DECLARATION

I hereby declare that the thesis entitled **'Carbohydrate based cyclopropyl methylene bromides as free radical precursors: Application in the synthesis of *oxa*-triquinanes, spirosugars and synthetic studies toward the C_{19}- C_{28} fragment of phorboxazole'** submitted for Ph. D. degree to the University of Pune has been carried out at Indian Institute of Chemical Technology, Hyderabad, India and National Chemical Laboratory, Pune, India under the supervision of **Dr. Mukund. K. Gurjar,** Deputy director and Head, Division of organic chemistry: Technology, National Chemical Laboratory, Pune-411008. The work is original and has not been submitted in part or full by me for any degree or diploma to this or any other University.

Date: August 13th, 2001 **(Somu. V. Ravindranadh)**

Division of Organic Chemistry: Technology

National Chemical Laboratory

Pune - 411 008.

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NATIONAL CHEMICAL LABORATORY

Dr. Homi Bhabha Road, PUNE. 411 008 INDIA.

Dr.M.K. Gurjar
Head & Deputy Director
Division of Organic Chemistry: Technology

Telephone and Fax: + 91-20-5893614
+ 91-20-5882456
E-mail: gurjar@dalton.ncl.res.in
Website: http://www.ncl-india.org

CERTIFICATE

The research work presented in thesis entitled **'Carbohydrate based cyclopropyl methylene bromides as free radical precursors: Application in the synthesis of *oxa*-triquinanes, spirosugars and synthetic studies toward the C_{19}- C_{28} fragment of phorboxazole'** has been carried out under my supervision and is bonafide work of Mr. Somu. V. Ravindranadh. This work is original and has not been submitted for any other degree or diploma of this or any other University.

Pune-8

13th August, 2001

(Dr. M. K. Gurjar)

Research Guide

CONTENTS

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Ravindranadh

GENERAL REMARKS

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

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

- 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}

- Proton magnetic resonance spectra were recorded on Varian FT-200 MHZ (Gemini), AC-200 MHz, MSL-300 MHz, Bruker-500 MHz and Varian Unity-400 MHz spectrometer using tetramethyl silane (TMS) as an internal standard. Chemical shifts have been expressed in ppm units downfield from TMS.

- ^{13} C Nuclear magnetic spectra were recorded on Varian FT-50 MHz (Gemini), AC-50 MHz, MSL-75 MHz spectrometer.

- Mass spectra were recorded on a CEC-21-110B, Finnigan Mat 1210 or MICRO MASS 7070 spectrometer at 70 eV using a direct inlet system. FABMS were recorded on a VG autospec mass spectrometer at 70 eV using a direct inlet system.

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

- All evaporation were carried out under reduced pressure on Buchi rotary evaporator below 50 °C.

- All solvents and reagents were purified and dried by according to procedures given in Vogel's Text Book of Practical Organic Chemistry.

- Silica gel (60-120) used for column chromatography was purchased from ACME Chemical Company, Bombay, India.

ABBREVIATIONS

Ac	-	Acetyl
AcOH	-	Acetic acid
Ac_2O	-	Acetic anhydride
AIBN	-	Azaisobutyronitrile
Bn	-	Benzyl
BnBr	-	Benzyl bromide
DCM	-	Dichloromethane
DIPEA	-	Di-isopropylethylamine
DMAP	-	*N,N'*-Dimethylaminoformamid
DMSO	-	Dimethyl sulfoxide
EtOAc	-	Ethyl acetate
HMDS	-	Hexamethyldisilazane
IBX	-	Iodoxybenzoic acid
Im	-	Imidazole
MeOH	-	Methanol
MeI	-	Methyl iodid
NaH	-	Sodium hydride
PDC	-	Pyrydenium dichromate
Py	-	Pyridine
TEA	-	Triethyl Amine
TBDMS-Cl	-	*tert*-Butyldimethylchlorosilane
TPP	-	Triphenyl Phosphine
pTSA	-	*para*-Toluenesulfonic acid
TBTH	-	Tri n-butyltin hydride
TrCl	-	Trityl Chloride

ABSTRACT

TITLE: CARBOHYDRATE BASED CYCLOPROPYL METHYLENE BROMIDES AS FREE RADICAL PRECURSORS: APPLICATION IN THE SYNTHESIS OF *OXA*TRIQUINANES, SPIRO SUGARS AND SYNTHETIC STUDIES TOWARD THE C_{19}-C_{28} FRAGMENT OF PHORBOXAZOLE.

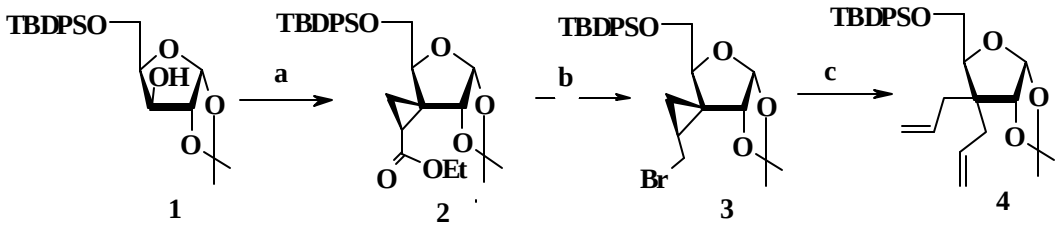
This thesis is divided into three chapters. Chapter 1 deals with the development of a method for the synthesis of geminal diallyl systems on carbohydrate and noncarbohydrate synthons and their elaboration to spiro compounds using Grubbs' catalyst.

Chapter 2 deals with the development of a radical cascade cyclization method for the synthesis of novel oxa and dioxa triquinanes. and the establishment of the mechanistic pathway of this cascade cyclization.

Chapter 3 deals with the attempts to synthesize the stereochemically dense central pyran core spanning C_{19}- C_{28} carbon fragment of the Phorboxazole A, a marine isolation of phorbos species, having a phenomenal levels of cytostatic activity.

CHAPTER 1

Incorporation of *gem*-diallyl groups is usually achieved by base catalyzed dialkylation of active methylene group with allyl halides. However, we realized that this approach might not be appropriate for carbohydrate molecules. We are particularly interested in developing a neutral and versatile method to generate *gem*-diallyl system in a carbohydrate unit by quenching the allylic radical generated *in situ*, with allyltri-n-butylstannane.



1 2 3 4

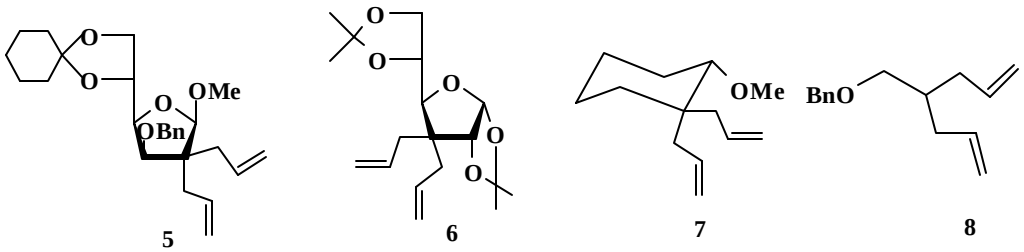
Scheme 1 *Reagents and Conditions:* (a) i) IBX, DMSO, rt; ii) PPh_3= $CHCO_2Et$, CH_2Cl_2, reflux; iii) Me_2SOCH_3I, NaH, DMSO, rt, 3 h; (b) i) DIBAL-H, -78 ^oC;(ii) PPh_3, CBr_4, pyridine, 0 ^oC; (c) allyltri-n-butylstannane, AIBN (5 Mol %), benzene, 80 ^oC.

In accordance with our plan, 5-*O*-(*tert*-butyldiphenylsilyl)-1,2-*O*-isopropylidene-α-D-xylofuranose (**1**) was converted to **2**. The ester compound was converted to the corresponding bromo derivative. Treatment of **3** with allyl tri-*n*-butylstannane in presence of catalytic amount

of AIBN in refluxing benzene under argon atmosphere for 12 h gave the *gem*-diallyl compound **4** in good yield (Scheme 1).

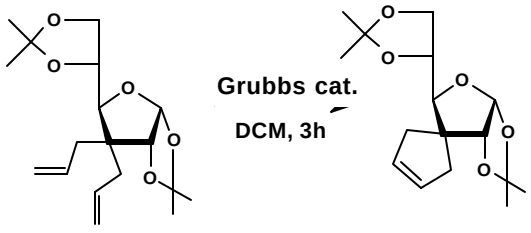
Accordingly, number of precursors were prepared and converted to the corresponding gem-diallyl compounds. These potential RCM precursors can be converted to their carbocycle counter parts with Grubbs' catalyst. For example, **6** on treatment with Grubbs' catalyst has given **7** in good yield (Scheme 2).

Figure 1



5 **6** **7** **8**

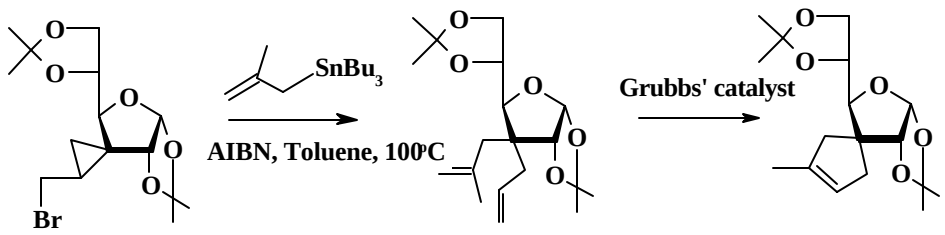
Scheme 2



6 **9**

Similarly, the cyclopropyl methyl bromide **10** when treated with (Scheme 7), methallyl tri-*n*-butyl stannane under argon atmosphere, in refluxing benzene for 24h, afforded the diastereomer **11**, in >98 % de, where in the newly coming methallyl group was introduced form â position, because of the stereocontrolling properties of the acetonide, whose structure was confirmed by

Scheme 3



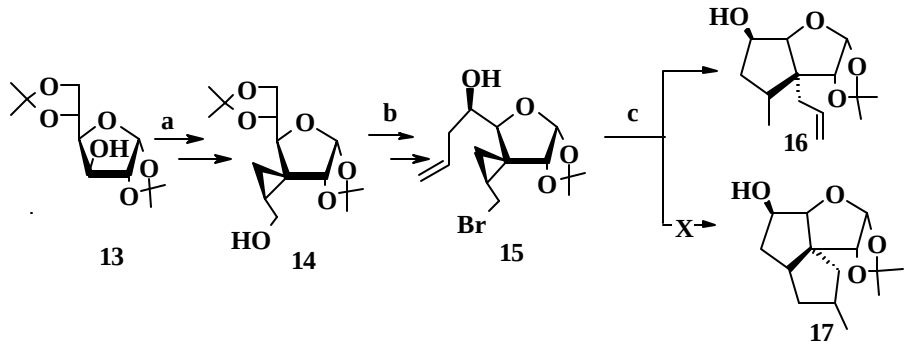
10 **11** **12**

extensive COSY and NOESY studies. Compound **11** on treatment of Grubbs' catalyst provided the corresponding spiro compound **12** (Scheme 3).

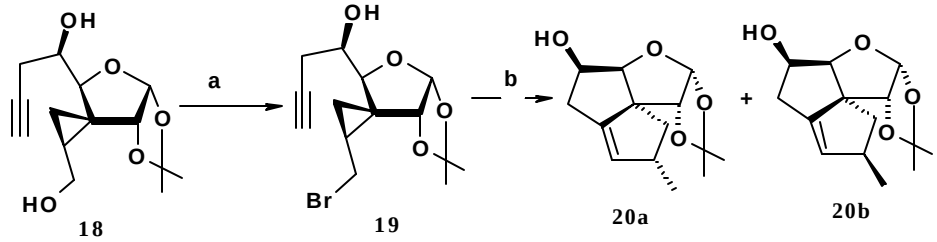
CHAPTER 2

The angularly fused triquinanes have attracted intense attention of synthetic organic chemists as challenging targets. Structural complexity associated with significant biological activity has necessitated development of several new approaches. The work embodied in this chapter, demonstrates a successful method for the construction of the oxa and di-oxa triquinanes using radical cascade cyclization as an efficient synthetic tool. In this method, tertiary radical generated by the opening of cyclopropyl methyl bromide adds on to a suitable radical acceptor, which further adds on to the incipiently formed allyl group to give the triquinane skeletons.

Accordingly, as per the scheme1, 1,2:5,6-Di-*O*-isopropylidene-α-D-glucofuranose **(13)** was converted to the cyclopropyl methanol derivative (**14**) over five steps. Deprotection of 5,6 isopropylidene and oxidative cleavage yielded the aldehyde, which when treated with Zn, allyl bromide under aqueous Barbier conditions gave allyl addition product which upon treatment with CBr_4/ PPh_3 in CH_2Cl_2 gave the corresponding bromo derivative (**15**). Treatment of **15** with tri n-butyl tinhydride (TBTH), AIBN in toluene (0.05 M) at 100 ^oC gave a product whose structure was assigned as **16** based on NMR studies. In order to circumvent this problem we sought vinyl radicals. Accordingly, intermediate aldehyde was subjected to aqueous Barbier reaction with propargyl bromide to afford **18** as an exclusive product. The transformation of **18** into **19** was achieved using PPh_3, CBr_4.



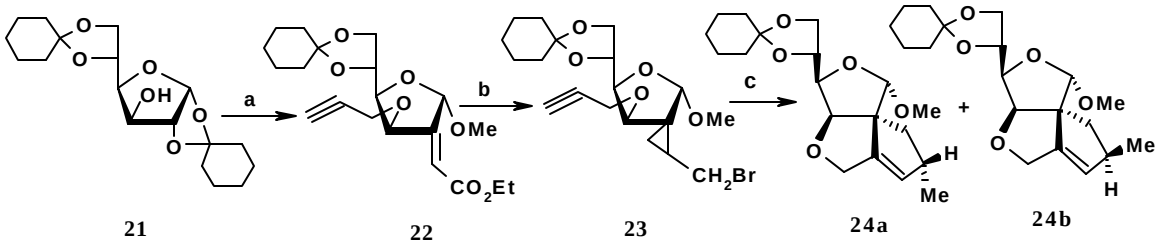
Scheme 4 Reagents and conditions: (a) i) PDC, Ac_2O, 4A° MS Powder, CH_2Cl_2, ii) $PPh_3=CH_2CO_2Et$, C_6H_6; iii) Me_2SOCH_3I, NaH, DMSO; iv) DIBAL-H, CH_2Cl_2, -78°C (b) i) 0.8% aq. H_2SO_4, methanol; ii) Silica adsorbed $NaIO_4$; iii) allyl bromide, Zn, aq. NH_4Cl, THF, 0°C; iv) TPP, CBr_4, Pyridine, CH_2Cl_2, rt; (c) tri n-butyl tin hydride, AIBN (5mol%), toluene, 100°C.



Scheme 5: *Reagents and conditions:* (a) TPP, CBr_4, pyridine, CH_2Cl_2, rt; (c) tri *n*-butyl tin hydride, AIBN (5mol%), toluene, 100°C.

The radical reaction of **19** with TBTH and AIBN (cat.) gave angularly fused oxa-triquinqne derivative. COSY and NOSY studies revealed the absolute stereochemistry of the major isomer **20a**.

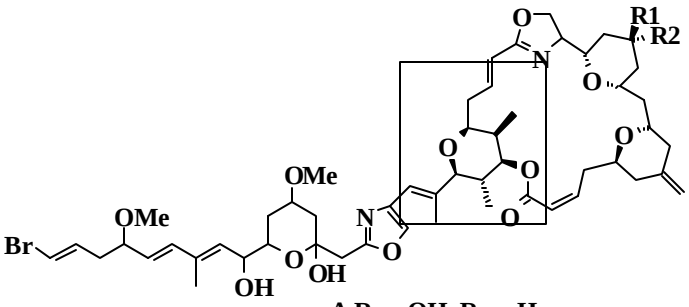
Similarly, radical precursor **23** was prepared from starting from **21** and was treated with Bu_3SnH and AIBN to give the cyclization product **24a**.



Scheme 6: *Reagents and conditions:* (a) (i) NaH, propargyl bromide, DMF, 0°C; (ii) cat. H_2SO_4, refluxing methanol, á/â: 40/60 separated by column chromatography; iii) *O*-Iodoxybenzoic acid, DMSO, rt; iv) PPh_3= $CHCO_2Et$, benzene, 80 °C; (b) i) Me_2SOCH_3I, NaH,

DMSO; ii) DIBAL-H, -78 ^{o}C; iii) PPh_3, CBr_4, pyridine, 0 ^{o}C; (c) tributyltin hydride, AIBN (5 mol %), toluene, 100 ^{o}C.

Chapter III: Synthetic studies towards the *C19- C27* fragment of Phorboxazole A

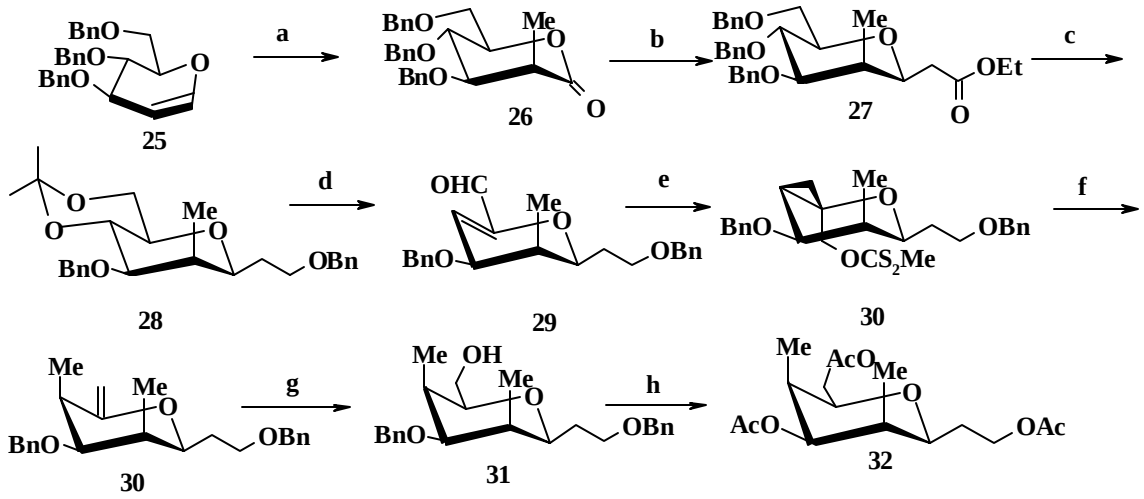


A R_1 = OH, R_2 = H

B R_1 = H, R_2 = OH

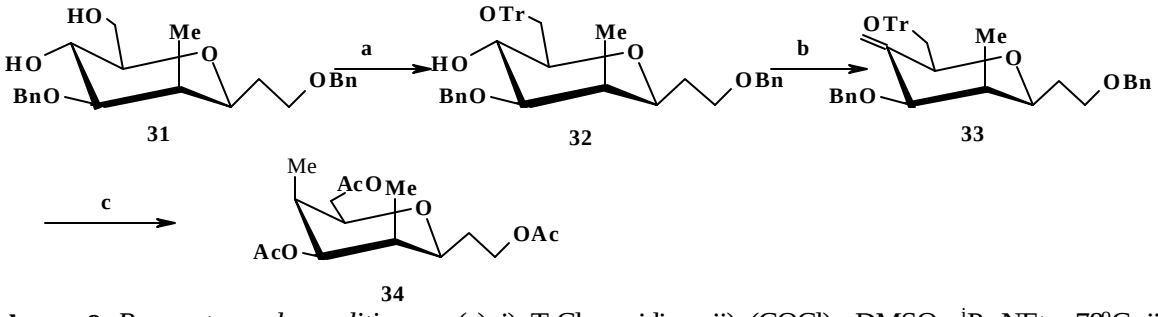
Figure 3

Phorboxazoles A and B are remarkably novel and structurally interesting marine natural product isolated from an extract of the Indian ocean sponge species *Phorbos* with profound and potent cytotoxic activity against an astonishing range of human tumor cells lines. The relative configuration of phorboxozole has been assigned by Searl and Molinski. Later the same group has reported the absolute configuration. This chapter deals with the attempted the synthesis of *C_{19}- C_{28}* fragment of this molecule, adorned with five contiguous stereogenic centers. D-glucopyronaside was chosen to be the suitable starting material (Scheme 8). It was planned to install the methyl groups at *C-2* and *C-4* positions with relevant chirality through diastereoselective cyclopropanation followed by electrophilic/ free radical ring cleavage. Accordingly, xanthate derivative (**29**), which was synthesised as per the scheme, when subjected to free radical mediated ring opening with TBTH, followed by hydroboration gave compound **31**. Compound **31** on hydrogenalysis followed by acetylation gave triacetyl derivative whose structure was assigned to be **32**. But equatorial methyl was required.



Scheme 3 *Reagents and conditions*:(a) i) CH_2I_2, Zn-Cu Couple, Cu(I)Cl, Cat. AcCl, Ether, reflux; ii) Hg $(OAc)_2$, THF/Water (3:1), NaCl, TBTH, AIBN; iii) PDC, DCM; (b) i) CH3CO2Et, Li HMDS, -78°C, THF; ii) BF_3: Et_2O, Et_3SiH, DCM, -78°C to 0°C;(c) i) LAH, THF, 0°C; ii) Pd/C, H_2 atm; iii) DMP, acetone, pTSA; iv) NaH, DMF, BnBr, 0°C; (d) i) pTSA, MeOH; ii) TBDMSCl, Imidazole, DCM; iii) Ac_2O, Pyridine, Cat. DMAP, DCM; iv) $(COCl)_2$, DMSO, *i*Pr_2EtN, -78°C; (e) i) DIBAL-H, DCM, -78°C; ii) TBDMSCl, Imidazole, DCM; iii) Et_2Zn, CH_2I_2, DCM, -20°C; iv) TBAF, THF;) NaH, CS_2, MeI, THF, 0 °C; (f) i) TBTH, AIBN, Toluene, reflux; (g) BH_3: DMS, THF, 0°C; h) Pd/C, MeOH, H_2 tam; ii) Ac_2O, Pyridine, Cat. DMAP, DCM

As an alternative strategy, oxidation of hydroxyl group at *C-4*, followed by Wittig methylenation and hydrogenation was attempted, which also produced the axial methyl at *C-4*. Efforts are now underway to direct the selective cyclopropanation and hydroboration- oxidation by steric tuning of the existing functionalities that will pave the way for right stereochemistry at *C-4* position.



Scheme 9 *Reagents and conditions*: (a) i) TrCl, pyridine; ii) $(COCl)_2$, DMSO, $^{i}Pr_2NEt$, -78°C; iii) PPh_3CH_3I, BuLi, Ether, -78°C; (b) i) Pd/C, MeOH, H_2 atm; ii) Ac_2O, Pyridine, Cat. DMAP, DCM

The practice of organic synthesis, when it comes to the synthesis of natural products, continues to expand in a relentless manner. Urge to synthesize increasingly complex synthetic targets pushed the limitless horizons of achievements even further. This art of total synthesis has profound implications on other branches of science, because application of its methodology can result in the construction of manifold compounds, thus opening new avenues of research in medicinal chemistry, biochemistry, biology and bio organic chemistry. This impact results in the improvement of existing methods and generation of novel and elegant products of ever increasing complexity. Construction of asymmetric quarternary carbon is one of such kind in organic synthesis.

Chirality in the context of biological activity is an important phenomenon. Although chirality is not a prerequisite for the activity, greater differences were found in the biological activity of enantiomers of a chiral compound. For example, the sedative thalidomide was marketed as recemate. The desired sedative activity resides in the R- isomer, but the contaminant S-isomer was found to be a teratogen, causing profound birth defects in babies born to the mothers served with the drug. The (R, R) enantiomer of tuberculostatic (S, S)-ethambutol can cause blindness and therefore there is more insistence in producing the drugs in optically pure forms. However, development of general methods for the generation of chiral centers, which can compete with efficacy and precision of nature, is very difficult though not impossible. In this perspective, the strategy of chiral pool approach seems more logical[1], wherein a synthesis is devised utilizing readily available and operationally versatile optically active starting materials. The use of amino acids, terpenes, chiral hydroxy acids and carbohydrates as potential chiral building blocks in the synthesis is well documented in the literature.

Over the decades, carbohydrates have been well recognized as naturally occurring organic compounds, endowed with a wealth of stereochemical attributes, which can fulfill the requirement of synthetic organic chemist. In brief, carbohydrates are relatively cheap, replenishable sources of chiral

carbon compounds present in cyclic and acyclic forms and different chain lengths. Plethora of functional groups, stereochemical and conformational features are some of the salient features amenable to exploitation. Main strategies that provide practical approach to asymmetric synthesis are employing carbohydrates as scaffolds, cores or templates on which the systematic functionalization and structural transformations are employed transforming them into the analogous entities, which resemble the targets or total transformation of carbohydrates to unrelated chiral compounds, which are suitable precursors (chirons), which can be used further in much broader variety of synthetic applications.

Quarternary Carbon:

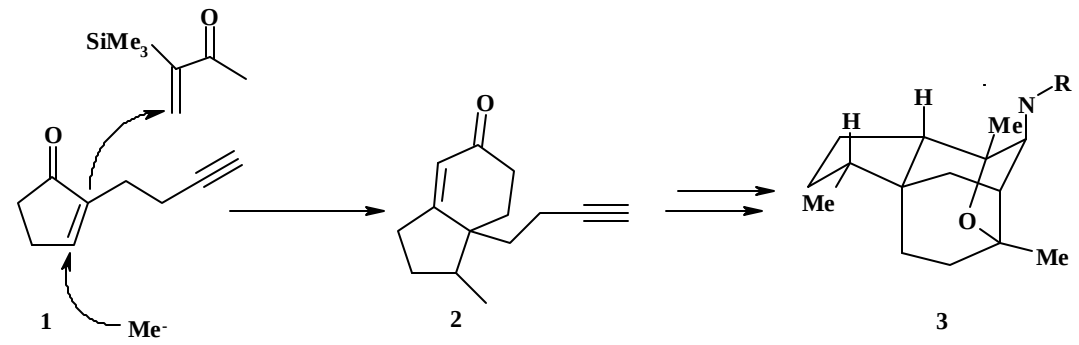
During the course of synthesis of bioactive natural products possessing complex molecular architecture, one of the challenges posed by nature is the presence of quarternary carbon, i.e., a carbon connected to four different carbons. Although there exist core strategies for C-C bond formation, some care must be taken in choosing appropriate methodologies and reagents that can survive labile functional groups. The C-C bond formation reaction frequently used in organic synthesis is not applicable for the formation of quarternary carbon center, because of the dominance of usual side reactions. To achieve this, a number of sophisticated approaches have been developed up to now.[3] A brief discussion is as follows.

Recent progress

Many strategies and tactics are reported to generate quarternary carbon center and to incorporate each of them is beyond the scope. Only important and recent strategies are dealt with.

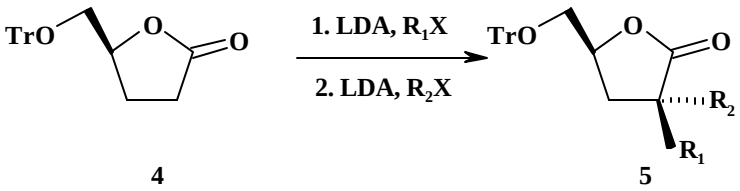
Danishefsky and coworkers[4] have used Michael addition i.e. 1,4-conjugate addition of dimethyl lithium cuprate to the cyclopentenone derivative **1** and trapped the generated site specific enolate with methyl vinyl ketone equivalent followed by site specific alkylation *en route* to Robinson annulation type product **2**, which was further elaborated to hipsidospermidine **3** (Scheme 1).

Scheme 1



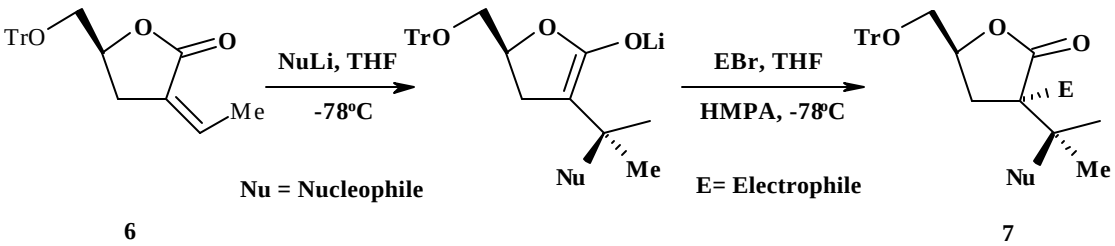
In another report Koga et al[5] described the asymmetric quarternisation of the α-carbons of enantiomerically pure γ-lactones **4** by consecutive alkylation of stereochemically biased quenching of the enolate leading to the *gem* disubstituted lactones (**5**) (Scheme 2).

Scheme 2



*In another approach,[6,7] 1,4-conjugate addition of á-ethylidene-g-lactone (**6**) and successive á-alkylation of the intermediate enolate has provided the diastereoselective C-C bond formation giving **7**,* via *stereo-differentiating environment of five membered skeleton (Scheme 3). A characteristic feature of this protocol is the introduction of two adjacent chiral carbon centers in one operation.*

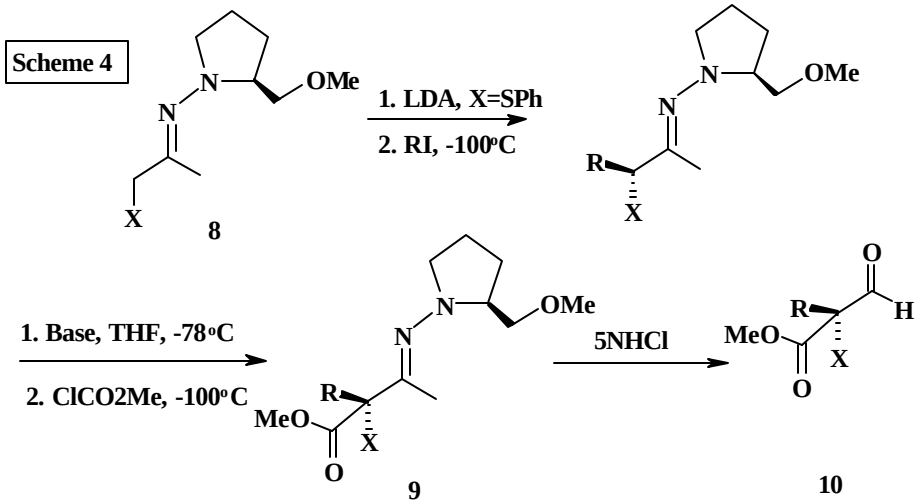
Scheme 3



Enders *et al.*[8] have used SAMP/RAMP hydrazones **8** as chiral auxiliaries for high regio-diastereo- and enantioselective consecutive electrophilic substitution at the α-position of the aldehydes

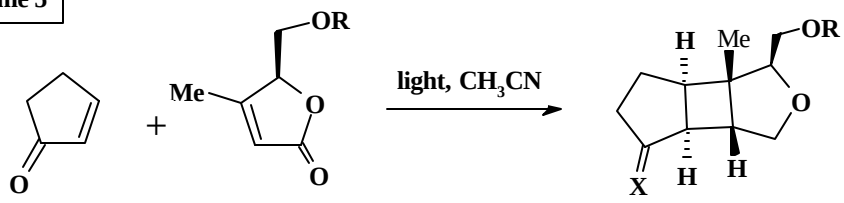
and ketones leading to the formation of di-alkylation products **9**, which was hydrolyzed to afford **10** in optically pure form (Scheme 4). This method was extended to synthesize several polyfunctional building blocks, bearing a quarternary stereogenic center.

Scheme 4



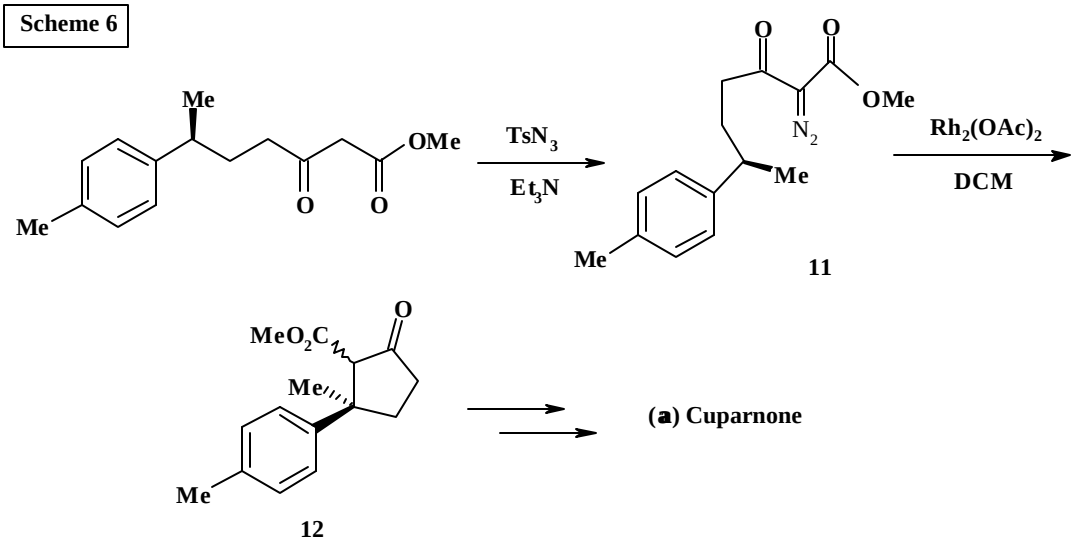
Another advancement achieved by Koga *et al.*[9] was the (2+2)-photo-cycloaddition of cyclopentenone and the chiral butenolides leading to the tricyclic skeleton including an angular chiral quarternary carbon (Scheme 5).

Scheme 5



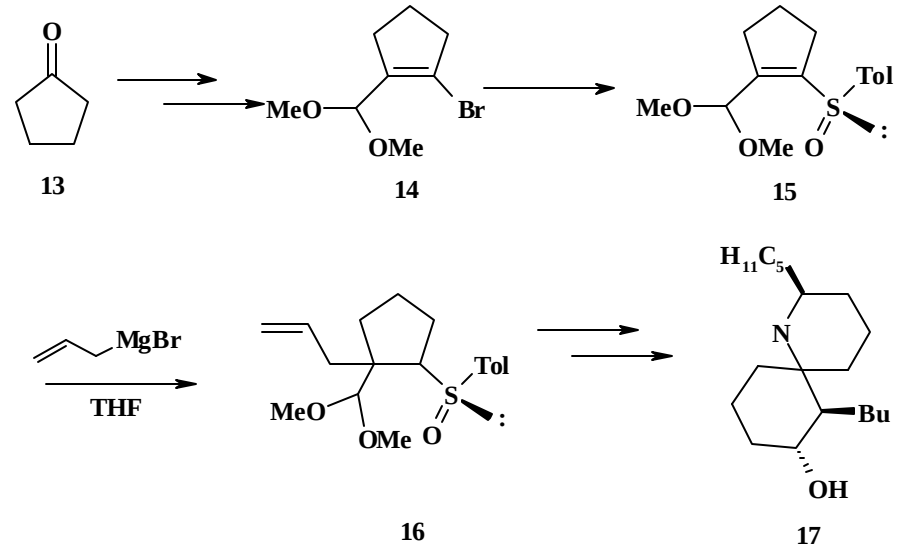
Taber and co-workers have demonstrated the rhodium (II) mediated intramolecular annulation[10] of α-diazo-β-keto-ester **11** resulting in the formation of cyclopentanone derivative **12** possessing a chiral quarternary chiral center (Scheme 6). Important feature of this reaction was the retention of absolute configuration pre-existing in the substrate **11**. The annulation product was further elaborated to (α)-cuparnone.

Scheme 6



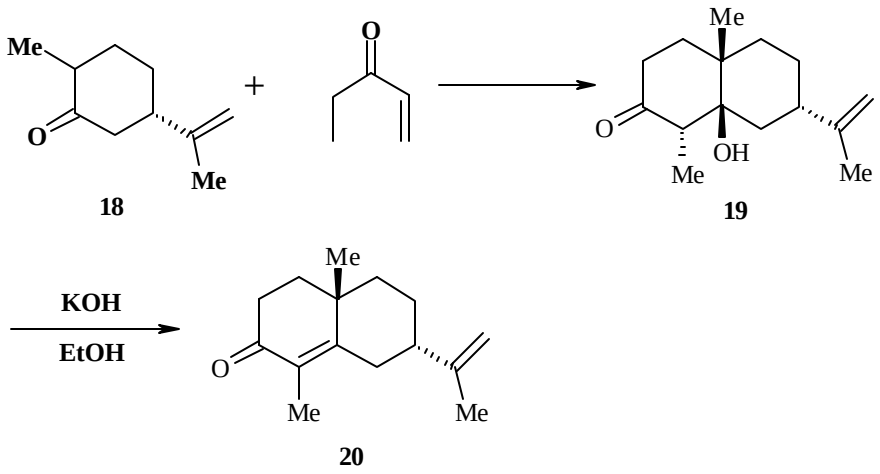
Itawa's group has demonstrated another method,[11] *in which addition of alkyl magnesium bromide onto the chiral vinyl sulphoxides* ***15*** *(synthesised form simple cyclopentanone* ***13****,* via ***14****, in a way of Pummerer like reaction) gave the quarternary chiral compound* ***16*** *in 90 % ee. This intermediate* ***16*** *was further elaborated for the synthesis of structurally complicated and pharmacologically active perhydrohistrianicotoxin (Scheme 7).*

Scheme 7



Ziegler et al. *reported*[12] *a practical synthesis of (+)-6-epi-α-cyperone, which possesses an angular methyl group. This was achieved by Robinson annulation of the Muller Li-bronge reduction product (****18****) of (+) carvone and ethyl vinyl ketone* ***19*** *giving the highly functionalized decalone system* ***20*** *in optically pure form (Scheme 8).*

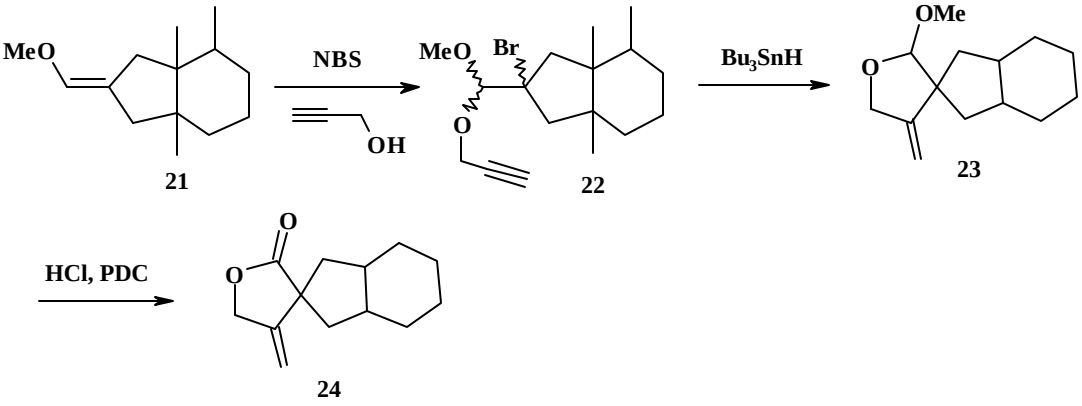
Scheme 8



18 **19** **20**

During the work on the synthesis of Dakkenolides, Shrikrishna and his colleagues[13-15] have used the 5-*exo*-trig radical cyclisation generating the spirolactone unit **24**. Bromoacetal **22** generated from **21** using NBS and propargyl alcohol, has undergone the radical cyclization to give the spiro acetal system **23** (Scheme 9).

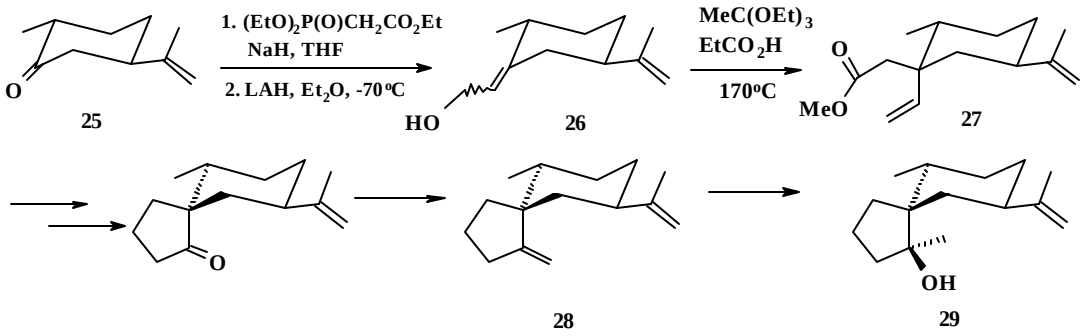
Scheme 9



21 **22** **23** **24**

Srikrishna *et al.* have also utilized the Claisen rearrangement[16] for generation of quarternary center. For example, they demonstrated the successful enantiospecific synthesis of the natural products (+) dihydrocrythrodienes (**28**), (+) dihydrospirojatamol (**29**)[17] using this protocol. Trans-dihydrocarvone **25**, derived from (R) carvone, gave the allylic alcohols **26**, which on treatment with triethyl orthoacetate in presence of catalytic

Scheme 10



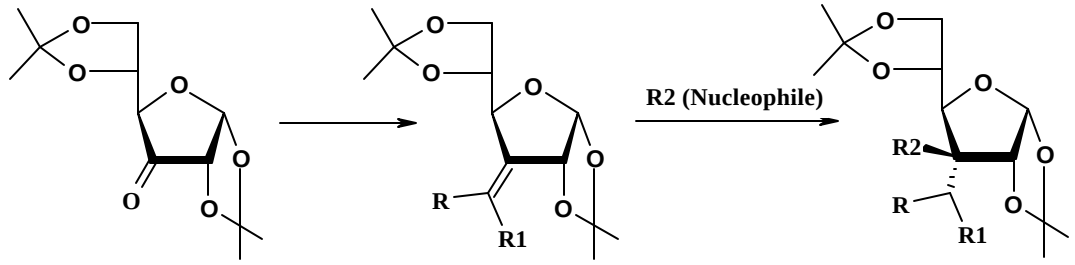
amount of acid at high temperature gave inseparable mixture of diene esters **27**, which were later converted to separable lactones and one of which was carried further for the synthesis of **28** and **29** (Scheme 10).

Introduction of quarternary chiral center on carbohydrate skeletons:

As mentioned before the usage of carbohydrate building blocks as starting materials, the so called Chiron approach, is a well established concept for the asymmetric natural product synthesis and introduction of quarternary center is an inevitable step in both the synthesis of many spirocarbocycles and many complex natural products. Many approaches based on carbohydrate precursors have been reported in literature, however only a few important protocols are discussed below.

Ali *et al.* reported[18,19] geminal C-alkylation at C-3 of glucose diacetonide. Substituted 3-C-methylene derivatives **30** when subjected to Michael addition reaction with a variety of nucleophiles have provided 3-C-dialkylated sugars **31** (Scheme 12).

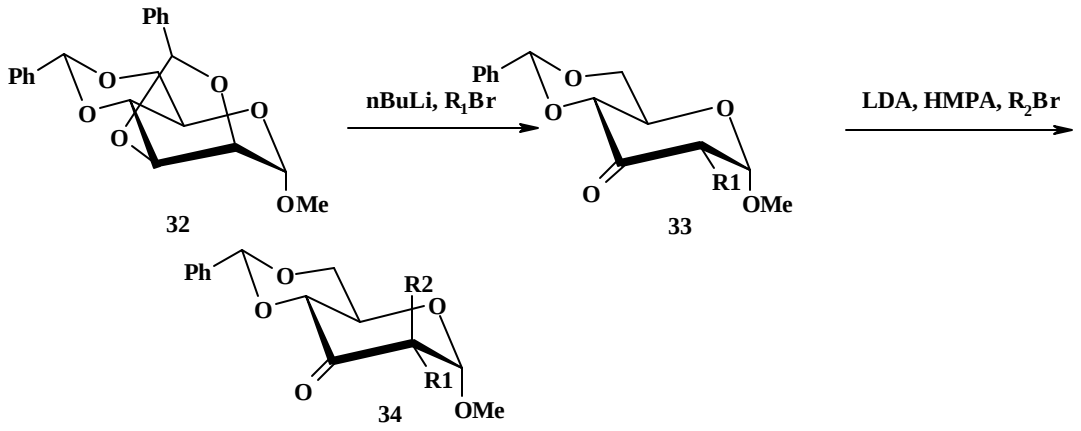
Scheme 12



Highly selective β- face reactivity of the nucleophiles at C-3 position of the derivative **30** can be explained by stereoelectronic effects posed by the 1,2-dioxalane groups.

Chapleur *et al.*[20] reported the dialkylation at C-2 of a D-mannose derived hexopyranoside. The key reaction being the alkylation of lithium enolate generated from the 2-C-alkyl-2-deoxy-3-ulose **33**, which in turn was prepared by 2,3:4,6-di-*O*-benzylidene-α-D-mannopyranoside **33** by BuLi treatment followed by electrophilic addition. The second alkylation has occurred from the less hindered β-face of the enolate to give **34** (Scheme 13).

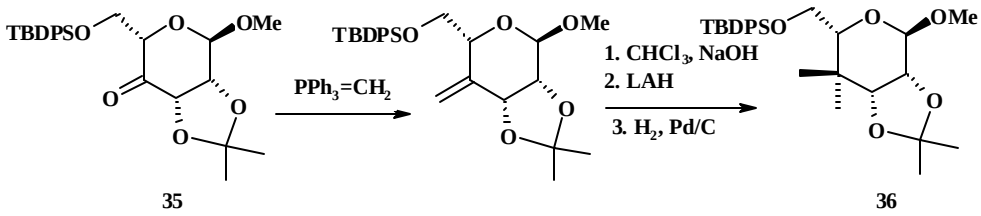
Scheme 13



Nicolaou *et al.* have reported[21] a concise synthesis of a key intermediate for the total synthesis of aurodox and cyrotomycin starting from suitably protected 4-ulose derivative of L-mannose **35**. Wittig olefination and dichlorocarbene addition to the alkene, followed by LAH

reduction and hydrogenolysis afforded the 4-*gem* dimethyl derivative **36**, which was further subjected for the carbon elongation (Scheme 14).

Scheme 14

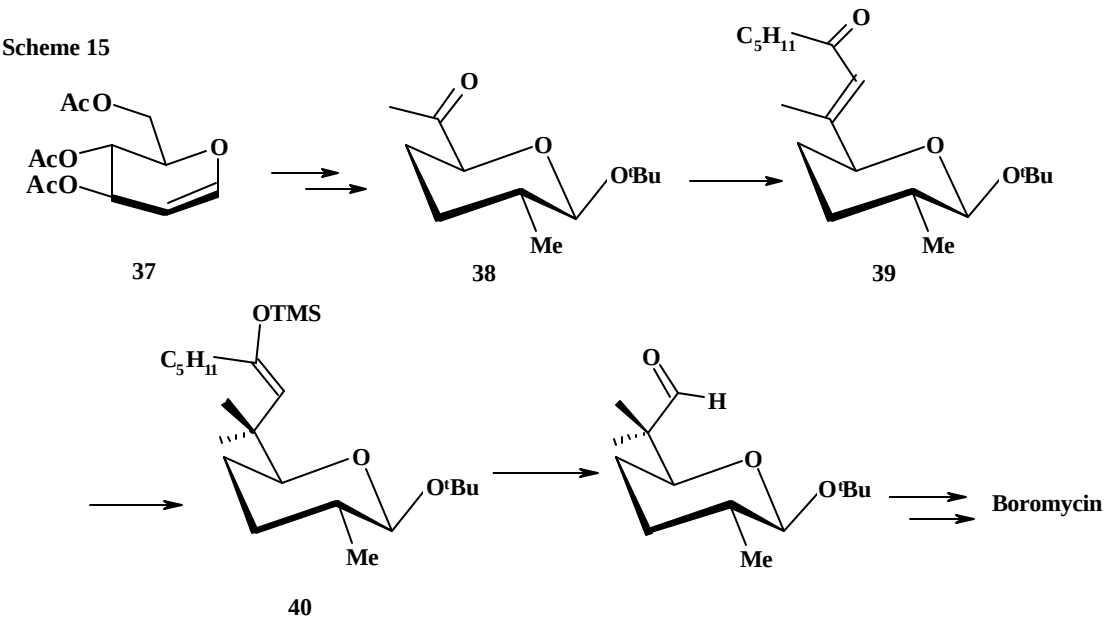


35 **36**

Kishi *et al*. employed[22] a similar geminal dimethylation protocol in the total synthesis of mycolamides A and B.

Hanessian *et al.* [23,24] have synthesised a 6,6-*di*-*C*-methyl heptopyranoside derivative in the total synthesis of boromycin. Readily available tri-*O*-acetyl-D-glucal **37** was converted to ^{t}butyl-2-*C*-methyl-2,3,4,7-tetradeoxyhept-6-ulopyranoside **38**. Wittig olefination has provided the á, â-unsaturated ketone derivative **39**, conjugate addition of the methyl anion generated from Me_2CuLi, on to the enone followed by the trapping of enolate by TMS-Br has provided the 6,6-*di*-*C*-methyl silyl enolate derivative **40**, which was further converted to aldehyde, subjected for the carbon elongation and was converted to boromycin (Scheme 15).

Scheme 15

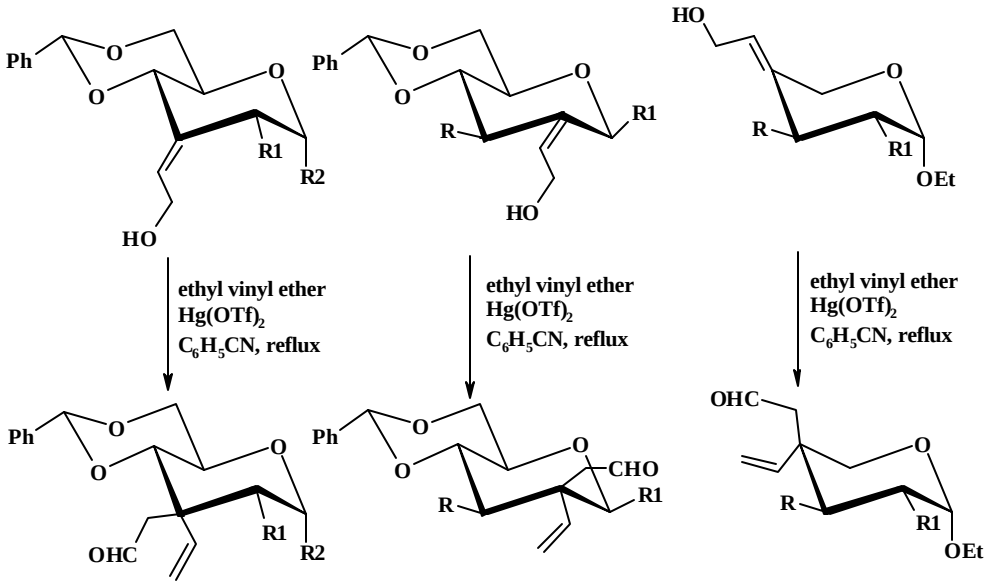


The Claisen rearrangement for the introduction of chiral quarternary center:

Fraser-Reid *et al*. have employed for the first time this Claisen rearrangement for quarternization of hexopyranose. Accordingly, different hexo-pyranosides having allylic alcohol were taken and treated with ethyl vinyl ether in presence of mercury (II) triflate at room temperature followed by refluxing in benzonitrile to give the Claisen rearrangement products (Scheme 16).[25-27]

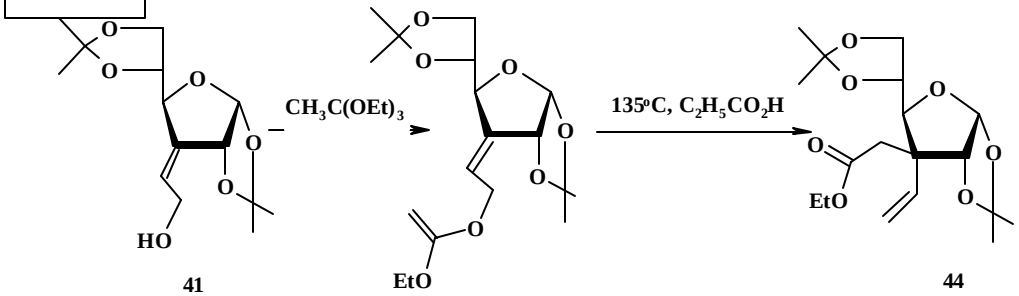
Fraser Reid's group has subsequently utilized these intermediates in the synthesis of tricothecane systems, diquinanes and several triquinanes[28-31]

Scheme 16

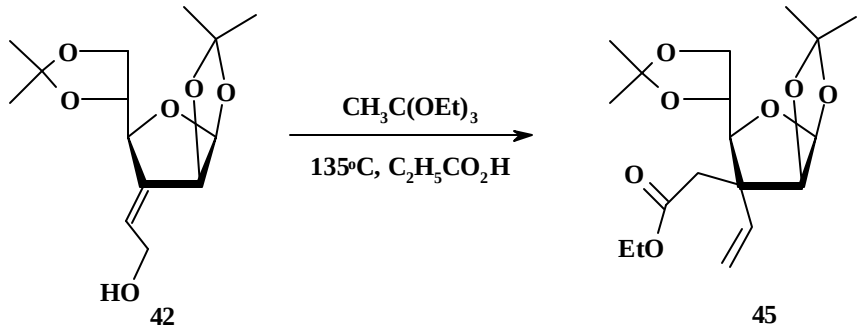


After pioneering research by Fraser-Reid on Claisen rearrangement of hexopyranose derivatives, Tadano *et al.*[32,33] investigated Johnson orthoester Claisen rearrangement on hexofuranose derivatives of α-D-glucose for introducing quarternary chiral center at C-3. Accordingly, they subjected the three set of furanose derivatives, **41-43** that possess *(E)*-3-C methylene group at C-3 to Claisen orthoester rearrangements, by heating with triethylorthoacetate and in catalytic propionic acid at 135° C to afford the stereoselectively rearranged products **44-46** (Scheme 17).

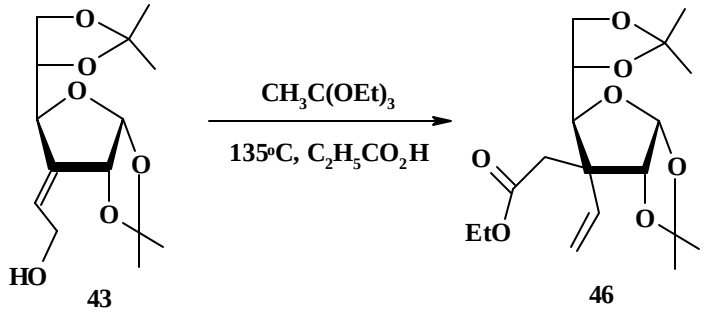
Scheme 17



41 **44**



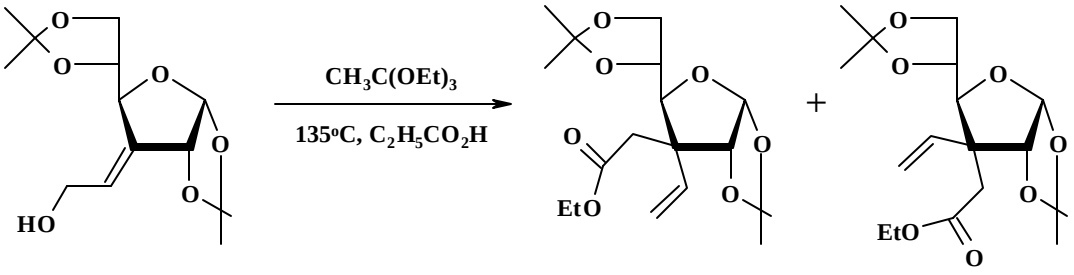
42 45



43 46

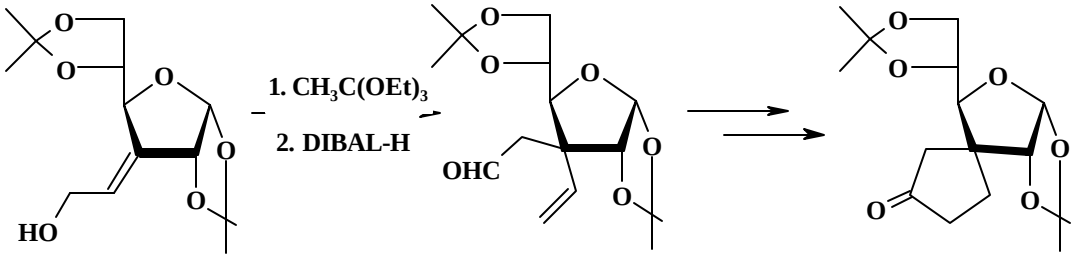
Corresponding *Z*- isomers, under similar conditions afforded same products with diminished yields and selectivities (Scheme 18). Tadano concluded that in case of *E*- isomer the *O*-isopropylidene is *syn* to the hydroxymethyl group, thus effectively blocking the rearrangement from that side.

Scheme 18



In another report[34], Tadano has converted the Claisen products into carbo spiro ketone **47** (Scheme 19).

Scheme 19

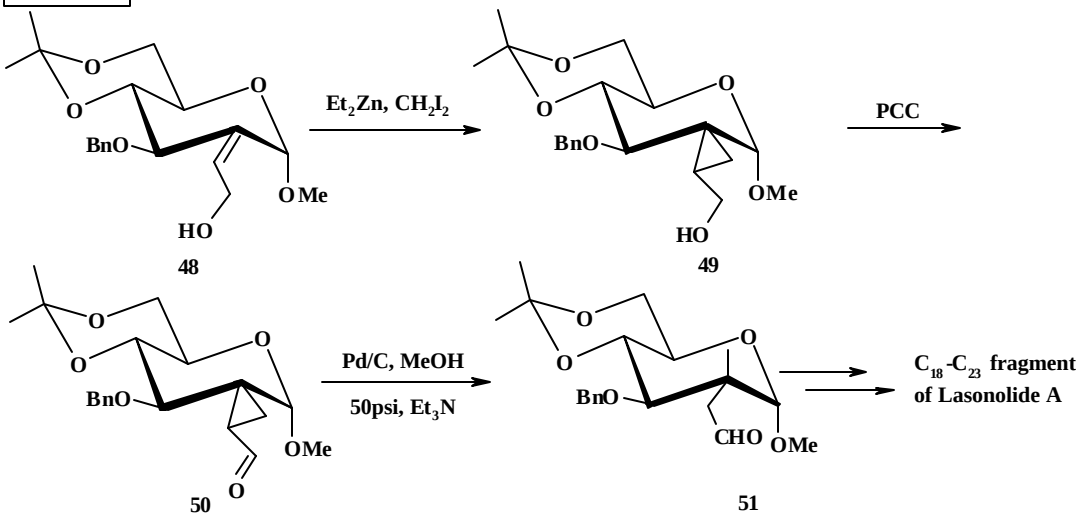


41 **47**

Gurjar *et al.*[35] have reported cyclopropane based routes for the asymmetric synthesis of quarternary chiral center in which hydrogenolysis of the activated cyclopropane aldehydes forms the main objective.

Accordingly, methyl 3-*O*-benzyl-4,6-*O*-isopropylidine-α-D-glucopyranose was converted to the allylic alcohol derivative **48**, and was cyclopropanated to **49** the oxidation of CH_2OH group gave the cyclopropyl-aldehyde compound **50**, which was subjected to hydrogenolysis to give the quarternary carbon compound **51**. Compound **51** was further elaborated to C_{18}-C_{23} fragment of lasonolide A (Scheme 20).

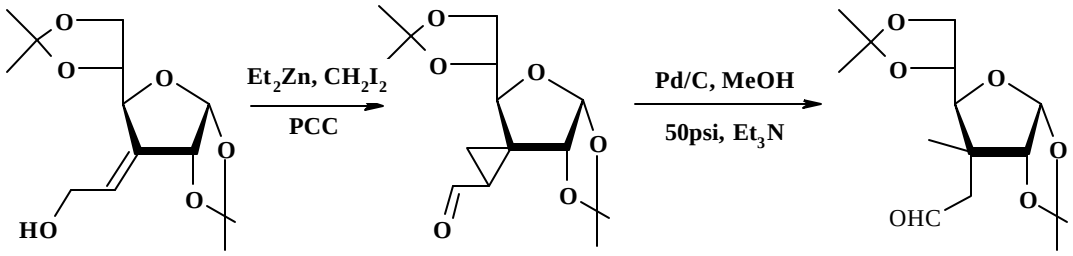
Scheme 20



48 **49** **50** **51**

In another report, Gurjar *et al.* have applied this strategy[36] successfully for the synthesis of furanoside based quarternary chiral building blocks starting from D-Glucose.

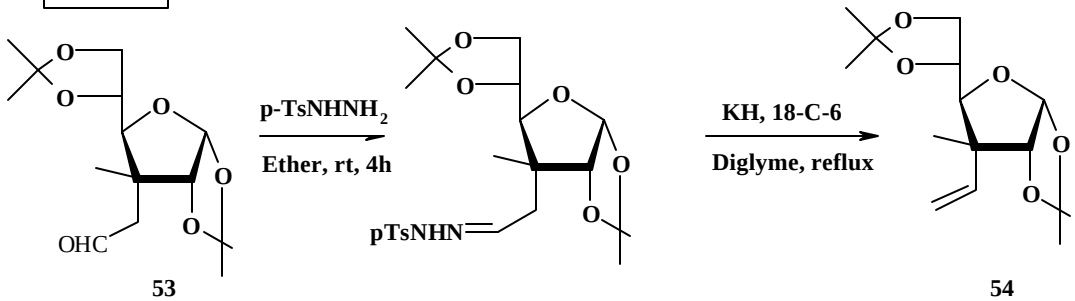
Scheme 21



52 **53**

The allylic alcohol compound was cyclopropanated and oxidized to give the corresponding aldehyde **52**, which on hydrogenalysis gave the quarternary compound **53** (Scheme 21). Compound **53** under Bamford-Stevens's reaction conditions gave **54**, a key intermediate in the synthesis of several natural products (Scheme 22).

Scheme 22



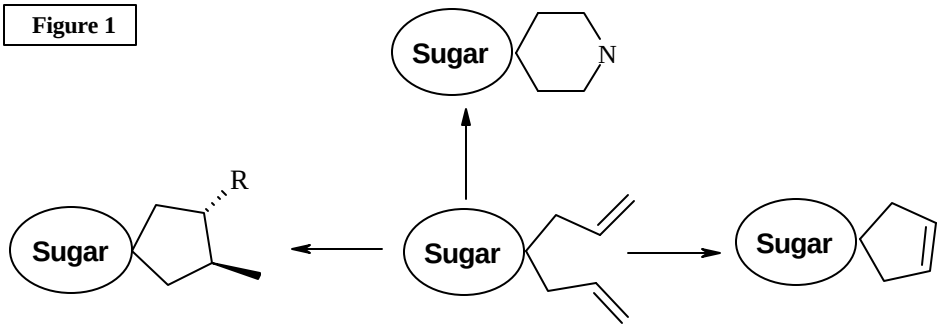
53 **54**

Present Work

Quarternary carbon center is an essential feature of the carbaspirocyclic compounds. It is an intriguing unit present in many natural products and havs attracted immense attention of organic chemists.[37-39] As a part of our ongoing efforts directed towards the synthesis of natural products containing spiro ring system, we envisioned that a *gem*-diallyl substituted carbohydrate backbone would be a potential precursor. There are several protocols available in literature for the cyclization/hydrosilylation[40] on *gem*-diallyl systems leading to the spiro carbocyclic skeleton. More

recently, there has been considerable interest in the application of ring closing metathesis,[41-45] which can straight away afford the required spiro compounds with an internal functionalizable olefin.

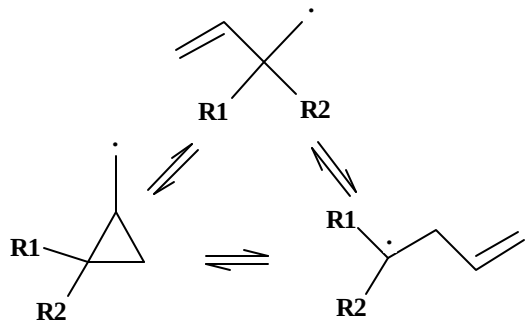
Figure 1



However, such *gem*-diallyl systems derived from carbohydrate derivatives are unknown, although they can form valuable synthons for many chemical transformations leading to functionalized products (Figure 1).

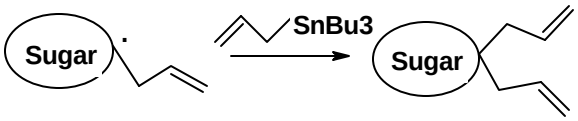
Incorporation of *gem*-diallyl group is usually achieved either by direct base mediated diallylation using allyl halides[46-48] or by Pd $(PPh_3)_4$ catalyzed allylation using allyl acetates.[49] Unfortunately, this method is limited only to active methylene groups. We have realized that this approach may not be appropriate for the carbohydrate system or any other system, which does not have an active methylene group. Thus, we were interested to develop a simple method using cyclopropyl methylbromides as indirect tools for the generation of *tert*-allyl radical system. From the literature,[50-52] it is evident that the cyclopropyl group can undergo several kinds of ring opening reaction like electrophilic, nucleophilic or radical kind of ring opening. For example, a cyclopropyl methyl radical can undergo ring opening to form a more stable allyl radical (Figure 2).[52]

Figure 2



We envisioned that the tertiary allyl radical when quenched with allyltributyl stannane under radical fragmentation conditions should lead to the formation of *gem*-diallyl system (Figure 3). But there are no reliable direct methods, where a tertiary allyl radical can be generated.

Figure 3



In this context, keeping our objectives in mind, it is pertinent to mention about the advantages of radical reactions over classical ionic reactions and also the advantages of radical fragmentation reactions over tinhydrate mediated reactions.[53,54]

Use of radicals in organic synthesis has increased dramatically over the past few decades. Previously it was limited to a few important functional group transformations (such as Barton McCombie's deoxygenation). However, during the past decade, radical C–C bond forming reactions have grown in importance to the point where they are now routinely considered in strategy level planning of complex targets. Radical reactions have several advantages over the conventional ionic reactions which can be manifested through literature. For example, carbon centered radicals are extremely reactive. This can be explained[55,56] by the relative half-life periods of the carbon radical to that of the corresponding ionic species.

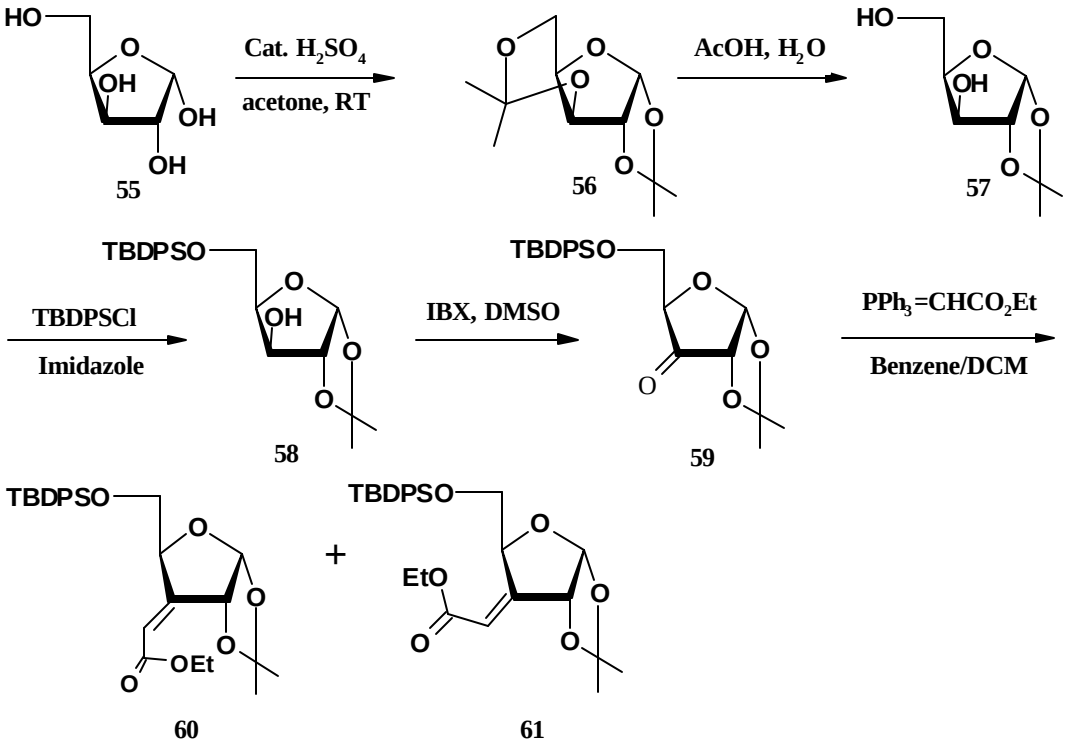
Radical additions to C=C or C≡C bonds are usually exothermic and irreversible and reactions under kinetic control often afford the products which are unavailable by ionic methods. Radical intermediates are ideally suited for synthesis of crowded bonds. Facile formation of quaternary and neopentyl centers is possible. Carbon centered radicals are inert towards OH and NH groups, thus protection of alcohols or amines and related functional groups is often unnecessary which is not possible in case of carbocations. In contrast to carbanions, carbon radicals are not subjected to β elemination of OR or NR_2 groups. In contrast to carbocations, carbon centered radicals are not captured by β-OR or NR_2 groups. Migration or elimination of HNR, CR_3 groups is not observed. However, radicals undergo β-eliminations with SR, SO_nR, Bu_3Sn groups and these are the key reactions in some useful radical chain propagation. Most alkyl or alkenyl radicals have negligible barriers for inter-conversion, thus possessing no importance for the initial stereochemistry at that center. This can be an advantage as it simplifies the synthesis of radical precursors.

Tributyl tin hydride (Bu_3SnH) is the most commonly used reagent for conduction of free radical reactions.[57] Available knowledge of the rates with which a radical is generated, reacted or rearranged and trapped by tin hydride, now permits the rational planning of the free radical reactions. However, conducting an intermolecular radical addition reaction is difficult by tin hydride method, because a radical must add selectively to the alkenes and should not be trapped by tin hydride, and the adduct radical formed should be quenched by tin hydride and should not add on to alkenes. The fragmentation method can be a clever alternative that avoids this selectivity problem where, chain carriers (Bu_3Sn radicals) are generated in the fragmentation step rather than during an atom transfer step (from Bu_3SnH). The fragmentation method differs from the tin hydride method in that the net effect is substitution rather than reduction. Fragmentation methods based on allyltrialkyl tin reagents are particularly useful. Keck has initially used such method in the synthesis of (+/-) perhydrohistrionicotoxin[58], a

potent neurotoxin. We were particularly interested to use this Keck's C-C bond formation methods[59] for the generation of required diallyl systems.

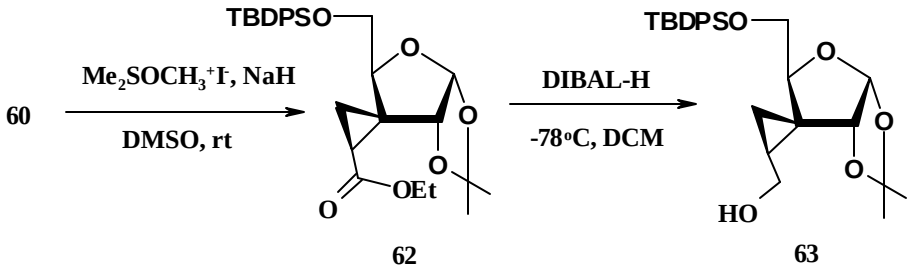
In accordance with our plan, we have attempted the preparation and reactions of the radical precursor **64** starting from the known 1,2:3,5-di-*O*-isopropylidene-á-D-xylofurnaose **56**.[60] Compound **56** was treated with AcOH: H_2O (80: 20) to undergo selective hydrolysis giving 1,2-*O*-isopropylidene-á-D-xylofurnose **57**. The PMR spectrum and the optical rotation of **57** were found to be comparable with the literature reports. [61,62] Compound **57** on treatment with *tert*-butyldiphenylsilyl chloride, imidazole in CH_2Cl_2 at 0 °C gave the 5-silyloxy derivative **58**, whose PMR spectrum has revealed resonances typical of TBDPS group. Compound **58** was oxidized using IBX-DMSO combination at rt to give the 3-ulose derivative **59**, which without purification was directly treated with PPh_3=$CHCO_2Et$ in refluxing benzene to give the *E/Z* mixture of á, â-unsaturated esters (**60** and **61**). The above Wittig reaction when performed in CH_2Cl_2 under reflux conditions gave predominantly ***E*** product (**60**) in good yield (Scheme 23). In the PMR spectrum of **60**, signals due to olefin protons and anomeric proton appeared in the region of δ 5.58-6.0. A down-field chemical shifts of H-2 (δ 5.71) and H-4 (δ 4.88) were observed. The cyclopropanation of **60** was affected using $Me_2SOCH_3^+I^-$-NaH in dry DMSO[63] to give **62.** Although the stereochemical identification of **62** was of no significance for the proposed study, we believe that the approach of ylide occured from the β face due to the stereocontrolling effect of adjacent 1,2-*O*-isopropylidene group.

Scheme 23

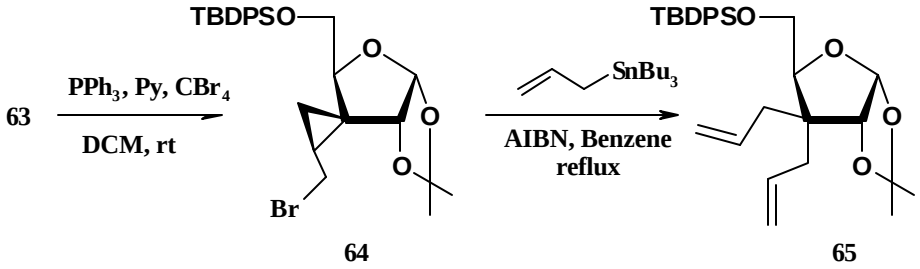


The conversion of ester group in **62** into the corresponding hydroxy-methyl (**63**) was accomplished by using DIBAL-H at −78 °C (Scheme 24). Absence of signals due to the ethyl ester group were noted in the PMR spectrum **63**. The methylene protons of CH_2OH were located at δ 3.16 as a triplet (J = 11.4 Hz) and at δ 3.97 as a doublet of doublet (J = 4.4, 11.4 Hz).

Scheme 24



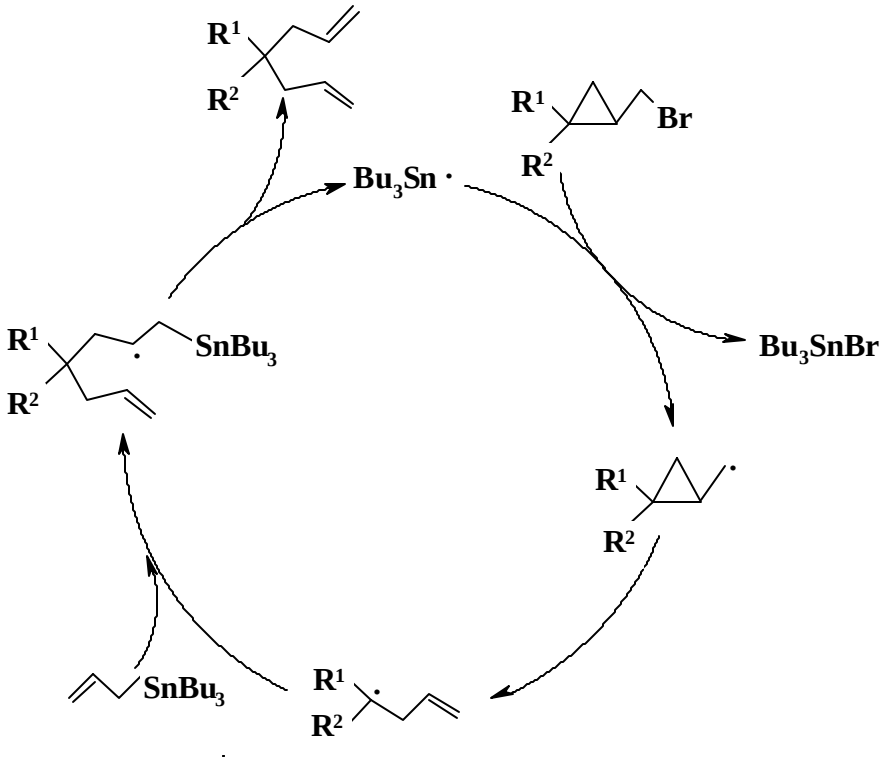
Scheme 25



Compound **63** on treatment of PPh_3-pyridine-CBr_4 in dry CH_2Cl_2 at rt gave the required bromo derivative **64** in good yield. The PMR, ^{13}C-NMR, mass and elemental analysis have substantiated the assigned structure of **64**. Treatment of **64** with allyl tributylstannane in the presence of catalytic amount of AIBN in refluxing benzene under argon atmosphere for 12 h gave the *gem*-diallyl compound **65**. In the PMR spectrum of **65**, the characteristic olefinic protons of two allylic groups appeared at 5.0 and 5.7 ppm, while the methylenes resonated in the region of 1.87- 2.25 ppm. The ^{13}C-NMR, mass and elemental analysis also substantiated the structure of **65**. The mechanism for the installation of *gem*-diallyl group starting from cyclopropyl bromide and allyl-n-tributylstannane is shown in Figure 4. In the first step, cyclopropyl methyl radical generated in the reaction from the corresponding bromo derivative, rapidly isomerises to the corresponding tertiary allyl radical. In the propagation step the tertiary allyl radical generated, adds to the allyl tributyltin leading to adduct radical. Under reflux in

toluene, this undergoes fragmentation reaction giving the diallyl derivative and a tributyl tin radical, which propagates the cycle.

Figure 4

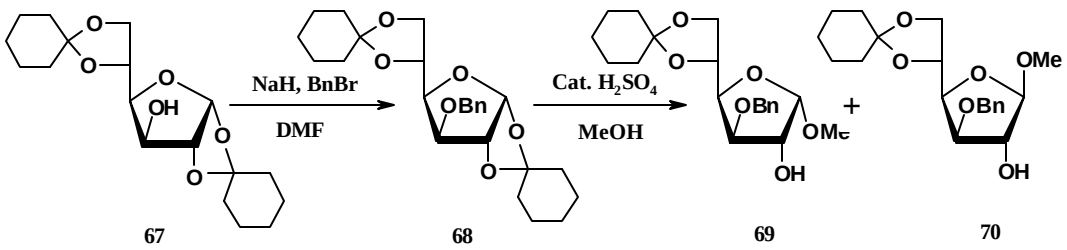


The euphoria generated with this success was carried through the synthesis of several diallyl systems on several carbohydrate templates.

Synthesis and reactions of radical precursor 75:

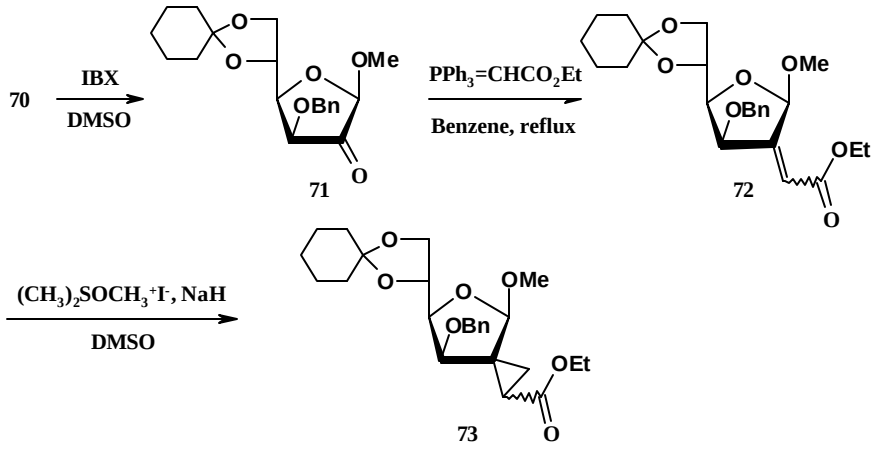
Synthesis of **75** was initiated with a known[64] and easily obtainable intermediate 1,2:5,6-di-*O*-cyclohexylidene-α-D-glucofuranose (**67**). Treatment of **67** with NaH and benzyl bromide in dry DMF afforded the 3-*O*-benzyl derivative **68**. The PMR spectrum of **68** confirmed the presence of benzyl group. Compound **68** upon hydrolysis in methanolic H_2SO_4 under reflux provided a mixture α- and β-methyl glycofuranosides (**69** and **70**) in a

Scheme 26



ratio of 3:2 (Scheme 26). In the PMR spectrum of **70**, a singlet due to anomeric proton was noted which suggested the â-anomeric structure. Compound **70** was oxidized using IBX in DMSO to give the 2-ulose derivative **71** which was immediately subjected to Wittig olefination reaction with PPh_3=$CHCO_2Et$ in refluxing benzene to yield the unsaturated ester

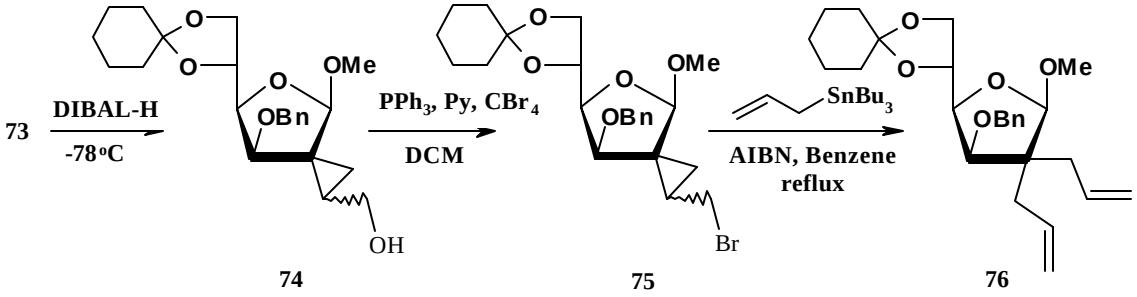
Scheme 27



72. Its PMR spectrum has suggested the formation of *E/Z* mixture. The protons H-1 and H-3 again showed expected downfield shifts. The ^{13}C-NMR of **72** was in conformity with the assigned structure. The IR spectrum of **72** revealed a strong carbonyl absorption peak at 1716 cm^{-1}. Cycloproporation of **72** was achieved by adopting the similar procedure as described earlier. Thus **72** was treated with $(CH_3)_2SOCH_3^+I^-$-NaH in DMSO to give the cyclopropanated ester **73** in moderate yield (Scheme 27). The PMR spectrum of **73** showed characteristic

signals of cyclopropane protons. Our next concern involved the reduction of **73** using DIBAL-H at −78 °C in dry CH_2Cl_2 to give **74**. The structure of **74** was fully confirmed by PMR, ^{13}C-NMR and mass spectral data. For example, signals due to cyclopropane group appeared as doublet of doublet at δ 0.75 (*J* = 4.8, 8.8 Hz) and as a triplet at δ 0.9 (*J* = 5.9 Hz) and signals due to CH_2OH have appeared at δ 3.26 as doublet of doublet (*J*= 8.7, 11.7 Hz) and at δ 3.71 as another doublet of doublet (*J*= 5.9, 11.7 Hz). All other protons appeared at the expected chemical shift values.

Scheme 28



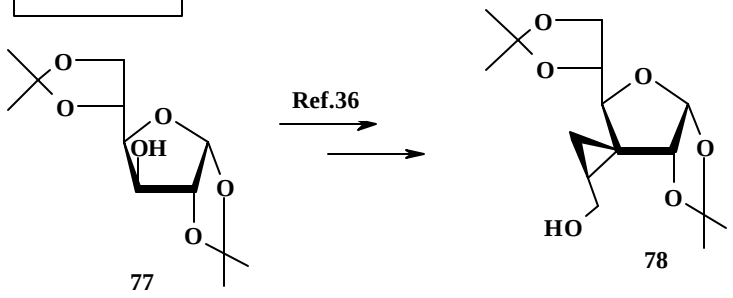
Conversion of **74** into its bromo derivative **75** was achieved by using PPh_3-CBr_4-pyridine in dry CH_2Cl_2 in good yield. The PMR and ^{13}C-NMR studies have revealed the occurrence of the transformation. The radical ring opening was achieved by heating **75** in refluxing benzene with allyl tributylstannane and catalytic amount of AIBN for 13 h to give the diallyl derivative **76**. The PMR and ^{13}C-NMR have substantiated the structure of **76**.

Synthesis and reactions of radical precursor 79:

Synthesis of **79** was initiated from 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (**77**). Compound **77** was converted into the cyclopropyl methanol **78** by the following

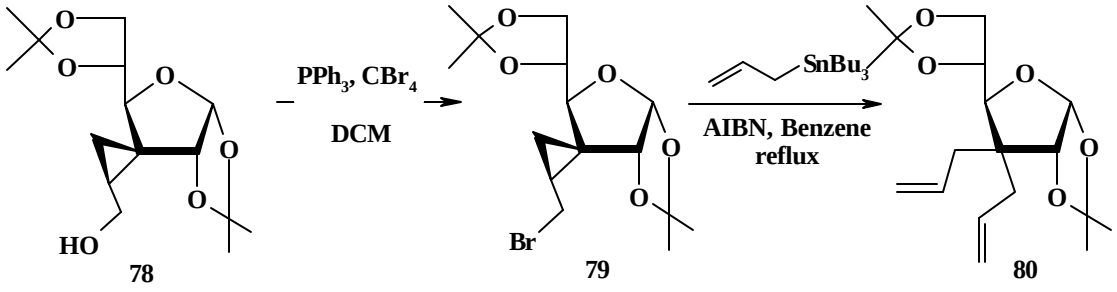
conventional set of reactions: 1) oxidation with PDC/Ac_2O to 3-ulose 2) Wittig reaction with $Ph_3P{=}CHCO_2Et$, 3) cyclopropanation with Me_2SOCH_3I-NaH 4) DIBAL-H reduction.[36]

Scheme 29



Treatment of **78** with PPh_3-CBr_4 in presence of pyridine in dry CH_2Cl_2 gave the bromide **79**. The radical ring opening reaction of **79** with allyltributyl tin in the presence of catalytic amount of AIBN in refluxing benzene gave **80** (Scheme 30). The PMR and ^{13}C-NMR spectra of **80** were consistent with the assigned structure.

Scheme 30

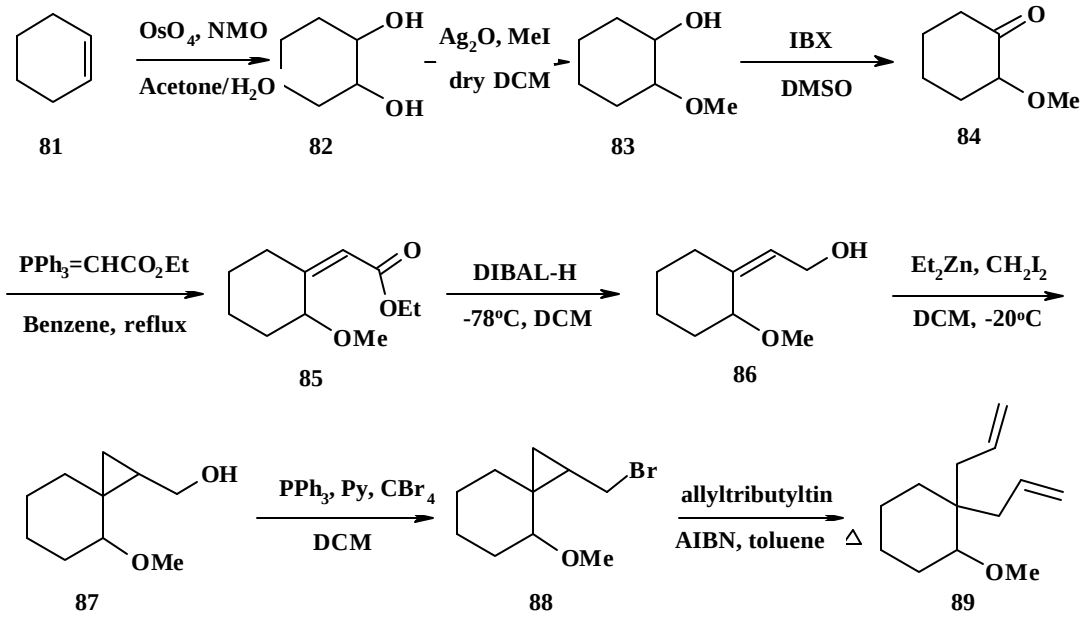


Synthesis and reactions of alicyclic precursor 88:

Having carried out successfully the fragmentation strategy described above with sugar cyclopropyl methyl bromide derivatives, it was apparent to extend the scope of this new rearrangement to alicyclic precursors, thereby expanding its horizon and versatility. For alicyclic radical precursor, compound **88** was chosen whose synthesis from cyclohexene (**81**) is described in scheme 30. Catalytic osmylation of **81** with OsO_4-NMO gave the *cis*-diol **82**. In

order to protect one OH group selectively, compound **82** was treated with freshly prepared Ag_2O and MeI in dry CH_2Cl_2 to give **83** in moderate yield. Compound **83** was oxidized using IBX in DMSO and treated with PPh_3=$CHCO_2Et$ in refluxing benzene to give the olefinic ester **85**. The PMR spectrum as well as ^{13}C-NMR confirmed the structure of **85**. DIBAL-H reduction of **85** at −78 °C gave the

Scheme 30

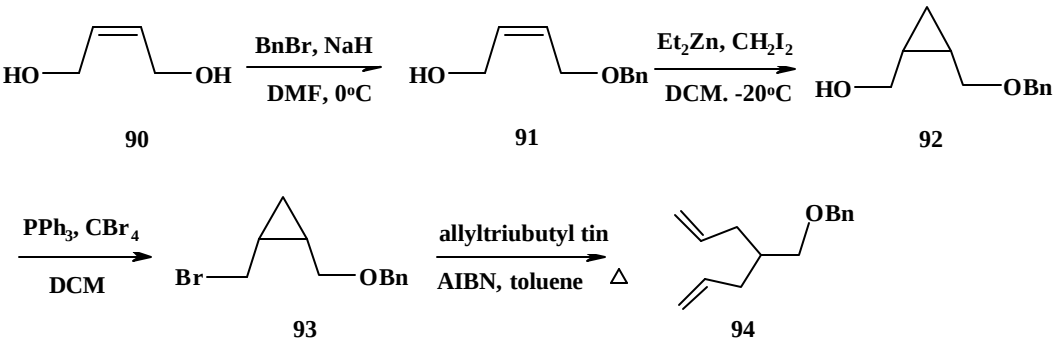


corresponding allylic alcohol **86** whose PMR spectrum showed peaks at δ 5.49 as a triplet and δ 4.13 as doublet, characteristic of allylic group. Compound **86** was treated with diethyl zinc and diiodomethane in CH_2Cl_2 at −20 °C to give cyclopropane product (**87**). The PMR spectrum of **87** showed resonance in the high field region attributed to cyclopropyl protons. Derivatisation to cyclopropyl bromide (**88**) from **87** was affected with PPh_3, CBr_4 in CH_2Cl_2. The rearrangement of **88** into the corresponding diallyl derivative **89** was successfully accomplished with allyl tributyltin and AlBN in refluxing toluene for 12 h after degassing thoroughly. The PMR spectrum has revealed the presence of the diallyl system.

Synthesis and reaction of radical precursor 93:

Synthesis of **93** was initiated from *cis*-butene-1,4-diol **90** which on treatment with one equivalent of benzyl bromide and NaH in DMF at 0 °C gave the monobenzyl ether **91**. The PMR spectrum revealed the presence of only one benzyl group. Cyclopropanation of **91** was achieved by the treatment with Et_2Zn and CH_2I_2 in dry CH_2Cl_2 under modified Furakawa conditions to give the cyclopropyl methanol derivative **92**. The cyclopropane proton signals appeared in the high field region at δ 0.2-1.33 ppm. Compound **92** was converted into its bromo-derivative **93** under the same conditions as described above.

Scheme 31



Compound **93** was treated with allyltributyl stannane in presence of catalytic amount of AIBN to give the diallyl systems **94** (Scehme 31), which was fully characterized by PMR and ^{13}C-NMR spectral data.

Ring Closing Metathesis

Ring closing metathesis (RCM), in which two un-substituted olefins undergo ring closure with formal loss of ethylene, is one of the most popular methods of present time. This has reached the mature level because of the great advances in recent years. The reasons being:

1) Catalyst was well designed, stable and highly active.

2) Very high turnover number was observed in the catalytic process

3) Its efficacy in medium to macro-ring cyclization.

4) Its superior over other cyclization methods like macrocyclization, Diels-Alder etc., because of favorable thermodynamic profile.

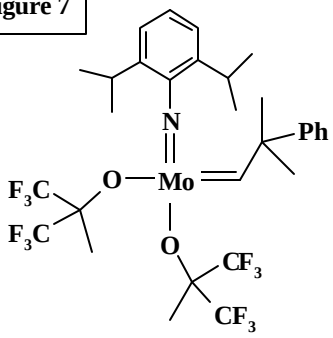
5) Adaptable for both solution and solid phase reactions.

6) Water solubility enabling the metathesis in water and methanol.

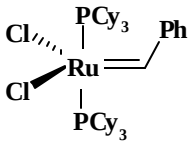
7) Eco-friendly profile, including viability in solvents like super critical CO_2.

8) Compatible with various functional groups.

Figure 7



Schrock's Catalyst

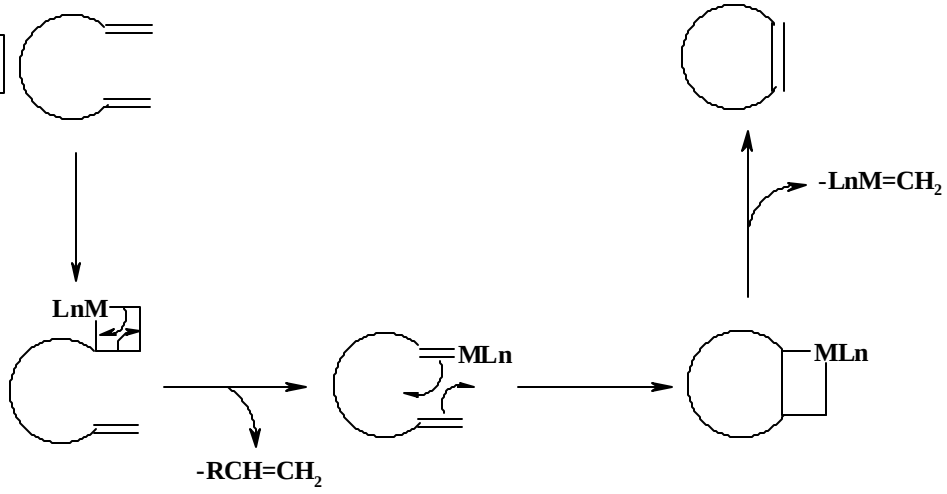


Grubbs' Catalyst

The pioneering efforts of Schrock and Grubbs[65,66] lead to the introduction of their respective catalysts (Figure 7), which find widespread use in several synthesis, although the discovery and development of new and robust catalysts is presently a hot pursuit. This reaction has changed the strategy of synthetic chemists to an extent that now a days it is very common to find RCM as key transformation in the recent total synthesis of natural products especially for ring construction.

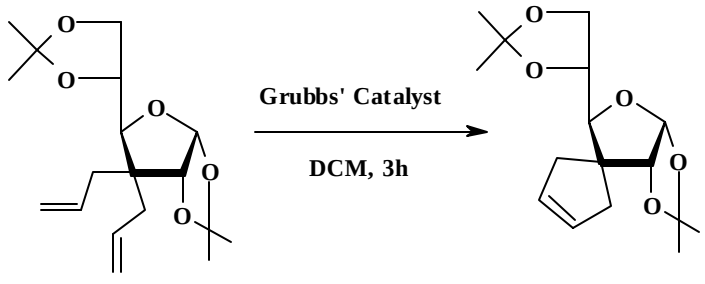
The postulated mechanism involves an iterative process of (2+2) cycloadditon between the olefin and metal alkylidene forming the metallo cyclobutane species and its cycloreversion, elemination of ethylene followed by [2+2] cycloaddition to the other olefin and cycloreversion of resulting metallo cyclobutane species leading to the metathesis product, as shown in scheme.

Figure 8



In a typical experiment compound **80** was exposed to Grubbs' catalyst (5 mol %) in CH_2Cl_2 at ambient temperature to give the spiro-cyclopentene derivative **95** (Scheme 33). The structure of **95** was characterized by the PMR spectrum in which signals due to olefinic protons appeared as a multiplet δ 5.69 and the ring methylene groups showed multiplet at δ 1.79 and at δ 2.57.

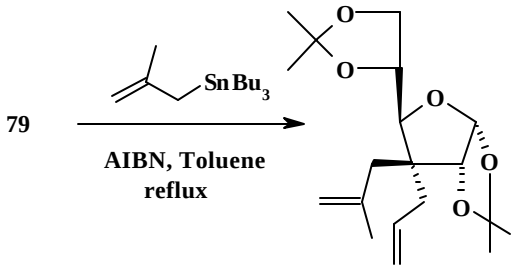
Scheme 33



80 **95**

Having achieved the required spiro compound successfully, our next goal was to synthesize the differentially substituted *gem*-diallyl systems. Accordingly, methallyl tributylstannane was prepared following the literature procedure.[59] When a solution of cyclopropyl methyl bromide derivative **79** in thoroughly degassed toluene was treated with 2.5 equivalents of methallyl tin in presence of catalytic amount of AIBN at 120 ^{o}C for 12 h gave the substituted diallyl system **96** in moderate yield (Scheme 34). Formation of the compound **96** was confirmed by PMR and mass spectra. For example, the characteristic singlet at δ 1.86 was accorded to the methyl group. Typical resonances due to both

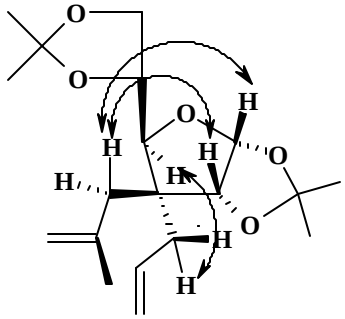
Scheme 34



96

methallyl and allyl groups were noticed in the PMR spectrum. However, the absolute stereochemistry at C-3 could not be ascertained from the PMR spectrum. Extensive 2D-COSY and NOESY studies on compound **96** indicated the structure as shown in scheme

Figure 9

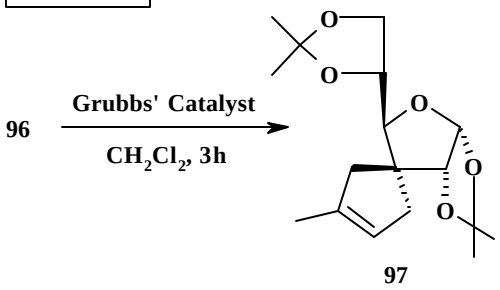


Observed NOE for 96

34. For example, in the NOESY spectrum, H-1 and H-2 showed strong coupling with methallyl methylene protons. On the other hand, H-4 showed strong coupling with allylic methylene

protons (Figure 9). The exclusive formation of **96** can be attributed to the 1,2-*O*-isopropylidene group, which directed the addition of methallyl group. The ring closing metathesis on **96** with Grubbs' catalyst gave the corresponding spiro-compound **97** (Scheme 35). In the PMR spectrum, only one olefinic signal at δ 5.31 appeared as a broad triplet.

Scheme 35



97

In conclusion, we have demonstrated a unique and interesting method for the generation of *gem*-diallyl systems by cascade ring opening and fragmentation technique. The versatality of this method was strikingly revealed when applied to 1,2:5,6-di-*O*-isopropylidene-á-D-glucopyranose with methallyl tributylstannane, which gave unsymmetrical *gem*-diallyl system with high diastereoselectivity. This method is a useful extension of Keck's radical methodology of C-C bond formation and will be an alternative for the incorporation of diallyl units in systems where active methylene groups are not present. [67]

1,2-*O*-Isopropylidine-α-D-xylofuranose (57):

Compound **56** (7 g, 30 mmol) was treated with AcOH-H_2O (8: 2) (75 mL) for 3 h at rt and concentrated below 50 °C. The residue was dissolved in ethyl acetate, washed with saturated $NaHCO_3$, brine and extracted with ethyl acetate. The ethyl acetate layer was dried (Na_2SO_4), concentrated and the residue purified on silica gel to give **57** (4.3 g, 75%).

$[á]_D$ = 18.7° (*c* 2.3, $CHCl_3$) Lit. [62] $[á]_D$ = 19° (*c* 1.0, $CHCl_3$)

^{1}H-NMR (300 MHz, $CDCl_3$) : δ 1.30, 1.46 (2 x s, 6H), 3.98 (m, 2H), 4.12 (m, 1H), 4.25 (br. d, 1H, J = 2.4 Hz), 4.48 (d, 1H, J = 3.4 Hz), 5.93 (d, 1H, J = 3.4 Hz).

5-*O*-(*tert*-Butyldiphenylsilyl)-1,2-*O*-isopropylidene-α-D-xylofuranose (58):

To a solution of **57** (3.5 g, 18.4 mmol) in CH_2Cl_2 (50 mL), imidazole (1.87 g, 27.6 mmol) and TBDPSCl (4.7 mL, 18.4 mmol) were added and stirred at rt for 5 h. The reaction mixture was washed with water, dried (Na_2SO_4), concentrated and the residue purified on silica gel using ethyl acetate-light petroleum (1:9) to afford **58** (5.5 g, 70%) as a white solid.

M.P = 92 °C Lit.[68] M.P = 92-94 °C

^{1}H-NMR (300 MHz, $CDCl_3$) : δ 1.07 (s, 9H), 1.33, 1.47 (2 x s, 6H), 4.05 (d, 1H, J = 2.9 Hz), 4.11 (s, 3H), 4.36 (m, 1H), 4.53 (d, 1H, J = 3.9 Hz), 6.0 (d, 1H, J = 3.9 Hz), 7.42 (m, 6H), 7.7 (m, 4H).

^{13}C-NMR (50 MHz, $CDCl_3$) : δ 19.1, 26.2, 26.7, 62.8, 7.3, 78.3, 85.4, 105.01, 111.5, 127.9, 130.0, 132.0, 132.5, 135.5, 135.7.

EIMS = m/z 413 $(M\text{-}Me)^+$

Anal. Calcd. for $C_{24}H_{32}O_5Si$: C,67.28; H, 7.47. Found: C, 67.35; H, 7.25.

(*E*)-5-*O*-(t*ert*-Butyldiphenylsilyl)-3-deoxy-1,2-*O*-isopropylidene-3,3-C-[(ethoxycarbonyl)methylene]-a -D-*threo*-pentofuranose (60):

A mixture of **58** (4.0 g, 9.3 mmol) and IBX (3.2 g, 14 mmol) in DMSO (10 mL) under argon was stirred for 10 h. The reaction was quenched with water and filtered, and the filtrate was extracted with EtOAc. The EtOAc layer was dried (Na_2SO_4), concentrated. The residue was dissolved in CH_2Cl_2 (20 mL) and PPh_3= $CHCO_2Et$ (4.8 g, 14.0 mmol) was added. The reaction mixture was refluxed for 4 h and evaporated and the residue was purified on silica gel using ethyl acetate-petroleum ether (1:9) to afford **60** (3.7 g, 80%) (over two steps).

$[á]_D$ = +76° (*c* 1.0, $CHCl_3$)

^{1}H-NMR (300 MHz, $CDCl_3$) : δ 1.05 (s, 9H), 1.35 (t, 3H, J = 7.3 Hz), 1.45, 1.49 (2 x s, 6H), 3.7 (dd, 1H, J = 3.9, 10.7 Hz), 3.87 (dd, 1H, J = 3.9, 10.7 Hz), 4.26 (q, 2H, J = 7.3 Hz), 4.88 (m, 1H), 5.71 (d, 1H, J = 4.4 Hz), 5.96 (m, 2H), 7.41 (m, 6H), 7.65 (m, 4H).

^{13}C-NMR(75 MHz, $CDCl_3$) : δ 14.1, 19.1, 26.7, 27.2, 27.5, 60.2, 65.9, 78.8, 81.1, 105.4, 112.6, 116.6, 127.7, 129.7, 132.8, 135.5, 156.5, 164.5.

EIMS = m/z 481(M^+-Me)

Anal. Calcd. for $C_{28}H_{36}O_6Si$: C,67.74; H, 7.25. Found: C, 67.53; H, 7.62.

5-*O*-*tert*-Butyldiphenylsilyl-3-deoxy-1,2-*O*-isopropylidene-3,3-C-[(ethoxycarbonyl) ethylene-a -D-*threo*-pentafuranose (62):

A suspension of NaH (0.42 g, 10.6 mmol), trimethylsulphoxonium iodide (2.34 g, 10.6 mmol) in DMSO (6 mL) under argon atmosphere was s tirred for 15 min. To this **60** (3.5 g, 7

mmol) in DMSO (8 mL) was added dropwise and further stirred for 3h at rt, quenched with ice-cold water (20 mL) and extracted with ether. The ether layer was dried (Na_2SO_4), concentrated and the residue purified on silica gel using ethyl acetate-petroleum ether (1:9) to give **62** (2.15 g, 60 %).

$[á]_D$ = +59° (*c* 0.5, $CHCl_3$)

^{1}H-NMR (300 MHz, $CDCl_3$) : δ 0.85-1.20 (m, 10H), 1.20-1.59 (m, 9H), 1.95-2.47(m, 2H), 3.30-3.47 (m, 1H), 3.70 (m, 1H), 4.05-4.30 (m, 2H), 4.42-4.61 (m, 1H), 5.76 (d, 1H, J = 3.6 Hz), 7.29-7.78 (m, 10H).

^{13}C-NMR (50 MHz, $CDCl_3$) : δ 14.2, 15.4, 19.2, 20.4, 26.4, 26.7, 27.0, 27.1, 29.7, 38.0, 60.7, 63.3, 77.2, 84.9, 104.3, 111.7, 127.8, 129.7, 129.9, 132.9, 134.9, 135.5, 135.6, 171.8.

EIMS = m/z 271 (M^+-*t*BuSiPh$_2$)

Anal. Calcd. for $C_{29}H_{38}O_6Si$: C,68.23; H, 7.45. Found: C, 68.62 ; H,7.45 .

(*E*)-5-*O*-(*tert*-Butyldiphenylsilyl)-3-Deoxy-1,2-*O*-isopropylidene-3,3-C[(hydroxy-methyl)ethylene]-α-D-*threo*-pentofuranose (63):

To a solution of **62** (1.0 g, mmol) in dry CH_2Cl_2 at −78 °C a 2.1 M solution of DIBAL-H (2.4 mL, 5.0 mmol) was added dropwise, stirred for 1 h and quenched with MeOH, saturated sodium potassium tartarate and stirred vigorously for 2 h. The CH_2Cl_2 layer was separated, dried (Na_2SO_4) and concentrated. The residue obtained was purified on silica gel using ethyl acetate and light petroleum (1: 3) to afford of **63** (0.78 gm, 85%).

$[á]_D$ = +11° (*c* 2.1, $CHCl_3$)

^{1}H-NMR (300 MHz, $CDCl_3$) : δ 0.5 (t, 1H, J = 5.1 Hz), 0.97 (s, 9H), 1.08 (m, 2H),

1.26, 1.52 (2 x s, 6H), 3.16 (t, 1H, J = 11.4 Hz), 3.29 (dd, 1H, J = 6.2, 10.6 Hz), 3.56 (dd, 1H, J = 4.7, 10.6 Hz), 3.97 (dd, 1H, J = 4.4, 11.4 Hz), 4.36 (m, 2H), 5.79 (d, 1H, J = 3.6 Hz).

^{13}C-NMR (75MHz, $CDCl_3$) : δ 12.5, 19.1, 20.7, 26.6, 26.8, 27.1, 33.8, 63.5, 65.1, 78.5, 86.4, 104.6, 111.7, 127.7, 129.8, 133.0, 135.6

EIMS = m/z 255(M^+-O*t*BuSiPh_2)

Anal. Calcd. for $C_{27}H_{36}O_5Si$: C,69.23; H, 7.69. Found: C, 68.96; H, 7.87.

(*E*)-5-*O*-(*tert*-Butyldiphenylsilyl)-3-deoxy-1,2-*O*-isopropylidene-3,3-C-[(bromomethyl)-ethylene]-α-D-*threo*-pentofuranose (64):

A solution of compound **63** (0.6 g, 1.3 mmol), PPh_3 (0.7 g, 2.7 mmol), pyridine (1 mL) and CBr_4 (0.5 g, 1.4 mmol) in CH_2Cl_2 (25 mL) was stirred for 0.5 h and evaporated. The residue obtained was purified on silica gel using ethyl acetate-light petroleum (1: 20) to afford **64** (0.61 g, 90%).

$[\alpha]_D$ = +86° (*c* 0.8, $CHCl_3$)

^{1}H-NMR (300 MHz, $CDCl_3$) : δ 0.50 (t, 1H, J = 5.8 Hz), 0.96 (s, 9H), 1.31 (s, 3H), 1.43 (m, 1H), 1.65 (m, 1H), 3.15 (t, 1H, J = 10.7 Hz), 3.39 (dd, 1H, J = 7.3, 10.7 Hz), 3.70 (dd, 1H, J = 4.4, 10.7 Hz), 4.05 (dd, 1H, J = 4.4, 10.7 Hz), 4.35 (d, 1H, J = 3.9 Hz), 4.41 (dd, 1H, J = 4.9, 6.8 Hz), 5.83 (d, 1H, J = 3.4 Hz).

^{13}C-NMR (50 MHz, $CDCl_3$) : δ 16.9, 19.2, 21.7, 26.7, 26.9, 27.2, 36.1, 38.5, 63.4, 78.1, 86.3, 104.5, 111.9, 127.8, 129.9, 132.9, 135.6.

Anal. Calcd. for $C_{27}H_{35}O_4SiBr$: C, 61.01; H, 6.59. Found: C, 61.53; H, 6.73.

5-*O*-(*tert*-Butyldiphenylsilyl)-3-deoxy-3,3-C-diallyl-1,2-*O*-isopropylidene-α-D-*threo*-pentofuranose (65):

A solution of **64** (0.18 g, 0.4 mmol), allyltri-n-butylstannane (0.25 mL, 0.8 mmol) and AIBN (25 mg) in dry benzene (3 mL) was degassed with argon for 30 min. The reaction mixture was heated under reflux for 12 h and concentrated, dissolved in ether, saturated solution of KF was added. After 1 h, solid was filtered, the filtrate was dried (Na_2SO_4) and concentrated. The crude product was purified on silica gel using ethyl acetate-hexane (1: 30) to afford **65** (0.15 g, 80%).

$[á]_D$ = +22° (*c* 1.0, $CHCl_3$)

^{1}H-NMR (300 MHz, $CDCl_3$) : δ 1.08 (s, 9H), 1.29 (s, 3H), 1.54 (s, 3H), 1.95-2.45 (m, 4H), 3.82 (m, 2H), 4.03 (t, 1H, J = 6.4 Hz), 4.25 (d, 1H, J = 3.4 Hz), 5.0 (m, 4H), 5.70 (d, 1H, J = 3.4 Hz), 5.80 (m, 2H), 7.35-7.77 (m, 10H).

^{13}C-NMR (50 MHz, $CDCl_3$) : δ 19.3, 26.5, 27.0, 35.6, 36.5, 50.0, 62.9, 84.7, 85.6, 104.2, 111.0, 117.7, 127.8, 129.8, 133.3, 133.5, 134.5, 135.0, 135.7.

EIMS = m/z 257(M^+- *t*-BuSiPh_2)

Anal. Calcd. for $C_{30}H_{40}O_4Si$: C, 73.17; H, 8.13. Found: C, 72.19; H, 8.78.

3-*O*-Benzyl-1,2:5,6-di-*O*-cyclohexylidene-α-D-glucofuranose (68):

To an ice-cold solution of **67** (15 g, 46.0 mmol) in dry DMF (40 mL), under argon atmosphere, was added NaH (4.1 g, 69.0 mmol) (60% in dispersion in oil) and stirred for 30 min at rt. Benzyl bromide (8.2 mL, 69.0 mmol) was added dropwise at 0° C and stirred for 1 h

at rt and quenched with water and partitioned between water and ether. The combined ether layer was dried (Na_2SO_4), concentrated. The residue was purified on silica gel using ethyl acetate and light petroleum as eluent (1:9) to furnish **68** (16.1 g, 85%) as colorless oil.

$[á]_D$ = -17° (*c* 1.1, $CHCl_3$) Lit.[69] $[á]_D$ = -17.3° (*c* 3.83, $CHCl_3$)

^{1}H-NMR (200 MHz, $CDCl_3$) : δ 1.32-1.85 (m, 20H), 3.94-4.18 (m, 4H), 4.86 (dt, 1H, J = 5.8, 7.8 Hz), 4.56 (d, 1H, J = 3.42 Hz), 4.68 (s, 2H), 5.87 (d, 1H, J = 3.42 Hz), 7.34 (m, 5H).

^{13}C-NMR ($CDCl_3$, 50 MHz) : δ 23.6, 23.8(2C), 24.1, 24.9, 25.2, 34.95, 35.8, 36.5(2C), 67.22, 72.07, 72.33, 81.52, 81.78, 82.37, 104.90, 109.46, 112.32, 127.58 (2C), 128.31 (3C), 137.76.

Methyl 3-*O*-benzyl-5,6-*O*-cyclohexylidene-á-D-glucofuranoside (69) and Methyl 3-*O*-benzyl-5,6-*O*-cyclohexylidene-b-D-glucofuranoside (70):

A solution of **68** (15.0 g, 40 mmol), H_2SO_4 (0.2 mL) in MeOH (250 mL) was refluxed on a water bath for 10 h. The reaction mixture was cooled to rt and neutralized with triethylamine, solvent evaporated and the residue was purified on silica gel using ethyl acetate and light petroleum (3:10) as eluent to provide **69** (2.8 g, 27% yield) and **70** (4.2 g, 33% yield) as pale yellow syrup.

$[á]_D$ = -41° (*c* 1.6, $CHCl_3$)

^{1}H-NMR ($CDCl_3$, 200 MHz) for **70** : δ 1.33-1.83 (m, 10H), 2.3 (br. d, J = 3.9 Hz), 3.37 (s, 3H), 3.89 (dd, 1H, J = 1.47, 4.89 Hz), 3.94-4.46 (m, 5H), 4.65 (s, 2H), 4.75 (s, 1H), 7.23-7.54 (m, 5H).

^{13}C-NMR ($CDCl_3$, 50 MHz) for **70** : δ 23.7, 23.8, 25.1, 34.8, 36.2, 55.3, 66.5, 72.0, 73.3, 78.5, 82.2, 82.8, 109.3, 109.6, 127.4, 128.1, 137.9.

Anal. Calcd. for $C_{20}H_{28}O_6$: C, 65.93; H, 7.69. Found: C, 66.44; H, 7.87.

(*E/Z*) Methyl 2-deoxy-3-*O*-benzyl-5,6-*O*-cyclohexylidene-2-C-[(ethoxycarbonyl)methyllene]-â-D-*arabino*-hexofuranoside (72):

Compound **72** was prepared form **70** as described previously. Compound **70** (3.5 g, 8.0 mmol) was oxidized using IBX (4.2 g, 15.0 mmol) in DMSO (7 mL). The crude ulose **71** was treated with PPh_3= $CHCO_2Et$ (5.2 g, 15.0 mmol) in refluxing benzene gave the **72** (3.2 g, 78% yield) as colorless syrup.

$[á]_D$ = -38° (*c* 1.2, $CHCl_3$)

^{1}H-NMR (200 MHz, $CDCl_3$) : 1.32(t, 3H, J = 6.9 Hz), 1.36- 1.72 (m, 10H), 3.41 (s, 0.75 H), 3.49 (s, 2.75 H), 4.0-4.53 (m, 6H), 4.0-4.53 (m, 7.25 H), 4.62-4.78 (m, 1.75H), 5.25 (d, 0.25H, J = 4.39 Hz), 5.26 (s, 0.25H), 5.75 (s, 0.75H), 6.03 (s, 0.75H), 6.15 (0.25 H).

Anal. Calcd. for $C_{24}H_{32}O_7$: C, 66.66; H, 7.40. Found: C, 66.71; H, 7.38.

(*E/Z*) Methyl 2-deoxy-3-*O*-benzyl-5,6-*O*-cyclohexylidene-2,2-C-[(ethoxycarbonyl) ethylene]-â-D-*arabino*-hexofuranoside (73):

Cyclopropanation of **72** was achieved as described previously. A solution of **72** (2.0 g, 4.6 mmol) in dry DMSO (4 mL) was added to the ylide generated from trimethyl sulfoxonium iodide (1.7 g, 7.9 mmol) and NaH (0.32 g, 7.9 mmol) in DMSO (4 mL). The reaction after work up and column purification on silica gel using ethyl acetate-light petroleum gave **73** (0.82 g, 40%).

$[á]_D$ = -20° (*c* 1.1, $CHCl_3$)

^{1}H-NMR ($CDCl_3$, 200 MHz) : 1.05 (dd, 1H, J = 4.9, 8.3 Hz), 1.21-1.30 (m, 3H), 1.56-1.95 (m, 11H), 2.06 (m, 1H), 3.34 (s, 3H), 3.82 (d, 1H, J = 4.39 Hz), 3.89-4.32 (m, 5H), 4.3-4.51 (m, 2H), 4.67-5.0 (m, 3H).

Anal. Calcd. for $C_{25}H_{34}O_7$: C, 67.26; H, 7.62. Found: C, 67.52; H, 7.66.

Methyl 2-deoxy-3-*O*-benzyl-5,6-*O*-cyclohexylidene-2,2-C-[(hydroxymethyl)ethylene]-â-D-*arabino*-hexofuranoside (74):

Compound **73** was converted to **74** using the procedure described previously. To a solution of **73** (0.8 g, 1.8 mmol) in dry CH_2Cl_2 at -78 °C, a 2.1 molar solution of DIBAL-H (2.1 mL, 4.5 mmol) was added and stirred for 1h, after the usual workup, the crude was purified on silica gel using ethyl acetate and light petroleum (3: 7) to give **74** (0.55 g, 79 %).

$[á]_D$ = +82° (*c* 0.5, $CHCl_3$)

^{1}H-NMR ($CDCl_3$, 200 MHz) : 0.75 (dd, 1H, J = 4.8, 8.8 Hz), 0.9 (t, 1H, J = 5.9 Hz), 1.39-1.75 (m, 11H), 2.31 (br. s, 2H), 3.26 (dd, 1H, J = 8.79, 11.72 Hz), 3.34 (s, 3H), 3.59 (d, 1H, J = 3 Hz),

3.71 (dd, 1H, J = 5.9, 11.7 Hz), 3.97-4.21 (m, 3H), 4.38 (m, 1H), 4.64 (d, 1H, J = 11.7 Hz), 4.79 (d, 1H, J = 11.7 Hz), 4.86 (s, 1H).

Anal. Calcd. for $C_{23}H_{32}O_6$: C, 68.31; H, 7.92. Found: C, 67.40; H, 7.68.

Methyl 3-*O*-benzyl-5,6-*O*-cyclohexylidene-2-deoxy-2,2-C-[(bromomethyl)ethylene]-â-D-*arabino*-hexofuranoside (75):

Compound **74** was converted to **75** using the same procedure described previously. Accordingly, **74** (0.50 g, 1.3 mmol), PPh_3 (0.7 g, 2.8 mmol), pyridine (1 mL) and CBr_4 (0.5 g, 1.4 mmol) was stirred in CH_2Cl_2 for 0.5 h at rt and the residue after workup was purified on silica gel using ethyl acetate and light petroleum to furnish **75** (0.42 g, 72%).

$[á]_D$ = +94° (*c* 0.6, $CHCl_3$)

^{1}H-NMR ($CDCl_3$, 200 MHz) : 0.85 (dt, 1H, J = 4.9, 8.79 Hz), 0.99 (t, 1H, J = 5.4 Hz), 1.35–1.69 (m, 10H), 1.74 (m, 1H), 3.18 (t, 1H, J = 8.79), 3.38 (s, 3H), 3.49 (dd, 1H, J = 6.84, 10.2 Hz), 3.56 (d, 1H, J = 3.4 Hz), 3.95-4.22 (m, 3H), 4.41 (dt, 1H, J = 5.8, 8.7 Hz), 4.61 (d, 1H, J = 11.7 Hz), d, 1H, J = 11.7 Hz), 5.01 (s, 1H).

^{13}C-NMR ($CDCl_3$, 50 MHz) : 15.7, 21.2, 24.0, 24.1, 25.3, 33.1, 35.0, 36.6, 37.9, 55.5, 67.26, 72.6, 73.0, 81.6, 84.2, 102.3, 109.7, 127.7, 128.0, 128.3, 138.5.

Anal. Calcd. for $C_{23}H_{31}O_5Br$: C, 59.10; H, 6.63. Found: C, 61.20; H, 6.67.

Methyl 3-*O*-benzyl-5,6-*O*-cyclohexylidene-2-deoxy-2,2-C-[diallyl]-â-D-*arabino*hexofuranoside (76):

The diallyl compound **76** was achieved by using the same procedure as described earlier. A solution of ompound **75** (0.17 g, 0.36 mmol), allyltri-n-butyl tin (0.22 mL, 0.72 mmol), AIBN (10 mg) in benzene (10 mL) was refluxed under argon atmosphere for 12 h. After usual work up with KF and purification of the residue on silica gel using ethyl acetate light petroleum (1: 20) to give **76** (97 mg, 63%).

$[á]_D$ = +66° (*c* 0.41, $CHCl_3$)

^{1}H-NMR (200 MHz, $CDCl_3$) : *d 1.58 (m, 10H), 2.05- 2.4 (m, 4H), 3.31 (s, 3H), 3.9 (d, 1H, J = 4.4 Hz), 3.95 (dd, 1H, J = 5.9 and 8.3 Hz), 4.08 (m, 2H), 4.31 (m, 1H), 4.49 (d, 2H, J = 11.0 Hz), 4.74 (d, 2H, J = 11.0 Hz), 4.71 (s, 1H), 5.06 (m, 4H), 5.77 (m, 1H).*

^{13}C-NMR (125 MHz, $CDCl_3$) : δ 23.9, 24.1, 25.2, 35.0, 35.3, 36.5, 52.6, 55.9, 67.2, 73.2, 74.2, 80.4, 84.4, 109.2, 109.6, 117.5, 117.7, 127.6, 128.0, 128.3, 135.0, 138.5.

Anal. Calcd. for $C_{26}H_{36}O_5$: C, 72.89; H, 8.41. Found: C, 73.33; H, 8.44.

3-Deoxy-1,2:5,6-di-*O*-isopropylidene-3,3-C-[(bromomethyl)methylene)-a-D-*ribo*-hexofuranose (79):

A solution of **78** (0.55 g, 1.8 mmol), PPh_3 (1.0 g, 3.8 mmol), pyridine (2 mL) and CBr_4 (0.7 g, 2 mmol) in CH_2Cl_2 (25 mL) was stirred at rt for 0.5 h. The reaction mixture was evaporated and the residue purified on silica gel using ethyl acetate and light petroleum (1:9) to afford **79** (0.66 g, 80 %).

$[á]_D$ = +127° (*c* 0.65, $CHCl_3$)

^{1}H-NMR (300 MHz, $CDCl_3$) : 0.61 (t, 1H, J = 5.9 Hz), 1.28 (s, 6H), 1.37, 1.53 (2 x s, 6H), 1.83 (m, 1H), 3.12 (t, 1H, J = 11.4 Hz), 3.7 (dt, 1H, J = 5.9, 8.9 Hz), 3.91 (dd, 1H, J = 5.1, 8.5 Hz), 3.91 (dd, 1H, J = 5.1, 8.5 Hz), 3.98 (dd, 1H, J = 4.7, 10.6 Hz), 4.07 (m, 2H), 4.82 (d, 1H, J = 3.7 Hz), 5.80 (d, 1H, J = 3.7 Hz).

Anal. Calcd. for $C_{15}H_{23}O_5Br$: C, 49.58; H, 6.33. Found: C, 51.07; H, 6.47.

3-Deoxy-1,2:5,6-di-*O*-isopropylidene-3,3-C-diallyl-a -D-*ribo*-hexofuranose (80):

The diallyl compound **80** was achieved by using the same procedure as described earlier. A solution of compound **79** (0.2 g, 0.55 mmol), allyltri-n-butyl tin (0.4 mL, 1.1 mmol), AIBN (10 mg) in benzene (6 mL) were refluxed under argon atmosphere for 12 h. After usual work up with KF and purification of the residue on silica gel using ethyl acetate light petroleum (1: 20) gave **80** (0.13 g, 76%).

$[á]_D$ = +36^o (*c* 2.1, $CHCl_3$)

^{1}H-NMR (300 MHz, $CDCl_3$) : 1.27, 1.33, 1.40, 1.50 (4 x s, 12H), 2.18 (t, 2H, J = 6.0 Hz), 2.37 (m, 2H), 3.72 (d, 1H, J = 10.6 Hz), 3.78 (m, 1H), 4.09 (m, 2H), 4.24 (d, 1H, J = 3.4 Hz), 5.03 (m, 4H), 5.57 (d, 1H, J = 3.4 Hz), 5.9 (m, 1H).

^{13}C-NMR (50 MHz, $CDCl_3$) : 25.5, 26.4, 26.8, 27.1, 36.1, 37.0, 50.6, 69.0, 73.5, 85.2, 86.0, 104.4, 109.5, 111.3, 117.6, 134.8, 135.5

Anal. Calcd. for $C_{18}H_{28}O_5$: C, 66.66; H, 8.64. Found: C, 66.46; H, 8.92.

1,2-Cyclohexanediol (82):

To a solution of **81** (6 mL, 4.9 g, 59 mmol) in acetone- water (4: 1), NMO (50% aq) (148.5 mmol) and a 0.05 molar solution of OsO_4 (0.6 mL) were added and stirred for 10 h at rt. The reaction mixture was concentrated and washed with saturated Na_2SO_3, extracted with ethyl acetate. Combined ethyl acetate fractions were dried (Na_2SO_4), concentrated, to give diol **82** (6.2 g, 90 %) as white crystalline solid.

M.P = 99-101 ^oC Lit[70]. M.P = 97- 101^oC

^{1}H-NMR (200 MHz, $CDCl_3$) : 1.10-1.90 (m, 8H), 3.02 (br. s, 2H), 3.49 (m, 2H).

^{13}C-NMR (50 MHz, $CDCl_3$/DMSO-d_6) : 20.80, 29.10, 69.54

EIMS = m/z 116(M^+)

2-Methoxy-cyclohexanol (83):

A suspension of freshly prepared silver oxide (6.0 g, 26 mmol), **82** (2.0 g, 17.2 mmol) and methyl iodide (1.6 mL, 17.2 mmol) in dry CH_2Cl_2 (50 mL) stirred for 10 h at rt. The reaction mixture was filtered through Celite and concentrated and the residue was column purified on silica gel using ethyl acetate-light petroleum to give **83** (1.34 g, 60 %). Further elution of the column afforded unreacted **82** (0.5 g).

^{1}H-NMR (300 MHz, $CDCl_3$) : 1.12 – 1.85 (m, 8H), 3.25 (m, 1H), 3.37 (s, 3H), 3.82 (m, 1H).

^{13}C-NMR (50 MHz, $CDCl_3$) : 20.9, 21.8, 25.6, 30.1, 55.5, 68.0, 80.1.

EIMS = m/z 130(M^+)

Ethyl 2(E/Z)-2-methoxy cyclohexylidene ethanoate (85):

A solution of **83** (0.9 g, 7 mmol) and IBX (3.0 g, 10.3 mmol) in DMSO (4 mL) at rt was stirred for 8 h. The reaction mixture was quenched with water and the solid was filtered through a bed of celite and extracted with ethyl acetate. Combined Ethyl acetate layer was dried (Na_2SO_4), and concentrated and the residue was directly treated with PPh_3= $CHCO_2Et$ in benzene and refluxed for 8 h. Solvent was removed and the residue purified on silica gel to give **85** (0.7 g, 54 %) and further elution of the column afforded unreacted **83** (28%).

^{1}H-NMR (300 MHz, $CDCl_3$) : 1.30 (t, 3H, J = 6.4 Hz), 1.53-1.95 (m, 6H), 2.48-2.69 (m, 1H), 2.95-3.13 (m, 1H), 3.31 (s, 3H), 3.67 (s, 1H), 4.18 (q, 2H, J = 7.3 Hz), 5.80 (s, 1 H).

^{13}C-NMR (75 MHz, $CDCl_3$) : 14.4, 22.7, 27.2, 27.8, 34.6, 56.6, 59.7, 82.6, 113.0 160.9, 166.9.

EIMS = m/z 198(M^+)

(2E)-2-(2-methoxy cyclohexylidene) ethanol (86):

To a solution of **85** (0.6 g, 3.0 mmol) in dry CH_2Cl_2 (25 mL) under argon atmosphere at –78 °C was added a 2.1 M solution of DIBAL-H (3.6 mL, 7.6 mmol) dropwise and the reaction was stirred for 1 h. The reaction was quenched with MeOH and saturated solution of sodium potassium tartarate and stirred vigorously for 2 h and the layers were separated. The CH_2Cl_2 layer was dried (Na_2SO_4), concentrated. The residue was purified on silica gel to give **86** (0.4 g, 85%).

^{1}H-NMR (200 MHz, $CDCl_3$) : 1.28 – 1.86 (m, 6H), 2.15 (t, 1H, J = 6.2 Hz), 3.2 (m, 3H), 3.5 (t, 1H, J = 3.9 Hz), 4.13 (d, 2H, J = 6.7 Hz), 5.49 (t, 1H, J = 6.7 Hz).

EIMS = m/z 156(M^+)

Cyclopropanation of 86 using Et_2Zn/CH_2I_2 to give 87

Experimental procedure was as described earlier. Compound **86** (0.35 g, 2.2 mmol) was treated with 1M solution of Et_2Zn (6.7 mL, 6.7 mmol) and CH_2I_2 (0.8 mL, 11.2 mmol) in dry CH_2Cl_2 (25 mL) for 12 h. The reaction after workup and purification of the residue on silca gel afforded **87** (0.26 g, 67%)

^{1}H-NMR (200 MHz, $CDCl_3$) : 0.14 (t, 1H, J = 5.13 Hz), 0.47 (dd, 1H, J = 5.1, 8.8 Hz), 1.25-1.95 (m, 9H), 2.53 (s, 1H), 2.95 (br. s, 1H), 3.34 (s, 3H), 3.53 (dd, J = 8.79, 11.0 Hz), 3.68 (m, 1H).

^{13}C-NMR (50 MHz, $CDCl_3$) : 13.7, 21.0, 24.9, 25.4, 25.9, 26.0, 28.7, 56.1, 62.2, 83.9.

EIMS = m/z 170(M^+).

1-Bromomethyl-4-methoxyspiro-(2,5)-octane (88):

Compound **87** (0.25 g, 1.4 mmol), PPh_3 (0.8 g, 3.0 mmol), pyridine (1 mL) and CBr_4 (0.52 g, 1.6 mmol) were taken in dry CH_2Cl_2 (10 mL), stirred for 30 min. The residue after purification gave **88** (0.26 g, 79 %).

^{1}H-NMR (300 MHz, $CDCl_3$) : 0.17 (t, 1H, J = 5.5 Hz), 0.45-1.05 (m, 2H), 1.25-1.80 (m, 8H), 2.63 (b. s, 1H), 3.29 (s, 3H), 3.6 (m, 2H).

EIMS = m/z 233(M^+).

1,1-diallyl-2-methoxycyclohexane (89):

The diallyl compound **89** was achieved by using the same procedure as described earlier. A solution of compound **88** (0.2 g, 0.54 mmol), allyltri-n-butyl tin, AIBN (20 mg) in toluene (10 mL) was refluxed under argon atmosphere for 12 h. After usual work up with KF

and purification of the residue on silica gel using ethyl acetate light petroleum (1: 20) to give **89** (0.12 g, 75 %) as a color less syrup.

^{1}H-NMR (200 MHz, $CDCl_3$) : δ 1.10-1.80 (m, 8 H), 1.92-2.30 (m, 4 H), 2.94 (dd, 1 H, J = 3.4, 7.8 Hz), 3.27 (s, 3 H), 4.94 (m, 4 H), 5.77 (m, 2 H);

^{13}C-NMR (50 MHz, $CDCl_3$) : δ 21.0, 22.9, 24.1, 31.4, 36.8, 39.8, 40.9, 56.3, 82.3, 117.0, 117.2, 135.1.

EIMS = m/z 194 (M^+)

2-(*Z*)-4-(Benzyloxy)-buten-1-ol (91):

To a solution of **90** (1.1 g, 12.5 mmol) in DMF (15 mL) at 0 °C, NaH (0.5 gm, 12.5 mmol) (60% suspension in oil) was added. After stirring for 0.5 h at rt, BnBr (1.4 mL, 11.3 mmol) was added dropwise and left at rt for 1 h. The reaction mixture was quenched with ice-cold water and extracted with ether. Combined ether layer was dried, (Na_2SO_4) and concentrated. The residue was column purified on silica gel using ethyl acetate and light petroleum to give **91** (1.5 g, 70 %) and 13 % dibenzyl derivative.

^{1}H-NMR (300 MHz, $CDCl_3$) : 2.8 (br. s, 1H), 4.12 (m, 4H), 4.55 (s, 2H), 5.79 (m, 2H), 7.35 (m, 5H).

^{13}C-NMR (75 MHz, $CDCl_3$) : 57.9, 65.3, 72.1, 127.5, 128.1, 132.3, 137.7.

{2-[(Benzyloxy)methyl]cyclopropyl}methanol (92):

To a solution of **91** (1.4 g, 7.8 mmol) in CH_2Cl_2 (40 mL) at –20 °C under N_2 atmosphere, a 1M solution of Et_2Zn (23.5 mL, 23.5 mmol) and CH_2I_2 (2.8 mL, 39 mmol) were added dropwise and stirred for 12 h. The reaction mixture was quenched with slow addition of

saturated NH_4Cl and warmed to rt. The CH_2Cl_2 layer was separated and dried (Na_2SO_4) and concentrated. The residue was purified on silica gel column chromatography using ethyl acetate - light petroleum to give **92** (0.8 g, 52 %).

^{1}H-NMR (300 MHz, $CDCl_3$) : 0.2 (dd, 1H, J = 2.9, 7.0 Hz), 0.8 (m, 1H), 1.33 (m, 2H), 2.96 (s, 1H), 3.14 (m, 2H), 3.9 (m, 2H), 4.55 (q, 2H), 7.33 (m, 5H).

^{13}C-NMR (50 MHz, $CDCl_3$) : 8.6, 14.8, 18.5, 62.9, 70.7, 73.1, 127.9, 128.5, 137.5.

EIMS = m/z 161(M^+-CH_2OH), 101(M^+-Bn).

Benzyl[2-(bromomethyl)cyclopropyl]methyl ether (93):

A solution of compound **92** (0.4 gm, 2.0 mmol), PPh_3 (1.2 g, 4.3 mmol), pyridine (1.5 mL) and CBr_4 (0.75 g, 2.2 mmol) in dry CH_2Cl_2 (20 mL) was stirred at rt for 0.5 h, solvent was removed and the residue purified on silica gel using ethyl acetate-light petroleum to afford **93** (0.4 g, 75 % yield).

^{1}H-NMR (300 MHz, $CDCl_3$) : 0.4 (dd, 1H, J = 3.7, 7.9 Hz), 1.02 (m, 1H), 3.49 (m, 4H), 4.54 (m, 2H), 7.34 (m, 5H).

EIMS = m/z 148(M-OBn) $^+$.

2-Allylpent-4-enyl benzyl ether (94):

The diallyl compound **94** was achieved by using the same procedure as described earlier. Compound **93**, (0.3 g, mmol), allyltri-n-butyl tin, AIBN (10 mg) were refluxed in toluene (15 mL) under argon atmosphere for 12 h. After usual work up with KF and purification of the residue on silica gel using ethyl acetate light petroleum (5: 95) to give **94** (0.17 g, 70%).

^{1}H-NMR (200 MHz, $CDCl_3$) : δ 1.76 (m, 1H), 2.10 (m, 4H), 3.33 (dd, 2H, J = 5.9, 11.2 Hz), 4.46 (ABq, 2 H, J = 11.7 Hz), 5.00 (m, 4 H), 5.73 (m, 2 H), 7.26 (m, 5 H);

^{13}C-NMR (50 MHz, $CDCl_3$) : δ 35.4, 38.3, 72.4, 73.1, 116.3, 127.5, 128.3, 136.7.

EIMS = m/z 216 (M^+)

3-Deoxy-1,2:5,6-di-*O*-isopropylidene-3,3-C-(3-cyclopentenyl)-α-D-*ribo*-hexofuranose (95):

A solution of **80** (100 mg, 0.3 mmol) and Grubbs' catalyst (5 mg) in CH_2Cl_2 (8 mL) was stirred at rt for 3 h, solvent evaporated and the residue was purified on silica gel using ethyl acetate-light petroleum (1:25) to give **95** (73 mg, 80%) as a syrup.

$[á]_D$ = +43° (*c* 0.9, $CHCl_3$)

^{1}H-NMR (200 MHz, $CDCl_3$) : δ 1.31 (s, 6H), 1.40 (s, 3H), 1.52 (s, 3H), 1.79 (m, 1H), 2.57 (m, 3H), 3.96 (m, 2H), 4.10 (m, 2H), 4.24 (d, 1H, J = 3.7 Hz), 5.69 (m, 3H).

EIMS = m/z 281 $(M-Me)^+$

Anal. Calcd. for $C_{16}H_{24}O_5$: C, 64.86; H, 8.10. Found: C, 64.75; H, 8.23.

3-Deoxy-1,2:5,6-di-*O*-isopropylidene-3-C-allyl-3-C-methallyl-α-D-glucofuranose (96):

Compound **79** (0.2 g, 0.55 mmol), methallyltri-n-butyl tin (0.5 g, 1.4 mmol) and AIBN (15 mg) were refluxed in toluene under argon atmosphere for 12 hr. After usual work up with KF and purification of the residue on silica gel using ethyl acetate light petroleum (1: 49) to give **96** (97 mg, 52%).

$[á]_D$ = +57° (*c* 0.7, $CHCl_3$)

^{1}H-NMR (200 MHz, $CDCl_3$) : δ1.32, 1.36, 1.43, 1.54, 1.86 (5 s, 16H), 2.1 (d, 1H, J =

13.3 Hz), 2.35 (d, 1H, J = 13.3 Hz), 2.47 (d, 1H, J = 7.8 Hz), 3.89 (m, 2H), 4.09-4.33 (m, 2H), 4.49 (d, 1H, J = 3.9 Hz), 6.02 (m, 1H).

EIMS = m/z 338 (M^+)

Anal. Calcd. for $C_{19}H_{30}O_5$: C, 67.45; H, 8.87. Found: C, 67.51; H, 8.9.

3-Deoxy-1,2:5,6-di-*O*-isopropylidene-3,3-C-[(3-methyl)cyclopent-3-enyl]-α-D-glucofuranose (97):

A solution of **96** (75 mg, 0.22 mmol) and Grubbs' catalyst (5 mg) in CH_2Cl_2 (5 mL) was stirred at rt for 3h, solvent evaporated and the residue was purified on silica gel using ethyl acetate-light petroleum (1:25) to give **97** (52 mg, 75%) as a syrup.

$[á]_D$ = +46° (*c* 0.45, $CHCl_3$)

^{1}H-NMR (200 MHz, $CDCl_3$) : δ 1.25, 1.32, 1.41, 1.53, 1.73 (5 s, 15H) (s, 3H), 2.57 (m, 4H), 3.97 (m, 2H), 4.12 (m, 2H), 4.26 (d, 1H, J = 3.42 Hz), 5.31 (br. t, 1H), 5.70 (s, 1H).

^{13}C-NMR (50 MHz, $CDCl_3$) : δ 25.4, 26.4, 26.7, 27.0, 29.7, 34.9, 40.7, 55.8, 68.2, 74.7, 81.8, 87.4, 104.1, 109.3, 111.8, 123.6, 136.9

EIMS = m/z 295 $(M-Me)^+$

Anal. Calcd. for $C_{17}H_{26}O_5$: C, 65.80; H, 8.38. Found: C, 65.82; H, 8.63.

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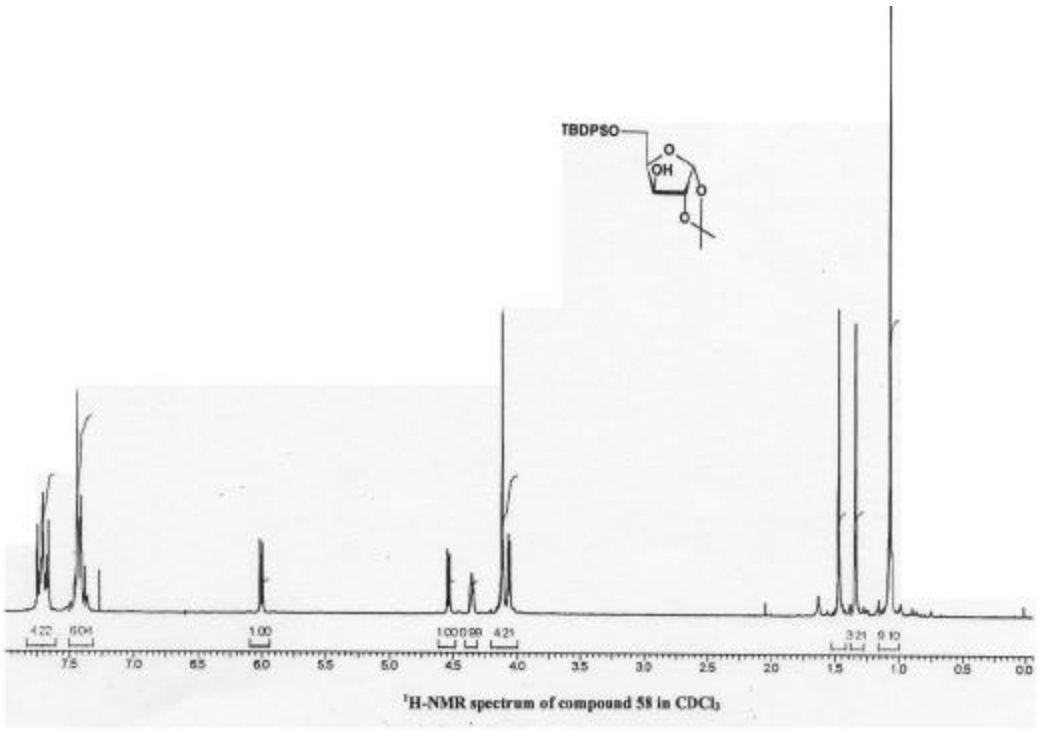
SPECTRA



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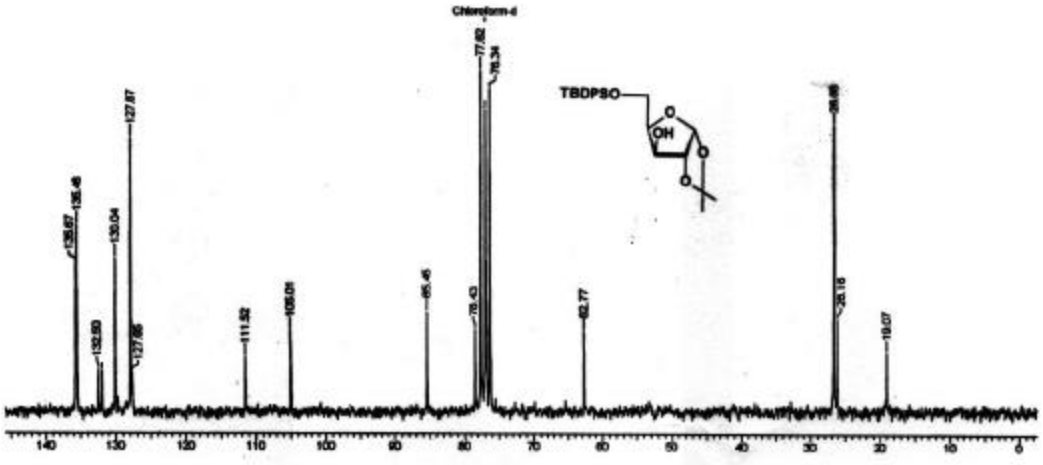

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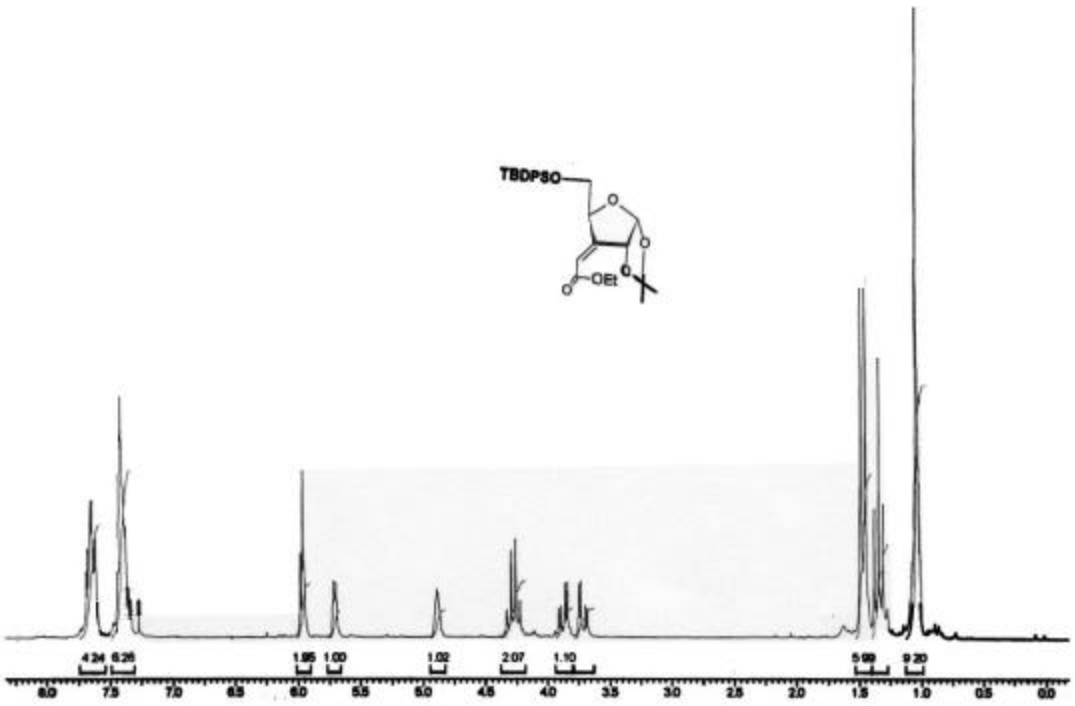

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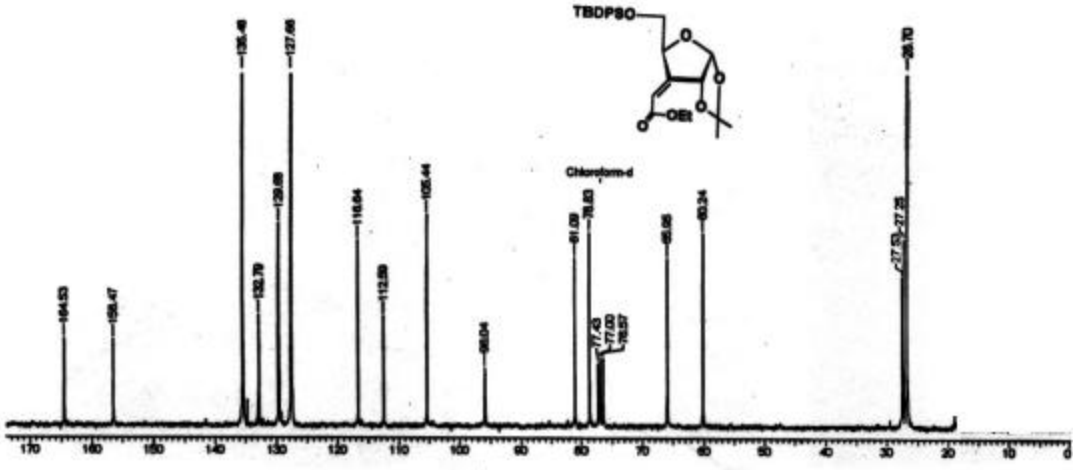

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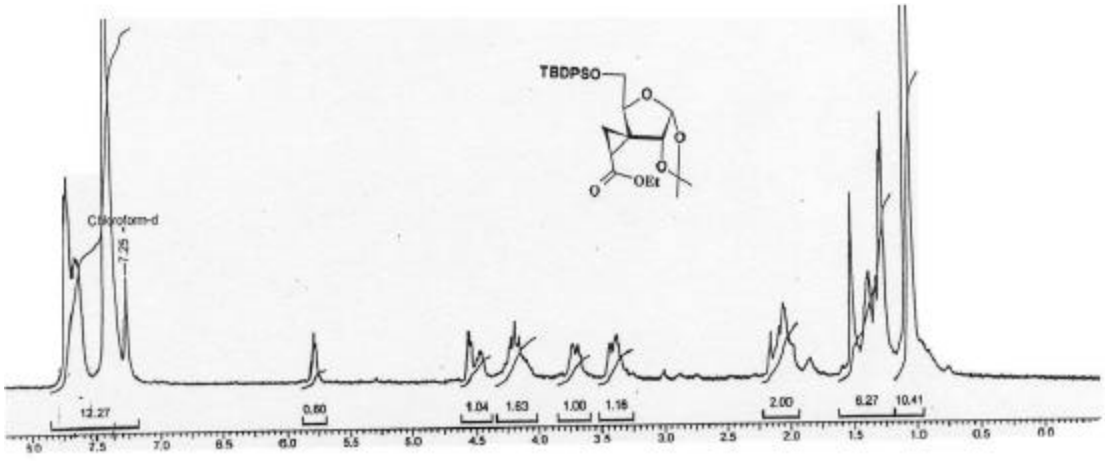

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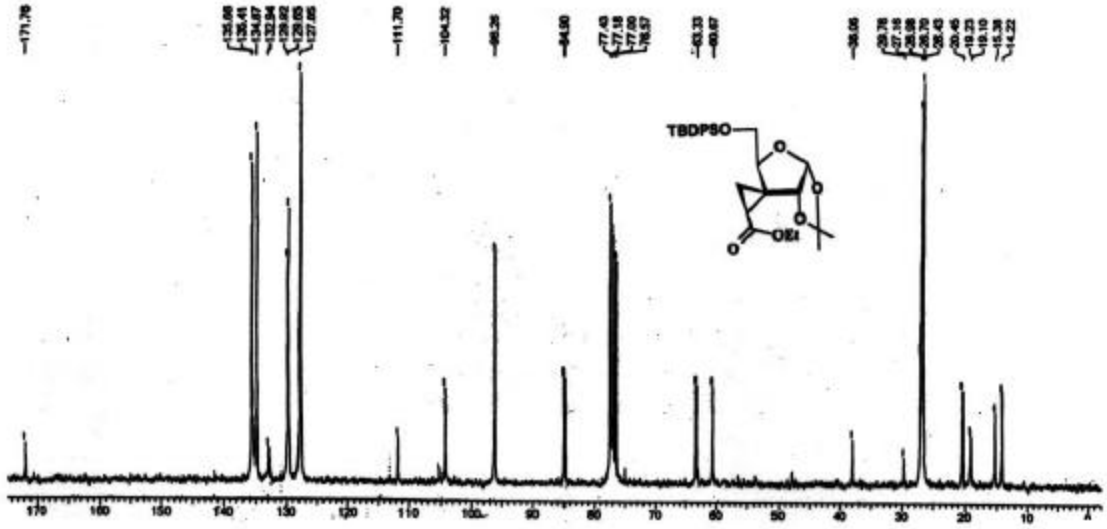

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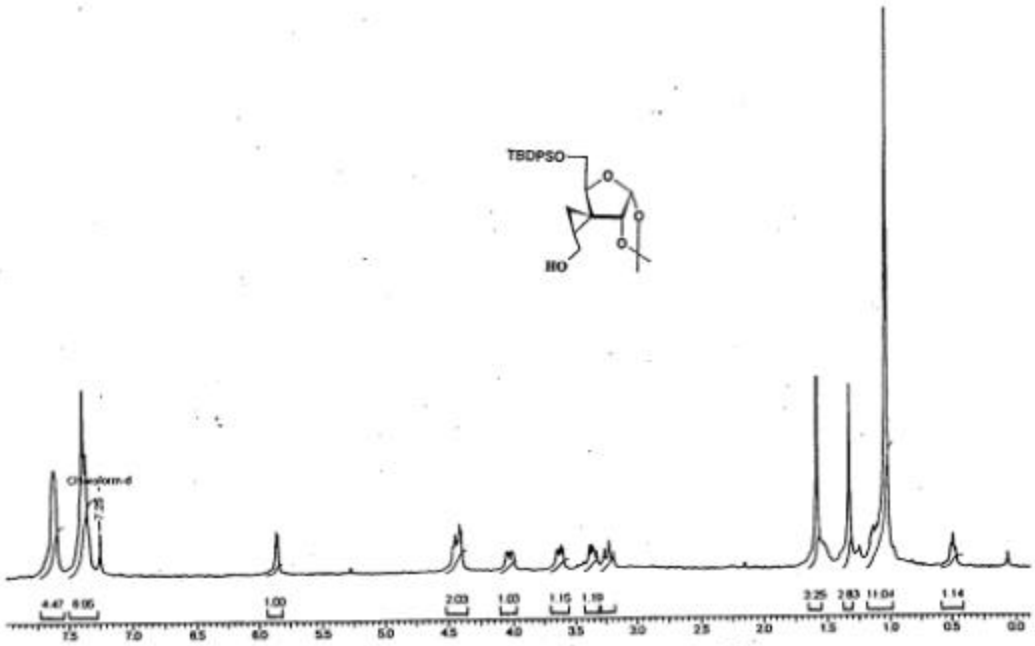

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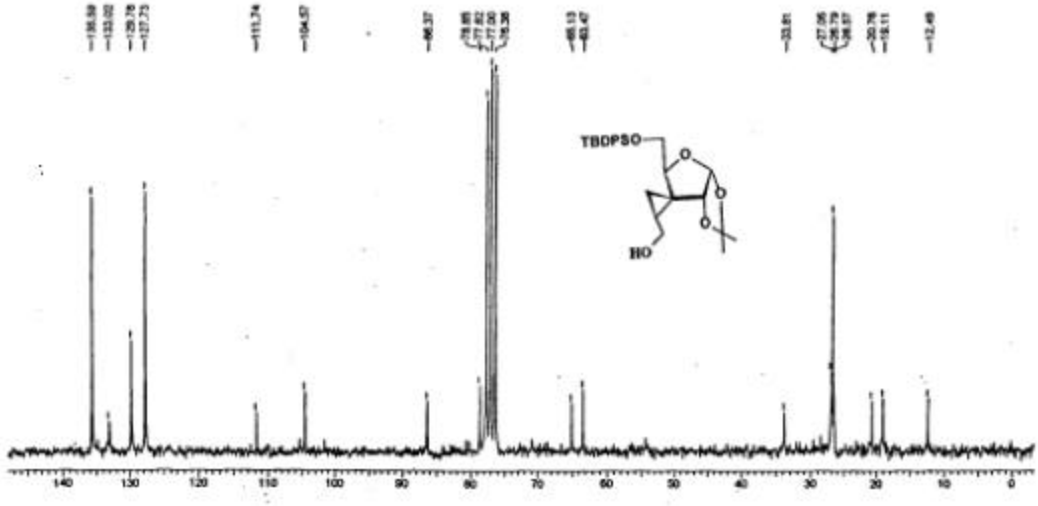

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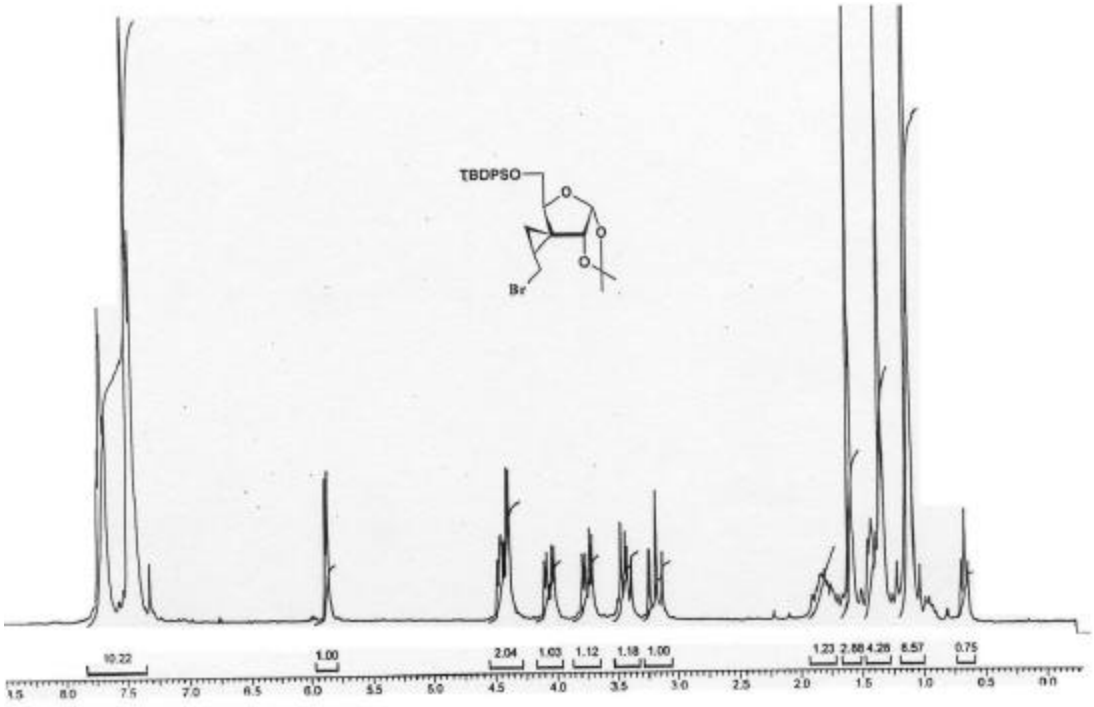

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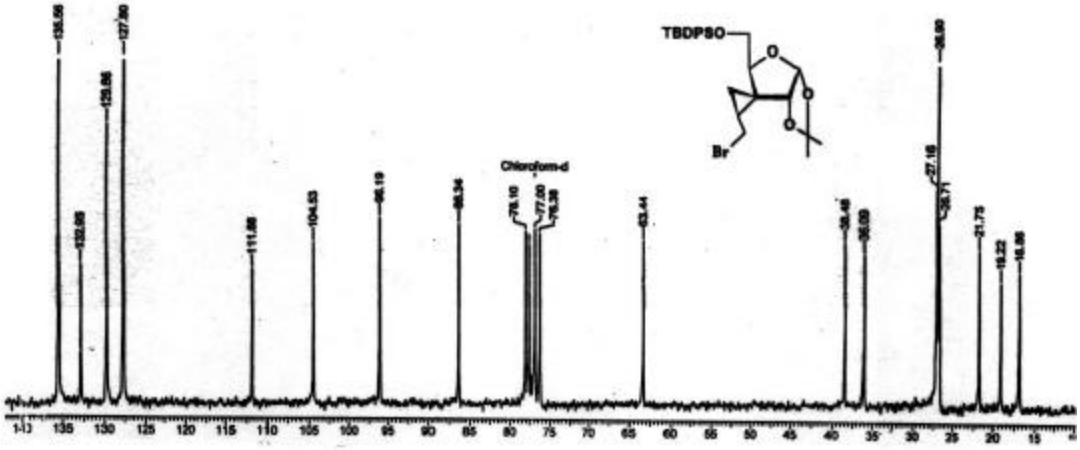

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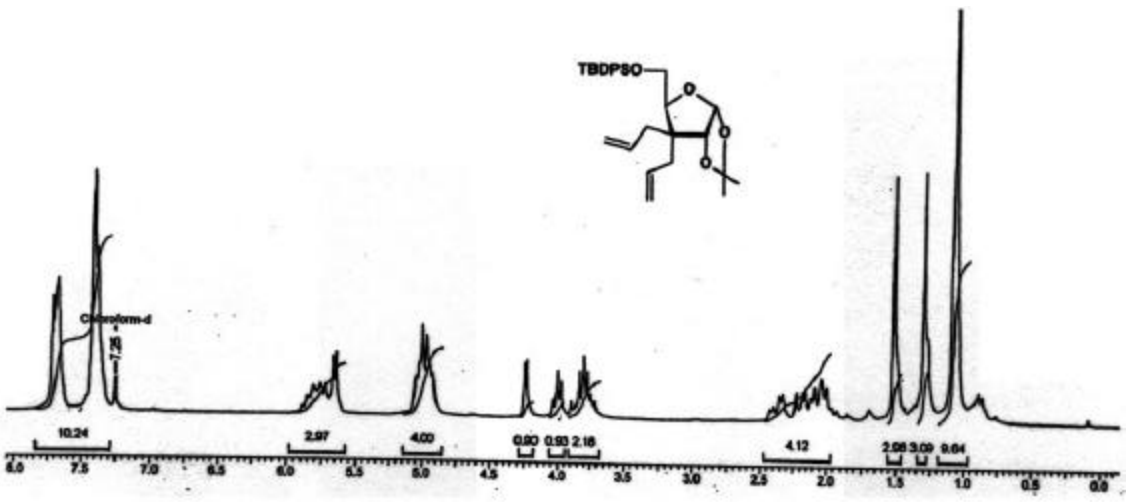

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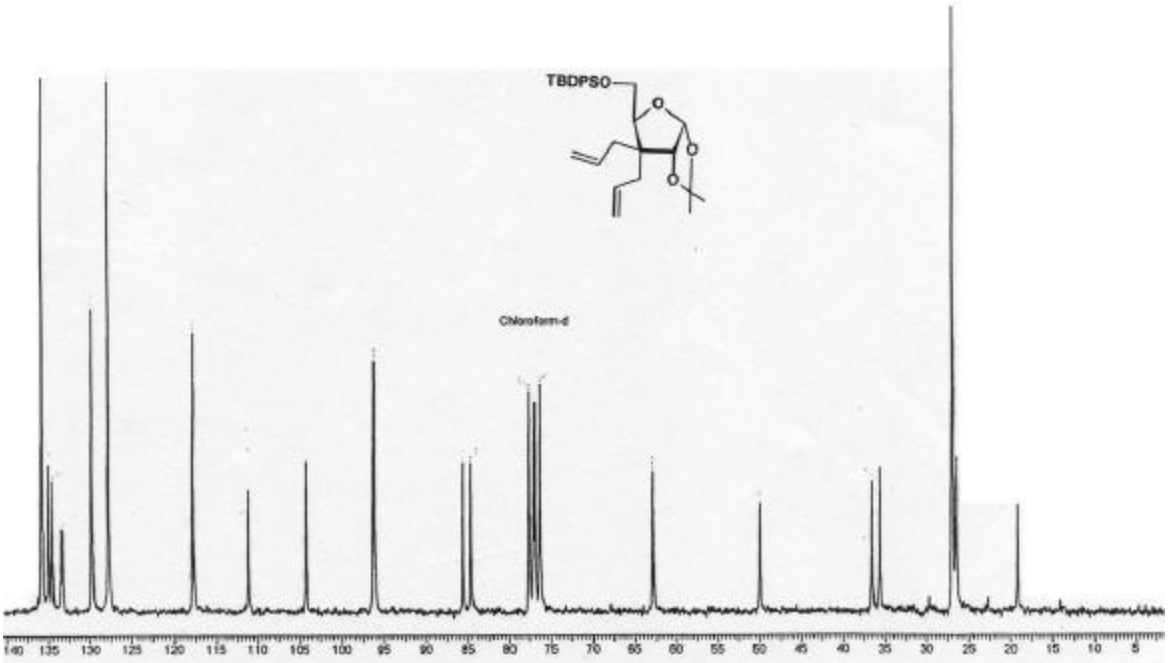

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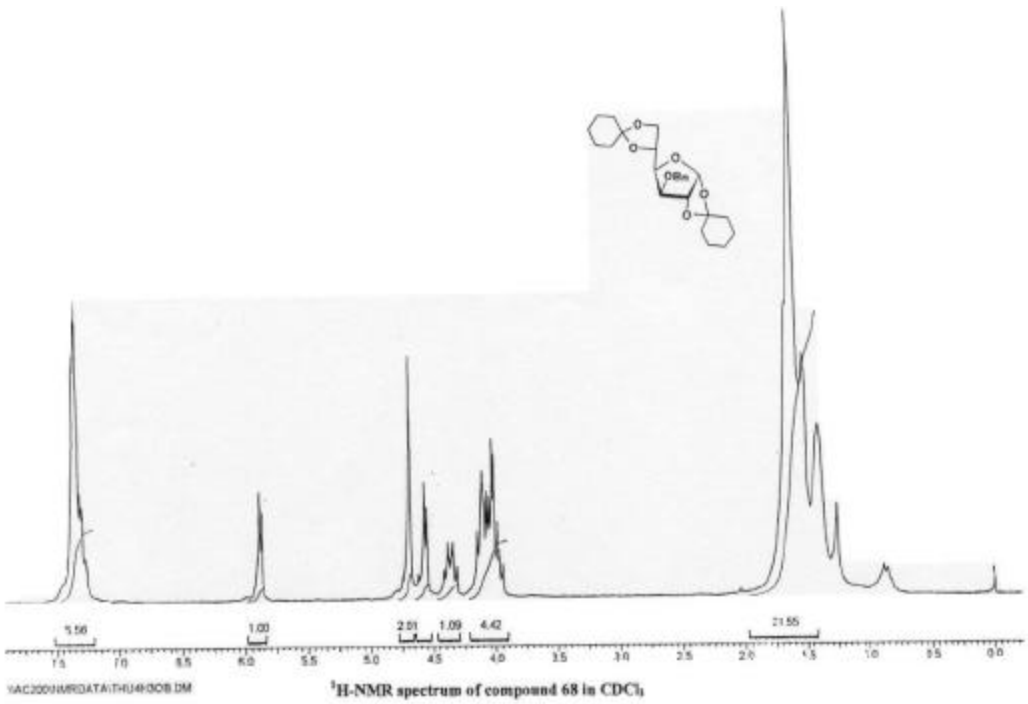

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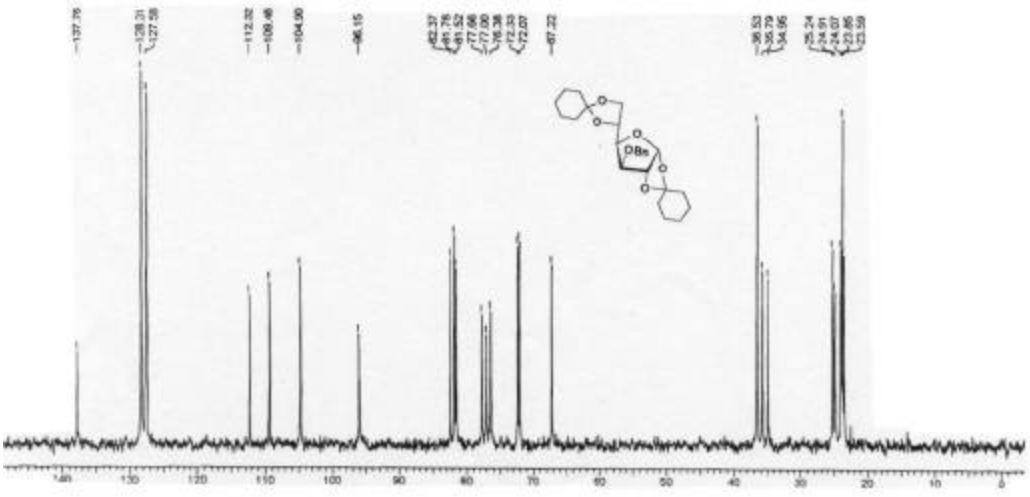

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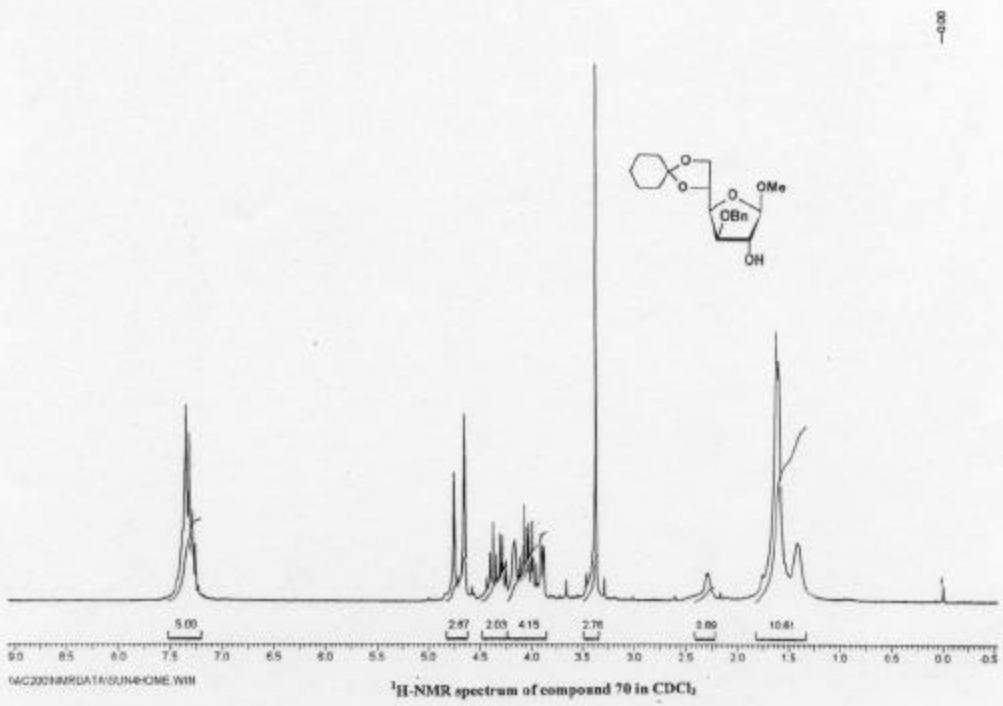

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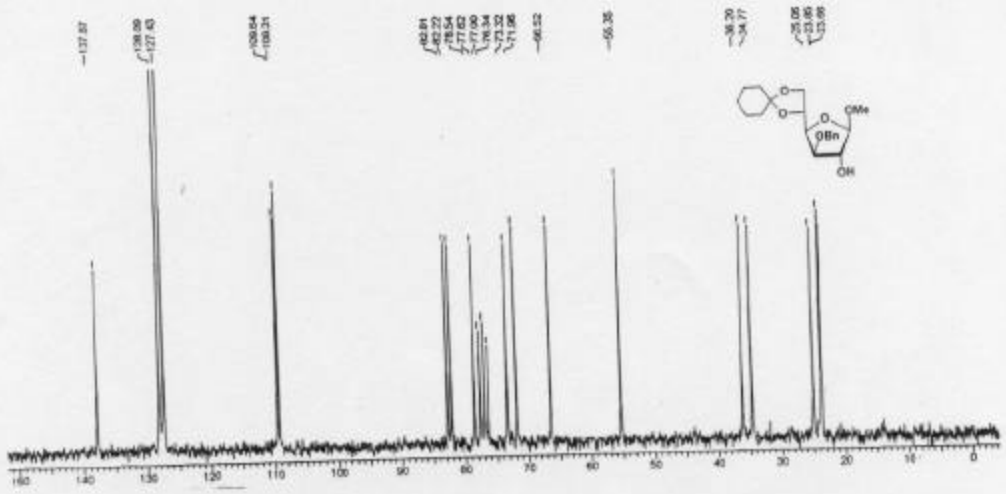

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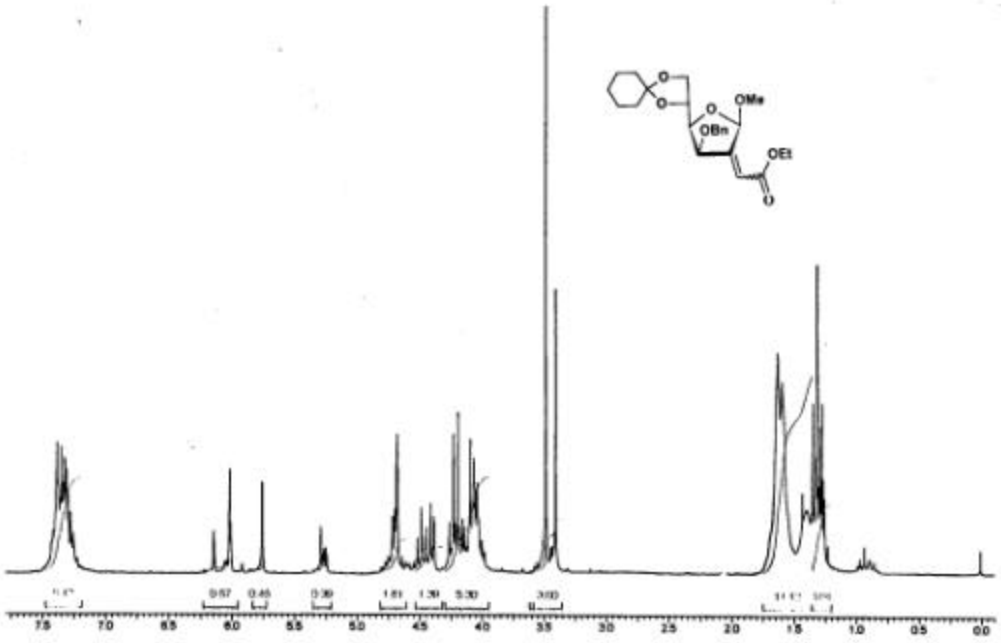

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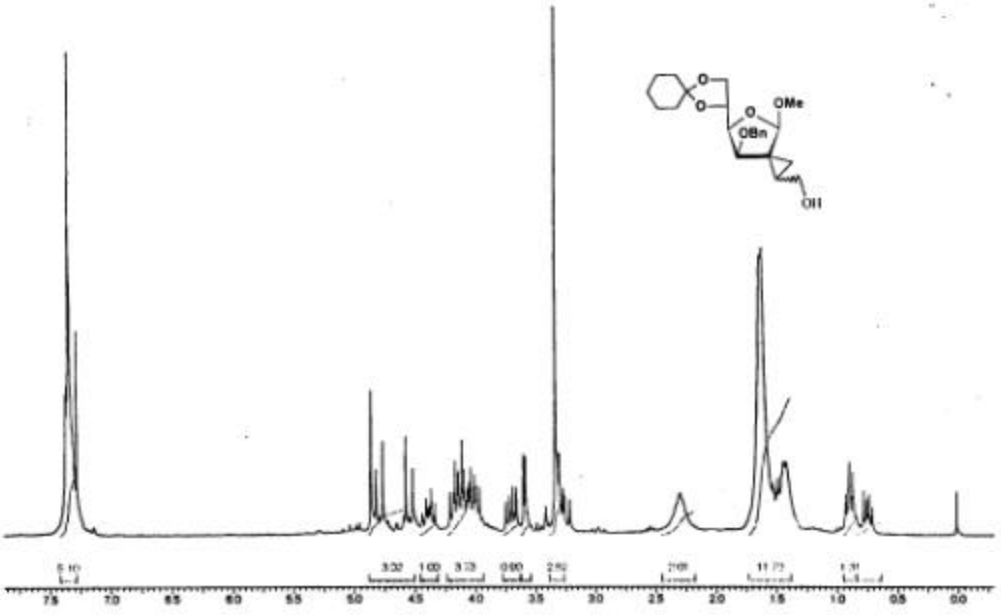

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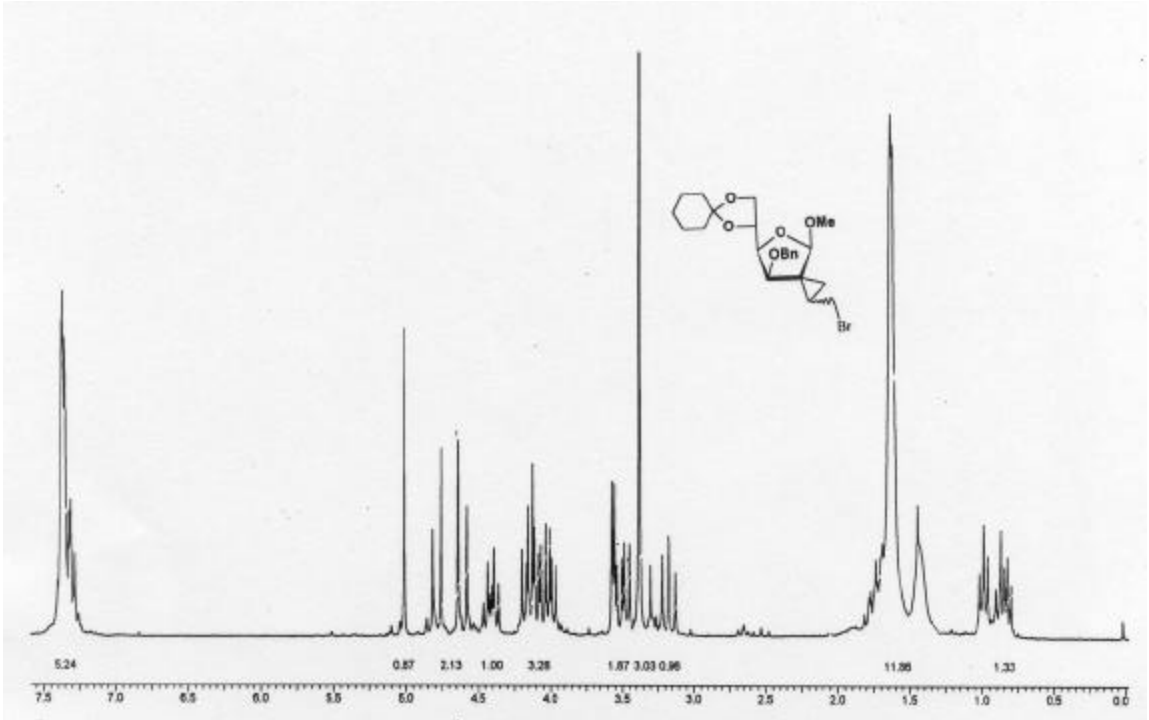

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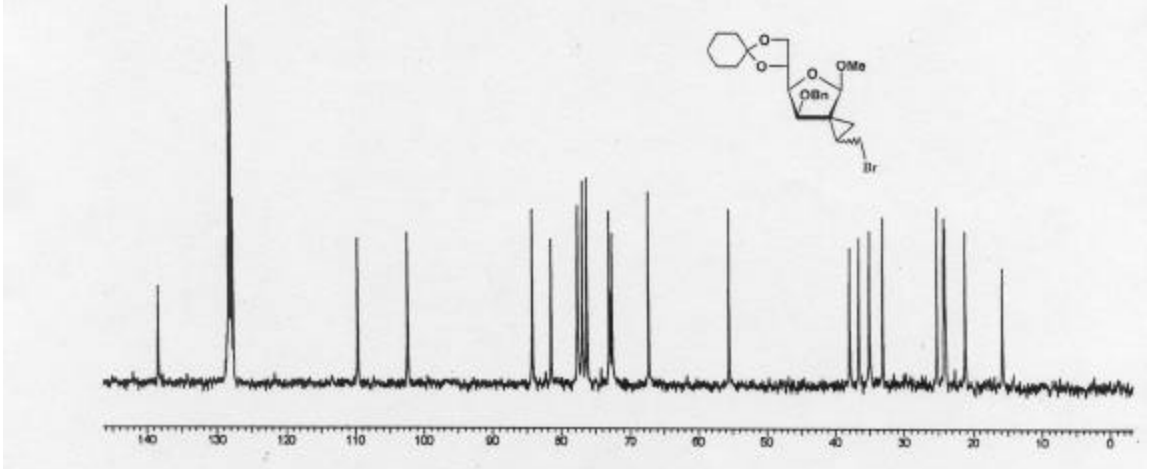

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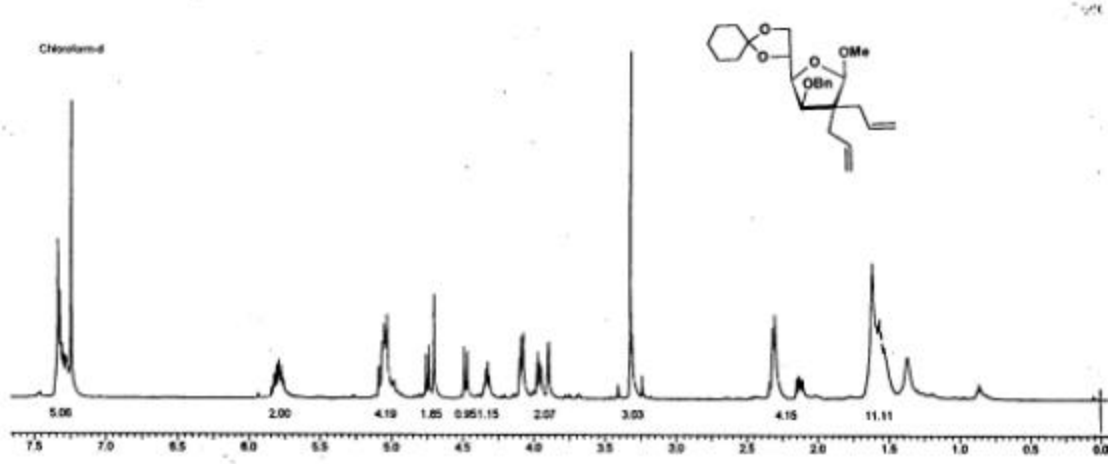

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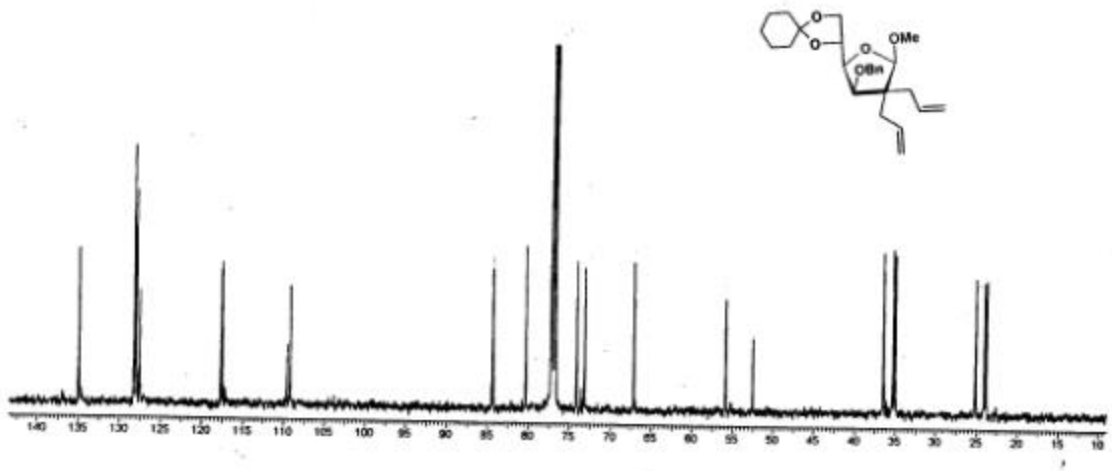

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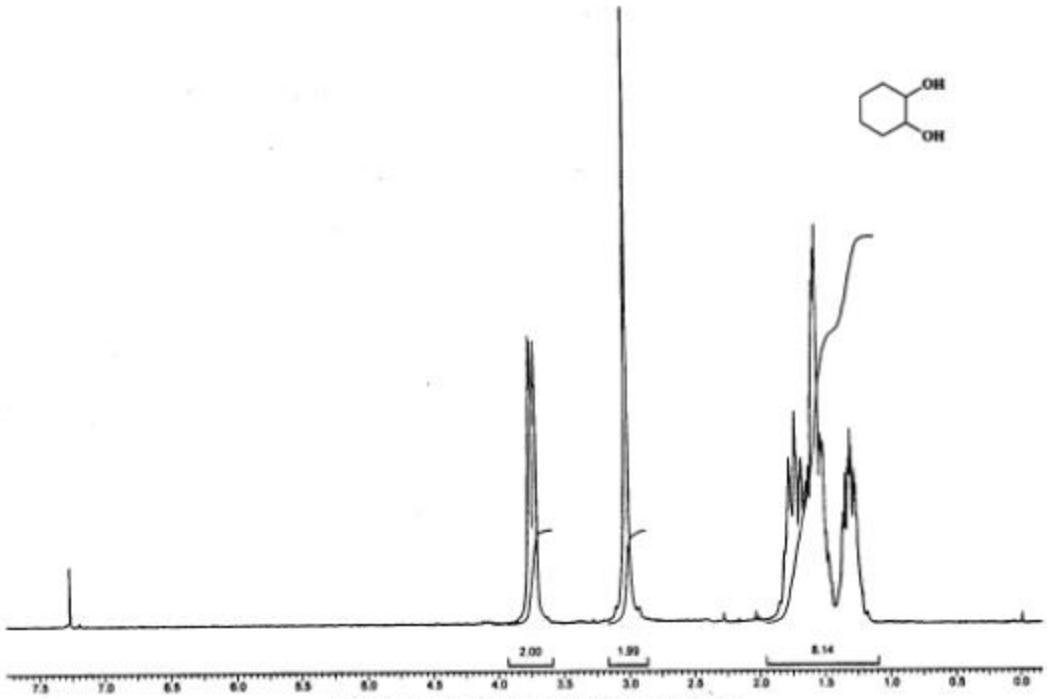

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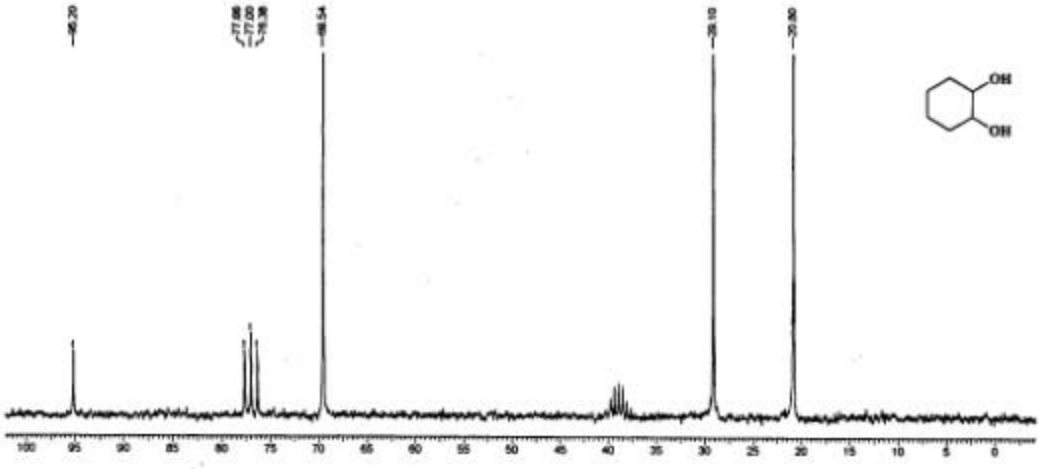

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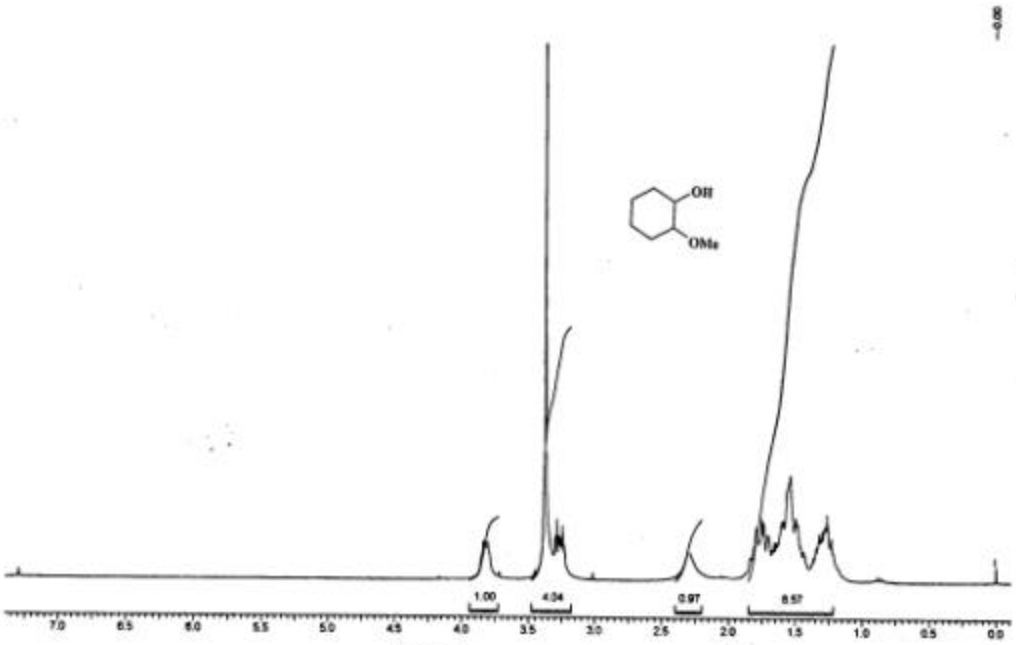

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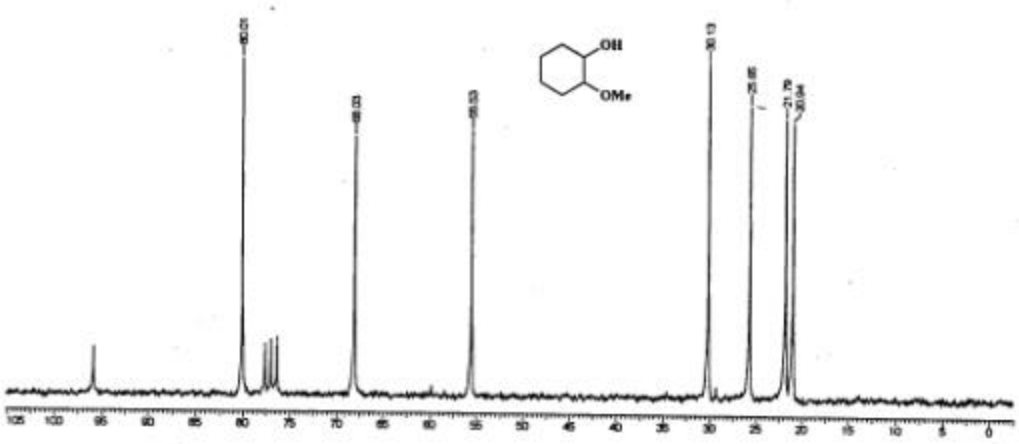

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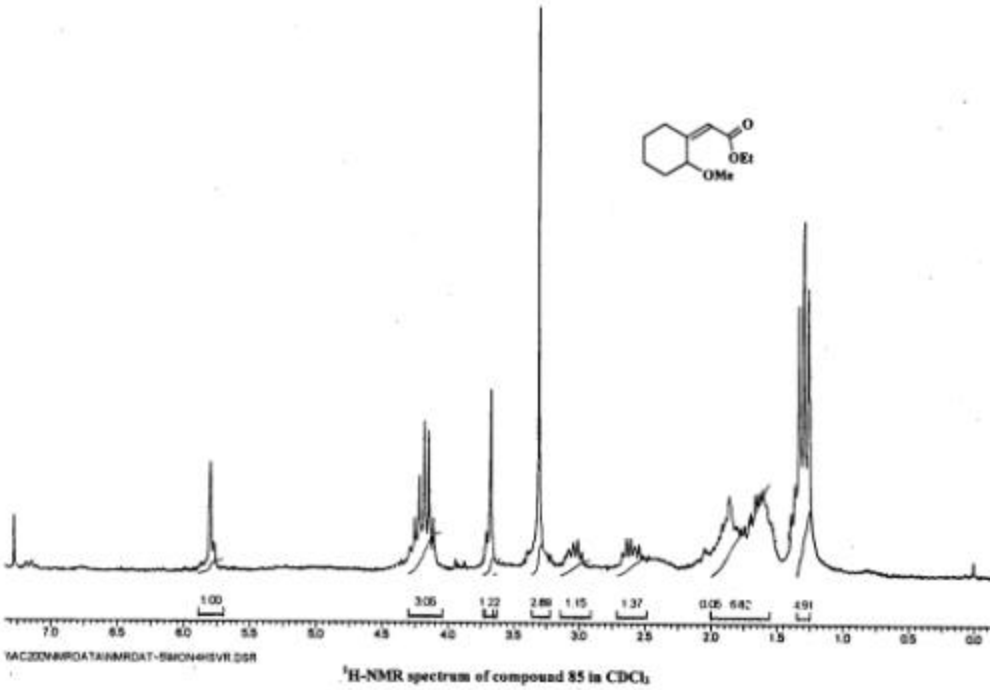

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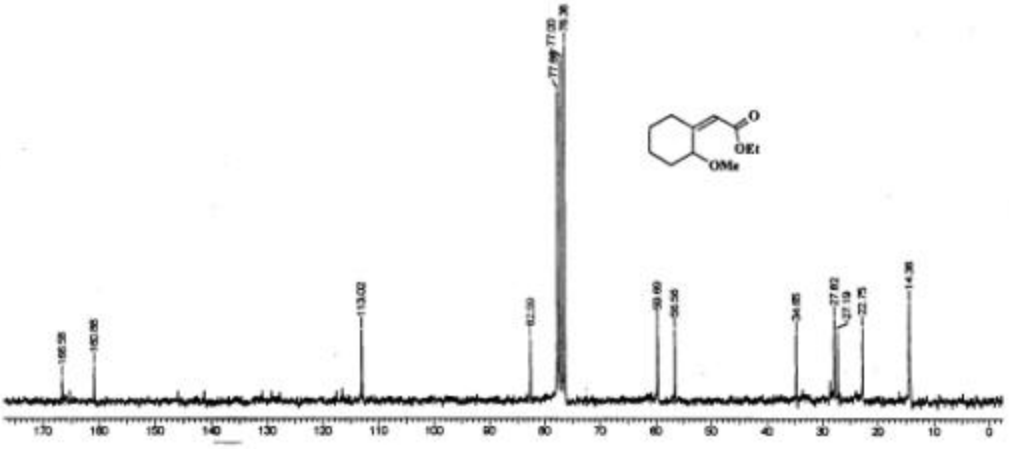

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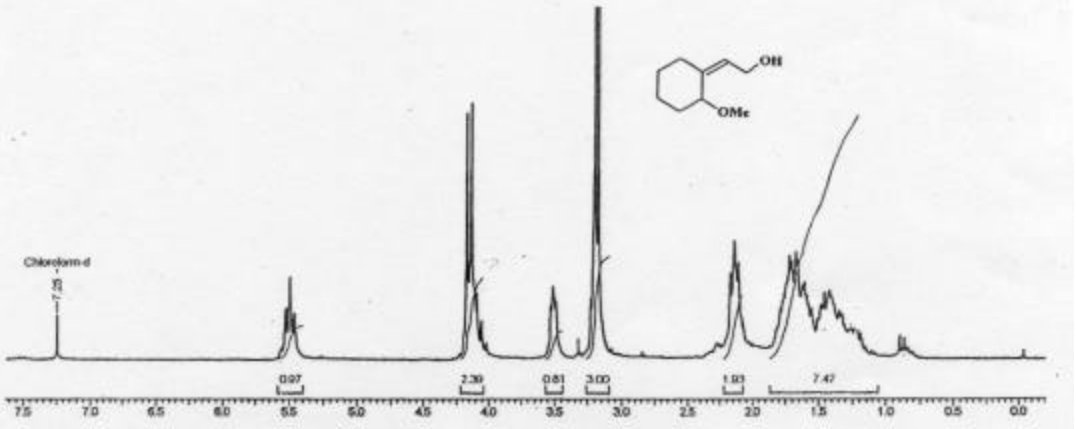

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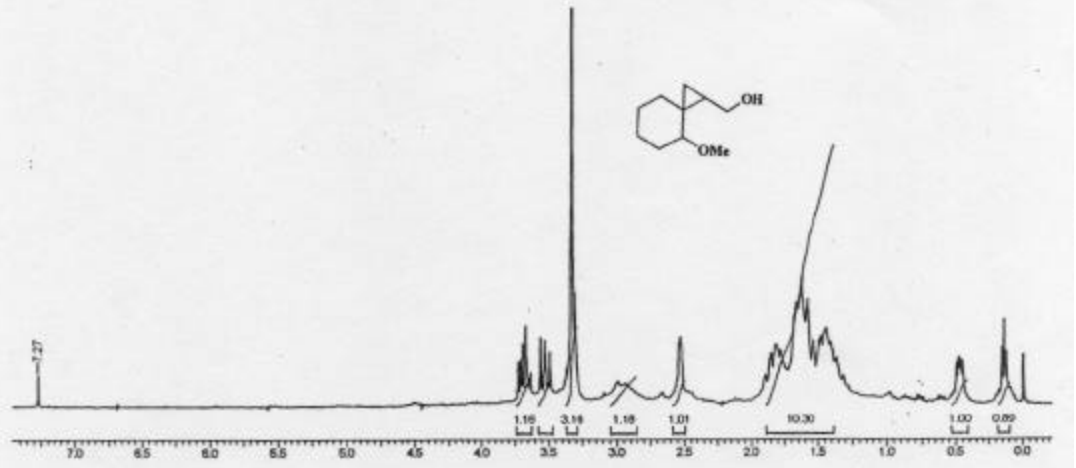

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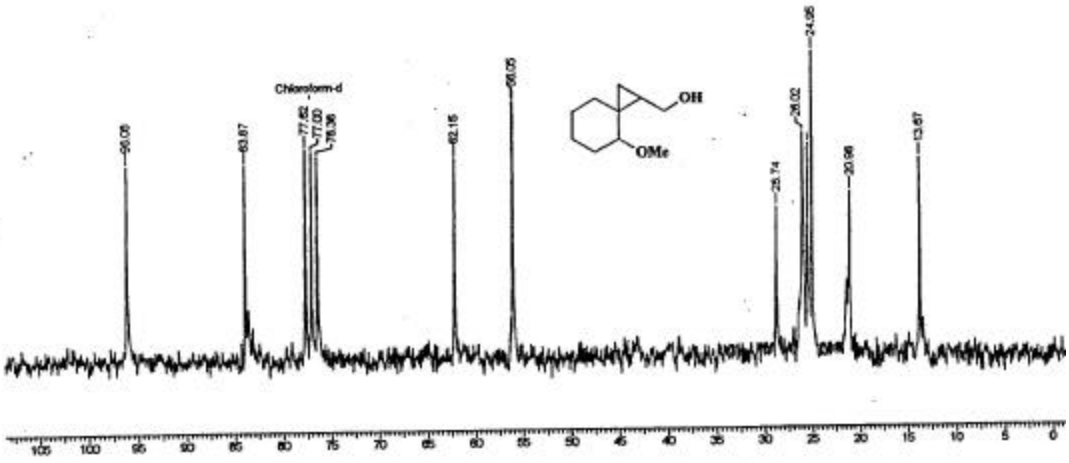

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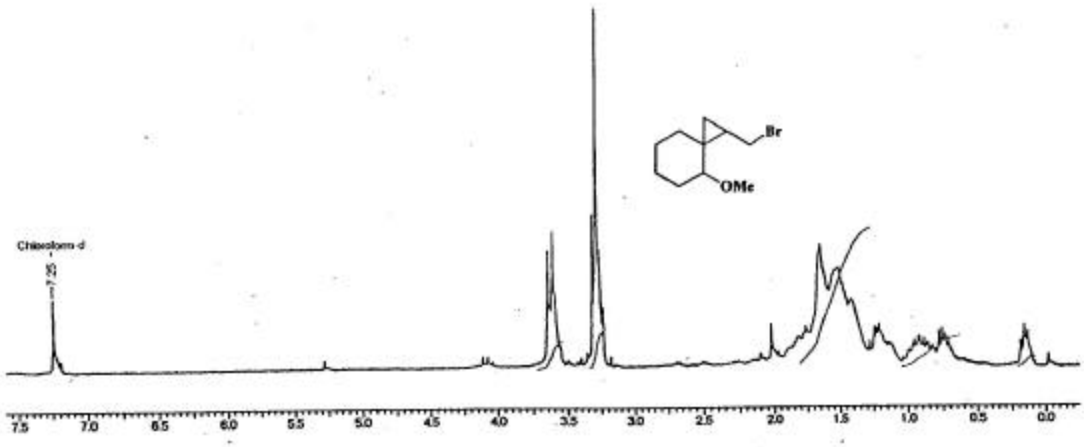

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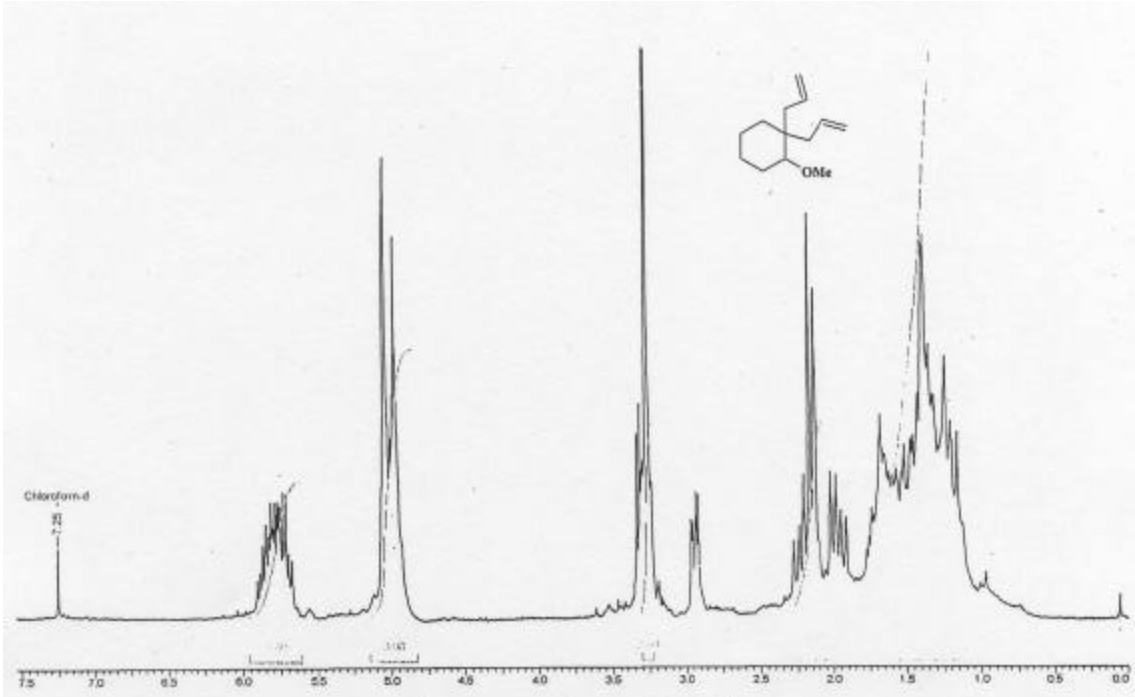

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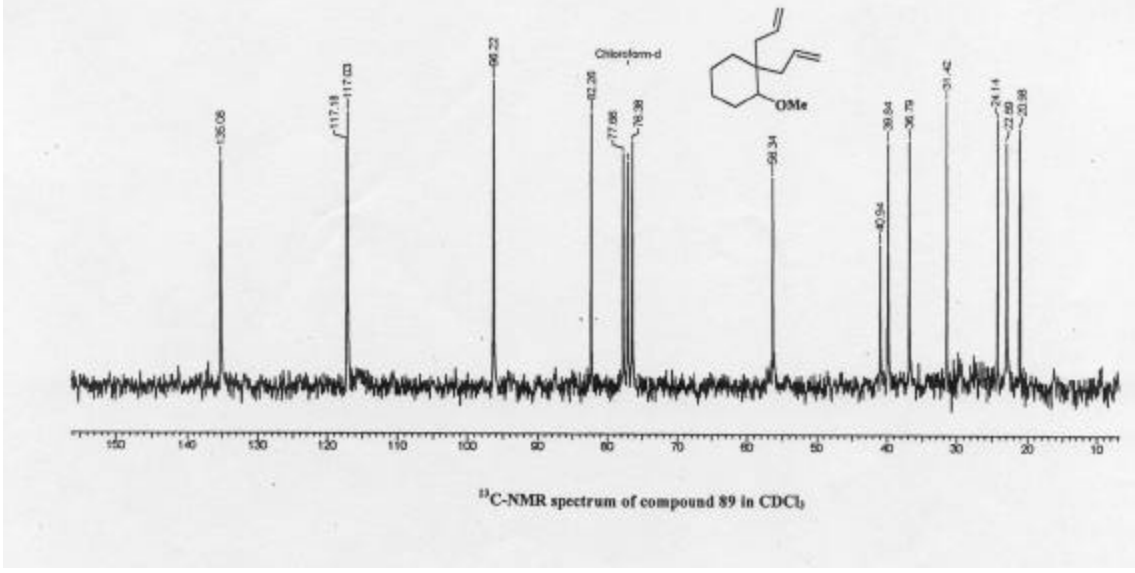

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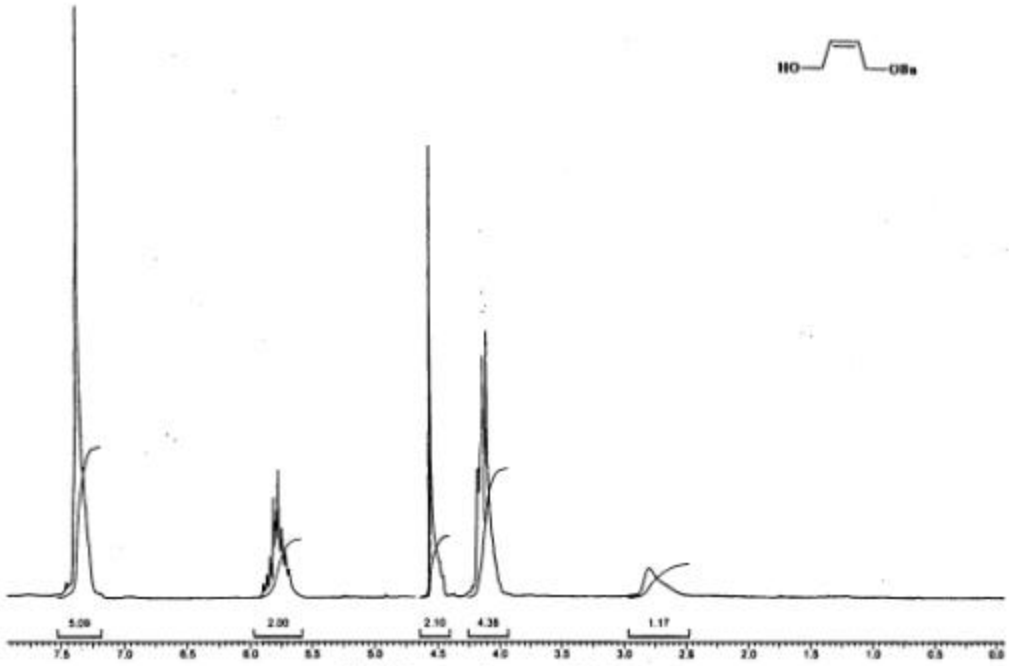

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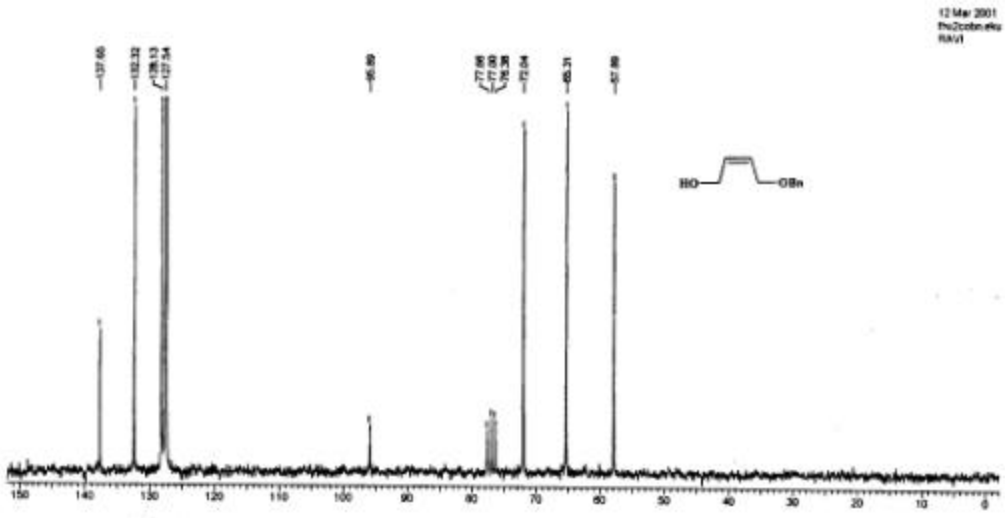
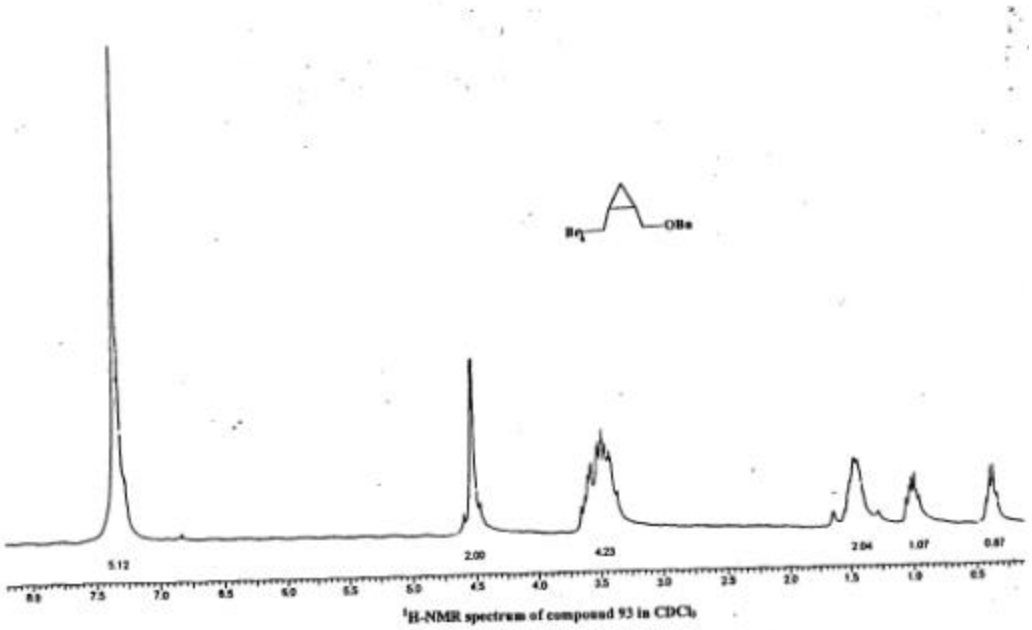
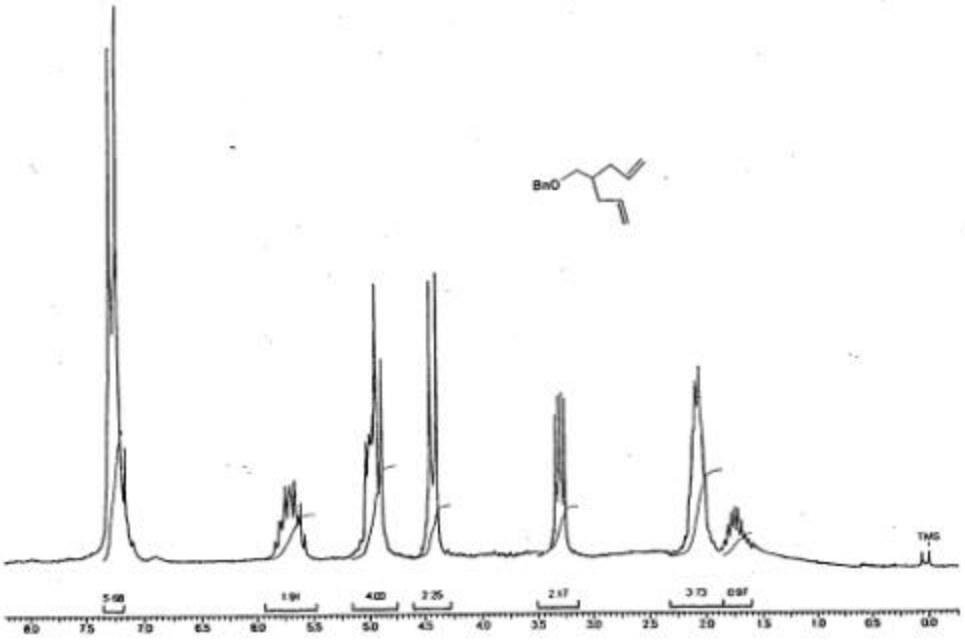


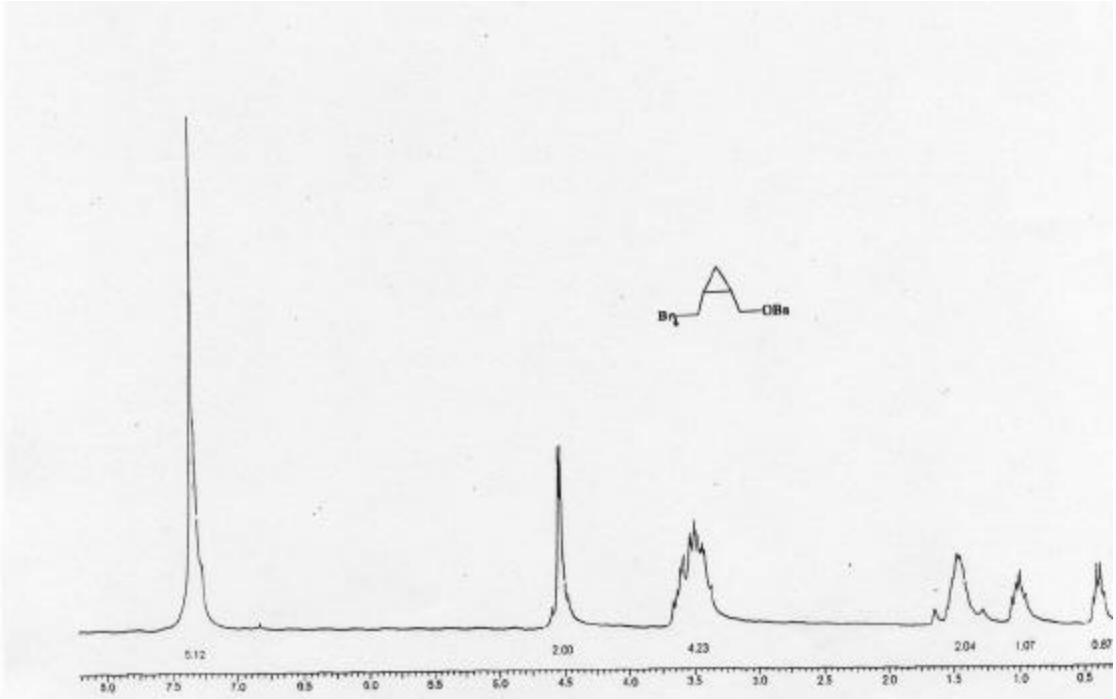
^{13}C- NMR spectrum of compound 91 in $CDCl_3$



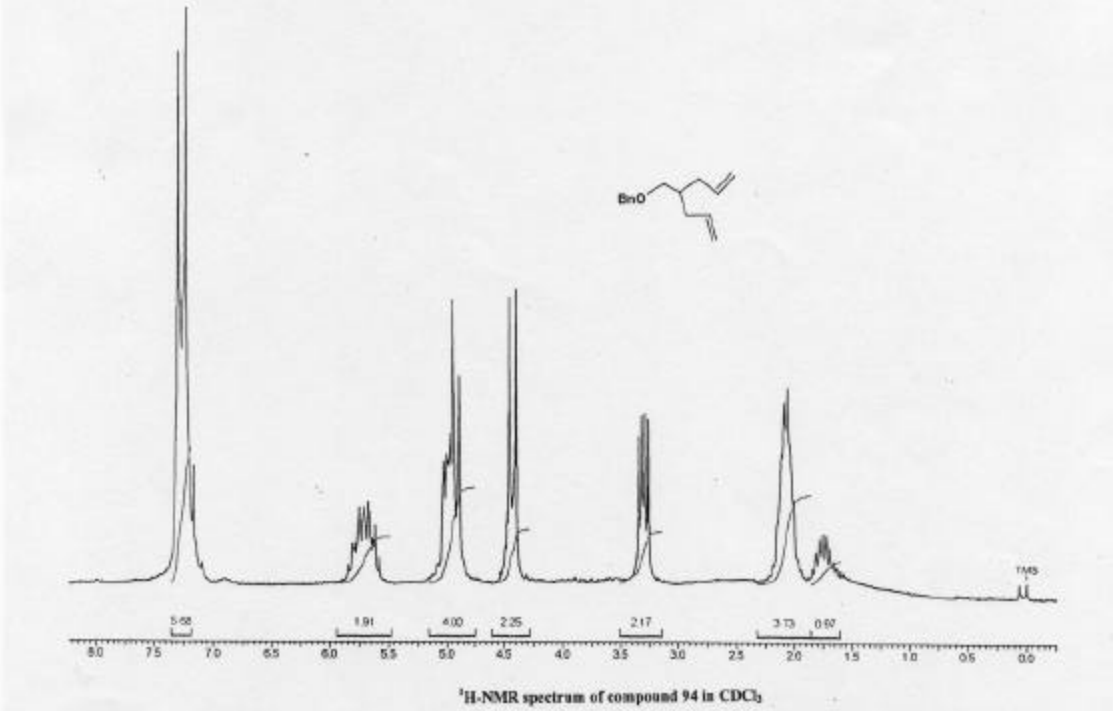
^{1}H-NMR spectrum of compound 93 in $CDCl_3$



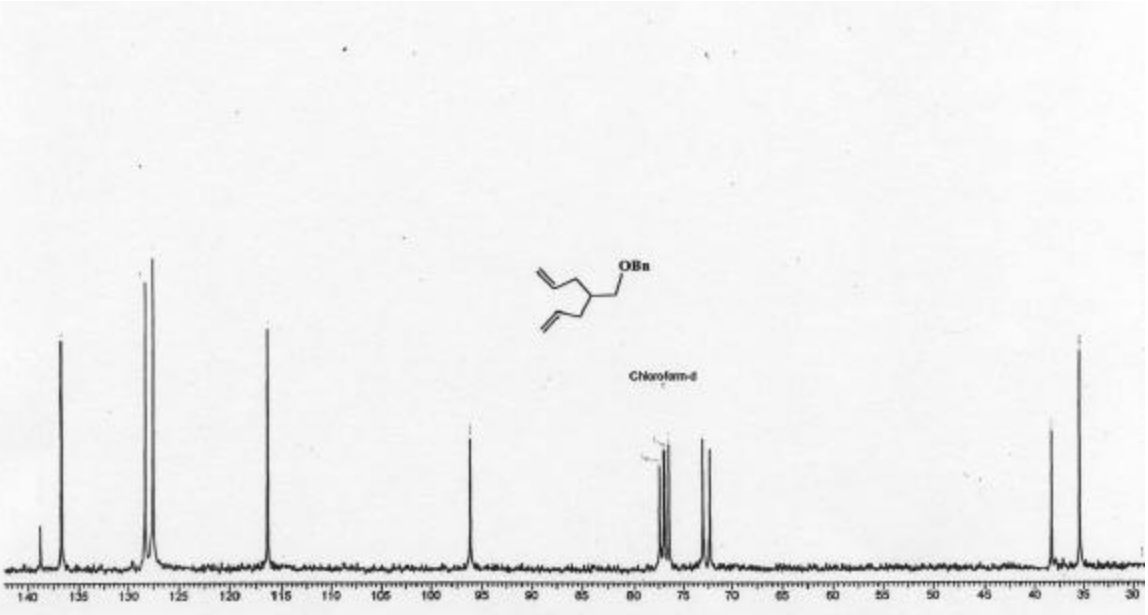
^{1}H-NMR spectrum of compound 94 in $CDCl_3$



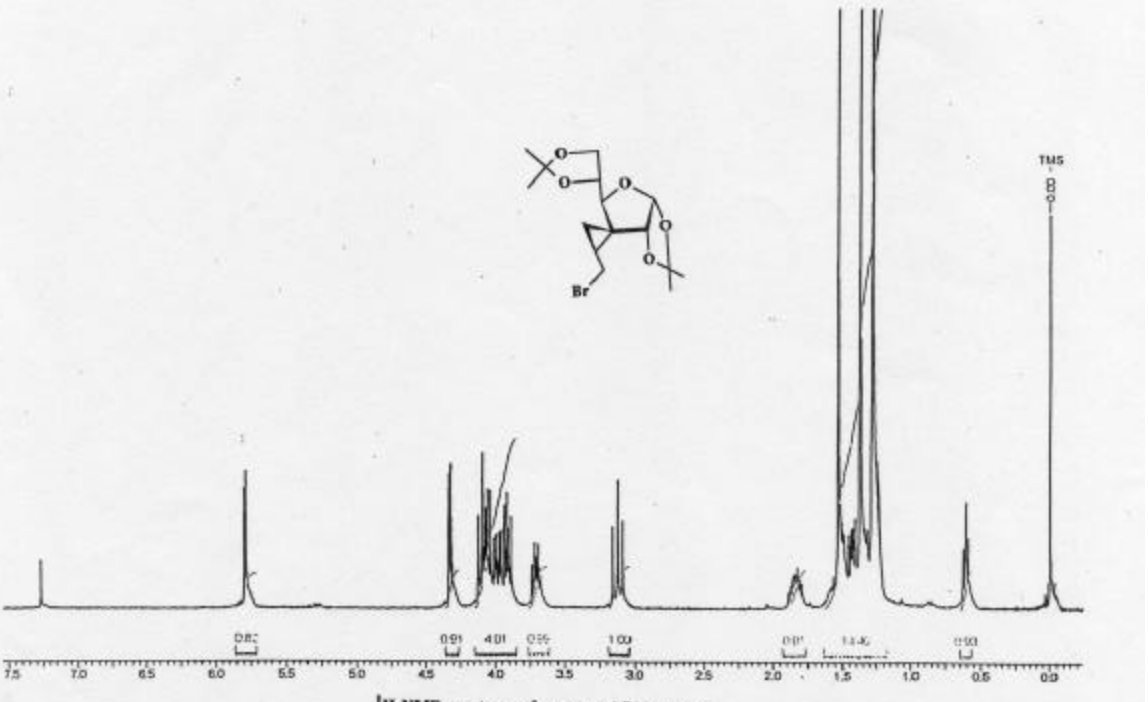
^{1}H-NMR spectrum of compound 93 in $CDCl_3$



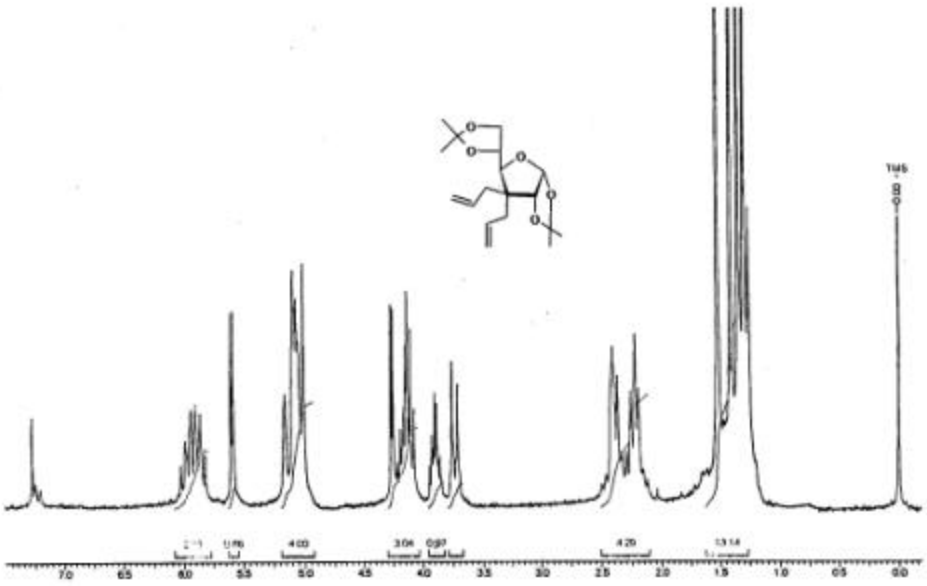
^{1}H-NMR spectrum of compound 94 in $CDCl_3$



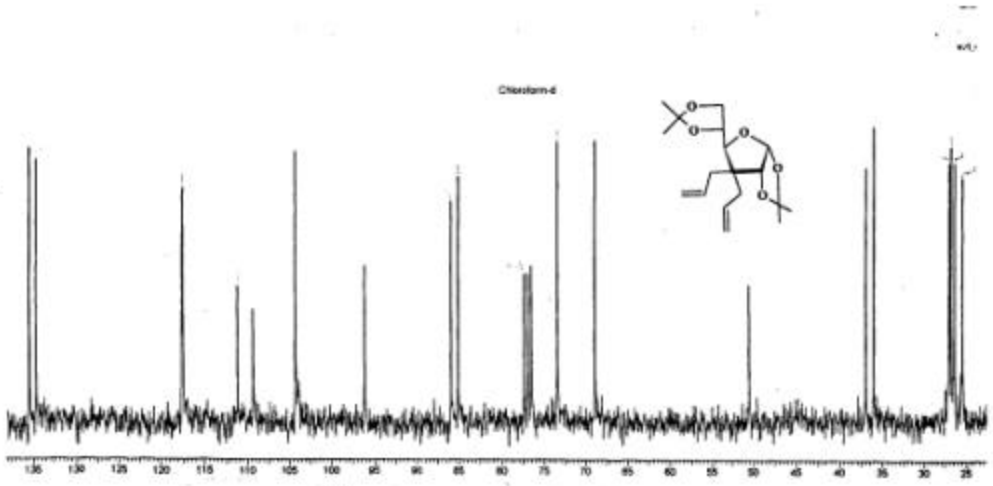
^{13}C-NMR spectrum of compound 94 in $CDCl_3$



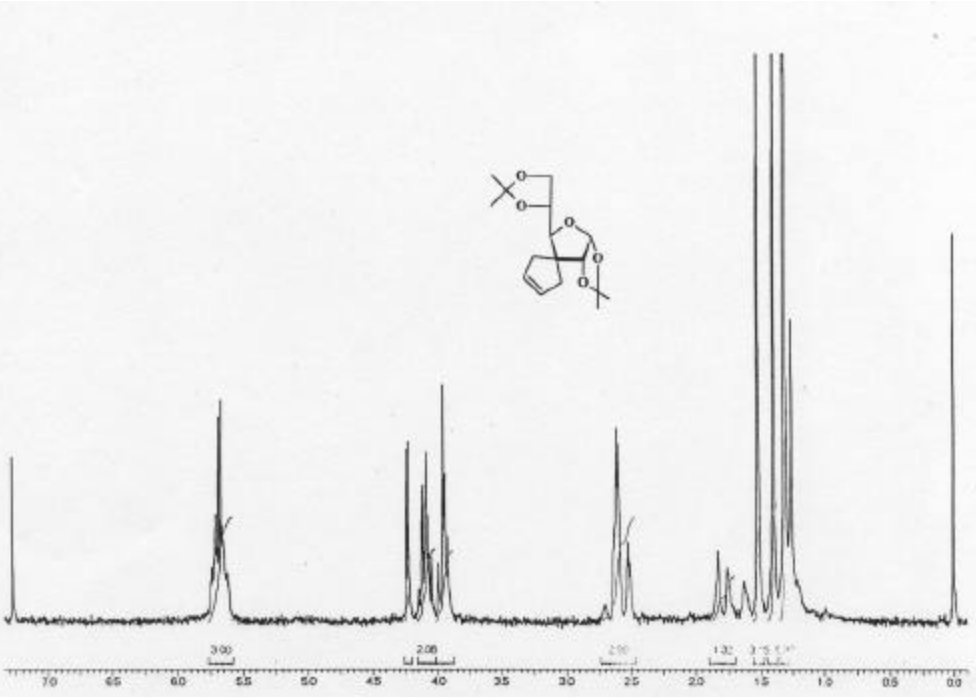
^{1}H-NMR spectrum of compound 79 in $CDCl_3$



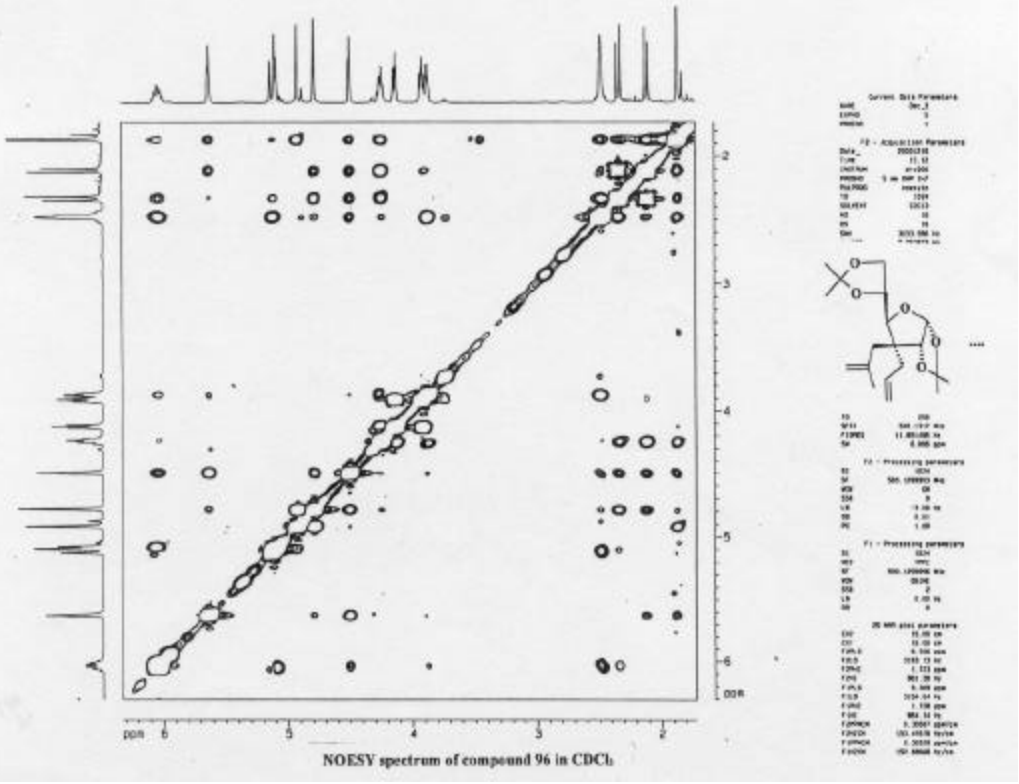
^{1}H-NMR spectrum of compound 80 in $CDCl_3$



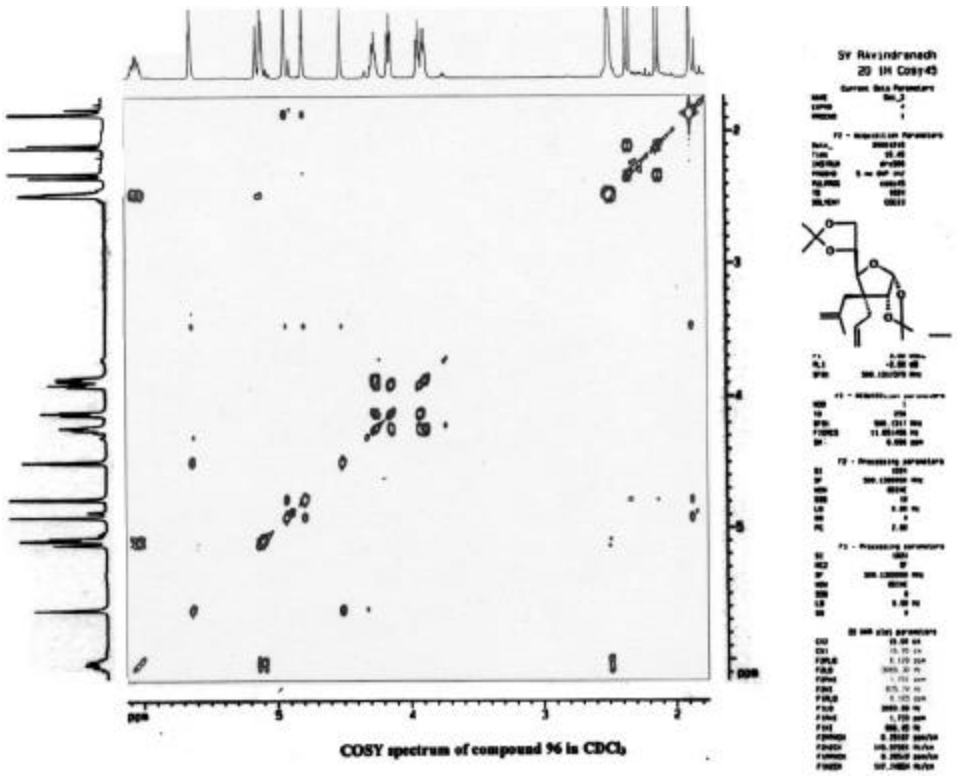
^{13}C- NMR spectrum of compound 80 in $CDCl_3$



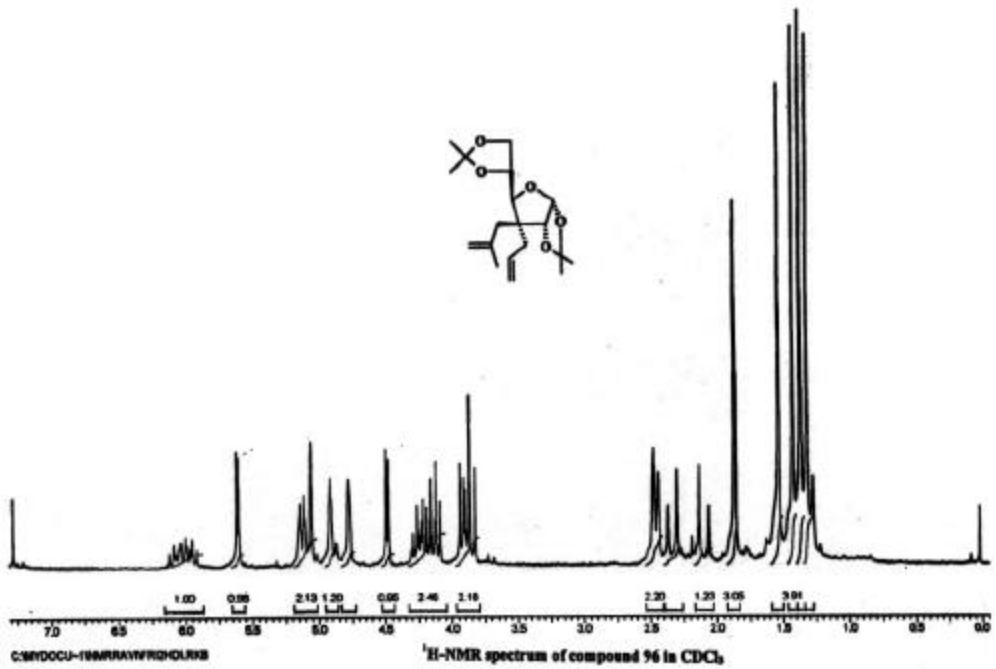
^{1}H-NMR spectrum of compound 95 in $CDCl_3$



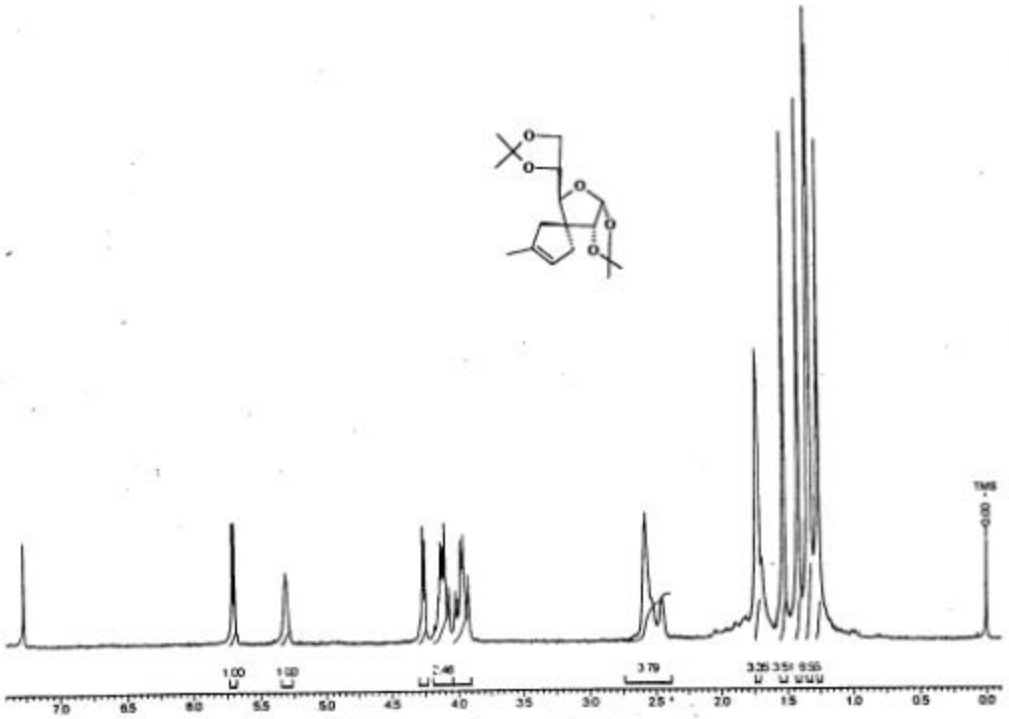
NOESY spectrum of compound 96 in $CDCl_3$



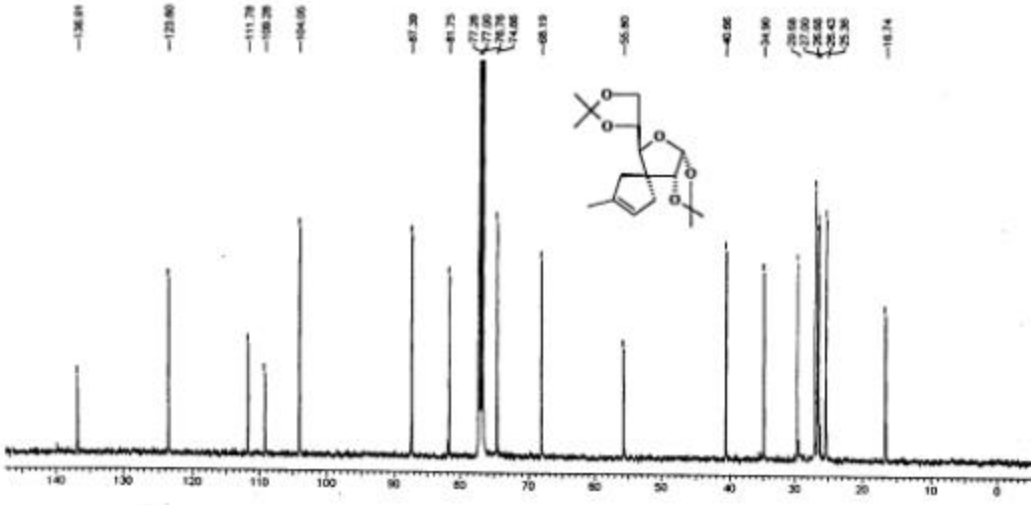
COSY spectrum of compound 96 in $CDCl_3$



^{1}H-NMR spectrum of compound 96 in $CDCl_3$



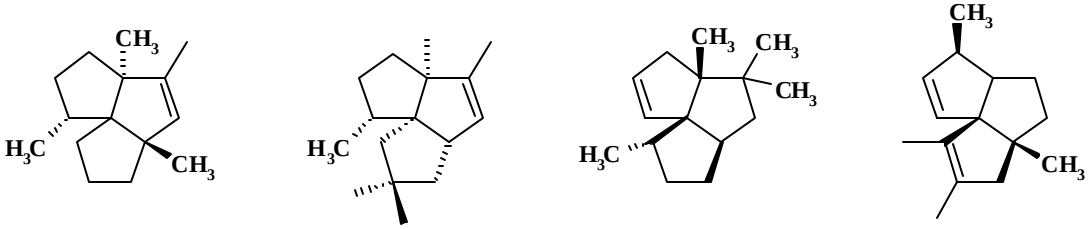
^{1}H-NMR spectrum of compound 97 in $CDCl_3$



^{13}C- NMR spectrum of compound 97 in $CDCl_3$

Research directed towards the preparation of members of the triquinanes class of compounds has progressed rapidly over the past several years. Paquette, an active contributor to this area, extensively reviewed the developments in this field. [1-3] Isocomene (**1**) [4], pentalenene (**2**) [5], silphinene (**3**), [6] and silphiperfolene (**4**) [7] represent this class of compounds (Figure 1). A variety of heteroannular relatives are also known.

Figure 1



1 Isocomene **2 Pentalenene** **3 silphinene** **4 Silphiperfolene**

Many synthetic studies have addressed the interesting problem posed by these multiply fused five membered rings and a number of general solutions have emerged. [8] Most strategies involved the sequential construction of each five membered ring in an appropriate angular arrangement. In a recent development, D.L.J Clive's group used iterative sequential Claisen rearrangement and ene-yne radical ring closure for the construction of triquinanes. Synthesis of (±) ceratopicnol and the synthesis of propellane systems were achieved using this protocol.[9] Chin-Kang Sha's α-carbonyl radical cyclization is worth mentioning where α-carbonyl radicals were utilized for ring closure leading to the functionalized bicyclic systems, which were further elaborated to triquinanes.[10] In another report D.L.J. Clive *et al.* have developed a general protocol[11] using the elegant combination of Pauson-Khand reaction and a radical ring closure leading to the formation of angular triquinanes and its *oxa* and *aza* analogs.

Among all strategies developed over time, radical cascade reactions are by far the most elegant and efficient methods for their synthesis. Cascade reactions, also called tandem, zip or domino reactions, are the multiple consecutive cyclization reactions, which have fascinated organic chemists for

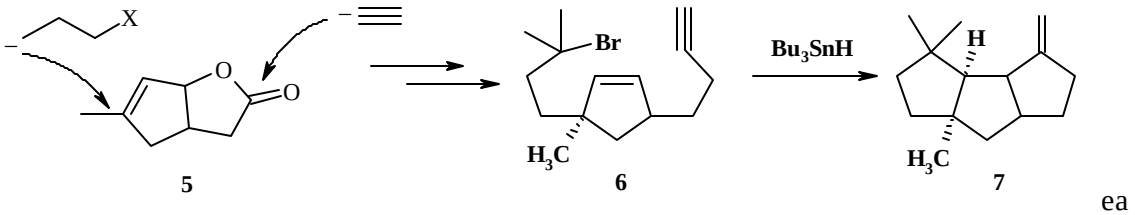
more than three decades. These are becoming increasingly popular because they lead to improvements in synthetic efficiency and decrease the environmental impact.[12,13] They deliver compact and elegant synthesis of natural products. Proper induction and termination of the cascade cyclization is a major challenge as it determines the chiral induction during the cascade cyclization during which several chiral centers are generated. This section is dealt with a brief discussion on recent developments in the synthesis of several triquinanes and related tricyclic analogs using cascade reaction as key strategy.

Past work:

Curran *et al*. have developed a method utilizing the one ring template strategy for the synthesis of triquinanes. This strategy utilizes precursors that already contain a ring to control stereochemistry of the subsequent two cyclizations. Both linear and angular triquninanes were synthesized using this strategy.

For example, compound **6** when subjected to radical cyclization conditions gave the linier triquinane capnellene **7**. Radical cyclization precursor **6** was synthesized from the

Scheme 1



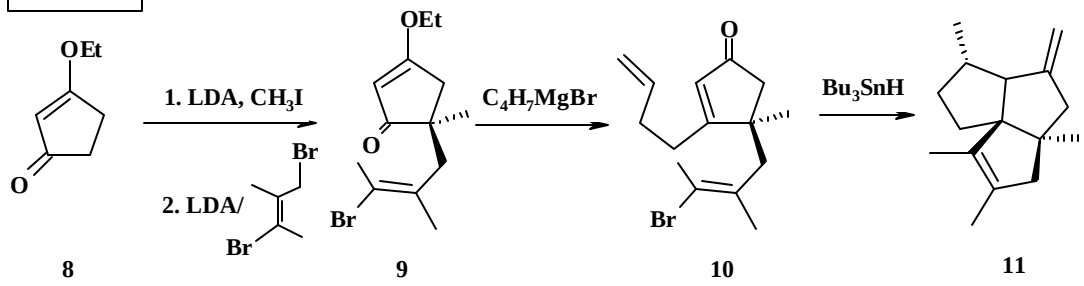
5 **6** **7**

easily available lactone **5** in six steps. Treatment of **6** with Bu_3SnH induced the radical cyclisation and produced capnellene in good yield (Scheme 1).[14]

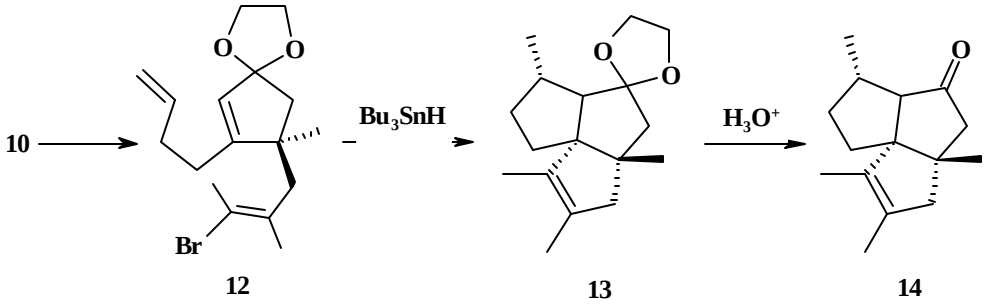
The same strategy was utilized for the synthesis of angularly fused triquinanes. For example, silphiperzolene was synthesized starting from the cyclopentenone derivative **8**.[14] Seqential alkylation of **8** with methyl iodide and allyl vinyl dibromide provided **9** in moderate yield. Addition of butyl magnesium bromide followed by hydrolytic work up gave the required cyclization precursor **10** in good yield. Standard tin hydride mediated radical

cyclization of **11** afforded an inseparable mixture of diastereomers with the wrong diastereomer as major product in a 5:1 ratio (Scheme 2). In a modification, the

Scheme 2

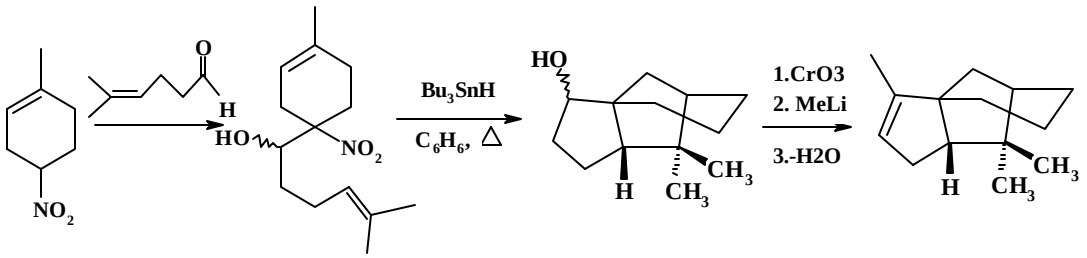


carbonyl group of **10** was sterically enlarged by conversion to the ketal **12** and was cyclized to give 1:2.5 mixture of isomers of **13**, with the required isomer predominating. Ketal was deprotected to give the required silphiperzolene **14**.



In another example, Y. –J. Chen *et al.* have reported[15,16] an elegant construction of Cedrane skeleton (**18**) in two steps from nitroolefin **15** and the ã, ä-unsaturated ester (Scheme 3). In another report, a similar strategy was utilized, for the synthesis of (+/-)-á-biotol and (+/-)-â-biotol. [17]

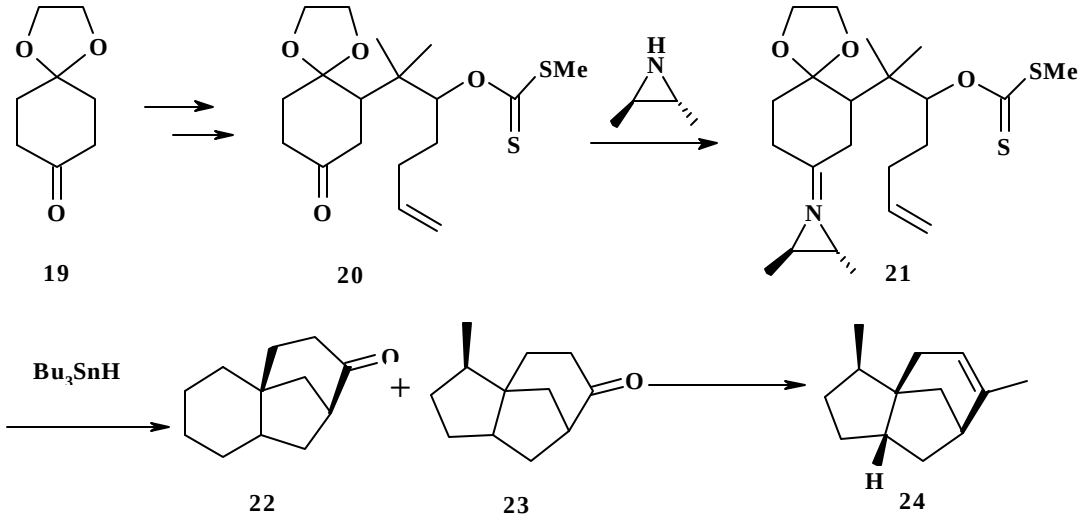
Scheme 3



15 **16** **17** **18**

H. -Y. Lee and coworkers have demonstrated the potential value of *N*-aziridinylimines as radical precursors in the cascade reactions by synthesizing á-cedrene. [18] The radical precursor **21** was synthesised starting form cyclohexenedione-*mono*-ethylene glycol **19**, which was converted to the ketone **20** and was condensed with aziridinylamine giving **21**. Treatment of **21** with TBTH under high dilution condition gave the cyclization products **22** and **23** smoothly. Compound **23** was further elaborated to á-cedrene.

Scheme 4



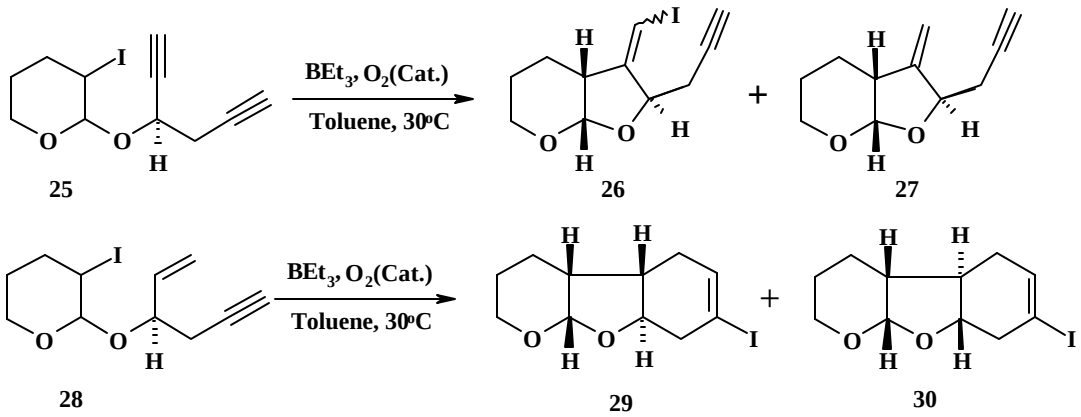
19 **20** **21**

22 **23** **24**

Hoffmann *et al*. have devised[19,20] a cascade radical cyclization route starting form ynynes and enynes, leading to bicyclic and tricyclic pyranofurans and furanofurans in a chemo and diastereoselective fashion. In a typical experiment compound **25** was treated with BEt_3, and catalytic amount of O_2, in toluene gave products **26** (5-*exo*-dig, 6-*endo*-dig) and **27** (5-*exo*-

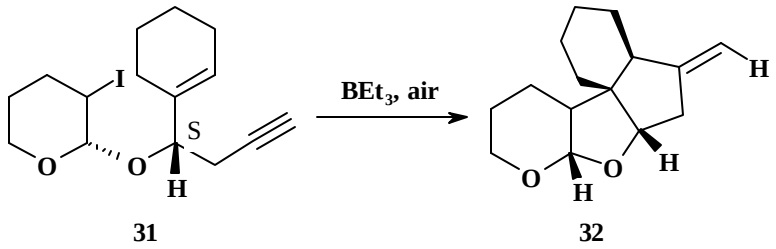
trig, 6-*endo*-dig) in varying ratios depending upon the temperature employed. Similarly, when ene-yne compound **28** was treated under the same conditions gave the tandem cyclization products **29** and **30** (Scheme 5).

Scheme 5



Incase of the precursors having S configuration, the cascade was mostly diverted to the corresponding 5-*exo*-trig, 6-*endo*-dig cyclization. For example, **31** gave the polycyclic compound **32** in good yield (Scheme 6).

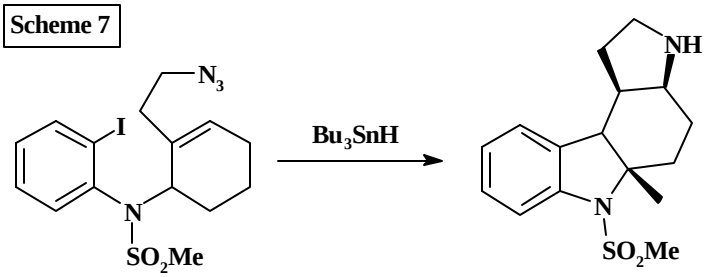
Scheme 6



Another attractive feature of this cyclization was the avoidance of organotin compound. These reactions are remarkable in that they allowed the construction of four or more chiral centers in a single convergent step.

In another report, Murphy *et al.* have reported[21] a cascade cyclization on to azide moiety leading to the formation of ABCD ring system of aspidospermidine **34** and related indole alkaloids (Scheme 7).

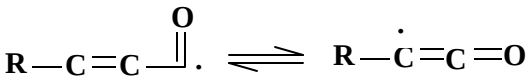
Scheme 7



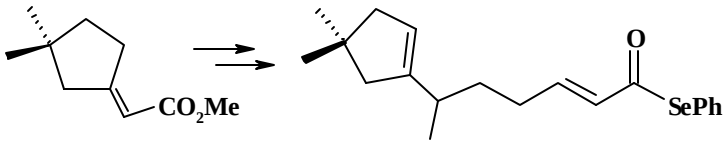
33 **34**

In a recent report, Pattenden *et al.* have demonstrated [22] a novel, tandem cyclization route for the synthesis of pentalenene using ketene radical intermediates. They have

Figure 2



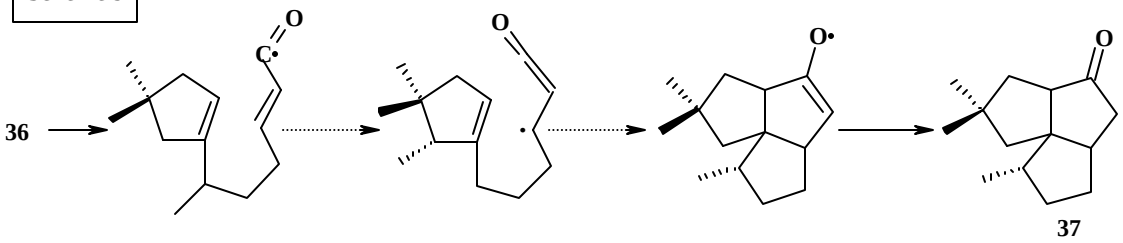
Scheme 8



35 **36**

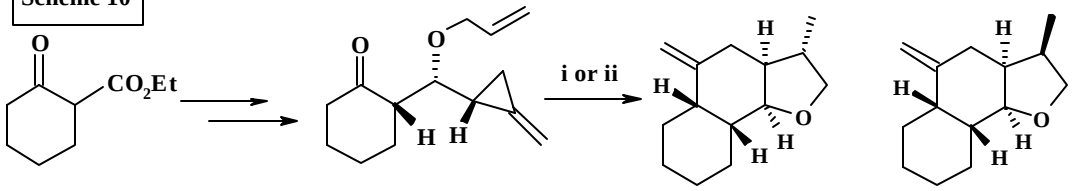
observed that α,β-unsaturated acyl radicals react via their corresponding α-ketenyl counterparts (Figure 2). Crucial Radical intermediate **36** in the synthesis of pentendene was prepared starting from α,β-unsaturated ester **35** in seven steps (Scheme 8). When a solution of **36** in benzene was refluxed with Bu_3SnH in the presence of catalytic amount of AIBN followed by workup provided the α-methyl epimer of tricyclic ketone **37** as major compound, which was converted to (±) pentalenene (Scheme 9).

Scheme 9



Kilburn *et al.* have reported[23] a novel SmI_2 mediated cascade radical cyclization leading to the cardesmane tricyclic framework. The radical precursor **40** required for the cyclization was prepared from the cyclohexanone derivative **39** in several steps.

Scheme 10



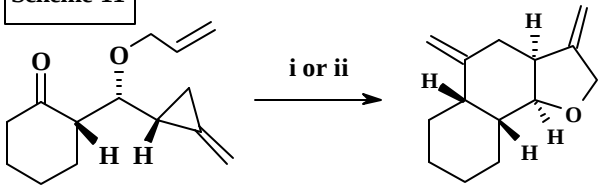
39 **40** **41** **42**

i. SmI_2, ^{t}BuOH, HMPA, THF, 0 ^{o}C	**5**	**50**
ii. SmI_2, THF/MeOH, 4:1, -78^{o}C	**70**	**20**

Compound **40,** when exposed to SmI_2-BuOH-HMPA at 0 °C gave the predominant product **42**, where as exposure to SmI_2-THF/MeOH at −78 °C gave **41** as major product which was explained by the role of HMPA (by breaking the chelation of Sm and oxygen of allyl ether leading to non-chelating transition state) (Scheme 10).

The corresponding propargyl compound **43** gave a single diastereomeric compound **44** (Scheme 11).

Scheme 11



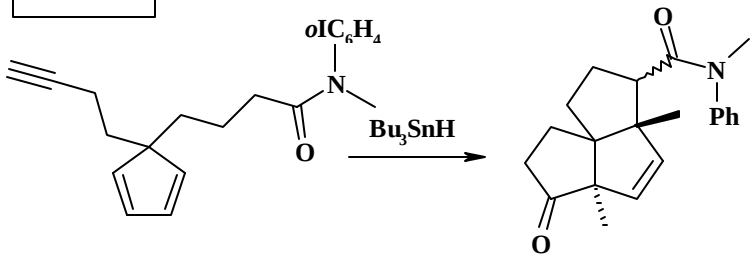
43 **44**

i. SmI_2, ^tBuOH, HMPA, THF, 0°C **50%**

ii. SmI2, THF/MeOH, 4:1, -78°C **60%**

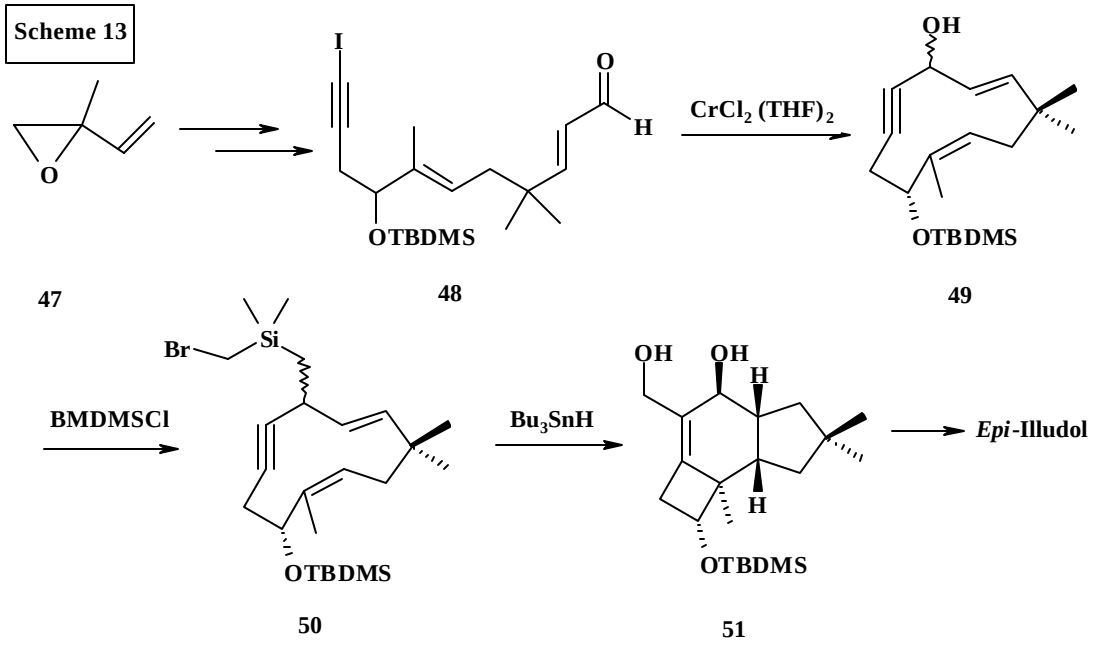
Curran *et al*. have reported[24] another method utilizing radical translocation strategy. For example, *o*-iodoanilide **45**, when treated with Bu_3SnH and AIBN resulted in radical generation followed by rapid translocation to produce radicals adjacent to carbonyls and cyclized to give **46** in good yield.

Scheme 12



45 **46**

Max Malacria has reported[25] a diastereoselective total synthesis of *epi*-Illudol (Scheme 13). It's synthesis was initiated with isoprene oxide **47**. $CrCl_2$ mediated macrocyclization of the substrate **48** gave the cyclic intermediate **49**. **49** on treatment with bromomethyldimethyl silyl chloride gave the required radical precursor **50**. The cascade transannular cyclization of the macrocycle **50** produced the intriguing tricyclic framework **51** containing five contagious stereocenters.

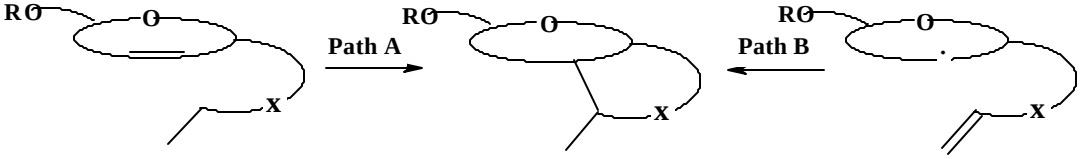


Application of carbohydrate templates for the synthesis of polyquinane frame works

Radical cyclizations on sugar templates have drawn considerable attention over the past few years.[26] Most of these studies, undertaken for the synthetic purpose, have not only opened the new ways for the synthesis of optically pure compounds but also provided a lot of mechanistic information. These are much fascinating because, the stereo controlling properties of sugars can facilitate the diastereoselective formation of new chiral centers during the cascade cyclization. Many groups have cleverly utilized this elegant combination of carbohydrates and free radicals for the synthesis of triquinanes and the potential precursors.

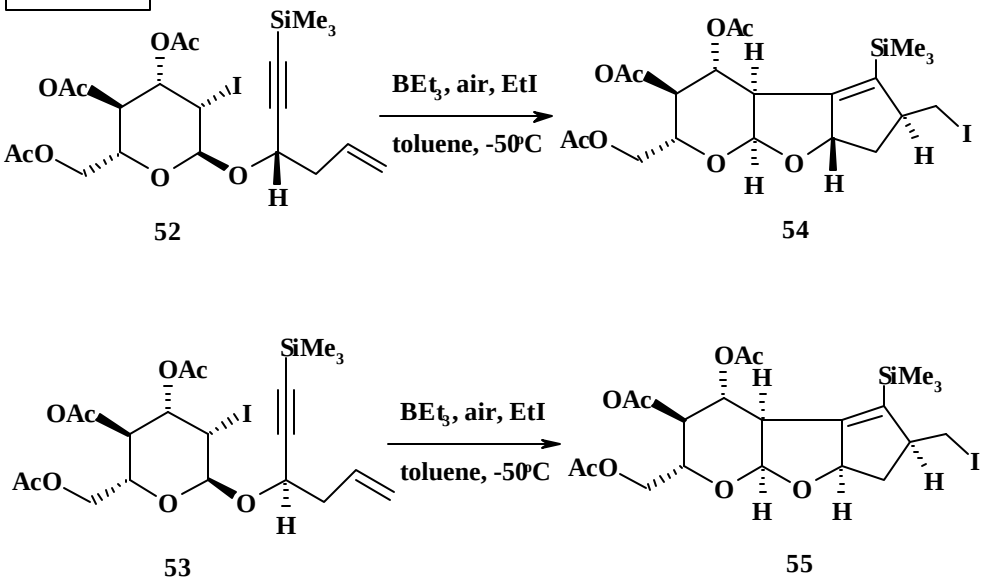
Robert Nouguier has initially demonstrated[27] the applicability of free radicals on carbohydrate templates for cyclopentanulation. Radical cyclization of unsaturated halo, seleno or thiocarbonyl sugars using tributyl tin hydride gave the cyclization products either in path A or B (Figure 3).

Figure 3



Hoffman *et al.* have reported cascade cyclization on furanose templates. [28] Iodoalkoxylation of glucals gave diestereomerically pure ene-yne compounds **52** and **53**.

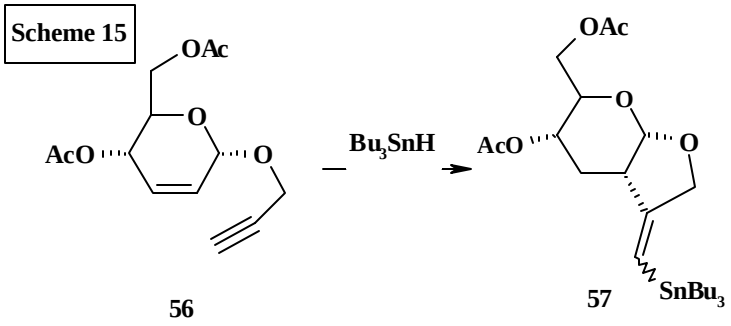
Scheme 14



Treatment of **52** with BEt_3, air, EtI gave the tricyclic enantiopure compound **54** in respectable yield (51%) by 5 *exo*-dig, 5 *exo*-trig radical cyclization whereas, the other isomer **53** reacted poorly and gave the diastereomer **55** in less yield.

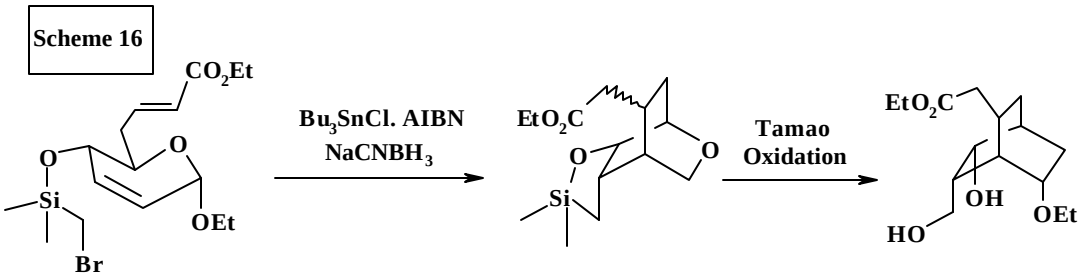
In another report, Hoffmann *et al.* reported[19] 5-*exo*-trig, 6-*endo*-dig radical cyclizations under iodine atom transfer conditions, leading to polyannulated glycopyranosides.

In another report, Chapleur *et al.* have reported[29] a stereospecific â-stannyl vinyl radical cyclizations on to olefinic carbohydrates **56** giving vinly stannanes **57**, which can be further elaborated to useful chiral intermediates like vinyl halides, vinyl carbanions or ketones.



56 57

Fraser-Ried *et al.* have utilized the bromometnyldimethylsilyl allyl ethers[30], a technique developed by Nishiyama *et al.*[31] for the cascade synthesis of **58**, starting from bromomethyldimethylsilyl derivative **56** followed by Tamao oxidation. Compound **58** is the precursor for reserpine in the chiral total synthesis by Woodward.



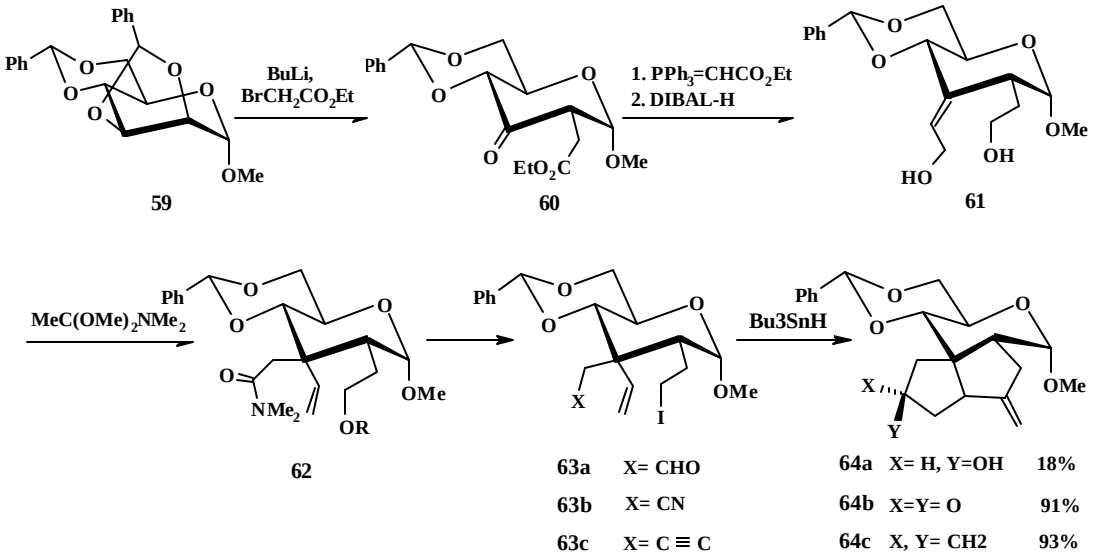
56 57 58

Fraser Reid *et al.* have also developed a *bis* annulation strategy for the bridging of five membered rings on carbohydrate templates.[32] They have synthesised pyranoside diquinanes, which were later elaborated to several naturally occurring triquinanes. They have developed a general strategy for the synthesis of triquinanes exploiting the inherent chirality, the latent functionalities and the stereo controlling properties of carbohydrates.

The radical precursor required for the cyclization was synthesised starting form methyl 2.3:4,6-di-*O*-benzylidene-á-D-mannopyranoside. Compound **59** was treated with BuLi and the intermediate enolate was trapped *in situ* with ethyl bromoacetate to give the keto ester **60**. The di-ester obtained after Witting reaction was reduced to the corresponding diol **61**. Eschenmoser-Claisen rearrangement on the diol gave the alcohol **62**,which was converted to

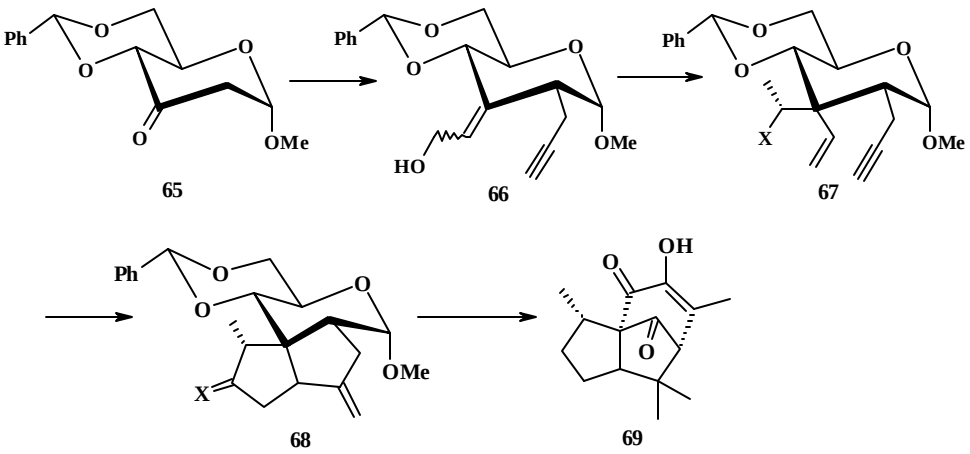
the iodo aldehyde compound **63a**. **63a** on treatment with TBTH gave the cyclization product in poor yield. In view of this, the substrate was converted to the iodo nitrile **63b** and alkyne **63c**, which gave the cyclization products **64b** and **64c** respectively in 91 and 93 % yields.[33]

Scheme 17



In a slight modification, a more substituted pyranoside diquinanes were synthesised by introducing methyl group at different positions of the intermediate **66**. For example, total synthesis of (α)-pipitazole (**69**), silphenene (**3**) and silphiperfolene (**4**) were achieved.[34,35]

Scheme 18



The importance of the synthesis of triquinanes and their hetero annular analogs as mentioned in the previous section, constitutes the synthetic drive to undertake efforts in the direction of developing new and versatile methods, which can give rapid entry into these triquinane skeletons. The literature emphasis on the merits of annulated sugars for the stereo controlled synthesis of triquinanes and the suitability of sugar templates for the required stereo selective annulations has prompted us to explore the new methods for their generation. We feel that radical cascade reactions on furanose ring system of sugar derivatives would be interesting to explore primarily to understand the stereochemical behavior but more importantly to obtain potentially useful synthons for angularly fused, unknown and structurally novel *oxa*/di-*oxa* triquinanes. Organic compounds with cyclopropyl functional groups are versatile intermediates. An electrophilic, nucleophilic or radical ring opening can be executed on cyclopropyl rings paving the way for molecularly diversified organic compounds. Preference for a particular bond cleavage of a cyclopropyl C-ring arises from the stereo- and electronic - factors originated from the ring substituents. Application of these reactions in the synthesis of several natural products was well documented and has been reviewed.[36,37]

The use of carbohydrates in the synthesis of several natural products and potential intermediates has been a theme of interest in our laboratory. In particular, the application of cyclopropyl sugar derivatives in the synthesis has been well demonstrated by our group.[38-40] However, scope exists in this domain. For example, cyclopropyl derivatives of furanoses have received very limited attention. Amongst cyclopropyl derivatives, the corresponding spiro-cyclopropyl compounds have been rarely synthesised. As a part of our on going research on spiro-cyclopropyl sugar derivatives, we have undertaken the development of new methodologies leading to the formation of potentially useful and novel oxa- and dioxa-triquinanes.

The direct and ideal approach would be to trigger a series of radical cyclization by generating a tertiary radical on a synthons with prefabricated radical acceptors (Figure 4).

Realistically, the formation of tertiary radical is a difficult proposition as its precursor namely a tertiary halide or tertiary thiocarbomate is not easily accessible by the conventional methods (Direct). However, the indirect formation of tertiary radicals by radical ring opening of spiro cyclopropyl methyl bromides should constitute a feasible proposition (Indirect). This basic study forms the basic premise of this chapter.

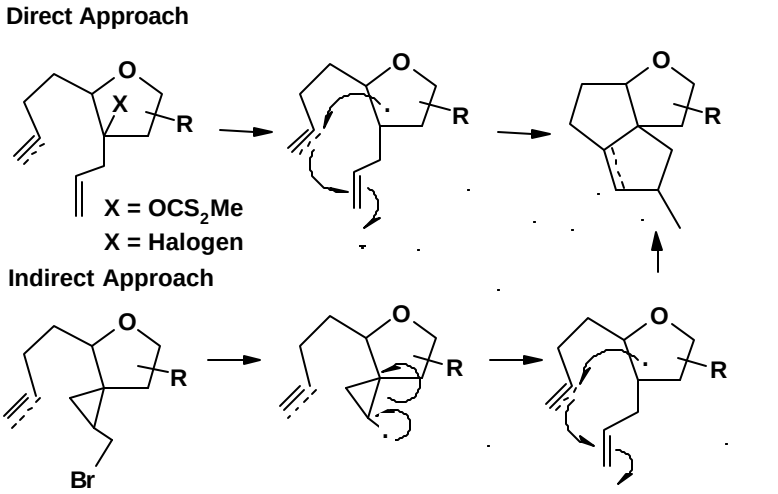
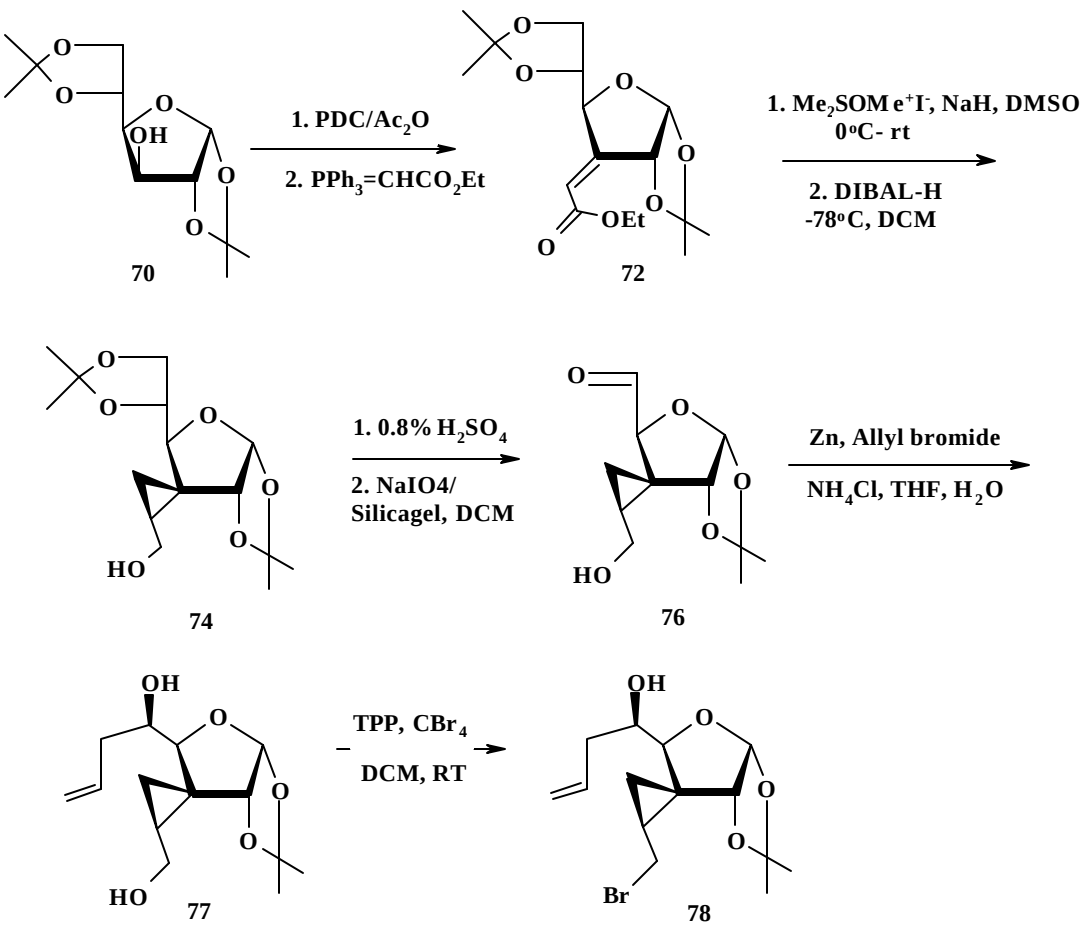


Figure 4

The synthesis of the required precursor **78** was initiated with the known á-D-glucose derivative, 1,2:5,6-di-*O*-isopropylidene á-D-glucofuranose **70**, which was converted into the corresponding 3,3-spiro-cyclopropyl methanol derivative **74** according to the procedure developed in this laboratory.[38] The spectral data and the optical rotation of **74** were in agreement with reported data. The formation of single diasteromeric cyclopropane during the cyclopropanation was attributed to the stereo-controlling effect of the 1,2-*O*-isopropylidene group. The cyclopropyl methanol derivative **74** was treated with 0.8% sulfuric acid in MeOH to effect selective hydrolysis of the 5,6-*O*-isopropyledene group and gave the corresponding triol derivative **75**. The oxidative cleavage of the 5,6- diol with silica gel adsorbed $NaIO_4$, in

dry CH_2Cl_2 gave **76** (quantitative).[41] The aldehyde **76** was treated with ally bromide in presence of

Scheme 18

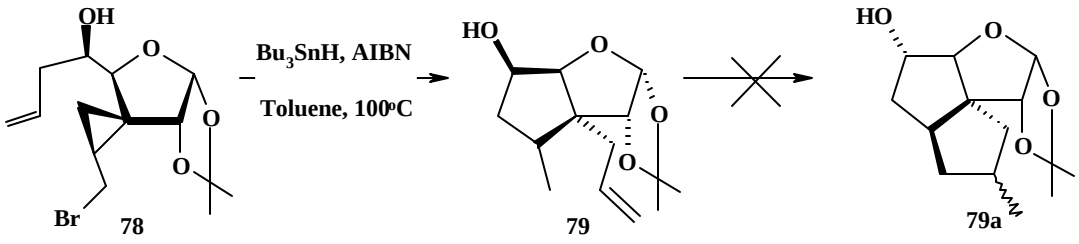


Zn and NH_4Cl in THF-water to provide chromatographically separable allyl products. [42,43] The literature precedents have revealed the stereochemistry of the major diastereomer to be of S-configuration.[44] We presumed our major product to have the stereochemistry as depicted in structure **77**. In the ^{1}H-NMR spectrum of the major product **77**, the olefin protons resonated at δ 5.15 and at δ 5.80. In the ^{13}C-NMR spectrum, signals corresponding to the allyl group were clearly observed at δ 39.1, 118.2 and 133.9 ppm, confirming the presence of an allyl group. Conversion of the diol (**77**) to the radical precursor, required for the serial radical cyclization,

was achieved with TPP-CBr_4-pyridine in CH_2Cl_2 at rt, which gave the corresponding mono-bromo derivative **78**. The ^{1}H-NMR and ^{13}C-NMR spectral studies have substantiated the formation of **78**. Protons corresponding to the CH_2Br were distinctly visible at δ 3.12 as a triplet (J = 12.0 Hz) and at δ 3.96 as a double doublet (J = 5.3, 11.0 Hz) while other protons were observed at expected chemical shifts. Our next objective was to perform the final radical cyclization. For this purpose, a typical tin hydride promoted reaction was attempted.

Upon treatment with tri-n-butyltinhydride (TBTH) in presence of catalytic amount of AIBN in toluene (0.05 M) at 100 ^{o}C, the bromo derivative **78** gave a single product (Scheme19). The ^{1}H-NMR spectrum of the product was not in conformity with the expected product **79a**. However the spectral studies suggested the new structure **79** to be the product. The signals corresponding to allyl group were observed in the ^{1}H-NMR spectrum. Other features of the spectrum proved the assigned structure. The formation of **79** indicated the premature termination of serial radical cyclization after first *exo*-trig

Scheme 19



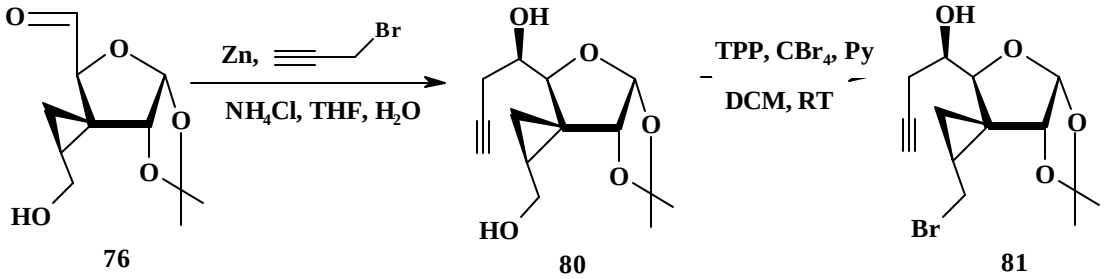
addition had taken place. This termination could be attributed to the low reactivity of the methyl radical[45] and/or the *trans* positioning of the newly formed methyl radical to the

incipiently formed allyl group. In order to circumvent this problem we sought to explore the vinyl radical primarily for the pronounced activity coupled with its ease of formation.[46-48] This is particularly important because such a process would result in the formation of a ring that will

have a double bond at a predictable position and serves as a site for further synthetic operations.

Consequently, the aldehyde **76** when treated with Zn, NH_4Cl and propargyl bromide under aqueous conditions gave a single compound **80**. (Scheme 20). In the ^{1}H-NMR spectrum, the signal due to acetylinic proton was observed at δ 2.72 as triplet. The ^{13}C-NMR spectrum further substantiated the assigned structure. Compound **80**

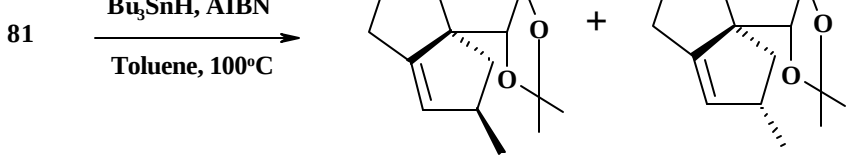
Scheme 20



76 **80** **81**

on treatment with TPP-CBr_4-pyridine in CH_2Cl_2 gave the bromo derivative **81** (Scheme 20) whose formation was confirmed by the analysis of its ^{1}H- and ^{13}C-NMR spectra. For example, signals corresponding to CH_2Br appeared distinctly at δ 3.15 as a triplet (J = 10.3 Hz) and at δ 4.01 as a double-doublet (J = 4.4, 10.3 Hz). The ^{13}C-NMR spectrum of **81** was in conformity with the structure. The TBTH/AIBN mediated radical reaction on **81** in dry toluene (0.05 M) at 100 °C gave the tricyclic derivative **82** (Scheme 21), whose formation could be attributed to the 5-*exo*-trig, 5-*exo*-dig radical cascade cyclization.

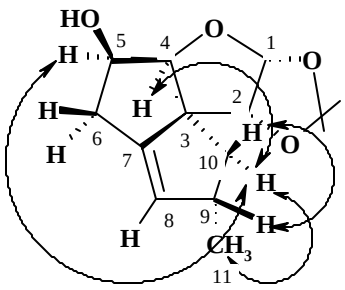
Scheme 21



82a (Minor) **82b (Major)**

Extensive ^{1}H- and ^{13}C-NMR spectral analysis coupled with mass spectrum revealed the formation of the *oxa*-triquinanes **82a** and **82b** in the ratio of 1.5:8.5. The major product (**82b**) showed in its ^{1}H-NMR spectrum the resonances due to methyl group at δ 0.97 as a doublet. The multiplet at δ 2.95 was attributed to H-9. The characterstic doublets due to H-1, H-2 and H-4 were located at δ 5.47, δ 4.28 and at δ 4.24 respectively. The extensive 2D-COSY and NOESY studies on **82** reveled the formation of **82b** as major isomer (Figure 5). For example, in the NOESY spectrum of **82**, the protons H-5 and H-10á showed strong NOE signals, and H-10á showed NOE signals with methyl group, confirming the á-

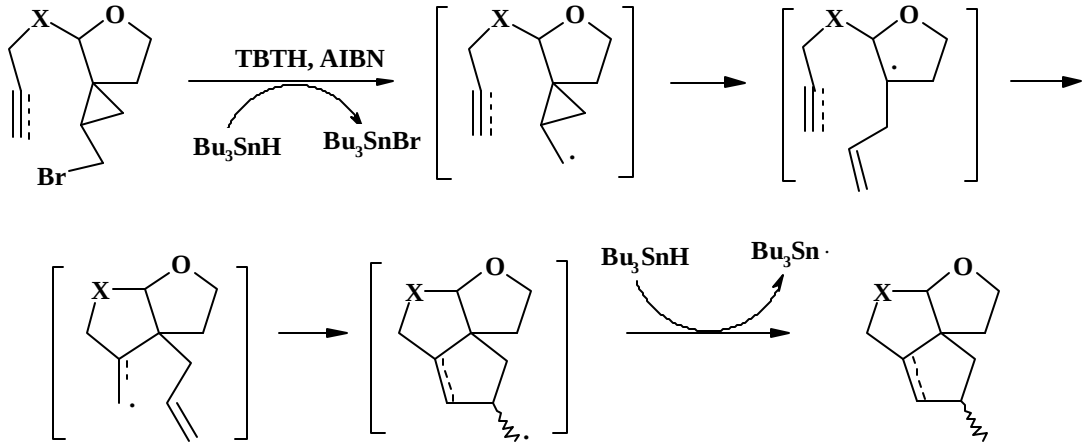
Figure 4



Observed NOE for 82b

configuration at the newly introduced methyl center. H-9 showed strong NOE interaction with H-10â which also confirmed the stereochemistry of the methyl group. The highest mass peak (M/Z 252) corresponding to $(M\text{-}Me)^{+}$ appeared at 252 while the elemental analysis was satisfactory. Hence, the synthesis of the furanoside *oxa*-triquinanes was achieved in a simple one-pot procedure with good diastereoselectivity. The conceivable mechanistic pathway is shown in figure **6**.

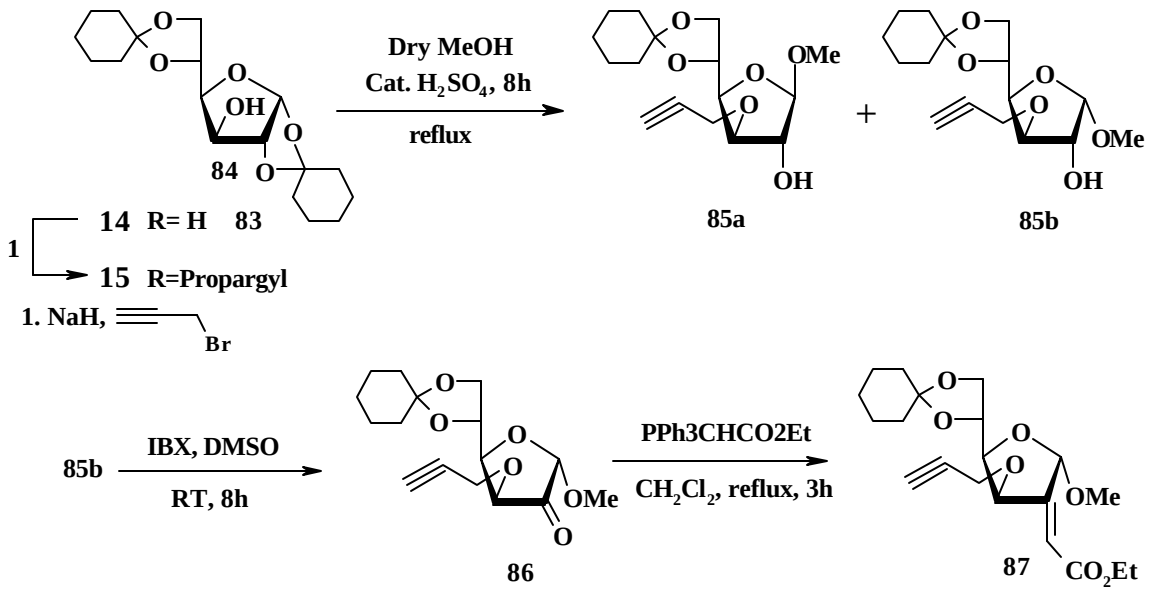
Figure 5



SYNTHEIS OF DIOXATRIQUINANES:

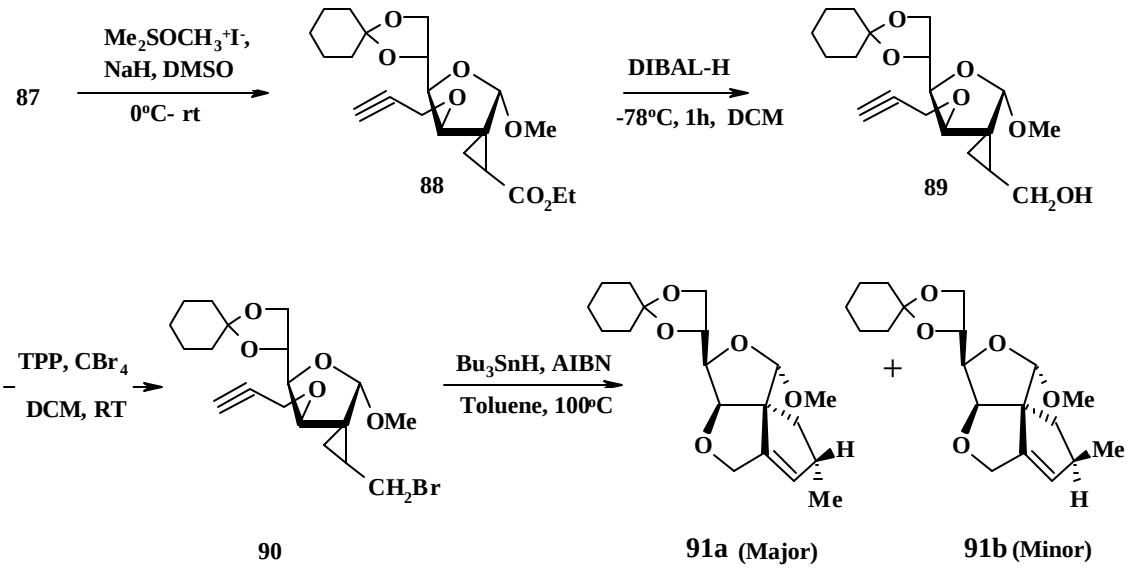
Success achieved in the preceding section prompted us to explore the scope and the synthetic utility of this method to fabricate dioxa triquinane systems such as **91**. Synthesis of **91** was initiated (scheme 22) from the known and easily available intermediate 1,2:5,6-di-*O*-cyclohexylidene-á-D-glucofuranose (**83**).[49] Compound **83** upon treatment with NaH-propargyl bromide in DMF provided the corresponding 3-*O*-propargyl derivative **84** in good yield. The ^{1}H-NMR spectrum of **84** revealed the presence of *O*-propargylic group with alkyne proton at 2.46 as a triplet. The propargyl methylene protons resonated at 4.29 as a doublet. Compound **84** when exposed to gently refluxing methanolic H_2SO_4 for 8 h, provided the mixture of glycosides that are chromatographically separable to give á- and â-methyl glycosides in the ratio of 2: 3 with 60% overall yield. The PMR spectrum of á-methyl furanoside derivative **85b** showed a doublet at δ 4.95 for H-1, indicating the á-configuration. The â-enantiomer gave a sharp singlet at 4.78 ppm for H-1.

Scheme 22



Oxidation with IBX (*o*-iodoxybenzoicacid) of **85b** in DMSO at rt for 6 h gave the corresponding 2-ulose derivative **86** which was treated with PPh_3=$CHCO_2Et$ in refluxing benzene to afford the á, â unsaturated ester **87** (Scheme 22). The PMR spectrum of **87** revealed that the compound was mixture of *E* and *Z* isomers in the ratio of 7:3. The same reaction when performed in refluxing CH_2Cl_2 gave predominantly the *E* isomer (95:5). The PMR spectrum of **87** showed the olefinic proton at δ 6.12. A down field shift was observed for the protons H-1 (δ 5.4) and H-3 (δ 5.15) observed. Remaining protons resonated at the expected chemical shifts. Compound **87** was treated with trimethylsulphoxonium iodide-NaH in dry DMSO to afford the cyclopropanated ester **88** (Scheme 23). The cyclopropyl protons were observed in the high field region of δ 1.62 and δ 2.25 ppm in the PMR spectrum of **88**. The reduction of cyclopropyl ester (**88**) to the corresponding cyclopropyl methanol derivative (**89**) was successfully achieved using DIBAL-H at −78 ^{o}C. In the PMR spectrum of compound **89** signals due to cyclopropyl protons showed an up field shift and located at δ 0.65 and at 1.3.

Scheme 23



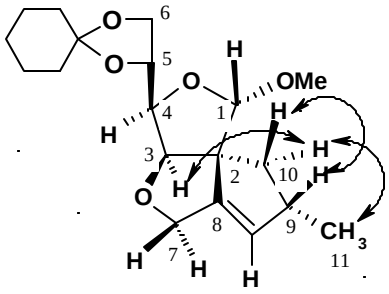
In ^{13}C-NMR spectrum, signal corresponding to carbonyl group was absent.

Our next objective was to convert **89** to the bromide **90** for which it was treated with TPP-CBr_4-pyridine in CH_2Cl_2 at rt. The PMR spectrum of **90** was in full agreement with the assigned structure. Treatment of **90** with TBTH in presence of catalytic amount of AIBN in dry toluene at 100 ^{o}C gave the tricyclic product **91** (Scheme 23). The PMR and ^{13}C-NMR spectra of the compound have revealed the presence of 8:2 mixtures of the diastereomers **91a** and **91b**.

The ^{1}H-, ^{13}C-NMR spectra coupled with 2D-COSY and NOESY studies revealed the structure of **91a/91b** unequivocally (Figure 7). The salient features of the major product are given below. A doublet at δ 1.09 (*J* = 10.5 Hz) corresponding to the methyl group was seen in the PMR spectrum. Two sets of double doublets at δ 1.49 and at δ 2.72 corresponding to H-10 and H-10` were noticed. The proton at C-9 showed a multiplet δ 3.41. Signals due to anomeric and olefinic protons were observed at δ 4.69 and δ 5.46 respectively. The ^{13}C-NMR and INEPT spectra further confirmed the formation of the *dioxa*triquinane (**91**). Particularly the methyl group (*C*-11) appeared at δ 20.11 while olefinic carbons at δ 128.60 and at δ 148.40.

However, the PMR and ^{13}C-NMR spectral data couldn't reveal the absolute stereochemistry of the major diastereomer. Extensive 2D-COSY and NOESY studies revealed the stereochemistry. Cross peaks between H-3 and one of H-10 protons showed NOE signals, revealing its á configuration, and the strong NOE signals between H-10á and the methyl group unequivocally confirmed á configuration of the methyl group thus confirmed the structure of the major isomer to be **91a**.

Figure 5



Observed NOSY for 90

In conclusion, we have demonstrated a novel and potential method for the synthesis of furanoside based *oxa*-and *dioxa*-triquinanes in good yields and diastereoselectivities starting from spiro cyclopropyl methyl bromides as radical cascade triggers.[50] Application of this strategy for the total synthesis of naturally occuring triquinane skeletons is under active investigation.

(*E*)-3-Deoxy-1,2:5,6-di-*O*-isopropylidine-3-[(ethoxycarbonyl)methylene]-α-D-*ribo*-hexofurnanose (72):

A mixture containing **70** (15.0 g, 57.7 mmol), 4 Å molecular sieves powder (32.5 g), PDC (32.5 g, 86.5 mmol) and Ac_2O (16.3 mL, 173 mmol) in dry CH_2Cl_2 (200 mL) was stirred at rt for 3 h. After the reaction completed, as judged by TLC, solvent was removed under reduced pressure, Celite and diethyl ether were added. The slurry was filtered through a pad of silica gel and washed with ether and concentrated to give the crude 3-ulose derivative (11.7 g, 79%) as a syrup.

The 3-ulose compound (11.0 g, 42.6 mmol) and PPh_3=$CHCO_2Et$ (18.5 g, 53.2 mmol) in C_6H_6 were refluxed for 1 h, concentrated. Solvent ether was added and was kept at 0 ^oC for 4 h and crystallized Ph_3P=O was filtered. The filtrate was concentrated, and the residue purified on silica gel using ethyl acetate-light petroleum (1:9) as eluent to afford á, â-unsaturated ester **72** (10.1g, 72%), as a white solid.

M.P = 70–71 ^oC Lit.[51] M.P = 69–70.5^oC

$[\alpha]_D$= 110^o (c 1.0, $CHCl_3$) Lit.[51] $[\alpha]_D$ = 114^o (c 0.9, $CHCl_3$)

^{1}H-NMR ($CDCl_3$, 200 MHz) : 1.34 (t, 3H, J = 7H), 1.37, 1.40, 1.44, 1.50 (4 s, 12H), 3.9-4.1(m, 3H), 4.25 (q, 2H, J = 9 Hz), 4.65 (d, 1H, J = 7.5 Hz), 5.74 (d, 1H, J = 3.8 Hz), 5.82 (d, 1H, J = 4 Hz), 6.32 (s, 1H).

^{13}C-NMR ($CDCl_3$, 75 MHz) : 14.1, 25.3, 26.6, 27.0, 27.2, 60.3, 67.2, 76.4, 76.7, 78.2, 79.7, 109.9, 112.5, 117.7, 155.6 164.8.

3-Deoxy-1,2:5,6-di-*O*-isopropylidene-3,3-C[(S)-(ethoxycarbonyl)ethylene]-α-D-*ribo*-hexofuranose (73):

To a stirred suspension of NaH (1.05 g, 26.3 mmol) (60% dispersion in oil) and trimethylsulfoxonium iodide (5.79 g, 26.3 mmol) in dry DMSO (10 mL) at 0°C was added **72** (6.0 g, 17.5 mmol) in DMSO (10 mL). The reaction mixture was stirred for 3 h at rt, quenched with ice-cold water and extracted with ether. The ether layer was dried, concentrated and the residue purified by silica gel chromatography using ethyl acetate-light petroleum (1:9) to afford **73** (2.9 g, 46%) as a syrup.

$[\alpha]_D$= +148° (c 1.2, $CHCl_3$) Lit.[38] $[\alpha]_D$=+155° (c 0.4, $CHCl_3$)

^{1}H-NMR ($CDCl_3$, 200 MHz) : 1-1.5 (m, 17H), 2.05 (dd, 1H, J = 6.5, 8.8 Hz), 3.64 (m, 1H), 3.83, (dd, 1H, J = 5.5, 8.8 Hz) 3.97-4.15 (m, 4H), 4.49 (d, 1H, J = 3.9 Hz), 5.70 (d, 1 H, J = 3.9 Hz).

^{13}C-NMR ($CDCl_3$, 50 MHz) 14.1, 15.4, 20.0, 25.2, 26.5, 26.6, 27.0, 38.3, 60.6, 68.2, 75.2, 78.4, 84.7, 104.3, 109.6, 112.0 171.8.

3-Deoxy-1,2:5,6-di-O-isopropylidene-3,3-C-[(S) (hydroxymethyl)ethylene]-α-D-ribo-hexofurnose (74):

To a solution of **73** (2.5 g, 7.3 mmol) in dry CH_2Cl_2 (40 mL) at -78 °C, 2.1 M solution of DIBAL-H (8.7 mL, 18.3 mmol) was added drop wise. The reaction mixture was stirred for 1 h and excess DIBAL-H quenched with MeOH and saturated solution of sodium potassium tartarate. The reaction mixture was stirred vigorously for further 2 h at rt and layers separated. The combined CH_2Cl_2 layer was dried (anhydrous Na_2SO_4), concentrated to give a residue which was purified on silica gel using ethyl acetate-light petroleum (1:3) to give **74** (2.0 g, 81%) as colorless oil.

$[\alpha]_D$ = +44° (c 1.6, $CHCl_3$) Lit[38] $[\alpha]_D$ = +46° (c 1.1, $CHCl_3$)

^{1}H-NMR ($CDCl_3$, 200 MHz) : 0.45 (t, 1H, J = 5.5 Hz), 1.17-1.37 (m, 10H, 1.56 (s, 3H), 3.0 (bd, 1H), 3.25 (t, 1H, J = 12 Hz), 3.7 (m, 1H), 3.88-4.20 (m, 4H), 4.45 (d, 1H, J = 4.5Hz), 5.85 (d, 1H, J = 4.5 Hz).

3,6,7,8-Tetradeoxy-1,2-*O*-isopropylidene-3,3-C-[(S)-(hydroxymethyl)ethylene]-á-D-*ribo*-oct-7-enofuranaose (77):

Compound **74** (1.4 g, 4.6 mmol) and 0.8 % H_2SO_4 (0.5 mL) in methanol (30 mL) were stirred for 8-10 h and neutralized with solid $BaCO_3$. Solid was filtered and filtrate concentrated to give the crude triol (1.3 g), which was dissolved in CH_2Cl_2 (20 mL) followed by addition of $NaIO_4$ adsorbed on silica gel (10.0 gm) (prepared by 2.57 g of $NaIO_4$ 10 g of silica gel and 5 mL H_2O). After 15 min. silica gel was filtered, washed with $CHCl_3$ and concentrated to give **76** (1.1 g).

To compound **76** (1.1g, 4.5 mmol), allyl bromide (0.85 mL, 10 mmol) and Zn dust (0.65 gm, 10 mmol) in THF (20 mL) at 0 °C was added saturated NH_4Cl (2 mL) dropwise. After 3 h, solid was filtered through a bed of celite, washed with THF and evaporated. The residue was partitioned between ethyl acetate and water. The organic layer was dried (anhydrous Na_2SO_4) and concentrated. The resulting syrup was chromatographed on silica gel using ethyl acetate-light petroleum (3:2) to afford **77** (0.4 gm, 32 %) (for three steps) as a colorless thick syrup.

$[\alpha]_D = +50^o$ (c 1.4, $CHCl_3$)

^{1}H-NMR ($CDCl_3$, 200 MHz) : 0.50 (t, 1H, J = 5.5 Hz) 1.26 (t, 1H, J = 5.5 Hz), 1.32 (s, 3H), 1.60 (s, 3H), 1.73 (m, 1H), 2.18 (m, 1H), 2.59 (dd, 1H, J = 5.6, 11.0 Hz), 3.07(br. d, 1H), 3.23 (t, 1H, J = 5.5 Hz), 3.4 (br t, 1H), 4.02

(m, 1H) 4.15 (d, 1H, J = 10.8 Hz), 4.42 (d, 1H, J = 3.1 Hz), 5.05-5.25 (m, 2H), 5.67-5.96 (m, 1H), 5.85 (d, 1H, J = 3.4 Hz)

EIMS = m/z 255 $(M-CH_3)^+$

Anal. Calcd. for $C_{14}H_{22}O_5$: C,62.23; H, 8.14. Found: C, 62.31; H, 8.19.

3,6,7,8-Tetradeoxy-1,2-O-isopropylidene-3,3-C-[(bromomethyl)ethylene]-á-D-ribo-oct-7-enofurnaose (78):

Compound **77** (0.35 g, 1.3 mmol), PPh_3 (0.86 g, 2.6 mmol), pyridine (1 mL) and CBr_4 (0.86 g, 2.6 mmol) in dry CH_2Cl_2 (20 mL) were stirred for 0.5 h at rt. Solvent was removed and residue purified on silica gel with ethyl acetate-light petroleum (1:9) to afford **78** (0.96 g, 78%), as a pale brown syrup.

$[\alpha]_D = +85^o$ (c 3.0, $CHCl_3$)

^1H NMR ($CDCl_3$, 200 MHz) : 0.57 (t, 1H, J = 5.6 Hz), 1.27 (s, 3H), 1.95 (m, 1H), 1.9 (m, 1H), 2.17 (m, 1H), 2.66 (dd, 1H, J = 5.3, 12.0 Hz) 3.12 (t, 1H, J = 12 Hz) 3.42 (dt, J = 3.2, 8.1Hz), 3.96 (dd, 1H, J = 5.3, 11.0 Hz), 4.07 (d, 1H, J = 8.0 Hz), 5.15 (m, 2H), 5.78 (m, 2H).

Anal. Calcd. for $C_{14}H_{21}O_4Br$: C,50.45; H, 6.30. Found: C, 50.31; H, 6.61

7a-allyl-2, 2-dimethyl-7-methylenehexahydro-3a*H*- cyclopenta[4,5]furo[2,3-*d*][1,3]dio-xol-5-ol (79):

*To a solution of compound **78** (100 mg, 0.3 mmol) in toluene (10 mL) at 100 ^oC under argon was added a solution of Bu_3SnH (0.12 mL, 0.45 mmol) and azoisobutyronitrile (AIBN) (10 mg) in toluene (5 mL) over a period of 10 h. Toluene was removed and the reaction mixture stirred with 15 % aqueous KF solution and solvent ether. Solid was filtered, dried (anhydrous Na_2SO_4),*

concentrated and chromatographed on silica gel using ethyl acetate-light petroleum to give ***79*** *(46 mg, 60 %).*

$[\alpha]_D$= -37^o (c 0.6, $CHCl_3$)

^{1}H-NMR ($CDCl_3$, 200 MHz) : 0.95 (d, 3H, J = 9.2 Hz), 1.1-1.4(m, 8H), 1.90-2.20(m, 3H), 2.62 (dd, 1H, J = 7.0, 13.0 Hz), 3.89 (m, 1H), 4.2 (t, 1H, J = 3.0 Hz), 4.5 (d, 1H, J = 3.5 Hz). 5.0-5.35 (m, 2H), 5.7 (d, 1H, J = 3.5 Hz), 5.83 (m, 1H).

EIMS: m/z 239$(M\text{-}Me)^+$

Anal. Calcd. for $C_{14}H_{22}O_4$: C,66.14; H, 8.66. Found: C, 66.41; H, 8.97.

3, 6, 7, 8-Tetradeoxy-1,2-*O*-isopropylidene-3,3-C-[(hydroxymethyl)ethylene]-á-D-*ribo* -oct-7-ynofuranose (80):

Compound **76** (2.3 g, 10 mmol) was dissolved in THF (20 mL) and then Zn dust (1.3 g, 20 mmol), propargyl bromide (1.98 mL, 20 mmol) were added. After cooling in ice water, saturated NH_4Cl (4 mL) was added dropwise. The reaction mixture was stirred for 3h, filtered through Celite and evaporated. The crude product was partitioned between ethyl acetate and water. The ethyl acetate layer was dried (Na_2SO_4), concentrated and chromatographed on silica gel using ethyl acetate-light petroleum (3:2) to afford **80** (1.16 g, 43%) as a pale yellow solid.

$[\alpha]_D$= 49^o (c 1.4, MeOH)

M.P = 83-85 ^{o}C

^{1}H-NMR ($CDCl_3$+DMSO-d_6, 200 MHz) : 0.45 (t, 1H, J = 4.8 Hz), 1.07 (dd, 1H, J = 4.4, 8.8 Hz), 1.40 (s, 1H), 1.52 (m, 1H), 2.24(dd, 1H, J = 2.9, 6.3 Hz), 2.35 (t, 1H, J = 2.9 Hz), 2.72 (t, 1H, J = 2.4 Hz), 3.71 (m, 1H), 4.04 (d, 1H, J = 8.8

Hz), 4.23 (t, 1H, J = 6.3 Hz), 4.38 (d, 1H, J = 3.9 Hz), 4.91 (d, 1H, J = 6.3 Hz), 5.70 (d, 1H, J = 3.9 Hz).

^{13}C-NMR ($CDCl_3$+DMSO-d_6, 50 MHz) 12.1, 20.9, 25.2, 26.6, 27.0, 33.3, 62.6, 69.2, 72.1, 78.2, 82.0, 86.1, 103.5, 110.6.

EIMS = m/z 253 $(M-CH_3)^+$

Anal. Calcd. for $C_{14}H_{20}O_5$: C,62.68; H, 7.46. Found: C, 62.46; H, 7.37.

3, 6, 7, 8-Tetradeoxy-1,2-*O*-isopropylidene-3,3-C-[(bromomethyl)ethylene]-á-D-*ribo*- oct-7-ynofurnaose (81):

A solution of **80** (1.0 g, 3.7 mmol), PPh_3 (2.45 g, 7.4 mmol), pyridine (2 mL) and CBr_4 (0.98 g, 3.7 mmol) in dry CH_2Cl_2 (20 mL) was stirred at rt for 0.5 h and then evaporated. The residue was purified on silica gel with ethyl acetate-light petroleum (1:9) to afford **81** (0.96 g, 78%), as a pale brown syrup.

$[\alpha]_D = 169^o$ (c 2.7, $CHCl_3$)

^{1}H-NMR ($CDCl_3$, 200 MHz) : 0.61 (t, 1H, J = 5.3 Hz), 1.3 (s, 3H), 1.47 (dd, 1H, J = 5.3, 8.8 Hz), 1.54 (s, 3H), 1.90-2.05 (m, 2H), 2.10 (t, 1H, J = 2.4 Hz), 2.45 (ddd, 1H, J = 2.4, 6.8, 17.1 Hz), 2.67 (dt, 1H, J = 2.9, 17.1), 3.15(t, 1H, J = 10.3 Hz), 3.48 (m, 1H), 4.01 (dd, 1H, J = 4.4, 10.3 Hz), 4.16 (d, 1H, J = 8.8 Hz), 4.31 (d, 1H, J = 3.9 Hz), 5.81(d, 1H, J = 3.9 Hz).

^{13}C-NMR ($CDCl_3$, 50 MHz) : 16.1, 21.5, 25.4, 26.6, 26.9, 36.1, 38.8, 69.6, 71.5, 78.4, 80.0, 86.4, 103.9, 111.8.

EIMS = m/z 316 $(M-CH_3)^+$

Anal. Calcd. for $C_{14}H_{19}O_4Br$: C,50.75; H, 5.74. Found: C, 51.13; H, 5.93

5-methyl-2, 3, 5, 7, 8, 8a-hexahydro-4H-pentaleno[1,6a-b]furan-2,3,-*O*-isopropy

lidene-8-ol (82):

To compound **81** (0.8 g, 2.4 mmol) in dry toluene (50 mL) under argon, TBTH (1.05 g, 3.6 mmol) and catalytic amount of AIBN (25 mg) were added. The reaction mixture was heated at 100°C for 30 min, cooled to rt, and worked up in the usual fashionas described earlier and the residue purified on silica gel using ethyl acetate-light petroleum to give **82** (0.45 g, 76% yield) as a pale yellow low melting solid.

$[\alpha]_D = -60^o$ (*c* 0.9, $CHCl_3$)

^{1}H-NMR ($CDCl_3$, 500 MHz) : 0.97 (d, 3H, J = 10.8 Hz), 1.26 (t, 1H, J = 10Hz), 1.34, (s, 3H), 1.47, (s, 3H), 1.80 (m, 1H), 2.5 (dd, 1H, J = 6.3, 13.5 Hz), 2.67(dd, 1H, J = 4.5, 12.6 Hz), 2.95 (m, 1H), 3.72 (m, 1H), 4.24 (d, 1H. J = 4.5 Hz), 4.28 (d, 1H, J = 3.5), 5.41 (s, 1H), 5.74 (d, 1H, J = 3.5 Hz)

^{13}C-NMR ($CDCl_3$, 125 MHz) : 20.0, 27.3, 27.6, 34.0, 40.5, 42.7, 65.5, 74.8, 85.7, 87.7, 106.5, 132.3, 144.7.

EIMS: m/z 252(M^+)

Anal. Calcd. for $C_{14}H_{20}O_4$: C,66.66; H, 7.93. Found: C, 66.35; H, 7.97

1,2:5,6-Di-*O*-cyclohexylidine-3-*O*-propargyl-α-D-glucofuranose (84):

To an ice-cold solution of **83** (12.0 g, 31.7 mmol) in dry DMF (100 mL) under argon, NaH (1.9 g, 47.6 mmol) (60% suspension in mineral oil) was added. The reaction mixture was stirred for further 30 min. at room temperature propargyl bromide (4.47 mL, 47.6 mmol) was added dropwise. After 1 h at rt, excess NaH was quenched with ice-cold water and extracted with ether. The ether layer was dried (Na_2SO_4), concentrated and purified on silica gel using ethyl acetate-light petroleum (1:9) as eluent, to afford propargyl derivative **84** (10.8 g, 81%) as pale yellow syrup.

$[\alpha]_D$ = - 2.6° (*c* 2.0, $CHCl_3$)

^{1}H-NMR ($CDCl_3$, 200 MHz) : 1.30-1.78 (m, 20H), 2.46 (t, 1H, J = 2.3 Hz) 3.92 (dd, 1H, J = 5.5, 8.8 Hz), 4.06 (m, 3H), 4.2 (t, 1H, J = 8.8 Hz), 4.29 (d, 2H, J = 2.3 Hz), 4.55 (d, 1H, J = 3.7 Hz) 5.82 (d, 1H, J = 3.7 Hz).

^{13}C-NMR ($CDCl_3$, 50MHz) : 23.6, 23.9 (2C), 24.1, 24.9, 25.2, 34.9, 35.9, 36.6, 58.1, 67.1, 72.1, 74.7, 79.5, 81.3, 81.8, 82.7, 104.9, 109.5, 112.4.

EIMS: m/z 378(M^+)

Anal. Calcd. for $C_{21}H_{30}O_6$: C,66.66; H, 7.93. Found: C, 66.91; H, 8.21

Methyl 5,6-*O*-cyclohexylidene-3-*O*-propargyl-α-D-glucofuranoside (85a) and Methyl 5,6-*O*-cyclohexylidene-3-*O*-propargyl-â-D-glucofuranoside (85b):

A solution of **84** (10.0 g, 26.45 mmol), H_2SO_4 (0.15 mL) in methanol (150 mL) was refluxed on water bath for 8 h. The reaction mixture was neutralized with triethylamine and methanol removed. The crude product was purified on silica gel using ethyl acetate–light petroleum (3:7) to afford **85a** (2.7 g, 33%) and further elution gave **85b** (2.3 g, 27 %).

$[\alpha]_D$ = +10° (c 3.1, $CHCl_3$)

^{1}H-NMR ($CDCl_3$, 200 MHz) for **85b** : 1.30-1.68 (m, 10H), 2.43 (t, 1H, J = 2.4) 2.82 (d, 1H, J = 6.2 Hz), 3.46 (s, 3H), 3.84-4.25 (m, 6H), 4.29 (d, 2H, J = 2.4 Hz) 4.95 (d, 1H, J = 3.9 Hz).

^{13}C-NMR ($CDCl_3$, 50 MHz) for **85b** : 23.8, 24.0, 25.2, 34.9, 36.4, 55.4, 58.0, 66.7, 73.4, 74.8, 79.3, 79.8, 82.1, 82.9, 109.5, 109.7

^{1}H-NMR ($CDCl_3$, 200 MHz) for **85a** : 1.31-1.74 (m, 10H), 2.45 (t, 1H, J = 2.4), 2.53 (br. s, 1H), 3.9–4.3 (m, 6H), 4.32 (d, 2H, J = 2.4 Hz), 4.78 (s, 1H).

EIMS: m/z 281$(M\text{-}OMe)^+$

Anal. Calcd. for $C_{16}H_{24}O_6$: C,61.53; H, 7.69. Found: C, 61.71; H, 7.74

(*E*)-Methyl 5,6-*O*-cyclohexylidene-2-deoxy-2-C-[(ethoxycarbonyl)methylene)]-3-*O*-propargyl-α-D-*arabino*-hexofurnoside (87):

A solution of **85b** (2.2 g, 7.05 mmol), IBX (2.17 g, 7.75 mmol) in DMSO (8 mL) was stirred for 8 h at rt. The reaction mixture diluted with water, solid was filtered, extracted with ether. Ether layer was dried (Na_2SO_4), concentrated to give **86** (1.9 g) and used for the next reaction.

86 (1.9 g, 6.1 mmol), PPh_3=$CHCO_2Et$ (3.0 g, 8.8 mmol) in CH_2Cl_2 (25 mL) was refluxed for 4 h. The reaction mixture was concentrated and purified on silica gel using ethyl acetate - light petroleum (1.5: 8.5) to give **87** (1.8 g, 67%) (two steps)

$[\alpha]_D$ = 14° (c 0.7, $CHCl_3$)

^{1}H-NMR ($CDCl_3$, 200 MHz) 1.32 (t, 3H, J = 7.3 Hz), 1.36-1.70 (m, 10H), 2.4 (t, 1H, J = 2.4 Hz), 3.42 (s, 3H), 3.87-4.52 (m, 8H), 5.15 (d, 1H, J = 3.9 Hz), 5.4 (s, 1H) 6.13 (s, 1H)

(d, 1H, J = 2.9 Hz), 5.4 (s, 1H) 6.12 (s, 1H).

^{13}C-NMR ($CDCl_3$, 50 MHz) 14.0, 23.7, 23.9, 25.1, 34.7, 36.3, 55.3, 58.4, 60.6, 66.5, 72.1, 73.9, 75.5, 80.1, 82.2, 103.3, 109.5, 120.3, 155.3, 165.0.

EIMS: m/z 349$(M\text{-}OMe)^+$

Anal. Calcd. for $C_{20}H_{28}O_7$: C,63.15; H, 7.37. Found: C, 63.43; H, 7.61

(*E/Z*)-Methyl 2-deoxy-5,6-*O*-cyclohexaledine-2,2-C[(ethoxycarbonyl)ethylene]-3-*O*-propargyl-α-D-*arabino*-hexofurnoside (88):

To an ice cooled suspension of NaH (0.28 g, 7.1 mmol) (60% dispersion on mineral oil) in dry DMSO (4 mL) trimethylsulfoxonium iodide (1.56 g, 7.1 mmol) was added followed by **87** (1.8 g, 4.73 mmol) in DMSO (4 mL). After 3 h at rt the reaction mixture was diluted with ice-water mixture and extracted with ether which was dried (Na_2SO_4), concentrated. The residue was purified on silica gel using ethyl acetate-light petroleum (1:9) to **88** (0.56 g, 50 %).

$[\alpha]_D = 84^o$ (c 1.6, $CHCl_3$)

^{1}H-NMR ($CDCl_3$, 200 MHz) 1.28 (t, 3H, J = 9 Hz), 1.32-165 (m, 12H), 2.25 (dd, 1H, J = 6.5, 8.5 Hz), 2.4 (t, 1H, J = 2.4 Hz), 3.3 (s, 3H), 3.85 (d, 1H, J = 3.9 Hz), 3.95 (dd, 1H, J = 5.6, 8.8 Hz), 4.02-4.35 (m, 8H), 4.8 (s, 1H).

Anal. Calcd. for $C_{21}H_{30}O_7$: C,63.95; H, 7.61. Found: C, 63.61; H, 7.43

Methyl (*E/Z*)-2-Deoxy-2,2-C-[(hydroxymethyl)ethylene]-5,6-*O*-cyclohexylidene-3-*O*-propargyl-α-D-*arabino*-hexofurnoside (89):

To a solution of **88** (0.8 g, 2.0 mmol) in dry CH_2Cl_2 (25 mL) at –78 °C, 2.1 molar solution of DIBAL-H (2.4 mL, 4.0 mmol) was added drop wise. After stirring for 1 h more at –78 °C, the reacion was worked up as described above. The residue was purified on silica gel using ethyl acetate-light petroleum (3:7) as eluent to afford **89** (0.56 g, 79%).

$[\alpha]_D = +6^o$ (c 0.83, $CHCl_3$)

^{1}H-NMR ($CDCl_3$, 200 MHz) 0.65 (dd, 1H, J = 6.3, 4.8 Hz), 1.28 (dd, 1H, J = 4.4, 9.3 Hz), 1.35-1.70 (m, 10H), 2.5 (t, 1H, J = 2.4 Hz), 2.92 (br. d, 1H, J = 11.7 Hz), 3.31 (m, 4H), 3.9-4.1 (m, 4H), 4.15-4.27 (m, 2H), 4.45 (dd, 2H, J = 2.4, 4.4 Hz), 4.84 (s, 1H)

^{13}C-NMR ($CDCl_3$, 50 MHz) 12.9, 23.5, 23.9, 24.0, 25.2, 35.0, 35.6, 36.5, 55.8, 58.4, 63.9, 67.7, 72.2, 75.2, 79.0, 82.1, 84.2, 106.2, 110.1.

EIMS: m/z 321 $(M\text{-}OMe)^+$

Anal. Calcd. for $C_{19}H_{28}O_6$: C,64.77; H, 7.95. Found: C, 64.81; H, 8.13.

Methyl (*E/Z*)-2-Deoxy-2,2-C-[(bromomethyl)ethylene]-5,6-*O*-cyclohexylidene-3-*O*-propargyl-α-D-*arabino*-hexofurnoside (90):

Compound **89** (0.5 g, 1.4 mmol), PPh_3 (0.74 g, 2.5 mmol), pyridine (1 mL) and CBr_4 (0.52 g, 1.6 mmol) in dry CH_2Cl_2 (20 mL) were stirred for 0.5 h at rt and then concentrated, worked up and purified to afford **90** (0.35 g, 61 %)as pale brown thick syrup.

$[\alpha]_D = +93^o$ (c 0.60, $CHCl_3$)

^{1}H-NMR ($CDCl_3$, 200 MHz) : 0.7 (t, 1H, J = 4.9 Hz) 1.36-1.69 (m, 13H), 2.46 (br. s, 1H), 3.25-3.43 (m, 4H), 3.88-4.05 (m, 4H), 4.11-4.20(m, 2H), 4.37 (d, 1H, J = 2.4 Hz), 4.83 (S, 1H)

EIMS: m/z 384$(M\text{-}OMe)^+$

Anal. Calcd. for $C_{19}H_{27}O_5Br$: C,54.93; H, 6.50. Found: C, 55.34; H, 5.91.

Further elution of the column furnished unreacted starting material **90** (0.13 g, 26%).

3-(2,2-Dimethyl-1,3-dioxalon-4-yl)-1-methoxy-7-methyl-3,3a,7,8-tetrahydro-5H-cyclopenta[C]furo[3,4-b]furan (91):

*Compound **90** (0.35 g, 0.84 mmol), Bu_3SnH (0.32 mL, 1.3 mmol) and AIBN (15 mg) in toluene (18 mL) were heated at 100 °C for 1h. The reaction mixture was worked up as described earlier to afford **91** (0.21 g, 71%).*

$[\alpha]_D = +8^o$ (*c* 0.75, $CHCl_3$)

^{1}H-NMR ($CDCl_3$, 500 MHz) : 1.09 (d, 3H. J = 10.5 Hz), 1.49 (t, 1H, J = 12.0 Hz), 1.56-1.7 (m, 10H), 2.72 (dd, 1H, J = 5.0, 12.0 Hz), 3.41 (m, 1H), 3.37 (s, 3H), 3.88 (dd, 1H, J = 2.6, 7.9), 3.97 (dd, 1H, J = 4.5, 8.2), 4.03 (ddd, 1H, J = 2.2, 3.7, 11.3 Hz), 4.12 (m, 2H), 4.29 (d, 1H, J = 10.5 Hz), 4.38 (m, 1H), 4.69 (s, 1H), 5.46 (s, 1H)

^{13}C-NMR ($CDCl_3$, 500 MHz): 20.1, 23.8, 24.0, 25.2, 34.8, 36.6, 40.9, 45.0, 54.9, 65.9, 66.7, 73.2, 81.8, 85.1, 108.32, 109.6, 128.6, 148.4.

EIMS: m/z 336(M^+)

Anal. Calcd. for $C_{19}H_{28}O_5$: C,67.85; H, 8.33. Found: C, 67.93; H, 8.56.

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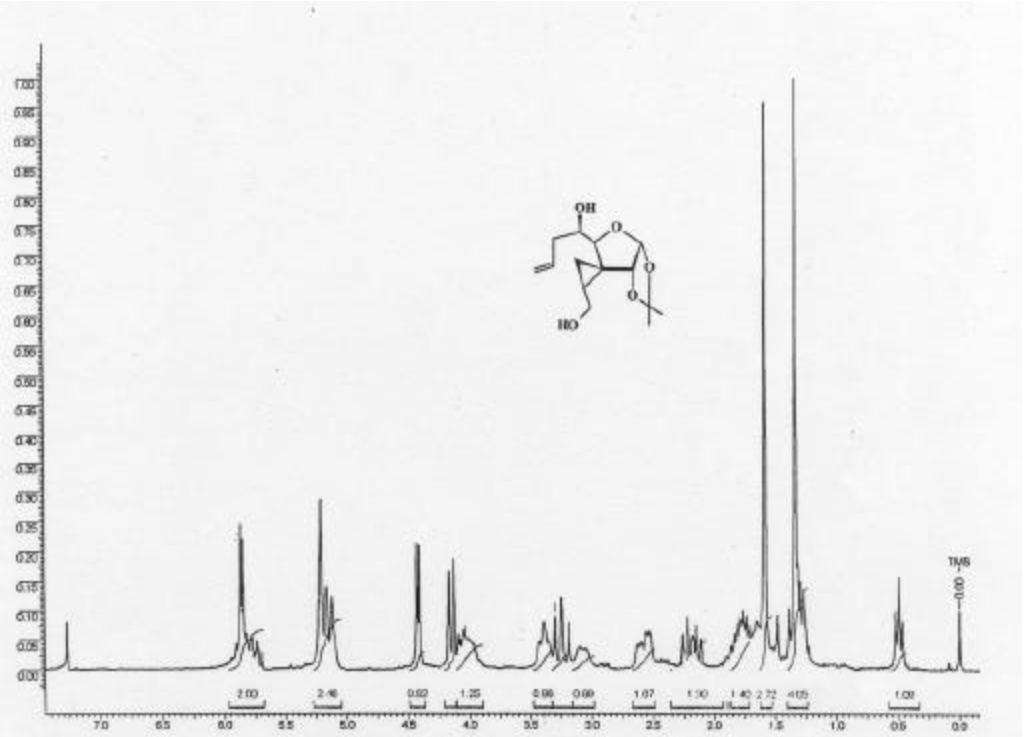
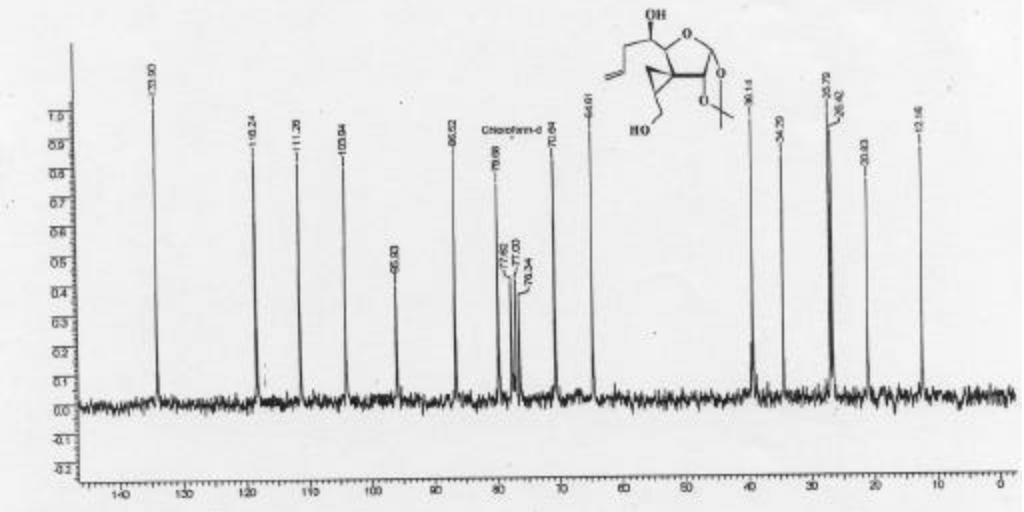
SPECTRA



^{1}H-NMR spectrum of compound 77 in $CDCl_3$



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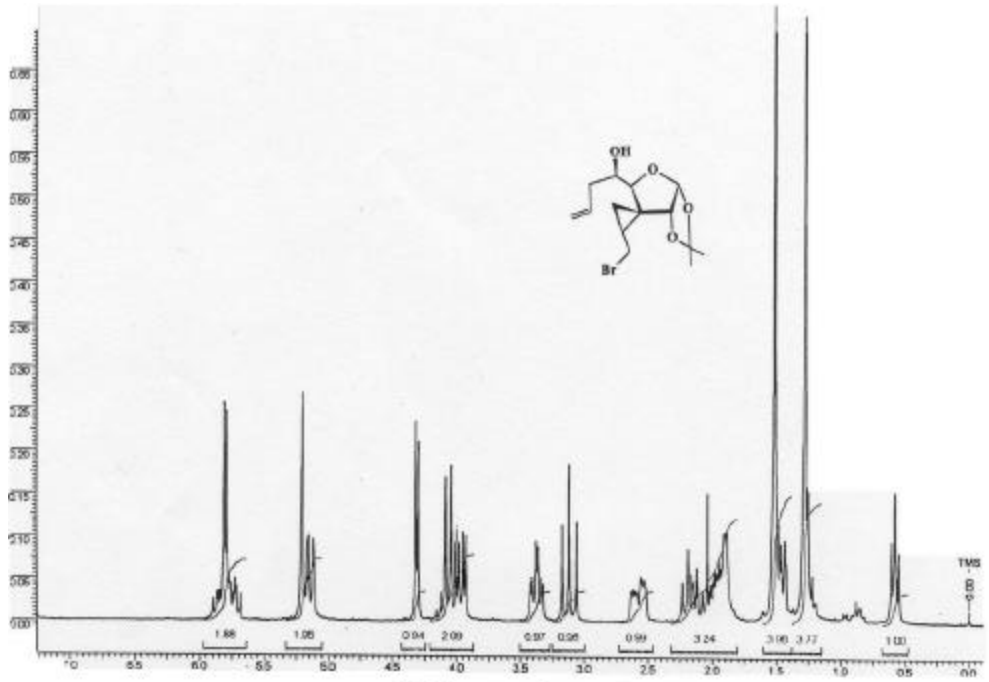

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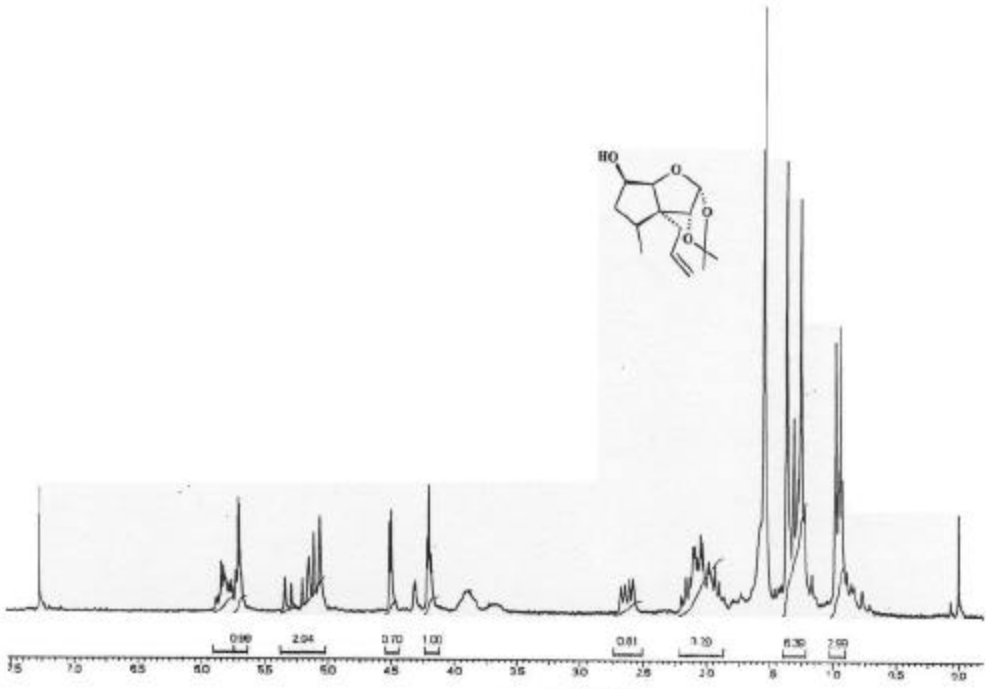

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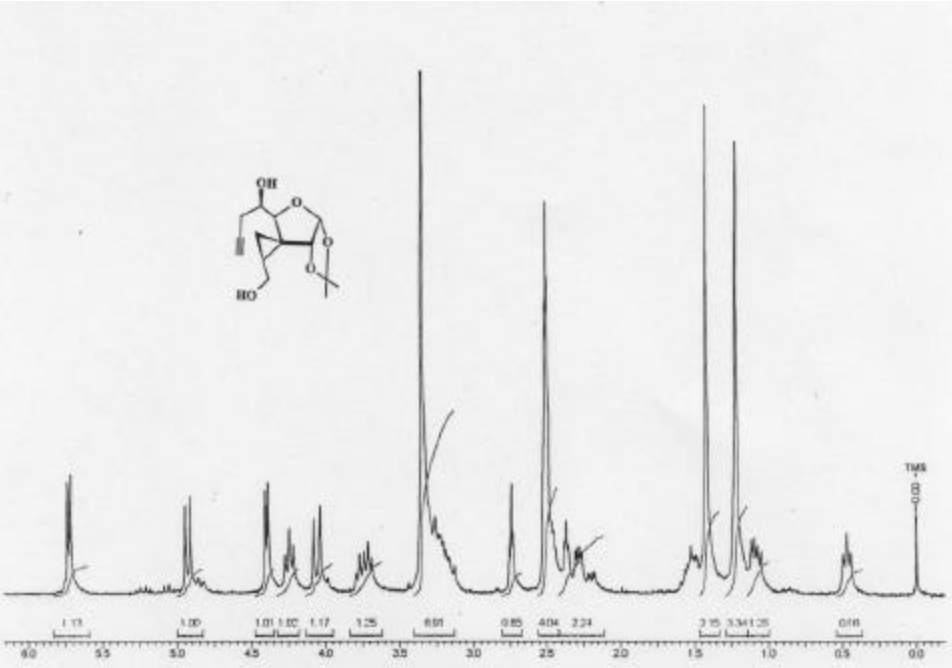
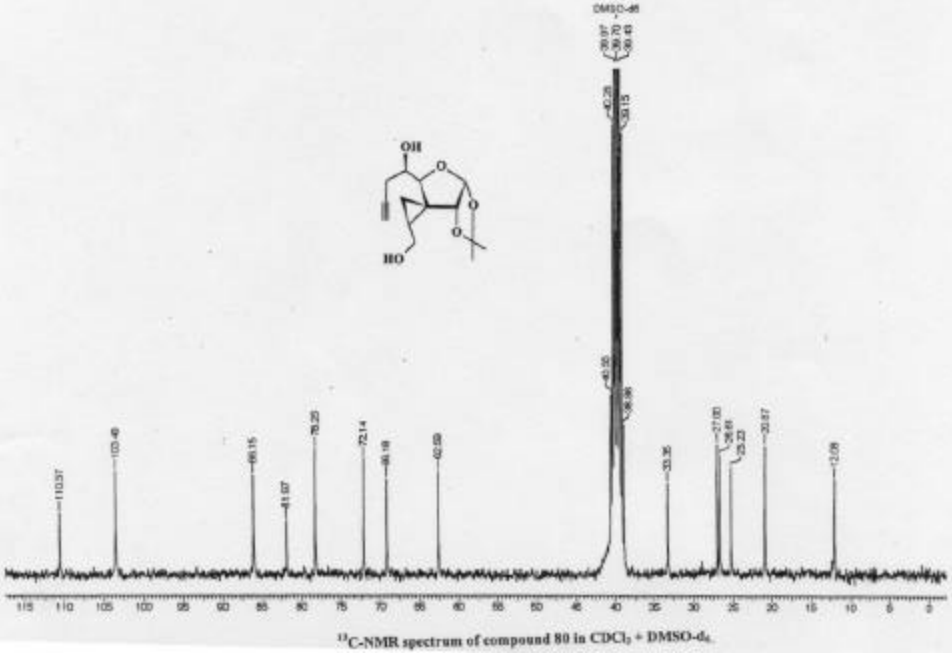
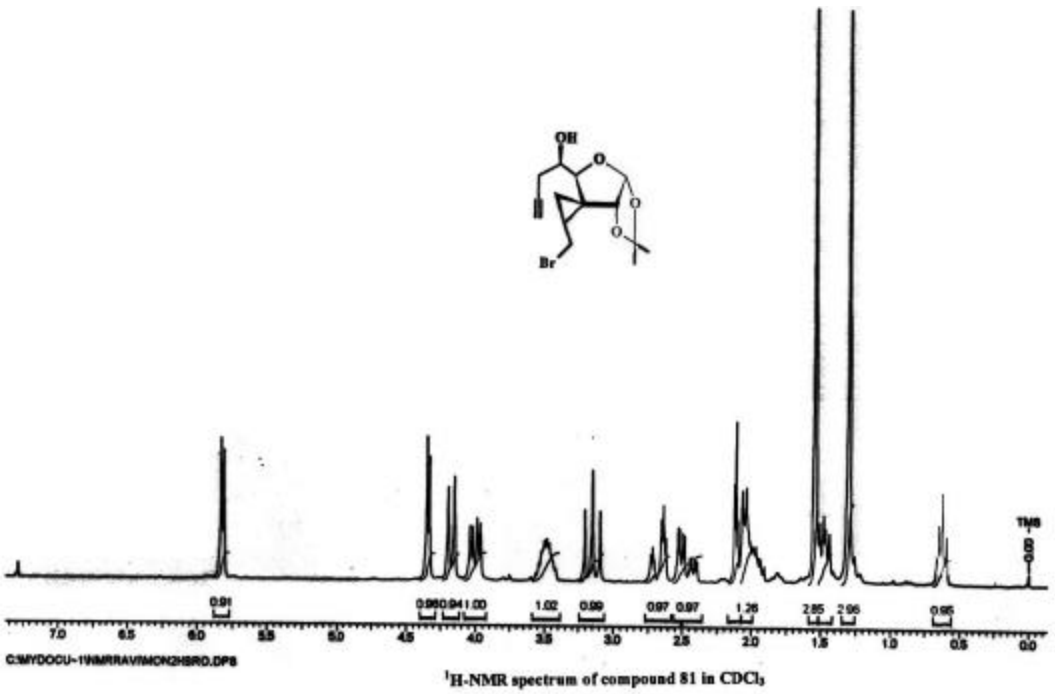


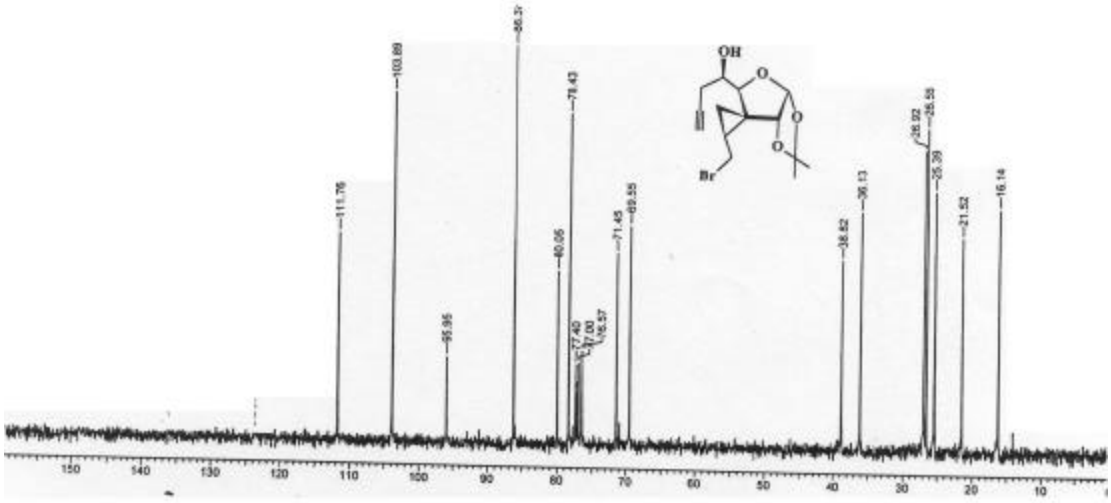
^{1}H-NMR spectrum of compound 80 in $CDCl_3$ + DMSO-d_6



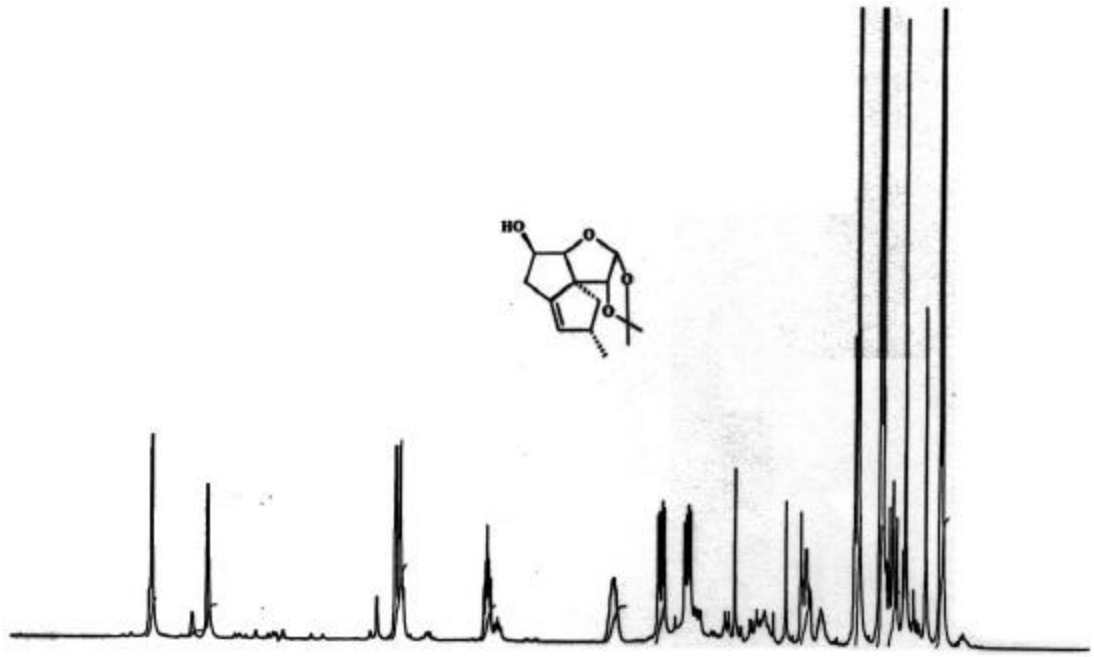
^{13}C-NMR spectrum of compound 80 in $CDCl_3$ + DMSO-d_6



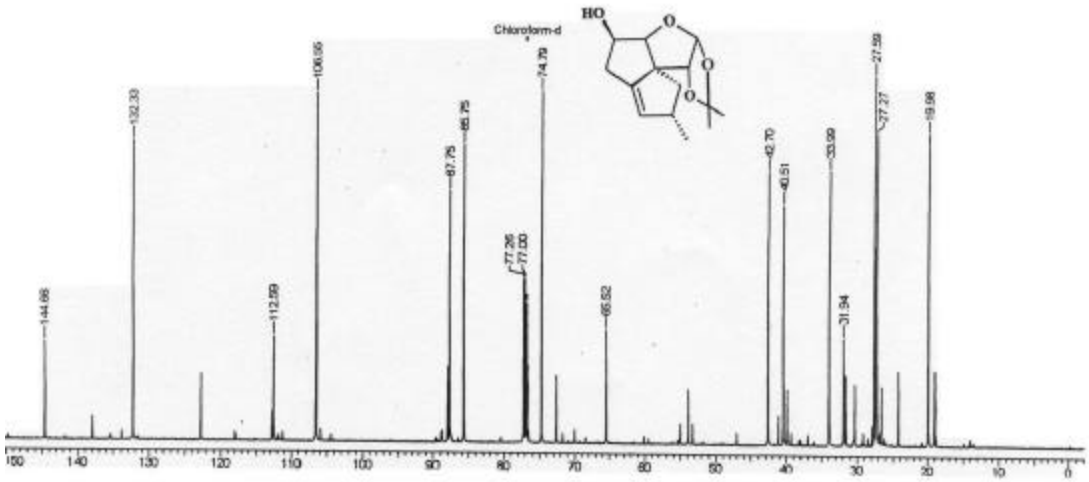
^{1}H-NMR spectrum of compound 81 in $CDCl_3$



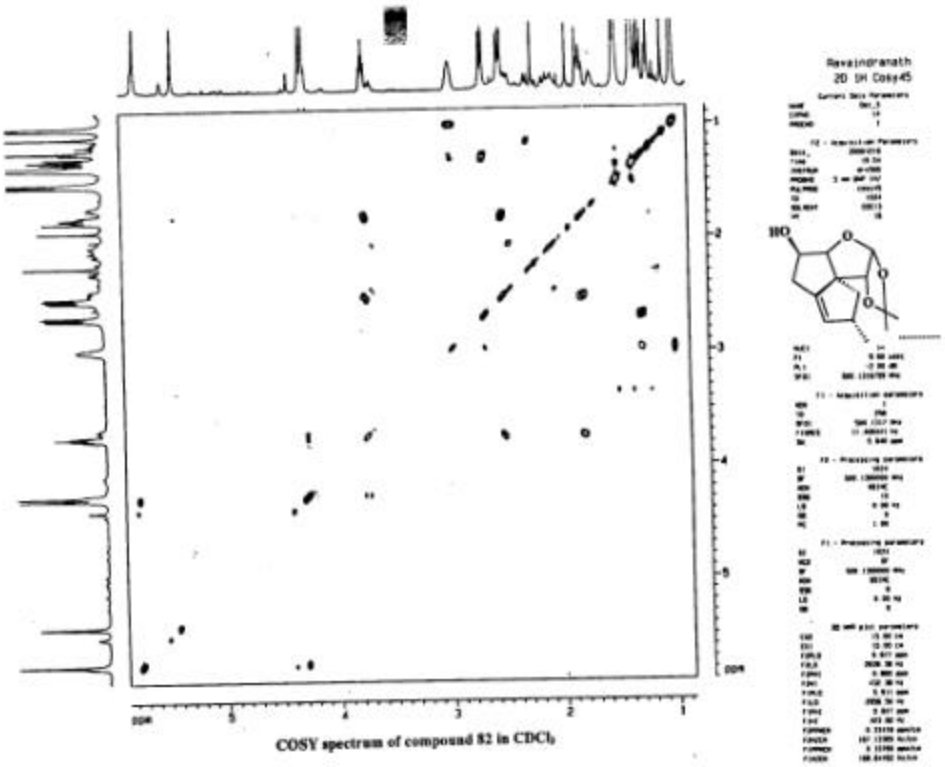
^{13}C-NMR spectrum of compound 81 in $CDCl_3$



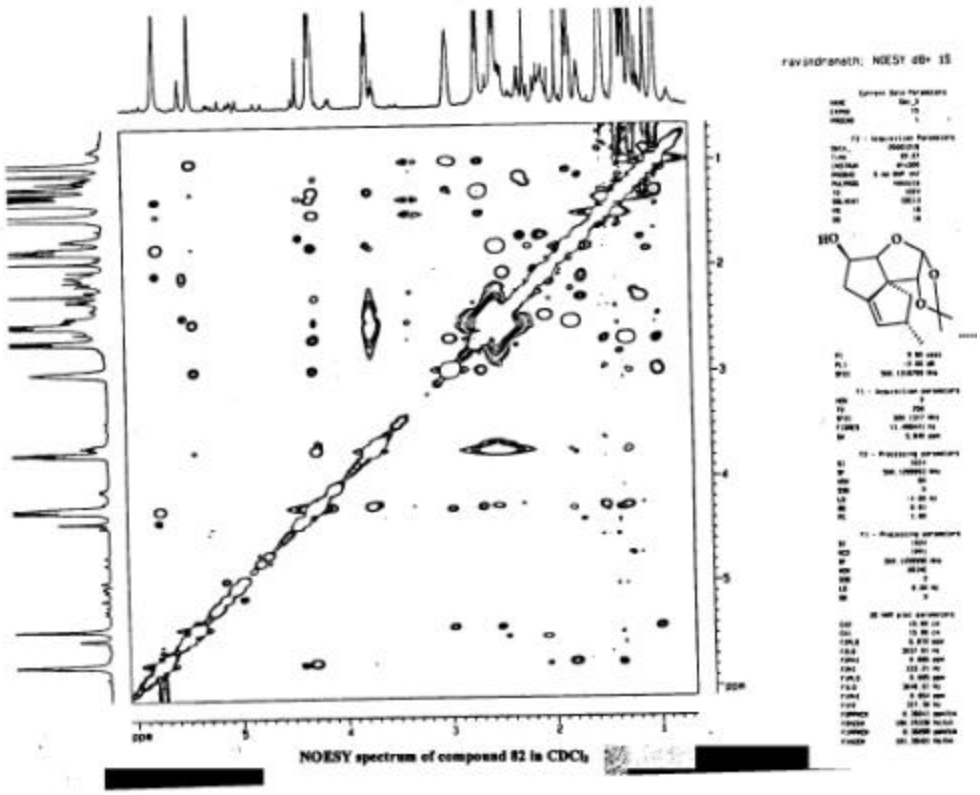
^{1}H-NMR spectrum of compound 82 in $CDCl_3$



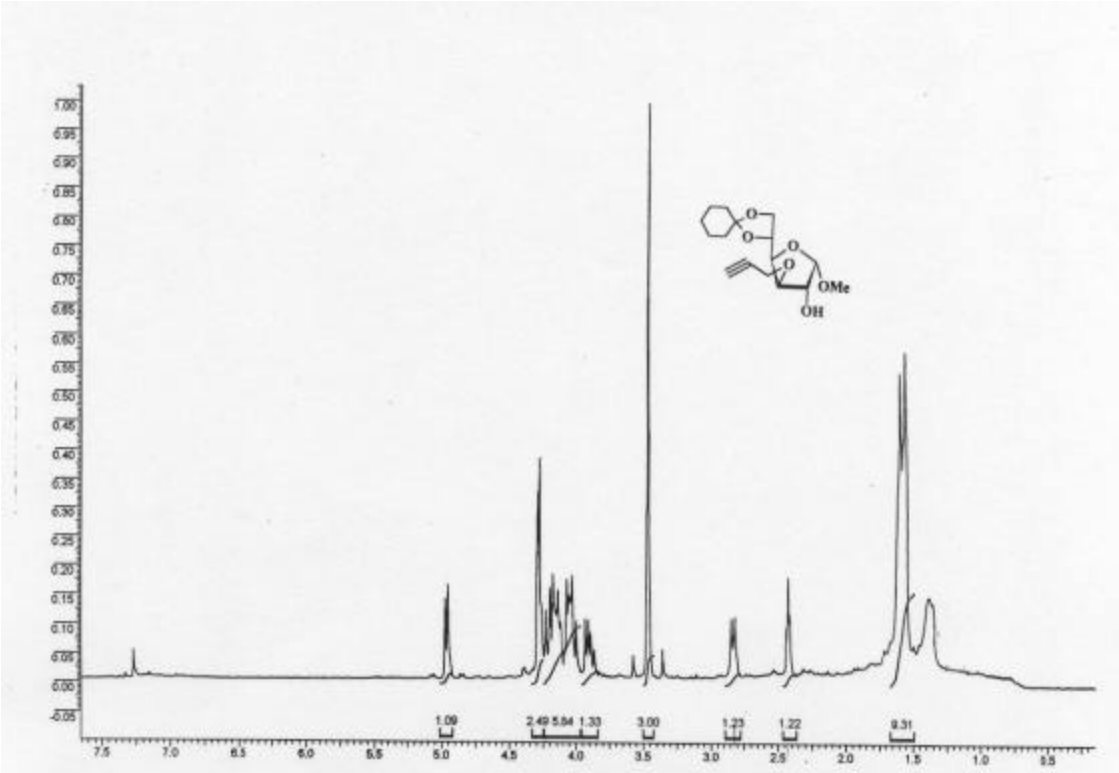
^{13}C-NMR spectrum of compound 82 in $CDCl_3$



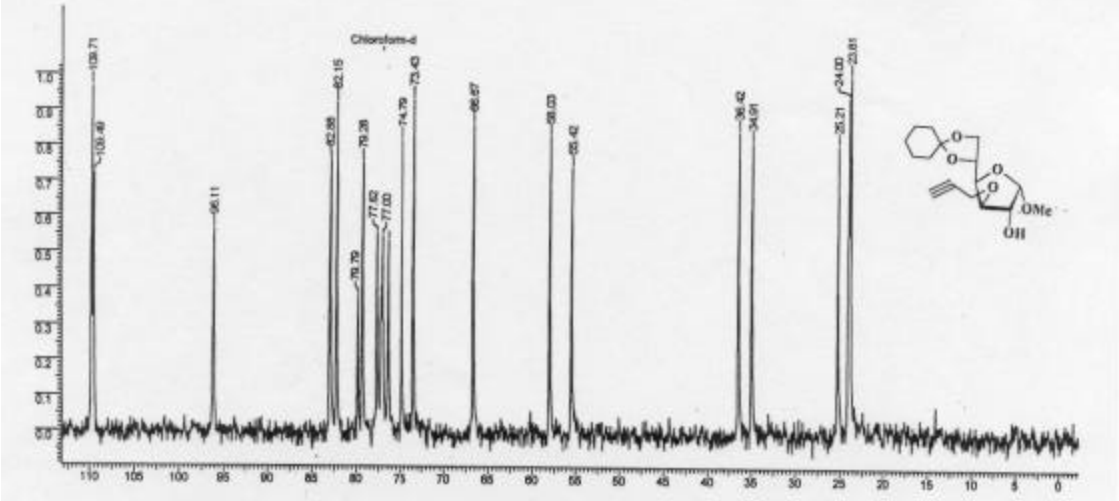
COSY spectrum of compound 82 in $CDCl_3$



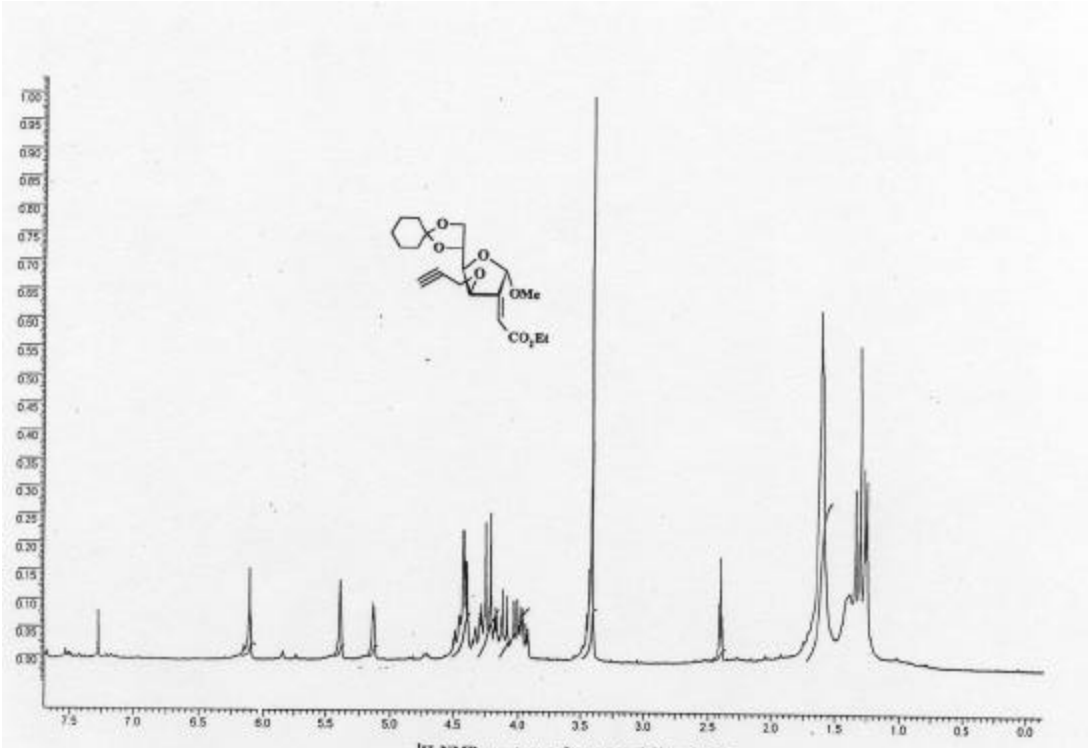
NOESY spectrum of compound 82 in $CDCl_3$



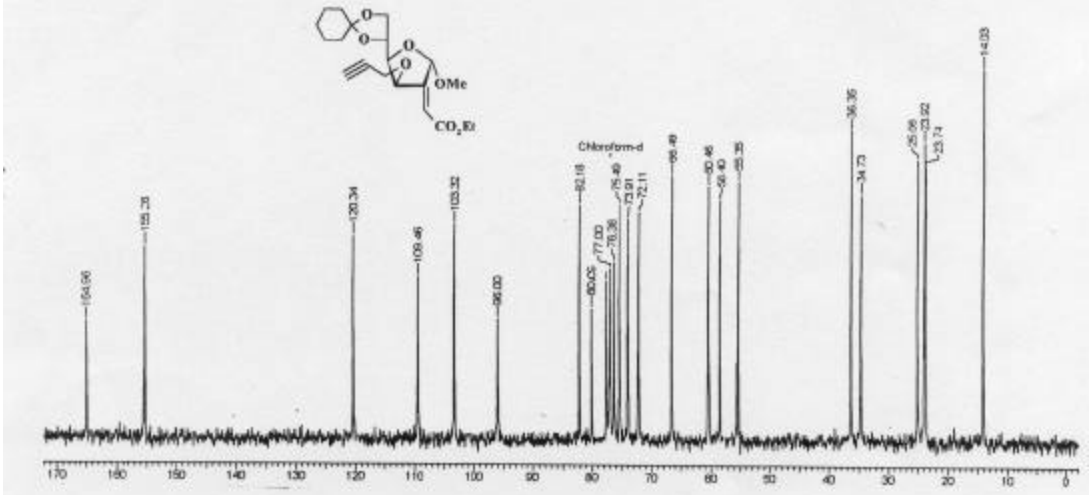
^{1}H-NMR spectrum of compound 85b in $CDCl_3$



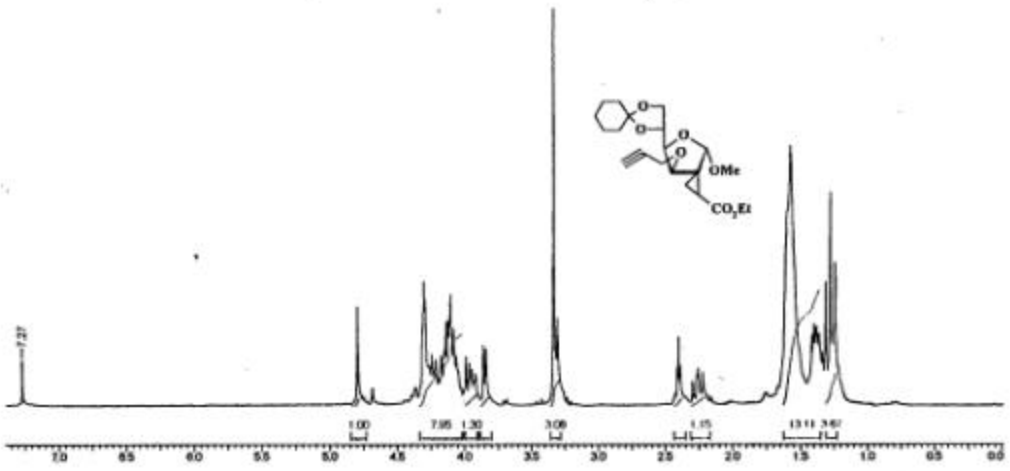
^{13}C-NMR spectrum of compound 85b in $CDCl_3$



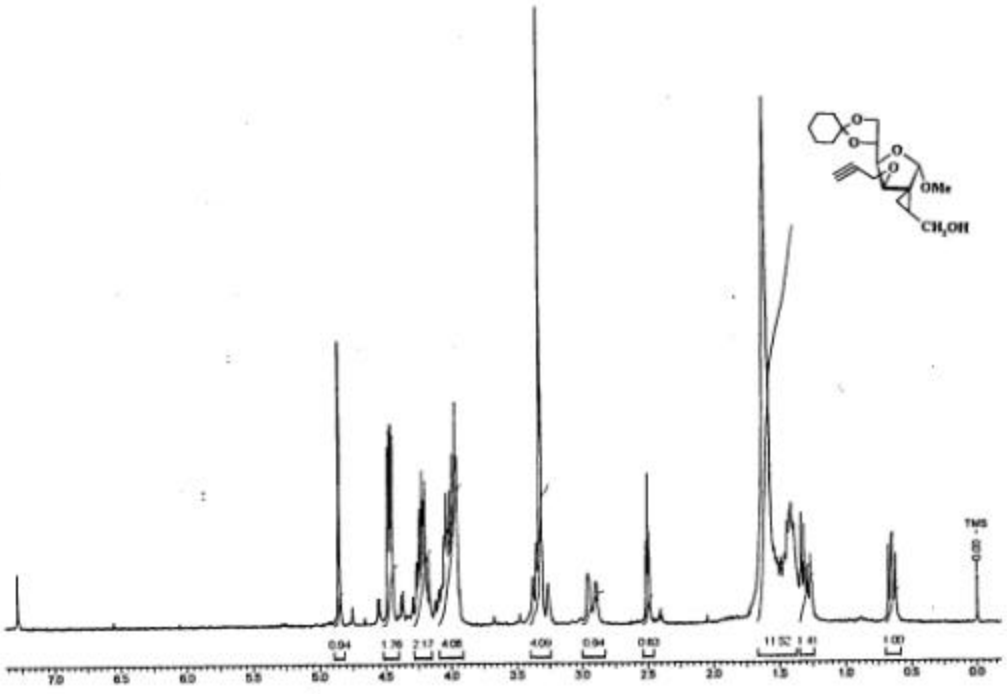
^{1}H-NMR spectrum of compound 87 in $CDCl_3$



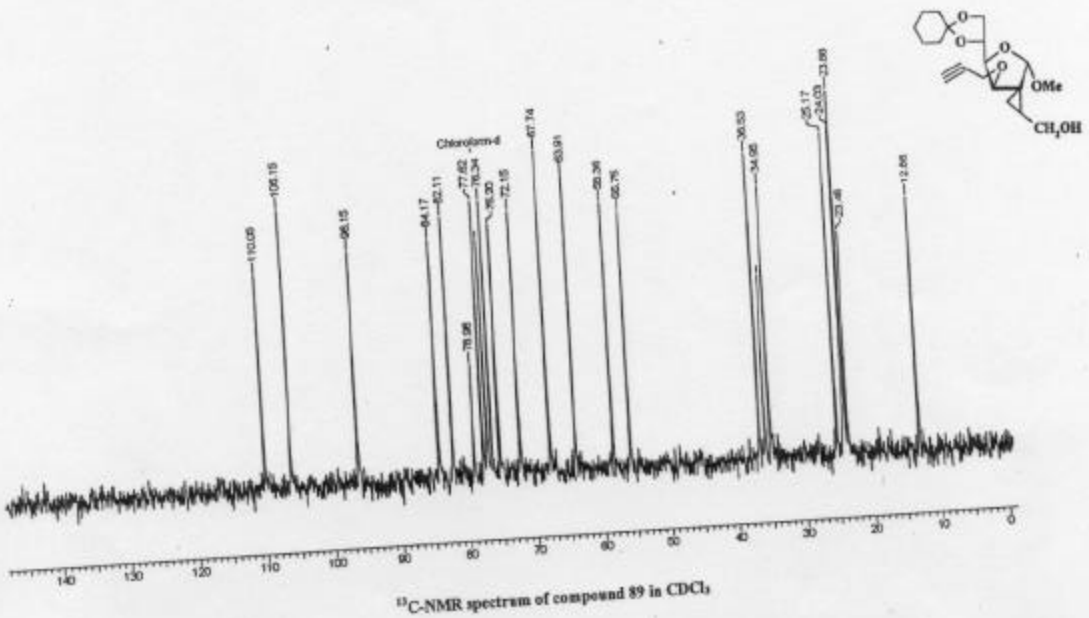
^{13}C-NMR spectrum of compound 87 in $CDCl_3$



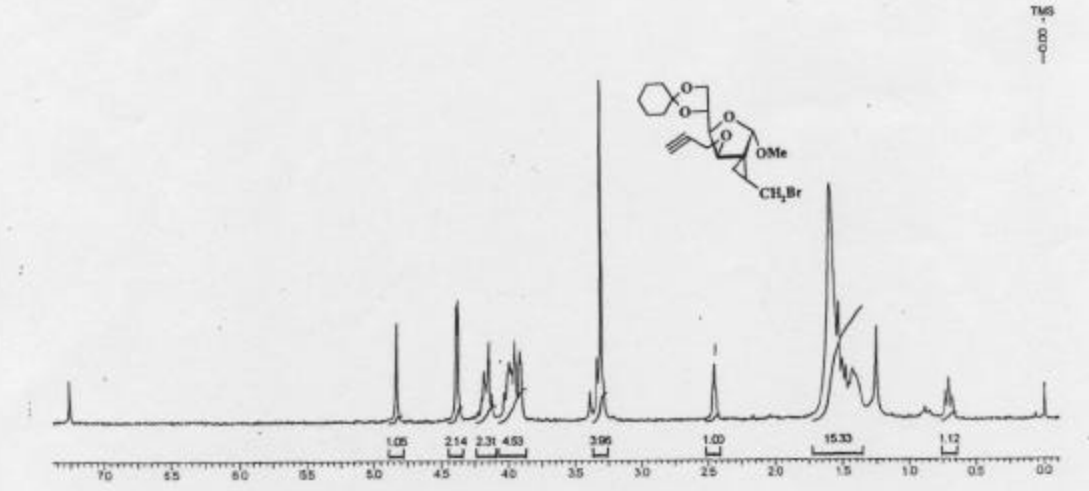
^{1}H-NMR spectrum of compound 88 in $CDCl_3$



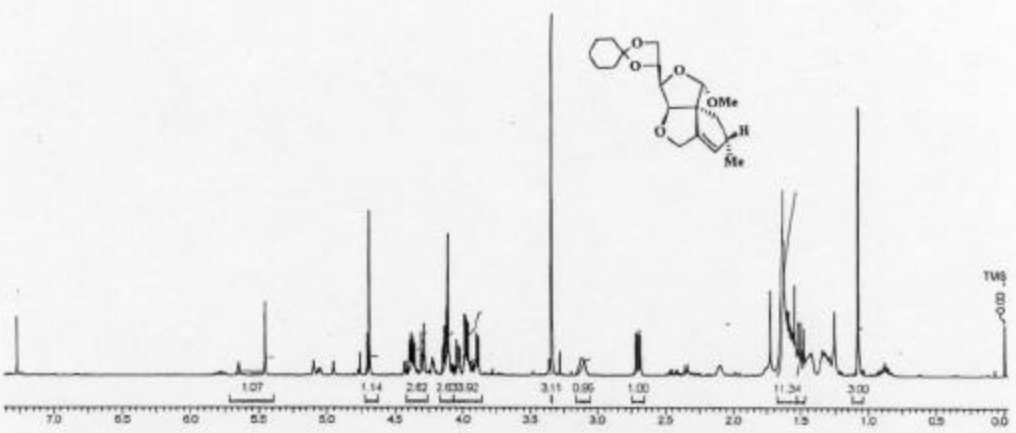
^{1}H-NMR spectrum of compound 89 in $CDCl_3$



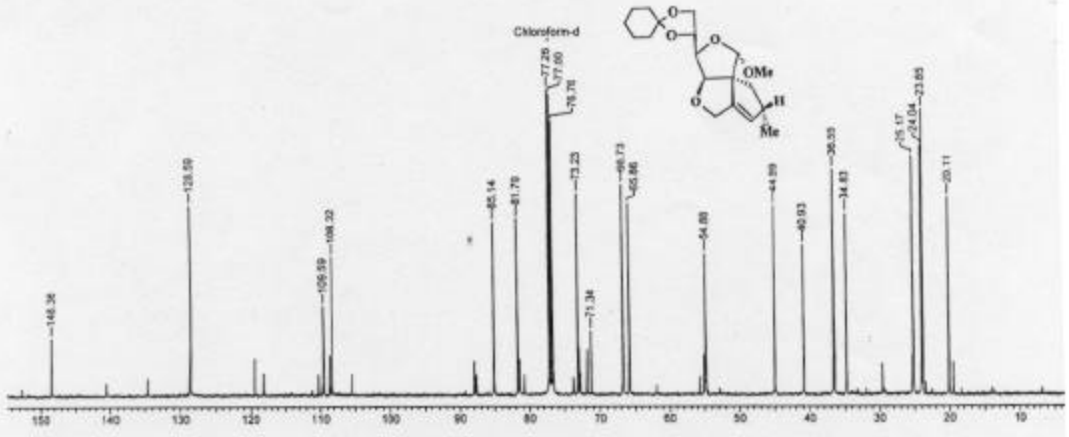
^{13}C-NMR spectrum of compound 89 in $CDCl_3$



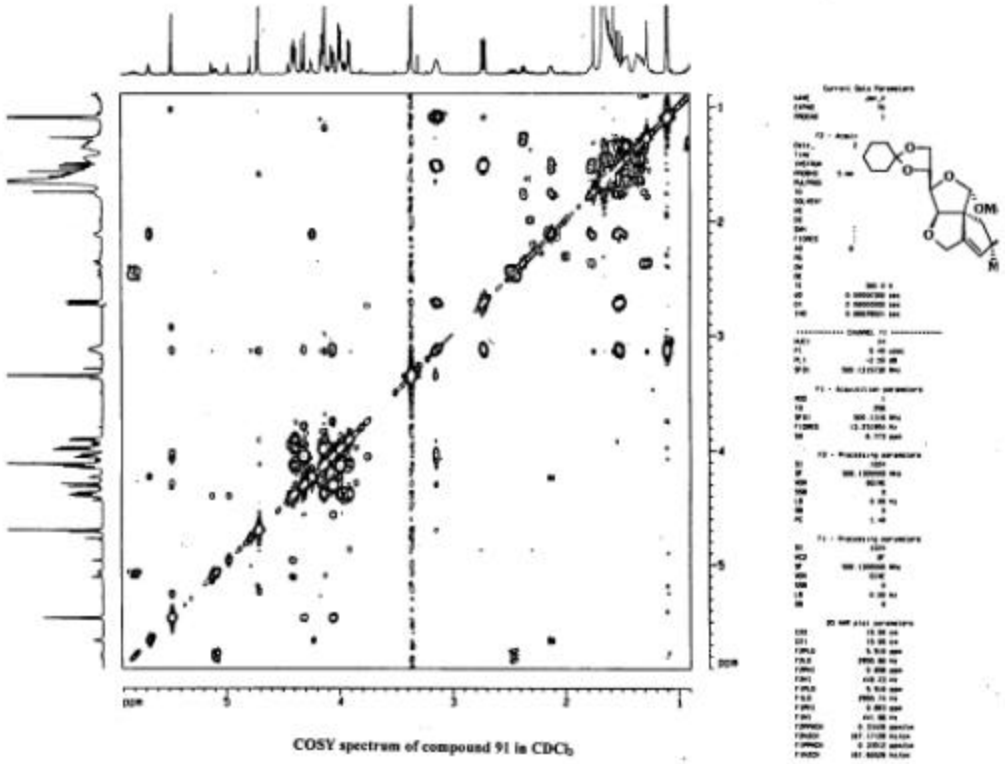
^{1}H-NMR spectrum of compound 90 in $CDCl_3$



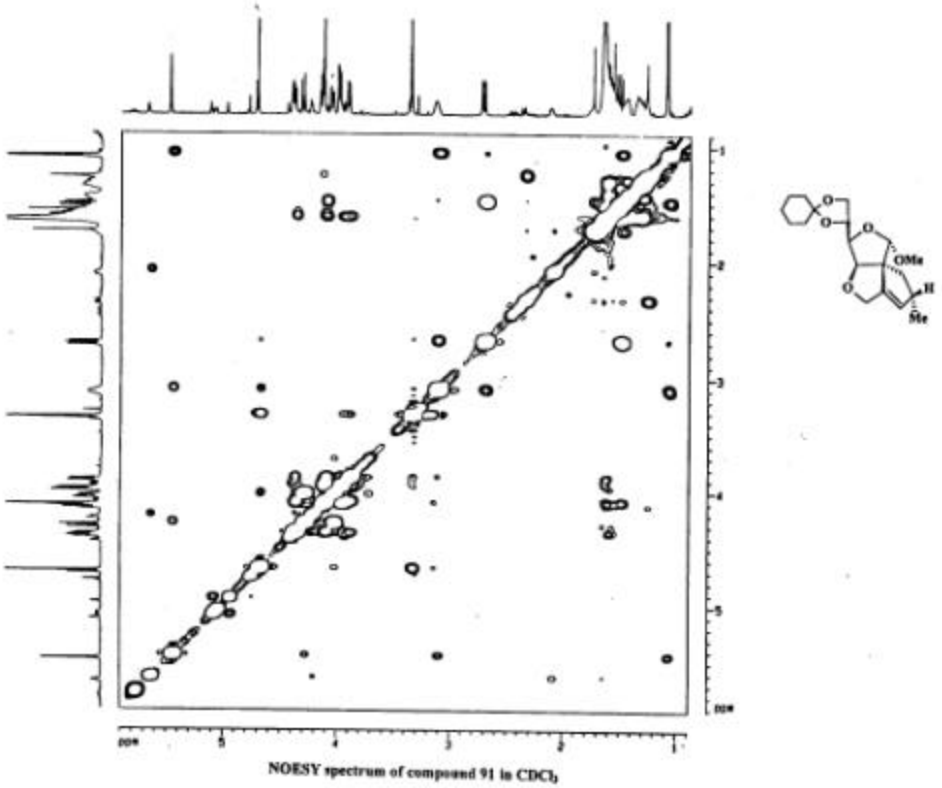
^{1}H-NMR spectrum of compound 91 in $CDCl_3$



^{13}C-NMR spectrum of compound 91 in $CDCl_3$



COSY spectrum of compound 91 in $CDCl_3$



NOESY spectrum of compound 91 in $CDCl_3$

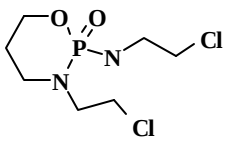
Introduction

The multiplication of cells is carefully regulated and responsive to specific needs of the body. Normally body cells grow, devide and die in an orderly fashion. During the early years of life normal cells devide more rapidly until the person becomes an adult. After that, normal cells of most tissues divide only to replace worn-out or dying cells and to repair injuries.

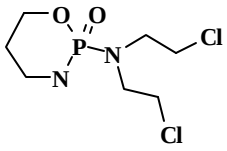
Very occasionally, the control that regulates the cell multiplication brakes down and cells continue to grow and divide with out responding to regulation. These cells accumulate and forms a mass called tumor that may compress, invade and destroy normal tissues. If cells break away from such a tumor, they can travel through the blood stream or the lymph system to other areas of the body. There they may settle and form colony of tumors. In the new location, the cancer cells continue growing. The spread of a tumor to a new site is called metastasis. When cancer spreads, though, it is still named after the part of the body where it started. For example, if prostate cancer spreads to the bones, it is still prostate cancer, and if breast cancer spreads to the lungs, it is still called breast cancer. Leukemia, a form of cancer, does not usually form a tumor. Instead, these cancer cells involve the blood and blood-forming organs (bone marrow, lymphatic system, and spleen), and circulate through other tissues where they can accumulate. It is important to realize that not all tumors are cancerous. *Benign* (noncancerous) tumors do not metastasize and, with very rare exceptions, are not life threatening.[1]

Cancer is a disease that has created panic in patients and frustration in doctors for several decades. The incidence of bronchogenic arcinoma has reached epidemic proportions in the developed world. The disease is the most common malignancy and leading cause of death from cancer among men in many countries. Cigarette smoking is the single major contributing factor.[2]

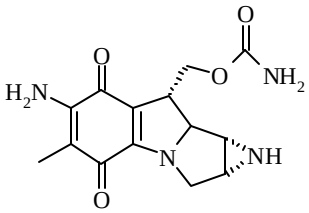
The treatment of individuals effected with metastatic disease consists of chemotherapy; however the best available single agents such as infortamide, mitomycin C,



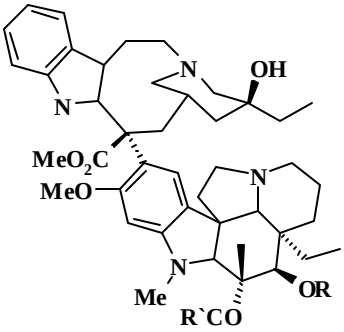
Infostamide



Cyclophospamide

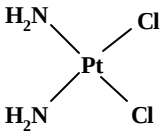


Mitomycin C

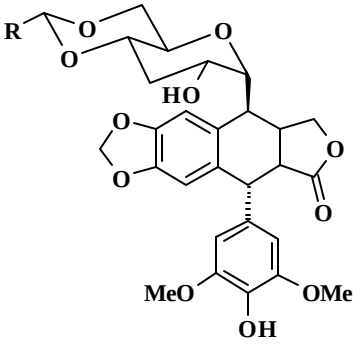


Vindesin R = H, R` = NH_2

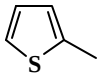
Vinblastin R= COMe, R`= OMe

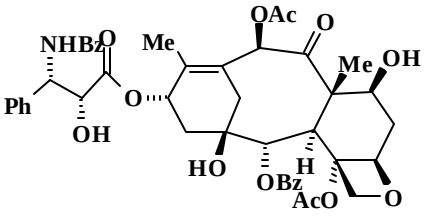


Cisplatin



Etoposide R= Me

Teniposide R= 

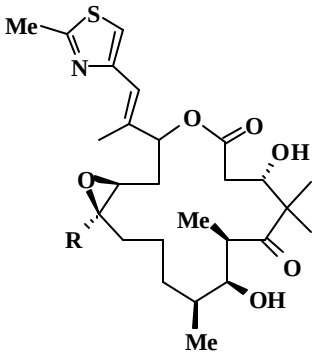


Taxol

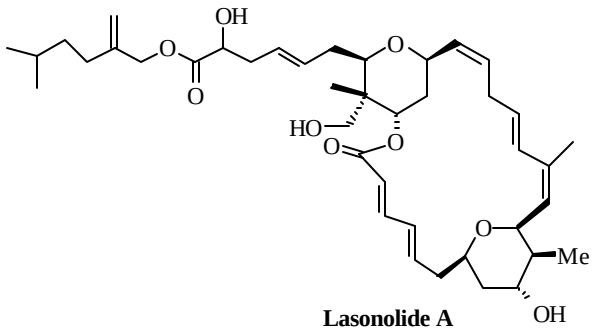
vindesine, cisplatin, doxorubicin, hexamethylamine, etoposide, metotrexate, paclitaxes, cyclophosphamide induced major responses in only 20-30 % patients. The combination of these agents may yield higher response rate, but the overall outcome remains dismal.[3]

Moreover, these antineoplastic drugs are always associated with high degree of myclotoxicity, nephrotoxicity, and other adverse side effects. Therefore, development of new agents is essential in order to prolong overall survival with minimized side effects of patients.[4]

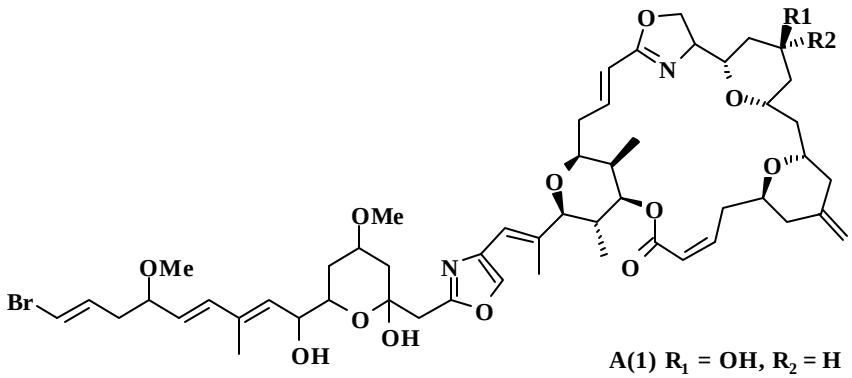
In search of new antitumor agents from different natural sources, every year thousands of natural products are isolated and screened by natural product chemists and phytochemists and new compounds of promising therapeutic value have been discovered. For examples, discodermalide,[5,6] epothilone[5-7] and lasonolide A.[8]



Epothilone A : R = H
Epothilone B : R = Me



Lasonolide A



Phorboxozole A and B

A(1) R_1 = OH, R_2 = H
B(2) R_1 = H, R_2 = OH

The most recent of all are the pharboxazoles (**1** and **2**).[9] These were isolated from the Indian ocean marine sponge *phorbes* sp. in 1993 near western Australia. These represent a new structural class of anticancer agents. These were reported to be extremely cytostatic towards the National Cancer Institutes panel of 60 tumor cell lines and inhibited the cells at lowest test concentration.[10,11] Hence, the phorboxazoles are among the most potent cytostatic agents yet discovered.

Synthetic studies towards phorboxazole:

The unique molecular frame work of the phorboxazoles comprised of a 21-membered macrolide and a side chain which together embody two oxazole rings, four pyran rings and fifteen stereo centers in all. The over all structure of the phorboxazole macrolide was determined by extensive NMR experiments. Initially, the relative stereochemistry of the C_{21} to C_{26} macrolide and C_{33}-C_{37} oxane ring were determined, and the configuration at C_{38} and C_{34} were undefined, and so considerable stereochemical ambiguity existed.[9]

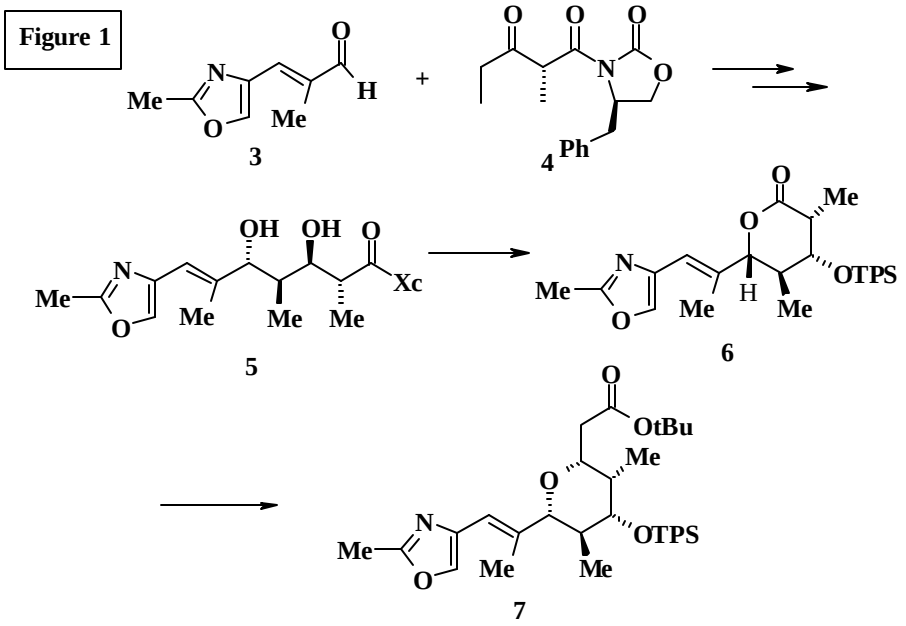
But later by using a modification of Mosher's ester method on the natural product and by synthesizing model compounds, Molinski *et al*. were able to establish both the relative and absolute configuration at C_{38} as well as at C_{13} and the complete stereochemistry of the phorboxazoles was assigned.[10]

Although the mechanism of action of **1** and **2** is unknown, it has been established that they cause cell arrest in the S-phase of the cell cycle and they do not inhibit tubulin polymerization.[11] Hence the combination of unique structure and intriguing cytostatic activities make the phorboxazoles an ideal focus of chemical and biological study.

So we have attempted the synthesis of C_{19}-C_{27} fragment of phorboxazole. However, before describing our attempts it is pertinent to briefly discuss the other methods reported in literature for the synthesis of this fragment.

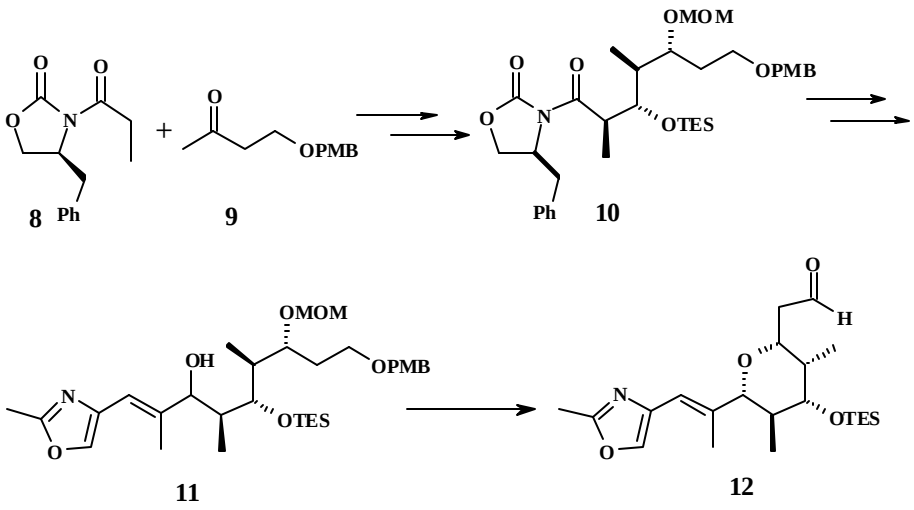
Evans and coworkers have reported[12] an aldol condensation route for the synthesis of the C_{19}-C_{30} core. Accordingly addition of boron enolate of **4** on to the aldehyde **3** gave the anti aldol adduct. Subsequent reduction of ketone followed by cyclization under basic conditions gave the product **6**. Addition of lithim enolate of *t*-butyl acetate, followed by reduction with triethyl silane gave the required oxalane core **7**.

Figure 1



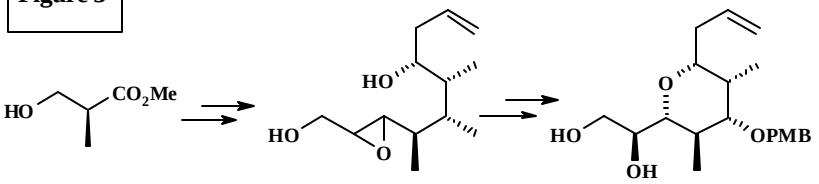
Williams and Clark have reported[13] an elegant synthesis of the C_{19}-C_{32} fragment by utilizing the two successive boron-aldol condensations of **8** and **9**, which gave four contiguous centers (**10**). After the cleavage of chiral auxiliary, compound **10** was converted to the corresponding â-keto phosphonate and was condensed with 2-methyloxazole-4-carboxaldehyde to afford the cyclization precursor **11**. This on treatment with Tf_2O underwent cyclization giving the required fragment **12**.

Figure 2



Pattenden *et al.* have reported[14] another approach for the C_{19}-C_{32} core. Synthesis was started with methyl (S)-3-hydroxy-2-methyl propionate (**13**). Brown's allylboration and Sharpless asymmetric epoxidation protocols were used to install several asymmetric centers, giving the cyclization precursor **14**. An intramolecular epoxide-ring opening gave the required oxalane ring (**15**).

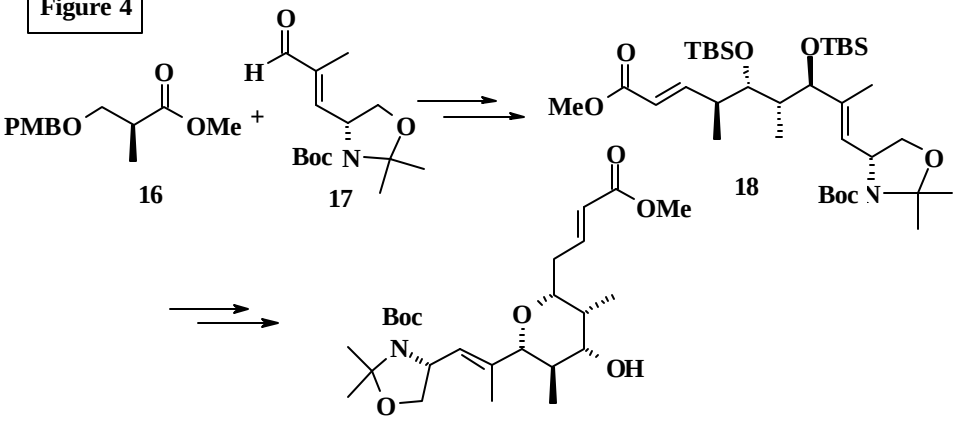
Figure 3



13 **14** **15**

Similarly Forsyth et al. *have reported*[15] *a synthesis of of C18-C30 core of the phorboxazole by constructing an alicyclic acrylate using Peterson's (*E*)-enol borinate aldol methodology followed by an intramolecular hetero-Michael addition to form the central pyran ring of the natural product.*

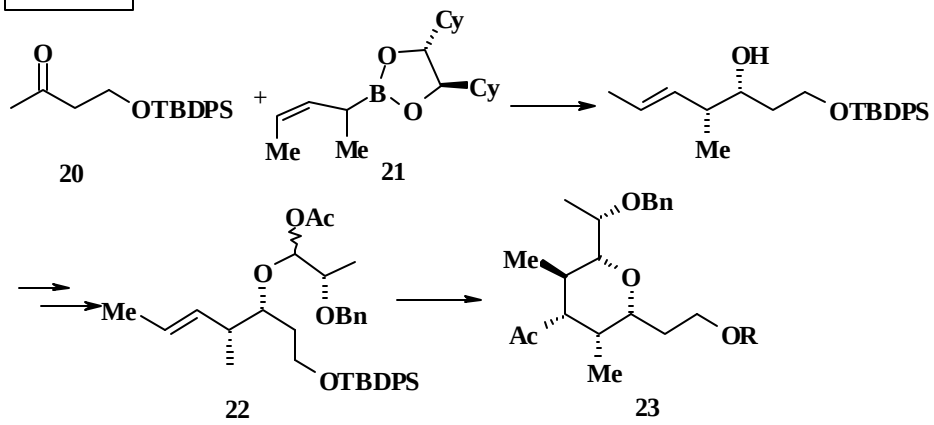
Figure 4



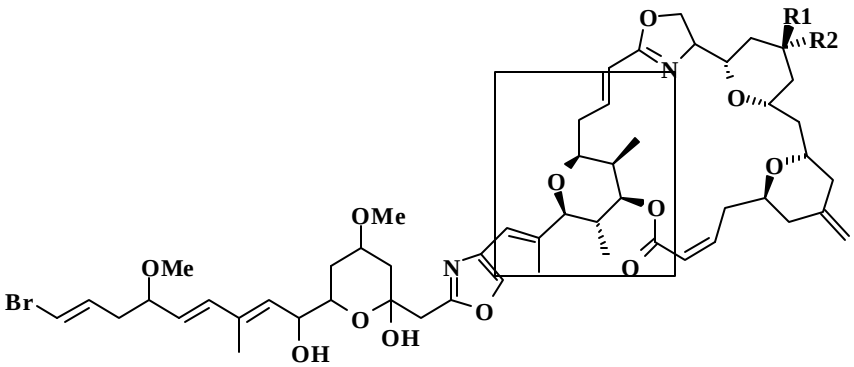
16 **17** **18** **19**

Recently Rychnovsky et al. *have reported*[16] *a synthesis of the C_{20}- C_{27} fragment by BF_3: Et_2O catalysed Prince cyclization as the key step for the cyclization. The cyclization precursor* ***22*** *was synthesised by coupling aldehyde* ***20*** *with Hoffman's optically pure (*Z*)-pentenyl boronate* ***21****, followed by coupling with* O*-benzyl S-lactic acid and reductive alkylation. Compound 22 when treated with 10mol % of Lewis acid and with 5 equivalents of AcOH gave the desired tetrahydropyran* ***23*** *in 52 % yield.*

Figure 5


O
OTBDPS
20
+
Cy
O
B
O
Cy
Me
Me
21
OH
OTBDPS
Me
OAc
O
OBn
Me
OTBDPS
22
OBn
Me
O
Ac
OR
Me
23

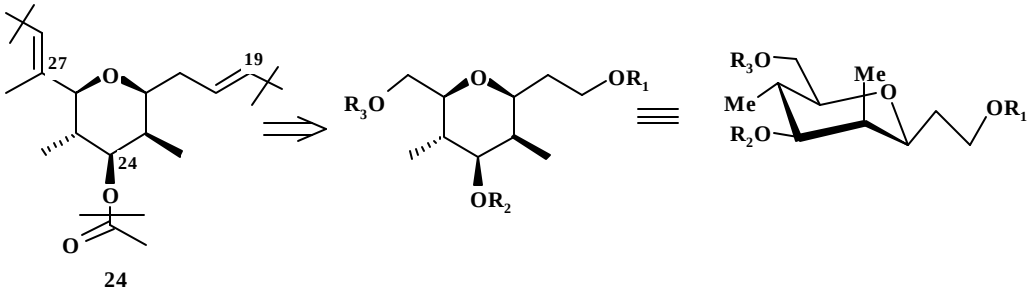
Phorboxazoles A and B (1 and 2) are the recently described marine natural products bearing an unprecedented array of structural features and phenomenal levels of cytotoxic activity.[9] Initially the relative configuration of the confirmationally rigid C_1-C_{26} macrolide portion, as well as the C_{33}-C_{35} oxane ring of the phorboxazole has been assigned by Searle and Molinski, on the basis of extensive NMR studies, but considerable stereochemical ambiguity remained.[9] Later the absolute stereo cheimistry was established. As a part of our



1 R_1 = OH, R_2 = H
2 R_1 = H, R_2 = OH

programme directed at developing a total synthesis of phorboxazoles, we have attempted an enantioselective synthesis of stereo chemically dense central core spanning carbons C_{19}-C_{27} of these natural products.

Figure 6

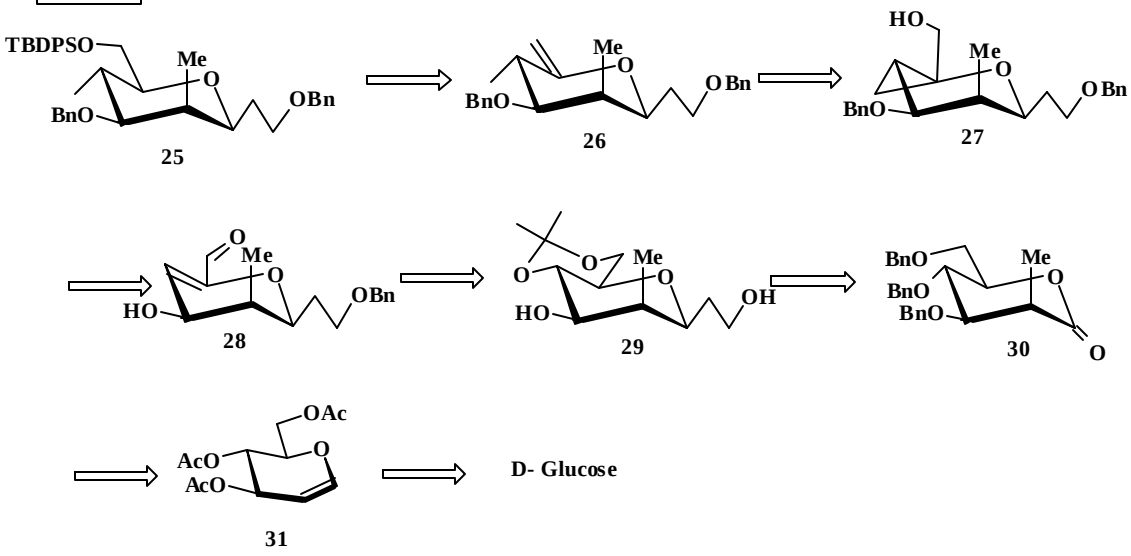


24

The C_{19}-C_{27} fragment of phorboxazoles consists of five chiral centers. The structural arrangement of the pyran ring is very much similar to pyranose sugar with D-

manno configuration. While planning the synthesis, a chiral pool approach was considered. The antithetic analysis of the target compound **24** was shown in the scheme 1. As per the antithetic analysis showed in scheme 1, synthesis can be initiated with easily and cheaply available D-glucose. Synthesis of the other isomer requires costly L-sugar and so once achieved, a similar sequence can be executed on the L-sugar for the synthesis of other isomer. A careful observation of the precursor **25** revealed the presence of the two-methyl groups at C-2 and C-4. We planned to execute a strategy that was developed in our

Scheme 1



laboratory for the construction of methyl at C-4, which involved stereoselective synthesis of 4,5 cyclopropanated sugar unit followed by radical mediated reductive ring opening to get 4-C-deoxy-4-C-methyl-5,6-exomethylene compound which could give the required intermediate after hydroboration and oxidation.[17]

As per the retero synthetic plan, our first objective was installation of C_2 methyl group. This was achieved by following the Heathcock's protocol of Hg(II) salt mediated ring opening of 1,2 cyclopropanated sugar.[36] Cyclopropanated sugars forms an important class of compounds, which are gaining lot of importance as chiral synthons[18], in particular a methyl group can be installed in the required orientation by stereoselective construction

and opening of cyclopropane. Therefore, before going into the synthesis, it is pertinent to look into some of these cyclopropanated sugars, their methods of preparation and application to organic synthesis.

Cyclopropanated sugars belong to the class of doubly branched carbohydrate derivatives. Their potential as useful intermediates in the synthesis of branched chain sugars and natural products has not been fully explored, as there are only few reports on their synthesis.

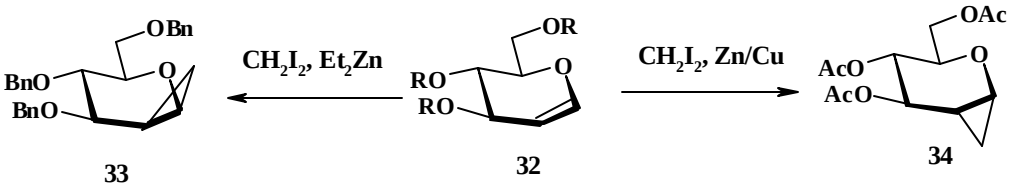
The three commonly used methods for cyclopropanation are the Simmons-Smith reaction,[19] transition metal catalyzed decomposition of diazo compounds[20] and dichlorocarbene method.[21]

Although there could be many types of cyclopropanated sugars, 1,2 cyclopropanated sugars are the most common. There are few reports on 2,3 cyclopropanated sugars. Fraser-Reid *et al*. have reported the preparation of diasteromeric 1,2-cyclopropanated sugars by insertion of carbon generated from ethyl diazoacetate. Nagarajan *et al*. have reported the synthesis of both forms of cyclopropanated sugars starting from glycals using (i) Simmons-Smith reaction and (ii) dichlorocarbene addition followed by dehalogenation.[22]

Cyclopropanation using Simmons-Smith reaction:

The Simmons-Smith reaction is an effective means of cyclopropanation for converting alkenes to cyclopropanes by use of diiodomethane and a zinc/ copper(I) chloride. It occurs by transfer of methylene group from the organometallic reagent and can occur in a stereoselective manner with allylic alcohols. An alternative method is the Furukawa modification,[23] where diethylzinc is used instead of the metallic couple. This modification is more reproducible and especially convenient on carbohydrates (Figure 7).

Figure 7



33 **32** **34**

At present a wide variety of protected glycols (**32**) have been cyclopropanated using this strategy and excellent yields and selectivities were observed. Efficiency of Furukawa's modification on glycals have been demonstrated with the formation of cyclopropanes, where yields up to 96 % and diastereoselectivities of >250:1 were obtained. Nagarajan and co-workers used acetyl chloride as an activator for cyclopropanation of several benzylated glycal systems, with this modification they reported greater than 80 % yield and formation of a single isomer **33**.[22] An unexpected product was reported by Lorica and co-workers, when attempted on triacetyl protected glucal, which gave α-cyclopropanated derivative **34** in 38 % yield.[24] Thus it is clear that protecting groups play a critical role during stereoselective cyclopropanation.

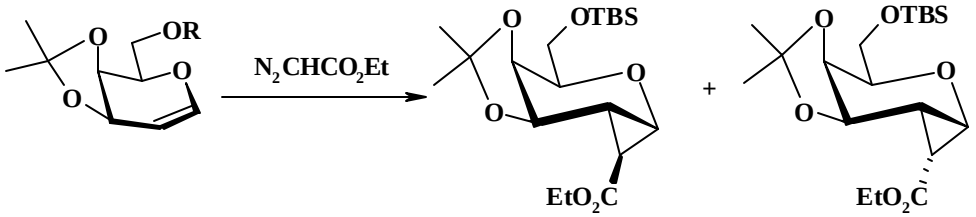
Cyclopropanation of 2,3- and 4,5-unsaturated carbohydrates has also been reported. For example, Fraser-Reid and co-workers have reported the syntheses of either isomer from a 2,3-unsaturated carbohydrate using Simmons-Smith method.[25]

Finally, only one example of 4,5 cyclopropanated sugar was reported by Gurjar *et al*[17] Synthesis of cyclopropane was performed by Furukawa's modification providing a mixture of diastereomers in a combined yield of 74 %. The diastereoselectivity of the compound was improved by switching the protecting groups from diacetates to the acetonide which gave the exclusive isomer, presumably by complexation of Zn to the acetonide oxygen.

Cyclopropanation using diazo compounds:

The initial examples of diazo-cyclopropanation of sugars were on triacetyl glucals, but suffered form the poor yields and selectivity problems. Recent studies have improved the yields and selectivity of cyclopropanation. Initially Fraser-Reid have reported the cyclopropanation using ethyl diazoacetate, but with poor selectivities (Figure 8).[26] *Van Boom and coworkers have studied the cyclopropanation of several furanose and pyranose*

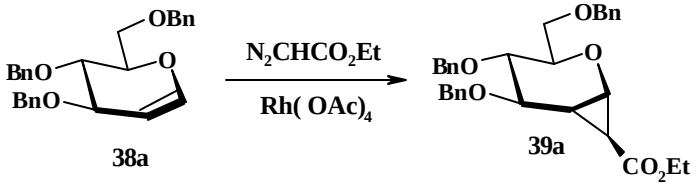
Figure 8



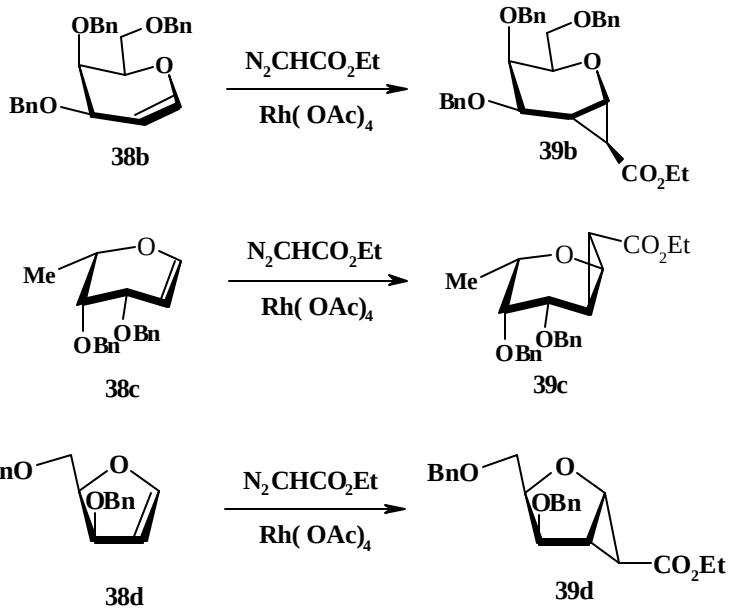
35 **36** **37**

and disaccharide systems. They observed that the use of transition metal catalysts and bulky substituents helped in achieving higher yields and selectivities.[27] Highest conversion was obtained with $Rh(OAc)_2$ (Figure 9). Henry and Fraser-Reid found that use of EDA and 5 equivalants of Cu(0) gave 90 % yield and 3.3:1 diastereoselectivity during cyclopropanation.[26]

Figure 9

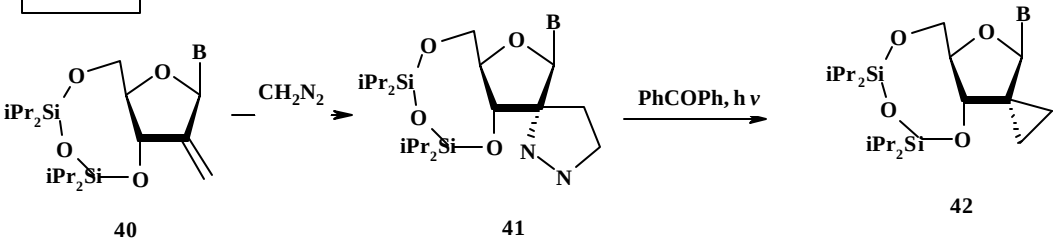


38a **39a**



A cyclopropanation using CH_2N_2 has been reported by Samano *et al.*[28] Simmons-Smith cyclopropanation failed to produce the required spiro cyclopropyl nucleosides **42**, however treatment of CH_2N_2 in ether for 48 h gave the spiropyrazoline **41** in 92 % yield with >90% de. Subsequent benzophenone sensitized photolysis provided the spirocyclopr-

Figure 10



opane in 92 % yield (Figure 10).

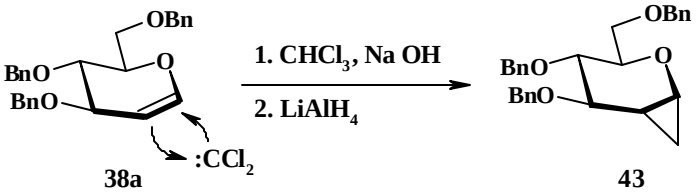
Cyclopropanation using dichlorocarbenes:

Another alternate route for cyclopropanation is the addition of dichlorocarbenes to glycals. Like diazocyclopropanation this is also sterically directed and is traditionally carried out in $CHCl_3$, NaOH. $LiAlH_4$ reduction of these compounds gave the de-halogenated cyclopropanes. Nagarajan *et al.* have reported the synthesis of unsubstituted

methylene cyclopropanes **43** using dichlorocarbene and phase transfer catalyst, which has the stereochemistry opposite to that of Simmons-smith cyclopropanation (Figure 11).[29]

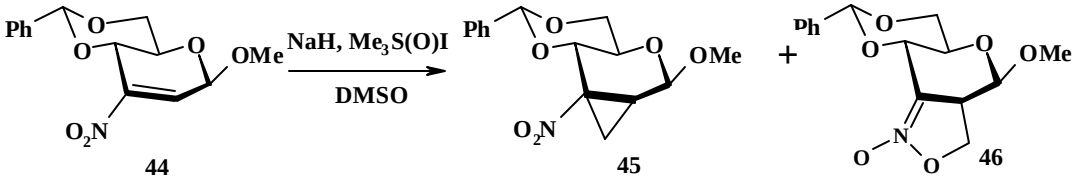
They have extended the method for the preparation of dibromo cyclopropanes also.

Figure 11



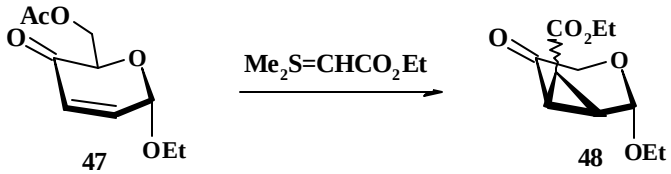
Use of sulfur ylides for cyclopropanation is also reported. There are only few reports on these, as it needs number of transformations for obtaining the required Michael acceptor. However, cyclopropanation of 2,3-unsaturated pyranosides containing vinyl nitro group **44** was achieved using trimethyl sulfoxonium iodide-NaH, which produced the desired nitro cyclopropane **45** and minor amount of isoxazoline N-oxide **46** (Figure 12).[30]

Figure 12



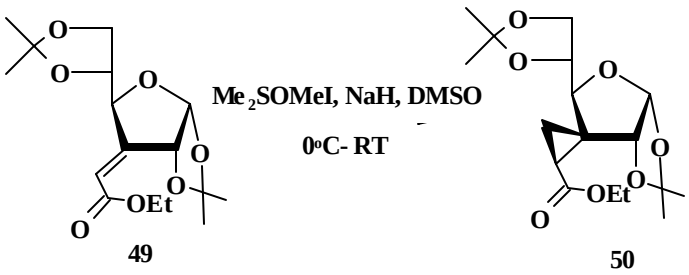
Later, Fraser-Reid *et al.* have reported[31] the formation of cyclopropyl derivatives using similar strategy. The stereochemistry found was observed to be originating with steric factors (Figure 13).

Figure 13



Gurjar *et al.* have reported the synthesis of spiro cyclopropanes using sulfoxonium ylides (Figure 14).[32] Several ulose derivatives were prepared and treated with PPh_3=$CHCO_2Et$ to give the α,β-unsaturated ester **49**. This on treatment with $(CH_3)_2S(O)MeI$, gave the cyclopropane ester **50** with varying diasteroselectivity. The stereochemistry was observed to be dependant on steric factors.

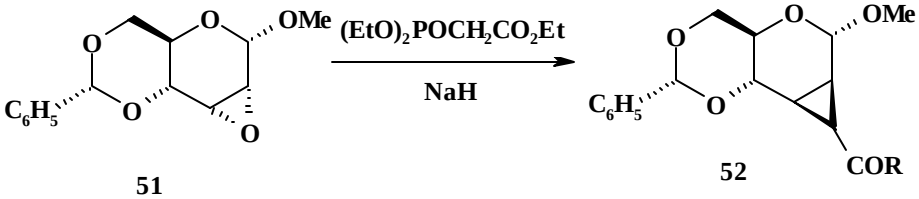
Figure 14



49 **50**

Several other methods were reported for the synthesis of cyclopropanes. For example, a synthesis of 2,3 cyclopropanated sugars was reported starting from the epoxide derivative.

Figure 15

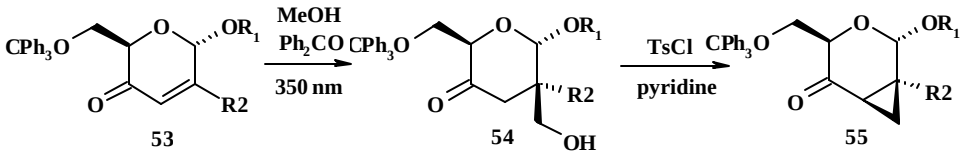


51 **52**

Reckendorf and Kamparth-Scholtz have treated the epoxide **51** with ethyldiethoxy phsophorylacetate and NaH for 3 days. Formation of cyclopropane product **52** was accomplished and was separated after hydrolysis to provide 46 % of the cyclopropyl ester (Figure 15).[33]

Fraser-Reid *et al.* have developed another method[34] by using bezophenone sensitized Michael addition of MeOH on to unsaturated sugars **53** to produce hydroxy methyl derivative **54**, which on treatment with TsCl and pyridine afforded the required cyclopropane **55** (Figure 16).

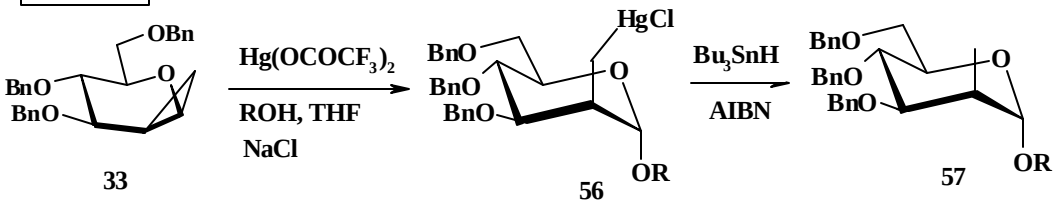
Figure 16



Reactions of cyclopropanes

Cyclopropanated carbohydrates are ideally suited for electrophilic ring opening. The use of Hg (II) ions to catalyze the ring opening of cyclopropanes is well documented. Heathcock used this strategy for the synthesis of 2-C-methyl-D-glucal derivatives.[35,36]

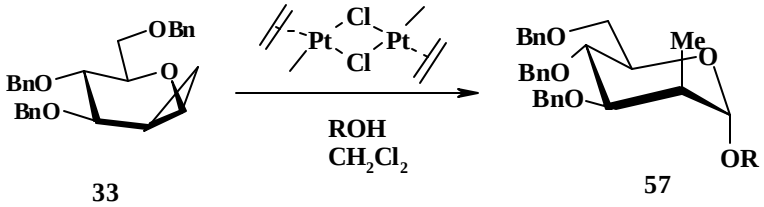
Figure 17



Treatment of 1,2 cyclopropanated glycals, with $Hg(OCOCF_3)_2$ in presence of THF-H_2O gave **56**, which on reductive cleavage of Hg using tributyl tin hydride provided the 2-C-methyl compound **57** with the 4:1 (α:β) selectivity at anomeric position, but could be increased to 10:1 when methanol was used (Figure 17).

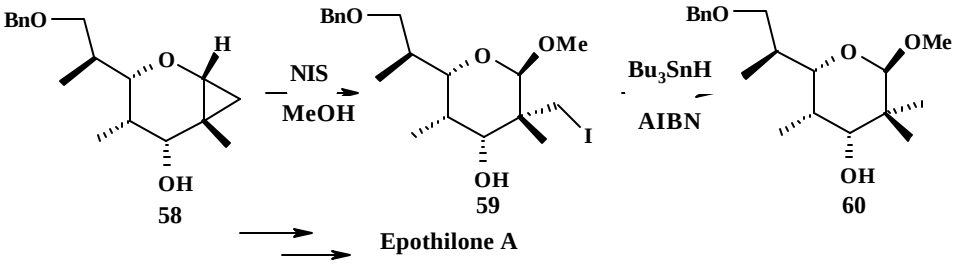
In another example, Madsen have developed a metal induced ring opening using catalytic amounts of platinum complex, Zeise's dimmer.[37] The ring opening was achieved with a variety of alcohols to give 2-C branched glycosides (Figure 18). Electron rich phenols also were used for the synthesis of glycosyl arene compounds in modest yield.

Figure 18



Another strategy for oxidative ring opening of cyclopropanes was reported by Danishefsky and coworkers. This method of cyclopropane opening of ***58*** *using NIS to provide C, C-gem-dimethyl derivative* ***60****, which was used in the synthesis of epothilones A and B (Figure 19).*[38]

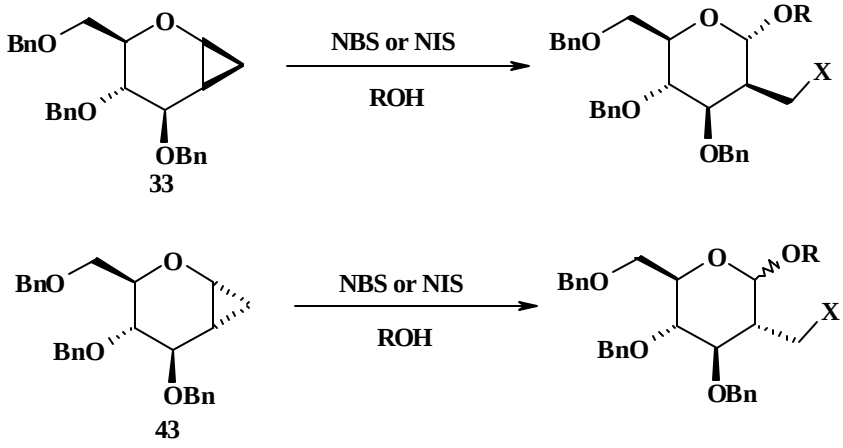
Figure 19



Also both Ley[39] *and Nagarajan*[40] *have reported the opening of cyclopropanes using NBS and NIS. Stereospecific ring opening was observed for the â- anomer, where as the corresponding á-cyclopropane compound gave mixture of anomers.*

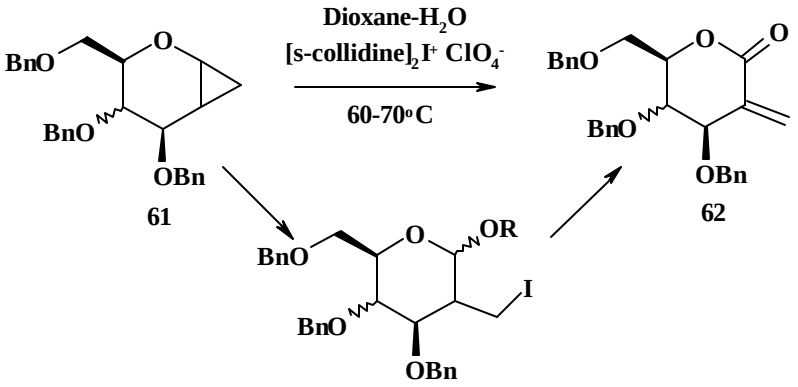
This was attributed to the S_N2 ring opening in case of more hindered â-cyclopropyl compound producing more favored á-glycoside, where as in case of á-isomer reaction presumably involved was S_N1 type path way, because of less steric hindrance (Figure 20).

Figure 20



Several other variations of this ring opening strategy have been reported. For example, Nagarajan et al. *reported*[40] *the reaction of cyclopropanated sugar* ***61*** *with*

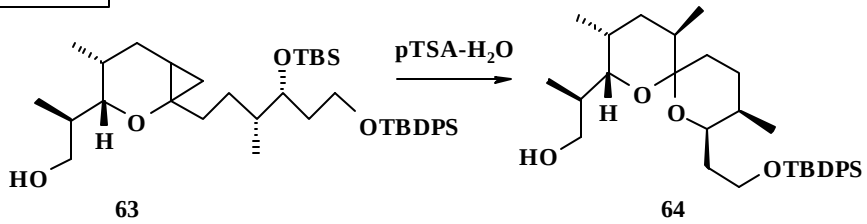
Figure 21



Iodonium di-(S-collidine) perchlorate in dioxane-water lead to the formation of a-methylidene-d-valerolactone ***62****. (Figure 21).*

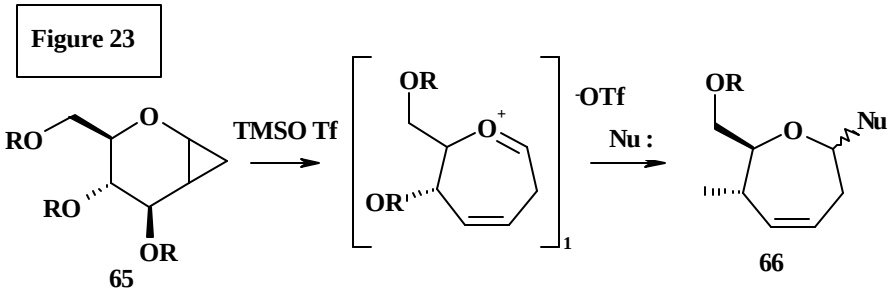
As a part of the total synthesis (-) A23187 (calcimycin), Beckman and co-workers reported[41] *the ring opening of* ***63*** *and intramolecular attack to form the spiro acetal* ***64*** *in 55 % yield (Figure 22).*

Figure 22



In the mid nineties Hoborg and co-workers have investigated for the ring expansion products of the cyclopropanated sugars.[42] Treatment of the cyclopropanes **65** with trimetyl-

Figure 23

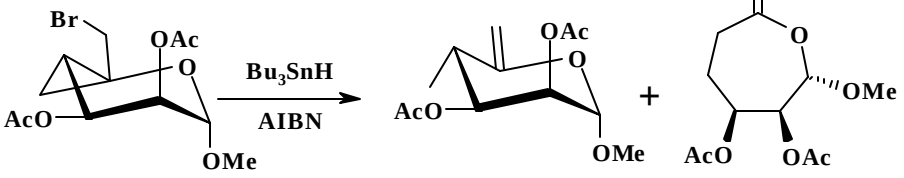


sillyl triflate in the presence of external nucleophile gave the ring expansion products **66** (Figure 23).

Gurjar *et al.* have reported first synthesis of 4,5 cyclopropanted sugars and its application of its bromo derivative **67** in the synthesis of C_7-C_{17} segment of Lasonolide A.

They have reported the ring opening (**68**) and ring expansion (**69**) products when treated with Bu_3SnH and AIBN in refluxing toluene (Figure 24).[17]

Figure 24

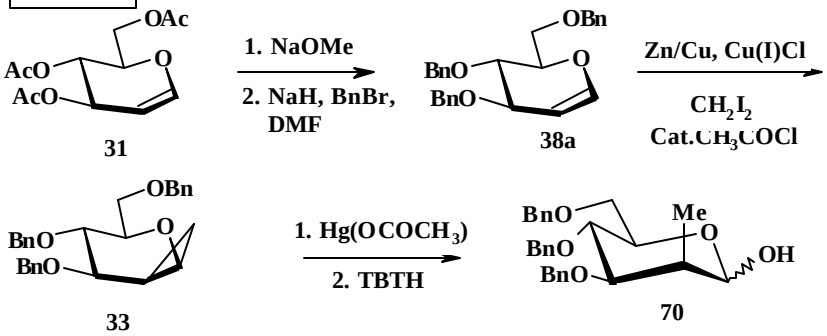


67 **68** **69**

From this discussion, it is clear that there could be many different cyclopropanated sugars. But there is only one report by our group on the applications of 4,5 cyclopropanated sugar derivatives. Thus, we thought of exploring the preparation and application of these derivatives in organic synthesis and attempted the synthesis of C_{19}-C_{27} fragment of phorboxazole.

As mentioned earlier, the synthesis was started with tri-*O*-acetylglucal (**31**), which was synthesised starting from D-Glucose. [43] Compound **31** on NaOMe catalysed deacetyla-

Scheme 2



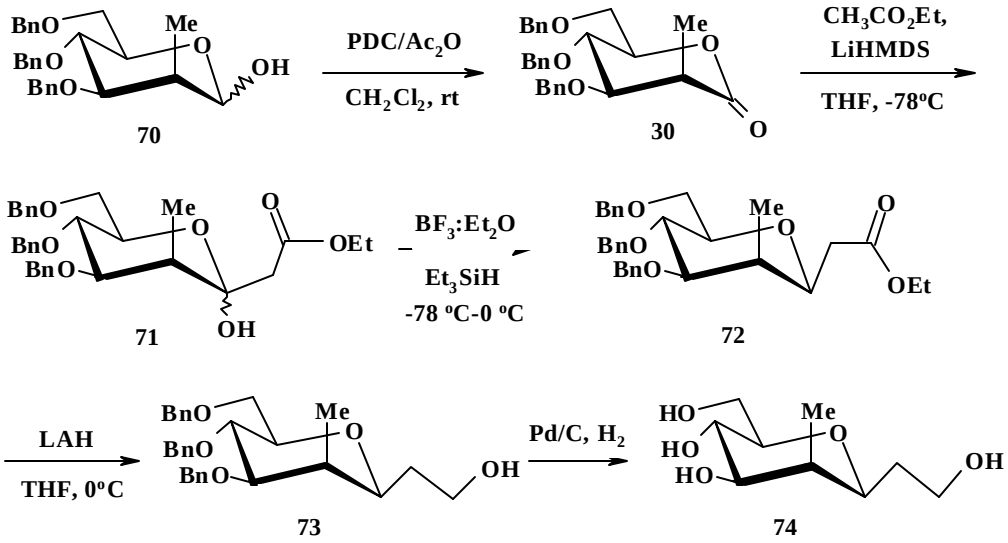
31 **38a**

33 **70**

tion followed by treatment with NaH-BnBr gave the tri-*O*-benzyl derivative **38a**. Compound **38a** on treatment with Zn-CH_2I_2-Cu(I)Cl and CH_3COCl as promoter[29] in dry ether gave the β-cyclopropane derivative **33** with high diastereoselectivity. The optical rotation and NMR data was found to be comparable with the reported values.[36] Treatment

of **33** with $Hg(OCOCF_3)_2$ in THF-H_2O gave the organomercury intermediate which was subjected to the exposure of Bu_3SnH to afford the 2-C-methyl derivative **70**. The demercuration reaction could also be performed with $NaBH_4$-alcoholic KOH with satisfactory yield. The use of $Hg(OAc)_2$ for the ring opening of cyclopropane was found to give less yield with long reaction time (3-4 h).[35] Having secured the installation of the C-2 methyl, we diverted our attention to introduce the C- side chain at C-1 position. Compound **70** was oxidized with PDC and Ac_2O in CH_2Cl_2 to give the lactone **30**. The formation of lactone was confirmed by ^{1}H-NMR analysis. Treatment of **30** with $LiCH_2CO_2Et$ (generated from LiHMDS and ethyl acetate at – 78 °C in THF) gave the corresponding product **71**.

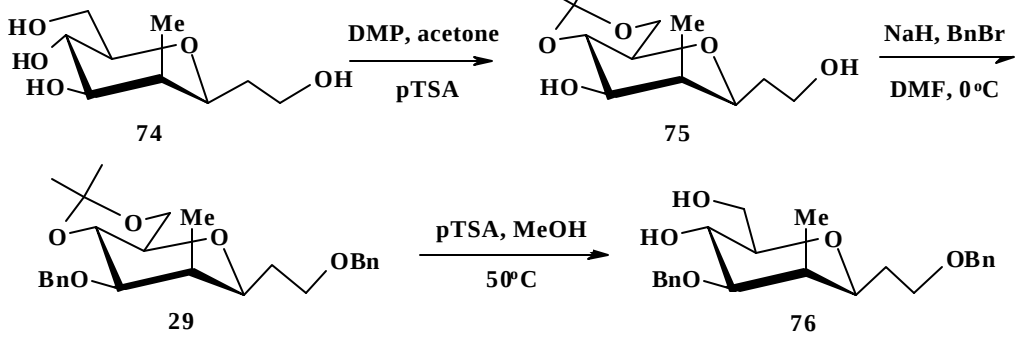
Scheme 3



In the ^{1}H-NMR spectrum of compound **71** the characteristic signals due to newly added CH_2CO_2Et group were clearly observed. Particularly the methylene group showed two sets of doublets at δ 2.46 and 2.83. Treatment of **71**, with Et_3SiH and BF_3: Et_2O gave the corresponding deoxy derivative **72**. Literature reports suggested that the reduction step exclusively leads to the formation of â-glycosides and our observation was agreeable.[44] For example, in the ^{1}H-NMR spectrum the methylene signals were observed as doublet of

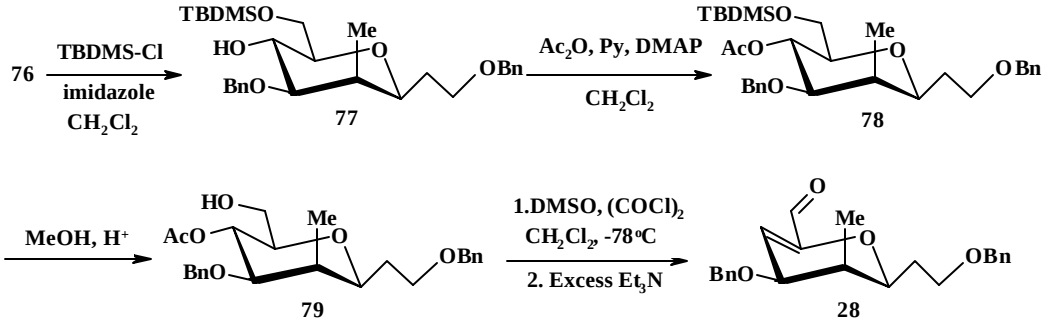
doublets at δ 2.41 (J = 8.8, 15.7 Hz) and 2.69 (J = 8.8, 15.7 Hz) while all other protons resonated at the expected chemical shifts.

Scheme 4



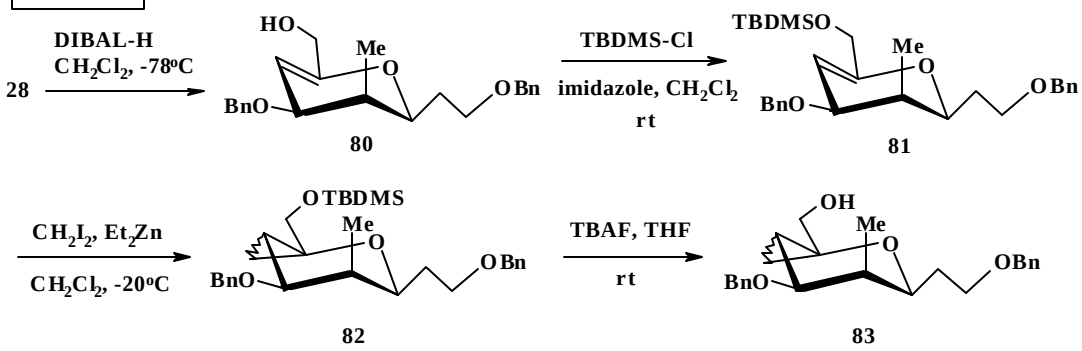
Compound **72** was reduced with LAH to the corresponding alcohol **73**, which was debenzylated using Pd/C to give the tetrol **74**(Scheme 3). In order to protect the hydroxy group at C-3 and side chain, compound **74** was treated with dimethoxy propane (DMP)-acetone and catalytic amount of *p*TSA to give the 4,6-*O*-isopropylidine derivative **75,** which when treated with NaH-BnBr in dry DMF afforded the dibenzyl derivative **29.** The ^{1}H-NMR spectrum of **29** confirmed the presence of two *O*-benzyl groups. The isopropylidene group of **29** was hydrolysed with *p*TSA, MeOH (Scheme 4). Compound **76** was selectively protected at *O*-6 with *tert*-butyldimethylsilyl chloride, imidazole in CH_2Cl_2 to give the 6-silyloxy derivative **77**. The C-4 hydroxy group of **77** was acetylated using Ac_2O-pyridine in presence of catalytic amount of DMAP to give **78**. The *tert*-butyldimethylsilyl group of **78** was deprotected using methanolic HCl at 0 °C and then the resulting compound **79** was oxidized under Swern reaction conditions using DMSO and oxalyl chloride in CH_2Cl_2 at −78 °C. Treatment with excess of Et_3N effected the â-elemination giving rise to the á,â-unsaturated aldehyde **28** (Scheme 5). Reduction of **28** with DIBAL-H at −78 °C for 30 min. afforded the corresponding allylic alcohol **80**. The ^{1}H-NMR spectrum of **80** revealed the presence of olefinic proton at δ 4.77 as a singlet.

Scheme 5



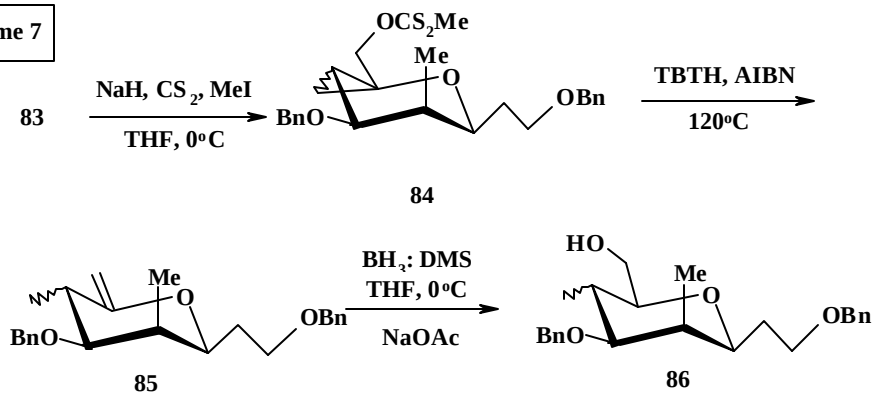
A downfield shift was observed for the protons, H-6 and H-6` and a broad singlet at δ 2.29 was attributed to the hydroxy group. Compound **80** was treated with *tert*-butyl dimethylchlorosilane and imidazole in CH_2Cl_2 to afford **81**, which when treated with Et_2Zn/CH_2I_2 gave a single diastereomer of the cyclopropane (**82)**, whose geometry could not be established at this stage. Our next concern was to produce the xanthate derivative **84** as radical precursor. Consequently, compound **82** was treated with $Bu_4N^+F^-$ in THF to cleave the TBDMS derivative (Scheme 6). and then the free OH group was subjected to the treatment of NaH, CS_2, MeI to produce the xanthate **84**. In the ^{1}H-NMR spectrum of **84**, the characteristic signal due to S-methyl group was located at δ 2.52 while peaks corresponding to H-6 and H-6` showed a down field shift as expected. Compound **84** was

Scheme 6



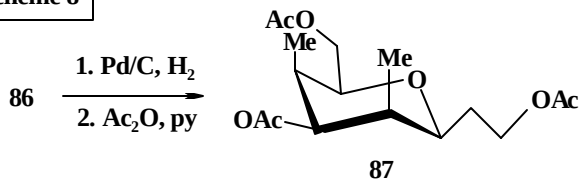
treated with Bu_3SnH, AIBN, in toluene at 120 °C. It was found appropriate to couple the

Scheme 7



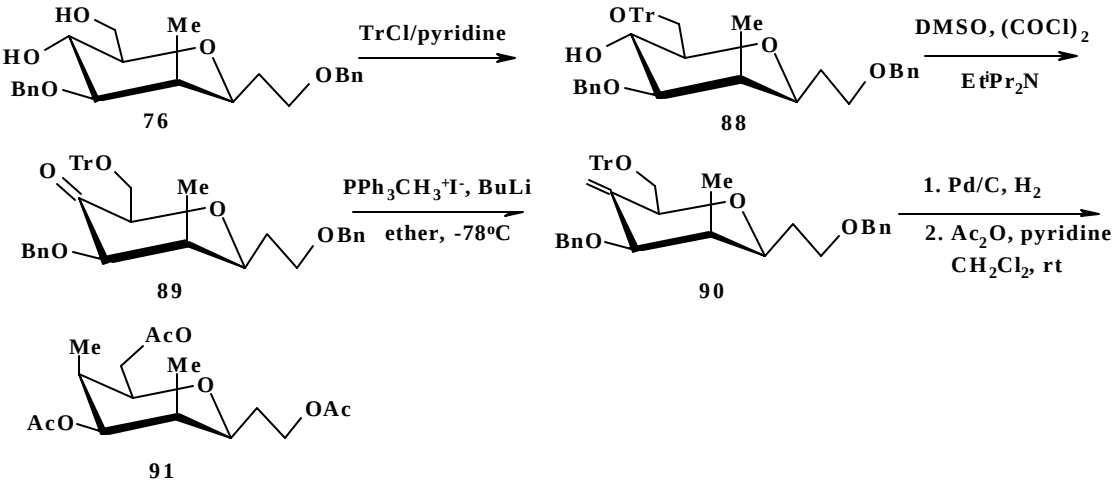
hydroboration-oxidation step and therefore the crude **85** was treated with BH_3: DMS and the major compound **86** was isolated by chromatographic purification(Scheme 7). Now our next aim was to establish the stereochemistry at C-4 and C-5. For this the splitting pattern of H-3 was crucial and it was felt necessary to produce the triacetate derivative **87** because acetyl groups shift the ring protons downfield by at least 1 ppm and then perhaps we could distinctively analyse resonance due to H-3 properly. To achieve this **86** was hydrogenated with Pd/C in MeOH followed by exhaustive acetylation using Ac_2O-pyridine (Scheme 8). In the ^{1}H-NMR spectrum of **87**, three singlets appeared at δ 2.06, 2.09 and 2.16 suggesting the presence of three acetyl groups. In addition, a doublet at δ 0.96 (6H, J = 7.3 Hz) was attributed to two methyl groups at C-2 and C-4. The signal due to H-1 was located as a doublet of triplet at δ 3.55. H-3 appeared at δ 5.0 as a triplet with coupling constant, J = 5.3 Hz. From the coupling constant value we argued that since H-2/H-3 bear equatorial-axial relationship, the relationship between H-3/H-4 must be axial-equatorial. This means that the methyl at C-4 was in axial configuration. The installed methyl group at C-4 was not what we desired and therefore there was not much choice left but to change our strategy for introducing C-4 methyl with equatorial configuration. This was planned by conventional olefination reduction protocol.[45]

Scheme 8



Accordingly, the diol **76** was treated with TrCl-pyridine to give the corresponding 6-*O*-trityl derivative **88**. The free OH group at C-4 was oxidized to the corresponding 4-ulose derivative **89** under Swern reaction conditions and was subjected to wittig reaction with $PPh_3{=}CH_2$ to provide the C-4 *exo*-methylene product **90**.[46] In the ^{1}H- NMR spectrum of **90**, signals due to exomethylene protons appeared at δ 4.83 and 5.23 as broad singlets. Finally reduction of double bond in **90** was carried out in presence of Pd-C. This step also deprotected the trityl protecting group. The resulting triol was acetylated to give the triacetate derivative. This spectrum was carefully compared to the ^{1}H-NMR spectrum of the previously prepared product **87** and found to identical and superimposable. The presence of a triplet at δ 5.0 with J = 5.3 Hz was clearly observed.

Scheme 9



From the above comparison of spectra, we assigned the structure as shown in **91**. It is pertinent to mention that the reduction of **90** occurred from the bottom face due to the steric factors posed by the methyl group present at C-2.

Due to these constrains in fixing the methyl group at C-4 by both the approaches, we decided to stop further studies.

Experimental Section

3,4,6-Tri-*O*-benzyl-2-deoxy-2-*C*-methyl-D-mannose (70):

To a solution of **33** (10.0 g, 23.1 mmol) in THF: H_2O (5: 1) (125 mL) was added mercuric trifloroacetate (19.8 g, 46.2 mmol) and stirred for 10 min at rt. A saturated solution of NaCl (100 mL) was added. After 15 min. CH_2Cl_2 was introduced and the two layers were separated. Organic phase was washed with 2 M NaOH, 2 M HCl, water, dried (Na_2SO_4) and concentrated. The residue was taken up in THF (150 mL), and Bu_3SnH (10.1 mL, 34.6 mmol) and AIBN (0.1 g) was added. After 30 min, 15 % KF solution and ether were introduced. The solid was filtered and organic layer separated and washed with brine, dried (Na_2SO_4) and concentrated. The residue was purified on silica gel using ethyl acetate and petroleum ether (3: 7) to give the lactol **70** (8.0 g, 78 %) as a syrup.

$[\alpha]_D$ = 22° (*c* 0.9, $CHCl_3$) Lit[36] $[á]_D$ = 24° (*c* 1.0, CH_2Cl_2)

3,4,6-Tri-*O*-benzyl-2-deoxy-2-*C*-methyl-D-mannonolactone (30):

A mixture containing **70** (8.0 g, 18.0 mol), PDC (5.4 g, 27mmol) and Ac_2O (1.7 mL, 18.0 mmol) in dry CH_2Cl_2 (200 mL) was stirred at rt for 3 h. Solvent was removed, Celite (20 g) and ether were added. The slurry was filtered through a short plug of silica gel and the residue after concentration was further loaded on silica gel and eluted with ethyl acetate and light petroleum (1: 3) to afford lactone **30** (6.2 g, 77 %) as a syrup.

$[\alpha]_D$ = +64° (*c* 1.5, $CHCl_3$)

^{1}H-NMR (200 MHz, $CDCl_3$) : (1.27, d, 3H, J = 7.6 Hz), 2.87 (ddd, 1H, J = 3.6, 4.1 Hz), 3.63-3.76 (m, 3H), 3.89 (d, 1H, J = 5.9 Hz), 4.22-4.34 (m, 1H), 4.36-4.64 (m, 6H), 7.13-7.40 (m, 15H).

FABMS m/z: 449 (M^++1)

***C*-Carboethoxymethyl 3,4,6-tri-*O*-benzyl-2-deoxy-2-*C*-methyl-á,â-D-mannose (71):**

Alcohol free ethyl acetate (1.63 mL, 16.7 mmol) was cooled to –78 °C and then a 0.8 M solution of Li-HMDS (20.9 mL, 16.7 mmol) was introduced and stirred for 30 min.

To a solution of lactone **30** (6.2 g, 13.9 mmol) in freshly distilled THF (100 mL) at –78 °C, above prepared solution of $LiCH_2CO_2Et$ in THF was added slowly. The reaction mixture was stirred for further two hours, quenched with saturated solution of NH_4Cl and warmed to room temperature. The reaction mixture was washed with cold dilute HCl (5 %), saturated Na or K bicarbonate, brine and extracted with CH_2Cl_2. Combined CH_2Cl_2 layer was dried (Na_2SO_4), concentrated and the residue was purified on silica gel using ethyl acetate and light petroleum (1: 3) as eluent afforded **71** (5.8 g, 77 %).

$[\alpha]_D$= +22.0 (*c* 1.05, $CHCl_3$)

^{1}H-NMR (200 MHz, $CDCl_3$) : 1.06 (d, 3H, J = 8.14 Hz), 1.31 (t, 3H, J = 6.9 Hz), 2.33 (m, 1H), 2.46 (d, 1H, J = 16.7 Hz), 2.83 (d, 1H, J = 16.7 Hz), 3.54-3.81 (m, 3H), 3.95 (d, 1H, J = 9.04 Hz), 4.14-4.30 (m, 3H), 4.40-4.70 (m, 4H), 4.85 (d, 1H, J = 11.3 Hz) 5.36 (s, 1H), 7.13-7.31 (m, 15H).

EIMS m/z: 443 $(M\text{-}Bn)^+$

C-Carboethoxymethyl 3,4,6-tri-*O*-benzyl-1,2-dideoxy-2-*C*-methyl-â-D-mannopyranoside (72):

To a solution of **71** (5.6 g, 10.5 mmol) in dry CH_2Cl_2 (75 mL) at –78 °C were added triethylsilane (5.1 mL, 31.5 mmol) and BF_3: Et_2O (4.0 mL, 31.5 mmol).After stirring for a period of 3 h the reaction mixture was quenched by addition of brine solution (20 mL), CH_2Cl_2 layer was separated, dried over Na_2SO_4 and concentrated. The residue was purified on silica gel using EtOAc and light petroleum (1: 4) to give **72** (4.1 g, 76 %).

^{1}H-NMR (200 MHz, $CDCl_3$) : 1.02 (d, 3H, J = 7.9 Hz), 1.27 (t, 3H, J = 7.3 Hz), 2.23 (m, 1H), 2.41 (dd, 1H, J = 8.8, 15.7 Hz), 2.69 (dd, 1H, J

= 8.8, 15.7 Hz), 3.38 (br. d, 1H, J = 8.0 Hz), 3.56-3.73 (m, 3H), 3.9 (t, 1H, J = 5.4 Hz), 4.13 (q, 2H, J = 8.0 Hz), 4.41-4.72 (m, 6H), 4.87 (d, 1H, J = 11.2 Hz), 7.09-7.46 (m, 15H).

EIMS m/z: 427 $(M-91)^+$

Anal. Calcd. for $C_{32}H_{38}O_5$: C,76.49; H, 7.56. Found: C, 76.61; H, 7.69.

***C*-(2-Hydroxyethyl) 3,4,6-tri-*O*-benzyl-1,2-dideoxy-2-*C*-methyl-â-D-mannopyranoside (73):**

To a solution of **72** (4.0 g, 7.7 mmol) in distilled THF (50 mL) at 0 °C was added in parts $LiAlH_4$ (0.3 g) and stirred for 3 h at rt. The reaction mixture was cooled in ice water and excess $LiAlH_4$ quenched with ethyl acetate and with saturated Na_2SO_4. The solid separated was filtered through celite and washed with ethyl acetate. The combined filtrate fraction was dried over Na_2SO_4 and concentrated. The crude obtained was purified on silica gel using ethyl acetate and light petroleum (1: 3) to give **73** (3.1 g, 84 %).

$[\alpha]_D$ = +1.7° (*c* 1.1, $CHCl_3$)

^{1}H-NMR (200 MHz, $CDCl_3$) : 1.03 (d, 3H, J = 8.1 Hz), 1.41-2.2 (m, 3H,), 3.33-3.87 (m, 7H), 4.42-4.07 (m, 6H), 4.87 (d, 1H, J = 10.9 Hz), 7.07-7.42 (m, 15H).

EIMS m/z: 385 $(M-Bn)^+$

C-(2-Benzyloxyethyl) 3-*O*-benzyl-1,2-dideoxy-4,6-*O*-isopropylidene-2-*C*-methyl-â-D-mannopyranoside (29):

73 (3.3 g, 6.9 mmol), 10 % Pd/C (0.34 g, 5 mol %) in MeOH (30mL) was stirred under hydrogen atmosphere for 12 h. The catalyst was filtered through celite and washed with MeOH. Combined MeOH layer was concentrated, and codistilled with toluene to remove traces of any moisture. The residue, DMP, acetone (30 mL) and *p*TSA (catalytic) were stirred for 10 h. The reaction mixture was neutralized with Et_3N and concentrated. The residue was dissolved in DMF (15 mL) and was treated with NaH (0.42 g, 10.4 mmol), BnBr (1.3 mL, 10.4 mmol) for 1 h at rt. Excess NaH was quenched with ice-water and the reaction mixture was extracted with ether. The ether layer was dried over Na_2SO_4, concentrated and the residue was purified on silica gel using ethyl acetate and light petroleum (1: 20) to give **29** (1.9 g, 65 %) (over three steps).

$[\alpha]_D$ = -27° (*c* 1.0, $CHCl_3$)

^{1}H-NMR (200 MHz, $CDCl_3$) : 0.98 (d, 3H, J = 7 Hz), 1.40 (s, 3H), 1.43 (s, 3H), 1.55-1.83 (m, 2H), 2.05-2.13 (m, 1H), 3.09-3.20 (m, 1H), 3.40-3.55 (m, 3H), 3.60-3.82 (m, 4H), 4.47 (d, 2H, J = 3.2 Hz), 4.64 (d, 2H, J = 4.0 Hz), 7.20-7.38 (m, 10 H).

EIMS m/z: 295 (M^+-Bn)

Anal. Calcd. for $C_{26}H_{34}O_5$: C,73.23; H, 7.98. Found: C, 73.27; H, 8.01.

***C*-(2-Benzyloxyethyl) 3-*O*-benzyl-6-*O*-(*tert*-butyldimethylsilyl)-1,2-dideoxy-2-*C*-methyl-â-D-mannopyranoside (77):**

A solution of compound **29** (1.5 g, 3.5 mmol), *p*TSA (15mg) in MeOH (25 mL) was heated to 50 °C for 30 min., reaction neutralized with triethylamine, solvent removed and the residue, imidazole (0.26 g, 5.7 mmol) and TBDMS-Cl (0.52 g, 3.5 mmol) in dry

CH_2Cl_2 (20 mL) were stirred for 1 h, the residue was purified on silica gel using ethyl acetate and light petroleum (1: 9) to afford **77** (1.3 g, 93 %).

$[\alpha]_D$ = -43° (*c* 1.2, $CHCl_3$)

^{1}H-NMR (200 MHz, $CDCl_3$) : 0.05 (s, 3H), 0.09 (s, 3H), 0.83-0.99 (m, 12H), 1.60-1.68 (m, 1H), 1.78-1.87 (m, 1H), 2.02-2.14 (m, 1H), 3.10-3.12 (m, 1H), 3.42-3.82 (m, 7H), 4.41-4.55 (m, 3H), 4.64 (d, 1H, J = 12.4 Hz), 7.18-7.42 (m, 10H).

C-(2-Benzyloxyethyl)4-*O*-acetyl- 3-*O*-benzyl-6-*O*-(*tert*-butyldimethylsilyl)-1,2-dideoxy-2-*C*-methyl-â-D-mannopyranoside (78):

To a solution of compound **77** (1.3 g, 2.6 mmol) in CH_2Cl_2 (25 mL) at 0 °C was added Ac_2O (0.4 mL, 3.9 mmol), pyridine (0.42 mL, 5.2 mmol) and DMAP (20 mg). After stirring for 30 min. at rt, reaction mixture was quenched with water and extracted with CH_2Cl_2. Combined CH_2Cl_2 layer was dried over Na_2SO_4 and concentrated. The residue was purified on silica gel using ethyl acetate and petroleum ether (1: 10) to afford **78** (1.1 g, 85 %).

$[\alpha]_D$ = -33° (*c* 3.2, $CHCl_3$)

^{1}H-NMR (200 MHz, $CDCl_3$) : 0.03 (s, 6H), 0.88 (s, 9H), 0.96 (d, 3H, J = 7.1 Hz), 1.60-1.72 (m, 1H), 1.83-1.96 (m, 1H), 2.01 (s, 3H), 2.07-2.16 (m, 1H), 3.20-3.29 (m, 1H), 3.43-3.64 (m, 6H), 4.37 (d, 1H, J = 13.1 Hz), 4.48 (s, 2H), 4.62 (d, 1H, J = 13.1 Hz), 4.96 (t, 1H, J = 6.7 Hz), 7.20-7.39 (m, 10H).

Synthesis of aldehyde 28:

Compound **78** (1.1 g, 2.0 mmol) and 2 % methanolic HCl (15 mL) were stirred at 0 °C, concentrated to afford desilylated compound **79.** The solution of **79** (0.8 g, 1.9 mmol) was added to DMSO (0.5 mL, 5.7 mmol) and oxalyl chloride (0.25 mL, 2.9 mmol) in CH_2Cl_2 at –78 °C. and

stirred for 45 min. To the reaction mixture, Et_3N (2.5 mL. 22.8 mmol) was added and brought to room temperature. The CH_2Cl_2 layer was washed with water, separated, dried (Na_2SO_4) and concentrated below 20 °C. The crude aldehyde **28** (0.6 g) was used directly for the next reaction without purification.

Reduction of the aldehyde 28 to give 80 ((3S,4R,5R)-3,7-anhydro-1,5-di-*O*-benzyl-2,4,6-trideoxy-4-methyloct-6-enitol):

To a solution of **28** (0.6 g, 1.8 mmol) in CH_2Cl_2 (25 mL) at −78 °C under argon, a 2.0 M solution of DIBAL-H (1.34 mL, 2.7 mmol) was added dropwise, stirred for 1h. The reaction mixture was quenched with MeOH and saturated sodium-potassium tartarate solution. After 3 h the CH_2Cl_2 layer was separated, dried (Na_2SO_4) and concentrated and the residue was purified on silica gel using ethyl acetate and light petroleum (1: 3) to give **80** (0.4 g, 69 %) (over three steps).

$[\alpha]_D = +32^o$ (*c* 1.1, $CHCl_3$).

^{1}H-NMR (200 MHz, $CDCl_3$) : 0.92 (d, 3H, J = 7.2 Hz), 1.62-1.87 (m, 1H), 1.9-2.15 (m, 2H), 2.29 (s, 1H), 3.44-3.68 (m, 2H), 3.79-3.99 (s, 2H), 4.06-4.27 (m, 2H), 4.33-4.63 (m, 4H), 4.77 (s, 1H), 7.1- 7.4 (m, 10H).

Anal. Calcd. for $C_{23}H_{28}O_4$: C,75.00; H, 7.60. Found: C, 75.21; H, 7.49.

Synthesis of compound 81((3S,4R,5R)-3,7-anhydro-1,5-di-*O*-benzyl-2,4,6-trideoxy-8-*O*-(*tert*-butyldimethylsilyl)-4-methyloct-6-enitol):

To a solution of **80** (0.4 g, 1.1 mmol) in dry CH_2Cl_2 (10 mL) at 0 °C, was added imidazole (0.1 g, 2.2 mmol) and TBDMSCl (0.2 g, 1.3 mmol) were added and stirred for 2 h. The reaction mixture was worked and the residue purified on silica gel using ethyl acetate and light petroleum (1: 20) to afford **81** (0.4 g, 80 %).

$[\alpha]_D = +20^o$ (*c* 0.85, $CHCl_3$)

^{1}H-NMR (200 MHz, $CDCl_3$) : 0.09 (s, 6H), 0.82-0.89 (m, 12H), 1.66–1.84 (m, 1H), 1.99-2.08 (m, 2H), 3.5-3.62 (m, 2H), 3.97 (s, 2H), 4.12 (dt, 1H, J = 3.9, 8.9 Hz), 4.22 (d, 1H, J = 5.5 Hz), 4.5 (d, 4H, J = 5.8 Hz), 4.78 (s, 1H), 7.12-7.40 (m, 10H).

EIMS m/z: 363 $(M\text{-}Bn)^+$

Synthesis of compound 82 ((3S,4R,5S,)-5-Benzyloxy-3-(2-benzyloxyethyl)-1-(*tert*-butyldimethylsilyloxymethyl)-4-methyl-2-oxabicyclo[4.1.0]heptane):

To a solution of **81** (0.4 g, 0.9 mmol) in dry CH_2Cl_2 (20 mL) at -20°C, was added in succession, a 1 M solution of Et_2Zn (4.5 mL, 4.5 mmol) and CH_2I_2 (0.7 mL, 9 mmol) and stirred for 6 h. The reaction mixture was quenched by addition of saturated NH_4Cl solution (10 mL), and warmed to room temperature. The CH_2Cl_2 layer was separated, dried over Na_2SO_4 and concentrated. The residue was purified on silica gel using EtOAc and light petroleum (1: 20) as eluent to afford **82** (0.3 g, 73 %) as a colorless syrup.

$[\alpha]_D = +13°$ (*c* 0.9, $CHCl_3$)

^{1}H-NMR (200 MHz, $CDCl_3$) : 0.08 (s, 6H), 0.72 (dd, 1H, J = 5.7, 8.9 Hz), 0.86-1.02 (m, 12H), 1.20-1.38 (m, 2H), 1.55-1.69 (m, 1H), 1.81-2.07 (m, 2H), 3.45 (d, 1H, J = 12.2 Hz), 3.5-3.68 (m, 3H), 3.88 (d, 1H, J = 12.2 Hz), 4.13 (t, 1H, J = 5.3 Hz), 4.52 (s, 2H), 4.65 (s, 2H), 7.18-7.47 (m, 10H).

Synthesis of compo und 84 ((3S,4R,5S)-*O*-{[5-Benzyloxy-3-(2-benzyloxyethyl)-4-methyl-2-oxabicyclo- [4.1.0]- hept-1-yl]methyl} *S*-methyl dithiocarbonate):

82 (0.3 g, 0.65 mmol), 1 M solution of TBAF (1.3 mL, 1.3 mmol) in THF (3mL) were stirred for 1 h at rt, concentrated and the residue was dissolved in ethyl acetate and washed with water. Combined EtOAc layer was dried (Na_2SO_4), concentrated and the residue was purified on silica gel using ethyl acetate and light petroleum (3: 7) as eluent to give **83** (0.21 g, 84 %) as colorless oil.

To compound **83** (0.2 g, 0.5 mmol) in THF (5 mL), NaH (32 mg, 0.8 mmol) (60 % dispersion in oil) was added, after 15 min. ,CS_2 (0.1 mL, 1.1 mmol) and MeI (0.1 mL, 1.3 mmol) were introduced. The reaction mixture was stirred for 30 min at rt and quenched with ice-water mixture and extracted with ethyl acetate. Combined ethyl acetate layer was dried over Na_2SO_4 and chromatographed on silica gel using ethyl acetate-light petroleum (1: 40) as eluent to give **84** (0.2 g, 81 %) as yellow liquid.

$[\alpha]_D$ = +26.08 (*c* 1.035, $CHCl_3$).

^{1}H-NMR (200 MHz, $CDCl_3$) : 0.83 (dd, 1H, J = 5.3, 7.7 Hz), 0.90 (d, 3H, J = 8.1 Hz), 1.19 (t, 1H, J = 5.3 Hz), 1.21-1.34 (m, 1H), 1.51-1.67 (m, 1H), 1.75-1.91 (m, 1H), 1.97-2.08 (m, 1H), 2.52 (s, 3H), 3.49-3.69 (m, 3H), 4.18 (t, 1H, J = 5.4 Hz), 4.73 (d, 1H, J = 12.8 Hz), 4.49 (d, 2H, J = 3.9 Hz), 4.61 (s, 2H), 4.87 (d, 1H, J = 12.8 Hz), 7.19-7.44 (m, 10H).

Radical induced ring opening of **84** and hydroboration of **85** to give **86**:

_C_-(2-Benzyloxyethyl) 3-_O_-benzyl-1,2,4-trideoxy-2,4-di-_C_-methyl-â-D-mannopyranosi de (86):

A solution of **84** (0.1 g, 0.21 mmol) Bu_3SnH (1.2 mL, 2.0 mmol) and AIBN (15 mg) in toluene (1.5 mL) was heated to 120 ^oC under argon for 30 min. The reaction

mixture was concentrated washed with aq. KF and extracted with ether, dried (Na_2SO_4) and residue (70 mg) was directly used for the next reaction.

To an ice cold solution of residue (70 mg, 0.19 mmol) dissolved in dry THF (2 mL) was added BH_3: DMS (0.05 mL, 0.5 mmol) and stirred at rt for 2 h. The reaction mixture was quenched with MeOH and then a 1:1 mixture of H_2O_2 (33 %) and 1 M aq. NaOAc was added at 0 °C and stirred for another 3 h at the same temperature. The THF was removed and the residue was partitioned between EtOAc and water. The organic layer was separated, dried (Na_2SO_4) and the crude syrup obtained was purified on silica gel using ethyl acetate and light petroleum to give **86** (23 mg, 30 %) (over two steps).

$[\alpha]_D$ = +26.08 (*c* 1, $CHCl_3$).

^{1}H-NMR (200 MHz, $CDCl_3$) : 0.87-1.05 (m, 3H), 1.55-1.79 (m, 2H), 1.95-2.16 (m, 2H), 3.29-3.78 (m, 7H), 4.38-4.59 (m, 4H), 7.15-7.42 (m, 10H).

_C_-(2-Acetoxyethyl) 3,6-di-_O_-acetyl-1,2,4-trideoxy-2,4-di-_C_-methyl-â-D-mannopyranoside (87):

To a solution of **86** (19 mg, 0.03 mmol) in methanol (3 mL), Pd/C (5 mg) was added and stirred for 8 h under hydrogen atmosphere. The catalyst was filtered, concentrated and the residue was dissolved in CH_2Cl_2 (3 mL) and treated with Ac_2O (0.1 mL, 30 mmol), pyridine (0.1 mL, 40 mmol) and DMAP (2 mg) at rt for 1 h. The reaction mixture was concentrated and the residue purified on silica gel using ethyl acetate and light petroleum (1: 4) as eluent, to give the tri acetyl derivative **87** (7 mg, 70 %).

$[\alpha]_D$ = + 3^o (*c* 0.5, $CHCl_3$)

^{1}H-NMR (200 MHz, $CDCl_3$) : δ 0.96 (d, 6H, J = 7.3 Hz), 1.62-1.71 (m, 2H) 1.86-1.96 (m, 1H), 1.97-2.3 (m, 1H), 2.06, 2.09, 2.16 (3 x s, 9H),

3.55 (dt, 1H, J = 3.4, 9.5 Hz), 3.68 (ddd, 1H, J = 2.6, 4.5, 7.7 Hz), 4.00 (dd, 1H J = 4.5, 11.1 Hz), 4.12 – 4.23 (m, 3H), 5.00 (t, 1H, J = 5.3 Hz).

FABMS m/z: (331 M^++1)

HRMS (FAB): Cacld. for ($C_{16}H_{27}O_7$, M^++1): 331.175679. Found 331.175731.

C-(2-Benzyloxyethyl) 3-O-benzyl-1,2-dideoxy-2-C-methyl-6-O-trityl-â-D-mannopyra- noside (88):

76 (0.2 g, 0.5 mmol), pyridine (2 mL), tritylchloride (0.22 g, 0.8 mmol) were stirred at rt for 4 h. The reaction mixture was co-distilled with toluene to remove excess pyridine. The residue was chromatographed on silica gel using ethyl acetate and petroleum ether (1: 9) to give **88 (**0.24 g, 74 %).

$[\alpha]_D$ = -37° (*c* 0.9 , $CHCl_3$)

^{1}H-NMR (200 MHz, $CDCl_3$) : δ 0.98 (d, 3H, J = 7.8 Hz), 1.58-1.67 (m, 1H) 1.83-2.0 (m, 1H), 2.03- 2.19(m, 1H), 2.36(br. s, 1H), 3.17-3.23(m, 2H), 3.40 (dd, 1H, J = 5.3, 9.3 Hz), 3.53-3.80 (m, 3H), 4.42 (d, 1H, J = 11.7 Hz), 4.5(s, 2H), 4.64 (d, 1H, J = 11.7 Hz), 7.10-7.56(m, 25 H).

***C*-(2-Benzyloxyethyl) 3-*O*-benzyl-1,2-dideoxy-2-*C*-methyl-6-*O*-trityl-4-ulo-â-D-mann-opyranoside (89):**

A solution of **88** (0.24 g, 0.38 mmol) in CH_2Cl_2 (4 mL) was added to the mixture of oxalyl chloride(0.13 mL, 1.2mmol) and DMSO(0.13 mL, 2.4 mmol) at –78°C and stirred for 45 min. and was quenched with diisopropylethyl amine (0.62 mL, 3.6 mmol) and brought to rt. The reaction mixture was quenched with water and extracted with CH_2Cl_2 and was concentrated to give the 4-ulose derivative.

$[\alpha]_D$ = +10(*c* 0.6, $CHCl_3$)

^{1}H-NMR (200 MHz, $CDCl_3$) : δ 0.96 (d, 3H, J = 7.5 Hz), 1.67-1.86 (m, 1H) 1.88-2.08 (m, 1H), 2.37- 2.53(m, 1H), 3.30-3.50(m, 2H), 3.57-3.80 (m, 2H), 3.89 (m, 1H), 4.02-4.18 (m, 2H), 4.40-4.59(m, 3H), 4.79 (d, 1H, J = 11.4 Hz), 7.10-7.57(m, 25 H).

***C*-(2-Benzyloxyethyl) 3-*O*-benzyl-1,2,4-trideoxy-2-*C*-methyl-4-methylene-6-*O*-trityl-â-D-mannopyranoside (90):**

Ketone **89** (0.2 g, 0.32 mmol) was diluted in ether, cooled –78 ^oC and the ylide generated from PPh_3CH_2I (0.65 g, 1.6 mmol) and 1.6 M solution of BuLi (0.6 mL, 1 mmol) in dry ether (15 mL) at –78 °C was added and stirred at 0 ^oC for 3 h and quenched with saturated NH_4Cl solution. The reaction mixture was washed with water, ether layer was separated, dried over Na_2SO_4 and concentrated. The crude obtained was purified on silica gel using ethyl acetate and light petroleum to afford **90** (90 mg, 45 %).

$[\alpha]_D$ = -8° (*c* 1.2, $CHCl_3$)

^{1}H-NMR (200 MHz, $CDCl_3$) : 0.86 (d, 3H, J = 7.2 Hz), 1.62-1.81 (m, 1 H), 1.86-2.03 (m, 1H), 2.08 – 2.21 (m, 1H), 3.36 (dd, 1H, J = 5.1, 8.7 Hz), 3.50 (dd, 1H, J = 5.1, 8.7 Hz), 3.61-3.97 (m, 4H), 4.05 (bd, 1H, J = 5.2 Hz), 4.5-4.67 (m, 4H), 4.83 (s, 1H), 5.23 (s, 1H), 7.14-7.71 (m, 25H).

FABMS m/z: 647 (M^++Na)

***C*-(2-Acetoxyethyl) 3,6-di-*O*-acetyl-1,2,4-trideoxy-2,4-di-*C*-methyl-â-D-mannopyranoside (91):**

To a methanolic solution (3 mL) of **90** (90 mg, 0.14 mmol), Pd/C (10 mg) was added and stirred under hydrogen atmosphere for 10 h. The reaction mixture was filtered

through a bed of celite and washed with MeOH. The residue was dissolved in CH_2Cl_2, added Ac_2O (0.1 mL, 8 mmol), pyridine (0.1 mL, 9.0mmol) and DMAP (10 mg). The reaction mixture was concentrated and the residue obtained was purified on silica gel by using EtOAc and light petroleum (1: 3) to afford **91** (36 mg, 74 %).

$[\alpha]_D = +4^o$ (*c*, 0.5, $CHCl_3$).

^{1}H-NMR (200 MHz, $CDCl_3$) : 0.96 (d, 6H, J = 7.3 Hz), 1.6-1.73 (m, 2H), 1.86-1.97 (m, 1H), 1.97-2.04 (m, 1H), 2.06, 2.07, 2.12 (3 x s, 9H), 3.55 (dt, 1H, J = 3.1, 9.5 Hz), 3.68 (ddd, 1H, J = 2.8, 4.5, 7.6 Hz), 4.00 (dd, 1H, 4.5, 11.4 Hz), 4.12-4.23 (m, 3H), 4.99 (t, 1H, J = 5.5 Hz).

FABMS m/z: (331 M^++1)

Anal. Calcd. for $C_{16}H_{26}O_7$: C,58.18; H, 7.87. Found: C, 58.31; H, 7.91.

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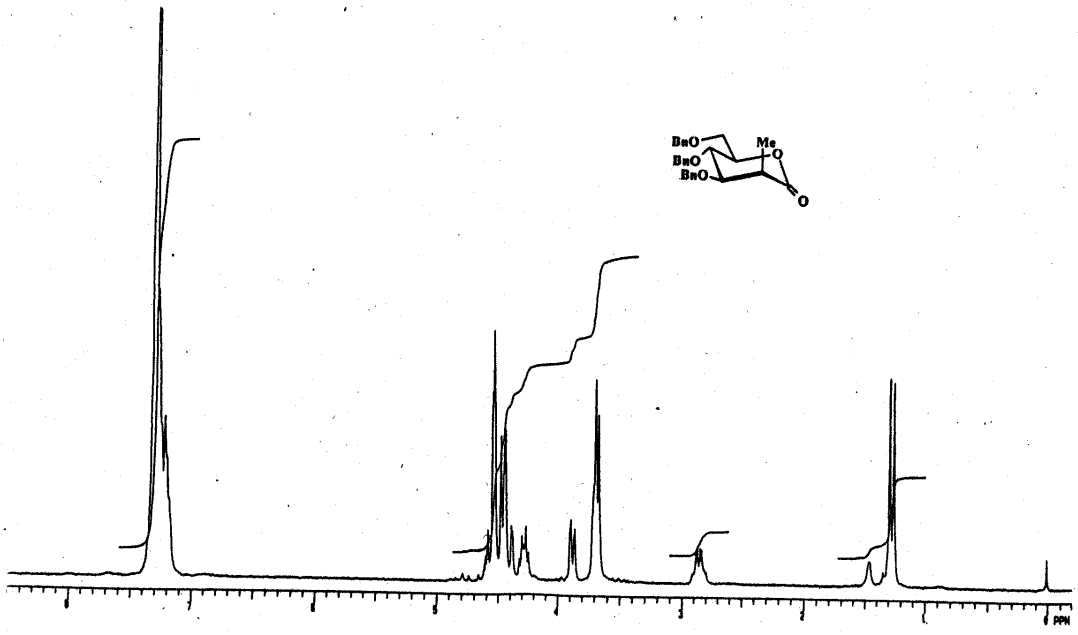
SPECTRA



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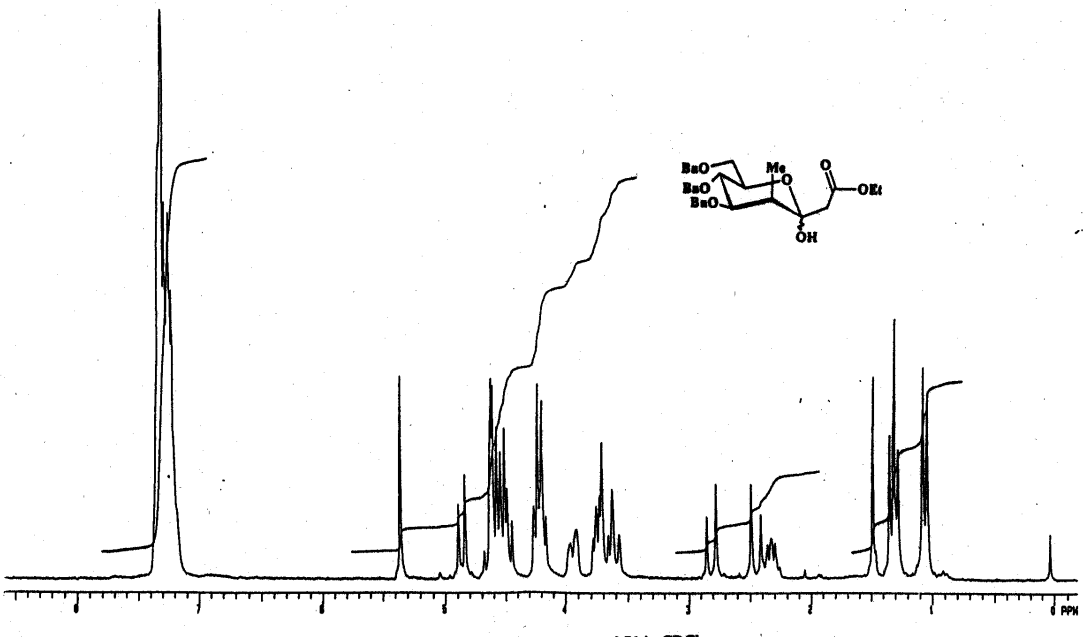

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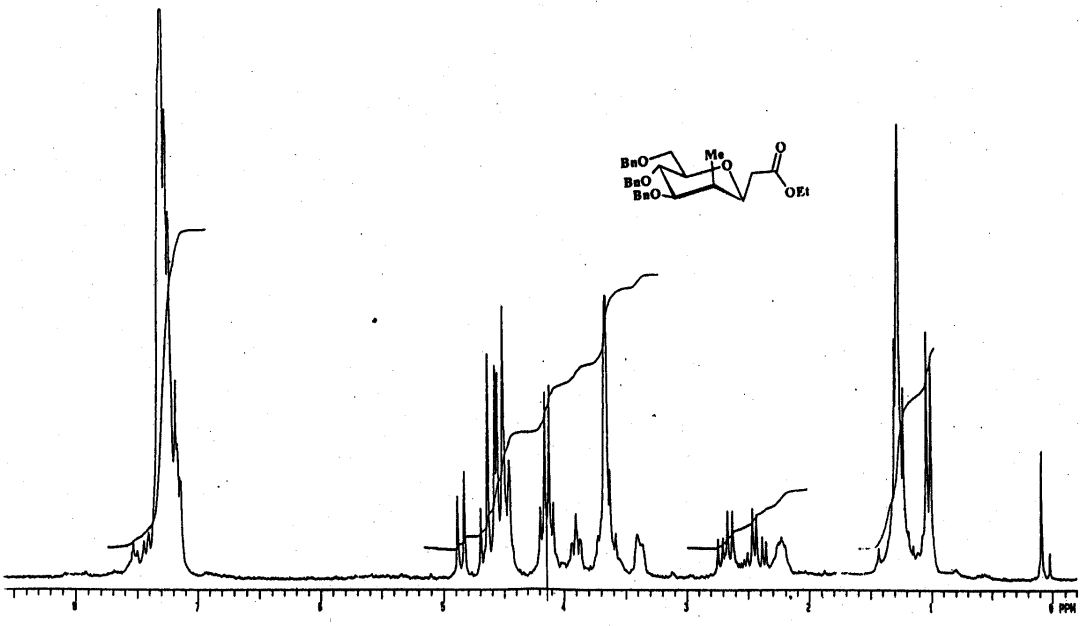

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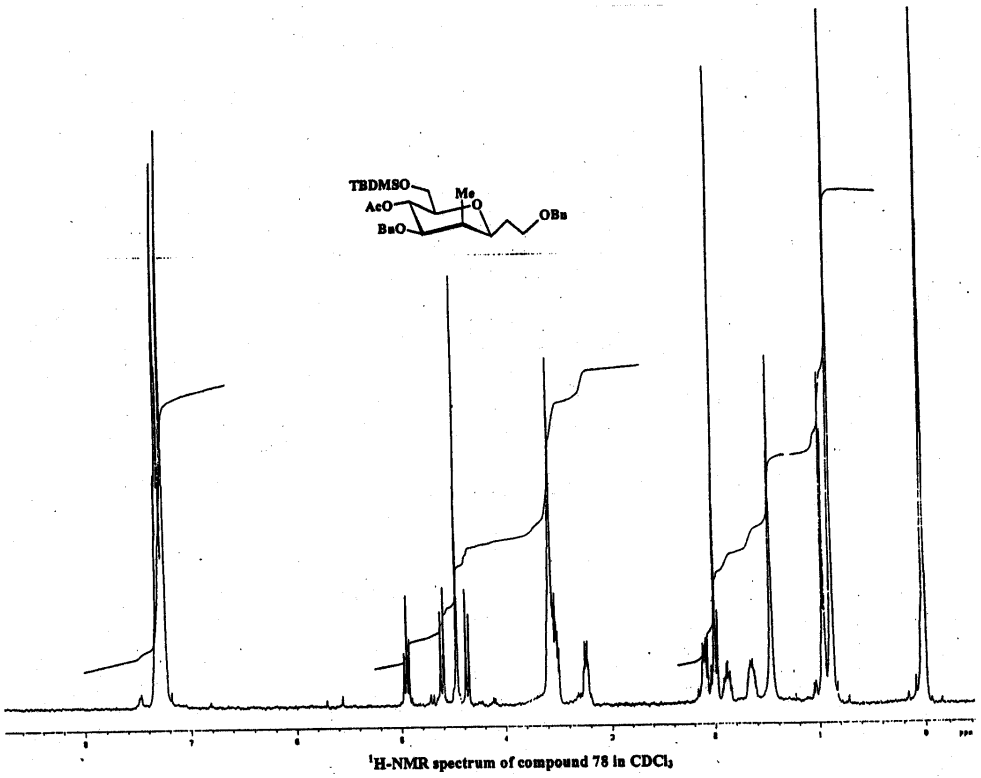

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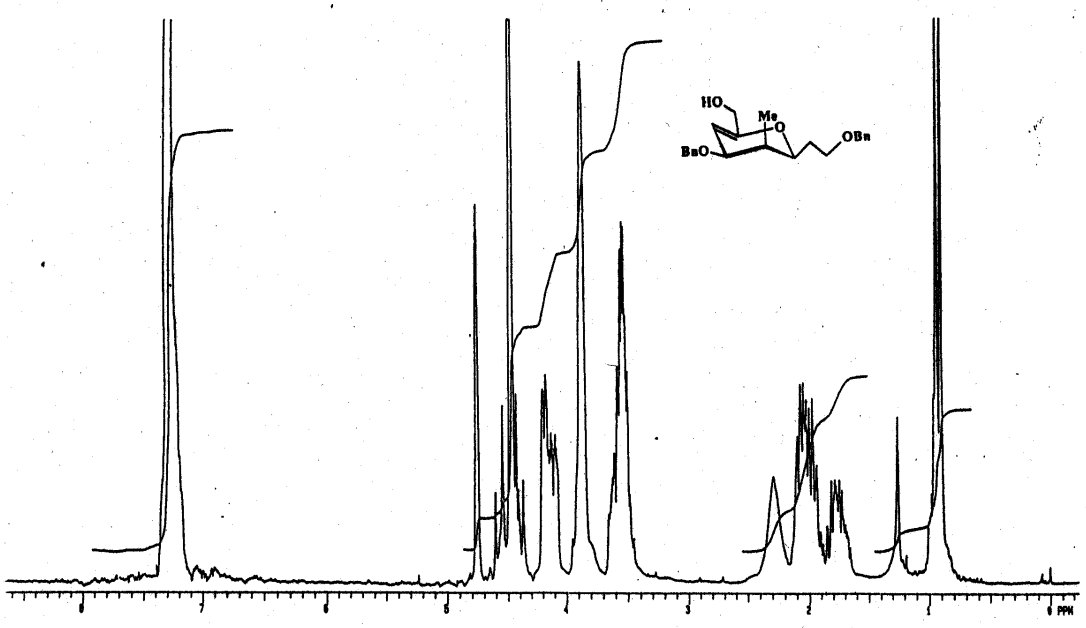

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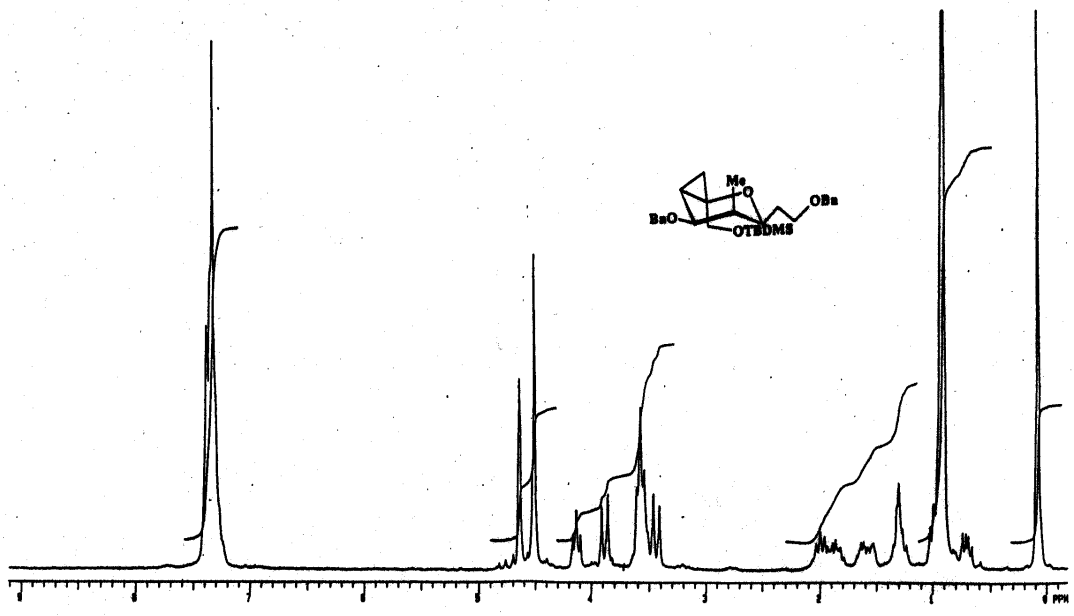

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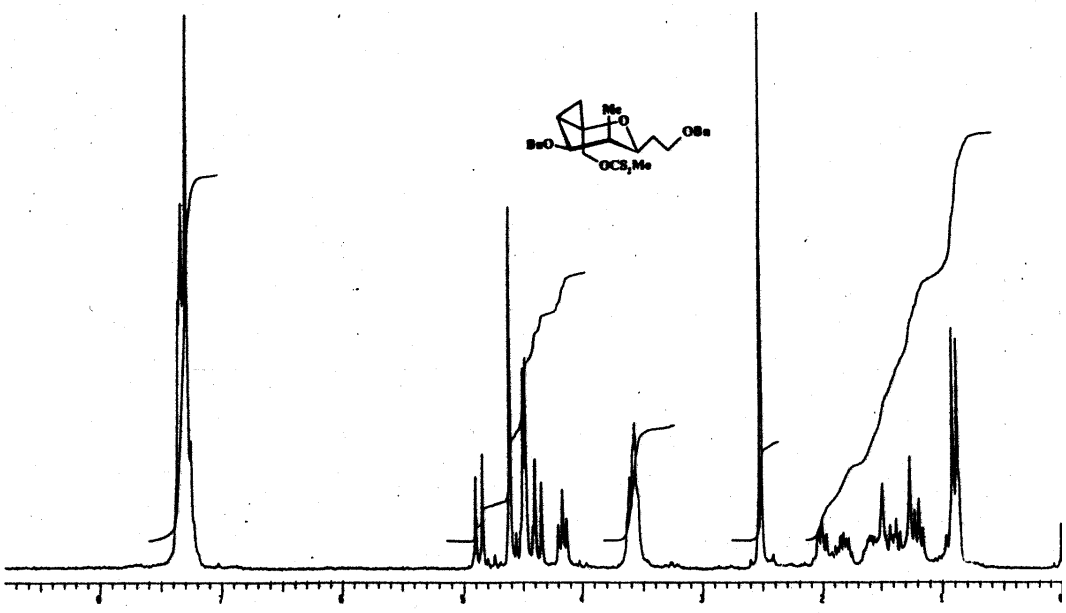

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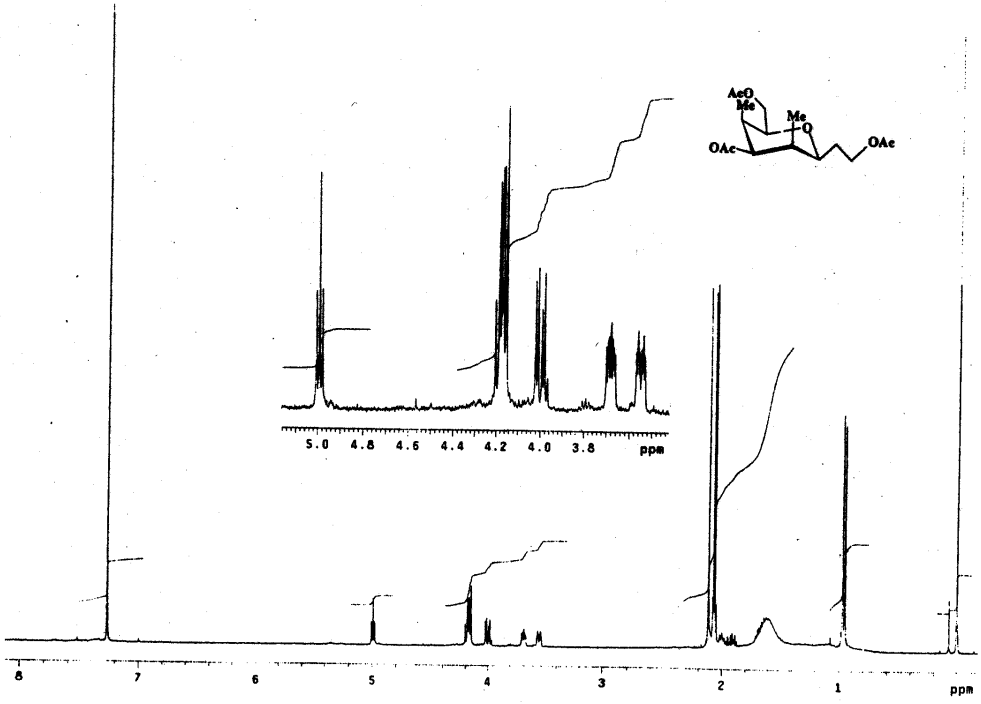

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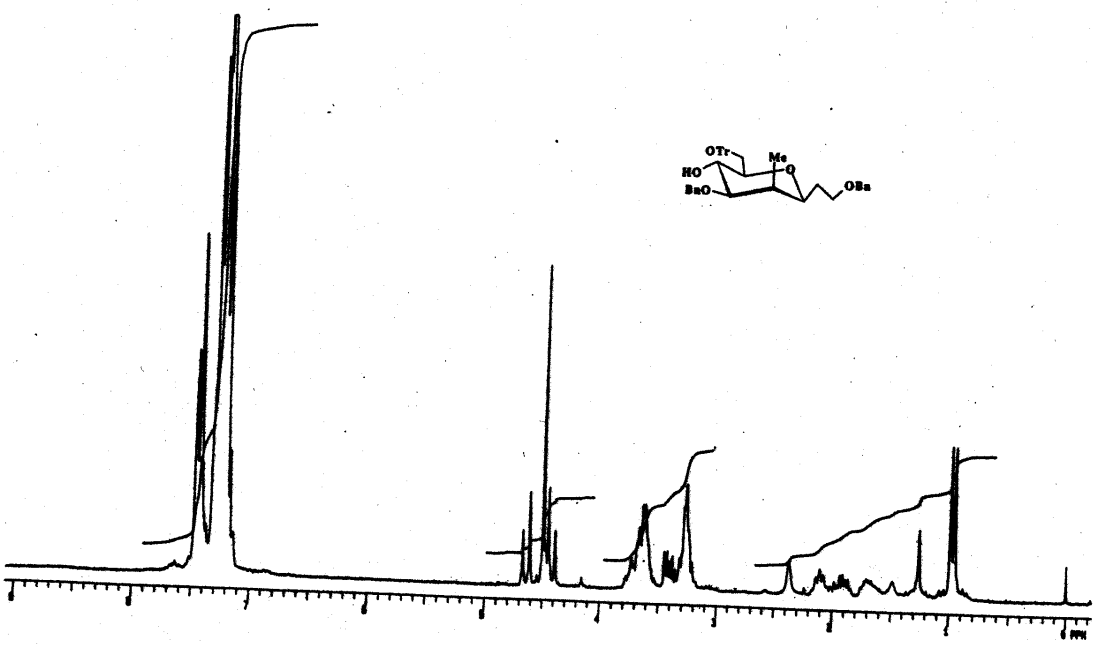

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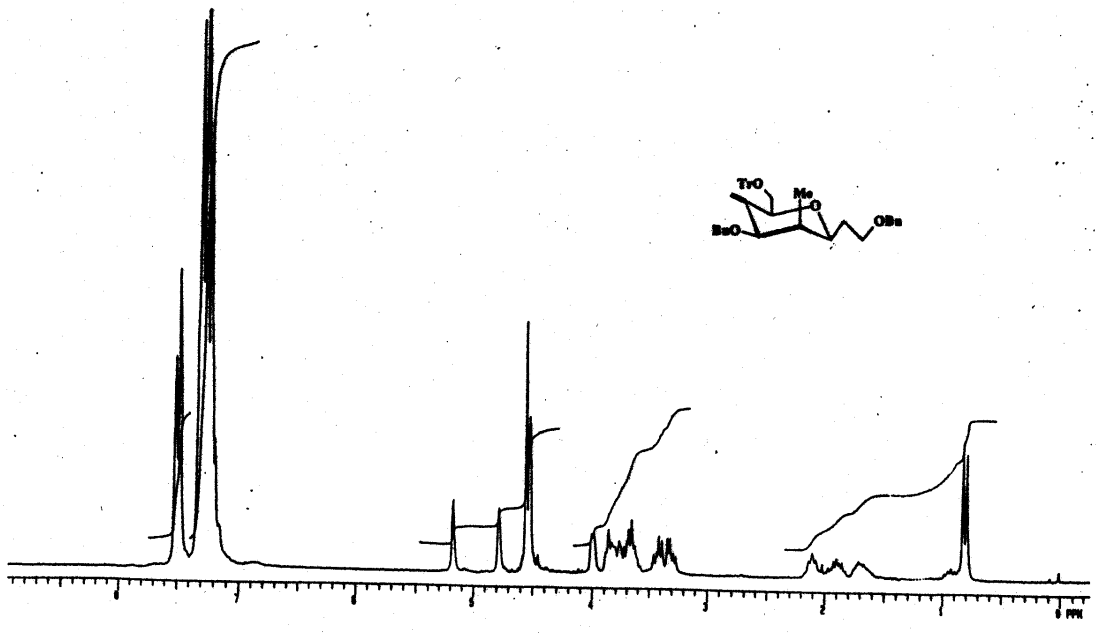

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