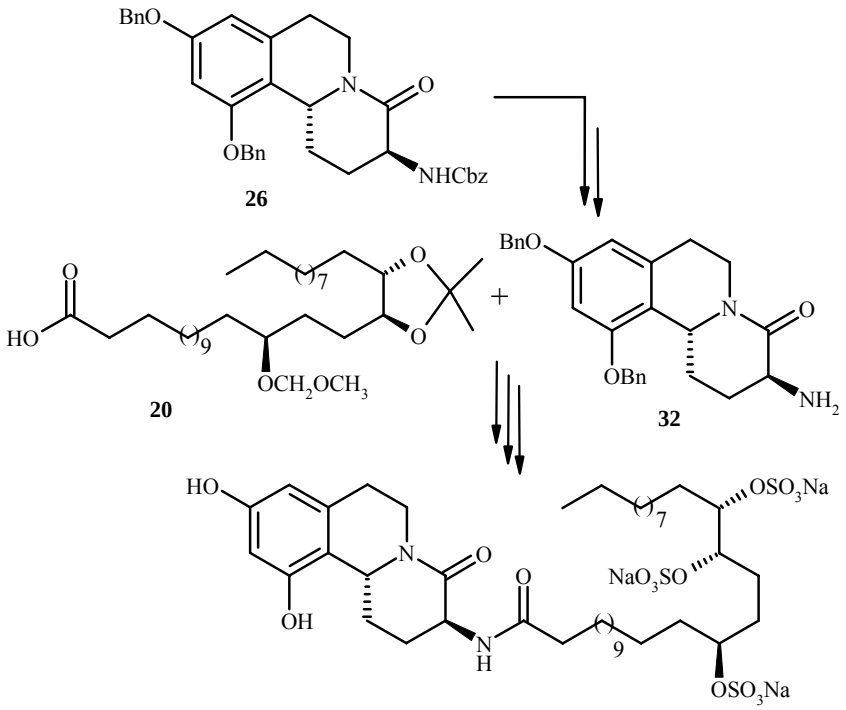
Scheme 14



Schulzeine B (2)

With the same approach, the schulzeines C (3) was synthesized (Scheme 15) and the spectral data was identical with the data reported for the natural product.

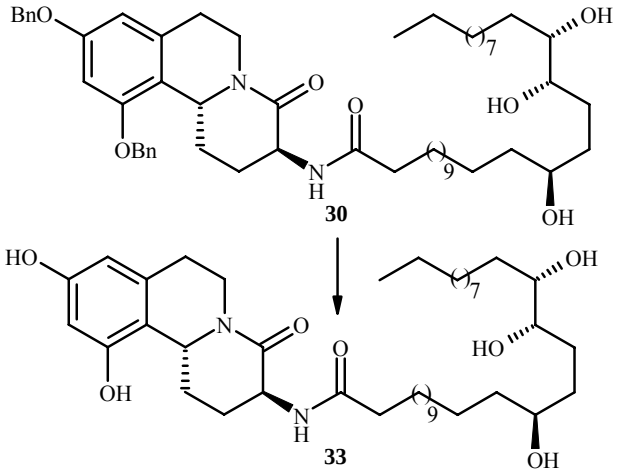
Scheme 15



Schulzeine C (3)

On benzyl deprotection of triol **30** gave rise to desulfated schulzeine C (Scheme 15).

Scheme 15

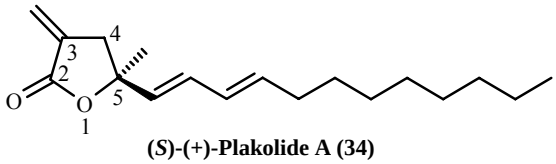


In conclusion, we have achieved the first total syntheses of schulzeines B and C. Bischler-Napieralski cyclization/reduction sequence was used for the construction of key

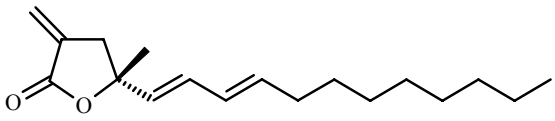
tetrahydroisoquinoline moieties. The reported approach is convergent in nature and provides considerable flexibility for the synthesis of related nonnatural analogues.

Chapter II: *Total syntheses of (S)-(+) and (R)-(–)- Plakolide A*

Plakolide A was isolated from shallow-water marine sponge of the genus *Plakotris* (Figure 4). It possesses a α-exomethylene-γ-disubstituted-γ-lactone moiety. It showed significant inhibitory activity in a cell-based assay designed to detect inducible nitric oxide synthese (iNOS) and cytotoxicity against panc-1 human pancreatic carcinoma and NCI/ADR human breast carcinoma cell lines with IC_{50} values of 3.8 and 3.7 μg/mL respectively.



(*S*)-(+)-Plakolide A (34)



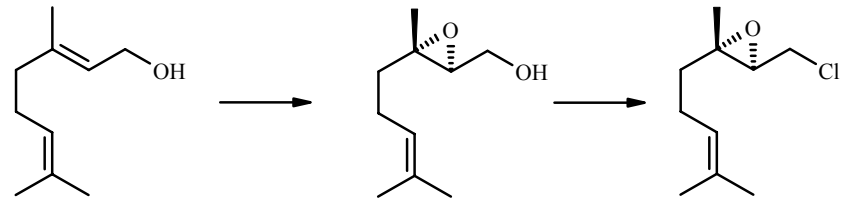
Revised (*R*)-(-)-Plakolide A (35)

Figure 4

The interesting biological activity and structural feature insisted us for its total synthesis. The initially proposed absolute stereochemistry of Plakolide A was revised by total synthesis at time when we were pursuing its synthesis from a commercially available geraniol as starting material.

First geraniol was converted to epoxymethylene chloride **37** through Sharpless asymmetric epoxidation followed by chlorination of alcohol using PPh_3 and CCl_4 under reflux condition (Scheme 17).

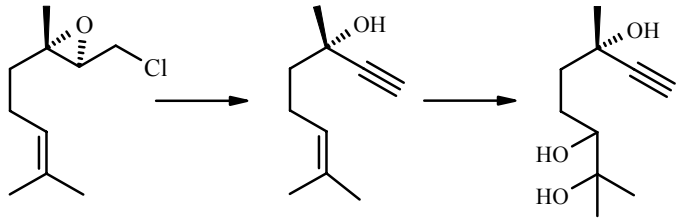
Scheme 17



Geraniol **36** **37**

Double elimination was effected by exposure of epoxymethylene chloride **37** to *n*-BuLi in THF at –40 ^{o}C subsequent dihydroxylation using OsO_4 and NMO in acetone-water mixture at ambient temperature afforded triol **39** (Scheme 18).

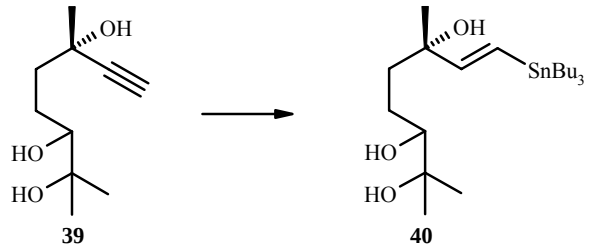
Scheme 18



37 **38** **39**

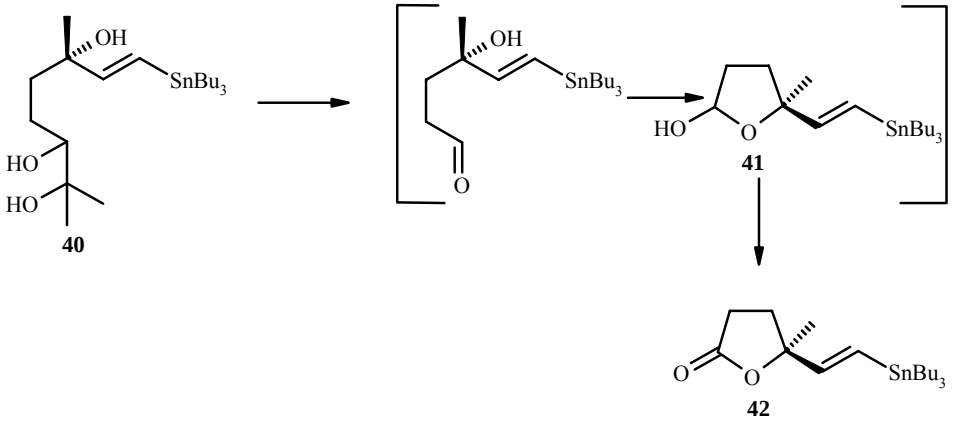
Vinylation with non-functionalized terminal alkyne proceeded smoothly with high yield and without formation of by products by using tributyltinhydride and catalytic AIBN in toluene under reflux condition provided vinyltin **40** (Scheme 19).

Scheme 19



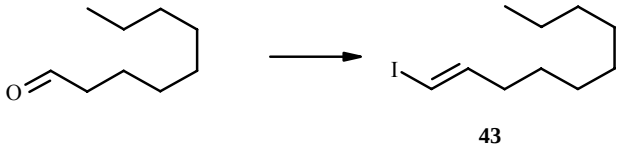
Cleavage of the diol using silica gel supported sodium meta-periodate followed by subsequent cyclization and oxidation of resulting lactol **41** afforded cyclic core **42** of Plakolide. NMR and analytical data confirmed structure of lactone **42** (Scheme 20).

Scheme 20



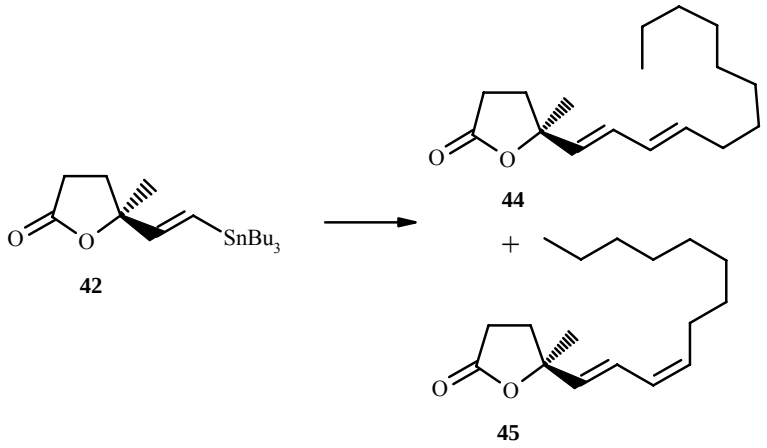
Vinyl iodide **43** was prepared from nonanal in one step applying Takai-olefination (Scheme 21).

Scheme 21



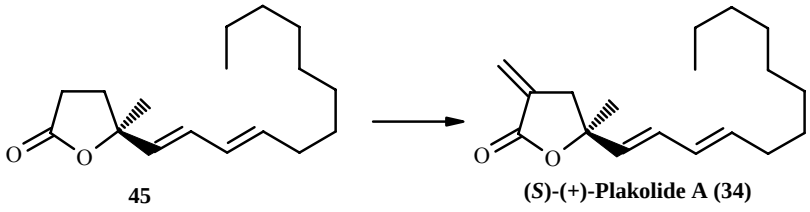
Our next attempt was to make the side chain using stille coupling reaction of lactone **42** with vinyl iodide **43** (Scheme 22).

Scheme 22



The expected coupled products *E*,*E*-**44** and *E*,*Z*-**45** were obtained in a 9:1 ratio using $Pd(PPh_3)_4$ in DMSO. The products were easily separated by flash silica gel column chromatography. Finally, treatment of the *E*,*E* isomer **44** with LDA and Eschenmoser's salt[10] furnished (*S*)-(+)-Plakolide A (**34**), which exhibited spectroscopic and physical properties identical with natural product; only the sign of optical rotation was different {$[\alpha]_D^{25}$ +43.2 (*c* 1.5, MeOH), lit[1] $[\alpha]_D$ –41.0 (c 0.12, MeOH)}. This reconfirmed the observation of Matsuo *et al*. that, the natural Plakolide A is not (*S*)-(+)-Plakolide A (**34**) but rather the (*R*)-(–)-Plakolide A (**35**) (Scheme 23).

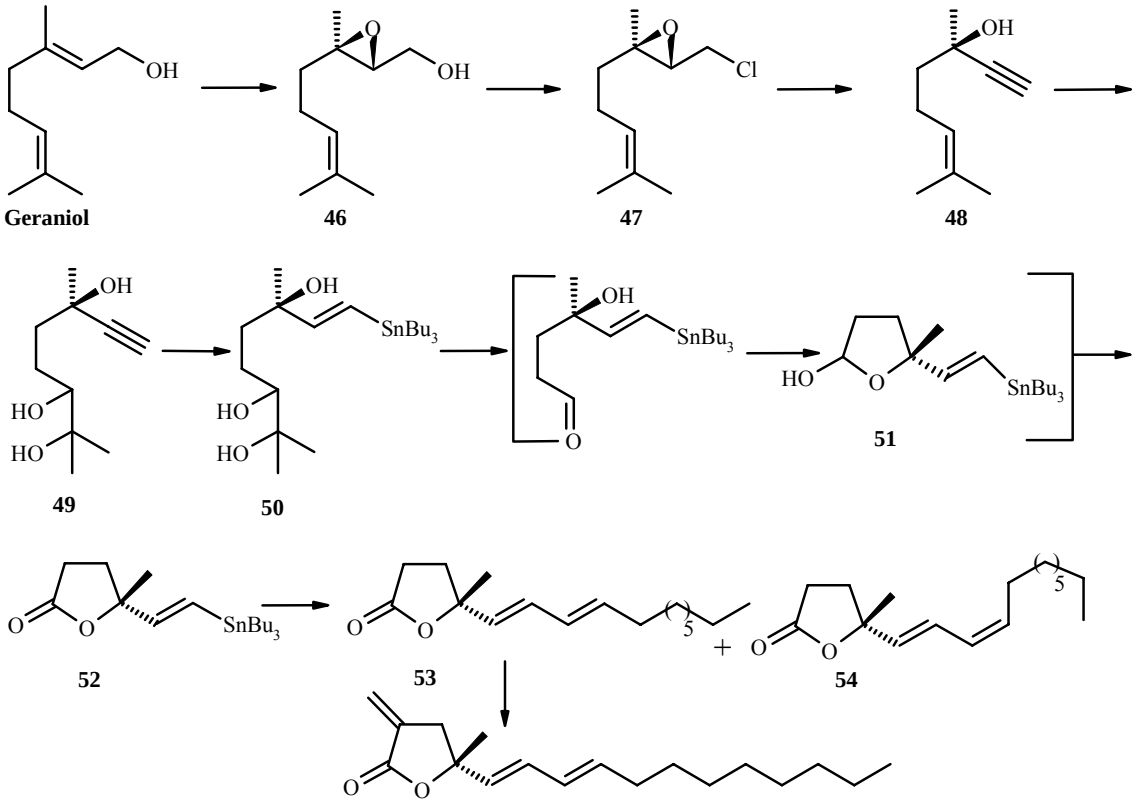
Scheme 23



Building on this approach, synthetic entry to the natural enantiomer (*R*)-(–)-Plakolide A (**35**) was also possible. Thus, starting from epoxygeraniol **39** obtained from commercially available geraniol using D-(–)-DIPT and following the same protocol described in case of (*S*)-(+)-Plakolide A (**34**), we arrived at (*R*)-(–)-Plakolide A (**35**)

{$[\alpha]_D^{25}$ –42.4 (*c* 1.2, MeOH), lit $[\alpha]_D^{25}$ –41.0 (*c* 0.12, MeOH)}in 8 steps with an overall 41% yield (Scheme 24).

Scheme 24



In conclusion, we developed efficient synthetic routes to enantiopure (*S*)-(+)-Plakolide A (**1**) and (*R*)-(–)-Plakolide A (**2**) starting from readily available geraniol as starting material and following a practical sequence of reactions. The obvious and noteworthy advantages of our protocol lie in high overall yields, ready access to the disubstituted γ-lactone moiety with high enantioselectivity, and various possibilities of side chain modifications

CHAPTER-I

Total Syntheses of Schulzeines B and C

INTRODUCTION

INTRODUCTION

α-Glucosidase inhibitor:

Glycosides are compounds containing a carbohydrate and a non-carbohydrate residue in the same molecule. The non-sugar component is called aglycone, which may be methyl alcohol, glycerol, sterol, phenol, etc. and the sugar component is called glycon. The glycon residue is attached by an acetal linkage at the anomeric carbon to a noncarbohydrate residue or aglycon part.

Enzymes are biocatalyst and essential for life processes because chemical reactions in living cells would occur too slowly or would lead to different products without enzymes. Therefore enzymes play fundamental roles in life processes. Glycosidase is an enzyme that cleaves this linkage between the aglycon and glycon and if the enzyme is specifically cleaving the linkage between glucose and aglycon then the enzyme is called glucosidase. In our human body for the digestion of complex carbohydrates there are two enzymes: α-glucosidase enzymes in the brush border of the small intestine and pancreatic α-amylase. Pancreatic α-amylase hydrolyzes complex starches to oligosaccharides in the lumen of the small intestine; whereas the membrane bound intestinal α-glucosidases hydrolyze oligosaccharides, trisaccharides and disaccharides to glucose and other monosaccharide in the small intestine.[1] Inhibition of these enzyme systems reduces the rate of glucose absorption from the intestine as the carbohydrates are not broken down into glucose molecules, resulting in a slower and lower rise in blood glucose level through the day, especially right after the meals. Any medicament that renders the function of α-glucosidase is called α-glucosidase inhibitor. This is a class of oral medication for Type 2 diabetes**.**

Diabetes:

Diabetes mellitus, commonly referred to as diabetes, is a medical condition associated with abnormally high levels of glucose (or sugar) in the blood (hyperglycemia).[2] Glucose is a type of sugar found in certain foods such as honey and some, but not all, fruits. It is also the form of sugar that all sugary and starchy foods are converted to in the body after digestion. The body to make energy uses glucose. Normally, blood glucose levels are tightly controlled by insulin, a chemical signaling substance (hormone) that is

produced by a gland near our stomach called the pancreas. Insulin lowers the blood glucose level because it stimulates the body to make use of glucose. When the amount of glucose in the blood increases, for example, after eating food, insulin is released from the pancreas to normalize the glucose level. However, in patients with diabetes mellitus, the elevated glucose levels cannot be normalized. This causes abnormally high levels of blood glucose, which ultimately leads to the presence of glucose in the urine (glucosuria). There are two main types of diabetes mellitus. These are known as Type 1 and Type 2. Type 1 diabetes mellitus used to be called insulin-dependent diabetes mellitus, or juvenile-onset diabetes mellitus, because it usually begins in childhood or adolescence. In this case diabetes mellitus, the pancreas releases no insulin at all because the body has destroyed the cells that produce it (islet cells). The patient therefore relies on treatment with insulin. The symptoms tend to occur suddenly after the onset of the disease and are usually more obvious than those of type 2. Type 2 diabetes mellitus is the most common form of diabetes. It used to be called non-insulin dependent diabetes mellitus or adult onset diabetes because it usually begins in adulthood (mainly after 40 years of age). In this case, patients can still produce insulin, but they do not produce enough and/or their bodies cannot use it properly. It develops gradually in most cases and may be present for several years before it is detected. Another form of diabetes, known as gestational diabetes, occurs in some women during pregnancy. It is a temporary condition caused by pregnancy and usually occurs in the later stages; once the baby has formed and usually goes away after the baby is born. Uncontrolled gestational diabetes can result in a large baby and a difficult birth. It can also increase the risk of developing Type 2 diabetes later in life. The early symptoms of untreated diabetes mellitus are related to the elevated blood glucose levels. Excess glucose in the blood ultimately results in high levels of glucose being present in the urine (glucosuria). This increases the urine output, which leads to dehydration and increased thirst. Other symptoms include extreme tiredness, weight loss, blurred vision, itchy skin and repeated minor infections such as thrush and boils. People with Type 1 diabetes must be treated with insulin in order to stay alive. If uncontrolled for many years, diabetes mellitus can lead to more serious health problems: Blood vessel damage within the eye (retinopathy). This can lead to blindness, Kidney disease (nephropathy) or kidney failure, Nerve damage (neuropathy) especially of the hands and feet, causing tingling,

numbness and weakness and narrowing of the blood vessels due to fat deposit (atherosclerosis).[3] This increases the risk of heart attack, stroke and poor blood flow in the legs.

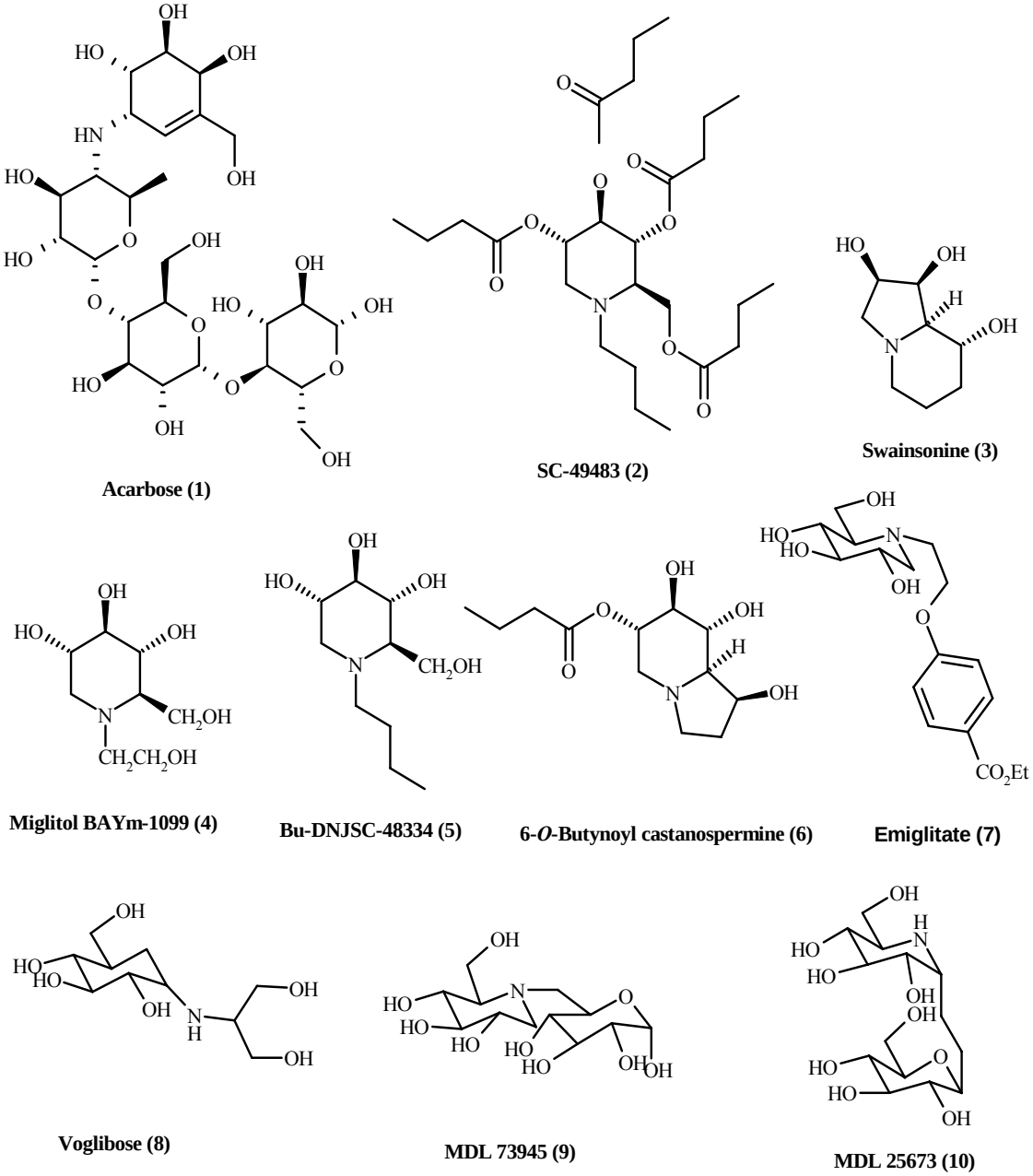


Figure 1. *The α-glucosidase inhibitors presently being explored in the clinic for the treatment of diabetes, AIDS and cancer.*

Diabetes Mellitus is a life-long, chronic condition. In 2006, according to the World Health Organization, at least 171 million people worldwide suffer from diabetes. Its

incidence is increasing rapidly, and it is estimated that by the year 2030, this number will double.

Diabetes mellitus occurs throughout the world, but is more common (especially Type 2) in the more developed countries. Over 40 million have now been diagnosed with diabetes in India.

Treatment is aimed at controlling the elevated blood glucose without causing an abnormally low glucose level (hypoglycemia). Type 1 diabetes mellitus is treated with insulin, exercise, and a healthy diet. Type 2 diabetes mellitus is first treated with weight reduction, a healthy diet and regular exercise. In Type 2 diabetes, if the above measures fail to control the elevated blood glucose, oral (by mouth) medicines are used to try to boost insulin production, improve the body's use of it, or *reduce the speed at which glucose enters the blood*. Treatment with insulin will be considered if these other medicines are insufficient. Gestational diabetes is usually controlled by a healthy diet and regular exercise. Some women may require treatment with insulin.

Besides the use of multiple approaches, α-glucosidase inhibitors are one of the alternative therapeutic approaches. There are some examples of α-glucosidase inhibitors (**1**-**10**, Figure 1), which are presently being explored in the clinic for the treatment of diabetes, cancer and AIDS.[4]

α-Glucosidase inhibitors as anti-viral agents:

Many animal viruses contain an outer envelope, which is composed of one or more viral glycoproteins. These glycoproteins are often essential proteins in that they are required in the viral life cycle, either in viron assembly and secretion and/or infectivity. Glycoproteins are a large and diverse group that has particular roles in enzymatic reaction, molecular recognition events and cell-cell interactions. The glycan attached to these proteins often vital for the correct performance of these functions. Alterations in glycan composition have been employed to investigate the way glycoproteins operate and to develop new ways of treating clinical conditions.[5]

Mechanism of Action

N-linked glycosylation is initiated by the cotranslational transfer of a 14-residue oligosaccharide precursor ($Glc_3Man_9GlcNAc_2$) to certain polypeptides, which contain Asn-Xaa-Ser/Thr glycosylation sequon.[6] After transfer the glycan chain is modified by a series of reactions within the endoplasmic reticulum (ER) and Golgi apparatus. The first processing event is the stepwise removal of the terminal glucose residue by ER α-glucosidase.

As processing of above mentioned glycoproteins occurs through cellular machinery, inhibitors of the N-glycan processing pathway have been used to study the role of the N-glycans in several viral systems including human immuno-deficiency virus (HIV-1),[7] human hepatitis B virus (HBV),[8] human cytomegalovirus (HCMV),[9] influenza,[10] Sinbis virus[11] and VSV.[12]

Human immunodeficiency virus (HIV):

Human immunodeficiency virus (HIV) is a retrovirus that can lead to *acquired immunodeficiency syndrome* (AIDS, a condition in humans in which the immune system begins to fail, leading to life-threatening opportunistic infections). Previous names for the virus include human T-lymphotropic virus-III (HTLV-III), lymphadenopathy-associated virus (LAV), or AIDS-associated retrovirus (ARV). [13]

In 1983 scientist led by Luc Monagnier at the Pasture Institute in France first discovered the virus that causes AIDS.[14] They called it lymphadenopathy-associated virus (LAV). A year later a team led by Robert Gallo of the United States confirmed the discovery of the virus, but they renamed it human T lymphotropic virus type III (HTLV-III).[15] The duel discovery led to considerable scientific disagreement, and it was not until President Mitterrand of France and President Regan of the USA met the major issues were resolved. In1986, both the French and the U. S. names for the virus itself were dropped in favor of the new term, human immunodeficiency virus (HIV).[16] HIV infection in humans is now pandemic. As of January 2006, the Joint United Nation Program on HIV/AIDS (UNAIDS) and the World Health Organization (WHO) estimated that AIDS has killed more than 25 million people since it was first recognized on December 1, 1981, making it one of the most destructive pandemics in recorded history. In 2005 alone, AIDS claimed

an estimated 2.4–3.3 million lives, of which more than 570,000 were children. It is estimated that about 0.6% of the world's living population is infected with HIV.[17] India is one of the largest and most populated countries in the world, with over one billion inhabitants. Of this number, at least five million are currently living with HIV.[18] Since the beginning of the pandemic; three main transmission routes for HIV have been identified.[19-25]

1. Sexual route: the majority of HIV infections are acquired through unprotected sexual relations. Sexual transmission can occur when infected sexual secretions of one partner come into contact with the genital, oral, or rectal mucus membranes of another.

2. Blood or blood product route: This transmission route can account for infections in intravenous drug users, hemophiliacs and recipients of blood transfusion and blood products. It is also concern for receiving medical care in regions where there is prevalent substandard hygiene in the use of injection equipment, such as the reuse of needles in Third World countries. HIV can also be spread through the sharing of needles. Health care workers such as nurses, laboratory workers, and doctors, have also been infected, although this occurs more rarely. People who give and receive tattoos, piercings, and scarification procedures can also be at risk of infection.

3. Mother to child transmission (MTCT): The transmission of the virus from the mother to the child occurs in utero during the last weeks of pregnancy and at childbirth. In the absence of treatment, the transmission rate between the mother and child is 25%. However, where drug treatment and caesarian section are available, this can be reduced to 1%. Breast feeding also presents a risk of infection for the baby. HIV primarily infects vital cells in the human immune system such as helper T cells (specifically $CD4^+$ T cells), macrophages and dendritic cells.

HIV infection leads to low levels of $CD4^+$ T cells through three main mechanisms: firstly, direct viral killing of infected cells; secondly, increased rates of apoptosis in infected cells; and thirdly, killing of infected $CD4^+$ T cells by CD8 cytotoxic lymphocytes that recognize infected cells. When $CD4^+$ T cell numbers decline below a critical level, cell-mediated immunity is lost, and the body becomes progressively more susceptible to opportunistic infections. If untreated, eventually most HIV-infected individuals developed AIDS (Acquired Immunodeficiency Syndrome) and die; however about one in ten remains

healthy for many years, with no noticeable symptoms. Treatment with anti-retroviral, where available, increases the life expectancy of people infected with HIV. It is hoped that current and future treatments may allow HIV-infected individuals to achieve a life expectancy approaching that of the general public.

Glucosidase inhibitors prevent the fusion of HIV. HIV-1 encodes two essential envelope glycoproteins (gp120 and gp41) through endoproteolytic cleavage of a precursor protein (gp160) within the *cis*-Golgi apparatus. Although proteolytically cleaved, gp120 remains non-covalently attached to the luminal portion of the transmembrane gp41 through conserved regions within the amino and carboxy terminus. Therefore gp120 is fully exposed on the outer face of the viral envelop, with the transmembrane gp41 acting as an anchor for the complex.[26]

During infection gp120 binds to the CD4 surface antigen (the cellular receptor) and undergoes a conformational change and cleavage, which exposes gp41. The exposure of gp41 allows fusion with the cellular membrane, thus mediating viral entry into the cell.[27] Both gp41 and gp120 are heavily N-glycosilated and normally contains a mixture of complex and oligomannose type glycans. Treatment of HIV-1 infected cell with N-butyldeoxynojirimycin, an inhibitor of α-glucosidases, inhibits syncytium formation and the formation of infectious virus.[28] The reduction in secretion of infectious virus caused by NB-DNJ is the result of impairments in post-CD4 binding steps.[29] Although binding to CD4 occurs, the conformational shift and cleavage of gp120 that results in the exposure of gp41 does not. Thus the process of viral fusion is prevented.

In case of HBV glucosidase inhibitor prevents the formation and secretion of the virus through the disruption of the viral envelope. A few misfolding are sufficient to prevent viron formation.

α-Glucosidase inhibitors reduces Dengue virus production by affecting the initial steps of viron morphogenesis in the endoplasmic reticulam.[30] Glucosidase inhibition strongly affects productive folding pathways of the envelope glycoproteins prM (the intracellular glycosylated precursor of M [membrane protein]) and E (envelope protein): the proper folding of prM bearing unprocessed N-linked oligosaccharide is inefficient, and this cause delayed formation of prME heterodimer. The complexes formed between incompletely folded prM and E appears to be unstable, leading to a nonproductive

pathway. Inhibition of α-glucosidase-mediated N-linked oligosaccharide trimming may thus prevent the assembly of Den virus by affecting the early stages of envelope glycoprotein processing.

Finally the process of N-linked glycosylation is a dynamic event, which plays many roles in the fate and function of proteins. One important function is to assist protein folding through enabling the interaction with lectin-like chaperones in the ER. The use of glucosidase inhibitors to prevent these interactions and have anti-viral activity may be especially promising in case where the virus buds through the ER (as in HBV).

Some natural structurally interesting α-glucosidase inhibitors:

It is of interest that nature seems to have selected non-carbohydrate mimics as natural inhibitors of glycosidase enzymes. α-Glucosidase inhibitors have been isolated from various food materials e.g. ougon, hijiki, tochu-cha, welsh onion and clove. Some naturally occurring compounds such as acarbose (**1**) and swaninsonine (**11**) are potent glycosidase inhibitors. Acarbose is currently used for the oral treatment of diabetes.[31] A new class of α-glucosidase inhibitors, namely salacinol (**12**)[32-33] and kotalanol (**13**) with an intriguing inner-salt sulfonium-sulfate structure was isolated from the roots and stems of the plant *salacis reticulate* which has been used as an antidiabetic Ayurvedic traditional medicine.[34-36] Salacinol showed the competitive inhibition for the intestinal α-glucosidase in vitro; IC_{50} values were 3.2 μg/mL to maltose, 0.84 μg/ml to sucrose, and0.59 μg/ml to isomaltose. It is belived that the inhibition of glucosidases by salacinol (**12**) and kotalanol (**13**) is in fact due to their ability to mimic both the shape and charge of the oxocarbanium-ion like transition state involved in the enzymatic reactions. The selenium congener of the salacinol was synthesized[37-39] and it was found that blintol (**14**) exhibited stronger inhibitory activities than salacinol. Moranoline (**15**),[40] another one α-glucosidase inhibitor, which was isolated from culture filtrates of a *Streptomuces* species. Compound **16** and **17** were isolated from aqueous methanol extract of *hyssop* (*Hyssopus officinalis*) leaves and showed considerable α-glucosidase activity.[41]

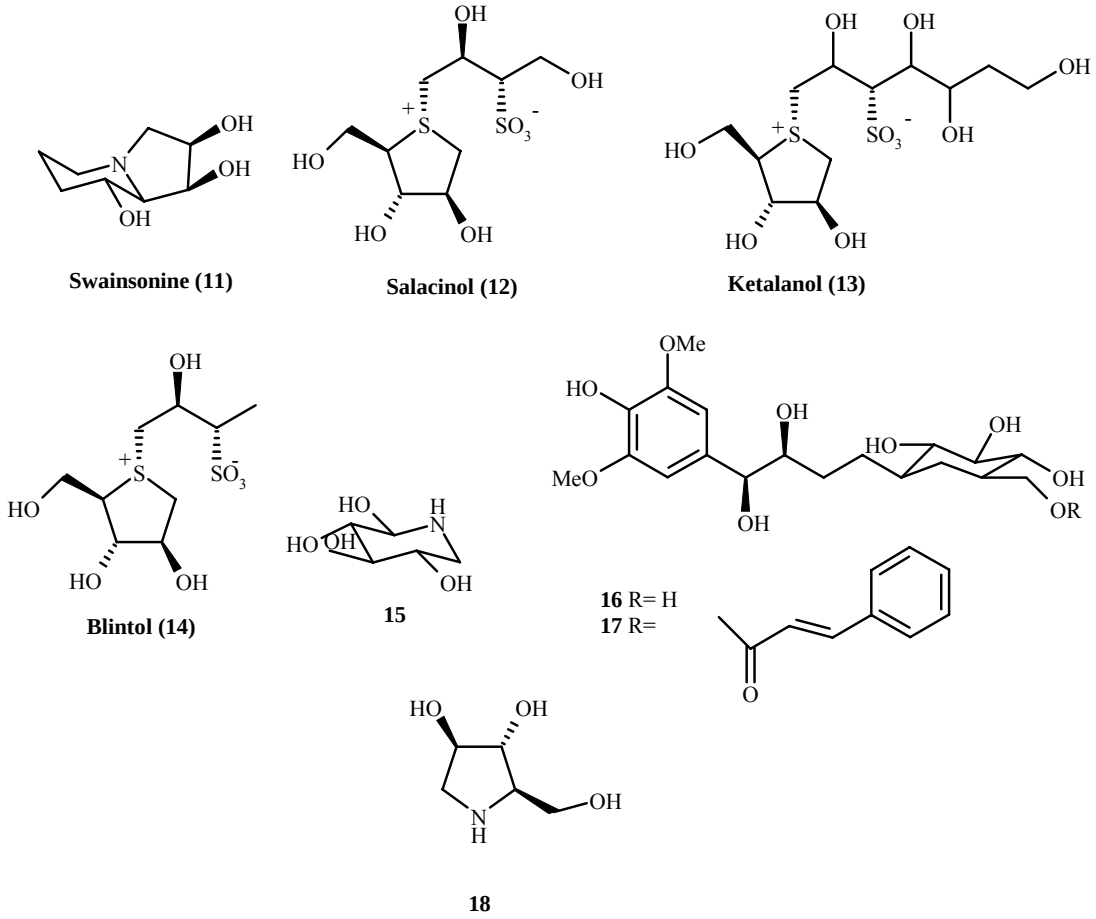


Figure 2. *Some natural structurally interesting α-glucosidase inhibitors.*

Iminopentitol (**18**),[42] an α-glucosidase inhibitor was isolated as a natural product from fruits of *Angylocalyx boutiqueanus*, the leaves and roots of *Morus spp* and also from two marine sponges collected in Western Australia[43-44] (Figure 2). Compound **20** was isolated from the water extracts of the seeds of *balsam pear* and the fruitbodies of *G. frondosa*, both of which were known as health promoting foods and antibiotic activities. Compound **19**, **21**, and **22,** which were isolated from the *Devil tree* (traditional Thai medicinal plant) showed potent α-glucosidase activity.[45] Penarolide sulfates A1 (**23**) and A2 (**24**) were isolated from a marine sponge *Penares Sp*. Penarolide sulfates A1 (**23**) and A2 (**24**) inhibites α-glucosidase with IC_{50} values of 1.2 and 1.5 μg/mL respectively.[46] Another one α-glucosidase inhibitor penasulfate-A (**25**) was also isolated from same sponge.[47] (Figure 3).

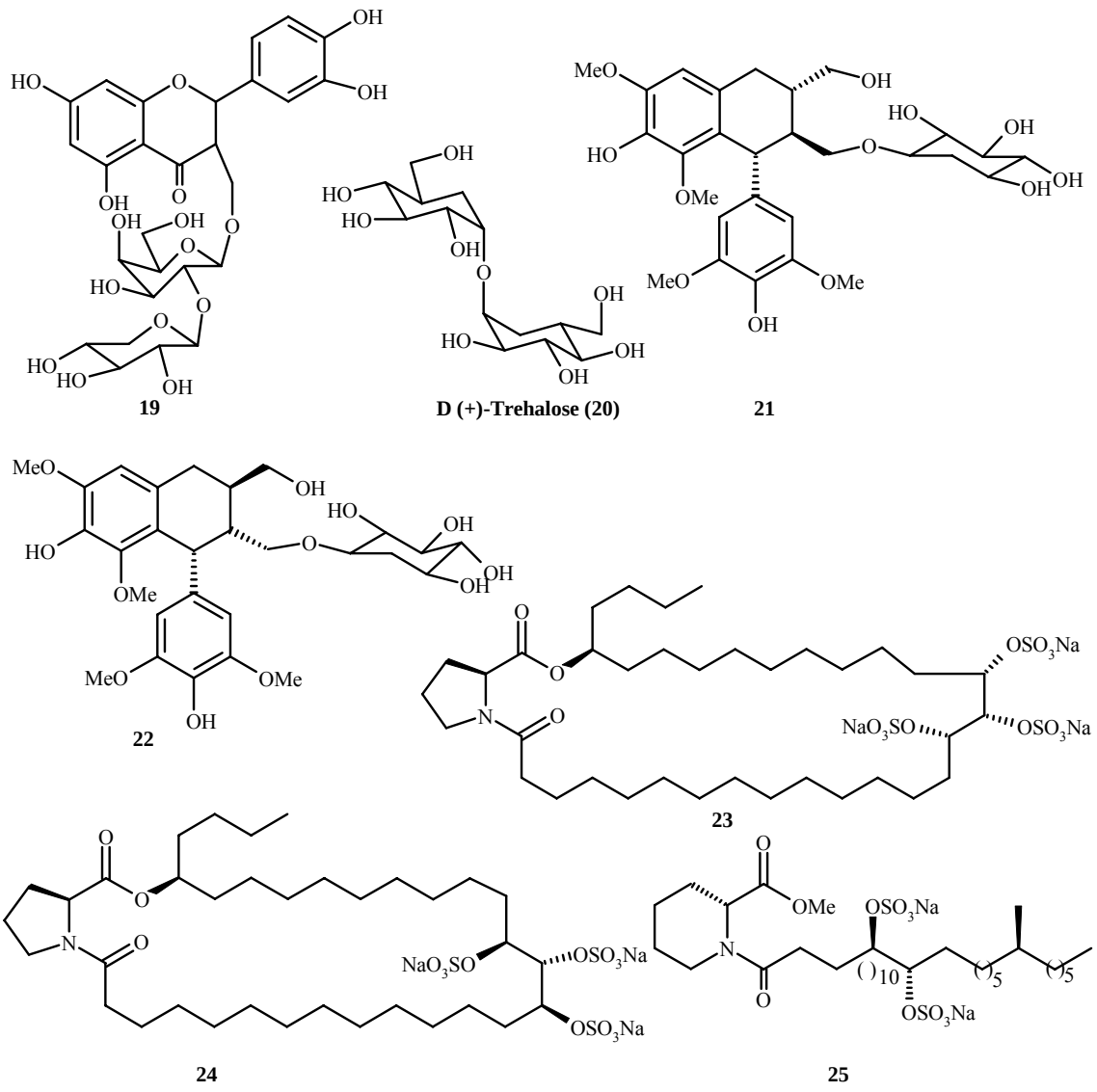
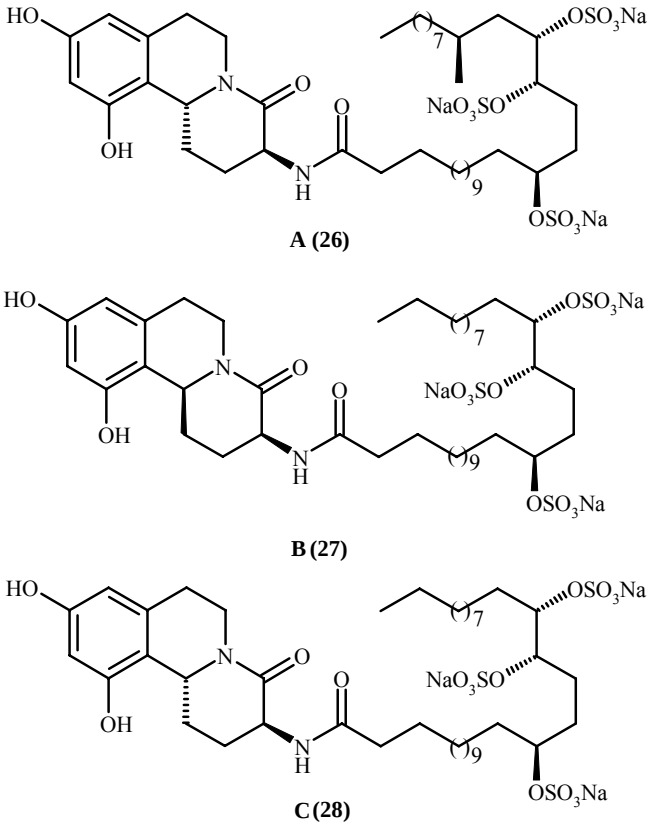


Figure 3. *Some natural structurally interesting α-glucosidase inhibitors.*

Schulzeines A-C (**26-28**) were isolated by Fusetani et al. from the hydrophilic extract of the marine sponge *Penares schulzeines* (Figure 4).[48] The structure of the schulzeines can be divided into two major components, namely, the tricyclic core containing tetrahydroisoquinoline fused with delta-lactam and the C28 fatty acid side chain. The tricyclic core bears two stereogenic centers at C-3 and C-11b. The stereo centers at C-3 is assigned as '*S'* in all members of this family whereas schulzeines A and C have C-11b '*R'* and schulzeines B has C-11b '*S'* configuration. The C28 fatty acid side chain of

schulzeines bear three stereogenic centers at C-14, C-17 and C-18 as sodium sulfate salts with the configuration assigned as *S*, *S*, *S*. Schulzeines A has an extra stereogenic centre at C-20 bearing a methyl substituent.



Schulzeines A-C (26-28)

Figure 4. *Structure of schulzeines A, B and C.*

These are new class of α-glucosidase inhibitors, inhibited α-glucosidase with IC_{50} values of 48-170 nm. Desulfated schulzeines (A and B) still retain activity (IC_{50} values of 2.5 and 1.1 μM respectively). Schulzeines were also having inhibitory activity against viral neuraminidase with IC_{50} values of 60 μM.

Full biological evolutions of such substances are however severely hampered as it is difficult and indeed ecologically undesirable, to harvest large quantities of the marine creatures from which they are isolated, or to grow such animals in the laboratory. Access to substantial quantities of these novel substances must then be by way of chemical synthesis.

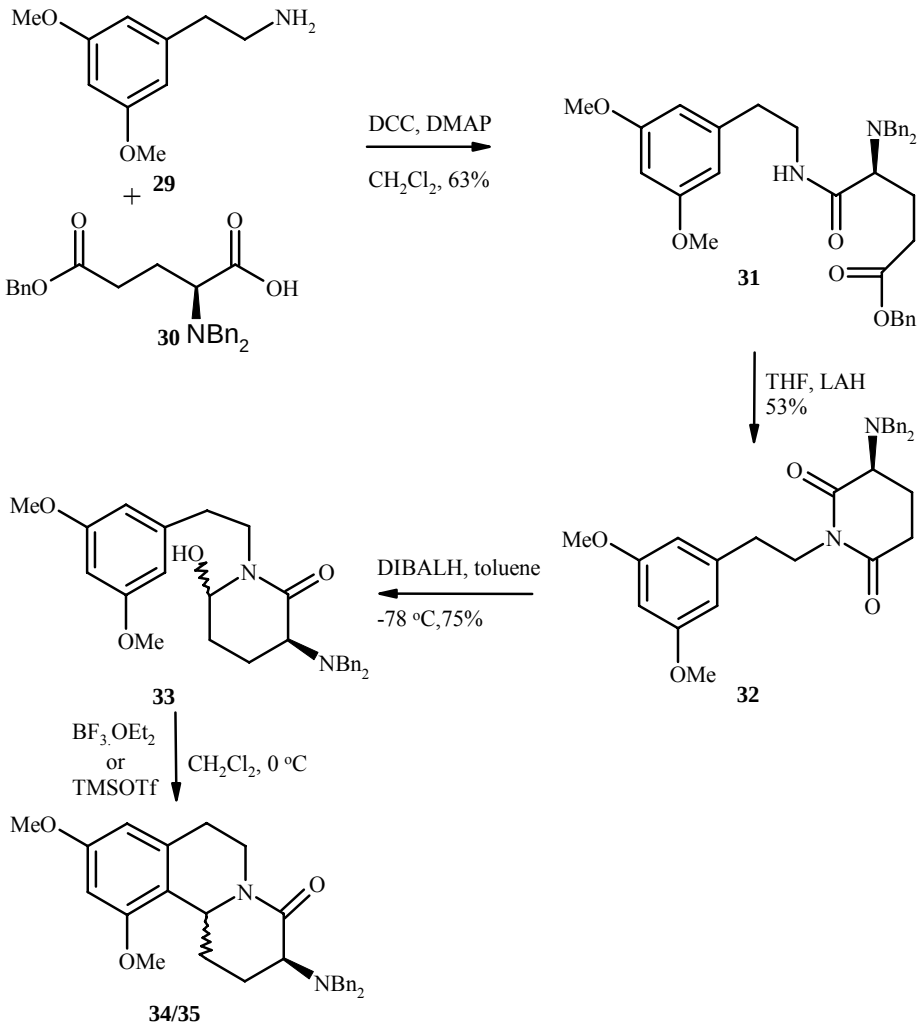
Studies Directed Towards the Syntheses of Tricyclic core of Schulzeines (A-C):

Past Work:

Kuntiyong Approach[49]

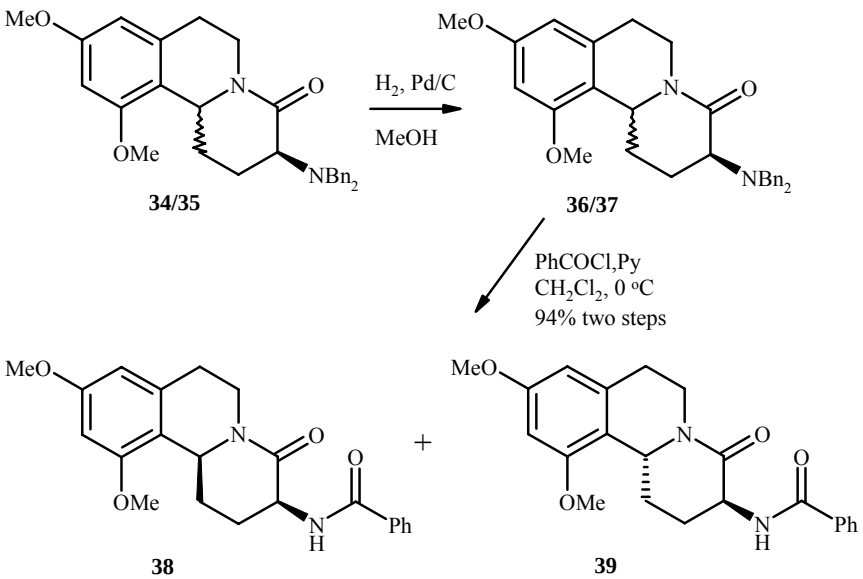
In 2004 Kuntiyong *et al.* reported the syntheses of tricyclic cores (**34** and **35**) of schulzeines using N-acyliminium ion cyclization[50] as key step (Scheme 1). 2-(3,5-Dimethoxyphenyl)ethylamine (**29**) was prepared in a straightforward fashion in 5 steps from 3,5-dihydroxy benzoic acid. Amide formation of this amine with 5-benzyl-N, N-dibenzyl-L-glutamate was afforded amide-ester **30**, which on reduction with lithium aluminium hydride produced gave imide **32** in 53% yield. Treatment of imide **32** with DIBALH in toluene at –78 ^{o}C followed by cyclization with $BF_3.Et_2O$ yielded tricyclic cores **34** and **35** of schulzeines as an inseparable mixture of two diastereomers at the C-11b. The configuration at C-11b of the major diastereomer **34** was assigned as '*S'* according to the NOESY experiment of the product mixture.

Scheme 1



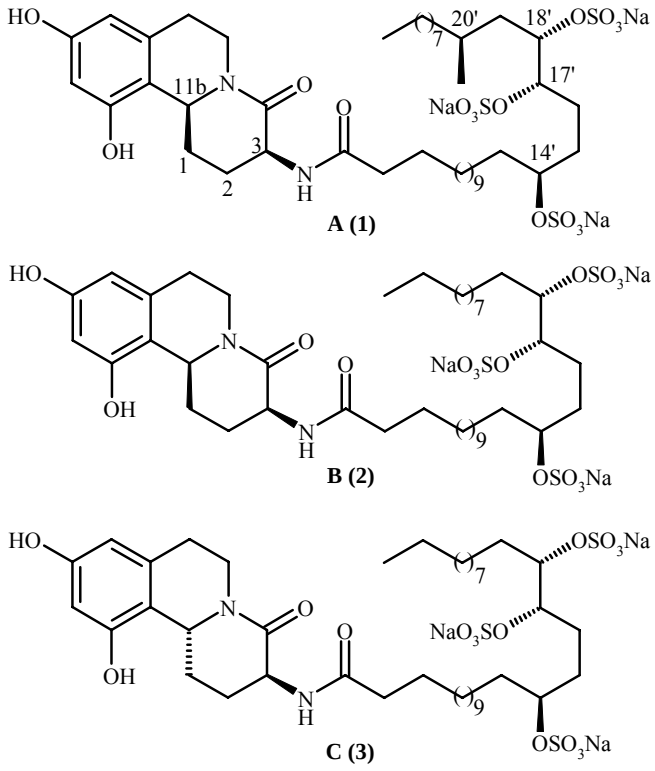
The two diastereomers at C-11b (**34**/**35**) were separated by flash column chromatography after conversion to their corresponding benzamide derivatives **38** and **39** respectively (Scheme 2).

Scheme 2


MeO
OMe
N
O
NBn2
34/35
H2, Pd/C
MeOH
36/37
PhCOCl,Py
CH2Cl2, 0 °C
94% two steps
38
39
Ph
NH

PRESENT WORK

Schulzeines A-C (**1-3**) were isolated by Fusetani et al. in 2004 from the hydrophilic extract of the marine sponge *Penares schulzeines* (Figure 1).[48] These are a new class of α-glucosidase inhibitors with IC_{50} value of 48-170 nM and also inhibitory against viral neuraminidase with IC_{50} values of 60 μM.



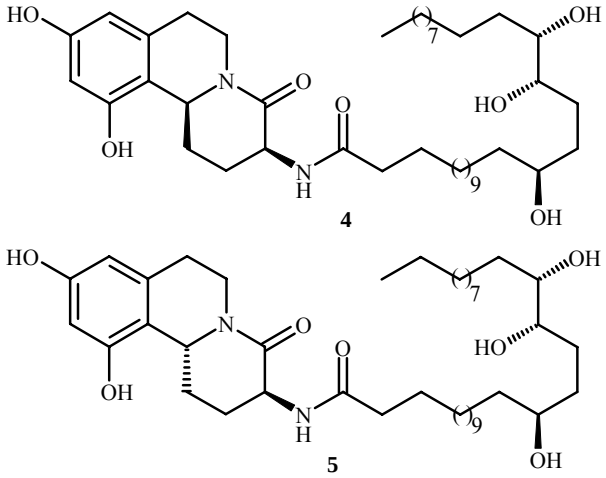
Schulzeines A-C (1-3)

Figure-1. *Structure of Schulzeines A, B, and C.*

The tricyclic core of schulzeines bears two stereogenic centers at C-3 and C-11b. The stereocenter at C-3 is assigned as '*S*' in all members of this family, but the C-11b stereocenter is '*R*' in case of schulzeines A (**1**) and C (**3**) whereas it is '*S*' in case if schulzeines B (**2**). The adjacent C28 fatty acid side chain of schulzeines bears three stereogenic centers at C-14, C-17 and C-18 as sodium sulfate salts each assigned as 'S'

configuration. Schulzeine A (**1**) on the other hand has an extra stereogenic centre at C-20 bearing a methyl substituent with '*S*' configuration.

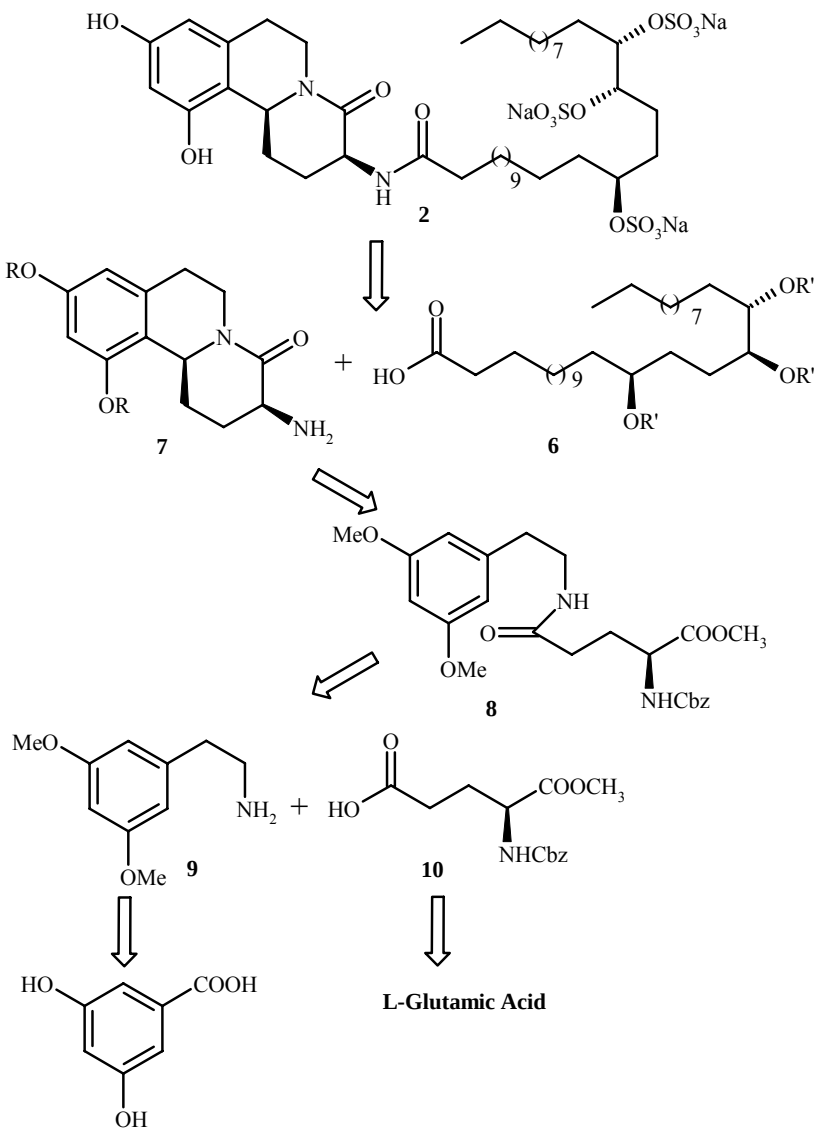
Their remarkable biological profiles and novel architecture have established the schulzeines as significant targets for total synthesis. We initially focused our endeavor towards the total syntheses of schulzeines B (**2**) and C (**3**). In keeping our goal to achieve their total syntheses, we viewed our initial target for the desulfated schulzeines since they still retain their activity.



desulfated Schulzeines B (4) and C (5)

Figure 2

Retrosynthetically, schulzeines could be divided into two parts (Scheme 1), one tricyclic core i.e. the tetrahydroisoquinoline part **7** and adjacent C28 fatty acid side chain **6** connected by an amide bond. Our synthetic strategy for the construction of the tricyclic core was aimed at $POCl_3$ mediated Bischler-Napieralski cyclization/reduction[51] sequence of the amide **8** as key step. The amide **8** could be obtained from the condensation of 3,5-dimethoxyphenethyl amine (**9**) with glutamic acid derivative **10**. Due to high cost of the commercially available amine **9**, we planned for its synthesis from inexpensive easily available 3,5-dihydroxy benzoic acid as starting material utilizing a known literature procedure.[52] The retrosynthetic plan is illustrated in Scheme 1.

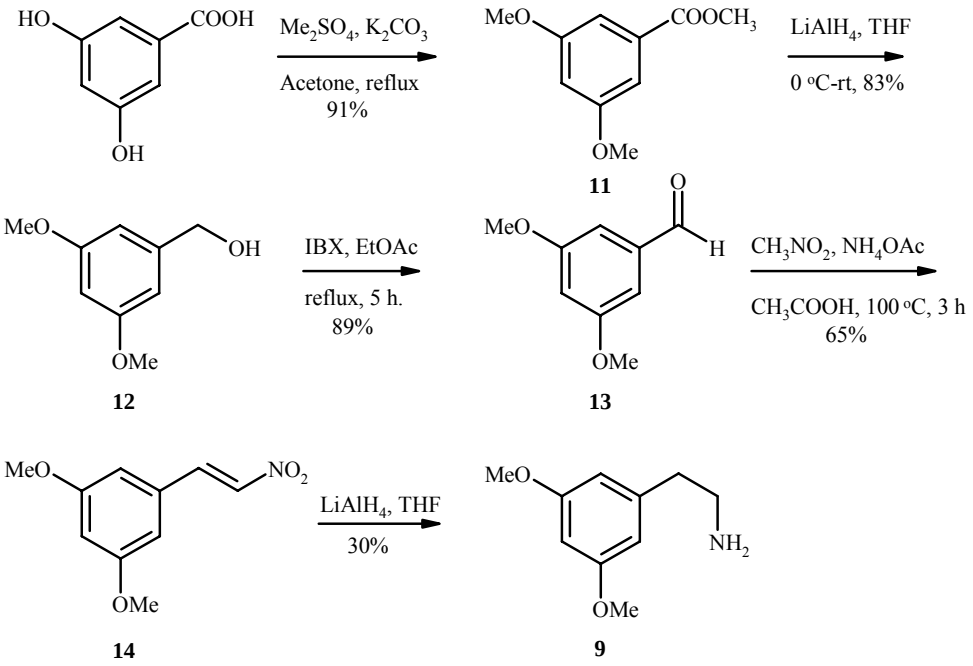


Scheme 1: *Retrosynthetic strategy for the construction of tricyclic core of schulzeines.*

Accordingly, the journey began with the synthesis of 3,5 dimethoxyphenethyl amine (**9**). 3,5-Dihydroxy benzoic acid was first subjected to excessive methylation using dimethylsulfate and potassium carbonate in acetone under reflux condition to afford the methyl ester derivative **11** in 91% yield. Reduction of the methyl ester with $LiAlH_4$ in THF and subsequent IBX oxidation of the benzyl alcohol **12** produced aldehyde **13**, which was then subjected to nitro aldol condensation with nitromethane under reflux condition

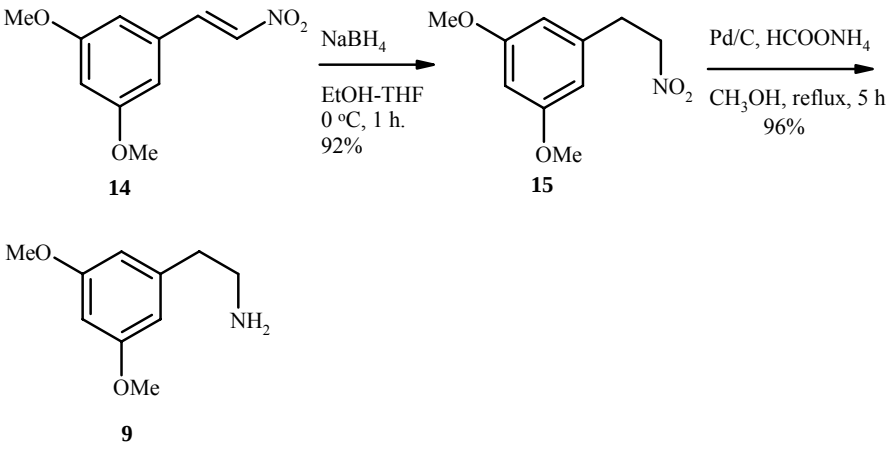
followed by in situ elimination of a molecule of water afforded nitro styrene derivative **14**.[53] In the ^{1}H NMR spectrum of **14**, the olefinic protons appeared at δ 7.9 and 7.6 ppm with coupling constant J = 13.7 Hz., confirmed the formation of *trans* nitro styrene derivative. Further its olefinic carbons appeared at δ 139 and 136 ppm in ^{13}C NMR spectrum (Scheme 2).

Scheme 2



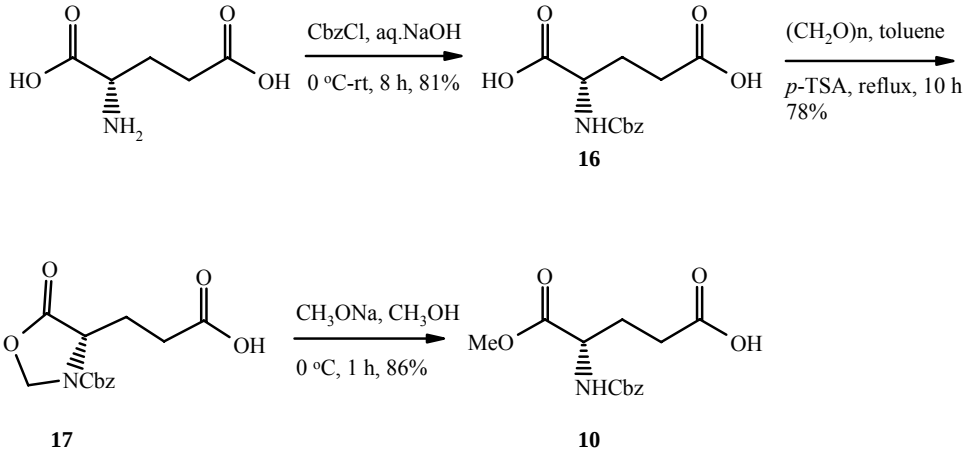
On reduction with $LiAlH_4$, the nitro styrene derivative **14** gave rise to amine **9**. But one important drawback of this method was low yield. To improve the yield we followed the two step reduction sequence. In the first step we reduced the *α-β*-unsaturated double bond using $NaBH_4$ to the corresponding nitro derivative **15**, which in subsequent step was treated with Pd/C and $HCOONH_4$ in CH_3OH to obtain the amine compound **9** in 88% yield over two step (Scheme 3).

Scheme 3



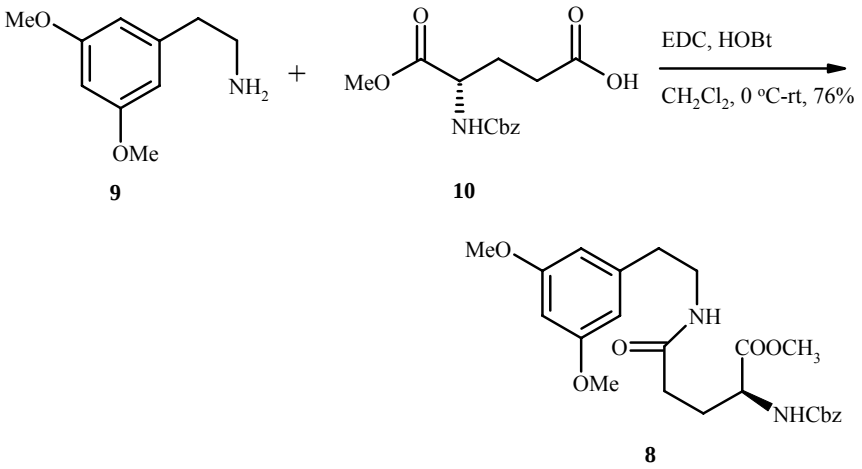
Following a known protocol,[54] L-Glutamic acid was converted to acid derivative **10** (Scheme 4). Accordingly, L-Glutamic acid was treated with CbzCl in presence of aqueous NaOH afforded compound **16** in 81% yield. Reaction of **16** with para formaldehyde and *p*-TSA in toluene reflux furnished compound **17**. In a subsequent step, on opening the ring with sodium methoxide at 0 ^{o}C in methanol, we obtained the required acid derivative **10**. The ^{1}H, ^{13}C NMR, and specific rotation were identical with the reported data. With gram quantities of both the amine **9** and acid **10** in hand our next step was to perform the coupling reaction.

Scheme 4



The coupling between the acid **10** with amine **9** was conducted in the presence of DCC/ HOBt in CH_2Cl_2 to afford the amide **8** in 60% yield (Scheme 5). The yield was improved to 76% when EDC was used in place of DCC as coupling reagent. The structure of amide **8** was thoroughly investigated with the help of ^1H, ^{13}C NMR, IR, mass spectra and elemental analysis. For instance, in the ^1H NMR spectrum, the signals located at δ 6.31 (multiplet) ppm indicating three aromatic protons appeared as multiplet, at δ 4.25 (multiplet) ppm due to proton α to amino group, a multiplet at δ 7.31 ppm integrating five for aromatic protons of the benzyloxycarbonyl group and two singlets at δ 3.74 and 3.71 ppm due to two methoxy and methyl ester groups respectively. All other peaks were in complete agreement with the assigned structure.

Scheme 5

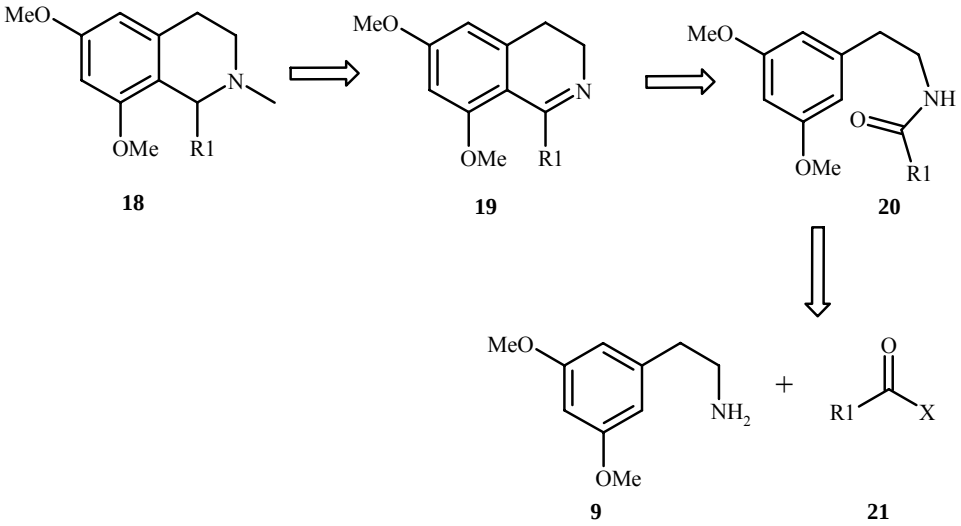


Next step of our synthesis involved the cyclization of amide **8** to isoquinoline derivative.

A brief review on tetrahydroisoquinoline synthesis by Bischler-Napieralski Cyclization/reduction:

*In the past decade the sequential Bischler-Napieralski cyclization/reduction has been explored and it became a well known approach for the asymmetric synthesis of the tetrahydroisoquinoline alkloids. In this synthesis, β-arylethylamide (**20**) is cyclized to 1-substituted 3,4-dihydroisoquinoline (**19**) or corresponding isoquinolinium salt, which is then reduced in the next step to the 1,2,3,4-tetrahydro derivative (**18**) (Scheme 6).*

Scheme 6



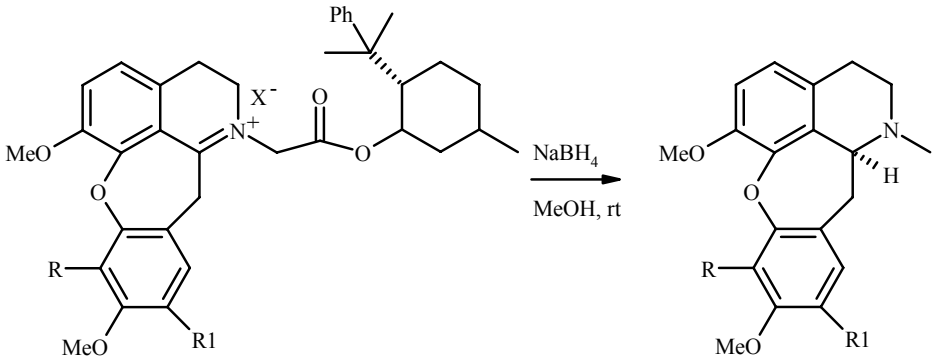
The reduction process is crucial for the stereochemical outcome of the synthesis because it creates a stereogenic centre. This step can be realized either by diastereoselective or enantioselective synthesis.

a) Diastereoselective approach:

In this approach a chiral auxiliary was attached with the 3,4-dihydroisoquinolines or corresponding 3,4-dihydroisoquinolinium salts and then the salt was subjected to either hydride reduction or catalytic hydrogenation.

i) Rodrigues et al.[55] used (+)-phenylmenthyl chloroacetate as chiral auxiliary for their synthesis of isoquinoline alkaloids. In their case, (S)-isomer was obtained selectively from the $NaBH_4$ reduction of the energetically favored conformer of the corresponding imine, which was further supported by molecular modeling (Scheme 7).

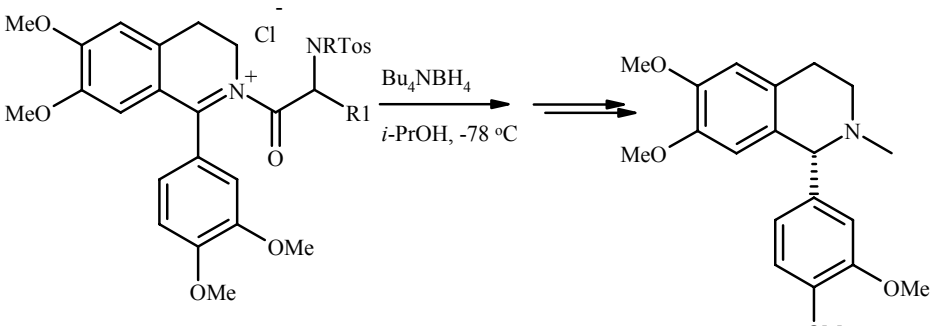
Scheme 7



	R	R1
22	H	OMe
23	H	OH
24	OH	H
25	OMe	H

*ii) Czarnocki' group[56] in their synthesis of N-methy-Cruptostyline II (**27**) and its enantiomer used chiral N-acyliminium salt model; type (**26a** and **26b**). The salt was generated in situ from dihydroisoquinoline and several acid chlorides; most of them were derived from N-protected amino acids of D-phenylalanine, D- and L-alanine, and L-proline. The reduction was carried out with tetrabutylammoniumborohydride as reducing agent in which the configuration of the product was determined by the configuration of the auxiliary amino acid. The D-amino acid gave 'S' isomer selectively where as 'R' isomer for L-amino acid (Scheme 8).*

Scheme 8

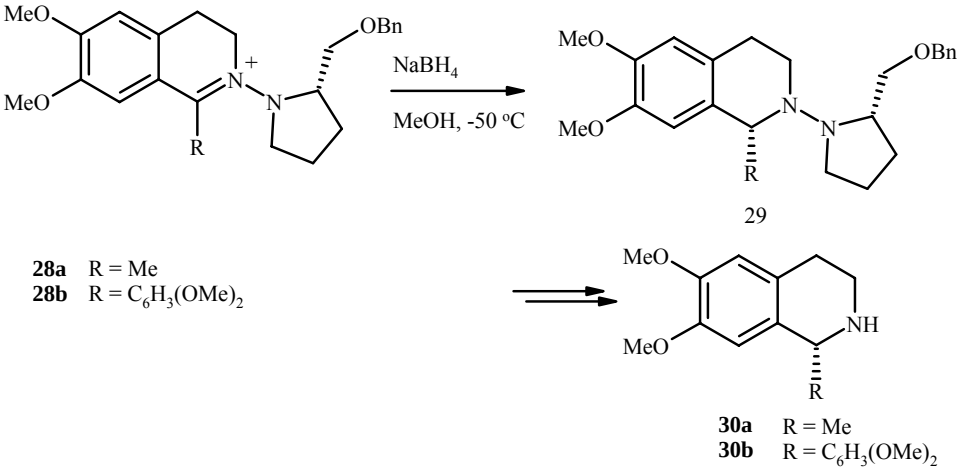


26a R = H, R1 = Me
26b R + R1 = $(CH_2)_3$

27

*iii) Kibayashi et al[57] incorporated a chiral hydrazonium functionality as chiral auxiliary, in their synthesis of salsolidine (**30a**) and cryptostyline II (**30b**) (Scheme 9). The effectiveness of the asymmetric induction was postulated to arise from the pyramidal stability of the pyrrolidine sp^3-hybridized nitrogen atom and the hydride-ion approached to the imine double bond from sterically less shielded site. The energetically favored conformer **31** (Figure 3) was postulated to explain the preferential formation of major isomer.*

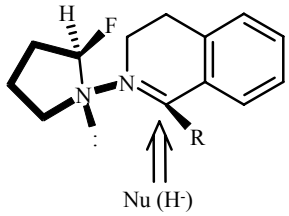
Scheme 9



28a R = Me
28b R = $C_6H_3(OMe)_2$

29

30a R = Me
30b R = $C_6H_3(OMe)_2$

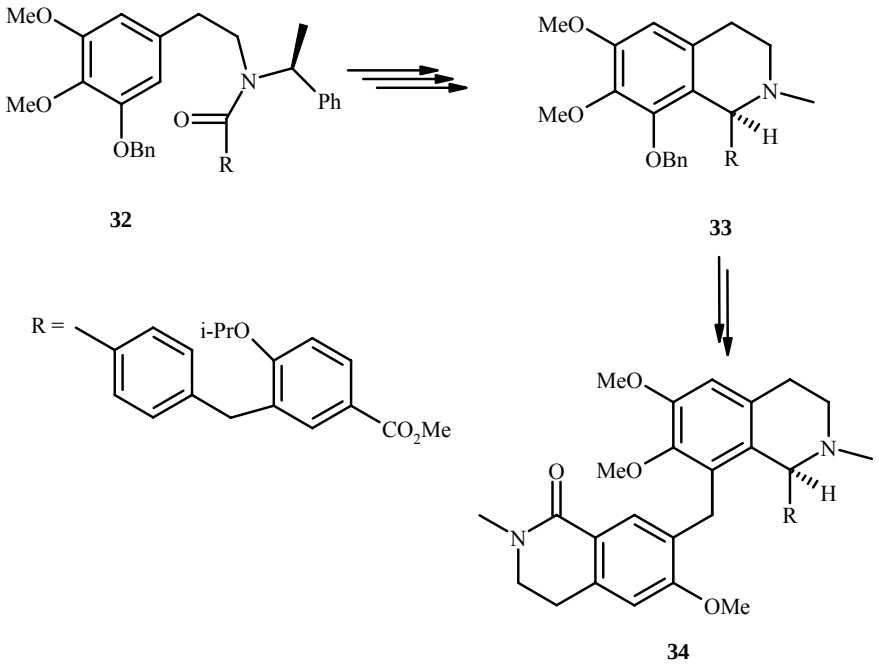


31

Figure 3

*iv) In the multistep synthesis of (–)-tejedine (**34**), Wang et al,[58] showed that (S)-α-methylnenbenzylamine was a very efficient chiral auxiliary (Scheme 10).*

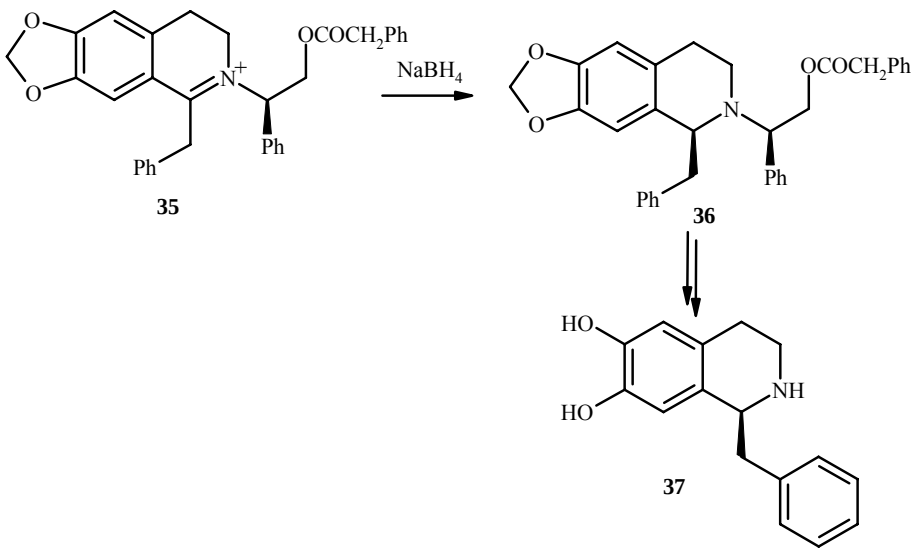
Scheme 10



32 **33** **34**

*v) Cabedo et al.[59] used (R)-phenylglycinol as chiral auxiliary for their synthesis of (S,R)-1-Benzyltetrahydroisoquinoline (**37**) with good diastereoselectivity (Scheme 11).*

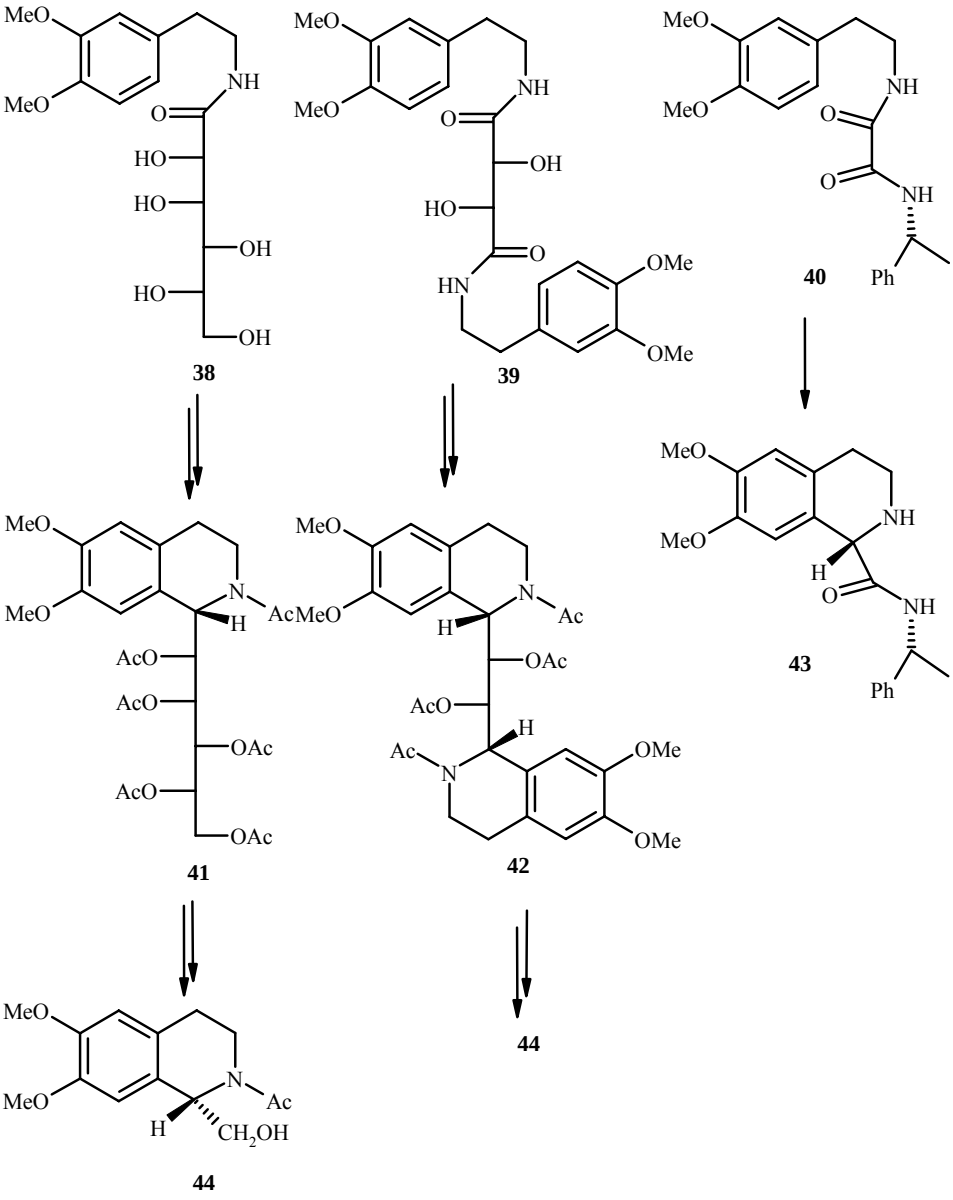
Scheme 11



35 **36** **37**

*vi) Czarnocki et al.[60-62] reported the synthesis of isoquinoline alkaloids according to the Bischler-Napieralski cyclization/reduction method of amides in which the chiral auxiliary was present as a part of the acid component. In this case amides (**38**–**40**) were prepared from β-(6,7-dimethoxyphenyl)ethylamine and L-(+)-ascorbic acid, L-(+)-tartaric acid and (S)-phenyl ethyl amide of oxalic acid chloride respectively. Following the standard procedures of cyclization (PCl_5/CH_2Cl_2/0 ^oC) the intermediate 3,4-dihydroisoquinolines were produced, which were subsequently reduced to the corresponding tetra hydro products (**41**–**43**). Compound **41** and **42** could be isolated after N,O-acylation (Scheme 12). The best selectivity was observed during the reduction leading the compound **42**, which was obtained as single diastereomer. The synthesis of **41** (via N-oxide) was characterized by lower selectivity, **43** and ent–**43**, could be obtained by choosing the appropriate reducing agent, either hydride reduction ($NaBH_4$/EtOH/–78 ^oC) or catalytic hydrogenation ($H_2/RhCl(PPh_3)$/100 atm/rt), respectively.*

Scheme 12

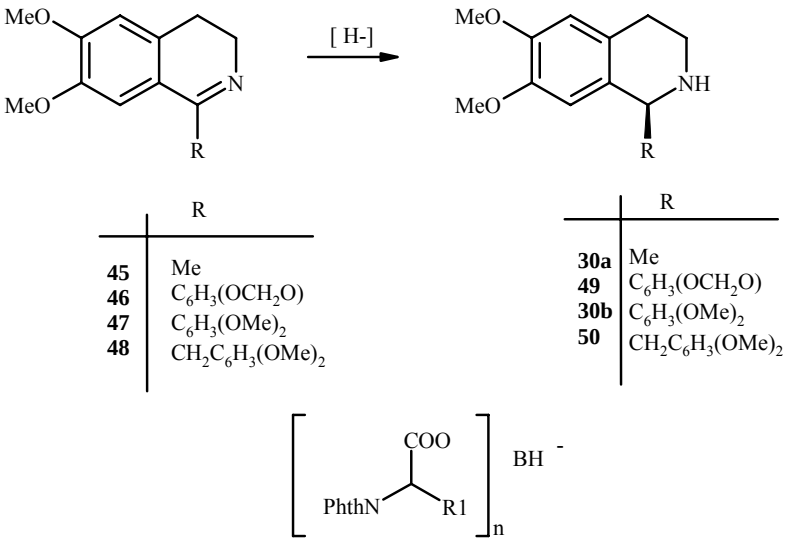


b) Enantioselective approach:

Enantioselective synthesis of isoquinoline alkaloids through Bischler-Napieralski cyclization/reduction approach is based on a reduction of prochiral 3,4-dihydroisoquinolines. For this purpose chiral hydride reducing agents are used or hydrogenation is carried out in the presence of chiral catalysts.

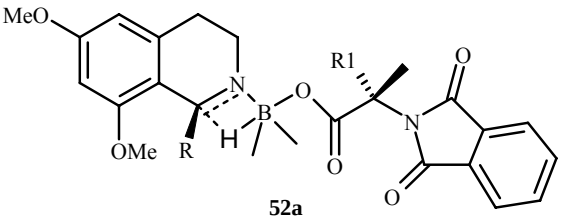
i) Hajipour and Hantehzadeh et al.[63] *used sodium triacyloxy borohydrides (**51**), which were prepared from $NaBH_4$ and N, N-phthaloyl-protected (Phth) amino acids, e.g. (S)-leucine, (S)-alanine, and (S)-phenylalanine, in the syntheses of (S)-salsolidine (ent-**10** **30a**), (S)-norcryptostyline I (**49**), (S)-norcryptostyline II (**30b**) and (S)- norlaudanosine (**50**) from corresponding imines (**45**), (**46**), (**47**), and (**48**) respectively with good yield and good ee (Scheme 12).*

Scheme 13

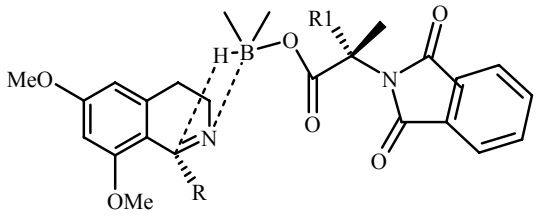


51

*It was observed that the enantioselectivity (65-75% ee) attained in reactions with (S)-leucine-derived **51,** increased when the reduction was performed in the presence of $ZnCl_2$ (72-80% ee) or carried out under solid-state conditions (83-100% ee). The (S)-selectivity was postulated to arise from a transition state (**52a**) favoring a re-face attack of hydride ion rather than from (**52b**) (Figure 4).*



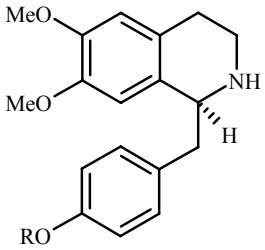
52a



52b

Figure 4

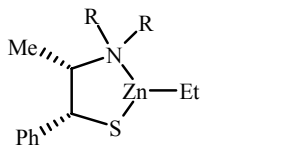
*In the synthesis of (R)-(+)- norroefractin (**53**, R = Me)[64] and (–)-norarmepavine (**54**, R = H),[65] (Figure 5) sodium borohydride modified with (S)–N-Cbz-proline was used successfully as reducing agent.*



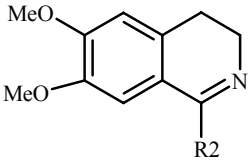
53 R= Me
54 R= H

Figure 5

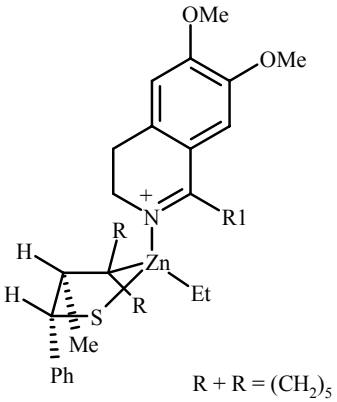
*ii) Kang et al.[66] used BH_3.THF for the reduction of imines (**45**, **47** and **48**), in their syntheses of tetrahydroisoquinoline alkaloids such as (R)-sasolidine, (R)-norcryptostyline II and (R)-norcryptostyline. The reaction was carried out in the presence of a catalytic amount of a complex of organozinc reagents with chiral aminothiols. Among the catalysts investigated, thiazazincolidine complex **55** (R+R = $(CH_2)_5$) (Figure 6) was shown to be the most effective one.*



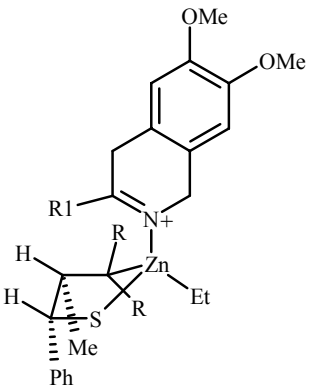
55



45 R2 = Me
47 R2 = $C_6H_3(OCH_3)_2$
48 R2 = $CH_2C_6H_3(OMe)_2$



56a

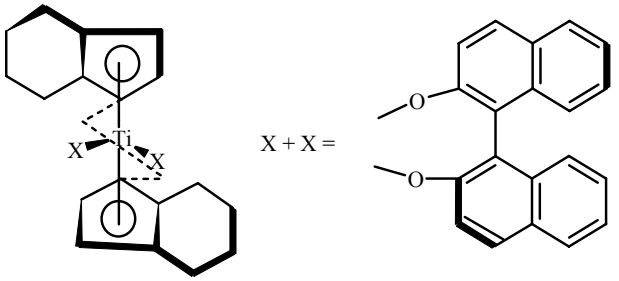


56b

Figure 6

The preference of formation of (1R) isomers in all the synthesized alkaloids was explained by assuming that of the two working models, ***56a*** *and* ***56b*** *(Figure 6), the former was less favorable because of the steric interaction between the R1-substituent and the ethyl group on the zinc atom as well as electronic effects caused by the syn-relationship between the C=N double bond and the Zn-C bond.*

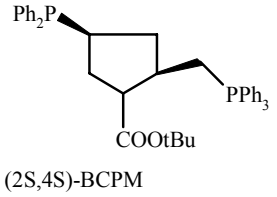
iii) Buchwald and Willoughby et al.[67] *used titanocene catalyst* ***57*** *(Figure 7) to control the stereochemistry of hydrogenation of cyclic imines, allowed the synthesis of tetrahydroisoquinolines with excellent levels of enantiomeric excess (95-99%).*



57

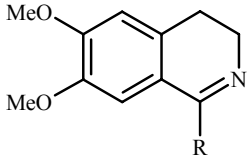
Figure 7

iv) Achiwa, Morimoto et al.[68] carried out extensive studies on catalytic asymmetric hydrogenation of various 3,4-dihydroisoquinolines of the type ***59*** *using various biphosphine-transition-metal complexes. They found iridium(I) complexes with (R)- and (S)-BINAP and (2S,4S)-BCPM (****58****) to be the most effective catalytic system, particularly when used in the presence of cyclic imides as cocatalyst.*



(2S,4S)-BCPM

58

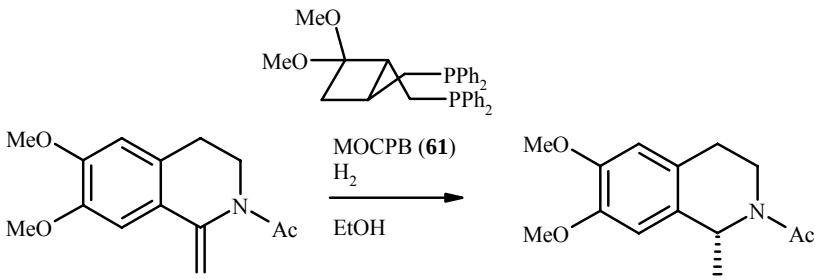


59

Figure 8

They also used the rhodium(I) complex with a biphosphine legend ***61*** *(MOCBP) of cyclobutane framework for the synthesis of (R)-(–)-N-acetylsalsolidine (****62****) in quantitative yield with 80.6% ee by hydrogenation of enamide* ***60*** *(Scheme 14).[28]*

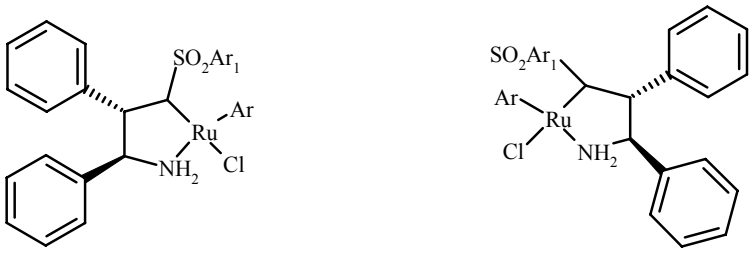
Scheme 14



60 **62**

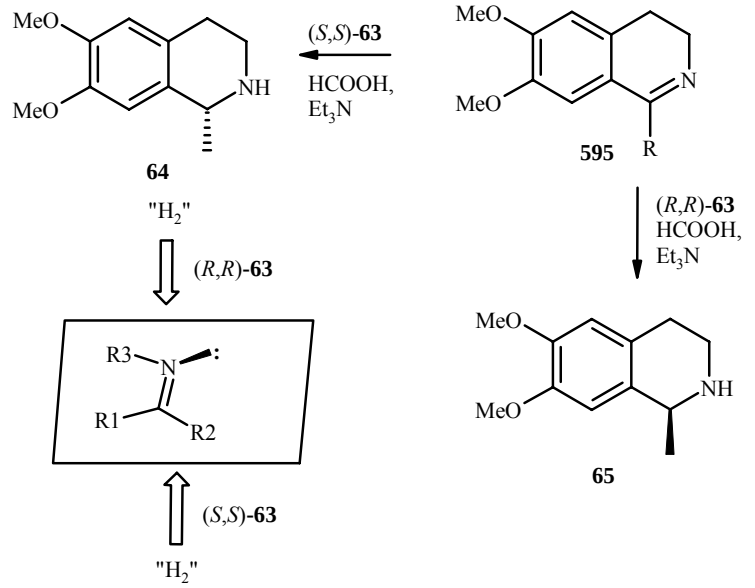
*v) Noyori et al.[69] designed chiral N-sulfonated diamine-Ru(II)-η^6arene complexes of type (**63**) (Scheme 15) as catalyst, attainable in both enantiomeric forms for the asymmetric transfer hydrogenation of imines with formic acid/triethylamine.*

Scheme 15



(*S*,*S*)-63 **(*R*,*R*)-63**

Ar = *p*-cymene, benzene, cyclopentadiene
Ar_1 = 4-MeC_6H_4, 2,4,6-$Me_3C_6H_2$, 1-naphtyl

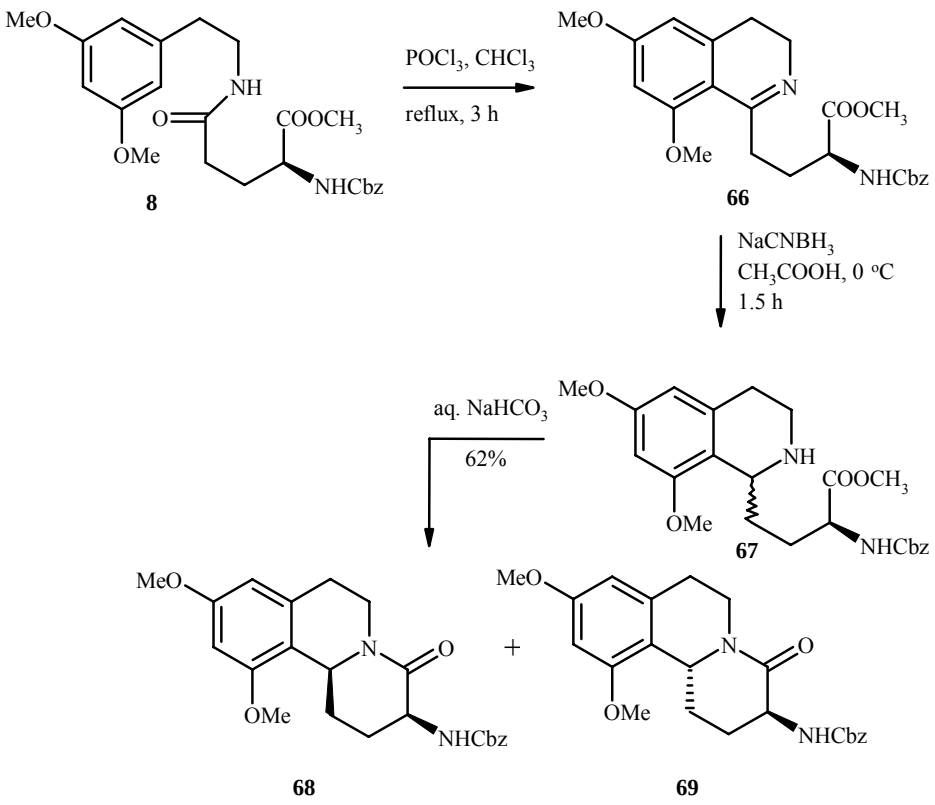


*Among the amines synthesized by Noyori's group, several isoquinoline alkaloids have been prepared in high yield with ee values ranging from 90% to 97%. It has been shown that the stereochemistry of the resulting amine depends on the stereochemistry of the catalyst employed. As such, products with (1R) configuration were obtained when the (S,S)-**63** were used, whereas the (1S) isomers were obtained when the (R,R)-**63** were applied, as illustrated in Scheme 12. The same catalytic system has been successfully*

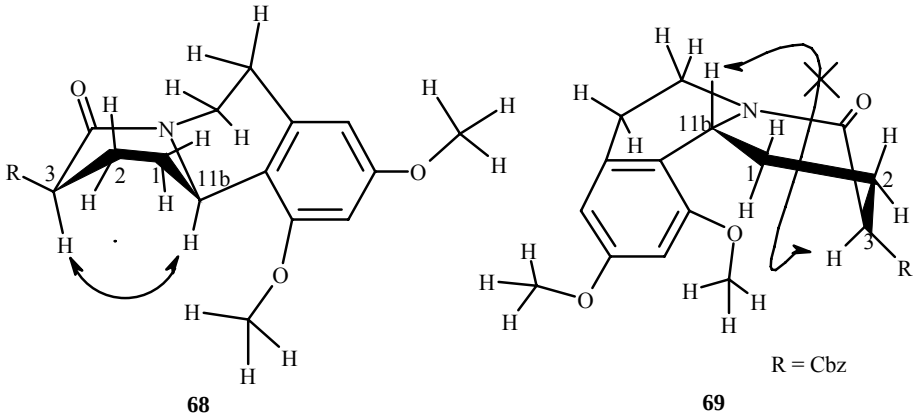
applied by many other research groups, affording tetrahydroisoquinolines in high yield and with a high level of enantioselectivity.

In our strategy, we used Bischler-Napearalski cyclization/reduction sequence for the construction of the tetrahydroisoquinoline moiety. Accordingly, the amide **8** was treated with $POCl_3$ and $CHCl_3$ (1:3) under reflux for 3 h (Scheme 15). The imine **66** thus formed, after workup was subjected to $NaCNBH_3$ reduction[70] in acidic medium to afford the amine **67** as its acetate salt. On basification with aq. sat $NaHCO_3$ solution, the free amine underwent in situ cyclization resulting the formation of **68** and **69** with 2:3 ratio (Scheme 16). The compounds **68** and **69** were separated by simple silica gel column chromatography and were characterized with the help of ^1H and ^{13}C NMR, mass spectra, IR and elemental analysis. For instance, in the ^1H NMR spectrum of **68**, the protons at 11b position, was located at δ 4.77 ppm and at δ 6.28 and 6.21 ppm for the two aromatic protons and rest of the signals were also in complete agreement with the assigned structure. Disappearance of the singlet for the methyl ester also supported the formation tricyclic-core. In case of isomer **69**, the signals for H-11b was appeared at δ 4.65 ppm. As both the isomers **68** and **69** could be used for the syntheses of schulzeines B (**2**) and C (**3**) respectively, we did not search for the stereoselective imine reduction.

Scheme 16



The stereochemistry of the newly formed chiral centre was determined using 2D NMR studies. In case of compound **68,** H-11b showed strong NOESY correlation with H-3 and demonstrating their cis geometry. As H-3 was α so H-11b must be α. That means C-11b in **68** was having '*S'* configuration. But in case of (**69**), H-11b and H-3 protons showed no such NOESY correlation. They must be in different face; resulting C-11b in **68** was having '*R'* configuration (Figure 9).

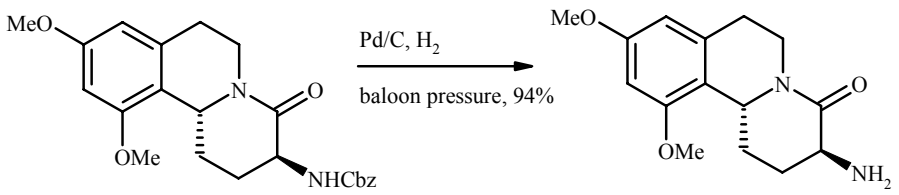


68 **69**

Figure 9

The benzyloxycarbonyl group of **68** was easily removed using Pd/C under hydrogen atmosphere to furnish the free amine **70** with good yield (Scheme 17).[71]

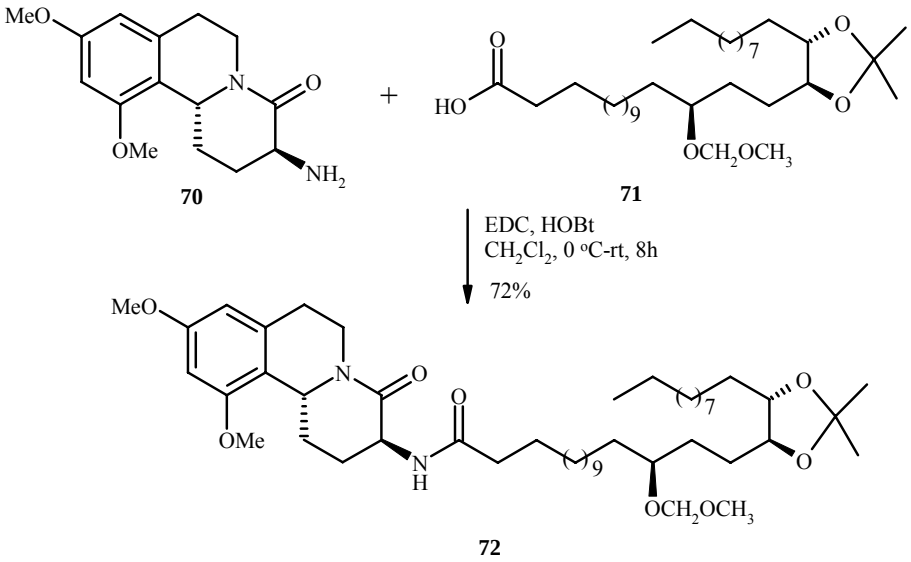
Scheme 17



68 **70**

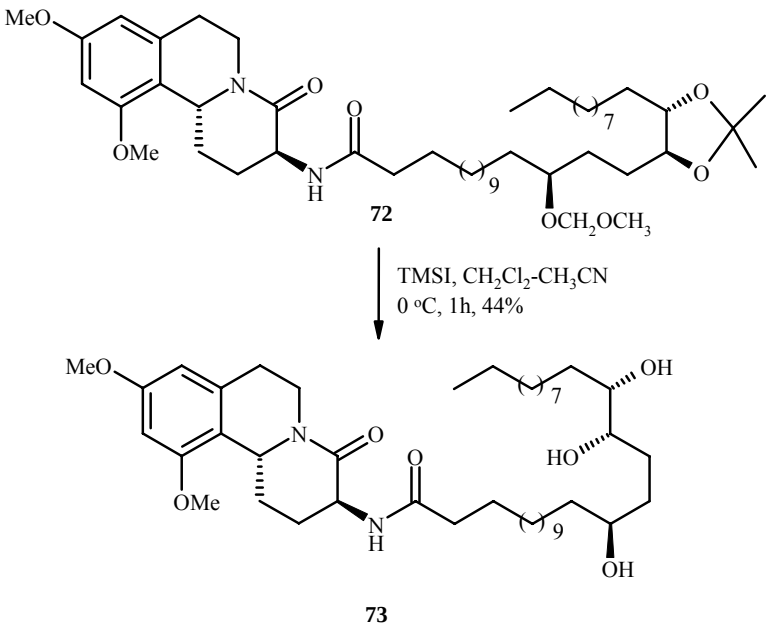
Having both the C28 fatty acid part **71** and tricyclic tetrahydroisoquinoline part **70** in hand, our next concern was to assemble them to obtain the main skeleton of schulzeine. Condensation of the amine **70** with the suitable protected C28 fatty acid derivative **71** using EDC as coupling reagent in the presence of HOBt in CH_2Cl_2 secured the amide **72** in 72% yield (Scheme 18).

Scheme 18



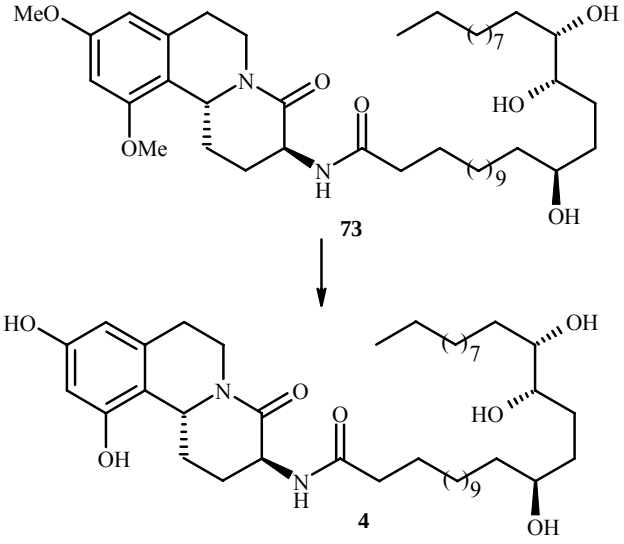
The product **72** was thoroughly investigated with the help of the ^{1}H, ^{13}C NMR, IR, HPLC, mass spectra and elemental analysis. Our earnest attempt was to deprotect the entire protecting group to afford the desulfated schulzeine. Both the acetonide and MOM ether protecting groups in **72** were acid labile, but direct deprotection under acidic condition was unsuccessful due to competitive decomposition. Under various conditions reported in the literature,[72] we could not achieve the MOM-deprortection but in all the cases ended up with a complex mixture of products. Gratifyingly, when the amide **72** was treated with freshly prepared TMSI in a 1:3 mixture CH_3CN-CH_2Cl_2 solution at 0 ^{o}C, both the acetonide and MOM ether were cleaved resulting the formation of the triol **73** (Scheme 19) with 44% yield.[73] In ^{1}H NMR spectrum signals due to acetonide and MOM ether were disappeared. All other peaks were in complete agreement with the assigned structure. Further the structure of **73** was completely secured on the basis of ^{13}C NMR, IR, mass spectra and elemental analysis.

Scheme 19



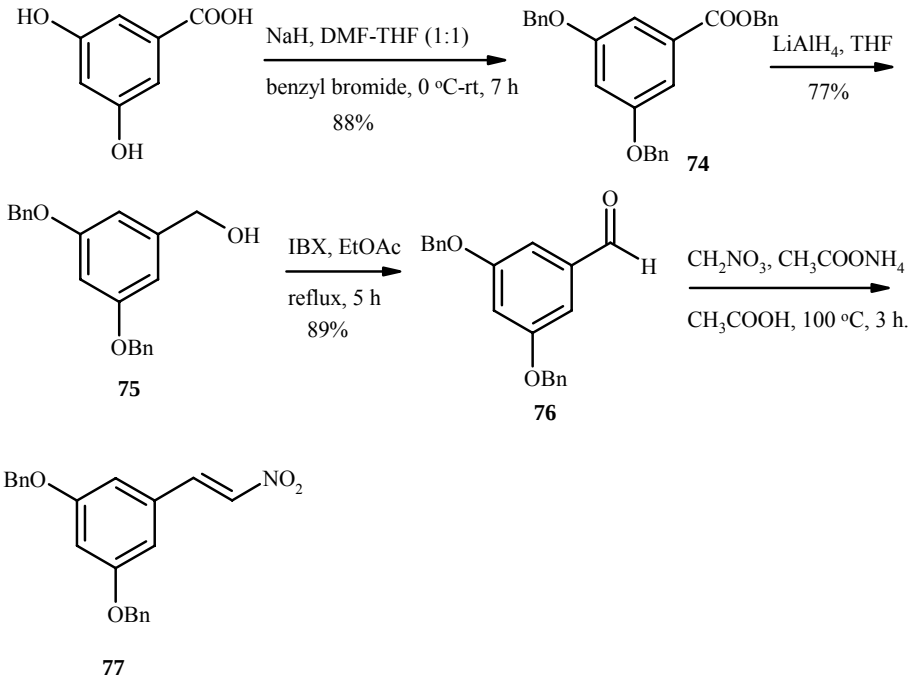
After establishing the full skeleton of schulzeine B, we set out to cleave the methyl ether in triol **73**. Although several methods for the deprotection of methyl ether are available in literature (i.e. $AlCl_3$, CH_2Cl_2 25 °C;[74] $AlCl_3$, CH_2Cl_2 reflux condition;[75] BBr_3, CH_2Cl_2, –78 °C[76]) but unfortunately none of these were successful in our case.

Scheme 20



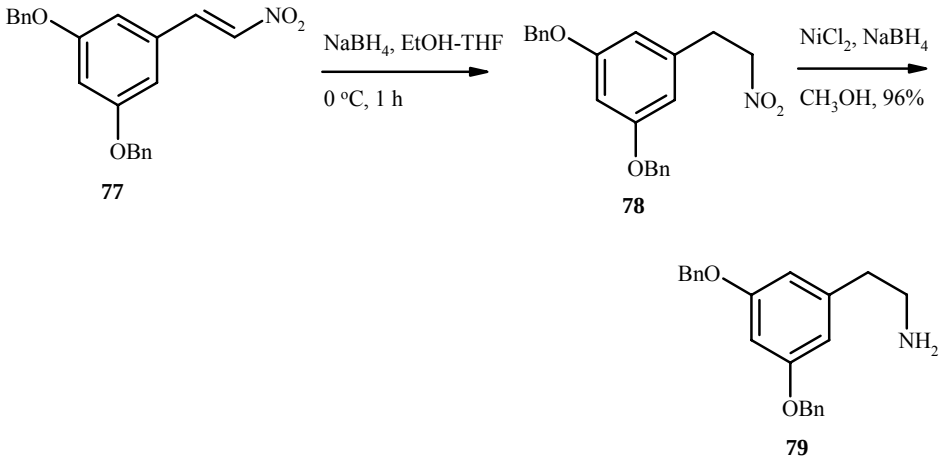
These unpleasant results prompted us to substitute the methyl-protecting group of starting by benzyl group at the early stage of our synthetic route. Accordingly, the starting material 3,5-dihydrohydroxy benzoic acid was converted to amine **79** following the same reaction sequence as in case of **9**.[77] First 3,5-dihydroxy benzoic acid treated with benzyl bromide, sodium hydride in a mixture of DMF-THF (1:1) solvent at room temperature to afford ester **74**. Benzyl ester **74** was then reduced with lithium aluminum hydride in THF to furnish the alcohol **75**, which on subsequent oxidation with IBX afforded aldehyde **76** with 89% yield. Following the same reaction condition as in case of **14**, aldehyde **76** on nitro aldol condensation with nitromethane furnished nitro styrene derivative **77** and without any further purification, this product was used in the next reaction (Scheme 21).

Scheme 21



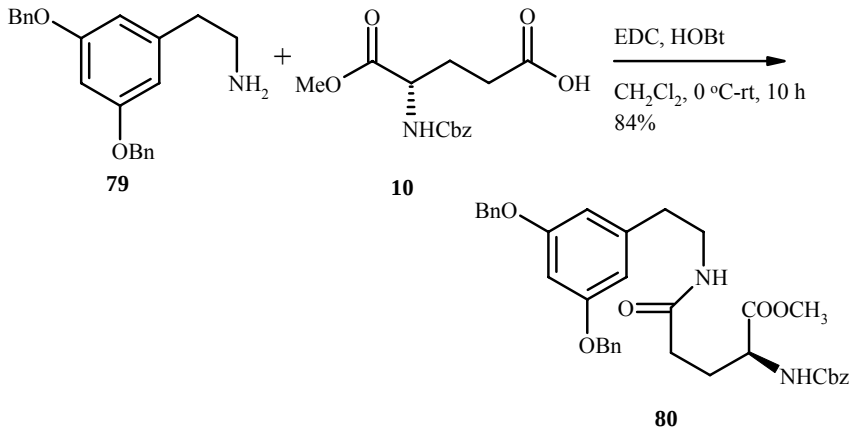
Compound **77** on $NaBH_4$ reduction in THF-EtOH yielded nitro compound **78** in 62.5% yield in two step. Next, the reduction of nitro to amine **79** was carried with $NaBH_4$ and $NiCl_2$ as catalyst (Scheme 22).[78] The amine **79** was characterized with the ^1H and ^{13}C NMR spectral analysis.

Scheme 22



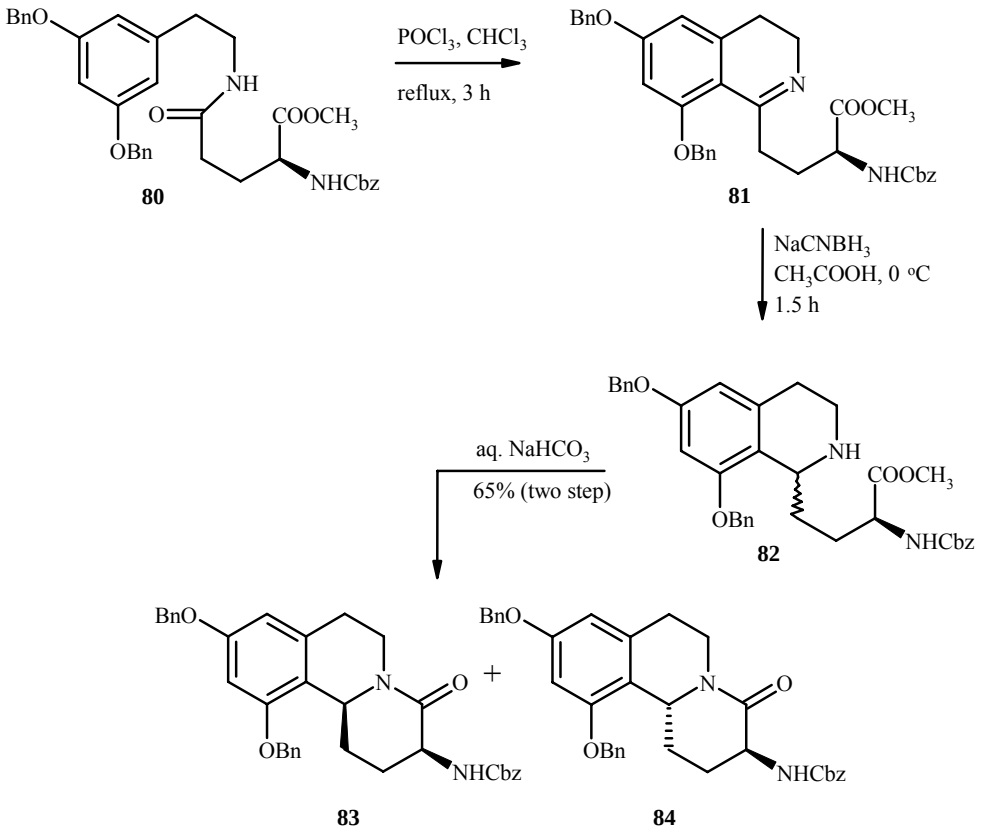
Coupling of amine **79** with glutamic acid derivative **10** using EDC/HOBt, produced amide **80** with 84% yield (Scheme 23). Its ^1H NMR, ^{13}C NMR, mass spectroscopy and elemental analysis supported the structure of **80**.

Scheme 23

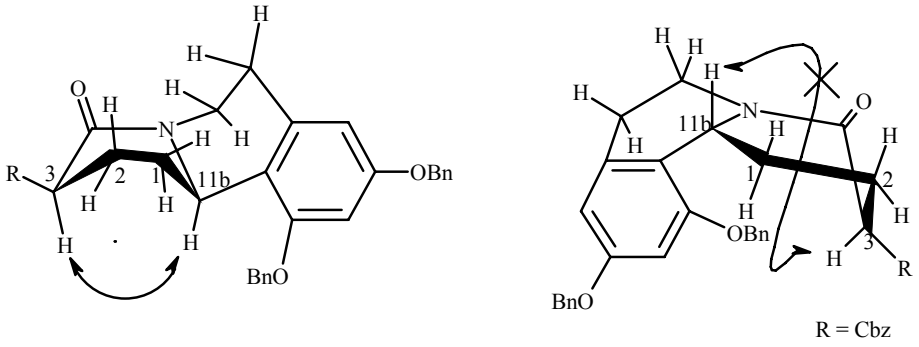


Next, on treatment with $POCl_3$ in $CHCl_3$ on refluxing condition, amide **80** was cyclised to afford imine **81**, which on concomitant reduction by $NaCNBH_3$ followed by aqueous bicarbonate quenching gave free amine **82** (Scheme 24). In basic condition both the amine **82** underwent cyclization to furnish the tricyclic core **83** and **84** with a 2:3 ratio. Compound **83** and **84** were separated by silica gel column chromatography and analyzed spectroscopically. The structural feature of **83** and **84** was unambiguously corroborated from the combined ^1H, ^{13}C NMR and mass spectroscopic data.

Scheme 24



The stereochemistry C-11b position was confirmed by 2D NMR studies as in case of **68** and **69** as key NOE interactions remained unchanged. In **83** hydrogen at C-11b and C-3 showed strong NOESY correlation whereas no such interaction was observed in case of **84** (Figure 10).

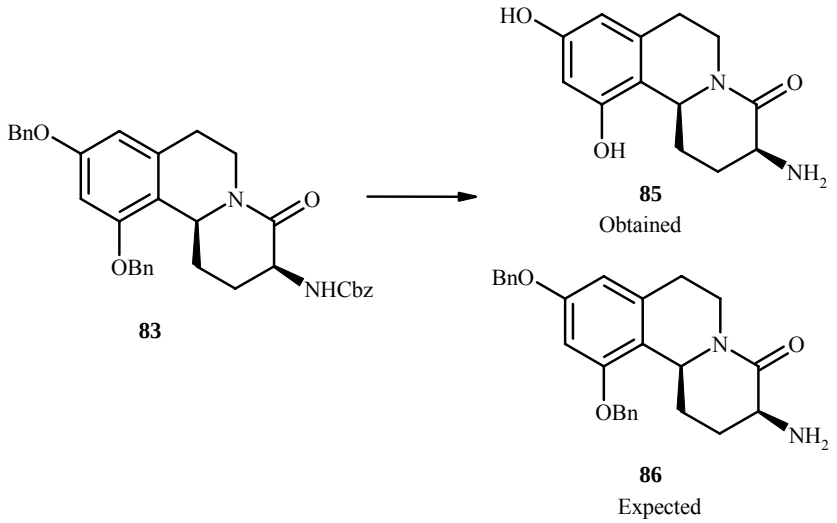


83 **84**

Figure 10

We performed various reactions according to literature[79] for the selective deprotection of benzyloxycarbonyl group, to our surprise all efforts proved fruitless. In all the case we obtained the dihydroxy amine **85**.

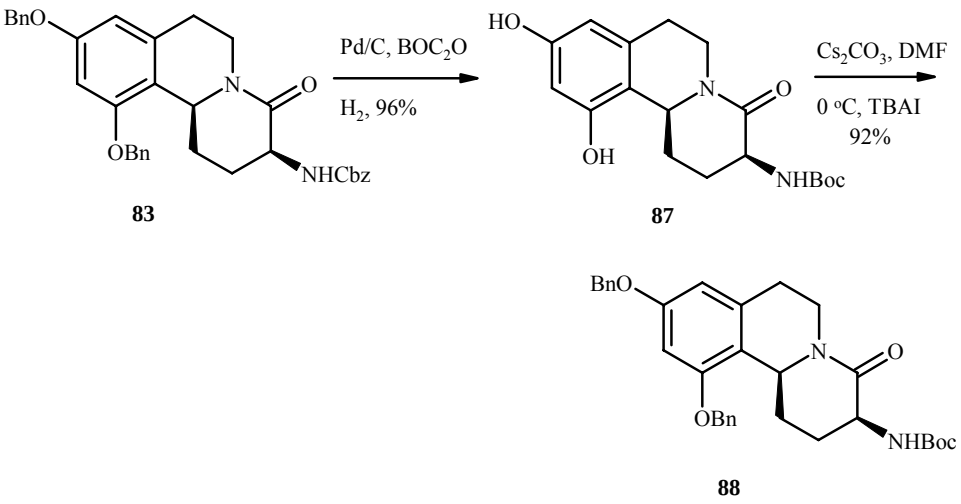
Scheme 25



83 **85** Obtained **86** Expected

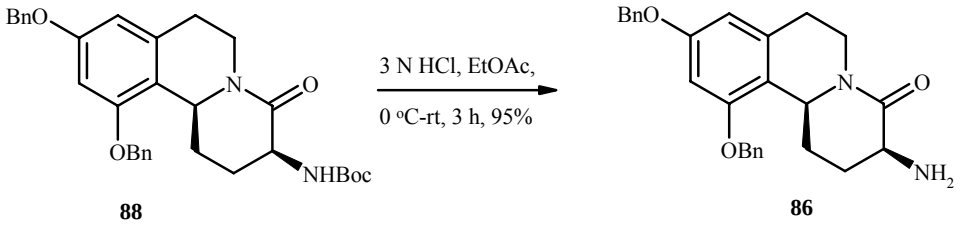
In order to circumvent this unanticipated difficulty as revealed above it was apparent that a simple protecting group manipulation of **83** could be an appropriate choice. The exchange of Cbz functionality to Boc in **83** was carried out applying the procedure developed by Ohfune et al.[80] The phenolic hydroxyl groups of the dihydroxy Boc amide **87** were subjected for benzyl ether protection using $CsCO_3$, BnBr, and cat. TBAI at 0 ^oC (Scheme 26).[81]

Scheme 26



Compound **88** on treatment with 3 N HCl in ethyl acetate at room temperature for 3 h resulted in Boc deprotection to afford the free amine **86** (Scheme 27),[82] which was directly used for the next reaction without any further purification.

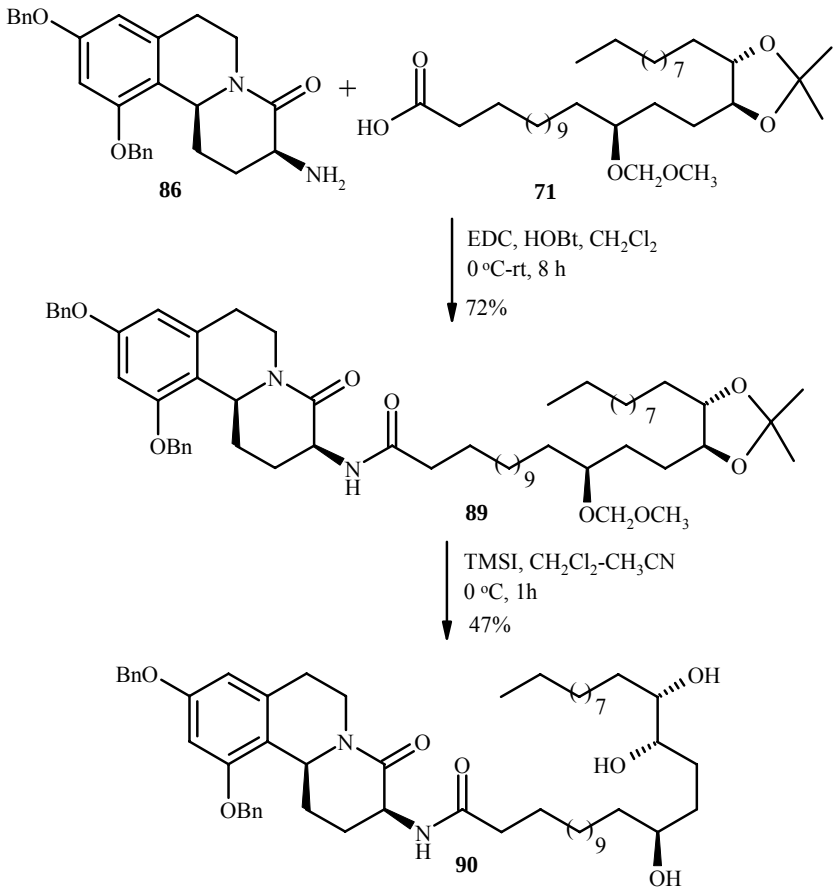
Scheme 27



The condensation reaction was effected with EDC/HOBt protocol with 72% yield. The structural feature of **89** was explicitly supported from the combined spectral data of the ^{1}H, $^{13}CNMR$, IR and mass spectroscopic data. For instance in ^{1}H NMR spectrum, signals located at δ 6.47 (d, J = 2.2 Hz, 1H), and 6.39 (d, J = 2.2 Hz, 1H) ppm showing two aromatic protons (H-8 and H-10), at δ 4.54 ppm due to H-3, at δ 3.65-3.49 (m, 3H) ppm indicating three protons at C-14', C-17', and C-18'. Deprotection of acetonide and MOM

ether protecting group were effected by using TMSI at 0 ^{o}C as in case of **73** (Scheme 28) and characterized spectroscopically. The ^{1}H NMR spectrum of **90** showed the absence signals for acetonide and MOM, while rest of the spectrum was compatible with assigned structure.

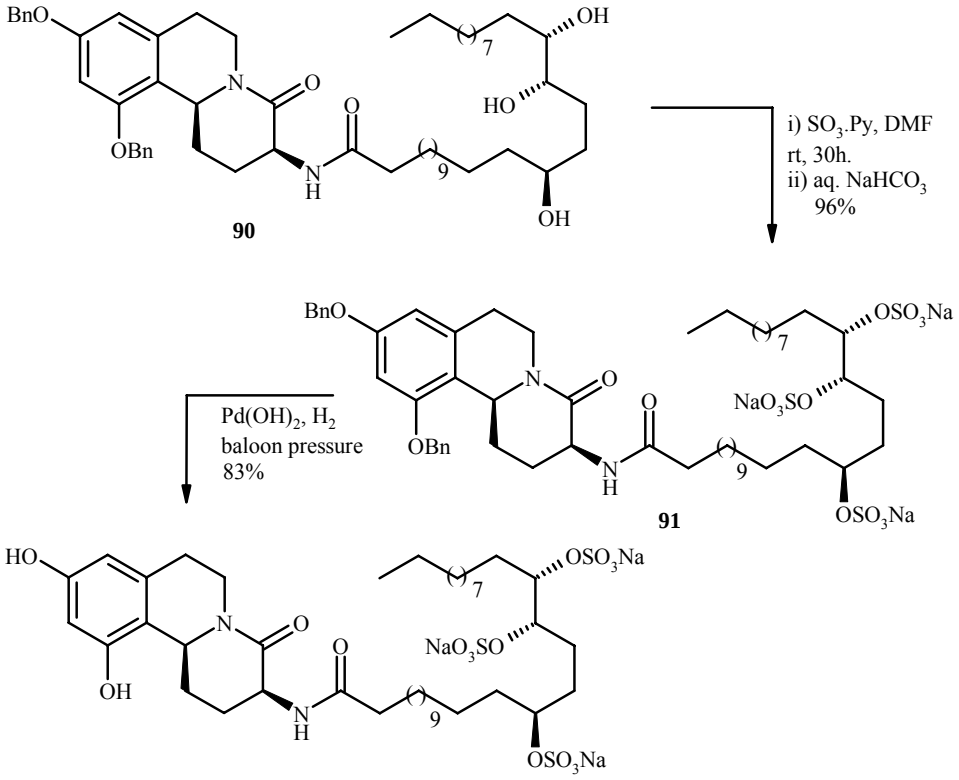
Scheme 28



With compound **90** in hand, the stage was set for the introduction of the sulphonate at the three secondary hydroxyl groups. Accordingly, triol **90** was treated with SO_3.Py complex in dry DMF at room temperature to afford **91**,[83] which was fully analyzed by the ^{1}H, ^{13}C NMR, and mass spectroscopic data. For example, in its ^{1}H NMR spectrum the three protons at C-14', C-17' and C-18' resonated at high frequency region (δ 4.90 and 4.65 ppm) indicating complete sulfation of the three hydroxyl groups. Simultaneous

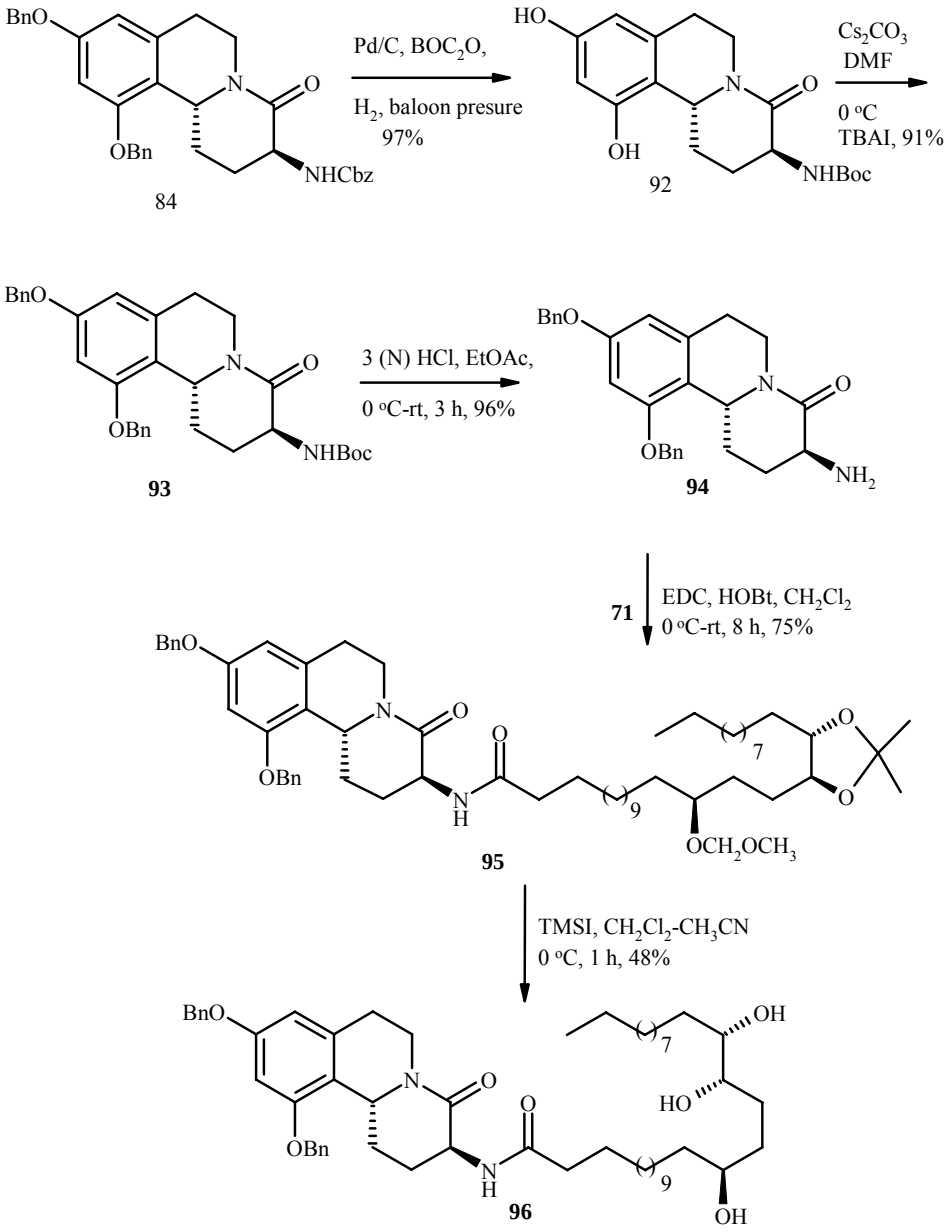
hydrogenolytic removal of both the benzyl groups with $Pd(OH)_2/C$ (H_2, balloon pressure) afforded the target schulzeines B (**2**) in 83% yield (Scheme 29). The spectroscopic data of the synthetic (**2**) were in consistent with those reported for the natural product.

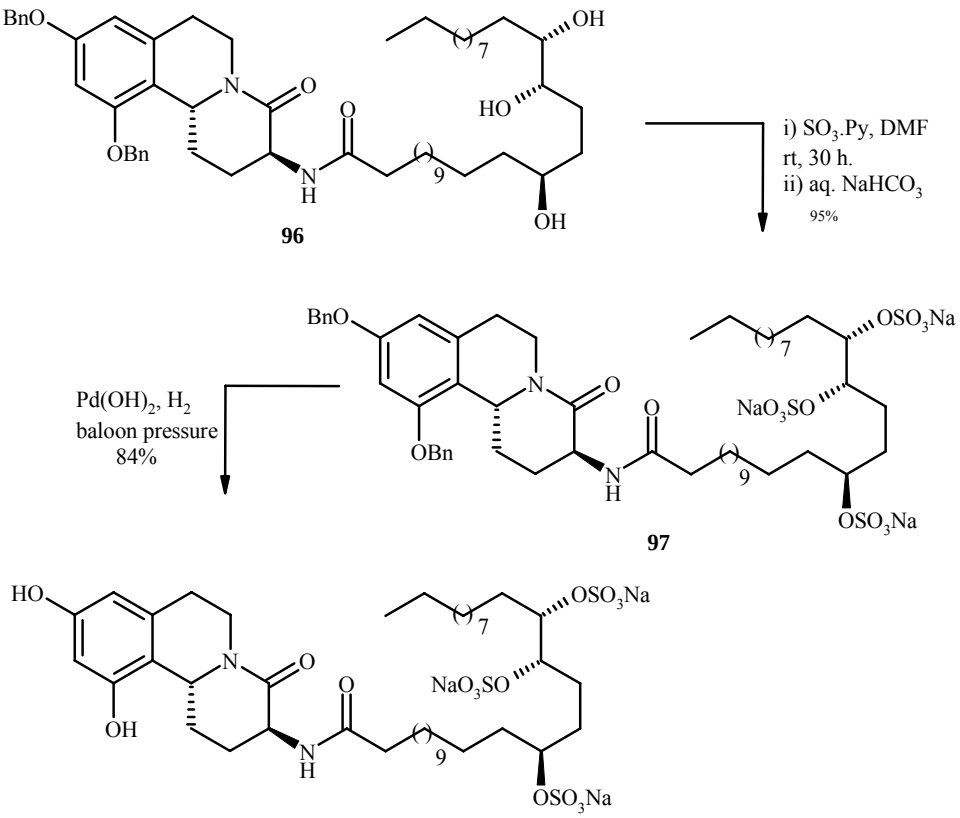
Scheme 29



With the same approach, the schulzeines C (3) was synthesized from **84** (Scheme 30) and the spectral data was identical with the data reported for the natural product.

Scheme 30

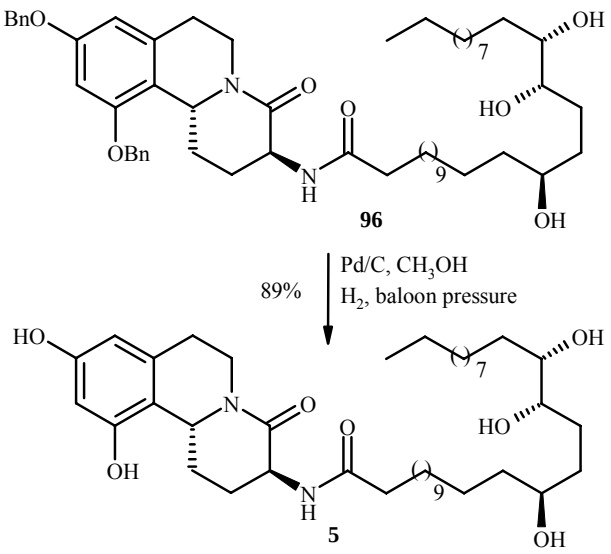

BnO
OBn
NHCbz
84
Pd/C, BOC2O,
H2, baloon presure
97%
HO
OH
NHBoc
92
Cs2CO3
DMF
0 oC
TBAI, 91%
93
3 (N) HCl, EtOAc,
0 oC-rt, 3 h, 96%
94
NH2
71
EDC, HOBt, CH2Cl2
0 oC-rt, 8 h, 75%
95
OCH2OCH3
TMSI, CH2Cl2-CH3CN
0 oC, 1 h, 48%
96



Schulzeine C (3)

On direct benzyl deprotection of triol **96** gave rise to desulfated schulzeine C (**5**). (Scheme 31).

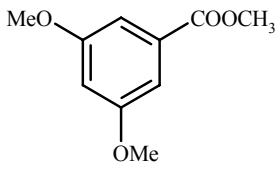
Scheme 31



In conclusion, we have achieved the first total syntheses of schulzeines B (**2**) and C (**3**). Bischler-Napieralski cyclization/reduction sequence was used for the construction of key tetrahydroisoquinoline moieties. The reported approach is convergent in nature and provides considerable flexibility for the synthesis of related nonnatural analogues.

EXPERIMENTAL

Methyl 3,5-dimethoxybenzoate (11)



11

To a stirring mixture of 3,5 dihydroxy benzoic acid (15 g, 97.3 mmol) and K_2CO_3 (67.2 g, 487 mmol) in acetone (450 mL), dimethyl sulfate (44.2 mL, 467 mmol) were added and the reaction mixture was refluxed for 8 h. After cooling, solvent was removed under reduced pressure and residue was diluted with ethyl acetate (350 mL). The combined organic layers were washed with brine, dried over Na_2SO_4. Removal of the solvent followed by silica gel column chromatographic purification of the residue using ethyl acetate and light petroleum (1:9) as eluent furnished **11** (17.4 g, 91% yield) as white solid.

Melting point: 41 ^{o}C [lit mp: 42-43 ^{o}C].

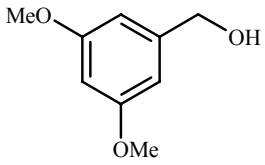
^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.15 (d, 2H, *J* = 2.4 Hz), 6.61 (t, 1H, *J* = 2.4 Hz), 3.90 (s, 3H), 3.81 (s, 6H).

^{13}C NMR ($CDCl_3$, 50 MHz): δ 166.3, 160.4, 131.7, 106.8, 105.4, 58.1, 55.1, 51.9.

MS (ESI) m/z: 197.08 (M^+ + H).

Anal Calcd for $C_{10}H_{12}O_4$: C, 61.22; H, 6.16; **Found:** C, 61.10; H, 6.24.

(3,5-Dimethoxyphenyl)methanol (12)



12

To a stirring solution of the ester **11** (13.2 g, 67.3 mmol) in dry THF (300 mL), lithium aluminum hydride (3.8 g, 101 mmol) was added at 0 ^{o}C under nitrogen atmosphere and stirred at room temperature for 6 h. After completion, the reaction was quenched by the dropwise addition of a cooled saturated aq. Na_2SO_4 solution and filtered through celite. The residue was washed with ethyl acetate thoroughly (3 × 300 mL) and the filtrate was dried over anhydrous Na_2SO_4. Removal of the solvent followed by silica gel column chromatographic purification using ethyl acetate and light petroleum (1:4) as eluent afforded **12** (9.4 g, 83% yield) as a white solid.

Melting point: 48 ^{o}C [lit mp: 47-50 ^{o}C].

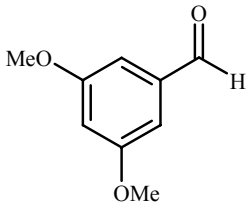
^{1}H NMR ($CDCl_3$, 200 MHz): δ 6.53 (d, 2H, *J* = 2.4 Hz), 6.39 (t, 1H, *J* = 2.4 Hz), 4.63 (s, 2H), 3.79 (s, 6H), 1.80 (brs, 1H).

^{13}C NMR ($CDCl_3$, 50 MHz): δ 160.8, 143.4, 104.5, 99.5, 64.9, 55.1.

MS (ESI) m/z: 169.09 (M^+ + H).

Anal Calcd for $C_9H_{12}O_3$: C, 64.27; H, 7.19; **Found:** C, 61.23; H, 6.90.

3,5-Dimethoxybenzaldehyde (13)



13

To a stirring solution of the alcohol **12** (9.4 g, 55.9 mmol) in ethyl acetate (freshly distilled, 300 mL), IBX (20.4 g, 72.7 mmol) was added and the reaction mixture was refluxed under nitrogen atmosphere for 5 h. After cooling, the reaction mixture was filtered through celite and the residue was washed with ethyl acetate (3 × 300 mL). Concentration of the filtrate followed by silica gel column chromatographic purification of the residue using ethyl acetate and light petroleum (1:9) as eluent furnished **13** (8.3 g, 89% yield) as a white solid.

Melting point: 45 ^{o}C [lit mp: 45-48 ^{o}C].

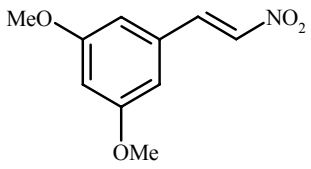
^{1}H NMR ($CDCl_3$, 200 MHz): δ 9.90 (s, 1H), 7.01 (d, 2H, *J* = 2.4 Hz), 6.70 (t, 1H, *J* = 2.4 Hz), 3.84 (s, 6H).

^{13}C NMR ($CDCl_3$, 50 MHz): δ 191.7, 161.1, 138.3, 106.9, 55.4.

MS (ESI) m/z: 189.05 (M^+ + Na).

Anal Calcd for $C_9H_{10}O_3$: C, 65.05; H, 6.07; **Found:** C, 65.1; H, 6.05.

(E)-1,3-Dimethoxy-5-(2-nitrovinyl)benzene (14)



14

A stirring mixture of aldehyde **13** (12.2 g, 73.4 mmol), nitromethane (5.17 ml, 95.4 mmol), acetic acid (40 mL) and ammonium acetate (4.04 g, 52.5 mmol) was gently refluxed for 4 h. On cooling to room temperature, yellow crystals were appeared. It was then filtered and recrystallization from acetic acid gave **14** (10 g, 65% yield) as orange needles.

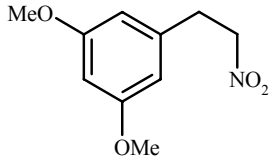
Melting point: 95 ^{o}C [lit mp: 94-95 ^{o}C].

^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.93 (d, 1H, *J* = 13.6 Hz), 7.55 (d, 1H, *J* = 13.6 Hz), 6.67 (d, 2H, *J* = 2.2 Hz), 6.58 (t, 1H, *J* = 2.2 Hz), 3.83 (s, 6H).

^{13}C NMR ($CDCl_3$, 50 MHz): δ 161.3, 139.0, 137.6, 131.8, 106.9, 104.5, 55.4.

Anal Calcd for $C_{10}H_{11}NO_4$: C, 57.41; H, 5.30; N, 6.70; **Found:** C, 57.50; H, 5.14; N, 6.55.

1,3-Dimethoxy-5-(2-nitroethyl)benzene (15)



15

To a stirring solution of **14** (8.6 g, 41.1 mmol) in a mixture of THF (150 mL) and ethanol (50 mL), $NaBH_4$ (6.2 g, 164.4 mmol) was added portionwise over a period of 40 min. After completion, the reaction was quenched by the addition of saturated aq. NH_4Cl solution and filtered through celite. The filtrate was concentrated under reduced pressure and diluted with ethyl acetate (100 mL). The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4. Removal of the solvent followed by silica gel column chromatographic purification of the crude liquid using ethyl acetate and light petroleum (1:19) as eluent afforded **15** (8 g, 92% yield) as a clear liquid.

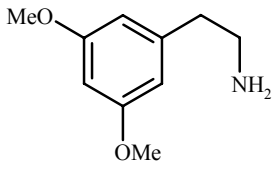
^{1}H NMR ($CDCl_3$, 200 MHz): δ 6.32 (m, 3H), 4.58 (t, 2H, *J* = 7.5 Hz), 3.77 (s, 6H), 3.24 (t, 2H, *J* = 3.2 Hz).

^{13}C NMR ($CDCl_3$, 50 MHz): δ 138.1, 137.3, 133.4, 128.3, 127.7, 127.5, 81.4, 74.4, 70.8, 40.6.

MS (ESI) m/z: 234.08 (M^+ + Na).

Anal Calcd for $C_{10}H_{13}NO_4$: C, 56.86; H, 6.20; N, 6.63; **Found:** C, 56.66; H, 6.35; N, 6.45.

2-(3,5-Dimethoxyphenyl)ethanamine (9)



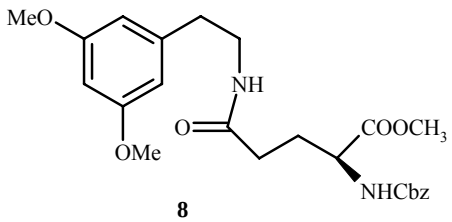
9

To a stirring solution of nitro compound **15** (3.6 g, 17.05 mmol) in CH_3OH (40 mL), Pd/C (0.2 g), ammonium formate (5.0 g, 78.4 mmol) were added and the reaction flask was equipped with a reflux condenser, a piece of tubing was attached to the top of the condenser, and the end of the tubing was submerged in a container of water. Then the reaction mixture was gently refluxed for 20 h, cooled, filtered through celite and the solvent was evaporated. The residue was diluted with 70 mL of Et_2O and the pH adjusted to >12 with 20% NaOH. The mixture was shaken well and separated. The aqueous layer was extracted with (2 × 60 mL) portions of Et_2O. The combined organic layer was dried over anhydrous Na_2SO_4, concentrated to afford free amine **9** (2.96g, 96% yield) as a liquid.

^{1}H NMR ($CDCl_3$, 200 MHz): δ 6.32 (m, 3H), 3.77 (s, 3H), 3.76 (s, 3H), 3.58 (m, 1H), 2.98 (t, 1H, *J* = 6.7 Hz), 2.73 (t, 2H, *J* = 6.62).

MS (ESI) m/z: 182.12(M^+ + H).

(*S*)-Methyl 2-(benzyloxycarbonylamino)-5-(3,5-dimethoxyphenethylamino)-5-oxopentanoate (8)



8

To a stirring solution of **10** (6.5 g, 22.0 mmol) in dry dichloromethane (100 mL) at 0 ^{o}C under nitrogen, HOBt (5.94 g, 44.0 mmol), EDC (6.33 g, 33.0 mmol) and a solution of **9** (4 g, 22.0 mmol) in dry dichloromethane (30 mL) were added. After stirring at room temperature for 10 h, the reaction mixture was diluted with water, extracted with dichloromethane (100 mL × 2). The combined organic layer was washed with water, brine and dried over anhydrous Na_2SO_4. Removal of the solvent followed by silica gel column chromatographic purification of the residue using ethyl acetate and light petroleum (2:3) afforded **8** (7.9 g, 76%) as a gummy paste.

$[\alpha]_D$ = –1.78 (*c* 1.0, $CHCl_3$).

IR (liquid film, $CHCl_3$) ν_{max} (cm^{-1}): 3324, 3006, 2951, 2839, 1715, 1651, 1596, 1539, 1455, 1432.

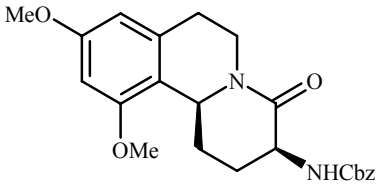
^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.31 (m, 5H), 6.31 (m, 3H), 6.19 (brs, 1H), 5.84 (d, 1H, *J* = 7.9 Hz), 5.07 (s, 2H), 4.25 (m, 1H), 3.74 (s, 6H), 3.71 (s, 3H), 3.46 (m, 2H), 2.71 (t, 2H, *J* = 7.0 Hz), 2.25-2.09 (m, 3H) 1.91 (m, 1H).

^{13}C NMR ($CDCl_3$, 50 MHz): δ 172.3, 171.8, 160.7, 156.1, 141.0, 136.0, 128.2, 127.9, 127.8, 106.5, 98.1, 66.6, 54.9, 53.4, 52.1, 40.3, 35.6, 32.1, 27.8.

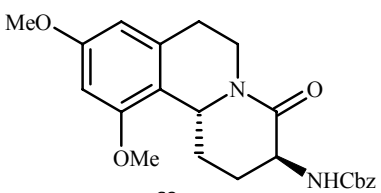
MS (ESI) m/z: 481.18(M^+ + Na).

Anal Calcd for $C_{24}H_{30}N_2O_7$: C, 62.87; H, 6.59; N, 6.11; **Found:** C, 62.81; H, 6.44; N, 6.16.

Benzyl (3*S*,11b*S*)-9,11-dimethoxy-4-oxo-2,3,4,6,7,11b-hexahydro-1H-pyrido[2,1-a]isoquinolin-3-ylcarbamate (68) and benzyl (3*S*,11b*R*)-9,11-dimethoxy-4-oxo-2,3,4,6,7,11b-hexahydro-1H-pyrido[2,1-a]isoquinolin-3-ylcarbamate (69)



68



69

A stirring solution of compound **8** (3.2 g, 6.8 mmol), $POCl_3$ (15 mL) and dry $CHCl_3$ (15 mL) was heated under reflux for 3 h. After cooling, reaction mixture was concentrated and co-distilled with benzene. The residue was triturated with cold hexane (30 mL) and decanted. The reddish gum was dissolved in glacial acetic acid (5 mL) and methylene chloride (30 mL), cooled to 0 ^oC and then solid sodium cyanoborohydride (1.5 g, 23.8 mmol) was added. After 1.5 h, sodium bicarbonate solution was introduced till the reaction mixture rendered basic. After 3 h of stirring at room temperature, it was diluted with dichloromethane and layers separated. The aqueous layer was extracted with dichloromethane (30 mL × 3). The combined layer was washed with water, brine and dried over Na_2SO_4. Evaporation of the solvent followed by silica gel column purification of the orange residue using ethyl acetate and light petroleum (1:3) furnished the *cis* isomer **68** (0.52 g, 30%) as a gummy past.

$[\alpha]_D$ = – 79.89 (*c* 0.8, $CHCl_3$).

IR (liquid film, $CHCl_3$) ν_{max} (cm^{-1}): 3019, 2940, 1714, 1656, 1611, 1498, 1466, 1436, 1308, 1147.

^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.33-7.22 (m, 5H), 6.28 (d, 1H, *J* = 2.3 Hz), 6.21 (d, 1H, *J* = 2.3 Hz), 6.03 (d, 1H, *J* = 5.1 Hz), 5.07 (d, 2H, *J* = 1.3 Hz), 4.77 (dd, 1H, *J* = 10.7, 4.2 Hz), 4.63 (m, 1H), 4.33 (m, 1H), 3.75 (s, 3H), 3.72 (s, 3H), 2.76-2.51 (m, 4H), 2.38-2.27 (m, 1H), 1.40-1.18 (m, 2H).

^{13}C NMR ($CDCl_3$, 50 MHz): δ 169.9, 159.3, 156.7, 155.82, 136.8, 136.4, 128.3, 127.9, 127.8, 116.5, 104.2, 96.8, 66.5, 55.1, 50.0, 48.4, 38.7, 29.4, 28.1, 25.4.

MS (ESI) m/z: 433.19 (M^+ + Na).

Anal Calcd for $C_{23}H_{26}N_2O_5$: C, 67.30; H, 6.38; N, 6.82; **Found:** C, 67.40; H, 6.27; N, 6.77.

Further elution gave the *trans* isomer **69** (0.55 g, 32%) as a white solid.

Melting point: 121 ^oC.

$[\alpha]_D$ = +216.78 (*c* 1.25, $CHCl_3$).

IR (liquid film, $CHCl_3$) ν_{max} (cm^{-1}): 3019, 2940, 1718, 1638, 1609, 1496, 1464, 1438, 1313, 1148, 1098, 1056.

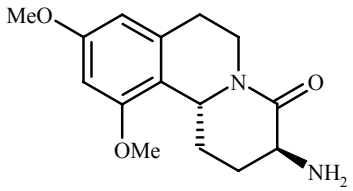
^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.30-7.19 (m, 5H), 6.26 (d, 1H, *J* = 2.2 Hz), 6.18 (d, 1H, *J* = 2.2 Hz), 5.65 (d, 1H, *J* = 5.2 Hz), 5.05 (s, 2H), 4.88-4.80 (m, 1H), 4.65 (d, 1H, *J* = 9.8 Hz), 3.99 (m, 1H), 3.73 (s, 3H), 3.71 (s, 3H), 2.96-2.70 (m, 2H), 2.60-2.38 (m, 2H), 1.86-1.67(m, 1H), 1.43-1.18 (m, 2H).

^{13}C NMR ($CDCl_3$, 50 MHz): δ 168.3, 159.1, 157.6, 156.5, 137.7, 136.5, 128.40, 128.0, 127.9, 117.7, 104.6, 97.2, 66.7, 56.0, 55.2, 55.1, 52.9, 39.5, 30.6, 27.8.

MS (ESI) m/z: 433.17 (M^+ + Na).

Anal Calcd for $C_{23}H_{26}N_2O_5$: C, 67.30; H, 6.38; N, 6.82; **Found:** C, 67.35; H, 6.34; N, 6.69.

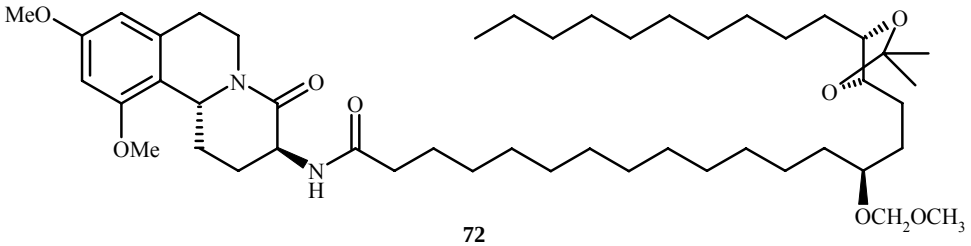
(3*S*,11b*R*)-3-Amino-9,11-dimethoxy-2,3,6,7-tetrahydro-1H-pyrido[2,1-a]isoquinolin-4(11bH)-one (70)



70

To a stirring solution of the compound **69** (0.4 g, 0.97 mmol) in CH_3OH (5 mL), Pd/C (50 mg) was added and stirred under hydrogen atmosphere for 8 h. After complete deprotection, the reaction mixture was filtered through a pad of celite and the filtrate was concentrated to afford the crude amine **70** (0.25 g, 94%).

(*S*)-16-((4*S*,5*S*)-5-Decyl-2,2-dimethyl-1,3-dioxolan-4-yl)-N-((3*S*,11b*S*)-9,11-dimethoxy-4-oxo 2,3,4,6,7,11b-hexahydro-1H-pyrido[2,1-a]isoquinolin-3-yl)-14-(methoxymethoxy)hexadecanamide (72)



72

To a stirring solution of **71** (200 mg, 0.36mmol), HOBt (98 mg, 0.72 mmol), EDC (103.5 mg, 0.54 mmol) in dry dichloromethane (6 mL) was added a solution of **70** (100 mg, 0.36 mmol) in dry dichloromethane (3 mL) followed by dry triethylamine (0.13 mL, 0.9 mmol). After stirring for 15 h at room temperature, the reaction mixture was diluted with water, extracted with dichloromethane (20 mL × 2). The combined organic layer was washed

with water, brine and dried over anhydrous Na_2SO_4. Removal of the solvent followed by silica gel column chromatographic purification of the residue using ethyl acetate and light petroleum (1:3) afforded **72** (mg, 72%) as colorless liquid.

$[\alpha]_D$ = +91.98 (*c* 1.2, $CHCl_3$).

IR (liquid film, $CHCl_3$) ν_{max} (cm^{-1}): 3018, 2929, 2856, 1609, 1638, 1499, 1465, 1439, 1308, 1150, 105468.

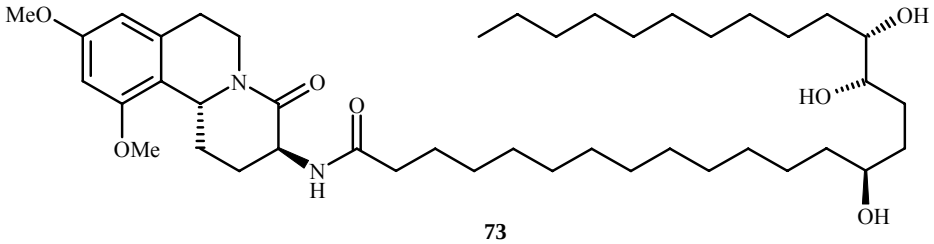
^{1}H NMR ($CDCl_3$, 200 MHz): δ 6.32 (d, 1H, *J* = 2.3 Hz), 6.23 (d, 1H, *J* = 2.3 Hz), 4.92 (dd, 1H, *J* = 4.3, 11.0 Hz), 4.74 (dd, 1H, *J* = 3.6, 11.0 Hz), 4.63 (s, 2H), 4.19 (m, 1H), 3.80 (s, 3H), 3.78 (s, 3H), 3.57 (m, 3H), 3.36 (s, 3H), 3.01-2.78 (m, 2H), 2.67-2.52 (m, 2H), 2.23 (t, 2H, *J* = 7.2 Hz), 1.68-1.46 (m, 13H), 1.36 (s, 6H), 1.26 (m, 34H), 0.88 (t, 3H, *J* = 6.3 Hz).

^{13}C NMR ($CDCl_3$, 50 MHz): δ 173.6, 168.8, 159.2, 157.7, 137.6, 117.7, 107.8, 104.6, 97.3, 96.2, 95.32, 80.9, 80.9, 77.2, 56.2, 55.5, 55.2, 55.1, 52.0, 39.6, 36.7, 34.2, 33.0, 32.0, 30.6, 30.4, 29.83, 29.7, 29.7, 29.4, 29.3, 28.2, 27.8, 27.4, 27.3, 26.2, 25.7, 25.4, 22.7, 14.2.

MS (ESI) m/z: 837.57 (M^+ + Na).

Anal Calcd for $C_{48}H_{82}N_2O_8$: C, 70.72; H, 10.14; N, 3.44; **Found:** C, 70.80; H, 10.20; N, 3.10.

(14*S*,17*S*,18*S*)-N-((3*S*,11b*S*)-9,11-Dimethoxy-4-oxo-2,3,4,6,7,11b-hexahydro-1H-pyrido[2,1-a]isoquinolin-3-yl)-14,17,18-trihydroxyoctacosanamide (73)



73

A solution of **72** (140 mg, 0.17 mmol) and TMSI (freshly prepared from TMS-Cl and sodium iodide in acetonitrile) (0.7 g, 3.4 mmol) in dichloromethane (6 mL) and acetonitrile (2 mL) under nitrogen at 0 °C was stirred for 1 h and then 10% $NaHCO_3$ solution was added and layers separated. The aqueous layer was extracted with dichloromethane (10 mL × 3), the combined organic layer was dried over anhydrous Na_2SO_4, concentrated and purified on silica gel by using ethyl acetate to afford **73** (126 mg, 44%) as a gummy liquid.

$[\alpha]_D$ = + 38.5 (*c* 1.1, $CHCl_3$).

IR (liquid film, $CHCl_3$) ν_{max} (cm^{-1}): 3394, 3014, 2927, 2852, 1638, 1608, 1493, 1466, 1377, 1358, 1310, 1274, 1154, 1090, 1047.

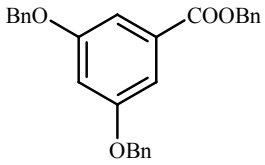
^{1}H NMR ($CDCl_3$, 200 MHz): δ 6.35 (d, 1H, *J* = 2.3 Hz), 6.27 (d, 1H, *J* = 2.3 Hz), 4.92 (m, 1H), 4.73 (m, 1H), 4.23 (m, 1H), 3.80 (s, 3H), 3.79 (s, 3H), 3.63 (m, 1H), 3.41 (m, 2H), 3.03-2.81 (m, 2H), 2.70-2.57 (m, 3H), 2.24 (t, 2H, *J* = 7.4 Hz), 1.77-1.66 (m, 8H), 1.50-1.40 (m, 6H), 1.33-1.26 (m, 33H), 0.88 (t, 3H, *J* = 6.30 Hz).

^{13}C NMR ($CDCl_3$, 50 MHz): δ 173.7, 168.8, 159.6, 157.8, 137.6, 117.7, 104.7, 97.3, 77.2, 74.7, 72.3, 56.2, 55.3, 55.2, 52.0, 39.6, 37.8, 36.8, 33.8, 33.7, 31.9, 30.6, 30.4, 29.7, 29.6, 29.6, 29.4, 29.3, 29.3, 29.3, 29.2, 29.2, 27.7, 27.2, 25.7, 25.6, 25.6, 22.7 14.1.

MS (ESI) m/z: 751.56 (M^+ + Na).

Anal Calcd for $C_{43}H_{74}N_2O_7$: C, 70.65; H, 10.20; N, 3.83; **Found:** C, 70.58; H, 10.34; N, 3.72.

Benzyl 3,5-bis(benzyloxy)benzoate (74)



74

To a stirring solution of 3,5-dihydroxy benzoic acid X (20g, 130mmol) in a mixture of THF:DMF (1:1, 150 mL), NaH (18.2 g, 454 mmol) was added at 0 ^oC followed by the addition of benzyl bromide (47.9 mL, 403 mmol) under nitrogen atmosphere. Then the reaction mixture was allowed to stir at room temperature for next 7 h. After completion, the reaction was quenched by the addition of ice and extracted with ether (3 × 200 mL). The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4. Removal of the solvent followed by silica gel column chromatographic purification of the residue using ethyl acetate and light petroleum (1:9) as eluent furnished **74** (48.4 g, 88% yield) as a white solid.

IR (liquid film, $CHCl_3$) ν_{max} (cm^{-1}): 3031, 1718, 1595, 1444, 1217, 1159.

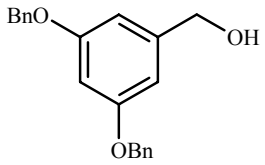
^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.41-7.33 (m, 15H), 7.3 (d, 2H, *J* = 2.3 Hz), 6.77 (t, 1H, *J* = 2.3 Hz), 5.33 (s, 2H), 5.05 (s, 4H).

^{13}C NMR ($CDCl_3$, 50 MHz): δ 165.8, 159.7, 136.4, 135.9, 132.0, 128.5, 128.1, 128.1, 128.0, 127.5, 108.5, 107.1, 70.1, 66.7.

MS (ESI) m/z: 447.05 (M^+ + Na).

Anal Calcd for $C_{28}H_{24}O_4$: C, 79.22; H, 5.70; **Found:** C, 79.30; H, 5.58.

(3,5-Bis(benzyloxy)phenyl)methanol (75)



75

To a stirring solution of the ester **74** (15.4 g, 36.3 mmol), in dry THF (250 mL), lithium aluminum hydride (2.1 g, 54.5 mmol) was added at 0 ^{o}C under nitrogen atmosphere and the reaction mixture was stirred at room temperature for 6 h. After completion, the reaction mixture was quenched by the dropwise addition of a cooled saturated aq. Na_2SO_4 solution and filtered through celite. The filtrate was dried over anhydrous Na_2SO_4, concentrated to leave a crude residue. Silica gel column chromatographic purification of the residue using ethyl acetate and light petroleum (1:4) as eluent afforded **75** (9 g, 77% yield) as solid.

Melting point: 71–72 ^{o}C [lit mp: 72–74 ^{o}C].

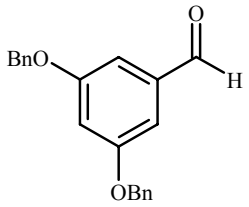
^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.42-7.30 (m, 10 H), 6.60 (d, 2H, *J* = 2.2 Hz), 6.52 (t, 1H, *J* = 2.2 Hz), 5.03 (s, 4H), 4.61 (s, 2H), 1.59 (br s, 1H).

^{13}C NMR ($CDCl_3$, 50 MHz): δ 159.9, 143.5, 136.8, 128.4, 127.8, 127.4, 105.6, 101.2, 69.9, 64.9.

MS (ESI) m/z: 343.08 (M^+ + Na).

Anal Calcd for $C_{21}H_{20}O_3$: C, 78.73; H, 6.29; **Found:** C, 78.60; H, 6.25.

3**,5-Bis(benzyloxy)benzaldehyde (76)**



76

To a stirring solution of the alcohol **75** (12.5 g, 39.0 mmol) in distilled ethyl acetate (260 mL), IBX (14.2g, 50.7 mmol) was added and it was refluxed under nitrogen for 5 h. After cooling, the reaction mixture was filtered through celite. Removal of the solvent followed by silica gel column chromatographic purification of the residue using ethyl acetate and light petroleum (1:9) as eluent furnished **76** (11.1 g, 89% yield) as oil.

IR (liquid film, $CHCl_3$) ν_{max} (cm^{-1}): 3019, 1697, 1593, 1450, 1294, 1160, 1056.

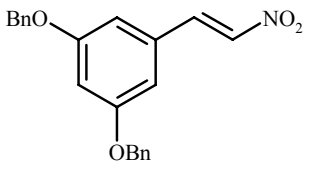
^{1}H NMR ($CDCl_3$, 200 MHz): δ 9.98 (s, 1H), 7.43-7.31 (m, 10H), 7.09 (d, 2H, *J* = 2.3 Hz), 6.64 (t, 1H, *J* = 2.3 Hz), 5.08 (s, 4H).

^{13}C NMR ($CDCl_3$, 50 MHz): δ 191.4, 160.4, 138.5, 136.3, 128.7, 128.2, 127.5, 108.6, 108.3, 70.3;

MS (ESI) m/z: 341.04 (M^+ + Na).

Anal Calcd for $C_{21}H_{18}O_3$: C, 79.22; H, 5.70; **Found:** C, 79.08; H, 5.65.

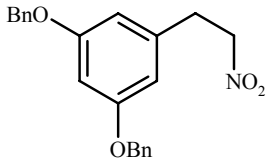
(E)-1,3-Bis(benzyloxy)-5-(2-nitrovinyl)benzene (77)



77

A stirring mixture of aldehyde **76** (9 g, 28.3 mmol), nitromethane (2 mL, 36.7 mmol), acetic acid (17 mL) and ammonium acetate (1.6 g, 20.2 mmol) ware heated to 80 ^{o}C for 6 h. It was then cooled to room temperature, basified with saturated solution of sodium bicarbonate and extracted with ethyl acetate (3 × 15 mL). The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4, and concentrated to leave a crude residue which was used for the next reaction without any further purification.

1,3-Bis(benzyloxy)-5-(2-nitroethyl)benzene (78)



78

In THF-EtOH (2:1) (300 mL) solution of the above residue, $NaBH_4$ (4.3 g, 113.0 mmol) was added portionwise over a period of 30 min. After completion, the reaction was quenched by the addition of saturated aq. NH_4Cl solution and filtered through celite. The filtrate was concentrated under reduced pressure and extracted with ethyl acetate (2 × 100 mL). The combined organic layer was dried over anhydrous Na_2SO_4. Removal of the solvent followed by silica gel column chromatographic purification of the residue using ethyl acetate and light petroleum (1:19) as eluent afforded **78** (6.4 g, 62.5% yield) as a colorless oil.

IR (liquid film, $CHCl_3$) ν_{max} (cm^{-1}): 3019, 1596, 1557, 1453, 1382, 1159, 1066.

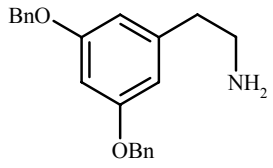
^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.37 (m, 10 H), 6.49 (m, 1H), 6.41 (m, 2H), 4.99 (s, 4H), 4.55 (t, 2H, *J* = 7.0 Hz), 3.22 (t, 2H, *J* = 7.6 Hz).

^{13}C NMR ($CDCl_3$, 50 MHz): δ 160.4, 137.9, 136.7, 128.6, 128.0, 127.5, 107.8, 100.9, 75.9, 70.1, 33.6.

MS (ESI) m/z: 364.09 (M^+ + H).

Anal Calcd for $C_{22}H_{21}NO_4$: C, 72.71; H, 5.82; **Found:** C, 72.63; H, 5.92.

2-(3,5-Bis(benzyloxy)phenyl)ethanamine (79)



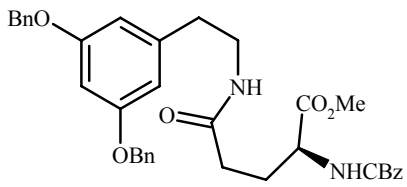
79

To a stirring solution of $NiCl_2.6H_2O$ (1.8 g, 7.7 mmol) in CH_3OH (50 mL), solid $NaBH_4$ (0.9 g, 23.1 mmol) was added portionwise. After 30 minutes stirring at room temperature, a solution of nitro compound **78** (5.6 g, 15.4 mmol) in CH_3OH (20 mL) was added followed by more solid $NaBH_4$ (2 g, 53.9 mmol) over a 5 minutes period. After complete consumption of starting material, reaction mixture was quenched by the addition of saturated aq. NH_4Cl solution and then filtered through celite. The filtrate was concentrated and extracted with ethyl acetate (3 × 80 mL). The combined organic layer was dried over anhydrous Na_2SO_4, concentrated to obtain free amine **79** (4.9 g, 96%) as colorless oil.

^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.44 -7.31 (m, 10 H), 6.50-6.46 (m, 3H), 5.02 (s, 4H), 2.95 (m, 2H), 2.69 (m, 2H).

^{13}C NMR ($CDCl_3$, 50 MHz): δ 159.9, 142.1, 136.8, 128.5, 128.2, 127.9, 127.4, 108.0, 99.8, 69.9, 43.05, 40.1.

(*S*)-Methyl 2-(benzyloxycarbonylamino)-5-(3,5-bis(benzyloxy)phenethylamino)-5-oxopentanoate (80)



80

To a stirring solution of **10** (8.5 g, 29.4 mmol) in dry dichloromethane (100 mL) at 0 ^{o}C under nitrogen, EDC (6.77 g, 35.3 mmol), HOBt (4.76 g, 35.3 mmol) and compound **79** (8.83 g, 26.5 mmol) in dry dichloromethane (50 mL) were added. After stirring at room temperature for 10 h, the reaction mixture was diluted with water, extracted with dichloromethane (100 mL × 2). The combined organic layer was washed with water, brine and dried over anhydrous Na_2SO_4. Removal of the solvent followed by silica gel column chromatographic purification of the residue using ethyl acetate and light petroleum (2:3) furnished **80** (15.1 g, 84%) as a white solid.

Melting point: 114 °C.

$[\alpha]_D$ = –3.5 (*c* 1.1, $CHCl_3$).

IR (liquid film, $CHCl_3$) ν_{max} (cm^{-1}): 3325, 3032, 2950, 1719, 1654, 1593, 1528, 1453, 1157, 1050, 753.

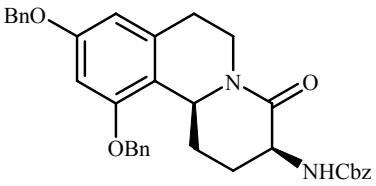
^{1}H NMR (200 MHz, $CDCl_3$): δ 7.43-7.31 (m, 15 H), 6.50 (t, 1H, *J* = 2.2 Hz), 6.45 (d, 2H, *J* = 2.2 Hz), 5.83 (t, 1H, *J* = 6.2 Hz), 5.69 (d, 1H, *J* = 8.0 Hz), 5.08 (s, 2H), 5.01 (s, 4H), 4.31 (m, 1H), 3.71 (s, 3H), 3.48 (dt, 2H, *J* = 6.9, 6.2 Hz), 2.73 (t, 2H, *J* = 6.9 Hz), 2.18 (m, 2H), 1.96 (m, 1H), 1.66 (m, 1H).

^{13}C (50 MHz, $CDCl_3$): δ 172.3, 171.6, 160.0, 156.2, 141.1, 136.7, 136.1, 128.4, 128.4, 128.2, 128.0, 127.9, 127.8, 127.4, 107.8, 100.0, 69.9, 66.9, 53.4, 52.3, 40.3, 35.7, 32.2, 28.2.

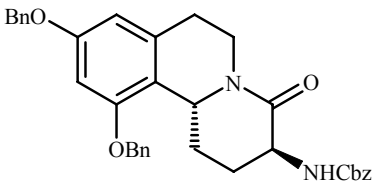
MS (ESI) m/z: 633.42 (M^+ + Na).

Anal. Calcd for $C_{36}H_{38}N_2O_7$: C, 70.80; H, 6.27; N, 4.59. **Found:** C, 70.8; H, 6.22; N, 4.46.

Benzyl (3*S*, 11b*S*)-9,11-bis(benzyloxy)-4-oxo-2,3,4,6,7,11b-hexahydro-1H-pyrido[2,1-a]isoquinolin-3-ylcarbamate (83) and benzyl (3*S*,11b*R*)-9,11-bis(benzyloxy)-4-oxo-2,3,4,6,7,11b-hexahydro-1H-pyrido[2,1-a]isoquinolin-3-ylcarbamate (84).



83



84

A stirring mixture of compound **80** (3.6 g, 5.90 mmol), $POCl_3$ (10 mL) and dry $CHCl_3$ (10 mL) was heated under reflux for 3 h, concentrated and co-distilled with benzene. The residue was triturated with cold hexane (30 mL) and decanted. The reddish gum was dissolved in glacial acetic acid (5 mL) and methylene chloride (30 mL), cooled to 0 ^oC and then solid sodium cyanoborohydride (1.30 g, 20.68 mmol) was added. After 1.5 h, sodium bicarbonate solution was introduced till the reaction mixture rendered basic. After 3 h of stirring at room temperature, it was diluted with dichloromethane and layers separated. The aqueous layer was extracted with dichloromethane (30 mL x 3). The combined layer was washed with water, dried over Na_2SO_4, evaporated and the orange residue purified on silica gel column using ethyl acetate and light petroleum (1:3) to afford the *cis* isomer **83** (860 mg, 26%) as a solid.

Melting point: 130 °C.

$[\alpha]_D$ = –82.2 (*c* 1.2, $CHCl_3$).

IR (liquid film, $CHCl_3$) ν_{max} (cm^{-1}): 3408, 3019, 1797, 1718, 1655, 1609, 1499, 1441, 1147.

^{1}H NMR (200 MHz, $CDCl_3$): δ 7.40-7.29 (m, 15H), 6.45 (d, 1H, *J* = 2.1 Hz), 6.37 (d, 1H, *J* = 2.1 Hz), 6.05 (d, 1H, *J* = 5.3 Hz), 5.12 (s, 2H), 5.08 (s, 2H), 4.99 (s, 2H), 4.90 (dd, 1H, *J* = 10.6, 4.0 Hz), 4.75-4.69 (m, 1H), 4.36 (m, 1H), 2.89-2.40 (m, 5H), 1.48-1.34 (m, 2H).

^{13}C (50 MHz, $CDCl_3$): 170.0, 158.4, 156.0, 155.8, 137.2, 136.6, 136.4, 136.4, 128.7, 128.5, 128.4, 128.1, 128.0, 127.9, 127.4, 127.0, 117.1, 105.7, 98.9, 70.0, 66.6, 50.0, 48.7, 38.8, 29.6, 28.3, 25.5.

MS (ESI) m/z: 585.63 (M^+ + Na).

Anal. Calcd for $C_{35}H_{34}N_2O_5$: C, 74.71; H, 6.09; N, 4.98. **Found:** C, 74.93; H, 6.02; N, 4.88.

Further elution gave the *trans* isomer **84** (1.3 g, 39%) as a liquid.

$[\alpha]_D$ = +93.6 (*c* 1.05, $CHCl_3$).

IR (liquid film, $CHCl_3$) ν_{max} (cm^{-1}): 3405, 3019, 1797, 1720, 1650, 1609, 1499, 1441, 1147.

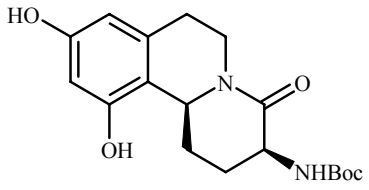
^{1}H NMR (200 MHz, $CDCl_3$): δ 7.42-7.26 (m, 15 H), 6.47 (d, 1H, *J* = 2.2 Hz), 6.34 (d, 1H, *J* = 2.2 Hz), 5.70 (br. s, 1H), 5.09 (s, 2H), 5.02 (d, 2H, *J* = 2.5 Hz), 5.00 (s, 2H), 4.96-4.87 (m, 1H), 4.77 (dd, 1H, *J* = 10.9, 3.4 Hz), 4.04 (m, 1H), 3.08-3.02 (m, 1H), 2.93-2.73 (m, 1H), 2.66-2.43 (m, 3H), 1.77 (dt, 1H, *J* = 13.5, 12.3 Hz), 1.54-1.34 (m, 1H).

^{13}C (50 MHz, $CDCl_3$): 168.3, 158.0, 156.6, 156.3, 137.7, 136.6, 136.4, 136.3, 128.5, 128.4, 128.4, 128.2, 127.9, 127.9, 127.7, 127.3, 126.9, 118.1, 106.0, 99.0, 70.0, 69.9, 66.4, 55.8, 52.7, 39.3, 30.4, 27.9, 27.3.

MS (ESI) m/z: 585.63 (M^+ + Na).

Anal. Calcd for $C_{35}H_{34}N_2O_5$: C, 74.71; H, 6.09; N, 4.98. **Found**: C, 74.85; H, 5.95; N, 4.76.

tert-Butyl (3*S*,11b*S*)-9,11-dihydroxy-4-oxo-2,3,4,6,7,11b-hexahydro-1H-pyrido[2,1-a]isoquinolin-3-ylcarbamate (87)



87

A suspension of **83** (1.8 g, 3.2 mmol) and 10% Pd/C (100 mg) in methanol (15 mL) was hydrogenated at normal pressure and temperature for 5 h. Boc_2O (1.0 mL, 4.16 mmol) was added to the reaction mixture and stirred for 5 h at room temperature. The catalyst was removed by filtration through a pad of Celite and the filtrate was concentrated. The residue was purified on silica gel by eluting with ethyl acetate and light petroleum (1.5:3.5) to afford **87** (1.08 g, 96%) as a gummy paste.

$[\alpha]_D$ = –49.1 (*c* 0.9, CH_3OH).

IR (nujol) ν_{max} (cm^{-1}): 3274, 2924, 2854, 1683, 1646, 1511, 1464, 1376, 1277, 1251, 1159, 1055, 947, 842.

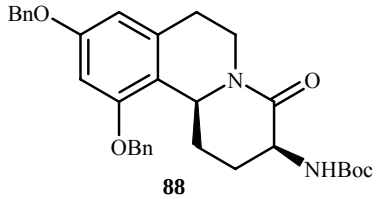
^{1}H NMR (200 MHz, CD_3OD): δ 6.18 (d, 1H, *J* = 2.3 Hz), 6.11 (d, 1H, *J* = 2.3 Hz), 4.81 (dd, 1H, *J* = 11.2, 3.8 Hz), 4.56 (m, 1H), 4.31 (dd, 1H, *J* = 10.6, 7.3 Hz), 2.70-2.27 (m, 5H), 1.56-1.49 (m, 1H), 1.46 (s, 9H), 1.37-1.31 (m, 1H).

^{13}C (50 MHz, CD_3OD): 172.3, 157.8, 156.0, 138.3, 115.0, 107.2, 101.9, 80.5, 51.0, 50.7, 40.3, 30.2, 29.1, 28.7.

MS (ESI) m/z: 371.64 (M^+ + Na).

Anal. Calcd for $C_{18}H_{24}N_2O_5$: C, 62.05; H, 6.94; N, 8.04. **Found:** C, 62.0; H, 6.74; N, 7.81.

***tert*-Butyl (3*S*,11b*S*)-9,11-bis(benzyloxy)-4-oxo-2,3,4,6,7,11b-hexahydro-1H-pyrido[2,1-a]isoquinolin-3-ylcarbamate (88)**



88

To a solution of the above diol **87** (840 mg, 2.41 mmol), $CsCO_3$ (2.36 g, 7.24 mmol), TBAI (20 mg) in dry DMF (5 mL) at 0 ^oC, benzyl bromide (0.63 mL, 5.3 mmol) was added. After 1 h, the reaction was diluted with ice-water and extracted with ethyl acetate (20 mL x 3). The combined organic layer was washed with water, dried over anhydrous Na_2SO_4, concentrated and the residue was purified on silica gel by eluting with ethyl acetate and light petroleum (1:3) to afford (3*S*,11b*S*)-**88** (1.18 g, 92%), as a white powder.

Melting point: 118 °C.

$[\alpha]_D$ = −102 (c 1.1, $CHCl_3$).

IR (liquid film, $CHCl_3$) ν_{max} (cm^{-1}): 3412, 3018, 2931, 1707, 1653, 1609, 1497, 1442, 1367, 1147, 1060.

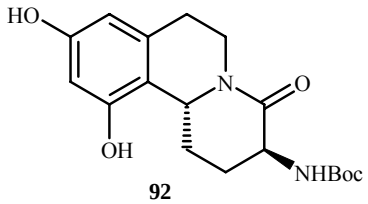
^{1}H NMR (200 MHz, $CDCl_3$): δ 7.35 (m, 10 H), 6.45 (d, 1H, *J* = 2.2 Hz), 6.36 (d, 1H, *J* = 2.2 Hz), 5.75 (d, 1H, *J* = 5.3 Hz), 5.05 (s, 2H), 4.97 (s, 2H), 4.89 (dd, 1H, *J* = 10.3, 4.0 Hz), 4.76-4.68 (m, 1H), 4.30 (m, 1H), 2.86-2.40 (m, 5H), 1.46 (s, 9 H), 1.42-1.34 (m, 2H).

^{13}C (50 MHz, $CDCl_3$): δ 170.1, 158.2, 155.7, 155.4, 137.0, 136.5, 136.2, 128.5, 128.3, 127.9, 127.8, 127.2, 126.8, 117.1, 105.7, 98.8, 79.0, 69.9, 69.8, 49.5, 48.5, 38.6, 29.5, 29.4, 28.3, 28.2.

MS (ESI) m/z: 551.91 (M^+ + Na).

Anal. Calcd for $C_{32}H_{36}N_2O_5$: C, 72.70; H, 6.86; N, 5.30. **Found:** C, 72.85; H, 6.98; N, 5. 17.

tert-Butyl (3*S*,11b*R*)-9,11-dihydroxy-4-oxo-2,3,4,6,7,11b-hexahydro-1H-pyrido[2,1-a]isoquinolin-3-ylcarbamate (92)



92

Compound **84** was transformed into **92** (97%) by using the same procedure as in case of **87**.

$[\alpha]_D$ = +122 (*c* 1.4, CH_3OH).

IR (nujol) ν_{max} (cm^{-1}): 3274, 2924, 2854, 1683, 1646, 1511, 1464, 1376, 1277, 1251, 1159, 1055, 947, 842.

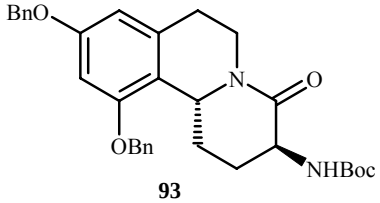
^{1}H NMR (200 MHz, CD_3OD): δ 6.16 (d, 1H, *J* = 1.9 Hz), 6.08 (d, 1H, *J* = 1.9 Hz), 4.80 (dd, 1H, *J* = 3.3 Hz), 4.74 (dd, 1H, *J* = 2.8), 3.96 (m, 1H), 3.15-3.0 (m, 1H), 2.72-2.48 (m, 3H), 2.19-1.76 (m, 3H), 1.45 (s, 9H).

^{13}C (50 MHz, CD_3OD): 171.0, 159.6, 157.6, 156.6, 138.6, 115.9, 107.6, 102.1, 57.2, 40.8, 31.0, 29.4, 28.7.

MS (ESI) m/z: 371.61 (M^+ + Na).

Anal. Calcd for $C_{18}H_{24}N_2O_5$: C, 62.05; H, 6.94; N, 8.04. **Found:** C, 61.96; H, 6.70; N, 7.85.

***tert*-Butyl (3*S*,11b*R*)-9,11-bis(benzyloxy)-4-oxo-2,3,4,6,7,11b-hexahydro-1H-pyrido[2,1-a]isoquinolin-3-ylcarbamate (93)**



93

Compound **92** was transformed into **93** (91%) by using the same procedure as in case of **88**.

$[\alpha]_D$ = +116 (*c* 1.35, $CHCl_3$).

IR (liquid film, $CHCl_3$) ν_{max} (cm^{-1}): 3412, 3018, 2931, 1707, 1653, 1609, 1497, 1442, 1367, 1147, 1060.

^{1}H NMR (200 MHz, $CDCl_3$): δ 7.42-7.34 (m, 10H), 6.47 (d, 1H, *J* = 2.3Hz), 6.35 (d, 1H, *J* = 2.3 Hz), 5.33 (d, 1H, *J* = 5.0 Hz), 5.04-5.0 (m, 4H), 4.96-4.88 (m, 1H), 4.78 (dd, 1H, *J*

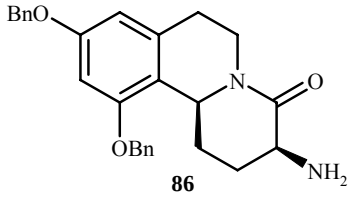
= 11.0, 3.7 Hz), 3.99 (m, 1H), 3.13-2.78 (m, 2H), 2.69-2.41 (m, 3H), 1.83-1.64 (m, 2H), 1.45 (s, 9H).

^{13}C (50 MHz, $CDCl_3$): 168.7, 158.1, 156.7, 156.1, 137.8, 136.6, 136.4, 128.6, 128.5, 128.0, 127.4, 127.1, 118.3, 106.0, 99.0, 79.4, 70.1, 70.0, 56.1, 52.7, 39.4, 30.5, 29.6, 28.3, 27.9.

MS (ESI) m/z: 551.91 (M^+ + Na).

Anal. Calcd for $C_{32}H_{36}N_2O_5$: C, 72.70; H, 6.86; N, 5.30. **Found:** C, 72.61; H, 6.77; N, 5.23.

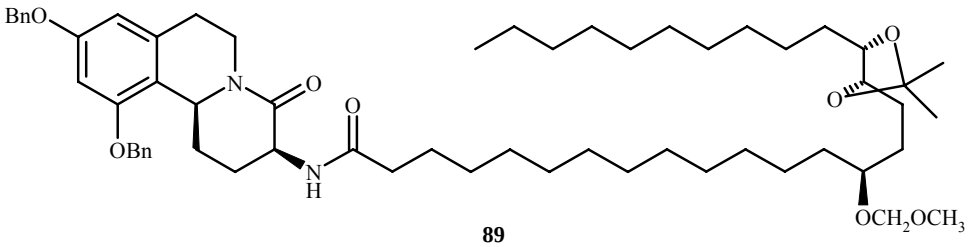
(3*S*,11b*S*)-3-Amino-9,11-bis(benzyloxy)-2,3,6,7-tetrahydro-1H-pyrido[2,1 a]isoquinolin-4(11bH)-one (86)



86

A suspension of compound **88** (450 mg, 0.84 mmol) and 3N-HCl in ethyl acetate (8 mL) were stirred for 3 h at room temperature, diluted with ethyl acetate and neutralized with sodium bicarbonate solution. The aqueous phase was extracted with ethyl acetate (10 mL x 3). The combined organic layer was dried over anhydrous Na_2SO_4 and concentrated to give the free amine **86** (346 mg).

(*S*)-N-((3*S*,11b*S*)-9,11-Bis(benzyloxy)-4-oxo-2,3,4,6,7,11b-hexahydro-1H-pyrido[2,1-a]isoquinolin-3-yl)-16-((4*S*,5*S*)-5-decyl-2,2-dimethyl-1,3-dioxolan-4-yl)-14-(methoxymethoxy)hexadecanamide (89)



89

To a solution of **71** (200 mg, 0.36 mmol), HOBt (73 mg, 0.54 mmol), EDC (90 mg, 0.47 mmol) in dry dichloromethane (5 mL) was added a solution of **86** (170 mg, 0.39 mmol) in dry dichloromethane (2 mL) followed by dry triethylamine (0.1 mL). After stirring for 15 h at room temperature, the reaction mixture was diluted with water, extracted with dichloromethane (10 mL x 2). The combined organic layer was washed with water, dried over anhydrous Na_2SO_4 and concentrated to give a crude oil which was purified on silica gel by using ethyl acetate and light petroleum (1:3) to afford **89** (252 mg, 72%) as colorless liquid.

$[\alpha]_D$ = –52.9 (*c* 0.65, $CHCl_3$).

IR (liquid film, $CHCl_3$) ν_{max} (cm^{-1}): 3395, 3011, 2926, 2854, 1731, 1646, 1609, 1498, 1465, 1378, 1150, 1095, 1040.

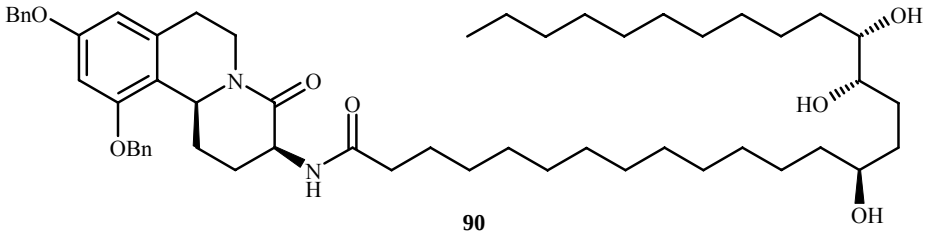
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.41-7.32 (m, 10 H), 6.78 (d, 1H, *J* = 5.3 Hz), 6.46 (d, 1H, *J* = 2.2 Hz), 6.39 (d, 1H, *J* = 2.2 Hz), 5.09 (s, 2H), 4.99 (s, 2H), 4.93 (dd, 1H, *J* = 10.5, 4.0 Hz), 4.79-4.70 (m, 1H), 4.65 (s, 2H), 4.54 (m, 1H), 3.65-3.49 (m, 3H), 3.38 (s, 3H), 2.89-2.62 (m, 4H), 2.57-2.43 (m, 1H), 2.25 (t, 2H, *J* = 7.5 Hz), 1.79-1.45 (m, 15H), 1.37 (s, 6H), 1.35-1.20 (m, 31H), 0.88 (t, 3H, *J* = 6.5 Hz).

^{13}C (50 MHz, $CDCl_3$): 172.9, 170.4, 158.3, 155.8, 137.0, 136.5, 136.3, 128.7, 128.5, 128.0, 127.9, 127.3, 126.9, 117.0, 107.6, 105.7, 98.9, 95.3, 81.1, 80.9, 77.4, 70.0, 55.4, 48.6, 38.7, 36.6, 34.3, 32.8, 31.8, 30.8, 29.7, 29.6, 29.5, 29.4, 29.3, 29.2, 29.2, 29.1, 28.7, 28.4, 27.2, 26.0, 25.6, 25.1, 25.1, 22.5, 14.0.

MS (ESI) m/z: 989.75 (M^+ + Na).

Anal. Calcd for $C_{60}H_{90}N_2O_8$: C, 74.50; H, 9.38; N, 2.90. **Found:** C, 74.33; H, 9.25; N, 2.84.

(14*S*,17*S*,18*S*)-N-((3*S*,11b*S*)-9,11-Bis(benzyloxy)-4-oxo-2,3,4,6,7,11b-hexahydro-1H-pyrido[2,1a]isoquinolin-3-yl)-14,17,18-trihydroxyoctacosanamide (90)



90

A solution of **89** (120 mg, 0.12 mmol) and TMSI (freshly prepared from TMS-Cl and sodium iodide in acetonitrile) (0.5 g, 0.25 mmol) in dichloromethane (6 mL) and acetonitrile (2 mL) under nitrogen at 0 °C was stirred for 1 h and then 10% $NaHCO_3$ solution was added and layers separated. The aqueous layer was extracted with dichloromethane (25 mL x 3), the combined organic layer was dried over anhydrous Na_2SO_4, concentrated and purified on silica gel by using ethyl acetate to afford **90** (44 mg, 47%).

$[\alpha]_D$ = –79.4 (*c* 0.5, $CHCl_3$).

IR (liquid film, $CHCl_3$) ν_{max} (cm^{-1}): 3394, 3016, 2925, 2853, 1636, 1608, 1498, 1465, 1375, 1358, 1308, 1271, 1151, 1090, 1048.

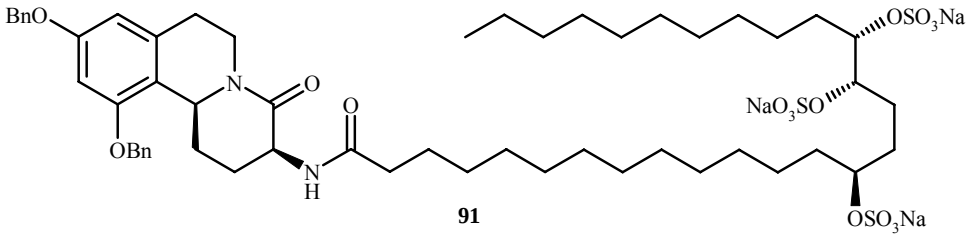
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.41-7.33 (m, 10 H), 6.78 (d, 1H, *J* = 5.4 Hz), 6.47 (d, 1H, *J* = 2.2 Hz), 6.39 (d, 1H, *J* = 2.2 Hz), 5.09 (s, 1H), 5.09 (s, 1H), 4.99 (s, 2H), 4.94 (dd, 1H, *J* = 10.7, 4.2 Hz), 4.74-4.70 (m, 1H), 4.53 (m, 1H), 3.70-3.64 (m, 1H), 3.47-3.42 (m, 2H), 2.86-2.75 (m, 2H), 2.72-2.65 (m, 2H), 2.52-2.47 (m, 1H), 2.25 (t, 2H, *J* = 7.6 Hz), 1.72-1.40 (m, 15H), 1.37-1.25 (m, 31H), 0.88 (t, 3H, *J* = 6.8 Hz).

^{13}C (100 MHz, $CDCl_3$): 173.1, 170.5, 158.5, 155.9, 137.1, 136.7, 136.4, 128.8, 128.6, 128.1, 128.1, 127.5, 127.0, 117.2, 105.8, 99.1, 74.6, 74.4, 71.9, 70.1, 48.8, 38.9, 37.5, 36.7, 33.5, 33.0, 31.8, 29.6, 29.5, 29.5, 29.4, 29.4, 29.3, 29.2, 28.5, 25.7, 25.6, 25.2, 22.6, 14.0.

MS (ESI) m/z: 905.38 (M^+ + Na).

Anal. Calcd for $C_{55}H_{82}N_2O_7$: C, 74.79; H, 9.36; N, 3.17. **Found:** C, 74.82; H, 9.18; N, 2.92.

Sodium (11*S*,12*S*,15*S*)-28-((3*S*,11b*S*)-9,11-bis(benzyloxy)-4-oxo-2,3,4,6,7,11b-hexahydro-1H-pyrido[2,1-a]isoquinolin-3-ylamino)-28-oxooctacosane-11,12,15-triyl trisulfate (91)



91

Sulfur trioxide/pyridine complex (110 mg, 0.69 mmol) was added to a solution of the 28 (20 mg, 0.023 mmol) in dry DMF (3 mL) under nitrogen and then stirred at room temperature for 30 h. The reaction mixture was basified by adding $NaHCO_3$ solution. After stirring for 30 min, the resulting solution was concentrated in *vacuo.* The residue was triturated with ethyl acetate and filtered. The residue was purified on silica gel column by using methanol and ethyl acetate (1:4) to afford sulfate salt **91** (27 mg, 96%).

$[\alpha]_D$ = –24.0 (*c* 0.5, CH_3OH).

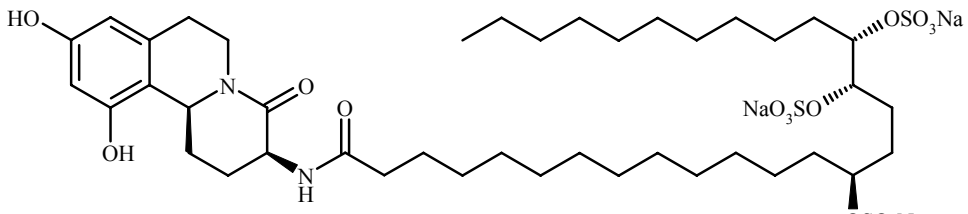
IR (nujol) ν_{max} (cm^{-1}): 2923, 2853, 1631, 1464, 1378, 1221, 1109, 1090, 824.

^{1}H NMR (400 MHz, CD_3OD): δ 7.42-7.28 (m, 10 H), 6.57 (d, 1H, *J* = 2.1 Hz), 6.45 (d, 1H, *J* = 2.1 Hz), 5.09 (d, 2H, *J* = 6.8 Hz), 5.03 (s, 2H), 4.90 (dd, 2H, *J* = 11.0, 3.8 Hz), 4.65 (m, 2H), 4.59 (dd, 1H, *J* = 9.7, 7.9 Hz), 4.36 (m, 1H), 2.78-2.69 (m, 3H), 2.50 (m, 1H), 2.26 (t, 2H, *J* = 7.4 Hz), 2.21 (m, 1H), 1.95-1.90 (m, 2H), 1.87-1.81 (m, 1H), 1.75-1.50 (m, 10H), 1.45-1.36 (m, 3H), 1.30-1.22 (m, 30H), 0.87 (t, 3H, *J* = 6.6 Hz).

^{13}C (100 MHz, CD_3OD): 176.1, 171.7, 159.8, 157.3, 138.6, 138.4, 138.2, 129.6, 129.4, 129.0, 128.8, 128.4, 128.3, 118.1, 107.4, 100.1, 81.1, 79.9, 78.8, 71.2, 71.0, 51.3, 49.5, 40.1, 36.9, 35.3, 32.9, 31.5, 30.8, 30.7, 30.7, 30.6, 30.5, 30.4, 30.3, 30.2, 29.7, 29.3, 26.8, 25.9, 25.8, 25.7, 24.2, 23.6, 14.4.

MS (ESI) m/z: 1211.48 (M^+ + Na).

Schulzeine B (2)



2

A solution of sulfate salt **91** (24 mg) and 10% Pd/C in methanol (4 mL) was hydrogenated at normal temperature and pressure for 3 h and filtered. The catalyst was washed with methanol (2 x 2 mL) and combined filtrate concentrated to obtain Schulzeine B (**2**) (17 mg, 83%).

$[\alpha]_D$ = –24.4 (*c* 0.6, CH_3OH).

Lit **$[\alpha]_D$** = –23 (*c* 0.1, CH_3OH).

IR (nujol) ν_{max} (cm^{-1}): 3416, 2923, 2853, 1628, 1460, 1376, 1220, 1063, 1002, 773.

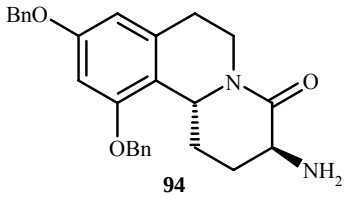
^{1}H NMR (400 MHz, CD_3OD): δ 6.21 (d, 1H, *J* = 2.3 Hz), 6.13 (d, 1H, *J* = 2.3 Hz), 4.84 (m, 1H), 4.64 (m, 4H), 4.36 (m, 1H), 2.74-2.53 (m, 4H), 2.28 (t, 2H, *J* = 7.5 Hz), 2.24 (m, 1H), 1.93 (m, 2H), 1.85 (m, 1H), 1.77-1.53 (m, 10H), 1.45-1.37 (m, 3H), 1.28 (m, 30H), 0.88 (t, 3H, *J* = 6.8 Hz).

^{1}H NMR (400 MHz, Pyridine-d_5): δ 8.26 (d, 1H, *J* = 6.85 Hz), 6.89 (d, 1H, *J* = 2.03 Hz), 6.61 (d, 1H, *J* = 2.03 Hz), 5.79 (m, 1H), 5.47 (m, 1H), 5.25 (dd, 1H, *J* = 11.0, 4.0 Hz), 5.17-5.09 (m, 2H), 5.99 (m, 1H), 2.91-2.62 (m, 4H), 2.50 (t, 2H, *J* = 7.34 Hz), 2.40 (m, 1H), 2.16 (m, 2H), 1.96 (m, 1H), 1.91-1.55 (m, 10 H), 1.45 (m, 3H), 1.31-1.22 (m, 30 H), 0.92 (t, 3H, *J* = 6.8 Hz).

^{13}C (100 MHz, CD_3OD): δ 176.2, 171.8, 157.9, 156.1, 138.3, 115.0, 107.3, 101.9, 81.2, 80.0, 80.0, 51.7, 49.6, 40.4 37.0, 35.4, 31.6, 30.8, 30.7, 30.7, 30.5, 30.4, 30.3, 30.3, 30.2, 29.8, 28.9, 26.9, 26.8, 26.0, 25.9, 23.6, 14.4.

MS (ESI) m/z: 1031.71 (M^+ + Na).

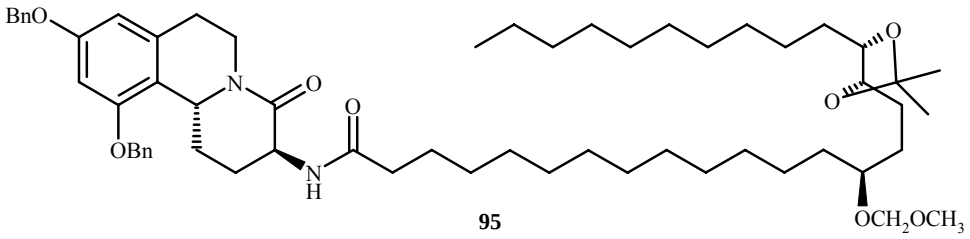
(3*S*,11b*R*)-3-Amino-9,11-bis(benzyloxy)-2,3,6,7-tetrahydro-1H-pyrido[2,1-a]isoquinolin-4(11bH)-one (94)



94

The free amine **94** was prepared as described above from compound **93** and used immediately for the next reaction.

(*S*)-N-((3*S*,11b*R*)-9,11-Bis(benzyloxy)-4-oxo-2,3,4,6,7,11b-hexahydro-1H-pyrido[2,1-a]isoquinolin-3-yl)-16-((4*S*,5*S*)-5-decyl-2,2-dimethyl-1,3-dioxolan-4-yl)-14(methoxymethoxy)hexadec-anamide (95)



95

Compound **95** was prepared by applying the same procedure as described for **89**.

$[\alpha]_D$ = +76.7 (*c* 2.4, $CHCl_3$).

IR (liquid film, $CHCl_3$) ν_{max} (cm^{-1}): 3317, 3009, 2928, 2855, 1635, 1607, 1498, 1463, 1378, 1307, 1269, 1151, 1093, 1039.

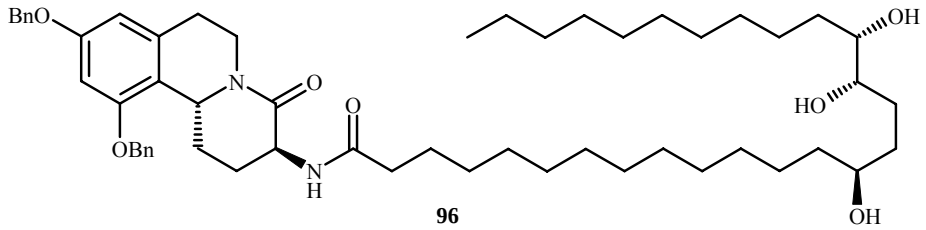
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39-7.31 (m, 10H), 6.48 (d, 1H, *J* = 2.1 Hz), 6.35 (d, 1H, *J* = 2.1 Hz), 6.30 (d, 1H, *J* = 4.9 Hz), 5.07-4.97 (m, 4H), 4.93-4.88 (m, 1H), 4.78 (dd, 1H, *J* = 10.9, 3.6 Hz), 4.64 (s, 2H), 4.19 (m, 1H), 3.63-3.48 (m, 3H), 3.37 (s, 3H), 3.07 (dq, 1H, *J* = 13.7, 3.5 Hz), 2.91-2.77 (m, 1H), 2.67-2.54 (m, 3H), 2.21 (t, 2H, *J* = 7.5 Hz), 1.77-1.59 (m, 7H), 1.55-1.42 (m, 8H), 1.36 (s, 6H), 1.34-1.20 (m, 31H), 0.88 (t, 3H, *J* = 6.7 Hz).

^{13}C (50 MHz, $CDCl_3$): δ 173.5, 168.7, 158.1, 156.7, 137.7, 136.6, 136.3, 128.6, 128.5, 128.5, 128.0, 127.9, 127.3, 127.0, 118.1, 107.7, 105.9, 99.1, 95.4, 81.1, 80.9, 77.4, 70.1, 69.9, 56.1, 55.4, 51.9, 39.5, 36.6, 34.4, 32.9, 31.8, 30.9, 30.5, 29.8, 29.7, 29.6, 29.5, 29.5, 29.4, 29.3, 29.3, 29.2, 28.8, 27.9, 27.3, 26.1, 25.6, 25.2, 22.6, 14.1.

MS (ESI) m/z: 989.75 (M^+ + Na).

Anal. Calcd for $C_{60}H_{90}N_2O_8$: C, 74.50; H, 9.38; N, 2.90. **Found:** C, 74.68; H, 9.17; N, 2.87

(14*S*,17*S*,18*S*)-N-((3*S*,11b*R*)-9,11-Bis(benzyloxy)-4-oxo-2,3,4,6,7,11b-hexahydro-1H-pyrido[2,1-a]isoquinolin-3-yl)-14,17,18-trihydroxyoctacosanamide (96)



96

Compound **96** was prepared from **95** by applying the same procedure as described for **90**.

$[\alpha]_D$ =+ 92.3 (*c* 1.2, $CHCl_3$).

IR (liquid film, $CHCl_3$) ν_{max} (cm^{-1}): 3394, 3016, 2925, 2853, 1636, 1608, 1498, 1465, 1375, 1358, 1308, 1271, 1151, 1090, 1048.

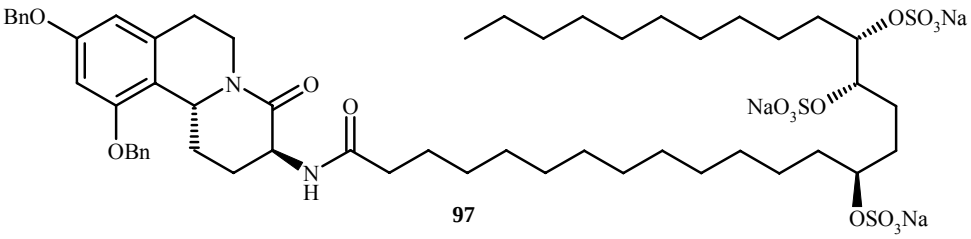
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.43-7.32 (m, 10H), 6.50 (d, 1H, *J* = 2.2 Hz), 6.37 (d, 1H, *J* = 2.2 Hz), 5.08-5.00 (m, 4H), 4.94-4.88 (m, 1H), 4.79 (dd, 1H, *J* = 11.0, 3.2 Hz), 4.21 (m, 1H), 3.65 (m, 1H), 3.44 (m, 2H), 3.11-3.04 (m, 1H), 2.91-2.78 (m, 1H), 2.68-2.52 (m, 3H), 2.22 (t, 2H, *J* = 7.6 Hz), 1.71-1.60 (m, 7H), 1.57-1.38 (m, 8H), 1.36-1.20 (m, 31H), 0.88 (t, 3H, *J* = 6.8 Hz).

^{13}C (100 MHz, $CDCl_3$): δ 173.7, 168.8, 158.2, 156.8, 137.7, 136.6, 136.4, 128.6, 128.6, 128.5, 128.1, 127.5, 127.1, 118.1, 106.1, 99.1, 74.5, 74.4, 71.8, 70.2, 70.1, 56.2, 51.9, 39.5, 37.4, 36.7, 33.5, 33.1, 31.9, 30.6, 29.7, 29.6, 29.5, 29.3, 29.2, 29.2, 27.7, 27.2, 25.7, 25.6, 25.6, 22.7, 14.1.

MS (ESI) m/z: 905.38 (M^+ + Na).

Anal. Calcd for $C_{55}H_{82}N_2O_7$: C, 74.79; H, 9.36; N, 3.17. **Found:** C, 74.65; H, 9.22; N, 3.12.

Sodium (11*S*,12*S*,15*S*)-28-((3*S*,11b*R*)-9,11-bis(benzyloxy)-4-oxo-2,3,4,6,7,11b-hexahydro-1H-pyrido[2,1-a]isoquinolin-3-ylamino)-28-oxooctacosane-11,12,15-triyl trisulfate (97)



97

Compound **97** was prepared from **96** by applying the procedure described for **91**.

$[\alpha]_D$ = +24.1 (*c* 1, CH_3OH).

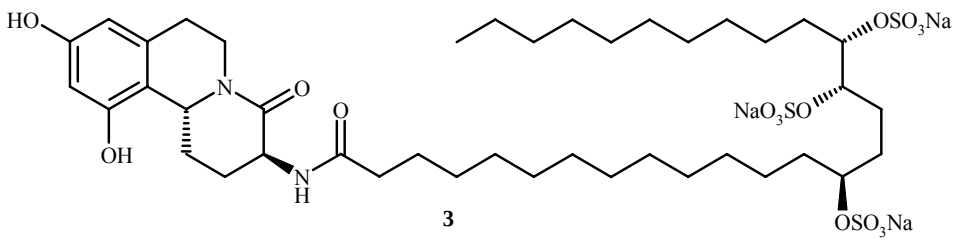
IR (liquid film, CH_3OH) ν_{max} (cm^{-1}): 2947, 2835, 1650, 1449, 1418, 1220, 1113, 1026.

^{1}H NMR (400 MHz, CD_3OD): δ 7.42-7.29 (m, 10H), 6.58 (d, 1H, *J* = 2.2 Hz), 6.42 (d, 1H, *J* = 2.2 Hz), 5.12-5.04 (m, 4H), 4.77 (m, 2H), 4.67 (m, 2H), 4.35 (dt, 1H, *J* = 11.1, 5.7 Hz), 4.22 (dd, 1H, *J* = 11.5, 6.9 Hz), 2.95 (dq, 1H, *J* = 13.5, 3.2 Hz), 2.77 (m, 1H), 2.66-2.60 (m, 2H), 2.22 (dt, 2H, *J* = 7.4, 2.2 Hz), 2.06 (m, 1H), 1.94 (m, 1H), 1.90 (m, 1H), 1.75-1.51 (m, 10H), 1.40 (m, 4H), 1.27 (m, 30H), 0.88 (t, 3H, *J* = 6.7 Hz).

^{13}C (100 MHz, CD_3OD): δ 176.1, 170.5, 159.7, 158.0, 139.0, 138.6, 138.3, 129.6, 129.5, 129.0, 128.8, 128.5, 128.4, 119.1, 107.7, 100.2, 81.2, 80.0, 79.9, 71.3, 71.1, 56.9, 52.0, 40.6, 37.1, 35.54, 31.7, 31.2, 30.8, 30.8, 30.7, 30.7, 30.7, 30.6, 30.4, 30.4, 30.2, 29.9, 29.8, 28.7, 28.4, 26.9, 26.8, 25.9, 25.8, 23.7, 14.4.

MS (ESI) m/z: 1211.48 (M^+ + Na).

Synthesis of Schulzeine C (3)



3

Schulzeine C (**3**) was prepared from **97** by applying the same procedure described for schulzeine B (**2**).

$[\alpha]_D$ = +35.5 (*c* 1.2, CH_3OH).

Lit **$[\alpha]_D$** = +33 (*c* 0.1, CH_3OH).

IR (nujol) ν_{max} (cm^{-1}): 3341, 2923, 2853, 1603, 1462, 1376, 1253, 1220, 1150, 1063, 951.

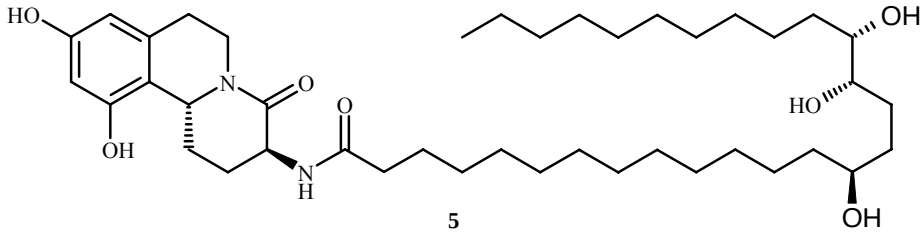
^{1}H NMR (400 MHz, CD_3OD): δ 6.19 (d, 1H, *J* = 2.3 Hz), 6.09 (d, 1H, *J* = 2.3 Hz), 4.79 (m, 2H), 4.66 (m, 2H), 4.35 (q, 1H, *J* = 5.6 Hz), 4.28 (dd, 1H, *J* = 11.8, 6.8 Hz), 3.07 (dq, 1H, *J* = 14.0, 3.4 Hz), 2.69 (d, 1H, *J* = 13.2 Hz), 2.63 (dt, 1H, *J* = 11.7, 2.0 Hz), 2.53 (d, 1H, *J* = 16.6 Hz), 2.23 (dt, 2H, *J* = 7.4, 2.4 Hz), 2.09 (m, 1H), 1.94 (m, 2H), 1.75-1.50 (m, 10H), 1.42-1.39 (m, 4H), 1.36-1.25 (m, 30H), 0.88 (t, 3H, *J* = 6.8 Hz).

^{1}H NMR (400 MHz, Pyridine-d_5): δ 8.58 (d, 1H, *J* = 7.3 Hz), 6.86 (d, 1H, *J* = 2.0 Hz), 6.59 (d, 1H, *J* = 2.0 Hz), 5.76 (m, 1H), 5.45 (m, 1H), 5.20 (dd, 1H, *J* = 12.4, 3.9 Hz), 5.14-5.08 (m, 2H), 4.88 (m, 1H), 3.53 (dq, 1H, *J* = 13.6, 3.5 Hz), 2.91 (m, 1H), 2.68 (m, 1H), 2.59-2.35 (m, 4H), 2.21-2.15 (m, 2H), 1.99-1.68 (m, 11H), 1.62-1.56 (m, 3H), 1.48-1.41 (m, 4H), 1.34-1.22 (m, 26H), 0.91 (t, 3H, *J* = 7.0 Hz).

^{13}C (100 MHz, CD_3OD): δ 176.1, 170.5, 157.6, 156.7, 138.6, 115.9, 107.6, 102.1, 81.2, 80.0, 79.9, 57.2, 52.0, 40.8, 37.1, 35.4, 31.7, 30.8, 30.8, 30.7, 30.7, 30.7, 30.6, 30.4, 30.4, 30.2, 29.8, 29.4, 28.4, 26.9, 26.8, 25.9, 25.8, 23.7, 14.4.

MS (ESI) m/z: 1031.71 (M^+ + Na).

Desulfated schulzeine C (5)



5

A solution of triol **96** (20 mg) and 10% Pd/C in methanol (4 mL) was hydrogenated at normal temperature and pressure for 3 h and filtered. The catalyst was washed with methanol (2 × 2 mL) and combined filtrate concentrated to obtain de-schulzeine C (**5**) (14 mg, 89%).

$[\alpha]_D$ = +73.86 (*c* 0.6, CH_3OH).

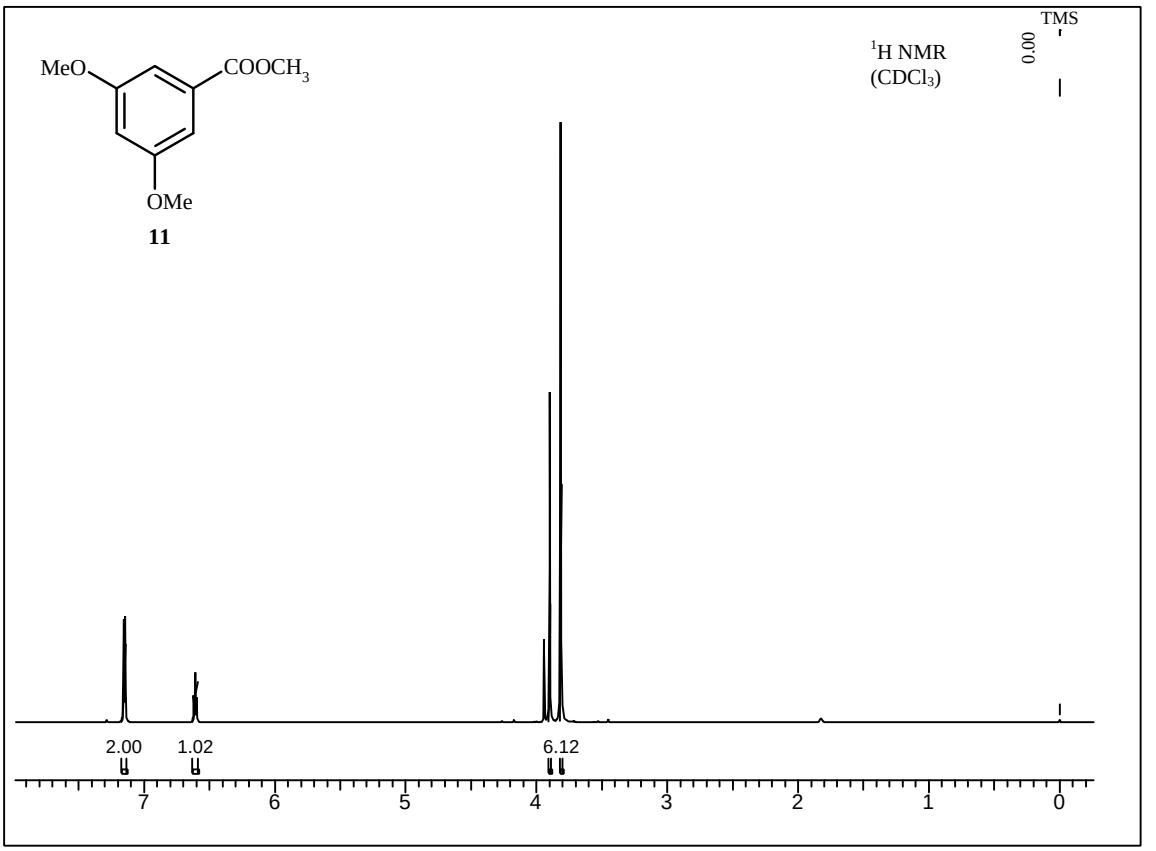
IR (liquid film, CH_3OH) ν_{max} (cm^{-1}): 3299, 2924, 2854, 1654, 1633, 1543, 1461, 1377.

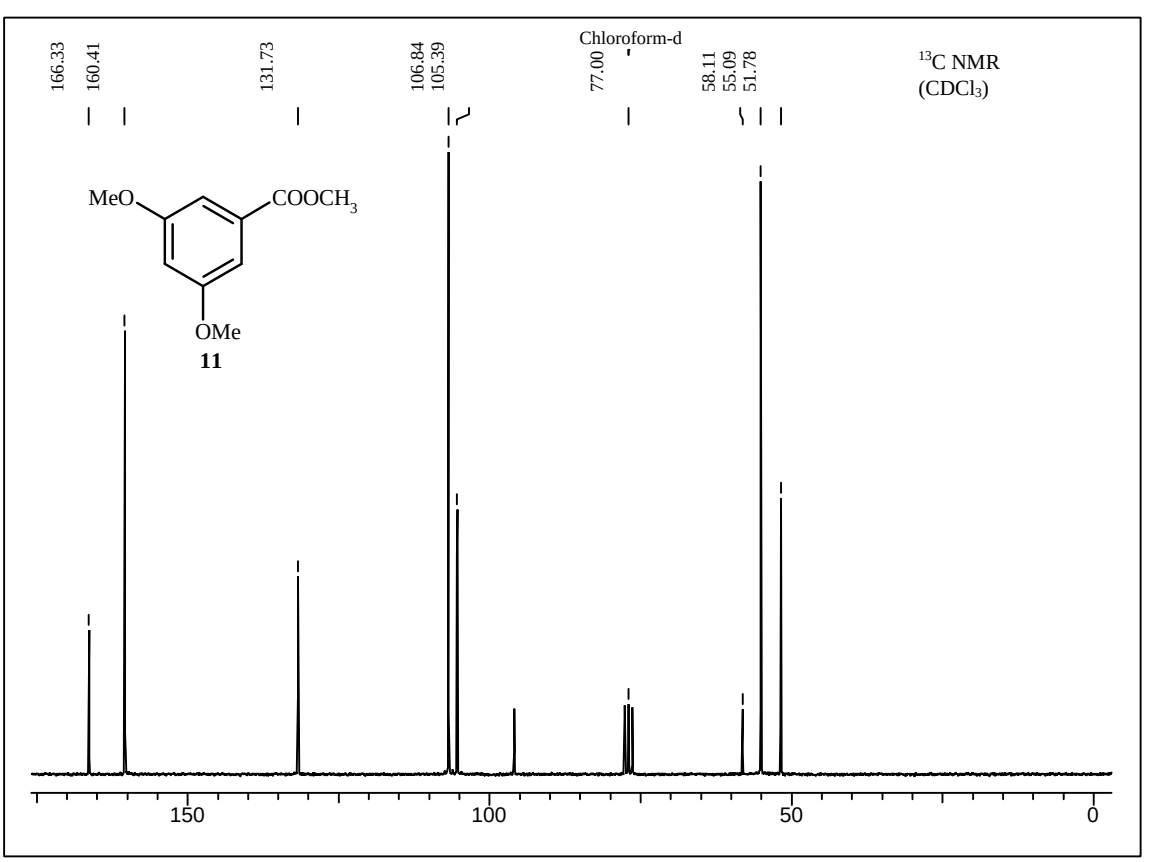
^{1}H NMR (400 MHz, CD_3OD): δ 6.18 (d, 1H, *J* = 2.3 Hz), 6.09 (d, 1H, *J* = 2.3 Hz), 4.79-4.76 (m, 2H), 4.25 (m, 1H), 3.52 (m, 1H), 3.37 (m, 2H), 3.08 (dq, 1H, *J* = 3.4, 13.9 Hz), 2.74-2.51 (m, 3H), 2.22 (dt, 2H, *J* = 7.5, 3.0 Hz), 2.10 (m, 1H), 1.96-1.87 (m 1H), 1.68-1.58 (m, 5H), 1.46-1.38 (m, 6H), 1.26 (m, 34H), 0.87 (t, 3H, *J* = 6.9 Hz).

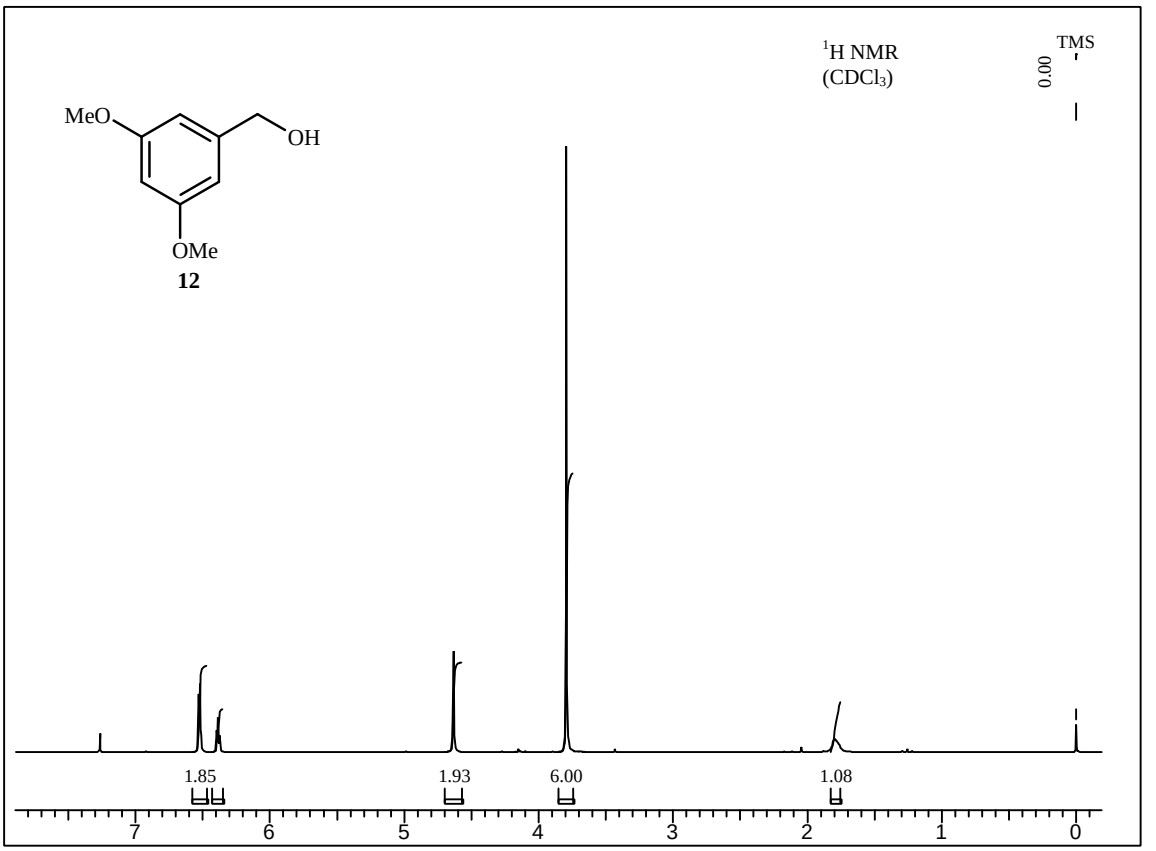
^{13}C (100 MHz, CD_3OD): δ 175.9, 170.3, 157.3, 156.5, 138.5, 115.8, 107.5, 102.1, 75.4, 75.1, 72.6, 57.1, 51.9, 40.7, 38.2, 37.0, 34.6, 33.8, 32.9, 30.9, 30.7, 30.6, 30.4, 30.3, 30.2, 30.1, 29.2, 28.3, 26.8, 23.6, 14.4.

MS (ESI) m/z: 725.69 (M^+ + Na).

SPECTRA


MeO
COOCH3
OMe
11
1H NMR
(CDCl3)
TMS
0.00
2.00
1.02
6.12
7
6
5
4
3
2
1
0


166.33
160.41
131.73
106.84
105.39
Chloroform-d
77.00
58.11
55.09
51.78
13C NMR
(CDCl3)
MeO
COOCH3
OMe
11
150
100
50
0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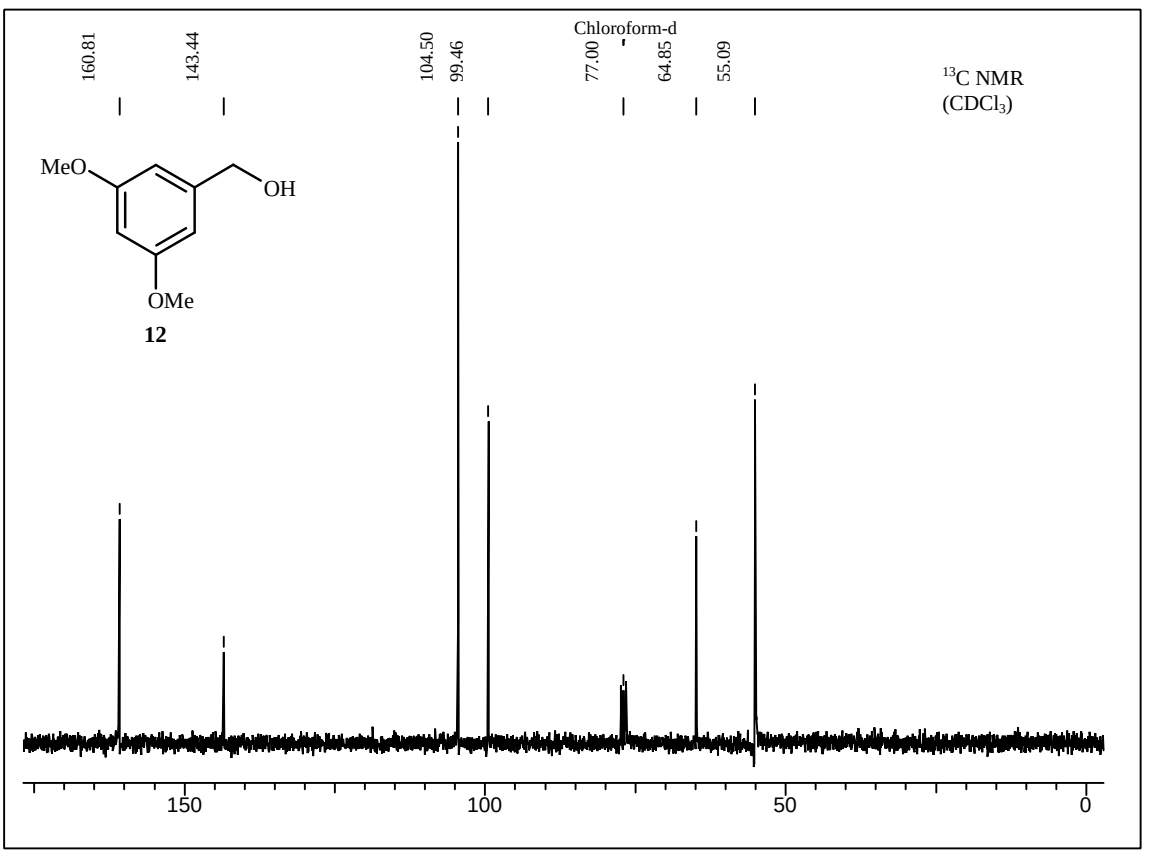
1.85
1.93
6.00
1.08
7
6
5
4
3
2
1
0


160.81
143.44
104.50
99.46
Chloroform-d
77.00
64.85
55.09
^{13}C NMR
(CDCl$_3$)
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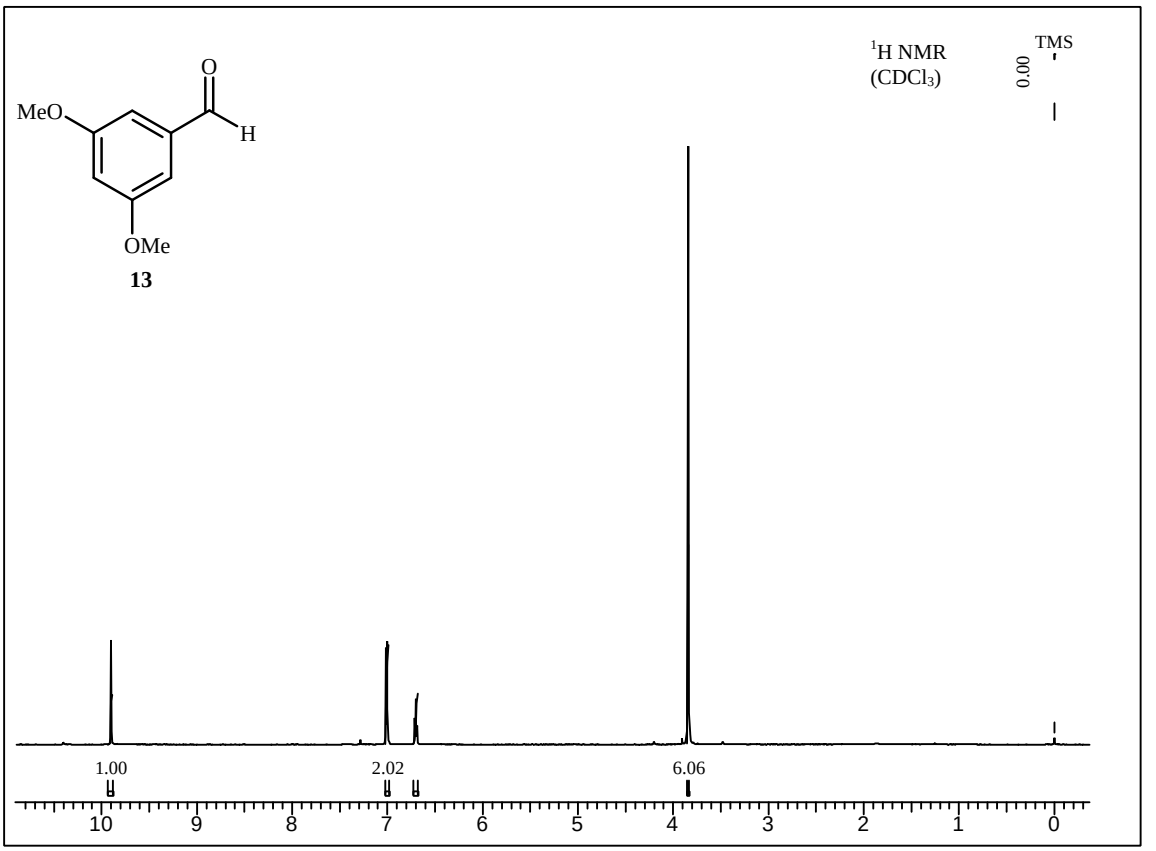
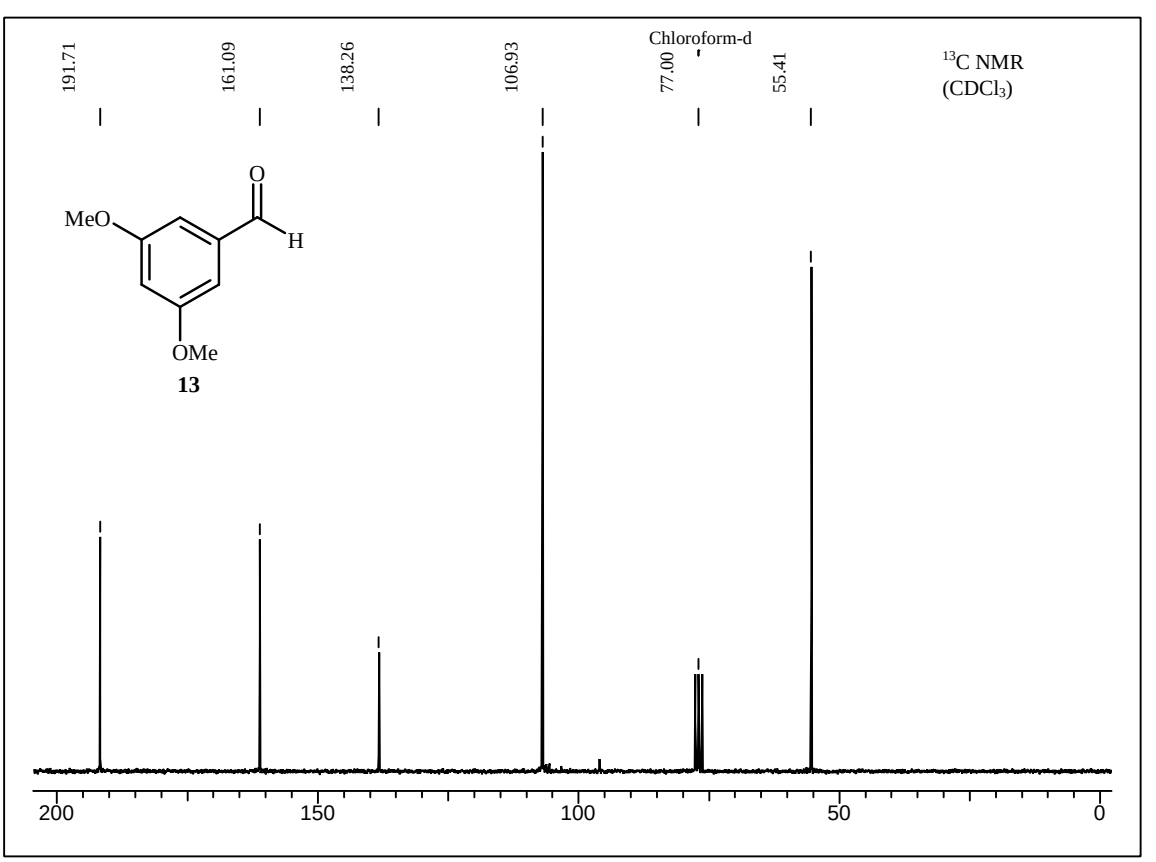
OH
OMe
12
150
100
50
0


MeO
O
H
OMe
13
^{1}H NMR
(CDCl$_3$)
TMS
0.00
1.00
2.02
6.06
10
9
8
7
6
5
4
3
2
1
0


191.71
161.09
138.26
106.93
Chloroform-d
77.00
55.41
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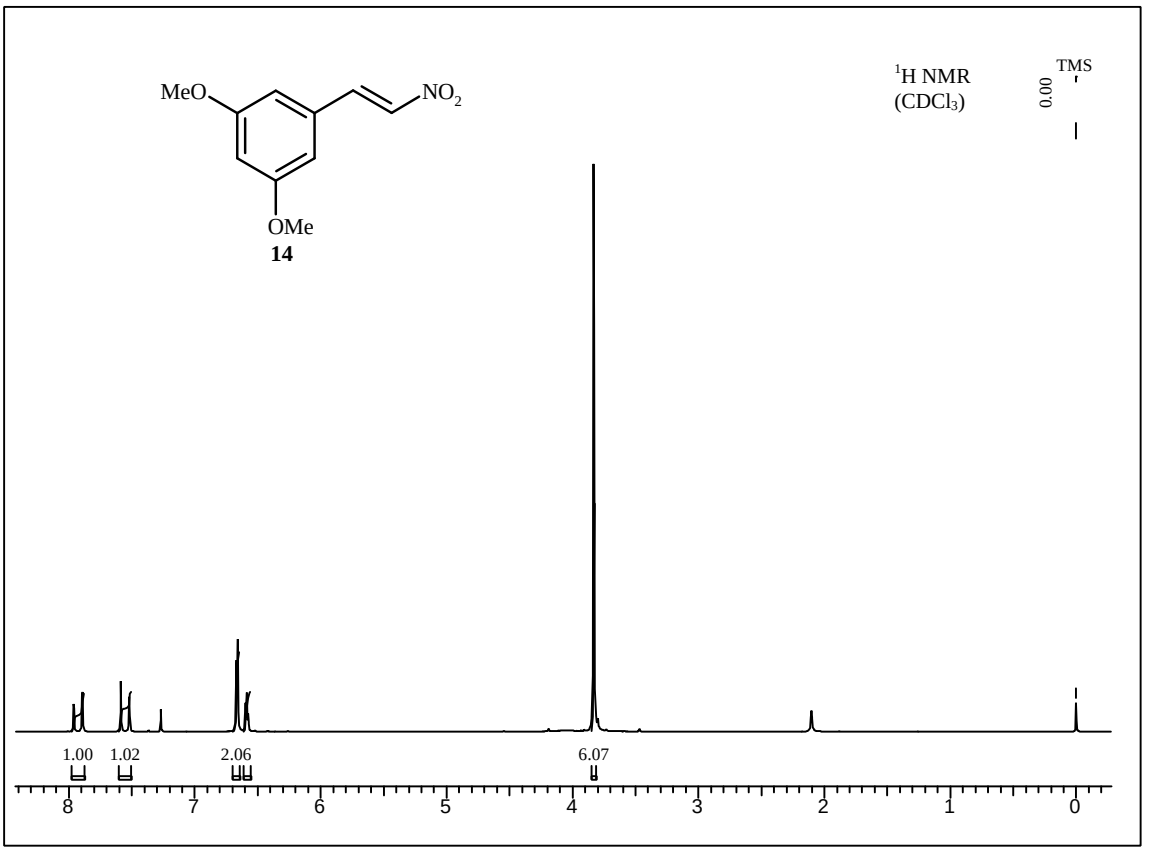
(CDCl$_3$)
MeO
O
H
OMe
13
200
150
100
50
0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OMe
14
1H NMR
(CDCl3)
TMS
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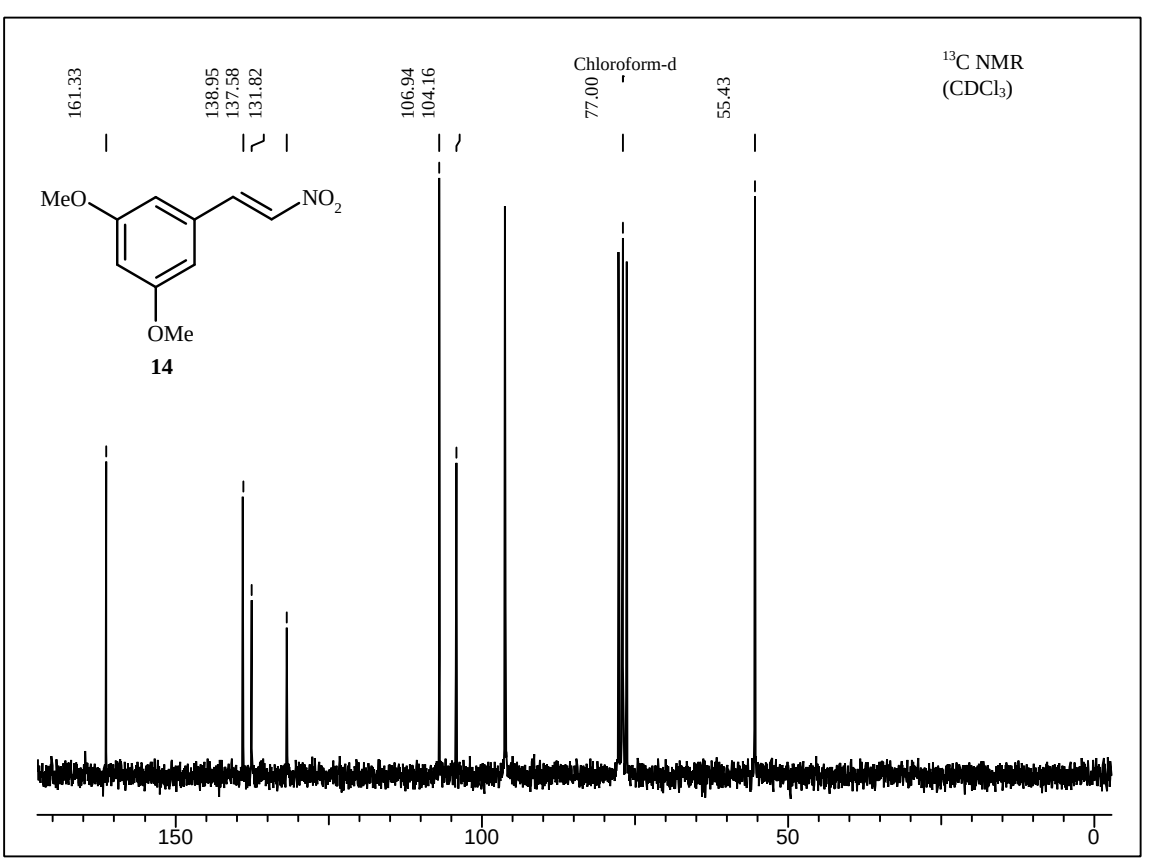
1.00
1.02
2.06
6.07
8
7
6
5
4
3
2
1
0


161.33
138.95
137.58
131.82
106.94
104.16
Chloroform-d
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13C NMR
(CDCl3)
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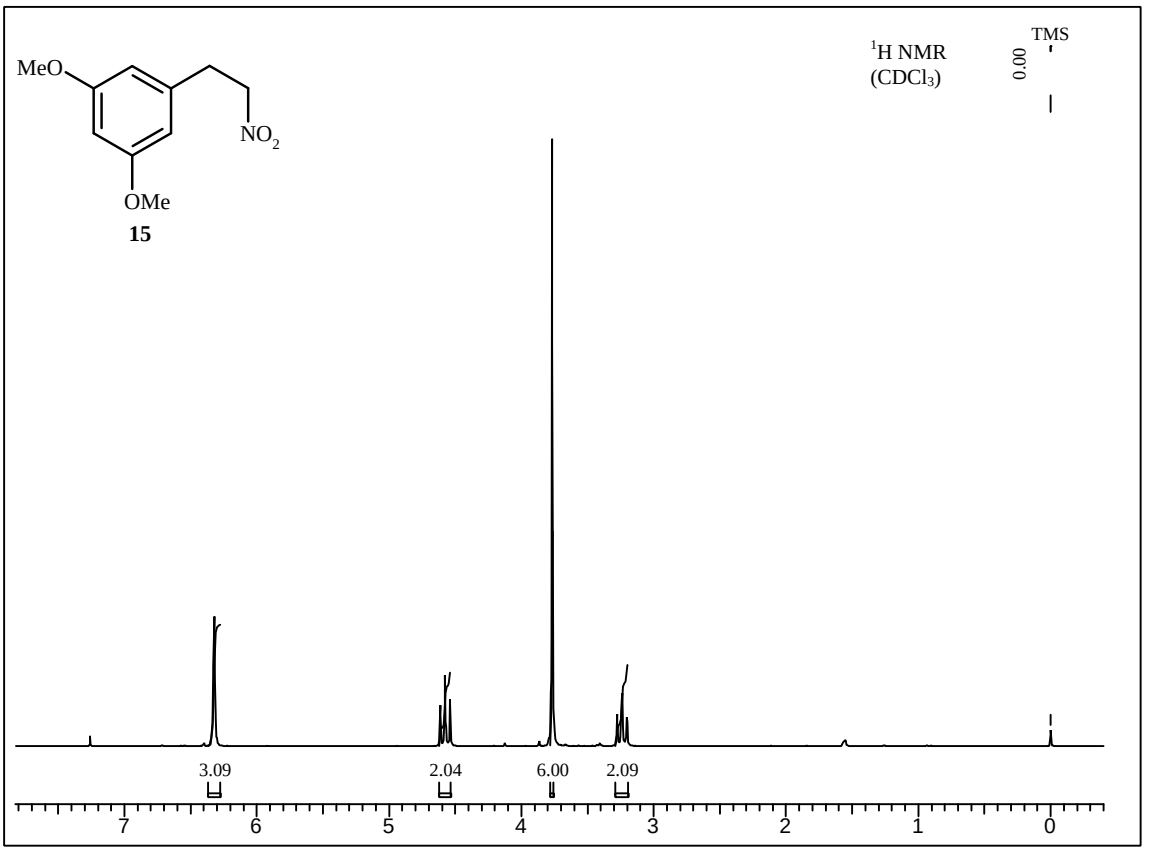
NO2
OMe
14
150
100
50
0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NO2
OMe
15
1H NMR
(CDCl3)
TMS
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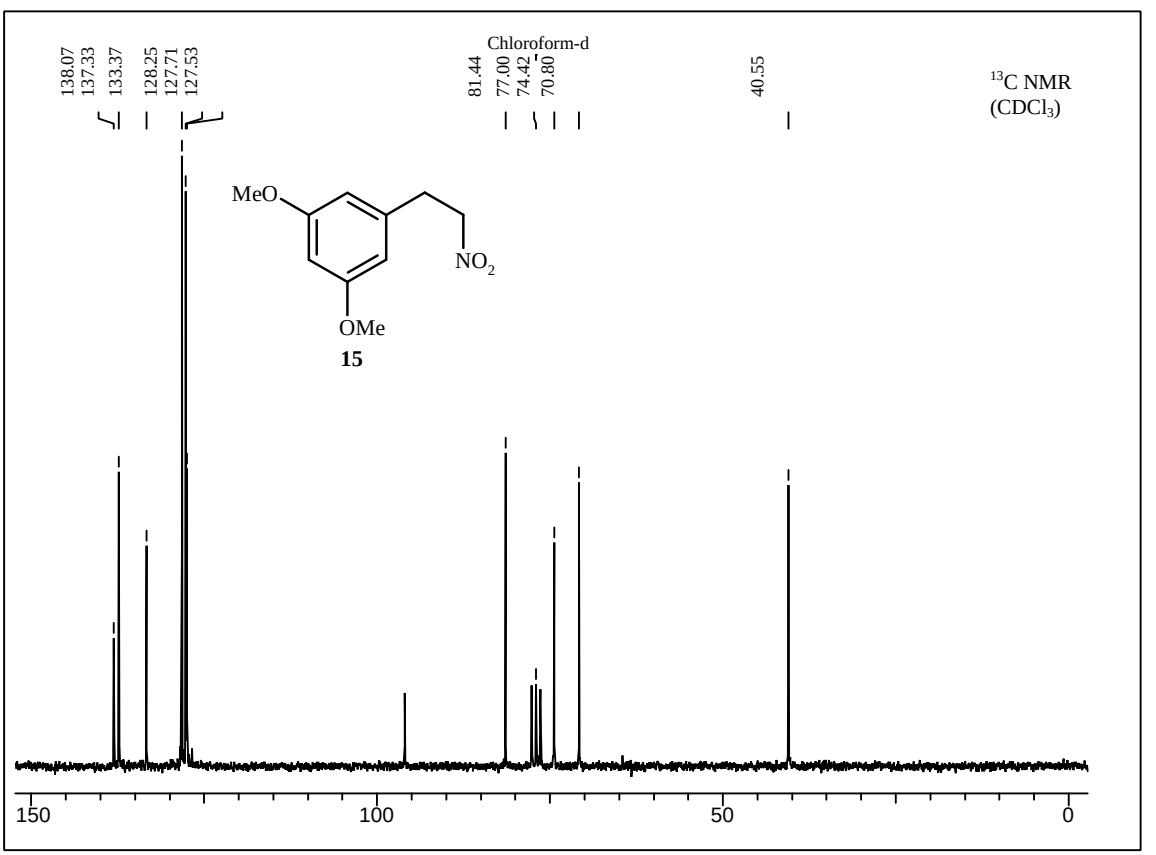
3.09
2.04
6.00
2.09
7
6
5
4
3
2
1
0


138.07
137.33
133.37
128.25
127.71
127.53
Chloroform-d
81.44
77.00
74.42
70.80
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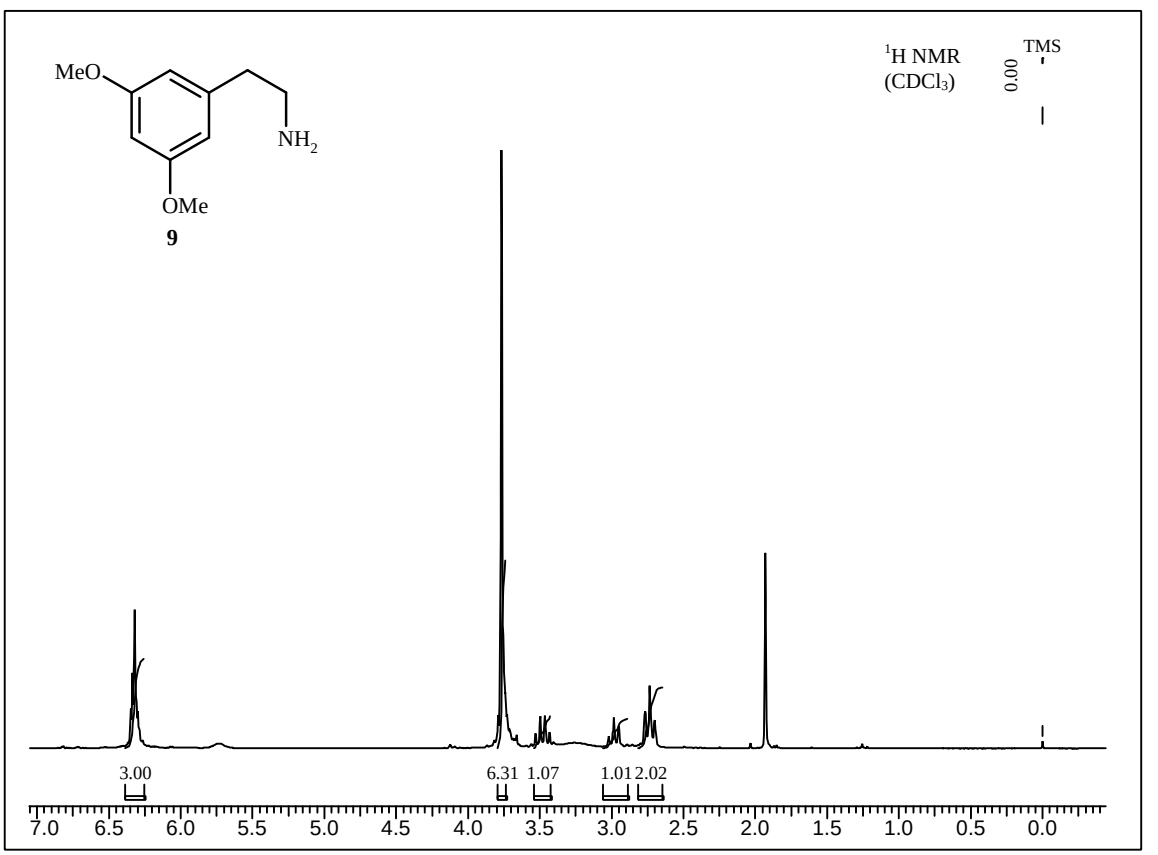
MeO
NO2
OMe
15
150
100
50
0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NH2
OMe
9
1H NMR
(CDCl3)
TMS
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3.00
6.31
1.07
1.01
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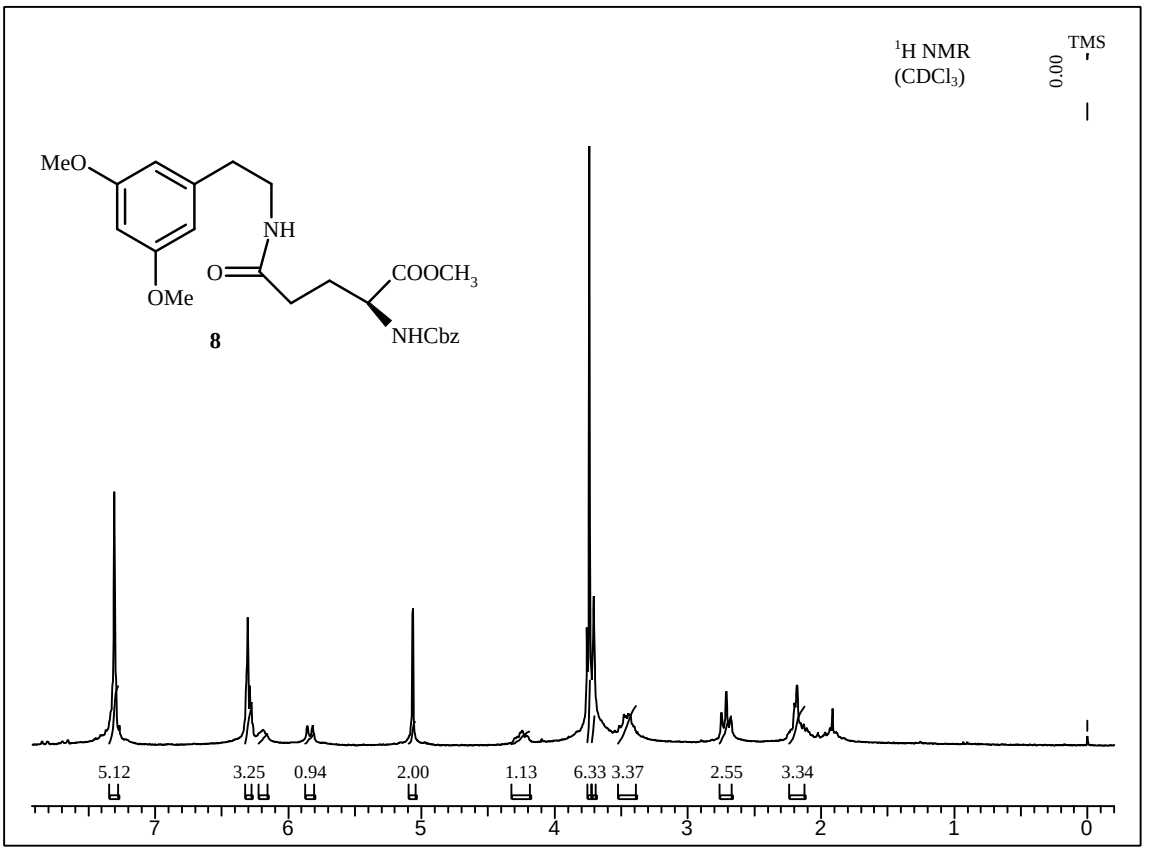
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0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(CDCl$_3$)
TMS
0.00
MeO
NH
O
COOCH$_3$
OMe
NHCbz
8
5.12
3.25
0.94
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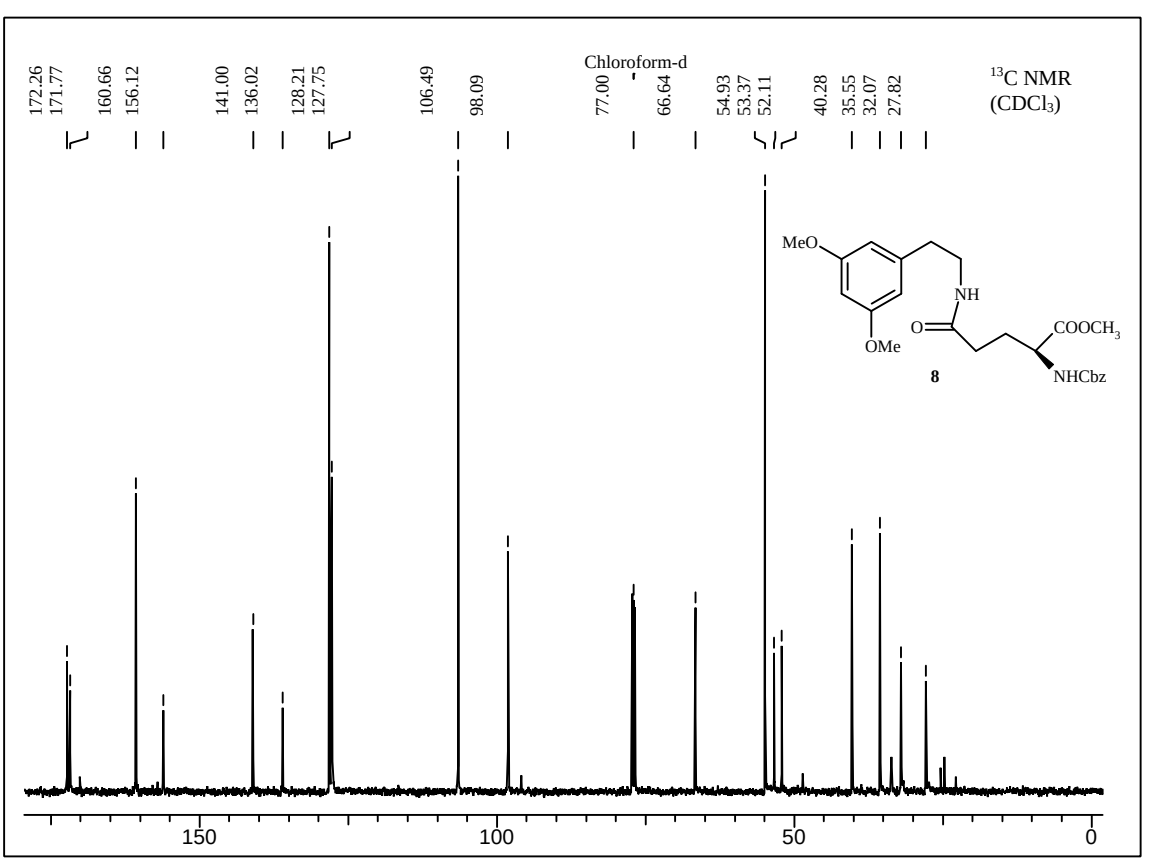
6.33
3.37
2.55
3.34
7
6
5
4
3
2
1
0


172.26
171.77
160.66
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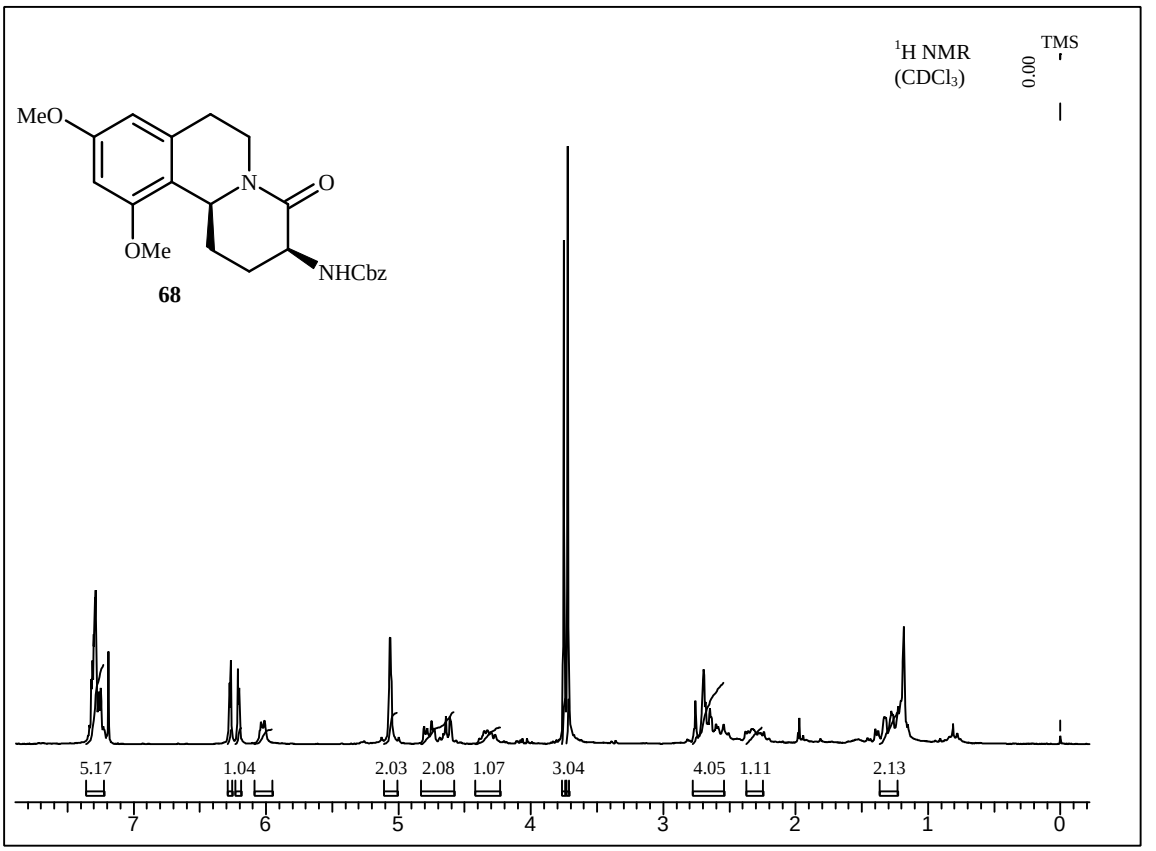
136.02
128.21
127.75
106.49
98.09
Chloroform-d
77.00
66.64
54.93
53.37
52.11
40.28
35.55
32.07
27.82
^{13}C NMR
(CDCl$_3$)
MeO
NH
O
COOCH$_3$
OMe
NHCbz
8
150
100
50
0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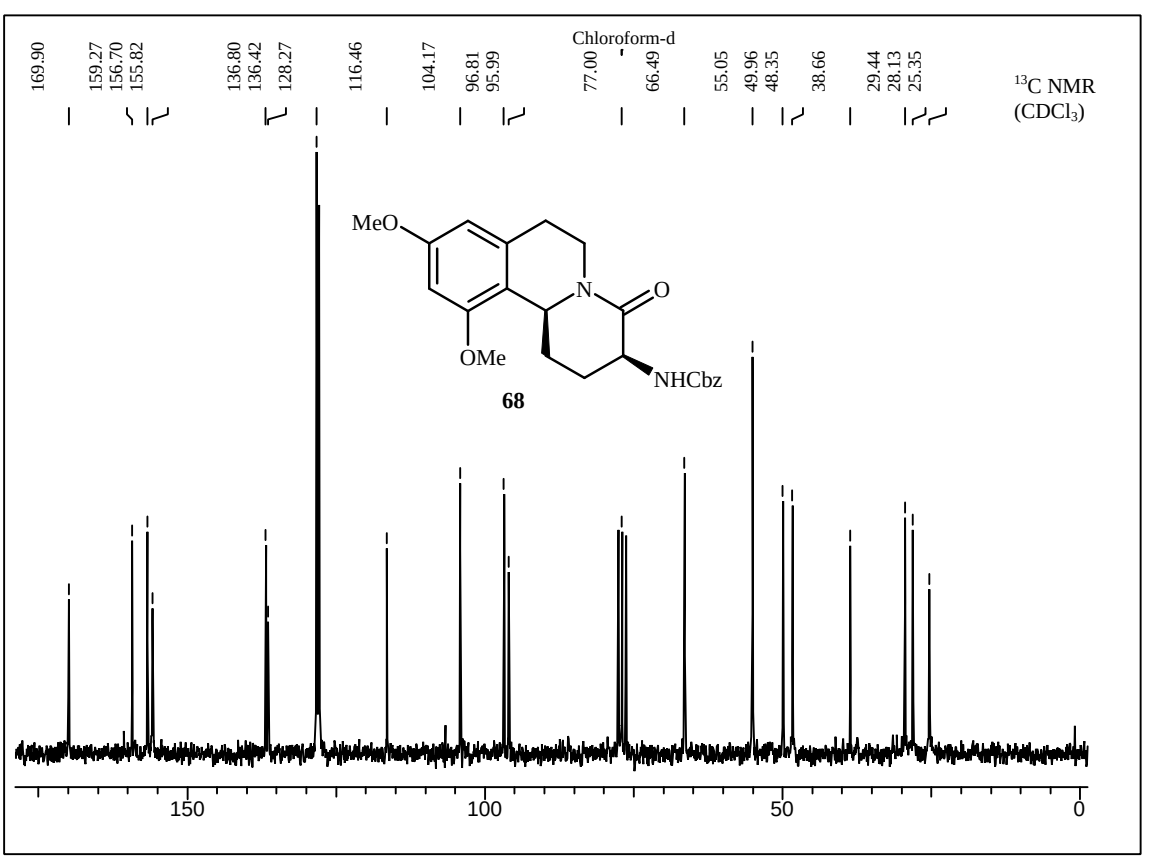
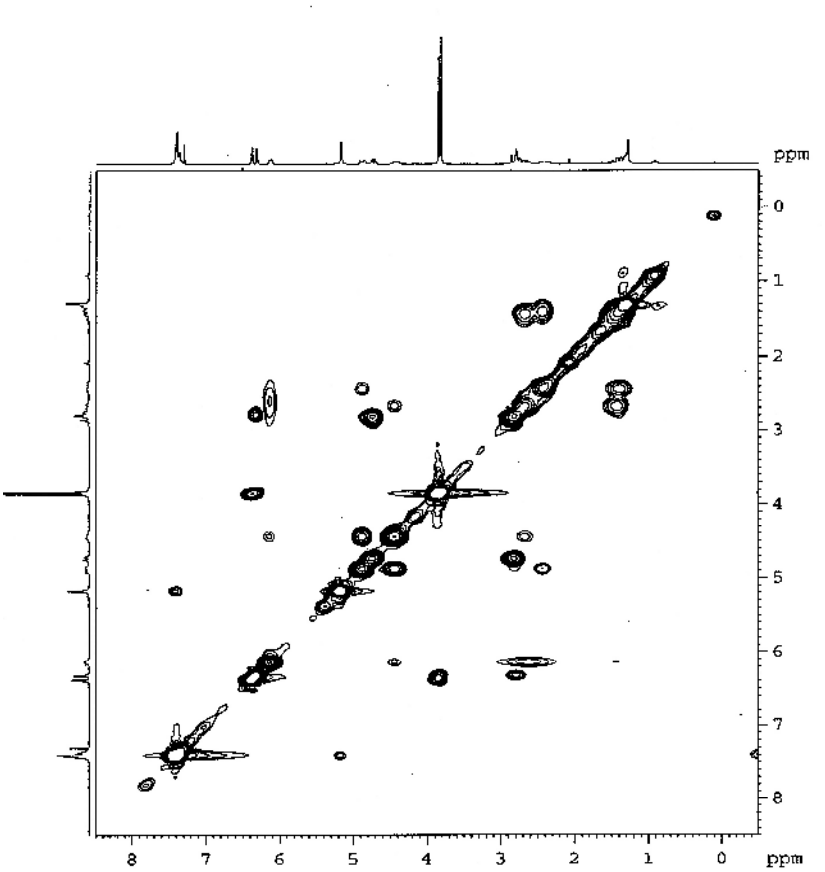
($CDCl_3$)
TMS
0.00
MeO
N
O
OMe
NHCbz
68
5.17
1.04
2.03
2.08
1.07
3.04
4.05
1.11
2.13
7
6
5
4
3
2
1
0


169.90
159.27
156.70
155.82
136.80
136.42
128.27
116.46
104.17
96.81
95.99
Chloroform-d
77.00
66.49
55.05
49.96
48.35
38.66
29.44
28.13
25.35
^{13}C NMR
($CDCl_3$)
MeO
N
O
OMe
NHCbz
68
150
100
50
0



BRUKER

```
Current Data Parameters
NAME          Fri2av2#023
EXPNO                   3
PROCNO                  1

F2 - Acquisition Parameters
Date_              20041211
Time                   1.15
INSTRUM               Av200
PROBHD   5 mm QNP 1H/13
PULPROG           LOcHyDH
TD                     1024
SOLVENT               MeOH
NS                       32
DS                       16
SWH                2603.205 Hz
FIDRES             1.956255 Hz
AQ                 0.2556404 sec
RG                       256
DW                   249.600 usec
DE                     6.00 usec
TE                     0.0 K
D0                 0.00023278 sec
D1                 2.00000000 sec
D8                 1.00000000 sec
IN0                0.00049967 sec
MCREST             0.00000000 sec
MCWRK              1.00000000 sec
ST1CNT                  128

======== CHANNEL f1 ========
NUC1                    1H
P1                   13.40 usec
PL1                   1.00 dB
SFO1           200.1309006 MHz

F1 - Acquisition parameters
NDO                      1
TD                     256
SFO1           200.1309 MHz
FIDRES             7.617582 Hz
SW                10.000 ppm
FnMODE         States-TPPI

F2 - Processing parameters
SI                     1024
SF             200.1300000 MHz
WDW                      GM
SSB                       0
LB                    -3.00 Hz
GB                     0.01
PC                     1.40

F1 - Processing parameters
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MC2            States-TPPI
SF             200.1300000 MHz
WDW                   QSINE
SSB                       2
LB                    0.00 Hz
GB                        0
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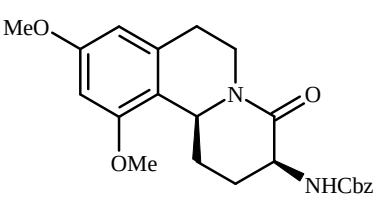

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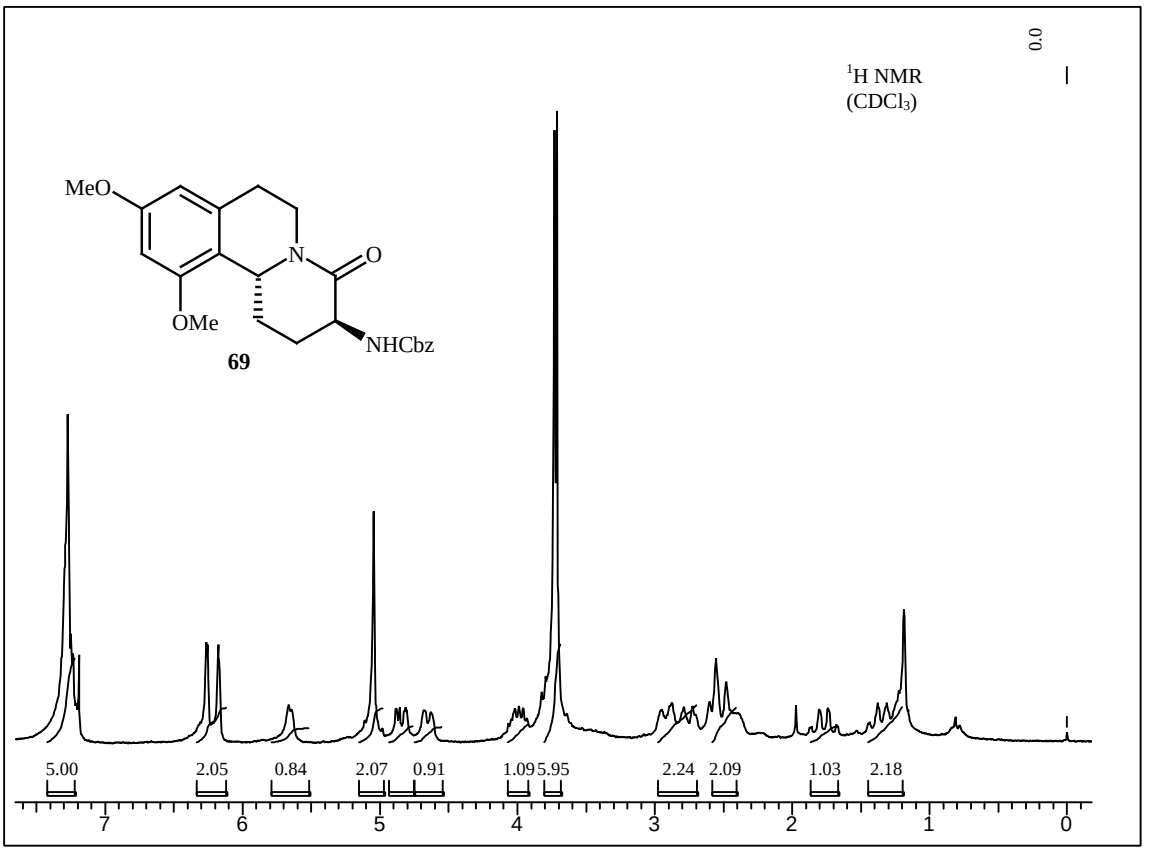
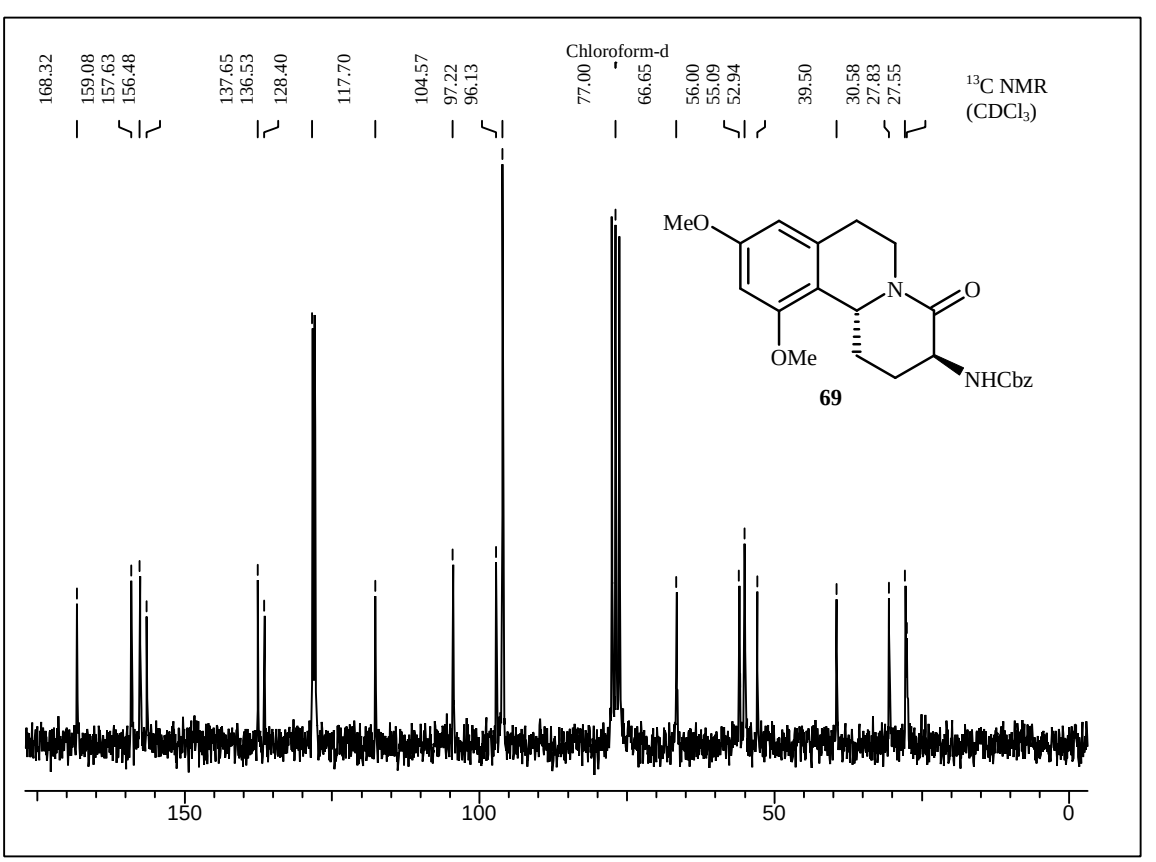
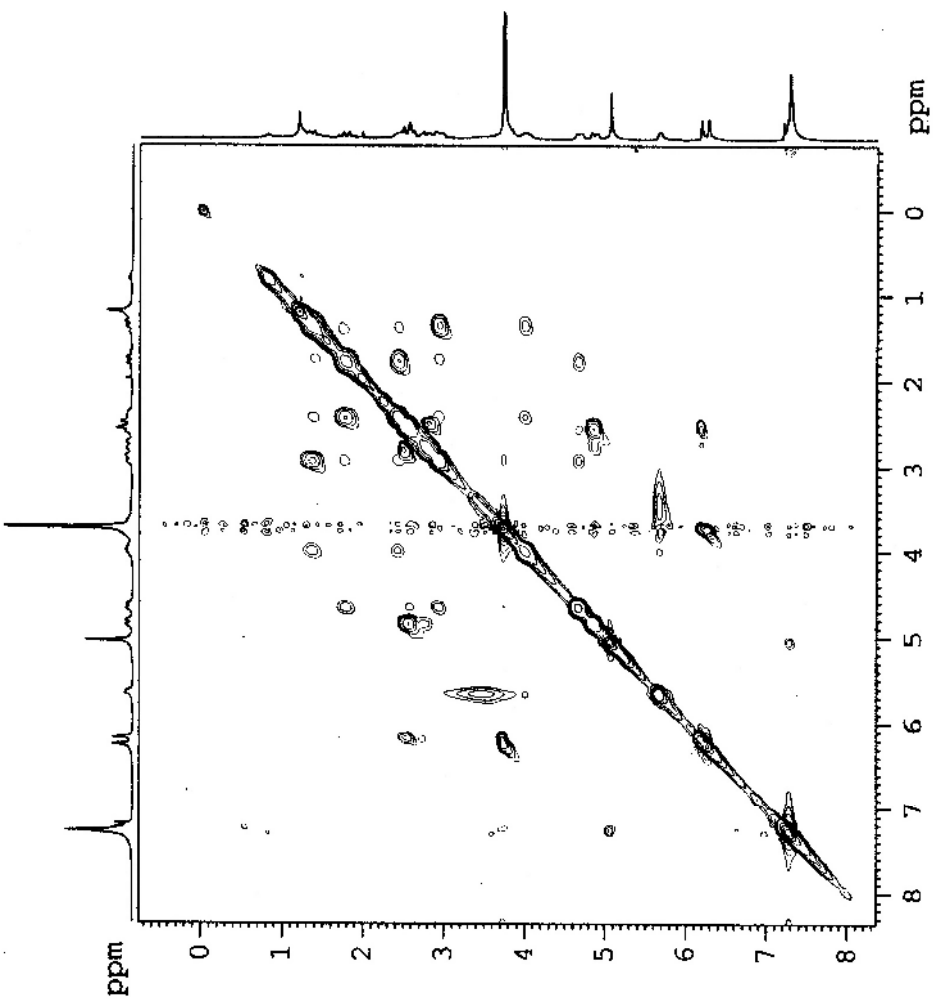
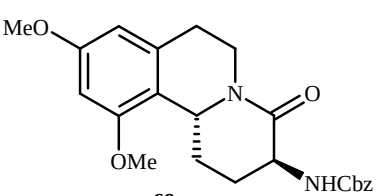

0.0
^{1}H NMR
($CDCl_3$)
MeO
N
O
OMe
NHCbz
69
5.00
2.05
0.84
2.07
0.91
1.09
5.95
2.24
2.09
1.03
2.18
7
6
5
4
3
2
1
0


168.32
159.08
157.63
156.48
137.65
136.53
128.40
117.70
104.57
97.22
96.13
Chloroform-d
77.00
66.65
56.00
55.09
52.94
39.50
30.58
27.83
27.55
^{13}C NMR
($CDCl_3$)
MeO
N
O
OMe
NHCbz
69
150
100
50
0





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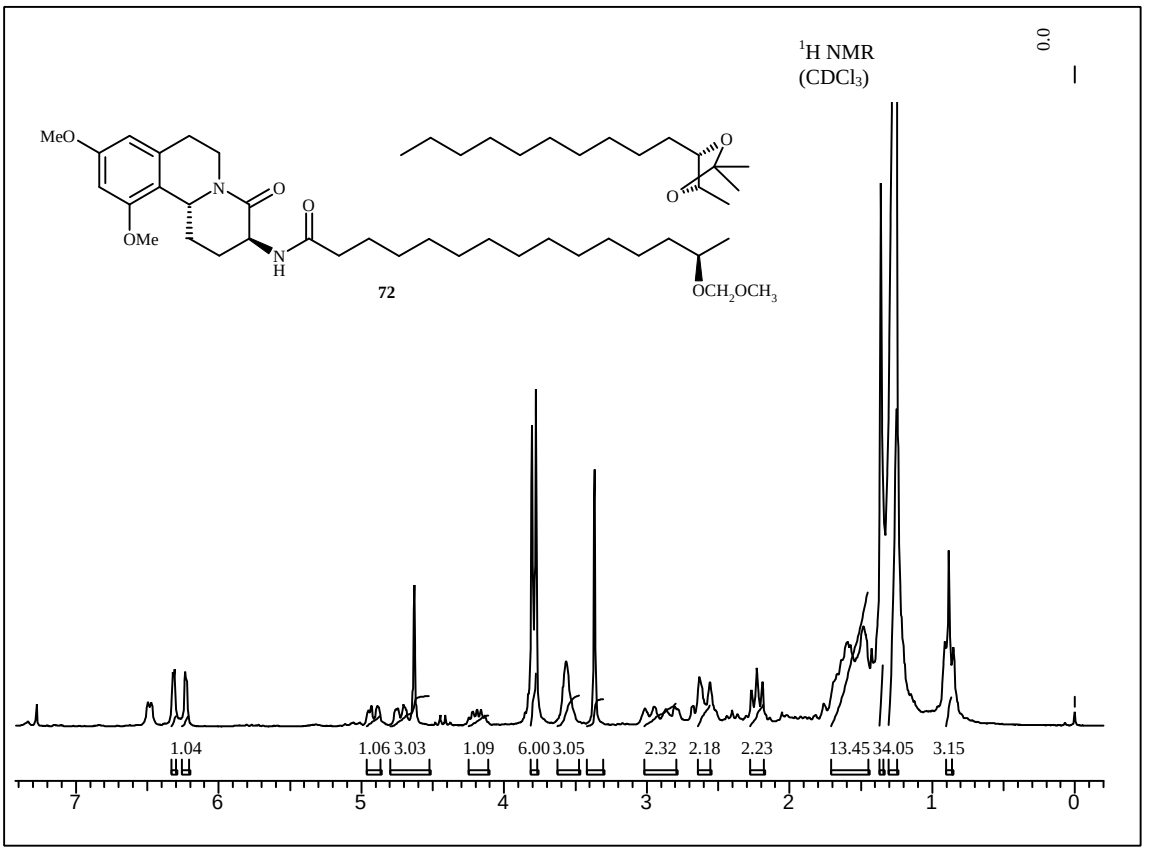
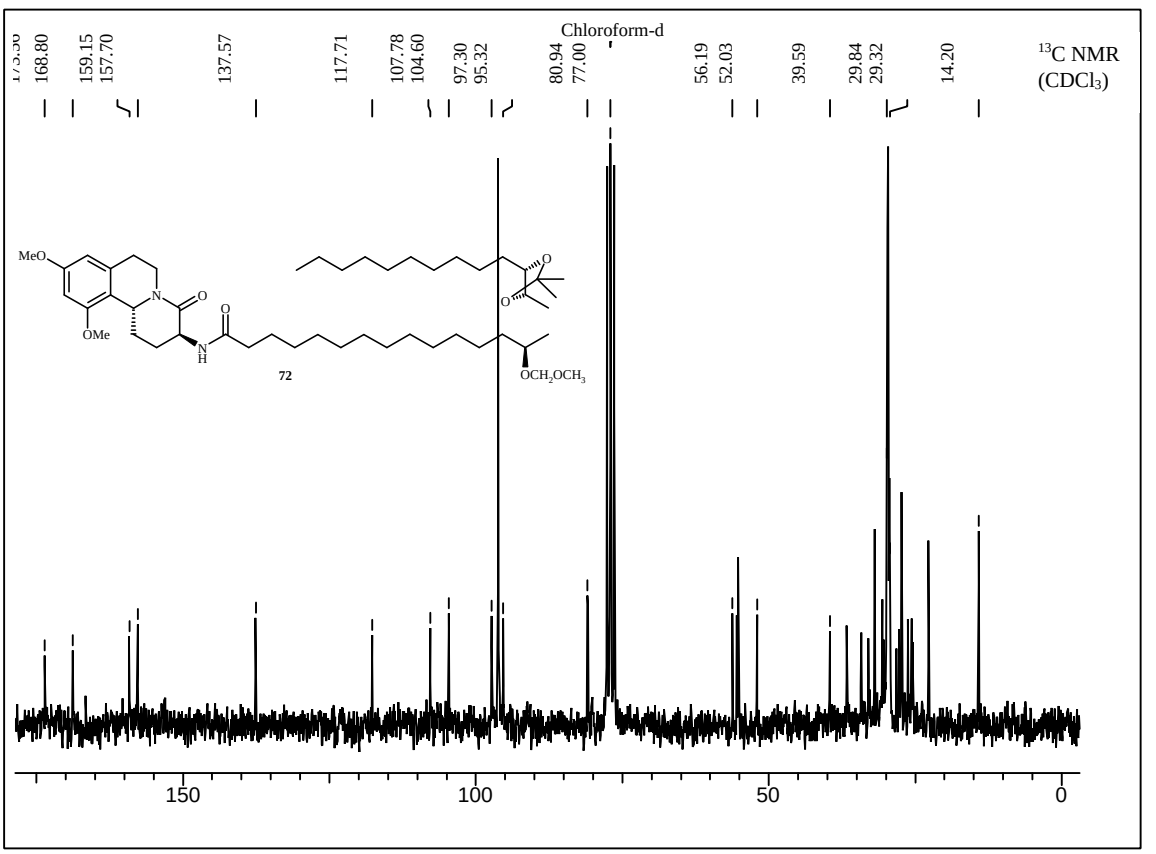
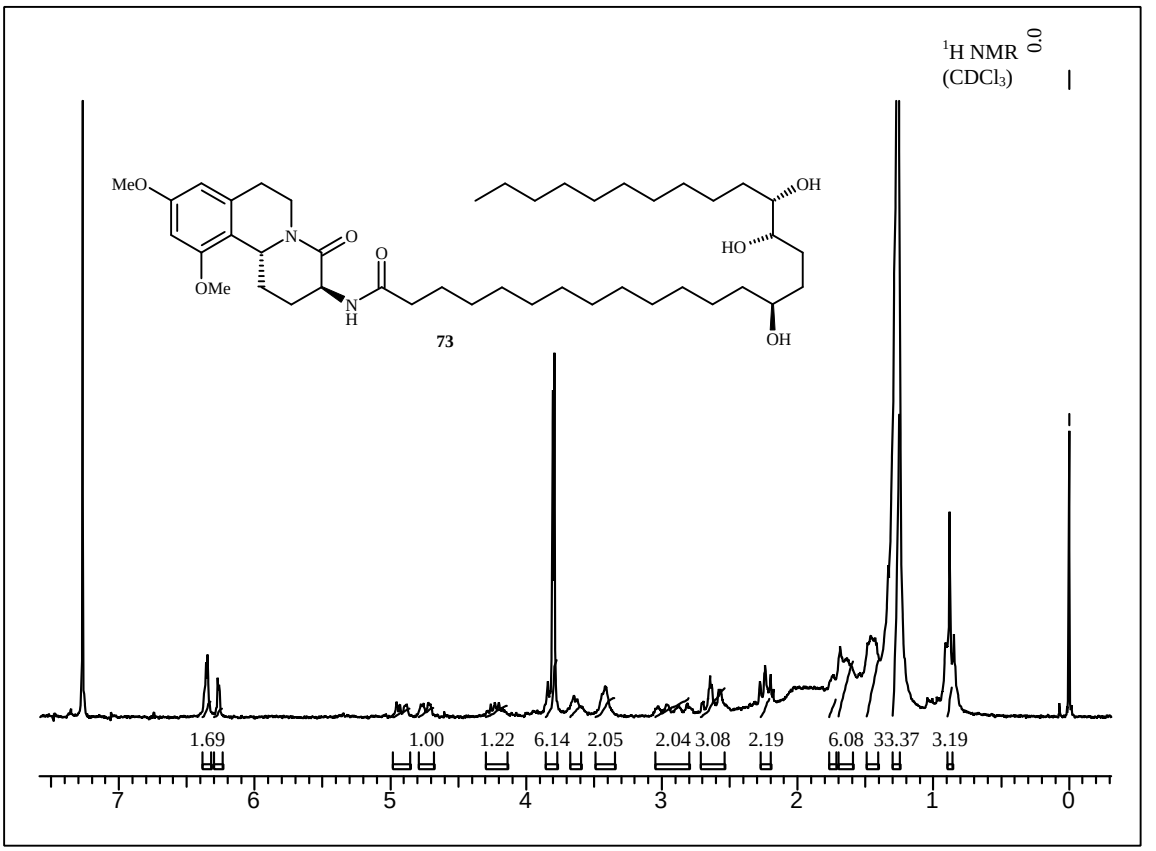
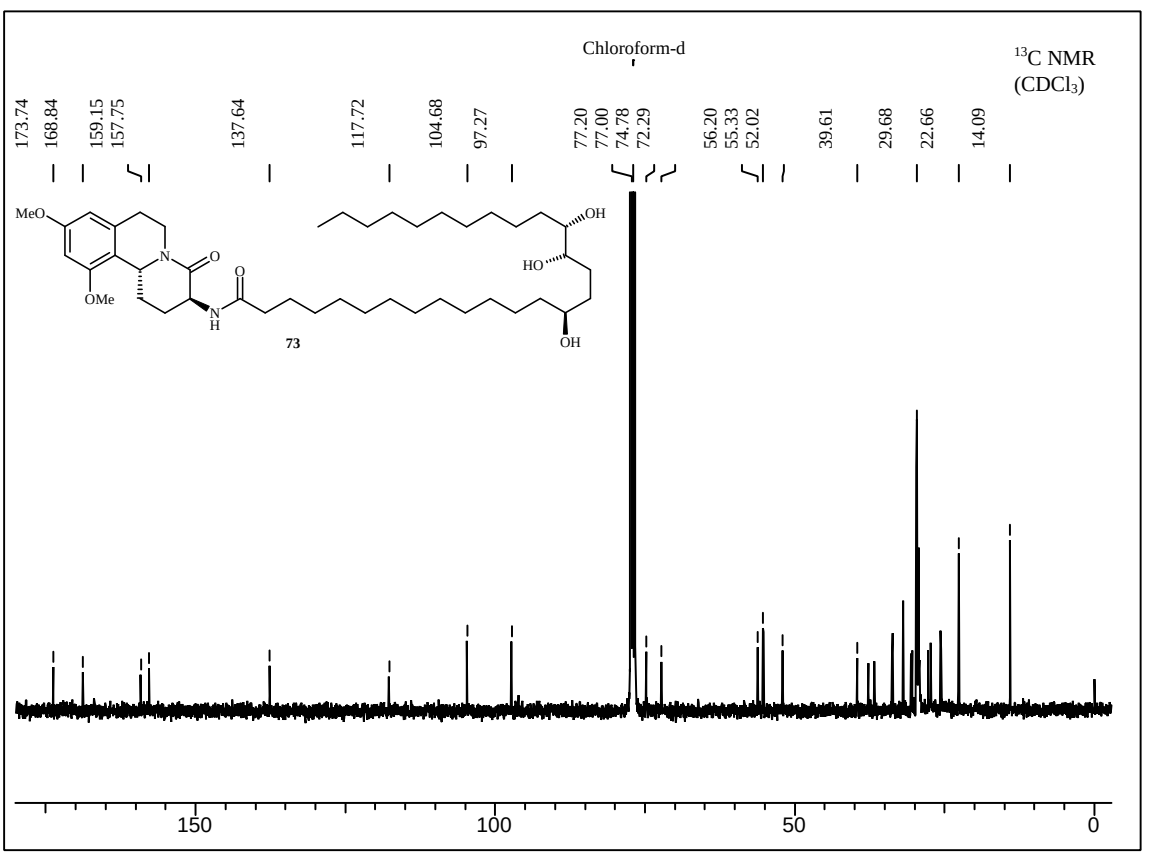
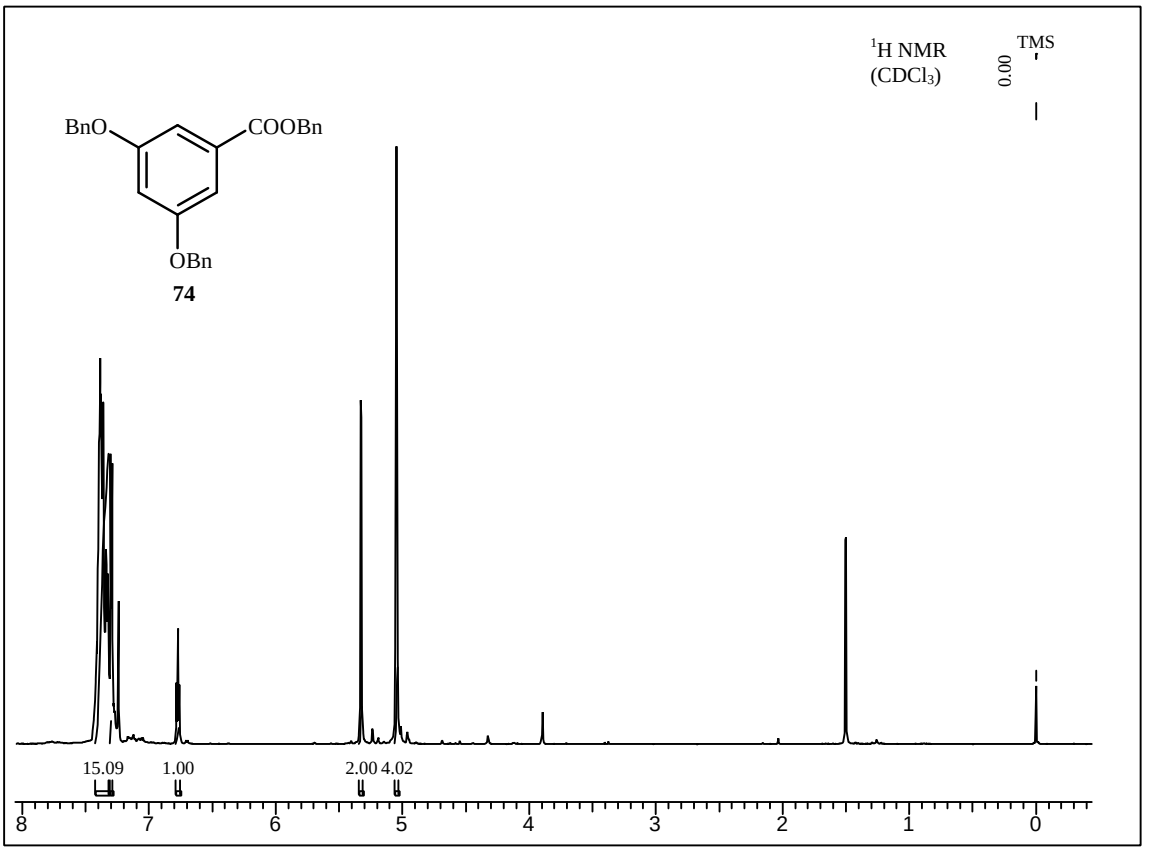
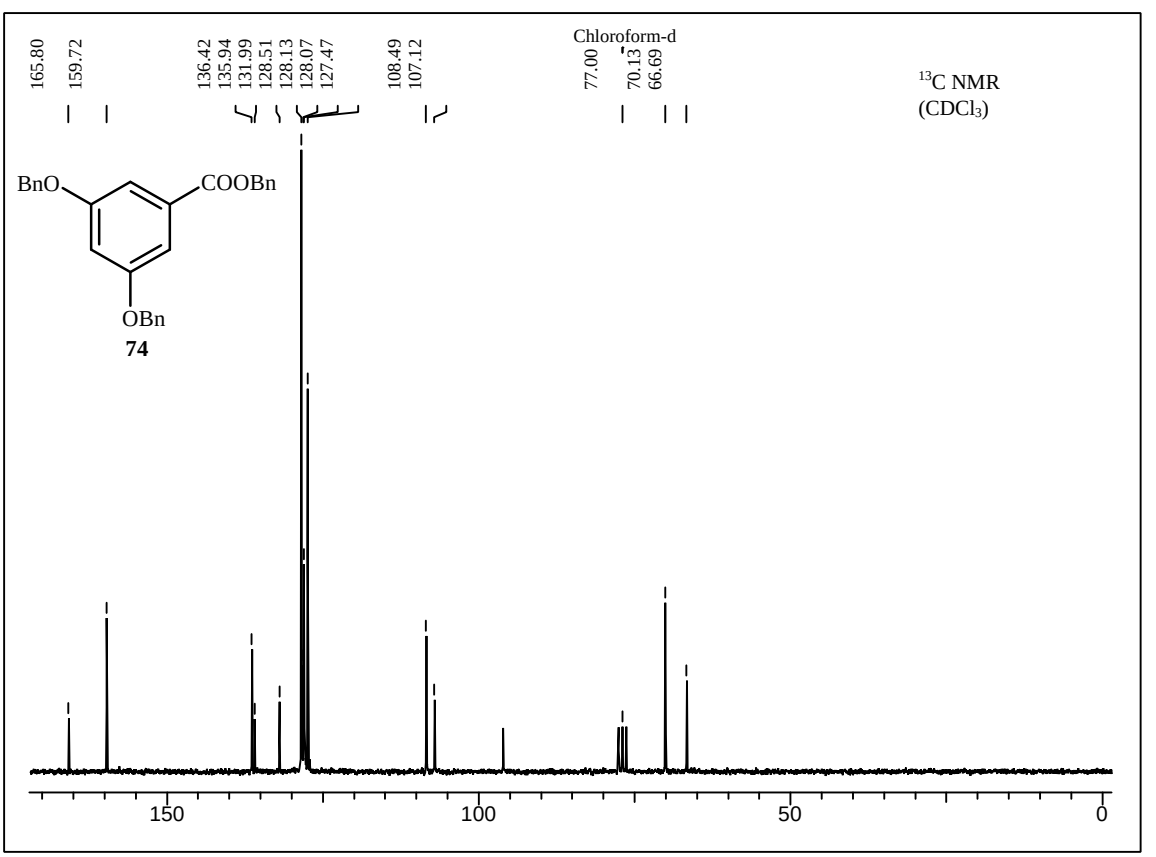

^{1}H NMR
(CDCl$_3$)
0.0
MeO
OMe
N
O
O
N
H
O
O
OCH$_2$OCH$_3$
72
1.04
1.06
3.03
1.09
6.00
3.05
2.32
2.18
2.23
13.45
34.05
3.15
7
6
5
4
3
2
1
0

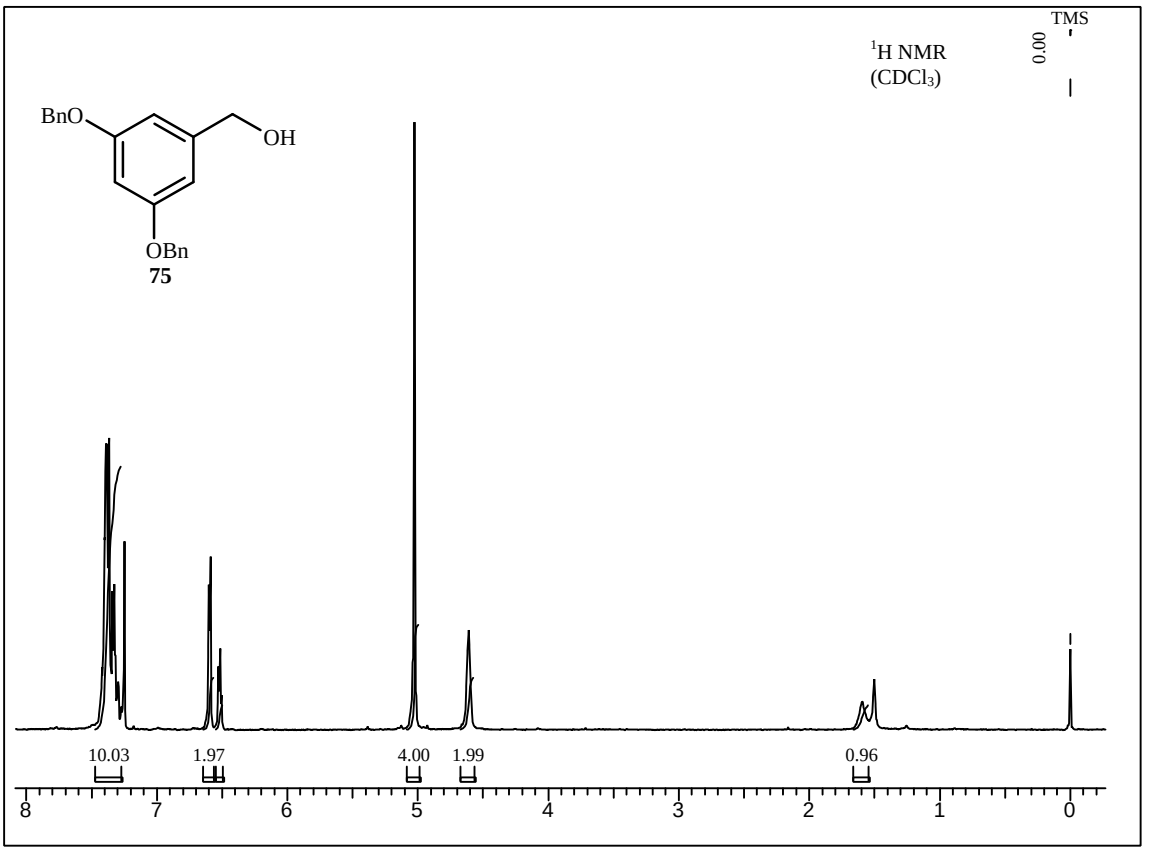

Chloroform-d
168.80
159.15
157.70
137.57
117.71
107.78
104.60
97.30
95.32
80.94
77.00
56.19
52.03
39.59
29.84
29.32
14.20
^{13}C NMR
(CDCl$_3$)
MeO
OMe
N
O
O
N
H
O
O
OCH$_2$OCH$_3$
72
150
100
50
0

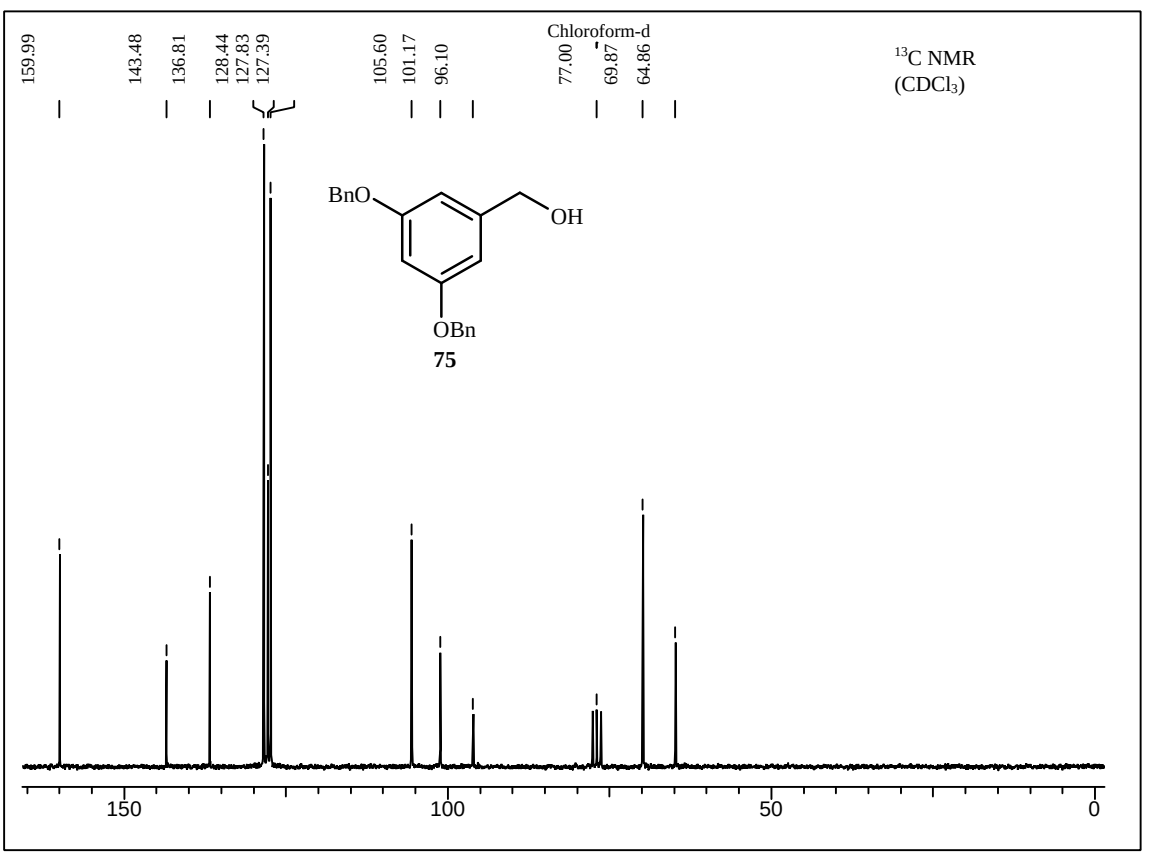

^{1}H NMR
(CDCl$_3$)
0.0
MeO
OMe
N
O
N
H
O
OH
HO
OH
73
1.69
1.00
1.22
6.14
2.05
2.04
3.08
2.19
6.08
33.37
3.19
7
6
5
4
3
2
1
0

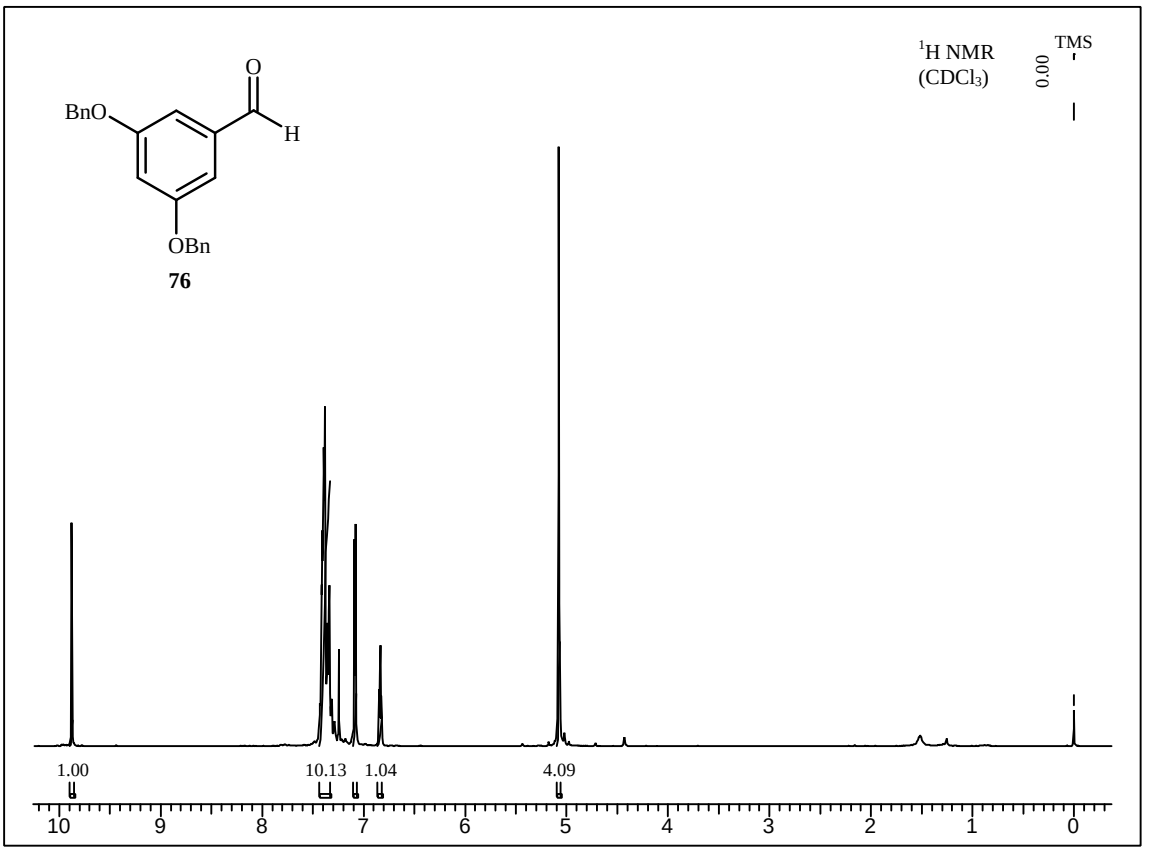

Chloroform-d
^{13}C NMR
(CDCl$_3$)
173.74
168.84
159.15
157.75
137.64
117.72
104.68
97.27
77.20
77.00
74.78
72.29
56.20
55.33
52.02
39.61
29.68
22.66
14.09
MeO
OMe
N
O
N
H
O
OH
HO
OH
73
150
100
50
0

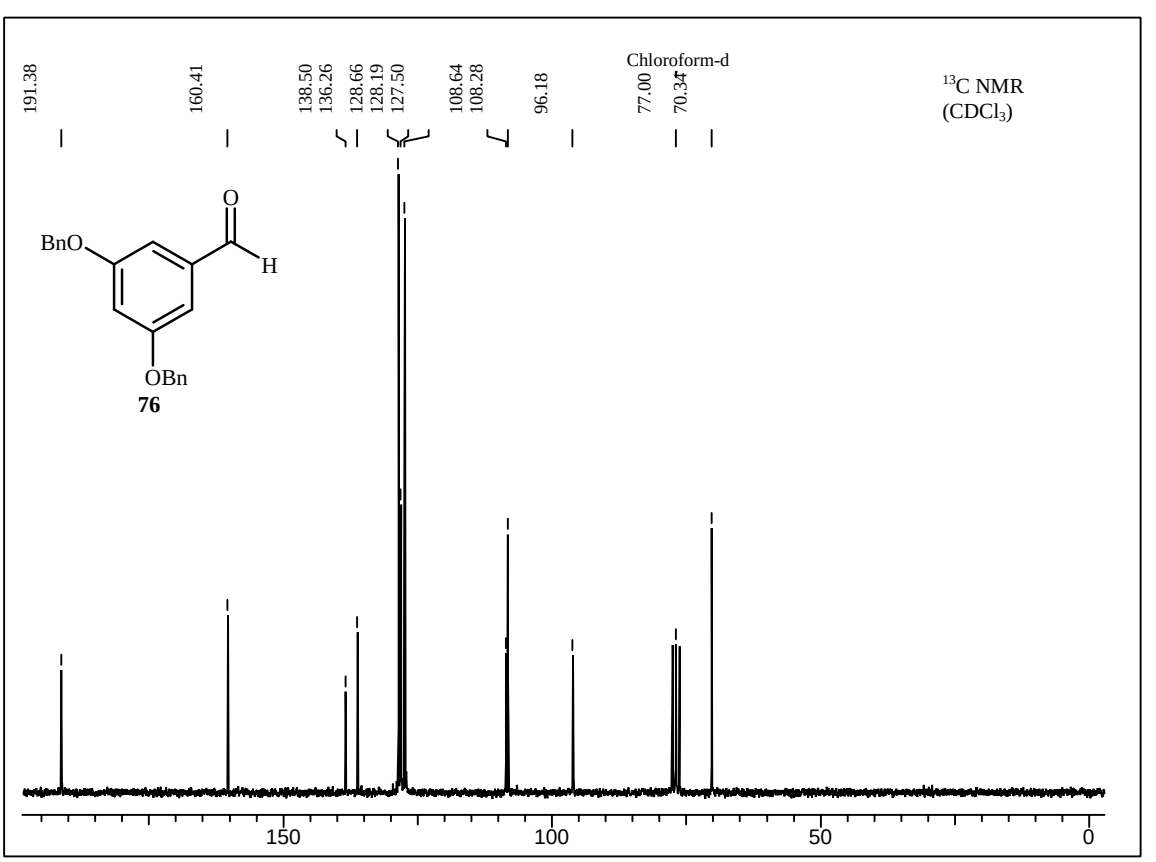

^{1}H NMR
(CDCl$_3$)
TMS
0.00
BnO
COOBn
OBn
74
15.09
1.00
2.00
4.02
8
7
6
5
4
3
2
1
0

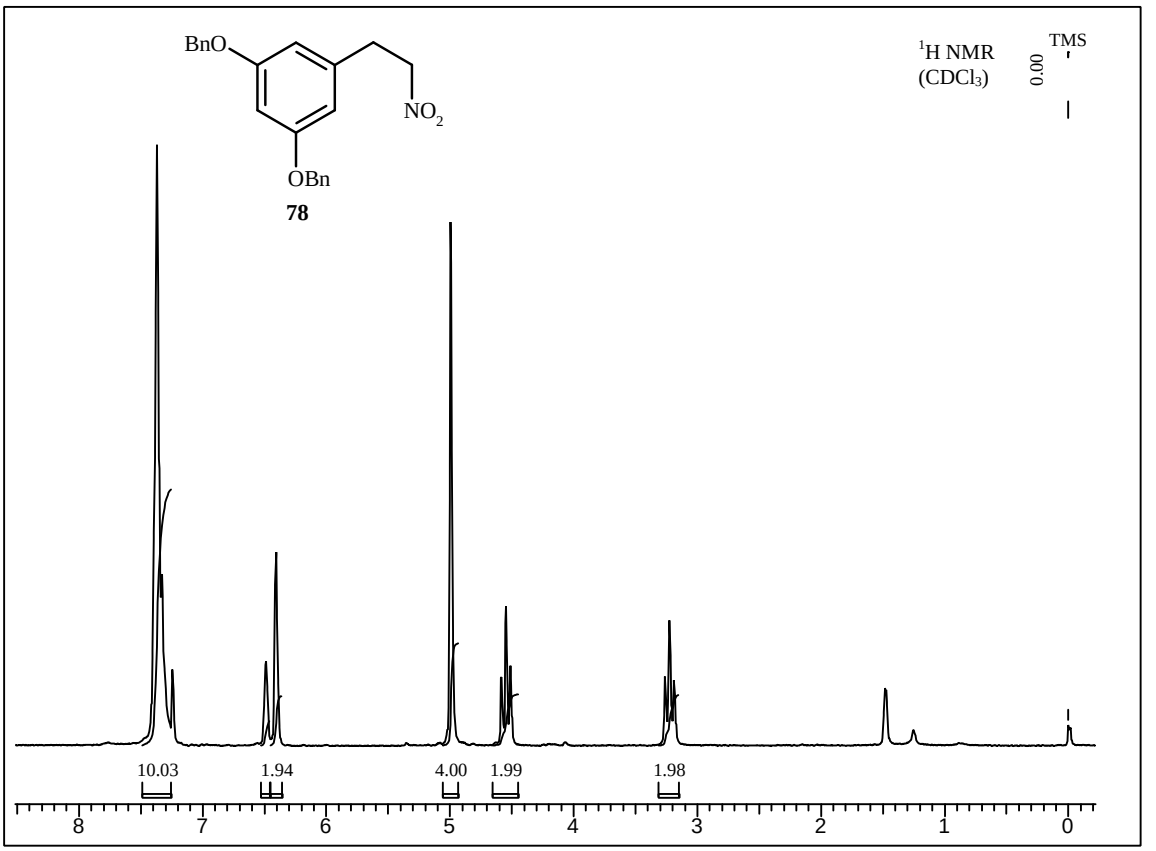

165.80
159.72
136.42
135.94
131.99
128.51
128.13
128.07
127.47
108.49
107.12
Chloroform-d
77.00
70.13
66.69
^{13}C NMR
(CDCl$_3$)
BnO
COOBn
OBn
74
150
100
50
0

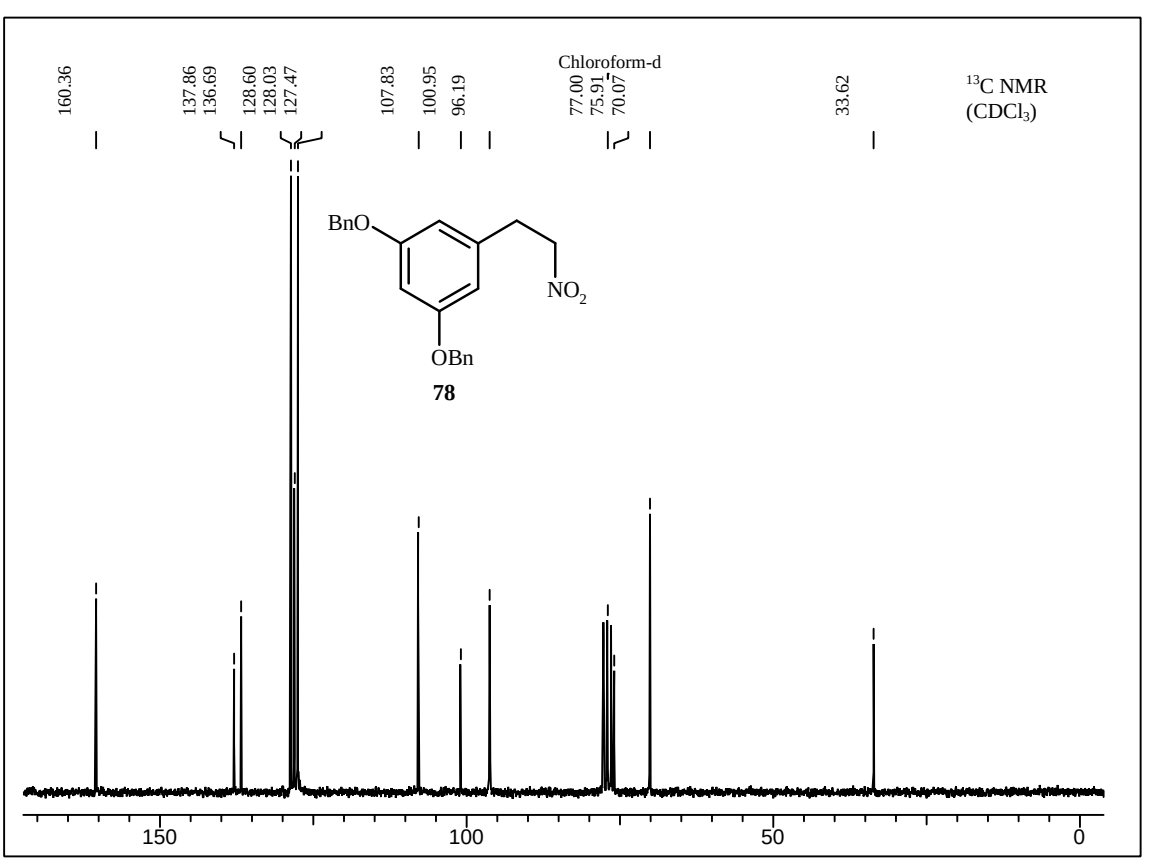

TMS
0.00
^{1}H NMR
($CDCl_3$)
BnO
OH
OBn
75
10.03
1.97
4.00
1.99
0.96
8
7
6
5
4
3
2
1
0

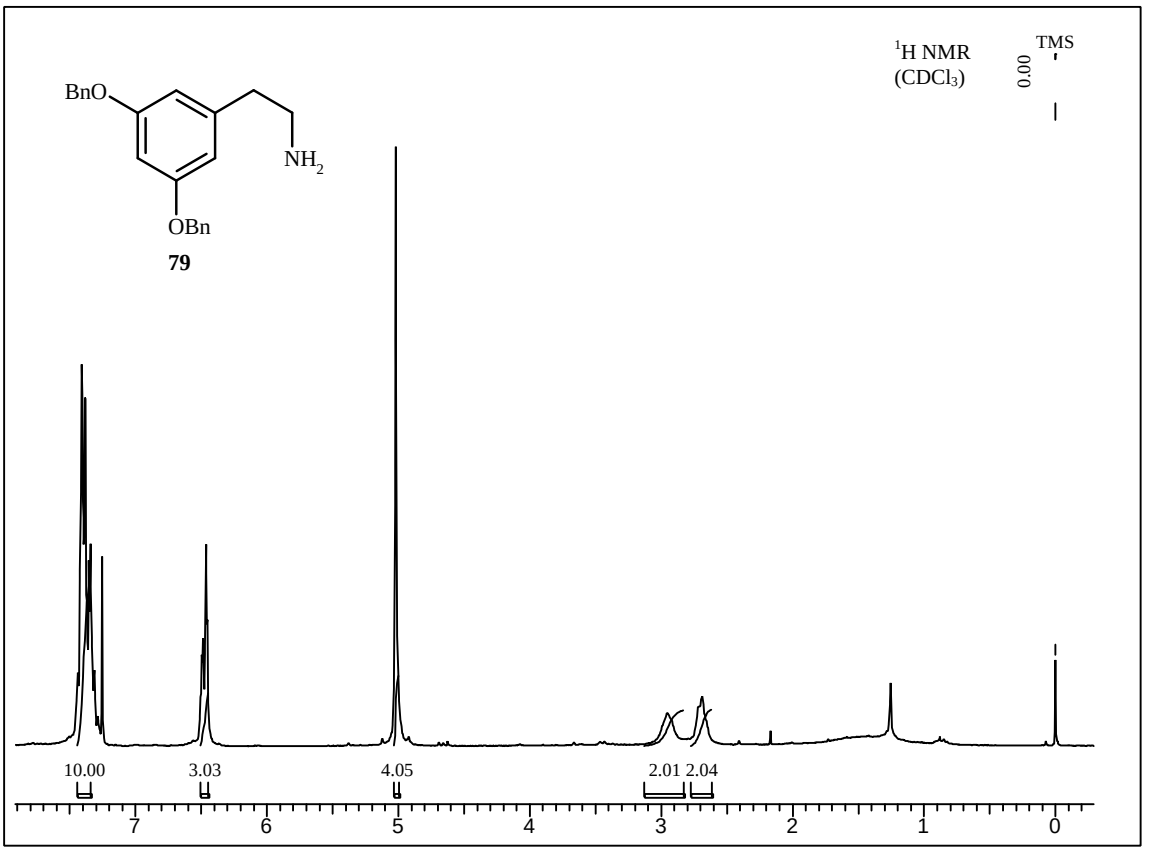

159.99
143.48
136.81
128.44
127.83
127.39
105.60
101.17
96.10
Chloroform-d
77.00
69.87
64.86
^{13}C NMR
($CDCl_3$)
BnO
OH
OBn
75
150
100
50
0

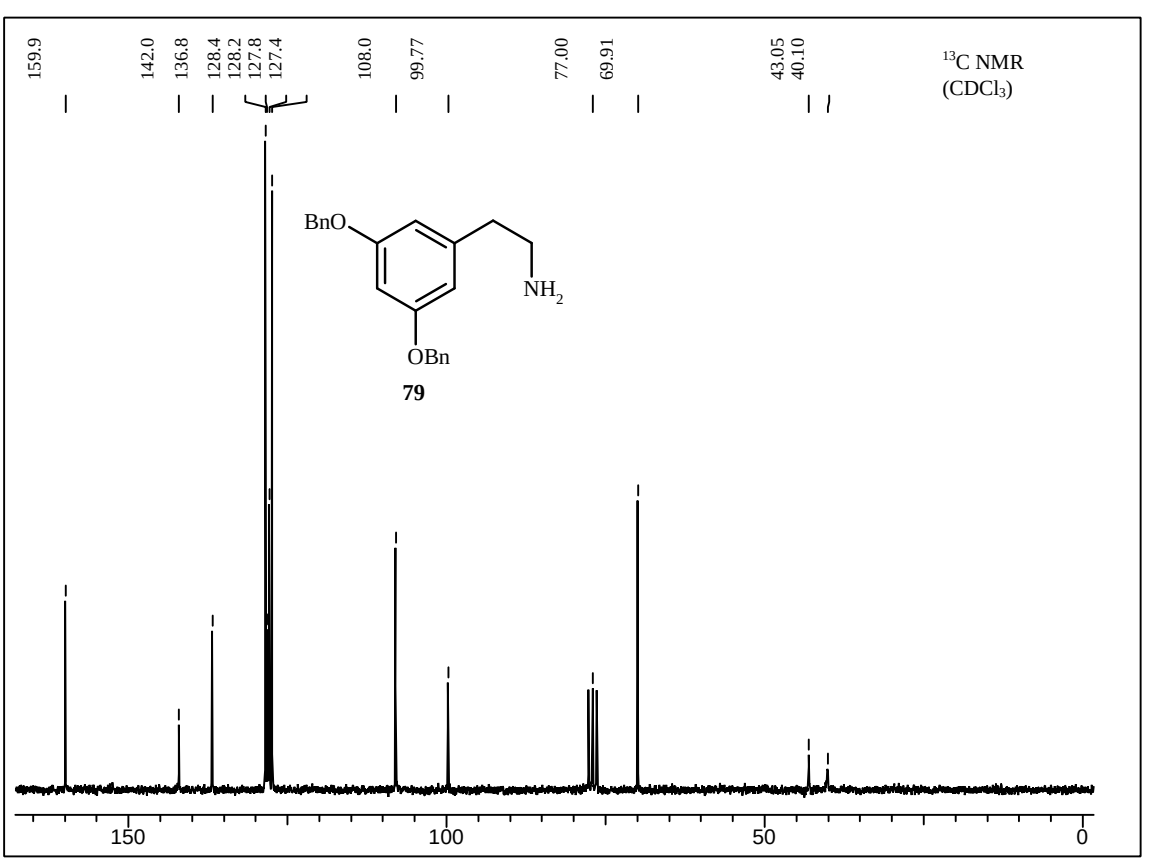

BnO
O
H
OBn
76
^{1}H NMR
(CDCl$_3$)
TMS
0.00
1.00
10.13
1.04
4.09
10
9
8
7
6
5
4
3
2
1
0

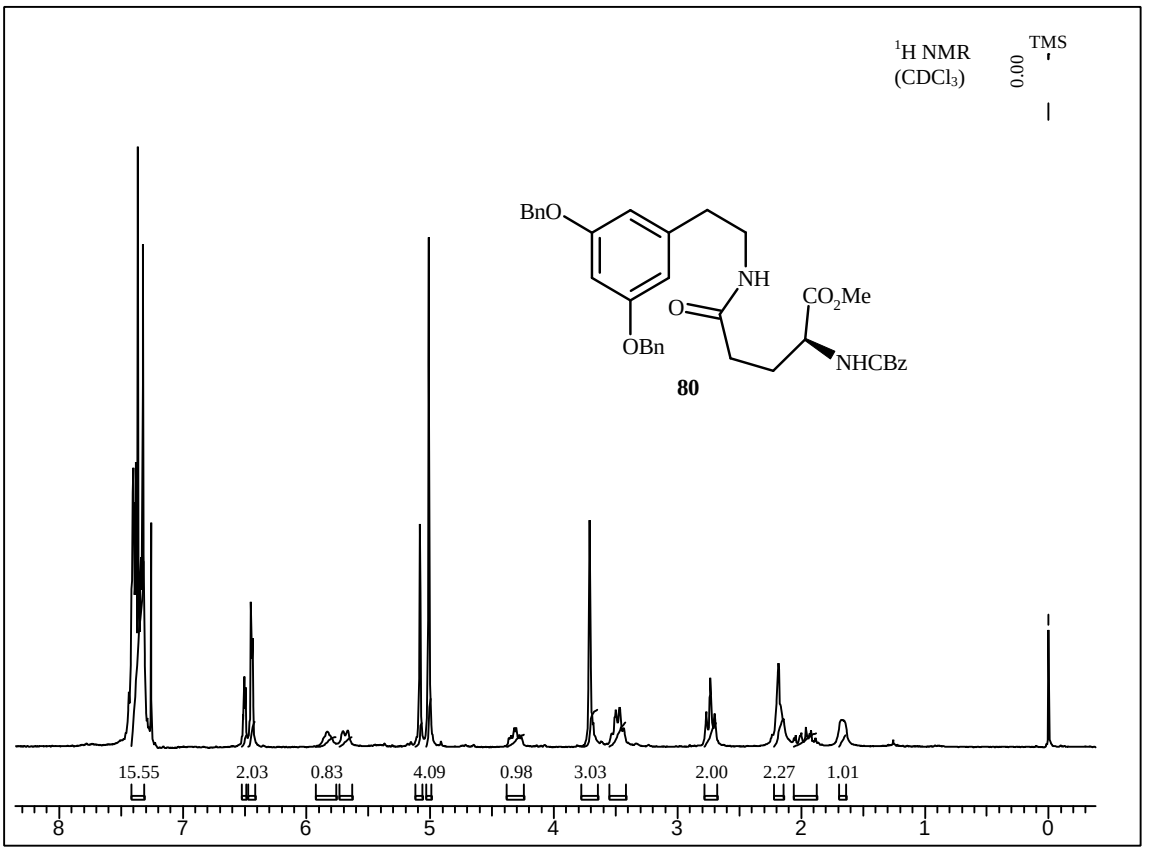

191.38
160.41
138.50
136.26
128.66
128.19
127.50
108.64
108.28
96.18
Chloroform-d
77.00
70.34
^{13}C NMR
(CDCl$_3$)
BnO
O
H
OBn
76
150
100
50
0

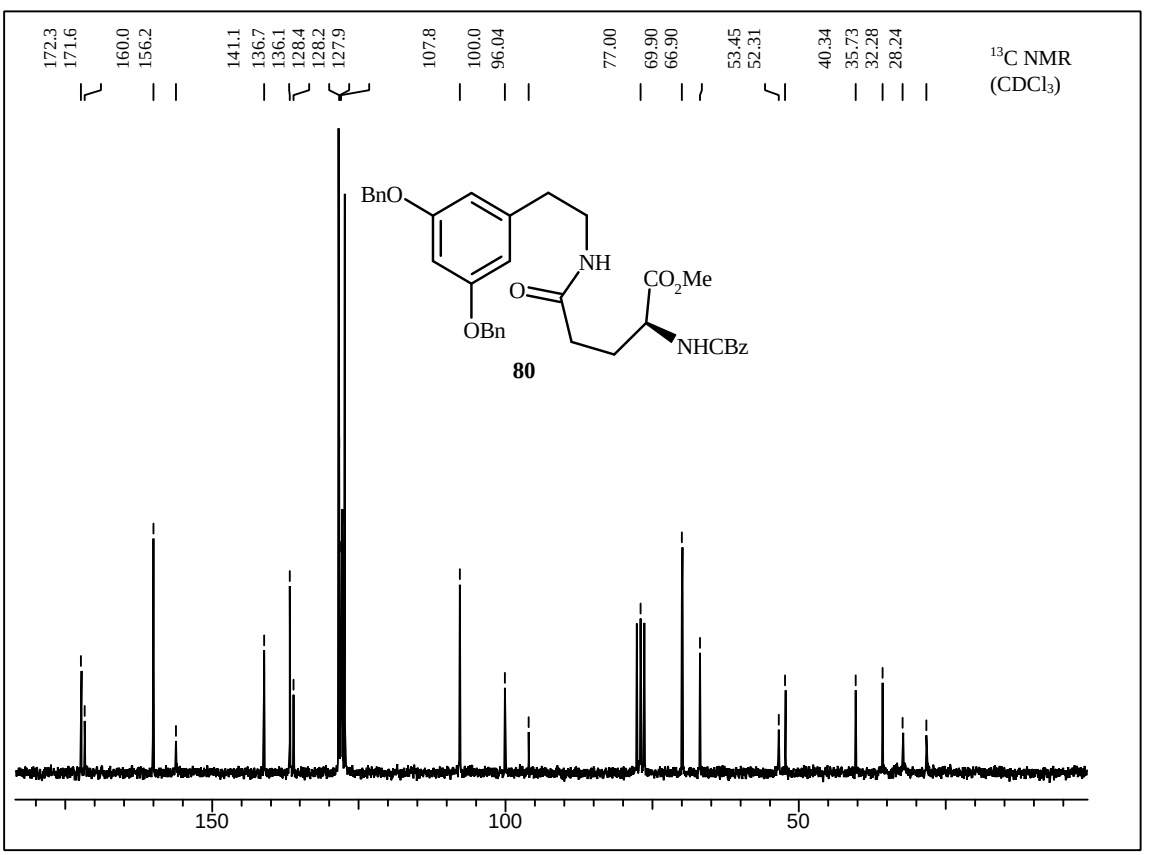

BnO
NO2
OBn
78
1H NMR
(CDCl3)
TMS
0.00
10.03
1.94
4.00
1.99
1.98
8
7
6
5
4
3
2
1
0

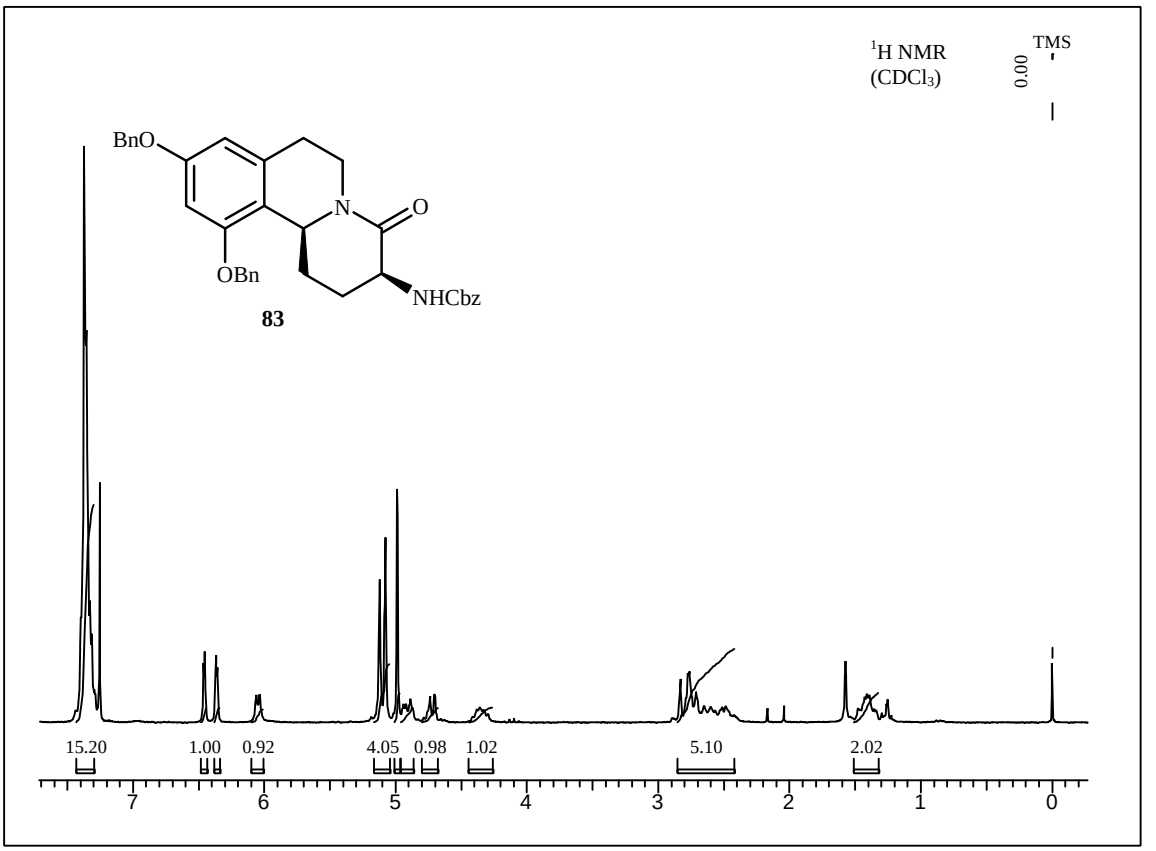

160.36
137.86
136.69
128.60
128.03
127.47
107.83
100.95
96.19
Chloroform-d
77.00
75.91
70.07
33.62
13C NMR
(CDCl3)
BnO
NO2
OBn
78
150
100
50
0

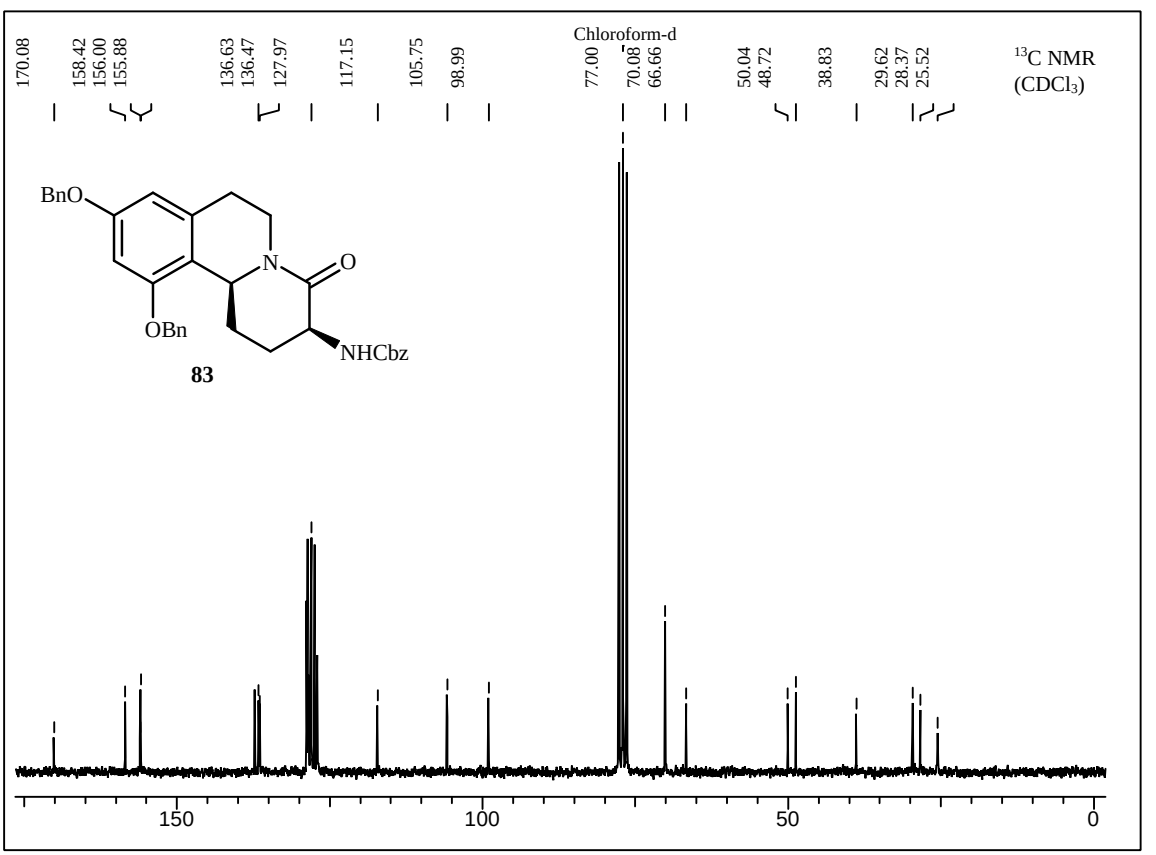

^{1}H NMR
(CDCl$_3$)
TMS
0.00
BnO
NH$_2$
OBn
79
10.00
3.03
4.05
2.01 2.04
7
6
5
4
3
2
1
0

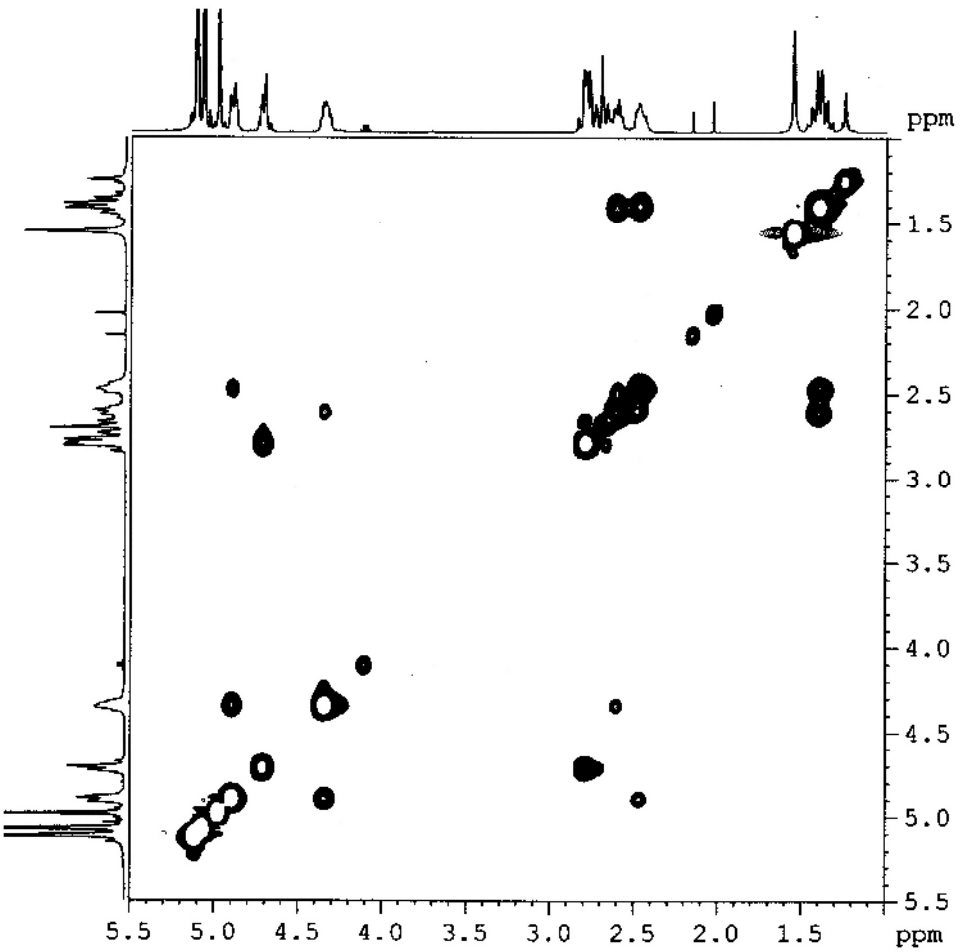

159.9
142.0
136.8
128.4
128.2
127.8
127.4
108.0
99.77
77.00
69.91
43.05
40.10
^{13}C NMR
(CDCl$_3$)
BnO
NH$_2$
OBn
79
150
100
50
0


^{1}H NMR
(CDCl$_3$)
TMS
0.00
BnO
NH
O
CO$_2$Me
OBn
NHCBz
80
15.55
2.03
0.83
4.09
0.98
3.03
2.00
2.27
1.01
8
7
6
5
4
3
2
1
0


172.3
171.6
160.0
156.2
141.1
136.7
136.1
128.4
128.2
127.9
107.8
100.0
96.04
77.00
69.90
66.90
53.45
52.31
40.34
35.73
32.28
28.24
^{13}C NMR
(CDCl$_3$)
BnO
NH
O
CO$_2$Me
OBn
NHCBz
80
150
100
50


^{1}H NMR
(CDCl$_3$)
TMS
0.00
BnO
N
O
OBn
NHCbz
83
15.20
1.00
0.92
4.05
0.98
1.02
5.10
2.02
7
6
5
4
3
2
1
0


170.08
158.42
156.00
155.88
136.63
136.47
127.97
117.15
105.75
98.99
Chloroform-d
77.00
70.08
66.66
50.04
48.72
38.83
29.62
28.37
25.52
^{13}C NMR
(CDCl$_3$)
BnO
N
O
OBn
NHCbz
83
150
100
50
0


ppm
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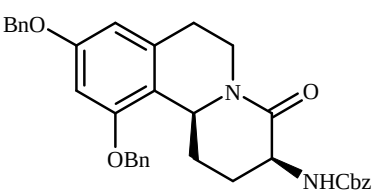
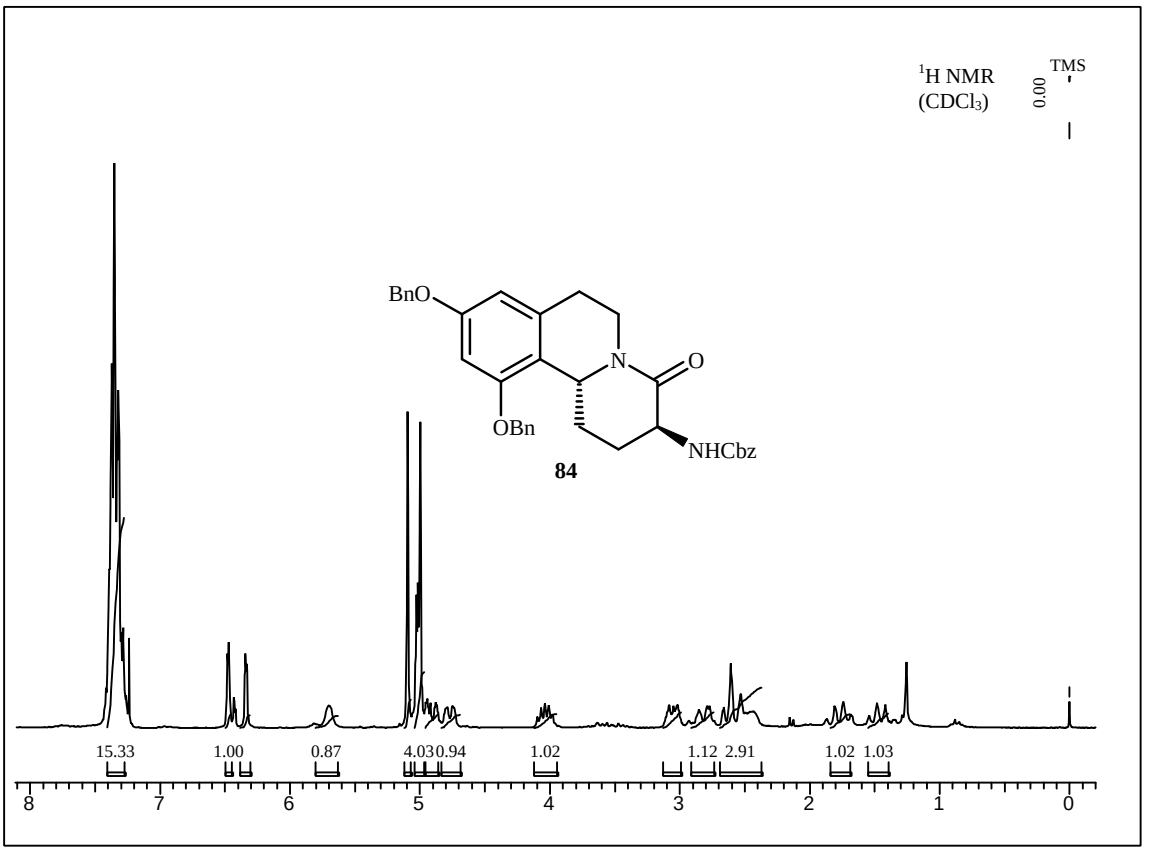
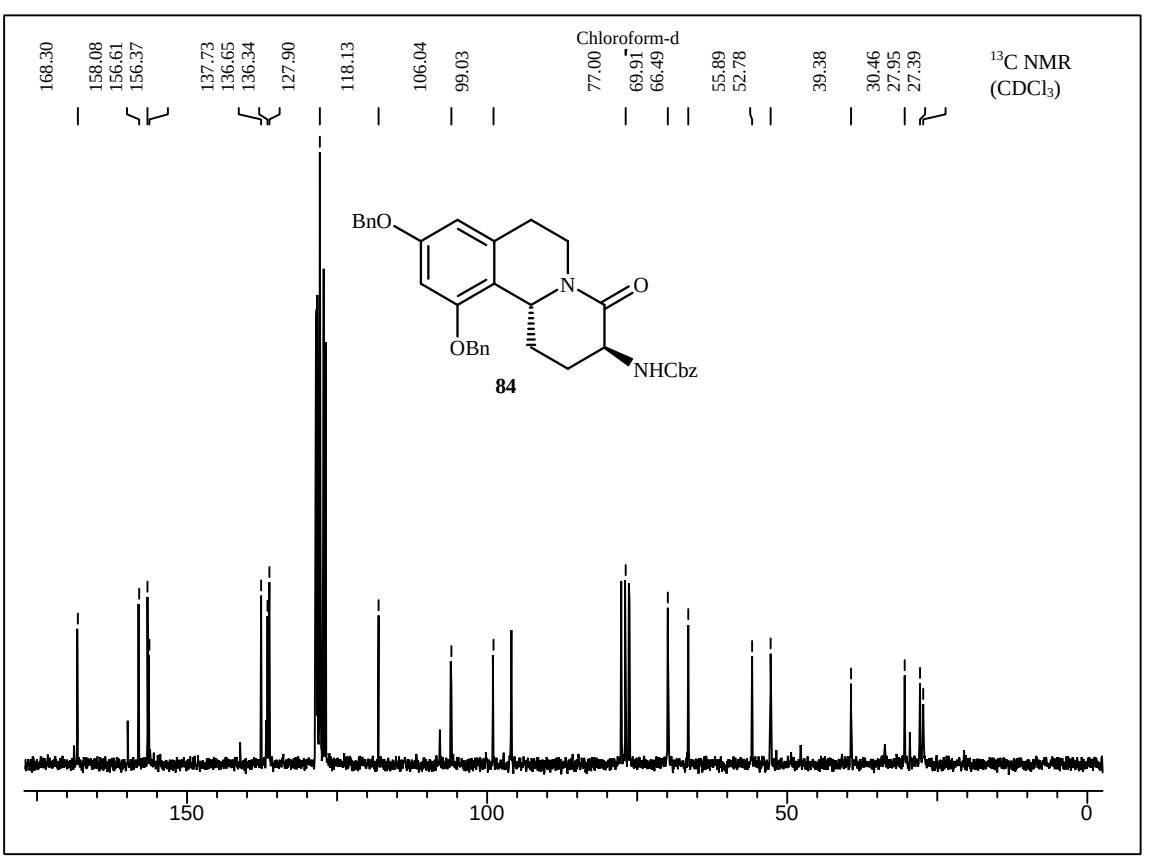
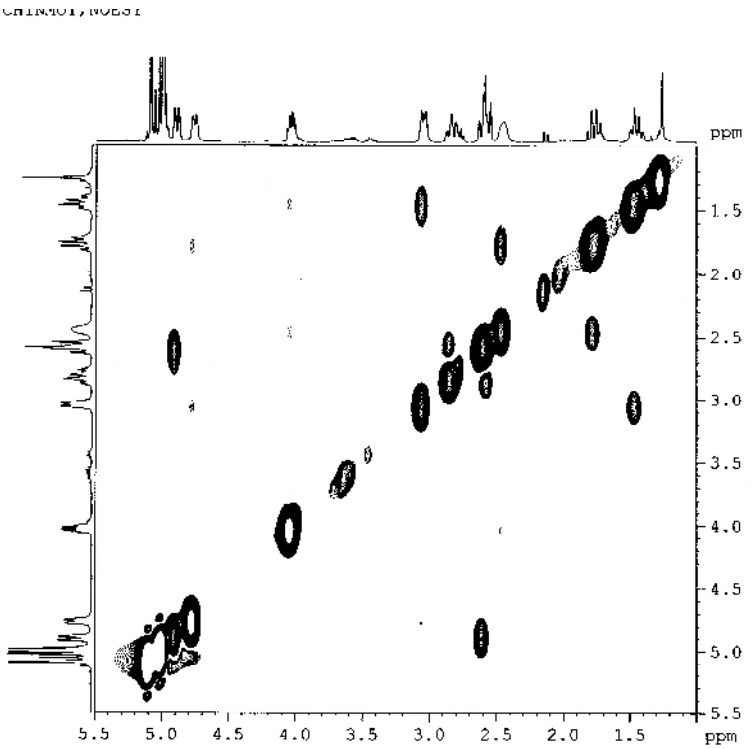
2.5
3.0
3.5
4.0
4.5
5.0
5.5
5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5
ppm


BnO
N
O
OBn
NHCbz

83


^{1}H NMR
(CDCl$_3$)
TMS
0.00
BnO
N
O
OBn
NHCbz
84
15.33
1.00
0.87
4.03
0.94
1.02
1.12
2.91
1.02
1.03
8
7
6
5
4
3
2
1
0


168.30
158.08
156.61
156.37
137.73
136.65
136.34
127.90
118.13
106.04
99.03
Chloroform-d
77.00
69.91
66.49
55.89
52.78
39.38
30.46
27.95
27.39
^{13}C NMR
(CDCl$_3$)
BnO
N
O
OBn
NHCbz
84
150
100
50
0


ppm
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5
ppm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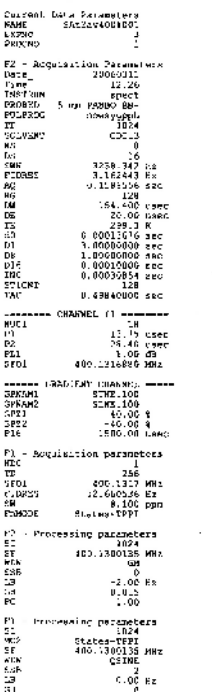
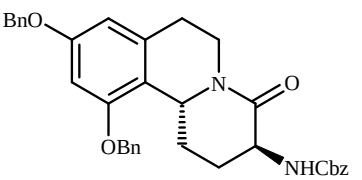
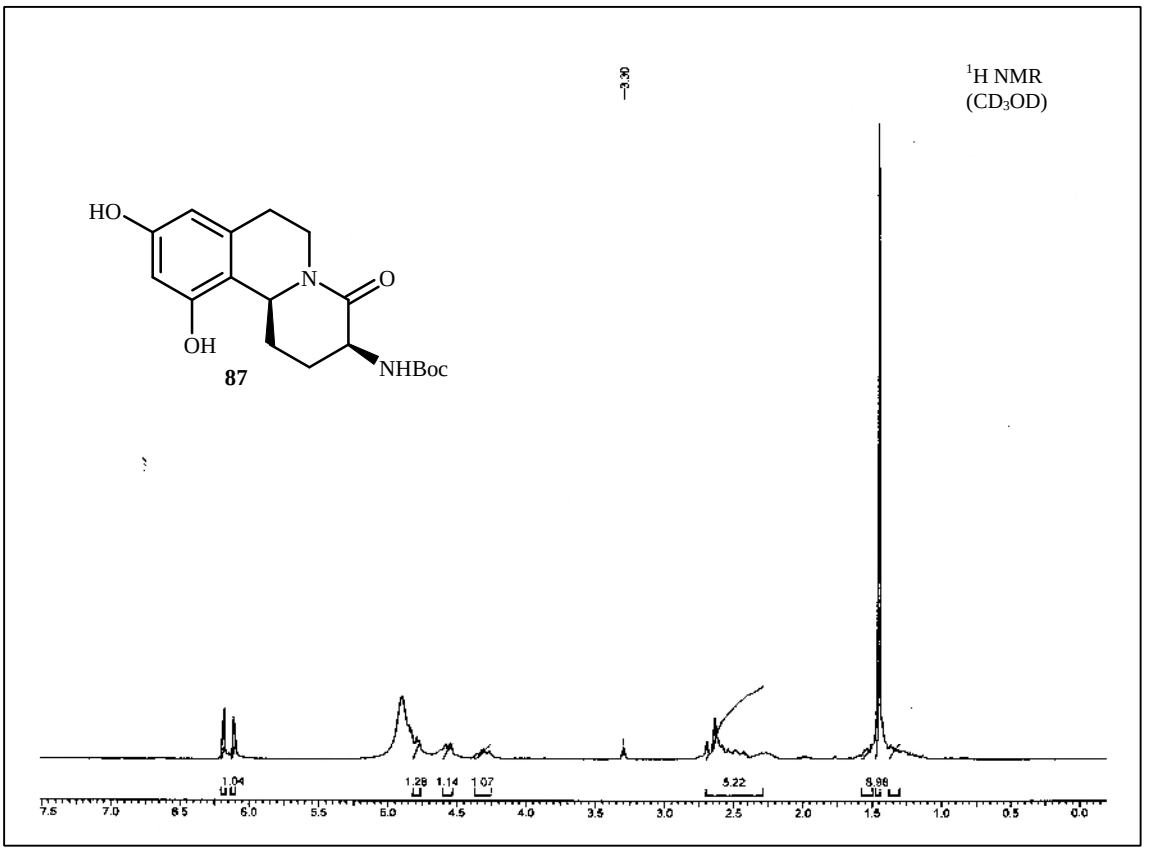
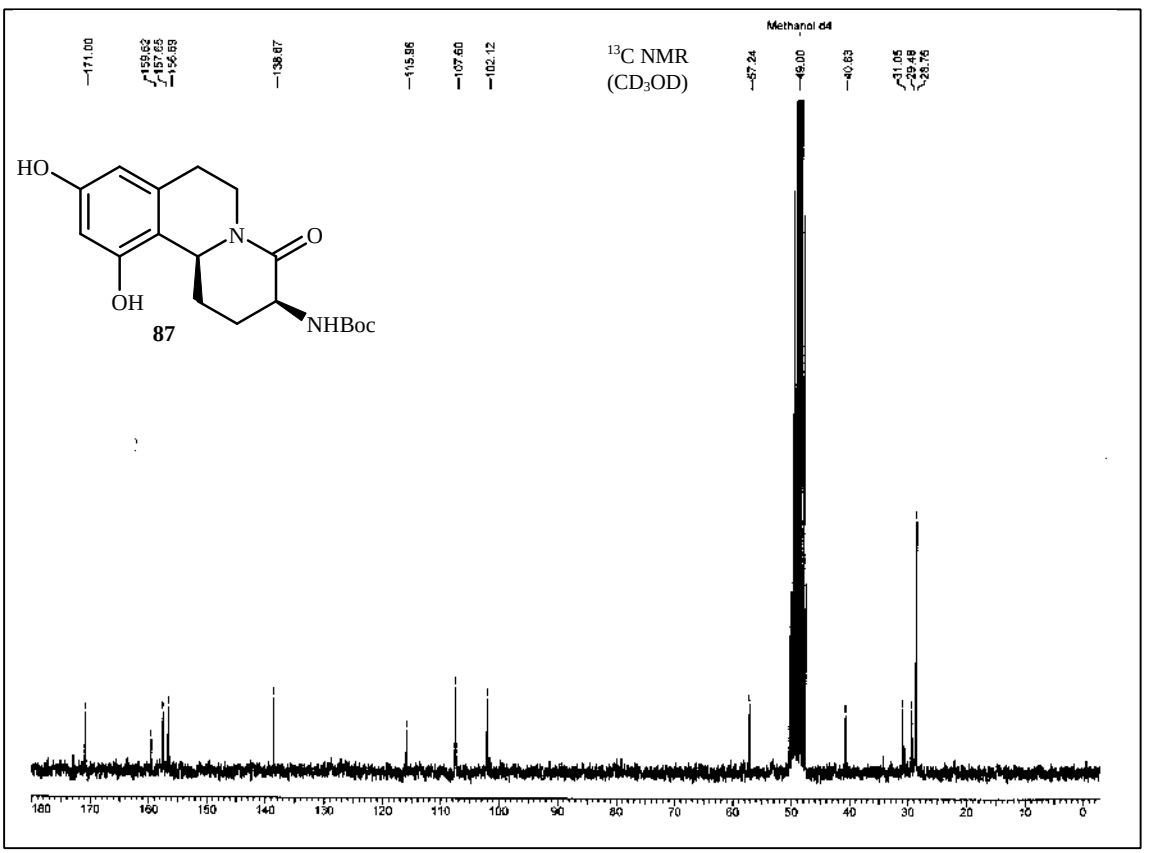
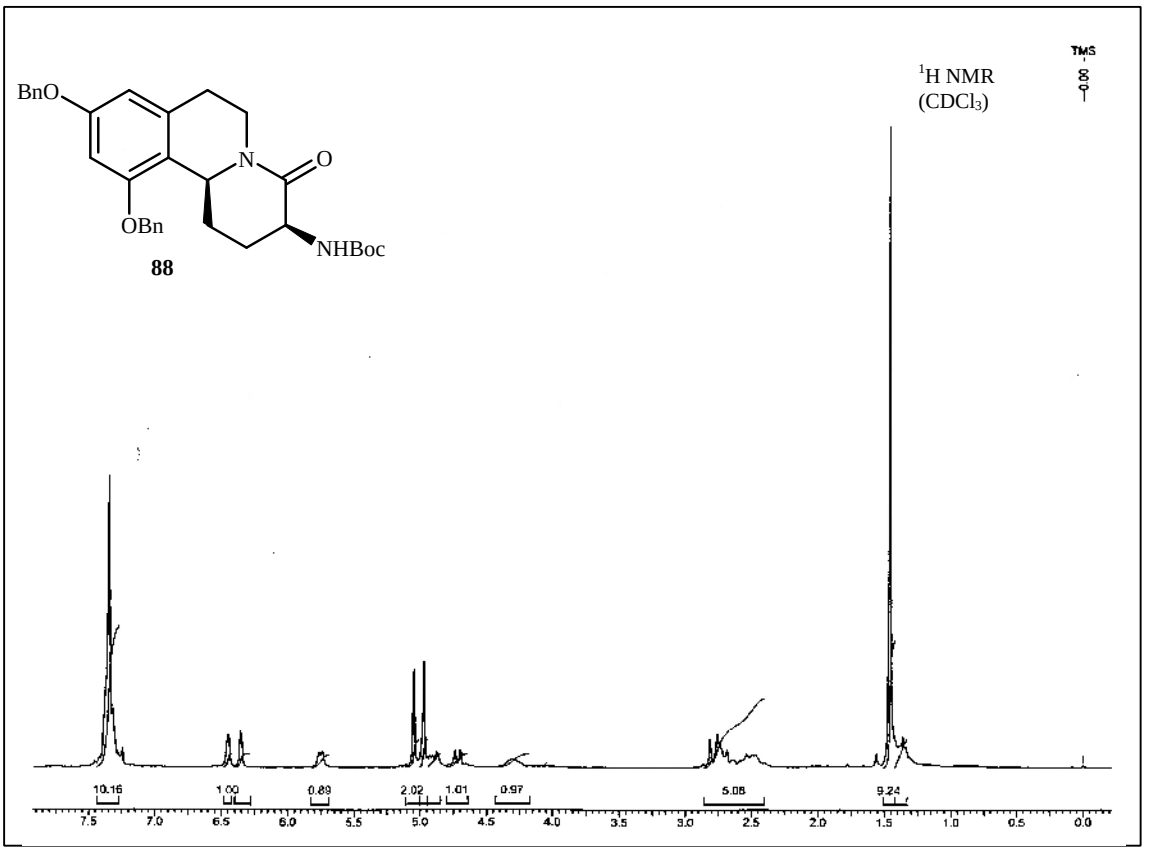


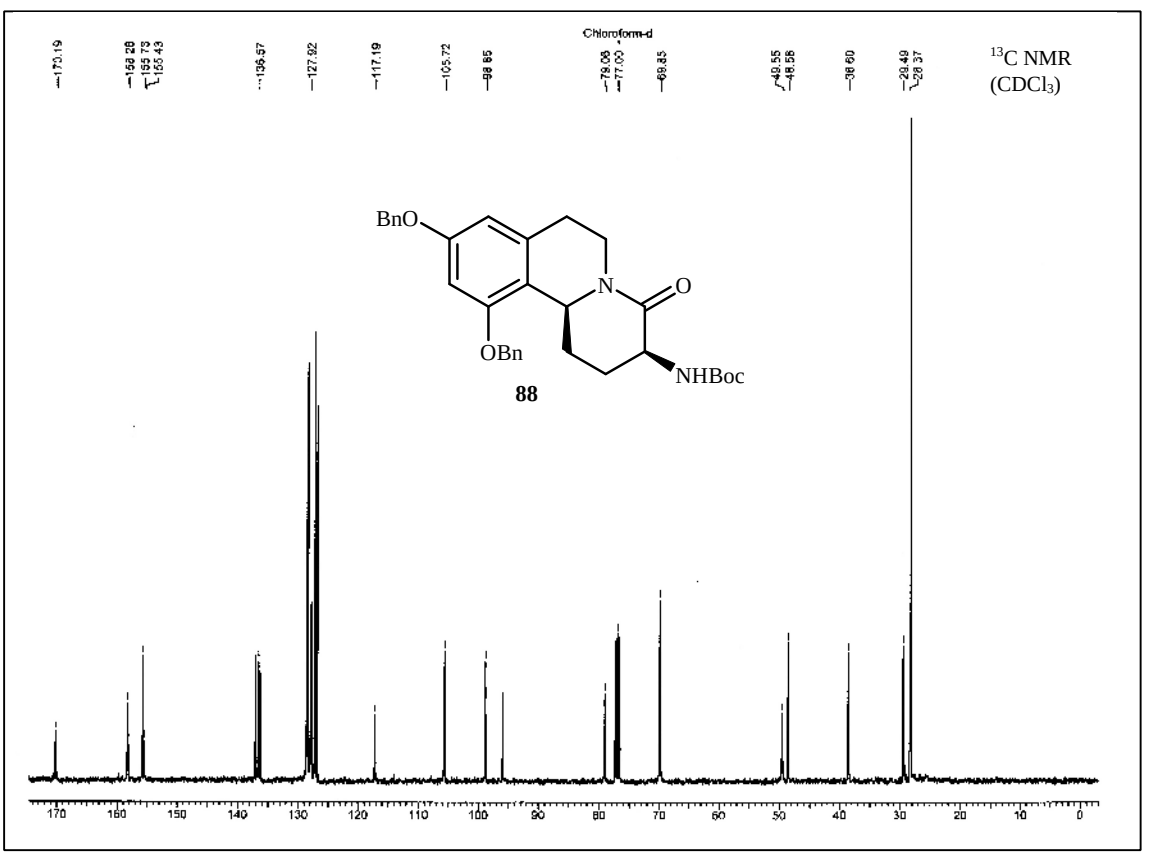

BnO
N
O
OBn
NHCbz

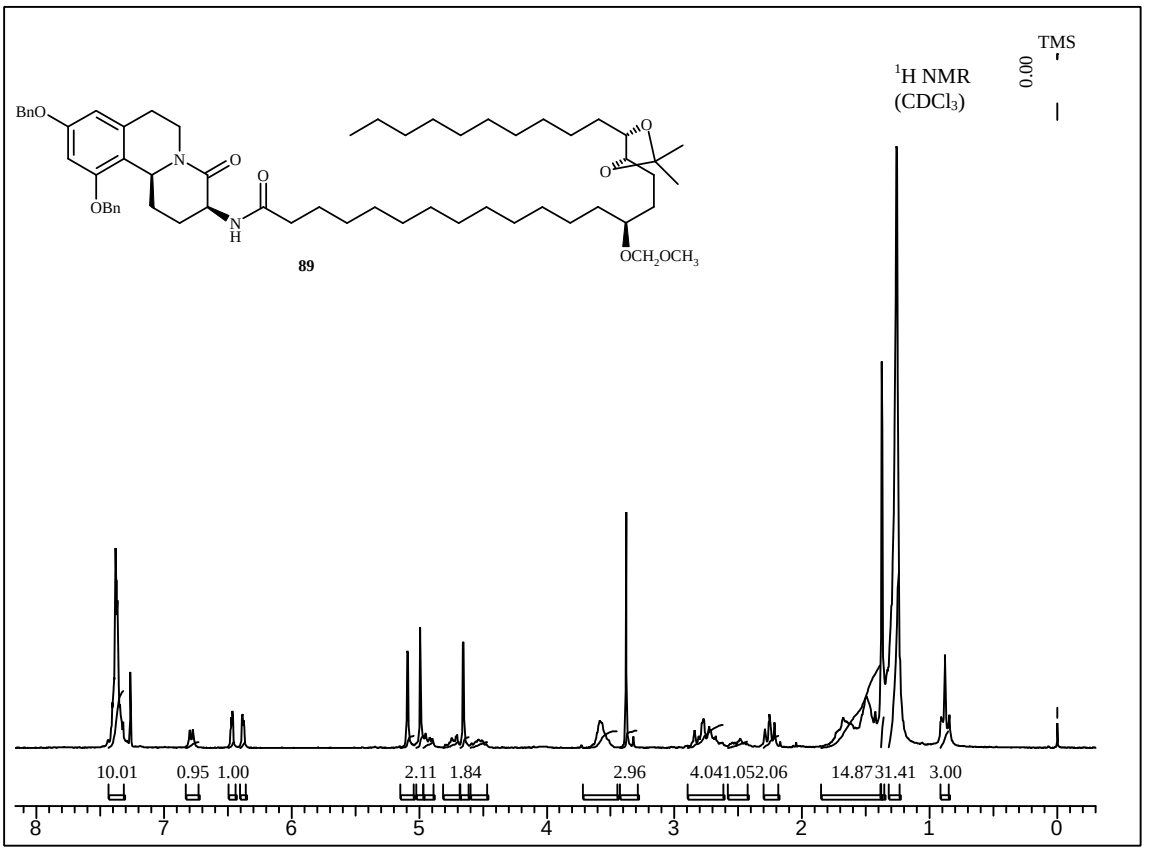
84

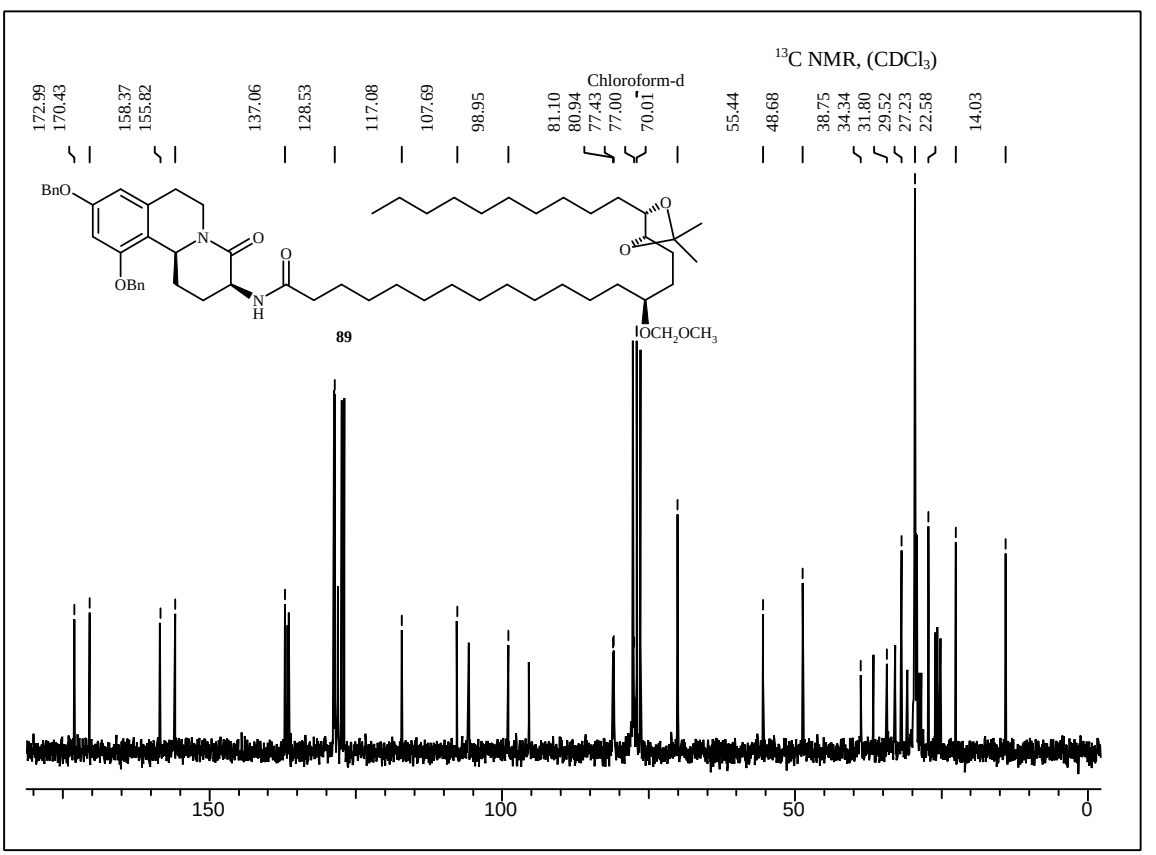

^{1}H NMR
(CD_3OD)
HO
N
O
OH
NHBoc
87
3.30
1.04
1.28
1.14
1.07
5.22
8.86

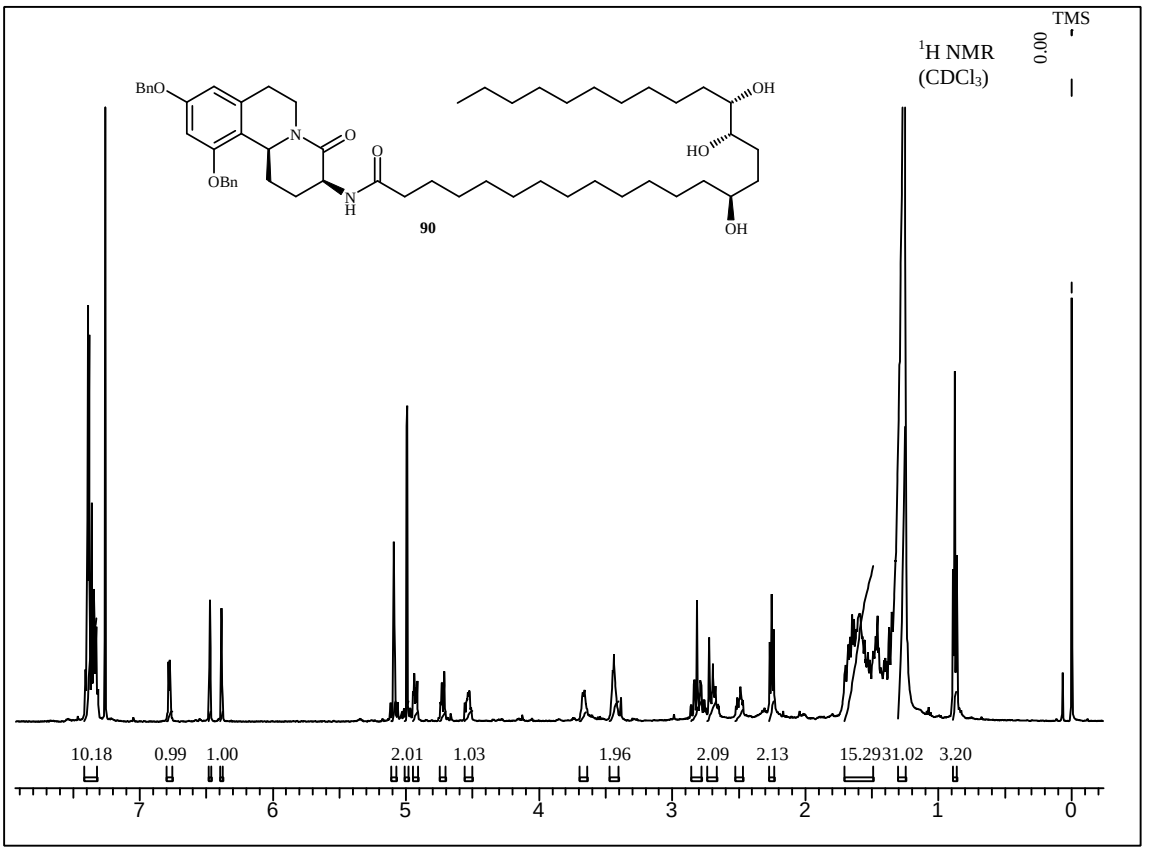

^{13}C NMR
(CD_3OD)
Methanol d4
171.00
159.62
157.65
156.69
138.87
115.96
107.60
102.12
57.24
49.00
40.83
31.05
29.49
28.76
HO
N
O
OH
NHBoc
87

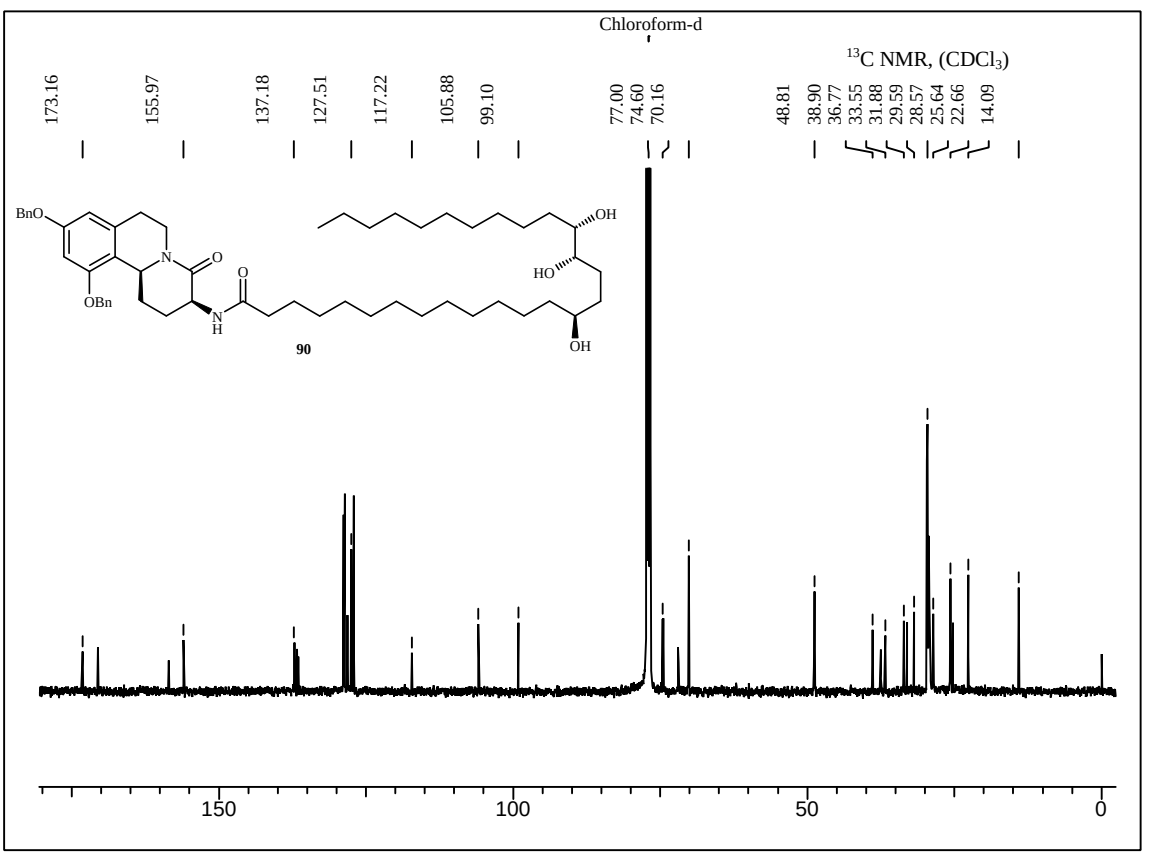

BnO
N
O
OBn
NHBoc
88
^{1}H NMR
($CDCl_3$)
TMS
10.16
1.00
0.89
2.02
1.01
0.97
5.08
9.24

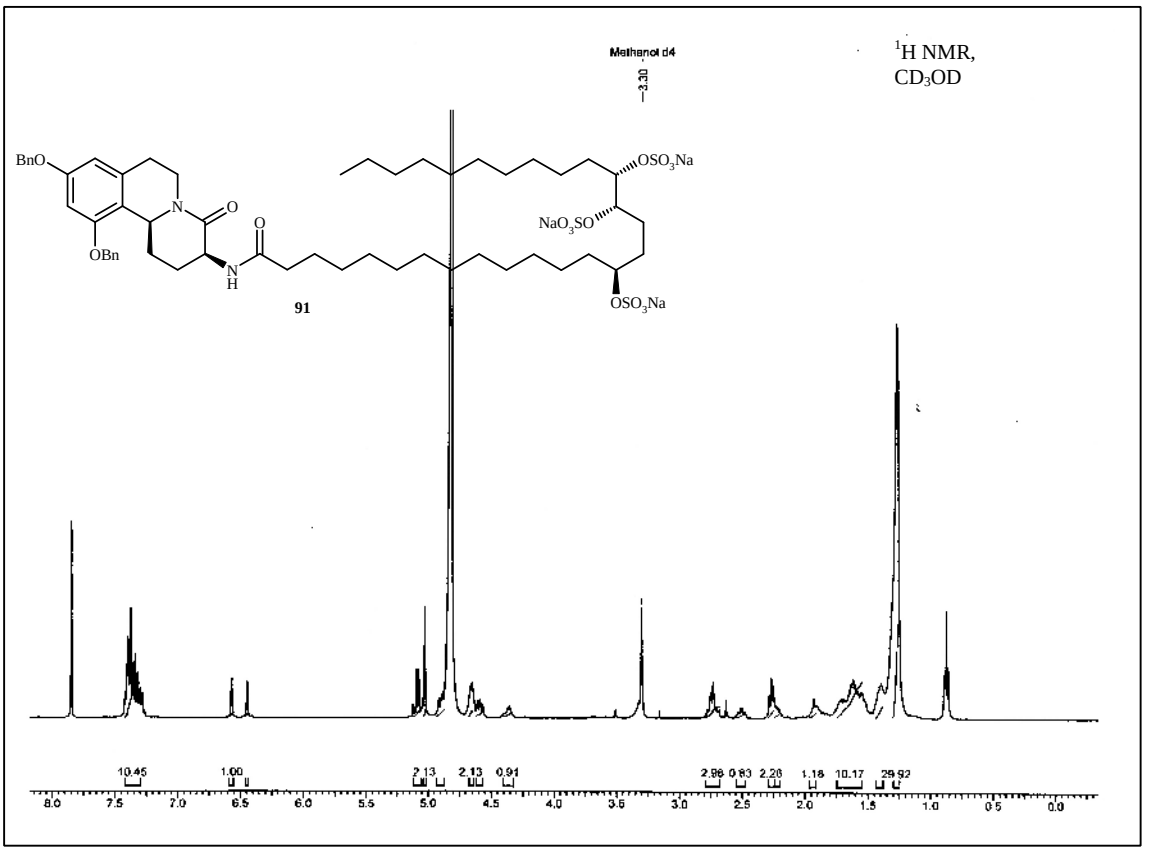

Chloroform-d
BnO
N
O
OBn
NHBoc
88
^{13}C NMR
($CDCl_3$)

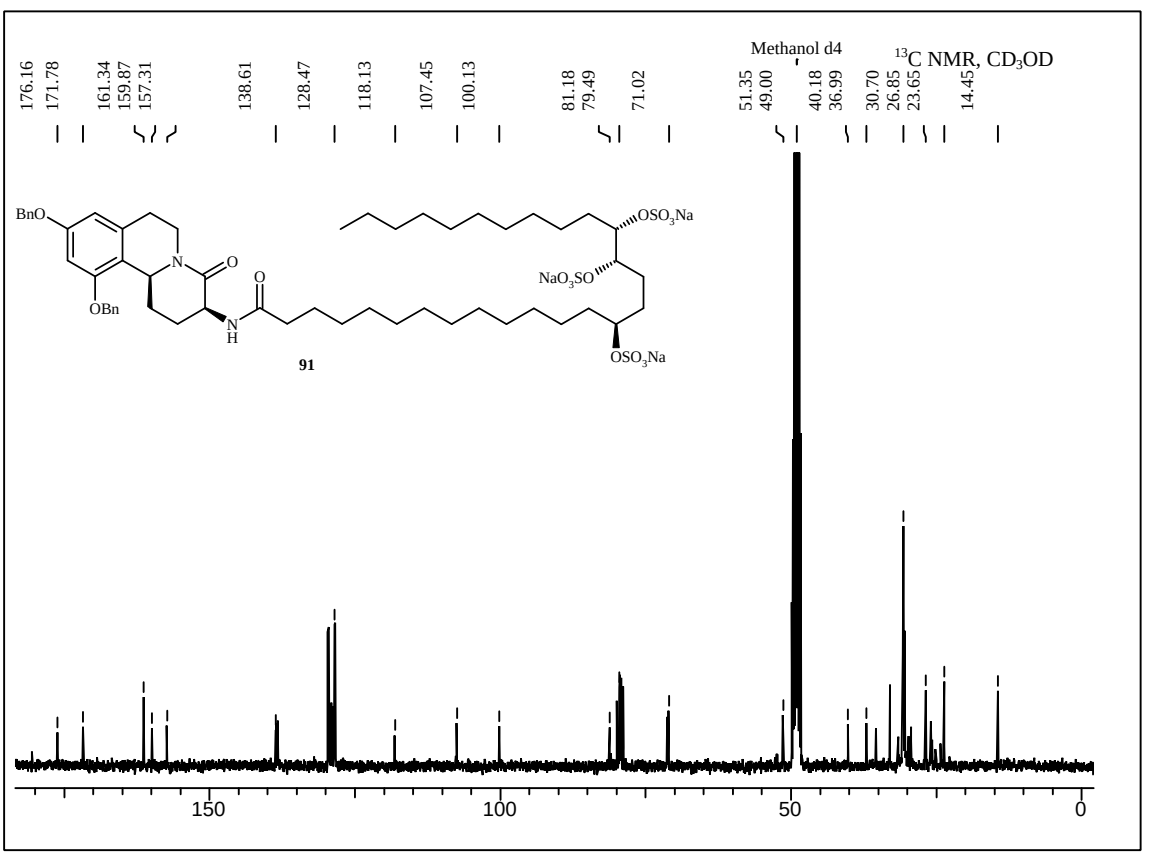

TMS
0.00
^{1}H NMR
(CDCl$_3$)
BnO
OBn
N
O
O
N
H
O
O
O
OCH$_2$OCH$_3$
89
10.01
0.95
1.00
2.11
1.84
2.96
4.04
1.05
2.06
14.87
31.41
3.00
8
7
6
5
4
3
2
1
0

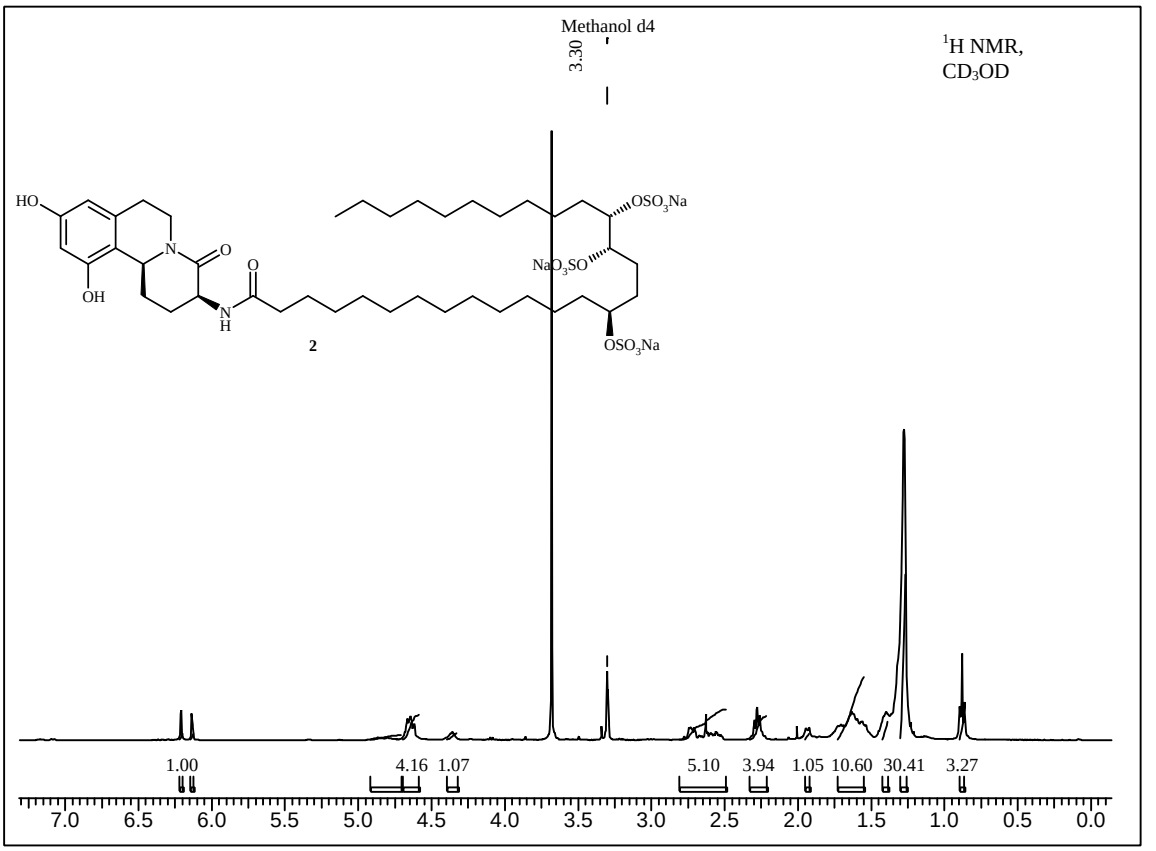

^{13}C NMR, (CDCl$_3$)
Chloroform-d
172.99
170.43
158.37
155.82
137.06
128.53
117.08
107.69
98.95
81.10
80.94
77.43
77.00
70.01
55.44
48.68
38.75
34.34
31.80
29.52
27.23
22.58
14.03
BnO
OBn
N
O
O
N
H
O
O
O
OCH$_2$OCH$_3$
89
150
100
50
0

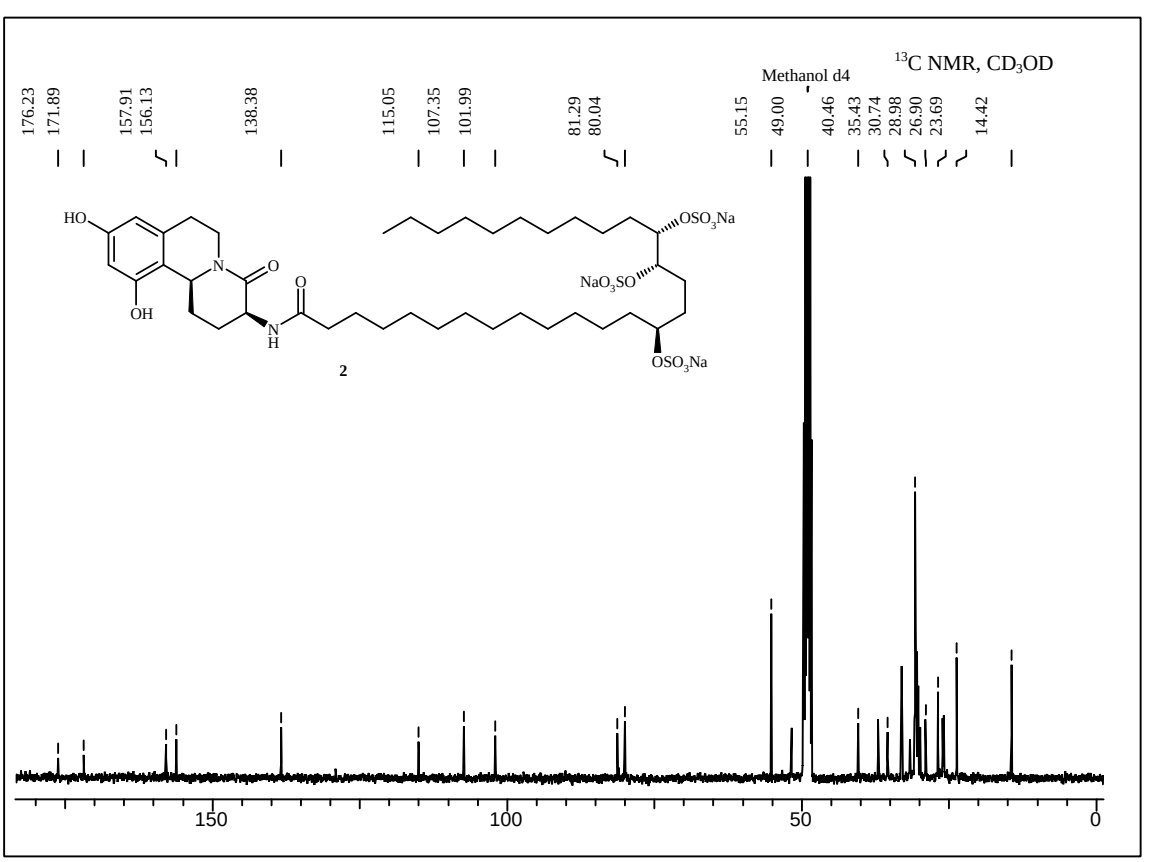

TMS
0.00
^{1}H NMR
(CDCl$_3$)
BnO
OBn
N
O
O
N
H
OH
HO
OH
90
10.18
0.99
1.00
2.01
1.03
1.96
2.09
2.13
15.29
31.02
3.20
7
6
5
4
3
2
1
0

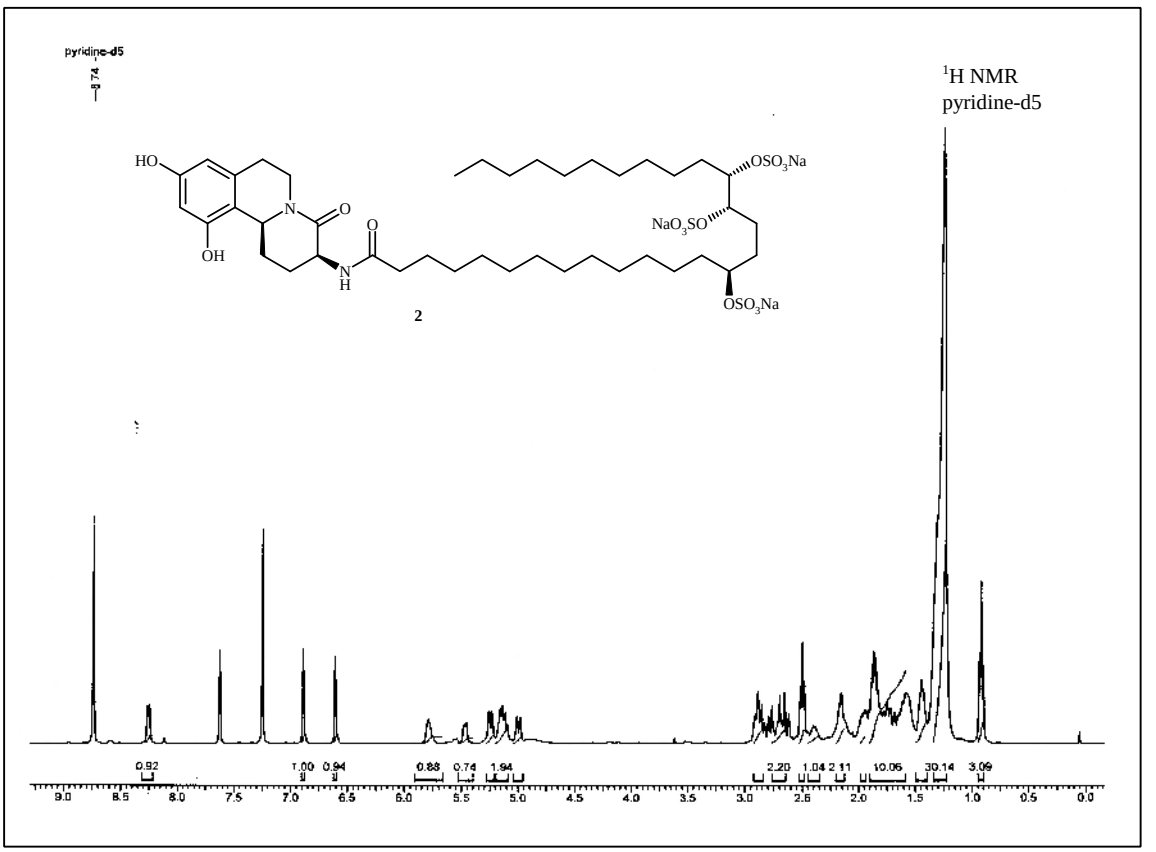

Chloroform-d
^{13}C NMR, (CDCl$_3$)
173.16
155.97
137.18
127.51
117.22
105.88
99.10
77.00
74.60
70.16
48.81
38.90
36.77
33.55
31.88
29.59
28.57
25.64
22.66
14.09
BnO
OBn
N
O
O
N
H
OH
HO
OH
90
150
100
50
0

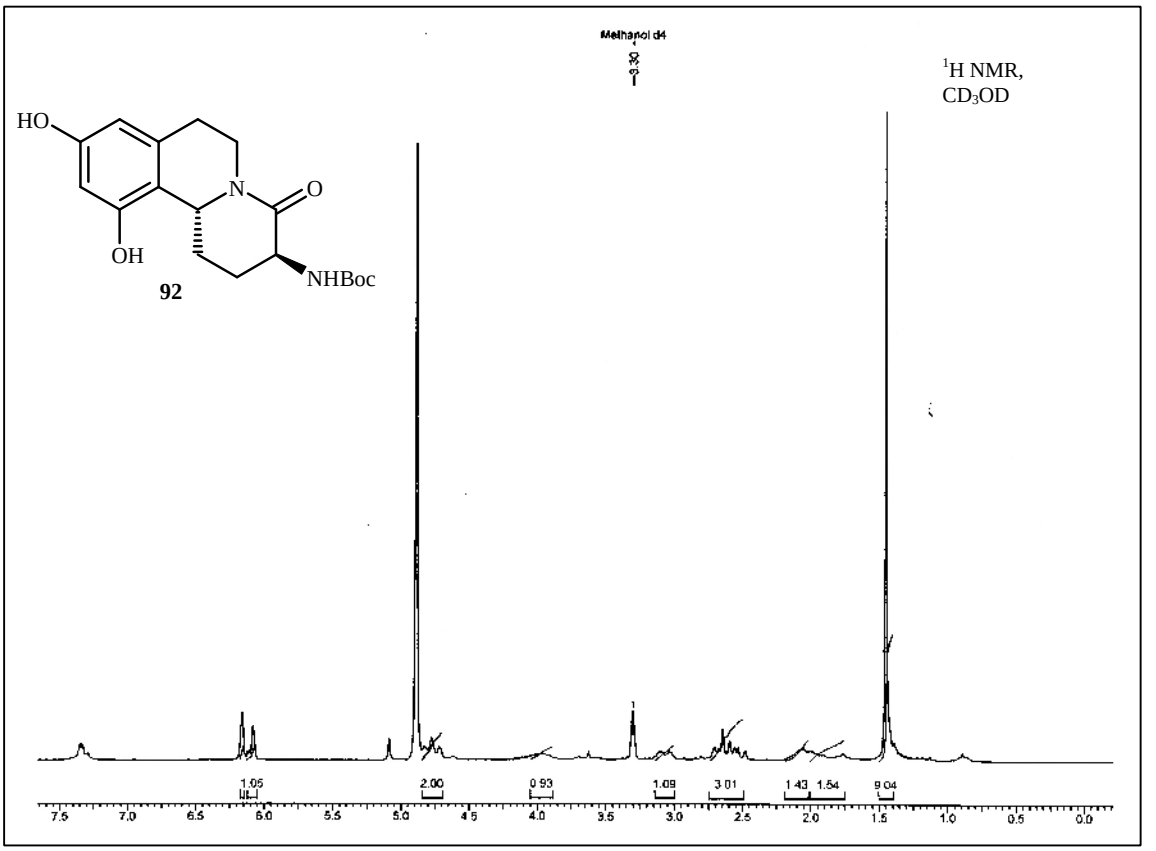

Methanol d4
3.30
^{1}H NMR,
CD_3OD
BnO
OBn
N
O
O
N
H
OSO_3Na
NaO_3SO
OSO_3Na
91
10.45
1.00
2.13
2.13
0.91
2.98
0.83
2.28
1.18
10.17
29.92

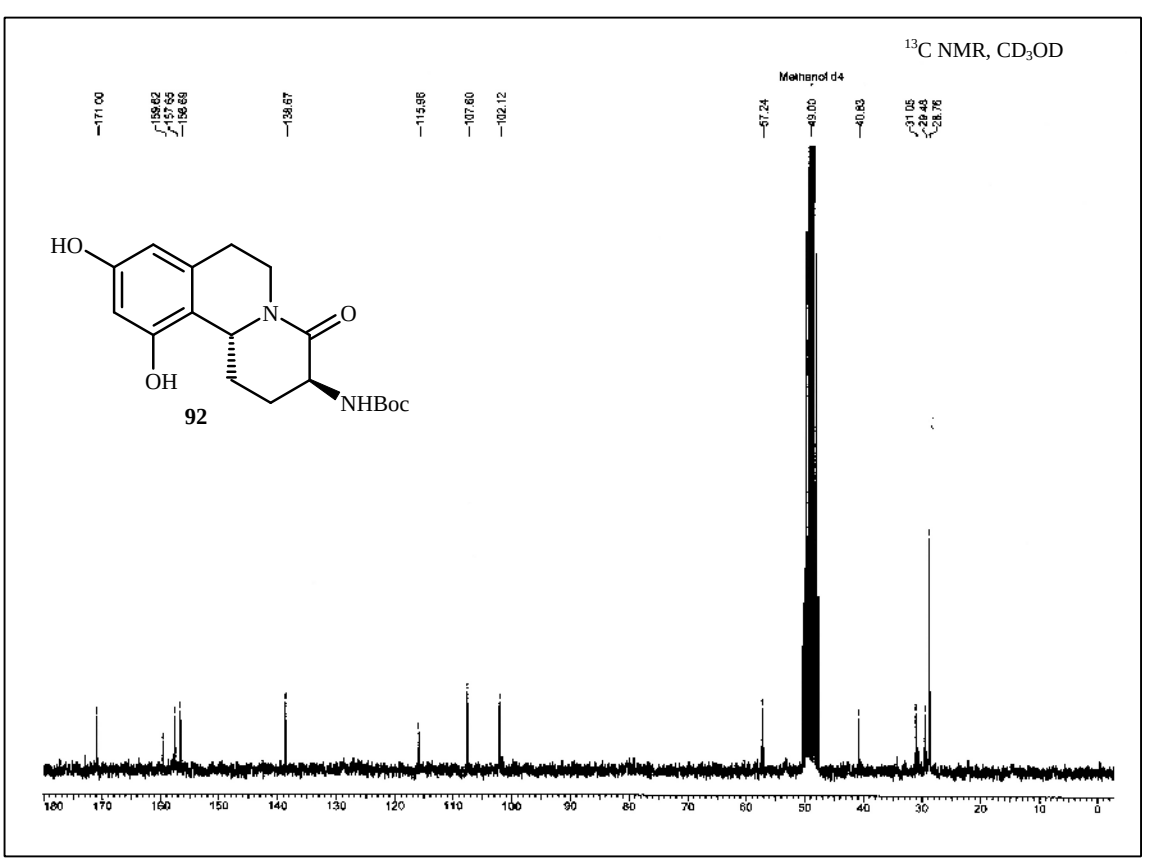

176.16
171.78
161.34
159.87
157.31
138.61
128.47
118.13
107.45
100.13
81.18
79.49
71.02
51.35
49.00
Methanol d4
40.18
36.99
30.70
26.85
23.65
14.45
^{13}C NMR, CD_3OD
BnO
OBn
N
O
O
N
H
OSO_3Na
NaO_3SO
OSO_3Na
91
150
100
50
0

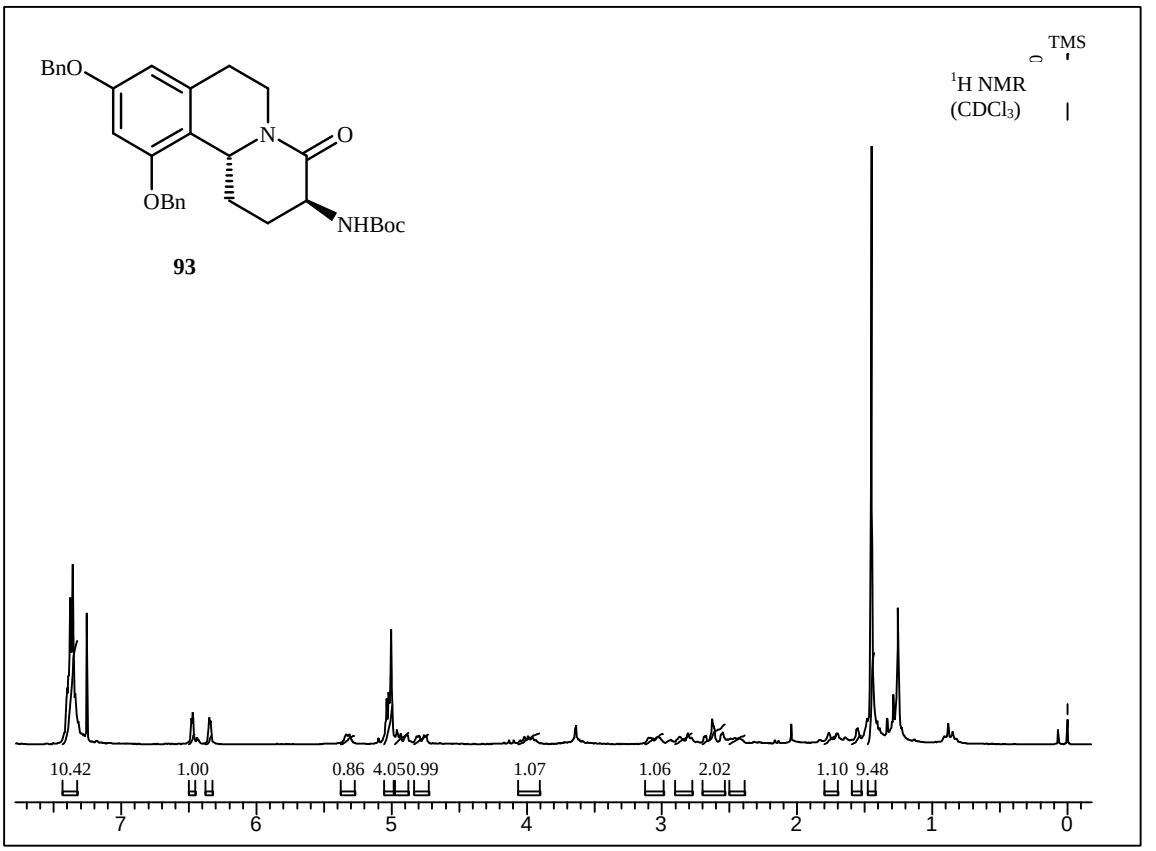

Methanol d4
3.30
^{1}H NMR,
CD_3OD
HO
OH
N
O
O
N
H
OSO_3Na
NaO_3SO
OSO_3Na
2
1.00
4.16
1.07
5.10
3.94
1.05
10.60
30.41
3.27
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

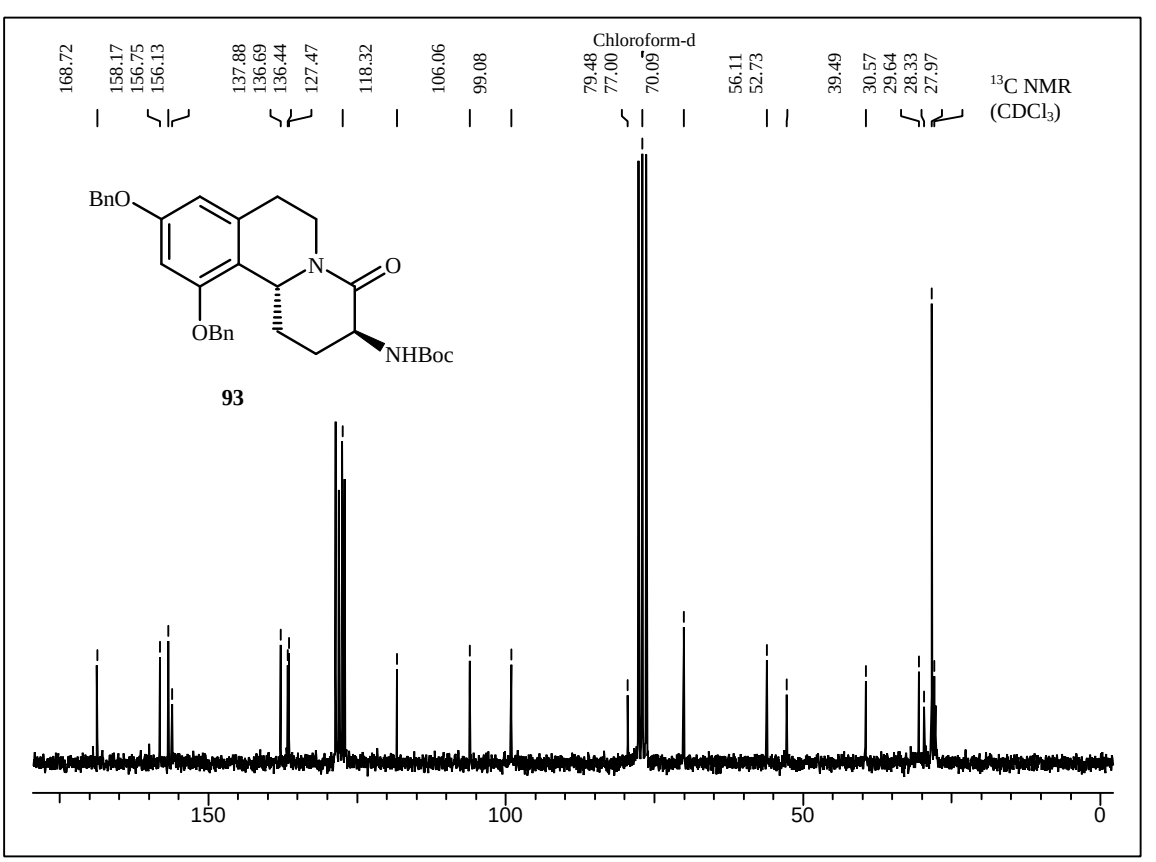

^{13}C NMR, CD_3OD
Methanol d4
176.23
171.89
157.91
156.13
138.38
115.05
107.35
101.99
81.29
80.04
55.15
49.00
40.46
35.43
30.74
28.98
26.90
23.69
14.42
HO
OH
N
O
O
N
H
OSO_3Na
NaO_3SO
OSO_3Na
2
150
100
50
0

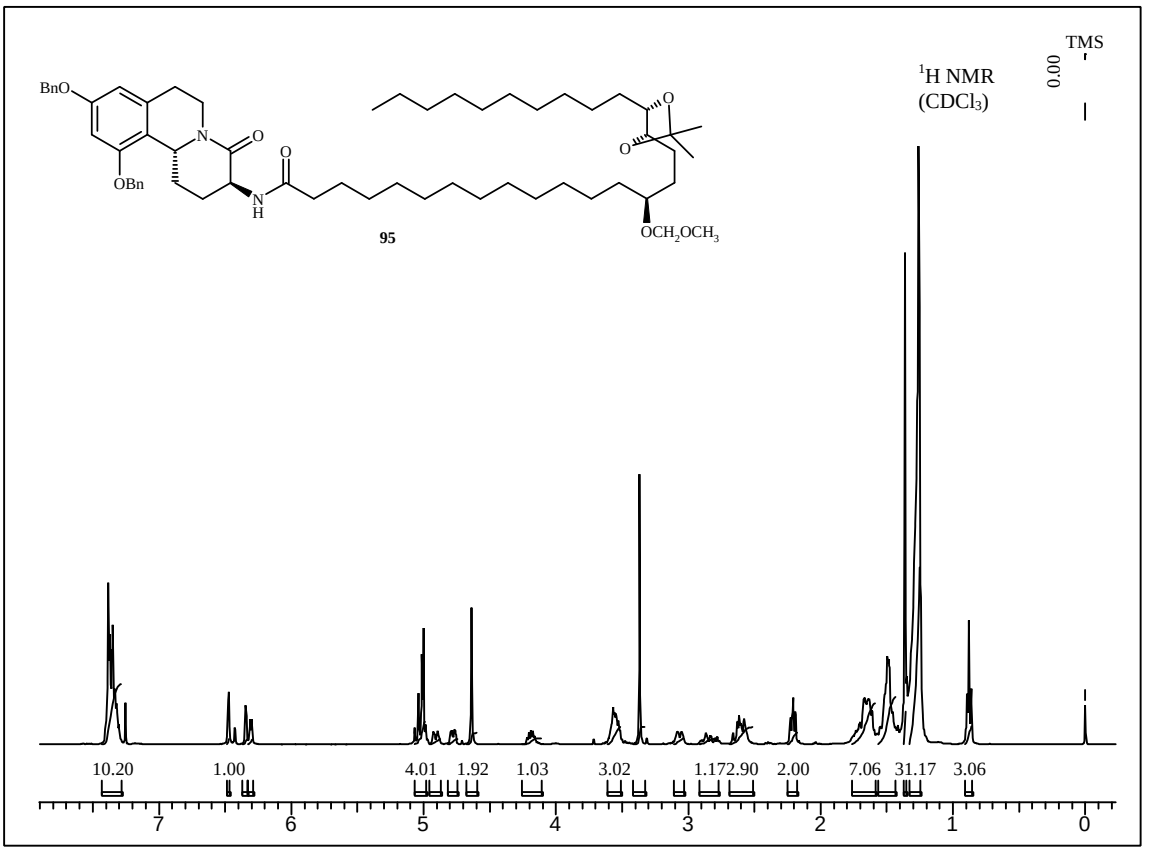

pyridine-d5
7.74
^{1}H NMR
pyridine-d5
HO
OH
N
O
O
N
H
OSO_3Na
NaO_3SO
OSO_3Na
2
0.92
1.00
0.94
0.88
0.74
1.94
2.20
1.04
2.11
10.06
30.14
3.09
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

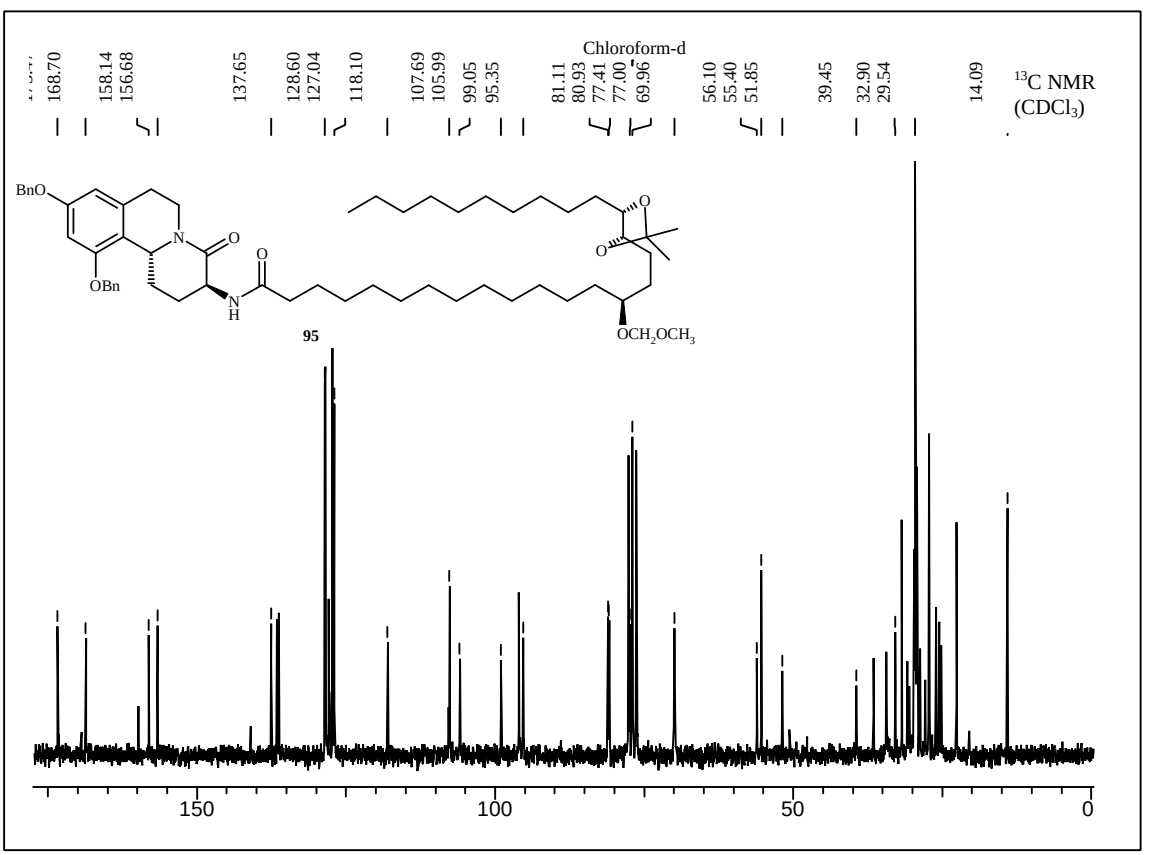

Methanol d4
HO
N
O
OH
NHBoc
92
1H NMR,
CD3OD

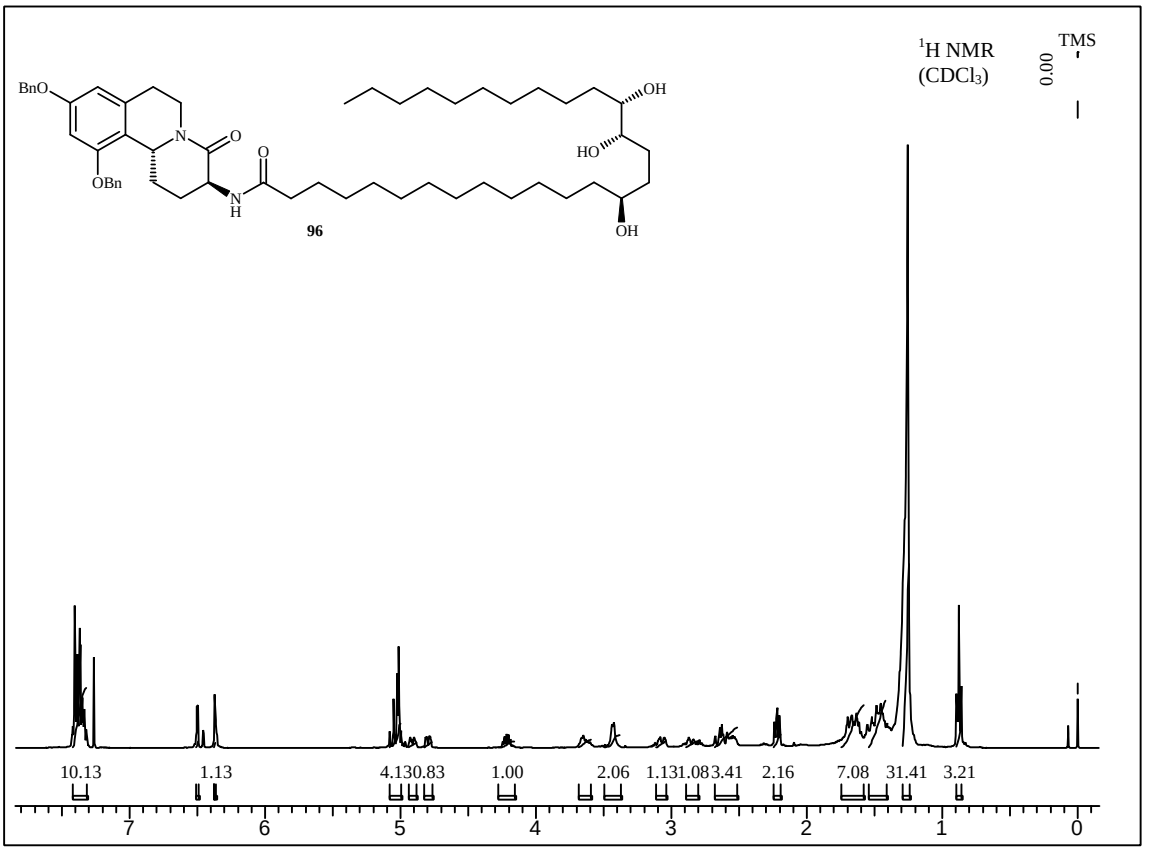

13C NMR, CD3OD
Methanol d4
HO
N
O
OH
NHBoc
92

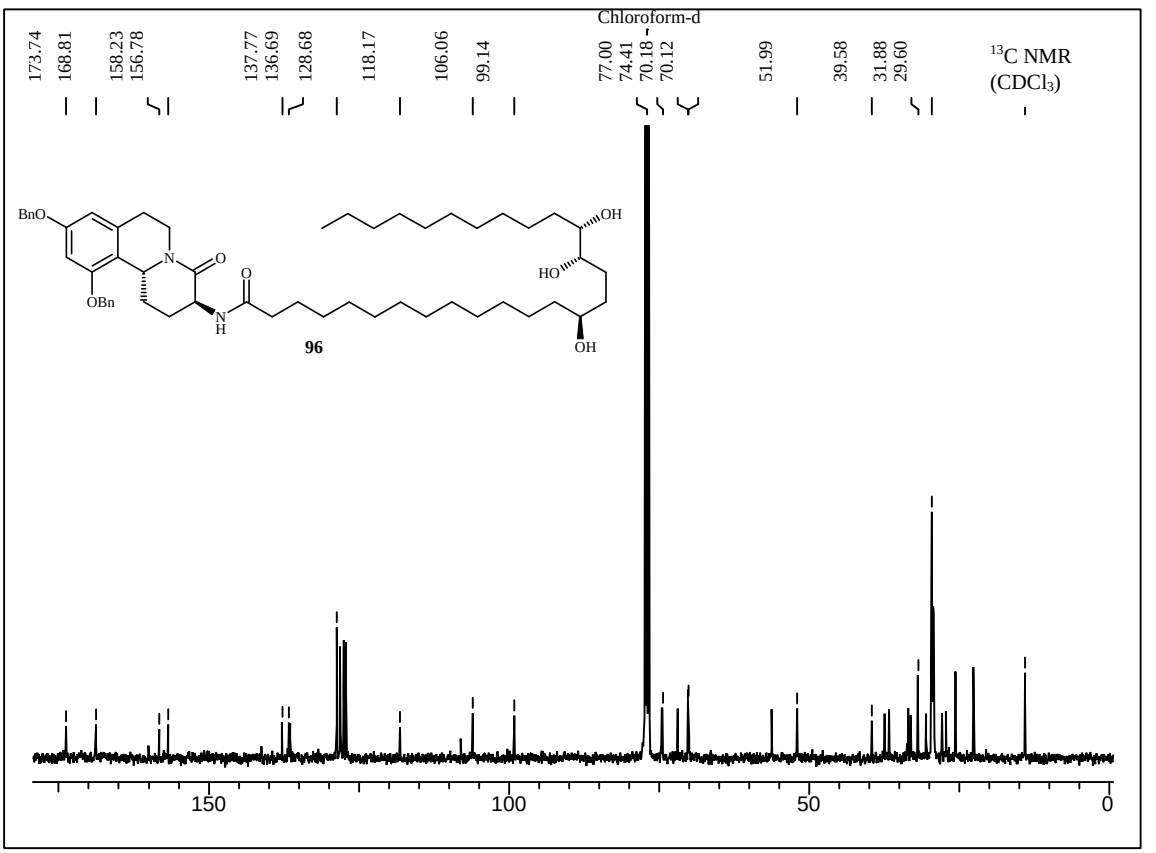

BnO
N
O
OBn
NHBoc
93
TMS
^{1}H NMR
($CDCl_3$)
10.42
1.00
0.86
4.05
0.99
1.07
1.06
2.02
1.10
9.48
7
6
5
4
3
2
1
0

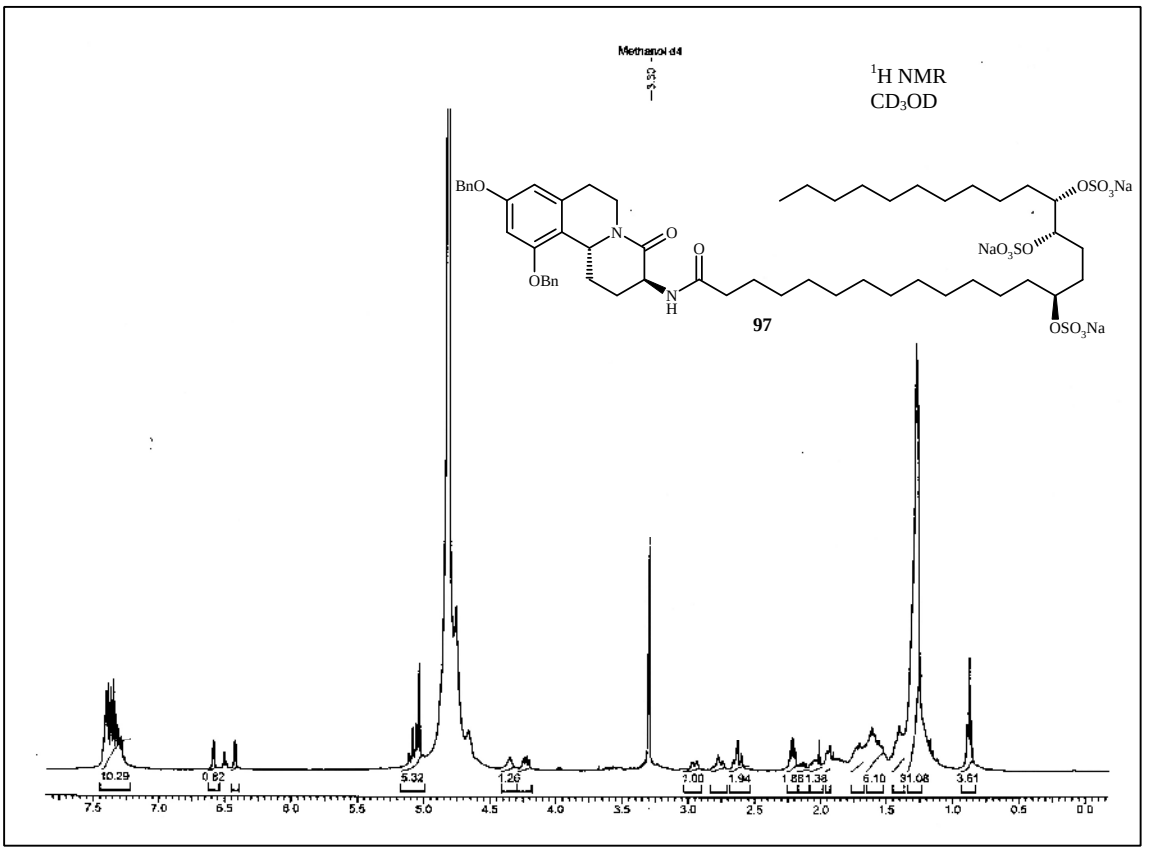

168.72
158.17
156.75
156.13
137.88
136.69
136.44
127.47
118.32
106.06
99.08
79.48
77.00
70.09
56.11
52.73
39.49
30.57
29.64
28.33
27.97
Chloroform-d
^{13}C NMR
($CDCl_3$)
BnO
N
O
OBn
NHBoc
93
150
100
50
0


BnO
OBn
N
O
O
N
H
O
O
OCH2OCH3
95
1H NMR
(CDCl3)
TMS
0.00
10.20
1.00
4.01
1.92
1.03
3.02
1.17
2.90
2.00
7.06
31.17
3.06
7
6
5
4
3
2
1
0

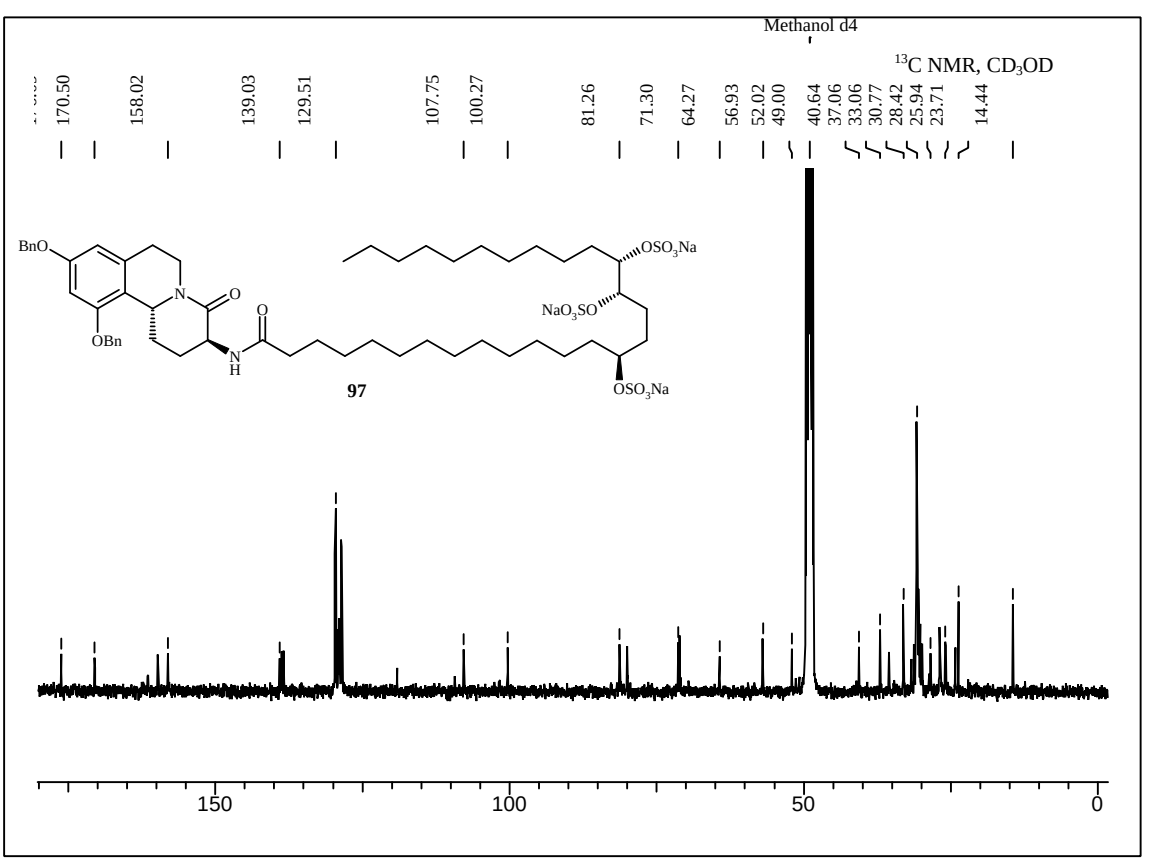

Chloroform-d
168.70
158.14
156.68
137.65
128.60
127.04
118.10
107.69
105.99
99.05
95.35
81.11
80.93
77.41
77.00
69.96
56.10
55.40
51.85
39.45
32.90
29.54
14.09
13C NMR
(CDCl3)
BnO
OBn
N
O
O
N
H
O
O
OCH2OCH3
95
150
100
50
0


BnO
OBn
N
O
N
H
O
HO
OH
OH
96
^{1}H NMR
(CDCl$_3$)
TMS
0.00
10.13
1.13
4.13
0.83
1.00
2.06
1.13
1.08
3.41
2.16
7.08
31.41
3.21
7
6
5
4
3
2
1
0

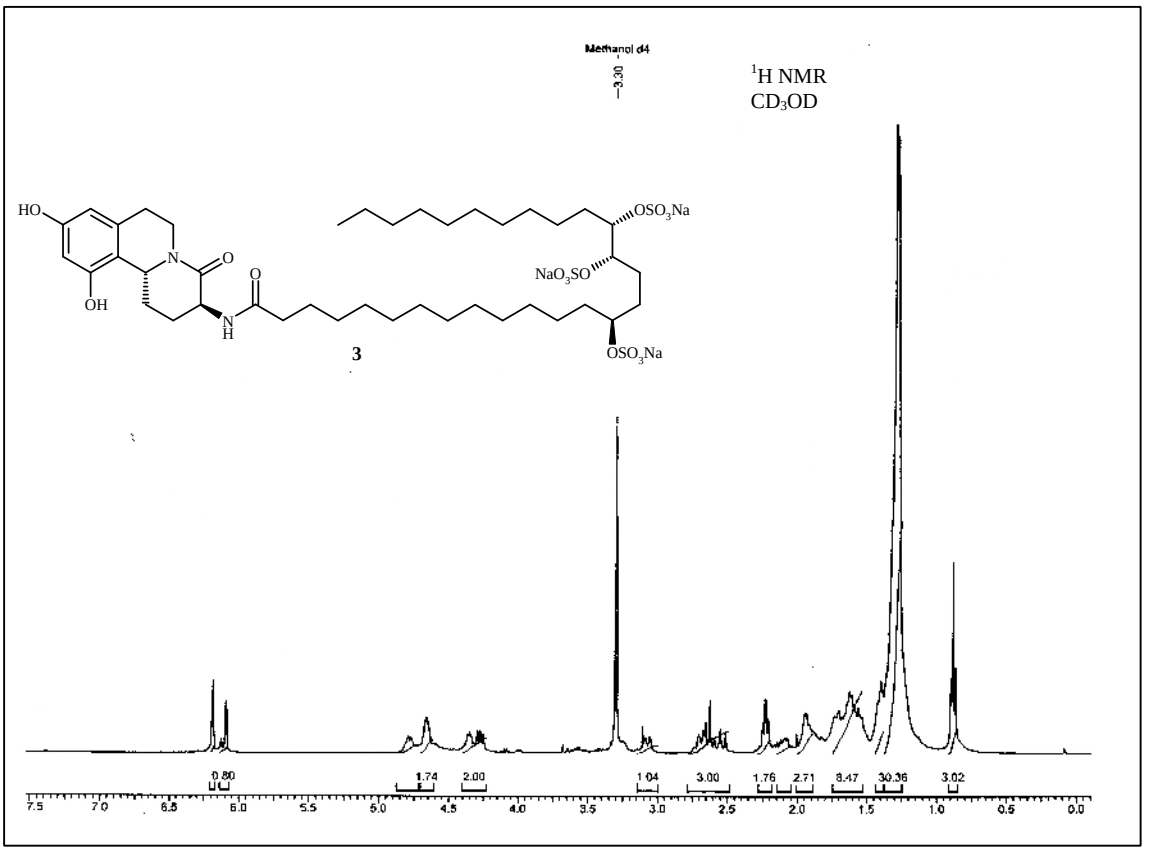

Chloroform-d
173.74
168.81
158.23
156.78
137.77
136.69
128.68
118.17
106.06
99.14
77.00
74.41
70.18
70.12
51.99
39.58
31.88
29.60
^{13}C NMR
(CDCl$_3$)
BnO
OBn
N
O
N
H
O
HO
OH
OH
96
150
100
50
0


Methanol d4
3.30
^{1}H NMR
CD_3OD
BnO
OBn
N
O
O
N
H
OSO_3Na
NaO_3SO
OSO_3Na
10.29
0.82
5.32
1.26
1.00
1.94
1.88
1.38
6.10
31.08
3.61
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

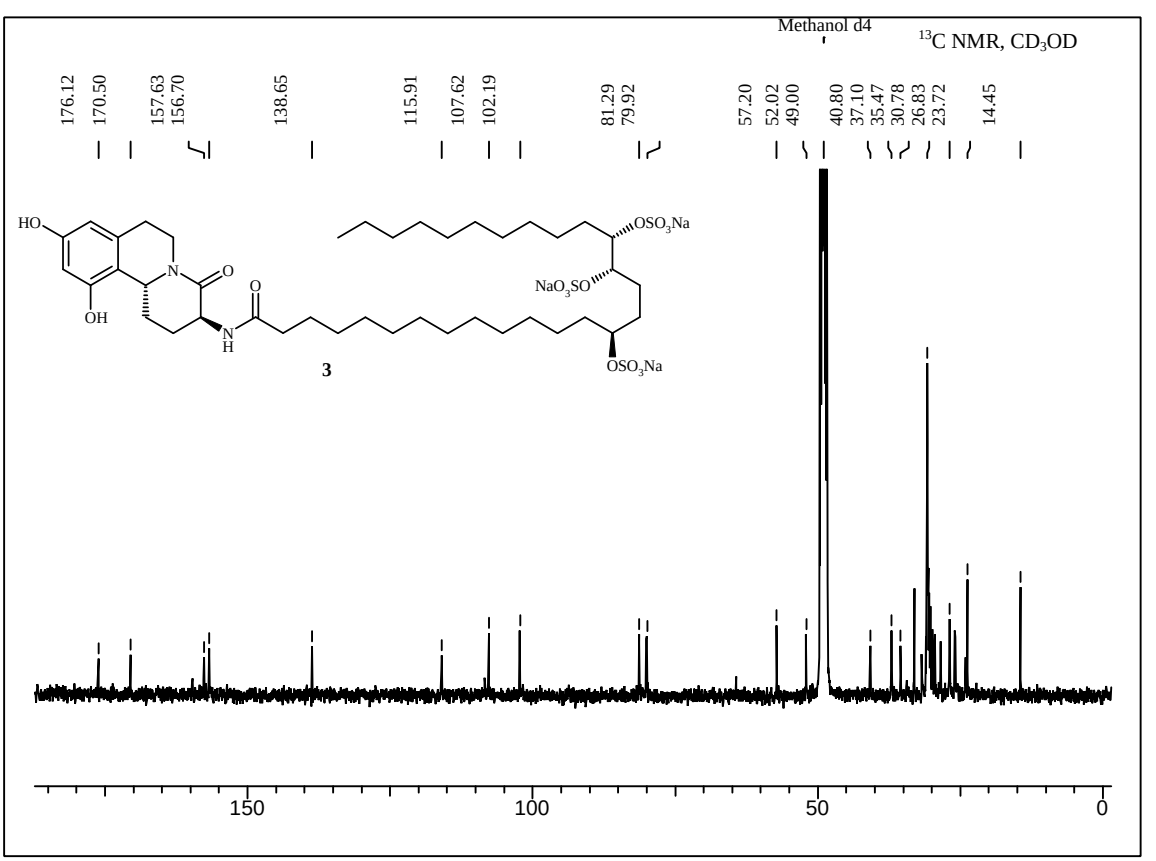
97


Methanol d4
^{13}C NMR, CD_3OD
170.50
158.02
139.03
129.51
107.75
100.27
81.26
71.30
64.27
56.93
52.02
49.00
40.64
37.06
33.06
30.77
28.42
25.94
23.71
14.44
BnO
OBn
N
O
O
N
H
OSO_3Na
NaO_3SO
OSO_3Na
150
100
50
0

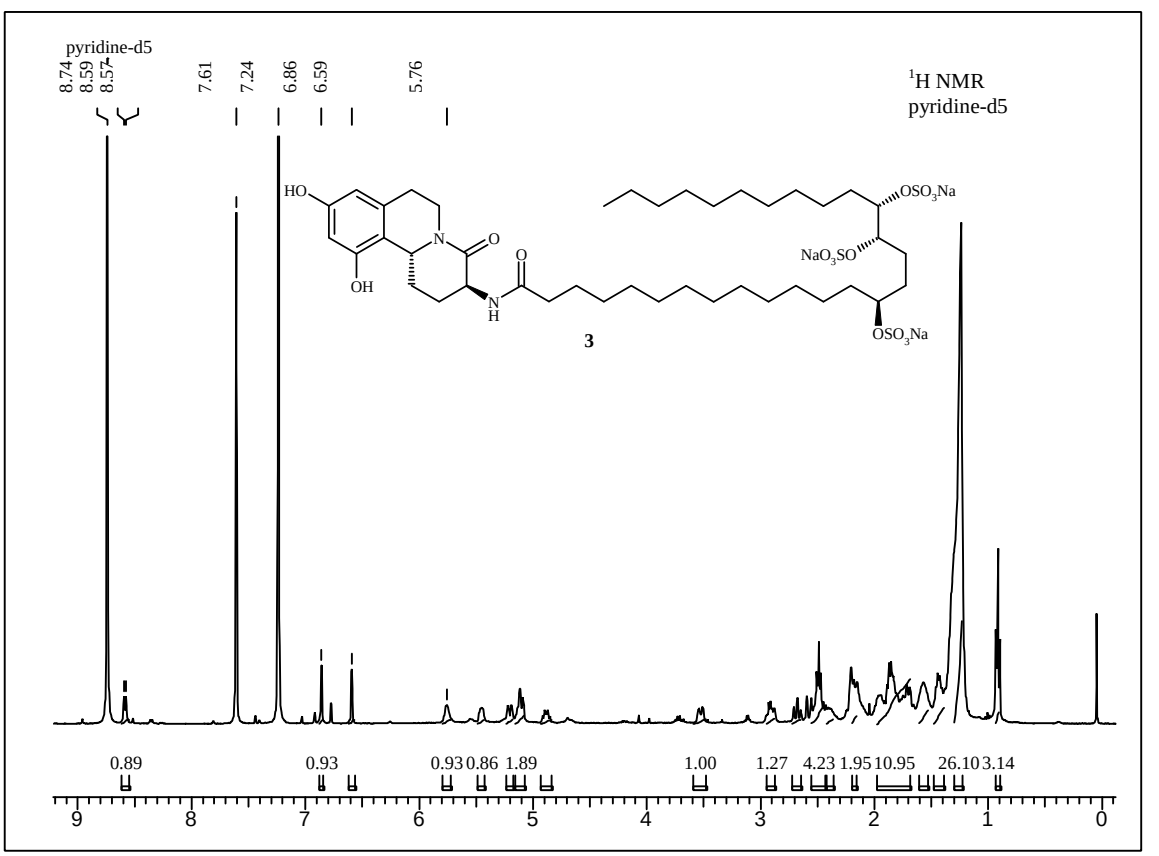
97

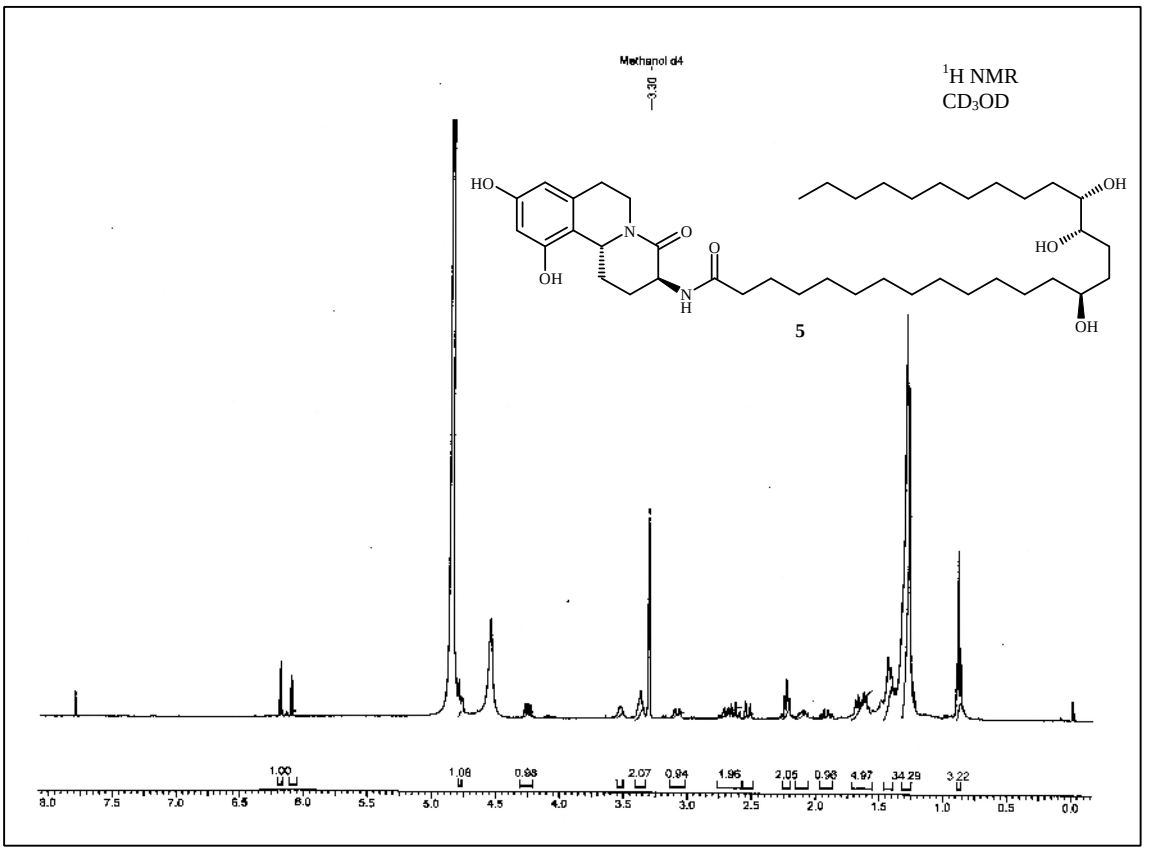

Methanol d4
3.30
^{1}H NMR
CD_3OD
HO
OH
N
H
O
O
N
O
OSO_3Na
NaO_3SO
OSO_3Na
0.80
1.74
2.00
1.04
3.00
1.76
2.71
8.47
30.36
3.02
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

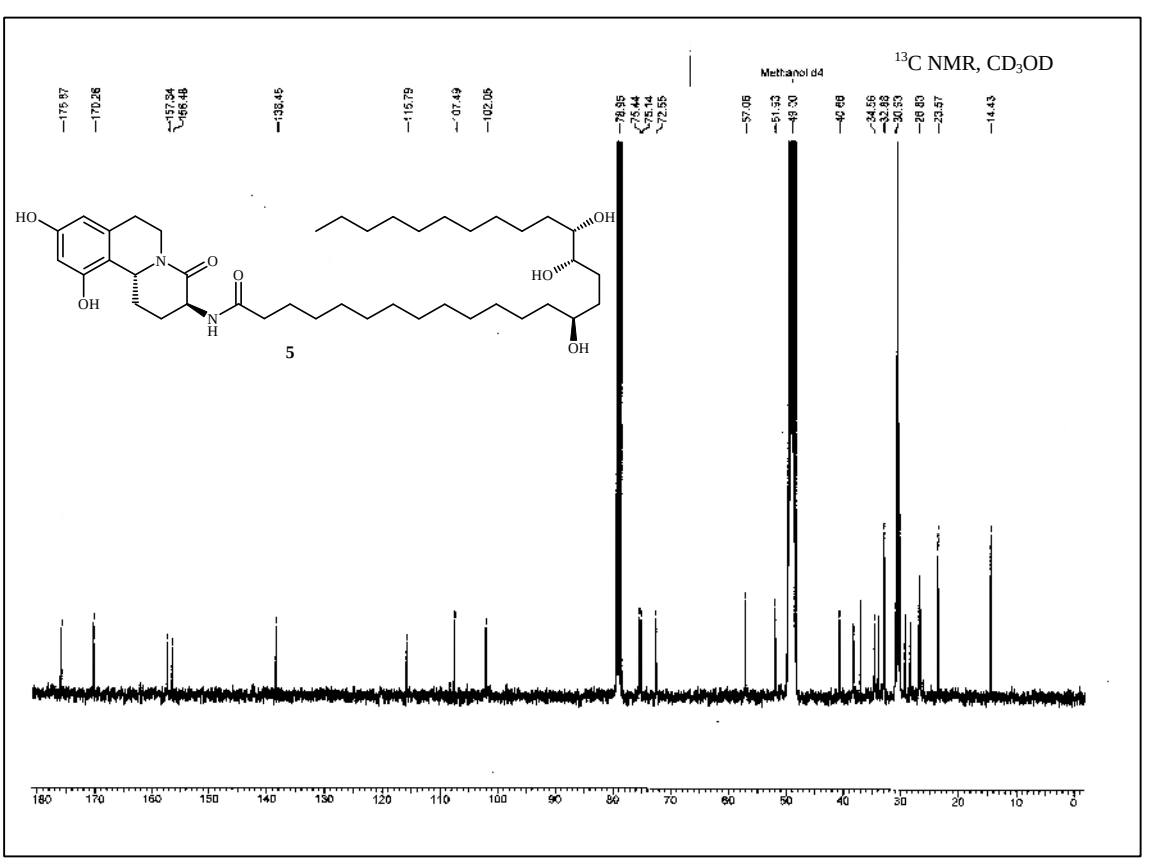
3


Methanol d4
^{13}C NMR, CD_3OD
176.12
170.50
157.63
156.70
138.65
115.91
107.62
102.19
81.29
79.92
57.20
52.02
49.00
40.80
37.10
35.47
30.78
26.83
23.72
14.45
HO
OH
N
H
O
O
N
O
OSO_3Na
NaO_3SO
OSO_3Na
150
100
50
0

3


pyridine-d5
8.74
8.59
8.57
7.61
7.24
6.86
6.59
5.76
1H NMR
pyridine-d5
HO
OH
N
O
O
N
H
NaO3SO
OSO3Na
OSO3Na
3
0.89
0.93
0.93
0.86
1.89
1.00
1.27
4.23
1.95
10.95
26.10
3.14
9
8
7
6
5
4
3
2
1
0


Methanol d4
3.30
^{1}H NMR
CD_3OD
HO
OH
N
O
O
N
H
HO
OH
OH
5
1.00
1.08
0.88
2.07
0.94
1.96
2.05
0.98
4.97
34.29
3.22


^{13}C NMR, CD_3OD
Methanol d4
175.87
170.26
157.34
136.45
115.79
107.49
102.05
78.95
75.44
75.14
72.55
57.06
51.93
49.00
40.68
34.56
32.88
30.53
26.83
23.57
14.43
HO
OH
N
O
O
N
H
HO
OH
OH
5

REFERENCES

REFERENCES

1. Truscheit, E.; Frommer, W.; Junge, B.; Muller, L.; Schmidt, D. D. and Wingender, W. *Angew. Chem. Int. Ed. Engl.* **1981**, *20*, 744-761.
2. Ross, S. A.; Gulve, F. A. and Wang, M. *Chem. Rev*. **2004**, *104*, 1255-1282.
3. Weiss, J. and Sumpio, B. *Eur J Vasc Endovasc. Surg.* **2006**, *31* (2), 143-50.
4. Jacob, G. S.; Scarle, G. D. and Louis, St. *Current Opinion in Structural Biology.* **1995**, *5*, 605-611.
5. Mehta, A.; Zitzmann, N.; Rudd, P. M.; Block, T. M. and Dwek, R. A. *FEBS Letters* **1998**, *430*, 17-22.
6. Elbein, A. and Semin, D. *Cell Biol*. **1991**, *2*, 309-317.
7. Karpas, A.; Fleet, G. W. J.; Dwek, R. A.; Petursson, S.; Namgoon, S.; Ramsden, N. G.; Jacob, G. S. and Rademacher, T. W. *Proc. Natl. Acad. Sci. USA.* **1988**, *85*, 9229-9233.
8. Block, T.; Platt, F.; Lu, X.; Gerlich, W.; Foster, G. Blumberg, B. and Dwek, R. A. *Proc. Natl. Acad. Sci.USA.* **1994**, *91*, 2235-2239.
9. Taylor, D. L.; Fellows, L. E.; Farrar, G. H.; Nash, R. J., Taylor-Robinson, D.; Mobberlay, M. A.; Ryder, T. A.; Jeffries, D. J. and Tyms, A. S. *Antiviral Res*. **1988**, *10*, 11-26.
10. Detema, R.; Olofsson, S. and Romero, P. *Pharmacol. Ther*, **1987**, *33*, 221-286.
11. Schlesinger, S., Koyama, A. H., Malfar, C., Gee, S. L. and Schlesinger, M.J. *Virus Res*. **1985,** *2*, 139-149.
12. Schlesinger, S.; Miller, C. and Schlesinger, M. J. *J. Biol Chem*. **1984,** *259*, 7597-7601.
13. Coffin, J.; Haase, A.; Levy, J. A.; Montagnier, L.; Oroszlan, S.; Teich, N.; Temin, H.; Toyoshima, K.; Varmus, H.; Vogt, P. and Weiss, R. A. *Nature* **1986**, *321,* 6065.
14. Barré-Sinoussi, F.; Chermann, J. C.; Rey, F.; Nugeyre, M. T.; Chamaret, S.; Gruest, J.; Dauguet, C.; Axler-Blin, C.; Vezinet-Brun, F.; Rouzioux, C.; Rozenbaum, W. and Montagnier, L. *Science* **1983,** *220*, (4599): 868-871.

15. Popovic, M.; Sarngadharan, M. G.; Read, E. and Gallo, R. C. *Science* **1984**, *224,* (4648): 497-500.
16. Coffin, J.; Haase, A.; Levy, J. A.; Montagnier, L.; Oroszlan, S.; Teich, N.; Temin, H.; Toyoshima, K.; Varmus, H.; Vogt, P. and Weiss, R. A. *Nature* **1986**, *321,* (6065): 10.
17. Joint United Nations Programme on HIV/AIDS (**2006**). "Overview of the global AIDS epidemic", 2006 Report on the global AIDS epidemic.
18. UNAIDS, 2006 Peport on the global AIDS epidemic NACO (April **2006**), HIV/AIDS epidemiological Surveillance and Estimation report for the year 2005.
19. Smith, D. K.; Grohskopf, L. A.; Black, R. J.; Auerbach, J. D.; Veronese, F.; Struble, K. A.; Cheever, L.; Johnson, M.; Paxton, L. A.; Onorato, I. A. and Greenberg, A. E. *MMWR* **2005**, *54* (*RR02*): 1-20.
20. Donegan, E.; Stuart, M.; Niland, J. C.; Sacks, H. S.; Azen, S. P.; Dietrich, S. L.; Faucett, C.; Fletcher, M. A.; Kleinman, S. H. and Operskalski, E. A. *Ann. Intern. Med.* **1990,** *113* (10): 733-739.
21. Coovadia, H. N. *Engl. J. Med.* **2004,** *351* (*3*): 289-292.
22. Kaplan, E. H. and Heimer, R. *J. Acquir. Immune Defic. Syndr. Hum. Retrovirol.* **1995,** *10 (2)*: 175-176.
23. European Study Group on Heterosexual Transmission of HIV. *BMJ.* **1992,** *304 (6830)*: 809-813.
24. Varghese, B.; Maher, J. E.; Peterman, T. A.; Branson, B. M. and Steketee, R. W. *Sex. Transm. Dis.* **2002,** *29* (*1*): 38-43.
25. Bell, D. M. *Am. J. Med.* **1997,** *102* (*5B*): 9-15.
26. Hansen, J. E. S. *APMIS* **1992**, *100*, (Suppl. 27) 96-108.
27. McCune, J. M.; Rabin, L. B.; Feiberg, M. B.; Lieberman, M.; Kosek, J. C.; Reyes, G. R. and Weissmann, I. L. *Cell* **1988,** *53*, 55-67.
28. Fisher, P. B.; Collin, M.; Karlsson, G. B.; James, W.; Butters, T. D.; Davis, S. J.; Gordon, S.; Dwek, R. A. and Platt, F. M. *J. Virol*. **1995,** *69*, 5791-5797.
29. Fisher, P. B.; Karlsson, G. B.; Butters, T. D.; Dwek R. A. and Platt, F. M. *J. Virol*. **1996,** *70*, 7153-7160.

30. Courageot, M. P.; Frenkiel, M. P.; Santos, C. D. D.; Deubel, V. and Desprès, P. *J. Virology*, **2000,** *74*, 564-572.
31. (a) Holman, R. R.; Cull, C. A. and Turner, R. C. *Diabetes Care* **1999**, *22*, 960-964. (b) Jacob, G. S. *Curr. Opin. Struct. Biol.* **1995**, *5*, 605-611.
32. Ghavami, A.; Johnston, B. D. and Pinto, B. M. *J. Org. Chem.* **2001,** *66,* 2312-2317.
33. Yuasa, H.; Takada, J. and Hashimoto, H. *Tetrahedron Letters,* **2000**, *41*, 6615-6618.
34. Yoshikawa, M.; Murakami, T.; Shimada, H.; Matsuda, H.; Yamahara, J.; Tanabe, G. and Muraoka, O. *Tetrahedron Letters,* **1997,** *38*, 8367-8370.
35. Yoshikawa, M.; Murakami, T.; Yashiro, K. and Matsuda, H. *Chem. Pharm. Bull*. **1998**, *46*, 1339-1340.
36. Yoshikawa, M.; Murikawa, T.; Matsuda, H.; Tanabe, G. and Muraoka, O. *Bioorg. Med. Chem*. **2002**, *10*, 1547-1550.
37. Johnston, B. D.; Ghavami, A.; Jensen, M. T.; Svensson, B. and Pinto, B. M. *J. Am. Chem. Soc*. **2002**, *124*, 8245-8250.
38. Liu, H. and Pinto, B. M. *J. Org. Chem*. **2005**, *70*, 753-755.
39. Pinto, B. M.; Johnston, B. D.; Ghavami, A.; Szczepina, M. G.; Liu, H. and Sadalapure, K. *US Patent,* Filed June 25, **2004**.
40. Ezure, Y.; Yoshikuni, Y.; Ojima, N. and Sugiyama, M. *Acta Cryst*. **1987**. *C43*, 1809-1811.
41. Matsuura, H.; Miyazaki, H.; Asakawa, C.; Amano, M.; Yoshihara, T. and Mizutani, J. *Phytochemistry.* **2004,** *65*, 91-97.
42. Nash, R. J.; Bell, E. A. and Williams, J. M. *Phytochemistry* **1985**, *24*, 1620-1622.
43. Asano, N.; Oseki, K.; Tomioka, E.; Kizu, H. and Matsui, K. *Carbohydr. Res.* **1994**, *259,* 243-255.
44. Saludes, J. P.; Lievens, S. C. and Molinski, T. F. *J. Nat. Prod*. **2007,** *70*, 436-438.
45. Jong-Anurakkun, N.; Bhandari, M. R. and Kawabata, J. *Food Chemistry* **2007,** *103,* 1319-1323.
46. Nakao, Y.; Maki, T.; Matsunaga, S.; Soest, R. W. M. V. and Fusetani, N. *Tetrahedron*. **2000,** *56*, 8977-8987.

47. Nakao, Y.; Maki, T.; Matsunaga, S.; Soest, R. W. M. V. and Fusetani, N. *J. Nat. Prod,* **2004**, *67*, 1346-1350.
48. Takada, K.; Uehara, T.; Nakao, Y.; Matsunaga, S.; van Soest, R. W. M.; Fusetani, N. *J. Am. Chem. Soc*. **2004**, *126*, 187-193.
49. Kuntiyong, P.; Akkarasamiyo, S. and Eksinitkun, G. *Chemistry letters* **2006,** *35,* 1008-1009.
50. Maryanoff, B. E.; Zhang, H. C.; Cohen, J. H.; Turchi, I. J. and C. A. Maryanoff, *Chem. Rev*. **2004**, *104*, 1431-1628.
51. (a) Bischler, A. and Napieralski, B. *Chem. Ber.* **1893**, 1903. (b) Kametani, T.; Sugahara, T. and Fukumoto, K.; *Tetrahedron* **1971**, *27*, 5367. (c) Banwell, M. G.; Cowden, C. J. and Mackay, M. F. *J. Chem. Soc. Chem. Commun.* **1994**, *61*, (d) Angle, S. R.and Boyce, J. P. *Tetrahedron Lett.* **1995**, *36*, 6185-6188.
52. (a) Merchant, J. R. and Khan, M. S. *J. Indian Chem. Soc*. **1962**, *39*, 227-230. (b) Erne and Ramirez, *Helv. Chem. Acta* **1950**, *33*, 912. (c) Ramirez and Burger, *J. Am. Chem. Soc.* **1950**, *72*, 2781-2782.
53. (a) Trost, B. M. and Fleming, I. (Eds) *Comprehensive Organic Synthesis*, **1999**, *Vol. 1* (Oxford: Pergamon Press). (b) Trost, B. M. and Fleming, I. (Eds) *Comprehensive Organic Synthesis,* **1999,** *Vol. 2* (Oxford: Pergamon Press).
54. (a) Nefkens, G. H. L. and Nivard, J. F. *Rec. Trav. Chim. Pays Bas.* **1964**, *83*, 199. (b) Shirude, P. S.; Kumar, V. A. and Ganesh, K. N. *Tetrahedron* **2004**, *60*, 9485-9491.
55. Sousa, J. D. F. and Rodrigues, J. A. R. *J. Am. Chem. Soc*. **1994**, *116*, 9745-9746.
56. Czarnocki, Z. and Mieczkowski, J. B. *Pol. J. Chem.* **1995**, *69*, 1447.
57. Suzuki, H.; Aoyagi, S. and Kibayashi, C. *Tetrahedron Lett.* **1995**, *36*, 6709-6712.
58. Wang, Y. and Georghiou, P. E. *Org. Lett.* **2002**, *4*, 2675-2678.
59. Cabedo, N.; Andreu, I.; Ramirez de Arellano, C.; Chagraoui, A.; Serrano, A.; Bermejo, A.; Protais, P. and Cortes, D. *J. Med. Chem*. **2001**, *44*, 1794-1801.
60. Czarnocki, Z.; Mieczkowski, J. B. and Zio´łkowski, M. *Tetrahedron: Asymmetry* **1996**, *9*, 2711-2720.
61. Zio´łkowski, M. and Czarnocki, Z. *Tetrahedron Lett.* **2000**, *41*, 1963-1966.

62. Zio´łkowski, M.; Czarnocki, Z.; Leniewski, A. and Maurin, J. K. *Tetrahedron: Asymmetry* **1999**, *10*, 3371-3380.
63. Hajipour, A. R. and Hantehzadeh, M. *J. Org. Chem.* **1999**, *64*, 8475-8478.
64. Cabedo, N.; Protais, P.; Cassels, B. K. and Cortes, D. *J. Nat. Prod.* **1998**, *61*, 709-712.
65. Baxendale, I. R.; Davidson, T. D.; Ley, S. V. and Perni, R. H. *Heterocycles* **2003**, *60*, 2707.
66. Kang, J.; Kim, J. B.; Cho, K. H. and Cho, B. T. *Tetrahedron: Asymmetry* **1997**, *8*, 657-660.
67. (a) Willoughby, C. A. and Buchwald, S. L. *J. Am. Chem. Soc.* **1994**, *116*, 8952-8965. (b) Willoughby, C. A. and Buchwald, S. L. *J. Am. Chem. Soc.* **1992**, *114*, 7562-7564.
68. (a) Morimoto, T. and Achiwa, K. *Tetrahedron: Asymmetry* **1995**, *6*, 2661-2664. (b) Morimoto, T.; Suzuki, N. and Achiwa, K. *Heterocycles* **1996**, *43*, 2557-2560. (c) Morimoto, T.; Suzuki, N. and Achiwa, K. *Tetrahedron: Asymmetry* **1998**, *9*, 183-187. (d) Morimoto, T.; Nakajima, N. and Achiwa, K. *Synlett* **1995**, 748-750. (e) Morimoto, T.; Nakijama, N. and Achiwa, K. *Tetrahedron: Asymmetry* **1995**, *6*, 75-78.
69. (a) Uematsu, N.; Fujii, A.; Hashiguchi, S.; Ikariya, T. and Noyori, R. *J. Am. Chem. Soc.* **1996**, *118*, 4916-4917. (b) Noyori, R.; Hashiguchi, S. *Acc. Chem. Res.* **1997**, *30*, 97.
70. Ziólkowski, M; Czarnocki, Z.; Leniewski, A. and Maurin, J. K. *Tetrahedron: Asymmetry.* **1999**, *10*, 3371-3380.
71. Bergmanm M. and Zervas, L. *Ber.*, **1932,** *65*, 1192.
72. (a) Auerbach, J. and Weinreb, S. M. *J. Chem. Soc., Chem. Commun*., **1974**, 298-299. (b). Meyers, A. I.; Durandetta, J. L. and Munavu, R. *J. Org. Chem*., **1975,** *40*, 2025-2029. (c) Woodward, R. B. and 48 Co-workers., *J. Am, Chem, Soc*., **1981,** *103*, 3210-3213. d) Szarek, W. A.; Zamojski, A.; Tiwari, K. N. and Isoni, E.R. *Tetrahadron Lett.,* **1986**, *27*, 3827-3830. (e) Ichihara, A.; Ubukata, M. and Sakamura, S. *Tetrahedron Lett*., **1977**, 3473-3476. (f) (i) Ho, P. T. *Tetrahedron*

Lett. **1978**, 1623-1626. (ii) Leblanc, Y.; Fitzsimmons, B.; Adams, J. J.; Perez, F. and J. Rokach, *J. Org. Chem*., **1986**, *51*, 789-793.

73. (a) Jung, M. A. and Lyster, M. A. *J. Org. Chem.* **1977**, *42*, 3761-3764. (b) Jung, M. E.; Andrus, W. A. and Ornstein, P. L. *Tetrahedron Lett*. **1977**, *18*, 4175-4178. (c) Hanessian, S.; Delorme, D. and Dufresne, Y. *Tetrahedron. Lett.* **1984**, *25*, 2515-2518.
74. Node, M.; Ohta, K.; Kajimoto, T.; Nishide, K.; Fujita, E. and Fuji, K. *Chem. Pharm. Bull*.**1983**, *31*,4178-4180.
75. M. Node, K. Nishide, M. Sai, K. Ichikawa, K. Fuji and E. Fujita, *Chem. Lett*., **1979**, *97*.
76. Demuynck, M.; Clercq, P.D. and Vandewalle, M. *J. Org. Chem*. **1979**, *44*, 4863-4866.
77. (a) Zhao, H.; Neamati, N.; Mazumder, A.; Sunder, S.; Pommier, Y. and Burke, T. R. *J. Med. Chem.* **1997**, *40*, 1186-1194.
78. Osby, J. O. and Ganem, B. *Tetrahedron Lett.* **1985**, *26*, 6413-6419.
79. (a) Sakaitani, M.; Hori, K. and Ohfune,Y. *Tetrahedron Lett*. **1988**. *29*, 2983-2984. (b) Kurokawa, N. and Ohfune, Y. *J. Am. Chem. Soc.* **1986**, *108,* 6041-6043. (c) Sajiki, H.; Kuno, H. and Hirota, K. *Tetrahedron Lett.* **1998**, *39*, 7172-7130. (d) Sajiki, H. and Hirota, K. Tetrahydron, **1998**, 54, 13981-13996. (e) Sajiki, H. **1995**, 36, 3465-3468.
80. Sakatani, M.; Hori, K. and Ohfune, Y. *Tetrahedron Lett*. **1988**, *29*, 2983-2984. (d) Sajiki, H. and Hirot
81. Evans, D. A.; Dinsmore, C.J. Ratz, A. M.; Evrard, D. A. and Barrow, J. C. *J. Am. Chem. Soc.* **1997**, *119*,3417-3418.
82. G. L. Stahl, R.Walter, and C.W. Smith, *J. Org. Chem*., **1978**, *43*, 2285-2286.
83. (a) Lazar, L.; Csavas, M.; Borbas, A.; Gyemant, G.; Liptap, A. *Arkivoc* **2004**, *vii*, 196-207. (b) Lu, L. D.; Shie, C. R.; Kulkarni, S. S.; Pan, G. R.; Lu, X. A.; Hung, S. C. *Org. Lett.* **2006**, *8*, 5995-5998.

CHAPTER-II

Total syntheses of (S)-(+) and (R)-(–)- Plakolide A

INTRODUCTION

INTRODUCTION

Nature has been producing a range of diverse and highly complex secondary metabolites, which exhibit variety of pharmacological activities. In this regard, marine environment is an exceptional reservoir of secondary metabolites, many of which exhibit structural/chemical features not found in terrestrial natural products.[1] Marine organisms have evolved biochemical and physiological mechanisms that include the production of bioactive compounds for the purposes such as reproduction, communication, and protection against predation, infection and competition.[2] Because of the physical and chemical conditions in the marine environment, almost every class of marine organism produce a variety of bioactive molecules with unique structural features. Till date, researchers have isolated approximately 7000 marine natural products, 25 percent of which are from algae, 33 percent from sponges, 18 percent from coelenterates (sea whips, sea fans and soft corals), and 24 percent from representatives of other invertebrate phyla such as ascidians (also called tunicates), opisthobranch molluscs (nudibranchs, sea hares etc), echinoderms (starfish, sea cucumbers *etc*) and bryozoans (moss animals).[3] In the future, these marine compounds are likely to yield entirely new classes of drugs, which would be a valuable contribution to our ability to treat human disease.

CANCER:

Cancer is an uncontrolled cellular growth, which is characterized by the unique property of metastasis. One of the most important properties of cancer cell is that they fail to commit suicide when a normal cell would honourably do so. This uncontrolled cell growth rise to cell masses called tumors (neoplasm). There are two types of neoplasm: (a) Benign and (b) Malignant.

Benign Tumor:

It is a mass of cells with limited growth capacity and remains localized in the tissue of origin. They are encapsulated and never metastasised. They do not usually kill the host unless they are in locations where they block the flow of blood or lymph or

impair vital function, functions by applying pressure, as is the case with benign brain tumors.

Malignant Tumor:

It is the mass of cells, which invade the adjacent tissues as well as metastasize. They are not encapsulated they almost always kill the host. This is because the cancer cells push out and replaces the normal cells in competition for space and nutrients, with resulting loss of function of the affected tissue.

Both the tumors are classified into 3 categories according to the type of cell from which they arise. They are as follows:

1) **Carcinoma**: Which include approximately 90% of human cancers, are malignancies of epithelial cells (such as gastrointestinal organs and tissues).

2) **Sarcoma**: Which are rare in humans, are solid tumors of connective tissues, such as muscles, bone cartilage etc.

3) **Leukemia** and **lymphomas**: Which accounts for approximately 7 % of the tumors malignancies, arise from blood forming cells and cells of immune system respectively.

According to World Health Organization cancer is one of the leading causes of death in the world, particularly in developing countries.

Treatment:

It is unpredictable, it is uncanny. It may be lurking within a body and the body wouldn't know. Many a minor ache quietly ignored and quickly discarded in the past, may be the begetter of that which is pernicious, lethal and detrimental to life. It shrouds itself in dubious obscurity till the time comes for it to reveal the first symptoms. All this while, the fatal cell stealthily multiplies and spreads. It disseminates its devastating influence till it aborts the very functional mechanism of the human body. Such is the effect of cancer.

Today, a remarkable advancement is available for the treatment of cancer. The choice of a particular alternative cancer treatment depends on the stage of the cancerous tumor. Traditional or conventional treatment options may include biologic therapy,

bone marrow transplants, clinical trials, gene therapy, hormone therapy, proton therapy, surgical oncology, chemotherapy, radiation therapy, immunotherapy, monoclonal antibody therapy, or other methods. These therapies have all been tested in clinical research trials and proven to be acceptable, safe and effective, although with often-unpleasant side effects. Depending on the type of the disease, these cancer cures are used alone or in combination, to either control cancer cell growth or to eliminate the disease entirely. Complete removal of the cancer without damage to the rest of the body is the goal of treatment.

Chemotherapy :

The first drug used for cancer chemotherapy was not originally intended for that purpose. Mustard gas was used as a chemical warfare agent during World War I and was studied further during World War II. During a military operation in World War II, a group of people was accidentally exposed to mustard gas and was later found to have very low white blood cell counts. It was reasoned that an agent that damaged the rapidly growing white blood cells might have a similar effect on cancer. Therefore, in the 1940s, several patients with advanced lymphomas (cancers of certain white blood cells) were given the drug by vein, rather than by breathing the irritating gas. Their improvement, although temporary, was remarkable. That experience led researchers to look for other substances that might have similar effects against cancer. As a result, many other drugs have been developed to treat cancer.[4] Alkylating agents, antimetabolites, anthracyclines, plant alkaloids, topoisomerase inhibitors, monoclonal antibodies, and other antitumor agents are generally used as chemotherapeutic drugs for the treatment of cancer. The main function of all of these drugs is to affect cell division or DNA synthesis.[5a]

Marine Natural Products as Anticancer Drug:

Because of the chemical and biological diversity of the marine environment, it is an extraordinary resource for the discovery of new anticancer drugs.[5b] Recent technological and methodologic advances in structure elucidation, organic synthesis,

and biological assay have resulted in the isolation and clinical evaluation of various novel anticancer agents from marine sources. These compounds range in structural class from simple linear peptides, such as dolastatin 10 (**12**), to complex macrocyclic polyethers, such as halichondrin B (**13**); equally as diverse are the molecular modes of action by which these molecules impart their biological activity. Bryostatin I (**1**),[6] which was isolated from the marine filter feeder *Bugula neritina,* is a potential therapeutic for cancer and is in clinical trial (Figure 1).

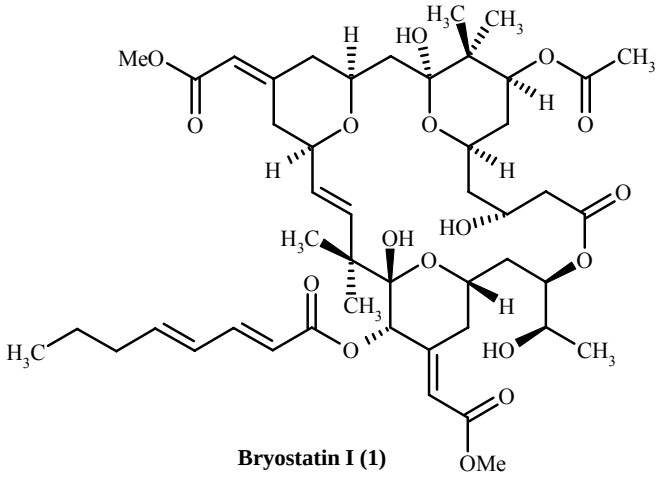
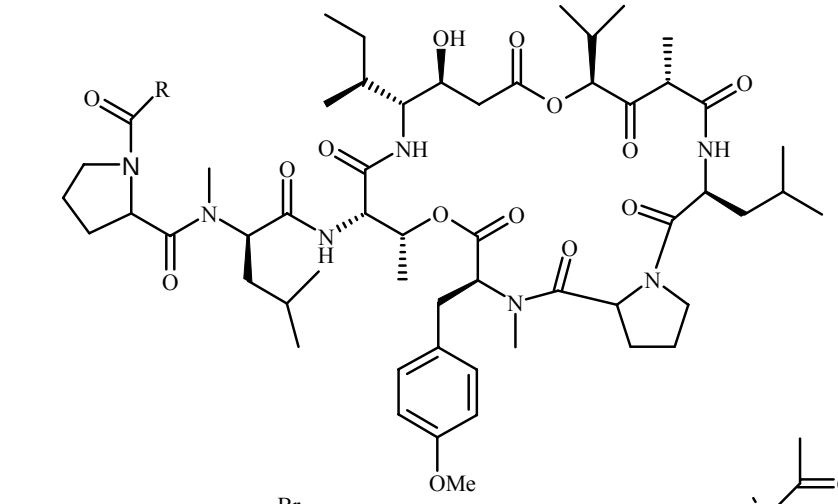


Figure 1

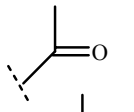
Similarly, Aplidine (**2**), Didemnin B (**3**), halomon (**4**), mycaperoxide B (**6**), Ecteinascidin 743 (**7**), cyptophycines (**8** and **9**), khahalalide F (**10**), Discodermolide (**11**), Dolastatin 10 (**12**), and halicondrin B (**13**) are also in clinical trial for their anti-cancer activity (Figure 2).

Didemnin B (**3**),[7] a cyclic antiproliferative depsipeptide isolated from the Caribbean tunicate *Tridemnum solidum*, was the first marine natural product to enter clinical trial as an antitumor agent. Halomon (**4**)[8] was isolated from extracts of the red alga *Portieria hornemanni* in 1992. Mycaperoxides A (**5**) and B (**6**)[9] have been isolated from a Thai sponge of the genus *Mycale*. Cryptophycins[10] are a family of macrocyclic depsipeptides, was isolated from terrestrial blue-green algae *Nostoc* sp. GSV 224. Cryptophycin 52 (**9**), a synthetic analogue, is currently undergoing phase II clinical trials. This derivative has shown exceptional in vivo potency and tumor-selective cytotoxicity. Ecteinascidin 743 (**7**) was isolated from the caribbean tunicate *Ecteinascidia turbinate*. More than 10 different Ecteinascidins have been isolated,

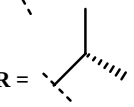
among which Ecteinascidin 743 was found to be a potent compound and appeared to be the most abundant in the tunicate.[11]

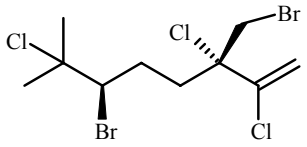


Aplidine (2), R =

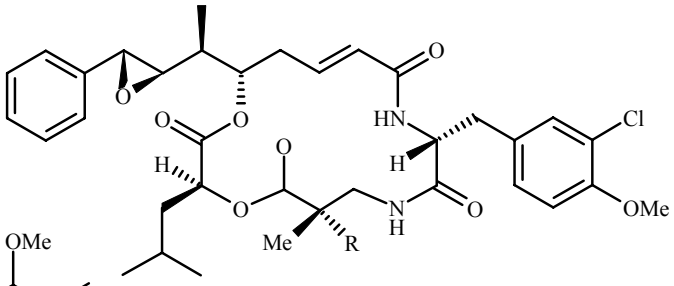


DIdemnin B (3), R =

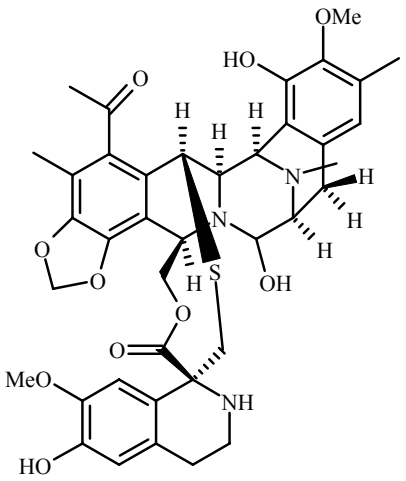




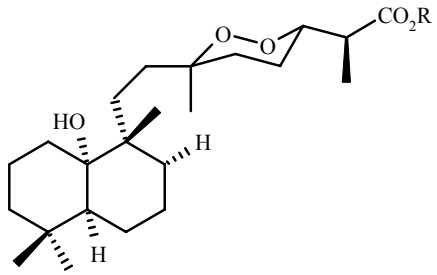
Halomon (4)



Cryptophycin A (8, R = H)
Cryptophycin 52 (9, R = Me)



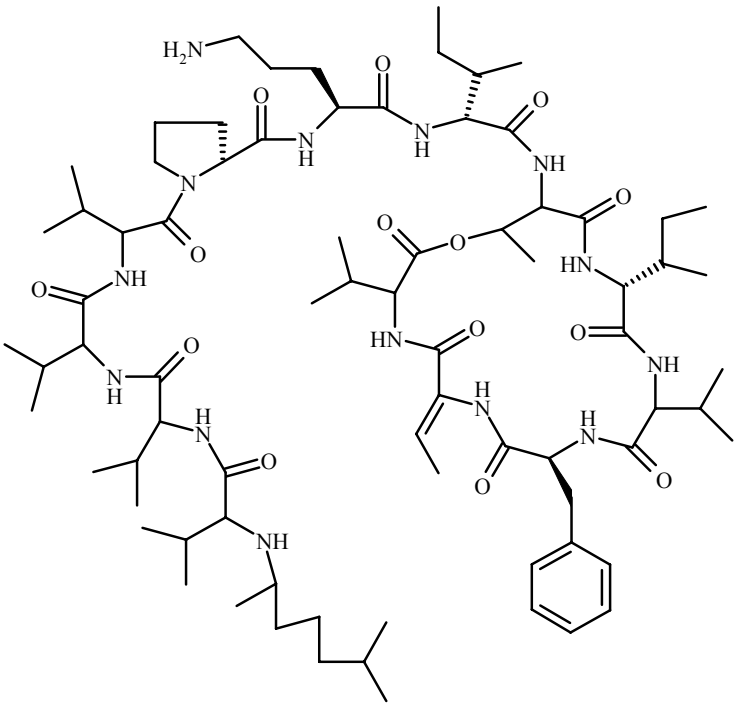
Ecteinascidin 743 (7)



Mycaperoxide A (5), R = H
Mycaperoxide B (6), R = Me

Figure 2

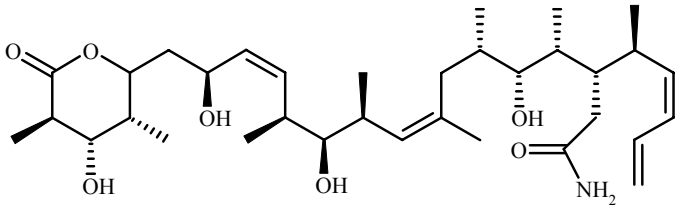
Kahalalide F (**10**) was isolated from Sacoglossan Mullusk *Elysia rufescens* and also from Alga *Bryopsis* (Figure 3).[12]



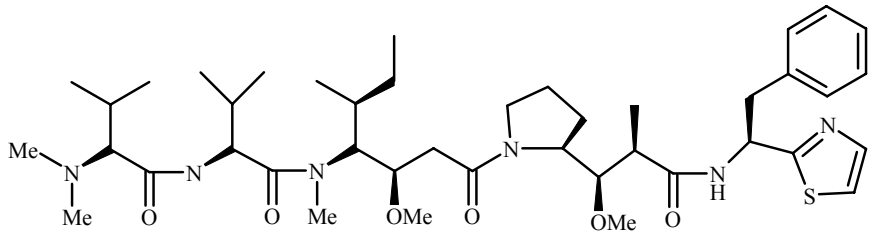
Kahalalide F (10)

Figure 3

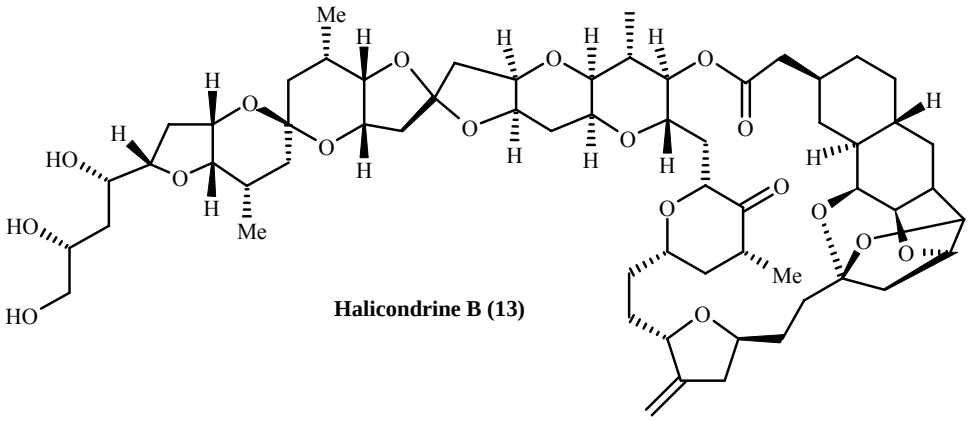
Discodermolide (**11**)[13] is a polyhydroxylated lactone, isolated from the deep-sea sponge *Discodermia* ssp. Dolastatin 10 (**12**)[14] is a linear peptide isolated from the sea hare *Dollabella auricularia* available in the Indian Ocean. In 1986, Hirata and Uemura reported that extracts of Japanies marine sponge *Halichondria okadai,* displayed compelling in vivo antitumor activity. Eight active compounds were separated from these extracts and purified and were subsequently named the halichondrins. The most potent of these was halichondrin B (**13**) (Figure 4).[15]



Discodermolide (11)



Dolastatin 10 (12)



Halicondrine B (13)

Figure 4

Plakotris sp as a source of antitumar agent:

Over the years many *Plakotris sp* sponges[16] have provided chemically interesting metabolites having γ-butyrolactone ring as an integral building block with considerable antitumor activity.

The amphiasterins A1–4 (**20-23**), B1–5 (**28-32**), C1–4 (**24**– **27**), D1–3 (**34-36**), and E (**33**) have been isolated from *Plakortis quasiamphiaster* collected in Vanuatu (Figure 5).[17]

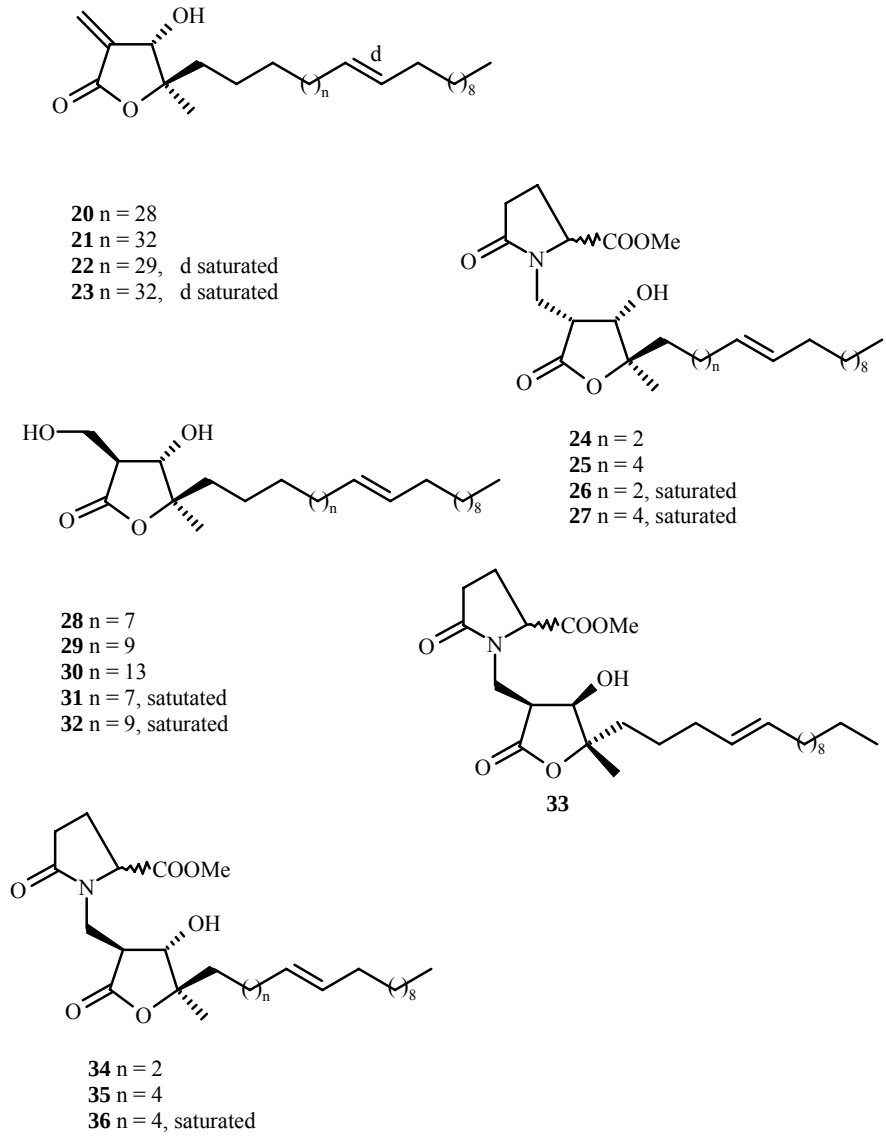
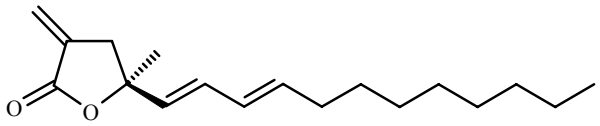


Figure 5

Plakolide A, is an *α*-exomethylene-*γ*-disubstituted-*γ*-lactone isolated recently from a shallow-water marine sponge of the genus *plakortis* collected from La Palma Islands and was found to exhibit inducible nitric oxide synthase (iNOS) activity in a cell based assay (IC_{50} value of 0.2 μg/mL).[18] It exhibited 72 h cytotoxicity against the cultured P-388 marine lymphoma and A-549 human lung adenocarcinoma cell lines with IC_{50} values of 1.1 and 5.0 μg/mL, respectively. It also showed cytotoxicity against PANC-1 human pancreatic carcinoma and NCI/ADR human breast carcinoma cell lines with IC_{50} values of 3.8 and 3.7 μg/mL, respectively.



(*S*)-(+)-Plakolide A (37)

Figure 6

Full biological evaluations of such substances are however severely hampered by the difficulty of obtaining substantial quantities, as it is difficult, and indeed ecologically undesirable, to harvest large quantities of the marine creatures from which they are isolated; it is also difficult to grow such animals in the laboratory. Access to substantial quantities of these novel substances must then be by way of chemical synthesis, which also has the very considerable additional advantage that it, and only it allows analogues to be prepared and thus desirable biological activities to be maximised and any undesirable side-effects minimised as the natural substance is, in the jargon of pharmaceutical industry, a 'lead compound'.

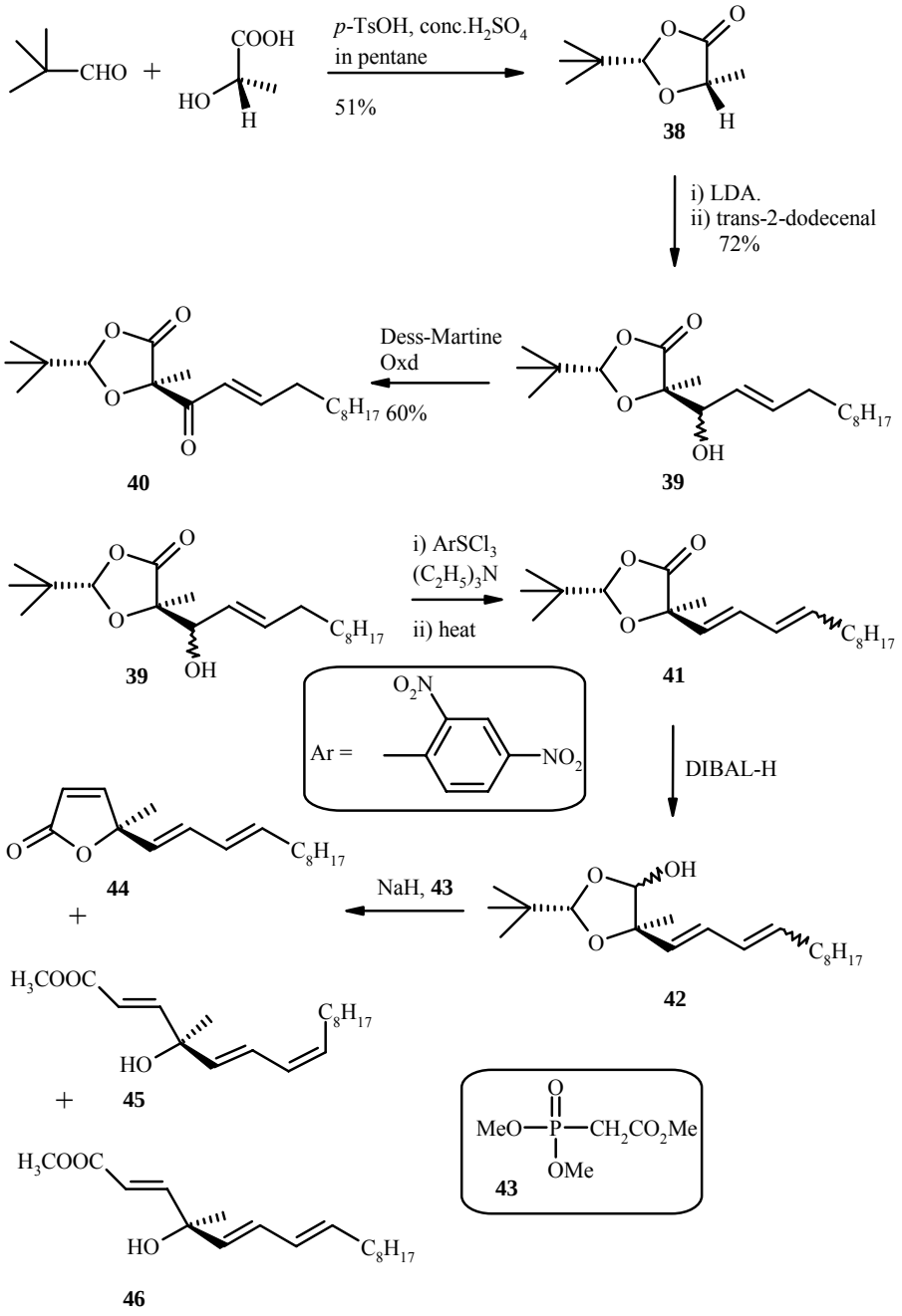
Studies Towards the Total Synthesis of Plakolide A

Past work:

Matsuo Approach

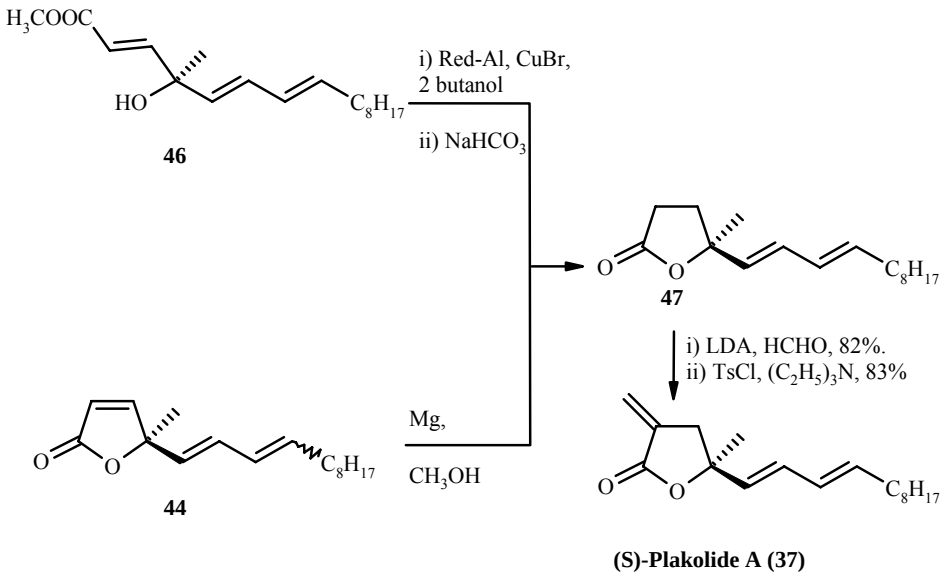
The first synthesis of (*S*)-Plakolide A (**37**), and revision of the absolute stereochemistry was reported by Matsuo and co-workers in 2006.[19a] For the synthesis of (*S*)-Plakolide A, they selected (2*S*,5*S*)-2-(1,1-dimethylethyl)-5-methyl-1,3-dioxolan-4-one (**38**), which was readily derived from (*S*)-lactic acid and 2,2 dimethyl-propanol, as starting material. The addition of *trans*-2-dodecenal to the enolate derived from **38** gave the alcohol **39** as a 1:1 mixture of diastereomers, concerning with the orientation of the hydroxyl group. They confirmed the newly formed stereochemistry in **39** by NOE study of the corresponding enone **40**. By using [2,3] Sigmatropic rearrangement they converted alcohol **39** to 1,3-diene **41**. Successive DIBAL-H reduction, and Wittig reaction afforded **44**, **45** and **46** with 17%, 10% and 63% yield respectively.

Scheme 1



Compound **44** was treated with Mg in ethanol to form **47** and compound **46** was also converted to **47** by treatment with Red-Al followed by aq. $NaHCO_3$ workup. Finally, they obtained (*S*)-Plakolide A (**37**) by introducing the exodouble bond by using LDA and formaldehyde followed by tosylation of the resulting alcohol in presence of triethylamine (Scheme 2).

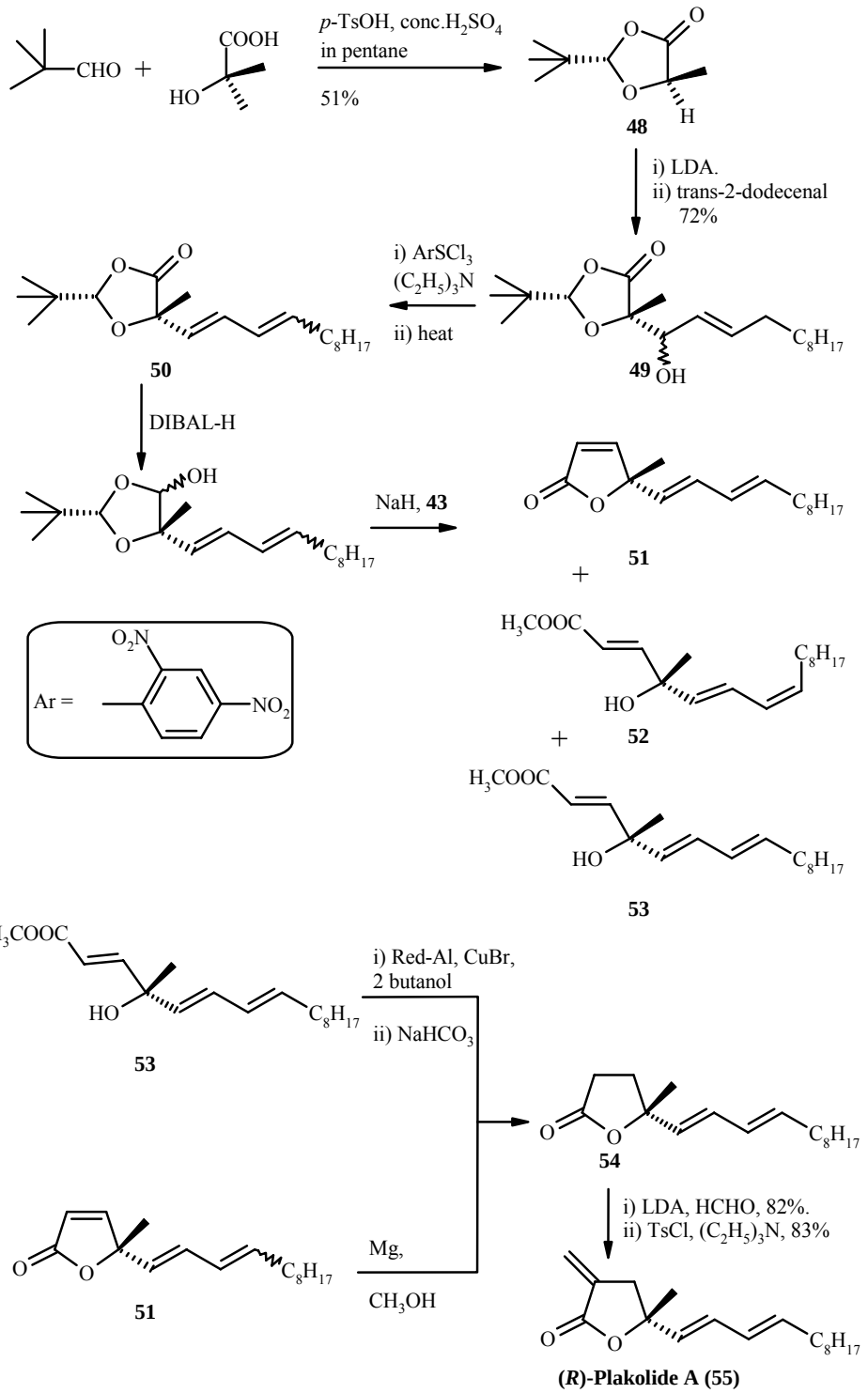
Scheme 2



But, the specific rotation of the synthesized compound showed $[\alpha]_D$ +45° (*c* 0.12, CH_3OH), whereas reported value of the natural Plakolide A is $[\alpha]_D$ –41° (*c* 0.1, CH_3OH). Furthermore CD spectrum study, they proved that stereochemistry at C5 in natural Plakolide is (*R*).

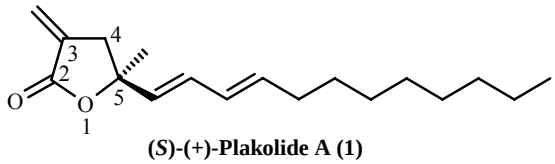
In their next report[19b] they synthesized (*R*)-Plakolide A following the same strategy as in case of (*S*)-Plakolide A (Scheme 3).

Scheme 3

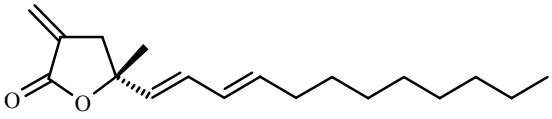

CHO
COOH
HO
p-TsOH, conc.H2SO4
in pentane
51%
48
i) LDA.
ii) trans-2-dodecenal
72%
i) ArSCl3
(C2H5)3N
ii) heat
49
OH
50
DIBAL-H
NaH, 43
51
Ar =
O2N
NO2
H3COOC
HO
52
53
i) Red-Al, CuBr,
2 butanol
ii) NaHCO3
Mg,
CH3OH
54
i) LDA, HCHO, 82%.
ii) TsCl, (C2H5)3N, 83%
(R)-Plakolide A (55)

PRESENT WORK

Plakolide A is an α-exomethylene-γ-disubstituted-γ-lactone (Figure 1), isolated recently from a shallow-water marine sponge of the genus *plakortis* collected from La Palma Islands and was found to exhibit inducible nitric oxide synthase (iNOS) activity in a cell based assay (IC_{50} value of 0.2 μg/mL).[18] It exhibited 72 h cytotoxicity against the cultured P-388 marine lymphoma and A-549 human lung adenocarcinoma cell lines with IC_{50} values of 1.1 and 5.0 μg/mL, respectively. It also showed cytotoxicity against PANC-1 human pancreatic carcinoma and NCI/ADR human breast carcinoma cell lines with IC_{50} values of 3.8 and 3.7 μg/mL, respectively. Persuasive data mainly based upon extensive investigation of the structure by its synthesis, specific rotation and CD spectrum, led to the revision of the stereochemistry of the lactone at C-5.[19]



(*S*)-(+)-Plakolide A (1)



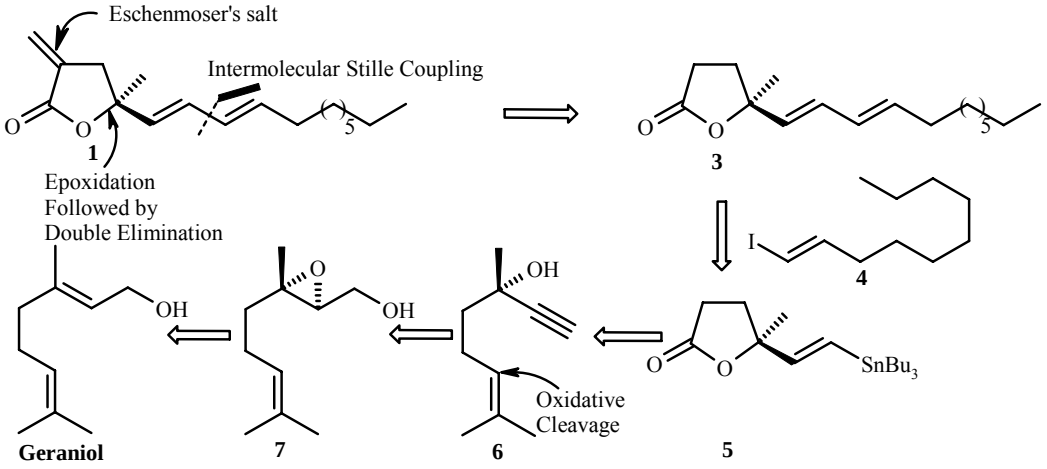
Revised (*R*)-(-)-Plakolide A (2)

Figure 1. *Structure of (S)-(+) and (R)-(-)-Plakolide A.*

The interesting pharmacological activity and unique structural features prompted us to devise a new, short and efficient strategy for its total synthesis. The initially proposed absolute stereochemistry of Plakolide A was revised by total synthesis at time when we were pursuing its synthesis from a commercially available geraniol as starting material.

Our retrosynthetic strategy for (*S*)-(+)-Plakolide A (**1**) is outlined in Scheme 1. We planned to assemble the key intermediate **3** by intermolecular stille coupling of the vinyl stannane **5** with vinyl iodide **4**. The vinyl stannane derivative **5** could be obtained from propargyl alcohol **6** via a lactol. Alcohol **6** could be obtained from epoxy alcohol **7** in two

discrete steps, namely chlorination followed by double elimination reaction. Epoxy alcohol **7** could be generated by the Sharpless epoxidation of geraniol.

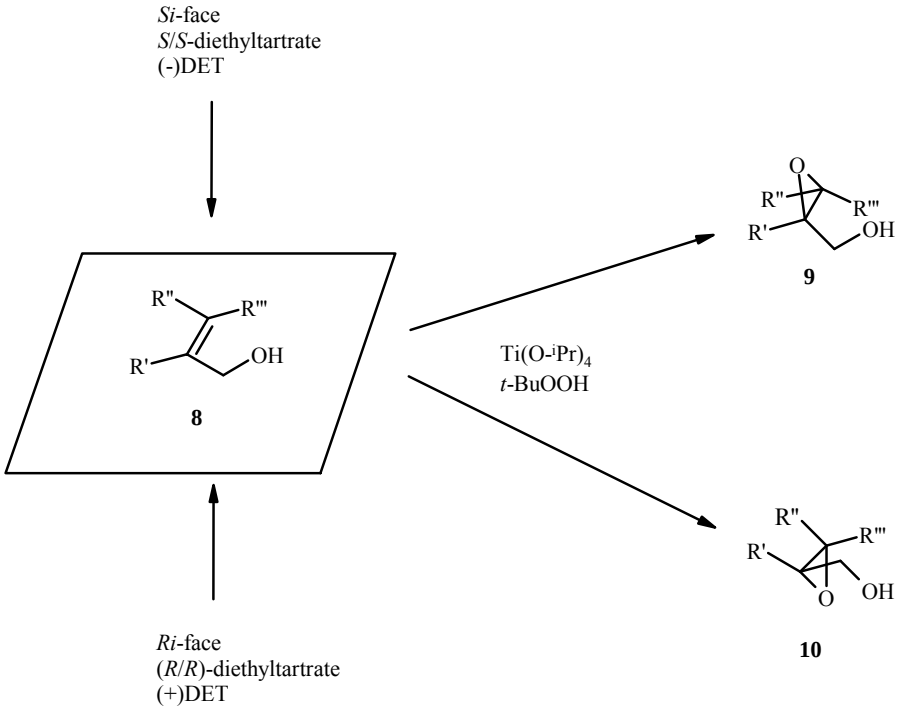


Scheme 1: *Retrosynthetic strategy for the enantioselective synthesis of (S)-(+)-Plakolide A (1).*

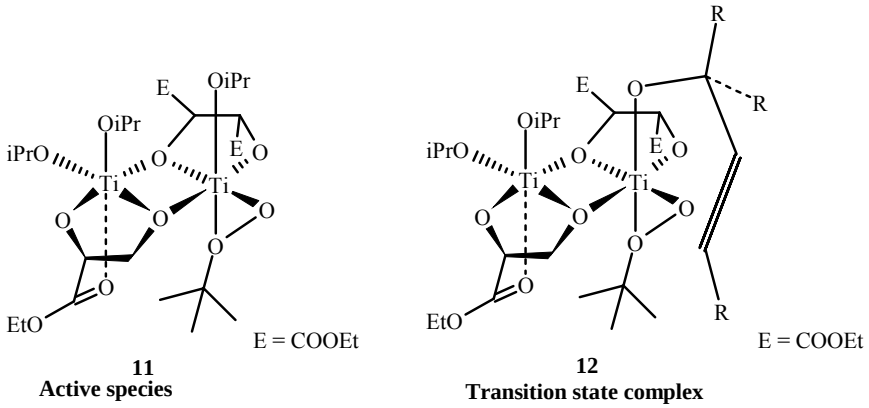
A brief review on Sharpless asymmetric epoxidation:[20]

Epoxides are versatile and important intermediates in organic synthesis. The strain of the three-membered heterocyclic ring makes them accessible to a large variety of reagents. This metal catalyzed epoxidation process was discovered by K. Barry Sharpless in 1980 and allows the transformation of a prochiral substrate into an optically active (or optically pure) product using a chiral catalyst. The asymmetric induction is achieved by adding an enantiomerically enriched tartrate derivative. This epoxidation is arguable one of the most important reaction discovered in the last 30 years. This has been recognized by the award of the 2001 Noble Prize to Professor Barry Sharpless.

Scheme 2



*In this epoxidation reaction double bond of allylic alcohols are converted into epoxides using a transition metal catalyst (Ti(O-^{i}Pr)$_4$, titanium tetra-isopropoxide) and a chiral additive (DET, diethyltartrate) (Scheme 2). The oxidant for the epoxidation is tert-butylhydroperoxide. It is proposed that, co-ordination of the chiral ligand DET and the oxidant source TBHP to the metal center forms the catalytically active species (**11**) (Figure 2). It is generally belived that this species is dimeric, i. e. two metal centres are bridged via two oxygen ligand giving the overall shape of two edge-fused octahedral. Co-ordination of the substrate can only occur in one orientation without causing severe steric interactions (Figure 2, **12**). Co-ordination in the complex on the left brings the double bond over the peroxide oxygen of the TBHP ligand. Oxidation can only occur from the bottom face, leading overall to a highly enantioselective process (Scheme 3).*

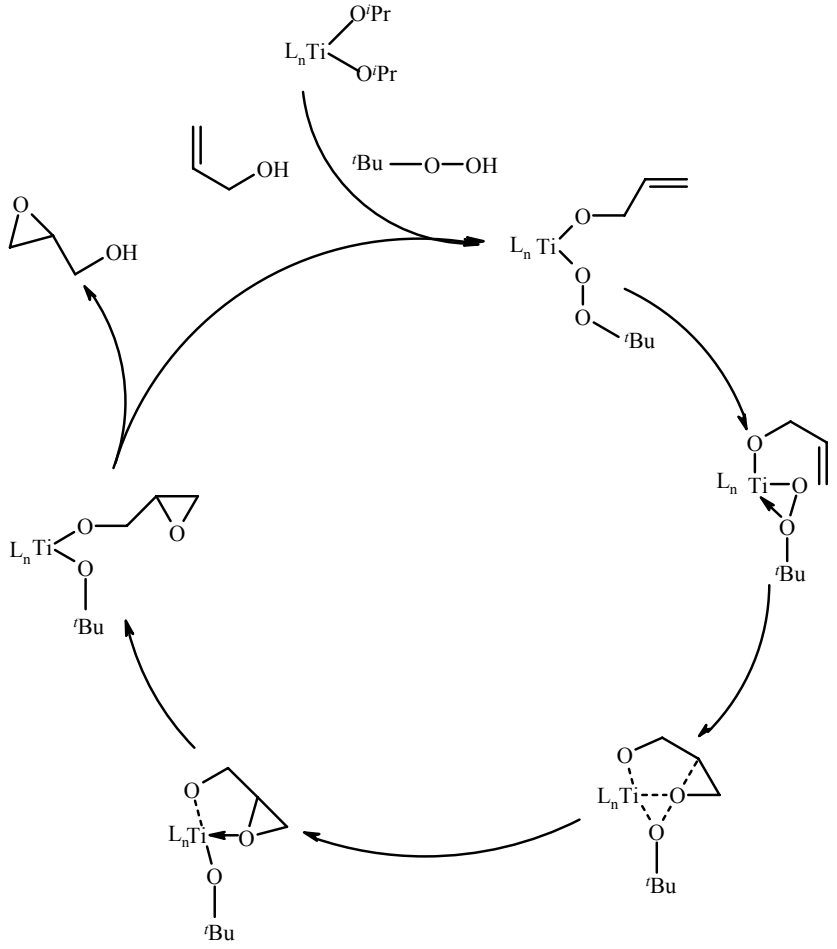


11
Active species

12
Transition state complex

Figure 2*: Putative transition state for the Sharpless asymmetric epoxidation.*

The catalytic cycle for the epoxidation process is depicted below.

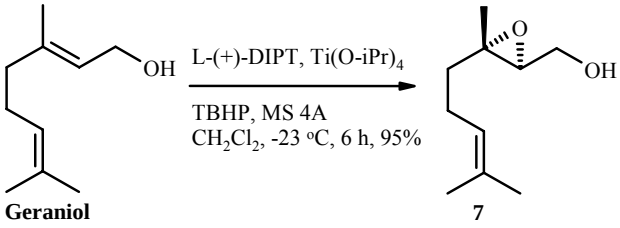


Scheme 3. *The catalytic cycle for Sharpless asymmetric epoxidation.*

Our synthesis for the main core commenced with commercially available geraniol which was subjected to Sharpless asymmetric epoxidation with L-(+)-DIPT as chiral

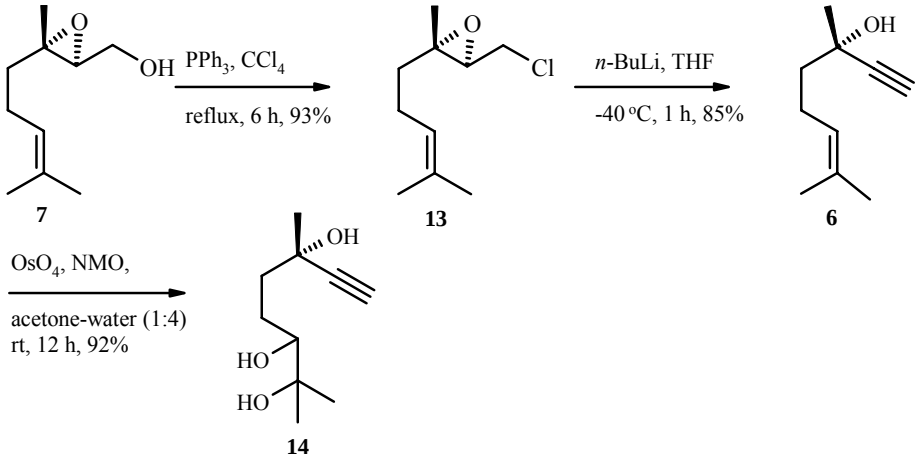
reagent to yield epoxide **7** {$[\alpha]_D^{25}$ –5.1 (*c* 3.0, $CHCl_3$), lit [21] $[\alpha]_D^{25}$ –5.3 (*c* 3.0, $CHCl_3$)} in ≥ 95% ee (Scheme 4).

Scheme 4



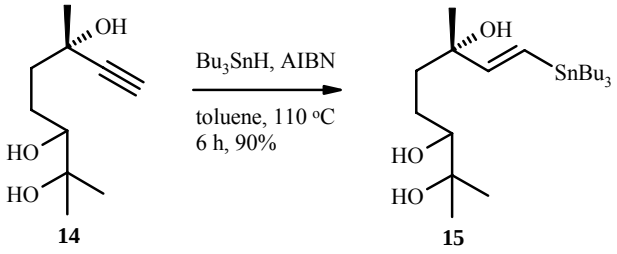
Chlorination[22] of alcohol **7** was effected with TPP in CCl_4 to afford the chloroepoxide **13** followed by double elimination with *n*-BuLi in THF at –40 °C to yield the carbinol **6** with 85% yield.[23] The structure of **6** was completely secured on the basis of ^1H, ^{13}C NMR, IR and mass spectral analysis. The ^1H NMR spectrum of **6** showed a singlet at δ 2.43 ppm integrating for one proton, which was assigned to terminal alkyne. Dihydroxylation of the tri-substituted double bond in **6** with OsO_4 and NMO in acetone-water at ambient temperature gave the triol **14** as a diastereomeric mixture (1:1) in 92% yield (Scheme 5).

Scheme 5



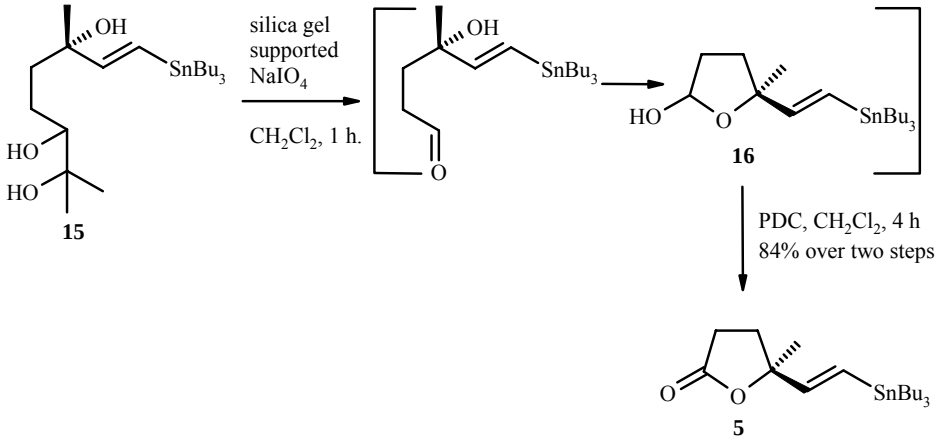
The structure of **14** was concluded by the assistance of the ^{1}H, ^{13}C NMR spectra, mass spectra and elemental analysis. In next step the required vinyl stannane **15** (1:1 diastereomeric mixture) was easily obtained from **14** by radical hydrostannylation with Bu_3SnH and catalytic amount of AIBN in toluene under refluxing condition (Scheme 6).[24]

Scheme 6



The structure of **15** was explicitly supported from the combined spectral data of the ^{1}H, ^{13}C NMR and mass spectroscopic data. Oxidative cleavage of the diol **15** using $NaIO_4$-impregnated silica gel[25] in dichloromethane and treatment of the resulting lactol with PDC in the same pot afforded the required lactone **5** in 84% overall yield (Scheme 7).

Scheme 7



It's ^{1}H-and ^{13}C-NMR spectra were in good agreement with the assigned structure, further elemental analysis confirmed the chemical composition of **5**. In the ^{1}H NMR spectrum signals located at δ 6.27 (d, 1H, *J* = 19.3 Hz), and 5.92 (d, 1H, *J* = 19.3 Hz) ppm confirmed the *trans* double bond, and at δ 2.52 (dt, 2H, *J* = 6.8, 2.2 Hz) ppm presented the *α*-methylene protons and its ^{13}C spectrum showed a peak due to carbonyl carbon at δ 176.5 ppm. Characteristic IR absorption peak at 1768 cm^{-1} further supported the formation of γ-lactone.

A brief review on Takai olefination:[26]

Olefination is the construction of an alkene from two different components, viz., a carbonyl compound and an olefinating agent, which allows broad variation of the nature of substituents at the double bond. The striking progress in this field of organic synthesis is associated with the use of various transition metals, reagents based on them and organoelemental compounds. The carbonyl carbon atoms bear a partial positive charge; therefore, general olefination procedures include, as a rule, the addition of various C-nucleophiles (both preformed and prepared in situ) to the carbonyl group. Depending on the methods used for the conversion of carbonyl group into the C=C, olefination reaction can be divided into four categories.

I) Addition of ylides or carbanions stabilized by heteroatom in the α-position to the carbonyl group.

II) Condensation of carbonyl compounds with various CH-acids.

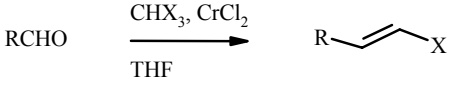
III) Olefination with reagents based on metals.

The methods not included in the first three groups are considered in IV category.

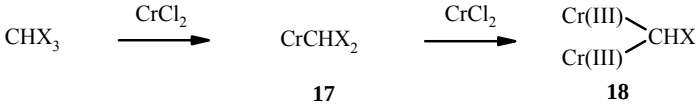
Takai Olefination belongs to the third-category i.e. olefination based on metals. It is a simple and stereoselective method for the conversion of aldehyde to the corresponding (E)-alkenyl halide predominantly utilizing an organochromium reagent.

General equation:

Scheme 8

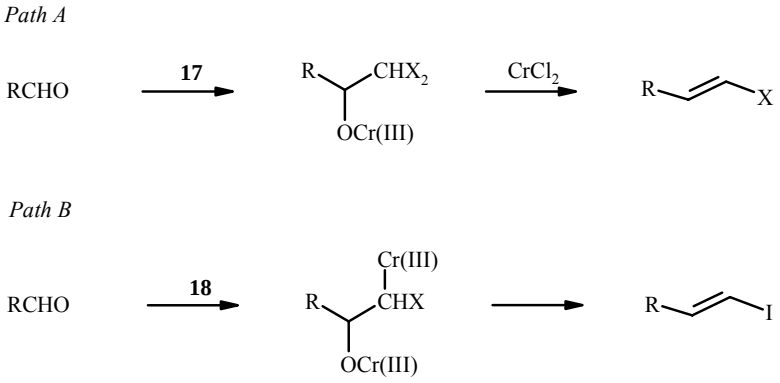


Mechanism:



*There are two possible reactive species generated from haloform and $CrCl_2$. One is a chromiumdihalocarbinoid (**17**) (Path A) and the other is a carbodianion species (**18**) (Path B).*

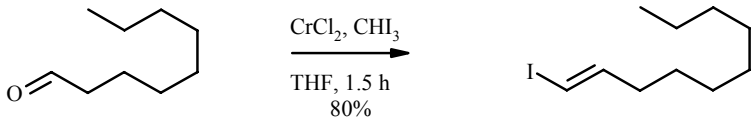
Scheme 9



The E/Z ratios of the alkenyl halides increase in the order I<Br<Cl and the rate of reaction of the haloform are in the sequence I>Br>Cl. High yields and high stereoselectivity are indisputable advantages of this method.

With the lactone vinyl stannane **5** in hand, the vinyl iodide side chain **4** was constructed from nonan-1-al by a Takai olefination reaction with (9:1) *E*/*Z* ratio (Scheme 10).[10]

Scheme 10



4

A brief review on Stille coupling:[27]

There are relatively few basic reaction types that generate a new carbon-carbon bond, although this is one of the most critical operations in the synthesis of organic molecules. Organometallic chemistry has provided important new methods to carry out carbon-carbon or carbon-heteroatom bond formation. Such processes, termed coupling reactions, now have a central place in organic chemistry. Group VIII transition metals, particularly nickel and palladium, are effective in catalyzing the cross coupling of organometallic reagents with organic halides and related electrophiles. The Stille coupling is a versatile C-C bond forming reaction between organo stannanes as the organometallic reagent and halides or pseudohalides lacking a sp^3-hybridised β-hydrogen, catalyzed by palladium. This mild, versatile reaction is tolerant of a wide variety of functional groups on either coupling partner, stereospecific and regioselective, and gives high yields of product. Organotin compounds containing a variety of reactive functional groups can be prepared by a number of routes; moreover, these reagents are not particularly air or moisture sensitive. The Stille reaction will continue to be a favorite method for carbon-carbon bond formation, owing to the lack of cross-reactivity displayed by the

organostannanes with most functional groups. Since its first reported use in the late 1970's, the reaction has been widely used for the coupling of both aromatic and vinyl systems. The Stille coupling represents over half of all current cross-coupling reactions.

General equation of the reaction:

Scheme 11

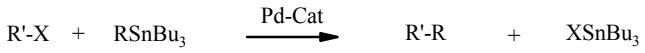
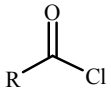
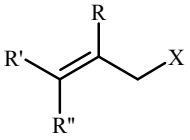
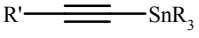
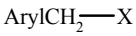
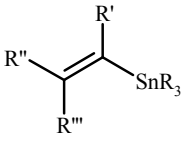
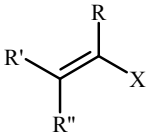
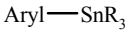
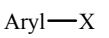
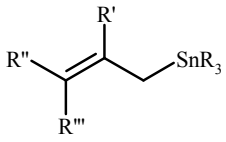
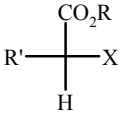
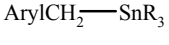
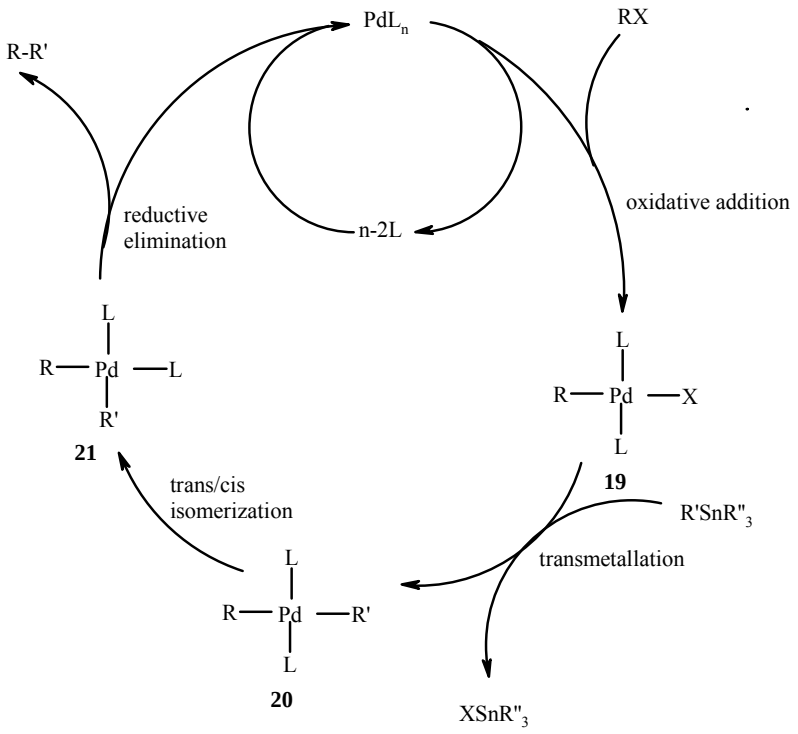


Table 1 highlights a list of organotin reagents and electrophiles suitable for coupling reactions.

Table 1

Electrophile	Organotin reagent
	
 [X = Cl, Br]	
 [X = Cl, Br]	
 [X = OTf, Br]	
 [X = I, Br]	
 [X = I, Br]	

A simple working model for Stille-coupling reaction is represented below.

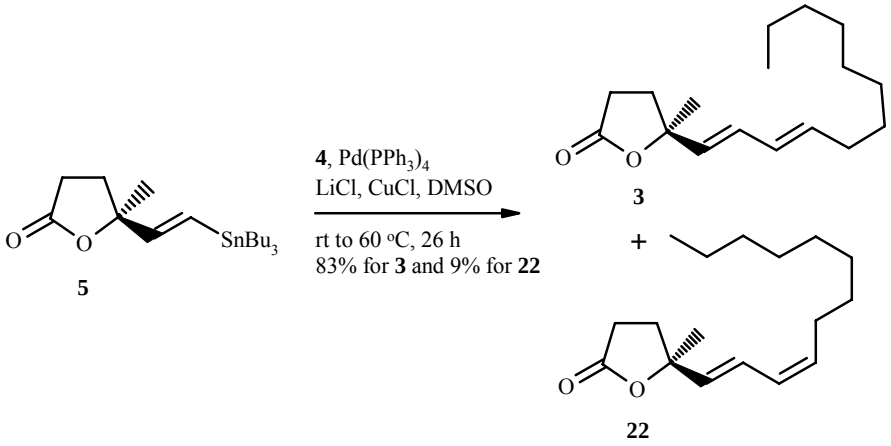


Scheme 12. *A simple working model for Stille-coupling reaction.*

The mechanism involves oxidative addition of the halide or triflate to the initial Pd(0) Phosphine complex to form a Pd(II) species. The key slow step is a transmetallation, so called because the nucleophile (R') is transferred from the metal in the organometallic reagent to the Palladium and the counterion (X = halide or triflate) moves in the opposite direction. The new Pd(II) complex with two organic ligands undergoes reductive elimination to give the coupled product and the Pd(0) catalyst ready for another cycle.

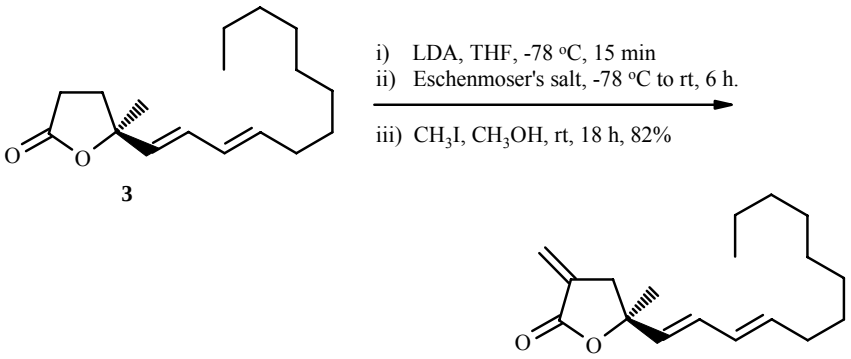
Our next earnest attempt was the coupling of these entities (**4** and **5**) to construct the main skeleton of Plakolide A **3**, which was achieved via a cuprous chloride accelerated Stille coupling under conditions reported by Corey and co-workers.[28] The expected coupled products *E*,*E*-**3** and *E*,*Z*-**22** were obtained in a 9:1 ratio using $Pd(PPh_3)_4$ in DMSO (Scheme 13).

Scheme 13



The products were easily separated by flash chromatography on silica gel and characterized spectroscopically. ^{1}H NMR spectrum of **3** showed signals for four olefinic protons at δ 6.14 (dd, 1H, *J* = 15.2, 10.1 Hz), 5.92 (dd, 1H, *J* = 15.0, 10.1 Hz), 5.67 (dt, 1H, *J* = 15.0, 6.8 Hz), and 5.51 (d, 1H, *J* = 15.2 Hz) ppm indicating *E*,*E* configuration , whereas for **22**, four olefinic proton signals located at δ 6.52 (dd, 1H, *J* = 15.3, 11.0 Hz), 5.94 (t, 1H, *J* = 10.0 Hz), 5.67 (d, 1H, *J* = 15.4 Hz), and 5.5 (dt, 1H, *J* = 10.8, 7.6 Hz) ppm indicating *E*,*Z* configuration. Having developed a highly efficient route to this intermediate what remaining was the introduction of the *exo*-methylene group at α-position to the ring carbonyl. This was effected by the use of Eschenmoser's salt.[29] Treatment of the *E*,*E* isomer **3** with LDA and Eschenmoser's salt furnished (*S*)-(+)-Plakolide A (**1**) (Scheme 14).

Scheme 14

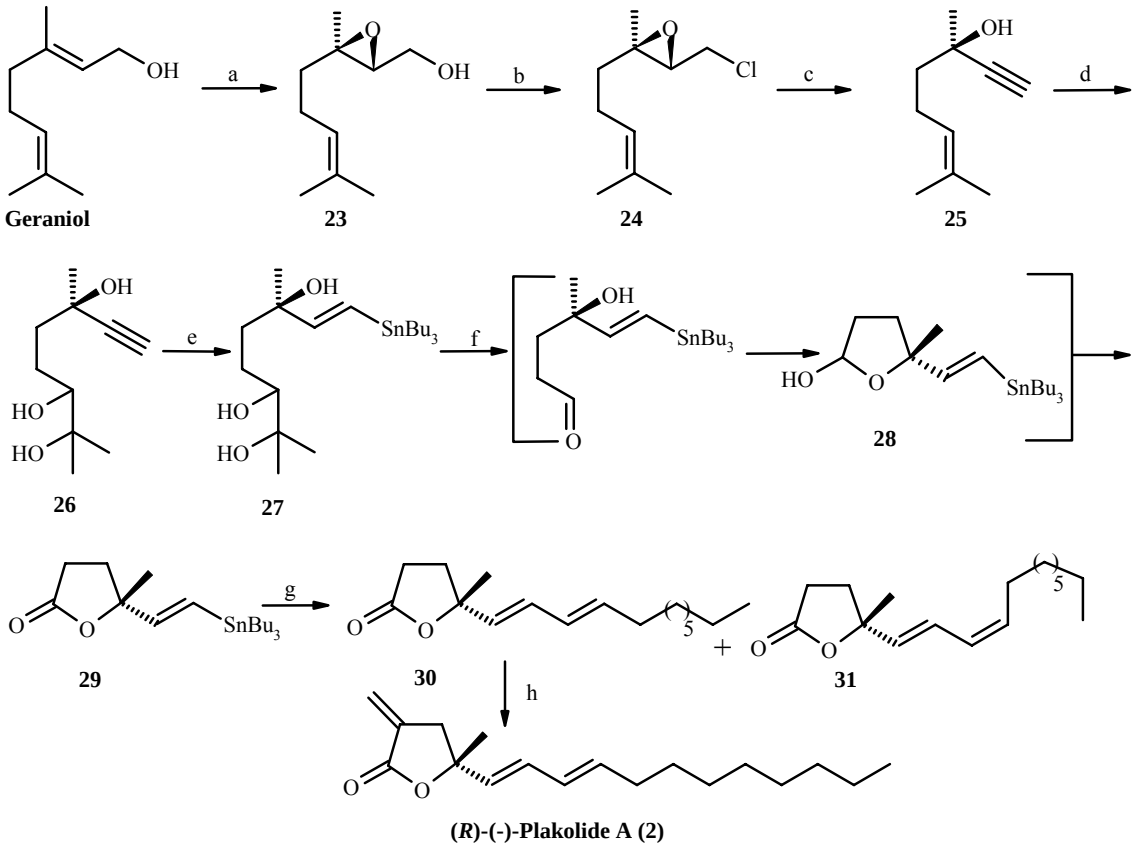


3

(*S*)-(+)-Plakolide A (1)

It exhibited spectroscopic and physical properties identical to those of literature value; the sign of optical rotation was different {$[\alpha]_D^{25}$ +43.2 (*c* 1.5, MeOH), lit[18] $[\alpha]_D^{25}$ –41.0 (*c* 0.12, MeOH)}. This reconfirmed the observation of Matsuo et al. that, natural Plakolide A is not (*S*)-(+)-Plakolide A (**1**) but rather (*R*)-(–)-Plakolide A (**2**).[19a]

Using exactly the same approach, the revised enantiomer (*R*)-(–)-Plakolide A (**2**) was synthesized from geraniol as well by using D-(–)-DIPT for the Sharpless epoxidation and following the same protocol as depicted in Scheme 15. We arrived at (*R*)-(–)-Plakolide A (**2**) {$[\alpha]_D^{25}$ –42.4 (*c* 1.2, MeOH), lit[18] $[\alpha]_D^{25}$ –41.0 (*c* 0.12, MeOH)} in 8 steps with an overall 41% yield.

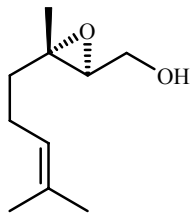


Scheme 15. ***Synthesis of revised (R)-(–)-Plakolide A (2) Reagents and conditions*:** (a) D-(–)-DIPT, Ti(O-^{i}Pr)$_4$, TBHP, MS 4Å, CH_2Cl_2, –23 ^{o}C, 6 h, 98%; (b) PPh_3, CCl_4, reflux, 6 h, 91%; (c) *n*-BuLi, THF, –40 ^{o}C, 1 h, 84%; (d) OsO_4, NMO, acetone-water (1:4), rt, 12 h, 93%; (e) Bu_3SnH, AIBN, toluene, 110 ^{o}C, 6 h, 91%; (f) (1) silica gel supported $NaIO_4$, CH_2Cl_2, 1 h; (2) PDC, CH_2Cl_2, 4 h, 83% over two steps; (g) **4**, $Pd(PPh_3)_4$, LiCl, CuCl, DMSO, from rt to 60 ^{o}C, 26 h, 84% for **31** and 9% for **32**; (h) (1) LDA, THF, –78 ^{o}C, 15 min, (2) Eschenmoser's salt, –78 ^{o}C to rt, 6 h, (3) CH_3I, CH_3OH, rt, 18 h, 83%.

In conclusion, we developed efficient synthetic routes to enantiopure (*S*)-(+)-Plakolide A (**1**) and (*R*)-(–)-Plakolide A (**2**) starting from readily available geraniol as starting material and following a practical sequence of reactions. The obvious and noteworthy advantages of our protocol lie in high overall yields, ready access to the disubstituted γ-lactone moiety with high enantioselectivity, and various possibilities of side chain modifications

EXPERIMENTAL

(2*S*,3*S*)-3-Methyl-3-(4-methylpent-3-enyl)oxiran-2-yl)methanol (7)



7

A stirred mixture of activated 4 Å molecular sieves (5.0 g) and dichloromethane (30 mL) was cooled to –10 ^{o}C. L-(+)-diisopropyl tartrate (0.86 mL, 4.1 mmol), freshly distilled titanium isopropoxide (1.20 mL, 4.1 mmol) and *tert*-butyl hydroperoxide (5 M solution in decane, 9.72 mL, 48.6 mmol) were added sequentially. After stirring for ten minutes, the mixture was cooled to –23 ^{o}C and freshly distilled geraniol (5.0 g, 32.4 mmol) in dichloromethane (10 mL) was added at a rate sufficient to ensure that the temperature remained under –20 ^{o}C. The mixture was stirred at –23 ^{o}C for an additional 6 h and water was (10 mL) then added with vigorous stirring. After 30 min, 3M aqueous NaOH (20 mL) was added, the mixture stirred at room temperature for additional 30 min and filtered through Celite. The filtrate was stirred vigorously with 10% citric acid (30 mL) at room temperature for 2 h. After the organic layer was separated, the aqueous layer was extracted twice with dichloromethane (2 × 50 mL). The combined organic layer was washed with brine (40 mL), dried over Na_2SO_4, and concentrated in vacuo. Bulb to bulb distillation (100 ^{o}C at 0.1 mm Hg) of the crude product yielded epoxide **7** (5.24 g, 95%) as a colorless liquid.

$[\alpha]_D^{25}$ = –5.1 (*c* 3.0, $CHCl_3$).

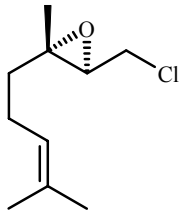
IR (liquid film, $CHCl_3$) ν_{max} (cm^{-1}): 3418, 1672, 1452, 1384, 1094, 864.

^{1}H NMR ($CDCl_3$, 200 MHz): δ 5.07 (t, 1H, *J* = 7.08 Hz), 3.81 (dd, 1H, *J* = 12.13, 4.29 Hz), 3.66 (dd, 1H, *J* = 12.13, 6.70 Hz), 2.96 (dd, 1H, *J* = 6.70, 4.29 Hz), 2.07 (dt, 2H, *J* = 7.59, 7.08 Hz), 1.69 (m, 1H), 1.68 (s, 3H), 1.61 (s, 3H), 1.48 (m, 1H), 1.30 (s, 3H).

^{13}C NMR ($CDCl_3$, 50 MHz): δ 132.0, 123.4, 63.1, 61.3, 61.1, 38.5, 25.7, 23.7, 17.6, 16.7.

Anal. Calcd for $C_{10}H_{18}O_2$: C, 70.60; H, 10.58; **Found:** C, 70.82; H, 10.46.

(2*R*,3*S*)-3-(Chloromethyl)-2-methyl-2-(4-methylpent-3-enyl)oxirane (13)



13

A stirred mixture of epoxy alcohol **7** (4.2 g, 24.7 mmol), PPh_3 (7.76 g, 29.6 mmol) and $NaHCO_3$ (0.42 g, 10% w/w) in CCl_4 (50 mL) was heated at reflux, under nitrogen atmosphere, for 6 h. After completion of the reaction, CCl_4 was removed under reduced pressure and the residue was purified by silica gel column chromatography (4% ethyl acetate/light petroleum) to furnish the epoxy chloride **13** (4.3 g, 93%) as a colorless liquid.

$[\alpha]^{25}_D$ = +9.95 (*c* 2.9, $CHCl_3$).

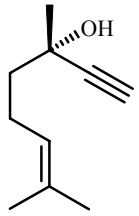
IR (liquid film, $CHCl_3$) ν_{max} (cm^{-1}): 1653, 1451, 1385, 1263, 1113, 1072, 914, 860.

^{1}H NMR ($CDCl_3$, 200 MHz): δ 5.08 (t, 1H, *J* = 7.1 Hz), 3.69 (dd, 1H, *J* = 11.4, 5.8 Hz), 3.41 (dd, 1H, *J* = 11.4, 7.3 Hz), 3.01 (dd, 1H, *J* = 7.3, 5.8 Hz), 2.09 (dt, 2H, *J* = 7.5, 7.1 Hz), 1.68 (m, 1H), 1.68 (s, 3H), 1.44 (m, 1H), 1.32 (s, 3H).

^{13}C NMR ($CDCl_3$, 50 MHz): δ 132.0, 123.2, 61.7, 61.3, 42.0, 38.2, 25.5, 23.6, 17.5, 16.1.

Anal Calcd for $C_{10}H_{17}OCl$: C, 63.65; H, 9.00. **Found:** C, 63.78; H, 9.14.

(*S*)-3,7-Dimethyloct-6-en-1-yn-3-ol (6)



6

To a stirred solution of epoxy chloride **13** (3.5 g, 18.5 mmol) in dry THF (25 mL) at –40 ^{o}C under an argon atmosphere, *n*-BuLi (34.77 ml, 55.6 mmol) was added dropwise and the mixture was allowed to stir for additional 1 h. After quenching by aqueous NH_4Cl solution (20 mL), THF was removed under reduced pressure. The aqueous layer was extracted with ethyl acetate (2 × 50 mL), dried over Na_2SO_4 and concentrated. The residue was purified by silica gel column chromatography (3% ethyl acetate/light petroleum) to afford propargyl alcohol derivative **6** (2.2 g, 85%) as a colorless liquid.

$[\alpha]^{25}_{D}$ = –13.24 (*c* 0.65, $CHCl_3$).

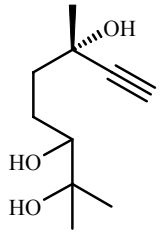
IR (liquid film, $CHCl_3$) ν_{max} (cm^{-1}): 3398, 3308, 2110, 1672, 1451, 1376, 1121, 908.

^{1}H NMR ($CDCl_3$, 200 MHz): δ 5.15 (t, 1H, *J* = 7.2 Hz), 2.43 (s, 1H), 2.17 (m, 2H), 1.7 (m, 2H), 1.65 (s, 3H), 1.49 (s, 3H).

^{13}C NMR ($CDCl_3$, 50 MHz): δ 132.3, 123.8, 87.7, 71.4, 68.1, 43.2, 29.8, 25.7, 23.5, 17.7.

Anal Calcd for $C_{10}H_{16}O$: C, 78.90; H, 10.60. **Found:** C, 79.06; H, 10.78.

(6*S*)-2,6-Dimethyloct-7-yne-2,3,6-triol (14)



14

Osmium tetroxide (catalytic) was added to a stirred mixture of the carbinol **6** (2.20 g, 14.5 mmol) and NMO (50% aqueous solution, 6.77 mL, 28.9 mmol) in acetone-water (1:4, 10 mL) at 0 ^{o}C. The mixture was stirred overnight at room temperature. After completion of the reaction, it was quenched with a saturated solution of sodium sulfite (10 mL). The mixture was stirred vigorously for 1 h. Acetone was removed under reduced pressure and the aqueous layer was extracted with ethyl acetate (3 x 50 mL). The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo to leave a residue, which on silica gel column chromatography (70% ethyl acetate/light petroleum) furnished **14** (1:1 diastereomeric mixture) (2.6 g, 92%) as a viscous liquid.

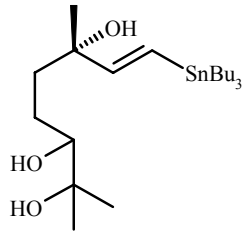
IR (liquid film, $CHCl_3$) ν_{max} (cm^{-1}): 3397, 3307, 2109, 1452, 1374, 1167, 1071, 945.

^{1}H NMR ($CDCl_3$, 200 MHz): δ 3.44 (m, 1H), 2.46 (s, 1H), 2.01-1.69 (m, 4H), 1.54 (s, 1.5H), 1.53 (s, 1.5H), 1.24 (s, 3H), 1.20 (s, 1.5H), 1.19 (s, 1.5H).

^{13}C NMR ($CDCl_3$, 50 MHz): δ (88.0/87.6), (78.8/78.1), 73.3, (71.7/71.4), 67.5, (40.9/40.2), (30.5/29.5), 26.7, (26.4/26.4), (23.4/23.3).

Anal Calcd for $C_{10}H_{18}O_3$: C, 64.49; H, 9.74. **Found:** C, 64.56; H, 9.82.

(6*S*,*E*)-2,6-Dimethyl-8-(tributylstannyl)oct-7-ene-2,3,6-triol (15)



15

To a stirred solution of **14** (2.4 g, 12.9 mmol) in toluene (30 mL) were added *n*-Bu_3SnH (4.0 mL, 15.5 mmol) and AIBN (30 mg) at room temperature. The reaction mixture was degassed with Argon and gently refluxed with stirring for 6 h. The solvent was removed and the residue was purified by silica gel column chromatography (40% ethyl acetate/light petroleum) to give **15** (1:1 diastereomeric mixture) (5.5 g, 90%) as a colorless liquid.

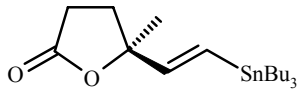
IR (liquid film, $CHCl_3$) ν_{max} (cm^{-1}): 3393, 1641, 1599, 1463, 1376, 1166, 1071, 994.

^{1}H NMR ($CDCl_3$, 200 MHz): δ 6.12 (d, 0.5H, *J* = 19.3 Hz), 6.12 (d, 0.5H, *J* = 19.3 Hz), 6.0 (d, 0.5H, *J* = 19.3 Hz), 5.95 (d, 0.5H, *J* = 19.3 Hz), 3.35 (dd, 0.5H, *J* = 6.9, 2.3 Hz), 3.35 (dd, 0.5H, *J* = 6.8, 2.1 Hz), 1.88-1.57 (m, 4H), 1.54-1.25 (m, 18H), 1.19 (s, 1.5H), 1.18 (s, 1.5H), 1.14 (s, 1.5H), 1.12 (s, 1.5H), 0.93 (s, 1.5H), 0.89 (s, 1.5H), 0.89 (t, 9H, *J* = 7.48 Hz).

^{13}C NMR ($CDCl_3$, 50 MHz): δ (154.7/154.2), (123.8/123.3), (79.1/78.5), (74.6/73.2), (39.3/38.8), (29.3/29.2), 29.1, 28.9, (27.8/27.8), 27.2, (26.5/26.4), (26.1/26.0), (23.2/23.1), 13.7, 9.5.

Anal Calcd for $C_{22}H_{46}O_3Sn$: C, 55.36; H, 9.70. **Found**: C, 55.49; H, 9.88.

(*S*,*E*)-5-Methyl-5-(2-(tributylstannyl)vinyl)-dihydrofuran-2(3*H*)-one (5)



5

To a vigorously stirred suspension of silica gel-supported $NaIO_4$ reagent (12.0 g) in CH_2Cl_2 (50 mL) was added a solution of the triol **15** (2.0 g, 4.2 mmol) in CH_2Cl_2 (20 mL). After completion of the reaction, PDC (2.02 g, 5.4 mmol) was added at 0 ^oC. The reaction mixture was stirred at room temperature for an additional 4 h period and filtered through a pad of silica gel, which was washed with CH_2Cl_2 (2 x 50 mL) and the solvent was evaporated. Silica gel column chromatography (5% ethyl acetate/light petroleum) of the residue afforded lactone **5** (1.4 g, 84% over two steps) as a colorless liquid.

$[\alpha]^{25}_D$ = –8.17 (*c* 1.0, $CHCl_3$).

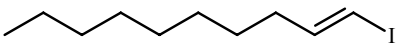
IR (liquid film, $CHCl_3$) ν_{max} (cm^{-1}): 1768, 1463, 1377, 1262, 1143, 1073, 992.

^{1}H NMR ($CDCl_3$, 200 MHz): δ 6.27 (d, 1H, *J* = 19.3 Hz), 5.92 (d, 1H, *J* = 19.3 Hz), 2.52 (dt, 2H, *J* = 6.8, 2.2 Hz), 2.28-1.97 (m, 2H), 1.60-1.21 (m, 18H), 0.90 (m, 14H**).**

^{13}C NMR ($CDCl_3$, 50 MHz): δ 176.5, 148.6, 127.0, 86.6, 33.8, 29.0, 28.7, 27.1, 26.3, 13.6, 9.4.

Anal. Calcd for $C_{19}H_{36}O_2Sn$: C, 54.96; H, 8.70. **Found:** C, 55.14; H, 8.93.

(E)-1-iododec-1-ene (4)



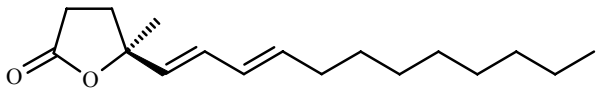
4

Anhydrous $CrCl_2$ (15.6 g, 126.5 mmol) was suspended in dry THF (100 mL) under argon atmosphere. A solution of nonanal (3 g, 21.1 mmol) and iodoform (16.6 g, 42.2 mmol) in THF (100 mL) was added dropwise to the suspension at 0 ^oC. After stirring at 0 ^oC for 4 h, the reaction mixture was poured into water and extracted with ether (2 × 100 mL). The combined organic layers were dried over anhydrous Na_2SO_4, concentrated and residue was purified by column chromatography on silica gel to afford **4** (4.5 g, 80% yield, E/Z = 9:1)

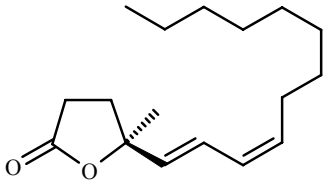
^{1}H NMR ($CDCl_3$, 200 MHz): δ 6.50 (dt, 1H, *J* = 14.4, 7.15 Hz), 5.96 (dt, 1H, *J* = 14.4, 1.40 Hz), 2.12-1.99 (m, 2H), 1.38-1.26 (m, 12H), 0.88 (t, 3H, *J* = 6.2 Hz).

^{13}C NMR ($CDCl_3$, 50 MHz): δ 146.8, 74.2, 36.0, 31.8, 29.3, 29.12, 28.9, 28.4, 22.6, 14.1.

(*S*)-5-((1*E*,3*E*)-Dodeca-1,3-dienyl)-5-methyl-dihydrofuran-2(3*H*)-one (3) and (*S*)-5-((1*E*,3*Z*)-Dodeca-1,3-dienyl)-5-methyl-dihydrofuran-2(3*H*)-one (22)



3



22

A 50 mL two-necked round-bottom flask was charged with LiCl (0.59 g, 13.8 mmol) and flame dried under high vacuum. With cooling, $Pd(PPh_3)_4$ (0.27 g, 0.23 mmol) and CuCl (1.27 g, 13.8 mmol) were added and the mixture was degassed (4 ×) under high vacuum with an Ar purge. DMSO (20 mL) was introduced with concomitant stirring, followed by the addition of vinyl iodide **4** (0.60 g, 2.3 mmol) and vinyl stannane **5** (1.40 g, 3.4 mmol). The resulting mixture was vigorously degassed (4 ×) under high vacuum with an Ar purge.

The reaction mixture was stirred at room temperature for 2 h, and then heated to 60 ^{o}C for 24 h. After completion of reaction, as monitored by TLC, the reaction mixture was cooled, diluted with ethyl acetate (50 mL), and washed with a mixture of brine (40 mL) and 5% aqueous NH_4OH (20 mL). The aqueous layer was further extracted with ethyl acetate (2 × 50 mL), and the combined organic layers were washed with water (50 mL) then brine (50 mL), dried over Na_2SO_4, and concentrated. The crude product was purified by flash silica gel column chromatography (50% benzene/light petroleum) to obtain the *E*,*E* (**3**) (0.496 g, 83%) and *E*,*Z* (**22**) (0.054 g, 9%) as colorless liquids.

For *E*,*E*-isomer (3):

$[\alpha]^{25}_{D}$ = –2.42 (*c* 1.0, $CHCl_3$).

IR (liquid film, $CHCl_3$) ν_{max} (cm^{-1}): 3020, 1768, 1658, 1523, 1457, 1420, 1378, 1073, 992, 929, 669.

^{1}H NMR ($CDCl_3$, 200 MHz): δ 6.14 (dd, 1H, *J* = 15.2, 10.1 Hz), 5.92 (dd, 1H, *J* = 15.0, 10.1 Hz), 5.67 (dt, 1H, *J* = 15.0, 6.8 Hz), 5.51 (d, 1H, *J* = 15.2 Hz), 2.54-2.45 (m, 2H), 2.20-1.93 (m, 4H), 1.45 (s, 3H), 1.30 (m, 2H), 1.17-1.26 (br m, 12H), 0.81 (t, 3H, *J* = 6.5 Hz).

^{13}C NMR ($CDCl_3$, 50 MHz): δ 176.5, 137.0, 132.0, 129.4, 128.8, 85.2, 34.4, 32.7, 31.9, 29.5, 29.3, 29.2, 29.1, 28.9, 26.7, 22.7, 14.1.

For *E*,*Z*-isomer (22):

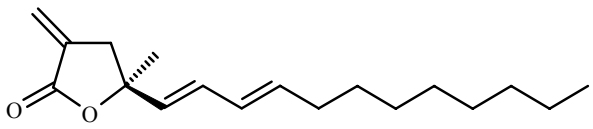
$[\alpha]^{25}_{D}$ = + 9.37 (*c* 0.65, $CHCl_3$).

IR ($CHCl_3$) ν_{max} (cm^{-1}): 3019, 1770, 1651, 1460, 1419, 1378, 1289, 1141, 1073, 987, 949, 932, 667.

^{1}H NMR ($CDCl_3$, 200 MHz): δ 6.52 (dd, 1H, *J* = 15.3, 11.0 Hz), 5.94 (t, 1H, *J* = 10.0 Hz), 5.67 (d, 1H, *J* = 15.4 Hz), 5.5 (dt, 1H, *J* = 10.8, 7.6 Hz), 2.58 (m, 2H), 2.25-2.08 (m, 4 H), 1.53 (s, 3H), 1.42-1.25 (m, 14 H), 0.88 (t, 3H, *J* = 6.4 Hz).

Anal Calcd for $C_{17}H_{28}O_2$: C, 77.22; H, 10.67. **Found**: C, 77.04; H, 10.82.

(*S*)-(+)-Plakolide A (1)



(*S*)-(+)-Plakolide A (1)

To a stirred solution of diisopropylamine (0.17 mL, 1.3 mmol) in anhydrous THF (20 mL) at –20 ^oC was added *n*-BuLi (1.6 M solution in hexane, 0.78 mL, 1.3 mmol). The solution was stirred for 15 minutes and cooling bath was maintained at –78 ^oC. Lactone **3** (0.3 g, 1.1 mmol) in THF (5 mL) was added and the reaction mixture was stirred for 15 minutes followed by addition of dimethyl(methylene)ammonium iodide (0.44 g, 2.4 mmol) in THF (5 mL). The reaction mixture was stirred for 6 h and gradually allowed to warm to room temperature. Solvent was removed at reduced pressure, the residue was dissolved in methanol (10 mL), to this excess methyl iodide (0.17 ml, 2.8 mmol) was added and the resulting mixture was stirred at room temperature for 18 h. Solvent was removed by rotary evaporation, giving a solid residue that was washed with aqueous $NaHCO_3$ solution (20 mL) and ethyl acetate (50 mL). The aqueous layer was extracted with ethyl acetate (2 × 25 mL). The combined organic layers were dried over Na_2SO_4 and solvent was removed under vacuum to afford a crude residue, which on purification by silica gel column chromatography (5% ethyl acetate/light petroleum) furnished **1** (0.26 g, 82%) as a colorless liquid.

$[\alpha]^{25}_D$ = +43.2 (*c* 1.5, MeOH).

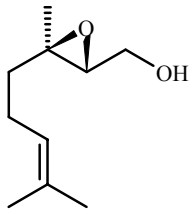
IR (liquid film, $CHCl_3$) ν_{max} (cm^{-1}): 1762, 1664, 1624, 1458, 1377, 1281, 1051, 990, 940.

^{1}H NMR ($CDCl_3$, 200 MHz): δ 6.22 (dd, 1H *J* = 15.1, 10.1 Hz), 6.23 (t, 1H, *J* = 2.7 Hz), 5.99 (dd, 1H, *J* = 15.0,10.1, Hz), 5.76 (dt, 1H, *J* = 15.0, 6.8 Hz), 5.61 (d, 1H, *J* = 15.2 Hz), 5.61 (t, 1H, *J* = 2.4 Hz), 2.93 (dt, 1H, *J* = 16.6, 2.6 Hz), 2.79 (dt, 1H, *J* = 16.6, 2.6 Hz), 2.07 (dt, 2H, *J* = 7.2, 6.9 Hz), 1.53 (s, 3H), 1.40-1.25 (m, 12H), 0.88 (t, 3H, *J* = 6.5 Hz).

^{13}C NMR ($CDCl_3$, 50 MHz): δ 169.78, 137.37, 135.31, 132.20, 129.67, 128.68, 122.26, 82.37, 40.79, 32.65, 31.85, 29.42, 29.23, 29.18, 29.09, 27.10, 22.64, 14.08.

Anal. Calcd for $C_{18}H_{28}O_2$: C, 78.21; H, 10.21. **Found:** C, 78.36; H, 10.42.

(2*R*,3*R*)-3-Methyl-3-(4-methylpent-3-enyl)oxiran-2-yl)methanol (23)



23

The same procedure as for **7** starting from geraniol (6.0 g, 38.9 mmol) gave **23** (6.5 g, 98% yield) as colorless oil.

$[\alpha]^{25}_D$ = +5.2 (*c* 1.65, $CHCl_3$).

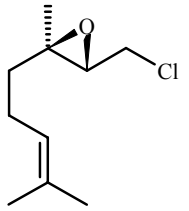
IR (liquid film, $CHCl_3$) ν_{max} (cm^{-1}): 3411,1615, 1508, 1452, 1385, 1033, 862.

^{1}H NMR ($CDCl_3$, 200 MHz): δ 5.07 (t, 1H, *J* = 7.1 Hz), 3.81 (m, 1H), 3.66 (dd, 1H, *J* = 12.1, 6.6 Hz), 2.96 (t, 2H, *J* = 5.4 Hz), 2.28 (br. s, 1H), 2.07 (dt, 2H, *J* = 7.4, 8.5 Hz), 1.69 (m, 1H), 1.68 (s, 3H), 1.60 (s, 3H), 1.46 (m, 1H), 1.30 (s, 3H).

^{13}C NMR ($CDCl_3$, 50 MHz): δ132.0, 123.3, 63.1, 61.3, 61.1, 38.4, 25.6, 23.6, 17.6, 16.7.

Anal Calcd for $C_{10}H_{18}O_2$: C, 70.60; H, 10.58; **Found:** C, 70.82; H, 10.46.

(2*S*,3*R*)-3-(Chloromethyl)-2-methyl-2-(4-methylpent-3-enyl)oxirane (24)



24

The same procedure as for **13** starting from **23** (5.5 g, 32.3 mmol) furnished **24** (5.6 g, 91% yield) as a colorless liquid.

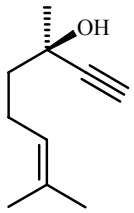
$[\alpha]^{25}_D$ = –10.26 (*c* 2.1, $CHCl_3$).

IR (liquid film, $CHCl_3$) ν_{max} (cm^{-1}): 1616, 1508, 1451, 1386, 1072, 915; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 5.09 (t, 1H, *J* = 7.1 Hz), 3.69 (dd, 1H, *J* = 5.8, 11.4 Hz), 3.42 (dd, 1H, *J* = 11.4, 7.3 Hz), 3.01 (dd, 1H, *J* = 7.1, 6.0 Hz), 2.09 (q, 2H, *J* = 7.1 Hz), 1.71 (m, 1H), 1.69 (s, 3H), 1.61 (s, 3H), 1.44 (m, 1H), 1.32 (s, 3H).

^{13}C NMR ($CDCl_3$, 50 MHz): δ 131.9, 123.1, 61.7, 61.2, 42.0, 38.1, 25.5, 23.6, 17.5, 16.1.

Anal Calcd for $C_{10}H_{17}OCl$: C, 63.65; H, 9.00. **Found:** C, 63.78; H, 9.14.

(*R*)-3,7-Dimethyloct-6-en-1-yn-3-ol (25)



25

The same procedure as for **6** starting from **24** (3.8 g, 20.1 mmol) furnished **25** (2.6 g, 84% yield) as a colorless liquid.

$[\alpha]^{25}_{D}$ = +12.64 (*c* 2.1, $CHCl_3$).

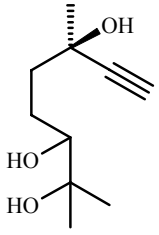
IR (liquid film, $CHCl_3$) ν_{max} (cm^{-1}): 3425, 3307, 1618, 1508, 1376, 1251, 1119, 906.

^{1}H NMR ($CDCl_3$, 200 MHz): δ 5.15 (t, 1H, *J* = 7.2 Hz), 2.43 (s, 1H), 2.23 (m, 3H), 1.69 (m,1H), 1.69 (s, 3H), 1.65 (s, 3H), 1.49 (s, 3H).

^{13}C NMR ($CDCl_3$, 50 MHz): δ 132.3, 123.8, 87.7, 71.4, 68.1, 43.2, 29.8, 25.7, 23.5, 17.7.

Anal Calcd for $C_{10}H_{16}O$: C, 78.90; H, 10.60**. Found**: C, 79.06; H, 10.78.

(6*R*)-2,6-Dimethyloct-7-yne-2,3,6-triol (26).



26

The same procedure as for **14** starting from **25** (3.2 g, 21.0 mmol) afforded **26** (3.6 g, 93% yield) as colorless oil.

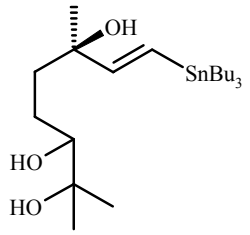
IR (liquid film, $CHCl_3$) ν_{max} (cm^{-1}): 3390, 3306, 1374, 1071, 945.

^{1}H NMR ($CDCl_3$, 200 MHz): δ 3.49-3.36 (m, 1H), 2.86 (brs, 3H), 2.45 (s, 1H), 2.01-1.62 (m, 4H), 1.53 (s, 1.5 H), 1.52 (s, 1.5H), 1.23 (s, 3H), 1.19 (s, 1.5H), 1.18 (s, 1.5H).

^{13}C NMR ($CDCl_3$, 50 MHz): δ (87.9/87.5), (78.5/78.1), 73.3, (71.8/71.5), 67.4, 40.7/40.3), (30.2/29.2), 26.5/26.3), (26.1/26.1), 23.5/23.4).

Anal Calcd for $C_{10}H_{18}O_3$: C, 64.49; H, 9.74. **Found:** C, 64.56; H, 9.82.

(6*R*,*E*)-2,6-Dimethyl-8-(tributylstannyl)oct-7-ene-2,3,6-triol (27).



27

The same procedure as for **15** starting from **26** (2.0 g, 10.7 mmol) gave **27** (1:1 diastereomeric mixture) (4.7 g, 91% yield) as a colorless liquid.

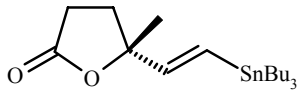
IR (liquid film, $CHCl_3$) ν_{max} (cm^{-1}): 3401, 1731, 1464, 1376, 1070.

^{1}H NMR ($CDCl_3$, 200 MHz): δ 6.06 (m, 2H), 3.36 (m, 1H), 1.88-1.13 (m, 28H), 0.93-0.85 (m, 12H).

^{13}C NMR ($CDCl_3$, 50 MHz): δ (154.7/154.1), (123.7/123.3), (79.0/78.5), 74.5/74.5), 73.2/73.2), (39.2/38.7), 29.0, 27.2, (26.4/26.3), 26.1/26.0), 23.2/23.0), 13.7, 9.4.

Anal Calcd for $C_{22}H_{46}O_3Sn$: C, 55.36; H, 9.70. **Found:** C, 55.49; H, 9.88.

(*R*,*E*)-5-Methyl-5-(2-(tributylstannyl)vinyl)-dihydrofuran-2(3*H*)-one (29).



29

The same procedure as for **5** starting from **27** (2.8 g, 5.9 mmol) furnished **29** (2.03 g, 83% yield) as colorless oil.

$[\alpha]^{25}_D$ = +9.55 (*c* 1.3, $CHCl_3$).

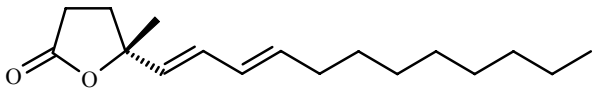
IR (liquid film, $CHCl_3$) ν_{max} (cm^{-1}): 1768, 1644, 1463, 1377, 1142, 1073.

^{1}H NMR ($CDCl_3$, 200 MHz): 6.22 (d, 1H, *J* = 19.3 Hz), 5.98 (d, 1H, *J* = 19.3 Hz), 2.52 (dd, 2H, *J* = 6.8, 9.2 Hz), 2.28-1.97 (m, 2H), 1.57-1.21 (m, 18H), 0.94-0.85 (m, 12H).

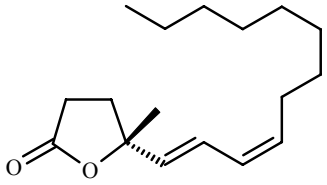
^{13}C **NMR ($CDCl_3$, 50 MHz):** δ 176.6, 148.6, 127.1, 86.7, 33.8, 29.0, 28.8, 27.2, 26.6, 26.3, 13.7, 9.5.

Anal. Calcd for $C_{19}H_{36}O_2Sn$: C, 54.96; H, 8.70. **Found:** C, 55.14; H, 8.93.

(*R*)-5-((1*E*,3*E*)-Dodeca-1,3-dienyl)-5-methyl-dihydrofuran-2(3*H*)-one (30) and (*R*)-5-((1*E*,3*Z*)-Dodeca-1,3-dienyl)-5-methyl-dihydrofuran-2(3*H*)-one (31).



30



31

The same procedure as for **3** starting from **29** (1.18 g, 2.85 mmol) and **4** (0.5 g, 1.9 mmol) afforded **30** (0.42 g, 84% yield) and **31** (0.045 g, 9% yield) as colorless liquids.

For *E*,*E*-isomer (30):

$[\alpha]^{25}_{D}$ = +2.68 (*c* 1.8, $CHCl_3$).

IR (liquid film, $CHCl_3$) ν_{max} (cm^{-1}): 1776, 1658, 1460, 1377, 1137, 1074, 991.

^{1}H NMR ($CDCl_3$, 200 MHz): 6.21 (dd, 1H, *J* = 15.2, 10.1 Hz), 5.98 (dd, 1H, *J* = 15.0, 10.1 Hz), 5.74 (dt, 1H, *J* = 15.0, 6.8 Hz), 5.58 (d, 1H, *J* = 15.2 Hz), 2.56 (m, 2H), 2.27-2.00 (m, 4H), 1.52 (s, 3H), 1.40-1.20 (m, 14H), 0.88 (t, 3H, *J* = 6.6 Hz).

^{13}C NMR ($CDCl_3$, 50 MHz): δ 176.5, 137.1, 132.0, 129.4, 128.8, 85.2, 34.4, 32.7, 31.9, 29.5, 29.3, 29.2, 29.2, 28.9, 26.8, 22.7, 14.1.

For *E*,*Z*-isomer (31):

$[\alpha]^{25}_{D}$ = –10.74 (*c* 1.4, $CHCl_3$).

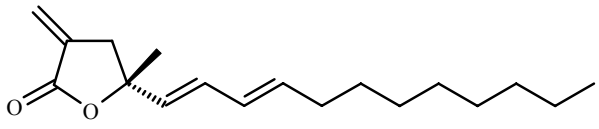
IR (liquid film, $CHCl_3$) ν_{max} (cm^{-1}): 1770, 1650, 1457, 1378, 1073.

^{1}H NMR ($CDCl_3$, 200 MHz): 6.51 (dd, 1H, *J* = 15.3, 11.0 Hz), 5.93 (t, 1H, *J* = 11.0 Hz), 5.66 (d, 1H, *J* = 15.3 Hz), 5.50 (dt, 1H, *J* = 7.6, 11.0 Hz), 2.57 (m, 2H), 2.28-2.02 (m, 4H), 1.53 (s, 3H), 1.42-1.25 (m, 14H), 0.88 (t, 3H, *J* = 6.5 Hz).

^{13}C NMR ($CDCl_3$, 50 MHz): δ 176.3, 134.5, 134.3, 127.1, 124.3, 85.2, 34.5, 31.9, 29.8, 29.6, 29.5, 29.3, 28.9, 27.9, 26.9, 22.7, 14.2.

Anal Calcd for $C_{17}H_{28}O_2$: C, 77.22; H, 10.67. **Found:** C, 77.04; H, 10.82.

(*R*)-(–)-Plakolide A (2).



(*R*)-(-)-Plakolide A (2)

The same procedure as for **1** starting from **30** (0.2 g, 0.76 mmol) gave **2** (0.17 g, 83% yield) as a colorless liquid.

$[\alpha]^{25}_D$ = –42.4 (*c* 1.2, CH_3OH).

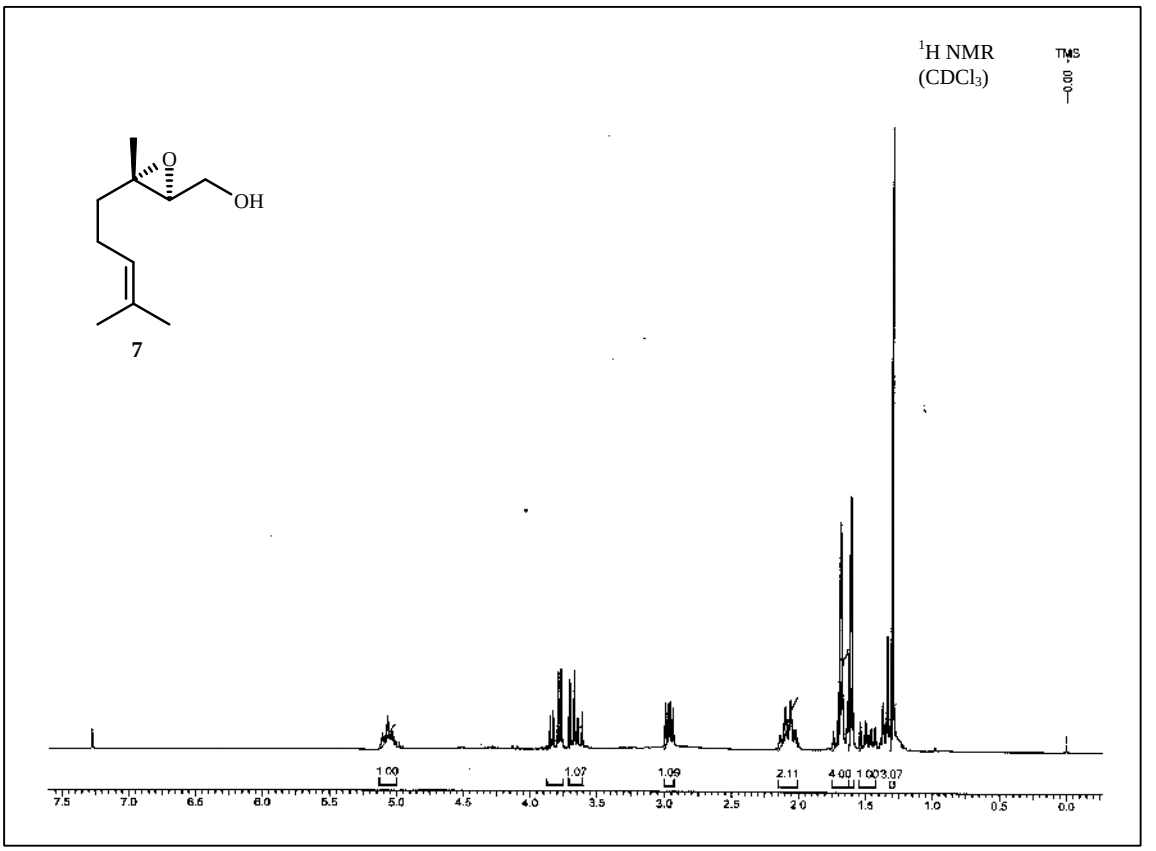
IR (liquid film, $CHCl_3$) ν_{max} (cm^{-1}): 1766, 1660, 1463, 1279, 1105, 1051.

^{1}H NMR ($CDCl_3$, 200 MHz): δ 6.21 (dd, 1H, *J* = 15.1, 10.1 Hz), 6.23 (t, 1H, *J* = 2.7 Hz), 5.98 (dd, 1H, *J* = 15.0, 10.1 Hz), 5.76 (dt, 1H, *J* = 15.0, 6.9 Hz), 5.6 (d, 1H, *J* = 15.1 Hz), 5.60 (t, 1H, *J* = 2.5 Hz), 2.92 (dt, 1H, *J* = 16.6, 2.5 Hz), 2.78 (dt, 1H, *J* = 16.6, 2.5 Hz), 2.07 (dt, 2H, *J* = 7.3, 6.9 Hz), 1.53 (s, 3H), 1.38-1.25 (m, 12H), 0.88 (t, 3H, *J* = 6.4 Hz).

^{13}C NMR ($CDCl_3$, 50 MHz): δ 169.53, 137.32, 135.41, 132.28, 129.73, 128.80, 122.19, 82.80, 40.90, 32.74, 31.94, 29.52, 29.32, 29.26, 29.18, 27.21, 22.72, 14.19.

Anal. Calcd for $C_{18}H_{28}O_2$: C, 78.21; H, 10.21. **Found:** C, 78.36; H, 10.42.

SPECTRA


^{1}H NMR
(CDCl$_3$)
TMS
0.00
O
OH
7
1.00
1.07
1.09
2.11
4.00
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3.07
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
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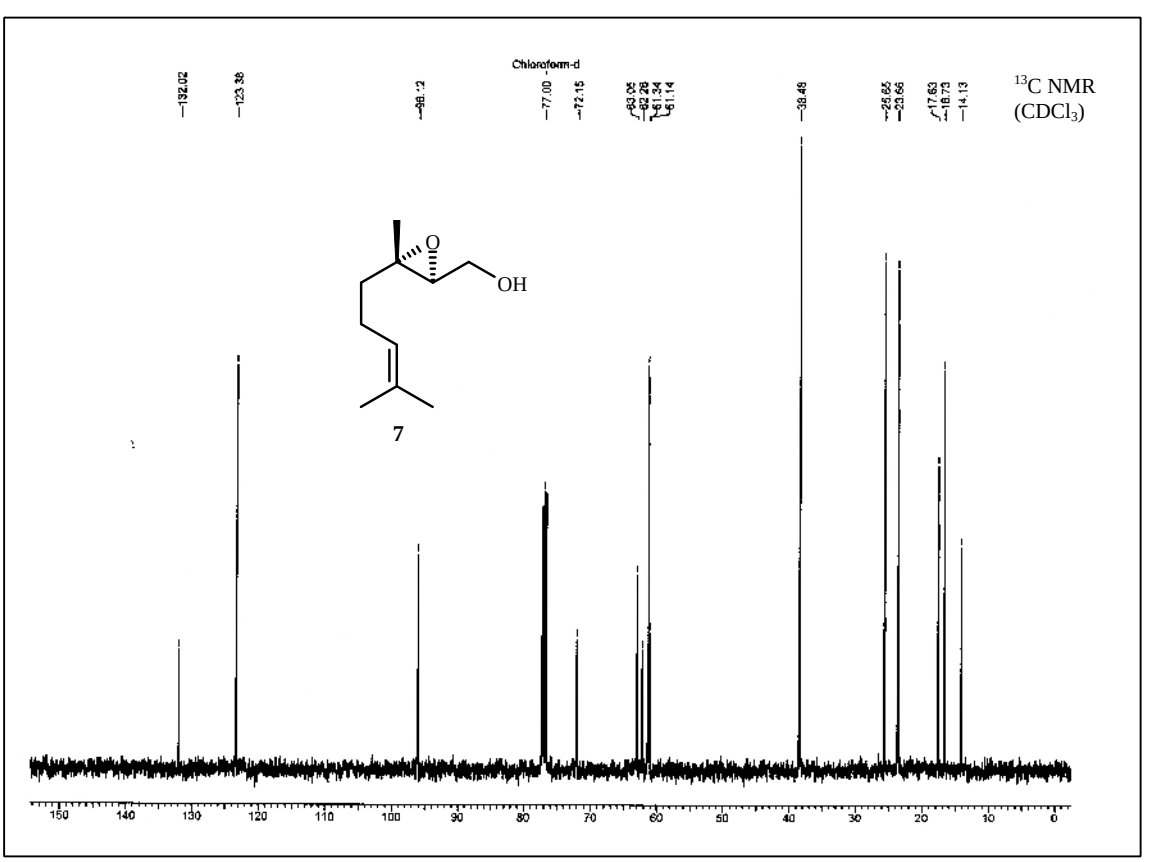
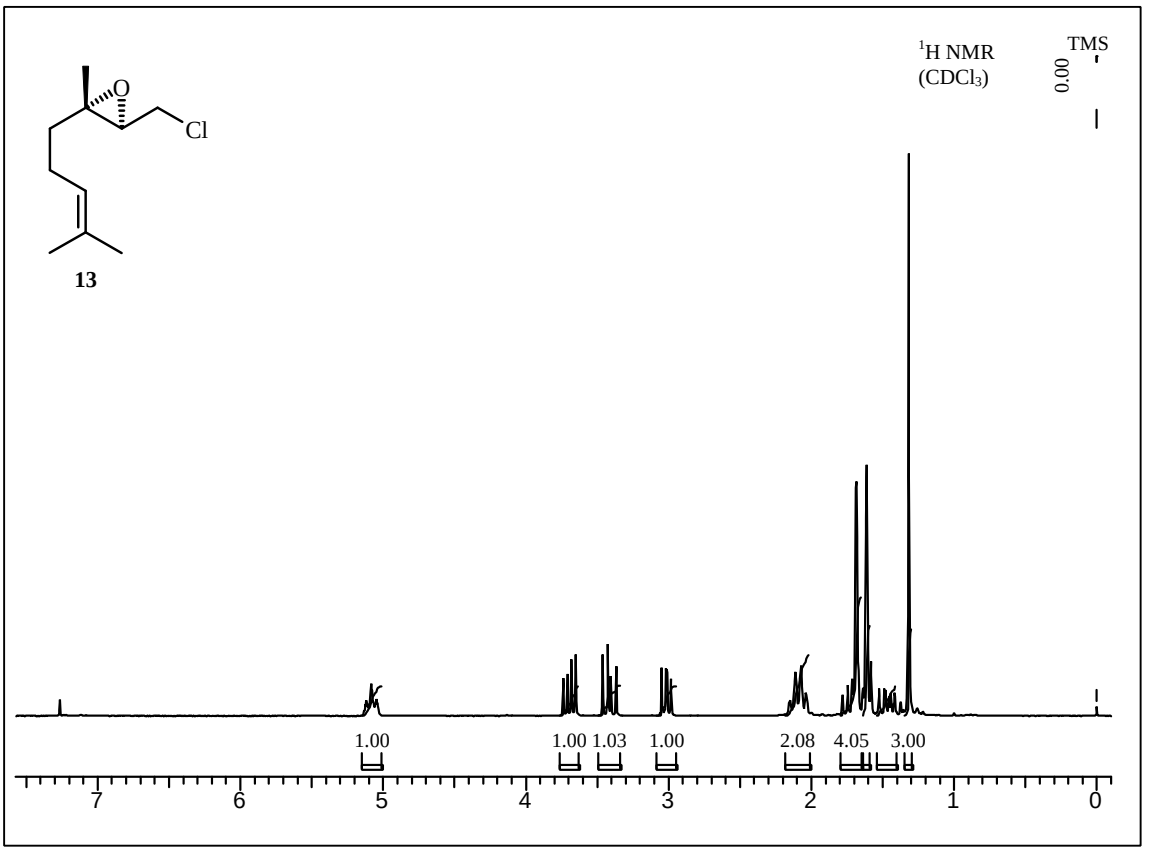
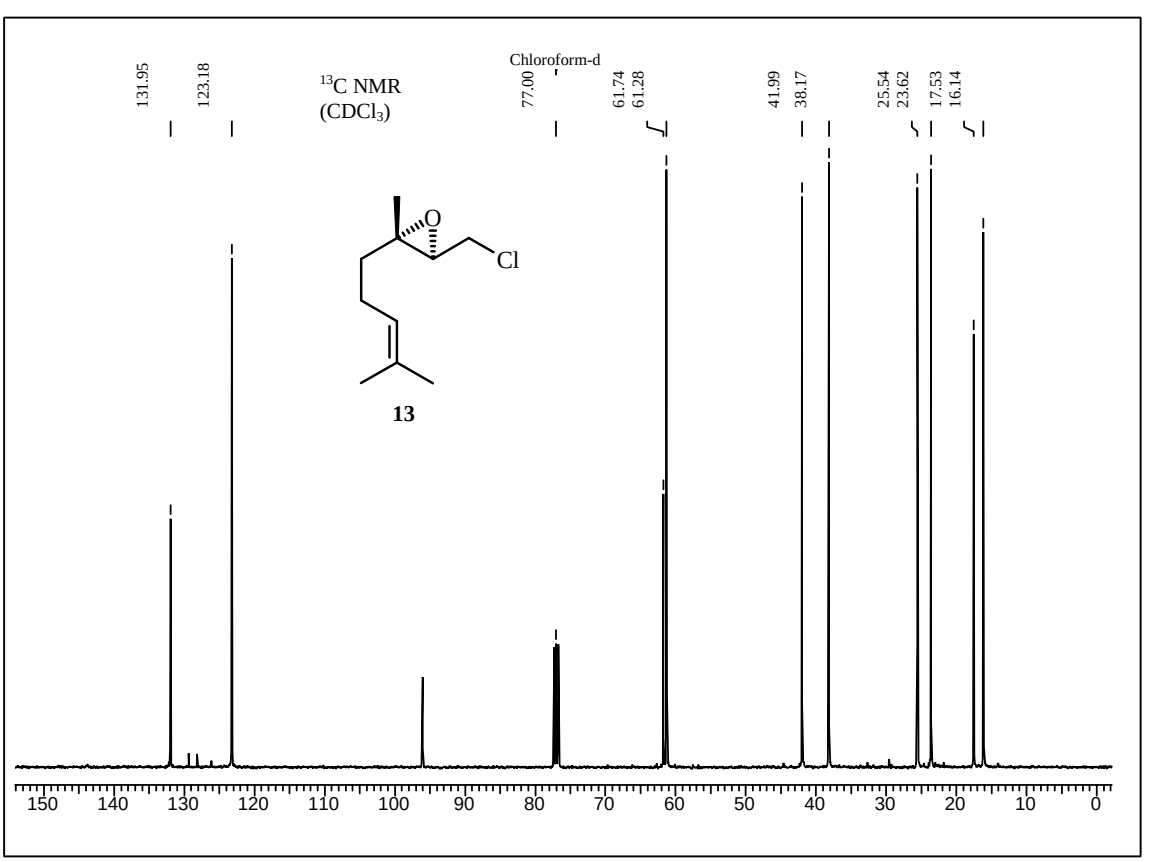
0.0


^{13}C NMR
(CDCl$_3$)
Chloroform-d
132.02
123.38
96.12
77.00
72.15
63.05
62.28
61.34
61.14
38.49
25.65
23.66
17.63
16.73
14.13
O
OH
7
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0


O
Cl
13
^{1}H NMR
(CDCl$_3$)
TMS
0.00
1.00
1.00
1.03
1.00
2.08
4.05
3.00
7
6
5
4
3
2
1
0


131.95
123.18
^{13}C NMR
(CDCl$_3$)
Chloroform-d
77.00
61.74
61.28
41.99
38.17
25.54
23.62
17.53
16.14
O
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140
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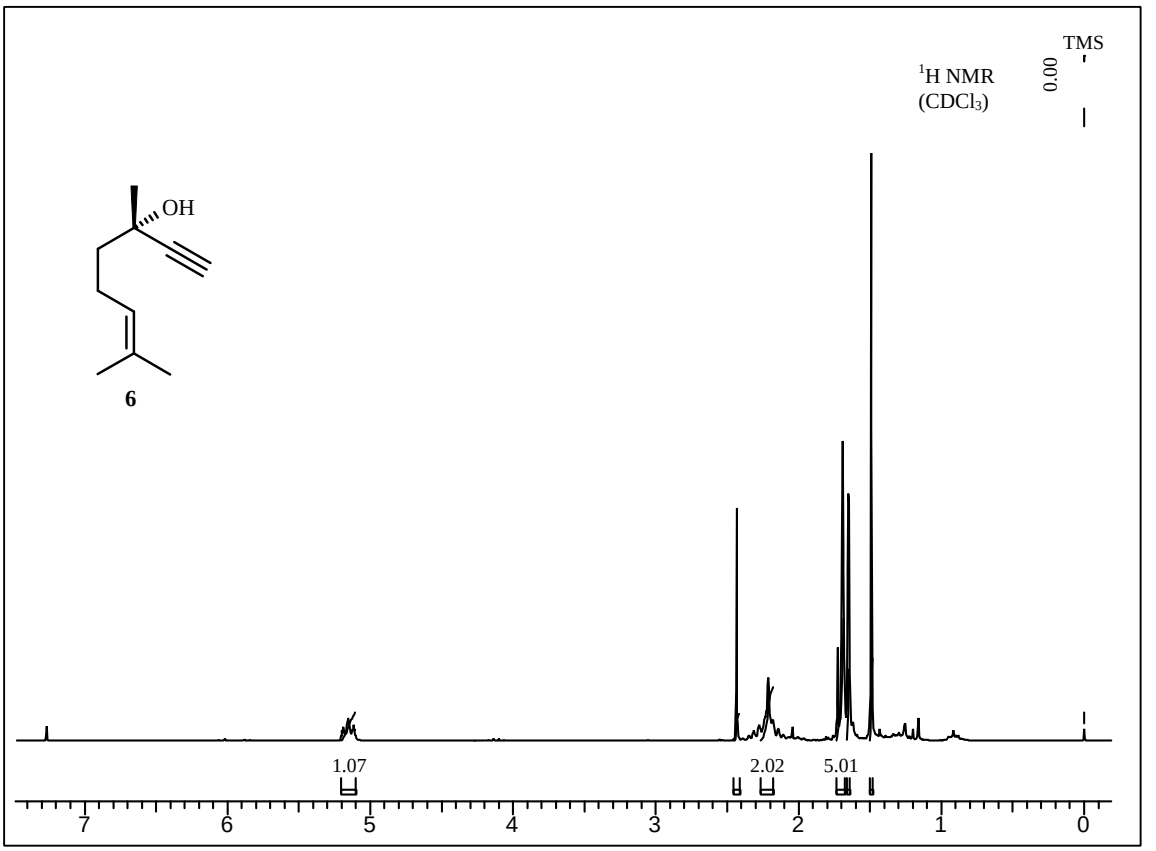
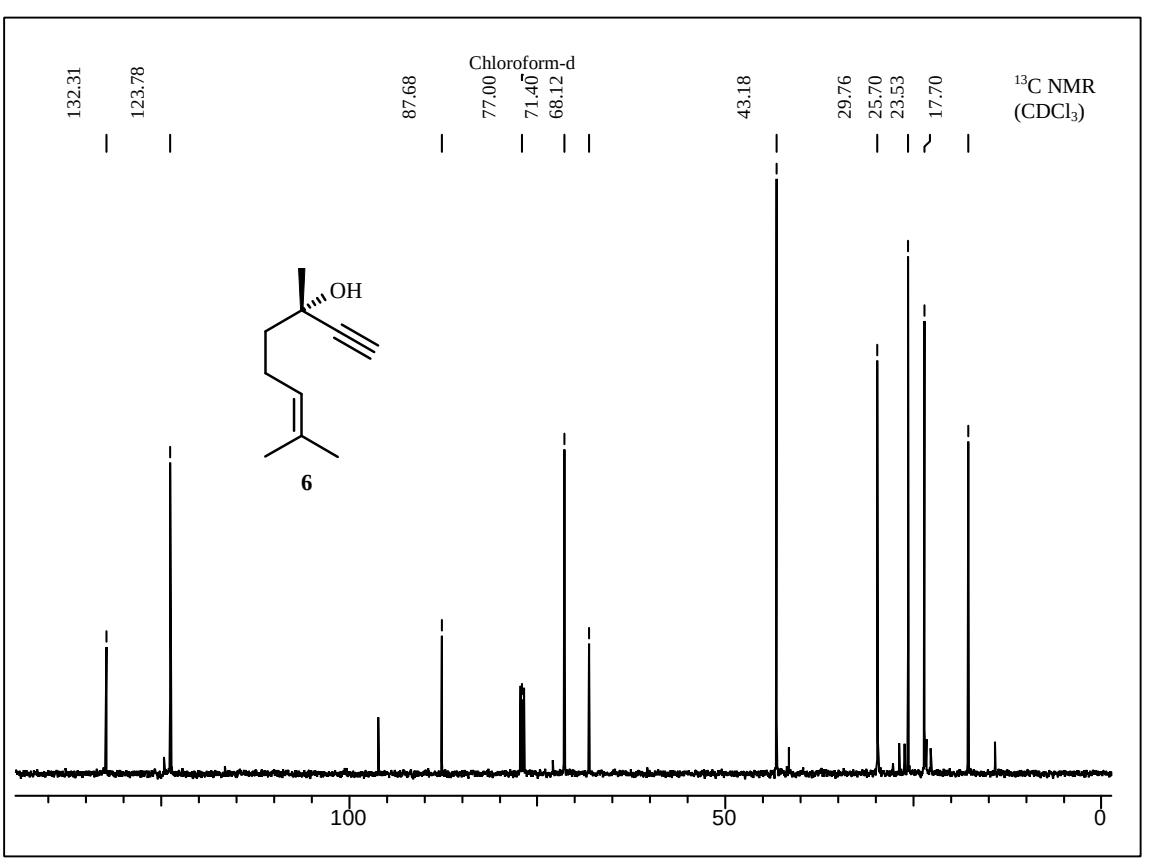
90
80
70
60
50
40
30
20
10
0


TMS
0.00
^{1}H NMR
($CDCl_3$)
OH
6
1.07
2.02
5.01
7
6
5
4
3
2
1
0


132.31
123.78
87.68
Chloroform-d
77.00
71.40
68.12
43.18
29.76
25.70
23.53
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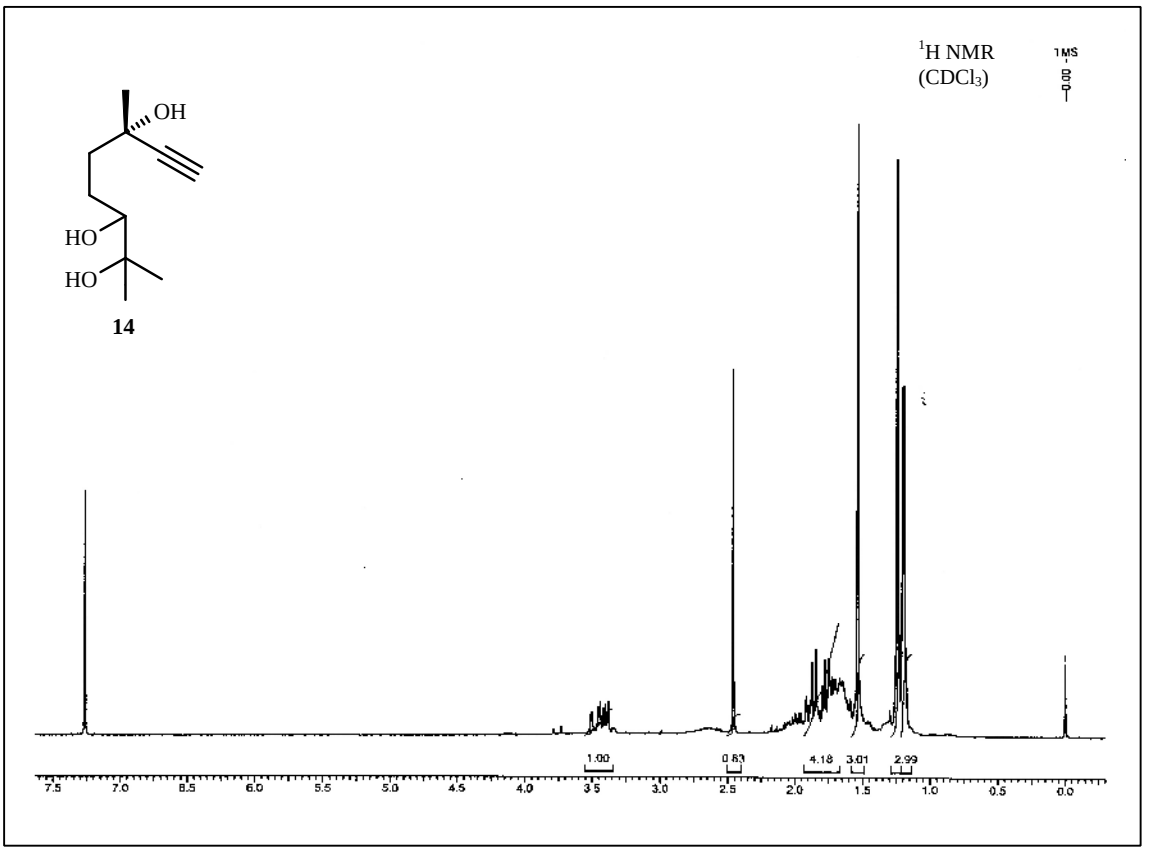
^{13}C NMR
($CDCl_3$)
OH
6
100
50
0


^{1}H NMR
($CDCl_3$)
TMS
OH
HO
HO
14
1.00
0.83
4.18
3.01
2.99
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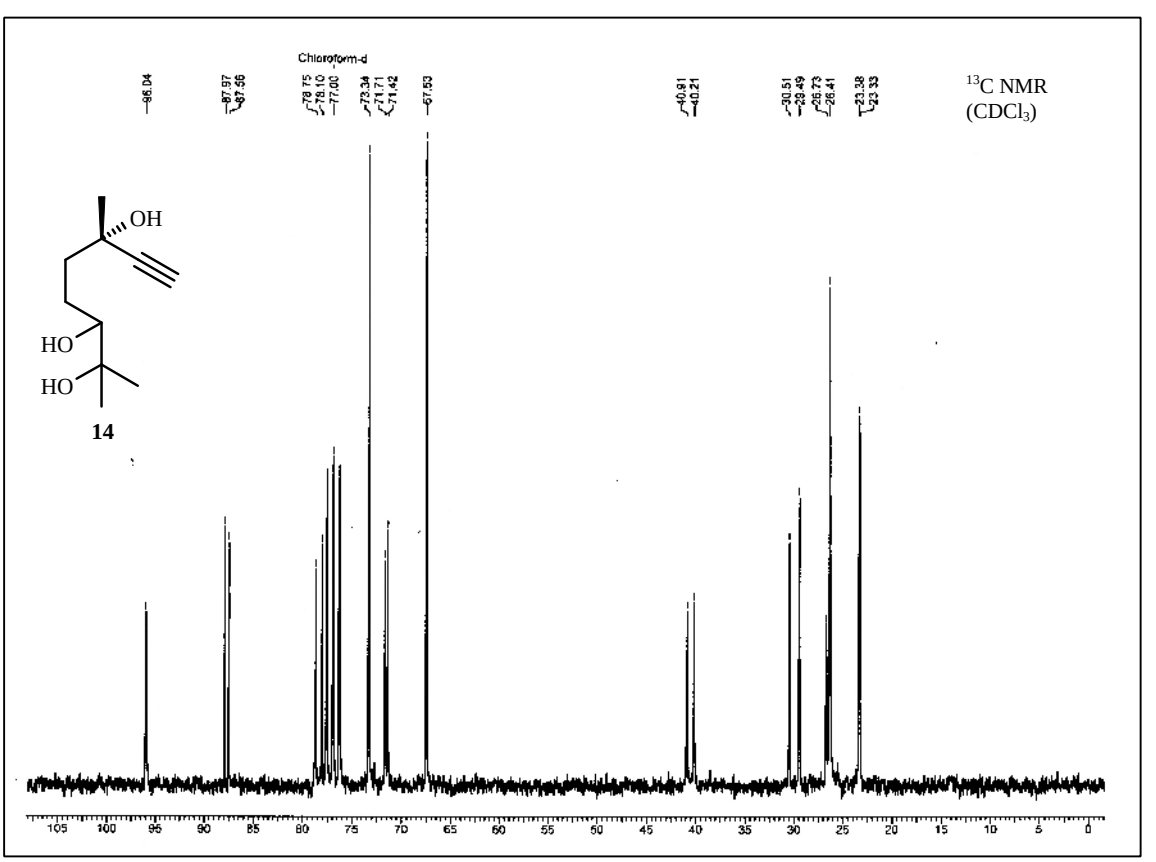
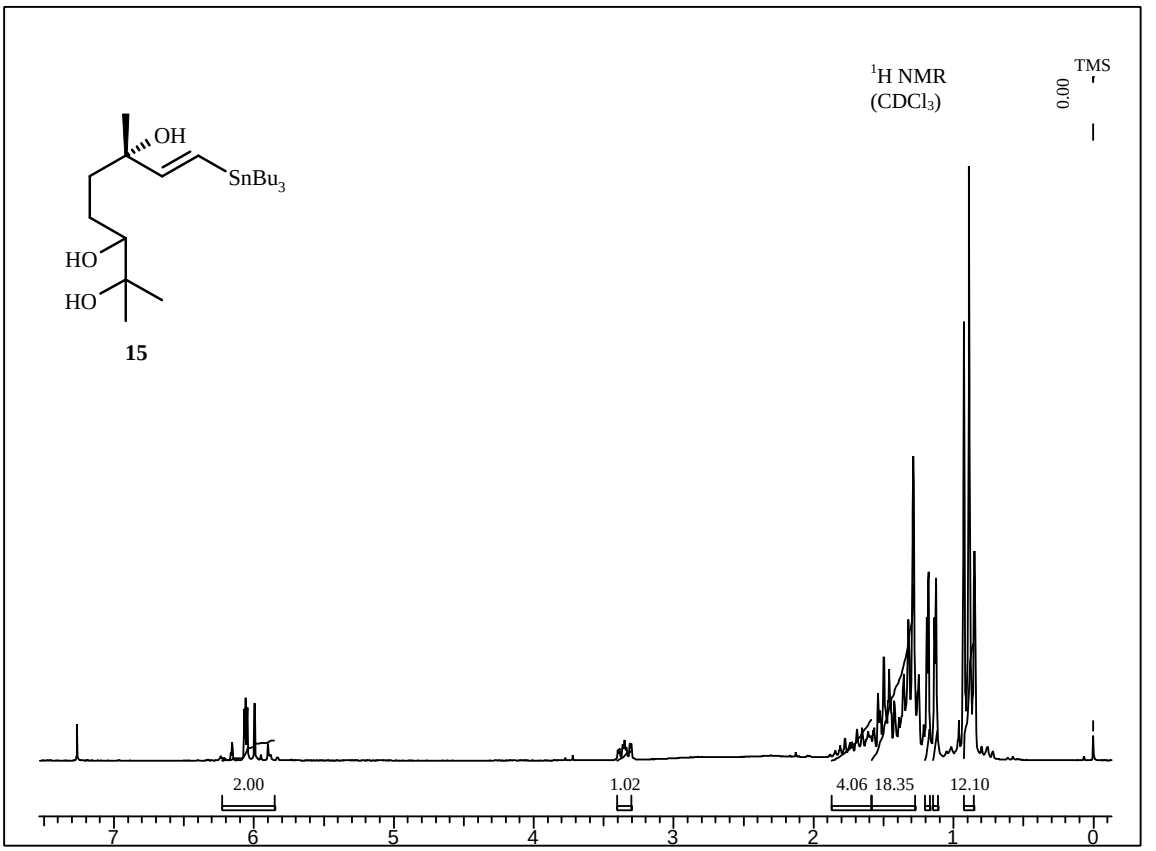
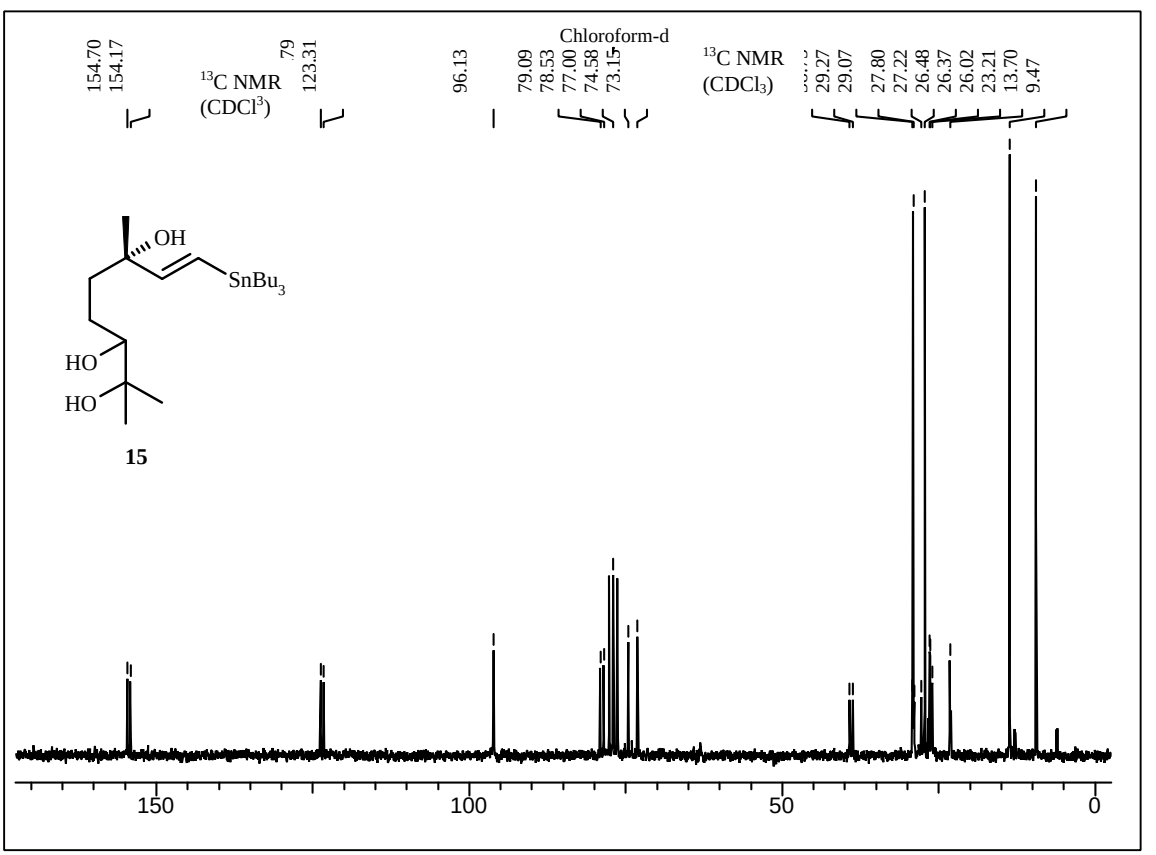
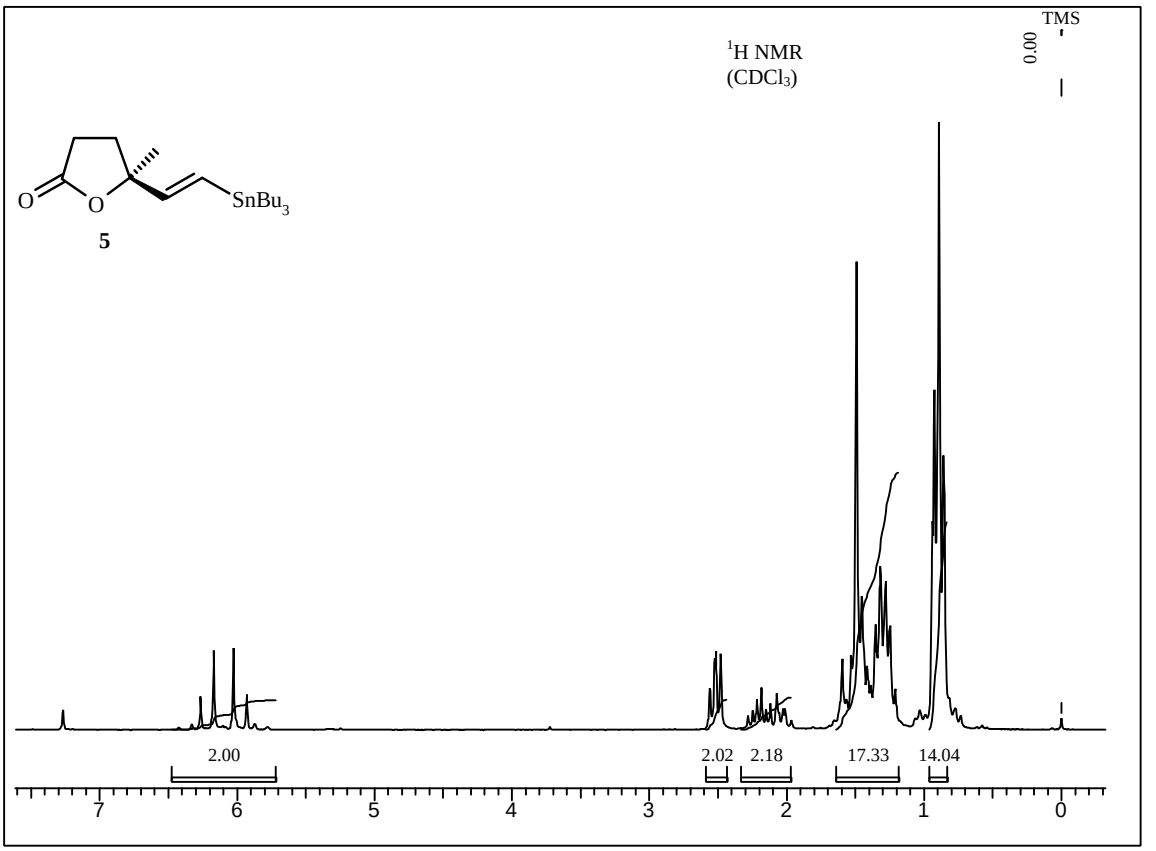
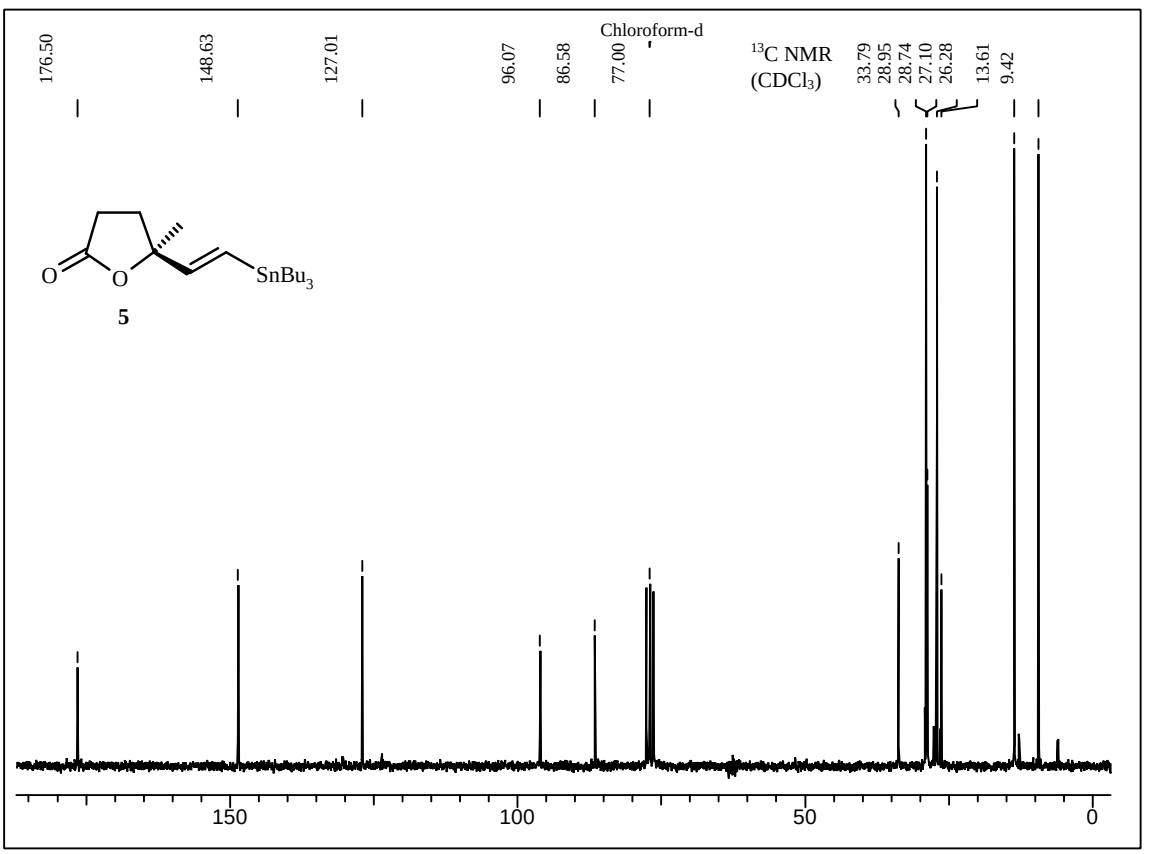
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

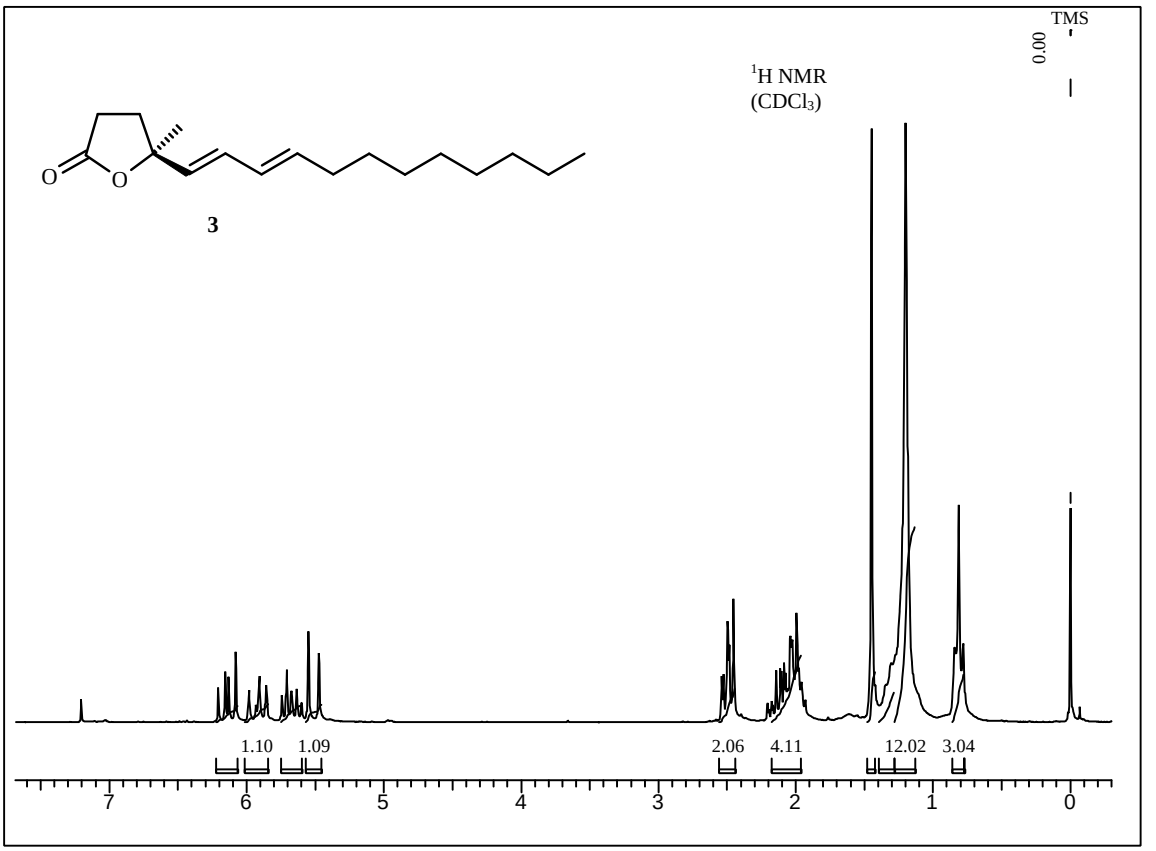

Chloroform-d
96.04
87.97
87.56
79.75
78.10
77.00
73.34
71.71
71.42
67.53
40.91
40.21
30.51
29.49
26.73
26.41
23.38
23.33
^{13}C NMR
($CDCl_3$)
OH
HO
HO
14
105
100
95
90
85
80
75
70
65
60
55
50
45
40
35
30
25
20
15
10
5
0

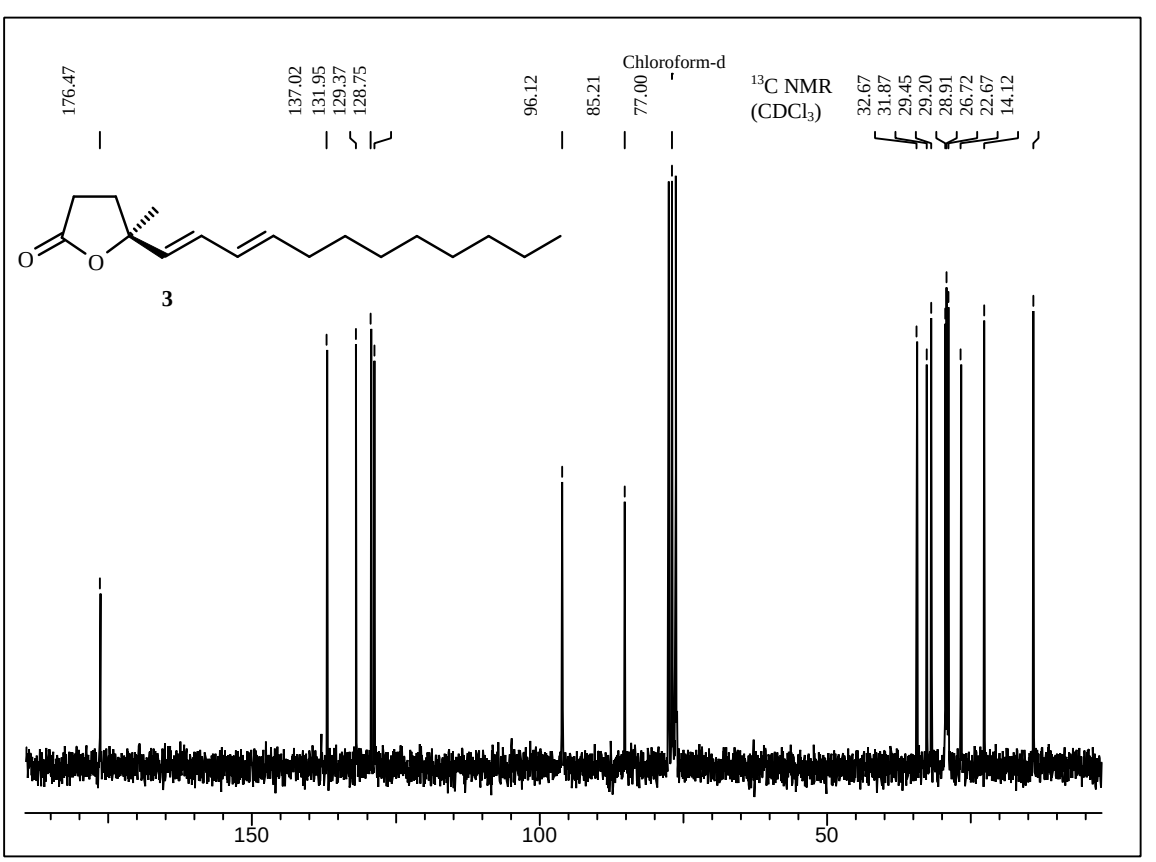

OH
SnBu3
HO
HO
15
1H NMR
(CDCl3)
TMS
0.00
2.00
1.02
4.06
18.35
12.10
7
6
5
4
3
2
1
0

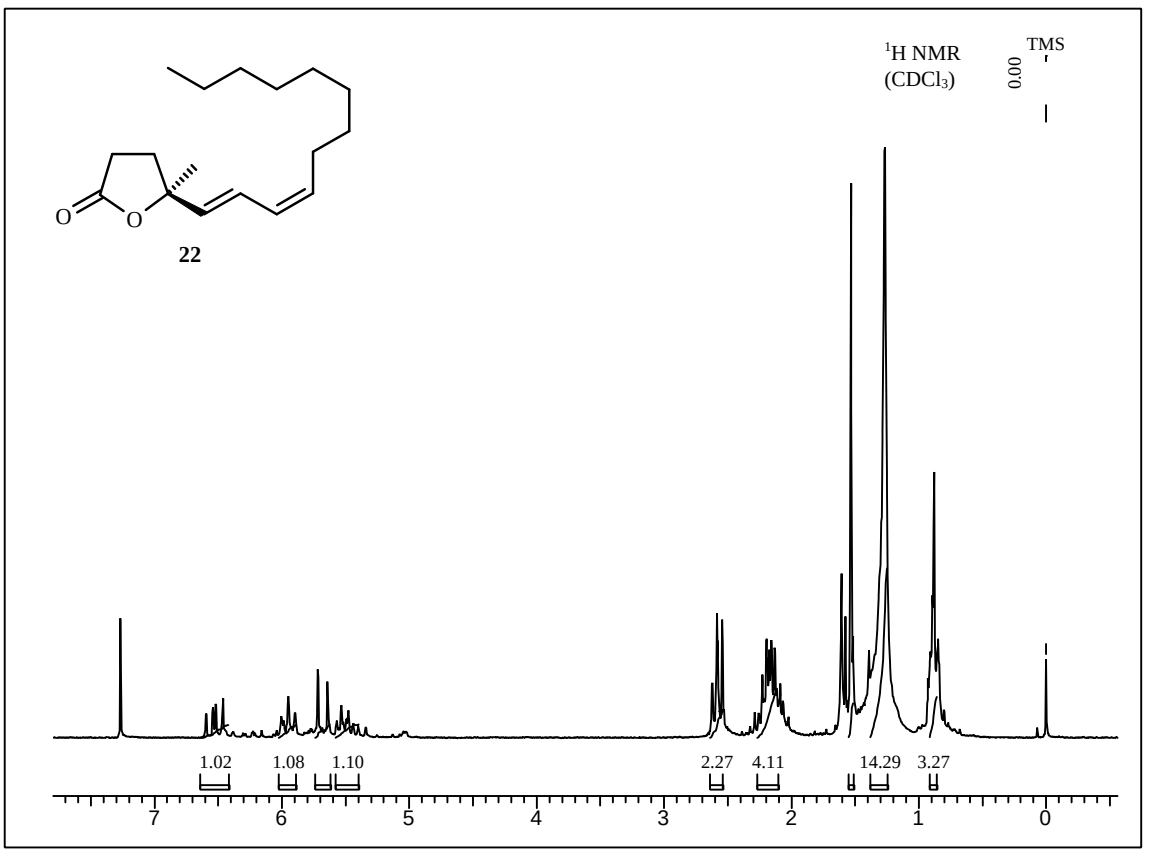

154.70
154.17
13C NMR
(CDCl3)
79
123.31
96.13
79.09
78.53
77.00
74.58
73.15
Chloroform-d
13C NMR
(CDCl3)
29.27
29.07
27.80
27.22
26.48
26.37
26.02
23.21
13.70
9.47
OH
SnBu3
HO
HO
15
150
100
50
0

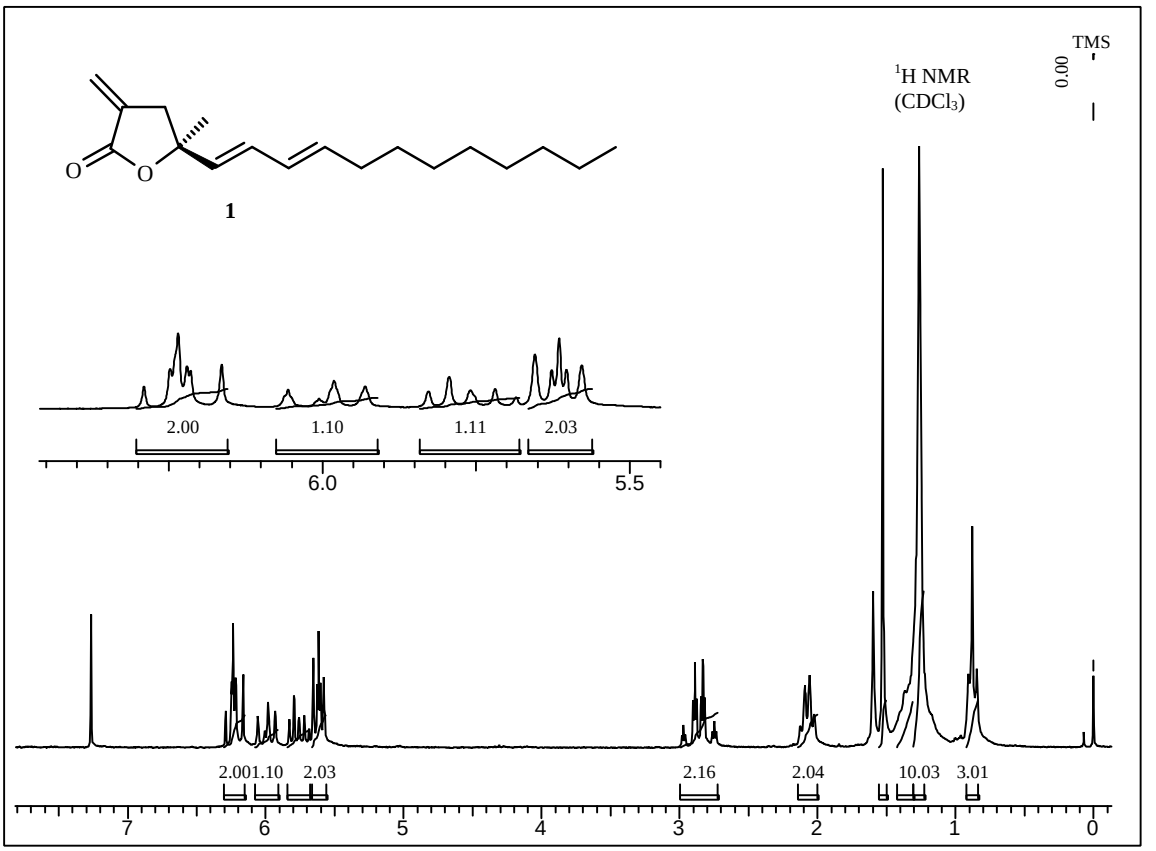

TMS
0.00
^{1}H NMR
(CDCl$_3$)
O
O
SnBu$_3$
5
2.00
2.02
2.18
17.33
14.04
7
6
5
4
3
2
1
0

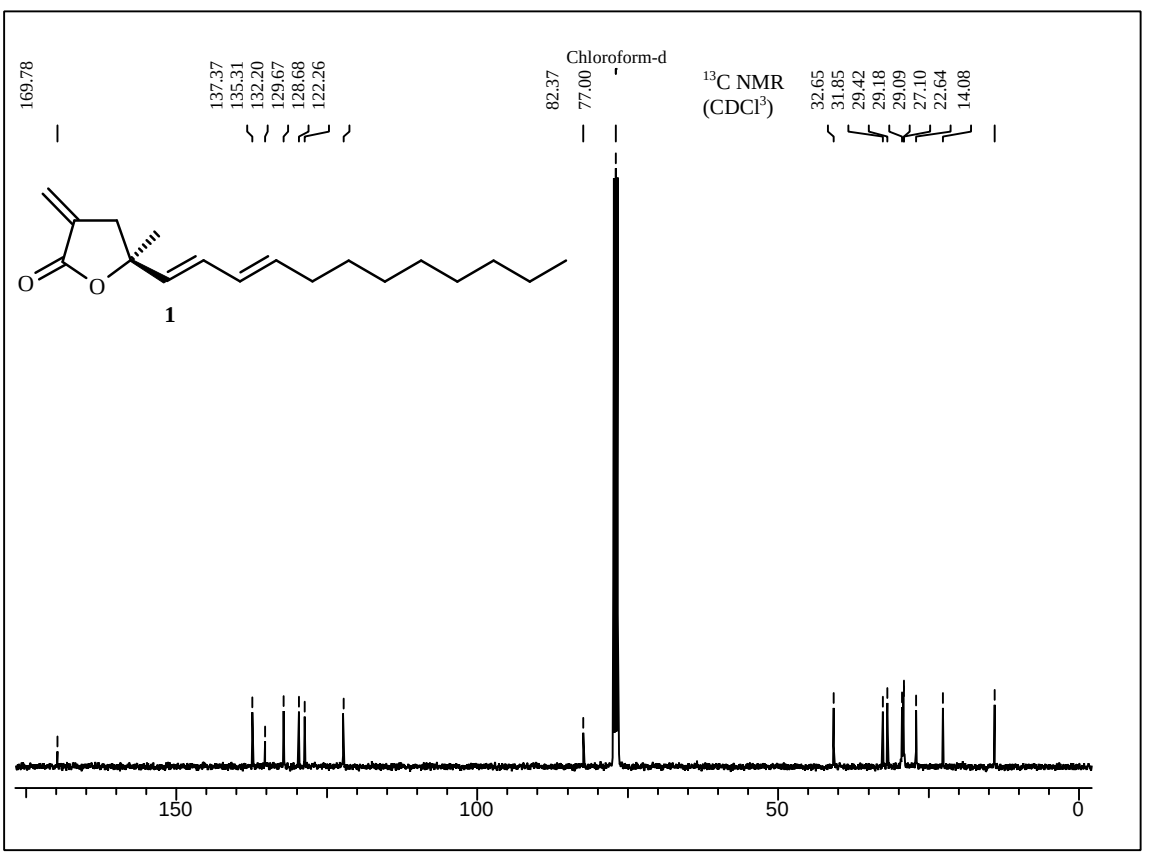

176.50
148.63
127.01
96.07
86.58
77.00
Chloroform-d
^{13}C NMR
(CDCl$_3$)
33.79
28.95
28.74
27.10
26.28
13.61
9.42
O
O
SnBu$_3$
5
150
100
50
0

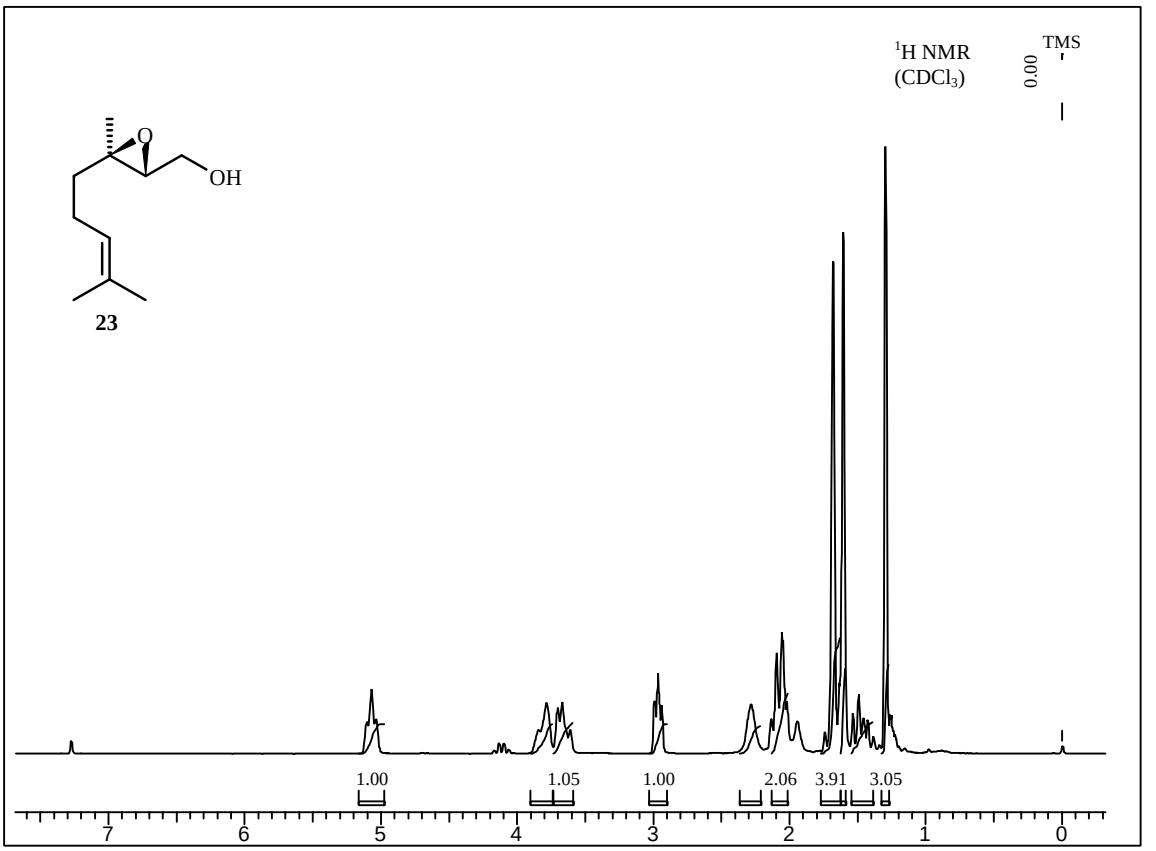

TMS
0.00
^{1}H NMR
($CDCl_3$)
O
O
3
1.10
1.09
2.06
4.11
12.02
3.04
7
6
5
4
3
2
1
0

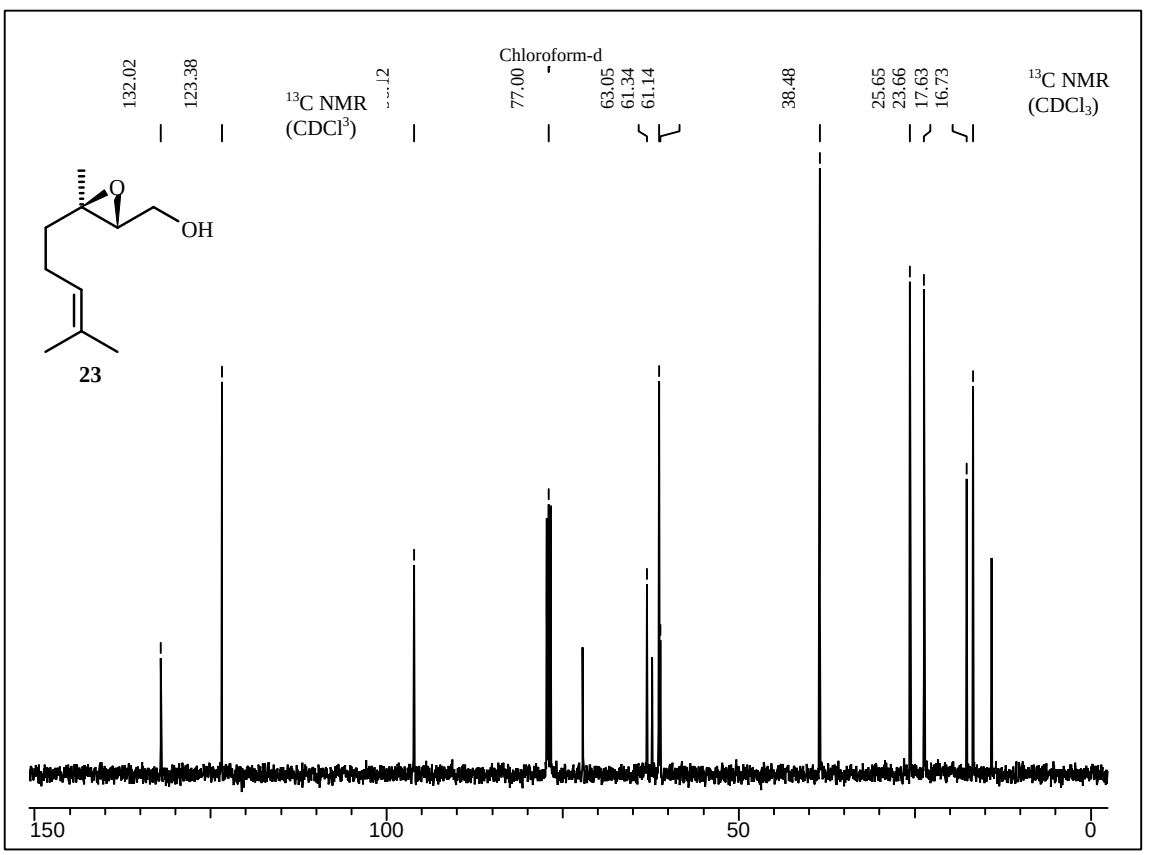

176.47
137.02
131.95
129.37
128.75
96.12
85.21
77.00
Chloroform-d
^{13}C NMR
($CDCl_3$)
32.67
31.87
29.45
29.20
28.91
26.72
22.67
14.12
O
O
3
150
100
50

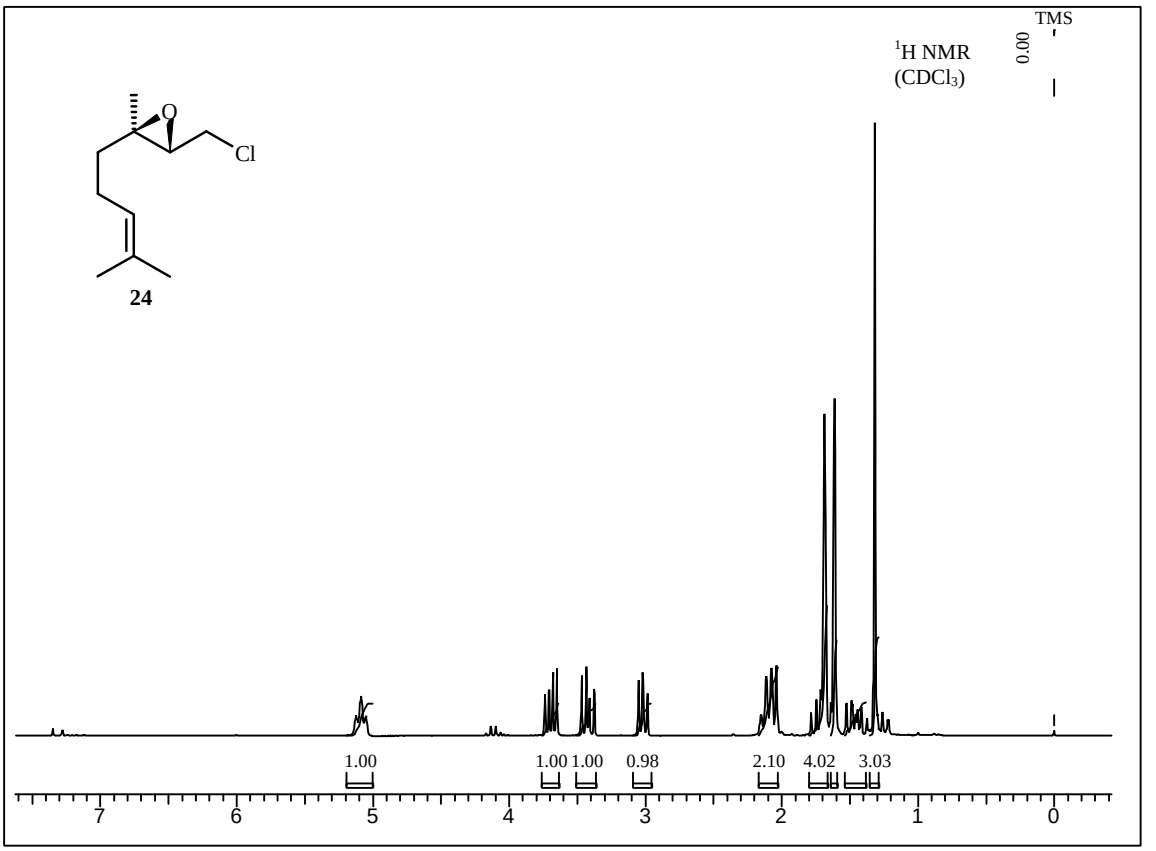

O
O
22
^{1}H NMR
(CDCl$_3$)
TMS
0.00
1.02
1.08
1.10
2.27
4.11
14.29
3.27
7
6
5
4
3
2
1
0

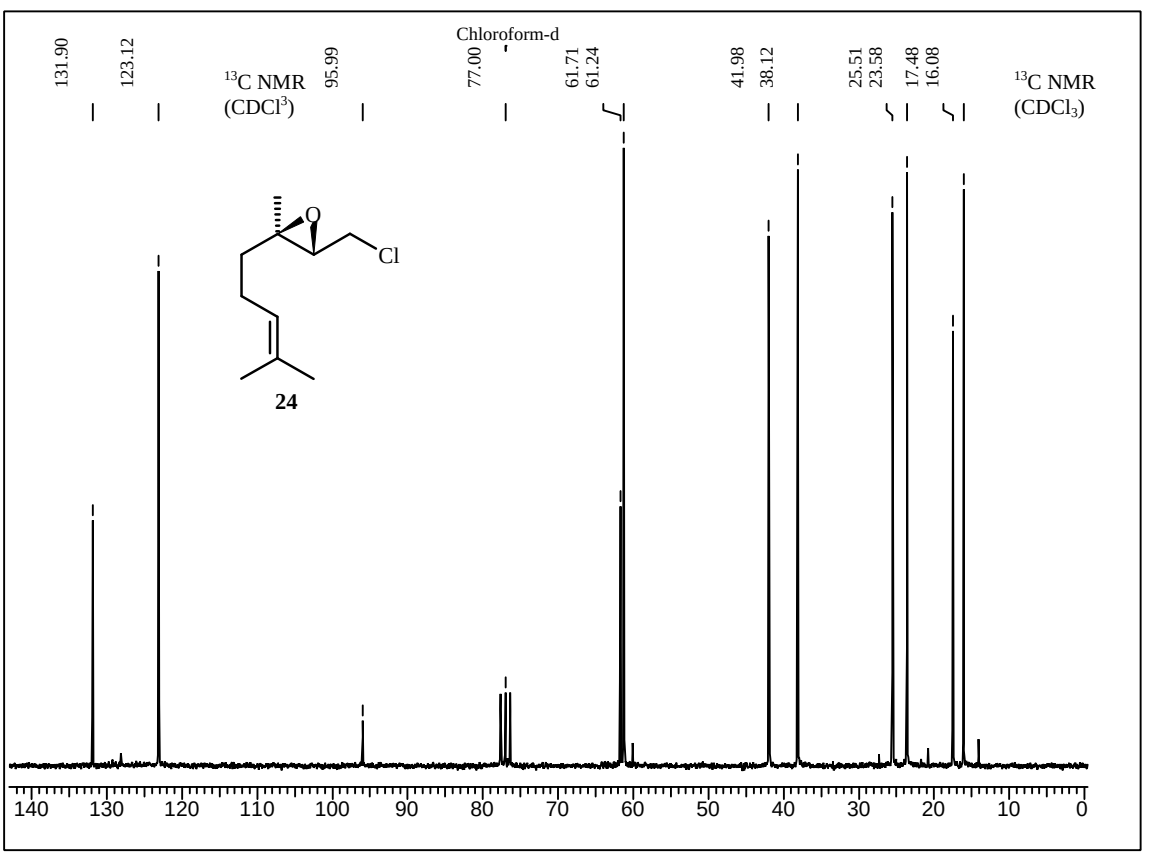

TMS
0.00
^{1}H NMR
(CDCl$_3$)
O
O
1
2.00
1.10
1.11
2.03
6.0
5.5
2.00
1.10
2.03
2.16
2.04
10.03
3.01
7
6
5
4
3
2
1
0

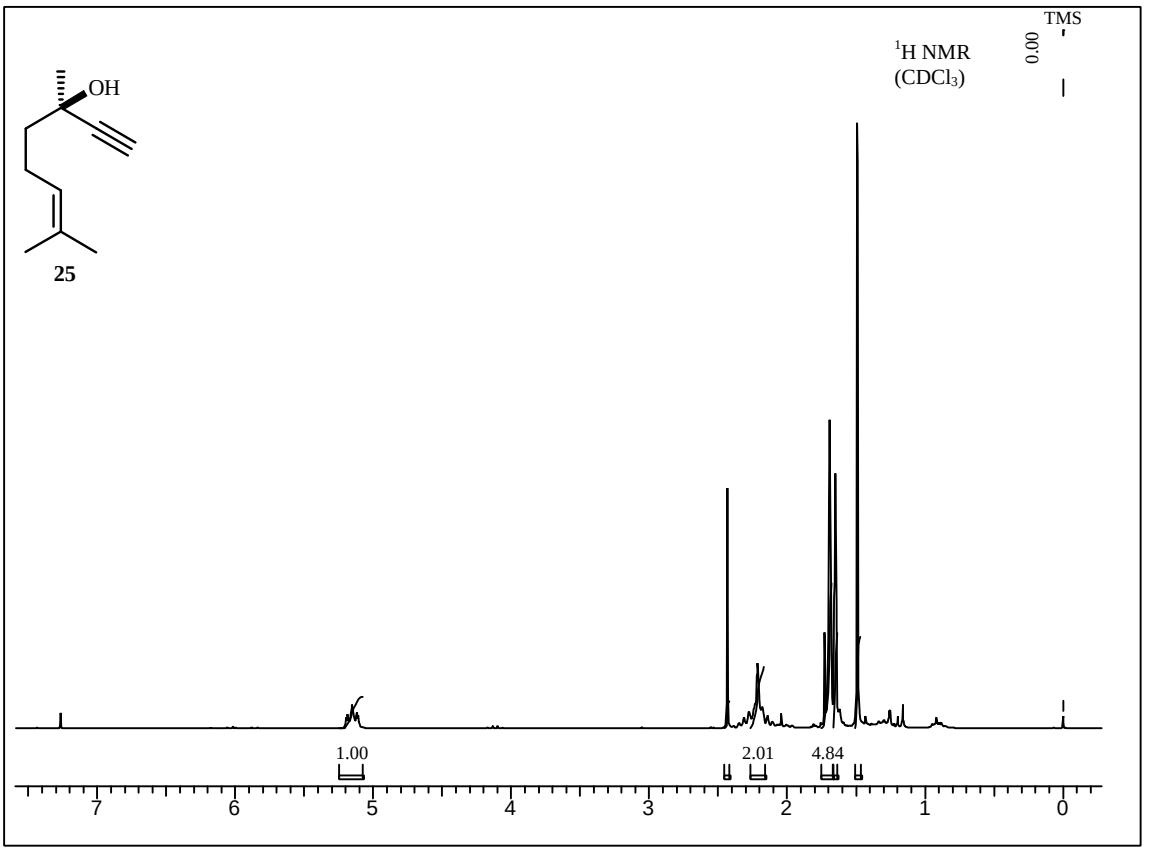

169.78
137.37
135.31
132.20
129.67
128.68
122.26
82.37
77.00
Chloroform-d
^{13}C NMR
(CDCl^3)
32.65
31.85
29.42
29.18
29.09
27.10
22.64
14.08
O
O
1
150
100
50
0

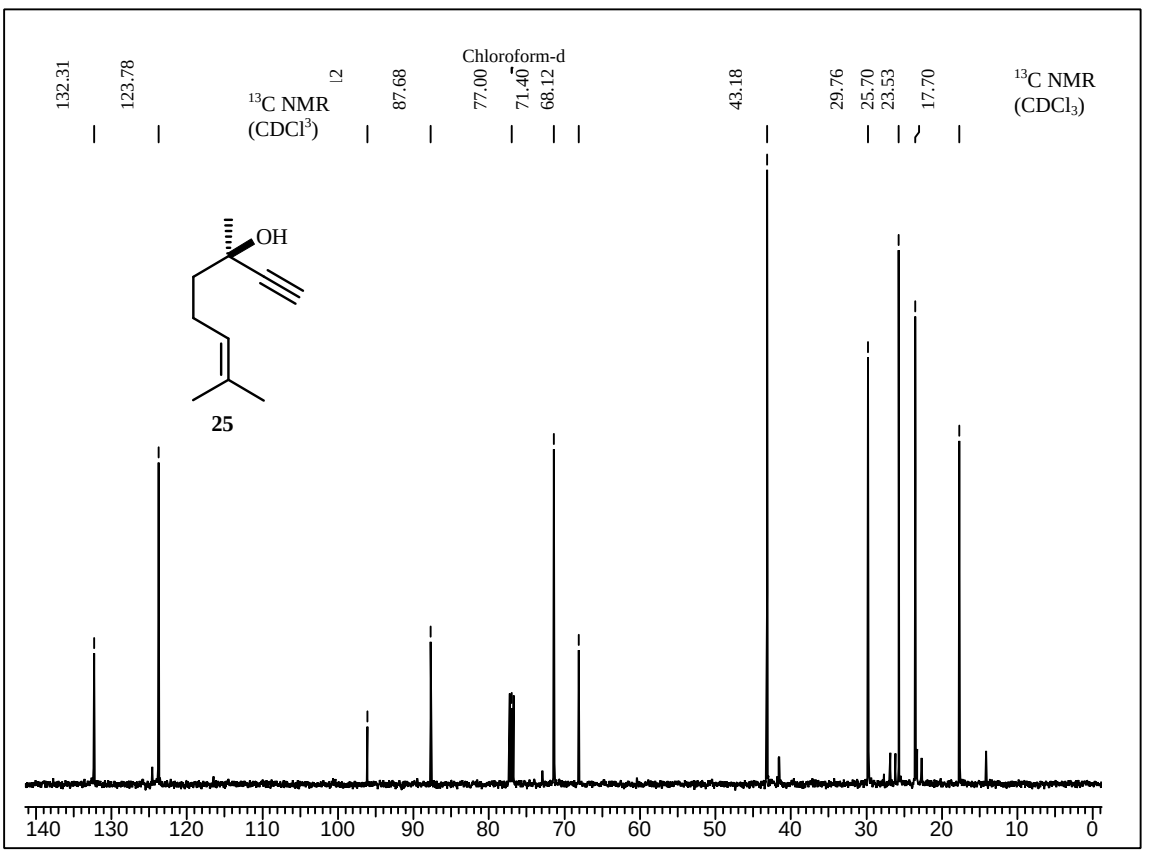

^{1}H NMR
($CDCl_3$)
TMS
0.00
O
OH
23
1.00
1.05
1.00
2.06
3.91
3.05
7
6
5
4
3
2
1
0

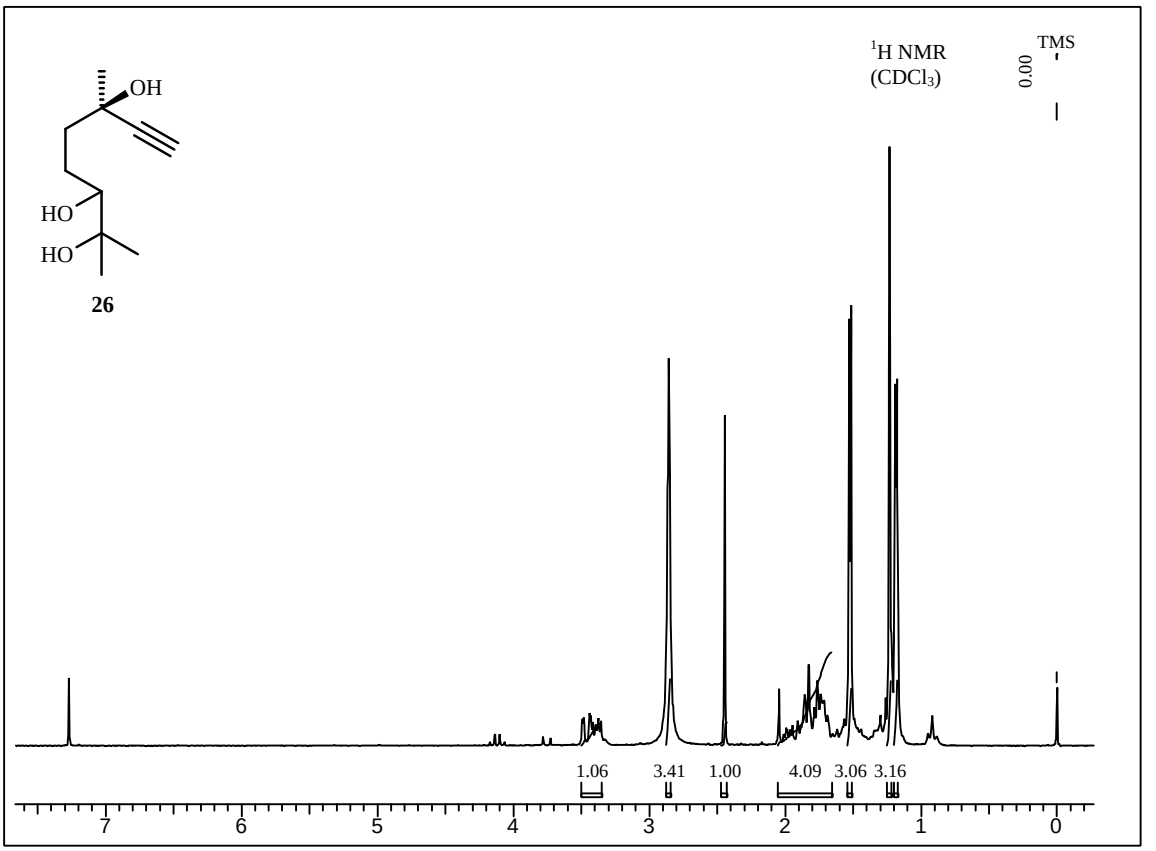

132.02
123.38
^{13}C NMR
($CDCl^3$)
77.00
Chloroform-d
63.05
61.34
61.14
38.48
25.65
23.66
17.63
16.73
^{13}C NMR
($CDCl_3$)
O
OH
23
150
100
50
0

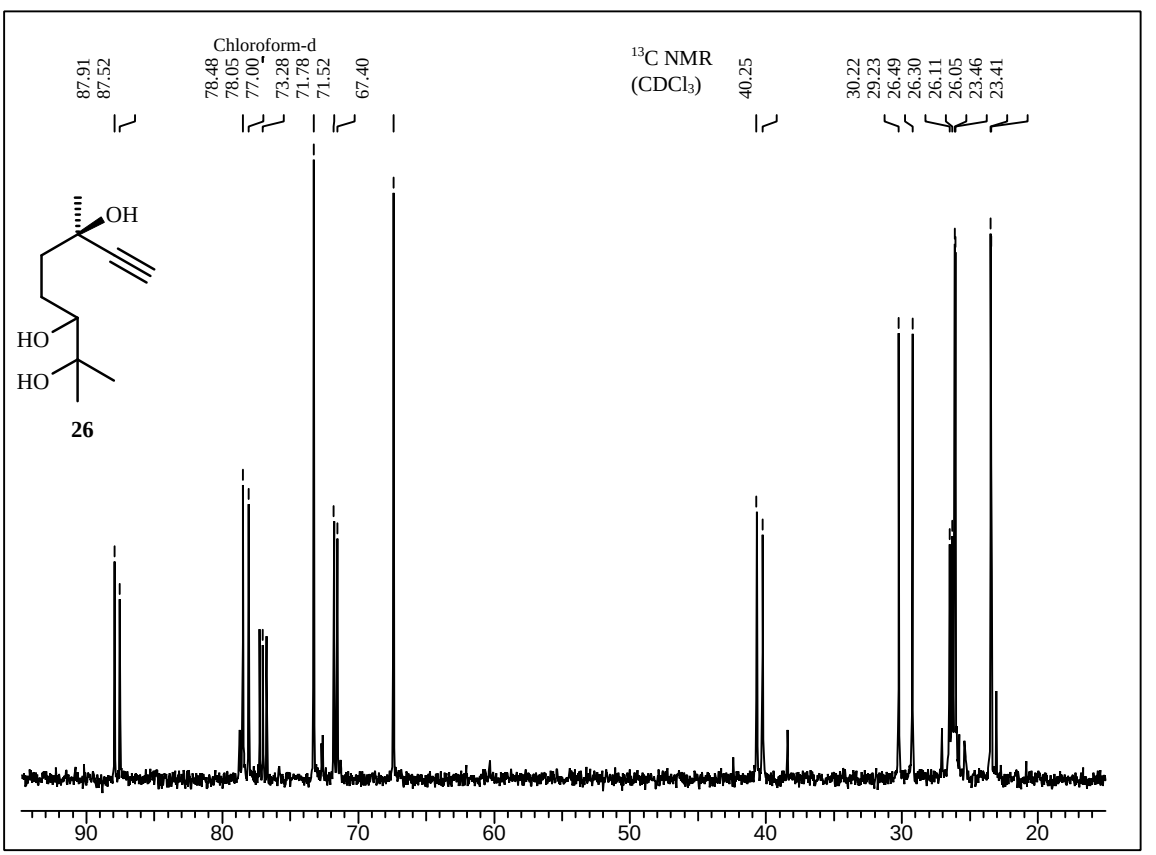

TMS
0.00
^{1}H NMR
($CDCl_3$)
O
Cl
24
1.00
1.00 1.00
0.98
2.10
4.02
3.03
7
6
5
4
3
2
1
0

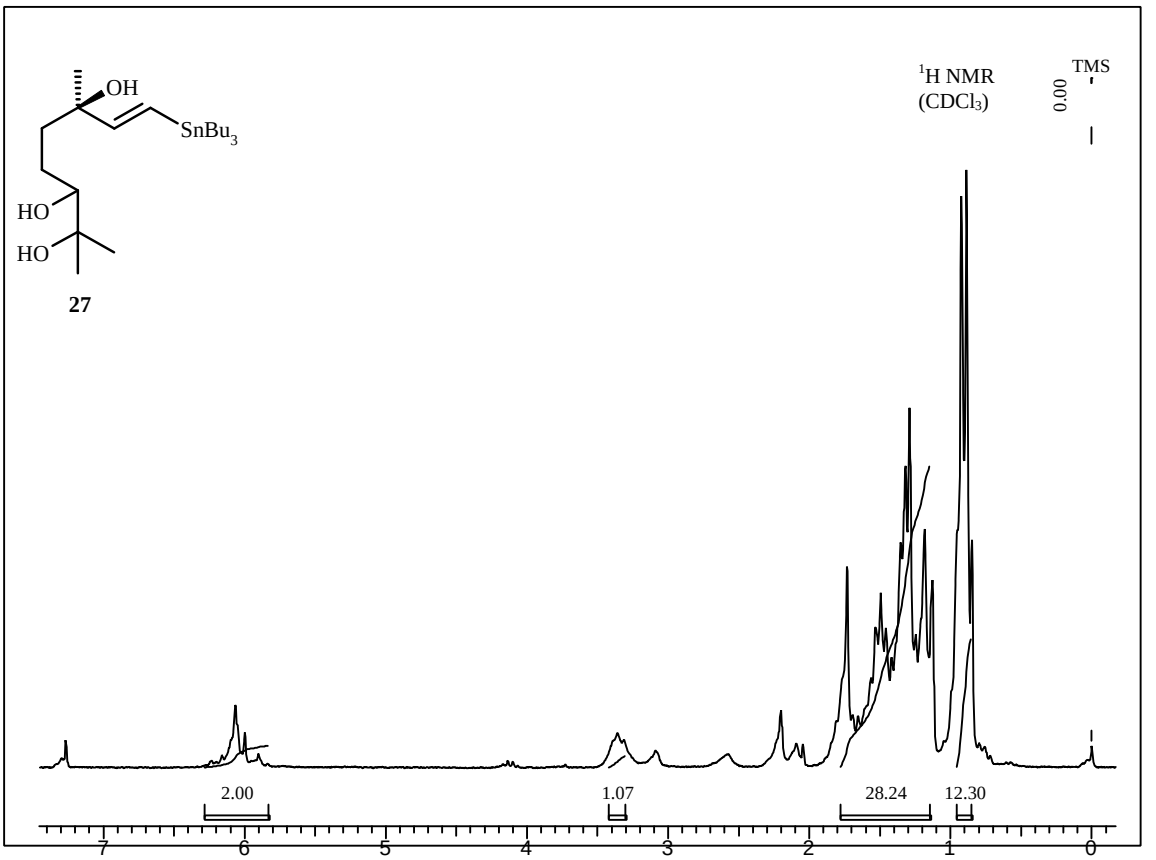

131.90
123.12
^{13}C NMR
($CDCl^3$)
95.99
Chloroform-d
77.00
61.71
61.24
41.98
38.12
25.51
23.58
17.48
16.08
^{13}C NMR
($CDCl_3$)
O
Cl
24
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

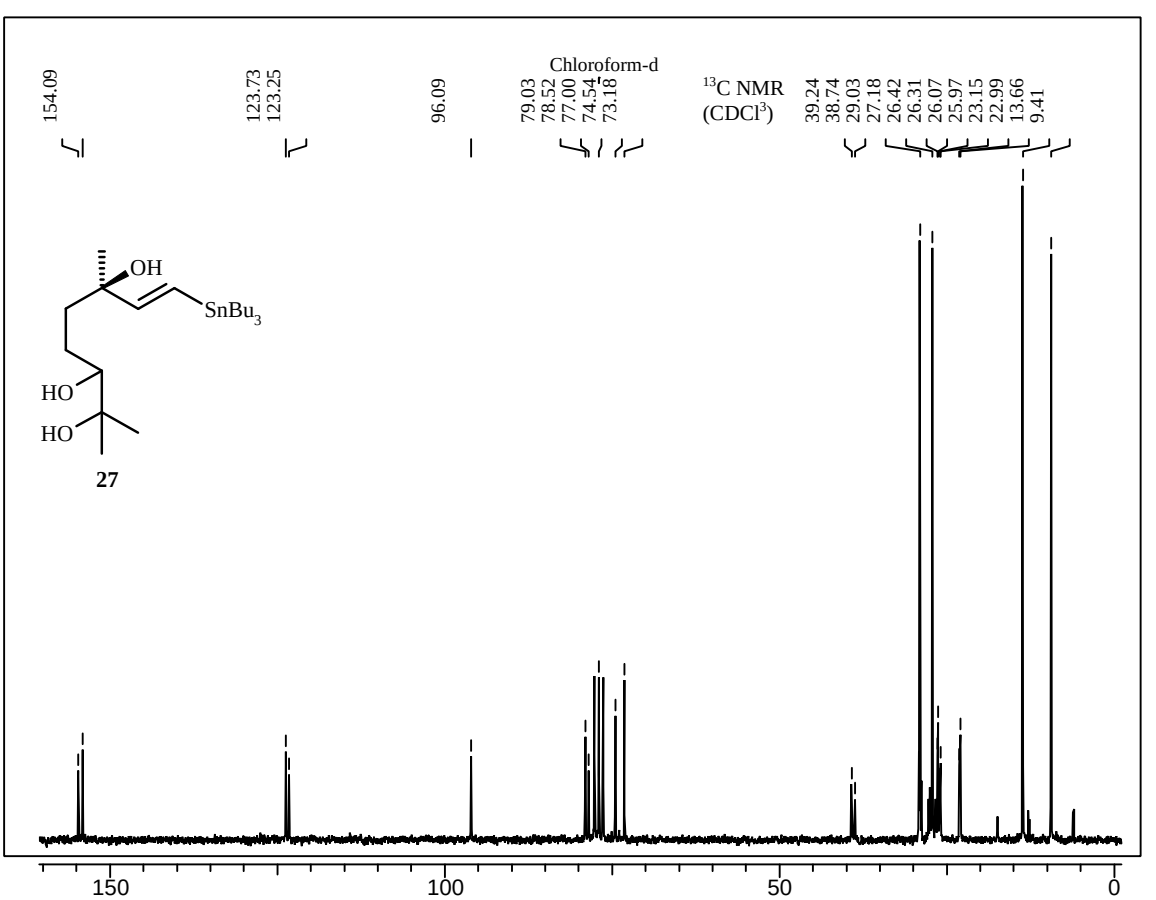

TMS
0.00
^{1}H NMR
($CDCl_3$)
OH
25
1.00
2.01
4.84
7
6
5
4
3
2
1
0

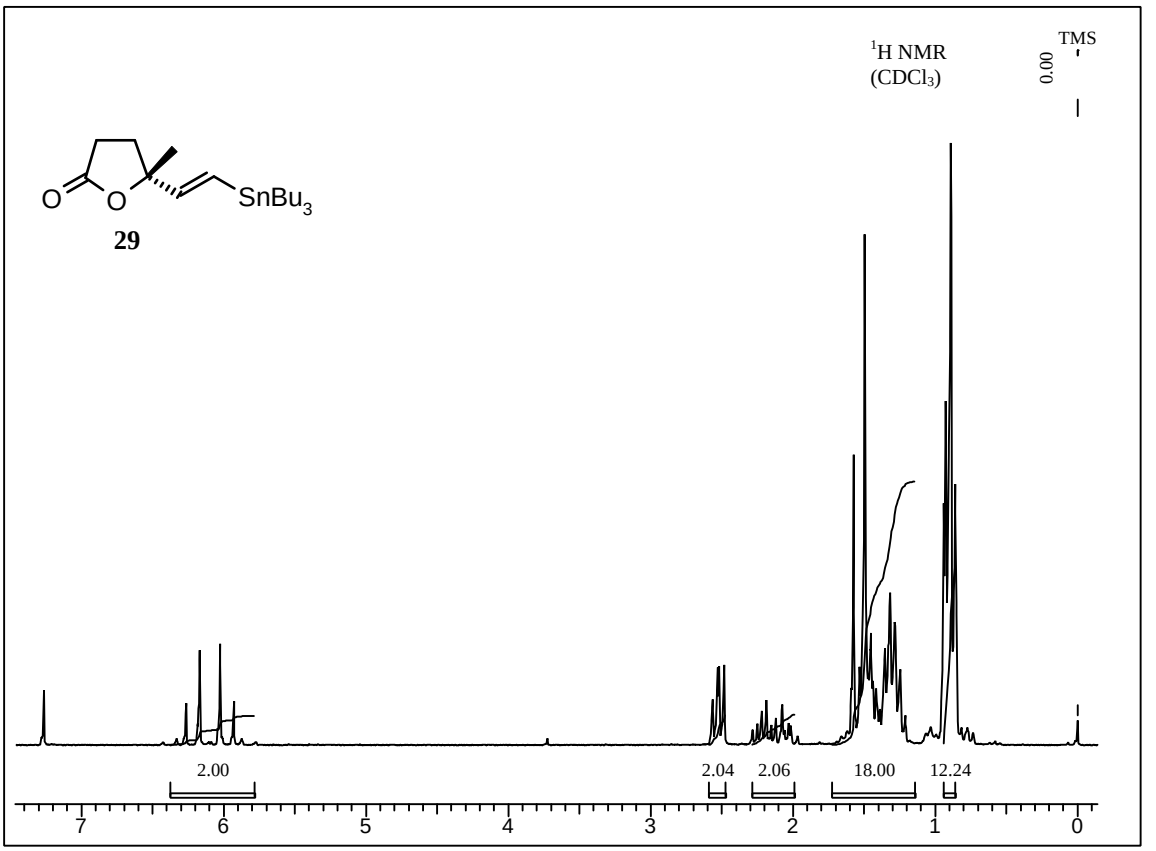

132.31
123.78
^{13}C NMR
($CDCl^3$)
87.68
Chloroform-d
77.00
71.40
68.12
43.18
29.76
25.70
23.53
17.70
^{13}C NMR
($CDCl_3$)
OH
25
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

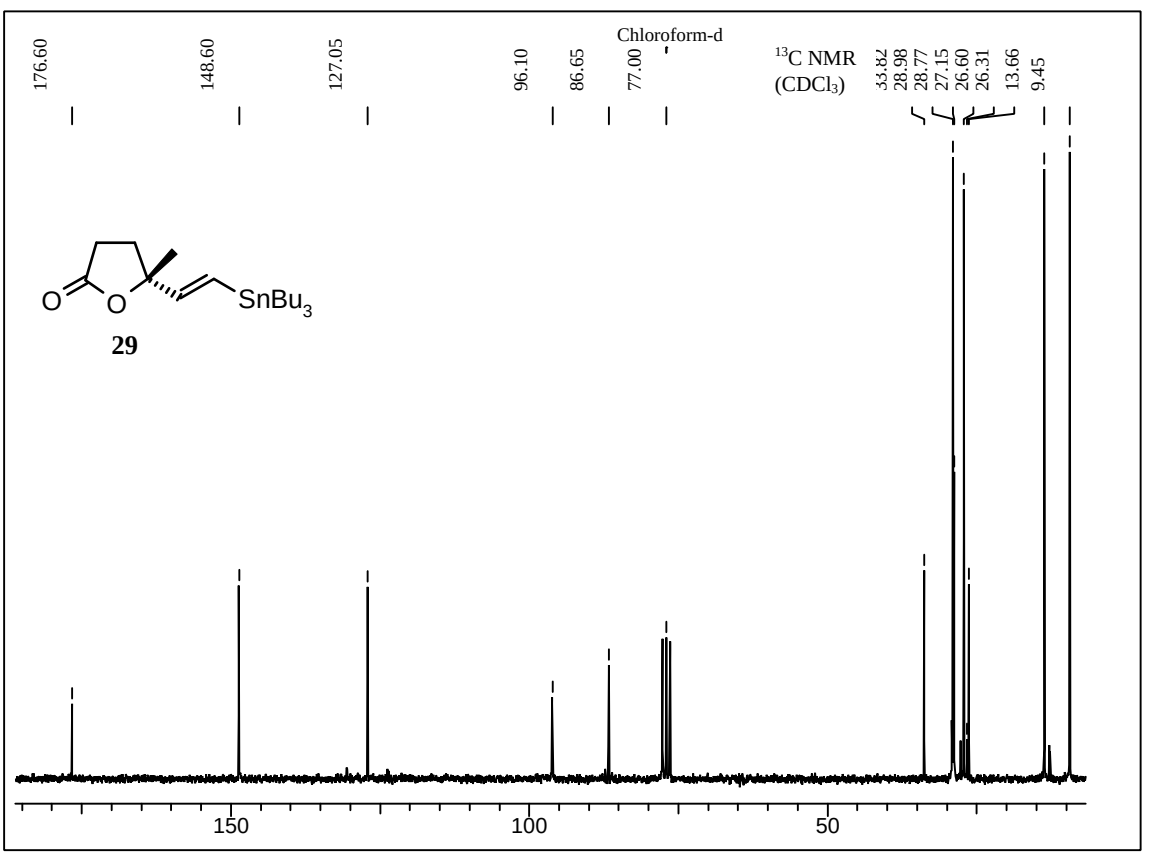

OH
HO
HO
26
^{1}H NMR
(CDCl$_3$)
TMS
0.00
1.06
3.41
1.00
4.09
3.06
3.16
7
6
5
4
3
2
1
0

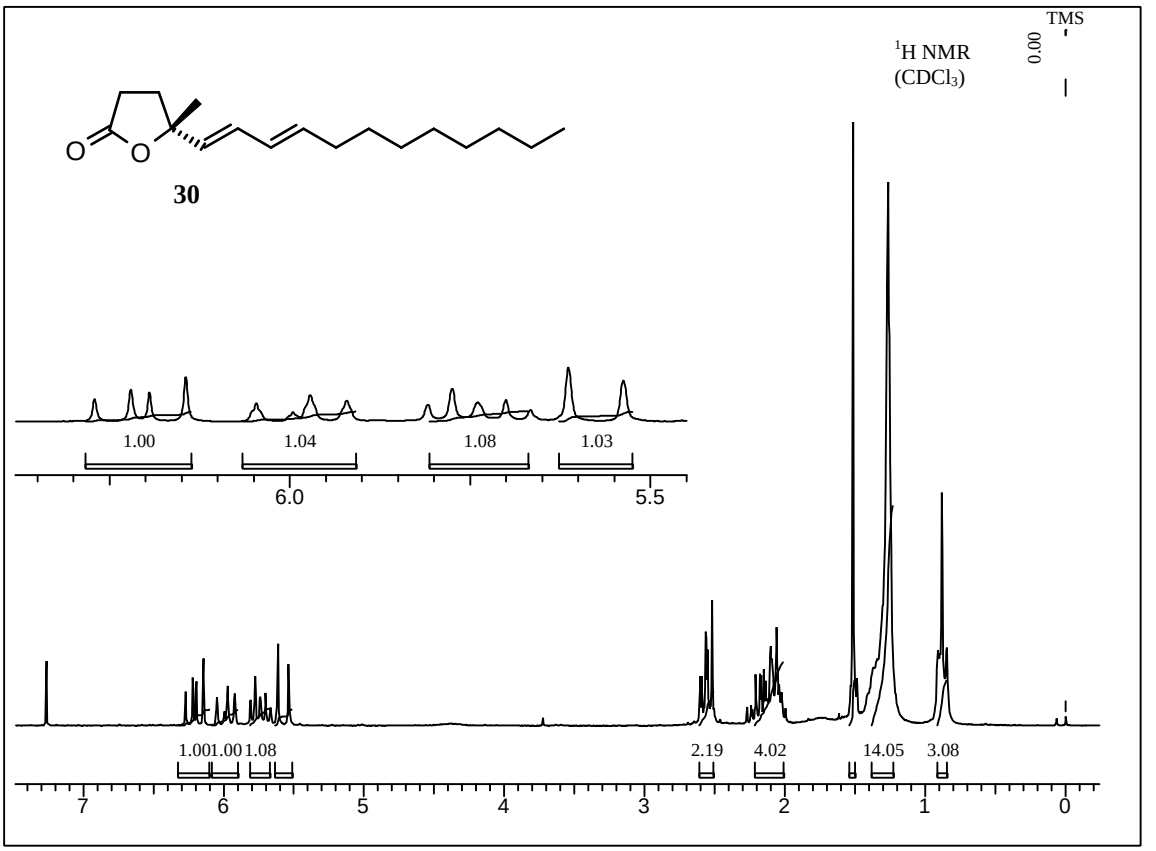

87.91
87.52
Chloroform-d
78.48
78.05
77.00
73.28
71.78
71.52
67.40
^{13}C NMR
(CDCl$_3$)
40.25
30.22
29.23
26.49
26.30
26.11
26.05
23.46
23.41
OH
HO
HO
26
90
80
70
60
50
40
30
20

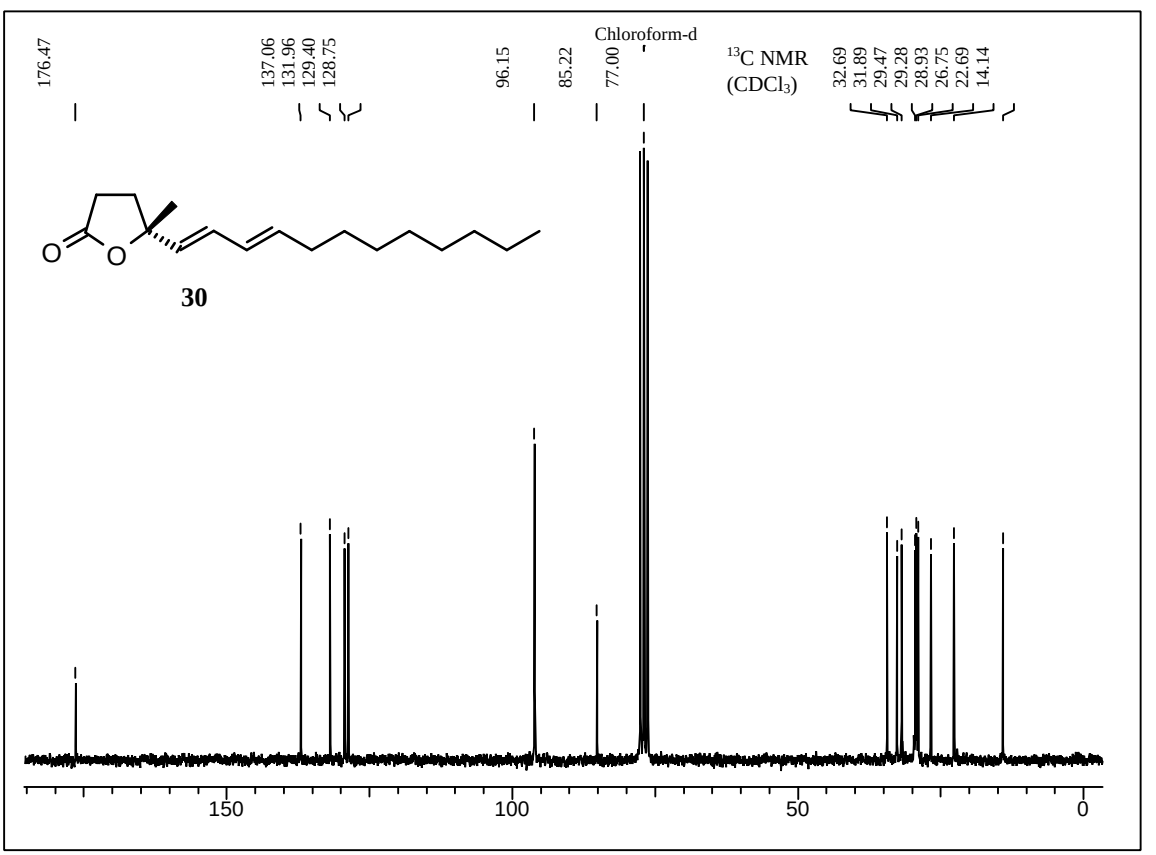

OH
SnBu3
HO
HO
27
1H NMR
(CDCl3)
TMS
0.00
2.00
1.07
28.24
12.30
7
6
5
4
3
2
1
0

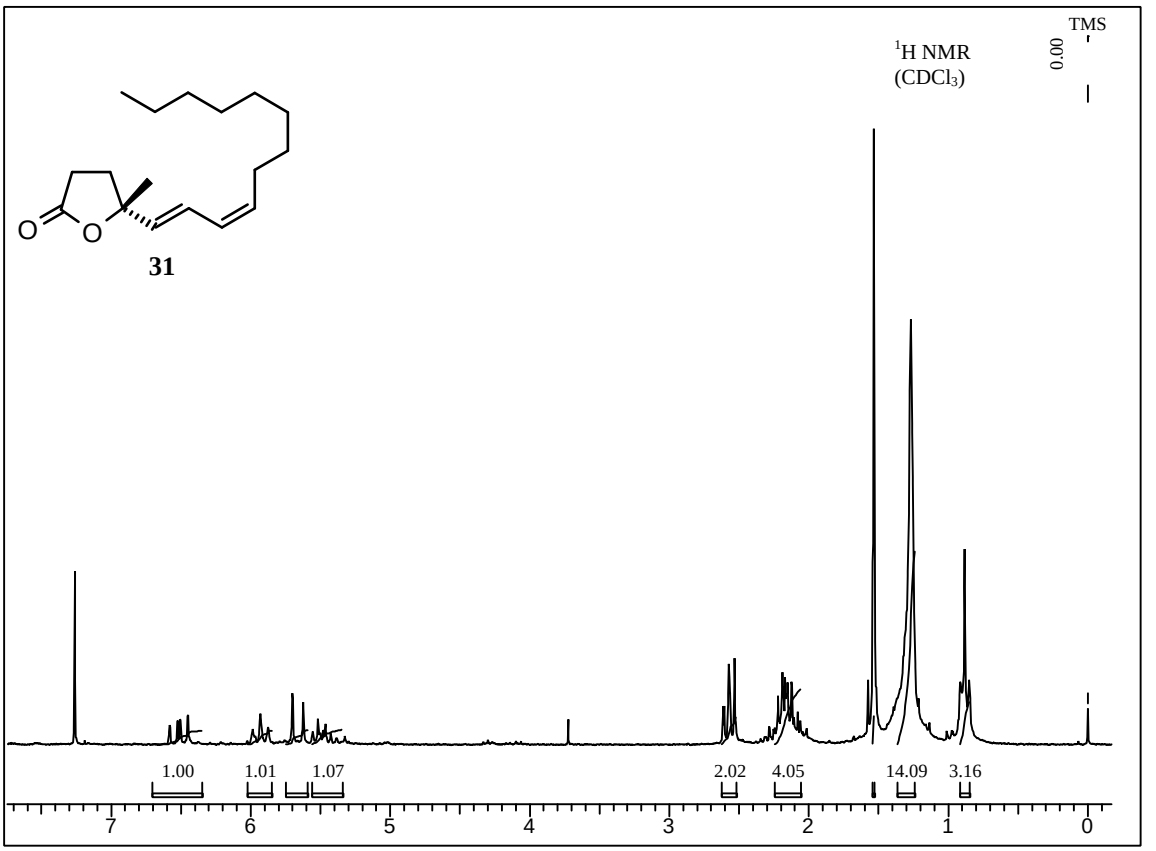

154.09
123.73
123.25
96.09
79.03
78.52
77.00
74.54
73.18
Chloroform-d
13C NMR
(CDCl3)
39.24
38.74
29.03
27.18
26.42
26.31
26.07
25.97
23.15
22.99
13.66
9.41
OH
SnBu3
HO
HO
27
150
100
50
0

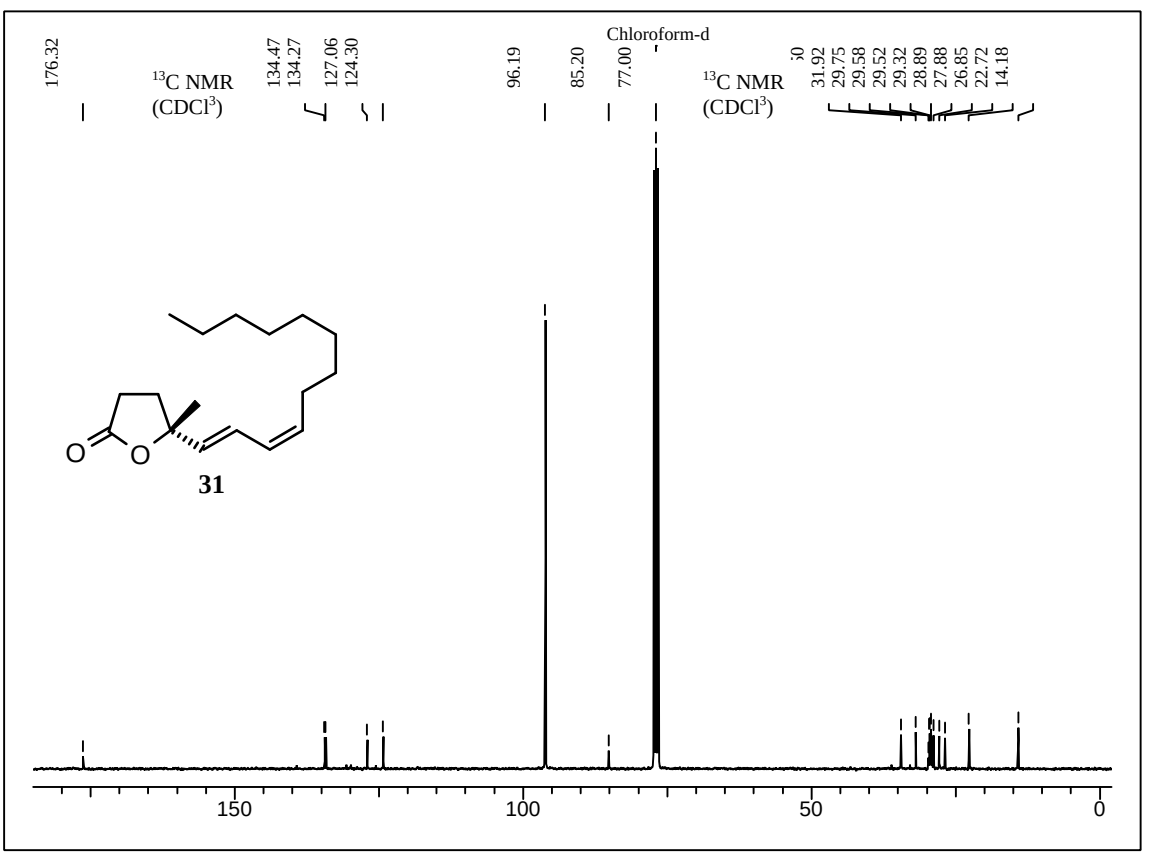

^{1}H NMR
(CDCl$_3$)
TMS
0.00
O
O
SnBu$_3$
29
2.00
2.04
2.06
18.00
12.24
7
6
5
4
3
2
1
0

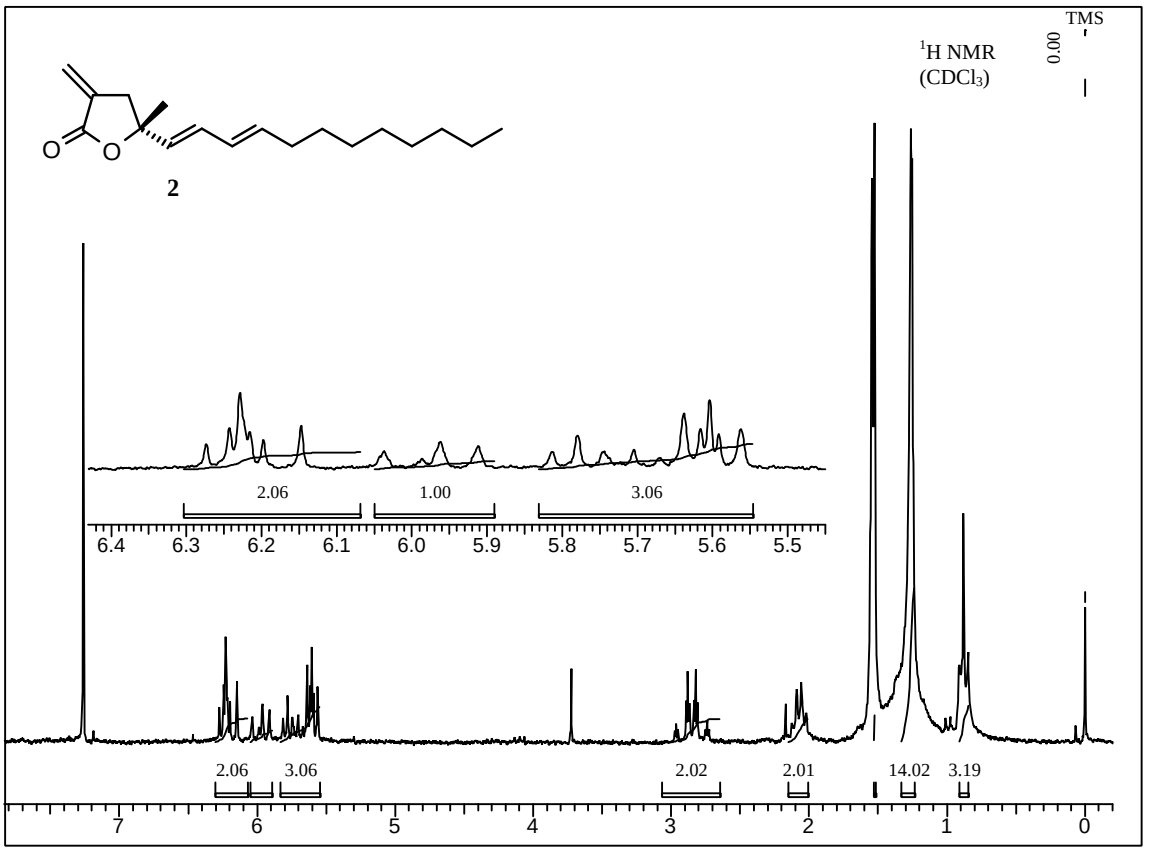

176.60
148.60
127.05
96.10
86.65
77.00
Chloroform-d
^{13}C NMR
(CDCl$_3$)
33.82
28.98
28.77
27.15
26.60
26.31
13.66
9.45
O
O
SnBu$_3$
29
150
100
50

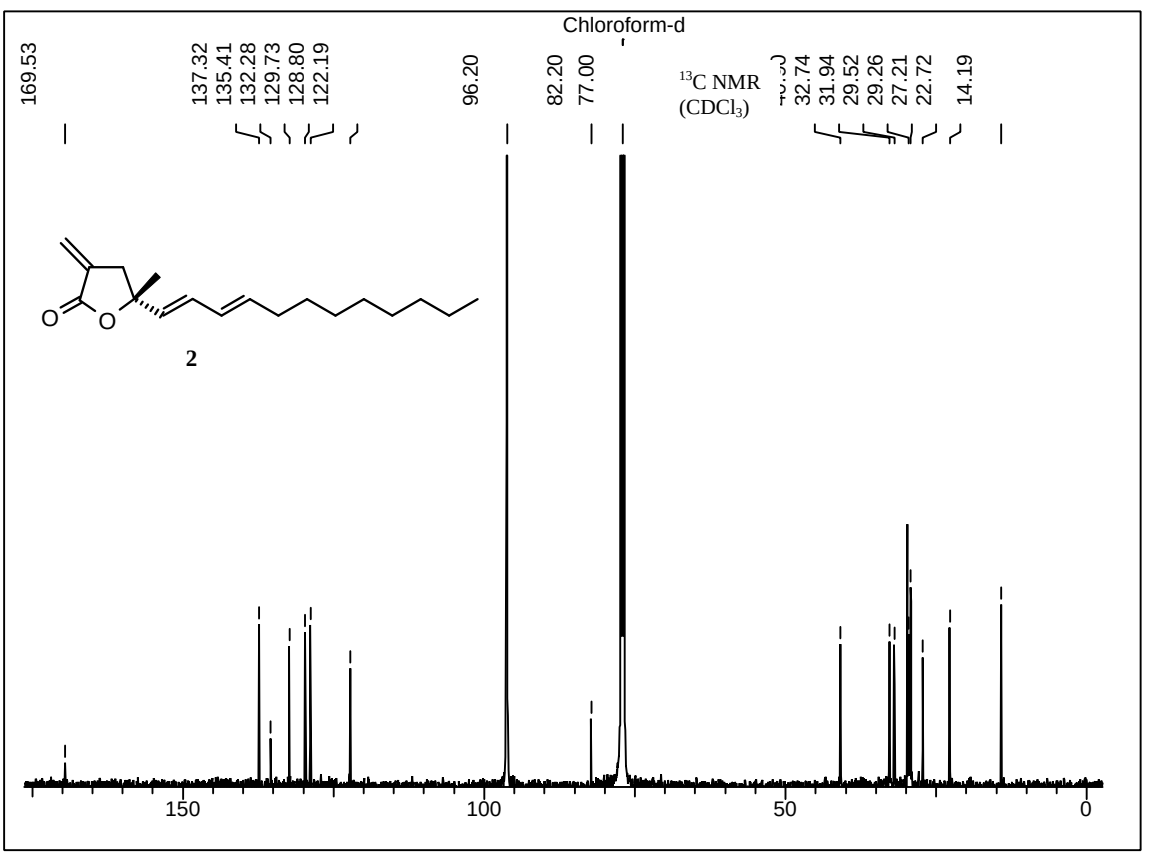

TMS
0.00
^{1}H NMR
($CDCl_3$)
30
1.00
1.04
1.08
1.03
6.0
5.5
1.00 1.00 1.08
2.19
4.02
14.05
3.08
7
6
5
4
3
2
1
0


176.47
137.06
131.96
129.40
128.75
96.15
85.22
77.00
Chloroform-d
^{13}C NMR
($CDCl_3$)
32.69
31.89
29.47
29.28
28.93
26.75
22.69
14.14
30
150
100
50
0


TMS
0.00
^{1}H NMR
($CDCl_3$)
O
O
31
1.00
1.01
1.07
2.02
4.05
14.09
3.16
7
6
5
4
3
2
1
0


176.32
^{13}C NMR
($CDCl^3$)
134.47
134.27
127.06
124.30
96.19
85.20
77.00
Chloroform-d
^{13}C NMR
($CDCl^3$)
31.92
29.75
29.58
29.52
29.32
28.89
27.88
26.85
22.72
14.18
O
O
31
150
100
50
0


TMS
0.00
^{1}H NMR
(CDCl$_3$)
2
2.06
1.00
3.06
6.4
6.3
6.2
6.1
6.0
5.9
5.8
5.7
5.6
5.5
2.06
3.06
2.02
2.01
14.02
3.19
7
6
5
4
3
2
1
0


Chloroform-d
169.53
137.32
135.41
132.28
129.73
128.80
122.19
96.20
82.20
77.00
^{13}C NMR
(CDCl$_3$)
32.74
31.94
29.52
29.26
27.21
22.72
14.19
2
150
100
50
0

REFERENCES

REFERENCES

1. Carté, B. K. *Biosciences* **1996**, 271-286.
2. Halvorson, H. O. Aquaculture, Marine Sciences and Oceanography: A Confluence Connection. *New Engl. J. Higher Ed. Econ. Dev.* **1998**, *13*, 28-42.
3. Faulkner, D. J. *Chem. Brit.* **1995**, 680-684.
4. Goodman, L.S.; Wintrobe, M. M.; Dameshek, W.; Goodman, M. J.; Gilman, A. and McLennan, M. T. *J Am Med Assoc,* **1946**, *105,* 475-476. Reprinted in *J Am Med Assoc,* **1984,** *251,* 2255-2261.
5. (a) Silverman, R. B. *The Organic Chemistry of Drug Design and Drug Action"* **2004,** (*2nd edition*). (b) Kijjoa, A. and Sawangwong, P**.** *Mar. Drugs* **2004**, *2*, 73-82.
6. (a) Mutter, R. and Wills, M. *Bioorg. Med. Chem*. **2000**, *8*, 1841-1860; (b) Hale, K. J.; Hummersone, M. G.; Manaviazar, S. and Frigero, M. *Nat. Prod. Rep*. **2002**, *19*, 413-453. (c) Ball, M.; Baron, A.; Bradshaw, B.; Omori, H. MacCormick, S. and Thomas, E. J. *Tetrahedron Letters*, **2004**, *45*, 8737–8740.
7. (a) Celli, N.; Mariani, B.; Carlo, F. D.; Zucchetti, M.; Lopez-Lazaro, L.; D'Incalci M. and Rotilio D. *Journal of Pharmaceutical and Biomedical Analysis* **2004**, *34(3),* 619-630. (b) Rinehart, K. L., Jr.; Gloer, J. B.; Cook, J. C., Jr.; Mizsak, S. A. and Scahill, T. A. *J. Am. Chem. Soc.* **1981**, *103*, 1857-1859. (c) Sakai, R.; Rinehart, K. L.; Kishore, V.; Kundu, B.; Faircloth, G.; Gloer, J. B.; Carney, J. R.; Namikoshi, M.; Sun, F.; Hughes, J. R. G.; Gravalos, G.; de Quesada, T. G.; Wilson, G. R. and Heid, R. M. *J. Med. Chem.* **1996**, *39*, 2819-2834.
8. Fuller, R. W.; Cardellina, J. H., 11; Kato,Y**.;** Brinen, L. S.; Clardy, J.; Snader, K. M. and Boyd, M. R. *J. Med. Chem***. 1992,** *35***,** 3007-3011**.**
9. J. Tanaka, T. Higa, K. Suwanborirux, U. Kokpol, G. Bernardinelli and C. W. Jefford, *J. Org. Chem.*, **1993**, *58*, 2999-3002.
10. (a) Schwarz, R. E.; Hirsch, C. F.; Sesin, D. F.; Flor, J. E.;Chartrain, M.; Fromtling, R. E.; Harris, G. H.; Salvatore, M. J.; Liesch,J. M. and Yudin, K. *J. Ind. Microbiol.* **1990**, *5*, 113. (b) Kobayashi, M.; Aoki, S.; Ohyabu, N.; Kurosu, M.; Wang, W. and

Kitagawa, I. *Tetrahedron Lett.* **1994**, *35*, 7969-7972. (c) Koiso, Y.; Morita, K.; Kobayashi, M.; Wang, W.; Ohyabu, N. and Iwasaki, S. *Chem. Biol. Interact.* **1996**, *102*, 183. (d) Trimurtulu, G.; Ohtani, I.; Patterson, G. M. L.; Moore, R. E.; Corbett, T. H.; Valeriote, F. A. and Demchik, L. *J. Am. Chem. Soc.* **1994**, *116*, 4729-4737. (e) Golakoti, T.; Ogino, J.; Heltzel, C. E.; Husebo, T. L.; Jensen, C. M.; Larsen, L. K.; Patterson, G. M. L.; Moore, R. E.; Mooberry, S. L.Corbett, T. H. and Valeriote, F. A. *J. Am. Chem. Soc.* **1995**, *117*, 12030-12049. (f) Ghosh, A. K.; and Swanson, L. *J. Org. Chem.* **2003**, *68*, 9823-9826.

11. Kesteren, C.V.; Cvitkovic, E.; Taamma, A.; López-Lázaro, L.; Jimeno, J.M.; Guzman, C.; Mathôt, R.A.A.; Schellens, J.H.M.; Misset, J.L.; Brain, E.; Hillebrand, M.J. X.; Rosing, H. and Beijnen, J. H. *Clinical cancer research*, **2000**, *6*, 4725-4732.

12. Hamann, M. T. and Scheuer, P. J. *J. Am. Chem. Soc,* **1993**, *115*, 5825-5826.
13. Gunasekera, S. P., Gunasekera, M., Longley R. E. and Schulte, G. K. *J. Org. Chem.* **1990**, *55*, 4912-4915.
14. Yamada, K, Okija, M., Kigoshi, H.; Suenaga, K.; *Cytotoxic Substances from Opisthobranch Molluscs: In Drugs From The Sea*; Fusetani, N., Ed.; Karger AG: Basel, **2000**, 59-73.

15. (a) Hirata, Y. and Uemura, D. *Pure Appl. Chem.* **1986**, *58*, 701-710. (b) Stamos, D.P.; Chen, S. S. and Kishi, Y. *J. Org. Chem.* **1997**, *62*, 7552-7553. (c) Lambert, W. T.; Hanson, G.H.; Benayoud, F. and Burke, S. D. *J. Org. Chem.* **2005**, *70*, 9382-9398.
16. Patil, A. D.; Freyer, A.J.; Bean, M.F.; Carte, B.K.; Westley, J. W. and Johnson, R. K. *Tetrahedron,* **1996**, *52*, 377-394.
17. Zampella, A.; Giannini, C.; Debitus, C. and D'Auria, M. V. *Tetrahedron*, **2001**, *57*, 257-263.
18. Gunasekara, S. P.; Isbrucker, R. A.; Longley, R. E.; Wright, A. E.; Pomponi, S. A. and Reed, J. K. *J. Nat. Prod.* **2004**, *67*, 110–111
19. (a) Kanayama, M. K. and Matsuo, N. K. *Heterocycles* **2006**, *68*, 233–236; (b) Matsuo, K. M. and Nishiwaki, K. K. *Heterocycles* **2006**, *68*, 1401–1407.

20. (a) Katsuki, T. and Sharpless, K. B. *J. Am. Chem. Soc.* ***19*80**, *102,* 5976-5978. (b) Williams, I. D.; Pedersen, S. F.; Sharpless, K. B. and Lippard, S. J. *J. Am.* Chem. Soc. **1984**, *106*, 6431-6433. (c) Pedersen, S. F.; Dewan, J. C.; Eckman, R. R. and Sharpless, K. B. *J. Am.* Chem. *Soc*., **1987**, *109*, 1279-1282. (d) Finn, M. G. and Sharpless, K. B. *J. Am.* Chem. *Soc.,* **1991**, *113,* 113-126. (e) *Synthesis*, **1986**, 89-116.
21. (a) Gao, Y.; Hanson, R. M.; Klunder, J. M.; Ko, S. Y.; Masamune, H. and Sharpless, K. B. *J. Am. Chem. Soc.* **1987**, *109*, 5765–5780; (b) Hashimoto, M.; Harigaye, H.; Yamagiya, M. and Shirahama, H. *J. Org. Chem.* **1991**, *56*, 2299–2311.
22. (a) Aneja, R.; Davis, A. P. and Knaggs, P. *Tetrahedron Lett.* **1974**, *15*, 67–70; (b) Haylock, C. R.; Melton, L. D.; Slessor, K. N. and Tracey, A. S. *Carbohydr. Res.* **1971**, *16*, 375–382; (c) Lee, J. B. and Nolan, T. J. *Can. J. Chem.* **1966**, *44*, 1331.
23. (a) Takano, S.; Samizu, K.; Sugahara, T. and Ugasawara, K. *J. Chem. Soc. Chem. Commun.* **1989**, 1344–1345; (b) Yadav, J. S.; Deshpande, P. K. and Sharma, G. V. M. *Tetrahedron* **1990**, *46*, 7033–7046.
24. (a) Corey, E. J. and Wollenberg, R. H. *J. Org. Chem.* **1975**, *40*, 2265–2266; (b) Jung, M. E. and Light, L. A. *Tetrahedron Lett.* **1982**, *23*, 3851–3854.
25. Zhong, Y. L. and Shing, T. K. M. *J. Org. Chem.* **1997**, *62*, 2622–2624.
26. (a) Korotchenks, V. N.; Nenajdenko, V. G.; Balenkova, E. S. and Shastin, A. V. *Russion Chemical Reviews*, **2004**, *73 (10)*, 957-989. (b) Williams, J. M. J. *Preparations of Alkenes*, **1996**, *Oxford University Press.* (c) Takai, K.; Nitta, K. and Utimoto, K. *J. Am. Chem. Soc.* **1986**, *108*, 7408–7410; (d) Okazoe, T.; Takai, K. and Utimoto, K. *J. Am. Chem. Soc.* **1987**, *109*, 951–953; (e) Evans, D. A. and Black, W. C. *J. Am. Chem. Soc.* **1993**, *115*, 4497–4513.
27. Stile, J. K. *Angew. Chem. Int. Ed. Engl*. **1986,** *25*, 508-524.
28. Han, X.; Stoltz, B. M. and Corey, E. J. *J. Am. Chem. Soc.* **1999**, *121*, 7600–7605.
29. (a) Schreiber, J.; Maag, H.; Hashimoto, N. and Eschenmoser, A. *Angew. Chem. Int. Ed. Engl.* **1971**, *10*, 330–331; (b) Bryson, T. A.; Bonitz, G. H.; Reichel, C. J. and Dardis, R. E. *J. Org. Chem.* **1980**, *45*, 524–525.

PUBLICATION

PUBLICATIONS

1. Total syntheses of Schulzeines B and C. Mukund K. Gurjar, **Chinmoy Pramanik**, Debabrata Bhattasali, C. V. Ramana and Debendra K. Mohapatra. ***J. Org. Chem***, **2007,** *72*, 6591-6594.

2. A short and efficient Synthetic Strategy for the Total Syntheses of *S*-(+) and *R*-(–)-Plakolide A. Debendra K. Mohapatra, **Chinmoy Pramanik**, Mukund S. Chorghade and Mukund K. Gurjar. ***Eur. J. Org. Chem***., *Early View.*