Order Number 9119634

Application of the Bradsher cycloaddition for the syntheses of naproxen and sakyomicin A and glycosidation via glycals and phenyl(bisphenylthio)sulfonium salts: Effect of the glycal structure on the face selectivity

Grewal, Gurmit, Ph.D.

City University of New York, 1991

U·M·I
300 N. Zeeb Rd.
Ann Arbor, MI 48106

A

APPLICATION OF THE BRADSHER CYCLOADDITION FOR THE SYNTHESES OF NAPROXEN AND SAKYOMICIN A

AND

GLYCOSIDATION VIA GLYCALS AND PHENYL(BISPHENYLTHIO)SULFONIUM SALTS: EFFECT OF THE GLYCAL STRUCTURE ON THE FACE SELECTIVITY

by

GURMIT GREWAL

A dissertation submitted to the Graduate Faculty in Chemistry in partial fulfillment of the requirements for the degree of Doctor of Philosophy, The City University of New York

1991

This manuscript has been read and accepted for the Graduate Faculty in Chemistry in satisfaction of the dissertation requirements for the degree of Doctor of Philosophy.

12·21·90
Date

Chairman of Examining Committee

1/3/91
Date

Executive Officer

Supervisory Committee

The City University of New York

Abstract

APPLICATION OF THE BRADSHER CYCLOADDITION FOR THE SYNTHESES OF NAPROXEN AND SAKYOMICIN A

AND

GLYCOSIDATION VIA GLYCALS AND PHENYL(BISPHENYLTHIO)SULFONIUM SALTS: EFFECT OF THE GLYCAL STRUCTURE ON THE FACE SELECTIVITY

by

Gurmit Grewal

Advisor: Professor Richard W. Franck

Part 1: Attempts are made for the syntheses of bioactive compounds naproxen and sakyomicin A using the Bradsher cycloaddition as the key reaction. Naproxen, a non-steroidal antiinflammatory compound, has a 6-methoxy-naphthalene moiety with a chiral substituent at its C-2. The required alkyl chain is appended to the naphthalene nucleus using the Bradsher reaction between a vinyl ether bearing the chiral alkyl chain and an isoquinolinium salt.

The ABC-ring analog of sakyomicin A, an angucycline antibiotic, is the other target. The key reaction in the proposed synthesis of this target molecule is an intramolecular version of the Bradsher reaction, which requires a 3-susbtituted-4-alkoxy-isoquinoline. The precursors for the chiral alkyl side chain and the 4-alkoxy-isoquinoline are synthesized and an attempt is made to couple them so as to obtain the desired 3-substituted-4-alkoxy-isoquinoline.

Part 2: Glycosyl transfer via glycals, activated by phenyl(bisphenylthio)sulfonium salts to a variety of nucleophiles is studied. The method shows preferential β selectivity leading to 2-phenylthio substituted 2-deoxy-β-glycosides. A series of glycals are examined in order to determine the effect of their structure on the glycosidation stereochemistry. The face selectivity is strongly influenced by the substituents on the glycal. Glycals with rather rigid structures also give β-glycosides as the major products. The allylic 3-pseudoequatorial and 4-equatorial substituents have little contribution in the stereochemical outcome of the reaction while allylic 3-pseudoaxial and 4-axial substituents act as major directors.

This glycosidation method is applied to the synthesis of 1-O-phenyl-2-deoxy-β-D-fucopyranoside, the AA'-ring analog of aureolic acid.

TO

NEELU

Acknowledgements

I wish to express my deep sense of gratitude to Prof. R. W. Franck for his invaluable guidance, patience and encouragement throughout this work. I thank Dr. M. Blumenstein for his help in NMR experiments and Prof. Franck's group: Drs. R. B. Gupta, S. Ramesh and N. Kaila, A. Chowdhury, H. Yin, T. Nicolas, C. Soll for many helpful discussions and suggestions. Finally I wish to express my gratitude to my wife Neelu for her love, support and inspiration.

TABLE OF CONTENTS

PART 1

I. Introduction

(a) Naproxen 2

(b) Sakyomicin 5

(c) Cycloadditions of Isoquinolinium Salts 18

II. Proposed Schemes

(a) Naproxen 22

(b) Sakyomicin 24

III. Results and Discussions

(a) Naproxen

Synthesis of the Vinyl Ether Portion 30

Synthesis of the Isoquinoline Portion 32

Cycloaddition of Vinyl Ether and Isoquinoline Portions 33

(b) Sakyomicin

Synthesis of the Chiral Side Chain 36

Synthesis of the Isoquinoline Portion 37

Aldol Condensation of Side Chain and Isoquinoline Portions 38

Direct Lithiation of 4-Alkoxyisoquinoline 39

IV Experimental

(a) Naproxen

Preparation of the Isoquinoline Portion 42

Preparation of the Vinyl Ether Portion 44

Cycloadditions of Vinyl Ether and Isoquinoline Portions 45

(b) Sakyomicin

Preparation of the Isoquinoline Portion 47

Direct Lithiation of 4-Alkoxyisoquinoline 48

V Appendix 50

VI References 65

PART 2

I. Introduction 70

(a) Electrophilic Activation of Glycals 74

H^+ as Electrophile 75

Mercury Electrophiles 78

Halogen Electrophiles 79

Nitrogen Electrophiles 82

Oxygen Electrophiles 84

Carbon Electrophiles 85

Selenium Electrophiles 87

Sulfur Electrophiles 89

II. Results and Discussions 91

Structure Assignments 98

Effect of Glycal Structure 101

Glycosidations Using Different Glycals 106

Mechanistic Speculations 112

Synthesis of AA'-Ring Analog of Aureolic Acid 120

III. Experimental 125

General Procedure for Benzylation of Glycals 125

General Procedure for Preparation of Phenyl(bisphenylthio)-

-sulfonium Salt Reagent 127

General Procedure for Glycosidation Using Methanol

as the Nucleophile 128

General Procedure for Glycosidation Using

1,2,3,4-diisopropylidenegalactose as the Nucleophile 134

Synthesis of AA'-Ring Analog of Aureolic Acid 138

IV. Appendix 142

V. References 187

List of Tables

Table 1.	Glycosyl Transfers Using Reagent **20**	93
Table 2.	Glycosyl Transfers Using Reagent **22**	100
Table 3.	Glycosyl Transfers to Methanol Using Different Reagents	101
Table 4.	Glycosyl Transfers to Methanol Using Different Glycals	108
Table 5.	Glycosyl Transfers to Diisopropylidenegalactose Using Different Glycals	109
Table 6.	Low temperature ^{13}C NMR data	117

PART 1

APPLICATION OF THE BRADSHER CYCLOADDITION FOR THE SYNTHESES OF NAPROXEN AND SAKYOMICIN A

INTRODUCTION

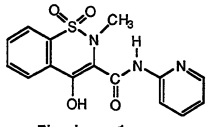
Naproxen:

Non-steroidal antiinflammatory (NSAI) agents are one of the largest classes of drugs. Besides being antiinflammatory they are analgesic as well as antipyretic. All these compounds have a similar mode of action. In 1969 Collier proposed that aspirin blocks the actions of humoral inflammatory mediators that are formed as a result of the body's defense reactions.[1] Two years later, it was shown by different groups of workers that NSAI agents like aspirin, sodium salicylate and indomethacin inhibit prostaglandin synthesis.[2,3,4] These results combined with the findings from other groups that injected prostaglandins evoke inflammatory[5] or pyretic[6] responses, clearly demonstrated that Collier's humoral mediators are the prostaglandins. Observations at Syntex have established that, by cyclooxygenase inhibition, NSAI agents stop the arachidonic acid cascade to prostaglandins and thromboxane A_2 which are responsible for the inflammation mechanism.[7]

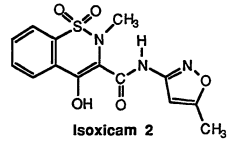
Except for the latest class of Oxycams e.g. Piroxicam **1** and Isoxicam **2**, most of these antiinflammatory agents can be catagorized into three main classes:

1. *Benzoic Acid Derivatives*: Represented by Aspirin **3**, Mefenamic Acid **4** etc.
2. *Arylacetic Acid*: Represented by Ibufenac **5**, Diclofenac **6** etc.
3. *α-Arylpropionic Acids*: Represented by Ibuprofen **7**, Naproxen **8** etc.

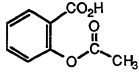
Introduction of the α-methyl group in arylacetic acids seems to have an important role in the biological action, since ibuprofen **7** has a higher activity



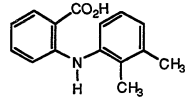
Piroxicam 1



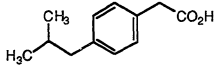
Isoxicam 2



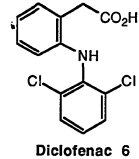
Aspirin 3



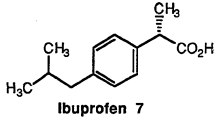
Mefenamic Acid 4



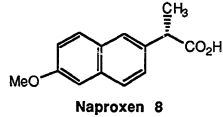
Ibufenac 5



Diclofenac 6



Ibuprofen 7

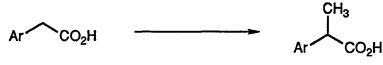


Naproxen 8

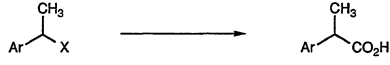
than ibufenac **5**. Another structure activity relationship is that the inflammatory activity is enhanced by the substitution of small lipophilic groups in the aryl portion. Thus the presence of 6-methoxy group in naproxen **8** enhances its activity 11 times. These properties are widely developed and several

derivatives have been marketed. This success probably explains the proliferation of synthetic methods for these types of structures. According to the building mode for the aliphatic side chain these methods can be differentiated into four main groups:[8]

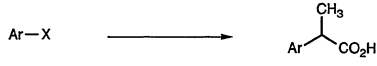
1. Introduction of the methyl group at α-position in arylacetic acids.



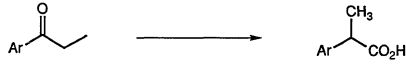
2. Terminal building of the carboxylic function.



3. Simultaneous introduction of the propionic group.



4. Transposition of α-substituted alkyl aryl ketones.



Most of the syntheses of these α-aryl propionic acids start from the aryl carbonyl compounds,[9] which can be prepared in high yields by selective electrophilic acylation, these are then converted into the target carboxylic acids by many different routes. Initially the method of choice for this conversion was the Willgerodt-Kindler reaction.[10] There were limitations for its synthetic utility.e.g. reaction conditions involving high temperatures and high pressures,

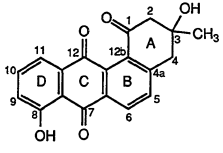
complicated isolation technique and low yields etc. The Darzens reaction[11] was also used, where an α-haloester is condensed with an aldehyde or ketone under alkaline catalysis to give an α,β-epoxy ester. Which in turn is converted into the desired acid by a multi step process. Subsequently, more convenient syntheses were developed based on the rearrangement of α-halo, α-thallio(III) or α-diazo alkyl aryl ketones[12].

These acids have an asymmetric center at the α-carbon atom and each (S)-enantiomer shows much higher pharmacological activity than its antipode e.g. (S)-naproxen is 28 times as active as its (R)-isomer.[13] Therefore, methods leading to the physiologically more active compounds in enantiomerically pure form have received considerable attention. While many approaches have been developed, the majority lack simplicity and high stereoselectivity.[14]

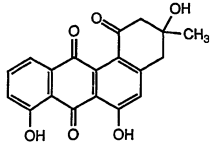
Sakyomicin:

The benz(a)anthraquinones are a well known and very important class of biologically active compounds. Besides being antibiotic, they constitute one of the most important group of chemotherapeutic agents available for the treatment of some cancers. There is a more specific sub-group of these benz(a)anthraquinones, the angucyclines which contain a modified chromophoric system. These antibiotics are also reported to be enzyme inhibitors and antitumor agents. The trivial name given to them "angucyclines",[15] refers to the angle (Latin: angus), a characteristic feature of their structure and biosynthesis.[16] Tetrangomycin **9** is the simplest structure among these antibiotics and it was the first one discovered.The angucyclines can be classified into two groups depending on their oxidation state. The "real"

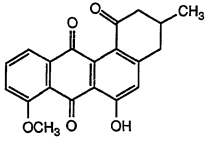
anthraquinones, exemplified by ochromycinone, fujiamycins A and B, tetrangomycin **9**, rabelomycin **10**, X-14881 **11** and tetrangulol **12**.[17]



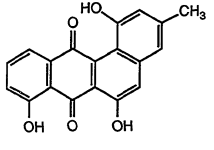
9 Tetrangomycin



10 Rabelomycin

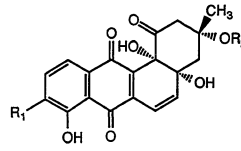


11 X-14881

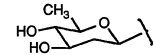


12 Tetrangulol

The oxidized anthraquinones where the A-B ring junction is hydroxylated have cis-oriented angular hydroxyl groups at C-atoms 4a and 12b. In aquayamycin **13**,[18,19] the chromophore has a β-olivose residue attached to it through a C-glycosidic linkage at C-9, with further derivatization at the 3', 4' and/or 12b hydroxyls, e.g. vineomycin A1 **14** (also called P-1894 B),[19,20] the saquayamycins,[21] the kerriamycins,[22,23] the urdamycins **15**[15] and capoamycin **16**.[24] None of these compounds is clinically used, but they show a range of interesting biological activity, including antitumor activity. Aquayamycin has been shown to be an inhibitor of tyrosine hydroxylase[25] and dopamine hydroxylase.[26] Vineomycin A1 is a potent *in vitro* inhibitor of proline hydroxylase.[27]

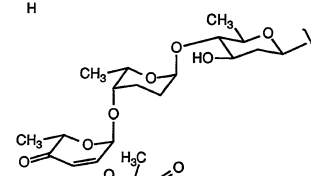


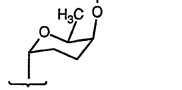
13 Aquayamycin

R_1= 

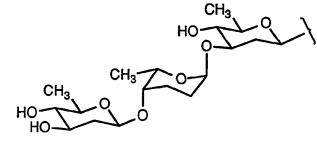
R_2= H

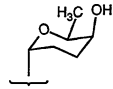
14 Vineomycin A_1

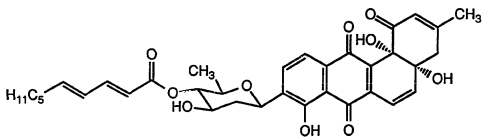
R_1= 

R_2= 

15 Urdamycin A

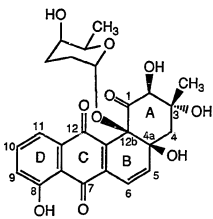
R_1= 

R_2= 

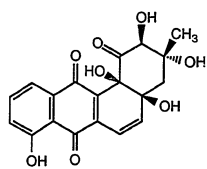


16 Capoamycin

The family of angucyclines epimeric to aquayamycins at C-atoms 4a and 12b is called the sakyomicins, which also differ in the absence of C-glycoside at C-9,[28] e.g. sakyomicin A **17** and sakyomicin B **18** etc.They have modest activity against gram-positive bacteria.



17 Sakyomicin A



18 Sakyomicin B

Sakyomicin A **17** recently has gained a lot more importance since there are several reports that it inhibits proliferation of HIV (AIDS virus).[28,29] In terms of molecular biology, HIV (Human Immunodeficiency Virus) belongs to the family of retroviruses. The most distinguishing feature of retroviruses is that their core contains two strands of RNA as the genetic material and this RNA, using the enzyme called reverse transcriptase, makes DNA (which is opposite of what

normal viruses do, i.e. DNA makes the RNA, hence the term retrovirus). The AIDS virus, when replicating, destroys the T-cells of human immune system. A recent review of AIDS therapies lists six ways to intervene in the HIV life cycle:

(i) By blocking binding of virus to host cell surface.

(ii) By inhibiting uncoating of virus.

(iii) By inhibiting reverse transcriptase.

(iv) By arresting translation.

(v) By inhibiting protein modifications.

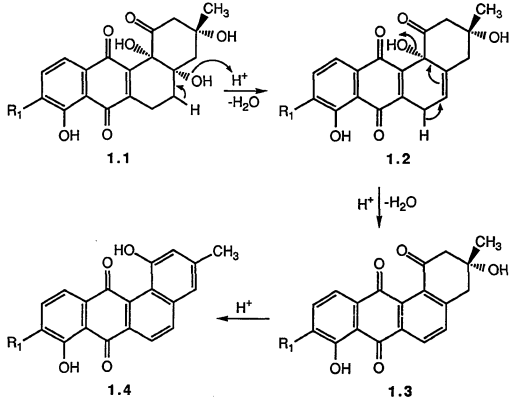
(vi) By inhibiting assembly and budding.

The one drug in clinical use, AZT, operates by mechanism (iii).[30] Sakyomicin A is also a reverse trancriptase inhibitor. It appears that sakyomicin A is unique in that it inhibits avian myeloblastosis virus (AMV) reverse transcriptase at ca. 0.082 mmolar, HIV reverse transcriptase with similar concentrations and also inhibits the proliferation of HIV growing in MT-4 cells at 0.0025 mmolar concentrations. Futhermore, it does not have any significant cytotoxicity at these dose levels. In the mechanism of activity of sakyomicin A the quinone function and its electron transfer properties seem essential features.[31]

Angucyclines have a very brief history in terms of their synthesis, little attention has been devoted to this subject. The key problem is the construction of their angular framework (i.e. the phenanthrene structure) and the oxygenation pattern of the region immediately adjacent and at the "elbow bend". While there are only a few reports in the literature dealing with the structures based on tetrangulol **12** (where rings A and B are aromatic), there is no published

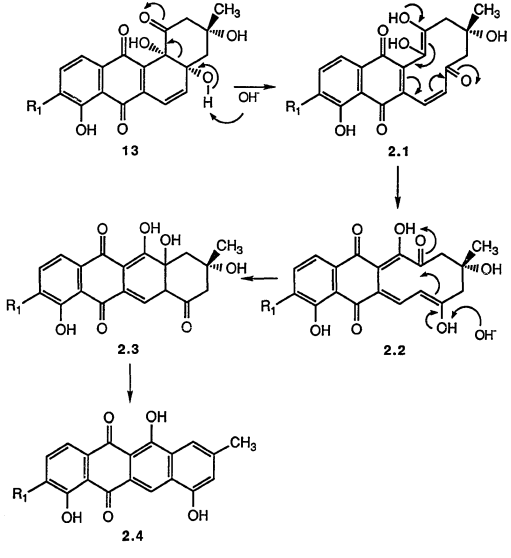
approach towards aquayamycin **13** type of structures (rings A and B are not aromatic and have cis-oriented angular hydroxyl groups at the ring junction). These molecular frameworks are difficult to come by because of their sensitivity towards acidic, basic, thermal and photochemical conditions.[18] Aquayamycin, in acidic conditions, dehydrates to a tetrangulol type of structure **(Scheme 1).**

Scheme 1: Acidic degradation of aquayamycin.

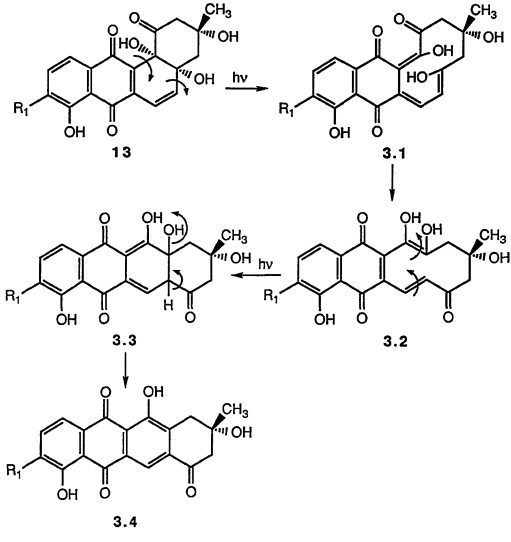


When heated at 220 °C or treated with $Ba(OH)_2$ at r.t., aquayamycin transforms into a 1,6-dihyroxynaphthacenequinone (**Scheme 2**). An interesting photochemical transformation of aquayamycin gives a dehydrated product having 1,5-dihydroxyanthraquinone skeleton (**Scheme 3**).

Scheme 2 : Basic degradation of aquayamycin.



Scheme 3 : Photochemical degradation of aquayamycin.



There are two key approaches for obtaining the "elbow bend" of these angucyclines:

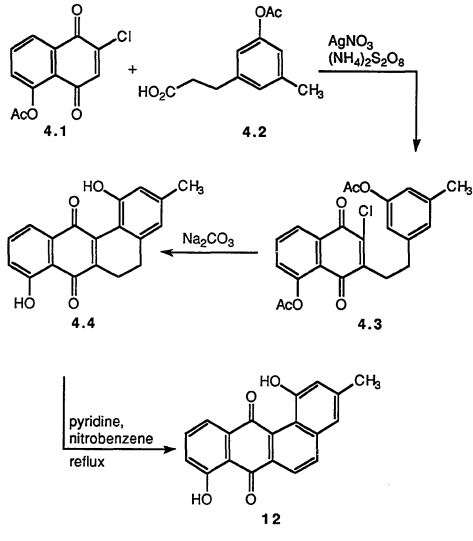
(i) Forming ring B, by ring closure across C-atoms 12a and 12b.[32,33,34]

(ii) Diels Alder cycloaddition using a styrene diene and a quinone dienophile.[35,36]

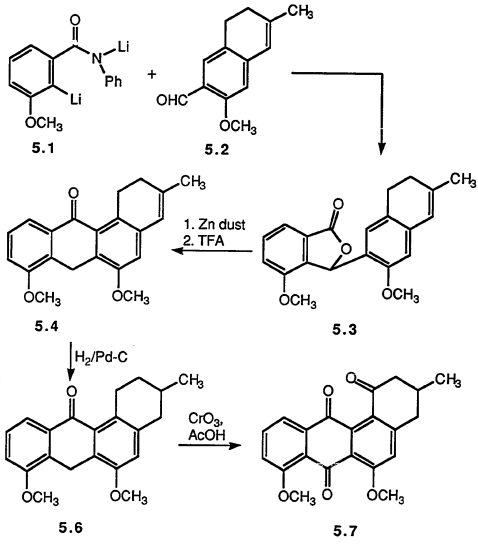
Tetrangulol **12** was synthesized using approach (i)[32] where a 2-chloro-1,4-naphthoquinone **4.3** cyclizes under basic conditions (**Scheme 4**). A similar approach has been used by Uemura et. al.,[33] where acid catalyzed ring closure in phthalide **5.3** yields the elbow bend (**Scheme 5**). Kelly et.al.[34] used a Mallory photochemical phenanthrene synthesis for this purpose in their elegent synthesis of cervinomycin A2 **6.4** (**Scheme 6**).

The cycloaddition approach has been used in the synthesis of ochromycinone **7.4.**[35] The reaction needs a Lewis acid catalyst therefore the intermediate cycloadduct **7.3** could not be isolated (**Scheme 7**). Parker and Ruder[36] have suggested the use of the synthetic equivalent of styrene, a non-aromatic vinylquinone bis-ketal **8.1** (**Scheme 8**), to avoid problems like low reactivity and self polymerization associated with styrene when used as the diene in Diels Alder reactions.

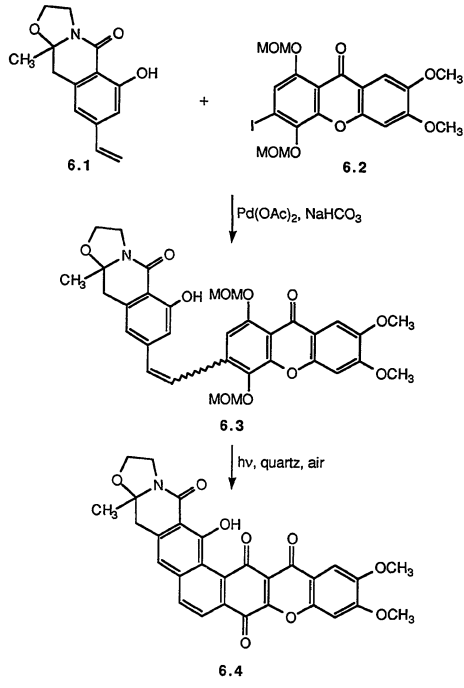
Scheme 4:



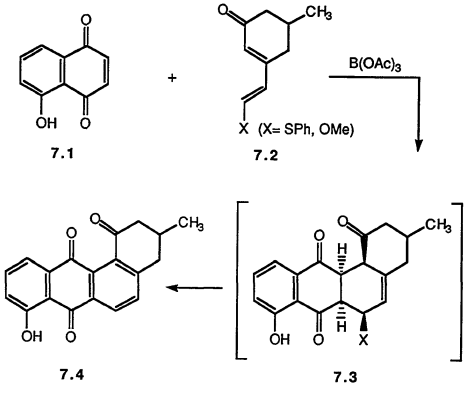
Scheme 5:



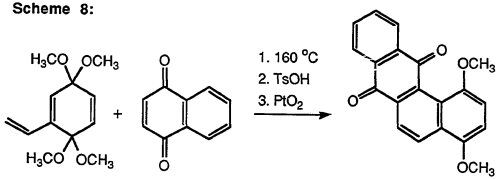
Scheme 6:



Scheme 7:

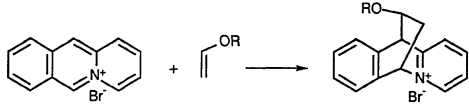


Scheme 8:

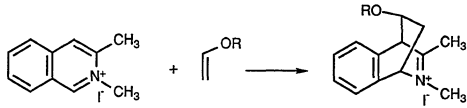


Cycloadditions of Isoquinolinium Salts:

The "inverse"-electron-demand (IED) Diels Alder reaction, follows the converse of the Alder rule,[37] i.e., an electron poor diene reacts with an electron rich dienophile. Bachmann and Deno,[38] in 1949, were the first to suggest this exchange of electronic roles. One example of the IED reaction is the "Bradsher reaction" (named after its inventor). It was first reported in 1968,[39,40] where acridizinium ion **19** reacted with an electron-rich dienophile such as vinyl ether **20**, to form adduct **21**. Later, it was demonstrated that isoquinolinium salt **22**, a system analogous to acridizinium ion, also undergoes a similar reaction to give adduct **23**. These reactions were found to be regiospecific and highly stereospecific, taking place predominantly via *exo*-addition. The substituent at 3-position of the isoquinolinium salt was required to avoid the attack of a second mole of the dienophile on the adduct **23** to give a 2:1 adduct.[41]



19 **20** **21**

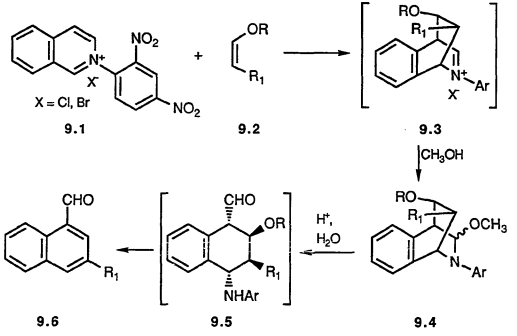


22 **20** **23**

This limitation was overcome in Falck's modification,[42] where a 2,4-dinitrophenyl salt of isoquinoline was used and methanol, used as the solvent,

trapped the cycloadduct **9.3**, to give a tricyclic adduct **9.4**. This trapped adduct was converted to aromatic aldehyde **9.6** (**scheme 9**). The intermediate tetralin **9.5** could not be isolated because of the aqueous acidic conditions used. Because of this limitation this cycloaddition reaction had only a few synthetic applications.[42,43]

Scheme 9: Falck's modification of Bradsher's reaction

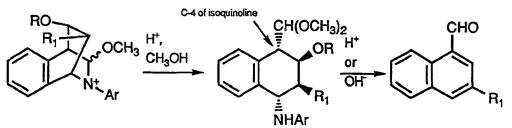


9.1 **9.2** **9.3** **9.4** **9.5** **9.6**

Later, it was shown by Gupta and Franck[44] that, by using anhydrous acidic conditions the tricyclic adduct **9.4** can be opened to give the tetralin (where the aldehyde group is trapped as its acetal) retaining all 4 stereocenters generated in the cycloaddition step. This modification has considerably increased the scope of this reaction, the principal synthetic utility being the facile, stereoselective and high yield preparation of tetralins. The cycloaddition was shown to take place in two steps going via a "one bond product", an

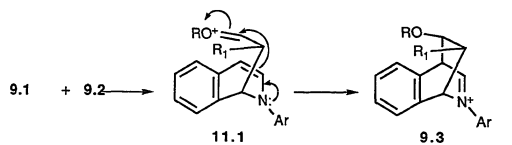
oxocarbonium ion **11.1**, which is then trapped in an intramolecular fashion, by the enamine generated in the first step (**scheme 11**).

Scheme 10: Franck's modification of Bradsher's reaction



9.4 **9.5** **9.6**

Scheme 11: Franck's two step mechanism for Bradsher's reaction



11.1 **9.3**

The important features of this reaction are:

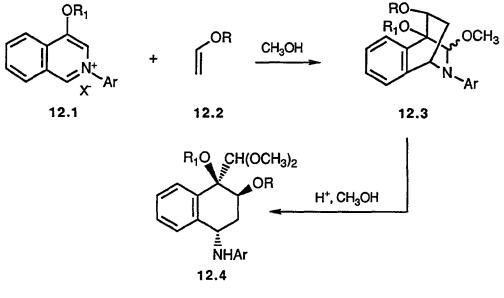
(i) The positioning of the alkyl group of the enol ether **9.2** at C-3 of the naphthaldehyde **9.6**, when the tricyclic adduct **9.4** is opened by aqueous acid.

(ii) The *cis* relationship obtained, between the hydrogen at C-4 of the isoquinolinium salt **9.1** and the alkoxy group of the enol ether **9.2**, in the tetralin **9.5** when the tricyclic adduct **9.4** is opened by anhydrous acid.

We have attempted to utilize the ability of this reaction to give substituted naphthaldehydes, to synthesize naproxen **8**. The unique feature of our approach is, appending a chiral aliphatic chain on the naphthalene nucleus using the Bradsher reaction.

Since, the stereospecificity of the reaction puts a hydrogen at C-4 of the isoquinolinium salt and the alkoxy group of the enol ether in *cis* orientation, in the tetralin **9.5**, we reasoned that if a 4-alkoxy-substituted isoquinolinium salt **12.1** were used, the tetralin product **12.4** would have vicinal alkoxy groups in a *cis* orientation (**scheme 12**). We have attempted to utilize this possibility, in our synthesis of angucyclines like sakyomicin **17** and aquayamicin **13**, which have *cis* oriented angular hydroxyls at their C-atoms 4a and 12b.

Scheme 12:



12.1 **12.2** **12.3** **12.4**

Proposed Schemes:

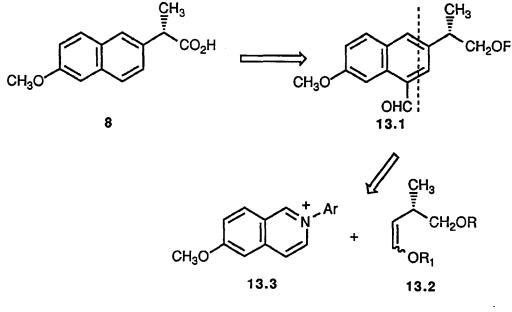
Naproxen: The synthetic program based on a Bradsher reaction, for naproxen, can be divided into three parts (**scheme13**):

(i) Synthesis of the chiral alkyl chain **13.2**, with (S) chiral center as in naproxen, and having a enol ether residue for cycloaddition.

(ii) Synthesis of 6-methoxyisoquinolinum 2,4-dinitrophenyl salt **13.3.**

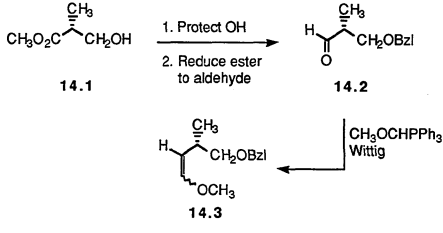
(iii) Cycloaddition between **13.2** and **13.3**.

Scheme 13:



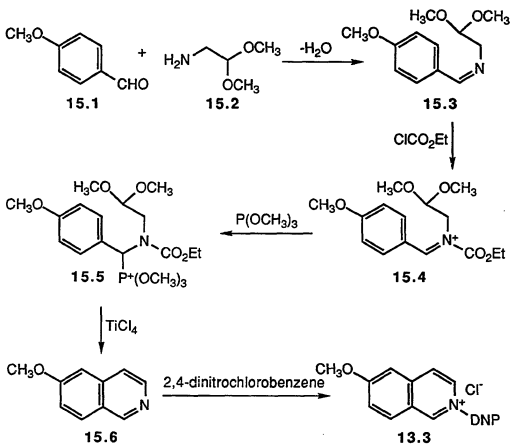
The chiral enol ether will be synthesized starting with commercially available (R)-Roche alcohol **14.1**. The chiral center will become the α-C-atom in naproxen. The enol ether residue will be generated by methoxymethylenation using a Wittig reaction[45] (**scheme 14**). 6-Methoxyisoquinoline will be prepared using Hendrickson's method,[46] starting from 4-methoxybenzaldehyde (**scheme 15**), whereupon quaternization of the nitrogen, with 2,4-dinitrochlorobenzene, will yield the desired salt **13.3**. Bradsher cycloaddition between the diene (isoquinolinium salt) and the dienophile (enol ether) will yield the naphthaldehyde **13.1**, which will then be converted into naproxen via decarbonylation and oxidation of the primary alcohol to carboxylic acid.

Scheme 14: Synthetic scheme for side chain of naproxen



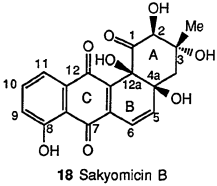
14.1 **14.2** **14.3**

Scheme 15: Hendrickson's isoquinoline synthesis

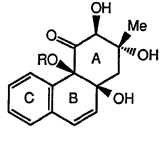


Sakyomicin and Aquayamycin: Our model compound for these angucyclins is the ABC ring analog **24**. The synthetic scheme can be explained on the basis of the retrosynthetic analysis (**scheme 16**). The target molecule **24** can be obtained by generating the 5-6 double bond using Hoffmann degradation method, from the amine **16.1**. This amine is the hydrolysis product of aminal **16.2**, which , by doing a retro Bradsher reaction, shows that it can be obtained from the enol ether **16.3**. Thus the key step in this synthesis is an

intramolecular version of Bradsher cycloaddition, which in one step, will generate the "elbow bend" of the angucyclins with *cis* oriented angular hydroxyls at the AB ring junction (these hydroxyls correspond to the hydroxyls at C-atoms 4a and 12b in sakyomicin and aquayamycin). The precursor required for this intramolecular cycloaddition is a 4-alkoxyisoquinoline, with a chiral alkyl chain substituted at its C-3 **16.3.** The chiral C-atom of this alkyl chain will be C-3 of the angucyclin and the enol ether precursor on its distal end will be used as the dienophile in the proposed intramolecular cycloaddition.

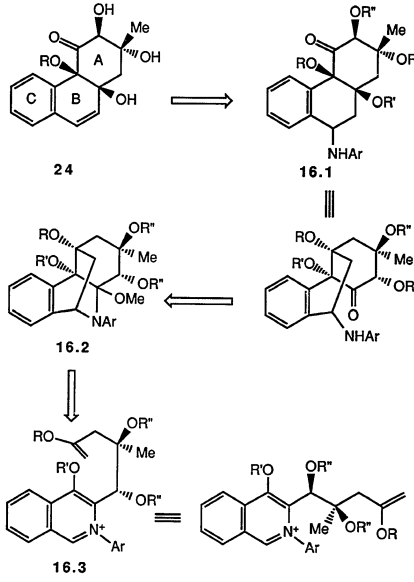


18 Sakyomicin B



24

Scheme 16: Retrosynthesis for angucyclins



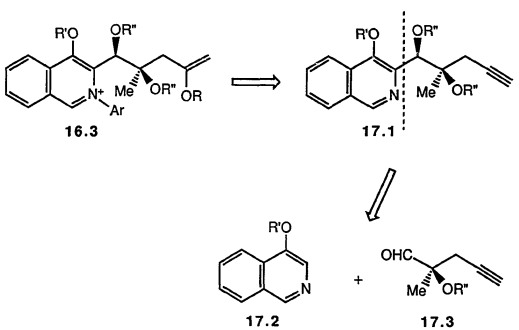
The synthetic scheme for this special isoquinoline **16.3** consists of three parts (**scheme 17**):

(i) Synthesis of isoquinoline portion.

(ii) Synthesis of the alkyl chain.

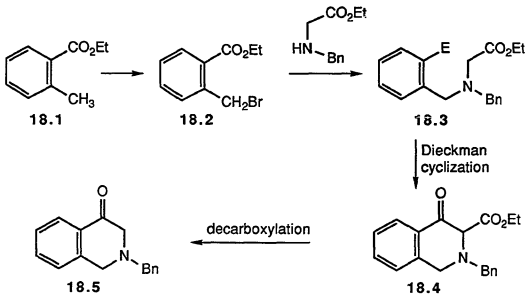
(iii) Merging the two portions to generate the desired isoquinoline.

Scheme 17:

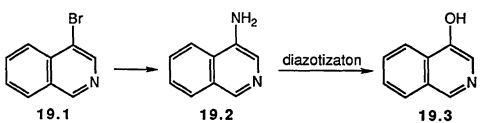


The isoquinoline portion can be synthesized, either using a Roche isoquinoline synthesis[47] (**scheme 18**) or starting from 4-bromoisoquinoline in two steps, first converting the bromo into a amino group[48] and then diazotization[49] to give 4-hydroxy derivative (**scheme 19**).

Scheme 18: Roche isoquinoline synthesis

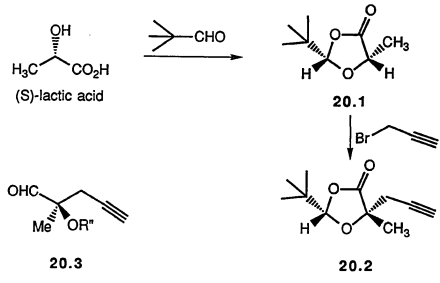


Scheme 19:



The alkyl chain with desired stereochemistry at the future C-3 of the angucycline will be synthesized by Seebach's method of asymmetric alkylation[50] (**scheme 20**) starting from (S)-lactic acid. The two portions will be merged via an aldol reaction between C-3 anion of the isoquinoline **18.5** or **19.3** and the aldehyde **20.3** or a Claisen condensation with the lactone **20.2**.

Scheme 20: Seebach's asymmetric alkylation

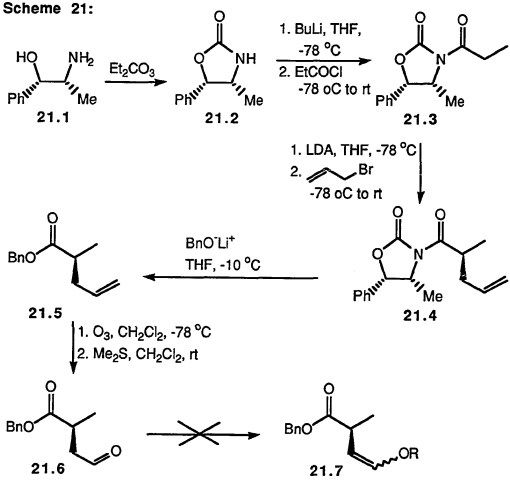


RESULTS AND DISCUSSION

Naproxen:

(i) Synthesis of the Vinyl Ether Portion: Our first attempt to generate the chiral center of naproxen relied on Evan's chiral auxiliary **21.2** [51] **(scheme 21)**. Commercially available (1S,2R)-(+)-norephedrine **21.1** was converted into oxazolidone **21.2**, by reaction with diethyl carbonate.

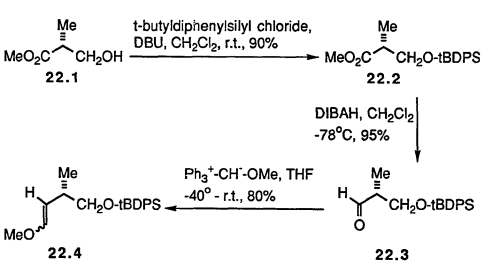
Scheme 21:



The N-propionyloxazolidone **21.3** was prepared in 85% yield, by lithiation of **21.2** and subsequent reaction with propionyl chloride. The chiral amide **21.3** was alkylated using LDA and propenyl bromide to give **21.4** (S-epimer/R-epimer > 99/1, after purification). Trans esterification with $PhCH_2O^-Li^+$ gave benzyl ester **21.5**, which was subjected to ozonolysis to give aldehyde **21.6**. Conversion of this aldehyde to enol ether **21.7** proved unsuccessful. In all the attempts for this conversion either the starting aldehyde or its acetal was recovered. We abandoned this scheme because of the problem in the final step.

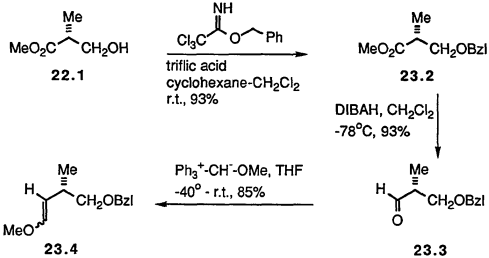
The alternate route to **21.2** (**scheme 22**) involved the use of a chiral building block, the Roche alcohol (both R and S isomers are commercially available). Starting with the R-isomer **22.1**, the hydroxyl group was protected as the t-butyldiphenylsilyl ether **22.2** using t-butyldiphenylsilyl chloride and DBU. Racemization at the α C-atom of **21.1** under these basic conditions was of concerned, therefore benzyl ether was also used for this purpose (benzyl trichloroacetimidate and triflic acid, these conditions have been reported not to

Scheme 22:



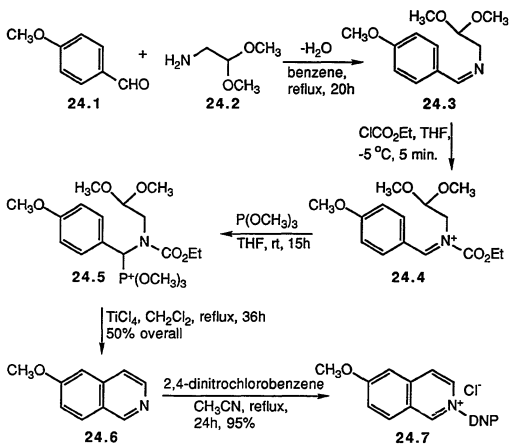
interfere with the chiral center, **scheme 23**).[52] The ester function of **22.2** was reduced to an aldehyde (**22.3**)[53] in 95% yield and subsequent methoxymethylenation using a Wittig reaction[45] gave the desired vinyl ether **22.4** as a mixture of its *cis* and *trans* isomers (*trans* being the major isomer), which was used for further reaction without any separation.

Scheme 23:



(ii) Synthesis of the Isoquinoline Portion: 6-Methoxyisoquinoline was prepared using Hendrickson's method[46] (**scheme 24**). 4-Methoxybenzaldehyde and aminoacetaldehydedimethylacetal were condensed by azeotropic removal of water to give aldimine **24.3.** Quaternization of the nitrogen with ethylchloroformate followed by the treatment with trimethylphosphite gave **24.5,** which was cyclized and then aromatized by $TiCl_4$ treatment to give desired isoquinoline **24.6**. Overall yield of 6-methoxyisoquinoline was 50% (reported 75%). 2,4-Dinitrophenyl salt of **24.7**

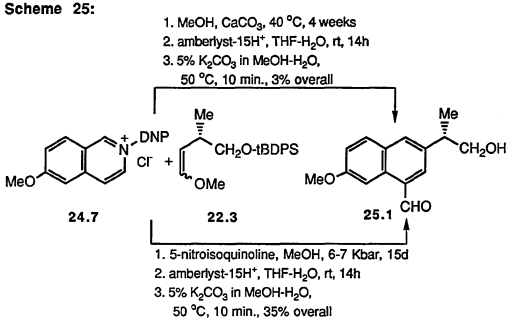
Scheme 24:



was made in 95% yield by refluxing it with 2,4-dinitrochlorobenzene in acetonitrile.

(iii) Cycloaddition of the Isoquinoline and the Vinyl Ether Portions: Cycloaddition of the isoquinolinium salt **24.7** with the vinyl ether **22.3** using our standard protocol,[44] i.e. methanol as the solvent and $CaCO_3$ as the buffer at 40 °C, followed by acid catalyzed (amberlyst-H+, aq. THF) opening of the cycloadduct and aromatization (K_2CO_3, aq. methanol) gave the naphthaldehyde **25.1** in only 3% overall yield **(scheme 25).**

Scheme 25:

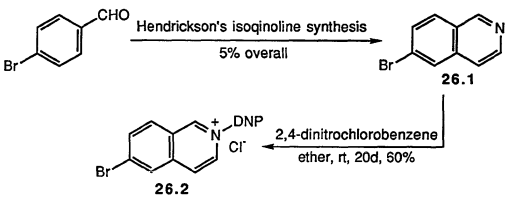


The reaction time was unexpectedly long and >10 equivalents of the vinyl ether were added during this period. The cycloaddition under high pressure (6-7 Kbar), where 5-nitroisoquinoline replaced $CaCO_3$ as the acid scavenger, increased the yield to 30%. However, the reaction took 15 days and 7 equivalents of the vinyl ether.

It was thought that the slow rate of reaction might be due to the 6-methoxy group, which is in conjugation with positively charged nitrogen, therefore it can deactivate the isoquinolinium salt **24.7** for the cycloaddition (the vinyl ether **22.3** adds to isoquinolinium salt, with no 6- methoxy group, in good yields). Based on this reasoning we modified our synthetic scheme and replaced the 6-methoxy substituent with a bromo. The 6-bromo substituent would not deactivate the isoquinolinium salt and could be converted into the corresponding methoxy by the treatment with copper methoxide.[54] 6-Bromoisoquinoline **26.1** was synthesized using Hendrickson's method starting

with 4-bromobenzadehyde, in 5% overall yield only. On the treatment with 2,4-dinitrochlorobenzene in ether at room temperature, **26.1** gave the salt **26.2**, in 60% yield (**scheme 26**).

Scheme 26:



The cycloaddition of this salt **26.2** with the vinyl ether **22.3**, at atmospheric pressure, followed by ring opening and aromatization gave the naphthaldehyde in 20% overall yield. This yield could be increased to 50% by using the high pressure conditions. Though the reaction times were shorter (14 days at atmospheric pressure and 4 days at high pressure) as compare to those in the case of 6-methoxy series, an excess of vinyl ether **22.3** was needed (5 equivalents).

We abandoned this scheme because of the unsatisfactory results in the cycloaddition and also due to the low yields in the synthesis of 6-bromoisoquinoline (5%), the low yields in its salt formation (60%) and the probability of racemization on the treatment with copper methoxide during the convertion of 6-bromo into 6-methoxy group.

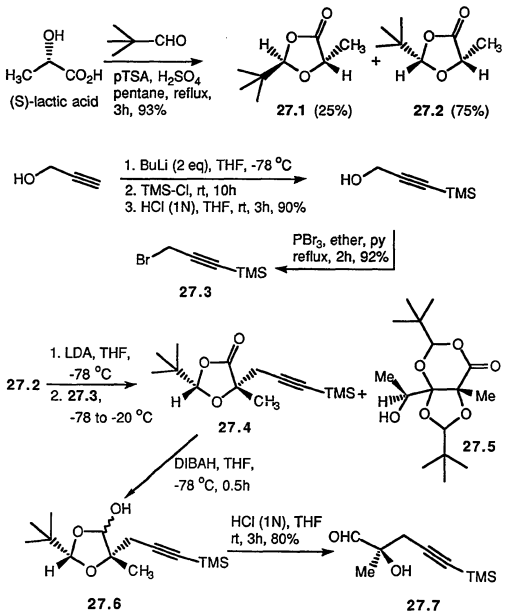
Our approach to the synthesis of naproxen was disappointing because of low yields, long reaction times and requirement of excess of vinyl ether, which itself

is synthesized in three steps. Attempts to circumvent these shortcomings were not pursued, however, we feel that better results could be obtained if the cycloaddition is carried out at 16-17 Kbar pressure, for which the equipment is now available.

Sakyomicin and Aquayamycin:

(i) Synthesis of the Chiral Side Chain: Seebach's asymmetric alkylation worked well for the synthesis of the side chain with the desired stereochemistry at the carbon atom which will become the C-3 in the target molecule (**scheme 27**). Thus S-lactic acid on reaction with pivalaldehyde under acid catalyzed conditions and azeotropic removal of water gave a crude mixture of the acetals **27.1** and **27.2** in a 4:1 ratio favoring the *cis* isomer **27.2**. Two crystallizations from hexane/ether at -78 °C gave the desired isomer **27.2** in > 96% purity. The alkylation of **27.2** using LDA and trimethylsilylpropargyl bromide **27.3** (made from trimethylsilylation of the dianion of propargyl alcohol and subsequent partial hydrolysis to give trimethylsilylpropargyl alcohol followed by the conversion of the hydroxyl to a bromo using PBr_3),[55] proceeded in low yields due to the self-condensation of **27.2** to give **27.5** (Seebach has also reported formation of this product in his alkylations). Replacement of LDA by lithium bis(trimethylsilyl)amide did not solve the problem but reverse addition did, *ie*, dropwise addition of a solution of **27.2** to the lithium base. The alkylation product **27.4** was obtained in 75% yield following these modifications. DIBAH reduction of **27.4** gave the hemiacetal **27.6** which was hydrolyzed to the aldehyde **27.7** in 80% yield.

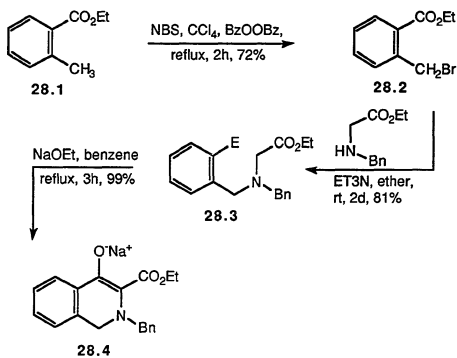
Scheme 27:



(ii) Synthesis of the Isoquinoline Portion: The isoquinoline part was synthesized using the Roche isoquinoline synthesis[47] **(scheme 28)**. Methyl-o-toluate **28.1** on NBS bromination gave the benzyl bromide **28.2** in 72% yield.

Reaction of **28.2** with N-benzylglycine ethyl ester gave the diester **28.3** in 81% yield, which was quantitatively converted into **28.4** after Dieckman cyclization.

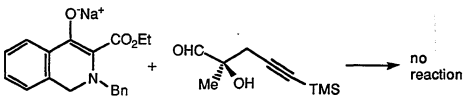
Scheme 28:



(iii) Aldol Condensation: The sodium salt **28.4** did not react with the aldehyde **27.7** (**scheme 29**). This was probably due to the steric bulk of the quaternary α-carbon of **27.7**. Compound **28.4** was then hydrolyzed and decarboxylated to give a very unstable ketone **30.1** in low yield (25%). The LDA anion of **30.1** showed no reaction with **27.7** (**scheme 30**).

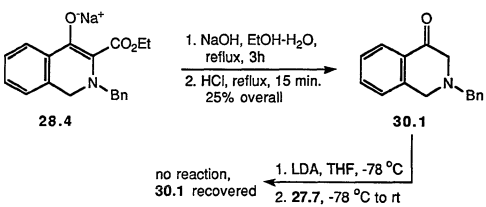
Since the hydrolysis and decarboxylation of **28.4** gave very low yields and also the product **30.1** was difficult to handle, we changed our synthetic scheme for the required isoquinoline portion.

Scheme 29:



28.4 **27.7**

Scheme 30:



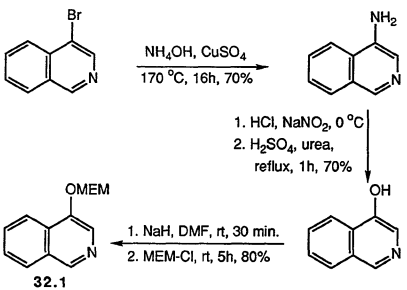
28.4 **30.1**

(iv) Direct Lithiation of 4-Alkoxyisoquinoline: Isoquinoline itself is known to give lithiation at its C-1 position,[56] when reacted with LDA (however with the bases like BuLi, nucleophilic addition takes place at C-1). We thought of directing the lithiation to the C-3 by using a chelating group at the 4-hydroxy. Protecting group methoxyethoxymethyl (MEM) was selected for this purpose, which can serve as a handle for the lithiation at C-3 by chelation via its ether oxygen (**scheme 31**).

Scheme 31:

4-Hydroxyisoquinoline was synthesized in two steps, starting with 4-bromoisoquinoline (**scheme 32**). The 4-bromo group was converted into an amino[48] which was diazotized and replaced with a hydroxyl.[49] This 4-hydroxy group was protected as its MEM ether by the treatment with NaH and then MEM-chloride.

Scheme 32:

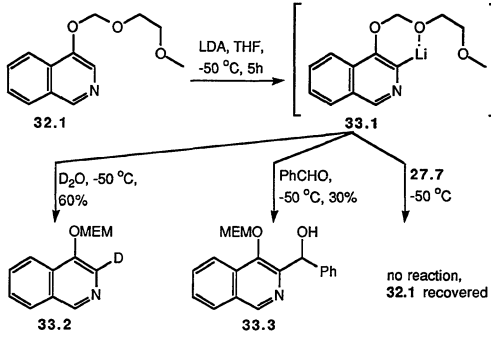


32.1

The treatment with LDA (in THF at -50 °C) of **32.1** gave lithiation at the C-3, which could be detected by the D_2O-trapping and ^1H nmr of the deuterated product **33.2**, showing that deprotonation at C-3 could be achieved in 60% yield (**scheme 33**). The formation of this anion was further confirmed by reacting it with benzaldehyde to give the product **33.3**. The reaction of the

lithium anion **33.1** with the aldehyde **27.7** did not give the desired aldol product, the isoquinoline was recovered unchanged and the aldehyde **27.7** got transformed into unidentifiable products.

Scheme 33:



Since a large excess of LDA was required for the deprotonation of **32.1** it could be destroying the aldehyde **27.7** before it could react with the anion of the isoquinoline. For the completion of this synthesis we feel that the anion **33.1** could be trapped as its tri-alkyltin derivative, which could be isolated and purified. This tin derivative then, could be trans metalated using stoichiometric amounts of LDA or BuLi and used in an aldol reaction with the aldehyde **27.7** or a Claisen reaction with the lactone **20.2.**

EXPERIMENTAL

General Experimental: NMR spectra were recorded on GE QE 300, JEOL FX 400 instruments with $CDCl_3$ as solvent. Elemental analyses were performed by Spang Microanalytical Laboratory, Eagle Harbor, MI. Melting points were determined on a Fisher-John melting point apparatus and are uncorrected. Optical rotations were determined using a Rudolph Research AUTOPOL III automatic polarimeter. Thin-layer chromatograms were done on precoated TLC sheets of silica gel 60 F_{254} (E. Merck) and short- long-wave ultraviolet light was used to visualize the spots. PLC plates were prepared by using Kieselgel 60 PF_{254} (E. Merck), and chromatotron (radial chromatography) plates were prepared by using Kieselgel 60 PF_{254} gipshaltig (E. Merck). Flash chromatography was performed with silica gel (230-400 mesh) purchased from Aldrich Chemical Co. Methanol was distilled from Mg and stored over 3 A° MS. Dry THF was obtained by distillation, under nitrogen, from sodium-benzophenone ketyl. Dichloromethane was distilled from P_2O_5. Other solvents were purified and dried by using standard procedures.

General Procedure for Synthesis of Isoquinolines:[46] Aromatic aldehyde (70 mmol) and aminoacetaldehydedimethylacetal (7.8 g, 70 mmol) in 50 ml of benzene are refluxed into a Dean-Stark trap for 20 h. The solvent is evaporated under reduced pressure, twice with added benzene. The resultant thick oil is dissolved in dry THF and the solution is cooled to -5 °C. 7.1 ml (70 mmol) of ethylchloroformate is added with rapid stirring. After 5 min 10.5 ml (90 mmol) of trimethylphosphite is added, cooling bath is removed and stirring is continued for 15 h. The solvent is removed under reduced pressure, twice with added toluene to remove traces of trimethylphosphite. The residue is dissolved

in dry methylene chloride and 50 ml (0.45 mmol) of $TiCl_4$ is added. The reaction mixture is refluxed under a drying tube for 36 h and after cooling the mixture is added dropwise to a stirred ice cold solution of NaOH. An additional amount of NaOH is added to maintain a strong alkaline pH. The resultant mixture is filtered, the paste of TiO_2 is washed with ethyl acetate several times. The combined organic washings are extracted with 3N HCl (3X50 ml) and the extract is washed with methylene chloride. The aqueous layer is made alkaline with NaOH solution, extracted with methylene chloride (3X50 ml), the combined extract is washed with brine and dried over $MgSO_4$. Evaporation of the solvent under reduced pressure gives pure isoquinoline.

6-Methoxyisoquinoline(24.6): Yield 50% (reported 75%); Colorless oil; ^1H NMR (300 MHz, $CDCl_3$) δ 9.107 (s, 1H), 8.45 (d, J = 6 Hz, 1H), 7.83 (d, J = 9 Hz, 1H), 7.53 (d, J = 6 Hz, 1H), 7.23 (dd, J = 9 Hz, 2 Hz, 1H), 7.03 (d, J = 2 Hz, 1H), 3.92 (s, 3H).

6-Bromoisoquinoline(26.1): Yield 5%; Colorless oil; ^1H NMR (300 MHz, $CDCl_3$) δ 9.123 (s, 1H), 8.536 (d, J = 6.0 Hz, 1H), 7.990 (s, 1H), 7.830 (d, J = 9 Hz, 1H), 7.675 (dd, J = 9.0, 1.8 Hz, 1H), 7.552 (d, J = 6.0 Hz, 1H).

2,4-Dinitrophenylisoquinolinium Salts:

General Procedure A: Isoquinoline (5.5 mmol) and 1.114 g (5.5 mmol) of 2,4-dinitrochlorobenzene in 5 ml of acetonitrile are refluxed under nitrogen for 24 h. The salt precipitates out of the reaction mixture which is cooled, filtered and washed with ethyl ether.

General Procedure B: Isoquinoline (5.5 mmol) and 1.114 g (5.5 mmol) of 2,4-dinitrochlorobenzene in 5 ml of ethyl ether are stirred at r.t. The progress of

the reaction is monitored by tlc for disappearance of the isoquinoline. After the completion of the reaction salt is filtered off and washed with ethyl ether.

2-(2',4'-Dinitrophenyl)-6-methoxyisoquinolinium Chloride(24.7): Yield 95%; Yellow solid; ^{1}H NMR (300 MHz, CD_3OD) δ 9.92 (s, 1H), 9.28 (d, J = 2.4 Hz, 1H), 8.92 (dd, J = 8.7, 2.4 Hz, 1H), 8.70 (dd, J = 1.5, 6.9 Hz, 1H), 8.46 (d, J = 6.9 Hz, 1H), 8.44 (d, J = 9 Hz, 1H), 8.33 (d, J = 8.7 Hz, 1H), 7.84 (d, J = 2.4 Hz, 1H), 7.75 (dd, J = 9.0, 2.4 Hz, 1H), 4.19 (s, 3H).

2-(2',4'-Dinitrophenyl)-6-bromoisoquinolinium Chloride(26.2): Yield 60%; ^{1}H NMR (300 MHz, CD_3OD) δ 10.26 (s, 1H), 9.31 (d, J = 2.4 Hz, 1H), 8.90-9.00 (m, 2H), 8.77 (s, 1H), 8.64 (d, 6.9 Hz, 1H), 8.46 (s, 1H), 8.30-8.40 (m, 2H).

Methyl-3-t-butyldiphenylsilyloxy-2-methylpropionate (22.2): To a stirred solution of (R)-Roche alcohol (**22.1**, 8.3 ml, 75 mmol) and t-butyldiphenylsilyl chloride (22 g, 80 mmol) in methylene chloride (150 ml) was added DBU (15.2 g, 100 mmol) under argon atmosphere. After stirring for 18 h at r.t. the reaction mixture was washed with water (150 ml), a saturated solution of $NaHCO_3$ (100 ml), water (100 ml) and brine (100 ml). The organic layer was dried over $MgSO_4$ and concentrated in vacuo followed by distillation of the residue to obtain 24.06 g (90%) of **22.2**; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.06 (s, 9H), 1.21 (d, J = 6.3 Hz, 3H), 2.70-2.82 (m, 1H), 3.73 (s, 3H), 3.76-3.81 (m, 1H), 3.85-3.92 (m, 1H), 7.40-7.51 (m, 6H), 7.68-7.80 (m, 4H).

3-t-butyldiphenylsilyloxy-2-methylpropionaldehyde (22.3):[53] A solution of **22.2** (2.0 g, 5.62 mmol) in 30 ml of dry methylene chloride was treated with DIBAH (6.7 ml of 1M solution in hexane, 6.7 mmol) at -78 °C for 15 min. The reaction was quenched with a saturated solution of NH_4Cl. The reaction mixture was filtered through a pad of celite. Evaporation of the solvent

under reduced pressure gave **22.3** which was pure enough for further use. Yield 1.74 g (95%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.03 (s, 9H), 1.08 (d, J = 6.9 Hz, 3H), 2.50-2.60 (m, 1H), 3.80-3.95 (m, 2H), 7.35-7.46 (m, 6H), 7.60-7.70 (m, 4H), 9.75 (d, J = 1.8 Hz, 1H).

4-Methoxy-2-methylbut-3-ene-1-ol t-butyldimethylsilyl Ether (22.4): To a stirred suspension of methoxymethyltriphenylphosphonium chloride (2.6 g, 90%, 6.8 mmol) in dry THF (25 ml) was added n-BuLi dropwise (3.1 ml, 2.2 M solution, 6.8 mmol) at -78 °C. After stirring at -78 °C for 0.5 h, the reaction mixture was slowly warmed to 0 °C (the formation of the ylide was indicated by the appearance of red color and disappearance of insoluble phosphonium salt). The ylide solution was added dropwise to a solution of the aldehyde **22.3** (1.708 g, 5.23 mmol) in 20 ml of dry THF at -40 °C. The stirring was continued at -40 °C for 2 h and then the reaction mixture was warmed to room temperature over a period of 3 h. The reaction mixture was filtered and the solvent was evaporated under reduced pressure. The residue was washed with pentane and the pentane solution was washed with water, brine and dried over $MgSO_4$. The solvent was evaporated under reduced pressure to get **22.4** as a mixture of its *cis* and *trans* isomers (1.48 g, 80%); ^{1}H NMR (300 MHz, $CDCl_3$), characteristic signals of **trans 22.4** δ 3.53 (s, 3H, OCH_3), 4.68 (dd, J = 12.6, 8.1 Hz, 1H, MeOCH:C*H*), 6.35 (d, J = 12.6 Hz, 1H, MeOC*H*); characteristic signals of **cis 22.4** δ 3.59 (s, 3H, OCH_3), 4.28 (dd, J = 9.0, 6.3 Hz, 1H, MeOCH:C*H*), 5.90 (d, J = 6.3 Hz, 1H, MeOC*H*).

Cycloaddition of Isoquinolinium Salts and Vinyl Ethers:

General Procedure A: A mixture of the isoquinolinium salt (0.3 mmol), $CaCO_3$ (180 mg,1.8 mmol) and the vinyl ether (0.6 mmol) is stirred in dry

methanol (1.0 ml) at 40°C. Progress of the reaction is followed by tlc. Additional amounts of vinyl ether are added whenever it is absent from the reaction mixture (due to decomposition). After completion of the reaction (disappearance of salt on tlc) $CaCO_3$ is filtered off through celite and the solvent is evaporated under reduced pressure.

General Procedure B: The isoquinolinium salt (0.3 mmol), 5-nitroisoquinoline (103.5 mg, 0.6 mmol) and the vinyl ether (0.6 mmol) are dissolved in 1 ml of dry methanol. This solution is taken in a 3 cc syringe and is put into high pressure equipment. It is kept at 6-7 Kbar till the reaction is complete (followed by tlc). The reaction mixture is filtered through celite and solvent is removed under reduced pressure.

Ring Opening of Initial Cycloadducts to Tetralins: General Procedure: The crude cycloadduct is dissolved in 10 ml of THF-H_2O (15:1) mixture and 100 mg of amberlyst-15H^+ is added. The reaction mixture is stirred overnight at r.t. The resin is filtered off , the filtrate is added to 100 ml of water and extracted with ethyl acetate (3X25 ml). The combined organic extracts are dried over $MgSO_4$ and the solvent is evaporated under reduced pressure to give crude tetralins.

Aromatization of Tetralins to Naphthaldehydes: General Procedure: The crude tetralin is dissolved in THF (10 ml) and is treated with 5% solution of K_2CO_3 in methanol-water (10:1) mixture, at 50 °C for 5-10 min. The reaction mixture is added to 100 ml of water and is extracted with ethyl acetate (3X25 ml). The combined organic extracts are dried over $MgSO_4$ and the solvent is evaporated under reduced pressure to give crude product which is purified by

radial chromatography (ethyl acetate-petroleum ether 5:95) to give pure naphthaldehyde.

Methoxy-naphthaldehyde (25.1): Yield 50% (Using **procedure B** for cycloaddition); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.44 (d, J = 6.9 Hz, 3H, CH_3), 1.77 (br s, 1H, O*H*), 3.21 (hextet, J = 6.9 Hz, 1H, C*H*-CH_3), 3.87 (d, J = 6.9 Hz, 2H, CH_2OH), 4.01 (s, 3H, OCH_3), 7.25 (dd, J = 9.0, 2.7 Hz, 1H, Ar-*H*), 7.80 (d, J = 9.0 Hz, 1H, Ar-*H*), 7.87 (d, J = 1.5 Hz, 1H, Ar-*H*), 7.91 (s, 1H, Ar-*H*), 8.68 (d, J = 2.1 Hz, 1H, Ar-*H*), 10.31 (s, 1H, C*H*O).

o-Carboethoxybenzyl Bromide (28.2):[47] To a solution of ethyl o-toluate **28.1** (8 ml, 50 mmol) and NBS (8.9 g, 50 mmol) in CCl_4 (125 ml), was added dibenzoylperoxide (250 mg). The reaction mixture was refluxed for 2 h, cooled and then filtered. The filtrate was washed successively with saturated solution of $NaHCO_3$, 0.1 N HCl and H_2O. Evaporation of the solvent followed by distillation of the resulting residue (bp 93 °C at 0.4 mm Hg) gave 8.68 g of **28.2** (72%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.40 (t, J = 5.4 Hz, 3H), 4.38 (q, J = 5.4 Hz, 2H), 4.94 (s, 2H), 7.50-7.30 (m, 3H), 7.96 (d, J = 8.7 Hz, 1H).

N-Benzyl-N-(o-carboethoxybenzyl)-glycine Ethyl Ester (28.3):[47] A solution of **28.2** (5.167 g, 21.26 mmol), N-benzylglycine ethyl ester (4.0 ml, 21.26 mmol) and triethylamine (4.1 ml, 30 mmol) in dry ether (30 ml) was refluxed for 36 h. Triethylamine hydrobromide thus formed was filtered off and the filtrate was concentrated on a rotary evaporator, to obtain **28.3** (6.03 g, 81%), which was used without further purification; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.23 (t, J = 7.2 Hz, 3H), 1.36 (t, J = 7.2 Hz, 3H), 3.23 (s, 2H), 3.76 (s, 2H), 4.11 (q, J = 7.2 Hz, 2H), 4.18 (s, 2H), 4.32 (q, J = 7.2 Hz, 2H), 7.30-7.15 (m, 6H), 7.42 (dt, J = 7.5, 1.2 Hz, 1H), 7.61 (d, J = 7.5 Hz, 1H), 7.74 (dd, J = 7.5 and 1.2 Hz, 1H).

Sodium Salt (28.4): To a suspension of NaH (132.25 mg, 80%, 4.41 mmol) in benzene (30 ml), 0.5 ml of ethanol was added. After the evolution of H_2 gas had ceased, the diester **28.3** (1.252 g, 3.5 mmol) in 10 ml of benzene was added dropwise. The reaction mixture was refluxed for 2.5 h and then the solvent was evaporated. The resultant yellow solid (**28.4**) was washed with ether; Yield = 1.135 g (99%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.37 (t, J = 7.2 Hz, 3H), 3.53 (s, 2H), 3.73 (s, 2H), 4.23 (q, J = 7.2 Hz, 2H), 7.50-7.20 (m, 9H).

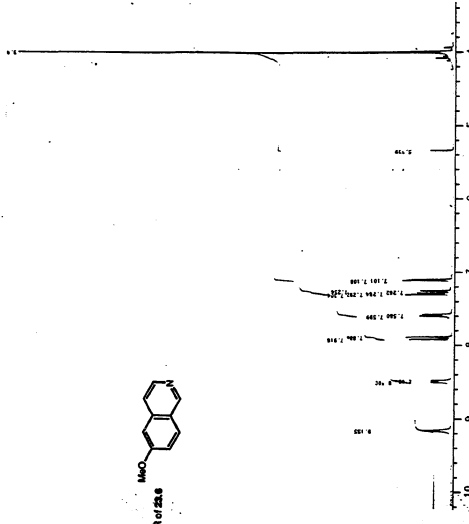
N-Benzyl-1,2,3,4-tetrahydroisoquinolin-4-one (30.1):[47] To a solution of the sodium salt **28.4** (331 mg, 1 mmol) in 8 ml of degased ethanol was added 6 ml of degased 2N NaOH. The reaction mixture was refluxed for 4 h. The resulting mixture was acidified with excess of degased conc. HCl and heating was continued for additional 15 min. After cooling, the reaction mixture was made alkaline by adding 6N NaOH and extracted with ethyl acetate (4X25 ml). The combined organic extracts were dried over $MgSO_4$ and the solvent was evaporated under reduced pressure. Radial chromatography of the residue gave **30.1** in 25% yield; ^{1}H NMR (300 MHz, CD_3COCD_3) δ 3.33 (s, 2H), 3.76 (s, 2H), 3.83 (s, 2H), 7.45-7.25 (m, 7H), 7.56 (dt, J = 7.2, 2.4 Hz, 1H), 7.93 (d, J = 7.2 Hz, 1H).

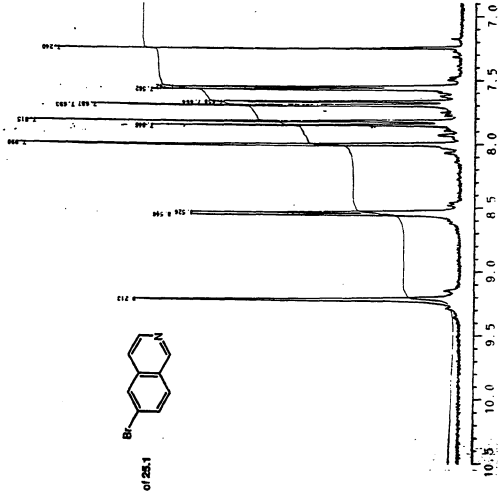
4-Methoxyethoxymethyl Ether of 4-Hydroxy-isoquinoline (32.1): A solution of 4-hydroxy-isoquinoline[48,49] (145 mg, 1 mmol) in dry DMF (4 ml) was added dropwise to a stirred suspension of oil free NaH (80%, 420 mg 1.4 mmol) in 2 ml of dry DMF under nitrogen atmosphere at room temperature. After stirring the reaction mixture for 30 min MEM-Cl (120 µl, 1.05 mmol) was added to it and the stirring was continued for an additional 4 h. The reaction mixture was poured into 150 ml of water and extracted with ethyl acetate (4X30 ml).

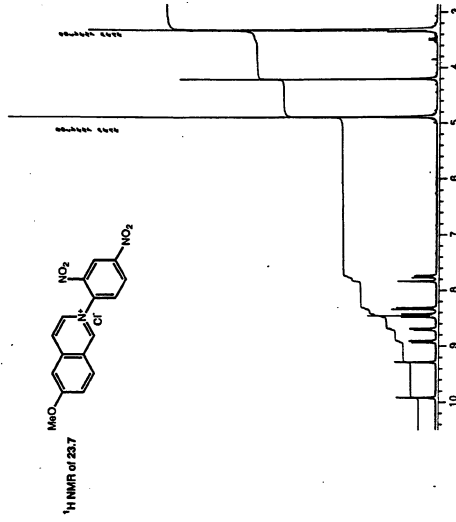
Combined organic extracts were dried over $MgSO_4$ and the solvent was removed under vacuo. Column chromatography of the residue over florisil (methanol-methylene chloride 1:9) gave 213 mg of **32.1**; Yield 91%;; ^1H NMR (300 MHz, $CDCl_3$) δ 3.36 (s, 3H, OCH_3), 3.55-3.60 (m, 2H), 3.87-3.93 (m, 2H), 5.48 (s, 2H, OCH_2O), 7.58 (dt, J = 7.3, 0.6 Hz, 1H), 7.67 (dt, J = 7.3, 0.6 Hz, 1H), 7.92 (d, J = 7.3 Hz, 1H), 8.16 (d, J = 7.3 Hz, 1H), 8.33 (s, 1H, C_3-*H*), 8.92 (s, 1H, C_1-*H*).

Aldol Condensation of the C3-Anion of 32.1 and Benzaldehyde: To a solution of LDA (0.59 mmol) in 1.5 ml of ether was added dry HMPA (0.1 ml) and the solution was cooled to -78 °C. A solution of **32.1** (114 mg, 0.5 mmol) in ether (1.5 ml) was added to the above LDA solution over a period of 2 h with stirring under argon atmosphere. The reaction mixture was stirred for additional 3 h (at ~ -50 °C). The formation of the anion was indicated by the appearence of a red color. The reaction mixture was cooled to -78 °C and benzaldehyde (75 µL, 0.73 mmol) was added. The reaction mixture was allowed to warm up to room temperature, poured into 50 ml of water and extracted with ethyl acetate (3X30 ml). The organic extract was dried over $MgSO_4$ and the solvent was removed under vacuo. Radial chromatography of the residue (methanol-methylene chloride 1:25) gave 6 mg of **33.3**; Yield 2%;; ^1H NMR (300 MHz, $CDCl_3$) δ 3.38 (s, 3H, OCH_3), 3.55-3.61 (m, 2H), 3.85-3.95 (m, 1H), 3.97-4.05 (m, 1H), 4.96 (br s, 2H, O*H*), 5.12 (AB q, Δν = 22.0 Hz, J_{AB} = 6.8 Hz, 2H, OCH_2O), 6.28 (s, 1H, PhC*H*), 7.16-7.30 (m, 3H), 7.42 (d, J = 7.3 Hz, 2H), 7.56 (dt, J = 7.4, 0.5 Hz, 1H), 7.71 (dt, J = 7.4, 0.5 Hz, 1H), 7.96 (d, J = 7.4 Hz, 1H), 8.12(d, J = 7.4 Hz, 1H), 9.07 (s, 1H, C_1-*H*).

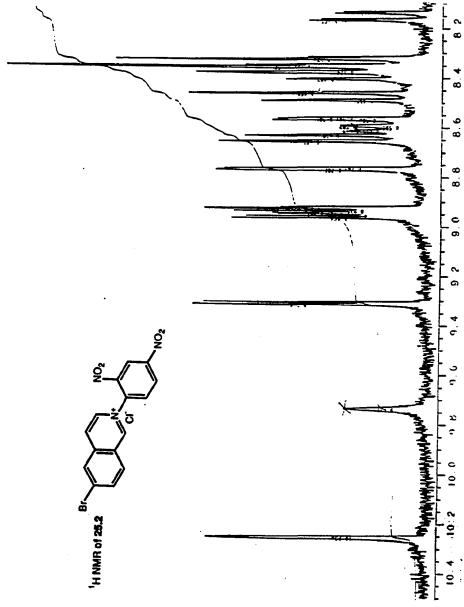
APPENDIX

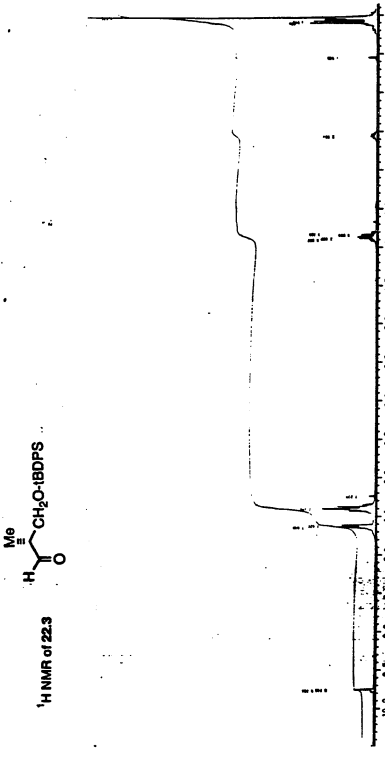


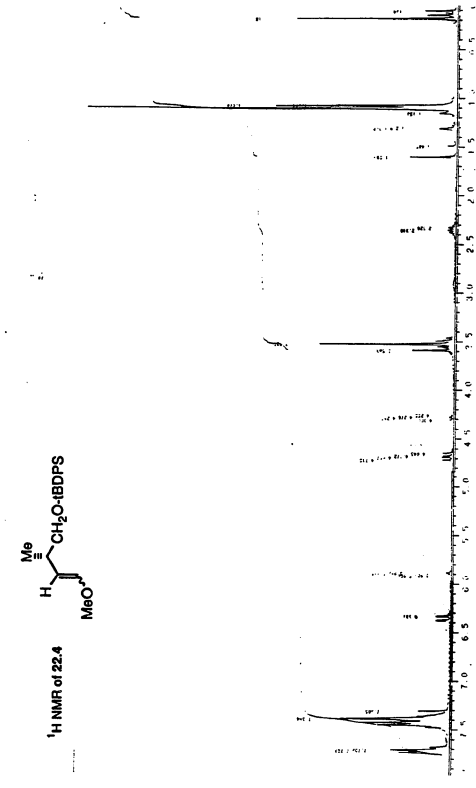




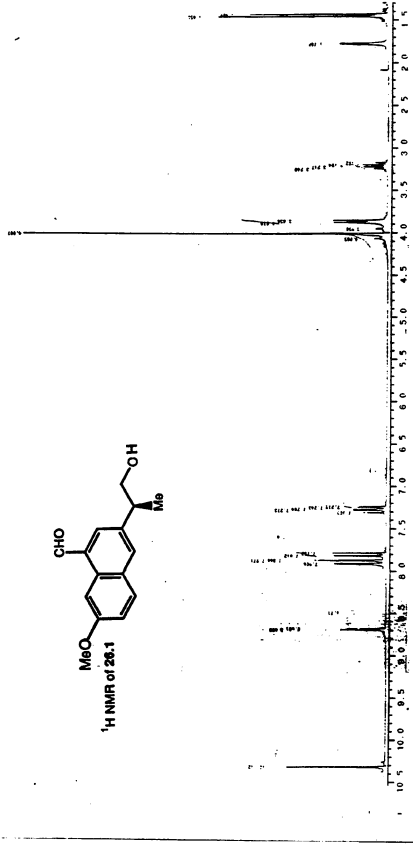
^{1}H NMR of 23.7



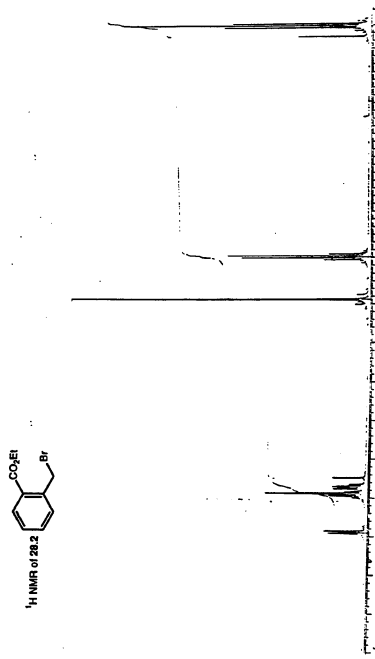




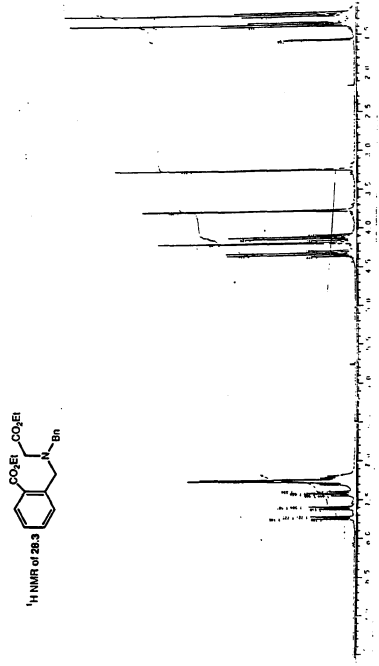
^{1}H NMR of 22.4



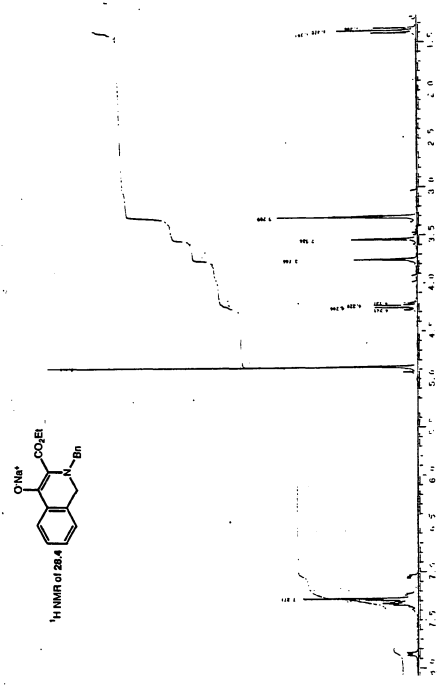
^{1}H NMR of 26.1



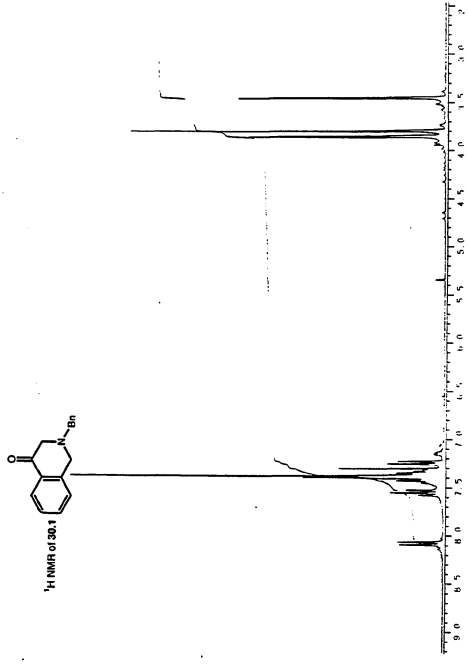
^{1}H NMR of 28.2

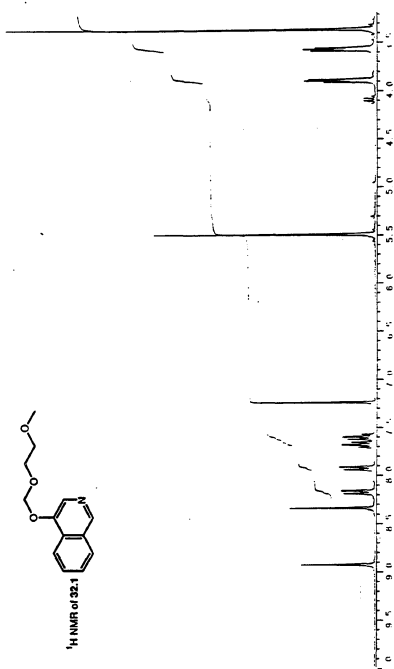


^{1}H NMR of 28.3

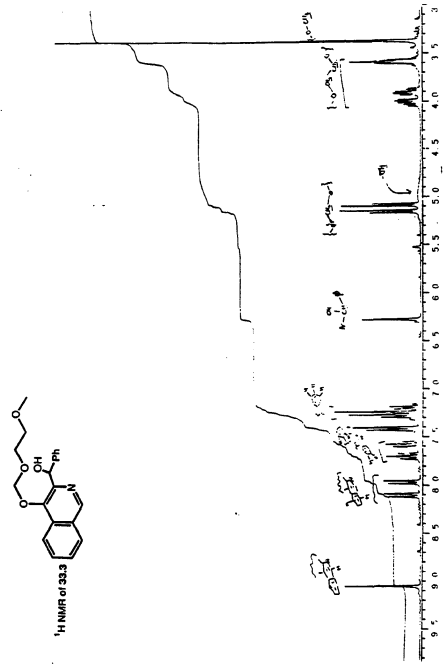


^{1}H NMR of 28.4





^{1}H NMR of 32.1



^{1}H NMR of 33.3

REFERENCES

1. Collier, H. O. J. *Nature* **1969**, *223*, 35.
2. Vane, J. R. *Nature (New Biology)* **1971**, *231*, 232.
3. Ferreira, S. H.; Moncada, S.; Vane, J. R. *Nature (New Biology)* **1971**, *231*, 237.
4. Smith, J. B.; Willis, A. L. *Nature (New Biology)* **1971**, *231*, 235.
5. Crunkhorn, P.; Willis, A. L. *Brit. J. Pharmacol.* **1971**, *41*, 49.
6. Milton, A. S.; Wendlandt, S. *J. Physiol.* **1970**, *207*, 76P.
7. Tomlinson, R. V.; Ringold, H. J.; Qureshi, M. C.; Forchielli, E. *Biochem. Biophys. Res. Commun.* **1972**, *46*, 552.
8. Rieu, J-P.; Boucherle, A.; Cousse, H.; Mouzin, G. *Tetrahedron* **1986**, *42*,4095.
9. (a) Lednicer, D.; Mitscher, L. A. *The Organic Chemistry of Drug Synthesis Wiley, New York* **1977**, Chap. 6. (b) Shen, T. Y. *Angew. Chem. Int. Ed. Engl.* **1972**, *6*, 460. (c) Ferreira, S. H.; Vane, J. R. *Antiinflammatory Drugs* Springer, Berlin **1979**, 321. (d) *Script World Pharm. News* **1980**, *10*, 497.
10. Brown, E. V. *Synthesis* **1975**, 358.
11. (a) Ballester, M. *Chem. Rev.* **1955**, *55*, 283. (b) Cannata, V.; Tamberlani, G. DOS 3212170 **1982**; *Chem. Abstr.* **1983**, *98*, 53448g.
12. Giordano, C.; Castaldi, G.; Uggeri, F. *Angew. Chem. Int. Ed. Engl.* **1984**, *23*, 413.
13. Harrison, I. T.; Lewis, B.; Nelson, P.; Rooks, W.; Roszkowsky, A.; Tomalonis, A.; Fried, J. H. *J. Med. Chem.* **1970**, *13*, 203,
14. (a) Larsen, R. D.; Corley, E. G.; Davis, P.; Reider, P. J.; Grabowski, E. J. J. *J. Am Chem. Soc.* **1989**, *111*, 7650. (b) Lubell, W. D.; Rapoport, H. *J. Am Chem. Soc.* **1988**, *110*, 7447. (c) Castaldi, g.; Cavicchioli, S.; Giordano,

C.; Uggeri, F. *J. Org. Chem.* **1987**, *52*, 3018. (d) Honda, Y.; Ori, A.; Tsuchihashi, G. *Bull. Chem. Soc. Jpn.* **1987**, *60*, 1027. (e) Ando, A.; Shioiri, T. *J. Chem. Soc. Chem. Commun.* **1987**, 656. (e) Piccolo, O.; Spreafico, F.; Visentin, G. *J. Org. Chem.* **1985**, *50*, 3945.

15. Drautz, H.; Zahner, H. *J. Antibiotics*, **1986**, *39*, 1657.
16. Kuntsmann, M. P.; Mitscher, L. A. *J. Org. Chem.* **1966**, *31*, 2920.
17. (a) Rickards, R. W.; Wu, J-P, *J. Antibiotics*, **1985**, *38*, 513; a lead reference to the structural variations of the anthraquinone class. (b) Katsuura, K.; Snieckus, V. *Tetrahedron Lett.* **1985**, *26*, 9; a lead reference to the synthetic studies in this series.
18. Sezaki, M.; Kondo, S.; Maeda, K.; Umezawa, H.; Ohno, M. *Tetrahedron*, **1970**, *26*, 5171.
19. Ohta, K.; Mizuta, E.; Okazaki, H.; Kishi, T. *Chem. Pharm. Bull*, **1984**, *32*, 4350.
20. Imamura, N.; Kakinuma, K.; Ikekawa, N.; Tanaka, H.; Omura, S. *Chem. Pharm. Bull*, **1981**, *29*, 1788.
21. Uchida, T.; Imoto, M.; Watanabe Y.; Miura, K.; Dobashi, T.; Matsuda, N.; Sawa, T.; Naganawa, H.; Hamada, M.; Takeuchi, T.; Umezawa, H. *J. Antibiotics*, **1985**, *38*, 1171.
22. Hayakawa, Y.; Iwakiri, T.; Imamura, K.; Seto, H.; Otake, N. *J. Antibiotics*,**1985**, *38*, 960.
23. Hayakawa, Y.; Furihata, K.; Seto, H.; Otake, N. *Tetrahedron Lett.* **1985**, *26*, 3475.
24. Hayakawa, Y.; Iwakiri, T.; Imamura, K.; Seto, H.; Otake, N. *J. Antibiotics*,**1985**, *38*, 957.
25. Ayukawa, S.; Takeuchi, T.; Sezaki, M.; Hara, T.; Umezawa, H.; Nagatsu, T. *J. Antibiotics*, **1968**, *21*, 324.

26. Nagatsu, T.; Ayukawa, S.; Umezawa, H. *J. Antibiotics*, **1968**, *21*, 354.
27. Ishimara, T.; Kanamaru, T.; Takahashi, T.; Ohta, K.; Okazaki. H. *Biochem. Pharm.* **1982**, *31*, 915.
28. (a) Iric, H.; Mizuno, Y.; Kouno, I.; Nagasawa, T.; Tani, Y.; Yamada, H.; Taga, T.; Osaki, K. *J. Chem. Soc. Chem. Commun.* **1983**, 174. (b) Nagasawa, T.; Fukao, H.; Iric, H.; Yamada, H. *J. Antibiotics*, **1984**, *37*, 693.
29. Tanaka, N.; Okabe, T. Take, Y.; Inouye, Y.; Nakamura, S.; Nakashima, H.; Yamamoto, N. *Jpn. J. Cancer Res.* **1986**, *77*, 324.
30. Yarchoan, R.; Mitsuya, H.; Broder, S. *Scientific American*, **1988**, *259*, 110.
31. (a) Hafuri, Y.; Takemori, E.; Oogose, K.; Inouye, Y.; Nakamura, S. *J. Antibiotics*, **1988**, *41*, 1471. (b) Take, Y.; Inouye, Y.; Nakamura, S. *J. Antibiotics*, **1989**, *42*, 107.
32. Brown, P. M.; Thomson, R. H. *J. Chem. Soc. Perkin Trans.I*, **1976**, 997.
33. Uemura, M.; Take, K.; Hayashi, Y. *J. Chem. Soc. Chem. Commun.* **1983**, 858.
34. Kelly, T. R.; Jagoe, C. t.; Li, Q. *J. Am. Chem. Soc.* **1989**, *111*, 4522.
35. Guingant, A.; Barreto, M. M. *Tetrahedron Lett.* **1987**, *28*, 3107.
36. Parker, K. A.; Ruder, S. M. *J. Am. Chem. Soc.* **1989**, *111*, 5948.
37. Alder, K.; Stein, G. *Angew. Chem. Int. Ed. Engl.* **1962**, *1*, 269.
38. Bachmann, W. E.; Deno, N. C. *J. Am. Chem. Soc.* **1949**, *71*, 3062.
39. (a) Bradsher, C. K.; Stone, J. A. *J. Org. Chem.* **1968**, *33*, 519. (b) Bradsher, C. K. *Adv. Heterocycl. Chem.* **1974**, *16*, 289 (and references there in).
40. (a) Fields, D. L.; Regan, T. H.; Dignan, J. C. *J. Org. Chem.* **1968**, *33*, 390. (b) Fields, D. L.; Regan, T. H. *Ibid.* **1970**, *35*, 1870. (c) Fields, D. L.; Regan, T. H. *Ibid.* **1971**, *36*, 2986, 2991, 2995 and 3002.
41. Reference 3(b), page 303.
42. Manna, S.; Falck, J. R.; Mioskowski, C. *J. Org. Chem.* **1982**, *47*, 5021.

43. (a) Sammes, P. G.; Watt, R. A. *J. Chem. Soc. Chem. Commun.* **1976**, 367. (b) Gisby, G. P.; Sammes, P. G.; Watt, R. A. *J. Chem. Soc. Perkin Trans. 1* **1982**, 249. (c) Falck, J. R.; Manna, S.; Mioskowski, C. *J. Am. Chem. Soc.* **1983**, *105*, 631. (d) Franck, R. W.; Gupta, R. B. *J. Chem. Soc. Chem. Commun.* **1984**, 761. (e) Franck, R. W.; Gupta, R. B. *Tetrahedron Lett.* **1985**, *26*, 293. (e) Franck, R. W.; Gupta, R. B. *J. Org. Chem.* **1985**, *50*, 4632.

44. Franck, R. W.; Gupta, R. B. *J. Am. Chem. Soc.* **1987**, *109*, 5393.

45. Danishefsky, S.; Nagasawa, K.; Wang, N. *J. Org. Chem.* **1975**, *40*, 1989.

46. Hendrickson, J. B.; Rodriguez, C. *J. Org. Chem.* **1983**, *48*, 3344.

47. Grethe, G.; Lee, H. L.; Uskokovic, M.; Brossi, A. *J. Org. Chem.* **1968**, *33*, 494.

48. Craig, J. J.; Cass, W. E. *J. Am. Chem. Soc.* **1942**, *64*, 783.

49. Ochiai, E.; Ikehara, M. *Chem. Pharm. Bull. Jpn.* **1955**, *3*, 454.

50. Seebach, D.; Naef, R.; Calderari, G. *Tetrahedron,* **1984**, *40*, 1313.

51. (a)Evans, D. A.; Ennis, M. D.; Mathre, D. J. *J. Am. Chem. Soc.*, **1982**, *104*, 1737. (b) Evans, D. A.; Bartroli, J.; Shih, T. L. *J. Am. Chem. Soc.*, **1981**, *103*, 2127.

52. Widmer, U. *Synthesis* **1987**, 568.

53. Banfi, L.; Bernardi, A.; Colombo, L.; Gennari, C.; Scolastico, C. *J. Org. Chem.*, **1984**, *49*, 3784.

54. (a) Bacon, R. G. R.; Rennison, S. C. *J. Chem. Soc. (c)* **1969**, 308 and 312. (b) Whitesides, G. M.; Sadowski, J. S.; Lilburn,J. *J. Am. Chem. Soc.* **1974**, *96*, 2829.

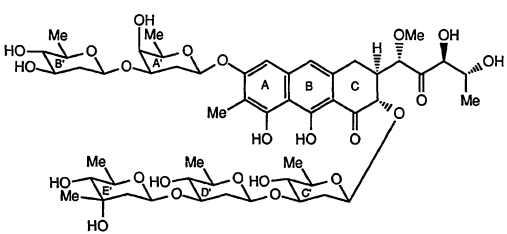
55. Miller, R. B. *Syn. Commun.* **1969**, 308 and 312.

PART 2

GLYCOSIDATION VIA GLYCALS AND PHENYL(BISPHENYLTHIO)SULFONIUM SALTS: EFFECT OF THE GLYCAL STRUCTURE ON THE FACE SELECTIVITY

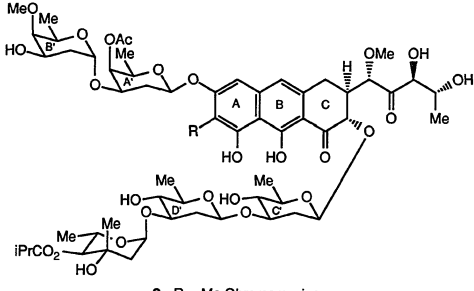
INTRODUCTION

The aureolic acids are a group of highly toxic antibiotics which also have significant antitumor properties.[1] The first member of this family, aureolic acid **1**, from which the group name derives, was first isolated by Grundy and coworkers[2] at Abbott laboratories in 1953, from an unidentified Streptomyces species. They named it aureolic acid because of its yellow color and weakly acidic properties. Although it showed activity against Gram (+) bacteria, high toxicity prevented its further development as an antibacterial agent. The same compound was rediscovered in 1957 at Lepetit as LA 7017, and its antitumor activity was first noted.[3] A third independent discovery was made at Pfizer laboratories, where it was named mithramycin.[4] Its toxicity did not stop the Pfizer group from developing it into the product Mithracin, which has limited use in the chemotherapy of malignant testicular tumors and in controlling cancer induced hypercalcemia and hypercalciuria that do not respond to other therapeutic agents. Its properties (which are influenced by traces of metals and other impurities) and its complex glycosidic structure delayed the establishment of the identities of aureolic acid, LA 7017 and mithramycin until 1968.[5]



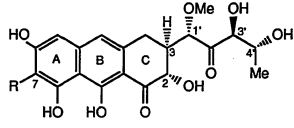
1 AUREOLIC ACID

Chromomycins, exemplified by chromomycin A_3 **2**, which show very similar biological activity, were discovered in Japan.[6] A related series of antibiotics, the Olivomycins (e.g. olivomycin A **3**), were discovered in Soviet Union[7] in 1962 and have been developed into clinical anticancer agents which are used in Eastern European countries. In 1968, a Soviet team made a careful series of chemical and physical comparisons among these groups of compounds.[5] Based on these results all of these antibiotics were put together in the aureolic acid group.



2 R = Me Chromomycins
3 R = H Olivomycins

The structures of the aureolic acid group of compounds are based upon two aglycones, chromomycinone **4** and olivin **5**, which differ only by the C-7 methyl group. The aglycones are linked at their 2- and 6- positions to chains of one, two or three sugars.



4 R = Me Chromomycinone
5 R = H Olivin

The spectrum of biological activity of aureolic acid group is similar to that of actinomycins and anthracyclines. They strongly inhibit Gram (+) bacteria, DNA virus (such as adenovirus type V, parainfluenza, influenza, fowl plague, pseudorabies and murine cytomegalovirus), certain tumors and normal mammalian cells.[8] Gram (-) bacteria E. Coli, and RNA viruses poliovirus, newcastle disease and group A arbovirus are less susceptible.

Their mode of action, in common with the actinomycins and anthracyclines, involves complexation with the double helical DNA to prevent the action of DNA dependent RNA polymerase.[9] Very recently Gao and Patel[10] have done proton NMR studies on the nature of Chromomycin-DNA binding, using a deoxyoctanucleotide duplex. Intermolecular NOE results suggest that two chromomycin molecules as a symmetrical dimer share the minor groove at a G.C rich site. The C-D-E trisaccharide chain extends towards the 3'-end and the A-B disaccharide chain as well as the hydrophilic side chain extends towards the phosphate backbone of the DNA. This complex formation results in a transition to a wider and shallower minor groove at the binding site, switching the configuration of DNA. The sugar chains of the antibiotics are essential for binding in the complex.[11] Analogs in which some of the chain have been cleaved bind weakly, with rates of dissociation of their complexes increasing as

the number of sugars decreases.[12] Variation in the nature of the sugars in these glycosides is also responsible for the differences among the individual members. Although the optimal number and arrangement of sugars for biological activity has not been determined, at least some sugars must be present since the aglycones do not complex with DNA and are inactive against tumors and microorganisms. Since sugars play an important role in binding to the DNA, they constitute a "site" where modifications can be done to understand the binding hypothesis as well as to make better drugs with less toxicity and higher activity.

The total synthesis of aureolic acids has been a topic of interest among several groups. The synthetic program for the members of the aureolic acid group can be logically divided into three parts, each with its own sub-goal.

(i) Synthesis of the aglycone

(ii) Synthesis of A'B' disaccharide and C'D'E' trisaccharide.

(iii) The final convergent link between the aglycone and the saccharides.

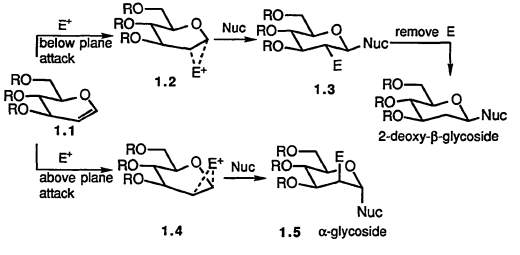
Parts (i) and (ii) have been achieved many times.[13] The aglycone **5** has been synthesized by three different groups. Several synthesis of the di- and tri-saccharides of both all β-glycoside series (aureolic acid) and mixed α,β- series (chromomycin and olivomycin) have been reported. The third and most important part, which will also lead to the synthesis of semi-synthetic drugs has not yet been done. A practical 2-deoxy-β-glycosidation method needs to be developed so as to attach the sugars to the aglycone.

There is an extensive literature on controlling the stereochemistry of glycosidation.[14] The α-glycosidic links required for the aureolic acids proved to

be accessible using a variety of well known methods, it is the 2-deoxy-β problem which remains a difficult one. Most solutions offered in the literature for the preparation of 2-deoxy-β-sugars require the participation of a neighboring group in the glycosidation process.[15]

Electrophilic Activation of Glycals: One of the common methodologies used for making glycosidic linkages in a stereospecific way is activation of glycals by electrophilic attack and subsequent addition of the nucleophile. **(Scheme 1).**

Scheme 1:

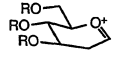


The general scheme involves the initial electrophilic attack on the glycal, giving the onium species **1.2** and **1.4** followed by the nucleophilic ring opening to form **1.3** and **1.5**. If the C-2 substituent 'E' in **1.3** is removed the product is a 2-deoxy-β-sugar. This addition to the double bond takes place with

regiospecificity; the electronic effect of the ring oxygen ensures that the electrophile enters at position 2.

In principle, it is a variation of the same theme which is involved in the glycosidation methods based on neighboring group participation. A wide variety of electrophilic reagents have been used for this purpose:

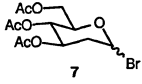
(i) H^+ as Electrophile: H^+ is probably the oldest example of an electrophile attacking glycals. The onium species **1.2** or **1.4** in **Scheme 1** do not exist, the intermediate is an oxonium species **6.**



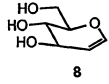
6

Thus the stereochemical outcome at C-1 mainly depends on the anomeric effect i.e. α is the major isomer. Fisher et. al.[16] in 1920 reacted triacetyl-D-glucal with HBr in acetic acid and obtained a crystalline product they called "diacetyl-D-glucal hydrobromide" which on reacetylation gave the triacetyl derivative. This work was repeated by Daroll and Lythgoe in 1949[17] and they reported the product to be, in fact, 3,4,6-triacetyl-1-bromo-1,2-dideoxyglucose **7.** A number of 2-deoxy glycosides have been prepared in this way, involving the addition of water, alcohols, phenols and carboxylic acids to glycals. Stacey and coworkers[18] reported addition of methanol to glucal **8** by reacting it with methanolic hydrogen chloride, to give α-methyl-2-deoxy-D-glucopyranoside **9**

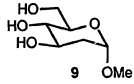
and to galactal **10** to give α-methyl-2-deoxy-D-galactose **11**. These workers also report the formation of a dehydrated side product **12**.[19]



7

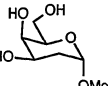


8

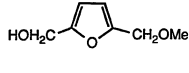


9

10

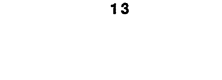


11



12

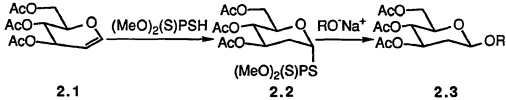
2-Deoxy-pentoses, hexoses and disaccharides,[20] methyl-2-deoxy-α-D-arabino-hexo-pyranoside,[21] phenyl-3,4,6-tri-O-acetyl-2-deoxy-α-D-lyxo-hexopyranoside[22] and 1,3,4,6-tetra-O-acetyl-2-deoxy-α-D-lyxo-hexopyranoside[23] are a few examples of a large number of 2-deoxy sugars prepared from glycals or their acetates, in this manner. Nitrogen nucleophiles have also been used e.g. when 3,4-di-O-acetyl-D-arabinal and 6-chloropurine are fused in presence of pTSA the product is a mixture of the anomeric 6-chloro-9-(3,4-di-O-acetyl-2-deoxy-D-erythro-pento-pyranosyl)purines **13**.



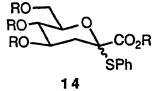
13

Introduction of nucleophiles at the anomeric carbon which can be used for further reactions, gives an indirect way of making glycosides in a stereocontrolled fashion. Michalska and Bosowiecka[24] have introduced a dithiophosphate group at anomeric carbon of triacetyl glucal by reacting it with O,O-dialkylphosphorodithioic acids (**Scheme 2**). The product is exclusively the α-anomer. A nucleophilic displacement of the dialkyldithiophosphoryl group of **2.2** by alkoxide of the alcohol, which proceeds with full inversion of configuration at the anomeric carbon gives 2-deoxy-β-glycosides. Crich and Ritchie[25] added thiophenol to protected glycals to give thiosugars **14** The latter are then used for syntheses of 2-deoxy-β-glycosides via stereoselective free radical decarboxylation.

Scheme 2:



2.1 **2.2** **2.3**

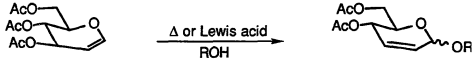


14

In neutral conditions or with Lewis acid catalysis Ferrier rearrangement takes place giving 2,3-unsaturated product (**Scheme 3**).[26] This rearrangement

reaction has been used many times to make 2,3-unsaturated C-glycosides,[27] glyconolactones,[28] glycosyl azides[29] etc.

Scheme 3:



2.1 **3.1**

(ii) Mercury Electrophiles: Methoxymercuration followed by reductive demercuration of a double bond, is an indirect method of adding an element of methanol to olefinic bonds,[30] as well as to enol ethers.[31] The first examples of this reaction in carbohydrate chemistry came from two groups, Inglis et. al.[32] and Manolopoulos et. al.[33] The triacetyl ester of glucal on methoxymercuration followed by demercuration gives 2-deoxy-β-D-glucopyranoside as the major product, while D-glucal itself on undergoing these reactions gives 2-deoxy-α-D-glycoside. In the case of the triacetyl derivative the bulky 3-acetyl substituent probably blocks the β face of glucal and Hg^{2+} attacks from the α face giving β-anomer as the final product. On the other hand, in the case of D-glucal, oxygen of 3-hydroxyl group coordinates with attacking Hg^{2+} so that it attacks from the β face resulting in α-anomer of the final product. The stereochemistry of methoxy mercuration was studied in detail by Takiura and Honda[34] using acetates of D-glucal, D-galactal, L-arabinal and D-xylal showing that trans-addition to the double bond takes place and the proportion of diaxial to diequatorial addition is strongly affected by the protecting groups at C-4 and C-5. The same group also did a study for the optimal reaction conditions for equimolar oximercuration of D-glucal triacetate using various mercuric salts bases and reaction solvents.[35] They found acetonitrile as the solvent, mercuric perchlorate as the salt and *sym*-collidine as the base to be the best conditions. Using these conditions they

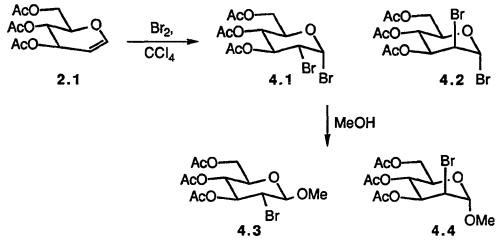
synthesized a few disaccharides also. Hydroxy- and acetoxy-mercuration of the glucal triacetate has also been studied.[36]

On replacement of the ionic acetates by chloride the initial addition products, 2-(acetomercuri)-2-deoxy-glycosides give the 2-(chloromercuri)- analogs and at this stage both isomers (β-gluco and α-manno) can be isolated in satisfactory yield. Demercuration can be brought about either by reductive cleavage of the carbon-metal bond or by photolysis[37] of these organomercurials to yield corresponding 2-deoxy-glycosides.

This versatile reaction has been used repeatedly in carbohydrate chemistry. Goodman et. al. used it for the key intermediate in their synthesis of daunosamine,[38] by Corey et. al. in the total synthesis of (-)-N-methyl maysenine,[39] by Keck and Kachensky in the synthesis of (+)-Compactin[40] and to synthesize various sugar derivatives.[41]

(iii) Halogen Electrophiles: In 1920, Fisher et. al.[42] reported the reaction of D-glucal triacetate with molecular bromine. Methanolysis of the dibromide products **4.1** and **4.2** gave bromohydrin glycosides **4.3** and **4.4** (**Scheme 4**).The mechanism and stereochemistry of this reaction have been studied by Lemieux and Fraser-Reid.[43] The results show that halogenation depends on the structure of the glycal and more importantly on the solvent used for the reaction e.g. in the reaction of chlorine with tri-O-acetylglucal, diequatorial addition takes place in carbon tetrachloride and it takes a diaxial course in methanol (**Scheme 5**). More recently this reaction was investigated again using different solvents, halogens and glycals,[44] suggesting that either the reaction conditions or the substituent at C-6 govern the extent to which the ring oxygen participates

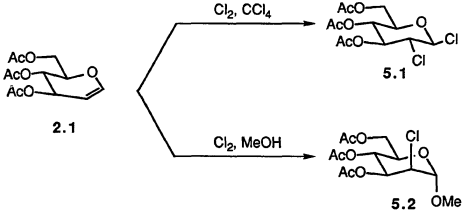
Scheme 4:



to stabilize the positive charge of the intermediate carbonium ion.

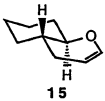
But there is no proposed rationale for the face selectivity at C-2.

Scheme 5:



Chlorination of rather rigid glycals like trans-1-oxa-octalin **15** and 6-t-butyldihydropyran **16** also has been carried out.[45] Participation by the solvents other than alcohols,[46] has also been observed e.g. 3-nitroglucal **6.1** gives normal addition products when reacted with chlorine in carbon tetrachloride, but

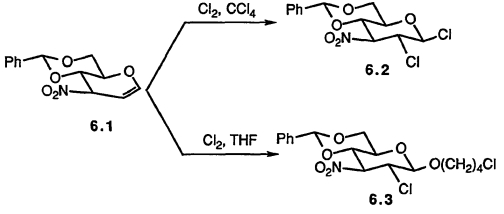
in solvents like THF the product **6.3** has a THF molecule incorporated in it (**Scheme 6**).



15

16

Scheme 6:



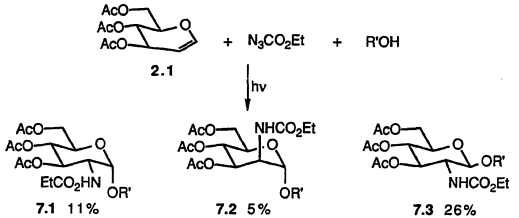
The halogenation of glycals is not completely understood. Nevertheless, by using different reaction conditions this method can be applied to the synthesis of 2-deoxysugars.[47] Glycals can also be activated with halonium reagents e.g. NIS, NBS etc. Lemieux et. al.[48] discovered iodonium (symcollidine)$_2$perchlorate as the I^+ reagent to activate glycals for haloetherification. Quite recently Danishefsky elaborated the use of this reagent coupled with Fraser-Reid's arm-disarmed strategy,[49] to synthesize oligosaccharides having 2-deoxy-α-glycosidic linkages. The first synthesis of sucrose was carried out[50] using I^+ (*sym*-collidine) reagent and methoxy bromination (Br_2 and Ag^+). Addition reactions between D-glucal triacetate and the element of "BrF" has been carried

out using anhydrous hydrogen fluoride and NBS[51] or bromine and silvermonofluoride[52], giving principally 2-bromo-2-deoxy-α-D-mannosylfluoride. Thiem has used the NIS/ROH system to make 2-deoxyglycosides.[53] This method almost always gives exclusively α-glycosides and it has been used in several carbohydrate syntheses.[54] Very recently a non-stereospecific addition of iodoazide to glycals has appeared in literature[55] giving 2-deoxy-2-iodo-glycosylazides which are then converted to 2-deoxy-2-aminosugars by several steps involving 1,2 migration of nitrogen via an aziridine intermediate.

Fluorinated carbohydrates have attracted much interest,[56] mainly because of the use of their ^{18}F labelled analogs as the imaging agents in studies of regional cerebral metabolism. There are many reports for the synthesis of 2-deoxy-2-fluoro-sugars from glycals using acetyl hypofluorite,[57],trifluoromethyl fluorite,[58] elemental fluorine,[59] Xenon difluoride.[60]

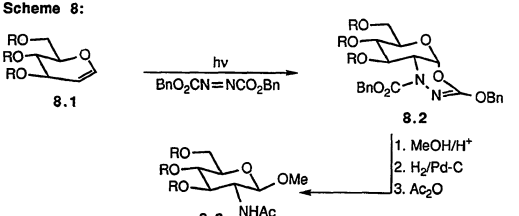
(iv) Nitrogen Electrophiles: These electrophiles are mainly used to synthesize 2-deoxy-2-aminosugars. Such compounds have been synthesized by the addition of nitrosyl chloride to acetylated glycals, e.g. D-glucal triacetate on reaction with nitrosyl chloride gives 2-deoxy-2-nitroso-α-D-glucopyranosyl chloride, which on treatment with silver acetate and then reduction with copper-zinc gives 2-deoxy-2-amino-sugars.[61] Chloro-azide adds to mono-acetyl-di-benzyl ethers of galactal[62] giving 2-deoxy-2-azido-glycosyl chlorides. It was noticed that the 3-acetate substitution reduces the reactivity a lot. Ethyl azidoformate adds to glucal triacetate photochemically in presence of alcohols to give mixture of 2-deoxy-glycosides[63] **(Scheme 7)**.

Scheme 7:

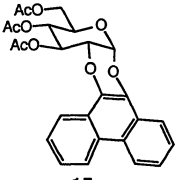


Lessard et. al.[64] added n-chloroacetamide to glucal triacetate to get 2-deoxy-2-chloroacetylamino-glucosylchlorides. In further reaction with alcohols, nitrogen at C-2 directs the nucleophile to come from the β-face giving β-glycosides. (2+4) Cycloaddition of glucal and dibenzyl diazocarboxylate has been carried out[65] and the cycloadduct is then converted into 2-deoxy-2-amino-β-glycosides (**Scheme 8**).

Scheme 8:



(v) Oxygen Electrophiles: Oxidation of unprotected glycals with peroxy benzoic acid yields epoxide mainly cis to the 3-hydroxy group, subsequent opening of the epoxide gives a cis-2,3-diol arrangement. In 3-protected glycals, the hydrogen bonding responsible for epoxidation cis to the 3-hydroxyl group, is not possible. Therefore the epoxide is formed trans to the 3-substituent and gives corresponding trans-2,3-diol arrangement. This strategy is used to make D-mannose derivatives from glucals with the 3-hydroxyl free and D-glucoses with 3-hydroxyl differentiated from 3-protected glucals.[66] When hydrogen peroxide is used in tert-butylalcohol in the presence of osmium tetraoxide both D-glucal and its triacetate give D-gluco products. Hydrogen peroxide in presence of molybdenum trioxide converts glycals into 2,3-cis-diols.[67] Phenanthrene quinone in boiling benzene under UV light gives adduct **17**.[68]

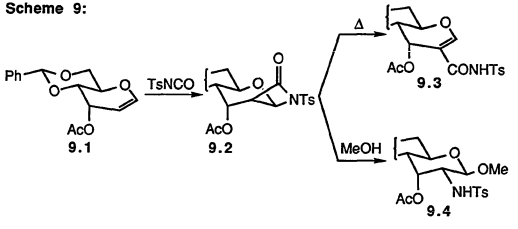


17

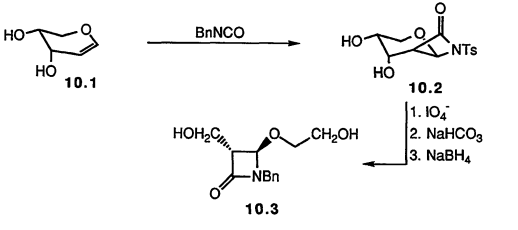
There are many examples of epoxidation of glycals using peracids,[69] where difficulties were faced in the isolation of the epoxides. Danishefsky,[70] very recently, has used dimethyldioxirane for the direct epoxidation of glycals, where the epoxides can be isolated and then subjected to nucleophilic ring opening giving β-glycosidic linkages. When the nucleophile used in the latter step is a glycal itself this process can be repeated, thus leading to a reiterative strategy for the synthesis of β-linked oligosaccharides.

(vi) Carbon electrophile: Isocyanates add to glycal double bonds in a (2+2) fashion to give β-lactams[71] **(Scheme 9)**. These β-lactams on thermolysis rearrange to α,β-unsaturated amides **9.3**, reverse to starting materials when kept at room temperature and react with methanol to give β-glycosides **9.4** .[72] Periodate cleavage of such a β-lactam was used to synthesize chiral β-lactam **10.3 (Scheme 10)**[73].

Scheme 9:

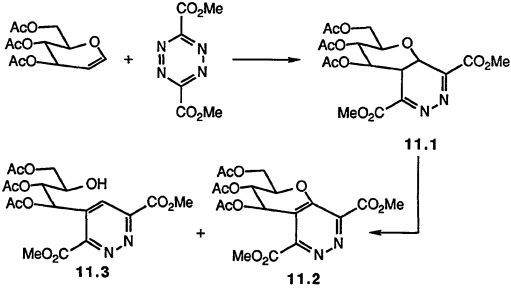


Scheme 10:

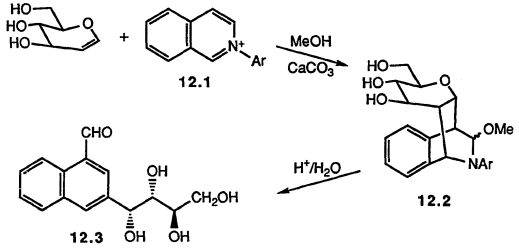


(4+2) Cycloaddition of a glycal double bond with 1,2,4,6-tetrazine-3,6-dimethyldicarboxylate (**Scheme 11**),[74] trichloroacetyl isocyanate,[75] cyclobutane[76] and isoquinolium salts (**Scheme 12,** this cycloaddition between fucal and 5-methoxy isoquinolinium salt was used for first synthesis of enantiomerically pure cryptosporin)[77] have been used very often.Triacetyl-glucal reacts with ethyl diazoacetate to give cyclopropane arising from below the plane attack.[78]

Scheme 11:

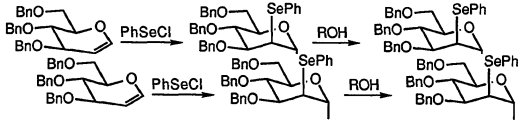


Scheme 12:



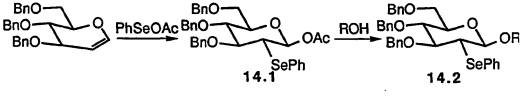
(vii) Selenium Electrophile: Alkoxy selenation of both cyclic and acyclic vinyl ethers[79] is the basis of glycosyloxy-selenation of glycals,[80] which coupled with reductive deselenation, is a convenient method for synthesizing 2-deoxy-carbohydrates. Phenylselenyl chloride in acetonitrile gives the α-manno type of adduct with tri-O-benzyl-D-glucal which after subsequent treatment with a sugar alcohol gives α-disaccharides, because of the directing participation of the selenyl group at C-2 (**Scheme 13**).

Scheme 13:



On the other hand phenylselenyl acetate gives diequatorial addition (β-gluco type), which can be used to make 2-deoxy-β-glycosides (**Scheme 14**).[81] These authors have shown a strong dependence of the face-selectivity on the metal acetate used for in situ preparation of phenylselenyl acetate, the protecting groups on glycal and the solvent used.

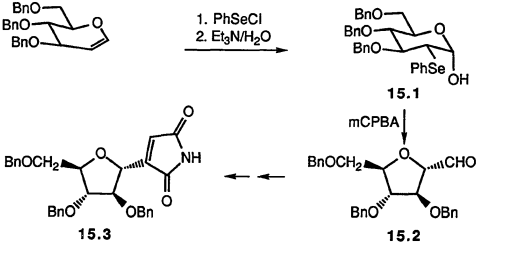
Scheme 14:



14.1 **14.2**

Selenium electrophiles have been repeatedly used in carbohydrate chemistry, e.g. glycals with phenylselenyl triflate,[82] in glycosidation of sialic acid[83] and for the synthesis of various other glycosides.[84] Reese and coworkers[85] have used the oxidative ring contraction of phenylselenate adducts of glycal ethers [86] in their synthesis of showdomycin **15.3** analogs (**Scheme 15**).

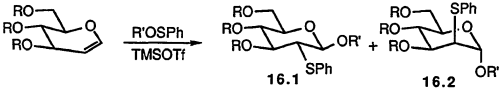
Scheme 15:



15.1 **15.2** **15.3**

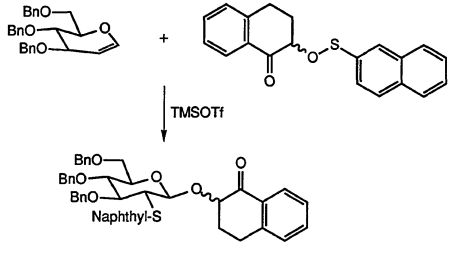
(viii) Sulfur Electrophiles: Though sulfonium salts and their reactivity towards alkenes is known,[87] the use of sulfur nucleophiles with glycals in carbohydrate chemistry is relatively new. In 1986, Livinghouse[88] used a benzenesulfenate ester and Lewis acid catalysis to carry out an arene-alkene cyclization. Ito and Ogawa[89] developed this reaction using glycals as the alkene to make 2-deoxy-glycosides (**Scheme 16**). The reaction presumably goes via an episulfonium ion, which on nucleophilic ring opening gives a trans relationship between thiophenyl at C-2 and nucleophile at C-1. The face selectivity in the attack of the sulfenate ester-Lewis acid complex on glycal depends on the Lewis acid, nucleophile and the solvent used.

Scheme 16:



Working along parallel lines, Franck and Ramesh,[90] used naphthylsulfenate ester and synthesized the first 2-deoxy-β-glycoside of an acyloin (**Scheme 17**), a linkage required for the aureolic acid synthesis.

Scheme 17:

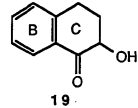


Direct addition of phenylsulfenyl chloride to tri-O-benzyl glucal, was carried out by Schmidt and Preuss.[91] The resulting 2-deoxy-2-phenylthio-glucosylchloride was hydrolyzed and used for further reactions leading to their method for 2-deoxy-β-glycosidation. Ogawa's phenylsulfenate ester-Lewis acid couple has been used many times in the glycosidation of Sialic acids.[92] Goto et. al.[93] have used phenyl sulfenyl chloride, for glycosidation of sialic acids.

RESULTS AND DISCUSSION

The specific requirements for making 2-deoxy-β-linkages for the synthesis of aureolic acids is that the procedure(s) work with phenols **18** (model for ring A of aureolic acid) and acyloin **19** (model for rings A and C of aureolic acid) under mild enough conditions so that acid and base sensitive aglycones can survive the glycosidation procedure(s).

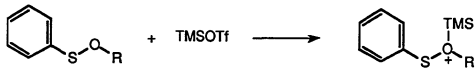
18



19

A glycosidation method which does not involve specialized sugar derivatives as glycosyl transfer agents would be more appropriate. Glycosidations brought about by electrophillic activation of glycals can be used within these limits. In a preliminary study in our laboratory, Ogawa's approach[89] was examined, where a preformed arylsulfenate ester of the aglycone is apparently activated to a thiooxonium species by trimethylsilylation (**Scheme 18**). In this manner, the first realistic aureolic acid model, a 2-deoxy-β-glycoside of acyloin was synthesized (**Scheme 17**).[90] But the methodology could not be extended for the other model of aureolic acid i.e. phenol, because the required sulfenate ester of phenol could not be prepared.

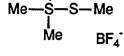
Scheme 18:



18.1 **18.2**

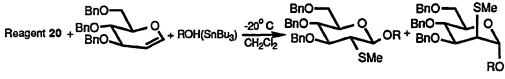
Since the attacking electrophile in Ogawa's method is the thiooxonium species **18.2**, other reactive thioonium salts might serve to activate glycals for glycosidation. On the basis of this speculation, three reagents were chosen for this purpose:

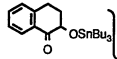
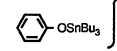
*(i) (Methyl thio)-sulfonium salt **20**:* The results from the glycosidation carried out using this commercially available salt are listed in **Table 1**. Problems arose during the desulfurization step.[94]



20

Table 1[a]: Glycosyl Transfers Using Reagent 20

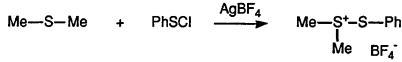


Entry	ROH(SnBu$_3$)	ratio β/α	Yield %
1	MeOH	1.3/1	75
2	 Models for aureolic acid	2.9/1	40
3		1/1	60

a: This work was done by S. Ramesh in our lab.

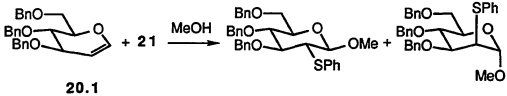
(ii) Dimethyl (phenylthio)sulfonium salt 21: This reagent was prepared by the reaction of phenylsulfenyl chloride[95] and dimethyl sulfide in the presence of silvertetrafluoroborate (**Scheme 19**). The reaction of methanol with glucal **20.1** using **21** as the electrophile afforded β and α glycosides in 2/1 ratio (**Scheme 20**). However, the reaction was not very clean.

Scheme 19:



21

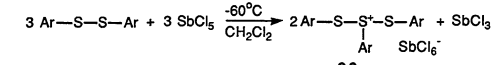
Scheme 20:



20.1

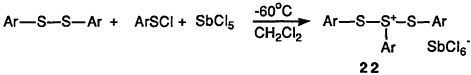
(iii) Phenyl(bis phenylthio)sufonium salts 22: Diaryl disulfides on reaction with the Lewis acid antimony pentachloride give aryl(bisarylthio)sulfonium hexachloroantimonates (**Scheme 21**).[96] This method, however, gives 0.5 equivalent of $SbCl_3$ with the reagent. Reagent **22** free of $SbCl_3$ can be made in an alternative way by the reaction of arylsulfenyl chloride, diaryl disulfide and antimony pentachloride (**Scheme 22**).

Scheme 21:



22

Scheme 22:

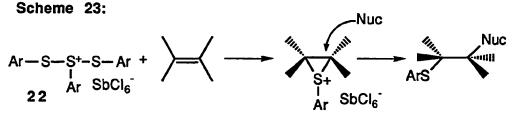


22

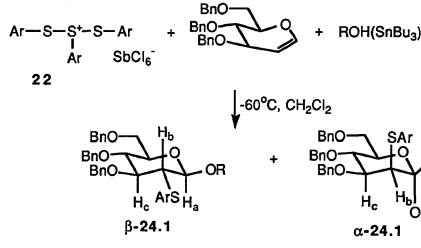
The aryl(bisarylthio)sulfonium salts have been shown to activate simple alkenes towards nucleophilic addition (**Scheme 23**).[97] In our laboratory, we used these salts to activate the double bond of glycals and in fact **22** have proven to be exceptionally useful reagents for glycosyl transfer of glycals to a variety of

hydroxyl donors (in some cases the nucleophilicity of the hydroxyl donor must be enhanced by prior stannyl ether formation) (**Scheme 24**).[98]

Scheme 23:



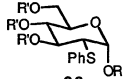
Scheme 24:



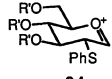
The glycosidation procedure is very simple, the reagent **22** (1.1 equiv) at -60 °C (prepared using **Scheme 21** or **22**) is added to a mixture of tribenzylglucal (1 equiv) and alcohol (2 equiv) in dichloromethane at -60 °C. The reaction is over within ten minutes and quenched with saturated sodium bicarbonate. During our search for the optimal glycosidation conditions we observed that the

procedure also works well if glucal is added to a mixture of alcohol and thiosulfonium salt **22** at -60 °C. But, the third alternative that is addition of alcohol to a mixture of glucal and reagent **22** at -60°C results in uncharacterizable products. In the latter case the glucal and thiosulfonium reagent react to give products, which do not subsequently react with the alcohol to form glycosides.

The two glycosides formed in this reaction are the 3,4,6-tri-O-benzyl-1-O-substituted-2-deoxy-2-phenylthio-β-D-glucopyranosides, **β-24.1** (referred to as the β-glycoside), and the 3,4,6-tri-O-benzyl-1-O-substituted-2-deoxy-2-phenylthio-α-D-mannopyranosides **α-24.1** (referred to as the α-glycosides). In some of the reactions we could isolate small amounts of the 3,4,6-tri-O-benzyl-1-O-substituted-2-deoxy-2-phenylthio-α-D-glucopyranosides **23** (referred to as the α'-glycosides).



23

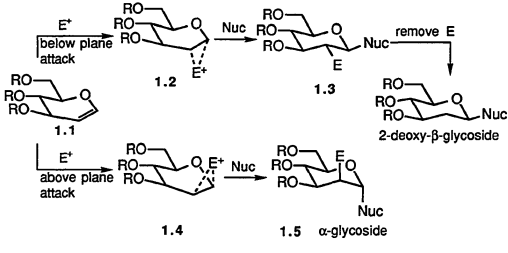


24

Formation of β and α' glycosides can be envisioned as a result of below plane electrophillic attack on glycal **1.1** to give intermediate onium species of type **1.2** (E^+=PhS^+) **Scheme 1**, (repeated below). Nucleophillic ring opening of **1.2** from the top face will give the β glycosides **β-24.1**. Where as attack of nucleophile from the bottom face of **1.3** results in α' glycoside **23**. The latter is sterically unfavorable but favored by anomeric effect.[99] Glycoside **23** can also

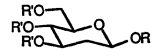
be derived from axial attack of nucleophile on the oxonium species **1.2**. A third possibility is the epimerization of β glycoside at the anomeric center catalysed by traces of acid, by endocyclic or exocyclic cleavage to give **23.** The top face electrophillic attack on glycal will give intermediate of type **1.4** (E^+=PhS^+, **Scheme** 1). Below plane ring opening of **1.4** by a nucleophile results in α glycoside α-**24.1**.

Scheme 1:



We think that the aqueous solution of sodium bicarbonate at -60 °C (used to quench the reaction) does not act effectively to scavenge traces of $HSbCl_6$. To test whether these traces of acid caused epimeriztion of β to α', we used an anhydrous secondary amine[100] (such as diethylamine) as a soluble quencher but could not improve the yields. We have not been able to discover an appropriate non-aqueous base to neutralise these reactions. Since our target

molecules are 2-deoxy-β-glycosides **25**, we have used W-2 Raney Nickel in THF[10] to desulfurize glycosides **25** in reasonable yields.



25

Structure Assignment :

We have used proton NMR data to assign the relative stereochemistry of the isomeric glycosides. The chemical shift values of the protons of different glycosides do not vary much but coupling constant values give conclusive information and have been used for structural proof. The glycosides **β-24.1** have been assigned on the basis of the proton H_b signal. This proton appears at high field compared to the other ring protons since it is attached to the thiophenyl substituted carbon C-2 and has an axial orientation. It appears as a doublet of doublets with two large diaxial couplings (J = 8-12 Hz), to H_a and H_c. The peak for H_a proton is mixed with the ring protons (due to its axial orientation it comes at high field compared to the H_a proton in α-glycosides, see below).

The glycosides **α-24.1** were characterized by the proton H_a. This proton is at low field compared to the other ring protons because it is anomeric and has an equatorial orientation. It appears as a doublet with small diequatorial coupling (J = 0-4 Hz) to H_b. In some of the α-glycoside cases, proton H_b appears at high field enough to be resolved from the remaining ring protons. It shows a doublet of doublets due to two small couplings with H_a (diequatorial) and H_c

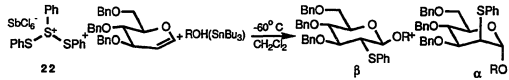
(equatorial-axial, J = 0-4 Hz). For compounds where the H_b proton (because of its equatorial position it comes at low field compared to the H_b proton for β-glycosides) is mixed with other protons the glycoside structure is assigned by process of elimination or by proton NMR comparison with α-glycosides of similar structure. These assignments were further comfirmed by 2D homonuclear COSY of one representative example from the β and α series where each ring proton was identified.

The α'-glycosides, **23**, show a low field doublet for H_a. This proton appears separate from the ring protons and shows small equatorial-axial coupling with H_b. Most of the times the H_b proton signal is at high field and appears as a doublet of a doublet showing one large diaxial (with H_c) and one small equatorial-axial (with H_a) coupling.

In the proton decoupled ^{13}C NMR of the glycosides the sulfur substituted C-2 carbon can be identified at higher field (chemical shift 55-60 ppm) than the other oxygen substituted ring carbons. The anomeric C-1 carbon shows a low field signal, chemical shift between 100-105 ppm.

This reaction has been developed as a general method for 2-deoxy-glycosidation using a variety of hydroxyl donors (**Table 2**) and different aryl groups in the reagent **22** (**Table 3**). The reagent **22** have been found to be more β selective compared to sulfonium salts **20** and **21**. The face selectivity depends on the nature of the nucleophile (bulkier sugar nucleophiles affording better selectivity as compare to methanol, entries 1, 3 and 4 **Table 2**) as well as the nature of the reagent [p-methylphenyl{bis(p-methylphenyl)thio}sulfonium reagent giving the best selectivity, entry 2, **Table 3**]. This work was done by N.Kaila of our laboratory.

Table 2: Glycosyl Transfers Using Reagent 22



22 β α

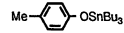
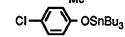
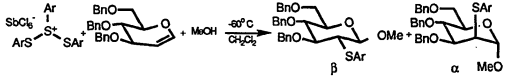
Entry	ROH($SnBu_3$)	ratio β/α	Yield %
1	MeOH	3.7/1	92
2	isopropanol	2.7/1	59
3		5.3/1	70
4		11.5/1	75
5		no α isolated	45
6		3.0/1	64
7		5.3/1	43
8		3.7/1	30
9		4.9/1	53
10		5.7/1	60

Table 3: Glycosyl Transfers to Methanol Using Different Reagents



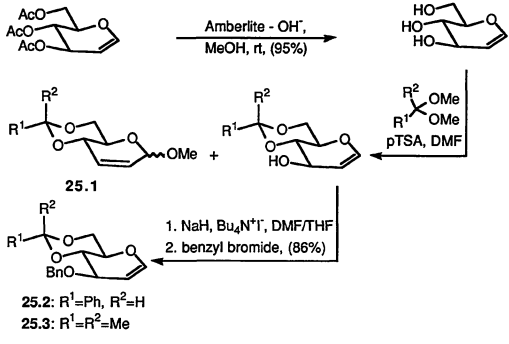
Entry	Ar—	ratio β/α	Yield %
1		2.5/1	91.4
2		4.4/1	91.7
3		2.4/1	82
4		4.1/1	90
5		2.2/1	86.8
6		2.6/1	71.2

Effect of Glycal Structure: A variety of glycals were synthesized to be used in studying the role of glycal in our glycosidation procedure.

(i) Glycals with Cyclic Protecting Groups: Commercially available tri-O-acetyl-D-glucal was deacetylated by treatment with basic resin (amberlite-OH^-) in methanol (**Scheme 25**). The resulting D-glucal was reacted with 2,2-dimethoxy-propane or benzaldehyde dimethylacetal under acid catalysis[101] to give 4,6-O-isopropylidene or 4,6-O-benzylidene derivatives respectively. The Ferrier product **25.1**, was isolated as the side product. The 3-hydroxyl was

protected as its benzyl ether using NaH/benzyl bromide, to give glucals **25.2** and **25.3**.

Scheme25:

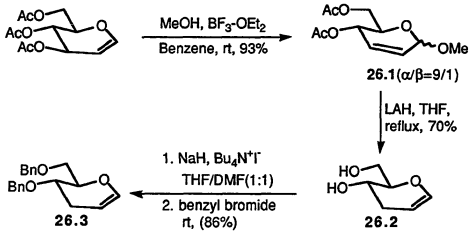


25.1

25.2: R^1=Ph, R^2=H
25.3: R^1=R^2=Me

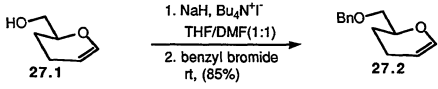
(ii) 3-Deoxy-glucal: Tri-O-acetyl-D-glucal was subjected to Ferrier rearrangement conditions (MeOH, $BF_3.OEt_2$)[102] to give **26.1** as a mixture of anomers, which, without separation, was treated with LAH in refluxing THF[103] to give 3-deoxy-D-glucal. Hydroxyls at C-4 and C-6 were protected as benzyl ethers to give the di-O-benzyl derivative **26.3** (**Scheme 26**).

Scheme 26:



(iii) 3,4-Dideoxy-glucal: Benzylation of commercially available racemic 3,4-dihydro-2H-pyran-2-methanol **27.1** using NaH/BnBr pair gave desired 6-O-benzyl-3,4-dideoxy-glucal **27.2** as a racemic mixture (**Scheme 27**).

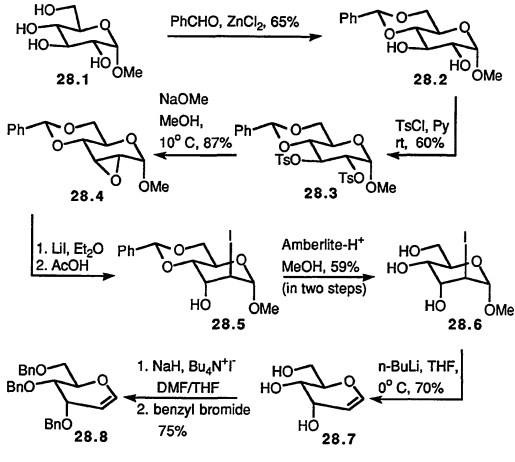
Scheme 27:



(iv) Tri-O-benzyl-allal: Methyl-α-D-glucopyranoside was converted into its 4,6-O-benzylidene derivative **28.2** (**Scheme 28**) by treatment with benzaldehyde and $ZnCl_2$.[104] Compound **28.2**, was treated with tosyl chloride in pyridine to give **28.3**, which on reaction with NaOMe in methanol gave the 2,3-anhydro-sugar **28.4**. The epoxide ring of **28.4** was opened with LiI[105]

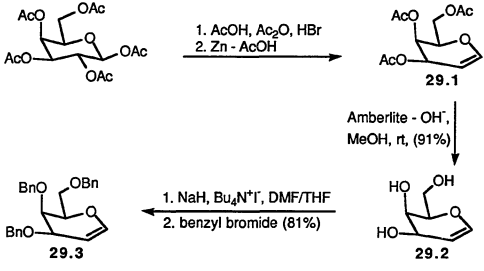
giving 2-deoxy-2-iodo-glycoside **28.5**, having allose stereochemistry at C-3. The benzylidene protection was hydrolyzed and **28.6** treated with n-BuLi in THF[106] to give D-allal **28.7**, which was subsequently converted into its tribenzyl ether **28.8**.

Scheme28:



(v) Tri-O-benzyl-galactal: D-galactose pentaacetate was reacted with HBr/HOAc to give corresponding galactosyl bromide which without isolation was subjected to reductive elimination conditions (Zn-acetic acid) to give 3,4,6-tri-O-acetyl-D-galactal **29.1 (Scheme 29)**. Deacetylation (amberlite-OH^-, methanol) followed by benzylation (NaH/BnBr) gave 3,4,6-tri-O-benzyl-D-galactal **29.3**.

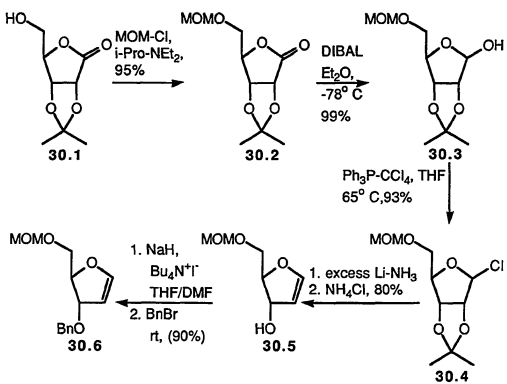
Scheme29:



(vi) Ribal: Using Ireland's method,[107] starting with 2,3-O-isopropylidene-ribonolactone **30.1**, ribose derivative **30.3** was prepared by first protecting 5-hydroxyl and then reducing lactone **30.2 (Scheme 30)**. Compound **30.3** was converted to glycosyl chloride **30.4** by reacting it with Ph_3P-CCl_4 complex, which was then subjected to reductive elimination conditions (Li-liq. NH_3) to

give dihydrofuran derivative **30.5**. The 3-Hydroxyl was protected as its benzyl ether to get desired **30.6**.

Scheme 30:



Glycosidations Using Different Glycals: The glycals described above were examined in order to determine the effect of their structure and stereochemistry on the glycosidation stereochemistry. Phenyl(bisphenylthio)sulfonium reagent (**22** , Ar = phenyl) was our standard electrophile and the results are listed in **Tables 4** and **5**. First glycals with cyclic acetal protecting groups **25.2** and **25.3** were studied in order to see the

effect of rigidity of the glycal ring (**Table 4**, entries 2 and 3, **Table 5**, entries 2 and 3). These rather rigid glycals gave β-glycosides **β-27, β-28, β-35** and **β-36** as the major products indicating that the diequatorial addition path does not have to go through a flipped conformation of the substrate. Thiem and Ossowosky[108] had proposed that flipped chair forms of glycals underwent diaxial attack in order to explain the formation of diequatorial products (**scheme 30a**). The cyclic acetal protecting groups were partially cleaved during the glycosidation process. Probably when the reaction is quenched with aqueous sodium bicarbonate, antimony Lewis acid(s) hydrolyzed these acetals faster than the acid could be neutralized. Quenching the reactions with a soluble anhydrous base (e.g. Et_3N) reduced the extent of this hydrolysis but did not stop it altogether.

Scheme 30a:

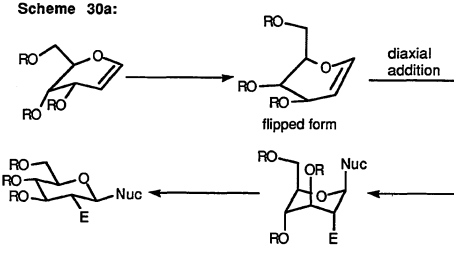
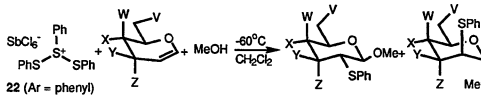


Table 4: Glycosyl Transfers to Methanol Using Different Glycals



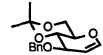
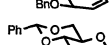
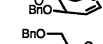
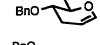
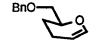
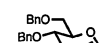
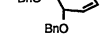
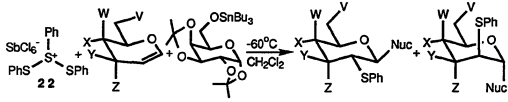
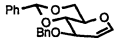
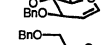
Entry	Glycal Substrate	ratio β/α	Yield %
1		3.7/1 (26)	94
2	 (25.3)	2.7/1 (27)	86
3	 (25.2)	2/1 (28)	76
4	 (26.3)	2/1 (29)	62
5	 (27.2)	2/1 (30)	93
6	 (28.8)	1/10 (31)	80
7	 (29.3)	12/1 (32)	92
8	 (30.6)	2/1 (33)	90

Table 5: Glycosyl Transfers to Diisopropylidenegalactose Using Different Glycals



Entry	Glycal Substrate	ratio β/α	Yield %
1		5.3/1 (**34**)	70
2	 (**25.2**)	5.7/1 (**35**)	79
3	 (**25.3**)	5.2/1 (**36**)	73
4	 (**26.3**)	3.1/1(**37**)	74

To see the effect of pseudoequatorial allylic 3-substituent, 3-deoxy-4,6-O-dibenzyl-glucal **26.3** was glycosylated. The results β/α=2/1 with methanol and 3.1/1 with galactose nucleophile (**Table 4**, entry 4 and **Table 5**, entry 4) when compared to those from the glycosidations of the parent 3,4,6-tri-O-benzyl-D-glucal (**Table 4**, entry 1 and **Table 5** entry 1. β/α=3.7/1 with methanol and 5.3/1 with galactose as nucleophile) show that the steric effect of pseudoequatorial 3-substituent is only partially accountable for the observed stereochemical outcome. Also, since 3,4-dideoxy-6-O-benzyl-glucal **27.2** gives similar selectivity (β/α=2/1, **Table 4**, entry 5) as does 3-deoxy-glucal **26.3** (**Table 4**, entry 4), the equatorial 4-substituent does not have any contribution in the resultant selectivity and the reagent **22** has some inherent tendency of attacking glycals from below the plane. In glycosidation of **26.3** α' glycoside was also formed in 10% yield. The structure assignments for the glycosidation

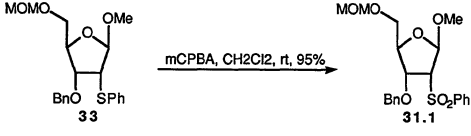
products **29, 30,** and **37** in these deoxy cases were done using ^1H NMR as described earlier, except that the dd for the C-2 proton was further split into a ddd by additional coupling with C-3 equatorial proton. In these deoxy cases glycosidation products could not be separated. The product distribution ratios were determined from the proton NMR for products **29** and **30** (Table 4, entries 4 and 5) and from the carbon NMR for product **37** (Table 5, entry 4).

A pseudoaxial allylic 3-substituent shows a large steric effect. Thus, when 3,4,6-tri-O-benzyl allal **28.8** was subjected to glycosidation, a complete turn over of face selectivity from β/α=3.7/1 (in case of parent glucal) to β/α=1/10 (**Table 4**, entry 6) was observed. In fact, this is the only case in our entire study where α-glycoside was formed as the major product. Thus, the pseudoaxial 3-substituent blocks the α-face of glycal and forces the reagent to attack from the β-face which results in α-glycoside. In this case, as expected the C-2 proton in the proton NMR of the β-glycoside **β-31** had a different splitting pattern, showing one large diaxial coupling to C-1 proton and one small axial-equatorial coupling to C-3 (in this case equatorial) proton.

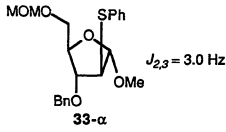
When 3,4,6-tri-O-benzyl-galactal (4-substituent axial) **29.3** was used as the substrate, β-selectivity increased to β/α=12/1 (**Table 4**, entry 7) (as compared to 3.7/1 in case of parent glucal). Thus, axial 4-substituent, like pseudoequatorial 3-substituent, plays a major role in directing the attack of reagent, by blocking the β-face of the glycal ring so that the reagent attacks from α-face giving β-glycoside as the product. Unexpectedly, in the proton NMR of the β-product **β-32**, the C-2 proton was not as high field as it is in other glycals. The structure assignment was done with the help of proton-carbon correlated spectroscopy coupled with information from the proton and carbon 1D spectra.

This glycosidation procedure was extended to furano-glycals also, by using the representative ribal derivative **30.6**. Glycosidation takes place giving good yield (90%, β/α=2/1, **Table 4**, entry 8). Though the allylic 3-substituted has α-orientation the stereochemical outcome was not reversed as it was in the allal case (**Table 4**, entry 6). Thus, in 5-membered ring glycals stereochemistry of the 3-substituent does not play the same role as it does in 6-membered glycals. Proton NMR of the products was not straight forward since the coupling constants for five membered rings are not as well defined as they are for six membered rings. Using proton-proton correlated spectroscopy the signals were assigned to individual protons. Sulfone **31.1** of the major product was made (**Scheme 31**) hoping that it would be a crystallizable solid whose crystal structure could have solved the problem, but **31.1** could not be crystallized. In the literature we located furano sugars[109] **38** and **39** closely related to ours where the structure assignment was done on the basis of coupling between C-2 and C-3 protons. By correlation we assigned the structures for glycosides **33**.

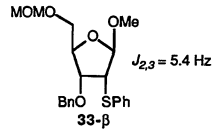
Scheme 31:



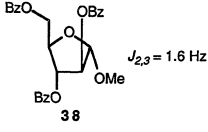
33 **31.1**



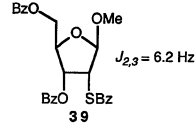
33-α



33-β



38



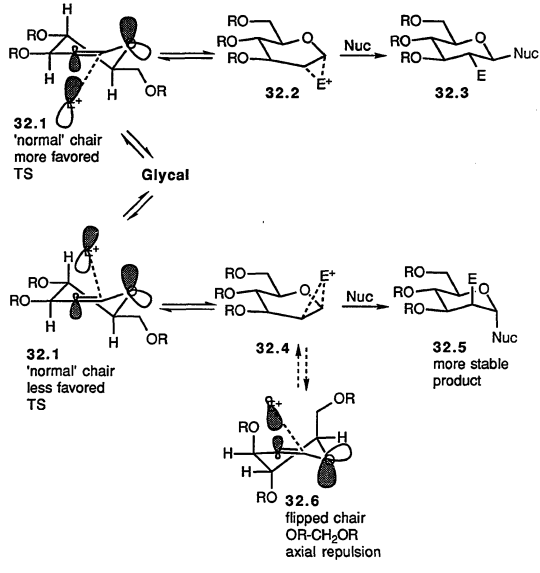
39

Mechanistic Speculations: The results of our glycosidation reaction documented above show that:

(i) The reagent prefers to attack on the α-face of the substrate glycal (allal being the exception).

(ii) The face selectivity (β/α ratio) depends on the nature of the nucleophile, the reagent as well as the glycal structure.

Scheme 32:

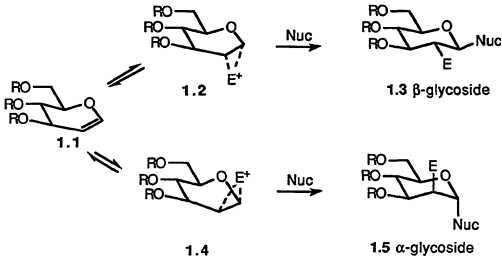


To explain the preference for α-attack we postulate that the transition-state for addition to a glycal with a chiral center at C-5 behaves as if it has a pyramidalized lone-pair as shown in **32.1 (scheme 32)**. Then kinetic attack of

an electrophile is favored on the face anti to the lone-pair. This rationalization is similar to that put forward by Magnus to explain alkylations in non-planar amide enolates.[110] Thus intermediate **32.2** would form faster than **32.4**. However **32.2** is probably less stable than **32.4** if the reverse anomeric effect is operative. In pyranoses, it is well known that there is a strong driving force, which is called the reverse anomeric effect, for positively charged groups at C-1 to avoid the axial position. In **32.2**, the charged heteroatom is axial-like and destabilizing. Thus, if the glycal reaction to form **32.2** is reversible and the nucleophilic ring-opening to form **32.3** is rate-determining, it is conceivable that product **32.5** where the thermodynamic benefit of the normal anomeric effect is operative, would accumulate via **32.1** and **32.4**. However, if **32.2** reverts to starting material **32.1** slowly and its opening by nucleophile is fast, then **32.3** should predominate. Another pathway to **32.4** and **32.5** is via flipped glycal transition-state **32.6** which would be pyramidalized in the opposite sense of **32.1**. However a large A value of an alkyl group at C-2 or C-5 of sugars makes this transition-state conformer less likely.

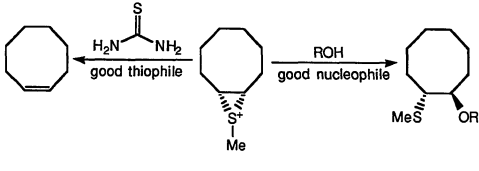
On the other hand reconsidering the mechanism proposed earlier **Scheme 1** (repeated below), if the trapping of onium species (**1.2** or **1.4**) is fast, compared to their formation or reversal to glucal, then changing the alcohol nucleophilicity should have no effect on the product ratio. The use of an alcohol that is a poor nucleophile might change the rate determining step. If alcohol trapping is slow compared to equilibration between **1.2** and **1.4**, then product ratios should be a function of alcohol nucleophilicity.

Scheme 1:



The other factor which will affect product distribution is the ease of reversibility of the initial electrophillic attack. An example of reversibility is shown in **scheme 33.**[87A]

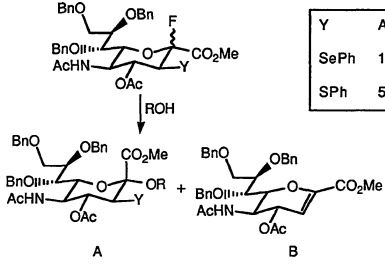
Scheme 33:



When the olefin is part of a sugar ring (glycal) reversibility of the electrophillic attack has been observed in case of selenium electrophiles by Ogawa and

Ito.[111] But when they replaced selenium with sulfur no products arising from the reversibility were observed (**Scheme 34**).

Scheme 34:



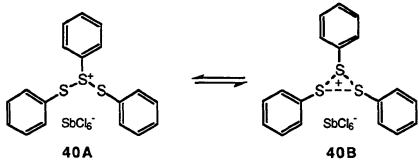
Y	A%	B%
SePh	18	69
SPh	58	0

Another possibility is that alcohols react with the sulfonium reagent to form sulfenate esters and the latter then attack the glycal as in the case of Ogawa's method.[89] But comparison of the results from common cases, shows that our method does not involve sulfenate ester. A further proof was obtained by carrying out a ^{13}C NMR experiment which was done at -60 °C to mimic the reaction conditions (**Table 6**). The signal for the methyl carbon in methanol appears at δ 49.0, in sulfenate ester, MeOSPh, at δ 65.2. This signal in the mixture of reagent and methanol appears at δ 59.4, indicating that methanol is not in a free state, has not formed a sulfenate ester but is "attached" to the reagent in some way. The reagent itself shows three peaks in the ^{13}C NMR

indicating that it exists in a cyclic form **40B**.[96b] On addition of methanol to the reagent we observed ten peaks for the reagent indicating that the cyclic structure has been perturbed making the three phenyl rings nonequivalent. Due to the problems with our NMR instrument at low temperature we could not repeat or do any further experiments.

Table 6: Low temperature ^{13}C NMR data

	δ
$H_3\underline{C}OSPh$	65.2
$H_3\underline{C}OH$	49.0
Reagent **22** + $\underline{C}H_3OH$	59.4
Reagent **22**	124.3, 132.7, 136.7
Reagent **22** + $\underline{C}H_3OH$	124.8, 125.4, 125.7, 127.5, 129.0, 129.2, 132.7, 134.4, 135.0, 135.6

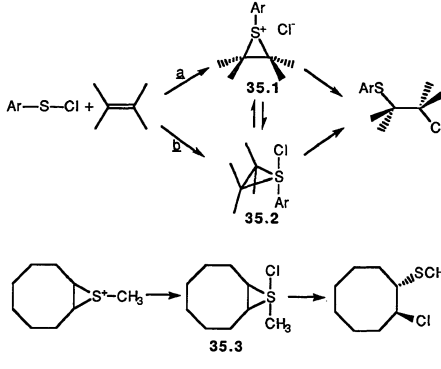


40A **40B**

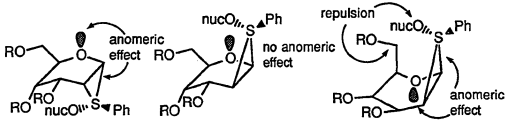
In the addition of arenesulphenyl halides to alkenes to form β-haloalkyl sulfides[112], one possible mechanism is the nucleophillic attack by olefin on the sulfur to form a episulfonium ion **35.1** which is ring opened by nucleophilic attack on carbon by the chloride ion (**Scheme 35,** path a) similar to our **scheme 1**. An alternative mechanism has been proposed which involves nucleophilic attack at sulfur to form a chlorosulfurane **35.2** which may

rearrange directly to product or ionize to form the episulfonium ion **35.1**. Intermediate **35.2**, a less polar species than **35.1**, is especially favorable in less polar solvents. Chlorosulfurane **35.3**, an example of intermediate **35.2** along path b, was observed in the reaction between the corresponding methylepisulfonium ion and a stoichiometric amount of chloride ion at -5 °C by proton NMR[113]. The lesser strain in a three membered ring spanning apical-equatorial or equatorial-equatorial sites in triagonal bypyramidal sulfurane **35.2** compared to a tetrahedral episulfonium ion **35.1** also indicates preference for path b.

Scheme 35:



Our results can also be rationalized by considering sulfuranes as reaction intermediates (**41** and **42**). These bicyclic species, with the nucleophile attached at a congested site, would explain the dependence of face selectivity on nucleophile in a more satisfying way than the postulate that isomeric onium species **1.2** and **1.4** are differently sensitive to the several nucleophiles attacking C-1. Thus the Dreiding models suggest that the boat form of sulfurane **41** is the stable form and benefits from an anomeric effect. One boat form of **42** (**42a**) has the anomeric effect but suffers fron severe steric repulsions; whereas the less congested boat of **42** has no anomeric effect. Though the mechanism involving sulfuranes as the intermediates in our system is purely speculative, it explains our observations in a convincing manner.

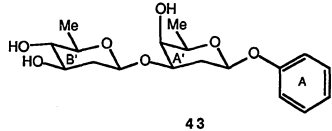


41 **42** **42a**

In conclusion, we believe that this glycosyl transfer method should be useful in the field of 2-deoxy-β-glycoside chemistry. The face selectivity data will help in rationalizing the rather extensive, but confusing literature on the electrophillic addition to glycals, one of the important glycosyl transfer processes.

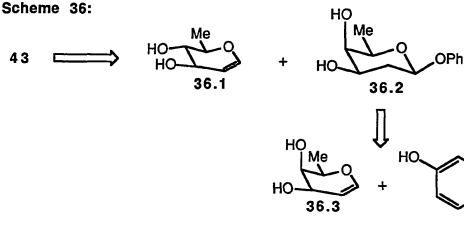
Synthesis of AA'B' ring analog of aureolic acid: Our target was the AA'B' ring analog **43** of aureolic acid. The retrosynthetic analysis (**Scheme**

36) shows that the synthesis of **43** can be achieved in two glycosydation steps from D-fucal **36.3**and D-rhamnal **36.1**.



43

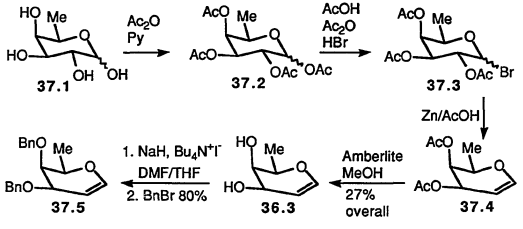
Scheme 36:



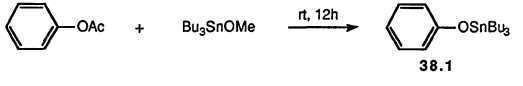
Precursor **37.6** was synthesized from D-fucose using the reductive elimination method of Ziegler et. al.[68] (**Scheme 37**). Peracetylation of D-fucose (Ac_2O/pyridine) gave the tetraacetate **37.2** which was converted to corresponding glycosyl bromide **37.3** by reacting it with HBr/AcOH pair. Compound **37.3** was subjected to reductive elimination condition (Zn/AcOH) to give D-fucal diacetate **37.4**, which was deacetylated by treatment with basic resin (amberlite-OH^-) in methanol. At this stage D-fucal **36.3**, was purified

simply by washing the crude reaction product with chloroform. Evaporation of the chloroform washings gave D-fucal (overall yield from fucose is 27%), pure enough for further reaction. By treating **37.5** with NaH followed by BnBr, the dibenzyl ether **37.5** was, prepared in 80% yield.

Scheme37:



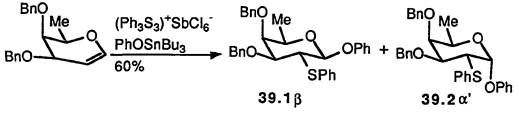
Scheme 38:



The nucleophile required for the first glycosidation step, phenyl tributyltin ether was prepared by stirring an equimolar mixture of phenyl acetate and tributyltin methoxide. overnight at room temperature. Glycosidation between **37.5** and **38.1** was carried out using **22** as the reagent following our standard procedure

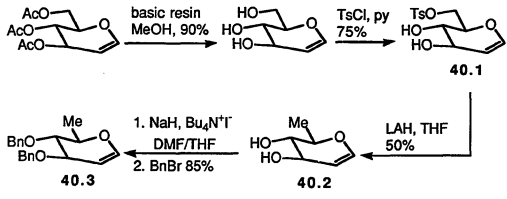
(**scheme 39**). A high β selectivity was expected, since glycosidation with galactal **29.3** (both fucal and galactal have a 4 axial substituent) had given β/α=12/1 (**Table 4**, entry 7). No α glycoside was isolated, but the major product was the α' glycoside **39.2**, not the desired β-isomer **39.1** (β/α'=1/2). Reagent **22** used in this procedure was made using **Scheme 21** i.e. it had half a equivalent of $SbCl_3$, which is a Lewis acid and could be catalyzing anomerization of **39.1** to give thermodynamically more stable **39.2**. Glycoside **39.1**, being a 6-deoxy sugar, is more susceptible to anomerization as compare to normal sugars because of the increased electron density on the sugar ring. Therefore, the glycosidation between **37.5** and **38.1** was repeated using reagent **22** free of $SbCl_3$ (from **Scheme 22**). The β/α' ratio improved to 2/1 but α' could not be avoided completely. Secondary amines are known to complex with antimony salts, therefore we added trimethylsilyldiethylamine (1 equiv) to the reagent and used the mixture for glycosidation. This variation was of no help since the β/α' ratio remained the same (2/1).

Scheme 39:



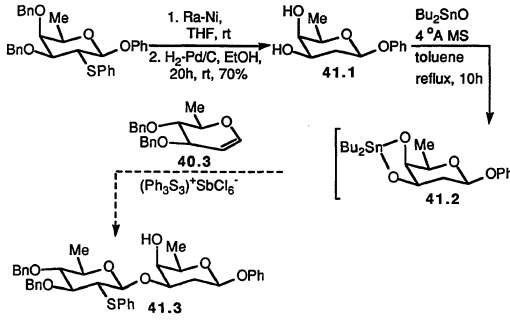
Reagent with $SbCl_3$	1	:	2
Reagent without $SbCl_3$	2	:	1
Reagent with TMS-NEt_2	2	:	1

Scheme 40:



The β-glycoside **39.1** was separated and subjected to desulfurization (Ra-Ni) followed by debenzylation (H_2/Pd-C) to get phenyl-2-deoxy-β-fucose **41.1** in 70% yield. The next requirement was selective glycosidation using the 3-OH of **41.1**. We thought of using the methodology invoving cyclic tin ethers to differentiate between hydroxyls of carbohydrates.[114] The 3-hydroxyl of **41.1**, being equatorial is expected to be more easily accessible as compare to the 4-axial-hydroxyl. Cyclic tin derivative **41.2** was synthesized by refluxing **41.1** and Bu_2SnO with 4A° molecular sieves in toluene. D-Rhamnal dibenzyl ether **40.3** was synthesized from tri-O-acetyl-D-glucal using Fraser-Reid's method (**Scheme 40**)[103] Deacetylation of glucal triacetate followed by tosylation (TsCl/pyridine) gave 6-O-tosyl-D-glucal **40.1** which was deoxygenated by reacting it with LAH to give D-rhamnal **40.2** in 50% yield. Compound **40.2** was converted to its dibenzyl ether by treating it with NaH and then BnBr to give **40.3** in 85% yield.

Scheme 41:



Glycosidation between **40.3** and **41.2** using reagent **22** ($SbCl_3$ free) was attempted but no characterizable products could be isolated. In our glycosidations we have observed that phenyl glycosides are labile to the glycosidation conditions. The 6-deoxy sugars also have proved to be more unstable than normal sugars in our glycosidation conditions. Thus **41.1**, being a phenyl-2,6-dideoxy-glycoside, could get hydrolyzed during its glycosidation with **41.2** . Therefore a synthetic scheme involving the construction of the glycosidic linkage between the A' and B' rings before the glycosidation with phenol nucleophile, could be a better approach for the target AA'B' ring analog of aureolic acid.

EXPERIMENTAL

General Experimental: NMR spectra were recorded on GE QE 300, JEOL FX 400 instruments with $CDCl_3$ as solvent. Elemental analyses were performed by Spang Microanalytical Laboratory, Eagle Harbor, MI. Melting points were determined on a Fisher-Johns melting point apparatus and are uncorrected. Optical rotations were determined using a Rudolph Research AUTOPOL III automatic polarimeter. Thin-layer chromatograms were done on precoated TLC sheets of silica gel 60 F_{254} (E. Merck) and short- long-wave ultraviolet light was used to visualize the spots. PLC plates were prepared by using Kieselgel 60 PF_{254} (E. Merck), and chromatotron (radial chromatography) plates were prepared by using Kieselgel 60 PF_{254} gipshaltig (E. Merck). Flash chromatography was performed with silica gel (230-400 mesh) purchased from Aldrich Chemical Co. Methanol was distilled from Mg and stored over 3 A^o MS. Dry THF was obtained by distillation, under nitrogen, from sodium-benzophenone ketyl. Dichloromethane was distilled from P_2O_5. Other solvents were purified and dried by using standard procedures.

General Procedure for Benzylation of Glycals: A NaH oil suspension (1.5 equivalents for each hydroxyl to be benzylated) is washed with dry hexane and suspended in dry DMF (1.0 ml/100 mg of NaH) To this suspension a solution of the glycal in DMF/THF (1:1 mixture, 1.0 ml/100 mg of the glycal) is added dropwise with stirring at room temperature. After the addition is complete the reaction mixture is stirred for 30 min and then tetra-n-butylammonium iodide (10 mg for each equivalent of NaH) and benzyl bromide (1.2 equivalent for each hydroxyl to be benzylated) are added to it. After stirring for 6 h the reaction mixture is poured into water (100 ml/5 ml of the reaction mixture volume) and is

extracted three times with ethyl acetate (50 ml/100 ml of water). Combined organic extracts are dried over anhydrous sodium sulfate. Evaporation of the solvent gives the crude product which is subjected to radial chromatography (ethyl acetate-Hexane 1:9).

4,6-O-Benzylidene-3-O-benzyl-D-glucal (25.2): Benzylation was carried out starting with 4,6-O-benzylidene-D-glucal[101]. Product **25.2** was obtained in 86% yield as a colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.78-3.95 (m, 3H), 4.01 (t, J = 8.4 Hz, 1H), 4.32-4.39 (m, 2H), 4.75 (AB q, Δν = 28.6 Hz, J_{AB} = 12.1 Hz, 2H, PhCH_2), 4.80 (m, 1H), 5.62 (s, 1H), 6.33 (dd, J = 6.3, 1.3 Hz, 1H, C_1-*H*), 7.26-7.55 (m, 10H, Ar-*H*).

4,6-O-Isopropylidene-3-O-benzyl-D-glucal (25.3): Benzylation was carried out starting with 4,6-O-isopropylidene-D-glucal[101]. The product **25.3** was obtained in 86% yield; Colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.42 (s, 3H, CH_3), 1.49 (s, 3H, CH_3), 3.65-3.75 (m, 1H), 3.82 (t, J = 10.8 Hz, 1H), 3.90-3.96 (m, 1H), 3.97-4.04 (m, 1H), 4.15-4.20 (m, 1H), 4.68 (AB q, Δν = 27.6 Hz, J_{AB} = 12.0 Hz, 2H, PhCH_2), 4.74 (m, 1H), 6.29 (dd, J = 6.3, 1.8 Hz, 1H, C_1-*H*), 7.24-7.40 (m, 5H, Ar-*H*).

4,6-di-O-benzyl-3-deoxy-D-glucal (26.3): Benzylation was carried out starting with 3-deoxy-D-glucal (**26.2**).[103] The product **26.3** was obtained in 86% yield; Colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.05 (ddt, J = 16.5, 12.4, 2.5 Hz, 1H), 2.30-2.42 (m, 1H), 3.70-3.85 (m, 3H), 3.85-3.93 (m, 1H), 4.48-4.66 (m, 5H), 6.34 (dt, J = 6.0, 1.9 Hz, 1H, C_1-*H*), 7.22-7.40 (m, 10H, Ar-*H*).

6-O-Benzyl-3,4-dideoxy-glucal (27.2): Benzylation was carried out starting with 3,4-dideoxy-glucal (**27.1**). The product **27.2** was purified by distillation (bp 105-108 °C at 0.5 mm Hg); yield 85%; Colorless oil; ^{1}H NMR

(300 MHz, $CDCl_3$) δ 1.60-1.74 (m, 1H), 1.77-1.88 (m, 1H), 1.89-2.01 (m, 1H), 2.01-2.16 (m, 1H), 3.49-3.61 (m, 2H), 3.96-4.08 (m, 1H), 4.50-4.63 (m, 2H), 4.65-4.70 (m, 1H), 6.39 (d, J = 6.3 Hz, 1H, C_1-*H*), 7.21-7.42 (m, 5H, Ar-*H*); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.41, 24.62, 72.50, 73.45, 74.10, 100.51, 127.68, 127.77, 128.42, 138.15, 143.63.

3,4,6-tri-O-benzyl-D-galactal (29.3): Benzylation was carried out starting with D-galactal (**29.2**). The product **29.3** was obtained in 81% yield; Thick colorless oil ^1H NMR (300 MHz, $CDCl_3$) δ 3.62 (dd, J = 10.2, 5.1 Hz, 1H), 3.76 (dd, J = 10.2, 7.0 Hz, 1H), 3.90-3.95 (m, 1H), 4.12-4.20 (m, 2H), 4.44 (AB q, Δν = 25.6 Hz, J_{AB} = 11.6 Hz, 2H, PhC*H*$_2$), 4.55-4.68 (m, 3H), 4.80-4.90 (m, 2H), 6.36 (d, J = 5.6 Hz, 1H, C_1-*H*), 7.20-7.40 (m, 15H, Ar-*H*).

3-O-Benzyl-5-O-methoxymethyl-D-ribal (30.6): Benzylation was carried out starting with 5-O-methoxymethyl-D-ribal (**30.5**). The product **30.6** was obtained in 90% yield; Colorless oil; ^1H NMR (300 MHz, $CDCl_3$) δ 3.34 (s, 1H, OC*H*$_3$), 3.45-3.60 (m, 2H), 4.40-4.70 (m, 6H), 5.16 (t, J = 2.5 Hz, 1H, C_1-*H*), 7.24-7.38 (m, 5H, Ar-*H*); ^{13}C NMR (75 MHz, $CDCl_3$) δ 55.35, 67.61, 69.61, 82.62, 84.86, 96.69, 100.55, 127.65, 127.83, 128.40, 138.27, 150.37.

General Procedure for Preparation of Phenyl(bisphenylthio)sulfonium Salt Reagent (22):

Method A (Scheme 21): A solution of diphenyldisulfide (1.5 mmol) in 2.5 ml of dry methylene chloride is added dropwise to antimony pentachloride (1.5 ml of 1M solution in CH_2Cl_2, bought from Aldrich) at -60 °C (under argon). The mixture is stirred for 30 min at -60 °C to give a 0.25 M solution of **22**.

Method B (Scheme 22): A solution of diphenyldisulfide (1 mmol) and phenylsulfenyl chloride (1.1 mmol) in 3.0 ml of dry methylene chloride is added dropwise to antimony pentachloride (1.0 ml of 1M solution in CH_2Cl_2) at -60 °C (under argon). The mixture is stirred for 30 min at -60 °C to give a 0.25 M solution of **22**.

General Procedure for Glycosidation Using Methanol as the Nucleophile: To a solution of the glycal (0.25 mmol) and 50 μL of methanol in dry methylene chloride at -60 °C (under argon), 1.2 ml of the reagent solution (0.30 mmol) is added by syringe technique. After the reaction is complete (about 10 min) saturated aqueous sodium bicarbonate solution (15 ml) is added and the mixture is stirred for 30 min at room temperature. The reaction mixture is extracted with dichloromethane (3X25 ml). The combined organic extracts were dried over anhydrous Na_2SO_4. Evaporation of the solvent gave the crude product mixture which was subjected to radial chromatography.

4,6-O-Isopropylidene-3-O-benzyl-D-glucal (25.3) + Methanol: Glycosidation was carried out using reagent **22** prepared by **method A**. Radial chromatography (ethyl acetate-Hexane 1:20 to 2:1) gave 57 mg of methyl-3-O-benzyl-2-deoxy-2-phenylthio-β-D-glucopyranoside (**β-27**) and 21.5 mg of methyl-3-O-benzyl-2-deoxy-2-phenylthio-α-D-mannopyranoside (**α-27**); total yield 86%; β/α 2.7/1.

Physical data: Fraction 1: **α-27:** Colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.23 (t, J = 6.4 Hz, 1H, C_6-O*H*), 2.67 (d, J = 2.2 Hz, 1H, C_4-O*H*), 3.37 (s, 3H, OCH_3), 3.7-3.75 (m, 1H), 3.825(dd, J = 4.7, 1.3 Hz, 1H), 3.85-4.0 (m, 3H), 4.11 (dd, J = 9.4, 4.7 Hz, 1H), 4.54 (AB q, Δν = 61.7 Hz, J_{AB} = 11.2 Hz, 2H, PhCH_2), 4.91 (s, 1H, C_1-*H*), 7.26-7.55 (m, 10H, Ar-*H*).

Fraction 2: **β-27 :** mp 100 °C; $[\alpha]^{25}_D$ -31.2° (c 0.4, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 2.20 (br s, 1H, C_6-O*H*), 2.595 (d, *J* = 3.0 Hz, 1H, C_4-O*H*), 3.12 (dd, *J* = 10.8, 8.8 Hz, 1H, C_2-*H*), 3.30-3.36 (m,1H), 3.44 (dd, *J* = 10.8, 8.6 Hz, 1H), 3.54 (s, 3H, OCH_3), 3.67 (dt, *J* = 9.3, 3.0 Hz, 1H, C_4-*H*), 3.74-3.96 (br m, 2H, CH_2O*H*), 4.337 (d, *J* = 8.8 Hz, 1H, C_1-*H*), 4.98 (AB q, Δν = 81.3 Hz, J_{AB} = 11.1 Hz, 2H, PhCH_2), 7.26-7.65 (m, 10H, Ar-*H*); ^{13}C NMR (75 MHz, $CDCl_3$) δ 55.49, 57.28, 62.26, 71.50, 74.69, 75.36, 82.95, 104.37, 127.24, 127.93, 128.03, 128.52, 128.73, 132.46, 134.40, 138.20. Anal. Calcd for $C_{20}H_{24}O_5S$: C, 63.81; H, 6.43; S, 8.52. Found: C, 63.46; H, 6.43; S, 8.53.

4,6-O-Benzylidene-3-O-benzyl-D-glucal (25.2) + Methanol: Glycosidation was carried out using reagent **22** prepared by **method A**. Radial chromatography (ethyl acetate-Hexane 1:20 to 2:1) gave 35 mg of methyl-4,6-O-benzylidene-3-O-benzyl-2-deoxy-2-phenylthio-β-D-glucopyranoside (**β-28**), 9.4 mg of methyl-4,6-O-benzylidene-3-O-benzyl-2-deoxy-2-phenylthio-α-D-mannopyranoside (**α-28**), 19 mg of methyl-3-O-benzyl-2-deoxy-2-phenylthio-β-D-glucopyranoside (**β-27**) and 14.6 mg of methyl-3-O-benzyl-2-deoxy-2-phenylthio-α-D-mannopyranoside (**α-27**); total yield 76%; β/α 2/1.

Physical data: Fraction 1: **α-28:** mp 95-97 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 3.36 (s, 3H, OCH_3), 3.815 (dd, *J* = 4.8, 1.2 Hz, 1H), 3.88-3.97 (m, 3H), 4.14 (dd, *J* = 9.1, 8.9 Hz, 1H), 4.3-4.4 (m, 2H), 4.73 (AB q, Δν = 24.7 Hz, J_{AB} = 12.2 Hz, 2H, PhCH_2), 4.93 (d, *J* = 1 Hz, 1H, C_1-*H*), 5.7 (s, 1H), 7.2-7.6 (m, 15H, Ar-*H*).

Fraction 2: **β-28:** mp 84 °C; $[\alpha]^{25}_D$ -48.2° (c 0.4, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 3.144 (dd, *J* = 10.3, 8.8 Hz, 1H, C_2-*H*), 3.4-3.47 (m, 1H), 3.58 (s, 3H, OCH_3), 3.69 (dd, *J* = 10.2, 8.8 Hz, 1H), 3.78-3.88 (m, 2H), 4.38-4.43 (m, 2H), 4.91 (AB q, Δν = 43.3 Hz, J_{AB} = 10.9 Hz, 2H, PhCH_2), 5.65 (s, 1H), 7.3-7.65 (m,

15H, Ar-*H*); ^{13}C NMR (75 MHz, $CDCl_3$) δ 55.84, 57.40, 65.69, 68.70, 75.42, 79.00, 82.96, 101.16, 104.59, 125.92, 127.55, 127.67, 128.22, 128.75, 128.94, 133.29, 133.94, 137.24, 138.17. Anal. Calcd for $C_{27}H_{28}O_5S$: C, 69.80; H, 6.07; S, 6.90. Found: C, 69.55; H, 6.17; S, 7.00.

4,6-di-O-benzyl-3-deoxy-D-glucal (26.3) + Methanol: Glycosidation was carried out using reagent **22** prepared by **method A**. Radial chromatography (ethyl acetate-Hexane 1:9) did not separate the isomeric glycosides. PLC (ethyl acetate-Hexane 1:9) gave 46.5 mg of methyl-4,6-O-dibenzyl-2,3-dideoxy-2-phenylthio-β-D-glucopyranoside (β-**29**) and 44.5 mg of a mixture of methyl-4,6-O-dibenzyl-2,3-dideoxy-2-phenylthio-α-D-mannopyranoside (α-**29**) and methyl-4,6-O-dibenzyl-2,3-dideoxy-2-phenylthio-α-D-glucopyranoside (α'-**29**), ratio α-**29**/α'-**29** 2/1 (from ^{1}H NMR); total yield (β-**29**+α-**29**) 62%; β/α 2/1. α'-**29** was formed in an additional 10% yield.

Physical data: Faster moving band: α-**29** + α'-**29:** ^{1}H NMR (300 MHz, $CDCl_3$), characteristic signals δ 1.95-2.07 (m, C_3-H_{ax} of α'), 2.13-2.31 (m, C_3-H_{ax} and C_3-H_{eq} of α), 2.35-2.46 (m, C_3-H_{eq} of α'), 3.30-3.40 (m, C_2-*H* of α'), 3.42 (s, OCH_3 of α), 3.47 (s, OCH_3 of α').

Slower moving band: β-**29:** Colorless oil; $[\alpha]^{25}_D$ +5.4° (c 1.35, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.52-1.64 (m, 1H, C_3-*H*), 2.50-2.56 (m, 1H, C_3-*H*), 3.11 (ddd, *J* = 13.1, 8.6, 4.4 Hz, 1H, C_2-*H*), 3.51-3.57 (m, 2H), 3.58 (s, 3H, OCH_3), 3.72 (dd, *J* = 9.3, 3.7 Hz, 1H), 3.82 (d, *J* = 10.2 Hz, 1H), 4.28 (d, *J* = 9.3 Hz, 1H, C_1-*H*), 4.51 (AB q, Δν = 46.5 Hz, J_{AB} = 11.6 Hz, 2H, PhCH_2), 4.64 (AB q, Δν = 23.2 Hz, J_{AB} = 12.5 Hz, 2H, PhCH_2), 7.21-7.57 (m, 15H, Ar-*H*); ^{13}C NMR (75 MHz, $CDCl_3$) δ 35.2, 46.74, 56.88, 69.19, 71.49, 72.89, 73.49, 78.39, 105.52,

127.52, 127.58, 127.81, 128.36, 128.43, 128.78, 133.17, 133.28, 137.87, 138.33.

6-O-Benzyl-3,4-dideoxy-glucal (27.2) + Methanol: Glycosidation was carried out using reagent **22** prepared by **method A**. Radial chromatography (ethyl acetate-Hexane 1:20 to 1:4) gave 53.1 mg of methyl-6-O-benzyl-2,3,4-trideoxy-2-phenylthio-β-glucopyranoside (**β-30**) and 26.6 mg of methyl-6-O-benzyl-2,3,4-trideoxy-2-phenylthio-α-mannopyranoside (**α-30**); total yield 93%; β/α 2/1.

Physical data: Fraction 1: **α-30:** Colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.41-1.52 (m, 1H), 1.73-1.90 (m, 2H), 2.19-2.34 (m, 1H), 3.30-3.60 (m, 3H), 3.37 (s, 3H, OCH_3), 3.93-4.02 (m, 1H), 4.58 (AB q, Δν = 16.7 Hz, J_{AB} = 7.4 Hz, 2H, $PhCH_2$), 4.76 (s, 1H, C_1-*H*), 7.16-7.45 (m, 10H, Ar-*H*); ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.94, 23.38, 46.58, 54.76, 68.21, 73.40, 99.93, 126.81, 127.56, 127.61, 128.37, 129.06, 131.07, 131.73, 138.44.

Fraction 2: **β-30:** Colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.30-1.72 (m, 3H), 2.05-2.15 (m, 1H), 3.00 (ddd, *J* = 12.5, 8.5, 4.4 Hz, 1H, C_2-*H*), 3.40-3.60 (m, 2H), 3.51 (s, 3H, OCH_3), 4.23 (d, *J* = 8.5 Hz, 1H, C_1-*H*), 4.56 (AB q, Δν = 16.3 Hz, J_{AB} = 11.6 Hz, 2H, $PhCH_2$), 7.20-7.53 (m, 10H, Ar-*H*); ^{13}C NMR (75 MHz, $CDCl_3$) δ 28.58, 29.93, 48.26, 56.68, 72.78, 73.50, 75.36, 105.77, 127.25, 127.67, 128.43, 128.72, 133.02, 133.76, 138.26.

3,4,6-tri-O-benzyl-D-allal (28.8) + Methanol: Glycosidation was carried out using reagent **22** prepared by **method A**. Radial chromatography (ethyl acetate-Hexane 1:20 to 2:3) gave 10.1 mg of methyl-3,4,6-O-tribenzyl-2-deoxy-2-phenylthio-β-D-allopyranoside (**β-31**) and 101.1 mg of methyl-3,4,6-O-

tribenzyl-2-deoxy-2-phenylthio-α-D-altropyranoside (α-**31**); total yield 80%; β/α 1/10.

Physical data: Fraction 1: β-**31:** Colorless oil; $[\alpha]^{25}_D$ -50.8° (c 0.2, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 3.15 (dd, *J* = 8.8, 2.6 Hz, 1H, C_2-*H*), 3.50 (s, 3H, OCH_3), 3.63 (dd, *J* = 10.2, 2.3 Hz, 1H, C_4-*H*), 3.66-3.70 (m, 2H), 4.06-4.13 (m, 1H, C_5-*H*), 4.24 (t, *J* = 2.5 Hz, 1H, C_3-*H*), 4.45-4.95 (m, 7H), 7.15-7.50 (m, 20H, Ar-*H*).

Fraction 2: α-**31:** Colorless oil; $[\alpha]^{25}_D$ +45.6° (c 0.6, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 3.40 (s, 3H, OCH_3), 3.93-4.02 (m, 1H), 3.64 (d, *J* = 3.3 Hz, 1H), 3.75-3.81 (m, 2H), 3.84-3.90 (m, 1H), 4.04 (dd, *J* = 9.6, 2.9 Hz, 1H), 4.31-4.74 (m,7H), 4.91 (s, 1H, C_1-*H*), 7.15-7.40 (m, 20H, Ar-*H*); ^{13}C NMR (75 MHz, $CDCl_3$) δ 49.62, 55.59, 67.41, 69.61, 71.36, 71.38, 71.80, 73.53, 73.80, 101.10, 127.48, 127.62, 127.73, 127.97, 128.13, 128.20, 128.32, 129.25, 131.81, 134.55, 138.17, 138.52.

3,4,6-tri-O-benzyl-D-galactal (29.3) + Methanol: Glycosidation was carried out using reagent **22** prepared by **method A**. Radial chromatography (ethyl acetate-Hexane 1:20 to 2:3) gave 118.3 mg of methyl-3,4,6-O-tribenzyl-2-deoxy-2-phenylthio-β-D-galactopyranoside (β-**32**) and 10.0 mg of methyl-3,4,6-O-tribenzyl-2-deoxy-2-phenylthio-α-D-talopyranoside (α-**32**); total yield 92%; β/α 12/1.

Physical data: Fraction 1: α-**32:** Colorless oil; ^1H NMR (300 MHz, $CDCl_3$) δ 3.36 (s, 3H, OCH_3), 3.54 (d, *J* = 1.5 Hz, 1H), 3.56 (d, *J* = 2.2 Hz, 1H), 3.90-3.94 (m, 4H), 4.47 (AB q, Δν = 25.6 Hz, J_{AB} = 11.6 Hz, 2H, $PhCH_2$), 4.70 (AB q, Δν = 102.3 Hz, J_{AB} = 11.2 Hz, 2H, $PhCH_2$), 4.72 (AB q, Δν = 15.3 Hz, J_{AB} = 11.6 Hz, 2H, $PhCH_2$), 7.10-7.50 (m, 20H, Ar-*H*).

Fraction 2: **β-32:** Colorless oil; $[\alpha]^{25}_D$ +43.3° (c 0.2, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 3.37 (dd, *J* = 9.0, 2.7 Hz, 1H, C_3-*H*), 3.49 (s, 3H, OCH_3), 3.50-3.63 (m, 4H), 3.93 (d, *J* = 2.6 Hz, 1H), 4.21 (d, *J* = 9.0 Hz, 1H, C_1-*H*), 4.44 (AB q, Δν = 15.8 Hz, J_{AB} = 11.8 Hz, 2H, $PhCH_2$), 4.71 (AB q, Δν = 25.4 Hz, J_{AB} = 11.4 Hz, 2H, $PhCH_2$), 4.74 (AB q, Δν = 89.4 Hz, J_{AB} = 11.4 Hz, 2H, $PhCH_2$), 7.20-7.58 (m, 20H, Ar-*H*); ^{13}C NMR (75 MHz, $CDCl_3$) δ 52.17, 57.00, 68.92, 72.05, 72.78, 73.35, 73.59, 74.45, 80.71, 104.15, 127.05, 127.62, 127.80, 127.91, 128.22, 128.34, 128.43, 128.49, 128.62, 132.76, 134.55, 137.91, 138.56.

3-O-Benzyl-5-O-methoxymethyl-D-ribal (30.6) + Methanol: Glycosidation was carried out using reagent **22** prepared by **method A**. Radial chromatography (ethyl acetate-Hexane 1:20 to 2:3) gave 58.5 mg of methyl-3-O-benzyl-5-O-methoxymethyl-2-deoxy-2-phenylthio-β-D-ribofuranoside (**β-33**) and 29.3 mg of methyl-3-O-benzyl-5-O-methoxymethyl-2-deoxy-2-phenylthio-α-D-arabinofuranoside (**α-33**); total yield 90%; β/α 2/1.

Physical data: Fraction 1: **α-33:** Colorless oil; ^1H NMR (300 MHz, $CDCl_3$) δ 3.29 (s, 3H, OCH_3), 3.36 (s, 3H, OCH_3), 3.55-3.68 (m, 2H), 3.70 (d, *J* = 3.0 Hz, 1H, C_2-*H*), 3.81 (dd, *J* = 5.8, 3.2 Hz, 1H, C_3-*H*), 4.24 (dt, *J* = 5.6, 3.8 Hz, 1H, C_4-*H*), 4.50 (AB q, Δν = 63.4 Hz, J_{AB} = 12.1 Hz, 2H), 4.60 (d, *J* = 3.0 Hz, 2H), 4.93 (s, 1H, , C_1-*H*), 7.20-7.40 (m, 10H, Ar-*H*). Anal. Calcd for $C_{21}H_{26}O_5S$: C, 64.59; H, 6.71; S, 8.21. Found: C, 64.64; H, 6.78; S, 8.08.

Fraction 2: **β-33:** Colorless oil; ^1H NMR (300 MHz, $CDCl_3$) δ 3.35 (s, 3H, OCH_3), 3.40 (s, 3H, OCH_3), 3.52-3.60 (m, 2H), 3.98 (dd, *J* = 5.4, 1.2 Hz, 1H, C_2-*H*), 4.38-4.45 (m, 2H), 4.67 (AB q, Δν = 69.6 Hz, J_{AB} = 11.5 Hz, 2H), 4.70 (s, 2H), 4.99 (d, *J* = 1.2 Hz, 1H, C_1-*H*), 7.18-7.45 (m, 10H, Ar-*H*). Anal. Calcd for $C_{21}H_{26}O_5S$: C, 64.59; H, 6.71; S, 8.21. Found: C, 64.56; H, 6.66; S, 8.24.

Preparation of Sulfone of β-33 (31.1): To a solution of of **β-33** (20 mg, 0.05 mmol) in 5 ml of dry methylene chloride was added m-CPBA (9.7 mg, 1.1 equiv.). The reaction mixture was stirred at room temperature for 30 min (tlc showed completion of the reaction), diluted with 10 ml of methylene chloride and was washed with water (20 ml), saturated sodium bicarbonate (2X20 ml) and finally with water (20 ml) again. The organic layer was dried over anhydrous sodium sulfate. Evaporation of the solvent gave 20.3 mg (96 %) of **31.1**. Thick oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.26 (s, 3H, OCH_3), 3.28 (s, 3H, OCH_3), 3.35-3.50 (m, 2H), 3.90 (dd, J = 6.7, 2.4 Hz, 1H), 4.36 (t, J = 6.0 Hz, 1H), 4.51 (AB q, Δν = 6.9 Hz, J_{AB} = 6.9 Hz, 2H), 5.42 (d, J = 2.4 Hz, 1H, C_1-*H*), 7.25-7.40 (m, 5H), 7.46 (t, J = 7.9 Hz, 2H), 7.59 (t, J = 7.9 Hz, 1H), 7.92 (d, J = 7.9 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 55.28, 55.61, 68.07, 71.09, 73.33, 78.74, 81.56, 96.57, 104.75, 128.05, 128.19, 128.43, 128.82, 129.33, 133.85, 136.97, 139.41.

General Procedure for Glycosidation Using 1,2,3,4-diisopropylidenegalactose as the Nucleophile: Diisopropylidene galactose (0.50 mmol) and bis-tri-n-butyltin oxide (0.25 mmol) are dissolved in 10 ml of dry toluene and 3.0 g of activated powdered 4A° MS are added to this solution. The reaction mixture is refluxed for 12 h (under argon) and thereafter toluene is distilled off. To the residue is added the solution of the glycal (0.25 mmol) in dry methylene chloride (3 ml) and the reaction mixture is cooled to -60 °C. The reagent solution (1.2 ml, 0.30 mmol) is added by syringe technique. After the reaction is complete (about 10 min) saturated aqueous sodium bicarbonate solution (15 ml) is added and the mixture is stirred for 30 min at room temperature. The reaction mixture is filtered through celite (the celite is washed with 50 ml of methylene chloride) and the organic layer of the filtrate is

dried over anhydrous Na_2SO_4. Evaporation of the solvent gives the crude product mixture which is subjected to radial chromatography.

4,6-O-Isopropylidene-3-O-benzyl-D-glucal (25.3) + 1,2,3,4-diisopropylidene-galactose: Glycosidation was carried out using reagent **22** prepared by **method A.** Radial chromatography (ethyl acetate-Hexane 1:20 to 2:1) gave 56 mg of 3-O-benzyl-1-O-6'(1'2'3'4'-diisopropylidene)-galactosyl-4,6-isopropylidene-2-deoxy-2-phenylthio-β-D-glucopyranoside (β-**36**), 9.0 mg of 3-O-benzyl-1-O-6'(1'2'3'4'-diisopropylidene)-galactosyl-4,6-isopropylidene-2-deoxy-2-phenylthio-α-D-mannopyranoside (α-**36**), 4.6 mg of 3-O-benzyl-1-O-6'(1'2'3'4'-diisopropylidene)-galactosyl-4,6-isopropylidene-2-deoxy-2-phenylthio-α-D-glucopyranoside (α'-**36**), 36 mg of 3-O-benzyl-1-O-6'(1'2'3'4'-diisopropylidene)-galactosyl-2-deoxy-2-phenylthio-β-D-glucopyranoside (β-**36, 4,6-isopropylidene hydrolyzed**), 7 mg of 3-O-benzyl-1-O-6'(1'2'3'4'-diisopropylidene)-galactosyl-2-deoxy-2-phenylthio-α-D-mannopyranoside (α-**36, 4,6-isopropylidene hydrolyzed**) and 11 mg of 3-O-benzyl-1-O-6'(1'2'3'4'-diisopropylidene)-galactosyl-2-deoxy-2-phenylthio-α-D-glucopyranoside (α'-**36, 4,6-isopropylidene hydrolyzed**); total yield (β-**36**+α-**36**) 69%; β/α 5.7/1. α'-**36** was formed in an additional 10% yield.

Physical data: Fraction 1: α'-**36:** ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.21 (s, 3H, C*H*$_3$), 1.32 (s, 6H, 2XC*H*$_3$), 1.40 (s, 3H, C*H*$_3$), 1.42 (s, 3H, C*H*$_3$), 1.47 (s, 3H, C*H*$_3$), 3.30 (dd, J = 10.7, 4.6 Hz, 1H, C_2-*H*), 3.65-3.87 (m, 7H), 4.02 (dt, J = 6.9, 2.1 Hz, 1H), 4.30 (dd, J = 6.0, 3.1 Hz, 1H), 4.43 (dd, J = 8.4, 2.1 Hz, 1H), 4.62 (dd, J = 8.4, 3.0 Hz, 1H), 4.78 (AB q, Δν = 25.6 Hz, J_{AB} = 11.6 Hz, 2H, PhC*H*$_2$), 4.58 (m, 1H), 4.97 (d, J = 4.6 Hz, 1H, C_1-*H*), 5.52 (d, J = 5.6 Hz, 1H C_1-*H*), 7.10-7.50 (m, 10H, Ar-*H*).

Fraction 2: α-**36:** Oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.28 (s, 3H, CH_3), 1.30 (s, 3H, CH_3), 1.39 (s, 3H, CH_3), 1.47 (s, 3H, CH_3), 1.57 (s, 3H, CH_3), 1.60 (s, 3H, CH_3), 3.20 (s, 3H, OCH_3), 3.60 (dd, J = 11.2, 6.5 Hz, 1H), 3.68-3.87 (m, 4H), 3.88-3.95 (m, 2H), 4.00-4.17 (m, 2H), 4.29 (dd, J = 5.6, 2.4 Hz, 1H), 4.57 (AB q, Δν = 37.4 Hz, J_{AB} = 12.2 Hz, 2H, PhCH_2), 5.01 (s, 1H, C_1-*H*), 5.50 (d, J = 5.0 Hz, 1H C_1-*H*), 7.10-7.45 (m, 10H, Ar-*H*).

Fraction 3: β-**36:** Colorless oil; $[\alpha]^{25}_D$ -56.1° (c 0.6, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.24 (s, 3H, CH_3), 1.32 (s, 3H, CH_3), 1.40 (s, 6H, 2XCH_3), 1.45 (s, 3H, CH_3), 1.53 (s, 3H, CH_3), 3.05 (dd, J = 10.5, 8.9 Hz, 1H, C_2-*H*), 3.15-3.25 (m, 1H), 3.41 (dd, J = 10.4, 8.7 Hz, 1H), 3.62-3.79 (m, 3H), 3.86-4.01 (m, 4H), 4.26 (dd, J = 5.0, 2.3 Hz, 1H), 4.46-4.50 (m, 2H), 4.81 (AB q, Δν = 21.0 Hz, J_{AB} = 11.0 Hz, 2H, PhCH_2), 5.51 (d, J = 5.0 Hz, 1H, C_1-*H*), 7.15-7.66 (m, 10H, Ar-*H*); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.16, 24.29, 25.01, 25.94, 26.21, 29.21, 56.45, 62.20, 66.57, 66.69, 68.90, 70.48, 70.55, 70.71, 75.33, 75.62, 79.74,96.30, 99.46, 104.63, 108.56, 109.10, 126.97, 127.60, 128.14, 128.20, 128.74, 132.64, 135.39, 138.60.

Fraction 4: α'-**36 (4,6-propylidene hydrolyzed):** Oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.31 (s, 6H, 2XCH_3), 1.43 (s, 3H, CH_3), 1.57 (s, 3H, CH_3), 1.95 (br s, 1H, O*H*), 2.33 (br s, 1H, O*H*), 3.26 (dd, J = 10.2, 4.0 Hz, 1H, C_2-*H*), 3.38 (s, 3H, OCH_3), 3.52-3.38 (m, 7H), 4.02 (dt, J = 6.0, 1.5 Hz, 1H), 4.29 (dd, J = 5.6, 2.5 Hz, 1H), 4.39 (dd, J = 8.0, 1.5 Hz, 1H), 4.62 (dd, J = 8.4, 2.5 Hz, 1H), 4.82 (AB q, Δν = 83.2 Hz, J_{AB} = 11.6 Hz, 2H, PhCH_2), 4.96 (d, J = 4.0 Hz, 1H, C_1-*H*), 5.51 (d, J = 4.6 Hz, 1H C_1-*H*), 7.15-7.50 (m, 10H, Ar-*H*).

Fraction 5: α-**36 (4,6-propylidene hydrolyzed):** Oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.28 (s, 3H, CH_3), 1.30 (s, 3H, CH_3), 1.38 (s, 3H, CH_3), 1.44 (s, 3H,

CH_3), 2.10 (br s, 1H, OH), 2.52 (br s, 1H, OH), 3.50-3.95 (m, 8H), 4.05 (dd, J = 9.4, 4.7 Hz, 1H), 4.16 (d, J = 9.3 Hz, 1H), 4.28 (dd, J = 5.6, 2.8 Hz, 1H), 4.45 (AB q, $\Delta\nu$ = 58.1 Hz, J_{AB} = 11.6 Hz, 2H, PhCH_2), 4.58 (m, 1H), 5.06 (s, 1H, C_1-H), 5.50 (d, J = 5.6 Hz, 1H, C_1-H), 7.15-7.45 (m, 10H, Ar-H).

Fraction 6: **β-36 (4,6-propylidene hydrolyzed):** Oil; $[\alpha]^{25}_D$ -28.4° (c 0.1, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.27 (s, 3H, CH_3), 1.32 (s, 3H, CH_3), 1.40 (s, 3H, CH_3), 1.53 (s, 3H, CH_3), 3.11 (dd, J = 10.8, 8.8 Hz, 1H, C_2-H), 3.25-3.40 (m, 2H), 3.55 (t, J = 9.1 Hz, 1H), 3.62-3.72 (m, 2H), 3.76-4.00 (m, 4H), 4.27 (dd, J = 5.0, 2.3 Hz, 1H), 4.46 (d, J = 8.9 Hz, 1H C_1-H), 4.49 (dd, J = 8.0, 2.2 Hz, 1H), 4.91 (AB q, $\Delta\nu$ = 86.9 Hz, J_{AB} = 11.2 Hz, 2H, PhCH_2), 5.49 (d, J = 5.0 Hz, 1H, C_1-H), 7.15-7.58 (m, 10H, Ar-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.24, 24.93, 25.87, 26.10, 55.76, 62.54, 66.39, 68.33, 70.45, 70.52, 71.71, 74.74, 75.60, 83.10, 96.32, 104.03, 108.57, 109.13, 126.91, 128.08, 128.65, 128.76, 132.12, 135.19, 138.22.

4,6-Di-O-benzyl-3-deoxy-D-glucal (26.3) + 1,2,3,4-diisopropylidene-galactose: Glycosidation was carried out using reagent **22** prepared by **method A**. Radial chromatography (ethyl acetate-Hexane 1:20 to 2:1) did not separate the isomeric disaccharides, 4,6-O-dibenzyl-1-O-6'(1'2'3'4'-diisopropylidene)-galactosyl-2,3-dideoxy-2-phenylthio-β-D-glucopyranoside (β-**37**) and 4,6-O-dibenzyl-1-O-6'(1'2'3'4'-diisopropylidene)-galactosyl-2,3-dideoxy-2-phenylthio-α-D-mannopyranoside (α-**37**); total yield (β-**37**+α-**37**) 125 mg (74%); β/α 3.1/1 (from ^{13}C NMR).

Physical data: β-**37**+α-**37:** ^{1}H NMR (300 MHz, $CDCl_3$), characteristic signals δ 2.24-2.31 (m, C_3-H_{eq} of α), 2.61 (dt, J = 13.0, 3.5 Hz,C_3-H_{eq} of β), 3.22 (ddd, J = 13.0, 6.5, 4.1 Hz, C_2-H of β), 5.02 (d, J = 1.0 Hz,C_1-H of α); ^{13}C NMR (75 MHz,

$CDCl_3$) characteristic signals of **β-37** δ 24.36, 25.07, 26.03, 26.27, 35.34, 46.82, 66.72, 68.09, 69.00, 70.50, 70.67, 71.45, 72.63, 73.49, 78.41, 96.32, 105.85, 108.50, 108.97, 134.65, 137.97, 138.40; characteristic signals of **α-37** δ 24.57, 24.66, 26.17, 29.82, 47.39, 65.56, 69.31, 70.04, 70.88, 71.00, 71.11, 71.16, 72.21, 73.41, 98.33, 108.58, 109.32, 135.07, 138.24, 138.57.

3,4-Di-O-benzyl-D-fucal (37.5): NaH (45 mg, 80% suspension, 1.5 mmol) was washed with dry hexane and suspended in 1 ml of dry DMF. To this suspension a solution of D-fucal (**36.3**, 130 mg, 1 mmol) in 2 ml of DMF/THF (1:1 mixture) was added dropwise with stirring at room temperature. After the addition was complete the reaction mixture was stirred for 30 min and then tetra-n-butylammonium iodide (15 mg) and 145 μL of benzyl bromide (1.2 mmol) were added to it. After stirring for 6 h the reaction mixture was poured into 50 ml of water and was extracted with ethyl acetate (3X25 ml). Combined organic extracts were dried over anhydrous sodium sulfate. Evaporation of the solvent gave the crude product which was subjected to radial chromatography (ethyl acetate-Hexane 1:9) to give 248 mg of **37.5**; yield 80%.

Physical data: Colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.37 (d, J = 6.6 Hz, 3H, CH_3), 3.76-3.80 (m, 1H), 4.13 (q, J = 6.6 Hz, 1H, C_5-H), 4.74 (AB q, Δν = 22.4 Hz, J_{AB} = 12.2 Hz, 2H, PhCH_2), 4.92 (dt, J = 6.3, 1.7 Hz, 1H, C_2-H), 4.93 (AB q, Δν = 73.3 Hz, J_{AB} = 12.0 Hz, 2H, PhCH_2), 6.45 (dd, J = 6.3, 1.6 Hz, 1H, C_1-H), 7.30-7.50 (m, 10H, Ar-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.58, 70.78, 72.17, 72.87, 73.10, 73.74, 99.49, 127.45, 127.58, 127.65, 128.28, 128.36, 128.41, 138.54, 138.59, 144.60.

3,4-Di-O-benzyl-D-fucal (37.5) + phenyl tri-n-butyltin ether (38.1): To a solution of **37.5** (78 mg, 0.25 mmol) and 200 μL of **38.1** (0.50 mmol) in dry

methylene chloride at -60 °C (under argon), 1.2 ml of the reagent solution (**22**, prepared using **method B**, 0.30 mmol) was added by syringe technique. After the reaction was complete (about 10 min) saturated aqueous sodium bicarbonate solution (15 ml) was added and the mixture was stirred for 30 min at room temperature. The reaction mixture was filtered through celite (and the celite was washed with 50 ml of methylene chloride) and the organic layer of the filtrate was dried over anhydrous Na_2SO_4. Evaporation of the solvent gave the crude product mixture which was subjected to radial chromatography (ethyl acetate-Hexane 1:20 to 1:2) to give 51.2 mg of 3,4-O-dibenzyl-2-deoxy-1-O-phenyl-2-phenylthio-β-D-fucopyranoside (**39.1**, β-glycoside), 25.6 mg of 3,4-O-dibenzyl-2-deoxy-1-O-phenyl-2-phenylthio-α-D-fucopyranoside (**39.2**, α'-glycoside) and 6.1 mg of 3,4-O-dibenzyl-2-deoxy-2-phenylthio-α-D-fucopyranoside (**39.3**); total yield (**39.1+39.2**) 60%; β/α' 2/1.

Physical data: Fraction 1: **39.2:** Colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.23 (d, J = 6.5 Hz, 3H, CH_3), 3.81 (s, 1H), 4.08-4.24 (m, 3H), 4.89 (AB q, Δν = 90.6 Hz, J_{AB} = 11.4 Hz, 2H, PhCH_2), 4.92 (AB q, Δν = 21.4 Hz, J_{AB} = 11.5 Hz, 2H, PhCH_2), 5.69 (d, J = 3.1 Hz, 1H, C_1-H), 7.06-7.62 (m, 20H, Ar-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.92, 50.52, 67.88, 73.25, 75.02, 76.68,79.85, 99.13, 116.95, 122.38, 125.35, 127.64, 127.74, 128.28, 128.36, 128.47, 128.72, 129.52, 130.77, 136.45, 138.23, 138.52, 157.30.

Fraction 2: **β-39.1:** Colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.30 (d, J = 6.4 Hz, 3H, CH_3), 3.52 (dd, J = 11.4, 2.7 Hz, 1H, C_3-H), 3.63 (q, J = 6.4 Hz, 1H, C_5-H),3.71 (d, J = 2.7 Hz, 1H, C_4-H), 3.95 (dd, J = 11.4, 8.8 Hz, 1H, C_2-H), 4.85 (AB q, Δν = 14.7 Hz, J_{AB} = 11.5 Hz, 2H, PhCH_2), 4.91 (AB q, Δν = 84.5 Hz, J_{AB} = 11.8 Hz, 2H, PhCH_2), 4.98 (d, J = 8.8 Hz, 1H, C_1-H), 6.89-7.65 (m, 20H, Ar-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.26, 52.30, 70.54, 73.17, 74.64, 74.73, 80.73,

101.99, 116.73, 122.24, 126.88, 127.69, 127.93, 128.03, 128.25, 128.50, 128.64, 129.24, 132.38, 135.16, 137.89, 138.44, 157.49.

Fraction 3: **39.3:** Colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.20 (d, J = 6.4 Hz, 3H, C*H*$_3$), 2.88 (d, J = 3.0 Hz, 1H, O*H*), 3.72 (s, 1H), 3.97 (s, 2H), 4.19 (q, J = 6.4 Hz, 1H, C_5-*H*), 4.82 (AB q, Δν = 14.0 Hz, J_{AB} = 11.2 Hz, 2H, PhC*H*$_2$), 4.86 (AB q, Δν = 87.4 Hz, J_{AB} = 12.1 Hz, 2H, PhC*H*$_2$), 5.38 (br s, 1H, C_1-*H*), 7.20-7.60 (m, 15H, Ar-*H*).

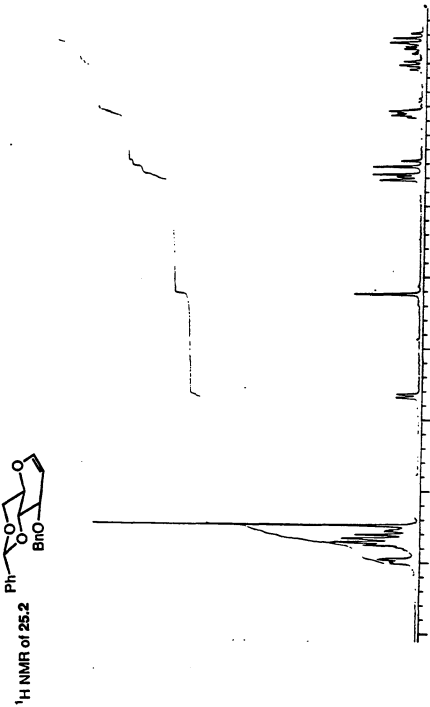
Preparation of the Sulfone of 39.2 (for confirmation of structure of **39.2**)**:** To a solution of of **39.2** (20 mg, 0.04 mmol) in 5 ml of dry methylene chloride was added m-CPBA (9.7 mg, 1.1 equiv.). The reaction mixture was stirred at room temperature for 30 min (tlc showed completion of the reaction), diluted with 10 ml of methylene chloride and was washed with water (20 ml), saturated sodium bicarbonate (2X20 ml) and finally with water (20 ml) again. The organic layer was dried over anhydrous sodium sulfate. Evaporation of the solvent gave 19.5 mg (92 %) of the sulfone. Thick oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.19 (d, J = 6.4 Hz, 3H, C*H*$_3$), 3.78 (s, 1H, C_4-*H*), 4.16 (q, J = 6.4 Hz, 1H, C_5-*H*), 4.23 (dd, J = 11.2, 3.2 Hz, 1H, C_2-*H*), 4.67 (dd, J = 11.2, 2.4 Hz, 1H, C_3-*H*), 4.69 (AB q, Δν = 90.7 Hz, J_{AB} = 11.3 Hz, 2H, PhC*H*$_2$), 4.84 (AB q, Δν = 24.4 Hz, J_{AB} = 11.2 Hz, 2H, PhC*H*$_2$), 5.94 (d, J = 3.1 Hz, 1H, C_1-*H*), 7.05-7.88 (m, 20H, Ar-*H*).

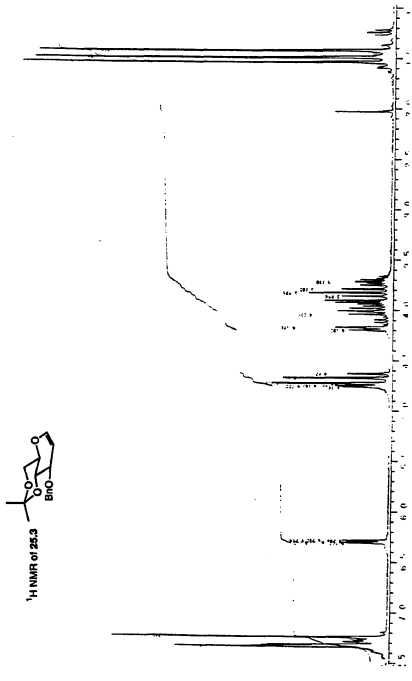
Desulfurization of 39.1: A solution of **39.1** (20 mg, 0.04 mmol) in dry THF (2 ml) was added to a stirred suspension of Raney-Nickle (approx. 60 mg) in 2 ml of THF at room temperature. The reaction was complete (monitored by tlc) in 30 min. The reaction mixture was filtered through celite. Evaporation of the solvent gave 3,4-O-dibenzyl-2-deoxy-1-O-phenyl-β-D-fucopyranoside (**39.1a**), which was used for further reaction with out any purification. ^{1}H NMR (300 MHz,

$CDCl_3$) δ 1.20 (d, J = 6.8 Hz, 3H, CH_3), 2.10-2.28 (m, 1H, C_2-H_{eq}), 2.30-2.43 (m, 1H, C_2-H_{ax}), 3.32-3.47 (m, 1H), 3.50-3.62 (m, 1H), 4.57-4.78 (m, 3H), 4.95-5.08 (m, 2H), 6.80-7.50 (m, 15H, Ar-*H*).

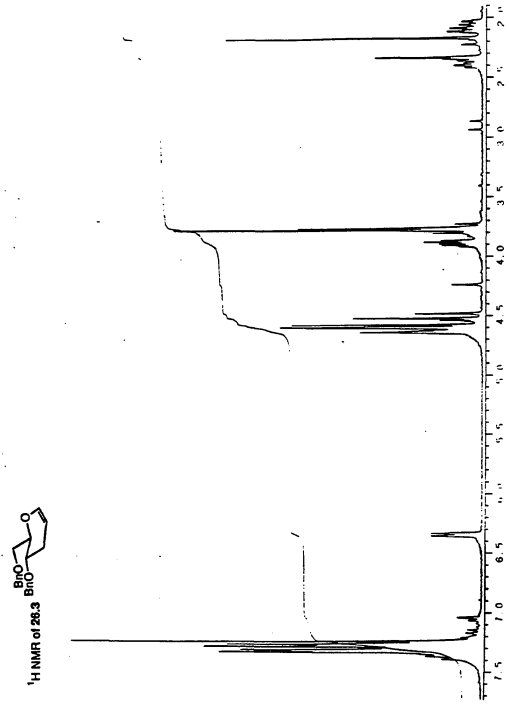
Debenzylation of 39.1a: A solution of **39.1a** (obtained from desulfurization of **39.1**) in absolute ethanol (3 ml) was added to a stirred suspension of 10% palladium on charcoal (50 mg) in 1 ml of ethanol at room temperature under a hydrogen atmosphere. The reaction completed (monitored by tlc) in 12 h. The reaction mixture was filtered through celite. Evaporation of the solvent gave crude 2-deoxy-1-O-phenyl-β-D-fucopyranoside (**41.1**) which was purified by flash column chromatography (methanol-ethyl acetate 1:9); yield 6 mg (70% in two steps); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.40 (d, J = 6.5 Hz, 3H, CH_3), 1.97 (dt, J = 12.3, 10.0 Hz, 1H, C_2-H_{ax}), 2.26 (ddd, J = 12.3, 5.0, 2.3 Hz, 1H, C_2-H_{eq}), 2.78 (br s, 1H, O*H*), 3.06 (br s, 1H, O*H*), 3.35-3.52 (m, 1H), 3.60-3.75 (m, 2H), 5.08 (dd, J = 10.0, 2.3 Hz, 1H, C_1-*H*), 6.98-7.10 (m, 3H, Ar-*H*), 7.25-7.35 (m, 2H, Ar-*H*); ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.72, 34.69, 68.80, 70.33, 70.83, 97.78, 116.50, 122.45, 129.45, 156.99.

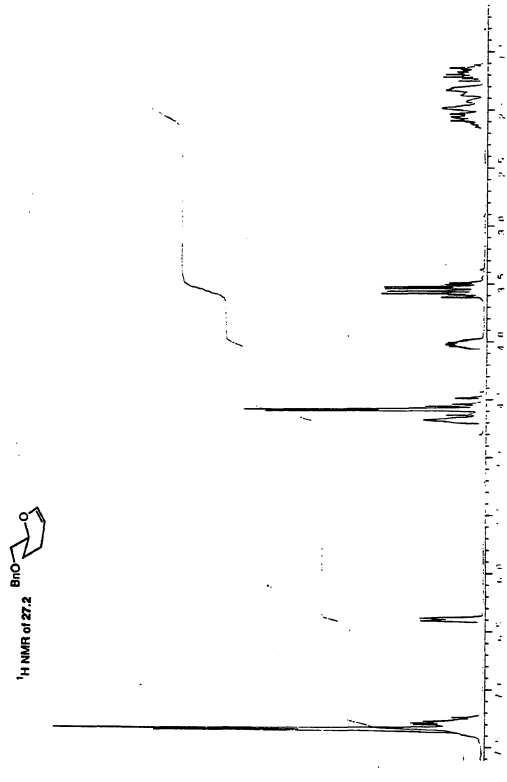
APPENDIX

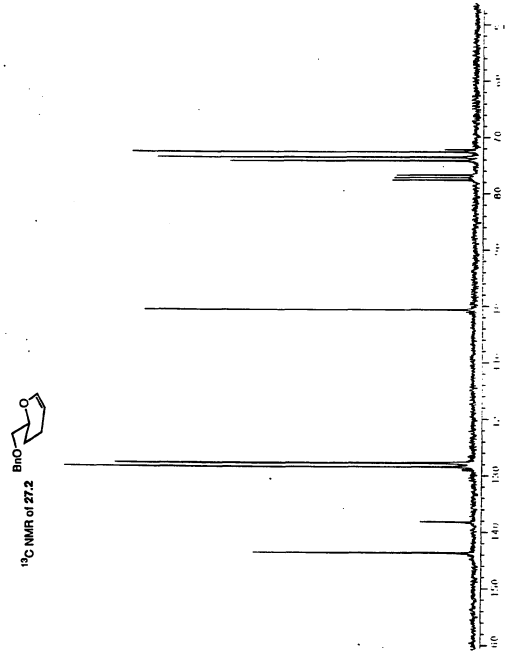


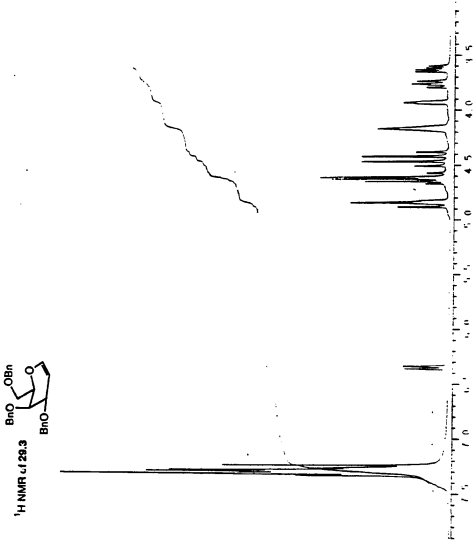


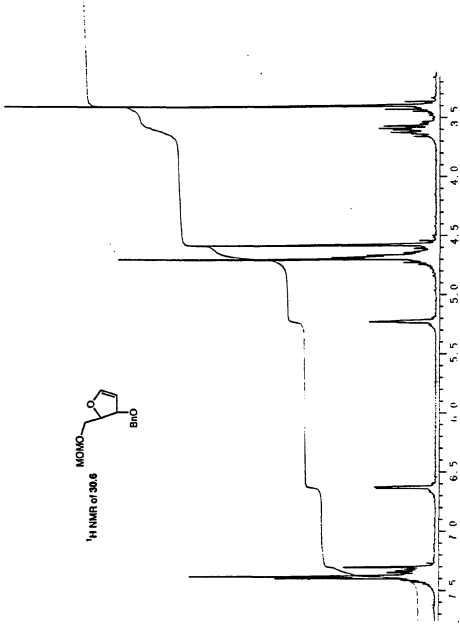
^{1}H NMR of 25.3

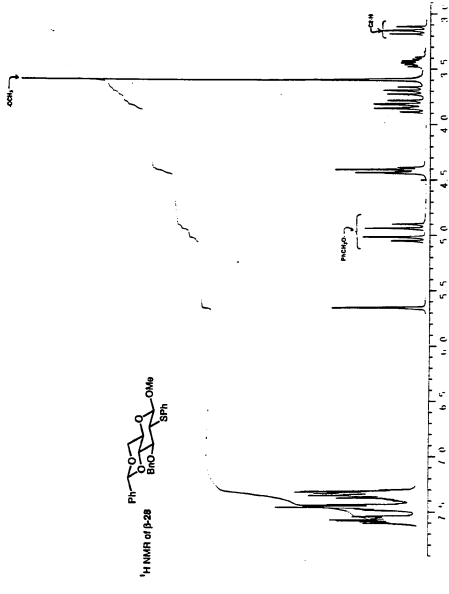


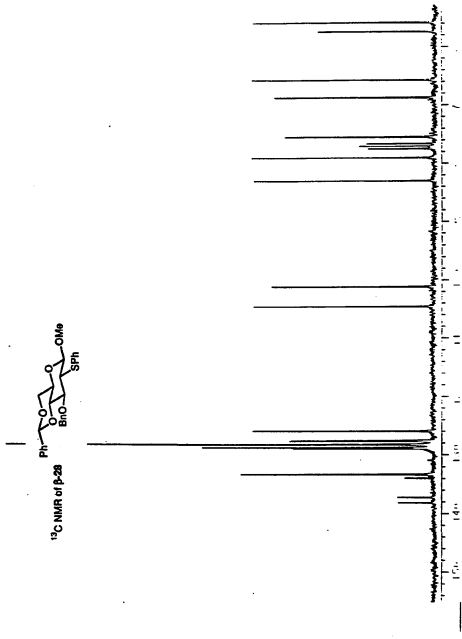


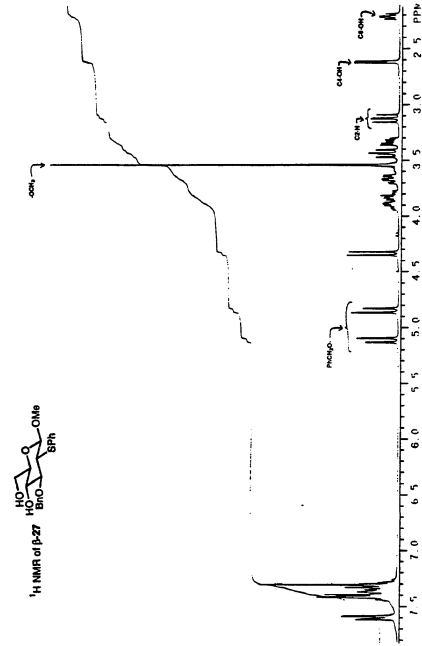


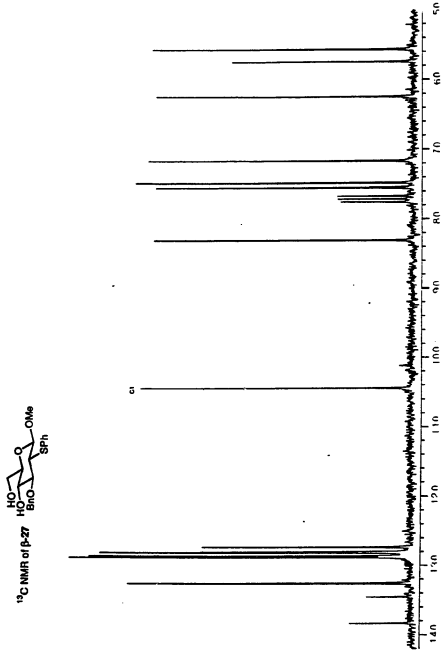


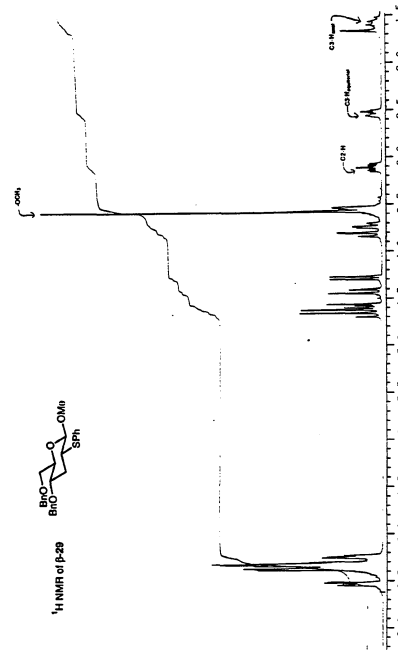


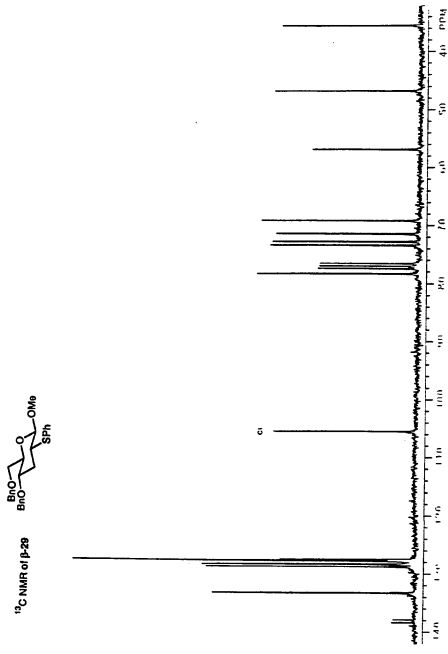


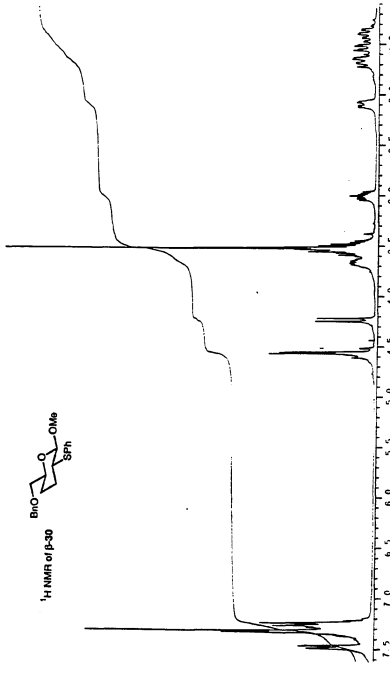


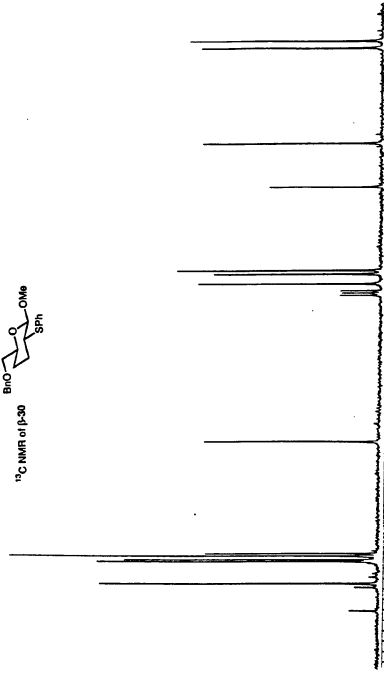


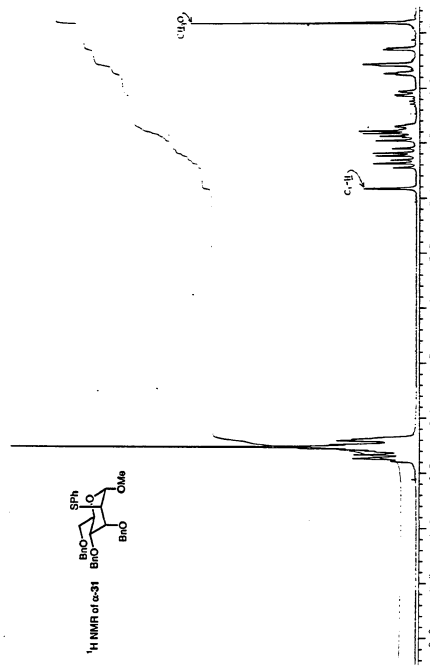


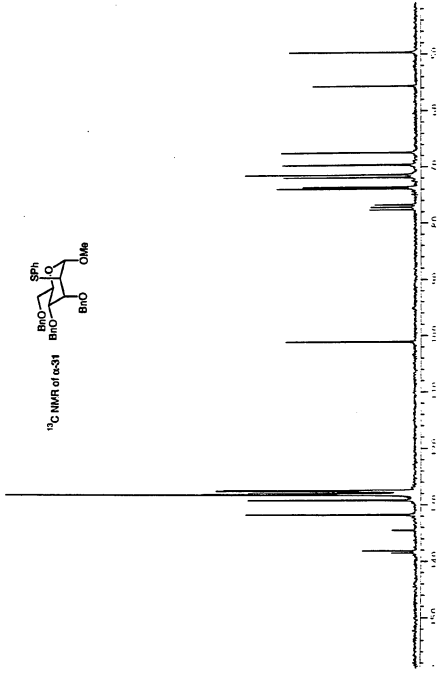


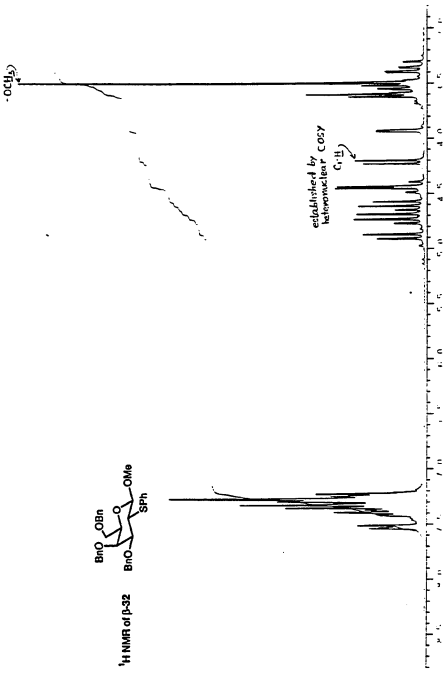


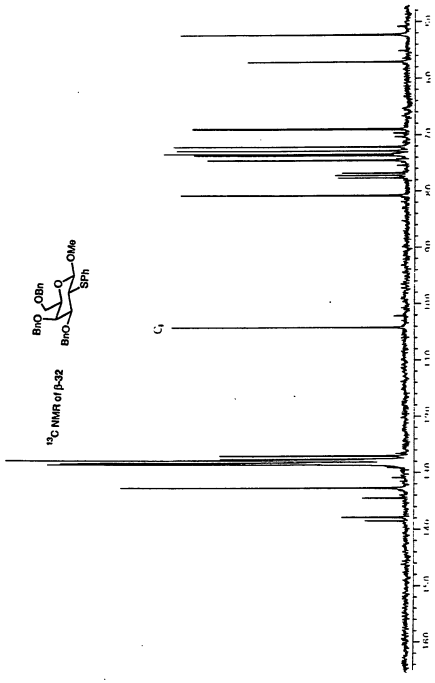


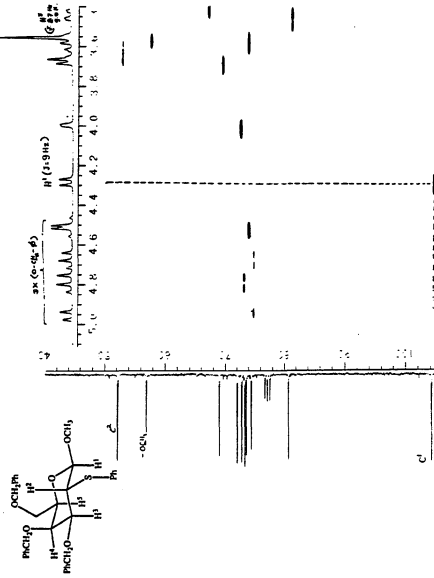


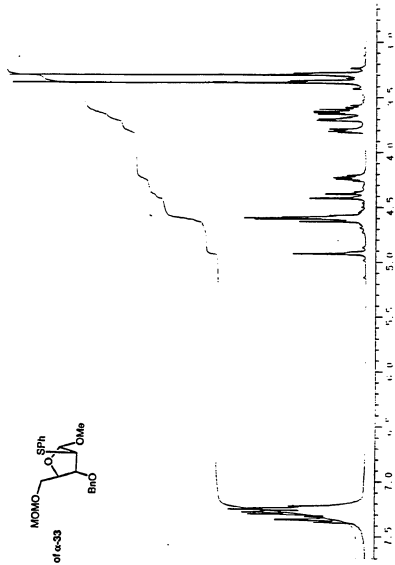


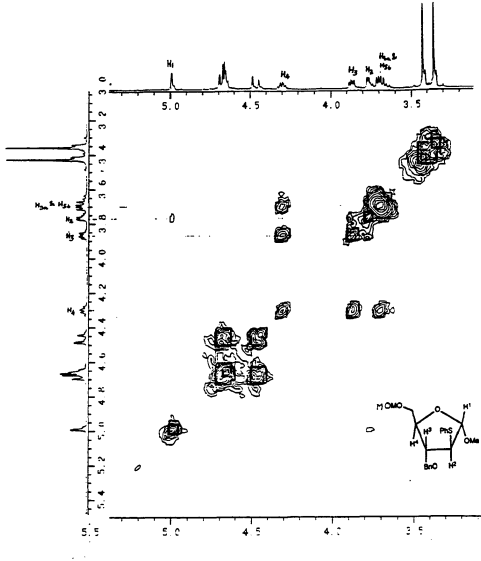


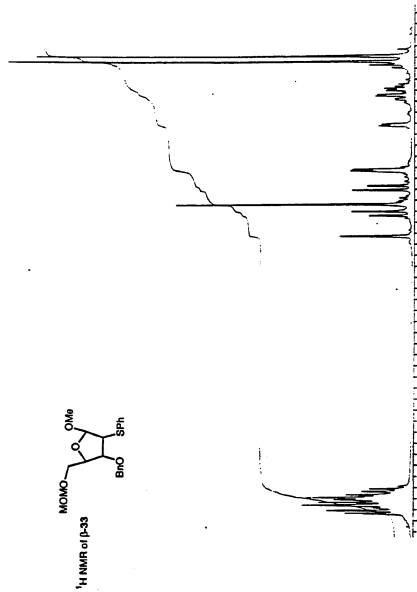




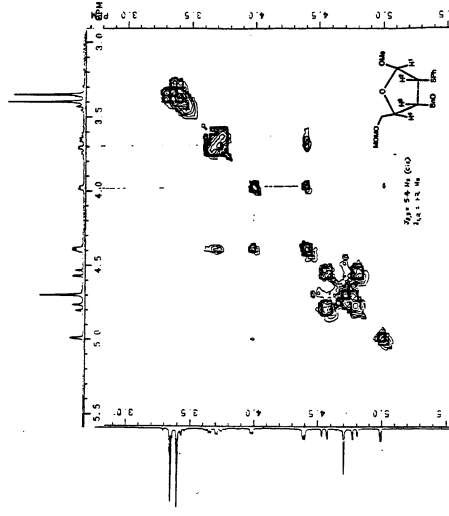


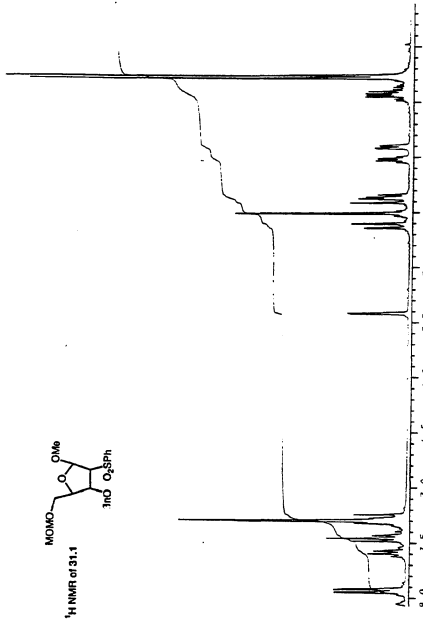


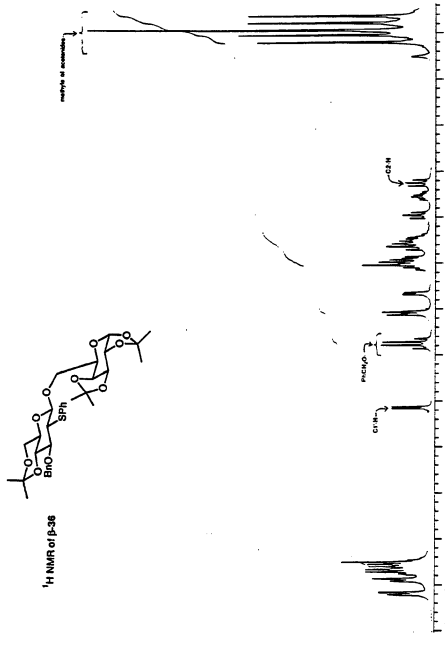


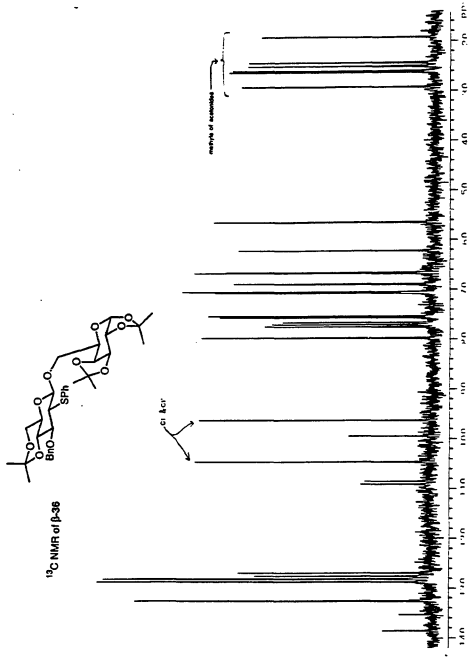


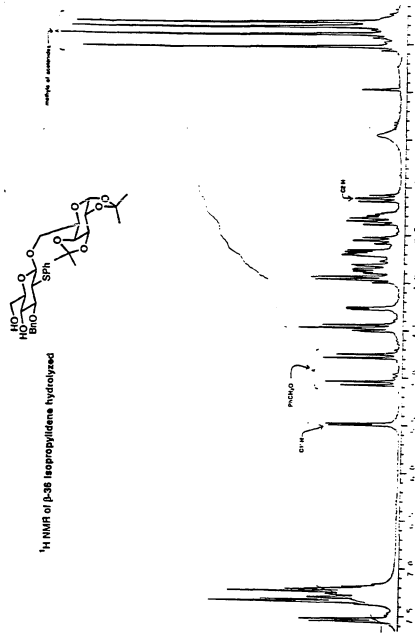
^{1}H NMR of β-33

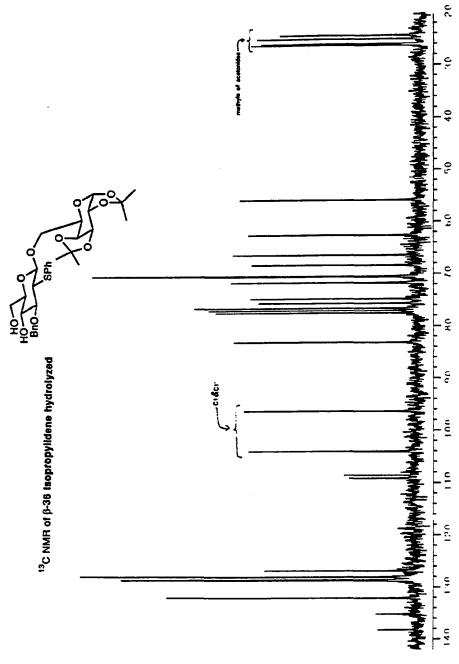


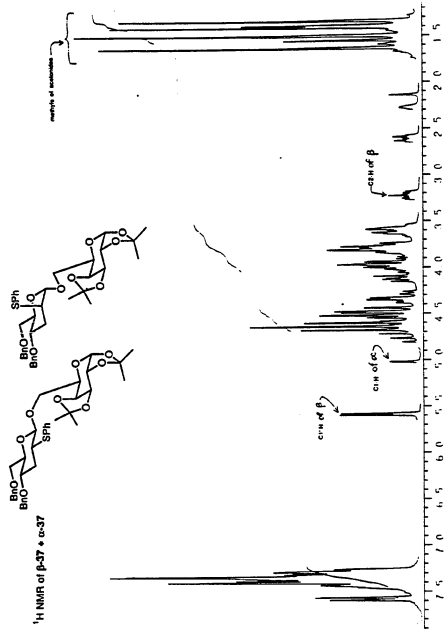


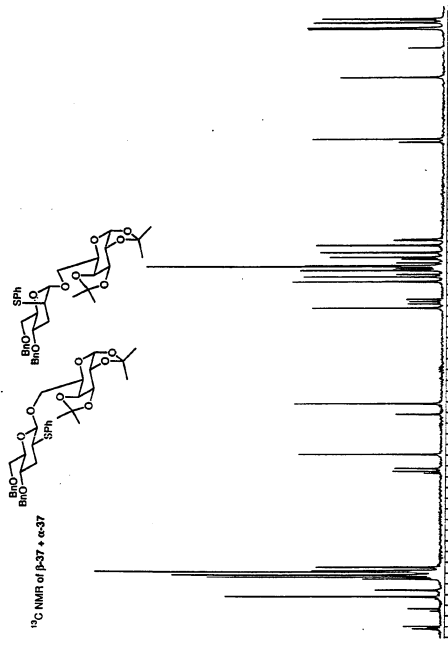


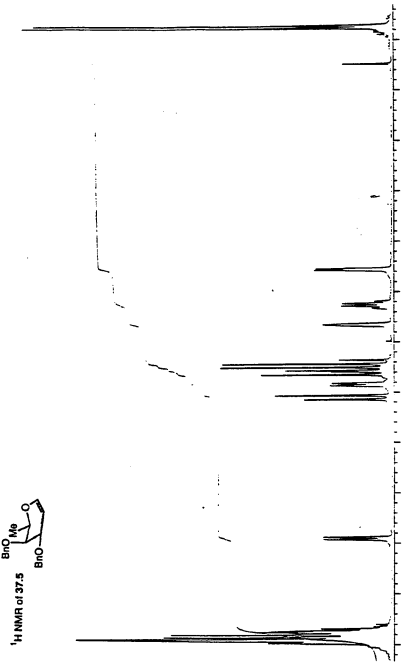




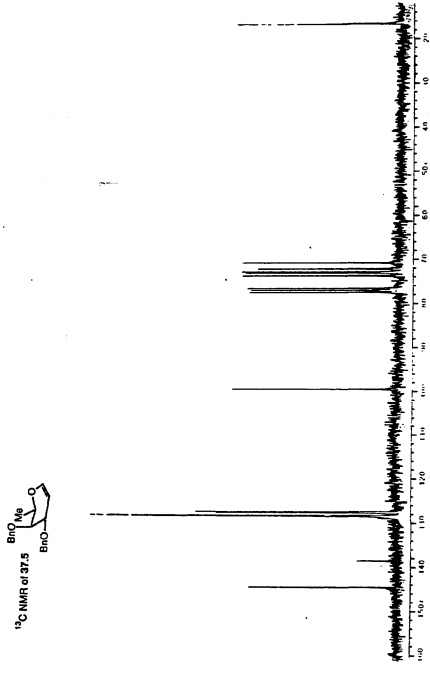


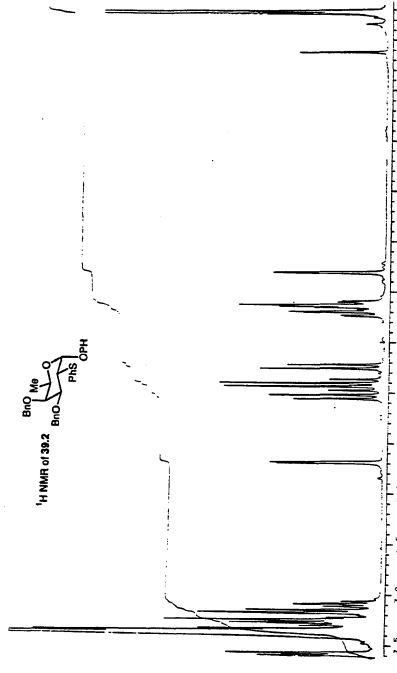


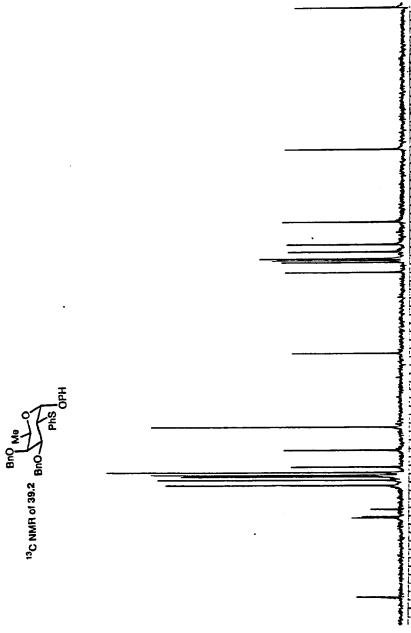




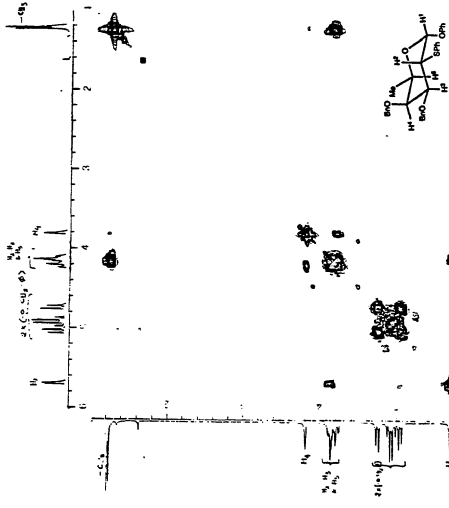
^{1}H NMR of 37.5

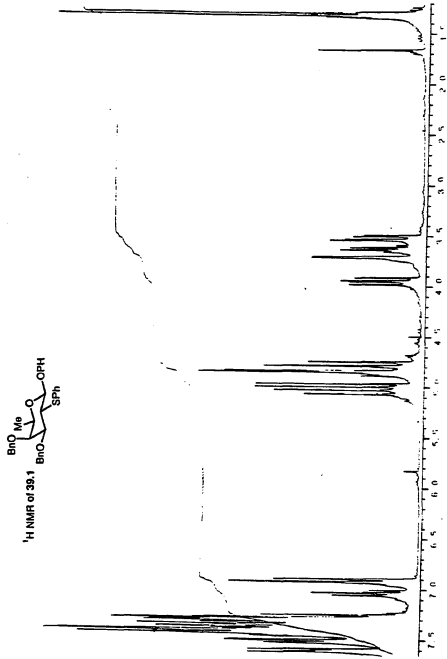




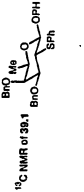


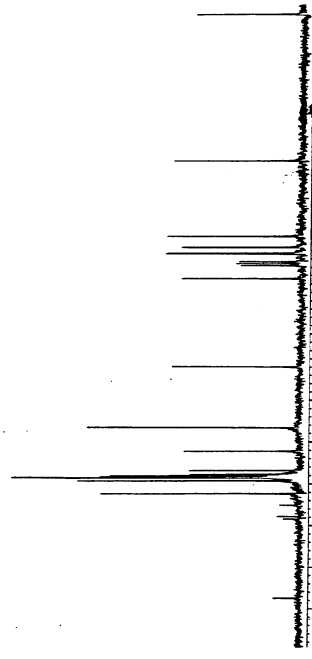
^{13}C NMR of 39.2

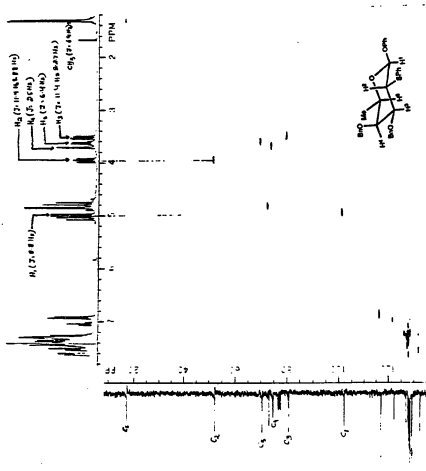


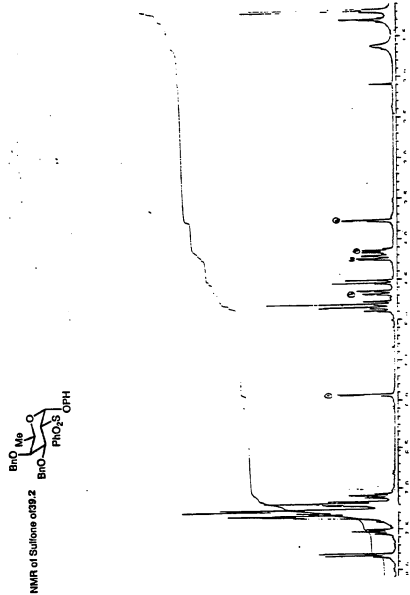


^{13}C NMR of 3b.1

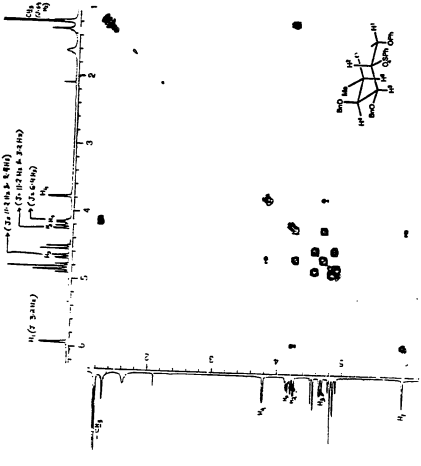


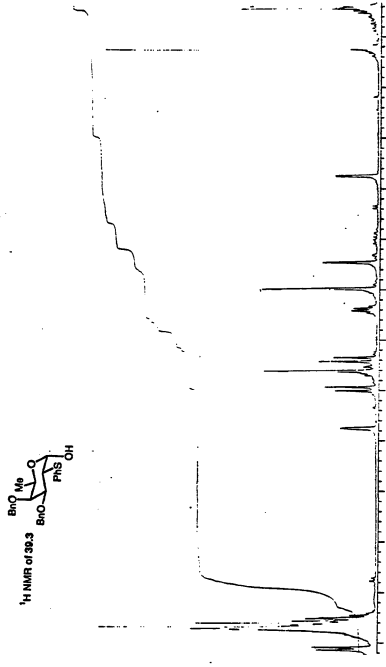


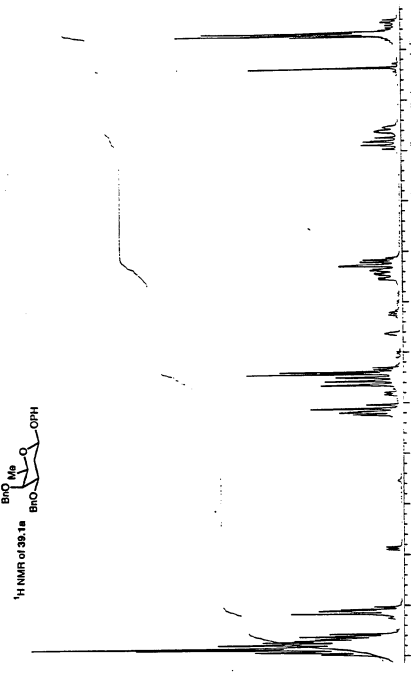


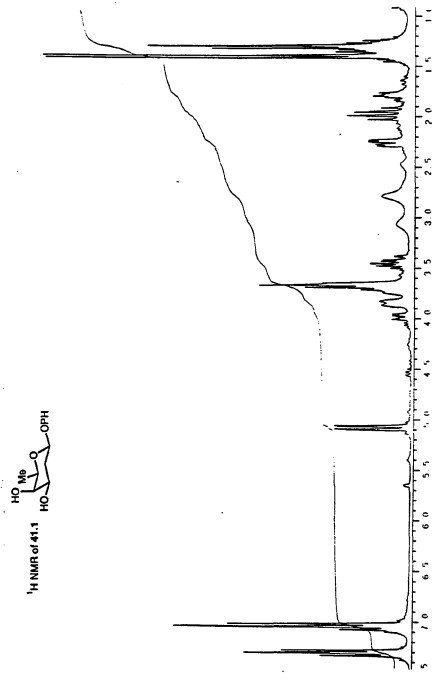


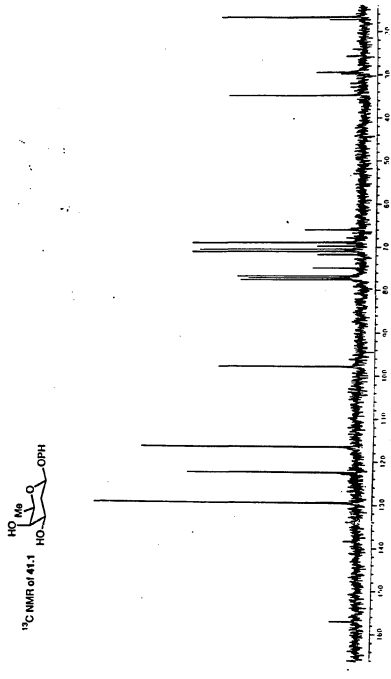
^{1}H NMR of Sulfone of 39.2











REFERENCES

1. Remers, W. *The Chemistry of Antitumor Antibiotics*, Wiley, New York **1979**, *1*, Ch. 3.
2. (a) Grundy, W. E.; Goldstein, A. W.; Riekher, C. J.; Hanes, M. E.; Warren, H. B. Jr.; Sylvester, J. E. *Antibiot. Chemother.* **1953**, *3*, 1215. (b) Philips, J. E.; Schenck, J. R. *Antibiot. Chemother.* **1953**, *3*, 1218.
3. Sensi, P.; Greco, A. M. Pagani, H. *Antibiot. Chemother.* **1958**, *8*, 241.
4. Rao, K. V.; Cullen, W. P.; Sobin, B. A. *Antibiot. Chemother.* **1962**, *12*, 182.
5. Berlin, Yu. A.; Kiseleva, O. A.; Kolosov, M. N.; Shemyakin, M. M.; Soifer, V. S.; Vasina, I. V.; Yartseva, I. V.; Kuznetsov, V. D. *Nature* **1968**, *218*, 193.
6. Nishimura, H.; Kimura, T.; Tawara, K.; Sasahi, K.; Nakajima, K.; Shimaoka, N,; Shimohira, N.; isono, J. *J. Antibiot. (Tokyo), Ser. A* **1957**, *10*, 205.
7. (a) Gause, G. G.; Ukholina, R. S.; Sveshnikova, M. A. *Antibitiki (Moscow)* **1962**, *1*, 34. (b) Brazhnikova, M. G.; Kruglyak, E. B.; Kovsharova, I. N.; Konstantinova, N. V.; Proshylakova, V. V. *Antibiotiki (Moscow)* **1962**, *1*, 34.
8. Gauze, G. F. *Progr. Antimicrob. Anticancer Chemother. Proc. 6th Int. Congr. Chemother.* **1969**, *2*, 428.
9. Kerstin, W. *Abh. Deut. Akad, Wiss, Berlin Kl. Med.* **1968**, 593.
10. Gao, X.; Patel, D. J. *Biochemistry* **1989**, *28*, 751.
11. Koshel, K.; Hartmann, G.; Kersten, W.; Kersten, H. *Biochem. Z.* **1966**, *344*, 76.
12. Behr, W.; Honikel, K.; Hartmann, G. Eur, *J. Biochem.* **1969**, *9*, 82.
13. (a) Franck, R. W. and Weinreb, S. M. *Studies in Natural Product Chem.*, ed. A. Rahman, Elsvier, Amsterdam. **1989**, 173. (b) Dodd, J. H.; Starrett, J. E., Jr.; Weinreb, S. M. *J. Am. Chem. Soc.* **1984**, *106*, 1811. (c) Franck, R. W. ; Bhat, V.; Subramaniam, C. S. *J. Am. Chem. Soc.* **1986**, *108*, 2455. (d)

Roush, W. R.; Michaelides, M. R.; Tai, D. F.; Chong, W. K. M. *J. Am. Chem. Soc.* **1987**, *109*, 7575. (e) Thiem, J.; Schottmer, B. *Angew Chem. Int. Ed.* **1987**, *26*, 555. (f) Theim, J. *Topics in Current Chemistry,* Carbohydrate Chemistry, Springer Verlag. **1988**.

14. (a) Igarishi, K. *Adv. Carbohydr. Chem. Biochem.* **1977**, *34*, 243. (b) Bochkov, A. E.; Zaekov, Z. E. *Chemistry of O-glycosidic bond: Formation and cleavage*, Pergamon Press, Oxford, **1979**. (c) Paulsen, H. *Angew Chem. Int. Ed. Engl.* **1982**, *21*, 155.
15. A detailed discussion is given in: Kaila, N.; Ph.D. Thesis, CUNY, **1991**.
16. Fischer; Bergmann; Schotte; *Ber.* **1920**, *53*, 517.
17. Davoll; Lythgoe; *J.* **1949**, 2526.
18. Hughes, I. W.; Overend, W. G.; Stacey, M. *J. Chem. Soc.* **1949**, 2846.
19. Shafizadeh, F.; Stacey, M. *J. Chem. Soc.* **1952**, 3608.
20. Staneck, J.; Cerny, M.; Kocourek, J.; Pacak, J. *The Monosaccharides, Academic Press, New York*, **1963**.
21. See ref. 19.
22. Wallenfels, K.; Lehmann, J. *Ann.* **1960**, *635*, 166.
23. Ciment, D. M.; Ferrier, R. J. *J. Chem. Soc. (C)* **1966**, 441.
24. (a) Michalska, M.; Borowiecka, J. *J. Carbohydr. Chem.*, **1983**, *2*, 99. (b) Bielawska, H.; Michalaska,M. *J. Carbohydr. Chem.*, **1986**, *5*, 445.
25. (a) Crich, D.; Ritchie, T. J. *Chem. Commun.* **1988**, 985. (b) Crich, D.; Ritchie, T. J. *Carbohydr. Res.* **1989**, *190*, C3.
26. (a) Ferrier, R. J. *J. Chem. Soc.* **1964**, 5443. (b) Lohaus, H.; Widmaier, O. *Ann.* **1935**, *520*, 301. (c) See ref. 23.
27. (a) Czernecki, S.; Deccavanne, V. *Can. J. Chem.* **1983**, *61*, 533. (b) Hacksell, U.; Daves, G. D. *J. Org. Chem.* **1983**, *48*, 166.
28. Jarglis, P.; Lichtenthaler, F. W. *Tet. Lett.* **1982**, *23*, 3781.

29. Paulsen, H.; Patt, H. *Justus Liebigs Ann.Chem.* **1981**, 1633.

30. (a) Chatt, J. *Chem. Rev.* **1951**, *48*, 7. (b) Henbest, H. B.; Nicholls, B. *J.* **1959**, 227. (c) Henbest, H. B.; McElhinney, R. S. *J.* **1959**, 1834. (d) Henbest, H. B.; Nicholls, B.; Jackson, W. R.; Wilson, R. A. L; Crossley, N. S.; Meyers, M. B.; McElhinney, R. S. *Bull. Soc. Chim. France* **1960**, 1365.

31. Kreevoy, M. M.; Kowitt, F. R. *J. Amer. Chem. Soc.* **1960**, *82*, 739.

32. Inglis, G. R.; Schwarz, J. C. P.; McLaren, L. *J. Chem. Soc.* **1962**, 1014.

33. Manolopoulos, P. T.; Mednick, M.; Lichtin, N. N. *J. Am. Chem. Soc.* **1962**, *84*, 2203.

34. Takiura, K.; Honda, S. *Carbohydr. Res.* **1972**, *21*, 379.

35. Honda, S.; Kaheki, K.; Takai, H.; Takiura, K. *Carbohydr. Res.* **1973**, *29*, 477.

36. Takiura, K.; Honda, S. *Carbohydr. Res.* **1972**, *23*, 369.

37. Horton, D.; Tarelli, J. M.; Wander, J. D. *Carbohydr. Res.* **1972**, *23*, 440.

38. Marsh, J. P.Jr.; Mocher, C. W.; Acton, E. M.; Goodman, L. *Chem. Commun.* **1967**, 973.

39. Corey, E. J.; Weigel, L.; Chamberlin, D.; Lipshutz, B. *J. Am. Chem. Soc.* **1980**, *102*, 1439.

40. Keck, G. E.; Kachensky, D. F. *J. Org. Chem.* **1986**, *51*, 2487.

41. (a) Honda, S.; Izumi, K.; Takiura, K. *Carbohydr. Res.* **1972**, *23*, 427. (b) Goodman, L.; Acton, E. M.; Moshier, C. W.; Marsh, J. P. jr. *Methods in Carbohydr. Chem. Vol. 8*, 207. (c) Korytnyk, J. R.; Sufrin, J. R.; Bernacki, R. J. *Carbohydr. Res.* **1982**, *103*, 176. (d) Gakhokidze R. A.; Chan, V. T. Soobshch. *Akad. Nauk. Gruz. SSR.* **1986**, *124*, 529.

42. Fischer, E.; Bergmann, M.; Schotte, H. *Ber.* **1920**, *53*, 509.

43. (a) Lemieux, R. U.; Fraser-Reid, B. *Can. J. Chem.* **1964**, *42*, 532. (b) Lemieux, R. U.; Fraser-Reid, B. *Can. J. Chem.* **1965**, *43*, 1460. (c) Ferrier,

R. J. 1965, *Advan. Carbohydr. Chem.* **1965**, *20*, 67. (d) Ferrier, R. J. 1965, *Advan. Carbohydr. Chem.* **1969**, *24*, 199.

44. Horton, D.; Priebe, W.; Varela, O. *J. Org. Chem.* **1986**, *51*, 3479.
45. (a) Anderson, C. B.; Geis, M. P. *Tetrahedron.* **1975**, *31*, 1149. (b) Gutsche, C. D.; Tao, I. Y. C.; Kozma, J. A. *J. Org. Chem.* **1967**, *32*, 1782. (c) Carlson, R. G.; Blecke, R. G. *J. Org. Chem.* **1967**, *32*, 3538.
46. Sakakibara, T.; Nomura, Y.; Yoshino, K.; Sudoh, R. *J. Chem. Soc. Chem. Commun.* **1983**, 449.
47. (a) Vargha, L.; Kuszmann, J. *Ber.* **1963**, *96*, 411. (b) Davoll, J.; Lythgoe, B. *J. Chem. Soc.* **1949**, 2526. (c) Hurd, C. D.; Jenkins, H. *Carbohydr. Res.* **1966**, *2*, 240. (d) Bradley, P. R.; Buncel, E. *Can. J. Chem.* **1968**, *46*, 3001. (e) Gakhokidze, A. M. *J. Gen. Chem. USSR (Eng. Transl.) 1946*, *16*, 1914. (e) Igarashi, K.; Honma, T.; Imagawa, T. *J. Org. Chem.* **1970**, *35*, 610. (f) Es Van, T. *J. S. Afr. Chem. Inst.* **1973**, *26*, 152.
48. (a) Lemieux, R. U.; Morgan, A. R. *Can. J. Chem.* **1965**, *43*, 2190. (b) Lemieux, R. U.; Fraser-Reid, B. *Can. J. Chem.* **1964**, *42*, 539. Also see references 43(a) and 43(b).
49. Mootoo, D. R.; Konradsson, P.; Udodong, U.; Fraser-Reid, B. *J. Am. Chem. Soc.* **1988**, *110*, 5583.
50 Iley, D. E.; Fraser-Reid, B. *J. Am. Chem. Soc.* **1975**, *97*, 2563.
51. (a) Campbell, J. C.; Dwek, R. A.; Kent, P. W.; Prout, C. K. *Carbohydr. Res.* **1969**, *10*, 71. (b) Hall, L. D.; Manville, J. F. *Can. J. Chem.* **1969**, *47*, 361.
52. Hall, L. D.; Manville, J. F. *Chem. Commun.* **1968**, *35*, 37.
53. Thiem, J.; Karl, H.; Schwentner, J. *Synthesis.* **1978**, 696.
54. (a) Thiem, J.; Gerken, M. *J. Org. Chem.* **1985**, *50*, 954. (b) Thiem, J.; Karl, H. *Tetrahedron Lett.* **1978**, *19*, 4999. (c) Thiem, J.; Elvers, J. *Chem. Ber.* **1979**, *112*, 818.

55. Lafont, D.; Guillouse, P.; Descotes, G. *Carbohydr. Res.* **1989**, *193*, 61.

56. (a) Foster, A. B.; Westwood, J. H. *Pure Appl. Chem.* **1973**, *35*, 147. (b) Kent, P. W. *'Ciba Foundation Symposium on Carbon-Fluorine Compounds' Elsevier, New York* **1972**, 169. (c) Penglis, A. A. E. *Adv. Carbohydr. Chem. Biochem.* **1981**, *38*, 195.

57. (a) Adam, M. J. *J. Chem. Soc. Chem. Commun.* **1982**, 730. (b) Tada, M.; Matsuzawa, T.; Yamaguchi, K.; Abe, Y.; Fukuda, H.; Itoh, M.; Sugiyama, H.; Ido, T.; Takahashi, T. *Carbohydr. Res.* **1987**, *161*, 314. (c) Dax, K.; Glanezer, B. I.; Schulz, G.; Vyplel, H. *Carbohydr. Res.* **1987**, *162*, 13.

58. Adamson, J.; Foster, A. B.; Hall, L. D. Johnson, R. N.; Hesse, R. H. *Carbohydr. Res.* **1970**, *15*, 351.

59. Ido, T.; Wan, C. N.; Fowler, J. S.; Wolf, A. P. *J. Org. Chem.* **1977**, *42*, 2341.

60. Korytnyk, W.; Valentekovic-Horvat, S.; *Tetrahedron Lett.* **1980**, *21*, 1493.

61. Serfontein, W. J.; Jordaan, J. H.; White, J. *Tetrahedron Lett.* **1964**, 1069.

62. Bovin, N. V.; Zurabyan, S. E.; Khorlin, A. Y. *J. Carbohydr. Res.* **1983**, *2*, 249.

63. Kozlowska-Gramsz, E. *Can. J. Chem.* **1982**, *60*, 558.

64. Lessard, J.; Mondon, M.; Touchard, D. *Can. J. Chem.* **1981**, *59*, 431.

65. Fitzsimmons, B. J.; Leblanc, Y.; Rokach, J. *J. Am. Chem. Soc.* **1987**, *109*, 285.

66. Kuhm, R.; Low, I.; Trischmann, H. *Ber.* **1957**, *90*, 203.

67. (a) Bilik, V.; Kucar, S. *Carbohydr. Res.* **1970**, *13*, 311. (b) Bock, K.; Pederson, C. *Acta. Chem. Scand.* **1971**, *25*, 1021.

68. Helferich, E. N.; Mulcahy, E. N.; Ziegler, H. *Ber.* **1954**, *87*, 233.

69. (a) Bergmann, M.; Schotte, H. *Ber. Dtsch. Chem. Ges.* **1921**, *54*, 440. (b) Levene, P. A.; Raymond, A. L. *J. Biol. Chem.* **1930**, *88*, 513. (c) Haworth, W. N.; Hirst, E. L. *J. Chem. Soc.* **1930**, 2615. (d) Haworth, W. N.; Hirst, E.

L.; Streight, H. R. L.; Thomas, H. A.; Webb, J. I. *J. Chem. Soc.* **1930**, 2637. (e) Hirst, E. L.; Woolvin, L. S. *J. Chem. Soc.* **1931**, 1131. (f) Levene, P. A.; Tipson, R. S. *J. Biol. Chem.* **1931**, *93*, 631. (g) Wood, H. B. jr.; Fletcher, H. G. jr.; *J. Am. Chem. Soc.* **1957**, *79*, 3234. (h) Sweet, F.; Brown, R. K. *Can. J. Chem.* **1966**, *44*, 1571.

70. Halcomb, R. L.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1989**, *111*, 6661.
71. Chmielewski, M. et. al. *Tetrahedron Lett.* **1984**, *25*, 4797.
72. Chmielewski, M.; Kaluza, Z.; Belzecki, C.; Salanski, J. Jurczak, J.; Adamowicz, H. *Tetrahedron.* **1985**, *41*, 2441.
73. (a) Chmielewski, M.; Kaluza, Z.; Belzecki, C.; Abramski, W. *Tetrahedron Lett.* **1987**, *28*, 3035. (b) Chmielewski, M.; Jurczak, J.; *J. Carbo. Chem.* **1987**, *6*, 1.
74. Gnichtel, H.; Gumprecht, C. *Liebigs Ann. Chem.* **1985**, 628.
75. Chmielewski, M.; Kaluza, Z., Mostowicz, D., Belzecki, C.; Baranowska, E; Jacobsen, J. P.; Salanski, P.; Jurczak, J.; *Tetrahedron*, **1987**, *43*, 4555.
76. Franck, R. W.; John, T. V. *J. Org. Chem.* **1980**, *45*, 1170.
77. (a)Franck, R. W.; Gupta, R. B. *Chem. Commun.* **1984**, 761. (b) Franck, R. W.; Gupta, R. B. *J. Am. Chem.Soc.* **1987**,*109*, 5393. (c) Franck, R. W.; Gupta, R. B. *J. Am. Chem.Soc.* **1987**,*109*, 6554. (d) Franck, R. W.; Gupta, R. B. *J. Am. Chem.Soc.* **1989**,*111*, 7668.
78. Baidzhigiton, E. A.; Afanas'ev, V. A.; Dolgii, I. E. *Izv. Akad. Nauk. Kirg. SSR.* **1981**, *50*.
79. (a) Petrzilka, M. *Helv. Chim. Acta.* **1978**, *61*, 2286. (b) Petrzilka, M. *Helv. Chim. Acta.* **1979**, *61*, 3075. (c) Pitteloud, R.; Petrizilka, M. *Helv. Chim. Acta.* **1979**, *62*, 1319. (d) Garratti, D. G. *Can. J. Chem.* **1978**, *56*, 2184. (e) Kozikowski, A. P.; Sorgi, K. L.; Schmiesing, R. J. *J. Chem. Soc. Chem.*

Commun. **1980**, 477. (f) Pitteloud, R.; Petrizilka, M. *J. Am. Chem. Soc.* **1980**, *102*, 6577.

80. Jaurand, G.; Jean-Marie, B.; Sinay, P. *J. Chem. Soc. Chem. Commun.* **1981**, 572.
81. Perez, M.; Beau, J. M. *Tetrahedron Lett.* **1989**, *30*, 75.
82. (a) Murata, S.; Suzuki, T. *Chem. Lett.* **1987**, 849. (b) Murata, S.; Suzuki, T. *Tetrahedron. Lett.* **1987**, *28*, 4415.
83. (a) Kiyoshi, I.; Seijira, A.; Achiwa, K. *Carbohydr. Res.* **1989**, *189*, C1. (b) Ikeda, K.; Akamatsu, S.; Achiwa, K. *Carbohydr. Res.* **1989**, *189*, C1. (c) Yukishige, I.; Ogawa, T. *Tetrahedron* **1990**, *46*, 89. (d) Yukishige, I.; Ogawa, T. *Tetrahedron Lett.* **1987**, *28*, 6221. (e) Okamoto, K.; Goto, T. *Tetrahedron* **1990**, *46*, 5835.
84. (a) Ogawa, T.; Ito, Y. *Tetrahedron Lett.* **1987**, *28*, 6221. (b) Vorbruggen, H.; Krolikiewicz, K.; Blunuf, B. *Chem. Ber.* **1981**, *93*, C6. (c) Ogawa, T.; Beppu, K.; Nakabayashi, S. *Carb. Res.* **1981**, *93*, C6.
85. Kaye, A.; Neidle, S.; Reese, C. B. *Tetrahedron Lett.* **1988**, *29*, 2711.
86. Uemure, S.; Fukusama, S.; Toshimitsu, A. *Chem. Commun.* **1983**, 1501.
87. (a) For a reveiw of reactive sulfonium salts, see Capozzi, G.; Modena, G.; *Organic Sulfur Chemistry: Theoretical and Experimental Advances* Bernardi, F.; Csizmadia, I. G.; Mangini, A. eds., Elsevier, Amsterdam **1985**. (b) O'Malley, G. J.; Cava, M. P. *Tetrahedron Lett.* **1985**, *26*, 6159. (c) Capozzi, G,; Lucchini, V.; Marcuzzi, V.; Modena, G. J. *Chem. Soc. Perkin 1.* **1981**, 3106.
88. Edstrom, E. D.; Livinghouse, T. *J. Am. Chem. Soc.* **1986**, *108*, 1334.
89. Ito, Y.; Ogawa, T. *Tetrahedron Lett.* **1987**, *28*, 2723.
90. Franck. R. W.; Ramesh, S. *J. Chem. Soc. Chem. Commun.* **1989**, 960.
91. Schmidt, R. R.; Preuss, R. *Synthesis.* **1988**, 694.

92. (a) Ito, Y.; Ogawa, T. *Tetrahedron. Lett.* **1988**, *29*, 3987. (b) See references 83c and 83e.

93. Kondo, T.; Abe, H. Goto, T. *Chem. Lett.* **1988**, 1657.

94. Some of the methods tried by S. Ramesh of our laboratory are (a) W-2 Raney/Nickel; (b) Bu_3SnH, AIBN.

95. Fieser & Fieser *Reagents for Organic Synthesis* **1975**, *5*, 523.

96. (a) Capozzi, G.; Lucchini, V.; Modena, G. *Rev. Chem. Intermediates.* **1979**, *2*, 347. (b) Gybin, A. S.; Smit, W. A.; Bogdanov, V. S.; Krimer, M. Z.; Kalyan, J. B. *Tetrahedron Lett.* **1980**, *21*, 383.

97. (a) Bolster, J. M.; Hogeveen, H.; Kellogg, R. M.; Zwart, L. *J. Amer. Chem. Soc.* **1981**, *103*, 3955. (b) See reference 96(b).

98. Ramesh, S.; Kaila, N.; Grewal, G.; Franck, R. W. *J. Org. Chem.* **1990**, *55*, 5.

99. Deslongchamps, P. *Stereoelectronic Effects in Organic Chemistry* Baldwin, J. E. Ed. **1983**, *1*, chap. 2.

100. Secondary amines are known to coordinate with antimony-based Lewis acids. Smith, I. D. *Comprehensive Inorganic Chemistry. Vol. 2*, Chap.21.

101. (a) Fraser-Reid, B.; *Can. J. Chem.* **1973**, *51*, 3950. (b) Garegg, et. al. *Methods in Carbohydr. Chem. Vol. 8*, 317

102. Ferrier, R. J.; Prasad, N. *J. Chem. Soc.* **1969**, 570.

103. Fraser-Reid, B., Radatus, B. *J. Am. Chem. Soc.* **1970**, *92*, 6661.

104. Richtmyer, N. K. *Methods in Carbohydr. Chem. Vol. 1*, 107.

105. Lemieux, R. U.; Fraga, E.; Watanabe, K. A. *Can. J. Chem.* **1968**, *46*, 61.

106. Guthrie, R. D.; Irvine R. W. *Carbohydr. Res.* **1979**, *72*, 285.

107. Ireland, R. E.; Thaisrivongs, S.; Vanier, N.; Wilcox, C. S. *J. Org. Chem.* **1980**, *45*, 48.

108. Thiem, J.; Ossowski, P. *J. Carbo. Chem.* **1984**, *3*, 287.

109. (a) Stevens, J. D.; Fletcher, H. G. *J. Org. Chem.* **1968**, *33*, 1799. (b) Ryan, K. J.; Acton, E. M.; Goodman, L. *J. Org. Chem.* **1971**, *36*, 2646.

110. Magnus, P.; Matthews, I. R.; Schultz, J.; Waditschatka, R.; Huffman, J. C. *J. Org. Chem.* **1988**, *53*, 5772 and references therein.

111. Ogawa, T.; Ito, Y. *Tetrahedron*, **1990**, *46*, 89.

112. For reviews on this topic, see: (a) Schmid, G. H.; Garratt, D. G. *The chemistry of double bonded functional groups* Supplement A, Part 2, Patai, S. Ed., Wiley. London **1977**. (b) Smit, W. A.; Zefirov, S.; Bodrikov, I. V. Krimer, M. Z. *Acc. Chem. Res.* **1979**, **12**, 282.

113. Owsley, D. C.; Helmkamp, G. K.; Rettig, M. F. *J. Am. Chem. Soc.* **1969**, *91*, 5239.