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SYNTHETIC STUDIES RELATED TO THIATHROMBOXANE A_2 AND MACROLIDES

by

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A THESIS

SUBMITTED TO THE FACULTY OF GRADUATE STUDIES AND RESEARCH

IN PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR THE DEGREE

OF

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THIATHROMBOXANE A_2 AND MACROLIDES

submitted by VILĀS NATHURĀM KĀLE in partial fulfilment of the requirements for the degree of DOCTOR OF PHILOSOPHY.

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(supervisor)

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(external examiner)

Date . . June 29, 1983 . . . . .

TO MY PARENTS

AND MY TEACHERS

ABSTRACT

The major portion of this thesis deals with the use of carbohydrates as "chiral templates" for the synthesis of thiathromboxane A_2, the chiral segment of the macrolide antibiotics and related compounds.

In the first chapter, the [redacted] model compound 31 having the representative 2-oxa-6-thiabicyclo-[3.1.1]heptane system present in the thiathromboxane A_2 (a thromboxane A_2 analogue) is described. The detailed NMR analysis of 31 is carried out to determine the favored conformation of this rigid system. The latter part of this chapter deals with the formal total synthesis of 9α,11α-thiathromboxane A_2 methyl ester 7 starting from levoglucosan (1,6-anhydro-β-D-glucopyranose). Levoglucosan is converted into the 9-epi-thromboxane B_2 derivative 48 which has been converted into 7 by Hamanaka and coworkers. The configurations of 48 and its diastereomer 49 at the C(15) are discussed.

In the second chapter, an operationally simple process to introduce stereoselectively a methyl group at the C(6)-position of the pyranosyl enone 56 involving 'conformational diastereoface-differentiation' in the conjugate additions of $CH_3Cu.BF_3$ and methyllithium-HMPA is described. The preferred conformations of the conjugate adducts 57 and 53 are investigated by nuclear Overhauser enhancement

experiments. In the last part of this chapter, the preparation of a chiral synthon suitable for the synthesis of the C(11)-C(15) and C(11')-C(15') segments of the macrolide antibiotic elaiophylin (azalomycin-B) is discussed. An efficient method for the regio- and stereocontrolled epoxide ring opening of the conformationally rigid epoxy-tosylate 33 with trialkylalanes is described.

In the final chapter, a method for generation of carbon-carbon double bonds from β-oxygenated phenylseleno, phenylthio, and iodo species is described. It is shown that chlorotrimethylsilane and sodium iodide in acetonitrile is a useful reagent for such a transformation. The reaction is efficient and has a predictable stereochemical outcome.

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ABBREVIATIONS

AcO	=	acetoxy
ax	=	axial
Bn	=	benzyl
br	=	broad
Bu	=	n-butyl
t-Bu	=	tert-butyl
BzO	=	benzoyloxy
d	=	doublet
d.e.	=	diastereomeric excess
DMAP	=	4-dimethylzminopyridine
DMF	=	dimethylformamide
eq	=	equatorial
Et	=	ethyl
HMPA	=	hexamethylphosphorotriamide
m	=	multiplet
m-CPBA	=	4-chloroperbenzoic acid
MsO	=	methanesulfonyloxy
n.O.e.	=	nuclear Overhauser enhancement
PGH_2	=	prostaglandin endoperoxide
PGI_2	=	prostacyclin
Ph	=	phenyl
Py	=	pyridine
q	=	quartet
S.M.	=	starting material
t	=	triplet

THF	=	tetrahydrofuran
THP	=	tetrahydropyranyl
TLC	=	thin layer chromatography
Tr	=	triphenylmethyl (trityl)
TsO	=	p-toluenesulfonyloxy
TXA_2	=	thromboxane A_2
TXB_2	=	thromboxane B_2
VPC	=	vapor phase chromatography

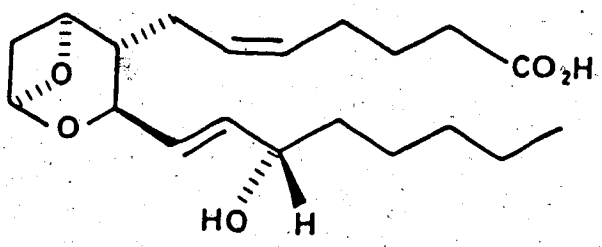
CHAPTER I

SYNTHETIC AND CONFORMATIONAL STUDIES OF COMPOUNDS RELATED TO 9α,11α-THIATHROMBOXANE A_2.

A. Introduction

a. Thromboxane A_2 and its analogues: One of the major developments in the study of arachidonic acid metabolites[1] has been the discovery of thromboxane A_2[2] (TXA_2, 1) and prostacyclin[3] (PGI_2, 2) (Fig. 1). These molecules, which originate from the same precursor, prostaglandin endoperoxide (PGH_2), are produced by the body to maintain a delicate balance between opposing biological functions. The blood vessels convert PGH_2 to PGI_2, which prevents platelets from aggregating and adhering to blood vessel walls. Further, PGI_2 causes smooth muscles, particularly blood vessels, to relax.[4] On the other hand, the blood platelets convert the PGH_2 into TXA_2, which causes the platelets to aggregate, and to adhere to blood vessels and also causes the vessels to contract.[5]

PGI_2 and TXA_2 are similar in several respects: they are both very unstable, having half lives of less than a couple of minutes in the aqueous media of their generation[4,5] (e.g., TXA_2, half life: ca. 32 s at 37 °C in



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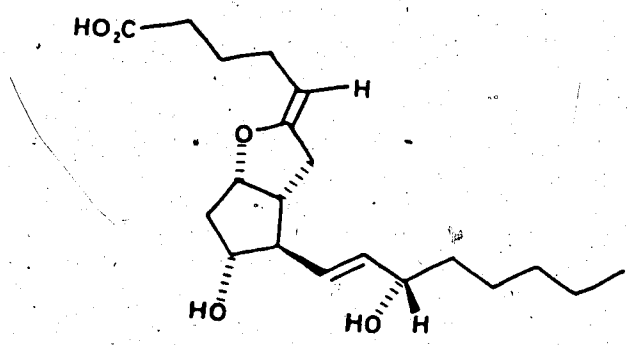
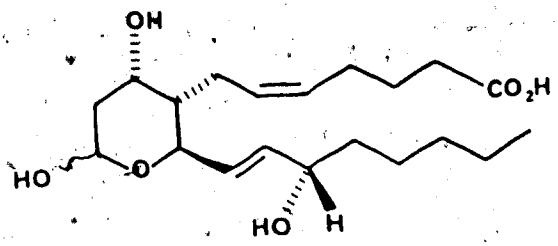


2

Fig. 1: The structures of thromboxane A_2 (TXA_2, 1) and prostacyclin (PGI_2, 2).



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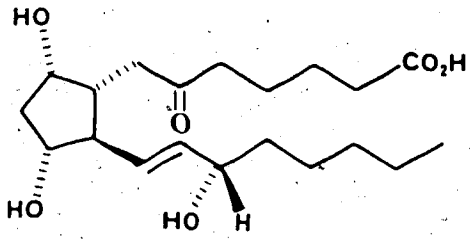

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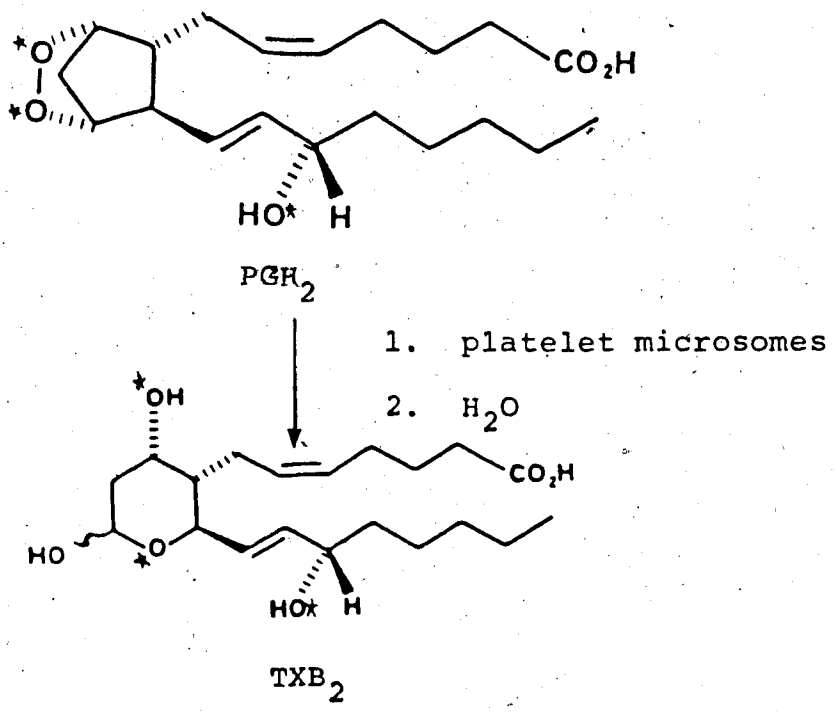
Fig. 2: The structures of thromboxane B_2 (TXB_2, 3) and 6-keto $PGF_{1\alpha}$ (4): detected from platelet microsomes.[4,5]

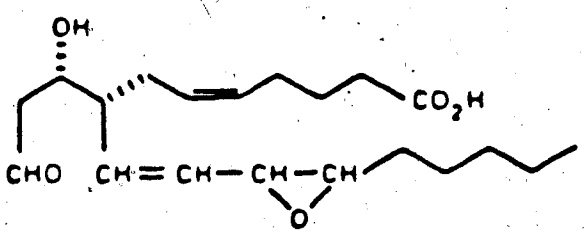
pH 7 aqueous solution); they are both highly reactive and extremely small amounts are required to produce biological effects.[4,5]

The structures of TXA_2 and PGI_2 were derived from the isolated metabolites namely, thromboxane B_2 (TXB_2, 3) and 6-keto $PGF_{1\alpha}$ (4) (Fig. 2) and their derivatives. The structure of PGI_2 was conclusively established by chemical synthesis and comparison of the biological activity of the natural and synthetic material.[6] Samuelsson and coworkers formulated structure 1 for TXA_2 based on the following data: 1) All the three ^{18}O atoms from ^{18}O labeled PGH_2 were incorporated into the TXB_2 as shown



Scheme 1.

(Scheme 1). 2) When TXA_2 was treated with deutero-methanol the TXB_2 methyl acetal was found to contain no deuterium. To the best of our knowledge there is no spectral data on TXA_2 itself. Baldwin suggested alternative structure 5 for TXA_2, which has been conclusively eliminated by its total synthesis and comparison of biological properties.[7] Thus, structure 1 (Fig. 1) remains the widely accepted structure for TXA_2.



5

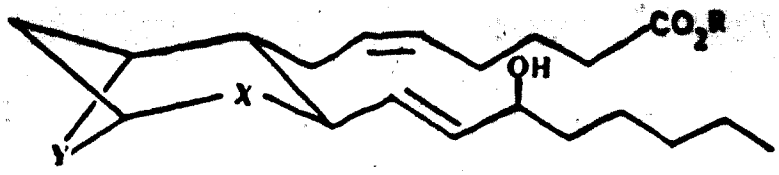
Thromboxane A_2 has been found in many tissues including platelets, leucocytes, spleen, inflammatory granuloma, brain and kidney.[8] It is of considerable pathophysiological interest in thrombotic diseases, and in anaphylactic reactions, and it is believed to play a physiological role in hemostasis. The chemical instability of TXA_2 has prevented extensive evaluation of its potent pharmacological effects (e.g., platelet aggregation and vasoconstriction).[9]

Because of the chemical instability of TXA_2, it is desirable to synthesize stable analogues having TXA_2 synthetase-inhibiting or TXA_2 antagonist activity.

Similarly, synthesis of analogues having TXA_2 agonist activity without appreciable thromboxane-inhibiting activity will greatly simplify the pharmacological evaluation of the parent compound.[10] In order to have a better understanding of the action of TXA_2 several carbon congeners[11] and related compounds in which one of the carbons in the bicyclic skeleton is replaced by oxygen[12] or sulfur[13] have been synthesized and found to have either partial TXA_2 antagonist or agonist or TXA_2 synthetase-inhibiting activity.

Based upon the above reports it is expected that analogues mentioned in Scheme 2 will have interesting biological activity. In each case one or both oxygen atoms of the parent bicyclic system are replaced by other heteroatoms. Examination of structures 6—9[14] shows their close structural resemblance with the natural molecule. It is reasonable to expect that the replacement of a ring oxygen atom of 1 by sulfur will change the chemical stability of the bicyclo[3.1.1]heptane portion of compounds 6—9 from that of 1. Also, it will not drastically alter the hydrophobicity of the head portion, possibly important at the receptor site.[15]

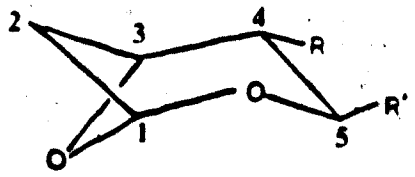
In this regard, it was decided to synthesize 6 or 7[16] in optically active form with the hope that it might mimic the activity of TXA_2.



1	Y = O,	X = O	and R = H
6	Y = S,	X = O	and R = -Na
7	Y = S,	X = O	and R = $-CH_3$
8	Y = O,	X = S	and R = -Na
9	Y = O,	X = S	and R = $-CH_3$
10	Y = S,	X = S	and R = -Na
11	Y = S,	X = S	and R = $-CH_3$
12	Y = NH,	X = O	and R = -Na
13	Y = NH,	X = O	and R = $-CH_3$
14	Y = O,	X = NH	and R = -Na
15	Y = O,	X = NH	and R = $-CH_3$
16	Y = NH,	X = NH	and R = -Na
17	Y = NH,	Y = NH	and R = $-CH_3$

Scheme 2: Some of the possible analogues of TXA_2 (1)

b. Synthetic strategy: Examination of the structures 1 and 6—17 shows that TXA_2 or its analogues can be viewed as an 1,3-anhydro-2,4,6-trideoxy-α-D-*ribo*-hexopyranose having appropriate substituents at C(4) and C(5) positions (Scheme 3). A crucial step in the synthesis of these



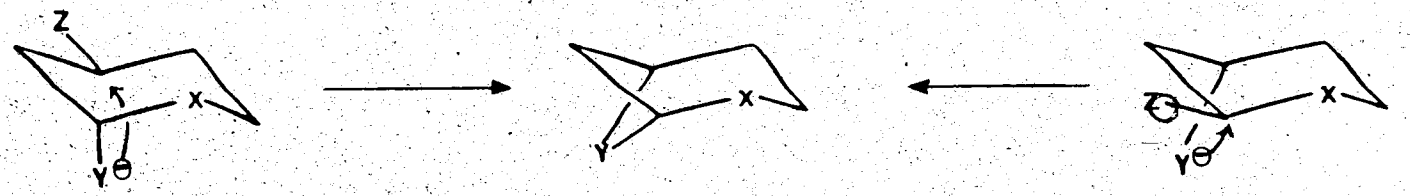
R and R' are side chains of TXA_2

Scheme 3:

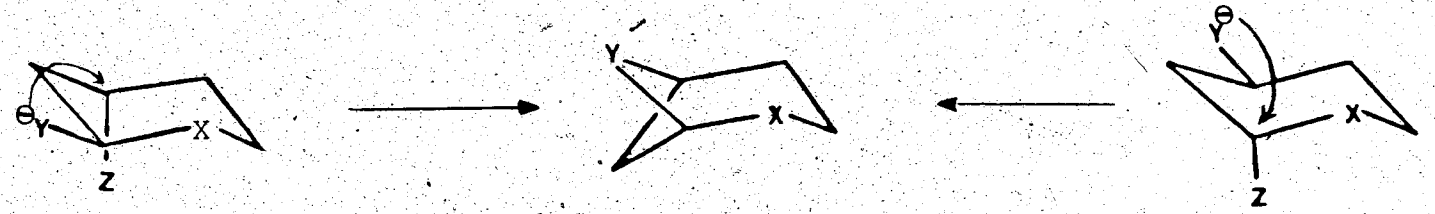
compounds is the construction of the bicyclic framework (i.e., 1,3-anhydrosugar portion). A general method for the synthesis of bicyclic acetals is the same as that for the synthesis of anhydrosugars, namely, rearside attack of an alkoxide ion on a carbon bearing a leaving group.[17] The main restraints of this general approach appear to be that 1) the reacting alcohol and the leaving group should bear a trans relationship, 2) in approaching the transition state, no steric restraints should develop that might direct reaction elsewhere and 3) the reactivity of the leaving group and reactant alcohol, or alkoxide, should permit reaction under conditions that

do not break the resulting anhydro ring.

This general approach involves the use of internal, nucleophilic substitution of the S_N2 type. Reactions leading to the formation of bicyclic acetals can be divided into two types depending upon the position of the leaving group on the sugar ring (Fig. 3). In method 1, the attacking nucleophile is on the anomeric carbon[18] while in method 2 (hereafter called internal glycosidation) the leaving group is on the anomeric carbon[19] as illustrated in Fig. 3. Method 1 is suitable for the synthesis of α-D-1,3-anhydro-sugars where the attacking nucleophile at the anomeric centre is predominantly in the more stable α-position as a result of an anomeric effect.[20] On the other hand, precursors leading to β-D-1,3-anhydrosugars via method 2 are more readily accessible. Thus, it is conceivable that the 2-oxa-6-thiabicyclo[3.1.1]heptane framework of the 9α,11α-thiathromboxane A_2 6 or 7 could be synthesized from a precursor of the type 18 involving mode 1 of ring closure (Scheme 4). When S^- on the anomeric carbon of 18 serves as the nucleophile, the transition state leading to the ring closure will involve a conformation close to $^5S_1$[21]. In this conformation, the C(5)-substituent will be in quasi-axial orientation and steric resistance to ring closure might be greater. Nevertheless, this type of internal alkylation was considered possible.



α-D-1,3-anhydrosugars



β-D-1,3-anhydrosugars

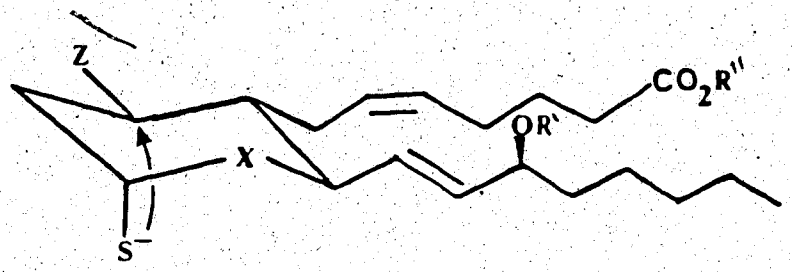
Method 1

Internal alkylation

Method 2

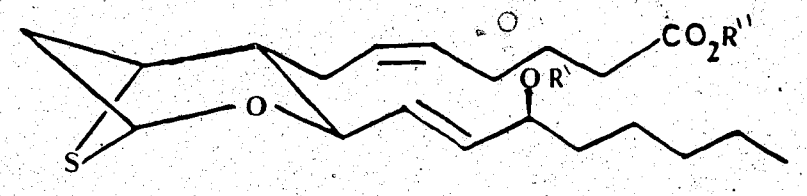
Internal glycosidation

Fig. 3. A general approach for the formation of bicyclic acetals.



Z = leaving group

18



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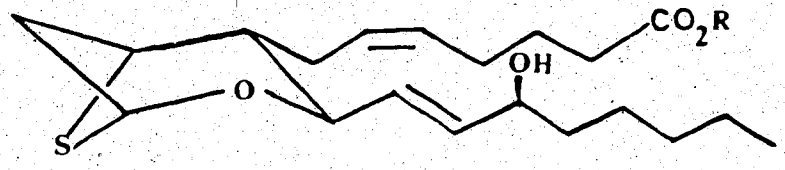


6 R = Na

7 R = $-CH_3$

Scheme 4:

Before proceeding to the synthesis of 6 or 7 it was decided to synthesize a model compound 31 (p. 17) which represents a typical 2-oxa-6-thiabicyclo[3.1.1]heptane system, so that the stability of the hemithiaacetal moiety could be assessed.

c. Conformational study: The model compound 31 was also of interest for the study of its conformational properties, since its conformational analysis might provide information about the shape of the head of TXA_2 and its analogues. The direct conformational investigation of the bicyclic head of TXA_2 is not possible due to its short half life.

It was planned to investigate the solution conformations of 9-epi-thromboxane B_2 derivative 46, its diastereomer 47 and their benzoates 48 and 49 (Scheme 11, p. 31) in order to determine the configurations of 46 and 47 at C(15).

The solid state conformations of thromboxane B_2 (3) which has side chains similar to those of 46 and 47 have been studied.[22] Although, the chemistry and binding preferences of the pyranoside head groups of TXA_2 and TXB_2 compounds are sufficiently different to insure the differentiation of these hormones at the molecular level, the ring junction geometries of the side chains to the head groups are constrained so as to suggest that

the side chain conformations of related TXA and TXB compounds are similar.[22] Therefore, the conformational studies of TXB-related compounds are of interest.

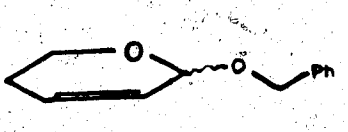
The structure-activity relationship of prostaglandins[23] and thromboxane A_2 analogues[11,12,13] shows that in most cases compounds having an unnatural configuration (i.e. R) at C(15) are biologically less active. It may be possible that this difference in biological activity of C(15)-diastereomers is because of their preferred conformations. Thus, it was expected that apart from indicating the configurations at C(15), at least a qualitative picture of conformations of these molecules could be obtained from these studies.

B. Synthesis of 2-oxa-6-thiabicyclo[3.1.1]heptane derivative 31.

As mentioned earlier it was decided to synthesize 1,3-anhydro-2-O-n-butyl-3,4-dideoxy-3-mercapto-β-DL-threo-pentopyranose (7-exo-n-butoxy-2-oxa-6-thiabicyclo-[3.1.1]heptane 31). The synthesis of 31 was accomplished from readily available benzyl 2,3-anhydro-β-DL-erythro-pentopyranoside 21[24] as outlined in Scheme 5. Epoxidation of 2-(benzyloxy)-5,6-dihydro-2H-pyran 20 with m-chloroperbenzoic acid gave a mixture of two epoxides in a ratio about 1:3 in contrast to results of Mochalin and coworkers who probably did not isolate the minor isomer.[24] The configurations of epoxides 21 and 22, which could be inferred on the assumption that the major product was the trans isomer, in analogy with the similar reaction of 2-(ethoxy)-5,6-dihydro-2H-pyran,[25c] was confirmed by their ^{1}H-NMR spectra.

It is known that in the ^{1}H-NMR spectra of compounds of type 21, the signal due to the anomeric hydrogen is found as a broad singlet ($J_{1,2} \approx 1$ Hz) at about 5.0 ppm, while in the compounds of the type 22 the anomeric hydrogen appears as a doublet ($J_{1,2} = 3$ Hz).[25] In fact, in the ^{1}H-NMR spectrum of the major epoxide, the anomeric hydrogen appeared as a broad singlet at 5.03 ppm and consequently this confirmed the trans configuration of the major epoxide 21.

22

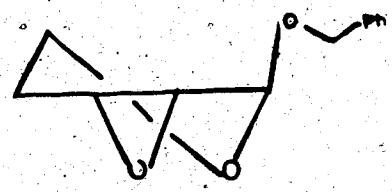


m-CPBA

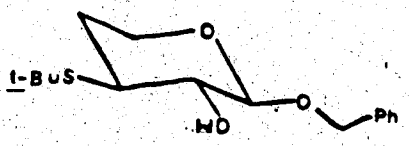
CH_2Cl_2

+

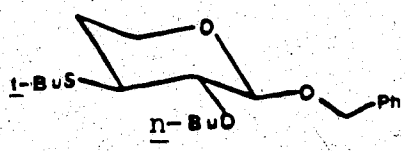
20



21

21 → (t-BuSH, $NaOCH_3$; CH_3OH, reflux) → 

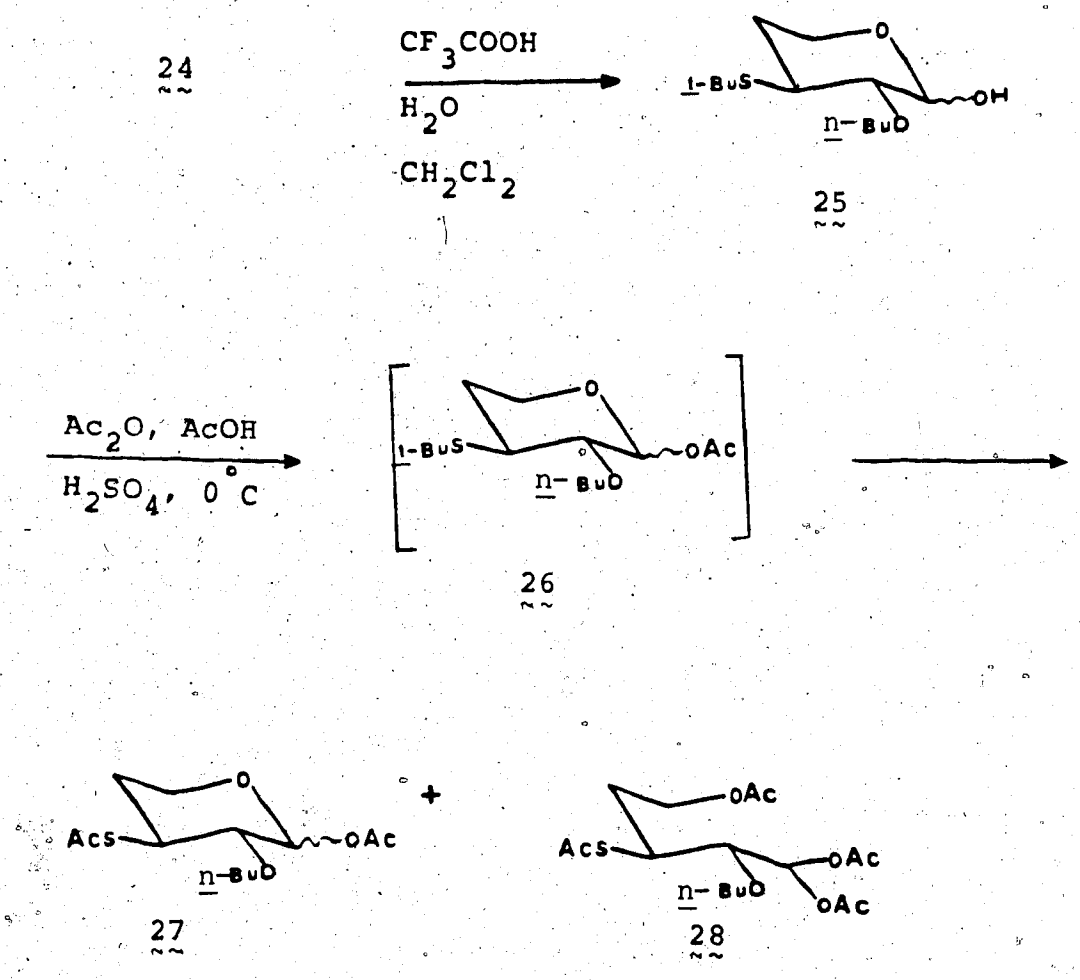
23

23 → (NaH, DMF; n-BuI) → 

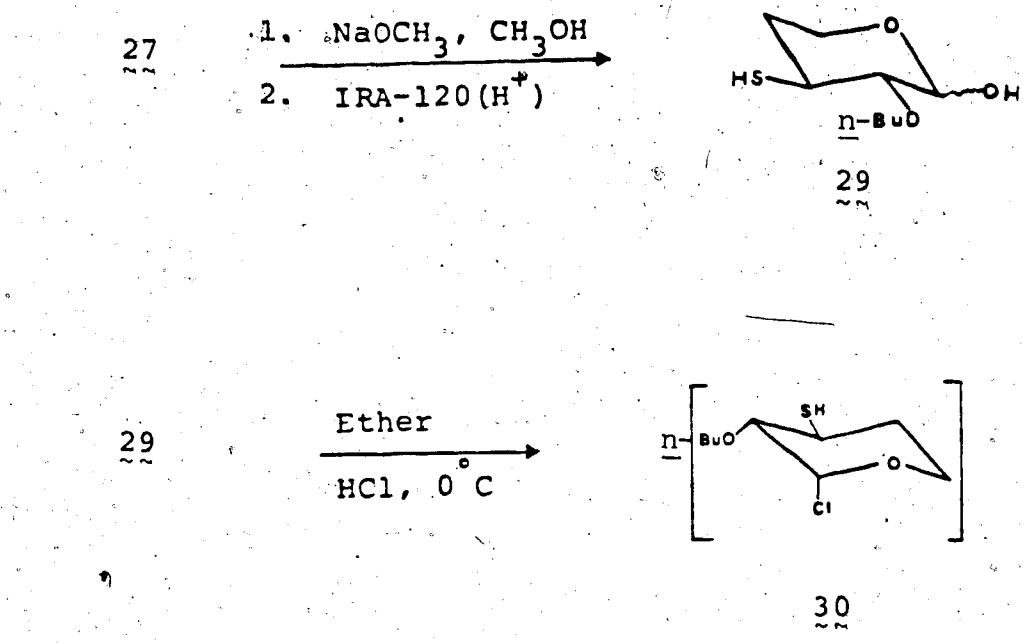
24

Scheme 5:

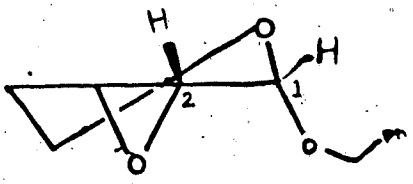
Scheme 5 (continued)



Scheme 5 (continued)

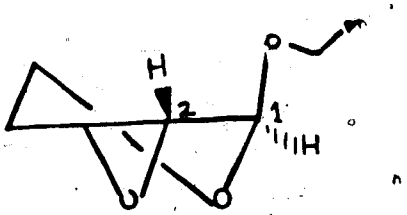


By similar comparison, the structure of the minor product could be established as 22 (Scheme 6).



22

$J_{1,2}$ = 3 Hz

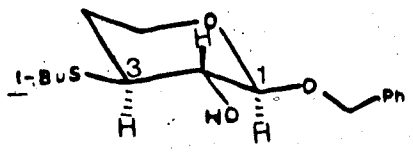


21

$J_{1,2}$ = < 1 Hz

Scheme 6:

The next step involved the regio- and stereoselective opening of the epoxide ring of 21 to introduce sulfur moiety at C(3) position. The choice of t-butyl mercaptan, a rather unusual nucleophile to introduce sulfur functionality was guided by the fact that the use of the more common nucleophile, benzyl mercaptan, would have required reductive deprotection of the mercapto group. Treatment of 21 with t-butyl mercaptan and sodium methoxide gave almost exclusively one product in 92% yield. The ^{1}H-NMR spectrum of the product 23 indicated the configuration at C(2) and C(3) to be trans. Based on the decoupling experiments a multiplet at 2.66 ppm ($J_{2,3}$ = 10.25 Hz, $J_{3,4eq}$ = 5 Hz, $J_{3,4ax}$ = 12 Hz) in the ^{1}H-NMR spectrum of 23 could be assigned to 3-H_{ax} (Scheme 7). The values of coupling constants $J_{1,2}$ (7 Hz) and $J_{2,3}$ (10.25 Hz), established that the substituents on C(1), C(2) and C(3) of the pyranose



$J_{1,2}$ = 7 Hz

$J_{2,3}$ = 10.25 Hz

23

Scheme 7:

ring in 23 are trans to each other. The regiochemistry observed in the above reaction is in accordance with that reported in the literature where 2,3-anhydro-β-D-erythro-pyranosides and analoguous pyran derivatives are known to be opened by nucleophiles at C(3).[25,26]

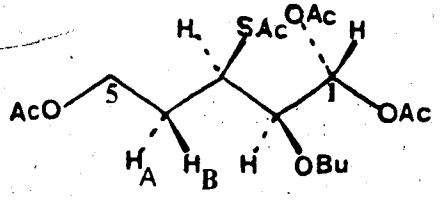
Alkylation of 23 with 1-iodobutane proceeded smoothly to give 24 in 90% yield (Scheme 5, p. 15).

The deprotection of anomeric hydroxyl and mercapto functionalities was achieved in three steps. Benzyl glycoside 24 was hydrolyzed with 90% aqueous trifluroacetic acid in dichloromethane to provide 25. The aldose 25 was then subjected to acetolysis to remove the t-butyl group. Thus, treatment of 25 with acetic anhydride, acetic acid and a catalytic amount of concentrated sulfuric acid gave one major and one minor product. The major product was found to be the desired thioacetate 27 as a mixture of α- and β-anomers (ratio: 2:1, ^{1}H-NMR) from its ^{1}H- and ^{13}C-NMR spectra. This reaction probably proceeds via the formation of 1-O-acetate 26 since the ^{1}H-NMR spectrum of

the crude product obtained when the amount of concentrated sulfuric acid used was less, showed the presence of a signal due to the t-butyl group and absence of a thioacetate methyl signal in the 2.3—2.4 ppm region. Acetolysis as described above is a novel method[27] to remove the t-butyl group and affords a thioacetate functionality which can be easily modified in subsequent steps.

Methyl glycosides are known to give 1-acetates in high yield under acetolysis conditions.[28] However, benzyl glycoside 24 gave a complex mixture under similar conditions.[29] The alternative two step sequence involving hydrolysis of the benzyl glycoside followed by acetolysis seems to be better in this particular case.

The minor product obtained during acetolysis of 25 was found to be the ring opened product 28 as was evident from its ^{1}H- and ^{13}C-NMR spectra. In the ^{1}H-NMR spectrum of 28 the couplings $J_{1,2}$ and $J_{2,3}$ were found to be 7 and 2.5 Hz respectively, indicating that this compound exists predominantly in an extended conformation[30] (Fig. 4) in $CDCl_3$.



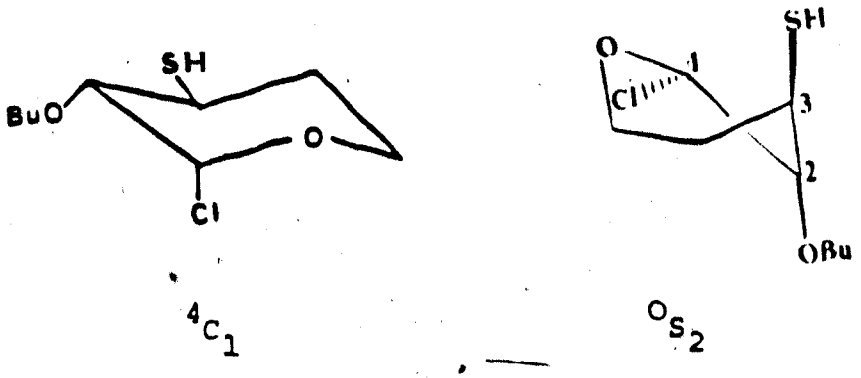
$J_{1,2}$ = 7 Hz
$J_{2,3}$ = 2.5 Hz
$J_{3,4A}$ = 5 Hz
$J_{3,4B}$ = 10 Hz

Figure 4: Extended conformation of 28 in $CDCl_3$.

Treatment of thioacetate 27, with a catalytic amount of sodium methoxide in methanol effected solvolysis of the acetyl groups, and upon neutralization with IRA - 120 (H^+) resin, mercapto-aldose 29 (α:β ratio, 2:1, ^{1}H-NMR) was isolated in 84% yield after chromatography over silica gel. ^{1}H- and ^{13}C-NMR spectra are consistent with the assigned structure 29. This compound is stable when stored under a nitrogen atmosphere.

In the final stage, compound 29 was treated with a saturated solution of hydrogen chloride in anhydrous ether at 0°C for a period of two days. These conditions were reported by Micheel and Kreutzer[19d] for displacement of the anomeric hydroxyl group with chloride. Although the product from this reaction could not be characterized owing to its instability, it was expected to be the desired α-pyranosyl chloride[19d,20] 30 and hence was employed directly in the next step.

The precursor of type 30 should lead to 31 via internal glycosidation for the formation of bicyclic acetals (method 2, Fig. 3). In the $^4C_1$ conformation of 30, the mercapto group is equatorial and the C(1)-leaving group is axial. However, in the skew conformation $^OS_2$, the steric relationship of the C(3)-mercapto and anomeric chloride groups is nearly ideal for ring closure (Scheme 8). The energy requirement for the molecule to adopt this conformation must not be excessive and indeed,



$^4C_1$ $^OS_2$

30

Scheme 8:

ring-closure does occur on treatment with a base.

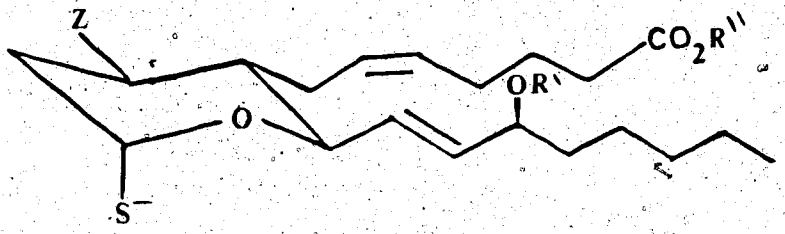
The ring-closure of 30 was achieved by refluxing a solution of crude 30 with an excess of sodium hydride in THF-benzene. The desired 2-oxa-6-thiabicyclo[3.1.1]heptane derivative 31 was isolated by chromatography on silica gel and could be stored at 0 °C for several days. Compound 31 could be distilled under vacuum with slight decomposition (^{1}H-NMR). The purity of 31 was established by TLC (silica gel, 1:9 ethyl acetate—hexane), by absence of a carbonyl absorption peak in the IR spectrum and by correct chemical analysis. In the ^{13}C-NMR spectrum, there were no signals which could be assigned to olefinic carbons indicating the absence of elimination product. In the ^{1}H-NMR spectrum of 31 the anomeric proton resonates at 5.54 ppm as a doublet of doublets and a long-range coupling of 5.25 Hz with H-5 is observed ($^4J_{1,5}$ = 5.25 Hz). The ^{13}C-chemical shift of the anomeric carbon is 89.5 ppm whereas

the shift of C(5) is 48.54 ppm which is about 8 ppm downfield from the C-3 of the mercapto-aldose 29 indicating sulfur in 31 has undergone alkylation. Thus, ^{1}H-, and ^{13}C-spectra are consistent with proposed structure 31 (see also discussion on conformational analysis of 31).

C. Total synthesis of optically active 9α,11α-thiathromboxane A_2 methyl ester from starch.

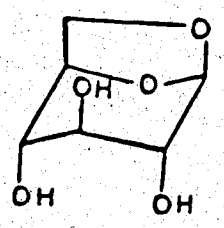
Since the model compound 31 having the representative 2-oxa-6-thiabicyclo[3.1.1]heptane skeleton appeared reasonably stable, it was decided to proceed with the synthesis of the target molecule, 9α,11α-thiathromboxane A_2 methyl ester 7 or the sodium salt 6. As discussed earlier, compound 6 or 7 can be considered as a sulfur analogue of 1,3-anhydro-2,4,6-trideoxy-α-D-ribo-hexopyranose having appropriate substituents at C(4) and C(6). The immediate task was to synthesize a precursor of the type 18 (Scheme 9) which, via internal alkylation (method 1, Fig. 3) for the formation of a bicyclic acetal, should lead to 6 or 7. It was decided to synthesize an optically active precursor of the type 18 from readily available levoglucosan 32[31] as outlined in Scheme 11 (p. 27).

When the synthetic transformations as outlined in Scheme 11 were at an advanced stage using the tosylate (4-methylphenylsulfonate) as a leaving group, Hamanaka and coworkers published the synthesis of 9α,11α-thiathromboxane A_2 methyl ester 7.[32] Their synthesis starts from compound 40[33] (Scheme 10) which in turn is obtained from 11,15-ditetrahydropyranyl PGF_2 39.[34] The synthesis of 39 involves a multistep sequence.[34] Hamanaka's synthesis



Z = leaving group

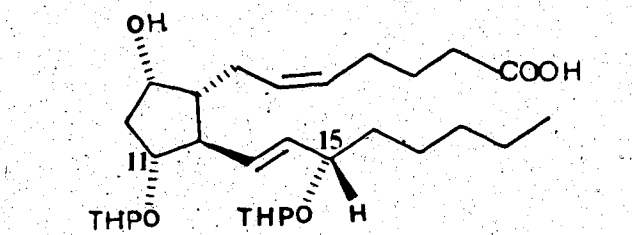
18



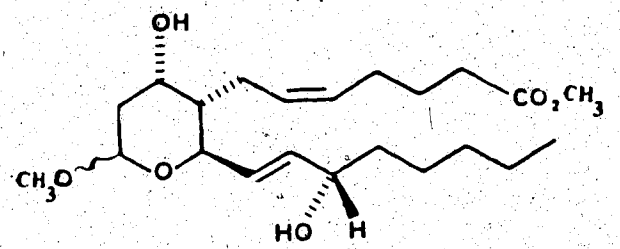
32

STARCH

Scheme 9.



39



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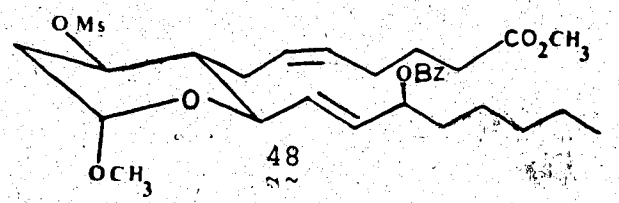
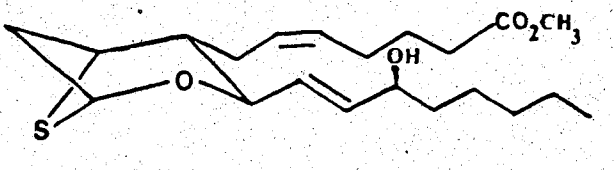
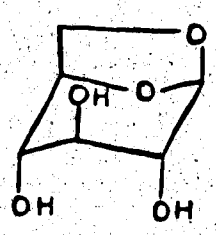


48

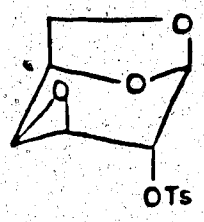


7

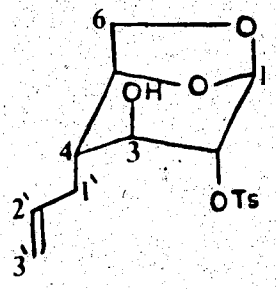
Scheme 10.

STARCH $\xrightarrow{\text{pyrolysis}}$ 

32

$\xrightarrow[CHCl_3,\ CH_3COCH_3]{TsCl,\ Py}$ $\xrightarrow[CH_3OH,\ CHCl_3]{NaOCH_3}$ 

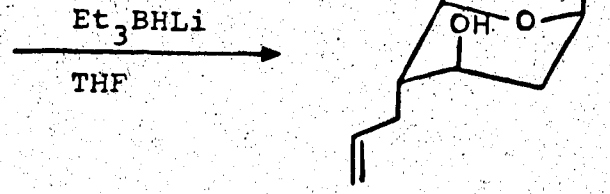
33

33 $\xrightarrow[CuCl,\ THF,\ 0\ ^{\circ}C]{CH_2=CHCH_2MgCl}$ 

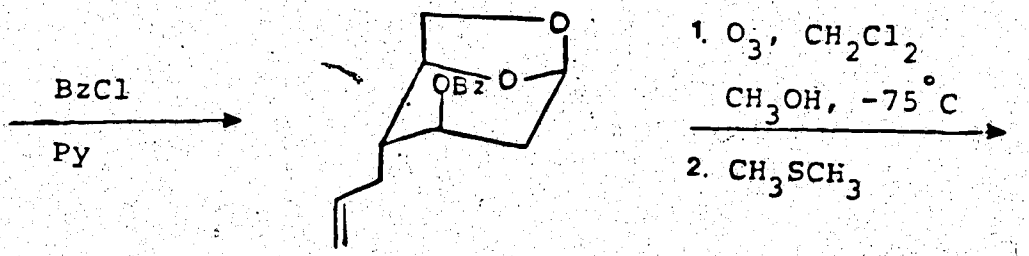
34

Scheme 11.

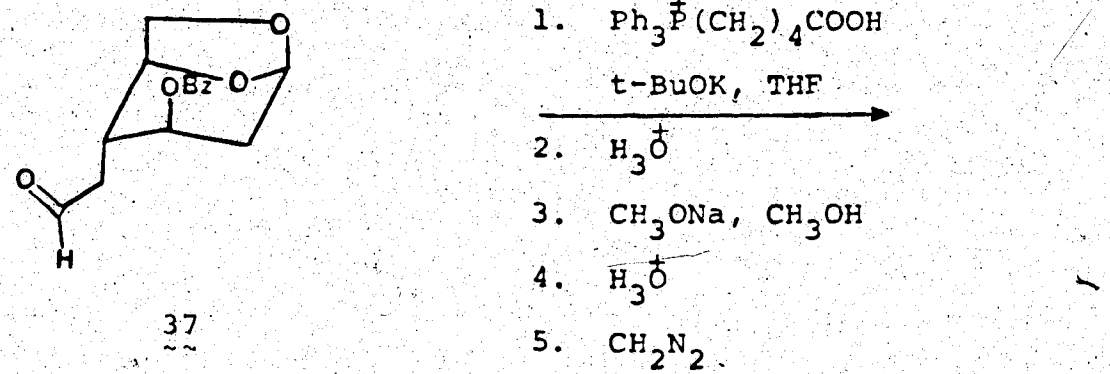
Scheme 11 (continued)



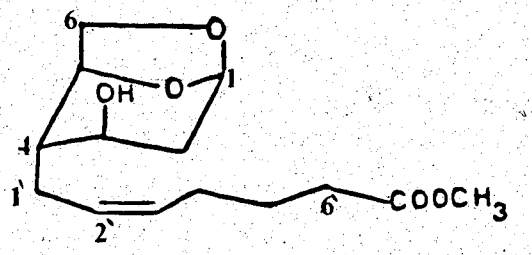
34 ~~ 35 ~~



36 ~~

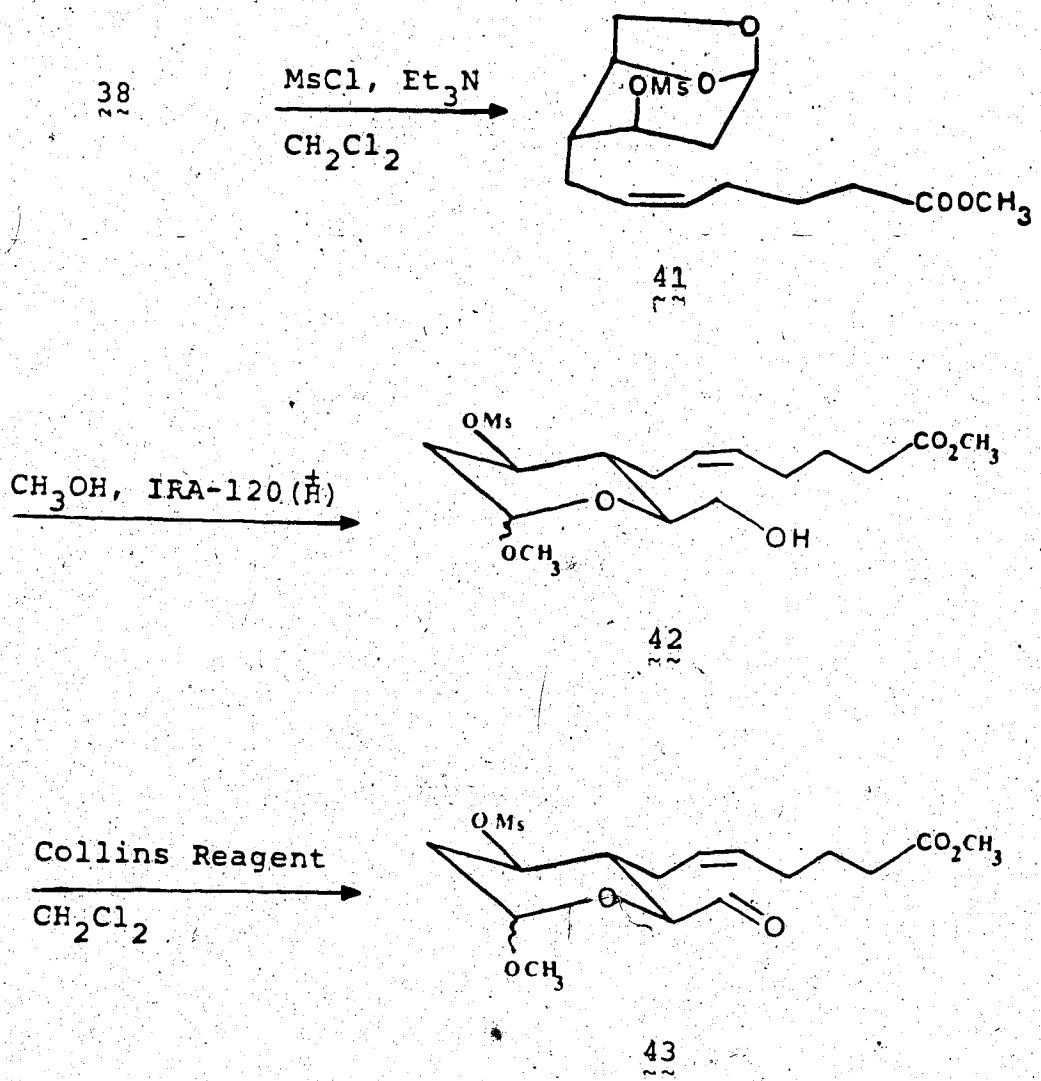


37 ~~

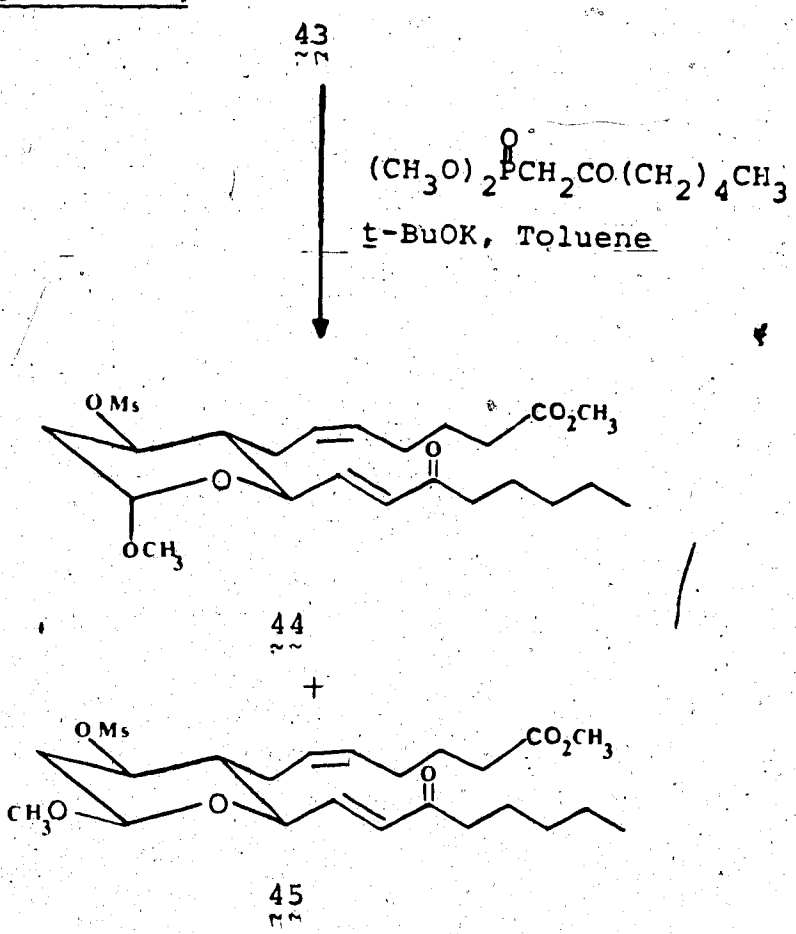


38 ~~

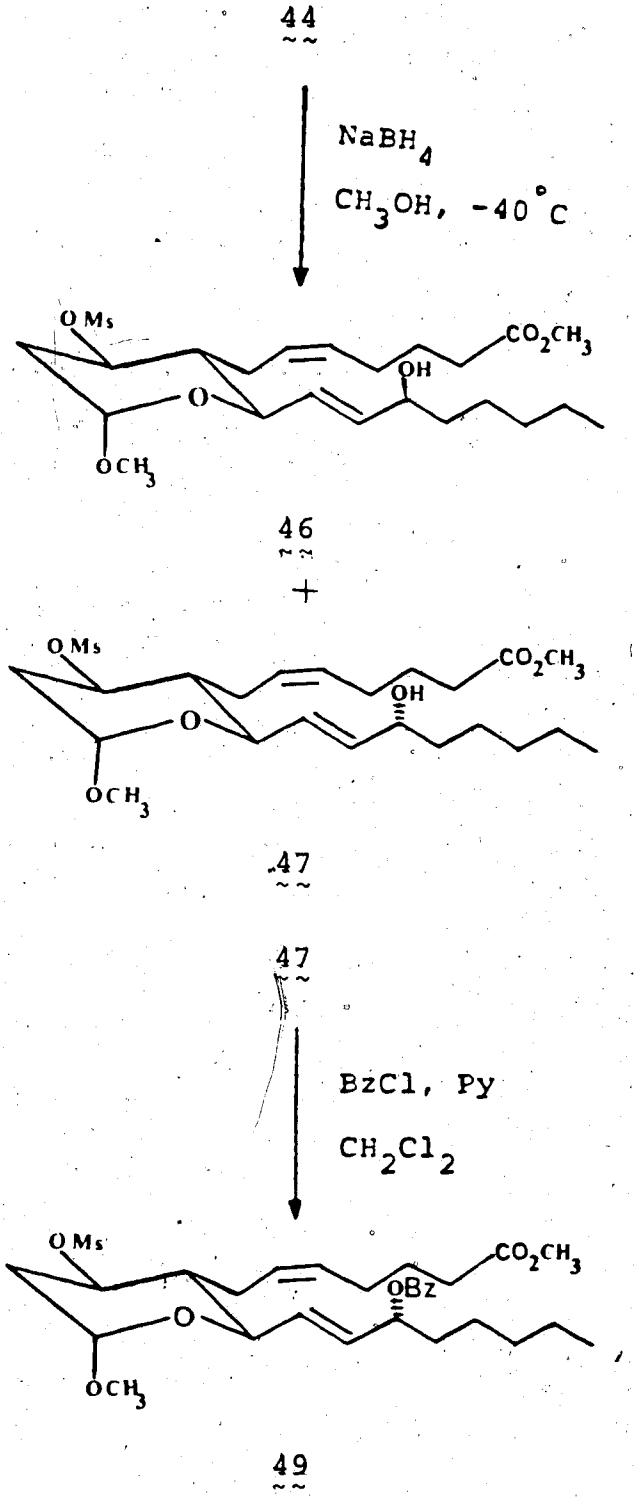
Scheme 11 (continued)



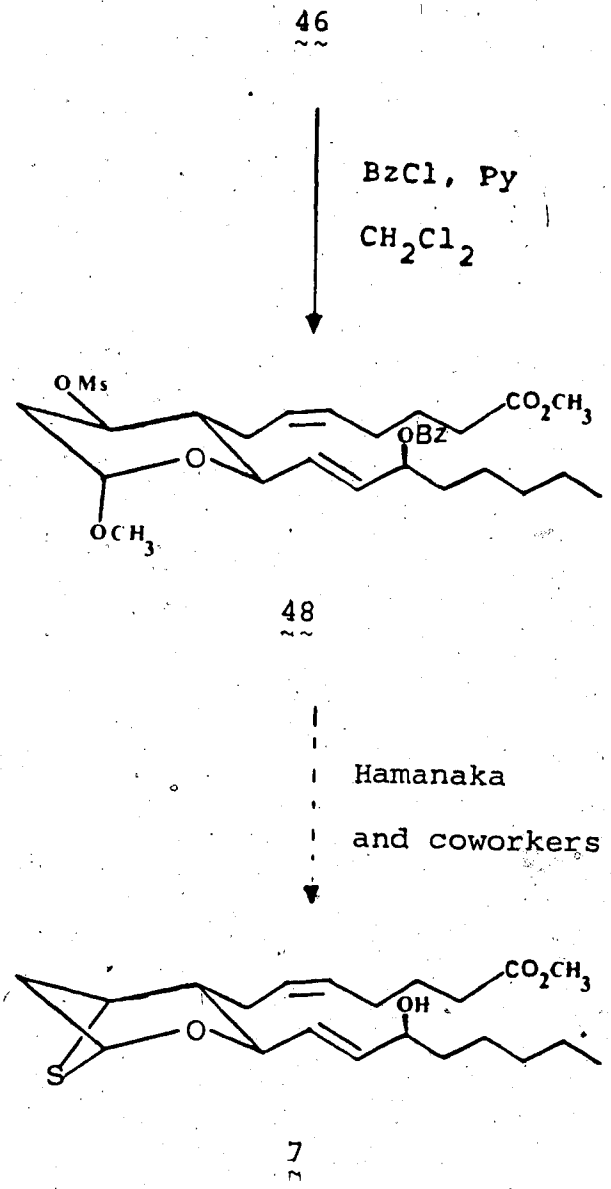
Scheme 11 (continued)



Scheme 11 (continued)



Scheme 11 (continued)



of 7 proceeds via a key intermediate 48 in which the leaving group is a mesylate (methanesulfonate). Although, compound 40 can be obtained in optically active form,[33] Hamanaka and coworkers have not commented on the optical activity of the intermediates or the final product. Since the latter synthetic strategy planned in this project was similar to that of Hamanaka and coworkers, it seemed reasonable to complete the total synthesis of optically active 7 by synthesizing Hamanaka's intermediate 48 from levoglucosan by a shorter route.

Levoglucosan (1,6-anhydro-β-D-glucopyranose, 32) is readily available in large quantities by pyrolysis of starch[31] and is an ideal starting material for the synthesis of 48 since it already contains the tetrahydropyran portion of the target. Also, it can be seen from its structure that the anomeric and C(6)-hydroxyl groups are protected in the form of an 1,6-anhydrolinkage and can be released subsequently. The bicyclic framework of 32 enables excellent regio- and stereocontrol.[17e] The C(3)-hydroxyl group in 32 is suitably disposed to serve as a leaving group after conversion to a mesylate. Replacement of the hydroxyl moiety at C(2) by hydrogen, introduction of the carboxylic acid side chain (α-chain) on C(4) and an appropriate chain extension at C(6) (ω-chain) of 32 should provide the required gross structure of 48.

Levoglucosan obtained by pyrolysis of starch[31] was treated with 4-methylphenylsulfonyl chloride and pyridine in chloroform-acetone according to the literature procedure.[35] The crude product 1,6-anhydro-2,4-di-O-(4-methylphenylsulfonyl)-β-D-glucopyranose[35] was subjected to treatment with sodium methoxide in methanol-chloroform. The product of this reaction was crystallized from methanol-chloroform to obtain 1,6:3,4-dianhydro-2-O-(4-methylphenylsulfonyl)-β-D-galactopyranose 33,[35] m.p. 148—150°C (lit.[35] 150—151°C) in 50—60% yield.

An allyl group suitable to construct the carboxylic acid side chain was introduced on C(4) of 33 following a slightly modified procedure that was reported by Roberts and Kelly.[36] Thus, treatment of the epoxy-tosylate 33 with allylmagnesium chloride in the presence of a catalytic amount of cuprous chloride in THF gave the allyl derivative 34[36] in 75—80% yield. Similar results were obtained using allylmagnesium bromide and cuprous iodide, although yields were slightly lower (70—75%).

The evidence for the stereochemistry of the allyl group was obtained from the ^{1}H-NMR spectrum of 34. A quartet at 3.70 ppm in the ^{1}H-NMR spectrum of 34 (Fig. 5) could be assigned to H-6_{exo} (Scheme 12) by comparison with the well-known 1,6-anhydrosugars.[17e,37] The H-6_{exo} multiplet appears usually at much higher field than the H-5 doublet

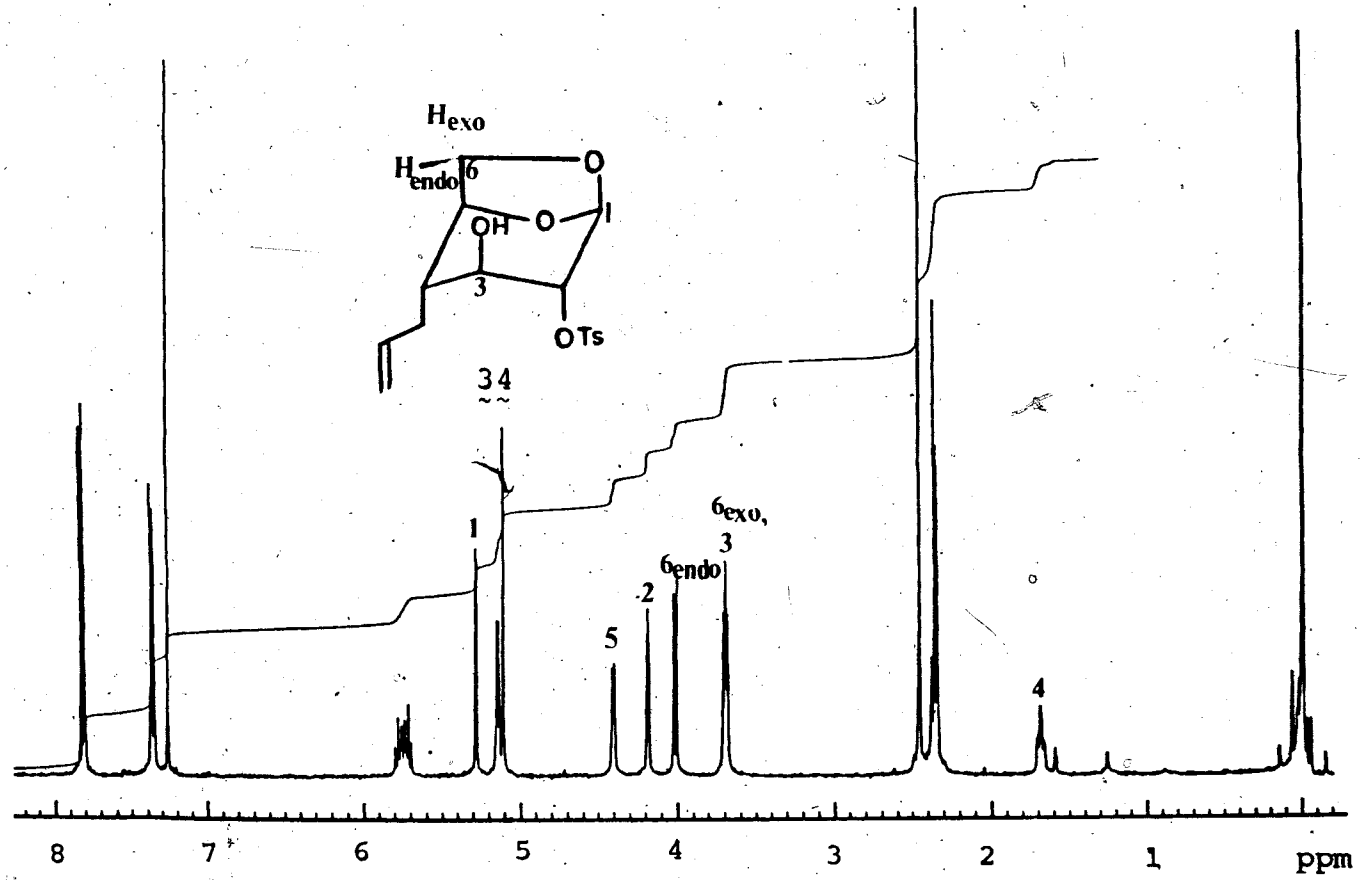
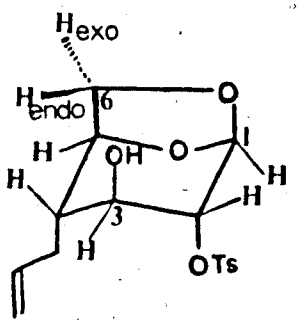


Fig. 5. The ^{1}H-NMR spectrum of 3 4 at 400 MHz in $CDCl_3$.

(about 1 ppm upfield from H-5) and at slightly higher field than the H-6_{endo} doublet.[17e] The H-5, H-6_{endo}, H-6_{exo} system has been studied carefully so that its identification causes no difficulty.[17e] Thus, a broad



$J_{4,5}$ = 1 Hz

$J_{3,4}$ = 2.5 Hz

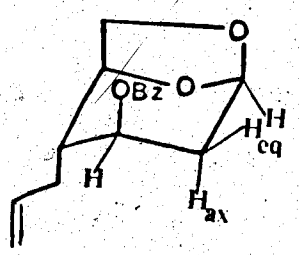
34

Scheme 12

doublet at 4.41 ppm was assigned to H-5 ($J_{5,6exo}$ = 5 Hz). A coupling constant of 1 Hz was found between H-5 and H-4 (at 1.68 ppm). In addition, the multiplet due to H-4 showed a coupling of 2.5 Hz with H-3 (H-3 overlaps with H-6_{exo} quartet). The coupling constants $J_{1,2}$, $J_{2,3}$, $J_{3,4}$ and $J_{4,5}$ reflect the conformation of the ring protons and, consequently, the configuration of an 1,6-anhydropyranose. For the compounds, having only syn-clinal arrangement of H-1 to H-5 (H-1 and H-5 occupy equatorial positions), the analysis is facilitated by the flattening of the pyranoid chair, which is accompanied by an increase

in the torsion angle of eq-eq oriented atoms and by decrease in the ax-eq arrangement.[17e,37] This fact finds practical application in the case of $J_{4,5}$; $J_{4ax,5}$ lies in the range of 3.0—5.0 Hz, whereas $J_{4eq,5}$ has the range 1.5—2.5 Hz. In the case of $J_{2,3}$ and $J_{3,4}$ the differences are even more pronounced, the ax-eq arrangement having the range 4 to 6 Hz, whereas, in the eq-eq arrangement, the J value does not usually exceed 2.5 Hz.[17e,37] Hence, the observed coupling constants $J_{4,5}$ (1 Hz) and $J_{3,4}$ (2.5 Hz) in the ^{1}H-NMR spectrum of 34 clearly established that the allyl group is in axial orientation at C(4). The $[\alpha]_D^{23}$ value [-58.4° (c 0.9, chlorbform)] of 34 is comparable with the reported one[36] [-58° (c 0.9, chloroform)].

Reduction of 34 using lithium triethylborohydride provided alcohol 35.[36] Its structure was established by ^{1}H-NMR analysis of its benzoate derivative 36. The crude 35 was converted directly to the benzoate 36. The protection of the hydroxyl group of 35 was necessary for further synthetic transformations. In the ^{1}H-NMR spectrum of 36, protons at 2.11 ppm (m) and at 1.96 ppm (broad doublet) were found to be coupled with H-1 (at 5.60 ppm) and H-3 (at 5.08 ppm). The multiplet at 2.11 ppm could be assigned to H-2_{ax} ($J_{2ax,3}$ = 5.25 Hz) and similarly the doublet at 1.96 ppm was assigned to H-2_{eq} ($J_{2eq,3}$ = about 1 Hz) (Scheme 13). This indicated that 35 and 36 are 2-deoxy sugars and the C(3)-hydroxyl group is in axial orientation.



$J_{2eq,3}$ = ca. 1 Hz

$J_{2ax,3}$ = 5.25 Hz

36

Scheme 13

In initial attempts, oxidation of the olefinic bond of 36 using sodium metaperiodate and a catalytic amount of osmium tetroxide in aqueous dioxane gave more than one product (TLC control). However, ozonolysis of the benzoate 36 in methanol at -78°C followed by reductive workup with dimethyl sulfide provided aldehyde 37 in 88% yield. An interesting feature of the ^{1}H-NMR spectrum of 37 (Fig. 6) was the unusual deshielding of the H-4 proton (at 2.54 ppm) as compared to the H-4 shifts of 35 and 36 (about 0.6 ppm lower field than the H-4 signals of 35 and 36). It is believed that this is probably because of the anisotropic deshielding by the aldehyde carbonyl. In contrast, the ^{13}C-chemical shift of C(4) of 37 was found to be 5.24 ppm upfield from the shift of the C(4) of the allyl compound 36 (Table 1). These observations suggest that the aldehyde group of 37 exists extensively

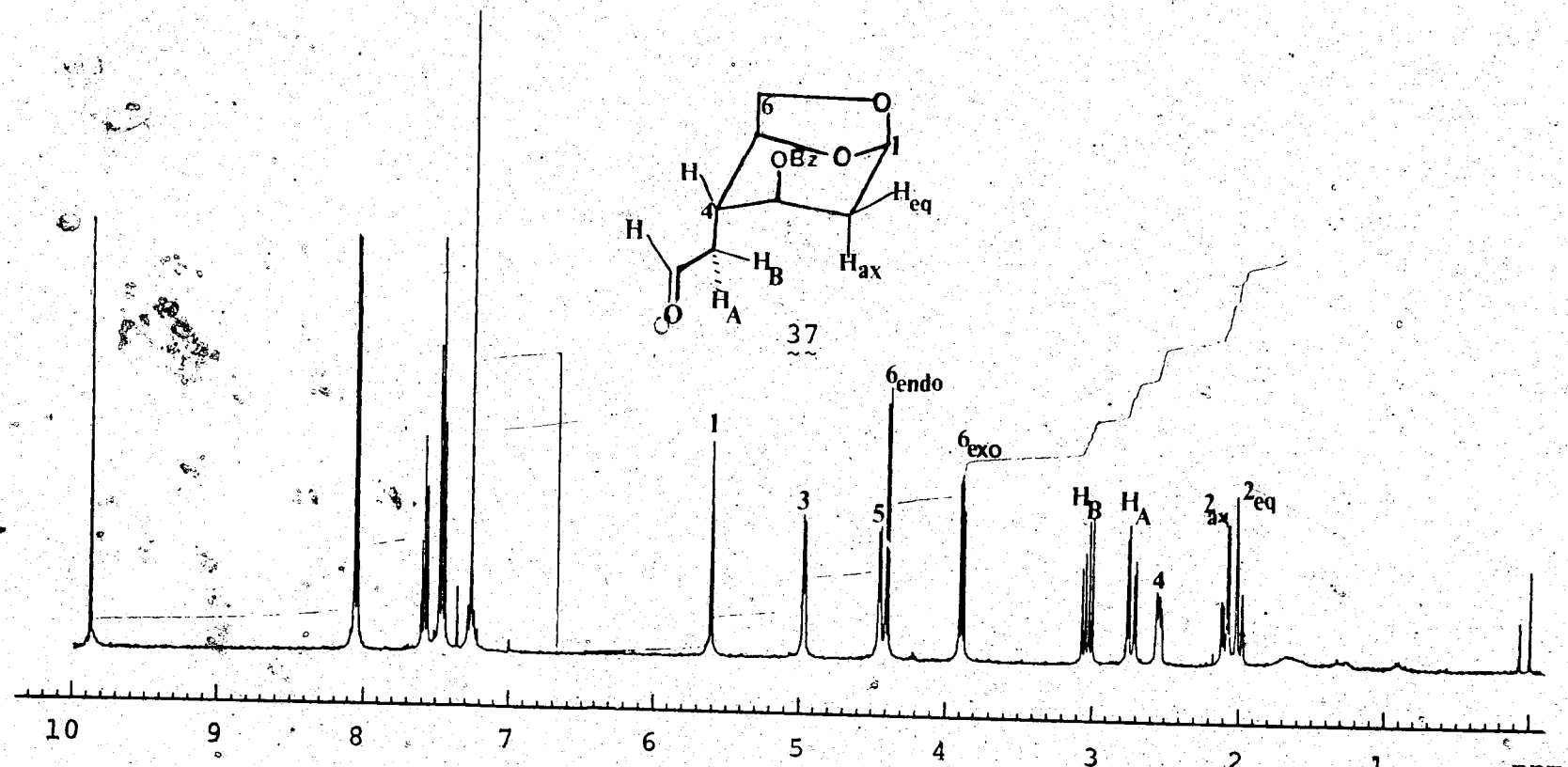


Fig. 6. The ^{1}H-NMR spectrum of 37 at 400 MHz in $CDCl_3$.

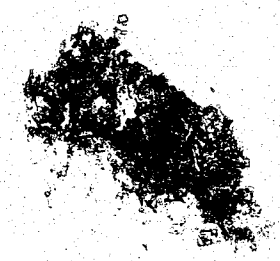
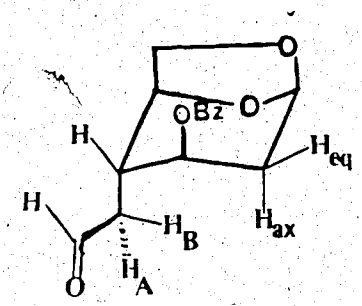


Table 1: ^{13}C-NMR data[a] of compounds 34—38 and 41.

Carbon atom	1	2	3	4	5	6	1'[b]	2'	3'	4'	5'	6'	7'	-COOCH$_3$	-O$_3$S-CH$_3$	Ar-CH$_3$
										aromatic carbons				-COOPh		
34	99.63	78.80	69.81	43.09	74.27	68.21	35.35	135.51	117.91	127.89	130.07	133.27	145.35			21.62
35	101.15	36.18[c]	67.81	44.94	74.79	67.92	35.50[c]	136.16	117.12							
36[d]	100.15	33.50	69.77	42.67	73.99	67.79	35.26	135.52	117.71							
37	99.97	33.68	69.96	37.43	74.17	67.83	44.70	199.63		133.05	129.49	128.39		165.67		
38	101.20	36.18	68.10	45.63	74.78	67.94	28.81	128.04	131.10	26.58	24	33.39	173.87	51.36		
41	99.30	33.89	76.68	43.68	73.69	67.48	28.20	126.65	132.07	26.53	24	33.28	173.74	51.36	38.82	

a. Chemical shift values in ppm from TMS.
b. This numbering starts from C(4)-CH$_2$(1')CH=CH (See: Scheme 11).
c. These values can be reversed within the same row.
d. The chemical shifts of aromatic carbons are not listed here.

in an arrangement in which the H-4 lies in the deshielding zone of the aldehyde carbonyl. An approximate conformation of 37 is proposed in Scheme 14. The chemical shifts of



J_{4,H_B} = 9 Hz

J_{4,H_A} = 5 Hz

37

Scheme 14

the two hydrogens (H_A and H_B) adjacent to the aldehyde group are substantially different [$\Delta\delta(H_A, H_B)$ = 0.38 ppm, compare with 35 (0.12 ppm) and 36 (0.07 ppm)]. The coupling constants J_{4,H_B} and J_{4,H_A} were found to be 9 and 5 Hz respectively. This further supports the fact that there is a preferred orientation of the aldehyde carbonyl[38] in 37.

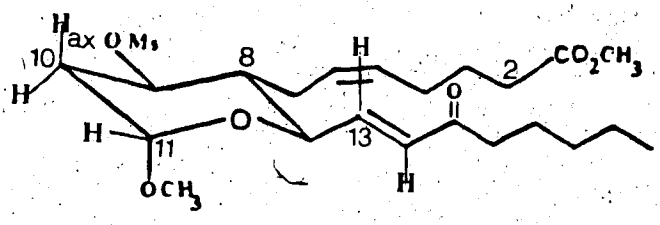
The construction of the α-chain was completed following the known methodology used in prostaglandin synthesis.[39] The aldehyde 37 was treated with the Wittig reagent generated from (4-carboxybutyl)triphenylphosphonium bromide in the presence of potassium t-butoxide in THF. The resultant crude acid was debenzoylated with

an excess of sodium methoxide in methanol to give the expected cis-olefin 38 after esterification. The olefin 38 was contaminated, probably due to the formation of trans-olefin (≤ 10%), since extra signals were found in the olefinic region of the ^{13}C-NMR spectrum. The Wittig reaction was also attempted using dimethyl sulfoxide as a solvent, but this did not significantly change the product distribution. No attempt was made to investigate this reaction and the product was employed as such in the next step. The impurities were removed at a later stage.

At this point, the introduction of the leaving group at C(3) of 38 was made to avoid further protection-deprotection of the C(3)-hydroxyl group. Treatment of 38 with methanesulfonyl chloride and triethylamine in dichloromethane[40] at room temperature afforded 41 in 85% yield. In view of the trans arrangement of the mesyl group and the hydrogen on C(2) of the pyranose ring, it was necessary to use milder conditions during the following synthetic transformations of 41. Methanolysis of 41 using IRA-120(H^+) resin as a catalyst at room temperature provided methyl glycoside 42 as a mixture of α- and β-anomers in a ratio about 85:15 (^{1}H-NMR). The reaction was very slow at room temperature (even after 3 days a small amount of starting material was recovered). Although the reaction

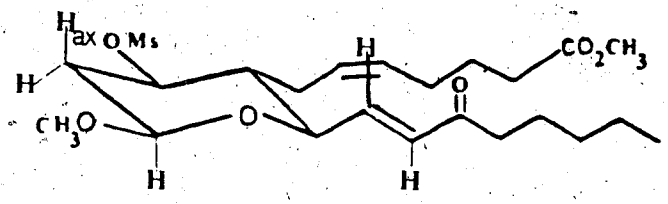
rate could be enhanced by using reflux temperature, the yield of the desired product 42 was low. The alcohol 42 was oxidized to the aldehyde 43 with Collins reagent according to its adaptation to carbohydrates.[41]

Introduction of the lower side chain (ω-chain) and establishment of the 13,14-trans double bond was readily accomplished using a Wadsworth-Emmons modification of the Wittig reaction. Thus, reaction of the aldehyde 43 with dimethyl (2-oxoheptyl)phosphonate, adapting a published procedure,[42] in which the carbanion was generated with potassium t-butoxide in anhydrous toluene, proved highly efficient and led to a mixture of α,β-unsaturated ketones 44 and 45. No elimination products could be detected in this reaction (^{1}H-NMR). The α- and β-anomers, 44 and 45 were separated by careful chromatography and were identified by typical signals in their ^{1}H- and ^{13}C-NMR spectra. The chemical shift of the anomeric proton in the ^{1}H-NMR spectrum of 44 was found to be 4.87 ppm ($J_{10ax,11}$ = 4 Hz), whereas in 45, it was 4.41 ppm ($J_{10ax,11}$ = 9.25 Hz) (Scheme 15). The IR spectra of 44 and 45 (1676 and 1675 cm^{-1} respectively) indicated that both the compounds possess an α,β-unsaturated ketone system. Their ^{1}H-NMR spectra showed large trans-ethylenic couplings ($J_{13,14}$ = 16 and 15.5 Hz for 44 and 45 respectively).



44

$J_{10ax,11}$ = 4 Hz, $J_{13,14}$ = 16 Hz



45

$J_{10ax,11}$ = 9.25 Hz, $J_{13,14}$ = 15.5 Hz.

Scheme 15

In the ^{13}C-NMR spectra of 44 and 45, the chemical shifts of anomeric carbons were 98.36 and 100.01 ppm respectively (Table 2). Although, in principle, the β-anomer 45 could be utilized in the following steps, separation at this stage was necessary to avoid the formation of a mixture of diastereomers.

Reduction of 44 was effected with sodium borohydride in absolute methanol at -40°C, whereby two diastereomeric alcohols were formed almost in equal quantities which

Table 2: ^{13}C-NMR data[a] of compounds 42—47.[a]

Carbon atom[b]	42[c]	43[c]	44	45	46	47
1	173.87	173.36	173.80	173.72	174.18	174.28
2	33.42	33.23	33.43	33.38	33.42	33.40
3	24.48[d]	24.21[d]	24.70[d]	24.53[d]	24.58[d]	24.57[d]
4	26.79	26.57	26.92	26.87	26.86	26.88
5	131.09	132.16	131.32	131.70	130.66	130.64
6	126.00	125.07	125.87	125.21	126.04	126.26
7	24.56[d]	24.38[d]	24.58[d]	24.20[d]	24.86[d]	24.94[d]
8	41.49	40.66	46.08	45.59	45.77	45.88
9	77.35	76.54	77.12	78.06	77.74	77.80
10	37.28	36.03	37.27	38.50	37.08[e]	37.13[e]
11	98.19	97.94	98.36	100.01	98.20	98.22
12	71.57	75.19	70.53	74.39	71.67[f]	71.80[f]
13	62.98	198.12	141.68	140.75	127.79	127.54
14			130.93	130.84	138.01	138.25
15			200.12	199.99	71.87[f]	72.01[f]
16			40.67	40.76	37.33[e]	37.36[e]
17			23.69[d]	23.66[d]	25.06[d]	25.11[d]
18			31.47	31.43	31.71	31.72
19			22.46	22.42	22.55	22.56
20			13.89	13.86	13.94	13.86
$-COO\underline{C}H_3$	51.54	51.27	51.41	51.41	51.44	51.51
$-O_3S\underline{C}H_3$	38.82	38.69	38.90	39.28	38.87	38.88
$-O\underline{C}H_3$	54.74	55.19	54.96	56.65	54.78	54.78

a. Chemical shift values in ppm from TMS.
b. Carbon position labels are as used for thromboxanes.
c. These values are for α-anomer.
d. These numbers can be interchanged within the same column.
e. These numbers can be reversed within the same column.
f. These assignments were confirmed by single frequency decoupling experiments.

were separated by chromatography. The 15S-configuration was tentatively assigned to the more polar alcohol 46 (Rf. 0.31, TLC, silica gel, 1:1 ethyl acetate—hexane) based upon literature precedent in the area of prostaglandin synthesis[43] (see discussion on configuration of 46 and 47 for confirmation of this assignment). The isomeric alcohols, 46 and 47 appeared to be free of the impurity encountered during the first Wittig reaction (^{13}C-NMR).

Benzoylation of 46, provided the chiral 15S-benzoate 48, which has been synthesized by Hamanaka and coworkers as a mixture of α- and β-anomers and has been subsequently converted into 7. The ^{1}H-NMR spectrum of 48 is comparable with the one obtained by Hamanaka and coworkers.[44] Thus, the synthesis of 48 completed the formal total synthesis of optically active 9α,11α-thiathromboxane A_2 methyl ester 7 starting from starch. The synthetic methodology described in preceeding pages have potential to synthesize other thromboxane A_2 analogues and possibly, thromboxane A_2 derivatives.

The diastereomeric alcohol 47 was converted to 15R-benzoate 49 which was used for comparison in the configurational assignments.

The ^{13}C-NMR chemical shift assignments listed in Tables 1 and 2 are based upon the chemical shifts, signal multiplicity (obtained either from off resonance or Spin Echo-Fourier Transform[45]) and literature precedent

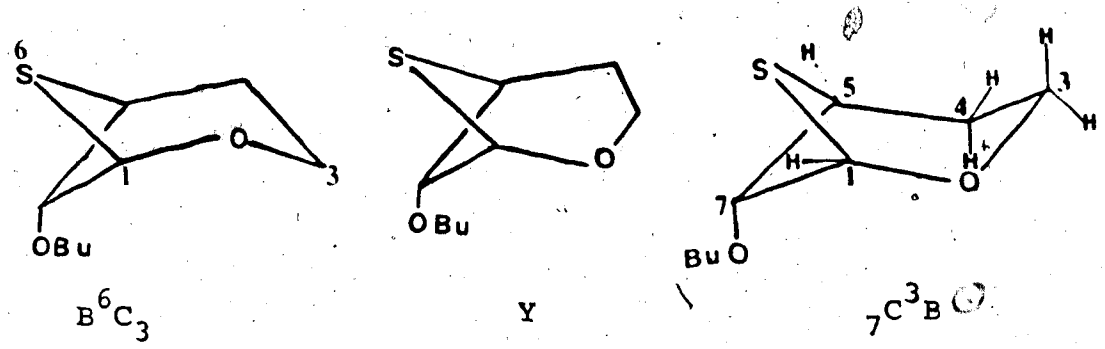
in the areas of carbohydrates,[46,47,48] prostaglandins[49,50] and thromboxanes.[51] Some of the assignments were confirmed by the single frequency proton-decoupling experiments.

D. Conformational studies

a. Conformational analysis of 31: The various synthetic analogues of TXA_2[11—13] having a bicyclo[3.1.1]-heptane skeleton are reported to have either partial TXA_2 antagonist or partial agonist or TXA_2 synthetase-inhibiting activity. The dithia-analogue 10 (Scheme 2) showed properties very similar to natural TXA_2.[14] 11α,9α-Epoxymethanothromboxane A_2 in which the labile oxetane ring of TXA_2 is replaced by a stable tetrahydrofuran moiety, has been found to be 25—30 times less potent in contracting rabbit aorta strips and 700—1000 times less effective in inducing reversible platelet aggregation in platelet rich plasma than TXA_2.[52] The TXB_2 (3, Fig. 2) lacks the biological profile displayed by TXA_2.[8] These observations suggest that the rigid bicyclo[3.1.1]heptane skeleton plays a key role in the hormonal activity of TXA_2 and its synthetic congeners. Compound 31 seemed to be a reasonable model for the conformational studies of the bicyclo[3.1.1]heptane framework of TXA_2 and its analogues.

Examination of molecular models of 31 indicates that there are three conformations possible for this compound similar to those of the pinanes.[53] In the skeletal structure of 31, the thietane ring [-C(1)-S(6)-C(5)-C(7)-portion] is rigid and only the bridging fragment,

-O(2)-C(3)-C(4)- is conformationally flexible. The first of the conformations is a B^6C_3 (Scheme 16) in which the oxa-thiane ring is in a chair-form and the pyranose ring in a boat-form. This form will experience severe 1,4 syn-interactions between the axial n-butoxy group and the hydrogen on C(3). In the second conformer (Y)



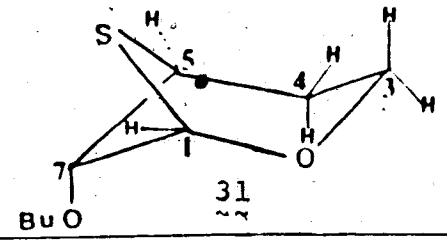
B^6C_3 Y $_7C^3B$

Scheme 16.

the bridging fragment [-O(2)-C(3)-C(4)-] is flattened. The third possible conformer is the $_7C^3B$, in which C(3) bends away from the C(7)-substituent and the less hindered position of C(3) should favor this conformation rather than B^6C_3.

The ^1H- and ^{13}C-NMR data for the ring portion of 31 are listed in Table 3. The H-1 proton was expected to be at the lowest field because of the acetal linkage and hence the signal at 5.54 ppm in the ^1H-NMR spectrum of 31 (Fig. 7) was assigned to it. A multiplet at 2.61 ppm ($W_{½}$ = 32 Hz) was assigned to H-4_{ax} and it was 0.47 ppm lower field than the H-4_{eq} multiplet ($W_{½}$ = 26 Hz). The deshielding of

Table 3: Partial nuclear magnetic resonance data of 31.



31

Carbon No	1	3 $^{3}_{ax}$	3 $^{3}_{eq}$	4 $^{4}_{ax}$	4 $^{4}_{eq}$	5	7
NMR δ	5.54,q	4.51,m	3.99,br q	2.61,m	2.14,m	3.72,m	4.31,q
$J_{H,H}$[a]	1,5 = 5.25	$^{3}_{ax},^{3}_{eq}$ = 11.0	$^{3}_{eq},^{3}_{ax}$ = 11.0	$^{4}_{ax},^{4}_{eq}$ = 13.0	$^{4}_{eq},^{4}_{eq}$ = 13.0	5,1[b] = 5.25	7,1 = 3.25
	1,7 = 3.25	$^{3}_{ax},^{4}_{ax}$ = 9.5	$^{3}_{eq},^{4}_{ax}$ = 8.0	$^{4}_{ax},^{3}_{ax}$ = 9.5	$^{4}_{eq},^{3}_{ax}$ = 6.7	5,7[b] = 5.00	7,5 = 5.00
		$^{3}_{ax},^{4}_{eq}$ = 6.7	$^{3}_{eq},^{4}_{eq}$ = 1.0	$^{4}_{ax},^{3}_{eq}$ = 8.0	$^{4}_{eq},^{3}_{eq}$ = 1.0	5,$^{4}_{eq}$[b] = 5.00	
				$^{4}_{ax},5$ = 1.5	$^{4}_{eq},5$ = 5.0	5,$^{4}_{ax}$ = 1.5	
CMR ppm[c]	89.51	60.23		25.84		48.54	74.64
	dt	t		t		d	d
$^{1}J_{C-H}$ Hz[d]	177.6	147.5		128		157.9	157.3
$^{3}J_{C-H}$ Hz	7.0 Hz	7.0 Hz					3 Hz

a. The coupling constants are calculated to first order and are expected to be within 0.2 Hz.
b. Values obtained from decoupled spectra.
c. Chemical shift assignments are confirmed by single frequency decoupling experiments.
d. Measured from the coupled spectrum obtained using C-H dual probe at 100.6 MHz.

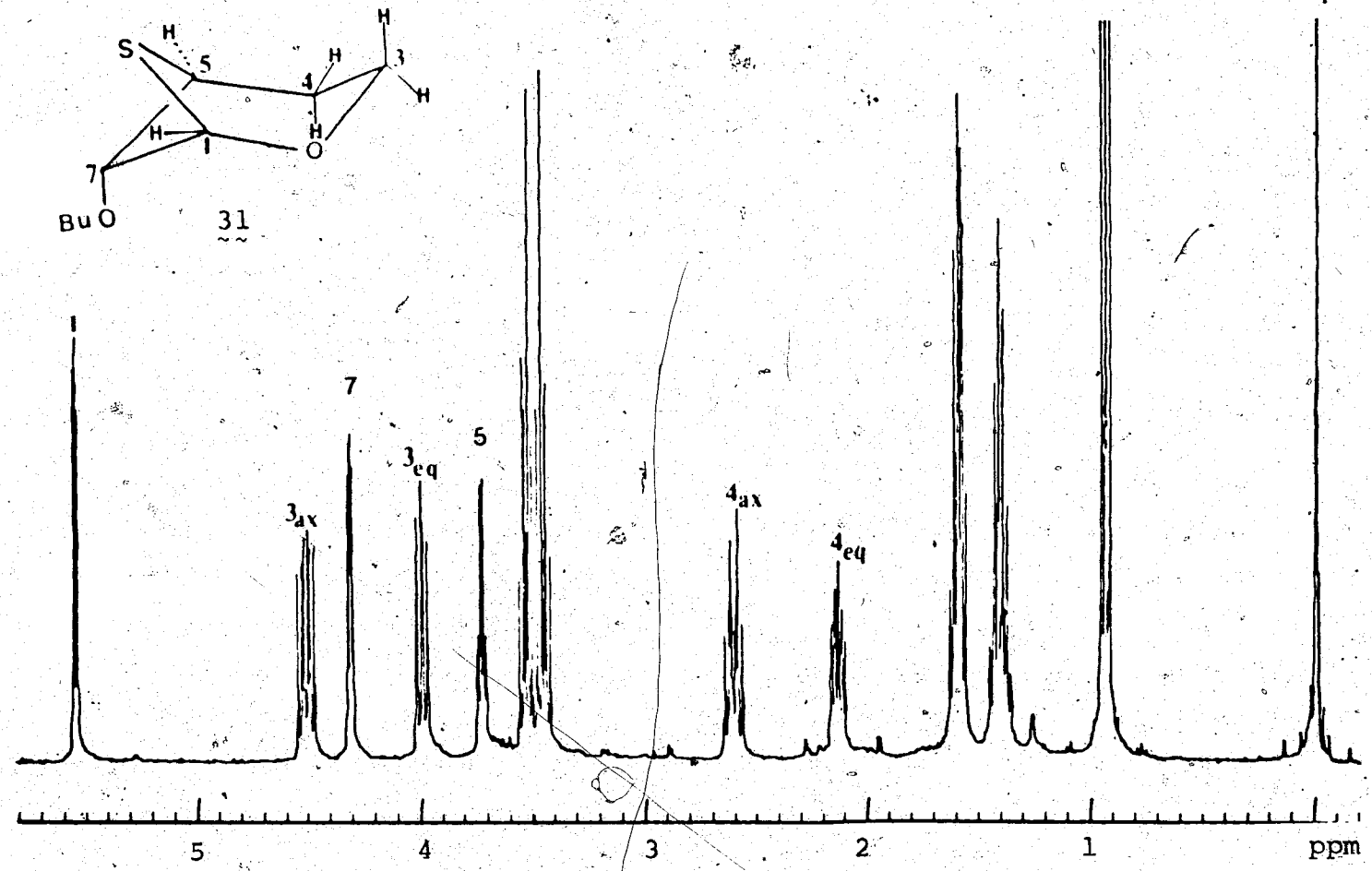


Fig. 7. The ^{1}H-NMR spectrum of 31 at 400 MHz in $CDCl_3$.

H-4_{ax} is probably because of the electrostatic interaction between this proton and the C(7)-O- and this type of interaction could be expected in ^3CB form. Similarly, the H-3_{ax} multiplet (at 4.51 ppm, $W_{\frac{1}{2}}$ = 28 Hz) was found to be 0.52 ppm lower field than the H-3_{eq} signal ($W_{\frac{1}{2}}$ = 22 Hz).

The anomeric proton appeared as a doublet of doublets (J = 3.25, 5.25 Hz) demonstrating the presence of a vicinal and a long-range coupling. The long-range coupling could be expected between H-1 and H-5 or H-1 and H-3 since it is known that in saturated systems the largest four-bond coupling could be observed for protons which are separated in planar zig-zag or W arrangement.[54,55] The double resonance experiments established that in 31 the long-range coupling is with H-5 ($^4J_{1,5}$ = 5.25 Hz). The corresponding long-range coupling in thietane itself is reported to be about 1.2 Hz.[56] This proved that in 31, the arrangement of H-1 and H-5 approaches the planar, zig-zag form more closely than in thietane itself, since the thietane ring in 31 is more puckered because of the C(5) and C(1)-substituents. It has been shown previously that in mono or 1,3-disubstituted cyclobutane compounds, the value of ^4J increases rapidly with the puckering of the ring.[57] In addition, very large values for four-bond couplings have been observed for bicyclo[1.1.0]butane (^4J = 10 Hz),[58] bicyclo[1.1.1]pentane

(^4J = 10, 18 Hz), bicyclo[2.1.1]hexane (^4J = 6.8 to 8.1 Hz), unsaturated bicyclo[3.1.1]heptanes[59] (^4J = 8.5 and 5.5 to 6 Hz) and a dioxabicyclo[3.1.1]heptane derivative (^4J = 4 Hz).[19e] It is noteworthy that the long-range coupling observed for the substituted oxa-thia[3.1.1]-heptane derivative 31 ($^4J_{1,5}$ = 5.25 Hz) is intermediate between that of thietane ($^4J_{2,4}$ = 1.2 Hz) and that of bicyclo[2.1.1]hexane (^4J = 6.8 to 8.1 Hz).

It could be expected that in the Y conformer the torsional angles H-5/H-4_{ax} and H-5/H-4_{eq} will be nearly equal whereas in $_7C^3B$ form the torsional angle H-5/H-4_{ax} (about 100°) will be larger than the H-5/H-4_{eq} one. This difference should be reflected in the values of the coupling constants for these protons.[55] Indeed, the observed coupling constants between H-5 and H-4_{eq}, H-5 and H-4_{ax} are substantially different ($J_{4ax,5}$ = 1.5 Hz and $J_{4eq,5}$ = 5 Hz) and therefore the -O(2)-C(3)-C(4)- fragment in 31 must be bent at C(3) as in $_7C^3B$ conformer.

A partial theoretical ^{1}H-NMR spectrum of 31 involving the 7 spin system of the ring protons was calculated using the PANIC version of the LAOCOON computer program[60] in order to confirm the values of various coupling constants measured from the experimental spectrum. This involves: feeding the computer estimated values of the chemical shifts and coupling constants from the experimental spectrum and the program will predict

the theoretical spectrum. The spectral parameters are refined to get the best fit with the observed spectrum. This enabled us to confirm the coupling constants of the various ring protons listed in Table 3. However, in the case of $H\text{-}3_{eq}$ and $H\text{-}4_{eq}$ multiplets a best fit was obtained only when a long-range coupling between $H\text{-}3_{eq}$ and H-5, $H\text{-}4_{eq}$ and H-7 (about < 0.75 Hz) was taken into account (Fig. 8). The double resonance experiments confirmed the coupling $^{4}J_{3eq,5}$ (< 0.75 Hz). These results are in accordance with the $_{7}C^{3}B$ conformer for 31. Unfortunately, the long-range coupling between the $H\text{-}4_{eq}$ and H-7 could not be confirmed.

In the ^{13}C-NMR spectrum of 31, the low field signal at 89.5 ppm was assigned to the anomeric carbon. The ^{13}C-shifts for the anomeric carbon of 2,3,4-tri-O-acetyl-1,6-anhydro-6-thia-β-D-glucopyranose[61] and C(2) of 1-oxa-3-thiane[62] are observed at 81.8 and 71.23 ppm respectively. The assignment of ^{13}C-shifts of 31 (Table 3) was confirmed by single-frequency proton decoupling experiments. The $^{1}J_{C-H}$ coupling constants for C(5) ($^{1}J_{C-H}$ = 158 Hz) and C(7) ($^{1}J_{C-H}$ = 157 Hz) were found to be larger than those reported for 3-hydroxythietane [$^{1}J_{C(2)-H}$ = 147.4 Hz and $^{1}J_{C(3)-H}$ = 150.7 Hz].[63] In addition to the one-bond coupling, the anomeric carbon of 31 showed two three-bond couplings of about 7 Hz. These couplings are assigned to $^{3}J_{C(1),H-5}$ and $^{3}J_{C(1),H-3eq}$

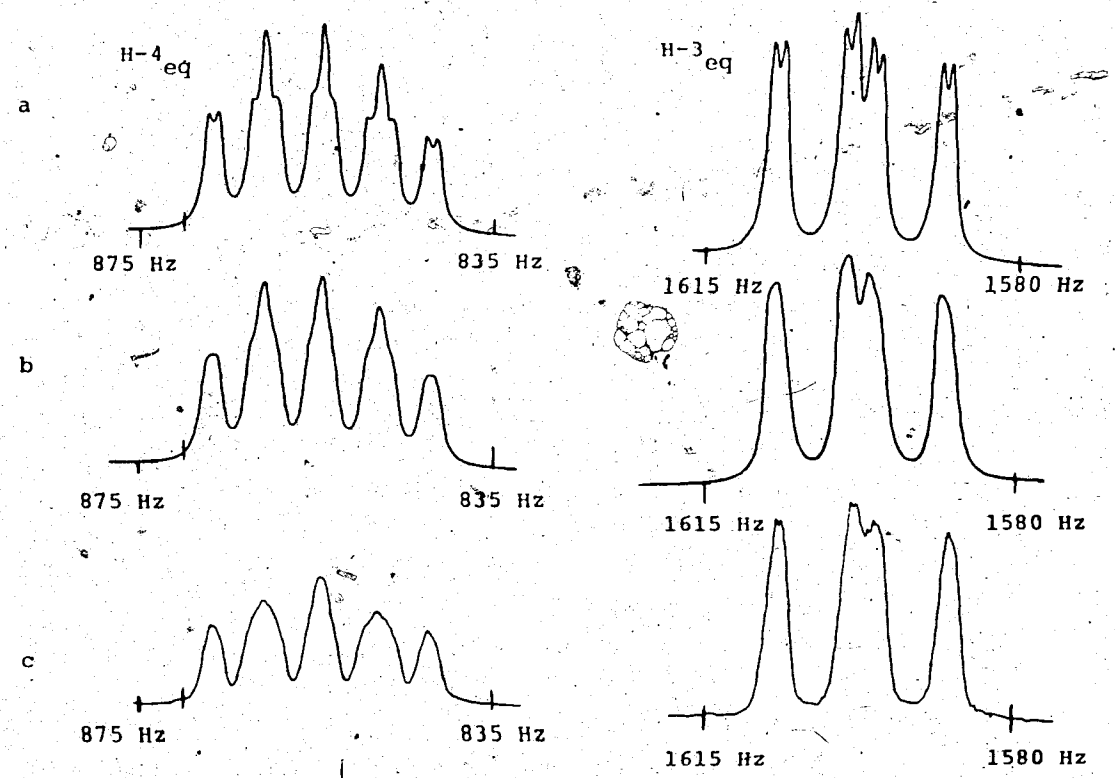


Fig. 8. The simulated and observed spectra for the H-4_{eq} and H-3_{eq} regions of 31 at 400 MHz. A. The simulated spectra calculated using the chemical shifts and couplings given in Table 3 ($W_{½}$ = 1.3 Hz). b. In this simulation long-range couplings ($J_{4eq,7}$ = 0.5 Hz and $J_{3eq,5}$ = 0.5 Hz) were used. c. The observed spectra.

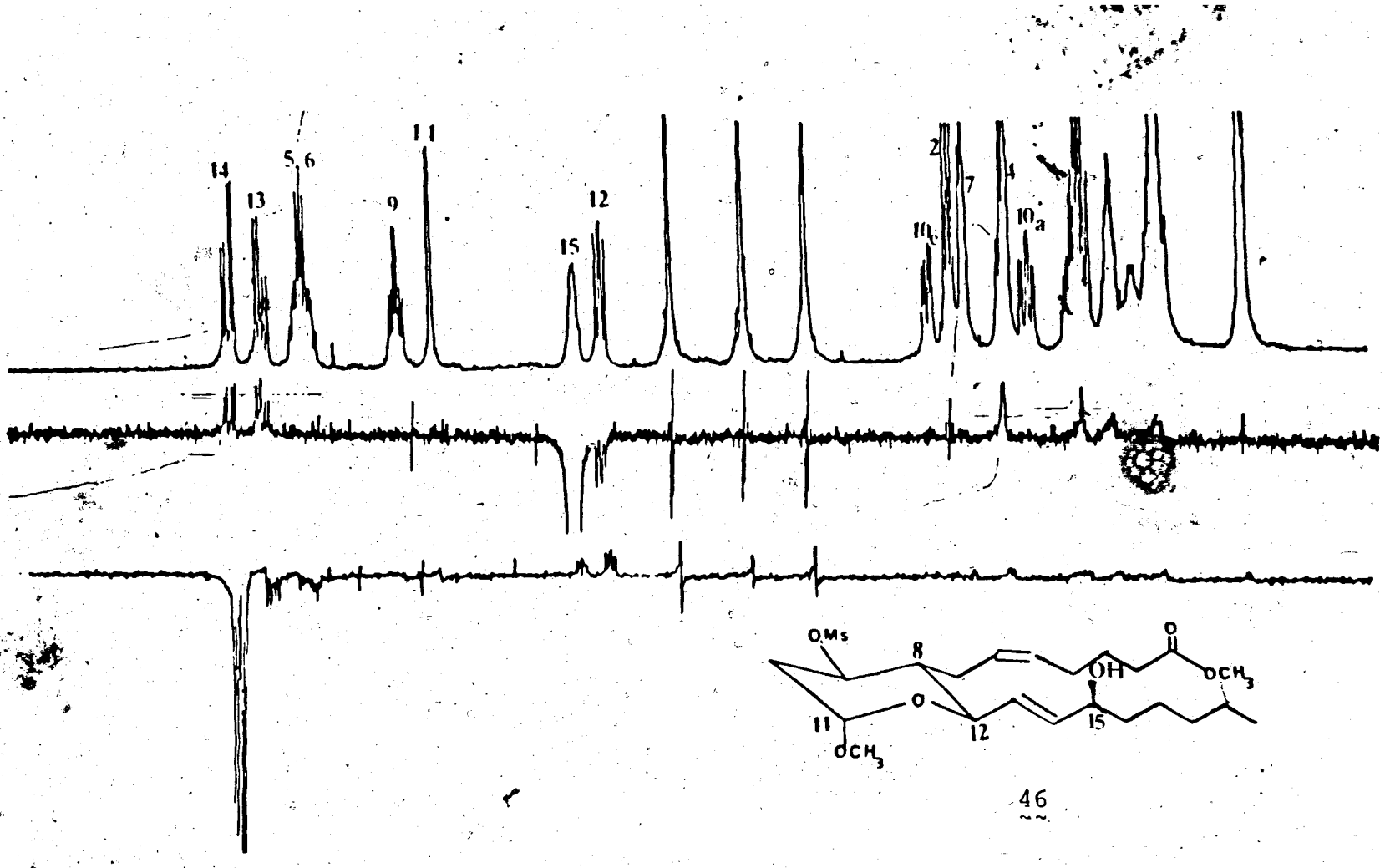
because of the nearly anti-periplanar arrangement of H-5 and C(1)-C(7) bond, and $H\text{-}3_{eq}$ and C(1)-O(2) bond.[47]

In summary, the detailed NMR analysis of 31 indicates that the compound must exist extensively in conformation $_7C^3B$ in $CDCl_3$. The conformational studies of 31 provide valuable information about the shape of the bicyclic skeleton of TXA_2 and its analogues.

b. Configurations of 46 and 47 at C(15):

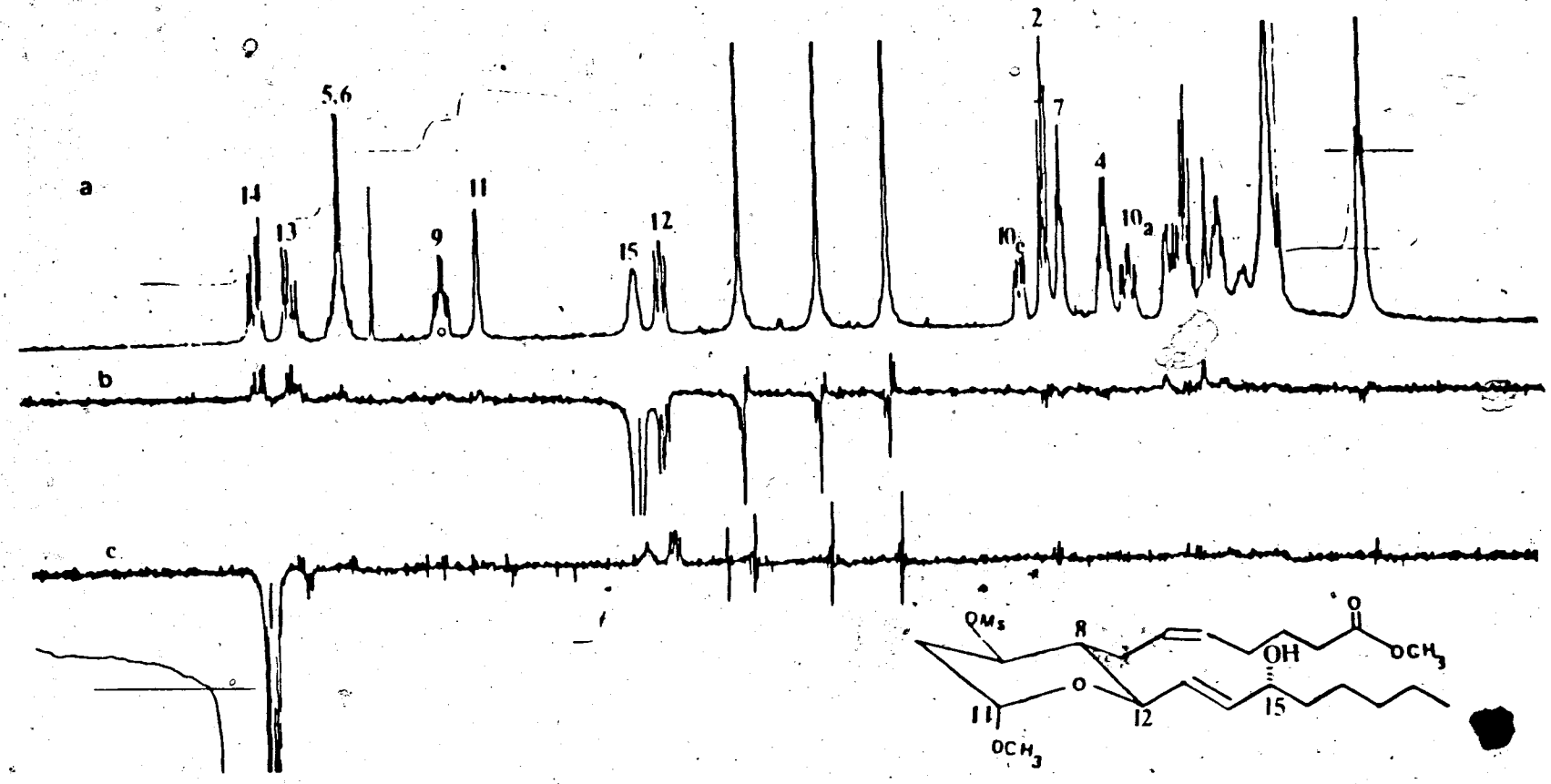
The configurations of the enones 44 and 45 (Scheme 15) could be established by spectral analysis and by the modes of formation of their precursors. However, the assignment of the configurations at C(15) of the diastereomeric alcohols, 46 and 47 was made on the basis of their relative thin-layer chromatographic mobilities:[43] the slightly more polar isomer was assigned the 15-S configuration. It was necessary to support this by comparison of the spectral properties of 46 and 47 or their benzoates 48 and 49.

The comparison of ^1H- (Fig. 9 and 10) and ^{13}C-NMR (Table 2) spectra of 46 and 47 did not reveal any significant difference between these two diastereomers. Similarly, the nuclear Overhauser enhancement (n.O.e.) experiments[64] did not lead to any conclusion about the conformations of these molecules about the C(14)-C(15) bond. Thus, saturation of H-15 signals of 46 and 47 showed



46

Fig. 9. The results of the n.O.e. experiments performed on 46 at 400 MHz at 298 K. The normal spectrum is seen in a. In b, H-15 is saturated. In c, H-14 is saturated.

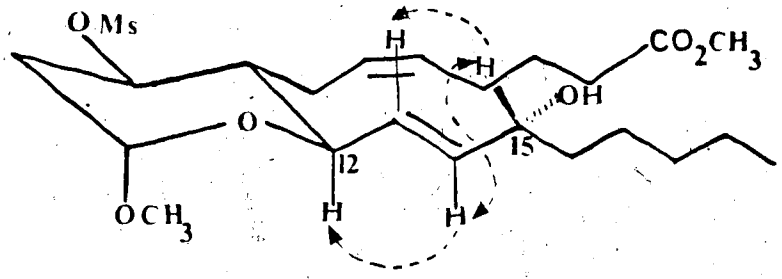


47

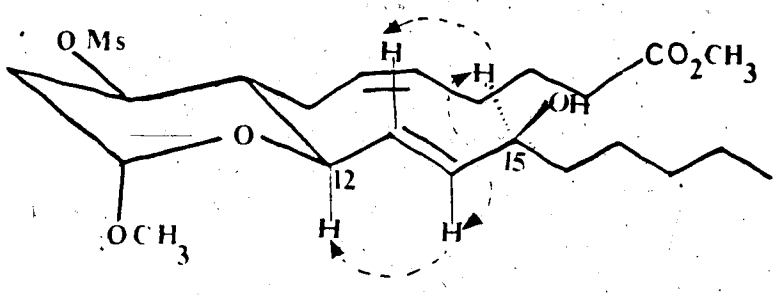
Fig. 10. The n.O.e. experiments performed on 47 at 400 MHz at 298 K. The normal spectrum is seen in a, whereas in b H-15 is saturated. In c, H-14 is saturated.

enhancement of both the H-13 and H-14 signals, whereas saturation of H-14 signals resulted in the enhancement of the multiplets of H-12 and H-15 (Fig. 9 and 10). These results are summarized in Scheme 17.

The effect of temperature on the coupling constants $J_{12,13}$ and $J_{14,15}$ in the ^{1}H-NMR of 46 and 47 was studied to determine the conformational preference of these molecules about the C(12)-C(13) and C(14)-C(15) bonds. If the coupling constant undergoes a change with temperature, this likely results from a conformational equilibrium.[55] Thus, determination of ^{1}H-NMR spectra at two widely different temperatures can be useful to establish conformational predominance of a compound.[55,38] The similar values of $J_{12,13}$ in the ^{1}H-NMR spectra of 46 and 47 (7.6 Hz for both 46 and 47 in $CDCl_3$) indicated that these two molecules must exist extensively in a conformation in which the hydrogens at C(12) and C(13) are in near anti-periplanar arrangement.[38,65] At low temperature, the population of this conformer should increase and this should result in an increase of the $J_{12,13}$ value.[38,66] The measurement of the ^{1}H-NMR spectra of the allylic alcohol 46 in CD_2Cl_2 at three different temperatures (298, 233, 203 K) showed that there was a trend towards the larger $J_{12,13}$ values at low temperature ($J_{12,13}$ = 7.6 ± 0.2 Hz at 298 K and 8.6 ± 0.4 Hz at 203 K in CD_2Cl_2[67]). Similarly, an increase



47



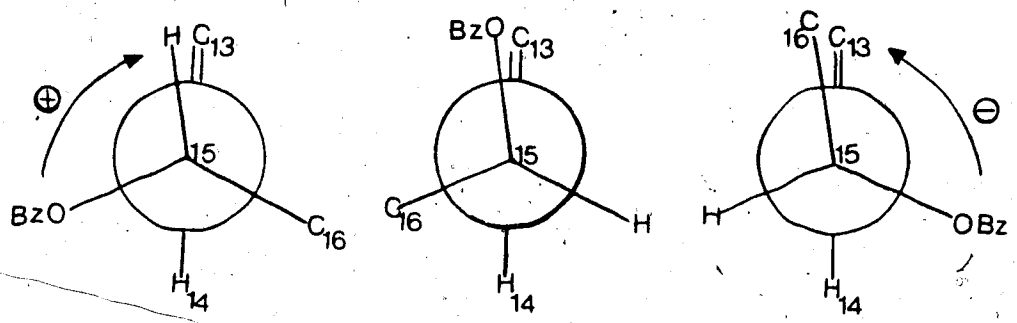
46

Scheme 17: Schematic representation of n.O.e. experiments performed on 46 and 47.

in the $J_{12,13}$ value in the ^{1}H-NMR spectrum of 47 in CD_2Cl_2 was observed at low temperature. These results indicated qualitatively that the predominant conformational geometry about the C(12)-C(13) bond for these molecules (46 and 47) is near anti-periplanar (Scheme 17). The increase in the $J_{14,15}$ value in the ^{1}H-NMR spectra of 46 and 47 at low temperature was small and therefore, conformational preference about the C(14)-C(15) bond could not be established.

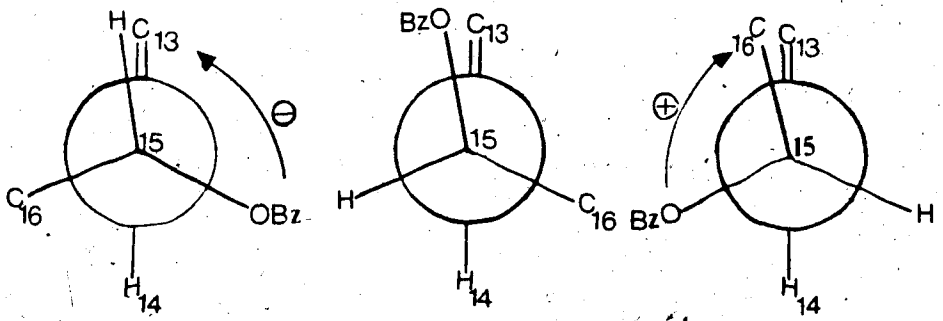
Since the predominant conformations about the C(14)-C(15) bond could not be determined for the allylic alcohols 46 and 47, conformational analysis of their benzoates 48 and 49 was carried out. Three sets of limiting conformations can be considered for the allylic benzoates 48 (Fig. 11) and 49 (Fig. 12). The conformations 48A and 49A should be favored since C(16) and benzoate are both bulkier than hydrogen.[38,65] In these conformations, the H-15 is in near syn-periplanar arrangement with the C(13)-double bond and H-13, and H-14 and H-15 are in anti-periplanar orientation.

The comparison of ^{1}H-NMR spectra of 48 and 49 is shown in Fig. 13. The multiplets of H-13 and H-14 in the ^{1}H-NMR spectrum of 48 are well separated (5.72 ppm and 5.85 ppm respectively; $J_{12,13}$ = 7.4 Hz) whereas in 49 the multiplets of H-5 and H-6 are separated but the H-13 and H-14 signals are very close to each other



48A 48B 48C

Fig. 11. Limiting conformations for 48 about the C(14)-C(15) bond. Signs on the curved arrows show predicted signs of the Cotton effect.[68]



49A 49B 49C

Fig. 12. Limiting conformations for the allylic benzoate 49 about the C(14)-C(15) bond. Signs on the curved arrows show predicted signs of the Cotton effect.[68]

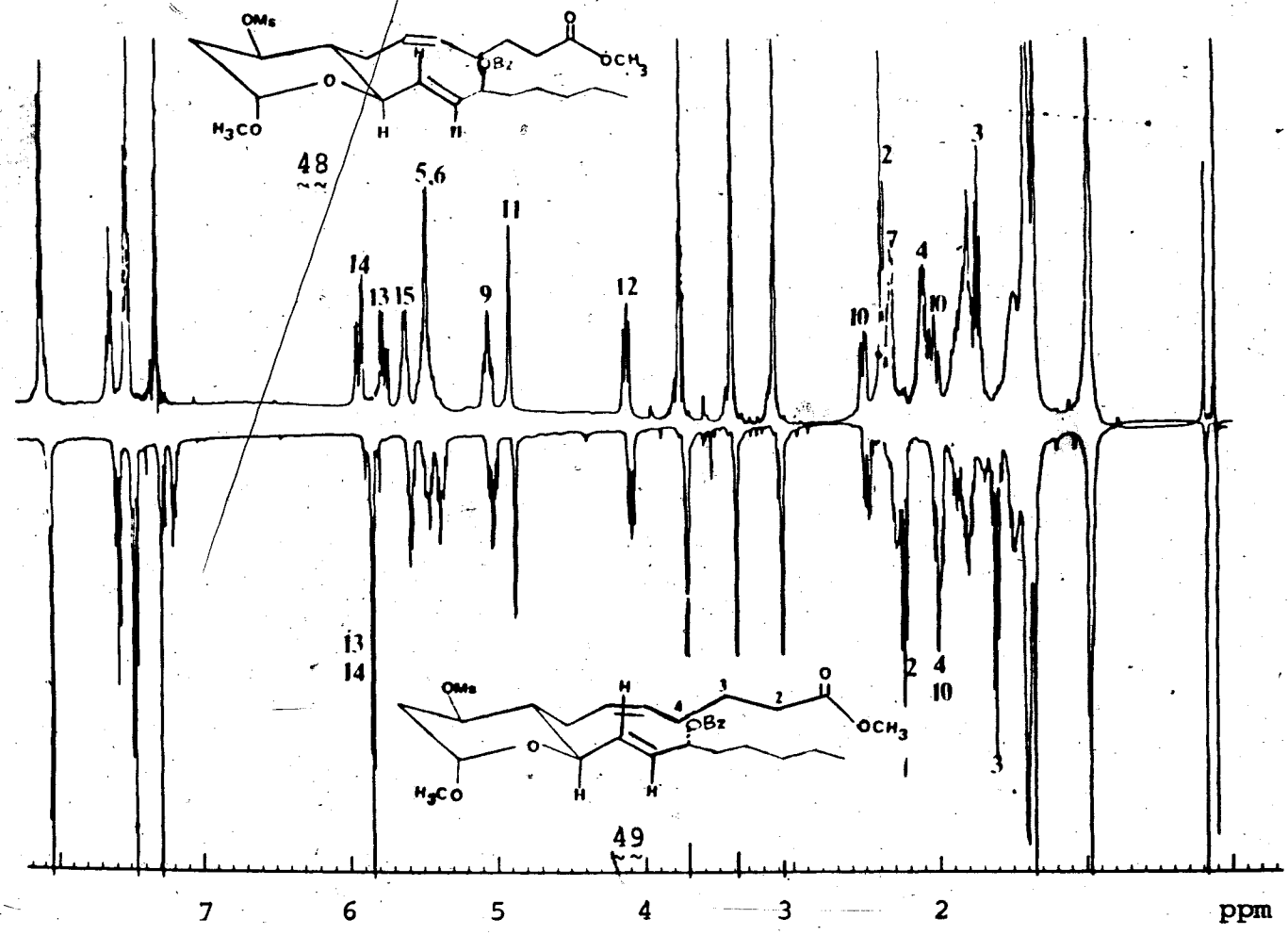


Fig. 13. The comparison of the ^{1}H-NMR spectra of diastereomeric benzoates 48 and 49 at 400 MHz in $CDCl_3$. The C(2)—C(4)-hydrogen signals of 49 are shielded.

($J_{12,13}$ = 6.25 Hz). Another important difference between the ^{1}H-NMR spectra of these compounds (48 and 49) is found in the aliphatic region. The multiplets for the C(2), C(3) and C(4) protons in 49 are more shielded than the corresponding hydrogens in 48 (Fig. 13). This upfield shift of about 40—50 Hz (at 400 MHz in $CDCl_3$ at 298 K) of the C(2)—C(4) hydrogens in 49 is probably due to anisotropic shielding because of the close vicinity of the phenyl and/or the benzoate carbonyl group. The two hydrogens at C(2) appear as a triplet (at 2.28 ppm) in 48, whereas the C(2)-protons in 49 appear as two sets of closely separated triplets (at 2.15 ppm) (Fig. 14) indicating that these two hydrogens are in very different environments in 49. This type of shielding of the C(2)—C(4) hydrogens and the splitting of the triplet for the C(2)-protons could be expected for compound 48, if the predominant conformer is 48C. However, this possibility can be eliminated on steric grounds.[38,65] The above mentioned observations suggest that the predominant conformation for 49 is the 49A and that the less polar (TLC mobility) alcohol 47 is the 15-R isomer since its benzoate 49 has slightly different chemical shifts for the C(2)-methylene protons in the ^{1}H-NMR spectrum.

The effect of temperature on the extent of shielding of the C(2)—C(4) hydrogens in the ^{1}H-NMR spectrum of 49 was studied to obtain further evidence for the predominance

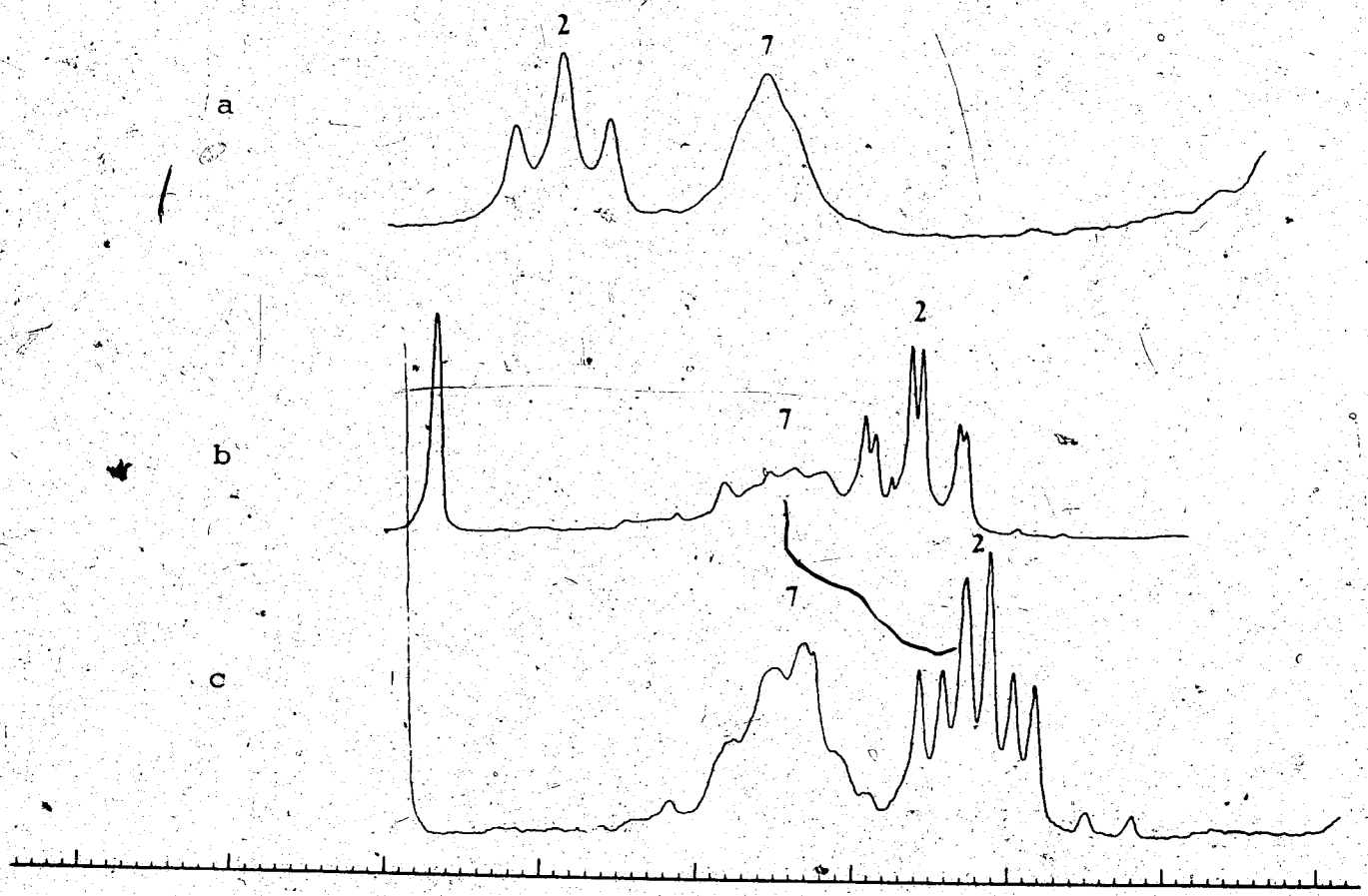
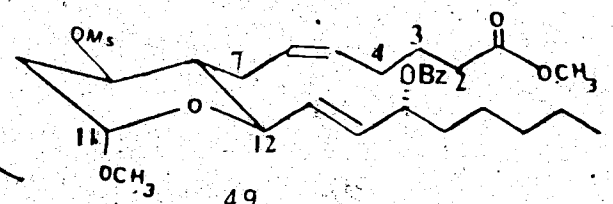


Fig. 14. The HH-2 and HH-7 region in the ^{1}H-NMR spectra of 48 and 49 at 400 MHz in $CDCl_3$. The upper trace (a) is that of 48 at 298 K. b and c are those of 49 at 298 and 263 K respectively.

of the conformer 49A. It was expected that at low temperature, the population of 49A should increase and this should result in further shielding of these protons. The measurement of the ^{1}H-NMR spectra of 49 at three temperatures (298, 263 and 233 K) showed that there was a gradual shielding of the C(2)—C(4) protons at low temperature (Fig. 15, a shielding of 30--45 Hz was observed at 400 MHz at 233 K in $CDCl_3$). The lines of the multiplet for the C(2)-hydrogens were further separated at low temperature (Fig. 14). This supported the conclusion that 49 exists extensively in the conformation 49A and that the phenyl group in 49A must be in close vicinity to the C(2)—C(4) side chain.

The predominance of the conformers 48A and 49A was further supported by circular dichroic (CD) measurements.[68] The predicted signs of the Cotton effect for the different conformers for 48 and 49 according to Nakanishi and coworkers[68] are shown in Fig. 11 and 12. In the region around 230 nm, the CD spectrum of 49 in methanol exhibited a negative Cotton effect, the sign of which showed that the overall chirality between the benzoate and double-bond chromophores in this flexible system is negative as in 49A. While the diastereomeric benzoate 48 showed a positive Cotton effect at about 230 nm as in 48A. The negative and positive signs of the CD spectra of the allylic benzoates have been correlated to the R and S



49

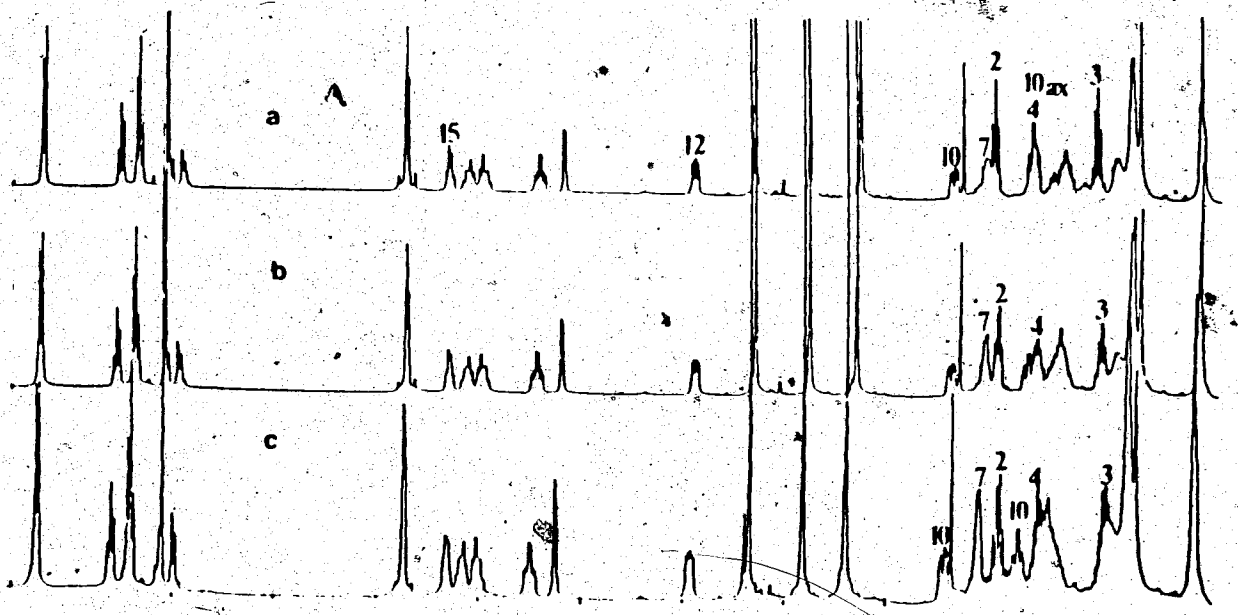


Fig. 15. Effect of temperature on the ^{1}H-NMR spectrum of 49 in $CDCl_3$ a at 298 K, b at 263 K and c at 233 K.

configurations respectively.[68,69]

In summary, the extra shielding of the C(2)—C(4) hydrogens of 49 compared to the same hydrogens of 48 and the observed multiplicity of the C(2)-hydrogens in the ^{1}H-NMR spectrum of 49 as well as the observed signs of the Cotton effects for 48 and 49 indicated that the allylic alcohols 46 and 47 have S and R configurations at C(15) respectively. This was further supported by comparison of the ^{1}H-NMR of 48 with the one obtained by Hamanaka and coworkers. In addition, these studies gave some idea about the approximate conformations of 46—49.

CHAPTER II

SYNTHETIC AND CONFORMATIONAL STUDIES OF COMPOUNDS RELATED TO MACROLIDE ANTIBIOTICS

A. 'Conformational diastereoface-differentiating' conjugate additions[70] of a methyl group to enone 56.

a. Introduction: In connection with the preparation of "chiral synthons" for the synthesis of macrolide antibiotics and related natural products, it was necessary to introduce stereoselectively an alkyl substituent (either in a threo- or erythro-relationship with respect to the C(5)-O- group) at the C(6)- position of the hexopyranosides (for example Prelog-Djerassi lactone[71]). Recently, a few reports about the conjugate additions of the alkyl groups to the enoate,[72,73] oxazoline[74] and hetero-olefin[75] derivatives of sugars have appeared. These reactions are useful to introduce stereoselectively an alkyl substituent adjacent to the ring-oxygen on a sugar derivative. However, these reactions have limitations since only one of the diastereomers is available from the same substrate. It was considered that a pyranosyl enone of the type 50 (Fig. 16) would be an ideal substrate to study the conjugate additions of alkyl groups since it could be readily obtained from the corresponding

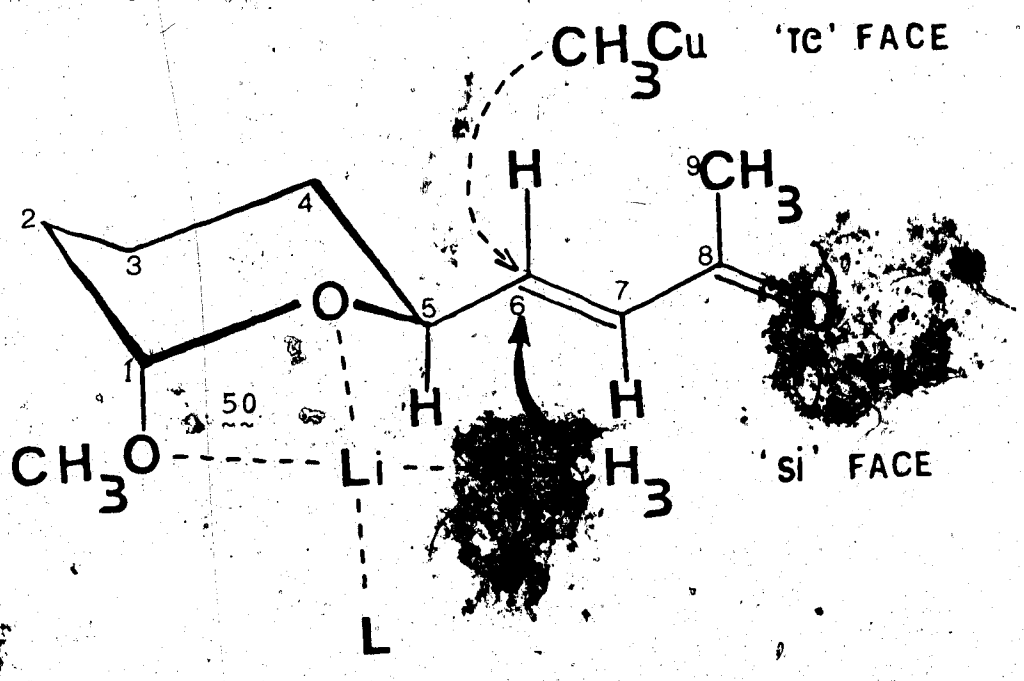
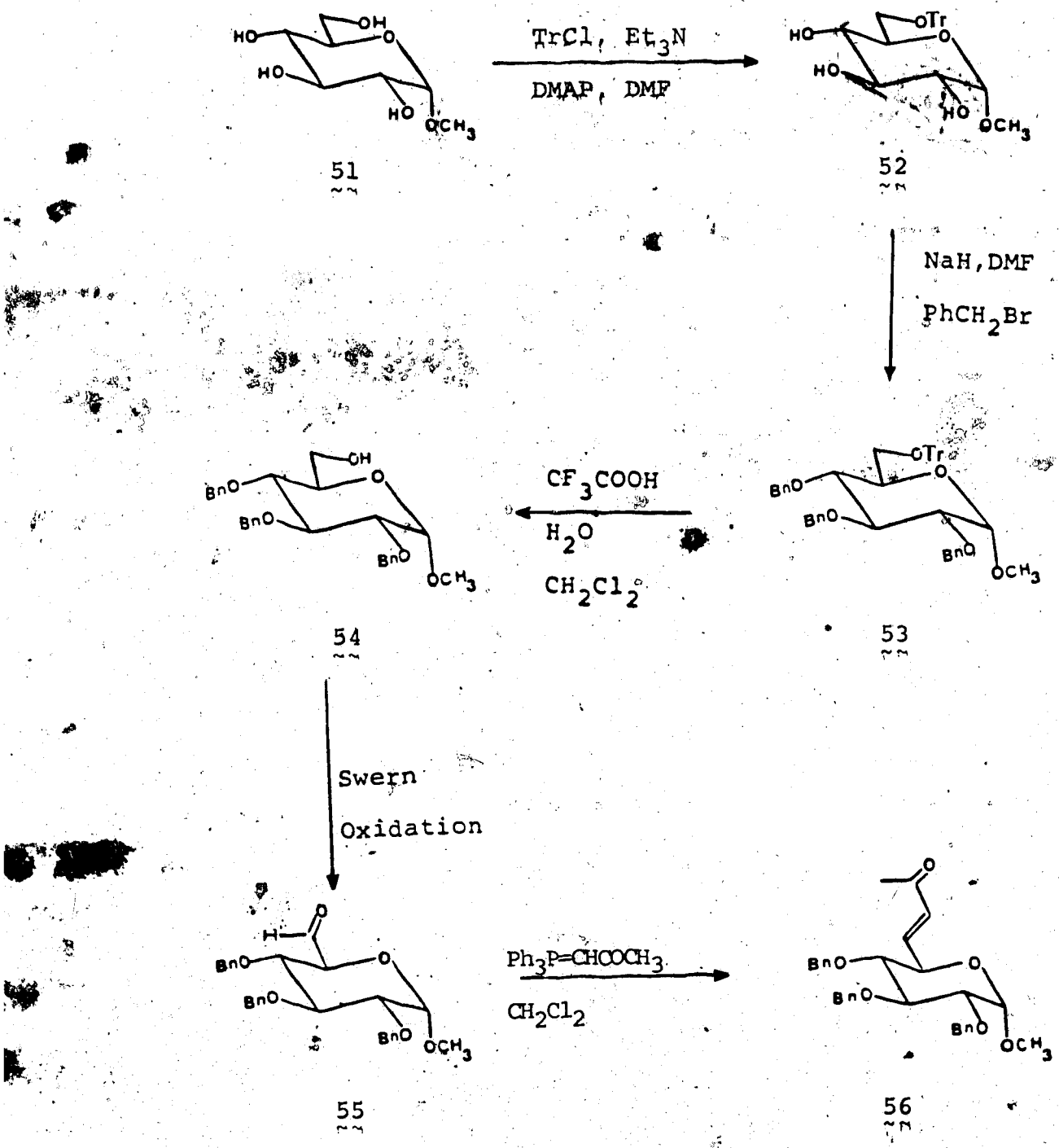


Fig. 16. 'Conformational diastereoface-differentiating' conjugate additions of a methyl group to an enone of the type 50.

6-aldehydo sugar derivative. Both of the C(6)-diastereomers could be obtained from 50 if a high re and si[76] diastereofacial selectivity could be obtained in the conjugate addition reactions (Fig. 16). To explore this possibility, it was decided to study the conjugate additions of the organometallic reagents to a simple model system of the pyranosyl enone 56.

b. Synthesis of diastereomeric C(6)-methyl derivatives of glucose. The pyranosyl enone 56 was prepared from the commercially available methyl α-D-glucopyranoside as outlined in Scheme 18. The compound 51 was converted to the trityl derivative 52 according to Chaudhary and Hernandez.[77] A higher yield of methyl 2,3,4-tri-O-benzyl-α-D-glucopyranoside 54 was obtained from 52 by modifying the procedure of Schuerch and Eby.[78] Thus, treatment of 52 with sodium hydride and benzyl bromide in DMF gave crude 53 which was hydrolyzed directly to give 54, m.p. 63—65 °C (lit.[78] 66.5—67 °C) in 75—82% yield (two steps) after chromatography on silica gel. The oxidation of the alcohol 54 to the aldehyde 55 with the Collins reagent[41] was not a clean reaction (other products were observed by TLC). However, Swern oxidation[79] of 54 afforded a single product, the aldehyde 55, without the need of chromatographic purification. The ^{1}H- and ^{13}C-NMR spectra are consistent

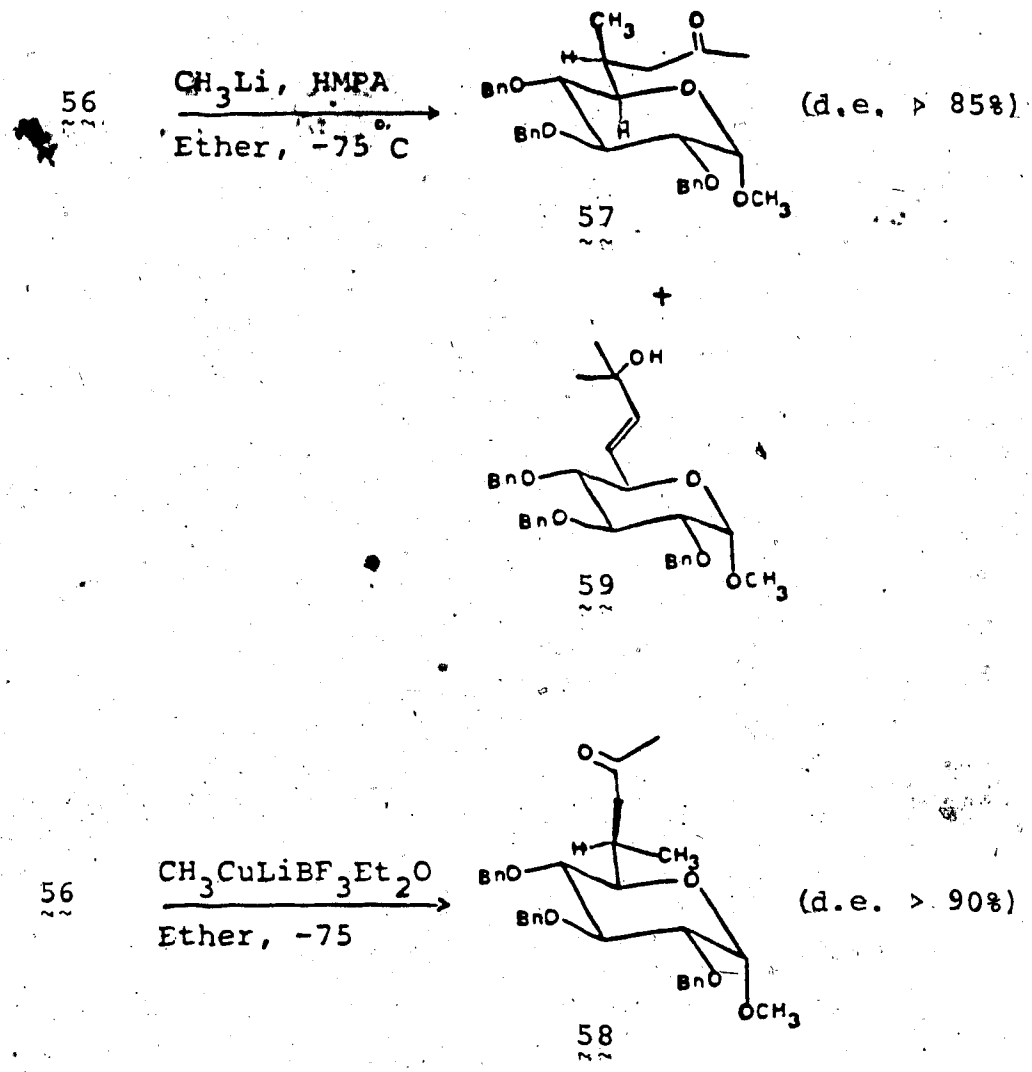


51 52 53 54 55 56

Scheme 18.

with the structure 55. Treatment of 55 with the stabilized Wittig reagent, acetylmethylenetriphenylphosphorane[80] provided, after chromatography, methyl (E)-2,3,4-tri-O-benzyl-6,7,9-trideoxy-α-D-gluco-non-6-enopyranosid-8-ulose 56 in 86% yield. The IR spectrum (1677 cm^{-1}) indicated that the compound 56 possesses an α,β-unsaturated ketone system. The ^{1}H-NMR spectrum of 56 showed a large trans-ethylenic coupling ($J_{6,7}$ = 16 Hz).

Conjugate addition of alkyllithiums to an α,β-unsaturated carbonyl compound is generally not a synthetically useful process, since the 1,2-adduct is the major product.[81] However, it was expected that in the case of the highly oxygenated enone 56, the chelation of the lithium cation might give a high diastereofacial selectivity. In fact, when an ether solution of methyllithium (high halogen content) was treated with 56 at -75°C, two 1,4-adducts 57 and 58 (Scheme 19) were isolated in low yield (total yield of 1,4-adducts, 31%). The two adducts were separated by chromatography on silica. The diastereofacial selectivity of this reaction was very high in favor of 57 (d.e.[82] > 85%). The assignment of configuration at C(6) of 57 and 58 will be discussed in the following section. The total amounts of the conjugate adducts could be increased dramatically (total yield of 1,4-adducts, 61%), retaining the selectivity (d.e. > 85%), by the introduction of HMPA


56
CH3Li, HMPA
Ether, -75 °C
(d.e. > 85%)
57
59
56
CH3CuLiBF3Et2O
Ether, -75
(d.e. > 90%)
58

Scheme 19.

into the reaction mixture prior to the addition of the enone. Since the products and the starting material could be readily identified by TLC due to the difference in their polarity and appearance, an approximate estimation of the various reaction conditions could be made (Table 4). From Table 4, it is evident that the choice of solvent, the total amount of methyllithium and the ratio of methyllithium to HMPA (about 1:1) seem to be crucial for the success of the reaction. The reason for this HMPA-promoted increase in the amount of the conjugate adducts of this unstabilized alkyllithium is not clear,[83] although there are some reports in the literature where the use of HMPA has increased the ratio of 1,4-adduct versus 1,2-adduct of heteroatom-stabilized alkyllithiums.[84]

The high diastereofacial selectivity of this reaction may be explained by a pseudo-intramolecular addition of the methyllithium, chelated with the etherial oxygen atoms, onto the enone which may exist in near anti-periplanar arrangement about the C(5)-C(6) bond (Fig. 16). Thus, the ring- and anomeric-oxygen atoms of the enone 56 can coordinate with the lithium atom of the methyllithium to render its attack onto the enone from the si face. There are several other reports where the stereoselectivity in conjugate additions of organometallic reagents has been explained on the basis of chelation of the metal ion.[73,75b,85]

Table 4: Conjugate addition of methyllithium to the enone 56.

No	S.M.[a,b]	CH_3Li[a]	HMPA[a]	Solvent	Unreacted S.M.[c]	1/4-Adduct '6-R' 58[c]	1/4-Adduct '6-S' 57[c]	1,2-Adduct	d.e.[d]
1	1	1.5	-	ether	not present	2%[e]	29%[e]	54%	ca. 87%
2	1	1.5	1.5	ether	present	not present	not present	not present	-
3	1	1.64	3.19	ether	present	not present	not present	present	-
4	1	2.81	2.56	ether	not present	4%[e]	57%[e]	27%[e]	ca. 86%
5	1	2.71	2.40	ether	not present	4%[e]	61%[e]	27%[e]	ca. 87%
6	1	2.6	2.34	THF	not present	not present	not present	present	-

a. number of equivalents of the reagent
b. all the reactions were carried out on 0.3-0.4 mmol scale at -75 °C following the procedure similar to one described in experimental section for the preparation of the compound 57.
c. whereever quantities of the products are not mentioned, their presence was detected by TLC, over silica gel using 3:7 ethylacetate-hexane
d. calculated according to ref. 82.
e. isolated yield.

The reaction of the enone 56 with an excess of $CH_3Cu.BF_3$[86] in ether afforded 58 as the major 1,4-adduct (d.e. ▷ 90%) in which the methyl group has added from the 're' face of the enone (Fig. 16). A small amount of the other 1,4-adduct 57 (< 5%) was detected by TLC and ^{1}H-NMR. The reaction of 56 with lithium dimethylcuprate in ether showed similar diastereofacial selectivity. The reason for this reversal of stereoselectivity with the copper reagents is not clear. A similar change in stereoselectivity with the copper-catalyzed conjugate addition of Grignard reagents to the sugar esters of crotonic acid has been reported by Kawana and Emoto.[87] This was explained on the basis of the different sites of co-ordination for the Grignard and copper-reagent.[87,88] However, it is worth noting that the simple dialkyl-cuprates have shown opposite stereoselectivity to that of the diallyl-cuprates in conjugate additions to sugar enoates.[74]

In summary, both the C(6)-methyl diastereomers of the glucose derivative (57 and 58) were obtained from the same substrate by an operationally simple process involving the 'conformational diastereoface-differentiation' in the conjugate additions of $CH_3Cu.BF_3$ and methyllithium-HMPA. The latter methodology is highly advantageous for the formation of the carbon-carbon bond and also applicable to the synthesis of optically active

segments of the antibiotics and modified sugars. I plan to continue further work regarding the generality of the HMPA assisted conjugate addition of the alkyllithiums and the use of this reaction for natural product synthesis.

c. Configurations and conformations of 57 and 58:

The configurations of the two 1,4-adducts, 57 and 58 at C(6) were indicated by NMR studies. The limiting conformations about the C(5)-C(6) bond for these two diastereomers are shown in Fig. 17. In the three limiting conformations for the configuration shown in Fig. 17a, 57A should be the most favored since the other two, 57B and 57C will experience 1,3-syn-periplanar interactions between the two bulky groups, namely C(7) and C(4)-O- in 57B and C(6)-CH_3 and C(4)-O- in 57C.[89,90] For the same reason, the conformer 58A for the configuration shown in Fig. 17b should be of lower energy than the 58B and 58C.[89,90]

The ^{1}H-NMR spectra of 57 and 58 are compared in Fig. 18. The chemical shifts of the H-1, H-2 and H-3 were essentially the same for the two molecules. The shift of the H-4 was 3.26 ppm for both the enone 56 and the ketone 58, but the signal for H-4 of the ketone 57 was 0.13 ppm to lower field. The two hydrogens at the C(7) were found to be about 0.1 ppm apart in 58 (Fig. 18) and also, they were upfield (about 0.1—0.2 ppm) from the hydrogens on the C(7) of 57. The doublet for the methyl

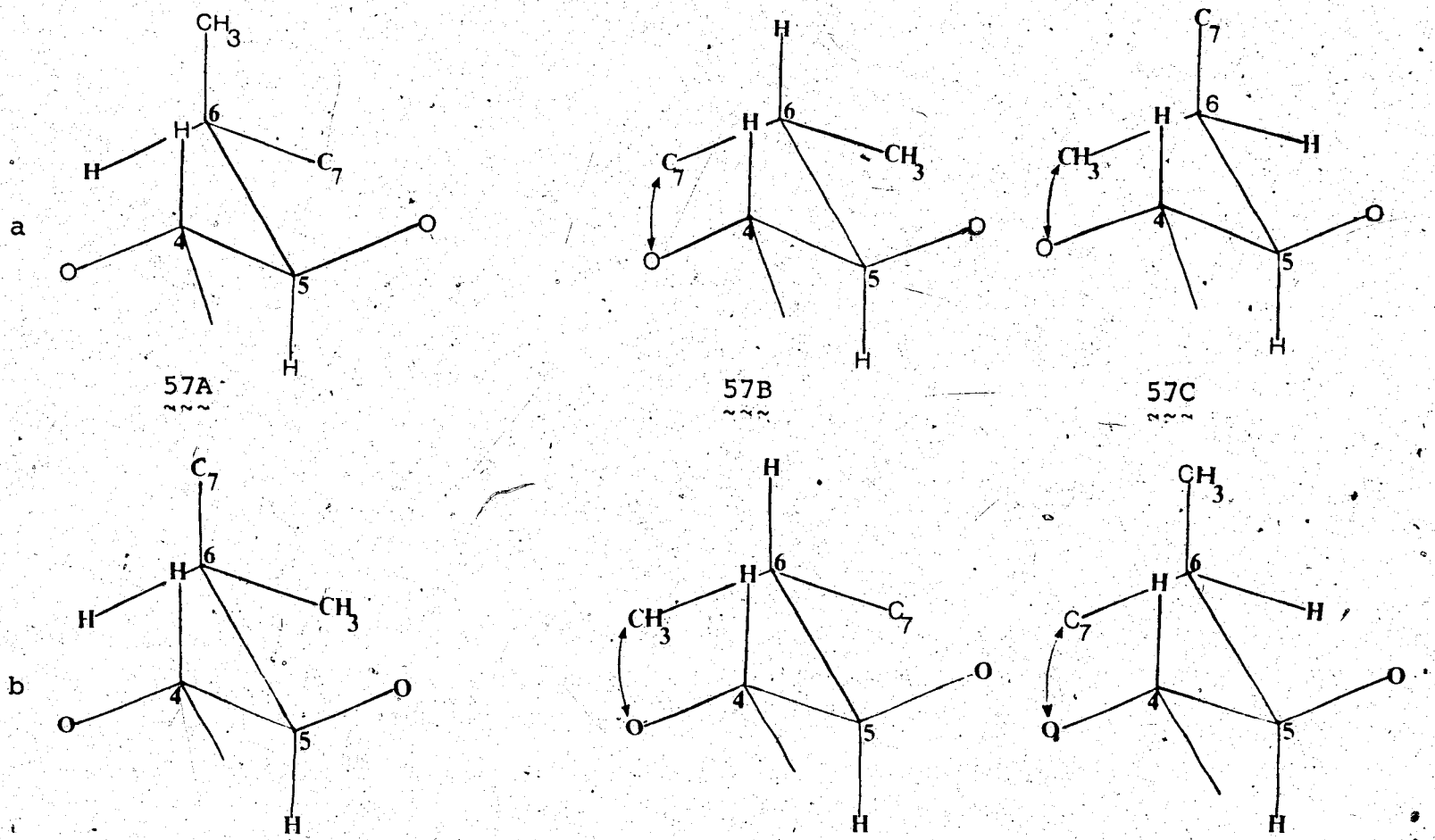


Fig. 17. The limiting conformations of 57 and 58 about the C(5)-C(6) bond. The curved arrows indicate the 1,3-syn-periplanar interactions.

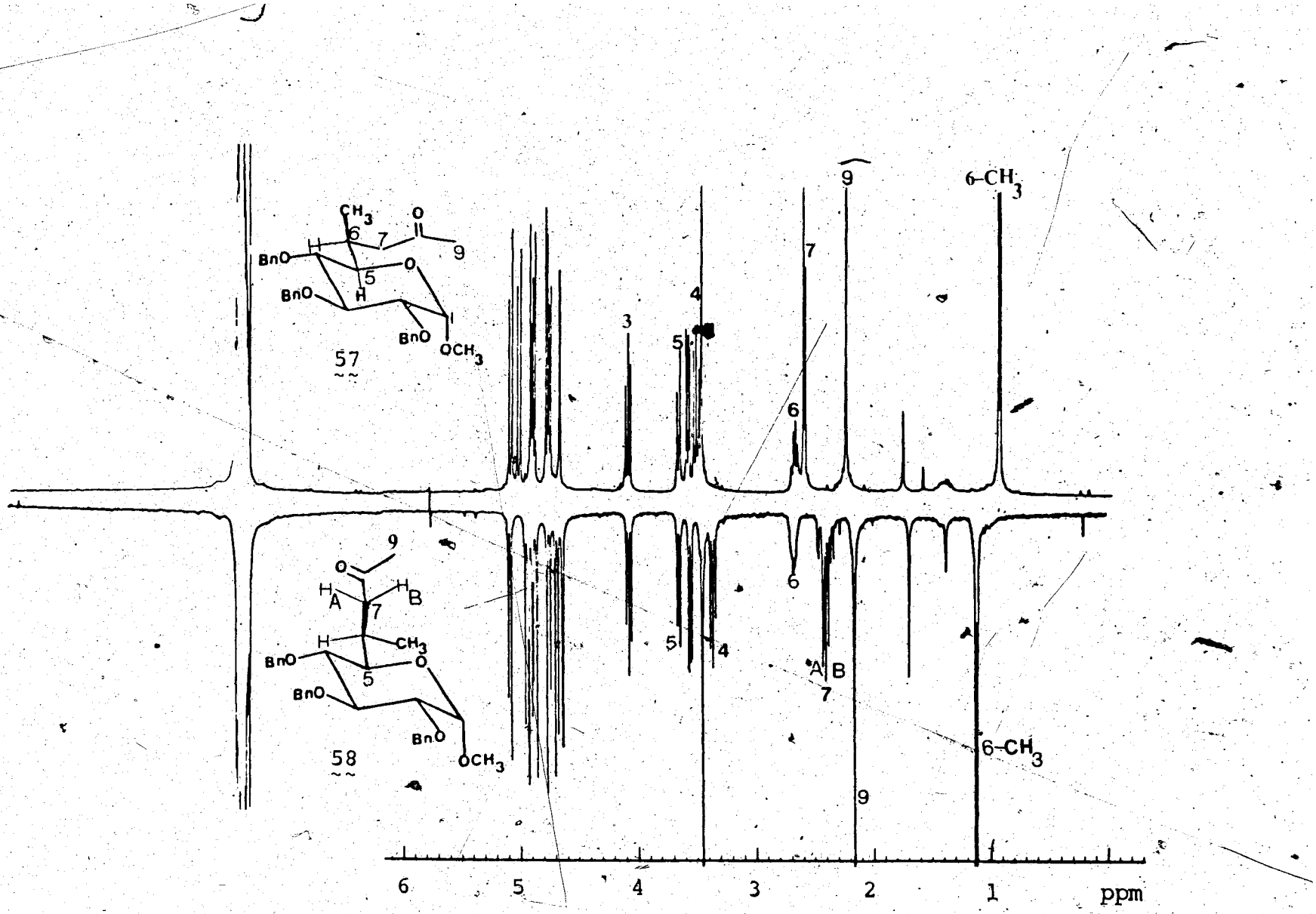
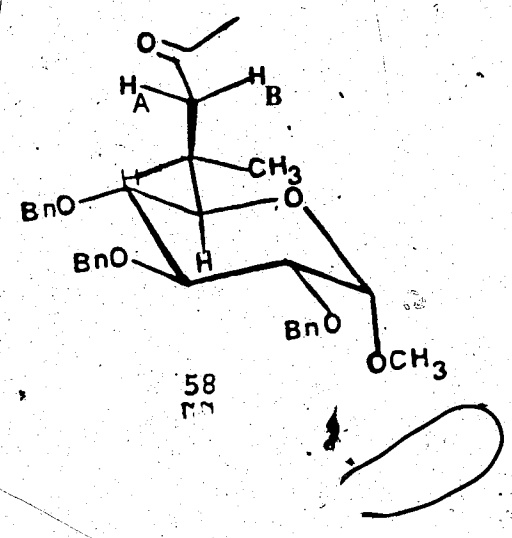


Fig. 18. The comparison of the ^{1}H-NMR spectra of 57 and 58 at 400 MHz in $CDCl_3$.

at C(6) of 58 was 0.14 ppm downfield from the C(6)-methyl of 57. This shift to lower field of the C(6)-methyl in 58 and the hydrogens at C(7) in 57 is probably because of the electrostatic deshielding by 5-O-.

The spacings for the signals for the hydrogens of the pyranose ring in the ^{1}H-NMR spectra of the compounds 57 and 58 were virtually the same. The pyranose ring in these molecules is in the $^4C_1$ conformation. In view of the magnitudes of the coupling constants for H-5 and H-6 (about 1.5 Hz for both the compounds, 57 and 58), the compounds must exist extensively in a conformation which maintains these two hydrogens in a near syn-clinal orientation. The coupling constants between the H-6 and the two hydrogens at the C(7) in 58 are substantially different ($J_{6,HA}$ = 3.5 Hz and $J_{6,HB}$ = 9.5 Hz, Scheme 20).



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$J_{5,6}$ = 1.5 Hz
$J_{6,HA}$ = 3.5 Hz
$J_{6,HB}$ = 9.5 Hz

Scheme 20.

This indicates that there is a preferred orientation about the C(6)-C(7) bond in 58.

It was planned to determine the configurations of the conjugate adducts (57 and 58) by nuclear Overhauser enhancement (n.O.e.) experiments. Homonuclear ^{1}H-^{1}H n.O.e. studies have found wide application in structural and stereochemical work.[64] The n.O.e. experiment consists of selectively irradiating the signal for one or more protons in the ^{1}H-NMR spectrum of a compound and observing the enhancements of the signals for other protons present in the same molecule. The r^{-6} dependance of this enhancement, where r is the distance between the irradiated and observed protons, makes such measurements highly sensitive to small changes in the separation of these protons.

With the advent of Fourier-Transform high-field spectrometers, measurement of n.O.e.s can be made with confidence to within $\pm$ 2%.[91] Absolute n.O.e. effects are highly sensitive to a number of experimental factors including concentration, the presence of paramagnetic substances, the complexity and nature of the molecule under investigation, the strength of the magnetic field and the measurement itself. Therefore, the absolute value of an n.O.e. is not itself significant except in the sense that a strong observed n.O.e. requires the close proximity of the two hydrogen atoms. However, the relative values of n.O.e.s for two or more hydrogens within the same molecule and obtained at the same time through

the irradiation of a specific hydrogen are significant in the sense that the hydrogen which has the greatest n.O.e. must be closest to the hydrogen that was irradiated. Thus, although the absolute value is only of qualitative value, the ratios of n.O.e.'s measured at the same time are at least of semi-quantitative value.

The results of a typical n.O.e. experiment are presented in Fig. 19, where the effect of irradiating the C(6)-methyl signal of 58 is shown. Such experiments could be conducted since the signals to be irradiated were well separated from the other signals in the spectrum. The n.O.e.'s can be most conveniently determined by recording, in alternating fashion, the normal and irradiated spectrum and then computer-substracting one spectrum from the other.

In the spectrum where the C(6)-methyl of 58 is being irradiated, and is therefore saturated, these hydrogens will no longer provide a signal while the signals of hydrogens proximate to the C(6)-CH_3 will be enhanced (Fig. 19b). Consequently, substraction of the irradiated spectrum from the normal spectrum (Fig. 19a) will provide a difference spectrum (Fig. 19c) where the C(6)-CH_3 will appear as a negative signal of full intensity (i.e., this signal will integrate for three protons), the unenhanced signals will cancel out and the enhanced signals will appear as signals of fractional positive

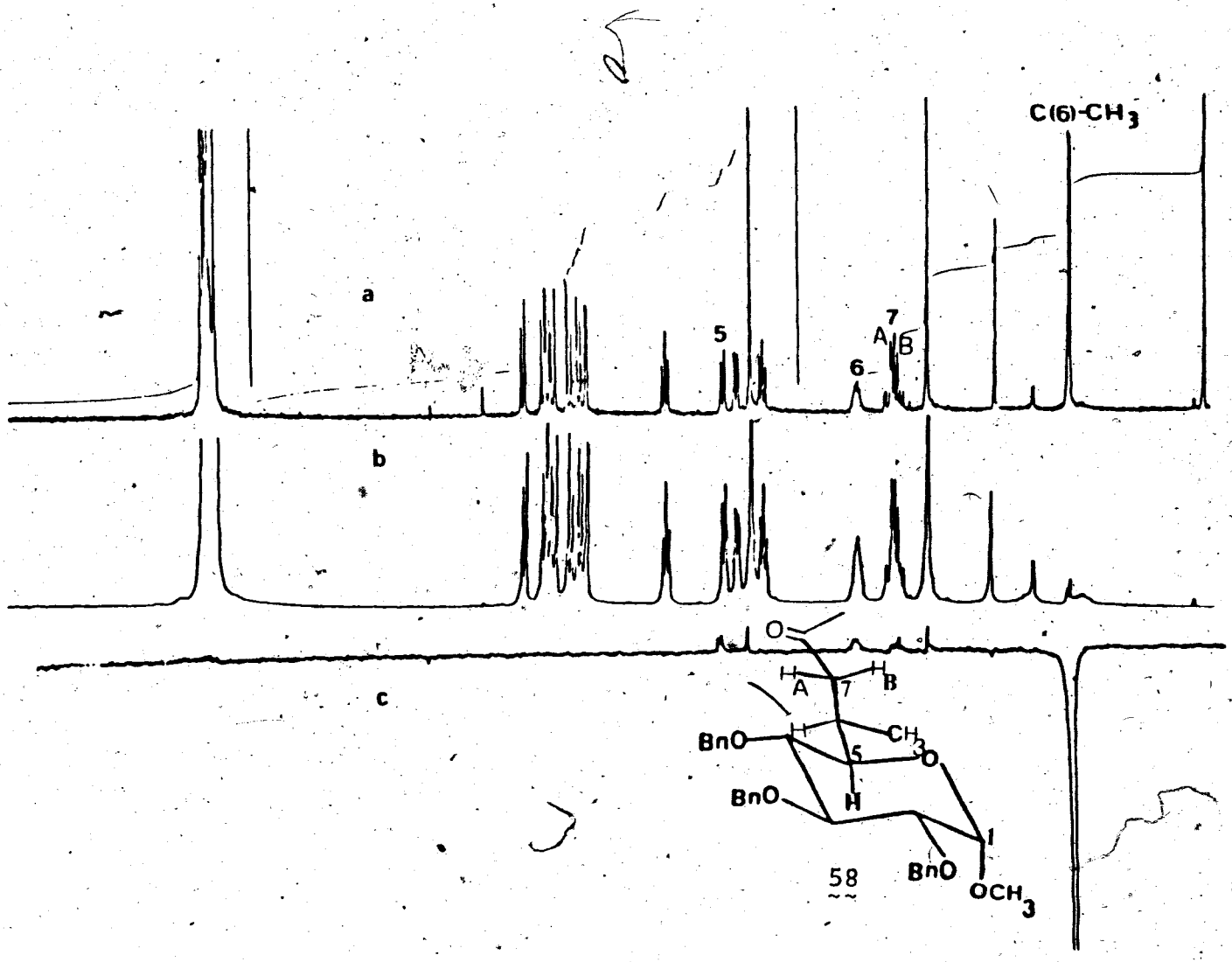


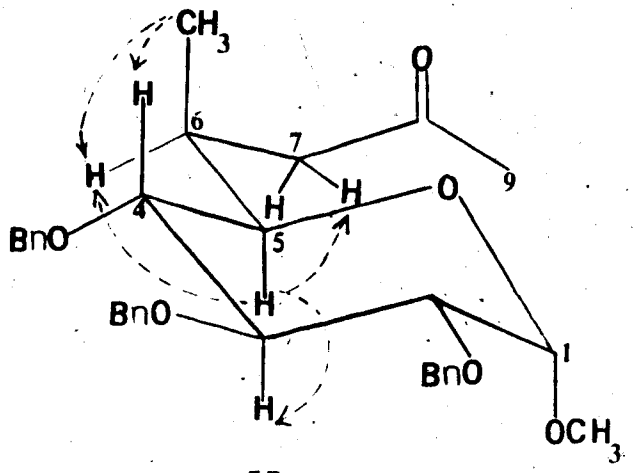
Fig. 19. Illustration of an n.O.e. experiment performed on 58 at 400 MHz in $CDCl_3$. a. normal spectrum. b. spectrum in which C(6)-methyl is saturated. c. subtracted spectrum showing enhancements of H-5, H-6 and H_B-7.

intensity. The n.O.e.'s of these latter signals may then be expressed as a percentage of the irradiated signal.

Examination of molecular models of the favored conformation of the configuration [illegible] in Fig. 17b shows that the C(6)-methyl [illegible] to the H-5 and H-6. Out of the two hydrog[illegible] the one having a coupling constant of 3.5 Hz with H-6 (i.e., H_A, Scheme 20) is expected to be in the close vicinity of the H_B, H-4 and H-6 only. Saturation of the C(6)-methyl signal of 58 led to the nuclear Overhauser enhancement of the signals due to H-5, H-6 and H_B-7 (Fig. 19). Irradiation of the H-4 signal till saturation led to the n.O.e. of the H_A-7 and H-2 signals (Fig. 20b). These n.O.e.'s could be expected only for the conformation 58A of the configuration shown in Fig. 17b. Thus, the observed n.O.e.'s indicated that the product obtained from the conjugate addition of $CH_3Cu.BF_3$ to the enone 56 is the one having an R configuration at the C(6) as in 58 (hereafter called R-isomer) and it exists extensively in the conformation shown in Fig. 20b in $CDCl_3$. Therefore, the diastereomeric product obtained from the conjugate addition of methyllithium must have an S-configuration at the C(6) as in 57 (hereafter called S-isomer).

In the preferred conformation of the S-isomer (Fig. 17a), the H-4, H-6 and C(6)-CH_3 are expected to be closer to each other. In fact, significant enhancements

a.



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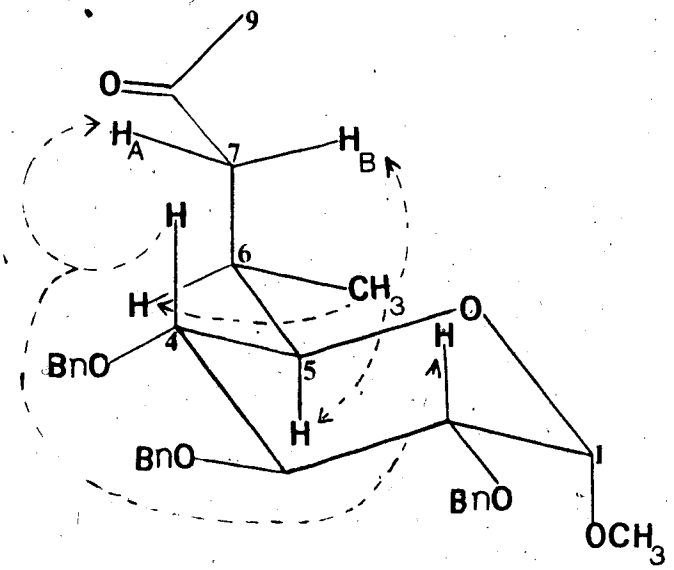
b.

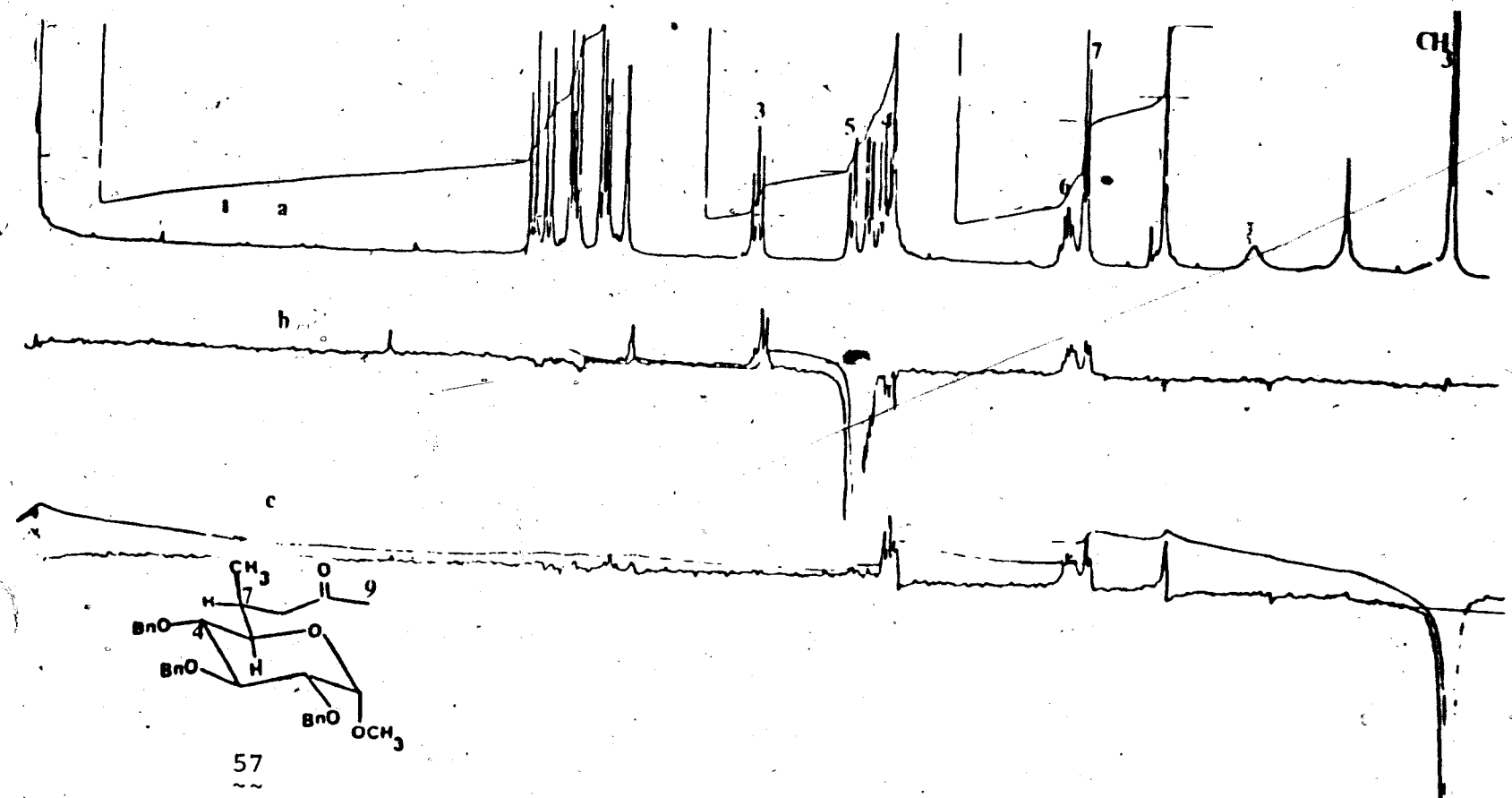


58

Fig. 20. Conformations of 57 and 58 and the schematic representation of the n.O.e. experiments.

of the H-4 and H-6 signals were observed on saturation of the C(6)-CH_3 signal in 57 (Fig. 21). A reverse experiment involving the saturation of H-5 signal resulted in the enhancements of the H-3, H-6 and HH-7 signals. These results indicated that the compound 57 has the S-configuration at C(6) and it exists predominantly in the conformation as shown in Fig. 20a.

The conclusions reached by n.O.e. experiments were strengthened by the observed chemical shifts of the C(6)-methyl and C(7) in the ^{13}C-NMR spectra of both the isomers (Table 5). The C(6)-methyl and H-4 are in near syn-periplanar arrangement in the conformer 57A of the S-isomer and the methyl group exists in gauche orientation, with respect to the C(4) and 5-O-. On the other hand, the methyl group in 58A of the R-isomer is in anti arrangement with respect to the C(4). An upfield shift is generally expected for any carbon which can exist in gauche orientation, with respect to another carbon or heteroatom, relative to the shielding of its anti counterpart.[92,93,94] In fact, the C(6)-methyl carbon in the S-isomer is shielded by 5.27 ppm from its counterpart in the R-isomer. Similar shielding of the methyl carbons which could be rationalized on the basis of conformational properties has been observed by Pavia and Lacombe[95,96] for threonine-containing glycopeptides. As expected, the C(7) carbon



57

Fig. 21. The results of n.O.e. experiments performed on 57 at 400 MHz at 298 K. The normal spectrum is seen a, whereas in b, H-5 is saturated. In c, C(6)-CH_3 is saturated.

Table 5: Comparison of ^{13}C-NMR chemical shifts[a] found for 56—58.

Carbon atom	1	2	3	4	5	6	7	8	9	$^{+}C(6)-CH_3$	$-OCH_3$	Benzylic carbons[b]		
56	98.20	79.87[c]	81.96[c]	81.43	69.21	142.54	130.77	197.92	27.17	-	55.38	73.44	75.26	75.85
57	98.04	80.35	82.37[c]	78.46[c]	72.35	28.32	48.70	207.74	30.03	12.70	55.12	73.28	74.70	75.71
58	97.60	80.17	82.47[c]	78.19[c]	73.38	28.15	43.99	207.81	30.47	17.97	54.81	73.10	74.65	75.57

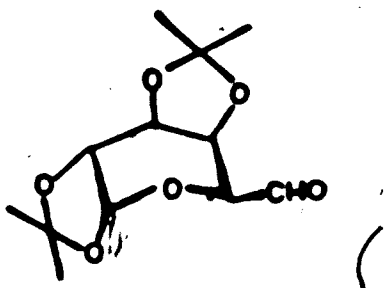
a. In $CDCl_3$ at 298 with TMS as internal reference and measured at 50.3 MHz.
b. Chemical shift values for aromatic carbons are not listed here, (See: Experimental).
c. These chemical shift assignments were confirmed by single frequency decoupling experiments.

in the R-isomer is 4.71 ppm upfield from the C(7) carbon of the S-isomer. The chemical shifts of the C(4) carbon of both the isomers are very similar ($\Delta\delta$ = 0.27 ppm).

d. Synthesis of diastereomeric C(6)-methyl derivatives of galactose. In order to test the generality of the 'conformational diastereoface-differentiating' additions discussed earlier for the enone 56, another example of enone 56gal was studied (Scheme 20a). The example of enone 56gal as a substrate for conjugate additions is more interesting, since the protecting groups in 56gal are different than 56 and the pyranose ring in 56gal is strongly distorted away from the $^4C_1$ conformation as is implied in the conformational formulas (Scheme 20a).

The enone 56gal was prepared from the readily available aldehyde 55gal.[41] Treatment of 55gal with the stabilized Wittig reagent, acetylmethylenetriphenylphosphorane[80] in refluxing dichloromethane provided, after chromatography, the trans-enone 56gal in 74% yield (Scheme 20a). The IR spectrum (1670 cm^{-1}) indicated that the compound 56gal possesses an α,β-unsaturated ketone system. The ^{1}H-NMR spectrum of 56gal showed a large trans-ethylenic coupling ($J_{6,7}$ = 16.0 Hz).

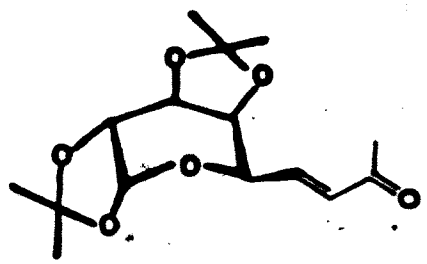
The HMPA assisted conjugate addition of methyllithium to the enone 56gal provided 57gal in 32% yield. The ^{1}H-NMR and TLC (silica gel, 1:9 ethyl acetate--1,2-dichloroethane) showed the presence of small amount of other conjugate



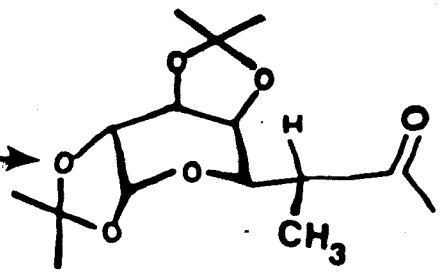
55gal

$Ph_3PCHCOMe$

CH_2Cl_2, 87%

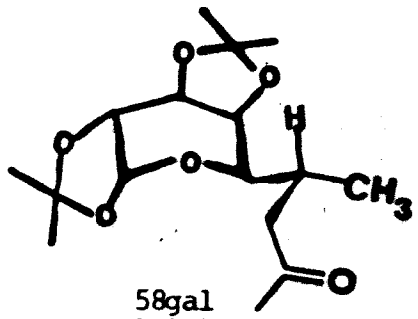


56gal



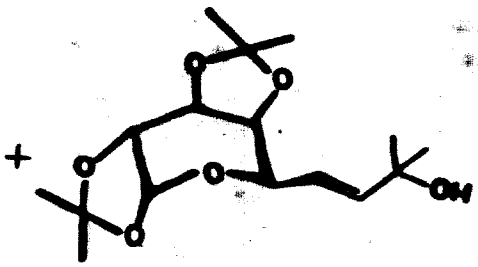
57gal

+



58gal

+



59gal

56gal →

i.	CH_3Li-HMPA, Ether, -75 °C	32%	< 3%	47% (d.e. > 83%)
ii.	$(CH_3)_2CuLi$, Ether, -75 °C	25%	59%	- (d.e. > 40%)

Scheme 20a.

adduct 58gal (< 3%). The major product in this reaction was the 1,2-adduct 59gal (47%). The configuration at C-6 of 57gal was tentatively assigned in analogy with compound 57 (see discussion in the following section). It is noteworthy that structurally and conformationally different pyranosyl enone 56gal also showed high diastereofacial selectivity in favor of 57gal similar to the enone 56 in this reaction.

Treatment of 56gal with excess of $(CH_3)_2CuLi$ in ether at -75°C provided a mixture of 57gal and 58gal in 84% yield. The ratio of 57gal to 58gal was found to be 3:7 by ^{1}H-NMR spectrum. The two diastereomers were separated by chromatography over silica gel using 3% ethyl acetate in 1,2-dichloroethane. The less polar diastereomer (TLC, silica gel, 1:9 ethyl acetate—1,2-dichloroethane) was found to be identical with 57gal (^{1}H-NMR). The major diastereomer was assigned the configuration as shown in 58gal in analogy with 58. Although, the selectivity with $(CH_3)_2CuLi$ in this case is less than with the enone 56 the major diastereomer is the one obtained from 're' facial addition of the methyl group to 56gal as is the case with 56 (Fig. 16).

e. Conformations and configurations of 57gal and 58gal.

The tentative assignments of the configurations of the 1,2-adducts 57gal and 58gal at C(6) were supported by NMR studies. The limiting conformations about the C(5)—C(6) bond for these two diastereomers are shown in Fig. 21a. In the three limiting conformations for the configuration shown in Fig. 21aA, 57galB

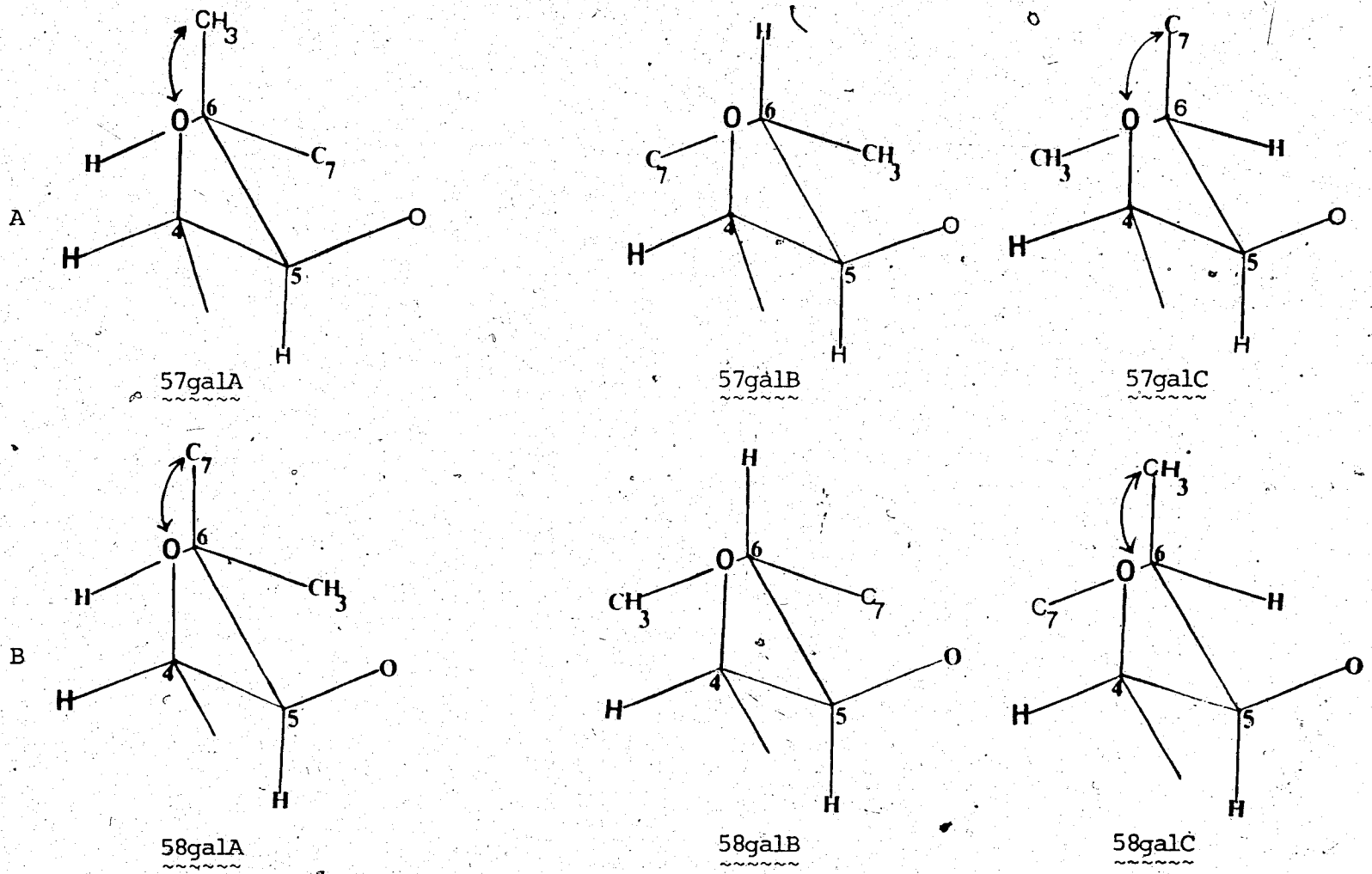
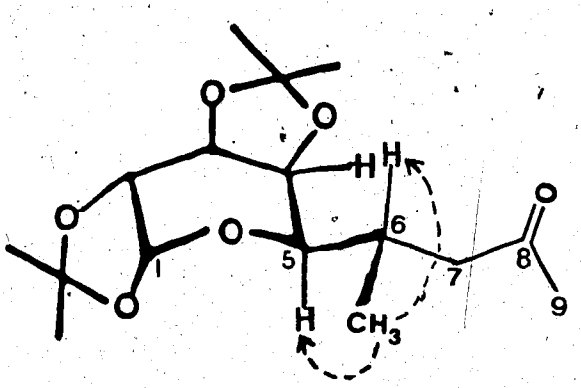


Fig. 21a. The limiting conformations of 57gal and 58gal about the C(5)—C(6) bond. The curved arrows indicate the 1,3-syn-periplanar interactions.

should be the most favored since the other two, 57galA and 57galC will experience 1,3-syn-periplanar interactions between the two bulky groups, namely C(7) and C(4)-O- in 57galC and C(6)-CH_3 and C(4)-O- in 57galA. For the same reason, the conformer 58galB should be of lower energy, than the 58galA and 58galC.

The chemical shifts of H-1, H-2 and H-3 in ^{1}H-NMR spectra of 57gal and 58gal were essentially the same. The shift of the H-5 was 3.43 ppm for 58gal, but the signal for H-5 of the ketone 57gal was 0.14 ppm to lower field. The spacings for the signals for the hydrogens of the pyranose ring in the ^{1}H-NMR spectra of the compounds 57gal and 58gal were virtually the same. The pyranose ring in these molecules is strongly distorted away from the $^4C_1$ conformation as is implied in the conformational formulas (Fig. 21b). In view of the magnitutes of the coupling constants for H-5 and H-6 (7.0 Hz for 57gal and 9.25 Hz for 58gal), the compounds must exist extensively in a conformation which maintains these two hydrogens in a near anti-periplanar orientation (i.e. 57galB and 58galB).

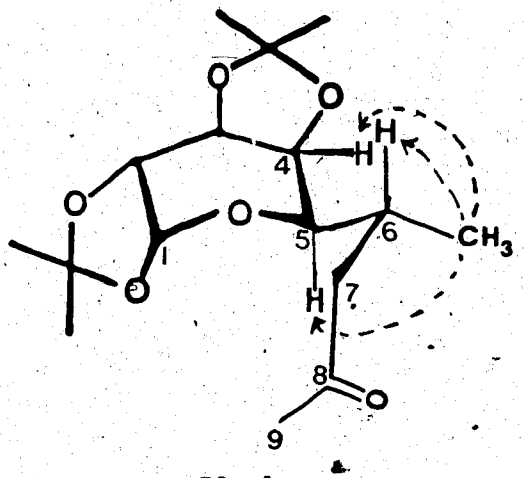
The favored conformations and therefore the configurations at C-6 of 57gal and 58gal were supported with n.O.e. experiments. The irradiation of the signal due to 6-CH_3 in the ^{1}H-NMR spectrum of 57gal led to the nuclear Overhauser enhancement of the signals due to H-5 and H-6. The enhancement of the H-4 signal was very little or none. These results indicated that compound 57gal has S configuration at C-6 and the prefered conformation is



$J_{5,6}$ = 7.0 Hz

δ 6-$\underline{C}H_3$ = 16.36 ppm

57gal



$J_{5,6}$ = 9.25 Hz

δ 6-$\underline{C}H_3$ = 16.06 ppm

58gal

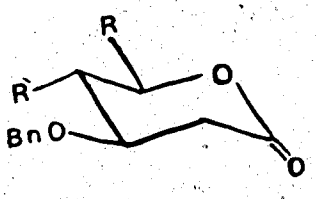
Fig. 21b. Conformations of 57gal and 58gal the schematic representation of the n.O.e. experiments.

as shown in Fig. 21b. Significant enhancements of the H-4 and H-6 signals were observed on saturation of the 6-CH_3 signal in 58gal (Fig. 21d). The enhancement of H-5 signal was half times less than that of H-4. These n.O.e. results indicated that compound 58gal has R configuration at C-6 and it exists extensively in a conformation as shown in Fig. 21b. There was no substantial difference in the ^{13}C-NMR chemical shifts of the 6-$\underline{C}H_3$ of 57gal and 58gal ($\Delta\nu$ = 0.3 ppm) since in both compounds C(6)-CH_3 bond is in gauche-relationship with respect to C(5)—C(4) bond or C(5)-O- bond.[92,93,94]

The configurations of the compounds 57, 58, 57gal and 58gal as well as their predominant conformations in $CDCl_3$ are indicated by the results of the n.O.e. experiments and the ^{13}C-chemical shifts of the C(6)-methyl and C(7) carbons. It is believed that the NMR studies (especially the n.O.e.s) described here should find use in establishing the stereochemical arrangement of a disubstituted chiral center adjacent to the pyranose ring and related cyclic compounds which carry a substituent at the β-position with respect to the chiral center [for example, 4-O- is in the β-position with respect to the chiral center at C(6) of 57 and 58].

B. Regio and stereocontrolled opening of the conformationally rigid epoxide 33—Synthetic studies towards chiral 3-benzyloxy-5-hydroxy-4-alkylhexanoic acid lactones.

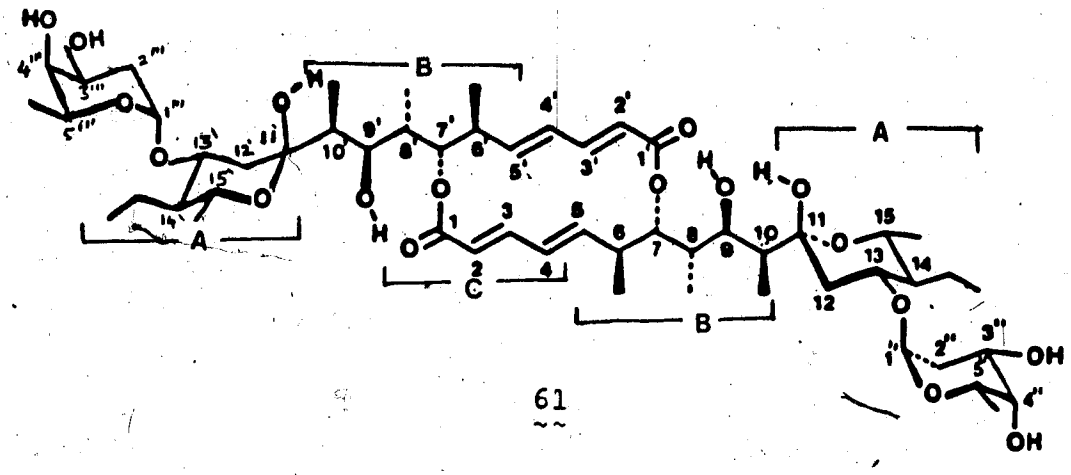
a. Introduction: Recent efforts toward the total synthesis of natural products that are biosynthetically derived by the so called "propionate pathway"[98] have necessitated the development of synthetic routes leading to carbon chains with multiple centers of chirality. In spite of several innovative approaches realized through elaboration of acyclic[71,99] or cyclic precursors,[100] achieving high levels of diastereomeric purity continues to be a major synthetic challenge. An alternate, operationally different strategy which addresses itself to this fundamental problem is based on the concept of "chiral templates"[101] derived from carbohydrates. Following this strategy a simple route for introducing three consecutive chiral centers in a six carbon unit of the type 60 (where R and R' are alkyl substituents) is described.



60

The lactones of the type 60 are useful synthons for the synthesis of macrolide antibiotics. For example, recently, two groups[102,103] independently reported the X-ray crystal structure of the antibiotic elaiophylin (azalomycin-B) 61 (Fig. 22) which was isolated from Streptomyces species.[104,105] One logical retrosynthesis of 61 dissects, as indicated in Fig. 22, the aglycone (the non sugar-portion of 61) into chiral segments A and B. The segment A, having three consecutive chiral centers and representing C(11)—C(15) and C(11')—C(15') carbon-backbone of 61 can be readily derived from 67. The lactone 67 can be obtained in principle from the 1,6-anhydropyranose 66.

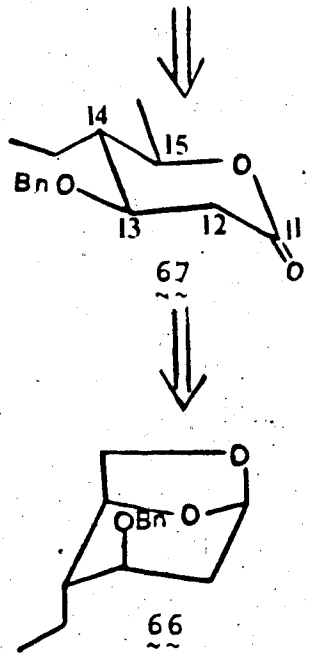
b. Synthetic studies towards chiral 3-benzyloxy-5-hydroxy-4-alkylhexanoic acid lactones: An alkyl substituent on a pyranose ring can be readily introduced by opening an epoxide with a carbon nucleophile.[36,101b,106,107] 1,6:3,4-Dianhydro-α-O-(4-methylphenylsulfonyl)-β-D-galactopyranose[35] (33, Scheme 20) is an ideal starting material for this purpose since it is readily prepared from levoglucosan (a product of starch or cellulose pyrolysis[31]). This compound has several advantages, including cost, conformational rigidity due to the presence of the tricyclic skeleton and temporary protection of the C(6) hydroxyl and



61

elaiophylin (azalomycin-B)

'Segment A'



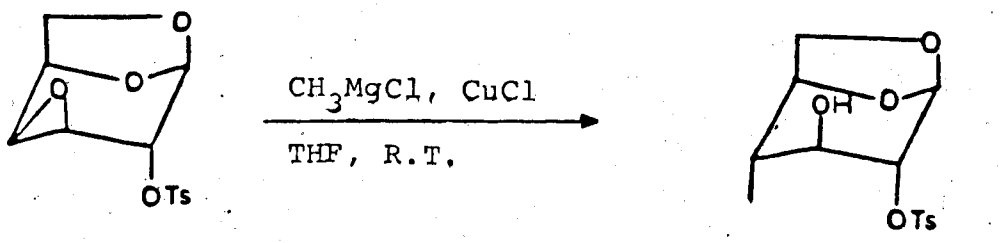
67

66

Fig. 22. The structure and retrosynthetic dissection of the antibiotic elaiophylin (azalomycin-B).

anomeric hydroxyl groups in the form of an 1,6-anhydro-linkage. Furthermore, cleavage of the oxirane ring in 33 by nucleophiles, electrophiles and reducing agents proceeds with high regio- and stereospecificity.[17e]

Initially, the reaction of the epoxy-tosylate 33 with methylmagnesium chloride was investigated. After trying several variations, the maximum yield of the epoxide-ring opened product 62 was about 50 to 60%, when 33 was allowed to react with methylmagnesium chloride in the presence of a catalytic amount of cuprous chloride in THF at room temperature (Scheme 20). These yields are not



33 62

Scheme 20.

synthetically attractive. However, treatment of 33 with an excess of trimethylalane in the presence of 0.3 equivalent of n-butyllithium[108] under the conditions described for 63 afforded 62 in 68% yield. No attempt was made to optimize this yield. The structure of the ring opened product was established to be 62 from its ^{1}H-NMR spectrum (Fig. 23). Thus, the chemical shift of H-4

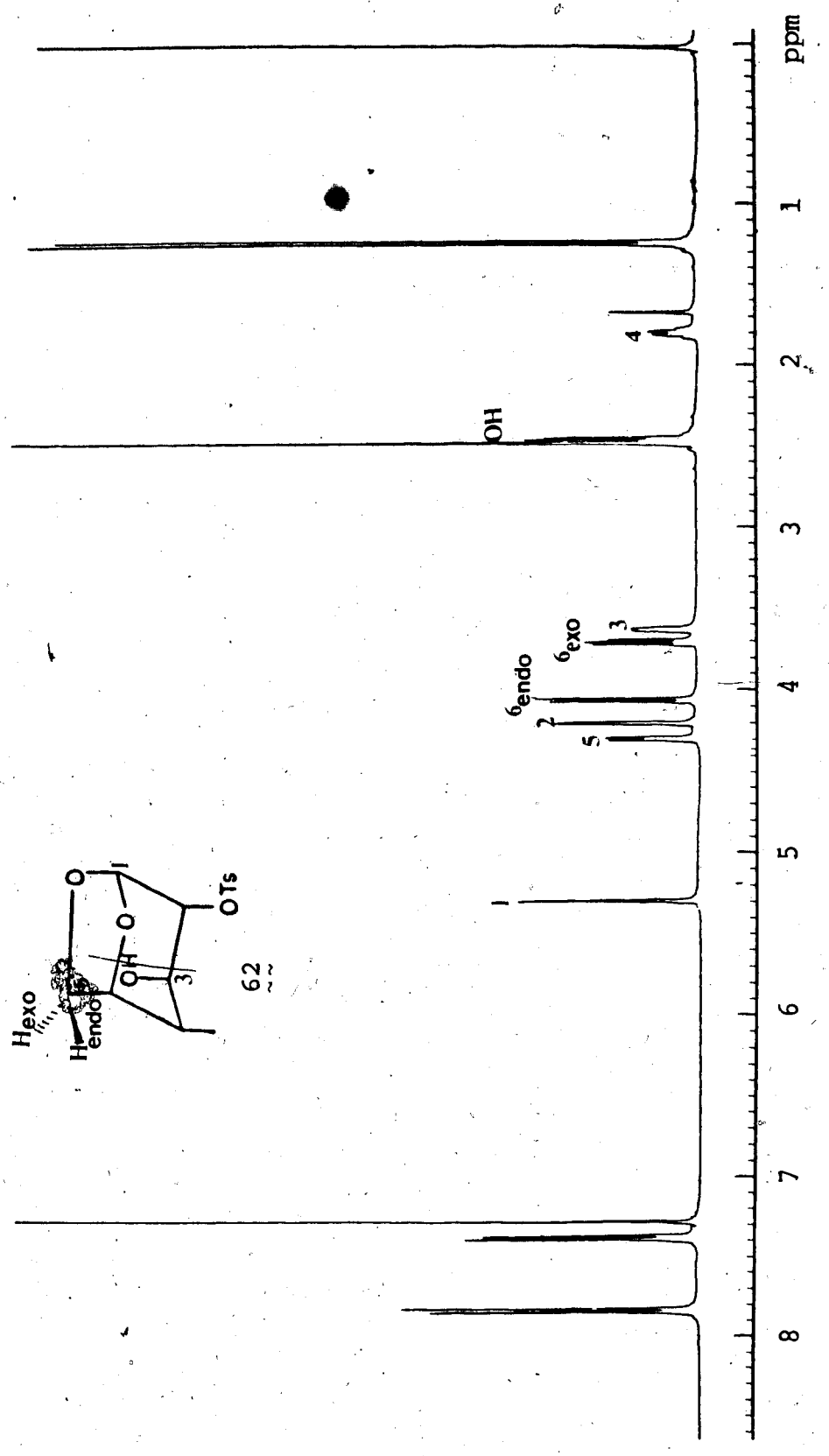
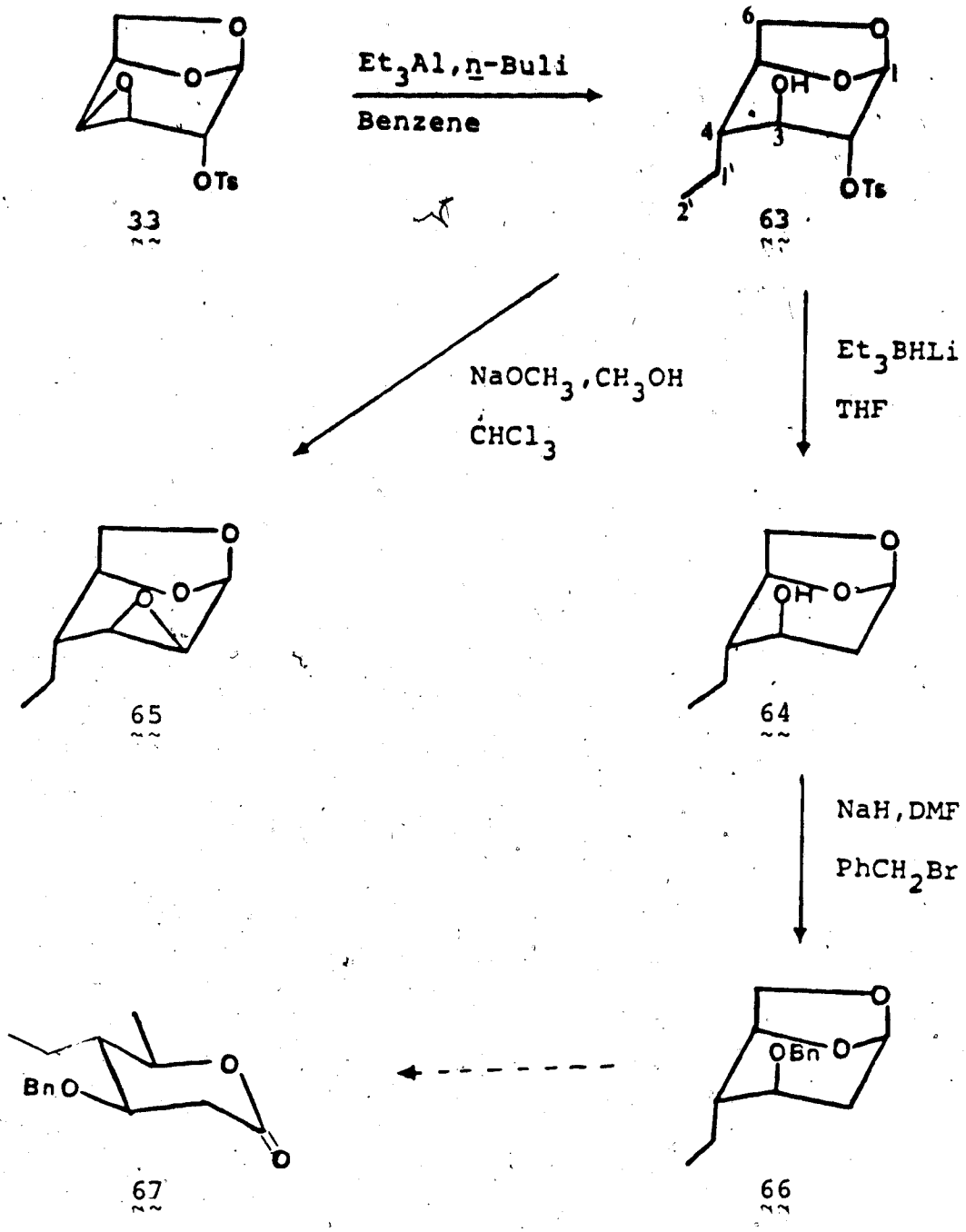


Fig. 23. The ^{1}H-NMR spectrum of 62 at 400 MHz in $CDCl_3$.

was found to be 1.79 ppm and the values of the coupling constants $J_{3,4}$ and $J_{4,5}$ were observed to be less than 2.5 Hz which proved that the methyl group in 62 is in axial orientation at C(4).

Treatment of epoxide 33 with an excess of triethylalane and 0.3 equivalent of n-butyllithium in benzene gave hydroxy tosylate 63 (Scheme 21) in 66% yield along with the epoxide 65 (18% yield). The epoxide 65 was formed in this reaction probably because of the presence of n-butyllithium. This was verified from the fact that the yield of 63 could be raised to 90% when the amount of n-butyllithium was reduced to about 0.05 equivalent and consequently, the yield of the epoxide 65 was decreased to 2.5%. There was no reaction in the absence of n-butyllithium (TLC control). In the ^{1}H-NMR spectrum of 63 (Fig. 24) the broad triplet at 1.50 ppm could be assigned to H-4 and the couplings $J_{3,4}$ and $J_{4,5}$ were found to be less than 2.5 Hz which confirmed the structure 63.

Lithium triethylborohydride reduction of the hydroxy tosylate 63 gave almost exclusively one product (95% yield). The ^{1}H-NMR spectrum of the product showed that it was the 2-deoxy sugar 64. The upfield multiplets at 1.82 and 2.02 ppm could be assigned to the H-2_{eq} ($J_{2eq,3} \approx < 2$ Hz) and H-2_{ax} ($J_{2ax,3} = 5$ Hz) respectively. A similar order of the chemical shifts for the C(2)-hydrogens of the C(4)-allyl



33 63 65 64 66 67

Scheme 21.

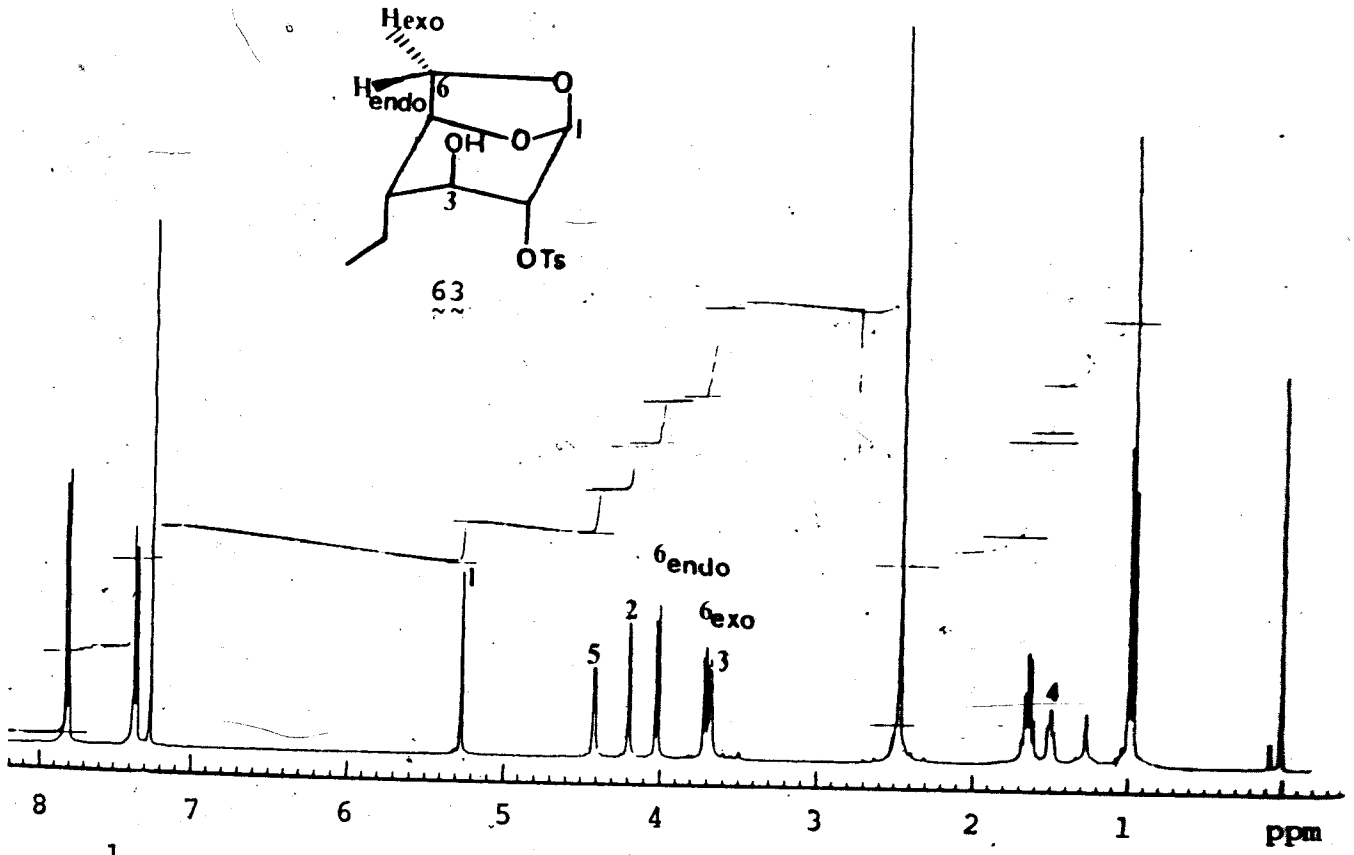


Fig. 24. The ^{1}H-NMR spectrum of 63 at 400 MHz in $CDCl_3$.

derivatives 35 and 36 (Scheme 11) was observed. It can be visualized that the reduction of 63 proceeds by way of the epoxide intermediate 65 and subsequent attack at C(2) by the hydride to give 64. The complete regiospecificity of this reduction is probably due to the presence of the C(4)-axial ethyl group, which hinders the attack at C(3), since a small amount of the product of di-equatorial opening of the epoxide was observed in the reduction of 33.[109] Benzylation of 64 proceeded smoothly to afford suitably protected 66 in 91% yield. In the ^{1}H-NMR spectrum of 66 (Fig. 25) the multiplets for H-2_{ax} and H-2_{eq} were found to be at 1.92 ($J_{2ax,3}$ = 5 Hz) and 1.98 ppm ($J_{2eq,3}$ = < 2 Hz). This order of the chemical shifts is opposite to the one observed for the C(2)-hydrogens of 64.

Treatment of 63 with sodium methoxide in chloroform-methanol gave an epoxide (93% yield) which was identical (^{1}H- and ^{13}C-NMR) with the one obtained as the minor product in the reaction of 33 with triethylalane. The structure of this epoxide was established to be 65 from its spectral properties. The oxirane ring in 65 should lead to an almost complete restriction of the 1,6-anhydropyranose system and to a planarization of the pyranose ring. The fixation of four carbon atoms in a plane [C(1)—C(4)] in 65 should enforce a flattened half-chair conformation of the type $^5H_0$[17e,110] (Scheme 22). In the ^{1}H-NMR spectrum

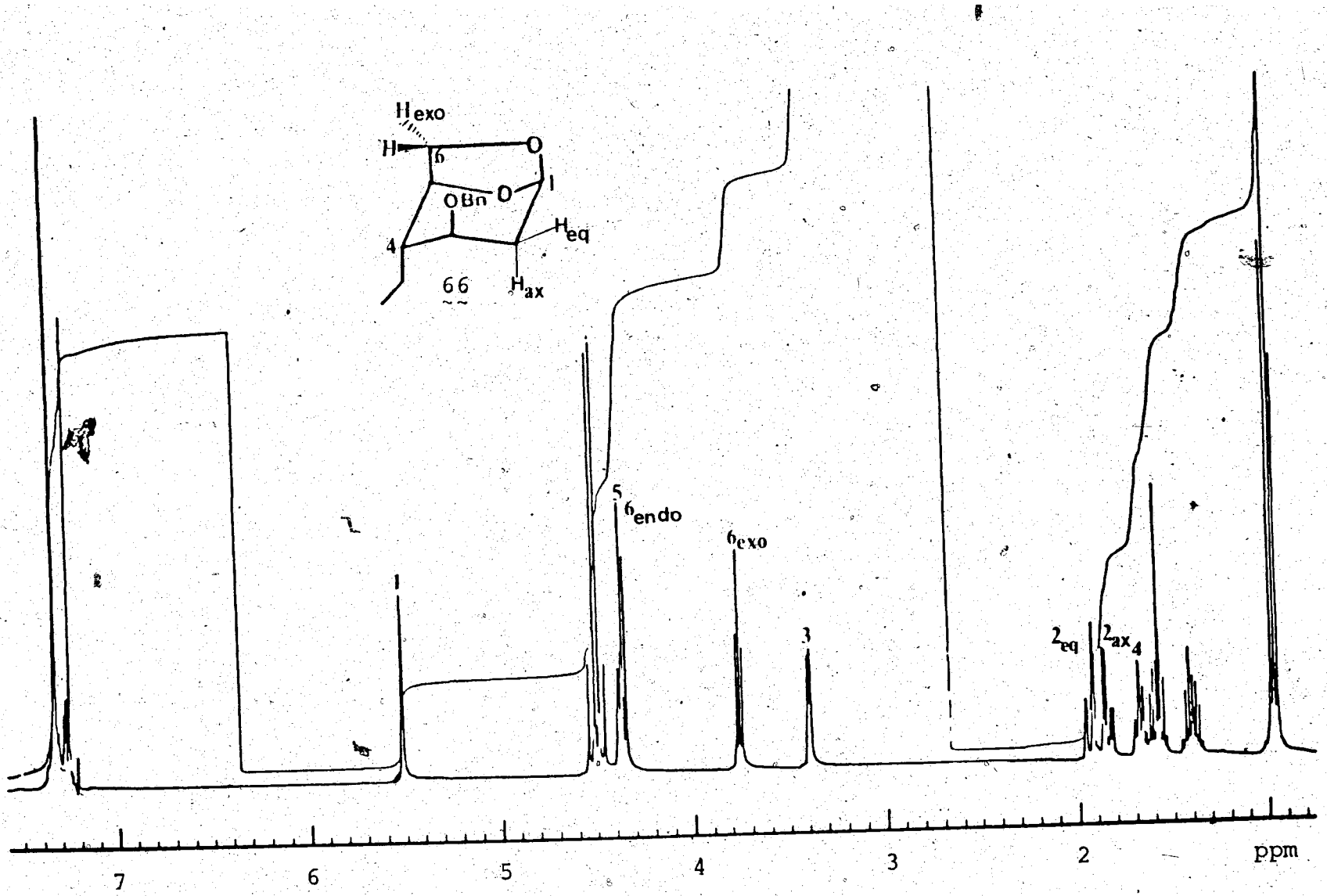
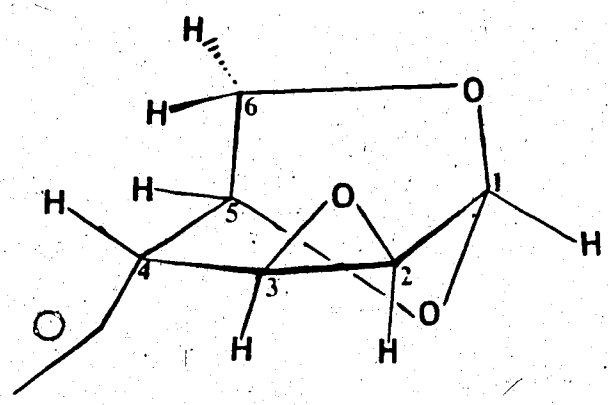


Fig. 25. The ^{1}H-NMR spectrum of 66 in $CDCl_3$ at 400 MHz.



$J_{1,2}$ = 3 Hz
$J_{3,4}$ = 0 Hz
$J_{4,5}$ = 0.5 Hz
$J_{3,5}$ = 1 Hz
$J_{1,4}$ = 0.5 Hz

65

Scheme 22.

of 65 (Fig. 26), the two hydrogens at C(6) appear at 3.75 ppm. This is in contrast to the ^{1}H-NMR spectrum of 64 where the H-6_{endo} is shielded by 0.57 ppm more than the H-6_{exo} (at 3.77 ppm). The extra shielding of H-6_{endo} in 65 is probably because of the flattening of the pyranose ring which reduces the electrostatic interaction between the C(3)-oxygen and the H-6_{endo}. The chemical shift of the H-4 multiplet was found to be at 1.86 ppm. The vicinal couplings between the H-4 and H-5, the H-3 and H-4 were found to be 0.5 Hz and 0 Hz respectively from the decoupling studies. These values indicate that there is a flattening of the C(1)—C(4) portion in 65.[110] In addition, two four-bond ($^4J_{2,4}$ = about 0.5 Hz and $^4J_{3,5}$ = 1 Hz) and one five-bond ($^5J_{1,4}$ = 0.5 Hz) long-range couplings were observed.

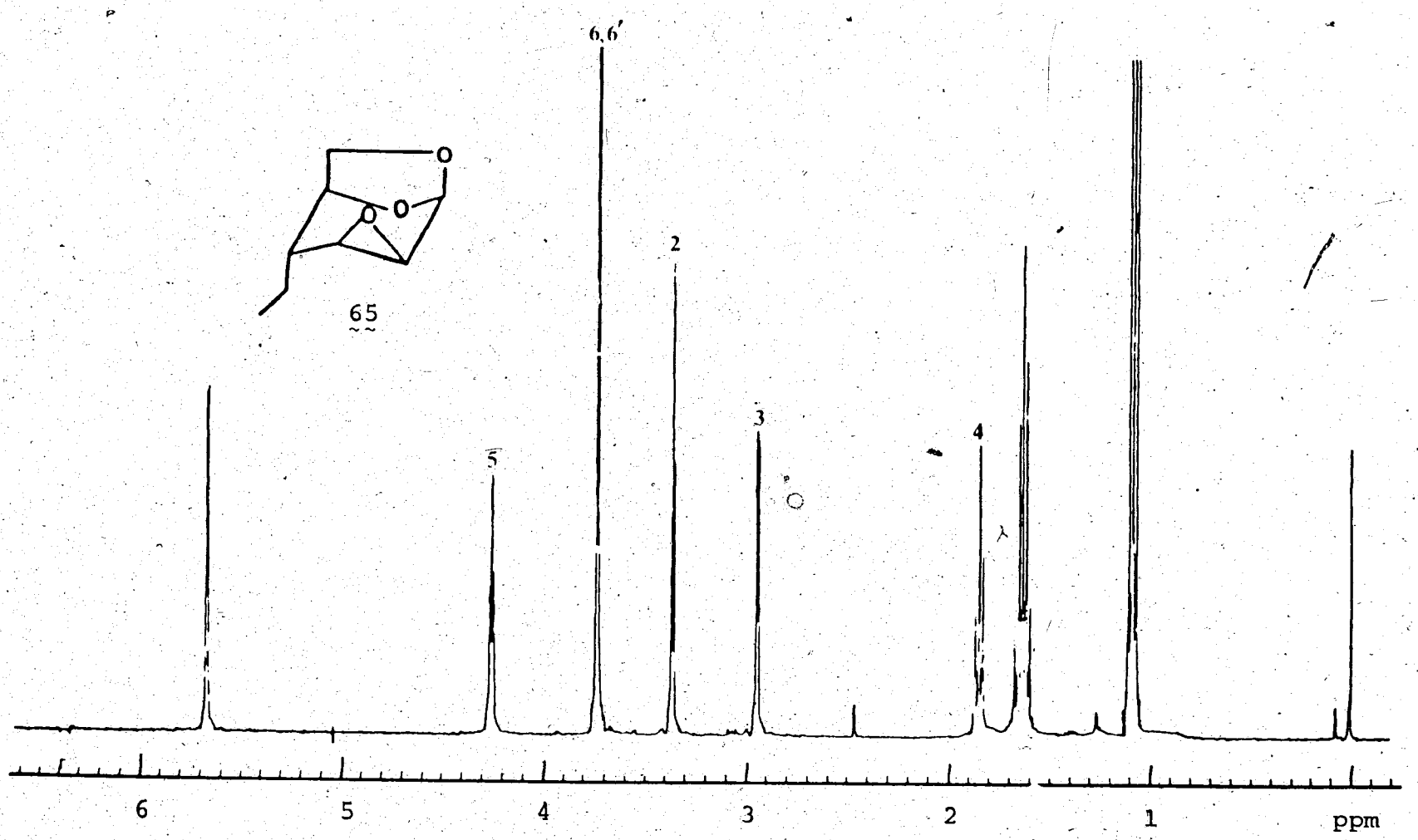


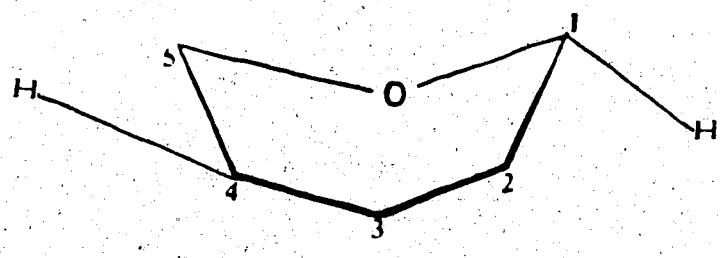
Fig. 26. The ^{1}H-NMR spectrum of 65 in $CDCl_3$ at 400 MHz.

Table 6: ^{13}C-NMR data[a] of compounds 63—66.

Carbon atom	1	2	3	4	5	6	1`	2`	$\underline{C}H_2Ph$	Ar-$\underline{C}H_3$	Aromatic carbons			
63	99.87	79.33	70.44	45.54	74.44	68.53	24.12	11.69		21.68	127.98	130.13	133.42	145.38
65	98.02	53.88	50.63[c]	41.34	71.32	68.64	23.86	11.90						
64	101.39	36.33	68.58	47.39	74.94	68.04	24.05	12.20						
66	100.28	33.20	74.04[b]	44.63	74.53[b]	67.52	24.17	12.20	70.50		127.44	128.35	138.69	

a. Chemical shift values in ppm from TMS.
b. These numbers can be reversed within the same row.
c. This chemical shift assignment was confirmed by single frequency decoupling experiment.

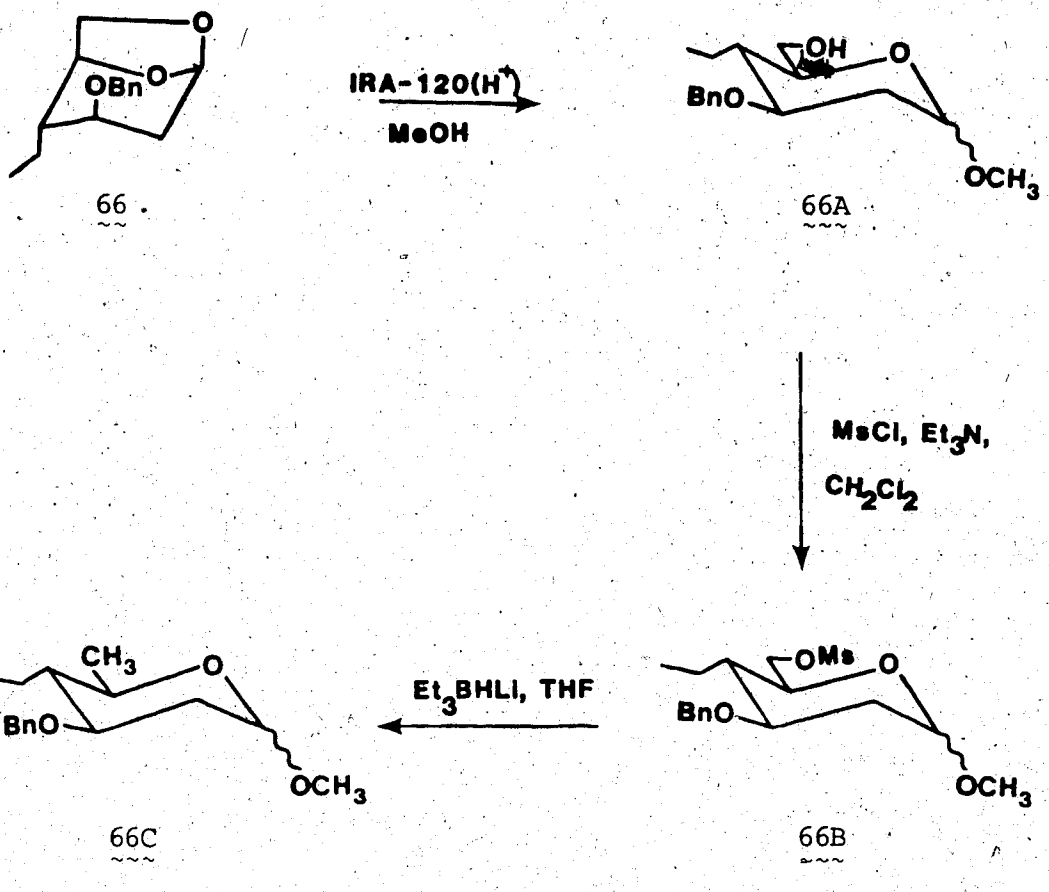
A relatively large value of $^{5}J_{1,4}$ coupling indicates the antiperiplanar arrangement of the alternate 6 bonds and that all the six atoms must be near one plane[111] (Scheme 23).



Scheme 23.

The ^{13}C-chemical shift assignments listed in Table 6 are based upon the literature precedent in the area of carbohydrates.[46,47,48]

Compound 66 was converted into lactone 67 in five steps using standard reactions (Scheme 23a). Methanolysis of 66 using IRA-120(H^+) resin as a catalyst at room temperature provided methyl glycoside 66A as a mixture of α- and β-anomers in a ratio about 85:15 (^{1}H-NMR). Treatment of 66A with methanesulfonyl chloride and triethylamine in dichloromethane[40] at 0 °C afforded 66B in 80% yield. Deoxy-functionality at C-6 of 66B was introduced by reduction with lithium triethylborohydride. Treatment of 66B with lithium triethylborohydride in THF at room temperature gave 66C in 69% yield.



66 66A

66C 66B

66D 67

Scheme 23a

Methyl glycoside 66C was hydrolyzed with 50% aquous acetic acid at 60°C to give 66D in 83% yield. Lactol 66D exists as a 3:2 mixture of α- and β-anomers (^{1}H-NMR) in $CDCl_3$. Compound 66D was oxidized with pyridinium chlorochromate in dichloromethane to give the target lactone 67 in 76% yield.

The IR spectrum (1748 cm^{-1}) indicated that the compound 67 is a δ-lactone. The large vicinal coupling $J_{4,5}$ = 9.75 Hz (δ H-5 = 4.06 ppm) indicated that there has been no isomerisation at the chiral centre C-5. The ^{13}C-NMR spectrum is consistent with the proposed structure 67.

The protected lactone 67 having three consecutive chiral centers represents the C(11)—C(15) and C(11')—C(15') segments (segment A, Fig. 22) of elaiophylin (azalomycin-B) 61.

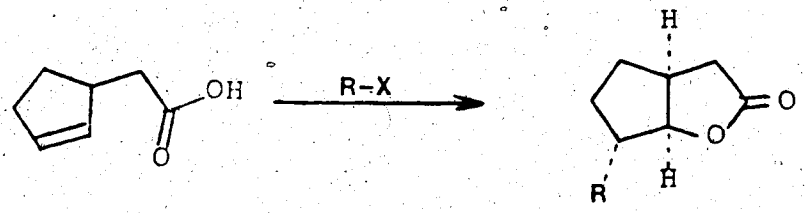
I plan to continue further work on the synthesis of other lactones of the type 60 and on the use of these chiral precursors for the synthesis of macrolide antibiotics.

CHAPTER III

REVERSAL OF CYCLOFUNCTIONALIZATION USING CHLOROTRIMETHYLSILANE-SODIUM IODIDE IN ACETONITRILE.

A. Introduction.

The synthetic methodology based on cyclofunctionalization using halogens,[112] benzenesulfenyl chloride,[113] and phenylselenenyl chloride[114] is well developed. The transformation of eq. (1) is representative of a large class of such cyclofunctionalizations that are useful for the synthesis of lactones,[112,113,115] ethers,[116,117] thioethers,[118] and amines.[119] (R = PhSe, PhS, Br, I; X = Cl, Br, I).

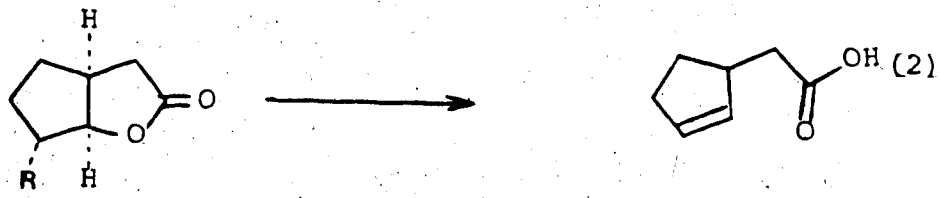


(1)

68a

68: R = PhSe

Although, regeneration of unsaturated acids from halolactones [e.g., eq. (2)] has been investigated,[112] little is known about methods for reversing selenium based reactions.[120]



(2)

The unsaturated acid is customarily regenerated from a halolactone using zinc in acetic acid.[112] The existing methods for reversal of phenylselenenolactonization make use of basic (NH_3/Li) or acidic reagents[120] and, therefore, a reversal method carried out essentially under neutral conditions will be a welcome addition. Also, the conversion shown in eq. (1) and (2) can be used to protect a double bond and an attached nucleophile.

In continuation of our effort to investigate the synthetic methodology based on selenium chemistry, it was found that many of the cyclofunctionalizations represented by eq. (1) can be reversed under mild conditions by the action of chlorotrimethylsilane and sodium iodide in acetonitrile in very good yields.

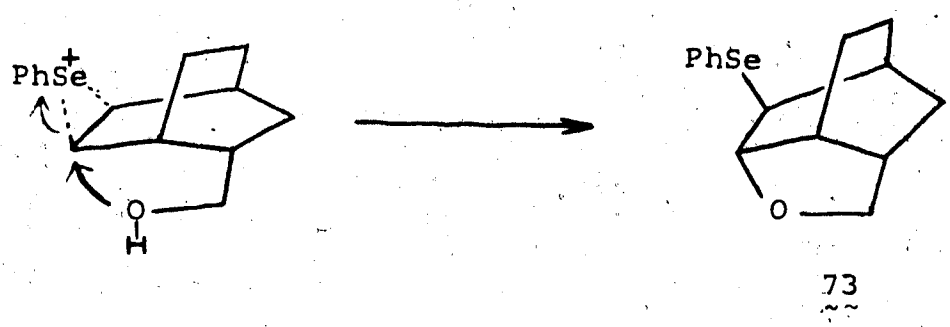
Similar to selenolactones and ethers, β-hydroxy phenylselenides are converted stereospecifically into the corresponding olefins. Since, hydroxy selenides are available by a variety of carbon-carbon connective routes[114,121] this method constitutes a novel approach

to the formation of carbon-carbon double bonds.

B. Discussion.

The cyclofunctionalised starting materials for this study were prepared from the corresponding olefinic compounds according to the standard general methods in reasonable yields. In the case of the phenythiolactone 70 no attempt was made to improve the yield as a sufficient amount had been made for the present studies and compounds of the same general class are known[113] to be available, generally, in good yield.

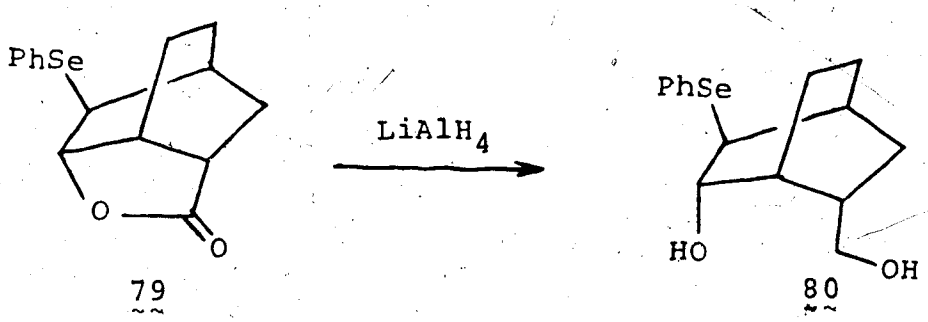
Some comment is necessary about the preparation (See eq. 3) of the phenylselenoether 73. The ring closure can take place in two ways to give either 73 or 78 as shown[115b] (cf. Scheme 24). The material isolated (72% yield) has the structure assigned and not the alternative 78. This was established chemically by the experiments summarised in eq. 4, the material obtained by the methods of eq. 3 and 4 being identical (TLC, IR, ^{1}H- and ^{13}C-NMR, mass). The lactone 79 is a known substance;[115b] it is recoverable unaltered from boiling toluene but, when treated in boiling toluene with Ph_3SnH, it is converted into 4-oxatricyclo[4.3.1.$0^{3,7}$]decan-5-one,[115b] which is spectroscopically (e.g., ^{13}C-NMR) distinguishable from the isomer, 4-oxatricyclo-[4.4.0.$0^{3,8}$]decan-5-one.



73

(3)

78



79 80

(4)

TsCl
Pyridine

73

Scheme 24.

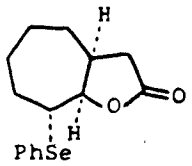
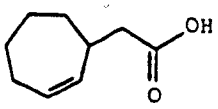
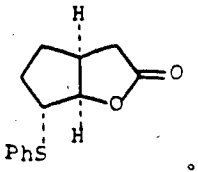
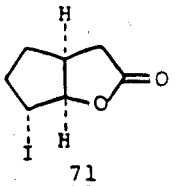
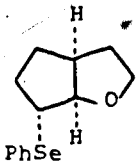
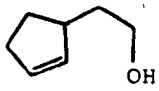
The results of the reaction of ten representative β-oxygenated phenylseleno, phenythio, and iodo species with chlorotrimethylsilane and sodium iodide in acetonitrile are summarised in Table 7. In a typical experiment, the substrate and anhydrous sodium iodide were dissolved in anhydrous acetonitrile under nitrogen to give a solution that was 0.04--0.5 M in substrate. Chlorotrimethylsilane was injected and, after an appropriate time (TLC control) the iodine liberated was destroyed with aqueous sodium thiosulfate and the product could be isolated in the yields specified.

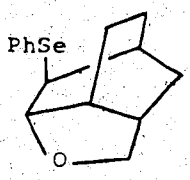
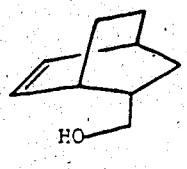
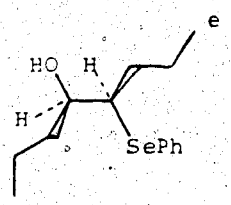
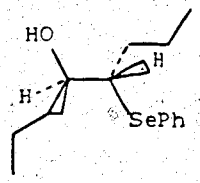
The reaction was very slow when one equivalent of the reagents was employed. Using 68 as a test case, it was found that reaction in dichloromethane is inconveniently slow. Reaction of 74 with chlorotrimethylsilane and sodium cyanide in refluxing acetonitrile is also slow [88% (vpc) of 1-decene after 20 h].

Most of the examples studied are β-oxygenated selenides, which react at room temperature, but the experiments with compounds 70 and 71 establish that the process can be extended to thio and iodo species. Although the iodolactone 71 reacts at room temperature, the thiolactone 70 requires refluxing conditions and a longer reaction time.

The isomeric purity of the hydroxy selenides 76 and 77 was checked by careful integration (400 MHz) of

Table 7: Reversal of Cyclofunctionalization.

Substrate	Me$_3$SiCl [mmol/mmol substrate]	NaI	Time (h)	Product	Yield %
68[115b]	6	6	3	68a	84
 69[115b]	4	4	4		83
 70	6	6	17[b]	68a	91[c]
 71	5	5	≤5	68a	70
 72[117]	2	2	1		75

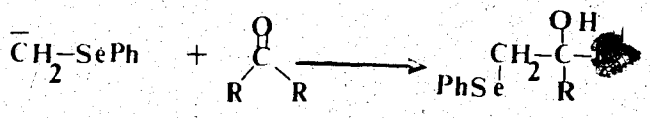
Substrate	Me_3SiCl [mmol/mol substrate]	NaI	Time (h)	Product	Yield %
 73	2	2	1.5		78[d]
$C_8H_{17}CH(OH)CH_2$ | SePh 74	2	2	0.3	1-decene	88% (VPC)
$C_9H_{19}CHCH_2OH$ | SePh 75	3	3	0.5	1-undecene	83% (VPC)
 76	3.3	3.3	0.67	(Z)-4-octene[f]	>90% (VPC)
 77	2.7	2	0.5	(E)-4-octene[g]	>90% (VPC)

Footnotes to Table 7.

a. Except where indicated, reactions were run at room temperature and yields refer to isolated, distilled material better than 99% pure as judged by VPC. Isolated products were identified by comparison with authentic samples. Where yields were determined by VPC an internal standard was used and, in the case of compound 74 a portion of the olefin was isolated and characterized.
b. Reaction run at reflux temperature of MeCN.
c. Better than 98% pure by VPC.
d. Homogeneous by t.l.c.
e. The 400 MHz NMR spectrum showed <2% erythro isomer.
f. Contains 2% (E)-isomer as judged by VPC analysis on a $AgNO_3$-impregnated column.
g. Contains 1% (Z)-isomer (VPC).

appropriate nmr signals. The chemical shifts of H-5 and H-4 protons of threo-5-(phenylseleno)octan-4-ol 76 are δ 3.06—3.19 (m, 1 H), and 3.5—3.62 (m, 1 H), whereas those for erythro-5-(phenyseleno)octan-4-ol) 77 are δ 3.23—3.4 (m, 1 H) and 3.6—3.72 (m, 1 H). Therefore it was possible to detect the extent of isomeric impurity by this method.

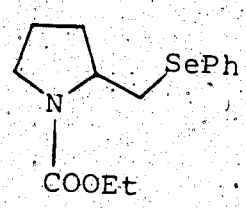
The hydroxy selenides react faster and with a smaller excess of reagents than the selenolactones. In the case of compound 74, a portion of the product, 1-decene, was isolated by silica gel column chromatography and characterised. The hydroxy selenides 76 and 77 gave the corresponding olefins with little, if any, loss of stereochemistry and so this reaction differs from that based on lithium-ammonia reduction[115c] in being stereospecific. The hydroxy selenides are available by a variety of routes involving carbon-carbon bond formation[114,121] [e.g., reaction of a selenium stabilized carbanion with an aldehyde or ketone (See: eq. 5)].



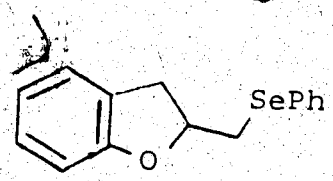
(5)

Therefore the experiments with 74—77 also illustrate a synthesis — as opposed to protection-deprotection— of double bonds.

Of the cases studied (cf. Table 7) there were two types of substrates for which the chlorotrimethylsilane-sodium iodide system is unsuitable. The urethane 81[119] appeared (TLC control) to be essentially inert even in refluxing acetonitrile (32 h). cis-N-Carbethoxy-2-methyl-6-undecylpiperidine also failed to react at a satisfactory rate (≈ 21% conversion after 96 h at reflux).[123] Evidently, ethyl carbamates of secondary amines are not always dealkylated easily.[124] The reaction of phenol ether 82[116] is not a clean process; more than one product is obtained as judged by VPC.



81



82

The precise nature of the chlorotrimethyl-silane-sodium iodide system has not been established.[124b,125] The hydroiodic acid formed by adventitious hydrolysis with water should be trapped as an adduct with acetonitrile (See Scheme 25a) and so the reaction is carried out essentially under neutral conditions. Although we did not investigate the detailed mechanism of this reaction, a tentative proposal can be outlined based on the stereospecificity of the reaction and the nature of the products formed (See Scheme 25b). Our reaction does work when pyridine is used as the solvent, at least as judged by an experiment with 68, but the process is inefficient (< 21% yield after 24 h). Aqueous hydroiodic acid (47% w/v, 5 equivalent) in acetonitrile afforded 33% yield after a reaction period of 3.5 h. The yield was 64% when only 2 equivalent of hydroiodic acid was used. The higher yields of the silicon-mediated process are due to the fact that the unsaturated acid generated is in the form of its trimethylsilyl ester (cf. Scheme 25b) and hence it is not available for further reaction as is the case when a strong acid is used[126] (See eq. 6).

To conclude, apart from examples 81 and 82, the reaction with chlorotrimethylsilane-sodium iodide is a general one for reversal of cyclofunctionalizations. The ease with which unsaturated acids and alcohols may be converted into cyclofunctionalised compounds and

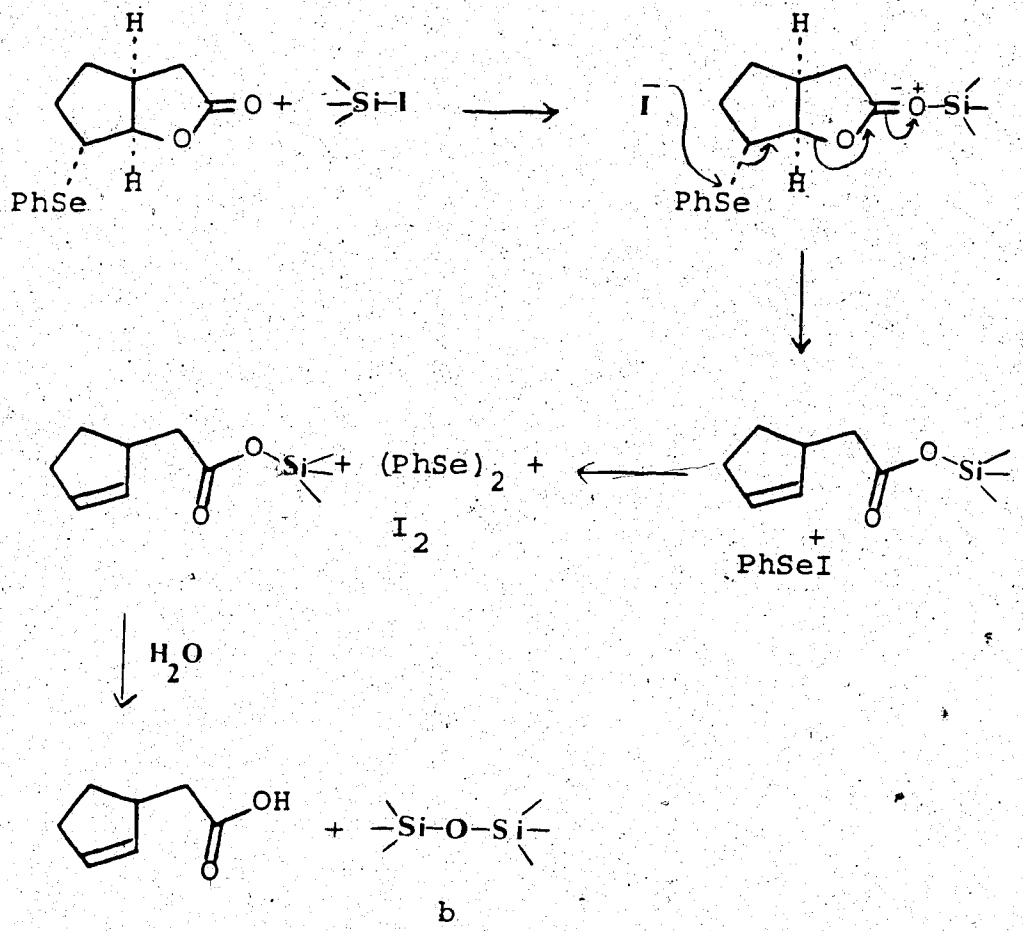
$NaI + (CH_3)_3SiCl \longrightarrow NaCl + (CH_3)_3SiI$

$CH_3C{\equiv}N + (CH_3)_3SiI \rightleftharpoons CH_3-\underset{\underset{I}{|}}{C}=N-Si(CH_3)_3$

$2(CH_3)_3SiI + H_2O \longrightarrow 2HI + (CH_3)_3Si-O-Si(CH_3)_3$

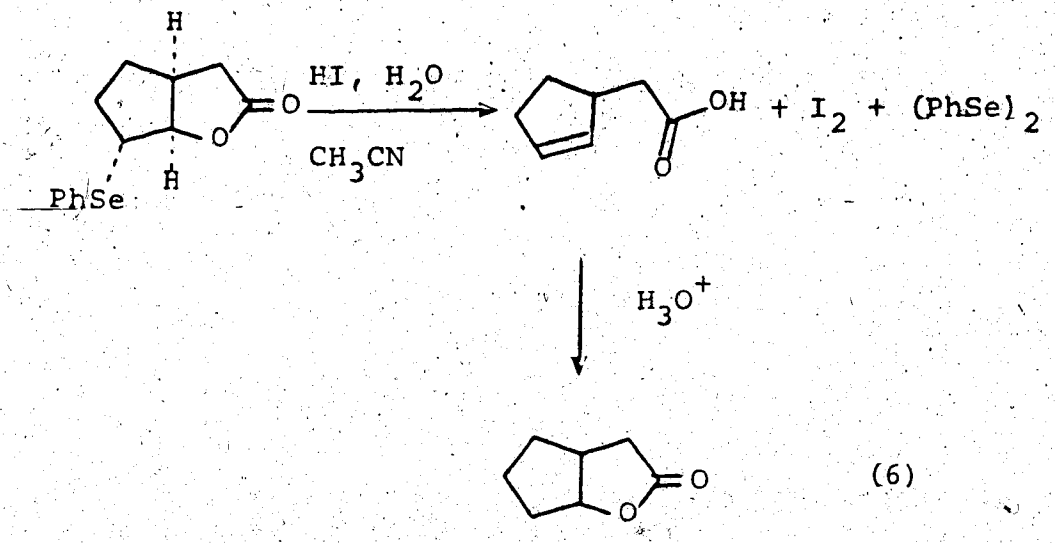
$CH_3C{\equiv}N + HI \rightleftharpoons CH_3-\underset{\underset{I}{|}}{C}=NH$

a



b

Scheme 25.



(6)

the unsaturated acids and alcohols subsequently regenerated from β-oxygenated phenylseleno, phenylthio and iodo species suggests that cyclofunctionalisation has potential as a method for the protection of unsaturation.

In addition, dehydroxyselenation of β-hydroxy selenides is also an efficient and stereospecific process for formation of carbon-carbon double bonds.

CHAPTER IV

EXPERIMENTAL

A. General

Except where stated to the contrary, the following particulars apply. For reactions carried out under nitrogen, oven-dried glassware (130°C, 12-24 h) was used. The apparatus was allowed to cool in a desiccator or assembled hot, capped with rubber septa, and swept with nitrogen for ca. 15 min. Reactions were performed (after removal of the exit needle, unless gas was to be generated) under a slight static pressure of nitrogen. The nitrogen used was purified by passage through a column (3.5 x 40 cm) of R-311 catalyst[127] and then through a similar column of Drierite. All solvents were distilled before use for chromatography. Solvents were dried, where specified, by distillation, under a static nitrogen atmosphere, from suitable desiccants and transferred via oven-dried syringes. Dry ether, THF and dioxane, were distilled from sodium (benzophenone, indicator); dichloromethane, chloroform, benzene, toluene, hexane, pyridine, acetonitrile, dimethylformamide, dimethyl sulfoxide and hexamethyl phosphorotriamide (HMPA) from calcium hydride [the latter three under reduced pressure]; acetone from

anhydrous potassium carbonate; methanol from magnesium methoxide. The following reagents were also purified before use and dispensed by syringe: thionyl chloride simply by distillation; chlorotrimethylsilane, triethylamine and diisopropylamine were distilled from calcium hydride.

Benzeneselenenyl chloride from Aldrich was used as received. During product isolation, solutions were dried over magnesium sulfate or potassium carbonate (where necessary) and evaporated under water-pump vacuum at room temperature. Where compounds were isolated simply by evaporation of their solutions, the residues were kept under oil pump vacuum and checked for constancy of weight. Isolated products were submitted directly for combustion analysis without need for additional purification, unless otherwise stated.

All vapor phase chromatography (VPC) were performed on a Hewlett-Packard 5830A gas chromatograph equipped with an FID detector and, unless otherwise noted, with prepacked Hewlett-Packard 6 ft, 1/8" o.d. stainless steel analytical columns with nitrogen as the carrier gas. Yields were evaluated by VPC in the following way: a standard solution was prepared composed of the compounds to be analyzed plus an inert internal standard diluted with appropriate solvent to the approximate concentration expected to occur from the reaction. Response factor of each component, compared to the internal standard

were calculated. The absolute yield of a specified product was then calculated by addition of a known amount of internal standard to the reaction mixture and quenching the reaction, followed by VPC analysis.

Commercial thin-layer chromatography (TLC) plates were used: silica gel was Camag type DF-B or Merck 60F-254; alumina was Camag type DSF-B or Merck 60F-254. UV active spots were detected at 254 nm; spots detected by spraying with sulfuric acid (50% in methanol) were charred on a hot plate. Silica gel for column was Merck type 60, 70-230 mesh ASTM; silica gel for flash chromatography[128] was Merck type 60, 230-400 mesh ASTM.

Infrared spectra were recorded on a Perkin-Elmer 297 infrared spectrometer, or on a Nicolet 7199 FT-IR spectrometer. Liquids and oils were usually run as thin film on sodium chloride plates; solids were run as solutions in the specified solvent, using 0.5 mm sodium chloride cells or as a nujol mull. Proton NMR spectra were recorded on Varian HA-100 (at 100 MHz), Bruker WH-200 (at 200 MHz) or Brucker WH-400 (at 400 MHz) spectrometers, in the specified deuterated solvent with tetramethylsilane (TMS) as an internal standard. ^{13}C-NMR spectra were recorded on a Brucker HFX-90 (at 22.6 MHz), Brucker WH-200 (at 50.2 MHz) or Brucker WH-400 (at 100.4 MHz) spectrometers with tetramethylsilane

(TMS) or deuterated chloroform as an internal standard. The coupled ^{13}C-NMR spectra were obtained using a C/H dual probe. The concentrations of the compounds used for nuclear Overhauser experiments were 10--15% w/v and solutions were degassed prior to the experiment. Electron-impact mass spectra were determined on an Associated Electrical Industries (AEI) MS-9 double-focusing high-resolution mass spectrometer and chemical-ionization mass spectra were recorded on an AEI MS-12 mass spectrometer using ammonia as reagent gas.[129] Optical rotations were recorded on a Perkin-Elmer 241 polarimeter at 589 nm in a 1 dm cell. Melting points were determined on a Kofler block melting point apparatus.

For reactions run at 0°C the reaction flasks were cooled in an ice water bath; lower temperatures were obtained by the use of dry ice-acetone mixtures. Unless otherwise stated, stirring refers to the use of a Teflon coated magnetic bar.

The commercial (Aldrich) solutions of methyllithium in ether and n-butyllithium in hexane were titrated, before use, by the diphenylacetic acid method.[130] Triethylalane, lithium triethylborohydride, (4-carboxybutyl)triphenylphosphonium bromide and dimethyl (2-oxoheptyl)phosphonate were commercially available and were used without further purification. Cuprous chloride was freshly prepared by the literature method.[131]

B. Synthesis of 1,3-anhydro-2-O-n-butyl-3,4-dideoxy-3-mercapto-β-DL-threo-pentopyranose (7-exo-n-Butoxy-2-oxa-6-thiabicyclo[3,1,1]heptane) 31. Benzyl 2,3-anhydro-4-deoxy-β-DL-erythro-pentopyranoside 21 and benzyl 2,3-anhydro-4-deoxy-α-DL-erythro-pentopyranoside 22. A solution of m-chloroperbenzoic acid (16 g, 85%, 78 mmol) in dichloromethane (100 mL) was added dropwise to a solution (130 mL) of 2-benzyloxy-5,6-dihydro-α-pyran 20^{24} (27.51 g, 144 mmol) in the same solvent. A further portion of m-chloroperbenzoic acid (10.4 g, 85%, 51 mmol) in dichloromethane (100 mL) was added after 6 h. The mixture was stirred for an additional 4 h and filtered. The solids were washed with hexane (500 mL) and the combined organic phase was washed with 10% w/v aqueous sodium thiosulfate (200 mL), with saturated aqueous sodium bicarbonate (2 x 200 mL), with water (2 x 150 mL) and brine (150 mL). The organic extract was dried and evaporated. Flash chromatography of the residue over silica gel (5 x 20 cm) with 1:9 ethyl acetate—hexane gave the epoxide 21^{24} (14.8 g, 49%) as a homogeneous (TLC, silica gel, 1:9 ethyl acetate—hexane) oil. Compound 21 had: FT-IR (mull) 1447, 1010, 695 cm^{-1}; NMR ($CDCl_3$, 400 MHz) δ 1.81 (m, J = 2.5, 4.5, 5, 15 Hz, 1 H, H-4_{eq}), 2.08 (m, 1 H, H-4_{ax}), 3.05 (br d, J = 4 Hz, 1 H, H-2), 3.34 (m, J = 1, 4, 5 Hz, 1 H, H-3),

3.42 (m, J = 1, 2.5, 7, 12 Hz, 1 H, H-5_{eq}), 3.77 (m, J = 0.75, 5, 11, 12 Hz, 1 H, H-5_{ax}), 4.56 and 4.81 (AB q, J = 11.5 Hz, 2 H, -$\underline{C}H_2Ph$), 5.03 (br s, 1 H, H-1), 7.3 (m, 5 H, aromatic protons); CMR ($CDCl_3$, 22.6 MHz) ppm 23.41 (C-4), 49.86 (C-2 and C-3), 54.47 (C-5), 69.93 (-$\underline{C}H_2Ph$), 94.56 (C-1), 127.86, 128.05, 128.48 and 137.41 (aromatic carbons); exact mass 206.0938 (calcd for $C_{12}H_{14}O_3$, 206.0943). Anal. Calcd for $C_{12}H_{14}O_3$: C, 69.88; H, 6.84. Found: C, 69.63; H, 6.91.

On further elution, epoxide 22 (4.63 g, 15%) was obtained. Compound 22 had: FT-IR (film) 1045, 1020 cm^{-1}; NMR ($CDCl_3$, 400 MHz) δ 1.95 (m, 2 H, HH-4), 3.25 (q, J = 3, 4 Hz, 1 H, H-2), 3.33 (br t, 1 H, H-3), 3.43 (m, 1 H, H-5_{eq}), 3.85 (m, 1 H, H-5_{ax}), 4.60 and 4.80 (AB q, J = 12 Hz, 2 H, -$\underline{C}H_2Ph$), 5.00 (d, J = 3 Hz, 1 H, H-1), 7.3 (m, 5 H, aromatic protons); CMR ($CDCl_3$, 22.6 MHz) ppm 24.76 (C-4), 49.77 and 51.29 (C-2 and C-3), 55.43 (C-5), 68.95 (-$\underline{C}H_2Ph$), 92.68 (C-1), 127.71, 128.15, 128.41 and 137.71 (aromatic carbons); exact mass 206.0942 (calcd for $C_{12}H_{14}O_3$, 206.0943). Anal. Calcd for $C_{12}H_{14}O_3$: C, 69.88; H, 6.84. Found: C, 69.73; H, 6.90.

Benzyl 3-S-t-butyl-3,4-dideoxy-β-DL-threo-pentopyranoside

23. t-Butyl mercaptan (1.46 g, 1.83 mL, 16 mmol) was added to a solution of sodium methoxide (0.88 g, 16 mmol) in absolute methanol (10 mL). The solution was stirred for 15 min and then epoxide 21 (3.05 g, 14 mmol) in methanol (10 mL) was added. The mixture was refluxed for 2 h, cooled and diluted with water (10 mL). Most of the methanol was evaporated and the residue was extracted with ether (2 x 75 mL). The organic phase was washed with water (50 mL), brine (50 mL), dried and evaporated to give compound 2[illegible] (4.07 g, 92%) which was used for the next stage [illegible]out further purification. An analytical sample was pr[illegible] by crystallization from hexane. The purified material had: FT-IR (nujol) 3420, 1455, 1077 cm^{-1}; NMR ($CDCl_3$, 200 MHz) δ 1.34 (s, 9 H, $-C(CH_3)_3$), 1.70—2.09 (m, 2 H, HH-4), 2.66 (m, J = 5, 10.25, 12 Hz, 1 H, H-3), 2.76 (d, J = 1.75 Hz, 1 H, -OH), 3.22 (m, J = 1.75, 7, 10.25 Hz, 1 H, H-2), 3.49 (m, J = 3, 11.25, 11.75 Hz, 1 H, $H\text{-}5_{ax}$), 3.97 (m, J = 2, 4.5, 11.75 Hz, 1 H, $H\text{-}5_{eq}$), 4.37 (d, J = 7 Hz, 1 H, H-1), 4.66 and 4.91 (AB q, J = 11.5 Hz, 2 H, $-CH_2Ph$), 7.3 (m, 5 H, aromatic protons); CMR ($CDCl_3$, 22.6 MHz) ppm 31.63 ($-C(CH_3)_3$), 35.66 (C-4), 43.79 ($-C(CH_3)_3$), 45.35 (C-3), 64.20 (C-5), 70.44 and 72.72 (C-2 and $-CH_2Ph$), 103.39 (C-1), 127.76, 128.03, 128.42 and 137.52 (aromatic carbons); exact mass 296.1451 (calcd for

$C_{16}H_{24}O_3S$, 296.1446). Anal. Calcd for $C_{16}H_{24}O_3S$: C, 64.84; H, 8.16; S, 10.82. Found: C, 65.04; H, 8.23; S, 10.84.

Benzyl 2-O-n-butyl-3-S-t-butyl-3,4-dideoxy-β-DL-threo-pentopyranoside 24.

Sodium hydride (50% w/w as an oil dispersion, 2.0 g, 40 mmol) was added to a solution (50 mL) of compound 23 (8.28 g, 27.8 mmol) in dry DMF. The mixture was stirred for 30 min. and then 1-iodobutane (7.71 g, 4.7 mL, 40 mmol) was added over 0.5 h. After 5 h, more sodium hydride dispersion (1.5 g, 30 mmol) and a further portion of 1-iodobutane (4.85 g, 3 mL, 26 mmol) were added. Stirring at room temperature was continued overnight. The mixture was diluted with water (100 mL) and extracted with ether (3 x 100 mL). The combined organic extract was washed with water (2 x 50 mL) and with brine (1 x 50 mL). The extract was dried and evaporated. Flash chromatography of the residue over silica gel (5 x 18 cm) with 1:19 ethyl acetate—hexane gave pure 24 (9.0 g, 90%) as a colorless oil. The compound had: FT-IR (film), 1115, 1085 cm^{-1}; NMR ($CDCl_3$, 400 MHz) δ 0.89 (t, J = 7.25 Hz, 3 H, $-CH_2\underline{CH_3}$), 1.34 (s, 9 H, $-C(\underline{CH_3})_3$), 1.35 (m, 2 H, $-\underline{CH_2}CH_3$), 1.54 (m, 2 H, $-\underline{CH_2}CH_2CH_3$), 1.74 (m, 1 H, H-$4_{ax}$), 2.07 (m, 1 H, H-$4_{eq}$), 2.68 (m, J = 4.5, 8, 13.5 Hz, 1 H, H-3), 2.97 (q, J = 5.25, 8 Hz, 1 H, H-2), 3.43 (m, 1 H, H-5_{ax}), 3.65 (dt, 1 H) and 3.75 (dt, 1 H) [C(2)-O-$\underline{CH_2}$-], 3.94 (dt, 1 H, H-5_{eq}), 4.43 (d, J = 5.25 Hz, 1 H, H-1), 4.60 and 4.87 (AB q,

J = 12 Hz, 2 H, -C$\underline{H}_2$Ph), 7.3 (m, 5 H, aromatic protons); CMR ($CDCl_3$, 100.6 MHz) ppm 13.92 (q, -$CH_2\underline{C}H_3$), 19.31 (t, -$\underline{C}H_2CH_3$), 31.53 [q, -$C(\underline{C}H_3)_3$], 32.32 [t, C(2)-O-$CH_2\underline{C}H_2$-], 34.87 (q, C-4), 42.47 (d, C-3), 43.50 [s, -$\underline{C}(CH_3)_3$], 62.23 (q, C-5), 70.33 (t) and 72.78 (t) [-$\underline{C}H_2$Ph and C(2)-O-$\underline{C}H_2$-], 80.72 (d, C-2), 103.21 (d, C-1), 127.52, 127.79, 128.30 and 138.04 (aromatic carbons); exact mass 352.2072 (calcd for $C_{20}H_{32}O_3S$, 352.2072). Anal. Calcd for $C_{20}H_{32}O_3S$: C, 68.13; H, 9.15; S, 9.09. Found: C, 67.97; H, 9.12; S, 9.35.

2-O-n-Butyl-3-S-t-butyl-3,4-dideoxy-α,β-DL-threo-pentopyranose 25. Trifluoroacetic acid (80% in water, 20 mL) was added to a solution of compound 24 (9.50 g, 26 mmol) in dichloromethane (25 mL). The mixture was stirred at room temperature for 40 h, cooled in an ice bath and diluted slowly with triethylamine (32 mL). The mixture was stirred at room temperature for 3 h and washed with water. The organic layer was dried and evaporated. Flash chromatography of the residue over silica gel (5 x 20 cm) with 0.75:9.25 ethyl acetate—hexane gave compound 25 (4.32 g, 61%) as a pure, pale yellow oil. The compound had: FT-IR (film) 3400, 1115 cm^{-1}; NMR ($CDCl_3$, 400 MHz) δ 0.93 (two sets of t, J = 7.25 Hz, 3 H, $-CH_2\underline{C}H_3$), 1.3—1.4 (m, 11 H, $-C(\underline{C}H_3)_3$ and $-C\underline{H}_2CH_3$), 1.59 (m) and 1.72 (m) (3 H, H-4_{ax} and $-C\underline{H}_2CH_2CH_3$) 2.15 (m, 1 H, H-$4_{eq}$), 2.76 (m, 0.5 H, H-3) of β-isomer), 2.98 (q, J = 5.5, 8 Hz, 0.5 H, H-2 of β-isomer), 3.10 (br q, 0.5 H, H-3 of α-isomer, 3.25 (q, J = 2.25, 6 Hz, 0.5 H, H-2 of α-isomer), 3.45—3.86 [three sets of m, 4 H, HH-5 and C(2)-O-$C\underline{H}_2$-], 3.53 (d, J = 8 Hz, 0.5 H, α-O<u>H</u>), 3.84 (d, J = 6 Hz, 0.5 H, β-OH), 4.70 (t, J = 5.50, 6 Hz, 0.5 H, H-1 of β-isomer: collapsed to a doublet with J = 5.5 Hz on D_2O exchange), 4.98 (q, J = 2.25, 8 Hz, 0.5 H, H-1 of α-isomer: collapsed to a doublet with J = 2.25 Hz on D_2O exchange);

CMR ($CDCl_3$, 22.6 MHz) ppm 13.70 and 13.75 ($-CH_2\underline{C}H_3$), 19.12 ($-\underline{C}H_2CH_3$), 31.15 and 31.28 [$-C(\underline{C}H_3)_3$], 31.86, 32.02 and 34.11 [C-4 and $C(2)-O-CH_2-\underline{C}H_2-$], 38.33 and 41.65 (C-3), 43.56 and 43.69 [$-\underline{C}(CH_3)_3$], 60.72 and 61.69 (C-5), 70.66 and 72.49 [$C(2)-O-\underline{C}H_2-$], 79.60 and 80.91 (C-2), 91.44 (C-1 of α-isomer), 97.74 (C-1 of β-isomer); exact mass 262.1600 (calcd for $C_{13}H_{26}O_3S$, 262.1603). Anal. Calcd for $C_{13}H_{26}O_3S$: C, 59.49; H, 9.98; S, 12.21. Found: C, 59.53; H, 10.00; S, 12.09.

1-O-Acetyl-3-S-acetyl-2-O-n-butyl-3,4-dideoxy-α,β-DL-threo-pentopyranose 27 and (±) threo-pentopyranose 27 and (±) threo-1,1,5-triacetoxy-3-thioacetylpentane 28.

Concentrated sulfuric acid (0.75 mL) was added over 10 min to a stirred, ice cold solution of 25 (4.1 g, 15.6 mmol) in acetic anhydride (35 mL). Stirring at 0 °C was continued for a further 30 min and then anhydrous sodium acetate (2.00 g) was added. The mixture was allowed to attain room temperature and was then evaporated. Ethanol (50 mL) was added and the solution was again evaporated. This evaporation procedure was repeated with ethanol (2 x 50 mL) and then with toluene (1 x 50 mL). The residue was partitioned between ether and saturated aqueous sodium bicarbonate. The organic extract was washed with brine, dried and evaporated. Flash chromatography of the residue over silica (5 x 16 cm) with 1:9 ethyl acetate—hexane gave 27 (2.60 g, 57%) as a homogeneous (TLC, silica gel, 1:9 ethyl acetate—hexane), pale yellow oil. Compound 27 had: FT-IR (film) 1742.4, 1692.3, 1229.0, 1117.7 cm^{-1}; NMR ($CDCl_3$, 400 MHz) δ 0.87 (two sets of t, J = 7.25 Hz, 3 H, $-CH_2CH_3$), 1.35 (m, 2 H, $-CH_2CH_3$), 1.51 (m, 2 H, $-CH_2CH_2CH_3$), 1.61—2.28 (series of m, 2 H, HH-4), 2.11 (s) and 2.14 (s) (3 H, $-OCOCH_3$), 2.05—2.3 (m, 1 H, H-3), 2.34 (s) and 2.35 (s) (3 H, $-SCOCH_3$), 3.16 (q, J = 5, 7 Hz, 0.31 H, H-2 of β-isomer), 3.36 (q, J = 3, 11 Hz, 0.66 H, H-2 of α-isomer),

3.39—3.98 (series of m, 4 H, HH-5 and C(2)-O-$\underline{CH}_2$-), 5.69 (d, J = 5 Hz, 0.31 H, H-1 of β-isomer), 6.30 (d, J = 3 Hz, 0.66 H, H-1 of α-isomer); CMR ($CDCl_3$, 22.6 MHz) ppm 13.78 (-$CH_2\underline{CH}_3$), 19.07, 19.17 and 21.02 (-$\underline{CH}_2CH_3$ and -OCO$\underline{CH}_3$), 29.73, 30.63, 30.84, 31.81, 32.07 and 32.31 (-SCO$\underline{CH}_3$, -$\underline{CH}_2CH_2CH_3$ and C-4) 41.34 and 41.49 (C-3), 60.90 and 62.01 (C-5), 70.81 and 71.85 [C(2)-O-$\underline{CH}_2$-], 76.73, 76.40 (C-2), 89.98 (C-1 of α-isomer), 94.43 [C-1 of β-isomer], 169.01 and 169.63 (-O$\underline{C}$OCH$_3$), 194.75 (-S$\underline{C}$OCH$_3$); exact mass 290.1177 (calcd for $C_{13}H_{22}O_5S$, 290.1187). Anal. Calcd for $C_{13}H_{22}O_5S$: C, 53.76; H, 7.63; S, 11.04. Found: C, 53.82; H, 7.76; S, 11.16.

On further elution, compound 28 (0.72 g, 11.74%) was obtained as a colorless thick oil, which solidified on standing. An analytical sample was obtained by keeping the material for one day under oil pump vacuum. The material was homogeneous by TLC (silica gel, 1:9 ethyl acetate—hexane). Compound 28 had: FT-IR (nujol) 1689.3, 1734.8, 1748.9, 1766.9 cm^{-1}; NMR ($CDCl_3$, 400 MHz) δ 0.90 (t, J = 7.25 Hz, 3 H, -$CH_2\underline{CH}_3$), 1.34 (m, 2 H, -$\underline{CH}_2CH_3$), 1.52 (m, 2 H, -$\underline{CH}_2CH_2CH_3$), 1.92 (m, 1 H, H-4), 2.07 (s, 3 H, -OCO$\underline{CH}_3$), 2.08 (s, 3 H, -OCO$\underline{CH}_3$), 2.09 (s, 3 H, -OCO$\underline{CH}_3$), 2.14 (m, 1 H, H-4), 2.31 (s, 3 H, -SCO$\underline{CH}_3$), 3.57 (dt) and 3.67 (dt) (C(2)-O-$\underline{CH}_2$-), 3.63 (q, J = 2.5, 7 Hz, 1 H, H-2), 3.91 (m, J = 2.5, 10 Hz, 1 H, H-3), 4.14 (m, 2 H, HH-5), 6.91 (d, J = 7 Hz, 1 H, H-1);

CMR ($CDCl_3$, 22.6 MHz) ppm 13.56 (q, $-CH_2\underline{C}H_3$), 18.90 (t, $-\underline{C}H_2CH_3$), 20.42 and 20.58 ($-OCO\underline{C}H_3$), 30.20, 31.47 and 31.89 ($-SCO\underline{C}H_3$, $-\underline{C}H_2CH_2CH_3$ and C-4), 41.16 (d, C-3), 61.24 (t, C-5), 72.94 [t, C(2)$-O-\underline{C}H_2-$], 80.94 (d, C-2), 87.99 (d, C-1); mass (chemical ionization, NH_3) 410 (M + 18). Anal. Calcd for $C_{17}H_{28}O_8S$: C, 52.02; H, 7.19; S, 8.17. Found: C, 52.05; H, 7.30; S, 8.34.

2-O-n-Butyl-3,4-dideoxy-3-mercapto-α,β-DL-threo-pentopyranose 29. A solution (6.5%, w/v, 1 mL) of sodium methoxide in methanol was added to a solution of the diacetate 27 (2.00 g, 6.88 mmol) in dry methanol (25 mL). The mixture was stirred for 3.5 h, neutralized with IRA-120 (H^+) resin, filtered and concentrated at room temperature. Flash chromatography of the residue over silica gel (4.5 x 16 cm) with 2:8 ethyl acetate—hexane gave the mercapto-alcohol 25 (1.20 g, 84%) as a homogeneous (TLC, silica gel, 2:8 ethyl acetate—hexane) oil which solidified on standing for several days. Compound 29 had: FT-IR (nujol) 3400, 1460 cm^{-1}; NMR ($CDCl_3$, 400 MHz) δ 0.93 (br t, J = 7.25 Hz, 3 H, $-CH_2\underline{CH}_3$), 1.3—2.08 (series of m, 6 H), 1.97 (d, J = 4.5 Hz, -S<u>H</u>), 2.85—4.1 (series of m, 7 H), 4.52 (q, J = 5.5, 6.5 Hz, 0.31 H, H-1 of β-isomer: collapsed to a doublet, J = 6.5 Hz on D_2O exchange), 5.27 (t, J = 3 Hz, 0.63 H, H-1 of α-isomer: collapsed to a doublet, J = 3 Hz on D_2O exchange); CMR ($CDCl_3$, 22.6 MHz) ppm 13.70 (q, $-CH_2\underline{C}H_3$), 19.14 (t, $-\underline{C}H_2CH_3$), 31.89, 32.16, 33.39 and 34.05 ($-\underline{C}H_2CH_2CH_3$ and C-4), 35.59 and 39.83 (d, C-3), 58.74 and 63.74 (t, C-5), 70.56 and 72.90 [t, C(2)-O-$\underline{C}H_2$-], 82.39 and 85.06 (d, C-2), 90.45 (d, C-1 of α-isomer), 98.64 (d, C-1 of β-isomer); exact mass 188.0870 [calcd for $C_9H_{16}O_2S$ (M - H_2O), 188.0871],

173.1176 [calcd for $C_9H_{17}O_3$ (M - SH), 173.1178].

Anal. Calcd for $C_9H_{18}O_3S$: C, 52.35; H, 8.71; S, 15.54.

Found: C, 52.53; H, 8.85; S, 15.53.

1,3-Anhydro-2-O-n-butyl-3,4-dieoxy-3-mercapto-β-DL-threo-pentopyranose (7-exo-n-Butoxy-2-oxa-6-thiabicyclo[3.1.1]-heptane) 31. The mercapto-alcohol 29 (0.182 g, 0.88 mmol) was dissolved in dry ether (20 mL) and the solution was cooled in an ice bath. A slow stream of nitrogen was passed over the solution and dry hydrogen chloride was passed through it with magnetic stirring. After an arbitrary period of 30 min, the reaction flask was tightly stoppered and the mixture was kept at 0 °C (refrigerator) for 2 days. The mixture was then allowed to attain room temperature, the stopper was replaced by a septum and excess of hydrogen chloride was removed with a stream of nitrogen. Dry benzene (10 mL) was injected and bubbling of nitrogen was continued for 30 min. Powdered 3A° molecular sieves (0.8 g) were added and passage of nitrogen was continued for 1 h with magnetic stirring. By using a syringe and a sintered funnel the mixture was filtered under nitrogen into a flask containing sodium hydride [0.81 g, 50% w/v in mineral oil, 17 mmol, washed with dry hexane (3 x 5 mL) in THF (15 mL)]. Quantitative transfer was achieved by using dry benzene (2 x 3 mL) as a rinse. The THF solution was refluxed for 1.5 h, cooled, filtered and evaporated. Flash chromatography over silica gel (1 x 10 cm) using 2:98 ether—hexane gave a colorless liquid which was diluted with benzene (10 mL) and

evaporated. The residue weighed 0.073 g, (44%) after being kept under oil-pump vacuum for 20 min. Trace impurities were detected by TLC (silica gel, 1:9 ethyl acetate—hexane) but a satisfactory analysis was obtained on this material. Compound 31 had: FT-IR (film) 1462, 1120 cm^{-1}; NMR ($CDCl_3$, 400 MHz) δ 0.93 (t, 3 H), 1.40 (m, 2 H), 1.60 (m, 2 H), 2.14 (m, 1 H), 2.61 (m, 1 H), 3.45 (m, 1 H), 3.52 (m, 1 H), 3.72 (m, 1 H), 3.99 (br q, 1 H) 4.31 (q, 1 H), 4.51 (m, 1 H), 5.54 (q, 1 H); CMR ($CDCl_3$, 50.32 MHz) ppm 13.78 (q), 19.28 (t), 25.84 (t), 31.75 (t), 48.54 (d), 60.23 (tq), 67.21 (t), 74.64 (d), 89.51 (dt); mass (chemical ionization, NH_3) 206 (M + 18), exact mass 126.1045 [calcd for $C_8H_{14}O$ (M - CH_2OS), 126.1046]. Anal. Calcd for $C_9H_{16}O_2S$: C, 57.40; H, 8.56; S, 17.03. Found: C, 57.63; H, 8.74; S, 16.92.

C. Total synthesis of optically active 9α,11α-thiathromboxane A_2 methyl ester 7.

1,6-Anhydro-4-deoxy-4-C-allyl-2-O-(4-methylphenylsulfonyl)-β-D-glucopyranose 34. Allyl magnesium chloride (∿ 2.5 M, THF solution, 175 mL, ∿ 6 equivalents) was added slowly to a stirred, cooled (0°C) mixture of 1,6:3,4-dianhydro-2-O-(4-methylphenylsulfonyl)-β-D-galactopyranose 33[35] (17.20 g, 57 mmol) and cuprous chloride (0.57 g, 5.7 mmol) in THF (75 mL). Stirring at 0°C was continued for 10 h by which stage the reaction was over (TLC control, silica gel, 1:1 ethyl acetate—hexane). The mixture was cooled to -20°C and acetic acid (22 mL) was injected slowly, followed by water (10 mL). The mixture was partitioned between dichloromethane (1 L) and water. The organic layer was washed with brine, dried and evaporated. Flash chromatography of the residue over silica gel (6 x 18 cm) with 3.5:6.5 ethyl acetate—hexane gave pure 34 as a white crystalline solid (14.55—15.90 g, 75—82%), homogeneous by TLC (silica gel, 1:1 ethyl acetate—hexane). The compound had: m.p. 70—71°C (lit.[36] 65—67°C); $[\alpha]_D^{23}$ - 58.4° (c, 0.9, chloroform) [lit.[36] -58° (c, 0.9, chloroform)]; IR ($CHCl_3$) 3595, 3500, 1360, 1197, 1182 cm^{-1}; NMR ($CDCl_3$, 400 MHz) δ 1.68 (m, J = 1, 2.5, 7.5 Hz, 1 H, H-4), 2.36 (m, 3 H, $-CH_2CH=CH_2$ and -OH), 2.40 (s, 3 H, $-CH_3$), 3.70 (m, 2 H, H-3

and H-6_{exo}), 4.02 (br d, J = 6.75 Hz, 1 H, H-6_{endo}), 4.18 (br t, J = 1.5 Hz, 1 H, H-2), 4.41 (br d, J = 5 Hz, 1 H, H-5), 5.12 (m, 2 H, -CH=C$\underline{H}_2$), 5.28 (br s, 1 H, H-1), 5.75 (m, 1 H, -C$\underline{H}$=CH_2), 7.36 (d) and 7.82 (d) (4 H, aromatic protons); CMR ($CDCl_3$, 50.3 MHz) ppm 21.62 (q, -$\underline{C}H_3$), 35.35 (t, -$\underline{C}H_2$-CH=CH_2), 43.08 (d, C-4), 68.22 (t, C-6), 69.81 (d, C-3), 74.27 (d, C-5), 78.80 (d, C-2), 99.63 (d, C-1), 117.91 (t, -CH=$\underline{C}H_2$), 127.89, 130.07, 133.27 and 145.35 (aromatic carbons), 135.51 (d, -$\underline{C}$H=CH_2); exact mass 185.0812 [calcd for $C_9H_{13}O_4$ (M - $C_7H_7SO_2$), 185.0814], 167.0706 (calcd for $C_9H_{11}O_3$ [M - ($C_6H_7SO_2$ + H_2O)], 167.0708).

1,6-Anhydro-4-C-allyl-3-O-benzoyl-2,4-dideoxy-β-D-arabino-hexopyranose 36. Lithium triethylborohydrode (150 mL, THF solution, ca. 4 equivalent) was added dropwise at room temperature to a solution (50 mL) of the hydroxy tosylate 34 (13.52 g, 37 mmol) in dry THF. The mixture was stirred overnight and the excess of reagent was destroyed by addition of water. A cold (0 °C) mixture of 30% hydrogen peroxide (80 mL) and sodium hydroxide (3 N, 100 mL) was added slowly with ice-bath cooling. The mixture was allowed to attain room temperature and was stirred for 3 h. It was then extracted with dichloromethane (5 x 100 mL). The extract was dried and concentrated. The residue was diluted with toluene (50 mL) and concentrated again in vacuo. The resulting oil was kept for 3 h under oil-pump vacuum to afford crude 1,6-anhydro-4-C-allyl-2,4-dideoxy-β-D-arabino-hexopyranose 35 (5.77 g) which was used directly for the next step.

Attempted distillation of a portion of the crude product resulted in decomposition (TLC control, silica gel, 1:1 ethyl acetate—hexane). For characterization, a sample was purified by flash chromatography over silica gel (1.5 x 15 cm) with 1:1 ethyl acetate—hexane). Compound 35 had: IR (film) 3440, 3080, 1640, 1130, 1050, 870 cm^{-1}; NMR ($CDCl_3$, 400 MHz) δ 1.85 (br d, J = 15 Hz, 1 H, H-2_{eq}), 1.90 (br t, 1 H, H-4), 2.06 (m, J = 1.5, 5,

15 Hz, 1 H, H-2_{ax}), 2.20 and 2.32 (two sets of m, 2 H, -$C\underline{H}_2CH=CH_2$), 2.85 (d, J = 7.5 Hz, 1 H, -O$\underline{H}$), 3.73 (m, 1 H, H-3: collapsed into a broad doublet with J = 5 Hz on D_2O exchange), 3.77 (q, J = 5, 7 Hz, H-6_{exo}), 4.32 (br d, J = 7 Hz, 1 H, H-6_{endo}), 4.41 (br d, J = 5 Hz, 1 H, H-5), 5.09 and 5.13 (two sets of m, 2 H, -CH=$C\underline{H}_2$), 5.60 (br s, 1 H, H-1), 5.82 (m, 1 H, -$C\underline{H}$=CH_2); CMR ($CDCl_3$, 50.3 MHz) ppm 35.50 (t) and 36.18 (t) (C-2 and -$\underline{C}H_2CH=CH_2$), 44.94 (d, C-4), 67.81 (d, C-3), 67.92 (t, C-6), 74.79 (d, C-5), 101.15 (d, C-1), 117.12 (t, -CH=$\underline{C}H_2$), 136.16 (d, -$\underline{C}H$=CH_2); mass (chemical ionization, NH_3) 188 (M + 18), 153 (MH - H_2O).

Benzoyl chloride (9.08 g, 7.5 mL, 64 mmol) was added dropwise to a solution of crude 35 (5.52 g) in dry pyridine (15 mL). The mixture was stirred overnight and the excess of reagent was destroyed by addition of water. The mixture was stirred at room temperature for 2 h and was extracted with dichloromethane (4 x 75 mL). The organic extract was washed with hydrochloric acid (2 N, 50 mL), saturated aqueous sodium bicarbonate solution (50 mL), water (50 mL), brine (50 mL), dried and evaporated. Flash chromatography of the residue over silica gel (5 x 18 cm) with 1:9 ethyl acetate—hexane gave 36 (7.33 g, 71% overall yield) as a homogeneous (TLC, silica gel, 1:9 ethyl acetate—hexane oil. Compound 36 had: $[\alpha]_D^{23}$ -121.6° (c, 1, $CHCl_3$); FT-IR (film) 1717,

1450, 1280, 1115, 1028, 715 cm^{-1}; NMR ($CDCl_3$, 400 MHz) δ 1.91 (br t, 1 H, H-4), 1.96 (br d, J = 15.5 Hz, 1 H, H-2_{eq}), 2.11 (m, J = 1.5, 5.25, 15.5 Hz, 1 H, H-2_{ax}), 2.42 (m, 2 H, -$\underline{CH_2}$CH=CH_2), 3.87 (q, J = 5.5, 7 Hz, 1 H, H-6_{exo}), 4.33 (d, J = 7 Hz, 1 H, H-6_{endo}), 4.45 (br d, J = 5.5 Hz, 1 H, H-5), 5.08 (br d, J = 5.25 Hz, 1 H, H-3), 5.17 (m, 2 H, -CH=$\underline{CH_2}$), 5.60 (br s, 1 H, H-1), 5.89 (m, 1 H, -$\underline{CH}$=CH_2), 7.44—8.1 (three sets of m, 5 H, aromatic protons); CMR ($CDCl_3$, 22.6 MHz) ppm 33.50 (C-2), 35.26 (-$\underline{C}H_2$CH=CH_2), 42.67 (C-4), 67.79 (C-6), 69.77 (C-3), 73.99 (C-5), 100.15 (C-1), 117.71 (-CH=$\underline{C}H_2$), 128.47, 129.60 and 133.04 (aromatic carbons), 135.52 (-$\underline{C}$H=CH_2), 165.87 (-OO$\underline{C}$Ph); exact mass 274.1203 (calcd for $C_{16}H_{18}O_4$, 274.1205). Anal. Calcd for $C_{16}H_{18}O_4$: C, 70.05; H, 6.61. Found: C, 69.86; H, 6.57.

1,6-Anhydro-4-C-(2-ethanal)-3-O-benzoyl-2,4-dideoxy-β-D-arabino-hexopyranose 37. A stream of ozone was passed into a cold (-78°C) solution of 36 (0.34 g, 1.2 mmol) in methanol (10 mL) until a blue coloration developed. Nitrogen was then passed through the solution for 10 min and then an excess of dimethyl sulfide (0.5 mL) was added. The mixture was allowed to stand at room temperature overnight and it was then concentrated. Flash chromatography of the residue over silica gel (1.5 x 15 cm) using 2:8 ethyl acetate—hexane gave 37 (0.3 g, 88%) as a white, homogeneous (TLC, silica gel, 3:7 ethyl acetate—hexane) solid. The compound had: m.p. 88—91°C; $[\alpha]_D^{23}$ - 118.2° (c 1, $CHCl_3$); IR ($CHCl_3$) 1717, 1710, 1600, 1115, 1017, 867 cm^{-1}; NMR ($CDCl_3$, 400 MHz) δ 2.00 (br d, J = 15.5 Hz, 1 H, H-2_{eq}), 2.10 (m, J = 2, 5.25, 15.5 Hz, 1 H, H-2_{ax}), 2.54 (br q, J = 5, 9 Hz, 1 H, H-4), 2.73 (m, J = 1, 5, 18 Hz, 1 H) and 3.11 (m, J = 1, 9, 18 Hz, 1 H) (-CH_2CHO), 3.89 (q, J = 6, 7 Hz, 1 H, H-6_{exo}), 4.40 (q, J = 1, 7 Hz, 1 H, H-6_{endo}); 4.45 (br d, J = 6 Hz, 1 H, H-5), 4.97 (m, 1 H, H-3), 5.61 (br s, 1 H, H-1), 7.48 (m, 2 H), 7.59 (m, 1 H) and 8.07 (m, 2 H) (aromatic protons), 9.89 (d, J = 1 Hz, 1 H, -CHO); CMR ($CDCl_3$, 100.6 MHz) ppm 33.69 (t, C-2), 37.52 (d, C-4), 44.70 (t, -CH_2CHO), 67.63 (t, C-6), 69.78 (d, C-3), 73.94 (d, C-5), 99.97 (d, C-1), 128.39, 129.49, 130.10 and 133.05

(aromatic carbons), 165.67 (s, -OOCPh), 199.63 (d, -CHO); exact mass 154.0629 [calcd for $C_8H_{10}O_3$ (M - $C_7H_6O_2$), 154.0630]; mass (chemical ionization, NH_3) 294 (M + 18). Anal. Calcd.for $C_{15}H_{16}O_5$: C, 65.20; H, 5.83. Found: C, 64.92; H, 5.95.

1,6-Anhydro-2,4-dideoxy-4-C-[6-(methoxycarbonyl)-2Z-hex-2-ene]-β-D-arabino-hexopyranose 38. (4-Carboxybutyl)triphenylphosphonium bromide (3.49 g, 7.8 mmol) was added in one lot to an ice-cold solution of potassium t-butoxide (1.76 g, 15.6 mmol) in dry THF (10 mL). The resulting dark red solution was stirred for 40 min at room temperature and then a solution (3 mL plus 0.5 mL as rinse) of the aldehyde 37 (0.540 g, 1.9 mmol) in dry THF was injected over 5 min. Stirring was continued for 45 min, the mixture was brought to pH 2 by addition of saturated aqueous sodium dihydrogen phosphate and then the solution was extracted with ether (4 x 75 mL). The ether layer was dried, concentrated, redissolved in ether (100 mL), filtered and concentrated. The resulting oil was evaporated from toluene (50 mL) and stirred for 48 h with sodium methoxide (0.75 g, 13.8 mmol) in dry methanol (10 mL). The solution was acidified with saturated aqueous sodium dihydrogen phosphate and extracted with ether (4 x 60 mL). The extract was dried, concentrated, dissolved in dichloromethane (10 mL) and was treated with an excess of diazomethane. Excess of reagent was destroyed by addition of small portions of silica gel and the solution was filtered. The filtrate was evaporated and flash chromatography of the residue over silica gel (3 x 14 cm) with 4:6 ethyl acetate—hexane gave 38 (0.348 g,

64% overall yield) as an apparently homogeneous (TLC, silica, 1:1 ethyl acetate—hexane) oil. The compound had: $[\alpha]_D^{23}$ - 61.2° (c 1, $CHCl_3$), IR (film) 3480, 1730, 1437, 1127, 1046, NMR ($CDCl_3$, 400 MHz) δ 1.71 (m, 2 H, $-C\underline{H}_2CH_2COOCH_3$), 1.83 (br t, J = 7.5 Hz, 1 H, H-4), 1.85 (br d, J = 15.5 Hz, 1 H, $H\text{-}2_{ax}$), 2.04 (m, J = 1.5, 5, 15.5 Hz, 1 H, $H\text{-}2_{eq}$), 2.12 (m, 3 H, $-C\underline{H}CH=CHC\underline{H}_2CH_2-$), 2.30 (m, 1 H, $-C\underline{H}CH=CHCH_2CH_2-$), 2.33 (t, J = 7 Hz, 2 H, $-C\underline{H}_2COOCH_3$), 2.86 (br d, J = 8 Hz, 1 H, $-O\underline{H}$), 3.67 (s, 3 H, $-COOC\underline{H}_3$), 3.70 (m, 1 H, H-3), 3.79 (q, J = 5, 7 Hz, 1 H, $H\text{-}6_{exo}$), 4.31 (d, J = 7 Hz, 1 H, $H\text{-}6_{endo}$), 4.37 (br d, J = 5 Hz, 1 H, C(5)-H), 5.47 (m, 2 H, $-C\underline{H}=C\underline{H}-$), 5.60 (br s, 1 H, H-1); CMR ($CDCl_3$, 100.6 MHz) ppm 24.72 (t, $-C\underline{H}_2CH_2COOCH_3$), 26.58 (t, $-\underline{C}H_2CH_2CH_2COOCH_3$), 28.81 (t, C(4)-$\underline{C}H_2CH=CH-$), 33.39 (t, $-\underline{C}H_2COOCH_3$), 36.19 (t, C-2), 45.63 (d, C-4), 51.36 (q, $-COO\underline{C}H_3$), 67.94 (t, C-6), 68.10 (d, C-3), 74.78 (d, C-5), 101.20 (d, C-1), 128.04 (d, C(4)-$CH_2\underline{C}H=CH-$), 131.10 (d, C(4)-$CH_2CH=\underline{C}H-$), 173.87 (s, $-\underline{C}OOCH_3$); mass (chemical ionization, NH_3) 288 (M + 18), 271 (MH), 253 (MH - H_2O); exact mass 252.1358 [calcd for $C_{14}H_{20}O_4$ (M - H_2O), 252.1362], 239.1282 [calcd for $C_{13}H_{19}O_4$, (M - OCH_3), 239.1283]. Anal. Calcd for $C_{14}H_{22}O_5$: C, 62.20; H, 8.20. Found: C, 62.44; H, 8.24.

1,6-Anhydro-2,4-dideoxy-3-O-methanesulfonyl-4-C-[6-(methoxycarbonyl)-2Z-hex-2-ene]-β-D-arabino-hexopyranose 41.

Methanesulfonyl chloride (0.178 g, 0.12 mL, 1.5 mmol) was added dropwise to a mixture of alcohol 38 (0.337 g, 1.2 mmol) and triethylamine (0.189 g, 0.26 mL, 1.86 mmol) in dry dichloromethane (5 mL). The mixture was stirred at room temperature for 15 min and was then diluted with dichloromethane (75 mL). The organic phase was washed with hydrochloric acid (2 N, 20 mL), saturated aqueous sodium bicarbonate (20 mL), water (1 x 20 mL), brine (20 mL), dried and evaporated. Flash chromatography of the residue over silica gel (2 x 12 cm) using 1:1 ether—hexane gave 41 (0.369 g, 85%) as an apparently homogeneous (TLC, silica gel, 1:1 ethyl acetate—hexane) oil. The compound had: $[\alpha]_D^{23}$ - 51.5° (c 1, $CHCl_3$); IR (film) 1730, 1436, 1340, 1170, 870 cm^{-1}; NMR ($CDCl_3$, 400 MHz) δ 1.71 (m, 2 H, $-C\underline{H}_2CH_2COOCH_3$), 2.01—2.14 (m, 5 H, HH-2, H-4, $-CH_2C\underline{H}_2CH=CH-$), 2.22—2.40 (m, 2 H, C(4)-$C\underline{H}_2CH=CH$), 2.33 (t, J = 7 Hz, 2 H, $-C\underline{H}_2COOCH_3$), 3.03 (s, 3 H, $-O_3SC\underline{H}_3$), 3.64 (s, 3 H, $-COOC\underline{H}_3$), 3.78 (q, J = 5.5, 7 Hz, 1 H, H-6_{exo}), 4.22 (d, J = 1, 7 Hz, 1 H, H-6_{endo}), 4.34 (br d, J = 5.5 Hz, 1 H, H-5), 4.72 (m, 1 H, H-3); 5.42—5.60 (two sets of m, 2 H, $-C\underline{H}=C\underline{H}-$), 5.54 (br s, 1 H, H-1); CMR ($CDCl_3$, 50.3 MHz) ppm 24.44 (t, $-\underline{C}H_2CH_2COOCH_3$), 26.38 (t, $-CH_2\underline{C}H_2CH=CH-$), 28.27 (t, C(4)-$\underline{C}H_2CH=CH-$),

33.12 (t, -$\underline{C}H_2COOCH_3$), 33.78 (t, C-2), 38.57 (q, $-O_3S\underline{C}H_3$), 43.55 (d, C-4), 51.17 (q, $-COO\underline{C}H_3$), 67.31 (t, C-6), 73.57 (d, C-5), 76.61 (d, C-3), 99.15 (d, C-1), 126.61 (d, C(4)-$CH_2\underline{C}H$=CH-), 131.87 (d, C(4)-CH_2CH=$\underline{C}H$-), 173.52 (-$\underline{C}OOCH_3$); mass (chemical ionization, NH_3) 366 (M + 18), 270 [(M + 18) -CH_3SO_3H].

Anal. Calcd for $C_{15}H_{24}O_7S$: C, 51.70; H, 6.90; S, 9.20.

Found: C, 51.46; H, 7.00; S, 8.93.

Synthesis of 42. A solution of mesylate 41 (0.572 g, 1.64 mmol) in absolute methanol (15 mL) was treated with dry Amberlite IRA-120 (H^+) resin (1.25 g). The mixture was stirred at room temperature for 60 h. The resin was removed by filtration and the filtrate was evaporated. Flash chromatography of the residue over silica gel (1.5 x 12 cm) using 4:6 ethyl acetate—hexane gave starting material 41 (0.032 g), followed by 42 (0.536 g, 90% yield, 95% conversion) as a mixture of α- and β-isomers (α/β ratio ca. 85:15, NMR). The α- and β-isomers were not seperable at this stage by column chromatography. The mixture was used for the next step without further purification. The spectral data for the α-isomer were obtained using this material. The compound had: IR (film) 3520, 1730, 1170 cm^{-1}; NMR ($CDCl_3$, 400 MHz) δ 1.69 (m, J = 7.5 Hz, 2 H, HH-3), 1.91 (m, 2 H, H-8 and $H\text{-}10_{ax}$), 1.99 (t, 1 H, J = 6 Hz, -OH), 2.09 (br q, 2 H, HH-4), 2.16—2.30 (m, 2 H, HH-7), 2.32 (t, J = 7.25 Hz, 2 H, HH-2), 2.41 (m, J = 1.5, 5, 12.5 Hz, 1 H, $H\text{-}10_{eq}$), 3.05 (s, 3 H, $-O_3SCH_3$), 3.33 (s, 3 H, $-OCH_3$), 3.68 (s, 3 H, $-COOCH_3$), 3.62—3.84 (m, 3 H, H-12 and HH-13), 4.86 (q, J = 1.5, 3.5 Hz, 1 H, H-11), 4.98 (m, J = 5, 11 Hz, 1 H, H-9), 5.49 (m, 2 H, -CH=CH-); CMR ($CDCl_3$, 50.3 MHz) ppm 24.48 (t) and 24.56 (t) (C-3 and C-7), 26.79 (t, C-4), 33.42 (t, C-2), 37.28 (t, C-10), 38.82 (q, $-O_3SCH_3$), 41.49 (d, C-8), 51.45 (q, $-COOCH_3$), 54.74 (q, $-OCH_3$), 62.98 (t, C-13), 71.57 (d, C-12),

77.35 (d, C-9), 98.19 (d, C-11), 126.00 (d, C-6), 131.09 (d, C-5), 173.87 (-$\underline{C}OOCH_3$); mass (chemical ionization, NH_3) 398 (M + 18), 366 [(M + 18) - CH_3OH].

Synthesis of 43. A solution containing 42 (0.51 g, 1.34 mmol) in dry dichloromethane (10 mL) was added rapidly to a solution of the Collins reagent prepared from chromium trioxide (1.46 g, 14.6 mmol) and dry pyridine (2.30 g, 2.36 mL, 29.3 mmol) in dichloromethane (90 mL). After being stirred vigorously for 1.5 h the mixture was partitioned between ice-water (50 mL) and dichloromethane (10 mL). The organic layer was washed with water (3 x 50 mL), brine (50 mL), dried and evaporated. The residue was dissolved in toluene (50 mL) and again evaporated. Flash chromatography over silica gel (1.5 x 15 cm) using 4:6 ethyl acetate—hexane gave the aldehyde 43 (0.38 g, 74%) as an apparently homogeneous (TLC, silica gel, 1:1 ethyl acetate—hexane) oil. The spectral data for the α-isomer were obtained using this material. The compound had: IR (film) 1735, 1440, 1355, 1175 cm^{-1}; NMR ($CDCl_3$, 400 MHz) δ 1.71 (m, J = 7.25 Hz, 2 H, HH-3), 1.98 (m, 2 H, H-8 and $H\text{-}10_{ax}$), 2.07 (m, 2 H, HH-4), 2.32 (t, J = 7.25 Hz, 2 H, HH-2), 2.32—2.4 (m, 3 H, HH-7 and $H\text{-}10_{eq}$), 3.05 (s, 3 H, $-O_3SCH_3$), 3.4 (s, 3 H, $-OCH_3$), 3.68 (s, 3 H, $-COOCH_3$), 4.02 (q, J = 1.5, 9.5 Hz, 1 H, H-12), 4.95 (t, 1 H, H-11), 5.03 (m, J = 5, 10 Hz, H-9), 5.40—5.55 (m, 2 H, H-5 and H-6), 9.48 (d, J = 1.5 Hz, 1 H, -CHO); CMR ($CDCl_3$, 50.3 MHz) ppm 24.21 (t) and 24.38 (t) (C-3 and C-7), 26.57 (t, C-4), 33.23 (t, C-2), 36.03 (t, C-10),

38.69 (q, $-O_3S\underline{C}H_3$), 40.66 (d, C-8), 51.27 (q, $-COO\underline{C}H_3$), 55.19 (q, $-O\underline{C}H_3$), 75.19 (d, C-12), 76.54 (d, C-9), 97.94 (d, C-11), 125.07 (d, C-6), 132.16 (d, C-5), 173.36 ($-\underline{C}OOCH_3$), 198,12 (d, $-\underline{C}HO$), mass chemical ionization, NH_3) 396 (M + 18).

Synthesis of 44 and 45. Dimethyl (2-oxoheptyl)-phosphonate (0.205 g, 0.19 mL, 0.92 mmol) was added dropwise and with stirring to a cold (0°C) suspension of potassium t-butoxide (0.103 g, 0.92 mmol) in toluene (10 mL). The mixture was stirred at room temperature for 1 h and then a solution (3 mL plus 1 mL rinse) of aldehyde 43 (0.28 g, 0.73 mmol) was added slowly. The solution was stirred for an additional 15 min and then it was diluted with ether (100 mL). The organic layer was washed with 10% aqueous sodium dihydrogen phosphate (20 mL), water (20 mL), brine (30 mL), dried and concentrated. Flash chromatography over silica gel (1.5 x 16 cm) using 2:8 ethyl acetate—hexane gave 44 (0.229 g, 66%), mixed fractions (0.0567 g, 16.7%) and 45 (0.0164 g, 4.7%) (total yield, 87%) in that order. Compound 44 had: $[\alpha]_D^{23}$ + 71° (c 1, $CHCl_3$); FT-IR (film) 2953, 2934, 1735, 1697, 1676, 1355, 1174, 1046, 939, 894 cm^{-1}; NMR ($CDCl_3$, 400 MHz) δ 0.90 (t, J = 7.0 Hz, 3 H, $-CH_2CH_3$), 1.31 (m, 4 H, HH-18 and HH-19), 1.58—1.82 (m, 5 H, HH-3, HH-17 and H-8), 1.95 (m, J = 4, 11, 12.5 Hz, 1 H, $H\text{-}10_{ax}$), 2.06 (br q, J = 7.25 Hz, 2 H, HH-4), 2.26 (m, 2 H, HH-7), 2.31 (t, J = 7.25 Hz, 2 H, HH-2), 2.44 (m, J = 1.5, 5, 12.5 Hz, 1 H, $H\text{-}10_{eq}$), 2.55 (t, J = 7.25 Hz, 2 H, HH-16), 3.03 (s, 3 H, $-O_3SCH_3$), 3.31 (s, 3 H, $-OCH_3$), 3.67 (s, 3 H, $-COOCH_3$), 4.20 (br q, J = 6, 10 Hz, 1 H, H-12), 4.87 (br d, J = 1.5, 4 Hz, 1 H,

H-11), 4.99 (m, J = 5, 10.5, 10.5 Hz, 1 H, H-9), 5.45 (m, 2 H, H-5 and H-6), 6.34 (q, J = 1, 16 Hz, 1 H, H-14), 6.75 (q, J = 6, 16 Hz, 1 H, H-13), CMR ($CDCl_3$, 100.6 MHz) ppm 13.89 (q, C-20), 22.46 (t, C-19), 23.69 (t), 24.58 (t) and 24.70 (t) (C-3, C-7 and C-17), 26.92 (t, C-4), 31.47 (t, C-18), 33.43 (t, C-2), 37.27 (t, C-10), 38.90 (q, $-O_3S\underline{C}H_3$), 40.67 (t, C-16), 46.08 (d, C-8), 51.41 (q, $-COO\underline{C}H_3$), 54.96 (q, $-O\underline{C}H_3$), 70.53 (d, C-12), 77.12 (d, C-9), 98.36 (d, C-11), 125.87 (d, C-6), 130.93 (d, C-14), 131.32 (d, C-5), 141.68 (d, C-13), 173.80 (s, C-1), 200.12 (s, C-15); mass (chemical ionization, NH_3) 492 (M + 18), 396 [(M + 18) - CH_3SO_3H], 364 [(M + 18) - (CH_3SO_3H + CH_3OH)]. Anal. Calcd for $C_{23}H_{38}O_8S$: C, 58.20; H, 8.07; S, 6.75. Found: C, 58.50; H, 8.19; S, 6.56.

Compound 45 had: $[\alpha]_D^{23}$ - 10° (c 1, $CHCl_3$); FT-IR (film) 2930, 1735, 1700, 1675, 1357, 1336, 1174, 1057, 932 cm^{-1}; NMR ($CDCl_3$, 360 MHz) δ 0.90 (t, J = 7.0 Hz, 3 H, $-CH_2\underline{C}H_3$), 1.32 (m, 4 H, HH-18 and HH-19), 1.63 (m, 2 H) and 1.71 (m, 3 H) (HH-17, HH-3 and H-8), 1.81 (m, 1 H, $H\text{-}10_{ax}$), 2.07 (br q, J = 7 Hz, 2 H, HH-4), 2.29 (m, 4 H, HH-7 and HH-2), 2.54 (m, J = 2, 5, 15 Hz, 1 H, $H\text{-}10_{eq}$), 2.55 (t, J = 7.25 Hz, 2 H, HH-16), 3.06 (s, 3 H, $-O_3S\underline{C}H_3$), 3.52 (s, 3 H, $-O\underline{C}H_3$), 3.68 (s, 3 H, $-COO\underline{C}H_3$), 3.88 (m, J = 1.25, 5.75, 10 Hz, 1 H, H-12), 4.41 (q, J = 2, 9.25 Hz, 1 H, H-11), 4.74 (m,

J = 5, 10.25 Hz, 1 H, H-9), 5.41 (m, 1 H) and 5.5 (m, 1 H) (H-5 and H-6), 6.37 (q, J = 1.25, 15.5 Hz, 1 H, H-14), 6.78 (q, J = 5.75, 15.5 Hz, 1 H, H-13); CMR ($CDCl_3$, 100.6 MHz) ppm 13.86 (C-20), 22.42 (C-19), 23.66, 24.20 and 24.53 (C-3, C-7 and C-17), 26.87 (C-4), 31.43 (C-18), 33.38 (C-2), 38.50 (C-10), 39.28 ($-O_3S\underline{C}H_3$), 40.76 (C-16), 45.59 (C-8), 51.41 ($-COO\underline{C}H_3$), 56.65 ($-O\underline{C}H_3$), 74.39 (C-12), 78.06 (C-9), 100.01 (C-11), 125.21 (C-6), 130.84 (C-13), 131.70 (C-5), 140.75 (C-13), 173.72 ($-\underline{C}OOCH_3$), 199.99 (C-15), mass (chemical ionization, NH_3) 492 (M + 18), 396 [(M + 18) - CH_3SO_3H], 364 [(M + 18) - (CH_3SO_3H + CH_3OH)]; exact mass 442.2023 [calcd for $C_{22}H_{34}O_7S$ (M - CH_3OH), 442.2026], 346.2146 (calcd for $C_{21}H_{30}O_4$ [M - (CH_3SO_3H + CH_3OH)], 346.2144), 317.2109 (calcd for $C_{20}H_{29}O_3$, 317.2117), 315.1960 (calcd for $C_{20}H_{27}O_3$ [M - (CH_3SO_3H + CH_3OH + CH_3O)], 315.1960).

Reduction of 44 and isolation of the "C(15)" diastereomeric alcohols 46 and 47. A solution of the enone 44 (57 mg, 0.12 mmol) in absolute methanol (1 mL plus 0.5 mL rinse) was added dropwise to a cold (-40°C) solution (3 mL) of sodium borohydride (17.3 mg, 0.45 mmol). The mixture was stirred for 1.5 h and excess of reagent was destroyed by addition of 10% aqueous sodium dihydrogen phosphate (3 mL). Most of the methanol was evaporated and the residue was extracted with ether (3 x 30 mL). The ether layer was washed with water (2 x 20 mL), brine (20 mL), dried and evaporated. Flash chromatography of the residue over silica gel (1 x 19 cm) using 3:7 ethyl acetate—benzene gave 47 (23 mg, 40%) as a homogeneous (Rf 0.38, TLC, silica gel, 1:1 ethyl acetate—hexane) oil and its "C(15)" epimer 46 (21 mg, 36%) as a homogeneous (Rf. 0.31, TLC, silica gel, 1:1 ethyl acetate—hexane) oil. Compound 47 had: $[\alpha]_D^{23}$ + 37.8° (c 1, $CHCl_3$); FT-IR (film) 3480, 2951, 2931, 1735, 1353, 1337, 1174, 1126, 1048, 972, 944, 894 cm^{-1}; NMR ($CDCl_3$, 400 MHz) δ 0.89 (t, J = 7.25 Hz, 3 H, $-CH_2\underline{CH}_3$), 1.25—1.37 (m, 6 H, HH-17, HH-18, HH-19), 1.47—1.59 (m, 2 H, HH-16), 1.62—1.76 (m, 3 H, H-8 and HH-3), 1.93 (m, J = 3.5, 11, 12.5 Hz, 1 H, $H\text{-}10_{ax}$), 2.05 (br q, 3 H, $-O\underline{H}$ and HH-4), 2.24 (br t, 2 H, HH-7), 2.32 (t, J = 7 Hz, 2 H, HH-2), 2.42 (m, J = 1.5, 5, 12.5 Hz, 1 H, $H\text{-}10_{eq}$), 3.01 (s, 3 H, $-O_3SC\underline{H}_3$), 3.29 (s, 3 H, $-OC\underline{H}_3$),

3.67 (s, 3 H, $-COOCH_3$), 4.01 (q, J = 7.6, 10.5 Hz, 1 H, H-12), 4.17 (m, 1 H, H-15), 4.83 (br d, J = 1.5, 3.5 Hz, 1 H, H-11), 4.99 (m, J = 5, 11, 11.25 Hz, 1 H, H-9), 5.42 (m, 2 H, H-5 and H-6), 5.65 (m, J = 1, 7.6, 15.25 Hz, 1 H, H-13), 5.79 (q, J = 6, 15.25 Hz, 1 H, H-14); CMR ($CDCl_3$, 100.6 MHz) ppm 13.86 (C-20), 22.56 (C-19), 24.57, 24.94 and 25.11 (C-3, C-7 and C-17), 26.88 (C-4), 31.72 (C-18), 33.40 (C-2), 37.13 and 37.36 (C-10 and C-16), 38.88 ($-O_3SCH_3$), 45.88 (C-8), 51.51 ($-COOCH_3$), 54.78 ($-OCH_3$), 71.80 (C-12), 72.01 (C-15), 77.80 (C-9), 98.22 (C-11), 126.26 (C-6), 127.54 (C-13), 130.64 (C-5), 138.25 (C-14), 174.28 ($-COOCH_3$); mass (chemical ionization, NH_3) 494 (M + 18), 36[illegible] - (CH_3SO_3H + H_2O)], 331 [MH - (CH_3SO_3H + H_2O + CH_3OH)]; exact mass 362.2460 (calcd for $C_{22}H_{34}O_4$ [M - (CH_3SO_3H + H_2O)], 362.2457), 330.2191 (calcd for $C_{21}H_{30}O_3$ [M - (CH_3SO_3H + H_2O + CH_3OH)], 330.2195).

Compound 46 had: $[\alpha]_D^{23}$ + 47° (c 1, $CHCl_3$); FT-IR (film) 3480, 2951, 2931, 1735, 1353, 1337, 1174, 1123, 1047, 940, 893 cm^{-1}; NMR ($CDCl_3$, 200 MHz) δ 0.89 (t, J = 7.25 Hz, 3 H, $-CH_2CH_3$), 1.20—1.40 (m, 6 H, HH-17, HH-18, HH-19), 1.46—1.58 (m, 2 H, HH-16), 1.60—1.77 (m, 3 H, HH-3, H-8), 1.79 (d, J = 5 Hz, 1 H, -OH), 1.93 (m, J = 3.5, 11, 12.5 Hz, 1 H, $H\text{-}10_{ax}$), 2.05 (br q, 2 H, HH-4), 2.24 (br t, 2 H, HH-7), 2.31 (t, J = 7 Hz, 2 H, HH-2), 2.42 (m, J = 1.5, 5, 12.5 Hz, 1 H, $H\text{-}10_{eq}$), 3.01 (s, 3 H,

$-O_3SCH_3$), 3.32 (s, 3 H, $-OCH_3$), 3.67 (s, 3 H, $-COOCH_3$), 4.04 (q, J = 7.6, 10.5 Hz, 1 H, H-12), 4.13 (m, 1 H, H-15), 4.83 (br d, J = 1.5, 3.5 Hz, 1 H, H-11), 4.98 (m, J = 5, 11, 11.25 Hz, 1 H, H-9), 5.44 (m, 2 H, H-5 and H-6), 5.66 (br q, J = 7.5, 15.5 Hz, 1 H, H-13), 5.84 (q, J = 5, 15.5 Hz, 1 H, H-14), CMR ($CDCl_3$, 100.6 MHz) ppm 13.94 (C-20), 22.55 (C-19), 24.58, 24.86 and 25.06 (C-3, C-7 and C-17), 26.86 (C-4), 31.71 (C-18), 33.42 (C-2), 37.08 and 37.33 (C-10 and C-16), 38.87 ($-O_3SCH_3$), 45.77 (C-8), 51.44 ($-COOCH_3$), 54.[illegible] ($-OCH_3$), 71.67 (C-12), 71.87 (C-15), 77.74 (C-9), 98.20 (C-11), 126.04 (C-6), 127.79 (C-13), 130.66 (C-5), 138.01 (C-14), 174.18 ($-COOCH_3$); mass (chemical ionization, NH_3) 494 (M + 18), 363 [MH - ($CH_3SO_3H + H_2O$)], 331 [MH - ($CH_3SO_3H + H_2O + CH_3OH$)]; exact mass 444.2156 [calcd for $C_{22}H_{36}O_7S$ (M - CH_3OH), 444.2182], 426.2067 (calcd for $C_{22}H_{34}O_6S$ [M - ($CH_3OH + H_2O$)], 426.2076), 362.2453 (calcd for $C_{22}H_{34}O_4$ [M - ($CH_3SO_3H + H_2O$)], 362.2457), 349.2370 (calcd for $C_{21}H_{33}O_4$ [M - ($CH_3SO_3H + CH_3O$)], 349.2379), 348.2298 (calcd for $C_{21}H_{32}O_4$ [M - ($CH_3SO_3H + CH_3OH$)], 348.2300), 330.2191 (calcd for $C_{21}H_{30}O_3$ [M - ($CH_3SO_3H + H_2O + CH_3OH$)], 330.2194), 299.2007 (calcd for $C_{20}H_{27}O_2$ [M - ($CH_3SO_3H + H_2O + CH_3OH + CH_3O$)], 299.2011), 291.1591 (calcd for $C_{17}H_{23}O_4$ [M - ($CH_3SO_3H + H_2O + C_5H_{11}$)], 291.1596), 221.1536 (calcd for $C_{14}H_{21}O_2$ [M - ($CH_3SO_3H + CH_3OH +$

$-CH=CH(CH_2)_3COOCH_3]]$, 221.1542).

Synthesis of "15-S" benzoate 48. Benzoyl chloride (0.05 mL, 0.4 mmol) was added to a solution of the alcohol 46 (12 mg, 0.025 mmol) and dry pyridine (0.075 mL, 0.9 mmol) in dry dichloromethane (1.5 mL). The solution was stirred at room temperature for 5 h. Most of the dichloromethane was evaporated and the residue was diluted with pyridine (0.5 mL) and water (0.5 mL). The mixture was allowed to stand for 2 h. The mixture was then extracted with ether (3 x 15 mL); the ether layer was washed with saturated aqueous sodium bicarbonate (2 x 10 mL), water (10 mL), brine (10 mL), dried and concentrated. The residue was diluted with toluene (10 mL) and was again evaporated. TLC of the residue over silica gel using 4:6 ethyl acetate—hexane gave 48 (13.5 mg, 92%) as a homogeneous (TLC, silica gel, 3:7 ethyl acetate—hexane) oil. The compound had: $[\alpha]_D^{23}$ + 40° (c 1, $CHCl_3$), FT-IR (film) 2930, 1735, 1718, 1450, 1355, 1272, 1175 cm^{-1}; NMR ($CDCl_3$, 400 MHz) δ 0.87 (t, J = 7.25 Hz, 3 H, $-CH_2\underline{CH_3}$), 1.27—1.35 (m, 6 H, HH-19, HH-18, HH-17), 1.57—1.84 (m, 5 H, HH-3, H-8, HH-16), 1.92 (m, J = 3.5, 11, 12.5 Hz, 1 H, H-10_{ax}), 2.02 (m, 2 H, HH-4), 2.13—2.25 (m, 2 H, HH-7), 2.28 (t, J = 7 Hz, 2 H, HH-2), 2.41 (m, J = 1.5, 5, 12.5 Hz, 1 H, H-10_{eq}), 2.99 (s, 3 H, $-O_3S\underline{CH_3}$), 3.31 (s, 3 H, $-O\underline{CH_3}$), 3.66 (s, 3 H, $-COO\underline{CH_3}$), 4.03 (q, J = 7.4, 10.5 Hz, 1 H, H-12), 4.82 (br d, J = 1.5, 3.5 Hz, 1 H, H-11), 4.97 (m, J = 5, 11, 11.25 Hz, 1 H, H-9),

5.4 (m, 2 H, H-5 and H-6), 5.55 (br, q, 1 H, H-15), 5.72 (m, J = 1, 7.4, 15.25 Hz, 1 H, H-13), 5.85 (q, J = 5.6, 15.25 Hz, 1 H, H-14), 7.42 (t, 2 H), 7.54 (t, 1 H) and 8.04 (q, 2 H) (aromatic protons); CMR ($CDCl_3$, 100.6 MHz) ppm 13.91 (C-20), 22.43 (C-19), 24.58, 24.66 and 24.82 (C-3, C-7 and C-17), 26.78 (C-4), 31.52 (C-18), 33.39 (C-2), 34.33 (C-16), 37.26 (C-10), 38.82 ($-O_3S\underline{C}H_3$), 45.75 (C-8), 51.37 ($-COO\underline{C}H_3$), 54.82 ($-O\underline{C}H_3$), 71.44 (C-12), 73.72 (C-15), 77.51 (C-9), 98.12 (C-11), 125.77 (C-6), 128.29, 129.38, 129.54, 130.83, 132.66, 132.83, 165.67 ($-OO\underline{C}Ph$), 173.74 ($-\underline{C}OOCH_3$). mass (chemical ionization, NH_3) 598 (M + 18); exact mass 549.2518 [calcd for $C_{29}H_{41}O_8S$ (M - CH_3O), 549.2512], 453.2621 (calcd for $C_{28}H_{37}O_5$ [M - (CH_3SO_3H + CH_3O)], 453.2641), 331.2246 (calcd for $C_{21}H_{31}O_3$ [M - (CH_3O + CH_3SO_3H + PhCOOH)], 331.2273), 330.2193 (calcd for $C_{21}H_{30}O_3$ [M - (CH_3OH + CH_3SO_3H + PhCOOH)], 330.2195).

Synthesis of "15-R" benzoate 49. Benzoyl chloride (0.05 mL, 0.4 mmol) was added to a solution of the alcohol 47 (13 mg, 0.027 mmol) and dry pyridine (0.075 mL, 0.9 mmol) in dry dichloromethane (1.5 mL). The solution was stirred at room temperature for 8 h. Most of the dichloromethane was evaporated and residue was diluted with pyridine (0.5 mL) and water (0.5 mL). The mixture was allowed to stand at room temperature for 2 h. The mixture was then extracted with ether (3 x 15 mL); the ether layer was washed with saturated aqueous sodium bicarbonate (2 x 10 mL), water (10 mL), brine (10 mL), dried and evaporated. The residue was diluted with toluene (15 mL) was again evaporated. TLC of the residue over silica gel using 4.5:6.5 ethyl acetate—hexane gave 49 (12.5 mg, 80%) as a homogeneous (TLC, silica gel, 3:7 ethyl acetate—hexane) oil. The compound had: $[\alpha]_D^{23}$ + 31.5° (c 1, $CHCl_3$); FT-IR (film) 2930, 1735, 1718, 1450, 1355, 1272, 1175 cm^{-1}; NMR ($CDCl_3$, 400 MHz) δ 0.87 (t, J = 7.25 Hz, 3 H, $-CH_2\underline{CH_3}$), 1.25—1.45 (m, 6 H, HH-17; HH-18 and HH-19), 1.5 (m, J = 7 Hz, 2 H, HH-3), 1.67—1.85 (m, 3 H, H-8 and HH-16), 1.92 (m, 3 H, HH-4 and $H\text{-}10_{ax}$), 2.15 (m, J = 7 Hz, 2 H, HH-2), 2.22 (m, 2 H, HH-7), 2.42 (m, J = 1.5, 5, 12.5 Hz, 1 H, $H\text{-}10_{eq}$), 2.99 (s, 3 H, $-O_3SC\underline{H_3}$), 3.31 (s, 3 H, $-OC\underline{H_3}$), 3.64 (m, 3 H, $-COOC\underline{H_3}$), 4.02 (q, J = 6.25, 11 Hz, 1 H, H-12),

4.82 (br d, J = 1.5, 3.5 Hz, 1 H, H-11), 4.92 (m, J = 5, 11, 11.25 Hz, 1 H, H-9), 5.32 (m, 1 H) and 5.42 (m, 1 H) (H-5 and H-6), 5.53 (br q, 1 H, H-15), 5.8 (m, 2 H, H-13 and H-14), 7.42 (t, 2 H), 7.54 (t, 1 H) and 8.04 (q, 2 H) (aromatic protons); CMR ($CDCl_3$, 50.3 MHz) δ 14.86 (C-20), 22.40 (C-19), 24.40, 24.62 and 24.77 (C-3, C-7 and C-17), 26.68 (C-4), 31.47 (C-18), 33.26 (C-2), 34.34 (C-16), 37.26 (C-10), 38.78 ($-O_3S\underline{C}H_3$) 45.74 (C-8), 51.32 ($-COO\underline{C}H_3$), 54.78 ($-O\underline{C}H_3$), 71.52 (C-12), 74.32 (C-15), 77.47 (C-9), 98.15 (C-11), 125.86 (C-6), 128.17, 128.29, 129.50, 130.50, 130.71, 132.59, 132.83, 165.67 ($-OO\underline{C}Ph$), 173.80 ($-\underline{C}OOCH_3$). mass (chemical ionization NH_3) 598 (M + 18); exact mass 549.2514 [calcd for $C_{29}H_{41}O_8S$ (M - CH_3O), 549.2524], 362.2461 (calcd for $C_{22}H_{34}O_4$ [M - (CH_3SO_3H + PhCOOH)], 362.2457), 330.2193 (calcd for $C_{21}H_{30}O_3$ [M - (CH_3OH + CH_3SO_3H + PhCOOH)], 330.2195).

D. Synthesis of diastereomeric 6-methyl glucose derivatives and epoxide ring opening of 32.

Methyl 2,3,4-tri-O-benzyl-α-D-glucopyranoside 54. Sodium hydride (50% w/w as an oil dispersion, 2.62 g, 54.4 mmol) was slowly added to a solution (30 mL) of methyl 6-O-trityl-α-D-glucopyranoside 52[77] (5.6 g, 12.8 mmol) in dry DMF. The mixture was stirred for 30 min and then benzyl bromide (8.8 g, 6.10 mL, 51.3 mmol) was added dropwise. The mixture was stirred for 1 h at room temperature and then it was diluted with methanol (10 mL). Stirring at room temperature was continued for 1 h and then the mixture was extracted with ether (400 mL). The organic layer was washed with water (3 x [redacted], brine (100 mL), dried and evaporated. The residue was dried at oil-pump vacuum to give crude methyl 2,3,4-tri-O-benzyl-6-O-trityl-α-D-glucopyranoside 53[78] (8.5 g) which was used in the next step without further purification.

Trifluoroacetic acid (90% in water, 10 mL) was added to a cooled (0 °C) solution of crude 53 (8.5 g, 12 mmol) in dichloromethane (85 mL). The mixture was stirred at 0 °C for 30 min and was then poured into ice-cold saturated aqueous sodium bicarbonate solution (100 mL). The mixture was extracted with dichloromethane (2 x 100 mL). The organic layer was washed with brine (100 mL), dried and evaporated. Flash chromatography

of the residue over silica gel (5 x 15 cm) with 3:7 ethyl acetate—hexane gave methyl 2,3,4-tri-O-benzyl-α-D-glucopyranoside 54 (4.98 g, 83%, two steps) as a thick syrup, which solidified on standing. The material was homogeneous by TLC (silica gel, 1:1 ethyl acetate—hexane). Compound 54 had: m.p. 63—65°C (lit.[78] 66.5—67°C); $[\alpha]_D^{23}$ + 23° (c 1, chloroform) (lit.[78] + 23.5°); NMR ($CDCl_3$, 400 MHz) δ 1.62 (br s, 1 H, -OH), 3.37 (s, 3 H, $-OCH_3$), 3.50 (q, J = 3.5, 9.5 Hz, 1 H, H-2), 3.53 (br t, J = 9 Hz, 1 H, H-4), 3.63—3.80 (m, 3 H, H-5, HH-6), 4.01 (br t, J = 9, 9.5 Hz, 1 H, H-3), 4.57 (d, J = 3.5 Hz, 1 H, H-1), 4.81—5.0 (three sets of AB q, 6 H, $-OCH_2Ph$), 7.32 (m, 15 H, aromatic protons); CMR ($CDCl_3$, 22.6 MHz) ppm 54.96 ($-OCH_3$), 61.40 (C-6), 70.90 (C-5), 73.10, 74.84, 75.52 (benzylic carbons), 77.44 (C-4), 80.04 (C-2), 81.83 (C-3), 97.99 (C-1), 127.43, 127.62, 127.78, 127.88, 128.30, 128.89, 138.14, 138.25, 138.77 (aromatic carbons).

Methyl 2,3,4-tri-O-benzyl-α-D-gluco-1,6-dialdo-hexopyranose

55. A solution of dimethyl sulfoxide (3.78 g, 3.43 mL, 48 mmol) in dichloromethane (10 mL) was added dropwise to a solution (30 mL) of oxalyl chloride (3.07 g, 2.11 mL, 24 mmol) at -60°C. The solution was stirred for 15 min and then a solution of methyl 2,3,4-tri-O-benzyl-α-D-gluco-pyranoside 54 (9.0 g, 19 mmol) in the same solvent (10 mL) was added slowly over 15 min. Stirring was continued for another 20 min and then triethylamine (13.72 g, 18.90 mL, 135 mmol) was added. The mixture was allowed to attain room temperature and was then diluted with dichloromethane (150 mL). The organic layer was washed with dilute hydrochloric acid (50 mL), saturated aqueous sodium bicarbonate (50 mL), water (2 x 50 mL), brine (2 x 50 mL), dried and evaporated. The residue 55 (8.25 g, 92%) was homogeneous by TLC (silica gel, 3:7 ethyl acetate—hexane) and was used for next step without further purification. The compound had: $[\alpha]_D^{23}$ + 19° (c 1, $CHCl_3$); IR (film) 1730, 1450, 1240, 1050 cm^{-1}; NMR ($CDCl_3$, 400 MHz) δ 3.37 (s, 3 H, $-OCH_3$), 3.50 (q, J = 3.25, 9.75 Hz, 1 H, H-2), 3.57 (q, J = 8.75, 10.5 Hz, 1 H, H-4), 4.08 (br t, J = 8.75, 9.75 Hz, 1 H, H-3), 4.16 (d, J = 10.5 Hz, 1 H, H-5), 4.63 (d, J = 3.25 Hz, 1 H, H-1), 4.61—5.01 (three sets of AB q, 6 H, $-OCH_2Ph$), 7.32 (m, 15 H, aromatic protons); 9.64 (s, 1 H, -CHO); CMR ($CDCl_3$, 22.6 MHz)

ppm 55.70 (-O<u>C</u>H$_3$), 73.53, 74.14, 75.04 and 75.87 (C-5 and -O<u>C</u>H$_2$Ph), 77.79 (C-4), 79.32 (C-2), 81.72 (C-3), 98.39 (C-1), 127.71, 127.94, 128.08, 128.46, 137.46, 137.85 and 138.44 (aromatic carbons), 197.32 (C-6); mass (chemical ionization, NH$_3$) 480 (M + 18).

Methyl (E)-2,3,4-tri-O-benzyl-6,7,9-trideoxy-α-D-gluco-non-6-enopyranosid-8-ulose 56. A solution of the aldehyde 55 (1.39 g, 3 mmol) in dichloromethane (5 mL) was added to a solution (15 mL) of 1-(triphenylphosphoranylidene)-2-propanone[80] (1.35 g, 3.7 mmol). The mixture was stirred for 24 h and then it was evaporated. Flash chromatography of the residue over silica gel (3 x 16 cm) using 1.5:8.5 ethyl acetate—hexane gave 56 (1.3 g, 86%) as a white homogeneous (TLC, silica gel, 3:7 ethyl acetate—hexane) solid. The compound had: m.p. 53—55 °C; $[\alpha]_D^{23}$ + 65° (c 1, $CHCl_3$); FT-IR ($CHCl_3$) 1698, 1677, 1630, 1452, 1370, 1250, 1090, 1070, 695 cm^{-1}; NMR ($CDCl_3$, 200 MHz) δ 2.18 (s, 3 H, $-COCH_3$); 3.26 (q, J = 9, 10 Hz, 1 H, H-4), 3.36 (s, 3 H, $-OCH_3$), 3.53 (q, J = 3.5, 9.5 Hz, 1 H, H-2), 4.05 (br t, J = 9.5 Hz, 1 H, H-3), 4.32 (m, J = 1.25, 5.0, 10 Hz, 1 H, H-5), 4.63 (d, J = 3.5 Hz, 1 H, H-1), 4.55—5.35 (three sets of AB q, 6 H, $-CH_2Ph$), 6.3 (q, J = 1.25, 16 Hz, 1 H, H-7), 6.75 (q, J = 5.0, 16 Hz, 1 H, H-6), 7.3 (m, 15 H, aromatic protons); CMR ($CDCl_3$, 22.6 MHz) ppm 27.17 (s, $-COCH_3$), 55.38 (q, $-OCH_3$), 69.21 (d, C-5), 73.44 (t), 75.26 (t), and 75.85 (t) ($-CH_2Ph$), 79.87 (d, C-2), 81.43 (d, C-4), 81.96 (d, C-3), 98.20 (d, C(1)), 127.70, 127.98, 128.09, 128.49, 129.47, 137.74, 138.05 and 138.63 (aromatic carbons), 130.77 (d, C-7), 142.54 (d, C-6), 197.92 (s, C-8);

mass chemical ionization, NH_3) 520 (M + 18), 488 [(M + 18) - CH_3OH]. Anal. Calcd for $C_{31}H_{34}O_6$: C, 74.07; H, 6.81. Found: C, 74.05; H, 6.80.

Methyl (6R)-2,3,4-tri-O-benzyl-6,7,9-trideoxy-6-C-methyl-α-D-gluco-nonopyranosid-8-ulose 58. Methyllithium (0.039 g, 1.3 mL, 1.4 M solution in ether containing ca. 22.5% lithium bromide, 1.77 mmol) was added to an ice-cold suspension of cuprous iodide (0.339 g, 1.77 mmol) in dry ether (15 mL). The resulting yellow suspension was cooled to -75°C and borontrifluoride etherate (0.253 g, 0.21 mL, 1.77 mmol) was added dropwise. The mixture was stirred for 10 min and a solution of the enone 56 (0.091 g, 0.18 mmol) in dry ether (5 mL) was added dropwise over 30 min. The mixture was allowed to warm up to -35°C over a period of 1.25 h and then it was diluted with saturated aqueous sodium bicarbonate (5 mL) and ether (50 mL). The mixture was filtered through Celite. The solids were washed with additional ether (25 mL). The organic layer was washed with saturated aqueous sodium bicarbonate (20 mL), water (25 mL), brine (25 mL), dried and evaporated. The ^{1}H-NMR and TLC (silica gel, 1:9 ethyl acetate—hexane) of the residue showed the presence of small amount (< 5%) of the isomer 57. Flash chromatography of the residue over silica gel (1.5 x 12 cm) using 1:9 ethyl acetate—hexane gave 58 (0.059 g, 62%) as a white homogeneous (TLC, silica gel, 1.5:8.5 ethyl acetate—hexane) solid. Compound 58 had: m.p. 90—92°C; $[\alpha]_D^{23}$ + 55° (c 1, $CHCl_3$);

IR ($CHCl_3$) 1715, 1500, 1460, 1365, 1080, 1055 cm^{-1}; NMR ($CDCl_3$, 400 MHz) δ 1.01 (d, J = 6.75 Hz, 3 H, C(6)-CH_3), 2.06 (s, 3 H, -$COCH_3$), 2.27 (q, J = 9.5, 17 Hz, 1 H, H-7), 2.35 (q, J = 3.5, 17 Hz, 1 H, H-7), 2.58 (m, 1 H, H-6), 3.26 (q, J = 9, 9.5 Hz, 1 H, H-4), 3.36 (s, 3 H, -OCH_3), 3.46 (q, J = 3.5, 9.25 Hz, 1 H, H-2), 3.56 (q, J = 1.5, 9.5 Hz, 1 H, H-5), 3.99 (br t, J = 9, 9.25 Hz, 1 H, H-3), 4.55 (d, J = 3.5 Hz, 1 H, H-1), 4.59—5.02 (three sets of AB q, 6 H, -CH_2Ph), 7.3 (m, 15 H, aromatic protons); CMR ($CDCl_3$, 50.3 MHz) ppm 17.97 [q, C(6)-CH_3], 28.15 (d, C-6), 30.47 (q, -$COCH_3$) 43.99 (t, C-7), 54.81 (q, -OCH_3), 73.38 (d, C-5), 73.10 (t), 74.65 (t) and 75.57 (t) (-CH_2Ph), 78.19 (d, C-4), 80.17 (d, C-2), 82.47 (d, C-3), 97.60 (d, C-1), 127.50, 127.83, 127.91, 128.33, 137.96, 138.11 and 138.67 (aromatic carbons), 207.81 (s, C-8); mass (chemical ionization, NH_3) 536 (M + 18). Anal. Calcd for $C_{32}H_{38}O_6$: C, 74.10; H, 7.30. Found: C, 73.94; H, 7.38.

Methyl (6S)-2,3,4-tri-O-benzyl-6,7,9-trideoxy-6-C-methyl-α-D-gluco-nonopyranosid-8-ulose 57 and Methyl (E)-2,3,4-tri-O-benzyl-6,7-dideoxy-8,8-dimethyl-α-D-gluco-oct-6-enopyranoside 59. HMPA (0.164 g, 0.16 mL, 0.92 mmol) was added dropwise to a solution of methyllithium (0.021 g, 0.6 mL, 1.6 M solution in ether containing ~ 22.5% lithium bromide, 0.96 mmol) in dry ether (4 mL) at -75°C. The resulting cloudy solution was stirred for 5 min and then a solution (5 mL) of the enone 56 was added over a period of 25 min. Stirring was continued for 5 min. The mixture was diluted with acetic acid (0.2 mL), allowed to attain room temperature and was extracted with ether (75 mL). The organic layer was washed with saturated aqueous sodium bicarbonate (20 mL), water (20 mL), brine (20 mL), dried and concentrated. Flash chromatography of the residue over silica gel (1.5 x 10 cm) with 1.5:8.5 ethyl acetate—hexane gave compounds 58 (0.008 g, 4%), 57 (0.105 g, 56%) and 59 (0.051 g, 27%) in that order of elution. Compound 58 was identified by m.p., TLC (silica gel, 1.5:8.5 ethyl acetate—hexane), ^{1}H-NMR and ^{13}C-NMR.

Compound 57 had: $[\alpha]_D^{23}$ + 41° (c 1, $CHCl_3$); IR (film) 1715, 1500, 1457, 1362, 1080, 1060 cm^{-1}; NMR ($CDCl_3$, 400 MHz) δ 0.88 (d, J = 6.5 Hz, 3 H, C(6)-CH_3), 2.10 (s, 3 H, -$COCH_3$), 2.46 (br d, 2 H, HH-7),

2.54 (m, 1 H, H-6), 3.36 (s, 3 H, $-OCH_3$), 3.39 (q, J = 9, 10 Hz, 1 H, H-4), 3.46 (q, J = 3.5, 9.5 Hz, 1 H, H-2), 3.54 (q, J = 1.5, 10 Hz, 1 H, H-5), 3.97 (br t, J = 9, 9.5 Hz, 1 H, H-3), 4.56 (d, J = 3.5 Hz, 1 H, H-1), 4.65—4.98 (three sets of AB q, 6 H, $-CH_2Ph$), 7.3 (m, 15 H, aromatic protons); CMR ($CDCl_3$, 100.6 MHz) ppm 12.70 [q, C(6)-CH_3], 28.32 (d, C-6), 30.03 (q, $-COCH_3$), 48.70 (t, C-7), 55.12 (q, $-OCH_3$), 72.35 (d, C-5), 73.28 (t), 74.70 (t) and 75.71 (t) ($-CH_2Ph$), 78.46 (d, C-4), 80.35 (d, C-2), 82.37 (d, C-3), 98.04 (d, C-1), 127.59, 127.72, 127.86, 128.00, 128.09, 128.26, 128.41, 128.45, 138.32 and 138.34 (aromatic carbons), 207.74 (C-8); mass (chemical ionization, NH_3) 536 (M + 18).

Anal. Calcd for $C_{32}H_{38}O_6$: C, 74.10; H, 7.38.
Found: C, 73.82; H, 7.36.

Compound 59 had: $[\alpha]_D^{23}$ + 20° (c 1, $CHCl_3$); IR (film) 3440, 1497, 1452, 1360, 1070, 740 cm^{-1}; NMR ($CDCl_3$, 400 MHz) δ 1.26 [s, 6 H, C(8)$(CH_3)_2$] 1.56 (br s, 1 H, -OH), 3.25 (br t, J = 9, 9.5 Hz, 1 H, H-4), 3.38 (s, 3 H, $-OCH_3$), 3.57 (q, J = 3.5, 9.5 Hz, 1 H, H-2), 4.00 (br t, J = 9, 9.5 Hz, 1 H, H-3), 4.08 (q, J = 7, 9.5 Hz, 1 H, H-5), 4.60—4.98 (three sets of AB q, 6 H, $-CH_2Ph$), 5.64 (q, J = 7, 15.5 Hz, 1 H, H-6), 5.96 (d, J = 15.5 Hz, 1 H, H-7), 7.30 (m, 15 H, aromatic protons); CMR ($CDCl_3$, 22.6 MHz) ppm 29.36 and 29.63 [C(8)$(CH_3)_2$], 55.23 ($-OCH_3$), 70.38 (C-8), 70.83 (C-5),

73.36, 74.98 and 75.58 ($-CH_2Ph$), 79.86 (C-2), 81.67 (C-4), 82.21 (C-3), 98.08 (C-1), 123.8 (C-6), 127.58, 127.70, 127.96, 128.35, 138.11, 138.22 and 138.74 (aromatic carbons), 141.93 (C-7); mass (chemical ionization, NH_3) 536 (M + 18), 504 [(M + 18) - CH_3OH], 414 [(M + 18) - (CH_3OH + $PhCH_2OH$)]; exact mass 427.2124 (calcd for $C_{25}H_{31}O_6$, 427.2127), 395.1857 (calcd for $C_{24}H_{27}O_5$ [M - ($PhCH_2$ + CH_3OH)], 395.1858).

(E)-1,2:3,4-Di-O-isopropylidene-α-D-galacto-non-6-enopyranos-8-ulose 56gal. A solution of 1,2:3,4-di-O-isopropylidene-α-D-galacto-1,6-dialdo-hexopyranose[41] (55gal) (2.0 g, 7.74 mmol) and 1-(triphenyl phosphoranylidene)-2-propanone (3.66 g, 11.6 mmol) in dichloromethane (20 mL) was refluxed for 3 h. The mixture was evaporated. Flash chromatography of the residue over silica gel (4 x 18 cm) using 2:8 ethyl acetate—hexane gave 56gal (1.712 g, 74%) after crystallization from ether—hexane. The compound had: m.p. 123—124 °C; $[\alpha]_D^{23}$ = - 129.6° (c 1, $CHCl_3$); FT-IR ($CHCl_3$) 1670, 1255, 1212, 1069, 973 cm^{-1}; NMR ($CDCl_3$, 200 MHz) δ 1.33 (s, 3 H, $-CH_3$), 1.35 (s, 3 H, $-CH_3$), 1.44 (s, 3 H, $-CH_3$), 1.52 (s, 3 H, $-CH_3$), 2.30 (s, 3 H, HHH-9), 4.30 (q, J = 2, 8.0 Hz, 1 H, H-4), 4.37 (q, J = 2.5, 5 Hz, 1 H, H-2), 4.48 (m, 1 H, H-5), 4.66 (q, J = 2.5, 8 Hz, 1 H, H-3), 5.60 (d, J = 5 Hz, 1 H, H-1), 6.36 (q, J = 1.75, 16 Hz, 1 H, H-7), 6.76 (q, J = 4.75, 16 Hz, 1 H, H-6); CMR ($CDCl_3$, 22.6 MHz) ppm 24.38, 24.83, 25.88 and 26.08 (isopropylidene methyl carbons), 27.24 (C-9), 67.66 (C-5), 70.46, 70.86 and 72.75 (C-2, C-3 and C-4), 96.39 (C-1), 108.68 and 109.65 (isopropylidene carbons), 131.28 (C-6), 141.76 (C-7), 197.85 (C-8); mass (chemical ionization, NH_3) 316 (M + 18). Anal. Calcd for $C_{15}H_{22}O_6$: C, 60.38; H, 7.43. Found: C, 60.05; H, 7.49.

(6R)-1,2:3,4-Di-O-isopropylidene-6,7,9-trideoxy-6-C-methyl-α-D-galacto-nonopyranos-8-ulose 58gal. Methyllithium (0.186 g, 8.45 mL, 1.0 M solution in ether containing ca. 22.5% lithium bromide, 8.46 mmol) was added to an ice-cold suspension of cuprous iodide (0.806 g, 4.23 mmol) in dry ether (7 mL). The resulting clear solution was cooled to -75°C and a solution of the enone 56gal (0.178 g, 0.59 mmol) in dry ether (4 mL) was added dropwise over 15 min. The mixture was stirred at -75°C for 15 mins and then it was allowed to warm to -40°C. The reaction mixture was stirred for 20 min and then it was diluted with saturated aqueous ammonium chloride (5 mL) and ether (75 mL). The mixture was filtered through Celite. The solids were washed with additional ether (50 mL). The organic layer was washed with saturated aqueous sodium bicarbonate (30 mL), water (30 mL), brine (30 mL), dried and evaporated. Flash chromatography of the residue over silica gel (1.5 x 12 cm) using 2:8 ethyl acetate—hexane gave a mixture of 58gal and 57gal (0.159 g, 84%) in the ratio 7:3 (^{1}H-NMR). Flash chromatography of the product over silica gel (1.5 x 20 cm) using 3% ethyl acetate in 1,2-dichloroethane gave compound 57gal (0.024 g, 13%), a mixture of 57gal and 58gal (0.045 g, 24%) and compound 58gal (0.075 g, 40%) in that order of elution. Compound 57gal was identified by TLC (silica gel, 1:9 ethyl acetate—1,2-dichloroethane), ^{1}H-NMR and ^{13}C-NMR. The compound 58gal had: $[\alpha]_D^{23} = -81.3^\circ$ (c 1, $CHCl_3$);

IR ($CHCl_3$) 1710, 1380, 1070 cm^{-1}; NMR ($CDCl_3$, 200 MHz) δ 1.02 (d, J = 6.5 Hz, 3 H, 6-$\underline{CH}_3$), 1.34 (s, 3 H), 1.36 (s, 3 H), 1.47 (s, 3 H), 1.53 (s, 3 H), 2.15 (s, 3 H, -COO$\underline{CH}_3$), 2.21 (q, J = 8, 15.5 Hz, 1 H, H-7) 2.40 (m, 1 H, H-6), 2.86 (q, J = 4, 15.5 Hz, 1 H, H-7), 3.43 (q, J = 1.5, 9.25 Hz, 1 H, H-5), 4.29 (m, 2 H, H-2 and H-4), 4.60 (q, J = 2, .8 Hz, 1 H, H-3), 5.51 (d, J = 5 Hz, 1 H, H-1); CMR ($CDCl_3$, 100 MHz) ppm 16.06 (6-$\underline{CH}_3$), 24.47, 24.94, 25.95 and 26.00 (isopropylidene methyl carbons), 30.03 and 30.39 (C-6 and C-9), 47.38 (C-7), 70.67, 70.97, 71.14 and 71.17 (C-2, C-3, C-4 and C-5), 96.64 (C-1), 108.41, 109.13, 208.65 (C-8); exact mass 314.1722 (calcd for $C_{16}H_{26}O_6$, 314.1730), 299.1494 [calcd for (M - CH_3), 299.1494].

(6S)-1,2:3,4-Di-O-isopropylidene-6,7,9-trideoxy-6-C-methyl-α-D-galacto-nonopyranos-8-ulose 57gal and (E)-1,2:3,4-Di-O-isopropylidene-isopropylidene-6,7-dideoxy-8,8-dimethyl-α-D-galacto-oct-6-enopyranose 59gal. HMPA (0.206 g, 0.2 mL, 1.15 mmol) was added dropwise to a solution of methyllithium (0.027 g, 1.22 mL, 1.01 M solution in ether containing ca. 22.5% lithium bromide, 1.23 mmol) in dry ether (6 mL) at -75°C. The resulting cloudy solution was stirred for 5 min and then a solution (2 mL) of the enone 56gal was added over a period of 7 min. Stirring was continued for 15 min. The mixture was diluted with acetic acid (0.3 mL), allowed to to attain room temperature and extracted with ether (100 mL). The organic layer was washed with saturated aqueous sodium bicarbonate (30 mL), water (30 mL), brine (30 mL), dried and concentrated. The ^{1}H-NMR and TLC (silica gel, 1:9 ethyl acetate—1,2-dichloroethane) of the residue showed the presence of small amount (< 5%) of the isomer 58gal. Flash chromatography of the residue over silica gel (2 x 14 cm) with 2:8 ethyl acetate—hexane gave compounds 57gal (0.048 g, 32%) and 59gal (0.074 g, 47%) in that order of elution.

Compound 57gal had: $[\alpha]_D^{23} = -40.2°$ (c 1, $CHCl_3$); FT-IR (film) 1714, 1372, 1255, 1211, 1068, 999 cm^{-1}; NMR ($CDCl_3$, 400 MHz) δ 1.04 (d, J = 6.5 Hz, 3 H, 6-CH_3), 1.33 (s, 6 H, -CH_3), 1.45 (s, 3 H, -CH_3), 1.51 (s, 3 H, -CH_3), 2.15 (s, 3 H, -$COCH_3$), 2.33 (m, 2 H, H-6 and H-7), 2.71 (q, J = 7.5, 19 Hz, 1 H, H-7),

3.57 (q, J = 2.0, 7 Hz, 1 H, H-5), 4.23 (q, J = 2, 8 Hz, 1 H, H-4), 4.29 (q, J = 2.25, 5 Hz, 1 H, H-2), 4.57 (q, J = 2.25, 8 Hz, 1 H, H-3), 5.54 (d, J = 5 Hz, 1 H, H-1); CMR ($CDCl_3$, 100.6 MHz) ppm 16.36 (6 - $\underline{C}H_3$), 24.41, 24.96, 25.93 and 25.97 (isopropylidene methyl carbons), 30.16 and 30.56 (C-6 and C-9), 46.88 (C-7), 70.30, 70.61, 71.11 and 71.66 (C-2, C-3, C-4 and C-5), 96.75 (C-1), 108.37, 109.11, 208.41 (C-8); mass (chemical ionization, NH_3) 332 (M + 18), 315 (M + 1), 299 (M - CH_3). Anal. Calcd for $C_{16}H_{26}O_6$: C, 61.12; H, 8.33. Found: C, 61.50; H, 8.43.

Compound 59gal had: $[\alpha]_D^{23} = -101.4^\circ$ (c 1, $CHCl_3$); FT-IR (film) 3425, 1382, 1212, 1068, 996 cm^{-1}; NMR ($CDCl_3$, 400 MHz) δ 1.34 (s, 12 H), 1.46 (s, 3 H, -$\underline{C}H_3$), 1.55 (s, 3 H, -$\underline{C}H_3$), 1.58 (br s, 1 H, -$\underline{O}H$), 4.17 (q, J = 2, 8 Hz, 1 H, H-4), 4.27 (br d, J = 6.5 Hz, 1 H, H-5), 4.31 (q, J = 2.25, 5 Hz, 1 H, H-2), 4.60 (q, J = 2.25, 8 Hz, 1 H, H-3), 5.57 (d, J = 5 Hz, 1 H, H-1), 5.78 (q, J = 6.5, 15.5 Hz, 1 H, H-6), 5.95 (q, J = 1, 15.5 Hz, 1 H, H-7); CMR ($CDCL_3$, 100.6 MHz) ppm 24.39, 24.86, 25.92, 26.07 (isopropylidene methyl carbons), 29.40 [8-$(CH_3)_2$], 68.58 (C-5), 70.32, 70.81 and 73.44 (C-2, C-3 and C-4), 70.52 (C-8), 96.43 (C-1), 108.42, 109.19, 122.44 (C-6), 141.50 (C-7); mass (chemical ionization, NH_3) 332 (M + 18), 314 [(M + 18) - H_2O]. Anal. Calcd for $C_{16}H_{26}O_6$: C, 61.12; H, 8.33. Found: C, 60.94; H, 8.18.

1,6-Anhydro-4-deoxy-4-C-methyl-2-O-(4-methylphenylsulfonyl)-β-D-glucopyranose 62. Methylmagnesium chloride

(THF solution, 2 mL, ca. 7 equivalents) was added slowly to a stirred mixture of 1,6:3,4-dianhydro-2-O-(4-methylphenylsulfonyl)-β-D-galactopyranose 33 (0.24 g, 0.8 mmol) and cuprous chloride (8.9 mg, 0.09 mmol) in dry THF (5 mL). Stirring at room temperature was continued for 3 h by which stage the reaction was over (TLC control, silica gel, 1:1 ethyl acetate—hexane). The mixture was cooled to 0 °C and acetic acid (0.4 mL) was injected slowly, followed by water (1 mL). The mixture was extracted with dichloromethane (4 x 30 mL). The organic layer was washed with water (30 mL), brine (30 mL), dried and evaporated. Flash chromatography of the residue over silica gel (1.5 x 12.5 cm) with 1:1 ethyl acetate—hexane gave 62 as a crystalline solid (0.126—0.147 g, 50—58%) homogeneous by TLC (silica gel, 1:1 ethyl acetate—hexane). The compound had: m.p. 91—93 °C; $[\alpha]_D^{23}$ - 48.5° (c 1, chloroform); FT-IR (CCl_4) 3535, 3395, 1595, 1357, 1175, 1027, 955 cm^{-1}; NMR ($CDCl_3$, 400 MHz) δ 1.23 (d, J = 7.0 Hz, 3 H, $-CH_3$), 1.79 (br q, 1 H, H-4), 2.44 (d, J = 6 Hz, 1 H, -OH), 2.46 (s, 3 H, Ar-CH_3), 3.62 (m, 1 H, H-3), 3.70 (q, J = 5, 7 Hz, 1 H, $H\text{-}6_{exo}$), 4.06 (d, J = 7 Hz, 1 H, $H\text{-}6_{endo}$), 4.20 (br t, 1 H, H-2), 4.29 (br d, J = 5 Hz, 1 H, H-5), 5.28 (br s, 1 H, H-1), 7.38 (d, 2 H) and 7.82 (d, 2 H)

(aromatic protons); CMR ($CDCl_3$, 22.6 MHz) ppm 17.47 ($-\underline{C}H_3$), 21.70 ($Ar-\underline{C}H_3$), 38.63 (C-4), 68.34 (C-6), 71.92 (C-3), 76.66 (C-5), 78.74 (C-2), 99.70 (C-1), 127.93 and 130.08 (aromatic carbons); mass (chemical ionization, NH_3) 332 (M + 18). Anal. Calcd for $C_{14}H_{18}O_6S$: C, 53.48; H, 5.77; S, 10.20. Found: C, 53.56; H, 5.94; S, 10.04.

1,6-Anhydro-4-deoxy-4-C-ethyl-2-O-(4-methylphenylsulfonyl)-β-D-glucopyranose 63. Triethylaluminium (52.56 mL, 25% w/v in toluene, 76 mmol) was added to a solution of 1,6:3,4-dianhydro-2-O-(4-methylphenylsulfonyl)-β-D-galactopyranose 33[35] (9.81 g, 32.8 mmol) in dry benzene (80 mL). The solution was stirred for 5 min and then n-butyllithium (0.08 g, 1 mL, 1.25 M solution in hexane, 1.24 mmol) was added. The mixture was stirred for 5 h; then it was cooled to -40°C and aqueous methanol (55 mL, 10% v/v) was added slowly with vigorous stirring, followed by slow addition of dilute hydrochloric acid (5%, 125 mL). The mixture was extracted with ether (3 x 125 mL). The organic extract was washed with saturated aqueous sodium bicarbonate (100 mL), water (100 mL), brine (100 mL), dried and evaporated. Flash chromatography of the residue over silica gel (7 x 20 cm) using 3:7 ethyl acetate—hexane gave epoxide 65 (0.128 g, 2.5%) as a thin liquid and 63 (9.71 g, 90%) as a white crystalline homogeneous (TLC, silica gel, 3:7 ethyl acetate—hexane) solid. The epoxide 65 was identified by TLC (silica gel, 1:9 ethyl acetate—hexane), ^{1}H-NMR and ^{13}C-NMR.

Compound 63 had: m.p. 67—68°C; $[\alpha]_D^{23}$ + 49.2° (c 1, $CHCl_3$); FT-IR (CCl_4) 3607, 3570, 3540, 2960, 1600, 1377, 1190, 1180, 995, 980 cm^{-1}; NMR ($CDCl_3$, 400 MHz) δ 0.99 (t, J = 7.25 Hz, 3 H, $-CH_2\underline{CH_3}$), 1.50 (br t, 1 H, H-4),

1.66 (m, 2 H, $-C\underline{H}_2CH_3$), 2.28 (s, 3 H, $-C\underline{H}_3$), 2.29 (br s, 1 H, O<u>H</u>), 3.94 (br s, 1 H, H-3), 3.97 (q, J = 5, 7 Hz, 1 H, $H\text{-}6_{exo}$), 4.03 (d, J = 7 Hz, 1 H, $H\text{-}6_{endo}$), 4.21 (br t, 1 H, H-2), 4.43 (br d, J = 5 Hz, 1 H, H-5), 5.28 (br s, 1 H, H-1), 7.36 (d, 2 H) and 7.82 (d, 2 H) (aromatic protons); CMR ($CDCl_3$, 22.6 MHz) ppm 11.69 ($-CH_2\underline{C}H_3$), 21.68 ($Ar\text{-}\underline{C}H_3$) 24.12 ($-\underline{C}H_2CH_3$), 45.54 (C-4), 68.53 (C-6), 70.44 (C-3), 74.44 (C-5), 79.33 (C-2), 99.87 (C-1), 127.98, 130.13, 133.42 and 145.38 (aromatic carbons); mass (chemical ionization, NH_3) ppm 346 (M + 18). Anal. Calcd for $C_{15}H_{20}O_6S$: C, 54.86; H, 6.13; S, 9.76. Found: C, 54.91; H, 6.18; S, 9.79.

1,6:2,3-Dianhydro-4-deoxy-4-C-ethyl-β-D-mannopyranose 65.

A solution (12% w/v, 22 mL) of sodium methoxide in methanol was added to a solution of 63 (6.41 g, 19.5 mmol) in dry chloroform (50 mL). The mixture was stirred overnight at room temperature and was then diluted with dichloromethane (300 mL). The organic layer was washed with water (3 x 75 mL), brine (100 mL), dried and evaporated. Flash chromatography of the residue over silica gel (4 x 13 cm) using 2:8 ether—hexane gave epoxide 65 (2.86 g, 93%) as a colorless homogeneous (TLC, silica gel, 1.5:8.5 ethyl acetate—hexane) liquid. The compound had: $[\alpha]_D^{23}$ - 28.7° (c 1, $CHCl_3$); FT-IR (film) 2965, 1462, 1158, 1130, 975 cm^{-1}, NMR ($CDCl_3$, 400 MHz) δ 1.1 (t, J = 7.25 Hz, 3 H, $-CH_2\underline{C}H_3$), 1.64 (m, 2 H, $-\underline{C}H_2CH_3$), 1.86 (br t, J = 7 Hz, 1 H, H-4), 2.97 (q, J = 1, 4 Hz, 1 H, H-3), 3.39 (m, J = 0.5, 3, 4 Hz, 1 H, H-2), 3.75 (d, J = 4 Hz, 2 H, HH-6), 4.26 (br t, J = 4 Hz, 1 H, H-5), 5.67 (q, J = 0.5, 3 Hz, 1 H, H-1); CMR ($CDCl_3$, 22.6 MHz) ppm 11.90 ($-CH_2\underline{C}H_3$), 23.86 ($-\underline{C}H_2CH_3$), 41.34 (C-4), 50.63 (C-3), 53.88 (C-2), 68.64 (C-6), 71.32 (C-5), 98.02 (C-1); exact mass 110.0731 [calcd for $C_7H_{10}O_1$ (M - CH_2O_2), 110.0731]. Anal. Calcd for $C_8H_{12}O_3$: C, 61.51; H, 7.74. Found: C, 61.66; H, 7.69.

1,6-Anhydro-2,4-dideoxy-4-C-ethyl-β-D-arabino-hexopyranose

64. Lithium triethylborohydride (6.22 mL, ca. 4 equivalent) was added dropwise at room temperature to a solution (5 mL) of the hydroxy tosylate 63 (0.51 g, 1.55 mmol) in dry THF. The mixture was stirred overnight and excess of reagent was destroyed by addition of water. A cold (0 °C) mixture of 30% hydrogen peroxide (10 mL) and sodium hydroxide (3 N, 12 mL) was added slowly with ice-bath cooling. The mixture was allowed to attain room temperature and was stirred for 3 h. It was then extracted with dichloromethane (4 x 40 mL). The extract was washed with water (20 mL), brine (20 mL), dried and evaporated. The residue was diluted with toluene (25 mL) and concentrated again in vacuo. The resulting oil was kept for 3 h under oil-pump vacuum to afford 64 (0.234 g, 95%) which was used directly for the next step. The compound had: $[\alpha]_D^{23}$ - 69° (c 1, $CHCl_3$); IR (film) 3460, 1462, 1140, 1050, 870 cm^{-1}; NMR ($CDCl_3$, 360 MHz) δ 0.90 (t, J = 7.25 Hz, 3 H, $-CH_2\underline{CH_3}$), 1.4—1.65 (m, 2 H, $-\underline{CH_2}CH_3$), 1.68 (br t, J = 7 Hz, 1 H, H-4), 1.82 (br d, J = 15 Hz, 1 H, $H\text{-}2_{eq}$), 2.02 (m, J = 1.25, 5, 15 Hz, 1 H, $H\text{-}2_{ax}$), 2.95 (d, J = 7 Hz, 1 H, $-\underline{OH}$), 3.72 (br t, 1 H, H-3), 3.77 (q, J = 5, 7 Hz, 1 H, $H\text{-}6_{exo}$), 4.34 (d, J = 7 Hz, 1 H, $H\text{-}6_{endo}$), 4.44 (br d, J = 5 Hz, 1 H, H-5), 5.59 (br s, 1 H, H-1); CMR ($CDCl_3$, 100.6 MHz) ppm 12.20 ($-CH_2\underline{CH_3}$), 24.05 ($-\underline{CH_2}CH_3$), 36.33 (C-2), 47.39 (C-4), 68.04 (C-6),

68.58 (C-3), 74.94 (C-5), 101.39 (C-1); exact mass 158.0942 (calcd for $C_8H_{14}O_3$, 158.0942).

1,6-Anhydro-3-O-benzyl-2,4-dideoxy-4-C-ethyl-β-D-arabino-hexopyranose 66. Sodium hydride (50% w/w as an oil dispersion, 0.143 g, 3 mmol) was added to a solution (3 mL) of compound 64 (0.227 g, 1.43 mmol) in dry DMF. The mixture was stirred for 30 min and then benzyl bromide (0.368 g, 0.25 mL, 2.15 mmol) was added dropwise. The mixture was stirred for 1 h at room temperature and then it was diluted with methanol (1 mL). Stirring at room temperature was continued for 1 h and then the mixture was extracted with ether (100 mL). The organic layer was washed with water (3 x 20 mL), brine (20 mL), dried and evaporated. Flash chromatography of the residue over silica gel (1.5 x 10 cm) using 0.5:9.5 ethyl acetate—hexane gave 66 (0.326 g, 91%) as a homogeneous (TLC, silica gel, 1:9 ethyl acetate—hexane) oil. The compound had: $[\alpha]_D^{23}$ - 80° (c 1, $CHCl_3$); FT-IR (film) 2880, 1497, 1332, 1137, 1095, 1072, 867 cm^{-1}; NMR ($CDCl_3$, 400 MHz) δ 0.96 (t, J = 7.25 Hz, 3 H, $-CH_2\underline{CH_3}$), 1.42 (m, 1 H) and 1.6 (m, 1 H) ($-\underline{CH_2}CH_3$), 1.7 (br t, J = 7 Hz, 1 H, H-4), 1.86 (m, J = 2, 5.5, 15 Hz, 1 H, $H\text{-}2_{ax}$), 1.96 (br d, J = 15 Hz, 1 H, $H\text{-}2_{eq}$), 3.41 (br d, J = 5.5 Hz, 1 H, H-3), 3.77 (br t, J = 6, 7.0 Hz, 1 H, $H\text{-}6_{exo}$), 4.36 (br d, J = 7 Hz, 1 H, $H\text{-}6_{endo}$), 4.39 (br d, J = 6 Hz, 1 H, H-5), 4.47—4.55 (AB q, J = 12 Hz, 2 H, $-\underline{CH_2}Ph$), 5.52 (br s, 1 H, H-1), 7.25—7.3 (m, 5 H, aromatic protons;

CMR (22.6 MHz) ppm 12.20 (-$CH_2\underline{C}H_3$), 24.17 (-$\underline{C}H_2CH_3$), 33.20 (C-2), 44.63 (C-4), 67.52 (C-6), 70.50 (-$\underline{C}H_2Ph$), 74.03 and 74.53 (C-3 and C-5), 100.28 (C-1), 127.44, 128.35 and 138.69 (aromatic carbons); exact mass 248.1405 (calcd for $C_{15}H_{20}O_3$, 248.1413). Anal. Calcd for $C_{15}H_{20}O_3$: C, 72.55; H, 8.11. Found: C, 72.51; H, 8.05.

Methyl 3-O-benzyl-2,4-dideoxy-4-C-ethyl-α,β-D-arabino-hexopyranoside 66A. A solution of 66 (1.37 g, 5.51 mmol) in absolute methanol (10 mL) was treated with dry Amberlite IRA-120(H^+) resin (1.25 g). The mixture was stirred at room temperature overnight. The resin was removed by filtration and filterate was evaporated. Flash chromatography of the residue over silica gel (2 x 12 cm) using 3:7 ethyl acetate--hexane gave 66A (1.26 g, 81% yield) as a mixture of α- and β-isomers (α/β ratio 85:15, ^{1}H-NMR). The compound had: FT-IR (film) 3470, 1125, 1072, 1049 cm^{-1}; NMR ($CDCl_3$, 400 MHz) δ 0.88 (two sets of t, 3 H, $-CH_2\underline{CH_3}$), 1.40--1.75 (m, 4 H), 2.06--2.20 (two sets of m, 1 H), 2.28--2.44 (two sets of m, 1 H), 3.36 (s) and 3.52 (s, 3 H, $-O\underline{CH_3}$) 3.57--3.82 (m, 4 H, 4 H), 4.34 (q, J = 2, 10 Hz, 0.15 H, H-1 of β-anomer), 4.43 and 4.63 (AB q, J = 11.5 Hz, 2 H, $-\underline{CH_2}Ph$), 4.87 (q, J = 1.5, 3.5 Hz, 0.85 H, H-1 of α-anomer), 7.35 (m, 5 H, aromatic protons); mass (chemical ionization, NH_3) 298 (M + 18). Anal. Calcd for $C_{16}H_{24}O_4$: C, 68.54; H, 8.62. Found: C, 68.05; H, 8.74.

Methyl 3-O-benzyl-2,4-dideoxy-4-C-ethyl-6-O-methanesulfonyl-α,β-D-arabino-hexopyranoside 66B. Methanesulfonyl chloride (0.947 g, 0.64 mL, 8.26 mmol was added dropwise to a mixture of 66A (1.2 g, 4.28 mmol) and triethylamine (1.116 g, 11.0 mmol) in dry dichloromethane (10 mL) at 0 °C. The mixture was stirred at 0 °C for 15 min and was then diluted with dichloromethane (100 mL). The organic phase was washed with dilute hydrochloric acid (50 mL), saturated aqueous bicarbonate (50 mL), brine (50 mL), dried and evaporated. Flash chromatography of the residue over silica gel (5 x 12 cm) using 3:7 ethyl acetate—hexane gave 66B (1.246 g, 80%). The compound had: FT-IR (film) 1355, 1176, 980 cm^{-1}; NMR ($CDCl_3$, 400 MHz) δ 0.86 (t, 3 H, $-CH_2\underline{CH_3}$), 1.42—1.8 (m, 4 H), 2.29 (m, J = 2, 5, 13 Hz, 1 H, H-2_{eq}), 3.06 (s) and 3.07 (s, 3 H, $-OSO_2\underline{CH_3}$), 3.34 (s) and 3.49 (s, 3 H, $-O\underline{CH_3}$), 3.74 (m, 1 H, H-3), 3.84 (m, 1 H, H-5), 4.31 (m) and 4.44 (m, 2 H, HH-6), 4.43 and 4.63 (AB q, 2 H, $-\underline{CH_2}Ph$), 4.51 (q, J = 2.25, 11.5 Hz, 0.15 H, H-1 of β-anomer), 4.87 (q, J = 2, 3.5 Hz, 0.85 H, H-1 of α-anomer), 7.35 (m, 5 H, aromatic protons); mass (chemical ionization) 376 (M + 18), 344 [(M + 18) - CH_3OH]; exact mass 358.1478 (Calcd for $C_{17}H_{26}O_5S$, 358.1450), 327.1268 [calcd for (M - CH_3O), 327.1266], 230.1309 (calcd for [M - (CH_3OH + CH_3SO_3)], 230.1307).

Methyl 3-O-benzyl-2,4-6-trideoxy-4-C-ethyl-α,β-D-arabino-hexopyranoside 66C. Lithium triethyl borohydride (7 mL, ca. 2 equivalent) was added dropwise to a solution (5 mL) of the tosylate 66B (1.2 g, 3.34 mmol) in dry THF. The mixture was stirred overnight at room temperature and the excess of reagent was destroyed by addition of water. A cold (0 °C) mixture of 30% hydrogen peroxide (10 mL) and sodium hydroxide (3 N, 12 mL) was added slowly with ice-bath cooling. The mixture was allowed to attain room temperature and was stirred for 1 h. It was then extracted with dichloromethane (3 x 50 mL). The extract was dried and concentrated. Flash chromatography of the residue over silica gel (2 x 16 cm) using 1:9 ethyl acetate—hexane gave 66C (0.615 g, 69%). The compound had: FT-IR (film) 2954, 1127, 1072, 1054, 970 cm^{-1}; NMR ($CDCl_3$, 400 MHz) δ 0.85 (two sets of t, 3 H, $-CH_2CH_3$), 1.23 (d) and 1.29 (d, 3 H, $-CH_3$), 1.35--1.75 (four sets of m, 4 H), 2.31 (m) and 2.37 (m, 1 H, H-2_{eq}), 3.33 (s) and 3.52 (s, 3 H, $-OCH_3$), 3.71 (m, 2 H, H-5 and H-3), 4.22 (q) and 4.84 (q, 1 H, H-1), 4.43 and 4.64 (AB q, 2 H, $-CH_2Ph$), 7.35 (m, 5 H, aromatic protons); mass (chemical ionization, NH_3) 282 (M + 18), 250 [(M + 18) - CH_3OH]. Anal. Calcd for $C_{16}H_{24}O_3$: C, 72.69; H, 9.15. Found: C, 72.80; H, 9.28.

3-O-Benzyl-2,4,6-trideoxy-4-C-ethyl-α,β-D-arabino-hexopyranose 66D.

A mixture of 66C (0.205 g, 0.78 mmol) and 50% aqueous acetic acid (7 mL) was heated at 60°C for 2 h. The mixture was diluted with toluene (30 mL) and concentrated. The residue was again diluted with toluene (30 mL) and concentrated. Flash chromatography of the residue over silica gel (1.5 x 12 cm) using 3:7 ethyl acetate--hexane gave 66D (0.163 g, 83%). The compound had: FT-IR (film) 3400, 2879, 1095, 1070, 972 cm^{-1}; NMR ($CDCl_3$, 200 MHz) δ 1.00 (t) and 1.05 (t, 3 H, $-CH_2\underline{CH_3}$), 1.42 (d) and 1.47 (d, 3 H, $-\underline{CH_3}$), 1.47--2.0 (m, 4 H), 2.5 (m) and 2.65 (m, 1 H, H-2_{eq}), 2.94 (t, 0.6 H, -OH), 3.38 (m, 1.2 H, H-5 and -OH), 3.78 (m) and 3.96 (m, 1 H, H-3), 4.44 (q) and 4.65 (q, 2 H, $-\underline{CH_2}Ph$), 4.68 (m, 0.4 H, H-1 of β-anomer), 5.40 (br s, 0.6 H, H-1 of α-anomer), 7.35 (m, 5 H, aromatic protons); mass (chemical ionization, NH_3) 268 (M + 18), 250 [(M + 18) - H_2O]; exact mass 250.1568 (calcd for $C_{15}H_{22}O_3$, 250.1569), 232.1460 [calcd for (M - H_2O), 232.1463].

(3R)-Benzyloxy-(4R)-ethyl-(5R)-hydroxyhexanoic acid lactone 67.

A solution (3 mL) of 66D (0.152 g, 0.6 mmol) was rapidly added to a mixture of pyridinium chlorochromate (0.199 g, 0.92 mmol) and sodium acetate (9 mg, 0.12 mmol) in dry dichloromethane (10 mL). The mixture was stirred at room temperature for 5 h and then it was diluted with ether (100 mL). The mixture was filtered through Celite and concentrated. Flash chromatography of the residue over silica gel (1.5 x 12 cm) using 3:7 ethyl acetate—hexane gave the lactone 67 (0.116 g, 76%). The compound had: $[\alpha]_D^{23} = +3.0^\circ$ (c 1, $CHCl_3$); FT-IR (film) 1748, 1218, 1088, 1067, 799 cm^{-1}; NMR ($CDCl_3$, 400 MHz) δ 0.92 (t, J = 7.5 Hz, 3 H, $-CH_2\underline{CH_3}$), 1.32 (m, 1 H) and 1.56 (m, 1 H, $-\underline{CH_2}CH_3$), 1.68 (m, 1 H, H-4), 2.65 (q, J = 4.5, 17 Hz, 1 H) and 2.77 (q, J = 4.5, 17 Hz, 1 H, HH-2), 3.74 (q, 1 H, H-3), 4.06 (m, 1 H, H-5), 4.45 and 4.62 (AB q, J = 12 Hz, 2 H, $-\underline{CH_2}Ph$), 7.35 (m, 5 H, aromatic protons); CMR ($CDCl_3$, 100.6 MHz) ppm 10.28 ($-CH_2\underline{CH_3}$), 19.56 ($-\underline{CH_3}$), 22.03 ($-\underline{CH_2}CH_3$), 34.37 (C-2), 47.35 (C-4), 70.07 ($-\underline{CH_2}Ph$), 74.11 (C-5), 76.77 (C-3), 127.58, 127.64, 128.26 and 137.48 (aromatic carbons), 170.75 (C-1); mass (chemical ionization, NH_3) 266 (M + 18), 248 (M + H). Anal. Calcd for $C_{15}H_{20}O_3$: C, 72.55; H, 8.11. Found: C, 72.54; H, 8.22.

E. Reversal of Cyclofunctionalizations.

Typical procedure for use of chlorotrimethylsilane—sodium iodide: Conversion of 68 into 2-cyclopentene-1-acetic acid. Acetonitrile (20 mL) was injected into a flask containing the lactone 68 (306 mg, 1.09 mmol) and anhydrous NaI (980 mg, 6.54 mmol). The mixture was stirred magnetically for 5 min. and Me_3SiCl (709 mg, 6.52 mmol) was injected. Stirring was continued for 3 h (TLC control) and 15% w/v aqueous $Na_2S_2O_3$ (25 mL) was then added and the mixture was extracted with CH_2Cl_2 (4 x 35 mL), the aqueous phase being saturated with NaCl to break up the resulting emulsion. The organic extract was evaporated and the residue was dissolved in CH_2Cl_2 (50 mL) and extracted with saturated aqueous $NaHCO_3$ (3 x 20 mL). The aqueous layer was washed with ether (2 x 30 mL), acidified (concentrated HCl) and extracted with CH_2Cl_2 (4 x 35 mL). The extract was dried and evaporated. Kugelrohr distillation of the residue (100—102°C, 43 mm Hg) gave 2-cyclopentene-1-acetic acid (116 mg, 84%) as a colorless liquid of better than 99% purity (VPC) and which was characterized by comparison (VPC, IR, NMR) with an authentic sample.

(3aα,6α,6a)-Hexahydro-6-iodo-2H-cyclopenta[b]furan-2-one

71. A solution of iodine (10.1 g, 40 mmol) and KI (20.1 g, 121 mmol) in water (60 mL) was added to a stirred solution of 2-cyclopentene-1-acetic acid (2.5 g, 19.8 mmol) in 0.5 M aqueous $NaHCO_3$ (120 mL). Stirring was continued for 48 h with protection from light. The mixture was decolorized by addition of 15% w/v aqueous $Na_2S_2O_3$ (ca. 20 mL) and extracted with ether (3 x 50 mL). The organic extract was washed successively with 15% w/v aqueous $Na_2S_2O_3$ (30 mL), saturated aqueous Na_2CO_3 (2 x 30 mL), water (2 x 30 mL), and brine (30 mL). It was dried, concentrated and passed, with ether, through a column (2.5 x 2.5 cm) of alumina. The filtrate was evaporated and the residue was kept under oil-pump vacuum (protection from light) for 14 h to afford 71 (2.8 g, 56%) as a homogeneous (TLC, silica, 1:3 ethyl acetate—2,2,4-trimethylpentane) oil: IR (film) 1775 cm^{-1}; NMR ($CDCl_3$) δ 1.28—3.4 (m, 6 H), 4.34—4.6 (m, 1 H), 5.18 [d (each signal having $W_{\frac{1}{2}}$ 2.2 Hz), J = 5.6 Hz, 1 H]; exact mass m/e 251.9649 (calcd for $C_7H_9O_2I$, m/e 251.9648. Anal. Calcd for $C_7H_9O_2I$: C, 33.36; H, 3.60; I, 50.35; O, 12.70. Found: C, 33.37; H, 3.43; I, 50.65; O, 12.92.

4-Oxa-2-exo-(phenylseleno)tricyclo[4.3.1.$0^{3,7}$]decane 73.

Phenylselenenyl chloride (563 mg, 2.94 mmol) in EtOAc (5 mL) was added dropwise over 15 min, to a stirred solution of endo-2-(hydroxymethyl)bicyclo[2.2.2]oct-5-ene[132] (378 mg, 2.73 mmol) in EtOAc (10 mL). A further portion (5 mL) of EtOAc was used to wash all the phenylselenenyl chloride from the addition syringe into the reaction mixture and stirring was continued for 24 h. The solution was then evaporated and chromatography of the residue over silica gel (1.5 x 30 cm) with 1:1.7 ethyl acetate—2,2,4-trimethylpentane gave 73 (580 mg, 72%) as a homogeneous (TLC, silica, 1:4 ethyl acetate—2,2,4-trimethylpentane) oil: NMR (400 MHz, $CDCl_3$) δ 1.0—1.38 (m, 1 H), 1.40—1.49 (br d, J = 13.8 Hz, 1 H), 1.70—1.95 (m, 4 H), 1.95—2.08 (m, 2 H), 2.15—2.25 (m, 1 H), 3.36 (q, J = 3.75, 1.25 Hz, 1 H), 3.49 (d, J^{23} = 6.75 Hz, 1 H), 3.74 (q, J = 6.75, 3.5 Hz, 1 H), 4.16 [d, ($W_{\frac{1}{2}}$ = 2.5 Hz) J = 5.5 Hz, 1 H], 7.15—7.37 (m, 3 H), 7.45—7.67 (m, 2 H); ^{13}C-NMR (100.6 MHz, $CDCl_3$) δ 15.6, 22.1, 26.9, 34.1, 35.6, 36.0, 51.0, 76.6, 81.4, 126.8, 129.2, 130.4, 132.7; exact mass m/e 294.0524 [calcd for $C_{15}H_{18}O^{80}Se$, m/e 294.0524]. Anal. Calcd for $C_{15}H_{18}OSe$: C, 61.43; H, 6.19; O, 5.46. Found: C, 61.33; H, 6.21; O, 5.29.

Conversion of 4-oxa-2-exo-(phenylseleno)tricyclo-[4.3.1.$0^{3,7}$]decan-5-one into 73. The lactone 79[115b] (215 mg, 0.70 mmol) in ether (15 mL) was injected dropwise over 10 min. into a stirred suspension of $LiAlH_4$ (66 mg, 1.74 mmol) in ether (20 mL). A further portion (10 mL) of ether was used as a rinse to complete transfer of all the lactone. After 30 min. (TLC control), wet ether and then water were added cautiously to the reaction mixture. Stirring was continued for 10 min, and the mixture was extracted with ether (2 x 50 mL). The extract was washed with water (3 x 30 mL) and brine (30 mL) and then dried. Evaporation afforded the crude diol 80 which was kept 12 h under oil-pump vacuum to remove traces of water: ^{13}C-NMR δ 20.1, 26.1, 29.8, 31.2, 36.7, 36.9, 53.8, 65.6, 127.4, 129.1, 134.0; exact mass m/e 312.0627 (calcd for $C_{15}H_{20}O_2{}^{80}Se$, m/e 312.0628). Anhydrous pyridine (15 mL) was added to the crude diol (200 mg) and the solution was stirred and cooled to -35°C. p-Toluenesulfonyl chloride (147 mg, 0.77 mmol) was added in one lot and stirring was continued at -20°C for 18 h, then at 0—5°C for 8 h and, finally, at room temperature for 5 days. The mixture was diluted with ether (100 mL) and washed with water (3 x 30 mL) and then with brine (2 x 30 mL). The ether solution was dried and evaporated. Flash chromatography of the residue over silica gel (2 x 15 cm) with 1:9 ethyl acetate—hexane gave 73

(100 mg, 52%) as a homogeneous (TLC, silica 1:4 ethyl acetate—2,2,4-trimethylpentane) oil. Comparison of its chromatographic and spectral properties (IR, NMR, ^{13}C-NMR, exact mass) with those of material obtained in the previous experiment showed both specimens to have the same structure.

(3aα,6α,6aβ)-Hexahydro-6-(phenylthio)-2H-cyclopenta[b]-furan-2-one, 70. Benzenesulfenyl chloride (1.446 g, 9.9 mmol) was injected dropwise into a stirred solution of 2-cyclopentene-1-acetic acid (1.261 g, 10 mmol) in EtOAc (10 mL) and then Et_3N (1.51 g, 14.9 mmol) was added in the same manner. The mixture was stirred overnight and then partitioned between water (50 mL) and ether (150 mL). The organic layer was washed with saturated aqueous Na_2CO_3 (2 x 20 mL). Chromatography over silica gel (45 x 1.5 cm) using 1:9 ethyl acetate—hexane gave 68 (600 mg, 25%) as a homogeneous (TLC, silica gel, 1:9 ethyl acetate—hexane), oil: IR (film) 1772 cm^{-1}; NMR ($CDCl_3$) δ 1.1—3.25 (m, 7 H), 3.69—3.97 (m, 1 H), 4.76 [d (each signal having $W_{\frac{1}{2}}$ 2.6 Hz), J = 6 Hz, 1 H], 6.8—7.7 (m, 5 H); exact mass m/e 234.0715 (calcd for $C_{13}H_{14}O_2{}^{32}S$, m/e 234.0715). Anal. Calcd for $C_{13}H_{14}O_2S$: C, 66.64; H, 6.02; S, 13.68. Found: C, 66.50; H, 6.11; S, 13.56.

2-(Phenylseleno)undecan-1-ol 75. Phenylselenenyl chloride (1.91 g, 10 mmol) in EtOAc (20 mL) was added from a syringe, with stirring, to undecanal (1.70 g, 10 mmol). A further portion of EtOAc (5 mL) was used as a rinse to transfer all of the phenylselenenyl chloride. Concentrated hydrochloric acid (1 drop) was added to the reaction mixture and stirring was continued for 4 h, by which time the color of the reagent had been discharged. The mixture was diluted with pentane (150 mL) and washed with water (5 x 15 mL) to remove all acid. The pentane layer was dried, and evaporation yielded 2-(phenylseleno)-undecanal,[133] which was dissolved in MeOH (20 mL). Sodium borohydride (401 mg, 10.6 mmol) was added in small portions with stirring and the mixture was immediately extracted with pentane (3 x 50 mL). The organic layer was washed with water (3 x 30 mL), dried, and evaporated. Chromatography of the residue over silica gel (1 x 45 cm) using 1:4 ethyl acetate—2,2,4-trimethyl-pentane gave 75 (250 mg, 9.8%) as a homogeneous (TLC, silica, 1:4 ethyl acetate—2,2,4-trimethylpentane) oil: NMR ($CDCl_3$) δ 0.62—1.96 (m, 20 H), 3.0—3.8 (m, 3 H), 7.16—7.4 (m, 3 H), 7.4—7.7 (m, 2 H); exact mass m/e 328.1303 (calcd for $C_{17}H_{28}O^{80}Se$, m/e 328.1305). Anal. Calcd for $C_{17}H_{28}OSe$: C,

Threo-5-(phenylseleno)octan-4-ol 76. Sodium borohydride (260 mg, 6.87 mmol) was added in portions from a side-arm addition funnel to a stirred solution of diphenyldiselenide (834.6 mg, 2.67 mmol) in absolute EtOH (30 mL). At this stage the reaction mixture was colorless and (Z)-4,5-epoxyoctane[134] (721 mg, 5.62 mmol) was then injected. Stirring at room temperature was continued overnight. The solvent was evaporated and the residue was dissolved in ether (100 mL). The solution was washed with water (2 x 20 mL), dried and evaporated. Chromatography of the residue over silica gel (1.5 x 60 cm) with 1:4 ethyl acetate—2,2,4-trimethylpentane gave 76 (1.230 g, 80%) as an apparently homogeneous (TLC, silica, 1:9 ethyl acetate—2,2,4-trimethylpentane) oil: NMR (400 MHz, $CDCl_3$) δ 0.78—1.02 (m, 6 H), 1.24—1.82 (m, 9 H), 2.35 (br s, 1 H), 3.06—3.19 (m, 1 H), 3.5—3.62 (m, 1 H), 7.2—7.33 (m, 3 H), 7.5—7.64 (m, 2 H); ^{13}C-NMR ($CDCl_3$) δ 13.8, 14.0, 19.1, 21.4, 34.7, 37.0, 56.3, 73.1, 127.5, 129.0, 134.8; exact mass m/e 286.0831 (calcd for $C_{14}H_{22}O^{80}Se$, m/e 286.0836). Anal. Calcd for $C_{14}H_{22}OSe$: C, 58.94; H, 7.77; O, 5.61. Found: C, 58.79; H, 7.88; O, 5.52.

Erythro-5-(phenylseleno)octan-4-ol 77.[135] This compound had NMR (200 MHz, $CDCl_3$) δ 0.8—1.0 (m, 6 H), 1.4—1.84 (m, 8 H), 2.3 (s, 1 H), 3.23—3.4 (m, 1 H), 3.6—3.72 (m, 1 H), 7.2—7.34 (m, 3 H), 7.52—7.64 (m, 2 H); ^{13}C-NMR ($CDCl_3$) δ 13.9, 14.0, 19.4, 21.7, 32.6, 35.9, 56.1, 72.7, 127.4, 129.1, 129.5, 134.4.

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