SYNTHETIC STUDIES TOWARDS QUASSINOIDS AND SOME REACTIONS OF UNSATURATED SUGARS

A THESIS SUBMITTED FOR THE DEGREE OP
DOCTOR OF PHILOSOPHY

BY

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dedicated to
the memory of
my late grandfather

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.

RAJAPPA MURALI

CERTIFICATE

This is to certify that the work described in this thesis entitled "SYNTHETIC STUDIES TOWARDS **QUASSINOIDS** AND SOME REACTIONS OF UNSATURATED SUGARS" has been carried out by Mr. Rajappa Murali, under my supervision and the same has not submitted elsewhere for any degree.

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ABBREVIATIONS

Ac	acetyl
Bn	benzyl
Bu	butyl
Bz	benzoyl
COSY	correlation Spectroscopy
CSA	camphorsulfonic acid
DBU	1,5-diazabicyclo [5.4.0] undec-7-ene
DCC	dicyclohexylcarbodiimide
DEPT	Distortionless Enhancement by Polarisation Transfer
DMAP	4-dimethylaminopyridine
DIPA	diisopropylamine
DMSO	dimethyl sulfoxide
E	electrophile
Et	ethyl
HBTBO	1-hydroxy-1,3-dihydro-3,3-bis(trifluoro-methyl)-1,2-benziodoxole-1-oxide
LAH	lithium aluminum hydride
MCPBA	m-chloroperbenzoic acid
Me	methyl
MOM	methoxymethyl
Ms	methanesulfonyl (mesyl)
NBS	N-bromosuccinimide
Nu	nucleophile
PCC	pyridinium chlorochromate

Ph	phenyl
Pr	propyl
Py	pyridine
TBDMS	t-butyldimethylsilyl
TBDPS	t-butyldiphenylsilyl
TCC	2,2,2-trichloroethoxycarbonyl
Tf	trifluoromethanesulfonyl
THF	tetrahydrofuran
TMS	trimethylsilyl
TMSOTf	trimethylsilyl trifluoromethanesulfonate
Ts	p-toluenesulfonyl (tosyl)

Abstract

This thesis deals with synthetic studies towards Quassinoids and some aspects of the Chemistry of unsaturated sugar. The thesis consists of two chapters. In chapter I, approaches towards the synthesis quassinoids in general bruceantin, in particular are presented, while chapter II contains the chemistry of unsaturated sugars. Each chapter is subdivided into three sections, comprising introduction, results and discussion and experiments, respectively.

The introductory section of chapter I briefly covers the biological activity of quassinoids and synthetic strategies culminating in the synthesis of bruceantin.

Quassinoids are a group of diterpenes isolated from the bitter principles of Simaronbaceae family. They have been shown to possess antitumour and many other medicinal properties. Bruceantin (1) is one of the most active member of the group and has been the subject of extensive synthetic and pharmacological investigations.

We conducted model studies towards the construction of BCD rings of the Quassinoids and towards this end, envisaged a strategy in which an intramolecular hetero Diels - Alder reaction find the key step. After a retrosynthetic analysis, we selected 4-(2-methyl-2-cyclohexen-l-yl) butyraldehyde (42) as the starting material. Compounds 42, when subjected to tandem Knoevanegal - hetero Diels - Alder reaction, failed to give any cycloadduct, but furnished only a condensation products. Several attempts to prepare the cycloadduct 53 were not fruitful.

In another approach, the BCD ring system was proposed to be synthesized by the nucleophilic ring opening of an appropriately substituted cyclopropane. We chose the diazosulfone ester 56 prepared from 2-methyl-2-cyclohexenol (43) as the substrate for this investigation. This compound, under several conditions tried, did not undergo intramolecular cyclopropanation. Another compound 62, prepared from 43, furnished the cyclopropane 64 in low yields when heated with excess of Cu powder in xylene. However, 64 could not be reproducible made and further studies in this direction could not carried out. Preliminary studies carried out using an intramolecular Michael reaction were also unsuccessful. In the light of these failures, further studies towards the synthesis of Quassinoids were not pursued.

Introduction to chapter II covers the various reactions glycals and 2,3-unsaturated sugars. Some of the general methods available for the synthesis of medium sized oxygen containing rings are also discussed.

We envisaged an insertion homologation strategy for the construction of functionalized seven membered oxygen heterocycles. Out strategy consisted of addition of dihalocarbenes to glycals and solvolyzing the resultant strained dihalo cyclopropanes. To this end, we investigated the addition of dibromo and dichloro carbenes to glycals 31, 32, 33 and 34. With dichlorocarbene, only a single adduct was furnished in each case. Glycals 31, 32 and 34 gave single dibromo cyclopropanes

with dibromocarbene while, 33 gave two adducts 41 and 42 in a 7 : 1 ratio.

We conducted solvolysis experiments with adducts 34 and 39 under several conditions. Solvolysis under basic conditions produced ring expanded products. Reactions of the dihalocyclopropanes with tributyl tinhydride and lithium aluminium hydride were examined next. Compound 34 gave cyclopropane 57 upon reduction LAH. While 39 produced a mixture of 35, 57 and 59. Direct cyclopropanation of glycals was also attempted and this produced cyclopropane having an opposite stereochemistry compared to the products of reductive dehalogenation. The utility of cyclopropanated sugars in the synthesis of glycosides has been examined with 57. NBS and Hg(OAc) have been used as electrophiles in these reactions, leading to 2-deoxy glucopyranosides 67 and 75, respectively.

Partially protected 1,5-anhydroalditols have been prepared by hydroboranation of glycals. Finally, the third section in both chapters I and II contains all the relevant experimental details, followed in each case by appropriate references.

Chapter I

Synthetic Studies towards Quassinoids

Introduction

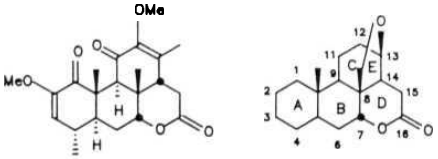
Organic synthesis can be classified into two broad categories: (i) Natural product synthesis and (ii) synthesis of non-natural compounds. The distinction between the two has been very clearly spelt out by Professor D. J. Cram in one of his articles. He observed : "Synthetic *organic chemists fall into two groups: those who prepare old naturally occurring compounds and those who prepare new compounds. The synthetic targets of the former group are provided by the evolutionary chemistry of Nature. The synthetic targets of the latter group are designed by the investigator*" . Synthetic organic chemists all over the world are pursuing the synthesis of both classes of compounds very actively. In the first category, some of the notable achievements in recent times include the synthesis of erythromycin [3], palytoxin [4], calicheamicin γ [5] and taxol [6]. On the other hand, some of the interesting non-natural products that have been synthesized over the past decade are pentaprismane [7], dodecahedrane [8] and a host of new supramolecules like the dendritic hydrocarbon $C_{1,268}H_{1,270}$ [9]. All these have been made possible by the availability of sophisticated synthetic, analytical, spectroscopic and chromatographic techniques. The presence of computers has given a new dimension to synthetic planning [10].

Among the natural products, synthesis of steroids, alkaloids, prostaglandins and terpenes have been the subject of several investigations. In recent years, compounds having diverse physiological and pharmacological activity have received

considerable attention from synthetic chemists worldwide. Some typical examples are the ene-diyne antibiotics[10] taxol and lnununosuppresants such as rapamycin and FK-506

Quassinoids, like many other group of naturally occurring compounds, have also been the subject of many synthetic endeavours.

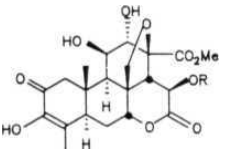
The quassinoids are a broad group of bitter principles isolated from the botanical family of *Simaroubaceae*. Extracts from the *Simaroubaceae* plants have been used in the folk medicine of Asia and Africa for centuries in the treatment of various ailments . Although the structure of the first quassinoid quassin (1) was established in 1962[14], there was no systematic investigation of these substances before the discovery in 1970 that halocanthone, a member of this family, possessed antineoplastic activity . Later, in 1973, Kupchan reported an investigation of *Brucea antidysenterica* . Eight new quassinoids were isolated and several of them were found to have significant antitumour and antileukemic activity . Kupchan's disclosure about the antineoplastic activity of bruceantin 2 generated



Quassin(1)

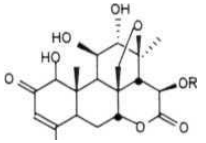
1ft

considerable interest in quassinoids . A brief discussion of the biological activity of quassinoids is presented in the following paragraphs.



Bruceantin(2)

R= COCH=C(Me)CH(Me)$_2$



Simalikalactone D(3)

R- COCH(Me)(Et)

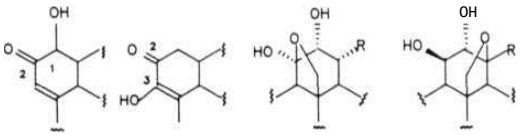
Bruceantinol(4)

R- COCH=C(Me)C(Me)$_2$(OAc)

Most of the quassinoids are biologically active. Bruceantin (2), simalikalactone D (3) and bruceantinol(4) are most active against P - 388 lymphocytic leukemia[19]. Bruceantin shows activity over a wide dose range and, in addition, is active against solid tumours. It was also found that bruceantin was active against L - 1210 lymphoid leukemia, Lewis lung carcinoma and B - 16 melanocarcinoma, resulting in it being selected for clinical trials by the US National Cancer Institute

Structure - activity studies reveal some of the structural requirements essential for optimal antineoplastic activity. They are a) ring A with either an α,β-unsaturated ketol at positions C1 and C2 or a diosphenol group at positions C2 and

C3 (structures a and b of chart 1) b) ring C with an epoxymethano bridge between C8 and C11 or between C8 and C13 (structures c and d) and c) a free hydroxyl group in ring C at C12 in addition to an ester group at C15.



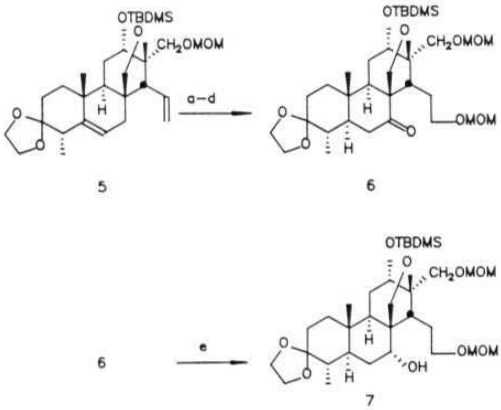
a **b** **c** **d**

Among other pharmacological properties, the growth of chloroquine resistant blood parasite *Plasmodium falciparum* was markedly inhibited in vitro by certain quassinoids . Bruceantin (2) and simalikalactone (3) and some other quasssinoids displayed activity against the parasite *Entamoeba histolytica* in Gillin's and Reiner's extensive study

The highly oxygenated carbon skeleton and wide ranging biological activity of quassinoids have attracted the attention of synthetic chemists in a big way. As a result, total syntheses of tetracyclic quassinoids like quassin [24], castalanolide [25], amarolide and kleineanone have been achieved. Besides this, there was also a great interest in the synthesis of pentacyclic quassinoids like bruceantin. Bruceantin has a complex structure with several different functional groups and has ten asymmetric centres. Despite its failure in phase II of the clinical trials at the National Cancer Institute, bruceantin still attracts intensive synthetic efforts from chemists all over the world .

To date, only two total syntheses of bruceantin have been achieved, despite intensive efforts by several research groups[29] A short summary of the efforts that culminated in the total synthesis of bruceantin is presented in the following paragraphs.

In a sustained effort lasting several steps, **Murae** and co - workers achieved a relay total synthesis of bruceantin Based on the previous experience gained **during** the synthesis of a pentacyclic intermediate , compound 5 was chosen as the starting material for the total synthesis.

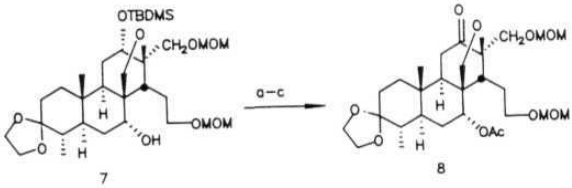


Reagents and conditios: *a) thexylborane, THF, 0 ; NaOH, H2O2;b) MOMCl, (iPr) NEt, CH2Cl2, 0°; c) CrO32Py, CH2Cl2; d) Li. NH3,*

Compound 5 was transformed into the tetracyclic ketone 6 by routine functional group manipulations. Selective reduction

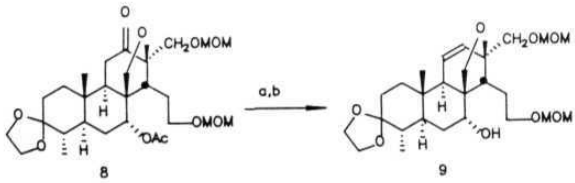
of the ketone 6 to the desired *la* alcohol 7 was achieved under chelation controlled conditions employing 1 eq. of LiBr along **with the** reducing agent LiEt BH.

Efforts were then directed to the introduction of C11 - C12 diol unit via the Cll - C12 double bond. For this, alcohol 7 was converted to the ketone 8 in 3 steps. The tosylhydrazone of ketone 8 when subjected to the Shapiro reaction afforded the hydroxy olefin 9 in 92% yield.



7 8

eagents and conditions: a) *Ac O, DMAP, Py, CH Cl ; b) n-Bu NF, **THF**, 50 ; c) CrO .2Py.*

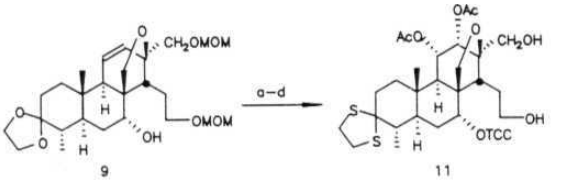


8 9

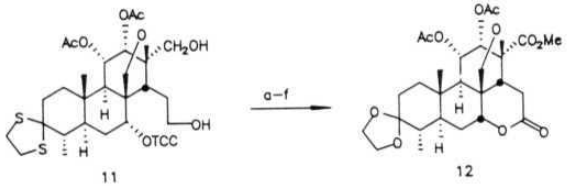
Reagents and conditions: *a) **TsNHNH2**, **TsOH**, **MgSO4**, THF; b) **MeLi**, THF.* 0°->*rt*

The Cll - C12 olefin was osmylated after protecting the hydroxy group in 9 as trichloroethylcarbonate (TCC) to give the

diol 10. Next, efforts were concentrated on building the *S* lactone moiety. To achieve this, the diol 10 was protected as its diacetate and the methoxymethyl protecting groups were cleaved using ethanedithiol and $BF_3.Et_2O$. This resulted in concomittant transthioketalization of the C3 carbonyl group. The thioketal 11 was then converted to the pentacyclic lactone 12 in several steps.

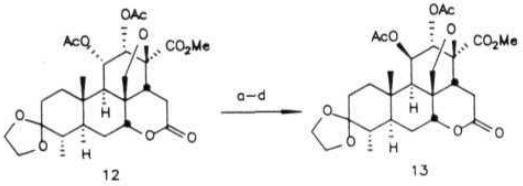


Py, THF, $NaHSO_3$; c) Ac_2O, DMAP, CH_2Cl_2; d) $(CH_2SH)_2$, BF_3Et_2O, CH_2Cl_2, 0°->rt.

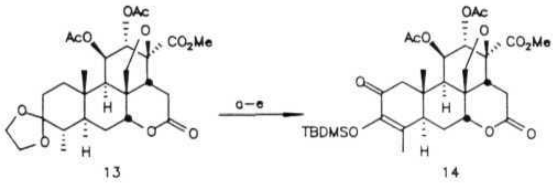


Reagents and conditions: *a) NBS, $CaCO_3$, H_2O-CH_3CN; b) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, -78°->rt; c) CrO_3, H_2SO_4, acetone d) CH_2N_2, Et_2O, EtOAc, 0°; e) $(CH_2OH)_2$, TsOH, C_6H_6, reflux; f) Zn-AcOH-THF (1:9), Py.*

Inversion of the hydroxy group at C11 in 12 was brought about by routine reactions. Functionalization of the A ring was



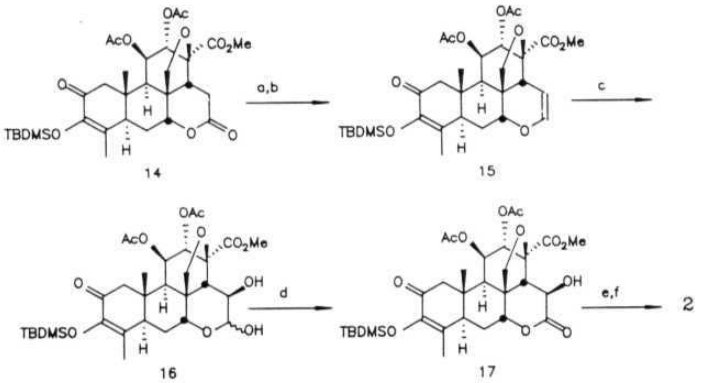
Reagents and conditions: *a) KOMe, MeOH; b) $(COCl)_2$, DMSO, (iPr)NEt, CH Cl , -78°->rt; c) nBu_4NBH, EtOAc, 0°; d) Ac_2O, DMAP, CH_2Cl_2.*



Reagents and conditions: *a) 2M HCl, THF; b) TMSOTf,* Et *N, CH_2Cl_2, -10° c) mCPBA, $NaHCO_3$, CH_2Cl_2; 2M HCl; d) Bi_2O_3, AcOH; e) TBDMSCl, imidazole, DMF.*

taken up next. This was accomplished in a 5 step sequence from lactone 13. Lactone 14 thus obtained was converted to the C15-C16 enol ether 15 by reducing the lactone carbonyl selectively with NaBH and dehydrating the lactol with POCl . This enol ether 15 was converted to α-hydroxy lactol 16 in one step by epoxidation with mCPBA and *in situ* ring opening of the reactive 15,16 epoxide

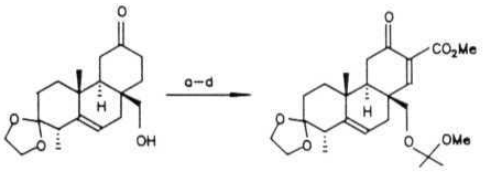
with water. The 3,4 epoxide was also obtained as an inseparable by-product in this reaction. The lactol 16 was oxidized with silver oxide to furnish the α-hydroxy lactone 17. Total synthesis of bruceantin was achieved by acylating the C15 hydroxyl group in 17 with 3,4-dimethyl-2- pentenoic acid and deacetylating the product, 11,12-di-O-acetyl- 3-O-(tert.butyldimethylsilyloxy)-bruceantin.



Reagents and conditions: *a) $NaBH_4$, EtOH, CH_2Cl_2, 0 ; b) $POCl_3$, Py, 100° c) mCPBA, $NaHCO_3$, CH_2Cl_2-H_2O; d) Ag_2O, CH_3CN, reflux; e) DCC, DMAP, $(Me)_2CH(Me)C=CHCOOH$, CH_2Cl_2; f) 3M H_2SO_4, MeOH (1:1), reflux.*

Grieco's synthesis starts from tricyclic ketone 18, which was recognized by many groups as the logical starting point for the synthesis of bruceantin ' . Compound 18 was trans-

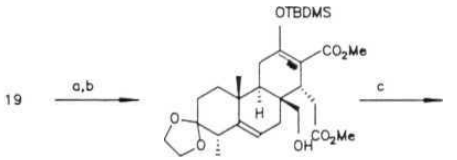
formed into an activated tricyclic α, β-unsaturated ketoester 19 by routine reactions.



18 19

Reagents and conditions: *a) 2-methoxypropene, PPTS,* 0 *b) NaH, $(MeO)_2CO$, MeOH(cat.), THF, reflux; c) NaH, PhSeCl, THF,* 0°; *d) mCPBA, THF,* -78°->0°.

β-Alkylation of the α,β-unsaturated ketoester 19 was achieved with excess of 1-methoxy-1-(tert-butyldimethylsilyloxy) ethylene at 40°in the presence of 1M LiClO -1,2-dimethoxyethane as promoter when other methods failed to give the desired results. This was followed by deprotection of the hydroxyl group to give 20. The C8 - C13 epoxymethano bridge was constructed based on a previous observation made in connection with quassinoid model studies . Thus, on bromination (NBS,THF,0) 20 gave bromosilylated hemiketal 21 which upon heating (DMF,collidine,130°) rearranged to 22. Introduction of the C11-C12 trans diaxial unit into ring C was accomplished in 9 steps starting from 22. This is shown in the accompanying scheme.



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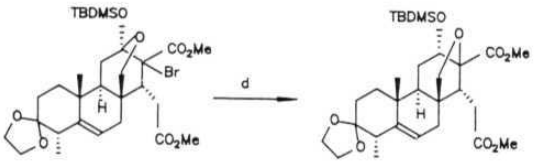
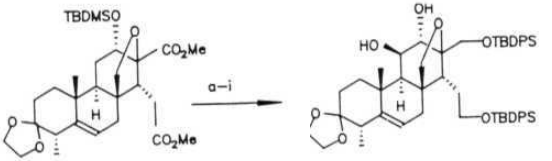


21 22

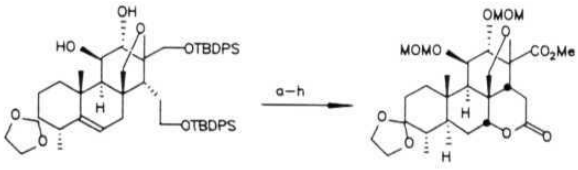
Reagents and conditions: *a) 1-methoxy-1-(tert.butyldimethyl-silyloxy) ethylene, 1M LiClO -1,2-dimethoxyethane, 40°; b) MeOH, PPTS, 0°; c) NBS. THF, 0° d) collidine, DMF, 130°.*



22 23

Reagents and conditions: *a) KF-MeOH; b) LAH, THF; c) TBDPSCl, imidazole, DMF; d) PCC, NaOAc, CH_2Cl_2, celite; e) $TsNHNH_2$, $MgSO$ THF; f) LDA, DIPA, THF, -78°->0°->rt g) OsO_4, Py, $NaHSO_3$; h) $(COCl)_2$, DMSO, CH_2Cl_2, -78° -> rt; i) $NaBH_4$, MeOH-THF.*

With all the C ring functionality in place, attention was focussed on the construction of the D ring 6 lactone, which was accomplished in several steps from 23 as outlined below.

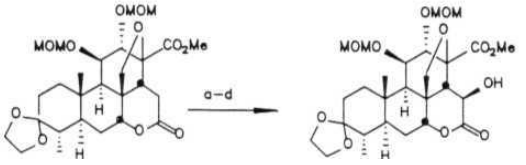


23 24

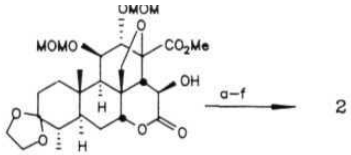
Reagents and conditions: *a) MOMCl, iPr NEt, (CH Cl) ; b) CrO . 3,5-dimethylpyrazole, -25°; c) Li, NH_3, t-BuOH, THF, -78°; d) 1.OM Superhydride, THF, -78°; e) n-Bu_4NF, THF; f) $(COCl)_2$, DMSO, Et_3N, -78°->rt; g)* Jones' *reagent,* 0°; *h)* CH_2N_2, Et_2O.

In the next stage of the synthesis, the C15 hydroxyl group was introduced into 24 by a) reduction of the lactone to lactol, b)dehydration with $POCl_3$ to dihydropyran, c) osmylation of the 15,16 double bond which took place from the desired β face, and d) oxidation with a periodinane reagent.

At this stage the tasks needed to be accomplished for the total synthesis of bruceantin are: a) acylation of the C15 hydroxyl group with 3,4-dimethyl-2-pentenoic acid b) introduction of the diosphenol unit into ring A and c) deprotection of the hydroxyl groups at C11 and C12. These were done in 6 steps from the pentacyclic lactone 25. Thus, the total synthesis of bruceantin was achieved.



Reagents and conditions: *a) $NaBH_4$, EtOH-CH_2Cl_2 (2:1); b) $POCl_3$, Py. 85°; c) OsO_4, Py, 0°, $NaHSO_3$; d) HBTBO, CH_2Cl_2.*

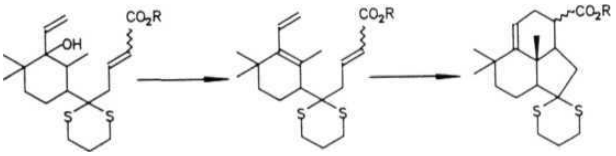


Reagents and conditions: *a) 1M HCl. THF, b) 3, 4-dimethyl-2-pentenoic acid, DCC, DMAP, THF; c) TMSOTf, Et_3N, CH_2Cl_2,-10°; d)*

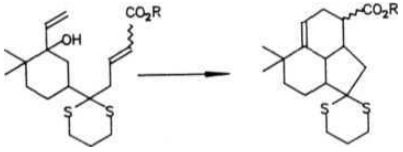
Other noteworthy efforts towards the pentacyclic skeleton of bruceantin are those by Kametani[3], Ganem[34], Ziegler and Fuchs. Recently, Fuchs and co-workers have published their work on the synthesis of **15-deoxy,16-ethoxy**

In our laboratory, we have been engaged in model studies towards the synthesis of quassinoids in general and

bruceantin in particular. In a study related to the model BCD ring system of quassinoids [38], tertiary alcohol 26 was synthesized as a precursor for an intramolecular Diels - Alder reaction. This compound, however, could not be converted to the tricyclic compound 28 in satisfactory yields. The tertiary alcohol 26 could not be dehydrated to the diene **27** under several conditions tried. Under drastic conditions, the tricyclic compound 28 was obtained in very low yields presumably via the diene 27. It was then believed that the methyl group at C2 was providing steric hindrance to the reaction as, the unmethylated compound underwent smooth intramolecular Diels - Alder reaction under dehydrating conditions.



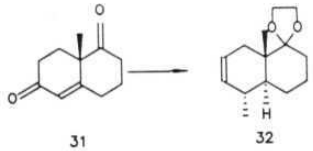
26 27 **28**



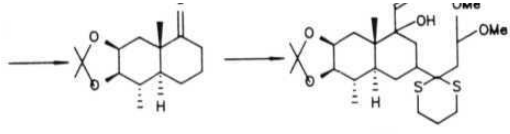
29 30

In another approach[39], a model AB ring system was constructed starting from the Wieland - Miesher ketone (31) in several steps which included stereoselective osmylation of the olefin 32. This is shown schematically below.

Compound 32 was transformed into 34 via the enone 33 in several steps. Meanwhile, difficulties surfaced in the dehydration of 26. Anticipating that a similar fate might befall the tertiary alcohol 34, further studies in this direction were not carried out.



31 32



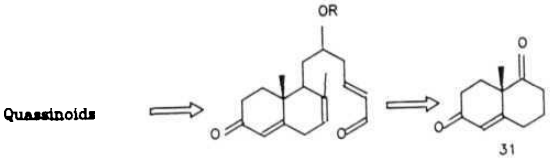
33 34

It was at this stage that we decided to synthesize a model system comprising the BCD rings and the results of this approach are presented in the next section.

Results and Discussion

Structures as complex as those of the quassinoids call for a carefully planned synthetic strategy. We planned a general strategy for the synthesis of quassinoids as there are only minor variations in the structures among the quassinoids. We chose bruceantin as our first target as this has the most promising biological activity and also because once the total synthesis of bruceantin is achieved, other simpler quassinoids could be readily synthesized following the same strategy.

Accordingly, we proposed a retrosynthetic scheme that employed an intramolecular hetero Diels - Alder reaction as the **key step,** to simultaneously set up the BCD ring systems. We planned to put the E ring last using the Barton reaction or one of its variants, as many quassinoids do not have the E ring. Further analysis of the structure led to the selection of Wieland - Miescher ketone as the appropriate starting material.



A brief discussion about the Diels - Alder reaction would be appropriate at this juncture. The Diels - Alder reaction, first discovered in 1928, has become one of the most important reactions for the construction of six membered rings. In this reaction, an olefin and a 1,3 diene undergo thermal

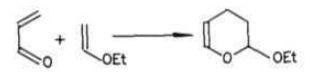
cycloaddition to give a six membered ring. In general, the reaction takes place readily, simply by mixing the components at room temperature or by heating in a suitable solvent, although in some cases drastic conditions have been used.

The rate of the Diels - Alder reaction is significantly altered by the presence of electron donating or withdrawing substituents on either the diene or dienophile[40]. Based on the substituent attached, the reaction can be classified as type I or the normal mode, in which the diene has electron donating groups and is therefore electron rich, and the olefin (also called the dienophile) has electron withdrawing groups and hence, electron deficient. In type II or the inverse mode, the diene is electron deficient and the dienophile electron rich. The essential feature, therefore, is that the two components have complementary electronic character.

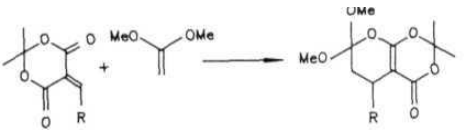
Frontier molecular orbital calculations reveal that for the type I reaction, HOMO-diene-LUMO-dienophile interactions are the most important. For the type II reactions, HOMO-dienophile - LUMO-diene energy separation is the dominating factor. These calculations also show that electron donating groups increase the energy level of the orbital concerned and electron withdrawing groups decrease it. The ease with which the reaction takes place

is determined by the HOMO-LUMO energy separation

For the normal mode reaction, electron donating groups increase the HOMO energy of the diene and electron withdrawing groups decrease the LUMO energy of the dienophile. In the case of the inverse electron demand reactions, favourable conditions can be created either by increasing the HOMO energy level of the dienophile by putting electron donating groups or by decreasing the LUMO energy level of the diene with electron withdrawing groups. Some typical examples of the inverse electron demand Diels - Alder reactions are given below [42,43,44]



ref-42



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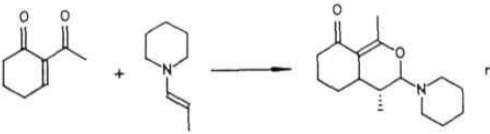
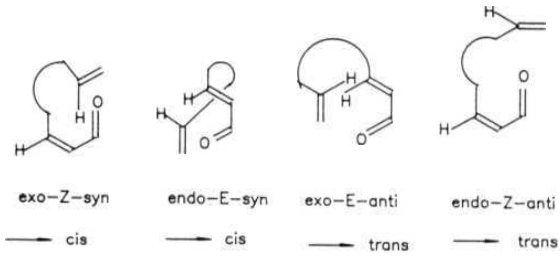


ref-44

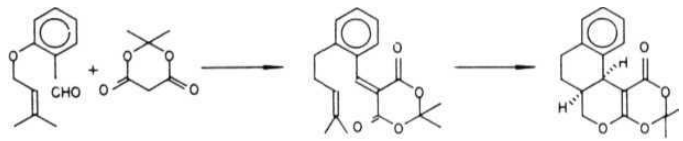
As is evident from the above examples, enol ethers, ketene acetals and enamines all react with α,β unsaturated carbonyl compounds to give dihydropyrans. In the intramolecular

version, both diene and the dienophile are in the same molecule thus forming **two** or **more** rings in one single operation.

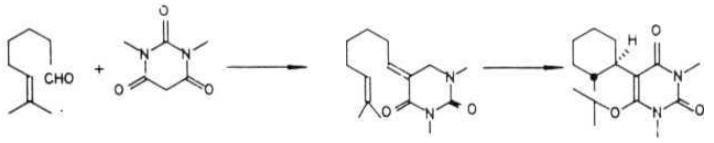
Tietze and coworkers in their work on tandem Knoevenegal - hetero Diels - Alder reactions[45], have rationalized the formation of different ring fusions by examining the four possible transition states that lead to products. These transition states are shown below.



They observed that aromatic aldehydes such as 35 gave cis cycloadducts via an endo-E-syn transition state.



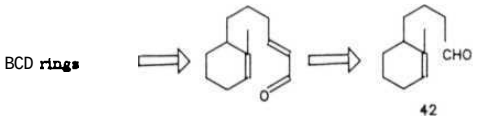
On the other hand, aliphatic ω-unsaturated aldehydes, **for example 37,** gave trans annelated products passing through **a** exo-E-anti transition state.



39 40 41

Based on the above observations, we anticipated that the hetero Diels - Alder reaction envisaged in the retrosynthetic analysis could give a trans fused product which would have to be epimerized to the desired cis stereomer during the course of the synthesis.

We thought it would be better to work on a model system before embarking on the total synthesis itself, and for this purpose, omitted the A ring. The retrosynthetic analysis for the model BCD rings is shown below. We envisaged a tandem Knoevenegal - hetero Diels - Alder reaction as key the step. This would furnish the BCD rings in one step.

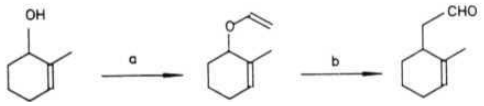


42

4-(2-methyl-2-cyclohexen-1-yl)-butyraldehyde 42 was arrived at as the suitable starting material. This aldehyde could, in principle, be transformed into a suitable Diels - Alder reaction substrate following Tietze's protocol . It has been

reported in the literature that α,β - unsaturated carbonyl compounds having an additional electron withdrawing group behave as excellent substrates for the hetero Diels - Alder reaction[43-45]. In the intramolecular version, the heterodiene moiety was appended to the ω - unsaturated aldehydes by a Knoevenegal reaction. In most cases, the condensation product underwent spontaneous Diels - Alder reaction to furnish the cycloadducts. This methodology has been advantageously used in the construction of cannabinoids by Tietze and coworkers

Our synthesis of aldehyde 42 began from 2-methyl-2-cyclohexen-1-ol (43)[47]. Alcohol 43 was converted to (2-methyl-2-cyclohexen-1-yl)-acetaldehyde (45) via the Claisen rearrangement of its enol ether 44 in excellent yields . Aldehyde 45 was

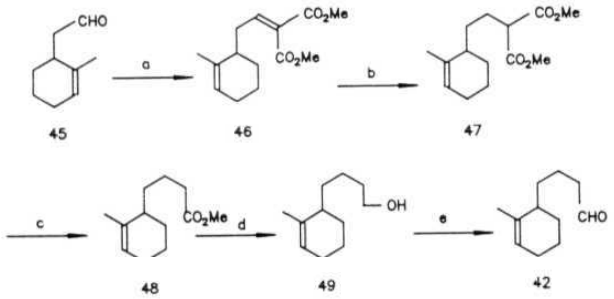


43 **44** **45**

reagents and conditions: *a) $Hg(OAc)_2$, ethyl vinyl ether, reflux; b) heat, 190-195°.*

homologated to aldehyde 42 by two different routes. In the first route, aldehyde 45 was subjected to a Knoevenegal condensation with dimethyl malonate in the presence of piperidine and acetic acid as catalysts. The reaction proceeded well giving the alkylidene malonate 46 in good yields (75-80%). The product was characterized from its IR and H NMR spectral data. In the IR spectrum, the carbonyl group absorption was observed at 1740 cm

and the characteristic aldehyde C-H absorption at 2750 cm^{-} of 45 was absent. In the H NMR spectrum, apart from other signals, a triplet at 7.0 ppm was seen. This was assigned to the (3 proton of the alkylidene malonate. The activated double bond in 46 was reduced with sodium borohydride to furnish the malonate 47, in very good yield. Compound 47 did not have 7.0 ppm signal in its H NMR spectrum. This indicated the absence of the activated double bond. A triplet at 3.32 ppm was attributed to the proton of the malonate group.

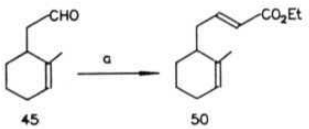


reagents and conditions: *a)* $CH_2(CO_2Me)_2$, *piperidine, AcOH,* C_6H_6 *reflux; b)* $NaBH_4$, *MeOH,* 0°; *c)* $NaCl$, H_2O-*DMSO, reflux, d)* $LiAlH_4$, *ether, 0°; e) PCC,* CH_2Cl_2, 0°.

Decarboxylation of 47 was effected following Krapcho's protocol[49] and a good yield of the butyrate 48 was obtained. Characterization of 48 was done based on its H NMR spectrum. The triplet at 3.32 ppm in the ^1H NMR spectrum of the starting

material was shifted upfield and now merged with other high field signals. The methoxyl signal now integrated only for three protons indicating loss of one methoxycarbonyl group. Next, ester 48 was transformed into aldehyde 42 in two steps by reduction with lithium aluminum hydride followed by oxidation of the resultant alcohol 49 with pyridinium chlorochromate to the aldehyde 42. The structural identity of 40 was readily established from its spectral data. The aldehydic proton resonated at 9.74 ppm and in the C nmr, the carbonyl carbon appeared at 207.8 ppm.

The second route to 42 had one step less. In this route, aldehyde 45 was homologated by a Wittig reaction. Surprisingly, 45 did not react efficiently with (carbethoxy methylene) triphenyl phosphorane. However, it underwent a clean Horner - Wadsworth - Emmons reaction with triethyl phosphonoacetate. Thus, when treated with triethyl phosphonoacetate and sodium hydride, aldehyde 45 furnished the α,β-unsaturated ester

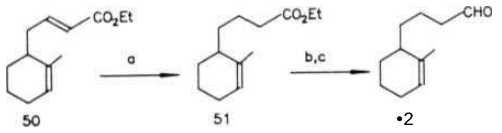


45 50

reagents and conditions: *a) triethylphosphonoacetate, NaH, ether, 0° -> reflux.*

50 in about 80% yield. Compound 50 was identified from its spectral characteristics. The C NMR spectrum has 13 lines of

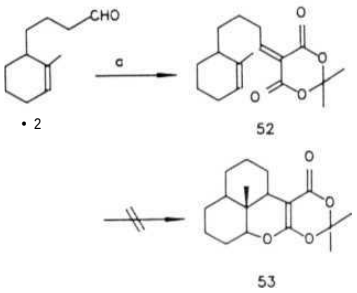
which 5 **are** in **the** 100 - 170 ppm region. The signal at 166.6 ppm was assigned to the carbonyl carbon and the other four lines to **the** olefinic carbons. The α hydrogen of the α,β - unsaturated ester was seen as a doublet at 5.84 ppm with a coupling constant of 16 Hz. This indicated that the double bond has the trans geometry. The β proton of the α,β - unsaturated ester was observed at 6.82 ppm and was consistent with its nature. Following the report by Narisada and co-workers on **the** selective reduction of a, β-unsaturated carbonyl compounds using sodium borohydride and cuprous chloride, we reduced the a,(3-unsaturated ester 50 to the saturated ester 51. Best yields were obtained when the solvents (MeOH, THF) were removed before work up. The compound was characterized from its spectral properties. The signals due to the protons of the activated double bond in 50 at 6.82 and 5.84 ppm were absent in the H NMR spectrum of 51. This compound was converted to aldehyde 42 as described above for 48.



reagents and conditions: *a) $NaBH_4$, CuCl, MeOH-THF (5:2), rt; b) LAH, ether,* 0°; *c) PCC, CH_2Cl_2,* 0°.

With the target aldehyde 42 available, we now **set out to perform the** crucial hetero Diels - Alder reaction following **the** conditions reported by Tietze and Kiedrowski . When treated

with Meldrum's acid (34), in the presence of ethylenediammonium diacetate, our aldehyde 42 furnished only the Knoevenegal product 52 and none of the cycloadduct 53. However, the yield of **52 was very** good (90-95%). The structure of 52 rests on its IR and H **NMR** data. In the IR spectrum, carbonyl groups in 52 showed absorptions at 1740 cm^{-} . The alkylidene proton showed up at 7.92 ppm in H NMR as expected for β olefinic proton on an electron deficient alkene. Also, it **was** observed that there was no signal corresponding to the aldehyde proton in the H NMR spectrum. Longer reaction times also gave only the condensation product, **with** no evidence for the formation of the hetero Diels-Alder reaction adduct.



• 2 52 53

reagents and conditions: *a) ethylenediammonium diacetate, CH_2Cl_2, rt.*

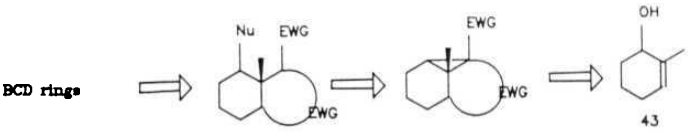
Proceeding on the assumption that the hetero Diels - Alder reaction may require a higher temperature, the condensation product was dissolved in benzene and heated at 140° in a sealed

tube for 3h. At this temperature also no cycloaddition was observed. At 160°, the material decomposed to many intractable products and no efforts were made to purify this mixture. Under classical Knoevenegal conditions employing piperidine and acetic acid, 42 and Meldrum's acid gave only a complex mixture. With the failure of these methods to yield the cycloadducts, further studies based on this strategy were not carried out.

It is not clear to us at the moment the reasons for the failure of this reaction. The present system is unique because both the diene and dienophile are cyclic systems linked by a carbon chain. One ring may sterically impede the approach of the other, creating unfavorable conditions for the reaction. In literature examples of this reaction, the dienophile component was always acyclic, though highly substituted double bonds have also been used. To the best of our knowledge, no cyclic olefin has been used as a dienophile in hetero Diel-Alder reaction. Since, cyclic olefins do not have the conformational flexibility of the acyclic ones this could be one of the reasons for the failure. In the present case, the methyl group on the cyclohexene ring could also be the cause of failure as past experience in our laboratory has indicated that highly substituted olefins were not good substrates for intramolecular Diels-Alder reactions ' The presence of the methyl group is essential for the construction of E ring in the later stages of the synthesis and it would be of very little use trying to experiment without the methyl group. Therefore, alternative approaches have to be found

by changing the diene moiety suitably.

With the failure of the intramolecular hetero Diels - Alder approach, an entirely different strategy was planned. The BCD rings were proposed to be constructed by intramolecular cyclopropanation of an appropriate substrate followed by ring opening of the cyclopropane with suitable nucleophiles. This is presented schematically below. This leads to 2-methyl-2-cyclohex-en-1-ol as the appropriate starting material. This would have to be esterified with a suitable acid to perform this sequence of reactions.



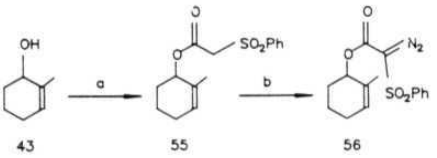
We elected to use cyclopropanes that are geminally substituted with two electron withdrawing groups for two reasons. i) the nucleophilic ring opening of the cyclopropane was expected to be facile with double activation and ii) further function-alization of the compound would be accomplished easily. It is known in the literature that cyclopropanes having geminal electron withdrawing groups undergo ring opening reaction in a homo - Michael 1,5 fashion with nucleophiles .

54

Different nucleophiles have been used to open electron deficient cyclopropanes and these include amines, mercaptans, enamines, cuprates and malonate anion. Except for organometallic nucleophiles, the reaction conditions for others are quite drastic. When there is double activation , the ring opening reaction is very facile and takes place under mild conditions. A high degree of stereoselectivity has been observed in these ring openings. This has been explained by invoking orbital interactions. It has been shown that the bond which is cleaved is the one best situated for simultanaeous overlap with both carbonyl groups

In order to experimentally test our strategy, we selected 2-methyl-2-cyclohexen-1-ol as the starting material. The necessary side chain was built by acylating this alcohol with phenylsulfonyl acetic acid. This furnished the phenylsulfonyl acetate 55 in good yields. 55 was characterized from its spectral data. The carbonyl group showed an absorption at 1720 cm in the IR spectrum and a singlet at 4.12 ppm in the H NMR spectrum was assigned to the active methylene group. It is to be noticed that compound 55 has two different electron withdrawing groups. This has two advantages. 1) This enables functional group differentiation between the two electron withdrawing groups and

2) sulfones can be removed, if necessary, under mild conditions during the course of the synthesis.



reagents and conditions: *a)* $PhSO_2CH_2CO_2H$, DCC, DMAP, CH_2Cl_2, 0°->rt. *b)* TsN_3, DBU, CH_2Cl_2, 0-5°.

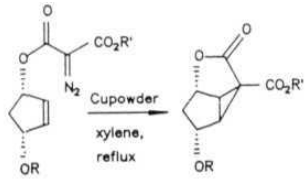
The active methylene group of 55 was converted into a diazo group following a procedure developed in our laboratory Thus, compound 55, when treated with tosyl azide and DBU in dichloromethane, underwent facile diazo group transfer giving rise to the diazo compound 56 in very good yields. The reaction product was identified from its spectral characteristics. A very strong IR absorption at 2150 cm indicated the presence of the diazo group and the carbonyl group absorption was seen at 1700 cm^{-} . Also, the 4.12 ppm signal in H NMR of 55 was absent.

The stage was now set for the decomposition of the diazo sulfone ester 56 and intramolecular capture of the resulting carbene by the alkene to give a doubly activated cyclopropane. No reaction was observed when 56 was heated in benzene at 130° for 5 min. At 150°, only a complex mixture was obtained. It is to be noted here that Kuwajima reported that diazosulfones when heated in n-decane, underwent decomposition to

give products, which were explained based on the formation of carbene and ketene intermediates. With the uncatalyzed thermolysis not being useful, we felt the need to use catalysts for the decomposition of 56. A search in the literature revealed that many transition metal salts and complexes catalyze the decomposition of diazo compounds

Of the many metals that catalyze the decomposition of diazo compounds, we used copper and its salts because they are cheap and readily available and are reported to give good yields. With Cu(acac) and at room temperature in benzene, no reaction was observed. At higher temperatures and with varying reaction times, only a complex mixture was obtained. No attempts were made to separate and identify the products.

During the course of his prostaglandin synthesis, Corey

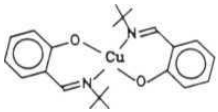


57 58

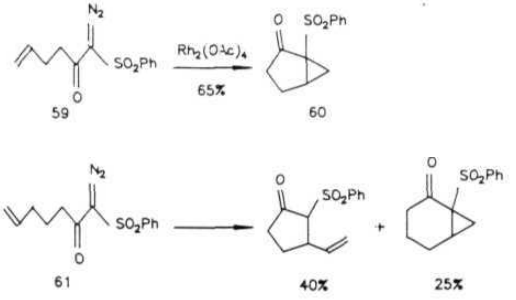
reported the use of copper powder for the decomposition of diazo compound 57 to the corresponding cyclopropane 58. Under similar conditions, when 56 was heated in chlorobenzene as the solvent, only an intractable mixture was obtained. The same was

the result when the decompostion was carried out in cyclohexane.

Later, in 1984, Corey reported another catalyst, bis (salicylaldiminato) copper(II) and he showed it to be a superior catalyst than copper powder for the decomposition of diazo compounds . We performed the experiment by adding a toluene solution of the diazo compound 56 over a period of 12h to a refluxing solution of this catalyst in toluene and obtained a mixture of products which also contained some starting material. Apart from the recovery of about 10% starting material, no other well defined products were isolable.



With copper and its salts failing to give any useful reaction, we turned our attention to the more expensive $Rh_2(OAc)_4$. This has been widely used in the decomposition of diazo carbonyl compounds [58]. Unfortunately, there was no decomposition of 56 at room temperature in ether. In refluxing chloroform, extensive decomposition of the diazo compound was observed. This is surprising in the light of observations made by Monteiro on the decomposition of 59. Good yields of cyclopropane 60 were obtained when 59 was treated with $Rh_2(OAc)_4$ in dichloromethane at room temperature



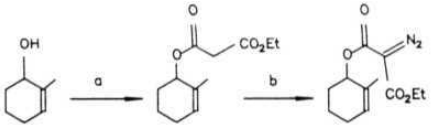
However, 61 gave allylic CH insertion as the major product along with minor amounts of the cyclopropane. The results of our decomposition experiments on 56 are collectively presented in the following table.

Table I

entry	conditions	result
1	0.05M C_6H_6;150°;	complex mixture
2	0.05M C_6H_6; 130°; 5min;	no reaction
3	0.05M C_6H_6; $Cu(acac)_2$;reflux, rt.	no reaction
4	0.056M C_6H_6M; $Cu(acac)_2$,reflux,8h	complex mixture
5	0.01M C_6H_6; $Cu(acac)_2$,reflux,5h	complex mixture
6	0.05M C_6H_{12};Cu powder, reflux	complex mixture
7	0.05M C_6H_5Cl;Cu powder;reflux90min	complex mixture
8	0.01M Corey's cat.;reflux 12h	complex mixture
9	0.01M ether; $Rh_2(OAc)_4$	no reaction
10	0.01M $CHCl_3$; $Rh_2(OAc)_4$; reflux	complex mixture

With the diazosulfone ester 56 failing completely to

meet our expectations, we chose to use a diazo malonate which has been used extensively for intramolecular cyclopropanation Therefore, we prepared the malonate ester 62 by acylating 2-methyl-2-cyclohexen-l-ol with the half ester of malonic acid Good yields of the ester 62 were obtained (77%) . Compound 62 showed a carbonyl absorption at 1720 cm in the IR spectrum. In the nmr spectrum, the active methylene protons were observed at 3.32 ppm. The diazo transfer reation of 62 proceeded uneventfully **and** in quantitative yields to provide 63. In the IR spectrum, compound 63 showed a very strong absorption at 2150 cm indicative of the presence of a diazo group. Now, we were ready for the cyclopropanation reaction. Thermolysis of 63 in benzene without any catalyst was not useful once again and an intractable mixture was the result.

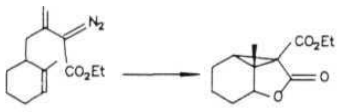


62 **63**

reagents and conditions: *a) EtO CCH CO H, DCC, DMAP, CHCl*, 0°-> *rt; b) TsN*$_3$, *DBU, CH*$_2$*Cl*, 0°.

We then followed Corey's conditions, and used copper powder as the promoter of cyclopropanation[52a]. To our relief, this provided the cyclopropane 64 in low yields (<40%) . However, **this** happiness was short lived as the yield of the product 64

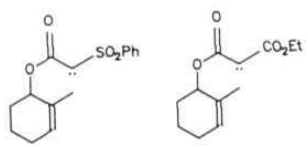
could not be improved in subsequent trials and was also non - reproducible, presumably due to the heterogeneity of the reaction



63 64

reagents and conditions: *a) Cu powder, xylene, reflux.*

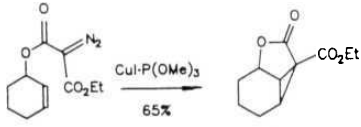
conditions. **When the** decomposition of 63 **was** carried out with $Rh_2(OAc)_4$ as the catalyst in chloroform at room temperature for 32h, (the time required for the complete disappearence of the starting material), no well defined product could be isolated. Further studies were not be carried out as the cyclopropanation could not be optimized.



65 66

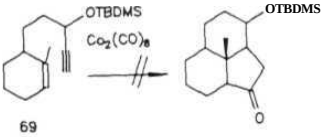
We hoped that the carbenes 65 and 66 generated by the decomposition of 56 and 63 would be more stable because of the electron withdrawing substituents attached to them and therefore more selective in their reactions than **alkyl** carbenes. It appears that these carbenes are also non-selective as evidenced by the **formation** of several products. We believe that the methyl group

on the double bond provides steric hindrance for the reaction to proceed in the case of these carbenes. With the methyl group blocking the approach of the carbene to the double bond and thus decreasing the rate of cyclopropanation, other side reactions become predominant, giving rise to a mixture of products. This argument finds support from the work of Ziegler, who reported that the diazomalonate 67 underwent intramolecular cyclopropanation in the presence of CuI.P(OMe) complex in 65%

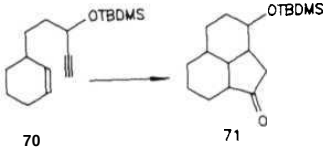


67 68

yield. Another reason to believe that the methyl group is probably the culprit is based on some findings in our laboratory. As it was pointed out in the introduction, alcohol 26 gave a very low yield of the cycloadduct 28 while its unmethylated counterpart gave good yields of the cycloadducts[38]. In another instance, compound 69 did not undergo intra- molecular Pauson - Khand reaction under several conditions tried, while its unmethylated counterpart 70 gave good yields of the cyclopentenone 71[39]. Further experiments have to be performed to hit upon the right set of conditions for the cyclopropanation reaction in synthe- tically useful yields with the vinylic methyl group intact.

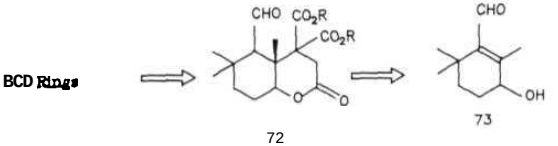


69



70 71

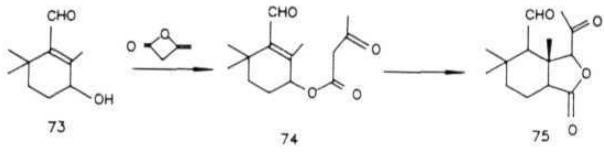
Once again, we had to revise our strategy for the construction of BCD rings. This time, we chose to use an intramolecular Michael reaction as the key step for the formation of the BD rings. The C ring was proposed to be formed later by alkylative cyclization on the aldehyde functionality. The retrosynthetic analysis on these lines is shown below.



72 73

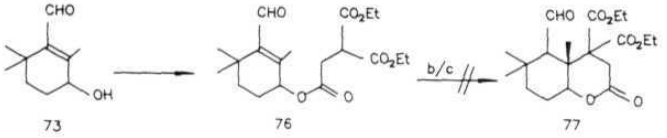
Li and Wu have applied the intramolecular Michael addition strategy for the synthesis of a forskolin intermediate . 3-Hydroxy-α-cyclocitral (73) when treated with diketene furnished an unstable product 74 which on reaction with sodium hydride in DMF underwent intramolecular Michael addition to produce 75 in 60% yield.

at.



73 74 75

We carried out preliminary studies using 3-hydroxy-α-cyclocitral as the starting material. We planned to use a side chain that would lead to six membered ring upon the Michael reaction. We chose 3-carbethoxysuccinic acid 4-ethyl ester as a suitable side chain. Thus, 73 on acylation with 3-carbethoxy succinic acid 4-ethyl ester gave 76 in 80% yield. It is to be noticed that this substrate would provide the D ring δ lactone moiety that lacks only the a hydroxy group, if the Michael reaction is successful. First, we attempted the Michael reaction under mild conditions employing DBU as the base at room temperature. However, no reaction was observed. Next, we used a stronger base sodium hydride and performed the reaction in a polar aprotic solvent DMF. Unfortunately, no reaction was observed in this case also. Probably the malonate anion was not nucleophilic enough to add to the α,β-unsaturated aldehyde to furnish the 5 lactone 77.



73 76 77

reagents **and** conditions: *a)* $(EtO_2C)CHCH_2CO_2H$, *DCC, DMAP,* CH_2Cl_2,

We **did** not pursue the synthesis of quassinoids further, in **the** light of all these failures.

Experimental

General techniques:

All reactions were conducted under nitrogen atmosphere unless otherwise mentioned. Reagents were transferred using standard septa-syringe techniques. All solvents were distilled **from** appropriate drying agents just before use. All the reagents **were** purified by appropriate methods before use. All the organic extracts after workup were dried using anhydrous magnesium sulfate, unless otherwise mentioned.

Solvents used for chromatography were of commercial grade and were fractionally distilled before use. Hexane refers to the petroleum fraction boiling between 60 - 70°. Column chromatography was performed using ACME 100 - 200 mesh silica gel using appropriate mixtures of hexane and ethyl acetate for elution. Analytical thin layer chromatography (tlc) was performed on home made plates using ACME silica gel GF254 grade containing 13% calcium sulfate as binder and were developed in appropriate solvent systems. Developed plates were visualized by shining ultraviolet light and/or by exposure to iodine vapours.

Infrared spectra were recorded on Perkin - Elmer infrared spectrophotometers models 1310 or 297. Solid samples **were** recorded as KBr wafers and liquid samples as thin films between NaCl plates. The spectra are calibrated against polystyrene absorption at 1601 cm . NMR spectra were recorded on a JEOL FX-100 fourier transform spectrometer operating at 23.5 Tesla magnetic field strength in chloroform - d as solvent with tetramethylsilane (TMS) as internal reference unless otherwise

mentioned. Chemical shifts are given downfield of tetramethylsilane in parts per million (ppm). Coupling constants are measured in Hertz. The multiplicity of the signals are denoted by the following symbols: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet and br = broad. Elemental analyses were performed on a Perkin - Elmer model 240C elemental analyzer.

2-Methyl-2-cyclohexen-1-ol vinyl ether (44):

To a stirred solution of mercuric acetate (11.2 g, 35.1 mmol) in ethyl vinyl ether (150 ml) was added a solution of 2-methyl-2-cyclohexen-l-ol (43) (5.0 g, 44.6 mmol) in ethyl vinyl ether (30 ml) and the solution was heated under reflux for 40h. The solution was concentrated, diluted with ether, washed with 5% aqueous potassium hydroxide (4x25 ml) and dried over anhydrous potassium carbonate. The residue after solvent evaporation was distilled under reduced pressure to yield the vinyl ether 44 as a colourless volatile liquid.

yield : 6.05g (98%)

b.p. : 60° (oil bath)/lmm/Hg.

IR (neat) : 2950, 1620, 1240, 1180, 1140, 1040, 920, 820 cm^{-1}.

(2-Methyl-2-cyclohexen-1-yl) acetaldehyde (45):

The vinyl ether 44 (6.0 g) was taken in a thick walled glass tube, sealed under nitrogen and maintained at 190-195° for 1h. The tube was cooled to room temperature and the contents were

distilled under reduced pressure to give pure 45 as a colourless volatile liquid.

yield : 5.6g (93%)

b.p. : 60° (oil bath)/1mm/Hg.

IR (neat) : 2900, 2800, 2750, 1720, 1440, 1020, 800 cm^{-1}.

Dimethyl 2-(2-methyl-2-cyclohexen-1-yl) ethylidene malonate (46):

A solution of 45 (303 mg, 2.2 mmol), dimethyl malonate (264 mg, 2.0 mmol), piperidine (7 mg, 0.08 mmol) and acetic acid (24 mg, 0.4 mmol) in benzene (2ml) was heated under reflux for 2h, cooled to room temperature, diluted with ether, washed several times with water and dried. The residue was purified by silica gel column chromatography. This furnished 46 as a colourless oil.

yield : 454 mg (82%) .

IR (Neat) : 2900, 1720, 1440, 1260, 1240, 1060 cm^{-1}.

^1H NMR : δ 1.20 - 2.60 (m, 12H), 3.80 (s, 3H, OCH_3), 3.84 (s, 3H, OCH_3), 5.40 (br, 1H, olefinic), 7.0 (t, J = 8 HZ, 1H, olefinic).

Dimethyl 2-(2-methyl-2-cyclohexen-1-yl)ethyl malonate (47):

To a stirred solution of the alkylidene malonate 46 (226 mg, 0.9 mmol) in methanol (1 ml) at 0° was added sodium borohydride (60 mg, 1.5 mmol)in portions and the reaction mixture was stirred at 0° for 90 min, diluted with water (5 ml) , acidifed to pH 1 with dilute hydrochloric acid and extracted several times

with ether. The organic layer was dried and concentrated to furnish the product 47 as an oil.

yield : 218 mg (95%)

IR (neat) : 2900, 2850, 1740, 1420, 1340 cm^{-} .

^{1}H NMR : & 1.20 - 2.12 (m, 14H) , 3.32 (t, J = 8HZ, 1H, C*H* $(COOMe)_2$), 3.72 (s, 6H, OCH_3), 5.40 (br, 1H, olefinic).

Methyl 4-(2-methyl-2-cyclohexen-1-yl)-butanoate (48):

The malonate ester 47 (190 mg, 0.75 mmol) was dissolved in dimethyl sulfoxide (1.5 ml) and water (13 μl) and sodium chloride (88 mg, 1.5 mmol) were added. The mixture was heated under reflux for 2h, cooled to room temperature, diluted with water (15 ml) and the solution extracted with ether (4x10 ml). The solution was concentrated, the residue was dissolved in hexanes (15 ml) and washed several times with water. The hexane solution was dried and concentrated to give the product 48 as an oil.

yield : 110 mg (74%)

IR (neat) : 2900, 2850, 1740, 1440, 1180cm^{-1}.

^{1}H NMR : δ 1.20 -2.40 (m, 16H) , 3.64 (s, 3H, OCH_3), 5.40 (br, 1H, olefinic).

4-(2-Methyl-2-cyclohexen-1-yl)-butan-1-ol (49):

To a stirred suspension of lithium aluminum hydride (100 mg, 2.5 mmol) in ether (2 ml) was added a solution of the

ester 48 (380 mg, 1.94 mmol) in ether (2 ml). The reaction mixture was stirred for 10h at room temperature, then cooled in ice and quenched with saturated aqueous sodium sulfate solution. The solids were filtered and washed several times with ethyl acetate. The filtrate was dried and concentrated. The residue was purified by chromatography.

yield : 307 mg (94%).

IR (neat) : 3340, 2920, 2840, 1450, 1060, 800 cm^{-1}.

^{1}H NMR : δ 0.80 - 2.08 (m, 16H), 3.64 (t, CH OH), 5.40 (br, 1H, olefinic).

^{13}C NMR : 19.65, 22.12, 23.41, 25.53, 27.30, 32.41, 33.00, 38.47, 62.70, 122.42, 137.30 ppm..

4-(2-Methyl-2-cyclohexen-1-yl)-butan-1-al (42):

A solution of the alcohol 49 (307 mg, 1.83 mmol) in dichloromethane (3 ml) was added to a stirred suspension of pyridinium chlorochromate (595 mg, 2.75 mmol) in dichloromethane (3 ml). After 1h, the reaction mixture was diluted with ether (20 ml) and filtered through a short column of fluorisil. The ether solution was concentrated to obtain the aldehyde 42.

yield : 207mg

IR (neat) : 2910, 2860, 2720, 1720, 1440, 800 cm^{-1}.

^{1}H NMR : δ 1.40 - 2.20 (m, 14H), 2.52 (m, 2H), 5.40 (m, 1H, olefinic), 9.74 (t, 1H, CHO).

^{13}C NMR : 15.53, 22.00, 21.35, 27.12, 32.00, 38.18, 44.06, 122.72, 134.59, 207.77 ppm.

Ethyl 4-(2-methyl-2-cyclohexen-1-yl) crotonate (50):

To a stirred suspension of sodium hydride (washed with hexanes to remove oil) (156 mg, 6.5 mmol) in dry ether (5 ml) at 0° was added triethyl phosphonoacetate (1.23 g, 5.5 mmol). After 15 min, aldehyde 42 (690 mg, 5 mmol) was added. The reaction mixture was stirred at 0° for 15 min and then heated under reflux for 15 min. The reaction mixture was cooled, quenched with water and extracted with ether (3x20 ml). The ether solution was dried and concentrated. The product was purified by column chromatography.

yield : 910 mg (88%).

IR (neat) : 2980, 2920, 2860, 1720, 1650, 1450, 1370, 1260, 1180, 1040, 800 cm^{-1}.

^1H NMR : 6 1.0 -2.20 (m, 15H), 3.20 (q, 2H, OCH_2CH_3), 5.40 (br, 1H, olefinic) 5.84 (d, J=16 Hz, 1H, H-2), 6.82 (m, 1H, H-3).

^{13}C NMR : 14.18, 15.41, 19.29, 22.00, 25.30, 27.53, 36.65, 60.06, 122.59, 123.77, 135.48, 148.42, 166.60 ppm.

Ethyl 4-(2-methyl-2-cyclohexen-1-yl) butanoate (51):

To a stirred solution of the unsaturated ester 50 (750 mg, 3.7 mmol) in 5:2 methanol-tetrahydrofuran (70 ml) was added cuprous chloride (527 mg, 5.32 mmol) and sodium borohydride (1.37 g, 36 mmol). After 30min, the solvent was removed under reduced pressure and the residue was taken up in water and extracted with ether (4x15 ml). The organic layer was dried, concentrated and

the residue was purified by chromatography.

yield : 500 rag (66%).

IR (neat) : 2950, 1740, 1440, 1380, 1160, 1040, 800 cm^{-1}.

^1H NMR : & 1.0 - 2.40 (m, 16H), 1.24 (t, 3H, CH_2CH_3), 4.12 (q, 2H, OCH_2CH_3), 5.40 (br, 1H, olefinic).

Condensation of aldehyde 42 with Meldrum's acid:

Ethylenediammonium diacetate (32 mg, 0.18 mmol) was added to a stirred solution of Meldrum's acid (52 mg, 0.36 mmol) in dichloromethane (0.4 ml). After 5min, a solution of the aldehyde 42 (60 mg, 0.36 mmol) in dichloromethane (0.4 ml) was added. After 15 min, the reaction mixture was diluted with dichloromethane (5 ml), washed with water (2x5 ml) and dried. The condensation product was obtained on evaporating the solvent.

yield : 97mg (92%)

IR (neat) : 3000, 2920, 2860, 1740, 1630, 1450, 1400, 1380, 1280, 1210, 810, 740 cm^{-1}.

^1H NMR : S 1.20 - 2.04 (m, 14H), 3.0 (br, 2H), 5.40 (br, 1H, olefinic), 7.92 (t, J=8Hz, 1H, olefinic).

Attempted Diels - Alder reaction of 52:

trial 1:

A solution of the compound 52 (20 mg, 0.07 mmol) in benzene (1 ml) was heated in a sealed tube at 140° for 3h. The reaction mixture was cooled to room temperature and the sovlent evaporated. Tlc of the reaction mixture showed the presence of

mainly the starting material. The material recovery was 17 mg.

trial 2:

A solution of the compound 52 (70 mg, 0.24 mmol) in toluene (2 ml) was heated in a sealed tube at 160° for 2h. The reaction mixture was cooled, solvent evaporated and the residue analyzed by tlc. Tlc of this mixture was very complex. No attempts were made to purify this mixture.

Attempted tandem Knoevenegal - hetero Diels - Alder reaction of aldehyde 42 :

The reaction mixture containing aldehyde 42 (23 mg, 0.14 mmol), Meldrum's acid (20 mg, 0.14 mmol), piperidine (1 drop) and acetic acid (1 drop) in benzene (0.5 ml) was heated under reflux for 2h. Tlc analysis of the reaction mixture at this stage showed the presence of a complex mixture. No attempts were made to isolate the products.

2-Methyl-2-cyclohexen-1-yl phenylsulfonylacetate (55):

To a stirred solution of 2-methyl-2-cyclohexen-l-ol (43) (336 mg, 3 mmol) in dichloromethane (20 ml) at 0° was added sequentially phenylsulfonylacetic acid (900 mg, 4.5 mmol), DCC (927 mg, 4.5 mmol) and 4-dimethylaminopyridine (37 mg, 0.3 mmol). The reaction mixture was stirred overnight at room temperature. It was then poured into water (25 ml), layers separated and the aqueous phase extracted with dichloromethane (3x20 ml). The

combined organic layers were washed with aqueous sodium bicarbonate solution and dried. The residue after solvent evaporation was purified by silica gel column chromatography.

yield : 747 mg (85%)

IR (neat) : 2900, 1720, 1440, 1380, 1320, 1280, 1100, 1080, 980, 920, 800, 720, 680 cm^{-1}.

^{1}H NMR : δ 1.20 - 2.08 (m, 9H), 4.12 (s, 2H, CH_2SO_2Ph), 5.20 (m,OCH), 5.64 (m, 1H, olefinic), 7.44 - 8.0 (m, 5H, Ar).

^{13}C NMR : 17.70, 20.29, 24.82, 28.35, 60.94, 73.06, 128.41, 128.89, 129.18, 130.48, 134.18, 138.89, 162.24 ppm.

Elemental analysis:

Calculated for $C_{15}H_{18}O_4S$: C = 61.20, H: 6.16.

Found : C = 61.18, H: 6.13.

The diazo transfer reaction:

To a stirred solution of the sulfone ester 55 (320 mg, 1.0 mmol) in dichloromethane (1.5 ml) at 0-5 , was added DBU (228 mg, 1.5 mmol) followed by dropwise addition of a solution of tosyl azide (197 mg, 1 mmol) in dichloromethane (1 ml). After 15min, the reaction mixture was diluted with dichloromethane, washed with 5% aqueous HC1 (3x5 ml), dried and concentrated. The residue was purified by silica gel column chromatography to furnish the diazo compound 56 as a pale yellow oil.

yield : 275mg (79%)

IR (neat) : 2900, 2150, 1700, 1440, 1340, 1280, 1140, 1100, 960,

900, 740, 600 cm^{-1}.

^1H NMR : δ 0.60 - 2.0 (m, 9H), 5.20 (m, 1H, OCH), 5.64 (m, 1H, olefinic), 7.60 - 8.0 (m, 5H, Ar).

Elemental analysis:

Calcd for $C_{\quad H \quad N \quad O_4S}$: C = 56.23, H - 5.03, N = 8.76.

Found : C - 56.22, H = 4.99, N = 8.71.

Decomposition experiments on the diazo compound 56:

All solvents used in these experiments were dried using appropriate drying agents and were degassed by bubbling nitrogen through them.

1. Thermolysis in benzene:

A solution of the diazo compound 56 (56 mg, 0.18 mmol) in benzene (3 ml) was heated at 150° in a sealed tube for 2h. The reaction mixture was cooled and analyzed by tlc. A complex tlc pattern was observed. No attempts were made to separate and identify the individual components.

2. A solution of the diazo compound 56 (50 mg, 0.16 mmol) in benzene (3 ml) was heated in a sealed tube at 130° for 5 min. The cooled reaction mixture was analyzed by tlc. Only the starting material was seen. No other products were observed.

Decompositions in the presence of $Cu(acac)_2$:

3. The benzene solution (2 ml) of 56 (35 mg, 0.11 mmol) and $Cu(acac)_2$ (4 mg) was stirred at room temperature for 10h.

Tlc of the reaction mixture at the end of this period showed only the starting material. Thus, no reaction was observed under these conditions.

4. A solution of 56 (447 mg, 1.29 mmol) and Cu(acac) (45 mg) in benzene (25 ml) was heated under reflux for 8h. Only a complex mixture was seen on the tlc plate. Therefore, no attempts were made to analyze the products.

5. A 0.01M solution of 56 (30 mg, 0.09 mmol) and Cu(acac) (3 mg) in benzene was heated under reflux for 5h. At this stage the tlc indicated the absence of the starting material. However, several other spots were also seen making the separation difficult. No characterizable product was isolated from this mixture.

Decomposition experiments with copper powder:

6. A solution of 56 (100 mg, 0.31 mmol) in chlorobenzene (7 ml) was heated at 160° in the presence of copper powder (electrolytic grade, 992 mg, 15.5 mmol) in a sealed tube for 90 min. The cooled reaction mixture was analyzed by tlc. A complex mixture was noticed. However, no attempts were made to separate and identify the components of the mixture.

7. A solution of the diazo compound 56 (115 mg, 0.36 mmol) in cyclohexane (0.5 ml) was slowly added to a refluxing

slurry of copper powder (0.912 g, 14.4 mmol) in cyclohexane (6 ml). Heating was continued for 6h and the reaction mixture was cooled, filtered and concentrated. Tlc of the reaction mixture revealed many spots which could not be separated.

Decomposition experiment with Corey's catalyst:

8. To a refluxing solution of bis (tert-butyl-salicylaldiminato) copper(II) (3 mg) in toluene (5 ml) was added a solution of 56 (45 mg, 0.14 mmol) in toluene (4 ml) over a period of 12h. The reaction mixture was allowed to cool to room temperature. The solvent was evaporated under reduced pressure and the residue was chromatographed on a silica gel column. The only isolable material was the starting diazo compound in 8% yield.

Experiments with rhodium acetate as catalyst for **cyclopropanation:**

9. A 0.01M solution of 56 (100 mg, 0.31 mmol) and rhodium acetate (2 mg) in ether was stirred at room temperature for 24h. No reaction was observed as indicated by tlc analysis.

10. To a refluxing solution of rhodium acetate (2 mg, 0.0033 mmol) in alcohol free chloroform (1 ml) was added a solution of the diazo compound 56 (107 mg, 0.33 mmol) in chloroform (2 ml) over a period of 5 min. Heating was continued for 48h. At this stage tlc indicated the presence of starting material along with many other products.

Ethyl **2-methyl-2-cyclohexen-1-yl malonate** (62):

To a stirred solution of 2-methyl-2-cyclohexen-1-ol (45) (112 mg, 1.0 mmol) in dichloromethane (1 ml) at 0° was added a solution of monoethyl malonate (198 mg, 1.5 mmol) in dichloromethane (1 ml) followed by DCC (309 mg, 1.5 mmol) and 4-dimethylaminopyridine (12 mg, 0.1 mmol). After stirring overnight at room temperature, the reaction mixture was worked up as described for 55.

yield : 173 mg (77%)

IR (neat) : 2900, 1720, 1300, 1160, 1040, 1000, 940 cm^{-1}.

^1H NMR : δ 1.28 (t, 3H, CH_2CH_3), 1.40 - 2.08 (m, 9H), 3.32 (s, 2H, CH_2COOEt), 4.20 (g, 2H, OCH_2CH_3), 5.20 (m, 1H, OCH), 5.64 (m, 1H, olefinic).

Diazo transfer reaction of 62:

The diazo transfer reaction of 62 was conducted as described for 55 to provide the diazomalonate 63.

yield : 100%

IR (neat) : 2950, 2150, 1760, 1720, 1680, 1380, 1300, 1260, 1100, 920, 760 cm^{-1}.

Cyclopropanation experiments of 63:

1. With copper powder :

To a boiling suspension of copper powder (500 mg, 7.8 mmol) in xylene (1 ml) was addded a solution of the diazomalonate 63 (50 mg, 0.2 mmol) in xylene (1 ml). The reaction mixture was

heated under reflux for 6h, cooled and filtered. The filtrate was concentrated and chromatographed on a silica gel column. The only isolable product was that of the cyclopropane 64.

yield : 17 mg (39%)

IR (neat) : 2950, 1740, 1440, 1240, 1060, 720 cm^{-1}.

^1H NMR : 5 0.40 - 2.40 (m, 13H), 4.24 (q, 2H, OCH_2CH_3), 4.60 (br s, 1H, OCH).

2. With $Cu(acac)_2$:

A solution consisting of the diazo compound 63 (40 mg, 0.16 mmol), Cu(acac) (4 mg) in benzene (2 ml) was heated in a sealed tube for 30 min. The cooled reaction mixture was filtered and concentrated. Tlc of this revealed an intractable mixture. Therefore no purification was attempted.

3. With rhodium acetate:

To a stirring solution of 63 (33 mg, 0.13 mmol) in alcohol free chloroform (1 ml) at room temperature was added rhodium acetate (2 mg) and the mixture was stirred for 32h, by which time the starting material was completely consumed. The reaction mixture was concentrated and analyzed by tlc. A complex mixture was seen.

Esterification of **3-hydroxy-α-cyclocitral** (73) with 3-carbetheoxy succinic acid **4-ethyl** ester.

To a stirred solution of the alcohol 73 (100 mg, 0.6

mmol) in dichloromethane (2 ml) at 0° was added dropwise a solution of 3-carbethoxysuccinic acid 4-ethyl ester (195 mg, 0.9 mmol) followed by DCC (184 mg, 0.9 mmol) and 4-dimethyl-aminopyridine (7 mg, 0.06 mmol). The resulting mixture was stirred overnight at room temperature. Water (5 ml) was added, layers separated and the aqueous layer extracted with hexanes (3x10 ml). The organic extracts were combined, dried and concentrated. The product was purified by chromatography to furnish 76 as an oil.

yield : 180 mg (82%)

IR (neat) : 3000, 2950, 2800, 1720, 1700, 1440, 1380, 1280, 1180, 1040, 860, 740 cm^{-1}.

Attempted Michael reactions of 76:

1. With DBU:

The substrate 76 (100 mg, 0.27 mmol) in benzene (1.5 ml) was treated with DBU (2 drops) and stirred at room temperature for 24h. No reaction was noticeable by tlc analysis.

2. With sodium hydride:

A solution of the substrate 76 (72 mg, 0.2 mmol) in dimethylformamide (0.5 ml) was added to an oil free suspension of sodium hydride (6 mg, 0.25 mmol) in dimethylformamide (0.5 ml) at room temperature. The reaction was monitored by tlc and no observable change was noticed even after 24h.

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Chapter II

Some Reactions of Unsaturated Sugars

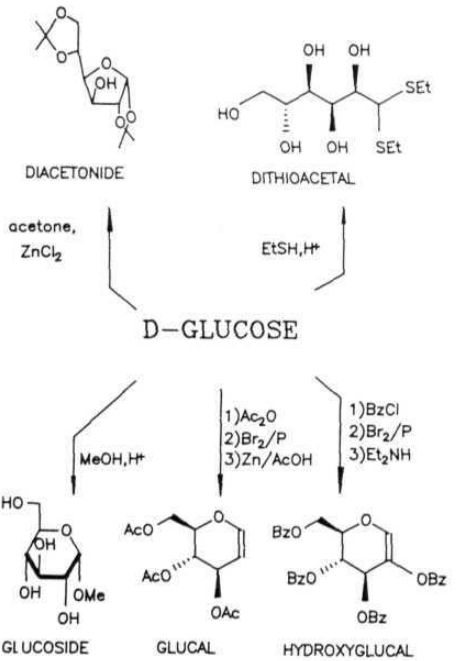
Introduction

Carbohydrates are one of the most important classes of naturally occurring compounds. Their importance in our lives cannot be over emphasized. Despite having such an exalted position in Nature, carbohydrates have not received much attention from mainstream organic chemists until recently. This negligence is surprising because our understanding of the relevance of conformation and stereoelectronic effects on chemical reactivity was derived from studying the reactions of carbohydrates. Additionally, the pioneering work of Lemieux in applying nmr as a tool for the structure elucidation of carbohydrates led to a better understanding of the interpretive power of nmr spectroscopy.

Due to the pioneering efforts of many distinguished carbohydrate chemists, sugars are now recognized as valuable starting materials. In sugars one finds a wealth of attributes that fulfill the requirements sought by organic chemist in the quest for conquering enantiomerically pure synthetic targets . Many of the total syntheses that have been achieved using carbohydrates as starting materials have been expertly summarized by Hanessian .

Carbohydrates are a cheap and replenishable source of chiral compounds, available in a variety of cyclic and acyclic forms, chain lengths and oxidation states. They are endowed with a plethora of functional, stereochemical and conformational features that are not matched by other classes of compounds. These features also ensure a fair degree of regio- and stereo

control in bond forming reactions. With carbohydrates as starting materials, one has the option of using a cyclic or acyclic carbon atom framework consisting of 3-7 carbon atoms, to modify either extremity and create or destroy chiral centres at will by chemical manipulation of existing functionality. The chemcial diversity of carbohydrates is illustrated below by taking D-glucose as an example.



On the industrial front, carbohydrates are being

recognized as valuable organic raw materials . The production of ethanol by fermentation of sucrose is well known. This process is gaining importance as ethanol is an efficient alternative to petroleum based fuels whose availability is on the decline. Sucrose based building blocks are being used as intermediates for the production of new surfactants and polymers. Also, fatty acid esters of sucrose, known as sucrose polyesters, have emerged as potential non-adsorbable substitutes for fats and oils in food. The biotransformation of D-glucose to aromatics and adipic acid, reported by Frost and coworkers is a notable achievement because they are basic feedstocks for chemical industry. This biocatalytic process is environment friendly and involves the use of non-toxic and renewable raw materils.

Modern carbohydrate chemistry deals extensively with the development of synthetic methods for the preparation of optically active compounds. This area of research has been necesitated by the discovery of several complex naturally occurring compounds.Many of them contain modified sugar units with more than the traditionally encountered 5 or 6 carbon atoms and some of them also have chain branching like in hikizimycin and calditol . In synthesizing these complex natural products, one finds that the normal or conventional sugars are not useful as these are devoid of functional groups like double bonds and carbonyl groups about which most of the organic transformations revolve. Therefore the study of unsaturated sugars becomes important.

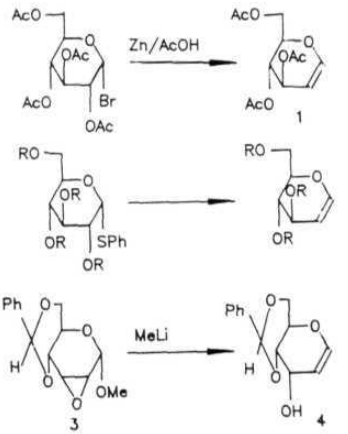
Introduction of specific carbonyl or olefinic unsaturation needs careful synthetic planning. As the hydroxyl groups in a sugar framework are of similar reactivity, this demands protecting groups capable of distinguishing the subtle reactivity differences among the hydroxyl groups. Fortunately, earlier generation of carbohydrate chemists have done wonderful work on the chemistry of protecting groups. This legacy, combined with the availability of modern synthetic reagents capable of effecting transformations under mild conditions, has led to new and exciting discoveries in the area of unsaturated sugars.

Several unsaturated sugars are known in the literature, containing double bonds almost anywhere in the chain or ring. Of all these sugars, the 1,2 and 2,3 unsaturated sugars are the most common ones, because of their easy accessibility. Since this part of the thesis deals with the reaction of unsaturated sugars, a discussion of some recent and important methods for their preparation follows.

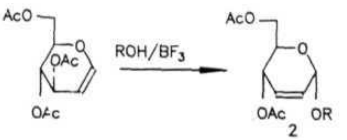
Historically, the first reported unsaturated sugar was 3,4,6-tri-O-acetyl-D-glucal (1). This was accidentally prepared by the legendary Emil Fischer. He named it glucal, having been misled by the positive fuchsin SO test on the crude material. However, this wrong nomenclature continues even today and all 1,2 unsaturated sugars go by the trivial name of glycal. The systematic nomenclature, however, is 1,5-anhydro-2-deoxy- alken-1-enitol.

Many methods of glycal synthesis are available, but the

one reported by Fischer is still the best method . In the Fischer method, a peracetylated glycosyl halide is treated with zinc dust in acetic acid to eliminate the halide and the adjacent acetate to furnish a glycal. A major disadvantage of the Fischer method is the instability of glycosyl halides and some of them are too unstable to be isolated. Several variations of this method have been proposed and have met with success in the synthesis of glycals.



Sinay and coworkers reported that reductive elimination of phenylthio glycosides leads to glycal formation . Base induced rearrangement of 2,3-anhydrosugars also produces glycals .

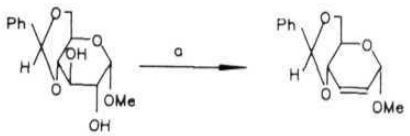


The 2,3-unsaturated sugars have been synthesized by several different methods. The easiest of them is by the Ferrier rearrangement of glycals[9].

2,3-Unsaturated sugars are also produced by 1) elimination of 2,3 hydroxyl groups or their derivatives, 2) base catalyzed elimination of deoxy sugars. These are discussed in the following paragraphs.

1. **Direct elimination** of a 2,3 **diol:**

In this method the diol is treated with a phosphine, an iodinating agent and imidazole in a solvent like toluene under reflux conditions. Good yields of unsaturated sugars have been reported.

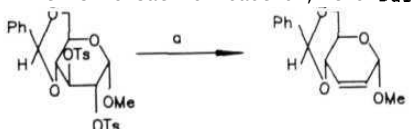


Reagents and conditions: *a) PPh , imidazole,* X. *[X = iodine, triiodoimidazole or iodoform]*

The iodinating agents that have been used are iodine , triiodoimidazole and iodoform

2. The Tipson - Cohen reaction:

In this versatile reaction, the sulfonate ester of a

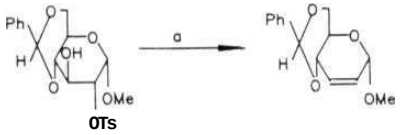


Reagents and conditions: *a) NaI, Zn dust, DMF retlux.*

vicinal diol is treated with sodium iodide and zinc dust in boiling DMF[13].

Moderate to good yields of olefins have been obtained in this reaction. Variations in this procedure involve the use of zinc - copper couple and potassium iodide[14] rather than sodium iodide and zinc.

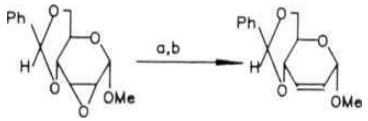
Vicinal diol mono tosylates can also be converted to olefins under slightly modified Tipson - Cohen conditions



Reagents and conditions: *a) Zn-Cu, NaI, DME - DMF,130°*

3. **From** anhydrosugars:

In a procedure developed by Lemieux , the anhydrosugar 3 was first converted to an iodohydrin and then treated with p-toluenesulfonic acid in pyridine to give the olefin 4.

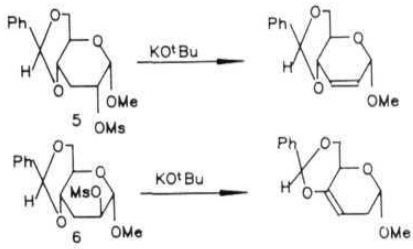


Reagents and conditions: *a) NaI, NaOAc, acetic acid, acetone, reflux; b) TsOH, Py, heat.*

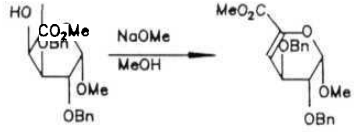
Several unsaturated sugars have been prepared by this procedure.

4. By elimination of HX from deoxy sugars:

When sulfonates of deoxy sugars are treated with strong bases, elimination of the sulfonyloxy group takes place and unsaturated sugars are formed. Epimeric sulfonates such as 5 and 6 give different olefins



Many of the 4,5-unsaturated sugars have been prepared from hexuronates[18]. The following example illustrates this reaction.



The reactions of unsaturated sugars have been extensively reviewed by Ferrier and in 1965 and 1969[19]. The coverage given here is to reactions of more recent vintage. Emphasis has been laid on the chemistry of glycals and 2,3-unsaturated sugars because of their ready availability. Several of the general reactions that give rise to routine or

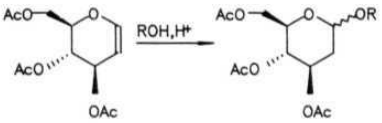
expected products have been omitted.

Electrophilic addition reactions of **glycals:**

Glycals display some unusual chemical properties which **are not observed** with other unsaturated sugars. The chemistry of the glycal double bond is dominated by the presence of the adjacent oxygen atom. The pyranoid oxygen atom makes this double bond electron rich and most of its reactions are therefore electrophilic in nature.

From the above canonical structures it can be seen that the (3 carbon has excess electron density and hence electrophiles attack this carbon exclusively. Several electrophiles have been added to glycals and some of the more interesting ones are discussed below.

In the presence of protic acids, alcohols and phenols add across the glycal double bond to give **2-deoxyglycosides.** Many catalysts have been used and these include strongly acidic ones like mineral acids[19] to the very mildly acidic triphenyl-phosphonium bromide . Heterogeneous catalysts like ion exchange resins have also been employed . Many different alcohols including sugar alcohols have been used and excellent yields of

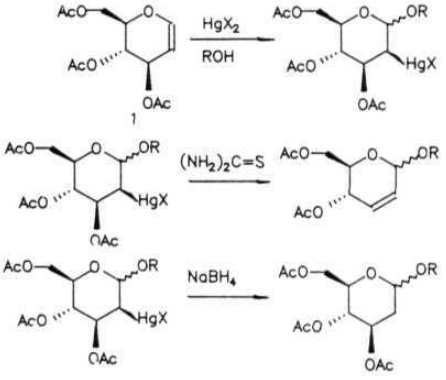


glycosides are obtained. When a sugar alcohol is used as a nucleophile, deoxy oligosaccharides are formed.

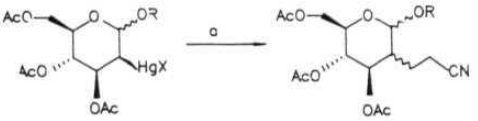
In many cases, the a anomer predominates in the product mixture. References 20 and 21 summarize the methods available for 2-deoxyglycoside synthesis.

Some of the other electrophiles used in this reaction are mercuric salts, electrophilic halogen reagents like N-haloamides/imides, and phenylselenenyl halides.

Mercuric salts (especially mercuric acetate and trifluoroacetate) give 2-deoxy-2-mercurio sugars which are very versatile compounds . These organomercury compounds when treated with thiourea undergo elimination to give unsaturated sugars.

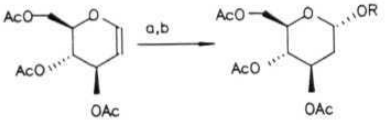


Reductive demercuration with sodium borohydride gives 2-deoxy-sugars in high yields. When this reaction is conducted in the presence of suitable olefins, C2 branched sugars are obtained[23]

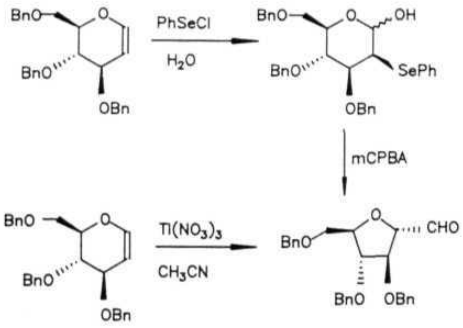


Reagents and conditions: *a)NaBH or Ph SnH, acrylonitrile, MeOH.*

2-Deoxysugars have also been synthesized by adding phenylselenenyl chloride to glycals in the presence of alcohols followed by reductive removal of the phenylselenenyl group



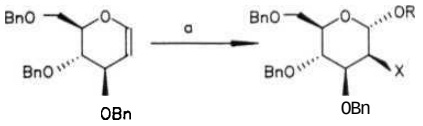
Reagents and conditions: *a) PhSeCl, collidine, ROH; b) Ph SnH, toluene, heat.*



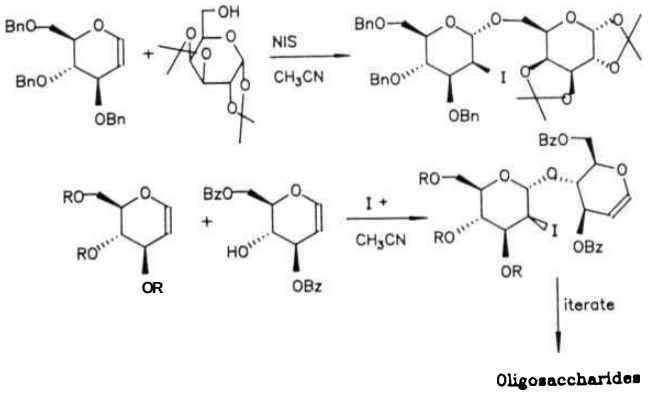
On **the** other hand, ring contraction was observed when

the phenylseleno sugar was oxidized with MCPBA . This reaction provides a very convenient method for the synthesis of chiral tetrahydrofurans. It important to note that all the carbon atoms of the thus produced tetrahydrofuran are chiral. Ring contraction of glycals are also observed when they are treated with thallium (III) nitrate in acetonitrile

Addition of electrophilic halogen reagents in the presence of nucleophiles produces 2-deoxy-2-halosugars . These halosugars on reductive removal of halogens provide 2-deoxy glycosides[28], which are important constituents of many antibiotics.



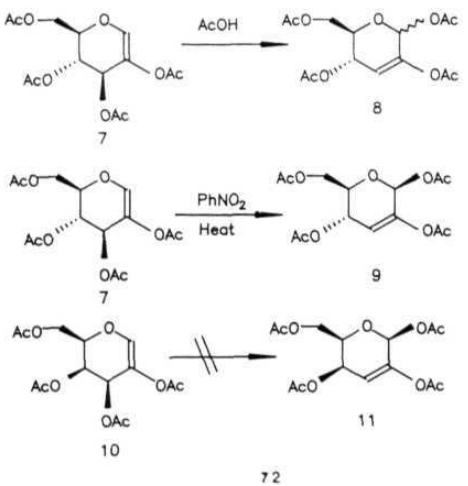
Reagents and conditions: *a) NXS (NIS or NBS), ROH.*



Danishefsky has used this methodology for the synthesis of oligosaccharides. He directed the growth of the sugar chain by choosing partially protected glycal esters as glycosyl acceptors and glycal ethers are glycosyl donors. Because of the presence of esters the corresponding glycal becomes electron deficient compared to the glycal ether and the added electrophile selectively attacks the more electron rich double bond

Rearragement reactions:

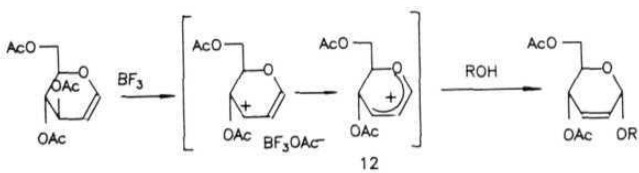
In his experiments with hydroxyglycals, Ferrier found that when 7 was heated in acetic acid, 8 was produced as an anomeric mixture in very good yields. Subsequent experiments revealed that 7 when heated in an inert solvent like nitrobenzene, produced the (3 anomer 9 exclusively. Anomerization was found to be very slow under these conditions.



It was also found that tetraacetyl-D-galactal (10) did not undergo this reaction under identical conditions. This difference in reactivity was explained by invoking participation of the trans C-4 acetoxy group in the rearrangement of 7

The Ferrier Rearrangement:

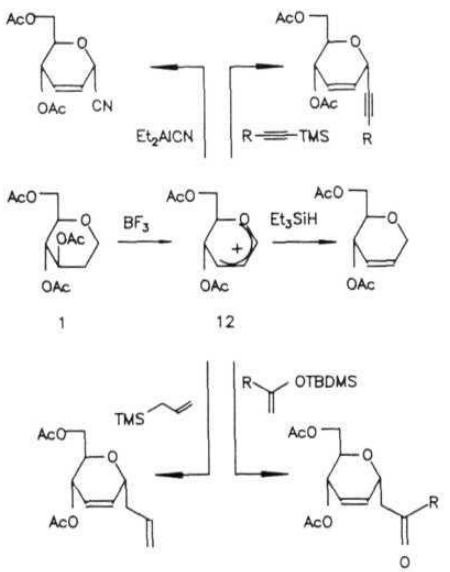
In the presence of Lewis acids, the reaction of glycals with alcohols takes an entirely different course. It was observed that when triacetyl glucal was treated with Lewis acids like BF .Et_O in an inert solvent like benzene in the presence of nucleophilic solvents like alcohols, rearrangement of the double bond took place with concomittant loss of one acetoxy group and addition of the nucleophile. This resulted in the formation a 2,3-unsaturated sugar . This reaction has been studied in detail by Ferrier and the following mechanism involving the four centre cation 12 is now widely accepted



12

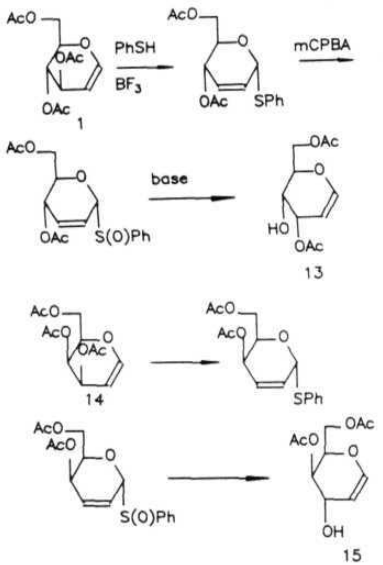
Several alcohols including sugar alcohols have been used and good yields of α anomers of 2,3-unsaturated sugars obtained.

During the course of time, the intermediate 12 has been trapped with several nucleophiles like hydride (Et_3SiH)[33] cyanide (Et_2AlCN)[34], enol silanes[35], allyl silanes[36] and



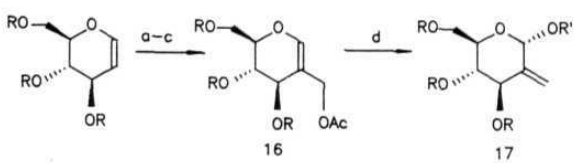
stannanes and silyl acetylenes . These modifications of the original reaction have given rise to new and versatile syntheses of C-glycosides from glycals. C-Glycosides have been used in the synthesis of many complex natural products '

This reaction has also been used for the synthesis of some other glycals. For example, D-allal and D-gulal derivatives 13 and 15 have been synthesized from triacetyl-D-glucal (1) and triacetyl-D-galactal (14), respectively[39].



Competitive Ferrier rearrangement:

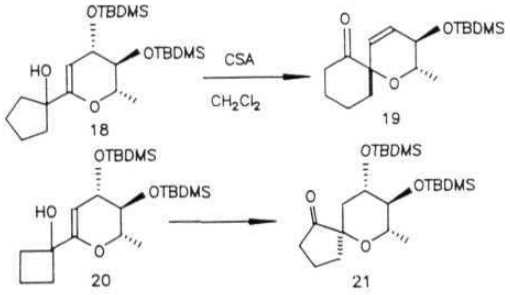
Tribenzyl glucal undergoes formylation under Vilsmeier conditions[40], and the product 2-formyl glucal has been used to



Reagents and conditions: *a) DMF,POCl ; b) NaBH,; c) Ac 0; d) R'OH, BF .Et 0.*

study competitive Ferrier rearrangement. Thus, when 16, prepared from a 2-formyl glucal by reduction of the aldehyde group followed by acetylation, is subjected to the Ferrier rearrangement, only an exo olefin 17 is formed and none of the 2,3 dideoxy sugar is seen

In synthesizing spiroannelated sugars, Paquette observed that steric factors could override the normal Ferrier rearrangement pathway in acid catalyzed reactions of C1-substituted glycals containing tertiary hydroxy groups[42] Compound 18, when treated with catalytic amounts of acid, furnished 19, a product of Ferrier rearrangement followed by

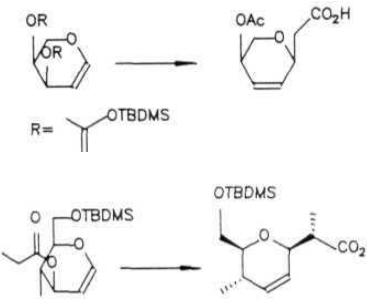


alkyl migration. On the other hand, 20 gave a different product 21 resulting from alkyl migration without Ferrier rearrangement. In the case of 20, relief of the inherent strain in the 4-membered ring directs the course of rearrangement.

Sigmatropic rearrangements:

Sigmatropic rearrangements such as the Claisen rearrangement provide a convenient route to the synthesis of

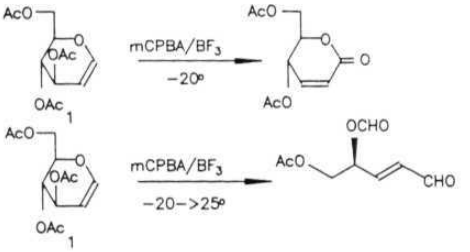
novel sugar derivatives. Since the Claisen rearragement provides stereospecificity, this methodology based on sugars is an attractive way to chiral starting materials. Thus, the Claisen rearrangement of glycals furnish C-glycosides. Some examples of this kind of reaction are given below[43]



Oxidation of glycals:

When treated with pyridinium chlorochromate, glycals undergo oxidation with rearrangement of the double bond to furnish lactones in good yields[44]. A more efficient method of oxidation of glycals was reported by Lichtenthaler[45]. He observed that glycal esters on treatment with mCPBA in the presence of Lewis acids like BF .Et O at -20°, were oxidized to ene lactones in high yields. This reaction has been found to be general **and** several glycals have been oxidized to the corres- ponding **ene** lactones in high yields. Temperature control is very essential for the success of the oxidation reaction. Best yields are obtained at -20°. When the reaction mixture is allowed to warm

upto to room temperature, ring cleavage is observed along with the loss of one carbon atom. This produces α, β-unsaturated aldehydes as products.

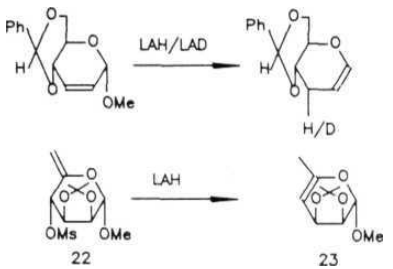


Chemistry of **2,3-unsaturated** sugars:

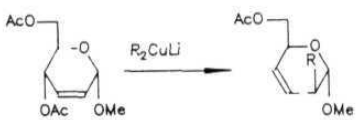
2,3-Unsaturated sugars are of less importance. They are useful chiral starting materials and have been employed in the synthesis of natural products. The fact that they are readily obtained from glycals makes them even more attractive. The chemistry of 2, 3-unsaturated sugars has been reviewed by Fraser-Reid . Some of the interesting reactions of 2,3- unsaturated sugars are discussed in the next few pages.

Allylic displacement reactions:

In 1970, Fraser-Reid observed that 2,3-unsaturated sugars can be converted to 3-deoxy glycals by treatment with lithium aluminum hydride. This is an important finding because **it** offers an easy way to label specific carbons in the sugar chain[47].



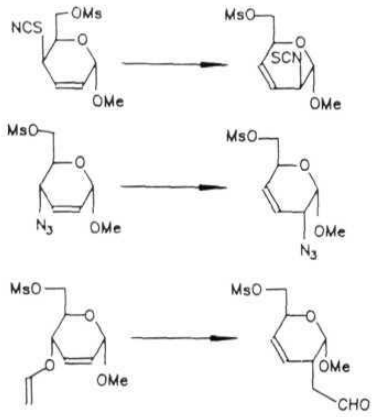
In a similar reaction, the exo glycal 22 was converted to a 4,5 unsaturated sugar 23 with allylic displacement of the mesylate group[48]



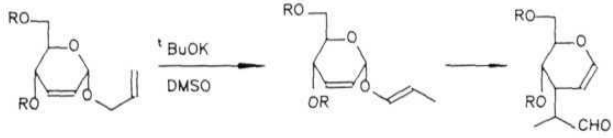
With organocuprates, 2,3-unsaturated sugars undergo displacement reaction and provide C-2 branched sugars[49]. This reaction is illustrated by taking 24 as an example.

Sigmatropic rearrangements:

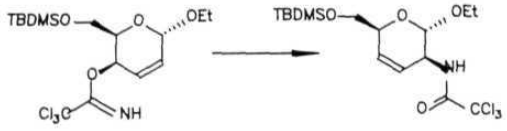
Sigmatropic rearrangement reactions are amongst the important reactions of 2,3-unsaturated sugars. As early as 1970, Ferrier found that 2,3-unsaturated sugars suitably substituted at C-4 undergo rearrangements to furnish 2-deoxy-2-amino or C-2 branched sugars . Examples of these types of reactions are illustrated below.



Heyns and co-workers studied another possibility in these rearrangements. Thus, alkenyl glycosides bearing vinyloxy substituents at C-1, rearrange, furnishing C-3 branched sugars A typical example is shown below.

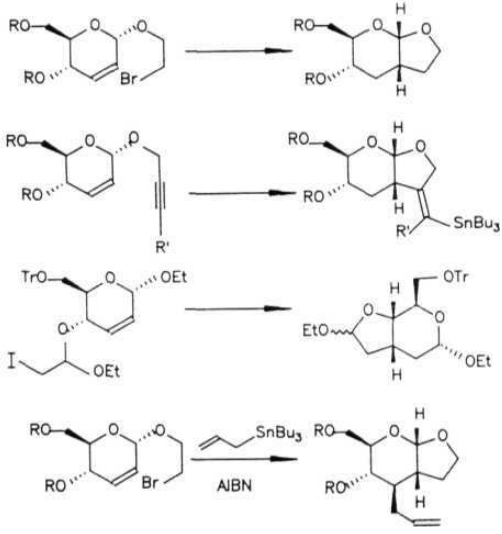


Recently, a synthesis of 2-deoxy-2-amino sugars was reported based on the 3,3 sigmatropic rearrangement of 4-trichloroacetimidate 25 of a 2,3-unsaturated sugar



Free radical cyclizations:

Free radical cyclization reactions are gaining importance in organic synthesis. Unsaturated carbohydrates provide ideal substrates for the study of these reactions. Various fused ring systems have been prepared by radical cyclization of suitable unsaturated sugars. Some examples of these cyclizations are given below[53]



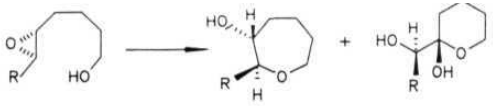
Our primary interest in the chemistry of unsaturated sugars was to develop a general method for the construction of functionalized medium sized ring systems especially oxepanes, from glycals. In recent years, several marine natural products have been isolated[54]. Many of them are substituted medium ring

oxygen heterocycles either monocyclic or more commonly fused. Examples include the toxins belonging to the brevetoxin and ciguatoxin families.

There are not many general methods for the synthesis of medium sized oxacycles. Some of the available methods for the construction of oxepanes are discussed below.

1) Cyclization of epoxy alcohols:

During their work on the syntheses of marine toxins, Nicolaou and co-workers discovered that the course of **acid** catalyzed cyclization of epoxy alcohols could be altered by suitable substituents . They found that epoxides having alkyl substituents followed an exo cyclization pathway and those having vinylic substituents followed an endo cyclization pathway.



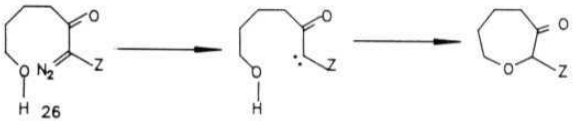
R = $CH_2CH_2CO_2Me$	0	100
R = E−CH=$CHCO_2Me$	22	78
R = −CH=CH_2	82	18
R = E−CH=CH_2	92	8

In epoxides having vinylic substituents, endo mode of cyclization was preferred owing to the stabilization of the developing positive charge by the adjacent double bond.

2) Insertion of carbenes into O-H bonds:

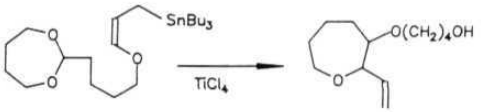
When carbenes derived from diazo compounds such **as** 26 insert into appropriately placed 0-H bonds intramolecularly,

oxepanes are formed . This is currently being used by Moody in the synthesis of hemibrevetoxin.

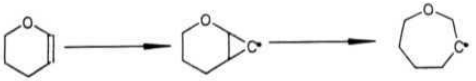


3) Cyclization of ω-trialkylstannyl ether acetals:

The reaction of acetals with allylstannanes in the presence of Lewis acids has been made use of by Yamamoto for the construction of medium sized ring systems. Thus, when treated **with Lewis** acids, **27** underwent cyclization to furnish oxepanes



It occurred to us that it should be possible to effect an insertion homologation of glycals by adding a suitable carbene and solvolyzing the resultant strained cyclopropane. This methodology would provide access to functionalized oxepanes containing several asymmetric centres. We anticipated that the solvolysis

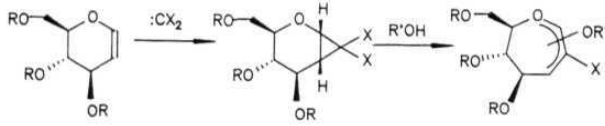


would be accelerated by the participation of the adjacent pyranoid oxygen atom. The results of this study are discussed in the next section.

Results and Discussion

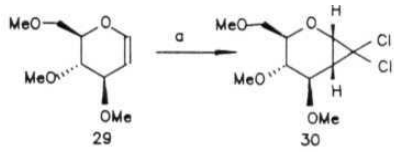
Synthesis of functionalized seven memebered oxygen heterocycles is a topic of current interest. This interest is due to the isolation of several marine natural products having very complex structures containing several fused ring systems of various sizes including seven membered ones . Many of these are highly toxic and are active even at nanogram levels. However, their scarce availability has hampered pharmacological investigations. Therefore their syntheses become important.

Our entry into this field was prompted by the lack of general methods for the synthesis of medium sized rings, some of which have been described in the previous section. We envisaged a strategy by which glycals were to be homologated by insertion of a suitable one carbon unit. Our strategy consisted of the addition of dihalocarbenes to glycals and solvolysis of the resultant dihalocyclopropanes. This is schematically shown below.



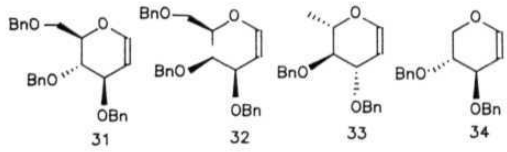
A search in the literature revealed that there are very few reports concerning sugar derived dihalocyclopropanes. Brimacombe was the first to report the addition of dichloro-carbene to glycals . He successfully added dichlorocarbene to 3,4,6-tri-O-methyl-D-glucal (29) to give 3,4,6-tri-O-methyl-1,5 anhydro-2deoxy-1,2-C-dichloromethylene-D-glycero-D-gulo-hexitol (30) in very good yields. The stereochemistry of the addition of

dichlorocarbene was assigned by analogy with the epoxidation of glycals with MCPBA, which are known to form a epoxides [59]. Later in 1979, Gross reported the addition of dibromo- and dichlorocarbenes to several unsaturated sugars



29 30

We decided to investigate this reaction in greater detail and also extend it to other glycals. We used **the** now standard phase transfer catalysis for the generation of dihalocarbenes. Four representative glycals, namely 3,4,6- tri-O-benzyl-D-glucal (31), 3,4,6-tri-O-benzyl-D-galactal (32), 3,4-di-O-benzyl-L-rhamnal (33) and 3,4-di-O-benzyl-D-xylal **(34) were** chosen as substrates. We used both dibromocarbene and dichlorocarbene for our studies.

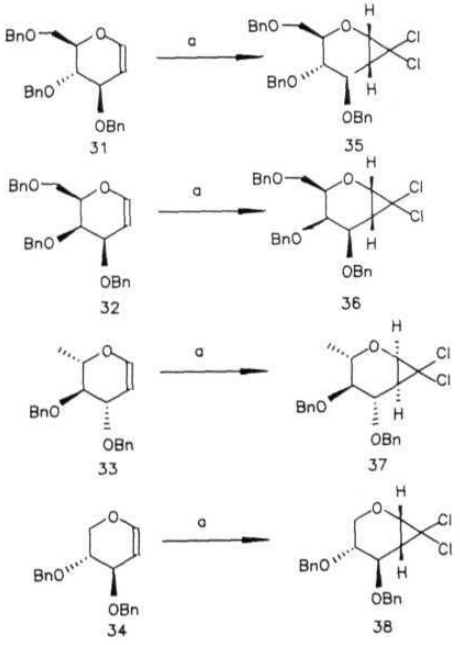


31 32 33 34

SYNTHESIS OF DIHALOCYCLOPROPANES FROM GLYCALS:

We chose to use the benzylated glycals in our investigations because they **are** stable to the strongly alkaline conditions of the dihalocarbene generation and also as they are

relatively non polar which makes their chromatographic purification easier. The benzylated glycals were prepared from free glycals employing standard benzylation conditions (sodium hydride and benzyl chloride). The glycals themselves were prepared by the well established procedure of Fischer . The identities of the benzylated glycals were established by comparing their spectral and physical data with that reported in the literature



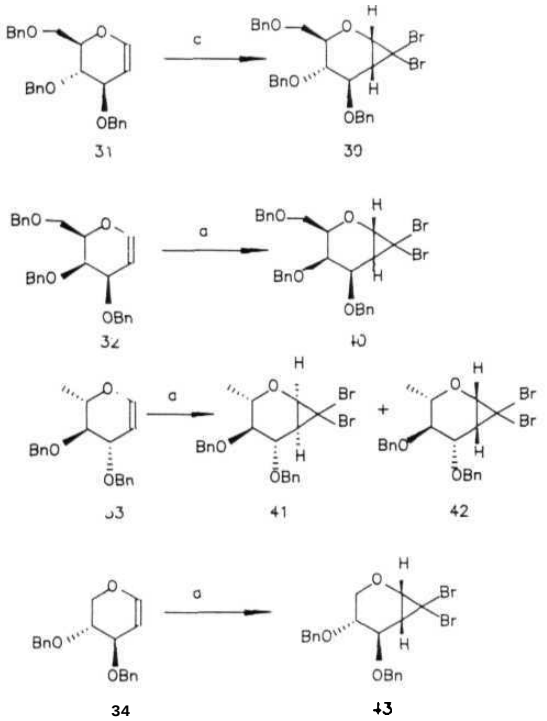
Reagents and conditions: *$CHCl_3$, 50% aq. NaOH, $BnEt_3NCl$ (cat.)*

The dichlorocyclopropanes were synthesized by treating chloroform solutions of the glycals containing a small amount of benzyl triethylammonium chloride as the phase transfer catalyst, with 50% aqueous sodium hydroxide. With all the four substrates, we obtained only a single adduct in fair to excellent yields . The individual results are tabulated below.

TABLE I

substrate	product	yield
31	35	84%
32	36	92%
33	37	95%
34	38	55%

When we performed the reaction replacing chloroform by bromoform under otherwise identical conditions, no product could be isolated. The reaction mixture turned black within a few minutes and also became very viscous. Decreasing the concentration of sodium hydroxide solution did not offer any useful results. Either the starting material was destroyed or there was no reaction. Fortunately, when we used a modified procedure employing a large excess of potassium fluoride and smaller amounts of alkali[63], the addition of dibromocarbene took place cleanly and the dibromocyclopropanes were obtained in good yields. Barring dibenzyl-L-rhamnal (33), which gave two adducts



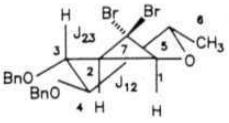
Reagents and conditions: *$CHBr_3$, KF* - 15% *NaOH, BnEt NCl (cat.)*

41 **and** 42 in a 7:1 ratio, the other glycals gave only single adducts. These results are presented in table II.

TABLE II

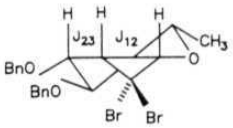
glycal	product	yield
31	**39**	**79%**
32	**40**	**71%**
33	**41,42**	**81%**
34	**43**	**64%**

We established the stereochemistry of the products of addition of dihalocarbenes to glycals **31**, 32, 33 and 34 by nmr spectroscopy. The chemical shift and splitting of the C-2 proton **were** the starting points for structure determination. The C-2 hydrogen, in all the adducts, resonated around 2.0 ppm and appeared as a doublet of doublet with the sole of exception of 42 in which it was an apparent triplet.



J_{12} = 8Hz J_{23} = 4Hz

41



J_{12} = J_{23} = 8Hz

42

The 4 line pattern of the C-2 hydrogen **had** coupling constants of around 8 and 4 **Hz.** The larger value **was assigned to** J_{12} **coupling as** evidenced from the **H-1** signal (a doublet with 8

Hz coupling constant). The smaller value of the coupling between C-2 and C-3 protons suggests a quasi axial - equatorial arrangement. In adduct 42, the H-2 proton appears as an apparent triplet with a coupling constant of 8 Hz. This is possible only if the concerned protons H-1, H-2 and H-3 are all on the same face of the molecule. Therefore, it is reasonable to assume that $J_{2,3}$ is around 4 Hz when H-2 and H-3 are trans to one another and is around 8 Hz when they are cis to one another. Our assignments were confirmed by 2D COSY experiments on adducts 41 (major) and 42 (minor) derived from dibenzyl rhamnal (33) (figures 1 and 2).

In the COSY spectrum of adduct 41, the signal at 1.88 ppm showed two cross peaks with signals at 3.50 and 3.80 ppm, respectively. Since the doublet at 3.80 ppm did not show cross peaks with any other signal, it was assigned as H-l. Consequently, the 1.88 ppm signal has to be H-2. It is now obvious that the 3.50 ppm signal corresponds to H-3. The COSY spectrum of 42 also showed similar cross peaks, thus assigning H-2 unambiguously. The magnitude of J_{23}, as mentioned above, indicates the stereochemistry of the adduct to be α. These experiments conclusively prove that Brimacombe's assignment was correct. Thus, the products of dihalocyclopropanation are either exclusively or predominantly formed on the face of the double bond away from the C-3 substitutent, as can be expected on steric grounds. A table showing the chemical shifts and different coupling constants of H-2 is given below. The table also gives the ^{13}C chemical shifts of the C-2 and C-7 carbons.

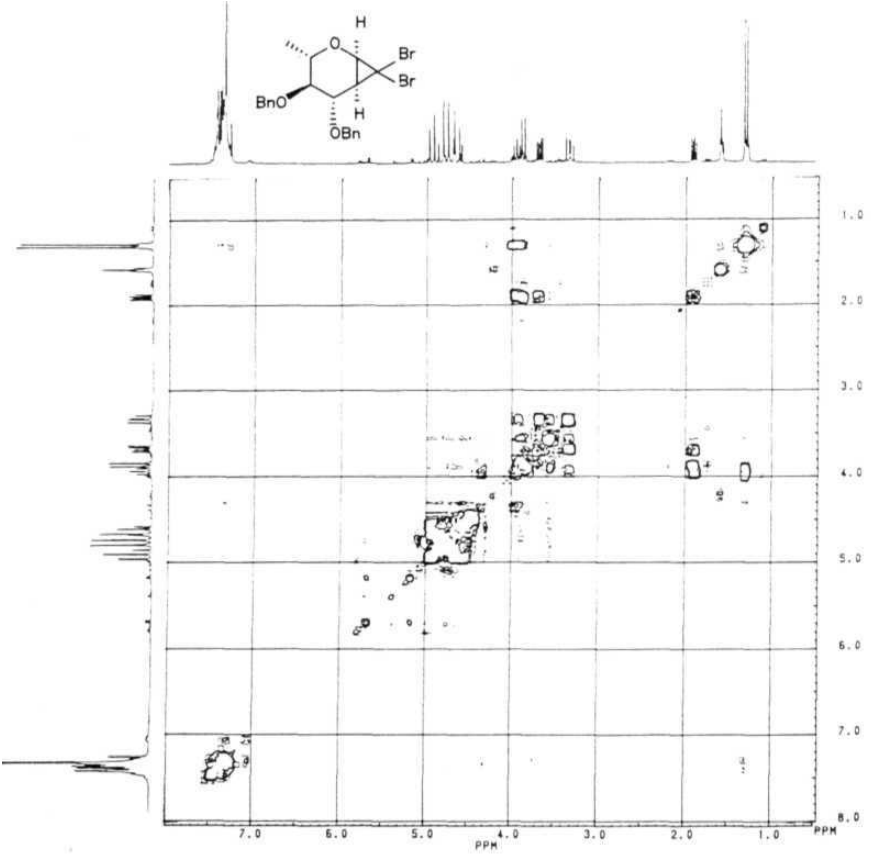


Figure 1: HH COSY spectrum of 41

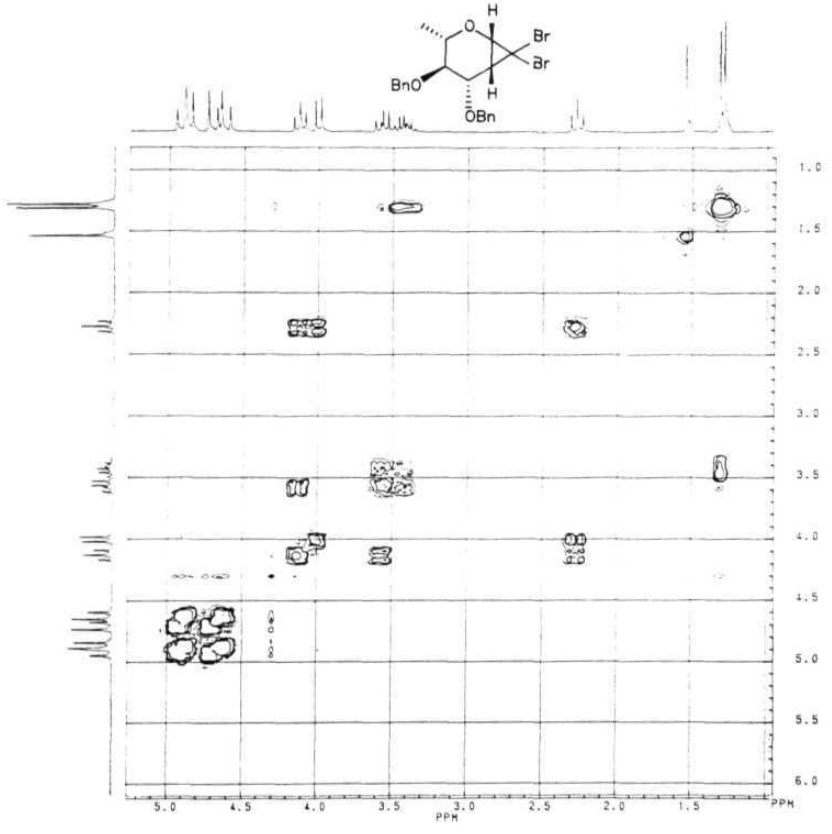


Figure 2: HH COSY spectrum of 42

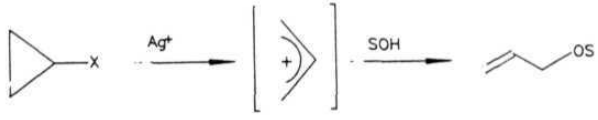
TABLE III

compound	H-2(6)	J_{12}(Hz)	J_{23}(Hz)	C-2(ppm)	C-7(ppm)
35	1.78	7.9	4.4	34.41	61.62
36	1.96	8.9	4.3	31.09	61.81
37	1.80	8.2	4.2	33.92	57.86
38	1.77	7.9	3.8	33.08	51.86
39	1.86	7.8	4.6	35.00	34.06
40	2.06	8.8	4.3	32.16	35.15
41	1.88	7.9	4.2	35.71	33.73
42	2.28	8.0	7.9	33.92	31.19
43	1.89	7.8	3.9	34.06	32.81

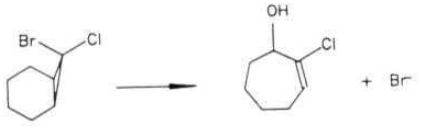
It is of interest to note that the chemical shifts of the carbon carrying chlorines are higher than their bromine containing counterparts. The C-2 chemical shifts remain more or less constant in both the series. These observations are in agreement with published values for 7,7-dibromo- and 7,7-dichloro norcaranes[64]

SOLVOLYSIS OF THE DIHALOCYCLOPROPANES:

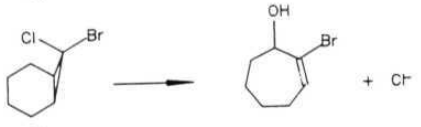
With the structure of the adducts secure, we set out to perform their solvolysis. Before explaining our results, a brief discussion on the solvolysis of cyclopropyl halides is presented.



Under solvolytic conditions, cyclopropyl halides give rise to cyclopropyl cations. These cations undergo electrocyclic ring opening to furnish the corresponding allyl cations, which are then captured by nucleophiles. In one of the early experiments on the solvolysis of cyclopropyl halides, Skell and Sandier observed that epimeric halides 44 and 45 give different solvolysis products . The results are readily explained by **the** principle of conservation of orbital symmetry . The cyclopropyl cations being two electron systems undergo thermal disrotatory ring opening. It is also known that the direction of ring opening is always opposite to the direction of halogen departure.



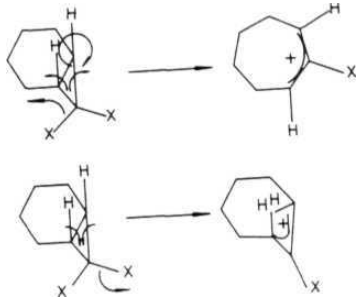
44



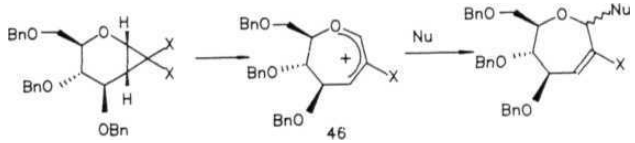
45

In bicyclic systems, of the two possible ring opening pathways, the one in which the endo halogen is lost is preferred over the pathway involving exo halogen loss.

During the disrotatory ring opening involving exo halogen loss, the cyclopropyl protons experience severe transannular interactions. Thus, exo-halogen loss is strongly



disfavoured. During the departure of endo halogen no such unfavourable interactions are present. Therefore, this becomes the favoured reaction pathway. The results of Skell and Sandier are readily explained on the basis of these arguments.



46

We anticipated that in our system, the cyclopropyl cation 46 resulting from the loss of endo halogen, would rearrange in such a way that the positive charge of the resultant allyl cation is placed at C-1. The driving force for this comes from the stabilization of the positive charge by the adjacent oxygen atom. Capture by a nucleophilic solvent like methanol would then provide a seven membered glycoside.

We attempted the solvolysis experiments on the

dichlorocyclopropane 35 derived from 31 because of its ready availability. When heated in acetic acid for 16h, no reaction was observed and only the starting material was recovered

Lewis acids such as boron trifluoride and aluminum chloride are known to promote ionisation of C-X bonds and therefore should be useful as catalysts in solvolysis reactions. When the dichlorocyclopropane 35 was treated with boron trifluoride in acetic acid, no reaction was observed even after one week at room temperature, while after refluxing for 24h a complex mixture was obtained. We thought the reaction conditions were too vigourous and repeated the experiment under less vigourous conditions. This time, the reaction mixture was heated for only one hour. But under these conditions, no reaction was observed. We conducted these experiments to see if the use of expensive silver salts, which could be avoided.Which have been known for a long time to be good catalysts for the solvolysis of C-X bonds . In such cases, reaction is driven to completion by the precipitation of silver halides. Since our attempts at solvolyzing the dichlorocyclopropane (35) in the absence of silver salts were unsuccessful, we next turned our attention to silver ion assisted solvolysis. In our experiments, we used silver salts of varying reactivities and our results are presented below.

When the solvolysis was conducted in refluxing methanol with silver nitrate as catalyst, no reaction was observed. The same was the result when silver acetate was used as catalyst in

refluxing acetic acid. We next used silver tetrafluoroborate as the catalyst. At room temperature in acetic acid, no solvolysis was observed. At higher temperatures also no reaction was seen. We suspected that acetic acid alone was not sufficiently nucleophilic and used its sodium salt along with silver tetrafluoroborate. But in this case also, no solvolysis was observed.

Silver perchlorate is known to be an effective catalyst in the solvolysis of cyclopropyl halides ' . It is soluble in many organic solvents thus increasing its effectiveness. Unfortunately, our solvolysis experiments with silver perchlorate in methanolic solutions were not fruitful. When the reaction was conducted in aqueous acetone, no solvolysis took place.

With the failure of silver salts to effect solvolysis, we looked for alternate methods to achieve the same. A search in the literature revealed that dihalocyclopropanes are cleaved under alkaline conditions also . Potassium t-butoxide was the base most often used in these reeactions. When the dichlorocyclopropane 35 was refluxed with potassium t-butoxide (prepared in situ by dissolution of the metal in excesst-butanol) , solvolysis took place as indicated by the presence of t-butyl and olefinic signals in the H nmr spectrum. However, the reaction could not be reproduced due to the sensitive nature of potassium metal. Commercial potassium t-butoxide was not useful in this reaction. This forced us to look for other bases. We opted to use sodium methoxide first.

With sodium methoxide in methanol the reaction was very sluggish and only an insigificant amount of product was formed after heating for 48h. We did not conduct any additional experiments in the light of these failures. A complete listing of the above experiments is provided in table IV.

TABLE IV

Solvolysis experiments on 35

Entry	Reaction Conditions	Result
1.	AcOH, reflux, 16h.	no reaction
2.	$BF_3.Et_2O$, AcOH, rt, 1week	no reaction
3.	$BF_3.Et_2O$, AcOH, reflux, 24h	complex mixture
4.	BF .Et 0, AcOH, reflux, 1h	no reaction
5.	AgNO , MeOH, reflux, 2h	no reaction
6.	AgOAc, AcOH, reflux, 4h	no reaction
7.	AgBF , AcOH, rt, 22h	no reaction
8.	AgBF , AcOH, 80°, 24h	no reaction
9.	AgBF , NaOAc, AcOH, 80°, 24h	no reaction
10.	AgCIO , MeOH, reflux, 16h	no reaction
11.	AgCIO , aq. acetone, rt	no reaction
12.	t-BuOK, t-BuOH, reflux	solvolysis
13.	NaOMe, MeOH, reflux, 2days	no reaction

We attribute the failure of the solvolysis experiments to the lower reactivity of the C-Cl bond. Generally, the bromo compounds are more reactive than their chloro counterparts.

Therefore, we expected the dibromocyclopropanes to solvolyze more readily and subjected the dibromocyclopropane 39 to silverion catalyzed solvolytic reactions. The results are discussed in the following paragraphs.

First, we used relatively inexpensive silver salts like silver acetate. In refluxing acetic acid, silver acetate did not bring about any reaction. Silver trifluoroacetate also did not effect any solvolysis. No reaction was observed when an aqueous acetone solution of the dibromocyclopropane 39 was treated with silver triflate at room temperature or at reflux temperature. The same reaction conducted in methanolic tetrahydrofuran failed to effect any solvolysis. A higher boiling solvent like aqueous dioxane also failed to bring about solvolysis. The solvolysis was now attempted under vigorous conditions. Thus, a solution of 39and silver triflate in acetic acid was heated under reflux for 16h. Under these conditions no solvolysis product could be isolated, although the H nmr spectrum of the crude product showed acetate signals. Only benzyl acetate was isolable by chromatography. This was identified by its pleasant smell and by comparison of its nmr spectrum with that reported in the literature.

As the above conditions proved to be too drastic, we repeated the reaction for only one hour under otherwise identical conditions. Again, except for benzyl acetate, no other product could be isolated. The same was the result when the reaction was run at a lower temperature of around 80°. It was not clear how

benzyl acetate was formed in these reactions. We did not investigate its mode of formation as our main interest was in the solvolysis reaction.

We next used silver tetrafluoroborate as silver triflate did not offer a clean reaction. Unfortunately, silver tetrafluoroborate did not effect any reaction. Silver perchlorate has been known to effect solvolysis of dibroraocyclopropanes under mild conditions and this was used next. In acetic acid solutions at 60-70 , silver perchlorate did not bring about solvolysis. In aqueous acetonitrile, under reflux conditions, only a complex mixture with some starting material was obtained. However, we did not attempt to purify this mixture. Our experimental results on the solvolysis of 39 are collected in the accompanying table.

We suspected that the benzyloxy methyl substituent at C5 might be blocking the approach trajectory of silver ion toward the endo bromine, and, as a consequence of this, no solvolysis was taking place. In the dibromocyclopropane 43 derived from 34, no such possiblity exists as it contains no substituent at C-5 and therefore, no steric hindrance should exist for the approach of silver ion. When we solvolyzed 43, with silver perchlorate in refluxing methanol, again no reaction was observed.

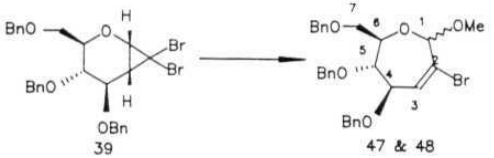
TABLE V

Solvolysis experiments on 39

Entry	Reaction Conditions	Result
1.	AgOAc, AcOH, reflux	no reaction
2.	$AgOCOCF_3$, CF_3CO_2H, rt, 2h	no reaction
3.	AgOTf, MeOH-THF, rt, 2d	no reaction
4.	AgOTf, MeOH-THF, reflux, 4h	no reaction
5.	AgOTf, aq. acetone, rt, 2h	no reaction
6.	AgOTf, aq. acetone, reflux, 8h	no reaction
7.	AgOTf, aq. dioxane, reflux, 4h	no reaction
8.	AgOTf, AcOH, reflux, 16h	complex mixture
9.	AgOTf, AcOH, reflux, 1h	complex mixture
10.	AgOTf, AcOH, 80°, 3h	complex mixture
11.	$AgBF_4$, AcOH, rt, 1h	no reaction
12.	$AgClO_4$, AcOH, 60-70°	no reaction
13.	$AgClO_4$, aq. CH_3CN, reflux, 24h	complex mixture

With the failure of the silver ion catalyzed solvolysis reaction, we turned our attention to alkaline solvolysis. Recently, Banwell and coworkers reported that dibromocyclopropanes of enol ethers undergo solvolysis in methanol in

the presence of excess potassium carbonate furnishing ring expanded products . We were elated to find that dibromocyclopropane 39 underwent smooth solvolysis under these conditions. Only two products were formed and they were separable by careful column chromatography. The total yield of the products was about 65%. The structures of these products were established by extensive nmr studies.



The H and C nmr spectra of the products were similar and this hinted that the products may have similar structures. The 1.88 ppm signal corresponding to H-2 of the starting compound was conspicuously absent in the products. In C nmr spectrum also, the signals at 34.06 and 35.0 ppm were absent. In the H nmr spectra of the products 47 and 48, a sharp singlet at 3.50 ppm integrating for 3 protons of a methoxyl group indicated that the solvolysis had indeed taken place. Additionally, in the H nmr spectrum of the major product 47, two narrow doublets at 5.15 and 6.80 ppm having a coupling constant of 1.7 Hz, each integrating for one proton were seen. In the H nmr spectrum of minor product 48, the doublets at 5.15 and 6.80 ppm had a coupling of 3.3 Hz.

In order to establish the connectivity network, a 2D

COSY experiment was performed. In the COSY spectrum of the major product 47, cross peaks were between signals at 5.15 and 6.80 ppm indicating coupling between them. The 6.80 ppm signal was further coupled to a signal at 4.80 ppm. Other couplings of the 4.80 ppm signal could not be established unambiguously because of the closeness of signals. As the 5.15 ppm signal showed no other cross peaks, it was assigned to H-1. The 6.80 ppm doublet was assigned to C-3 hydrogen based on the observation that solvolysis of dihalocyclopropanes produces an allylic system with the halogen on the middle carbon. The small value of J_{13} also supports this assignment (figures 3 and 4).

Further structural information was obtained from an analysis of the C nmr spectrum of 47. We used the results of DEPT experiments to establish the nature of the carbon atoms. The four signals around 138 ppm were identified as quarternary carbons due to their absence in the DEPT spectra. Three of these belong to the phenyl rings and the remaining one was assigned to the olefinic carbon carrying bromine. Furthermore, the DEPT experiments showed that there are five methine carbons, four methylene carbons and one methyl carbon in the molecule. The methyl carbon obviously belongs to the methoxyl group. Three of the four methylene signals were assigned to benzylic carbons and the remaining one to C-7. The methine carbons were assigned to carbons 1,3,4,5 and 6. The signals at 112.5 ppm of the major product 47 and 114.7 ppm of the minor product 48 being olefinic in nature, were assigned to C-3. The signals at 99.9 ppm in 47

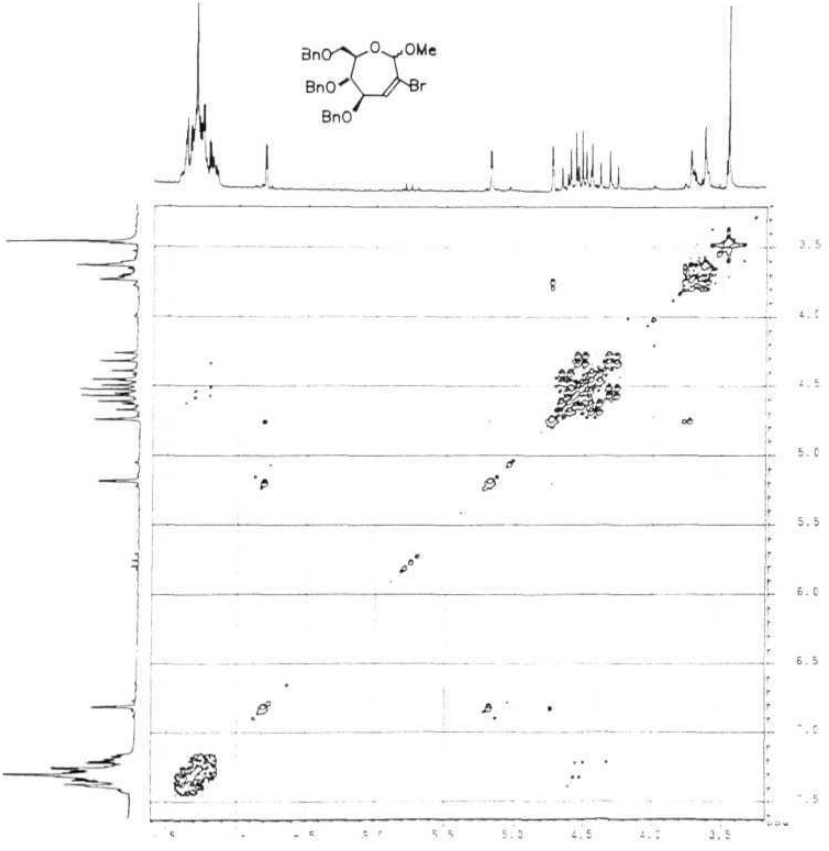


Figure 3: HH COSY spectrum of 47

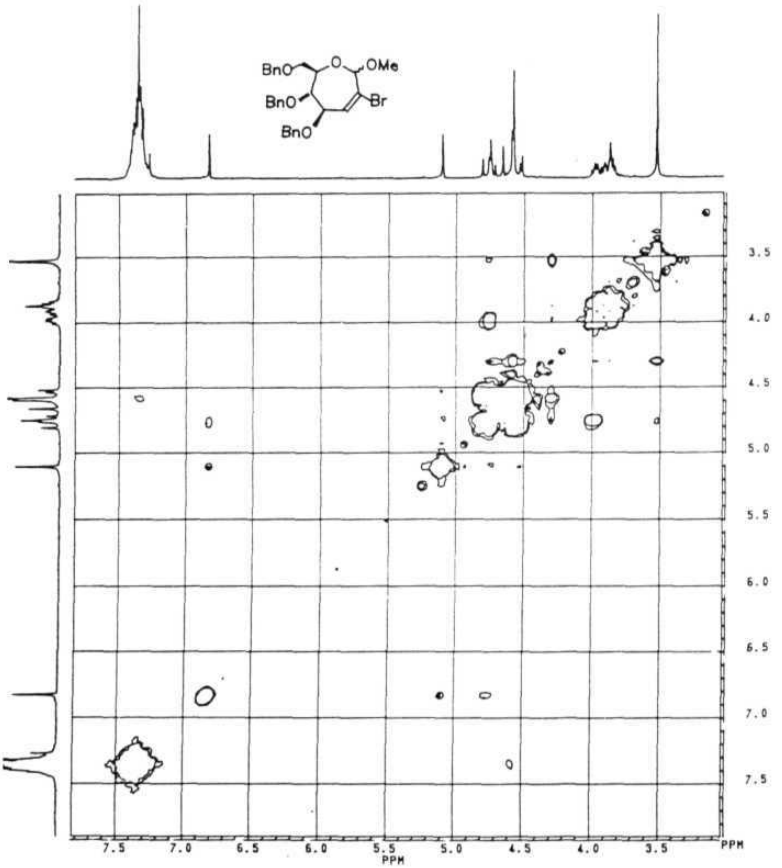
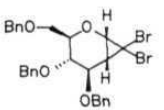
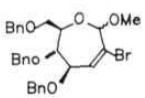
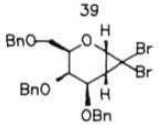
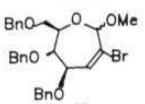
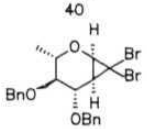
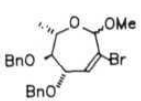
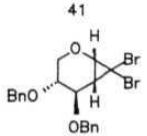
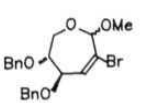


Figure 4: HH COSY spectrum of 48

and 101.1 ppm in 48 were assigned to C-1. These assignments were confirmed by C-H COSY spectra. In the C-H COSY spectrum of the major product 47, the 5.15 ppm signal (proton) correlated to 99.9 ppm signal (carbon), and 6.80 ppm (proton) signal correlated to 112.5 ppm (carbon). Likewise, correlations were found for the corresponding signals of the minor product 48. Unfortunately, we could not assign the anomeric stereochemistry of the products on the basis of the above information but the skeletal structure was established to be a seven membered ring (figures 5 and 6).

TABLE VI

Substrate	Products	Yield
 39	 47&48	67%
 40	 49	55%
 41	 50	70%
 43	 51	55%

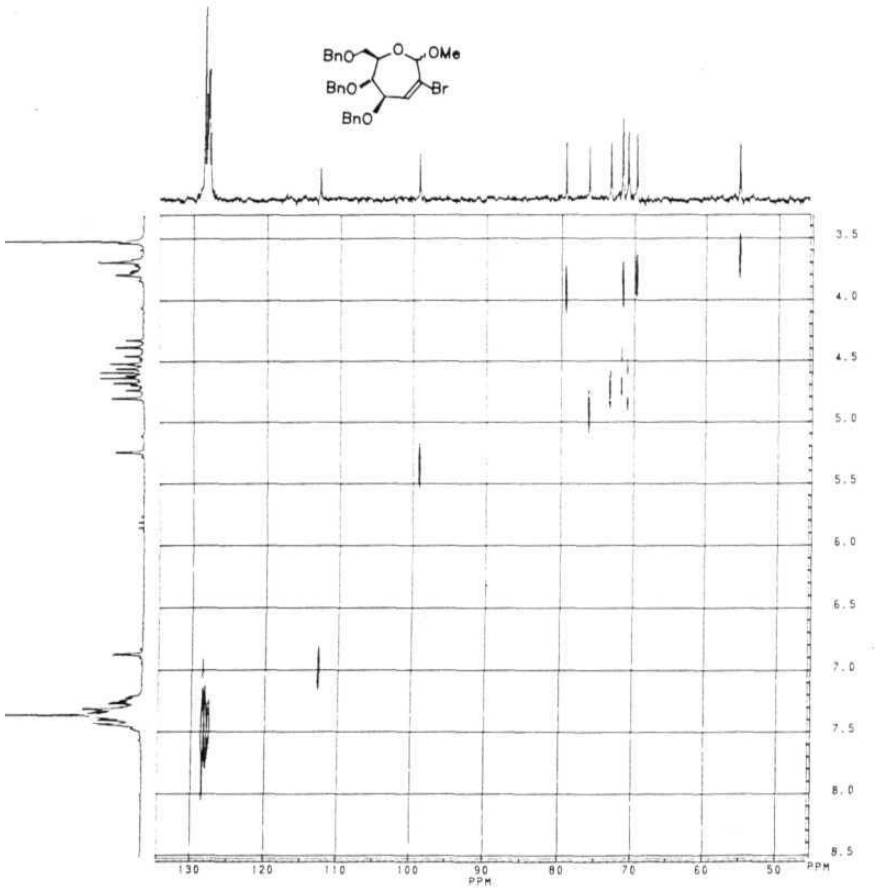


Figure 5: CH COSY spectrum of 47

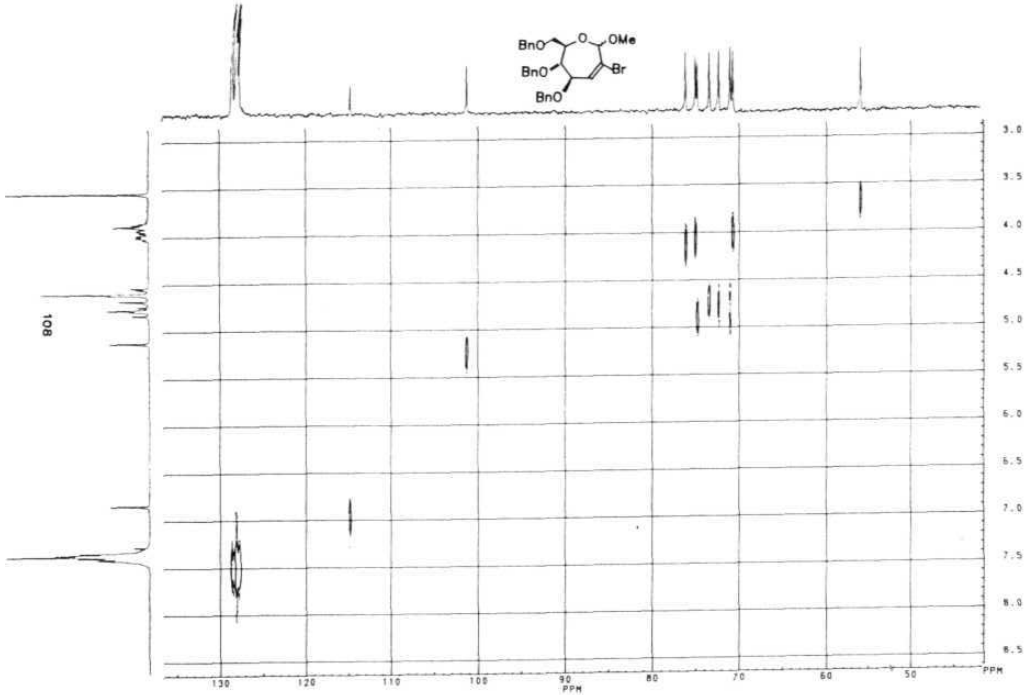


Figure 6: CH COSY spectrum of 48

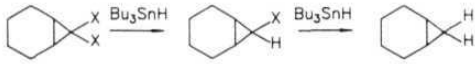
Encouraged by the success of the above reaction, we extended this procedure to other dibromocyclopropanes 40, 41 and 43. All of them underwent solvolysis to produce ring expanded systems. Unlike with 47 and 48, these products could not be satisfactorily separated by chromatography and also they were not very stable, decomposing over a period of 2 days. The results of these experiments are presented Table VI.

The failure of the silver ion catalyzed solvolysis proved to be a blessing in disguise as this method using potassium carbonate is definitely more economical. Thus, a general and versatile method has been developed for the synthesis of functionalized oxepanes, fulfilling one of our objectives as stated earlier in the beginning of this chapter.

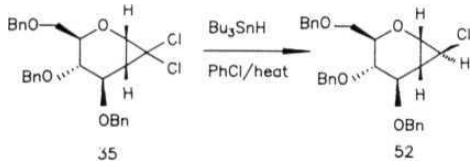
Recent developments in the synthesis of oligosaccharides from strained three membered rings fused to pyranoses prompted us to examine the possibility of using cyclopropanes derived from glycals as substrates for a similar reaction as they can be readily obtained by reduction of the corresponding dihalocyclopropanes. We tried some of the available dehalogenation methods and our results are discussed in the following pages.

Trialkyltin hydrides have been known for a long time as effective dehalogenating agents . They have been used in the dehalogenation of gem-dihalocyclopropanes also . In 1963, Seyferth reported the use of tributyltin hydride in reductive dehalogenation of cyclopropyl halides. He found that

7,7-dibromonorcarane reacted almost instantaneously with tributyltin hydride at room temperature and furnished in good yields 7-bromonorcarane. The corresponding dichloro compound did not react under these conditions and had to be heated to 140° for a successful reaction. Seyferth also reported that on further treatment with tributyltin hydride, the monohalocyclopropanes were reduced to cyclopropanes.



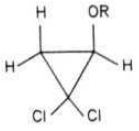
When heated with tributyltin hydride in chlorobenzene at 120° for 10h, the dichlorocyclopropane 35 underwent reduction and provided the monochlorocyclopropane. However, the yield of the pure product was not satisfactory because the tin impurities could not be removed completely by fluoride wash or by chromatography. The identity of the product was established from its nmr spectral data.



Ten signals were seen in the C nmr spectrum of 52 in addition to the aromatic signals. Of these, three signals were assigned to the benzylic carbons. The signal at 56.5 ppm was

assigned to C-1. Literature data for the C chemical shifts of cyclopropyl halides are available. The chlorine containing carbon resonates at a lower field compared to carbon atoms not having chlorine . Also, the exo and endo isomers have different chemical shifts. Based on the above information, we assigned the resonances at 26.4 and 34.1 ppm to C2 and C7 respectively.

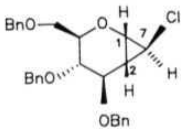
In the H nmr spectrum of 52, the C-2 proton shifted upfield to 1.50 ppm from 1.78 ppm in 35. As expected, its multiplicity also increased. There was an additional signal, a doublet of doublet with coupling constants of 4.2 and 1.6 Hz at 3.10 ppm. This signal was assigned to the C7 proton (for further confirmation see the nmr analysis of the bromocyclopropane 59). In cyclopropyl systems, the cis hydrogens have a coupling constant of around 8 Hz and the trans hydrogens show smaller coupling and are usually around 5 Hz . On the basis of these values it was determined that H-1 and H-2 are trans to H-7 and therefore the chlorine atom is exo in 52. Initially, we were puzzled to find that J_{17} and J_{27} were quite different from one another. This suggested that some



J_{cis} = 7·9 Hz

J_{trans} = 5·3 Hz

J_{gem} = 8·4 Hz

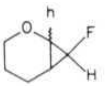


H–1 = 4·2ppm

H–2 = 1·5ppm

H–7 = 3·1ppm

other factors might be involved in determining the magnitude of J in such systems. After a search in the literature, we found that in fused cyclopropyl systems containing electron withdrawing atoms like fluorine and oxygen near the ring fusion, the coupling constants were no longer the same. The values were different for

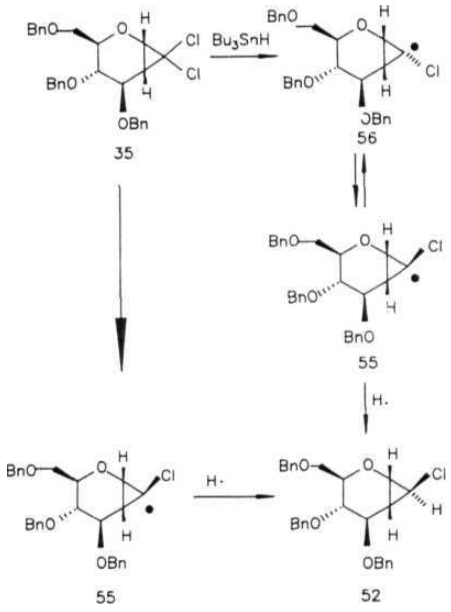


53 (cis) = J_{Hh} = 4·3Hz

54 (trans) = J_{Hh} = 0Hz

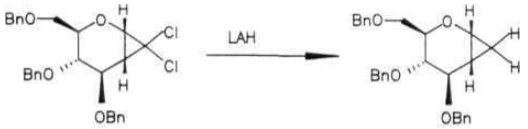
J and J in both cis and trans fluorides as exemplified in 53 and 54. This conveniently explains the different coupling constants observed in our system and confirms our earlier assignment of the structure of 52.

Mechanistically, the exo product can arise by two pathways. In one route, the loss of endo chlorine gives an endo radical 55, which subsequently gets reduced. On **the other** hand, exo chlorine could be lost first leading to an exo radical 56, which inverts to an endo radical 55 prior to reduction. It is not known which mechanism is operative here. The reductive debromination of 39 was not attempted in the light of the difficulties observed in removing the tin impurities during workup leading to 52



Lithium aluminum hydride (LAH) is also known to reduce halides, including cyclopropyl halides[78]. We opted to use this reagent because of the simplicity of product isolation. The dichlorocyclopropane 35 reacted smoothly and rapidly with excess LAH in tetrahydrofuran to furnish the fully reduced cyclopropane 57 in very good yield. Although this reaction was reported by Brimacombe[58], no nmr spectral details of the product were given.

We fully characterized the product from its analytical and spectral data.

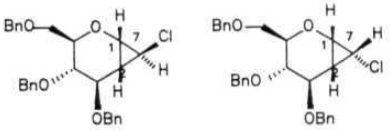


35 57

In the H nmr spectrum, the multiplicity of H-2 signal increased and also moved further upfield compared to both dichloro and monochloro cyclopropanes and lay centred at 0.90 ppm. The additional multiplets at 0.70 ppm integrating for two protons were assigned to the protons attached to C-7. In the C nmr spectrum, ten resonances were present in addition to the aromatic signals. The DEPT-135 experiment identified them to be methylene and methine carbons (5 each) The resonances at 11.6 and 14.9 ppm were assigned to cyclopropyl carbons C-7 and C-2, respectively. The remaining four methylene signals were assigned to C-6 and the three benzylic carbons.

We found this dehalogenation procedure to be highly dependent on the guality of LAH used. When aged samples of LAH were used, the reduction was slow and also gave a mixture of products. We isolated two products from the mixture by chromatography. The fast moving product was identical with the dehalogenation product 52 obtained by tin hydride reduction. The slow moving product was found to be a mixture of two products by nmr spectroscopy. In addition to the signals attributable to the

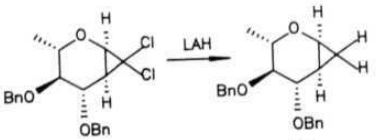
cyclopropane 57, we also observed signals at 1.40 and 3.20 ppm. The signal at 1.40 ppm was assigned to H-2, by comparison with chlorocyclopropane 52. The 3.20 ppm signal was a doublet of a doublet with coupling constants of 8 and 4 Hz. This was in contrast to the values observed for the exo chloride. A coupling of 8Hz indicated that the concerned hydrogens were cis to each other and this implied that the product has endo stereochemistry. The smaller coupling was now readily explained. Efforts to separate this endo isomer from the cyclopropane 57 were not successful.



J_{17} - 1·6 Hz J_{27} - 4·2 Hz

J_{17} - 4·0 Hz J_{27} - 8·0 Hz

The dichlorocyclopropane 37 derived from dibenzyl-L-rhamnal also underwent clean dechlorination with LAH providing the corresponding cyclopropane 58 in good yields. The product was characterized once again by nmr spectroscopy.



37 58

Encouraged by the clean reaction of 35 with LAH, we next attempted the debromination of 39. Surprisingly, this gave rise to three products under the same conditions as were employed for 35. The products were separable by careful column chromatography. The fastest moving component was isolated in 32% yield and was characterized by nmr spectroscopy as well as by elemental analysis. The H nmr spectrum of this compound was very similar to that of the exo-chloride 52. It showed signals at 1.50 and 3.0 ppm in addition to other signals. However, the 3.50 - 4.0 ppm region was more resolved compared to that of 52. We performed a 2D COSY experiment on the bromocyclopropane 59 in order to establish the coupling network (figure 7). The signals at 1.50, 3.0 and 3.80 ppm showed cross peaks with one another, indicating coupling between them. Further connectivities could not be established because of overlapping of multiplets. The 3.80 ppm signal was a doublet of doublet with coupling constants of 7.7 and 1.6 Hz. As observed previously in the case of dihalocyclopropanes, a coupling with magnitude of about 8 Hz arises due to the protons being cis to one another, which in this case are H-1 and H-2. On this basis, we assigned the 3.80 ppm signal to H-l. Therefore the 1.6 Hz coupling was assigned to J_{17}. The small J_{17} value indicated a trans arrangement of protons implying an exo bromide and it follows that the 3.0 ppm doublet of doublet belongs to H-7. It is now obvious that the 1.50 ppm

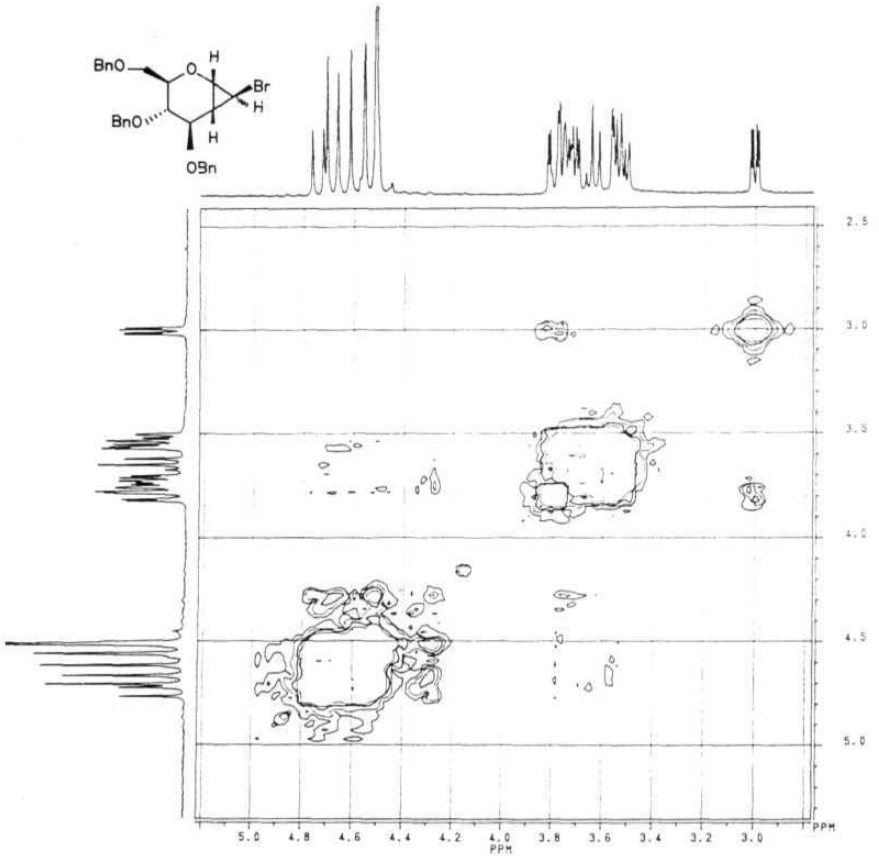
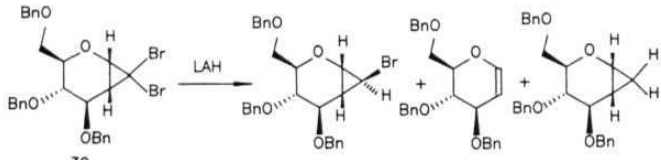


Figure 7: HH COSY spectrum of 59

signal is from H-2. In the ^{13}C nmr spectrum, the signals at 20.52, 26.39 and 56.67 were assigned to the cyclopropyl carbons.

The second product isolated in about 5% yield was identified as 3,4,6-tri-O-benzyl-D-glucal (31) by comparison of its physical data with that of an authentic sample.

The slowest moving component was the major product obtained in 42% yield. This material was identical with the cyclopropane **57** obtained by LAH reduction of 35.

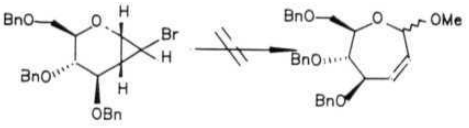


Reaction time = 1·5h	32%	5%	42%
Reaction time = 48h	–	15%	23%

In order to completely convert all the monobromocyclopropane into the fully reduced one, longer reaction times were used. After 48h, the monobromide 59 was completely consumed. Surprisingly, however the yield of cyclopropane 57 did not increase but the amount of glycal 31 produced increased to about 15%. A change in work up procedure from aqueous sodium sulfate quench to ethyl acetate quench did not change the product ratio. This indicated that the glycal formation took place before workup.

It is hard to find a suitable mechanism that would explain this unusual phenomenon, because the dehalogenation by LAH has been shown to proceed by nucleophilic substitution as well as by electron transfer processes . We did not undertake any investigations of this process as we were more interested in the synthetic applications of the cyclopropanes.

We were curious to examine the solvolytic behaviour of the bromocycloproane 59. We subjected 59 to silver ion catalyzed as well as alkaine solvolysis. In both cases, solvolysis did not take place.

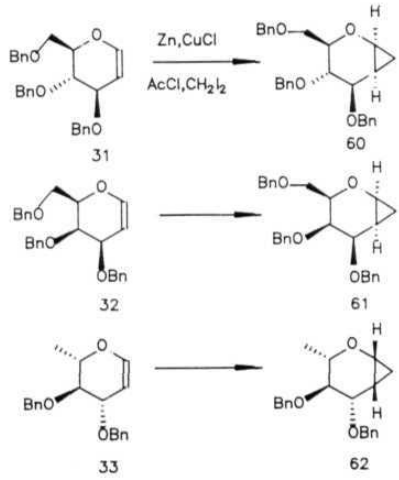


59

Cyclopropanes can also be obtained by reaction of olefins with diazomethane or under Simmons - Smith reaction conditions involving diiodomethanes and zinc[79]. There are very few reports on the direct cyclopropanation of unsaturated sugars and none of them deal with glycals. Therefore, we decided to attempt direct cyclopropanation of glycals. We elected to follow Simmons-Smith conditions and avoided using diazomethane because of its hazardous nature.

In recent years, there have been several modifications of the original Simmons - Smith procedure. Lewis acids like $TiCl_4$ and acid halides have been used as activators . We preferred

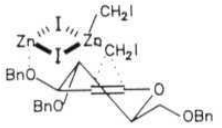
activation by acetyl chloride as glycals are sensitive to Lewis acids. Thus, when tribenzyl-D-glucal 31 was subjected to Friedrich's conditions using diiodomethane, zinc and cuprous chloride as reagents along with acetyl chloride as activator, a cyclopropane 60 was obtained in excellent yields. Therefore, we subjected two more glycals, tribenzyl-D-galactal (32) and dibenzyl-L-rhamnal (33) to the above reaction conditions. Both of them provided cyclopropanes once again in excellent yields.



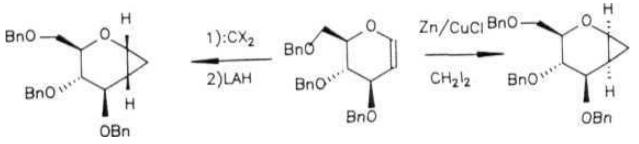
The products of the Simmons-Smith reaction were characterized by spectral methods. It was immediately obvious from the nmr spectra that these cyclopropanes were different from

the ones obtained by LAH reduction of 35 and 37. The striking difference between the two was that in the Simmmons - Smith product 60, the signals were spread out. The C-2 hydrogen in this product has moved downfield by about 0.4 ppm when compared to that in 57. A multiplet centred around 0.80 ppm integrating for two protons was assigned to C-7 hydrogens. From an analysis of the 2D COSY spectrum, we assigned the other signals. A multiplet at 3.75 ppm showed cross peaks to signals at 1.30 and 0.80 ppm and therefore was assigned as H-1. An apparent triplet at 4.07 ppm was assigned as H-3 from its coupling to H-2. Further assignments were not possible due to overlapping of signals. The stereochemistry of the new cyclopropane 60 was established from the coupling behaviour of the C-2 and C-3 hydrogens. The H-3 proton at 4.07 ppm was an apparent triplet with coupling constant of 6.8 Hz. This value of J is possible only if the concerned protons are on the same side of the molecule as the coupling constant due to trans coupling in cyclopropanes is small. It may be recalled that 42 also shows a similar coupling pattern. In the C nmr spectrum, the cyclo- propyl carbons C-1, C-2 and C-7 were observed at 53.96, 14.45 and 10.99 ppm, respectively. Similarly, the structures of 61 and 62 were assigned from their nmr data.

It is known in the literature that in allylic alcohols and ethers, cyclopropanation under Simmons - Smith conditions takes place from the side of the hydroxy or alkoxy substituent. This is explained by invoking coordination of the organozinc reagent with the oxygen atom of the substituent .



In our case, it meant that cyclopropanation must have taken place from the β face in D-glucal and D-galactal derivatives 31 and 32 and from the a face in the case of L-rhamnal derivative 33. We have shown that addition of dihalocarbenes proceeded from the a face in D-sugars and since reductive dehalogenation does not change the stereochemistry of the cyclopropane, we conclude that the Simmons - Smith reaction gives us a cyclopropane of opposite stereochemistry to the ones obtained by dehalogenation/reduction sequence.

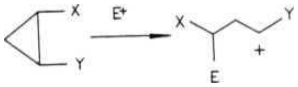


Thus, we have developed methods for the synthesis of cyclopropanated sugars of either α or (3 stereochemistry from glycals. With the cyclopropanes in hand, we were now ready to study some of their reactions.

REACTIONS OF SUGAR DERIVED CYCLOPROPANES:

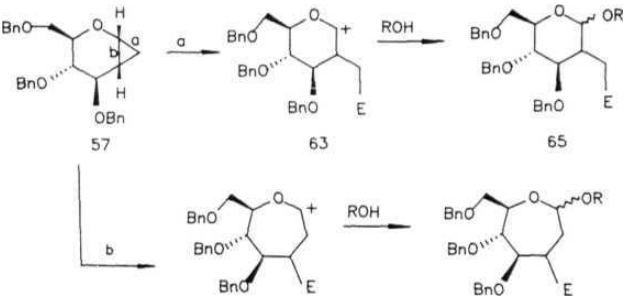
Cyclopropanes are a unique class of compounds. In many cases, their reactivity resembles that of a double bond. They undergo hydrogenation, halogenation and electrophilic additions **just like** double bonds . In fact, electrophilic additions **are** amongst the most important reactions of cyclopropanes . Some of **the commonly** used electrophiles are the proton, mercuric and thallic **salts and** N-haloamides/imides.

The electrophilic addition to cyclopropanes is illustrated schematically below. The regio- and stereochemistry of the addition depends on the nature of the substituents X and



We anticipated that cyclopropane 57 would open in such **a way that the** positive charge would reside at C-1, because of **the** stabilization provided by the adjacent ring oxygen. This **still leaves two** possibilities for the opening. Cleavage **of bond** marked **'a'** would provide **a** pyranosyl cation 64 whereas cleavage of bond **'b'** would lead to a septanosyl cation 65. An apriori prediction of **which** would prevail is difficult.

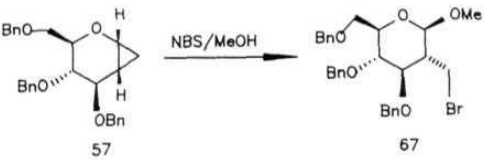
If alcohols **are** used as solvents, glycosides would result as a consequence of solvent capture at C-l. When sugar alcohols **are** used as nucleophiles, one would obtain di-/oligo



saccharides having a C-2 branching. Thus this methodology has potential for the synthesis of oligosaccharides.

We tested the above propositions by employing N-bromo succinimide and mercuric salts as electrophiles.

When treated with 1.2 equivalents of N-bromosuccinimide in methanol, cyclopropane 57 underwent a clean reaction furnishing the glycoside *61* as the only product in good yields (~60%). The product was readily characterized from its spectral



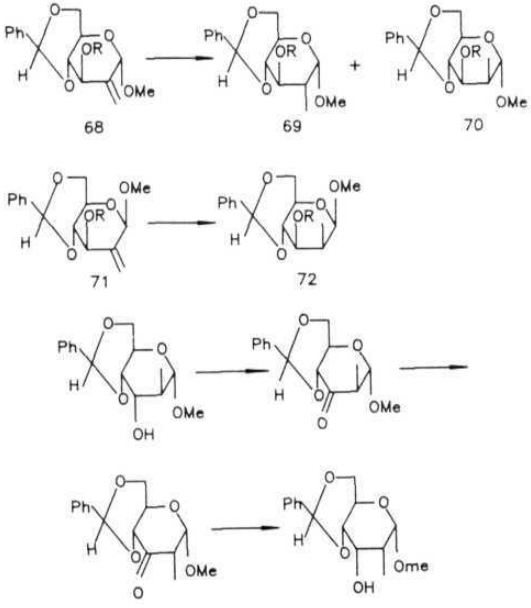
data. The mass spectrum of 67 showed the molecularion peak at m\z 540 and this suggested that bromine had reacted with the cyclopropane. In the C nmr spectrum, there were 11 lines in

addition to the aromatic signals. The signal at 57.2 ppm was assigned to the methoxide group. The high field signals at 31.6 and 47.7 ppm were assigned to C-7 and C-2, respectively. The anomeric carbon resonated at 102.3 ppm, which is in the normal range for anomeric carbons. This was a clear indication that the cyclopropane had opened to give a C1 cation.

In the ^{1}H nmr spectrum, there was only one high field signal integrating for one proton. This indicated that the ring opening had taken place to give a pyranoside and not a septanoside, since in the septanoside, the C-2 protons would each have appeared as a multiplet. The broad triplet at 1.70 ppm integrating for one proton, was therefore assigned to H-2. The anomeric signal was a doublet at 4.25 ppm with J = 8 Hz, suggestive of a trans coupling. Since an a cyclopropane was used, the mode of addition of methanol, by necessity, had to be β, unless a free cation was involved, in which case, mixture of a and β glycosides would have been produced. However, both H and C nmr clearly indicated that the product was a single anomer.

Thus, this method provides an interesting way to prepare 2-deoxy-2-bromomethyl-β-glycosides. The primary advantage of this method is that the branched chain glycosides are produced in just three steps from the readily available glycals. It is important to notice that this reaction produces a stereochemically well defined 1,2 trans-β-glycoside. This stereochemical arrangement is not easily attainable by other methods. For example, hydrogenation of the exo olefin 71 produced

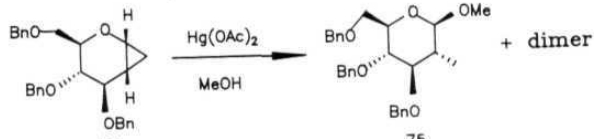
the β-manno isomer 72 exclusively, while 68 produced a mixture of α-gluco and α-manno isomers 69 and 70 respectively . In any case, these compounds are not easily synthesized. In another



instance, Hanessian has used a multiple step sequence to attain

this stereochemistry . Another advantage is that presence of bromine in the side chain enables further functionalization. Efforts are now underway to use this methodology for oligosaccharide synthesis using sugar alcohols as trapping agents for the pyranosyl cation.

We next studied the reaction of mercuric salts with cyclopropane 57. Mercuration of the cyclopropane was achieved by treating it with mercuric acetate in methanol. The reaction was rapid and the resultant mercurio sugar was demercurated by treatment with excess sodium borohydride. After chromatographic separation, two products were obtained. Once again, nmr spectroscopy was used in structure determinations. The fast moving fraction obtained in about 30% yield, showed a doublet



with a coupling constant of 6 Hz at 1.05 ppm in the H nmr spectrum, indicating the presence of a methyl group. This signal was assigned to a branched methyl group. A multiplet at 1.90 ppm was assigned to C-2 hydrogen from the analysis of the 2D COSY spectrum (figure 8). This signal showed cross peaks with signals at 1.05, 3.20 and 4.0 ppm. The 4.0 ppm signal was assigned to the anomeric proton as this did not show any other cross peaks. The 1.05ppm signal also did not show any cross peaks other than the one already described. Consequently, the 3.20 ppm signal was assigned to H-3. All these observations taken together strongly indicated the product was a 2-deoxy-2C-methyl glycoside 75. The stereochemistry of the glycosidic bond was established from the coupling constant values. The anomeric proton showed a coupling

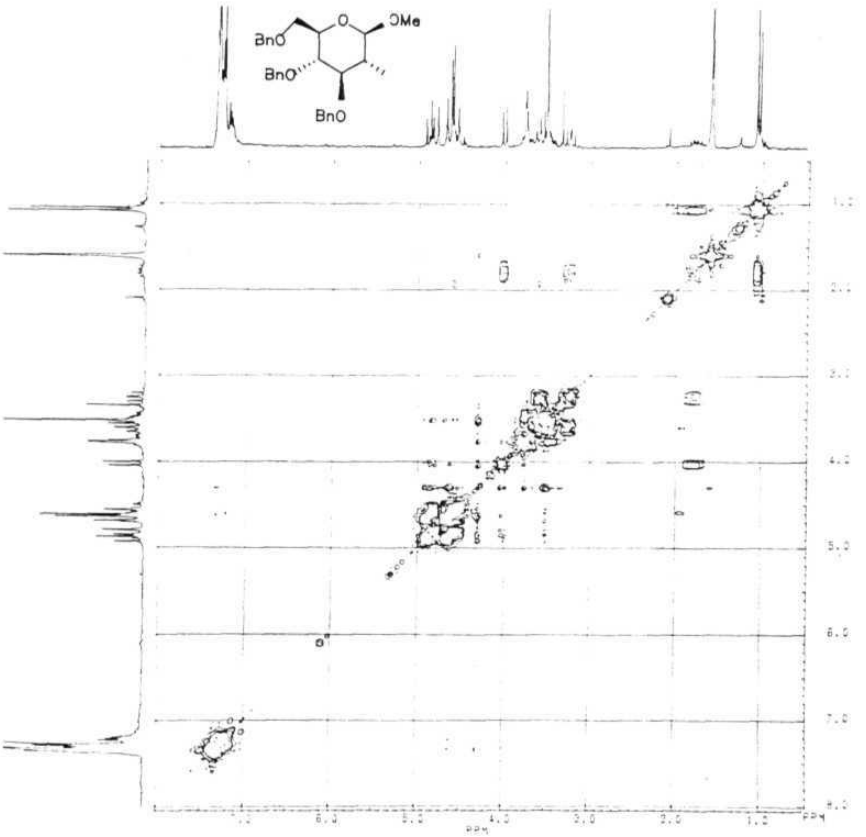
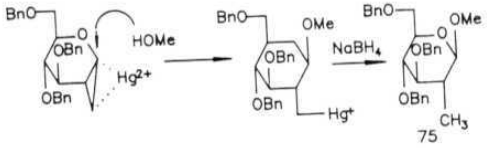


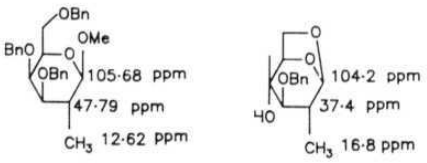
Figure 8: HH COSY spectrum of 75

of 8 Hz to H-2. Other couplings could not be determined because of several overlapping signals. In six membered rings, a coupling of this magnitude is normally associated with trans diaxial bonds. The trans coupling demands that H-1 be axial resulting in the glycoside having a (3 configuration.

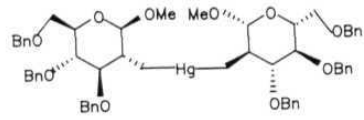
Mechanistically, this product can arise by the attack of mercuric ion on the 1,7-edge of the cyclopropane followed by attack by the solvent from the β side, since the solvent will **not** be able **to** approach C-1 from the a face. Subsequent reductive demercuration by sodium borohydride leads to 75.



Since this compound is not reported in the literature, no direct comparison was possible. However, we found a nearly identical model in 1,6-anhydro -3-O-benzyl - 2-deoxy - 2,4-di-C-methyl-4-O-mesyl-β-D-galactopyranose . The C rar values for the model compound and our compound are given below and these further substantiate our assignment.



The other product was isolated in 23% yield. This compound showed in its FAB mass spectrum a cluster of peaks at m/z 1120-1125. As the carbohydrate unit accounts only for 461 mass units, it is likely that the product is a bis (glycosyl)mercury compound 76, whose M = 1121 (for Hg).



76

NMR evidence also supports this structure. The C nmr spectrum showed only 11 signals apart from the aromatic signals, strongly indicating a symmetrical structure. In the high field region of the H nmr spectrum, multiplets each integrating for one proton, were seen at 0.80, 1.10 and 2.10 ppm. In order to assign these signals, a 2D COSY experiment was performed on this compound (figure 9) . The 2.10 ppm multiplet showed four cross peaks corresponding to signals at 0.80, 1.10, 3.20 and 4.0 ppm. As **the** 4.0 ppm signal (a doublet) did not show any other cross peak, it was assigned as H-1, and therefore, by correlation, 2.10, 0.80 and 1.10 ppm signals were assigned H-2, H-7, H-7', respectively. The triplet at 3.20 ppm was assigned as H-3. Further connectivities could not be established because of signal overlapping. The **37.7** and 47.9 ppm signals in the C nmr spectrum were shown to be methylene and methine carbons, respectively, by a DEPT-135 experiment. A CH-COSY experiment **was**

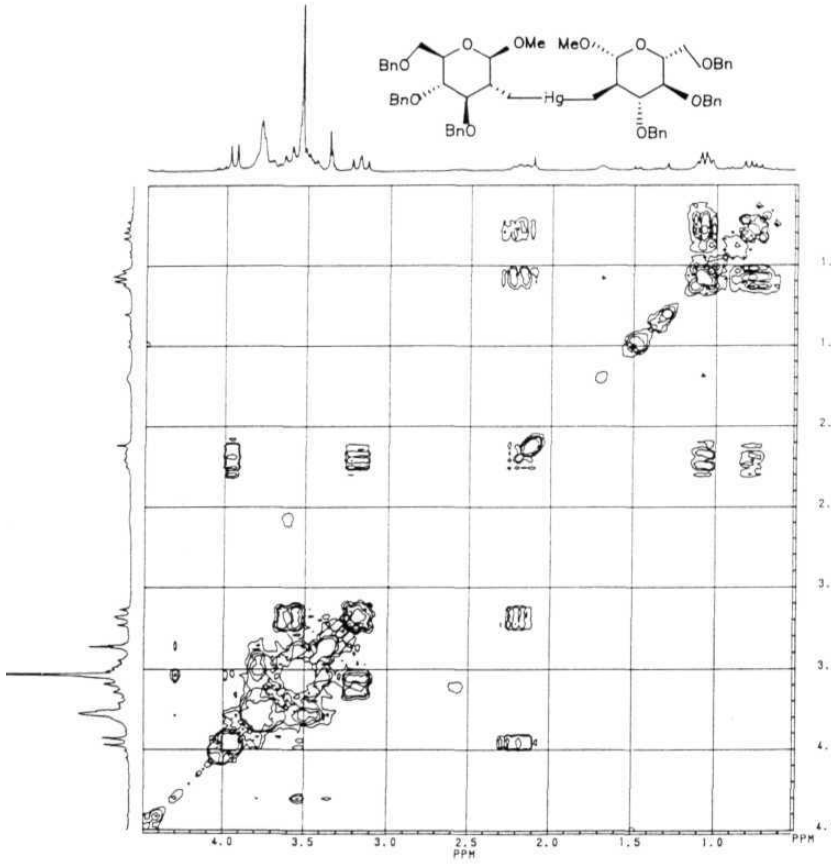
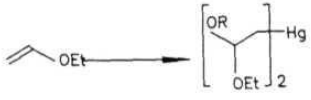


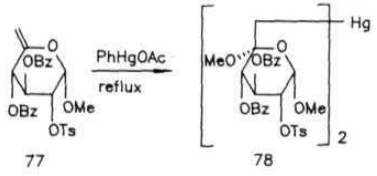
Figure 9: HH COSY spectrum of 76

performed in order to establish the CH connectivities unambigously. However, no cross peaks were observed between 37.7 (carbon) and 0.80 and 1.10 ppm (proton) signals. All other carbon signals were paired to their respective proton counterparts. As a result of this, we could establish the correlation between 37.7 ppm (carbon) and 0.80 and 1.10 ppm (proton) signals **only** indirectly. On the basis of the above experimental results, we assigned the structure 76 to this product.

There are isolated reports about the formation of dialkyl mercury compounds in the reaction of enol ethers with mercuric salts[88]

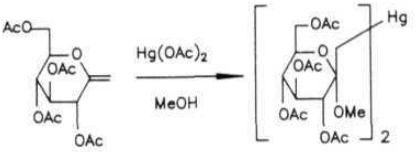


Ferrier reported that enolic sugar derivatives with an exocyclic double bond such as 77 when refluxed with phenylmercury acetate gave the organomercury compound 78. However, when mercurated with mercuric acetate, normal monomeric products **were** obtained.



77 78

In another instance, exocyclic olefinic sugars were reported to form bis organomercury compounds when treated with excess of mercuric acetate at room temperature[90]



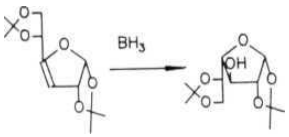
79 80

The formation of 78 was concluded to have taken place by a second alkylation with the sugar olefin cleaving the labile phenyl-Hg bond. In the present case, however, it is not clear enough which mechanism is operating. Further studies are necessary to provide a suitable explanation for this process.

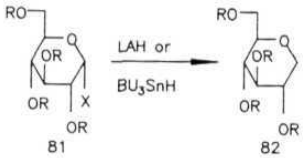
HYDROBORATION OF GLYCALS:

The hydroboration reaction invented, and developed by H.C. Brown, has become one of the most important methods for the hydroxylation of olefins[91]. Many hydroborating agents are now available that stereospecifically hydroborate olefins.

Several types of olefins have been hydroborated in the past. It is known that electron rich olefins like enol ethers undergo hydroboration exclusively at the β carbon atom, producing β-hydroxy ethers[92]. In one of the earliest examples of hydroboration of unsaturated sugars, the furanoid glycal A gave the galactofuranose with high stereoselectivity[93]. Surprisingly, no reports are available on the hydroboration of simple glycals.



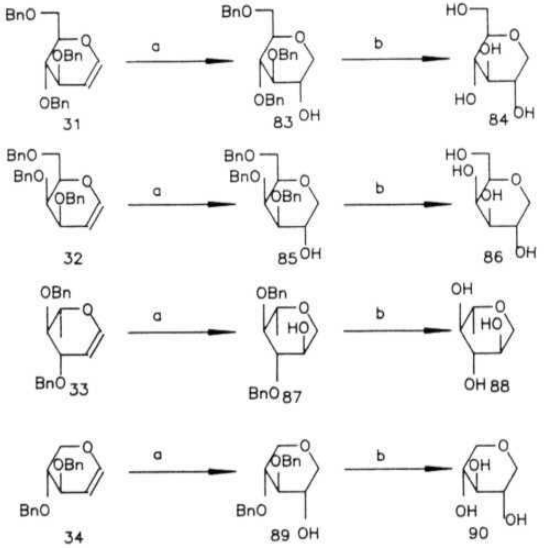
We anticipated that hydroboration of glycals would produce 1,5-anhydroalditols, based on the regiochemistry of hydroboration of enol ethers. The literature methods for the preparation of 1,5-anhydroalditols involve the reductive dehalogenation of glycosyl halides with either tributyltin hydride[94] or lithium aluminum hydride[9] and reductive desulfurization of thioglycosides using Raney Nickel[5].



81 82

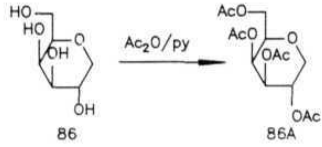
Our main interest was to see the directing influence of the adjacent chiral centre on the hydroboration reaction. We performed the hydroboration reaction using excess diborane on four representative glycals namely, 31, 32, 33 and 34. Without exception, all of them gave good yields of the corresponding alcohols. In the IR spectra, the O-H stretching vibration was observed at 3450 cm and in the H nmr spectra, olefinic signals

of the glycals were absent. Direct comparison of the spectral data of these compounds was not possible as these partially benzylated anhydro alditols are not reported in the literature. Therefore, the benzyl protecting groups were removed by hydrogenolysis.



Reagents and conditions: *a)* $BH_3.THF, 0^{\circ}$; H_2O_2, NaOH; *b)* 20% $Pd(OH)_2/C$, H

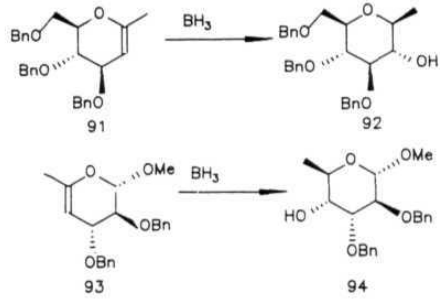
The product 83, from tribenzyl glucal, after debenzylation was identified as 1,5-anhydroglucitol 84 by comparison of its properties with literature data . Similarly, the xylal derivative 89 produced 1,5-anhydroxylitol 90. The rhamnal derivative 87 gave a compound whose physical data did not match with those of 1,5-anhydrorhamnitol[95]. A very good match was found in 1,5-anhydro-6-deoxy-D-glucitol **88A**[99]. The melting point and the magnitude of optical rotation of our compound were nearly identical with the values for **88A,** but the signs of rotation **were** opposite. Therefore, our compound is 1,5-anhydro-6-deoxy-L-glucitol (88). Surprisingly, the product **86** obtained debenzylating 85 did not crystallize. Therefore, we acetylated the material and obtained a tetraacetate whose optical rotation was very close to that reported for 2,3,4,6-tetra-O-acetyl 1,5-anhydro-D-galactitol **(86A).**



86 86A

We find that the hydroboration of glycals takes place **from the** opposite side of the C3 substituent, giving rise **to** an equatorial alcohol after oxidative work up. This is in contrast to the observation of Stevens who reported that 91 undergoes hydroboration by the axial attack leading to 92 . However, our results are in agreement with the observations made by Hanessian

on a related system . Further aspects of the chemistry of organoboranes derived from glycals are currently being pursued in our laboratory. Some of these include the possibility of



asymmetric hydroboration with these chiral organoboranes as well as conversion of the organoboranes into other functional groups.

CONCLUSIONS:

Our experiments with glycals have only reinforced the versatility of unsaturated sugars. We have been successful in our attempts to synthesize functionalized oxepins from glycals via dihalocarbene addition followed by solvolysis. Sugar derived cyclopropanes of either stereochemistry have been prepared using inexpensive reagents starting from glycals. Electrophile mediated solvolysis of these cyclopropanes has been **shown** to be a convenient method for the synthesis of C-2 branched sugars. Finally, hydroboration of glycals give differentially protected 1,5-anhydroalditols. It is our hope that the methods described in **this work** find use in organic synthesis.

Experimental

All reagents were purified by appropriate methods just before use. Solvents used for chromatography were of commercial grade and were fractionally distilled before use. Column chromatography was performed using ACME silica gel (100-200 mesh) and eluted with appropriate mixtures of hexane and ethyl acetate. Hexane refers to the petroleum fraction boiling between 60-70°. Thin layer chromatography (tlc) was performed on home made plates coated with ACME silica gel GF254 and were visualized 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 AUTOPOL polarimeter or on a SHIMADZU polarimeter at 25°. Infrared spectra were recorded on PERKIN - ELMER model 1310 spectrophotometer or on a JASCO FT-IR 5300 instrument and were calibrated against polystyrene absorption at 1G01 cm . H and C NMR spectra were recorded on a BRUKER AF 200 NMR Spectrometer operating at 4.7 Tesla magnetic field strength in chloroform-d solutions with tetramethylsilane (TMS) as internal standard unless otherwise stated. DEPT and 2D NMR data were processed using standard software provided with the instrument. The 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, dt = doublet of a triplet, t = triplet, q = quartet, and m • multiplet; br = broad; coupling constants (J) measured in Hertz; number of protons integrated for; assignments (wherever possible).

Elemental analyses were obtained using PERKIN-ELMER model 240C-CHN analyzer. Work up refers to extraction with dichloromethane and drying the organic extracts over anhydrous magnesium sulfate.

Glycals **31, 32,** 33 and 34 were prepared by benzylating the free glycals with sodium hydride and benzyl chloride and were identified by comparison of their properties with literature data[61].

Dichlorocarbene addition to tribenzyl-D-glucal (31):

Aqueous sodium hydroxide (5.0 g in 10 ml) was added to a vigorously stirred solution of tribenzyl-D-glucal (31)(1.60 g, 3.84 mmol) in chloroform (10 ml) containing benzyltriethyl ammonium chloride (20 mg). The reaction mixture was stirred at 35° for 4h, and then diluted with water (25 ml) and then worked up. The residue was purified by chromatography followed by crystallization from methanol to furnish 3,4,6-tri-O-benzyl 1,5-anhydro-2-deoxy-1,2-C-dichloromethylene-D-glycero-D-gulo-hexitol (35).

yield : 1.60 g (84%)

m.p. : 62-63°

IR (KBr) : 3034, 3870, 1497, 1453, 1364, 1208, 1167, 1130, 1084, 1045, 733, 696 cm^{-1}.

^1H NMR : 6 1.78 (dd, J = 4.4, 7.9 Hz, 1H, H-2), 3.53 (m, 2H), 3.74 - 3.81 (m, 3H), 3.88 (d, J = 7.9Hz, 1H, H-1)

4.40 - 4.92 (m, 6H, OCH_2Ph), 7.25 - 7.40 (m, 15H, ArH).

^{13}C NMR : 34.41, 59.05, 61.62, 70.30, 71.96, 73.44, 74.63, 75.33, 77.53, 80.01, 127.73, 127.81, 127.98, 128.20, 128.43, 128.51, 138.09, 138.34 ppm.

$[\alpha]_D$: $+78^{\circ}$ (c1, $CHCl_3$)

Elemental analysis:

Calcd. for $C_{28}H_{28}Cl_2O_4$: C = 67.33, H = 5.65.

Found : C - 67.13, H = 5.66.

Dichlorocarbene addition to tri-O-benzyl-D-galactal (32):

Aqueous sodium hydroxide (1.50 g in 3 ml) was added to a vigourously stirred solution of 32 (315 mg, 0.76 mmol) and benzyltriethylammonium chloride (10 mg) in chloroform (3 ml). The biphasic reaction mixture was vigourously stirred for 24h at room temperature, diluted with water (10 ml) and worked up. The residue was purified by chromatography to obtain 3,4,6- tri-O-benzyl-1,5-anhydro-2-deoxy-1,2-C-dichloromethylene-D-glycero-L-manno-hexitol (36) as a syrup.

yield : 347 mg (92%).

IR(neat) : 1495, 1454, 1364, 1229, 1173, 1128, 1090, 1069, 1026, 737, 698 cm^{-1}.

^{1}H NMR : δ 1.96 (dd, J = 8.9, 4.2 Hz, 1H, H-2), 3.5 - 3.6 (m, 3H), 3.75 - 3.9 (m, 3H), 4.3 - 5.0 (m, 6H, OCH Ph), 7.25 - 7.38 (m, 15H, ArH).

^{13}C NMR : 31.09, 58.69, 61.81, 69.16, 71.21, 71.70, 73.55,

74.58, 75.32. 78.05, 127.72, 127.86, 127.98, 128.38, 128.50, 128.63, 137.65, 138.0, 138.68 ppm.

[α] : +13.5° (c1.2, $CHCl_3$).

Elemental analysis:

Calcd. for $C_{28}H_{28}Cl_2O_4$: C - 67.34, H = 5.65.

Found : C = 68.06, H = 5.67.

Dichlorocarbene addition to **di-O-benzyl-L-rhamnal** 33:

To a vigourously stirred chloroform solution of 33 (257 mg, 0.83 mmol) containing benzyltriethylammonium chloride (10 mg) was added aqueous sodium hydroxide (1.50 g in 3 ml). The biphasic reaction mixture was vigourously stirred for 18h, diluted with water (15 ml) and extracted with chloroform (4x15 ml). The combined organic extracts was dried, concentrated and purified by chromatography to give 3,4-di-O-benzyl-1,5-anhydro- 2,6-dideoxy-1,2-C-dichloromethylene-L-glycero-L-gulo-hexitol (37) as a colourless syrup.

yield : 310 mg (95%)

IR(neat) : 3032, 2976, 2868, 1497, 1454, 1368, 1246, 1208, 1100, 1028, 909, 878, 829, 735, 698 cm^{-1}.

^1H NMR : δ 1.28 (d, J = 6.4 Hz, 3H, H-6), 1.8 (dd, J = 8.2, 4.2 Hz, 1H, H-2), 3.29 (t, J = 7.4 Hz, 1H, H-4), 3.56 (d, J = 8.2 Hz, 1H, H-1), 3.76 (dd, 1H, H-3), 3.88 (m, 1H, H-5), 4.57 - 4.94 (m, 4H, OCH_2Ph), 7.32 (m, 10H, ArH).

^{13}C NMR : 19.84, 33.92, 57.86, 61.42, 71.99, 74.49, 76.06, 77.04, 81.07, 127.75, 127.92, 127.99, 128.36, **128.52,** 137.73, 138.33 ppm.

$[\alpha]_D$: -40° (c1.2, $CHCl_3$)

Elemental Analysis:

Calcd for $C_{21}H_{22}Cl_2O_3$: C = 64.13, H = 5.64.

Found : C - 63.92, H = 5.62.

Dichlorocarbene addition to **di-O-benzyl-D-xylal 34:**

Aqueous sodium hydroxide (500 mg in 1 ml) was added to a vigourously stirred solution of 34 (45 mg, 0.15 mmol) in chloroform (1 ml) containing benzyltriethylammonium chloride (5 mg). The biphasic reaction mixture was stirred at room temperarture for 18h, diluted with water (10 ml) and worked up. 3,4-Di-O-benzyl-1,5-anhydro-2-deoxy-1,2-C-dichloromethylene-D-gulo- pentitol (38) was obtained as a syrup after chromatographic purification.

yield : 31 mg (55%)

IR(neat) : 3063, 3032, 2870, 1497, 1454, 1368, 1208, 1100, 1026, 843, 737, 698 cm^{-1}.

^1H NMR : 6 1.77 (dd, J = 7.9, 3.8 Hz, 1H, H-2), 3.75 (m, 5H), 4.6 - 4.8 (m, 4H, OCH_2Ph), 7.30 - 7.37 (m, 10H, **ArH**).

^{13}C NMR : 33.08, 59.86, 60.87, 68.98, 72.02, 72.83, 75.39, 76.04, 127.78, 128.01, 128.46, 128.60, 137.64, 138.20 ppm.

[α] : +17.3° (c1.1, $CHCl_3$).

Elemental analysis:

Calcd. for $C_{20}H_{20}Cl_2O_3$: C = 63.33, H = 5.32

Found : C = 63.25, H = 5.29

Dibromocarbene addition to **tribenzyl-D-glucal** (31):

A solution of sodium hydroxide (2.0 g) and potassium fluoride (15.0 g) in water (15 ml) was added to a vigourously stirred solution of 31 (2.50 g, 6 mmol) in bromoform (10 ml) containing benzyltriethylammonium chloride (20 mg). The biphasic mixture was stirred for 2 days at room temperature and then diluted with water (40 ml) and extracted with ether (4x40 ml). The combined ether extracts were washed with brine, dried and concentrated. The residue was purified by chromatography followed by crystallization from methanol-ethyl acetate to give 3,4,6-tri-O-benzyl-1,5-anhydro-2-deoxy-1,2-C-dibromomethylene-D-glycero-D-gulo-hexitol (39).

yield : 2.80 g (79%)

m.p. : 58-60°.

IR (KBr) : 1500, 1460, 1360, 1200, 1120, 1080, 740, 700 cm^{-1}.

^1H NMR : 6 1.86 (dd, J = 4.56, 7.8Hz, 1H, H-2); 3.58 (m, 2H); 3.60- 3.80 (m, 3H); 3.94 (d, J = 7.8HZ, 1H, H-1); 4.40-4.80 (m, 6H, OCH_2Ph); 7.25-7.40 (m, 15H, ArH).

C NMR : 34.06, 35.00, 59.06, 70.00, 71.53, 73.06, 74.30, 74.83, 79.71, 80.06, 127.59, 127.77, 128.07, 128.24, 128.36, 137.71, 137.89, 138.18 ppm.

$[\alpha]_D$: +72° (c1, $CHCl_3$).

Elemental analysis:

Calcd. for $C_{28}H_{28}Br_2O_4$: C = 57.16, H = 4.80.

Found : C = 57.00, H = 4.73.

Dibromocarbene addition to tribenzyl-D-galactal (32):

To a stirred solution of 32 (308 mg, 0.74 mmol) and benzyltriethylammonium chloride (10 mg) in bromoform (2 ml) was added an aqueous solution (2.5 ml) of sodium hydroxide (350 mg) and potassium fluoride (2.5 g). The biphasic mixture was vigourously stirred at room temperature for 24h, diluted with water (10 ml) and extracted with ether (4x15 ml). The combined ether extracts were washed with water, dried and concentrated. 3,4,6-Tri-O-benzyl-1,5-anhydro-2-deoxy-1,2-C-dibromomethylene -D-glycero-L- manno-hexitol (40) was obtained as a pale yellow syrup after chromatography.

yield : 311 mg (71%).

IR(neat) : 3050, 2900, 1510, 1460, 1370, 1240, 1180, 1100, 760, 710 cm^{-1}.

^1H NMR : 5 2.06 (dd, J = 8.8, 4.0 Hz, 1H, H-3), 3.55 (m, 3H), 3.88 (m, 2H), 3.97 (d, J = 8.8 Hz, H-1), 4.44 - 4.97 (m, 6H, OCH_2Ph),

^{13}C NMR : 32.16, 35.15, 59.13, 69.08, 71.13, 71.89, 73.52, 74.61, 77.70, 78.5, 127.69, 127.85, 128.35, 128.47, 128.61, 129.23, 137.63, 137.93, 138.62 ppm.

[α] : +20° (c1, $CHCl_3$).

High Resolution Mass data:

Calcd. for $C_{28}H_{28}Br_2O_4$: 589.0415

Found : 589.0414

Dibromocarbene addition to **dibenzyl-L-rhamnal** (33):

Dibenzyl-L-rhamnal (33) (540 mg, 1.74 mmol) and benzyl triethylammonium chloride (10 mg) were dissolved in bromoform (3 ml) and treated with an aqueous solution (3 ml) of sodium hydroxide (420 mg) and potassium fluoride (3.0 g). The biphasic mixture was stirred vigourously for 2 days at room temperature, diluted with water (30 ml) and extracted with ether (4x20 ml). The combined organic extracts were washed with water, dried and concentrated. The products were separated by chromatography.

Major product:

3,4-Di-O-benzyl-1,5-anhydro-2-deoxy-1,2-C-dibromomethylene-L-glycero-L-gulo-hexitol (41):

yield : 580 mg (69%)

IR(neat) 2850, 1440, 1360, 1200, 1100, 740, 720, 690 cm^{-1}.

^1H NMR *6* 1.27 (d, J = 6.4 Hz, 3H, H-6), 1.88 (dd, J 7.9, 4.2 Hz, 1H, H-2), 3.30 (dd, J = 9.1, 7.3 Hz, 1H, H-4), 3.65 (dd, J = 9.1, 4.3 Hz, 1H, H-3), 3.88 (m, 2H, H1,

^{13}C NMR 20.06, 33.73, 35.11, 58.33, 72.02, 74.58, 76.66, 79.66, 81.13, 127.83, 127.97, 128.08, 128.43, 128.60, 137.86, 138.34 ppm.

$[\alpha]_D$: -49° (cl, $CHCl_3$)

High Resolution Mass data:

Calcd. for $C_{21}H_{22}Br_2O_3$: 480.9838

Found : 480.9842

Minor product:

3,4-Di-O- benzyl- 1,5-anhydro- 2-deoxy- 1,2-C-dibromomethylene-L-glycero-L-talo-hexitol (42):

yield : 97 mg (12%).

m.p. : 104-106" (MeOH).

IR **(KBr)** : 1440, 1380, 1180, 1060, 1020, 900, 760, 700 cm^{-1}.

^1H **NMR** : 6 1.29 (d, J = 6 Hz, 3H, H-6), 2.27 (t, J = 8 Hz, 1H, H-2), 3.43 (m, 1H, H-5), 3.56 (dd, J = 7.2, 9.9 Hz, 1H, H-4), 4.00 (d, J 7.9 Hz, 1H, H-1), 4.12 (dd, J = 8.2, 7.2 Hz, 1H, H-3), 4.64 (dd, J = 11.7, 17.7 Hz, 2H, OCH_2Ph), 4.90 (dd, J = 9.8, 11.7 Hz, 2H, OCH_2Ph), 7.26 - 7.36 (m, 10H, ArH).

^{13}C **NMR** : 17.61, 31.19, 33.92, 62.68, 71.03, 74.86, 74.95, 78.46, 81.43, 127.79, 128.01, 128.13, 128.42, 128.65, 137.95, 138.38 ppm.

$[\alpha]_D$: +48° (cl, $CHCl_3$).

Elemental analysis :

Calcd. for $C_{21}H_{22}Br_2O_3$: C • 52.30, **H** = 4.60.

Found : C = 52.30, H = 4.59.

Dibromocarbene addition to **di-O-benzyl-D-xylal** (34):

An aqueous solution (2.5 ml) of sodium hydroxide (350 **mg**) and potassium fluoride (2.5 g) was added to a vigourously stirred solution of 34 (296 **mg**, 1 **mmol**) and benzyltriethyl **ammonium** chloride (5 mg) in bromoform (2 ml). Vigourous stirring was continued for 2 days, then the reaction mixture was diluted with water (30 ml) and extracted with ether (3x25 ml). The combined organic extracts were washed with water, dried and concentrated. The residue was purified by **chromatography** to furnish 3,4-di-O-benzyl-2-deoxy-1,2-C-dibromomethylene-D-gulo-pentitol (43) as a pale yellow syrup.

yield : 300 mg (64%)

^{1}H NMR : δ 1.88 (dd, J = 7.8, 3.8 Hz, 1H, H-3), 3.70 - 4.0 (m, 5H), 4.60 - 4.90 (m, 4H, OCH_2Ph), 7.26 - 7.42 (m, 10H, ArH).

^{13}C NMR : 32.81, 34.06, 60.37, 69.47, 71.97, 72.91, 75.40, 78.71, 127.78, 128.04, 128.22, 128.46, 128.58, 137.72, 138.24 ppm.

$[\alpha]_D$: +13.7 (c0.7, $CHCl_3$)

Mass spectral data: m/z 467 (M^+-1), 377, 325, 263, 182, 101, 91.

Solvolysis experiments with the dichlorocyclopropane 35 :

Without any catalysts:

1) A solution of the dichlorocyclopropane 35 (98 mg) in acetic acid (5 ml) was heated under reflux for 16h. The cooled reaction mixture was poured into water (20 ml) and extracted with

ether. The ether extracts were washed with sodium bicarbonate solution and dried. The starting material was recovered unchanged as indicated by tlc and H NMR analysis.

With boron trifluoride etherate:

2) To a stirred solution of the substrate 35 (49 mg, 0.1 mmol) in acetic acid (1 ml) was added a few drops of boron trifluoride etherate. No reaction was observed even after 1 week at room temperature.

3) To a solution containing the dichlorocyclopropane 35 (200 mg, 0.4 mmol) in acetic acid (5 ml), boron trifluoride etherate (0.5 ml) was addded and the solution was heated under reflux for 24h. Only a complex mixture was obtained as indicated by tlc.

4) A reaction mixture of the substrate (50 mg, 0.4 mmol) and boron trifluoride etherate (0.1 ml) in acetic acid (1 ml) was heated under reflux for 1h. No reaction was observed.

With silver nitrate:

5) A solution of the dichlorocyclopropane 35 (50 mg, 0.1 mmol) and silver nitrate (51 mg, 0.3 mmol) in methanol (1 ml) was heated under reflux for 2h. No reaction was observed and the starting material was recovered unchanged.

With silver acetate catalysis:

6) A solution containing the substrate 35 (15 mg, 0.03

mmol) and silver acetate (10 mg, 0.06 mmol) in acetic acid (0.2 ml) was heated under reflux for 4h. Tlc of the reaction mixture indicated that no reaction had taken place.

With silver tetrafluoroborate:

7) A solution containing 35 (10 mg, 0.02 mmol) and silver tetrafluoroborate (10 mg, 0.05 mmol) in acetic acid (0.2 ml) was stirred at room temperature for 22h. It was then diluted with water (5 ml) and extracted with dichloromethane (3x5 ml). The organic layer was washed with sodium bicarbonate solution and dried. Tlc of the residual material was identical with the starting material.

8) A mixture containing the substrate 35 (10 mg, 0.02 mmol) and silver tetrafluoroborate (10 mg, 0.05 mmol) in acetic acid (0.2 ml) was maintained at 75-80°. Tlc of the reaction mixture was identical to that of the starting material after 24h.

9) The substrate 35 (110 mg, 0.22 mmol), silver tetrafluoroborate (64 mg, 0.33 mmol) and sodium acetate (27 mg, 0.33 mmol) in acetic acid (1 ml) was heated to 75-80° and maintained at that temperature for 24h. No reaction was observed as indicated by tlc analysis.

With silver perchlorate:

10) The substrate 35 (50 mg, 0.1 mmol) and silver perchlorate (25 mg, 0.11 mmol) were dissolved in methanol (2 ml) and heated to reflux. No reaction was observed as indicated by

tlc analysis after 16h.

11) Water (0.1ml) was added to a stirred solution of the substrate 35 (125mg, 0.25mmol) and silver perchlorate (63mg, 0.3mmol) in acetone (5ml) at room temperature and stirring was continued for 24h. Tlc showed that no reaction was taking place.

With potassium t-butoxide:

12) To a stirred solution of the dichlorocyclopropane 35 (52 mg, 0.1 mmol) in t-butanol (1 ml) was added a small piece of potassium metal and the solution was refluxed overnight. The solution was poured into water (5ml) and extracted with ether (3xl0ml). The ether extracts were dried and concentrated. H NMR of the crude product and tlc indicated that solvolysis had taken place. This reaction, however, could not be reproduced. Commercial potassium t-butoxide was not useful in this reaction.

With sodium methoxide:

13) The dichlorocyclopropane 35 (50 mg, 0.1 mmol) was added to a solution of sodium methoxide (32 mg, 0.6 mmol) in methanol (1 ml) and the mixture was heated under reflux. The reaction was very sluggish and no appreciable amount of product was formed even after 48h of heating.

Solvolysis experiments with the dibromocyclopropane 39:

With silver acetate:

1) A solution containing the substrate 39 (84 mg, 0.14

mmol) and silver carbonate (40 mg, 0.14 mmol) in acetic acid (1 ml) was heated under reflux overnight. No reaction was observed and the starting material was recovered.

With silver trifluoroacetate:

2) The substrate 39 (30 mg, 0.05 mmol) and silver carbonate (17 mg, 0.06 mmol) were dissolved in trifluoroacetic acid (0.5 ml) and stirred at room temperature for 2h. The solution was diluted with water (5 ml) and extracted with ether (3x5 ml). The ether solution was dried and concentrated. The H NMR spectrum of the crude material showed that only the starting material was present.

With silver triflate:

3) A solution of the dibromocyclopropane 39 (194 mg, 0.33 mmol) and silver triflate (85 mg, 0.33 mmol) in acetic acid (5 ml) was heated under reflux for 16h. The reaction mixture turned black and became very thick, and extraction with ether was very difficult. The ether extracts were washed with water, sodium bicarbonate solution, dried and concentrated. From the residue only benzyl acetate was isolable by chromatography although the 'H NMR spectrum of the crude reaction mixture showed the presence of acetate signals. Benzyl acetate was identified by its characteristic smell and by comparison of its H NMR spectrum with literature data.

4) The substrate 39 (46 mg, 0.08 mmol) and silver triflate (20 mg, 0.08 mmol) in acetic acid (1 ml) was heated under reflux for 1h. Again only benzyl acetate was detected. No other products could be isolated.

5) A solution of the dibromocyclopropane 39 (84 mg, 0.14 mmol) and silver triflate (35 mg, 0.14 mmol) in acetic acid (2 ml) was maintained at 80° for 3h. It was then poured into water (5 ml) and extracted with ether (3x5 ml). The combined ether extracts were washed with sodium bicarbonate solution, dried and concentrated. No solvolysis product could be isolated from the residue although as many as five spots were seen in the tlc. Some benzyl acetate was isolated and identified by H NMR and by its characteristic smell.

6) A few drops of water were added to a stirred solution of the dibromocyclopropane 39 (34 mg, 0.06 mmol) and silver triflate (15 mg, 0.06 mmol) in acetone (1 ml) and the reaction mixture was stirred at room temperature for 24h. No reaction was observed at this temperature. The same solution was then heated at reflux for 8h. Again no reaction was observed.

7) A few drops of water were added to a solution of the substrate 39 (22 mg, 0.04 mmol) and silver triflate (15 mg, 0.06 mmol) in dioxane (1 ml) and the mixture was heated under reflux overnight. No reaction was observed as indicated by tlc analysis of the reaction mixture.

8) The dibromocyclopropane 39 (105 mg, 0.18 mmol) and silver triflate (50 mg, 0.20 mmol) were dissolved in 3:1

methanol:tetrahydrofuran (2 ml) and stirred at room temperature. Since, no reaction was observed at room temperature after 2 days, the solution was heated under reflux . After 4h, no reaction was observed as shown by tlc analysis.

With silver tetrafluoroborate :

9) The dibromocyclopropane 39 (12 mg, 0.02 mmol) and silver tetrafluoroborate (10 mg, 0.05 mmol) in acetic acid (0.1 ml) was stirred at room temperature for 1h, then poured into water (5 ml) and extracted with ether (3x5 ml). The ether extracts were washed with sodium bicarbonate solution, dried and then concentrated. The residual material was identical with the starting dibromocyclopropane 39 by tlc analysis.

With silver perchlorate:

10) The dibromocyclopropane 39 (34 mg, 0.06 mmol) and silver perchlorate (18 mg, 0.09 mmol) were dissolved in acetic acid (1 ml) and maintained at 60-70° for 8h. Tlc showed absence of any product. Only the starting material was recovered.

11) The reactants, 39 (78 mg, 0.13 mmol) and silver perchlorate (82 mg, 0.40 mmol) were dissolved in 4:1 acetonitrile - water (2 ml) and heated under reflux for 24h. Tlc analysis at this stage showed the presence of a complex mixture with starting dibromocyclopropane being the major component. However, no attempts were made to purify this mixture.

Solvolysis experiment with dibromocyclopropane 43:

A mixture containing the dibromocyclopropane 43 (120 mg, 0.26 mmol), silver perchlorate (108 mg, 0.52 mmol) and sodium carbonate (165 mg, 1.56 mmol) in methanol (5 ml) was heated under reflux. No noticeable change was seen in the tlc after 12h.

Solvolysis experiments with dibromocyclopropanes 39, 40, 41 and 43 under basic conditions:

The reaction mixture containing the dibromocyclopropane (1 eq.) and anhydrous potassium carbonate (6 eq.) in methanol (10 ml/mmol of substrate) was refluxed for 12h under a nitrogen atmosphere. The reaction mixture was cooled to room temperature, diluted with water and extracted with dichloromethane (4x). The combined organic extracts were dried, concentrated under reduced pressure and the products were separated by chromatography. The products derived from 40, 41, and 43 were found to be unstable and therefore their elemental analyses were not attempted. The dibromocyclopropane 39 gave the following products:

Major product 47:

yield : 38.4%

IR(neat) : 2850, 1440, 1340, 1200, 1160, 800, 730, 700 cm^{-1}.

^1H NMR : 6 3.45 (s, 3H, OCH_3), 3.59 - 3.72 (m, 4H, H-5, H-6, H-7, H-7')« 4.25 - 4.66 (m, 6H, OCH_2Ph), 4.73 (s, 1H, H-4), 5.17 (s, 1H, H-1), 6.79 (s, 1H, H-3), 7.14 - 7.34 (m, 15H, ArH).

^{13}C NMR : 55.19 (OCH), 69.73 (C-7), 70.86 (OCH_2Ph), 71.60 (OCH_2Ph, C-6), 73.21 (OCH_2Ph), 76.30 (C-4), 79.42 (C-5), 98.98 (C-l), 112.56 (C-3), 127.53, 127.73, 127.91, 128.06, 128.37, 137.64 (C-2), 137.78, 138.20, 138.44 ppm.

$[\alpha]_D$: +69° (c2,$CHCl_3$)

Elemental analysis:

Calcd. for $C_{29}H_{31}BrO_5$ C = 64.56, H - 5.79.

Found C = 64.75, H = 5.84.

Minor product 48:

yield : 29.3%

IR(neat) : 2850, 1620, 1440, 1340, 1200, 1100, 1020, 900, 800, 730, 690 cm^{-1}.

^1H NMR : 6 3.52 (s, 3H, OCH_3), 3.85 - 4.00 (m, 4H, H-5, H-6, H-7, H-7'), 4.50 - 4.80 (m, 7H, OCH_2Ph, H-4), 5.09 (s, 1H, H-1), 6.80 (s, 1H, H-3), 7.27 - 7.34 (m, 15H, ArH).

^{13}C NMR : 55.80 (OCH_3), 70.65 (C-7), 70.95 (OCH_2Ph), 72.25 (OCH_2Ph), 73.35 (OCH_2Ph), 74.73 (C-4), 74.97 (C-6), 76.11 (C-5), 101.20 (C-l), 114.70 (C-3), 127.63, 127.79, 128.00, 128.32, 128.41, 128.48, 137.10 (C-2), 137.87, 138.37, 138.46 ppm.

$[\alpha]_D$: +26.7 (c1, $CHCl_3$).

The dibromocyclopropane 40 gave an inseparable mixture of products 49.

yield : 55%

^1H NMR : 5 3.46 (s, 3H, OCH_3), 3.49 (s, 3H, OCH_3), 3.7 - 3.79 (m, 3H), 4.4 - 4.9 (m, 8H), 4.86 (s, 1H, H1), 6.67 (s, H-3), 7.32 - 7.41 (m, ArH).

^{13}C NMR : 55.56, 55.70. 68.46, 70.69, 70.76, 71.39, 72.23, 72.66, 73.47, 73.28, 73.39, 74.67, 75.95, 100.26, 101.52, 107.53, 112.65, 127.31, 127.63, 127.77, 128.06, 128.17, 128.32, 137.03, 137.16, 137.96, 138.19, 138.27, 138.35, 138.69 ppm.

The dibromocyclopropane 41 gave the following products:

yield : 60%

IR(neat) : 3032, 2934, 1684, 1628, 1454, 1358, 1146, 1090, 735, 698 cm^{-1}.

^1H NMR : *6* 1.43 (d, J = 6.3 Hz, 3H, H-7), 3.50 (s, 3H, OCH), 3.52 - 3.8 (m, 4H), 4.50 - 4.80 (m, 4H, OCH Ph), 5.06 (S, 1H, H-1), 6.81 (s, 1H, H-3), 7.30 - 7.43 (m, 10H, ArH).

^{13}C NMR : 19.35, 55.57, 70.97, 71.33, 72.43, 76.04, 81.66, 101.49, 114.02, 127.18, 127.54, 127.79, 127.92, 128.25, 128.40, 128.77, 137.68, 137.88, 138.46 ppm.

The dibromocyclopropane 43 gave an inseparable mixture of products.

yield : 50%

^1H NMR : δ 3.45 (s, 3H, OCH_3), 3.62 (br, 2H), 4.26 - 4.72 (m, 5H) 4.78 (d, J = 2.9 Hz, xH), 5.00 (s, 1H, H-1), 6.77 (S, 1H, H-3), 7.26 - 7.39 (m, 10H, ArH)

^{13}C NMR : 55.26, 58.59, 70.13, 71.23, 71.35, 74.94, 100.94, 114.90, 127.68, 127.70, 127.83, 127.94, 128.30, 128.45, 128.69, 135.73, 137.88, 138.46 ppm.

Reaction of dichlorocyclopropane 35 with Bu_3SnH:

To a stirred solution of the dichlorocyclopropane 35 (499 mg, 1.0 mmol) in degassed chlorobenzene (6 ml) was added tributyltin hydride (640 mg, 2.2 mmol) and the solution was maintained at 120° for 10h. The reaction mixture was cooled, concentrated under reduced pressure and the product, 3,4,6-tri-O-benzyl-2-deoxy-1,2-chloromethylene-D-glycero-D-gulo-hexitol (52) was obtained as a colourless syrup after chromatographic purification of the residue.

yield : 139 mg (30%)

IR(neat) : 3030, 2865, 1497, 1454, 1366, 1206, 1096, 1028, 737, 698 cm^{-1}.

H NMR : *i* 1.48 (m, 1H, H-2), 3.14 (dd, J = 4, 1.3 Hz, 1H, H-7), 3.50 - 3.90 (m, 6H), 4.50 - 4.80 (m, 6H, OCH_2Ph), 7.26 - 7.35 (m, 15H, ArH).

^{13}C NMR : 26.40, 34.08, 56.51, 69.45, 71.49, 73.08, 73.39, 74.88, 75.45, 75.51, 127.76, 127.95, 128.46, 128.55, 137.77, 138.11 ppm.

$[\alpha]_D$: +22.7° (c1.2, $CHCl_3$).

Elemental analysis:

Calcd. for $C_{28}H_{29}ClO_4$: C = 72.32, H = 6.29.

Found : C = 72.25, H = 6.28.

LAH reduction of dichlorocyclopropane 35:

To a stirred suspension of lithium aluminum hydride (277 mg, 7.29 mmol), in dry tetrahydrofuran (4 ml) was added, a solution of the dichlorocyclopropane 35 (400 mg, 0.80 mmol) in tetrahydrofuran (10 ml). After stirring for 2h at room temperature, the reaction mixture was cooled in ice and quenched by careful addition of saturated aqueous sodium sulfate. The salts were filtered and washed several times with ethyl acetate. The filtrate was dried and concentrated. The residue on chromatographic purification furnished 3,4,6-tri-O-benzyl-1,5-anhydro-2-deoxy-1,2-C-methylene-D-glycero-D-gulo-hexitol (57) as a colourless syrup.

yield : 270 mg (78%).

^1H NMR : *6* 0.67 - 0.75 (m, 2H, H-7), 0.80 - 1.0 (m, 1H, H-2), 3.55 - 3.72 (m, 6H), 4.53 - 4.82 (m, 6H, OCH_2Ph), 7.25 - 7.37 (m, 15H, ArH).

^{13}C NMR : 11.60, 14.93, 49.73, 70.21, 71.20, 73.36, 73.51, 76.90, 77.17, 80.17, 127.66, 127.76, 128.00, 128.45,

138.41, 138.55, 138.71.

$[\alpha]_D$: +62° (c1, $CHCl_3$).

Elemental analysis:

Calcd. for $C_{28}H_{30}O_4$: C = 78.11, H = 7.02.

Found : C = 78.00, H = 7.05.

LAH reduction of dichlorocyclopropane 37:

To a stirred suspension of lithium aluminum hydride (171 mg, 4.50 mmol) in tetrahydrofuran (4 ml) was added dropwise a solution of the dichlorocyclopropane 37 (177 mg, 0.45 mmol) in tetrahydrofuran (6 ml). After stirring at room temperature for 4h, the reaction mixture was cooled in ice and carefully quenched by adding saturated aqueous sodium sulfate. The salts were filtered, washed several times with ethyl acetate. The filtrate was dried and concentrated. 3,4-Di-O-benzyl-1,5-anhydro-2,6-dideoxy-1,2-C-methylene-L-glycero-L-gulo-hexitol (58) was obtained as a colourless syrup after chromatography.

yield : 98 mg (67%)

IR(neat) : 3065, 3030, 2973, 2870, 1605, 1497, 1454, 1370, 1312, 1213, 1100, 1028, 910, 812, 737, 698 cm^{-1}.

^1H NMR : *S* 0.61 (m, 2H, H-7), 0.97 (m, 1H, H-2), 1.29 (d, J = 6.5 Hz, 3H, H-6), 3.24 (t, J = 6.6 Hz, H-4), 3.46 (m, 1H, H-1), 3.67 (m, 2H, H-3, H-5), 4.53 (m, 2H, OCH_2Ph), 4.70 (d, 2H, OCH_2Ph), 7.33 (m, 10H, ArH).

^{13}C NMR : 10.15, 14.33, 18.91, 49.34, 71.21, 71.99, 73.63, 79.93, 81.83, 127.68, 127.79, 127.96, 128.42, 128.29,

138.57, 138.74 ppm.

$[\alpha]_D$: -11° (c1, $CHCl_3$).

Elemental analysis:

Calcd. for $C_{21}H_{24}O_3$: C = 77.75, H = 7.46.

Found : C = 77.56, H = 7.50.

LAH reduction of dibromocyclopropane 39:

To a stirred suspension of lithium aluminum hydride (100 mg, 2.60 mmol) in dry tetrahydrofuran (2 ml) was added dropwise a solution of the dibromocyclopropane 39 (188 mg, 0.32 mmol) in tetrahydrofuran (4 ml). After 90min, the reaction mixture was cooled in ice and quenched by careful addition of saturated aqueous sodium sulfate. The salts were filtered and washed several times with ethyl acetate. The filtrate was dried, concentrated, and the products were separated by chromatography.

Product 1:

3,4,6-tri-O-benzyl- 1,5-anhydro-2-deoxy- 1,2-C-bromomethylene-D-glycero-D-gulo-hexitol (59):

yield : 53 mg (32.5%)

IR(neat) : 3000, 2850, 1450, 1360, 1200, 1100, 750, 700 cm^{-1}.

^1H NMR : 6 1.50 (m, 1H, H-2), 3.0 (dd, J = 4.5, 1.6 Hz, 1H, H-7), 3.50 - 3.75 (m, 5H), 3.80 (dd, J = 7.7, 1.6 Hz, 1H, H-1), 4.50 - 4.77 (m, 6H, OCH_2Ph), 7.25 - 7.34 (m, 15H, ArH).

^{13}C NMR : 20.52, 26.39, 56.67, 69.39, 71.47,, 73.12, 73.36, 74.87, 75.36, 75.96, 127.73, 127.91, 128.41, 128.51, 137.71, 138.06 ppm.

[α] : +16° (c0.5, $CHCl_3$).

Elemental analysis:

Calcd. for $C_{28}H_{29}BrO_4$: C = 66.01, H = 5.74.

Found : C = 66.12, H = 5.75.

Product 2:

This product was found to be identical with **3,4,6-tri-O-benzyl-D-glucal** (31) by comparison with authentic sample.

yield: 9 mg (5.5%)

Product 3:

This product was identified as 3,4,6-tri-O-benzyl-1,5-anhydro-2-deoxy-1,2-C-methylene-D-glycero-D-gulo-hexitol (57) by comparison with authentic sample.

yield: 59 mg (42.8%)

LAH reduction of dibromocyclopropane 39 for longer times:

To a stirred suspension of lithium aluminum hydride (208 mg, 5.47 mmol) in tetrahydrofuran (3ml) at room temperature was added dropwise a solution of the dibromocyclopropane 39 (536 mg, 0.91 mmol) in tetrahydrofuran (5 ml). The reaction mixture was stirred at room temperature for 48h, then cooled in ice and carefully quenched with saturated aqueous sodium sulfate. The salts were filtered, washed several times with ethyl acetate and

the filtrate was dried. The product mixture after solvent evaporation was separated by chromatography.

Minor Product:

yield: 71 mg (15.3%)

The minor product was found to be identical with tribenzyl-D-glucal 31 in all respects.

Major product:

The major product was found to be the fully reduced cyclopropane 57 and was identical with the product obtained by LAH reduction of dichlorocyclopropane 35.

Solvolysis experiments with bromocyclopropane 59:

With silver perchlorate:

1) To a stirred solution of bromocyclopropane 59 (42 mg, 0.08 mmol) in methanol (2 ml) were added silver perchlorate (48 mg, 0.25 mmol) and sodium carbonate (49 mg, 0.50 mmol). The reaction mixture was heated under reflux for 24h. No reaction was observed and the starting material was recovered.

Under basic conditions:

2) The substrate 59 (25 mg, 0.05 mmol) was heated in methanol (1 ml) in the presence of potassium carbonate (36 mg, 0.27 mmol) for 24h. No noticeable reaction was observed as indicated by tlc analysis.

3) The substrate 59 (51 mg, 0.10 raraol) and sodium methoxide (56 mg, 1.04 mmol) were heated in methanol (3 ml) at reflux temperature. No reaction was observed after 24h and the starting material was recovered unchanged.

Simmons - Smith reaction of glycals:

Cyclopropanation of the (31):

To a stirred suspension of zinc dust (765mg, 11.7mmol) and cuprous chloride (250mg, 2.5mmol) in dry ether (1ml) at room temperature was added 1 equvalent of diiodomethane. After 5min, acetyl chloride (20μl) was added and the mixture heated for 5 min, and then a solution of tribenzylglucal **31** (1.10g, 2.65mmol) in ether (4ml) was added. Five minutes after the addition of the glucal, an additional 2 equivalents of diiodomethane were added and the heating was continued for 90min. The reaction mixture was diluted with ether (30 ml), washed with 5% aqueous sodium hydroxide solution, brine and then dried. The residue after solvent evaporation was purified by chromatography to furnish 3,4,6-tri-O-benzyl-1,5-anhydro-2-deoxy-1,2-C-methylene-D-glycero -D-talo- hexitol (60) as a low melting solid.

yield : 1.0 g (89%).

IR(neat) : 3063, 3029, 2866, 1497, 1454, 1094, 737, 698 cm^{-1}.

H NMR : & 0.60 - 0.77 (m, 2H, H-7), 1.24 - 1.33 (m, 1H, H-2), 3.25 - 3.48 (m, 3H, H-4 , H-5, H-6), 3.59 (d, J = 9.1HZ, 1H, H-6'), 3.69 - 3.77 (m, 1H, H-1), 4.10 (t, J • 6.8 Hz, 1H, H-3), 4.45 (t, 4H, OCH Ph), 4.71 (dd,

J = 11.7, 2.5 Hz, 2H, OCH_2Ph), 7.10 - 7.28 (m, **15H, ArH)** .

^{13}C NMR : 12.31 (C-7), 15.8 (C-2), 55.29 (C-1), 69.73, **69.95,** 73.71, 74.29 (CH_2's), 77.78, 78.72, 78.93 (CH's), 127.75, 128.03, 128.54, 138.62, 138.92 ppm.

$[\alpha]_D$: **-49°** (c0.9, $CHCl_3$) .

Elemental analysis:

Calcd. for $C_{28}H_{30}O_4$: C = 78.11, **H** = 7.02.

Found : C = 78.15, H = 7.12.

Cyclopropanation of tribenzyl-D-galactal 32:

The procedure described for 31 was followed and 3,4,6-tri-O-benzyl-1,5-anhydro-2-deoxy-1,2-C-methylene-D-glycero-L-allo-hexitol (61) was obtained as a colourless syrup.

yield : 80%

IR(neat) : 3000, 2800, 1440, 1360, 1100, 720, 680 cm^{-1}.

^1H NMR : 6 0.60 - 0.80 (m, 1H), 1.20 - 1.30 (m, 1H), 1.40 - 1.60 (m, 1H), 3.45 - 3.51 (m, 3H), 3.82 - 3.9 (m, 2H), 4.04 (t, J = 5.5HZ, 1H), 4.41 - 4.99 (m, 6H, OCH Ph), 7.31 (m, 15H, ArH).

^{13}C NMR : 12.09, 14.13, 53.90, 69.26, 69.54, 73.31, 73.76, 74.24, 74.59, 76.01, 127.28, 127.55, 127.77, 127.93, 127.99, 128.25, 137.91, 138.66, 138.83 ppm.

$[\alpha]_D$: -73.3° (c0.9,$CHCl_3$).

Elemental analysis:

Calcd. for $C_{28}H_{30}O_4$: C = 78.11, H = 7.02.

Found : C = 77.97, H = 7.10.

Cyclopropanation of dibenzyl-L-rhamnal 33:

The procedure described for **31** was followed and 3,4-di-O-benzyl-1,5-anhydro-2-deoxy-1,2-C-methylene-L-glycero-L-talo-hexitol (62) was obtained as a colourless syrup.

yield : 87%

IR(neat) : 2950, 2800, 1500, 1440, 1370, 1220, 1080, 720, 680 cm^{-1}.

^1H NMR : 6 0.75 - 0.80 (m, 2H, H-7), 1.21 (d, J - 6.6HZ, 3H, H-6), 1.27 - 1.40 (m, 1H, H-2), 3.02 (dd, J = 9.7, 7 Hz, 1H, H-4), 3.36 (m, 1H, H-5), 3.79 (m, 1H, H-1), 4.14 (t, J - 6.9HZ, 1H, H-3), 4.60 (dd, J = 11.2, 3.3 Hz, 2H, OCH_2Ph), 4.85 (dd, J = 11.6, 5.5 Hz, 2H, OCH_2Ph), 7.32 (m, 10H, ArH).

^{13}C NMR : 11.61, 15.30, 17.51, 54.42, 69.26, 73.63, 73.82, 78.24, 83.06, 127.11, 127.41, 127.86, 127.95, 138.41 ppm.

$[\alpha]_D$: +89° (c1.1, $CHCl_3$).

Elemental analysis:

Calcd. for $C_{21}H_{24}O_3$: C = 77.75, H 7.46.

Found : C = 77.79, H = 7.48.

Reaction of cyclopropane 57 with **N-bromosuccinimide:**

N-Bromosuccinimide (30 mg, 0.17 mmol) was added to a stirred solution of 57 (60 mg, 0.14 mmol) in methanol (1 ml). After 12h at room temperature, the solvent was removed under reduced pressure and the residue purified by chromatography to furnish methyl 3,4,6-tri-O-benzyl-2-deoxy-2-bromomethyl-β-D-glucopyranoside (67) as a syrup.

yield : 52 mg (69%)

IR(neat) : 3000, 2850, 1460, 1360, 1200, 1100, 1040, 740, 700 cm^{-1}.

^{1}H NMR : *6* 1.70 (br t, 1H, H-2), 3.30 - 3.70 (m, 10H), 4.26 (d, J = 8.1 Hz, 1H, H-1), 4.38 - 4.84 (m, **6H,** OCH_2Ph), 7.02 - 7.18 (m, 15H, ArH).

^{13}C NMR : 31.65, 47.70, 57.25, 69.04, 73.62, 74.84, 75.14, 79.85, 80.01, 102.29, 127.66, 127.86, 128.42, 128.52, 138.16, 138.30, 138.44 ppm.

$[\alpha]_D$: +22" (c1, $CHCl_3$).

Mass spectral data: m/z 540 (M^+), 449, 417, 401, 311, 295, 231, 91.

Solvomercuration of cyclopropane 57 :

Mercuric acetate (330 mg, 1.04 mmol) was added to a stirred solution of the cyclopropane 57 (296 mg, 0.69 mmol) in methanol (3 ml). After stirring at room temperature for 9h, the solution was cooled in ice and quenched with an excess of sodium borohydride. After 15 min, the reaction mixture was poured into

water (10 ml) and extracted with chloroform (4x10 ml). The combined organic extracts were dried, concentrated and the products separated by chromatography.

Product 1:

Methyl 3,4,6- tri-O-benzyl -2-deoxy- 2C-methyl- β-D- gluco-pyranoside (75) :

yield : 96 mg (30%)

m.p. : 104-105°

IR(KBr) : 3065, 3030, 2928, 2866, 1647, 1497, 1454, 1362, 1092, 1026, 736, 698 cm^{-1}.

^1H NMR : & 1.05 (d, J = 6.4 Hz, 3H, H-7), 1.80 (m, 1H, H-2), 3.25 (t, J = 9 Hz, H1, H-3), 3.40 - 3.80 (m, 7H), 4.01 (d, J = 8 Hz, 1H, H-1), 4.50 - 5.0 (m, 6H, OCH_2Ph), 7.26 - 7.35 (m, 15H, ArH).

^{13}C NMR : 12.62, 47.79, 56.85, 70.75, 73.62, 74.83, 75.32, 79.55, 85.37, 105.68, 127.71, 127.87, 127.96, 128.20, 128.49, 138.42 ppm.

Product 2:

yield : 150 mg (23%)

^1H NMR : 6 0.70 - 0.80 (m, 1H, H-7), 1.0 - 1.15 (m, 1H, H-7'), 2.10 - 2.30 (m, 1H, H-2), 3.20 (t, J = 9Hz, 1H, H-3), 3.35 - 3.80 (m, 7H, OCH_3, H-4, H-5, H-6, H-6'), 3.94 (d, J = 8HZ, 1H, H-l), 4.50 - 5.0 (m, 6H, OCH Ph), 7.27 - 7.30 (m, 15H, ArH).

C nmr : 37.71 (C-7), 47.53 (C-2), 56.71 (OCH), 69.44, 73.54, 74.63, 75.87, 79.92, 87.76 (C-3), 107.31 (C-1),

127.85, 128.37, 138.38, 138.70, 138.92 ppm.

FAB mass spectral data: Cluster at m/z 1119-1125.

Hydroboration of glycals:

General procedure:

To **a** stirred solution of the glycal in tetrahydrofuran cooled in an ice bath was added an excess of borane: tetrahydrofuran complex in tetrahydrofuran. **After stirring for 2h at** 0°, excess borane was destroyed by careful addition of water (0.5 ml). 3M Sodium hydroxide solution was then added all at once, followed by dropwise addition of 30% aqueous hydrogen peroxide. After 1h, the solution was diluted with ether, the layers separated and the aqueous layer extracted with ether (3x). The combined organic extracts were washed with brine, dried and concentrated. The product was purified by chromatography.

3,4,6-tri-O-benzyl 1,5-anhydro-D-glucitol (83):

yield : 69%

IR(neat) : 3449, 3030, 2865, 1497, 1454, 1362, 1209, 1092, 739, **698** cm^{-1}.

^{1}H **NMR** : 5 1.60 (br, 1H, OH), 3.11 (t, J - 11 Hz, 1H, **H-1a**), 3.27 - 3.64 (m, 6H, H-2, **H-3**, **H-4**, H-5, H-6, H-6'), 3.91 (dd, J = 11.0, 5.5 Hz, 1H, **H-1e**), 4.38 - **4.88** (m, 6H, OCH_2Ph), 7.0 - 7.24 (m, 15H, ArH).

^{13}C **NMR** : 68.94, 69.59, 70.22, 73.62, 74.86, 75.18, 78.03, 79.49, 86.93, 127.85, 127.93, 128.43, 128.65, 137.92,

138.05, 138.63 ppm.

$[\alpha]_D$: +53° (c1, $CHCl_3$) .

3,4,6-tri-O-benzyl 1,5-anhydro-D-galactitol (85):

yield : 65%

IR(neat) : 3449, 2865, 1497, 1454, 1364, 1209, 1088, 1028, 737, **698** cm^{-1}.

^1H NMR : *6* 2.20 (br, 1H, OH), 3.10 (t, J - 10.2 Hz, 1H, H-la), 3.26 (dd, J = 9, 2.5 Hz, 1H, H-le) , 3.41 - 3.51 (m, 3H), 3.89 - 4.06 (m, 3H), 4.36 - 4.79 (m, 6H, OCH_2Ph), 7.10 - 7.25 (m, 15H, ArH).

^{13}C NMR : 66.75, 69.08, 69.92, 71.86, 73.15, 73.59, 74.60, 77.99, 84.46, 127.74, 127.97, 128.12, 128.28, 128.43, 128.61, 137.92, 138.45 ppm.

$[\alpha]_D$: +22° (c1,$CHCl_3$).

3,4-di-O-benzyl 1,5-anhydro-6-deoxy-L-glucitol (87):

yield : **64%**

m.p. : 75-76° (hexane)

IR (KBr) : 3291, 3030, 2917, 1497, 1454, 1377, 1358, 1098, 1036, 752, 692, 660 cm^{-1}.

^1H NMR : δ 1.20 (d, J = 6.4 **Hz,** 3H, H-6) , 2.0 (br, 1H, OH), 3.08 (m, **2H, H-la, H-4),** 3.27 (m, 2H, H-3, **H-5),** 3.60 (m, **1H, H-2), 3.82 (dd,** J = **11,** 5 **Hz, 1H, H-le), 4.75** (m, **4H,** OCH_2Ph), **7.24** (m, **10H, ArH).**

^{13}C NMR : **18.24,** 69.43, 70.65, 75.27, 76.34, 83.91, **86.88,**

127.93, 128.01, 128.56, 138.73, 138.20, 138.74 ppm.

$[\alpha]_D$: -44.5° (c1.6, $CHCl_3$).

3,4-di-O-benzyl 1,5-anhydro-D-xylitol (89):

yield : 60%

m.p. : 50-52° (hexane/ethyl acetate).

IR (KBr) : 3439, 3063, 2861, 1497, 1454, 1069, 739, 698 cm^{-1}.

^1H **NMR** : 6 3.20 (br, 1H, OH), 3.50 - 3.70 (m, 5H), 3.80 - 4.0 (m, 2H), 4.64 - 4.74 (m, 4H, OCH_2Ph), 7.35 (m, 10H, **ArH)**.

^{13}C **NMR** : 66.70, 68.31, 69.45, 72.01, 73.38, 76.03, 78.28, 127.79, 127.96, 128.55, 137.71, 138.32 ppm.

$[\alpha]_D$: -9.2 (c1.3, $CHCl_3$).

Debenzylation of partially benzylated **1,5-anhydroalditols:**

General procedure:

The partially benzylated 1,5-anhydroalditols were dissolved in methanol and hydrogenated in a Parr hydrogenator with 20% $Pd(OH)_2/C$ for 4h. The catalyst was filtered off and the filtrate concentrated to furnish the 1,5-anhydro- alditols.

1,5-anhydro-D-glucitol (84)[97]:

yield : (81%)

m.p. : 138-140°

^1H **NMR** (D_2O) : & 3.04 - 3.26 (m, 4H), 3.36 - 3.54 (m, 2H), **3.68** - 3.85 (m, 2H).

^{13}C NMR : 61.75, 69.56, 70.15, 70.53, 78.29, 81.03.

$[\alpha]_D$: +40° (c1, H_2O).

1,5-anhydro D-galactitol (86)[100]:

yield : 90%

^1H NMR (D_2O) : *6* 3.06 (t, J = 10.3 Hz, 1H), 3.41 - 3.46 (m, 2H) , 3.56 - 3.71 (m,3H) , 3.82 - 3.91 (m, 2H) .

2,3,4,6-tetra-O-acetyl-1,5-anhydro-D-galactitol (86A):

A solution of **86** (329 mg, 2.0 mmol) in dry pyridine (5 ml) was treated with excess acetic anhydride and the reaction mixture was kept at room temperature for 2 days. The reaction mixture was poured into ice and extracted with chloroform (3x20 ml), dried and evaporated. The product 2,3,4,6-tetra-O-acetyl-1,5-anhydro-D-galactitol (86A) was obtained after purification. However, the product could not be crystallized.

^1H NMR : & 2.01, 2.05, 2.06, 2.15 (4s, 12H, $-OCOCH_3$), 3.34 (t, J = 10.2HZ, 1H), 3.85 (t, J = 5.9HZ, 1H), 4.11 (d, J = 11.6HZ, 2H), 4.19 (dd, J = 11.1, 5.3HZ, 1H), 5.08 (dd, J = 10.2, 3.3HZ, 1H), 5.21 (m, 1H), 5.44 (d, 1H).

$[\alpha]_D$: +43° (cl, $CHCl_3$). Lit.: +49.1° (c0.82, $CHCl_3$)[94]h.

1,5-anhydro-6-deoxy-L-glucitol (88):

yield : 85 **mg (94%)** .

m.p. : 144-146° (lit. 149-150°)".

IR (KBr) : 3343, 2901, 2853, 1100, 1069, 1030, 858 cm^{-} .

^{1}H NMR (D_2O) : 6 1.11 (d, J = 6.1 Hz, 3H, H-6), 3.00 (t, J = 9.2 Hz, 1H, H-1a), 3.05 - 3.27 (m, 3H), 3.35 -3.5 (m, 1H), 3.78 (dd, J = 11.0, 5.2 Hz, 1H, H-1e).

^{13}C NMR : 17.70, 69.48, 70.39, 75.79, 77.20, 77.99 ppm.

$[\alpha]_D$: -18.6° (c0.97, H_2O).

aQ

1,5-anhydro xylitol :

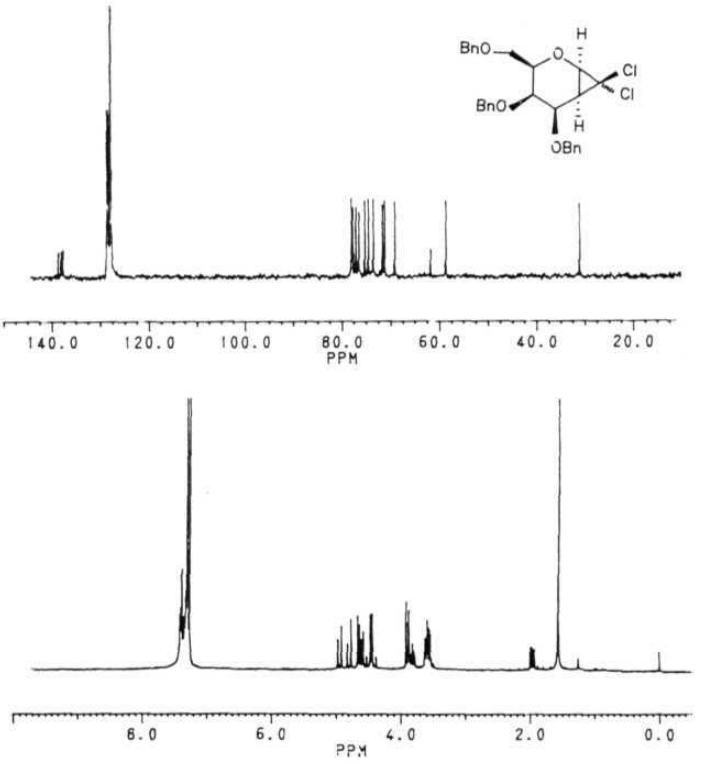
yield : 30 mg (81%)

m.p. : 90-91°

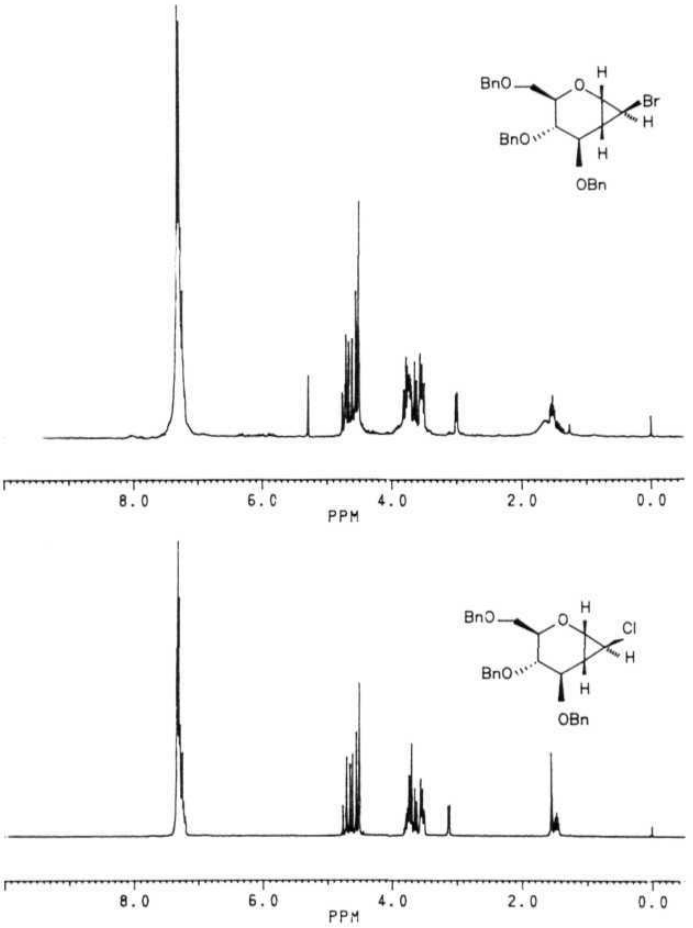
^{1}H NMR (D_2O) : 6 3.09 (t, J » 10.6 Hz, 2H, H-1a, H-5a), 3.27 (d, J = 8.7 Hz, 1H, H-3), 3.46 (m, 1H, H-2, H-4), 3.80 (dd, J = 11, 5 HZ, H-1e, H-5e).

^{13}C NMR : 56.76, 59.55, 59.70 ppm.

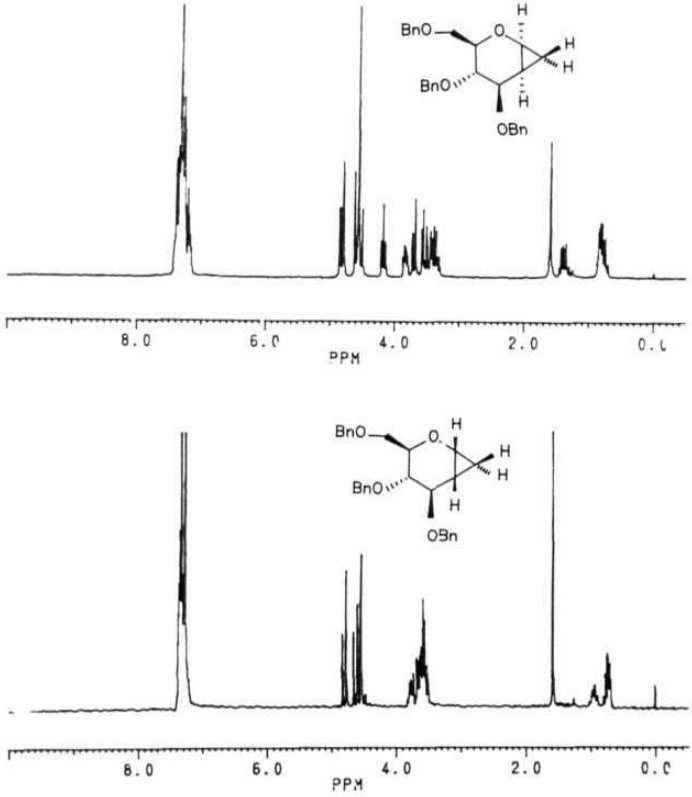
Spectra



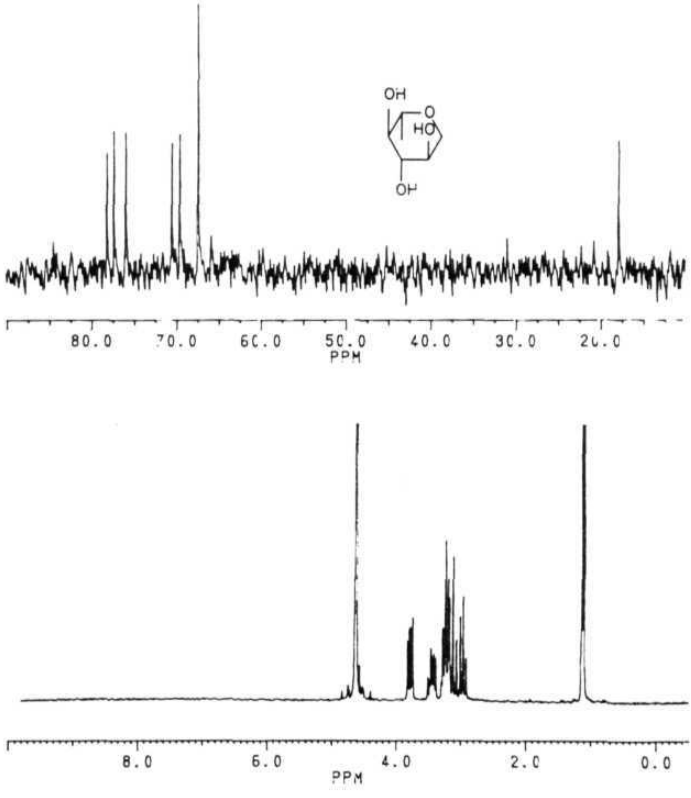
^{1}H and ^{13}C nmr spectra of 36



^{1}H nmr spectra of 52 and 59



^{1}H nmr spectra of 57 and 60



^{1}H and ^{13}C nmr spectra of 88

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