CYCLOISOMERIZATIONS OF SUGAR DERIVED ALKYNOLS AND STUDIES TOWARD THE TOTAL SYNTHESIS OF DIDEMNISERINOLIPID B AND SOME FUNCTIONALIZED NORTROPANE ALKALOIDS

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

TO
OSMANIA UNIVERSITY

BY
Ms. BODDETI INDUVADANA

Dr. M. N. Deshmukh

(Research Guide)

ORGANIC CHEMISTRY DIVISION
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PUNE-411008

AUGUST 2008

DEDICATED

TO

MY PARENTS,
BHUVAN, SEENU, SRINIVAS,
GAYATRI.

DECLARATION

The research work embodied in this thesis has been carried out at National Chemical Laboratory, Pune under the supervision of **Dr. M. N. Deshmukh**, Scientist F, Division of Organic Chemistry, National Chemical Laboratory, Pune - 411 008. This work is original and has not been submitted in part or full, for any degree or diploma of this or any other University.

Division of Organic Chemistry
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CERTIFICATE

The research work presented in thesis entitled **"Cycloisomerizations of Sugar Derived Alkynols and Studies Toward the Total Synthesis of Didemniserinolipid B And Some Functionalized Nortropane Alkaloids"** has been carried out under my supervision and is a bonafide work of **Ms. Boddeti Induvadana**. This work is original and has not been submitted for any other degree or diploma of this or any other University. The candidate's research work has been satisfactory and the thesis may be submitted for the award of the Degree of Doctor of Philosophy.

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- Indu

DEFINITIONS AND ABBREVIATIONS

ATBT	-	Allyl tributyltin
AcOH	-	Acetic acid
APA	-	1.3-aminopropyl amine
Ac_2O	-	Acetic anhydride
BORSM	-	Based On Recovered Starting Material
BnBr	-	Benzyl bromide
BzCl	-	Benzoyl chloride
$BF_3.Et_2O$	-	Boron trifluoride diethyl ether complex
n-BuLi	-	*n*-Butyl lithium
Bu_2SnO	-	Dibutyltin oxide
CH_3CN	-	Acetonitrile
$CH_2=CHCH_2TMS$	-	Allyl trimethyl silane
DCM	-	Dichloromethane
DIBAL-H	-	Diisobutylaluminiumhydride
DMF	-	N, N-Dimethyl formamide
DIPT	-	Diisopropyl tartrate
2,2'-DMP	-	2,2'-Dimethoxypropane
DMAP	-	4-Dimethylaminopyridine
DMSO	-	Dimethyl sulfoxide
Et_3N	-	Triethylamine
EtOH	-	Ethanol
EtOAc	-	Ethyl acetate
I_2	-	Iodine
IBX	-	2-Iodoxy benzoic acid
K_2CO_3	-	Potassium carbonate
KO^tBu	-	Potassium *tert*-butoxide
LAH	-	Lithium aluminium hydride
LiC≡CH.EDA	-	Lithium acetylide ethylene diamine complex
*m*CPBA	-	*meta*-chloro perbenzoic acid
MeOH	-	Methanol
MeMgBr	-	Methyl magnesium bromide
MsCl	-	Methane sulphonyl chloride

MVK	-	Methyl vinyl ketone
NaH	-	Sodium hydride
NaHMDS	-	Sodium 1,1,1,3,3,3-hexamethyldisilazane
$NaNH_2$	-	Sodium amide
$NaIO_4$	-	Sodium metaperiodate
NaI	-	Sodium iodide
NEt_3	-	Triethyl amine
Na-Hg	-	Sodium amalgum
Na_2HPO_4	-	Disodium hydrogen phosphate
NMO	-	N-Methyl morpholine N-oxide
NH_4Cl	-	Ammonium chloride
OsO_4	-	Osmium tetroxide
$PdCl_2$	-	Palladium chloride
PPh_3=CHCOOEt	-	(Carbethoxymethylene)triphenyl phosphorane
$Pd(PPh_3)_2Cl_2$	-	Bis(triphenylphosphine)palladium(II)dichloride
$Pd(OH)_2$	-	Palladium hydroxide
Py	-	Pyridine
$PdCl_2(CH_3CN)_2$	-	Bis(acetonitrile)dichloropalladium(II)
p-TSA	-	*p*-Toluenesulfonic acid
THF	-	Tetrahydrofuran
TBAF	-	Tetrabutylammonium flouride
TBSCl	-	*tert*-Butyldimethyl chlorosilane
TFA	-	Trifluoroacetic acid
TPP	-	Triphenylphosphine
TsCl	-	*para*-Toluenesulphonyl chloride

GENERAL REMARKS

- ^{1}H NMR spectra were recorded on AV-200 MHz, AV-400 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 AV-50 MHz, AV-100 MHz, and DRX-125 MHz spectrometer.
- EI 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_{α} 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 developing agents.
- 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 40 °C unless otherwise specified.
- Silica gel (60–120), (100-200), and (230-400) mesh were used for column chromatography.
- Different numbers were assigned for compounds in Abstract and Chapters.

CONTENTS

Abstract

The thesis entitled "**Cycloisomerizations of Sugar Derived Alkynols and Studies Toward the Total Synthesis of Didemniserinolipid B and Some Functionalized Nortropane Alkaloids**" consists of three chapters. First chapter describes cycloisomerizations of sugar derived alkynols, and second chapter deals with the formal total synthesis of didemniserinolipid B. Third chapter presents the synthetic studies toward the functionalized nortropane alkaloids.

Chapter I

Cycloisomerizations of Sugar Derived Alkynols

Transition metal-catalyzed reactions belong to the powerful tools of contemporary organic synthesis. They allow a considerable increase in the molecular complexity in a single operation and usually proceed with excellent chemo-, regio- and stereoselectivity. Designing effective routes to construct architecturally complex cyclic structures through organotransition metal-catalyzed reactions provides many attractive possibilities, which by conventional procedures would need a large number of synthetic transformations. Keeping the construction of densely functionalized bicyclic ketal as the main objective in this endeavour, validity and mechanistic investigations of palladium mediated cycloisomerizations has been our goal. A great deal of focus has been directed towards sugar based molecular diversity as these molecules offer inherent rigidity and molecular asymmetry.

We describe the Pd(II) catalyzed cyclizations of various aryl substituted alkynes and the mode of intramolecular cyclizations of the alkynediols. The key issue in our intended strategy is the mode of cyclization *i.e.* 6-*exo*-dig *vs.* 7-*endo*-dig (Figure 1).

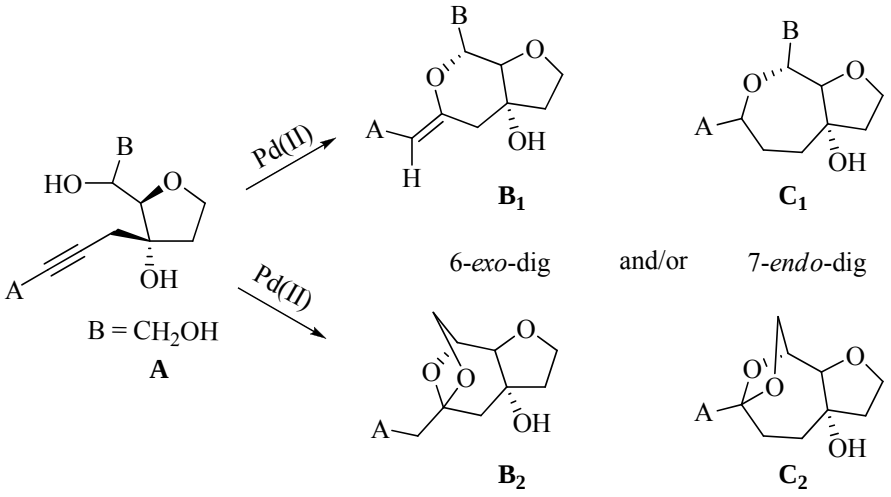
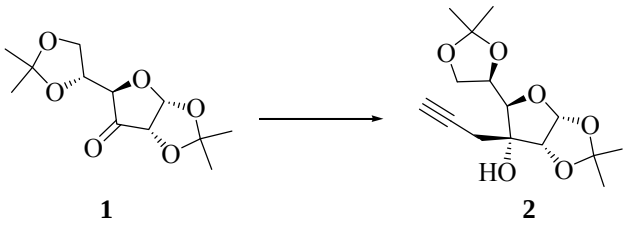


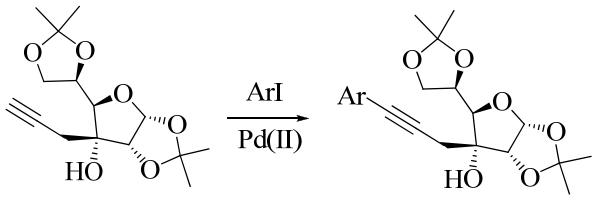
Figure 1: Possible modes of intramolecular cyclizations.

Our schematic investigations started from the known 3-*C*-propargyl allofuranose derivative **2** prepared from the known ulose derivative **1** according to the literature procedure employing the Barbier reaction conditions (Scheme 1).



Scheme 1: Synthesis of the parent substrate.

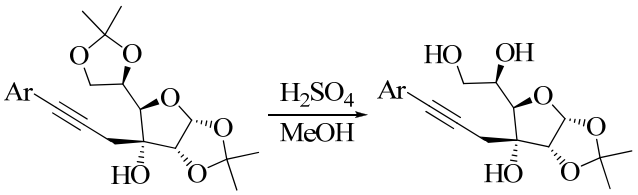
The allofuranose **2** was chosen as the pivotal precursor that paved the way for the synthesis of differently substituted alkynes *via* the Sonogashira coupling with different suitable aryl iodides (Scheme 2).



3 (Ar = Ph, 76%)
4 (Ar = 4-MeOPh, 70%)
5 (Ar = 4-O_2NPh, 63%)
6 (Ar = 3-O_2NPh, 67%)

Scheme 2: Sonogashira coupling with different aryl halides.

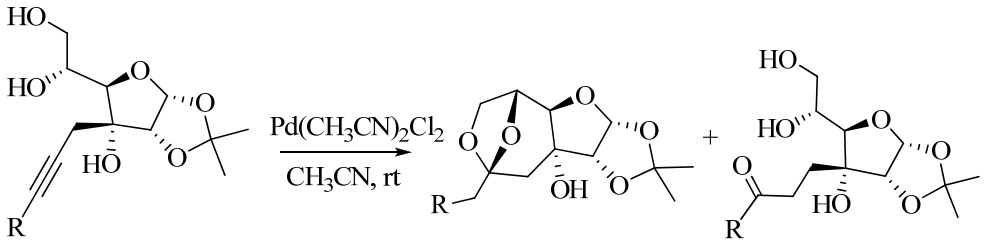
The selective acidic hydrolysis of the terminal 5,6-acetonide group of **2-6** completed the synthesis of the projected alkyne diols **7-11** which are the substrates for the intramolecular cycloisomerizations (Scheme 3).



2	(Ar = H, 79%)	**7**
3	(Ar = Ph, 75%)	**8**
4	(Ar = 4-MeOPh, 69%)	**9**
5	(Ar = 4-O_2NPh, 81%)	**10**
6	(Ar = 3-O_2NPh, 81%)	**11**

Scheme 3: Synthesis of the alkyne diols.

The results of the $Pd(CH_3CN)_2Cl_2$ catalyzed cycloisomerizations of the 3-*C*-propargyl-*allo*-furanose derivatives **7-11** are shown in Scheme 4.



7	R = H	**12** (70%)	--
8	Ph	--	**13** (66%)
9	4-MeOPh	--	**14** (60%)
10	4-O_2NPh	**15** (70%)	--
11	3-O_2NPh	--	**16** (60%)

Scheme 4: Cycloisomerization of the alkyne diols.

As indicated in Scheme 4, the cycloisomerization of monosubstituted alkynol **7** gave exclusively [3.2.1]bicyclic acetal **12**. The appearance of the methylene unit protons separately as doublets at δ 1.62 and 1.95 with large geminal coupling constant (14.7 Hz) in the ^{1}H NMR spectrum of **12** clearly indicated that the methylene unit has no coupled adjacent-H and thus establishing the assigned [3.2.1]bicyclic acetal structure. The presence of a quaternary carbon at 105.3 (s) ppm in the ^{13}C NMR spectrum corresponding to the ketal carbon

further confirmed the assigned structure to **12**. The cycloisomerization of *p*-nitrophenyl substituted alkynol **10** also gave exclusively the *exo*-cyclic product **15**.

The cycloisomerization of alkynols **8**, **9** and **11** gave exclusively the keto derivatives **13**, **14** and **16** respectively. The ^{1}H NMR spectrum of the keto compounds revealed all the four methylene protons resonated separately as dd or ddd in the range of δ 1.81–3.40 ppm thus displaying the through bond connectivity between all of them. The appearance of a carbon singlet in the range of 198-200 ppm in the ^{13}C NMR spectrum confirmed the presence of a carbonyl carbon. The characteristic NMR peaks of **13**, **14** and **16** are given in Table 1.

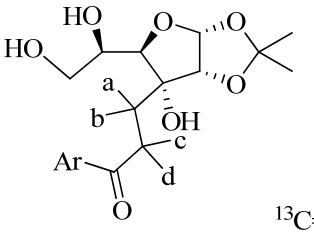
Ketone	Ar =	Ph (**13**)	4-MeOPh (**14**)	3-NO_2Ph (**16**)
	a	1.88	1.87	1.90
	b	2.30	2.30	2.31
	c	3.10	3.04	3.10
	d	3.39	3.33	3.40
	^{13}C=O	200.0	198.6	199.9

Table 1: Characteristic ^{1}H and ^{13}C NMR pattern for the ketones.

The formation of keto compounds with complete regioselectivity raised a couple of issues to be answered: a) could it be resulting either from the hydrolysis of the intermediate 7-*endo* products? or b) the regioselective alkyne hydration (path *i*, Figure 2)? or c) by the participation of a 3°-OH in a 5-*endo* manner and subsequent hydrolysis of intermediate dihydrofuran derivatives (path *ii*, Figure 2)? In the latter two instances, it looks as if the 7-*endo*- and *6-exo*-dig cyclizations with 2°-OH are relatively slower.

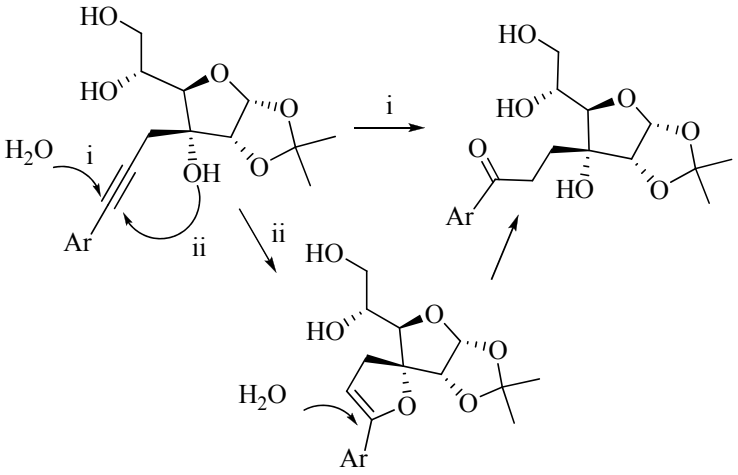
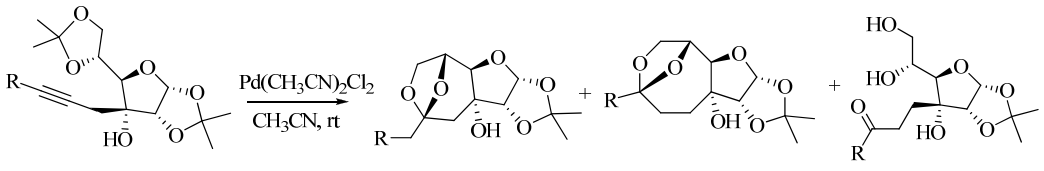


Figure 2: Possible modes of formation of the keto compounds.

Based on the above intriguing results, cyclizing the 3-hydroxyl of the glucofuranose onto the alkyne keeping the acetonide intact should lead us to desired spiroketals. In order to probe in this direction, we employed acetonides **2** - **6** as substrates for intramolecular cycloisomerization reactions. We invoked that results from these cycloisomerization reactions should atleast answer the issue of C(3)-OH participation.

The cycloisomerization of the alkynes **2**, **3** and **5** afforded **12**, **13** and **15** respectively. The 4-methoxyphenyl substituted alkyne **4** gave the 7-*endo* product **17** exclusively wherein the four methylene protons resonated separately in the range of δ 1.52–3.69 in the ^{1}H NMR and the quaternary carbon corresponding to the ketal at 110.7 (s) ppm in the ^{13}C NMR. The 3-nitrophenyl substituted alkyne **6** gave the *exo* product **18** with a similar NMR pattern observed for the ketal **15** (Scheme 5).



R = H	**2**	**12** (58%)	–	--
Ph	**3**	–	–	**13**(64%)
4-MeOPh	**4**	–	**17** (56%)	--
4-O_2NPh	**5**	**15** (72%)	–	--
3-O_2NPh	**6**	**18** (83%)	–	--

Scheme 5: Cycloisomezisation of the alkyne acetonides.

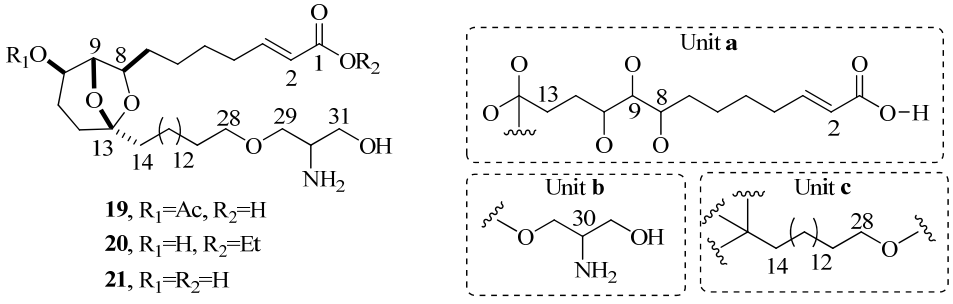
To summarize the cycloisomerization reactions of acetonides **2-6**, 4 out of 5 substrates employed gave bicyclic ketal products where the regiochemistry is entirely governed by electronic influence. These results obtained are quite surprising because the participation of ether oxygen in the cycloisomerization reactions, is rare. The isolation of bicyclic ketal **15**, resulting from an initial 7-*endo*-dig cyclization revealed that these products are stable. These results clearly indicate that the participation of a C(3)-OH in a 5-*endo* manner and hence the spiroketal formation can be ruled out and suggest that hydration is a competing reaction with the triol substrates **7-11**.

Chapter II

Studies towards the total Synthesis of Didemniserinolipid B

Marine tunicates belonging to the genus *Didemnum* have proven to be a particularly rich source of structurally diverse and biologically potent metabolites. The representative examples are the cyclic heptapeptides, such as mollamide and cyclodidemnamide, and the first sulfamic acid peptide guanidine derivatives, minalemines D-F, the novel predator-deterrent didemnimides A-D, and the *α*-carbolines, didemnolines A-D. Also, other metabolites with miscellaneous structures have been found, including the HIV-1 protease inhibitor didemnaketals A and B, and a number of enterocin derivatives.

As part of a continuing search for biologically active secondary metabolites from ascidians, particularly those belonging to the *Didemnum* genus, the tunicate *Didemnum* sp., was collected along the coast of Sulawesi Island (Indonesia), and a potent cytotoxic activity was found in its methanolic extract against several tumor cells. Thus the isolation and the structural elucidation of the first serinolipids from a marine organism was reported. These are 2-amino-1,3-propanediols linked to a hydroxylated α,*β*-unsaturated acid having an unusual 6,8-dioxabicyclo[3.2.1]octane structure (compounds **19-21**) (Figure 3).



19, R_1=Ac, R_2=H
20, R_1=H, R_2=Et
21, R_1=R_2=H

Figure 3: The first serinolipids from a marine organism.

Extensive NMR analysis (^{1}H NMR, ^{13}C NMR, DEPT, ^{1}H-^{1}H COSY, and HMQC) showed that the didemniserinolipids comprise three major structural subunits **a**, **b** and **c**. In the course of determining the absolute stereochemistry of the didemniserinolipid B **20** through synthesis, Ley *et al.* reassigned the structure of natural (+)-didemniserinolipid B **20a** as the 31-*O*-sulfate, and its absolute configuration was determined to be 8*R*,9*R*,10*R*,13*S*,30*S*.

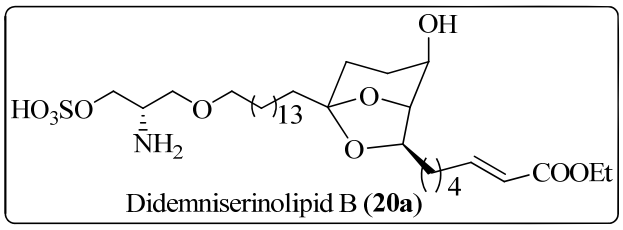


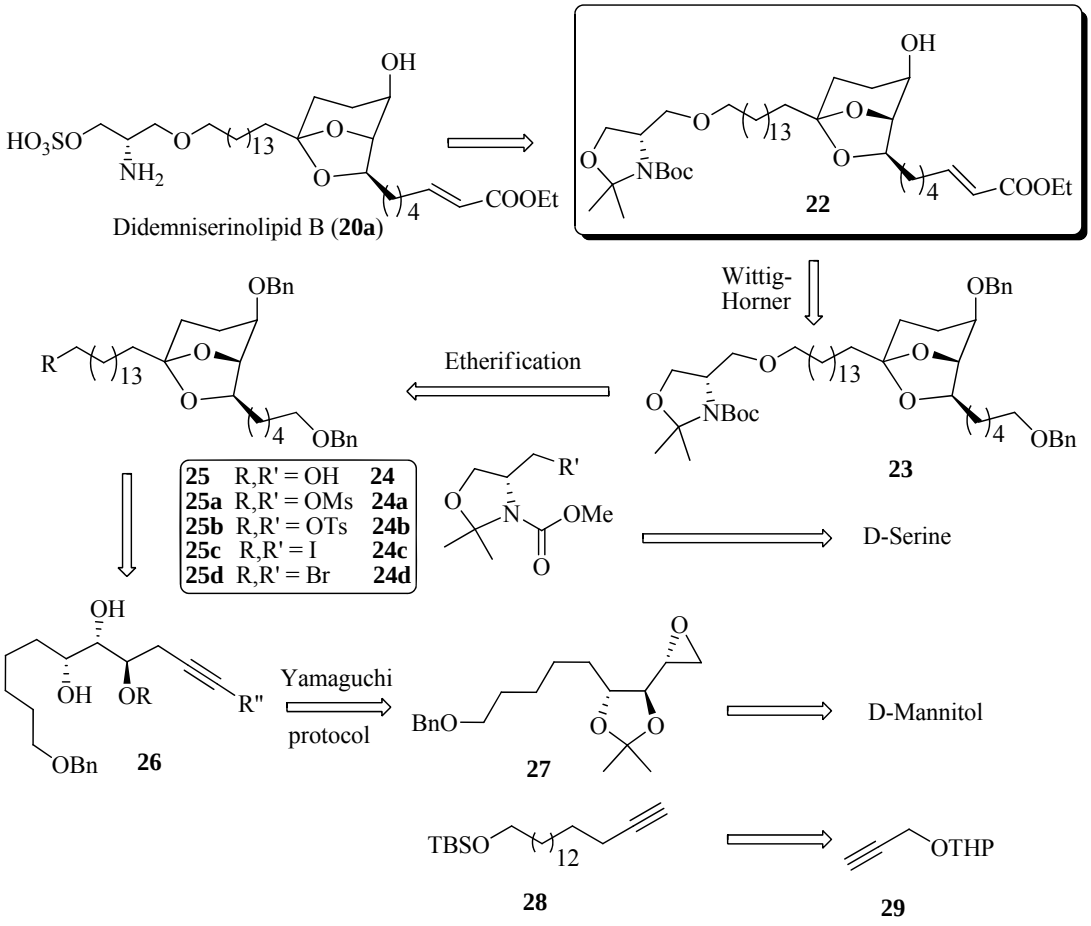
Figure 4: Reassigned structure of didemniserinolipid B.

The unique structures and biological activities of the didemniserinolipids have generated much excitement in the chemical communities and this motivated us to begin programs aimed at developing efficient routes to these compounds. Initially there was only one report for the synthesis of didemniserinolipid B (**20a**) by Ley *et al.* During the course of our synthesis of the same molecule, another report by Burke *et al.* prompted us to design a formal total synthesis for the serinolipid by way of the ketal **22**.

Our proposed synthetic route to the didemniserinolipids was influenced by our investigations of the reactivity and synthetic potential of alkyne diols towards the palladium mediated cycloisomerizations as described in the previous chapter.

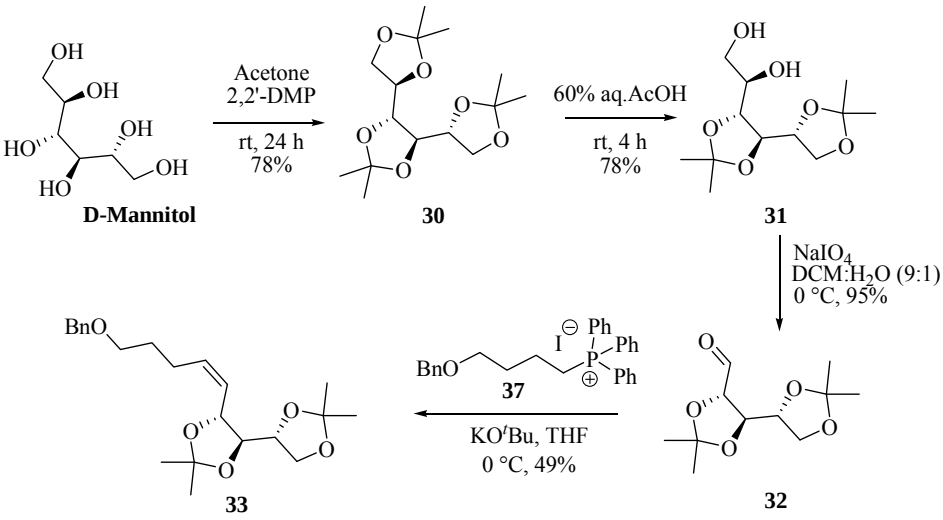
Retrosynthesis:

Our convergent strategy for the synthesis of **22** synthetic relied on the palladium mediated cycloisomerization of the homopropargyl alcohol obtained by the Yamaguchi coupling of the epoxide **27** derived from D-mannitol with the silyl alkynol **28** derived from propargyl alcohol by an acetylenic zipper reaction, and the subsequent etherification of the resulting ketalized homopropargyl alcohol with the D-serinol unit **24** and the final 2 carbon Wittig olefination (Scheme 6).



Scheme 6: Retrosynthetic analysis for didemniserinolipid B.

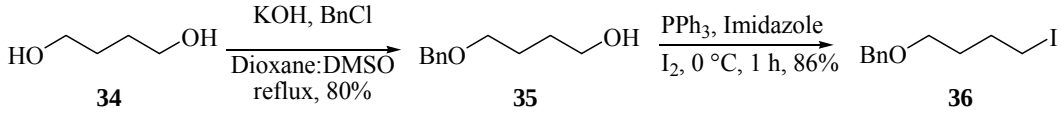
The synthetic strategy was based on the simple functional group transformations on D-Mannitol keeping the stereochemistry of the three hydroxyl groups intact. Accordingly, the synthetic endeavor started with the known mannitol diacetonide **31** wherein the aldehyde **32** obtained from the oxidative cleavage of the diol was subjected to 4 carbon Wittig olefination to afford the olefin **33**. The *cis*/*trans* geometry of the newly formed double bond was of little significance since it would be subjected to partial hydrogenation at the later stages of the synthesis. However the coupling constant (J = 10 Hz) proves that the *cis* olefin was formed exclusively (Scheme 7).



Scheme 7: Formation of the olefin.

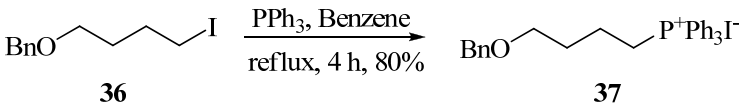
Formation of the Wittig salt:

1,4-butane diol was selectively protected to the known benzyl ether **35**. Iodination of the alcohol **35** afforded the iodide **36** (Scheme 8).



Scheme 8: Preparation of the iodide.

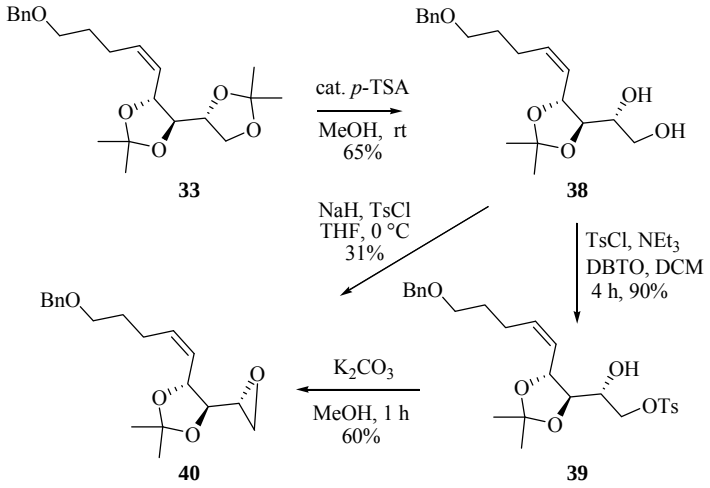
The preparation of the Wittig salt was standardized after trying different solvents such as ether, benzene, toluene. Best yields were obtained using benzene as the solvent. Thus the Wittig salt **37** was prepared from the alcohol by refluxing with triphenylphosphine in benzene for 4 h (Scheme 9).



Scheme 9: Preparation of the Wittig salt.

Synthesis of the epoxide:

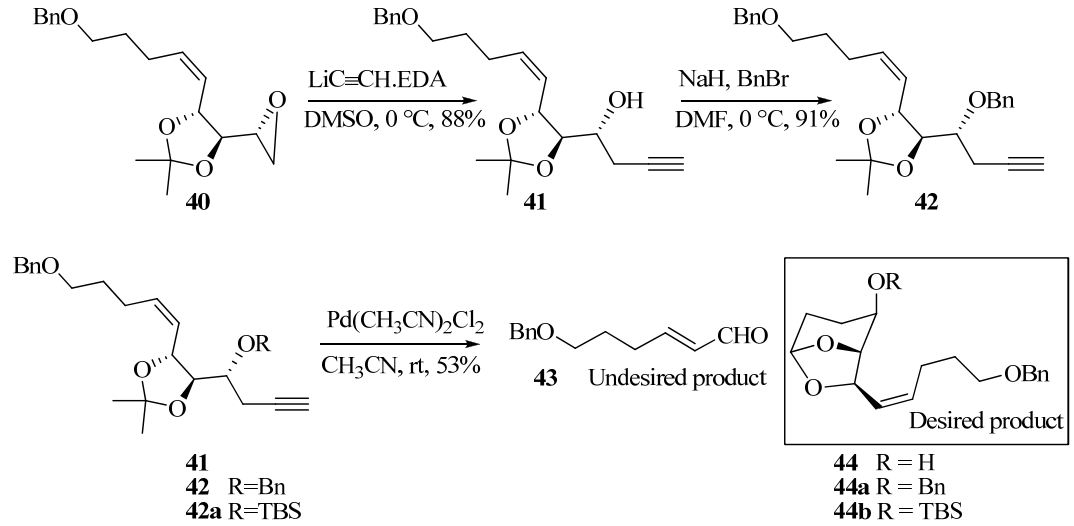
Acidic hydrolysis of the terminal isopropylidene moiety in **33** afforded the diol **38** which was converted to the epoxide **40** in a one pot reaction using two equivalents of sodium hydride and one equivalent of tosyl chloride. The epoxide was also synthesized using the two step process *via* the tosylate **39** (Scheme 10).



Scheme 10: Formation of the epoxide.

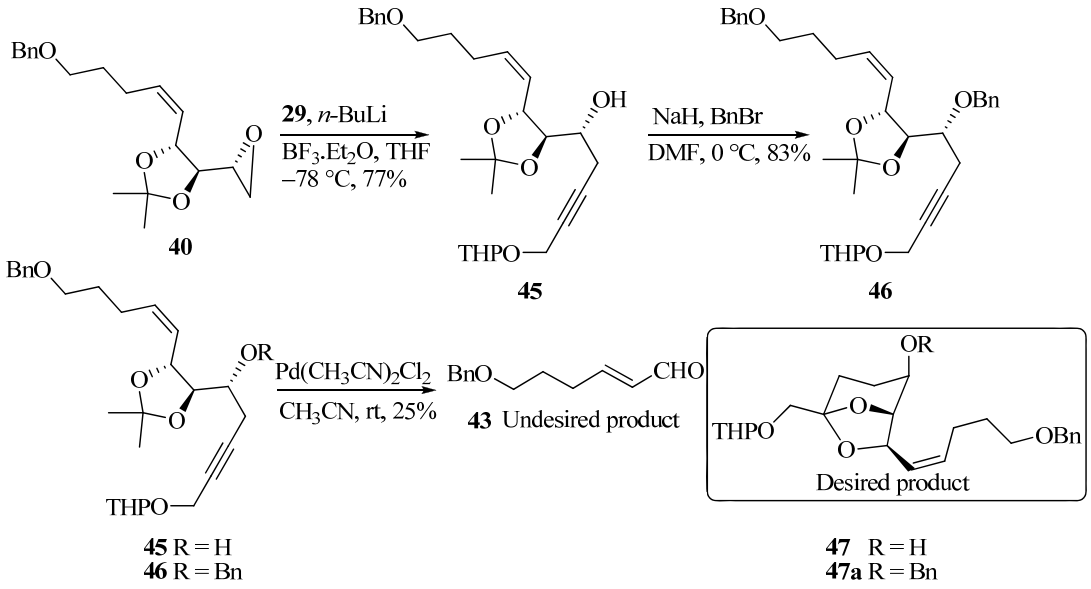
Substrates for the ketalization approaches:

Prior to the epoxide opening with the requisite 17 carbon alkynol, the initial ketalization was attempted with the alkyne diol **41**/**42** obtained by the treatment of the epoxide **40** with lithium acetylide. The homopropargyl alcohol **41** was protected as its benzyl/TBS ether **42** and was subjected to ketalization utilizing the palladium mediated cycloisomerization (banking on the expertise we gained in the previous chapter). However this resulted in the oxidative cleavage of the diol to the α,β-unsaturated aldehyde **43**, but not the desired ketal **44** (Scheme 11).



Scheme 11:

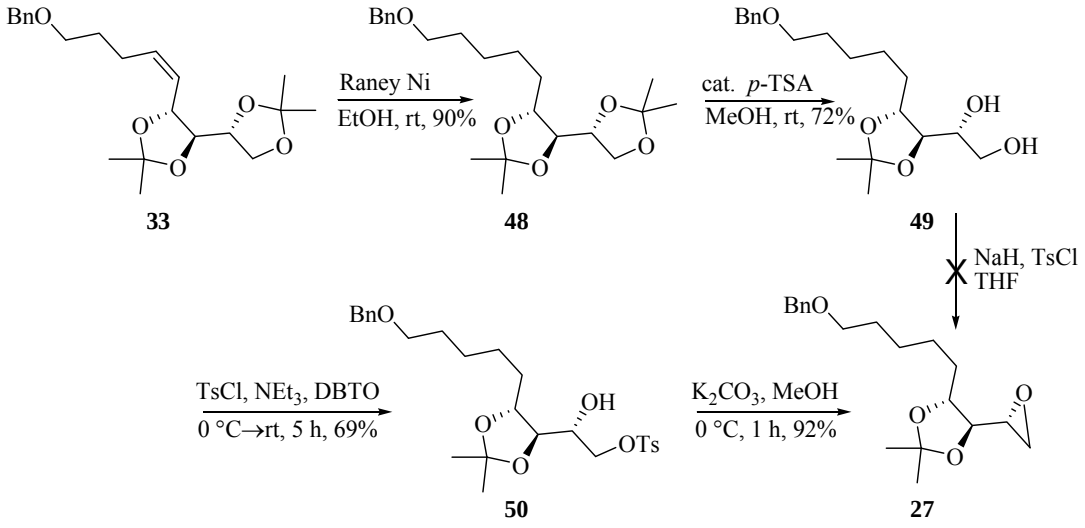
Similar set of reactions employing the same epoxide and the alkyne **29** i.e., Yamaguchi coupling followed by the ketalization yielded the α,β-unsaturated aldehyde **43** but not the expected product **47**/**47a** (Scheme 12).



Scheme 12:

Based on the above observations, we terminated the scheme at this juncture and proceeded further with the epoxide **27** obtained from **33** by a sequence of steps. The diacetonide was subjected to partial hydrogenation to afford the saturated diacetonide **48**. The diacetonide was subjected to acidic hydrolysis to afford the diol **49**. The attempted one pot conversion of the diol to the epoxide wasn't successful as

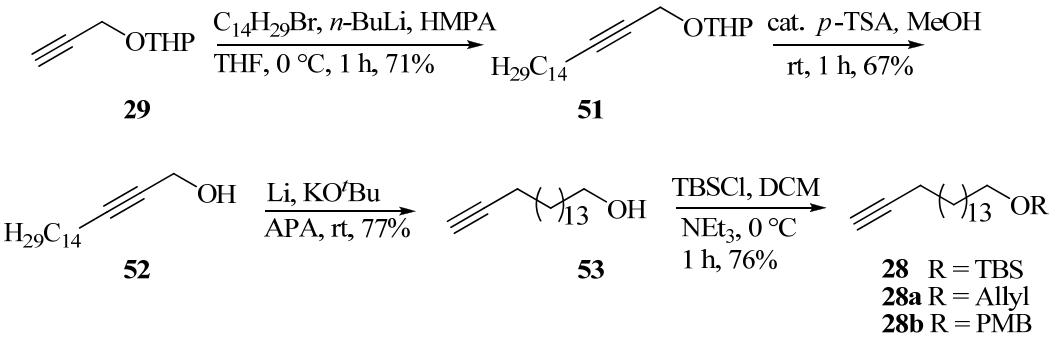
in the previous case. Hence we opted for the conventional two step process for the formation of the epoxide **27** *via* the tosylate **50** (Scheme 13).



Scheme 13:

Preparation of the alkyne fragments:

The requisite 17 carbon alkyne was prepared from the known THP ether of propargyl alcohol by a sequence of 3 steps. The alkyne was subjected to alkylation utilizing the requisite 14 carbon alkyl bromide. The deprotection of the THP ether under acidic conditions afforded the propargyl alcohol **52**, which was the substrate for the acetylenic zipper reaction (Scheme 14).

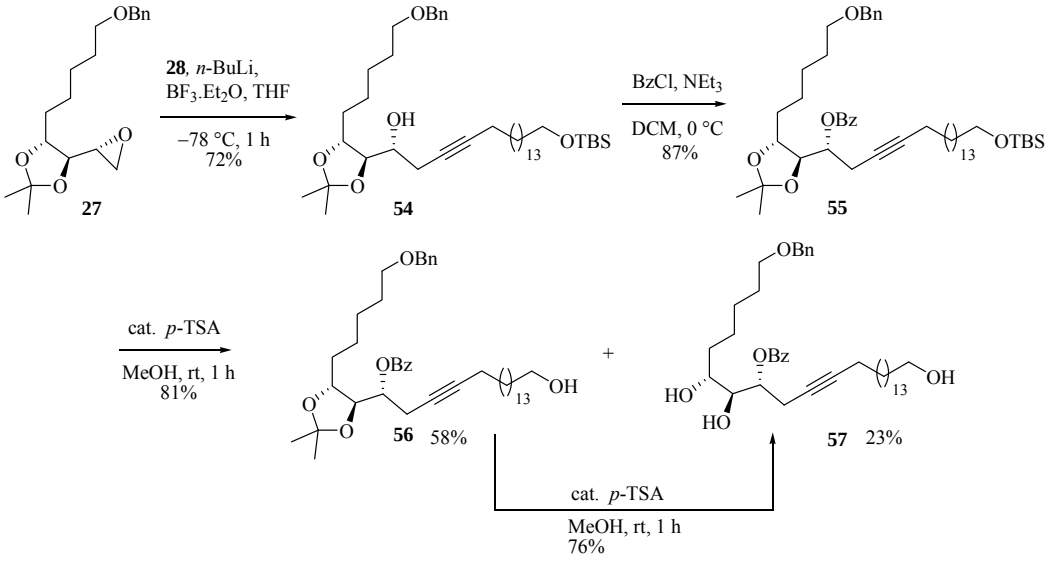


Scheme 14:

Having the required alkyne in hand, now the stage was set for the isomerization of the alcohol. Initial trials utilizing various reagents were unsuccessful. After rigorous efforts, the reaction was effected with Li/KO^{t}Bu/APA as the reagent.

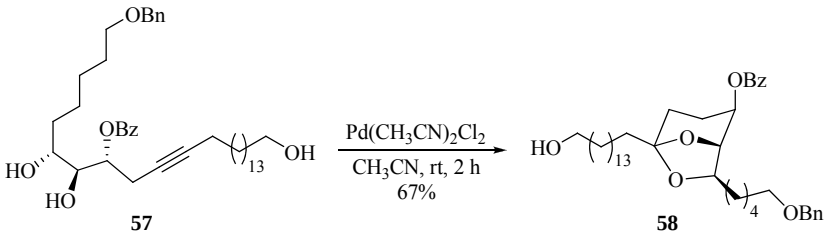
Formation of the homopropargyl alcohol:

The alkynol **53** was protected as its allyl/TBS/PMB ether and tested for its reactivity with the epoxide under Yamaguchi conditions. It was observed that the silyl alkynol **28** was ideal when compared to the allyl/PMB ether as the reaction wasn't reproducible in the case of the former and the reaction led to the deprotection of the PMB group in the latter case. The homopropargyl alcohol **54** resulting from the epoxide **27** under the Yamaguchi conditions with the alkyne **28** was protected as its benzoate **55** and subjected to acidic hydrolysis conditions to afford the alcohol **56** and also the triol **57**. The alcohol **56** was inturn converted to the triol **57** employing the same acidic conditions (Scheme 15).



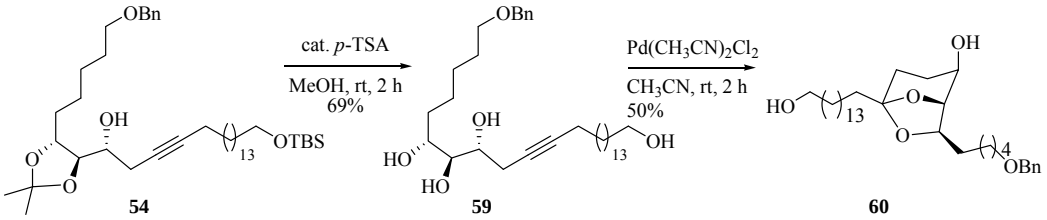
Scheme 15:

Capitalizing on the expertise we gained in the palladium mediated cyclisations of alkyne diols, we employed the same protocol to arrive at the 6,8-bicyclo[3.2.1]octane framework of the target molecule with **57** which has the alkyne and a diol unit suitably placed for the ketalisation to occur. Though a competition for *exo*/*endo* cyclization was expected, the reaction proceeded smoothly with the exclusive formation of the *endo* cyclized product **58** in 50% yield (Scheme 16).



Scheme 16:

The relatively low yield prompted us to think of an alternative i.e., the cyclisation of the alkyne tetrol **59** obtained from **54** by acidic hydrolysis. This would be an ideal option in the long run as it would save two steps of protection and deprotection in the overall synthetic sequence and its yield. To our good fortune, the cyclization was successful with the exclusive formation of the requisite *endo* product **60** (Scheme 17).

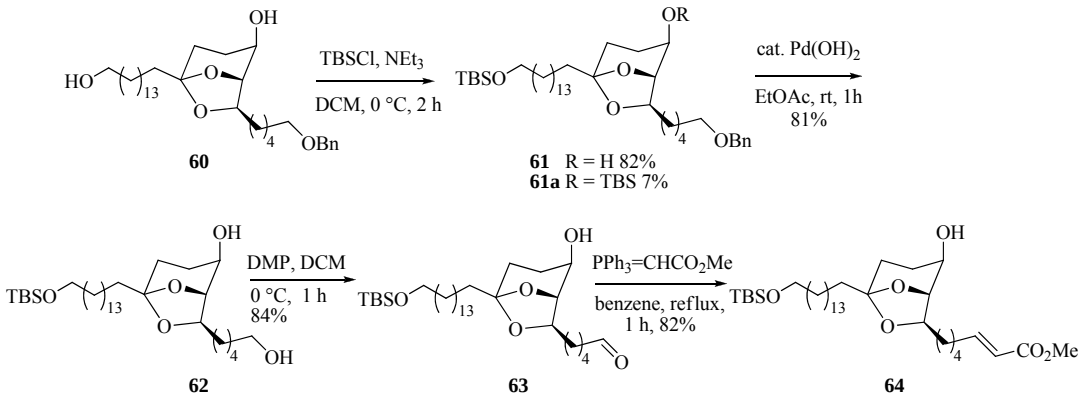


Scheme 17:

Wittig olefination *vs* etherification:

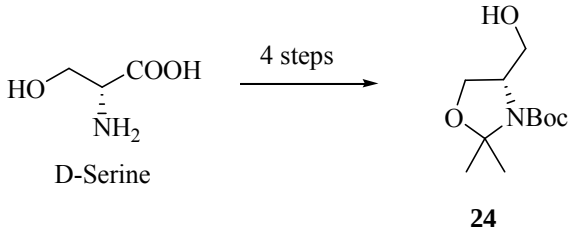
The ketal **60** has the added advantage of two alcoholic groups on either sides which could be functionalized to the target molecule by way of 2 carbon wittig olefination on the right end and etherification with the serinol unit on the left end employing certain functional group modifications. The desired task could be achieved by first conducting the wittig reaction followed by etherification or vice-versa.

Following the first case, the ketal **60** was protected as its TBS ether **61** followed by debenzylation to afford the diol **62**. The diol was selectively oxidized to its aldehyde **63** which was subjected to 2 carbon Wittig olefination to yield the α,*β*-unsaturated ester **64** (Scheme 18).



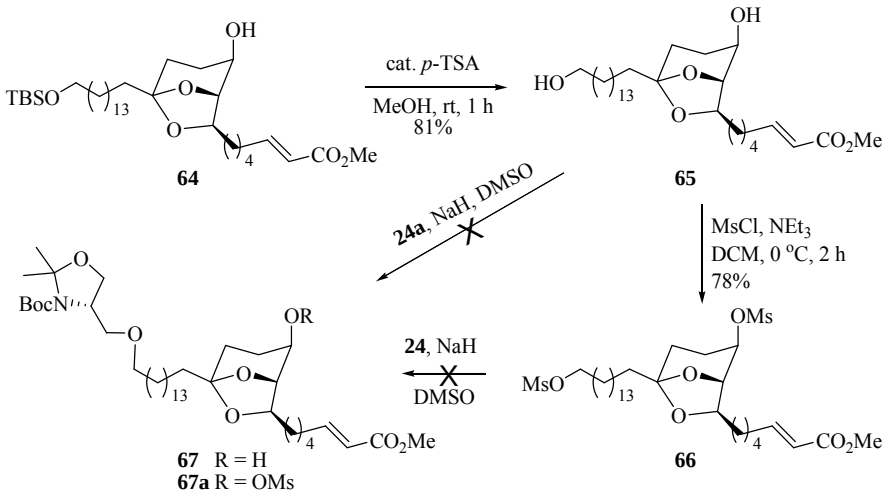
Scheme 18:

Now the stage was set for the etherification on the other end with the serinol unit [prepared from D-serine according to the literature procedure in 4 steps (Scheme 19).



Scheme 19:

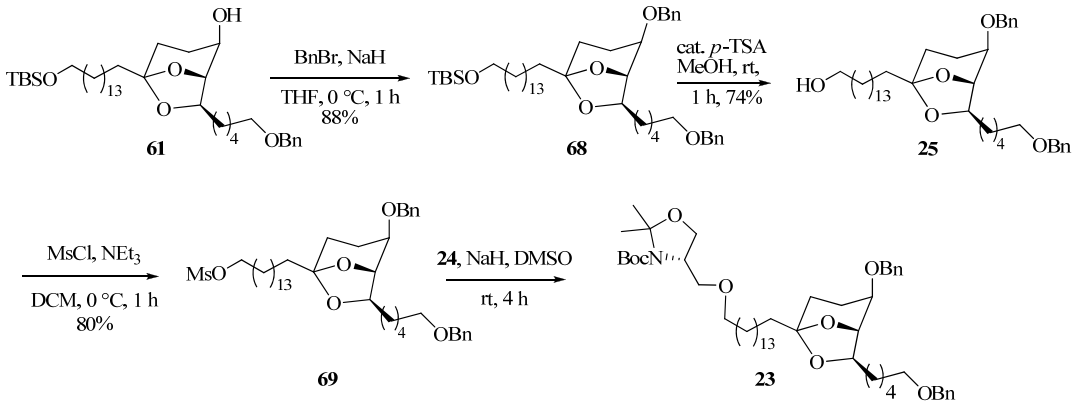
However the attempted etherification of the ketal **65** with the mesylate of the serinol **24a** to **67** or the dimesylate of the ketal **66** with the serinol unit **24** to **67a** did not meet any success (Scheme 20).



Scheme 20:

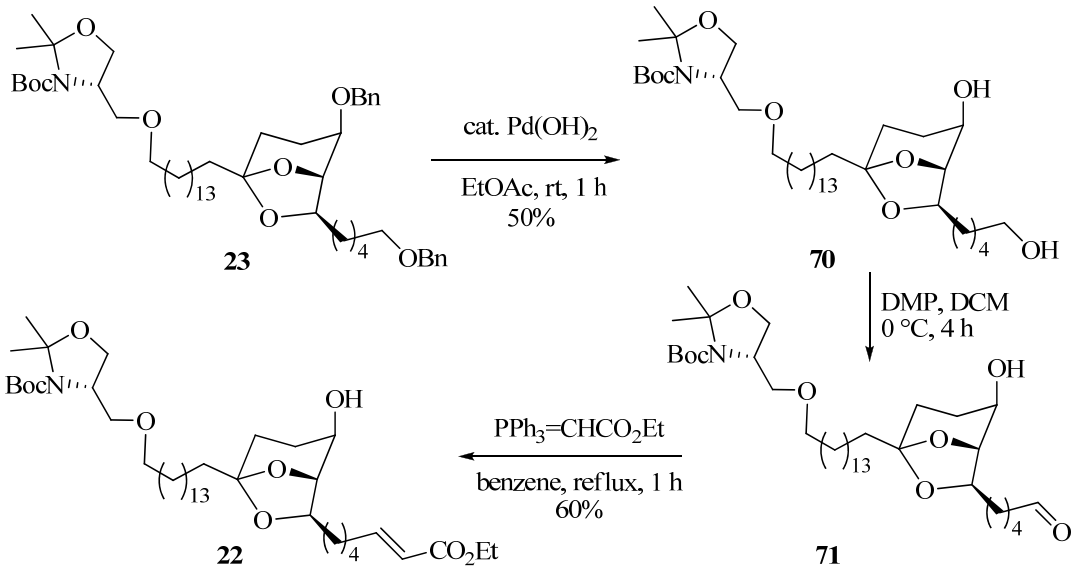
This prompted us to think of the other option i.e., etherification followed by Wittig olefination. Initial attempts of the etherification were unsuccessful either with the tosylate/iodide/bromide of the serinol and the ketal or the tosylate/iodide/bromide of the ketal with the serinol. The last option was the mesylate and this rationale was also supported by the recent report by the Burke group's synthesis wherein the etherification was successful employing the mesylate of the ketal and the serinol.

Employing the same strategy, the ketal was protected as its dibenzyl derivative **68** and the deprotection of the silyl ether **25** followed by the mesylation afforded the desired substrate **69** for the etherification with serinol **24**. The etherification of the mesylate with the serinol successfully afforded the ketal **23** in good yields (Scheme 21).



Scheme 21:

The final debenzylation to the diol **70**, oxidation to the aldehyde **71** and a two carbon Wittig olefination gave the desired target molecule **22** thus accomplishing the formal total synthesis of didemniserinolipid B (Scheme 22).



Scheme 22:

To conclude, a formal total synthesis of didemniserinolipid B was developed by employing a Pd-mediated cycloisomerization reaction. The reported synthesis is characterized by its flexibility at different stages and has the potential to synthesize didemniserinolipid analogues by incorporating changes at either end of the chain. Work in this direction is progressing in our group.

Chapter III

Studies towards the synthesis of some functionalized nortropane alkaloids

Numerous aza-sugars have been isolated and can be divided into five general classes: piperidines, pyrrolidines, indolizidines, pyrrolizidines, and nortropanes. Numerous polyhydroxylated alkaloids from these structural classes, synthetic and natural, have shown promise as anti-viral or anti-infective agents as well as in the treatment of diabetes. Aza-sugars inhibit glycosidases which are enzymes involved in sugar processing.

The discovery of polyhydroxy alkaloids, otherwise known as imino-sugars raised an awareness among phytochemists that compounds with structural similarities should have analogous glycosidase-inhibitory properties. Recognition of their structural affinities to castanospermine (**72**), with a pair of five and six-membered rings, albeit fused in a different manner (Figure 5), led to their characterization as potent inhibitors of β-glucosidase and α- and β-galactosidase. A new class of

nortropane polyhydroxylated alkaloids, called calystegines have been isolated which have been suggested to be nutritional mediators in the plant rhizosphere (plant-bacteria relationship). They also possess glycosidase inhibiting properties and an allelopathic activity (Figure 5).

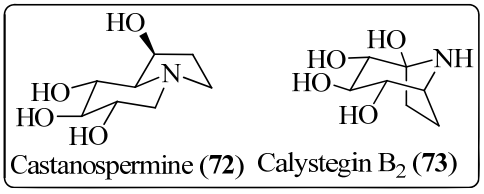
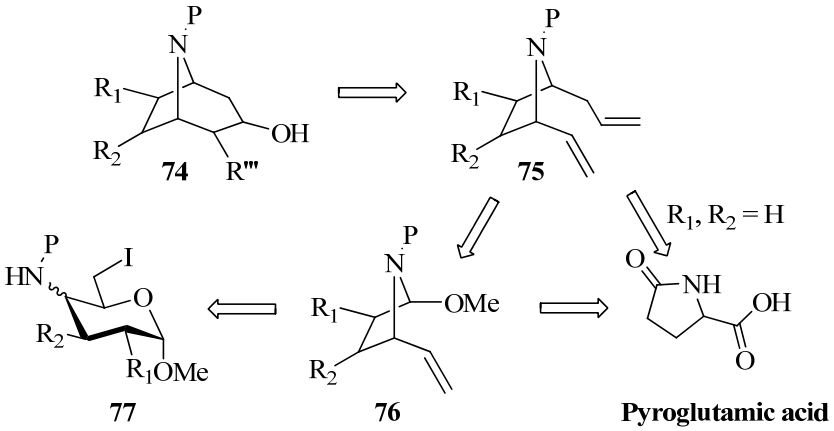


Figure 5:

The broad range of neurochemical activity associated with the 8-azabicyclo[3.2.1]octane framework (tropane) coupled with their unusual architecture makes short, versatile, stereocontrolled synthetic routes to these compounds of tremendous potential value.

The bicyclic skeleton can be envisaged from the diene **75** by way of the ring closing metathesis. The diene can be obtained from the aminal **76** which can be accomplished either from derivative of pyroglutamic acid or the derivative of D-Glucose **77** (Scheme 23).

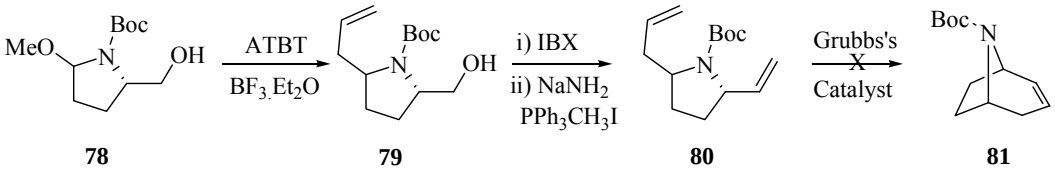


Scheme 23:

Pyroglutamate approach:

A short synthesis of the nortropane alkaloid has been attempted starting from the known compound **78** where the Lewis acid mediated dispalcement of the OMe group by the allyl group afforded the alcohol **79**. Oxidation of the alcohol **79** followed by one carbon Wittig olefination gave the required diene **80** for RCM. Unfortunately,

olefin metathesis of the diene **80** to the cyclic olefin **81** didn't work and the starting material was recovered (Scheme 24).



78 **79** **80** **81**

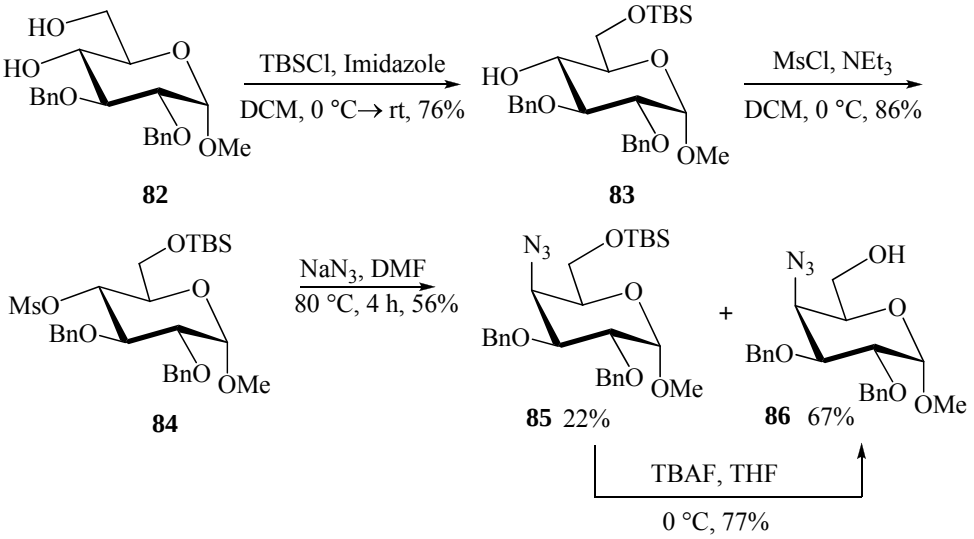
Scheme 24:

Sugar based approach:

Initial setback in the RCM reaction in the Scheme 24 prompted us to shift our focus to the sugar based strategy wherein the synthesis started with the known diol **82** prepared from D-Glucose in 3 steps.

Introduction of the amine functionality:

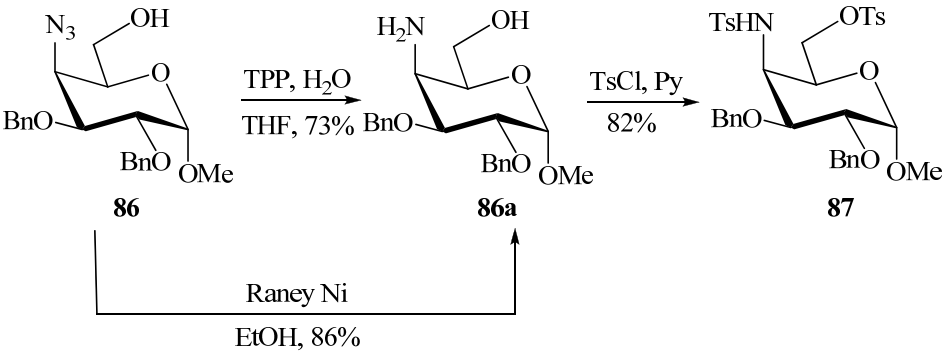
The diol was selectively protected as the monosilyl ether **83** followed by mesylation of the secondary alcohol to the mesylate **84**. The mesylate could be visualized as the substrate for the introduction of the amine functionality in the form of azide. SN^2 displacement of the mesyl group by the azide afforded the silyl azide **85** and the azido alcohol **86**. The silyl azide was also converted into the azidoalcohol by treatment with TBAF (Scheme 25).



82 **83** **84** **85** 22% **86** 67%

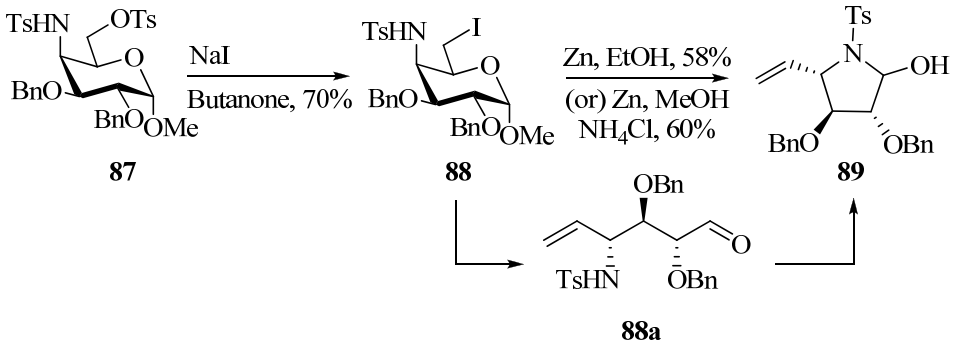
Scheme 25:

The amino functionality could be visualized by way of the azide reduction. The reduction was effected using the triphenylphosphine (Staudinger reaction) to form the aminoalcohol **86a** which was ditosylated to **87**. However, the reduction resulted in poor yields and also not reproducible. The other alternative would be the use of Raney nickel as the reducing agent. This reduction resulted in the formation of the aminoalcohol which was also ditosylated to afford the compound **87** (Scheme 26).



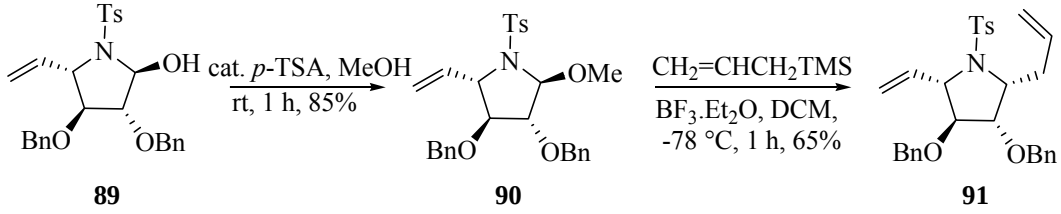
Scheme 26:

The displacement of the tosylate by the iodide afforded the compound **88** which was the substrate for the zinc mediated triple domino reaction. The iodide upon treatment with zinc in ethanol under refluxing conditions afforded the aldehyde **88a** which was immediately trapped by the amine to afford the pyrrolidine derivative **89**. The longer reaction times (1 day) made us switch to the reagent $Zn/NH_4Cl/MeOH$ in which the reaction was complete within 30 minutes though the yields were nearly the same (Scheme 27).



Scheme 27:

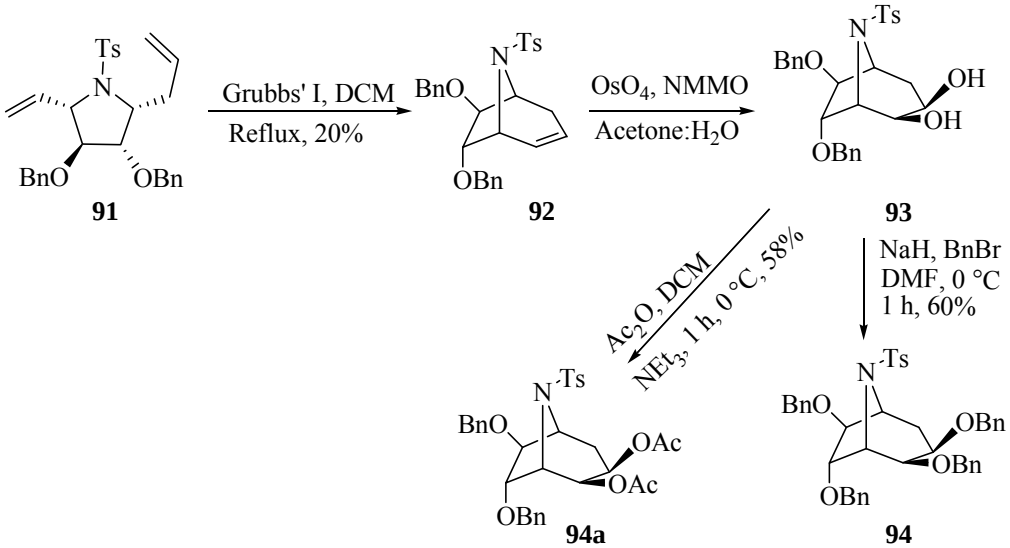
The hemiaminal was converted into the aminal **90** in MeOH using catalytic *p*-TSA. The Lewis acid mediated displacement of the OMe group by the allyl group using the reagent allyltrimethylsilane afforded the diene **91** (Scheme 28).



89 **90** **91**

Scheme 28:

The diene **91** served as the crucial substrate for the formation of the 8-azabicyclo[3.2.1]octane by performing the RCM reaction to afford the bicyclic olefin **92** in 75% yield (BORSM). The dihydroxylation of olefin afforded the β-diol **93** exclusively as indicated by the COSY and NOESY spectra of the diacetate **94a** obtained from the diol under acylation conditions using acetic anhydride (Scheme 29).

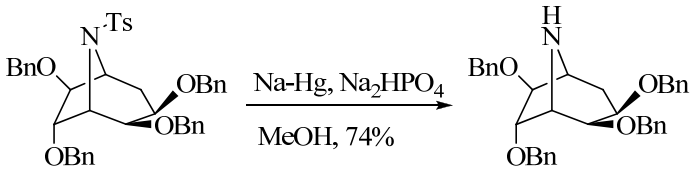


91 **92** **93** **94a** **94**

Scheme 29:

The initial efforts to detosylate the amine in **93**/**94a** were unsuccessful with either recovery of the starting material or the decomposition of the starting material. Hence as a last resort we thought of attempting the desulphonation with the tetrabenzyl derivative **94** obtained from the diol upon benzylation using benzyl

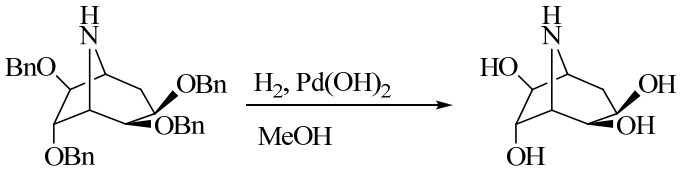
bromide. The desulphonation was now successful using Na-Hg (6%) under buffered conditions to afford the amine **95** (Scheme 30).



94 **95**

Scheme 30:

Final debenzylation should unmask the desired polyhydroxy analogue of the nortropane alkaloid series to afford **96** (Scheme 31).



95 **96**

Scheme 31:

Herein, we report the facile synthesis of polyhydroxylated azabicyclo[3.2.1]octane that can be selectively functionalized. A reliable and convenient method has been demonstrated for the construction of the nortropane alkaloid wherein the key steps are the zinc-mediated triple domino reaction and the ring closing metathesis.

CHAPTER-I

Cycloisomerizations of Sugar Derived Alkynols

Introduction

Heterocycles, especially oxygenated, are probably one of the most common structural motifs spread across natural products, from simple glucose to structurally complex metabolites such as leucascandrolide A, phorboxazole A and B, and the even more elaborated architectures present in palytoxin, maitotoxin, and other marine natural products. Due to the remarkably rich array of functionalities and chiral centers that these cyclic compounds can incorporate, their stereoselective preparation has become a continuous challenge for organic synthesis practitioners. They can be synthesized by means of five-membered ring expansions e.g., Baeyer-Villiger oxidation[1] of cyclopentanones, cycloaddition processes e.g., Hetero-Diels Alder reactions,[2] or intramolecular cyclizations.[3] Classical examples of these cyclizations are the lactonization of δ-hydroxy acids or the thermodynamically favorable conversion of δ-hydroxy aldehydes into the corresponding hemiacetals, which, in turn, can be easily modified (e.g., C-glycosidation reactions to provide other pyran-based structures). In addition to these processes, there is a set of important methodologies based on the cyclization of an oxygenated precursor that affords cyclic ethers in a highly efficient and straightforward manner. In spite of the achievements mentioned above, the use and removal of stoichiometric amounts of often toxic elements have fuelled research into alternative activators of unsaturated substrates that allow the desired intramolecular cyclizations under mild conditions and in a catalytic fashion.

In the last quarter of the 20th century, a new paradigm for carbon-carbon, carbon-heteroatom bond formation has emerged that has enhanced considerably the prowess of synthetic organic chemists to assemble complex molecular frameworks and has changed the way we think about synthesis. Based on transition-metal catalysis,[4] this newly acquired ability to forge carbon–carbon bonds between or within functionalized and sensitive substrates provided new opportunities, particularly in total synthesis but also in medicinal and process chemistry as well as in chemical biology and nanotechnology.

There are many issues that must be addressed to make organic synthesis more environmentally benign by design. One fundamental consideration is the stoichiometry of the process. Until the present, virtually all attention focused on solving problems of selectivity regardless of the price that might be paid in terms of

atom economy olefination protocols being a prime example. There is no reason to believe that selectivity and atom economy are mutually exclusive goals. The fact that we have barely begun to probe the possibilities offered by catalysis broadly speaking and transition metal catalysis[4,5] in particular emphasizes that extraordinary opportunities exist to improve our toolbox of methodologies that are more atom economical.

In this context, transition metals have been invaluable reagents for the organic chemist since the beginning of this century. In particular, palladium, formerly used only for redox reactions, has recently achieved a prominent role in synthesis due to the manifold and unique transformations that it is capable of mediating, often in a catalytic mode. The large number of organic transformations mediated, the wide functional group tolerance, and the catalytic nature of most of these processes, however, make palladium an ideal basis for devising new methodologies. There are important number of methodologies based on the intramolecular attack of an oxygenated nucleophile on an olefin activated by electrophiles which are otherwise unreactive. The most common precursors are δ-hydroxy alkenes, which afford the corresponding pyrans through highly regioselective 6-*exo* ring closures.

The rationale for these cyclizations assumes the reversible formation of a π-complex, which can proceed either directly to the corresponding heterocycle by reaction with the nucleophile or indirectly by first collapsing to an onium intermediate before undergoing nucleophilic attack. In any case, cyclization involves the attack of the oxygenated nucleophile on the opposite face of the electrophile. Therefore, the success of this strategy mostly relies on the stereocontrolled electrophilic addition to the alkene.[4,5] These cyclizations can be classified as stoichiometric or catalytic, according to the amount of electrophile engaged in the process. The stoichiometric electrophile-induced cyclizations routinely involve mercury(II) salts and halo or seleno reagents as activators of the carbonecarbon double bond. Otherwise, palladium chemistry dominates the catalytic counterparts, although other metals are being increasingly employed. In this context, catalytic methodologies based on the activation of unsaturated compounds are dominated by the palladium chemistry, which has achieved prominent levels of maturity.

Palladium is a member of the nickel triad in the periodic table. Palladium complexes exist in three oxidation states: Pd(0), Pd(II), and Pd(IV). The facile interconversion between these oxidation states is responsible for the broad utility of

palladium in organic chemistry, since each oxidation state exhibits different chemistry. Palladium(0) complexes are fairly nucleophilic, rather labile, and also easily oxidized, usually to the Pd(II) state. The most synthetically useful Pd(0) chemistry is based on the oxidative addition of aryl, vinylic or allylic halides or triflates to Pd(0). Palladium(II) complexes are extremely important in organopalladium chemistry. They are typically electrophilic, soluble in most common organic solvents, and stable to air. Thus, they are easily stored and handled. The most common organic substrates for Pd(II) are electron-rich species such as olefins, alkynes, and arenes.

The most useful Pd(II) complexes are $PdCl_2(PPh_3)_2$, $Pd(OAc)_2$, and $PdCl_2(RCN)_2$.[4,5] Pd(IV) complexes are quite rare, although a few complexes are known. These complexes have been little explored, but transient Pd(IV) species have been increasingly implicated as intermediates in palladium reactions. They appear to play little role in palladium π-olefin and π-alkyne chemistry directed toward heterocyclic synthesis. The intramolecular cyclization of palladium π-olefin and π-alkyne complexes is a powerful method for the construction of heterocycles. This process normally involves the fast and reversible complexation of the olefin or alkyne by a Pd(II) salt. The resulting π-olefin or π-alkyne complexes are stable but reactive in the presence of a nucleophile. Nucleophilic attack on the π-olefin species usually occurs *anti* to the metal at the more substituted vinylic carbon to give a σ-alkylpalladium(II) complex, which may then undergo a wide variety of processes resulting in the final heterocycle. Depending on the reaction conditions, these subsequent processes may involve palladium β-hydride elimination, reduction, nucleophilic substitution of the metal, transmetallation, or various insertion processes as outlined in Figure 1.[6] Pd(0) is usually produced in the final step, which means that a reoxidant is required to transform Pd(0) to Pd(II) to affect a process catalytic in palladium. Reoxidants commonly used are $O_2/CuCl_2$, benzoquinone, O_2/DMSO, $FeCl_3$, and $K_2S_2O_8$. The Pd(II)- catalyzed reactions of simple alkenes and dienes, olefins bearing internal nucleophiles, and alkynes thus provides a very valuable approach to a wide range of heterocycles.

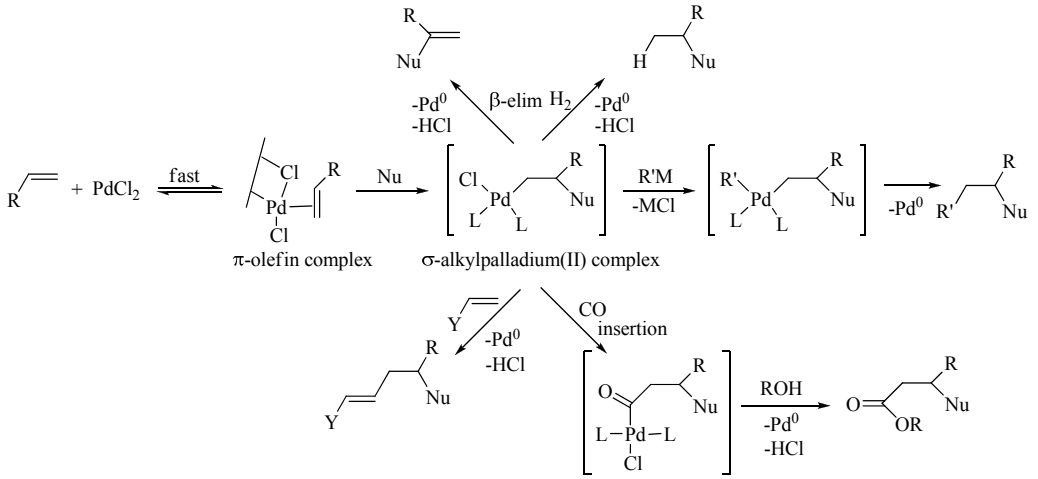


Figure 1: *Reaction Pathways Available to π-Olefin Palladium(II) Complexes*

Cycloisomerisations catalysed by Palladium:

The broad range of reactions catalyzed by palladium can be classified into two types based on the nature of products formed-

a) Those forming Carbocycles.

b) Those forming Heterocycles.

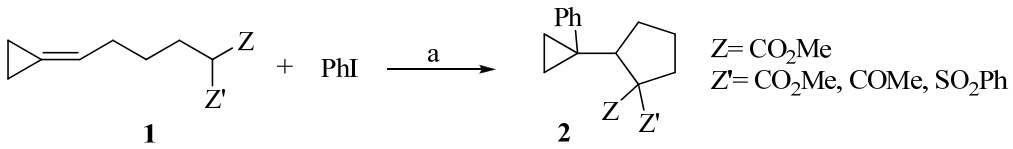
Carbocycle formation:

These set of reactions can be further classified into two types based on the substrates involved i.e., alkenes or alkynes.

Cyclisation of unactivated alkenes:

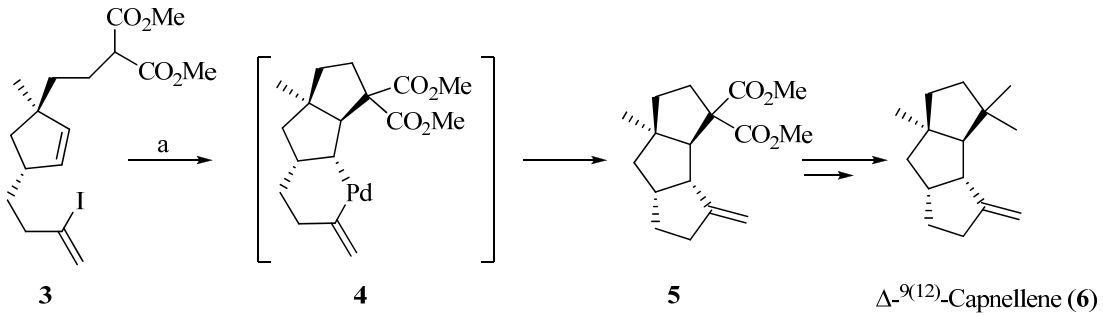
In 1987, Goré and Balme described the palladium-mediated reaction of alkylidene cyclopropanes **1** bearing a stabilized carbon nucleophile with phenyl iodide that yielded the bicyclic compound **2** (Scheme 1).[7] Although the mechanism of the cyclization process was not clear at that time, this was certainly the first reported example of an intramolecular nucleophilic attack on an unsaturated electrophile activated by an organopalladium species, a hitherto unknown phenomenon. Indeed, unactivated olefins are inert towards attack of nucleophiles. When complexed to palladium(II) salts, it is well known that stabilized carbanions may react with these olefin palladium(II) complexes to generate alkyl palladium complexes. In this new cyclization reaction, an organopalladium(II) halide, not a palladium(II) salt, acts as the electrophilic partner of the cyclization. Therefore, this reaction, which only

requires catalytic quantities of the metal, results in overall difunctionalization of the olefinic substrate.



Scheme 1: *Reagents and conditions:* a) NaH, $Pd(dba)_2$, dppe, DMSO, 95 °C, 60-87%.

By using the intramolecular version of this strategy, the stereocontrolled total synthesis of the fused tricyclopentanoid (±)-capnellene (**6**), a marine natural product, has been carried out by applying the palladium-mediated carbocyclization to the internal vinyl iodide **3** as the key step.[8] The reaction took place at room temperature in THF, in the presence of potassium hydride as base and $Pd(OAc)_2$/dppe as catalytic system leading to triquinane **5** which was converted into capnellene by standard methods (Scheme 2).

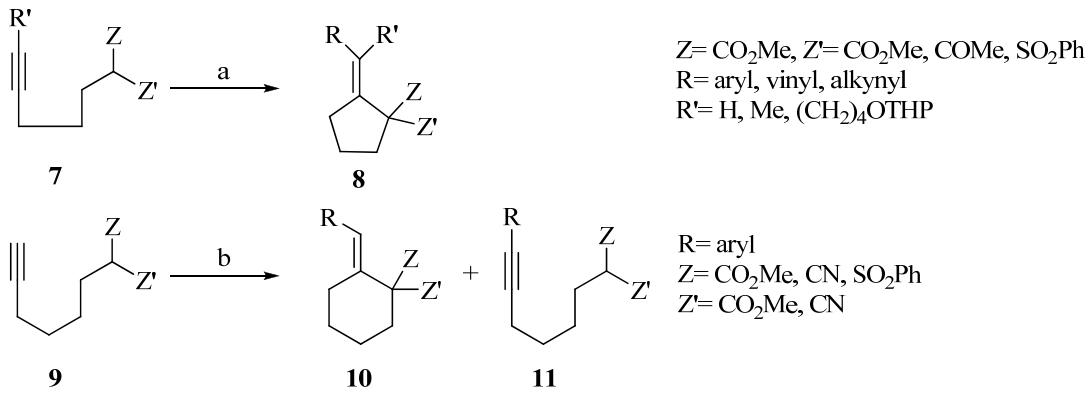


Scheme 2: *Reagents and conditions:* a) KH, Pd(dppe), THF, rt, 70%.

While the methodology for the preparation of cyclopentane derivatives has been well established, the construction of cyclohexane homologues proved to be more difficult. For instance, dimethyl 5-hexenylmalonate showed a strong tendency to give a direct coupling reaction of the alkene with the aryl halide (classical Heck reaction).[9] However, the cyclization/Heck reaction balance here was also strongly affected by the nature of the nucleophilic part of the precursors.

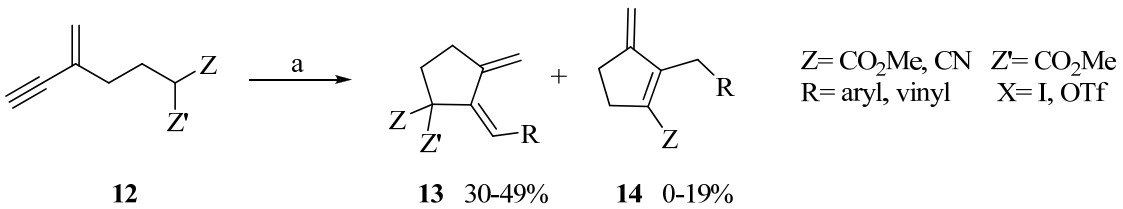
Cyclization of unactivated alkynes:

This new cyclopentannulation method was applied to the acetylenic homologues **21** and it must be emphasized that stereodefined exocyclic double bonds were formed even in the case of substituted alkynes ($R_1 \neq H$), the carbonucleophile and the organopalladium species adding in a *trans* fashion across the unsaturated bond. Unfortunately, for acetylenic compounds, the palladium-catalyzed tandem cyclization/coupling reaction remains limited to the formation of five membered rings **8**.[11] By using substrates **9** with one carbon more in the side chain, some severe limitations were observed: the palladium mediated reaction led to the formation of the desired stereodefined arylidene cyclohexane compound **10** accompanied by the linear coupling product **11** resulting from the classical Sonogashira type[10] reaction (Scheme 3).



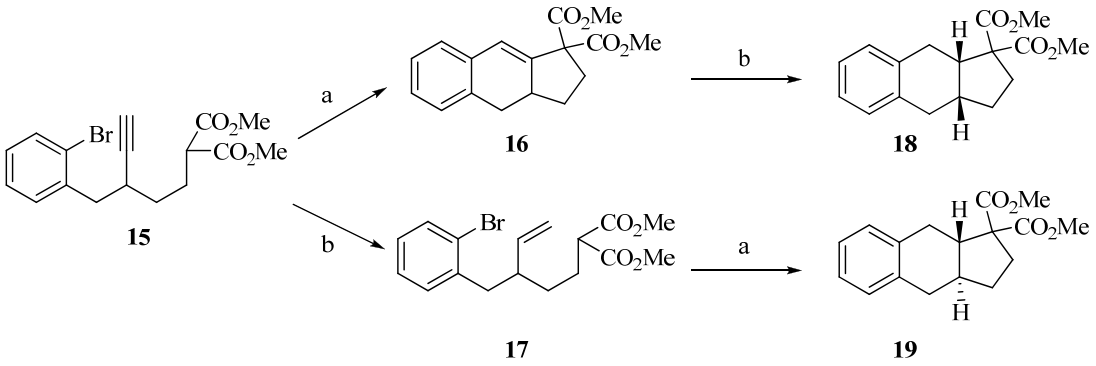
Scheme 3: *Reagents and conditions:* a) RX, $Pd(dba)_2$, dppe, *t*-BuOK, THF, rt; b) RX, $Pd(dba)_2$, dppe, *t*-BuOK, DMSO, 80 °C.

Recently, this strategy was extended to the formation of stereodefined functionalized 1,3-bis-exocyclic dienes **13** or **14** by cyclization of conjugated enynes **12** having a stabilized carbon nucleophile (Scheme 4).



Scheme 4: *Reagents and conditions:* a) RX, $PdCl_2(PPh_3)_2$, *n*-BuLi, KH, THF, rt.

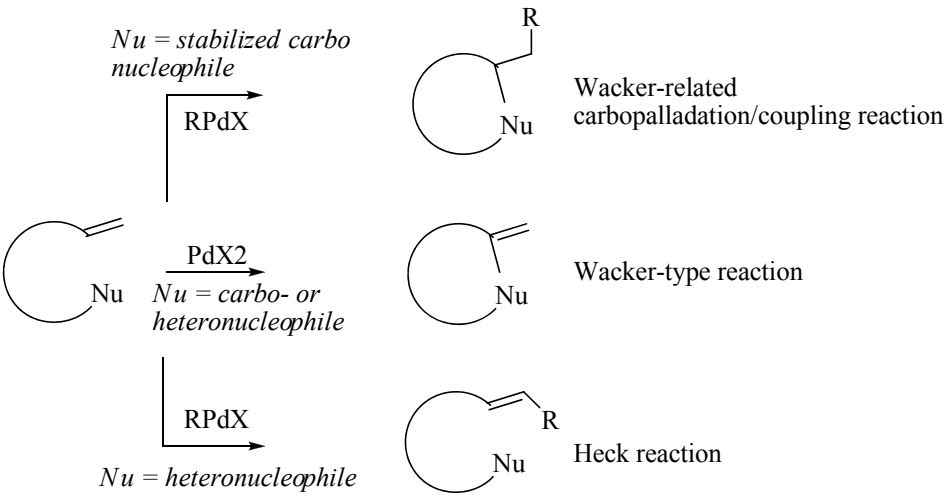
A practical and efficient strategy for the synthesis of either *cis*- or *trans*-hexahydro-1*H*-benz[*f*]indene **18** and **19** was developed starting from the common acetylenic precursor **15**. This compound was involved in a palladium-catalyzed cascade *bis*-cyclization process leading to the unsaturated tricyclic substrate **16**. Catalytic hydrogenation of **16** over Pd/C at atmospheric pressure occurred with complete selectivity from the least hindered face to afford the *cis*-hexahydro-1*H*-benz[*f*]indene **18** in essentially quantitative yield. By changing the order of the two preceeding steps, only the *trans*-hexahydro-1*H*-benz[*f*]indene structure **19** was obtained (Scheme 5).[12]



Scheme 5: *Reagents and conditions:* a) Pd(dppe), KH, NMP; b) H_2, Pd/C, EtOH.

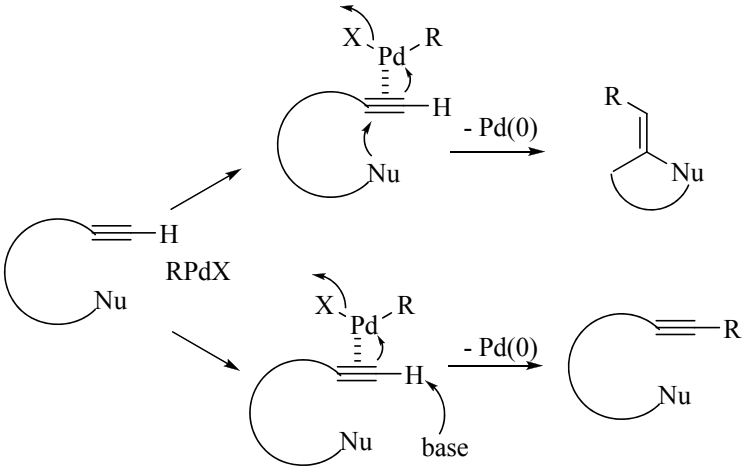
Heterocycle formation:

Although there are a number of examples of intramolecular reactions of soft carbo nucleophiles on alkenes coordinated by organopalladium complexes, there are no examples of the same reaction realized in the presence of heteronucleophiles. In this case, the palladium-catalyzed arylation of olefins (Heck reaction)[9] prevails over the intramolecular attack of the heteronucleophile on the activated carbon-carbon double bond, leading to the linear arylated product. Such difference in reactivity may be due, in part, to the higher basicity of heteronucleophiles. It is noteworthy that a variety of heterocyclic systems have been synthesized by attack of oxygen or nitrogen nucleophiles on alkenes coordinated by palladium salts such as palladium chloride or palladium acetate (Scheme 6).



Scheme 6: *Various Pd-catalyzed intramolecular cyclizations of alkenes.*

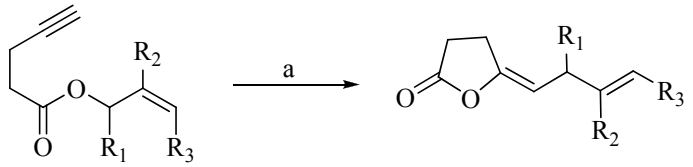
In marked contrast, various electrophilic organopalladium complexes are able to trigger the intramolecular nucleophilic attack of a heteronucleophile on alkynes through coordination, and a variety of heterocyclic systems have been elaborated using this strategy. However, a competitive reaction may arise when terminal alkynes are involved, i.e., the direct coupling reaction of the alkyne with the unsaturated halide or triflate (Scheme 7).



Scheme 7: *Intramolecular additions to Pd-complexed alkynes.*

Oxygen heterocycles:

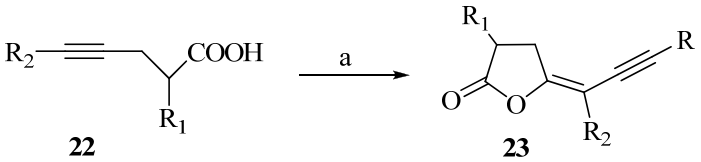
The first example of a cyclization of an acetylenic heteronucleophile catalyzed by organopalladium species was developed by Tsuda and Seagusa in 1988 on allyl 4-pentynoates **20** (Scheme 8) to produce the substituted unsaturated lactones **21** regio- and stereoselectively.[13]



20 **21**

Scheme 8: *Reagents and conditions:* a) $Pd_2(dba)_3.CHCl_3$, $P(OCH_2)_3CEt$, 24-86%.

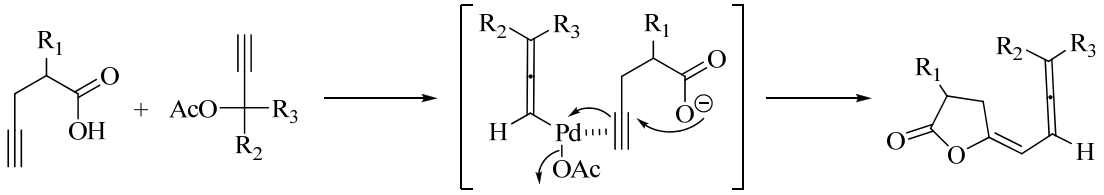
The transformation of the same pentynoates to the biologically active ynenol lactones **23,** under the influence of σ-ethynylpalladium complexes generated from alkynyl bromides was reported by Balme and co-workers (Scheme 9).[14]



22 **23**

Scheme 9: *Reagents and conditions:* a) RC≡CBr, $Pd(OAc)_2$, TFP, ^tBuOK, DMSO, 35-90%.

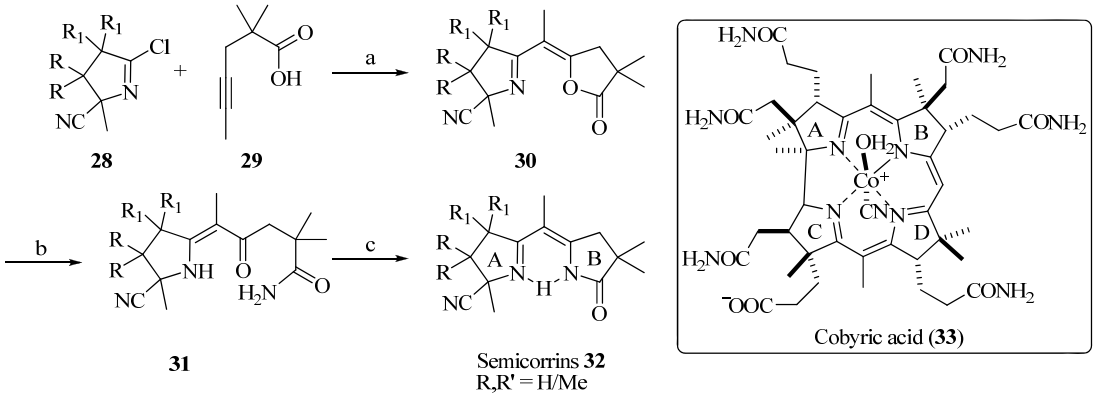
A similar procedure in which σ-allenylpalladium complexes **26** issued from propargyl acetates **25** activate the carbon-carbon triple bond was then developed to yield potentially bioactive new unsaturated *exo*-enol lactones **27** (Scheme 10).[15]



24 **25** **26** **27**

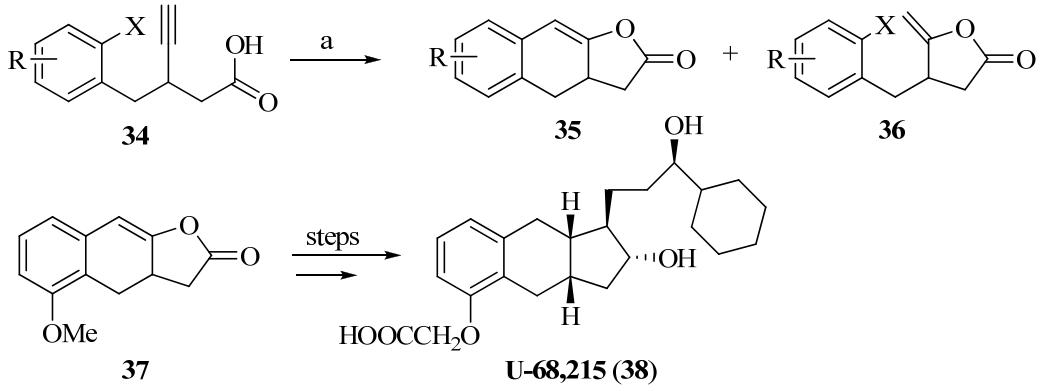
Scheme 10: *Reagents and conditions:* a) $Pd(OAc)_2$, TFP, K_2CO_3, DMSO, 50-62%.

The palladium-mediated coupling/cyclization reaction of alkynoic acids was recently extended by Jacobi and coworkers[16] to the preparation of meso-substituted semicorrins **32**, as an approach towards the synthesis of Corrin derivatives such as Cobyric acid **33** (Scheme 11). A similar strategy was used for the synthesis of compounds of the Chlorin family.



Scheme 11: *Reagents and conditions:* a) $Pd(PPh_3)_4$, $BnNEt_3Cl$, NEt_3, MeCN, 60 °C; b) NH_3; c) P_2O_5.

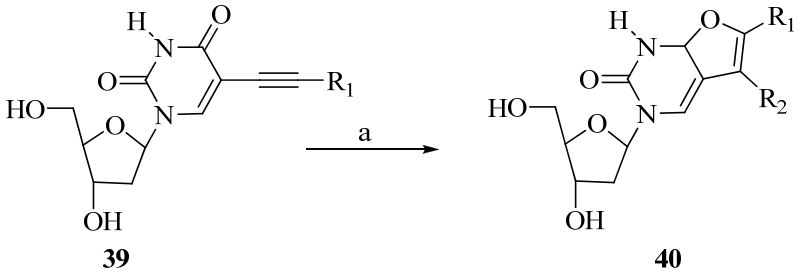
An intramolecular version of the cyclization/coupling reaction of alkynoic acids was developed by Balme and coworkers[17] for the synthesis of various benzo-annulated enol lactones **36**. Following this approach, the cytotoxic tricyclic compound U-68,215 (**38**) has been synthesized by the Balme's group (Scheme 12).



Scheme 12: *Reagents and conditions:* a) $Pd(OAc)_2$, TFP, KF, DMSO.

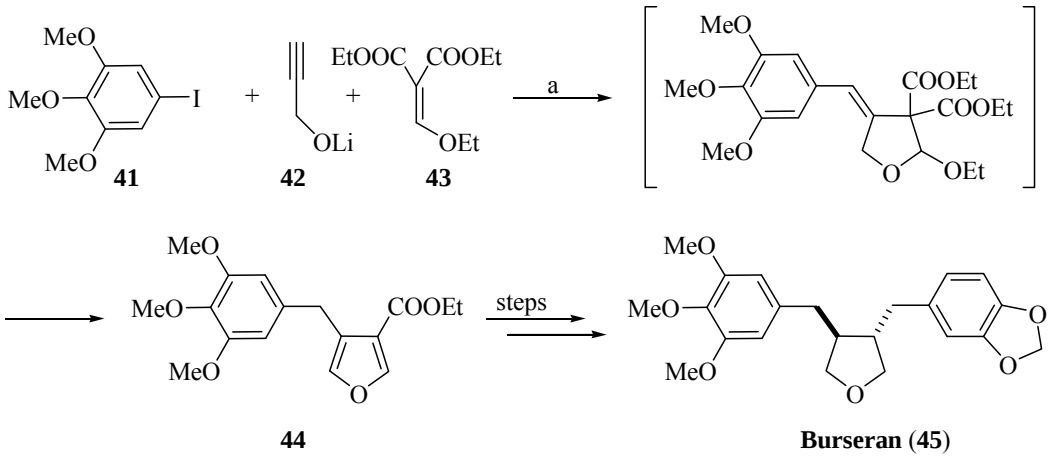
Deoxynucleoside analogues **40**, a series of inhibitors of varicella-zoster virus, have been synthesized from the corresponding alkynyl deoxyuridines **39** in moderate

to good yields (40–75%). The construction of the furo[2,3-*d*]pyrimidin-2-one nucleus has been achieved using $Pd(PPh_3)_4$ as catalyst and Et_3N as base (Scheme 13).[18]



Scheme 13: *Reagents and conditions:* a) R^2I, $Pd(PPh_3)_4$, NEt_3, DMF, 60 - 70 °C, 40 - 75%.

A novel one-pot, two-step synthetic entry into functionalized 4-benzylfuran derivatives of type **44** was then developed by extending this strategy to the commercially available diethyl ethoxymethylene malonate as conjugate acceptor. It involved a conjugate addition, a palladium-catalyzed cyclization/coupling reaction, an alkoxide-induced decarboxylative elimination, and finally a double bond isomerization.[19] A formal synthesis of the lignan anti-tumor Burseran (**45**) employed this process as a key step illustrating the potential utility of this concept in the synthesis of important natural products of the lignan family (Scheme 14).

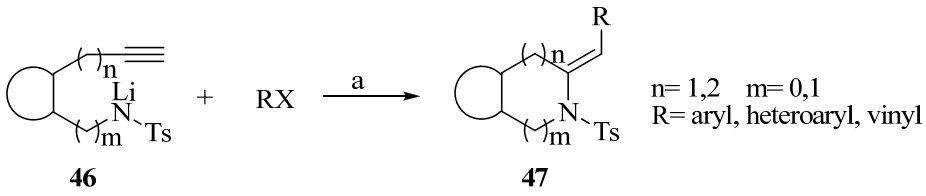


Scheme 14: *Reagents and conditions:* a) $PdCl_2(PPh_3)_2$, *n*-BuLi, DMSO-THF, 20 °C.

Nitrogen heterocycles:

The intramolecular *trans* addition of alkenyl or aryl groups and amines to internal or terminal alkynes has been shown to be an efficient route to various

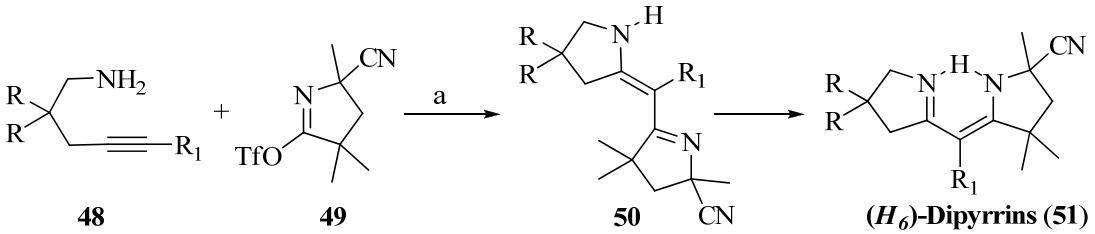
nitrogen heterocycles.[20] This strategy has been applied to the construction of stereodefined 2-alkylidene pyrrolidine or piperidine derivatives **47** (Scheme 15).



46 **47**

Scheme 15: *Reagents and conditions:* a) $Pd(OAc)_2$, PPh_3, THF, 60 °C, 58-86%.

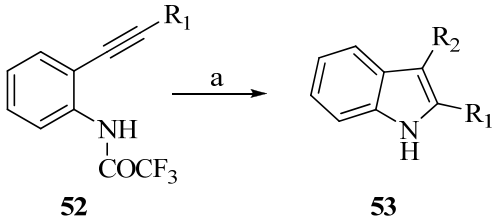
This strategy was used for the construction of hexahydrodipyrrins **50**, in a study directed toward the construction of Corrins **51**, a class of natural products having interesting biological activities, in particular a potential utility in photodynamic therapy (Scheme 16).[21]



48 **49** **50** **(*H*$_6$)-Dipyrrins (51)**

Scheme 16: *Reagents and conditions:* a) $Pd(PPh_3)_4$, THF, rt (or) Pd_2dba_3, TFP, MeCN, 80 °C, 70-85%.

The cyclization reaction of *o*-alkynyltrifluoroacetanilides **52** promoted by various organopalladium complexes generated *in situ* from C*sp*2 donors such as aryl and vinyl halides (or triflates), as well as allyl esters and alkyl halides have been thoroughly developed by Cacchi (Scheme 17).[22] It allowed for the preparation of a large variety of functionalized indole derivatives **53**.

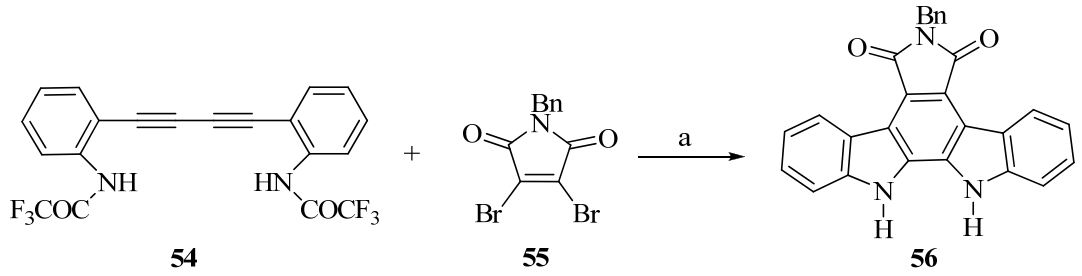


52 **53**

Scheme 17: *Reagents and conditions:* a) R^2X, $Pd(PPh_3)_4$, K_2CO_3, MeCN, 20-80 °C.

Based on the same strategy, the indolo[2,3-*a*]carbazole ring system **56**, common to Arcyriaflavin A and Rebeccamycin was prepared by palladium(0)-catalyzed poly annulation of diacetylene **54** with *N*-benzyl-3,4-dibromomaleimide **55**,

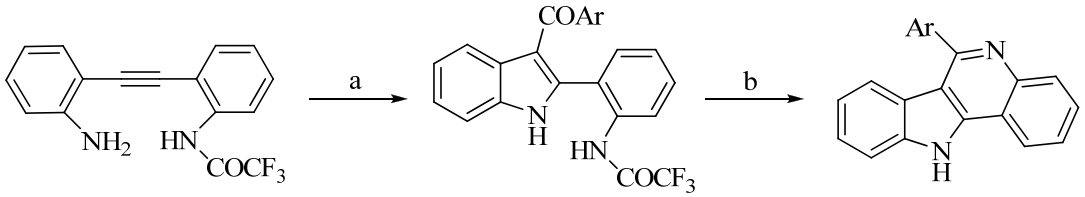
wherein two carbon-carbon, and two nitrogen-carbon bonds were formed in a single step (Scheme 18).[23]



54 **55** **56**

Scheme 18: *Reagents and conditions:* a) $Pd(PPh_3)_4$, K_2CO_3, MeCN, 50 °C, 52%.

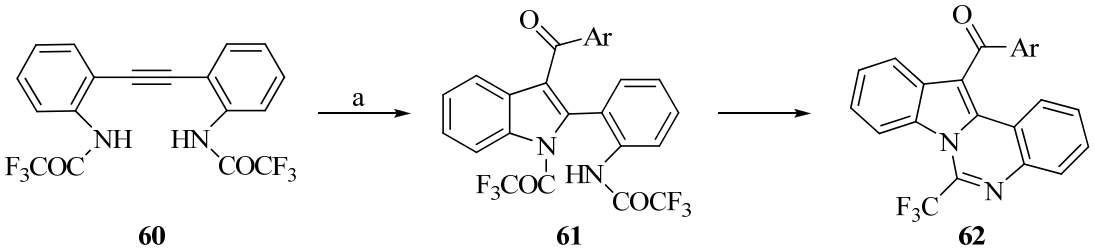
When the carbonylation of aryl iodides was performed in the presence of o-(*o*-aminophenyl) trifluoroacetanilide **57**, the palladium-catalyzed carbonylative cyclization was followed by the intramolecular reaction of the amino group on the 3-acylindole intermediate **58** to afford 6-aryl-11*H*-indolo[3,2-*c*]quinolines **59** in moderate to good yields (Scheme 19).[24]



57 **58** **59**

Scheme 19: *Reagents and conditions:* a) ArI, $Pd(PPh_3)_4$, K_2CO_3, MeCN, 50 °C, CO(3 atm); b) K_2CO_3, MeOH/H_2O, 80 °C, 35-86%.

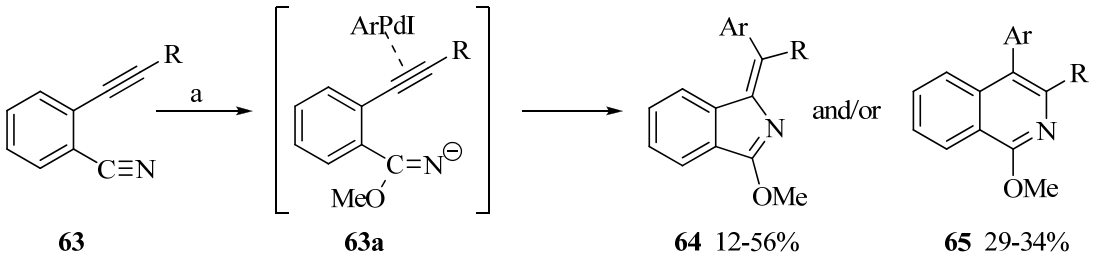
Interestingly, the same reaction developed on bis(*o*-trifluoro acetamidophenyl)acetylene **60** led to the formation 12-acylindolo[1,2-*c*]quinazolines **62**,[25] *via* the intermediate indole **61**, by intramolecular nucleophilic attack of the *ortho* nitrogen to the carbonyl of the indole trifluoroacetyl group (Scheme 20).



60 **61** **62**

Scheme 20: *Reagents and conditions:* a) ArI, CO, $Pd(PPh_3)_4$, K_2CO_3,DMSO, 50 °C, 34-98%.

The reaction of 2-alkynylbenzonitriles **63** with sodium methoxide and phenyl iodide, or other aryl iodides bearing electron-donating substituents, was developed using $Pd(PPh_3)_4$ as catalyst for the formation of five or/and six membered ring heterocycles, namely the isoindoles **64** and isoquinolines **65** respectively. The product distribution was shown to be dependent on the nature of the substituent on the terminal alkyne carbon (Scheme 21).[26]



63 **63a** **64** 12-56% **65** 29-34%

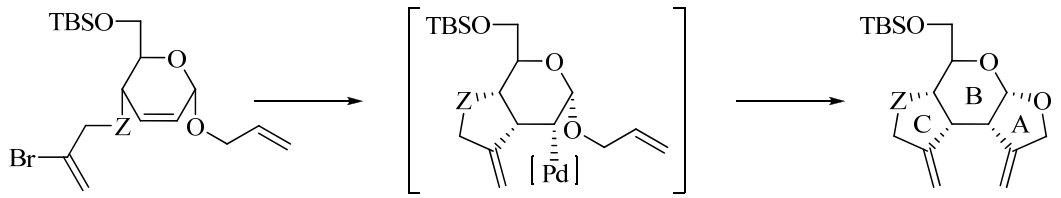
Scheme 21: *Reagents and conditions:* a) ArI, $Pd(PPh_3)_4$, Na/MeOH, reflux.

Cycloisomerisations on sugar templates:

Besides the above transformations, palladium catalyzed cycloisomerizations on sugar derived templates deserves a special mention, which is rather a remote area. Monosaccharides provide an excellent platform to tailor molecular diversity by appending desired substituents at selected positions around the sugar scaffold. The presence of five functionalized and stereocontrolled centres on the sugar scaffolds gives the chemist plenty of scope to custom design molecules to a pharmacophore model. In the current era of genomics, proteomics, glycomics and other –omics, the exponential increase in potential therapeutic targets is placing an ever-increasing demand on access to novel and diverse chemical libraries. The importance of carbohydrates in biochemistry, in medicinal chemistry, and in the various aspects of life processes coupled with the charm and structural diversity of their multichiral architecture have long challenged synthetic chemists toward a multitude of approaches to this rich class of compounds. The search for novel stereoselective and versatile methodologies to ascend the carbohydrate series represents an important goal of sugar research.

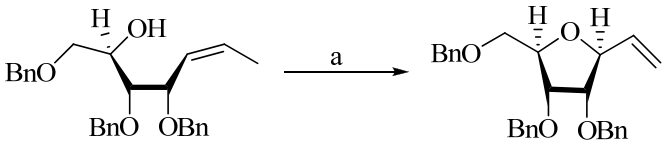
Over the past few years, the use of transition metal complexes has provided important new methodologies for the stereospecific elaboration of a variety of carbo- and heterocyeles, sometimes *via* cascade reactions. Despite the precise stereochemistry and rich functionality of the carbohydrate core in the synthesis of polycyclic molecules, the use of sugar templates for such organometallic-catalyzed stereoselective cyclization remains still quite rare. Some examples of homochiral substituted cyclopentanes and their heterocyclic analogues were prepared *via* palladium-mediated cyclization of the appropriate pseudoglycals. Bis-annulated pyranosides were also obtained by the Pauson-Khand reaction.[27] The carbohydrate derivatives **66** were converted into the corresponding bis-annulated pyranosides **67** *via* a 5-*exo* trig cascade cyclization, in the presence of a catalytic amount of $Pd(OAc)_2$ and PPh_3, under Jeffery's conditions, in quite good yields (Scheme 22).

1.



Scheme 22: Pd-mediated cascade cycliszations on sugar templates.

The increasing interest in bio-active carbohydrates stems from a new appreciation that carbohydrates can play an important role in normal and disease processes. Advances made in the understanding of glycobiology, led to the development of the synthetic routes to several glycosyl mimics such as *C*-glycosides, *C*-nucleosides etc. An intramolecular oxidative cyclization protocol, making use of the $Pd(OAc)_2$-NaOAc-O_2 system in DMSO, has been developed for the efficient conversion of sugar derived δ-olefinic alcohols into the *C*-vinyl furanoside class of compounds **69** (Scheme 23).[28]



68 **69**

Scheme 23: *Reagents and conditions:* a) $Pd(OAc)_2$-NaOAc-O_2, DMSO, 81%.

The monosaccharide-based scaffold contains four to five chiral, functionalized positions. In principle, various substituents can be appended at each position and chirality at that centre can be altered. Sugar scaffolds provide an unparalleled opportunity to generate libraries of high functional and structural diversity. If, for example, three different pharmacophore groups (read substituents) are positioned on glucose, 60 unique products are formed, all with similar molecular properties (e.g. same molecular weight and same type of functional groups) but with different orientations of the pharmacophore groups, which is achieved by just altering the position of each substituent (A, B and C) around the scaffold. In the mid-1970s, Vasella reported the 1,3-dipolar cycloaddition reactions of nitrones incorporated into sugar templates.[29] The Vasella's studies were regarded as seminal for the development of the stereoselective organic reactions achieved on sugar templates. Sugar-template-based stereoselective reactions have been actively investigated by a number of groups, especially in the past ten years.[30] The sugar-based templates utilized for asymmetric synthesis are mainly classified into five-membered glycofuranosidic frameworks or six-membered glycopyranosidic frameworks. Among glycofuranosidic templates, the utility of so-called diacetone-D-glucose i.e., 1,2:5,6-di-*O*-isopropylidene-*α*-D-glucofuranose has been extensively investigated.

Conclusions:

Palladium-catalyzed cyclization processes provide a powerful methodology for the elaboration of carbocyclic as well as heterocyclic derivatives, allowing for example the stereoselective formation of bridged rings or spirocycles. Recent studies in our laboratory were concerned with the use of palladium as a tool for the stereoselective transformation of carbohydrates. Pd mediated cyclizations on sugar derived templates comprise a very remote as well as a dormant area wherein several

carbon frameworks could be devised with an ease which would otherwise seem to be difficult using the conventional methods of carbon-carbon bond formation.

Hence devising a common strategy for sugar templates that enables suitable conditions for the synthesis of a plethora of compounds that would constitute a library of compounds is targeted. Further editing the target molecule *via* functional group modifications i.e., the preparation of analogues may provide sufficient insight into the biological activity of a particular compound/molecule.

Present Work

As the exploration of the properties of complex natural products becomes increasingly more sophisticated with the technological advances being made in their screening and evaluation and as structural details of their interaction with biological targets becomes more accessible, the importance and opportunities for providing unique solutions to complex biological problems has grown. Recent disclosures describing the unique structures and biological activities of recently isolated spiroketals like Cyclodidemniserinol trisulfate (**70**), Didemniserinolipid B (**71**) and Integrastatin (**72**) having prominent HIV-1 integrase inhibitory activity have generated much excitement in the chemical and pharmaceutical communities (Figure 2).[31] In search of better anti-retroviral chemotherapy, these compounds are emerged as potential targets for total synthesis on one hand as key pharmacophores on which the new leads can be build up. Their isolation has motivated many research groups to begin programs aimed at developing efficient routes to these compounds.

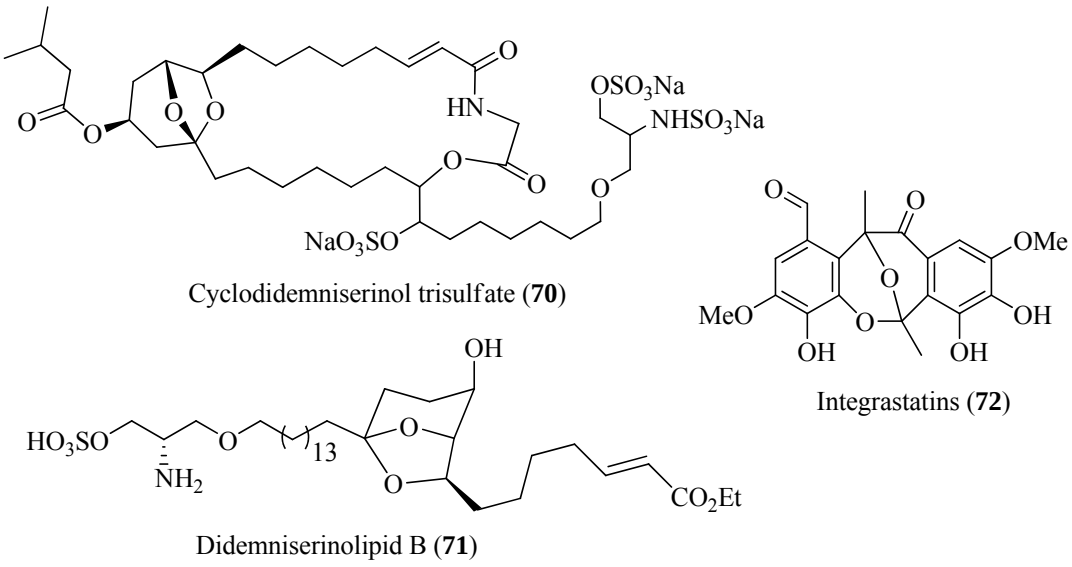


Figure 2: Novel HIV-Integrase inhibitors with spiroketal moieties.

Also, construction of architecturally complex molecules from simpler building blocks has emerged as a powerful tool in synthetic organic chemistry because of the increasing demand for molecules with unprecedented diversity. Transition metal-catalysed reactions belong to the powerful tools of contemporary organic synthesis.

They allow a considerable increase in the molecular complexity in a single operation and usually proceed with excellent chemo-, regio- and stereoselectivity. Designing effective routes to construct complex cyclic structures through organotransition-metal catalyzed reactions provides many attractive possibilities, which by conventional procedures would need a large number of synthetic transformations. Keeping the construction of densely functionalized bicyclic ketal as the main objective in this endeavour, validity and mechanistic investigations of palladium mediated cycloisomerisations[32] has been our goal. A great deal of focus has been directed towards sugar based molecular diversity as these molecules offer inherent rigidity and molecular asymmetry.

Although the primary significance of carbohydrates rests on their major importance in biology, they represent a unique family of polyfunctional compounds that can be chemically manipulated in a multitude of ways. Carbohydrates are used as valuable auxillaries in stereoselective synthesis. Hence sugar-based alkyne diols have been selected as the starting substrates owing to their ready availability and the ease of manipulation to bring about different functionalities. Organometallic chemistry, though widely used in organic chemistry, its impact on carbohydrate chemistry is still underdeveloped. A most attractive tactic in the requisite intramolecular heteroaromatic synthesis therefore would be to create the heterocycle *via* the projected palladium catalysed cycloisomerizations in sync with the carbohydrates which are long known in the literature for their charming multichiral architecture. It is pertinent to mention that the metal mediated hydroalkoxylation reactions of carbohydrate precursors have been less explored and mainly confined to glycals, *exo*-glycals and related derivatives. Cycloisomerization of alkynols is visualized as a tool to synthesize oxygen-containing heterocycles encompassing functionalized furan, pyran, benzopyran and spiroketal skeletons. Many of these cyclization studies occur *via* transition metal reactions of palladium, platinum, tungsten, molybdenum, ruthenium, rhodium, gold or iridium catalysts.[32]

Herein we describe the Pd(II) catalyzed cyclizations of various aryl substituted alkynes and the mode of intramolecular cyclizations of the alkynediols. The key issue in our intended strategy is the mode of cyclization *i.e.*, 6-*exo*-dig *vs.* 7-*endo*-dig.[33] There are several instances in the literature to indicate that the obtuse angle of 120–127° for the approach of a nucleophile to a triple bond triggers the

dominance of 6-*exo*-dig over 7-*endo*-dig for electronically unbiased acetylenes. However, the majority of theoretical and experimental studies reported to understand 6-*ex*o-dig *vs* 7-*endo*-dig cyclizations involve mainly the base mediated cyclization with hard nucleophiles, investigations dealing with metal catalyzed cyclizations[34] are however, rare (Figure 3).

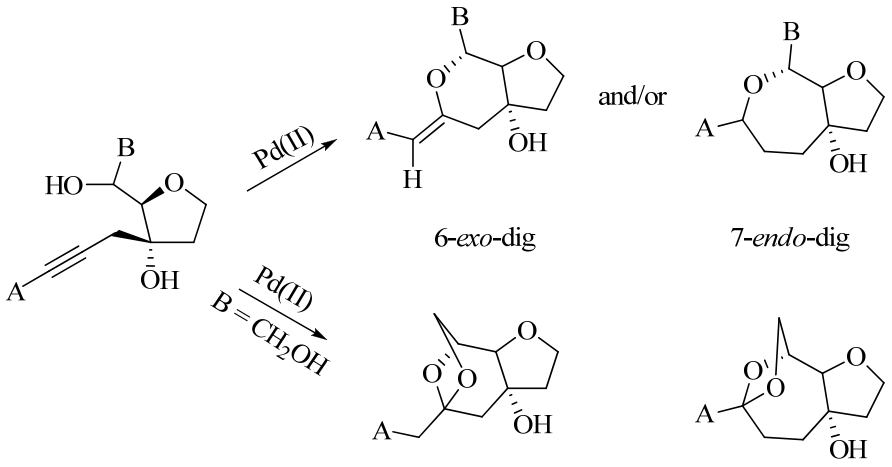
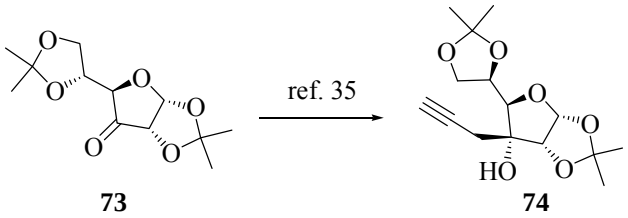


Figure 3: Key issue of *exo vs endo* dig cyclisations.

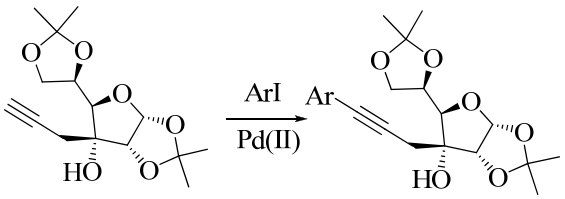
The utility of diacetone-D-glucose as a useful chiral template has been investigated wherein it was oxidized to the ulose derivative **73** using PDC as the oxidizing agent. The known 3-*C*-propargyl allofuranose derivative **74** prepared from the known ulose derivative **73** according to the literature procedure employing the Barbier reaction[35] conditions with propargyl bromide (Scheme 24).



73 **74**

Scheme 24:

The allofuranose **74** was chosen as the pivotal precursor that paved the way for the synthesis of differently substituted alkynes *via* the Sonogashira coupling[10] with different suitable aryl iodides. Accordingly the reaction was performed in a mixture of Et_3N:DMF (2:1) as the solvent using catalytic $Pd(PPh_3)_2Cl_2$ and CuI (Scheme 25).

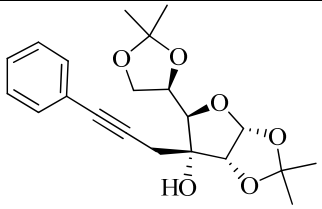
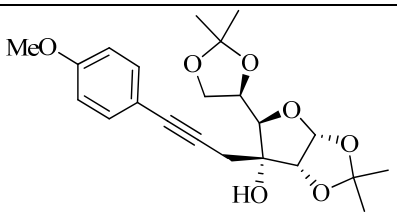
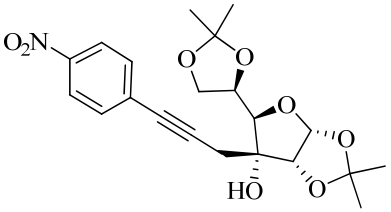


74

75 (Ar = Ph, 76%)
76 (Ar = 4-MeOPh, 70%)
77 (Ar = 4-O_2NPh, 63%)
78 (Ar = 3-O_2NPh, 67%)

Scheme 25: Sonogashira coupling on the parent alkyne.

All the substituted alkynes showed a similar pattern for the characteristic propargylic protons in the ^{1}H NMR as well as the acetylenic singlet carbons in the ^{13}C NMR spectra. The observations are tabulated below (Table 1).

Compound	^{1}H NMR values	^{13}C NMR values
 **75**	δ 2.75 and 2.94	79.0 and 84.0 ppm
 **76**	δ 2.74 and 2.86	79.2 and 90.8 ppm
 **77**	δ 2.72 and 2.98	79.0 and 90.4 ppm

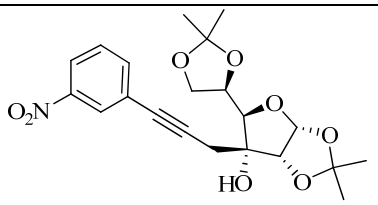
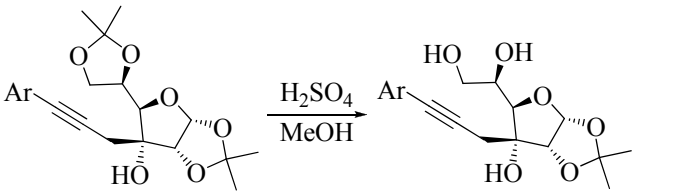
 **78**	δ 2.71 and 2.97	78.7 and 87.4 ppm

Table 1: Characteristic ^{1}H and ^{13}C chemical shifts of the alkynes.

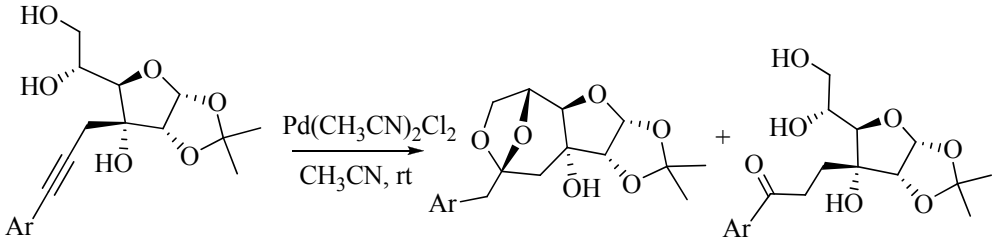
The selective hydrolysis of the terminal 5,6-acetonide group of **74** - **78** with cat. H_2SO_4 in methanol for 4 h completed the synthesis of projected cycloisomerization substrates **79 - 83** (Scheme 26).



79 (Ar = H, 79%)
80 (Ar = Ph, 75%)
81 (Ar = 4-MeOPh, 69%)
82 (Ar = 4-O_2NPh, 81%)
83 (Ar = 3-O_2NPh, 78%)

Scheme 26:

The results of the $Pd(CH_3CN)_2Cl_2$ catalyzed cycloisomerizations[4,32] of the 3-*C*-propargyl-*allo*-furanose derivatives **79-83** are shown in Scheme 27.



79	Ar = H	**84** (70%)	--
80	Ph	--	**85** (66%)
81	4-MeOPh	--	**86** (60%)
82	4-O_2NPh	**87** (70%)	--
83	3-O_2NPh	--	**88** (60%)

Scheme 27: Cyclisomerisation of the alkyne diols.

As indicated in Scheme 27, the cycloisomerization of monosubstituted alkynol **79** gave exclusively [3.2.1]bicyclic acetal **84**. The appearance of the methylene unit protons separately as doublets at δ 1.62 and 1.95 with large geminal coupling constant (14.7 Hz) in the ^{1}H NMR spectrum of **84** clearly indicates that this methylene unit has no coupled adjacent-H and thus establishing the assigned [3.2.1]bicyclic acetal structure. The presence of a quaternary carbon at 105.3 (s) ppm in the ^{13}C NMR spectrum corresponding to the ketal carbon further confirmed the assigned structure to **84**. The cycloisomerization of *p*-nitrophenyl substituted alkynol **82** also gave exclusively the *exo*-cyclic product **87** where the methylene protons resonated as doublets at δ 1.66 and 2.01 with large geminal coupling constant (14.4 Hz) in the ^{1}H NMR spectrum and the characteristic ketal carbon at 105.7 (s) ppm in the ^{13}C NMR spectrum. The characteristic peaks of the methylene unit in the ^{1}H NMR and of the ketal carbon in the ^{13}C NMR are tabulated below (Table 2).

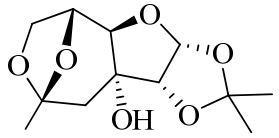
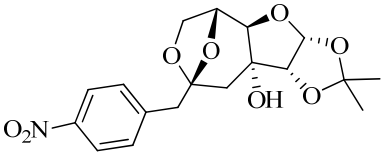
Compound	**^{1}H NMR values**	**^{13}C NMR values**
 **84**	δ 1.62 and 1.95	105.3 ppm
 **87**	δ 1.66 and 1.66 and 2.01	105.7 ppm

Table 2: Characteristic ^{1}H and ^{13}C chemical shifts of the bicyclic ketals.

The cycloisomerization of alkynols **80**, **81** and **83** gave exclusively the keto derivatives **85**, **86** and **88** respectively. The structure of **85** was deduced from the ^{1}H NMR spectrum where all the four methylene protons resonated separately as dd or ddd between δ 1.81–3.40 ppm thus displaying the through bond connectivity between all of them. The appearance of a carbon singlet in the range of 198-200

ppm in the ^{13}C NMR spectrum confirmed the presence of a carbonyl carbon. Characteristic NMR peaks of **85**, **86** and **88** are given in Table 3.

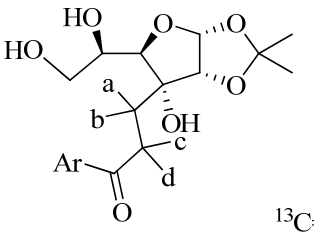
Ketone	Ar =	Ph (**85**)	4-MeOPh (**86**)	3-NO_2Ph (**88**)
	a	1.88	1.87	1.90
	b	2.30	2.30	2.31
	c	3.10	3.04	3.10
	d	3.39	3.33	3.40
	^{13}C=O	200.0	198.6	199.9

Table 3: Characteristic ^{1}H and ^{13}C chemical shifts of the ketones.

The formation of keto compounds with complete regioselectivity raised a couple of issues to be answered: a) could it be resulting either from the hydrolysis of the intermediate 7-*endo* products? or b) the regioselective alkyne hydration (path *i*, Figure 4)? or c) by the participation of a 3°-OH in a 5-*endo* manner and subsequent hydrolysis of intermediate dihydrofuran derivatives (path *ii*, Figure 4)? In the latter two instances, it looks as if the 7-*endo*- and *6-exo*-dig cyclizations with 2°-OH are relatively slower.

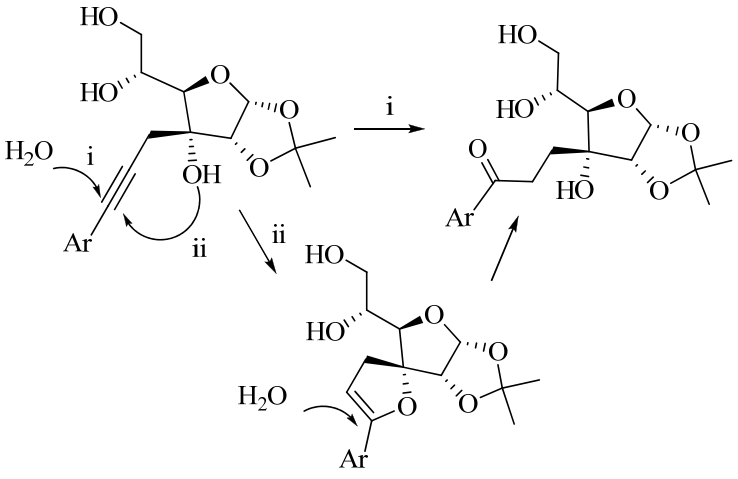
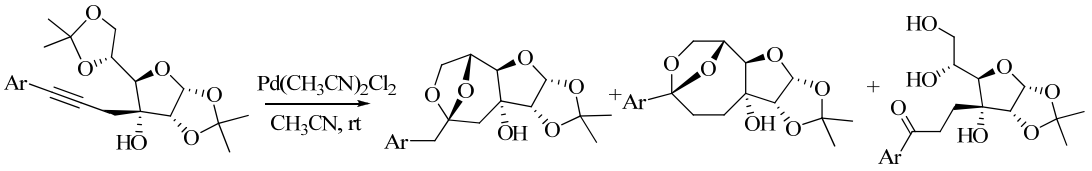


Figure 4: Possible modes of formation of the keto compounds.

The presence of a hydroxy group in position 3 of the sugar moiety should allow the design of a new route towards the development of scaffolds with spiroketal moieties. Based on the above intriguing results, cyclizing the 3-hydroxyl of the glucofuranose onto the alkyne keeping the acetonide intact should lead us to desired

spiroketals. In order to probe in this direction, we employed acetonides **74-78** as substrates for the cycloisomerization reactions. We invoked that results from these cycloisomerization reactions should atleast answer the issue of C(3)-OH participation.

The cycloisomerization of the alkynes **74**, **75** and **77** afforded **84**, **85** and **87** respectively. The 4-methoxyphenyl substituted alkyne **76** gave the 7-*endo* product **89** exclusively. The assigned structure for **89** was deduced from the NMR spectral analysis, wherein the four methylene protons resonated separately at δ 1.52, 2.05–2.21, 2.36–2.54 and 3.69 ppm in the ^{1}H NMR. The presence of a quaternary carbon at 110.7 (s) ppm in the ^{13}C NMR corresponding to the ketal carbon further confirmed the assigned structure to **89**. The 3-nitrophenyl substituted alkyne **78** gave the *exo* product **90** exclusively where the methylene protons corresponding to the [3.2.1]bicyclic acetal were seen at δ 1.69 and 2.03 ppm in the ^{1}H NMR while the ketal carbon was seen at 105.6 (s) ppm in the ^{13}C spectrum very much in correlation with the NMR data of the ketal **87** obtained with the 4-NO_2 derivative (Scheme 28).



74	Ar = H	**84** (58%)	–	--
75	Ph	--	–	**85** (64%)
76	4-MeOPh	--	**89** (56%)	–
77	4-O_2NPh	**87** (72%)	–	--
78	3-O_2NPh	**90** (72%)	–	–

Scheme 28: Cycloisomerisation of the alkyne acetonides.

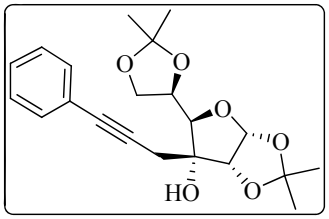
To summarize the cycloisomerization reactions of acetonides **74-78**, 4 out of 5 substrates employed gave bicyclic ketal products where the regiochemistry is entirely governed by electronic influence. These results obtained are quite surprising because the participation of ether oxygen in the cycloisomerization reactions, is rare. The isolation of bicyclic ketal **89**, resulting from an initial 7-*endo*-dig cyclization revealed that these products are stable. These results clearly indicate that the participation of a C(3)-OH in a 5-*endo* manner and hence the spiroketal formation can be ruled out and suggest that hydration is a competing reaction with the triol substrates **79-83**.

Conclusions:

Herein we report a systematic investigation which shows that the 6-*exo*/7-*endo* cyclization protocols in carbohydrate templates are possible and can be modulated to give polyhyroxylated heterocycles in enantiomerically pure form. The cycloisomerization of alkyne diols coupled to sugar templates aided us in devising a vast array of polyfunctionalized products well within the domain of regio- and stereoselectivity. These compounds present a high degree of molecular diversity which can be varied through modifications of the configuration of the stereocenters and the functionalities introduced on the scaffold by choice of suitable starting reagents. This new scaffold bears different points of substitution and therefore should be useful for the development of chemical libraries. The above set of cyclizations were extremely facile and the reaction conditions appeared to be more conducive. Being intramolecular in nature, they fulfill the desirable criterion for atom economy. And last but not the least they ensured ready access to the bicyclic [3.2.1] ketals which form a major structural entity in many natural products (discussed in the next chapter).

Experimental

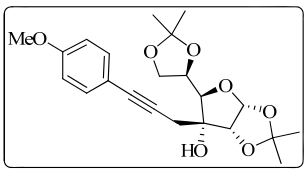
1,2:5,6-Di-*O*-isopropylidene-3-*C*-[3'-phenyl-prop-2'-ynyl]-*a*-D-allofuranose (75)



A solution of alkyne **74** (500 mg, 1.71 mmol), iodobenzene (291 mg, 1.42 mmol), Et_3N (6 mL), CuI (13 mg, 0.06 mmol), and $Pd(PPh_3)_2Cl_2$ (101 mg, 0.14 mmol) in DMF (3 mL) was flushed with argon for 30 min and stirred at rt for 2 h. The reaction mixture was taken in ethyl acetate, washed with water, brine, dried (Na_2SO_4) and concentrated. The crude extract was purified by column chromatography (10% ethyl acetate in petroleum ether) to obtain **75** (480 mg, 76%) as a yellow solid.

Mol. Formula	: $C_{21}H_{26}O_8$
M. P.	: 117–124 °C.
$[\alpha]_D$	: +5.8 (*c* 0.8, $CHCl_3$).
IR ($CHCl_3$) $\tilde{\nu}$	: 3305, 3020, 2936, 1384, 1216, 1084, 758, 669 cm^{-1}.
^{1}H NMR ($CDCl_3$, 200 MHz)	: δ 1.35 (s, 3H), 1.36 (s, 3H), 1.45 (s, 3H), 1.59 (s, 3H), 2.75 (d, *J* = 17.1 Hz, 1H), 2.88 (s, 1H), 2.94 (d, *J* = 17.1 Hz, 1H), 3.84 (d, *J* = 8.3 Hz, 1H), 3.93 (dd, *J* = 5.0, 8.3 Hz, 1H), 4.09-4.27 (m, 2H), 4.57 (d, *J* = 3.8 Hz, 1H), 5.80 (d, *J* = 3.8 Hz, 1H), 7.24-7.30 (m, 3H), 7.34-7.41 (m, 2H) ppm.
^{13}C NMR ($CDCl_3$, 50 MHz)	: δ 24.6 (t), 25.3 (q), 26.5 (q), 26.7 (q, 2C), 67.9 (t), 73.4 (d), 79.0 (s), 82.0 (d), 82.7 (d), 83.3 (s), 84.0 (s), 104.0 (d), 109.7 (s), 112.6 (s), 123.1 (s), 128.0 (d), 128.2 (d, 2C), 131.5 (d, 2C) ppm.
ESI-MS (*m/z*)	: 397.3 $[M+Na]^+$.
Elemental Analysis	Calcd.: C, 67.36; H, 7.00. Found: C, 67.19; H, 7.16.

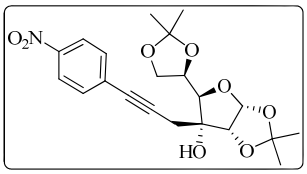
1,2:5,6-Di-*O*-isopropylidene-3-*C*-[3'-(4-methoxyphenyl)-prop-2'-ynyl]-*a*-D-allofuranose (76)



A solution of alkyne **74** (380 mg, 1.27 mmol), 1-iodo-4-methoxybenzene (291 mg, 1.42 mmol), Et_3N (6 mL), CuI (13 mg, 0.06 mmol), and $Pd(PPh_3)_2Cl_2$ (101 mg, 0.14 mmol) in DMF (3 mL) was flushed with argon for 30 min and stirred at rt for 4 h. The reaction mixture was taken in ethyl acetate, washed with water, brine, dried (Na_2SO_4) and concentrated. The crude extract was purified by column chromatography (10% ethyl acetate in petroleum ether) to obtain **76** (360 mg, 70%).

Mol. Formula	: $C_{22}H_{28}O_7$
$[\alpha]_D$	: +8.8 (*c* 1.1, $CHCl_3$).
IR ($CHCl_3$) $\tilde{\nu}$	: 3528, 3019, 1607, 1510, 1480, 1216, 1181, 835, 758 cm^{-1}.
^{1}H NMR ($CDCl_3$, 200 MHz)	: δ 1.35 (s, 3H), 1.36 (s, 3H), 1.44 (s, 3H), 1.59 (s, 3H), 2.74 (d, *J* = 17.0 Hz, 1H), 2.86 (d, *J* = 17.0 Hz, 1H), 2.86 (s, 1H), 3.78 (s, 3H), 3.84 (d, *J* = 8.3 Hz, 1H), 3.93 (dd, *J* = 5.1, 8.3 Hz, 1H), 4.08-4.27 (m, 2H), 4.56 (d, *J* = 3.8 Hz, 1H), 5.79 (d, *J* = 3.8 Hz, 1H), 6.79 (d, *J* = 8.8 Hz, 2H), 7.31 (d, *J* = 8.8 Hz, 2H) ppm.
^{13}C NMR ($CDCl_3$, 50 MHz)	: δ 24.7 (t), 25.4 (q), 26.6 (q), 26.8 (q, 2C), 55.2 (q), 68.1 (t), 73.5 (d), 79.2 (s), 82.1 (d), 82.3 (s), 82.8 (d), 90.8 (s), 104.2 (d), 109.8 (s), 112.7 (s), 113.9 (d, 2C), 115.3 (s), 133.0 (d, 2C), 159.4 (s) ppm.
ESI-MS (*m/z*)	: 427.3 $[M+Na]^+$.
Elemental Analysis	Calcd.: C, 65.33; H, 6.98.
	Found: C, 65.14; H, 7.14.

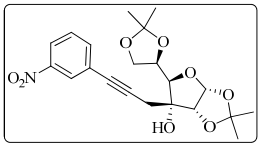
1,2:5,6-Di-*O*-isopropylidene-3-*C*-[3'-(4-nitrophenyl)-prop-2'-ynyl]-*a*-D-allofuranose (77)



A solution of alkyne **74** (426 mg, 1.43 mmol), 1-iodo-4-nitrobenzene (291 mg, 1.42 mmol), Et_3N (6 mL), CuI (13 mg, 0.06 mmol), and $Pd(PPh_3)_2Cl_2$ (101 mg, 0.14 mmol) in DMF (3 mL) was flushed with argon for 30 min and stirred at rt for 4 h. The reaction mixture was taken in ethyl acetate, washed with water, brine, dried (Na_2SO_4) and concentrated. The crude extract was purified by column chromatography (10% ethyl acetate in petroleum ether) to obtain **77** (380 mg, 63%).

Mol. Formula	: $C_{21}H_{25}NO_8$
$[\alpha]_D$	: 0.0 (*c* 1.0, $CHCl_3$).
IR ($CHCl_3$) $\tilde{\nu}$	: 3330, 2925, 1737, 1607, 1510, 1343, 1081, 855, 758 cm^{-1}.
^{1}H NMR ($CDCl_3$, 200 MHz)	: δ 1.32 (s, 3H), 1.35 (s, 3H), 1.42 (s, 3H), 1.57 (s, 3H), 2.72 (d, *J* = 17.2 Hz, 1H), 2.93 (s, 1H), 2.98 (d, *J* = 17.2 Hz, 1H), 3.79 (dt, *J* = 2.7, 8.4 Hz, 1H), 3.90 (dt, *J* = 2.7, 8.4 Hz, 1H), 4.06-4.18 (m, 2H), 4.52 (d, *J* = 3.8 Hz, 1H), 5.76 (d, *J* = 3.8 Hz, 1H), 7.50 (dt, *J* = 2.4, 8.8 Hz, 2H), 8.11 (dt, *J* = 2.4, 8.8 Hz, 2H) ppm.
^{13}C NMR ($CDCl_3$, 50 MHz)	: δ 24.6 (t), 25.3 (q), 26.6 (q), 26.7 (q), 26.7 (q), 68.0 (t), 73.4 (d), 79.0 (s), 81.8 (d), 81.8 (s), 82.5 (d), 90.4 (s), 103.9 (d), 109.9 (s), 112.8 (s), 123.5 (d, 2C), 130.0 (s), 132.4 (d, 2C), 146.9 (s) ppm.
ESI-MS (*m/z*)	: 442.1 $[M+Na]^+$.
Elemental Analysis	Calcd.: C, 60.14; H, 5.96; N, 3.34. Found: C, 59.99; H, 5.83; N, 3.12.

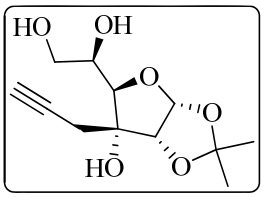
1,2:5,6-Di-*O*-isopropylidene-3-*C*-[3'-(3-nitrophenyl)-prop-2'-ynyl]-*a*-D-allofuranose (78)



A solution of alkyne **74** (640 g, 2.15 mmol), 1-iodo-3-nitrobenzene (291 mg, 1.42 mmol), Et_3N (6 mL), CuI (13 mg, 0.06 mmol), and $Pd(PPh_3)_2Cl_2$ (101 mg, 0.14 mmol) in DMF (3 mL) was flushed with argon for 30 min and stirred at rt for 4 h. The reaction mixture was taken in ethyl acetate, washed with water, brine, dried (Na_2SO_4) and concentrated. The crude extract was purified by column chromatography (10% ethyl acetate in petroleum ether) to obtain **78** (600 mg, 67%).

Mol. Formula	: $C_{21}H_{25}NO_8$
$[\alpha]_D$	: +3.1 (*c* 1.8, $CHCl_3$).
IR ($CHCl_3$) $\tilde{\nu}$	: 3552, 3020, 1532, 1375, 1216, 1075, 758, 669 cm^{-1}.
^{1}H NMR ($CDCl_3$, 200 MHz)	: δ 1.33 (s, 3H), 1.36 (s, 3H), 1.43 (s, 3H), 1.58 (s, 3H), 2.71 (d, *J* = 17.2 Hz, 1H), 2.94 (s, 1H), 2.97 (d, *J* = 17.2 Hz, 1H), 3.81 (dt, *J* = 2.9, 7.5 Hz, 1H), 3.91 (dt, *J* = 2.9, 7.5 Hz, 1H), 4.07-4.20 (m, 2H), 4.54 (d, *J* = 3.9 Hz, 1H), 5.77 (d, *J* = 3.9 Hz, 1H), 7.44 (t, *J* = 7.9 Hz, 1H), 7.67 (dt, *J* = 1.5, 7.9 Hz, 1H), 8.10 (ddd, *J* = 1.5, 2.4, 7.9 Hz, 1H), 8.20 (t, *J* = 1.5 Hz, 1H) ppm.
^{13}C NMR ($CDCl_3$, 50 MHz)	: δ 24.1 (t), 25.0 (q), 26.3 (q), 26.4 (q), 26.4 (q), 67.7 (t), 73.1 (d), 78.7 (s), 80.7 (s), 81.5 (d), 82.3 (d), 87.4 (s), 103.6 (d), 109.5 (s), 112.5 (s), 122.4 (d), 124.7 (s), 126.1 (d), 129.0 (d), 137.1 (d), 147.7 (s) ppm.
ESI-MS (*m/z*)	: 442.1 $[M+Na]^+$.
Elemental Analysis	Calcd.: C, 60.14; H, 5.96; N, 3.34.
	Found: C, 59.99; H, 6.08; N, 3.22.

1,2-*O*-Isopropylidene-3-*C*-[prop-2'-ynyl]-*a*-D-allofuranose (79)

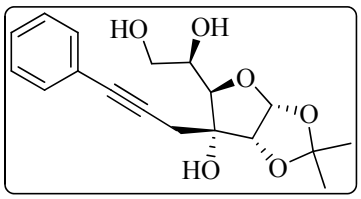


A solution of **74** (175 mg, 0.68 mmol) in MeOH (10 mL) was treated with dil. H_2SO_4 (10 mL, 0.8% in water) dropwise and stirred at rt for 5 h. The reaction mixture was quenched with $NaHCO_3$ (0.8 g), concentrated under reduced pressure. The residue was portioned between ethyl acetate-water and the aqueous layer was extracted with ethyl acetate. The combined organic layers were dried (Na_2SO_4) and concentrated. The crude extract was purified by column chromatography (60% ethyl acetate in petroleum ether) to obtain **79** (120 mg, 79%).

Mol. Formula	: $C_{12}H_{18}O_6$
$[\alpha]_D$	: +25.8 (*c* 1.0, $CHCl_3$).
IR ($CHCl_3$) $\tilde{\nu}$	: 3449, 2986, 1987, 1375, 1245, 1047, 874, 758, 669 cm^{-1}.
^{1}H NMR	: δ 1.35 (s, 3H), 1.58 (s, 3H), 2.09 (t, *J* = 2.6 Hz, 1H), 2.50

($CDCl_3$, 200 MHz)	(dd, *J* = 2.6, 17.2 Hz, 1H), 2.78 (dd, *J* = 2.6, 17.2 Hz, 1H), 3.21 (br s, 1H), 3.54-3.81 (m, 4H), 3.81 (br s, 2H), 4.50 (d, *J* = 3.8 Hz, 1H), 5.73 (d, *J* = 3.8 Hz, 1H) ppm.
^{13}C NMR	: δ 23.0 (t), 26.4 (q, 2C), 64.3 (t), 70.0 (d), 71.6 (d), 79.0
($CDCl_3$, 50 MHz)	(d), 82.1 (d), 83.2 (s), 90.5 (s), 103.5 (d), 112.9 (s) ppm.
ESI-MS (*m/z*)	: 281.1 $[M+Na]^+$.
Elemental Analysis	Calcd.: C, 55.81; H, 7.02.
	Found: C, 56.01; H, 7.18.

1,2-*O*-Isopropylidene-3-*C*-[3'-(phenyl)-prop-2'-ynyl]-*a*-D-allofuranose (80)

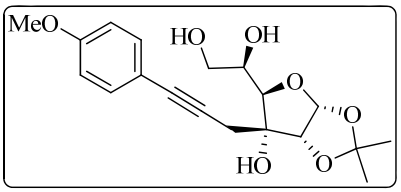


A solution of **75** (90 mg, 0.27 mmol) in MeOH (10 ml) was treated with dil. H_2SO_4 (10 ml, 0.8% in water) dropwise and stirred at rt for 5 h. The reaction mixture was quenched with $NaHCO_3$ (0.8 g), concentrated under reduced pressure. The residue was portioned between ethyl acetate-water and the aqueous layer was extracted with ethyl acetate. The combined organic layers were dried (Na_2SO_4) and concentrated. The crude extract was purified by column chromatography (50% ethyl acetate in petroleum ether) to obtain **80** (60 mg, 75%).

Mol. Formula	: $C_{18}H_{22}O_6$
M. P.	: 115–119 °C.
$[\alpha]_D$	: +22.7 (*c* 1.0, $CHCl_3$).
IR ($CHCl_3$) $\tilde{\nu}$	: 3439, 3020, 1385, 1216, 1084, 757, 669 cm^{-1}.
^{1}H NMR	: δ 1.34 (s, 3H), 1.57 (s, 3H), 2.75 (d, *J* = 17.2 Hz, 1H),
($CDCl_3$, 200 MHz)	2.97 (d, *J* = 17.2 Hz, 1H), 3.29 (br s, 3H), 3.66-3.89 (m, 4H), 4.55 (d, *J* = 3.7 Hz, 1H), 5.79 (d, *J* = 3.7 Hz, 1H), 7.25-7.28 (m, 2H), 7.37-7.54 (m, 3H) ppm.
^{13}C NMR	: δ 24.1 (t), 26.5 (q), 26.5 (q), 64.3 (t), 70.1 (d), 79.2 (d),
($CDCl_3$, 50 MHz)	79.3 (s), 82.4 (d), 83.4 (s), 84.2 (s), 103.7 (d), 112.8 (s), 123.0 (s), 128.1 (d), 128.2 (d, 2C), 131.6 (d, 2C) ppm.
ESI-MS (*m/z*)	: 357.2 $[M+Na]^+$.

Elemental Analysis Calcd.: C, 64.66; H, 6.63.
Found: C, 64.69; H, 6.89.

1,2-*O*-Isopropylidene-3-*C*-[3'-(4-methoxy-phenyl)-prop-2'-ynyl]-*a*-D-allofuranose (81)



A solution of **76** (80 mg, 0.22 mmol) in MeOH (10 ml) was treated with dil. H_2SO_4 (10 ml, 0.8% in water) dropwise and stirred at rt for 5 h. The reaction mixture was quenched with $NaHCO_3$ (0.8 g), concentrated under reduced pressure. The residue was portioned between ethyl acetate-water and the aqueous layer was extracted with ethyl acetate. The combined organic layers were dried (Na_2SO_4) and concentrated. The crude extract was purified by column chromatography (50% ethyl acetate in petroleum ether) to obtain **81** (50 mg, 69%).

Mol. Formula : $C_{19}H_{24}O_7$

M. P. : 130–132 °C.

$[\alpha]_D$: +21.9 (*c* 1.3, $CHCl_3$).

IR ($CHCl_3$) $\tilde{\nu}$: 3477, 3019, 1464, 1384, 1246, 1034, 728, 669 cm^{-1}.

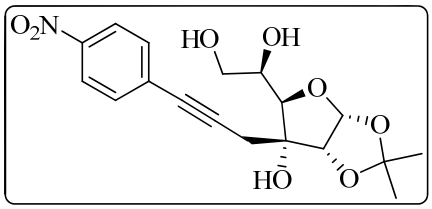
^{1}H NMR ($CDCl_3$, 400 MHz) : δ 1.37 (s, 3H), 1.59 (s, 3H), 2.67 (br s, 1H), 2.76 (d, *J* = 17.0 Hz, 1H), 2.94 (d, *J* = 17.0 Hz, 1H), 3.08 (br s, 1H), 3.70 (dd, *J* = 4.8, 11.5 Hz, 1H), 3.79 (s, 3H), 3.81-3.87 (m, 2H), 3.72 (br s, 1H), 3.94-4.02 (m, 1H), 4.52 (d, *J* = 3.9 Hz, 1H), 5.79 (d, *J* = 3.9 Hz, 1H), 6.80 (d, *J* = 8.9 Hz, 2H), 7.33 (d, *J* = 8.9 Hz, 2H) ppm.

^{13}C NMR ($CDCl_3$, 100 MHz) : δ 24.1 (t), 26.5 (q), 26.6 (q), 55.2 (q), 64.4 (t), 70.0 (d), 79.3 (d), 79.4 (s), 82.5 (s), 82.5 (d), 83.3 (s), 103.7 (d), 112.8 (s) 113.9 (d, 2C), 115.0 (s), 133.0 (d, 2C), 159.5 (s) ppm.

ESI-MS (*m/z*) : 387.2 $[M+Na]^+$.

Elemental Analysis Calcd.: C, 62.63; H, 6.64.
Found: C, 62.61; H, 6.41.

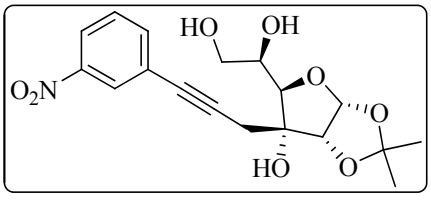
1,2-*O*-Isopropylidene-3-*C*-[3'-(4-nitrophenyl)-prop-2'-ynyl] -*a*-D-allofuranose (82)



A solution of **77** (150 mg, 0.39 mmol) in MeOH (10 ml) was treated with dil. H_2SO_4 (10 ml, 0.8% in water) dropwise and stirred at rt for 5 h. The reaction mixture was quenched with $NaHCO_3$ (0.8 g), concentrated under reduced pressure. The residue was portioned between ethyl acetate-water and the aqueous layer was extracted with ethyl acetate. The combined organic layers were dried (Na_2SO_4) and concentrated. The crude extract was purified by column chromatography (50% ethyl acetate in petroleum ether) to obtain **82** (110 mg, 81%).

Mol. Formula	: $C_{18}H_{21}NO_8$
$[\alpha]_D$	: +16.5 (*c* 0.8, $CHCl_3$).
IR ($CHCl_3$) $\tilde{\nu}$	: 3436, 3020, 1595, 1345, 1216, 1084, 750, 669 cm^{-1}.
^{1}H NMR ($CDCl_3$, 500 MHz)	: δ 1.36 (s, 3H), 1.58 (s, 3H), 2.77 (d, *J* = 17.3 Hz, 1H), 3.05 (d, *J* = 17.3 Hz, 1H), 3.47 (br s, 3H), 3.68-3.88 (m, 4H), 4.54 (d, *J* = 3.9 Hz, 1H), 5.80 (d, *J* = 3.9 Hz, 1H), 7.53 (dt, *J* = 2.2, 8.8 Hz, 2H), 8.13 (dt, *J* = 2.2, 8.8 Hz, 2H) ppm.
^{13}C NMR ($CDCl_3$, 125 MHz)	: δ 24.1 (t), 26.4 (q, 2C), 64.3 (t), 70.1 (d), 79.0 (d), 79.2 (s), 81.8 (s), 82.1 (d), 90.3 (s), 103.6 (d), 112.9 (s) 123.5 (d, 2C), 129.9 (s), 132.4 (d, 2C), 146.9 (s) ppm.
ESI-MS (*m/z*)	: 402.0 $[M+Na]^+$.
Elemental Analysis	Calcd.: C, 56.99; H, 5.58; N, 3.69. Found: C, 56.81; H, 5.45; N, 3.49.

1,2-*O*-Isopropylidene-3-*C*-[3'-(3-nitrophenyl)-prop-2'-ynyl]-α-D-allofuranose (83)

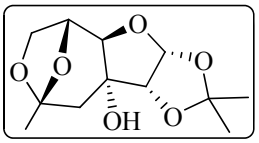


A solution of **78** (100 mg, 0.26 mmol) in MeOH (10 ml) was treated with dil. H_2SO_4 (10 ml, 0.8% in water) dropwise and stirred at rt for 5 h. The reaction mixture was quenched with $NaHCO_3$ (0.8 g), concentrated under reduced pressure. The

residue was portioned between ethyl acetate–water and the aqueous layer was extracted with ethyl acetate. The combined organic layers were dried (Na_2SO_4) and concentrated. The crude extract was purified by column chromatography (50% ethyl acetate in petroleum ether) to obtain **83** (70 mg, 78%).

Mol. Formula	: $C_{18}H_{21}NO_8$
$[\alpha]_D$	: +41.1 (*c* 2.0, $CHCl_3$).
IR ($CHCl_3$) $\tilde{\nu}$	: 3436, 3081, 1520, 1376, 1217, 1097, 758, 669 cm^{-1}.
^{1}H NMR ($CDCl_3$, 200 MHz)	: δ 1.36 (s, 3H), 1.58 (s, 3H), 2.74 (d, *J* = 17.3 Hz, 1H), 3.05 (d, *J* = 17.3 Hz, 1H), 3.37 (br s, 3H), 3.67-3.88 (m, 4H), 4.56 (d, *J* = 3.9 Hz, 1H), 5.79 (d, *J* = 3.9 Hz, 1H), 7.44 (t, *J* = 8.2 Hz, 1H), 7.69 (dt, *J* = 1.0, 8.2 Hz, 1H), 8.10 (ddd, *J* = 1.0, 1.9, 8.2 Hz, 1H), 8.21 (t, *J* = 1.9 Hz, 1H) ppm.
^{13}C NMR ($CDCl_3$, 50 MHz)	: δ 24.1 (t), 26.5 (q), 26.5 (q), 64.3 (t), 70.1 (d), 79.2 (d), 79.3 (s), 82.4 (d), 83.3 (s), 84.2 (s), 103.7 (d), 112.8 (s), 123.0 (s), 128.1 (s), 128.2 (d, 2C), 131.6 (d, 2C) ppm.
ESI-MS (*m/z*)	: 402.3 $[M+Na]^+$.
Elemental Analysis	Calcd.: C, 56.99; H, 5.58; N, 3.69.
	Found: C, 56.81; H, 5.25; N, 3.40.

1,2-*O*-Isopropylidene-3-*C*-(2'-oxopropyl)]-*a*-D-allofuranose-(2'-*C*,5-*O*,6-*O*)-ketal (84)

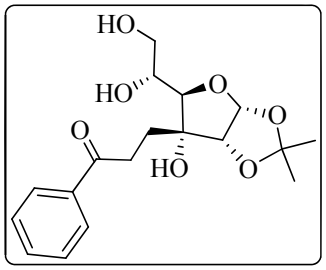


To a solution of **79** (50 mg, 0.19 mmol) in acetonitrile (10 ml) was added $Pd(CH_3CN)_2Cl_2$ (11 mg, 0.04 mmol) and the reaction mixture was stirred at rt under argon atmosphere for 1 h. The reaction mixture was concentrated and purified by silica gel chromatography (40% ethyl acetate in petroleum ether) to obtain **84** (35 mg, 70%) as a white solid.

Mol. Formula	: $C_{12}H_{18}O_6$
M. P.	: 139–140 °C.
$[\alpha]_D$	: –3.8 (*c* 2.2, $CHCl_3$).
IR ($CHCl_3$) $\tilde{\nu}$	: 3538, 3020, 1386, 1216, 1052, 730, 669 cm^{-1}.
^{1}H NMR	: δ 1.32 (s, 3H), 1.45 (s, 3H), 1.54 (s, 3H), 1.62 (d, *J* =

($CDCl_3$, 500 MHz)	14.7 Hz, 1H), 1.95 (d, *J* = 14.7 Hz, 1H), 3.04 (s, 1H), 3.70 (s, 1H), 3.82 (dd, *J* = 5.9, 7.2 Hz, 1H), 4.05 (d, *J* = 3.7 Hz, 1H), 4.13 (d, *J* = 7.2 Hz, 1H), 4.65 (d, *J* = 5.9 Hz, 1H), 5.82 (d, *J* = 3.7 Hz, 1H) ppm.
^{13}C NMR	: δ 24.0 (q), 26.6 (q), 26.8 (q), 41.8 (t), 65.2 (t), 73.7 (d),
($CDCl_3$, 125 MHz)	74.8 (s), 77.6 (d), 83.7 (d), 103.9 (d), 105.3 (s), 112.7 (s) ppm.
ESI-MS (*m/z*)	: 281.2 $[M+Na]^+$.
Elemental Analysis	Calcd.: C, 55.81; H, 7.02.
	Found: C, 55.67; H, 7.36.

1,2-*O*-Isopropylidene-3-*C*-[3'-oxo-3'-(phenyl)-propyl]-*a*-D-allofuranose (85)



To a solution of **80** (130 mg, 0.39 mmol) in acetonitrile (10 ml) was added $Pd(CH_3CN)_2Cl_2$ (11 mg, 0.04 mmol) and the reaction mixture was stirred at rt under argon atmosphere for 2 h. The reaction mixture was concentrated and purified by silica gel chromatography (40% ethyl acetate in petroleum ether) to obtain **85** (90 mg, 66%).

Mol. Formula	: $C_{18}H_{24}O_7$
$[\alpha]_D$	: +35.4 (*c* 2.0, $CHCl_3$).
IR ($CHCl_3$) $\tilde{\nu}$	: 3439, 3020, 1683, 1385, 1216, 1083, 758, 669 cm^{-1}.
^{1}H NMR	: δ 1.31 (s, 3H), 1.56 (s, 3H), 1.88 (ddd, *J* = 5.7, 8.3, 14.5
($CDCl_3$, 500 MHz)	Hz, 1H), 2.29 (br s, 1H), 2.30 (ddd, *J* = 6.1, 8.5, 14.5 Hz, 1H), 3.09 (br s, 1H), 3.10 (ddd, *J* = 5.7, 8.3, 14.5 Hz, 1H), 3.39 (ddd, *J* = 6.1, 8.5, 14.5 Hz, 1H), 3.40 (br s, 1H), 3.65 (dd, *J* = 3.7, 10.9 Hz, 1H), 3.80-3.86 (m, 3H), 4.25 (d, *J* = 3.7 Hz, 1H), 5.74 (d, *J* = 3.7 Hz, 1H), 7.39-7.51 (m, 3H), 7.93-7.98 (m, 2H) ppm.
^{13}C NMR	: δ 24.4 (t), 26.3 (q), 26.5 (q), 32.4 (t), 64.5 (t), 69.8 (d),
($CDCl_3$, 125 MHz)	79.2 (s), 79.4 (d), 80.9 (d), 103.4 (d), 112.7 (s), 128.0 (d,

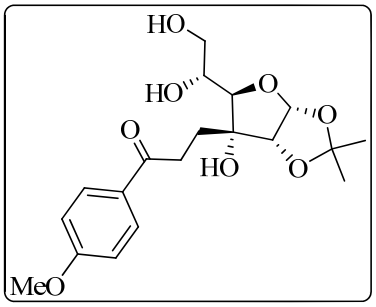
2C), 128.6 (d, 2C), 133.2 (d), 136.6 (s), 200.0 (s) ppm.

ESI-MS (*m/z*) : 375.3 $[M+Na]^+$.

Elemental Analysis Calcd.: C, 61.35; H, 6.86.

Found: C, 61.19; H, 7.04.

1,2-*O*-Isopropylidene-3-*C*-[3'-oxo-3'-(4-methoxyphenyl)-propyl]-*a*-D-allofuranose (86)



To a solution of **81** (40 mg, 0.11 mmol) in acetonitrile (10 ml) was added $Pd(CH_3CN)_2Cl_2$ (11 mg, 0.04 mmol) and the reaction mixture was stirred at rt under argon atmosphere for 4 h. The reaction mixture was concentrated and purified by silica gel chromatography (40% ethyl acetate in petroleum ether) to obtain **86** (25 g, 60%).

Mol. Formula : $C_{19}H_{26}O_8$

$[\alpha]_D$: +12.0 (*c* 0.8, $CHCl_3$)

IR (Neat) $\tilde{\nu}$: 3437, 2927, 1671, 1376, 1218, 1084, 771, 669 cm^{-1}.

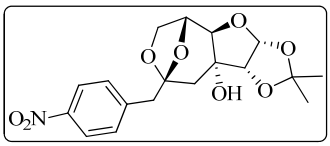
^{1}H NMR ($CDCl_3$, 400 MHz) : δ 1.31 (s, 3H), 1.55 (s, 3H), 1.87 (ddd, *J* = 5.9, 8.2, 14.5 Hz, 1H), 2.30 (ddd, *J* = 6.2, 8.3, 14.8 Hz, 1H), 3.04 (ddd, *J* = 5.9, 8.2, 14.5 Hz, 1H), 3.05 (br s, 1H), 3.29 (br s, 1H), 3.33 (ddd, *J* = 6.2, 8.3, 14.8 Hz, 1H), 3.65 (dd, *J* = 3.8, 10.8 Hz, 1H), 3.75-3.85 (m, 3H), 3.83 (s, 3H), 3.83 (br s, 1H), 4.25 (d, *J* = 3.8 Hz, 1H), 5.73 (d, *J* = 3.8 Hz, 1H), 6.90 (dt, *J* = 2.7, 8.9 Hz, 2H), 7.95 (dt, *J* = 2.7, 8.9 Hz, 2H).

^{13}C NMR ($CDCl_3$, 100 MHz) : δ 24.6 (t), 26.3 (q), 26.5 (q), 31.9 (t), 55.4 (q), 64.6 (t), 69.8 (d), 79.2 (s), 79.5 (d), 80.9 (d), 103.5 (d), 112.6 (s), 113.7 (d, 2C), 129.6 (s), 130.3 (d, 2C), 163.5 (s), 198.6 (s) ppm.

ESI-MS (*m/z*) : 405.1 $[M+Na]^+$.

Elemental Analysis Calcd.: C, 59.68; H, 6.85.
Found: C, 59.72; H, 6.70.

1,2-*O*-Isopropylidene-3-*C*-[2'-oxo-3'-(4-nitrophenyl)-propyl]-α-D-allofuranose-(2'-*C*,5-*O*,6-*O*)-ketal (87)



To a solution of **82** (50 mg, 0.13 mmol) in acetonitrile (10 ml) was added $Pd(CH_3CN)_2Cl_2$ (11 mg, 0.04 mmol) and the reaction mixture was stirred at rt under argon atmosphere for 6 h. The reaction mixture was concentrated and purified by silica gel chromatography (35% ethyl acetate in petroleum ether) to obtain **87** (35 mg, 70%).

Mol. Formula : $C_{18}H_{21}NO_8$

$[\alpha]_D$: +16.9 (*c* 2.2, $CHCl_3$).

IR ($CHCl_3$) $\tilde{\nu}$: 3462, 2985, 1638, 1374, 1241, 1047, 847, 634 cm^{-1}.

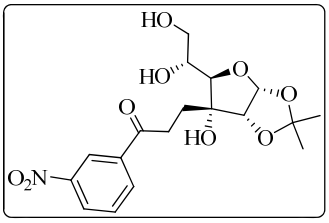
^{1}H NMR ($CDCl_3$, 200 MHz) : δ 1.35 (s, 3H), 1.56 (s, 3H), 1.66 (d, *J* = 14.4 Hz, 1H), 2.01 (d, *J* =14.4 Hz, 1H), 3.04 (d, *J* = 0.9 Hz, 1H), 3.10 (d, *J* = 16.3 Hz, 1H), 3.17 (d, *J* = 16.3 Hz, 1H), 3.55 (dd, *J* = 5.2, 7.2 Hz, 1H), 3.71 (br s, 1H), 4.09 (d, *J* = 3.7 Hz, 1H), 4.14 (d, *J* = 7.2 Hz, 1H), 4.62 (d, *J* = 5.2 Hz, 1H), 5.85 (d, *J* = 3.7 Hz, 1H), 7.44 (dt, *J* = 2.2, 8.7 Hz, 2H), 8.12 (dt, *J* = 2.2, 8.7 Hz, 2H) ppm.

^{13}C NMR ($CDCl_3$, 50 MHz) : δ 26.6 (q), 26.7 (q), 41.1 (t), 42.8 (t), 65.6 (t), 73.7 (d), 74.9 (s), 78.0 (d), 83.7 (d), 104.0 (d), 105.7 (s), 112.9 (s), 123.0 (d, 2C), 131.5 (d, 2C), 142.7 (s), 147.0 (s) ppm.

ESI-MS (*m/z*) : 402.1 $[M+Na]^+$.

Elemental Analysis Calcd.: C, 56.99; H, 5.58; N, 3.69.
Found: C, 56.84; H, 5.49; N, 3.44.

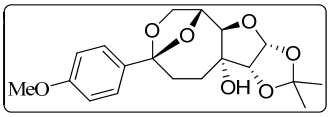
1,2-*O*-Isopropylidene-3-*C*-[3'-oxo-3'-(3-nitrophenyl)-propyl]-*a*-D-allofuranose (88)



To a solution of **83** (80 mg, 0.21 mmol) in acetonitrile (10 ml) was added $Pd(CH_3CN)_2Cl_2$ (11 mg, 0.04 mmol) and the reaction mixture was stirred at rt under argon atmosphere for 6 h. The reaction mixture was concentrated and purified by silica gel chromatography (40% ethyl acetate in petroleum ether) to obtain **88** (50 mg, 60%).

Mol. Formula	: $C_{18}H_{23}NO_9$
$[\alpha]_D$	: +11.4 (*c* 1.8, $CHCl_3$).
IR ($CHCl_3$) $\tilde{\nu}$	: 3439, 3020, 1683, 1385, 1216, 1083, 758, 669 cm^{-1}.
^{1}H NMR ($CDCl_3$, 200 MHz)	: δ 1.32 (s, 3H), 1.56 (s, 3H), 1.90 (ddd, *J* = 5.8, 8.3, 14.5 Hz, 1H), 2.31 (ddd, *J* = 6.2, 8.5, 14.8 Hz, 1H), 2.33 (br s, 1H), 3.10 (ddd, *J* = 5.8, 8.3, 14.5 Hz, 1H), 3.11 (br s, 1H), 3.39 (br s, 1H), 3.40 (ddd, *J* = 6.2, 8.5, 14.8 Hz, 1H), 3.66 (dd, *J* = 4.5, 11.4 Hz, 1H), 3.79-3.91 (m, 3H), 4.26 (d, *J* = 3.8 Hz, 1H), 5.75 (d, *J* = 3.8 Hz, 1H), 7.40-7.49 (m, 2H), 7.96 (dt, *J* = 1.5, 7.4 Hz, 1H), 8.81 (dt, *J* = 1.6, 5.1 Hz, 1H), ppm.
^{13}C NMR ($CDCl_3$, 50 MHz)	: δ 24.4 (t), 26.4 (q), 26.5 (q), 32.4 (t), 64.5 (t), 69.8 (d), 79.2 (s), 79.5 (d), 80.9 (d), 103.5 (d), 112.7 (s), 124.9 (d), 128.0 (d), 128.6 (d), 133.2 (s), 138.6 (d), 153.3 (s), 200.0 (s) ppm.
ESI-MS (*m/z*)	: 420.1 $[M+Na]^+$.
Elemental Analysis	Calcd.: C, 54.40; H, 5.83; N, 3.52.
	Found: C, 54.58; H, 5.55; N, 3.29.

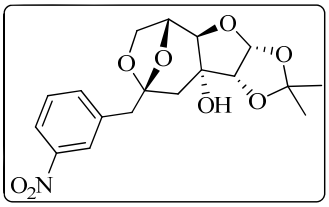
1,2-*O*-Isopropylidene-3-*C*-[3'-oxo-3'-(4-methoxyphenyl)propyl]-*a*-D-allofuranose-(3'-*C*,5-*O*,6-*O*)-ketal (89)



To a solution of **76** (50 mg, 0.12 mmol) in acetonitrile (10 ml) was added $Pd(CH_3CN)_2Cl_2$ (11 mg, 0.04 mmol) and the reaction mixture was stirred at rt under argon atmosphere for 6 h. The reaction mixture was concentrated and purified by silica gel chromatography (35% ethyl acetate in petroleum ether) to obtain **89** (25 mg, 56%) as a white solid.

Mol. Formula	: $C_{19}H_{24}O_7$
M. P.	: 175–178 °C.
$[\alpha]_D$	: -29.4 (*c* 1.0, $CHCl_3$).
IR ($CHCl_3$) $\tilde{\nu}$	: 3439, 3020, 1620, 1339, 1216, 929, 758, 669 cm^{-1}.
^{1}H NMR ($CDCl_3$, 200 MHz)	: δ 1.36 (s, 3H), 1.52 (dd, *J* = 5.0, 12.6 Hz, 1H), 1.61 (s, 3H), 2.05-2.21 (m, 2H), 2.36-2.54 (m, 1H), 3.69 (d, *J* = 8.3 Hz, 1H), 3.72 (d, *J* = 8.3 Hz, 1H), 3.79 (s, 3H), 3.98 (br s, 1H), 4.03 (d, *J* = 8.3 Hz, 1H), 4.20 (d, *J* = 3.7 Hz, 1H), 4.80 (br d, *J* = 5.3 Hz, 1H), 5.80 (d, *J* = 3.7 Hz, 1H), 6.84 (d, *J* = 8.9 Hz, 2H), 7.41 (d, *J* = 8.9 Hz, 2H) ppm.
^{13}C NMR ($CDCl_3$, 50 MHz)	: δ 26.2 (q), 26.7 (q), 28.4 (t), 36.6 (t), 55.2 (q), 65.5 (t), 76.7 (d), 79.5 (s), 81.7 (d), 85.9 (d), 102.7 (d), 110.7 (s), 112.8 (s), 113.5 (d, 2C), 125.8 (d, 2C), 135.0 (s), 159.4 (s) ppm.
ESI-MS (*m/z*)	: 387.1 $[M+Na]^+$.
Elemental Analysis	Calcd.: C, 62.63; H, 6.64.
	Found: C, 62.58; H, 6.62.

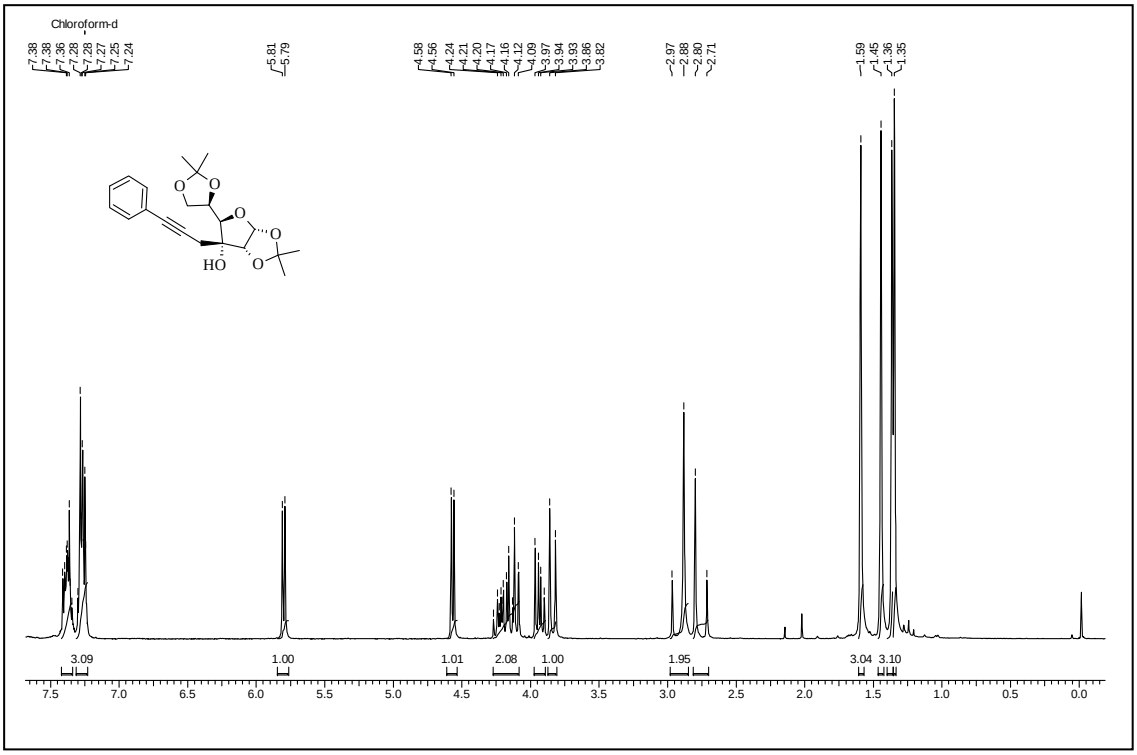
1,2-*O*-Isopropylidene-3-*C*-[2'-oxo-3'-(3-nitrophenyl)-propyl]-α-D-allofuranose-(2'-*C*,5-*O*,6-*O*)-ketal (90)



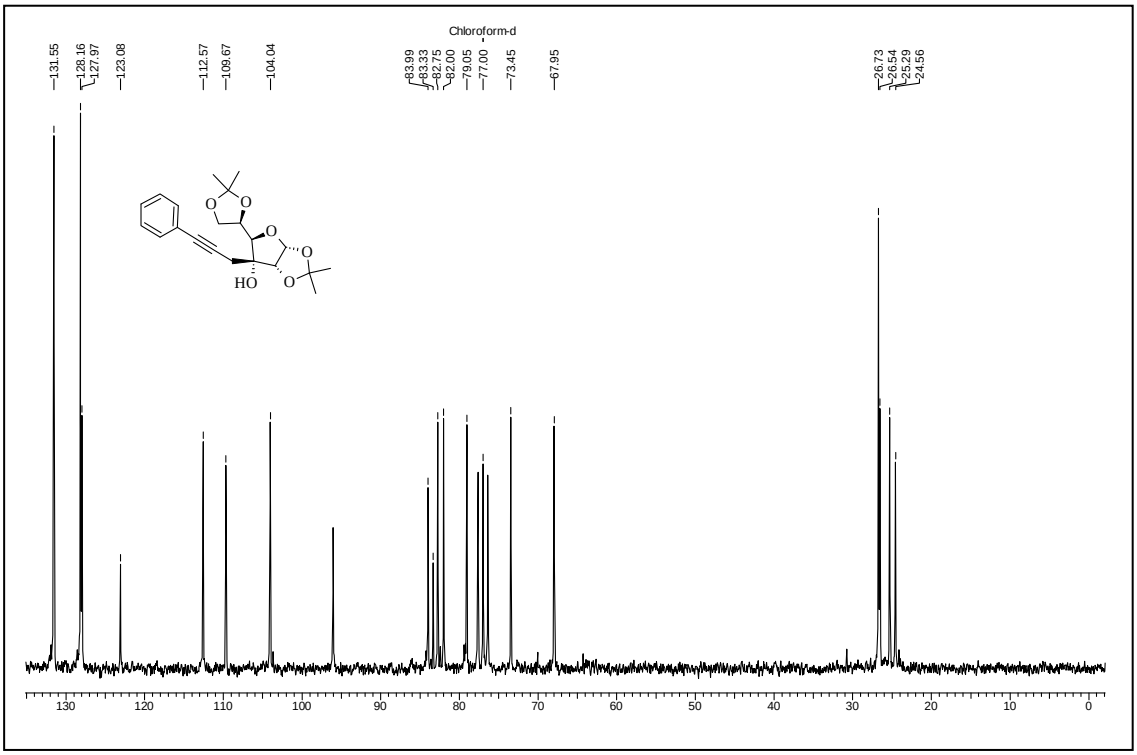
To a solution of **78** (80 mg, 0.19 mmol) in acetonitrile (10 ml) was added $Pd(CH_3CN)_2Cl_2$ (11 mg, 0.04 mmol) and the reaction mixture was stirred at rt under argon atmosphere for 2 h. The reaction mixture was concentrated and purified by silica gel chromatography (35% ethyl acetate in petroleum ether) to obtain **90** (58 mg, 72%) as a white solid.

Mol. Formula	: $C_{18}H_{21}NO_8$
M. P.	: 164–166 °C.
$[\alpha]_D$	: +33.8 (*c* 1.5, $CHCl_3$).
IR ($CHCl_3$) $\tilde{\nu}$	: 3437, 2938, 1781, 1593, 1376, 1216, 1086, 861, 694 cm^{-1}.
^1H NMR ($CDCl_3$, 200 MHz)	: δ 1.35 (s, 3H), 1.56 (s, 3H), 1.69 (d, *J* = 14.3 Hz, 1H), 2.03 (d, *J* = 14.3 Hz, 1H), 3.05 (br s, 1H), 3.10 (d, *J* = 15.7 Hz, 1H), 3.18 (d, *J* = 15.7 Hz, 1H), 3.55 (dd, *J* = 5.7, 7.2 Hz, 1H), 3.72 (br s, 1H), 4.11 (d, *J* = 5.7 Hz, 1H), 4.14 (d, *J* = 7.2 Hz, 1H), 4.63 (d, *J* = 4.4 Hz, 1H), 5.86 (d, *J* = 3.7 Hz, 1H), 7.42 (t, *J* = 8.0 Hz, 1H), 7.62 (dt, *J* = 1.4, 8.0 Hz, 1H), 8.09 (ddd, *J* = 1.4, 1.9, 8.0 Hz, 1H), 8.15 (t, *J* = 1.9 Hz, 1H) ppm.
^{13}C NMR ($CDCl_3$, 50 MHz)	: δ 26.6 (q), 26.7 (q), 40.9 (t), 42.5 (t), 65.6 (t), 73.6 (d), 74.9 (s), 77.9 (d), 83.5 (d), 103.9 (d), 105.6 (s), 112.8 (s), 121.7 (d), 125.5 (d), 128.6 (d), 136.8 (d), 136.8 (s), 147.9 (s) ppm.
ESI-MS (*m/z*)	: 402.1 $[M+Na]^+$.
Elemental Analysis	Calcd.: C, 56.99; H, 5.58; N, 3.69. Found: C, 56.48; H, 5.62; N, 3.45.

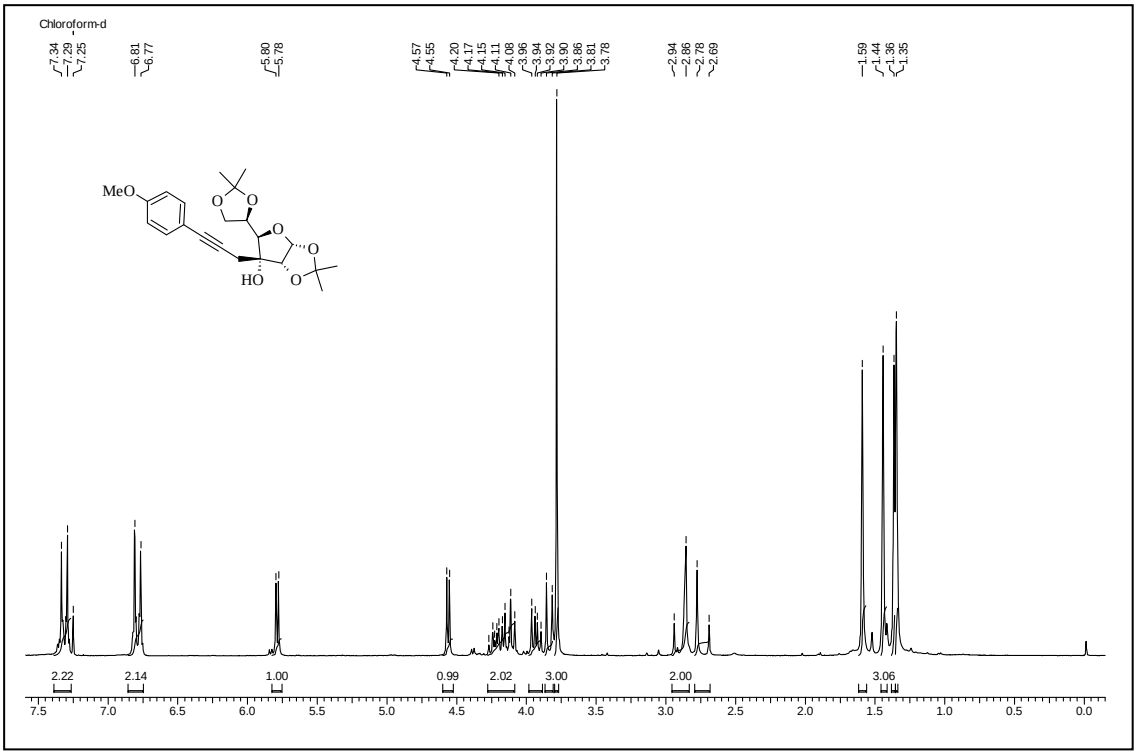
Spectroscopic Data



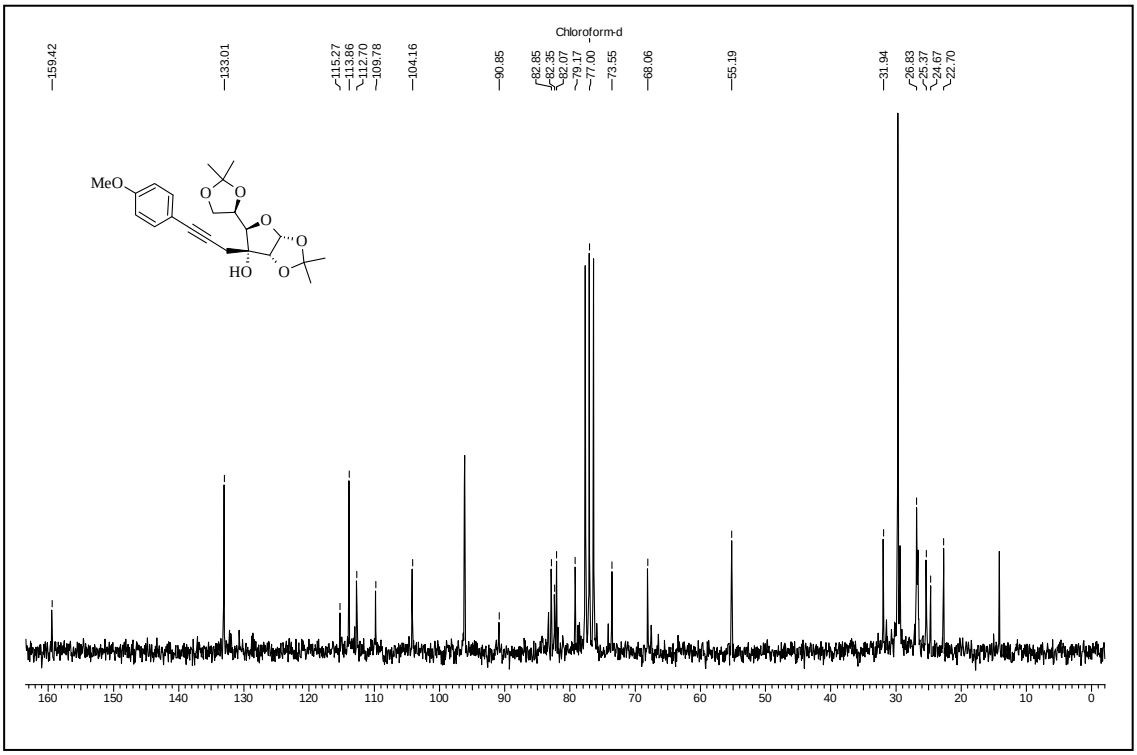
^{1}H NMR Spectrum of 75 in $CDCl_3$



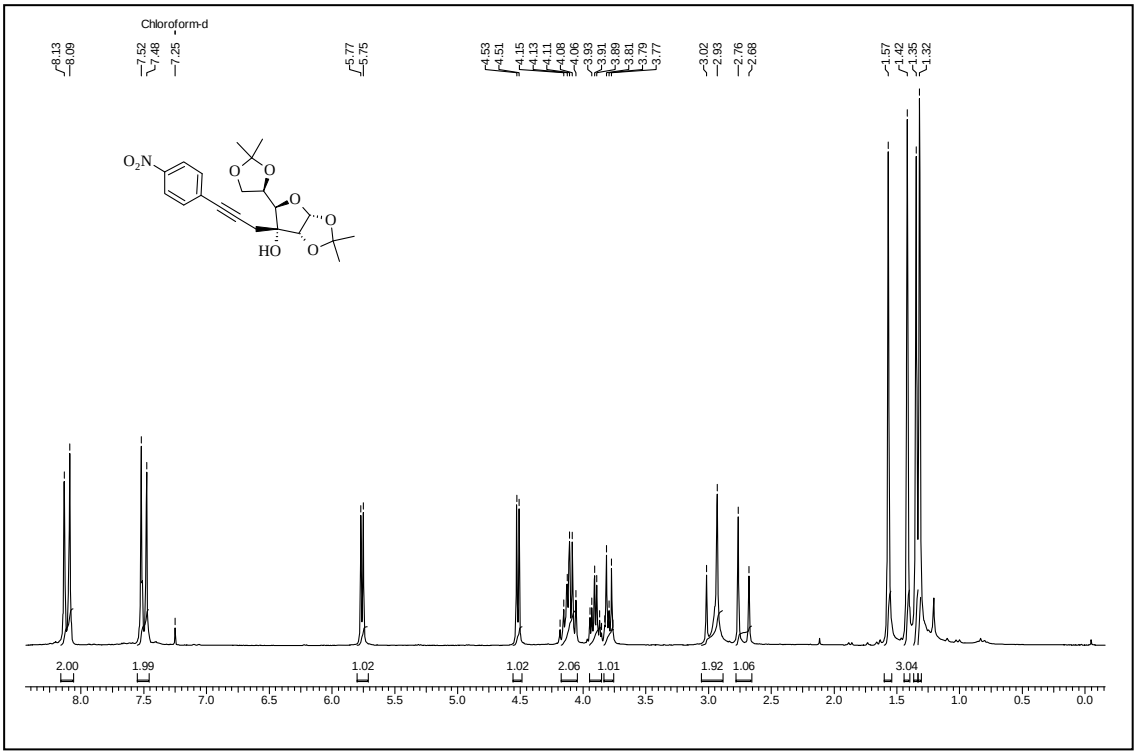
^{13}C NMR Spectrum of 75 in $CDCl_3$



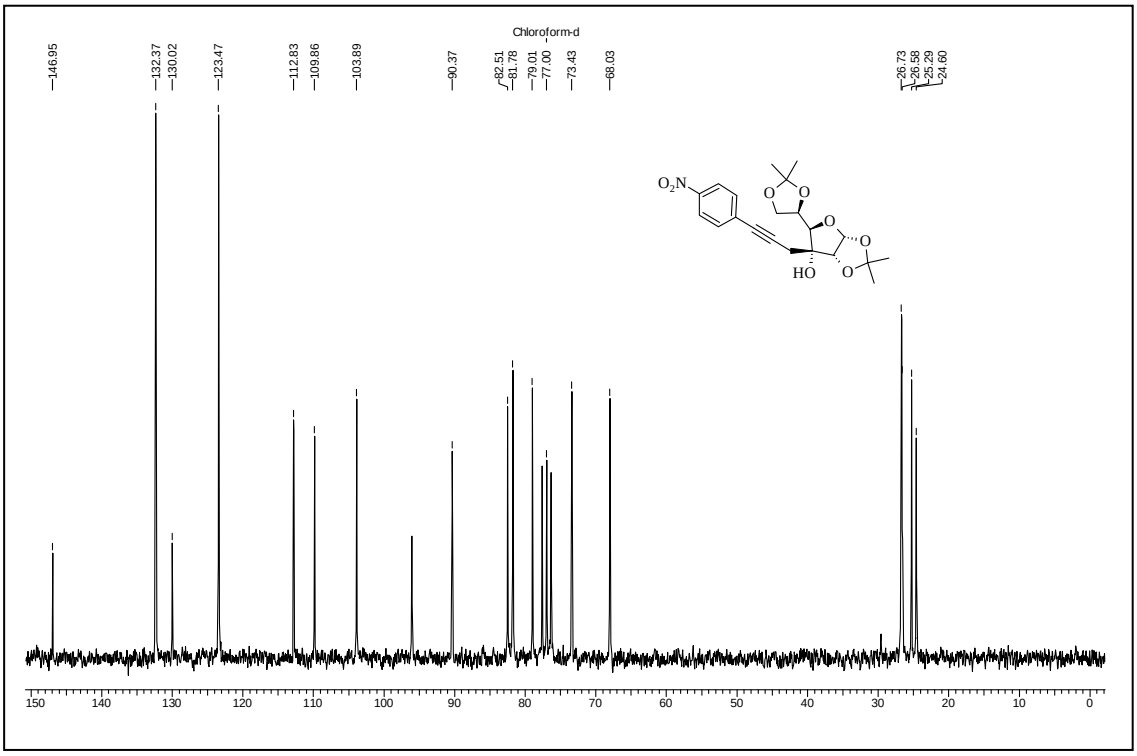
^{1}H NMR Spectrum of 76 in $CDCl_3$



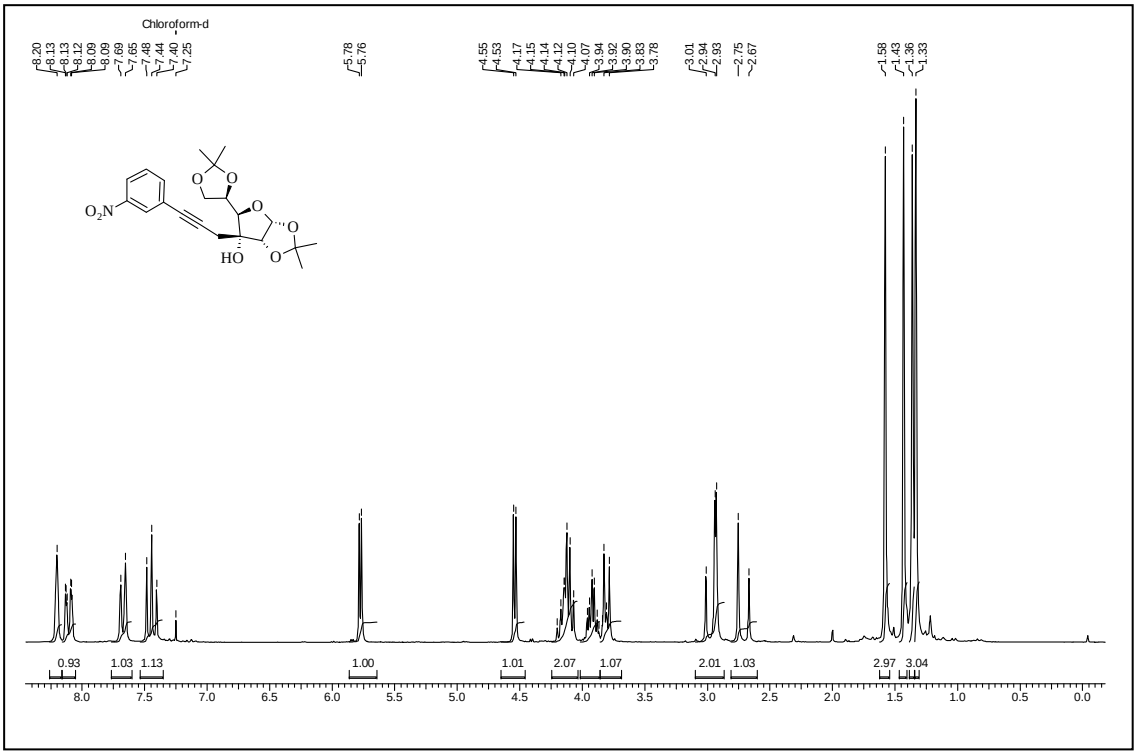
^{13}C NMR Spectrum of 76 in $CDCl_3$



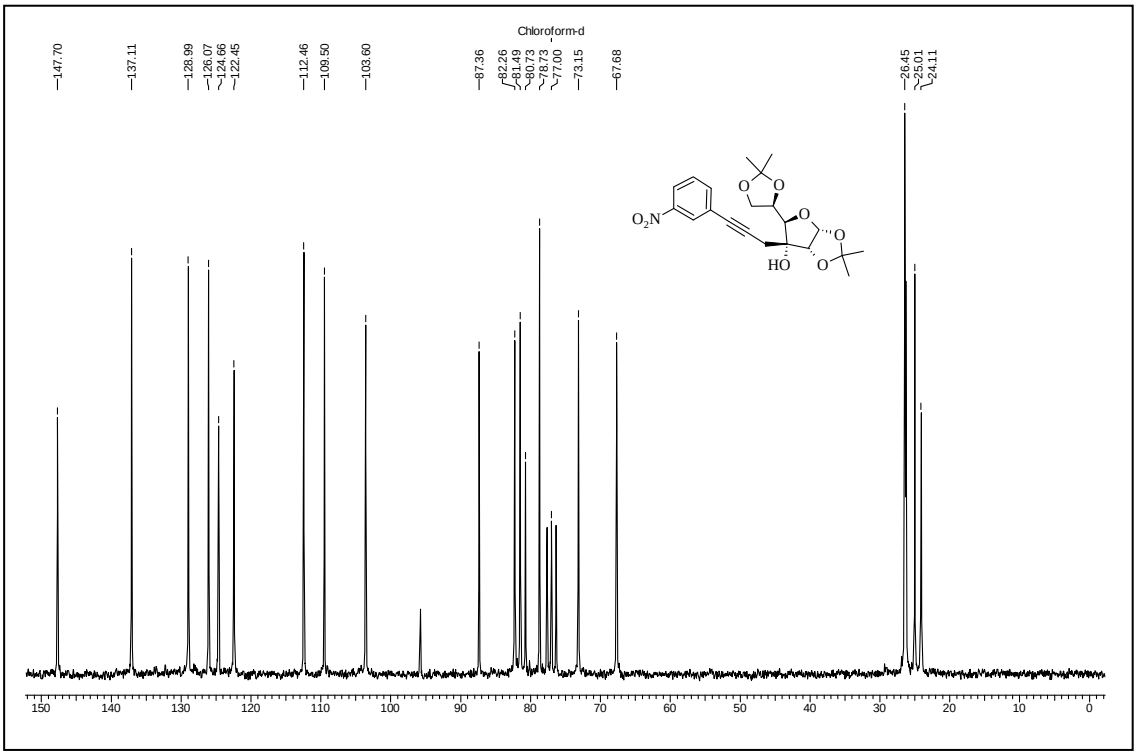
^{1}H NMR Spectrum of 77 in $CDCl_3$



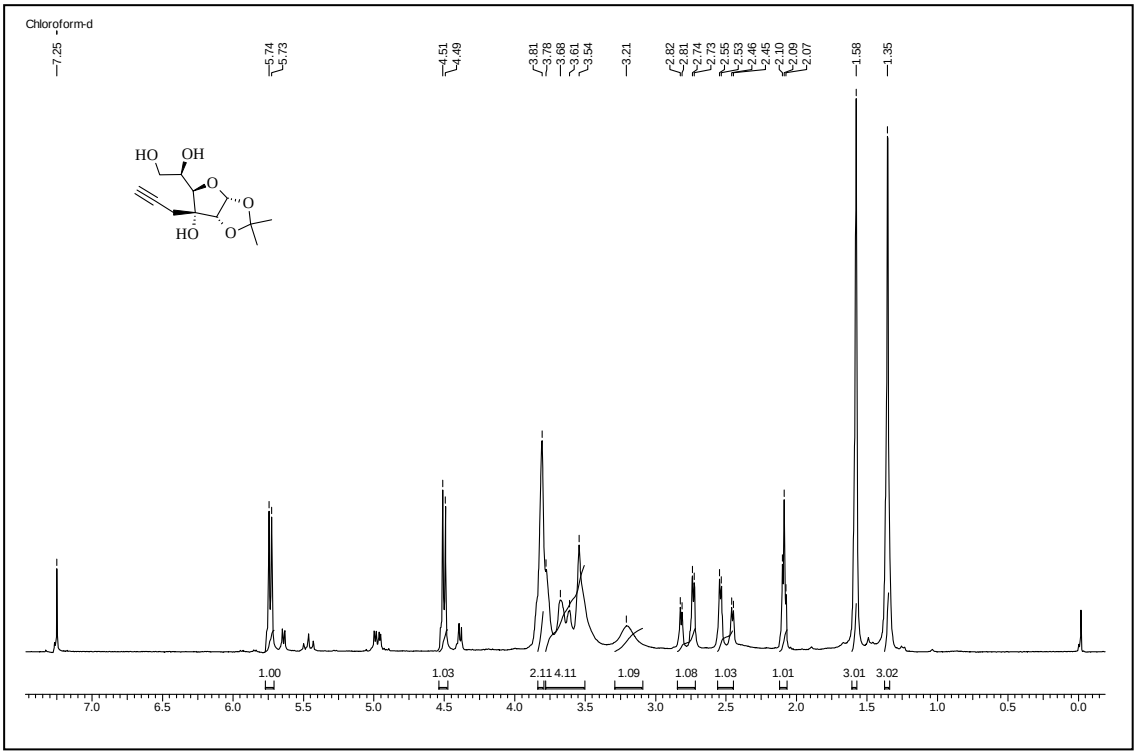
^{13}C NMR Spectrum of 77 in $CDCl_3$



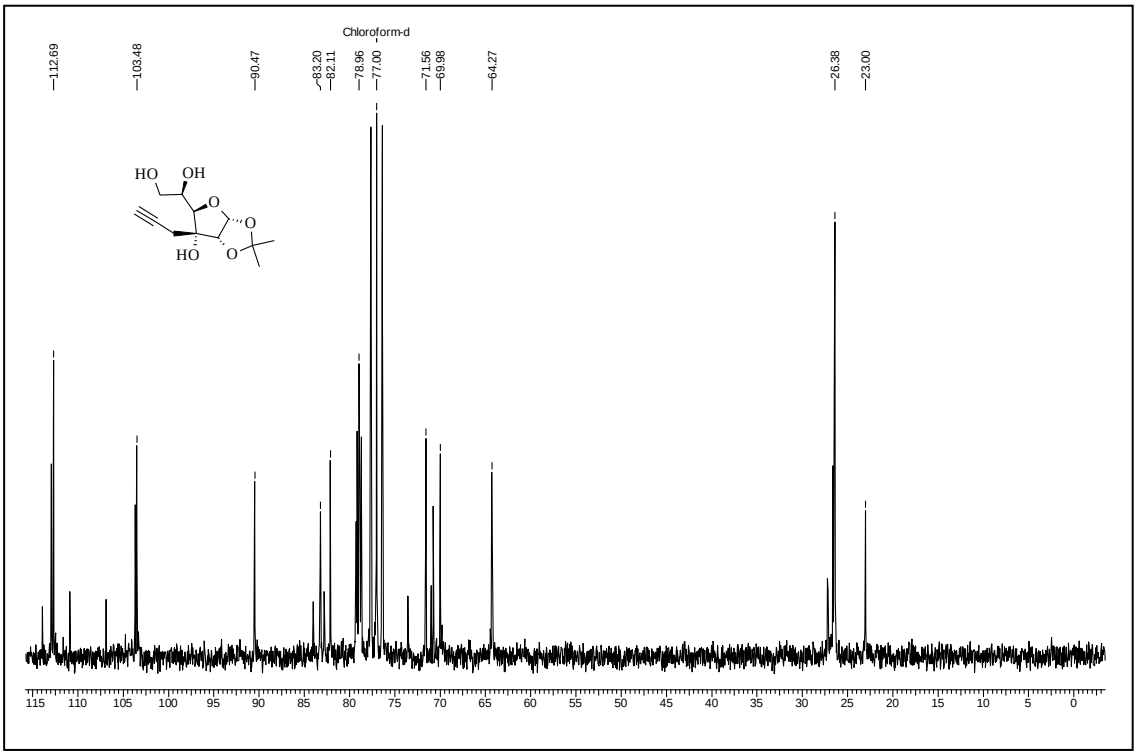
^{1}H NMR Spectrum of 78 in $CDCl_3$



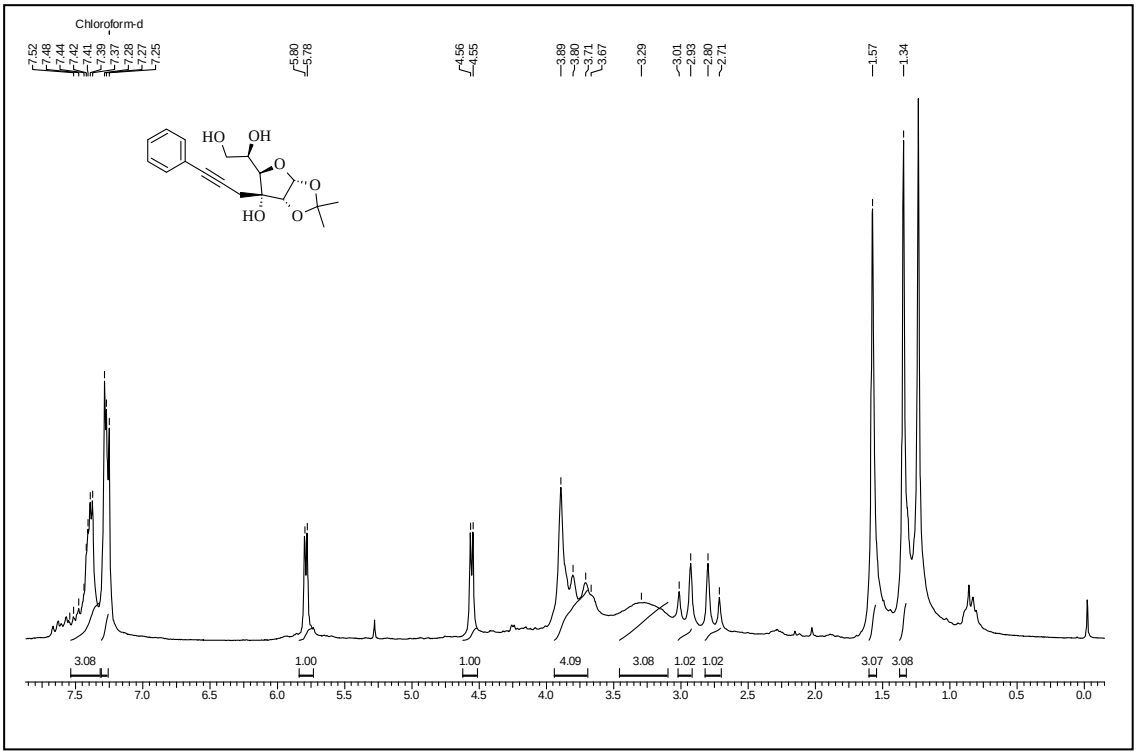
^{13}C NMR Spectrum of 78 in $CDCl_3$



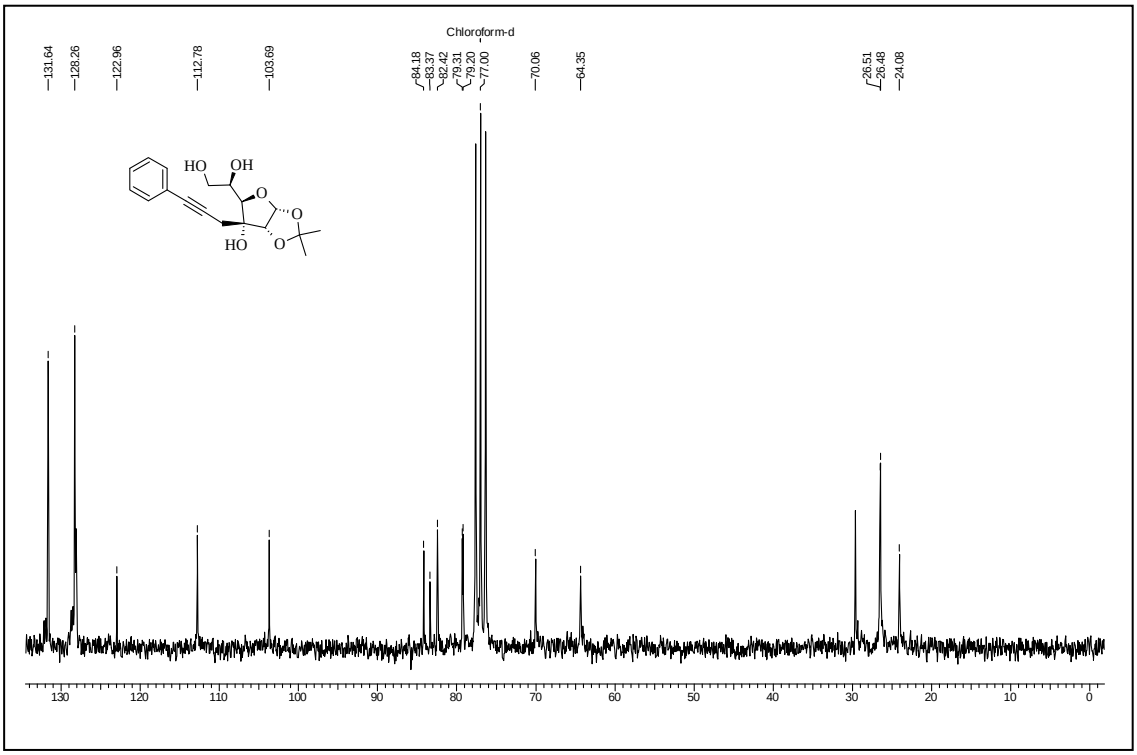
^{1}H NMR Spectrum of 79 in $CDCl_3$



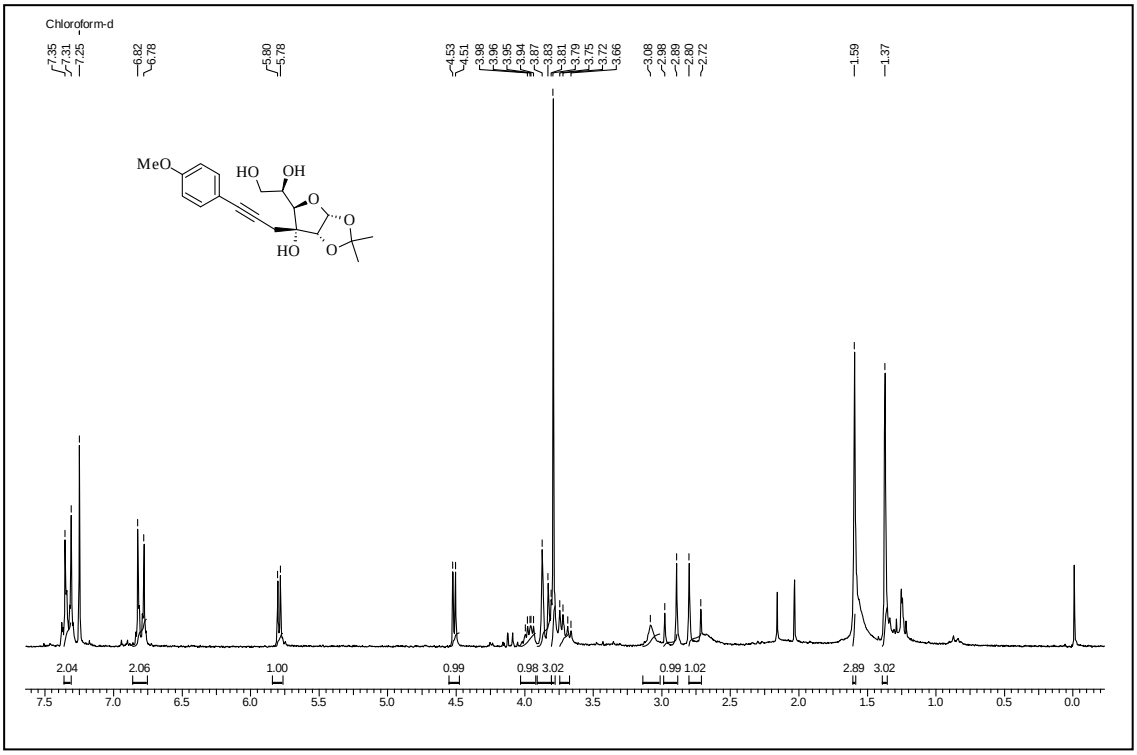
^{13}C NMR Spectrum of 79 in $CDCl_3$



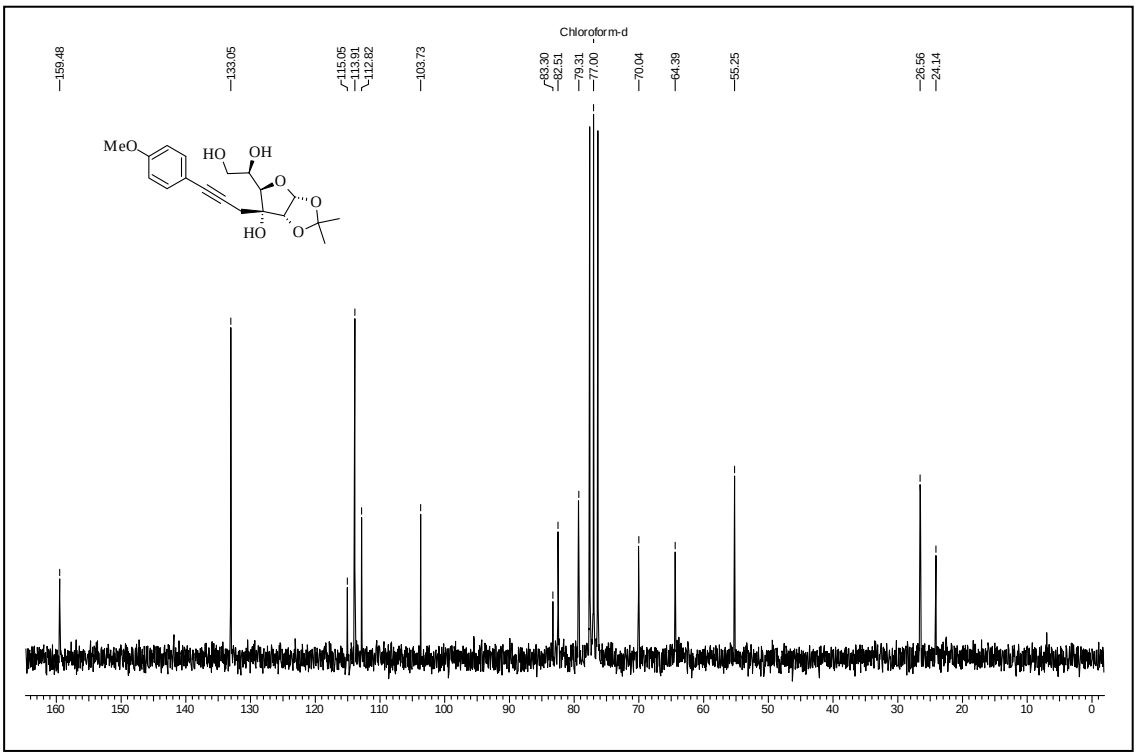
^{1}H NMR Spectrum of 80 in $CDCl_3$



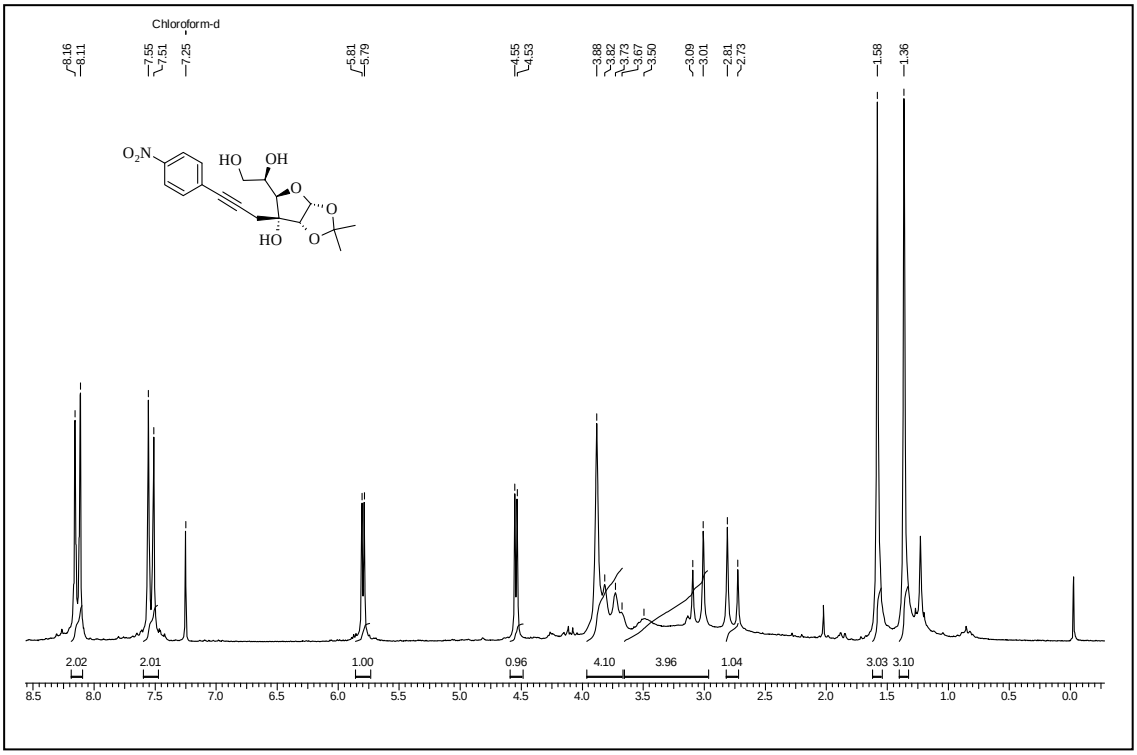
^{13}C NMR Spectrum of 80 in $CDCl_3$



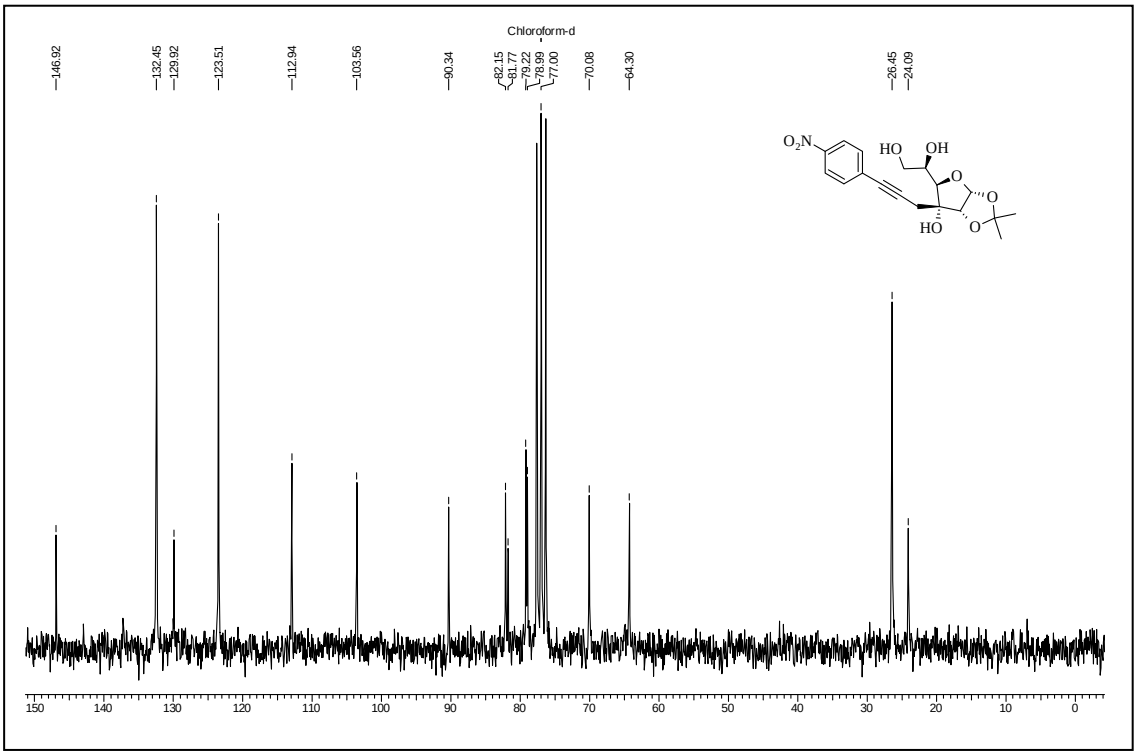
^{1}H NMR Spectrum of 81 in $CDCl_3$



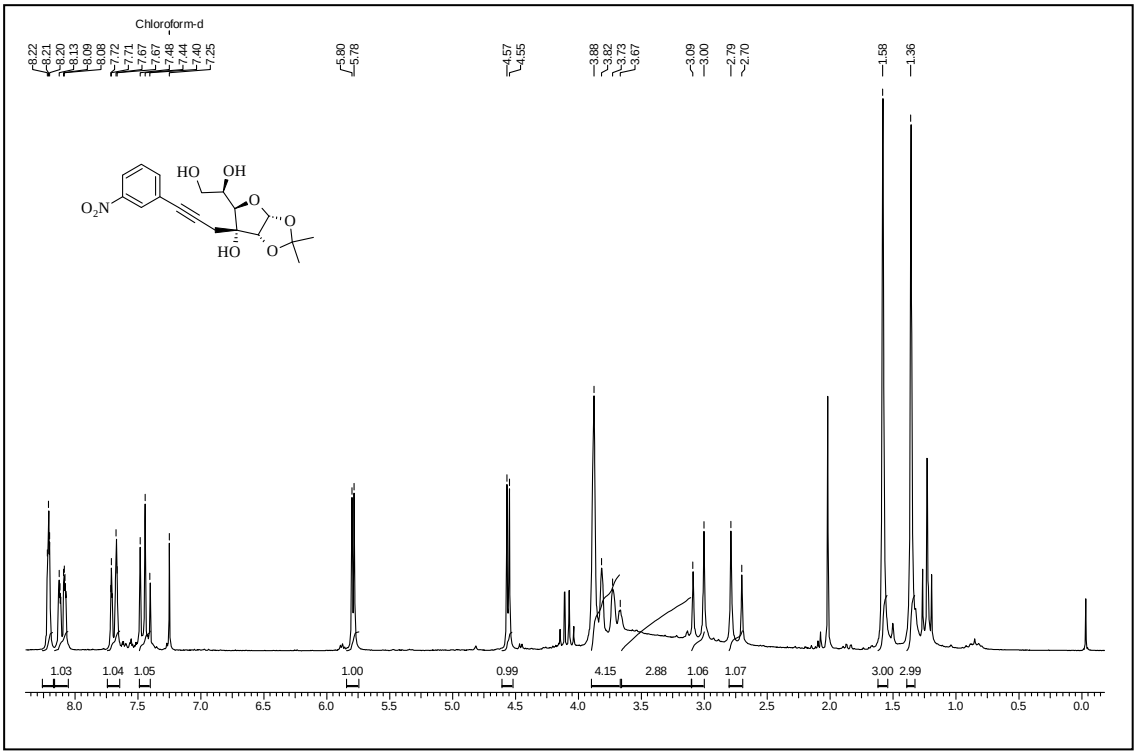
^{13}C NMR Spectrum of 81 in $CDCl_3$



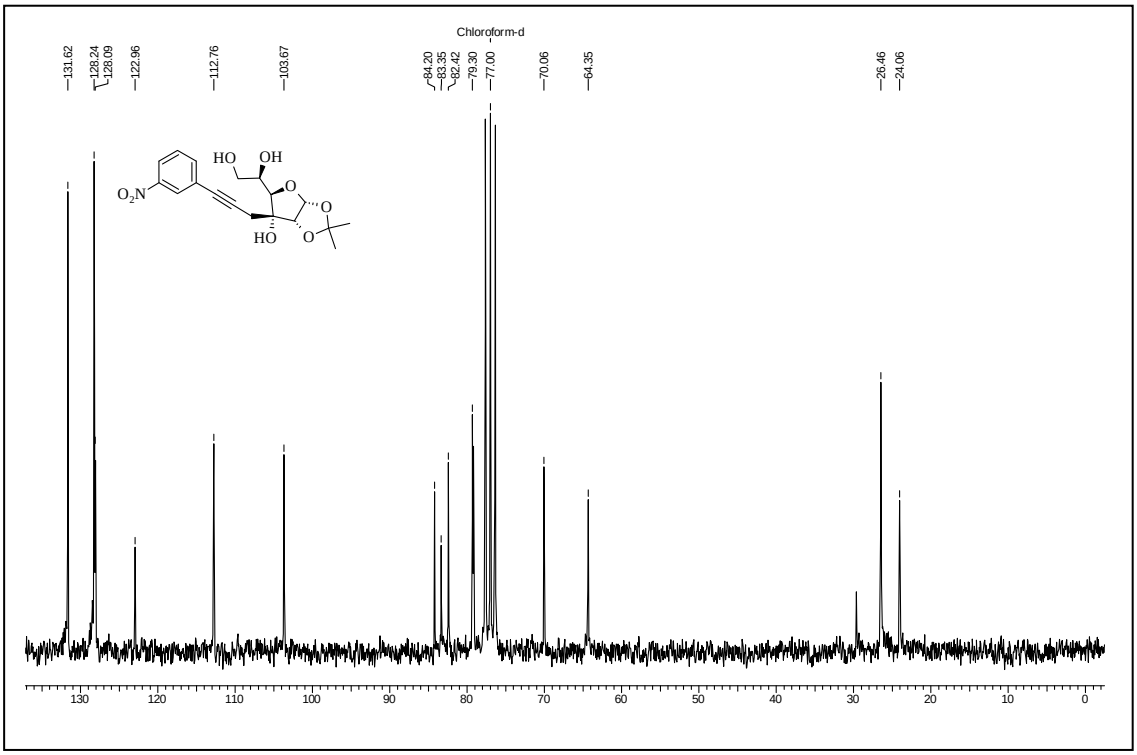
^{1}H NMR Spectrum of 82 in $CDCl_3$



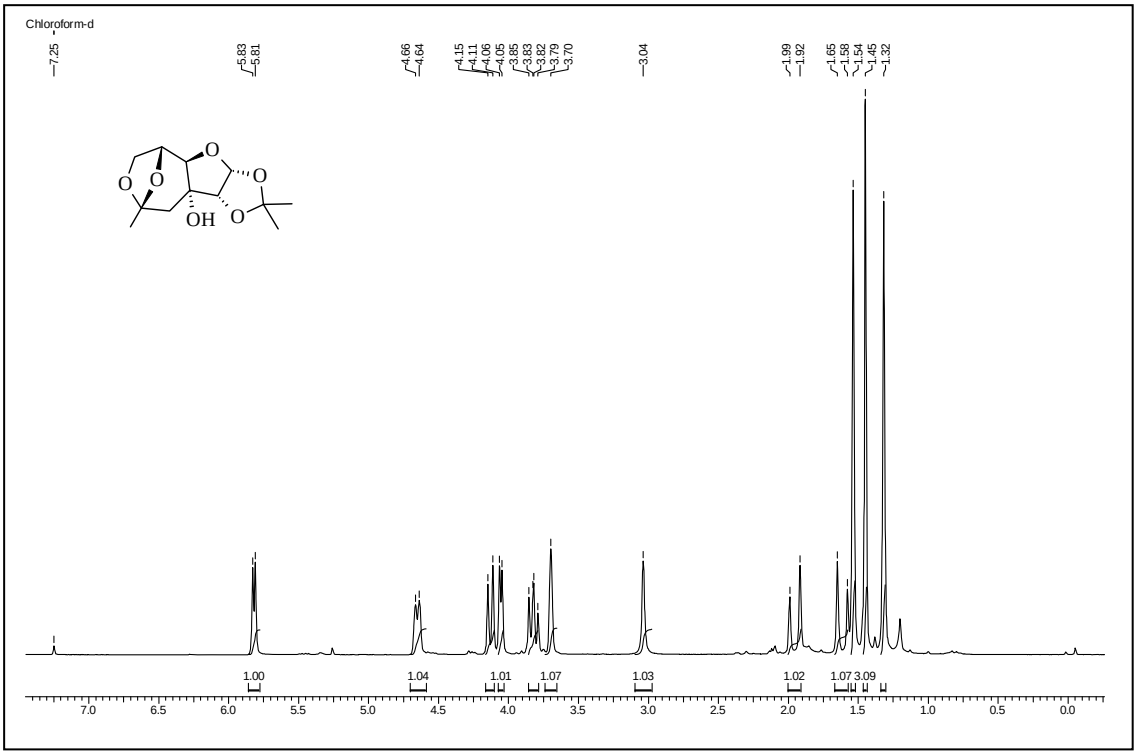
^{13}C NMR Spectrum of 82 in $CDCl_3$



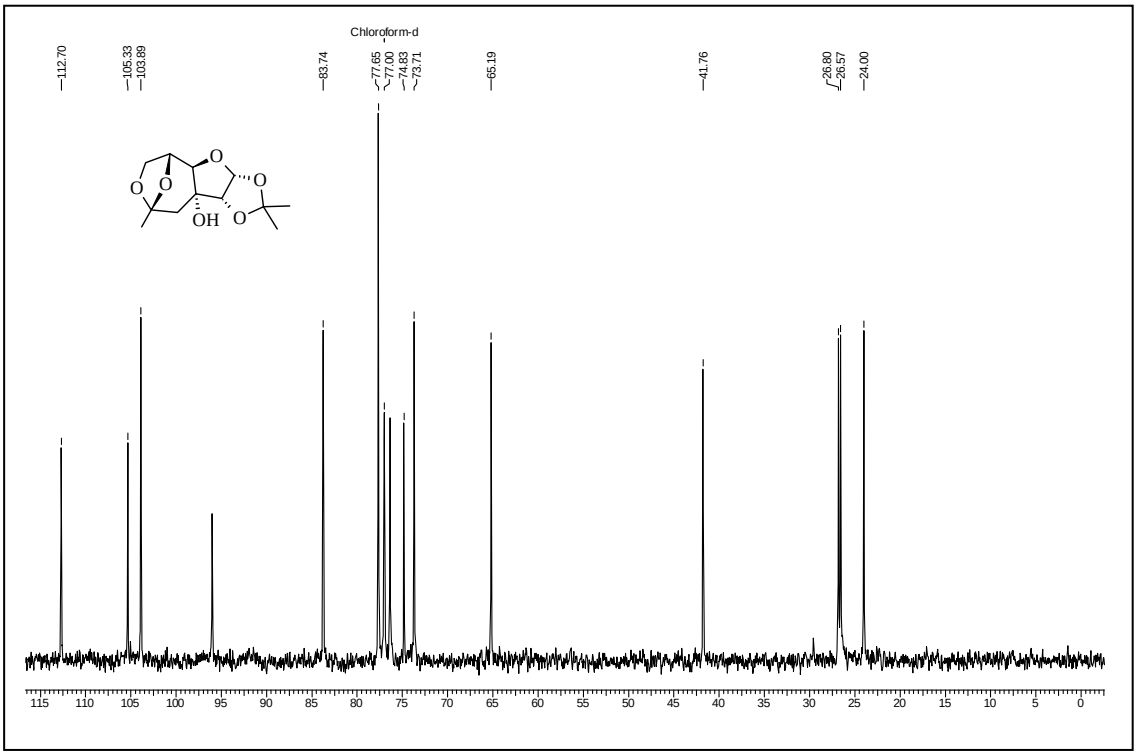
^{1}H NMR Spectrum of 83 in $CDCl_3$



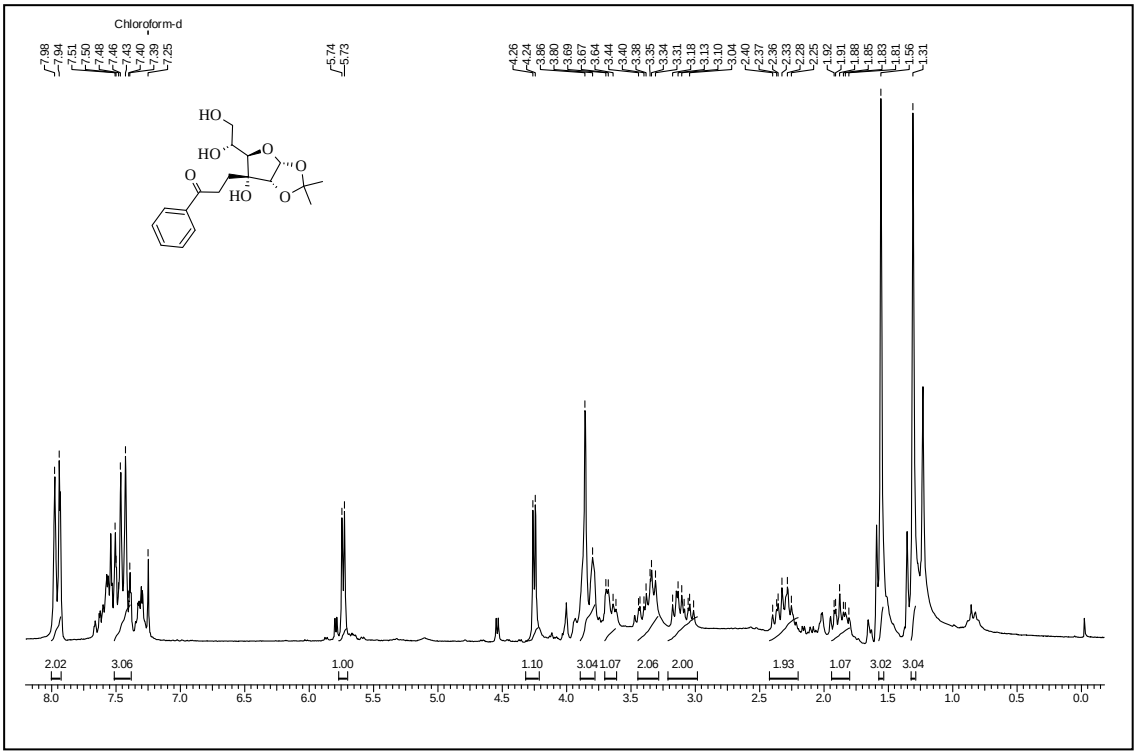
^{13}C NMR Spectrum of 83 in $CDCl_3$



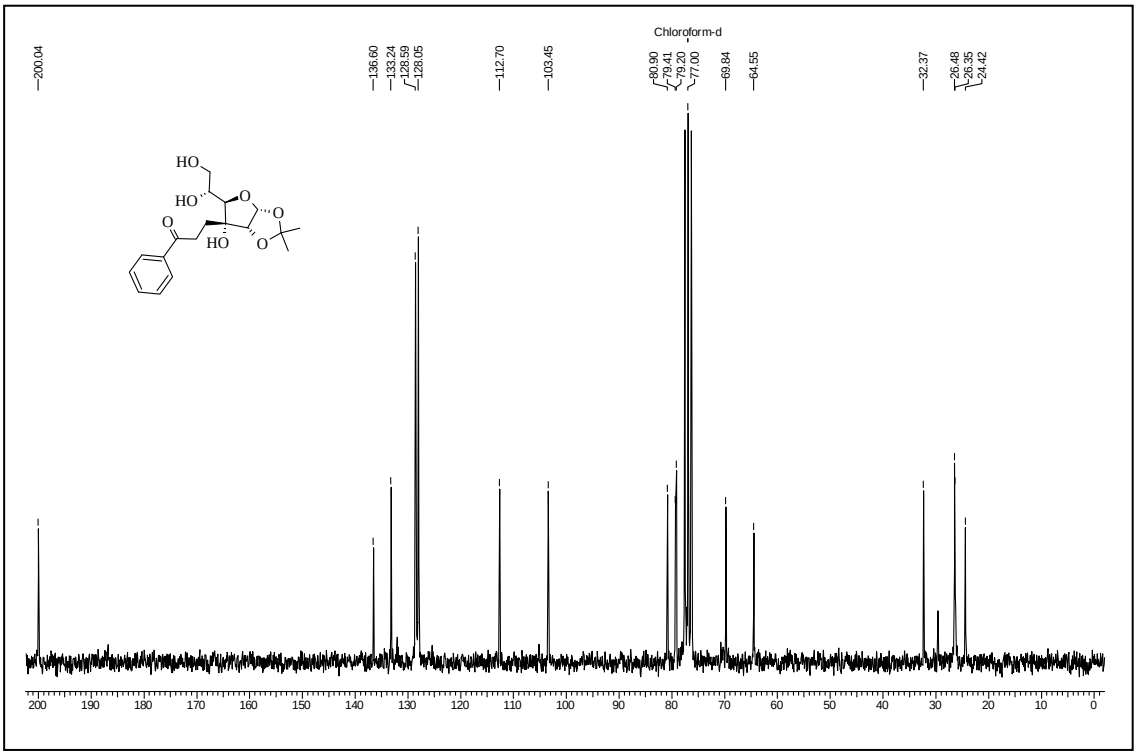
^{1}H NMR Spectrum of 84 in $CDCl_3$



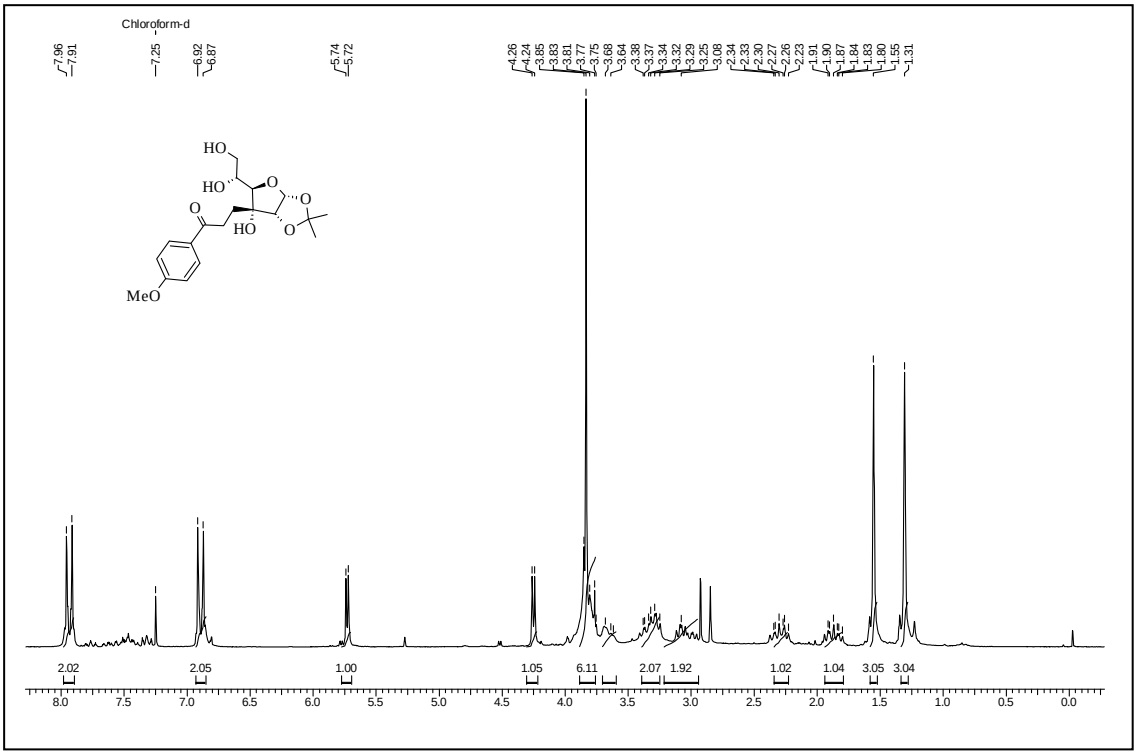
^{13}C NMR Spectrum of 84 in $CDCl_3$



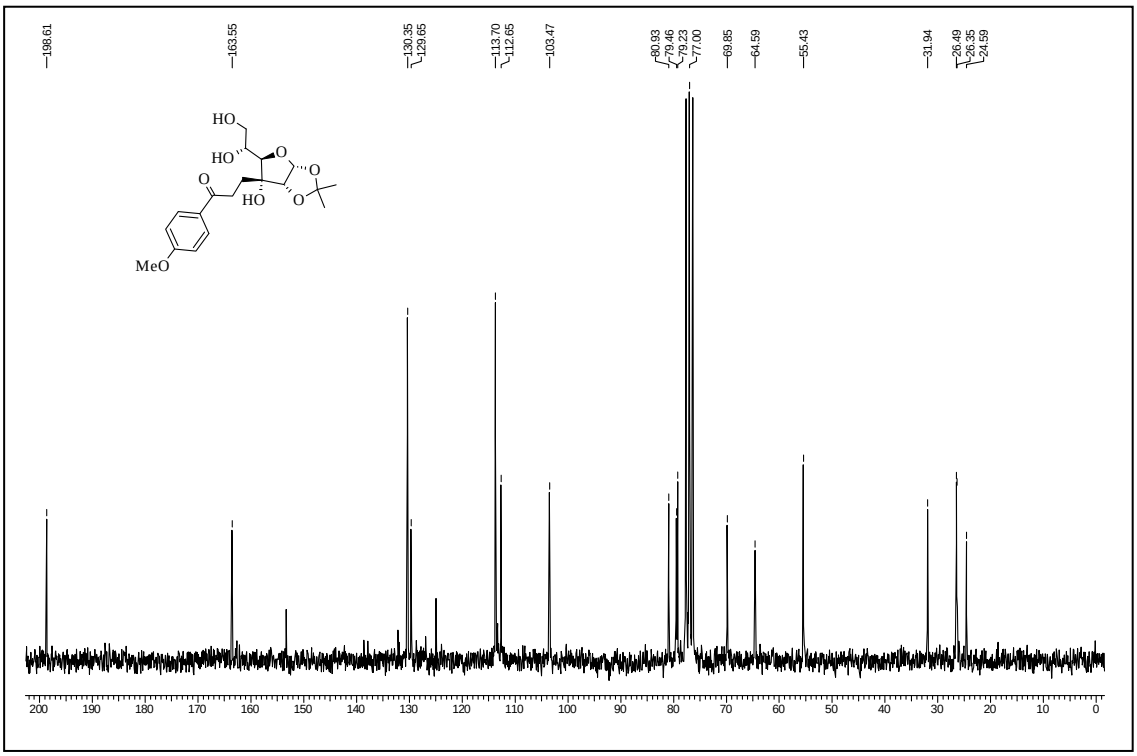
^{1}H NMR Spectrum of 85 in $CDCl_3$



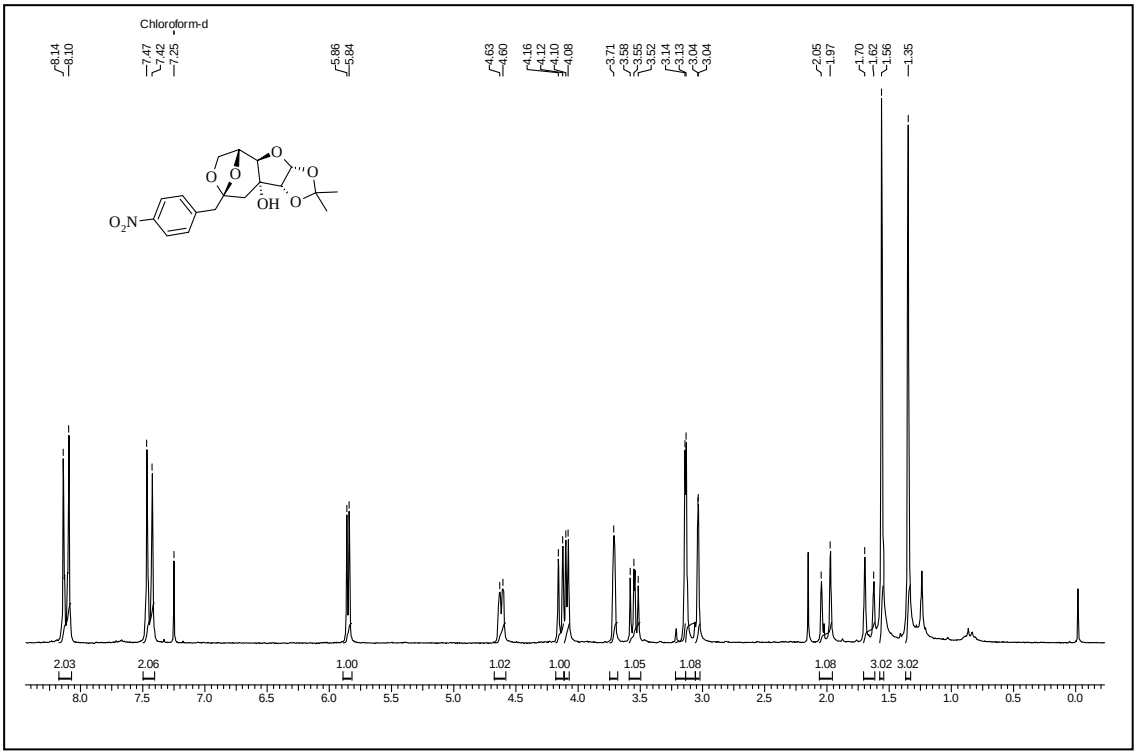
^{13}C NMR Spectrum of 85 in $CDCl_3$



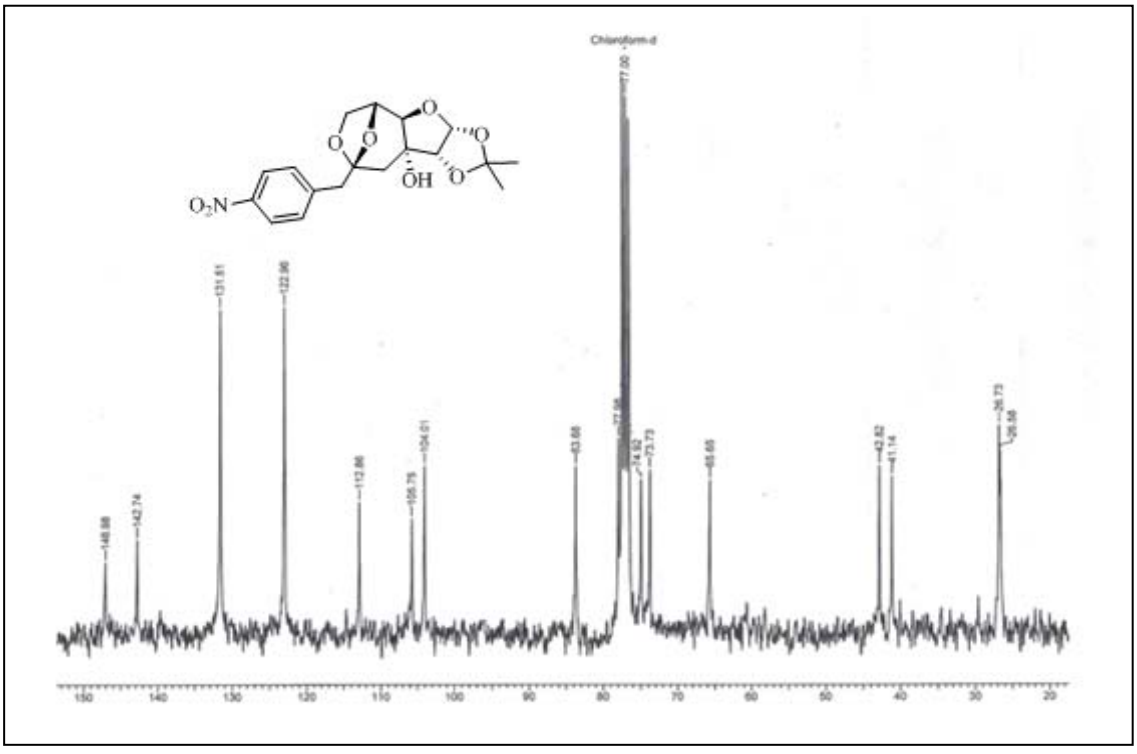
^{1}H NMR Spectrum of 86 in $CDCl_3$



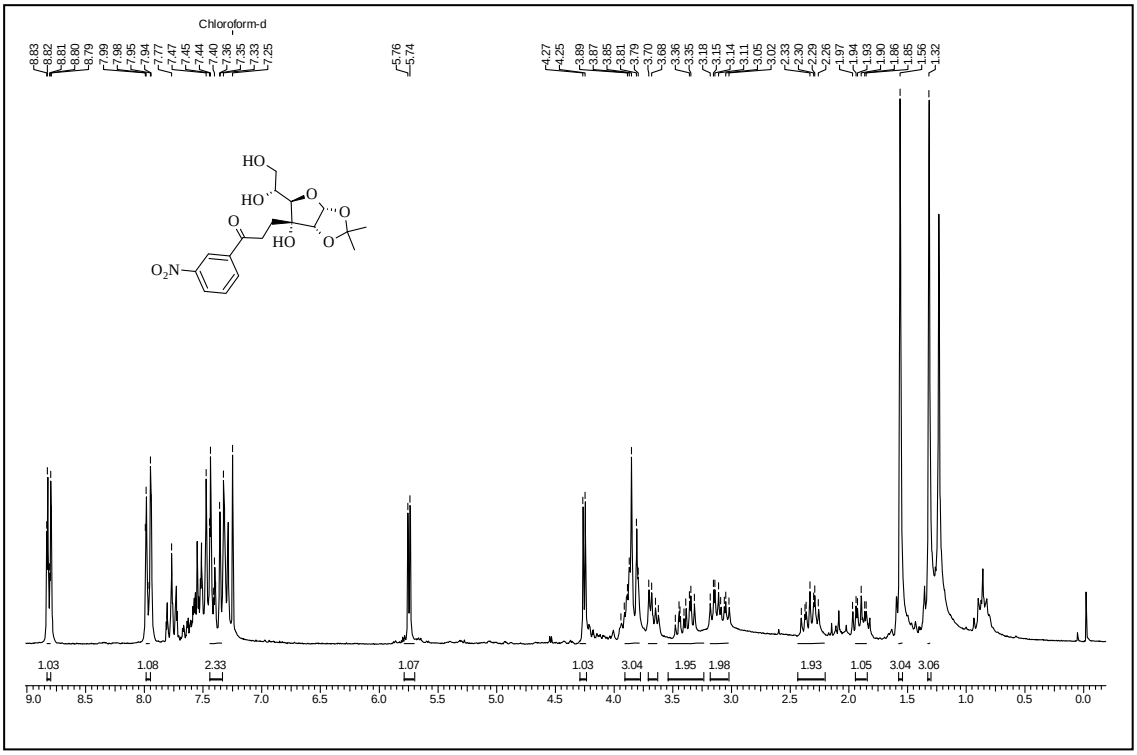
^{13}C NMR Spectrum of 86 in $CDCl_3$



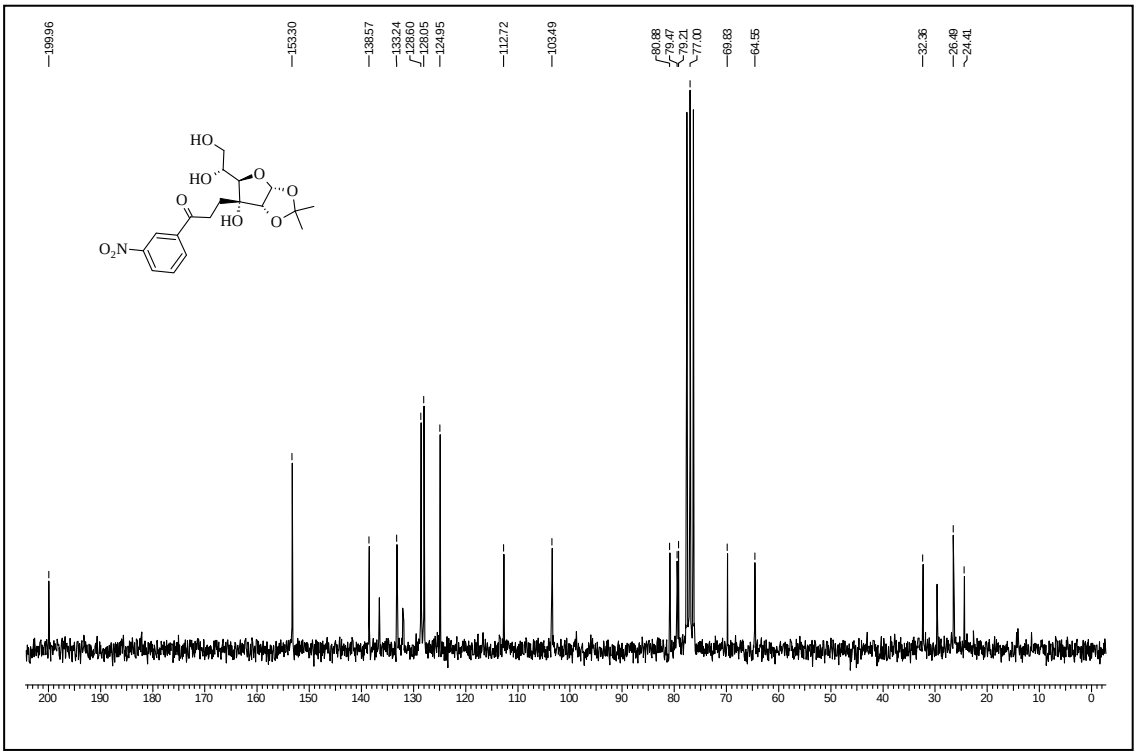
^{1}H NMR Spectrum of 87 in $CDCl_3$



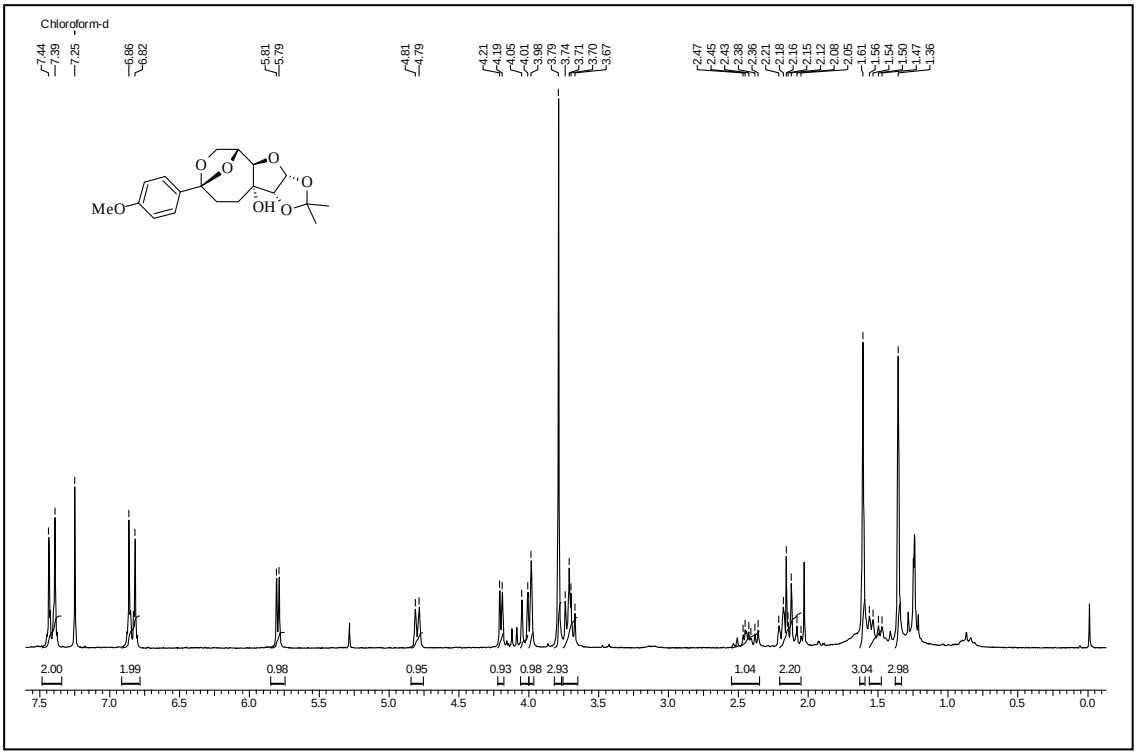
^{13}C NMR Spectrum of 87 in $CDCl_3$



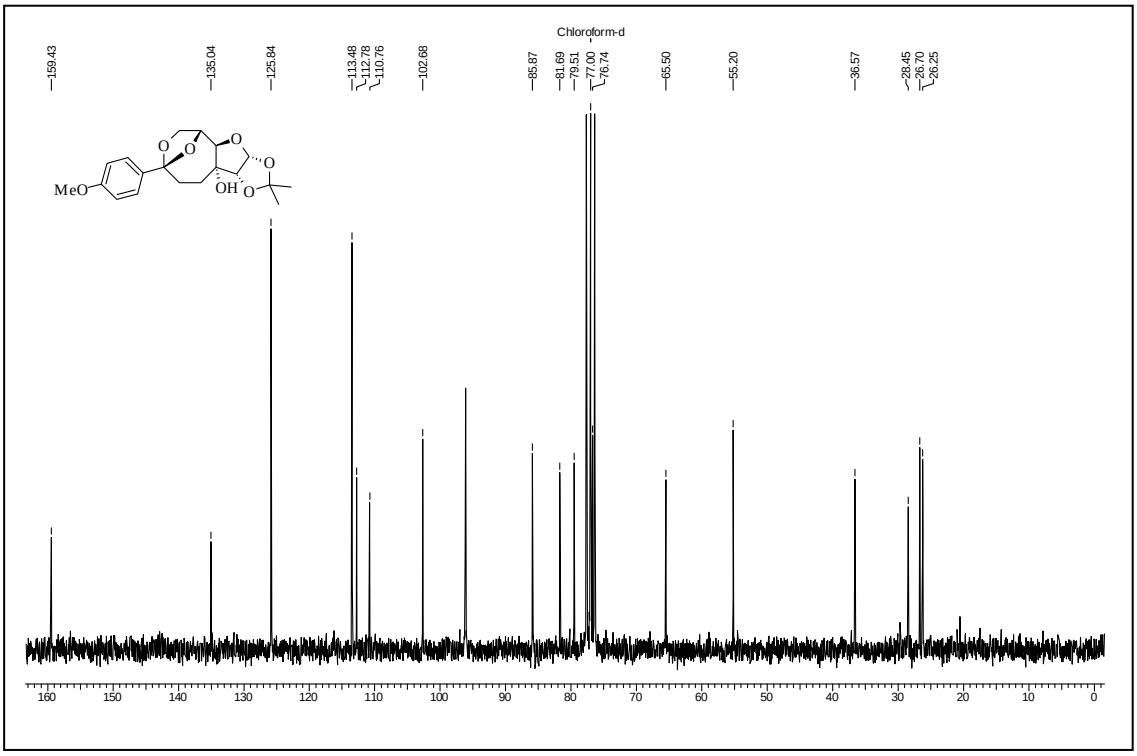
^{1}H NMR Spectrum of 88 in $CDCl_3$



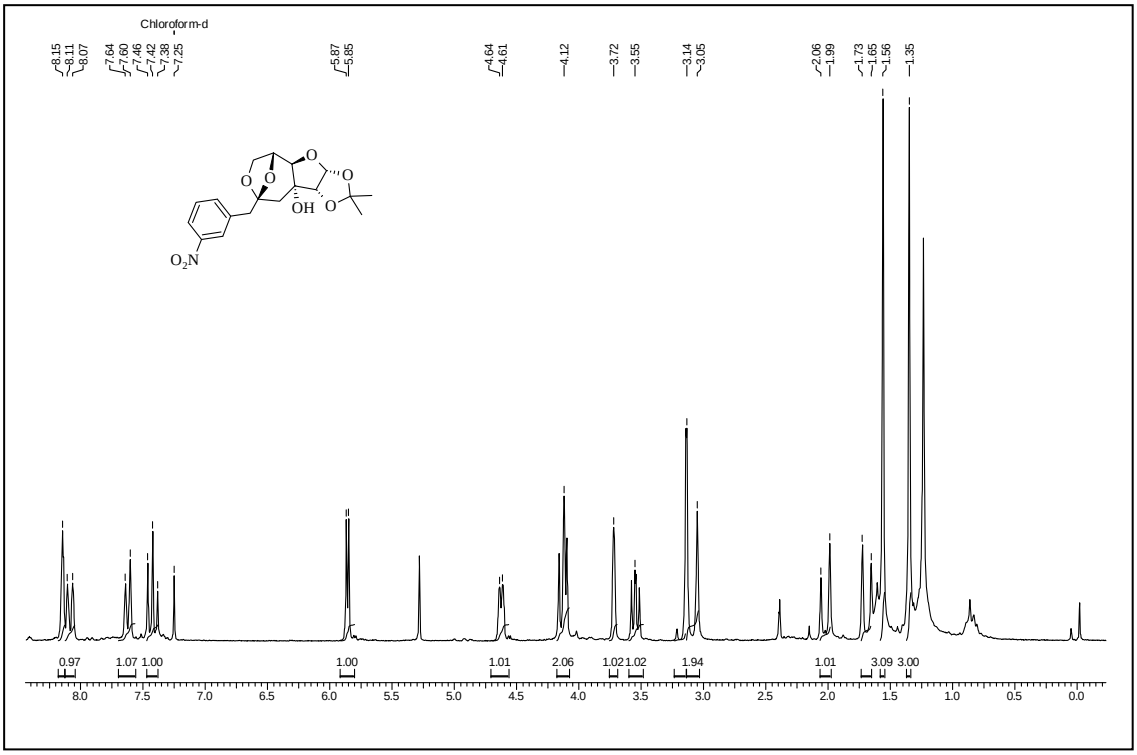
^{13}C NMR Spectrum of 88 in $CDCl_3$



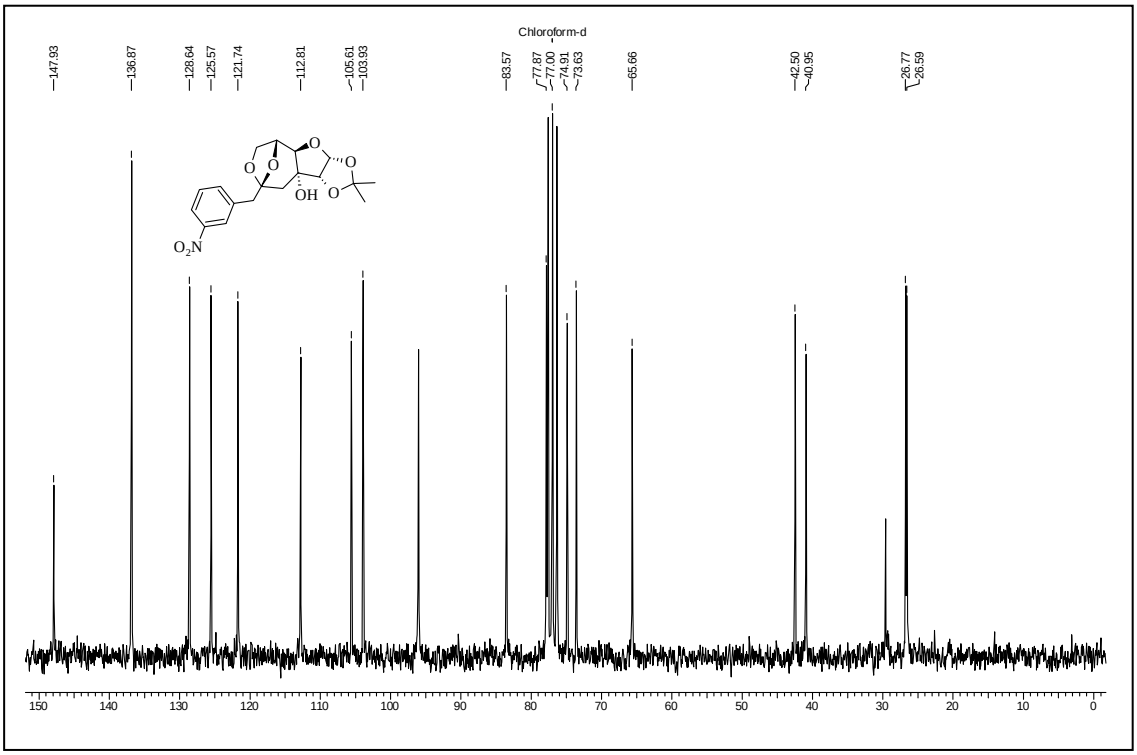
^{1}H NMR Spectrum of 89 in $CDCl_3$



^{13}C NMR Spectrum of 89 in $CDCl_3$



^{1}H NMR Spectrum of 90 in $CDCl_3$



^{13}C NMR Spectrum of 90 in $CDCl_3$

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CHAPTER-II

Studies Toward the Total Synthesis of Didemniserinolipid B

Introduction

The activity of total synthesis of complex natural products continues to be an indispensable tool in chemical research that provide impetus to the development of new methods, new protocols, sophistication of analytical tools, and sometimes even new theories. As the natural products with structures of previously undreamed complexity are being isolated, total synthesis becoming one of the difficult, daunting, and most rewarding challenge in organic chemistry. Danger with the total synthesis is unless one makes the final natural product, otherwise the whole exercise is unfinished. There are several instances, where the protective group create problem in the penultimate step of a synthesis. And sometimes, it may lead to conclude that the given structure of a natural product is a putative structure. Nonetheless, the surprises encountered on the journey are supposed to be as important as the destination. Otherwise, total synthesis has served as one of the important approach for acquiring complex natural products in sufficient quantity and purity for further experiments, where the isolation from natural sources turned out to be a difficult and time-consuming, if not impossible, task. Other important strategy that gained momentum recently, is the unrestricted access to natural product *congeners* by appropriate structural edits into the structure being synthesized far in advance of reaching the actual structure of natural product. This has served as a remarkable approach in the discovery of new medicinal agents.

Although a number of new medicines have been launched in recent decades, our armory against diseases is continually being depleted, as our microscopically small enemies are crafty warriors that develop resistance to current therapeutic agents. Natural products have always been an important source for the development of chemical tool compounds or drugs respectively in chemical biology and pharmaceutical research. Researchers frequently build up what are known as "combinatorial libraries" based on the structural characteristics of natural products. Natural products that act as highly specific, small-molecule protein-binding agents and as modulators of protein-protein interactions are highly complex and exhibit functional groups with three-dimensional and stereochemical diversity. Several classes of natural products with significant inhibitory activity against target enzymes involved in several diseases have been identified. The complex three-dimensional

display of chiral functional groups appears to be crucial for exhibiting specificity in protein binding and in differentiating between closely related proteins.

Ever since, in 1909, Paul Ehrlich (Ehrlich. *Dtsch. Chem. Ges.* 1909, 42: p.17) defined the pharmacophore as "a molecular framework that carries (*phoros*) the essential features responsible for a drug's (=*pharmacon's*) biological activity", the idea of building analogs of natural products for evaluation in the hope of finding better drugs in general is an old one, however, with successes ascertained. Though, the definition of the pharmacophore has been changed with time, however, molecular design around the natural product skeletons, synthesis of natural product analogues and hybrids continues to be one of the most rewarding strategy in new drug design, because they match the elements of conservatism and diversity simultaneously expressed by biological targets. As much as 75% of our current treatments for cancer and infectious disease as well as other indications are directly or indirectly related to natural products and thus indicate the contribution of natural products to the discovery and development of new medicines. A general starting point in natural product based drug design is to identify the common scaffold from natural products already known to have biological activity. A convergent total synthesis of these scaffolds with multiple diversity points (points around which the structure can be varied) that are distant from each other and focused/combichem library synthesis by decorating these diversity points with appropriate functional groups that address various pharmacokinetic parameters is one of the promising protocol in drug discovery and in integrating chemical genetics with the human genome to find new targets.

Bicyclic ketal unit, one of the common unit present in many of insect and animal pheromones. The initial interest in the field of bicyclic ketals synthesis thus stems from the fact that these constitute as a basic skeleton in a wide variety of these pheromones, and that physiological and biological aspects of pheromones which aid in the behavioural and ecological studies.[1] The pheromones frontalin (**1**), multistriatin (**2**), *exo*brevicomin (**3**) play a decisive role in the communication system of bark beetles and other insects and are used on a large scale in traps for the protection of forests. The male pheromone (**4**) of the hepialid moth, *Endoclita excrescens* represents one of the several important insect pheromones containing a bicyclic ketal core as in brevicomin (*vide infra*) (Figure 1).

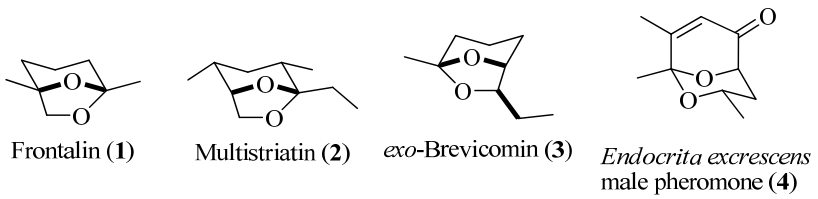


Figure 1: Some representative pheromones containing key bicyclic ketal unit.

The synthesis of **1 - 4** and their stereoisomers were highly desirable in the study of structure-activity relationships and in pest management and resulted in several syntheses since early 80's (Figure 2).

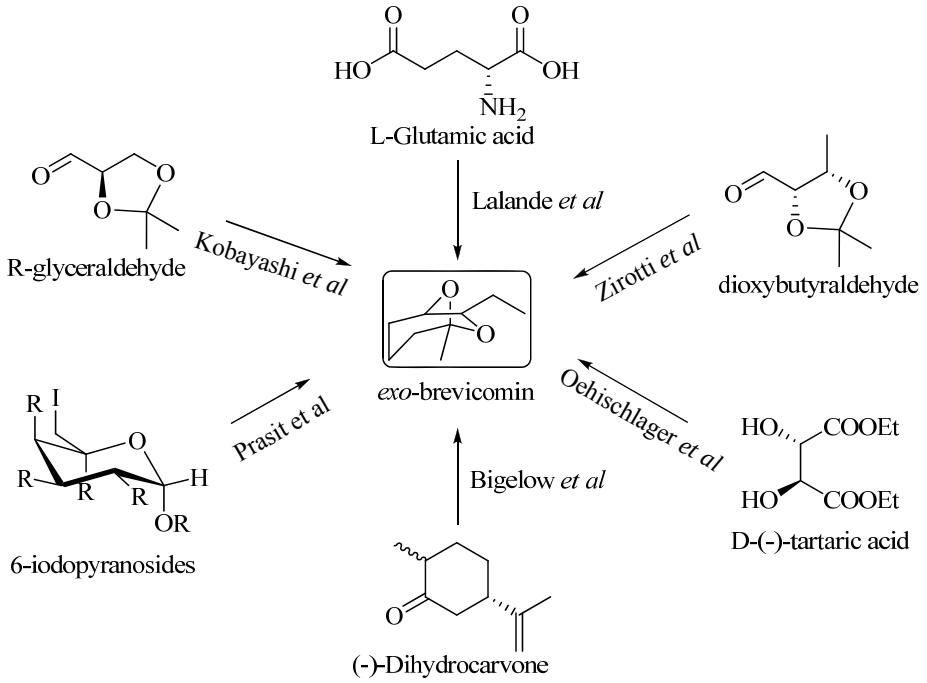


Figure 2: Literature syntheses of *exo* brevicomin (**3**).

However, new methodological advancements in the area of bicyclic ketal synthesis remained dormant until the recent isolation[2] of another class of bicycle [3.2.1] octanes wherein a renewed interest was observed owing to their marked biological significance in terms of potent HIV integrase activity in the case of Cyclodidemniserinol trisulfate (**9**), didemniserinolipids (**8**), squalene synthase activity in the case of zaragozic acid (**7**), shellfish toxicity as in palytoxins and pinnatoxins etc (Figure 3).

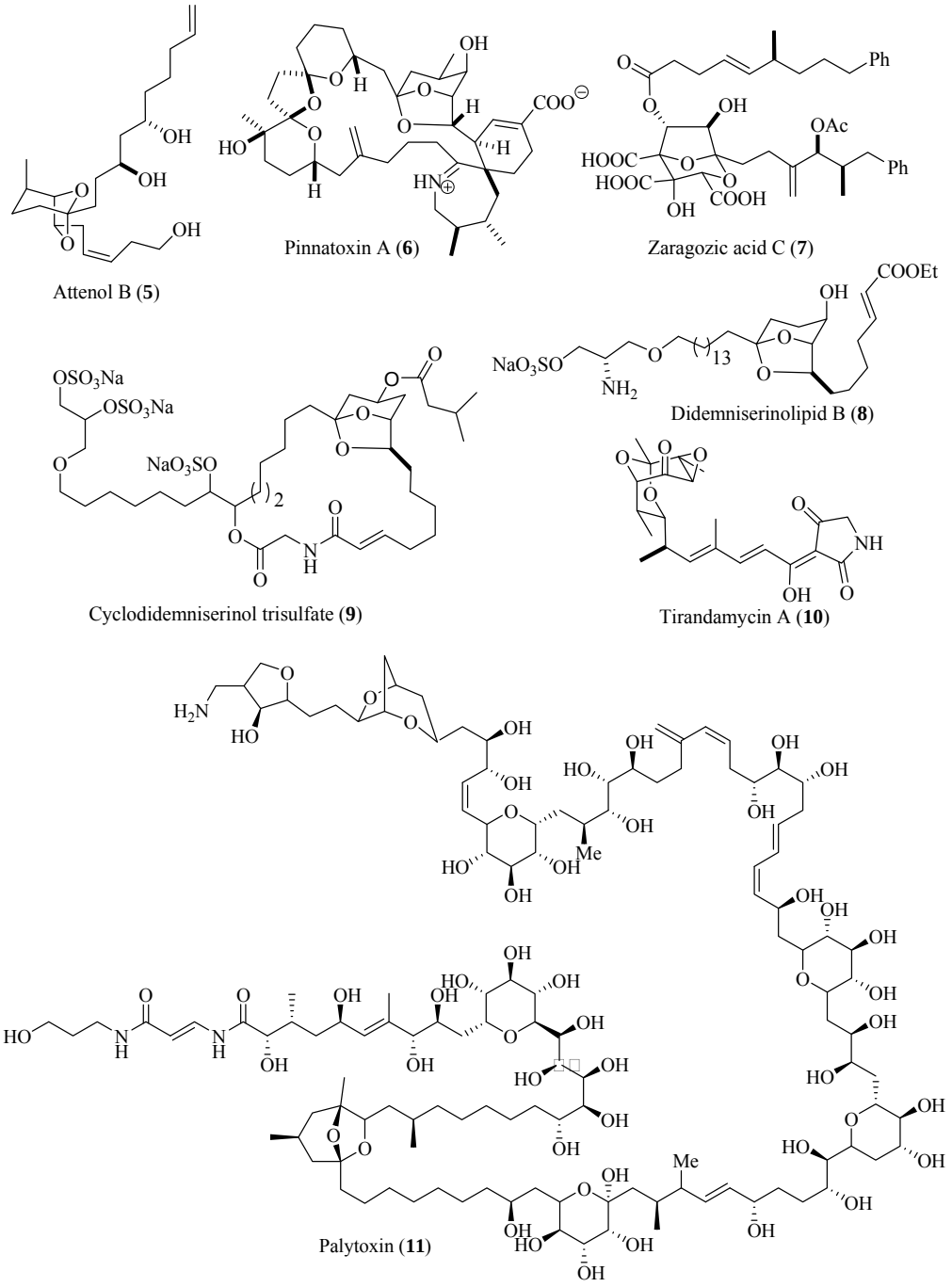


Figure 3: Novel Bicyclic ketals with potent HIV integrase activity.

Cyclodidemniserinol trisulfate (**9**) has shown potent HIV-1 integrase (IC_{50} = 60 μg/mL)[2] and MCV topoisomerase (72 μg/mL) inhibitory activities and is structurally similar to the didemniserinolipids (*vide infra*). Zaragozic acid A (**7**), were shown to be potent inhibitors of squalene synthase, the enzyme which catalyzes the first committed step in cholesterol biosynthesis. Therefore, the zaragozic acids are

promising lead compounds for the development of new cholesterol-lowering drugs. Additionally, members of this class of compounds were shown to inhibit ras farnesyl transferase, and thus have potential as antitumor agents. Attenol B (**5**) has shown cytotoxicity (IC_{50} = 24 μg/mL) against the P388 cancer cell line and tirandamycin A (**10**) is a potent inhibitor of terminal DNA transferase and bacterial RNA polymerase, as well as a strong antibiotic against Gram-positive organisms. Finally, the pinnatoxins (**6**) and palytoxin (**11**) are potent shellfishtoxins which also incorporate this bicyclic moiety. Clearly, a vast array of biological activities and structural complexities are encompassed among bicyclic ketal-containing natural products, making efficient and novel methods for their construction an important goal in organic synthesis.

Remarkable biological activities exhibited by some of these natural products, has provided interest in synthetic community to take explore new approaches for and the utilization of bicyclic ketal core as a suitable scaffold of focused compound libraries. Considering the content of the chapters 2 and 3, a brief summarization of available approaches for the construction of bicyclic ketal core will be presented in the proceeding sections. A major emphasis of the present introduction will be on the cycloisomerization of alkyne diols, where several groups around the globe have contributed to develop transition metal catalysts that address the key issue of this approach i.e., regio selectivity.

Traditional approaches to the bicyclic ketals:

The most common strategies for the construction of bicyclic ketal-containing natural products are represented in Figure 4. Starting from the multiple dissymmetric starting materials, a multistep sequence of intermolecular carbon-carbon bond forming reactions is used to construct a fully functionalized acyclic ketodiol or monocyclic hemiacetal (either protected or deprotected). After completing the construction of one of these key intermediates, an acid-catalyzed dehydration converts the ketodiol or hemiacetal to a bicyclic ketal, forming the carbon-oxygen bonds in an intramolecular reaction. Typically, a one-pot deprotection/ketal formation is used to minimize the number of steps in a reaction sequence. If multiple products can be formed in the ketalization step (i.e., a keto triol), then the most thermodynamically stable ketal is commonly the result.

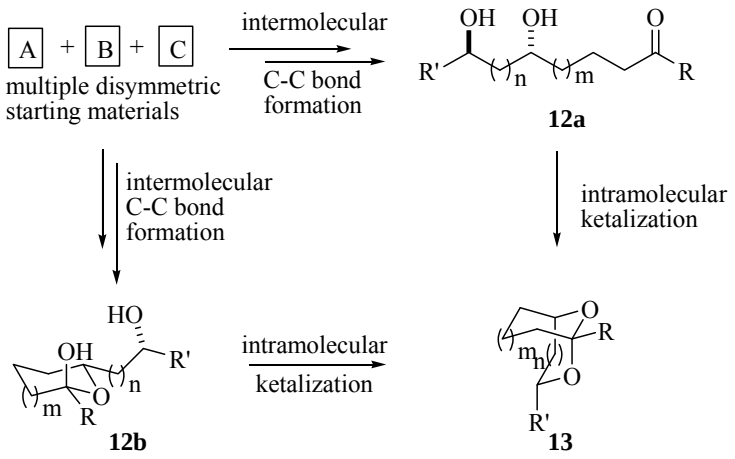
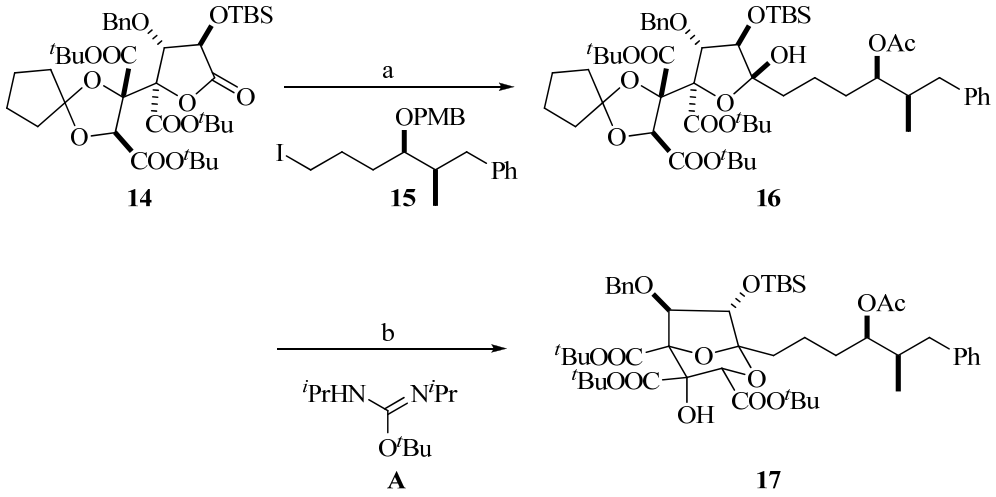


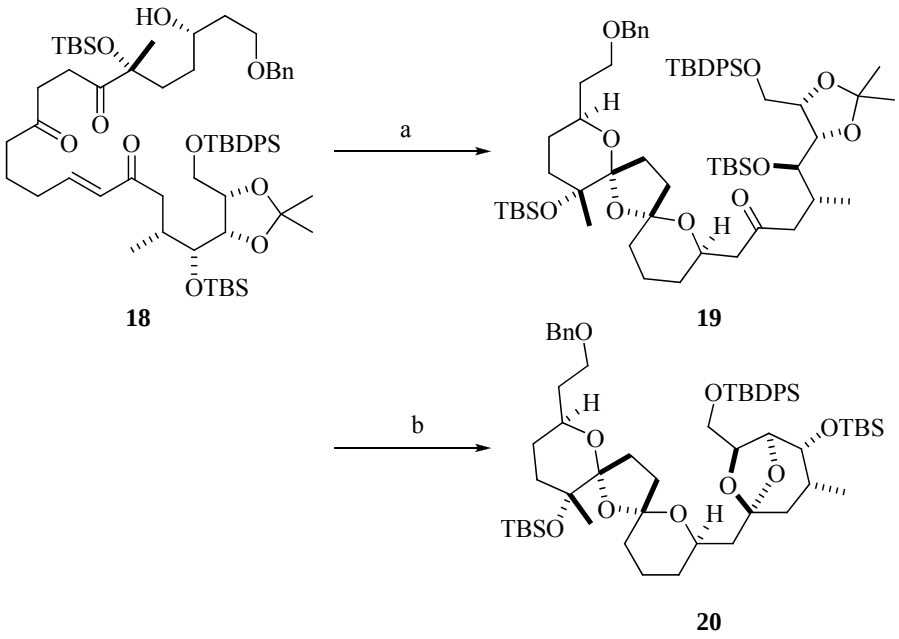
Figure 4: Traditional approach to the bicyclic ketals.

In Evans' total synthesis of zaragozic acid C,[3] bicyclic ketal intermediates was targeted through the hemiacetal dehydration route. Advanced intermediate prepared *via* a chelation-controlled tartrate-derived aldol reaction, was reacted with **15** after metallation of the latter with *t*-butyllithium. After protecting group exchange to prepare **16**, treatment with TFA accomplished deprotection of the cyclopentylidene ketal and bicyclic ketal formation simultaneously. Reesterification of any liberated carboxylic acids led to **17** (Scheme 1).



Scheme 1: *Reagents and conditions:* a) (i) *t*-BuLi, hexane, Et_2O; (ii) DDQ, CH_2Cl_2, H_2O; (iii) Ac_2O, DMAP, Py, PhH, 83% overall; b) (i) CH_2Cl_2, TFA, H_2O; (ii) **A**, CH_2Cl_2, 52% overall.

The BCDEF ring system of pinnatoxin A (**6**) (Figure 3) was recently constructed by Hashimoto and coworkers[4] *via* a two-step sequence assembling starting from acyclic triketone (Scheme 2). Treatment of **18** with lithium methoxide accomplished bis (spiroketal) formation providing tricyclic ketone **19**, together with 14% of minor diastereomers. When the resulting acetonide **19** was treated with camphorsulphonic acid, acetonide cleavage and bridged ketal formation resulted, leading to pentacyclic pinnatoxin intermediate **20**.



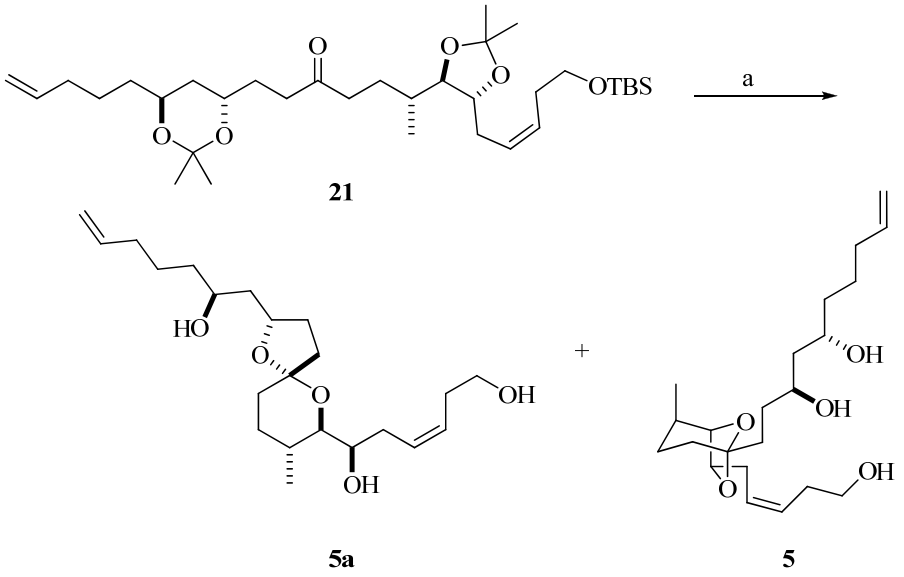
18 **19** **20**

Scheme 2: *Reagents and conditions:* a) LiOMe, THF, MeOH, 77%; b) CSA, DCM, 52%.

In each of the preceeding syntheses, the efficiency of the intramolecular carbon-oxygen bond formation is apparent. The drawbacks to this approach lie not in the ring system syntheses, but in the length of the synthetic routes for construction of the acyclic or monocyclic precursors.

Another drawback to the traditional bicyclic ketal approach is apparent in the Enders' recent Attenol A synthesis (Scheme 3).[5] Using their SAMP-hydrazone methodology, Enders' and coworkers constructed acyclic precursor **21**. Acid-catalyzed protecting group removal revealed a keto pentaol that cyclized under the reaction conditions to give a 6.3:1 ratio of spiroketal-containing attenol A (**5a**) to bicyclic ketal-containing attenol B (**5**) in 66% combined yield. Since attenol A (**5a**) is the more thermodynamically stable product under these conditions, a high yielding

synthesis of attenol B (**5**) by this method was not possible. A route to bicyclic ketals that did not depend upon equilibration between the acyclic, monocyclic and the bicyclic intermediates could provide a more efficient path to targets such as attenol B (**5**), where more than one ketal product can be formed in an intramolecular ketalization step.



Scheme 3: *Reagents and conditions:* a) *p*-TSA, MeOH, 66%.

Considering the drawbacks inherent in the traditional approach to bicyclic ketal-containing target and the advantages of using bicyclic acetal or ketal templates for stereoselective functionalization, the Burke group devised a new strategy for their construction (Figure 5).[6]

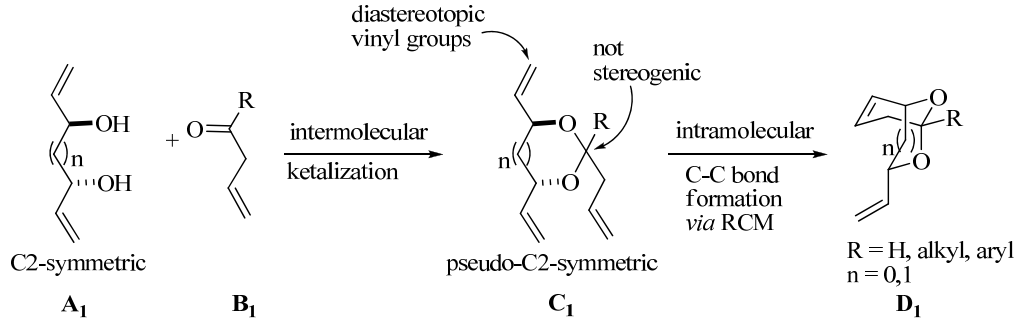
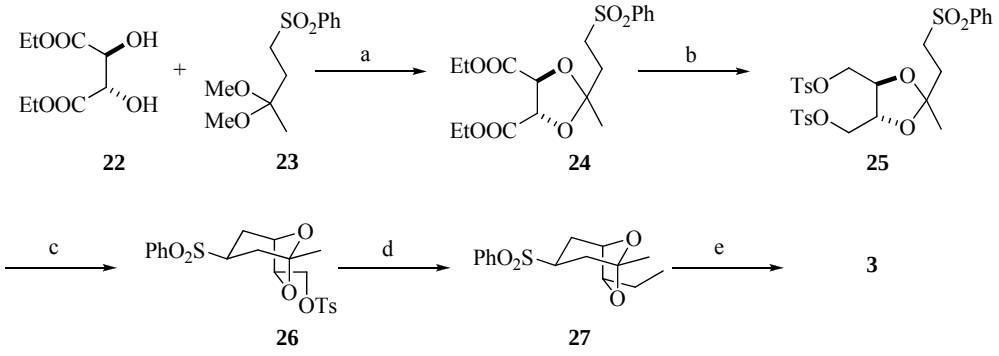


Figure 5: Burke's Ketalization/Ring Closing Metathesis.

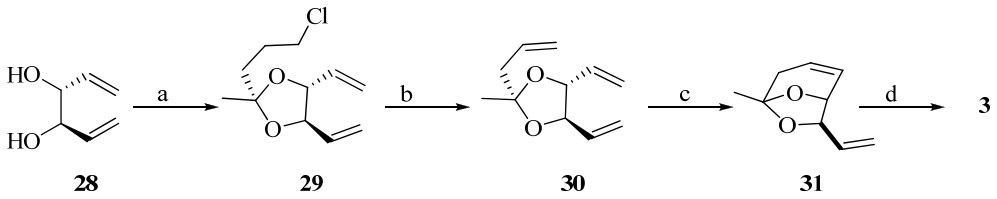
Olefin metathesis of the pseudo-C_2-asymmetric triene intermediate (**C_1**) could participate in the RCM reaction to give a bicyclic ketal product (**D_1**) with two olefins ready for further functionalization. This new strategy to assemble bicyclic ketals, desymmetrization by ketalization/RCM, appeared to be a promising route to a vast array of bicyclic ketal-containing natural products.

More than twenty years ago, Masaki and coworkers[7] used a pseudo-C_2-asymmetric end differentiation strategy for bicyclic acetal and ketal synthesis that most closely resembles the K/RCM desymmetrization approach (Scheme 4). In their total synthesis of (+)-exo-brevicomin (**3**), the aggregation pheromone of the western pine beetle, Dendroctonus brevicomis, D-(−)-diethyltartrate **22** was reacted with dimethyl ketal **23** to give ketal **24**. Conversion to ditosylate **25** was accomplished efficiently *via* ester reduction and sulfonylation. Treatment of the sulfone **25** with *n*-Butyllithium led to bicyclic ketal **26** as a single diastereomer after intramolecular alkylation. Displacement of the remaining tosylate with Me_2CuLi and reductive desulfonylation completed the total synthesis.



Scheme 4: *Reagents and conditions:* a) pTSA, C_6H_6, 87%; b) (i) $NaBH_4$, EtOH; (ii) TsCl, Py, 90% overall; c) *n*BuLi, THF, 81%; d) Me_2CuLi, Et_2O, Me_2S, 76%; e) Na, EtOH, THF, 67%.

The Burke group's first application of the desymmetrization by K/RCM strategy resulted in another short and efficient total synthesis of (+)-*exo*-brevicomin (**3**)[6] (Scheme 5). Diene diol **28** (*vide infra*) and commercially available ketone readily participated in an acid-catalyzed ketalization reaction providing ketal **30** in excellent yield. Elimination of HCl provided access to the bridged bicyclic ketal **31** *via* the RCM of the triene. Finally, hydrogenation of both olefins in diene **31** furnished (+)-*exo*-brevicomin (**3**).



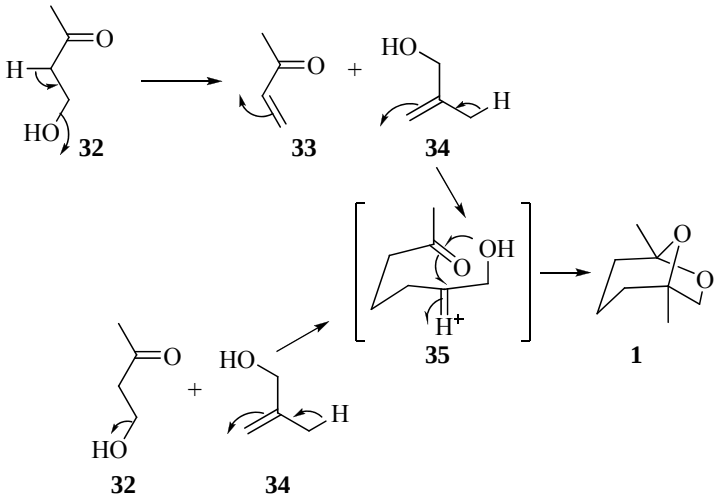
Scheme 5: *Reagents and conditions:* a) 5-Chloro-2-pentanone, *p*-TSA, C_6H_6, 96%; b) KO^{t}Bu, 18-C-6, pentane, 90%; c) Grubbs' I, CH_2Cl_2, 86%; d) H_2, Pd-C, MeOH, 82%.

While the brevicomin total synthesis was short and efficient, the bicyclic ketal was not used as a template for further functionalization, with hydrogenation eliminating both the olefins *en route* to the natural product. Application of this strategy towards the synthesis of more complex bicyclic ketal containing natural products seemed a logical next step, since a vast array of functional groups could be introduced selectively using different templates. Alternatively, late-stage acid-catalyzed hydrolysis of bicyclic ketals could lead to hemiacetal-containing natural products (i.e., sialic acids and bryostatins, *vide infra*), opening the door to another important class of target molecules. The testing of this hypothesis depended upon the judicious choice of target structures, carefully planned olefin functionalization strategies, and application of other synthetic methodology as required for the efficient completion of each total synthesis.

Besides the above mentioned approaches, many more syntheses for the formation of functionalized 6,8-dioxabicyclo[3.2.l]octanes have been reported. A few representative examples of the approaches are mentioned below:

1) D'Silva *et al.*:

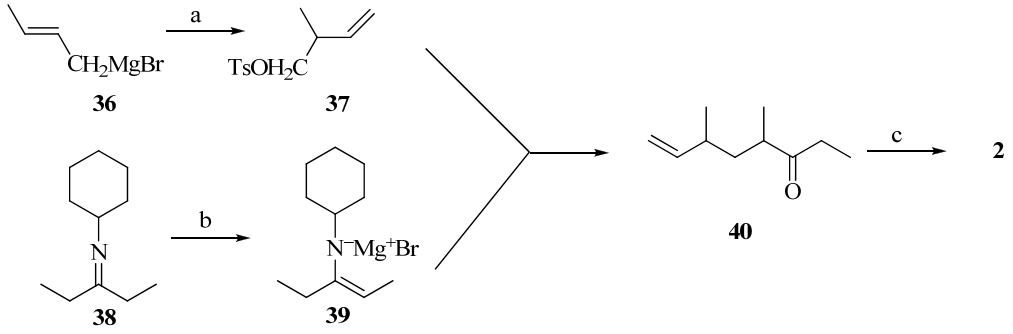
A simple, one-step synthesis of frontalin has been reported by heating a mixture of formaldehyde (as formalin, paraformaldehyde or trioxane), excess of acetone, and methallyl alcohol, *without* any *catalyst,* in a stainless steel autoclave or sealed glass tube at 250-275 °C for 1 h (Scheme 6).[8]



Scheme 6:

2) Silverstein *et al.*:

Alkylation of the magnesium bromide salt (**39**) of the ketimine (**38**) formed from 3-pentanone and cyclohexylamine with the tosylate (**37**) in THF gave, after acid hydrolysis, **40**. Epoxidation of **40** was accomplished with *m*-chloroperoxybenzoic acid in benzene, and cyclization was effected by removal of excess peracid and treatment with $SnCl_4$ to afford the racemic **2** (Scheme 7).[9]

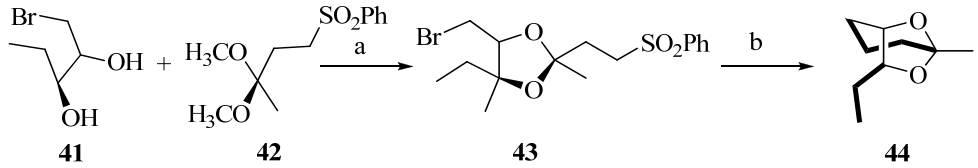


Scheme 7: *Reagents and conditions:* a) (i) CO_2; (ii) LAH, THF; (iii) TsCl, Py; b) EtMgBr/THF; c) (i) *m*CPBA, Benzene; (ii) $H^+/SnCl_4$.

3) Scharf *et al.*:

The chiral building blocks **41** was converted with 4-(phenylsulfonyl)-2-butanone dimethyl acetal **42** by stereoselective cycloacetalization under kinetic control into the chiral 1,3- dioxolane systems **43**. The intramolecular cyclization with

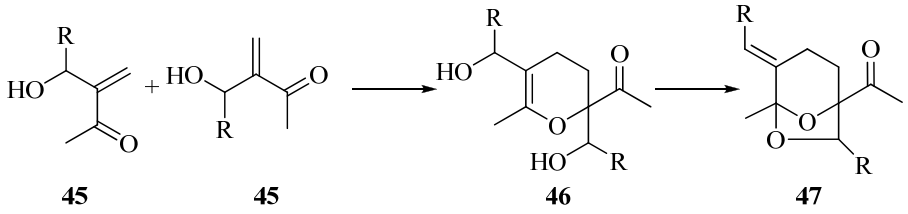
lithium diisopropylamide followed by reductive desulfonation yielded the (+)-(l*R*,5*S*,7*S*)-*endo*-brevicomin **44** (Scheme 8).[10]



Scheme 8: *Reagents and conditions:* a) *p*-TSA/CH_2Cl_2, –8 °C, 82%; b) (i) LDA/THF, –78 °C, 92%; (ii) Na-Hg/MeOH, 20 °C, 80%.

4) Hoffmann *et al.*:

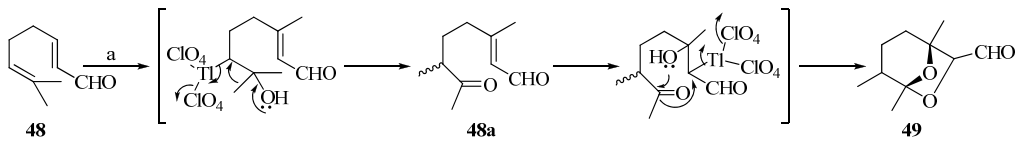
Coupling of aldehydes with methyl vinyl ketone in presence of 1,4-diazabicyclo [2.2.2]octane (DABCO) gave the 3-ketoallyl alcohols **45** which were heated in a high-boiling aromatic hydrocarbon to afford the bicyclic compounds **47** (Scheme 9).[11]



Scheme 9:

5) Yamada *et al.*:

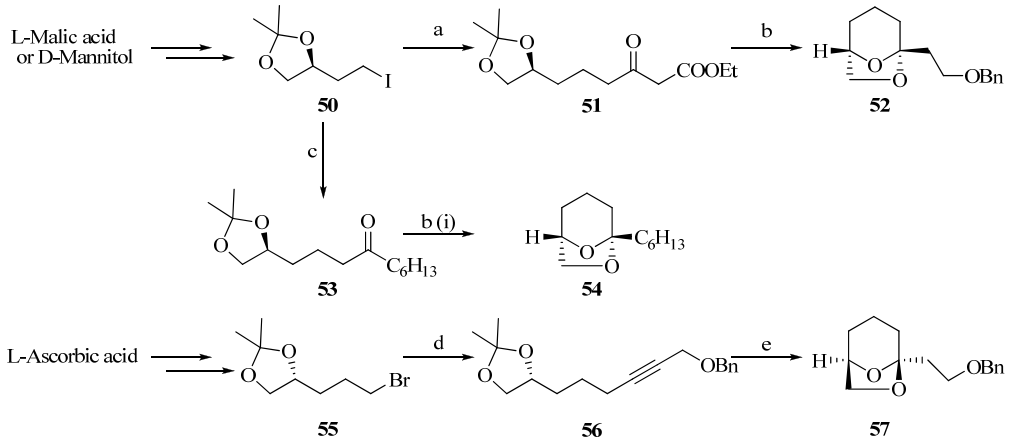
A novel synthesis of 6,8-dioxabicyclo[3.2.l]octane derivatives **49**[12] by the reaction of the 1,5-diene **48** with thallium(II1) perchlorate has been reported (Scheme 10).



Scheme 10: *Reagents and conditions:* a) $Tl(ClO_4)_3$, CH_2Cl_2, rt, 3 h.

6) Kotsuki *et al.*:

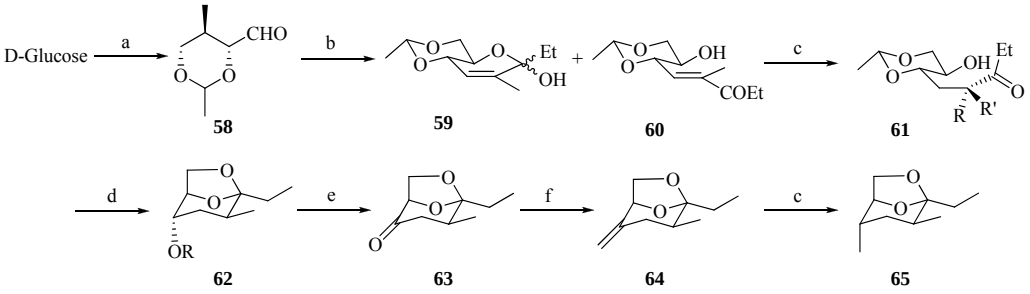
The optically active iodides **50** derived from L-malic acid or D-Mannitol were condensed with a dianion of acetoacetic ester. The subsequent bicyclic ketal formation was effected by treating with a catalytic amount of *p*-TSA in refluxing dichloromethane. Besides the ketodiol approach, the intrinsic nature of acetylenes as a carbonyl synthon was exploited wherein acetylene **56** derived from L-ascorbic acid was reacted after liberation of the diol unit, with a catalytic amount of mercury(II)oxide and *p*-TSA to afford the bicyclic ketal **57** (Scheme 11).[13]



Scheme 11: *Reagents and conditions:* a) Ethylacetoacetate, THF, 0 °C; b) (i) *p*-TSA, CH_2Cl_2, reflux; (ii) LAH, THF; (iii) NaH, BnBr; c) $C_6H_{13}CNNMe_2CH_2$, THF, –78 °C then silica gel, CH_2Cl_2; d) $LiC{\equiv}CCH_2OBn$, THF/HMPA, 76%; e) (i) H_3O^+; (ii) *p*-TSA, HgO, THF, 60 °C, 74%.

7) Izquierdo *et al.*:

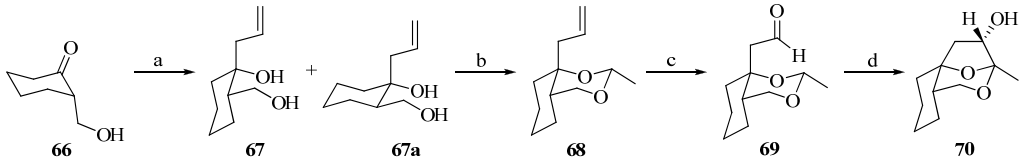
Reaction of **58** with triphenyl(1-propionylethylidene)phosphorane gave a mixture of **59** and **60** which upon hydrogenation yielded an inseparable mixture of **61** which upon treatment with *p*-TSA and 1,2-propylene glycol caused the loss of the ethylidene group by transketalization and promoted intramolecular double cyclization to produce **62**. Oxidation with PCC to the previously unknown ketone **63**, subsequent reaction with methylenetriphenylphosphorane to yield the vinylic compound **64** and finally hydrogenation over Pd/C to afford **65** as the major component (Scheme 12).[14]



Scheme 12: *Reagents and conditions:* a) 2 steps b) PPh_3=CHCOOEt; c) H_2, Pd/C; d) pTSA, $MeCHOHCH_2OH$; e) PCC, 4 Å MS, CH_2Cl_2; f) $Ph_3P=CH_2$.

8) Halcomb *et al.*:

The 2,8-dioxabicyclo[3.2.1]octane ring system of the zaragozic acids was synthesized by a Norrish Type II photochemical reaction.[15] This reaction occured through an unusual 1,6-hydrogen abstraction to generate an acetal derived 1,5-biradical. Reaction of **66** with allylmagnesium bromide afforded two diastereomeric products **67** and **67a** as a separable (1:1) mixture. The hydroxyl groups of **67** were engaged in a cyclic acetal to afford **68**, which was ozonized to give the photochemical precursor aldehyde **69**. Upon irradiation, an intramolecular hydrogen abstraction by the excited aldehyde and subsequent cyclization occurred to generate the bicyclic ketal **70** (Scheme 13).

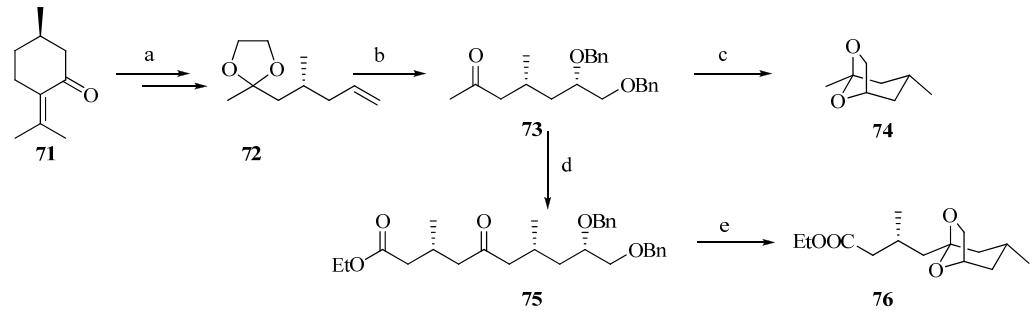


Scheme 13: *Reagents and conditions:* a) 2.2 eq $CH_2CH=CH_2MgBr$, THF, 0 °C→ rt, 65%; b) $CH_3CH(OCH_3)_2$, pTSA, 80 °C, 41%; c) (i) O_3, $MeOH/CH_2Cl_2$, −78 °C; (ii) Me_2S, 61%; d) *hv*.

9) Kitching *et al.*:

Model structures **74** and **76** were derived (Scheme 14) from protected enone **72** which was acquired from R-(+)-pulegone **71**.[16] Treatment of **72** with AD-mix-α and protection of the formed diol *(bis-benzylation),* followed by ketone release yielded **73**. On hydrogenation, **73** afforded the desired bicyclo[3.2.1]octane **74**. Alternatively, the SAMP derivative ((*S*)-l-amino-2-methoxymethylpyrrolidine) of **73**, was deprotonated and added to ethyl crotonate at −105 °C, followed by ozonolytic

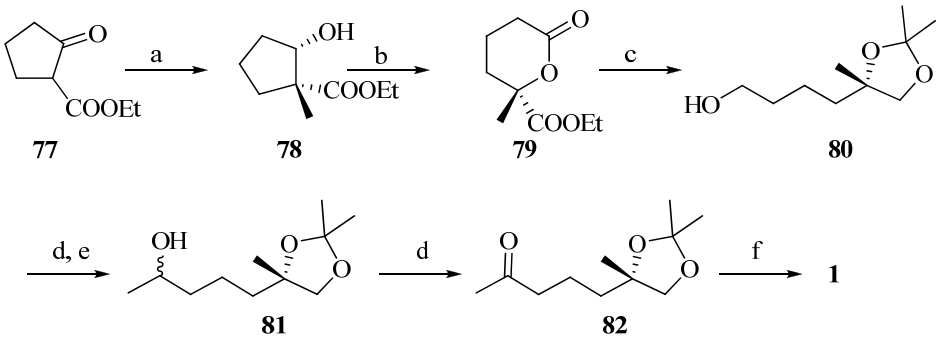
removal of hydrazone to yield **75**. Debenzylation by hydrogenolysis provided the desired dioxabicyclo[3.2.1] octane **76**.



Scheme 14: *Reagents and conditions:* a) 7 steps, 17%; b) (i) AD mix-α; (ii) KH, BnBr; (iii) AcOH-H_2O, 58% (3 steps); c) H_2/Pd, MeOH, 23%; d) (i) SAMP; (ii) LDA; (iii) *E*-Ethylcrotonate, −105 °C; (iv) O_3, −78 °C, 16%; e) H_2/Pd, MeOH, 78%.

10) Mori *et al.*:

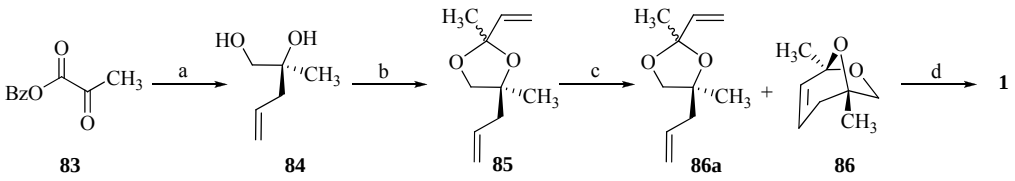
Asymmetric reduction of ethyl 2-oxocyclopentane-1-carboxylate **77** by Baker's yeast followed by methylation of the dianion derived from (1*R*,2*S*)-**78** gave (1*R*,2*S*)-**79**. Jones oxidation followed by Baeyer-Villiger oxidation gave the desired lactone **79**. Reduction of the lactone with lithium tetrahydridoaluminate was followed by acetonide formation to give **80** which was oxidized using PCC. Addition of methylmagnesium bromide afforded the alcohol **81**, which was oxidized with PCC to yield the methyl ketone **82**. Final acid treatment gave the desired frontalin (**1**) (Scheme 15).[17]



Scheme 15: *Reagents and conditions:* a) (i) Baker's yeast, sucrose, H_2O, 52%; (ii) 2.25 eq, LDA, 1.45 eq, MeI, THF, 87%; b) (i) Jones' CrO_3, Me_2CO, 87%; (ii) *m*CPBA, $NaHCO_3$, CH_2Cl_2, 59%; c) (i) $LiAlH_4$, Et_2O; (ii) $Me_2C(OMe)_2$, Me_2CO, $TsOH.H_2O$, 77% (2 steps); d) PCC, NaOAc, molecular sieves 3Å, CH_2Cl_2; e) MeMgBr, Et_2O, 84%; f) $TsOH.H_2O$, Et_2O, H_2O, 81%.

11) Grubbs *et al.*:

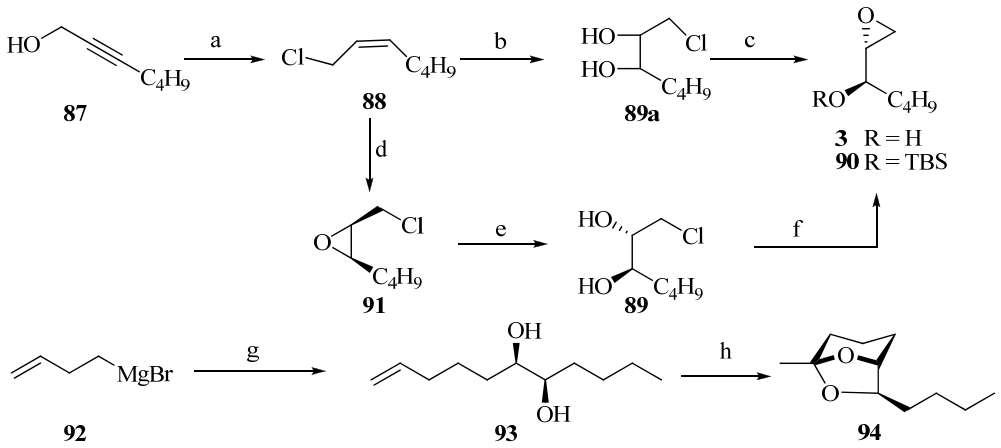
To utilize RCM for the formation of the bicyclic structures, the monocyclic dienes **85** was prepared starting from enantiopure **84**. The ketal **85** was synthesized under mild conditions using Noyori's TMS-OTf assisted ketal formation. RCM of the ketal followed by hydrogenation afforded the bicyclic ketal (**1**) (Scheme 16).[18]



Scheme 16: *Reagents and conditions:* a) (i) Sn(ll)-catecholate, (+)-DIPT, DBU, CuI, Allyl-Br, CH_2Cl_2, −78 °C, 81%; (ii) $LiAlH_4$, Et_2O, 0 °C, then 25 °C, 89%; b) (i) TMSCl, Et_3N, CH_2Cl_2, 0 °C to 25 °C, 83%; (ii) MVK, TMS-OTf, CH_2Cl_2, −78 °C, then –20 °C, 85%; c) 5 mol% Grubbs' I, CH_2Cl_2, rt, 10 min; d) 1 atm. H_2, Pd/C, $CHCl_3$, rt, 30 min.

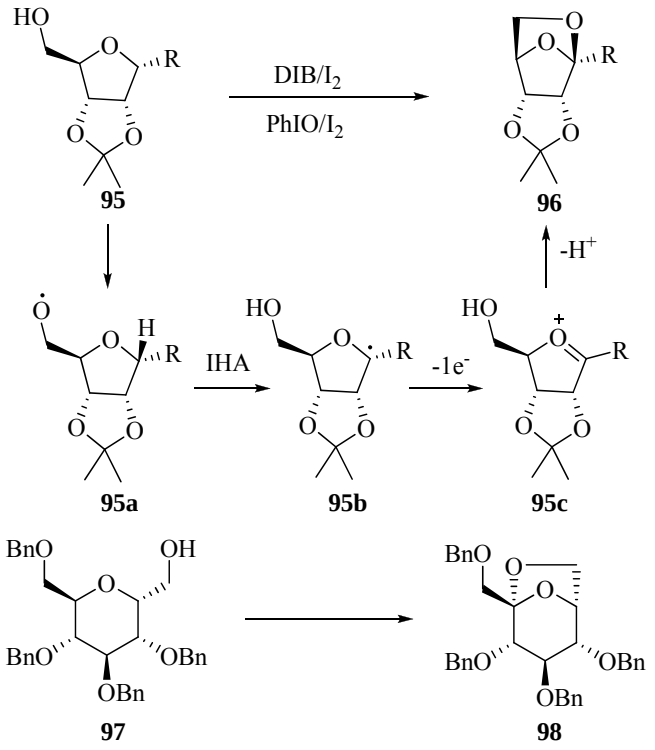
12) Faber *et al.*:

Alcohol **87** was selectively hydrogenated with Lindlar catalyst to give the corresponding *cis*-alkene and halogenation of the hydroxyl group *via* Appel conditions (PPh_3/CCl_4) gave haloalkene (*Z*)-**88**. Epoxidation of the latter using *m*-CPBA afforded (±)-*cis*-**91**. *cis*-selective dihydroxylation of (*Z*)-**88** with cat. OsO_4 afforded (±)-*threo*-diol **89a**. The latter compound was treated with NaH to give epoxy alcohol (±)-*cis*-**90** after ring-closure. The racemic substrate (±)-*cis*-**91** was subjected for biohydrolysis to furnish the corresponding diol **89** which underwent subsequent intramolecular cyclization to yield epoxy alcohol **3** which was silylated as its TBS ether **90**. Treatment of **92** with CuI and subsequent addition of (2*R*,3*R*)-**90**, followed by deprotection of the silyl ether using $Bu_4N^+F^-$ furnished diol (5*R*,6*R*)-**93**. Finally, Wacker oxidation employing $PdCl_2$ as catalyst, using $CuCl_2$ as re-oxidant, gave (+)-*exo*-**94** in 94% *ee* (Scheme 17).[19]



Scheme 17: *Reagents and conditions:* a) (i) Lindlar's cat, quinoline, EtOH, KOH, 83%; (ii) PPh_3, CCl_4, 80 °C, 73%; b) OsO_4, NMO, acetone, 53%; c) NaH, THF, 87%; d) *m*-CPBA, CH_2Cl_2, 85%; e) Mycobacterium parafficinum, NCIMB 10420, Tris-buffer, pH 8; f) –HCl, 81%; g) CuI, THF, –10 °C, 15 min; (ii) **90**, 3 h, rt; (iii) TBAF, THF, 30 min, rt, 59%; h) $PdCl_2/CuCl_2$, DME, 68%.

13) Saurez *et al.*:

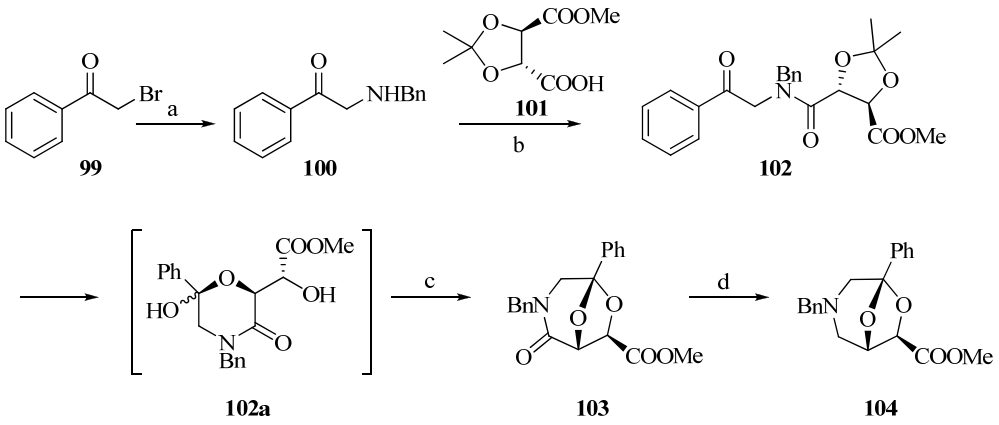


Scheme 18:

Synthesis of chiral 2,7-dioxabicyclo [2.2.1] heptane and 6,8-dioxabicyclo [3.2.1] octane ring systems, under neutral conditions, was achieved using an intramolecular hydrogen abstraction (IHA) reaction.[20] The reaction was triggered by alkoxy radicals generated *in situ* by reaction of alcohols **95** with (diacetoxyiodo)benzene (DIB) or iodosylbenzene in the presence of iodine. The *C*-radical **95b** generated by the IHA is subsequently oxidized with an excess of reagent to give an oxycarbenium ion **95c** that is then internally trapped by the nucleophilic alcohol (Scheme 18).

14) A. Guarna *et al.*:

α-amino acetophenone **100** (Scheme 19) was prepared by reacting benzylamine with α-bromoacetophenone. Condensation of this amino ketone with (*R*,*R*)-tartaric acid mono methyl ester **101** using PyBroP as a coupling reagent furnished amide 1**02**. Cyclization of **102** to the corresponding lactam **103** took place under *trans*-acetalization conditions. Selective reduction of the lactam moiety by BH_3·DMS in THF at room temperature to give aminoester **104**.[21]

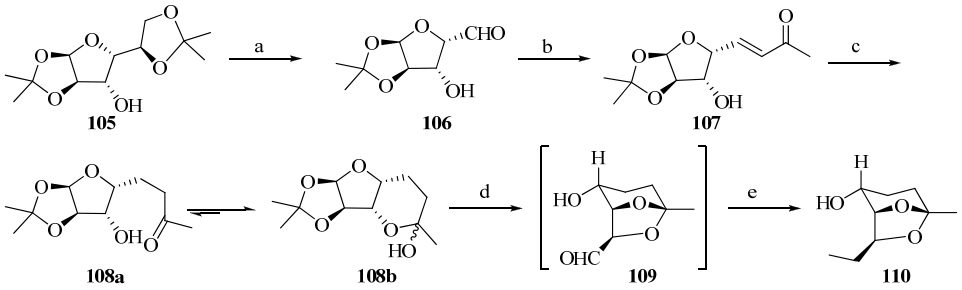


Scheme 19: *Reagents and conditions:* a) $BnNH_2$, 65%; b) PyBroP, 75%; c) H_2SO_4/SiO_2, toluene, reflux, 15 min, 85%; d) BH_3.DMS, THF, 16 h, 70%.

15) Venkateswar rao *et al.*:

The cleavage of the glycol moiety from **105** by periodate followed by Wittig olefination with (2-oxopropylidene)triphenylphosphorane resulted in the formation of the α,β-unsaturated ketone **107**. Hydrogenation gave an equilibrium mixture of **108a** and **108b** (3:7) which was converted to bicyclic ketal derivative **109** with TFA-water solution (3:2). The resultant aldehyde was directly subjected to a Wittig reaction with

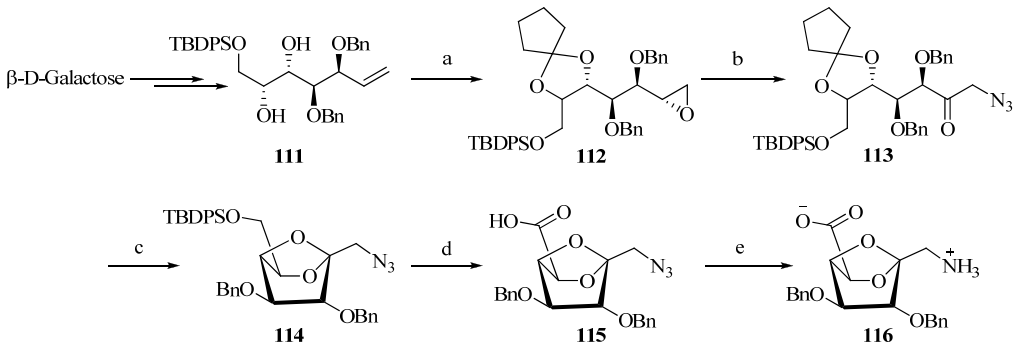
methylidene triphenylphosphorane to give the corresponding olefin. Finally, the palladium catalyzed hydrogenation gave (1*S*,2*R*,5*R*,7*S*)-2-hydroxy-*exo*-brevicomin *ent*-**3** (Scheme 20).[22]



Scheme 20: *Reagents and conditions:* a) (i) 60% aq. AcOH, 12 h, rt; (ii) $NaIO_4$, MeOH, rt, 1 h; b) $Ph_3PCHCOCH_3$, CH_2Cl_2, rt, 2 h; c) Pd/C, H_2, THF, rt, 2 h; d) TFA-H_2O (3:2), 0 °C-rt, 2 h; e) (i) $PPH_3{=}CH_2$, THF, –10 °C-rt, 3 h; (ii) Pd/C, H_2, MeOH, rt, 2 h.

16) Koert *et al.*:

The cyclopentylidene ketal of the diol **111** upon treatment with *m*CPBA gave the epoxide **112** as a diastereomeric mixture. The following epoxide opening yielded the corresponding azidoalcohol. Swern oxidation led to the ketone **113**, which was subjected to bicyclization in a mixture of CH_2Cl_2 and TFA. Cleavage of the TBDPS group and subsequent oxidation of the resulting primary alcohol to the corresponding carboxylic acid with diacetoxyiodobenzene afforded **115**. Final deprotection of the benzyl ethers and simultaneous reduction of the azide was accomplished by hydrogenation with $Pd(OH)_2/C$ (Scheme 21).[23]



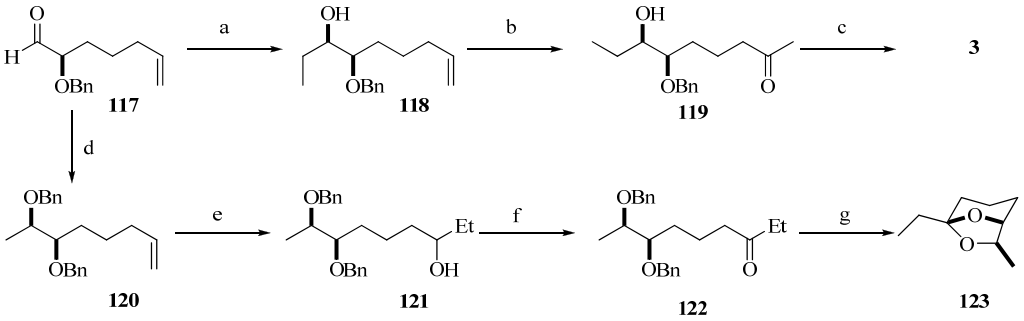
Scheme 21: *Reagents and conditions:* a) (i) 1,1-dimethoxycyclopentane, CSA, MeCN, rt, 25 min, 93%; (ii) *m*CPBA, CH_2Cl_2, 0 °C to rt, 60 h, 87%; b) (i) NaN_3, NH_4Cl, EtOH, 78 °C, 45 h, 94%; (ii) $(COCl)_2$, DMSO, TEA, CH_2Cl_2, –60 °C to rt, 1.5 h, 83%; c) TFA–CH_2Cl_2 (1:1), MS 4 Å, rt, 30 min, 89%; d) (i) TBAF, THF, rt, 1 h, 93%; (ii)

$PhI(OAc)_2$, cat. TEMPO, wet CH_2Cl_2, rt, 2 h, 83%; e) H_2, $Pd(OH)_2/C$, EtOAc–MeOH (2:1), rt, 4 h, quant.

17) Prasad *et al.*:

Aldehyde **117** was treated with ethylmagnesium bromide to yield the corresponding *threo* alcohol **118**. Wacker oxidation of alcohol with $PdCl_2/CuCl$ produced the ketone **119** which on hydrogenation resulted in (+)-*exo*-brevicomin (**3**) formed *via* simultaneous debenzylation and intramolecular ketalization.[24]

The synthesis of (+)-iso-*exo*-brevicomin **123**, was also accomplished in the same manner. The addition of MeMgBr to aldehyde **117** furnished *threo* alcohol which was converted to its benzyl ether **120**. Ozonolysis followed by the treatment of aldehyde with ethylmagnesium bromide afforded **121** as a mixture of diastereomers. Oxidation of the alcohol to ketone **122** and hydrogenation produced (+)-iso-*exo*-brevicomin **123** (Scheme 22).



Scheme 22: *Reagents and conditions:* a) EtMgBr, $MgBr_2$, CH_2Cl_2, –78 °C, 4.5 h, 78%; b) $PdCl_2/CuCl/O_2$, DMF-H_2O, rt, 2.5 h, 85%; c) 10% Pd/C, H_2, MeOH, 3N HCl, rt, 2.5 h, 72%; d) (i) MeMgBr, $MgBr_2.Et_2O$, CH_2Cl_2, –78 °C, 4 h, 70% (2 steps); (ii) NaH, BnBr, DMF, 0 °C-rt, 2 h; e) (i) O_3/O_2, Me_2S, CH_2Cl_2/MeOH, 0 °C, 5 h; (ii) EtMgBr, THF, 0 °C, 1 h, 60% (3 steps); f) IBX, DMSO, rt, 5 h, 90%; g) 10% Pd/C, H_2, MeOH, 3N HCl, rt, 2.5 h, 81%.

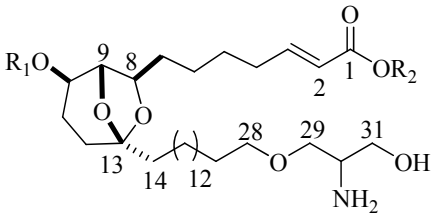
Conclusions:

Though a vast number of methods are available for the synthesis of bicyclic ketals as discussed earlier, only one group (Kotsuki *et al.*)[13] has utilized the synthetic potential of acetylene unit for the construction of the ketal. Further, having established our strategy for the synthesis of ketals by the palladium mediated cycloisomerizations on sugar based alkyne diols as described in Chapter I, we intended to synthesize the central bicyclic core of the Didemniserinolipid B by utilizing the Palladium-mediated cycloisomerization reaction of an alkyne diol as the key reaction.

Present Work

Marine tunicates belonging to the genus *Didemnum* (Phylum Chordata, class Ascidiacea) have proven to be a particularly rich source of structurally diverse and biologically potent marine metabolites. Most of these metabolites are nitrogen-containing compounds derived from amino acids, which can be classed into two major categories: (1) cyclic and acyclic peptides (2) and aromatic alkaloids. Some representative examples of the first group are the cytotoxic cyclic heptapeptides, such as mollamide and cyclodidemnamide, isolated from *Didemnum molle*, and the first sulfamic acid peptide guanidine derivatives, minalemines D-F, isolated from *Didemnum rodriguesi*. Some recent examples of aromatic alkaloids are the novel predator-deterrent didemnimides A-D, isolated from *Didemnum conchyliatum*, and the α-carbolines, didemnolines A-D.[25] Furthermore, other metabolites with miscellaneous structures have been found, including the HIV-1 protease inhibitor didemnaketals A and B, and a number of enterocin derivatives.

As part of a continuing search for biologically active secondary metabolites from ascidians, particularly those belonging to the *Didemnum* genus, the tunicate *Didemnum* sp., was collected along the coast of Sulawesi Island (Indonesia), and a potent cytotoxic activity was found in its methanolic extract against several tumor cells. Thus the isolation and the structural elucidation of the first serinolipids from a marine organism was reported. The didemniserinolipids A-C (compounds **124-126**) are 2-amino-1,3-propanediols linked to a hydroxylated α,β-unsaturated acid having an unusual 6,8-dioxabicyclo[3.2.1]octane structure (Figure 6).[25]



124 R_1=Ac, R_2=H
125 R_1=H, R_2=Et
126 R_1=R_2=H

Figure 6: Didemniserinolipids isolated from marine tunicates.

Extensive NMR analysis (^{1}H NMR, ^{13}C NMR, DEPT, ^{1}H-^{1}H COSY, and HMQC) showed that they contained three quaternary carbons, six methine carbons (two olefinic, three attached to oxygen, and the last one linked to nitrogen), an indeterminable number of methylene carbons (three of which are attached to oxygen), and one methyl carbon (Figure 7).

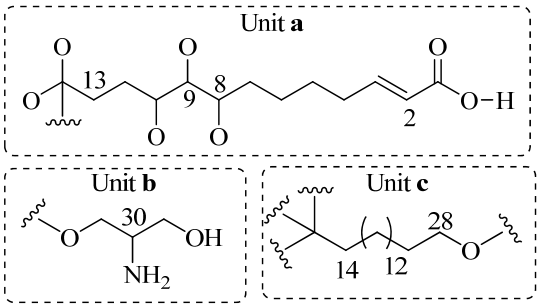


Figure 7: Three structural subunits of Didemniserinolipids.

The structure constituted three structural subunits: **a**, **b** and **c**. COSY experiments gave straightforward connectivities from H-2 to H-5 and from H-6 to H-12. TOCSY correlations from the olefinic proton H-3 to the methine H-8 linked the former spin systems. The *E* geometry of the Δ^2 double bond assigned to an *α,β*-unsaturated acid was derived from the coupling constant of 14.9 Hz between H-2 and H-3. The presence of a monosubstituted serinol moiety in the molecule was deduced from the ^{1}H-^{1}H COSY spectrum and proton and carbon chemical shifts at positions C-29 to C-31. Thus, the methine proton H-30 (δ_H = 3.82 m), linked to a nitrogen-bearing carbon (δ_C = 51.2), is coupled to two methylene protons linked to an oxygen-bearing carbon: H2-29 (δ_H = 4.23/4.30 m, δ_C = 65.3) and H_2-31 (δ_H = 3.64 m, δ_C = 67.0). A long saturated chain with 15 methylene carbons was deduced by the broad peak at δ_H = 1.0-1.3 and δ_C = 22.9-29.8 in the ^{1}H- and ^{13}C NMR spectra, respectively. HMQC and COSY experiments suggested this long saturated chain to be connected to oxygen at one end and to a quaternary carbon at the other end.

HMBC techniques revealed that these fragments were linked through cross-peaks due to 2*J*CH and 3*J*CH long range coupling. Thus, long-range couplings between the carbonyl C-1 and the olefinic protons H-2 and H-3 were consistent with the presence of an *α,β*- unsaturated acid, which was also supported by the UV

absorption at 215 nm and the IR band at 1730 cm^{-1}. The existence of the 6,8-dioxabicyclo[3.2.1]octane system was deduced from the HMBC correlations between the quaternary ketal carbon assigned as C-13 (δ_C = 109.4) to protons H-8, H-9, H_2-12, and H_2-14. Furthermore, HMBC cross-peaks between methylene protons H_2-12 and C-14 connected the long saturated chain (unit **c**) to the bicyclic system (unit **a**). At this point, the link between the monosubstituted serinol (unit **b**) and the long saturated chain through oxygen established the structure of the molecule. ^{1}H NMR coupling constants and NOESY data determined the relative stereochemistry around the [3.2.1]bicyclic system. An intense NOESY cross-peak between H-8 and H-10 revealed their *cis* relationship. The almost zero coupling constants between H-9/H-8 and H-9/H-10 agree with the relative stereochemistry.

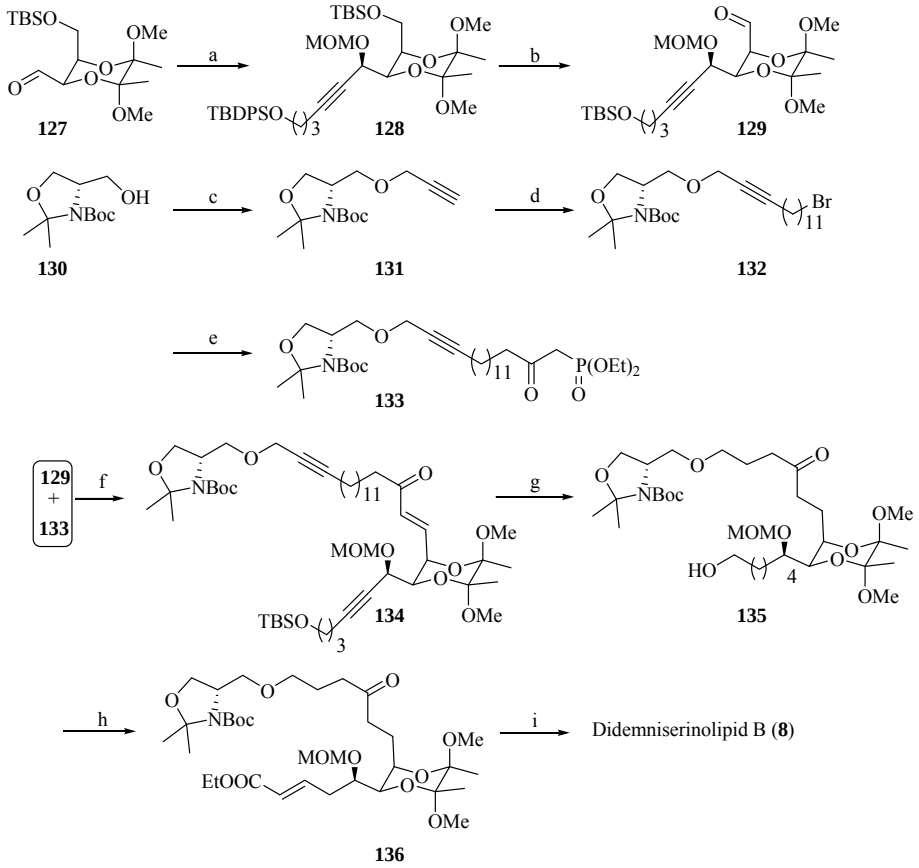
Total Synthesis and Confirmation of Absolute Configuration

There have been two synthesis of didemniserinolipid B reported so far by the Ley group and the Burke group.

Ley *et al.*:[26]

En route to proving the absolute and relative stereochemistry, through synthesis, of (+)-didemniserinolipid B (**8**) using the microwave-assisted method for the sulfation of unreactive hydroxyl groups. The synthesis of two possible diastereomers of (+)-didemniserinolipid B and their 31-*O*-sulfates was achieved starting from D-(or L-)serinol and the BDA protected chiral building block (Scheme 23). The structure of natural (+)-didemniserinolipid B was therefore reassigned as the 31-*O*-sulfate (**8**), and its absolute configuration was determined to be 8*R*,9*R*,10*R*,13*S*,30*S*.

Scheme 23: Ley's protocol for Didemniserinolipid synthesis.

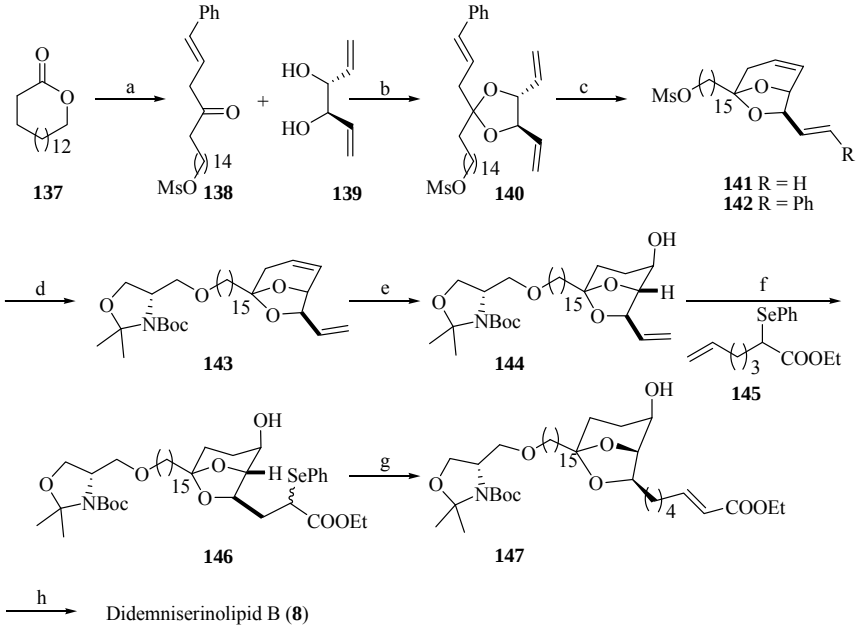


Reagents and conditions: a) (i) $TBDPSO(CH_2)_3CCLi$, THF, −78 °C, 74%; (ii) MOMCl, $^{i}Pr_2NEt$, DME, 60 °C, 75%; b) (i) TBAF, THF, quant.; (ii) TBSCl, Im, THF, 74%; (iii) DMSO, $(COCl)_2$, CH_2Cl_2, −78 °C then Et_3N, to rt, 99%; c) NaH, THF, $HCCCH_2Br$, toluene, 49%; d) *n*-BuLi, THF then $Br(CH_2)_{11}Br$, HMPA, 46%; e) $CH_3COCH_2PO(OEt)_2$, NaH, *n*-BuLi, THF, −78 °C, 97%; f) LiCl, $^{i}Pr_2NEt$, MeCN, 20 °C, 46%; g) (i) Raney-Ni, EtOH, H_2, 73%; (ii) TBAF, THF, 95%; h) (i) Dess-Martin periodinane, Py, CH_2Cl_2, 79%; (ii) triethyl phosphonoacetate, LiCl, $^{i}Pr_2NEt$, MeCN; 20 °C, 96%; i) (i) 1 N HCl, EtOH; 45 °C, 73%; (ii) FmocCl, K_2CO_3, dioxane-H_2O, 64%; (iii) SO_3.Py (10 eq), Na_2SO_4, DMF, microwave, 110 °C; (iv) Piperidine, DMF, 20 °C (84%).

Burke *et al.*:[27]

A modular synthesis of didemniserinolipid B was reported. Central to this synthesis was the use of a ketalization/ring-closing metathesis (K/RCM) strategy to establish the 6,8-dioxabicyclo[3.2.1]octane core (Scheme 24). The C10 axial alcohol was established via a selective epoxidation, followed by reductive *trans*-diaxial epoxide opening. The serinol and unsaturated ester side chains were introduced by a Williamson etherification and cross metathesis, respectively.

Scheme 24: Burke's protocol for Didemniserinolipid synthesis.



Reagents and conditions: a) (i) $CH_3PO(OCH_3)_2$, *n*-BuLi, THF; (ii) $PhCH_2CHO$, MeOH, H_2O, K_2CO_3, reflux; (iii) MsCl, Et_3N, CH_2Cl_2; b) CSA, PhH, reflux, 87%; c) Grubbs' I, CH_2Cl_2, 53% (83% BORSM); d) **130**, NaH, DMSO, 86%; e) i) mCPBA, DCM, 0-4 °C, 60% (1 recycle), (ii) $LiAlH_4$, THF, 0 °C→rt, 86%; f) (i) Grubbs' II, DCM, reflux, 74% (83% BORSM); (ii) NaOAc, H_2O, p-$CH_3C_6H_4SO_2NHNH_2$, DME, reflux, 96%; g) mCPBA, DCM, −78 °C; then Et_3N, warm to rt, 89%; h) (i) HCl, EtOH, 75%; (ii) FmocOSu, K_2CO_3, H_2O, THF, >99%; (iii) SO_3.Py, Na_2SO_4, DMF, 110 °C, microwave; (iv) DMF, piperidine, 27% for 2 steps.

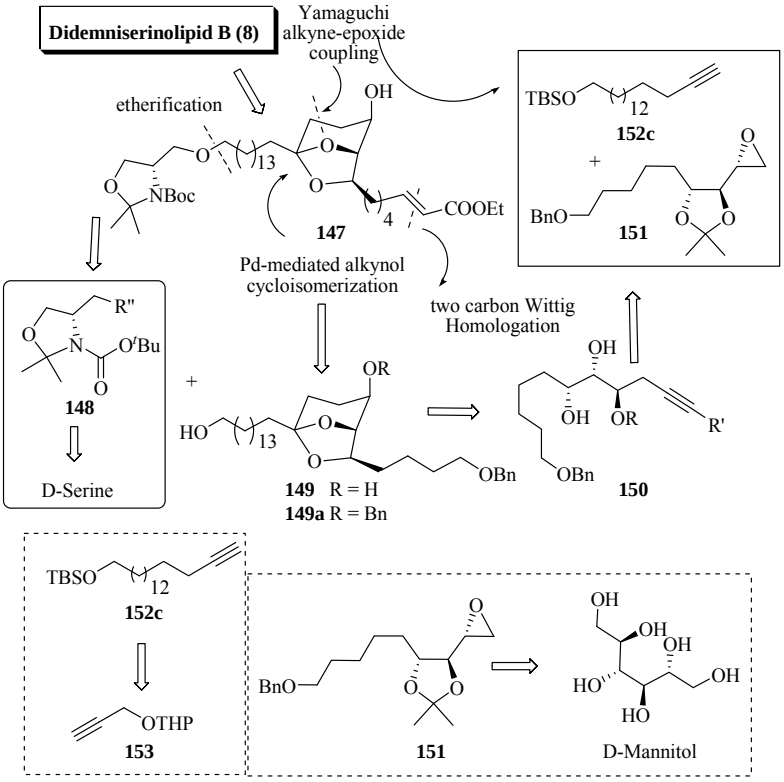
Present work:

Remarkable biological activities exhibited by these didemniserino lipids has provided sufficient window to explore new approaches for, and the utilization of bicyclic ketal core as a suitable scaffold of focused compound libraries. When we started this program, there is only a single report on the synthesis of **8**. As the synthesis of bicyclic ketal is constructed through the intramolecular ketalization, we were interested to explored the synthetic potential of alkynediol cycloisomerization for the construction of the ketal. Our basic idea behind this program is to provide sufficient scope for the library synthesis by functionalizing the alkyne end with a suitable functional group. Further, having established our strategy for the synthesis of ketals by the palladium mediated cycloisomerizations on sugar based alkyne diols as described in Chapter I, we intended to synthesize the central bicyclic core by using the Palladium-mediated cycloisomerization reaction of an alkyne diol. The key

features of our total synthesis program are depicted in the following retrosynthetic scheme.

Retrosynthesis:

Following the precedent synthesis, (Scheme 25), the target molecule can be visualized from the **147** by the deprotection of the acetonide and the Boc group and sulphonation of the primary hydroxyl group. The ketal **147** constitutes the penultimate target in total syntheis of Didemniserinolipid B, as its deprotection and sulfation is already documented by Ley group and the Burke group. The first disconnection is the ether link that combines serinol unit to the central lipid carbon frame work. Scheme 25 describes the salient bond disconnections made for a convergent synthesis of Didemniserinolipid B (**8**).



Scheme 25: Retrosynthetic strategy for Didemniserinolipid B (**8**).

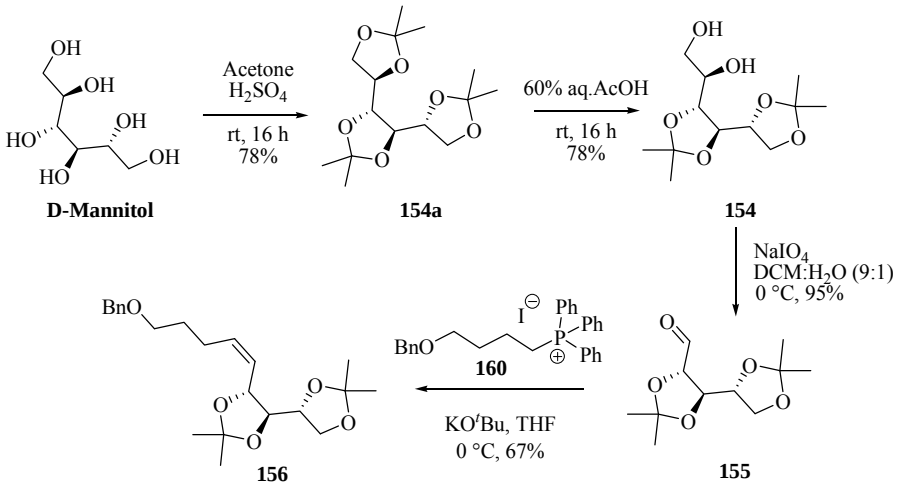
Considering the cycloisomerization as the key reaction, keeping the knowledge we acquired with the model cycloisomerization reactions, we have opted

to place the alkyne favorably for 7-*endo-dig* cyclization. This led us to identify Yamaguchi's alkyne-epoxide coupling[28] as the key carbon chain building reaction. Based upon these key transforms, we identified three fragments **151**, **152c**, **148** as important coupling partners representing the central bicyclic core, long chain alcohol and serinol portions respectively. As shown in Scheme 25, the penultimate ketal **147** was planned by 2 carbon Wittig olefination. The compound **149** was planned by the cycloisomerization of the alkyne triol **150**. The triol **150** can be obtained from the coupling of the epoxide **151** with the alkyne **152c** using the Yamaguchi protocol. After rigorous stereochemical comparisons, epoxide **151** synthesis was intended from D-Mannitol *via* oxidative cleavage of one of the terminal diol followed by a 4 carbon Wittig olefination. The alkyne **152c** can be envisioned from propargyl alcohol *via* alkylation with the requisite alkyl halide and a subsequent acetylenic Zipper reaction. The serinol derivative **148** could be prepared from the known literature methods using D-Serine.

Synthesis of the epoxide 151:

As intended the synthesis of epoxide started from the D-Mannitol which was converted to the corresponding triacetonide following the known procedure. Upon selective hydrolysis by employing 60% acetic acid, the triacetonide gave the known diacetonide **154** in good yields. The oxidative cleavage of the resulting diacetonide using $NaIO_4$ gave the intermediate aldehyde **155** which was further used for Wittig reaction without purification. The Wittig olefination of aldehyde needs a special mention here. The generation of corresponding ylide from the phosphonium salt **160** (derived from 1,4-butane diol in 3 steps, Scheme 27) could be effected by either of the three bases ca. *n*-BuLi/KO^{t}Bu/NaHMDS. When the reactions were attempted with the ylide generated through keeping the stoichiometry of the diol and the salt the same, it was observed that with *n*-BuLi generated ylide, though the olefination was effective, the yield is only 20%. With the ylide generated by using either KO^{t}Bu or NaHMDS base, the yield was improved to 55% yield. However, in case of NaHMDS, the formation of alcohol resulting from the reduction of the aldehyde **155** made the separation of the products a difficult task. Also, it was observed that addition of ylide generated in THF to a solution of the aldehyde in ether at 0 °C resulted in better yields.

Thus the Wittig homologation of aldehyde **155** with four Carbon Wittig ylide afforded the olefin **156** in an *Z*/*E* ratio of 9:1 as indicated by the ^{13}C NMR (Scheme 26). However the double bond was of no consequence for us as it would be reduced at the later stage of our synthesis. The ^{1}H NMR spectrum showed the presence of two olefinic protons at δ 5.42 and 5.64 with a relatively small coupling constant of 10.7 Hz indicative of a *cis* double bond. Five additional protons in the downfield region corresponding to the benzyl group were observed as multiplet at δ 7.27-7.35. The ^{13}C NMR spectrum of **156** showed two doublets of the olefinic carbons at 127.4 and 134.9 ppm and the corresponding doublets of the aromatic ring of the benzyl group at 127.5 and 128.3 ppm. All other analytical data were in accordance with the assigned structure.

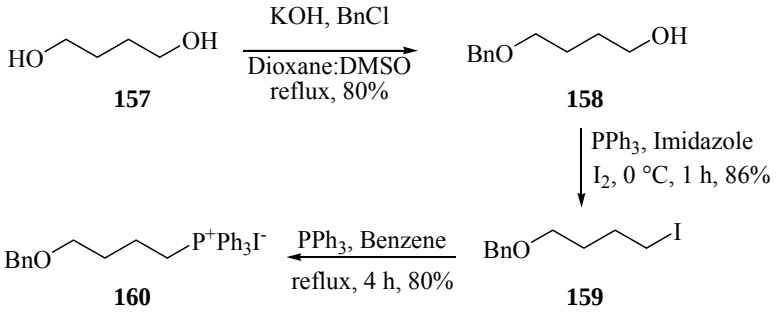


Scheme 26: Synthesis of *Z*-olefin **156**

Synthesis of Wittig Salt 160:

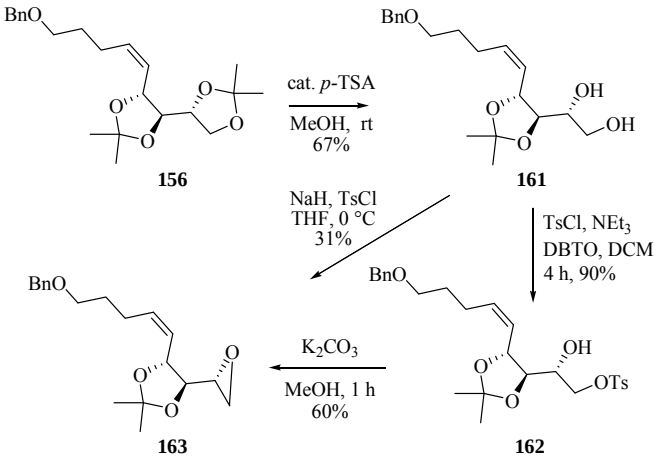
According the reported procedure,[29] 1,4-butane diol was selectively protected as its mono benzyl ether **158**. Iodination of the alcohol **158** using triphenylphosphine afforded the iodide **159** (Scheme 27). The ^{1}H NMR spectrum of **159** showed the upfield shift of two methylene protons to δ 3.19 and corresponding shift of the methylene carbon to 6.8 ppm in the ^{13}C NMR spectrum. IR, Mass and other analytical data were in accordance with the structure. The preparation of the Wittig salt was standardized after trying different solvents such as diethylether, benzene, toluene. Best yields were obtained using benzene as the solvent. The Wittig salt **160** was

prepared from the alcohol by refluxing **159** with triphenylphosphine in benzene for 4 h.



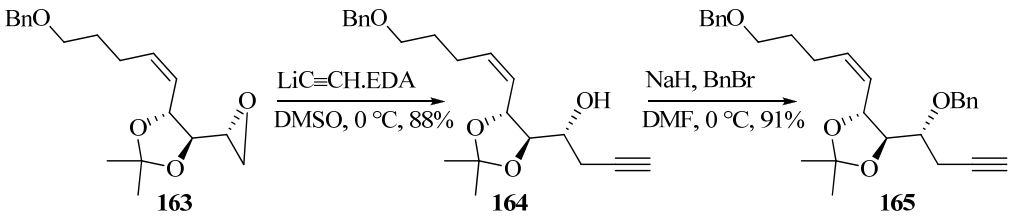
Scheme 27: Preparation of Wittig Salt **160**.

After establishing the constitution of the olefin intermediate **156**, we next intended to proceed for the synthesis of corresponding epoxide **163** by post poning the olefin hydrogenation during the debenzylation of terminal benzyl ether at an advanced stage, thus reducing the number of steps. The selective terminal acetonide deprotection olefin **156** was affected by using *p*-TSA in MeOH to afford the diol **161**. The ^{1}H NMR spectrum showed the absence of two singlets at δ 1.31 and 1.41 corresponding to the isopropylidene group. Also in the ^{13}C NMR spectrum, the disappearance of two quartets at 25.2 and 26.6 ppm and the ketal carbon at 109.4 ppm confirmed the deprotection. In the IR spectrum, the O-H stretching was observed at 3300 cm^{-1}. After confirming the selectivity of acetonide deprotection, the resulting diol was advanced to the epoxide **163** through the the monotosylate **162**. The diol was also converted into the epoxide **163** in one pot using 2 eq of NaH and 1 eq of TsCl (Scheme 28). In either cases, the yields were relatively the same. Hence the one pot reaction was preferred for the epoxide formation. The ^{1}H NMR spectrum showed the characteristic protons of the oxirane at δ 2.63 (dd), 2.75 (dd) and 2.97-3.03 (m) and carbons of the oxirane resonated at 44.4 and 50.9 ppm as triplet and doublet in the corresponding ^{13}C NMR spectrum.



Scheme 28: Formation of the epoxide.

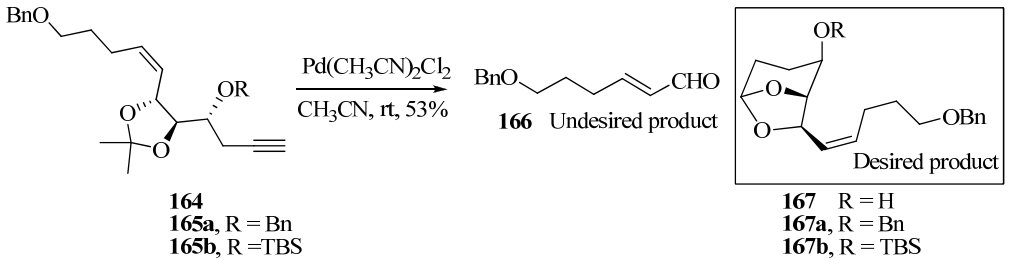
Having the epoxide in hand, now the stage was set for the epoxide opening with the requisite 17C alkynol. Prior to this, we thought of opening the epoxide with easily available alkynes and observe the pattern of cyclization whether it would follow an *exo* or an *endo* mode, out of which the 7-*endo* mode is the desirable one in the context of this molecule. Accordingly, opening of the epoxide **163** with lithium acetylide gave the homopropargylic alcohol **164**. The proton of the terminal alkyne resonated as a triplet at δ 2.0 and the propargylic protons as multiplets in the upfield region of δ 2.24-2.42 in the ^{1}H NMR spectrum. The acetylenic carbons resonated at 70.7 and 80.2 ppm as doublet and singlet respectively in the ^{13}C NMR spectrum. The IR spectrum showed the C≡C stretching at 2215 cm^{-1}. The alcohol **164** was protected as its benzyl ether **165** (Scheme 30). The ^{1}H NMR spectrum showed the presence of 5 protons in the downfield region at 7.26-7.36 ppm corresponding to the benzyl group. The benzylic protons resonated at δ 4.64 and 4.73 with a large coupling constant of 11.6 Hz. The ^{13}C NMR spectrum also showed five additional doublets in the region of 127.3-138.5 ppm corresponding to the benzyl group (Scheme 29).



Scheme 29: Formation of homopropargylic alcohol.

Mode of cyclization:

Attempts to arrive at the bicyclic ketal **167** were in vain utilizing the homopropargylic alcohol **164** or a silyl/benzyl ether **165** of the alcohol. The cyclization instead gave an α,β-unsaturated aldehyde **166** obtained by the oxidative cleavage of the olefin **164** (Scheme 30). The ^{1}H NMR spectrum showed the olefinic protons resonating at δ 6.10 and 6.84 with a large coupling constant of 15.7 Hz indicative of a *trans* double bond. Also the proton of the aldehyde resonated at δ 9.8 as a doublet. The IR spectrum showed a C=O stretching at 1689 cm^{-1} corresponding to the carbonyl carbon.

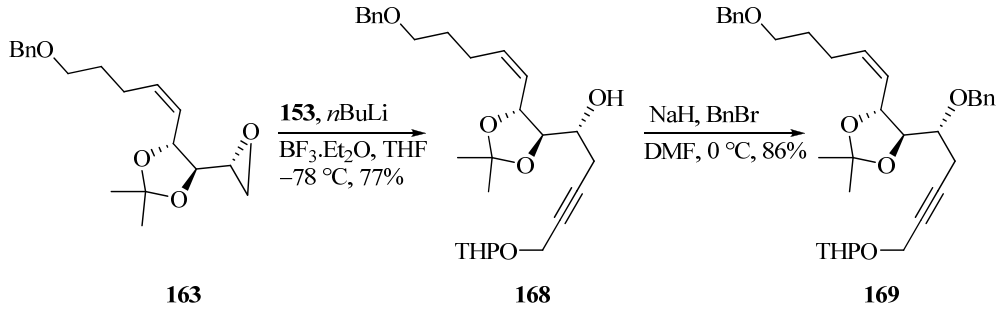


164
165a, R = Bn
165b, R =TBS

167 R = H
167a, R = Bn
167b, R = TBS

Scheme 30: Cycloisomerizations of the alkyne.

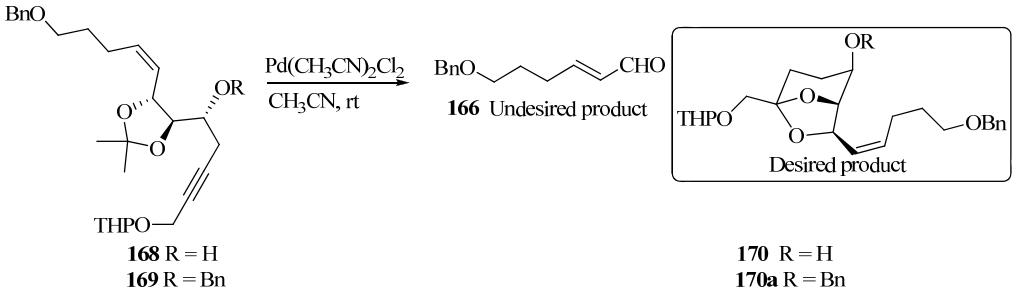
Next, applying the Yamaguchi protocol, the epoxide **163** was treated with the alkynyl borane of the THP ether of propargyl alcohol **153** to yield the homopropargyl alcohol **168**. The propargylic protons resonated at δ 2.28/2.44 (dq/dt) and at δ 4.17/4.27 (ddt) and the characteristic proton of the THP ring resonated at δ 4.79 in the ^{1}H NMR spectrum. The acetylenic carbons resonated at 78.6 and 82.2 ppm as singlets and the doublet of the THP ether resonated at 96.6 ppm in the ^{13}C NMR spectrum. The C≡C stretching was observed at 2190 cm^{-1} in the IR spectrum. The alcohol was protected as its benzyl ether **169** using benzyl bromide and sodium hydride as the base (Scheme 31). The presence of five additional protons in the downfield region at δ 7.27-7.38 corresponding to the benzyl group in the ^{1}H NMR spectrum confirmed the benzylation. The benzylic protons resonated as doublets at δ 4.65 and 4.73 with a large coupling constant of 11.7 Hz. The presence of an additional triplet at 72.8 ppm corresponding to the benzylic carbon in the ^{13}C NMR spectrum confirmed the benzylation.



163 **168** **169**

Scheme 31:

The compound **168/169** upon cyclization under the previous conditions also resulted in the α,β-unsatuarted aldehyde rather than the desired core **170** (Scheme 32).



168 R = H
169 R = Bn

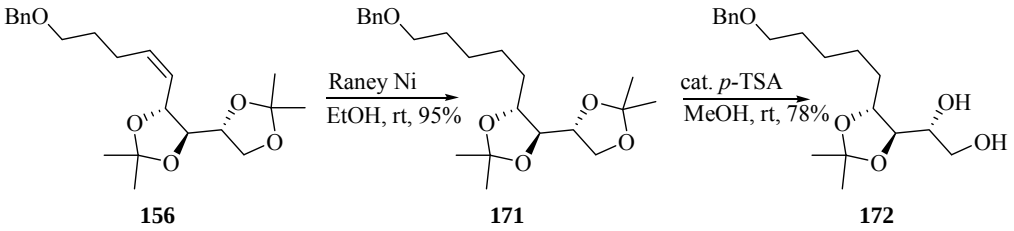
170 R = H
170a R = Bn

Scheme 32: Cycloisomerisation of the alkyne

Having encountered failures in the cycloisomerization, we assumed that the presence of the allylic acetonide might be creating the problem in the cyclization reaction. Hence, we oriented to original proposal, i.e., reduction of the double bond immediately after Wittig reaction and then proceeded to the epoxide formation.

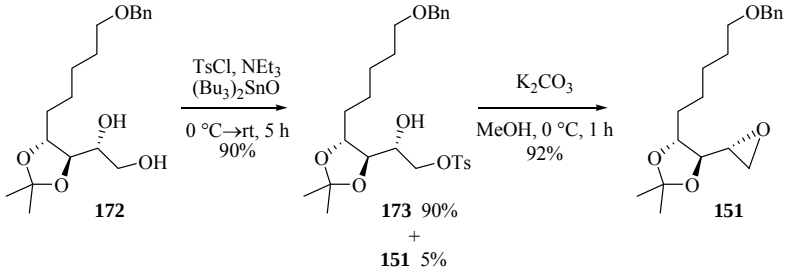
Hence, the olefin **156** was reduced using Raney Ni to afford the saturated dicetonide **171**. The disappearance of the two olefinic protons in the downfield region and the upfield shift of the two protons to δ 1.41-1.74 in the ^{1}H NMR spectrum confirmed the reduction of the double bond. Further, the ^{13}C NMR spectrum showed two new triplets at 26.3 and 33.7 ppm corresponding to the newly formed methylene groups. Selective deprotection of the acetonide using *p*-TSA in MeOH afforded the diol **172**. The disappearance of the two singlets at δ 1.32 in the ^{1}H NMR spectrum corresponding to the isopropylidene group and the corresponding quartets at 25.4 and

26.8 ppm and a singlet at 109.5 ppm in the ^{13}C NMR spectrum confirmed the deprotection (Scheme 33).



Scheme 33:

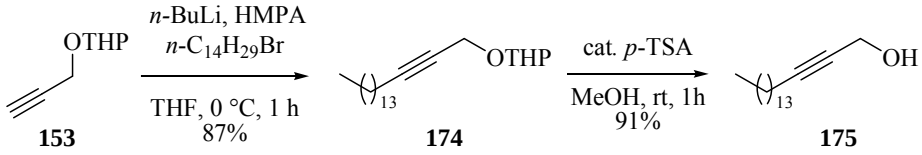
When attempted the one pot epoxide formation strategy as in Scheme 28, to arrive at the epoxide **151** from the diol **172** the reaction led to the complex mixture. The sequential mode of epoxide formation was next attempted *via* the monotosyl derivative. Thus, the 1°–OH of the diol **172** was selectively tosylated using tosyl chloride, dibutyltin oxide and triethylamine as the base to afford **173**. The ^{1}H NMR spectrum showed a singlet integrating for 3 protons at δ 2.45 corresponding to the methyl of the tosyl group. Also, two doublets at δ 7.34 and 7.79 due to the aromatic ring of the tosyl group were observed. The ^{13}C NMR spectrum showed a quartet at 21.7 ppm corresponding to the methyl of the tosyl group and two doublets at 127.6 and 129.9 ppm each integrating for two carbons corresponding to the tosyl group. Base treatment of the tosylate **173** with K_2CO_3 yielded the epoxide **151**. The oxirane protons resonated as multiplets at δ 2.63 (dd), 2.80 (dd), 2.94 (ddd) in the ^{1}H NMR spectrum while a triplet and doublet at 45.1 and 51.5 ppm in the ^{13}C NMR spectrum confirmed the formation of the epoxide (Scheme 34).



Scheme 34: Synthesis of the epoxide fragment **151**

Synthesis of alkyne 152:

The synthesis of the requisite 17C alkynol 1**74** was planned by employing a Zipper reaction[30] of corresponding propargyl alcohol. Accordingly, the known THP ether of propargyl alcohol **153** was alkylated with tetradecyl bromide using *n*-butyl lithium as a base to afford the substituted alkyne **174**. The propargylic protons on the aliphatic end resonated at δ 2.11-2.22 as multiplet while those on the THP end resonated at δ 4.14 and 4.25 as doublet of triplet in the ^{1}H NMR spectrum of **174**. The acetylenic carbons resonated at 75.8 and 86.6 ppm as singlets in the ^{13}C NMR spectrum. The C≡C stretching was observed at 2100 cm^{-1} in the IR spectrum. The deprotection of the THP ether **174** was effected using *p*-TSA and methanol to afford the alkylated propargyl alcohol **175**. In the ^{1}H NMR spectrum, the absence of triplet at δ 4.79 and 8 methylene protons in the upfield region of δ 1.46-1.58 corresponding to the THP ring confirmed the deprotection. Also the ^{13}C NMR spectrum showed disappearance of the doublet at 96.4 ppm corresponding to the hemiacetal carbon and also the other triplets of methylene units of the THP ring. The IR spectrum of **175** showed the O-H stretching at 3539 cm^{-1} (Scheme 35).



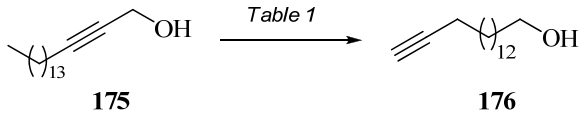
Scheme 35: Synthesis of Heptadec-2-yn-1-ol

Zipper reaction of Heptadec-2-yn-1-ol:

The isomerization of an internal alkyne to the terminal alkyne in the presence of a base is long known as the acetylenic zipper reaction.[30] After exploring a variety of bases and reaction conditions (Table 1) we concluded that the isomerization of alcohol **175** was to the requisite heptadec-16-yn-1-ol (**176**) could be conducted successfully by employing lithium metal in combination with potassium butoxide in aminopropylamine as the solvent/base. The ^{1}H and ^{13}C NMR spectra of **176** evidenced the presence of terminal acetylene. For example, in the ^{1}H spectrum of **176**, the acetylenic-H resonated as a triplet at 1.88 and the proapargylic protons resonated as dt at δ 2.16 ppm. The acetylenic carbons resonated as a doublet and a singlet at

68.2 and 84.6 ppm respectively in the ^{13}C NMR spectrum. The IR spectrum of **175** showed the O-H stretching at 3308 cm^{-1} (Scheme 36).

Scheme 36: Acetylenic zipper reaction



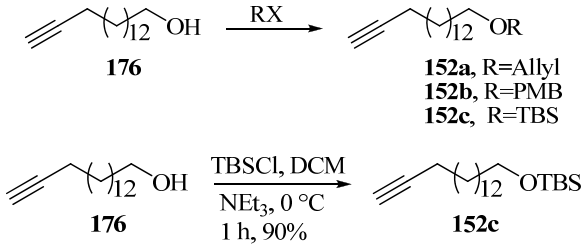
175 **176**

Table 1. *Conditions explored for the Zipper reaction*

S. No.	Reaction conditions	Results obtained
1	KO^{t}Bu, DMSO, rt	Starting material recovered
2	Na, liq. NH_3, -78 °C	Starting material recovered
3	Li, liq. NH_3, -78 °C	Starting material recovered
4	KO^{t}Bu, DMSO, 80 °C	Starting material recovered
5	Li, KO^{t}Bu, 1,3-diamino-propane, rt	Isomerization with 79% yield

Coupling of Key Fragments 151 and 152 under Yamaguchi Conditions

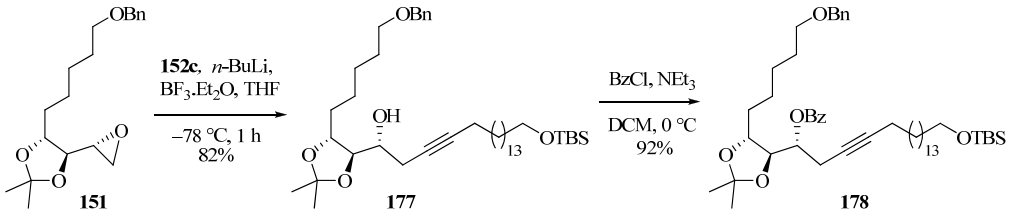
After having established the routes for the synthesis of the two key coupling partners, i.e., epoxide **151** and penultimate intermediate of alkyne **152**, i.e., alcohol **176**, our initial concern was the identification of suitable protecting group for the key alkynol **176** that can tolerate the strong Lewis acid conditions of Yamaguchi protocol and also which can be selectively removed for the second coupling with the serinol intermediate. In this regard we have initially explored the Yamaguchi coupling employing three different ethers of **152**: allyl ether **152a**, PMB ether **152b**, and TBS ether **152c**.



Scheme 37: Synthesis of differently protected ethers of **176**.

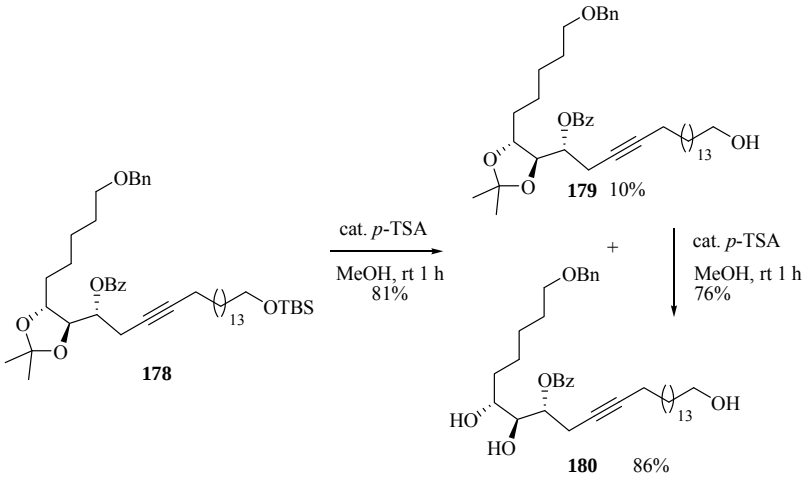
The reaction was successful using the allyl ether of the alkynol **152a** but wasn't reproducible. Yamaguchi protocol using the PMB ether resulted in the deprotection of the PMB ether **152b** in the alkynol as well as acetonide deprotection in the epoxide. Finally, TBS ether **152c** was found to be the ideal protecting group for the coupling wherein the acetonide and the silyl group were intact under the reaction conditions employed (Scheme 37). Henceforth, our investigation continued with the TBS ether **152c**. The ^{1}H NMR spectrum of **152c** showed the peaks of the TBS group at δ 0.03 and 0.88 corresponding to the methyl and the tertiary butyl group. In the ^{13}C NMR spectrum, the methyls resonated as quartets at −5.3 ppm, the tertiary butyl group as quartet at 26.0 ppm and the quaternary carbon at 18.4 ppm as a singlet.

The Yamaguchi coupling of the oxirane **151** with the alkynol **152c** resulted in the formation of homopropargylic alcohol **177**. The ^{1}H NMR spectrum of **177** showed the propargylic protons as multiplets at δ 2.10-2.19 and 2.43-2.49 (each integrating for two protons). Protons of the TBS group resonated at δ 0.03 and 0.88 integrating for six and nine respectively. The ^{13}C NMR spectrum showed the presence of two singlets at 74.9 and 84.0 ppm corresponding to the acetylenic carbon and two quartets at −5.3 ppm and three at 26.0 ppm and a singlet at 18.3 ppm corresponding to the TBS group. The IR spectrum showed the C≡C stretching at 2100 cm^{-1}. The alkynol **177** was protected as its benzoate **178**. The ^{1}H NMR spectrum showed the presence of five additional protons in the downfield region corresponding to the benzoyl group. The ^{13}C NMR spectrum showed the presence of a singlet at 165.6 ppm corresponding to the carbonyl carbon of the Bz group. The IR spectrum showed the C=O stretching at 1725 cm^{-1} corresponding to the carbonyl carbon of the benzoyl group (Scheme 38).



Scheme 38: Key Coupling Event under Yamaguchi Conditions

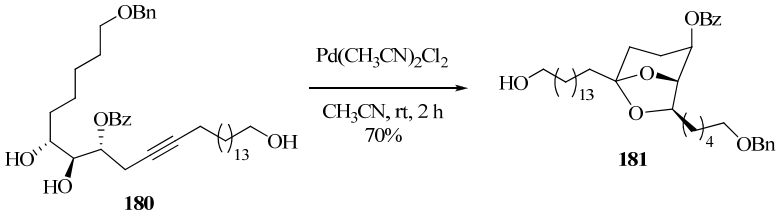
The benzoate **178** upon acid hydrolysis conditions under *p*-TSA in methanol afforded the monoalcohol **179** and the triol **180**. The ^{1}H NMR spectrum of **179** showed the absence of two singlets at 0.03 each integrating for 3 protons and a singlet integrating for 9 protons at 0.88 corresponding to the TBS group. The ^{13}C NMR spectrum showed a corresponding disappearance of the quartets at -5.3 and 26.0 ppm and the singlet at 18.3 ppm. The IR spectrum showed the O-H stretching at 3371 cm^{-1} and a C=O stretching at 1712 cm^{-1} confirming the structure. In the ^{1}H NMR spectrum of **180**, peaks at δ 1.36 and 1.41 due to the isopropylidene group disappeared and in the ^{13}C NMR spectrum, quartets at 27.0 and 27.5 ppm and singlet at 109.2 ppm corresponding to the isopropylidene group disappeared. The IR spectrum showed the O-H stretching at 3427 cm^{-1} and a C=O stretching at 1706 cm^{-1} confirming the structure The monoalcohol **179** was also converted into the triol **180** using the same acid hydrolysis conditions (Scheme 39).



Scheme 39: Hydrolysis of **178**.

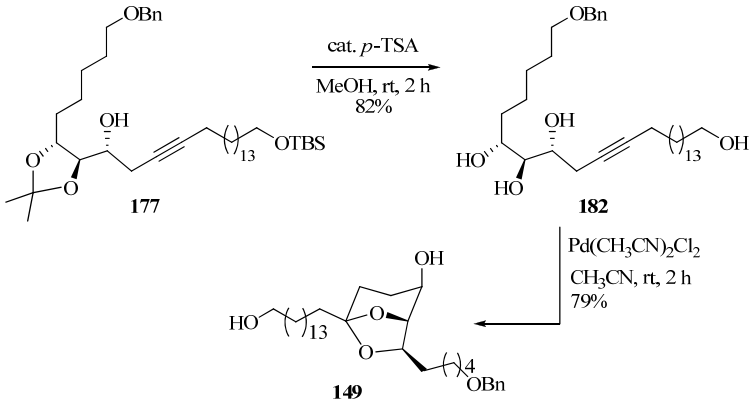
After having the key triol **180**, now the stage was set for executing the key complexity transform to build the requiste [3.2.1]-bicyclic ketal unit by employing Pd-mediated alkynol cycloisomerization[31] reaction. When employed $Pd(CH_3CN)_2Cl_2$ as the catalyst, the reaction advanced smoothly with the disappearance of starting compound with in 2 h and afforded the a single product **181** exclusively. The constitution of the bicyclic ketal unit present in **181** was investigated with the help of spectral data analysis. In the ^{1}H NMR spectrum of **181**, the three characteristic methine protons of the ketal are present at δ 3.97, 4.28 and 4.89. The two CH_2-CH_2 unit present in the bicyclic ketal were resonated separate from the rest of the alkane-H

as multiplets at down field. The presence of the characteristic ketal carbon at 109.4 ppm in the ^{13}C NMR spectrum (Scheme 40) and two CH_2's as triplets separately in the down field at 35.1 and 37.8 ppm indicated the presence of a [3.2.1] bicyclic ketal. The IR spectrum showed the O-H stretching at 3406 cm^{-1} and a C=O stretching at 1711 cm^{-1} confirming the structure.



Scheme 40: Pd(II)-Catalyzed Cycloisomerization of the Alkyne diol **180**.

Later, in order to reduce the number of steps, we also opted for the cycloisomerization of the tetrol **182**. Accordingly, the homopropargyl alcohol **177** was hydrolyzed under the optimized conditions to afford the tetrol **182**. In the ^{1}H NMR spectrum of **182**, peaks at δ 1.34 and 1.37 due to the isopropylidene group disappeared. Also, two singlets at 0.03 each integrating for 3 protons and a singlet integrating for 9 protons at 0.88 corresponding to the TBS group disappeared. In the ^{13}C NMR spectrum, quartets at 27.1 and 27.4 ppm and singlet at 108.6 ppm corresponding to the isopropylidene group and quartets at -5.3 and 26.0 ppm and the singlet at 18.3 ppm corresponding to the TBS group disappeared. The cycloisomerization of the tetrol **182** afforded the required ketal **149** following an *endo* dig mode of cyclization with the free axial alcohol at the C-10 position. In relevance with the NMR spectra of **181**, the ^{1}H NMR spectrum of **149** showed the three characteristic methine protons of the bicyclic ketal resonating at δ 3.58, 3.86, 4.04 ppm. The ^{13}C NMR spectrum showed a singlet corresponding to the ketal carbon at 109.5 ppm and the two triplets corresponding to ring CH_2 at 35.2 and 37.5 ppm (Scheme 41).



Scheme 41:

NOESY spectrum of 149:

The COSY, NOESY studies of **149** revealed strong n*O*e interactions between the C(a)-H and C(a)-H carbons.

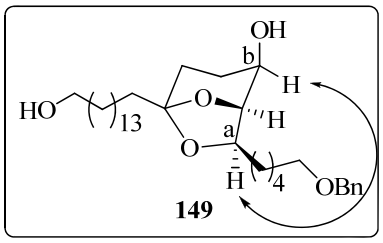
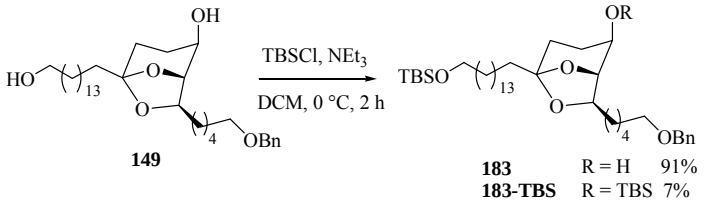


Figure 8: n*O*e interactions of the ketal **149**.

From this observation, it can be confirmed that the mode of cyclization is independent of the protecting group at the axial position. Further, following the synthesis according to the Scheme 38 would minimize the number of steps in the sequence by two i.e., protection and deprotection.

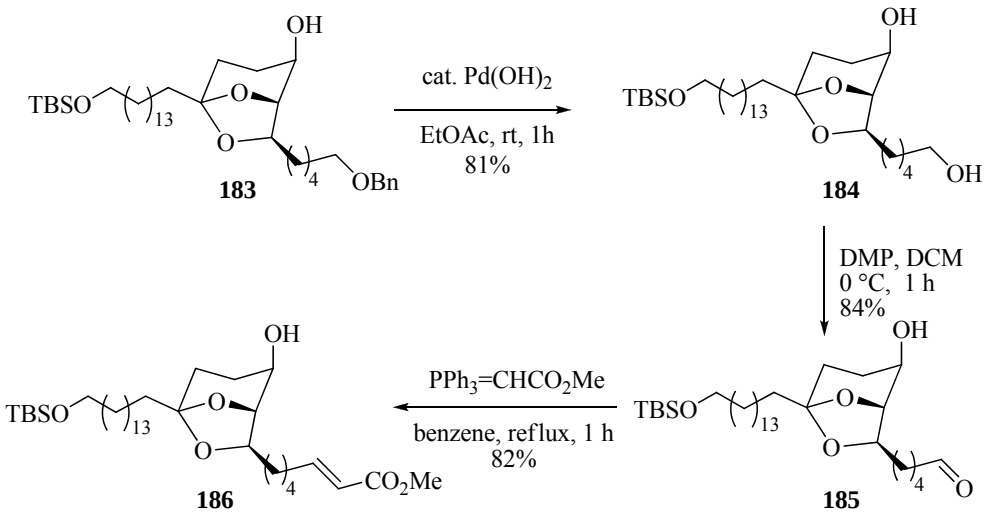
The primary hydroxyl group of **149** was protected as its TBS ether to afford **183** along with the disilyl ether **183-TBS**. The ^{1}H NMR spectrum showed the presence of protons at δ 0.03 integrating for 3 protons each and at δ 0.88 integrating for 9 protons. The ^{13}C NMR spectrum of **183** showed two quartets at −5.3 ppm and three at 26.0 ppm corresponding to the methyl and the tertiary butyl group respectively. It also showed an additional singlet corresponding to the tertiary butyl

group at 18.4 ppm. Other analytical data were in agreement with the assigned structure. Similarly, the ^{1}H NMR spectrum of **183-TBS** showed the peaks of the TBS group at δ 0.03, 0.06 integrating for six protons each and at δ 0.88, 0.9 integrating for nine protons each corresponding to the methyl and the tertiary butyl group respectively. The ^{13}C NMR spectrum showed quartets at −5.3, −4.7 ppm of two carbons each and quartets at 25.9 and 26.0 ppm of three carbons each confirming the formation of a disilyl ether (Scheme 42). IR, mass and other elemental analysis agreed with the structure.



Scheme 42: Silylation of bicyclic ketal **183**

The silyl ether **183** was subjected to debenzylation conditions using palladium hydroxide to afford the diol **184**. The ^{1}H NMR spectrum of compound **184** showed the absence of 5 aromatic protons in the downfield region corresponding to the benzyl group as well as corresponding absence of doublets in the region of 127.5-128.3 ppm. Also IR, Mass and other data confirmed the debenzylation. The diol **184** was oxidized to the aldehyde **185** using the Dess-Martin reagent.[32] The aldehyde **186** was used further for the next step without further purification. The 2 carbon Wittig olefination of the aldehyde **185** with the stable ylide afforded the α,β-unsaturated ester **186**.

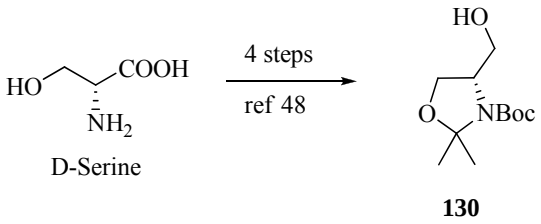


Scheme 43: Functionalization at one end.

The ^{1}H NMR spectrum of the ester **186** showed the presence of the two olefinic protons as doublet of triplets at δ 5.81 and 6.94 ppm with a large coupling constant of 15.6 Hz indicated the presence of a *E*-configured olefin and a singlet at δ 3.71 corresponding to the methyl group of the ester. Also, in the ^{13}C NMR spectrum, doublets at 121.1 and 149.2 ppm, quartet at 51.4 ppm and a singlet at 167.1 ppm confirmed the ester formation (Scheme 43). The IR spectrum of **186** showed the C=O stretching at 1727 cm^{-1} indicative of an ester functional group.

Execution of the Serinol Coupling Event:

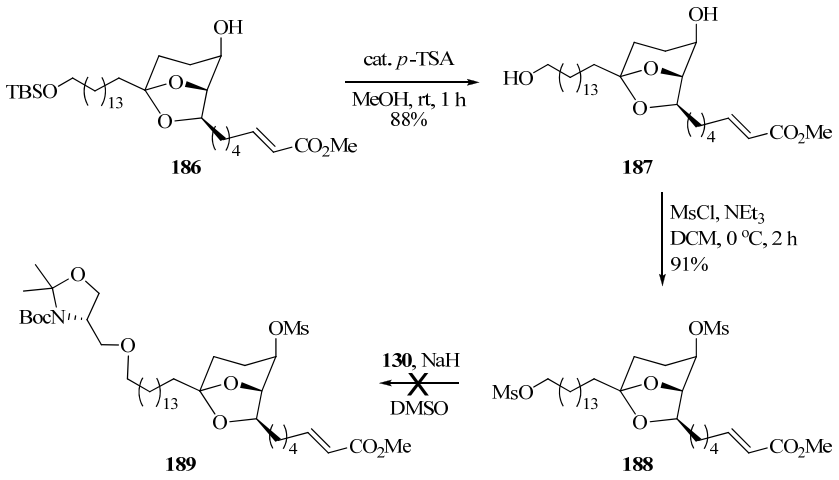
After having the established the first coupling event and also the key cycloisomerization followed by selective 1°–OH oxidation in presence of 2°–OH and subsequent Wittig olefination giving the right stereochemistry, our attention turned on the executing of the coupling of third fragment i.e., appropriately protected serinol derivative **130**. The known serinol derivative **130** required for the etherification was prepared from D-serine in 4 steps according to the literature procedures (Scheme 44).[33]



Scheme 44: Synthesis of serinol derivative **130**.

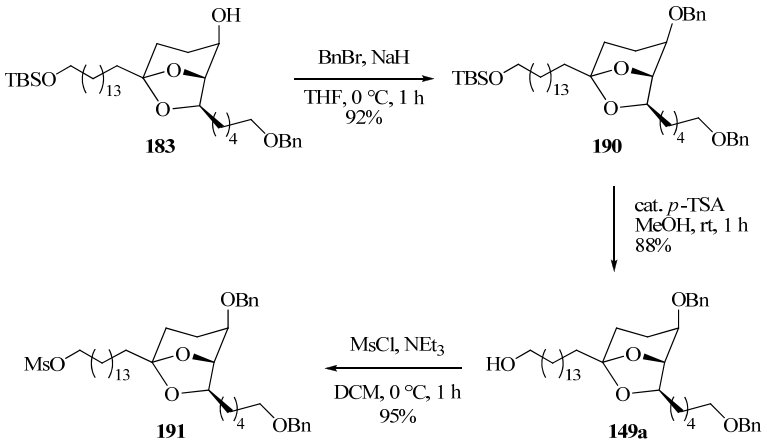
The etherification of the serinol with the ketal was attempted in a number of ways. Initially the etherification of the ketal **149** was attempted with the mesylate of the serinol **130**, but it did not result in the desired product. Changing the protecting group to good leaving groups like the triflate/tosylate/iodide/bromide (**148a-d**) did not bring about etherification. Changing the bases like NaH, NEt_3, *n*-BuLi also didn't help the course of the reaction. Modifications of the ketal **149** to its bromide/iodide/tosylate/triflate and subsequent etherification with the serinol **130** using any of the above bases proved to be futile. A recent publication by the Burke group in the synthesis of Didemniserinolipid B (**8**)[27] showed that the coupling was effective with the mesylate of the bicyclic ketal and the serinol **130** using sodium hydride as the base, and importantly DMSO as solvent.

Accordingly, the TBS deprotection of **186** was effected using *p*-TSA and methanol to afford the diol **187**. The mesylation of the diol **187** afforded the dimesylate **188** which was used further for the next step without purification. The coupling of the dimesylate **188** with the serinol **130** did not result in the required product **189** (Scheme 45).



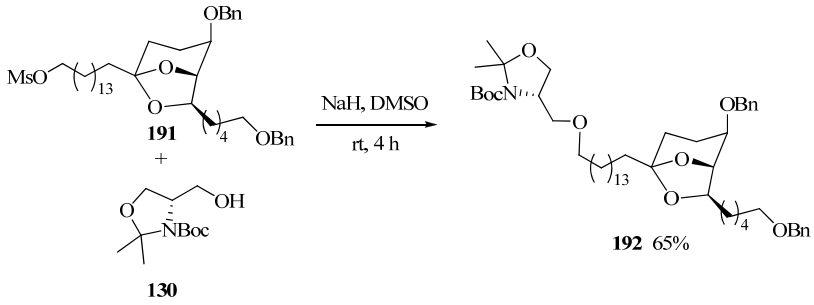
Scheme 45: Attempted Serinol Coupling with Bicyclic ketal **188**.

As the attempted serinol coupling with the unsaturated ester was found to be unsuccessful, we have modified our strategy by postponement of the two Carbon Wittig coupling reaction after the serinol coupling with a suitably functionalized bicyclic ketal unit. Accordingly, the ketal **183** was benzylated to form the dibenzyl ether **190**. The ^{1}H NMR spectrum of **190** showed five additional protons in the downfield region at δ 7.27-7.36 and the benzylic protons at δ 4.59 and 4.62 as doublets with a large coupling constant of 14.6 Hz corresponding to the benzyl group. The ^{13}C NMR spectrum showed the presence of five doublets in the range of 127.5-138.6 ppm confirming the benzylation. Deprotection of the silyl group in **190** by acidic hydrolysis afforded the alcohol **149a**. Peaks corresponding to the TBS group at δ 0.04 integrating for 3 protons each and at δ 0.89 integrating for 9 protons disappeared in the ^{1}H NMR spectrum. The ^{13}C NMR spectrum showed the absence of two quartets at –5.3 and three at 26.0 ppm corresponding to the methyl and the tertiary butyl group. The IR spectrum of **149a** showed the O-H stretching at 3437 cm^{-1}. The alcohol was mesylated using mesyl chloride and the mesylate **191** was used as such for the next step without further purification (Scheme 46).



Scheme 46: Synthesis of the coupling partner **191**.

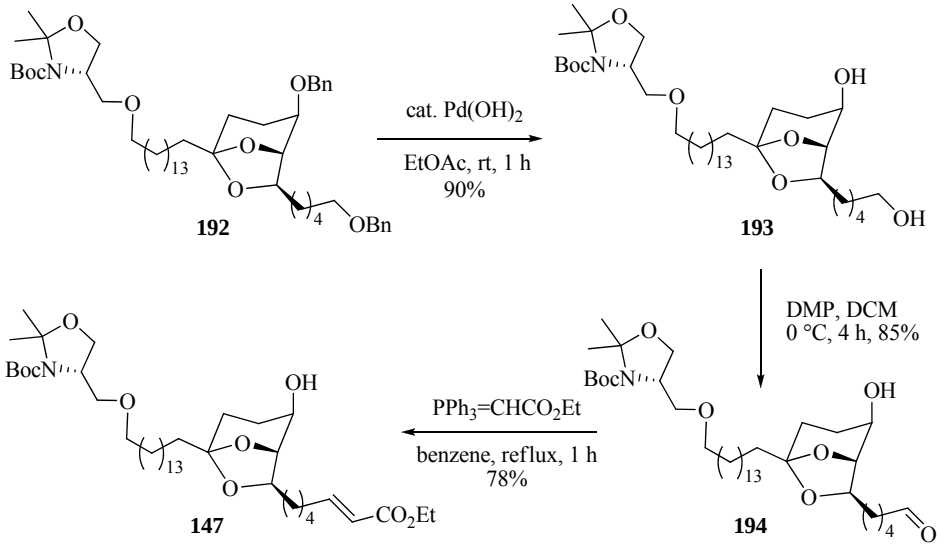
The etherification of the serinol **130** with the mesylate **191** resulted in the formation of the required ether **192** along with an unidentified mixture of products comprising an olefin probably obtained by demesylation. The ^{1}H NMR spectrum of **192** showed peaks at δ 1.46 integrating for nine protons acknowledging to the ^{t}Bu unit of the Boc group of the serinol unit. The appearance of two triplets at 65.4, 69.2 ppm and one doublet at 56.3 ppm of the serinol part and of the carbonyl carbon of the Boc group as a singlet at 151.7 ppm in the ^{13}C NMR spectrum confirmed the etherification. Further, the IR spectrum showed the C=O stretching at 1690 cm^{-1}. All other analytical data were in total agreement with the assigned structure (Scheme 47).



Scheme 47: Coupling of Serinol with the ketal

The compound **192** was subjected to debenzylation to afford the diol **193**. The absence of 10 aromatic protons and the characteristic bemzylic protons at δ 4.48 in the

^{1}H NMR spectrum and corresponding disappearance of 8 doublets and 2 singlets in the range of 125-135 ppm in the ^{13}C NMR spectrum confirmed the debenzylation. IR, elemental analysis and other data were in accordance with the assigned structure. The oxidation of the primary alcohol and subsequent 2 Carbon Wittig olefination should give the α,β-unsaturated ester and thus completing the formal synthesis of Didemniserinolipid B (Scheme 48). Accordingly, the diol **193** was oxidized selectively to the aldehyde **194** using DMP as the oxidizing agent. The aldehyde was used as such for the next step without further purification. The Wittig olefination of the aldehyde using the stable ylide Ph_3P=CHCOOEt in refluxing benzene afforded the desired α,β-unsaturated ester **147**. The ^{1}H NMR spectrum revealed the presence of the olefinic protons at δ 5.80 (d) and 6.94 (dt) with a coupling constant of 15.6 Hz indicative of a *trans* double bond. Also the quartet at δ 4.17 as a quartet was suggestive of the methylene group of the ethyl ester. The ^{13}C NMR spectrum showed doublets at 121.5 and 148.9 ppm corresponding to the olefinic carbons and the ester carbonyl resonated at 166.7 ppm. The IR spectrum showed the C=O stretching at 1693 cm^{-1} for the Boc group and at 1732 cm^{-1} for the ester. All other data were in total agreement with the structure (reported values by Burke group- the olefinic protons resonated at δ 5.81 (d) and 6.94 (dt) with J = 15.5 Hz in the ^{1}H NMR spectrum and the corresponding carbons at 121.5 and 148.8 ppm and the ester carbonyl at 166.6 ppm in the ^{13}C NMR spectrum). The specific rotation of the synthetic sample was found to be $[\alpha]_D$ +16.4 (*c* 0.5, $CHCl_3$) [lit. $[\alpha]_D$ +37.6 (*c* 0.98, $CHCl_3$)].



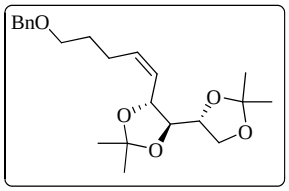
Scheme 48: Formal synthesis of Didemniserinolipid B (**8**).

Conclusions:

To conclude, a formal total synthesis of didemniserinolipid B was developed by employing a Pd-mediated cycloisomerization reaction. The reported synthesis is characterized by its flexibility at different stages and has the potential to synthesize didemniserinolipid analogues by incorporating changes at either end of the chain. Work in this direction is progressing in our group.

Experimental

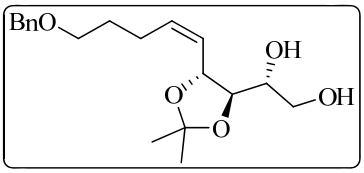
(4*S*,4'*R*,5*R*)-5-((*Z*)-5-(Benzyloxy)pent-1-enyl)-2,2,2',2'-tetramethyl-4,4'-bi(1,3-dioxolane) (156)



To a solution of the aldehyde **155** (4.0 g, 17.4 mmol) in ether (20 mL) at 0 °C, a solution of the ylide generated from $BnO(CH_2)_4P^+Ph_3I^-$ **160** (28.8 g, 52.2 mmol) using KO^tBu (4.9 g, 43.5 mmol) in THF was added dropwise at 0 °C and stirred for 30 min. The reaction mixture was quenched with saturated NH_4Cl (5 mL), the organic layer was separated and the aqueous layer was extracted with ethyl acetate. The combined organic layers were washed with brine, dried (Na_2SO_4) and concentrated. Purification of the crude product by column chromatography (10% ethyl acetate in petroleum ether) afforded **156** (4.4 g, 67%) as colorless syrup.

Mol. Formula	: $C_{22}H_{32}O_5$
$[\alpha]_D$	: +10.7 (*c* 1.3, $CHCl_3$).
IR ($CHCl_3$) $\tilde{\nu}$	: 2986, 1448, 1243, 1048, 847, 634, 467 cm^{-1}.
^{1}H NMR ($CDCl_3$, 200 MHz)	: δ 1.31 (s, 3H), 1.36 (s, 3H), 1.38 (s, 3H), 1.41 (s, 3H), 1.67-1.75 (m, 2H), 2.22-2.31 (m, 2H), 3.48 (t, *J* = 6.4 Hz, 2H), 3.70 (dd, *J* = 6.4, 7.6 Hz, 1H), 3.89-3.95 (m, 1H), 4.01-4.10 (m, 2H), 4.50 (s, 2H), 4.68 (ddd, *J* = 0.7, 7.6, 8.7 Hz, 1H), 5.42 (tt, *J* = 1.5, 10.7 Hz, 1H), 5.64 (tt, *J* = 7.7, 10.9 Hz, 1H), 7.27-7.35 (m, 5H) ppm.
^{13}C NMR ($CDCl_3$, 50 MHz)	: δ 24.4 (t), 25.2 (q), 26.6 (q), 26.9 (q), 27.2 (q), 29.3 (t), 66.8 (t), 69.5 (t), 72.8 (t), 74.9 (d), 76.3 (d), 81.1 (d), 109.2 (s), 109.4 (s), 127.4 (d, 2C), 127.5 (d, 2C), 128.3 (d, 2C), 134.9 (d), 138.5 (s) ppm.
ESI-MS (*m/z*)	: 399.4 $[M+Na]^+$.
Elemental Analysis	Calcd.: C, 70.18; H, 8.57. Found: C, 70.04; H, 8.73.

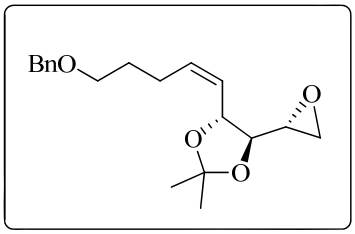
(*R*)-1-((4*R*,5*R*)-5-((*Z*)-5-(Benzyloxy)pent-1-enyl)-2,2-dimethyl-1,3-dioxolan-4-yl)ethane-1,2-diol (161)



To a solution of the diacetonide **156** (6.5 g, 22.6 mmol) in MeOH (100 mL), catalytic *p*-TSA (5 mg, 0.03 mmol) was added and the reaction mixture was stirred at rt for 2 h. The reaction mixture was quenched by the addition of few drops of triethylamine and the solvent was evaporated. The crude residue was purified by column chromatography (25% ethyl acetate in petroleum ether) to obtain **161** (3.75 g, 65%) as a colorless oil.

Mol. Formula	: $C_{19}H_{28}O_5$
$[\alpha]_D$	: –2.6 (*c* 1.5, $CHCl_3$).
IR ($CHCl_3$) $\tilde{\nu}$	: 3422, 2988, 1454, 1372, 1163, 1061, 879, 756, 698 cm^{-1}.
^{1}H NMR ($CDCl_3$, 200 MHz)	: δ 1.34 (s, 3H), 1.39 (s, 3H), 1.61-1.88 (m, 2H), 2.19-2.41 (m, 2H), 2.95 (br s, 1H), 3.40-3.56 (m, 3H), 3.60-3.74 (m, 3H), 4.45 (d, *J* = 11.6 Hz, 1H), 4.51 (d, *J* = 11.6 Hz, 1H), 4.68-4.78 (m, 1H), 5.45 (qt, *J* = 1.4, 9.2 Hz, 1H), 5.58-5.72 (m, 1H), 7.28-7.34 (m, 5H) ppm.
^{13}C NMR ($CDCl_3$, 50 MHz)	: δ 24.1 (t), 26.8 (q), 27.1 (q), 28.6 (t), 47.2 (t), 68.9 (t), 72.3 (d), 72.5 (t), 74.5 (d), 80.6 (d), 109.1 (s), 127.6 (d), 127.7 (d, 2C), 128.3 (d, 2C), 134.7 (d, 2C), 138.0 (s) ppm.
ESI-MS (*m/z*)	: 359.2 $[M+Na]^+$.
Elemental Analysis	Calcd.: C, 67.83; H, 8.39.
	Found: C, 67.80; H, 8.62.

(4*R*,5*S*)-4-((*Z*)-5-(Benzyloxy)pent-1-enyl)-2,2-dimethyl-5-((*R*)-oxiran-2-yl)-1,3-dioxolane (163)

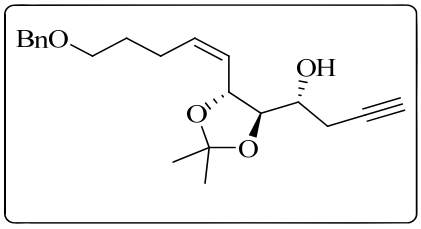


A solution of diol **161** (170 mg, 0.5 mmol) in THF (5 mL) was cooled to 0 °C and treated with NaH (24 mg, 1 mmol) followed by TsCl (96 mg, 0.5 mmol) and stirred for 2 h while warming the reaction mixture to rt. The reaction mixture was

quenched with ice, the organic layer was separated, washed with ethyl acetate, brine, dried (Na_2SO_4), and concentrated. The crude residue was purified by column chromatography (20% ethyl acetate in petroleum ether) to obtain **163** (50 mg, 31% over two steps) as a colorless oil.

Mol. Formula	: $C_{19}H_{26}O_4$
$[\alpha]_D$	: –9.7 (*c* 1.5, $CHCl_3$).
IR ($CHCl_3$) $\tilde{\nu}$	: 2988, 1599, 1496, 1381, 1216, 1060, 876, 753, 699 cm^{-1}.
^{1}H NMR ($CDCl_3$, 200 MHz)	: δ 1.41 (s, 6H), 1.65-1.79 (m, 2H), 2.21-2.39 (m, 2H), 2.63 (dd, *J* = 2.5, 5.0 Hz, 1H), 2.75 (dd, *J* = 4.0, 5.1 Hz, 1H), 3.01 (ddd, *J* = 2.6, 4.0, 6.6 Hz, 1H), 3.48 (t, *J* = 6.4 Hz, 2H), 3.52 (d, *J* = 7.9 Hz, 1H), 4.49 (s, 2H), 4.70 (ddd, *J* = 0.8, 7.8, 8.6 Hz, 1H), 5.41 (tt, *J* = 1.4, 10.7 Hz, 1H), 5.70 (dt, *J* = 7.2, 10.9 Hz, 1H), 7.27-7.32 (m, 5H) ppm.
^{13}C NMR ($CDCl_3$, 50 MHz)	: δ 24.4 (t), 26.6 (q), 27.0 (q), 29.3 (t), 44.4 (t), 50.9 (d), 69.3 (t), 72.7 (t), 74.4 (d), 80.3 (d), 109.4 (s), 126.3 (d), 127.4 (d), 127.5 (d, 2C), 128.2 (d, 2C), 135.8 (d), 138.4 (s) ppm.
ESI-MS (*m/z*)	: 341.3 $[M+Na]^+$.
Elemental Analysis	Calcd.: C, 71.67; H, 8.23. Found: C, 71.60; H, 8.32.

(*R*)-1-((4*R*,5*R*)-5-((*Z*)-5-(Benzyloxy)pent-1-enyl)-2,2-dimethyl-1,3-dioxolan-4-yl)but-3-yn-1-ol (164)

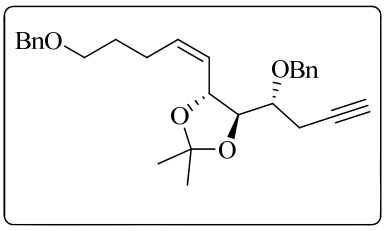


A solution of the epoxide **163** (0.65 g, 2.04 mmol) in DMSO (8 mL) was cooled to 0 °C and lithium acetylide-ethylenediamine complex (0.75 g, 8.2 mmol) was added at 0 °C and the reaction mixture was stirred while warming the reaction mixture to rt for 4 h. The reaction mixture was quenched with ice, partitioned between ethyl acetate, water and the organic layer was separated washed with ethyl acetate, brine, dried (Na_2SO_4), and concentrated. Purification of the residue by column

chromatography (25% ethyl acetate in petroleum ether) afforded **164** (0.62 g, 88%) as a colorless oil.

Mol. Formula	: $C_{21}H_{28}O_4$
$[\alpha]_D$	: +10.3 (*c* 1.0, $CHCl_3$).
IR ($CHCl_3$) $\tilde{\nu}$	: 3424, 2215, 1603, 1454, 1216, 1061, 878, 757 cm^{-1}.
^{1}H NMR ($CDCl_3$, 200 MHz)	: δ 1.36 (s, 3H), 1.40 (s, 3H), 1.62 (br s, 1H), 1.63-1.79 (m, 2H), 2.00 (t, *J* = 2.8 Hz, 1H), 2.30 (dq, *J* = 1.3, 7.4 Hz, 2H), 2.38-2.42 (m, 2H), 3.43-3.55 (m, 2H), 3.68-3.76 (m, 2H), 4.48 (s, 2H), 4.69-4.77 (m, 1H), 5.46 (tt, *J* = 1.6, 10.9 Hz, 1H), 5.65 (dt, *J* = 7.3, 10.9 Hz, 1H), 7.29-7.34 (m, 5H) ppm.
^{13}C NMR ($CDCl_3$, 50 MHz)	: δ 23.5 (t), 24.2 (t), 26.9 (q), 27.1 (q), 28.9 (t), 69.0 (t), 69.8 (d), 70.7 (d), 72.6 (t), 73.3 (d), 80.2 (s), 82.0 (d), 108.7 (s), 127.4 (d), 127.6 (d, 2C), 127.8 (d), 128.2 (d, 2C), 134.8 (d), 138.2 (s) ppm.
ESI-MS (*m/z*)	: 367.9 $[M+Na]^+$.
Elemental Analysis	Calcd.: C, 73.23; H, 8.19.
	Found: C, 73.48; H, 7.95.

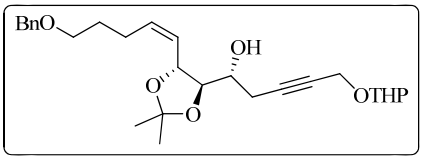
(4*R*,5*R*)-4-((*R*)-1-(Benzyloxy)but-3-ynyl)-5-((*Z*)-5-(benzyloxy)pent-1-enyl)-2,2-dimethyl-1,3-dioxolane (165)



To a solution of alkynol **164** (0.4 g, 1.17 mmol) in DMF (5 mL) at 0 °C was added NaH (42 mg, 1.75 mmol) and stirred for 30 min. BnBr (0.14 mL, 1.17 mmol) was added at the same temperature and the reaction mixture was stirred for 2 h. The reaction mixture was quenched with ice, partitioned between ethyl acetate, water and the organic layer was separated, washed with ethyl acetate, brine, dried (Na_2SO_4), and concentrated. Purification of the residue by column chromatography (15% ethyl acetate in petroleum ether) afforded **165** (0.46 g, 91%) as colorless syrup.

Mol. Formula	: $C_{28}H_{34}O_4$
$[\alpha]_D$	: +8.9 (*c* 1.0, $CHCl_3$).
IR ($CHCl_3$) $\tilde{\nu}$	: 3308, 2932, 1585, 1454, 1372, 1217, 878, 757, 698 cm^{-1}.
^{1}H NMR ($CDCl_3$, 200 MHz)	: δ 1.40 (s, 3H), 1.42 (s, 3H), 1.60-1.73 (m, 2H), 1.97 (t, *J* = 2.8 Hz, 1H), 2.04-2.38 (m, 2H), 2.46 (d, *J* = 6.1 Hz, 1H), 2.47 (d, *J* = 6.2 Hz, 1H), 3.43 (t, *J* = 6.4 Hz, 2H), 3.74 (dt, *J* = 6.1, 7.8 Hz, 1H), 3.93 (dd, *J* = 4.3, 7.7 Hz, 1H), 4.47 (s, 2H), 4.64 (d, *J* = 11.6 Hz, 1H), 4.73 (d, *J* = 11.9 Hz, 1H), 4.83 (t, *J* = 8.3 Hz, 1H), 5.46 (tt, *J* = 1.5, 10.9 Hz, 1H), 5.59-5.76 (dt, *J* = 7.3, 10.8 Hz, 1H), 7.26-7.36 (m, 10H) ppm.
^{13}C NMR ($CDCl_3$, 50 MHz)	: δ 21.0 (t), 24.4 (t), 26.9 (q), 27.2 (q), 29.4 (t), 69.3 (t), 70.3 (d), 72.6 (t), 72.7 (t), 73.0 (d), 76.8 (d), 80.6 (s), 81.7 (d), 108.7 (s), 127.3 (d), 127.4 (d), 127.4 (d, 2C), 127.6 (d, 2C), 127.7 (d), 128.1 (d, 2C), 128.1 (d, 2C), 135.0 (d), 138.0 (s), 138.5 (s) ppm.
ESI-MS (*m/z*)	: 457.3 $[M+Na]^+$.
Elemental Analysis	Calcd.: C, 77.39; H, 7.89. Found: C, 77.47; H, 7.94.

(1*R*)-1-((4*R*,5*R*)-5-((*Z*)-5-(Benzyloxy)pent-1-enyl)-2,2-dimethyl-1,3-dioxolan-4-yl)-5-(tetrahydro-2*H*-pyran-2-yloxy)pent-3-yn-1-ol (168)

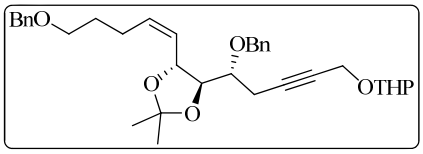


To a solution of alkyne **153** (1.43 mL, 10.2 mmol) in THF (20 mL) at −78 °C, *n*- BuLi (4.36 mL, 10.2 mmol) was added at −78 °C and stirred for an additional 15 min. To this, $BF_3.Et_2O$ (1.28 mL, 10.2 mmol) was added and stirred again for 15 min. A solution of the epoxide (0.65 g, 2.04 mmol) in THF (8 mL) was added at −78 °C and stirred further at the same temperature for another 30 min. The reaction mixture was quenched with THF-H_2O (1:1) at −78 °C. The organic layer was separated and the aqueous layer was washed with ethyl acetate. The combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated. Purification of the residue by

column chromatography (20% ethyl acetate in petroleum ether) afforded **168** (0.72 g, 77%) as colorless syrup.

Mol. Formula	: $C_{27}H_{38}O_6$
$[\alpha]_D$	: +19.1 (*c* 2.0, $CHCl_3$).
IR ($CHCl_3$) $\tilde{\nu}$	: 3412, 2940, 1455, 1372, 1216, 1020, 757, 668 cm^{-1}.
^{1}H NMR ($CDCl_3$, 200 MHz)	: δ 1.35 (s, 3H), 1.39 (s, 3H), 1.49-1.84 (m, 8H), 2.28 (br s, 1H), 2.28 (dq, *J* = 1.2, 7.6 Hz, 2H), 2.44 (dt, *J* = 2.2, 5.6 Hz, 2H), 3.42-3.52 (m, 3H), 3.66–3.86 (m, 3H), 4.17 (ddt, *J* = 1.5, 3.5, 15.3 Hz, 1H), 4.27 (ddt, *J* = 1.9, 4.0, 15.5 Hz, 1H), 4.48 (s, 2H), 4.69-4.79 (m, 2H), 5.44 (dt, *J* = 1.5, 10.7 Hz, 1H), 5.64 (dt, *J* = 7.4, 10.9 Hz, 1H), 7.27-7.33 (m, 5H) ppm.
^{13}C NMR ($CDCl_3$, 50 MHz)	: δ 19.0 (t), 24.1 (t), 24.3 (t), 25.3 (t), 27.0 (q), 27.2 (q), 29.0 (t), 30.2 (t), 54.5 (t), 61.8 (t), 69.2 (t), 70.1 (d), 72.7 (t), 73.5 (d), 78.5 (s), 82.2 (d), 82.2 (s), 96.6 (d), 108.8 (s), 127.5 (d), 127.6 (d, 2C), 128.3 (d, 2C), 134.9 (d, 2C), 138.3 (s) ppm.
ESI-MS (*m/z*)	: 481.3 $[M+Na]^+$.
Elemental Analysis	Calcd.: C, 70.71; H, 8.35. Found: C, 70.65; H, 8.24.

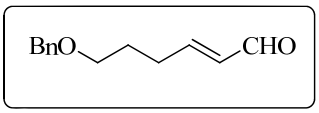
2-((*R*)-5-(Benzyloxy)-5-((4*R*,5*R*)-5-((*Z*)-5-(benzyloxy)pent-1-enyl)-2,2-dimethyl-1,3-dioxolan-4-yl)pent-2-ynyloxy)tetrahydro-2*H*-pyran (169)



To a cooled solution (0 °C) of alcohol **168** (0.6 g, 1.31 mmol) in DMF (10 mL), NaH (43 mg, 1.80 mmol) was added and stirred for 30 min. Benzyl bromide (0.23 mL, 1.96 mmol) was added to the reaction mixture at 0 °C and the reaction mixture was stirred for 1 h. The reaction mixture was quenched with ice, partitioned between ethyl acetate, water and the organic layer was separated, washed with ethyl acetate, brine, dried (Na_2SO_4), and concentrated. Purification of the residue by column chromatography (10% ethyl acetate in petroleum ether) afforded **169** (0.4 g, 86%) as colorless syrup.

Mol. Formula	: $C_{34}H_{44}O_6$
$[\alpha]_D$	: +20.7 (*c* 1.5, $CHCl_3$).
IR ($CHCl_3$) $\tilde{\nu}$	: 3301, 2960, 1455, 1215, 1110, 837, 757, 650 cm^{-1}.
^{1}H NMR ($CDCl_3$, 200 MHz)	: δ 1.40 (s, 3H), 1.41 (s, 3H), 1.47-1.73 (m, 8H), 2.07-2.37 (m, 2H), 2.48-2.52 (m, 2H), 3.43 (t, *J* = 6.6 Hz, 2H), 3.52 (dt, *J* = 1.6, 4.4 Hz, 1H), 3.71-3.83 (m, 2H), 3.92 (dd, *J* = 4.2, 7.7 Hz, 1H), 4.17 (ddt, *J* = 0.6, 2.2, 15.5 Hz, 1H), 4.27 (ddt, *J* = 0.8, 2.5, 15.5 Hz, 1H), 4.47 (s, 2H), 4.64 (d, *J* = 11.7 Hz, 1H), 4.72 (d, *J* = 11.7 Hz, 1H), 4.78 (t, *J* = 3.5 Hz, 1H), 4.84 (t, *J* = 8.3 Hz, 1H), 5.46 (tt, *J* = 1.5, 10.5 Hz, 1H), 5.65 (dt, *J* = 7.3, 10.9 Hz, 1H), 7.27-7.35 (m, 10H) ppm.
^{13}C NMR ($CDCl_3$, 50 MHz)	: δ 19.1 (t), 21.6 (t), 24.4 (t), 25.3 (t), 26.9 (q), 27.3 (q), 29.4 (t), 30.2 (t), 54.5 (t), 62.0 (t), 69.5 (t), 72.7 (t), 72.8 (t), 72.9 (d), 76.9 (d), 77.8 (s), 81.9 (d), 82.7 (s), 96.6 (d), 108.8 (s), 127.4 (d), 127.5 (d, 3C), 127.7 (d, 2C), 127.7 (d), 128.2 (d, 2C), 128.3 (d, 2C), 135.4 (d), 138.1 (s), 138.5 (s) ppm.
ESI-MS (*m/z*)	: 571.2 $[M+Na]^+$.
Elemental Analysis	Calcd.: C, 74.42; H, 8.08. Found: C, 74.20; H, 8.12.

(*E*)-6-(Benzyloxy)hex-2-enal (166)

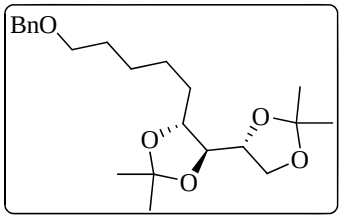


A solution of **165** (100 mg, 0.23 mmol) and $Pd(CH_3CN)_2Cl_2$ (7 mg, 0.03 mmol) in acetonitrile (5 mL) was stirred at rt under argon atmosphere for 3 h. The reaction mixture was concentrated and the crude residue obtained was purified by silica gel chromatography (30% ethyl acetate in petroleum ether) to obtain **166** (25 mg, 53%) as yellow syrup.

Mol. Formula	: $C_{13}H_{16}O_2$
IR ($CHCl_3$) $\tilde{\nu}$	: 3449, 3018, 1734, 1490, 1376, 1216, 875, 755, 667 cm^{-1}.
^{1}H NMR	: δ 1.78-1.85 (m, 2H), 2.40-2.51 (m, 2H), 3.49 (t, *J* = 6.06

($CDCl_3$, 200 MHz)	Hz, 2H), 4.49 (s, 2H), 6.10 (ddt, *J* = 1.5, 8.0, 15.5 Hz, 1H), 6.84 (dt, *J* = 6.7, 15.7 Hz, 1H), 7.28-7.34 (m, 5H), 9.48 (d, *J* = 7.9 Hz, 1H) ppm.
ESI-MS (*m/z*)	: 227.1 $[M+Na]^+$.
Elemental Analysis	Calcd.: C, 76.44; H, 7.90.
	Found: C, 76.25; H, 7.67.

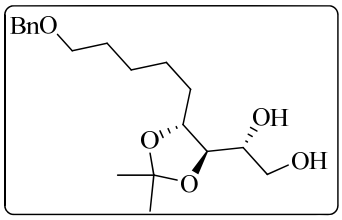
(4*S*,4'*R*,5*R*)-5-(5-(Benzyloxy)pentyl)-2,2,2',2'-tetramethyl-4,4'-bi(1,3-dioxolane) (171)



A suspension of the diacetonide of **156** (2.1 g, 5.5 mmol), Raney-Ni (0.1 g) in ethanol (20 mL) was flushed with hydrogen gas and stirred under hydrogen (20 *psi*) atmosphere for 30 min. The reaction mixture was filtered through celite, concentrated and the crude product was purified by column chromatography (10% ethyl acetate in petroleum ether) to yield **171** (2.0 g, 95%) as white syrup.

Mol. Formula	: $C_{22}H_{34}O_5$
$[\alpha]_D$	: +18.7 (*c* 0.6, $CHCl_3$).
IR ($CHCl_3$) $\tilde{\nu}$	: 3018, 1496, 1372, 1216, 1064, 758, 668 cm^{-1}.
^{1}H NMR	: δ 1.32 (s, 6H), 1.36 (s, 3H), 1.38 (s, 3H), 1.41-1.72 (m,
($CDCl_3$, 200 MHz)	8H), 3.45 (t, *J* = 6.4 Hz, 2H), 3.45 (t, *J* = 7.7 Hz, 1H), 3.82-4.12 (m, 4H), 4.48 (s, 2H), 7.21-7.32 (m, 5H) ppm.
^{13}C NMR	: δ 25.4 (q), 26.0 (t), 26.3 (t), 26.8 (q), 27.1 (q), 27.4 (q),
($CDCl_3$, 50 MHz)	29.7 (t), 33.7 (t), 67.7 (t), 70.3 (t), 72.8 (t), 77.3 (d), 80.5 (d), 81.2 (d), 108.7 (s), 109.5 (s), 127.4 (d), 127.6 (d, 2C), 128.3 (d, 2C), 138.6 (s) ppm.
ESI-MS (*m/z*)	: 401.9 $[M+Na]^+$.
Elemental Analysis	Calcd.: C, 69.81; H, 9.05.
	Found: C, 69.95; H, 9.17.

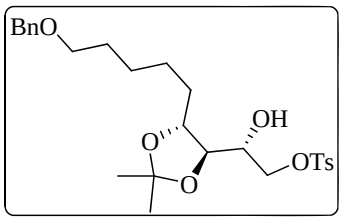
(*R*)-1-((4*R*,5*R*)-5-(5-(Benzyloxy)pentyl)-2,2-dimethyl-1,3-dioxolan-4-yl)ethane-1,2-diol (172)



To a solution of the diacetonide **171** (1.4 g, 3.7 mmol) in MeOH (10 mL), catalytic *p*-TSA (5 mg, 0.03 mmol) was added and the reaction mixture was stirred at rt for 2 h. The reaction mixture was quenched by the addition of few drops of triethylamine and the solvent was evaporated. The crude residue was purified by column chromatography (25% ethyl acetate in petroleum ether) to obtain **172** (1.0 g, 78%) as a colorless oil.

Mol. Formula	: $C_{19}H_{30}O_5$
$[\alpha]_D$	: +30.8 (*c* 1.0, $CHCl_3$).
IR ($CHCl_3$) $\tilde{\nu}$	: 3433, 2936, 1415, 1373, 1216, 1069, 759, 669 cm^{-1}.
^{1}H NMR ($CDCl_3$, 200 MHz)	: δ 1.35 (s, 3H), 1.37 (s, 3H), 1.40-1.49 (m, 2H), 1.45 (br s, 1H), 1.56-1.69 (m, 5H), 2.16 (br s, 1H), 2.53 (d, *J* = 4.0 Hz, 1H), 3.45 (t, *J* = 6.4 Hz, 2H), 3.57-3.78 (m, 4H), 3.92 (dt, *J* = 3.5, 7.7 Hz, 1H), 4.48 (s, 2H), 7.24-7.33 (m, 5H) ppm.
^{13}C NMR ($CDCl_3$, 50 MHz)	: δ 25.9 (t), 26.0 (t), 27.0 (q), 27.3 (q), 29.5 (t), 33.9 (t), 63.8 (t), 70.2 (t), 72.7 (d), 72.7 (t), 79.3 (d), 80.8 (d), 108.6 (s), 127.4 (d), 127.5 (d, 2C), 128.2 (d, 2C), 138.4 (s) ppm.
ESI-MS (*m/z*)	: 361.9 $[M+Na]^+$.
Elemental Analysis	Calcd.: C, 67.43; H, 9.93.
	Found: C, 67.25; H, 9.69.

(*R*)-2-((4*R*,5*R*)-5-(5-(Benzyloxy)pentyl)-2,2-dimethyl-1,3-dioxolan-4-yl)-2-hydroxyethyl 4-methylbenzenesulfonate (173)

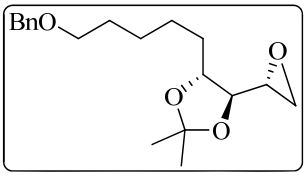


To a cooled solution (0 °C) of the diol **172** (500 mg, 1.48 mmol) in DCM (15 mL), Bu_2SnO (catalytic), DMAP (catalytic), and NEt_3 (0.31 mL, 2.22 mmol) were added and stirred for 0.5 h. TsCl (280 mg, 1.48 mmol) was added at 0 °C and the

reaction mixture was further stirred for 4 h while warming to rt. Solvent was evaporated under reduced pressure, the residue was purified by column chromatography (15% ethyl acetate in petroleum ether) to yield **173** (640 mg, 90%) as colorless syrup along with **151** (23 mg, 5%) as a colorless oil.

Mol. Formula	: $C_{26}H_{36}O_7S$
$[\alpha]_D$	: +33.0 (*c* 1.0, $CHCl_3$).
IR ($CHCl_3$) $\tilde{\nu}$	: 3434, 2984, 1560, 1375, 1247, 1047, 757, 668 cm^{-1}.
^{1}H NMR ($CDCl_3$, 200 MHz)	: δ 1.28 (s, 3H), 1.32 (s, 3H), 1.35-1.44 (m, 3H), 1.48-1.69 (m, 5H), 2.45 (s, 3H), 3.45 (t, *J* = 6.4 Hz, 2H), 3.48 (t, *J* = 3.4 Hz, 1H), 3.72–3.83 (m, 1H), 3.91 (dd, *J* = 3.2, 7.4 Hz, 1H), 4.01 (dd, *J* = 6.9, 10.5 Hz, 1H), 4.25 (dd, *J* = 2.8, 10.5 Hz, 1H), 4.48 (s, 2H), 7.23-7.32 (m, 5H), 7.34 (d, *J* = 8.2 Hz, 2H), 7.79 (d, *J* = 8.2 Hz, 2H) ppm.
^{13}C NMR ($CDCl_3$, 50 MHz)	: δ 21.7 (q), 25.9 (t), 26.1 (t), 27.0 (q), 27.4 (q), 29.6 (t), 34.0 (t), 70.3 (t), 71.5 (d), 72.1 (t), 72.8 (t), 79.4 (d), 80.1 (d), 109.9 (s), 127.5 (d), 127.6 (d, 2C), 128.1 (d, 2C), 128.3 (d, 2C), 129.9 (d, 2C), 132.7 (s), 138.6 (s), 144.9 (s) ppm.
ESI-MS (*m/z*)	: 515.2 $[M+Na]^+$.
Elemental Analysis	Calcd.: C, 63.39; H, 7.37; S, 6.51. Found: C, 63.28; H, 7.20; S, 6.12.

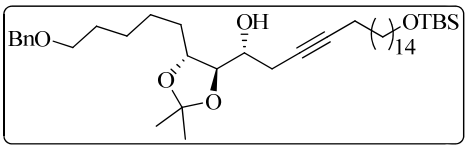
(4*R*,5*S*)-4-(5-(Benzyloxy)pentyl)-2,2-dimethyl-5-((*R*)-oxiran-2-yl)-1,3-dioxolane (151)



A solution of the tosylate **173** (0.5 g, 1.02 mmol), K_2CO_3 (0.21 g, 1.52 mmol) in MeOH (10 mL) were stirred at 0 °C under argon atmosphere for 1 h. The reaction mixture was concentrated and the crude residue obtained was purified by silica gel chromatography (15% ethyl acetate in petroleum ether) to obtain **151** (0.3 g, 92%) as colorless oil.

Mol. Formula	: $C_{19}H_{28}O_4$
$[\alpha]_D$	: +4.5 (*c* 1.2, $CHCl_3$).
IR ($CHCl_3$) $\tilde{\nu}$	: 2937, 2861, 1455, 1371, 1217, 1099, 876, 756, 698 cm^{-1}.
^{1}H NMR ($CDCl_3$, 200 MHz)	: δ 1.40 (s, 6H), 1.42-1.53 (m, 3H), 1.57-1.71 (m, 5H), 2.64 (dd, *J* = 2.5, 5.0 Hz, 1H), 2.80 (dd, *J* = 3.9, 5.0 Hz, 1H), 2.95 (ddd, *J* = 2.5, 3.9, 6.3 Hz, 1H), 3.28 (dd, *J* = 6.3, 7.8 Hz, 1H), 3.47 (tt, *J* = 6.6 Hz, 2H), 3.96 (dt, *J* = 4.7, 7.8 Hz, 1H), 4.49 (s, 2H), 7.22-7.34 (m, 5H) ppm.
^{13}C NMR ($CDCl_3$, 50 MHz)	: δ 25.6 (t), 26.1 (t), 26.6 (q), 27.1 (q), 29.5 (t), 33.1 (t), 45.1 (t), 51.5 (d), 70.2 (t), 72.7 (t), 79.5 (d), 81.1 (d), 109.0 (s), 127.4 (d), 127.5 (d, 2C), 128.2 (d, 2C), 138.6 (s) ppm.
ESI-MS (*m/z*)	: 343.3 $[M+Na]^+$.
Elemental Analysis	Calcd.: C, 71.22; H, 8.81.
	Found: C, 70.40; H, 8.43.

(*R*)-1-((4*R*,5*R*)-5-(5-(Benzyloxy)pentyl)-2,2-dimethyl-1,3-dioxolan-4-yl)-19-(*tert*-butyldimethylsilyloxy)nonadec-3-yn-1-ol (177)

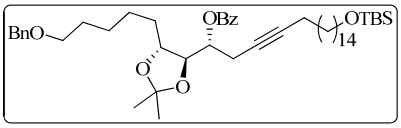


To a solution of alkyne **152c** (2.97 g, 8.12 mmol) in THF (15 mL) at −78 °C, *n*-BuLi (3.47 mL, 8.12 mmol, 2.34 M in hexane) was added at −78 °C and stirred for an additional 15 min. To this, $BF_3.Et_2O$ (0.9 mL, 7.15 mmol) was added and stirred again for 15 min. A solution of the epoxide **151** (0.65 g, 2.03 mmol) in THF (8 mL) was added at −78 °C and stirred further at the same temperature for another 30 min. The reaction mixture was quenched with THF-H_2O (1:1) at −78 °C. The organic layer was separated and the aqueous layer was washed with ethyl acetate. The combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated. Purification of the residue by column chromatography (15% ethyl acetate in petroleum ether) afforded **177** (1.14 g, 82%) as a colorless syrup.

Mol. Formula	: $C_{42}H_{74}O_5Si$
$[\alpha]_D$	: +9.5 (*c* 0.6, MeOH).
IR ($CHCl_3$) $\tilde{\nu}$	: 3439, 2929, 1463, 1370, 1254, 1101, 836, 697 cm^{-1}.

^{1}H NMR ($CDCl_3$, 200 MHz)	: δ 0.03 (s, 6H), 0.88 (s, 9H), 1.22-1.29 (m, 24H), 1.34 (s, 3H), 1.37 (s, 3H), 1.40-1.53 (m, 10H), 2.11-2.19 (m, 2H), 2.16 (br s, 1H), 2.43-2.49 (m, 2H), 3.45 (t, *J* = 6.6 Hz, 2H), 3.58 (t, *J* = 6.6 Hz, 2H), 3.59 (t, *J* = 6.7 Hz, 1H), 3.63-3.75 (m, 1H), 3.96 (dt, *J* = 3.5, 7.0 Hz, 1H), 4.48 (s, 2H), 7.24-7.33 (m, 5H) ppm.
^{13}C NMR ($CDCl_3$, 50 MHz)	: δ – 5.3 (q, 2C), 18.3 (s), 18.7 (t), 23.3 (t), 24.3 (t), 25.8 (t), 26.0 (q, 3C), 26.0 (t), 26.0 (t), 26.1 (t), 26.2 (t), 27.1 (q), 27.4 (q), 28.9 (t, 2C), 29.1 (t), 29.4 (t), 29.5 (t), 29.6 (t, 4C), 32.9 (t), 34.4 (t), 63.3 (t), 70.3 (t), 70.8 (d), 72.8 (t), 74.9 (s), 78.8 (d), 81.9 (d), 84.0 (s), 108.6 (s), 127.4 (d), 127.6 (d, 2C), 128.3 (d, 2C), 138.6 (s) ppm.
ESI-MS (*m/z*)	: 709.7 $[M+Na]^+$.
Elemental Analysis	Calcd.: C, 73.42; H, 10.86. Found: C, 73.38; H, 10.92.

(*R*)-1-((4*S*,5*R*)-5-(5-(Benzyloxy)pentyl)-2,2-dimethyl-1,3-dioxolan-4-yl)-19-(*tert*-butyldimethylsilyloxy)nonadec-3-ynyl benzoate (178)

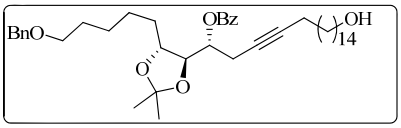


To a solution of **177** (0.7 g, 1.02 mmol) in DCM (10 mL) at 0 °C was added triethylamine (0.21 mL, 1.5 mmol), DMAP (catalytic) and stirred for 15 min. Benzoyl chloride (0.18 mL, 1.5 mmol) was added at 0 °C and stirred further for 2 h. The reaction mixture was extracted with DCM. The combined organic extracts were washed with brine, dried (Na_2SO_4), concentrated and the resulting crude product was purified by column chromatography (10% ethyl acetate in petroleum ether) to afford the benzoate **178** (0.74 g, 92%) as white syrup.

Mol. Formula	: $C_{49}H_{78}O_6Si$
$[\alpha]_D$	: –4.1 (*c* 1.0, $CHCl_3$).
IR ($CHCl_3$) $\tilde{\nu}$	: 2928, 1725, 1495, 1369, 1268, 1100, 836, 710 cm^{-1}.
^{1}H NMR ($CDCl_3$, 200 MHz)	: δ 0.04 (s, 6H), 0.89 (s, 9H), 1.15-1.30 (m, 26H), 1.36 (s, 3H), 1.41 (s, 3H), 1.46-1.80 (m, 10H), 2.04-2.11 (m, 2H), 2.67-2.70 (m, 2H), 3.39 (t, *J* = 6.4 Hz, 2H), 3.59 (t, *J* = 6.6 Hz, 2H), 3.95-4.09 (m, 2H), 4.45 (s, 2H), 5.23 (q, *J* = 5.7

	Hz, 1H), 7.27-7.34 (m, 5H), 7.38-7.46 (m, 2H),7.42 (tt, *J* = 1.4, 6.9, Hz, 2H), 7.55 (tt, *J* = 1.4, 7.3 Hz, 1H), 8.04 (dt, *J* = 1.3, 6.9 Hz, 2H) ppm.
^{13}C NMR ($CDCl_3$, 50 MHz)	: δ –5.3 (q, 2C), 18.4 (s), 18.7 (t), 21.6 (t), 25.8 (t), 25.9 (t), 26.0 (q, 3C), 26.1 (t), 27.0 (q), 27.5 (q), 28.8 (t), 29.2 (t), 29.4 (t), 29.5 (t), 29.5 (t), 29.7 (t, 7C), 32.9 (t), 34.2 (t), 63.3 (t), 70.2 (t), 72.8 (t), 72.8 (d), 74.6 (s), 78.8 (d), 80.3 (d), 82.9 (s), 109.2 (s), 127.4 (d), 127.6 (d, 2C), 128.3 (d, 2C), 128.4 (d, 2C), 129.7 (d, 2C), 129.9 (s), 133.1 (d), 138.6 (s), 165.6 (s) ppm.
ESI-MS (*m/z*)	: 813.6 $[M+Na]^+$.
Elemental Analysis	Calcd.: C, 74.38; H, 9.94.
	Found: C, 74.10; H, 9.78.

(*R*)-1-((4*S*,5*R*)-5-(5-(Benzyloxy)pentyl)-2,2-dimethyl-1,3-dioxolan-4-yl)-19-hydroxynonadec-3-ynyl benzoate (179)

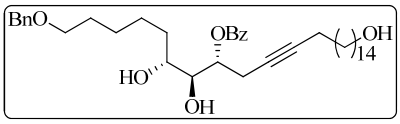


To a solution of the acetonide **178** (0.4 g, 0.51 mmol) in MeOH (10 mL), catalytic *p*-TSA (5 mg, 0.03 mmol) was added and the reaction mixture was stirred at rt for 2 h. The reaction mixture was quenched by the addition of few drops of triethylamine and the solvent was evaporated. The crude residue was purified by column chromatography (25%, 50% ethyl acetate in petroleum ether) to obtain **179** (34 mg, 10%) and **180** (0.28 g, 86%) as colorless syrups.

Mol. Formula	: $C_{43}H_{64}O_6$
$[\alpha]_D$	: –3.9 (*c* 1.0, $CHCl_3$).
IR ($CHCl_3$) $\tilde{\nu}$	: 3371, 3020, 1712, 1420, 1216, 1113, 757, 669 cm^{-1}.
^{1}H NMR ($CDCl_3$, 200 MHz)	: δ 1.25-1.29 (m, 27H), 1.36 (s, 3H), 1.40 (s, 3H), 1.36-1.57 (m, 7H), 2.08 (tt, *J* = 2.0, 6.6 Hz, 2H), 2.66-2.70 (m, 2H), 3.38 (t, *J* = 6.4 Hz, 2H), 3.61 (t, *J* = 6.6 Hz, 2H), 3.92-4.07 (m, 2H), 4.44 (s, 2H), 5.20 (q, *J* = 5.7 Hz, 1H), 7.24-7.33 (m, 5H), 7.41 (tt, *J* = 1.4, 7.1 Hz, 2H), 7.54 (tt, *J* = 1.5, 7.3 Hz, 1H), 8.03 (tt, *J* = 1.4, 7.0 Hz, 2H) ppm.

^{13}C NMR ($CDCl_3$, 50 MHz)	: δ 18.6 (t), 21.6 (t), 25.7 (t), 25.8 (t), 26.1 (t), 27.0 (q), 27.5 (q), 28.8 (t, 2C), 29.1 (t), 29.4 (t), 29.5 (t), 29.5 (t), 29.6 (t, 2C), 29.6 (t, 4C), 32.8 (t), 34.2 (t), 63.0 (t), 70.2 (t), 72.8 (t), 72.8 (d), 74.6 (s), 78.8 (d), 80.3 (d), 82.9 (s), 109.2 (s), 127.4 (d), 127.5 (d, 2C), 128.3 (d, 2C), 128.4 (d, 2C), 129.7 (d, 2C), 129.9 (s), 133.1 (d), 138.6 (s), 165.6 (s) ppm.
ESI-MS (*m/z*)	: 699.6 $[M+Na]^+$.
Elemental Analysis	Calcd.: C, 76.29; H, 9.53. Found: C, 76.58; H, 9.55.

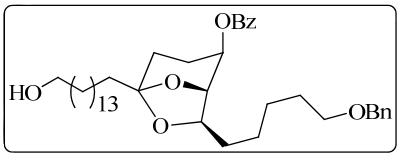
(6*R*,7*S*,8*R*)-1-(Benzyloxy)-6,7,26-trihydroxyhexacos-10-yn-8-yl benzoate (180)



Mol. Formula	: $C_{40}H_{60}O_6$
$[\alpha]_D$	: –3.9 (*c* 0.8, $CHCl_3$).
IR ($CHCl_3$) $\tilde{\nu}$	: 3427, 2929, 1706, 1453, 1276, 1116, 757, 668 cm^{-1}.
^{1}H NMR ($CDCl_3$, 200 MHz)	: δ 1.24-1.40 (m, 26H), 1.45-1.67 (m, 8H), 2.08 (tt, *J* = 2.0, 6.7 Hz, 2H), 2.54 (br d, *J* = 8.3 Hz, 1H), 2.65-2.81 (m, 2H), 2.92 (br s, 1H), 3.42 (t, *J* = 6.6 Hz, 2H), 3.55-3.65 (m, 2H), 3.62 (t, *J* = 6.6 Hz, 2H), 4.46 (s, 2H), 5.06 (ddd, *J* = 4.4, 6.3, 10.3 Hz, 1H), 7.23-7.31 (m, 5H), 7.44 (tt, *J* = 1.5, 7.1 Hz, 2H), 7.59 (tt, *J* = 2.3, 7.3 Hz,1H), 8.06 (tt, *J* = 1.5, 7.1 Hz, 2H) ppm.
^{13}C NMR ($CDCl_3$, 50 MHz)	: δ 18.6 (t), 21.7 (t), 25.7 (t), 25.8 (t), 26.2 (t), 28.8 (t), 28.8 (t), 29.1 (t), 29.4 (t), 29.5 (t), 29.6 (t, 6C), 29.6 (t), 32.7 (t), 33.0 (t), 63.0 (t), 69.2 (d), 70.2 (t), 72.8 (t), 73.2 (d), 73.6 (d), 75.1 (s), 82.7 (s), 127.4 (d), 127.6 (d, 2C), 128.3 (d, 2C), 128.4 (d, 2C), 129.5 (s), 129.9 (d, 2C), 133.5 (d), 138.6 (s), 167.1 (s) ppm.
ESI-MS (*m/z*)	: 659.1 $[M+Na]^+$.

Elemental Analysis	Calcd.: C, 75.43; H, 9.50
	Found: C, 75.70; H, 9.63.

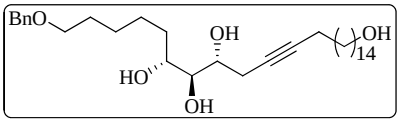
(1*S*,2*R*,5*S*,7*R*)-7-(5-(Benzyloxy)pentyl)-5-(15-hydroxypentadecyl)-6,8-dioxabicyclo[3.2.1]octan-2-yl benzoate (181)



A solution of the triol **180** (0.5 g, 0.79 mmol) and $Pd(CH_3CN)_2Cl_2$ (11 mg, 0.04 mmol) in acetonitrile (15 mL) was stirred at rt under argon atmosphere for 3 h. The reaction mixture was concentrated and the residue obtained was purified by silica gel chromatography (40% ethyl acetate in petroleum ether) to obtain **181** (0.35 g, 70%) as colorless syrup.

Mol. Formula	: $C_{40}H_{60}O_6$
$[\alpha]_D$	: +15.0 (*c* 2.5, $CHCl_3$).
IR ($CHCl_3$) $\tilde{\nu}$	: 3406, 2928, 1711, 1277, 1216, 758, 669 cm^{-1}.
^{1}H NMR ($CDCl_3$, 200 MHz)	: δ 1.25 (m, 22H), 1.37-1.72 (m, 14H), 1.80-1.96 (m, 2H), 2.06-2.21 (m, 2H), 3.45 (t, *J* = 6.4 Hz, 2H), 3.62 (t, *J* = 6.6 Hz, 2H), 3.97 (dd, *J* = 4.5, 7.1 Hz, 1H), 4.28 (br s, 1H), 4.48 (s, 2H), 4.89 (br s, 1H), 7.25-7.32 (m, 5H), 7.43 (tt, *J* = 1.5, 6.9 Hz, 2H), 7.55 (tt, *J* = 1.5, 7.1 Hz, 1H), 8.08 (dt, *J* = 1.6, 6.9 Hz, 2H) ppm.
^{13}C NMR ($CDCl_3$, 50 MHz)	: δ 22.7 (t), 22.8 (t), 25.4 (t), 25.8 (t), 26.1 (t), 29.5 (t), 29.7 (t), 29.7 (t), 29.7 (t, 7C), 29.8 (t), 30.8 (t), 32.8 (t), 35.1 (t), 37.5 (t), 63.0 (t), 68.9 (d), 70.2 (t), 72.9 (t), 77.8 (d), 79.7 (d), 109.4 (s), 127.5 (d), 127.6 (d), 128.3 (d, 3C), 128.4 (d), 129.8 (d), 130.2 (d), 130.4 (s), 133.0 (d), 133.5 (d), 138.6 (s), 166.1 (s) ppm.
ESI-MS (*m/z*)	: 659.3 $[M+Na]^+$.
Elemental Analysis	Calcd.: C, 75.43; H, 9.50.
	Found: C, 75.14; H, 9.42.

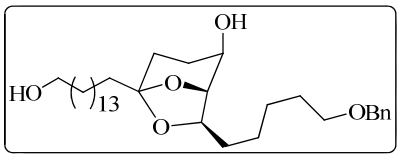
(19*R*,20*S*,21*R*)-26-(Benzyloxy)hexacos-16-yne-1,19,20,21-tetraol (182)



To a solution of the acetonide **181** (0.2 g, 0.29 mmol) in MeOH (5 mL), catalytic pTSA (5 mg, 0.03 mmol) was added and the reaction mixture was stirred at rt for 2 h. The reaction mixture was quenched by the addition of few drops of triethylamine and the solvent was evaporated. The crude residue was purified by column chromatography (60% ethyl acetate in petroleum ether) to obtain **182** (0.13 g, 82%) as a white solid.

Mol. Formula	: $C_{33}H_{56}O_5$
$[\alpha]_D$	: –3.2 (*c* 0.5, MeOH).
IR (nujol) $\tilde{\nu}$	: 3438, 2923, 1462, 1377, 1111, 1058, 737, 648 cm^{-1}.
^{1}H NMR (Methanol d_4, 200 MHz)	: δ 1.22 (m, 18H), 1.35-1.59 (m, 16H), 2.10-2.16 (m, 2H), 2.38 (ddt, *J* = 2.5, 5.8, 16.8 Hz, 1H), 2.54 (ddt, *J* = 2.5, 4.7, 16.9 Hz, 1H), 3.32 (dt, *J* = 1.6, 7.1 Hz, 1H), 3.48 (t, *J* = 6.6 Hz, 2H), 3.52 (t, *J* = 6.4 Hz, 2H), 3.70 (ddd, *J* = 4.7, 6.3, 10.5 Hz, 1H), 3.74-3.80 (m, 1H), 4.43 (s, 2H), 7.22-7.28 (m, 5H) ppm.
^{13}C NMR (Methanol d_4, 50 MHz)	: δ 19.1 (t), 21.5 (t), 24.3 (t), 26.0 (t), 26.1 (t), 26.5 (t), 29.3 (t), 29.4 (t), 29.5 (t), 29.8 (t), 29.9 (t), 30.0 (t, 6C), 32.7 (t), 33.7 (t), 62.8 (t), 70.5 (d), 70.8 (t), 71.6 (d), 73.3 (t), 74.3 (s), 76.4 (d), 83.0 (s), 128.0 (d), 128.1 (d, 2C), 128.7 (d, 2C), 138.6 (s) ppm.
ESI-MS (*m/z*)	: 555.4 $[M+Na]^+$.
Elemental Analysis	Calcd.: C, 74.39; H, 10.59. Found: C, 74.17; H, 10.44.

(1*S*,2*R*,5*S*,7*R*)-7-(5-(Benzyloxy)pentyl)-5-(15-hydroxypentadecyl)-6,8-dioxabicyclo[3.2.1]octan-2-ol (149)

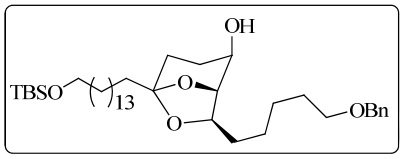


A solution of the tetrol **182** (0.5 g, 0.94 mmol) and $Pd(CH_3CN)_2Cl_2$ (7 mg, 0.03 mmol) in acetonitrile (10 mL) was stirred at rt under argon atmosphere for 6 h.

The reaction mixture was concentrated and the crude residue obtained was purified by silica gel chromatography (50% ethyl acetate in petroleum ether) to obtain **149** (0.38 g, 79%) as colorless syrup.

Mol. Formula	: $C_{33}H_{56}O_5$
$[\alpha]_D$	: +14.4 (*c* 1.0, $CHCl_3$).
IR ($CHCl_3$) $\tilde{\nu}$	: 3437, 2929, 1639, 1560, 1416, 1216, 757, 668 cm^{-1}.
^{1}H NMR ($CDCl_3$, 400 MHz)	: δ 1.24-1.32 (m, 23H), 1.35-1.44 (m, 5H), 1.49-1.58 (m, 4H), 1.60-1.69 (m, 6H), 1.77 (dt, *J* = 5.5, 12.3 Hz, 1H), 1.92-2.01 (m, 1H), 3.45 (t, *J* = 6.5 Hz, 2H), 3.58 (t, *J* = 1.5 Hz, 1H), 3.62 (t, *J* = 6.8 Hz, 2H), 3.86 (dd, *J* = 5.5, 7.4 Hz, 1H), 4.04 (br s, 1H), 4.48 (s, 2H), 7.26-7.35 (m, 5H) ppm.
^{13}C NMR ($CDCl_3$, 100 MHz)	: δ 22.9 (t), 25.0 (t), 25.3 (t), 25.7 (t), 26.0 (t), 29.4 (t), 29.5 (t), 29.6 (t), 29.6 (t, 6C), 29.7 (t), 29.8 (t), 30.1 (t), 32.8 (t), 35.2 (t), 37.5 (t), 63.0 (t), 66.3 (d), 70.3 (t), 72.9 (t), 77.8 (d), 82.3 (d), 109.5 (s), 127.5 (d), 127.6 (d, 2C), 128.3 (d, 2C), 138.6 (s) ppm.
ESI-MS (*m/z*)	: 555.7 $[M+Na]^+$.
Elemental Analysis	Calcd.: C, 74.39; H, 10.59. Found: C, 74.20; H, 10.46.

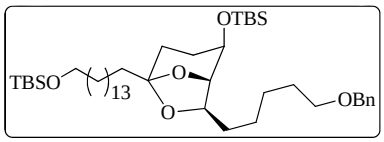
(1*R*,2*R*,5*S*,7*R*)-7-(5-(Benzyloxy)pentyl)-5-(15-(*tert*-butyldimethylsilyloxy)pentadecyl)-6,8-dioxabicyclo[3.2.1]octan-2-ol (183)



To a solution of **149** (0.5 g, 0.94 mmol) in DCM (5 mL) at 0°C was added imidazole (0.13 g, 1.9 mmol), DMAP (catalytic) and stirred for 15 min. TBSCl (0.21 g, 1.41 mmol) was added at 0 °C and stirred further for 1 h. The reaction mixture was extracted with DCM. The combined organic extracts were washed with brine, dried (Na_2SO_4), concentrated and the resulting crude product was purified by column chromatography (10%, 25% ethyl acetate in petroleum ether) to afford silyl ether **183-TBS** (50 mg, 7%) and **183** (0.55 g, 91%) as white syrups respectively.

Mol. Formula	: $C_{39}H_{70}O_5Si$
$[\alpha]_D$	: +21.4 (*c* 0.9, $CHCl_3$).
IR ($CHCl_3$) $\tilde{\nu}$	: 3428, 3019, 2929, 1464, 1216, 1097, 758, 669 cm^{-1}.
^{1}H NMR ($CDCl_3$, 400 MHz)	: δ 0.03 (s, 6H), 0.88 (s, 9H), 1.24-1.32 (m, 24H), 1.36-1.44 (m, 6H), 1.46-1.56 (m, 3H), 1.58-1.69 (m, 4H), 1.64 (br s, 1H), 1.77 (dt, *J* = 5.8, 12.3 Hz, 1H), 1.92-2.03 (m, 1H), 2.39 (br s, 1H), 3.46 (t, *J* = 6.5 Hz, 2H), 3.58 (t, *J* = 6.8 Hz, 2H), 3.58 (s, 1H), 3.87 (dd, *J* = 5.8, 7.5 Hz, 1H), 4.04 (br s, 1H), 4.49 (s, 2H), 7.24-7.28 (m, 1H), 7.29-7.35 (m, 4H) ppm.
^{13}C NMR ($CDCl_3$, 100 MHz)	: δ –5.3 (q, 2C), 18.4 (s), 23.0 (t), 25.1 (t), 25.4 (t), 25.8 (t), 26.0 (q, 3C), 26.0 (t), 29.4 (t), 29.6 (t), 29.6 (t), 29.7 (t, 7C), 29.8 (t), 30.1 (t), 32.9 (t), 35.2 (t), 37.5 (t), 63.3 (t), 66.3 (d), 70.3 (t), 72.9 (t), 77.9 (d), 82.4 (d), 109.5 (s), 127.5 (d), 127.6 (d, 2C), 128.3 (d, 2C), 138.6 (s) ppm.
ESI-MS (*m/z*)	: 669.7 $[M+Na]^+$.
Elemental Analysis	Calcd.: C, 72.39; H, 10.90. Found: C, 71.95; H, 10.75.

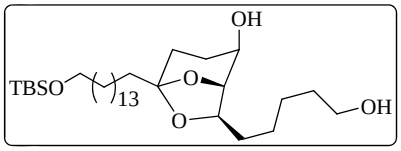
(15-((1*S*,2*R*,5*S*,7*R*)-7-(5-(Benzyloxy)pentyl)-2-(*tert*-butyldimethylsilyloxy)-6,8-dioxabicyclo[3.2.1]octan-5-yl)pentadecyloxy)(*tert*-butyl)dimethylsilane (183-TBS)



Mol. Formula	: $C_{45}H_{84}O_5Si_2$
$[\alpha]_D$	: +14.6 (*c* 1.2, $CHCl_3$).
IR ($CHCl_3$) $\tilde{\nu}$	: 2929, 1471, 1216, 1098, 836, 759, 668 cm^{-1}.
^{1}H NMR ($CDCl_3$, 400 MHz)	: δ 0.03 (s, 6H), 0.06 (s, 3H), 0.06 (s, 3H), 0.88 (s, 9H), 0.90 (s, 9H), 1.24-1.32 (m, 28H), 1.40-1.43 (m, 4H), 1.48-1.54 (m, 2H), 1.60-1.69 (m, 4H), 1.83 (dt, *J* = 5.5, 12.3 Hz, 1H), 1.90-2.00 (m, 1H), 3.46 (t, *J* = 6.5 Hz, 2H), 3.58 (t, *J* = 6.8 Hz, 2H), 3.58 (br s, 1H), 3.78 (dd, *J* = 5.2, 7.3 Hz, 1H), 3.92 (br s, 1H), 4.49 (s, 2H), 7.27-7.33 (m, 5H) ppm.

^{13}C NMR ($CDCl_3$, 100 MHz)	: δ –5.3 (q, 2C), –4.7 (q), –4.7 (q), 18.3 (s), 18.4 (s), 22.9 (t), 25.5 (t), 25.8 (t), 25.9 (q, 3C), 26.0 (q, 3C), 26.1 (t), 29.4 (t), 29.6 (t, 5C), 29.7 (t, 5C), 29.8 (t), 30.3 (t), 32.9 (t), 35.2 (t), 37.6 (t), 63.3 (t), 66.9 (d), 70.3 (t), 72.9 (t), 77.7 (d), 83.0 (d), 109.2 (s), 127.5 (d), 127.6 (d, 2C), 128.3 (d, 2C), 138.6 (s) ppm.
ESI-MS (*m/z*)	: 783.6 $[M+Na]^+$.
Elemental Analysis	Calcd.: C, 70.99; H, 11.12.
	Found: C, 70.75; H, 10.95.

(1*R*,2*R*,5*S*,7*R*)-5-(15-(*tert*-Butyldimethylsilyloxy)pentadecyl)-7-(5-hydroxypentyl)-6,8-dioxabicyclo[3.2.1]octan-2-ol (184)



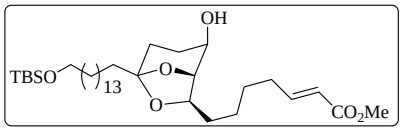
A suspension of **183** (0.25 g, 0.4 mmol), $Pd(OH)_2$ (5 mg,) in ethyl acetate (5 mL) was flushed with hydrogen gas and stirred under hydrogen (20 psi) atmosphere for 30 min. The reaction mixture was filtered through celite, concentrated and the crude product was purified by column chromatography (30% ethyl acetate in petroleum ether) to yield **184** (175 mg, 81%) as colorless oil.

Mol. Formula	: $C_{32}H_{64}O_5Si$
$[\alpha]_D$	:+37.4 (*c* 0.6, $CHCl_3$).
IR ($CHCl_3$) $\tilde{\nu}$	: 3395, 2928, 1463, 1254, 1101, 836, 757, 648 cm^{-1}.
^{1}H NMR ($CDCl_3$, 400 MHz)	: δ 0.03 (s, 6H), 0.88 (s, 9H), 1.24-1.27 (m, 24H), 1.35-1.42 (m, 4H), 1.47-1.59 (m, 6H), 1.63-1.70 (m, 4H), 1.77 (dt, *J* = 5.5, 12.3 Hz, 1H), 1.92-2.03 (m, 1H), 3.58 (t, *J* = 6.8 Hz, 2H), 3.60 (s, 1H), 3.63 (t, *J* = 6.5 Hz, 2H), 3.88 (dd, *J* = 5.5, 7.3 Hz, 1H), 4.05 (br s, 1H) ppm.
^{13}C NMR ($CDCl_3$, 100 MHz)	: δ –5.3 (q, 2C), 18.4 (s), 23.0 (t), 25.0 (t), 25.3 (t), 25.6 (t), 25.8 (t), 26.0 (q, 3C), 29.4 (t), 29.6 (t), 29.7 (t, 7C), 29.8 (t), 30.1 (t), 32.6 (t), 32.9 (t), 35.2 (t), 37.5 (t), 62.8 (t), 63.3 (t), 66.3 (d), 77.8 (d), 82.4 (d), 109.6 (s) ppm.
ESI-MS (*m/z*)	: 579.3 $[M+Na]^+$.

Elemental Analysis Calcd.: C, 69.01; H, 11.58.

Found: C, 68.90; H, 11.24.

(*E*)-Methyl 7-((1*R*,2*R*,5*S*,7*R*)-5-(15-(*tert*-butyldimethylsilyloxy)pentadecyl)-2-hydroxy-6,8-dioxabicyclo[3.2.1]octan-7-yl)hept-2-enoate (186)



To an ice-cooled solution of the diol **184** (0.3 g, 0.54 mmol) in DCM (5 mL), Dess-Martin periodinane (0.25 g, 0.59 mmol) was added in small portions and stirred for 6 h. The reaction mixture was quenched with ice, partitioned between DCM, water and the organic layer was separated, washed with ethyl acetate, brine, dried (Na_2SO_4), and concentrated to afford the aldehyde **185** (0.25 g, 84%) as colorless syrup. The crude aldehyde was used for the next step without purification.

To a solution of the aldehyde **185** (0.15 g, 0.27 mmol) in benzene (10 mL), the ylide [(carbmethoxymethylene)triphenyl phosphorane] (0.18 g, 0.54 mmol) was added and refluxed for 1 h. Solvent was evaporated under reduced pressure and the crude residue was purified by column chromatography (30% ethyl acetate in petroleum ether) to yield **186** (135 mg, 82%) as colorless oil.

Mol. Formula : $C_{35}H_{66}O_6Si$

$[\alpha]_D$: +14.9 (*c* 1.0, $CHCl_3$).

IR ($CHCl_3$) $\tilde{\nu}$: 3362, 2929, 1727, 1375, 1216, 759, 669 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz) : δ 0.03 (s, 6H), 0.88 (s, 9H), 1.25 (m, 24H), 1.39-1.58 (m, 9H), 1.66 (dt, *J* = 5.5, 14.6 Hz, 2H), 1.77 (dt, *J* = 5.8, 12.3 Hz, 1H), 1.92-2.01 (m, 1H), 2.20 (dq, *J* = 1.2, 7.0 Hz, 2H), 2.36 (d, *J* = 9.5 Hz, 1H), 3.58 (s, 1H), 3.58 (t, *J* = 6.5 Hz, 2H), 3.71 (s, 3H), 3.87 (dd, *J* = 5.3, 7.5 Hz, 1H), 4.04 (br s, 1H), 5.81 (dt, *J* = 1.5, 15.6 Hz, 1H), 6.94 (dt, *J* = 7.0, 15.6 Hz, 1H) ppm.

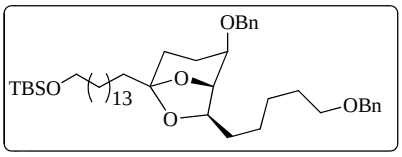
^{13}C NMR ($CDCl_3$, 100 MHz) : δ –5.3 (q, 2C), 18.4 (s), 23.0 (t), 25.1 (t), 25.8 (t), 26.0 (q, 3C), 27.8 (t), 29.4 (t), 29.6 (t), 29.6 (t), 29.7 (t, 7C), 29.8 (t), 30.1 (t), 32.1 (t), 32.9 (t), 35.1 (t), 37.5 (t), 51.4 (q), 63.3 (t), 66.3 (d), 77.7 (d), 82.4 (d), 109.6 (s), 121.1 (d), 149.2 (d), 167.1 (s) ppm.

ESI-MS (*m/z*) : 634.0 $[M+Na]^+$.

Elemental Analysis Calcd.: C, 68.80; H, 10.89.

Found: C, 68.71; H, 10.76.

(15-((1*R*,2*R*,5*S*,7*R*)-2-(Benzyloxy)-7-(5-(benzyloxy)pentyl)-6,8-dioxabicyclo[3.2.1]octan-5-yl)pentadecyloxy)(*tert*-butyl)dimethylsilane (190)



To an ice-cooled solution (0 °C) of alcohol **183** (0.2 g, 0.31 mmol) in DMF (10 mL), NaH (11 mg, 0.46 mmol) was added and stirred for 30 min. Benzyl bromide (0.06 mL, 0.46 mmol) was added to the reaction mixture at 0 °C and the reaction mixture was stirred for 1 h. The reaction mixture was quenched with ice, partitioned between ethyl acetate, water and the organic layer was separated, washed with ethyl acetate, brine, dried (Na_2SO_4), and concentrated. Purification of the residue by column chromatography (10% ethyl acetate in petroleum ether) afforded **190** (0.21 g, 92%) as colorless syrup.

Mol. Formula : $C_{46}H_{76}O_5Si$

$[\alpha]_D$: +20.2 (*c* 1.8, $CHCl_3$).

IR ($CHCl_3$) $\tilde{\nu}$: 2926, 1455, 1361, 1347, 1254, 1099, 836, 758, 697 cm^{-1}.

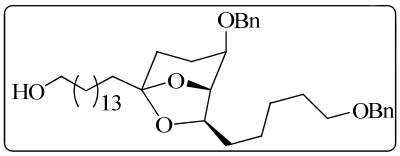
^{1}H NMR ($CDCl_3$, 400 MHz) : δ 0.04 (s, 6H), 0.89 (s, 9H), 1.24-1.25 (m, 28H), 1.34-1.44 (m, 4H), 1.49-1.53 (m, 4H), 1.63-1.67 (m, 2H), 1.79-1.87 (m, 2H), 3.28 (br s, 1H), 3.45 (t, *J* = 6.5 Hz, 2H), 3.59 (d, *J* = 6.5 Hz, 2H), 3.78 (dd, *J* = 4.8, 7.3 Hz, 1H), 4.17 (br s, 1H), 4.49 (s, 2H), 4.58 (d, *J* = 12.8 Hz, 1H), 4.62 (d, *J* = 12.5 Hz, 1H), 7.27-7.36 (m, 10H) ppm.

^{13}C NMR ($CDCl_3$, 100 MHz) : δ –5.3 (q, 2C), 18.4 (s), 21.9 (t), 22.7 (t), 25.4 (t), 25.8 (t), 26.0 (q, 3C), 29.4 (t), 29.6 (t), 29.7 (t, 8C), 29.8 (t), 30.7 (t), 31.9 (t), 32.9 (t), 35.2 (t), 37.4 (t), 63.3 (t), 70.3 (t, 2C), 72.3 (d), 72.9 (t), 77.7 (d), 80.0 (d), 109.3 (s), 127.5 (d, 2C), 127.6 (d, 2C), 127.6 (d, 2C), 128.3 (d, 2C), 128.4 (d, 2C), 138.5 (s), 138.6 (s) ppm.

ESI-MS (*m/z*) : 760.0 $[M+Na]^+$.

Elemental Analysis Calcd.: C, 74.95; H, 10.39.
Found: C, 74.80; H, 10.43.

15-((1*R*,2*R*,5*S*,7*R*)-2-(Benzyloxy)-7-(5-(benzyloxy)pentyl)-6,8 dioxabicyclo [3.2.1] octan-5-yl)pentadecan-1-ol (149a)



To a solution of **190** (0.2 g, 0.27 mmol) in MeOH (10 mL), catalytic *p*-TSA (5 mg, 0.03 mmol) was added and the reaction mixture was stirred at rt for 30 min. The reaction mixture was quenched by the addition of few drops of triethylamine and the solvent was evaporated. The crude residue was purified by column chromatography (40% ethyl acetate in petroleum ether) to obtain **149a** (0.15 g, 88%) as a colorless oil.

Mol. Formula : $C_{40}H_{62}O_5$

$[\alpha]_D$: +23.8 (*c* 1.4, $CHCl_3$).

IR ($CHCl_3$) $\tilde{\nu}$: 3437, 2927, 1596, 1384, 1217, 1027, 759, 698 cm^{-1}.

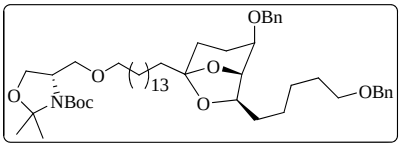
^{1}H NMR ($CDCl_3$, 200 MHz) : δ 1.24 (m, 26H), 1.35-1.46 (m, 4H), 1.49-1.70 (m, 8H), 1.79-1.87 (m, 2H), 3.28 (s, 1H), 3.45 (t, *J* = 6.5 Hz, 2H), 3.61 (d, *J* = 6.5 Hz, 2H), 3.78 (dd, *J* = 4.8, 7.3 Hz, 1H), 4.17 (br s, 1H), 4.49 (s, 2H), 4.59 (d, *J* = 12.5 Hz, 1H), 4.62 (d, *J* = 12.5 Hz, 1H), 7.25-7.28 (m, 2H), 7.32-7.37 (m, 8H) ppm.

^{13}C NMR ($CDCl_3$, 100 MHz) : δ 21.9 (t), 22.7 (t), 22.7 (t), 25.4 (t), 25.7 (t), 26.0 (t), 29.3 (t), 29.4 (t), 29.5 (t), 29.6 (t, 4C), 29.7 (t), 29.8 (t), 30.7 (t), 31.9 (t), 32.8 (t), 35.2 (t), 37.4 (t), 63.0 (t), 70.3 (t, 2C), 72.2 (d), 72.8 (t), 77.7 (d), 80.0 (d), 109.3 (s), 127.4 (d, 2C), 127.5 (d, 2C), 127.6 (d, 2C), 128.3 (d, 2C), 128.3 (d, 2C), 138.5 (s), 138.6 (s) ppm.

ESI-MS (*m/z*) : 645.8 $[M+Na]^+$.

Elemental Analysis Calcd.: C, 77.13; H, 10.03.
Found: C, 77.01; H, 9.86.

***tert*-Butyl 4-((15-((1*R*,2*R*,5*S*,7*R*)-2-(benzyloxy)-7-(5-(benzyloxy)pentyl)-6,8 dioxabicyclo[3.2.1]octan-5 yl)pentadecyloxy)methyl)-2,2-dimethyloxazolidine-3-carboxylate (192)**



At 0 °C, triethylamine (0.06 mL, 0.48 mmol) was added to a solution of the silyl ether **149a** (0.2 g, 0.32 mmol) in DCM and stirred for 30 min. MsCl (0.03 mL, 0.38 mmol) was added at 0 °C and stirred for 30 min. The reaction mixture was extracted with DCM. The combined organic extracts were washed with brine, dried (Na_2SO_4), concentrated and the resulting crude mesylate **191** (0.21, 95% yield) was used as such for the next step without purification.

Serinol derivative **130** (65 mg, 0.28 mmol) was dissolved in dry DMSO (3 mL) and treated with NaH (5 mg, 60% dispersion in mineral oil, 0.21 mmol) and mesylate **191** (100 mg, 0.14 mmol) was added sequentially. The reaction immediately changed color from nearly colorless to orangish red. The reaction was stirred at room temperature for 16 h, and was then quenched by the ice and diluted with ethyl acetate. The two layers were separated and the aqueous layer extracted with ethyl acetate (5 x 15 mL). The combined organic layers were dried (Na_2SO_4) and concentrated *in vacuo*. Purification by flash column chromatography (40% ethyl acetate in petroleum ether) yielded the serinol ether **192** (77 mg, 65% yield) as colorless oil.

Mol. Formula	: $C_{51}H_{81}NO_8$
$[\alpha]_D$	: +12.6 (*c* 0.2, $CHCl_3$).
IR ($CHCl_3$) $\tilde{\nu}$	: 3017, 2928, 1690, 1454, 1393, 1216, 1092, 757, 669 cm^{-1}.
^{1}H NMR ($CDCl_3$, 400 MHz)	: δ 1.23-1.28 (m, 28H), 1.38 (s, 3H), 1.40 (s, 3H), 1.46 (m, 9H), 1.51-1.71 (m, 10H), 1.79-1.89 (m, 2H), 3.28 (br s, 1H), 3.28-3.30 (br s, 1H), 3.37 (t, *J* = 6.5 Hz, 1H), 3.45 (t, *J* = 6.5 Hz, 2H), 3.78 (dd, *J* = 4.8, 7.5 Hz, 1H), 3.89-3.92 (m, 1H), 3.97-4.00 (m, 2H), 4.03-4.07 (m, 1H), 4.16 (br s, 1H), 4.48 (s, 2H), 4.58 (d, *J* = 12.5 Hz, 1H), 4.62 (d, *J* = 12.5 Hz, 1H), 7.25-7.28 (m, 3H), 7.32-7.37 (m, 7H) ppm.
^{13}C NMR ($CDCl_3$, 100 MHz)	: δ 21.9 (t), 22.7 (t), 22.7 (t), 24.4, 24.7 (2q, 1C), 25.4 (t), 26.0 (t), 26.1 (t), 26.2 (t), 26.7, 27.4 (2q, 1C), 28.4, 28.4 (2q, 3C), 29.3 (t), 29.5 (t), 29.6 (t, 2C), 29.7 (t, 4C), 29.8

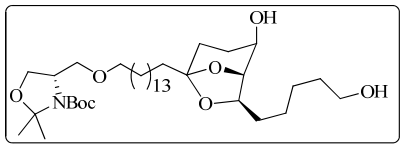
(t), 30.7 (t), 31.9 (t), 35.2 (t), 37.4 (t), 56.3, 56.5 (2d, 1C), 65.4, 65.7 (2t, 1C), 69.2, 70.0 (2t, 1C), 70.3 (t, 2C), 71.4 (t), 72.3 (d), 72.9 (t), 77.7 (d), 79.7, 80.2 (2s, 1C), 80.0 (d), 93.2, 93.7 (2s, 1C), 109.3 (s), 127.5 (d), 127.6 (d, 3C), 127.6 (d, 2C), 128.3 (d, 2C), 128.4 (d, 2C), 138.5 (s), 138.6 (s), 151.7, 152.2 (2s, 1C) ppm.

ESI-MS (*m/z*) : 858.8 $[M+Na]^+$.

Elemental Analysis Calcd.: C, 73.25; H, 9.76; N, 1.68.

Found: C, 72.80; H, 9.83; N, 1.42.

(*S*)-*tert*-Butyl 4-((15-((1*R*,2*R*,5*S*,7*R*)-2-hydroxy-7-(5-hydroxypentyl)-6,8 dioxabicyclo[3.2.1]octan-5-yl)pentadecyloxy)methyl)-2,2-dimethyloxazolidine-3-carboxylate (193)



A suspension of **192** (50 mg, 0.06 mmol), $Pd(OH)_2$ (5 mg) in ethyl acetate (5 mL) was flushed with hydrogen gas and stirred under hydrogen (20 *psi*) atmosphere for 30 min. The reaction mixture was filtered through celite, concentrated and the crude product was purified by column chromatography (30% ethyl acetate in petroleum ether) to yield **193** (35 mg, 90%) as colorless oil.

Mol. Formula : $C_{37}H_{69}NO_8$

$[\alpha]_D$: +36.3 (*c* 0.2, $CHCl_3$).

IR ($CHCl_3$) $\tilde{\nu}$: 3436, 2928, 1690, 1406, 1394, 1216, 758, 668 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz) : δ 1.24-1.35 (m, 24H), 1.40-1.46 (m, 6H), 1.46 (s, 9H), 1.51-1.70 (m, 14H), 1.77 (dt, *J* = 5.5, 12.3 Hz, 1H), 1.92-2.04 (m, 1H), 3.23-3.50 (m, 2H), 3.39 (dd, *J* = 2.7, 8.1 Hz, 1H), 3.46 (dd, *J* = 2.9, 8.1 Hz, 1H), 3.60-3.66 (m, 1H), 3.63 (t, *J* = 6.44 Hz, 2H), 3.85-4.00 (m, 3H), 3.97-4.05 (m, 1H), 4.05 (br s, 1H) ppm.

^{13}C NMR ($CDCl_3$, 100 MHz) : δ 22.7 (t), 22.9 (t), 23.1, 24.4 (2q, 1C), 25.0 (t), 25.3 (t), 25.6 (t), 26.1 (t), 26.7, 27.5 (2q, 1C), 28.4, 28.5 (2q, 3C), 29.1 (t), 29.3 (t), 29.4 (t), 29.6 (t, 2C), 29.6 (t, 3C), 29.8 (t), 30.1 (t), 31.9 (t), 32.6 (t), 35.2 (t), 37.5 (t), 56.3, 56.5 (2d, 1C), 62.8 (t), 65.4, 65.7 (2t, 1C), 66.3 (d), 69.3, 70.0

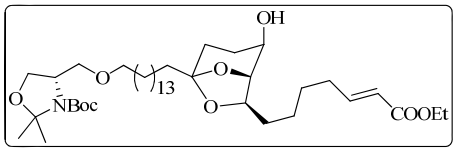
(2t, 1C), 71.4 (t), 77.8 (d), 79.7, 80.2 (2s, 1C), 82.4 (d), 93.3, 93.7 (2s, 1C), 109.6 (s), 151.7, 152.2 (2s, 1C) ppm.

ESI-MS (*m/z*) : 678.7 $[M+Na]^+$.

Elemental Analysis Calcd.: C, 67.75; H, 10.60; N, 2.14.

Found: C, 67.60; H, 10.43; N, 2.02.

(*S*)-*tert*-Butyl 4-((15-((1*R*,2*R*,5*S*,7*R*)-7-((*E*)-7-ethoxy-7-oxohept-5-enyl)-2-hydroxy-6,8-dioxabicyclo[3.2.1]octan-5-yl)pentadecyloxy)methyl)-2,2-dimethyloxazolidine-3-carboxylate (147)



To an ice-cooled solution of the diol **193** (35 mg, 0.05 mmol) in DCM (2 mL), DMP (0.22 g, 0.59 mmol) was added in small portions and stirred for 6 h. The reaction mixture was quenched with ice, partitioned between DCM, water and the organic layer was separated, washed with DCM, brine, dried (Na_2SO_4), and concentrated to afford the aldehyde **194** (29 mg, 85%) as colorless syrup. The crude aldehyde was used for the next step without purification.

To a solution of the aldehyde **194** (40 mg, 0.06 mmol) in benzene (2 mL), the ylide ((carbethoxymethylene)triphenyl phosphorane) (42 mg, 0.12 mmol) was added and refluxed for 1 h. Solvent was evaporated under reduced pressure and the crude residue was purified by column chromatography (20% ethyl acetate in petroleum ether) to yield **147** (34 mg, 78%) as colorless oil.

Mol. Formula : $C_{41}H_{73}NO_9$

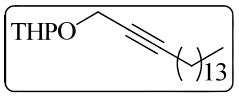
$[\alpha]_D$: +16.4 (*c* 0.5, $CHCl_3$).

IR ($CHCl_3$) $\tilde{\nu}$: 3451, 2928, 1732, 1693, 1465, 1393, 1247, 1046, 758, 667 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz) : δ 1.24-1.34 (m, 24H), 1.39-1.42 (m, 6H), 1.46 (s, 9H), 1.51-1.59 (m, 10H), 1.63-1.70 (m, 4H), 1.77 (dt, *J* = 5.5, 12.5 Hz, 1H), 1.92-2.05 (m, 1H), 2.20 (q, *J* = 6.5 Hz, 2H), 2.30-2.44 (m, 1H), 3.26-3.32 (m, 1H), 3.37-3.49 (m, 3H), 3.54-3.60 (m, 1H), 3.60 (br s, 1H), 3.66-3.92 (m, 3H), 3.97-3.99 (m, 1H), 4.05 (br s, 1H), 4.17 (q, *J* = 7.0 Hz, 2H), 5.80 (br d, *J* = 15.6 Hz, 1H), 6.94 (dt, *J* = 7.0, 15.6 Hz, 1H) ppm.

^{13}C NMR ($CDCl_3$, 100 MHz)	: δ 14.3 (q), 22.7 (t), 23.0 (t), 23.1, 24.4 (2q, 1C), 25.0 (t), 25.1 (t), 26.1 (t), 26.7, 27.5 (2q, 1C), 27.8 (t), 28.4, 28.5 (2q, 3C), 29.3 (t), 29.5 (t), 29.7 (t, 7C), 29.8 (t), 30.1 (t), 31.9 (t), 35.0 (t), 37.5 (t), 56.5, 56.3 (2d, 1C), 60.2 (t), 65.4, 65.7 (2t, 1C), 66.2 (d), 69.3, 70.0 (2t, 1C), 71.4 (t), 77.7 (d), 79.7, 80.2 (2s, 1C), 82.4 (d), 93.2, 93.7 (2s, 1C), 109.6 (s), 121.5 (d), 148.9 (d), 166.7 (s) ppm.
ESI-MS (*m/z*)	: 746.8 $[M+Na]^+$.
Elemental Analysis	Calcd.: C, 68.01; H, 10.16; N, 1.93. Found: C, 67.90; H, 10.03; N, 1.72.

2-(Heptadec-2-ynyloxy)tetrahydro-2*H*-pyran (174)

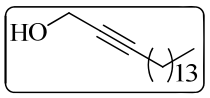


At −10 °C, a solution of the alkyne **153** (1 g, 7.1 mmol) in THF (10 mL) was treated with *n*-BuLi [(3.66 mL, 8.6 mmol) (2.34 M in hexane)] and stirred for 30 min. HMPA (1.53 mL, 8.6 mmol) was added and the reaction mixture was stirred at −10 °C for another 30 min. Myristyl bromide (2.37 g, 8.6 mmol) was dissolved in THF (20 mL) and stirred at −10 °C to which the solution of alkynyl lithium in THF was canulated and stirred for further 30 min. The reaction mixture was quenched with saturated NH_4Cl. The organic layer was separated and the aqueous layer was washed with ethyl acetate, the combined organic layers were washed with ethyl acetate, brine, dried and concentrated. Purification of the crude product by column chromatography (10% ethyl acetate in petroleum ether) afforded **174** (2.1 g, 87% yield) as colorless oil.

Mol. Formula	: $C_{22}H_{40}O_2$
IR ($CHCl_3$) $\tilde{\nu}$	: 2926, 1466, 1345, 1216, 1118, 1022, 903, 759, 668 cm^{-1}.
^{1}H NMR ($CDCl_3$, 200 MHz)	: δ 0.88 (t, *J* = 6.7 Hz, 3H), 1.24-1.34 (m, 24H), 1.46-1.88 (m, 6H), 2.11-2.23 (m, 2H), 3.44-3.55 (m, 1H), 3.81 (ddd, *J* = 3.3, 8.5, 11.7 Hz, 1H), 4.14 (dt, *J* = 2.1, 15.3 Hz, 1H), 4.25 (dt, *J* = 2.1, 15.3 Hz, 1H), 4.79 (t, *J* = 2.9 Hz, 1H) ppm.
^{13}C NMR	: δ 14.2 (q), 18.4 (t), 18.9 (t), 19.1 (t), 22.7 (t), 25.5 (t),

($CDCl_3$, 50 MHz)	28.5 (t), 28.6 (t), 28.8 (t), 28.9 (t), 29.2 (t), 29.4 (t), 29.6 (t), 29.7 (t), 29.7 (t), 30.3 (t), 32.0 (t), 54.5 (t), 61.8 (t), 75.8 (s), 86.6 (s), 96.4 (d) ppm.
ESI-MS (*m/z*)	: 359.5 $[M+Na]^+$.
Elemental Analysis	Calcd.: C, 78.51; H, 11.98.
	Found: C, 78.40; H, 12.13.

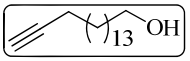
Heptadec-2-yn-1-ol (175)



To a solution of **174** (400 mg, 1.1 mmol) in MeOH (10 mL), catalytic *p*-TSA was added and the reaction mixture was stirred at rt for 30 min. The reaction mixture was quenched by the addition of few drops of triethylamine and the solvent was evaporated. The crude residue was purified by column chromatography (20% ethyl acetate in petroleum ether) to obtain **175** (200 mg, 91% yield) as a white solid.

Mol. Formula	: $C_{17}H_{32}O$
IR ($CHCl_3$) $\tilde{\nu}$	: 3539, 2944, 2254, 1631, 1444, 1376, 1040, 918, 759 cm^{-1}.
^{1}H NMR	: δ 0.87 (t, *J* = 6.7 Hz, 3H), 1.25-1.42 (m, 24H), 2.18 (tt, *J*
($CDCl_3$, 200 MHz)	= 2.1, 6.9 Hz, 2H), 4.22 (t, *J* = 2.1 Hz, 2H) ppm.
^{13}C NMR	: δ 14.2 (q), 18.8 (t), 22.7 (t), 28.6 (t), 28.9 (t), 29.2 (t),
($CDCl_3$, 50 MHz)	29.4 (t), 29.6 (t), 29.7 (t, 5C), 32.0 (t), 51.3 (t), 78.4 (s), 86.5 (s) ppm.
ESI-MS (*m/z*)	: 275.3 $[M+Na]^+$.
Elemental Analysis	Calcd.: C, 80.88; H, 12.78.
	Found: C, 80.60; H, 12.73.

Heptadec-16-yn-1-ol (176)

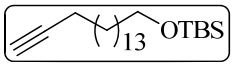


Lithium (0.04 g, 5.7 mmol) was added to freshly distilled 1,3-diaminopropane (5 mL) and stirred at rt till the reaction mixture turns into a deep purple suspension. The suspension was heated at 80 °C till the blue color disappears. The reaction mixture was cooled to rt and KO^{t}Bu (0.43 g, 3.8 mmol) was added and stirred for 30 min. Alkynol **175** (0.24 g, 0.9 mmol) was added to the reaction mixture and stirred at

rt for 1 h. The reaction mixture was quenched with ice, partitioned between DCM, water and the organic layer was separated, washed with DCM, brine, dried (Na_2SO_4), and concentrated. Purification of the residue by column chromatography (20% ethyl acetate in petroleum ether) afforded **176** (0.19 g, 79% yield) as white solid.

Mol. Formula	: $C_{17}H_{32}O$
IR ($CHCl_3$) $\tilde{\nu}$	: 3308, 2928, 1603, 1466, 1216, 1049, 758, 669 cm^{-1}.
^{1}H NMR ($CDCl_3$, 200 MHz)	: δ 1.25-1.41 (m, 22H), 1.48-1.58 (m, 4H), 1.88 (t, *J* = 2.5 Hz, 1H), 2.15 (dt, *J* = 2.5, 6.8 Hz, 2H), 3.61 (t, *J* = 6.7 Hz, 2H) ppm.
^{13}C NMR ($CDCl_3$, 50 MHz)	: δ 18.4 (t), 25.8 (t), 28.5 (t), 28.8 (t), 29.1 (t), 29.5 (t), 29.5 (t), 29.6 (t, 3C), 29.6 (t, 3C), 32.8 (t), 62.9 (t), 68.2 (d), 84.6 (s) ppm.
ESI-MS (*m/z*)	: 275.2 $[M+Na]^+$.
Elemental Analysis	Calcd.: C, 80.88; H, 12.78. Found: C, 80.70; H, 12.71.

tert-Butyl(heptadec-16-ynyloxy)dimethylsilane (152c)

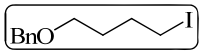


To a solution of **176** (1 g, 3.9 mmol) in DCM (5 mL) at 0°C was added triethylamine (0.83 mL, 5.9 mmol), DMAP (catalytic) and stirred for 15 min. TBSCl (0.89 g, 5.9 mmol) was added at 0°C and stirred further for 1 h. The reaction mixture was extracted with DCM. The combined organic extracts were washed with brine, dried (Na_2SO_4), concentrated and the resulting crude product was purified by column chromatography (5% ethyl acetate in petroleum ether) to afford silyl ether **152c** (1.3 g, 90% yield) as colorless oil.

Mol. Formula	: $C_{23}H_{46}OSi$
IR ($CHCl_3$) $\tilde{\nu}$	: 2944, 2253, 1444, 1376, 1040, 918, 751, 648 cm^{-1}.
^{1}H NMR ($CDCl_3$, 200 MHz)	: δ 0.03 (s, 6H), 0.88 (s, 9H), 1.25 (m, 25H), 1.46-1.55 (m, 5H), 1.77 (t, *J* = 2.5 Hz, 1H), 1.92 (t, *J* = 2.65 Hz, 1H), 2.16 (dt, *J* = 2.7, 6.9 Hz, 2H), 3.58 (t, *J* = 6.6 Hz, 2H) ppm.
^{13}C NMR	: δ -5.3 (q, 2C), 18.4 (t), 18.7 (s), 25.8 (t), 26.0 (q, 3C),

($CDCl_3$, 50 MHz)	28.5 (t), 28.8 (t), 29.1 (t), 29.5 (t), 29.5 (t), 29.6 (t, 3C), 29.7 (t, 3C), 32.9 (t), 63.3 (t), 68.0 (d), 84.7 (s) ppm.
ESI-MS (*m/z*)	: 389.2 $[M+Na]^+$.
Elemental Analysis	Calcd.: C, 75.33; H, 12.64.
	Found: C, 75.40; H, 12.43.

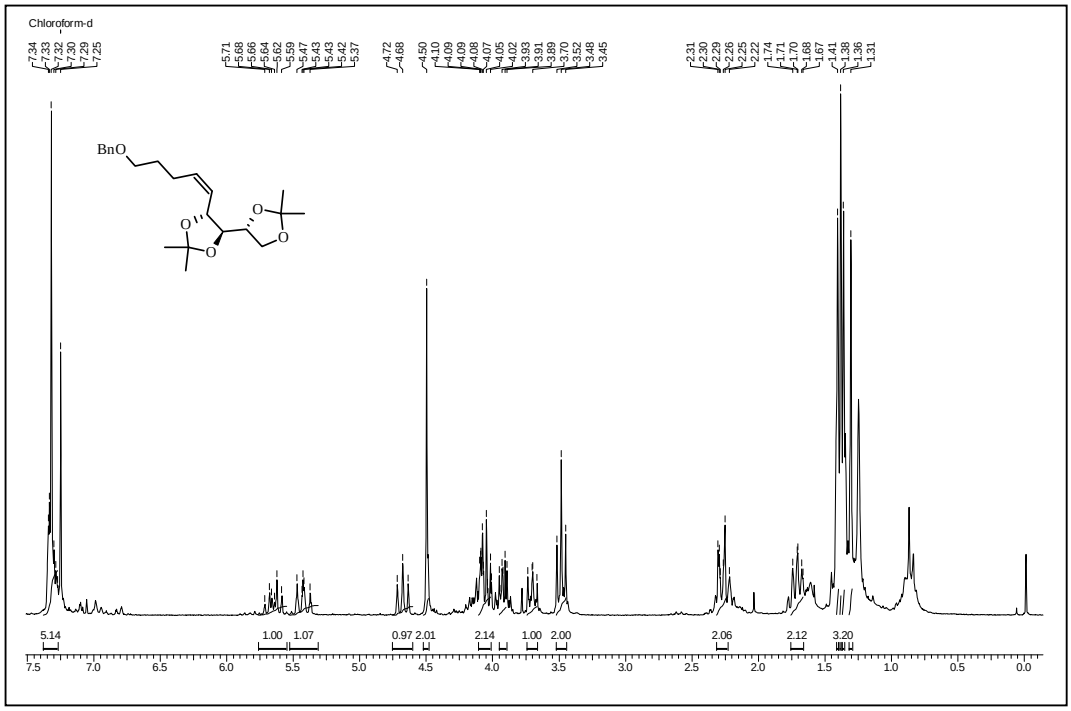
((4-Iodobutoxy)methyl)benzene (159)



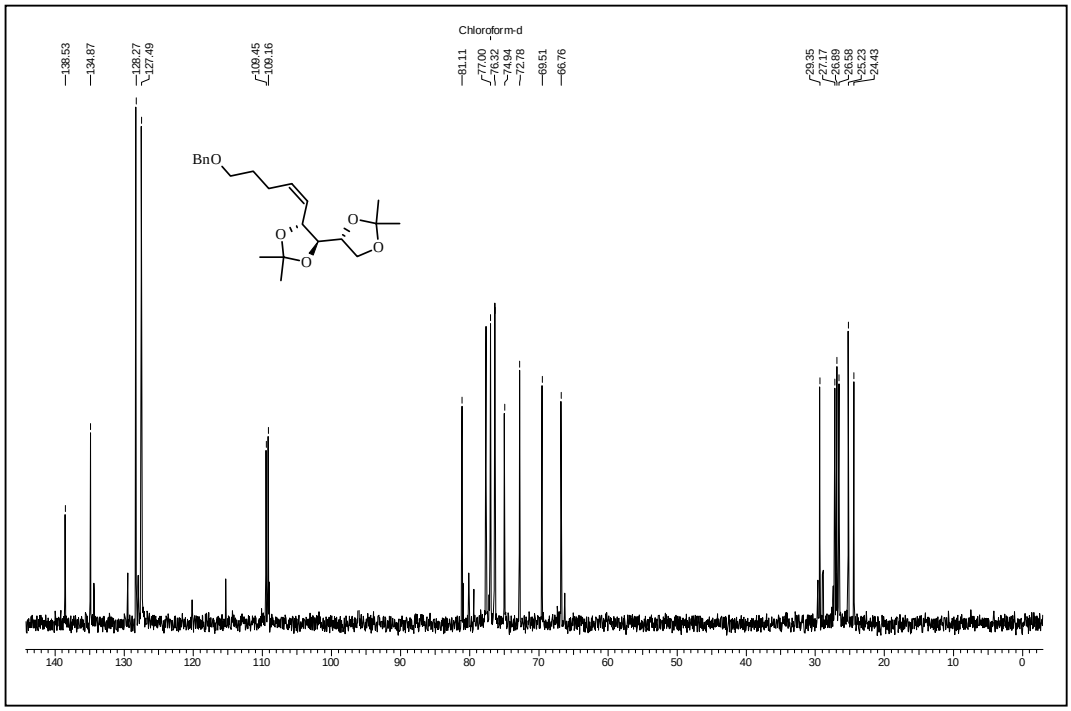
To an ice-cooled solution (0 °C) of the alcohol **158** (1 g, 5.5 mmol) in THF (20 mL), TPP (1.4 g, 5.5 mmol) and imidazole (0.75 g, 11.1 mmol) were added sequentially and stirred for 30 min. Iodine (1.41 g, 5.5 mmol) was added and the reaction was further stirred for 30 min. The reaction mixture was concentrated and the crude residue obtained was purified by silica gel chromatography (5% ethyl acetate in petroleum ether) to obtain **159** (1.36 g**,** 86%) as colorless oil.

Mol. Formula	: $C_{11}H_{15}IO$
IR ($CHCl_3$) $\tilde{\nu}$	: 2988, 1671, 1519, 1347, 875, 733, 648 cm^{-1}.
^{1}H NMR	: δ 1.64-1.78 (m, 2H), 1.88-2.02 (m, 2H), 3.20 (t, *J* = 6.9
($CDCl_3$, 200 MHz)	Hz, 2H), 3.49 (t, *J* = 6.1 Hz, 2H), 4.49 (s, 2H), 7.27-7.35 (m, 5H) ppm.
^{13}C NMR	: δ 6.8 (t), 30.2 (t), 30.4 (t), 68.8 (t), 72.7 (t), 127.4 (d, 3C),
($CDCl_3$, 50 MHz)	128.2 (d, 2C), 138.2 (s) ppm.
ESI-MS (*m/z*)	: 313.2 $[M+Na]^+$.
Elemental Analysis	Calcd.: C, 45.54; H, 5.21.
	Found: C, 45.40; H, 5.43.

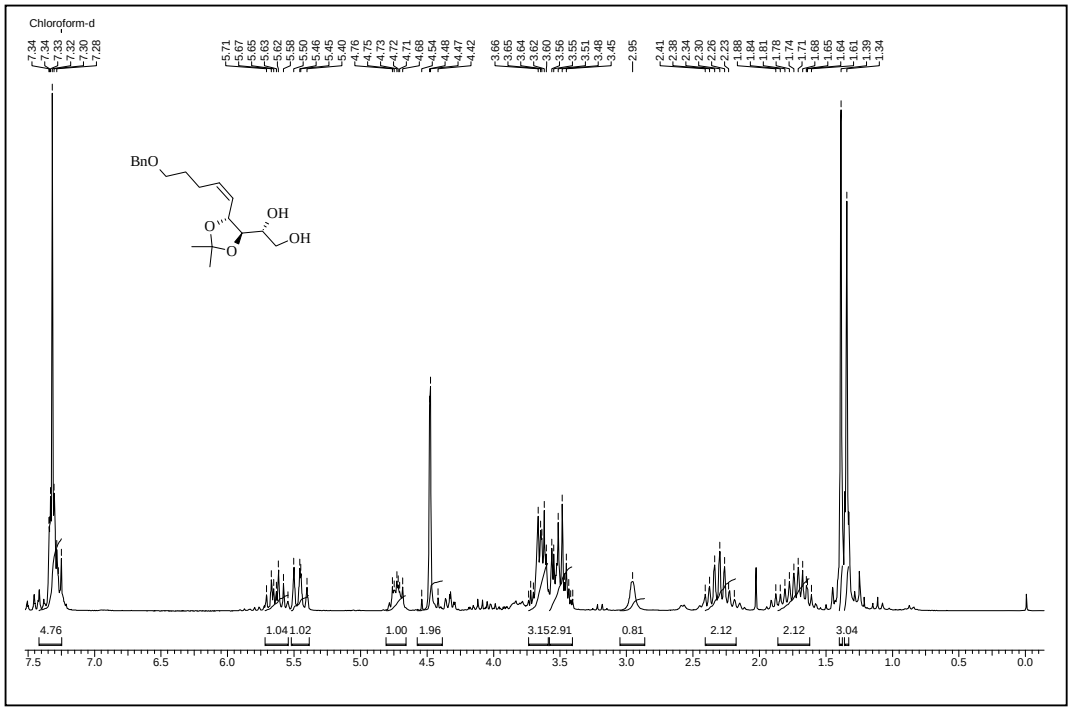
Spectroscopic Data



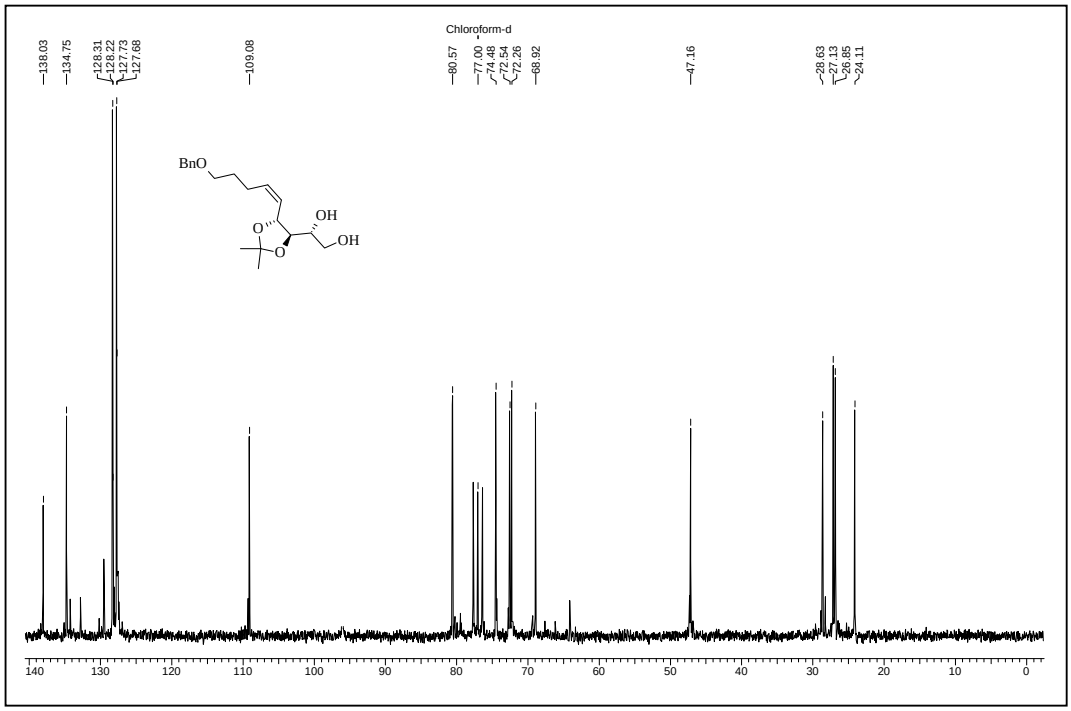
^{1}H NMR Spectrum of 156 in $CDCl_3$



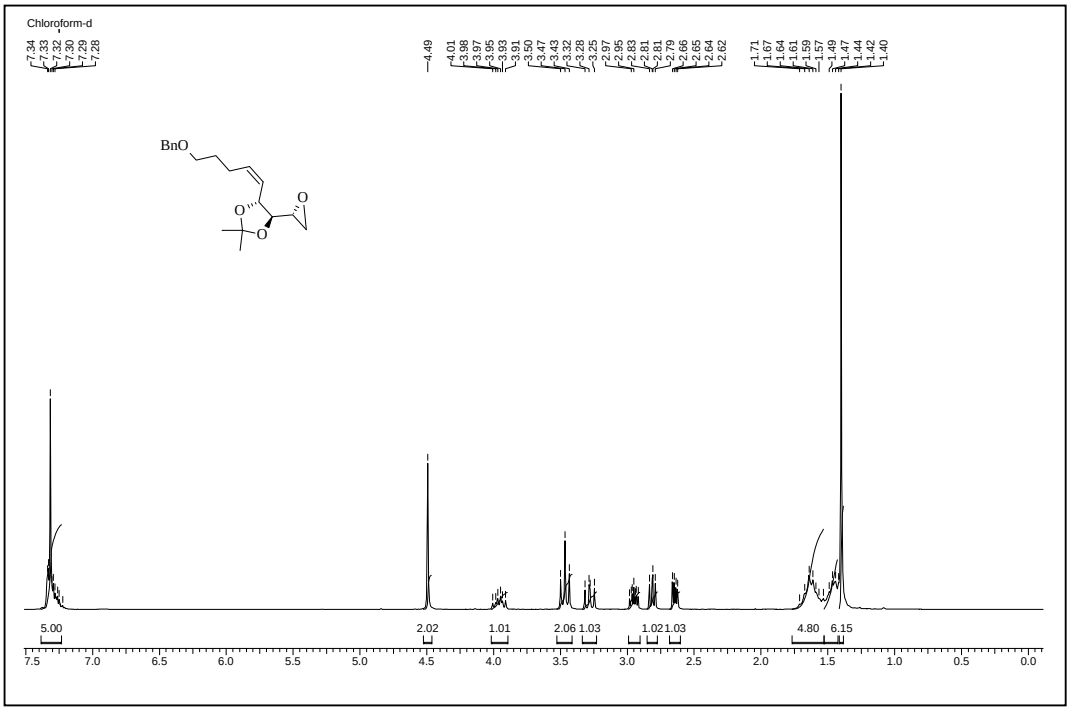
^{13}C NMR Spectrum of 156 in $CDCl_3$



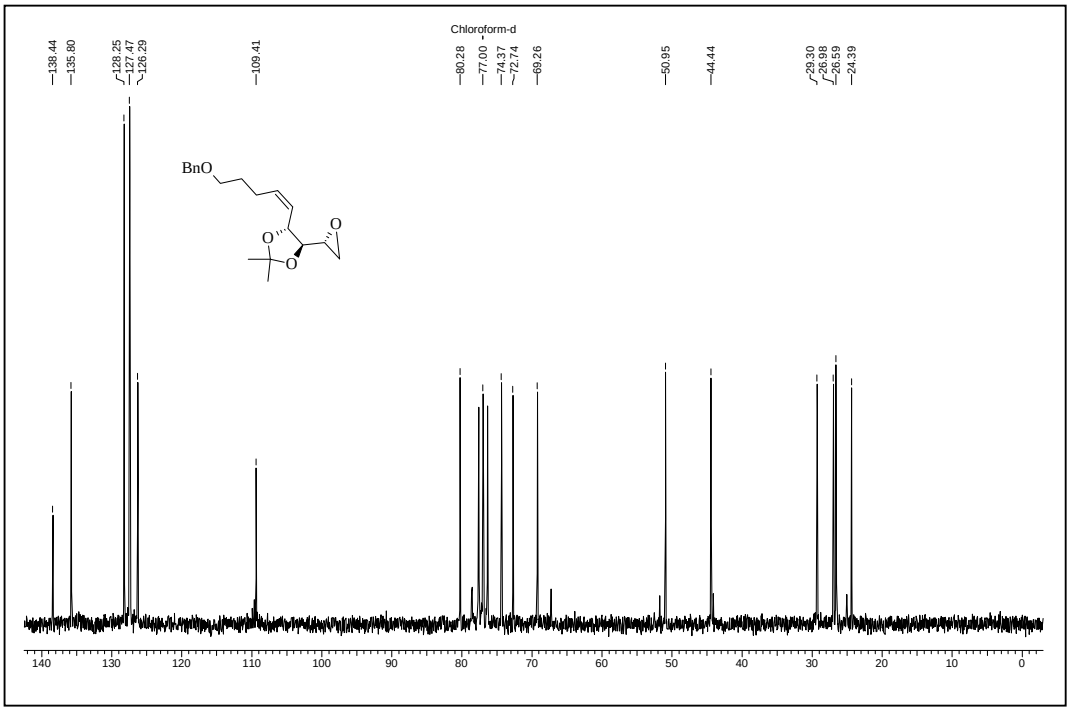
^{1}H NMR Spectrum of 161 in $CDCl_3$



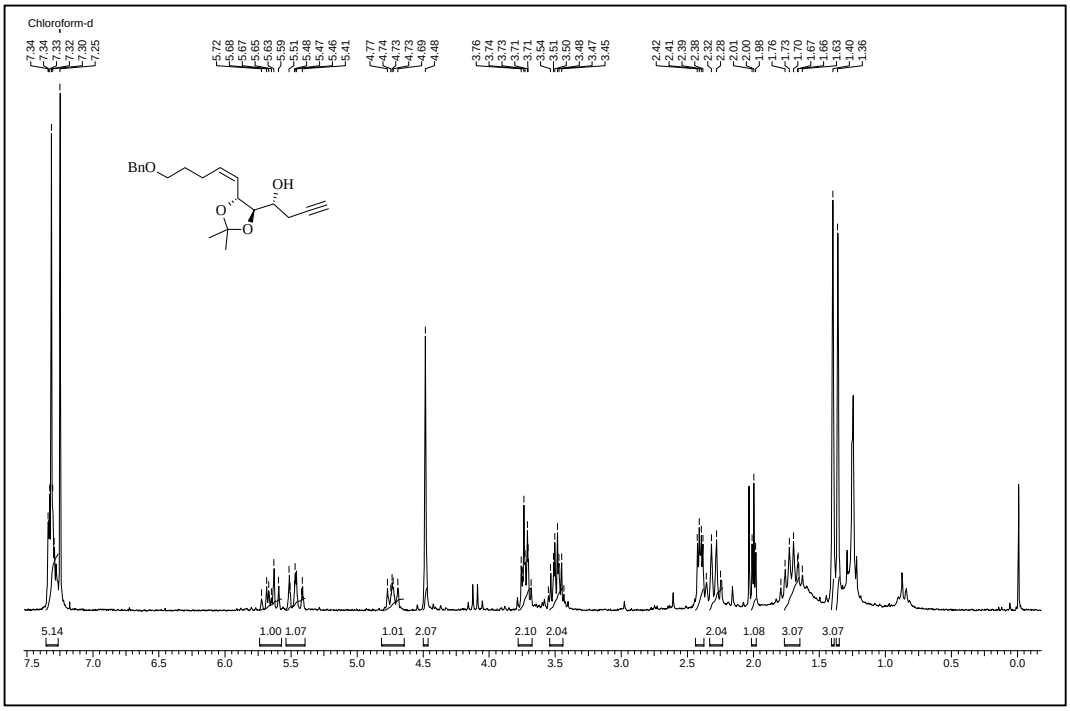
^{13}C NMR Spectrum of 161 in $CDCl_3$



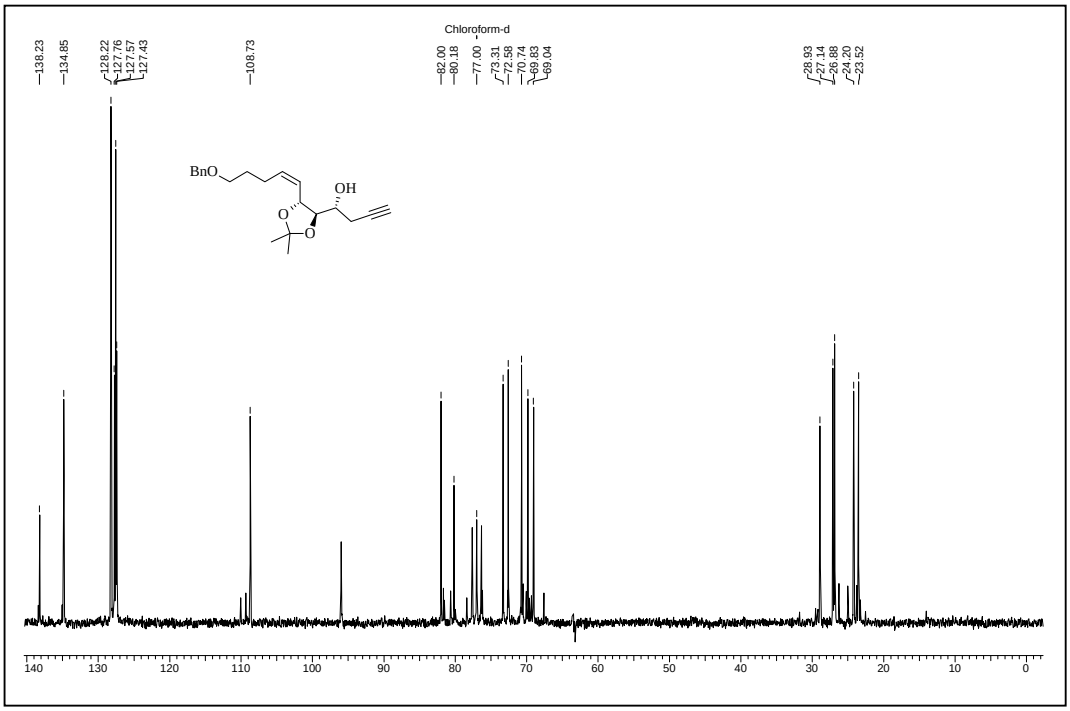
^{1}H NMR Spectrum of 163 in $CDCl_3$



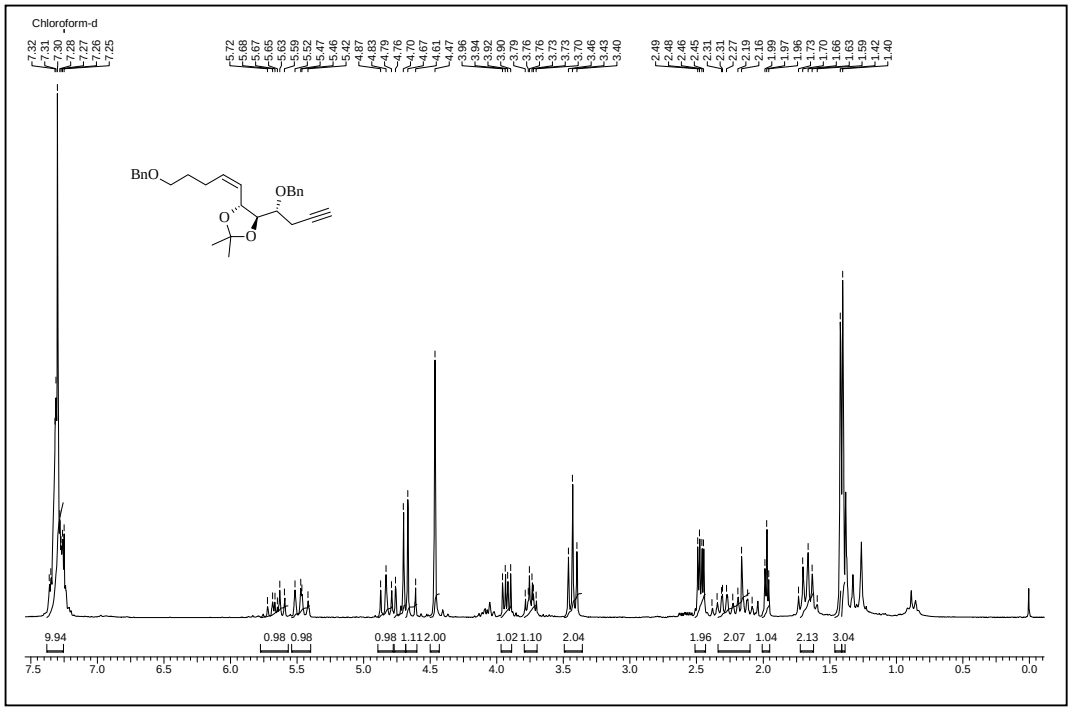
^{13}C NMR Spectrum of 163 in $CDCl_3$



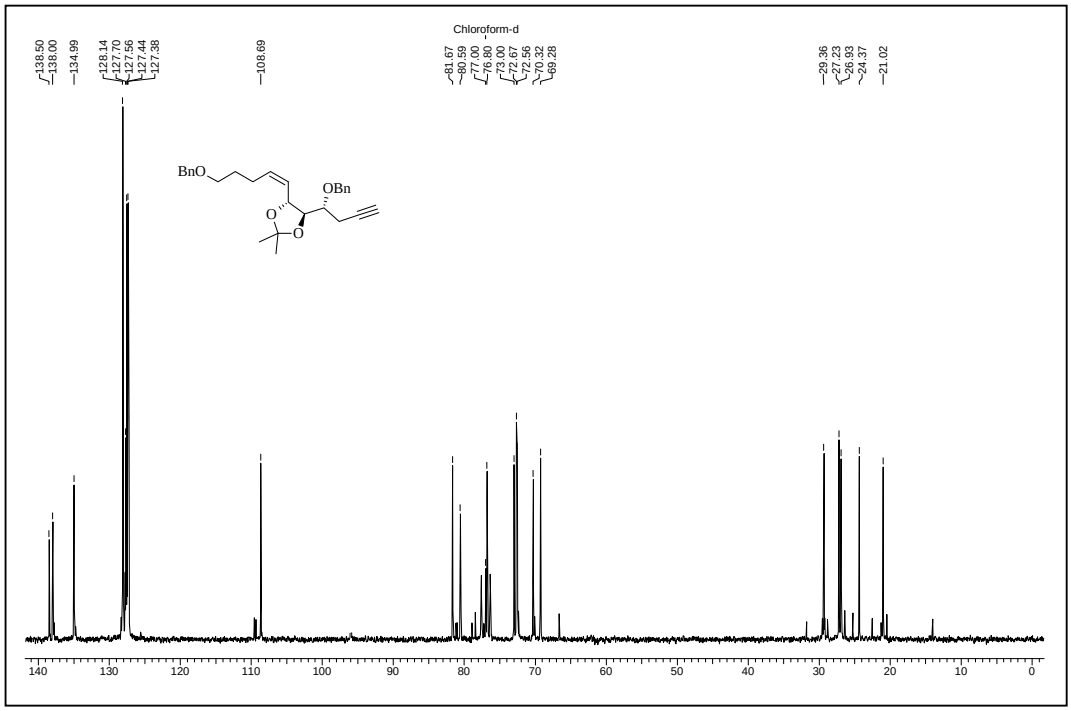
^{1}H NMR Spectrum of 164 in $CDCl_3$



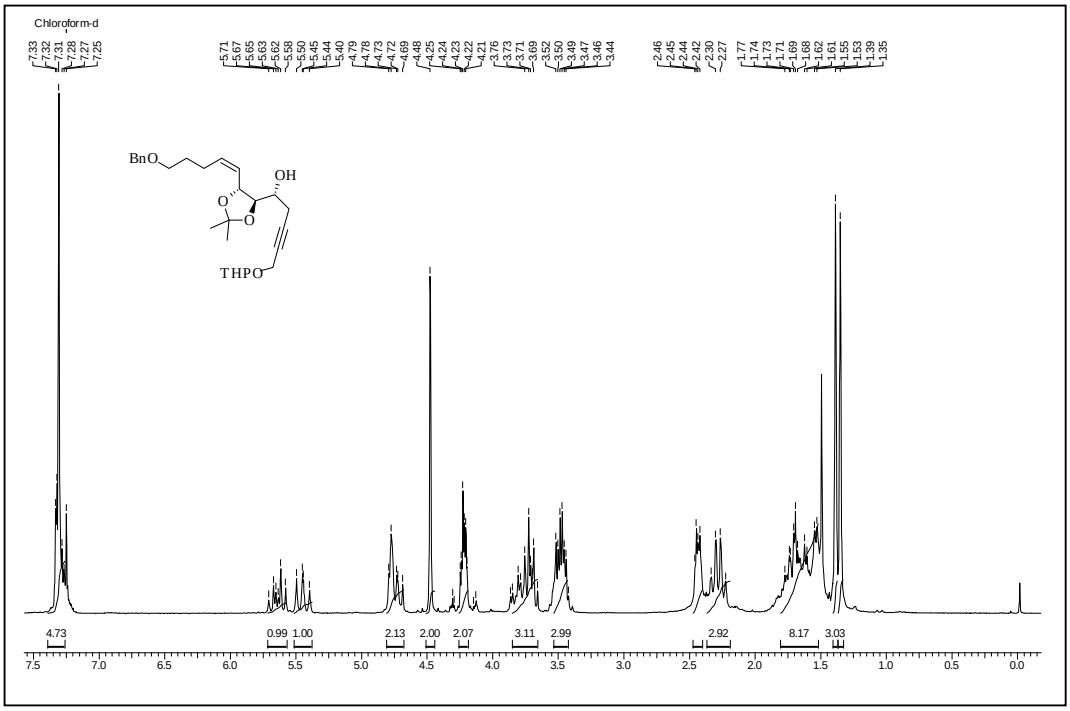
^{13}C NMR Spectrum of 164 in $CDCl_3$



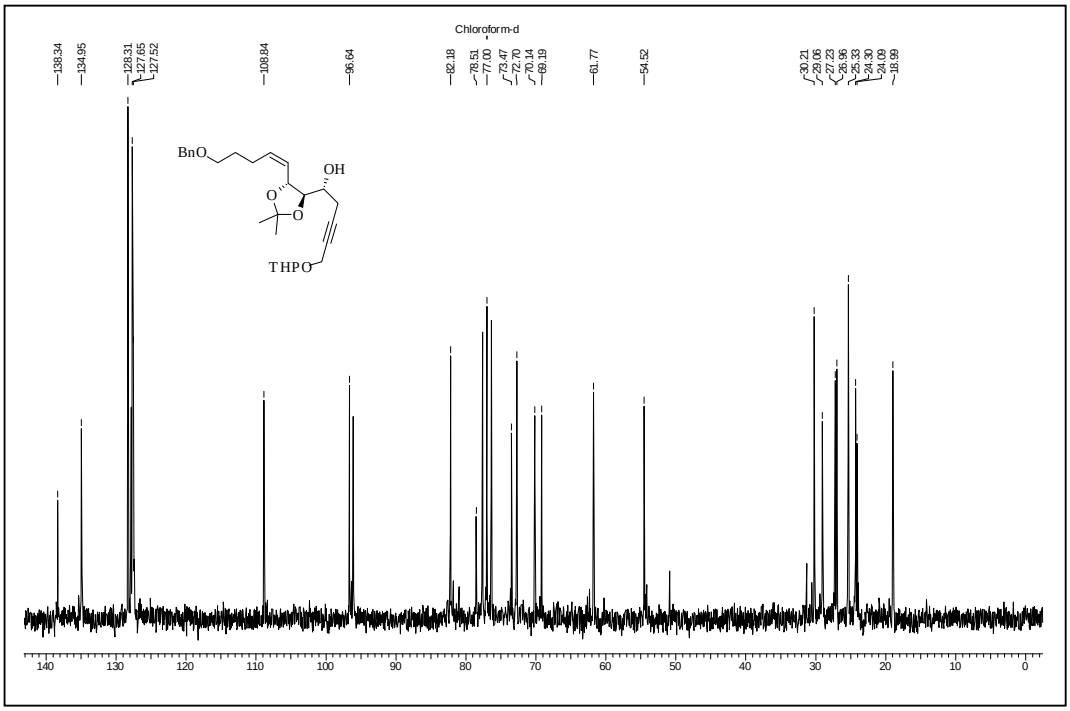
^{1}H NMR Spectrum of 165 in $CDCl_3$



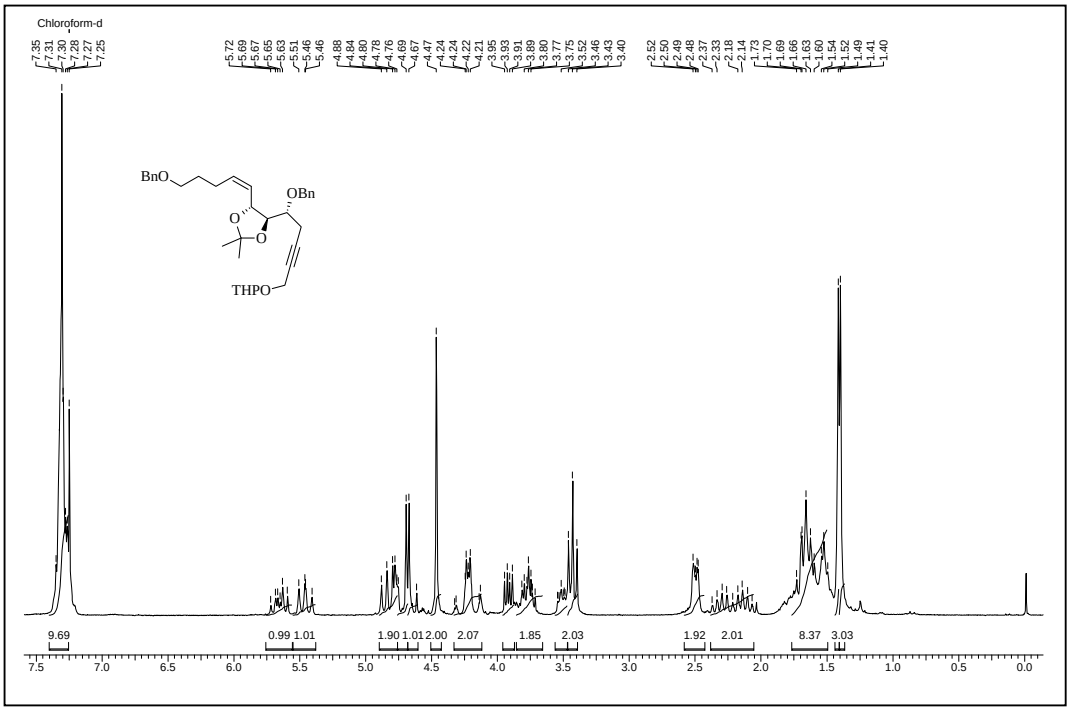
^{13}C NMR Spectrum of 165 in $CDCl_3$



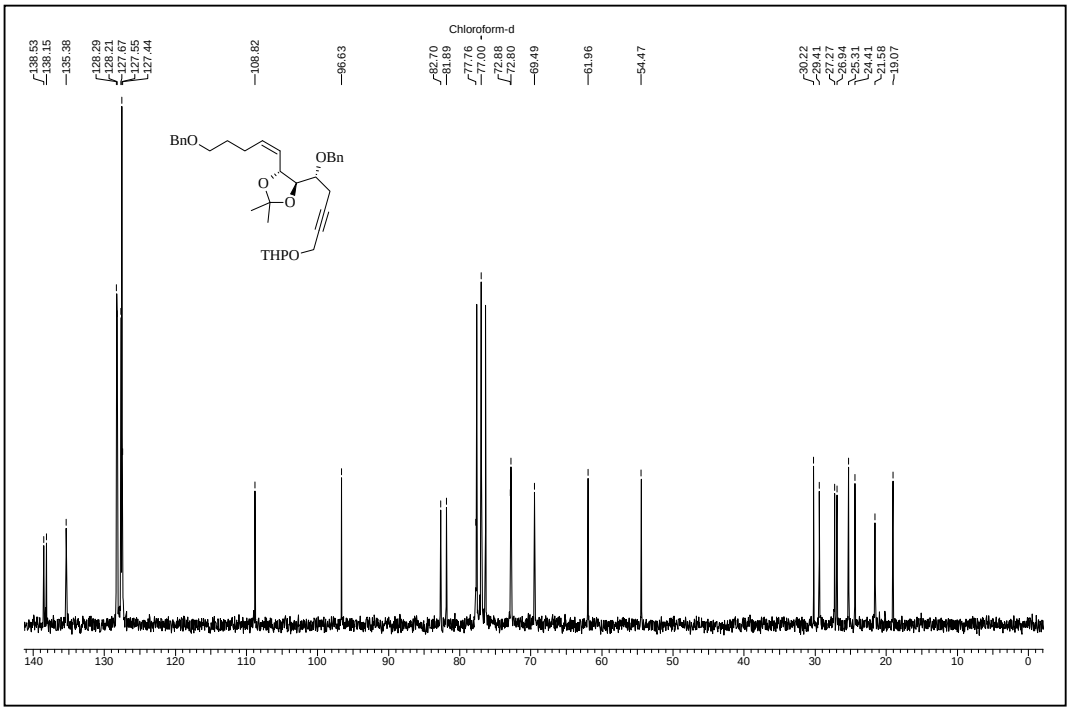
^{1}H NMR Spectrum of 168 in $CDCl_3$



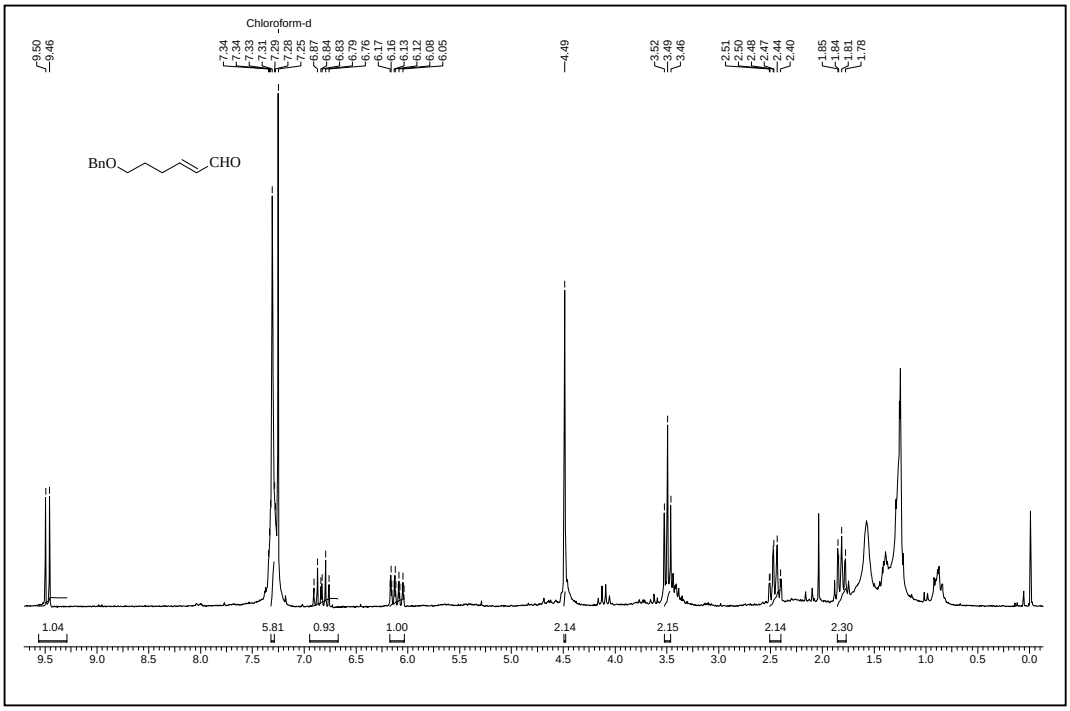
^{13}C NMR Spectrum of 168 in $CDCl_3$



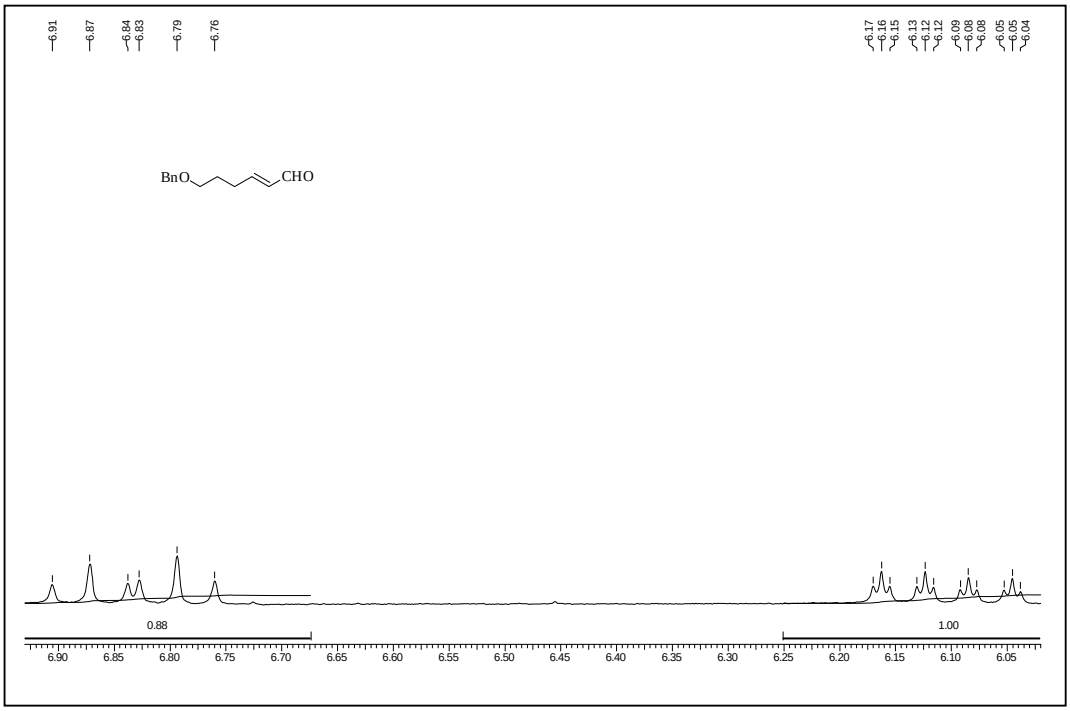
^{1}H NMR Spectrum of 169 in $CDCl_3$



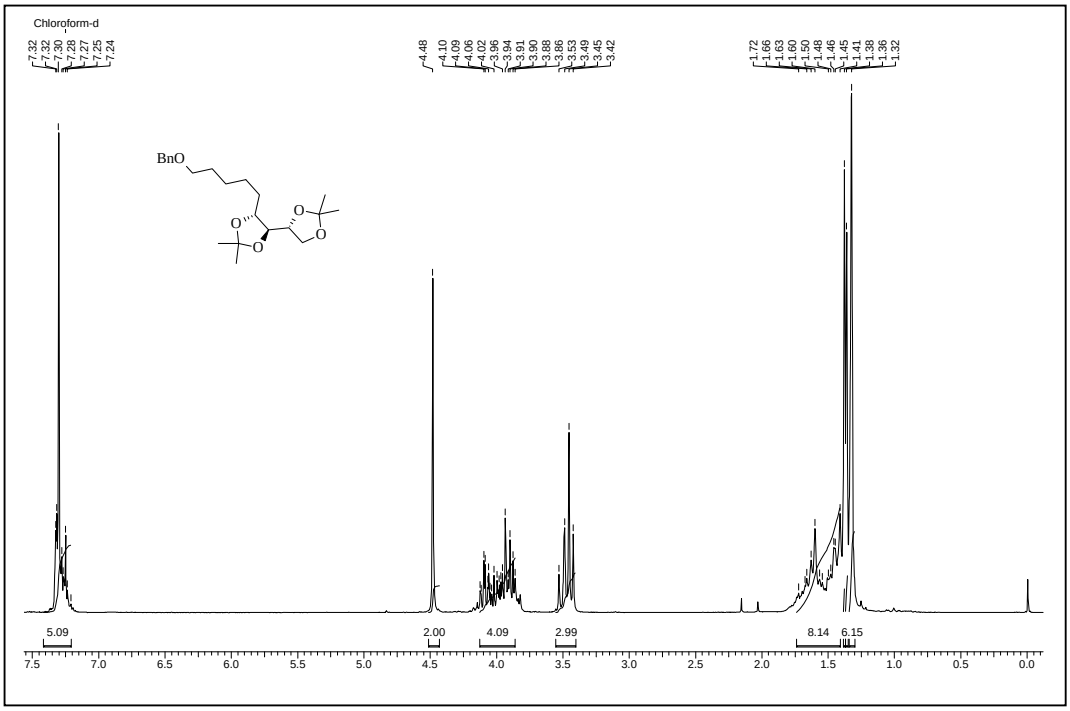
^{13}C NMR Spectrum of 169 in $CDCl_3$



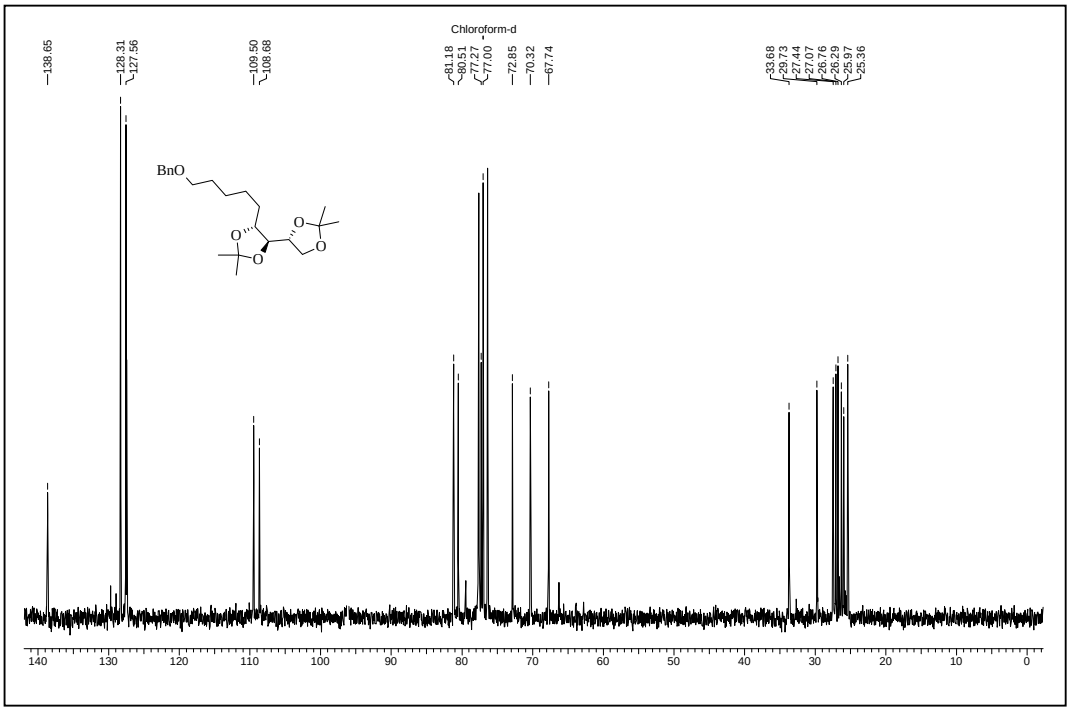
^{1}H NMR Spectrum of 166 in $CDCl_3$



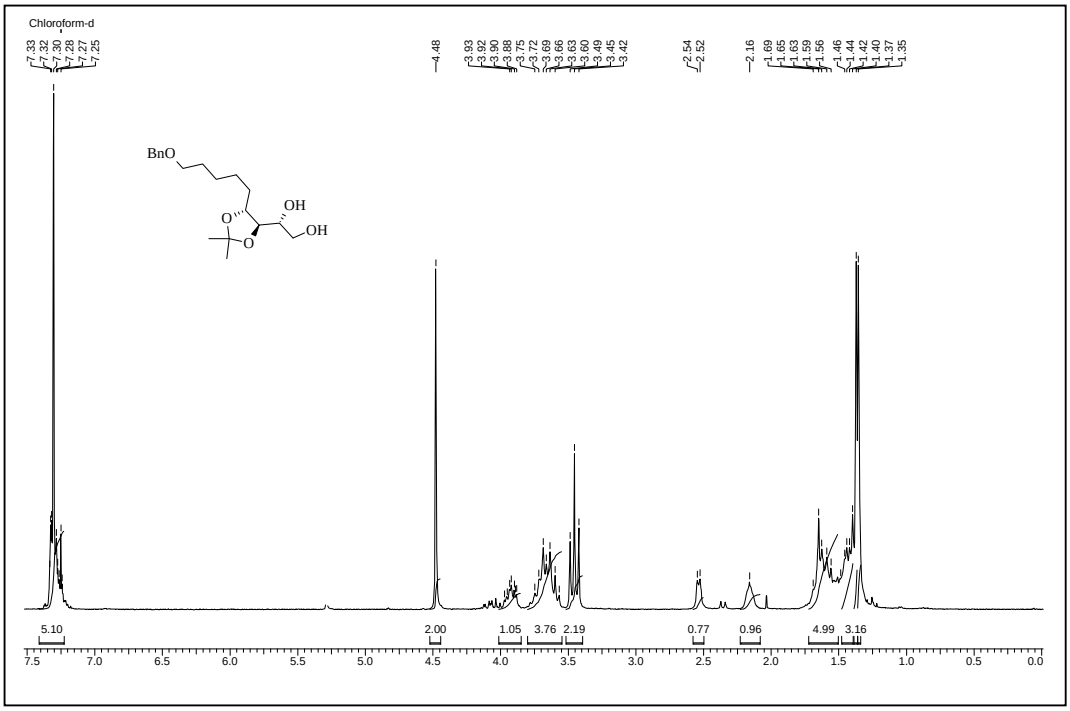
^{13}C NMR Spectrum of 166 in $CDCl_3$



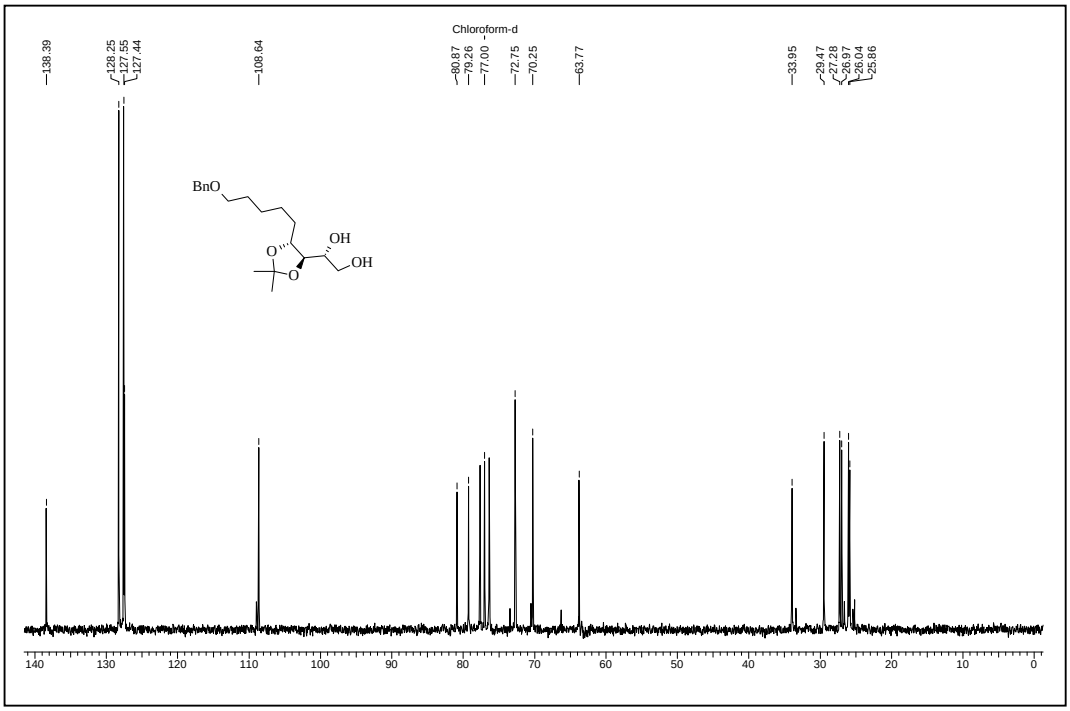
^{1}H NMR Spectrum of 171 in $CDCl_3$



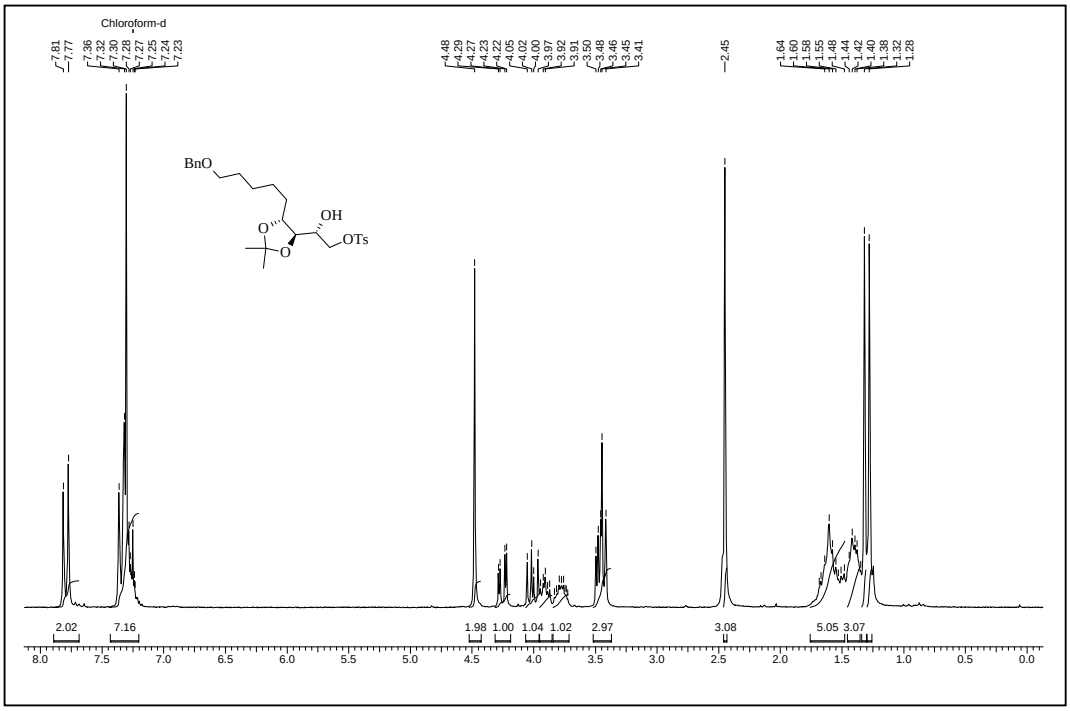
^{13}C NMR Spectrum of 171 in $CDCl_3$



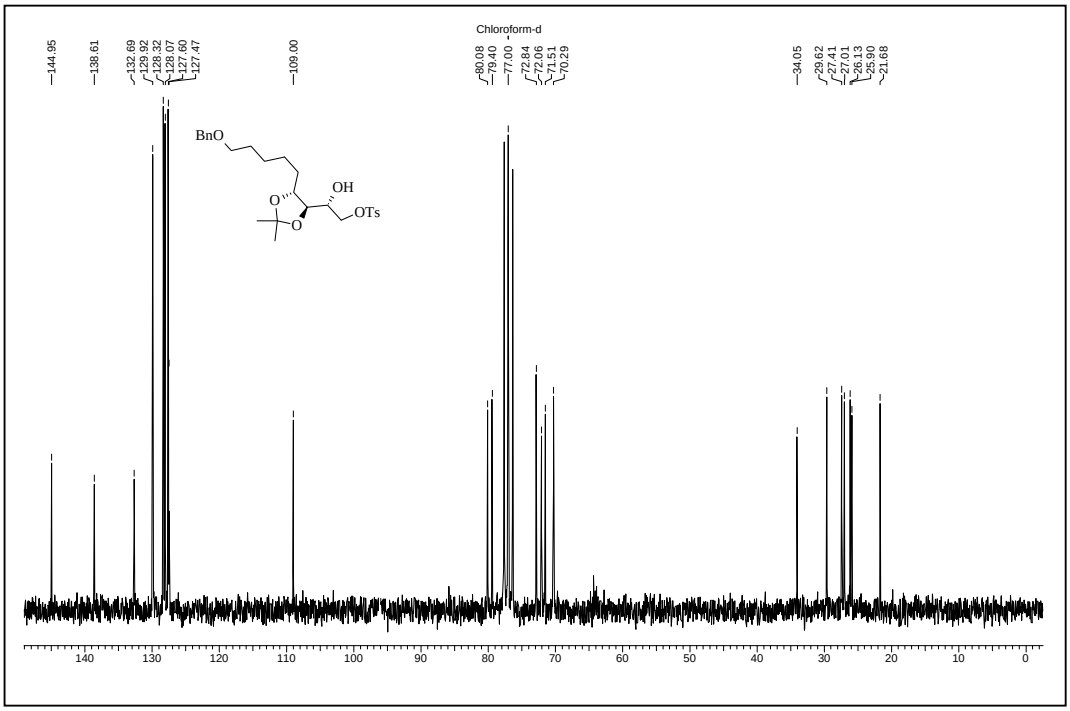
^{1}H NMR Spectrum of 172 in $CDCl_3$



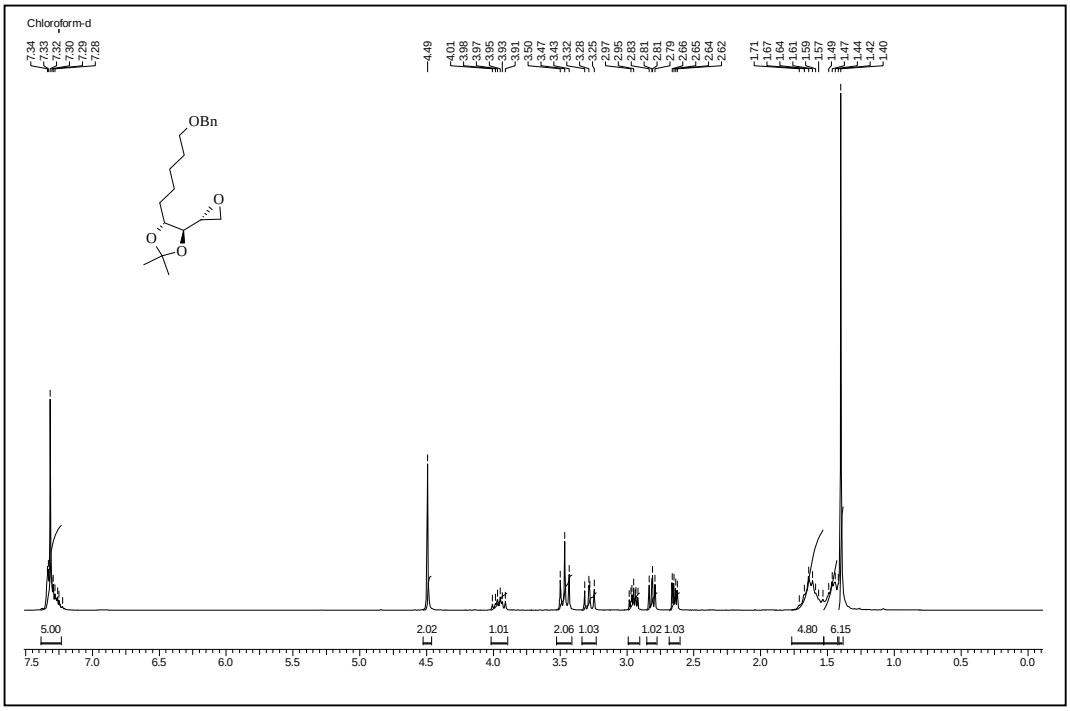
^{13}C NMR Spectrum of 172 in $CDCl_3$



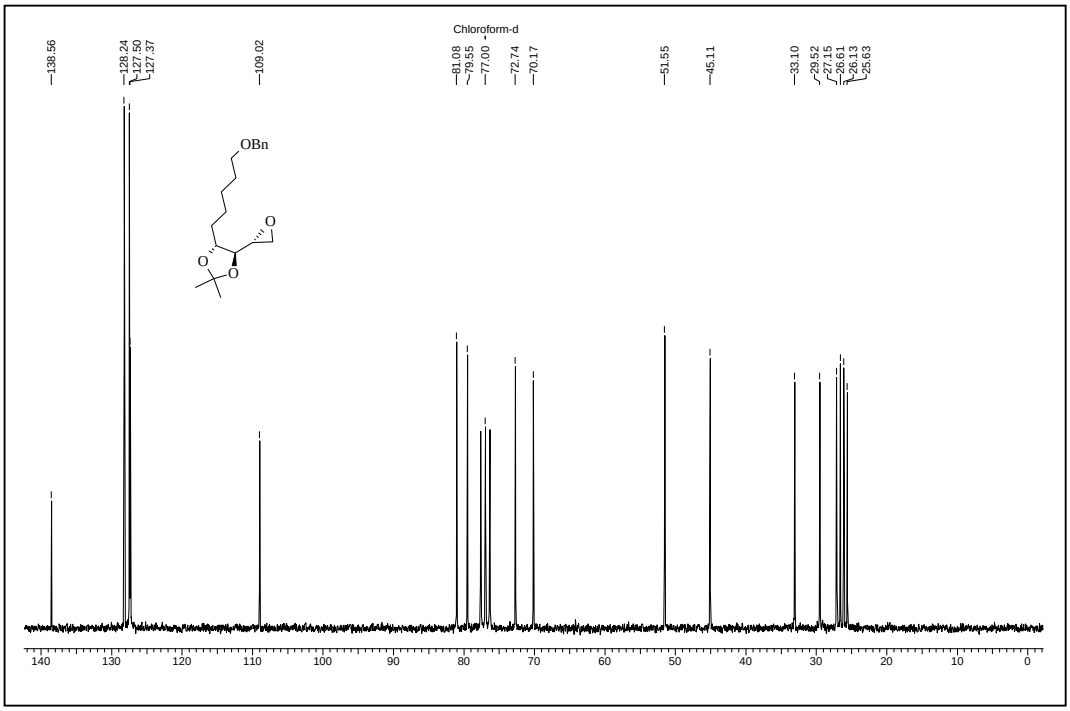
^{1}H NMR Spectrum of 173 in $CDCl_3$



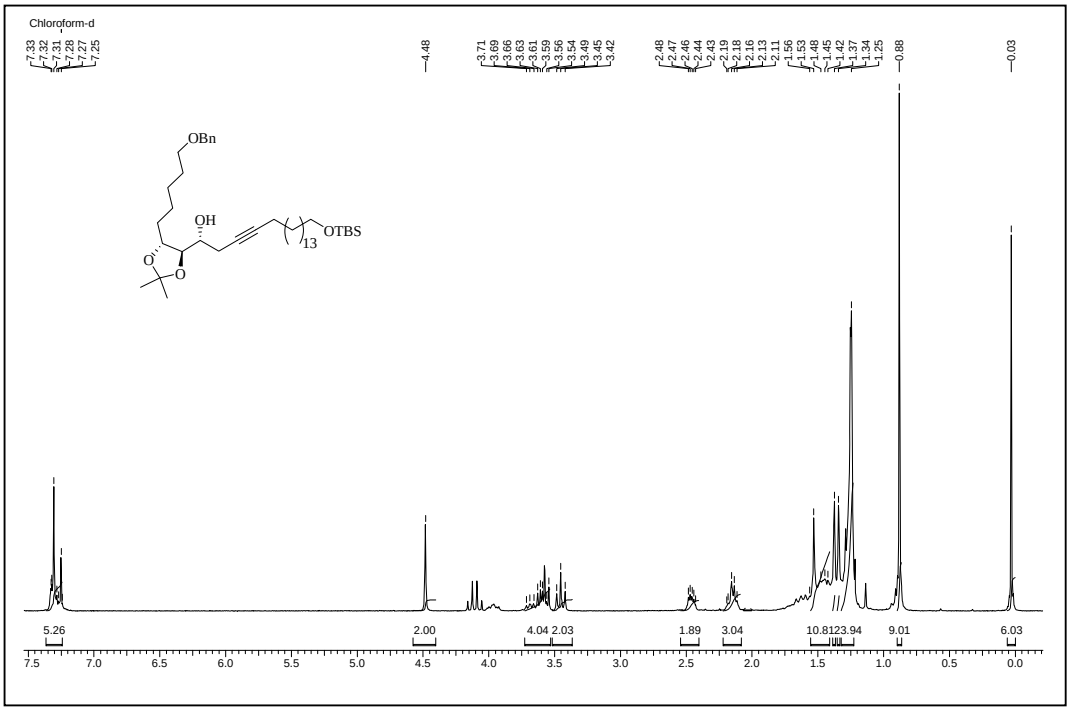
^{13}C NMR Spectrum of 173 in $CDCl_3$



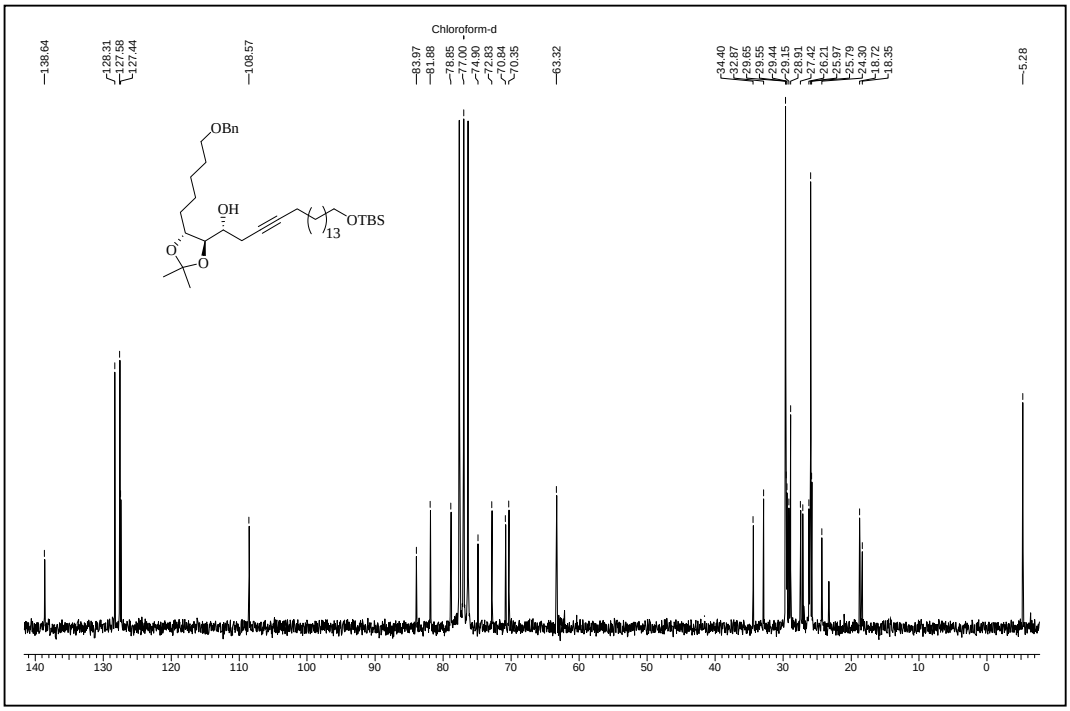
^{1}H NMR Spectrum of 151 in $CDCl_3$



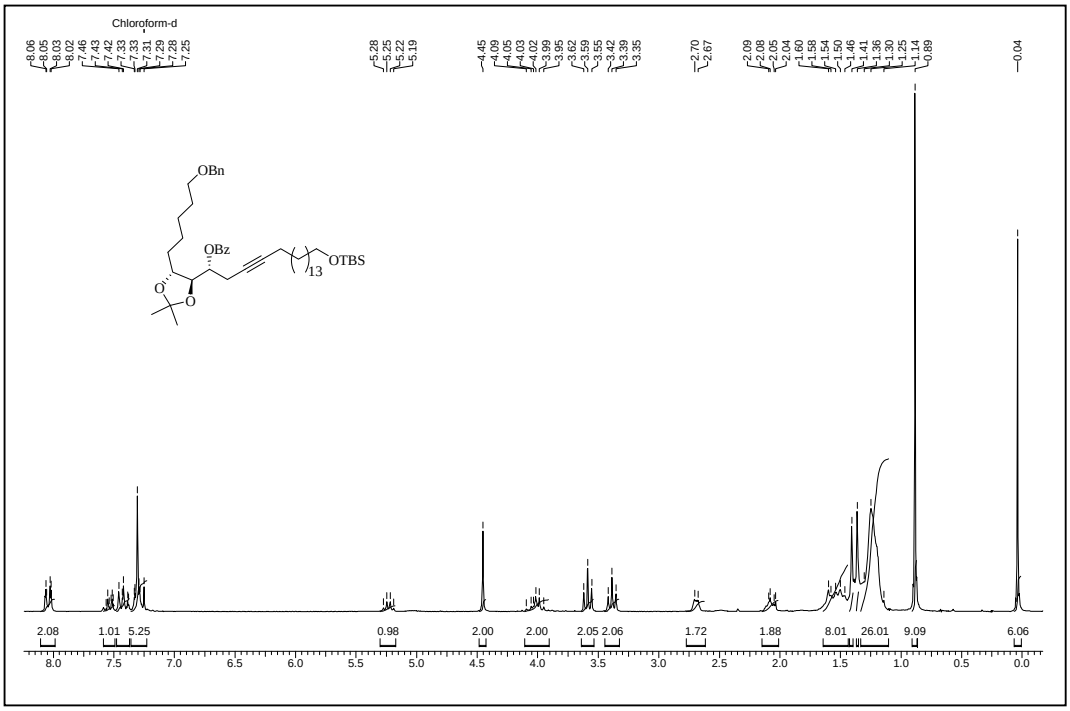
^{13}C NMR Spectrum of 151 in $CDCl_3$



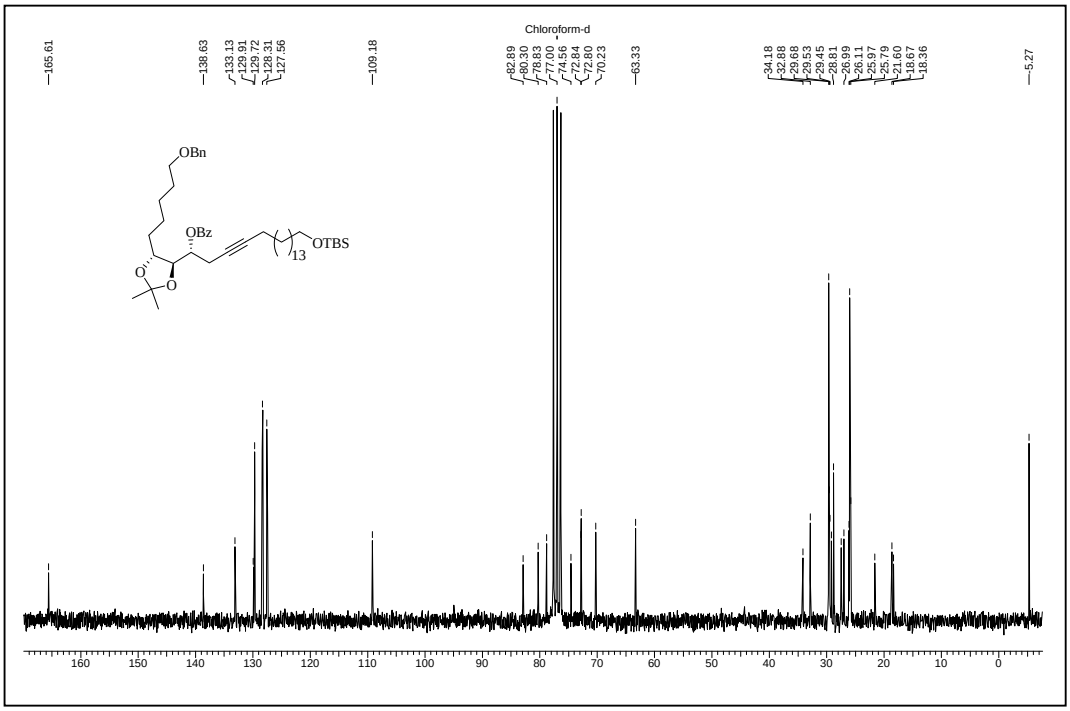
^{1}H NMR Spectrum of 177 in $CDCl_3$



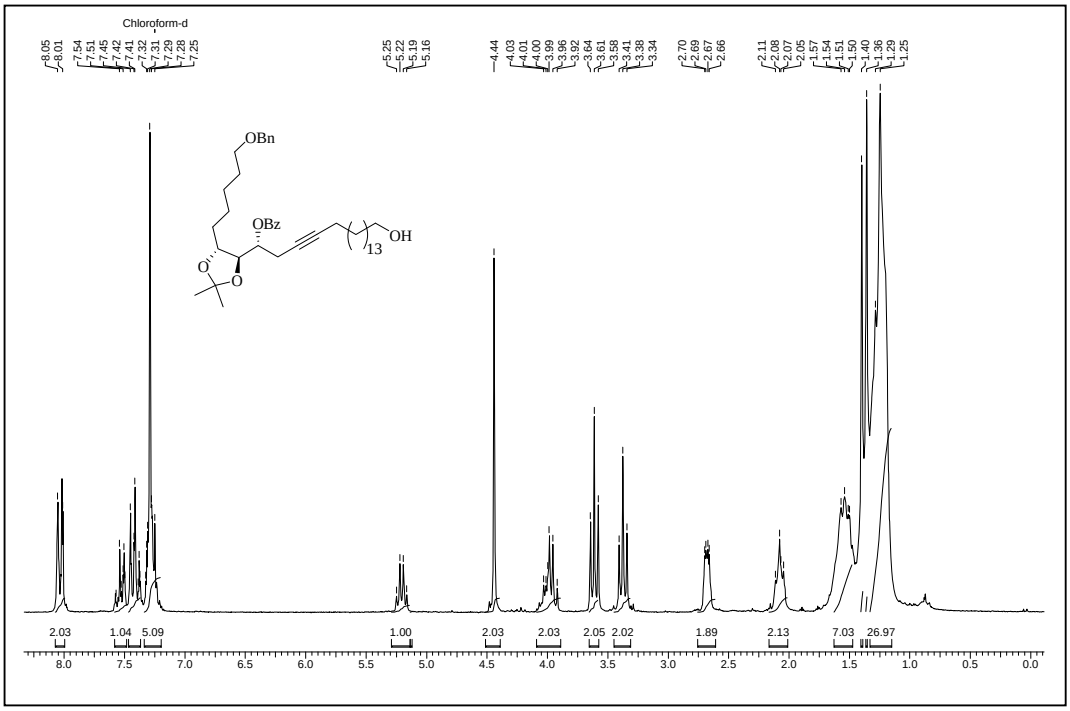
^{13}C NMR Spectrum of 177 in $CDCl_3$



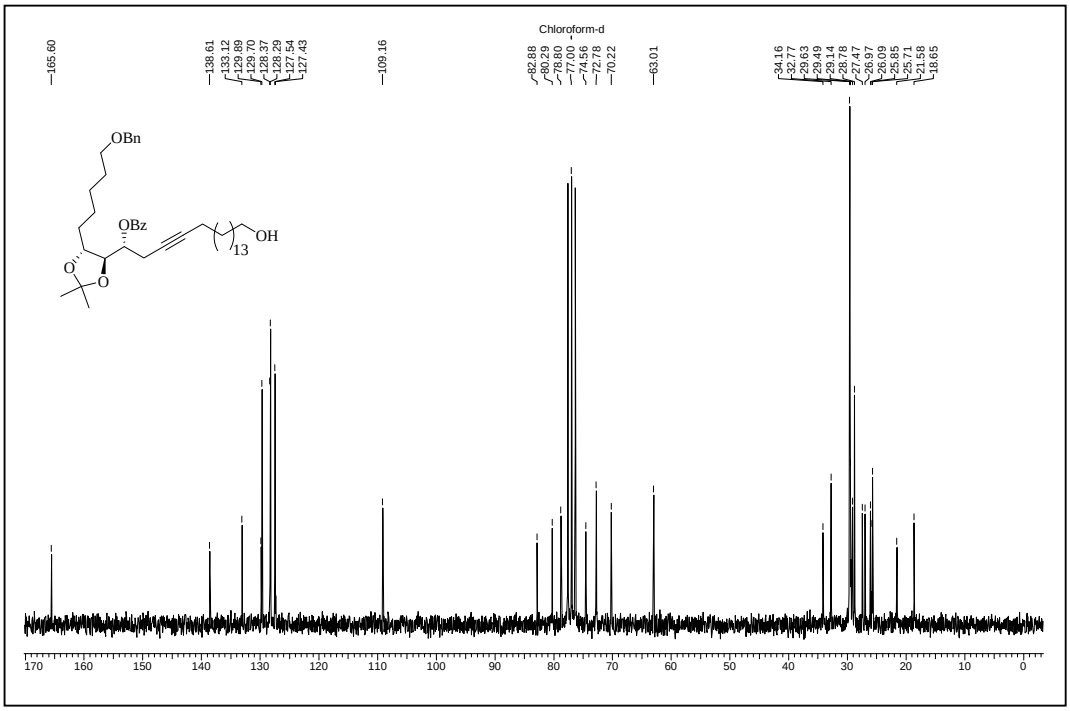
^{1}H NMR Spectrum of 178 in $CDCl_3$



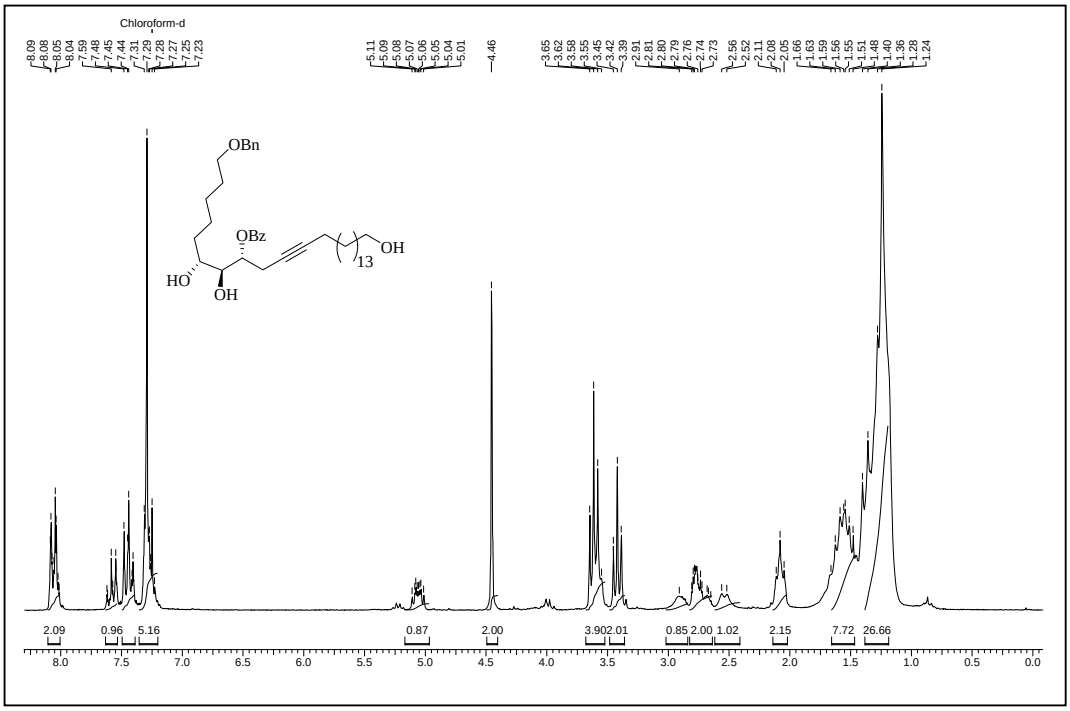
^{13}C NMR Spectrum of 178 in $CDCl_3$



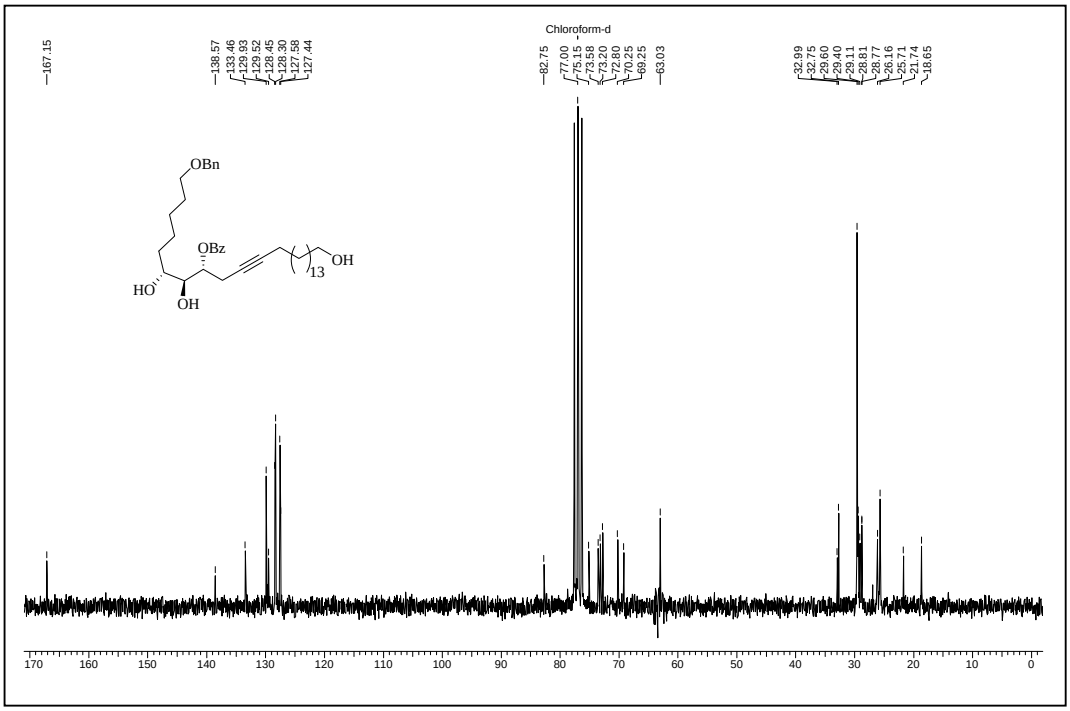
^{1}H NMR Spectrum of 179 in $CDCl_3$



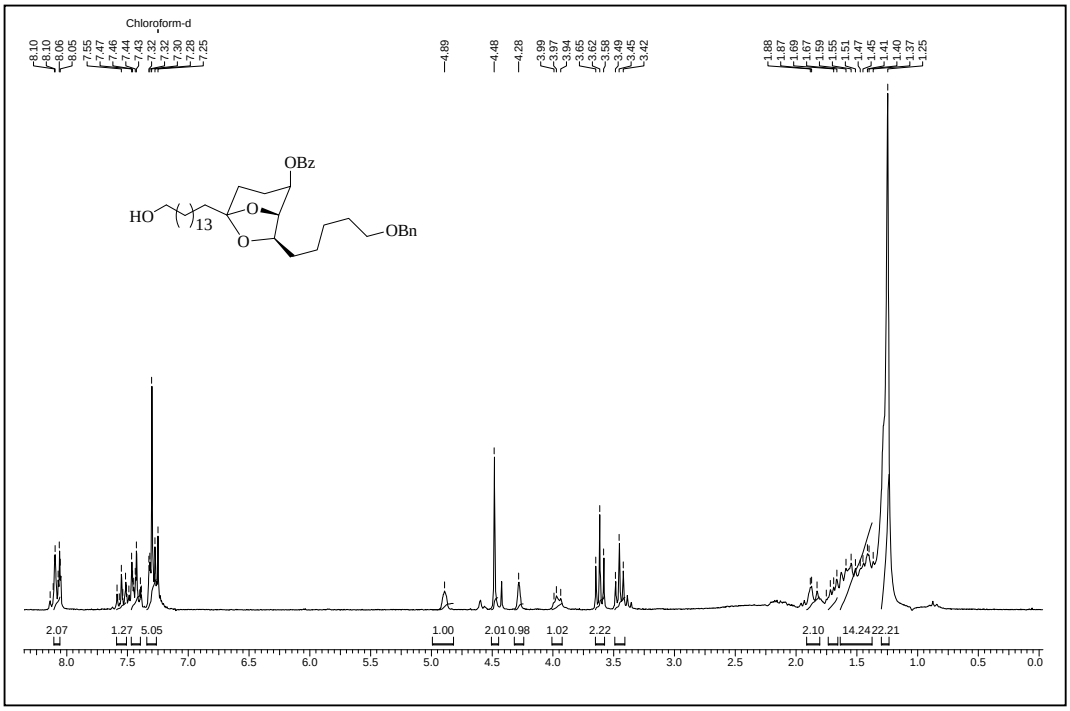
^{13}C NMR Spectrum of 179 in $CDCl_3$



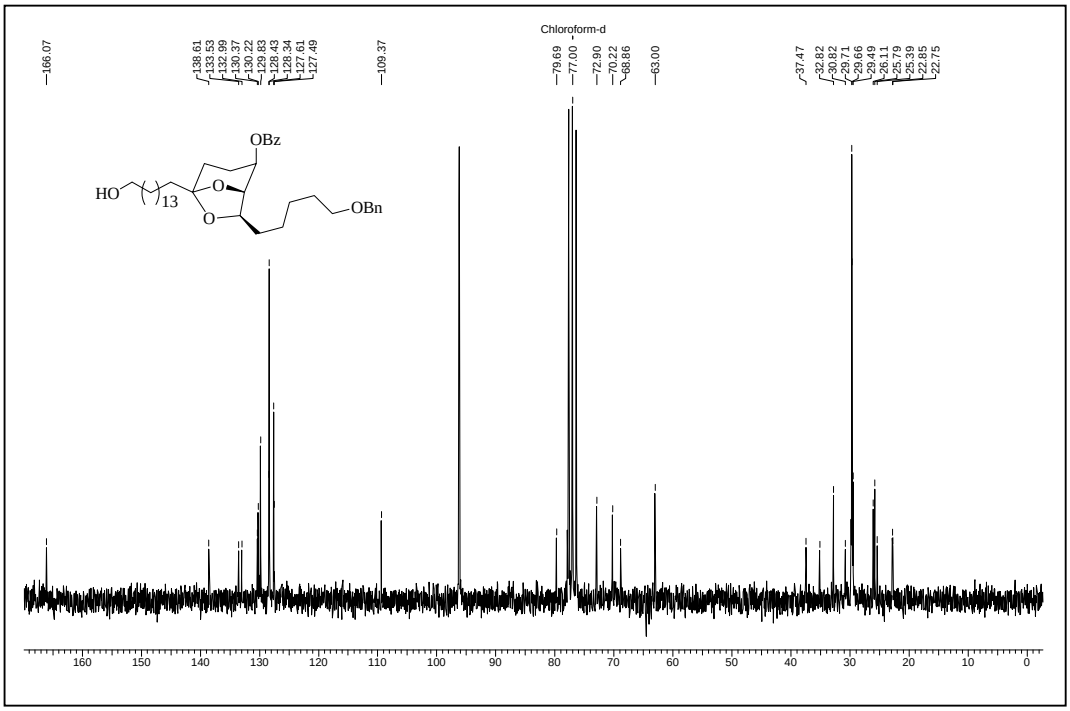
^{1}H NMR Spectrum of 180 in $CDCl_3$



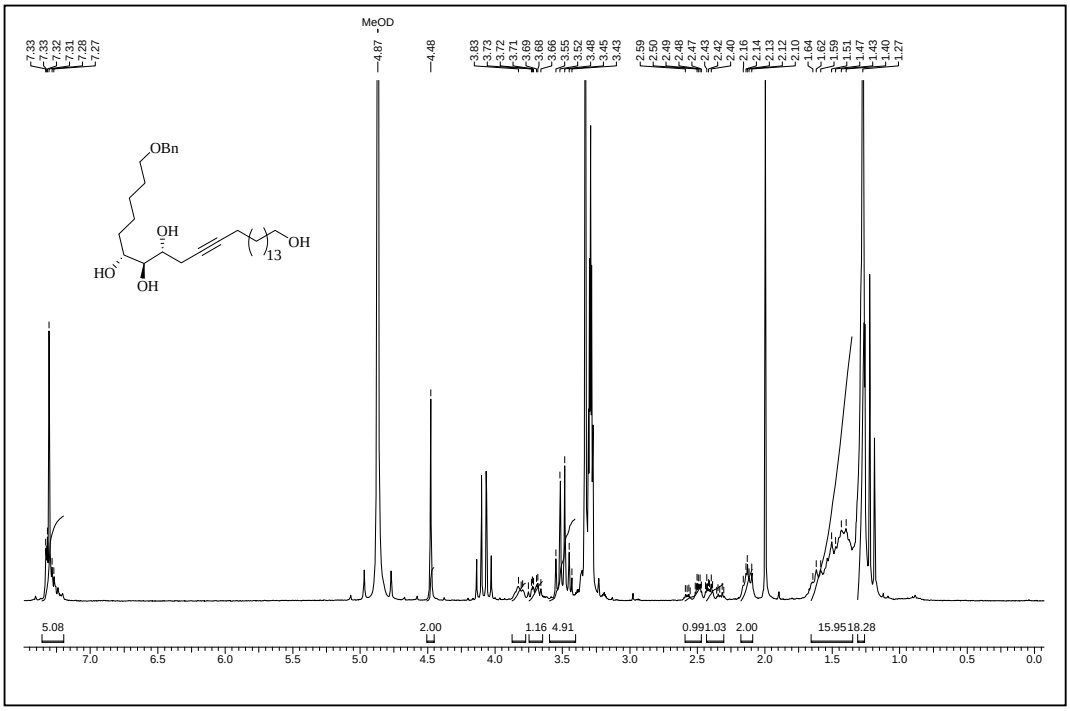
^{13}C NMR Spectrum of 180 in $CDCl_3$



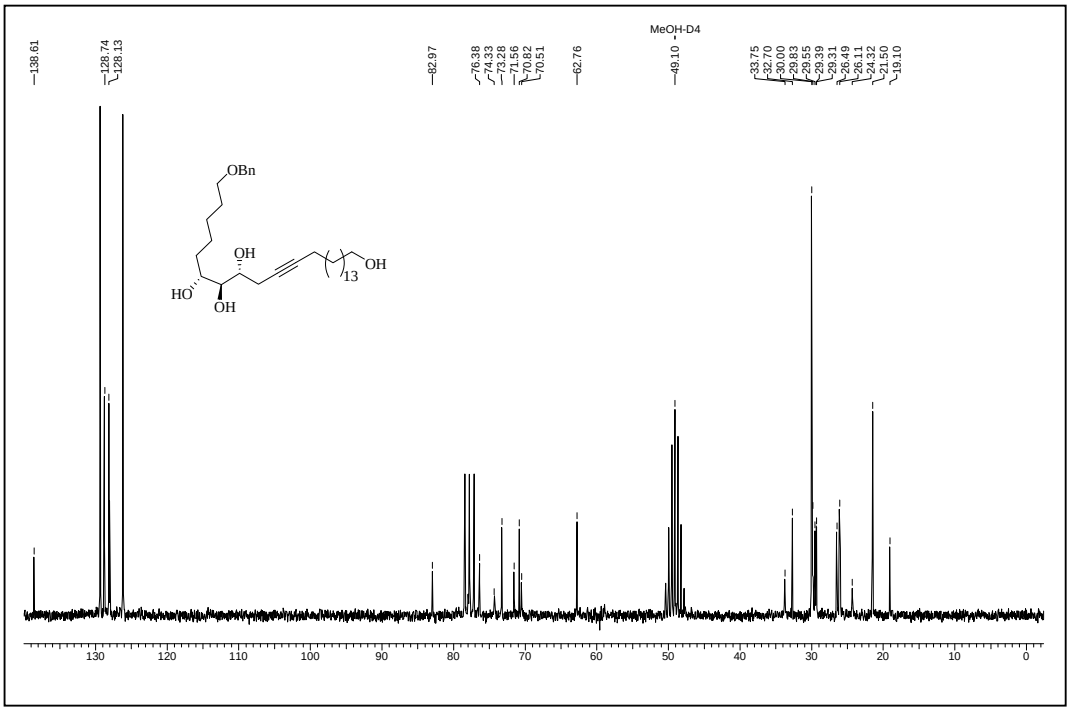
^{1}H NMR Spectrum of 181 in $CDCl_3$



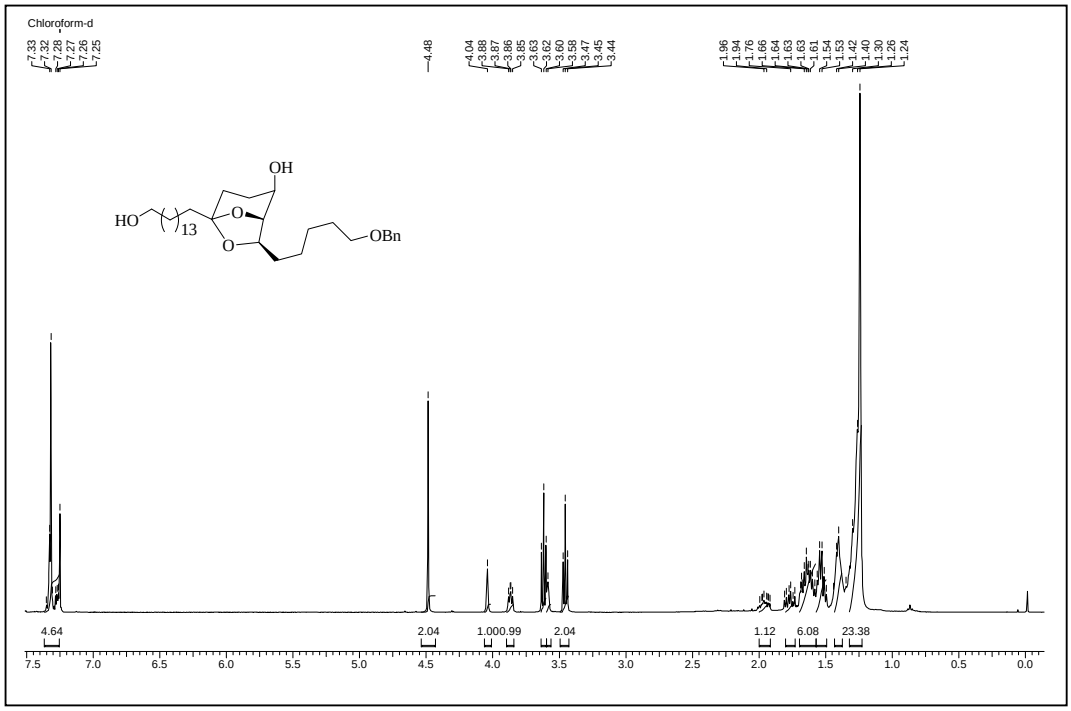
^{13}C NMR Spectrum of 181 in $CDCl_3$



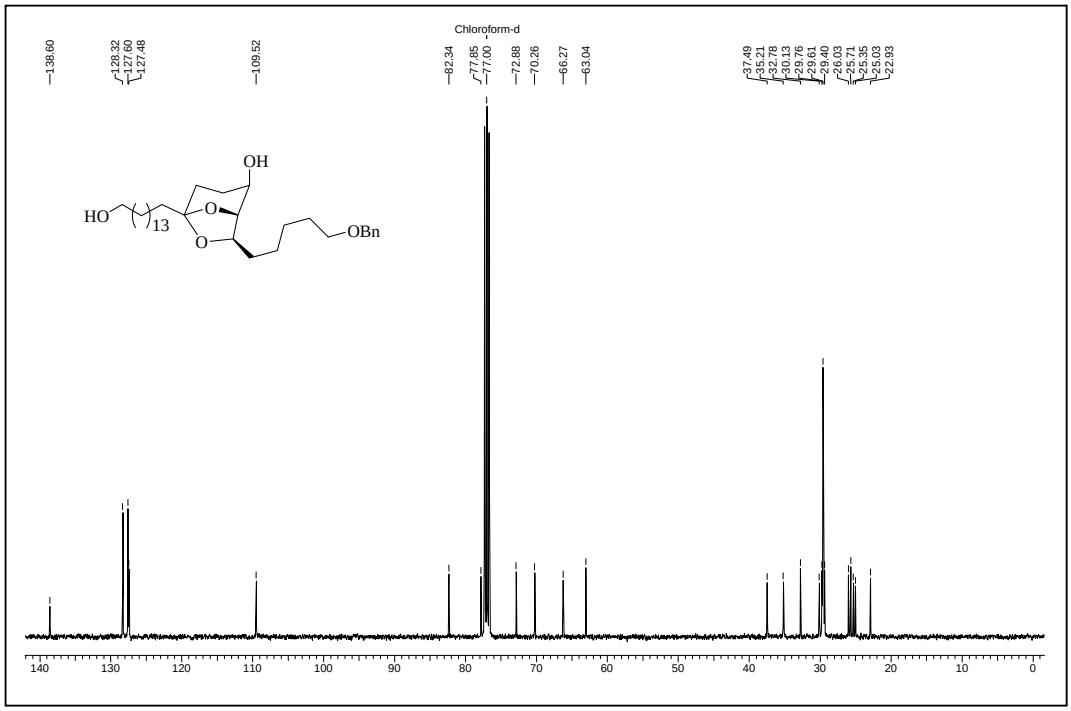
^{1}H NMR Spectrum of 182 in MeOH-d$_4$



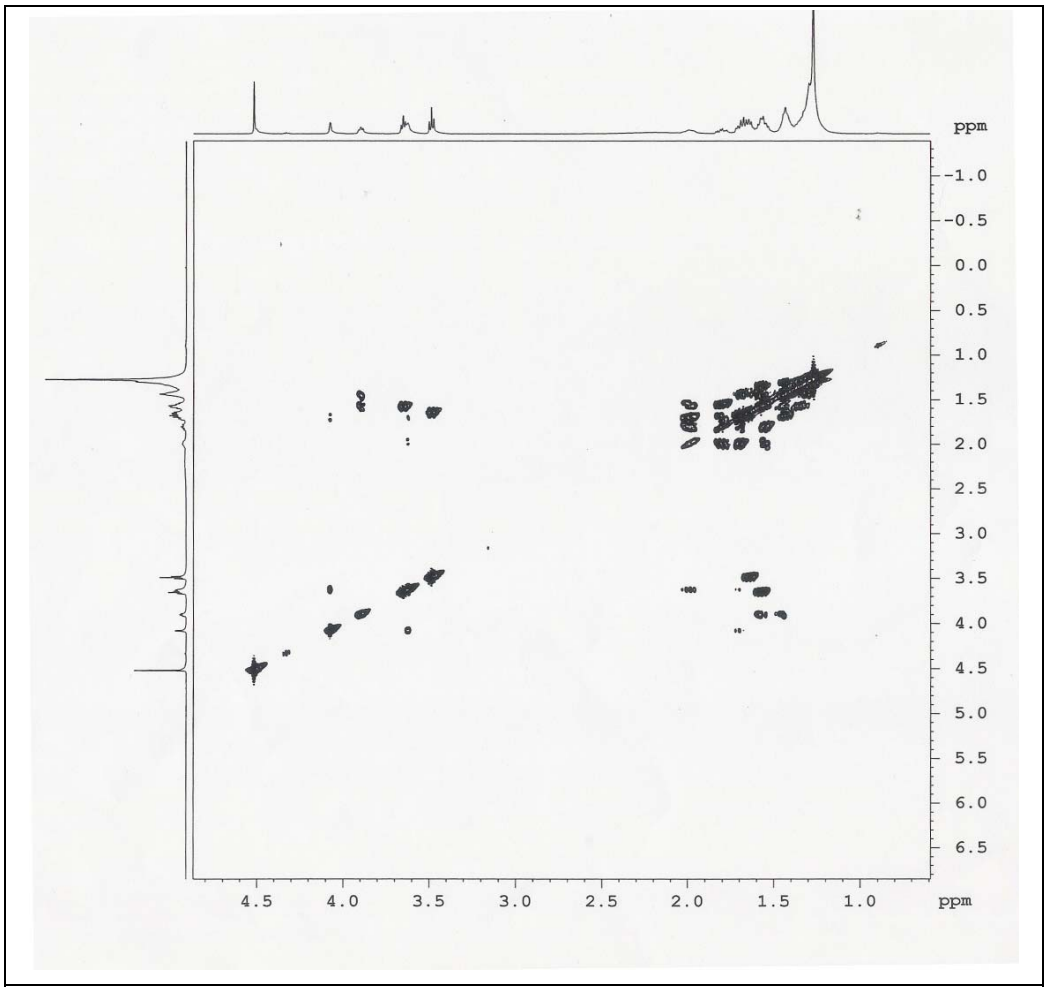
^{13}C NMR Spectrum of 182 in MeOH-d$_4$

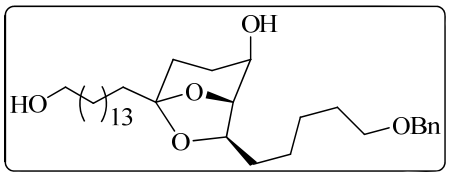


^{1}H NMR Spectrum of 149 in $CDCl_3$

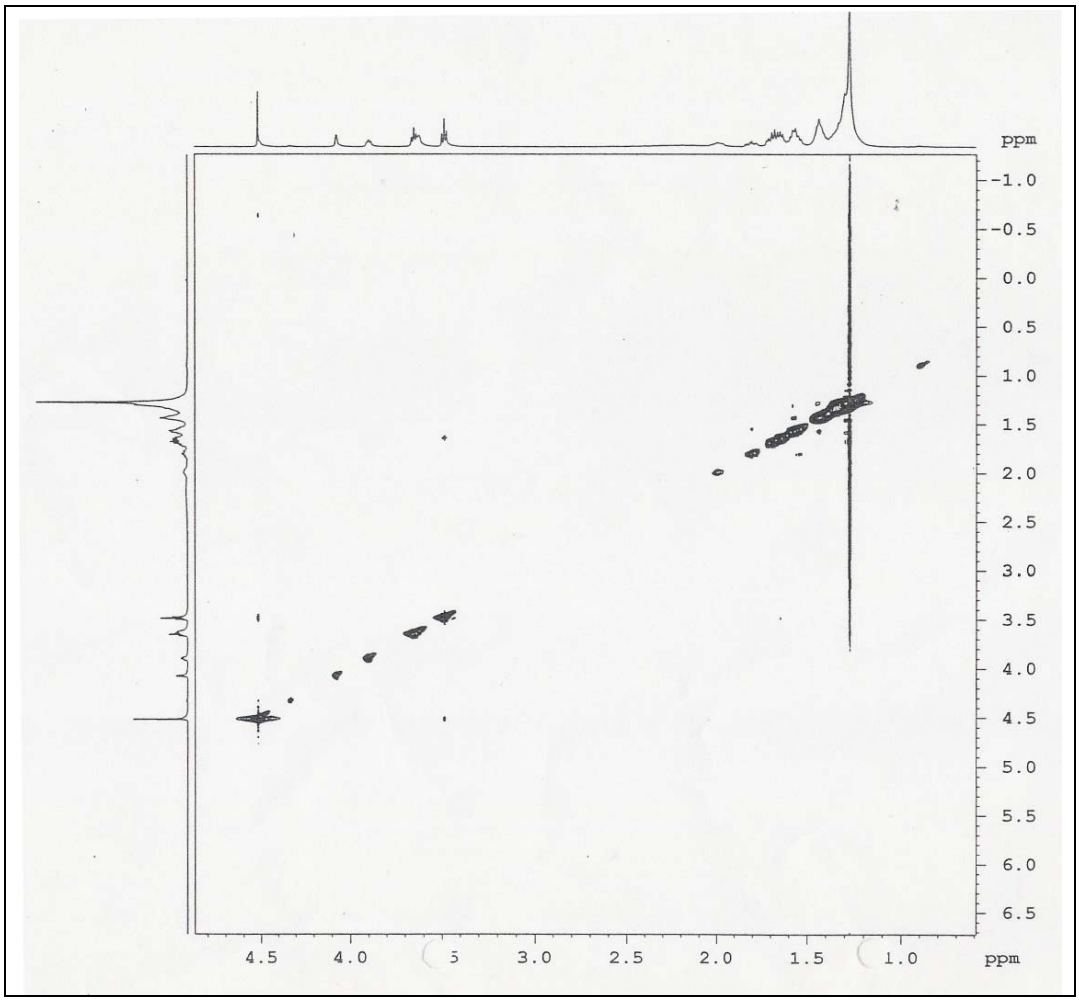


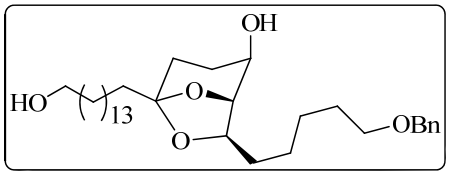
^{13}C NMR Spectrum of 149 in $CDCl_3$



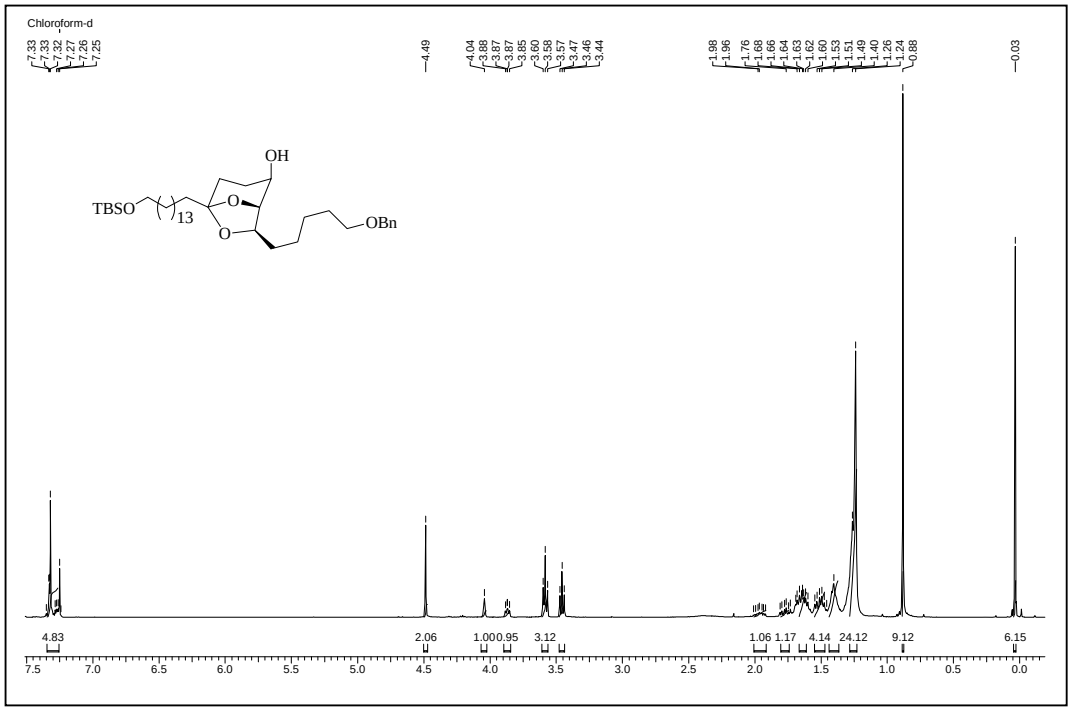


COSY Spectrum of 149

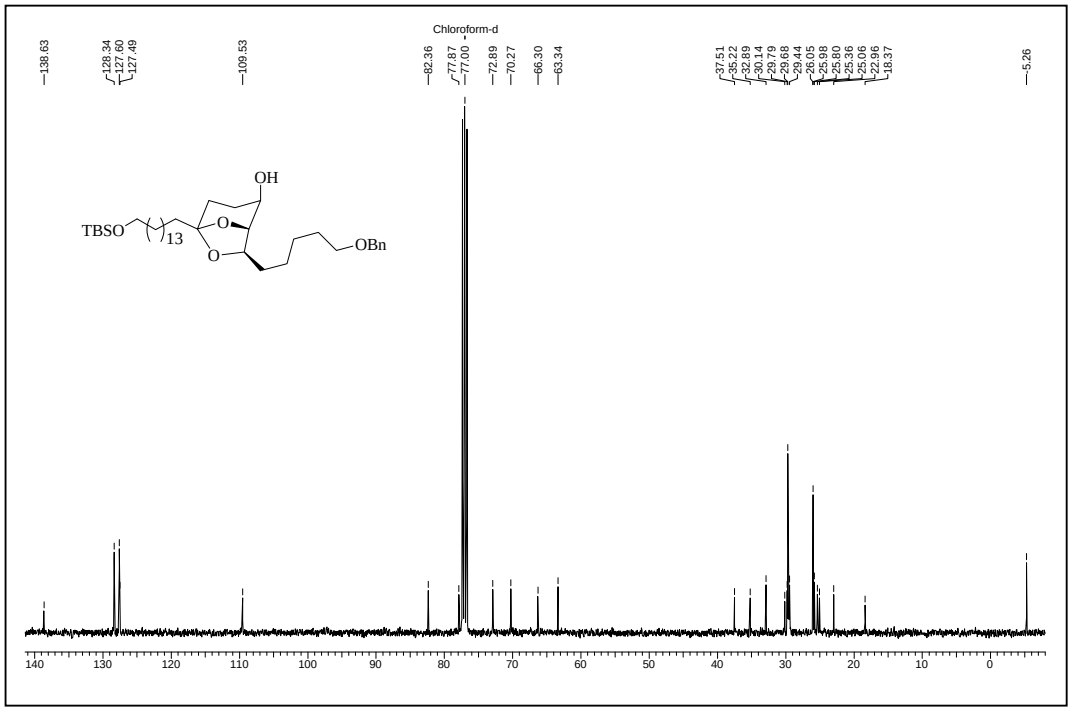




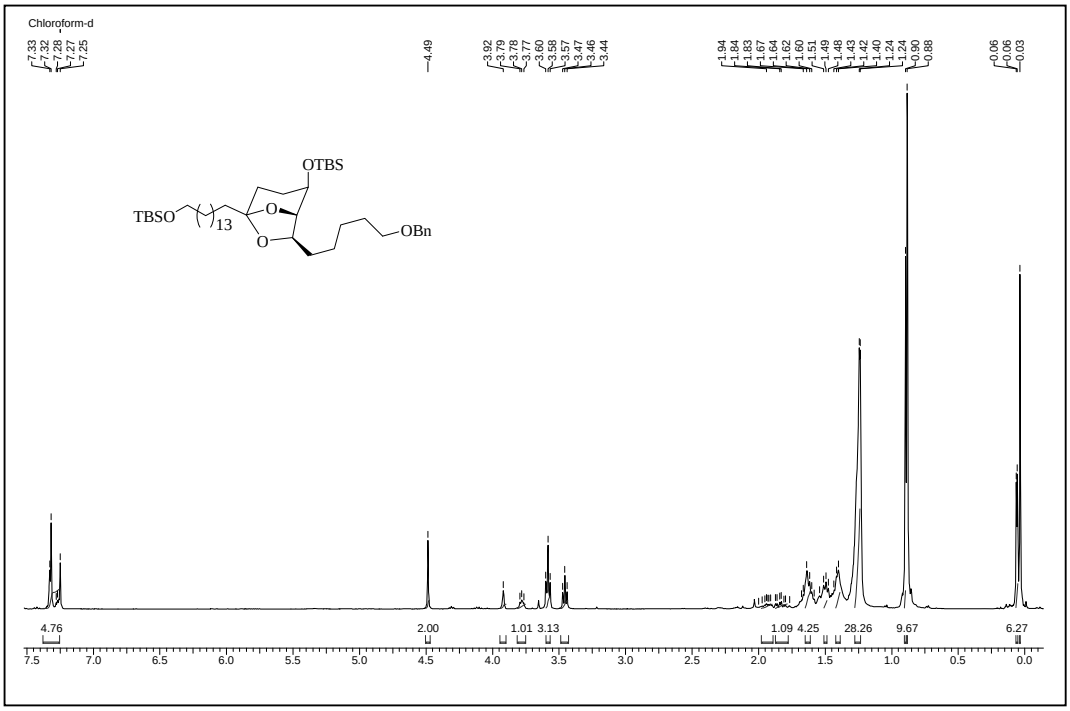
NOESY Spectrum of 149



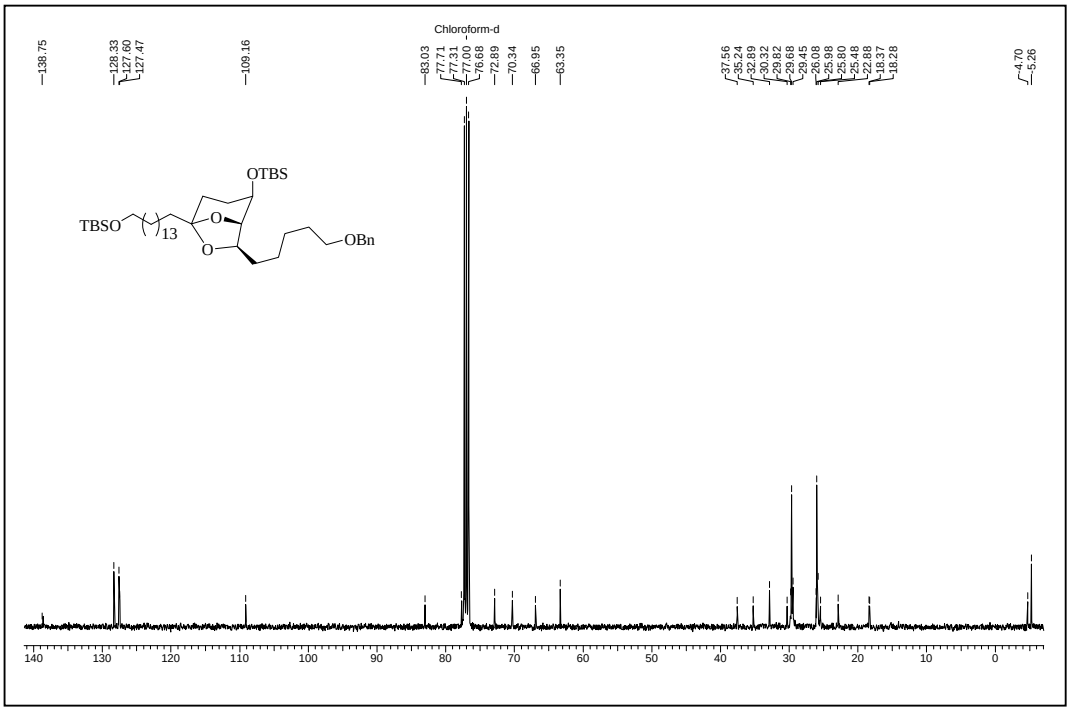
^{1}H NMR Spectrum of 183 in $CDCl_3$



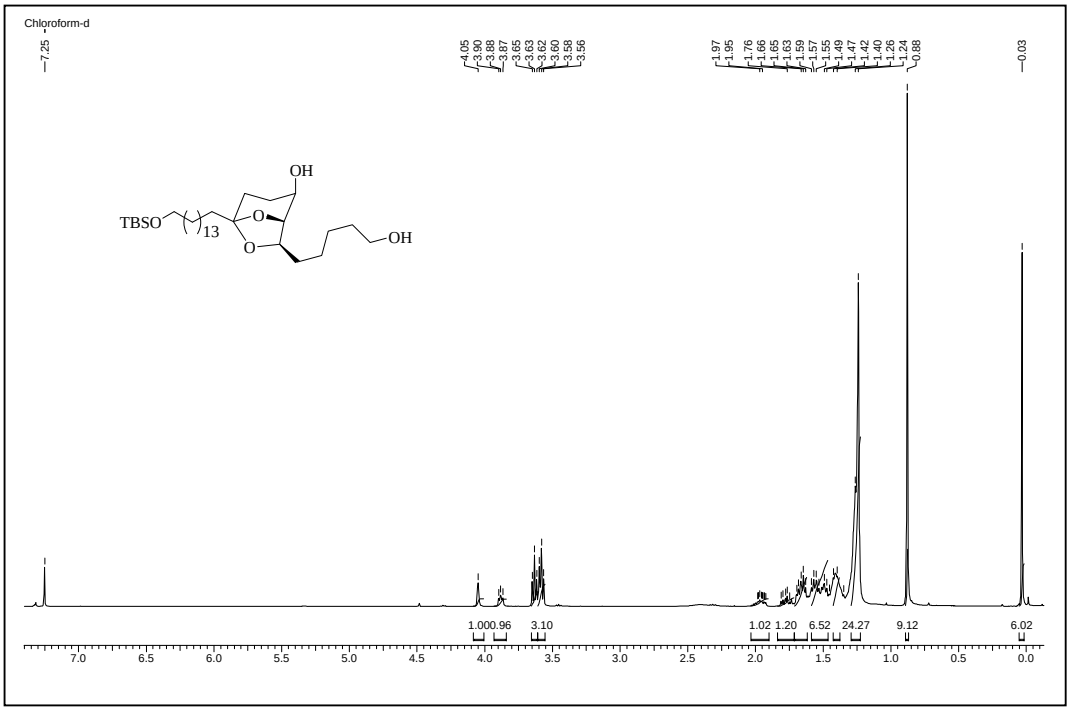
^{13}C NMR Spectrum of 183 in $CDCl_3$



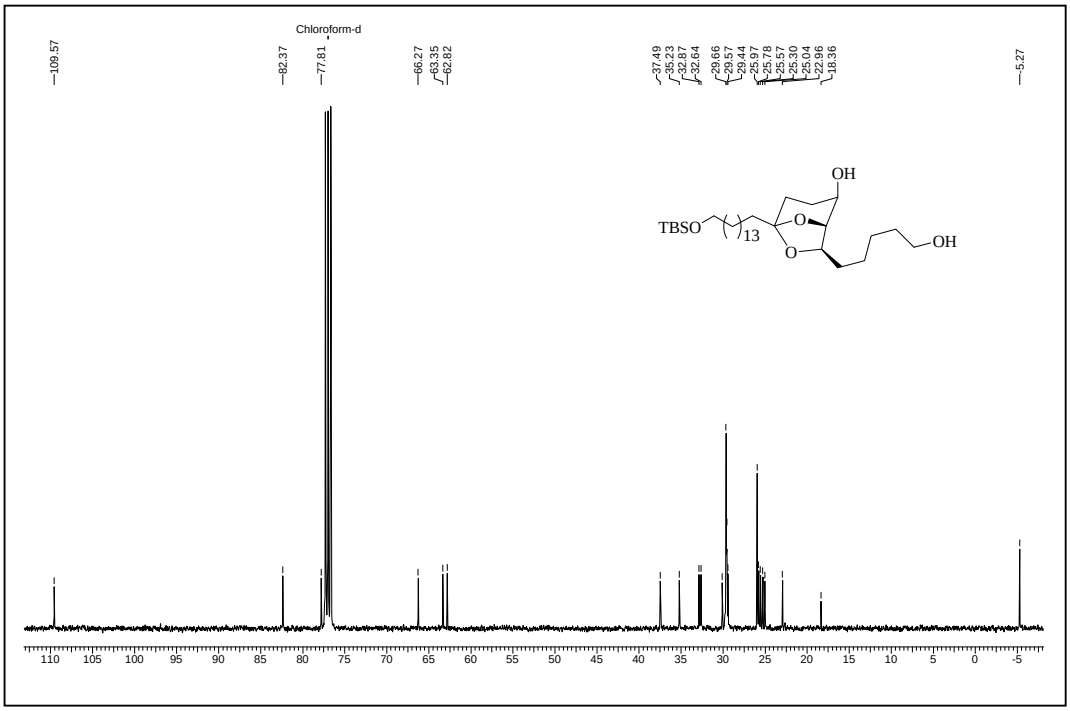
^{1}H NMR Spectrum of 183-TBS in $CDCl_3$



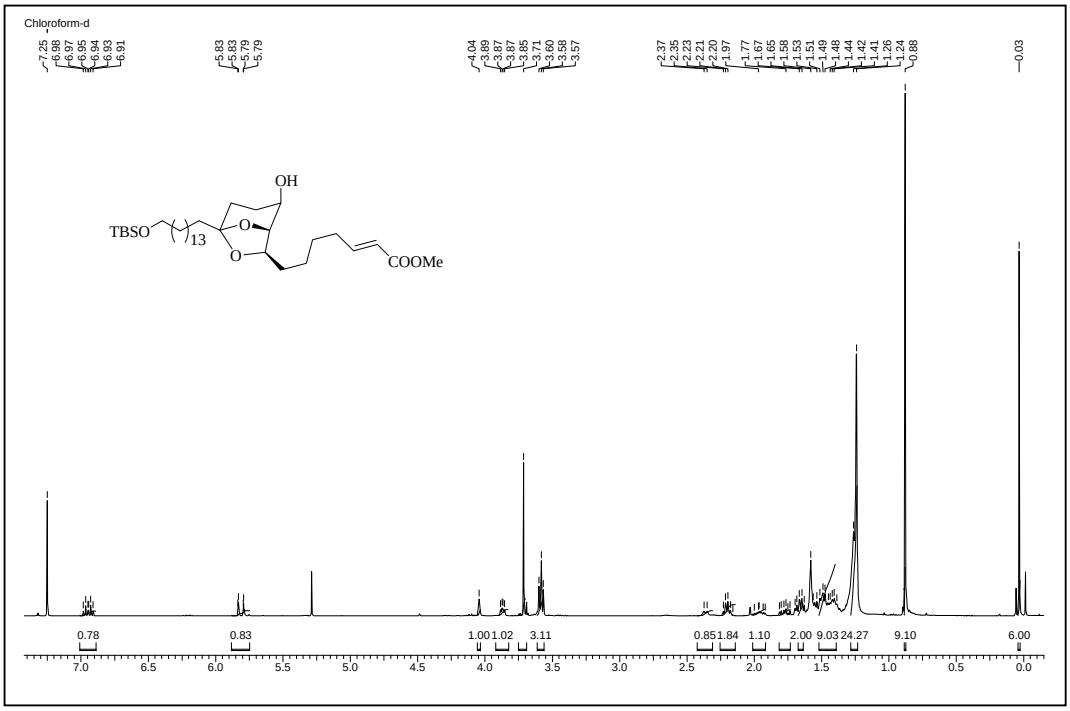
^{13}C NMR Spectrum of 183-TBS in $CDCl_3$



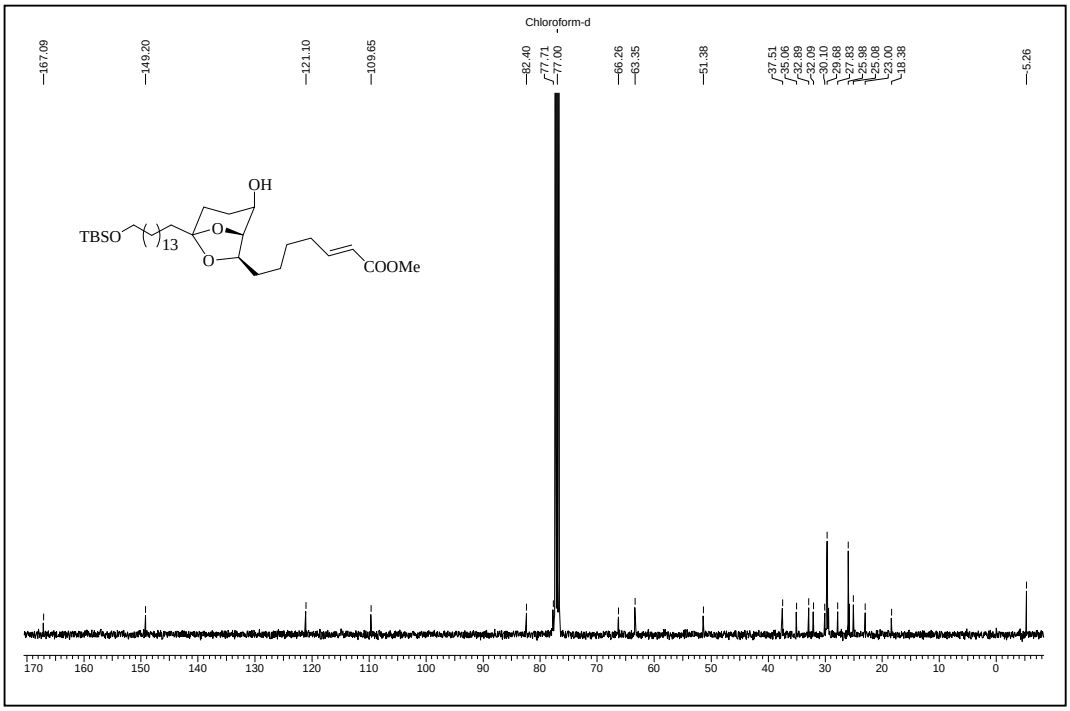
^{1}H NMR Spectrum of 184 in $CDCl_3$



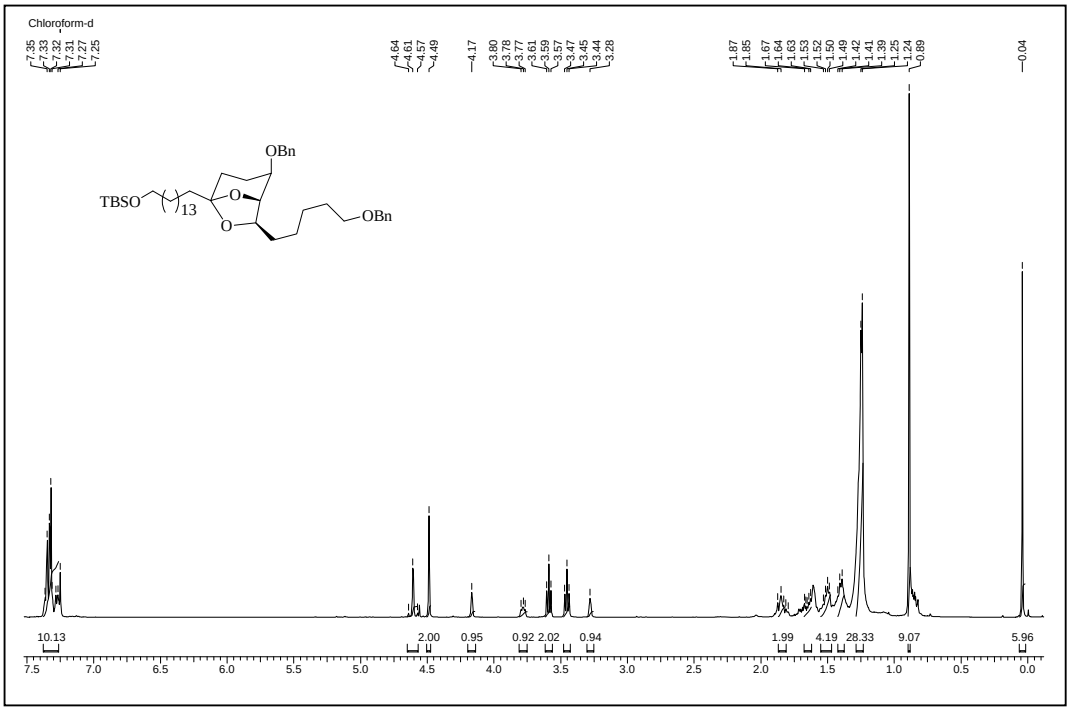
^{13}C NMR Spectrum of 184 in $CDCl_3$



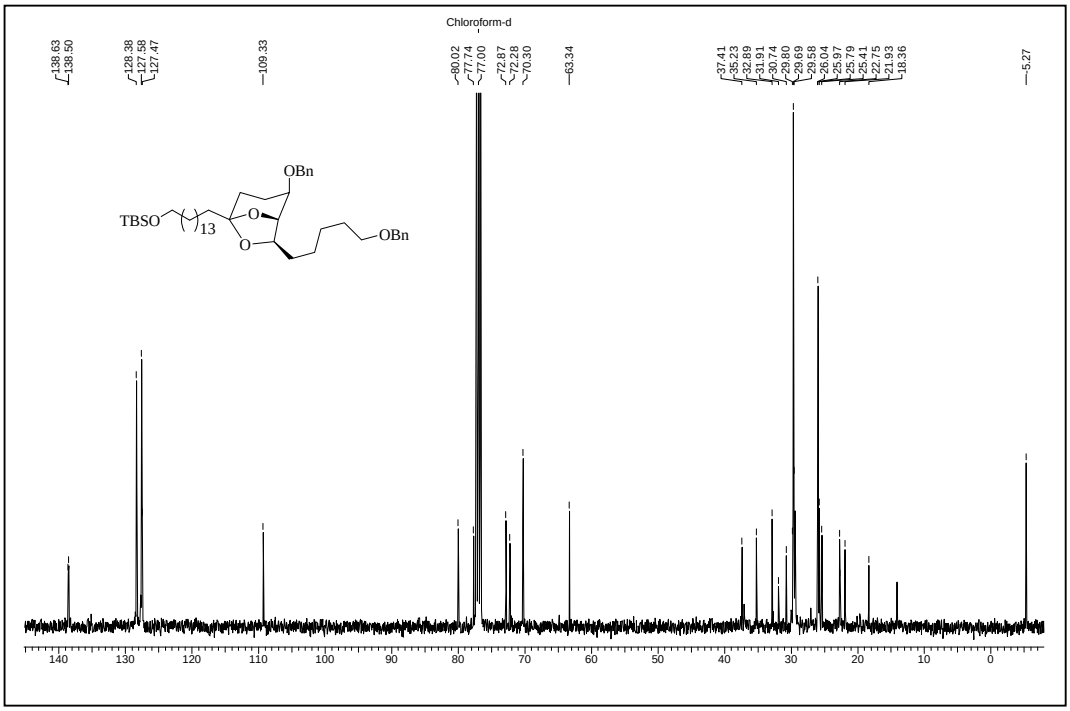
^{1}H NMR Spectrum of 186 in $CDCl_3$



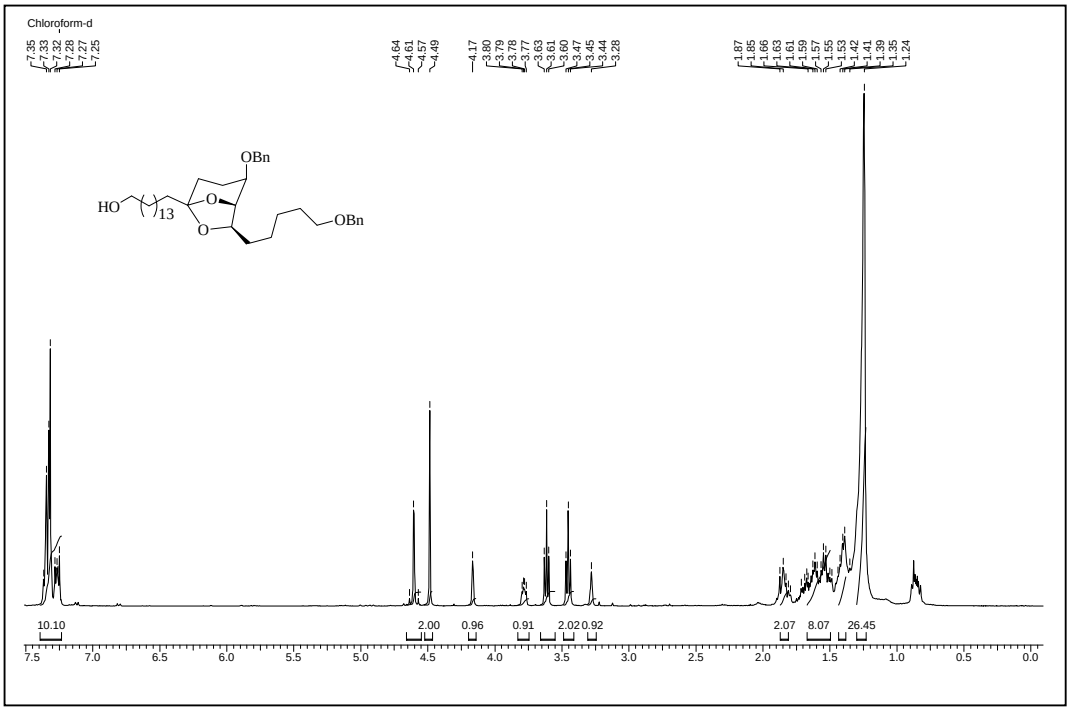
^{13}C NMR Spectrum of 186 in $CDCl_3$



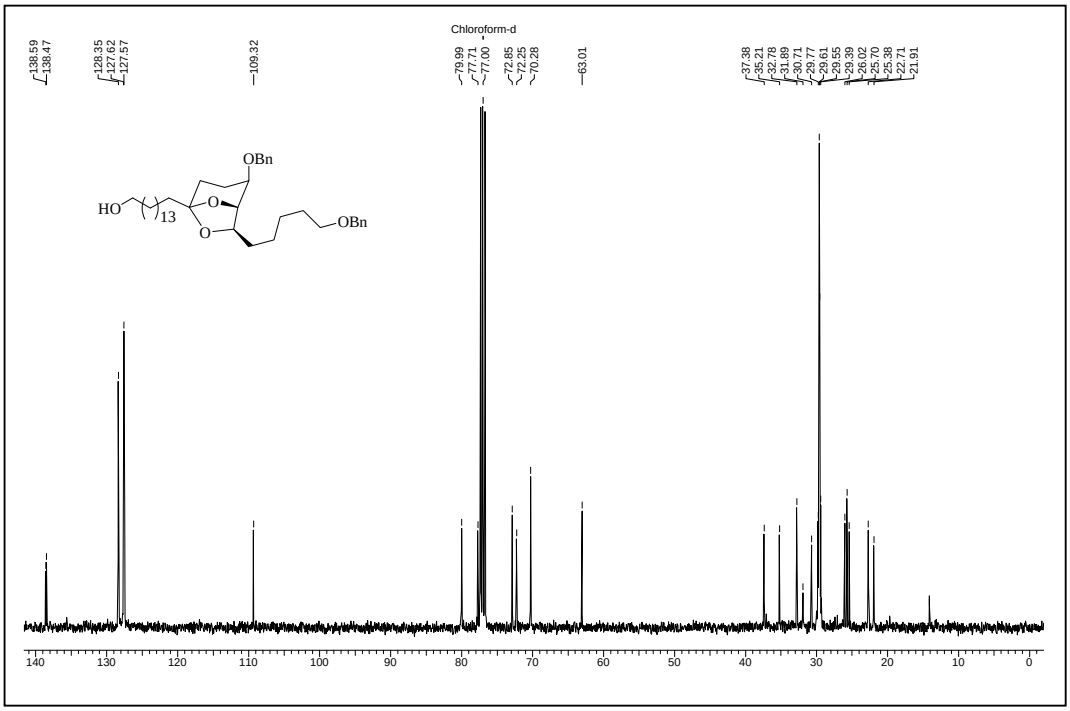
^{1}H NMR Spectrum of 190 in $CDCl_3$



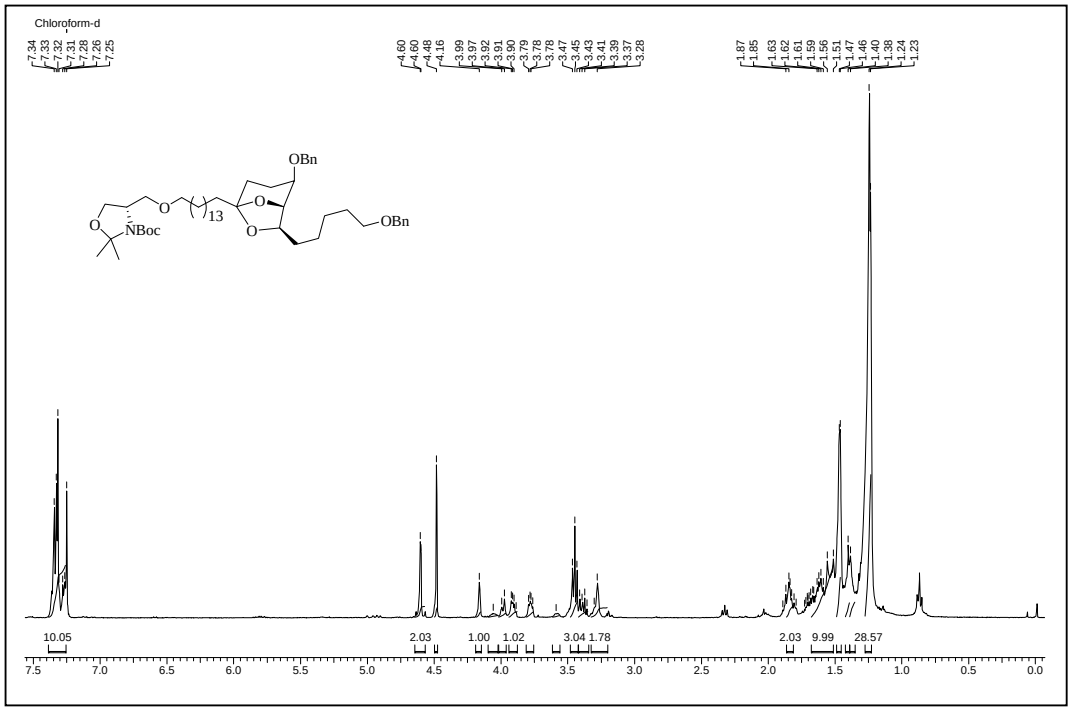
^{13}C NMR Spectrum of 190 in $CDCl_3$



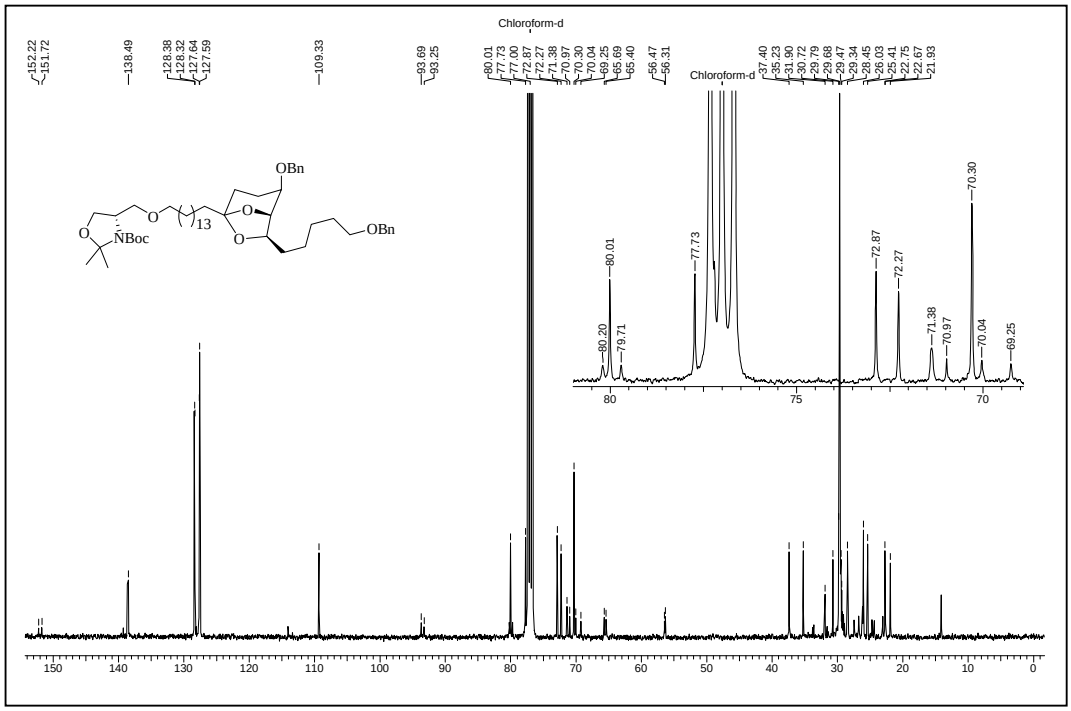
^{1}H NMR Spectrum of 149a in $CDCl_3$



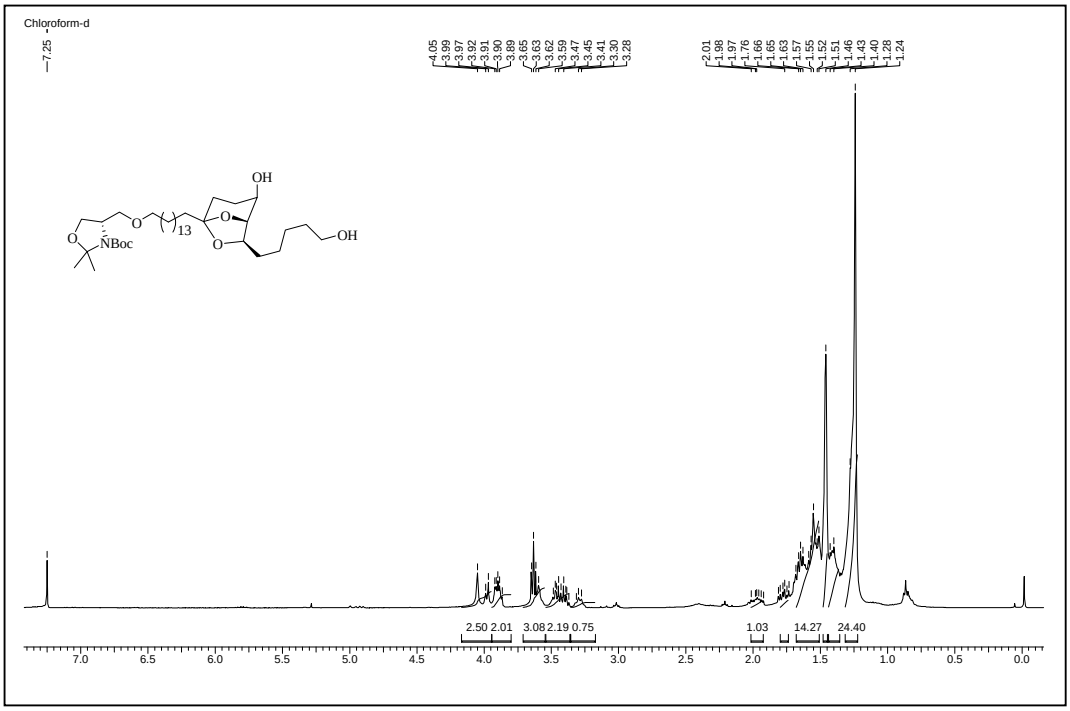
^{13}C NMR Spectrum of 149a in $CDCl_3$



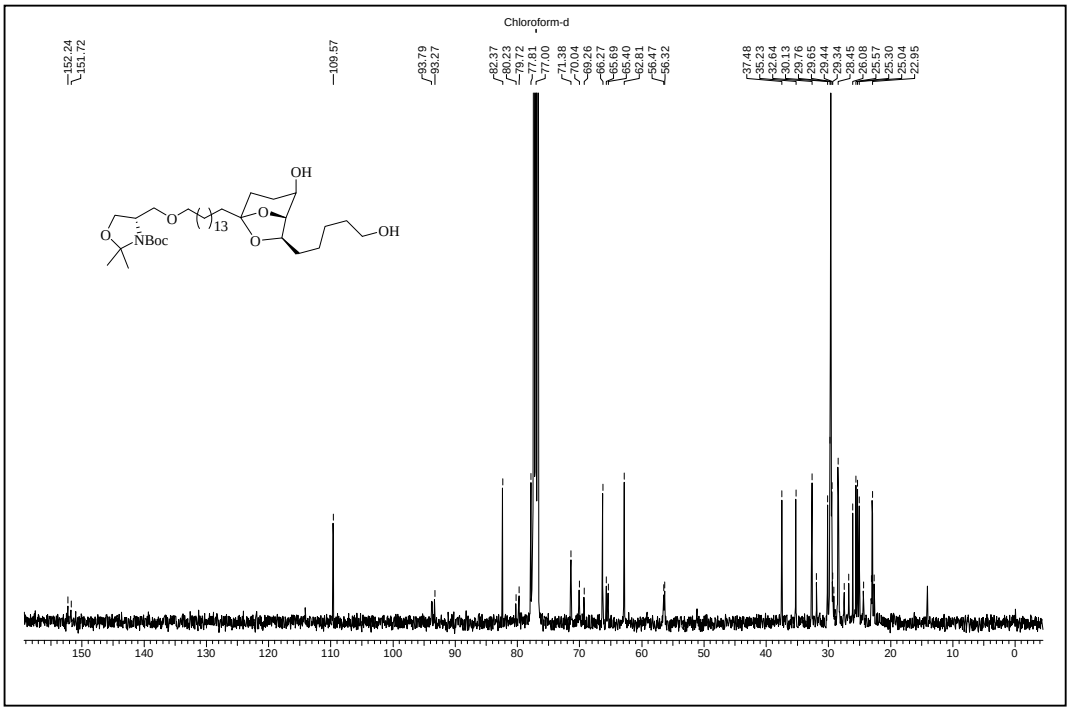
^{1}H NMR Spectrum of 192 in $CDCl_3$



^{13}C NMR Spectrum of 192 in $CDCl_3$



^{1}H NMR Spectrum of 193 in $CDCl_3$



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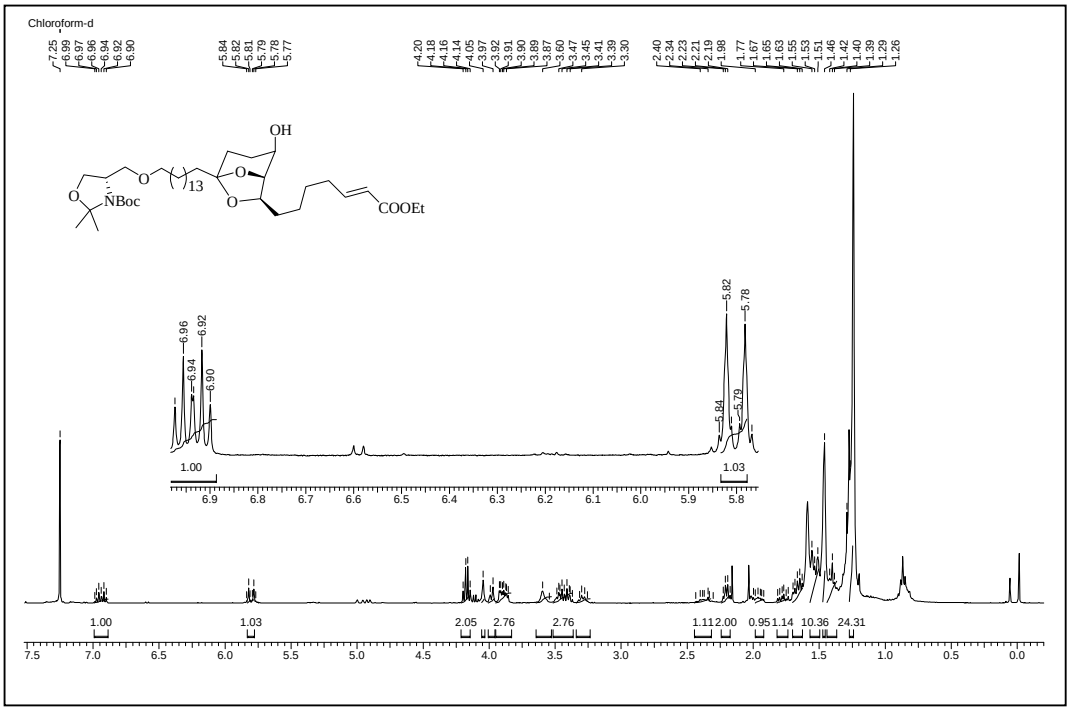
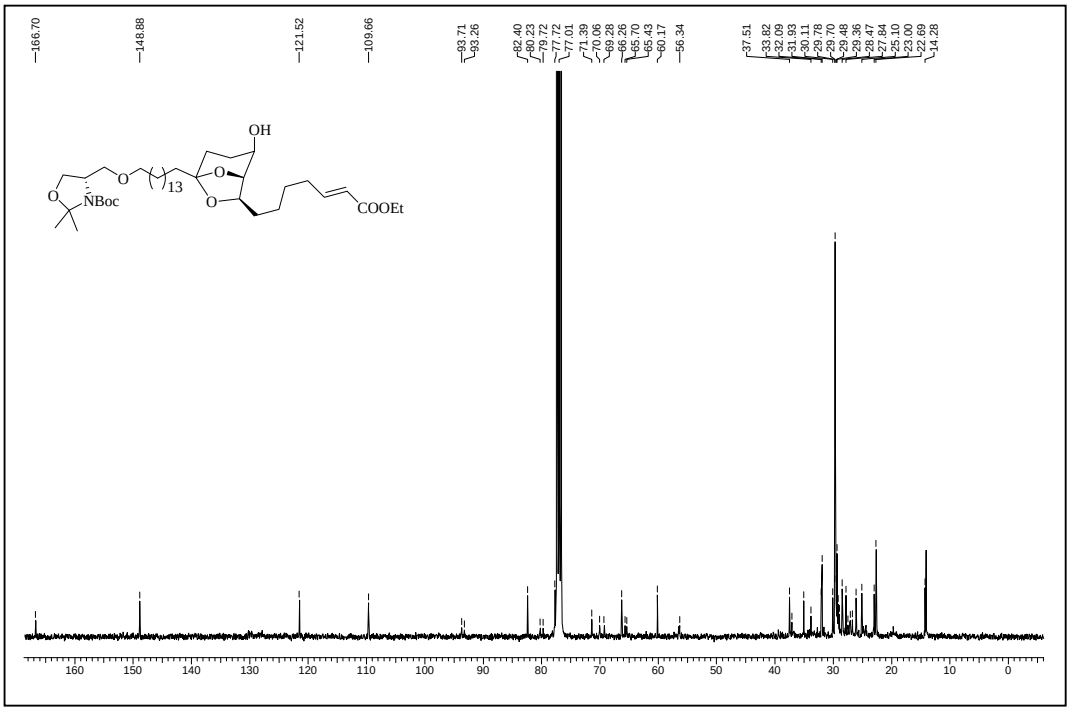
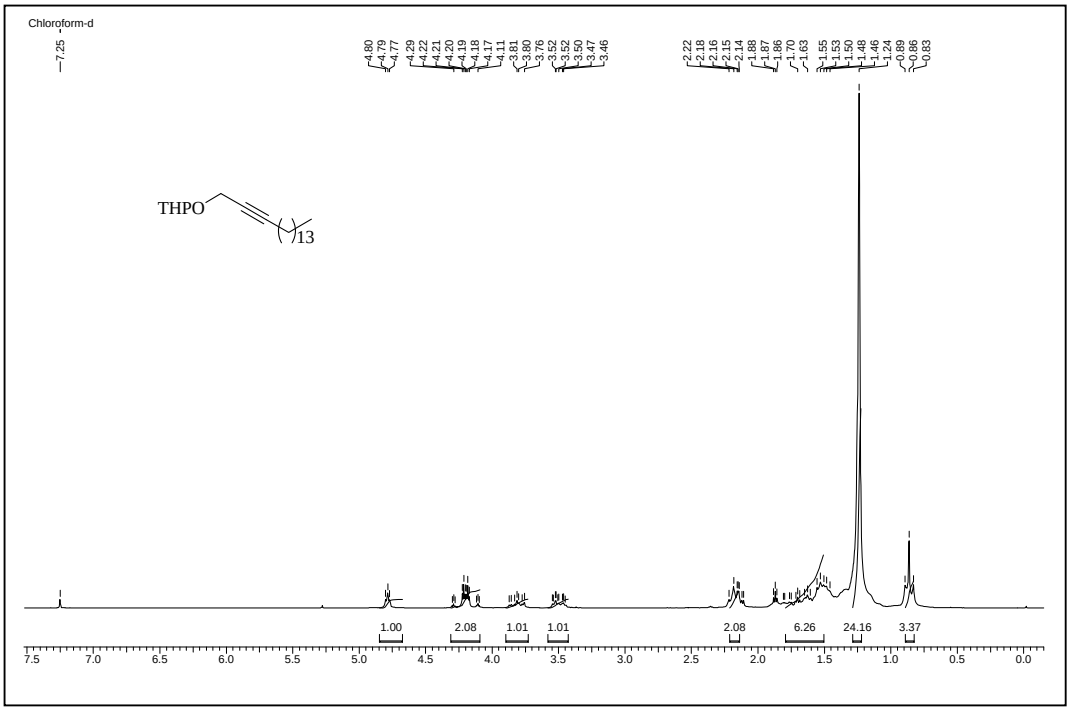


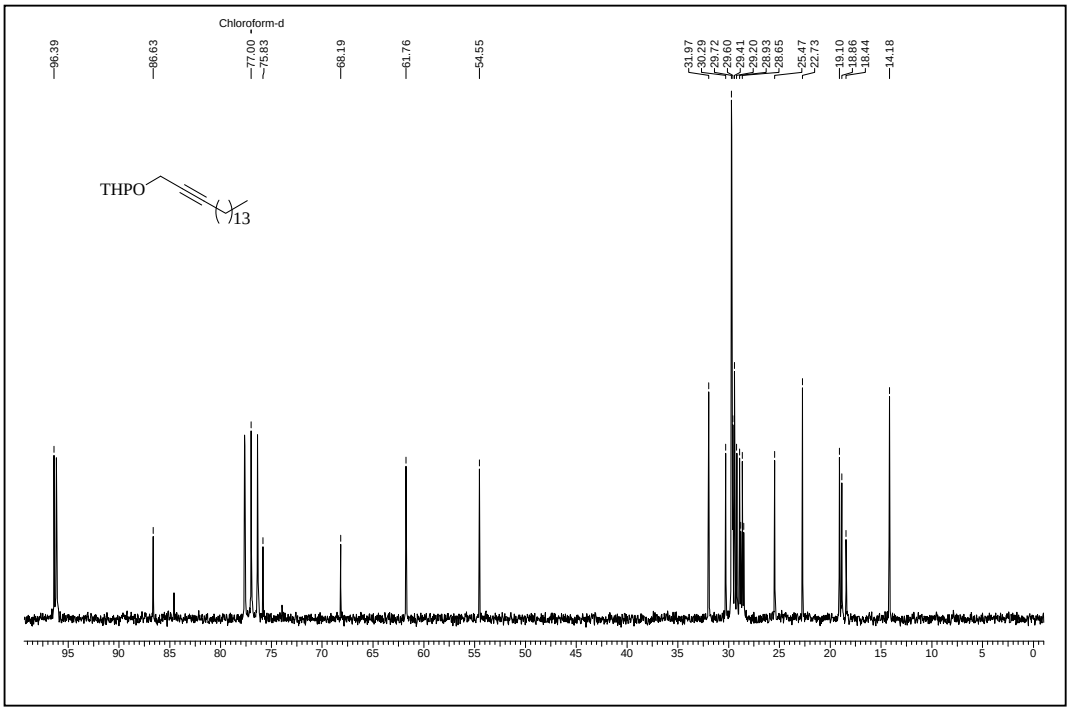
^{1}H NMR Spectrum of 147 in $CDCl_3$



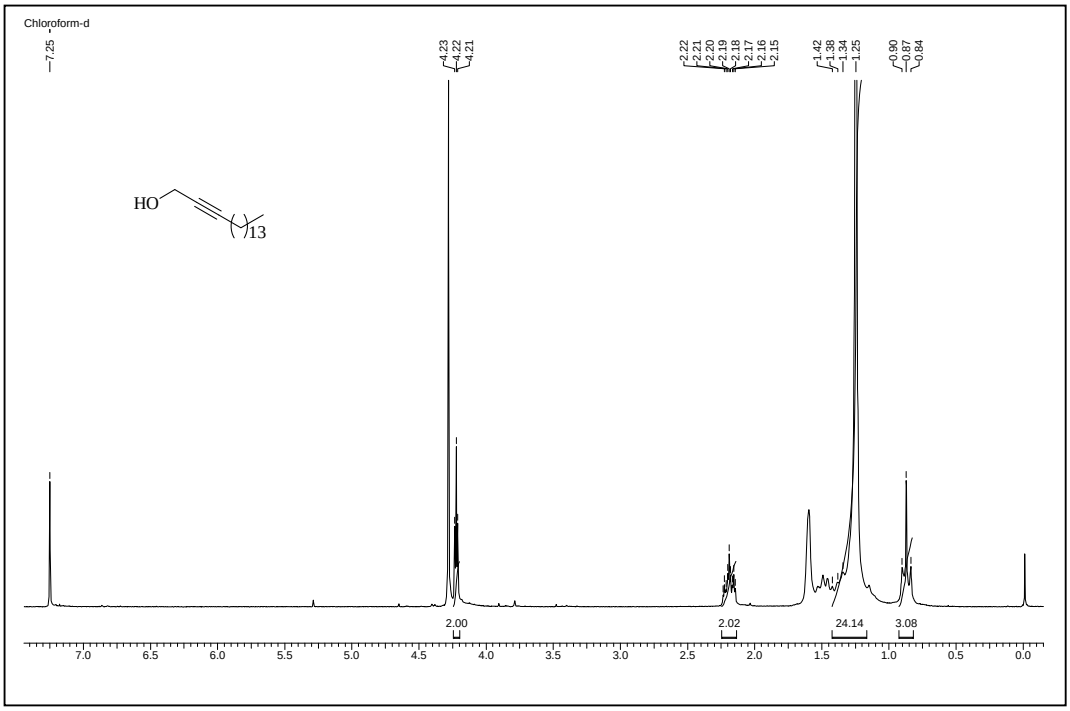
^{13}C NMR Spectrum of 147 in $CDCl_3$



^{1}H NMR Spectrum of 174 in $CDCl_3$



^{13}C NMR Spectrum of 174 in $CDCl_3$



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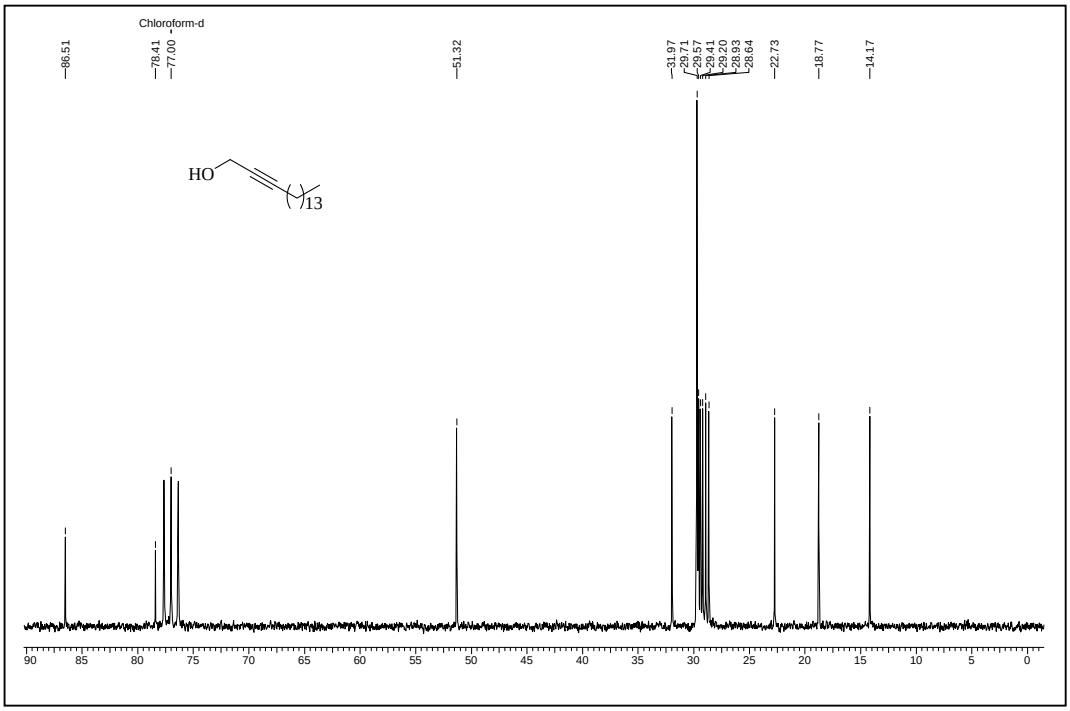
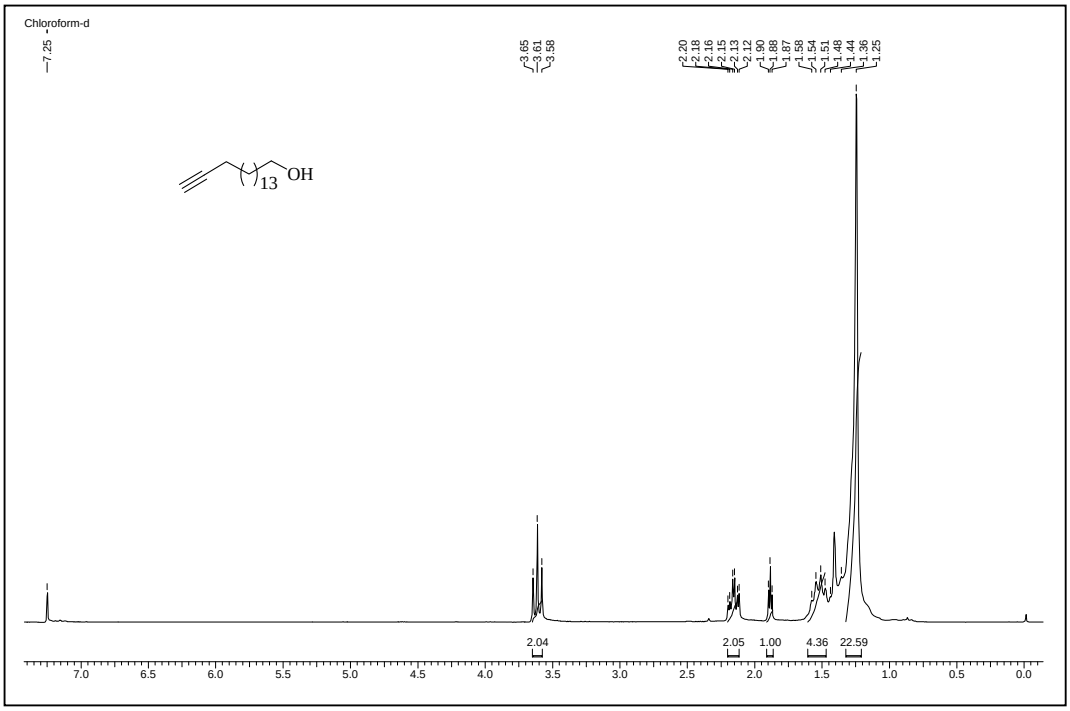
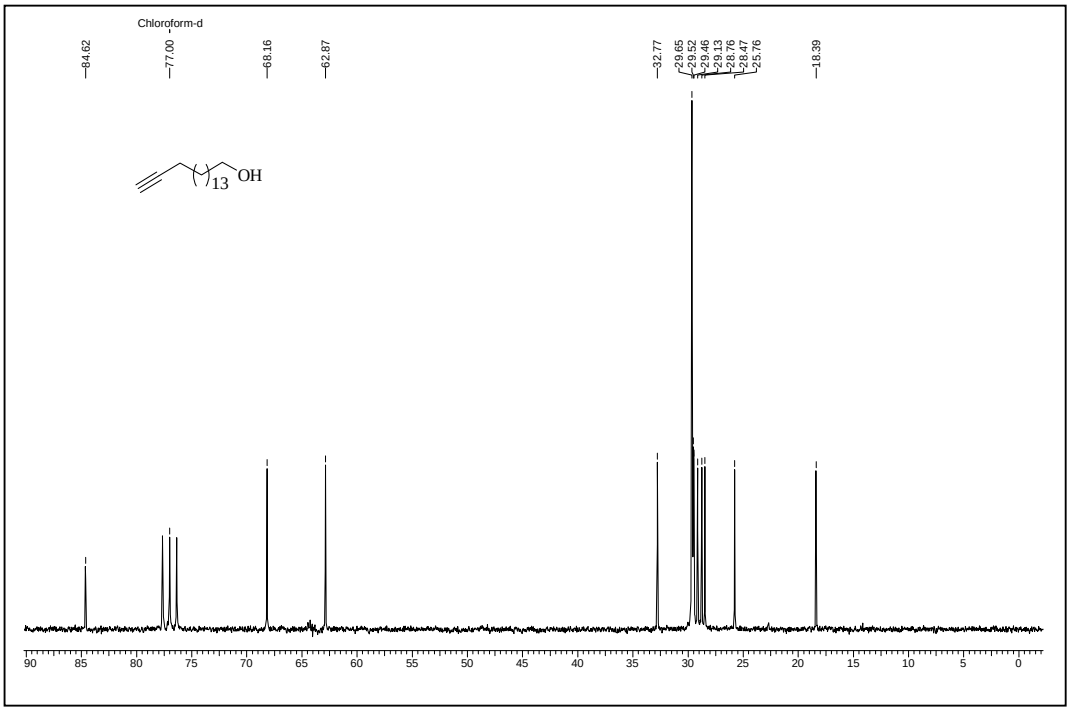


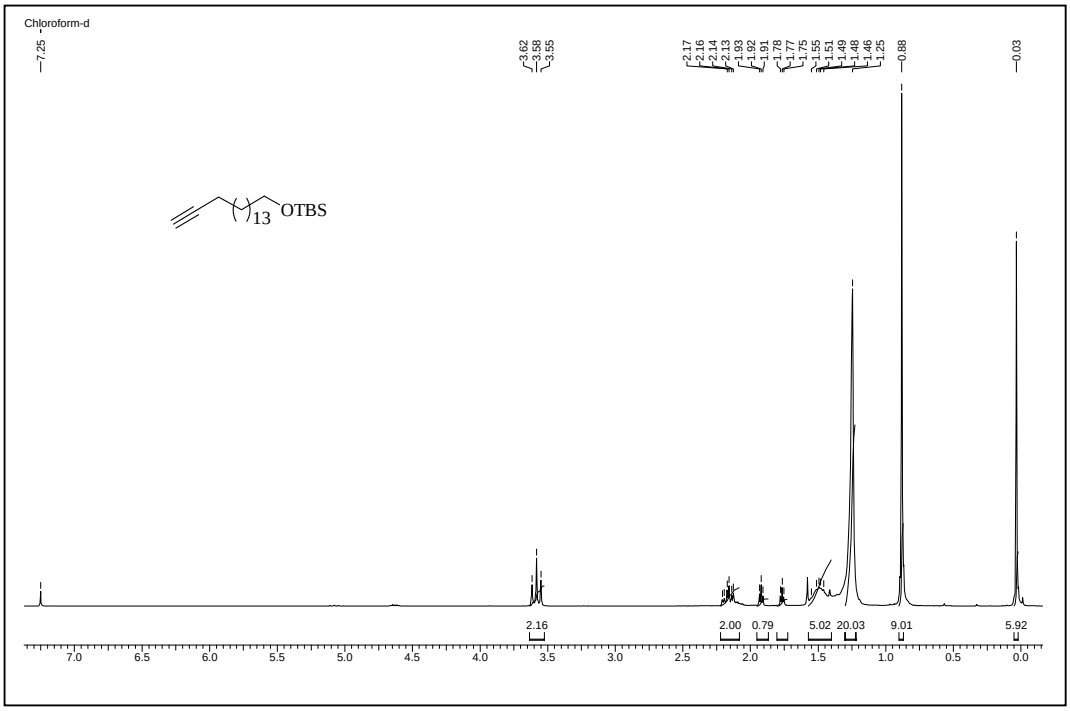
^{13}C NMR Spectrum of 175 in $CDCl_3$



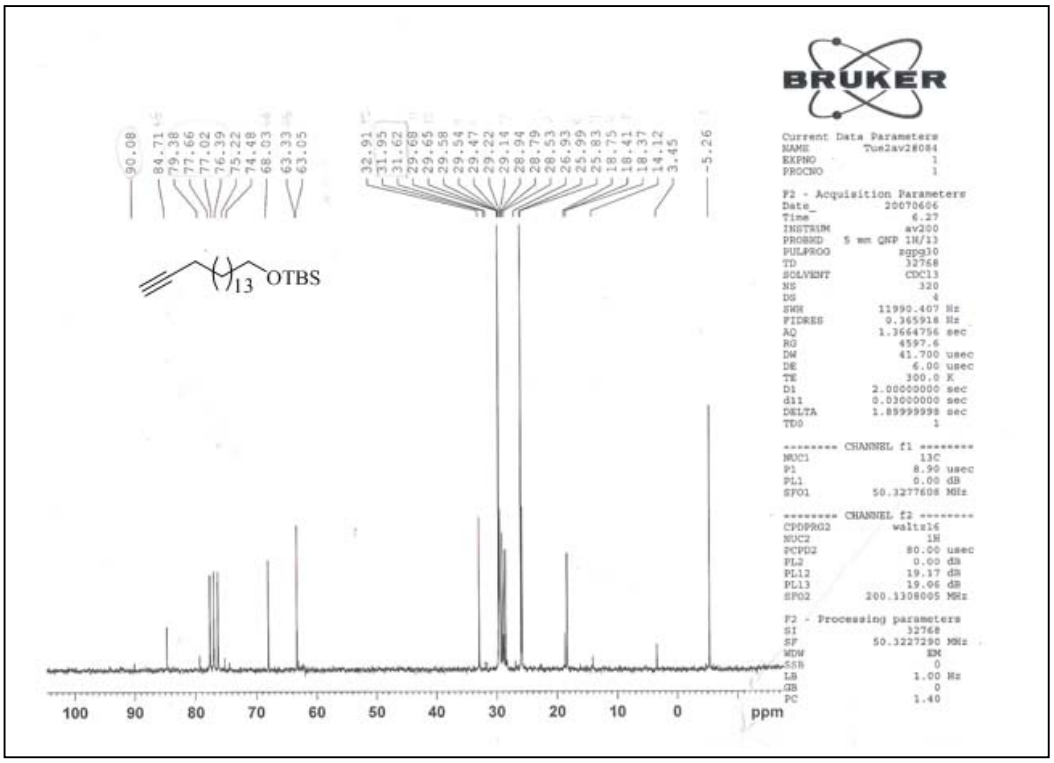
^{1}H NMR Spectrum of 176 in $CDCl_3$



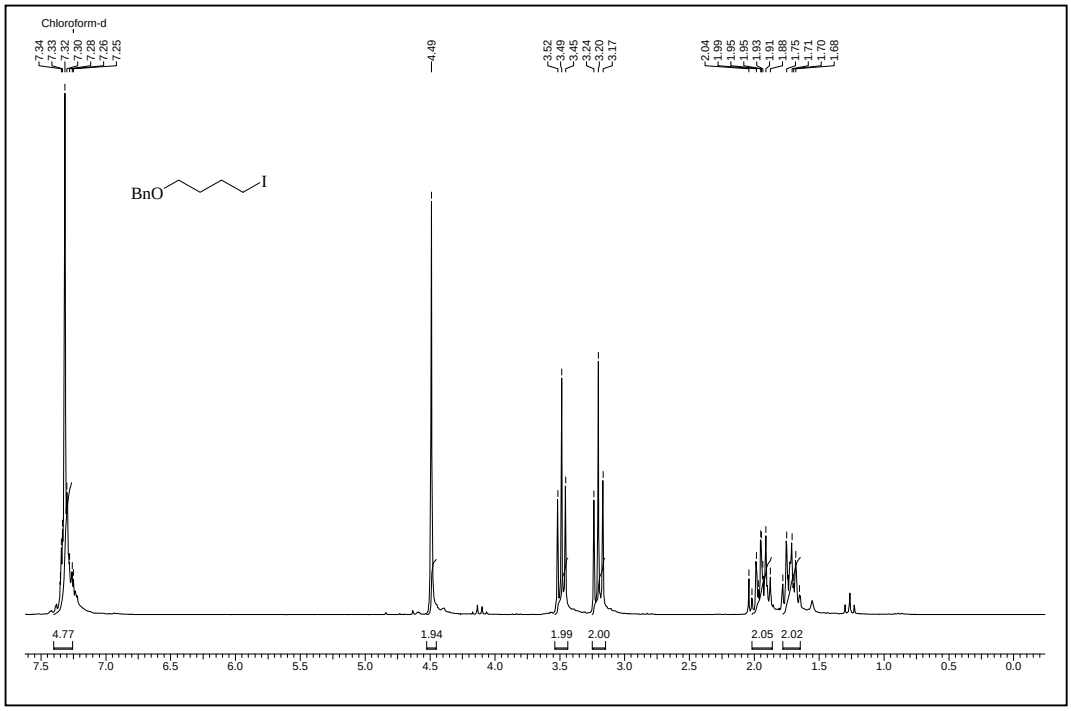
^{13}C NMR Spectrum of 176 in $CDCl_3$



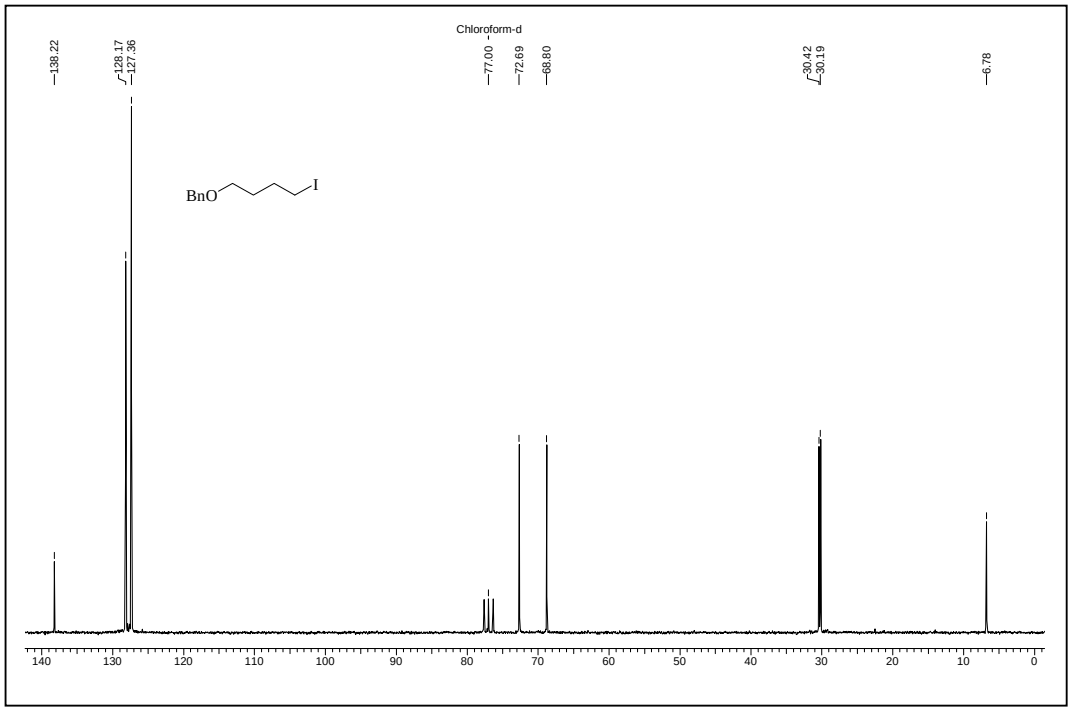
^{1}H NMR Spectrum of 152c in $CDCl_3$



^{13}C NMR Spectrum of 152c in $CDCl_3$



^{1}H NMR Spectrum of 159 in $CDCl_3$



^{13}C NMR Spectrum of 159 in $CDCl_3$

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CHAPTER-III

Studies Toward the Synthesis of Some Functionalized Nortropane Alkaloids

Introduction

The first naturally occurring sugar-mimic i.e., aza-sugar or polyhydroxylated alkaloid, was isolated in 1966. Since then, numerous aza-sugars have been isolated and can be divided into five general classes: piperidines, pyrrolidines, indolizidines, pyrrolizidines, and nortropanes.[1] Numerous polyhydroxylated alkaloids from these structural classes, synthetic and natural, have shown promise as anti-viral or anti-infective agents as well as in the treatment of diabetes. Aza-sugars inhibit glycosidases which are enzymes involved in sugar processing. Glycosidases are involved in a number of physiologically important processes such as intestinal digestion and the catabolism and post-translational processing of glycoproteins. The inhibitors of glycosidases have attracted increasing research interest not only as chemotherapeutic agents, but also as useful molecular probes to understand the function of glycoproteins and to study the structure and the catalytic mechanism of glycosidases. The inhibitors of glycosidases have generally been designed to mimic the charge and/or the shape of the oxocarbenium ion-like transition-state or intermediate: incorporating a basic nitrogen center or a positive charge at or adjacent to C-1 (anomeric carbon) into a sugar surrogate is a common practice in designing glycosidase inhibitors. The incorporation of a nitrogen positive center into a sugar pyranose ring requires a relatively long reaction sequence and often disrupts the stereochemistry at C-1 and the spatial arrangements of the hydroxyl groups which affect the selectivity of the inhibitor.

The discovery of polyhydroxy alkaloids, otherwise known as imino-sugars raised an awareness among phytochemists that compounds with structural similarities should have analogous glycosidase-inhibitory properties.[2] Recognition of their structural affinities to castanospermine (**1**), with a pair of five and six-membered rings, albeit fused in a different manner (Figure 1), led to their characterization as potent inhibitors of β-glucosidase and α- and β-galactosidase.

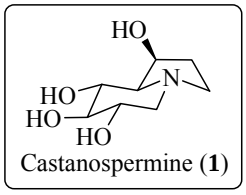


Figure 1: Structural compatibility of alkaloids with Castanospermine (**1)**

The tropane alkaloid family contains a large array of natural products sharing a common 8-azabicyclo[3.2.1]octane skeleton, endowed with numerous and remarkable biological activities. Substances in this family have been traditionally known and used for centuries in folk medicine. Since the middle of the 19th century, the elucidation of their structure and their synthesis have contributed to no small degree to the development of organic chemistry. The tropane alkaloids are a well-recognized group of structurally related natural products and include medicinally important alkaloids as cocaine (**2**), scopolamine (**3**), and atropine (**4**). Many tropane derivatives play a key role in a myriad of neurological and psychiatric diseases such as Parkinson, depression, schizophrenia, and panic disorder. Classical tropane alkaloids, in contrast, are either parasympatholytic, as with atropine (**4**) and scopolamine (**3**) or anaesthetic and sympathomimetic, as with cocaine (**2**). Cocaine antagonists, which are employed in the treatment of cocaine addiction, and tropane related compounds recently used as radiopharmaceuticals also deserve considerable attention.[3] Over 200 tropane alkaloids are known to occur in natural sources. While (−)-cocaine (**2**) is the flagship compound, the tropane alkaloid pathway is known to produce many medicinally important natural substances, with all of them featuring the aza-bridged bicyclic framework as the key structural element. Representative examples include hyoscyamine (**5**), scopolamine (**3**). Moreover, special attention has been given to the interesting tropane-type alkaloid (+)-ferruginine (**6**) (Figure 2).

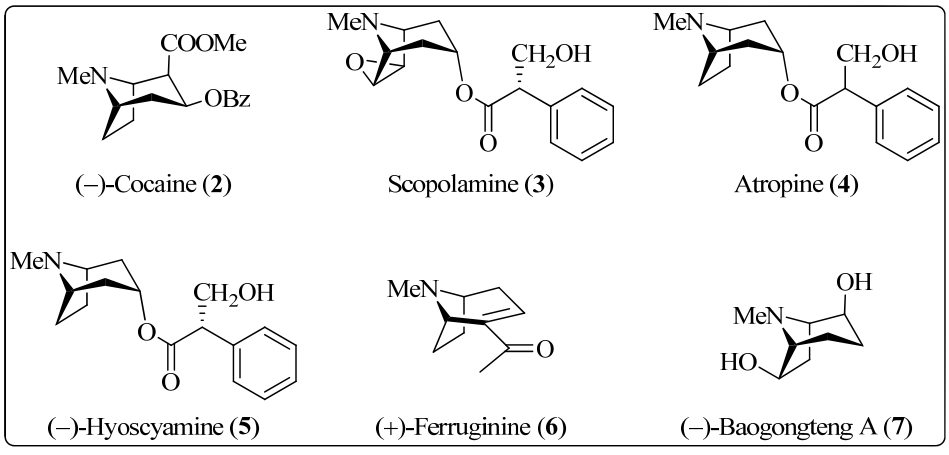


Figure 2: Representative examples of medicinally important tropane alkaloids.

Although tropane alkaloids from plant sources have been known for more than 170 years, it was only in 1990 that the structures of the first calystegines were published.[4] The name of the group of alkaloids derives from the first detection in roots of *Calystegia sepium* (Convolvulaceae).

Calystegines are novel allelochemicals: tropane alkaloids characterized by the absence of *N*-methylation (a nortropane ring system), a high degree of hydroxylation, and an unusual aminoketal functionality at the bridgehead position and are considered as conformationally restricted 6-membered ring iminosugars; It is evident that the naturally occurring calystegines have a preference for equatorial or *exo* hydroxy groups. Calystegines, differing in the number, position, and stereochemistry of the hydroxyl group substituents on the tropane ring, have been isolated. The known members of the class have been subdivided into three groups on the basis of the number of hydroxyl groups present, namely calystegines A, B, and C. Calystegines A_3 (**8**), A_4 (**9**), and A_5 (**10**) each have three, calystegines B_1 (**11**), B_2 (**12**), B_3 (**13**) and B_4 (**14**) have four, and calystegine C_1 (**15**) has five hydroxyl groups, respectively. To date, 14 calystegines have been isolated (Figure 3).

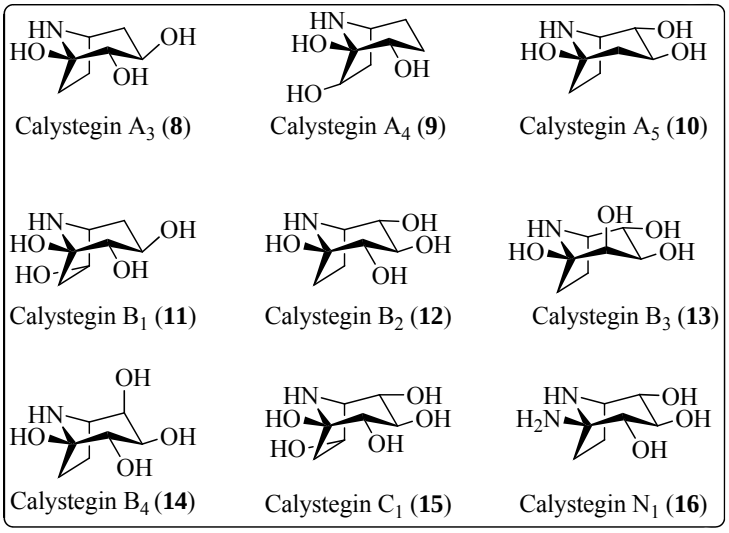


Figure 3: Structures of some naturally occurring Calystegines.

The relatively recent discovery of calystegines and their limited availability has provided little opportunity for evaluation for therapeutic properties. As inhibitors of α-galactosidase and α-glucosidase they offer potential for the development of

animal models of the human lysosomal storage defects, Fabry's and Gauchers's diseases.[5] Fabry's is caused by a deficiency of α-galactosidase, allowing the glycolipid, globotriaosylceramide, to accumulate in various organs, ultimately leading to renal insufficiency and cardiac complications. The disease can be treated by extremely expensive, recurrent enzyme replacement therapy. In contrast, Gaucher's occurs most frequently among Ashkenazi Jews and symptoms, depending on the disease type, are characterized by hepatomegaly, splenomegaly and neurological problems, the most serious of which are convulsions, mental retardation and dementia. The disease is caused by a genetic defect that catalyzes breakdown of lysosomal glucocerebrosidase, an α-glucosidase, resulting in an overall deficiency of the enzyme. Interestingly, *in vitro* experiments with human fibroblasts and lymphoblasts have shown that calystegines B_2 and C_1, as well as some polyhydroxy piperidine glycosidase inhibitors, may act as chemical chaperones, enhancing correct folding of residual enzyme and enabling improved trafficking to the lysosome, with consequent several-fold increase in enzyme activity. More calystegine type structures containing a glycoside, an *N*-methyl group, or an amino group, the latter instead of the tertiary hydroxy group have been isolated and are believed to possess biological activities. However, the calystegines have been significantly less explored than the other classes of sugar mimics with nitrogen in the ring, e.g. polyhydroxylated pyrrolidines, piperidines, pyrrolizidines, and indolizidines.

Synthesis:

The broad range of neurochemical activity associated with the 8-azabicyclo[3.2.1]octane framework (tropane) coupled with their unusual architecture makes short, versatile, stereocontrolled synthetic routes to these compounds of tremendous potential value. New calystegines or calystegine-like structures are constantly being published, and many more structures can be theoretically designed using the nortropane skeleton and assigning hydroxyl groups in all possible positions and arrangements.

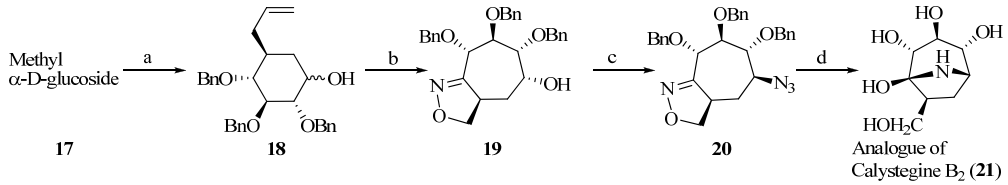
Of the known calystegines of natural origin, calystegines A_3, B_2, B_3, and B_4 have been synthesized. Several synthetic routes have been devised making use of sugars, aminoacids, hydroxy acids, cycloheptane derivatives, phenylglycinol derivatives and others.

1) Synthetic approaches based on Sugars:

a) Duclos, O. *et al.*:

The intramolecular cycloaddition of an olefinic nitrile oxide (INOC) derived from D-glucose was the key step of a new access to polyhydroxylated cycloheptane derivatives, suitable intermediates for further elaboration to a C7- substituted calystegine B_2 analogue **21** (Scheme 1).[6]

Scheme 1:

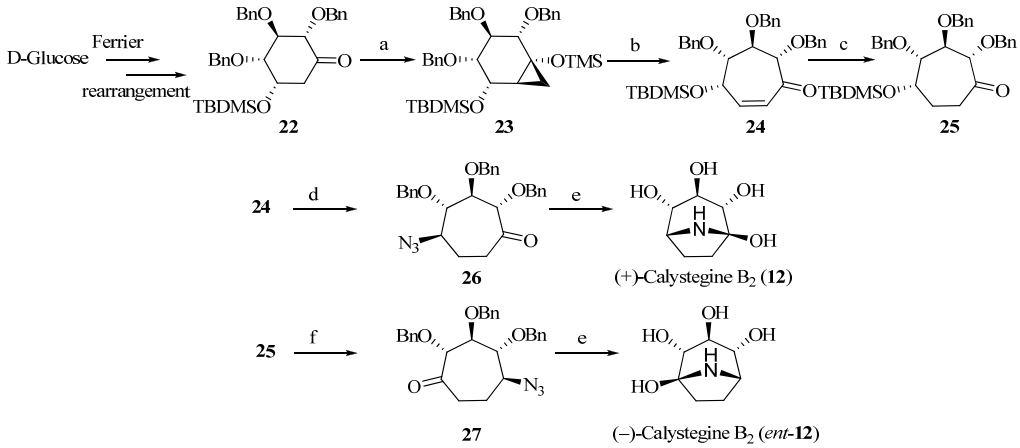


Reagents and conditions: a) NH_2OHHCl, CH_3ONa, CH_3OH, reflux; b) NaOCl, CH_2Cl_2; c) $ZnN_6.2py$, PPh_3, DIAD; d) H_2-Pd, $AcOH/H_2O$; e) CH_3OCH_2Cl, $^iPr_2NEt$, CH_2Cl_2 or TsCl, Py; f) H_2, Raney-Ni, CH_3OH/H_2O, $B(OH)_3$; g) $DMSO/(COCl)_2$, Et_3N, 60 °C; h) Zn, TMEDA, AcOH/EtOH.

b) Lallemand, J. Y. *et al.*:

A different approach to these polyhydroxylated nortropanes is based on a regiospecific ring enlargement of the polysubstituted cyclohexanone **22**, in turn prepared from D-glucose by standard carbohydrate chemistry. The pivotal ring expansion demanded the kinetically controlled silylenoletherification of compound **22** (Scheme 2).[7]

Scheme 2:



Reagents and conditions: a) (i) LDA, TMSCl, THF, -70 °C; (ii) Et_2Zn, CH_2I_2, toluene, 0 °C; b) (i) $FeCl_3$, DMF, 70 °C; (ii) AcONa, CH_3OH, reflux; c) H_2, Pd/C, EtOH; d) (i) Bu_4NF, THF; (ii) MsCl, DMAP; (iii) DIBAH, Et_2O, -60 °C; (iv) NaN_3,

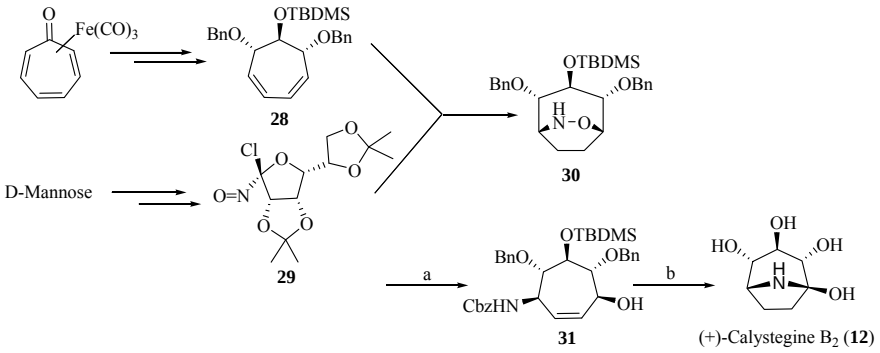
DMF; (v) Dess-Martin, CH_2Cl_2; e) i) H_2, Pd/C, AcOH/H_2O; (ii) NaOH, pH 11; f) (i) $NaBH_4$; (ii) d) (ii); (iii) d) (iv); (iv) d) (i); (v) PCC, CH_2Cl_2.

After that, the methylene ring insertion reaction was readily achieved in a two-step sequence involving cyclopropanation with diethylzinc- methylene iodide reagent followed by the opening of the resulting cyclopropane derivative by the treatment with $FeCl_3$. Further functional group transformations lead to calystegine and its enantiomer.

c) Soulie *et al.*:

A synthetic approach to (+)-calystegine B_2 taking advantage of a hetero-Diels-Alder cycloaddition reaction (Scheme 3). Soulie et al.[8] employed the chiral nitroso dienophile **29** derived from D-mannose as the counterpart of the known trisubstituted cycloheptadiene **28**, in turn previously taken to racemic calystegine B_2 by the same authors. The [4 + 2] cycloaddition readily gave the dihydrooxazine derivative **30** as a single enantiomer. After benzyloxycarbonyl N-protection, the $Mo(CO)_6$ reductive cleavage of the N-O bond gave compound. Oxidation of the allylic alcohol and O-desilylation produced the key cycloheptenone, which was eventually subjected to hydrogenation to give the natural alkaloid **12**.

Scheme 3:

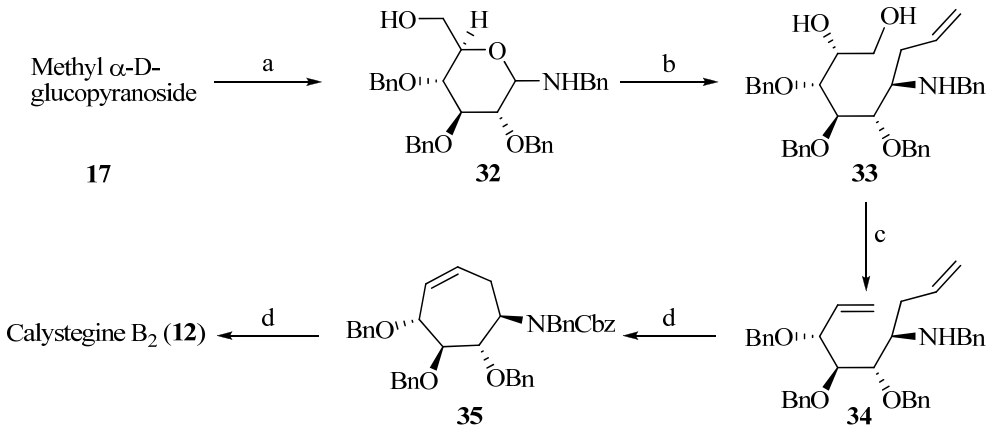


Reagents and conditions: a) (i) BnOCOCl, CH_2Cl_2, Na_2CO_3; (ii) $Mo(CO)_6$, CH_3CN/H_2O, 14% (2 steps); b) (i) PCC, CH_2Cl_2; (ii) HF, H_2O/CH_3CN; (iii) H_2, Pd/C, 49% (3 steps).

d) **Contelles *et al.*:**

The convenient carbocyclic derivative **35** was envisioned from the 1,8-nonadiene **34** for further transformation into the desired target molecule **12**. The synthesis of compound **34** started from methyl α-D glucopyranoside **17** (Scheme 4). The reaction of the lactol with benzylamine followed by treatment with allylmagnesium bromide gave an inseparable mixture of *syn*/*anti* isomers in a 3:1 ratio. The 1,2-diol was transformed into the desired olefin **34** using Garegg's protocol. The synthesis of compound **34** constituted a formal total synthesis of (+)-calystegine B_2 (**12**).[9]

Scheme 4:



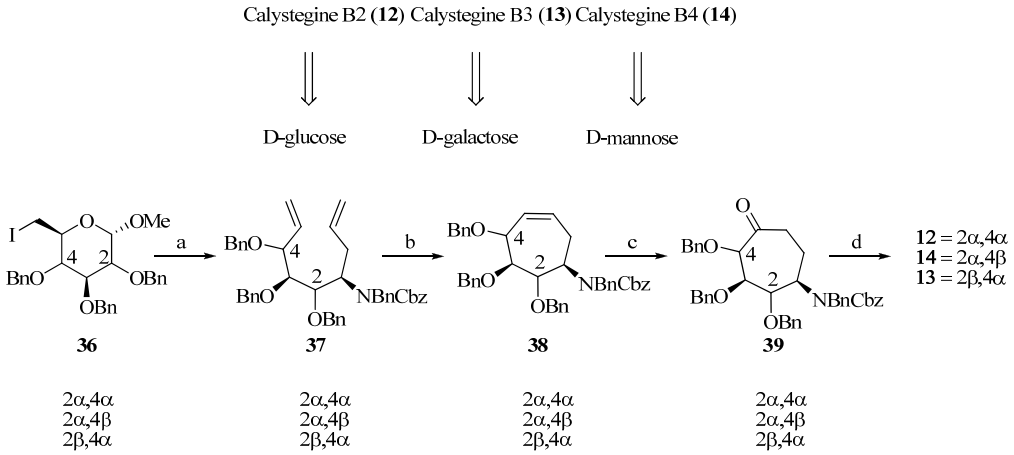
Reagents and conditions: a) $BnNH_2$, toluene, 80 °C, 2 h, 85%; b) CH_2=$CHCH_2MgBr$, Et_2O, rt, 88%; c) I_2, Ph_3P, imidazole, 15%; d) ref 10.

e) Madsen *et al.*:

Madsen et al. have reported an RCM based approach for the synthesis of calystegines B_2-B_4. The starting material for all three syntheses is the corresponding benzyl protected methyl 6-deoxy-6-iodo-α-D-glycopyranoside. Sonicating a mixture of glucopyranoside **36** and excess zinc dust in dry THF caused a reductive fragmentation to generate the 5,6-unsaturated aldehyde which was trapped *in situ* as the corresponding benzyl imine. Slow addition of allyl bromide to the mixture led to allylation of the imine to give a 5+1 mixture of amino dienes **37**. Cbz-protection of the amino group and metathesis of the protected amine gave the cycloheptene **38**. Hydroboration followed by oxidation in a one pot procedure gave a 3:1 mixture of

ketones. Major ketone isomer **39** was hydrogenated to give calystegines B_2- B_4 (Scheme 5).[10]

Scheme 5:

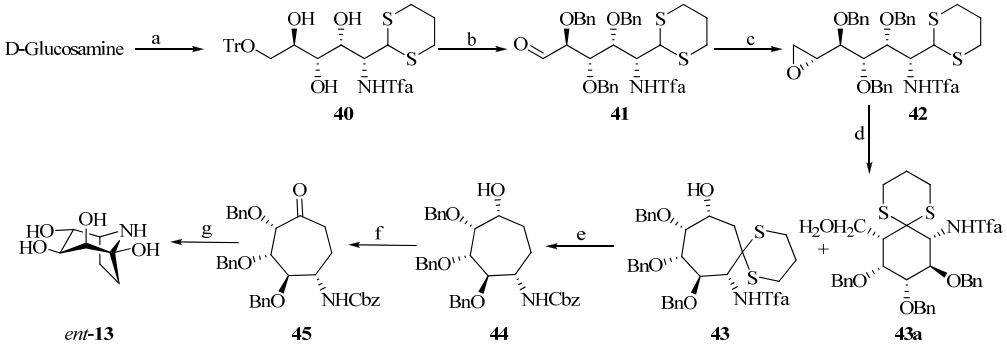


Reagents and conditions: a) (i) Zn, $BnNH_2$, CH_2=$CHCH_2Br$, THF, sonication, 40 °C; (ii) CbzCl, $KHCO_3$, EtOAc, H_2O; b) 2% Grubbs' II, CH_2Cl_2, rt; c) BH_3·THF, THF, −50 to 0 °C, then NaOH, H_2O_2, 0 °C, then Dess-Martin periodinane, CH_2Cl_2, rt; d) H_2, $Pd(OH)_2$, THF, H_2O.

f) Redlich *et al.*:

Starting from *N*-trifluoroacetyl D-glucosamine dithiane, *via* regioselective 6-*O* tritylation, per-*O*-benzylation, and de-*O*-tritylation, the *O*-Bn-*N*-Tfa derivative **40** was oxidized to aldehyde **41**. Corey-Chaykovsky epoxidation of the aldehyde followed by the intramolecular anionic cyclization of the epoxide according to the Corey-Seebach method gave a mixture of dithianes **43** and **43a**. Cleavage of the dithiane ring of compound **43** hydrogenolysis and removal of the *N*-Tfa protection followed by addition of $NaHCO_3$ and CbzCl to the reaction mixture produced the crude compound **44**. Oxidation with Dess-Martin reagent to the ketone **45** and subsequent hydrogenolysis cleaved *N*-Cbz completely. The following hydrogenolytic de-*O*-benzylation under acidic conditions led to (-)-calystegine B_3 (*ent*-**13**)(Scheme 6).[11a]

Scheme 6:



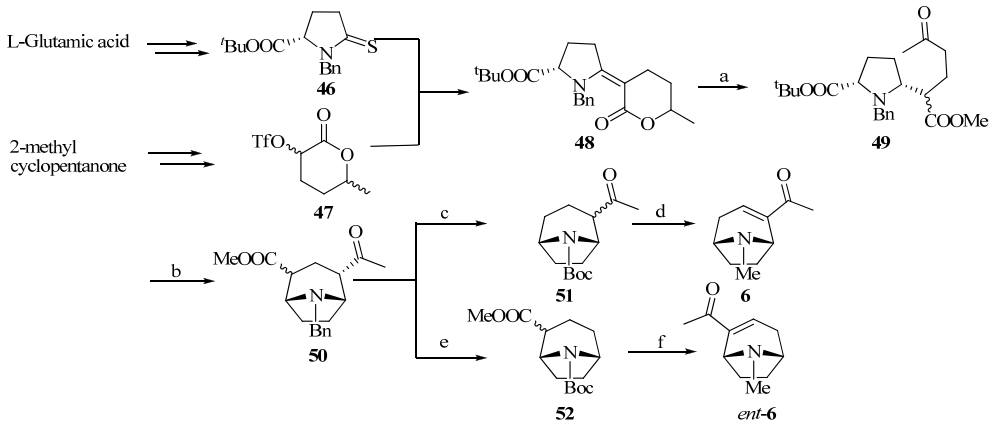
Reagents and conditions: a) (i) ref 11b,c (ii) TrCl, Py, DMAP, 95%; b) (i) BnCl, NaH, n-$Bu_4N^+I^-$, THF, 99%; (ii) MeOH, EtOAc, p-TSA, 78%; (iii) Dess–Martin reagent, 63%; c) Me_3SOI, NaH, DMSO, 61%; d) n-BuLi, THF, ~10 °C; (or) n-BuLi,THF, LiBr (1 eq), ~90 °C to ~50 °C; e) (i) Raney-Ni, EtOH, reflux; (ii) $Ba(OH)_2.8H_2O$, MeOH, water, 80 °C; (iii) CbzCl, $NaHCO_3$; f) Dess-Martin reagent, 43% for steps e and f; g) 1 atm H_2, 10% Pd/C, THF, water, rt, overnight, then 1 N HCl, 3 days, 81%.

2) Synthetic approaches based on Aminoacids:

a) Rapoport, H. *et al.:*

Rapoport *et al.*[12] described the syntheses of (±)-ferruginine (**6**) alkaloids by selective manipulation of the C2 and C4 side chains of a versatile chiro 2,4-disubstituted tropane derivative **50** (Scheme 7), with the asymmetry being introduced using L-glutamic acid for the preparation of the starting thiolactam **46**. Its alkylation with the 2-triflate δ-lactone **47**, in turn derived from 2-methylcyclopentanone, generated an *R*-thioiminium ion, which underwent the *S*-extrusion reaction producing the vinylogous carbamate **48**, further transformed to the *cis*-pyrrolidine keto acid through a sequence of steps including hydrogenation, N-rebenzylation, basic methanolysis, and final acid hydrolysis. The key 6-*endo*-*trig* iminium ion cyclization occurred with high stereoselectivity, with the acetyl group occupying an equatorial position on the six-membered ring. The divergent synthesis exploited the selective removal of the side chains at C2 or C4 through their transformation to carboxyl groups and subsequent reductive decarboxylation by photolysis of the corresponding thioxamate esters. In both cases, the introduction of the double bond was effected by *R*-selenation of the carbonyl function followed by oxidative elimination. Nitrogen-atom deprotection and subsequent methylation completed the syntheses.

Scheme 7:

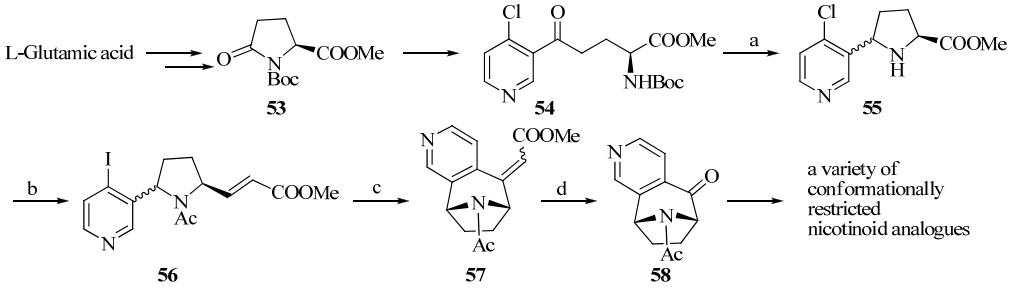


Reagents and conditions: a) (i) H_2, Pt/C; (ii) $NaHCO_3$, CH_3OH; (iii) $(COCl)_2$, DMSO; (iv) H^+, H_2O, 42% (4 steps); b) (i) $(COCl)_2$; (ii) 60 °C, 89%; c) (i) H_2, Pd/C, $(Boc)_2O$; (ii) KOH; (iii) $^iBuO_2CCl$; (iv) 2-mercaptopyridine *N*-oxide; (v) *hv*, *ter*BuSH, 74% (5 steps); d) (i) NaH; (ii) TBSCl; (iii) PhSeCl; (iv) *m*-CPBA; (v) Na_2CO_3; (vi) TFA; (vii) CH_2O, $NaBH_3CN$, 42% (7 steps); e) (i) H_2, Pd/C, $(Boc)_2O$; (ii) KHMDS; (iii) TMSCl; (iv) O_3, $(CH_3)_2S$; (v) c)(iii); (vi) c)(iv); (vii) c)(v), 60% (7 steps); f) (i) LDA; (ii) PhSeCl; (iii) $NaIO_4$; (iv) KOH; (v) $^iBuO_2CCl$, isoxazolidine; (vi) CH_3Li; (viii) TFA; (ix) CH_2O, $NaBH_3CN$, 62% (9 steps).

b) Turner, S. C. *et al.*:

The 4-chloropyridinyl ketone **54** was prepared by the regioselective addition of *ortho*-lithiated 4-chloropyridine to the pyroglutamate derivative **53**. Acidic *N*-deprotection followed by treatment with aqueous $NaHCO_3$ caused intramolecular cyclization to an imine intermediate, which was reductively converted to a *cis*/*trans* mixture of 2,5-disubstituted pyrrolidines **55**, with the major *cis* diastereomer being easily separated by a fortuitous exclusive N-protection occurring by treatment with $(Boc)_2O$ and Et_3N. Subsequent chloro-iodo exchange and side-chain extension gave the intermediate **56**, an immediate precursor for the [3.2.1] bicyclic skeleton. The construction of the pyrido[3,4-*b*]tropane framework was achieved by an intramolecular Heck cyclization to give **57** and the corresponding ketone **58**, derived by ozonolysis, could be tranformed into a wide variety of nicotine analogues (Scheme 8).[13]

Scheme 8:

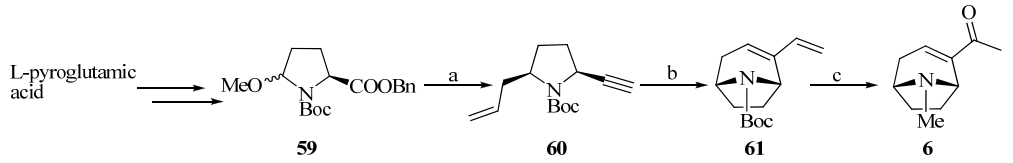


Reagents and conditions: a) (i) HCl, EtOAc; (ii) $NaHCO_3$; (iii) $NaBH_4$, CH_3COOH, 84% (3 steps); b) (i) $(Boc)_2O$, Et_3N; (ii) $CaCl_2$, $NaBH_4$; (iii) NaI, AcCl; (iv) K_2CO_3, CH_3OH; (v) $(COCl)_2$, DMSO, Et_3N; (vi) trimethyl phosphonoacetate, KHMDS, 39% (6 steps); c) $Pd(OAc)_2$, PPh_3, Et_3N, 89%; d) O_3, AcOH, $(CH_3)_2S$, 91%.

c) Aggarwal, V. K. *et al.*:

The salient feature of the approach to (+)- ferruginine (**6**) was an enyne metathesis reaction furnishing the enantiomerically pure tropane nucleus.[14] The known[15] aminal **59** was treated with BF_3 and allyltrimethylsilane to give the *cis* product as the major diastereomer. The aldehyde obtained by reduction of the benzyl ester was homologated to the required enyne **60**. Enyne metathesis reaction of **60** resulted in a clean construction of the tropane skeleton. Wacker oxidation of the exocyclic double bond of **61** produced the required methyl ketone moiety, with the remaining steps to complete the synthesis of the alkaloid (+)-ferruginine (**6**)[14] being N-Boc-deprotection and N-methylation (Scheme 9).

Scheme 9:



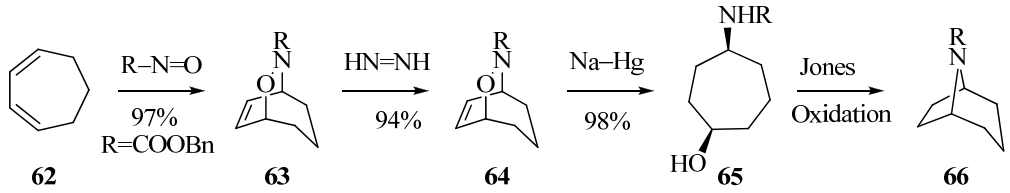
Reagents and conditions: a) (i) $BF_3.Et_2O$, allyltrimethylsilane; (ii) $LiAlH_4$, THF; (iii) Dess-Martin reagent, CH_2Cl_2, 62% (3 steps); b) (i) $CH_3COCN_2PO(OEt)_2$, K_2CO_3, CH_3OH; (ii) Grubbs' I, CH_2Cl_2, reflux, 80% (2 steps); c) (i) $PdCl_2$, $CuCl_2$, H_2O/DMF; (ii) TFA, CH_2Cl_2 then K_2CO_3; (iii) CH_2O, $NaCNBH_3$, CH_3CN, 73% (3 steps).

3) Synthetic approaches based on Cyclohepta-enes:

a) Malpass, J. R. *et al.*:

The key intermediate **5** was made from cyclohepta-1,3-diene **62** by addition of the nitroso compound formed *in situ* from benzyl *N*-hydroxycarbamate and tetramethylammonium periodate. The adduct **63** was reduced with diimide to **64** followed by reductive cleavage of the NO bond to yield **65**. Reduction with lithium tetrahydroaluminate followed by Jones oxidation provided physoperuvine **66** (Scheme 10).[15]

Scheme 10:

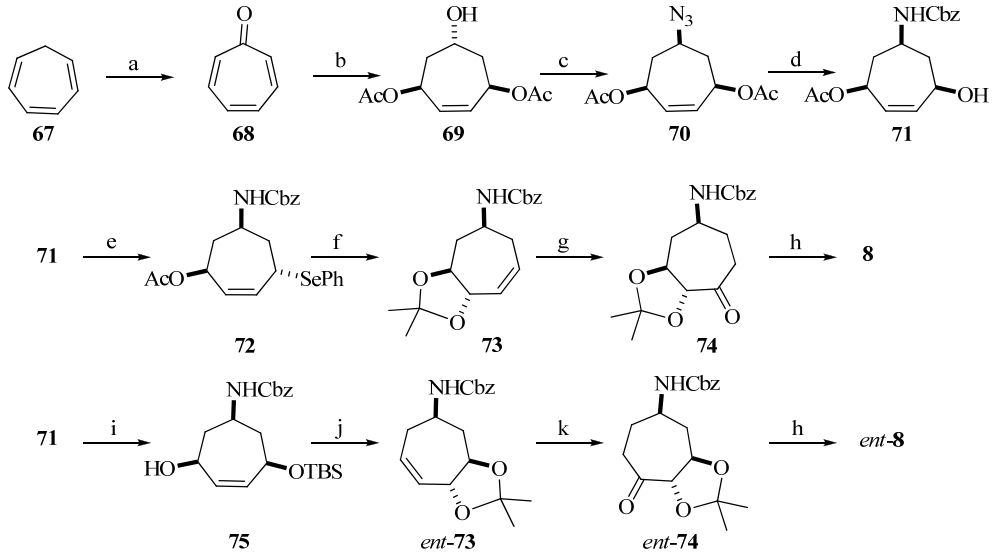


b) Johnson *et al.*:

Cycloheptatriene **67** was initially oxidized to tropone **68** utilizing the Reingold procedure. Reduction of tropone gave dienol which was subjected to Backval diacetoxylation conditions to produce the diacetoxy alcohol **69**. The treatment of the mesylate from alcohol with azide ion gave **70**. The azide was hydrogenated using Lindlar catalyst to give the primary amine which was protected as the benzyl carbamate. The diacetate was hydrolyzed to the diol and subjected to the enzyme-catalyzed transesterification to give the optically active monoacetate **71** (Scheme 11).[16]

Alcohol **71** was converted to the selenide **72** *via* mesylate. Oxidation of selenide **72** followed by the hydrolysis of the acetate provided diol which was protected as the acetonide **73**. Hydroboration followed by oxidation gave the desired ketone **74**. the benzyl carbamate was first removed by hydrogenation; the resulting amine was treated with HC1 in aqueous THF to produce the hydrochloride of calystegine A_3. On similar grounds, its enantiomer was obtained from the alcohol **71**.

Scheme 11:

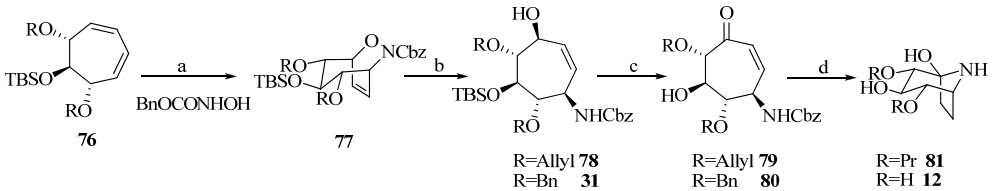


Reagents and conditions: a) (i) Ph_3COH, Ac_2O, HBF_4, 0 °C, 100%; (ii) Na_2CO_3, CH_3CN, 45 °C, 48%; b) (i) $NaBH_4$, MeOH, –15 °C, 98%; (ii) $Pd(OAc)_2$, MnO_2, benzoquinone, AcOH, LiOAc, 25 °C, 84%; c) (i) MsCl, Et_3N, CH_2Cl_2, 0 °C, 100%; (ii) NaN_3, DMF, 75 °C, 82%; d) (i) Lindlar's catalyst, H_2, EtOH, 12 h, 98%; (ii) ClCOOBn, EtOAc, Na_2CO_3, H_2O, 98%; (iii) K_2CO_3, MeOH, 93%; (iv) Amano P-30 lipase isopropenyl acetate, 50 °C, 91%; e) (i) MsCl, Et_3N, CH_2Cl_2, 0 °C, 100%; (ii) Se_2Ph_2, $NaBH_4$, 0 °C, 85%; f) (i) 30% H_2O_2, CH_2Cl_2, THF, –78 °C to 0 °C, 90%; (ii) K_2CO_3, MeOH, 100%; (iii) 2,2-DMP, acetone, *p*-TSA, 95%; g) (i) $ThexylBH_2$, Et_2O, –30 °C to –15 °C; (ii) 30% H_2O_2, 2N NaOH; (iii) PCC, NaOAc, 4Å mol.sieves, CH_2Cl_2, 34%; h) (i) H_2, Pd/C, EtOAc; (ii) HCl, THF, H_2O; (iii) NaOH, D_2O, pH > 11.0; i) (i) TBSCl, DMF, Imidazole, 99%; (ii) NaCN, MeOH, 95%; j) (i) MsCl, Et_3N; (ii) $NaBH_4$, Ph_2Se_2; (iii) H_2O_2, CH_2Cl_2, THF; (iv) HF, CH_3CN; (v) acetone, Amberlyst 15, 99%; k) (i) BH_3.DMS, Et_2O, –20 °C to 0 °C; (ii) 30% H_2O_2, 2N NaOH; (iii) PCC, 4Å mol.sieves, CH_2Cl_2, 27% (3 steps).

c) Soulie *et al.*:

Benzyloxynitroso carbamate **77** was prepared *in situ* by oxidation of the corresponding hydroxamic acid[17] with subsequent smooth cycloaddition to the diene. Sequential reductive cleavage of the N-O bond, oxidation, desilylation and finally hydrogenation yielded the tropane after 4 days (Scheme 12).

Scheme 12:



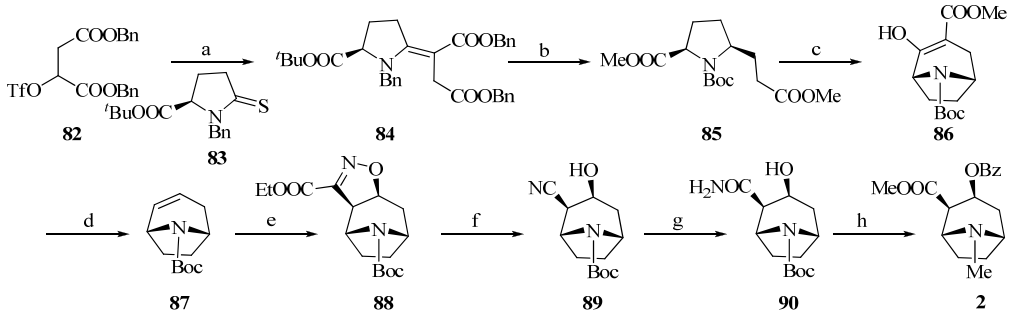
Reagents and conditions: a) $(n\text{-}C_4H_9)_4N,IO_4$, 0 °C, CH_2Cl_2, 80%; b) $Mo(CO)_6$, MeCN-H_2O (9:1), reflux, 91%; c) (i) PCC, CH_2Cl_2, 88%; (ii) MeCN-HF (95:5), 85%; d) H_2, Pd/C 10%, MeOH, 76%.

4) Synthetic approaches based on Hydroxy acids:

a) Rapoport, H. *et al.*:

Alkylation of the triflate **82** of dibenzyl D,L-malate with the (*R*)-thiolactam **83**, followed by sulfur extrusion, gave the vinylogous carbamate **84** as a mixture of isomers, which was directly reduced. A sequence of high yielding steps led to the *N*-protected diester **85**, which underwent Dieckmann cyclization producing the bicyclic derivative **86** which was converted to (1*R*,5*S*)-tropene **87** by the base-induced reaction of the tosylhydrazone derivative. The 1,3- dipolar cycloaddition between the *N*-Boc-nortropene and ethoxy carbonylformonitrile *N*-oxide afforded the expected cycloadduct **88**. Further functional group transformations yielded the enantiopure (–)-cocaine **2** in 8.5% yield over 16 steps (Scheme 13).[18]

Scheme 13:

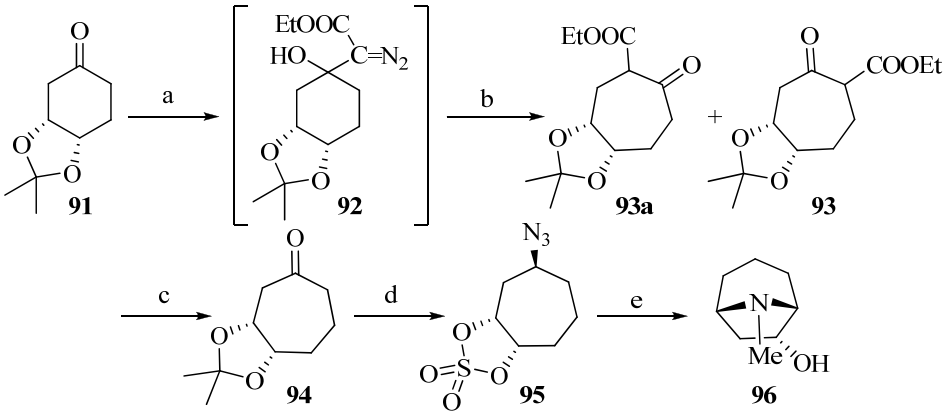


Reagents and conditions: a) (i) Ph_3P, CH_2Cl_2; (ii) *N*-methylpiperidine, 76% (2 steps); b) (i) NH_4HCO_2, Pd/C, CH_3OH; (ii) CH_3OH, HCl; (iii) $(Boc)_2O$, 77% (3 steps); c) KHMDS, THF, −78 °C, 85%; d) (i) NaI, pyridine, reflux; (ii) *p*-$TsNHNH_2$, (iii) NaH, 59% (3 steps); e) $Cl(C{=}NOH)CO_2Et$, Et_3N, 78%; f) (i) NaOH; (ii) H_3O^+; (iii) 110 °C, 76% (3 steps); g) Na_2CO_3, H_2O_2, 94%; h) (i) $(PhCO)_2O$, DMAP; (ii) TFA; (iii) CH_2O, $NaBH_3CN$; (iv) $NaNO_2$, $AcOH/Ac_2O$; (v) CH_2N_2, 57% (5 steps).

b) Pollini, G. P. *et al.*:

The reaction of the optically active cyclohexanone derivative **91**, prepared in a five-step sequence from D-quinic acid, with ethyl diazoacetate furnished the *R*-diazo intermediate **92**, which was then subjected to pyrolysis to yield a 3:7 regioisomeric mixture of the cycloheptanone derivatives **93** and **93a** (Scheme 14). Hydrogenolytic decarbalkoxylation of the corresponding benzyl ester and a series of stereocontrolled functional group manipulations yielded the chiral azido cyclic sulfate **95**, which, after a reductive step, underwent the expected intramolecular displacement reaction, giving rise to the optically active 6-*endo*-hydroxy tropane **96** (Scheme 14).[19]

Scheme 14:



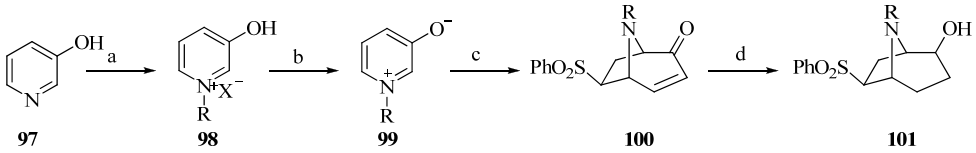
Reagents and conditions: a) N_2CHCO_2Et, LDA, THF; b) benzene reflux; c) (i) BnOH, DMAP, toluene reflux; (ii) H_2, Pd/C; (iii) DME reflux; d) (i) $NaBH_4$; (ii) MsCl, Et_3N; (iii) NaN_3, DMF; (iv) CH_3OH, HCl; (v) $SOCl_2$, Et_3N then $RuCl_3$, $NaIO_4$; e) (i) H_2, Pd/C, dioxane/H_2O/H_2SO_4; (ii) ClCOOEt, K_2CO_3; (iii) $LiAlH_4$, THF, reflux.

5) Synthetic approaches based on pyridines:

a) Ducrot, P.-H. *et al.*:

The tropane skeleton was synthesized by the dipolar addition of 3-oxopyridinium betaines to activated olefins like phenyl-vinyl sulfone (Scheme 15).[20]

Scheme 15:



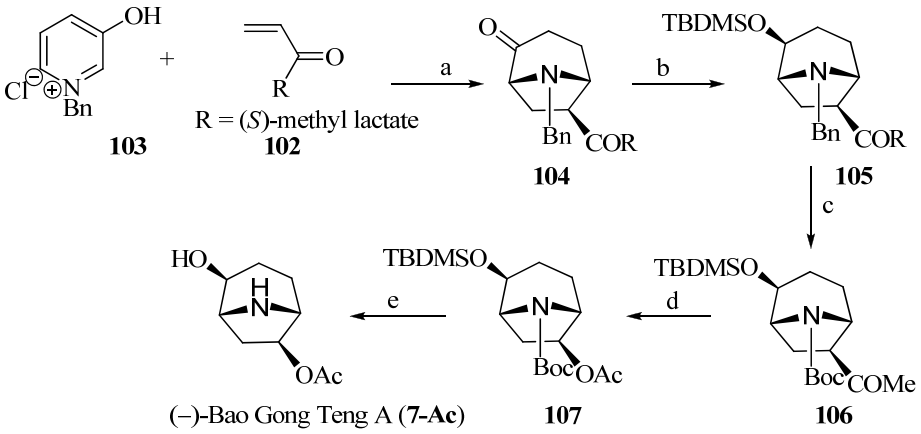
Reagents and conditions: a) BnBr, PrOH, reflux; b) MeONa, MeOH; c) CH_2=$CHSO_2Ph$, THF, reflux, 15%; d) (i) DIBAH, THF, 70%; (ii) H_2, Pd/C, EtOH, 80%.

b) Charlton, J. L. *et al.*:

Methyl (*S*)-lactate was employed as an inexpensive chiral auxiliary in the asymmetric synthesis of (−)-Bao Gong Teng A (**7**) (Scheme 16). The enantiospecific synthesis took advantage of the regio and diastereoselective 1,3-dipolar cycloaddition between the acrylate **102** and the betaine of *N*-benzyl-3-hydroxypyridinium chloride **103**. Hydrogenation of the adduct to the ketone **104** followed by its reduction, using

the bulky lithium tri-*tert*-butoxyaluminum hydride, gave predominantly the desired 2-*exo*-hydroxy compound easily protected as TBDMS derivative **105**. Debenzylation with simultaneous N-Boc protection was performed prior to transform the carboxy group into a methyl ketone. In the next step of the synthesis, the Bayer-Villiger oxidation of **106** gave the 6-*exo*-acetoxy derivative **107**, which by acid promoted removal of both protective groups, produced compound (–)-Bao Gong Teng **7**.[21]

Scheme 16:



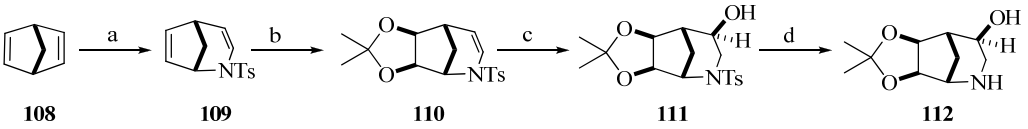
Reagents and conditions: a) (i) Et_3N, EtOAc, rt for 10 days; (ii) H_2, Pd/C, 61% over two steps, 65% *de*; b) (i) $LiAlH(O^tBu)_3$, THF; (ii) TBDMSOTf, CH_2Cl_2, 60%; c) (i) H_2, Pd/C, $(Boc)_2O$; (ii) KOH; (iii) $(COCl)_2$; (iv) Me_2CuLi, 77% over four steps; d) *m*CPBA, 52%; e) HCl/EtOH, 61%.

6) Miscellaneous methods:

a) Bergmeier *et al.*:

The reaction of tosyl azide with norbornadiene **108**, yielded the desired *N*-tosyl-2-azabicyclo[3.2.1]octa-3,6-diene **109** in good yield. Chemoselective dihydroxylation of the desired double bond by AD-mix α or β gave the racemic *exo* diol in excellent yield. The conversion of the diol as its acetonide **110** immediately after isolation and subsequent treatment with 9-BBN followed by an oxidative workup yielded the desired compound, **111**, albeit in moderate yields. The final step in this synthesis is the removal of the *N*-tosyl protecting group using the relatively mild photolytic N-detosylation. After optimizing irradiation time, compound **112** was isolated in consistently good yields (Scheme 17).[22]

Scheme 17:

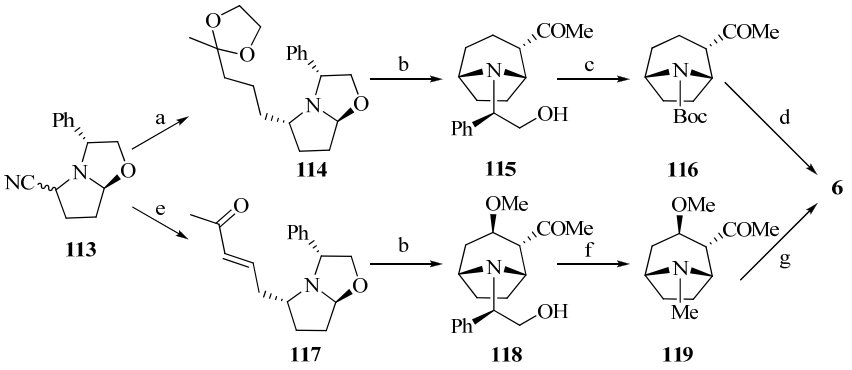


Reagents and conditions: a) TsN_3, C_6H_6, rt, 3 days, 66%; b) (i) OsO_4/NMO, 54% (or) AD-mix, 93%; (ii) 2,2-DMP, *p*-TSA, $MgSO_4$, 93%; c) 9-BBN, 54%; d) *hv*, $NaBH_4$, EtOH, H_2O, *p*-dimethoxybenzene, 86%.

b) Husson *et al.*:

A synthesis of (+)-ferruginine **6** using (*R*)-phenylglycinol as a chiral auxiliary for the construction of the 8-azabicyclo[3.2.1]octane nucleus has been described (Scheme 18).[23] The starting chiral material, 2-cyano-5-oxazolopyrrolidine **113**, was easily prepared in one step from (*R*)-phenylglycinol, dimethoxytetrahydrofuran, and potassium cyanide. Thus, the tropane derivatives **115** and **118** were stereoselectively obtained from **114** and **117** *via* Mannich-type cyclization. Further simple functional group transformations materialized into the alkaloid **6**.

Scheme 18:



Reagents and conditions: a) (i) Li/NH_3, (ii) LDA, $Br(CH_2)_3C(OCH_2$- $CH_2O)$ CH_3, 28% (3 steps); b) H_2SO_4, CH_3OH, 60 °C, 66%; c) H_2, Pd/C, $(Boc)_2O$, 85%; d) ref 11; e) (i) LDA, $BrCH_2CH(OEt)_2$; (ii) Li/NH_3; (iii) dil.HCl; (iv) $(MeO)_2POCH_2COCH_3$, DIPEA, 49% (4 steps); f) H_2, $Pd(OH)_2$, CH_2O, 73%; g) TsOH, benzene at reflux, 68%.

Conclusions:

Given the diverse range of activities displayed by molecules based on the tropane framework, it is reasonable to expect the discovery of new and interesting properties displayed by analogues based on this framework. Therefore, it is not

surprising that tropane-based compounds continue to attract the attention of researchers calling for the development of new synthetic methodologies to reproduce these natural products and synthesize their analogues stereoselectively, improving the existing methods. Enantioselective preparation, however, poses high demands, and the first synthetic approaches went through many steps, which resulted in a low overall yield. This prompted us to design a reliable approach for the nortropane skeleton wherein the key features comprise a highly stereoselective zinc mediated triple domino reaction[24] for the construction of the pyrrolidine ring and an RCM[25] for the construction of the bicyclic ring.

Present Work

Synthetic or natural aza-sugars have shown promise as a therapeutic approach to a variety of disease states by acting as transition state mimics to sugar processing enzymes. In the last 10 years, a large number of nitrogen-containing polyhydroxylated heterocyclic compounds have been isolated from plants. These natural products are competitive inhibitors of various glycosidases. The most efficient compounds are used to treat various diseases including diabetes, cancer, and viral infections. Furthermore, these compounds exhibit additional activities, such as immunomodulatory properties and inhibition of glycolipid synthesis. Among these metabolites, a new class of nortropane polyhydroxylated alkaloids, called calystegines[26] have been isolated which have been suggested to be nutritional mediators in the plant rhizosphere (plant-bacteria relationship). They also possess glycosidase inhibiting properties and an allelopathic activity.

The major analytical methods for structure elucidation of calystegines were high resolution mass spectrometry (MS) and proton and carbon nuclear magnetic resonance (NMR), including extensive homonuclear and heteronuclear decoupling and two-dimensional techniques. Nuclear Overhauser effect (NOE) enhancements, heteronuclear multiple quantum coherence (HMQC) and heteronuclear multiple bond coherence (HMBC) experiments were evaluated for the determination of interconnectivities and the stereochemistry of the alkaloids. Circular dichroism (CD) was necessary to determine the absolute configuration of the molecules.[26] The calystegines are well characterized by a [3.2.1]bicyclic skeleton endowed with a nitrogen at the bridge head position with hydroxyl group at the bridge position.

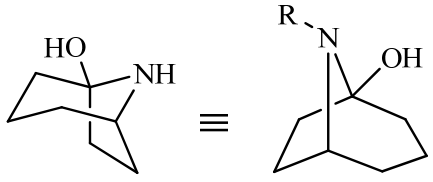


Figure 4: Basic skeleton of the calystegines.

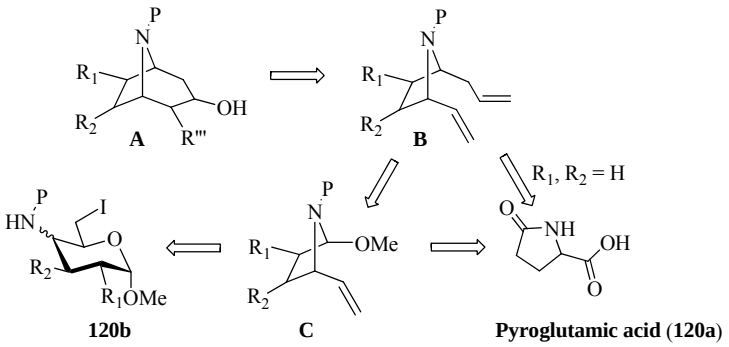
Several possible isomers of the calystegines are possible with different position and stereochemistry of the hydroxyl groups. These are classified as

nortropane di/trihydroxy triols and were found to be showing prominent glycosidase activity. Based on the predominant occurrence of the both the calystegines and the nortropane triols, we thought of synthesizing a hydroxyl analogue of the calystegine skeleton

Although the synthesis of functionalized bicyclo[3.2.1]octanes has been reported, the procedures are relatively long and low yielding. Moreover, the unusual structures and biological properties and a relatively lengthy processes reported earlier for their synthesis instigated us to take up this synthesis.

Retrosynthetic approach:

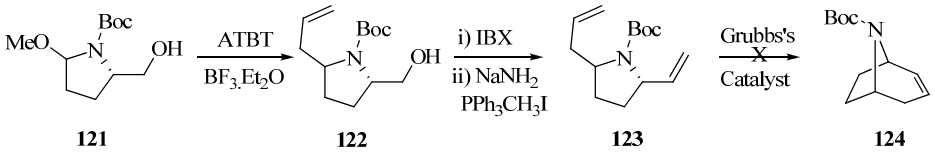
The bicyclic skeleton **A** can be envisaged from the diene **B** by way of the ring closing metathesis. The diene can be obtained from the aminal **C** which can be accomplished either from pyroglutamic acid **120a** or the derivative of D-Glucose **120b** (Scheme 19).



Scheme 19: Retrosynthetic approach to the bicyclic skeleton

Pyroglutamate approach:

A short synthesis of the nortropane alkaloid has been attempted starting from the known compound **121** (derived from pyroglutamic acid **120a**)[27] where the Lewis acid mediated displacement of the OMe group[28] by the allyl group afforded the alcohol **122**. Oxidation of the alcohol **122** followed by one carbon Wittig olefination gave the required diene **123** for RCM.[25] Unfortunately, olefin metathesis of the diene **123** to the cyclic olefin **124** didn't work and the starting material was recovered (Scheme 20).



121 **122** **123** **124**

Scheme 20: Synthesis based on pyroglutamic acid approach.

Being unsuccessful in the construction of the bicyclic skeleton using the pyroglutamic acid, we shifted our focus on the sugar based approach for the synthesis.

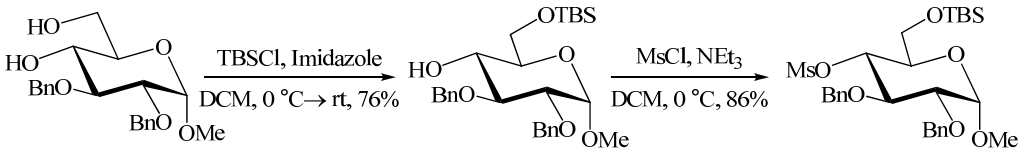
Sugar based approach:

Introduction of the amine functionality:

The introduction of the amine group into the carbocycle was envisioned *via* displacement of the mesylate by the azide. Later on, reduction of the azide would form the required amine suitably placed at the C-4 position.

The synthesis commenced with the known diol **125**. The diol was monosilylated using TBDMSCl and triethylamine as the base to afford the silyl ether **126**. The appearance of 2 singlets at δ 0.06 and 0.89 corresponding to six and nine protons respectively in the ^{1}H NMR spectrum and quartets at −5.6 and 25.6 ppm corresponding to the two methyls and the tertiary butyl group respectively in the ^{13}C NMR spectrum confirmed the formation of the silyl ether **126**. The other analytical data like IR, MASS were in total agreement with the assigned structure.

The silyl ether was converted into the mesylate **127** using MsCl and triethylamine as the base. The crude mesylate **127** was used as such for the next step without further purification (Scheme 21).

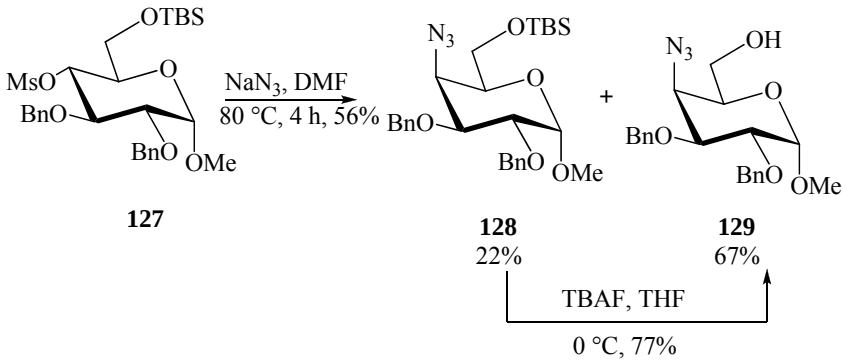


125 **126** **127**

Scheme 21:

The mesylate **127** was treated with sodium azide and heated at 80 °C in DMF to afford the silyl azide **128** as well as the azidoalcohol **129** obtained by the desilylation of the silyl azide in the reaction conditions itself. The ^{1}H NMR spectrum of **128** showed the presence of the peaks at δ 0.05, 0.06 and 0.88 which can be attributed to the TBDMS group. The ^{13}C NMR spectrum also showed the presence of peaks at −5.8 (q), 18.0 (s), 25.6 (q) ppm corresponding to the silyl group. The same set of peaks were conspicuous by their absence in the ^{1}H NMR spectrum of **129**. The rest of the signals in the ^{1}H and ^{13}C NMR spectrum were almost similar to that of the silyl azide **128**. Further, the IR spectrum of both the silanes **128** and **129** showed an absorption in the range 2106-2108 cm^{-1} corresponding to the azido group. Other analytical data like MASS and elemental analysis validated with the assigned structures.

The silyl azide **128** was also converted into the azidoalcohol **129** using TBAF in THF. The spectral data of the azidoalcohol was compatible with that of the alcohol obtained in the displacement of the mesyl group to the azide (Scheme 22).



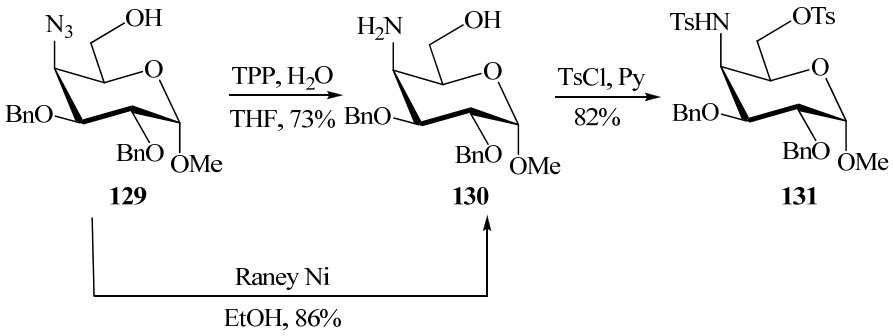
Scheme 22: Formation of the azidoalcohol

Reduction of the amine:

Now, the stage was set for the reduction of the azide **129** to the amine. We employed the Staudinger reaction[29] for this purpose which resulted in the formation of the desired amine **130**. The crude aminoalcohol was used as such for the next step, i.e., it was ditosylated to **131** using tosyl chloride and pyridine as the base. The ^{1}H NMR showed two singlets at δ 2.31 and 2.45 corresponding to the methyl group and 8 additional protons as doublets in the downfield region at δ 7.07, 7.33, 7.39 and 7.74

accounting for 2 protons each were observed which can be attributed to the aromatic region of the tosyl group. Also the ^{13}C NMR showed quartets at 21.4 (q), 21.6 (q) ppm corresponding to the methyl group of the tosyl moiety. Other analytical data proved the structure beyond doubt (Scheme 23).

However, the yields were not satisfactory and the reaction was not reproducible when applied to large scale preparation of the ditosyl derivative. Hence we thought of reducing the azide to amine using Raney Nickel in hydrogen atmosphere in methanol. The reaction was smooth in this case, the reduction occurred within 15 min with the benzyl group unaffected in contrast to the reduction by TPP and water wherein the reaction took 4 h for completion in refluxing conditions and involved the unfavourable formation of TPPO in the reaction mixture. Use of Raney nickel helped us to skip this and the aminoalcohol could just be filtered through celite pad and used for the next step without any workup. Besides, the yields of the reduction using Raney nickel were comparatively better than that of the reduction involving the use of triphenylphosphine.



Scheme 23: Reduction of the Amine.

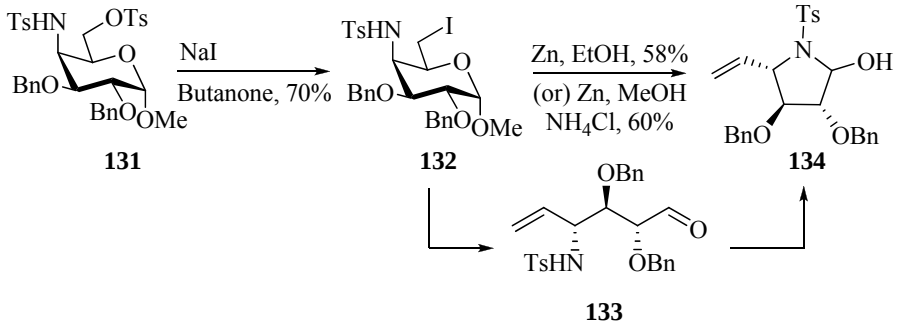
Formation of the pyrrolidine ring:

Having the required amine in hand, now the stage was set for the formation of the pyrrolidine ring by employing a zinc mediated triple domino reaction reaction of the iodopyranoside to the aptly substituted pyrrolidine.

The ditosylate **131** was converted to the iodopyranoside **132** by treating with sodium iodide in refluxing butanone for 4 h with sodium iodide being added in 4 portions in an interval of 1 h each. The same reaction was attempted in acetone as the solvent but it resulted in longer reaction times and less conversion to the desired

iodide (<20%). The apparent disappearance of a singlet at δ 2.45 and 4 aromatic protons in the downfield region at δ 7.33, 7.39 corresponding to one tosyl group in the ^{1}H NMR spectrum proved the displacement of the tosylate. Further, the absence of quartet at 21.4 ppm in the ^{13}C NMR spectrum and other analytical data clearly proved the structure.

In the first stage, methyl *ω*-deoxy-*ω*-iodo glycosides undergoes reductive elimination with zinc to produce a terminal double bond. Zinc plays a dual role by both promoting the reductive elimination and activating the alkyl halide. An amino group can be introduced by trapping the intermediate aldehyde as an imine. The zinc mediated fragmentation of the iodopyranoside[24] was initially attempted using zinc powder and refluxing in ethanol for 24 h which led to the initial formation of the aldehyde (as seen as a polar spot in TLC) which later disappeared into the faster moving spot i.e., the hemiaminal **134**. When a new stereogenic center is generated, moderate to excellent stereocontrol is generally observed. In our case the reaction proceeded with excellent stereoselectivity yielding only one diastereomer as proved by the NMR spectra of the aminal **135** derived from **134**. The ^{1}H NMR of **134** showed the absence of doublet of the anomeric proton and the presence of a multiplet at a relatively upfield region δ 3.95-4.21. The ^{13}C NMR revealed the absence of doublet at 105 ppm and a new doublet of the hemiaminal carbon of the pyrrolidine ring at 84.6 ppm. Other analytical data were in total agreement with the assigned structure (Scheme 24).

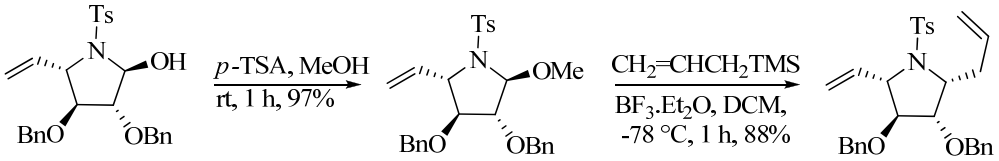


Scheme 24: Zinc mediated fragmentation.

Formation of the diene:

The hemiaminal was converted into the aminal **135** using methanol and catalytic *p*-TSA. The ^{1}H NMR spectrum showed the presence of a new singlet at δ 3.42 integrating for 3 protons corresponding to the OMe. The quartet at 55.5 ppm in the ^{13}C NMR spectrum further confirmed the formation of the aminal. The longer reaction times prompted us to think of an alternative for the fragmentation reaction. The same reaction was performed in methanol using zinc powder and a catalytic amount of ammonium chloride to afford the hemiaminal in one step whose analytical data matched with the one prepared by the previous method. Also, both the reactions led to the exclusive formation of a single diastereomer as is evident from the ^{1}H NMR and ^{13}C NMR spectra.

The aminal **135** was converted into the desired diene by treatment with allyltrimethylsilane in DCM in the presence of the Lewis acid $BF_3.Et_2O$. The diene formation was conspicuous by the presence of an additional proton at δ 5.00 and 5.04 corresponding to the terminal olefinic protons. Also, the internal olefinic protons resonated at δ 5.60 in the ^{1}H NMR spectrum. The ^{13}C NMR spectrum showed additional doublets at 134.7 and triplets at 118.1 ppm and the absence of peak at 55.4 ppm corresponding to the OMe group (Scheme 25). The allylation resulted in 90% diastereoselectivity in favor of *syn* isomer as evident in the ^{1}H NMR. Allylation was also attempted using allyltributyltin wherein no reaction was observed at −78 °C and the starting material was decomposed when the reaction mixture was gradually warmed to room temperature.



Scheme 25:

NOESY spectrum of 136:

The NOESY spectra of the diene **136** showed strong n*O*e interactions amongst the set of H-2 and H-3 protons and the set of H-2 and H-5 protons confirming the syn

orientation of the substituents. Besides, the absence of any interactions between the H-4 and any of the ring proton further confirmed the stereochemistry of **136** (Figure 5).

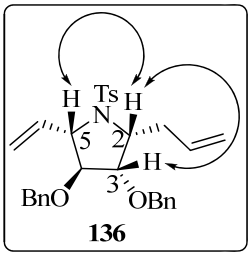
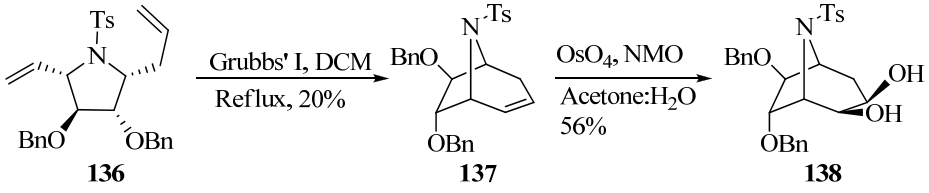


Figure 5: n*O*e observations for the diene **136**.

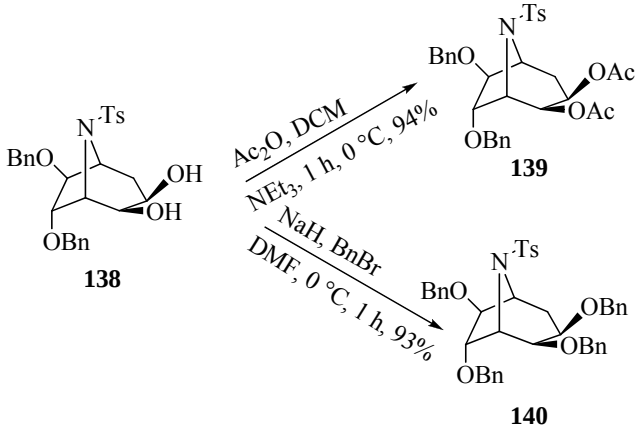
Having the diene in hand, the next task was the construction of the bicyclic framework using the ring closing metathesis. RCM[25] was performed using Grubbs' I catalyst in refluxing DCM to afford the bicyclic olefin **137**. The reaction was also attempted using Grubbs' II catalyst in refluxing benzene as the solvent, which however resulted in the formation of the undesired dimer rather than the required bicyclic olefin. The ^{1}H NMR spectrum showed the appearance of two internal olefinic protons at δ 5.58 as dt and 5.80-5.83 as multiplet. Also the vinylic protons were shifted from δ 2.42-2.90 to relatively upfield region (δ 2.17-2.36). Further the ^{13}C NMR spectrum showed the presence of two doublets at 129.2 ppm. There was an upfield shift of the triplet corresponding to the vinylic carbon from 37.2 to 25.1 ppm. All other analytical data were in full agreement with the assigned structure (Scheme 26).



Scheme 26:

However yield of the olefin was rather poor even though several attempts have been made to improvize the yield like addition of titanium isopropoxide and refluxing the reaction mixture for one hour prior to the addition of the catalyst. Also extensive degassing of the solvents prior to the reaction did not give any satisfactory yield. Since this is the penultimate step, much emphasis is not given to the yield of the core olefin.

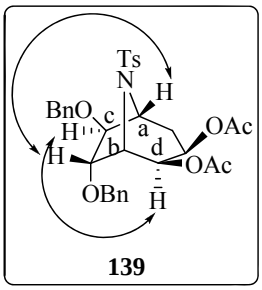
The olefin was dihydroxylated to the diol **138** using catalytic OsO_4 and NMMO as the cooxidant. The disappearance of the signals corresponding to the olefinic protons and the appearance of two new methine protons at δ 3.60-3.62 in the ^{1}H NMR spectrum confirmed the dihydroxylation. Doublets appeared at 64.6 and 64.8 ppm corresponding to the methine carbons in the ^{13}C NMR spectrum. The IR spectrum of the diol showed strong absorption peaks at 3400 cm^{-1} corresponding to the hydroxyl group. The diol was converted to its acetate to confirm the stereochemistry at the newly formed centres. Accordingly upon treatment with acetic anhydride and triethylamine as the base, the diol afforded diacetate **139**. Two additional singlets integrating for three protons each at δ 2.03 and 2.17 corresponding to the acetate group in the ^{1}H NMR spectrum and quartets at 20.9 and 21.1 corresponding to the methyls of acetate group were observed in the ^{13}C NMR spectrum. The carbonyl carbon of the acetate groups resonated at 169.7 and 170.6 ppm in the ^{13}C NMR spectrum. Further the presence of a strong absorption peak at 1724 cm^{-1} corresponding to the carbonyl group confirmed the structure of the diacetate (Scheme 27).



Scheme 27:

NOESY spectrum of 139:

The COSY and NOESY spectra of the diacetate **139** demonstrated that the isomer formed is the β-diol based on a set of complete cross peaks and a strong nOe interactions amongst the H-a and H-b protons and that of H-c and H-d protons (Figure 6).



139

Figure 6: n*O*e observations for the diacetate **139**

Desulphonation of 138:

Having the bicyclic frame in hand, final desulfonation and debenzylation would accomplish the desired nortropane skeleton. Several efforts to detosylate the amine failed and resulted in either complex reaction mixtures or the decomposition of the starting material (Table 1).

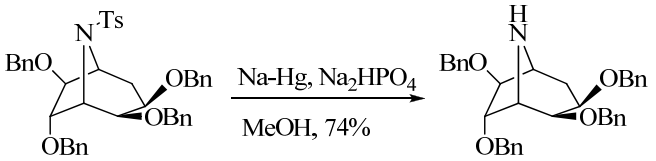
S.No.	Reaction conditions	Results
1	Red-Al, THF, -78 °C	Starting material recovered
2	TBAF, THF, 0 °C	Starting material recovered
3	Na, NH_3, THF, -78 °C	Decomposition of starting material
4	Li, NH_3, THF, -78 °C	Decomposition of starting material
5	Li, Naphthalene, -78 °C	Decomposition of starting material
6	I_2, MeOH, rt	Starting material recovered
7	Na, MeOH, rt	Starting material recovered
8	Mg, MeOH, reflux	Starting material recovered

Table 1: Different conditions employed

Based on the assumption that the free hydroxyl group might be the reason for the complex reactions, the diol was protected as its tetrabenzyl derivative **140** using benzyl bromide and sodium hydride as the base. The ^{1}H NMR spectrum showed additional 10 protons in the aromatic region at δ 7.13-7.46 corresponding to the two benzyl groups. The other analytical data were in total agreement with the assigned structure (Scheme 27).

Desulphonation of 140:

Detosylation of **140** was effected successfully by using sodium-amalgam[30] in buffered methanol which brought about 60% conversion to the amine (Scheme 28).

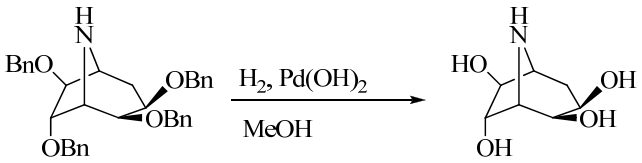


140 **141**

Scheme 28: Desulfonation of **140**.

The absence of the 4 aromatic protons of the tosyl group in the downfield region at δ 7.06 and 7.80 and absence of a singlet at δ 2.34 corresponding to the methyl group in the ^{1}H NMR spectrum and the corresponding absence of quartet at 21.5 ppm in the ^{13}C NMR spectrum confirmed the desulphonation. All other analytical data were in accordance with the structure.

The final debenzylation of **141** would provide the desired hydroxyl analogue **142** of the class of nortropane alkaloids. Further, the synthesis of Scopoline could be devised from the olefin **137** by *via* iodoetherification and dehalogenation (Scheme 29).



141 **142**

Scheme 29:

Conclusions:

Herein, we report the facile synthesis of polyhydroxylated azabicyclo[3.2.1]octane that can be selectively functionalized. A reliable and convenient method has been demonstrated for the construction of the nortropane alkaloid wherein the key steps are the zinc-mediated triple domino reaction and the ring closing metathesis.

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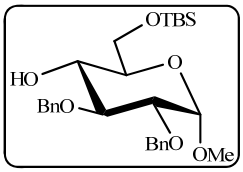
Experimental

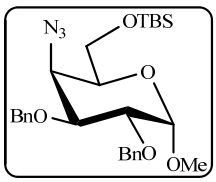
Methyl 2,3-*O*-dibenzyl 6-*O*-*tert*-butyldimethylsilyl-α-D-glucopyranose (126)



To a solution of **125** (0.5 g, 1.34 mmol) in DCM (5 mL) at 0°C was added triethylamine (0.22 mL, 1.6 mmol), DMAP (catalytic) and stirred for 15 min. TBSCl (0.22 g, 1.6 mmol) was added at 0 °C and stirred further for 1 h. The reaction mixture was extracted with DCM. The combined organic extracts were washed with brine, dried (Na_2SO_4), concentrated and the resulting crude product was purified by column chromatography (25% ethyl acetate in petroleum ether) to afford silyl ether **126** (0.5 g, 77%) as white syrup.

Mol. Formula	: $C_{27}H_{40}O_6Si$
$[\alpha]_D$	: +30.9 (*c* 4.5, $CHCl_3$).
IR ($CHCl_3$) $\tilde{\nu}$	: 3481, 2929, 1457, 1362, 1217, 1055, 837, 757, 667 cm^{-1}.
^{1}H NMR ($CDCl_3$, 200 MHz)	: δ 0.06 (s, 6H), 0.89 (s, 9H), 2.56 (d, *J* = 1.6 Hz, 1H), 3.37 (s, 3H), 3.47 (dd, *J* = 3.5, 9.8 Hz, 1H), 3.51-3.60 (m, 2H), 3.58 (d, *J* = 4.3, 9.4 Hz, 1H), 3.74-3.83 (m, 1H), 3.77 (d, *J* = 10.9 Hz, 1H), 3.81 (d, *J* = 10.6 Hz, 1H), 4.59 (d, *J* = 3.5 Hz, 1H), 4.64 (d, *J* = 12.1 Hz, 1H), 4.75 (d, *J* = 11.3 Hz, 1H), 4.77 (d, *J* = 11.7 Hz, 1H), 4.97 (d, *J* = 11.3 Hz, 1H), 7.27-7.39 (m, 10H) ppm.
^{13}C NMR ($CDCl_3$, 50 MHz)	: δ –5.6 (q, 2C), 18.0 (s), 25.6 (q, 3C), 54.6 (q), 63.3 (t), 71.0 (d), 71.1 (d), 72.6 (t), 74.9 (t), 79.6 (d), 81.2 (d), 97.7 (d), 127.2 (d), 127.4 (d), 127.5 (d, 4C), 128.0 (d, 4C), 138.0 (s), 138.7 (s) ppm.
ESI-MS (*m/z*)	: 511.4 $[M+Na]^+$.
Elemental Analysis	Calcd.: C, 66.36; H, 8.25. Found: C, 66.26; H, 8.15.

Methyl 4-deoxy-4-azido 2,3-*O*-dibenzyl 6-*O*-*tert*-butyldimethylsilyl-*α*-D-glucopyranose (128)



At 0 °C, triethylamine (0.17 mL, 1.23 mmol) was added to a solution of the silyl ether **126** (0.5 g, 1.02 mmol) in DCM and stirred for 30 min. MsCl (0.08 mL, 1.02 mmol) was added at 0 °C and stirred for 30 min. The reaction mixture was extracted with DCM. The combined organic extracts were washed with brine, dried (Na_2SO_4), concentrated and the resulting crude product **127** (0.5 g, 86%) was used as such for the next step without purification.

To a solution of mesylate **127** (1 g, 1.76 mmol) in dry DMF (10 mL) was added sodium azide (0.57 g, 8.83 mmol) and the reaction mixture was heated at 80 °C for 4 h. The reaction mixture was diluted with water and extracted with ethyl acetate. The combined organic extracts were washed with brine, dried (Na_2SO_4), concentrated and the resulting crude product was purified by column chromatography (10% ethyl acetate in petroleum ether) and (40% ethyl acetate in petroleum ether) to afford silyl azide **128** (0.2 g, 22%) as white syrup and azido alcohol **129** (0.47 g, 67%) as colorless oil respectively.

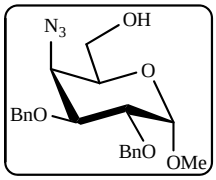
Mol. Formula	: $C_{27}H_{39}N_3O_5Si$
$[\alpha]_D$	: +10.7 (*c* 3.0, $CHCl_3$).
IR ($CHCl_3$) $\tilde{\nu}$	: 2930, 2106, 1497, 1353, 1256, 1052, 839, 757, 698 cm^{-1}.
^{1}H NMR ($CDCl_3$, 200 MHz)	: δ 0.05 (s, 3H), 0.07 (s, 3H), 0.88 (s, 9H), 3.34 (s, 3H), 3.62 (dd, *J* = 2.3, 6.7 Hz, 1H), 3.69-3.84 (m, 3H), 3.89-3.90 (m, 1H), 4.0 (dd, *J* = 3.5, 9.8 Hz, 1H), 4.54 (d, *J* = 3.5 Hz, 1H), 4.64 (d, *J* = 12.1 Hz, 1H), 4.73 (d, *J* = 11.7 Hz, 1H), 4.83 (d, *J* = 12.1 Hz, 1H), 4.86 (d, *J* = 12.1 Hz, 1H), 7.28-7.41 (m, 10H) ppm.
^{13}C NMR ($CDCl_3$, 50 MHz)	: δ –5.8 (q, 2C), 18.0 (s), 25.6 (q, 3C), 55.0 (q), 61.0 (d), 61.6 (t), 68.2 (d), 73.1 (t), 73.5 (t), 76.4 (d), 77.5 (d), 98.4 (d), 127.5 (d, 2C), 127.6 (d, 3C), 127.7 (d), 127.8 (d), 128.2 (d, 3C), 138.2 (s, 2C) ppm.
ESI-MS (*m/z*)	: 536.5 $[M+Na]^+$.

Elemental Analysis	Calcd.: C, 63.13; H, 7.65; N, 8.18.
	Found: C, 63.23; H, 7.85; N, 7.95.

Data for 129:

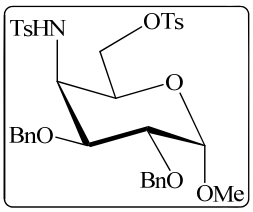
Mol. Formula	: $C_{21}H_{25}N_3O_5$
$[\alpha]_D$	: +3.3 (*c* 2.2, $CHCl_3$).
IR ($CHCl_3$) $\tilde{\nu}$	: 3478, 2930, 2108, 1497, 1351, 1277, 921, 698 cm^{-1}.
^{1}H NMR ($CDCl_3$, 200 MHz)	: δ 3.35 (s, 3H), 3.72 (d, *J* = 7.0 Hz, 1H), 3.81 (d, *J* = 7.4 Hz, 1H), 3.72-3.85 (m, 1H), 3.84 (dd, *J* = 3.5, 9.8 Hz, 1H), 3.90 (br d, *J* = 3.1 Hz, 1H), 4.03 (dd, *J* = 3.5, 9.8 Hz, 1H), 4.60 (d, *J* = 3.5 Hz, 1H), 4.65 (d, *J* = 12.1 Hz, 1H), 4.74 (d, *J* = 11.7 Hz, 1H), 4.81 (s, 1H), 4.84 (d, *J* = 11.7 Hz, 1H), 7.29-7.39 (m, 10H) ppm.
^{13}C NMR ($CDCl_3$, 75 MHz)	: δ 54.9 (q), 60.9 (d), 61.6 (t), 68.4 (d), 72.7 (t), 73.3 (t), 76.0 (d), 77.5 (d), 98.3 (d), 127.3 (d), 127.4 (d), 127.6 (d, 2C), 128.0 (d, 3C), 128.1 (d, 3C), 137.8 (s), 138.0 (s) ppm.
ESI-MS (*m/z*)	: 422.1 $[M+Na]^+$.
Elemental Analysis	Calcd.: C, 63.14; H, 6.31; N, 20.03.
	Found: C, 62.99; H, 6.30; N, 19.87.

Methyl 4-deoxy-4-azido 2,3-*O*-dibenzyl α-D-glucopyranose (129)



To a solution of silyl azide **128** (0.5 g, 0.97 mmol) in THF (10 mL) at 0 °C was added TBAF (0.97 mL, 1.46 mmol) and stirred for 1 h. Solvent was evaporated and the crude residue was purified by column chromatography (40% ethyl acetate in petroleum ether) to afford azido alcohol **129** (0.3 g, 77%) as colorless oil.

Methyl 2,3-*O*-dibenzyl 4-deoxy-4-*N*-methylbenzene sulphonyl 6-*O*-methylbenzene sulphonyl α-D-glucopyranose (131)

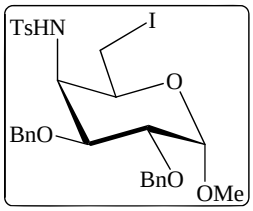


A suspension of azido alcohol **129** (0.5 g, 1.25 mmol), Raney-Ni (50 mg) in methanol (5 mL) was flushed with hydrogen gas and stirred under hydrogen (20 *psi*) atmosphere for 1 h. The reaction mixture was filtered (*Celite*), concentrated and crude amino alcohol was used for the next step without further purification.

At 0 °C, a solution of amino alcohol **130** (0.4 g, 1.07 mmol) in DCM (5 mL) was treated with triethylamine (0.45 mL, 3.22 mmol), DMAP (catalytic) and stirred for 30 min. To this, TsCl (0.61 g, 3.22 mmol) was added and stirring was continued for 2 h at rt. The reaction mixture was extracted with DCM. The combined organic extracts were washed with brine, dried (Na_2SO_4), concentrated and the resulting crude product was purified by column chromatography (20% ethyl acetate in petroleum ether) to afford sulphonate **131** (0.6 g, 82%) as a yellow frothy solid.

Mol. Formula	: $C_{35}H_{39}NO_9S_2$
$[\alpha]_D$	: +43.5 (*c* 2.6, $CHCl_3$).
IR ($CHCl_3$) $\tilde{\nu}$	: 2925, 1598, 1454, 1361, 1096, 851, 756, 667 cm^{-1}.
^{1}H NMR ($CDCl_3$, 200 MHz)	: δ 2.31 (s, 3H), 2.45 (s, 3H), 3.31 (s, 3H), 3.45 (dd, *J* = 3.9, 9.8 Hz, 1H), 3.76 (dd, *J* = 4.3, 9.8 Hz, 1H), 3.85-3.92 (m, 1H), 4.00-4.13 (m, 3H), 4.32 (br s, 2H), 4.48 (d, *J* = 11.7 Hz, 1H), 4.50 (d, *J* = 3.5 Hz, 1H), 4.66 (d, *J* = 12.1 Hz, 1H), 5.04 (d, *J* = 8.6 Hz, 1H), 7.07 (d, *J* = 8.2 Hz, 2H), 7.23-7.35 (m, 10H), 7.33 (d, *J* = 8.2 Hz, 2H), 7.39 (d, *J* = 8.2 Hz, 2H), 7.74 (d, *J* = 8.2 Hz, 2H) ppm.
^{13}C NMR ($CDCl_3$, 50 MHz)	: δ 21.4 (q), 21.6 (q), 53.3 (d), 55.3 (q), 67.4 (d), 69.9 (t), 72.1 (t), 73.4 (t), 75.5 (d, 2C), 98.0 (d), 126.9 (d, 2C), 127.3 (d), 127.5 (d), 127.6 (d), 127.8 (d, 3C), 127.9 (d), 128.0 (d, 2C), 128.2 (d, 3C), 129.4 (d), 129.7 (d, 3C), 133.0 (s), 137.9 (s), 137.9 (s), 143.1 (s, 2C), 144.6 (s) ppm.
ESI-MS (*m/z*)	: 704.4 $[M+Na]^+$.
Elemental Analysis	Calcd.: C, 61.66; H, 5.77; N, 2.05. Found: C, 61.76; H, 5.55; N, 1.99.

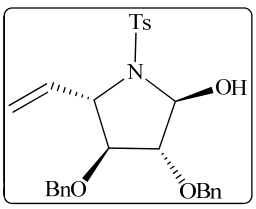
Methyl 2,3-*O*-dibenzyl 4-deoxy-4-*N*-methylbenzene sulphonyl 6-deoxy-6-iodo α-D-glucopyranose (132)



To a solution of ditosylate **131** (0.7 g, 1.03 mmol) in dry butanone (10 mL) was added sodium iodide (0.46 g, 3.08 mmol) and the reaction mixture was heated at 100 °C for 4 h. Solvent was evaporated and the crude residue was purified by column chromatography (15% ethyl acetate in petroleum ether) to afford **132** (0.45 g, 69%) as a white syrup.

Mol. Formula	: $C_{28}H_{32}INO_6S$
$[\alpha]_D$	: +73.5 (*c* 2.5, $CHCl_3$).
IR ($CHCl_3$) $\tilde{\nu}$	: 3019, 1599, 1327, 1216, 1039, 756, 698 cm^{-1}.
^{1}H NMR ($CDCl_3$, 200 MHz)	: δ 2.29 (s, 3H), 3.18 (d, *J* = 1.6 Hz, 1H), 3.22 (d, *J* = 5.5 Hz, 1H), 3.43 (s, 3H), 3.53 (dd, *J* = 3.9, 10.2 Hz, 1H), 3.78 (dd, *J* = 4.3, 10.2 Hz, 1H), 3.92-4.00 (m, 1H), 4.02-4.09 (m, 1H), 4.37 (s, 2H), 4.46 (d, *J* = 11.7 Hz, 1H), 4.49 (d, *J* = 3.1 Hz, 1H), 4.65 (d, *J* = 12.1 Hz, 1H), 5.37 (d, *J* = 8.6 Hz, 1H), 7.06 (d, *J* = 8.2 Hz, 2H), 7.08-7.13 (m, 2H), 7.21-7.32 (m, 8H), 7.76 (d, *J* = 8.2 Hz, 2H) ppm.
^{13}C NMR ($CDCl_3$, 50 MHz)	: δ 4.0 (t), 21.4 (q), 55.3 (q), 56.0 (d), 70.4 (d), 72.1 (t), 73.5 (t), 75.5 (d), 75.6 (d), 98.3 (d), 126.9 (d, 2C), 127.3 (d), 127.5 (d, 2C), 127.7 (d), 128.0 (d, 4C), 128.2 (d, 2C), 129.2 (d, 2C), 137.9 (s, 2C), 138.4 (s), 142.9 (s) ppm..
ESI-MS (*m/z*)	: 660.5 $[M+Na]^+$.
Elemental Analysis	Calcd.: C, 52.75; H, 5.06; N, 2.20.
	Found: C, 52.69; H, 4.95; N, 2.01.

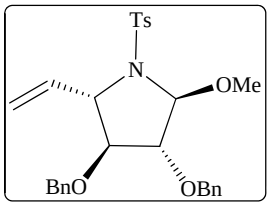
(3*R*,4*S*,5*S*)-3,4-Bis(benzyloxy)-1-tosyl-5-vinylpyrrolidin-2-ol (134)



Activated zinc powder (0.41 g, 6.28 mmol) and NH_4Cl were added to a solution of **132** (0.4 g, 0.63 mmol) in methanol (10 mL) at rt and the reaction mixture was stirred for 30 min. The reaction mixture was filtered (*Celite*), concentrated and crude product was purified by column chromatography (25% ethyl acetate in petroleum ether) to furnish **134** (0.17 g, 60%) as colorless oil.

Mol. Formula	: $C_{27}H_{29}NO_5S$
$[\alpha]_D$	: +25.9 (*c* 0.7, $CHCl_3$).
IR ($CHCl_3$) $\tilde{\nu}$	: 3482, 2924, 1598, 1455, 1342, 1162, 1014, 753, 669 cm^{-1}.
^{1}H NMR ($CDCl_3$, 200 MHz)	: δ 2.43 (s, 3H), 3.73-3.83 (m, 1H), 3.95-4.21 (m, 3H), 4.57 (s, 2H), 4.59 (d, *J* = 11.3 Hz, 1H), 4.68 (d, *J* = 12.1 Hz, 1H), 5.13 (d, *J* = 9.8 Hz, 1H), 5.33 (d, *J* = 16.8 Hz, 1H), 5.54 (d, *J* = 4.7 Hz, 1H), 5.60-5.83 (m, 1H), 7.21-7.38 (m, 12H), 7.76 (d, *J* = 8.2 Hz, 2H) ppm.
^{13}C NMR ($CDCl_3$, 50 MHz)	: δ 21.5 (q), 64.9 (d), 72.5 (t), 72.5 (t), 81.1 (d), 81.3 (d), 84.6 (d), 118.1 (t), 127.5 (d), 127.6 (d, 3C), 127.8 (d), 127.9 (d, 3C), 128.1 (d), 128.3 (d, 2C), 128.5 (d, 2C), 129.4 (d), 136.8 (s), 137.1 (s), 137.2 (d), 137.4 (s), 143.3 (s) ppm.
ESI-MS (*m/z*)	: 502.8 $[M+Na]^+$.
Elemental Analysis	Calcd.: C, 67.62; H, 6.09; N, 2.92. Found: C, 67.75; H, 6.06; N, 2.90.

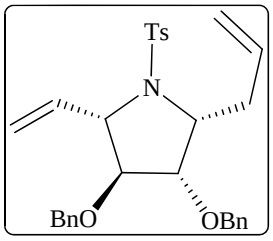
(2*S*,3*R*,4*S*,5*S*)-3,4-Bis(benzyloxy)-2-methoxy-1-tosyl-5-vinylpyrrolidine (135)



To a solution of hemiaminal **134** (0.5 g, 1.04 mmol) in methanol (5 mL) was added *p*-TSA (catalytic) and stirred for 30 min. The reaction mixture was neutralized by triethylamine (few drops) and the resulting mixture was concentrated and purified by column chromatography (15% ethyl acetate in petroleum ether) to afford **135** (0.5 g, 97%) as colorless oil.

Mol. Formula	: $C_{28}H_{31}NO_5S$
$[\alpha]_D$	: +60.3 (*c* 1.5, $CHCl_3$).
IR ($CHCl_3$) $\tilde{\nu}$	: 3017, 1598, 1454, 1351, 1166, 929, 755, 666 cm^{-1}.
^{1}H NMR ($CDCl_3$, 500 MHz)	: δ 2.41 (s, 3H), 3.18 (dd, *J* = 4.6, 8.2 Hz, 1H), 3.42 (s, 3H), 3.75 (t, *J* = 6.9 Hz, 1H), 4.06 (dd, *J* = 6.9, 8.2 Hz, 1H), 4.52 (s, 2H), 4.56 (d, *J* = 11.9 Hz, 1H), 4.63 (d, *J* = 11.9 Hz, 1H), 4.77 (d, *J* = 4.6 Hz, 1H), 5.15 (d, *J* = 10.5 Hz, 1H), 5.28 (d, *J* = 17.0 Hz, 1H), 5.83 (ddd, *J* = 7.8, 10.1, 17.4 Hz, 1H), 7.19-7.33 (m, 12H), 7.57 (d, *J* = 8.2 Hz, 2H) ppm.
^{13}C NMR ($CDCl_3$, 125 MHz)	: δ 21.5 (q), 55.4 (q), 64.0 (d), 72.4 (t), 73.0 (t), 81.9 (d), 85.5 (d), 88.3 (d), 117.2 (t), 127.3 (d, 2C), 127.6 (d, 3C), 128.0 (d), 128.1 (d, 2C), 128.2 (d, 2C), 128.4 (d, 2C), 129.7 (d, 2C), 136.0 (s), 137.3 (s), 138.0 (d), 138.0 (s), 143.6 (s) ppm.
ESI-MS (*m/z*)	: 516.4 $[M+Na]^+$.
Elemental Analysis	Calcd.: C, 68.13; H, 6.33; N, 2.84. Found: C, 67.95; H, 6.16; N, 2.60.

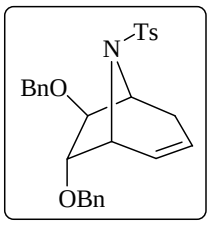
(2*R*,3*S*,4*S*,5*S*)-2-Allyl-3,4-bis(benzyloxy)-1-tosyl-5-vinylpyrrolidine (136)



To a solution of **135** (0.5 g, 1.01 mmol) in dry DCM (5 mL) at -78 °C, $BF_3.Et_2O$ (0.15 mL, 1.22 mmol) was added and stirred for 30 min. Allyltrimethylsilane (0.32 mL, 2.03 mmol) was added to the reaction mixture at -78 °C and stirred for 30 min at -20 °C for 1 h. The reaction was quenched by addition of triethylamine (few drops). Solvent was evaporated and the crude product obtained was purified by column chromatography (10% ethyl acetate in petroleum ether) to furnish **136** (0.47 g, 88%) as colorless oil.

Mol. Formula	: $C_{30}H_{33}NO_4S$
$[\alpha]_D$	: –7.9 (*c* 1.1, $CHCl_3$).
IR ($CHCl_3$) $\tilde{\nu}$	: 3030, 2925, 1599, 1454, 1344, 1218, 1028, 756, 669 cm^{-1}.
^{1}H NMR ($CDCl_3$, 500 MHz)	: δ 2.40 (s, 3H), 2.49-2.59 (m, 1H), 2.91-2.94 (m, 1H), 3.76 (br s, 1H), 3.90 (br s, 1H), 4.01 (dd, *J* = 3.7, 11.5 Hz, 1H), 4.35 (d, *J* = 11.9 Hz, 1H), 4.41 (d, *J* = 11.9 Hz, 1H), 4.43 (d, *J* = 4.6 Hz, 1H), 4.45 (d, *J* = 12.4 Hz, 1H), 4.54 (d, *J* = 11.9 Hz, 1H), 5.00 (d, *J* = 10.1 Hz, 1H), 5.04 (d, *J* = 11.0 Hz, 1H), 5.06 (d, *J* = 10.1 Hz, 1H), 5.22 (d, *J* = 16.9 Hz, 1H), 5.60 (dt, *J* = 10.1, 16.9 Hz, 1H), 5.69-5.79 (m, 1H), 7.08-7.13 (m, 2H), 7.19 (d, *J* = 8.2 Hz, 2H), 7.22-7.25 (m, 2H), 7.28-7.34 (m, 6H), 7.71 (d, *J* = 8.2 Hz, 2H) ppm.
^{13}C NMR ($CDCl_3$, 50 MHz)	: δ 21.5 (q), 37.2 (t), 66.0 (d), 69.2 (d), 70.9 (t), 71.6 (t), 83.2 (d), 87.2 (d), 117.6 (t), 118.1 (t), 127.4 (d, 5C), 127.5 (d, 2C), 127.7 (d), 127.8 (d), 128.3 (d), 128.4 (d, 2C), 129.1 (d, 2C), 134.7 (d), 136.1 (d), 137.3 (s), 137.4 (s), 139.2 (s), 142.6 (s) ppm.
ESI-MS (*m/z*)	: 526.7 $[M+Na]^+$.
Elemental Analysis	Calcd.: C, 71.54; H, 6.60; N, 2.78. Found: C, 71.43; H, 6.53; N, 2.84.

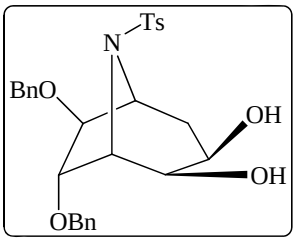
(1*R*,5*S*,6*S*,7*S*)-6,7-Bis(benzyloxy)-8-tosyl-8-azabicyclo[3.2.1]oct-2-ene (137)



To a degassed solution of the diene **136** (0.7 g, 1.39 mmol) in dry DCM (200 mL) was added Grubbs' I catalyst (5 mg) and the reaction mixture was refluxed for 24 h. Solvent was evaporated and the crude residue was purified by column chromatography (8% ethyl acetate in petroleum ether) to afford olefin **137** (0.15 g, 20%; 75% BORSM) as colorless oil.

Mol. Formula	: $C_{28}H_{29}NO_4S$
$[\alpha]_D$	: +25.5 (*c* 1.5, $CHCl_3$).
IR ($CHCl_3$) $\tilde{\nu}$	: 3029, 2924, 1598, 1496, 1345, 1161, 971, 755, 665 cm^{-1}.
^{1}H NMR ($CDCl_3$, 500 MHz)	: δ 2.17-2.21 (m, 1H), 2.29-2.36 (m, 1H), 2.38 (s, 3H), 3.75 (d, *J* = 0.9 Hz, 1H), 4.08 (d, *J* = 6.9 Hz, 1H), 4.18 (d, *J* = 5.5 Hz, 1H), 4.35 (d, *J* = 11.9 Hz, 1H), 4.37 (d, *J* = 5.8 Hz, 1H), 4.42 (d, *J* = 11.9 Hz, 1H), 4.45 (d, *J* = 11.9 Hz, 1H), 4.49 (d, *J* = 11.4 Hz, 1H), 5.58 (dt, *J* = 4.0, 9.6 Hz, 1H), 5.80-5.83 (m, 1H), 7.15 (d, *J* = 8.2 Hz, 2H), 7.24-7.25 (m, 4H), 7.28-7.34 (m, 6H), 7.73 (d, *J* = 8.2 Hz, 2H) ppm.
^{13}C NMR ($CDCl_3$, 125 MHz)	: δ 21.5 (q), 25.1 (t), 56.9 (d), 57.9 (d, 2C), 71.3 (d), 71.3 (t), 72.7 (t), 86.9 (d), 88.6 (d), 126.9 (d), 127.6 (d, 2C), 127.7 (d), 127.8 (d, 2C), 127.9 (d, 2C), 128.4 (d, 2C), 128.4 (d, 2C), 129.2 (d, 2C), 137.4 (s), 137.6 (s), 138.2 (s), 142.9 (s) ppm.
ESI-MS (*m/z*)	: 498.3 $[M+Na]^+$.
Elemental Analysis	Calcd.: C, 70.71; H, 6.15; N, 2.95. Found: C, 70.63; H, 6.33; N, 2.84.

(1*R*,2*S*,3*R*,5*S*,6*S*,7*S*)-6,7-Bis(benzyloxy)-8-tosyl-8-azabicyclo[3.2.1]octane-2,3-diol (138)

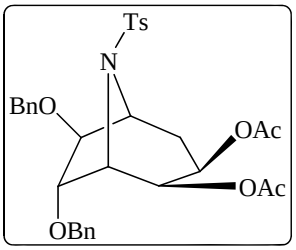


To a solution of the olefin **137** (0.5 g, 1.05 mmol) in acetone:water (1:1) (10 mL), NMO (0.54 mL, 5.26 mmol) was added at rt, followed by addition of OsO_4 (catalytic)(1 drop). The reaction mixture was stirred for 1 h and quenched with sodium sulfite (0.1 g, 0.8 mmol) and extracted with ethyl acetate, concentrated and crude product obtained was purified by column chromatography (50% ethyl acetate in petroleum ether) to furnish the diol **138** (0.3 g, 56%) as white frothy solid.

Mol. Formula	: $C_{28}H_{31}NO_6S$
$[\alpha]_D$	: +17.6 (*c* 1.3, $CHCl_3$).
IR ($CHCl_3$) $\tilde{\nu}$	: 3437, 2926, 1599, 1340, 1216, 1097, 756, 668 cm^{-1}.

^{1}H NMR ($CDCl_3$, 200 MHz)	: δ 1.68 (dd , *J* = 3.1, 10.5, 13.1 Hz, 1H), 2.13 (dq , *J* = 2.7, 12.5 Hz, 1H), 2.31 (s, 3H), 2.85 (br s, 1H), 3.60-3.62 (m, 2H), 3.82 (br s, 2H), 4.12 (d, *J* = 11.3 Hz, 1H), 4.20 (br s, 2H), 4.31 (d, *J* = 11.7 Hz, 1H), 4.33 (d, *J* = 11.7 Hz, 1H), 4.45 (d, *J* = 11.7 Hz, 1H), 7.01 (d, *J* = 8.2 Hz, 2H), 7.10 (d, *J* = 5.9 Hz, 1H), 7.11 (d, *J* = 7.4 Hz, 1H), 7.10 (d, *J* = 5.9 Hz, 1H), 7.20 (d, *J* = 7.4 Hz, 1H), 7.30-7.33 (m, 6H), 7.65 (d, *J* = 8.2 Hz, 2H) ppm.
^{13}C NMR ($CDCl_3$, 50 MHz)	: δ 21.5 (q), 31.9 (t), 56.4 (d, 2C), 64.6 (d), 64.8 (d), 68.5 (d), 71.0 (t), 72.5 (t), 84.2 (d), 127.4 (d, 2C), 127.7 (d), 127.8 (d, 2C), 128.1 (d), 128.3 (d, 3C), 128.5 (d, 2C), 129.4 (d, 3C), 136.9 (s, 3C), 143.5 (s) ppm.
ESI-MS (*m/z*)	: 532.1 $[M+Na]^+$.
Elemental Analysis	Calcd.: C, 65.99; H, 6.13; N, 2.75. Found: C, 65.83; H, 6.33; N, 2.84.

(1*S*,2*S*,3*R*,5*S*,6*S*,7*S*)-6,7-Bis(benzyloxy)-8-tosyl-8-azabicyclo[3.2.1]octane-2,3-diyl diacetate (139)



A solution of the diol **138** (0.2 g, 0.4 mmol) in dry DCM (5 mL) was cooled to 0 °C. To this, triethyl amine (0.07 mL, 0.5 mmol) was added and stirred for 30 min. Ac_2O (0.05 mL, 0.5 mmol) was added to the reaction mixture at 0 °C and stirred further for 30 min. Solvent was evaporated and the crude residue was purified by column chromatography (20% ethyl acetate in petroleum ether) to afford diacetate **139** (0.22 g, 94%) as white syrupy solid..

Mol. Formula	: $C_{32}H_{35}NO_8S$
$[\alpha]_D$	: +6.1 (*c* 1.0, $CHCl_3$).
IR ($CHCl_3$) $\tilde{\nu}$	: 3012, 1724, 1464, 1249, 1035, 755, 667 cm^{-1}.
^{1}H NMR ($CDCl_3$, 500 MHz)	: δ 2.03 (s, 3H), 2.05 (d, *J* = 8.7 Hz, 1H), 2.06 (d, *J* = 8.7 Hz, 1H), 2.17 (s, 3H), 2.33 (s, 3H), 3.71 (dd, *J* = 1.4, 6.4 Hz, 1H), 3.77 (d, *J* = 2.3 Hz, 1H), 4.12-4.14 (m, 1H), 4.21

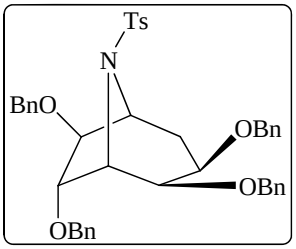
(d, *J* = 11.5 Hz, 1H), 4.40 (d, *J* = 5.8 Hz, 1H), 4.40 (d, *J* = 11.9 Hz, 1H), 4.43 (d, *J* = 11.7 Hz, 1H), 4.47 (d, *J* = 11.9 Hz, 1H), 5.10 (dd, *J* = 4.1, 7.8 Hz, 1H), 5.14 (dd, *J* = 4.1, 8.7 Hz, 1H), 7.05 (d, *J* = 8.2 Hz, 2H), 7.18-7.20 (m, 2H), 7.24-7.26 (m, 2H), 7.29-7.36 (m, 6H), 7.65 (d, *J* = 8.2 Hz, 2H) ppm.

^{13}C NMR ($CDCl_3$, 125 MHz) : δ 20.9 (q), 21.1 (q), 21.5 (q), 28.0 (t), 55.9 (d), 62.0 (d), 65.6 (d), 67.7 (d), 71.4 (t), 72.3 (t), 84.1 (d), 85.1 (d), 127.1 (d), 127.8 (d, 4C), 127.9 (d), 128.0 (d), 128.4 (d, 2C), 128.5 (d), 129.3 (d, 4C), 137.0 (s), 137.0 (s), 138.1 (s), 142.9 (s), 169.7 (s), 170.6 (s) ppm.

ESI-MS (*m/z*) : 616.4 $[M+Na]^+$.

Elemental Analysis Calcd.: C, 64.74; H, 5.94; N, 2.36.
Found: C, 64.83; H, 6.03; N, 2.14.

(1*R*,2*S*,3*R*,5*S*,6*S*,7*S*)-2,3,6,7-Tetrakis(benzyloxy)-8-tosyl-8-azabicyclo[3.2.1]octane (140)



To a solution of diol **138** (0.2 g, 0.39 mmol) in dry DMF (5 mL) was added NaH (0.03 g, 1.18 mmol) portionwise at 0 °C and stirred for 30 min. To this, benzyl bromide (0.16 mL, 1.18 mmol) was added at 0 °C and stirring was continued for 2 h at rt. The reaction mixture was quenched at 0 °C by adding ice and extracted with ethyl acetate. The combined organic extracts were washed with water, brine, dried (Na_2SO_4) and concentrated. Purification of the crude product by column chromatography (10% ethyl acetate in petroleum ether) furnished **140** (0.25 g, 93%) as a colorless oil.

Mol. Formula : $C_{42}H_{43}NO_6S$

$[\alpha]_D$: −13.0 (*c* 1.0, $CHCl_3$).

IR ($CHCl_3$) $\tilde{\nu}$: 3029, 2935, 1454, 1217, 1093, 756, 698 cm^{-1}.

^{1}H NMR ($CDCl_3$, 200 MHz) : δ 1.77-2.05 (m, 2H), 2.34 (s, 3H), 2.88-2.89 (m, 1H), 2.96-2.97 (m, 1H), 3.50 (br t, *J* = 2.4 Hz, 1H), 3.65 (br s,

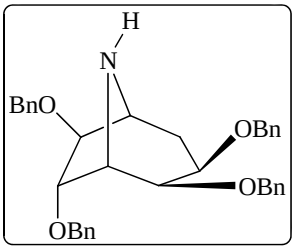
2H), 4.02 (t, *J* = 6.6 Hz, 1H), 4.28 (d, *J* = 11.7 Hz, 1H), 4.40 (d, *J* = 12.0 Hz, 1H), 4.43 (s, 2H), 4.45 (d, *J* = 10.5 Hz, 1H), 4.50 (d, *J* = 11.0 Hz, 1H), 4.59 (d, *J* = 12.6 Hz, 1H), 4.84 (d, *J* = 12.3 Hz, 1H), 7.06 (br d, *J* = 7.6 Hz, 2H), 7.13-7.46 (m, 20H), 7.80 (d, *J* = 7.2 Hz, 2H) ppm.

^{13}C NMR ($CDCl_3$, 75 MHz) : δ 21.5 (q), 28.3 (t), 55.9 (d), 60.9 (d), 70.2 (t), 70.5 (t), 71.0 (t), 71.5 (d), 72.4 (d), 72.6 (t), 84.2 (d), 85.7 (d), 127.4 (d, 2C), 127.5 (d, 4C), 127.7 (d), 127.7 (d), 127.8 (d, 3C), 128.0 (d, 3C), 128.1 (d, 3C), 128.2 (d, 3C), 128.2 (d, 3C), 129.1 (d), 137.1 (s), 137.2 (s), 137.8 (s), 137.9 (s) 138.1 (s), 142.6 (s) ppm.

ESI-MS (*m/z*) : 712.6 $[M+Na]^+$.

Elemental Analysis Calcd.: C, 73.12; H, 6.28; N, 2.03.
Found: C, 72.85; H, 6.50; N, 2.00.

(1*R*,2*S*,3*R*,5*S*,6*S*,7*S*)-2,3,6,7-Tetrakis(benzyloxy)-8-azabicyclo[3.2.1]octane (141)



To a solution of the benzyl ether **140** (0.21 g, 0.66 mmol) in dry MeOH (3 mL) was added Na_2HPO_4 (0.13 g, 2.64 mmol) and Na-Hg (6%) (0.6 g, 2.64 mmol) in 2 portions at 0 °C and stirred for 1 h at rt. The reaction mixture was filtered through celite, concentrated and the crude residue was purified by column chromatography (40% ethyl acetate in petroleum ether) to furnish **141** (0.12 g, 74%) as colorless oil.

Mol. Formula : $C_{35}H_{37}NO_4$

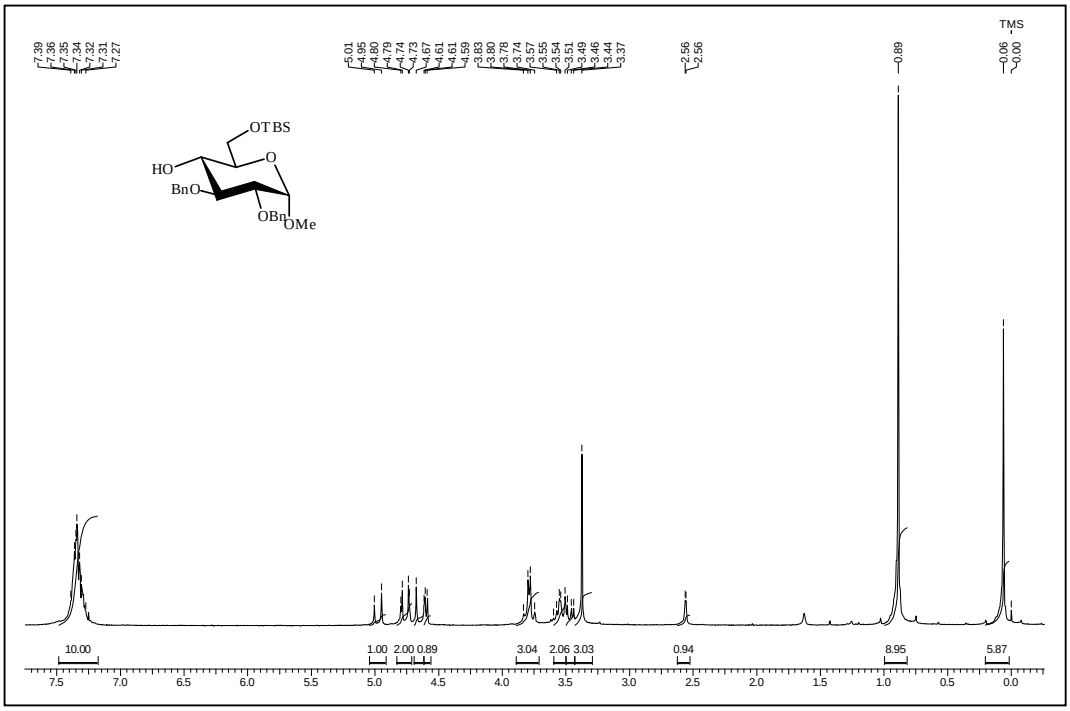
$[\alpha]_D$: –7.6 (*c* 0.6, $CHCl_3$).

IR ($CHCl_3$) $\tilde{\nu}$: 3361, 2984, 1612, 1463, 1248, 1058, 821, 749, 699 cm^{-1}.

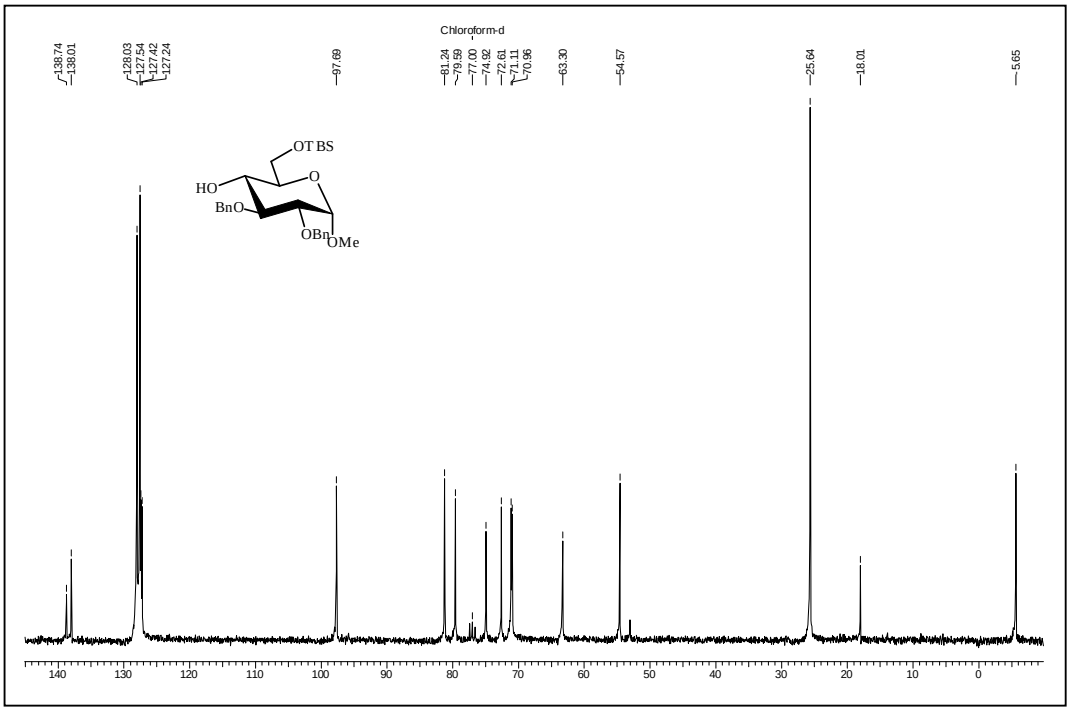
^{1}H NMR ($CDCl_3$, 400 MHz) : δ 1.72 (dt, *J* = 3.0, 11.0 Hz, 1H), 1.99-2.04 (m, 1H), 3.44 (d, *J* = 7.8 Hz, 1H), 3.45 (d, *J* = 8.3 Hz, 1H), 3.57-3.60 (m, 1H), 3.60-3.66 (m, 2H), 4.13 (dd, *J* = 1.2, 6.0 Hz, 1H), 4.39 (d, *J* = 12.0 Hz, 1H), 4.42 (d, *J* = 12.0 Hz, 1H), 4.43

	(d, *J* = 11.8 Hz, 1H), 4.45 (d, *J* = 11.8 Hz, 1H), 4.49 (d, *J* = 12.0 Hz, 1H), 4.53 (d, *J* = 11.5 Hz, 1H), 4.69 (s, 2H), 7.25-7.39 (m, 20H) ppm.
^{13}C NMR ($CDCl_3$, 100 MHz)	: δ 29.9 (t), 54.5 (d), 61.0 (d), 70.0 (t), 71.2 (t), 71.6 (t), 72.4 (t), 72.7 (d), 73.9 (d), 83.7 (d), 86.2 (d), 127.5 (d), 127.5 (d, 2C), 127.6 (d, 2C), 127.7 (d), 127.7 (d), 127.7 (d), 127.9 (d, 2C), 127.9 (d, 3C), 128.3 (d, 2C), 128.4 (d, 5C), 137.8 (s), 137.9 (s), 138.5 (s), 138.6 (s) ppm.
ESI-MS (*m/z*)	: 558.5 $[M+Na]^+$.
Elemental Analysis	Calcd.: C, 78.48; H, 6.96; N, 2.61.
	Found: C, 78.33; H, 6.83; N, 2.84.

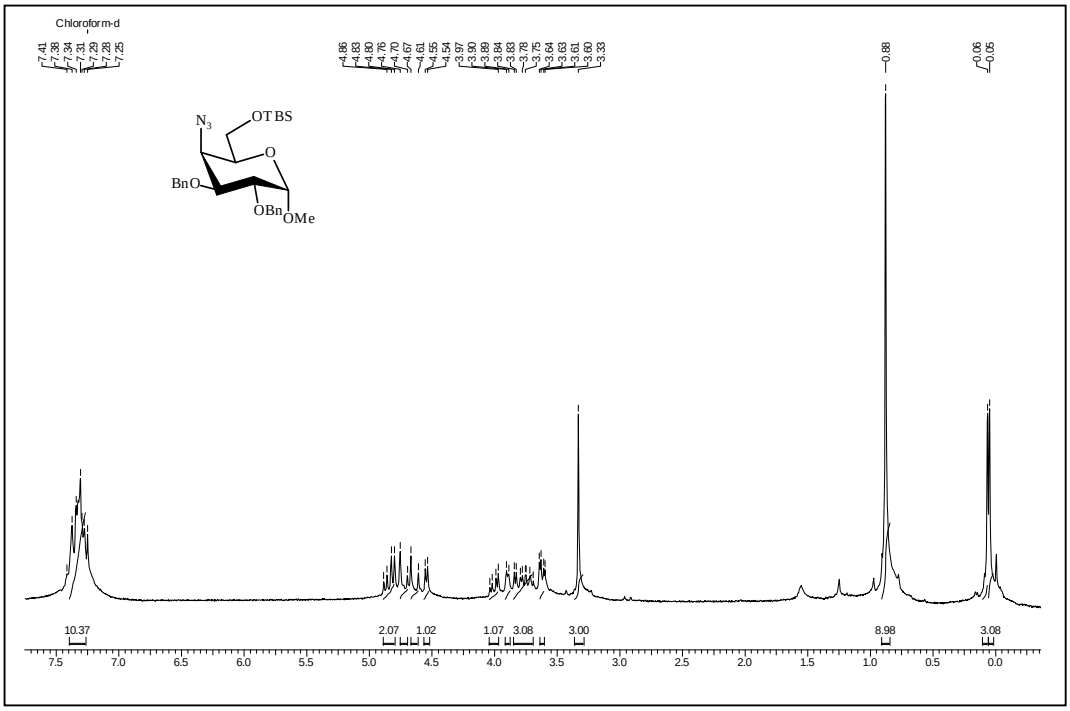
Spectroscopic Data



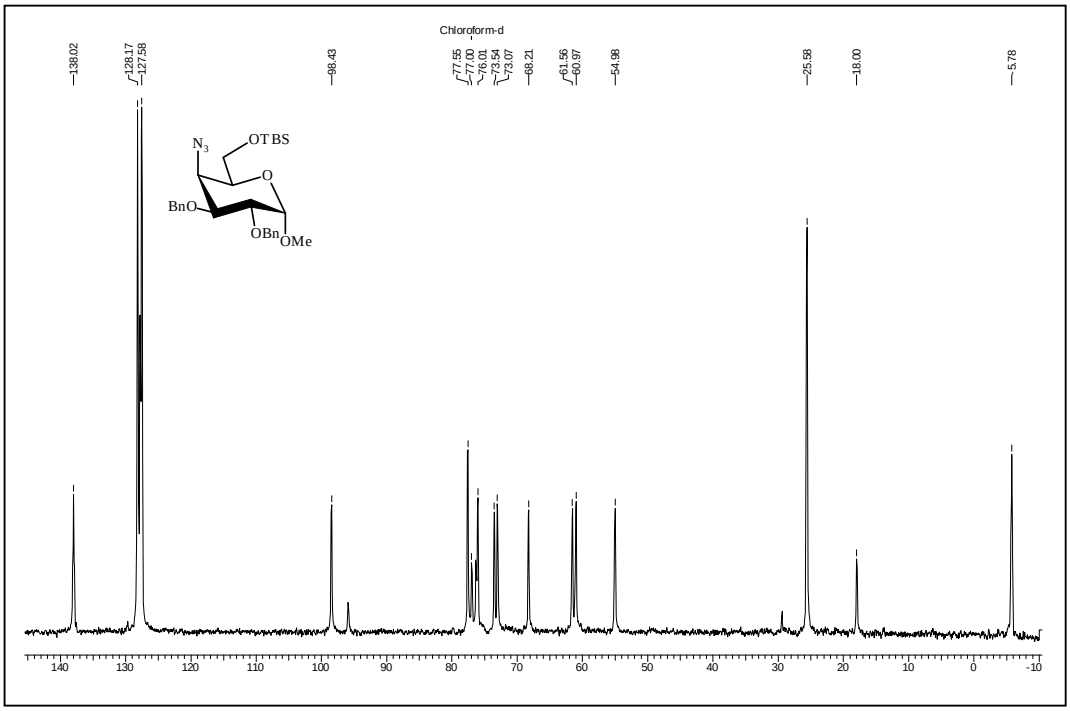
^{1}H NMR Spectrum of 126 in $CDCl_3$



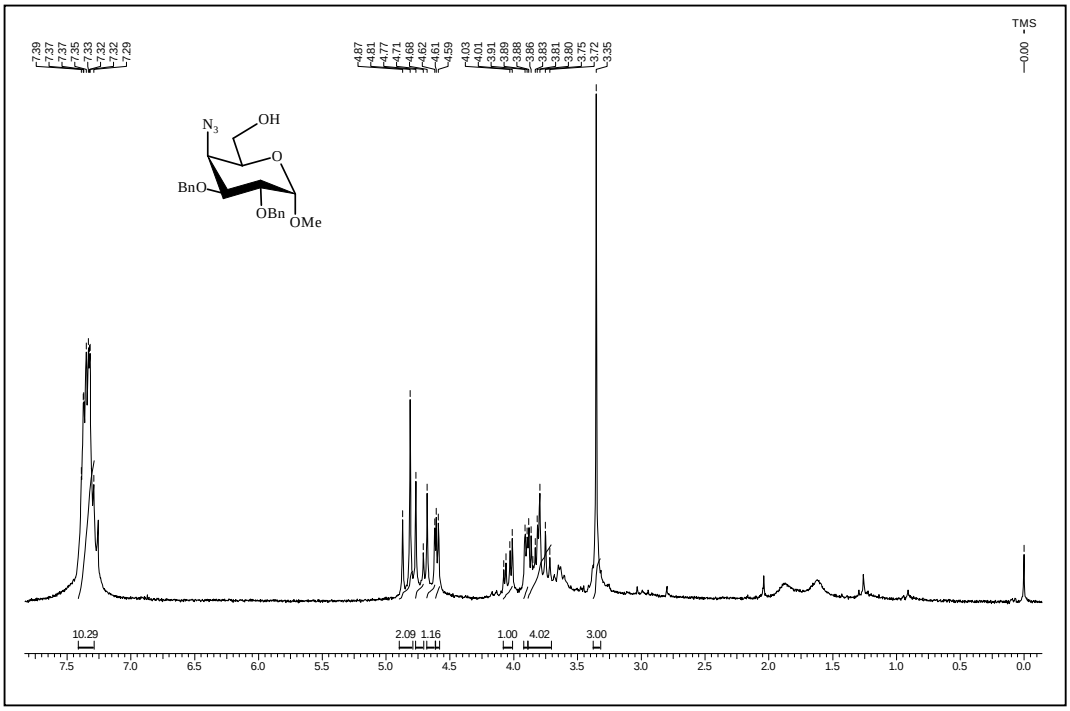
^{13}C NMR Spectrum of 126 in $CDCl_3$



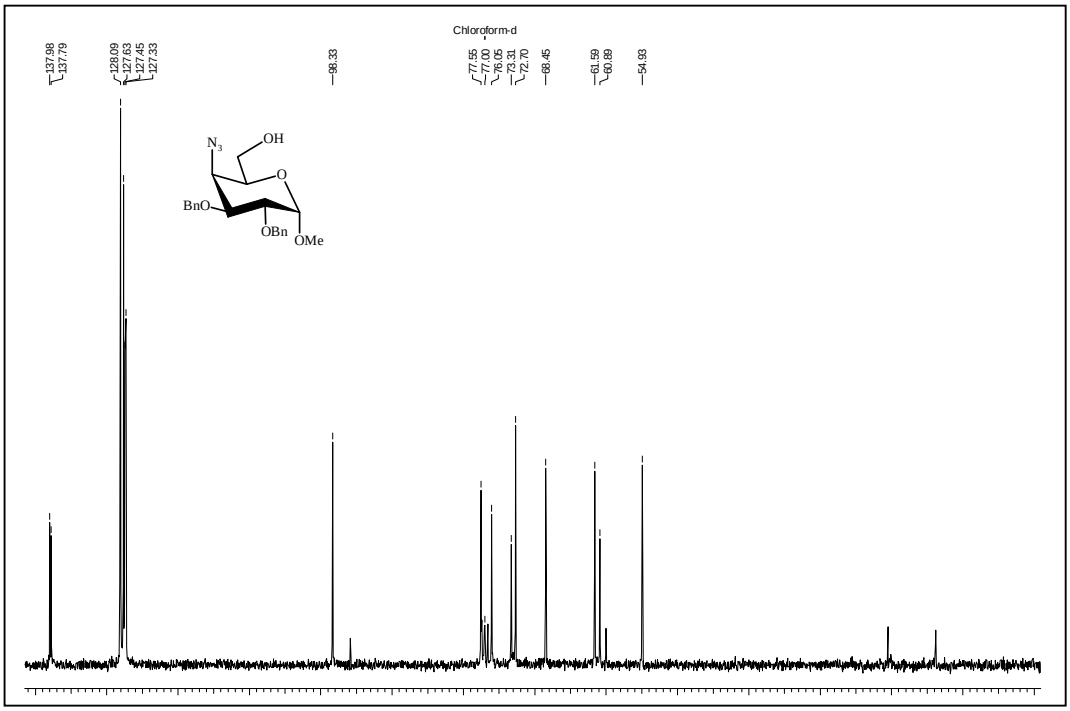
^{1}H NMR Spectrum of 128 in $CDCl_3$



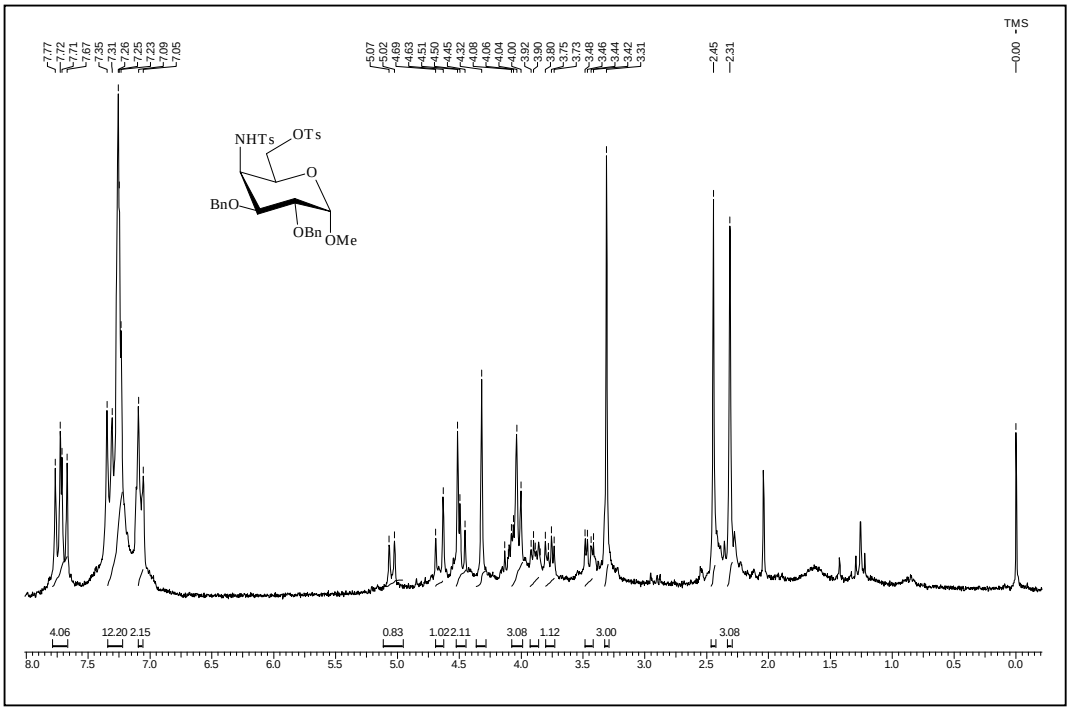
^{13}C NMR Spectrum of 128 in $CDCl_3$



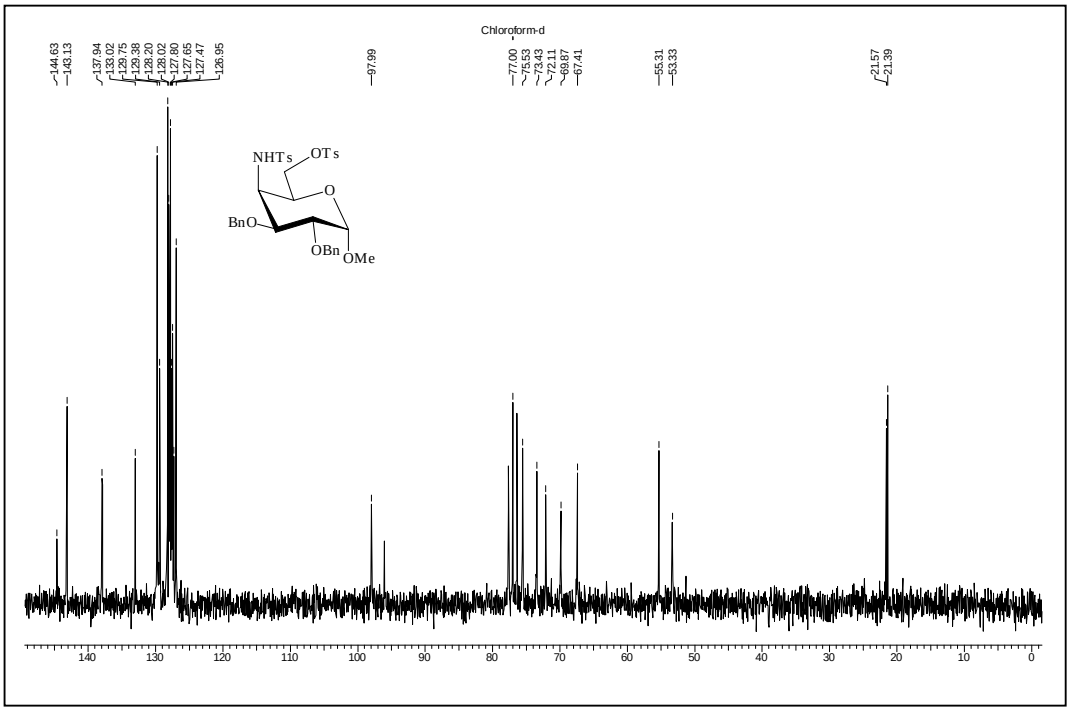
^{1}H NMR Spectrum of 129 in $CDCl_3$



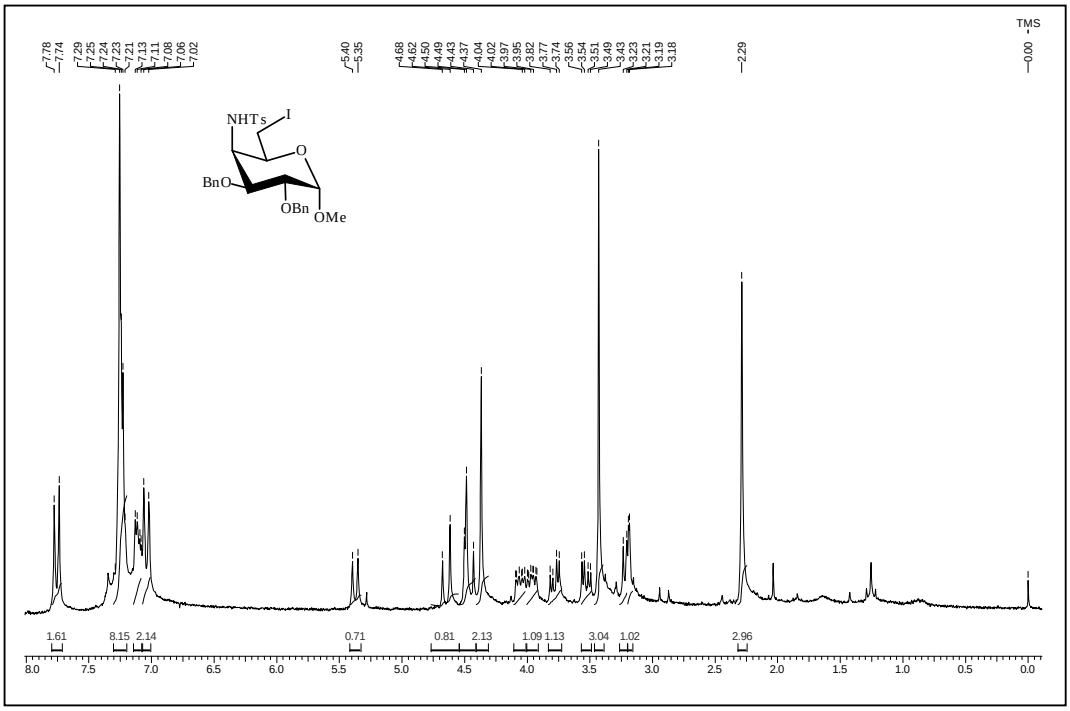
^{13}C NMR Spectrum of 129 in $CDCl_3$



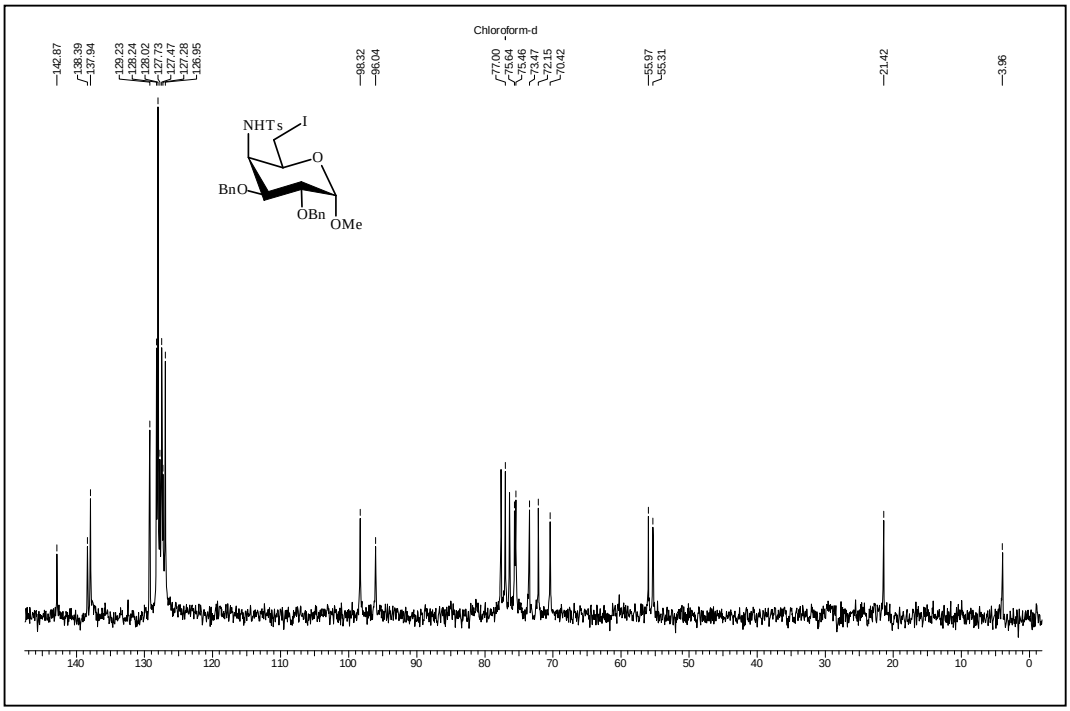
^{1}H NMR Spectrum of 131 in $CDCl_3$



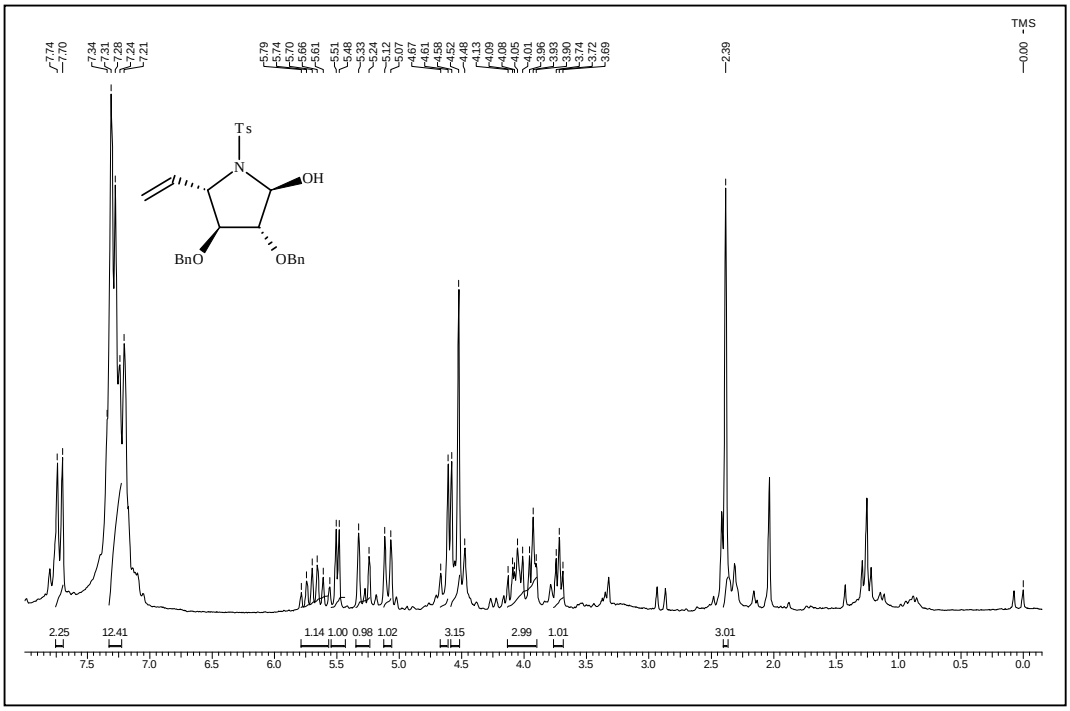
^{13}C NMR Spectrum of 131 in $CDCl_3$



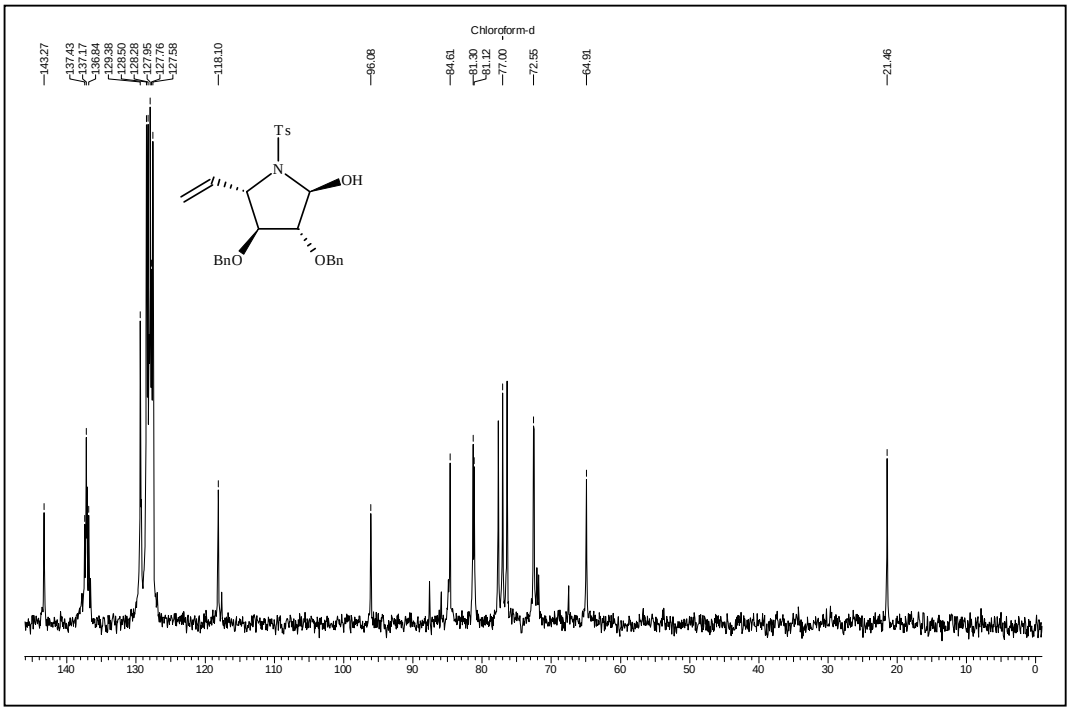
^{1}H NMR Spectrum of 132 in $CDCl_3$



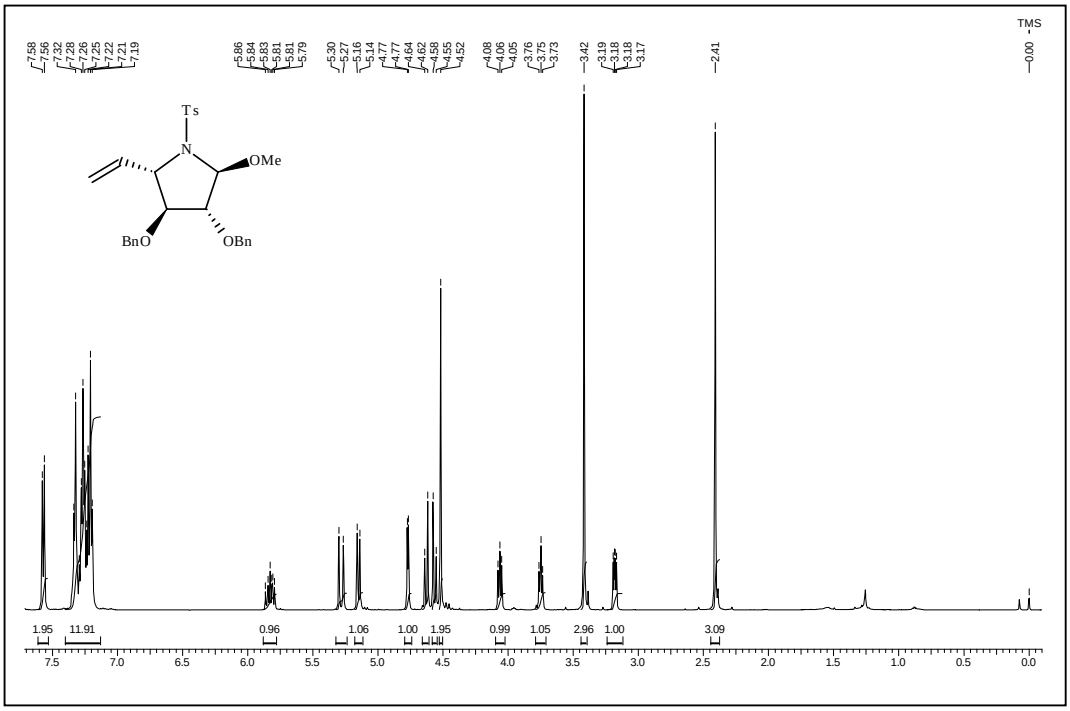
^{13}C NMR Spectrum of 132 in $CDCl_3$



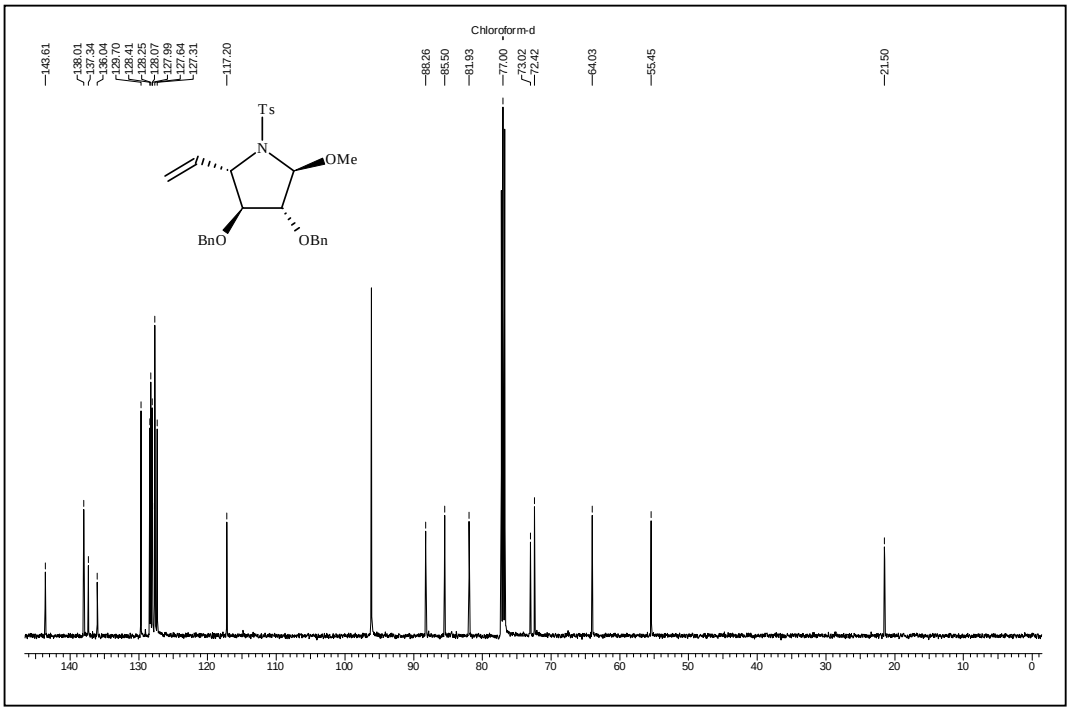
^{1}H NMR Spectrum of 134 in $CDCl_3$



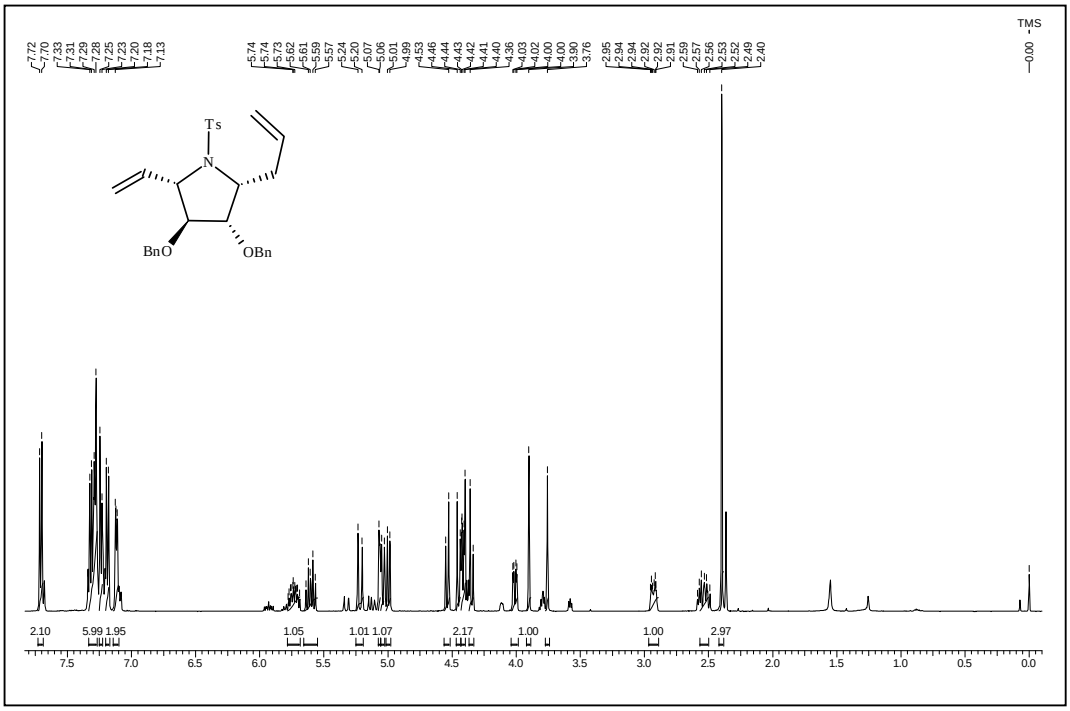
^{13}C NMR Spectrum of 134 in $CDCl_3$



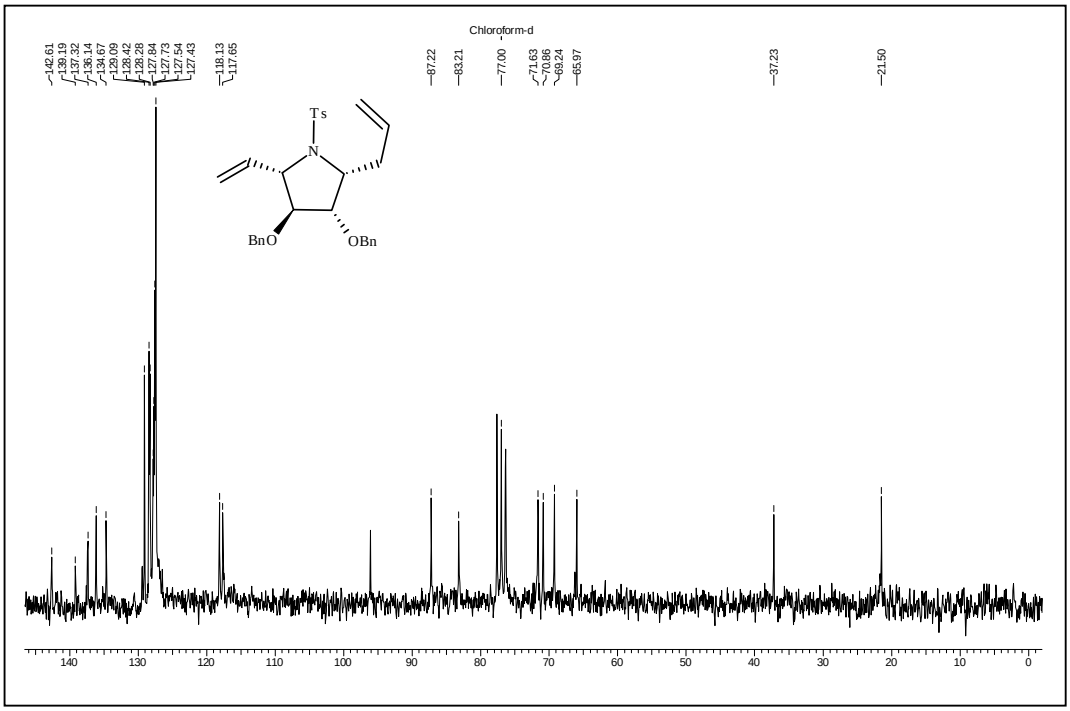
^{1}H NMR Spectrum of 135 in $CDCl_3$



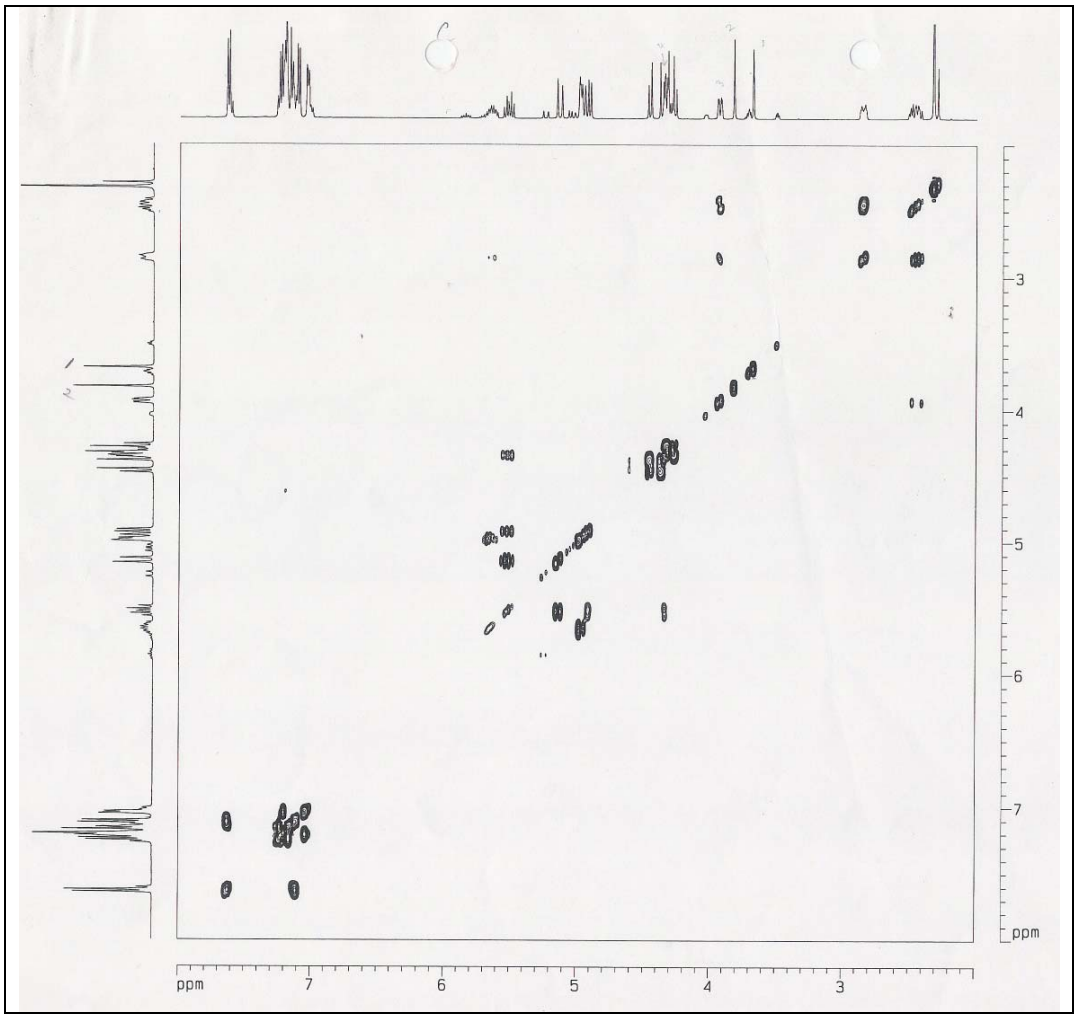
^{13}C NMR Spectrum of 135 in $CDCl_3$

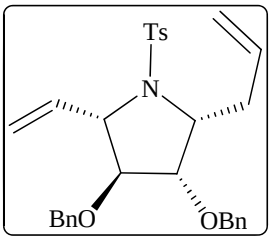


^{1}H NMR Spectrum of 136 in $CDCl_3$

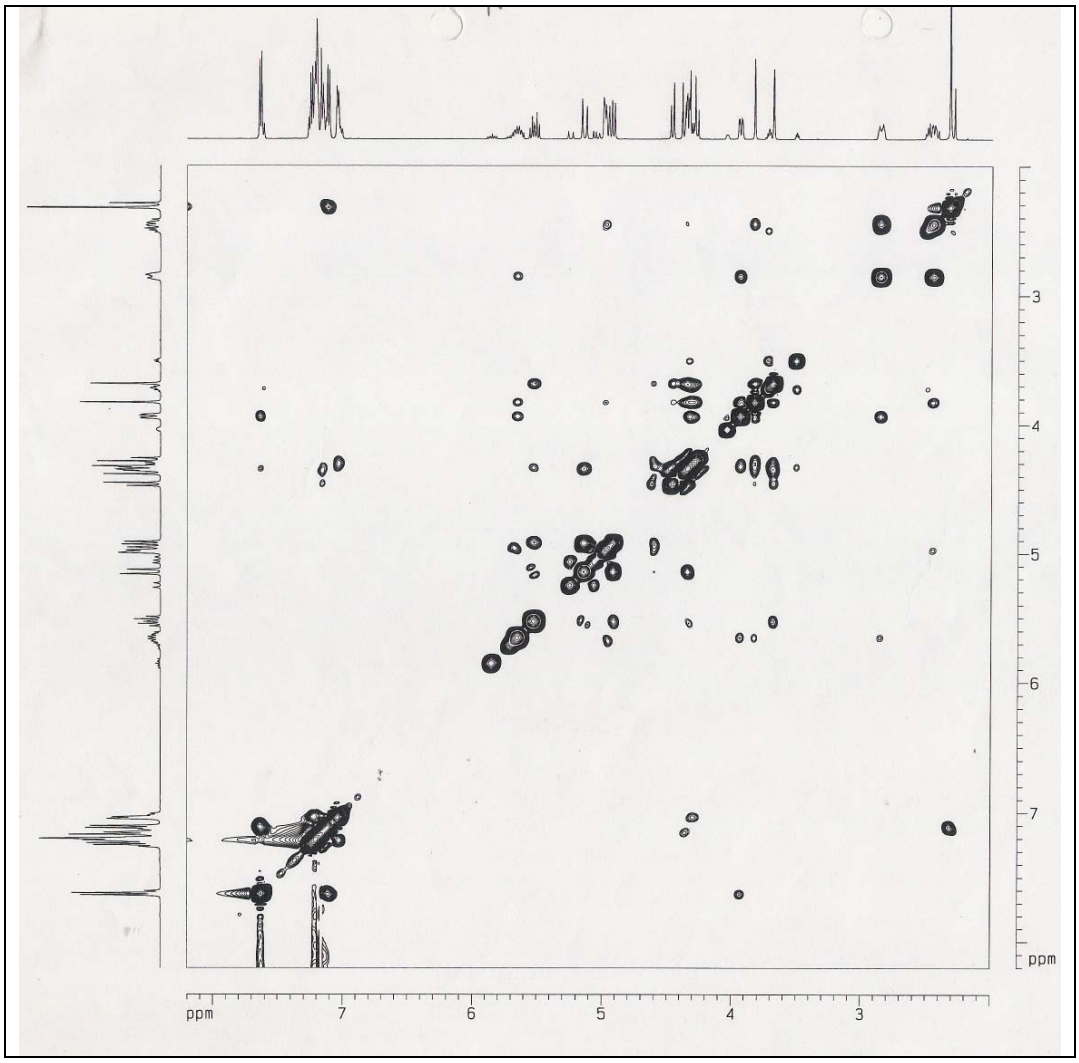


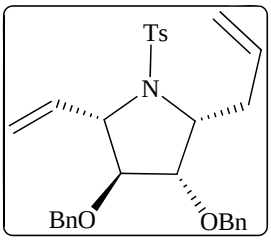
^{13}C NMR Spectrum of 136 in $CDCl_3$



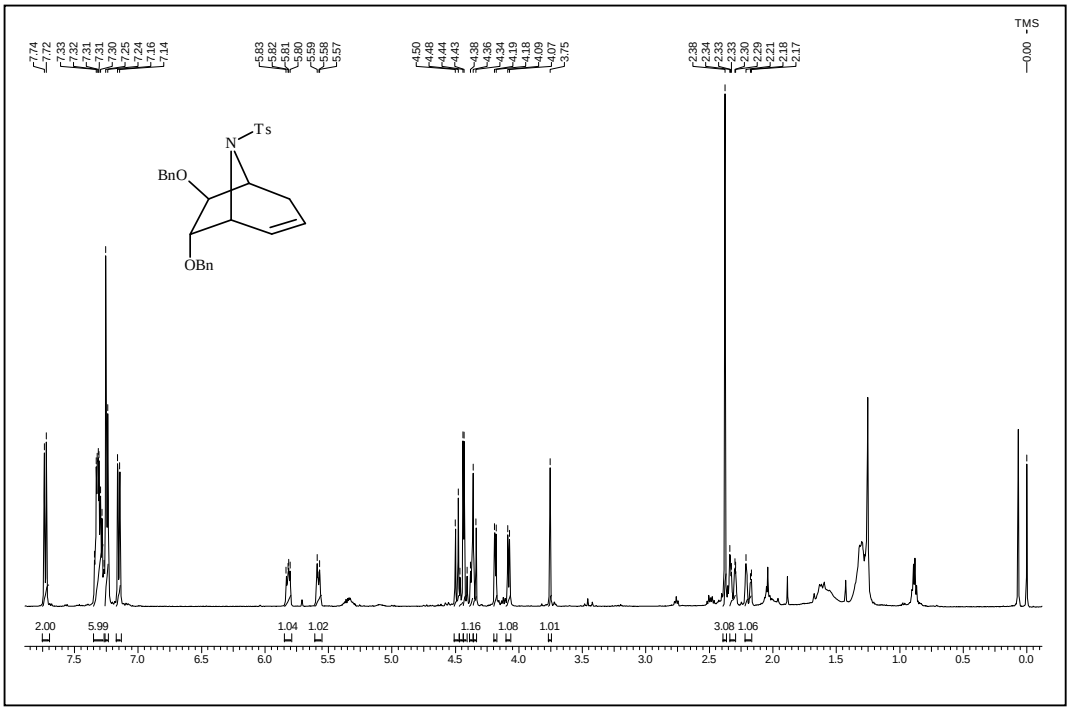


COSY Spectrum of 136

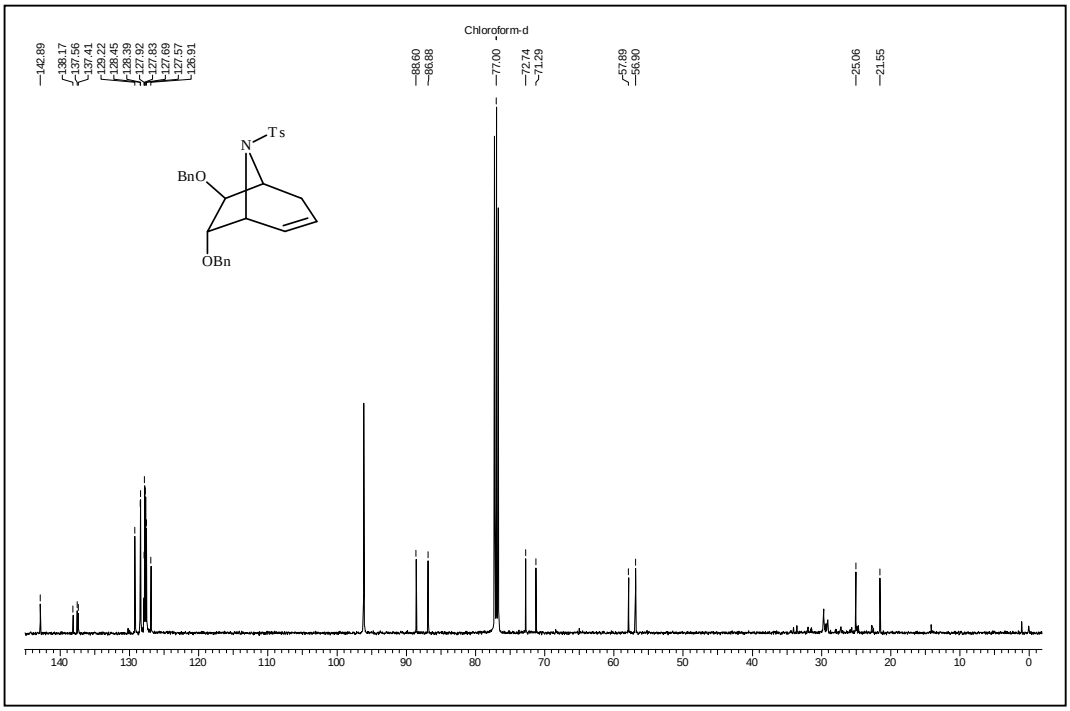




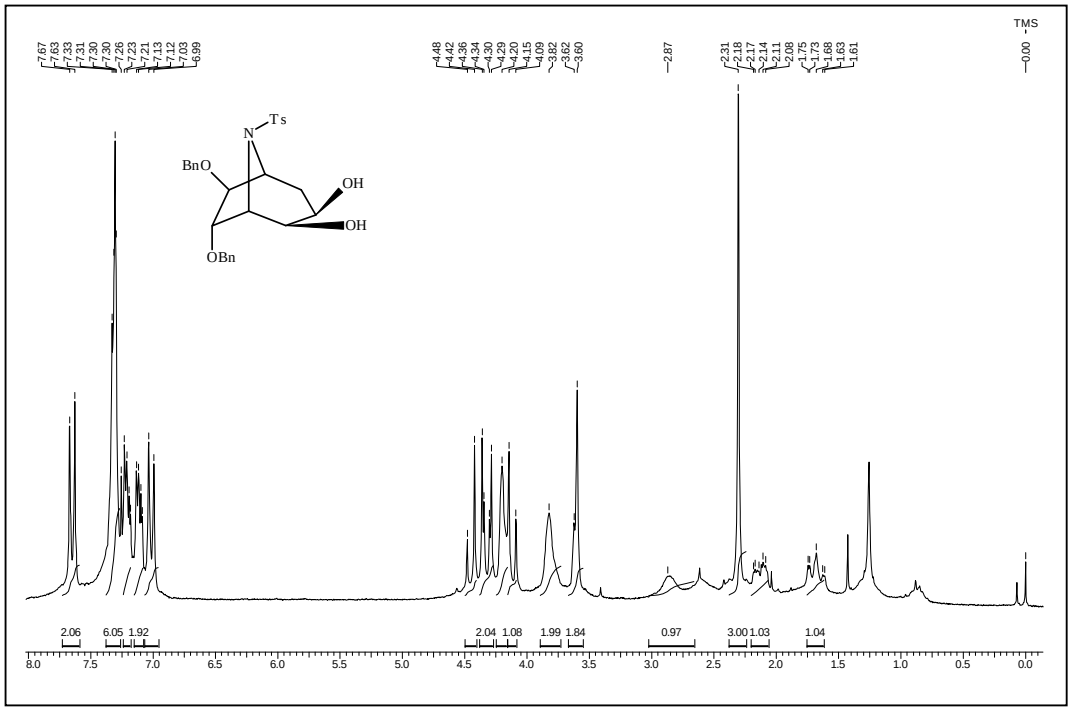
NOESY Spectrum of 136



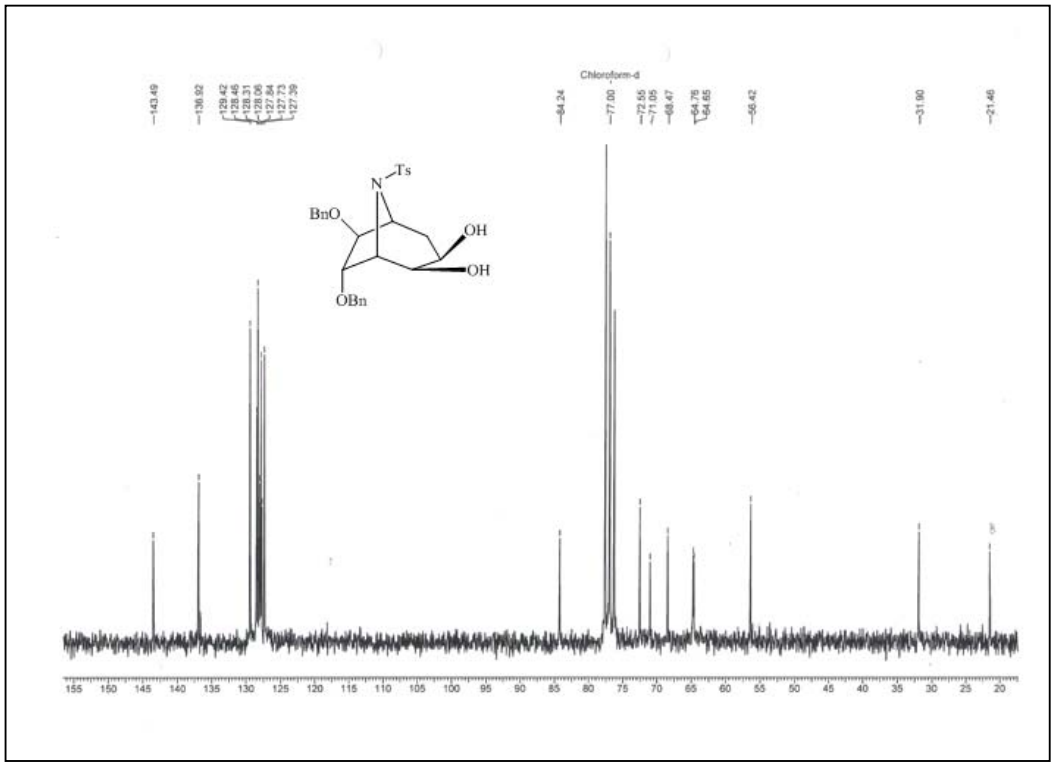
^{1}H NMR Spectrum of 137 in $CDCl_3$



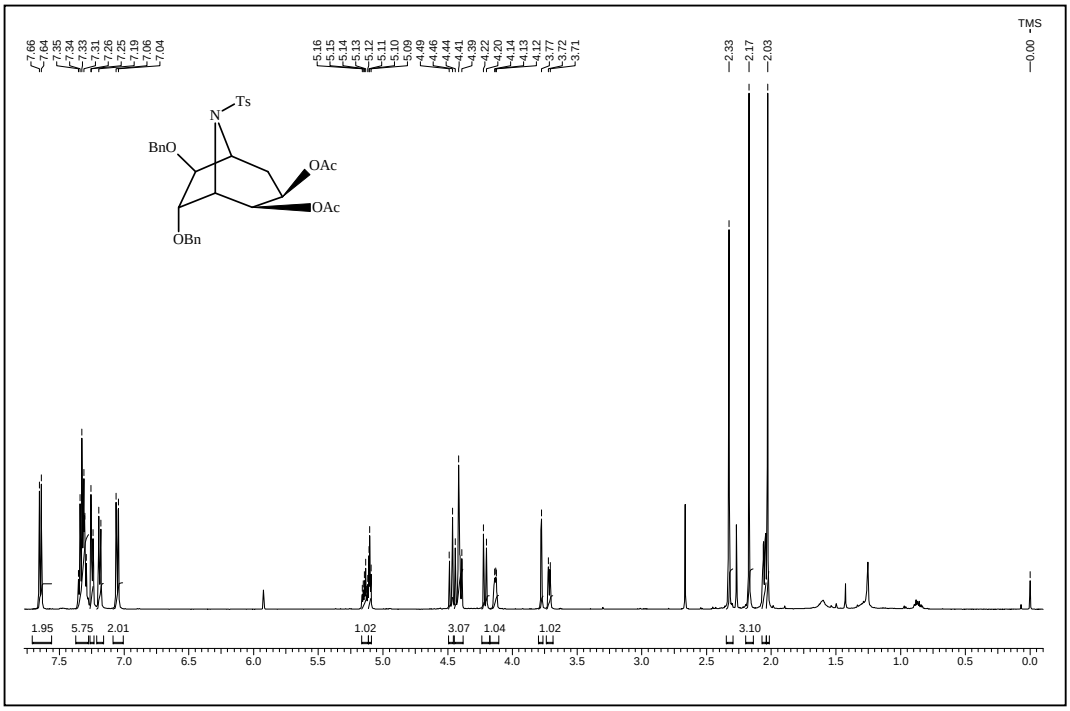
^{13}C NMR Spectrum of 137 in $CDCl_3$



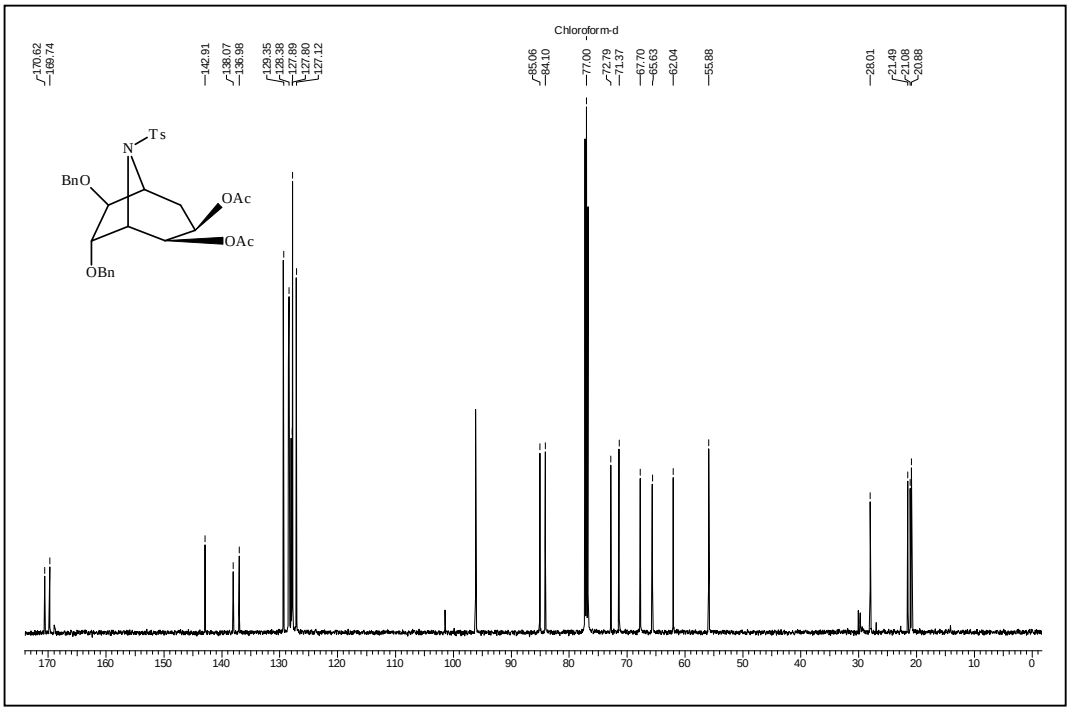
^{1}H NMR Spectrum of 138 in $CDCl_3$



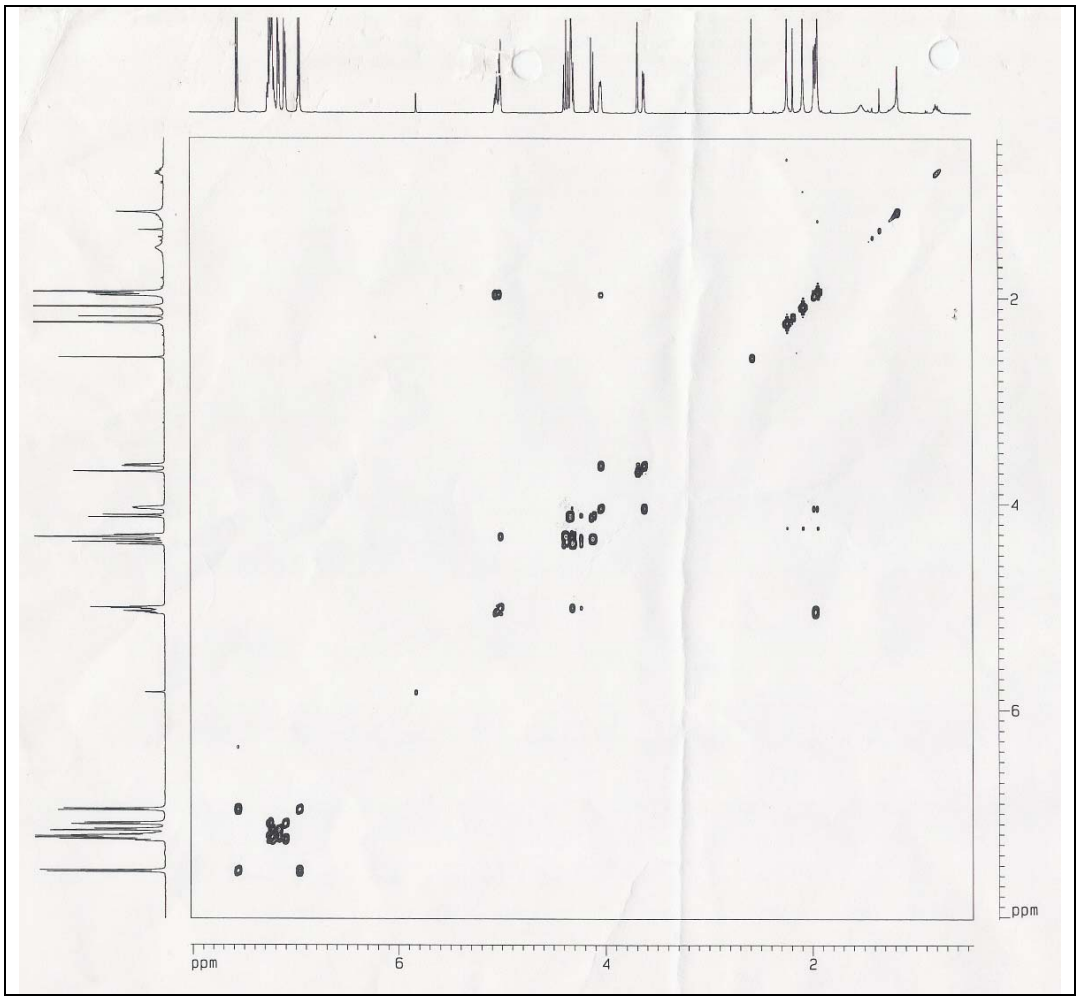
^{13}C NMR Spectrum of 138 in $CDCl_3$

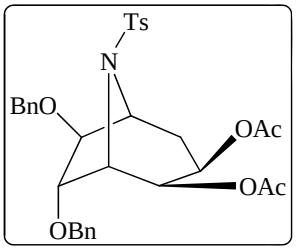


^{1}H NMR Spectrum of 139 in $CDCl_3$

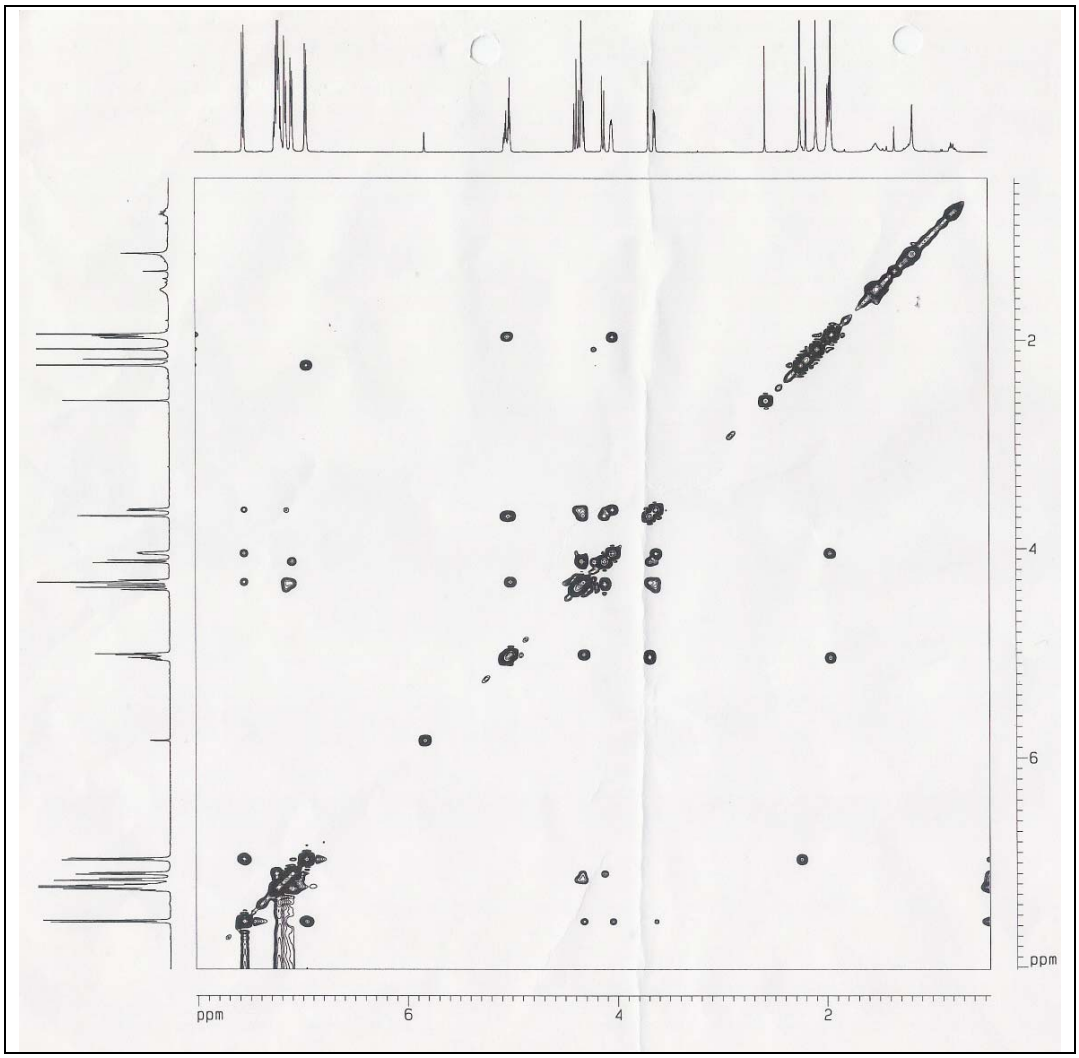


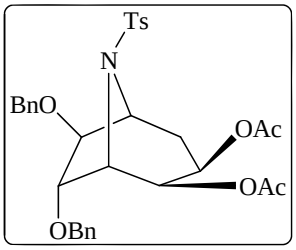
^{13}C NMR Spectrum of 139 in $CDCl_3$



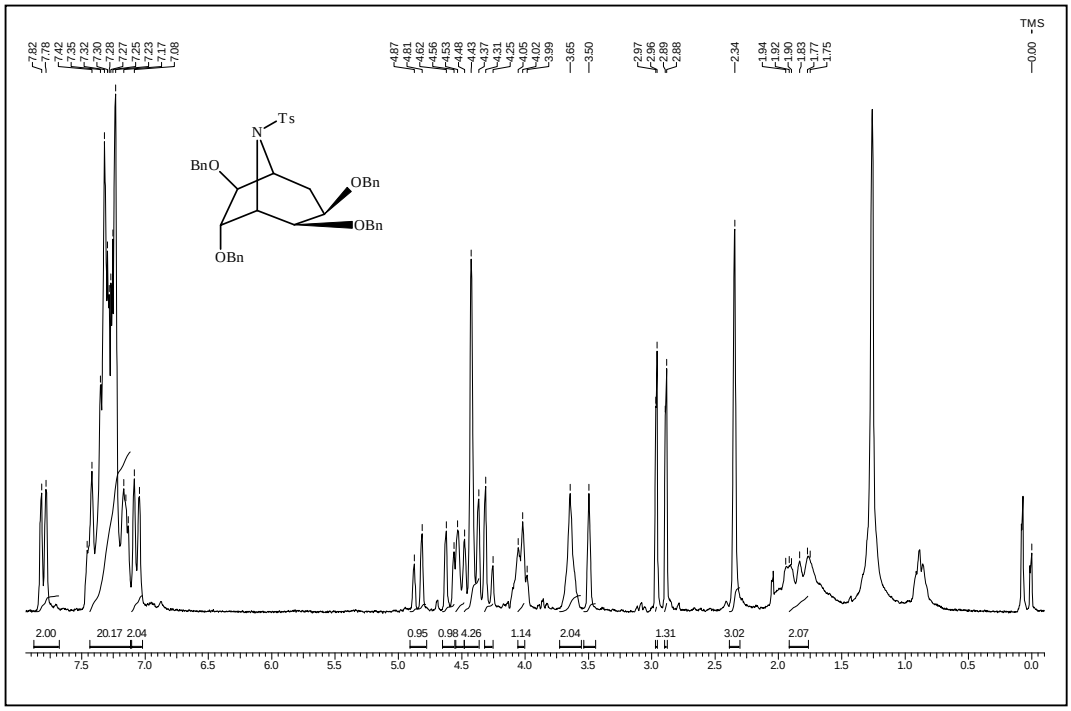


COSY Spectrum of 139

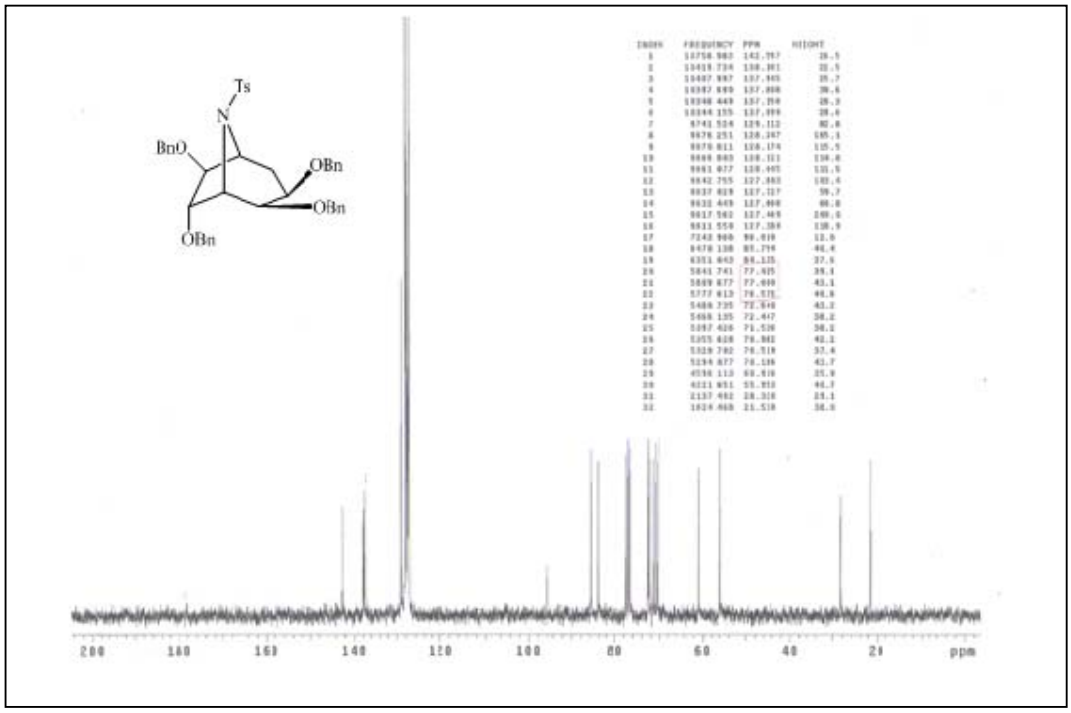




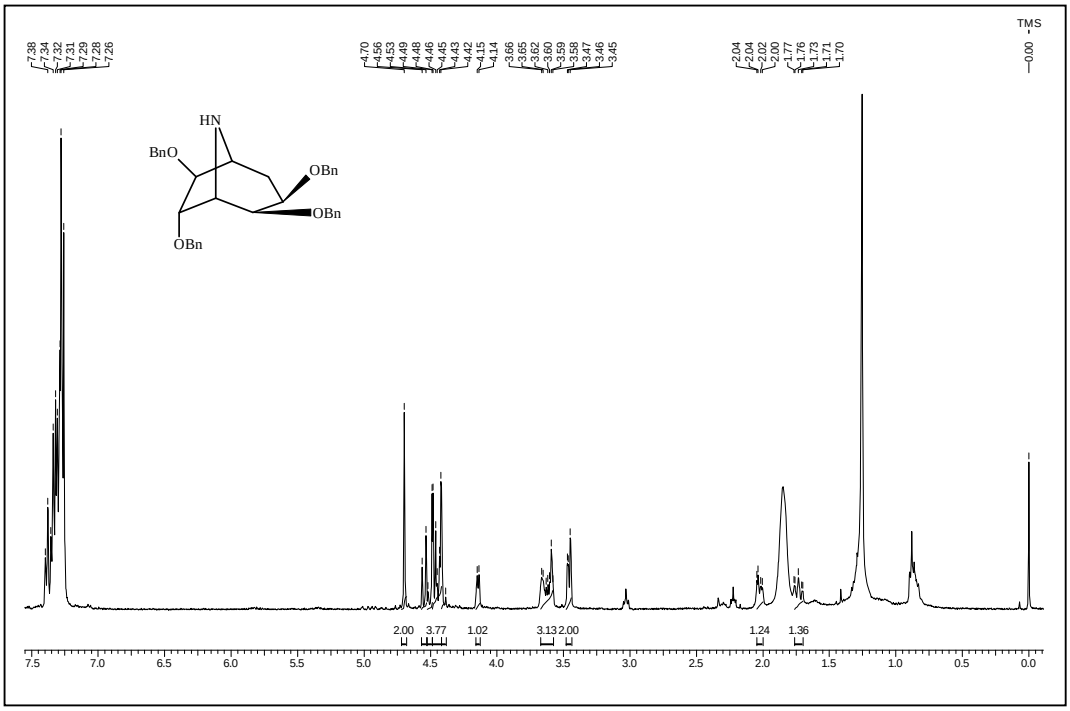
NOESY Spectrum of 139



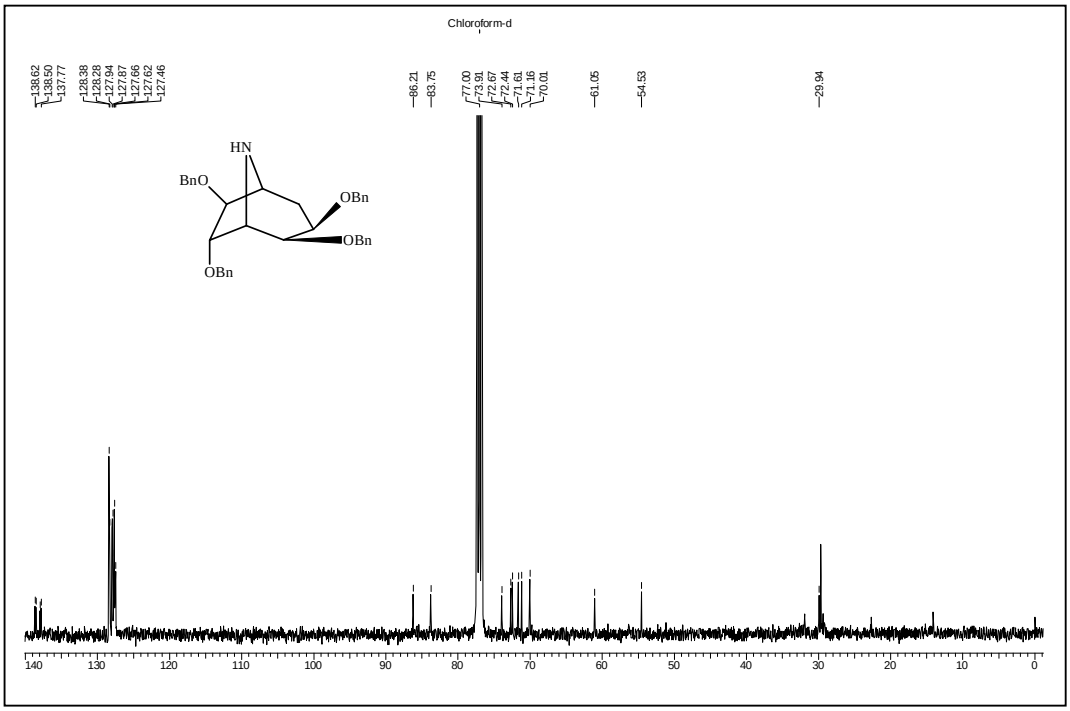
^{1}H NMR Spectrum of 140 in $CDCl_3$



^{13}C NMR Spectrum of 140 in $CDCl_3$



^{1}H NMR Spectrum of 141 in $CDCl_3$



^{13}C NMR Spectrum of 141 in $CDCl_3$

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