1,2-Cyclopropanated Sugars: Reactions and Synthetic Utility

A Thesis
Submitted for the Degree of
Doctor of Philosophy

C.V. Ramana

School of Chemistry
University of Hyderabad
Hyderabad 500 046
INDIA

September 1997

To My

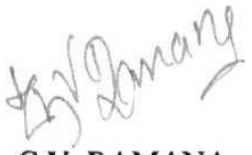
Parents
Teachers and Almighty

CONTENTS

DECLARATION

I hereby declare that the matter embodied in this thesis is the result of investigations carried out by me in the School of Chemistry, University of Hyderabad, Hyderabad under the supervision of Professor M. Nagarajan.

In keeping with the general practice of reporting scientific observations, due acknowledgements have been made wherever the work described is based on the findings of other investigators.



C.V. RAMANA

CERTIFICATE

This is to certify that the work described in this thesis entitled *1,2-Cyclopropanated Sugars: Reactions and Synthetic Utility* has **been** carried out by Mr. **C. V. Ramana** under my supervision and the same has not been submitted elsewhere for any degree.

M. NAGARAJAN
(THESIS SUPERVISOR)

DEAN

School of Chemistry,
University of Hyderabad,
Hyderabad - 500 046
INDIA

ACKNOWLEDGEMENTS

I am extremely grateful to Professor M. Nagarajan for his inspiration, guidance and support during the entire course of this work. I am indebted to him for his valuable comments and suggestions during the course of our discussions which enriched my knowledge in the area of study as well as for introducing me to diverse fields.

I thank Prof. P. S. Zacharias, Dean, School of Chemistry and other members of faculty for their support. I wish to express my gratitude to Dr. Bhaskar G. Maiya for his invaluably helpful discussions. I thank Prof. D. Basavaiah for extending instrumentation facilities.

I am grateful to Prof. S. Chandrasekharan, I.I.Sc., Bangalore for providing mass spectra or CHN analysis of some of the compounds.

I take this opportunity to thank all my colleagues in the group for their support and assistance throughout my stay. I am obliged to Murali, Narkunan, Vasudeva, Prabhavathi, Manjula, Sudha and Lakshmikanthan, who have been assiduous in their help and encouragement over the time period. I am grateful to Sudha for her keen interest in my endeavours. The suggestions and proof-reading of Manjula and Sudha have been invaluable in the preparation of this thesis.

A timely help during the thesis preparation from Prabhavathi, Kiran and Gautam Panda is gratefully acknowledged. I am grateful to Arounaguiri, Giribabu, Muthukumaran and Krishnamachari for their help. Being a wing mate, I would like to acknowledge the H(eroes)-wing mates: Venkat, Ravi, Prasad, Annayya, Kumar and Kiran and also to my neighbouring L(azy)-wingmates: Dean, Krishna, Ravi and DS Reddy.

Thanks are due to all the non-teaching staff, especially, Bhaskar Rao, Satyanarayana, Prasad, Ramana, Santosh and Vijayalakshmi, of School of Chemistry. Financial assistance from UGC is gratefully acknowledged.

I express my sincere thanks to R. Venkateswarlu, K. Mastanaiah and Manjula for standing by me in my hard times. The co-operative enthusiasm exhibited by my brothers-in-law Prasad, Murali and Ravi is highly appreciated.

I am deeply indebted to my parents, brother and sister for their unflinching belief and support, without which I would not have been here.

I wish to express my heartfelt appreciation to Vijaya, my wife, for her motivation, devotion, co-operation and endurance. I would like to recollect the wonderful times I spent with my adorable daughter Wine over the past year.

ABBREVIATIONS

A	Angstrom
Ac	acetyl
AcOH	acetic acid
AIBN	2,2'-azobisisobutyronitrile
aq	aqueous
Ar	aryl
Bn	benzyl
Bu	butyl
Bz	benzoyl
CSA	camphorsulfonic acid
DMAP	4-dimethylaminopyridine
DMF	dimethylformamide
DMSO	dimethyl sulfoxide
E	electrophile
Et	ethyl
h	hour(s)
LAH	lithium aluminum hydride
LDA	lithium diisopropylamine
LTMP	lithium tetramethylpiperidide
MCPBA	m-chloroperbenzoic acid
Me	methyl
min	minute(s)
ml	millilitre(s)
mmol	millimole(s)
Ms	methanesulfonyl (mesyl)
NBS	N-bromosuccinimide
NCS	N-chlorosuccinimide
NIS	N-iodosuccinimide

Nu	nucleophile
PCC	pyridinium chlorochromate
PDC	pyridinium dichlorochromate
Ph	phenyl
Piv	pivaloyl
Pr	propyl
PTSA	p-toluenesulphonic acid
rt	room temperature
TBDMS	t-butyldimethylsilyl
TBDPS	t-butyldiphenylsilyl
TBS	tributylsilyl
THF	tetrahydrofuran
TMS	trimethylsilyl
TMSOTf	trimethylsilyl trifluoromethanesulfonate
TPHB	triphenylphosphinehydrogen bromide
Tr	triphenylmethyl (trityl)
Ts	p-toluenesulfonyl (tosyl)

ABSTRACT

This thesis deals with the reactions and synthetic utility of 1,2-cyclopropanated sugars. The thesis consists of three sections, namely, introduction, results and discussion, and experimental. The introduction commences with the advantages offered by glycals for the synthesis of modified sugars and transmits the concept of strained 3-membered strategy towards the synthesis of higher order carbohydrates of biological significance. Finally, it provides an account of recent developments in 1,2-cyclopropanated sugars.

Towards the exploitation of 1,2-cyclopropanated sugars, which is the main thrust of this thesis, we focussed our attention on their synthetic utility and reactions. By nature, 1,2-cyclopropanated sugars are donor-activated by the pyranose oxygen and considering the electronic factors, their electrophilic ring openings provide products resulting from ring opening, rather than ring expansion.

a- and β-Cyclopropanes **106** and **109** respectively, derived from 2,4,6-tri-*O*-benzyl-D-glucal served as suitable substrates in this regard. The ring openings of **106** and **109** were carried out with different electrophiles in methanol as well as with N-bromosuccinimide (NBS) as the activator (source of Br^+) in various solvents.

The proton induced electrophilic ring opening of **106** in methanol at refluxing temperature was found to be sluggish and incomplete even after 15 days. It was even worse with cyclopropane **109** where no reaction occurred. The ring opening of **106** and **109** with Br^+ as electrophile in methanol resulted in the ring opened products in good yields. Although, the iodonium ion, using N-iodosuccinimide (NIS) as source, was able to open α-cyclopropane **106** in good yield, the inertness of β-cyclopropane **109** towards this reagent prompted us to employ iodoniumdi(s-collidine) perchlorate (IDCP). The reaction of α-cyclopropane **106** with IDCP gave the ring opened products in very good yield

and that of 109 resulted in partial conversion to the ring opened product in moderate yield. The reactions of **106** with both Br^+ and *V* resulted in a mixture of both anomers, whereas that of **109** gave only a-anomers.

Later, in order to show the flexibility of this method, the bromonium ion induced ring opening of cyclopropanes **106** and **109** were carried in 2-chloroethanol, 2,2,2-trichloroethanol, benzyl alcohol and water. α-Cyclopropane **106** underwent ring opening in a facile and high yielding manner, resulting always in anomeric mixtures. The ring openings of β-cyclopropane **109** were slow compared to 106 and resulted exclusively in a-anomers.

Towards further elaboration of this methodology, sugar alcohols were used as nucleophiles, leading to branched-chain disaccharides with defined C-2 stereochemistry. After monitoring the reaction conditions with varying concentrations of sugar alcohol and different reaction times (NBS activation), we succeeded in opening 106 and **109** with three sugars alcohols, 1,2:3,4-di-*O*-isopropylidine-α-D-galactopyranose (72), 1,2-*O*-isopropylidine-3-*O*-benzyl-α-D-xylofuranose **(150)** and 2,3:4,5-di-*O*-isopropylidine-D-arabinitol in acetonitrile in the presence of 4A molecular sieves in moderate to good yields. In a similar fashion as with other alcohols, the ring opening of **106** in all the three cases gave both the anomers and 109 resulted in exclusive a-anomers.

The scope of 1,2-cyclopropanated sugars as suitable precursors for the stereoselective construction of 2-deoxy-2C-methyl pyranose templates was extended by the mercuric ion mediated ring opening of 106 and **109,** as their direct protonation resulted in poor yields. Mercuric trifluoroacetate was found to be convenient in opening both the cyclopropanes. The methyl or n-butyl 2-deoxy-2C-methyl-β-D-glucopyranosides and 2-deoxy-2-C-methyl-α-D-mannopyranosides, resulting from 106 and 109, respectively, were obtained in good yields (when reaction was carried out in methanol and n-butanol). This methodology was further extended to the cyclopropanes **107** and **110, 108** and **111** derived from galactal and

rhamnal, respectively. However, with β-cyclopropanes **110** and **111**, competitive formation of bis(sugar)mercury compounds limits the applicability of this procedure in a more general fashion. It is interesting to note that in contrast to halonium ion mediated ring openings, in all the cases, the ring openings with mercuric ion were found to yield only one anomer with inversion at C-1.

These experiments clearly reveal that the reactions using halonium electrophiles with β-cyclopropane **109** are slower and display higher anomeric selectivity compared to those of the α-cyclopropane 106. The resulting anomeric ratio in the case of ring openings of 106 was found to be solvent dependent. This excludes the participation of either S_N1 or S_N2 alone in these ring openings. The formation of only a-anomers from cyclopropane 109 suggests that its ring openings involve only S_N2 type processes. However, dependence of the rate of the reactions on the nature of solvent in both the cases, as well as the formation of anomeric mixtures in the case of cyclopropane 106 clearly provides enough support for S_N1 participation.

To better understand the processes taking place, we prepared the a- and p-cyclopropanes 185 and 186, with a free 6-OH group, starting with 3,4-di-*O*-benzyl-6-*O*-trityl-D-glucal (182). Dichlorocarbene addition followed by detritylation using 1 : 2 formic acid/ether and dehalogenation with lithium aluminum hydride in THF yielded the corresponding α-cyclopropane 185. Under Simmons-Smith cyclopropanation conditions, 182 directly yielded the required β-cyclopropane 186.

The intramolecular ring opening of a-cyclopropane 185 in acetonitrile with NBS as an activator in the presence of 4A molecular sieves, took place smoothly within 5h, giving the levoglucosan derivative 187 in good yield. On the other hand, under similar conditions, the reaction with p-cyclopropane 186 was incomplete and yielded the levomannosan derivative **188** in poor yield after 36h. These results clearly indicate that the lower reactivity of the p-cyclopropane 186, when compared to 185, is due to steric hindrance to the approach of the electrophile. While

a-cyclopropane 185 reacts cleanly and rapidly by an S_N2 type process to give the levoglucosan derivative 187 in good yield, the β-cyclopropane 186, with no such option available, forms the levomannosan derivative **188** in much lower yield, probably through an S_N1 mechanism.

Towards further elaboration of the scope of 1,2-cyclopropanated sugars, we anticipated that the products derived from the ring openings of cyclopropanated sugars with electrophiles in water, would serve as a suitable starting point for the construction of chiral α-methylene-δ-valerolactones following a two step oxidation and dehydrohalogenation strategy. Initial failure in the attempts in oxidising halolactols with PCC, PDC and I_2 prompted us to search for a appropriate reagent. Gratifyingly, and most surpisingly, the reaction of p-cyclopropane 106 with IDCP in dioxane-water at 60 - 70° gave the desired α-methylene-δ-valerolactone 195 in moderate yield.

Generalisation of this reaction was made using the cyclopropanes 106, 107, 110, **111** and **112**. The corresponding chiral α-methylene-δ-valerolactones 195 - 198 were obtained in moderate to good yields.

All new compounds prepared in the course of this thesis were completely characterised by their analytical and/or spectral data as appropriate.

INTRODUCTION

The ingenuity of Nature lies in not only providing an innumerable number of esoteric molecular targets having strictly defined stereochemistry and often formidable frameworks for synthetic chemists to work on, but also at the same time placing at their disposal a wealth of different types of chiral pool molecules as resources. Amongst the various chiral pool molecules available in Nature, carbohydrates occupy a special place. The advantages of carbohydrates as chiral starting materials arise from the fact that they arc exuberantly available in Nature, are exceedingly cheap and, on top of this, are enantiomerically pure. The uniqueness of this situation becomes even more imposing while looking at sugars in comparison with other natural chiral resources like amino- and hydroxyacids and terpenes, especially when dealing with targets containing multiple centres of chirality. In such cases, the greater utility of carbohydrates as chirons is self-evident.[1]

The abundance of carbohydrates in Nature is not without any purpose. A well known fact is that they are energy storage molecules. A lesser known fact, which is being increasingly recognized, is their biological significance.[2] Carbohydrates on cell surfaces are information molecules. Oligosaccharides composed of more than one type of sugar unit such as the human blood group determinants and bacterial antigens are major carriers of biological information.[3] Biological polymers such as glycoconjugates of carbohydrates and proteins (glycoproteins) and lipids (glycolipids) or phospholipids (glycophospholipids) are the main constituents of cell membranes. Sialic acids, the most prominent of which is N-acetylneuraminic acid, represent a number of complex higher saccharides which are present in glycoconjugates of various tissues and cells of many animal species.[4] The oligosaccharide residue of these substances is crucial in the intercellular recognition that forms the basis of the immune system of mammalian organisms.[5] This biological significance of carbohydrates in Nature has generated a renewed interest to synthesize them in a stereo- and regiocontrolled fashion on a preparative

scale. On the other hand, numerous monosaccharides are attached to aglycon portions as 2-deoxy or 2-deoxy amino glycosides and are essential constituents of many drugs and various naturally derived antibiotics.[2,6] Amino and deoxy sugars are almost ubiquitously present in macrolide antibiotics and DNA damaging *cis*-ene-diyne anti-tumor agents.[7] Various aminohexoses such as daunosamine and its congeners are the glycosidic components of many anthracycline antibiotics.[2, 6b]

The recognition of *Carbohydrate Chemistry* as a separate branch of Organic Chemistry can be traced back to the late 19th century. ***Emil*** *Fischer's** seminal contributions towards the synthesis and structure determination of carbohydrates, culminating in the elucidation of the structure of glucose, were recognized with the Nobel prize in 1902. The exhaustive work done on selective manipulations, protection and/or transformation of different oxyfunctions in carbohydrates has led to the establishment of the relevance of conformational and stereoelectronic effects on chemical reactivity in general and carbohydrates in particular. The utility of nuclear magnetic resonance (NMR) spectroscopy in understanding the finer facets of the stereochemistry of carbohydrate derivatives has not only contributed to the development of conformational analysis, but also has further expanded the interpretive power of NMR spectroscopy. It follows, therefore, that the contribution of the chemistry of sugars in advancing our understanding of organic chemistry is profound.

Inspite of their large scale availability in various forms like mono, di-, oligo- and polysaccharides, the utilization of their vast synthetic potential was impeded by a number of obstacles in the early days of organic synthesis. They were regarded as too complex, with many chiral centres and lacking in functional groups suitable for facile alterations. A second difficulty was in the purification, identification and characterization of sugars and their derivatives. Today, this situation no longer obtains. Methods are now available for selective functional group manipulation as well as for purification and characterization. These advances, taken together with

the biological significance of many oligosaccharides, have driven the present research in carbohydrate chemistry towards the following achievements in the recent past.

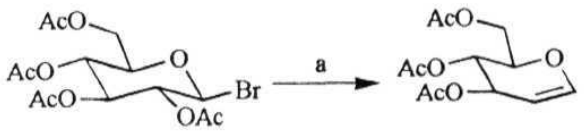
1. Utilization of low molecular weight carbohydrates (mono- and disaccharides) as raw materials for providing access to rare or modified sugars in general and construction of enantiomerically pure non-carbohydrate chiral precursors in particular. This has led to many interesting and novel synthesis of several polyfunctional compounds[9] starting with simple open chain molecules like (+)-sulcatol and (s)-(+)-ipsdienol to more complex macrolides like erythronolide A, rifamycin S and soraphen $A_{1\alpha}$.[9c]
2. Development of numerous methods for O-glycosidation,[10] applying diverse anomeric activating groups like halo, phenylthio, phenylseleno, orthoester, acetimidate, trichloroacetimidate, diazirine, of new concepts like temporary silicon connection approach, of double diastereodifferentiation using the matched-mismatched glycosidation, either to construct oligosaccharides of biological significance or to connect aglycons with sugars, in the total synthesis of naturally derived antibiotics.
3. Synthesis of sugars of biological interest from non-carbohydrate precursors or from modified monosaccharide units using either chemical or enzymatic methods. This includes the developments made by Sharpless's asymmetric epoxidation protocol," Danishefsky's Hetero Diels-Alder approach[12] and Wong's glucose aldolase methodology[13] towards the *ab-initio* synthesis of sugars.

A collection of synthetic transformations of simple sugars to complex natural products has been well summarized by Hanessian[9] in his book *"Total Synthesis of Natural Products: The Chiron Approach"* which details the transfer of the inherent chirality present in carbohydrates (as chiral templates) to the molecules

of attention. It also provides a new perception in the application of the tool of retrosynthetic analysis. Credit for much of the developmental work, concerned mainly with the conversion of carbohydrate derivatives into functionalized cyclohexanes and cyclopentanes, goes to Fraser-Reid and Ferrier. An unembellished account of all the published work in this regard was excellently reviewed recently by Ferrier and Middleton.[14]

The key to successful transformation of sugars into non-carbohydrate precursors lies in their conversion to '*modifiedsugars*' which can be derived from abundant monosaccharides, with a few simple and easy transformations. These loosely described modified sugars should, in general, contain the conventional functional groups that are encountered very regularly in organic synthesis like a carbonyl group or an olefin. In such a sense, considering the multifaceted synthetic transformations developed in organic synthesis utilizing the olefin moiety, the advantages offered by unsaturated sugars are many. Diverse applications of unsaturated sugars during the last two decades underscore the increasing role which such carbohydrates play in modern synthetic organic chemistry. Due to their easy accessibility amongst the various regioisomeric unsaturated sugars, the 1,2-, and 2,3-unsaturated sugars are central to most developments in this area. Since the main thrust of this thesis is on the reactions and synthetic utility of 1,2-cyclopropanated sugars, and considering the fact that cyclopropanes resemble double bonds, a brief summary of the recent applications of 1,2-unsaturated sugars in organic synthesis is appropriate. The emphasis is heavily on electrophilic additions. This is to be expected, especially as 1,2-unsaturated sugars or glycals are enol ethers and hence possess an electron rich double bond readily susceptible to electrophilic reactions. A second aspect, covered in the latter half of the introduction, pertains to recent developments in glycosidation techniques using glyeals, in view of the importance of oligosaccharides in many biological processes.

A common method for the synthesis of 1,2-unsaturated sugars on a large scale involves the treatment of peracetylated glycosyl halides with zinc in acetic acid, an age-old but efficient method even today.[15] The first synthesis of the earliest reported 1,2-unsaturated sugar, 3,4,6-tri-*O*-acetyl-D-glucal (1) was by Emil Fischer in the beginning of this century (glucal was the anomalous, trivial name given from the incorrect observation that it shows aldehydic properties, positive Fuschin SO_2 test). Various other alternative metals like alkali metals, Cr(II), Zn(Ag), Al(Hg), SmI_2, and Ti have been used to avoid the cumbersome acidic conditions associated with the Zn-AcOH reductive dehalogenation. [16]



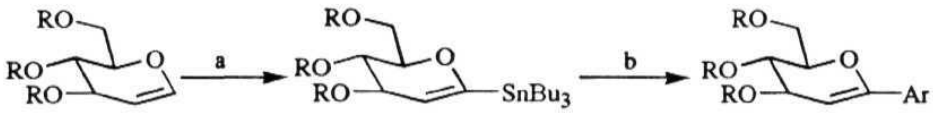
2 1

Scheme 1. *Reagents and Conditions:* a) Zn, $CuSO_4$, AcOH, -10 - 0°

Glycals can also be obtained by reductive elimination of phenyl thioglycosides,[17] base induced rearrangement of 2,3-anhydrosugars,[18] deoxygenation of 1,2-anhydroaldopyranoses[19] or by radical elimination[20] of 1,2-thiocarbonates. On the other hand, Danishefsky[12] has used the hetero Diels-Alder reaction of suitably substituted dienes and dienophiles to acquire highly functionalised glycals in an *ab-initio* synthesis of unsaturated sugars from non-carbohydrate precursors.

Routes for the synthesis of C-1 substituted glycals have also been developed. Recently, Lopez and Gomez[21] have reported a simple method for the synthesis of C-l alkylated glycals by treatment of haloglycosides with the corresponding alkyllithium. The presence of the C-aryl glycosidic linkage in different antitumor antibiotics[22] such as the ribuflavins, gilvocarcins and urdamycins has led to the development of various approaches for their construction utilizing C-l aryl glycals.[23] A general method to obtain C-l aryl glycals utilizes the Pd-mediated

coupling reaction (Scheme 2). Reaction of O-alkylated glycals with t-butyllithium (t-BuLi) results in lithiation at C-1, which on treatment with tributyltin chloride (Bu_3SnCl) provide stannylated glycals. These were converted into C-l aryl glycals by application of Pd-catalyzed coupling reactions.[24] In yet another approach, C-l aryl glycals were prepared by the addition of aryl Grignard reagents to sugar lactones, followed by dehydration with the Martin sulfurane ($Ph_2S[OC(CF_3)_2Ph]_2$).[25]

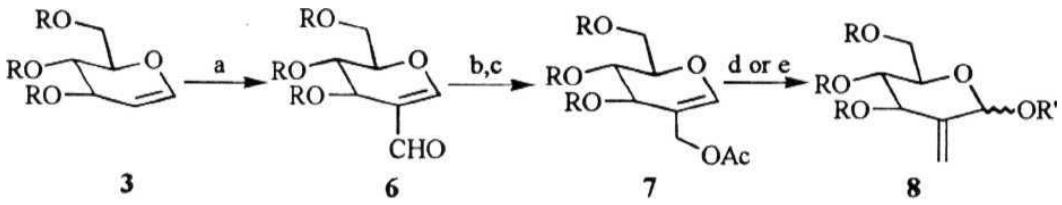


3 4 5

R = protecting group Ar = aryl

Scheme 2. *Reagents and Conditions*: a) t-BuLi, THF, -78° – 0°, Bu_3SnCl; b) $Pd(PPh_3)_4$, ArBr, toluene.

Vilsmeier forms lation of alkyl protected glycals,[26] on the other hand, has provided an easy access to C-2 formylated glycals (Scheme 3). The acetate 7 obtained from the unsaturated aldehyde 6 following a sequence of reduction and acetylation was shown to undergo the Ferrier rearrangement with various aliphatic and aromatic alcohols, providing C-2 methylene glycosides.[26b,c]



3 6 7 8

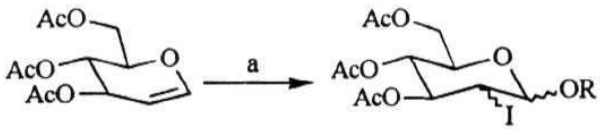
R = protecting group R' =Alkyl (d) or aryl (e)

Scheme 3. *Reagents and Conditions:* a) $POCl_3$, DMF, 0° - rt; b) $NaBH_4$, MeOH, rt; c) acetic anhydride, pyridine, cat. DM AP; d) ROH, BF_3:Et_2O, benzene; e) PPh_3, dicthyl azodicarboxylatc (DEAD), CH_2Cl_2, ArOH.

In contrast to other unsaturated sugars, in glycals, the presence of the ring oxygen makes the C-2 carbon more nucleophilic as in simple enol ethers. TTierefore, their most important reaction is with electrophiles. The directing effect of the bulky C-3 alkoxy or acyloxy substituent permits addition of a variety of electrophiles in both a regio- and stereoselective manner. Besides these, [4+2] and [2+2] cycloadditions, intramolecular [l,3]-nitrone and nitrile oxide cycloadditions, [2,3]-Wittig and [3,3]-Claiscn and a7.a-Claisen rearrangements are also known with glycals. In the following pages, some salient features of these reactions are presented.

The enhanced nucleophilicity of the glycal double bond taken together with the fact that various 2-deoxyglycosides are attached to the aglycon portions of naturally derived antibiotics, has led to the development of numerous methods to convert glycals into these modified sugar units. Direct conversion of glycals to 2-deoxyglycosides in the presence of mineral acids results in competing reactions leading to rearranged products. Therefore, electrophilic glycosidation of glycals, followed by reductive removal of the electrophile, constitutes a general method for the synthesis of 2-deoxyglycosides.

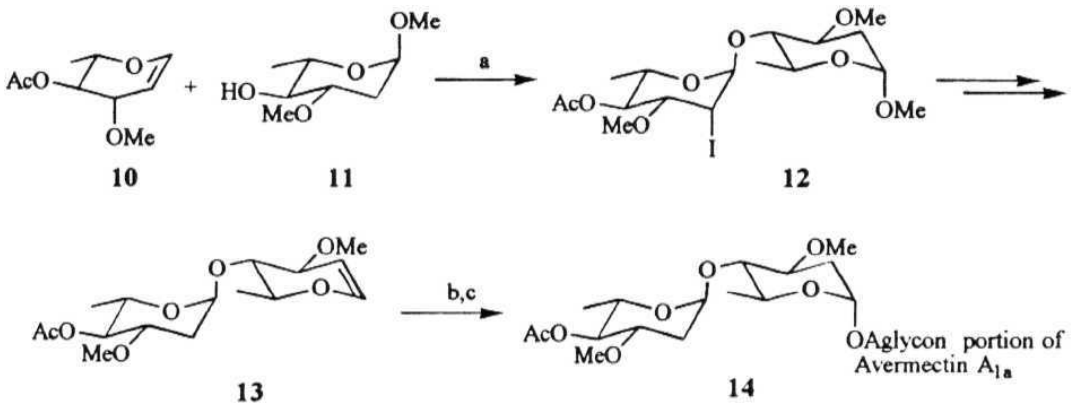
Since the earliest attempts by Lemieux[27] to add halonium ions to glycals in the presence of alcohols or sugar alcohols as nucelophiles three decades ago, this field has undergone an explosive expansion, resulting in several more practical electrophilic promoters in this pursuit. The original procedure developed by Lemieux[27"] involved the reaction of a glycal and an alcohol in the presence of iodine (I_2), a silver salt and a base, giving 2-deoxy-2-iodoglycosides in good yield (Scheme 4). Later, N-iodosuccinimide (NIS, Thiem), iodonium di-(*s*-collidine) perchlorate (IDCP - Lemieux[27b] and Danishefsky [29]), N-bromosuccinimide (NBS) and 1,3-dibromo-5,5-dimethylhydantoin (Tatsuta)[30] were used as sources of halonium ions.



1 9

Scheme 4. *Reagents and Conditions:* a) I_2, $AgClO_4$, *s*-collidine, ROH.

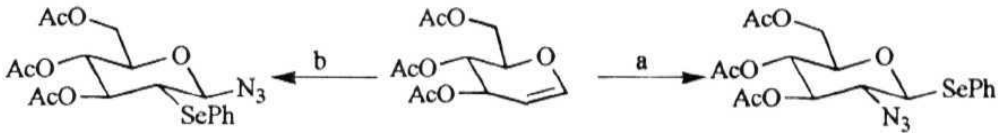
The NIS mediated addition to glycals as a glycosidation step was used by Danishefsky in the total synthesis of avermectin as shown below (Scheme 5).[31]



Scheme 5. *Reagents and Conditions*: a) NIS; b) NIS, HO-aglycon; c) $LiEt_3BH$.

Similarly, Tatsuta has used Br^+, either from NBS or 1,3-dibromo-5,5-dimethylhydantoin as an activator, in the total synthesis of carbomycin B and leucomycin A_3.[32] Many other electrophiles like NO^+ (from NOCl),[33] PhSeCl,[34,35] acetyl hypofluorite,[36] phenylsulfenate esters in the presence of TMSOTf,[37] and phenyl bis(phenylthio) sulfonium salts[38] were successfully added to glycals. Through nitrosochlorination[33] or azidonitration,[39] glycals have functioned as precursors for N-acetylglucosamine or N-acetylgalactosamine donors. The Markonikov or anti-Markonikov addition of azido or phenylseleno groups to glycals to procure either

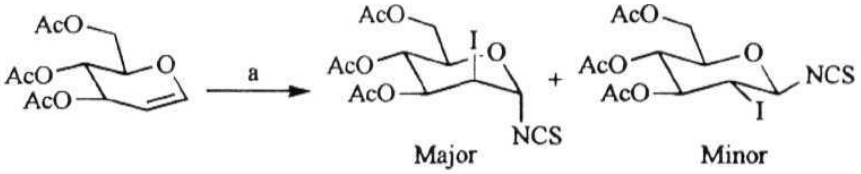
seleno[34] or azido[35] glycosides was carried out by proper tuning of the reaction conditions employed (Scheme 6).



16 1 **15**

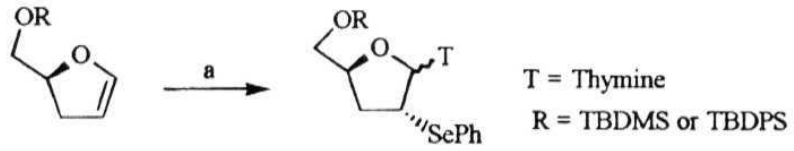
Scheme 6. *Reagents and Conditions:* a) NaN_3, $(PhSe)_2$, $PhI(OAc)_2$, CH_2Cl_2; b) PhSeCl, NaN_3, DMF.

Recently, iodine and phenylselenyl chloride mediated additions were shown to be useful to couple isothiocyanates,[40] amino acids[41] and nucleobases[42] to glycals (Schemes 7, 8 and 9).



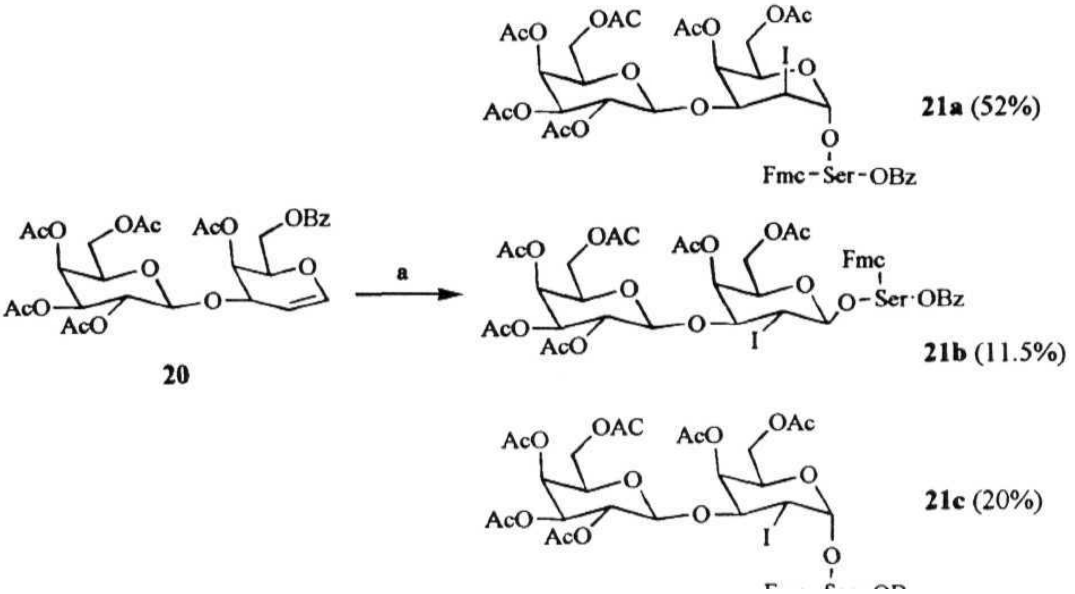
1 **17**

Scheme 7. *Reagents and Conditions*: a) I_2, KSCN, SiO_2, $CHCl_3$.



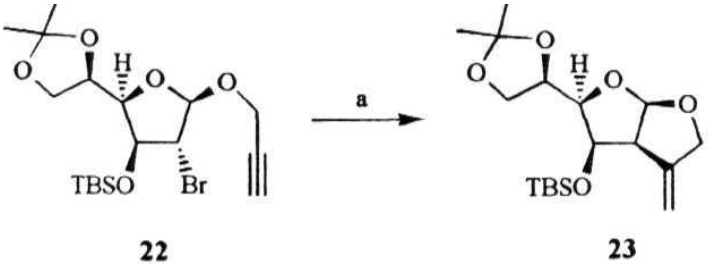
18 **19**

Scheme 8. *Reagents and Conditions*: a) Thymine$(TMS)_2$, PhSeCl, Ag(OTf), ether.



Scheme 9. *Reagents and Conditions:* a) NIS, CH_3CN-CH_2Cl_2, Fmc-Ser-OBz.

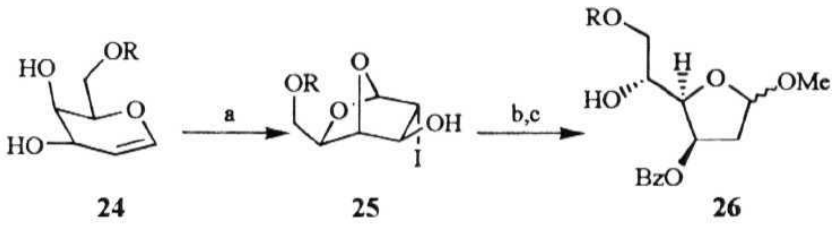
Such a halonium ion mediated oxidative addition of unsaturated alcohols followed by radical ring closure has been shown to be a facile method for the annelation of tetrahydrofuran units (Scheme 10).[43]



Scheme 10. *Reagents and Conditions:* a) AIBN, Bu_3SnH.

Recently, intramolecular nucleophilic participation of the 4-OH group, resulting in a bicylic system, in electrophilic additions of a suitably protected

galactal derivative was reported. The intermediate bicyclic derivatives were converted to functionalised tetrahydrofiirans (Scheme 11).[44]



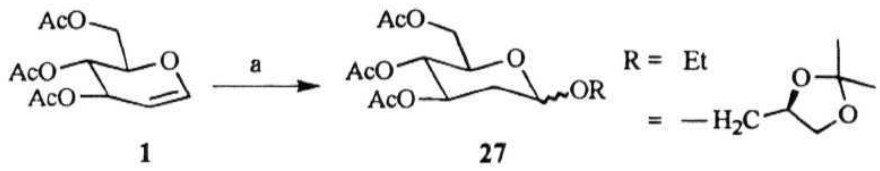
24 25 26

R = Piv or TBDMS

Scheme 11. *Reagents and Conditions*: a) $(Bu_3Sn)_2O$, 3Å sieves, CH_3CN, reflux; then NIS, 0°; b) BzCl; c) 0.01M HCl, MeOH.

The disadvantage associated with mineral acid-catalyzed addition of alcohols to glycals has led to the development of very mild activators like camphorsulphonic acid (CSA),[4] *p*-toluenesulphonic acid (PTSA),[46] triphenyphosphinehydronium bromide (PPH_3:HBr, TPHB)[47] and several acid resins[48] to convert glycals to the required 2-deoxyglycosides.

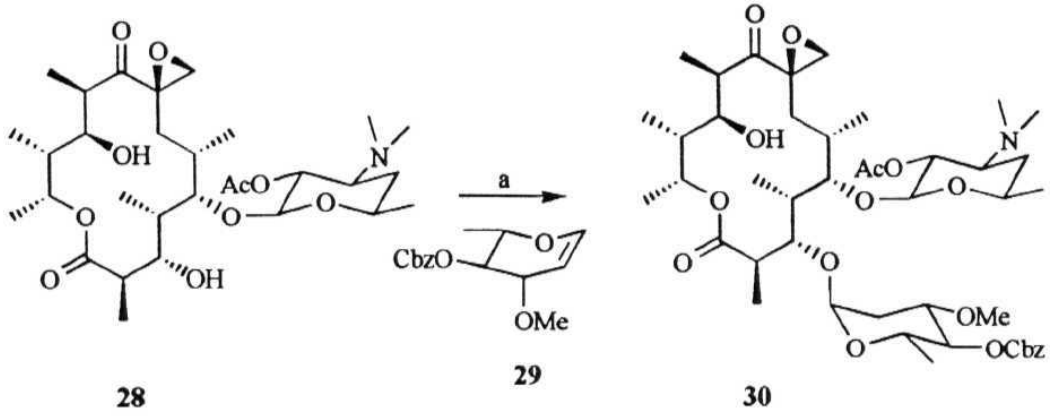
Thus, ethanol was added to triacetylglucal in the presence of a catalytic amount of PPh_3:HBr, resulting in the corresponding ethyl 2-deoxyglycoside with 78% α-anomeric selectivity. A similar addition of 1,2-*O*-isopropylidine-D-glycerol proceeded with about 95% α-selectivity (Scheme 12).[47]



1 27

Scheme 12. *Reagents and Conditions*: a) ROH, cat.TPHB, CH_2Cl_2.

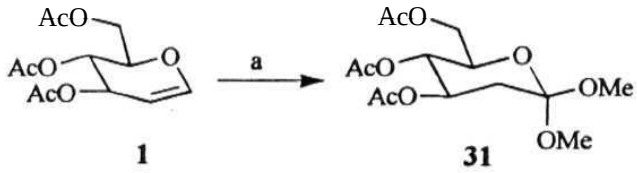
Likewise, camphorsulphonic acid has been employed as a promoter in the construction of the second glycosidic linkage of oleandomycin as illustrated in Scheme 13.[49]



28 29 30

Scheme 13. *Reagents and Conditions:* a) CSA, 32°.

Interestingly, the palladium mediated glycosidations of glycals led to the formation of 2-deoxyorthoester derivatives (Scheme 14).[50]

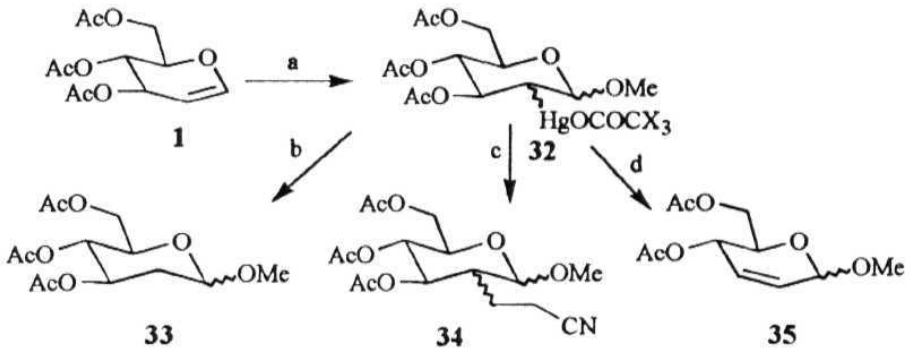


1 31

Scheme 14. *Reagents and Conditions*: a) MeOH, $PdCl_2(CH_3CN)_2$, $NaHCO_3$.

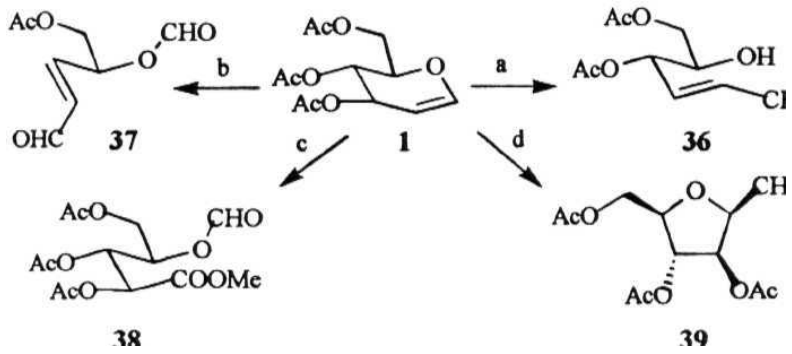
Addition of mercury salts to glycals result in 2-deoxy-2-mercurio sugars, which on subsequent reductive removal of mercury provide either 2-deoxyglycosides,[51] 2-deoxy-2-C-branched-chain glycosides[52] or 2,3-unsaturated sugars, depending upon the reagents and conditions employed.

The 2-deoxy-2-mercurioglycoside 32, obtained by the addition of mercuric acetate or mercuric trifluoroacetate in methanol to triacctylglucal 1, was converted to the 2-deoxyglycoside 33 by treating with sodium borohydride, while the same reductive demercuration in the presence of acrylonitrile resulted in a 2-deoxy-2-C-branched-chain glycoside 34. Treatment of 32 with thiourea gave the 2,3-unsaturated sugar 35 (Scheme 15).



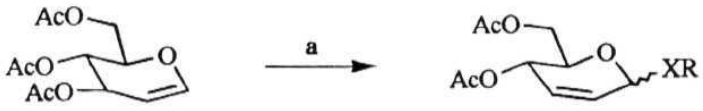
Scheme 15. *Reagents and Conditions*: a) $Hg(OAc)_2$ or $Hg(CF_3COO)_2$, ROH; b) $NaBH_4$, MeOH; c) $NaBH_4$ or Ph_3SnH, acrylonitrile, MeOH; d) $(NH_2)_2C=S$.

Reaction of triacetylglucal 1 with a catalytic amount of mercuric sulfate-sulfuric acid in water-dioxane provided the *trans*-unsaturated aldehyde **36**,[54] whereas the oxidation of 1 with *m*-chloroperbenzoic acid (MCPBA)[55] resulted in an unsaturated aldehyde 37 with one carbon loss. On the other hand, ozonolysis[56] of 1 resulted in an ester 38 also with one carbons loss, while the reaction with thallic nitrate[57] proceeded *via* ring contraction yielding the C-furanoside 39. These examples amply demonstrate the versatility of 1 to provide either open chain analogues with one, two or three chiral centres or furan derivatives, in a single step, possessing diverse functional groups and amenable to further modifications (Scheme 16).



Scheme 16. *Reagents and Conditions:* a) cat.$HgSO_4$-H_2SO_4, H_2O-dioxane; b) MCPBA, BF_3:Et_2O, -20° - 25°; c) O_3, CH_2Cl_2, MeOH; and Et_3N, Ac_2O; d) $Tl(NO_3)_3$, CH_3CN.

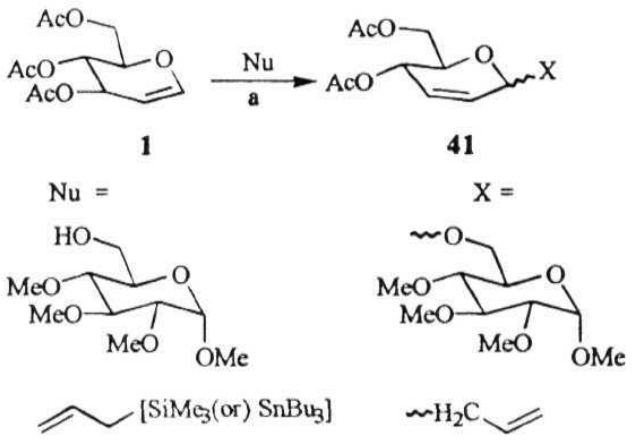
Another important reaction of glycals is the Ferrier rearrangement.[58] The reaction of glycals with various nucleophilic (O-, N-, S- and C-) agents, mediated by Lewis acids, yielding 2,3-unsaturated glycosides, is a widely employed general method for the synthesis of 2,3-unsaturated sugars (Scheme 17).



1 X = O, N, S or C 40

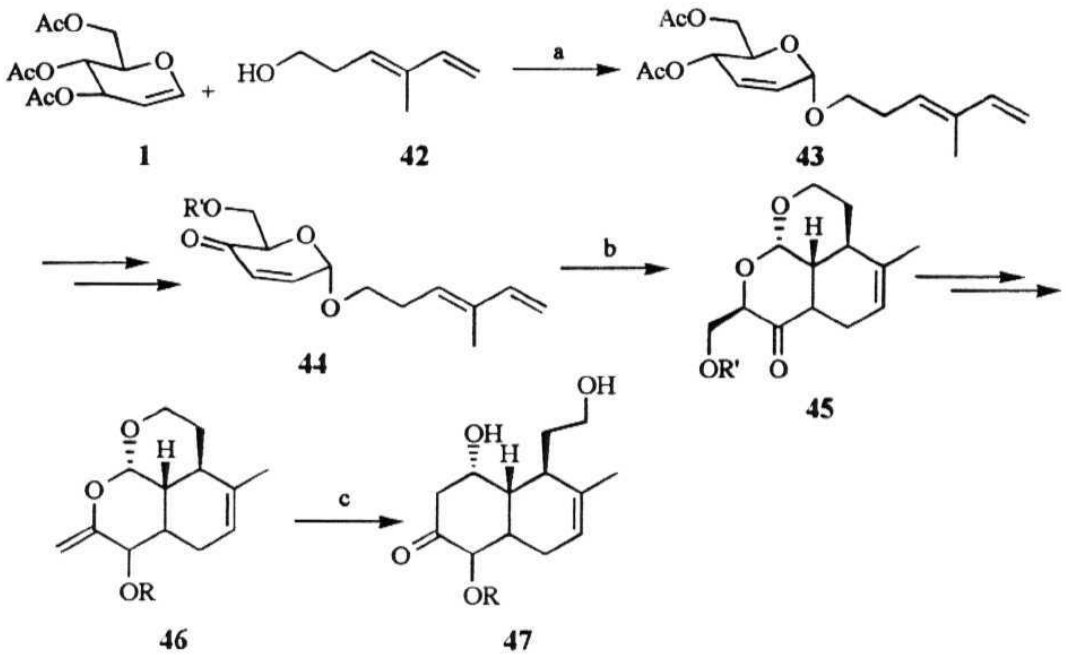
Scheme 17. *Reagents and Conditions:* a) BF_3:Et_2O, nucleophile, solvent.

Recently, such a rearrangement was shown to be feasible with the acidic clay montmorillonite K-10,[59] illustrating the potential use of glycals to derive natural and unnatural glycosides in an environmentally compatible manner (Scheme 18).



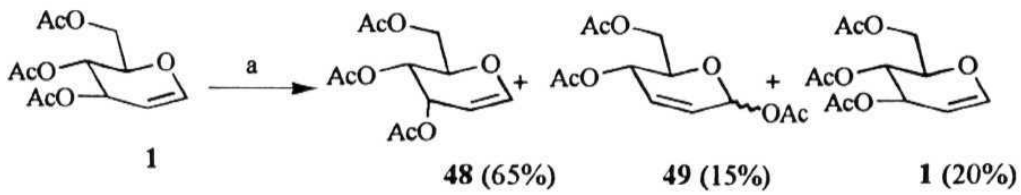
Scheme 18. *Reagents and Conditions*: a) 10 - 30% clay, CH_2Cl_2, 25°.

The acid catalyzed Ferrier rearrangement of glycals allows the anchoring of various dienic moieties at the glycosidic carbon. Subsequent use of the intramolecular Diels-Alder reaction (IMDA) in sugar templates constitutes a facile approach to fused carbocyclic systems. The highly oxygenated bicyclic system 47 was thus realized from 1 in a few steps, using a tandem oxy-Ferrier-IMDA-carbocyclic Ferrier rearrangement (Scheme 19).[60] Ferrier reaction of 1 with the diene alcohol 42, followed by saponification, selective 6-OH protection and subsequent oxidation gave the required system for the IMDA protocol. The IMDA reaction resulted in a single *endo*-isomer 45. This on further transformations *via* an exocyclic double bond from 6-OH followed by the carbocyclic Ferrier rearrangement resulted in 47.



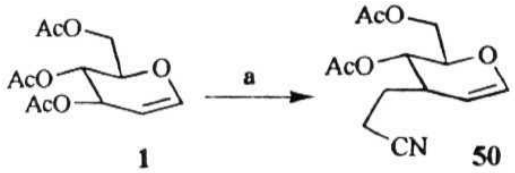
Scheme 19. *Reagents and Conditions*: a) $BF_3{:}Et_2O$, CH_2Cl_2; b) toluene, 155°; c) $Hg(OAc)_2$, AcOH, acetone-water, reflux.

The use of transition metal salts to carry out the Ferrier rearrangement led to an interesting observation. It was found that the use of molybdenum salts[61] resulted in a normal rearrangement, while nickel salts[62] were found to primarily epimerise the C-3 acetyloxy group. The major product was the C-3 epimeric glycal 48 along with small amounts of the rearranged product 49 (Scheme 20).



Scheme 20. *Reagents and Conditions*: a) $NiCl_2{\cdot}6H_2O$, Ac_2O, 100°.

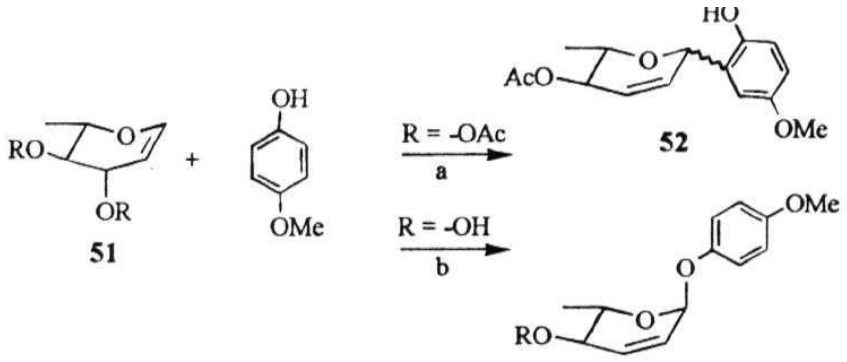
Under standard Lewis acid catalyzed conditions, as shown in Scheme 21, the use of Zn/Cu-nucleophiles resulted predominantly in C-3-branched carbohydrates with complete retention of stereochemistry at C-3.[63]



1 50

Scheme 21. *Reagents and Conditions*: a) BF_3:Et_2O, THF, -25° – rt, $NCCH_2CH_2Cu(CN)ZnI$.

An apparent disadvantage in the acid catalyzed Ferrier rearrangement with phenols is competitive C-glycosidation. However, Mitsunobu conditions were shown to be an useful alternative in this regard (Scheme 22).[64, 26c]

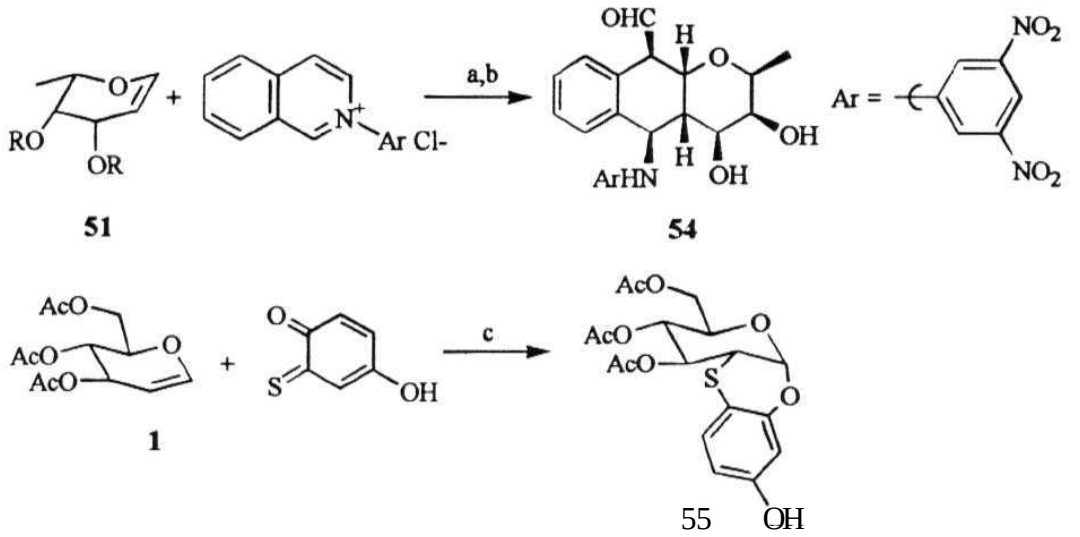


51 52 S3

Scheme 22. *Reagents and Conditions:* a) BF_3:Et_2O, CH_2Cl_2, -78°; b) DEAD, PPh_3, CH_2Cl_2, 0°.

The electron rich nature of the glycal double bond has also allowed them to partake as dienophiles in inverse electron demanding Diels-Alder processes, with

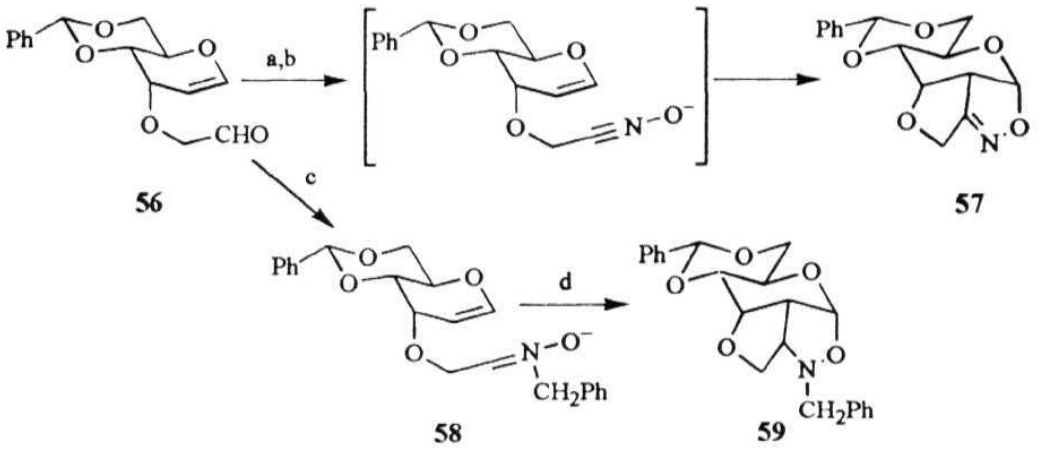
either isoquinolinium salts,[65] or as shown very recently, with *o*-thioquinone (*α*-oxothiones)[66] as heterodienes (Scheme 23).



Scheme 23. *Reagents and Conditions:* a) MeOH, $CaCO_3$, 55° - 60°; b) 1N HCl, CH_3CN, rt; c) DMF, 60°

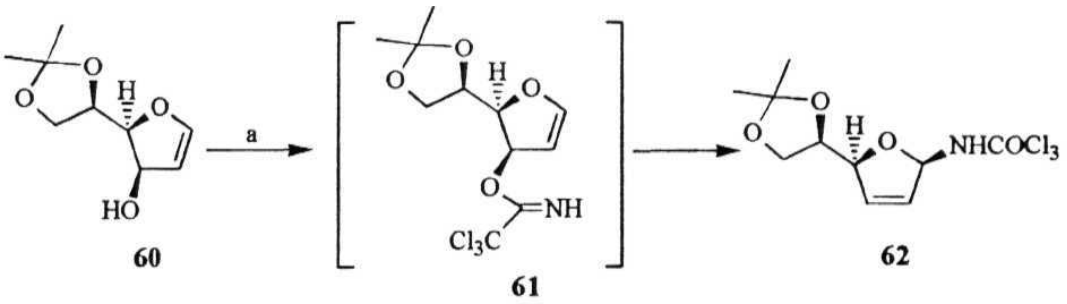
The 1,3-dipolar cycloaddition of nitrile oxides and nitrones to alkenes has proved extremely useful in synthesis, largely because the reaction usually proceeds in a highly stereocontrolled manner.[67] With glycals, of late, the viability of such a 1,3-dipolar cycloaddition in an intramolecular fashion has been demonstrated.

Condensation of the glycal derived aldehyde 56 with hydroxylamine and subsequent oxidation with N-chlorosuccinimide (NCS) provided for spontaneous intramolecular nitrile oxide cycloaddition, leading to isooxazoline 57 as a single isomer, whereas the nitrone 58, derived by the addition of N-benzy lhydroxylamine afforded exclusively the isooxazolidine 59 on standing (Scheme 24).[68]



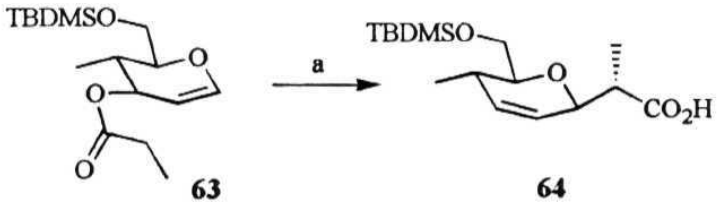
Scheme 24. *Reagents and Conditions*: a) NH_2OH; b) NCS, pyridine, CH_2Cl_2; c) N-benzylhydroxylamine, $CaCl_2$, ether; d) standing at rt.

On similar lines, an unusual and spontaneous [3,3]-aza-Claisen rearrangement was observed in glycal 60.[69] The alkylation of glycal 60 with trichloroacetonitrile directly resulted in the amide 62 in good yields, without isolation of any of the expected imidate derivative 61 as an intermediate (Scheme 25).



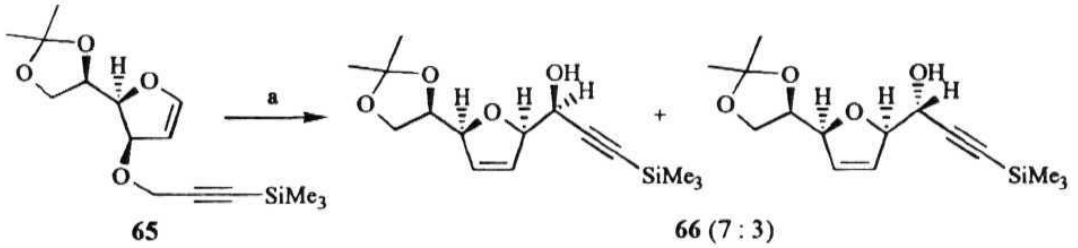
Scheme 25. *Reagents and Conditions*: a) NaH, Cl_3CCN, ether, 0°.

The Ireland modified Claisen rearrangement of 3-acyloxy substituted glycals (Scheme 26) has been established as a general method for the synthesis of C-saccharides.[70]



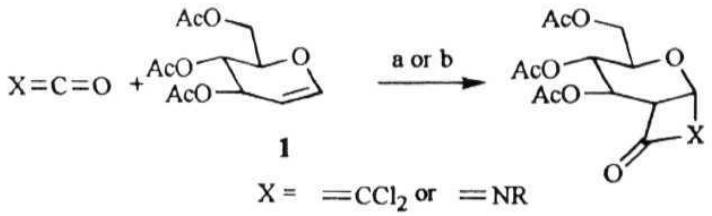
Scheme 26. *Reagents and Conditions*: a) LDA, THF, -78°, TMSCl then 70°.

As shown below (Scheme 27), the [2,3]-Wittig rearrangement of the trimethylsilyl-propargylic ether of glycal 65 was used to synthesize *cis-2,5*-disubstituted dihydrofurans 66 with a predominant *erythro* selectivity.[71]



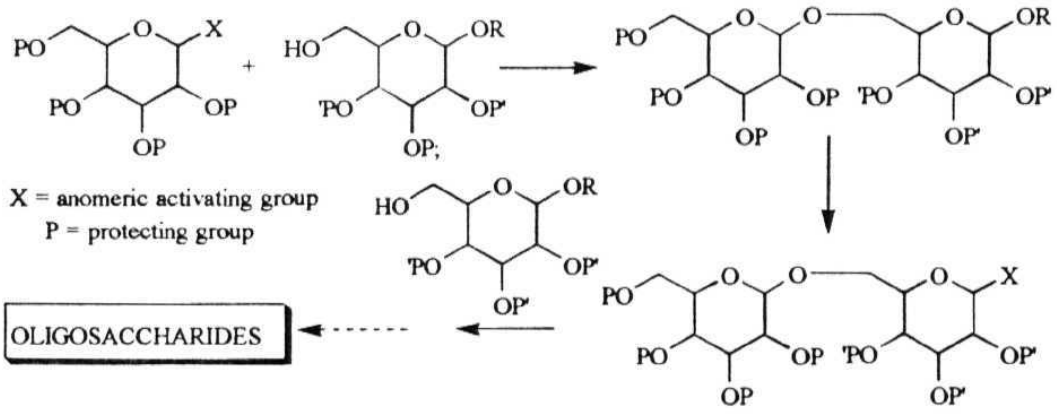
Scheme 27. *Reagents and Conditions*: a) n-BuLi, THF, -5°.

In recent times, the [2+2] cycloadditions of dichloroketene[72] and chlorosulfonyl isocyanate[73] were shown to proceed exclusively on the face opposite to the C-3 substituent (Scheme 28). The isocyanate addition to glycals has now been widely accepted as a general solution for the chiral construction of β-lactam containing antibiotics e.g., clavans and 1-oxacephems.[73]



Scheme 28. *Reagents and Conditions*: a) Cl_3CCOCl, Zn-Cu, ether, 0°; b) Na_2CO_3, chlorosulfonyl isocyanate.

Recently, glycals have served as precursors in a versatile route for the synthesis of oligosaccharides. The main challenge involved in the synthesis of oligosaccharides is the stereoselective formation of the glycosidic linkage between the activated centre of a glycosyl donor and the hydroxyl function of a suitably protected glycosyl acceptor (Scheme 29).



Scheme **29.**

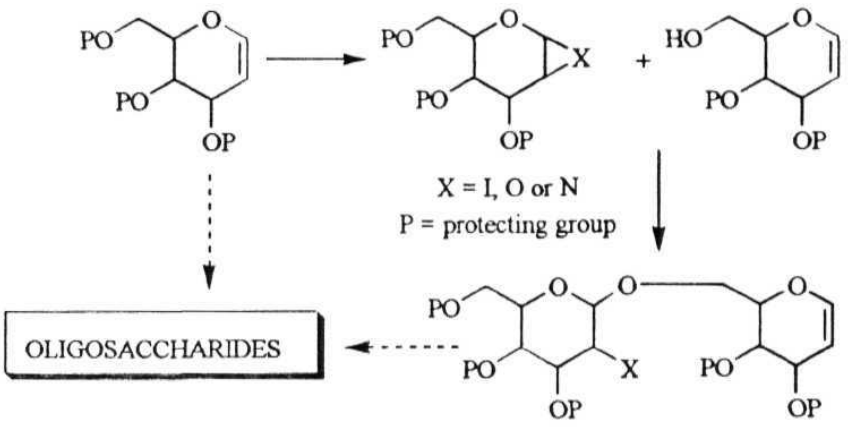
Controlling the stereochemical outcome of glycosidation has always been a major goal of carbohydrate chemists. Dating from the work of Fischer,[74] Koenig and Knorr,[75] extensive and ingenious approaches towards the stereocontrol led assembly of oligosaccharides from monosaccharides have revealed how fine tuning of various factors like variation of anomeric activating group, role of protecting groups at

various positions both in acceptor and donor glycoside, and the choice of activators employed play a crucial role in deciding the stereoselectivity of the glycosidic linkage. In the quest for stereoselective glycosidation, amongst the many methods evolved, the more notable recent ones are:

1. the trichloroacetimidate glycosidation procedure of Schmidt[76]
2. the armed-disarmed concept developed by Fraser-Reid involving 4-pentenyl glycosidic activation[77]
3. on similar lines, the 4-pentenoate glycosidic activation discovered by Kunz[78a] and Fraser-Reid[78b]
4. the two stage-activation protocol of Nicolau[79]
5. Vasella's use of glycoside diazirines[80]
6. the temporary silicon connection approach of Stork[81]
7. the matched-mismatched glycosidation technique of van Boeckel[82]

A common feature in all the above methods is the important role played by the C-2 substituent in the glycosyl donor as well as the leaving group at the anomeric centre, which also influences the mode of glycosidation.

In this context, an elegant approach evolved by Danishefsky,[83] without such manipulations either at the anomeric or C-2 carbons, takes advantage of the stereospecific formation of a 3-mcmbered intermediate from a glycal (donor unit), which is subsequently opened in a transannular fashion with a nucleophile (acceptor unit), resulting in a disaccharide. As shown in Scheme 30, the symbol X covers two possibilities. In one instance, X represents a non-isolable (onium) intermediate arising from the attack of E^+ on a glycal. Alternatively, X can be oxygen or nitrogen, thus representing an isolable epoxide or aziridine that subsequently reacts with the nucleophile.



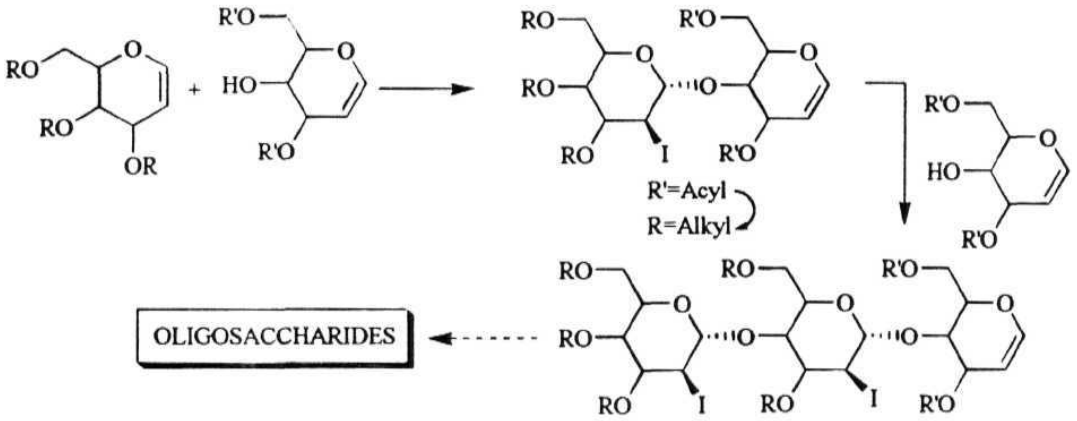
Scheme 30.

The participation of glycals as donors in glycosidations has been well established. The beauty of this process "aimed at exploiting glycals in the pursuit of iterative synthesis of oligosaccharides of biological significance",[84] is that all the intermediates can be derived from glycals, as the glycosyl acceptor is also **a** modified glycal with a free -OH group and the resulting disaccharide is also a glycal which in turn would readily (with/without modifications) act as a glycosyl donor.

According to the conventions used by Danishefsky, one can delineate the salient features of his achievements under different categories depending upon the type of 3-membered ring involved in the glycosidation step. Similar contributions from others are also included in the presentation which follows.

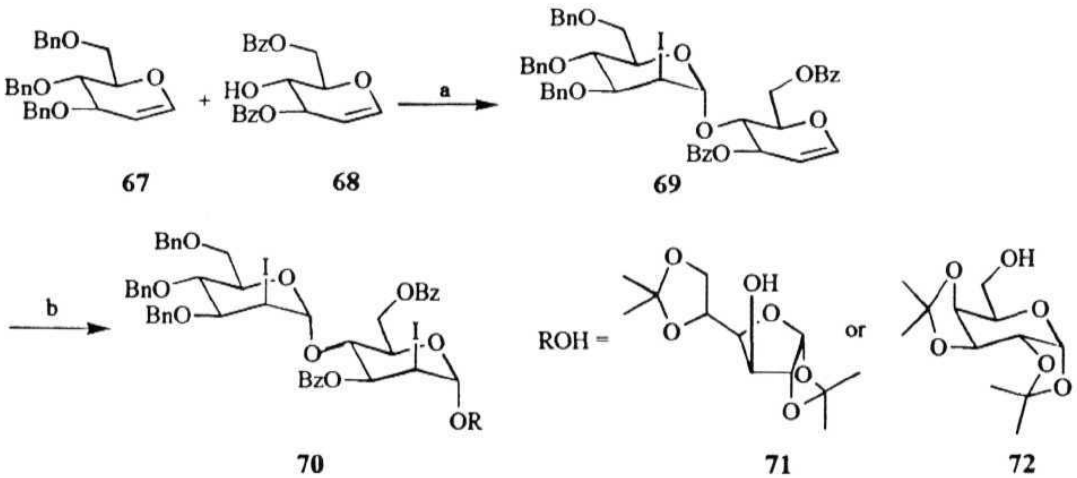
Oxidative coupling of glycals:

The experiments described by Danishefsky involve the oxidative coupling of glycals, using glycals as glycosyl donors as well as glycosyl acceptors, maintaining a subtle difference between the protecting groups employed on both donor and acceptor (Scheme 31).[29a]



Scheme 31.

Thus, iodonium ion mediated coupling of an acceptor glycal 68 containing one free -OH group (protecting the remaining two hydroxyls as benzoate esters, thus suppressing its glycosyl donating efficiency) and the donor glycal 67 protected with benzyl groups, gave the disaccharidic glycal 69, without any other glycals or stereoisomers of 69 as by-products (Scheme 32).

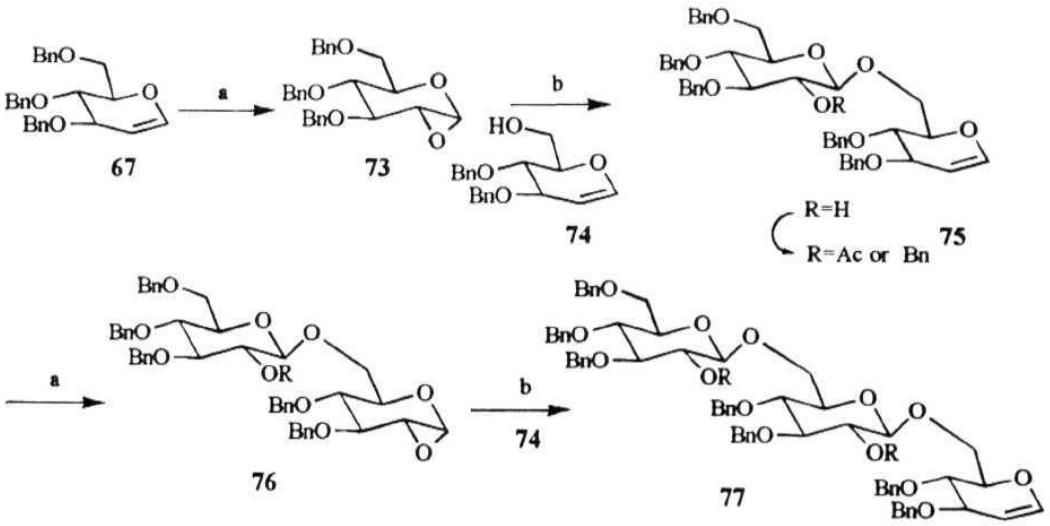


Scheme 32. *Reagents and Conditions*: a) IDCP, CH_2Cl_2, 4Å sieves; b) IDCP and **71** or **72**.

This disaccharidic glycal 69 serves as a donor glycal for the next glycosidation. However, a limitation of this procedure lies in the fact that it always produces trans diaxial α-glycosides.[29a]

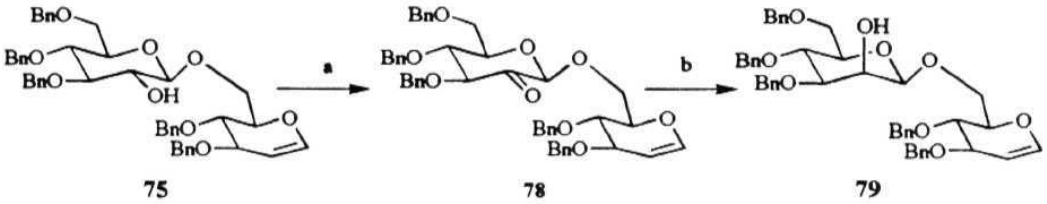
1,2-Anhydrosugars as glycosyl donors for iterative **oligosaccharide** synthesis:

Reactions utilizing the characteristic properties of small rings involving the relief of inherent strain, allow the development of several unique and useful techniques, once their construction can be arrived at in a stereospecific manner. Since the first 1,2-anhydrosugar, Brigl's anhydride,[85] was reported in 1922, several uses of 1,2-anhydrosugars in disaccharide synthesis were investigated. However, few significant advances appeared practical, probably due to the lack of broad availability of such oxiranes and their glycosidations were accompanied by low yields.



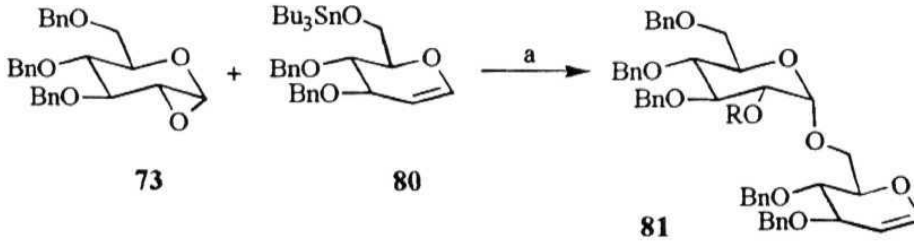
Scheme 33. *Reagents and Conditions*: a) dimethyldioxirane, acetone, CH_2Cl_2, 0°; b) $ZnCl_2$, THF, -78° – rt.

Recently, Danishefsky[86] has carried out the stereospecific synthesis of 1,2-frww-diequatorial β-glycosides. Oxidation of the glycal 67 with dimethyldioxirane yielded the α-oriented 1,2-anhydrosugar 73 which when opened with the glycal 74 under the influence of Lewis acid catalysis, led to the desired disaccharide 75. Upon repetition of the above process, tri- (77) tetra- and oligosaccharides result (Scheme 33).



Scheme 34. *Reagents and Conditions*: a) Ac_2O-DMSO (1 : 2), rt.; b) CH_2Cl_2-MeOH (1 : 1), $NaBH_4$, 0°.

To extend the scope of this methodology, the β-glucosidic disaccharide was converted to the corresponding p-mannosidic disaccharide by inverting the configuration at C-2 following a sequence of oxidation and reduction (Scheme 34).[87] The Barton type deoxygenation of the C-2 hydroxy group, *via* its pentafluorophenyl thiocarbonate, has been employed as an easy entry to 2-deoxy-β-glycosides.[88]

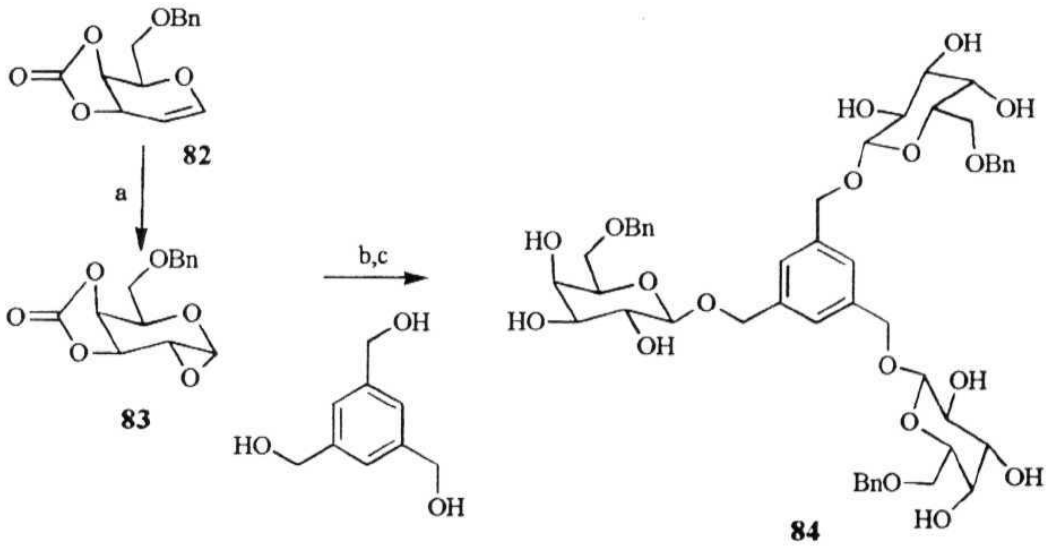


Scheme 35. *Reagents and Conditions*: a) $AgBF_4$, THF, 0°.

Later, it was demonstrated that use of silver tetrafluoroborate as an activator and a stannylated glycal as an acceptor selectively opened the epoxide of

the donor in a *cis* manner, resulting in the corresponding α-glucosidic disaccharide (Scheme 35).[89]

The reactivity of these 1,2-anhydrosugars as glycosidic donors thus can be manipulated in the desired manner to procure oligosaccharides with defined glycosidic linkages. The capability of this glycal-epoxide-glycosidation strategy has been established as a simple route for sugar dendrimers (Scheme 36) with an excellent stereoselectivity.[90] Osmylation of a glycal and trapping the resulting *cis*-diol as a cyclic Sulfate followed by an opening similar to that of the epoxide seems to be a viable alternative for this approach, but has not been as well established.[91]

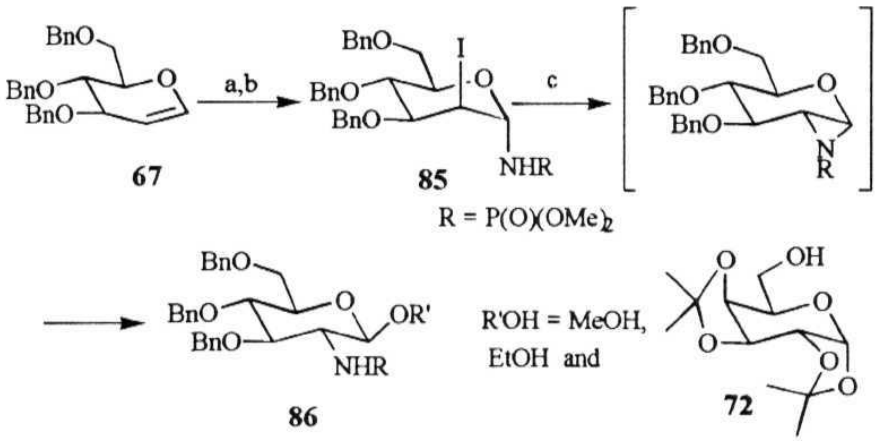


Scheme 36. *Reagents and Conditions*: a) dimethyldioxirane, acetone, CH_2Cl_2, 0°; b) $ZnCl_2$, THF, -78° – rt; c) MeOH, MeONa.

1,2-Azirdinosugars: an indirect aziridination protocol involving **sulfanamido glycosidation** of **glycals:**

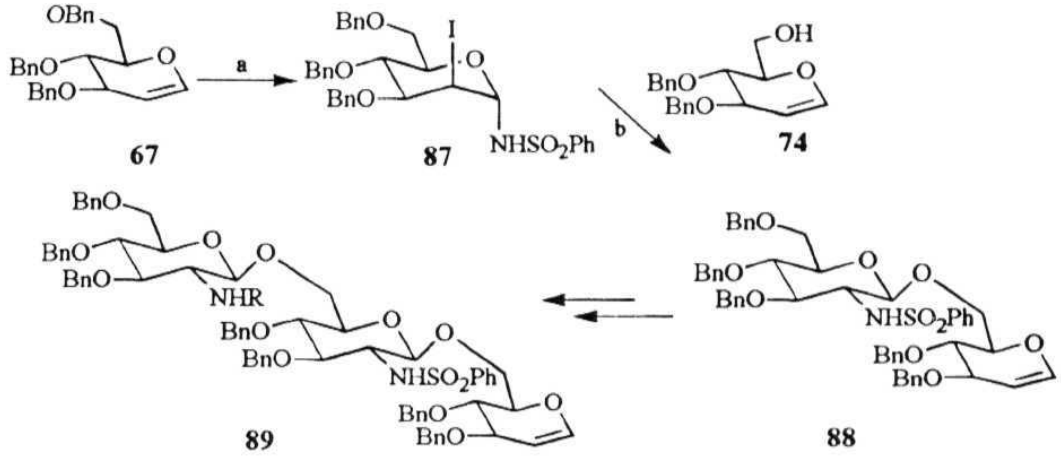
Descotes[92] has shown that a 1,2-aziridinosugar is the intermediate in the conversion of a 2-deoxy-2-iodoglycosylamine derivative to a 2-aminoglycoside (Scheme 37). The addition of iodonium azide to the glycal 61 followed by the

Staudinger reduction of the azide to the amine resulted in the P-iodo phosphoramidate 85. This on treatment with a base in the presence of a nucleophile gave 2-deoxy-2-aminoglycosides presumably through the intermediacy of a 1,2-aziridinosugar. A disaccharide, albeit in low yield has been synthesized by this procedure (Scheme 37).



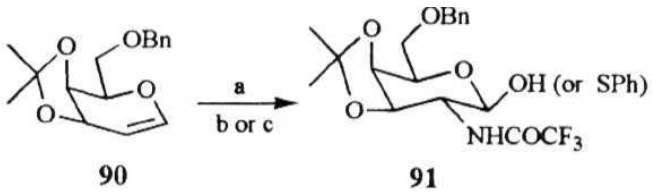
Scheme 37. *Reagents and Conditions*: a) IN_3, CH_3CN; b) $P(OMe)_3$, CH_2Cl_2; c) i) R'OH, R'ONa or ii) KH, DMSO, R'OH.

The method adopted by Danishefsky[93] involves the treatment of a glycal with benzenesulfonamide in the presence of IDCP (Scheme 38) followed by reaction of the resulting 2-deoxy-2-iodo-α-benzenesulfonamide glycoside with lithium tetramethylpiperidide (LTMP) in the presence of silver (I) triflate to generate an a-sulmamidoaziridine in situ. This on further treatment with an acceptor glycal gave the β-2-aminoglucosidic disaccharide. A routine iterative process results in a trisaccharide (Scheme 38).



Scheme 38. *Reagents and Conditions*: a) H_2NSO_2Ph, IDCP, CH_2Cl_2, 4Å sieves, 0^{O}; b) LTMP, AgOTf, THF, $-78^{O} - 0^{O}$.

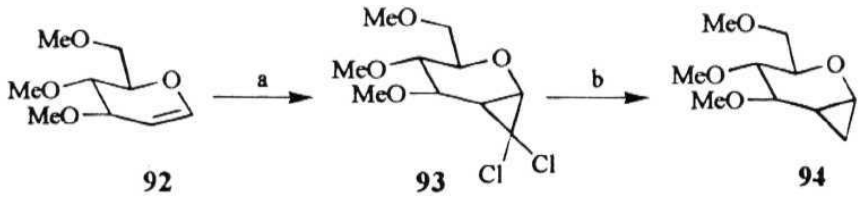
Recently, a similar indirect aziridination (or oxazoline) protocol using manganese reagents for glycal animations has been described by Carreira (Scheme 39). Slow addition of (saltmen) Mn(N) complex to a mixture of a glycal and trifluoroacetic anhydride exclusively transferred the nitrogen to the less hindered face. The resulting intermediate (it is not clear whether an aziridine or oxazoline is involved) was opened successfully with water and thiophenol, affording N-trifluoroacetyl-2-deoxy-2-aminosugars.



Scheme 39. *Reagents and Conditions*: a) (saltmen)Mn(N), $(CF_3CO)_2O$; b) silica gel or H_3O^+; c) PhSH, $BF_3.OEt_2$.

1,2-Cyclopropanated sugars:

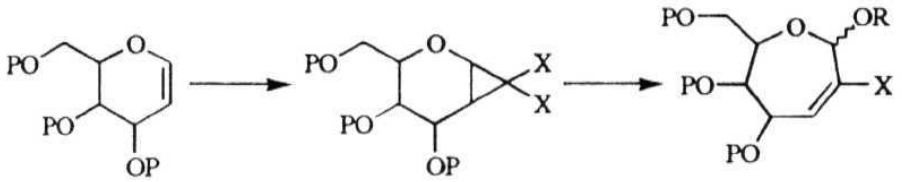
In an analogous way, the other **3-membered** ring that would immediately attract one's attention is a cyclopropane. Although a vast amount of information is available on the cyclopropanation of olefins and the multifaceted reactivity of glycals independently, their association **"glycal-cyclopropane"** has been neglected till recently by the chemical community. However, cyclopropanated sugars are not that rare. Fraser-Reid[95] has extensively studied the cyclopropanation of 2,3-unsaturated sugars and the synthetic utility of the derived **2,3-cyclopropanated** sugars. Gross[96] has reported an easy protocol for dichlorocarbene addition to various unsaturated sugars, with the omission of glycals. A **careful** examination of the literature revealed only a single example on the cyclopropanation of glycals. In 1967, **Brimacombe**[97] described the **synthesis** of **3,4,6-tri-*O*-methyl-1,5-anhydro-2-deoxy-1,2-C-methylene-D-*glycero*-D-*gulo*-hexitol** (94) by addition of dichlorocarbene to **trimethylglucal** 92 followed by **dechlorination** of the adduct with lithium aluminum hydride (Scheme 40). Attempts to add ethyl diazoacetate to triacetylglucal resulted in poor yields and also the stereochemistry of the products could not be determined.



Scheme 40. *Reagents and Conditions*: a) Cl_3CCO_2Et, NaOMe; b) LAH, ether.

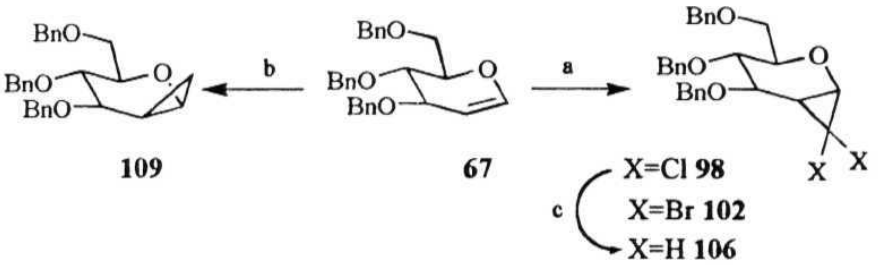
The high reactivity of cyclopropanes and the absence of further work in this area prompted us to study the synthesis and reactions of **1,2-cyclopropanated** sugars. Our interest in **1,2-cyclopropanated** sugars, as shown in Scheme 41, arose from the possibility that the solvolytic ring enlargement of dihalocyclopropanes

would yield chiral oxepins, which either alone or fused with other rings, are encountered in several complex natural products."



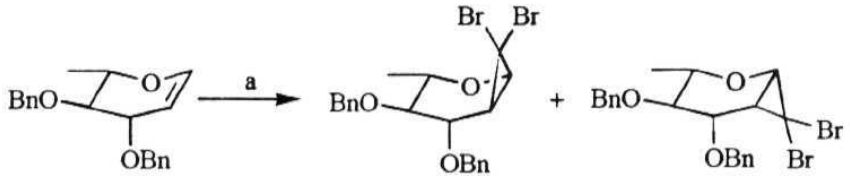
Scheme 41.

In this context, we have developed a convenient face-selective cyclopropanation of appropriately protected glycals.[100] Our strategy exploits the merits of a bulky C-3 benzyloxy substituent in directing the carbene/carbenoid addition. As shown in Scheme 42, the steric hindrance associated with the C-3 benzyloxy group, as expected, directed the bulky dihalocarbene to the less hindered α-face of 3,4,6-tri-*O*-benzyl-D-glucal 67, in agreement with that reported by Brimacombe, whereas the same C-3 benzyloxy group, by coordinating with zinc, directed the cyclopropanation of the glycal to the p-face under Simmons - Smith conditions.

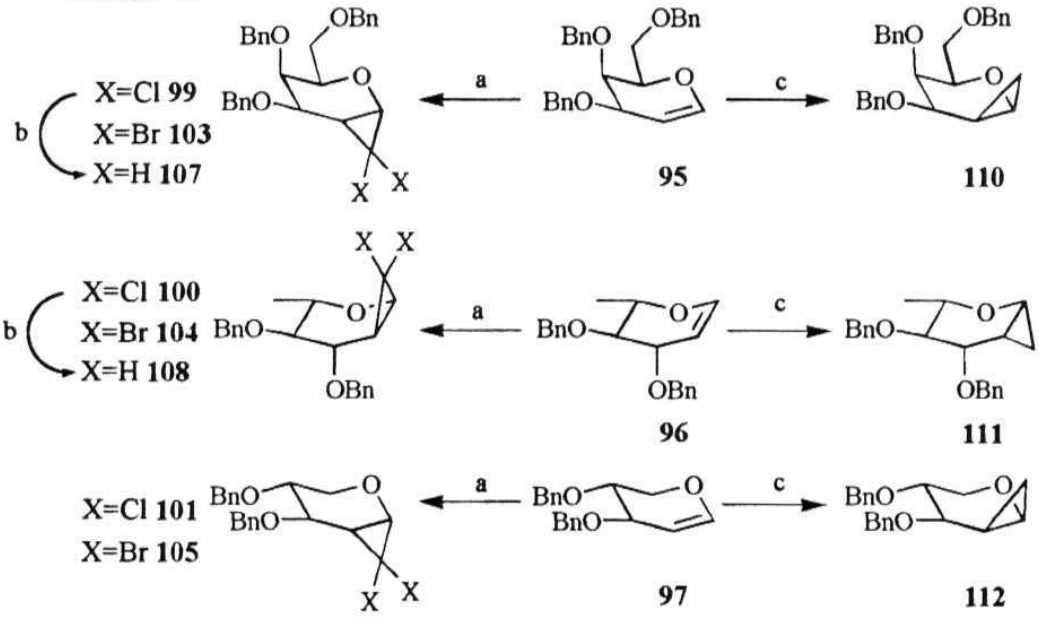


Scheme 42. *Reagents and Conditions:* a) $CHCl_3$, aq. NaOH, cat. $BnEt_3N^+Cl^-$ or $CHBr_3$, aq. NaOH, KF, cat. $BnEt_3N^+Cl^-$; b) Zn, CuCl, CH_2I_2, AcCl, ether, reflux; c) LAH, THF, rt.

The treatment of glycals with dihalocarbenes under phase-transfer conditions resulted in the dihalocyclopropanated derivatives 98 - **101,** and **102, 103 and 105** with an exclusive α-selectivity, barring 3,4-di-*O*-benzyl-L-rhamnal **(96) which** gave **two dibromo** adducts **104a** and **104b in a 7:1 ratio.** These results **are presented in** Schemes **42-44.**



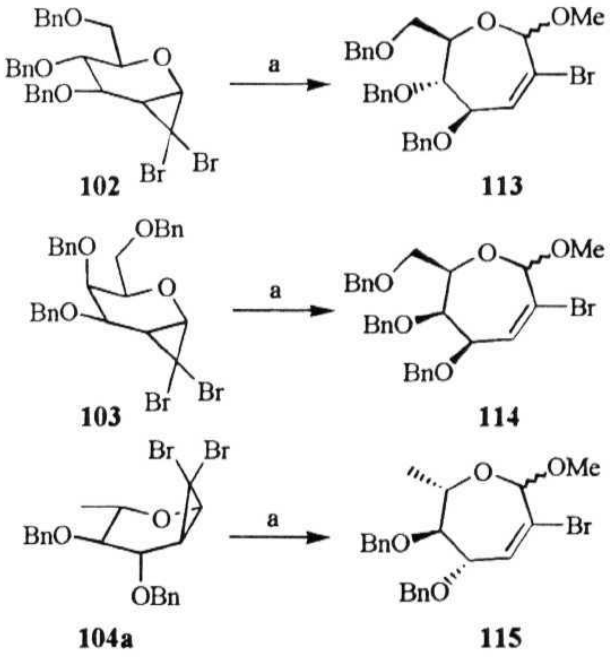
Scheme 43. *Reagents and Conditions*: a) $CHBr_3$, aq. NaOH, KF, cat. $BnEt_3N^+Cl^-$



Scheme 44. *Reagents and Conditions*: a) $CHCl_3$, aq. NaOH, cat. $BnEt_3N^+Cl^-$ or $CHBr_3$, aq. NaOH, KF, cat. $BnEt_3N^+Cl^-$; b) LAH, THF, rt; c) Zn, CuCl, CH_2I_2, AcCl, ether, reflux.

Dchalogenation of the adducts 98-100 with lithium aluminum hydride in THF yielded the parent cyclopropanes 106-108 in good yields. The Friedrich modified version of the Simmons-Smith reaction, using acetyl chloride as an activator, was found to be convenient and single diastereomers were obtained with glycals 67, 95 - 97.

When boiled with excess potassium carbonate in methanol, adducts 102, 103 and 104a underwent smooth solvolysis providing ring expanded oxepins 113 - 115 as anomeric mixtures in good yields (Scheme 45).[101]

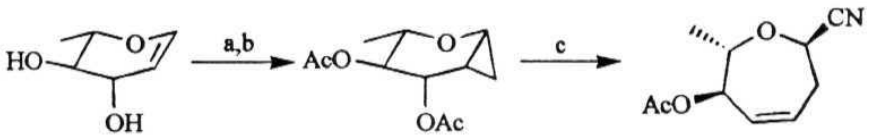


Scheme 45. *Reagents and Conditions*: a) MeOH, K_2CO_3, reflux, 2h.

A little later, Hoberg, Fraser-Reid and van Boom published their work on 1,2-cyclopropanated sugars. A brief description of their endeavors follows.

Hoberg has developed a facile method for the synthesis of highly functionalized seven-membered ring systems utilizing the glycal-cyclopropane-cum-

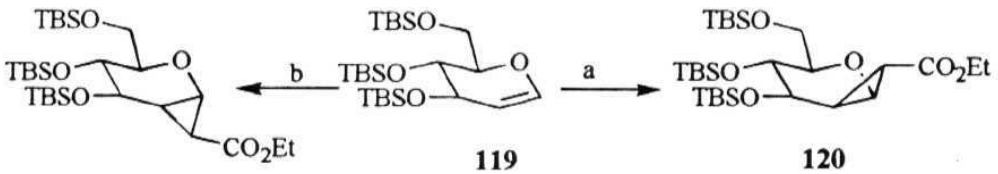
Ferrier rearrangement strategy.[102] The Simmons-Smith cyclopropanation of L-rhamnal 116 followed by acetylation resulted in 117 with 8.7 : 1 (β : a) diastereoselectivity (Scheme 46). This on treatment with trimethylsilyl triflate and trimethylsilyl cyanide in acetonitrile yielded the oxepane **118** in 47% yield.



116 **117** **118**

Scheme 46. *Reagents and Conditions*: a) Et_2Zn, CH_2I_2, toluene, reflux; b) acetylation; c) 10-40% TMSOTf, CH_3CN, TMSCN.

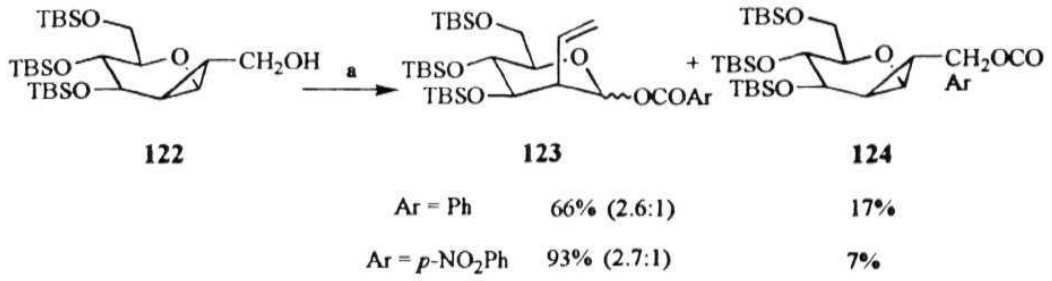
The copper catalyzed decomposition of ethyl diazoacetate in the presence of tri-*O*-tributylsilyl-glucal 119 resulted in stereoselective β-*exo*-carbethoxymethylene addition to give 120 (Fraser-Reid)[103] while the addition catalyzed by $Rh_2(OAc)_2$ gave exclusively the α-*exo* addition product 121 (van Boom[104] and Hoberg[105]) (Scheme 47).



121 **119** **120**

Scheme 47. *Reagents and Conditions*: a) ethyl diazoacetate, Cu, heat; b) ethyl diazoacetate, $Rh(OAc)_2$, CH_2Cl_2.

Thus, the β-*exo*-cyclopropylcarbinol 122 derived from 120 by lithium aluminum hydride reduction, gave an anomeric mixture of 2-deoxy-2C-vinyl mannopyranosides 123 (2.6 :1 anomeric selectivity) using benzoic and *p*-nitrobenzoic acid as nucleophiles under Mitsunobu conditions (Scheme 48).[103]

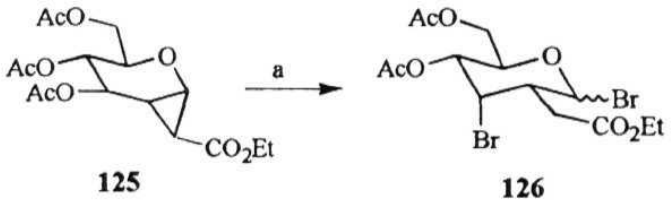


122 **123** **124**

Ar = Ph	66% (2.6:1)	17%
Ar = *p*-NO_2Ph	93% (2.7:1)	7%

Scheme 48. *Reagents and Conditions*: a) Ph_3P, DEAD, $ArCO_2H$, THF, rt.

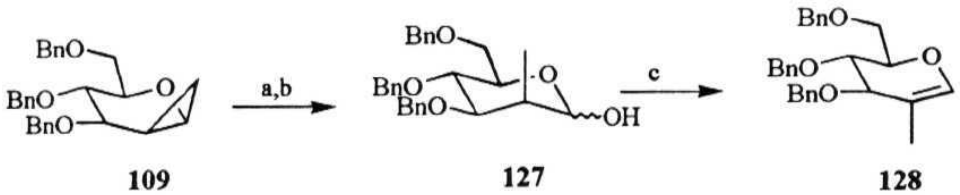
On the other hand, the α-*exo*-carboethoxycyclopropane **125**, prepared by Hoberg from triacetylglucal 1 on reaction with aq. hydrobromic acid gave the glycosyl bromide **126** in a 13 :1 ratio in favour of the p-anomer with displacement of 3-OAc with bromide (Scheme 49).[105]



125 **126**

Scheme 49. *Reagents and Conditions*: a) 30% HBr in AcOH.

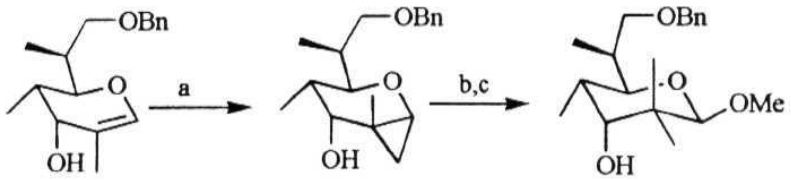
While our work was in progress, Heathcock[106] showed the potential of the cyclopropane ring opening strategy in the preparation of 3,4,6-tri-*O*-benzyl-2-*C*-methyl-D-glucal **128** (Scheme 50) by the electrophilic ring opening of **109** and subsequent dehydration employing mesyl anhydride and triethylamine.



109 **127** **128**

Scheme 50. *Reagents and Conditions*: a) $Hg(CF_3COO)_2$, H_2O-THF; NaCl, b) Bu_3SnH, AIBN; c) Ms_2O, Et_3N.

The modified glycal 129, prepared *via* the hetero Diels -Alder reaction by Danishefsky,[107] under Simmon-Smith conditions gave the cyclopropane 130. This on ring opening with excess NIS in methanol followed by dehalogenation gave the 2,2-dimethyl substituted glycopyranoside 131 (Scheme 51), which served as the C-3-C-9 segment for the synthesis of epothilone A.



129 **130** **131**

Scheme 51. *Reagents and Conditions*: a) Et_2Zn, CH_2I_2, toluene, reflux; b) NIS (excess) MeOH; c) $SnBu_3H$, AIBN.

From this brief survey, the important roles of glycals and glycal derived products in the construction of various chiral building blocks and biologically important sugar residues is instantly apparent. By virtue of the availability of 1,2-cyclopropanated sugars in both forms and their ability to undergo ready cleavage of the cyclopropane ring, it is clear that they can serve as useful precursors for a variety of 2-deoxy-2-C-branched glycosides. The results of our work on 1,2-cyclopropanated sugars are presented in the next chapter.

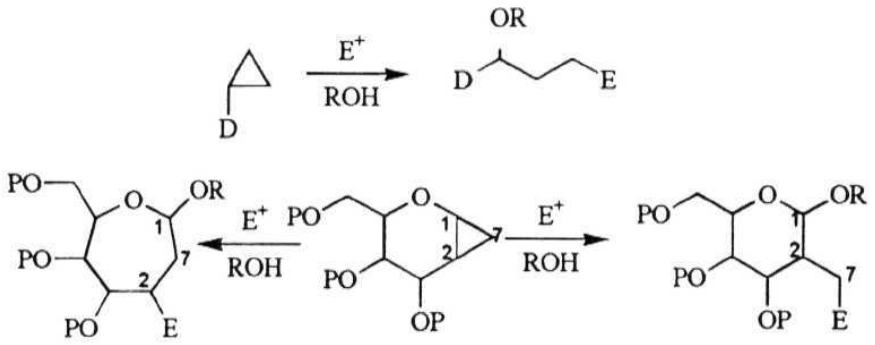
RESULTS AND DISCUSSION

Cyclopropane and its derivatives have been known for over a hundred years.[108] For long, they remained as curiosities, as there were no simple and general methods for their synthesis, till the advent of carbene chemistry in the fifties. Since then, their chemistry has expanded tremendously both in terms of their structure and bonding and their reactions. The similarities in their chemical reactivities to that of alkenes, though attenuated, have contributed to their utility in organic synthesis.[109]

The unusual bonding and strain present in cyclopropanes as well as their ability to interact with adjacent *n*- and p-electron centres enable them to undergo selective transformations. The far reaching analogy between the reactivity of olefins and cyclopropanes[110] makes possible hydrogenation,[111] halogenation, acid and electrophilic additions[112] on them accompanied by concomitant ring cleavage. Amongst the many applications of cyclopropane derivatives in organic synthesis are solvolytic one carbon homologation,[113] synthesis of allenes from double bonds *via* dihalocyclopropanes,[114] solvolytic ring opening of cyclopropyl carbinols,[115] ring enlargement (to five membered rings) of vinyl cyclopropanes[116] and Cope-rearrangement of *cis*-divinylic cyclopropanes for either synthesis or annelation of 7-membered rings.[117] Finally, these attractive building blocks provide a convenient key to enter into the field of homocnolate chemistry.[118]

Like that of most other functional groups, reactivity of the cyclopropane moiety is strongly influenced by substituents. By nature, cyclopropanes are nucleophilic though not to the extent of olefins. In a manner analogous to that of double bond, the philicity of a cyclopropane can be varied according to the functional groups attached. Substitution with electron-donating groups makes cyclopropanes more nucleophilic, while electron-withdrawing groups allow nucleophilic additions to cyclopropanes. Depending upon the nature of substitution, cyclopropanes can be classified as donor, acceptor or donor-acceptor.[119]

1,2-Cyclopropanated sugars are donor-activated cyclopropanes as the presence of the pyranose oxygen makes them more nucleophilic. Cleavage of a donor-activated cyclopropane by an electrophile affords the ring opened products as shown in Scheme 52. Here, the regiochemistry of cleavage is governed by the stabilizing ability of the donor substituent. In a similar fashion, if sugar derived cyclopropanes are opened, they would give functionalized 2-deoxy-2-branched chain pyranosides with defined C-2 configuration (Scheme 52). Though competitive formation of a septanoside resulting from the cleavage of the C-1–C-2 bond is possible, it is less likely due to preferential edge selection of the C-l-C-2 bond by the incoming electrophile based upon steric considerations. In this context, we have selected a- and β-cyclopropanes 106 and 109, respectively, derived from 3,4,6-tri-*O*-benzyl-D-glucal as model precursors to study the chemistry of 1,2-cyclopropanated sugars.

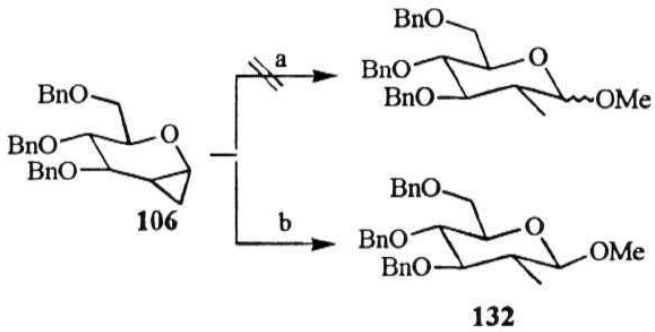


Scheme 52.

Acid or electrophile promoted ring cleavage of cyclopropanes has been investigated extensively. In general, the regiochemistry of the reaction is rationalized by a modified version of Markovnikov's rule,[120] which states that the ring opening occurs between the carbons bearing the largest and smallest number of alkyl

substituents, with the electrophile attaching itself to the latter atom. While considering the stereochemical aspects, different mechanisms involving differences in the attack of electrophiles on cyclopropanes either at edge/corner or constituting a one step S_E2 type have been proposed.[112] Unfortunately, the evidence available does not allow unequivocal selection of any one of these as the exclusive mechanism. In some cases, strong evidence for edge-attack with electrophiles like Br^+ and Cl,[121] and corner attack with proton, deuteron and mercury derived electrophiles[122] have been reported.

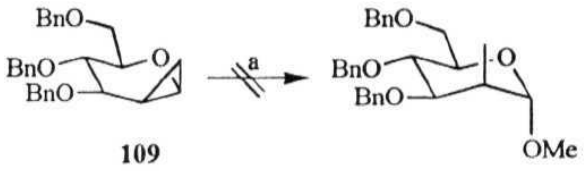
To examine the utility of 1,2-cyclopropanated sugars as precursors to modified glycosides, we first looked at their reactions with the simplest electrophile, the proton. When opening of the a-cyclopropane 106 was attempted with methanolic hydrochloric acid, at room temperature no ring opened product was formed, and only the starting material was recovered (Scheme 53). This was very suprising, as even unactivated cyclopropanes are easily opened with H^+ ion. Carrying out the reaction by replacing hydrochloric acid with either sulfuric, acetic or perchloric acids was also found to give a similar result. Heating the reaction mixture at higher temperatures or using excess acid yielded either the starting cyclopropane or unidentified products resulting from decomposition of the cyclopropane. Finally, when the reaction of 106 was performed in a sealed tube under refluxing conditions in methanol with 1.5 eq. of hydrochloric acid for 15 days,[123] we were able to obtain about 40% conversion of starting material. The ring opened product 132 was obtained in about 70% yield (Scheme 53).



Scheme 53. *Reagents and Conditions*: a) 1.5 eq. HCl or H_2SO_4 or $HClO_4$, MeOH, rt; b) 1.5 eq. HCl, MeOH, reflux, 15 days.

The structure of **132** was readily apparent from its spectral and analytical data. In the ^1H NMR spectrum, only one singlet (5 3.49) corresponding to -OMe was present. A doublet with a coupling constant of 6 Hz at high field (5 1.05) and a multiplet at 5 1.80 were assigned to the branched methyl group and to the H on the C-2 carbon. The anomeric proton appeared at 6 4.10 as a doublet with a coupling constant of 8 Hz, characteristic of axial protons in pyranose derivatives. This made it obvious that the product obtained was the p-anomer. The H-2 signal at 5 1.80 resonating for a single proton showed that ring opening, rather than ring expansion, had taken place. These assignments were further confirmed by 2D-homonuclear COSY. The H-2 multiplet at 6 1.80 showed cross peaks with signals at 1.05, 3.26 and **4.10 ppm**. As the signal at 5 4.10 did not show any other cross peaks, our assignment of it as H-1 is justified. The 5 1.05 signal also did not show any cross peaks other than the one already described. Consequently, the 3.26 ppm signal was assigned to H-3. All these observations taken together strongly indicate that the product is a 2-deoxy-2C-methyl-β-glucoside. However, an incisive assignment of the remaining ring protons was found to be difficult, as the rest of the signals overlapped and appeared as a multiplet from 5 3.80-3.40. In the ^{13}C NMR spectrum, the C-7 methyl appeared at high field (12.6 ppm) and the peak at 42.79 ppm was assigned as C-2. The anomeric carbon C-1 resonated at 105.60 ppm.

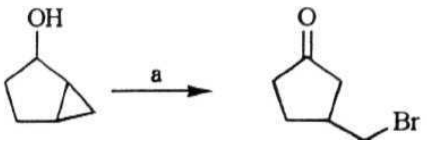
After accomplishing the ring opening of 106 in moderate yields, we attempted to open 109 under similar conditions. Discouragingly, there was no reaction even after 15 days (Scheme 54). Increasing the concentration of HC1 led to the decomposition of 109. These failures prompted us to focus our attention on other electrophile induced reactions.



109

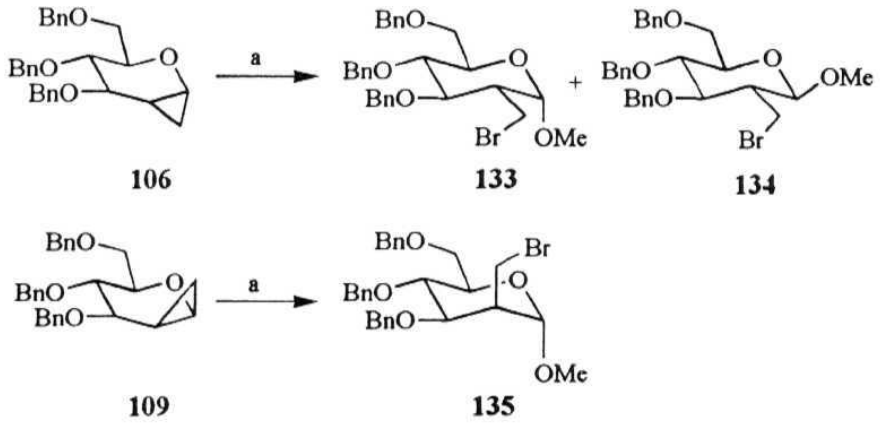
Scheme 54. *Reagents and Conditions*: a) 1.5 eq. HCl, MeOH, reflux, 15 days.

The addition of halogens (Cl_2 and Br_2),[121] acid chlorides[124] and other metallic electrophiles like mercury (II),[122] lead (IV) and thallium (III)[125] salts to cyclopropanes have been reported. However, a limitation in using halogens with our substrates was the possible bromination of the aromatic rings present. Recently, Cossy reported the oxidative ring opening of cyclopropyl carbinols with NBS in t-butanol, yielding the corresponding γ-halocarbonyl compounds (Scheme 55).[126] We also elected to use NBS as an activator. A more nucleophilic solvent like methanol, compared to t-butanol, is likely to reduce the possible oxidative opening reported by Cossy.[126]



Scheme 55. *Reagents and Conditions*: a) NBS (1.2 eq.), t-BuOH, reflux.

When 106 was treated with NBS in methanol, analysis of the tlc of the reaction mixture showed complete disappearance of the substrate after 8h (Scheme 56). The usual method followed involved addition of NBS (neat) to a precooled (0.1 M) solution of the cyclopropane and allowing it to stir at room temperature for the required time. The ^1H NMR spectrum of the crude product showed two well separated multiplets integrating in a 4 : 1 ratio, at 8 2.40-1.80, indicating the presence of two anomers. These two products were easily separable by column chromatography and were unambiguously characterized by their spectral and analytical data. It was found that the low polar minor product 133 was the a-anomer and the relatively more polar major product 134 was the p-anomer.



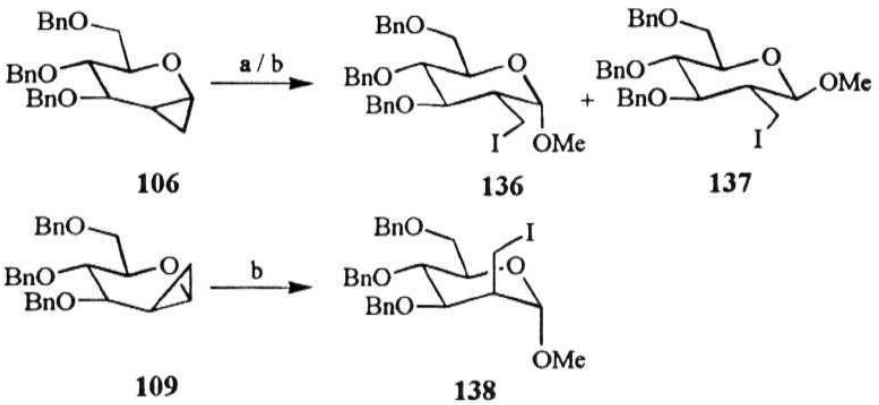
Scheme 56. *Reagents and Conditions*: a) NBS (1.2 eq.), MeOH, rt, 8 or 24h.

The ^{13}C NMR spectra of 133 and 134 showed only 11 lines each in addition to the aromatic signals. The configuration of both anomers was assigned from ^1H NMR data, focusing mainly on the H-1 of each isomer. In the major product 134, the anomeric proton appeared at a higher field (δ 4.43, doublet, J = 8.5 Hz) compared to that in the minor product 133 (8 5.0, doublet, J = 2.6 Hz). The appearance of the anomeric proton at high field with a characteristic diaxial coupling constant suggests that it is a β-glucoside. The broad multiplet at 8 1.88

integrating for one proton was assigned to H-2. The above findings have at the same time provided the necessary support for our prior assumption that ring opening would prevail over ring expansion in electrophilic ring openings also, based upon steric considerations.

In the minor product 133, the anomeric proton resonated as a doublet at 6 5.0 with J = 2.6 Hz. In the pyranose series, generally the anomeric protons which have an equatorial orientation arc deshielded more than those in the axial orientation.[127] The equatorial-equatorial coupling constants are also small. These observations clearly indicate that the minor product 133 is indeed the α-anomer. Another important observation made was that of the the chemical shift of the H-2 proton. In the a-anomer (at 5 2.25) it was relatively deshielded compared to the P-anomer (at 5 1.88). These anomeric assignments were further substantiated by ^{13}C NMR as well as optical rotation data. In ^{13}C NMR spectrum, the anomeric carbon of 133 resonated at 102.30 ppm, while it appeared at 99.23 ppm in the P-anomer 134, in agreement with earlier observations.[128] Finally the lower value of $[\alpha]_D$ observed for 134 (+22°) relative to that of 133 (+87.3°) is in accordance with Hudson's rule,[129] which states that generally a-anomers have greater positive rotation compared to their β-counterparts.

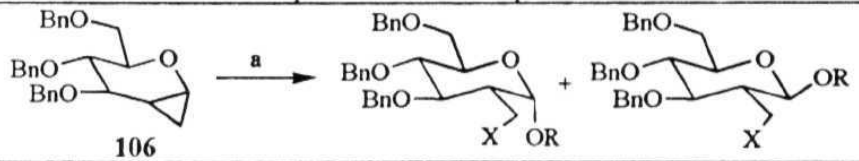
Having established the feasibility of the ring opening of 106 as well as the structures of the products obtained, we next focussed our attention on the ring opening reaction of 109. Under similar conditions, the ring opening of cyclopropane 109 was found to be slower compared to that of 106 and took 24h for complete conversion to the a-mannoside 135 in about 62% yield (Scheme 56), without any trace of the other anomer. The stereochemistry at the anomeric carbon was confirmed to be a- by ^{1}H NMR studies as before. The anomeric proton of 135 appeared as a singlet at 5 5.03 and H-2 at δ 2.64. In the α-manno series, where both H-1 and H-2 are equatorial, the anomeric proton usually appears as a singlet or sometimes as a doublet with J ≈ 2 Hz.[127]



Scheme 57. *Reagents and Conditions:* a) NIS, MeOH, rt, 12h; b) IDCP, MeOH, 6 or 36h.

In order to illustrate the flexibility of this strategy, we attempted to open both a- and β-cyclopropanes with iodonium ion as the electrophile. When NIS was used as a source of iodonium ion, **106** reacted within 12h, affording both a- and p-anomers **136** and **137,** respectively, in a 20 : 80 ratio (Scheme 57). The reaction of **109,** however, resulted only in 10% conversion (Scheme 57). Although NIS was successful in opening **106,** its inability to open **109** prompted us to employ other sources of I^+. An immediate option was iodonium di(*s*-collidine) perchlorate (IDCP).[27b] The higher reactivity of di(*s*-collidine) iodonium complexes has been well established in intramolecular cyclisations of unsaturated alcohols and acids, where they have been shown as convenient reagents in the synthesis of medium size rings (7-10).[130] On the other hand, it's potential in oxidative additions to glycals has been well established by Lemiuex[27b] and Danishefsky.[29] This prompted us to use it in our endeavors. As usual, **106** reacted within 6h yielding both a- and P-anomers **(136** and **137)** in a 15 : 85 ratio. The reaction of **109** with IDCP was found to be incomplete yielding the ring opened product **138** in 70% yield based on recovered starting material (Scheme 57), even after 36h.

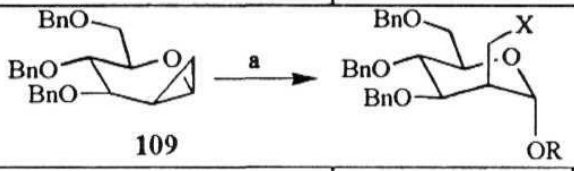
Table 1. Ring opening of α-cyclopropane 106 with alcohols.

Entry	Reagents\time	Products	(α: β) Yield %	
				
1	HCl\MeOH\15days	R = CH_3 X = H	---- **132**	70
2	NBS\MeOH\8h	R = CH_3 X = Br	**133** (20 : 80) **134**	72
3	NIS\MeOH\12h	R = CH_3 X = I	**136** (20 :80) **137**	86
4	IDCP\MeOH\6h	R = CH_3 X = I	**136** (15 : 85) **137**	86
5	NBS\$ClCH_2CH_2OH$\ 4h	R = CH_2CH_2Cl X = Br	**139** (35 :65) **140**	91
6	NBS\Cl_3CCH_2OH\1h	R = CH_2CCl_3 X = Br	**142** (50 : 50) **143**	89
7	NBS\$PhCH_2OH$\36h	R = CH_2Ph X = Br	**145** (35 : 85) **146**	91
8	NBS\H_2O-dioxane\8h	R = H X = Br	**148**	66

The ^{1}H and ^{13}C NMR spectral data of all the three diastereomeric iodo derivatives clearly provide strong support for the assignments as indicated in Scheme 57. The anomeric protons and carbons of 136 (H-l 5 4.95, d, J = 3.0, C-l 101.07 ppm), 137 (H-l 6 4.30, J = 8.6, C-l 104.4 ppm) and 138 (H-l 8 4.96, C-l 100.9 ppm) are similar to those observed for the corresponding bromo analogues.

Encouraged by this, and to further examine the generality of this method, the ring openings of **106** and **109** were carried out in different alcohols and the results are summarized in Tables 2 and 3.

Table 2. Ring opening of β-cyclopropane **109** with alcohols.

Entry	Reagents\time	Products		Yield %
	 **109**			
1	NBS\MeOH\24h	R = CH_3 X = Br	135	62
2	IDCP\MeOH\36h	R = CH_3 X = I	138	70
3	NBS\$ClCH_2CH_2OH$\ 12h	R = CH_2CH_2Cl X = Br	141	71
4	NBS\Cl_3CCH_2OH\8h	R = CH_2CCl_3 X = Br	144	72
5	NBS\$PhCH_2OH$\4days	R = CH_2Ph X = Br	147	40
6	NBS\H_2O-dioxane\8h	R = H X = Br	149	61

As shown in Table 1 (entry 5), reaction of **106** in 2-chloroethanol with NBS as an activator, was complete within 4h, whereas **109** (Table 2, entry 3) took 12h for completion. Suprisingly, the opening of **106** with Cl_3CCH_2OH was very rapid, giving the products in 1h. Under similar conditions, the reaction with **109** took 8h. On the contrary, the ring opening of **106** with benzyl alcohol was sluggish taking

36h, while even after 4 days only 20% conversion (40% yield) was observed with **109**

Table 3. Chemical shifts of some salient protons and carbons of products 133-149

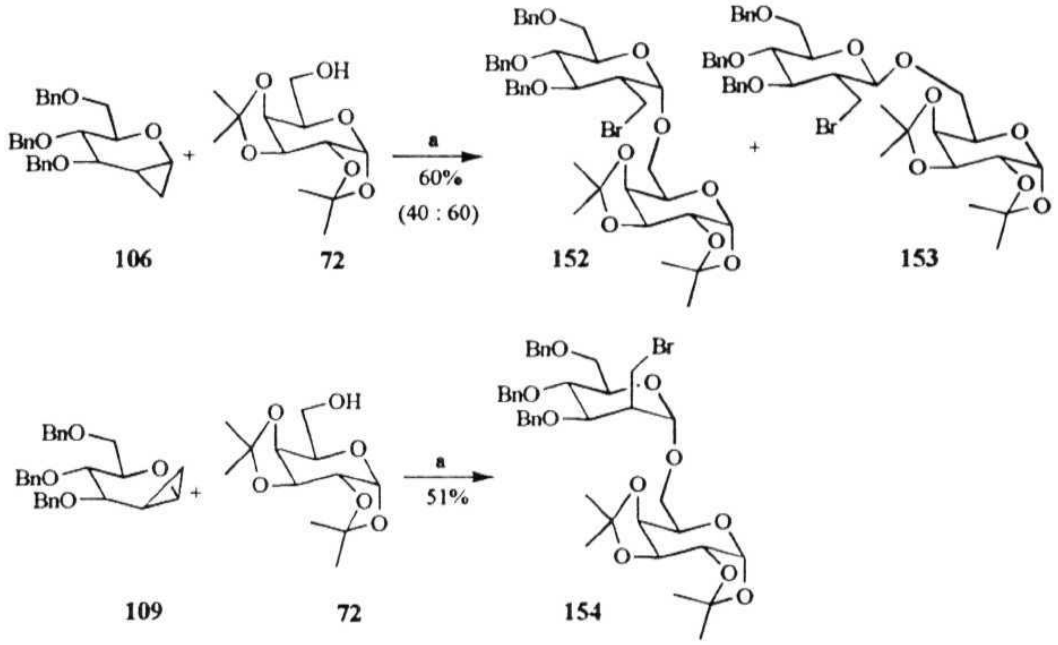
Entry	Substrate	H-1 (J in Hz)	H-2	C-1	C-2
1	**133**	5.0 (2.6)	2.25	99.23	30.60
	136	4.95 (3.0)	2.16	101.07	3.05
	139	5.15(3.4)	2.28	98.48	30.53
	142	5.35 (2.9)	2.33	98.83	29.94
	145	5.24 (3.2)	2.30	98.03	30.66
	148	5.53	**2.25**	92.43	30.92
2	**134**	4.43 (8.5)	**1.95**	102.29	31.60
	137	4.30(8.6)	1.28	104.39	6.97
	140	4.55(7.9)	1.90	101.35	**31.49**
	143	—	2.03	101.40	31.15
	146	—	1.96	100.47	31.61
	148	—	1.80	95.46	30.92
3	**135**	5.03 (s)	**2.64**	99.71	29.57
	138	**4.96**	**2.63**	100.92	2.0
	141	**5.13**	2.68	98.89	29.40
	144	5.33	**2.73**	100.03	29.21
	147	5.21	**2.68**	98.33	29.55
	149	5.50	**2.61**	93.16	**29.74**

The spectral data of all the diastereomeric sets of chloroethyl **(139 - 141),** trichloroethyl **(142 - 144)** and benzyl **(145 - 147)** glycosides followed a similar pattern as those of the corresponding methyl glycosides. In each case, while **106** yielded mixtures of both a- and P-anomers, only the a-anomer was obtained from **109.** The opening of **106** and **109** with water as a nucleophile was carried out in a 1 : 1 mixture of water and dioxane and the corresponding ring opened products **148** and **149,** respectively, were obtained in good yields. These reactions approximately took similar times and substantial benzyl ether cleavage was found in **109.** The important spectral features of all glycosides are given in Table 3.

Branched-chain disaccharides:

Towards further elaboration of this methodology, based on the information available with various alcohols, it was envisioned that the utilization of sugar alcohols in these openings would lead to functionalized branched-chain disaccharides with defined C-2 stereochemistry. In this pursuit, opening of cyclopropane **106** with NBS in the presence of 1.2 eq. of 1,2:3,4-di-*O*-isopropylidinc-α-D-galactose (72) in dichloromethane was first attempted. It resulted only in a trace amount of the disaccharidc with extensive loss of benzyl groups. This failure prompted us to carefully examine the methods generally employed for construction of disaccharides utilizing glycals. To this end, we chose acetonitrile as solvent and 4A molecular sieves as an additive. After monitoring the reaction conditions with varying concentrations of sugar alcohol and different reaction times, with 1.2 eq. NBS (with respect to cyclopropane), we succeeded in opening **106** with sugar alcohol **72.** The conditions employed involve treatment of a solution of **106** and 3 eq. of sugar alcohol **72** with 4Å molecular sieves for lh at rt followed by the addition of 1.2 eq. NBS and continuing the reaction for 4 days. Under these conditions, in a similar fashion to that observed in ring openings utilizing alcohols, cyclopropane **106** gave both a- and p-anomers (152 and 153) in a ratio of 40 : 60

(Scheme 58). Carrying out the reaction under similar conditions with 109 provided only one product **154** in moderate yield (Scheme 58).



Scheme 58. *Reagents and Conditions:* a) NBS, CH_3CN, 4A sieves, 4 days.

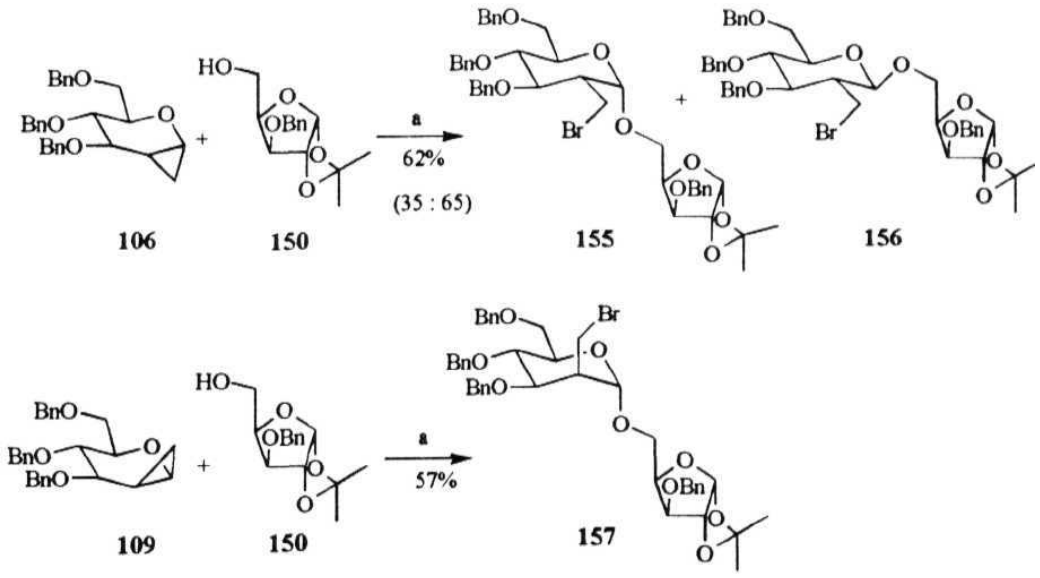
The characterization of the three disaccharides **152, 153** and **154** was next undertaken with the help of 2D-NMR COSY data. In the ^1H NMR spectra of **152** and **154,** two signals appeared in the region of anomeric protons. The low field signal at 5 5.53 with a coupling constant of 4.9 Hz in all three products was assigned to the anomeric proton of the galactose unit. The anomeric doublet at 8 5.14 with a coupling constant of 2.9 Hz in **152** suggests that it is an equatorial proton i.e., **152** is an a-anomer. The H-1 signal of **153** was found to be resonating along with those of the benzylic protons in the region 8 4.70-4.52. In consonance with the earlier observations in the ring openings with different alcohols, the H-2 of

152 resonated at a lower field (5 2.48-2.19) than that in its p-anomer **153** (5 1.97-1.80). In a similar fashion, in ^{13}C NMR spectra also, the anomeric carbon of **152** appeared at higher field (98.8 ppm) compared to that of **153** (101.8 ppm). In the COSY spectrum of 152, the signal at 6 5.54-5.52 showed one cross peak with the multiplet at 5 4.34-4.25. Since this multiplet integrated for two protons and appeared as a mixture of two dds, one dd was assigned as H-2 and other one as H-4 of galactose by comparison with the spectrum of 72. The signal corresponding to H-5 of galactose appeared as a multiplet at 5 4.07-3.93. In all the cases, the H-3 signal of galactose was buried in the benzylic protons signals. The multiplet resonating at 8 2.48-2.19, assigned as H-2 of the glucopyranoside, exhibited coupling with 3 peaks at 8 3.38-3.27, 3.86-3.61 and 5.14-5.13. Since the doublet at 8 5.14-5.13 did not show any cross peaks with any other signal, the assignment of this signal as the anomeric proton is justifiable. This was further substantiated by the HETCOR spectrum of **152,** where this doublet showed a cross peak with the carbon resonating at 98.76 ppm. Consequently, the two cross peaks at 8 3.38-3.27 (t) and 8 3.86-3.61 were assigned as H-7, H-7' and H-3, respectively. In a similar fashion, spectral analysis of 153 was carried out.

In the case of **154,** the two anomeric protons resonated at δ 5.55 (d) and 8 5.16 (s). They showed cross peaks with the carbons resonating at 98.4 and 96.4 ppm, respectively, in the HETCOR spectrum. The DEPT-135 spectrum showed that these two were -CH carbons. Additionally, six CH_2 carbons were found, in which the three carbons between 74-72 ppm showed cross peaks only with the benzylic protons. A comparison with the ^{13}C NMR data of methyl glycoside **135** showed that the two $-CH_2$ signals which appeared at 68.9 and 66.1 ppm were respectively C-6 of mannose and galactose. The remaining high field $-CH_2$ (29.71 ppm) was assigned as the halomethylene carbon C-7. This carbon exhibited two cross peaks with the protons resonating at 8 3.40-3.38 (t) and 3.70-3.65 (m), thus showing the separation between the two diastereotopic protons. These assignments

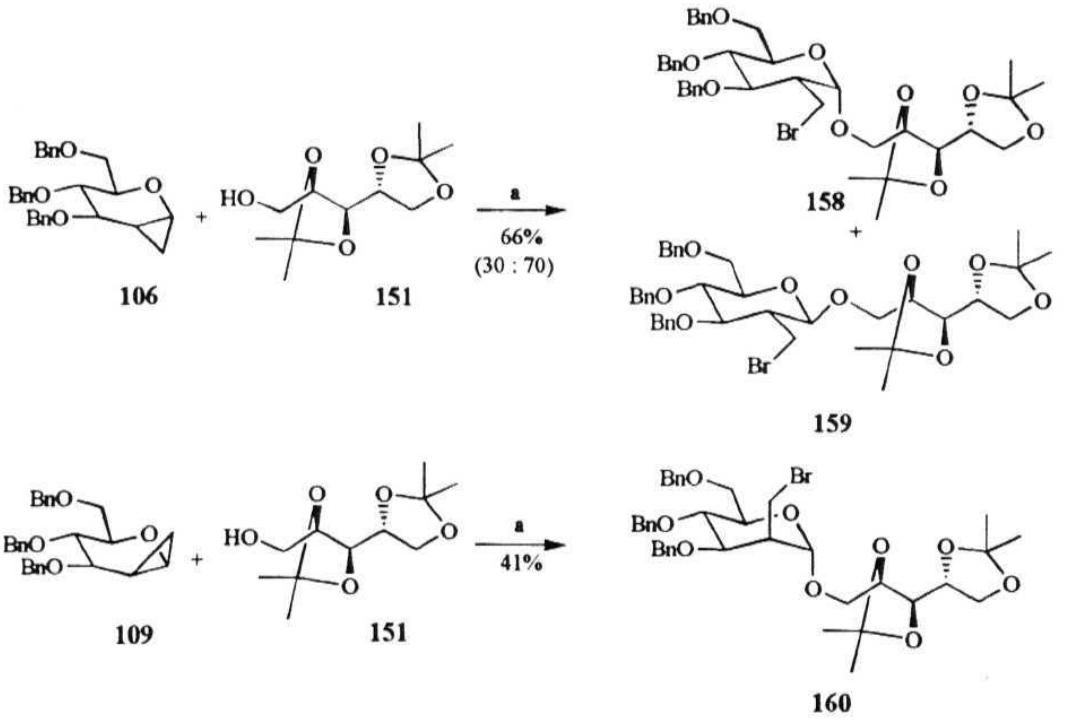
were further supported by the COSY spectrum of **154,** where the multiplet at 5 2.69 showed four cross peaks with the triplet (5 3.40-3.38, H-7), m (6 3.70-3.65, H-7'), dd (5 4.12-4.02, H-3) and a very weak coupling with the anomeric singlet (6 5.16, H-1). The proton resonating at 6 5.16 showed only one weak cross peak with the multiplet at 5 2.69. The weak coupling observed between H-l and H-2 clearly provides evidence for the diequatorial relationship between these two protons. Starting with the anomeric signal of the galactose moiety, the well separated dd at 6 4.36-4.31 was assigned as H-2 and another dd at 6 4.25-4.19 was found to be H-4 of galactose.

Satisfied with the stereochemical assignments of the three disaccharides and in order to generalize this cyclopropane opening protocol towards the construction of functionalized branched disaccharides, we attempted to use xylose **(150)** and arabinitol **(151)** derivatives in this pursuit.



Scheme 59. *Reagents and Conditions:* a) NBS, CH_3CN, 4A sieves, 4 days.

Under similar conditions as those followed for galactose 72, with xylose **150** (Scheme 59) and arabinitol **151** (Scheme 60), the ring opening of **106** and **109** proceeded smoothly and the products were obtained in moderate yields. The structural assignments of all three diastereomeric disaccharides obtained with **150** and **151** were straightforward. The chemical shifts of diagnostic protons and carbons are given in Table 4.



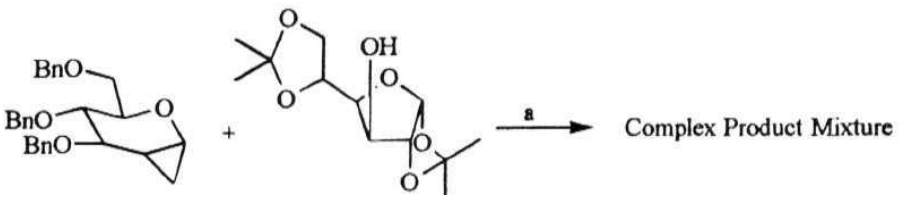
Scheme 60. *Reagents and Conditions:* a) NBS, CH_3CN, 4A sieves, 4 days.

In all the above cases, the sugar alcohols are primary. However, attempts to open cyclopropane **106** with 1,2:5,6-di-*O*-isopropylidine-α-D-glucofuranose (71, Scheme 61) yielded a complex mixture from which separation of the desired disaccharide was difficult. Hence this was not pursued further. Thus, this

methodology makes for an easy entry into the synthesis of functionalized branched disaccharides which are hitherto unknown.

Table 4. Chemical shifts of some salient protons and carbons of products 152-160

Entry	Compound	H-1 (J in Hz)	H-2	C-1	C-2
1	**152**	5.14 (3)	2.34	98.76	30.38
2	**153**	----	1.89	101.78	31.71
3	**154**	5.16	2.69	98.42	29.68
4	**155**	5.12 (3)	2.27	98.30	30.63
5	**156**	----	1.88	101.21	31.57
6	**157**	5.08	2.60	98.9	29.66
7	**158**	5.14 (3.1)	2.26	98.55	30.45
8	**159**	----	1.91	101.50	31.59
9	**160**	5.12	2.64	99.14	29.46

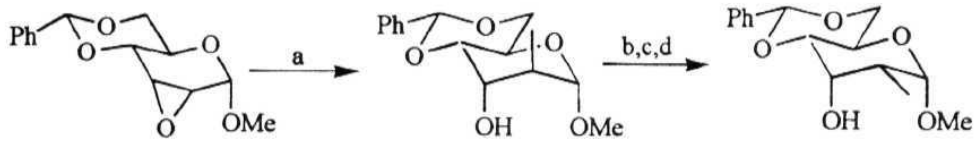


106 **71**

Scheme 61. *Reagents and Conditions:* a) NBS, CH_3CN, 4A sieves, 4 days.

3. Stereoselective construction of **2-deoxy-2-C-methyl** pyranose templates:

As mentioned previously, in dealing with targets containing multiple centres of chirality and functionality, carbohydrate derived precursors offer definite stereochemical and operational advantages. In this **context,** a perusal of the various approaches towards the synthesis of natural products containing either **tetrahydropyrans, δ-valerolactone** moieties or open chain templates for macrolide antibiotics showed that a common problem encountered is the introduction of a methyl group **stereoselectively** in the pyranose skeleton. Different strategies that have been used to address this problem are i) the ring opening of **2,3-anhydroglycosides** by lithium **dialkylcuprates,**[131] ii) conjugate addition of lithium dialkylcuprates to enones of type **164**[132] and iii) hydrogenation of **2-exomethylene glycosides.**[133]

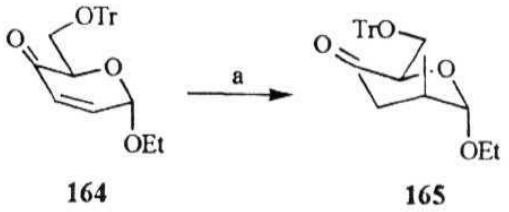


161 **162** **163**

Scheme 62. *Reagents and Conditions*: a) Me_2CuLi, ether; b) DMSO, Ac_2O; c) NaOMe, MeOH; d) $NaBH_4$.

The easily available epoxide derivative **161,**[131a] does infact undergo a highly regioselective opening with lithium dimethylcuprate to give the corresponding 2C-**methyl** derivative 162 with exclusive **β-orientation** (Scheme 62). Oxidation of the resulting 162, followed by base induced **epimerisation** at C-2 and reduction gave 2C-methyl derivative 163 with **α-orientation.**[131b]

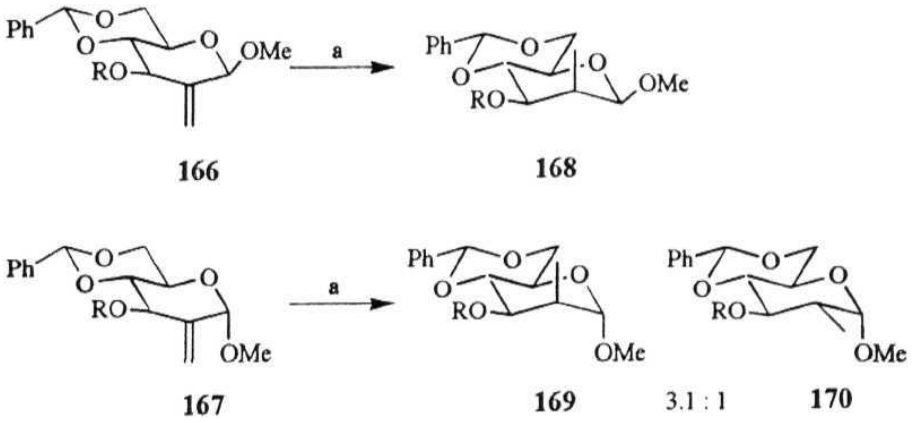
Addition of lithium dimethylcuprate to enone 164 resulted in 165 with branching at C-2 with **β-orientation** (Scheme 63).[132]



164 165

Scheme 63. *Reagents and Conditions:* a) Me_2CuLi, ether.

On the other hand, hydrogenation of 2-deoxy 2-methyleneglycosides has been used to introduce the methyl group selectively from either a- or P-face depending upon the anomeric configuration. For example, hydrogenation of the *exo*-olefin 166 produced exclusively the p-isomer 168, while 167 gave a mixture of manno and gluco isomers 169 and 170, respectively (Scheme 64).[133]



166 168

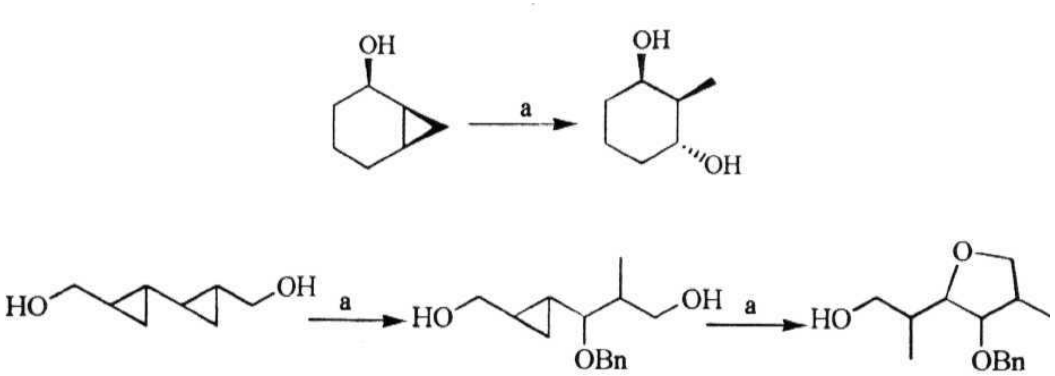
167 169 170

Scheme 64. *Reagents and Conditions:* a) H_2, Pd-C, toluene.

The availability of both forms of cyclopropanes from the same glycal intermediates and the extensive information available on their electrophilic openings prompted us to explore these valuable intermediates towards the stereoselective construction of 2-deoxy-2C-methylglycosides. Analogous to the synthesis of 2-deoxyglycosides from glycals, the strategies that can be followed in the case of 1,2-cyclopropanated sugars to procure 2-deoxy-2C-methylglycosides are halonium

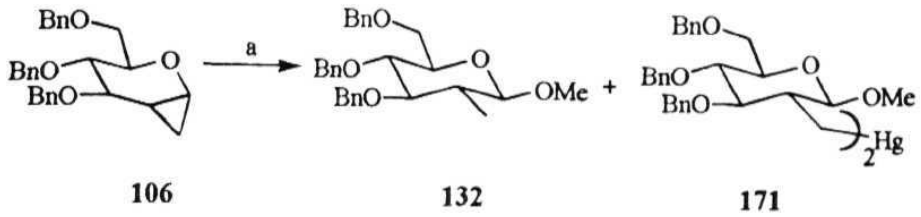
ion mediated openings followed by dehalogenation, direct solvolysis with mineral acids and other promoters like CSA,[45] PTSA[46] or TPHB[47] and oxymercuration[51] followed by demercuration.

Our initial failures in attempts at direct solvolysis with mineral acids prompted us to search for other alternatives. Mercuric ion mediated openings of cyclopropanes are well-documented and are known to occur with high regio- and stereoselectivity. The high regio- and stereoselectivity in these openings were explained as due to a corner attack of mercuric ion followed by concerted opening with nucleophiles.[122] Recently, Mohamadi and Collum[134] have shown that oxy-mercuration of cyclopropylcarbinols is a facile method for the construction of 2-methyl-1,3-diol units (polypropionate templates, Scheme 65). Recently, the mercuric ion mediated ring opening of bicyclopropanes and tercyclopropanes has been reported by Barrett for the first time.[135]



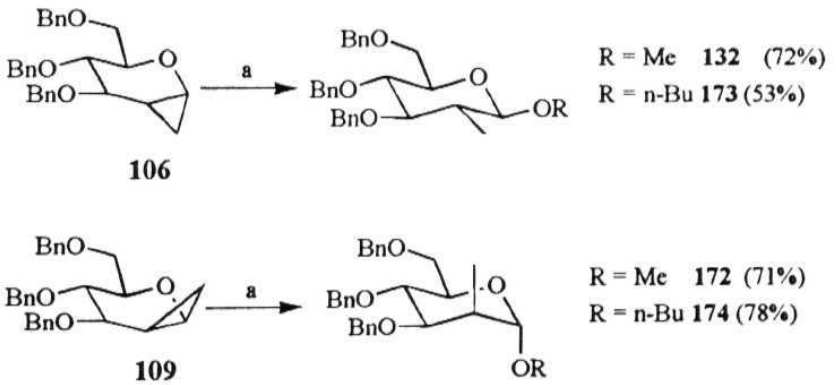
Scheme 65. *Reagents and Conditions*: a) i) $Hg(CF_3COO)_2$; ii) LAH.

Initial attempts to open 106 with mercuric acetate followed by reductive demercuration with sodium borohydride ($NaBH_4$) resulted in the formation of a bis(sugar) mercury derivative 171 in predominant amounts (Scheme 66).



Scheme 66. *Reagents and Conditions:* a) i) $Hg(CH_3COO)_2$, MeOH, 18h; ii) $NaBH_4$, MeOH, rt.

Replacing mercuric acetate with mercuric trifluoroacetate and switching over to the Mohamadi procedure[134] (Scheme 67), yielded exclusively the P-anomer **132.** The spectral data of the product was in agreement with that of **132** obtained from the HC1 solvolysis of 106.



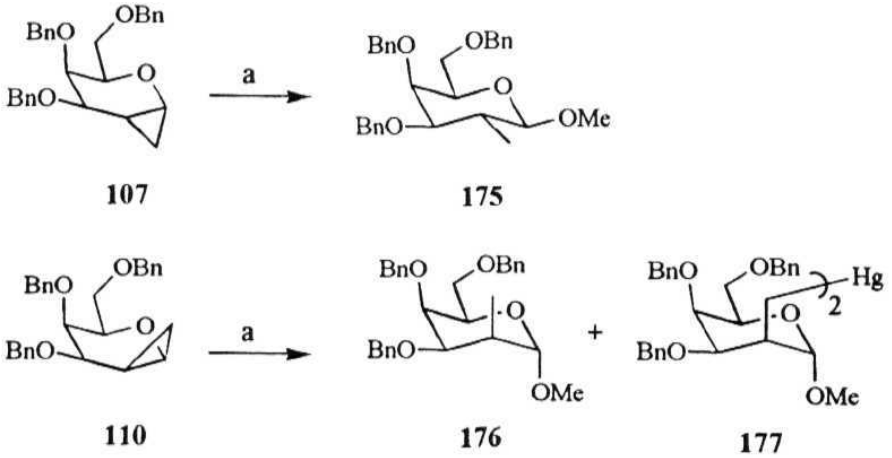
Scheme 67. *Reagents and Conditions:* a) i)$Hg(CF_3COO)_2$, ROH, 18h; ii) sat. NaCl, 15min; iii) LAH, THF, 0^{O} – rt, 3h.

Under similar conditions, cyclopropane **109** gave the corresponding 2-deoxy-2-methylmannoside **172** in 71% yield (Scheme 67). The ^{1}H NMR spectrum showed only one -OMe singlet resonating at 5 3.35, suggesting the presence of a single anomer. H-2 appeared as a multiplet at 5 2.50-2.33. The CH_3 doublet with

J = 7.4 Hz resonated at 8 1.13-1.09. The ^{13}C NMR spectral assignments are C-1 at 103.4, C-2 at 36.93 and C-7 at 11.41 ppm.

This methodology was further extended using n-butanol as solvent. The corresponding n-butyl glycosides **173** and **174** were obtained in 53 and 78% yields, respectively, from cyclopropanes **106** and **109.** A brief summary of the spectral details of **173** and **174** follows. H-1 appeared as a doublet at δ 4.10-4.06 (J = 8.1 Hz) and as a singlet at δ 4.71, whereas H-2 appeared as multiplets at δ 1.85-1.65 and δ 2.55-2.45 in **173** and **174,** respectively. The ^{13}C NMR spectra of **173** and **174** showed 14 carbons apart from the aromatic carbons and anomeric carbons were found at 104.7 ppm **(173)** and 102.12 ppm **(174).**

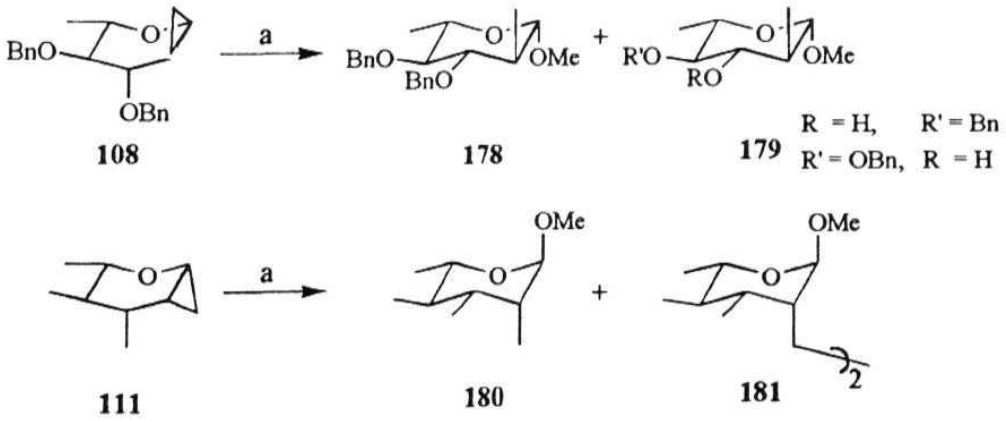
To extend the scope of this methodology, the mercuric ion mediated ring opening of the cyclopropanes derived from galactal **(107** and **110,** Scheme 68) and rhamnal (108 and **111**, Scheme 69) were carried out in methanol.



Scheme 68. *Reagents and Conditions:* a) i)$Hg(CF_3COO)_2$, ROH, 18h; ii) sat. NaCl, 15 min; iii) LAH, THF, 0° - rt, 3h.

Under similar conditions, ring opening of α-cyclopropane **107** yielded the desired 2-deoxy-2C-methyl glycoside **175** in 69% yield along with small amounts of bis(sugar)mercury compound. Reaction of the corresponding β-cyclopropane **110** resulted in substantial amounts of bis(sugar)mercury compound **177** along with desired product 176 (46%). Identity of this bis(sugar)mercury compound **177** was confirmed by ^{1}H and ^{13}C NMR spectra. In the ^{1}H NMR spectrum of product **176,** H-7 appeared as a doublet at 8 1.30-1.26 integrating for three protons, whereas in the case of the bis(sugar)mercury compound **177,** two multiplets integrating for two protons appeared in the region 8 1.30-0.75. In the ^{13}C NMR spectrum, C-7 of **177** resonated at 36.19 ppm and it was found to be a $-CH_2$ from its DEPT-135 spectrum.

The formation of bis(sugar)mercury compound in substantial amounts prompted us to vary the reaction conditions. However, increasing the temperature of the reaction mixture to 50° was found to give the product in poor yield and resulted in the bis(sugar)mercury compound as the major product.



Scheme 69. *Reagents and Conditions:* a) i)$Hg(CF_3COO)_2$, ROH, 18h; ii) sat. NaCl, 15min; iii) LAH, THF, 0^{o} – rt, 3h.

The ring opening of α-cyclopropane **108** derived from rhamnal provided two products **178** (36%) and **179** (47%). Interestingly, a careful analysis of the spectral data of the major product **179** showed that it lacked one benzyl group. **The** IR spectrum of **179** showed an **-OH** band 3389 cm^{-1}. In the proton spectra of **178 and 179,** the anomeric proton appeared at 8 4.0 with a J value of 8.6 Hz. This shows that both the products obtained have the same p anomeric configuration. This is also substantiated by the ^{13}C NMR spectra, where the anomeric carbons of **178** and **179** resonated with almost the same chemical shift (105.39, 105.41 ppm). However, attempts to determine the regiochemistry of the benzyl group cleavage were not made.

As observed for β-cyclopropane **110,** the ring opening of rhamnal derived cyclopropane **111** with mercury trifluoroacetate in methanol was also found to give **the 2-deoxy-2C-methyl** product **180** in 50% yield along with substantial amounts of bis(sugar)mercury compound **181.** The identities of both the products were established using ^{1}H and ^{13}C NMR spectra.

4. Mechanistic aspects of ring openings of cyclopropanes **106** and **109:** Synthesis **and** intramolecular nucleophile assisted ring openings of cyclopropanes **185** and **186.**

Although our stated goal of developing 1,2-cyclopropanated sugars as convenient intermediates for the construction of 2-deoxy-2-brached glycosides was realized, the results obtained raise some intriguing questions about the various factors involved in these ring opening reactions. Some of them are:

1. The higher reactivity of α-cyclopropane **106** over β-cyclopropane **109.**
2. The role of the electrophile employed.
3. The stereospecific ring opening of **109** in contrast to that of **106.**

4. The role of solvent (i.e. qualitatively, the reaction is fastest in Cl_3CCH_2OH and slowest in $PhCH_2OH$ in the order: Cl_3CCH_2OH > $ClCH_2CH_2OH$ > MeOH > $PhCH_2OH$).

As shown in Figure 1, there exist two possible conformers of **106** (**106A** and 106B) and that of 109 (**109A** and 109B). However, due to strong 1,3-diaxial repulsion in both the cases, the ones which have substituents in equatorial disposition are the favored conformers (106B and 109B).

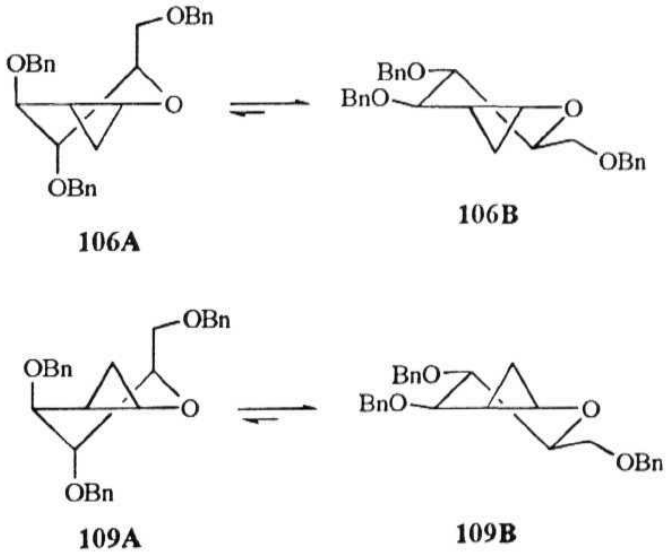


Figure 1.

The preference for these two conformers is substantiated by the ^1H NMR spectral data of **106**[100] and 109[106], where the $J_{3,4}$ coupling constants were found to be 9.1 and 7.0 Hz, respectively. These values are characteristic of diaxial coupling and clearly provide strong support that **106B** and **109B** are the preferred conformers.

1. Higher reactivity of α-cyclopropane 106 over β-cyclopropane 109

The ring openings of 106 and 109 with Br^+ and I^+ in methanol show a marked difference in reaction times. The openings of 106 with Br^+ and F take place smoothly and relatively faster than that of 109. In the case of 109, F was unable to induce the ring opening completely immaterial of the source of F employed (NIS or IDCP).

Looking at the conformers 106B and 109B, it is clear that in 109B, although C-3 and C-5 substituents are orientated equatorially, their disposition on the same side as that of the cyclopropane hinders attack of the incoming electrophile relative to 106B. This is particularly so for halonium ions due to their larger size and their edge-wise approach to cyclopropanes. The relatively high reactivity of cyclopropane 109 with Br^+ compared to F substantiates our argument that steric hindrance associated with electrophilic attack is the reason for the lower reactivity of 109 when compared to 106.

2. Roie of the electrophile employed

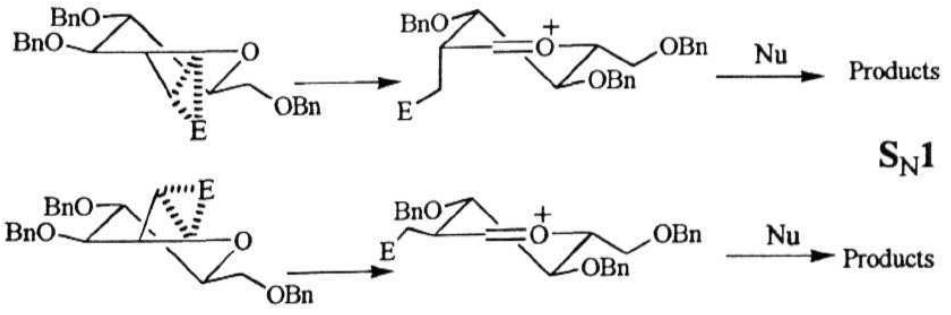
Amongst the four electrophiles used (Br^+, I^+, H^+ and Hg^{2+}), Br^+ and F give mixtures of anomers with 106 and only one anomer with 109, whereas H^+ and Hg^{2+} give a single anomer with 106. Further, H^+ does not react with 109, while Hg^{2+} again gives a single anomer. This can be explained from the earlier observations where it has been shown that the openings of cyclopropanes with mercuric ions are highly stereoselective and involve a corner attack resulting in products with double inversion.[122] It is also known that addition of H^+ to cyclopropanes takes place via a corner attack[122,123] and the high selectivity observed in the reaction of 106 with H^+

substantiates this. The lower reactivity of H^+ towards 106 and **109** when compared to Hg^+ is parallel to that observed in the reactions of alkenes with the same electrophiles. This is explainable by using HSAB principle according to which Hg^{2+} is a soft acid compared to the proton and the carbon substrate is a soft base. Differences observed between Br^+ and I^+ on the one hand and Hg^{2+} and H^+ on the other can be attributed to the edge-wise approach of the former and this aspect has been mentioned above.

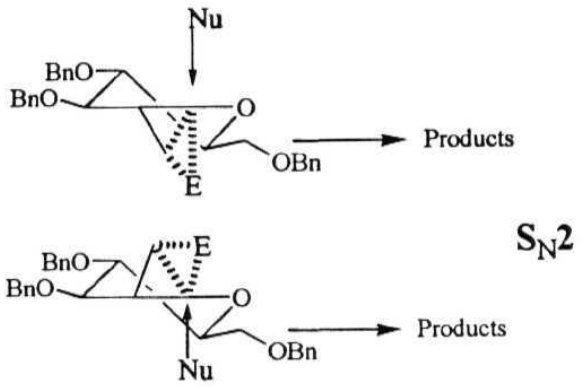
3. **Stereospecific** ring opening of 109 in contrast to that of 106

While the openings of 109 always proceeds with inversion at the anomeric centre, those of 106 display two pathways-inversion (major) and retention (minor). The mechanistic routes that are possible while considering the ring opening of both the cyclopropanes and the observed anomeric selectivities are:

1. The reaction takes place via an electrophile induced ring opening resulting a free carbocation, followed by its capture by the nucleophile. The ring opening may or may not be assisted by the pyranose oxygen. This pathway is labeled as "S 1"



2. An electrophilic addition followed by concomitant nucleophilic attack leading to ring opening ("SN2").



Exclusive formation of the a-anomer with cyclopropane **109** shows that its opening with all electrophiles perhaps occurs through the latter process. However, the information available from our experiments does not rule out the possibility of exclusive preference for axial attack on the oxonium ion resulting only in an a-anomer via an S_N1 path way. The formation of both anomers from **106** clearly provides strong evidence for the participation of the S_N1 pathway in the cyclopropane openings. At this stage, with the little information available, we are not in a position to assess the contribution of the two pathways in determining the outcome of the anomeric ratio.

4. **The role** of solvent

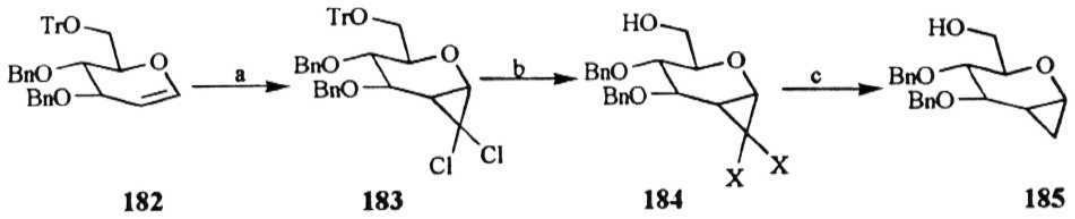
The strongly solvent-dependent nature of electrophilic additions to double bonds is well known.[136] It has been shown[137] that in the case of bromine addition to 1-pentene in solvents of different polarity (hexane to water), the overall rate varies by a factor of 10^{10}. It has been suggested in the case of electrophilic additions to double bonds that the observed rate enhancement and the lowering of

stereoselectivity in polar solvents is due to the greater onium character of the reactive intermediates due to their stabilization by polar solvents. However, in our examples, all the solvents used were protic solvents expect in the case of opening with sugar alcohols, where the aprotic dipolar solvent acetonitrile was used.

Speculation about the role of solvent on NBS activated openings of **106** and **109** has led us to the tentative conclusion that solvent polarity is not an important factor, but the extent of solvation of Br^+ is. A plausible explanation for this conclusion is as follows. In 2-chloroethanol, the inductive effect due to chlorine decreases the electron density around oxygen and thus the solvation of Br^+ in 2-chloroethanol becomes less than that in methanol and least in trichloroethanol. To a first approximation, this can be correlated with the pKa values of the alcohols. The corresponding values are 18, 15.5, 14.2 and 11.8, respectively, for benzyl alcohol, methanol, 2-chloroethanol and 2,2,2,-trichloroethanol.[138,139] Therefore, the degree of solvation of Br^+ will be in the order $PhCH_2OH$ > MeOH > $ClCH_2CH_2OH$ > Cl_3CCH_2OH, i.e., Br^+ will be most reactive towards 106 and 109 in Cl_3CCH_2OH and least in $PhCH_2OH$.

Exclusive formation of the α-glycoside from cyclopropane 109 is then a consequence of an elctrophile activated S_N2 type ring opening of the cyclopropane by an external nucleophile. With the a-cyclopropane **106**, the p-glycoside is formed predominantly by the same route, while simultaneous formation of the a-anomer in this case points to the possible involvement of an S_N1 pathway also. It may be noted in both instances that the a-glycoside is the one favored by the anomeric effect.

In order to better understand the processes taking place, we prepared the a- and ß-cyclopropanes **185** and 186, with a free 6-OH group, as outlined below (Schemes **70 and** 71).



182 183 184 185

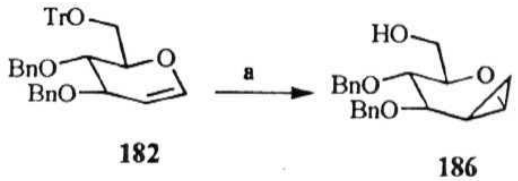
Scheme 70. *Reagents and Conditions*: a) $CHCl_3$, 50% aq. NaOH, cat. $BnEt_3N^+Cl^-$, 24h; b) 98% HCO_2H-ether (1 : 2), 1h; c) LAH, THF, 24h.

The addition of dichlorocarbene to 6-tritylglucal **182**[140] under phase transfer conditions[96] took place exclusively from the α-face, yielding the corresponding dichloro adduct **183** in 73% yield (Scheme 70). The spectral assignments of compound **183** are as follows. H-2 resonated as a dd at 5 1.93 with J = 4.1 and 7.8 Hz. The larger coupling was assigned to $J_{1,2}$ as evidenced from the H-1 signal, which appeared as a doublet at 5 4.08 with J = 7.8 Hz. The smaller value of coupling between H-2 and H-3 suggests a quasi axial-equatorial arrangement. This is in agreement the with spectral data of the dichloro adduct derived from 3,4,6-tri-*O*-benzyl-D-glucal (98).[100]

Assured of the inertness of dihalocyclopropanes and parent cyclopropanes towards mineral acids (as is evident from our earlier experiments), we directly proceeded to detritylate **183** employing formic acid in ether,[141] without opting for any mild reagents. The detritylated product **184** was obtained in 74% yield. The IR spectrum of **184** showed a strong -OH band at 3369 cm^{-1}. The dehalogenation of **184** was carried out with LAH (84%) and gave the required α-cyclopropane **185** in 45% overall yield starting from glycal **182.**

We next focussed our attention on the other diastereomeric cyclopropane **186.** Gratifyingly, the Simmon's-Smith cyclopropanation[142] of **182** gave directly the required β-cyclopropane **186** in 70% yield (Scheme 71). Under the mildly acidic conditions involved, detritylation can be expected to occur. It is not clear, however, whether detritylation precedes or follows cyclopropanation. The structures of **185**

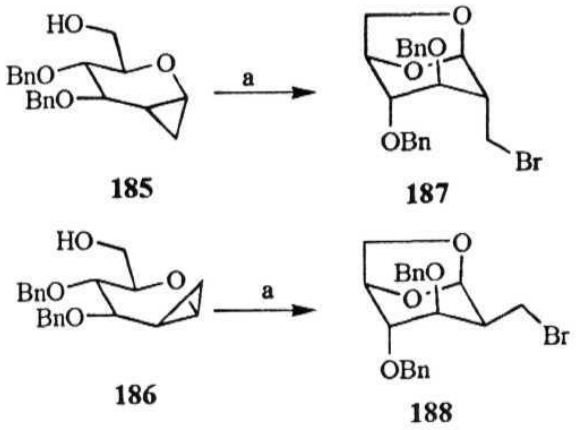
and 186 were established thoroughly from their ^{1}H and ^{13}C NMR data which are similar to those of **106** and **109**, respectively.



182 **186**

Scheme 71. *Reagents and Conditions*: a)Zn, CuCl, CH_2I_2, AcCl, ether, reflux, 2h.

The ring opening of these cyclopropanes with an electrophile in an aprotic solvent would result in the intramolecular attack of 6-OH at C-1, giving **a** levoglycosan derivative. This should be particularly favorable for the cyclopropane **185,** where the 6-OH group and the cyclopropane are well set to react in an S_N2 type process. In cyclopropane **186**, S_N2 type process can be ruled out, but formation of **a** levoglycosan derivative is possible by an S_N1 pathway. These intramolecular ring openings and ring closings of **185** and **186** would provide information about the difference in their reactivities. If a pure S_N1 mechanism is assumed, the difference in the reactivities of **185** and **186** will be due to the difference in the rate of first step, as the rate of intramolecular closure would be the same in both cases, considering the availability of **a** built-in nucleophile at C-6. An S_N2 type mechanism is possible only in **185** and is ruled out in **186.**

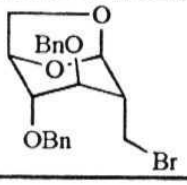
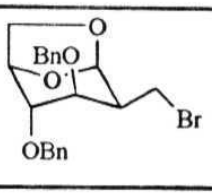
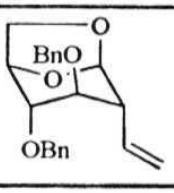


Scheme 72. *Reagents and Conditions*: a) NBS, CH_3CN, 4Å sieves, 5 or 36h.

The intramolecular ring opening of α-cyclopropane **185** in acetonitrile with NBS as an activator in the presence of 4A molecular sieves, took place smoothly within 5h giving the levoglucosan derivative **187** in 71% yield (Scheme 72). On the other hand, under similar conditions, the reaction with β-cyclopropane **186** was incomplete and yielded the levomannosan derivative 188 in 35% yield after 36h (Scheme 72). These results clearly indicate that the lower reactivity of the P-cyclopropane **186,** when compared to **185,** is due to steric hindrance to the approach of the electrophile. While a-cyclopropane **185** reacts clearly and rapidly by an S_N2 type process to give the levoglucosan derivative **187** in 71% yield, the β-cyclopropane **186,** with no such option available, forms the levomannosan derivative **188** in much lower yield, probably through an S_N1 mechanism.

The spectral assignments of products **187** and 188 were made using the data available for the known l,6-anhydro-2-deoxy-2-C-vinyl-p-glucopyranose derivative **189**.[143] The comparative spectral data are given in Table 5.

Table 5. Comparative spectral data of compound **187 - 189**:

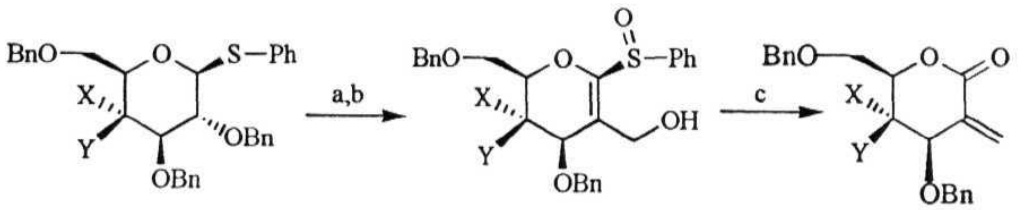
Entry				
		187	**188**	**189**
1	H-1	5.58 (s)	5.50 (s)	5.43 (s)
2	H-2	2.27 (t)	2.37 dd	2.49
3	H-3	4.3(d)	4.12	4.09
4	H-4	3.4 (s)	3.49	3.43 (s)
5	H-5	---	4.58 (d)	---
6	C-1	101.6	101.1	103.5
7	C-2	45.56	44.41	51.8
8	C-6	64.92	64.74	65.4

Synthesis of **α-methylene-δ-valerolactones:**

The significance of stereocontrolled carbon-carbon bond formation involving addition of carbon nucleophiles and radicals in organic synthesis has been well recognized. However, its appreciation in carbohydrates has commenced only recently.[144] While considering the various cyclic templates, unsaturated lactones and unsaturated carbonyl compounds stand out as suitable precursors towards enantiopure chemical synthesis of highly functionalized intermediates. *Exo*-cyclic α-methylene lactones have received much attention in this connection especially α-methylene-γ-butyrolactones. This is mainly due to the presence of this moiety in many natural products and its biological significance. A likely mechanism for the biological activity of these α-methylene-γ-lactones is through the conjugate addition

of a nucleophilic biomolecule.[145] In contrast to this, α-methylene-δ-valerolactones are less frequently encountered moieties in natural products, which perhaps is the reason for the limited number of reports towards their construction. Very few categories of compounds such as cembrane lactones and withanolides possess this moiety.[146] The methods available for their synthesis generally involve either methylenation of δ-lactones or lactonisation of α-methylene-δ-hexenoic acid derivatives.[147]

Recently, Schmidt and Giese[148] have made an entry into the synthesis and utility of sugar derived α-methylene-δ-valerolactone templates. The C-disaccharide synthesis developed by Giese and Schmidt[148b] permits the connection of two pyranoses by a methylene group, involving the addition of an anomeric pyranosyl radical derived from a pyranosyl halide to sugar derived α-methylene-δ-valerolactones.



190 **191**

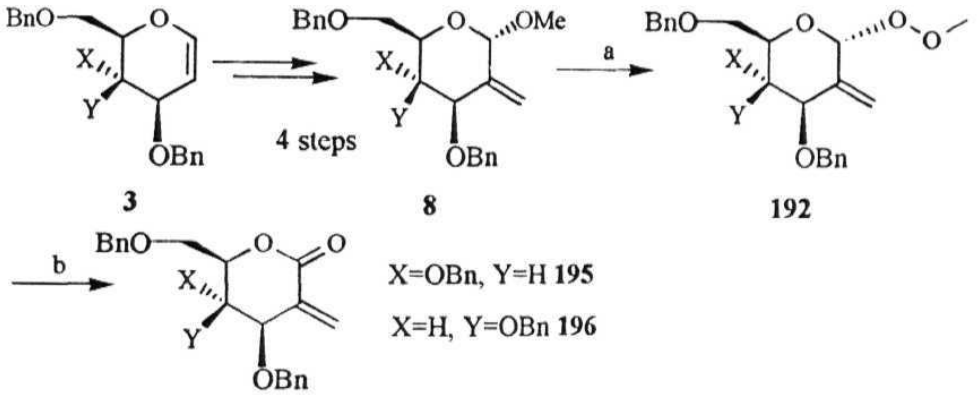
X=OBn, Y=H **195**

X=H, Y=OBn **196**

Scheme 73. *Reagents and Conditions*: a) MCPBA , CH_2Cl_2; b)2 eq. LDA, THF, HCHO; c) cat. PTSA, toluene, 70°;

The procedure developed by Schmidt, as shown in Scheme 73, involves the treatment of a glycopyranosyl sulfoxide with 2 eq. of LDA, followed by quenching of the resulting C-2 lithiated glycal with formaldehyde. Acid catalyzed rearrangement of the procured 2-hydroxymethyl derivatives yielded the respective α-methylene-δ-valerolactones.

In yet another protocol adopted, synthesis of α-methylene-δ-valerolactones has been achieved by Chmilewski[149] with glycals as starting compounds. Treatment of 2-deoxy-2-methylene methyl glycosides,[26b] derived from glycals in four steps as shown Scheme 3 (introduction), with hydrogen peroxide in the presence of molybdenum trioxide as catalyst provided anomeric hydroperoxides. Subsequent reaction of hydroperoxides with acetic anhydride-pyridine mixture afforded lactones **195** and **196,** respectively.



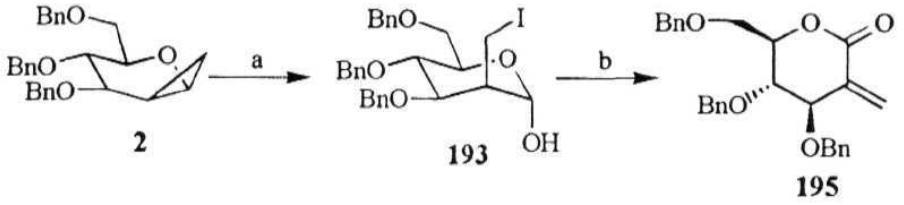
Scheme 74. *Reagents and Conditions*: a) molybdenum trioxide, 60% H_2O_2, rt; b) Ac_2O, pyridine, CH_2Cl_2, rt.

We conceived of synthesizing α-methylene-δ-valerolactone **195** from **149** following a sequence of oxidation and dehydrohalogenation. Extending this protocol to other cyclopropanated sugars obtained in one or two simple steps starting from glycals thus provides a facile and simple approach towards these chiral templates.

Initially, oxidation of lactol **149** was carried out with PCC and it was found that the resultant product was a mixture of a lactone and a lactol. The IR spectrum of the crude product showed a strong hydroxyl stretch at 3408 cm^{-1} and carbonyl stretch at 1732 cm^{-1} (which is also present in the lactol **149).** In general, the carbonyl band of δ-lactones appears around 1748 cm^{-1}. The absence this band adequately

proves that the oxidation with PCC is incomplete or did not take place. Replacing PCC with PDC also gave a similar result.

With the failure of attempts to oxidize lactol **149** with PCC or PDC, we looked for other methods. Among the various methods available for oxidation of lactols, oxidation with I_2 attracted our attention. The reason is that iodine can also open a cyclopropane. Although NIS failed to open **109** in methanol, we anticipated that at the higher temperature that is generally needed for the oxidation of lactols, the preceding ring opening can also be carried out. One advantage with opening of cyclopropanes with the iodonium ion when compared to the bromonium ion is the circumvention of O-benzylic cleavage, which we encountered occasionally with NBS. When the reaction of **109** with iodine in aq.dioxane was carried at 70°, discouragingly, it was found that the product obtained in 79% yield was exclusively the iodolactol **193** (Scheme 75).

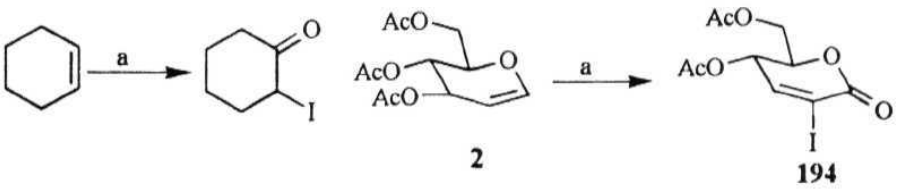


Scheme 75. *Reagents and Conditions*: a) I_2, dioxane-water (1 : 1), 70°, 8h; b) IDCP, dioxane-water (3 : 2), 60° – 70°, 18h.

The ^1H NMR spectrum of **193** showed a broad singlet at 5 5.45, characteristic of an unprotected anomeric proton. H-2 appeared as a multiplet at 5 2.60. No other signals corresponding to the possible β-anomer were found. This clearly indicates the strong preference of the H-1 proton for an equatorial orientation in manno derivatives. The ^{13}C NMR spectrum showed only 10 carbons excluding the aromatic carbons, again confirming the presence of a single anomer. In the case

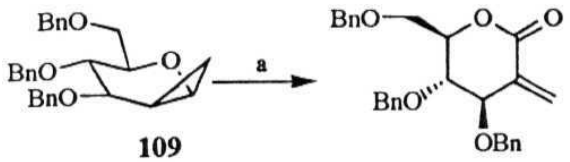
of 2-deoxy2-C-methyl mannose derivatives, Heathcock[106] reported the formation of a 10 : 1 a : β anomeric mixture. However, we did not find any evidence for an anomeric mixture either in bromo- or iodolactols 149 and 193, respectively. The anomeric carbon resonated at 94.4 ppm and the iodine bearing carbon at 2.14 ppm. These assignments clearly show the product obtained was an iodolactol and oxidation did not occur.

Increasing the temperature and/or reaction time was found to yield the lactol 193 and an uncharacterizable product whose structure was not established. The ^{1}H NMR spectrum of this product showed an aldehyde proton and a free anomeric proton. The presence of both anomeric carbon and aldehyde functionality was further substantiated by the ^{13}C NMR spectrum.



Scheme 76. *Reagents and Conditions*: a) $I^{+}[s\text{-collidine}]_2\ BF_4^-$, CH_2Cl_2, DMSO, rt.

Prompted by a report[150] on the reaction of olefins with a combination of iodonium di(*s*-collidine) tetrafluoroborate and DMSO yielding α-halocarbonyl compounds (Scheme 76), we looked at the reaction of 109 with IDCP in aq.dioxane. Gratifyingly and most suprisingly, the desired α-methylene-δ-valerolactone 195 was obtained in 57% yield, involving a sequence of ring opening, oxidation and elimination. The optimum conditions involved treatment of the cyclopropane 109 with 6 eq. of IDCP in 3 : 2 water-dioxane mixture at 60-70° for 18h (Scheme 77).



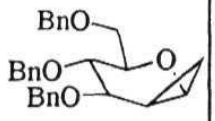
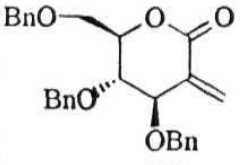
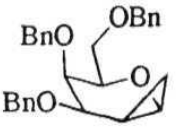
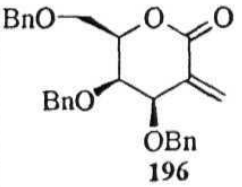
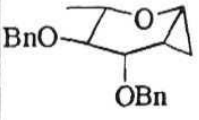
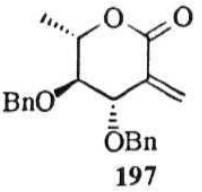
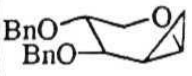
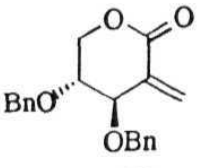
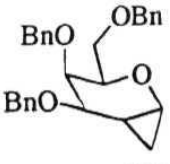
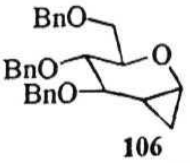
109 195

Scheme 77. *Reagents and Conditions*: a) IDCP, dioxane-water (3 : 2), 60°–70°, 18h.

The ^1H NMR spectrum and optical rotation data of compound **195** were in agreement with that reported by Schmidt.[148c] Incisive assignments of all ring carbons of **195** was made using DEPT-135 and HETCOR data. The DEPT-135 of **195** showed the presence of 5-CH_2 carbons at 129.92, 75.74 (2C), 73.56 and 68.60 ppm. The -CH_2 at 129.9 ppm clearly shows the presence of an exocyclic methylene. This was further substantiated from the HETCOR spectrum of **195,** where the two olefinic protons have cross peaks only with the carbon resonating at 129.92 ppm. The three -CH_2 carbons resonating at 75-73 ppm were assigned as benzylic and the remaining CH_2 as C-6. The other carbons C-3, C-4 and C-5 appeared at 79.05, 78.70 and 78.74 ppm, respectively. This was established by correlating with the corresponding protons using HETCOR data.

In order to generalize this methodology (Table 6), reaction of cyclopropanes **110, 111** and **112** (cyclopropane **112** was prepared by Simmons-Smith cyclopropanation of di-*O*-benzyl-D-xylal **97** in 63% yield) was carried out under similar conditions and the corresponding α-methylene-δ-valerolactones **196, 197** and **198** were obtained in 41, 83 and 68% yields, respectively. The low yield obtained in the case of **110** may be due to the more sterically crowded environment around the β-cyclopropane, which precludes the attack of I^+. This was substantiated by the reaction of its a-diastereomer **107** under similar conditions to provide **196** in 82% yield. In a similar fashion, **195** was obtained in 75% yield from the cyclopropane

Table 6. Conversion of 1,2-cyclopropanated sugars to α-methylene-δ-valerolactones.

Entry	Substrate	Product	Yield %
1	 **109**	 **195**	57
2	 **110**	 **196**	41
3	 **112**	 **197**	83
4	 **113**	 **198**	68
5	 **107**	**196**	82
6	 **106**	**195**	75

The physical data of compound **196** was in agreement with that reported earlier.[148c] A careful analysis of the ^{13}C NMR spectrum of compound **196** was carried out and the all ring carbons were assigned unambiguously. The identities of compounds 197 and 198 were established by their spectral (IR, ^{1}H and ^{13}C NMR) as well as mass spectral data. The salient features of the spectral assignments of **197** follows.

The IR spectrum of compound 197 showed a strong carbonyl band at 1730 cm^{-1}, characteristic of an unsaturated lactone. The two singlets at 8 6.49 and δ 5.88 clearly showed the presence of olefinic protons. The 6-CH_3 resonated at high field (δ 1.46) with J being 6.7 Hz. In the ^{13}C NMR spectrum, C-1 and C-7 resonated at 165.8 and 131.7 ppm, respectively.

Reaction of iodolactol 193 with IDCP (5 eq.) under similar conditions resulted in 195 in 77% yield, thus implying that **193** is an intermediate in the tandem three step sequence of ring opening, oxidation and elimination, the last step being brought about by *s*-collidine. When the reaction of 109 was carried out either for 8h or using 4eq. of IDCP, it was found that 195 was obtained along with substantial amounts of iodolactol 193. This clearly shows that amongst the three steps involved, dehydrohalgcnation is rapid and oxidation step is comparatively slower than the remaining two steps. The possibility of dehydrohalogenation being the second step and oxidation of the corresponding unsaturated lactol to unsaturated lactone can not be ruled out. However, we have not come across products having the unsaturated lactol moiety in our experiments.

Thus, the utilization of 1,2-cyclopropanated sugars in the construction of various functionalised 2-deoxy-2-C-branched-chain glycosides and disaccharides has been explored. As can be seen from the alcohols chosen, the glycosides formed from them can be hydrolyzed to the free sugars under acidic or neutral conditions, imparting flexibility to the method, if needed. On the other hand, this methodology makes for an easy entry into the synthesis of functionalised branched disaccharides

which are hitherto unknown, using sugar alcohols. The mercuric ion mediated opening of both forms of cyclopropanes affords an easy entry to the synthesis of modified sugars with defined 2-C-methyl stereochemistry which can serve as valuable precursors in natural product synthesis. Admittedly, the competing formation of bis(sugar)mercury compounds with β-cyclopropanes derived form galactal and rhamnal derivatives prevents generalization of this strategy at present.

The intramolecular participation of the 6-OH group in the ring opening reaction has been demonstrated and attempts have been made to understand the differences in the reactivity and anomeric selectivity of cyclopropanes 106 and 109. The inertness of cyclopropanes towards mineral acids has allowed the oxidation of the cyclopropane 185 under Jones conditions followed by esterification yielding the corresponding uronate. Further manipulations of this product towards its applicability as a starting point for the partial construction of various natural products like Prelog-Djerassi lactonic acid are in progress. A simple, one pot conversion of 1,2-cyclopropanated sugars to chiral α-methylene-δ-valerolactones has been developed. This easy method for their construction will definitely allow for the expansion of their synthetic potential as valuable Michael acceptors.

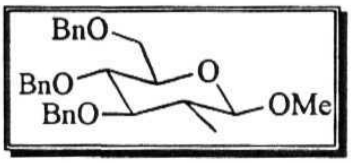
EXPERIMENTAL

All reagents were purified by appropriate methods just before use. All cyclopropanes were prepared according to the procedures reported.[100, 101] Solvents were dried using appropriate drying agents. Freshly recrystallized NBS (water) and IDCP ($CHCl_3$) were used. Solvents used for chromatography were of commercial grade and were fractionally distilled before use. All organic extracts were dried over $MgSO_4$. Column chromatography was performed using ACME silica gel (100-200 mesh) and eluted with appropriate mixtures of hexane and ethyl acetate. Thin layer chromatography (tlc) was performed on home made plates coated with ACME silica gel GF 254 (with 13% calcium sulphate as binder) and were visualised by shining UV light or exposing to iodine vapours. Melting points were determined on a SUPERFIT melting point apparatus and are uncorrected. Optical rotations were measured on a SHIMADZU polarimeter at 25°. Infrared spectra were recorded on a JASCO FT-IR 5300 instrument. ^{1}H and ^{13}C NMR spectra were recorded on a BRUKER AF 200 NMR Spectrometer operating at 4.7 Tesla magnetic field strength in chloroform-d, with tetramethylsilane (TMS) as internal standard. DEPT and 2D NMR data were processed using standard software provided with the instrument. The ^{1}H NMR spectral data are listed as follows: signals are reported in parts per million (ppm) downfield of TMS; signal multiplicity is denoted as s = singlet, d = doublet, dd = doublet of a doublet, t = triplet, q = quartet, br = broad and m = multiplet; coupling constant (J) measured in Hertz; number of protons integrated for and assignments, wherever possible. Elemental analyses were obtained using PERKIN-ELMER model 240C-CHN analyser. High Resolution Mass Spectra were recorded on a JEOL SX 102/DA-6000 Spectrometer. Low Resolution Mass Spectra were recorded on VG 70-70H Mass Spectrometer.

Ring opening **of** cyclopropane 106 with **HCl/MeOH:**

A solution of cyclopropane **106** (165 mg, 0.38 mmol) and acetyl chloride (0.38 ml) in methanol (5 ml) was heated at 80° for 15 days. The reaction mixture was diluted with dichloromethane, treated with solid sodium bicarbonate and concentrated. On purification by column chromatography, followed by recrystallisation, the product **132** (49 mg, 70% with respect to the recovered cyclopropane, 98 mg) was obtained as a colourless solid.

Methyl 3,4,6-tri-*O*-benzyl-2-deoxy-2-C-methyl-β-D-glucopyranoside (132)



M.p = 104 - 105° (ether/hexane).

$[\alpha]^{25}_{D}$ = +4.5° (c 0.2, $CHCl_3$).

IR (KBr): 3065, 3030, 2928, 1647, 1497, 1454, 1362, 1092, 1026, 736, 698 cm^{-1}.

^1H NMR: δ 7.35–7.26 (m, 15H, ArH), 5.0–4.50 (m, 6H, $-OCH_2Ph$), 4.03–3.99 (d, J = 8.0 Hz, 1H, H-1), 3.80–3.40 (m, 7H), 3.27–3.24 (t, 1H, H-3), 1.85–1.75 (m, 1H, H-2), 1.06–1.03 (d, J = 6.4 Hz, 3H, H-7).

^{13}C NMR: 138.42, 128.49, 128.20, 127.96, 127.87, 127.71, 105.68, 85.37, 79.55, 75.32, 75.23, 74.83, 73.62, 70.75, 56.85, 42.79, 12.62 ppm.

Anal. Calcd for $C_{29}H_{34}O_5$: C, 75.29; H, 7.41.

Found: C, 75.31; H, 7.45.

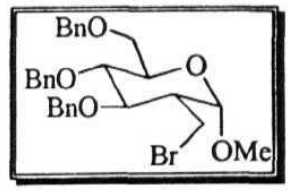
General procedure for NBS activated ring opening reactions of **cyclopropanes 106** and 109 with different solvents:

To a stirred solution of the cyclopropane (215 mg, 0.5 mmol) in 5 ml of solvent at 0°, under nitrogen, was added NBS (107 mg, 0.6 mmol) and the stirring was continued until the reaction mixture showed the absence of starting material on tlc. Except with benzyl alcohol, where the reaction mixture was concentrated by

distilling out the benzyl alcohol under reduced pressure, in general, the reaction mixture was evaporated with toluene in vacuo. An aqueous workup was found to be less efficient in all cases. Chromatographic purifications were carried out using 5% ethyl acetate in hexane. Yields are based on the amount of pure material obtained. The anomeric ratios were obtained from H NMR data by integrating the H-2 multiplets in the crude mixture wherever possible. In all cases, the anomeric ratios were also obtained by separating the mixture and weighing the individual constituents.

Ring opening of cyclopropane 106 with NBS/MeOH:

As described above, stirring cyclopropane 106 (290 mg, 0.67 mmol) with NBS (145 mg, 0.81 mmol) in MeOH (6 ml) for 8h and purification of the reaction mixture gave the anomers 133 (53 mg) and 134 (210 mg) in 72% overall yield.



Methyl 3,4,6-tri-*O*-benzyl-2-deoxy-2-C-(bromomethyl)-α-D-glucopyranoside (133) Colourless syrup

$[\alpha]^{25}_D$ = +87.3° (c 1, $CHCl_3$).

IR (neat): 3030, 2922, 1496, 1454, 1361, 1209, 1049, 916, 736 cm^{-1}.

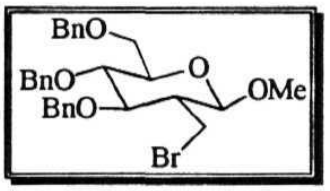
^1H NMR: δ 7.36–7.16 (m, 15H, ArH), 5.0–4.99 (d, J = 2.6 Hz, 1H, H-1), 4.92–4.53 (m, 6H, $-OCH_2Ph$), 3.85–3.57 (m, 6H), 3.40 (s, 3H, -OMe), 3.35–3.25 (t, 1H, H-7'), 2.34–2.17 (m, 1H, H-2).

^{13}C NMR: 138.22, 138.09, 128.52, 128.40, 127.86, 127.72, 99.23, 80.35, 79.48, 75.27, 74.79, 73.61, 70.96, 68.79, 55.26, 48.51, 30.60 ppm.

Anal. Calcd for $C_{29}H_{33}BrO_5$: C, 64.32; H, 6.14.

Found: C, 64.30; H, 6.35.

Methyl 3,4,6-tri-*O*-benzyl-2-deoxy-2-C-(bromomethyl)-β-D-glucopyranoside (134). Colourless syrup,



$[\alpha]^{25}_D$ = $+22^{O}$ (c 1, $CHCl_3$).

IR (neat): 3000, 2850, 1460, 1360, 1200, 1100, 1040, 740 cm^{-1}.

^1H NMR: δ 7.34–7.19 (m, 15H, ArH), 5.0–4.58 (m, 6H, $-OCH_2Ph$), 4.45–4.41 (d, J = 8.5 Hz, 1H, H-1), 3.87–3.46 (m, 10H), 1.95–1.81 (m, 1H, H-2).

^{13}C NMR: 138.44, 138.30, 138.11, 128.52, 128.42, 127.86, 102.29, 80.01, 79.85, 75.58, 75.14, 74.84, 73.62, 69.04, 57.25, 47.70, 31.60 ppm.

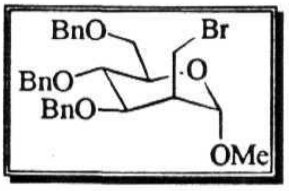
Anal. Calcd for $C_{29}H_{33}BrO_5$: C, 64.32; H, 6.14.

Found: C, 64.25; H, 6.18.

Ring opening of cyclopropane 109 with NBS/MeOH:

Stirring cyclopropane **109** (215 mg, 0.5 mmol) with NBS (108 mg, 0.6 mmol) in MeOH (5 ml) for 24h and chromatographic purification yielded the ring opened product **135** (170 mg, 62%) as a colourless syrup.

Methyl 3,4,6-tri-*O*-benzyl-2-deoxy-2-C-(bromomethyl)-α-D-mannopyranoside (135)



$[\alpha]^{25}_D$ = $+36^{O}$ (c 0.8, $CHCl_3$).

IR (neat): 3030, 2914, 1496, 1454, 1365, 1273, 1099, 1053, 983, 736, 698 cm^{-1}.

^1H NMR: δ 7.39–7.22 (m, 15H, ArH), 5.03 (s, 1H, H-1), 4.83–4.40 (m, 6H, $-OCH_2Ph$), 4.07–4.0 (dd, J = 8.9, 5.2 Hz, 1H), 3.85–3.40 (m, 6H), 3.38 (s, 3H, -OMe), 2.69–2.58 (m, 1H, H-2).

^{13}C NMR: 138.34, 138.26, 138.15, 128.51, 128.39, 127.91, 127.79, 99.71, 79.57, 74.88, 74.33, 73.53, 71.92, 71.11, 68.99, 55.03, 46.24, 29.57 ppm.

Anal. Calcd for $C_{29}H_{33}BrO_5$: C, 64.32; H, 6.14.
Found: C, 64.25; H, 6.0.

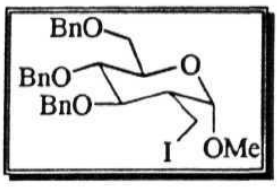
Ring opening of cyclopropane 106 with NIS/MeOH:

As mentioned above for NBS, after stirring cyclopropane **106** (200 mg, 0.46 mmol) with NIS (125 mg, 0.55 mmol) in MeOH for 12h and purification of the reaction mixture, the anomers **136** (47 mg) and **137** (196 mg) were obtained in a 20 : 80 ratio (86%).

Ring opening of cyclopropane 106 with IDCP/MeOH:

To a stirred solution of cyclopropane **106** (207 mg, 0.48 mmol) in methanol (5 ml), was added IDCP (325 mg, 0.69 mmol). After 6h, the reaction mixture was concentrated in vacuo and the crude product was dissolved in dichloromethane, washed with saturated sodium bisulfite, brine and purified by column chromatography. The anomers **136** (37 mg) and **137** (208 mg) were obtained (overall yield 86%).

Methyl 3,4,6-tri-*O*-benzyl-2-deoxy-2-C-(iodomethyl)-α-D-glucopyranoside (136) Colourless syrup,



$[\alpha]^{25}_D$ = +69.2° (c 0.4, $CHCl_3$).

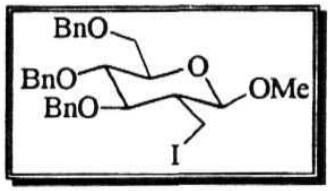
IR (neat): 3030, 2916, 1496, 1454, 1361, 1201, 1049, 910, 812, 698 cm^{-1}.

^1H NMR: δ 7.36–7.15 (m, 15H, ArH), 4.96–4.95 (d, J = 3.0 Hz, 1H, H-1), 4.93–4.51 (m, 6H, $-OCH_2Ph$), 3.82–2.97 (m, 10H), 2.24–2.08 (m, 1H, H-2).

^{13}C NMR: 138.40, 128.57, 128.47, 127.89, 127.77, 101.07, 81.29, 79.16, 75.45, 74.84, 73.66, 71.09, 68.79, 55.38, 48.46, 3.05 ppm.

Anal. Calcd for $C_{29}H_{33}IO_5$: C, 59.19; H, 5.65.
Found: C, 59.22; H, 5.68.

Methyl 3,4,6-tri-*O*-benzyl-2-deoxy-2-C-(iodomethyl)-β-D-glucopyranoside (137) Waxy solid,



$[\alpha]^{25}_{D}$ = +53.2° (c 0.5, $CHCl_3$).

IR (neat): 3032, 2864, 1496, 1454, 1361, 1313, 1267, 1211, 1103, 1055, 910, 733, 698 cm^{-1}.

^1H NMR: δ 7.36–7.19 (m, 15H, ArH), 4.97–4.58 (m, 6H, $-OCH_2Ph$), 4.32–4.28 (d, J = 8.6 Hz, 1H, H-1), 3.78–3.49 (m, 10H), 1.35–1.21(m, 1H, H-2).

^{13}C NMR: 138.45, 138.24, 138.08, 129.79, 128.59, 128.54, 128.44, 127.89, 127.70, 104.39, 81.65, 79.75, 75.63, 75.13, 74.80, 73.61, 68.96, 57.34, 46.32, 6.97 ppm.

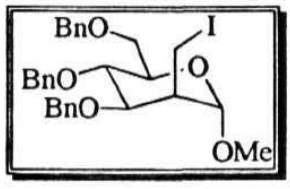
Anal. Calcd for $C_{29}H_{33}IO_5$: C, 59.19; H, 5.65.

Found: C, 59.45; H, 5.72.

Ring opening of cyclopropane 109 with IDCP/MeOH:

As described above, after stirring cyclopropane **109** (310 mg, 0.72 mmol) for 36h with IDCP (405 mg, 0.87 mmol) in MeOH (6 ml), followed by the usual workup and purification of the reaction mixture, the corresponding ring opened product **138** was obtained as a colourless syrup (134 mg, 70% with respect to recovered **109**, 173 mg).

Methyl 3,4,6-tri-*O*-benzyl-2-deoxy-2-C-(iodomethyl)-α-D-mannopyranoside (138)



$[\alpha]^{25}_{D}$ = +32.3° (c 0.3, $CHCl_3$).

IR (neat): 3030, 2906, 1604, 1496, 1454, 1365, 1265, 1147, 908, 736, 698 cm^{-1}.

^1H NMR: δ 7.35–7.14 (m, 15H, ArH), 4.96 (s, 1H, H-1), 4.85–4.43 (m, 6H, $-OCH_2Ph$), 3.98–3.91 (m, 1H), 3.81–3.65 (m, 5H), 3.42 (s, 3H, -OMe), 3.22–3.11 (t, 1H, H-7'), 2.69–2.58 (m, 1H, H-2).

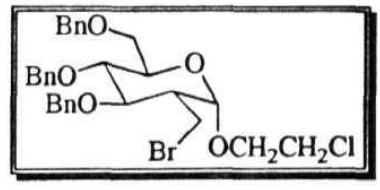
^{13}C NMR: 138.41, 138.30, 138.21, 128.51, 128.38, 127.90, 127.76, 127.66, 100.92, 80.16, 74.81, 74.11, 73.53, 71.90, 71.38, 69.07, 55.0, 46.77, 2.0 ppm.

Anal. Calcd for $C_{29}H_{33}IO_5$: C, 59.19; H, 5.65.
Found: C, 59.29; H, 5.70.

Ring opening of cyclopropane 106 with NBS/$ClCH_2CH_2OH$:

After stirring cyclopropane **106** (110 mg, 0.25 mmol) with NBS (50 mg, 0.28 mmol) in 2–chloroethanol (3 ml) for 4h, the tlc showed clearly the disappearance of starting compound and the formation of two new products. They were separated and identified as **139** (48 mg) and **140** (89 mg) (91% overall yield).

(2'-Chloroethyl) 3,4,6-tri-*O*-benzyl-2-deoxy-2-C-(bromomethyl)-α-D-glucopyranoside (139)



Colourless syrup,

$[\alpha]^{25}_D$ = +78.9° (c 0.9, $CHCl_3$).

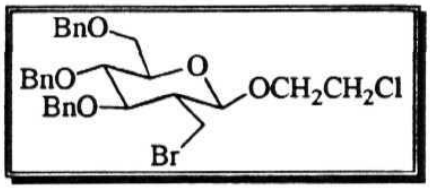
IR (neat): 3032, 2920, 1496, 1454, 1361, 1207, 1089, 738, 698 cm^{-1}.

^{1}H NMR: δ 7.34–7.12 (m, 15H, ArH), 5.15–5.14 (d, J = 3.4 Hz, 1H, H-1), 4.94–4.49 (m, 6H, -OCH_2Ph), 3.93–3.60 (m, 10H), 3.41–3.30 (t, 1H), 2.36–2.19 (m, 1H, H-2).

^{13}C NMR: 138.0, 128.56, 128.45, 127.94, 127.82, 98.48, 80.22, 79.29, 75.40, 74.91, 73.59, 71.38, 68.57, 68.33, 48.44, 42.83, 30.53 ppm.

Anal. Calcd for $C_{30}H_{34}BrClO_5$: C, 61.08; H, 5.83.
Found: C, 61.0; H, 5.85.

(2'-Chloroethyl) 3,4,6-tri-*O*-benzyl-2-deoxy-2-C-(bromomethyl)-β-D-glucopyranoside (140)



Waxy solid,

$[\alpha]^{25}_{D}$= +22.5° (c 0.8, $CHCl_3$).

IR (neat): 3032, 2868, 1496, 1454, 1363, 1209, 1055, 736, 698 cm^{-1}.

^1H NMR: δ 7.34–7.18 (m, 15H, ArH), 4.94–4.58 (m, 6H, $-OCH_2Ph$), 4.56-4.53 (d, J = 7.9 Hz, 1H, H-1), 4.21–4.07 (m, 1H), 3.86–3.66 (m, 9H), 3.51–3.41 (m, 1H), 1.97–1.84 (m, 1H, H-2).

^{13}C NMR: 138.34, 138.14, 138.04, 128.49, 128.43, 127.84, 101.35, 79.86, 79.59, 75.54, 75.10, 74.83, 73.56, 69.84, 68.89, 47.54, 42.62, 31.49 ppm.

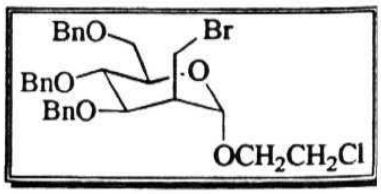
Anal. Calcd for $C_{30}H_{34}BrClO_5$: C, 61.08; H, 5.83.

Found: C, 61.22; H, 5.82.

Ring opening of cyclopropane 109 with NBS/$ClCH_2CH_2OH$:

The reaction took 12h for completion and yielded the corresponding ring opened product **141** (192 mg) in 71% yield (as a colourless syrup) starting with **109** (200 mg, 0.46 mmol) and NBS (100 mg, 0.56 mmol).

(2'-Chloroethyl) 3,4,6-tri-*O*-benzyl-2-deoxy-2-C-(bromomethyl)-α-D-mannopyranoside (141)



$[\alpha]^{25}_{D}$= +38.4° (c 0.9, $CHCl_3$).

IR (neat): 3032, 2870, 1604, 1496, 1454, 1363, 1207, 1095, 983, 738, 698 cm^{-1}.

^1H NMR: δ 7.36–7.17 (m, 15H, ArH), 5.13 (s, 1H, H-1), 4.82–4.41 (m, 6H, $-OCH_2Ph$), 4.11–4.04 (dd, J = 5.2, 9.3 Hz, 1H), 3.95–3.50 (m, 9H), 3.48–3.38 (t, 1H), 2.71–2.65 (m, 1H, H-2).

^{13}C NMR: 138.09, 128.25, 127.80, 127.59, 98.89, 79.09, 74.61, 74.09, 73.33, 71.83, 71.45, 68.80, 67.92, 46.06, 42.62, 29.40 ppm.

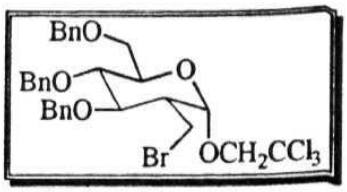
Anal. Calcd for $C_{30}H_{34}BrClO_5$ C, 61.08; H, 5.83.

Found: C, 61.25; H, 5.91.

Ring opening of cyclopropane 106 with NBS/Cl_3CCH_2OH:

The ring opening of **106** (85 mg, 0.197 mmol) with NBS (44 mg, 0.25 mmol) in 2,2,2-trichloroethanol was complete within 1h and yielded both α- and β-anomers in equal amounts (116 mg, 89%).

(2',2',2'-Trichloroethyl) 3,4,6-tri-*O*-benzyl-2-deoxy-2-C-(bromomethyl)-α-D-glucopyranoside (142)



Colourless syrup,

$[\alpha]^{25}_D$= +70° (c 0.5, $CHCl_3$).

IR (neat): 3032, 2866, 1496, 1454, 1359, 1209, 1103, 812, 735, 698 cm^{-1}.

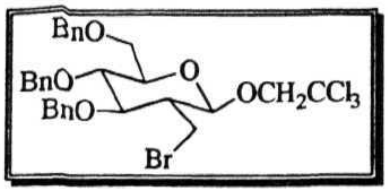
^{1}H NMR: δ 7.38–7.21 (m, 15H, ArH), 5.35–5.34 (d, J = 2.9 Hz, 1H, H-1), 4.96–4.51 (m, 6H, -OCH_2Ph), 4.29–4.07 (m, 2H), 3.86–3.66 (m, 6H), 3.47–3.35 (t, 1H), 2.42–2.24 (m, 1H, H-2).

^{13}C NMR: 137.92, 128.49, 127.91, 98.83, 96.01, 79.91, 79.57, 79.16, 75.49, 75.07, 73.65, 72.42, 68.02, 48.72, 29.94 ppm.

Anal. Calcd for $C_{30}H_{32}BrCl_3O_5$: C, 54.69; H, 4.90.

Found: C, 54.75; H, 4.91.

(2',2',2'-Trichloroethyl) 3,4,6-tri-*O*-benzyl-2-deoxy-2-C-(bromomethyl)-β-D-glucopyranoside (143) Colourless syrup,



$[\alpha]^{25}_D$= +24° (c 0.2, $CHCl_3$).

IR (neat): 3030, 2870, 1496, 1454, 1361, 1267, 1207, 1099, 814, 734, 698 cm^{-1}.

^{1}H NMR: δ 7.38–7.21 (m, 15H, ArH), 5.01–4.54 (m, 6H, -OCH_2Ph, H-1), 4.52–4.46 (d, J = 12.6 Hz, 1H, -OCH_2Ph), 4.20–4.15 (d, J = 11.7 Hz, 1H), 3.97–3.45 (m, 8H), 2.10–1.97 (m, 1H, H-2).

^{13}C NMR: 138.35, 137.99, 128.50, 127.85, 101.40, 96.03, 80.73, 79.78, 79.41, 75.54, 75.26, 74.86, 73.61, 68.74, 48.57, 31.15 ppm.

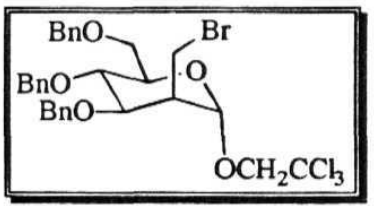
Anal. Calcd for $C_{30}H_{32}BrCl_3O_5$: C, 54.69; H, 4.90.

Found: C, 54.65; H, 4.91.

Ring opening of cyclopropane 109 with NBS/Cl_3CCH_2OH:

The ring opening of **109** (375 mg, 0.87 mmol) with NBS (186 mg, 1.05 mmol) in 2,2,2-trichloroethanol took 8h for completion and yielded the corresponding ring opened product **144** (350 mg, 72%) as a pale yellow syrup.

(2',2',2'-Trichloroethyl) 3,4,6-tri-*O*-benzyl-2-deoxy-2-C-(bromomethyl)-α-D-mannopyranoside (144):



$[\alpha]^{25}_D$ = +51.3° (c 1, $CHCl_3$).

IR (neat): 3030, 2928, 1496, 1454, 1363, 1273, 1209, 1099, 979, 815, 736,698 cm^{-1}.

^{1}H NMR: δ 7.35–7.13 (m, 15H, ArH), 5.33 (s, 1H, H-1), 4.81–4.41 (m, 6H, -OCH_2Ph), 4.26–4.08 (m, 3H), 3.86–3.61 (m, 5H), 3.48–3.37 (t, 1H), 2.79–2.68 (m, 1H, H-7).

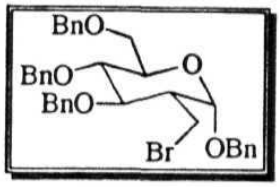
^{13}C NMR: 138.27, 138.0, 128.57, 128.47, 127.97, 127.79, 100.03, 96.64, 79.44, 78.79, 74.75, 74.14, 73.60, 72.50, 72.27, 68.97,46.09, 29.21 ppm.

Anal. Calcd for $C_{30}H_{32}BrCl_3O_5$: C, 54.69; H, 4.90.

Found: C, 54.32; H, 4.88.

Ring opening of cyclopropane 106 with NBS/$PhCH_2OH$:

Cyclopropane **106** (295 mg, 0.69 mmol) was treated with benzyl alcohol and NBS (193 mg, 1.08 mmol). After 36h, benzyl alcohol was distilled from the reaction mixture and the crude product was purified. Products **145** (134 mg) and **146** (249 mg) were obtained in a 35 : 65 ratio (383 mg, 91%).



Benzyl 3,4,6-tri-*O*-benzyl-2-deoxy-2-C-(bromomethyl)-α-D-glucopyranoside (145) Colourless syrup,

$[\alpha]^{25}_D$= +85.5° (c 1, $CHCl_3$).

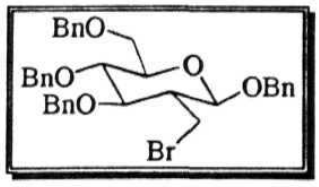
IR (neat): 3030, 2920, 1496, 1454, 1359, 1207, 1045, 736, 698 cm^{-1}.

^1H NMR: δ 7.38–7.14 (m, 20H, ArH), 5.25–5.24 (d, J = 3.2 Hz, 1H, H-1), 4.92–4.49 (m, 8H, -OCH_2Ph), 3.83–3.64 (m, 6H), 3.42–3.32 (dd, J = 10.0, 11.4 Hz, 1H, H-7), 2.38–2.22 (m, 1H, H-2).

^{13}C NMR: 138.23, 137.66, 128.61, 128.52, 127.90, 98.03, 80.57, 79.63, 77.45, 75.41, 74.99, 73.71, 71.48, 70.06, 68.85, 48.73, 30.66 ppm.

Anal. Calcd for $C_{35}H_{37}BrO_5$: C, 68.07; H, 6.04.

Found: C, 68.10; H, 6.10.



Benzyl 3,4,6-tri-*O*-benzyl-2-deoxy-2-C-(bromomethyl)-β-D-glucopyranoside (146) Colourless solid,

M.p = 91–93° (ether/hexane).

$[\alpha]^{25}_D$= -7.5° (c 1, $CHCl_3$).

IR (KBr): 3032, 2870, 1604, 1496, 1452, 1358, 1309, 1277, 1209, 1059, 844, 734, 694 cm^{-1}.

^1H NMR: δ 7.38–7.12 (m, 20H, ArH), 4.99–4.59 (m, 9H, -OCH_2Ph, H-1), 3.92–3.69 (m, 6H), 3.54–3.45 (m, 1H), 2.02–1.89 (m, 1H, H-2).

^{13}C NMR: 138.48, 138.38, 138.24, 128.49, 128.35, 127.88, 100.47, 80.09, 79.87, 75.57, 75.23, 74.85, 73.64, 71.44, 69.07, 47.73, 31.61 ppm.

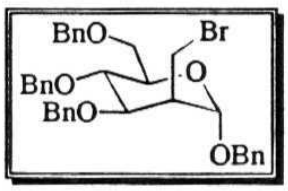
Anal. Calcd for $C_{35}H_{37}BrO_5$: C, 68.07; H, 6.04.

Found: C, 67.98; H, 6.11.

Ring opening of cyclopropane 109 with NBS/PhCH$_2$OH:

The reaction of cyclopropane **109** (392 mg, 0.91 mmol) with NBS (195 mg, 1.1 mmol) and benzyl alcohol was incomplete even after 4 days. Distillation of excess benzyl alcohol, followed by purification afforded 45 mg of **147** (40% yield, with respect to 314 mg of cyclopropane recovered) as a colourless syrup .

Benzyl 3,4,6-tri-*O*-benzyl-2-deoxy-2-C-(bromomethyl)-α-D-mannopyranoside (147)



$[\alpha]^{25}_D$ = +59.8^O (c 0.5, $CHCl_3$).

IR (neat): 3032, 2918, 1604, 1496, 1454, 1361, 1273, 1209, 1209, 1095, 736, 698 cm^{-1}.

^{1}H NMR: δ 7.35–7.18 (m, 20H, ArH), 5.21 (s, 1H, H-1), 4.82–4.41 (m, 8H, -OCH$_2$Ph), 4.14–4.07 (dd, J = 5.4, 9.2 Hz, 1H, H-3), 3.86–3.58 (m, 5H), 3.49–3.33 (t, J = 10.4 Hz, 1H, H-7), 2.77–2.64 (m, 1H, H-2).

^{13}C NMR: 138.27, 137.52, 128.38, 127.94, 127.75, 126.98, 98.33, 79.50, 74.86, 74.43, 73.52, 71.99, 71.51, 69.55, 68.97, 46.39, 29.55 ppm.

Anal. Calcd for $C_{35}H_{37}BrO_5$: C, 68.07; H, 6.04.

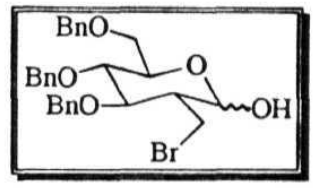
Found: C, 67.96; H, 6.08.

Ring opening of cyclopropane 106 with NBS/H$_2$O:

To a solution of cyclopropane **106** (250 mg, 0.58 mmol) in 2 : 1 dioxane/water (6 ml) was added NBS (125 mg, 0.70 mmol) and the stirring was continued for 8h. The reaction mixture was then concentrated to half its volume in

vacuo and extracted with dichloromethane. The combined extracts were dried and concentrated. Purification by chromatography and recrystallisation yielded **148** (198 mg, 66% yield) as a colourless solid.

3,4,6-Tri-*O*-benzyl-2-deoxy-2-C-(bromomethyl)-D-glucopyranose (148)



M.p = 110–112° (ether/hexane).

$[\alpha]^{25}_{D}$ = +61.2° (c 1, $CHCl_3$).

IR (KBr): 3364, 3030, 2914, 1730, 1494, 1452, 1361, 1209, 1039, 868, 740, 696 cm^{-1}.

^1H NMR: δ 7.34–7.18 (m, 15H, ArH), 5.54–5.51 (br s) and 4.92–4.56 (m, 7H, $-OCH_2Ph$, H-1), 4.14–3.26 (m, 8H), 2.33–2.17 and 1.89–1.72 (ms, 1H).

^{13}C NMR: 138.07, 137.92, 128.21, 128.08, 127.93, 95.46, 92.43, 79.83, 79.67, 75.54, 75.39, 74.91, 74.73, 73.59, 70.91, 68.98, 48.71, 48.62, 30.92 ppm.

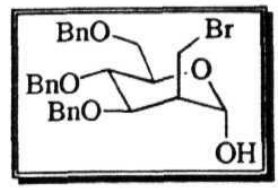
Anal. Calcd for $C_{28}H_{31}BrO_5$: C, 63.76; H, 5.92.

Found: C, 64.09; H, 6.07.

Ring opening of cyclopropane 109 with NBS/H_2O:

On carrying out the reaction under similar conditions as described above, cyclopropane **109** (294 mg, 0.68 mmol) provided the corresponding ring opened product **149** (210 mg, 61%) as a colourless solid.

3,4,6-Tri-*O*-benzyl-2-deoxy-2-C-(bromomethyl)-D-mannopyranose (149)



M.p = 90–91° (ether/hexane).

$[\alpha]^{25}_{D}$ = +23.9° (c 1, $CHCl_3$).

IR (KBr): 3408, 3063, 2866, 1732, 1496, 1454, 1365, 1257, 1099, 738, 698 cm^{-1}.

^1H NMR: δ 7.34–7.14 (m, 15H, ArH), 5.50 (s, 1H, H-1), 4.82–4.41 (m, 6H, $-OCH_2Ph$), 4.16–4.02 (m, 2H), 3.84–3.35 (m, 5H), 3.12 (s br, 1H), 2.69–2.57 (m, 1H, H-2).

^{13}C NMR: 138.27, 138.16, 137.95, 128.53, 128.49, 128.01, 127.80, 93.16, 78.98, 74.72, 74.63, 73.45, 71.98, 71.03, 69.35, 46.39, 29.74 ppm.

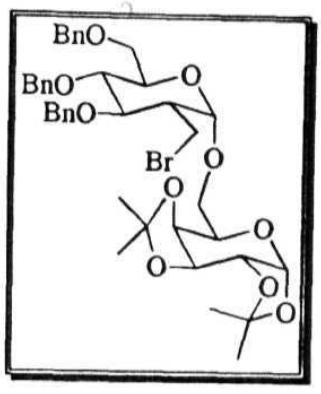
Anal. Calcd for $C_{28}H_{31}BrO_5$: C, 63.76; H, 5.92.

Found: C, 63.84; H, 6.09.

Ring opening of cyclopropane 106 with NBS/1,2:3,4-di-*O*-isopropylidine-α-D-galactopyranose (72):

To a solution of α-cyclopropane **106** (350 mg, 0.81 mmol) and 1,2:3,4-di-*O*-isopropylidine-α-D-galactopyranose (**72**) (635 mg, 2.44 mmol) in dry acetonitrile (8 ml), was added powdered 4Å molecular sieves (equal to the amount of alcohol used) under nitrogen atmosphere and the contents were stirred for 1h. To the above reaction mixture, NBS (174 mg, 0.98 mmol) was added all at once as a solid and it was then stirred for 4 days. The contents were diluted with toluene (25 ml), filtered and evaporated at reduced pressure. The crude product after column chromatographic purification afforded the disaccharides **152** (150 mg) and **153** (225 mg) as colourless gums (overall yield 60%).

3,4,6-Tri-*O*-benzyl-2-deoxy-2-C-(bromomethyl)-α-D-glucopyranosyl-(1→6)-1,2:3,4-di-*O*-isopropylidine-α-D-galactopyranose (152)



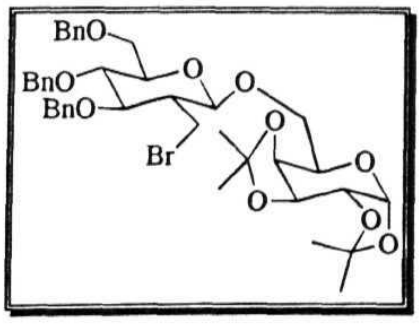
$[\alpha]^{25}_{D}$= +40° (c 0.5, $CHCl_3$).

IR (neat): 3032, 2986, 2905, 1604, 1496, 1454, 1381, 1255, 1211, 1070, 898, 698 cm^{-1}.

^{1}H NMR: δ 7.33–7.18 (m, 15H, ArH), 5.54–5.52 (d, J = 4.9 Hz, 1H, H-1_{gal}), 5.14–5.13 (d, J = 2.9 Hz, 1H, H-1_{glu}), 4.92–4.87 (d, J = 11.2 Hz, 1H, -OCH_2Ph), 4.81–4.71 (t, 1H, -OCH_2Ph), 4.65–4.48 (m, 5H, -OCH_2Ph and H-3_{gal}), 4.34–4.25 (m, J = 2.6, 4.9 Hz, 2H, H-2_{gal}, H-4_{gal}), 4.07–3.93 (m, 1H), 3.86–3.61 (m, 8H), 3.38–3.27 (t, J = 10.7 Hz, 1H, H-7), 2.48–2.19 (m, 1H, H-2_{glu}), 1.58 (s, 3H, -CMe_2), 1.45 (s, 3H, -CMe_2), 1.34 (s, 6H, -CMe_2).

^{13}C NMR: 138.26, 138.20, 128.51, 128.42, 127.97, 127.84, 109.28, 108.53, 98.76 , 96.32, 80.20, 79.45, 75.25, 74.79, 73.60, 71.21, 71.02, 70.76, 70.68, 68.63, 66.91, 66.52, 48.72, 30.38, 26.27, 26.03, 25.01, 24.46 ppm.

3,4,6-Tri-*O*-benzyl-2-deoxy-2-C-(bromomethyl)-β-D-glucopyranosyl-(1→6)-1,2:3,4-di-*O*-isopropylidine-α-D-galactopyranose (153)



$[\alpha]^{25}_{D}$= -20.3° (c 0.5, $CHCl_3$).

IR (neat): 3063, 2986, 1604, 1496, 1454, 1381, 1255, 1167, 1118, 1005, 898, 698 cm^{-1}.

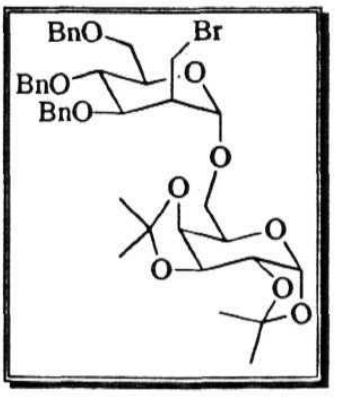
^{1}H NMR: δ 7.33–7.18 (m, 15H, ArH), 5.54–5.52 (d, J = 4.9 Hz, 1H, H-1_{gal}) 4.98–4.93 (d, J = 10.8 Hz, 1H, -OCH_2Ph), 4.83–4.78 (d, J = 10.6 Hz, 2H, -OCH_2Ph), 4.70–4.52 (m, 5H, -OCH_2Ph, H-1_{glu} and H-3_{gal}), 4.34–4.30 (dd, J = 2.2, 4.8 Hz, 1H, H-2_{gal}), 4.29–4.25 (d, J = 8.2 Hz, 1H, H-4_{gal}), 4.14–4.01 (m, 2H), 3.89–3.68 (m, 7H), 3.53–3.42 (m, 1H, H-7), 1.97–1.80 (m, 1H, H-2_{glu}), 1.54 (s, 3H, -CMe_2), 1.46 (s, 3H, -CMe_2), 1.34 (s, 6H, -CMe_2).

^{13}C NMR: 138.56, 138.34, 138.27, 128.45, 128.38, 127.80, 127.61, 109.38, 108.58, 101.78, 96.46, 80.15, 79.81, 75.41, 75.15, 74.74, 73.59, 71.31, 70.90, 70.74, 69.06, 68.79, 67.08, 47.70, 31.71, 26.18, 26.11, 25.09, 24.62 ppm.

Ring opening of cyclopropane 109 with NBS/1,2:3,4-di-*O*-isopropylidine-α-D-galactopyranose (72):

Carrying out the reaction of β-cyclopropane **109** (270 mg, 0.63 mmol) and alcohol **72** (500 mg, 1.90 mmol) in acetonitrile containing 4Å molecular sieves (500 mg) and NBS (135 mg, 0.75 mmol), followed by the usual workup after 4 days, afforded the disaccharide **154** (250 mg, 51%) as a colourless gum.

3,4,6-Tri-*O*-benzyl-2-deoxy-2-C-(bromomethyl)-α-D-mannopyranosyl-(1→6)-1,2:3,4-di-*O*-isopropylidine-α-D-galactopyranose (154)



$[\alpha]^{25}_D$= -6.5^O (c 0.5, $CHCl_3$).

IR (neat): 3032, 2988, 1496, 1454, 1373, 1255, 1211, 1070, 1005, 910, 734, 698 cm^{-1}.

^{1}H NMR: δ 7.36–7.15 (m, 15H, ArH), 5.56–5.54 (d, J = 4.9 Hz, 1H, H-1_{gal}), 5.16 (s, 1H, H-1_{man}), 4.81–4.76 (d, J = 10.9 Hz, 1H, -OCH_2Ph), 4.69–4.60 (m, 4H,

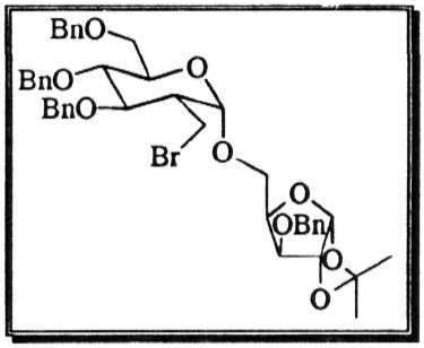
$-OCH_2Ph$), 4.52–4.47 (d, J = 11.3 Hz, 1H, $-OCH_2Ph$), 4.45–4.41 (d, J = 8.2 Hz, 1H, $H\text{-}3_{gal}$), 4.36–4.31 (dd, J = 4.9 Hz, 1H, $H\text{-}2_{gal}$), 4.24–4.20 (d, J= 8.0 Hz, 1H, $H\text{-}4_{gal}$), 4.12–4.02 (dd, J = 8.9, 5.2 Hz, 1H, $H\text{-}3_{man}$), 3.95–3.92 (d, J = 5.1 Hz, 1H) 3.88–3.61 (m, 7H), 3.40–3.38 (t, 1H, H-7), 2.75–2.63 (m, 1H, $H\text{-}2_{man}$), 1.55 (s, 3H, $-CMe_2$), 1.46 (s, 3H, $-CMe_2$), 1.36 (s, 6H, $-CMe_2$).

^{13}C NMR: 138.39, 128.46, 128.37, 127.89, 127.78, 127.73, 109.38, 108.60, 98.42, 96.36, 79.32, 74.69, 74.35, 73.49, 71.98, 71.44, 71.07, 70.70, 68.89, 65.98, 65.83, 46.26, 29.68, 26.29, 26.03, 24.99, 24.56 ppm.

Ring opening of cyclopropane 106 with NBS/1,2-*O*-isopropylidine-3-*O*-benzyl-α-D-xylofuranose (150):

To a solution of α-cyclopropane **106** (350 mg, 0.81 mmol) and 1,2-*O*-isopropylidine-3-*O*-benzyl-α-D-xylofuranose **(150)** (683 mg, 2.43 mmol) in dry acetonitrile (8 ml), was added powdered 4Å molecular sieves (683 mg) under nitrogen atmosphere and the contents were stirred for 1h. To the above reaction mixture NBS (175 mg, 0.98 mmol) was added as a solid and then it was allowed to stir for 4 days. The contents were diluted with toluene (25 ml), filtered and evaporated under reduced pressure. The crude product after chromatographic purification afforded the disaccharides **155** (128 mg) and **156** (269 mg) as colourless gums (in an overall yield of 62%).

3,4,6-Tri-*O*-benzyl-2-deoxy-2-C-(bromomethyl)-α-D-glucopyranosyl-(1→5)-1,2-*O*-isopropylidine-3-*O*-benzyl-α-D-xylofuranose (155)



$[\alpha]^{25}_D$ = +31° (c 0.1, $CHCl_3$).

IR (neat): 3030, 2928, 1496, 1454, 1373, 1213, 1078, 736, 698 cm^{-1}.

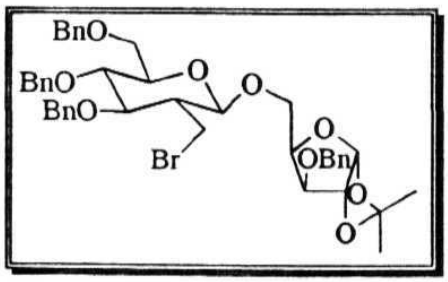
^{1}H NMR: δ 7.34–7.16 (m, 20H, ArH), 5.94–5.92 (d, J = 3.8 Hz, 1H, H-1_{xyl}), 5.12–5.11 (d, J = 3.0 Hz, 1H, H-1_{glu}), 4.93–4.87 (d, J = 10.9 Hz, 1H, -OCH_2Ph), 4.81–4.75 (d, J = 10.8 Hz, 1H, -OCH_2Ph), 4.72–4.40 (m, 7H, -OCH_2Ph, H-2_{xyl}), 4.43–4.34 (m, 1H, H-4_{xyl}), 3.99–3.98 (d, J = 3.0 Hz, 1H, H-3_{xyl}), 3.94–3.91 (d, J = 5.9 Hz, 1H), 3.84–3.63 (m, 7H), 3.39–3.28 (dd, J = 9.7, 10.9 Hz, 1H, H-7), 2.36–2.18 (m, 1H, H-2_{glu}), 1.53 (s, 3H, -CMe_2), 1.34 (s, 3H, -CMe_2).

^{13}C NMR: 138.19, 128.55, 128.45, 128.01, 127.83, 127.78, 111.77, 105.08, 98.30, 82.29, 81.96, 80.19, 79.37, 79.01, 75.37, 74.86, 73.59, 72.15, 71.05, 68.50, 65.12, 48.47, 30.63, 26.91, 26.34 ppm.

Anal. Calcd for $C_{43}H_{49}BrO_9$: C, 65.40; H, 6.25.

Found: C, 65.98; H, 6.45.

3,4,6-Tri-*O*-benzyl-2-deoxy-2-C-(bromomethyl)-β-D-glucopyranosyl-(1→5)-1,2-*O*-isopropylidine-3-*O*-benzyl-α-D-xylofuranose (156)



$[\alpha]^{25}_D$ = -17.8° (c 1, $CHCl_3$).

IR (neat): 3030, 2932, 1454, 1373, 1213, 1076, 736, 698 cm^{-1}.

^{1}H NMR: δ 7.35–7.20 (m, 20H, ArH), 5.93–5.91 (d, J = 3.8 Hz, 1H, H-1_{xyl}), 5.0–4.95 (d, J = 10.8 Hz, 1H, -OCH_2Ph), 4.85–4.77 (dd, J = 4.2, 10.8 Hz, 2H, -OCH_2Ph), 4.71–4.53 (m, 7H, -OCH_2Ph, H-2_{xyl}, H-1_{glu}), 4.50–4.48 (m, 1H, H-4_{xyl}), 4.24–4.14 (dd, J = 4.4, 8.7 Hz, 1H), 4.02–3.99 (d, J = 3.3 Hz, 1H), 3.98–3.86 (m, 1H), 3.83–3.63 (m, 6H), 3.53–3.43 (m, 1H), 1.94–1.82 (m, 1H, H-2_{glu}), 1.50 (s, 3H, -CMe_2), 1.33 (s, 3H, -CMe_2).

^{13}C NMR: 138.56, 138.35, 137.74, 127.87, 127.55, 111.76, 105.24, 101.21, 82.66, 81.78, 80.06, 79.83, 79.25, 75.50, 75.16, 74.79, 73.63, 72.11, 69.15, 66.58, 47.78, 31.57, 27.0, 26.49 ppm.

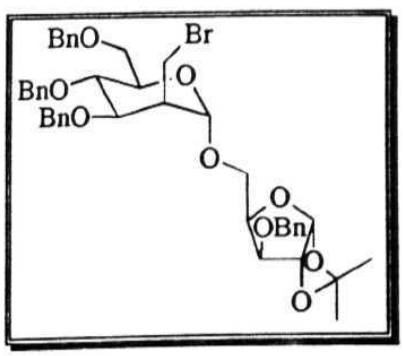
Anal. Calcd for $C_{43}H_{49}BrO_9$: C, 65.40; H, 6.25.

Found: C, 64.84; H, 6.35.

Ring opening of cyclopropane 109 with NBS/1,2-*O*-isopropylidine-3-*O*-benzyl-α-D-xylofuranose (150):

The disaccharide **157** (430 mg, 57%) was obtained as a colourless gum by the opening of β-cyclopropane **109** (410 mg, 0.95 mmol) with NBS (205 mg, 1.15 mmol) in the presence of 1,2-*O*-isopropylidine-3-*O*-benzyl-α-D-xylofuranose **(150)** (800 mg, 2.85 mmol) and 4Å molecular sieves (800 mg) in acetonitrile (10 ml) after 4 days.

3,4,6-Tri-*O*-benzyl-2-deoxy-2-C-(bromomethyl)-α-D-mannopyranosyl-(1→5)-1,2-*O*-isopropylidine-3-*O*-benzyl-α-D-xylofuranose (157)



$[\alpha]^{25}_D$ = +6.5° (c 0.5, $CHCl_3$).

IR (neat): 3032, 2926, 1496. 1454, 1373, 1213,1078, 910, 862,734, 698 cm^{-1}.

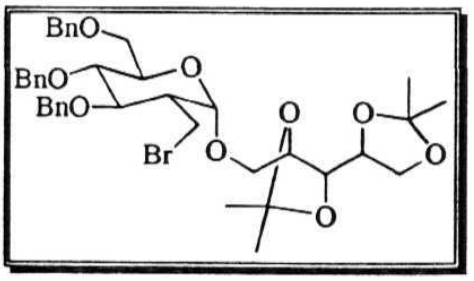
^{1}H NMR: δ 7.38–7.15 (m, 20H, ArH), 5.95–5.93 (d, J = 3.8 Hz, 1H, H-1_{xyl}), 5.08 (s, 1H, H-1_{man}), 4.82–4.42 (m, 9H, -OCH_2Ph, H-2_{xyl}), 4.40–4.34 (m, 1H, H-4_{xyl}), 4.09–4.01 (m, 1H), 3.96–3.94 (d, J = 3.6 Hz, 1H, H-3_{xyl}), 3.90–3.60 (m, 7H), 3.48–3.37 (t, 1H, H-7), 2.65–2.55 (m, 1H, H-2_{man}), 1.52 (s, 3H, -CMe_2), 1.34 (s, 3H, -CMe_2).

^{13}C NMR: 138.34, 138.21, 137.41, 128.59, 128.49, 128.38, 127.93, 127.81, 127.72, 111.78, 105.14, 98.90, 82.37, 81.60, 79.38, 78.67, 74.91, 74.29, 73.51, 72.09 (2C), 71.28, 68.73, 64.92, 46.54, 29.66, 26.92, 26.36 ppm.

Ring opening of cyclopropane 106 with NBS/2,3:4,5-di-*O*-isopropylidine-D-arabinitol (151):

The reaction of α-cyclopropane **106** (250 mg, 0.58 mmol) with NBS (125 mg, 0.70 mmol) and alcohol **151** (385 mg, 1.66 mmol) afforded the disaccharides **158** (86 mg) and **159** (199 mg) as colourless syrups (total yield 66%).

2,3:4,5-Di-*O*-isopropylidine-D-arabinityl-(1→1)-3,4,6-tri-*O*-benzyl-2-deoxy-2-C-(bromomethyl)-α-D-glucopyranoside (158)



$[\alpha]^{25}_{D}$ = +69.3° (c 0.3, $CHCl_3$).

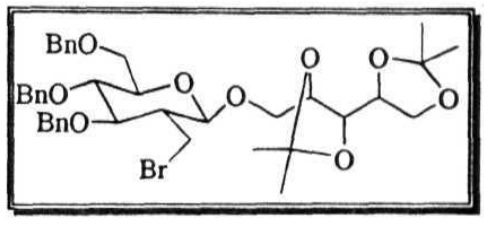
IR (neat): 3032, 2986, 1496, 1454, 1371, 1213, 1066, 738, 698 cm^{-1}.

^{1}H NMR: δ 7.39–7.18 (m, 15H, ArH), 5.15–5.13 (d, J = 3.1 Hz, 1H, H-1), 4.93–4.88 (d, J = 10.7 Hz, 1H, -OCH_2Ph), 4.82–4.77 (d, J = 11.7 Hz, 1H, -OCH_2Ph), 4.71–4.65 (d, J = 12.3 Hz, 1H, -OCH_2Ph), 4.60–4.52 (m, 3H, -OCH_2Ph), 4.19–4.01 (m, 4H), 3.98–3.57 (m, 9H), 3.42–3.31 (dd, J = 9.8, 10.9 Hz, 1H, H-7), 2.28–2.24 (m, 1H, H-2), 1.39 (s, 9H, -CMe_2), 1.35 (s, 3H, -CMe_2).

^{13}C NMR: 138.06, 128.45, 127.83, 109.75 (2C), 98.55, 80.17, 79.41, 78.03, 75.32, 74.89, 73.60, 71.13, 68.54 (2C), 67.72, 48.65, 30.45, 27.23 (2C), 26.77, 25.29 ppm.

MS m/z: 649 $(M\text{-}Bn)^+$, 545, 419, 417, 311, 231.

2,3:4,5-Di-*O*-isopropylidine-D-arabinityl-(1→1)-3,4,6-tri-*O*-benzyl-2-deoxy-2-C-(bromomethyl)-β-D-glucopyranoside (159)



$[\alpha]^{25}_D$= +24.8^O (c 1.8, $CHCl_3$).

IR (neat): 3032, 2986, 1454, 1371, 1213, 1070, 844, 736, 698 cm^{-1}.

^{1}H NMR: δ 7.36–7.17 (m, 15H, ArH), 5.0–4.95 (d, J = 10.8 Hz, 1H, $-OCH_2Ph$), 4.84–4.79 (d, J = 10.6 Hz, 2H, $-OCH_2Ph$), 4.70–4.53 (m, 4H, $-OCH_2Ph$, H-1), 4.17–3.60 (m, 13H), 3.54–3.45 (m, 1H), 1.97–1.86 (m, 1H, H-2), 1.43 (s, 3H, $-CMe_2$), 1.41 (s, 3H, $-CMe_2$), 1.39 (s, 3H, $-CMe_2$), 1.33 (s, 3H, $-CMe_2$).

^{13}C NMR: 138.38, 138.24, 138.09, 128.47, 128.37, 128.09, 127.81, 127.61, 109.91, 109.65, 101.50, 80.87, 79.96, 79.68, 78.13, 75.49, 75.14, 74.79, 73.55, 70.31, 68.94, 67.64, 62.78, 47.61, 31.59, 27.22, 26.97, 26.75, 25.29 ppm.

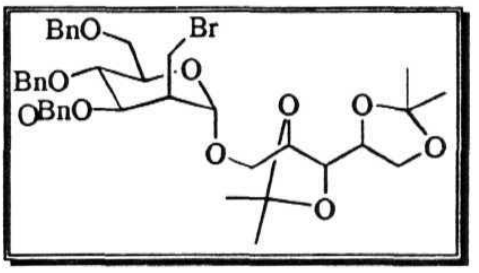
Anal. Calcd for $C_{39}H_{49}BrO_9$: C, 63.16; H, 6.66.

Found: C, 63.09; H, 6.69.

Ring opening of cyclopropane 109 with NBS/2,3:4,5-di-*O*-isopropylidine-D-arabinitol (151):

160 was procured in 41% yield (243 mg) by treating cyclopropane **109** (345 mg, 0.80 mmol) with NBS (175 mg, 0.98 mmol) and alcohol **151** (560 mg, 2.41 mmol).

2,3:4,5-Di-*O*-isopropylidine-D-arabinityl-(1→1)-3,4,6-tri-*O*-benzyl-2-deoxy-2-C-(bromomethyl)-α-D-mannopyranoside (160)



$[\alpha]^{25}_{D}$= +25.9° (c 0.8, $CHCl_3$).

IR (neat): 3065, 2984, 1602, 1454, 1371, 1271, 1093, 844, 700 cm^{-1}.

^{1}H NMR: δ 7.40–7.21 (m, 15H, ArH), 5.12 (s, 1H, H-1), 4.80–4.42 (m, 6H, $-OCH_2Ph$), 4.18–3.92 (m, 5H), 3.84–3.58 (m, 8H), 3.48–3.34 (t, 1H), 2.70–2.58 (m, 1H, H-7), 1.38 (s, 9H, $-CMe_2$), 1.30 (s, 3H, $-CMe_2$).

^{13}C NMR: 138.32, 129.80, 128.48, 128.36, 127.93, 127.75, 109.72, 99.14, 79.56, 79.33, 77.05, 74.86, 74.39, 73.51, 71.99, 71.37, 68.93, 67.71, 67.50, 46.25, 29.46, 27.15, 26.77, 25.31 ppm.

Anal. Calcd for $C_{39}H_{49}BrO_9$: C, 63.16; H, 6.66.

Found: C, 63.25; H, 6.67.

Ring opening of cyclopropane 106 with $Hg(CF_3COO)_2$ in methanol:

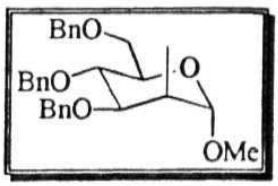
A solution of cyclopropane **106** (210 mg, 0.49 mmol) and mercuric trifluoroacetate (415 mg, 0.97 mmol) in dry methanol (5 ml) was stirred at room temperature for 18h. Brine solution (10 ml) was added and the contents were stirred vigorously for 30 min. The aqueous phase was then extracted with dichloromethane. The combined extracts were dried and concentrated. The residue obtained was dissolved in THF (5 ml) and added to a suspension of LAH (190 mg, 5 mmol) in 4 ml THF at 0° under nitrogen. After 3h at rt, the reaction mixture was quenched with water and diluted with ethyl acetate, filtered and the precipitate was washed with hot ethyl acetate. The filtrate was dried and concentrated. Purification of the crude product by column chromatography (10% ethyl acetate/hexane) afforded **132** as a

colourless oil, which was crystallized from ether/hexane (166 mg, 72%). Its properties were identical to that prepared by the acid catalysed ring opening of **106**.

Ring opening of cyclopropane 109 with $Hg(CF_3COO)_2$ in methanol:

Carrying out the reaction with β-cyclopropane **109** (210 mg, 0.49 mmol) under similar conditions as described above, yielded 163 mg (71%) of methyl 3,4,6-tri-*O*-benzyl-2-deoxy-2-C-methyl-α-D-mannopyranoside (**172**) as a colourless oil.

Methyl 3,4,6-tri-*O*-benzyl-2-deoxy-2-C-methyl-α-D-manopyranoside (172)



$[\alpha]^{25}_D$= +60.6 ° (c 0.3, $CHCl_3$).

IR (neat): 3063, 3030, 2912, 1604, 1496, 1454, 1363, 1292, 1084, 1028, 966, 736, 698 cm^{-1}.

^1H NMR: δ 7.36–7.27 (m, 15H, ArH), 4.89–4.84 (d, J = 11.8 Hz, 1H, $-OCH_2Ph$), 4.65–4.43 (m, 6H, $-OCH_2Ph$, H-1), 4.09–3.96 (m, 1H, H-3), 3.78–3.75 (m, 4H), 3.35 (s, 3H, -OMe) 2.50–2.33 (m, 1H, H-2), 1.13–1.09 (d, J = 7.4 Hz, 3H, H-7).

^{13}C NMR: 138.92, 138.59, 128.44, 127.99, 127.78, 127.61, 103.36, 79.92, 74.95, 74.44, 73.53, 71.47, 71.22, 69.51, 54.75, 36.93, 11.41 ppm.

Anal. Calcd for $C_{29}H_{34}O_5$: C, 75.30; H, 7.41.

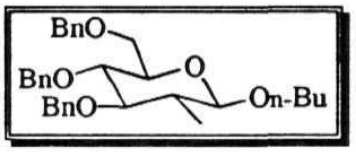
Found: C, 75.18; H, 7.42.

Ring opening of cyclopropane 106 with $Hg(CF_3COO)_2$ in n-butanol:

A solution of cyclopropane **106** (615 mg, 1.43 mmol) and mercuric trifluoroacetate (1.23 gm, 2.86 mmol) in dry n-butanol (15 ml) was stirred at room temperature for 18h. The reaction mixture was concentrated in vacuo and the residue was dissolved in dichloromethane (10 ml). Saturated sodium chloride (30 ml) was added and the contents were stirred vigorously for 30 min. The aqueous

phase was extracted with dichloromethane, dried and concentrated. This residue was dissolved in THF (15 ml) and added to a suspension of LAH (570 mg, 15 mmol) in 10 ml of THF at 0° under nitrogen. The reaction was worked up as described above after 3h. Purification of the crude product by column chromatography (10 % ethyl acetate/hexane) afforded **173** (388 mg, 53%) as a colourless waxy solid.

n-Butyl 3,4,6-tri-*O*-benzyl-2-deoxy-2-C-methyl-β-D-glucopyranoside (173)



$[\alpha]^{25}_{D}$= $+3^{\circ}$ (c 1, $CHCl_3$).

IR (neat): 3063, 3030, 2930, 2870, 1498, 1454, 1311, 1161, 1095, 1028, 736, 698 cm^{-1}.

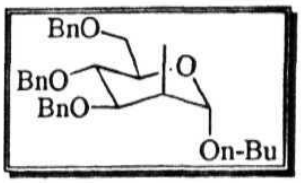
^{1}H NMR: δ 7.34–7.19 (m, 15H, ArH), 4.92–4.55 (m, 6H, -OCH_2Ph), 4.10–4.06 (d, J = 8.4 Hz, 1H, H-1), 4.06–3.90 (m, 1H), 3.76–3.73 (m, 2H), 3.56–3.52 (d, J = 8.4 Hz, 1H, H-3), 3.50–3.47 (m, 2H), 3.43–3.24 (t, 1H) 1.85–1.65 (m, 1H, H-2), 1.63–1.56 (m, 2H), 1.54–1.38 (m, 2H), 1.07–1.04 (d, J = 6.0 Hz, 3H, H-7), 0.97–0.90 (t, 3H).

^{13}C NMR: 138.56, 138.47, 138.37, 128.46, 127.93, 127.80, 127.60, 104.69, 85.44, 79.57, 75.34, 75.15, 74.78, 73.56, 69.48, 69.29, 42.85, 31.80, 19.32, 13.94, 12.67 ppm.

Ring opening of cyclopropane 109 with $Hg(CF_3COO)_2$ in n-butanol:

As described above, the n-butyl mannopyranoside derivative **174** was obtained in 78% yield by opening of β-cyclopropane **109** (900 mg, 2.10 mmol) with $Hg(CF_3COO)_2$ (1.80 g, 4.20 mmol) in n-butanol (15 ml) followed by reductive demercuration, as a colourless oil.

n-Butyl 3,4,6-tri-*O*-benzyl-2-deoxy-2-C-methyl-α-D-mannopyranoside (174)



$[\alpha]^{25}_{D}$= +54° (c 1, $CHCl_3$).

IR (neat): 3088, 3063, 2912, 1606, 1496, 1454, 1358, 1205, 1141, 1078, 954, 736, 698 cm^{-1}.

^{1}H NMR: δ 7.36–7.19 (m, 15H, ArH), 4.88–4.82 (d, J = 10.8 Hz, 1H, -OCH_2Ph), 4.71 (s, 1H, H-1), 4.64–4.48 (m, 5H, -OCH_2Ph), 4.09–3.98 (m, 1H), 3.77–3.63 (m, 5H), 3.44–3.34 (m, 1H) 2.55–2.45 (m, 1H, H-2), 1.64–1.46 (m, 2H), 1.44–1.27 (m, 2H), 1.13–1.10 (d, J = 7.1 Hz, 3H, H-7), 0.98–0.87 (t, 3H).

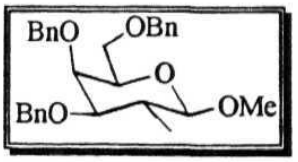
^{13}C NMR: 138.92, 138.74, 138.52, 128.33, 128.03, 127.68, 127.51, 102.12, 79.97, 74.96, 74.47, 73.42, 71.40, 71.15, 69.43, 67.22, 37.02, 31.71, 19.51, 13.95, 11.35 ppm.

MS m/z 503 $(M-H)^+$, 413, 339, 233, 193, 181, 163.

Ring opening of α-cyclopropane 107 with $Hg(CF_3COO)_2$ in methanol:

As described for cyclopropane **106**, carrying out the reaction with 3,4,6-tri-*O*-benzyl-1,5-anhydro-2-deoxy-1,2-C-methylene-*D-glycero-L-manno*-hexitol (**107**, 270 mg, 0.63 mmol) under similar conditions, afforded the ring opened product **175** (200 mg) in 69% yield as a colourless oil.

Methyl 3,4,6-tri-*O*-benzyl-2-deoxy-2-C-methyl-β-D-galactopyranoside (175)



$[\alpha]^{25}_{D}$= +27.5° (c 0.65, $CHCl_3$).

IR (neat): 3063, 3030, 2930, 1602, 1496, 1454, 1363, 1275, 1205, 1072, 752, 698 cm^{-1}.

^{1}H NMR: δ 7.36–7.26 (m, 15H, ArH), 4.88–4.51 (m, 6H, -OCH_2Ph), 3.98–3.90 (m, 2H), 3.68–3.49 (m, 4H), 3.35 (s, 3H, -OCH_3) 2.52–2.43 (m, 1H, H-2), 1.05–1.03 (d, J = 4.2 Hz, 3H, H-7) .

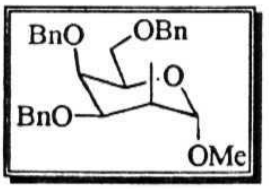
^{13}C NMR: 139.02, 138.55, 138.25, 128.39, 128.18, 128.08, 127.77, 127.70, 127.43, 102.52, 79.99, 74.41, 73.55, 72.58, 71.86, 69.79 (2C), 55.16, 35.51, 12.53 ppm.

MS m/z: 339 (M-OMe, $C_7H_8)^+$, 253, 233, 193, 159, 127.

Ring opening of β-cyclopropane 110 with $Hg(CF_3COO)_2$ in methanol:

The ring opening of 3,4,6-tri-*O*-benzyl-1,5-anhydro-2-deoxy-1,2-C-methylene-*D-glycero-L-allo*-hexitol (**110**) was carried out in two ways, at rt (method a) as well as by refluxing the reaction mixture (method b). The reductive workup followed in both the cases was the same. Purification of the crude product gave the required ring opened product **176** (100 mg from 200 mg of **110**, 46% in method a, 50 mg from 150 mg of **110**, 16% in method b) and the mercury bis(sugar) compound **177** (49 mg and 78 mg from method a and b, respectively).

Methyl 3,4,6-tri-*O*-benzyl-2-deoxy-2-C-methyl-α-D-talopyranoside (176)



$[\alpha]^{25}_D$= +25.5° (c 1.7, $CHCl_3$).

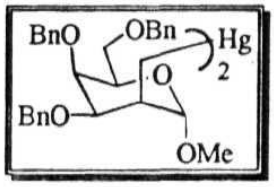
IR (neat): 3063, 3032, 2930, 1602, 1496, 1454, 1363, 1273, 1207, 1087, 736, 698 cm^{-1}.

^{1}H NMR: δ 7.36–7.25 (m, 15H, ArH), 5.01–4.95 (d, J = 11.6 Hz, 1H, -OCH_2Ph), 4.66–4.49 (m, 6H, -OCH_2Ph, H-1), 4.08–3.97 (m, 1H), 3.90–3.86 (m, 2H), 3.70–3.67 (d, J = 6.0 Hz, 2H), 3.36 (s, 3H, -OMe), 2.38–2.24 (m, 1H, H-2), 1.30–1.27 (d, J = 7.2 Hz, 3H, H-7).

^{13}C NMR: 139.38, 138.86, 138.34, 128.38, 128.14, 127.69, 127.41, 127.17, 103.97, 76.44, 74.84, 74.19, 73.53, 70.26, 69.86 (2C), 54.86, 36.44, 12.62 ppm.

MS m/z: 339 (M-OMe, C_7H_8)$^+$, 253, 233, 193, 181, 163.

Bis(sugar)mercury compound 177



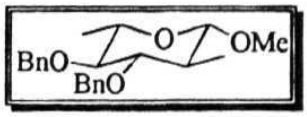
^{1}H NMR: δ 7.36–7.25 (m, 15H, ArH), 4.93–4.88 (d, J = 9.6 Hz, 1H, -OCH_2Ph), 4.60–4.45 (m, 6H, -OCH_2Ph, H-1), 4.05–3.90 (m, 1H), 3.66–3.63 (d, J = 6.0 Hz, 1H), 3.36–3.34 (d, J = 3.8 Hz, 1H), 3.30 (s, 3H, -OMe), 2.38–2.24 (m, 1H, H-2), 1.30–0.75 (m, 2H, H-7).

^{13}C NMR: 139.19, 138.77, 138.41, 128.37, 128.20, 127.93, 127.75, 127.62, 127.42, 106.97, 77.60, 74.98, 74.26, 73.52, 70.74, 70.01, 69.87, 54.96, 41.87, 36.19 ppm.

Ring opening of α-cyclopropane 108 with $Hg(CF_3COO)_2$ in methanol:

As described for cyclopropane **108**, carrying out the reaction with 3,4-di-*O*-benzyl-1,5-anhydro-2,6-dideoxy-1,2-C-methylene-*L-glycero-L-gulo*-hexitol (**108**, 235 mg, 0.72 mmol) under similar conditions, afforded the products **178** (93 mg) and **179** (90 mg) in 36% and 47% yields, respectively.

Methyl 3,4-di-*O*-benzyl-2,6-dideoxy-2-C-methyl-β-L-glucopyranoside (178) Colourless waxy solid,



$[\alpha]^{25}_D$ = −39.0^O (c 1.25, $CHCl_3$).

IR (neat): 3059, 2961, 2878, 1597, 1491, 1448, 1381, 1219, 1157, 1078, 1045, 902, 763, 706 cm^{-1}.

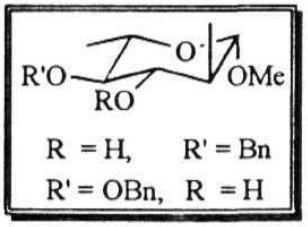
^{1}H NMR: δ 7.38–7.30 (m, 10H, ArH), 4.92–4.85 (m, 2H, -OCH_2Ph), 4.70–4.62 (m, 2H, -OCH_2Ph), 4.02–3.98 (d, J = 8.7 Hz, 1H, H-1), 3.50 (s, 3H, -OMe), 3.45–3.26 (m, 1H), 3.33-3.32 (d, J = 1.7 Hz, 1H), 3.24–3.15 (m, 1H), 1.82–1.67 (m, 1H, H-2) 1.37–1.34 (d, J = 6.6 Hz, 3H, H-6), 1.07–1.04 (d, J = 6.8 Hz, 3H, H-7).

^{13}C NMR: 138.37, 128.65, 128.51, 127.97, 127.55, 126.99, 105.41, 85.57, 76.89, 75.11, 71.13, 65.11, 56.78, 42.99, 18.35, 12.37 ppm.

Anal. Calcd for $C_{22}H_{28}O_4$: C, 74.13; H,7.92.

Found: C, 74.73; H, 7.89.

Methyl 3 or 4-*O*-benzyl-2,6-dideoxy-2-C-methyl-β-L-glucopyranoside (179) Colourless solid,



M.p = 152-154^O (hexane).

$[\alpha]^{25}_D$ = +11.1^O (c 0.75, $CHCl_3$).

IR (KBr): 3308, 2988, 2910, 11454, 1369, 1317, 1203, 1122, 1093, 1043, 1016, 910, 731, 694 cm^{-1}.

^{1}H NMR: δ 7.36–7.26 (m, 5H, ArH), 4.83–4.66 (dd, J = 11.2, 22.8 Hz, 2H, -OCH_2Ph), 4.00–3.96 (d, J = 8.6 Hz, 1H, H-1), 3.49 (s, 3H, -OMe), 3.41–3.22 (m, 2H), 3.08-3.04 (d, J = 8.8 Hz, 1H), 2.11–2.09 (d, J = 3.6 Hz, 1H, H-2), 1.41–1.38 (d, J = 6.6 Hz, 3H, H-6), 1.07–1.04 (d, J = 6.8 Hz, 3H, H-7).

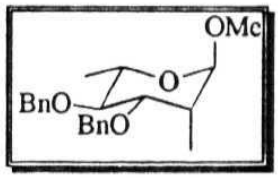
^{13}C NMR: 138.50, 128.63, 128.36, 127.88, 105.39, 85.69, 75.07, 71.12, 56.67, 42.91, 18.32, 12.28 ppm.

Anal. Calcd for $C_{15}H_{22}O_4$: C, 67.65; H, 8.33.

Found: C, 67.68; H, 7.85.

Ring opening of β-cyclopropane 111 with $Hg(CF_3COO)_2$ in methanol:

The reaction of 3,4-di-*O*-benzyl-1,5-anhydro-2-deoxy-1,2-C-methylene-*L-glycero-L-talo*-hexitol (**111**, 225 mg, 0.69 mmol)) with mercuric trifluoroacetate (587 mg, 1.38 mmol) in methanol yielded the desired ring opened product **180** (122 mg, 50%) as a colourless oil along with the more polar bis(sugar)mercury compound **181** (55 mg).



Methyl 3,4-di-*O*-benzyl-2,6-dideoxy-2-C-methyl-α-L-mannopyranoside (180) Colourless syrup,

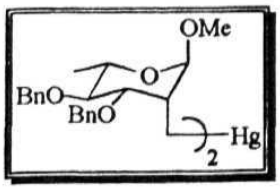
$[\alpha]^{25}_D$= -35.0° (c 0.8, $CHCl_3$).

IR (neat): 3065, 3032, 2972, 1496, 1454, 1363, 1203, 1136, 1072, 966, 748, 698 cm^{-1}.

^{1}H NMR: δ 7.35–7.26 (m, 10H, ArH), 4.95–4.90 (d, J = 10.9 Hz, 1H, -OCH_2Ph), 4.70–4.51 (m, 4H, -OCH_2Ph, H-1), 4.00–3.93 (dd, J = 5.4, 8.9 Hz, 1H), 3.85–3.62 (m, 1H), 3.38–3.22 (m, 4H), 2.48–2.33 (m, 1H. H-2), 1.32–1.29 (d, J = 6.5 Hz, 3H, H-6), 1.10–1.06 (d, J = 7.6 Hz, 3H, H-7).

^{13}C NMR: 138.86, 128.33, 127.94, 127.59, 103.20, 80.31, 79.67, 75.06, 71.08, 67.48, 54.54, 36.94, 18.34, 11.39 ppm.

MS m/z: 356 $(M)^+$, 325, 265, 240, 233, 193, 159.



Bis(sugar)mercury compound 181 Colourless syrup,

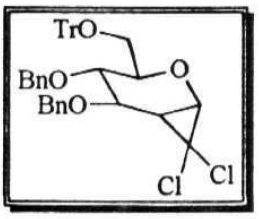
^{1}H NMR: δ 7.35–7.26 (m, 10H, ArH), 4.95–4.89 (d, J = 10.9 Hz, 1H, -OCH_2Ph), 4.70–4.55 (m, 3H, -OCH_2Ph), 4.36 (s, 1H), 4.00–3.93 (dd, J = 5.1, 8.9 Hz, 1H), 3.84–3.58 (m, 1H), 3.40–3.22 (m, 4H), 2.55–2.44 (m, 1H, H-2), 1.31–1.28 (d, J = 6.1 Hz, 4H), 0.82–0.78 (d, J = 8.0 Hz, 1H).

^{13}C NMR: 138.86, 128.37, 128.07, 127.98, 127.60, 105.92, 80.68, 74.92, 71.92, 67.97, 54.64, 42.60, 36.90, 18.49 ppm.

Dichlorocarbene addition to 3,4-di-*O*-benzyl-6-*O*-triphenylmethyl-D-glucal (182):

Aqueous sodium hydroxide (4.0 g in 8 ml) was added to a vigorously stirred solution of the glucal **182** (1.88 g, 3.31 mmol) in chloroform (8 ml) containing benzyltriethylammonium chloride (20 mg). The reaction mixture was stirred at rt for 36h, then diluted with water (25 ml) and extracted with dichloromethane. The combined extracts were dried and concentrated. The residue was purified by chromatography to furnish **183** (1.58 g, 73%) as a colourless syrup.

3,4-Di-*O*-benzyl-6-*O*-triphenylmethyl-1,5-anhydro-2-deoxy-1,2-C-dichloromethylene-*D-glycero-D-gulo*-hexitol (183)



$[\alpha]^{25}_{D}$ = +42.3^{O} (c 1, $CHCl_3$).

IR (neat): 3032, 2872, 1493, 1450, 1365, 1207, 1095, 908, 735, 700 cm^{-1}.

^{1}H NMR: δ 7.50–7.0 (m, 25H), 4.84–4.68 (m, 4H, -OCH_2Ph), 4.29–4.24 (d, J = 10.7 Hz, 1H), 4.08–4.05 (d, J = 7.8 Hz, 1H, H-1), 3.90 (m, 3H) 3.52–3.47 (d, J = 10 Hz, 1H), 1.93 (dd, J = 4.1, 7.8 Hz, 1H, H-2).

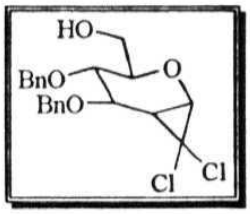
^{13}C NMR: 143.90, 138.28, 137.81, 128.85, 128.61, 128.30, 128.01, 127.67, 127.25, 86.99, 80.54, 77.61, 76.09, 74.79, 72.18, 63.95, 61.82, 59.26, 34.77 ppm.

Anal. Calcd for $C_{40}H_{36}Cl_2O_4$: C, 73.73; H, 5.57.

Found: C, 73.65; H, 5.55.

Detritylation of 183 with formic acid-ether:

To a solution of **183** (1.41 g, 2.16 mmol) in ether (6 ml) was added 5 ml of 98% formic acid and stirred at rt for 1h. The reaction mixture was concentrated in vacuo and the residue diluted with dichloromethane. The dichloromethane layer was washed with saturated sodium bicarbonate solution and brine, dried and concentrated. Purification of the crude product by column chromatography using initially 5% ethyl acetate in hexane to elute triphenylcarbinol and then with 25% ethyl acetate yielded the detritylated product (**184**) as a colourless solid (650 mg, 74%).



3,4-Di-*O*-benzyl-1,5-anhydro-2-deoxy-1,2-C-dichloromethylene-*D-glycero-D-gulo*-hexitol (184)

M.p = 83-84^{O} (ether/hexane).

$[\alpha]^{25}_{D}$ = +74.2^{O} (c 1.5, $CHCl_3$).

IR (KBr): 3369, 3034, 2864, 1496, 1454, 1361, 1327, 1203, 1091, 989, 837, 733, 694 cm^{-1}.

^{1}H NMR: δ 7.42–7.31 (m, 10H, ArH), 5.0–4.66 (m, 4H, $-OCH_2Ph$), 3.91– 3.87 (d, J = 8.7 Hz, 1H, H-1), 3.85–3.80 (dd, J = 9.8, 3.9 Hz, 1H, H-3), 3.78–3.60 (m, 4H), 1.98 (s br, 1H), 1.89–1.80 (dd, J = 3.9, 8.7 Hz, 1H, H-2).

^{13}C NMR: 138.11, 137.58, 128.59, 128.17, 128.06, 79.77, 77.14, 74.97, 74.79, 72.11, 62.76, 61.04, 58.81, 33.90 ppm.

Anal. Calcd for $C_{21}H_{22}Cl_2O_4$: C, 61.62; H, 5.42.

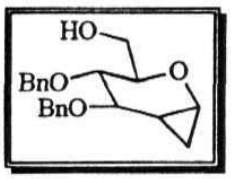
Found: C, 61.68; H, 5.42.

LAH reduction of 184:

To a stirred suspension of LAH (455 mg, 12 mmol) in dry THF (4 ml) was added a solution of the dichlorocyclopropane **184** (330 mg, 0.80 mmol) in THF (10

ml). After stirring for 24h at rt, the reaction mixture was cooled in ice and quenched with saturated aqueous sodium sulfate. The usual workup and purification yielded **185** (228 mg, 84%) as a colourless waxy solid.

3,4-Di-*O*-benzyl-1,5-anhydro-2-deoxy-1,2-C-methylene-*D*-*glycero*-*D*-*gulo*-hexitol (185)



$[\alpha]^{25}_{D}$= +24.5° (c 0.9, $CHCl_3$).

IR (neat): 3450, 3068, 2870, 1496, 1454, 1379, 1170, 1087, 1028, 821, 738, 698 cm^{-1}.

^{1}H NMR: δ 7.35–7.29 (m, 10H, ArH), 4.89–4.62 (m, 4H, -OCH_2Ph), 3.87–3.40 (m, 6H), 2.11 (b, 1H), 1.08–0.93 (m, 1H), 0.81–0.69 (m, 2H).

^{13}C NMR: 138.49, 138.35, 128.51, 128.0, 127.79, 126.98, 79.61, 76.91, 76.53, 73.61, 71.25, 62.58, 49.98, 14.43, 10.29 ppm.

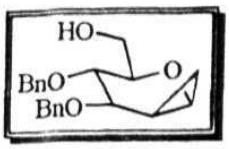
HRMS Calcd for [(M – Bn)$^+$, $C_{14}H_{17}O_4$]: 249.1127.

Found: 249.1128.

Simmons-Smith cyclopropanation of 3,4-Di-*O*-benzyl-6-*O*-triphenylmethyl-D-glucal (182):

To a stirred suspension of zinc dust (330 mg, 5.03 mmol) and cuprous chloride (108 mg, 1.08 mmol) in dry ether (1 ml) was added diiodomethane (327 mg, 1.12 mmol). After 5 min, acetyl chloride (20 μl) was added and the mixture was heated for 5 min at 40°. A solution of glucal **182** (670 mg, 1.12 mmol) in ether (3 ml) was then added. Five minutes after the addition of the glucal, an additional amount (2 eq.) of diiodomethane was added and the heating was continued for 2h. Usual workup and purification by chromatography furnished **186** as a pale yellow coloured syrup (282 mg, 70%).

3,4-Di-*O*-benzyl-1,5-anhydro-2-deoxy-1,2-C-methylene-*D*-*glycero*-*D*-*talo*-hexitol (186)



$[\alpha]^{25}_{D}$= -70.1° (c 1, $CHCl_3$).

IR (neat): 3458, 3030, 2872, 1604, 1496, 1454, 1377, 1221, 1168, 1087, 1026, 821, 738, 698 cm^{-1}.

^1H NMR: δ 7.39–7.21 (m, 10H, ArH), 4.89–4.58 (m, 4H, $-OCH_2Ph$), 4.24–4.16 (m, 1H), 3.85–3.74 (m, 2H), 3.69–3.54 (m, 1H), 3.38–3.32 (m, 2H), 1.98 (s br, 1H), 1.50–1.25 (m, 1H), 0.88–0.73 (m, 2H).

^{13}C NMR: 138.54, 138.42, 128.43, 128.03, 127.87, 127.74, 127.57, 78.74, 78.55, 77.92, 74.21, 70.0, 62.52, 55.10, 15.69, 11.98 ppm.

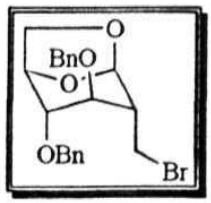
Anal. Calcd for $C_{21}H_{24}O_4$: C, 74.09; H, 7.11.

Found: C, 73.98; H, 7.09.

Intramolecular 6-OH assisted ring opening of α-cyclopropane 185 with NBS:

To a solution of the substrate **185** (70 mg, 0.21 mmol) in acetonitrile (5 ml), 140 mg of 4Å molecular sieves were added and the contents stirred for 30min. To this, NBS (44 mg, 0.25 mmol) was added and the stirring was continued for 5h. The reaction mixture was diluted with toluene and filtered, concentrated in vacuo without any aqueous workup and the crude product was purified chromatographically to yield the levoglucosan derivative **187** (61mg, 70%) as a colourless syrup.

3,4-Di-*O*-benzyl-2-deoxy-2-C-(bromomethyl)-1,6-anhydro-β-D-glucopyranose (187)



$[\alpha]^{25}_{D}$= -70.8° (c 0.75, $CHCl_3$).

IR (neat): 3030, 2958, 2897, 1496, 1454, 1363, 1284, 1210, 1031, 981, 912, 869, 735, 698 cm^{-1}.

^1H NMR: δ 7.38–7.26 (m, 10H, ArH), 5.58 (s, 1H, H-1), 4.64–4.51 (m, 5H, $-OCH_2Ph$ and H-5), 4.17–4.14 (d, J = 6.9 Hz, 1H, H-3), 3.77–3.68

(m, 2H), 3.51–3.47 (t, J = 8.6 Hz, 2H), 3.40 (s, 1H, H-4), 2.31–2.23 (t, J = 7.6 Hz, 1H, H-2).

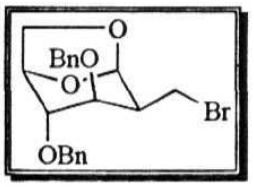
^{13}C NMR: 137.99, 137.67, 128.56, 128.49, 127.97, 127.78, 101.55, 76.46, 74.80, 74.56, 71.49, 71.32, 64.92, 45.56, 31.70 ppm.

Anal. Calcd for $C_{21}H_{23}BrO_4$: C, 60.15; H, 5.53.
Found: C, 60.07; H, 5.61.

Intramolecular 6-OH assisted ring opening of β-cyclopropane 186 with NBS:

To a solution of **186** (110 mg, 0.32 mmol) in acetonitrile (7 ml), 220 mg of 4Å molecular sieves were added and it was stirred for 30 min. NBS (70 mg, 0.39 mmol) was then added to the mixture and the stirring continued. The reaction was found to be incomplete even after 36h. It was diluted with toluene and filtered. It was then concentrated in vacuo and the crude product was purified as described above to yield the levomannosan derivative **188** (47 mg, 35%) as a colourless syrup.

3,4-Di-*O*-benzyl-2-deoxy-2-*C*-(bromomethyl)-1,6-anhydro-β-D-mannopyranose (188)



$[\alpha]^{25}_D$= -12.4° (c 0.5, $CHCl_3$).

IR (neat): 2964, 2897, 3032, 2964, 2897, 1496, 1454, 1363, 1286, 1215, 1128, 1028, 981, 910, 869, 735, 698 cm^{-1}.

^{1}H NMR: δ 7.38–7.25 (m, 10H, ArH), 5.50 (s, 1H, H-1), 4.64 (s, 2H, -OCH_2Ph), 4.59–4.56 (d, J = 5.5 Hz, 1H, H-5), 4.46–4.45 (d, J = 1.7 Hz, 2H, -OCH_2Ph), 4.14–4.11 (d, J = 6.9 Hz, 1H, H-3), 3.77–3.75 (dd, J = 4.4 Hz, 1H), 3.72–3.65 (t, J = 6.6 Hz, 1H), 3.52–3.44 (m, 3H), 2.43–2.32 (dd, J = 6.8, 13.8 Hz, 1H, H-2).

^{13}C NMR: 137.69, 128.63, 128.51, 128.10, 127.87, 101.12, 75.0, 73.91, 73.74, 73.17, 71.35, 64.74, 44.41, 30.38 ppm.

Calcd for [(M - Br)$^+$, $C_{21}H_{23}O_4$]: 339.1596.

Found: 339.1615.

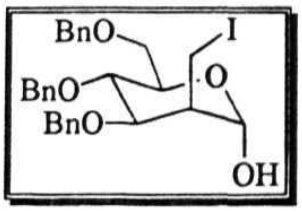
Attempted oxidation of 149 with PCC:

To a solution of **149** (150 mg, 0.28 mmol) in dichloromethane (5 ml) at 0^O was added PCC (306 mg, 1.42 mmol) and contents were stirred at rt for 4h. The reaction mixture was transferred to a small silica gel column and eluted with ethyl acetate. The IR spectrum of the crude product showed the presence of starting compound predominantly, along with a weak carbonyl band for the lactone.

IR (neat): 3410, 2866, 1749, 1730, 1496, 1454, 1257, 1089, 738, 698 cm^{-1}.

Ring opening of cyclopropane 109 with I_2:

A solution of cyclopropane **109** (140 mg, 0.33 mmol) and I_2 (990 mg, 3.9 mmol) in 1 : 1 H_2O : dioxane (10 ml) was heated at 70^O for 8h. The reaction mixture was diluted with ether and washed with saturated sodium bisulphite solution and brine, dried and concentrated. Purification by column chromatography (10% ethyl acetate/hexane) yielded the iodolactol **193** (226 mg, 79%) as a colourless solid.



3,4,6-Tri-*O*-benzyl-2-deoxy-2-C-(iodomethyl)-D-mannopyranose (193)

M.p 102-104^O (ether/hexane).

$[\alpha]^{25}_D$ = +3.4^O (c 1.3, $CHCl_3$).

IR (KBr): 3408, 3010, 2924, 1732, 1496, 1454, 1365, 1099, 848, 738, 698 cm^{-1}.

^{1}H NMR: δ 7.35–7.17 (m, 15H, ArH), 5.45 (s br, 1H, H-1), 4.83–4.78 (d, J = 10.9 Hz, 1H, -OCH_2Ph), 4.63–4.62 (d, J = 1.2 Hz, 1H, -OCH_2Ph), 4.57–4.54 (d, J = 6.6 Hz, 2H, -OCH_2Ph), 4.46–4.41 (d, J = 11.3 Hz, 1H,

$-OCH_2Ph$), 4.08-3.98 (m, 2H), 3.67-3.66 (d, J = 3.8 Hz, 2H), 3.66–3.52 (m, 2H), 3.19-3.09 (dd, J = 11.0, 10.4 Hz, 1H), 3.0–2.96 (m, 1H), 2.67-2.57 (m, 1H, H-2).

^{13}C NMR: 138.27, 138.11, 138.01, 128.50, 128.41, 127.93, 127.79, 94.37, 79.52, 74.62, 74.34, 73.45, 71.96, 71.36, 69.38, 46.87, 2.14 ppm.

Anal. Calcd for $C_{28}H_{31}IO_5$: C, 58.54; H, 5.44.
Found: C, 58.39; H, 5.40.

Ring opening of cyclopropane 109 with I_2 **at** 100°:

A solution of cyclopropane 109 (110 mg, 0.26 mmol) and I_2 (648 mg, 2.6 mmol) in 1:1 H_2O/dioxane (8 ml) was heated at 100° for 36h. The reaction mixture was diluted with ether and washed with saturated sodium bisulphite solution and brine, dried and concentrated. Purification by column chromatography (10% ethyl acetate/hexane) yielded 193 (60 mg) and an unidentified product (39 mg) as a pale yellow oil.

^1H NMR: 5 9.50 (s) 7.40-7.30 (m), 6.85 (s), 5.50 (s), 4.80–4.50 (m), 4.45 (s br), 4.10 (m), 3.82-3.20 (3ms), 2.30 (m), 1.80 (m).

^{13}C NMR: 191.29, 145.30, 138.96, 138.56, 138.30, 128.5, 128.4, 128.1, 127.9, 127.8, 101.8, 75.81, 73.9, 73.65, 73.40, 72.19, 71.37, 70.48, 68.93, 64.72, 63.67, 44.98, 2.74 ppm.

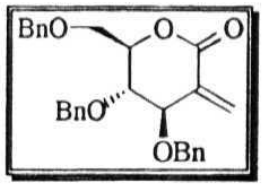
General procedure for the conversion of cyclopropane derivatives to a-methylene-δ-valerolactones:

To a solution of β-cyclopropane 109 (180 mg, 0.42 mmol) in 7.5 ml of 3 : 2 dioxane-H_2O was added IDCP (1.18 g, 2.50 mmol) and the resulting solution was heated at 60 - 70° for 18h. The reaction mixture was cooled and diluted with ether and the ether solution was subsequently washed successively with 5% HC1,

water, saturated sodium bisulphite and brine and dried over anhydrous magnesium sulphate. The crude product obtained on evaporation of the solvent was purified by column chromatography using 10% ethyl acetate/hexane as eluent. The unsaturated lactone **195** was obtained as a colourless oil (107 mg, 55%).

Following similar conditions, reaction of α-cyclopropane **106** (120 mg, 0.28 mmol) with IDCP (783 mg, 1.67 mmol) resulted in **195** (94 mg) in 75% yield.

3,4,6-Tri-O-benzyl-2-deoxy-2-methylene-D-arabino-hexono-1,5-lactone (195):



$[\alpha]^{25}_D$= +56.1° (c 0.75, $CHCl_3$);

lit.[149c] $[\alpha]^{25}_D$= +61° (c 0.5, $CHCl_3$).

IR (neat): 3063, 3032, 2868, 1730, 1633, 1496, 1363, 1259, 1209, 1028, 808, 738, 698 cm^{-1}.

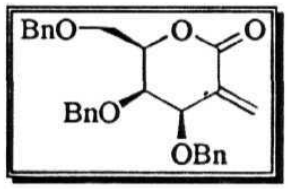
^{1}H NMR: δ 7.36–7.22 (m, 15H, ArH), 6.52 (br s, 1H, H-7), 5.91 (br s, 1H, H-7'), 4.72–4.54 (m, 6H, -OCH_2Ph), 4.38–4.28 (m, 2H, H-3 and H-5), 4.06–3.97 (t, 1H, H-4), 3.78–3.76 (d, J = 3.8 Hz, 2H, H-6 and H-6').

^{13}C NMR: 164.95, 137.84, 137.48, 134.63 (C-2), 129.92 (C-7), 128.57, 128.49, 128.03, 127.95, 127.84, 79.12 (C-3), 78.75 (C-5), 75.79 (C-4), 73.53, 72.20, 68.71 (C-6) ppm.

Reaction of D-galactal derived cyclopropanes 110 and 107 with IDCP:

The α-methylene-D-valerolactone **196** (54mg, 42% and 98 mg, 82%) was obtained respectively from **110** (125 mg, 0.29 mmol) and from **107** (115 mg, 0.27 mmol) using the procedure given above.

3,4,6-Tri-O-benzyl-2-deoxy-2-methylene-D-lyxo-hexono-1,5-lactone (196): Colourless oil,



$[\alpha]^{25}_D$= +45.8° (c 1, $CHCl_3$);

lit.[149c] $[\alpha]^{25}_D$= +46.2° (c 1, $CHCl_3$).

IR (neat): 3063, 3032, 2929, 2870, 1728, 1637, 1496, 1265, 1101, 808, 738, 806, 738, 698 cm^{-1}.

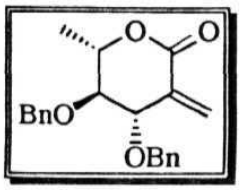
^1H NMR: δ 7.37–7.28 (m, 15H, ArH), 6.79 (br s, 1H, H-7), 6.23–6.21 (dd, J = 1.5, 2.4 Hz, 1H, H-7'), 4.94–4.38 (m, 7H, $-OCH_2Ph$, H-5), 4.36–4.35 (d, J = 2.1 Hz, 1H, H-4), 4.25 (br s, 1H, H-3), 3.78–3.66 (m, 2H, H-6, H-6').

^{13}C NMR: 163.87, 137.96, 137.56, 137.30, 134.44 (C-2), 129.08 (C-7), 128.69, 128.54, 128.34, 128.15, 128.02, 127.84, 127.51, 78.19, 77.34, 73.72, 73.59, 71.77, 70.16, 68.10 ppm.

Reaction of cyclopropane 111 with IDCP:

To a solution of **111** (163 mg, 0.5 mmol) in 7.5 ml of 3 : 2 dioxane–H_2O was added IDCP (1.41 g, 3 mmol) and the resulting solution was heated at 60–70° for 18h. As described above, workup and purification by column chromatography on silica gel using 10% ethyl acetate–hexane as eluent afforded **197** as a colourless oil (141 mg, 83%).

3,4-Di-*O*-benzyl-2,6-dideoxy-2-methylene-L-arabino-hexono-1,5-lactone (197)



$[\alpha]^{25}_D$= -51.0° (c 1.3, $CHCl_3$).

IR (neat): 3032, 2876, 1730, 1167, 696 cm^{-1}.

^1H NMR: δ 7.36–7.26 (m, 10H, ArH), 6.49 (bs, 1H, H-7), 5.88 (bs, 1H, H-7'), 4.81–4.55 (m, 4H, $-OCH_2Ph$), 4.29–4.27 (m, 2H), 3.61–3.59 (m, 1H), 1.48–1.45 (d, J = 6.7 Hz, 3H).

^{13}C NMR: 165.76, 137.29, 134.83, 129.82, 128.61, 128.03, 127.78, 81.09, 79.05, 75.84, 73.46, 71.86, 18.73 ppm.

MS m/z 338 (M^+), 180, 91.

Simmons-Smith cyclopropanation of D-xylal 97:

To a stirred suspension of zinc dust (290 mg, 4.40 mmol) and cuprous chloride (90 mg, 1.10 mmol) in dry ether (1 ml) at rt was added diiodomethane (306 mg, 1.05 mmol). After 5 min, acetyl chloride (10 µl) was added and the mixture was heated for 5 min at 40°. A solution of **97** (0.320 g, 1.05 mmol) in ether (4 ml) was then added. Five minutes later, an additional amount of diiodomethane (2 eq.) was added and the heating was continued for 60 min. The reaction mixture was then diluted with ether, washed with 5% sodium hydroxide solution, brine and dried. The residue obtained after removal of the solvent was purified by chromatography to furnish **112** as a pale yellow coloured oil (210 mg, 63%).

3,4-Di-*O*-benzyl-1,5-anhydro-2-deoxy-1,2-C-methylene-D-talo-pentitol (112)

$[\alpha]^{25}_D$= -53.3° (c 0.6, $CHCl_3$).

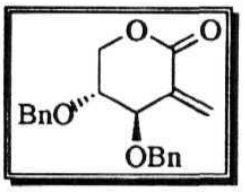
^{1}H NMR: δ 7.36–7.18 (m, 10H, ArH), 4.86–4.60 (m, 4H, -OCH_2Ph), 4.14–4.07 (dd, J = 5.5, 7.0 Hz, 1H, H-1), 3.82–3.72 (m, 1H), 3.68–3.61 (dd, J = 3.9, 10.6 Hz, 1H), 1.46–1.29 (m, 1H), 0.82–0.77 (m, J = 1.9, 3.8 Hz, 2H)

^{13}C NMR: 138.85, 138.65, 131.66, 129.79, 128.36, 127.74, 127.66, 126.68, 77.84, 77.12, 73.45, 70.37, 66.33, 55.63, 15.64, 11.68 ppm.

Reaction of cyclopropane 112 with IDCP:

On treating with IDCP (1.09 g, 2.32 mmol) in 10 ml of 2 : 3 H_2O-dioxane at 60 – 70° for 18h, cyclopropane **112** (105 mg, 0.34 mmol) gave the unsaturated lactone **198** (73 mg, 66%) as a pale yellow oil.

3,4-Di-*O*-benzyl-2-deoxy-2-methylene-D-threo-pentano-1,5-lactone (198)



$[\alpha]^{25}_D$ = -44.6° (c 1.3, $CHCl_3$).

IR (neat): 3032, 2924, 1726, 1165, 698 cm^{-1}.

^1H NMR: δ 7.39–7.25 (m, 10H, ArH), 6.72–6.71 (d, J = 1.4 Hz, 1H, H-6), 5.78–5.77 (dd, J = 1.3, 0.7 Hz, 1H, H-6'), 4.71–4.61 (m, 4H, -OCH_2Ph), 4.46–4.45 (m, 1H), 4.39 (br s, 1H), 4.28–4.26 (m, 1H), 3.68–3.61 (m, 1H).

^{13}C NMR: 164.14, 137.22, 133.73, 132.46, 128.61, 128.09, 127.81, 127.76, 126.99, 75.29, 72.79, 71.09, 70.09, 67.39 ppm.

MS m/z: 324 (M^+), 232, 181, 127, 107.

REFERENCES

1. *Carbohydrates as Organic Raw Materials;* Lichtenthaler, F.W., Ed.; VCH Publishers: Weinheim/New York, 1991.
2. a) *Bioactive Carbohydrates in Chemistry, Biochemistry and Biology;* Kennedy, J. F.; White, C. A.; Halsted Press: New York, 1983. b) Kennedy, J. F. *Carbohydrate Chemistry*; Clarendon Press, Oxford, 1988.
3. a) Lowe, J. B. Red cell membrane antigens, *The molecular Basis of Blood Diseases;* Stanatoyannopoulos, etal., Eds.; W. B. Saunders Company: Philadelphia, P. A., 1994, p293. b) Ichikawa, Y.; Halcomb, R L.; Wong, C - H. *Chem. Britain* 1994, *117.*
4. *Sialic Acids, Chemistry, Metabolism and Function;* Schauer, R.; Ed.; Springer-Verlag: Wien, 1982.
5. Hakamori, S. *Ann. Rev. Biochem.* 1981, *50,* 733.
6. a) Hauser, F. M.; Ellenberger, S. *Chem. Rev.* 1986, *86,* 35. b) Halcomb, R. L.; Boyer, S. H.; Danishefsky, S. J. *Angew. Chem. Int. Ed. Engl.* 1992, *31,* 338. c) *Recent Progress in the Chemical Synthesis of Antibiotics;* Lukacs, G; Ohno, M.; Eds.; Springer-Verlag, Berlin-Heidelberg, 1990.
7. Meyers, A. G. *Tetrahedron lett.* 1987, *28,* 4493. b) Zeing, N.; Sinha, A. M.; McGahren, W. J.; Ellestad, G. A. *Science* 1988, *240,* 1198.
8. a) Fischer, E. *Ber. Dtsch. Chem. Ges.* 1891, *24,* 1836 and 2683. b) Lichtenthaler, F. W. *Angew. Chem. Int. Ed. Engl.* 1992, *31,* 1541. c) Kauffman, G. B.; Ciula, R. P. *J. Chem. Educ.* 1977, *54,* 295.
9. a) Hanessian, S. *Total Synthesis of Natural Products: the "Chiron" Approach;* Pergamon: Oxford, 1983. b) Lichtenthaler, F. W. *Modern Synthetic Methods, 1992* Scheffold, R. Ed.; VCH: New York, p.273. c) Abel, S.; Faber, D.; Huter, O.; Giese, B. *Angew. Chem. Int. Ed. Engl.* 1994, *33,* 2466.
10. a) Schmidt, R. R. *Pure & Appl. Chem.* 1989, *61,* 1257. b) Schmidt, R.R. *Comprehensive Organic Synthesis;* Pergamon Press: Oxford, 1991, Vol.(5, p.33. c) Sinay, P. *Pure & Appl. Chem.* 1991, *63,* 519. d) Schmidt, R.R.

Carbohydrates, Synthetic Methods and Applications in Medicinal Chemistry; Kodansha: Tokyo, 1992, p.66. e) **Toshima,** K.; **Tatsuta,** K. *Chem. Rev.* 1993, *93,* 1503. f) Boons, G. J. *Tetrahedron* 1996, *52,* 1095.

11. a) **Ko**. S.Y.; Lee, A. W. M.; **Masamune,** S.; **Reed,** III, L. A.; Sharpless, K. B.; Walker, F. J. *Tetrahedron* 1990, *46,* 245. b) Masamune, S.; Chay, W.; **Petersen,** J. S.; **Sita,** L. R. *Angew. Chem. Int. Ed. Engl.* 1985, *24,* 1. c) **Minami,** N.; Ko, S. S.; Rishi, Y. *J. Am. Chem. Soc.* **1982,** ***104,*** **1109**.
12. Danishefsky, S. J.; DeNinno, M P . *Angew. Chem. Int. Ed. Engl.* 1987, *26,* **15**.
13. Wong, C.-H.; **Halcomb,** R. L.; **Ichikawa,** Y; **Kajimoto,** T. *Angew. Chem. Int. Ed. Engl.* 1994, *34,* 412 and 521.
14. **Ferrier,** R. J.; **Middleton,** S. *Chem. Rev.* 1993, *93,* 2779.
15. a) Fischer, E.; Zach. **K**. *Sitzber. kgl. preuss. Akad. Wiss.,* 1913, *16,* **311**. b) Helferich, B ; Mulcahy, E. W ; Ziegler, H. *Chem. Ber.* 1954, *87,* 233.
16. Cavallaro, C. L.; Schwartz, J. *J. Org. Chem.* 1995, *60,* 7055 and references cited therein.
17. Lancelin, J.-M.; **Morin-Allory,** L.; Sinay, P. *J. Chem. Soc. Chem. Commun.* 1984, **355**
18. Feast, A. A.; Overend, W. **G**.; Williams, N. R. *J. Chem. Soc.* 1965, 7378
19. Kudelska, W.; Michalska, M. *Tetrahedron* 1981, *37,* 2989.
20. Patroni, J. J.; Stick, R. V.; Tilbrook, D. M. G.; Sketton, B. W.; White, A. H. *Aust. J. Chem.* 1989, *42,* 2127.
21. Gomez, A. M.; Casillas, M.; Valverde, S.; Lopez, J. C. *J. Chem. Soc. Chem. Commun.* 1996, 2357.
22. Hacksell, U; Daves, G. D., Jr. *Prog. Med. Chem.* 1985, *22,* 1.
23. a) **Jaramillo,** C; Knapp, S. *Synthesis* 1994, 1. b) Daves, G. D. Jr. ***Acc. Chem. Res.*** 1990,23,201.
24. a) Dubois, E.; Beau, J.-M. *Tetrahedron Lett.* 1990, *31,* 5165. b) Dubois, E.; Beau, **J.-M** . *J. Chem. Soc. Chem. Commun.* 1990, **1191**.

25. Boyd, V. A.; Drake, B. E.; Sulikowski, G. A. *J. Org. Chem* 1993, *58,* 3191.

26. a) Ramesh, N. G.; Balasubramanian, K. K. *Tetrahedron Lett.* **1991,** *32,* 3875. b) Booma, C; Balasubramanian, K. K. *J. Chem. Soc. Chem. Commun.* **1993, 1394.** c) Ramesh, N. G.; Balasubramanian, K. K. *Tetrahedron* **1995,** *51,* 255.

27. a) Lemieux, R. U.; Levine, S. *Can. J. Chem.* 1964, *42,* 1473. b) Lemieux, R. U.; Morgan, A. R. *Can. J. Chem.* 1965, *43,* 2190. c) Lemieux, R. U.; Fraser* Reid, B. *Can. J. Chem.* 1965, *43,* 1460.

28. a) Thiem, J; Karl, H; Schwentner, J. *Synthesis* 1978, 696. b) Thiem, J; Karl, H. *Tetrahedron lett.* 1978, 4999.

29. a) Friesen, R. W.; Danishefsky, S. J. *J. Am. Chem. Soc.* 1989, *111,* 6656. b) Danishefsky, S. J.; Armistead, D. M; Wincott, F. E.; Selnick, H. G.; Hungate, R. *J. Am. Chem. Soc.* 1989, *111,* 2967. c) Friesen, R. W.; Danishefsky, S. J. *Tetrahedron* 1990, *46,* 103. c) Suzuki, K; Sulikowski, G. A., Friesen, R. W.; Danishefsky, S. J. J. *Am. Chem. Soc.* **1990,** *112,* 8895.

30. Tatsuta, K.; Fujimoto, K; Kinoshita, M.; Umczawa, S. *Carbohydr. Res.* 1977, *54,* 85.

31. Danishefsky, S. J.; Selnick, H. G.; Armistead, D. M.; Wincott, F. E. *J. Am. Chem. Soc.* **1987,***109,* 8199.

32. a) Tatsuta, K.; Tanaka, A.; Fujimoto, K; Kinoshita, M.; Umezawa, S. *J. Am. Chem. Soc.* 1977, *99,* 5826. b) Tatsuta, K; Amemiya, Y.; Maniwa, S.; Kinoshita, M. *Tetrahedron lett.* 1980, *21,* 2837. c) Tatsuta, K; Yamamuchi, T.; Kinoshita, M. *Bull. Chem. Soc. Jpn.* **1978,** *51,* 3035.

33. Lemieux, R. U.; Nagabhushana, T. L. *Can. J. Chem.* **1968,** *46,* 401.

34. Czernecki, S.; Ayadi, E.; Randriamandimby, D. *J. Chem. Soc. Chem. Commun.* **1994,** 35.

35. Giuliano, R. M.; Davis, R. S.; Boyko, W. J. *J. Carbohydr. Chem.* **1994,** *13,* **1135.**

36. Dax, K.; Glanzer, B. I. *Carbohydr. Res.* **1987,** *162,* 13.

37. Ito, Y.; Ogawa, T. *Tetrahedron Lett.* **1987,** *28,* 2723.

38. Grewal, G.; Kaila, N.; Franck, R. W. *J. Org. Chem.* 1992, *57,* 2084.

39. Lemieux, R. U.; Ratcliffe, R. M. *Can. J. Chem.* **1979,** *57,* 1244.

40. Gonzalez, F.S.; Flores, F.G.-C; García, J.-C; Mateo, F. H.; Mendoza, P. G.; Diaz, R. R *Tetrahedron* **1994,** *50,* 2877.

41. a) Kessler, H.; Kling, A.; Kottenbahn, M. *Angew. Chem. Int. Ed. Engl.* **1990,** *29,* 425. b) Kessler, H.; Kottenbahn, M; Kling, A.; Kolar, C. *Angew. Chem. Int. Ed. Engl* **1987, *26,* 888.**

42. a) Lee, D. H.; Kim, J. Y.; Kim, Y. H. *Arch Pharmacal. Res.* **1994,** *17,* 207. **b)** Diaz, Y.; El.langhdach, A.; Matheu, M. I.; Castillon, S. *J. Org. Chem.* **1997,** *62,* **1501.**

43. Sharma, G. V. M.; Krishnudu, K. *Carbohydr. Res.* 1995, *268,* 287.

44. Jaouen, V.; Jegou, A.; Veyrieres, A. *Synlett* 1996, 1218.

45. a) Wakamatsu, T.; Nakamura, H.; Naka, E.; Ban, Y. *Tetrahedron Lett.* **1986,** *27,* 3895. b) Toshima, K.; Tatsuta, K.; Kinoshita, M. *Bull. Chem. Soc. Jpn.* **1988,** *61,* 2369.

46. Tu, C. J.; Lednicer, D. *J. Org. Chem.* **1987,** *52,* 5624.

47. Bolitt, V.; Mioskowski, C ; Lee. S.-G.; Falck, J. R. *J. Org. Chem.* **1990,** 55, 5812.

48. Sabesan, S.; Neira, S. *J. Org. Chem.* **1991,** *56,* 5468.

49. Tatsuta, K.; Kobayashi, Y.; Gunji, H.; Masuda, H. *Tetrahedron Lett.* **1988,** *29,* 3975.

50. Holzapfel, C. W.; Engelbrecht, G. J.; Verdoon, G. H. *Heterocycles* **1989,** *28,* 433.

51. **a)** Inglis, G. R.; Schwarz, J. C. P.; McLaren, L. *J. Chem. Soc.* **1962, 1014. b)** Manolopoulos, P. T.; Mednick, M.; Lichtin, N. N. *J. Am. Chem. Soc.* **1962,** *84,* 2203.

52. Giese, B ; Groninger, R. *Tetrahedron Lett.* 1984, *25,* 2743.

53. Leftin, J. H.; Lichtin, N. N. *Israeli Chem.* 1965, 5, 107.
54. Gonzales, F.; Lesage, S.; Perlin, A. S. *Carbohydr. Res.* 1975, *42,* 267.
55. Lichtenthaler, F. W.; Ronninger, S.; Jarglis, P. *Liebigs Ann. Chem.* 1989, 1153.
56. Hilles, S.; Niklaus, A.; Reiser, 0. *J. Org. Chem.* 1993,*58,* 3169.
57. Kaye, A.; Neidle, S.; Reese, C. B. *Tetrahedron Lett.* 1988, *29,* 1841.
58. a) Ferrier, R. J.; Prasad, N.; Sankey, G. H. *J. Chem. Soc. (C)* 1968, 974. b) Ferrier, R. J.; Prasad, N. *J. Chem. Soc. (C)* 1969, 570. c) Paulscn, H.; Thiem, J. *Chem. Ber.* 1973, *106,* 3850. d) Guthrie, R. D.; Irvine, R. W. *Carbohydr. Res.* 1980, *82,* 207.
59. a) Toshima, K.; Ishizuka, T.; Matsuo, G.; Nakata, M. *Synlett* 1995, 306. b) Toshima, K.; Miyamoto, N.; Matsuo, G.; Nakata, M.; Matsumura, S. *J. Chem. Soc. Chem. Commun.* 1996, 1379.
60. Taillefumier, C; Chapleur, Y.; Bayeul, D.; Aubry, A. *J. Chem. Soc. Chem. Commun.* 1995, 937.
61. Klaic, B.; Raza, Z.; Sankovic, M.; Sunjic, V. *Helv. Chim. Acta* 1987, *70,* 59.
62. Inaba, K.; Mastumura, S.; Yoshikawa, S. *Chem. Lett.* 1991, 485.
63. Thorn, S. N.; Gallagher, T. *Synlett* 1996, 856.
64. Sobti, A.; Sulikowski, G. A. *Tetrahedron Lett.* 1994, 55, 3661.
65. Gupta, R. B.; Frank, R. W. *J. Am. Chem. Soc.* 1989, *111,* 7668.
66. Capozzi, G.; Falciani, C; Menichetti, S.; Nativi, C; Franck, R. W. *Tetrahedron Lett.* 1995, *36,* 6755.
67. Fredrickson, M. *Tetrahedron* 1997, *53,* 403.
68. Hewson, A. T.; Jeferry, J.; Szczur, N. *Tetrahedron Lett.* 1995, *36,* 7731.
69. Armstrong, P. L.; Coull, I. C; Hewson, A. T.; Slater, M. *Tetrahedron Lett.* 1995, *36,* 4311.

70. a) Tadano, K. In *Studies in Natural Products Chemistry;* Atta-Ur-Rahman; Ed.; Elsevier Science Publishers B.V.: 1992, *10,* 405. b) Rolin, P.; Sinay, P. ***Carbohydr. Res.*** **1981,** *98,* 139.

71. Bertrand, P.; Geson, J.-P.; Renoux, B.; Tranoy, I. *Tetrahedron Lett.* 1995, *36,* 4073.

72. a) Redlich, H.; Lenfers, J. B.; Kopf, J. ***Angew****. Chem. Int. Ed.* ***Engl.*** 1989, *28,* 777. b) Oh, J. *Tetrahedron Lett.* 1997, *38,* 3249.

73. a) Chmielewski, M; Kaluza, Z.; Belzeck, C; Salanski, P.; Jurcazk, J.; Adamowicz, H. *Tetrahedron* 1985, *41,* 2441. b) Kaluza, Z ; Abramski, W.; Belzecki, C; Grodner, J.; Mostowicz, D.; Urbanski, R.; Chmielewski, M. *Synlett* 1994, 539. c) Grodner, J.; Chmielewski, M. *Tetrahedron* 1995, *51,* 829.

74. Fischer, E. *Ber. Dtsch. Chem. Ges.* 1891, *24,* 2683.

75. Koenig, W.; Knorr, *Ber. Dtsch. Chem. Ges.* 1901, *34,* 957.

76. a) Schmidt, R. R.; Michel, J. *Angew. Chem. Int. Ed. Engl.* 1980, *19,* 731. b) Schmidt, R. R.; Kinzy, W. *Adv. Carbohydr. Chem.* 1994, *50,* 21.

77. a) Fraser-Reid, B.; Konradsson, P.; Mootoo, D. R.; Udodong, U. *J. Chem. Soc. Chem. Commun.* 1988, 823. b) Mootoo, D. R.; Konradsson, P.; Udodong, U.; Fraser-Reid, B. *J. Am. Chem. Soc.* 1988, ***110,*** 5583. c) Fraser-Reid, B.; Wu. Z.; Udodong, U.; Ottosson, H. *J. Org. Chem.* 1990, 55, 6068.

78. a) Kunz, H.; Wernig, P.; Schultz, M. *Synlett* 1990, 631. b) Lopez, J. C; Fraser-Reid, B. *J. Chem. Soc. Chem. Commun.* **1991,** 159.

79. Nicolaou, K. C; Dolle, R. E.; Papahatjis, D. P.; Randall, J. L. *J. Am. Chem. Soc.* **1984**, *106*, 4189.

80. a) Briner, K.; Vasella, A. ***Helv. Chim. Acta*** 1989, *72,* 1371. b) Vasella, A. ***Pure & Appl. Chem.*** **1991,** *63,* 507.

81. a) Stork, G.; Kim, G. *J. Am. Chem. Soc.* **1992**, *114*, 1087. b) Stork, G.; Clair, **J. J. L.** *J. Am. Chem. Soc.* **1996**, *118*, **247.**

82. Spijker, N. M.; van Boeckel, C. A. A. *Angew. Chem. Int. Ed. Engl.* 1991, *30,* 180.

83. Danishefsky, S. J.; Roberge, J. Y. *Pure & Appl. Chem.* 1995, *67,* 1647.

84. a) McClure, K.F.; Randolph, J.; Ruggeri, R.; Danishefsky, S. J. *Science* 1993, *260,* 1307. b) Roberge, J. Y.; Beebe, X.; Danishefsky, S. J. *Science* 1995, *269,* 202.

85. Brigl, P. *Z Physiol. Chem.* **1922**, *122*, 257.

86. Halcomb, R. L.; Danishefsky, S. J. *J. Am. Chem. Soc.* 1989, *111*, 6661.

87. Liu, K. K.-C.; Danishefsky, S J. *J. Org. Chem.* 1994, *59,* 1892.

88. Gervay, J.; Danishefsky, S. J. *J. Org. Chem.* 1991, *56,* 5448.

89. Liu, K. K.-C; Danishefsky, S. J. *J. Org. Chem.* 1994, *59,* 1895.

90. Patch, R. J.; Chen, H.; Pandit, C. R. *J. Org. Chem.* 1997, *62,* 1543.

91. Sanders, W. J.; Kiessling, L. L. *Tetrahedron lett.* 1994, *35,* 7335.

92. a) Lafont, D.; Descotes, G. *Carbohydr. Res.* 1987, *166,* 195. b) Lafont, D.; Descotes, G. *Carbohydr. Res.* **1988**, *175*, 35.

93. a) Griffith, D. A.; Danishefsky, S. J. *J. Am. Chem. Soc.* 1990, *112,* 5811. b) Park, T. K.; Kim, I. J.; Danishefsky, S. J. *Tetrahedron Lett.* 1995, *36,* 9089. c) Kim, I. J.; Park, T. K.; Hu, S.; Abrampah, K.; Zhang, S.; Livingston, P. 0.; Danishefsky, S. J. *Org. Chem.* 1995, *60,* 7716.

94. Bois, J. D.; Tomooka, C. S.; Hong, J.; Carreira, E. M. *J. Am. Chem. Soc.* 1997,779,3179.

95. a) Radatus, B. K.; Fraser-Reid, B. *Can. J. Chem.* 1969, *47,* 4095. b) Radatus, B. K.; Fraser-Reid, B. *Can. J. Chem.* 1970, *48,* 2146. c) Radatus, B. K.; Fraser-Reid, B. *Can. J. Chem.* 1972, *50,* 2909. d) Radatus, B. K.; Fraser-Reid, B. *Can. J. Chem.* 1972, *50,* 2919.

96. Duchaussoy, P.; Cesare, P. D.; Gross, B. *Synthesis* 1979, 198.

97. Brimacombe, J. S.; Evans, M. E.; Forbes, E. J.; Foster, A. B.; Webber, J. M. *Carbohydr. Res.* 1967, *4,* 239.

98. Baidznigitova, E. A.; Afanasev, V. A.; Dolgii, I. E. *Izvi. Akad, Nauk Kig. SSR.* 1981, *(J),* 50 (CA 95:98188b).

99. Yasumoto, T. ; Murata, M. *Chem. Rev.* 1993, *93,* 1897.

100. Murali, R.; Ramana, C. V.; Nagarajan, M. *J. Chem. Soc. Chem. Commun.* 1995,217.

101. a) Part of this work has been taken from the Ph. D dissertation submitted by Murali, R. 1994, University of Hyderabad, Hyderabad, India. b) Ramana, C. V.; Murali, R.; Nagarajan, M. *J. Org. Chem.* 1997, *62,* 0000.

102. Hoberg, J. O.; Bozell, J. J. *Tetrahedron Lett.* 1995, *36,* 6831.

103. Henry Jr., K. J.; Fraser-Reid, B. *Tetrahedron Lett.* 1995, *36,* 8901.

104. Timmers, C. M.; Leeuwenburgh, M. A.; Verheijen, J. C; van der Marel, G. A.; van Boom, J. H. *Tetrahedron: Asymmetry* 1996, 7, 49.

105. Hoberg, J. O.; Claffey, D. J. *Tetrahedron Lett.* 1996, *37,* 2533.

106. Scott, RW.; Heathcock, C. H. *Carbohydr. Res.* 1996, *291,* 205.

107. Bertinato, P.; Sorensen, E. J.; Meng, D.; Danishefsky, S. J. *J. Org. Chem.* 1996, *61,* 8000.

108. a) Bayer, A. *Chem. Ber.* 1855, *18,* 2277. b) Perkin, W. H.; *Chem. Ber.* 1884, *17,* 54. c) Roder, F. *Ann. Chem.* 1885, *227,* 13. d) Fittig, R. *Ann. Chem.* 1885, *227,* 25.

109. For recent reviews covering this area see a) Rappoport, Z. *The Chemistry of Cyclopropyl Group* Wiley-Interscience, New York 1987. b) de Meijere, A.; Wessjohann, L. *Synlett* 1990, 20. c) Wong, H. N. C. In *Rodds Chemistry of Carbon Compounds Vol II*^{a}*/II*^{b}Chapter 2, Sainsbury, M. Ed.; Elsevier Science Publishers B.V.: Amsterdam, 1992. d) Nair, V. In *Comprehensive Organic Synthesis* Pergamon Press: Oxford, 1991, *4,* 999.

110. de Meijere, A. *Angew. Chem. Int. Ed. Engl.* 1979, *18,* 809 and references cited therein.

111. a) Newham, J. *Chem. Rev.* 1963, *63,* 123. b) Bruchner, C; Reiβig, H.-U. *Chem. Ber.* **1987,***120,* 627.

112. a) Breslow, R. In *Molecular Rearrangements* de Mayo, P.; Ed.; Interscience: New York, 1963, p.233. b) DePuy, C. H. *Top. Curr. Chem.* 1973, *40,* 73. c) Gibson, D. H.; DePuy, C. H. *Chem. Rev.* 1974, *74,* 605.

113. a) Skatteb<j>l, L. *J. Org. Chem.* 1970, *35,* 3200. b) Groves, J. T.; Ma, R. W. *Tetrahedron left.* 1974, 909. c) Hickmott, P.W. *Tetrahedron* 1984, *40,* 2989.

114. a) Moore, W. R.; Bach, R. D. *J. Am. Chem. Soc.* 1972, *94,* 3148. b) Christl, M.; Braun, M. *Chem. Ber.* 1989, *122,* 1939.

115. a) Wenkert, E. *Acc. Chem. Res.* 1980, *13,* 27. b) Trost, B. M. *Acc. Chem. Res.* 1974, 7, 85.

116. a) Ramaiah, M. *Synthesis* 1984, 259. b) Sarel, S. *Acc. Chem. Res.* 1978, *11,* 204. c) Corey, E. J.; Myers, A. G. *J. Am. Chem. Soc.* **1985**, *107*, 5574.

117. a) Wong, H. N. C; Hon, M.-Y.; Tes, C.-W.; Yip, Y.-C; Tanko, J.; Hudlicky, T. *Chem. Rev.* **1989,** *89,* 165. b) Piers, E. In *Comprehensive Organic Synthesis* Pergamon: Oxford, 1991, 5, 971. c) Lee, J.; Kim, H ; Cha, J. K. *J. Am. Chem. Soc.* **1995**, *117*, 9919.

118. a) Kawazima, I.; Nakamura, E. *Top. Curr. Chem.* **1990**, *155*, 1. b) Kawazima, I.; Nakamura, E. In *Comprehensive Organic Synthesis* Pergamon: Oxford, 1991,2,441.

119. Reipig, H. U. *Top. Curr. Chem.* **1988**, *144*, 73.

120. a) Collins, C. J. *Chem. Rev.* 1969, *69,* 543. b) Zimmerman, M. P.; Li, H. T.; Duax, W. L.; Weeks, C. M.; Djerassi, C. J. *J. Am. Chem. Soc.* 1984, *106,* 5602.

121. Lambert, J. B.; Chelius, E. C; Schulz, W. J., Jr.; Carpenter, N. E. *J. Am. Chem. Soc.* 1990, **112, 3156**.

122. a) Lambert, J. B.; Chelius, E. C; Bible, R.Y., Jr.;Hajdu, E. *J. Am. Chem. Soc.* 1991, **113,** 1331. b) Coxon, *J.* M.; Steel, P. J.; Battiste, M. A. *J. Org.*

Chem 1989, 54, 3702. c) Coxon, J. M; Steel, P. J.; Whittington, B. I.; Battiste, M. A. *J. Org. Chem* 1989, 54, 1383. d) Coxon, J. M; Steel, P. J.; Whittington, B. I.; Battiste, M. A. *J. Am. Chem. Soc.* 1988,*110,* 2988.

123. Buritt, A.; Coxon, J. M; Steel, P. J. *J. Org. Chem.* 1995, *60,* 7670.

124. Wiberg, K. B.; Kass, S. R. *J. Am. Chem. Soc.* 1985, *107,* 988.

125. Kocovsky, P.; Grech, J. M.; Mitchell, W. *J. Org. Chem.* 1995, *60,* 1482 and references cited therein.

126. Cossy, J.; Furet, N. *Tetrahedron Lett.* 1995, *36,* 3691.

127. a) Bundle, D. R.; Lemieux, R. U. *Methods Carbohydr. Chem.,* 1976, 7, 79. b) Hall, L. D. In *The Carbohydrates: Chemistry and Biochemistry;* vol.IB, 2nd edn., Pigman, W.; Horton, D.; Eds.; Academic Press: New York, 1980, p. 1299. c) Coxon, B. *Adv. Carbohydr. Chem. Biochem.* 1972, *27,* 7.

128. a) Bock, K.; Pedersen, C. *Adv. Carbohydr. Chem. Biochem.* 1983, *41,* 27. b) Haverkamp, J.; van Dongen, J. P. C. M.; Vliegethart, J. F .G. *Tetrahedron* 1973, *29,* 3431.

129. Hudson, C. S. *J. Am. Chem. Soc.* 1909, *31,* 66.

130. a) Evans, R. D.; Magee, J. W.; Schauble, J. H. *Synthesis* 1988, 862. b) Simonot, B.; Rosseau, G. *J. Org. Chem.* 1993, *58,* 4. c) Simonot, B.; Rosseau, G. *Tetrahedron lett.* 1993, *34,* 4527. c) Simonot, B.; Rosseau, G. *J. Org. Chem.* 1994, *59,* 5919. e) Brunei, Y.; Rosseau, G. *Synlett* 1995, 323.

131. a) Richtmyer, N. K. *Methods Carbohydr. Chem.* 1962, *1,* 107. b) Hanessian, S.; Rancourt, G. *Can. J. Chem.* 1977, *55,* 1111. c) Faghih, R. J. *J. Carbohydr Chem.* 1987, *6,* 619.

132. a) Yunker, M. B.; Plaumann, D.-E.; Fraser-Reid, B. *Can. J. Chem.* 1977, 55, 4002. b) Fraser-Reid, B.; Anderson, R. C ; Hicks, D. R.; Walker, D. L. *Can. J. Chem.* 1977, *55,* 3986.

133. Miljkovic, M.; GliŠin, B. *J. Org. Chem.* 1975, *40,* 3357.

134. Collumn, D.B; Still, W.C; Mohamadi, F. *J. Am. Chem. Soc.* 1986, 108, 2094.

135. Barrett, A. G. M; Tarn, W. *J. Org Chem.* 1997, *62,* 4653.

136. a) Hanna, J. G.; Siggia, S. *Anal. Chem.* 1965, *37,* 690. b) de la Mare, P. B. D.; Bolton, R. *Electrophilic Additions to Unsaturated Systems;* 2nd edn., Elsevier: Amsterdam, 1981.

137. Dubois, J.E.; Garnier, F. *J. Chem. Soc. Chem. Commun.* 1968, 241.

138. *Organic Solvents,* Techniques of Chemistry, Vol II, Riddick, J. A.; Bunger, W. B.; Wiley-Interscience: New York, 1970.

139. Haszeldine, R. N. *J. Chem. Soc.* 1953, 1757.

140. Esswein, A.; Rembold, H.; Schmidt, R. R. *Carbohydr. Res.* 1990, *200,* 287.

141. Bessodes, M; Komiotis, D.; Antonakis, K. *Tetrahedron Lett.* 1986, *27,* 579.

142. Friedrich, E. C ; Lewis, E. J. *J. Org. Chem.* 1990, *55,* 6892.

143. a) Inghardt, T.; Frejd, T. *Synthesis* 1990, 285. b) Jespersen, T. M.; Bols, M.; Sierks, M. R.; Skrydstrup, T. *Tetrahedron* 1994, *50,* 13449.

144. a) Herradon, B.; Fenude, E.; Bao, R.; Vaverde, S. *J. Org. Chem.* 1996, *61,* 1143. b) Csuk, R.; Schaade, M.; Krieger, C. *Tetrahedron* 1996, *52,* 6397. c) Lopez, J. C; Gomez, A. M; Fraser-Reid, B. *J. Chem. Soc. Chem. Commun.,* 1994, 1533. d) Hsia, K. Y.; Ward, P.; Lamont, R. B.; de Q. Lilley, P. M.; Watkin, D. J.; Fleet, G. W. J. *Tetrahedron Lett.* 1994, *35,* 4823.

145. Wantabe, M.; Yoshikoshi, A. *J. Chem. Soc. Perkin Trans. I* 1987, 2833.

146. a) Tius, M. A. *Chem. Rev.* 1988, *88,* 719. b) Kametani, T.; Tsubuki, M.; Hondo, T. *Heterocycles* 1989, *28,* 59.

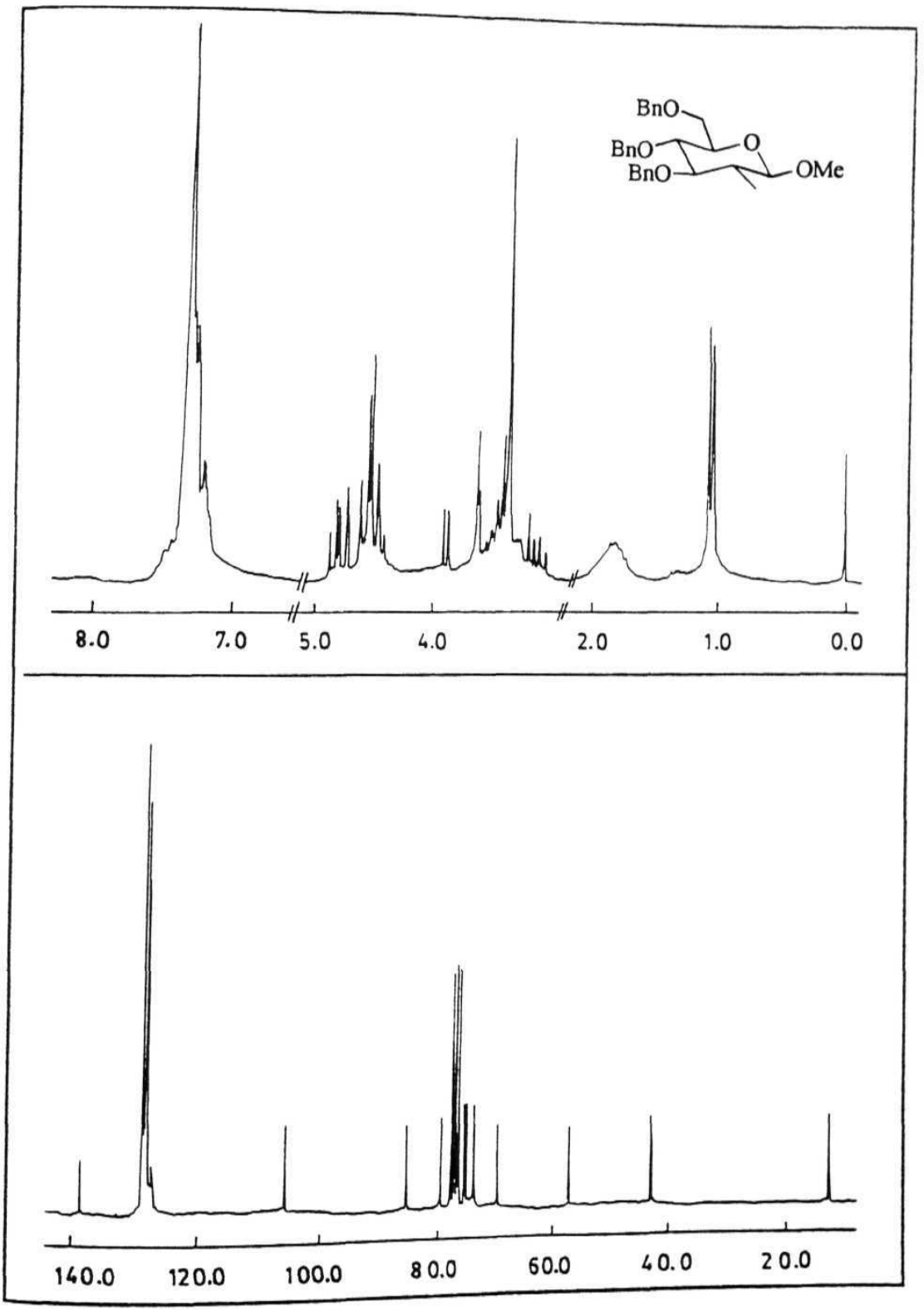
147. a) Ksander, G. M; McMurry, J. E. Johnson, M. *J. Org. Chem.* 1977, *42,* 2065. b) McMurry, J. E.; Dushin, R. G. *J. Am. Chem. Soc.* 1990, *112,* 6942. c) Nishitani, K.; Harada, Y.; Nakamura, Y.; Yokoo, K.; Yamakawa, K. *Tetrahedron Lett.* 1994, *35,* 7809. d) Solladie, G.; Boeffel, D.; Maignan, J. *Tetrahedron* 1996, *52,* 2065.

148. a) Schmidt, R. R.; Kast, J. *Tetrahedron Lett.* 1986, *27,* 4007. b) Giese, B.; Hoch, M.; **Lamberth, C.;** Schmidt, R. R. *Tetrahedron Lett.* **1988,** *29,* 1375. c) Kast, **J.; Hoch, M.; Schmidt,** R. R. *Liebigs Ann. Chem.,* **1991, 481**.

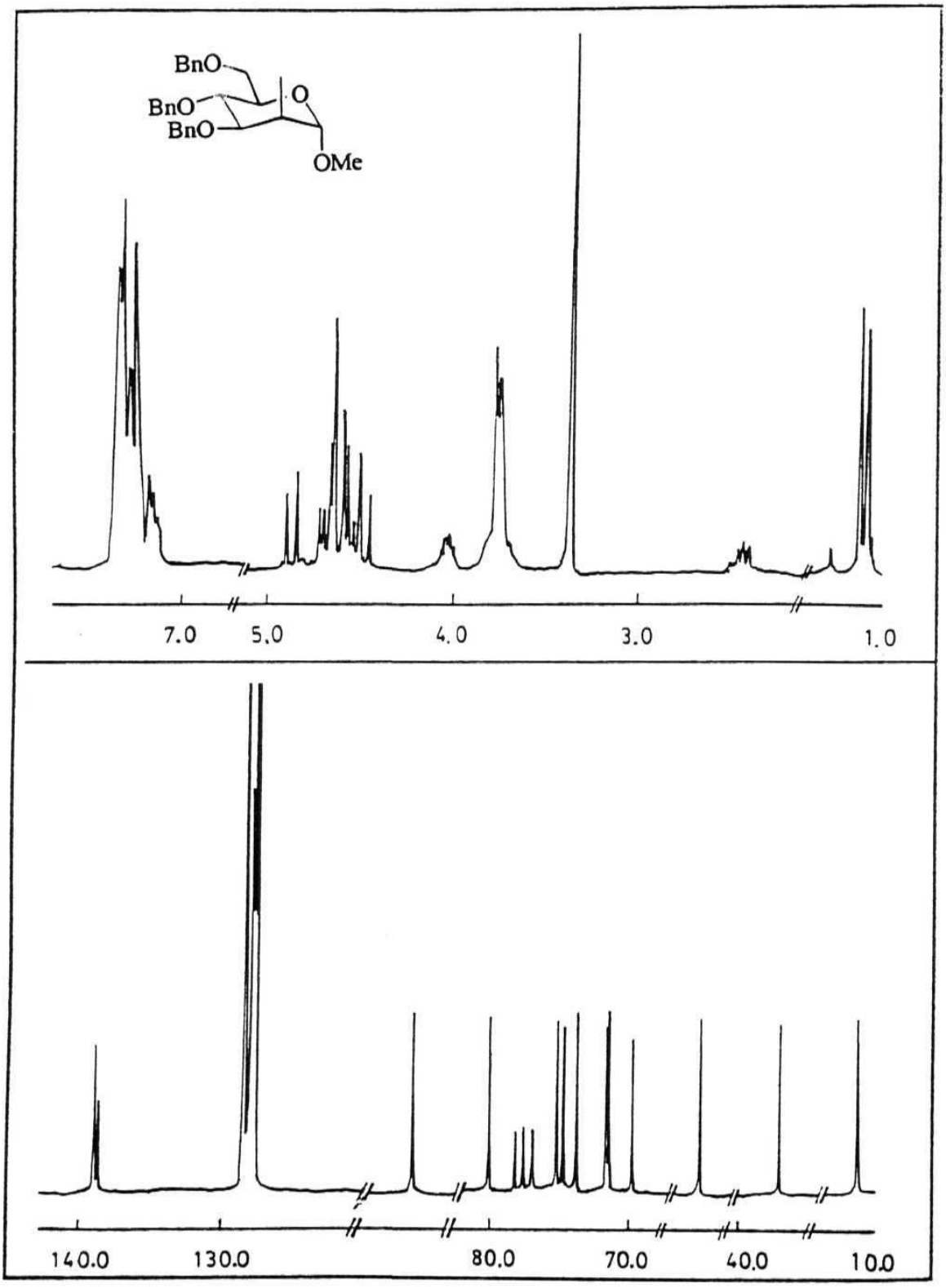
149. Hamann, H.-J; **Höft,** E.; Mostowicz, D.; Mishnev, A.; **Urbanczyl-Lipkowska,** Z.; **Chmielewski,** M. *Tetrahedron* 1997, *53,* 185.

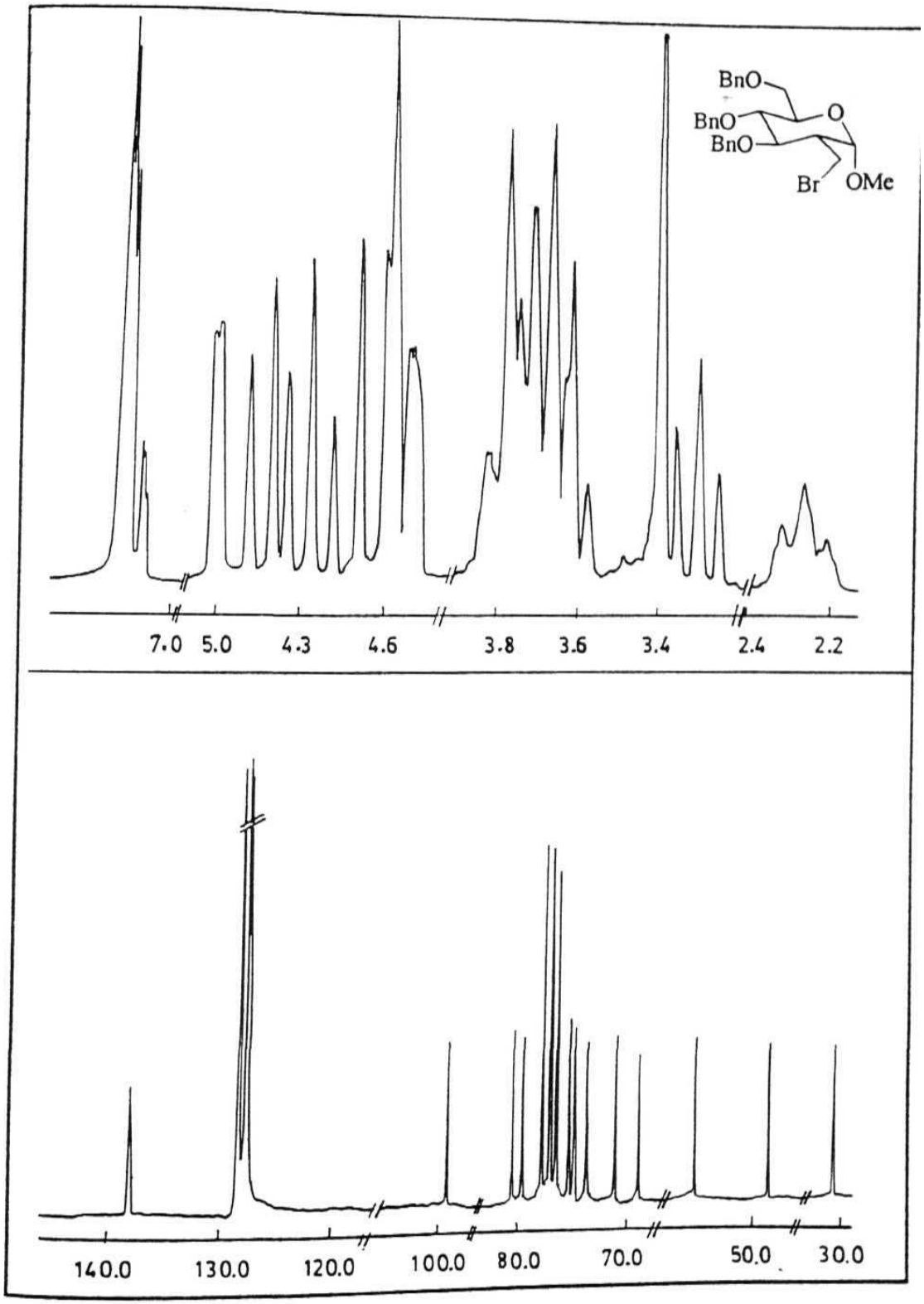
150. Evans, R.D.; Schauble, J. H. *Synthesis* 1986, 727.

SPECTRA

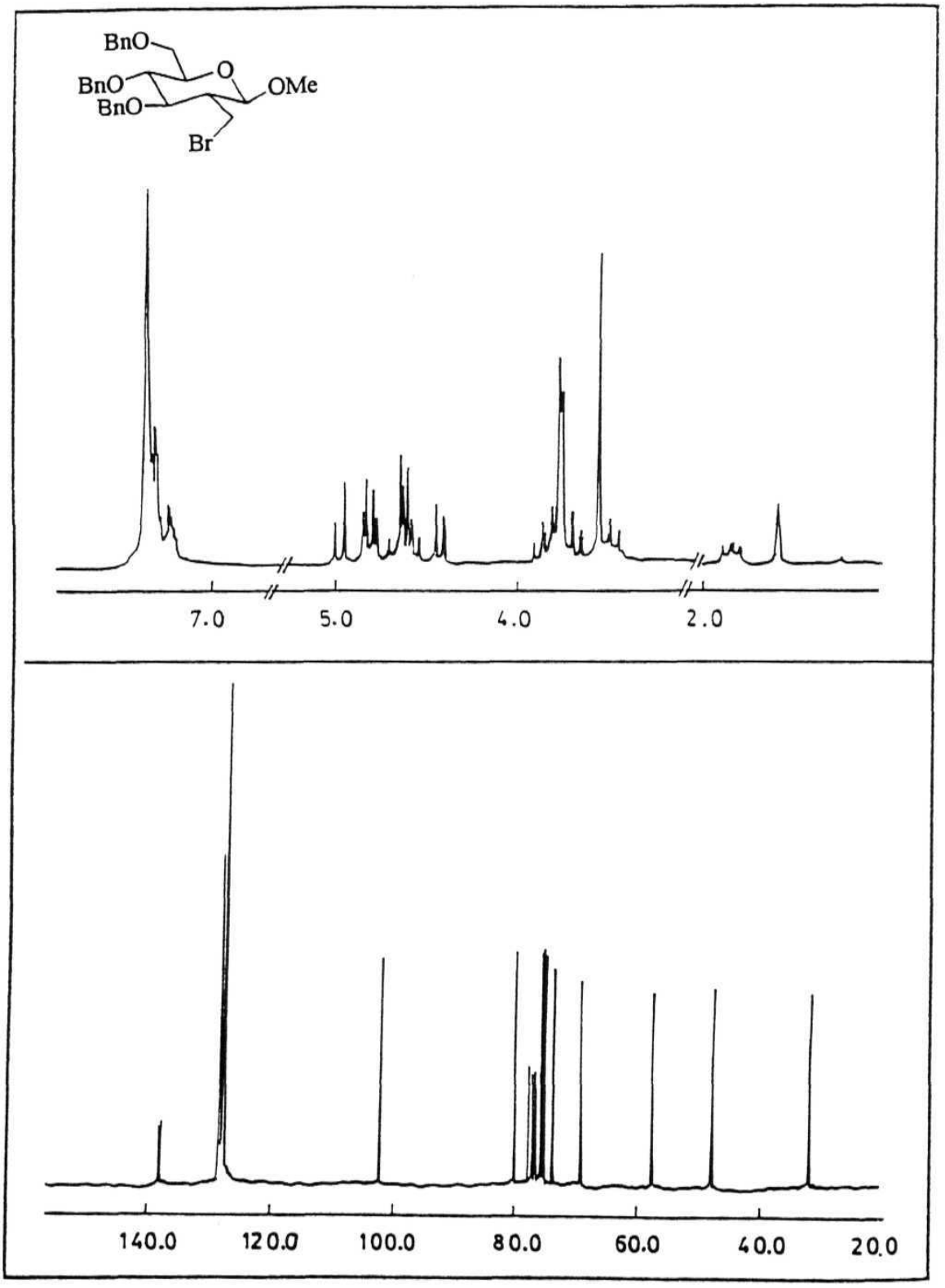

BnO
BnO
BnO
O
OMe
8.0
7.0
5.0
4.0
2.0
1.0
0.0
140.0
120.0
100.0
80.0
60.0
40.0
20.0

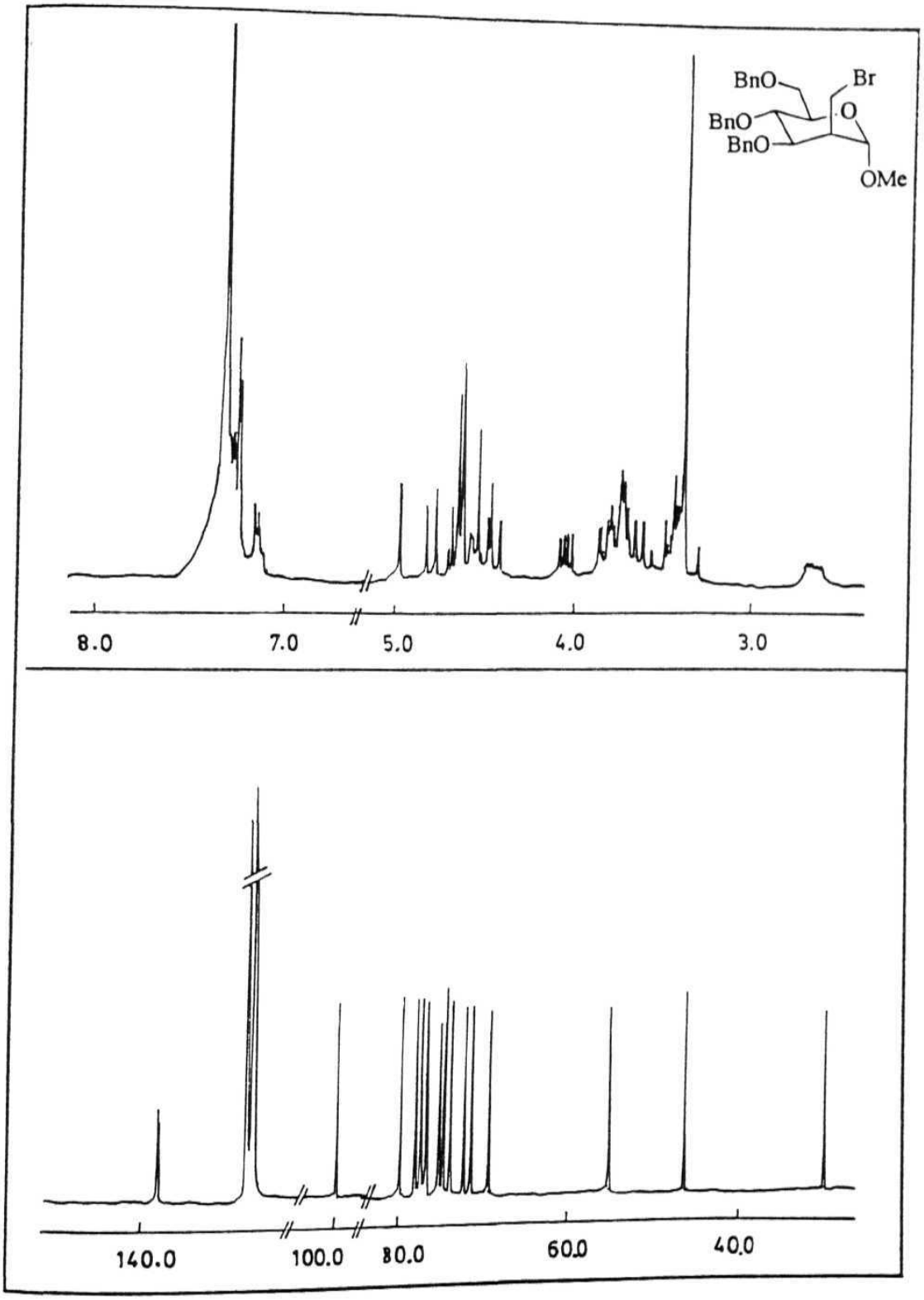
^{1}H and ^{13}C NMR Spectra of Compound **172**



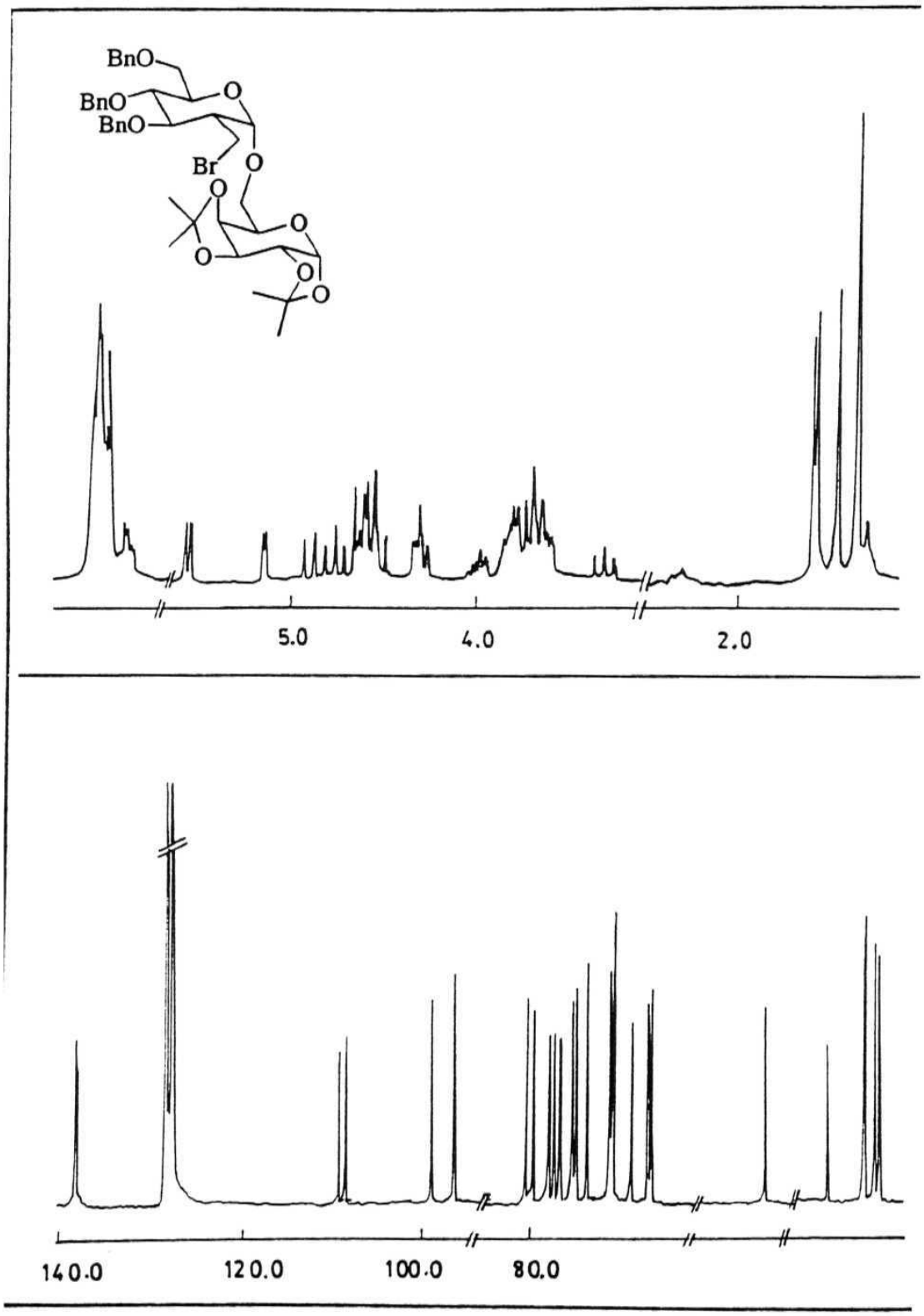

BnO
BnO
BnO
O
Br
OMe
7.0
5.0
4.3
4.6
3.8
3.6
3.4
2.4
2.2
140.0
130.0
120.0
100.0
80.0
70.0
50.0
30.0

134 ^{1}H and ^{13}C NMR Spectra of Compound 134

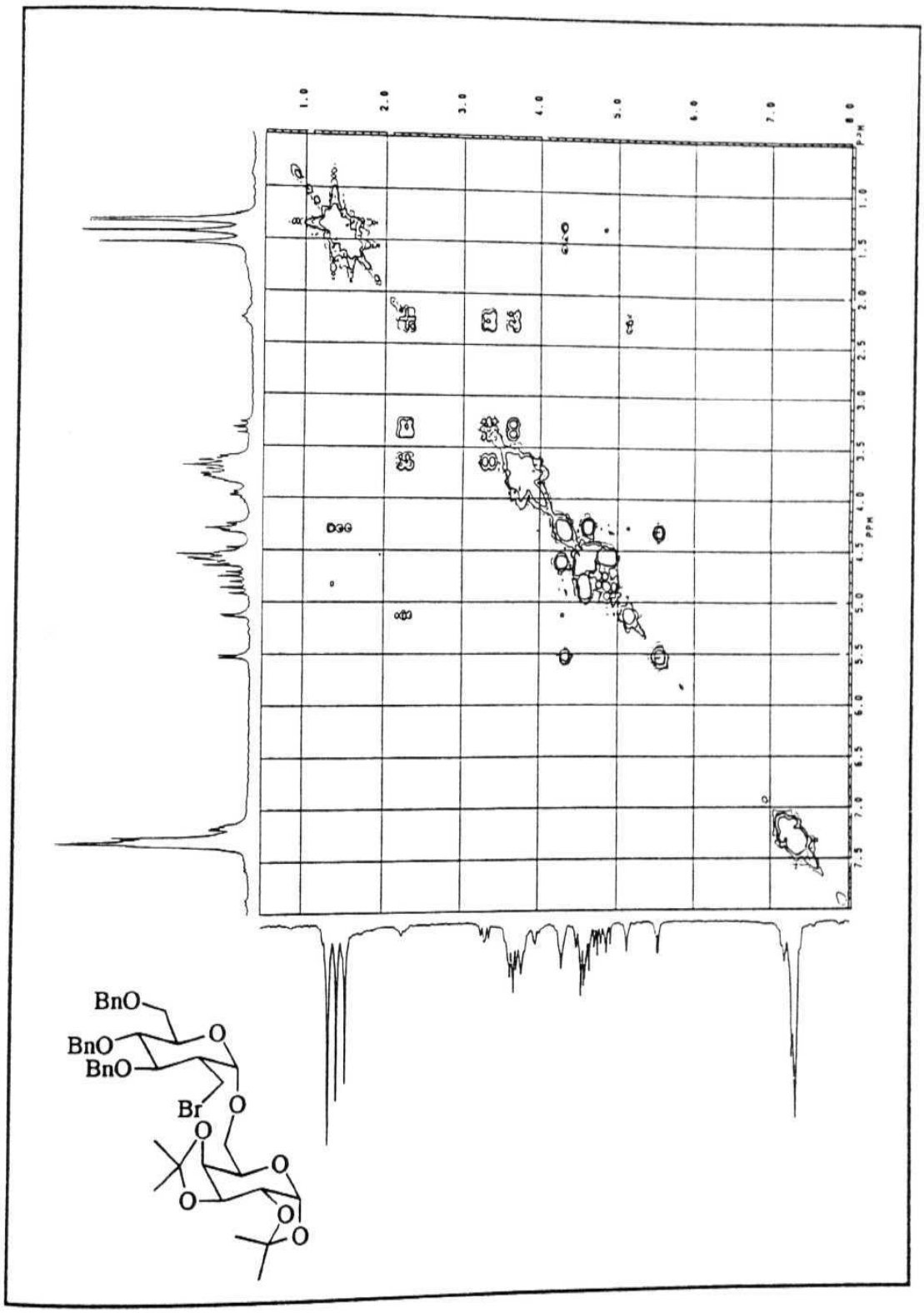



BnO
Br
BnO
O
BnO
OMe
8.0
7.0
5.0
4.0
3.0
140.0
100.0
80.0
60.0
40.0

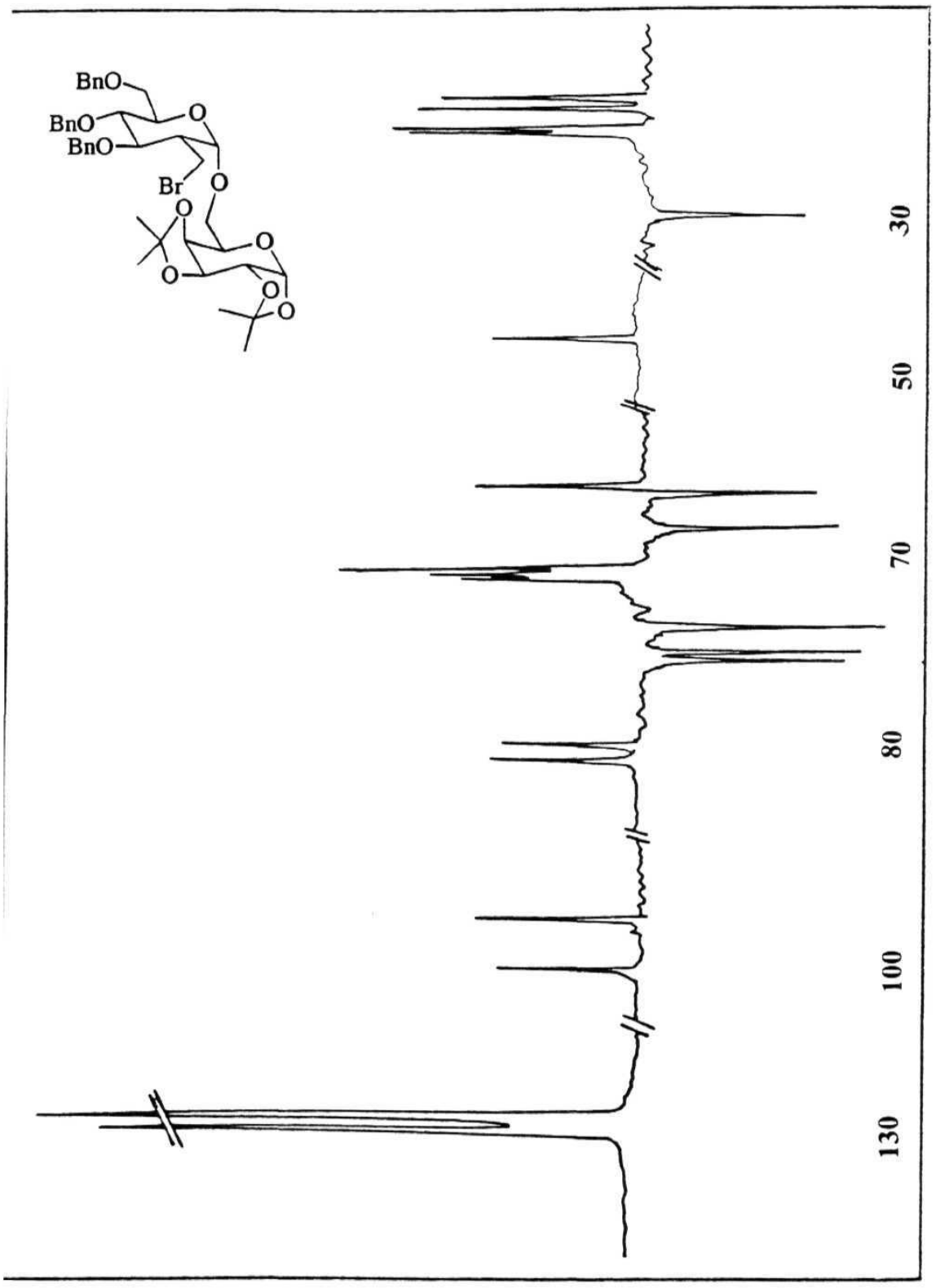
^{1}H and ^{13}C NMR Spectra of Compound 152

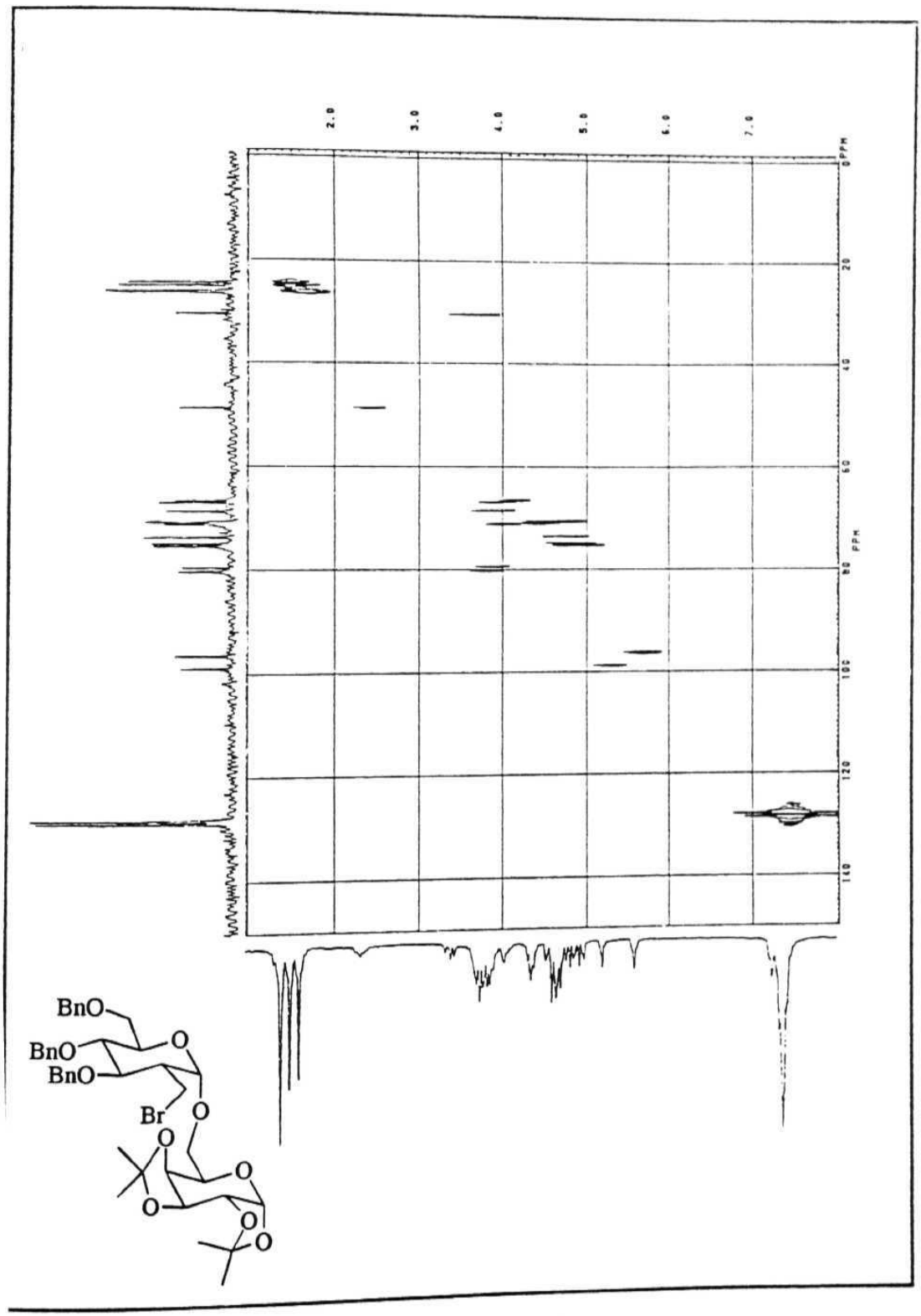


COSY Spectrum of Compound 152

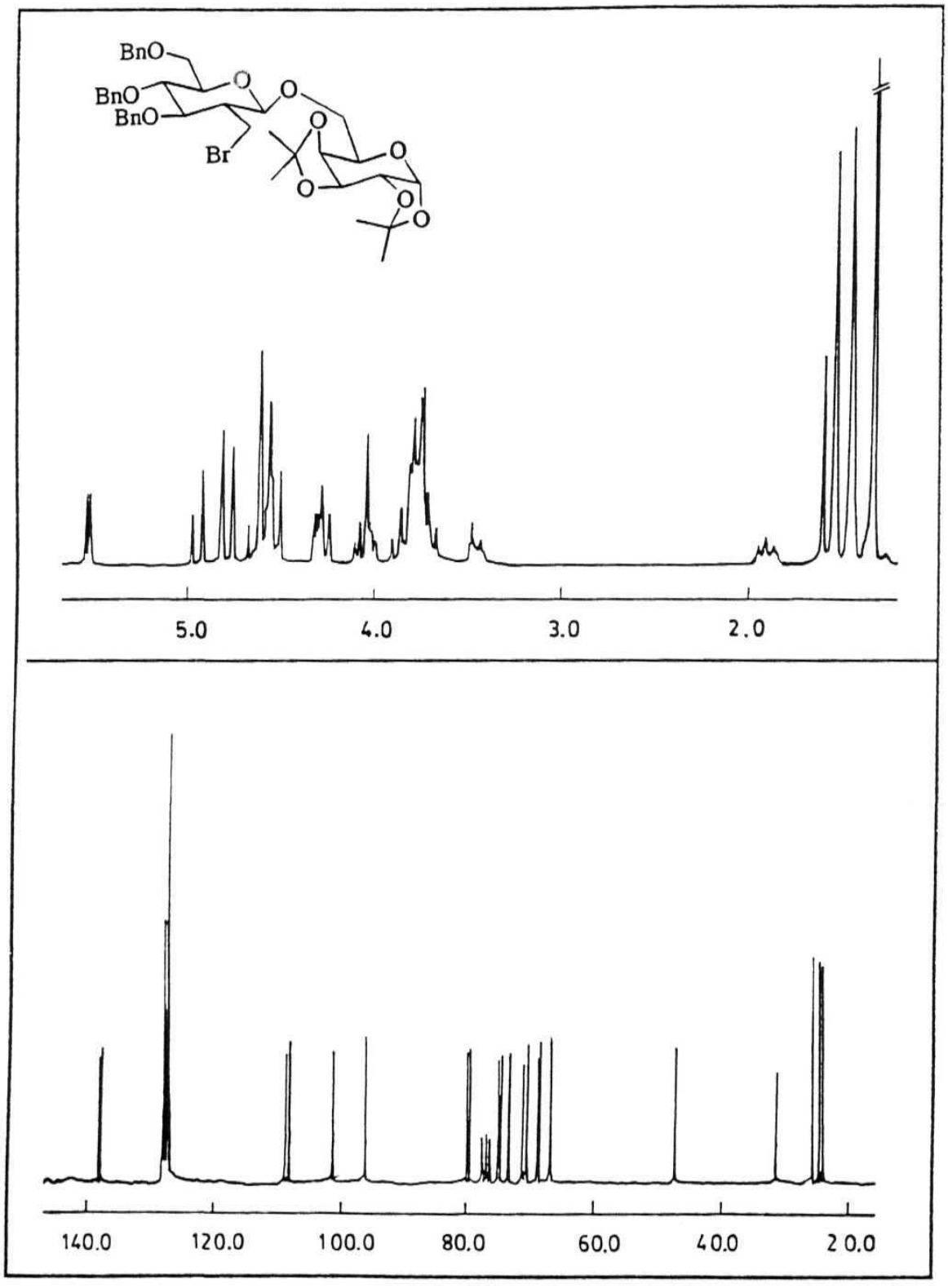


DEPT-135 Spectrum of Compound 152

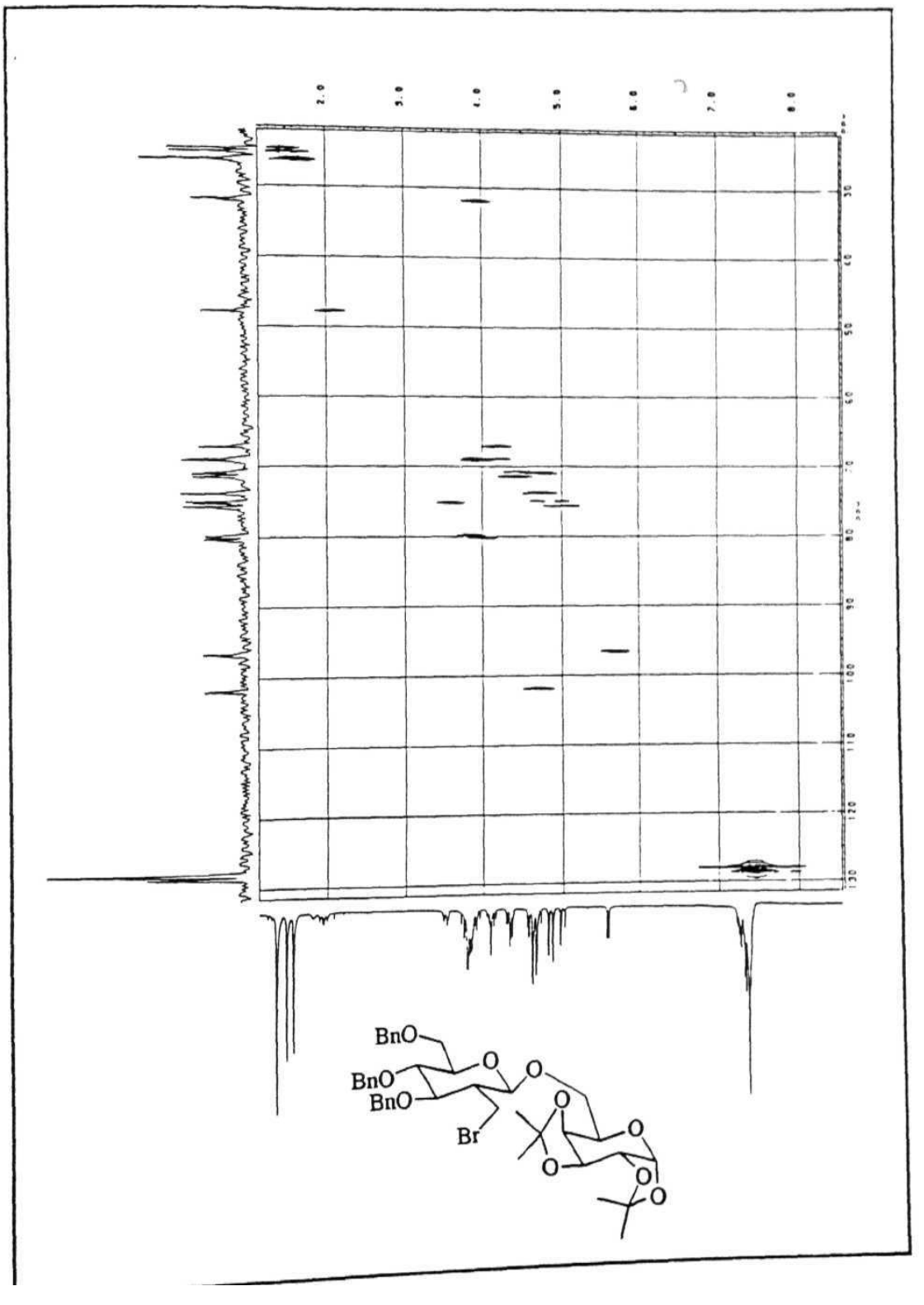



2.0
3.0
4.0
5.0
6.0
7.0
PPM
BnO
BnO
BnO
O
Br
O
O
O
O
O
O
O

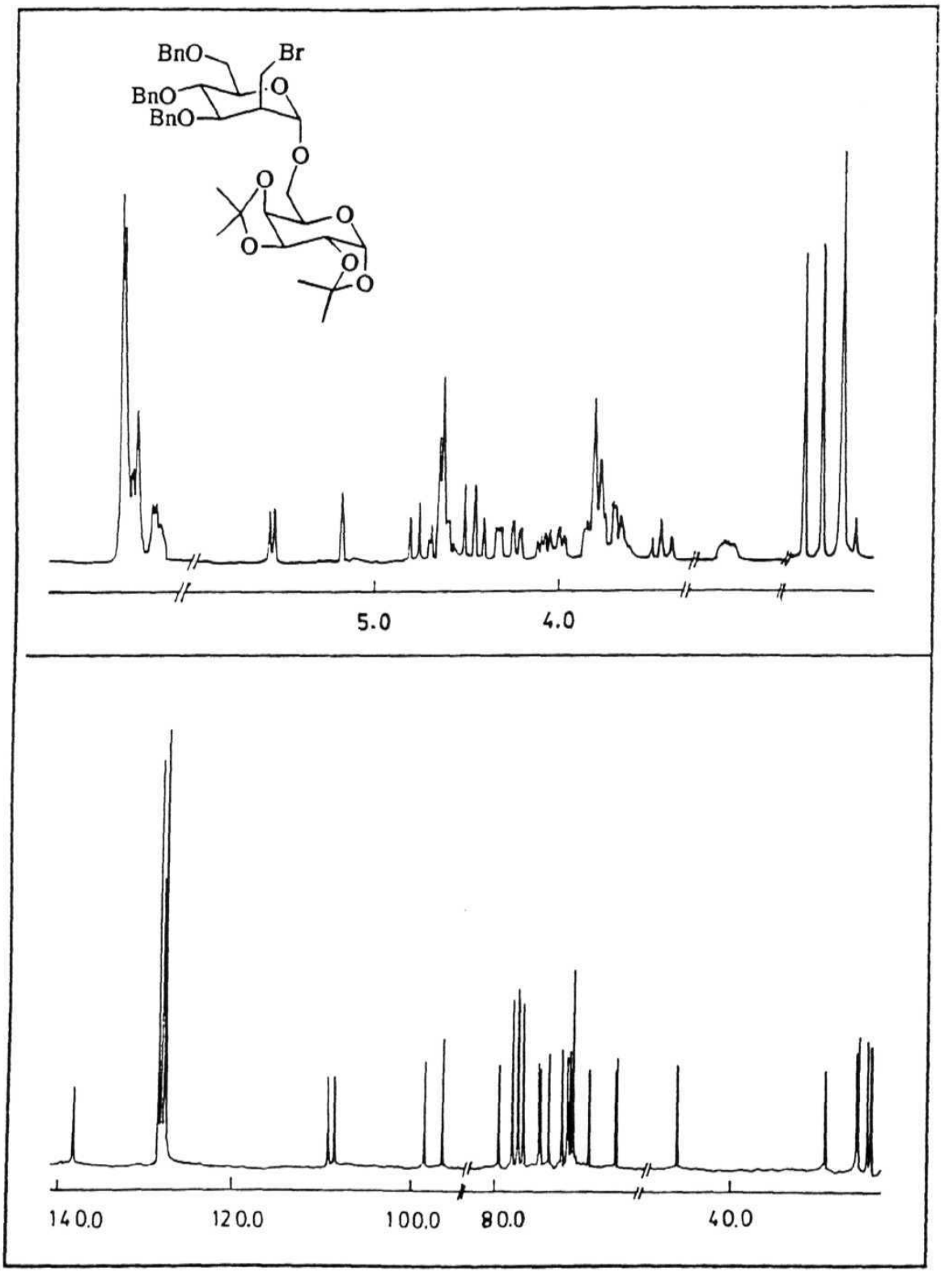
^{1}H (partial) and ^{13}C NMR Spectra of Compound 153

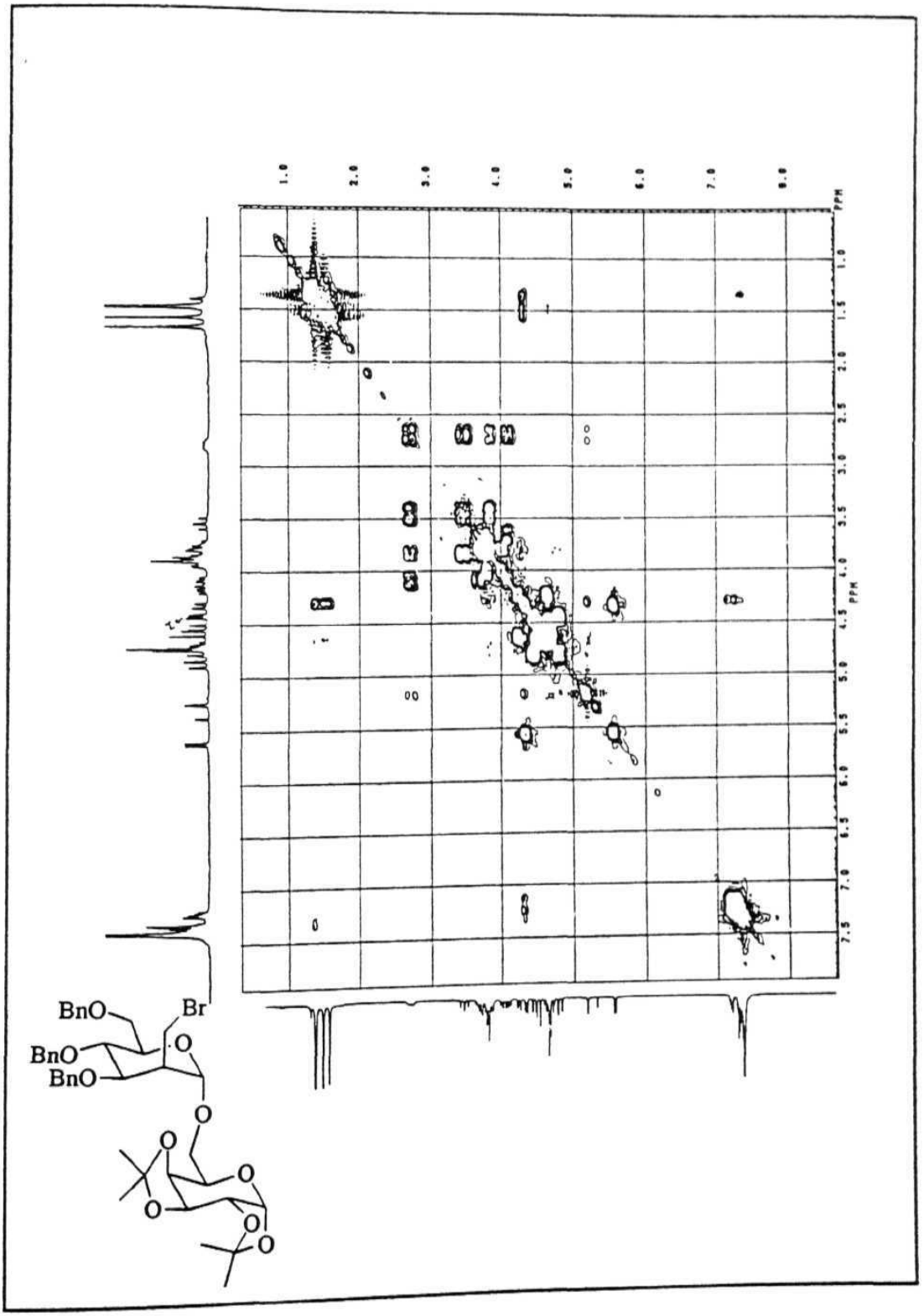


HETCOR Spectrum of Compound 153

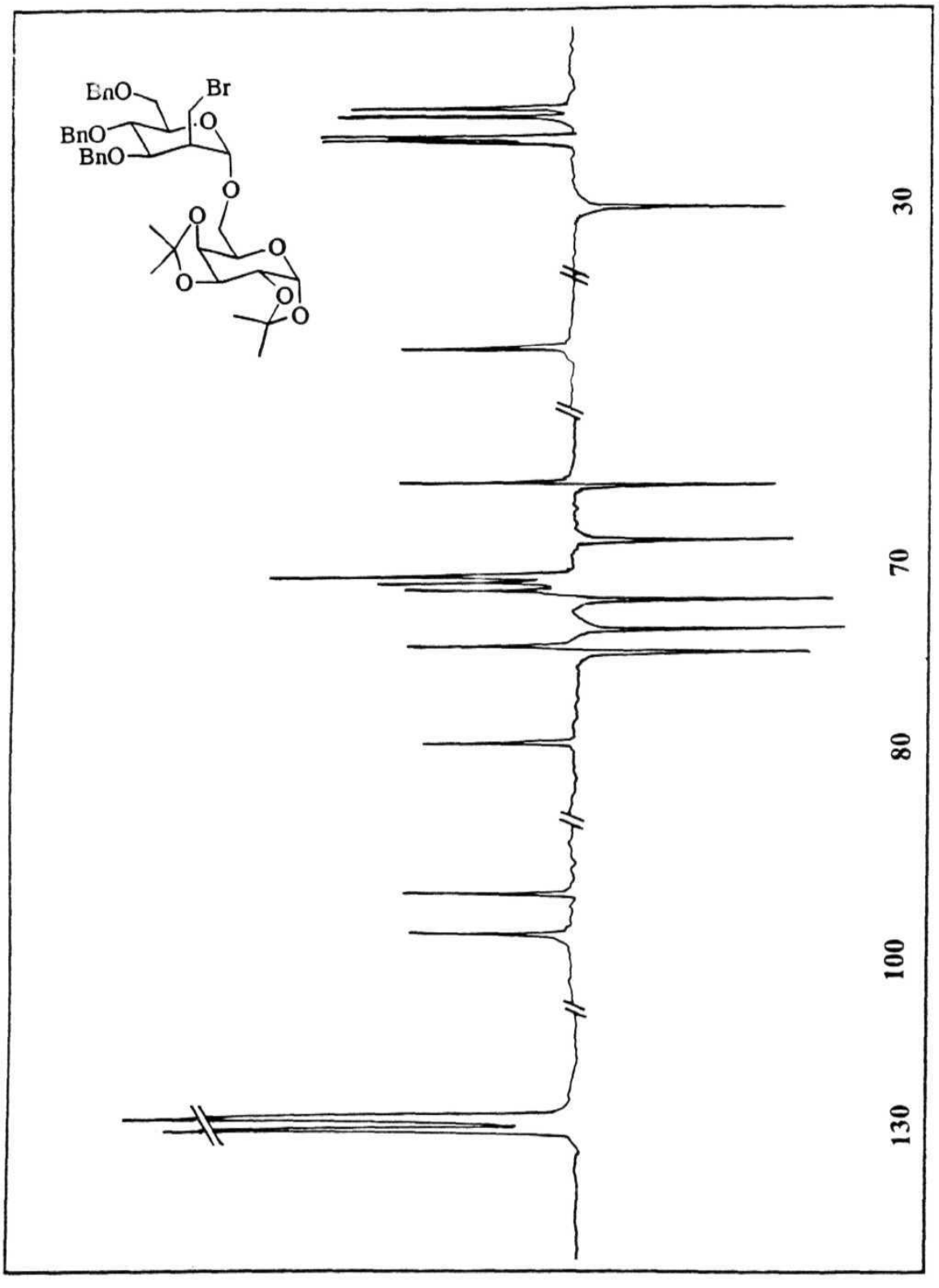


^{1}H and ^{13}C NMR Spectra of Compound 154

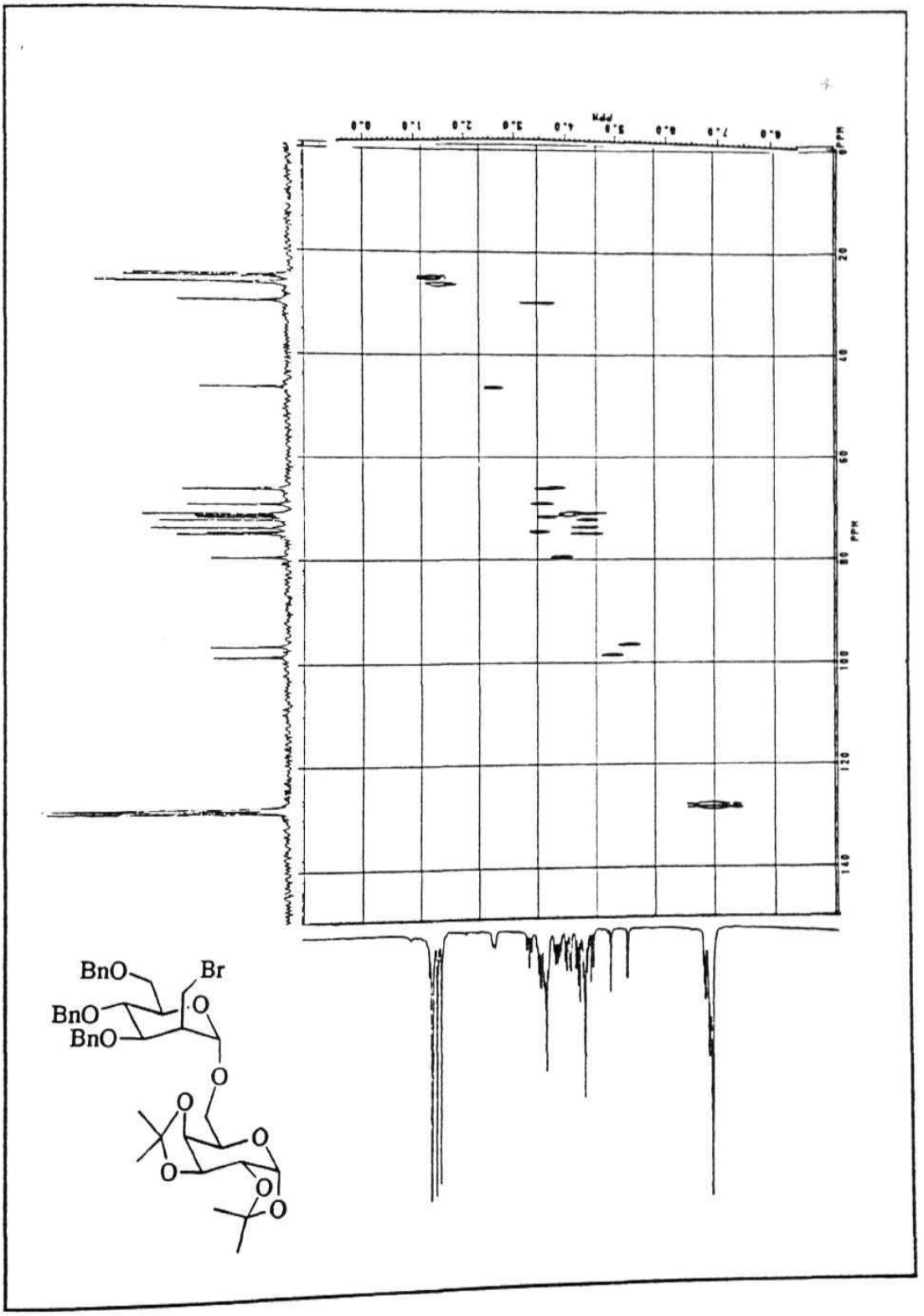



BnO
BnO
BnO
Br
O
O
O
O
O
O
O
O
PPM
PPM

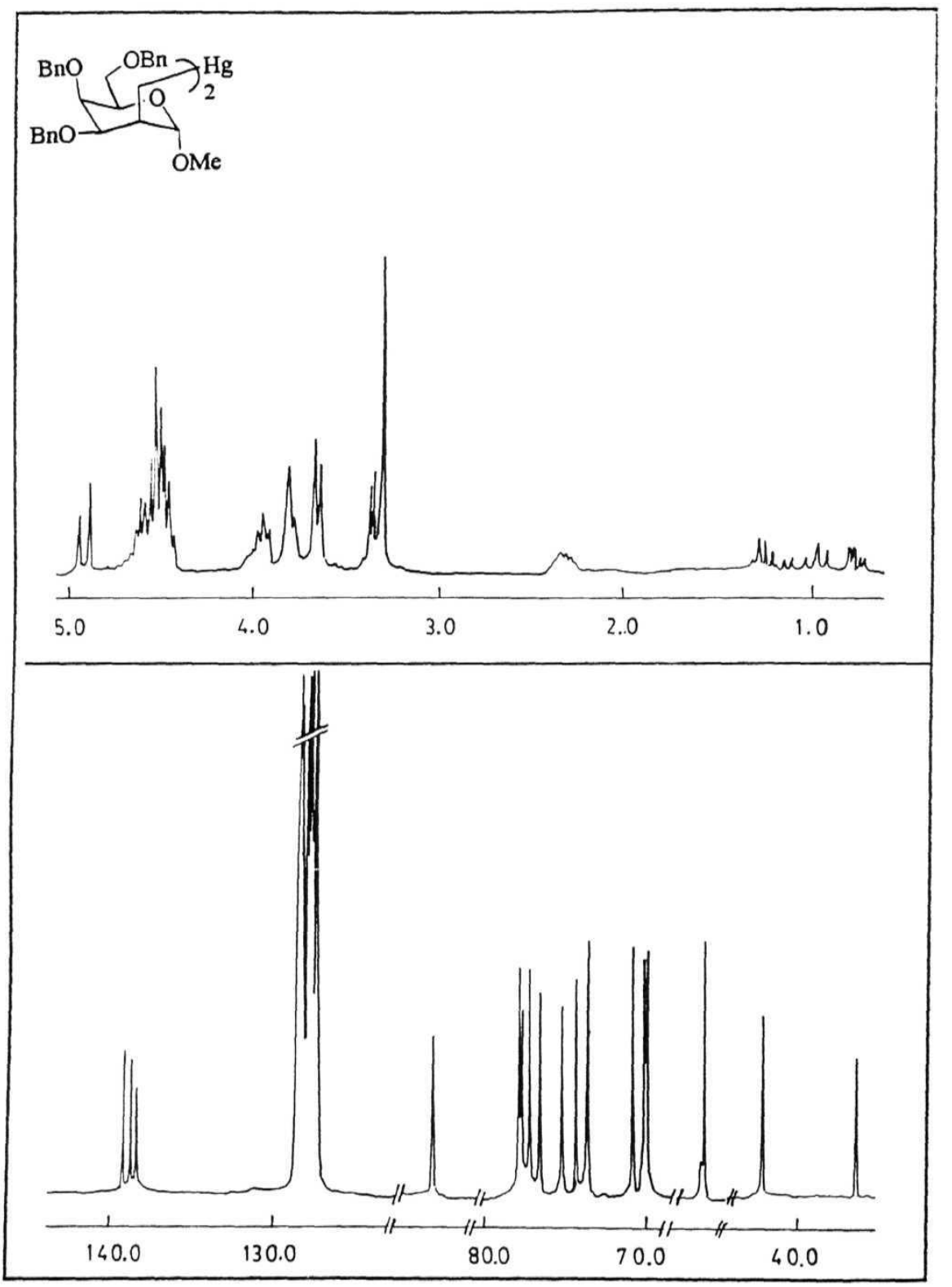
144 DEPT-135 Spectrum of Compound **154**



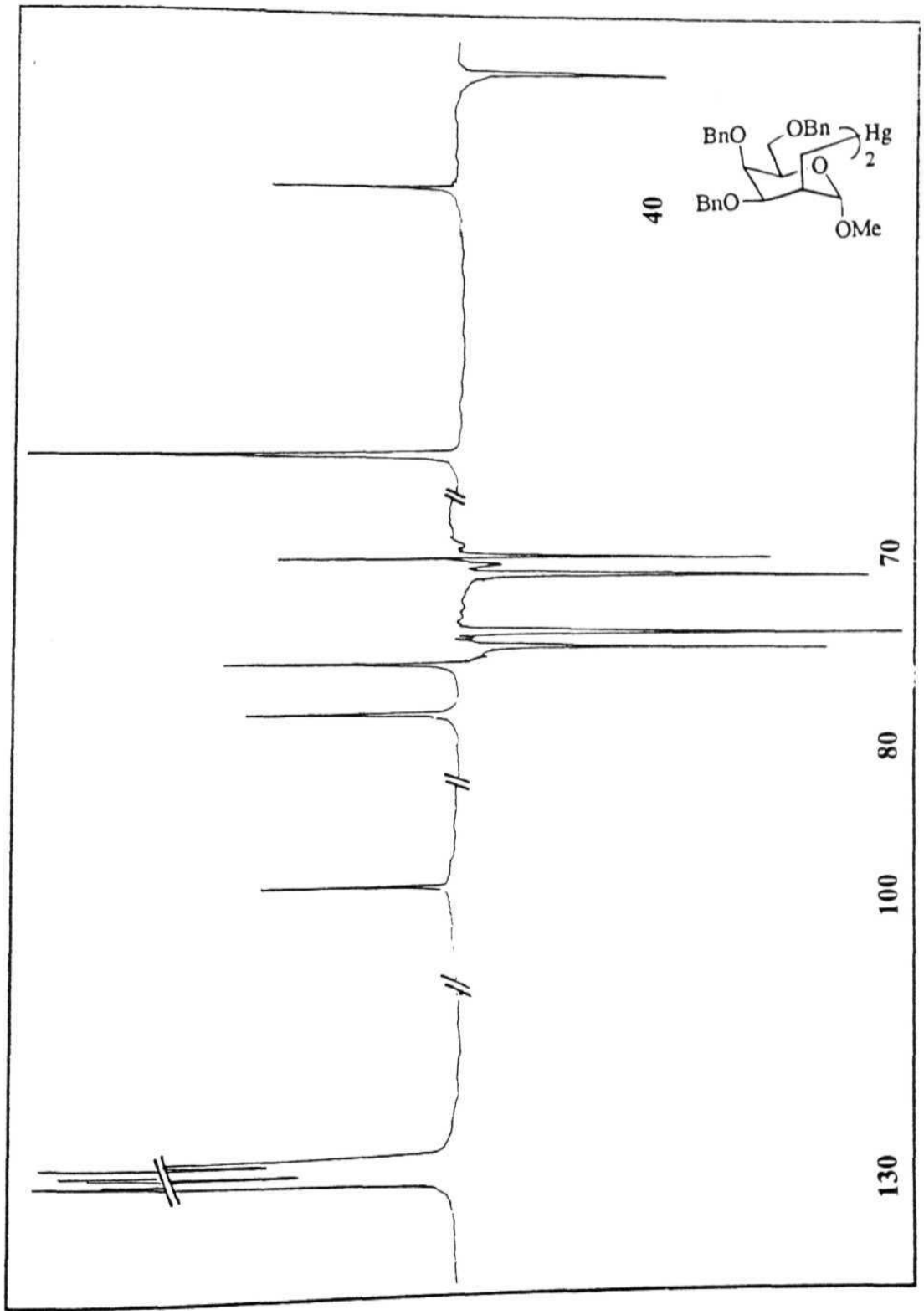
HETCOR Spectrum of Compound 154



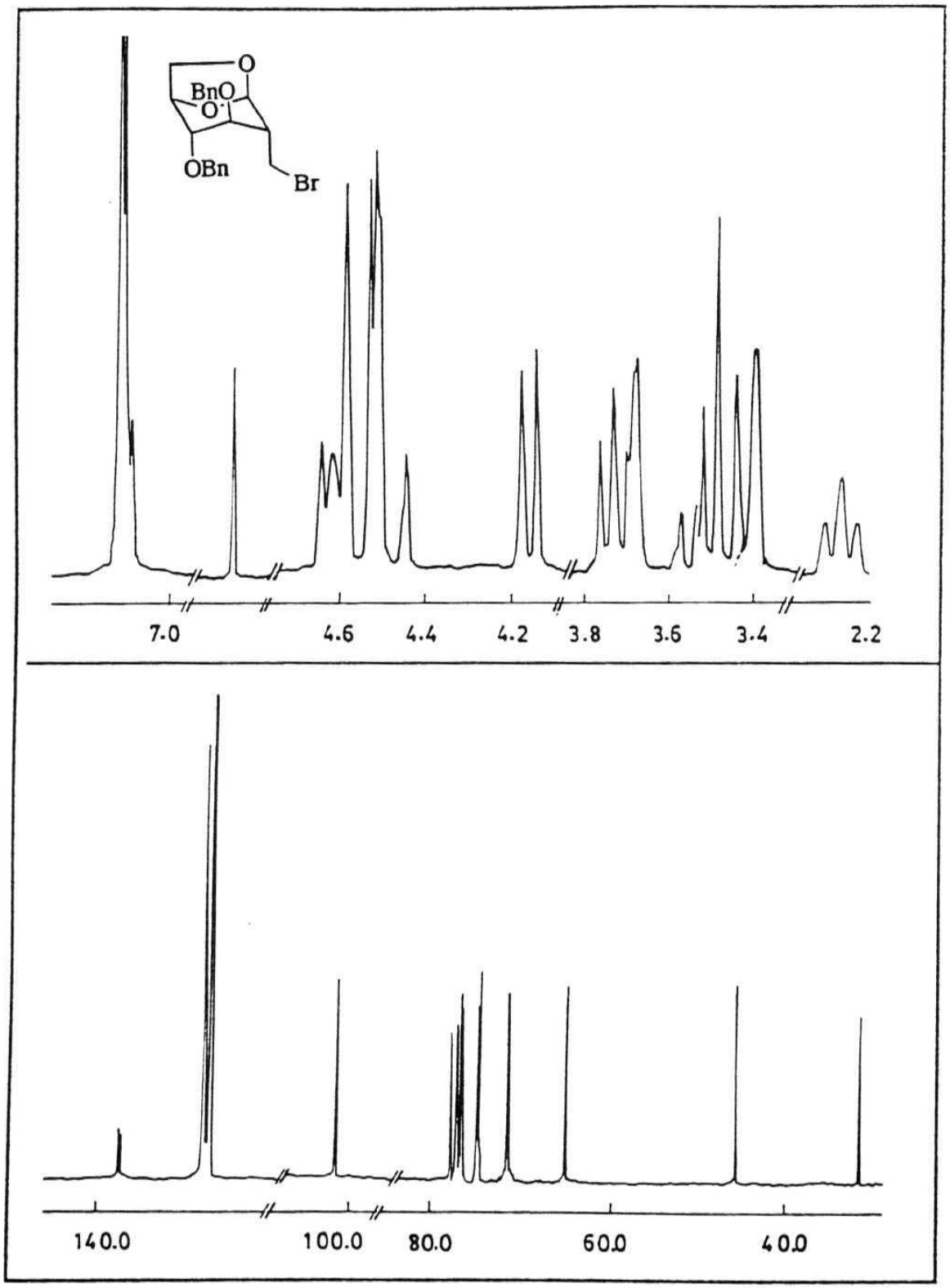
^{1}H (partial) and ^{13}C NMR Spectra of Compound 177

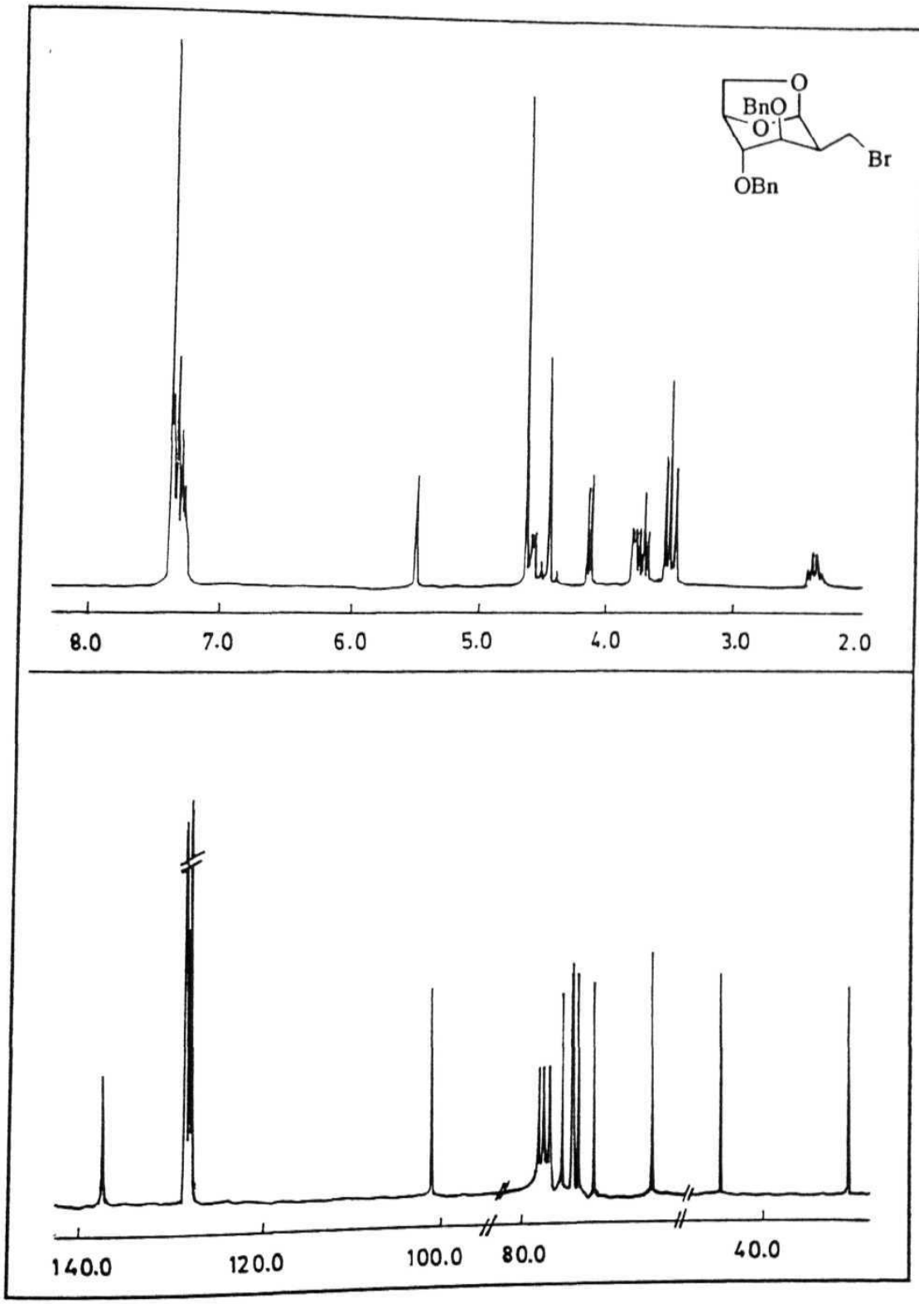


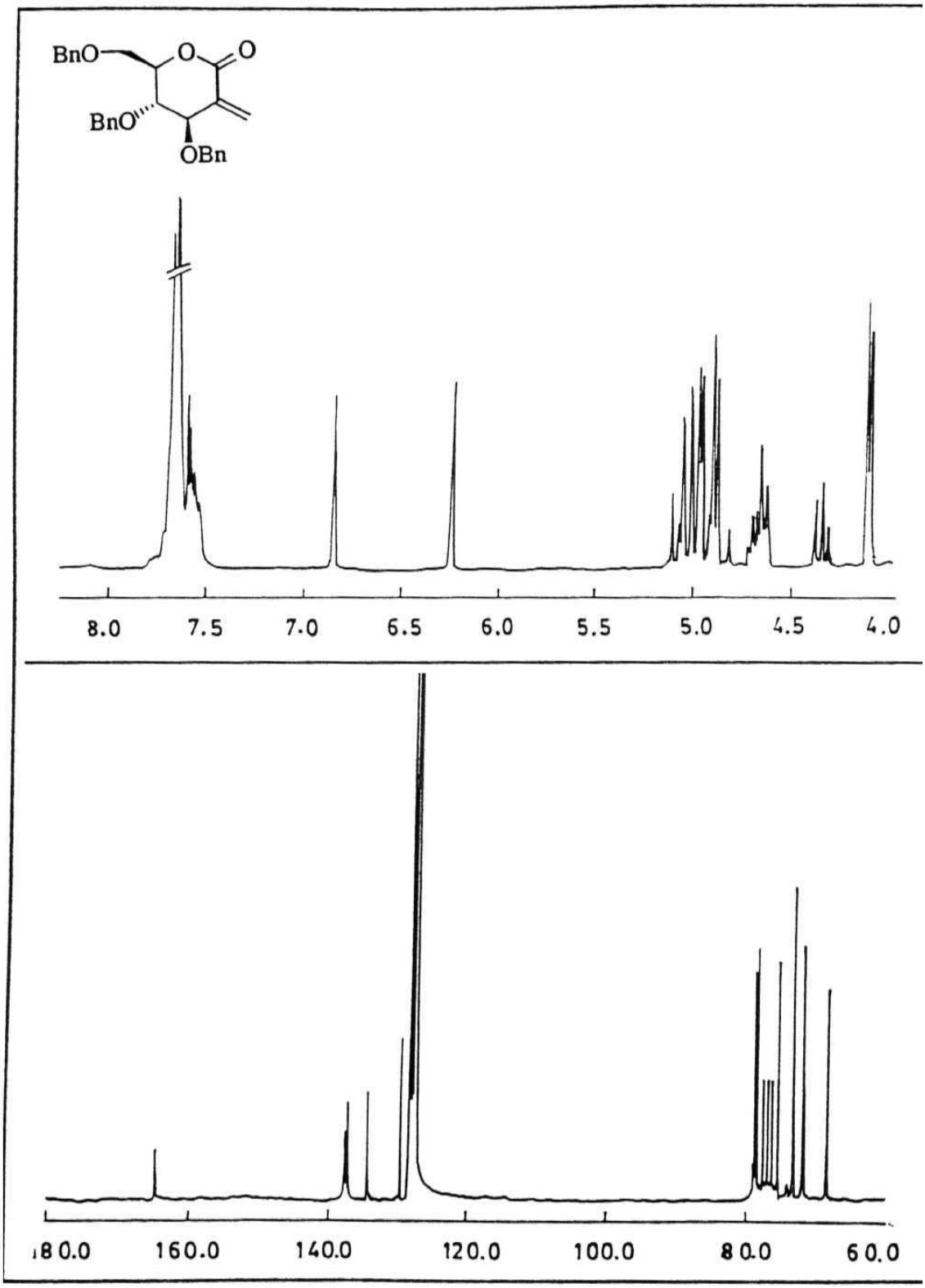
DEPT-135 Spectrum of Compound 177



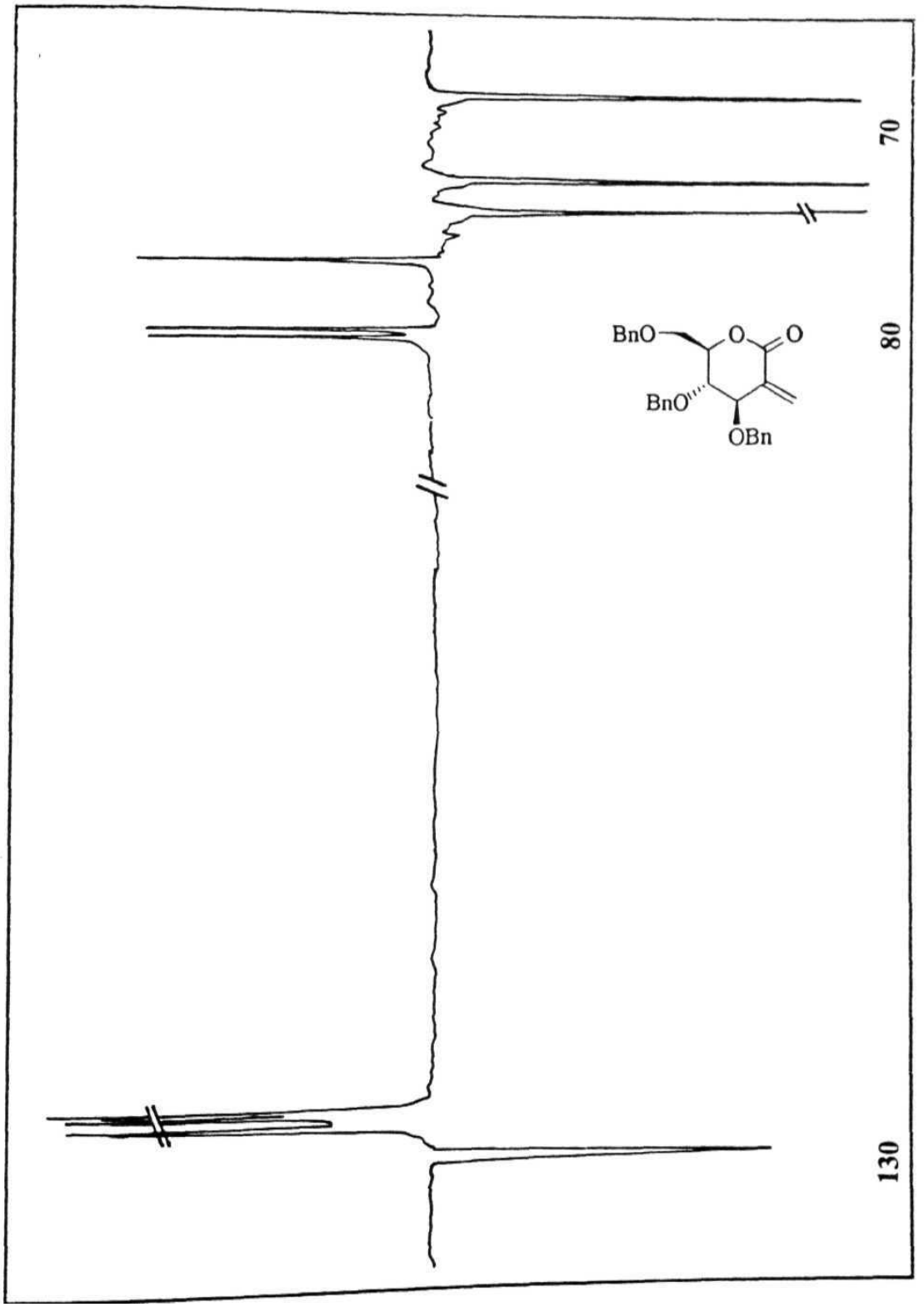
^{1}H and ^{13}C NMR Spectra of Compound 187



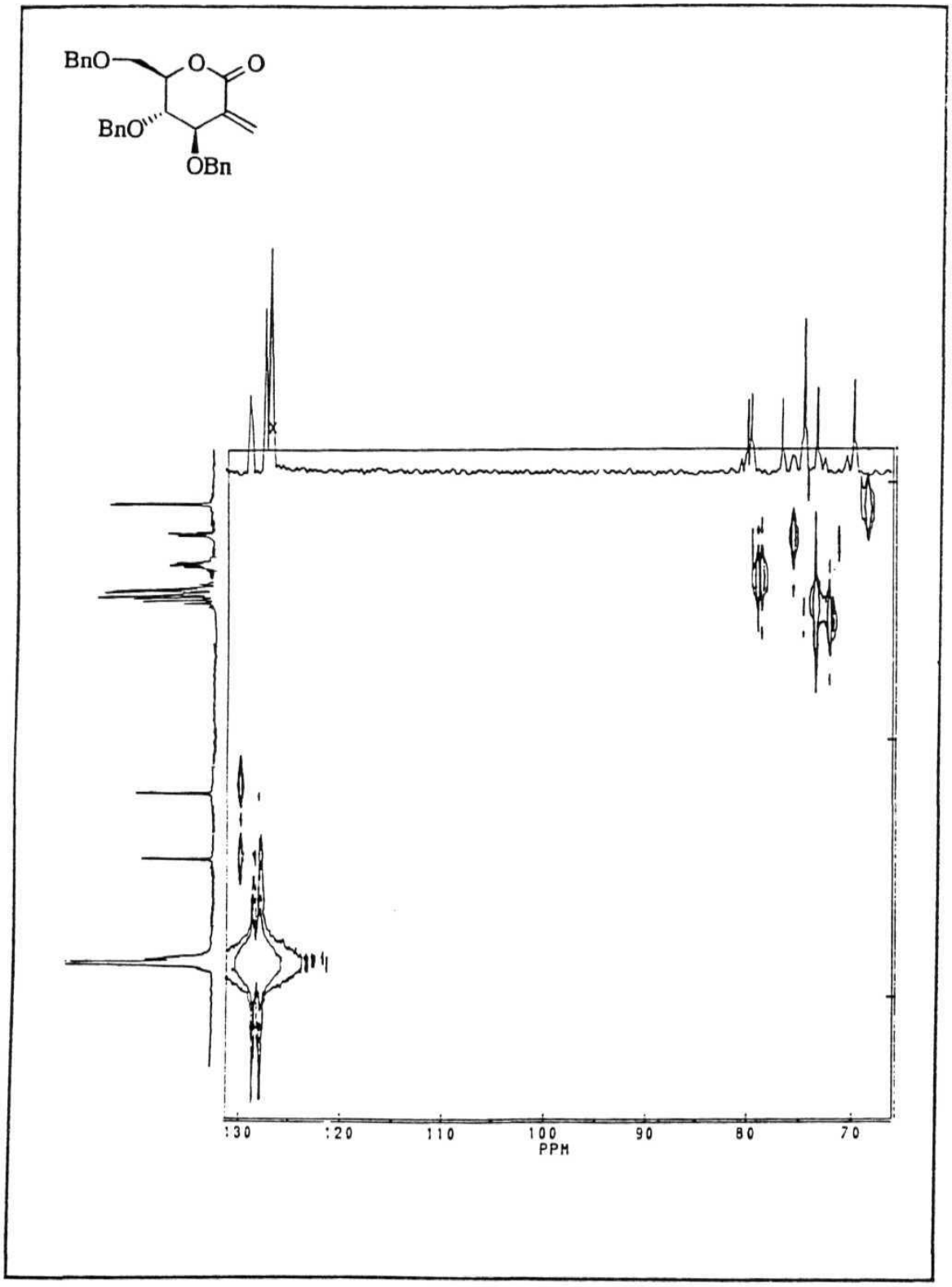

O
BnO
O
Br
OBn
8.0
7.0
6.0
5.0
4.0
3.0
2.0
140.0
120.0
100.0
80.0
40.0

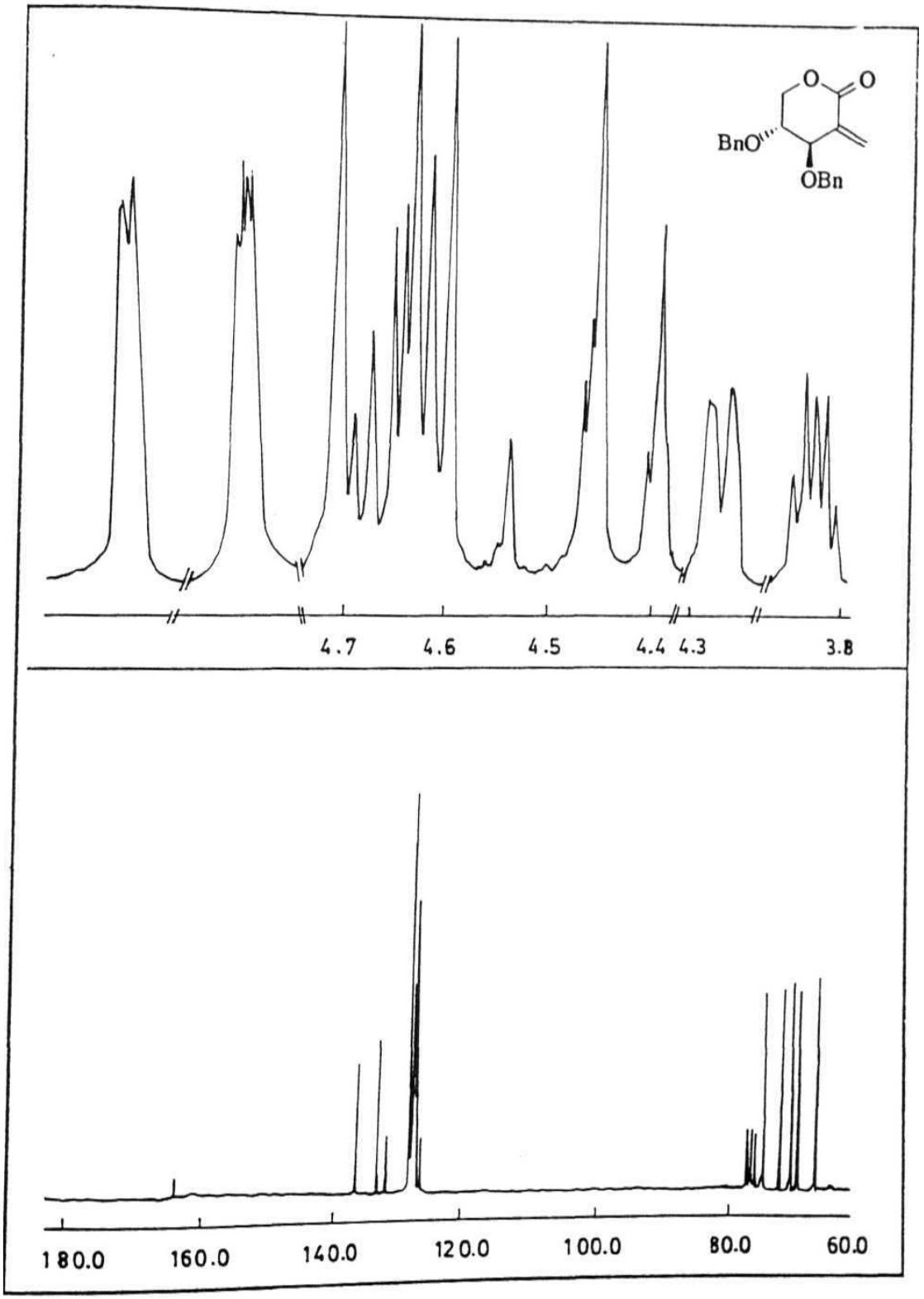

BnO
O
O
BnO
OBn
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
180.0
160.0
140.0
120.0
100.0
80.0
60.0

DEPT-135 Spectrum of Compound 195



HETCOR Spectrum of Compound 195




BnO
OBn
4.7
4.6
4.5
4.4
4.3
3.8
180.0
160.0
140.0
120.0
100.0
80.0
60.0

Vitae

The author was born on 10th May 1968 at Vinukonda, Andhra Pradesh. Following his early education at Addanki, he joined VRS & YRN College, Chirala and obtained B.Sc. degree from Nagarjuna University in 1988. After completing M. Sc. from Andhra University, he joined the research group of Prof. M. Nagarajan for the Ph.D. programme. He was awarded JRF and SRF by UGC.

List of Publications

1. Synthesis of 1,2-Cyclopropanated Sugars from Glycals. Murali, R.; Ramana, C. V.; Nagarajan, M. *J. Chem. Soc, Chem. Commun.*, 1995, 217-218.
2. Competitive 5-exo vs. 6-exo Ring Closure in Electrophile Induced Etherification Reactions. Ramana, C.V.; Murali, R; Ravikumar, K; Nagarajan, M. *J. Chem. Res. (S)* 1996, 226-227 and J. *Chem. Res. (M)*, 1996, 1267-1284.
3. Competitive 5-exo vs 6-exo Ring Closure in Intra- and Intermolecular Electrophile Induced Lactonization Reactions. Ramana, C.V.; Rajenderreddy, K.; Nagarajan, M. *Ind. J. Chem.*, 1996, *35B*, 534-540.
4. A Facile Synthesis of Chiral α-Methylene-δ-Valerolactones, Ramana, C.V.; Nagarajan, M. *Synlett*, 1997, 763.
5. DNA Cleavage by Photoexcited Diazoarenes, Bhaskar G. Maiya, Ramana, C. V.; Arounaguiri, S.; Nagarajan, M. *Bioorganic & Medicinal Chemistry Letters* 1997, 7,2141.
6. Synthesis and Reactions of 1,2-Cyclopropanated sugars, Ramana, C.V.; Murali, R; Nagarajan, M. *J. Org. Chem.*, 1997, 0000.