DISSERTATION

CARBOHYDRATES AS CHIRAL TEMPLATES

Submitted by

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In partial fulfillment of the requirements

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Colorado State University

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WE HEREBY RECOMMEND THAT THE THESIS PREPARED UNDER OUR SUPERVISION BY ANDREW O. STEWART ENTITLED CARBOHYDRATES AS CHIRAL TEMPLATES BE ACCEPTED AS FULFILLING IN PART REQUIREMENTS FOR THE DEGREE OF DOCTOR OF PHILOSOPHY.

Committee on Graduate Work

Advisor

Department Head

ABSTRACT OF DISSERTATION

CARBOHYDRATES AS CHIRAL TEMPLATES

Carbohydrates can serve as a source of functionalized asymmetric carbon atoms. The synthesis of a carbon fragment derived from 2-deoxy-glucose is described as an optically pure intermediate (**34**) for the synthesis of the antibiotic thienamycin.

Natural products containing sugar moieties are direct targets for synthetic strategems utilizing carbohydrate precursors. The synthesis of naturally occurring C-glycosides from readily available sugars require carbon bond formation at the acetal carbon. Reported, herein, is methodology for the conversion of hemiacetals to the corresponding 2'-thiopyridyl acetals and subsequent metal activation toward nucleophilic displacement by carbon species resulting in efficient C-glycosidation. A glucosyl substrate (**122**) and two ribosyl substrates (**147**, **154**) are described and their stereoselective reactions with different carbon nucleophiles are examined. The glucose substrate (**122**) shows general α-selectivity in carbon-carbon bond formation. The selectivity in the ribosyl

substrates is quite good but, exhibits a large dependence on the particular nucleophile. The total synthesis of (+)-showdomycin is achieved employing a β-selective coupling of trimethoxybenzene and the ribosyl thioacetal (**154**) utilizing silver (I) activation. Preparation of other useful C-nucleoside precursors containing the required β-stereochemistry are reported.

The use of these metal activated thiopyridyl acetals for intramolecular O-glycosidations are also investigated. Approaches to the [3.1.1] bycyclic oxetane of the thromboxane A_2 nucleus using this methodology are examined. The use of a polymer bound mercury(II) salt (**226**) for activation of the thio-residue is shown to be useful in an intramolecular O-glycosidation resulting in the 1,5 anhydro-furanose (**186**). This polymer bound reagent should potentially represent an advantageous heterogeneous alternative to the homogeneous metal salts; particularly for glycosidations of sensitive substrates. In general, these thiopyridyl-acetals are stable precursors that may be readily activated by thiophilic metal salts for efficient nucleophilic substitution reactions.

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CHAPTER I

INTRODUCTION

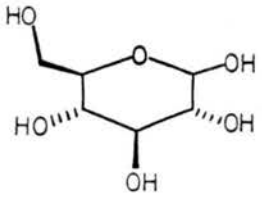
A synthetic chemist's desire to produce enantiomerically pure intermediates is maintained by the asymmetric three-dimensional nature of the binding sites of biologically active compounds. As a result often only one enantiomer of the active compound displays the desired therapeutic properties. The other enatiomer can display complete inactivity or even undesired side effects. Therefore the requirement of optical purity is paramount for biochemical and pharmacological evaluation of any chiral compound. Carbohydrates can play a key role toward this goal, functioning as a source of inexpensive, optically pure functionalized asymmetic carbon centers. These may be manipulated and incorporated into the framework of the desired molecular target structure.

Sugars or monosaccharides have been an integral part of the development of modern organic chemistry. Early man's desire for sweetening agents led to the isolation and purification of several crystalline sugars.[1] It was soon found that identical compounds could be isolated from

different sources. The recognition of different sugars with the same constitutional formula required the explanation of isomers of a type other than structural isomers. This observation led to the development and acceptance of the LaBell, van't Hoff theory of tetrahedral and therefore asymmetric carbon atoms.[2] This must be considered the beginning of modern stereochemistry. The term, conformation, was originally used by Haworth to describe the chair conformers of hexoses.[3] The consequences and resulting conformational bias resulting from a low energy conformer was first described by Lemieux as the "anomeric effect".[4] This will soon be shown to be a major influence in the stereoselectivity observed in the reactions of carbohydrates. Lemieux also demonstrated the usefulness of NMR spectroscopy in the configurational analysis based upon torsional angles of projected C-H bonds. This observation has led to the current use of NMR spectroscopy as a fundamental tool of organic chemistry. In view of the wealth of information available on the structure elucidation employing physical methods and the selective synthetic manipulations that can be performed upon the carbon skeleton of carbohydrates, it is not surprising that sugars have more recently become a significant source of asymmetric carbon fragments for the enantiospecific synthesis of many natural products.[5]

The sugars have many advantages over other chiral synthons. These may be classified according to the

following three general categories: 1) optical purity; D-glucose (1) contains 4 contigious stereogenic centers.

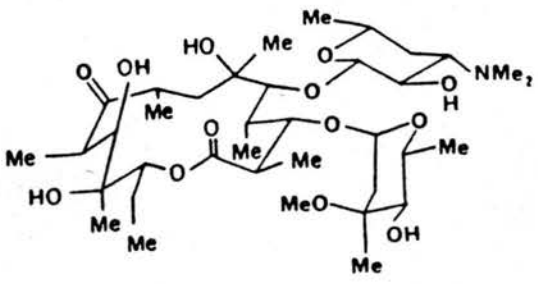


1

There are theoretically 16 stereoisomers of a compound of this constitution. However, D-glucose is available in crystalline form for less than 0.2¢ per gram as a single optically pure compound. 2) Conformational bias of the cyclic structure is enhanced due to the anomeric effect. Often an electronegative anomeric substituent will greatly favor the axial position, and rigidly lock the compound into a low energy conformer. Reactions of high stereoselectivity are often observed since the course of the reaction is influenced by the configuration of adjacent centers and the strong bias of a single branched chair conformation. Unless all of the multiple stereogenic centers are simultaneously manipulated, the resulting diastereomers are easily observable by a number of physical methods and often easily separated on a preparative scale. Furthermore the absolute configuration of the new stereogenic center(s) can be assigned; often from a first order ^{1}H NMR spectrum at the high fields of super

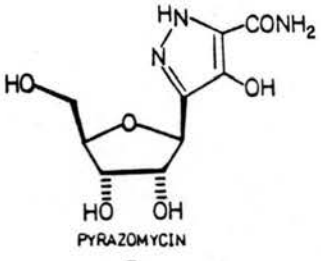
conducting NMR spectrometers. 3) Carbohydrate precursors are highly functionalized poly-hydroxyl, carbonyl compounds. What appears at first glance a difficult task, the selective manipulation of each hydroxyl group of a penta-ol, has in fact been accomplished in many ingenious ways. The carbohydrate literature is rich in this respect and allows each carbon to be selectively oxidized, homologated or reduced in order to serve its role as a "chiral template".

The term chiral template has been used to describe this functional and chiral overlap inherent in carbohydrates.[5c] Combined with the conformational bias associated with these cyclic structures, sugars can be utilized for generating useful chiral synthetic intermediates. The use of sugars as chiral synthons has been successful for the two broad classes of natural products; 1) those in which the relation of the sugar residue to the target structure is readily apparent and 2) compounds whose symmetry with carbohydrates is hidden or the compounds contains a small chiral carbon fragment that could be obtained from a carbohydrate skeleton. As examples of the first class, a large number of biologically important compounds contain sugar moieties. Erythromycin (2), a commercial antibiotic, is an example of an economically important O-glycoside. Clearly any totally synthetic or semisynthetic approach to this compound or potentially interesting analogs would involve both



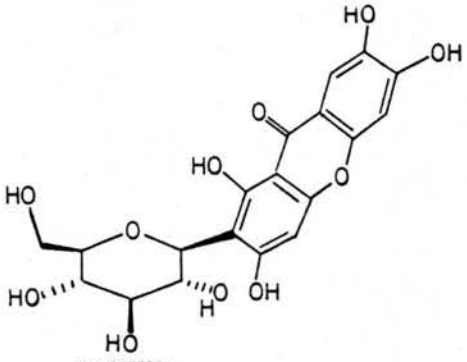
ERYTHROMYCIN

2



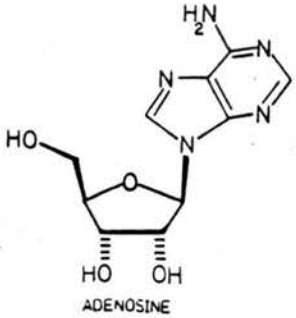
PYRAZOMYCIN

3



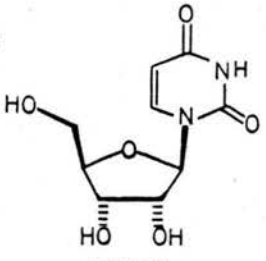
MANGIFERIN

4



ADENOSINE

5



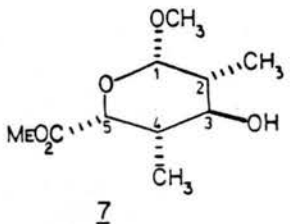
URIDINE

6

attachment and synthesis of the sugars. Important classes of new compounds, the C-nucleosides (3) and C-glycosides (4) contain an obvious sugar residue. The C-nucleosides (3) are analogous to the fundamental biological monomers the nucleosides (5, 6). A straight forward synthetic approach to these compounds would involve the attachment of a C-C bond or a C-N bond to a natural sugar derivative.

As an example of the second class of compounds the erythronolide A precursor (9), has been elegantly approached by Hanessian from two hexoses[4c] (7, 8) (Scheme 1). Chiral carbon elements of prostaglandins have also been obtained from natural sugars as in the synthesis of PGE 1(10) and PGE 2 (11) by Stork[4d,e] (Scheme 2).

The intensity of research in the area of C-glycosidation undoubtedly shows the potential for carbohydrates as precursors for the first class of compounds. A detailed account of glycosidations and the anomeric effect will be given in Chapter 3. The success of using carbohydrates for the second class of compounds is unclear. The future of this application is complicated by the number of manipulations required to tailor the carbon fragment to be incorporated into the target. Despite this drawback the ultimate success of this approach will depend on the cleverness and creativity of the chemist to identify these hidden elements of symmetry that new promising compounds have in common with readily available carbohydrate derived templates.



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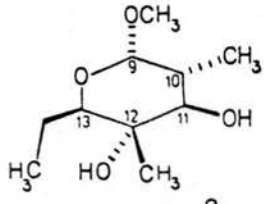

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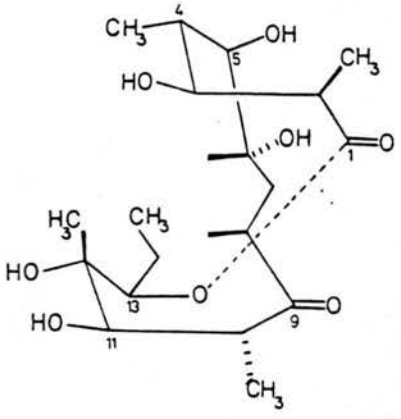
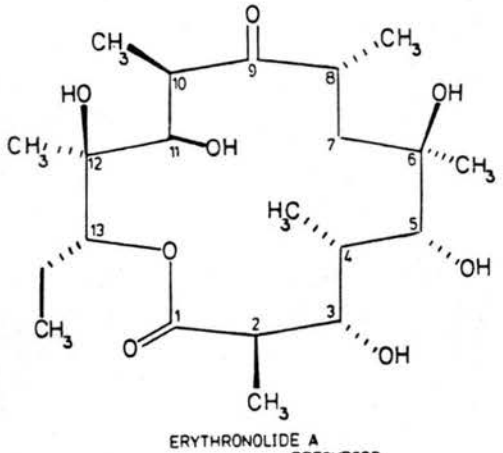


III



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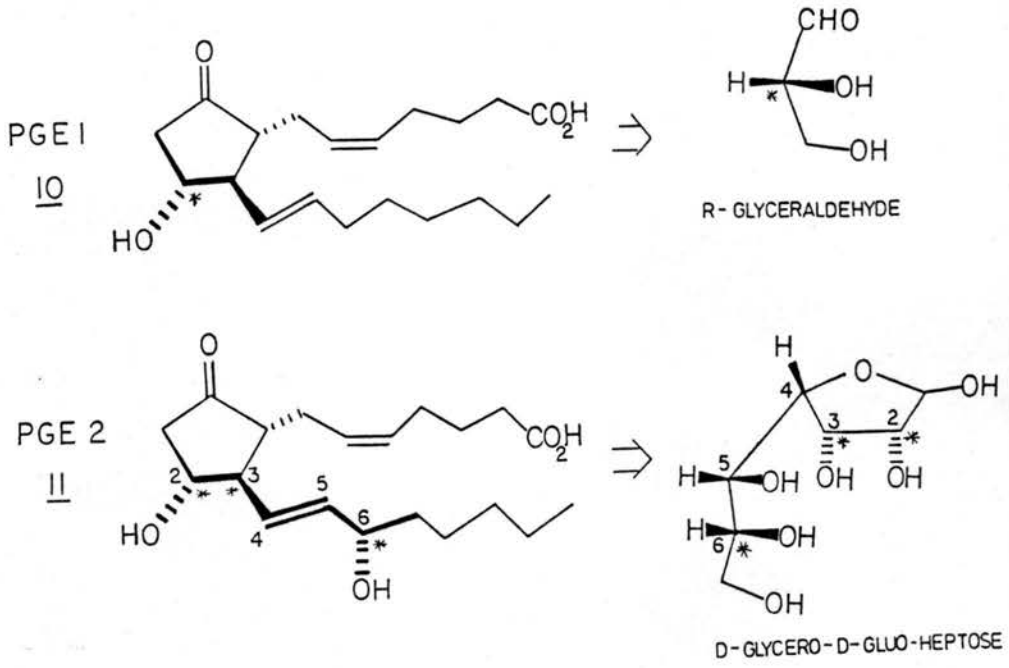
SCHEME 1

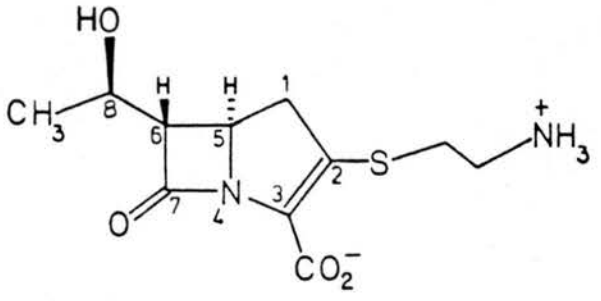


SCHEME 2

CHAPTER II

THIENAMYCIN

Thienamycin (12) is one of the most potent, new generation β-lactam antibiotics. This compound was first

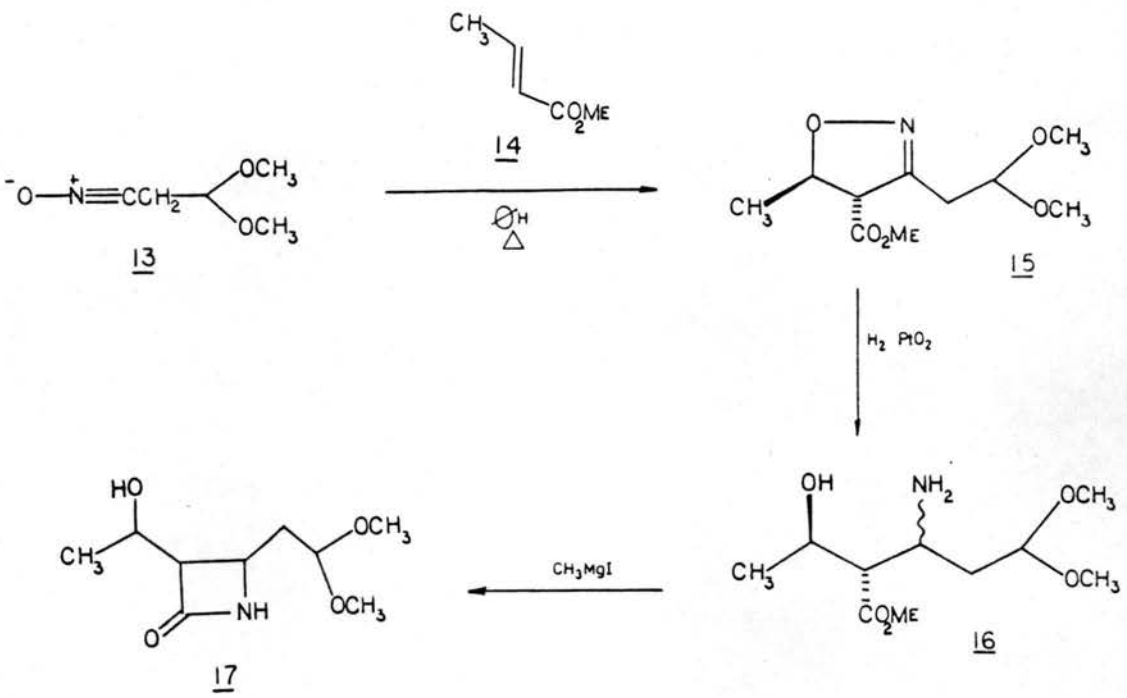


12

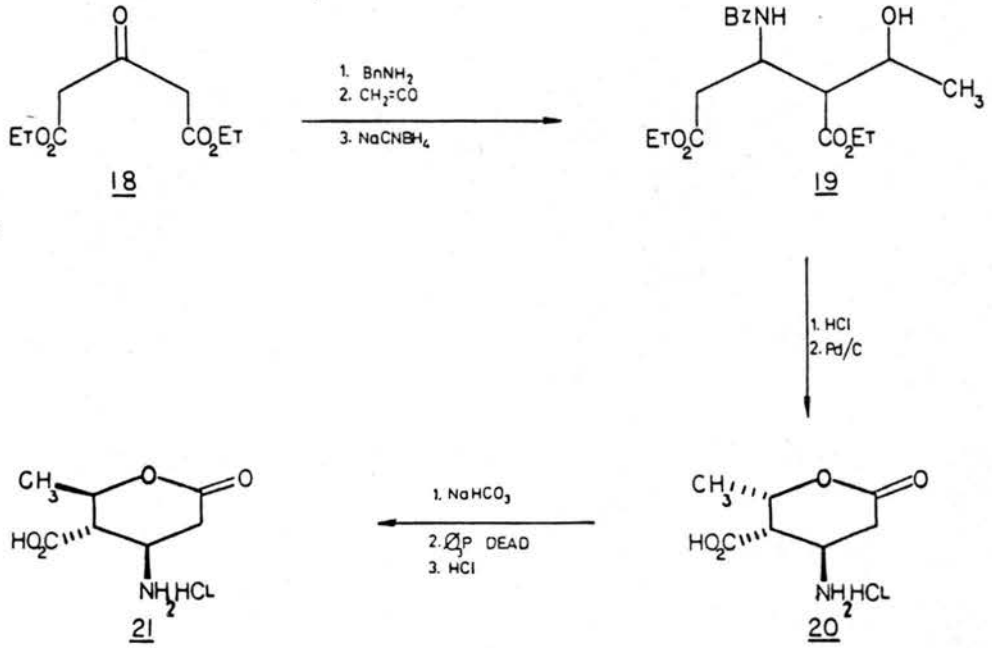
isolated from fermentation broths of the soil microorganism Streptomyces cattleya by the Merck Chemical Company. It's extremely high antibacterial activity combined with the very modest fermentation yields of this compound established it as competitive synthetic target. Only the naturally occurring enantiomer displays the desired biological activity and therefore any viable synthesis must address the absolute stereochemistry of the three contiguous stereogenic centers, 5R, 6S, 8R. Soon after publication of the isolation and structure of this new exciting antibiotic, total syntheses were published by

Merck[7a] and a Japanese group.[7b] In the Japanese route the precursor to the three chiral centers and the β-lactam nucleus was constructed by a 1,3-dipolar cycloaddition (Scheme 3). Compound **15** was reduced to give **16**; which was cyclized by the action of MeMgI as a base to give the β-lactam **17**. The Merck group published another approach.[7c,d] Diethyl 1,3-acetonedicarboxylate (**18**) was converted via the enamine to give the mono-C-acylated product **19** (Scheme 4). Compound **19** could be converted by a two-step sequence to give the isomerically pure lactone. The lactone **21** could be converted to thienamycin in 35% overall yield by first opening of the lactone with benzyl alcohol to give **23** (Scheme 6). Once the relative configuration of the three chiral centers had been achieved the remaining synthesis was quite straight forward. The rhodium catalyzed decomposition of the diazo compound **24** to give a carbene which inserts into the NH bond of the lactam giving the bicyclic **25** is a noteworthy and efficient cyclization (Scheme 5). These early syntheses, however, resulted in racemic compounds. Initially this is the desired approach, when a new drug shows the incredible potential that thienamycin had displayed, an attempt is made to cover as many new analogs (epimers, etc.) as possible for patent protection. The problem of an industrial preparation of the enatiomerically pure compound still remained.

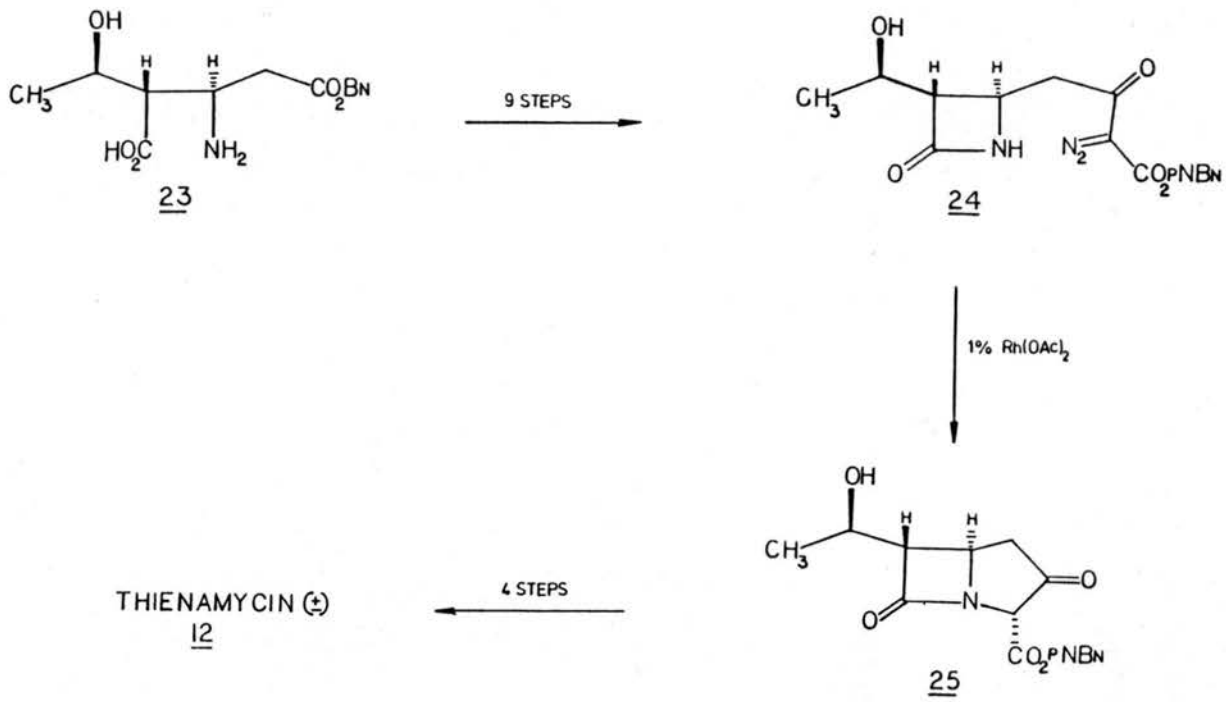
The hidden symmetry in lactone **21** (called the Melillo lactone) and 2-deoxyglucose presented a possible solution



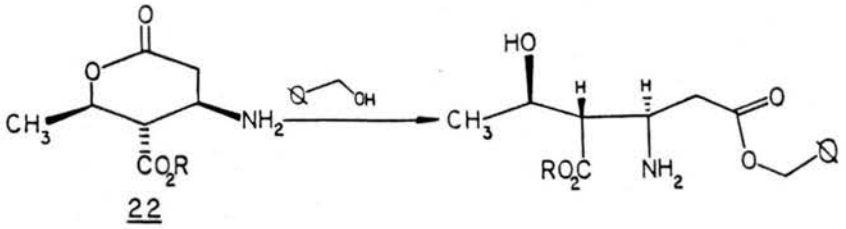
SCHEME 3



SCHEME 4


OH
H
H
CH3
CO2BN
HO2C
NH2
23
9 STEPS
OH
H
H
CH3
O
NH
N2
CO2PNBN
O
24
1% Rh(OAc)2
OH
H
H
CH3
O
N
O
CO2PNBN
25
4 STEPS
THIENAMYCIN (±)
12

SCHEME 5

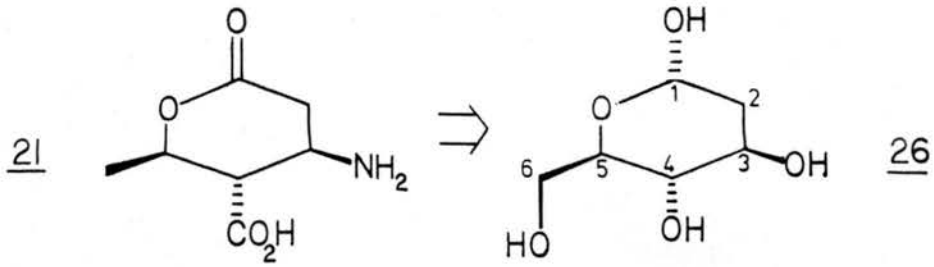


22

23

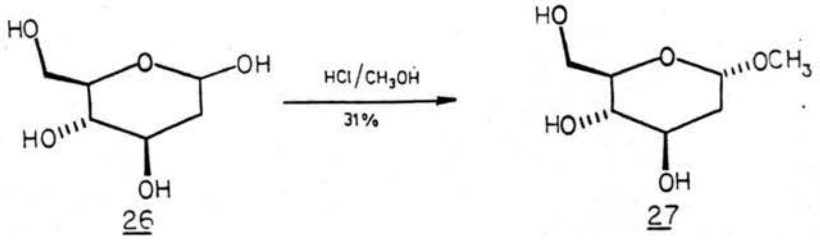
SCHEME 6

to the enantiospecific synthesis of this key intermediate lactone that had previously been prepared only in racemic form. The absolute configuration of centers 3, 4, 5 of glucose correspond to that of thienamycin 5R, 6S, 8R. The transformation of 21 into 26 would require (carbohydrate numbering) deoxygenation of C_6 and one carbon homologation of C_4 to the one carbon extended acid (Scheme 7). Thirdly, conversion of the hydroxyl of C_3 to an amino functionality must proceed with overall retention. We felt that the conversion at C_3 could be accomplished by a double inversion using an amino nucleophile for the second displacement resulting in overall retention of the desired R-absolute configuration. The homologation at C_4 was envisioned using standard Wittig chemistry on the derived C_4 ketone. It was assumed that the conformational bias of the cyclic carbohydrate would lead to the desired configuration at C_4 after hydrolysis. Finally the C_6 deoxygenation could be performed by a number of literature



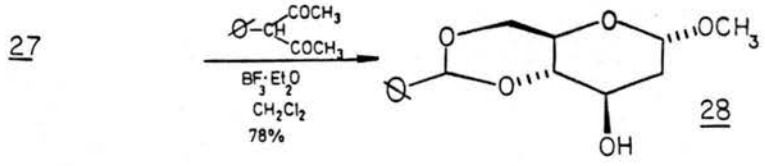
SCHEME 7

methods. We began our approach to the lactone from the readily available bromobenzoate 29 (Scheme 10). In an alternate procedure 29 was prepared from 2-deoxyglucose on multigram scale requiring no chromatography. The crystalline α-methyl glycoside (27) was prepared from commercial 2-deoxy-D-glucose by the action of HCl/MeOH. The benzylidene derivative 28 was formed by reaction of the triol (27) with the dimethyl acetal of benzaldehyde and a catalytic amount of boron-trifluoride etherate in methylene chloride at 0°C. The product could be obtained by direct recrystallization on a preparative scale. Oxidation of 28 by NBS under conditions developed by Haessian[9] gave the literature bromobenzoate (29).[9] Dehalogenation of this material using Raney Nickel W-5[10] in isopropanol afforded, in quantitative yield, the 2,6,dideoxy-arabino-hexose (30) (Scheme 11). Rapid dehalogenation required freshly prepared W-5 Raney Nickel in isopropanol. In a modification of this procedure, ethanol is replaced by



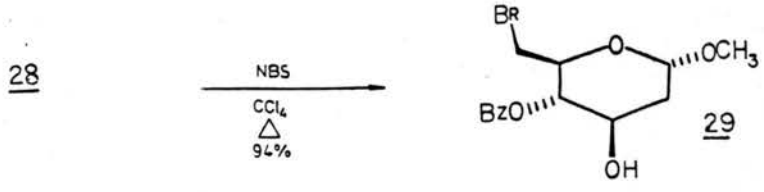
26 27

SCHEME 8



28

SCHEME 9



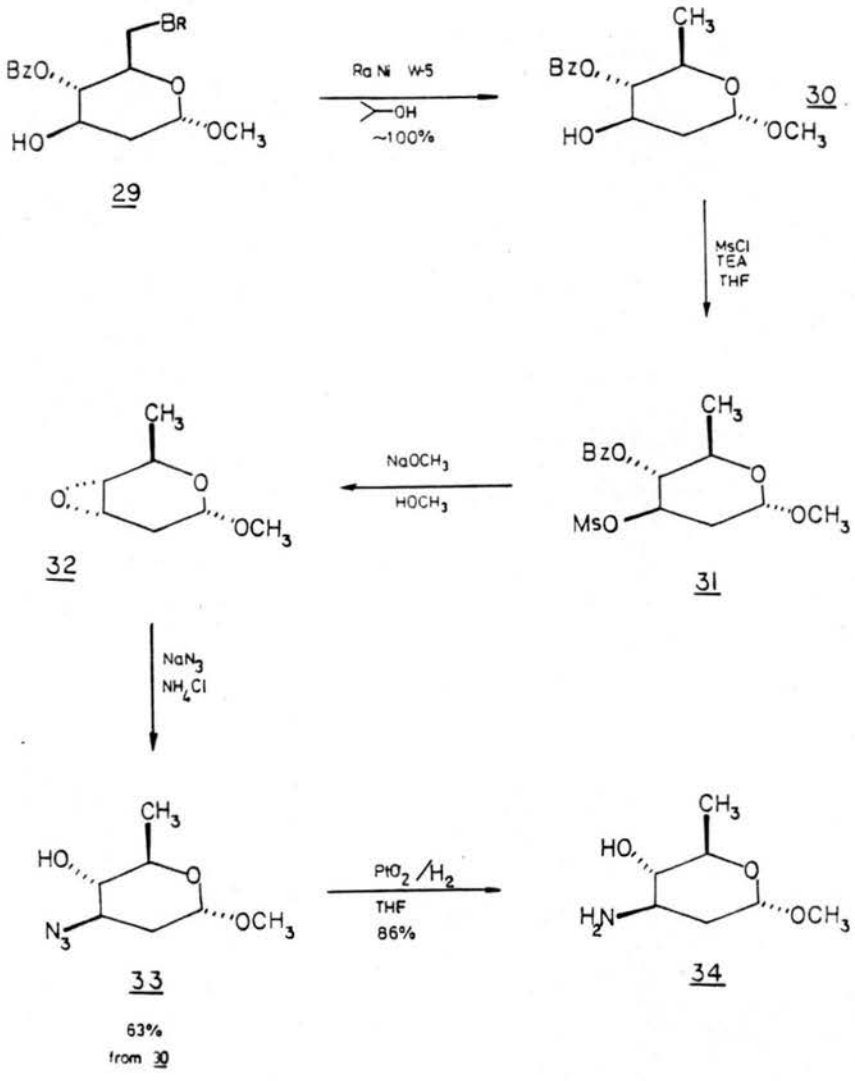
29

SCHEME 10

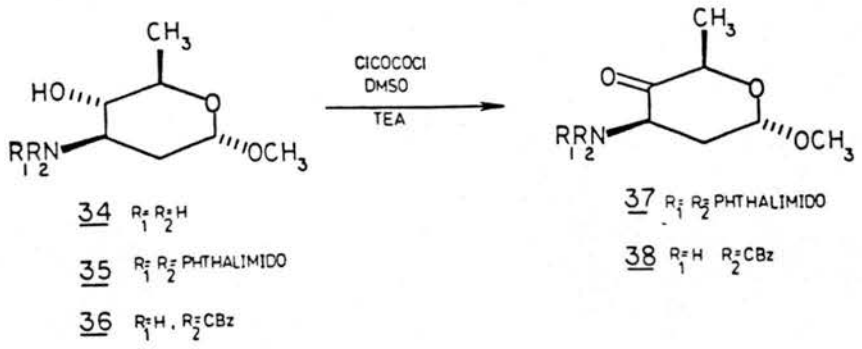
isopropanol in the final washings of the activated catalyst. It was found that the use of ethanol as a solvent employing the same W-5 catalyst yielded a mixture of benzoates (C_3 and C_4) and diol. The integrity of the monoprotected diol is maintained in isopropanol and the reaction can be performed overnight under an atmosphere of H_2. The yield, ease of handling and isolation proved this method superior to the tri-n-butyl tin hydride reductions on this substrate.

The mesylate **31** was found to undergo facile epoxide formation under basic conditions via the C-4 alkoxide generated from cleavage of the benzoate. The epoxide (**32**) was not isolated; the crude reaction mixture was neutralized and underwent mild stereoselective epoxide opening with sodium azide.[11] The resulting azide **33** could be reduced using PtO_2 in THF at room temperature under an atmosphere of hydrogen. The crystalline amino alcohol **34** now possesses the requisite deoxygenated C_6 carbon and the exchange of amine for hydroxyl functionality with overall retention of configuration at C_3. What remained seemed to be a straight forward oxidation of the C-4 alcohol to the ketone followed by Wittig olefination to give the C-4 homologated species. The oxidation state of the new carbon did not seem critical in view of a subsequent oxidation that would be required of the anomeric carbon.

Oxidation of the protected amino alcohol (**35**) gave the crystalline ketone **37** in good yield (Scheme 12). This


BR
BzO
HO
OCH3
29
Ra Ni W-5
OH
~100%
CH3
BzO
HO
OCH3
30
MsCl
TEA
THF
CH3
BzO
MsO
OCH3
31
NaOCH3
HOCH3
CH3
O
OCH3
32
NaN3
NH4Cl
CH3
HO
N3
OCH3
33
63%
from 30
PtO2 /H2
THF
86%
CH3
HO
H2N
OCH3
34

SCHEME 11



SCHEME 12

ketone proved to be relatively unreactive, presumably due to steric hinderance. Many reagents known to homologate less hindered, more reactive carbonyl compounds were unreactive with ketone (37). Table I summarizes some reagents that were used to attempt this one carbon homologation but led, in most cases only to recovery of unreacted starting material.

At the suggestion of Dr. S.F. Martin a diazo phosphonate reagent (39) developed by Gilbert[12] was examined. The potassium salt of this compound was found to add quite readily to ketone 37 at 0° in MeOH. Immediate disappearance of starting material and evolution of N_2

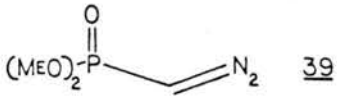


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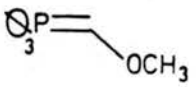
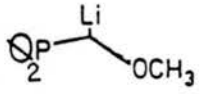
TABLE I

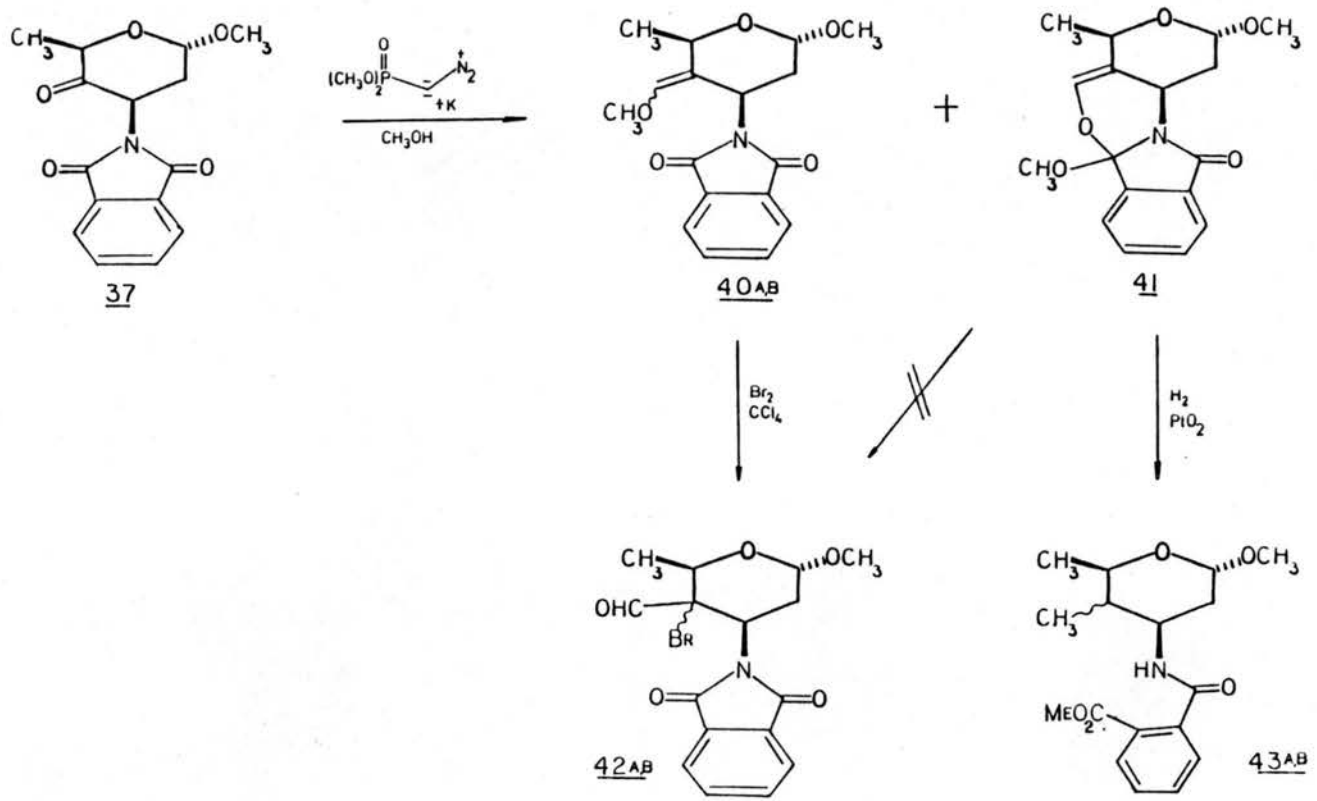
REAGENT	REACTION TEMP. °C	RESULT
	0° ⟶ 25°	RECOVERED KETONE
	-90° ⟶ 25°	〃
	50°	〃
CH_2N_2	25°	〃
CH_2I_2 Mg\Hg	25°	COMPLEX MIXTURE

characterized this facile reaction. Anticipating the production of two regio-isomers, we were quite surprised to find three isolable products that each exhibited a new enol ether and a new methoxy resonance in the proton NMR spectrum. Column chromatography separated the major compound from a mixture of two minor components. The three compounds were produced in an approximate 4:1:1 ratio. Further investigation revealed a chemical selectivity between the major and mixture of minor components. It was found that the two minor components rapidly decolorized bromine in CCl_4 to efficiently produce diasteromeric aldehydes, on the other hand, the major isomer was completely stable to the bromonation conditions. The major isomer could be hydrogenated by PtO_2 in THF under one atmosphere of hydrogen to give new diastereomeric compounds

that exhibited a new methyl doublet in the ^1H spectrum. The mixture of minor components proved to be stable under these hydrogenation conditions. Based on these observations and the IR spectrum of the hydrogenation product (**43**) of the major adduct (**41**) the structural assignments in Scheme 13 were tentatively made. The structure of the major component resulted from an intramolecular trapping of the diazo-intermediate. This seemed to be confirmed by the action of this reagent on ketone **38**. Under the same reaction condition **38** was rapidly consumed and a single isolable compound was obtained that showed no new methoxy resonance in the 60 MHz proton spectrum. The new unidentified product presumably arises from reaction of the CBZ protecting group intramolecularly with the diazo intermediate.

During the time we were experiencing difficulty in the homologation of this C_4 ketone several groups published almost identical routes to the Melillo lactone in optically pure form from D-glucose.[8b-f] These publications essentially terminated this project which was eventually published as a synthesis of compound **32**.

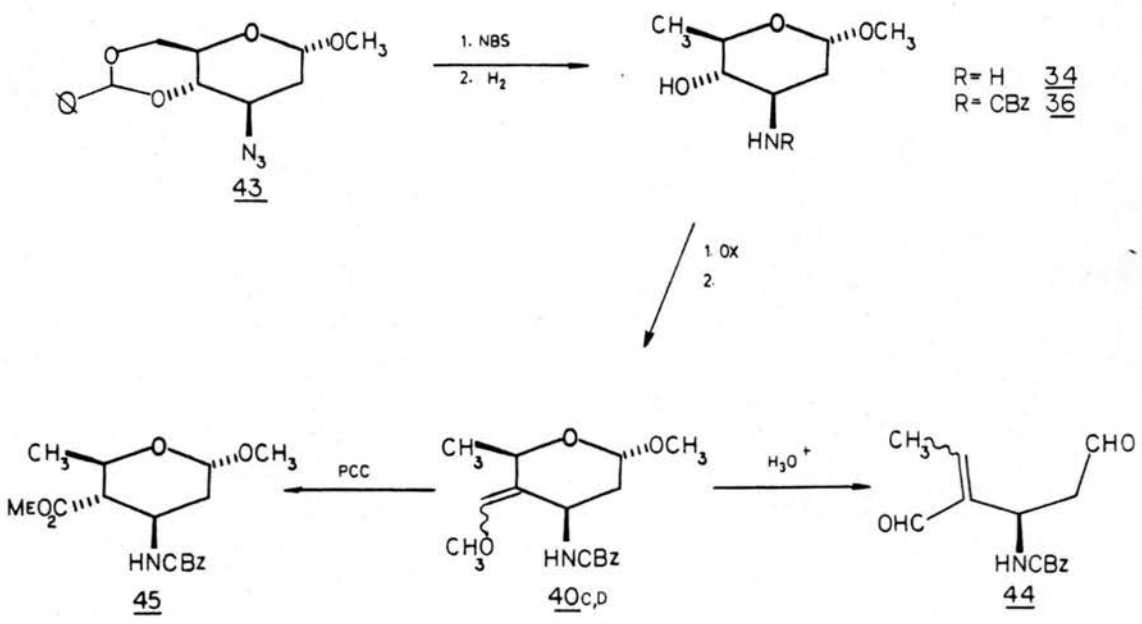
The report by Koga et al. was quite similar to our approach. The azido benzylidene derivative **43** was transformed into the same amino alcohol (**34**), in a two step sequence (Scheme 14). Protection of the amine and oxidation afforded the ketone identical with our compound **38**. Homologation using a modified Horner-Emmons reagent



SCHEME 13

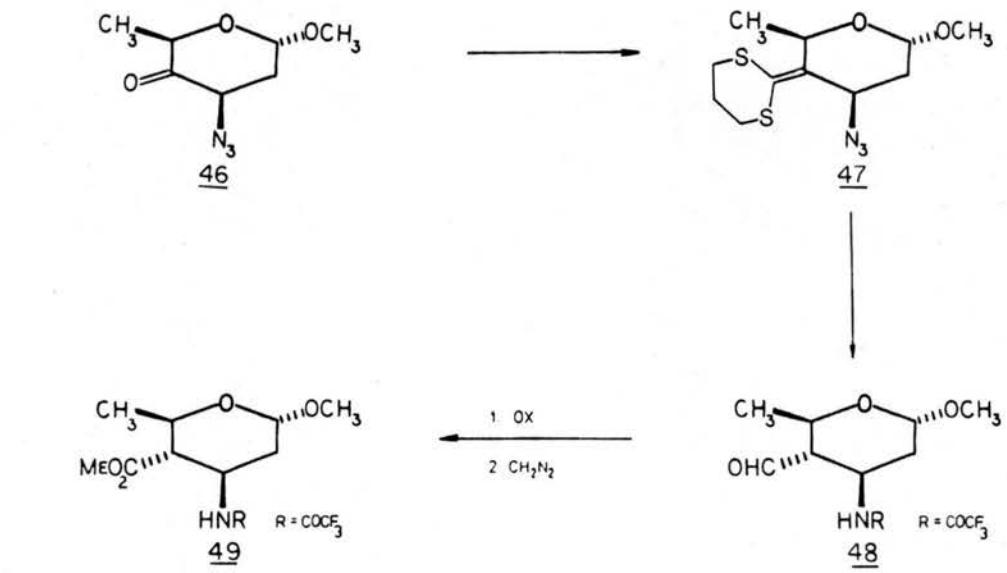
gave the desired enol ether **40c,d**. This is the same compound we had tried to obtain using the Gilbert Reagent and ketone **38**. Upon attempted acid hydrolysis Koga observed elimination to give the ring-opened dialdehyde **44** and the destruction of two stereogenic centers (Scheme 14). We also observed this identical reaction upon the hydrolysis of the minor enol ether isomers obtained from our phathalimido series. Koga overcame this problem by direct oxidation of compound **40c,d** to the desired methyl ester **45** using PCC. Although this was accomplished in modest yield it avoided acid hydrolysis of the enol ether. Hanessian[8c,d] appears to have encountered similar problems in his approach. A homologation of ketone **46** gives the ketene dithioacetal (**47**) (Scheme 15). This material contains a new carbon atom of the appropriate oxidation state. However, it was reduced, hydrolyzed to the aldehyde **48**, then later oxidized back to the required acid oxidation state **49**. The precursor to Hanessian's ketone **46** is the azido alcohol **33**. Our attempts to oxidize this compound to the α-azido-ketone failed; we attributed this result to the instability of the product. Hanessian reports this oxidation in 95% yield by the action of PCC in the presence of 4A sieves, a method we did not attempt. The use of this ketone may avoid the protecting group problems and consequent prohibitive steric restrictions observed in reactions of our C4 ketones. Our route, however, affords gram quantities of either the azido alcohol **33** or amino

KOGA SYNTHESIS REF. 8E



SCHEME 14

HANNESSIAN SYNTHESIS REF. 8D



SCHEME 15

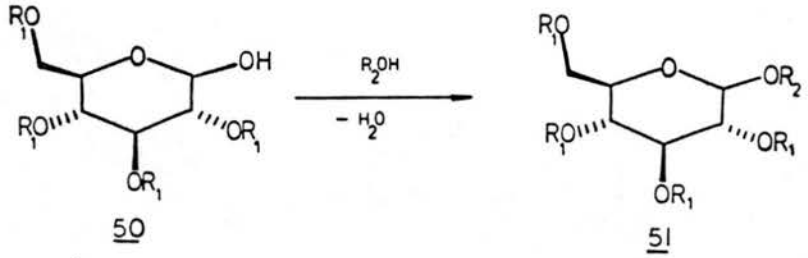
alcohol **34** using the only published experimental procedure. The amino alcohol (**34**) represents a formal total synthesis of (+)-thienamycin based on the work of Koga.[8e]

The amount of experimental activity utilizing the common symmetry of the Melillio lactone and optically pure D-glucose show the powerful potential of approaches using carbohydrate chiral templates. This is one of the more successful examples of an optically active intermediate that can be produced from a readily available carbohydrate.

CHAPTER 3

C-GLYCOSIDATION OF PYRIDYL-THIOACETALS

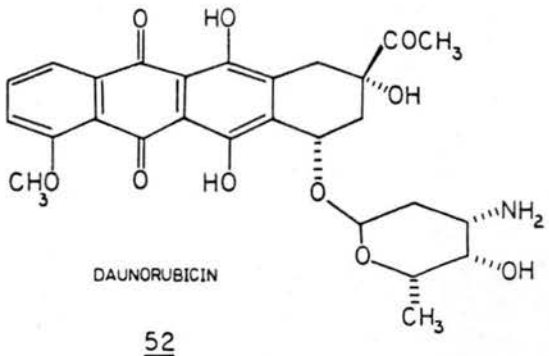
The importance of the glycosidic bond cannot be overestimated. O-glycosides are produced when the hemiacetal (50) of a sugar is transformed into a mixed acetal (51). The resulting OR_2 group of 51 is known as the aglycone (Scheme 16). This term was originated by Japanese



SCHEME 16

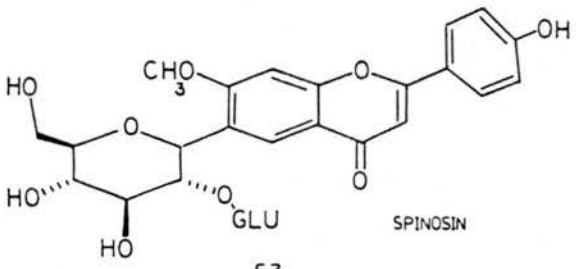
chemists[12] and represents a variety of structures and a large number of diverse biologically important compounds. Oligo- and polysaccharides are biological polymers, in which the aglycone is another sugar residue. These sugar polymers serve as polar components of glycolipids and

glycoproteins. It is now known that poly-saccharides are responsible for the immunoactivity of bacterial cell walls[13a]. Many antibiotics contain sugar moieties that are thought to have functions ranging from transport to active binding site capacities. Erythromycin (2) is an example of a glycoside in which the aglycone is the macrolide-antibiotic. Daunorubicin (52) is a member of the tetracyclines[14], another important class of antibotics having an O-glycosidic bond as an important structural feature. It has been stated, "The specificity of many natural polymers is written in terms of sugar residues, not amino acids or nucleotides".[16]



DAUNORUBICIN

52

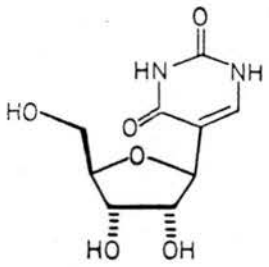


SPINOSIN

53

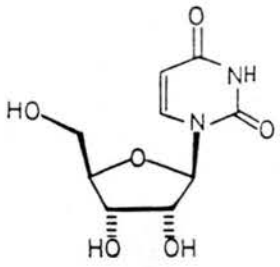
Recently, due to modern analytical techniques, new classes of compounds containing a C-glycosidic bond have been isolated and subsequently have become targets for natural product synthesis. These compounds can be viewed as reductive alkylation products of sugar hemi-acetals; a process requiring a carbon-carbon bond being formed at C_1 (the carbon previously in the acetal or aldehyde oxidation state). The resulting ether is now catabolically stable. Not only do these compounds show a large range of desirable activities but they potentially represent models to study inhibition and function of a wide variety of enzymes involved in saccharide interaction. These sugar derivatives are reasonably stable to hydrolysis and are known in both the pyranose and furanose series.

C-glycosylflavinoids, such as spinosin (53), represent a small but important class of plant glycosides that have a sugar residue attached directly to the A ring of a flavinoid by a carbon-carbon bond. A larger class of more intensely investigated C-glycosylated heterocycles are the C-nucleosides.[16] Psuedouridine (54) was the first example to be isolated as a minor component of t-RNA hydrolysates and from human urine.[16a] The resemblence to uridine (6), a fundamental N-nucleoside, is striking. The incorporation of these C-nucleosides into nucleic acids or nucleotide coenzymes is responsible for their diverse biological activities; "Pseudouridine being recognized as uridine at



PSEUDOURIDINE

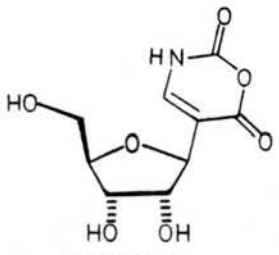
54



URIDINE

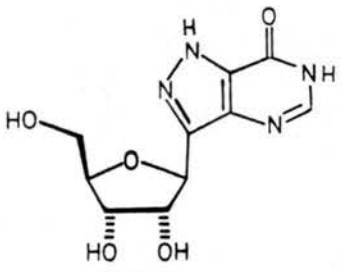
6

the nucleotide and polynucleotide levels."[16a] Recently several other C-nucleosides (55-58) have been isolated, mainly from fermentation, and show a wide variety of



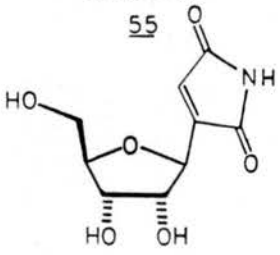
OXAZINOMYCIN

55



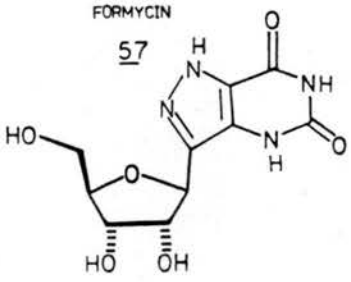
FORMYCIN

57



SHOWDOMYCIN

56



FORMYCIN B

58

biological activities. Most of these compounds show antibiotic activity. This can be attributed "to the way in which they, or their corresponding nucleotides, inhibit

important enzymatic processes such as nucleotide and nucleic acid metabolism, protein biosynthesis, biological methylation and chitin biosynthesis".[16a] Many, particularly showdomycin (56), exhibit "remarkable antitumor activity"[16a] against certain cancer tumors in mice and cultured cells. A common feature of these interesting compounds is that the small unsaturated heterocycle is attached to the furanosyl unit by a carbon-carbon bond in the beta configuration. This will become a significant synthetic requirement with all glycoside formation. The anomeric* center is a stereogenic center and a selective method to generate a specific configuration is required.

The main objective of our research in this area was to produce a stable precursor that could be readily activated and efficiently coupled with carbon nucleophiles in a stereospecific manner. A firm understanding of the mechanism of substitution at the anomeric center of sugars is required and many insights may be gained from a review of the immense amount of work in the glycosidation field.

Three general classes of successful C-glycosidations have been reported.

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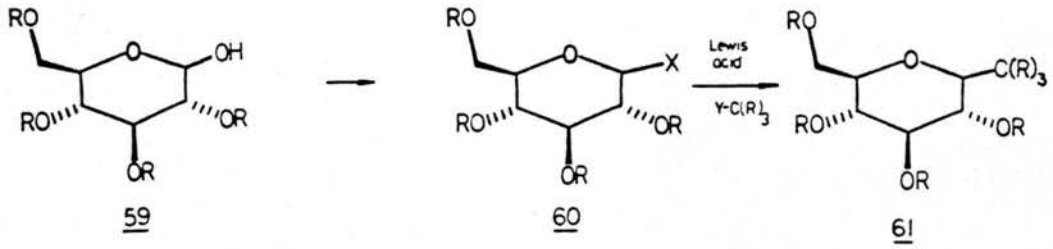
* Technically the term anomer does not apply to C-glycosidated sugars, however the term has been commonly adopted and will be used throughout this manuscript.

1. Conversion of the hemiacetal (**59**) to a mixed acetal (**60**) (Scheme 17). This mixed acetal is now activated, usually under acidic conditions. Subsequent nucleophilic displacement gives the C-glycoside **61** directly. A large number of leaving groups, as in the mixed acetal form (**60**), can be activated under Lewis acid conditions and have been used for this type of scheme.[17] The most successful examples are represented by X = OAC, halogen, $OCOC_6H_4NO_2$ and $OCNHCCl_3$. Since most glycosidations are of this type, a more detailed discussion of this mechanism, will be given later in this chapter.

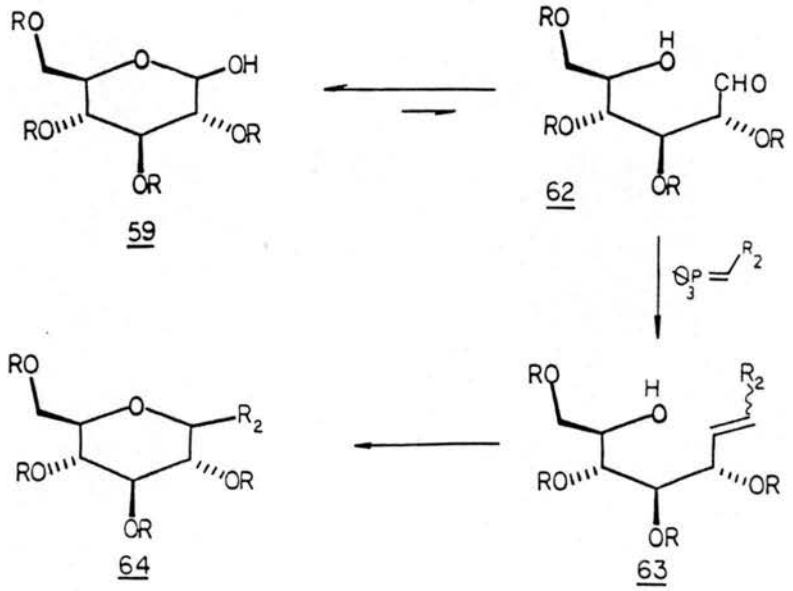
2. Utilization of the open chain aldehyde (**62**), followed by cyclization to give the C-glycoside (**64**). A very common strategy is Wittig olefination[18] (shown in Scheme 18).

A similar cyclization approach is the addition of organometallics to the open chain aldehyde in equilibrium with the cylic acetal to give adducts of the type **66** (Scheme 19). Activation via the tosylate and cyclization yield the C-glycoside[19] (**67**).

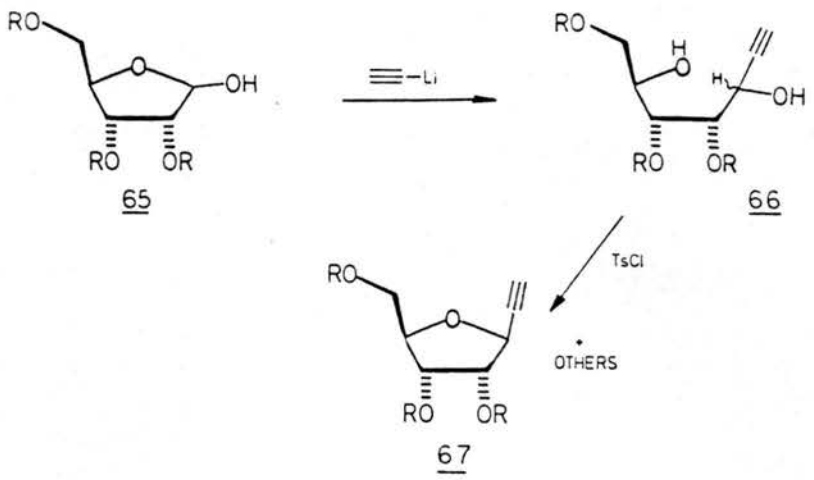
3. Addition of organometallics to the anomeric carbon in the lactone oxidation state.[20] These additions lead to hemiketals of the type (**69**) (Scheme 20). A reduction is then required to obtain the C-glycoside (**70**). The most widely used and successful approach has been the first class, activation of some leaving group in the mixed acetal form and subsequent substitution giving the C-glycoside



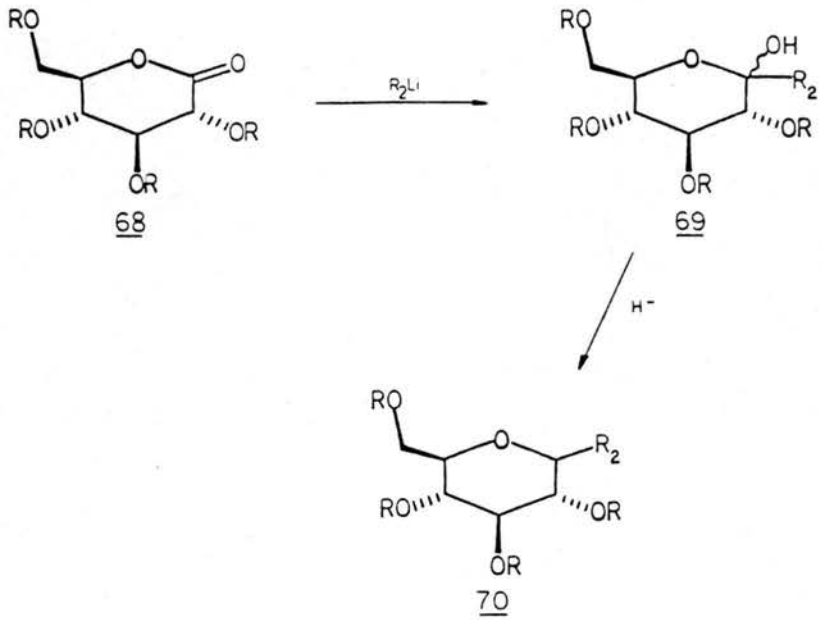
SCHEME 17



SCHEME 18



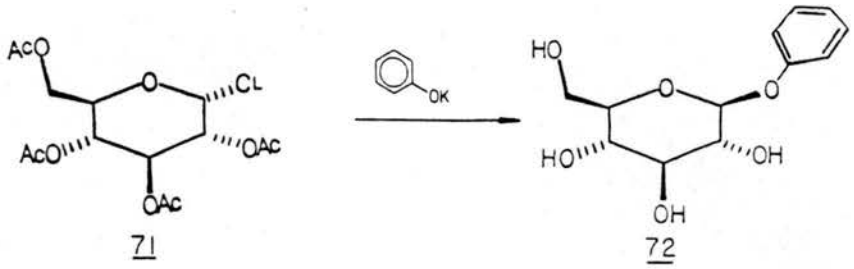
SCHEME 19



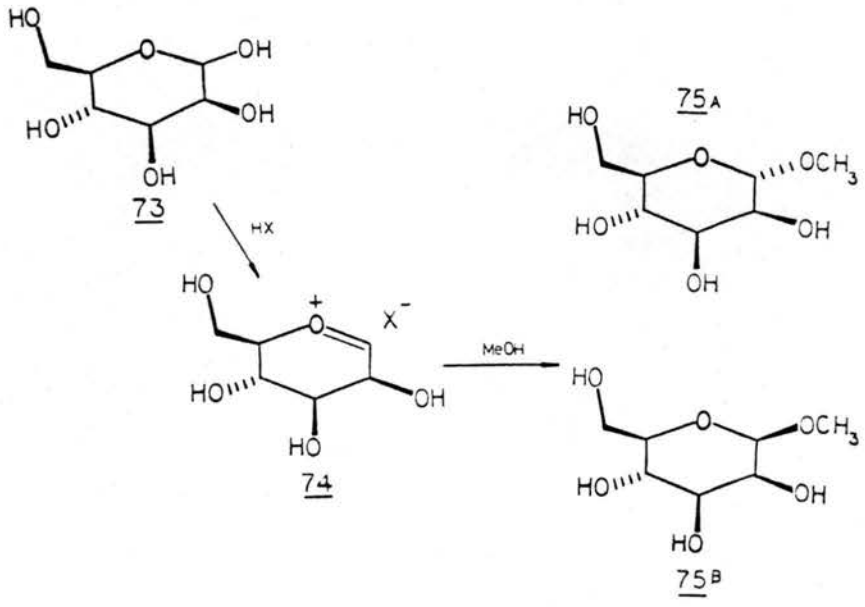
SCHEME 20

directly. The interesting relationship between the configuration of the anomeric center of the starting acetal and the resulting stereochemistry of the anomeric center in the substitution products reveal a unique role played by both the ring oxygen and the nature of the aglycone. A quick summary of some mechanistic studies on O-glycosidation is useful in understanding the stereoselectivity of C-glycosidations which must surely employ a similar mechanism involving a special role by the ring heteroatom.

The first successful glycoside was prepared by Michael in 1879, by the action of the potassium salt of phenol on the tetracetyl-α-D-glycopyranosyl chloride (**71**).[21] The phenyl glycoside (**72**) was produced in the beta configuration with simultaneous loss of the protecting groups (Scheme 21). The Fischer glycoside synthesis,[22] described in 1893, reported the condensation of sugars such as glucose and arabinose with methanol and ethanol under the influence of a Bronsted acid (Scheme 22). A mixture of glycosides, or anomers, is produced. This is evidence of participation of the ring oxygen giving an oxonium intermediate of type **74**. Attack of the alcohol from the α, or β face gives rise to the two diastereomeric glycosides (**75a, b**) known as anomers. It was soon confirmed under these acidic, thermodynamic conditions that one anomer was often greatly favored. This "anomeric effect"[25a] reflects a free energy difference in the ground state of these glycosides and often plays an important role especially in

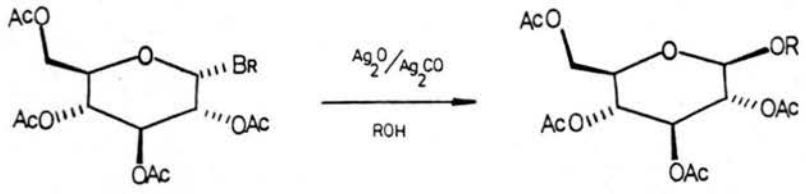


SCHEME 21



SCHEME 22

the hexopyranose sugars. In 1901 the Koenigs-Knorr reaction, in which tetra-O-acetyl-β-D-glycopyranosides (77) could be prepared by silver(I) salt activation of the α-bromide (76)in the presence of an alcohol[23] (Scheme 23) was



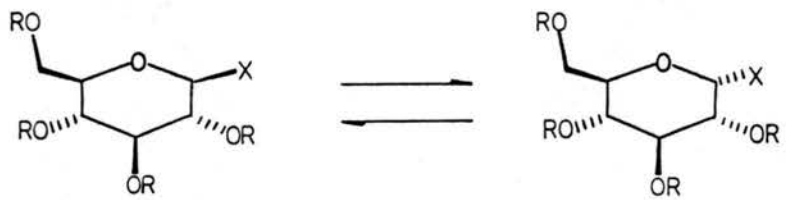
76 77

SCHEME 23

reported. Although a clean inversion of the anomeric center as in the Michael reaction was observed, a mechanism which involves heterolytic cleavage assisted by a lone pair of the ring oxygen has been invoked. Deslongchamps has shown the importance of p-orbital to bond orientation in cleavage of these type bonds through stabilization of the transition state.[24] This participation as stated by Lemieux "is clearly involved in the first stage of all displacement reactions at the anomeric center of sugar structures".[25b] Most O-glycosidations may be explained using the following two criteria: (1) The anomeric effect; a significant difference in free energies are often

observed between the two anomers dependent on the nature of the aglycone. (2) The Rhind-Tutt and Vernon mechanism which requires only slight modification to account for the most recent complex glycoside synthesis.[27]

The term "anomeric effect"[26] describes a conformational effect that is reflected in the observed position of the equilibrium in Scheme 24. Depending on the electronic nature of X the equilibrium can favor, dramatically in some cases, structure (**78**) or (**79**). That is, the consequences of the ring oxygen having lone pairs in an sp^3 disposition will dictate the configuration of an easily epimerizable center in the low energy conformer. This has been explained in two ways: (1) It can be argued that **78** is destabilized due to unfavorable dipole



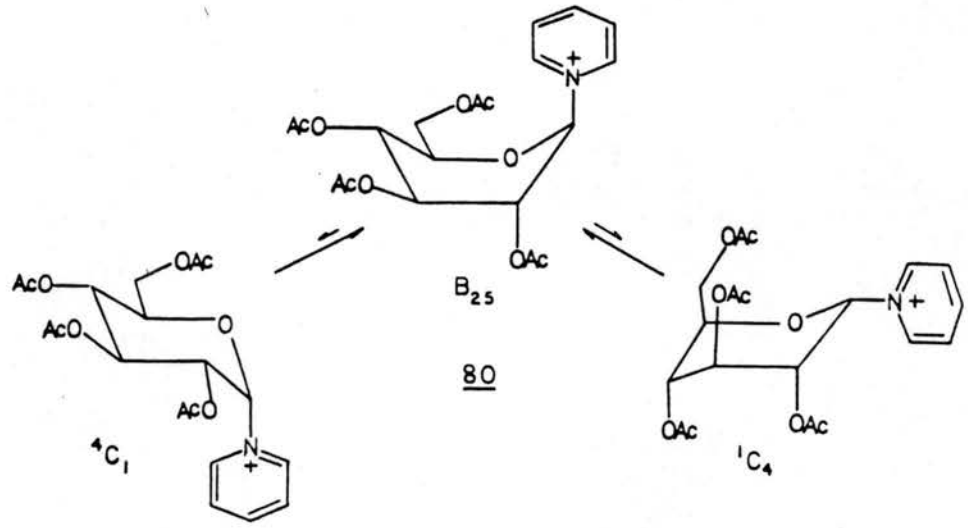
78 79

SCHEME 24

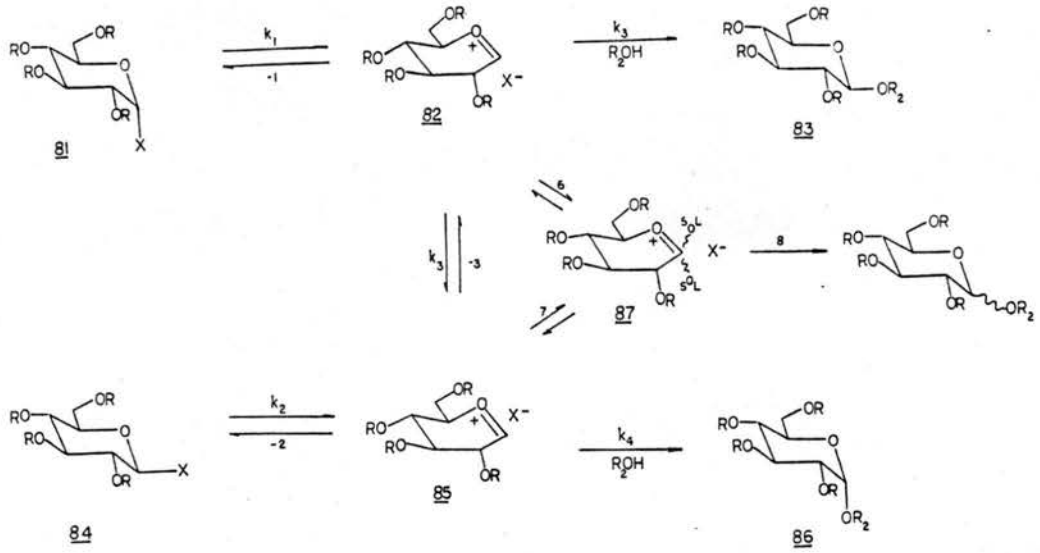
interaction with the ring oxygen. 2) the alternative is stabilization of **79** by p-orbital bond overlap available only to structure 79. Where X = Cl, an electronegative halogen, there is an experimentally observed 3 kcal difference between the α- and β-anomers of tetra-O-acetyl-D-glycopyranosyl chloride. The α-halopyranosides are known to be much more stable and this is reflected in the 100:1 ratio observed favoring the α-anomer mentioned above. Similar mixtures, found to favor the α-anomer, are known in methylglycosides produced under thermodynamic conditions.[3]

Anomalous behavior is seen for aglycones bearing a formal positive charge. Pyranose sugar structures containing a quarternized nitrogen or other oxidized heteroatom (S, P, O) aglycone are known to be more stable in the β-configuration. The equilibrium in Scheme 24 favors structure **78** for these species and has been termed the "reverse anomeric effect". A related phenomenon is the observation that the unstable α-tetra-O-acetyl-glycosyl-pyridinium bromide (**80**) exists in the B_{25} conformation. The apparent instability of the quarternized nitrogen anomeric substitutent in the axial position results in adoption of the boat conformer, confirmed by x-ray and NMR spectrum (Scheme 25).

A modified Rind-Tutt and Vernon reaction scheme is detailed in Scheme 26. The facile preparation of β-glycosides from α-haloses may result from the alcohol reacting directly with the α-tight ion pair (**82**) to give



SCHEME 25



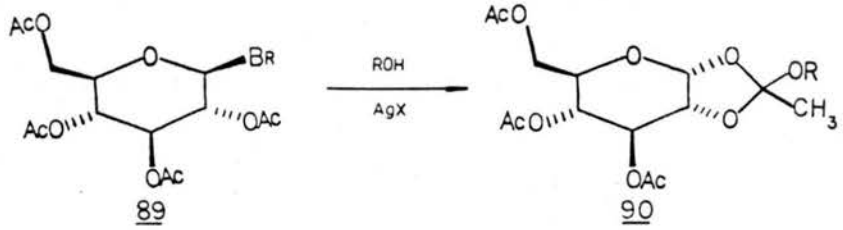
MECHANISM OF GYCOSIDATION (RHIND-TUTT AND VERNON[26] MODIFIED)[27]

SCHEME 26

the β-glycosides (83). A dramatic reversal of this selectivity has been observed by the addition of excess halide ion.[28] This has been explained as catalysis by halide ion to convert 82 to 85 with inversion. The more reactive β-halide ion pair reacts to give the α-glycoside. It is well known that tight ion pairs can react with complete inversion. Clearly a subtle relationship exists between the rate of glycosidation (k_2 or k_5) and the rate of ion pair equilibration (k_3) for α-selectivity from an α-precursor to be understood. This particular example has been explained on the basis of the higher ground state of the less stable β-halose or ion pair. If k_3 is rapid enough relative to k_2 then only α-product is observed even though the concentration of β-ion pair is low. In silver assisted glycosidations the halide complex ion pair may react to give a new species (ion pair) which may show a configurational preference due to the anomeric effect.[29] It is known that incubation of the α-halose with certain silver salts may give rise to reactive perchlorate or triflate esters in the case of $AgClO_4$ and AgOTf.[29] Schuerch has shown that incubation of tetra-O-benzyl-α-D-glycopyranosyl bromide with silver triflate in CH_2Cl_2 followed by addition of 1.3 moles of methanol gives exclusive β-methyl glycoside.[29] This incubation could be envisioned to produce the triflate ion pairs which could show a strong preference for the α-triflate due to the strong electronegative character of the triflate. This

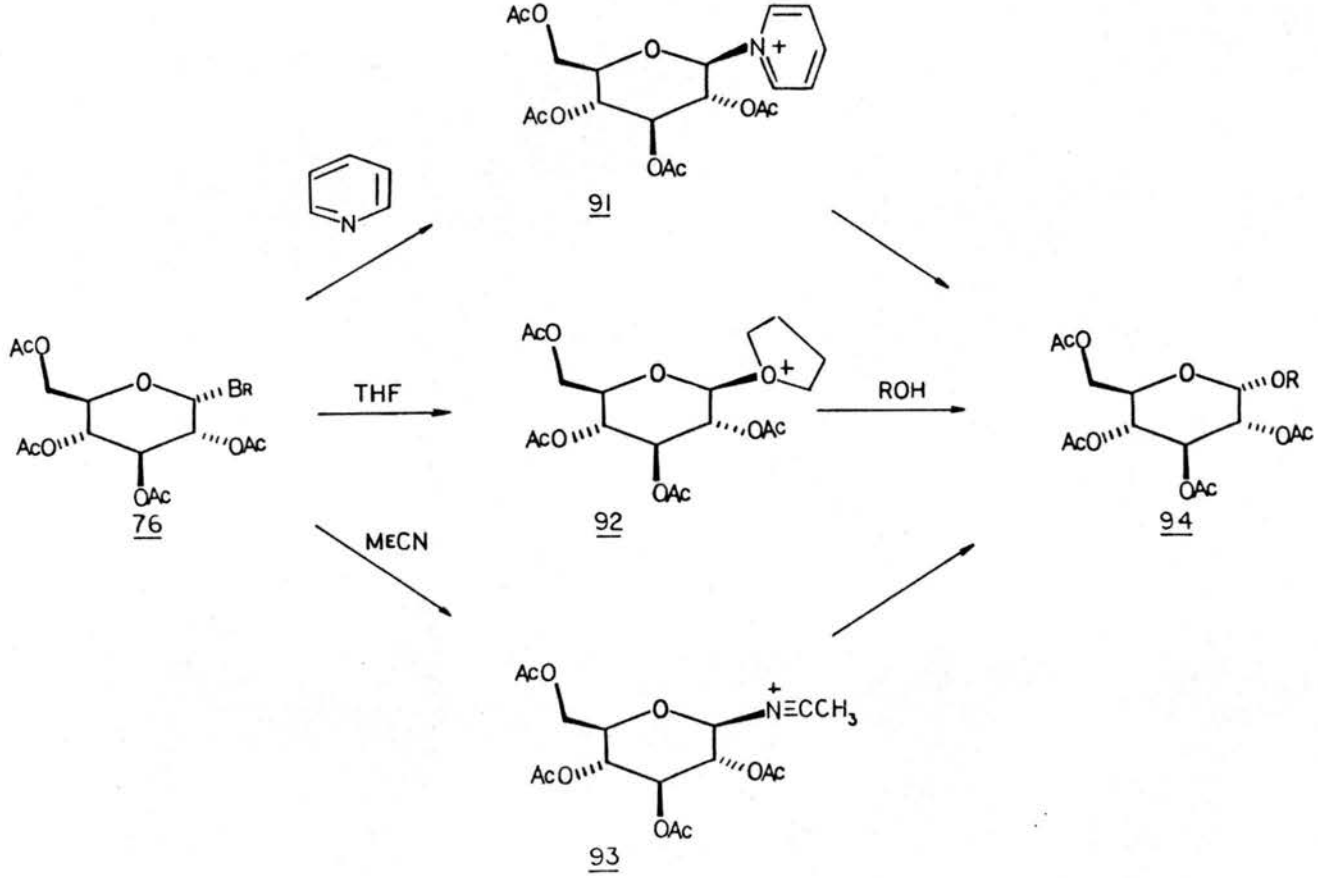
α-triflate (or α-ion pair) could react with inversion to give the observed β-glycoside.

Other important considerations in the synthesis of pyranosyl-glycosides are neighboring group participation and solvent participation. Early attempts to produce cis-glycosides from the usually unstable β-halose (89) often led to exclusive unwanted orthoester formation (90) (Scheme 27) in acyl-protected sugars.[30] However, cis-glycosides of



SCHEME 27

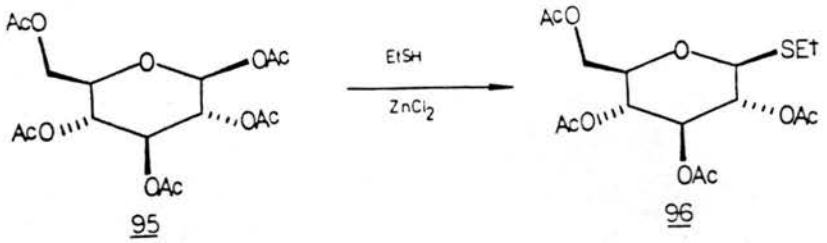
this type have been prepared from the α-halose by intervention of solvent. In the presence of pyridine, β-pyridinium salts have been prepared and characterized by NMR.[31a] These compounds possessing an activated aglycone) stable in the β-configuration due to the reverse anomeric effect give rise to α-glycosides by inversion when treated with alcohol (Scheme 28). α-glycosides have also been prepared from the α-haloses in the presence of THF.[31b] The



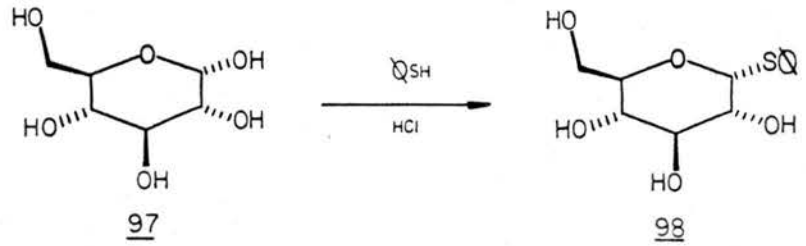
SCHEME 28

presumed intermediate (92) would be expected to be more stable in the β-configuration and give the α-glycoside once treated with alcohol (Scheme 28). When acetonitrile is used as a solvent the same α-selectivity is observed in the product. This can be attributed to a β-nitrilium ion (93) which again could be observed by NMR.[31b] The reverse-anomeric effect favors this β-configuration and inversion results in α-product (94).

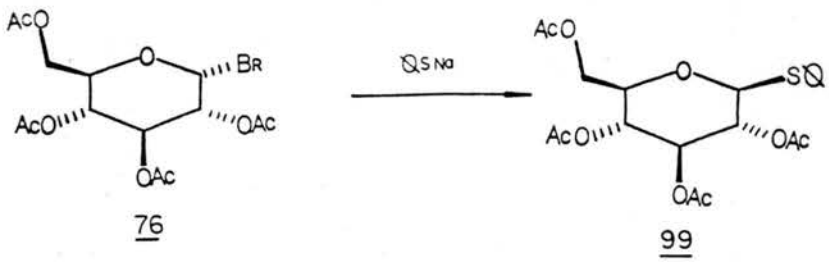
Another class of sugar derivatives that have been used for this type of glycosidation are the 1-thiosugar derivatives. These have been known since 1825 when the first thio-glycosides were isolated from white mustard seed.[32] 1-thioglycosides of glucose have been prepared from the Lewis acid treatment of the β-penta-acetate in the presence of the thiol[33a] (Scheme 29). The resulting β-configuration might result from intermediate orthoester formation or by some other type of α-stabilization. It is interesting to note that the α-penta-acetate was unreactive under these conditions. The α-phenylthio derivative of unprotected glucose was obtained under thermodynamic conditions[33b] and this is what we would expect due to the anomeric effect, albeit small for sulfur (Scheme 30). In protected glucose derivatives the β-thioacetals have been obtained by treatment of the α-halo compound with thiolate[33c] (Scheme 31). These thio-aglycones can be readily activated by metal salts, under conditions similar to the Koenigs-Knorr reactions, and used for efficient



SCHEME 29



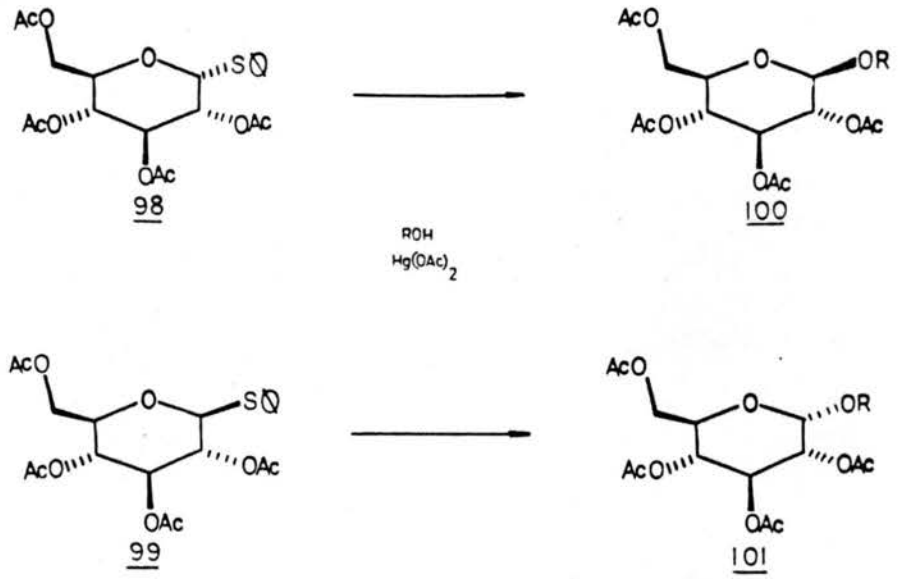
SCHEME 30



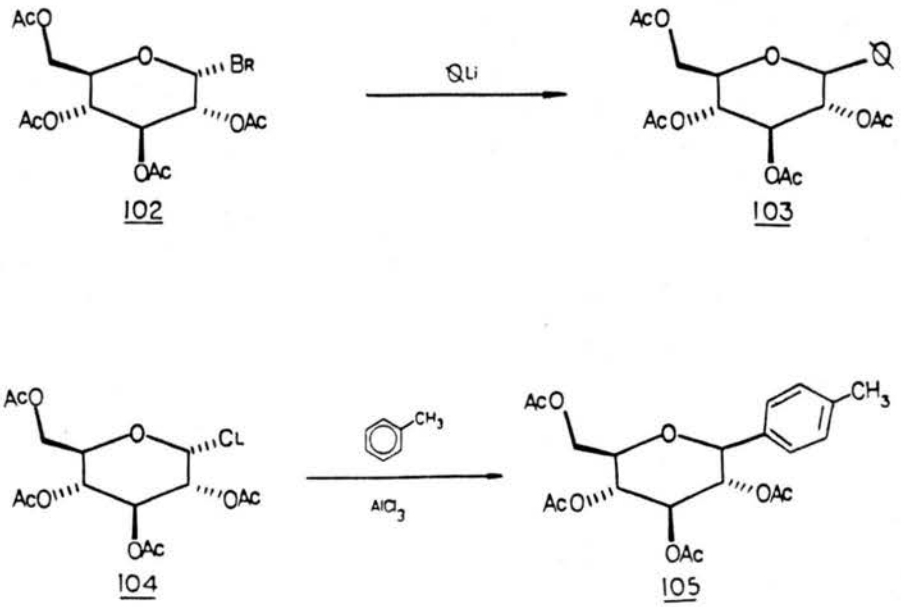
SCHEME 31

glycosidations. The report of Ferrier is particularly intriguing.[33d] Ferrier stereospecifically prepared the desired configuration of O-glycoside by using the opposite configuration of starting 1-thio derivative. The mercury(II) salt activation of either anomer by a "push pull" mechanism leading to inversion of the ion pair or complex is represented in Scheme 32. Similar reports by Hanessian[33e] and Mukaiyama[33f] show a general α-selectivity in metal activated glycosidations of 1-thiosugars. Williams accomplished the glycosidation of erythromycin, in the Woodward total synthesis using 1-thiol derivatives and soft thiophillic metals.[33g] The reports reveal how these stable thio-acetals may be readily activated toward glycosidations using metals or bromide/NBS.

We were interested to see how these thioacetals, in particular the 2'-thiopyridyl derivatives, used by Williams and Woodward, could be activated toward C-glycosidation. It should be pointed out that our studies would be primarily synthetic in objective. Mechanistic questions concerning the relationship of the specific nucleophile to anomeric selectivity under defined reaction conditions would presumably result in an empirically derived lexicon of useful nucleophiles that produced the required C-glycosides with predictable stereochemistry. Many interesting mechanistic questions could not be addressed. A final quick review of the existing methods of



SCHEME 32

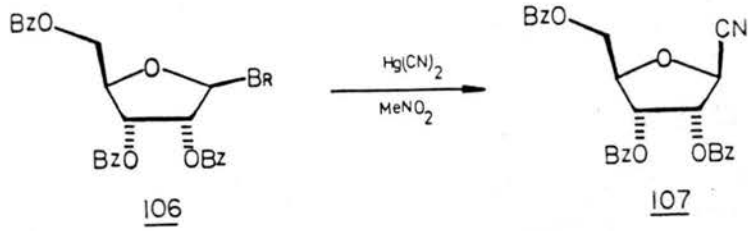


SCHEME 33

glycosidation will be given before discussion of our results.

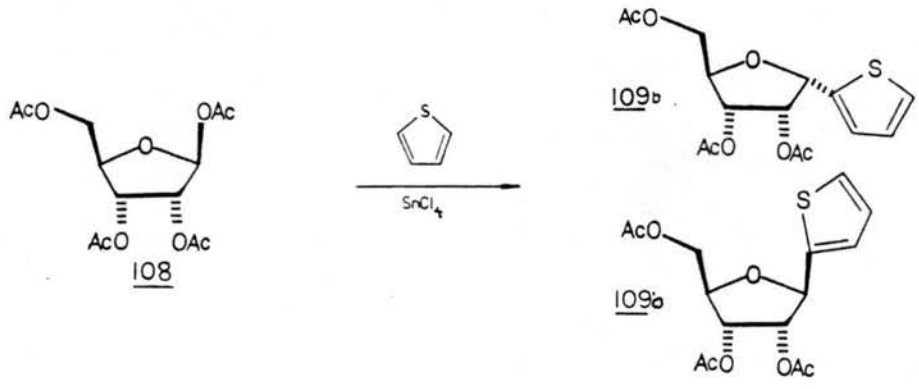
Early C-glycosidations, primarily by Bonner,[34a,b] using organometallic reagents with protected pyranosyl halides led to successful carbon-carbon bond formation, but in low yield (Scheme 33). Bonner also discovered that Friedel-Crafts type reaction could be carried out on the reactive sugars using Lewis acid, but again in low yields[34b] (Scheme 33).

The first highly successful C-glycosidation was reported by Farkas.[35a] He prepared the crystalline β-cyano derivative (**107**) in 88% yield from the protected bromide (**106**) (Scheme 34). The first new generation C-glycosidation was performed by Ohrhi in 1972 by Lewis acid treatment of a β-tetra-acetyl-ribose derivative (**108**) in the presence of aromatic compounds to give C-glycosidation by an electrophillic aromatic substitution pathway.[35b] However, these reactions led to a 1:1 mixture of compounds (**109a,b**) (Scheme 35). In 1973, Hanessian reported a new and powerful method for C-glycosidation[35c]; carbonyl compounds, as their silyl-enol ethers, would react smoothly under Lewis acid catalysis with reactive sugar derivatives (Scheme 36) to furnish the C-glycosides. He also revealed that unactivated olefins such as hexene would react under these conditions to give an unidentified mixture of anomers in 75% yield (**113a, b**). The surprising stereochemical results of the carbonyl couplings afford a β-product from a



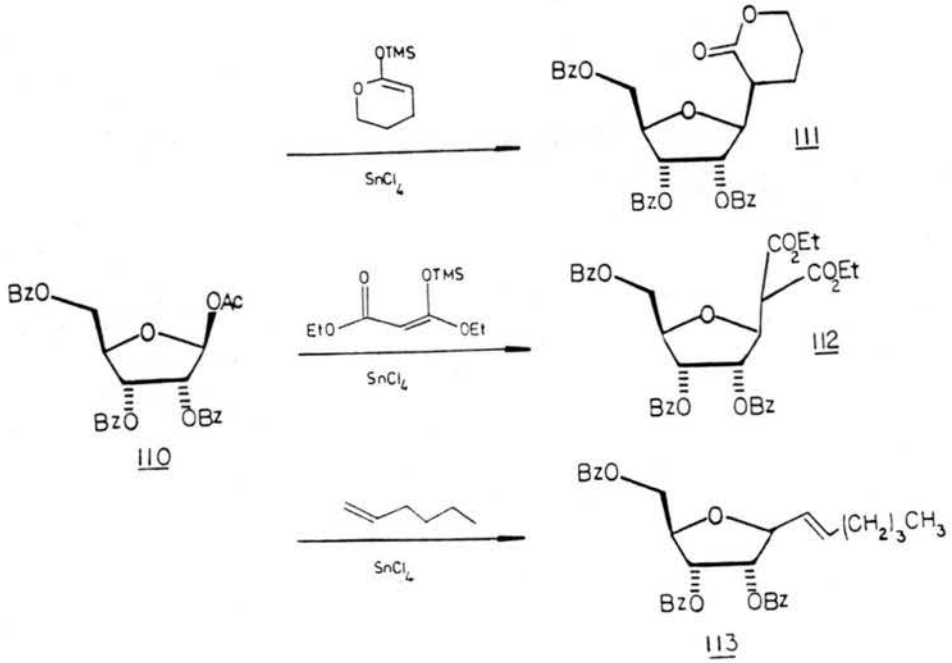
106 107

SCHEME 34



108 109b 109a

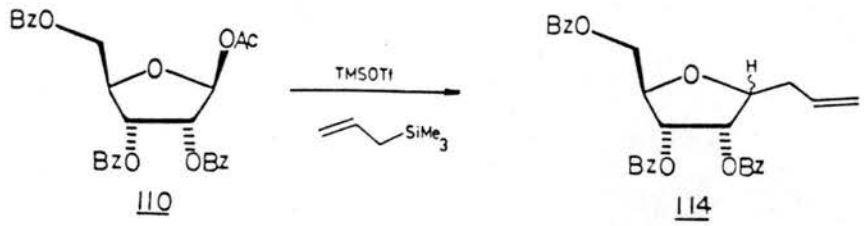
SCHEME 35



110 111 112 113

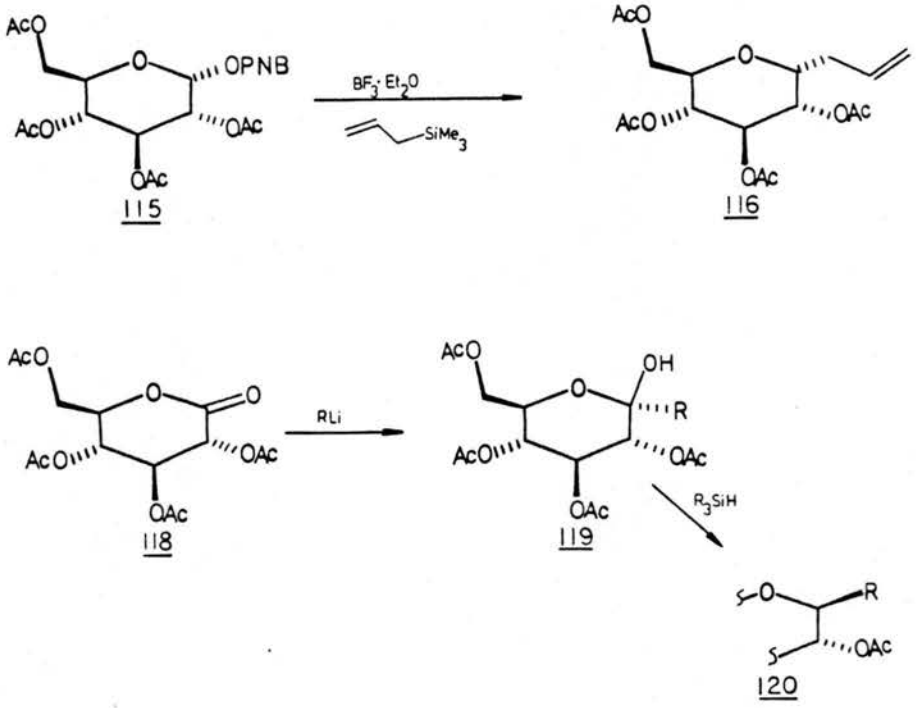
SCHEME 36

β-acetate. This means that the immediate precursor to this product could not be a β-ion pair formed by complexation with the Lewis acid. Also interesting is the desirable complete β-selectivity; no ortho ester formation is observed. However, orthoester or an α-stabilized acetoxyonium ion could be responsible for the β-selectivity. A similar selectivity with silyl-enol ethers and a ribosyl-β-acetate was reported by Inoue.[35d] Another nucleophilic carbon species found to add readily to these intermediates is the allytrimethyl silane reagent[36]. Two groups simultaneously showed the nucleophilicity of these silyl compounds under Lewis acid conditions (Scheme 35).[36a,b] It was soon reported by Kishi[17d] that the allyl silane would readily add to pyranose derivatives obtained by Lewis acid activation of the α-para-nitrobenzoate derivatives (Scheme 36). These reactions were shown to give high α-selectivity from α-precursors. Kishi prepared β-C-glycosides by addition of organometallics to the lactone (118). The resulting ketal was converted to the β-product by delivery of the silyl-hydride in the same α-manner to give 120. In related pyranose series Schmidt[17e] has reported the reaction of both TMS-carbonyl compounds and electron-rich aromatics with activated trichloro-acetimidate precursors and also observed high α-selectivity of carbon addition. Similar reactivity has also been observed by Frasier-Ried in extended oxocarbonium ions obtained by similar Lewis acid treatment of the



110 114

SCHEME 37

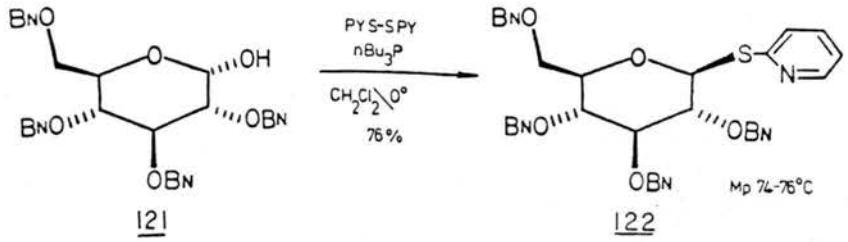


115 116 118 119 120

SCHEME 38

tri-acetyl-glucal.[37] Other C-glycosidation methods involving one electron radical couplings have been reported but will not be discussed herein.[38]

There had been no reports of activation of 1-thio sugar derivatives for C-glycosidation. We wanted to investigate the use of these compounds for carbon bond formation under thiophilic metal activation. Ideally we wanted to prepare both anomers of a 1-thiopyridyl protected glucose. If mild conditions were found for coupling we might be able to prepare either anomer of a C-glycoside from the opposite configuration thioacetal precursor; similar to the "push pull" mechanism successfully employed by Ferrier in simple O-glycosidations. The method of Williams, Woodward et al., in preparing these thioacetal derivatives seemed operationally the simplest. In this method, an Arbuzof type reaction produces the thioacetal by treatment of the hemiacetal in the presence of the disulfide with tri-n-butylphosphine (Scheme 37). The commercially available crystalline tetra-O-benzyl-α-D-glucose (121) was treated at 0°C in methylene chloride with a slight excess of disulfide and tri-n-Butyl-phosphine; a single product rapidly formed. Silica gel column chromatography yielded a single crystalline β-isomer of the thiopyridyl acetal (122) (Scheme 39). This single β-isomer must be formed from the initial α-ion pair resulting from phosphine oxide formation. Although this ion-pair might be more stable in the β-configuration due to the reverse-anomeric effect, the reactive α-species

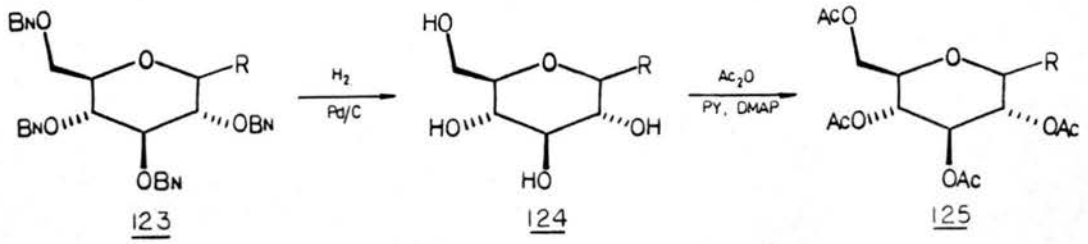


SCHEME 39

is intercepted by the very nucleophilic thiolate giving the β-product. Nominal attempts to obtain α-thioacetal by epimerization of 122 using $BF_3 \cdot Et_2O$, or H^+ failed. Based on the earlier reports of successful C-glycosidation by electrophilic aromatic substitution (especially that of Schmidt,[17e]) we investigated reaction of 122 in solution in the presence of electron rich aromatic species. It was found that both trimethyoxybenzene and dimethyoxybenzene underwent smooth reaction with 122 when treated with silver(I) triflate in methylene chloride at room temperature. At low dilution a single compound was obtained in each case. Anomeric composition was determined by H_1H_2 spin-spin coupling constants. The use of NMR for this type of physical analysis, based on the Karplus equation, could be readily applied to the low energy conformers of these pyranose derivatives. Due to the nature of the tetrabenzyl glucose derivatives the anomeric proton resonance

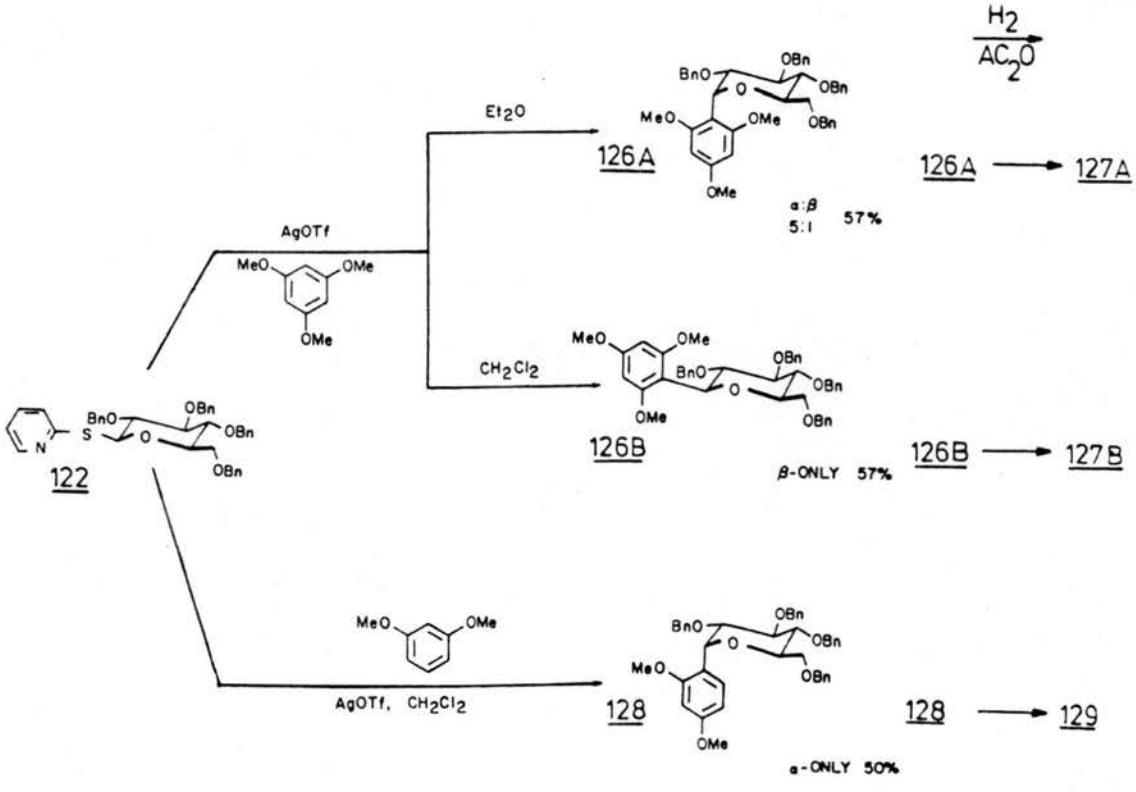
was often obscured by the four-sets of benzylic protons in the NMR spectrum. This required a benzylation/acetylation manipulation on the coupled products. Hydrogenation of the benzyl groups to give the very polar tetraols, followed by acetylation using pyridine/AC_2O/DMAP gave the tetra-acetates. At high field these compounds generally displayed a near first order proton spectrum (Scheme 40). Homode-coupling at 360 MHz then provided JH_1H_2 values that allowed anomeric assignment. Table 3 shows the results obtained from the reaction of **122** with dimethyoxy and trimethyox-benzene.

The α-selectivity observed in the dimethoxybenzene reaction can be explained by a simple inversion of the β-ion pair obtained by metal complexation of the sulfur or nitrogen of the β-thiopyridyl ligand. An intermediate of this type having an activated substitutent in the equitorial position should be stabilized by the powerful reverse-anomeric effect exhibited by such oxidized heteroatom aglycones. The observed α-selectivity from a β-thioacetal are consistent with the mercury(II) salt activations reported by Ferrier. In the non-participating solvent dichloromethane, it seems unlikely that the β-thio-metal complex could be transformed to an α-triflate which then equilibrates to give an unfavored β-triflate as a reactive species. The trimethyoxybenzene exhibits anomalus β-selectivity. This product could be envisioned to result from inversion of an α-triflate. This would require that



SCHEME 40

TABLE 3



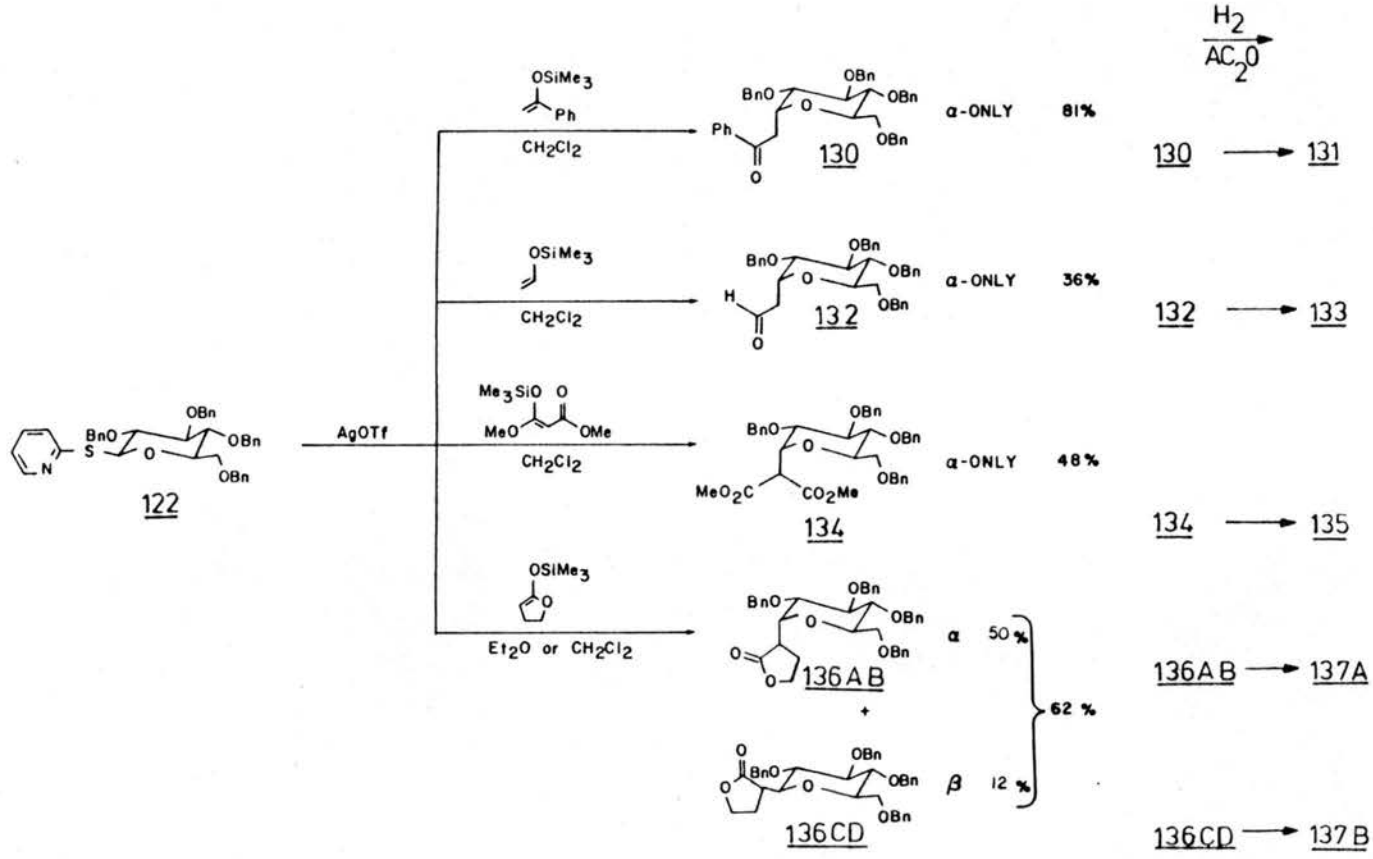
the trimethyoxybenzene be a less reactive nucleophile than dimethoxybenzene. This would allow the β-metal-thio complex to be displaced by the triflate anion; resulting in the α-triflate as suggested by Schuerch.[29] Replacement of methylene chloride by diethyl ether allows solvent participation. This could result from displacement of the metal-thio complex by ether and subsequent anomerization or by inversion of an α-triflate; in both cases a β-dioxonium ion would be produced which would favor the β- or equitorial position due to the reverse anomeric effect. The alternative, of course, is that trimethoxybenzene is a more reactive nucleophile than dimethyoxybenzene. It could intercept a rapidly formed α-triflate giving the observed β-product. The reaction performed in ether would give an α-product from a double inversion. This seems unlikely since the β-selectivity was found to be the highest at low concentrations; it seems feasible that at higher concentrations of nucleophile there may be more direct inversion of the initially formed β-metalthio complex. This is very consistent with the Rind-Tutt and Vernon mechanism.

We were quite pleased with the activation of this 1-thiolpyridyl derivative by silver triflate and the subsequent facile carbon bond forming reaction. Examining other carbon nucleophiles and the important stereoselectivities of these couplings remained to be elucidated.

Treatment of 122 in methylene chloride with trimethylallylsilane resulted in no reaction. A sufficient nucleophile concentration may not have been obtained. One reported coupling of this type required elevated temperature and high concentration.[36a] The recovery of starting material (122) was unusual and seemed to suggest complexation of the Lewis acid to the allysilane. Starting material was often converted to an internal product in the absence of an effective nucleophile.

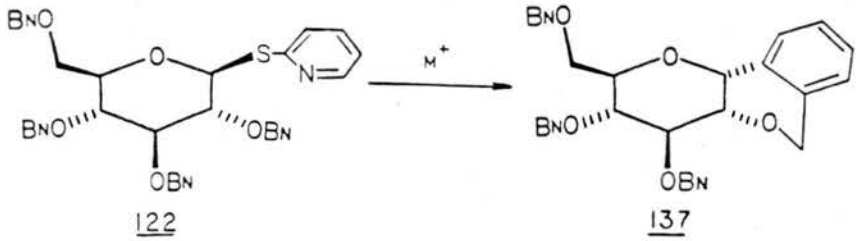
The use of TMS enol ethers as nucleophiles was also investigated. Several TMS-enol-ethers were prepared and their reactions with 122 under standard conditions are summarized in Table 4. These reactions proved quite general with regard to the type of carbonyl compound used, ester, ketone, aldehyde, etc. The α:β ratios were again determined on the corresponding tetra acetates after hydrogenation and acylation of the coupled products. The yields and ratios reflect optimum yields of isolated purified materials after silica gel chromatography. The only β-product observed is a minor component of the butyrolactone coupling (135a). If a similar argument may be used, the general α-selectivity reflects direct displacement of the β-thiometal complex, or ion pair. Again the anomalous β-behavior could result from a less reactive nucleophile allowing some equilibration of the reactive intermediate, presumably to the α-triflate. Extensive solvent studies were conducted and no significant difference in the α:β ratio of this reaction

TABLE 4


H2
AC2O
OSiMe3
Ph
CH2Cl2
130
α-ONLY
81%
130 → 131
OSiMe3
CH2Cl2
132
α-ONLY
36%
132 → 133
122
AgOTf
Me3SiO O
MeO OMe
CH2Cl2
134
α-ONLY
48%
134 → 135
OSiMe3
Et2O or CH2Cl2
136AB
α 50%
+
136CD
β 12%
62 %
136AB → 137A
136CD → 137B

could be found between cold diethylether and refluxing benzene as reaction solvent.

Compound 122 appears to be a very convenient precursor for α-C-glycosidations. The stability of this crystalline compound in the absence of thiophillic metal cations is highly desirable. The reactive intermediate produced by the metal activation of 122 and mechanism of its formation are not entirely clear. A reasonable explanation for the observed α selectivity seems to be an inversion of the activated β-thio complex by the nucleophile. A push pull type mechanism observed by Ferrier seems reasonable. Attempted incubation of this complex led only to the above mentioned "internal product". This internal product apparently arises from intramolecular Friedel-Crafts reaction of the C-2 benzl protecting group and reactive oxonium ion (Scheme 41). This same compound was observed in attempted activation by other thiophillic metals. The use of $Cu(OTf)_2$, $Hg(ClO_4)$, or $Pb(ClO_4)_2$) led to slow reaction and very little intermolecular coupling. Although



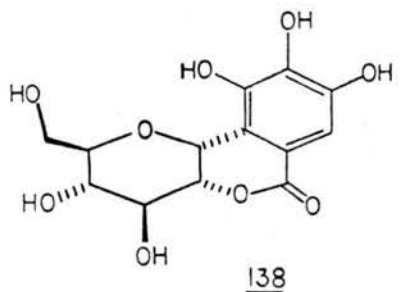
122 137

SCHEME 41

activation of the thiopyridyl residue was observed, only significant amounts of **138** or hydrolysis product were observed after prolonged reaction times. THF and acetonitrile also proved ineffective solvents for these reactions. Formation of compound **138** was very facile in THF even in the presence of reactive nucleophiles. In general it is known that selective glycosidation occurs more efficiently in non-polar solvents! It is important to realize, however, that the stereoselective C-glycosidations of Kishi and others exhibit this same α-selectivity but from an α-precursor. In these cases a rapid equilibrium must be involved to establish a reactive β-intermediate that can give the α-product. An activated carbonyl type aglycone resulting from lewis acid complexation of Kishi's starting p-nitro benzoate would be expected to be more stable in the β or equitorial position. The equilibrium to produce this β-species from the α-complex of the starting material must be very facile relative to glycosidation. A solvent separated oxonium ion showing a preference for addition does not seem to adequately explain the extremely high stereoselectivity observed in the case of **122** and related systems. A solvent separated oxonium ion could, however be influenced by secondary orbital interactions which could direct the course of addition. It is possible that the C_6 oxygen could participate in stabilization of the oxonium ion and favor α-addition. Secondary orbital interactions have been used to explain asymmetric induction

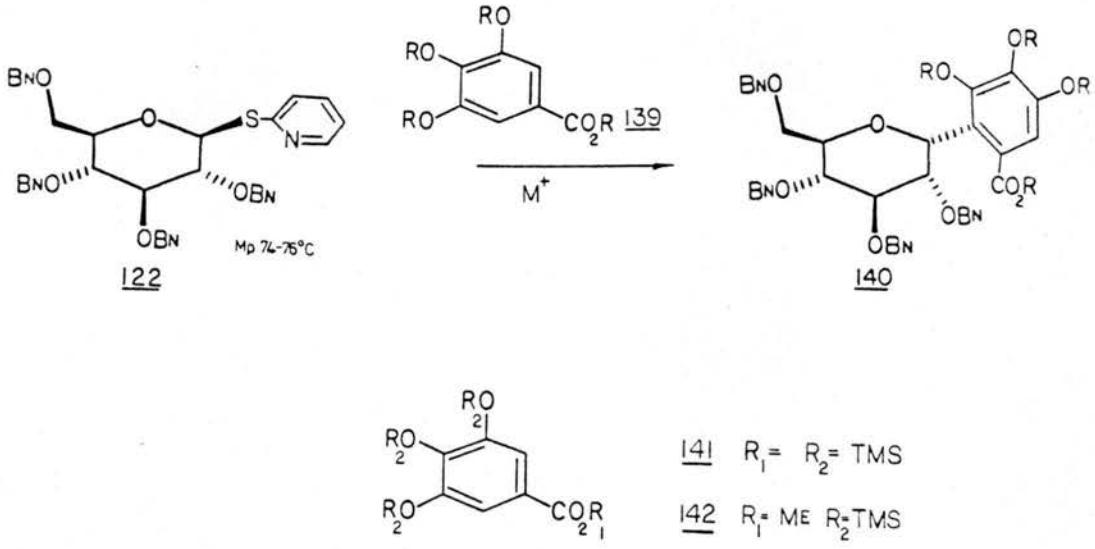
of nucleophilic additions to other oxo-carbonium systems.[59] The efficient activation and α-selective alkylation of this stable 1-thioglucose derivative (122) under mild conditions at room temperature makes this methodology useful in preparative synthetic organic chemistry.

The plant C-glycosides which contain an aromatic ring attached to a sugar residue by a carbon-carbon bond seemed a very natural target for the electrophilic aromatic substitution reactions described above. The recent report of Norbergenin (138) was of special interest.[39] A

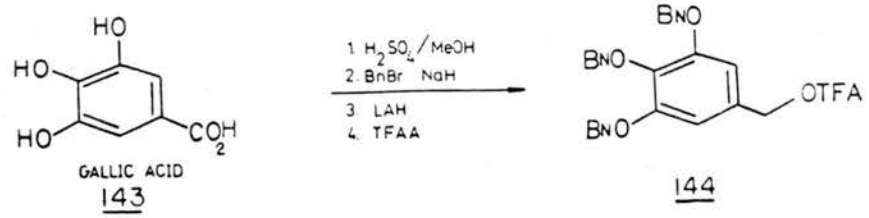


138

successful coupling with a gallic acid derivative (139) and compound 122 could in theory produce a protected form of (138) in one step (Scheme 42). Deprotection of the adduct with the correct α-configuration should lead to spontaneous lactonization yielding Norbergenin (138). The first compound we prepared was the per-O-TMS gallic acid derivative (141). No coupling reaction of 141 and 122 was observed under standard conditions. The corresponding methyl ester 142 was prepared and no coupling reaction



SCHEME 42



SCHEME 43

could be induced with **122** in methylenechloride using silver triflate. The proton NMR spectrum of **141** and **142** exhibited the aromatic proton resonance at approximately 7.2 ppm a normal region for the chemical shift of aromatic protons. However, we had noted the appearance of trimethoxy benzene aromatic protons in the ^{1}H NMR spectrum at approximately 6.5 ppm indicating a much more electron rich system. The gallic acid ester does have an electron withdrawing effect on the aromatic ring and this inductive effect apparently prevents facile electrophilic aromatic substitution with our electrophile. Thus a change in oxidation state of the ester carbon seemed to be a promising solution, therefore compound **144** was prepared.* This compound was prepared from gallic acid as described in Scheme 43. The aromatic protons of **144** had now moved upfield to approximately 6.8 ppm indicating a more electron rich system. Reaction of **144** and **122** under standard conditions gave a new coupled compound. The ^{1}H NMR spectrum of the hepta-benzyl coupled product was very difficult to interpret. The IR spectrum revealed the loss of the TFA protecting group but showed no resulting hydroxyl absorption. This confusing spectral data made a structural assignment unfeasible. These studies demonstrated the need for a relatively electron rich aromatic compound for a successful Friedel-Crafts

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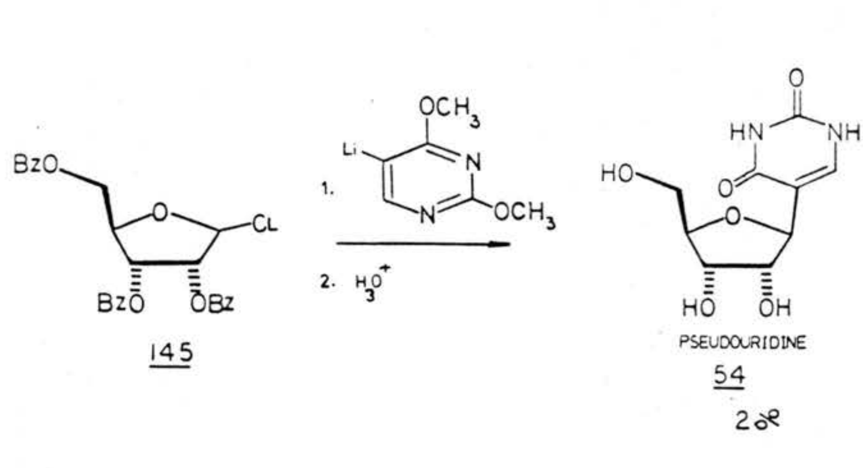
* These compounds were prepared and their coupling reactions were studied by C-440 student Jay Snowroute

reaction. The loss of an undergraduate assistant combined with the frustrating problem of the oxidation state of the external carbon terminated efforts to synthesize Norbergenin.

We were eager to investigate how these 1-thiopyridyl derivatives could be applied to the ribose series; since these would be such obvious precursors to the important C-nucleosides. The concept of a one-step coupling reaction leading to an optically active C-nucleoside was very attractive. Shapiro's[40] reported two-step synthesis of pseudouridine from the ribosyl chloride (145) and the lithio compound (146) proceeded, however, in low yield (Scheme 42). Several reviews on the construction of these heterocyclic-ribosyl compounds are available.[16]

The desired approach obviously would involve, if not a direct coupling, the coupling of a highly functionalized fragment that could rapidly be transformed to the desired heterocycle. We hoped the metal activation of these

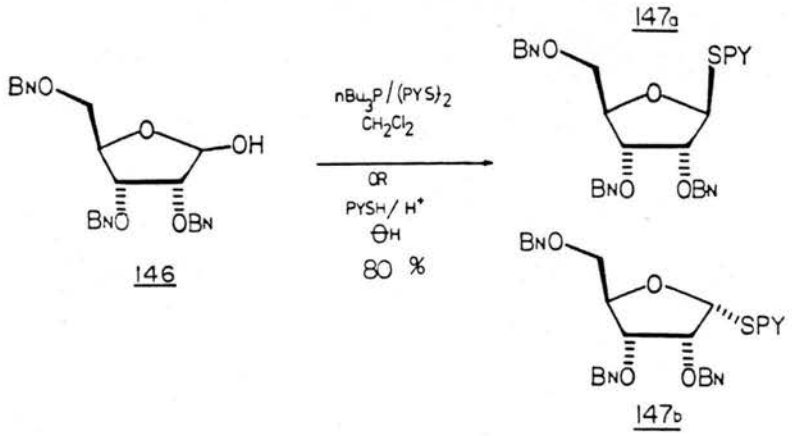


SCHEME 44

1-thioribosyl compounds would be efficient and give intermediates that could readily couple with desired heterocyclic precursors.

The first ribose compound that was prepared was the corresponding tri-O-benzyl-D-ribose (146) (Scheme 45). This reaction produced a diastereomeric mixture of thioacetals in roughly equal amounts of each anomer. (147A,B).

When 146 was treated with tri-n-butylphosphine in the presence of the disulfide, an undesired yellow side product prevented chromatographic isolation of the desired thioacetals on a preparative scale. Both anomers could be produced on a large scale and easily separated by column chromatography when prepared by the simple acid catalyzed acetal exchange in refluxing benzene with azeotropic removal of water. The β-isomer proved to be a crystalline



SCHEME 45

solid and due to ease of handling was used for most coupling reactions. This seemed justified since none of the ribosyl-thioacetal substrates examined displayed a sterochemical dependence on the anomeric configuration of starting material! From a mechanistic point of view it seemed a luxury to have both anomers since only a single β-isomer had been accessible in the tetra-O-benzylglucose derivative. The independence of configuration of the starting material to the final product stereochemistry in this riboysl series seemed to confirm a dissociative mechanism, which must involve heterolytic cleavage of the leaving group assisted by the ring oxygen before attack by the nucleophile.

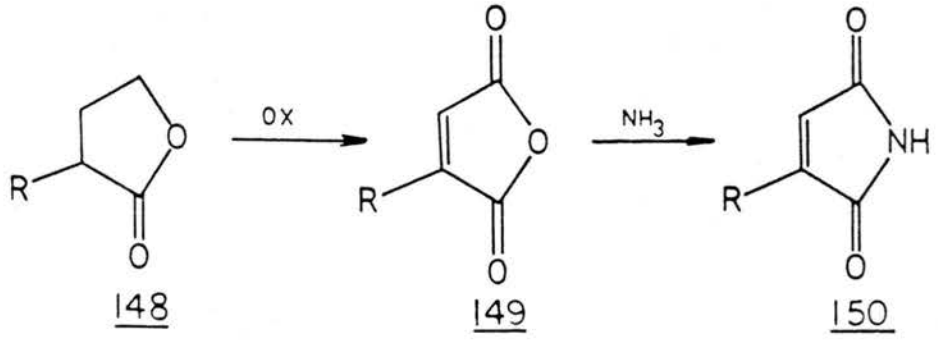
An immediate problem inherent in these five-membered rings is the assignment of the anomeric configuration of coupled derivatives. The type of physical analysis based on spin-spin coupling constants obtained from the ^{1}H NMR, are of little value in the absence of a low energy ring conformer. The following comparison criteria have proved useful in determining the α or β anomeric configuration in furanoside-derivatives: 1) H_1 of the α-isomer usually resonates at a higher field.[42a] 2) The H_1H_2 coupling constant is usually smaller, sometimes approximately 0 Hz in the α-isomer.[42b] 3) The β-isomer usually exhibits a less dextrotatory rotation.[43c] When the 2,3-O-isopropylidene derivatives are prepared, the following are empirically known to be significant:[18d] 1) The ^{13}C

resonance of the isopropylidene carbons fall in a distinct narrow range for each anomer. 2) The α-anomer, especially with aromatic substituents cause a large difference in the $\Delta\delta$'s of the methyl signals of the isopropylidene in the ^1H NMR spectrum. 3) Finally, the α-isomers show a JH_3,H_4 value of near zero Hz resulting in H_4 appearing as a pseudo-triplet. The β-isomer having $JH_3H_4 \cong JH_4H_5$ causes H_4 in these compounds to appear as a pseudo-quartet. All of the criteria mentioned above work well when both anomers are in hand for comparison. However, anyone who has worked with these compounds knows how little value these comparison criteria can be when only one anomer is available. When possible the anomeric composition of coupling products in these ribosyl series were assigned by direct comparison to known compounds. Although N.O.E. experiments[42f] have had limited success in anomeric assignments, attempted application to thioacetals of known configuration failed. In the program attempted enhancement by all vicinal protons was observed. This ambiguous data resulted in the omission of N.O.E. for anomeric determination in these compounds.

The target C-nucleosides can be divided into compounds containing a three carbon fragment attached to a ribosyl moiety and those having a four carbon fragment. The three carbon class being represented by oxazinomycin[55] and pseudouridine[54]; examples of the four carbon fragment can be found in showdomycin,[56] pyrazomycine, and the

formycins.[57,58] The strategy for the rapid construction of these compounds is the stereoselective coupling of the entire carbon skeleton in a single step.

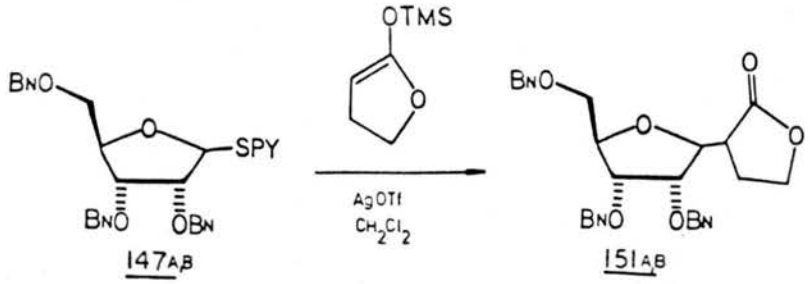
Of the several TMS-enol-ether examined in the glucose series, the ketene silylacetal of butyrolactone seemed well suited for this design. If this unit could be attached with β-stereoselectivity we felt that the butyrolactone moiety could be rapidly transformed into the desired maleimide, as shown in Scheme 46. Oxidation of **148** to



148 149 150

SCHEME 46

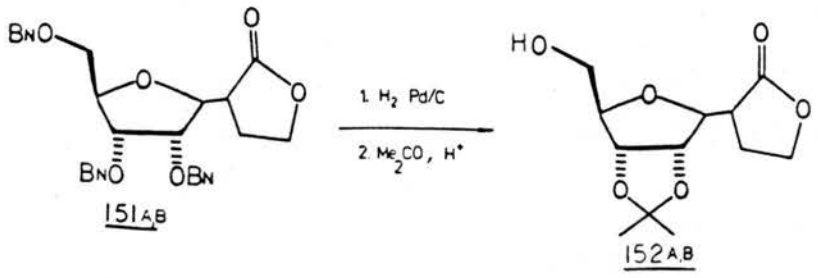
give **149** followed by conversion to the maleimide (**150**) would result in a very efficient construction of the four carbon maleimide from the four carbon lactone. Reactions of **147A** or **147B** with the ketene silylacetal of butyrolactone under conditions identical to those developed for the glucose series, produced in an approximate 1:1 ratio the isomeric lactones (**151A,B**) (Scheme 47) in over 70% purified yield. These two isomeric lactones could be



SCHEME 47

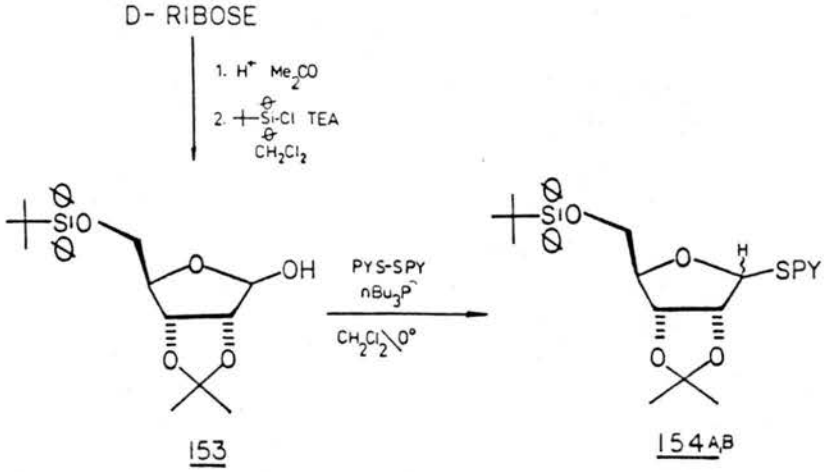
separated by flash chromatography on silica gel. The ^1H NMR and IR spectrum of the compounds indicated the successful nature of this coupling reaction. Identification of the anomeric composition proved very difficult. Treatment of the lower R_f compound **151B** with base converted it efficiently to **151A**, the isomeric higher R_f component. The similar optical rotations of these compound suggested that they might be of the same anomeric configuration and only differed in configuration at the α-lactone carbon. In order to apply the "Moffat rules"[18d] to our compounds they had to be converted to the corresponding 2,3-O-acetonide derivatives. This was accomplished as shown in Scheme 48. When subjected to these conditions separately, each distinct diastereomer (**151A** or **B**) gave a different derivative (**152A** or **B**). That is, the higher R_f benzyl compound reproducibly gave a distinct higher R_f hydroxymethylacetonide **152A**. Similar behavior was observed for the conversion of the lower R_f compound **151B** to **152B**. The acidic conditions employed for this sequence suggested,

however, that some anomerization could occur. Partly in response to this possibility, the following ribose substrate was prepared (Scheme 49). 2,3-O-acetonide formation and selective silyation of the 1° hydroxyl at C_5 afforded the protected ribose **153**. Application of the n-butylphosphine, disulfide reaction to this substrate gave a high yield of a mixture of anomers **154A** and **154B**. The α-compound was favored in an approximate 3:1, α:β ratio. This substrate possessed significant advantages over the tribenzyl compound: 1) mild fluoride treatment would yield compounds that could be directly examined using the Moffat NMR rules. 2) The protecting groups could be removed in the presence of a hydrogenation sensitive unsaturated heterocyclic appendage. 3) Finally this cis-fused bicyclic system might either lend more steric control to the incoming nucleophile or possibly effect the orientation of the reactive intermediate. The 3:1, α:β ratio observed in thioacetal formation seemed to indicate a higher selectivity than had been observed in the analogous reaction of the tribenzyl substrate. The NMR spectra of these interesting compounds (**154A, 154B**) are represented in Figures 1 and 2 and some of the comparison criteria are pointed out in these ^1H spectrum. Reaction of a mixture of anomers (**154A,B**) with the ketene silylacetal of γ-butyrolactone under standard conditions gave again a 1:1 mixture of isomeric compounds in high yield. Chromatographic separation gave useful quantities of each isomer



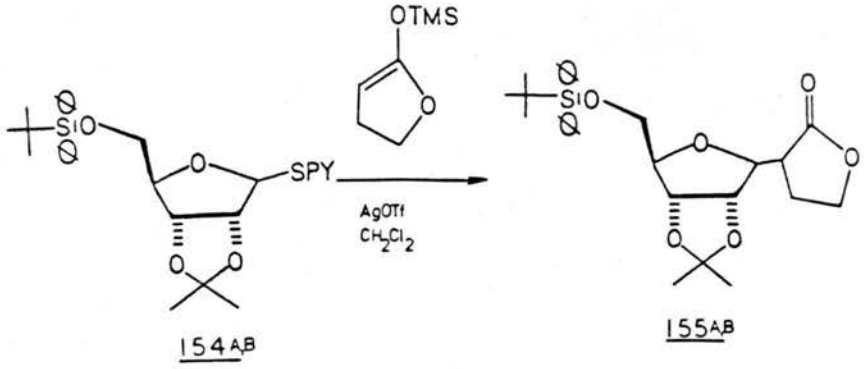
151A,B 152A,B

SCHEME 48



153 154A,B

SCHEME 49



154A,B 155A,B

SCHEME 50

155A and **155B** (Scheme 50). It was found that treatment of each isomer separately with $nBu_4NF \cdot 3H_2O$ in THF at room temperature gave the same hydroxymethyl compound (**152A**) that had been obtained from the conversion of **151A** by hydrogenation and acid catalyzed acetonide formation. Milder HF deprotection of the lower isomer **155B** gave the same compound (**152B**) that was obtained by similar derivatization of **151B** obtained in the tribenzyl series (Scheme 51). Examination of the NMR spectrum of compounds **152A,B** suggested the α-anomeric composition depicted in Scheme 51. The ^{13}C spectrum revealed chemical shifts of δ112.8 and δ112.9 for the isopropylidene carbons of **152A**, **152B**, respectively. These are very similar and in the predicted range for α-compounds. The JH_3H_4 of both compounds, was approximately 0 Hz, and is consistent with the Moffat rules for the α-anomeric configuration. It was concluded that only α products were formed and these reactions, while efficient, gave none of the β-anomers required for C-nucleoside synthesis.

To circumvent the undesired stereoselectivity of this coupling reaction, anomerization of the α-anomer to the desired β-anomer was a possible alternative. The literature seemed ambiguous on the feasibility of this transformation. The success of this epimerization is apparently very substrate dependent with the following examples cited for both cases. The condensation of the 5-O-trityl-ribosyl chloride (**156**) with the sodio-malonate

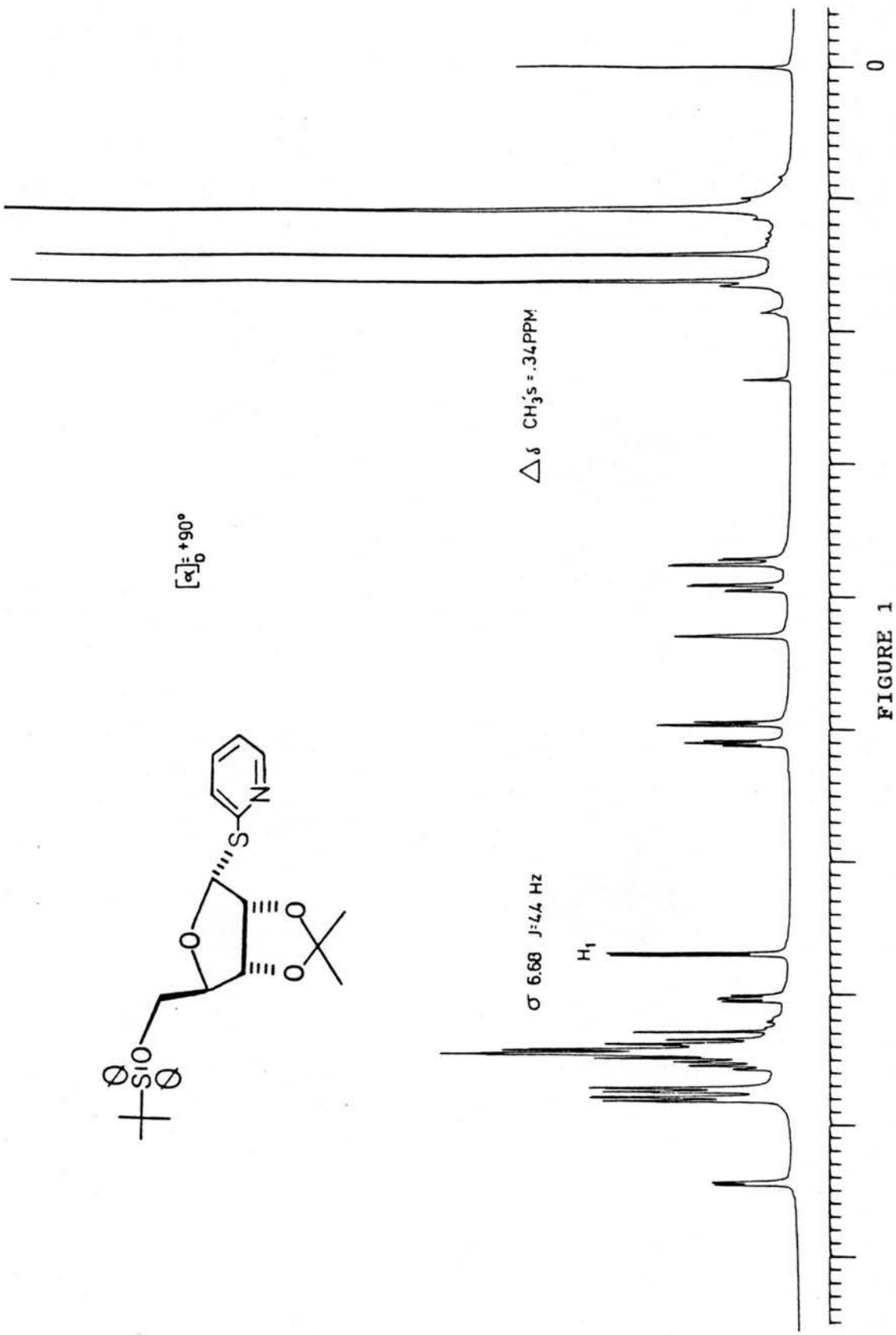


FIGURE 1

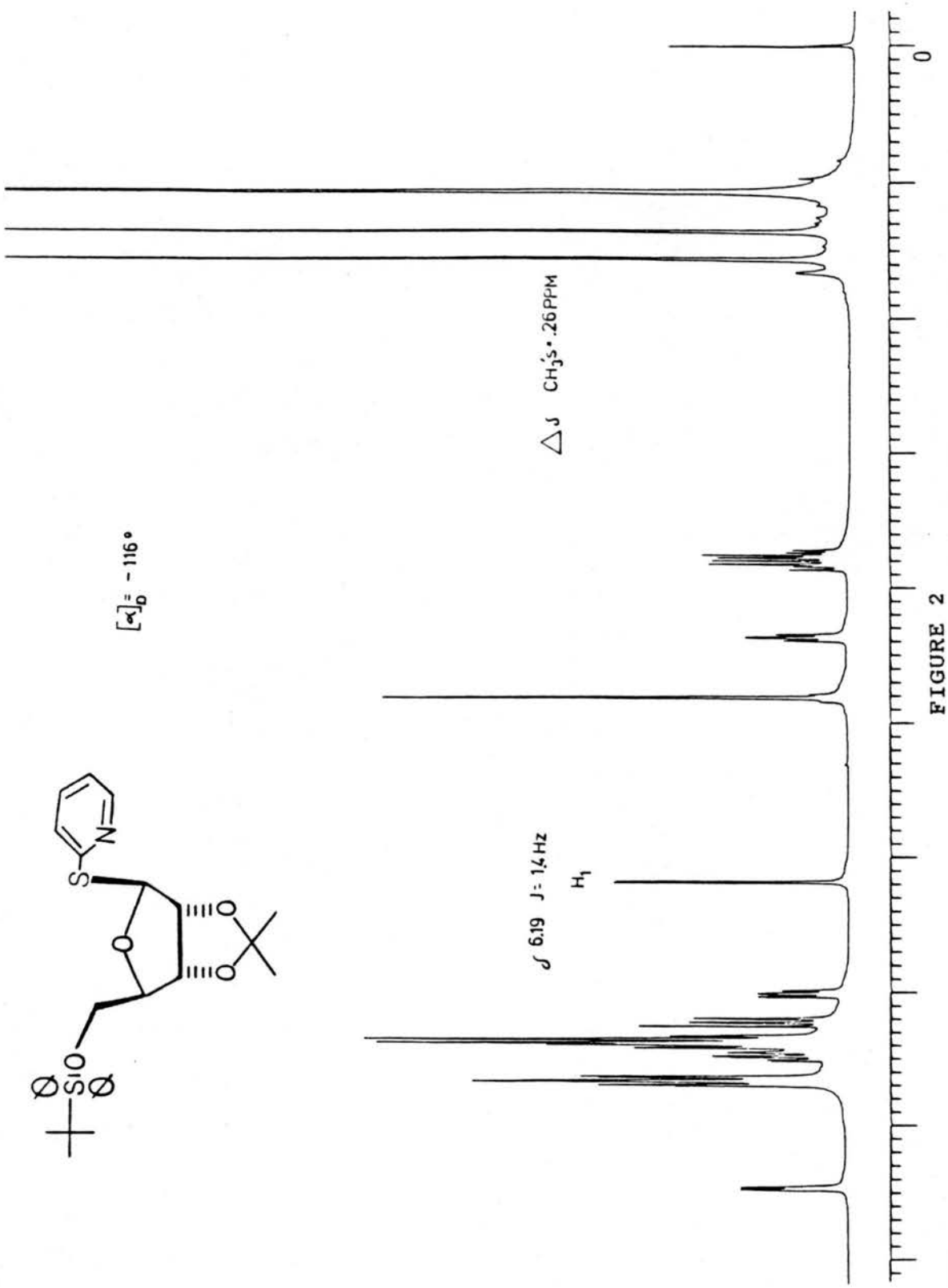
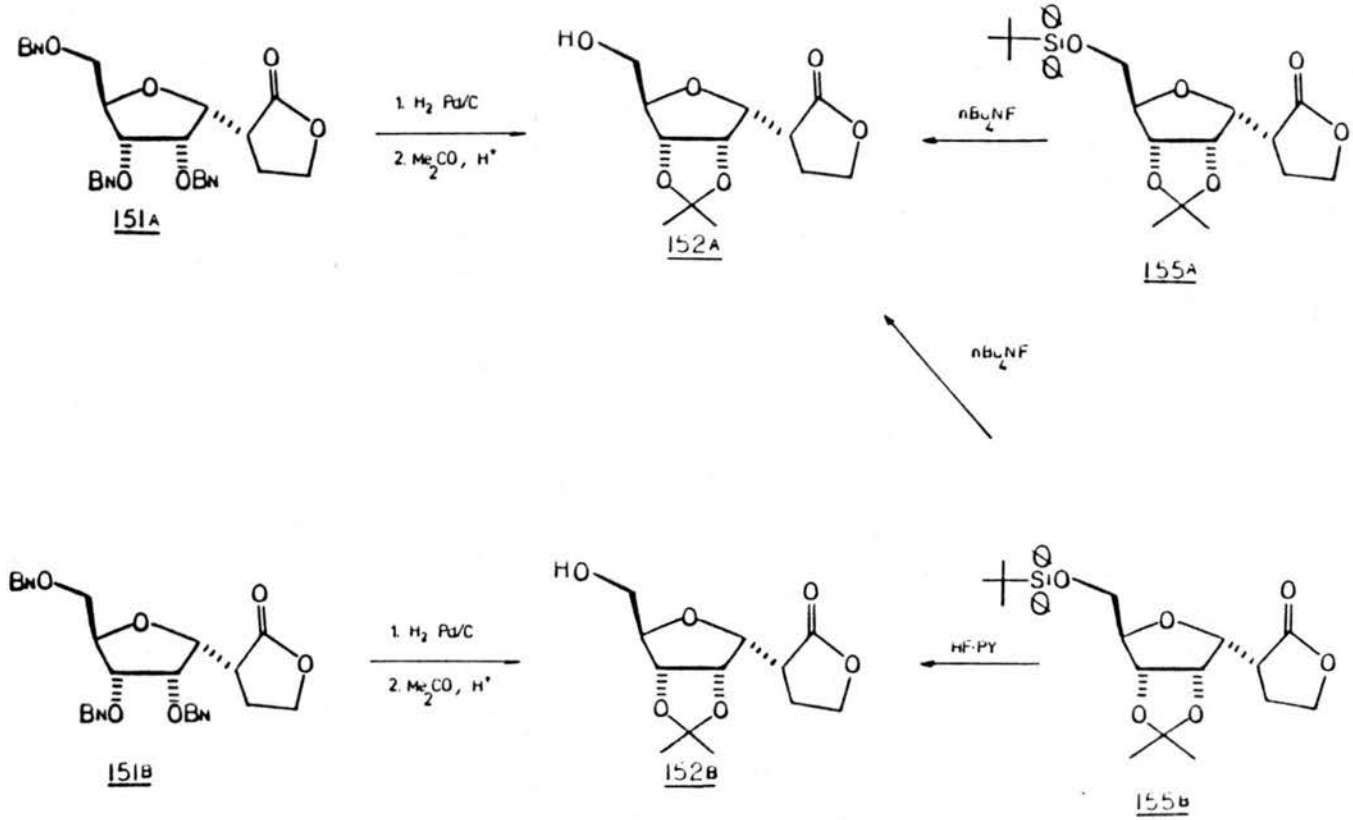
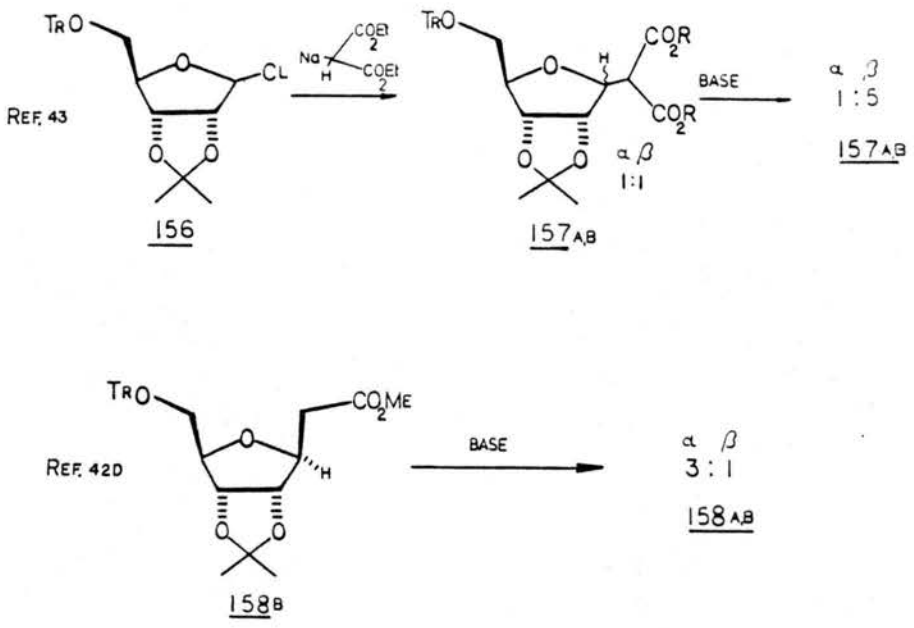


FIGURE 2

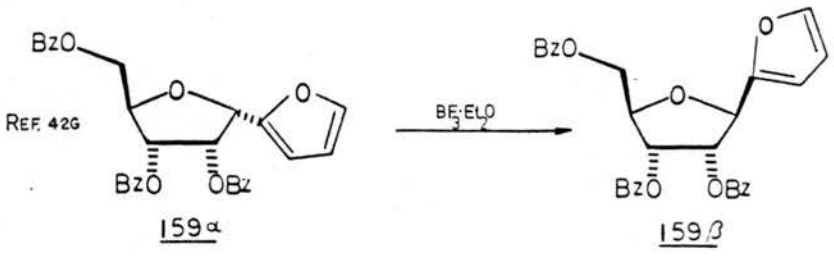

BnO
OBn
151A
1. H2 Pd/C
2. Me2CO, H+
HO
152A
nBu4NF
155A
nBu4NF
151B
152B
HF·PY
155B

SCHEME 51

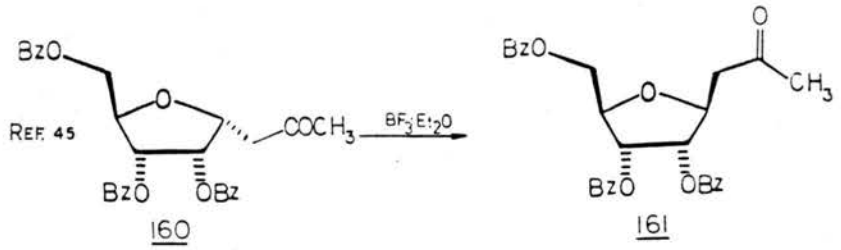
derivative yields two compounds[43] (**157A,B**) (Scheme 52). The original reaction mixture showed a 1:1 mixture of compounds **157A,B**. It was reported that prolonged reaction times under these basic conditions led to one predominate isomer. The favored isomer was identified as the desired β-isomer. This was rationalized by unfavorable steric interaction of the carbon appendage and the isopropylidene moiety. Moffat carefully showed that under basic conditions, a related α-anomer (**158**) was clearly the thermodynamically favored isomer[42d] (Scheme 52). These compounds were prepared by Wittig olefination of the free aldehyde followed by cyclization. If the trityl protecting group at C_5 was not present, a 1:30 (α:β) ratio was observed, indicating unfavorable steric interaction with the trityl group. This mixture, however, went to a 3:1 ratio, favoring the α-anomer under epimerization conditions similar to those described for **158**. A recent Japanese report[44] states that the following epimerization was successful (**159α** **159β**), patterned after a similar result obtained by Fox (Scheme 53). A very recent report[45] details the acid catalyzed epimerization of **160** to **161** (Scheme 54). The previous examples hint at possible success in an α to β epimerization. However, our lactone compounds proved configurationally stable at the anomeric center to the conditions attempted (NaOMe/MeOH) except for presumed epimerization of the lactone-α carbon.



SCHEME 52

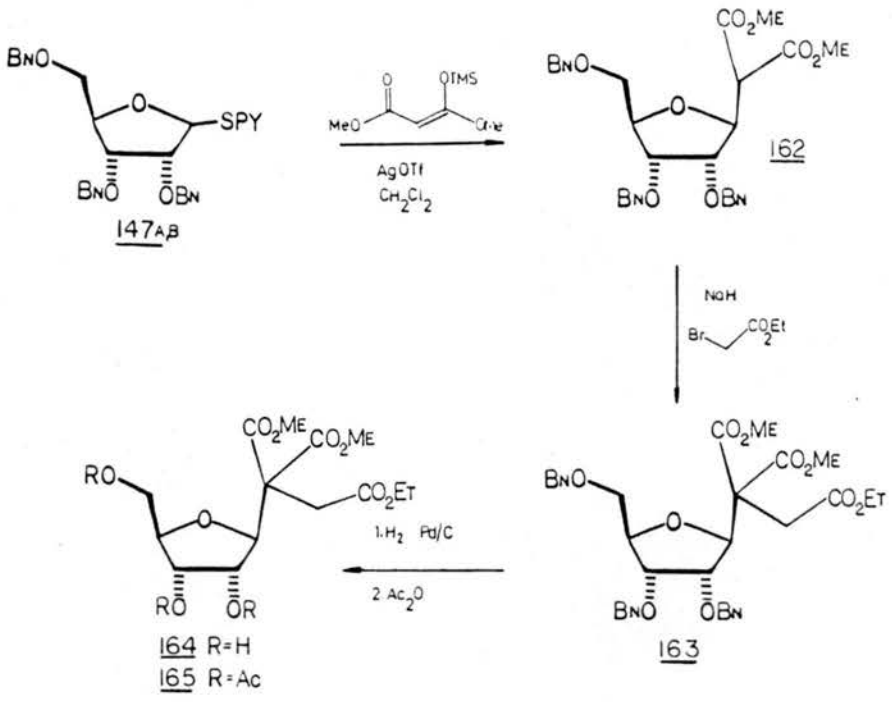


SCHEME 53

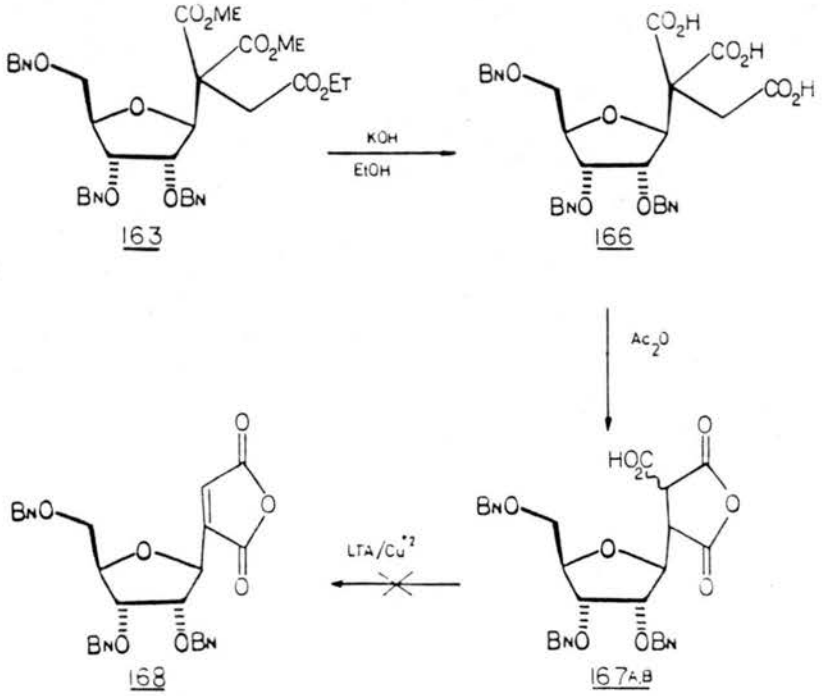


SCHEME 54

In order to determine if the α-selectivity observed in the TMS-enol ether coupling with **147A,B** or **154A,B** was a general trend, these materials were allowed to react with the ketenesilylacetal of dimethyl malonate. To our surprise a single isomer was obtained in high yield (Scheme 55). It was demonstrated that this compound could be further, elaborated by alkylation of the malonate residue with α-bromoethylacetate to give a single tri-ester **163** in good yield. Confirmation of the β-linkage was obtained by simple hydrogenation of the benzyl groups. The resulting triol **164** appeared to be completely recalcitrant to lactone formation. Based on the work of Pernet and Hanessian[46] we felt that this was good evidence for our anomeric assignment. In related α-systems these workers observed spontaneous lactone formation upon deprotection of the tribenzyl ethers. Compound **164** could be acetylated to give the triacetate (**165**) which showed no evidence for epimerization at C_1. The triester **163**, is a promising substrate for C-nucleoside preparation. It was shown that the tri-ester **163**, could be saponified to the triacid **166** and that this compound could be cyclized to a mixture of diastereomeric α-carboxy-anhydrides **167A,B** (Scheme 56). It was hoped that these unstable compounds could be converted to the same maleic anhydride derivative **168** by a metal-assisted oxidative decarboxylation. This reaction, however, failed under the conditions attempted.[58] The resemblance of **167** to the maleimide moiety of showdomycin



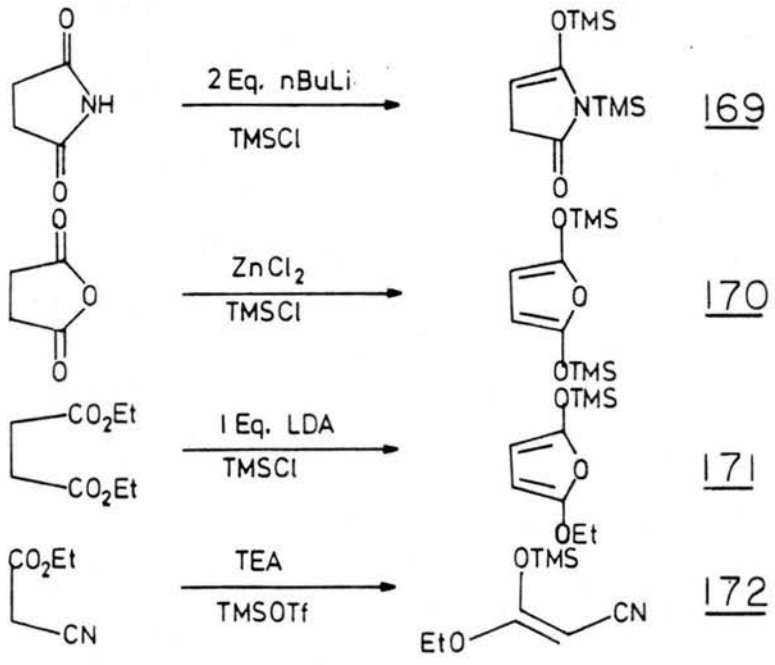
SCHEME 55



SCHEME 56

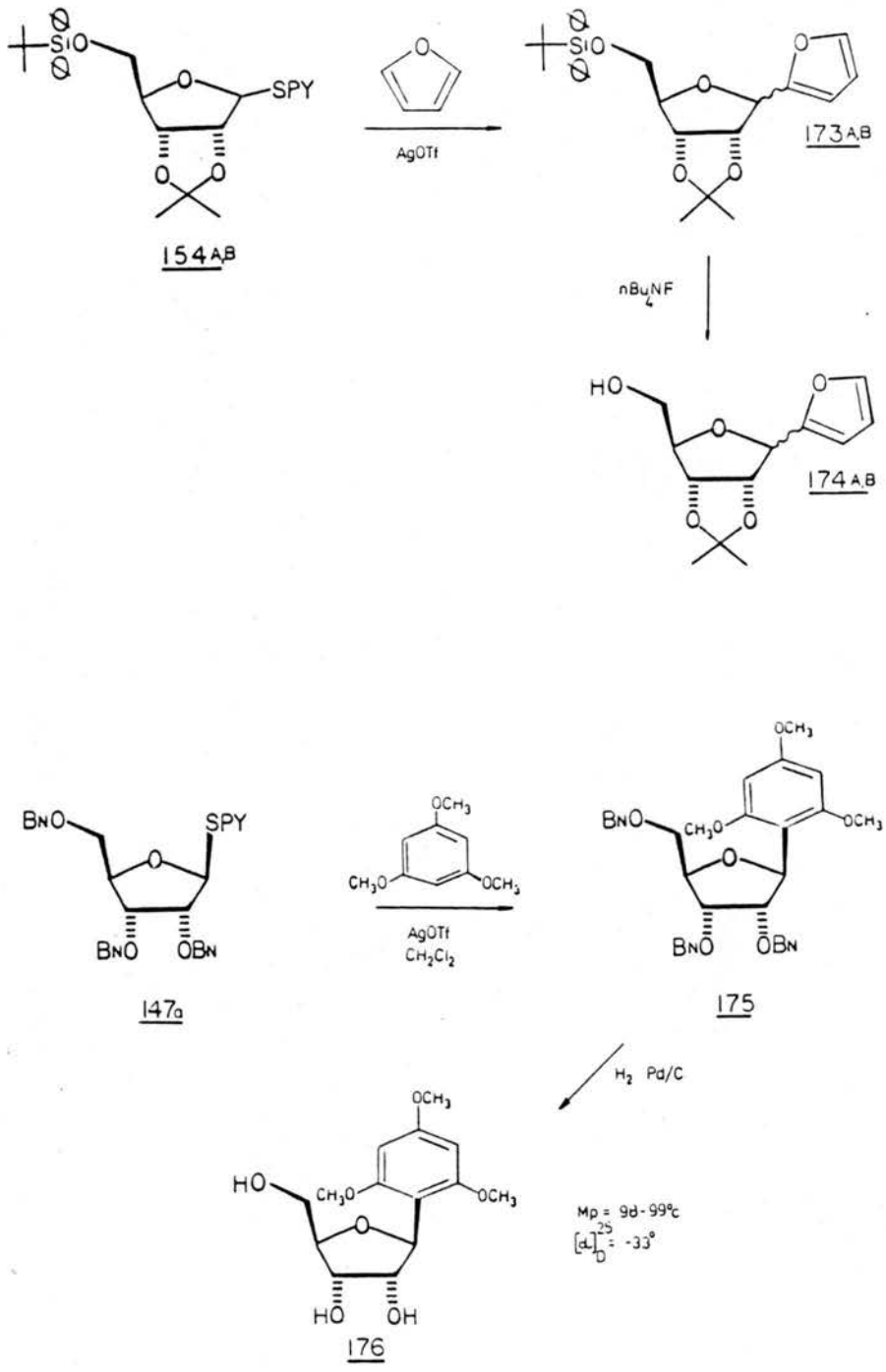
had stimulated this proposal. It was anticipated that the five carbon unit present in the tri-ester (**163**) should prove useful as a precursor to the desired 3 or 4 carbon heterocyclic moieties of C-nucleosides. Other unsuccessful attempts to attach the desired carbon skeleton via the TMS-enol ether derivatives are represented in Table 5.

TABLE 5



Attempted synthesis of the unknown **169**, gave a mixutre which could not be adequately purified and attempted reaction of **147B** using crude **168** gave no desired reaction. Use of the known aromatic compound **170**[47a] as a nucleophile also proved unsuccessful. Addition of silver triflate to a solution of thioacetal and **170** resulted in the silver salt turning immediately black and no consumption of starting material. Attempted preparation of a mono TMS derivative of the methylsuccinate led only to the formation of the aromatic compound **171**. This compound interacted with Ag^+ similar to **170** and proved unusable for C-glycosidations under our conditions. Successful preparation of the literature compound (**172**) and reaction under silver catalysis led to a complex reaction mixture and no identifiable desired product.

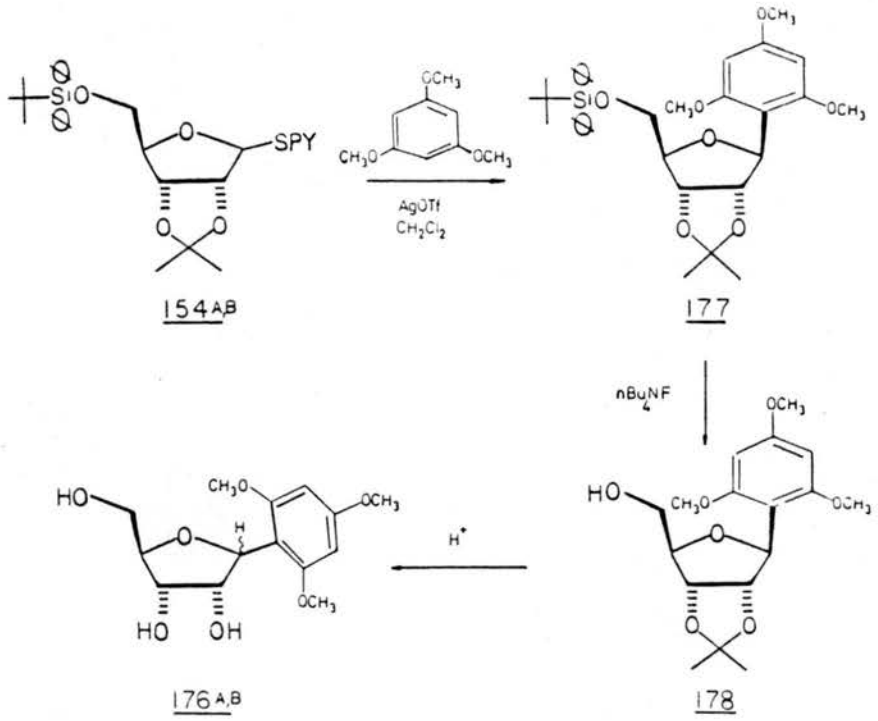
We also examined Friedel-Crafts type reactions with aromatic compounds and these ribosyl-thioacetals. Reaction of a mixture of **154A,B** using furan as a solvent in the presence of silver triflate led to rapid formation of a 5:1 mixture of two substituted furans (**173A,B**) (Scheme 57). Fluoride deprotection of the separated diastereomers (**174A,B**) gave the 2,3-O-isopropylidene derivatives that were correlated to the known literature compounds (**174A,B**).[44] Based on this correlation it seemed clear that the major isomer was the α-furan. Investigations using Et_2O or CH_2Cl_2 as a solvent with two equivalents of furan led to similar ratios with the α-isomer predominating.


SPY
AgOTf
173 A,B
nBu4NF
HO
174 A,B
154 A,B
BnO
OBn
147a
OCH3
CH3O
AgOTf
CH2Cl2
175
H2 Pd/C
176
Mp = 98-99°C
[α]D25 = -33°

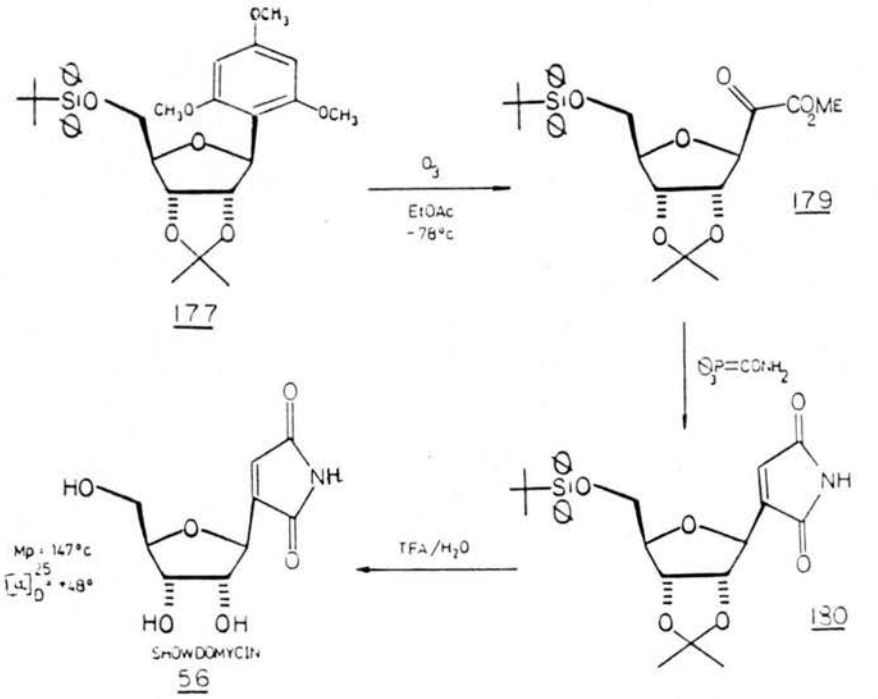
SCHEME 57

Opposite selectivity was observed in the electrophilic aromatic substitution reaction with trimethoxybenzene and either isomer of **147**. In either case, an identical single ribosyl-trimethoxybenzene compound (**175**) was observed (Scheme 57). Catalytic hydrogenation of this compound gave the known β-triol **176**. These results indicated a single desired β-isomer had been formed independent of the anomeric composition of starting material. Similarly, a mixture of **154A** and **B** led to the formation of a single compound **177** (Scheme 58). Fluoride deprotection of this compound gave a single hydroxymethyl derivative (**178**) that exhibited NMR data consistent with the β structure, based on the Moffat rules. Attempted acid catalyzed deprotection of **178** to give the same known compound (**176a**) led to scrambling of the anomeric configuration. The anomeric center containing the very electron rich aromatic substituent proved to be very labile under acid conditions. Even Dowex ion exchange resin resulted in rapid anomerization of the deprotected triol.

In order to demonstrate the β-stereochemistry of the direct coupling product **177**, conversion to showdomycin[48] by a combination of literature procedures was accomplished. Following the precedent of Kalvoda in his total synthesis of showdomycin (Scheme 59),[48c] ozonolysis of the symmetrical trimethyoxybenzene derivative (**177**) gave a single unstable α-keto-ester (**178**). Using the superior olefination strategy developed by Moffat as a modification of



SCHEME 58



SCHEME 59

Kalvoda's work, the maleimide was obtained directly from the Wittig reaction of compound **178**.[48d] The resulting "protected showdomycin" is the desired (+)-antipode of the racemic compound prepared by Kowzikowski in a multi-step synthesis starting from furan.[48e] Simultaneous desilylation and hydrolysis using conditions developed by Kowzikowski, yielded crystalline showdomycin. This material proved identical in all respects to an authentic sample of natural showdomycin kindly provided by Dr. J. Moffat of Syntex. The proton NMR spectrum of both the natural and authentic materials are shown in Figure 3. This procedure provides (+)-showdomycin in seven overall steps from D-ribose. The key step in this sequence is the stereoselective coupling of the trimethyoxybenzene and the 1-thio-ribose derivatives (**154A,B**).

The important role of the ring oxygen and the associated anomeric effect as consequences of the heterocyclic structure surely are responsible for the selective reactions observed with both the glucose and ribose substrates. The glucose substrate (122) gave consistent α-selectivity from a β-precursor. This same "α-trend", however is observed in many glucose substrates with precursors having an α-configuration of the anomeric mixed acetal. This must indicate a rapid preglycosidation equilibrium. The selectivity of nucleophilic additions observed with the activated ribosyl substrates is equally high but unpredictable. Little is known about the anomeric

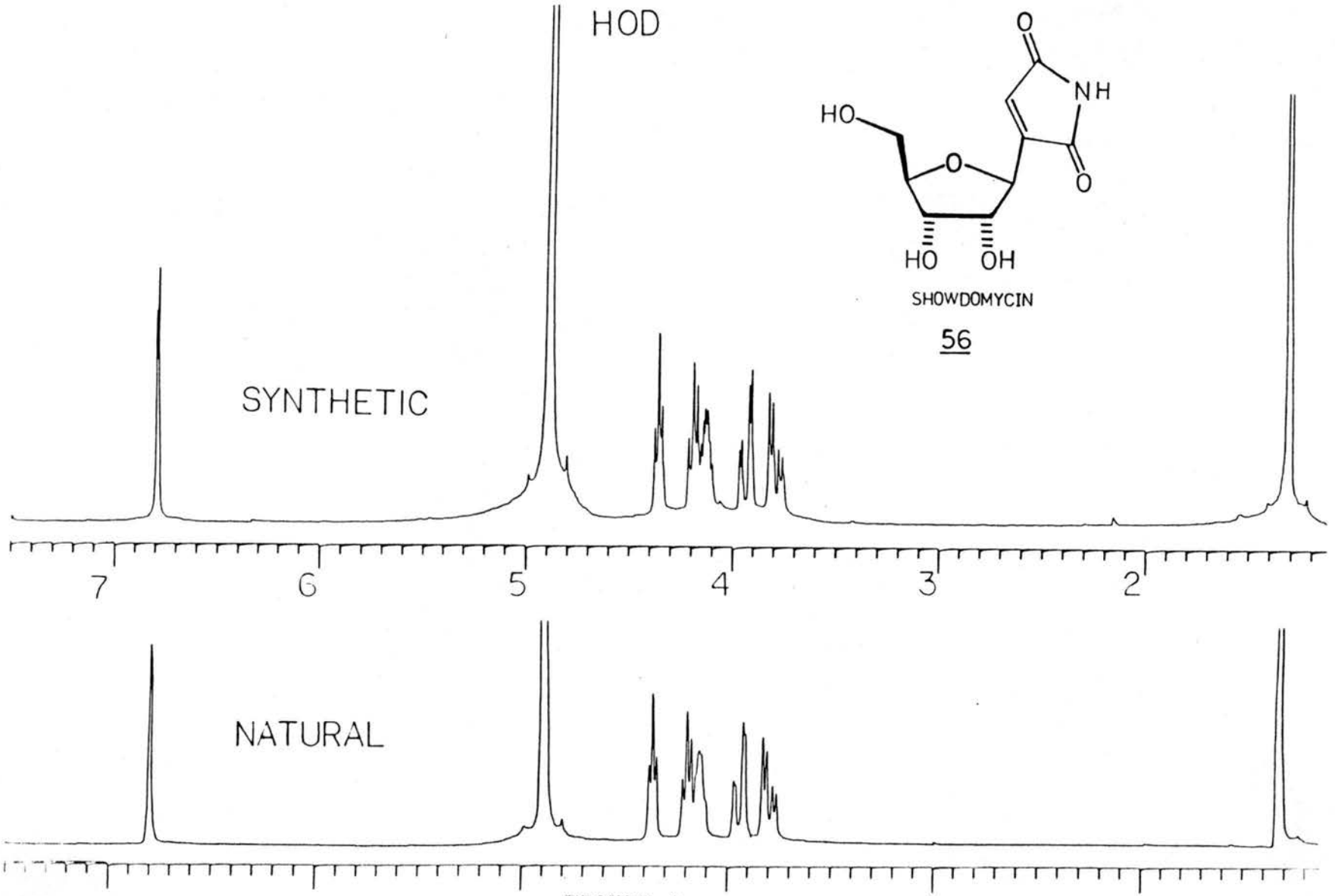
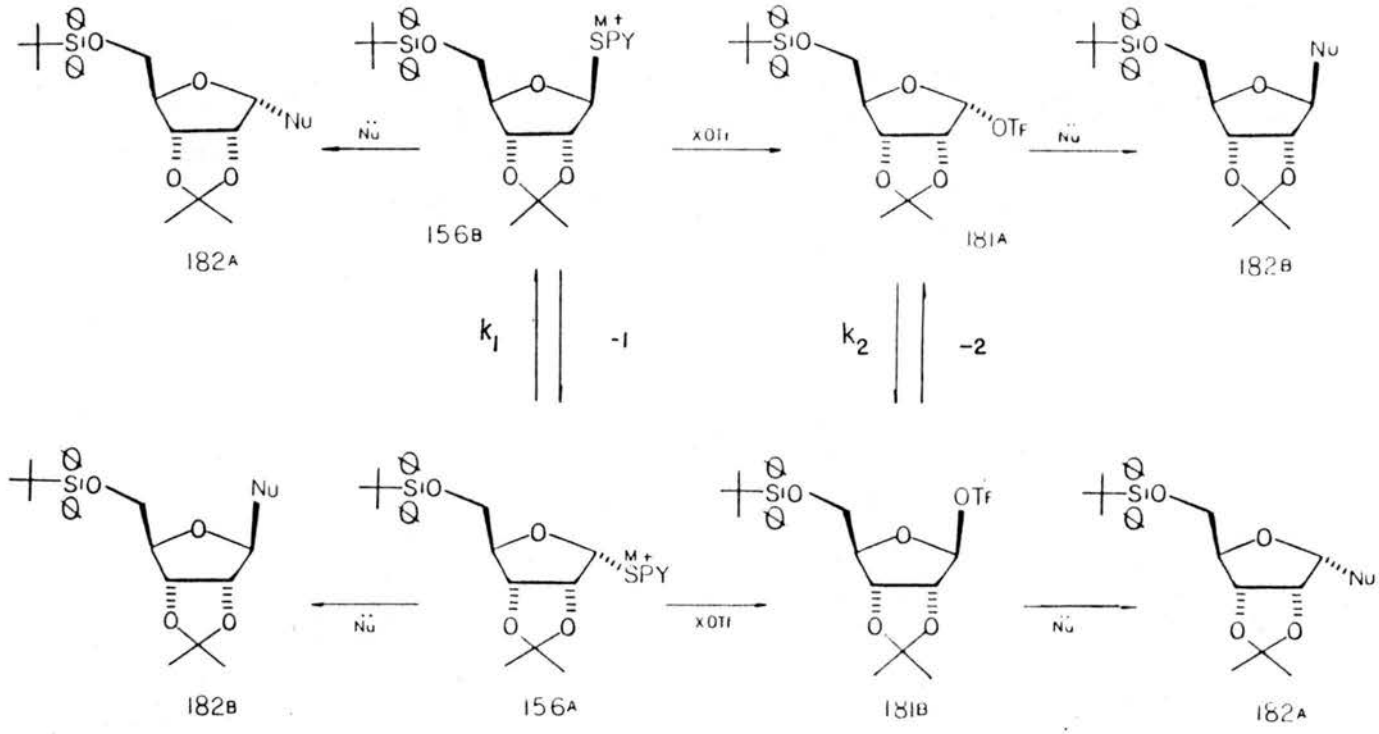


FIGURE 3

effect in these furanoside species. The complex conformational behavior and resulting higher reactivity of these five-membered heterocycles have been difficult to study. In our work the isolation of a single product from a mixture of thioacetal anomers must indicate a rapid equilibrium (k_1 or k_2) (Scheme 60) of reactive intermediates and or a diastereoselective reactivity between the anomers of the reactive intermediate.

Rapid equilibrium of the initially formed thio-silver complex (**156a,b**, Scheme 60) could be governed by a reverse anomeric effect. In the absence of a sufficiently reactive nucleophile it seems reasonable that in turn these species would be converted to triflate esters (**181a,b**). The electronegative nature of the triflate aglycone would generate glycosidation precursors influenced by the anomeric effect and therefore adopt the opposite anomeric configuration of the thio-metal complex precursor.

Insight as to which anomeric configuration is favored by an anomeric effect in these ribosyl substrates may be gained by the observation that a single β-methyl-glycoside is produced from D-ribose under thermodynamic conditions;[41] whereas a predominate α-methyl glycoside results from similar treatment of D-glucose. The predominate anomer of the hemiacetal of the 2,3-O-acetonide derivative (**153**) is the β-isomer. The tri-n-butyl-phosphine reaction on this substrate produced predominately the α-anomer of **154**. The production of the thioacetal from the hemiacetal, under

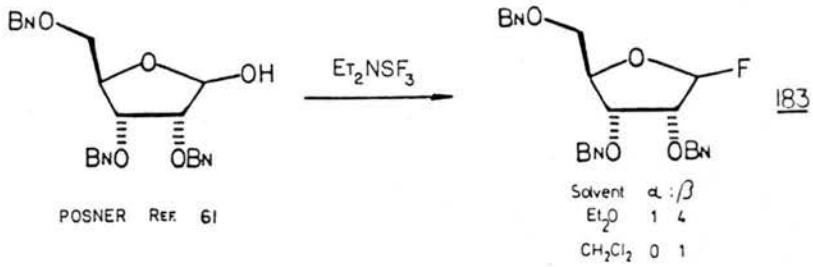

SiO
Nu
SPY
OTf
xOTf
182A
156B
181A
182B
k1
-1
k2
-2
182B
156A
181B
182A

SCHEME 60

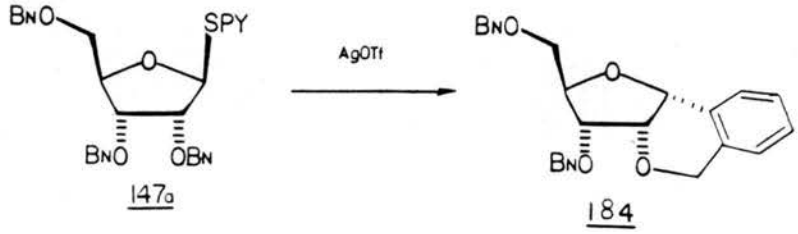
these conditions, resulting in inversion of the anomeric center is analogous behavior seen in the glucose series. However, the β-anomer of the ribose substrates appears to be stabilized by the anomeric effect. Based on this analysis we would expect **156A** or **181B** (Scheme 60) to be the predominate species in the respective equilibrium. We can envision **182B** being produced from a reactive nucleophile by inversion of the α-metalthio complex (**156A**). In the presence of a less reactive nucleophile **156A** could be converted to the triflate ester (**181**). If the β-anomer (**181b**) of this species predominated; inversion of the anomeric center by the nucleophile would result in α-product (**182A**). Alternatively the reaction products could result from a diastereoselectivity of the reactive intermediate. The successful production of an α-glycoside from an α-halosugar by the addition of excess halide ion (ref. 28) in pyranose substrates indicate the feasibility of this mechanism. The unfavored configuration of the reactive intermediate (**156B** or **181A**) (Scheme 60) might be responsible for the observed product based on a higher groundstate and resulting greater reactivity. Both explanations require a preglycosidation equilibrium (k_1 or k_2) that is very rapid relative to attack by the nucleophile. Also essential to either type of argument is inversion of a reactive intermediate showing a configurational identity and preference.

Many parameters can influence this preglycosidation equilibrium and the resulting selectivity of the glycosidation reactions. Solvent can obviously effect the rates and course of preglycosidation equilibria. In the glucose series we demonstrated a dramatic role of diethyl ether in interacting with an intermediate during the trimethyoxybenzene coupling. A very recent report by Posner[61] describes significant solvent effects in fluoro-glycosidation. Treatment of an anomeric mixture of hemiacetals of tri-O-benzylribose with diethylamonium-sulfurtrifluoride (D.A.S.T.) in diethyl ether results in a 1:4, α:β, ratio of ribosyl fluorides. If the solvent is changed to methylene chloride a single β-fluoro compound is obtained (Scheme 61). There seems no question that solvent may play a role in effecting the rates of these equilibria and with participating solvents form reactive intermediates influenced by a reverse anomeric effect.

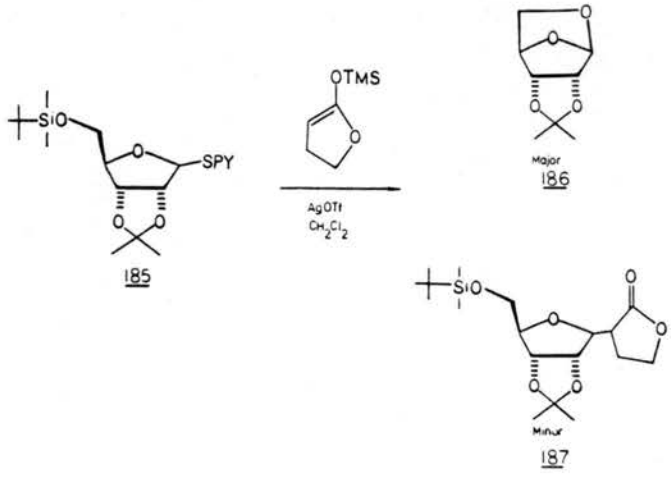
As in the glucose series we attempted preincubation of the ribosyl thioacetals with the silver salt in an attempt to convert all the substrate into the reactive triflate species. In the absence of a nucleophile a similar intramolecular Friedel-Crafts reaction with the adjacent C_2 benzyl ether was observed (Scheme 62). Another interesting protecting group problem arose when the 2,3-O-acetonide ribosyl thioacetals were first prepared. The C_5-dimethyl-t-butyl silyl ether (185) (Scheme 63) proved unsuitable even in the presence of reactive nucleophiles. The



SCHEME 61



SCHEME 62



SCHEME 63

1,5-anhydro compound (186) from an intramolecular O-glycosidation was the major product with only minor amounts of the desired coupled compound (187) being produced. It was found that the corresponding diphenyl-t-butyl silyl ether was stable to the lewis acid conditions of these reactions. Attempted preincubation of the diphenyl substrate led to rapid disappearance of starting material and an unidentifiable mixture of compounds.

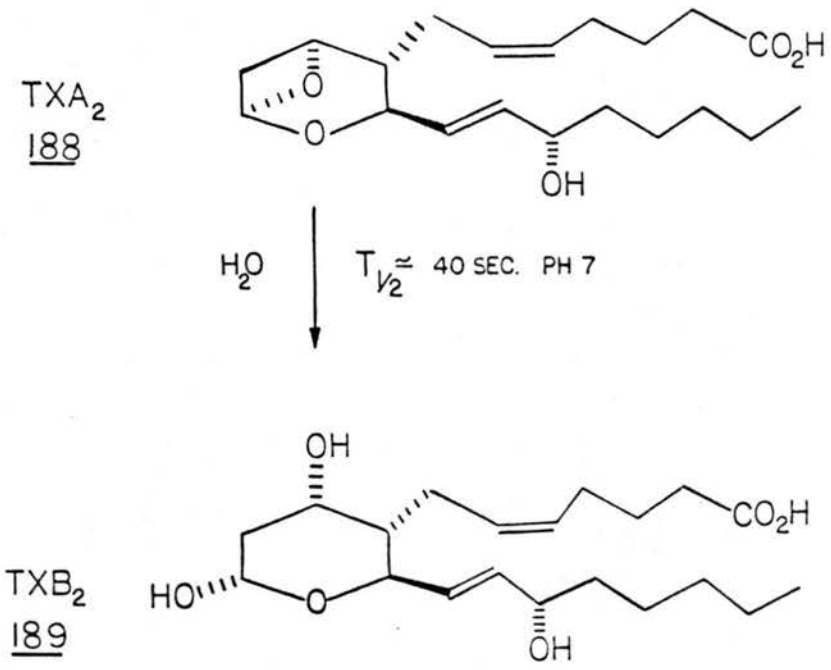
The C-glycosidation of carbohydrate derivatives can yield useful precursors for C-nucleosides or chiral templates of other natural products. However, the formation of a new asymmetric center in this carbon-carbon bond forming sequence requires that a selective process be utilized to produce a specific desired configuration. The silver (I) activation of thiopyridylacetals give reactive intermediates that under the influence of the ring oxygen can react with a wide variety of nucleophiles in highly selective substitution reactions. The β-thiopyridyl-tetrabenzyl glucose substrate (122) should prove to be a very useful precursor for selective α-carbon bond formation with carbonyl compounds and electron rich aromatic species. The stability of this crystalline compound is superior to other mixed acetals used in similar glycosidations. The ribosyl substrates while unpredictable with respect to a given nucleophile displayed high stereoselectivity under mild reaction conditions. While β-selectivity is required for C-nucleosides; selective methods to produce the

opposite anomeric configuration may be desirable for the elaboration of sugars as chiral templates since the anomerization of these centers seems unpredictable. For example, the butyrolactone coupling with either ribosyl substrate gives access to a single stereoisomer out of a possible four. Another significant feature of the ribosyl substrates reported herein is the range of compatible protecting groups on the sugar. The tri-O-benzyl substrate can be deprotected under neutral hydrogenation conditions after glycosidation. The acetonide substrate can alternatively, be deprotected under conditions compatible with unsaturated heterocyclic appendages. 1-thiopyridyl sugar derivatives must be classified as useful glycosidation precursors due to ease of preparation and isolation, stability, efficiency of activation by thiophilic metals and the selectivity of their reactions under mild conditions.

CHAPTER 4

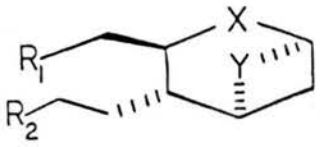
APPROACHES TO THE [3.1.1] BICYCLIC OXETANE OF THROMBOXANE A_2 (TXA_2)

Our work on C-glycosidation[60] and the related O-glycosidations[33d-g] using 1-thio sugar derivatives demonstrate the efficiency with which the sulfur residue can be activated by thiophilic metals. The reactive intermediate can be utilized in a number of solvents to give clean, high yield glycosidations. This system seemed applicable to the construction of the unique unstable bicyclic acetal of thromboxane A_2[49] (188). Thromboxane A_2 is a labile major metabolite in the arachadonic acid cascade and is found in blood platelets and other tissues. The strained four-membered acetal has a half-life of only 30-40 sec at 37°C in an aqueous medium (pH = 7). The resulting thromboxane B_2 (189) is a stable crystalline solid (Scheme 64). Thromboxane B_2 has been synthesized by a number of groups. However, TXA_2 remained an elusive compound whose structure has not been confirmed by direct methods. This structure (188) proposed by Samuelson was based solely on stable degradation products and biological



SCHEME 64

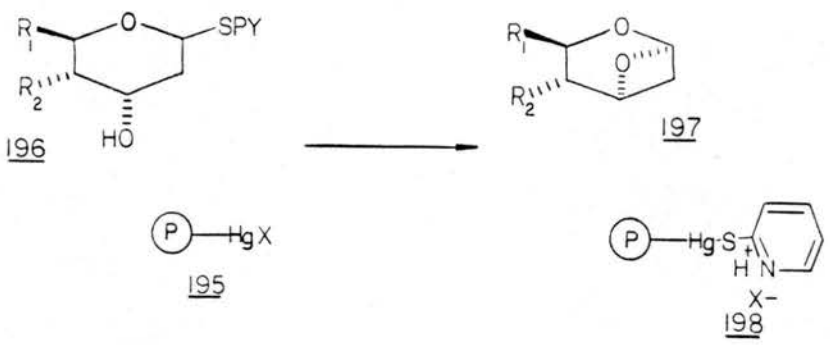
TABLE 5



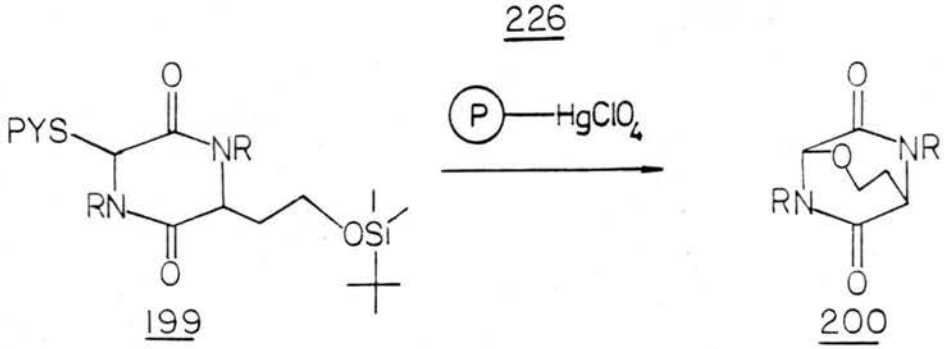
190	X = Y = S
191	X = Y = CH_2
192	X = NH, Y = CH_2
193	X = O, Y = CH_2O
194	X = CH_2, Y = CMe_2

activity of several stable analogs.[50a-e] The most often studied analogs include those formed by replacement of one or both oxygens by another heteroatom, carbon congeners and homo TXA_2. The only source of TXA_2 is from cellular systems and under these conditions it is too short lived for spectroscopic description or experiments designed to reveal the important biological role of this compound. TXA_2 shows remarkable thrombotic and vascoconstricting properties and it is this unique activity that has generated the intense interest in its synthesis and biomechanism. The absence of synthetic methods to produce usable quantities of TXA_2 for active site investigation severely limit this area of research. The inherent problems in constructing the dioxabicyclo [3.1.1] nucleus are linked to the unstable nature of the strained bicyclic acetal which precludes chromatographic isolation or the use of acidic conditions. The previously described methodology for activation of thioacetals is probably unsuited for this system. These reactions often required an excess of metal salt for rapid reaction and complete consumption of starting material. Chromatographic isolation was often necessary to separate product from excess reagent. A second feature of the homogeneous metal salts is the trace quantities of the toxic metals that can accompany desired products; an unacceptable situation for pharmacological evaluation.

The advantages of a heterogeneous metal for the activation of the thiopyridyl residue were extremely attractive not only for this system but any sensitive glycosidation. In principle activation of the thioacetal by a polymer bound metal salt would allow a simple filtration to afford a non-polar solution of internally glycosidated product that would require no work up or chromatography. Even the most sensitive glycosides might be prepared under mild conditions and temperatures. Another significant feature of the thiopyridyl residue is the multi-lewis basicity of the dual heteroatom moiety. Based on other work in this laboratory[51] the thiopyridyl residue is strongly bound to the metal cation after activation. In this manner the thiopyridyl ligand would be anchored to the heterogeneous support allowing for removal of salts and acting as a bound proton sponge to remove the potentially product-destroying acid from the reaction mixture (Scheme 65). Polymer bound arylmercury(II) salts have been previously prepared in our laboratory[52] and have proven useful in related thiopyridyl activation. This reagent has been shown to effect silyl-ether cleavage and cyclization of **199** to **200** (Scheme 66). Of the heavy thiophillic metals, Hg(II) was chosen due to stability of the mercury-carbon bond. The loading (mmol/gm) of the polymer bound metal species was determined empirically by combustion analysis.



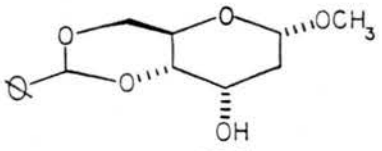
SCHEME 65



SCHEME 66

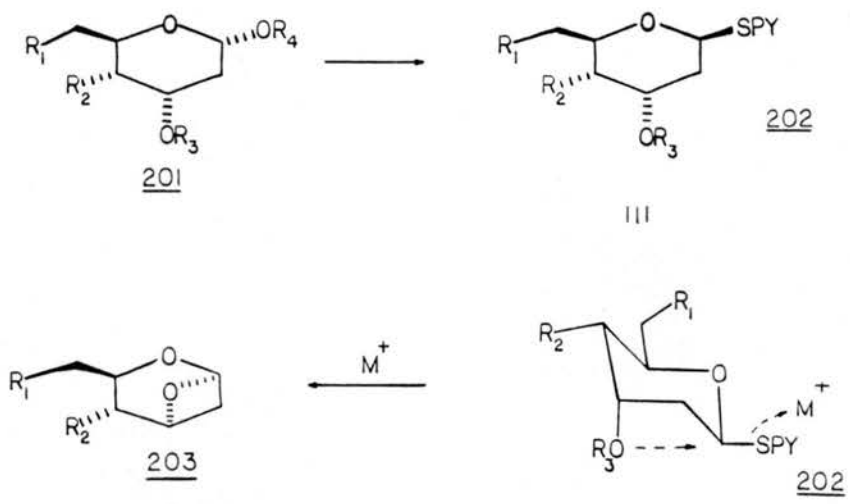
The remaining objective was to prepare a model compound to test the cyclization. A 2,4,6-trideoxy-ribo-hexose (201) that could be converted to the corresponding thioacetal derivative (203) was the target (Scheme 67). The diequatorial relationship of the C_4 and C_5 appendages should lock the ring in the stable chair conformation (202). In this conformation the C_3-hydroxyl group is held axially, the desired position for cyclization.

The most convenient starting material seemed to be the benzylidene-ribo-hexose derivative (204) used by Hanessian in his elegant stereoselective synthesis of TXB_2.[53] In an

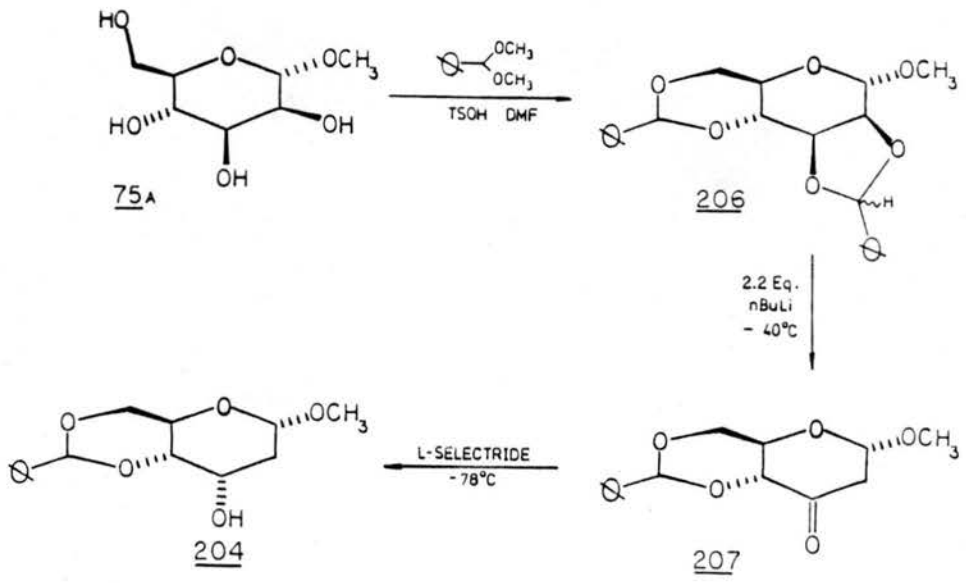


204

alternate procedure this compound could be prepared from methyl-α-D-manno-pyranoside (75A) on a multigram scale requiring no chromatography. The dibenzylidene derivative (206) as a mixture of diasteromers is prepared from commercially available methylmannose (75A) in 40% yield (Scheme 68) and obtained by direct recrystallization. Both diastereomers are converted to the same ketone (208). Treatment with two equivalents of nBuLi produces the erythro-3-ulose derivative (207) in high yield and again



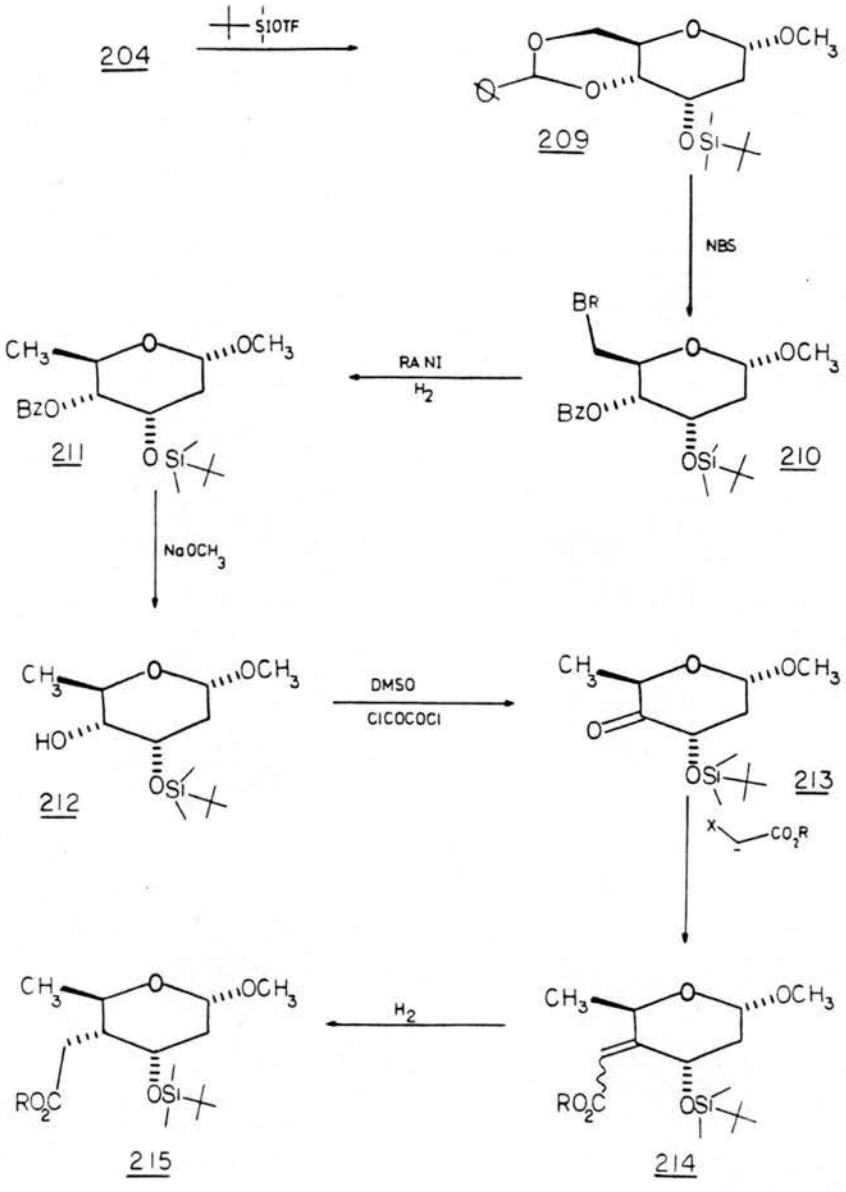
SCHEME 67



SCHEME 68

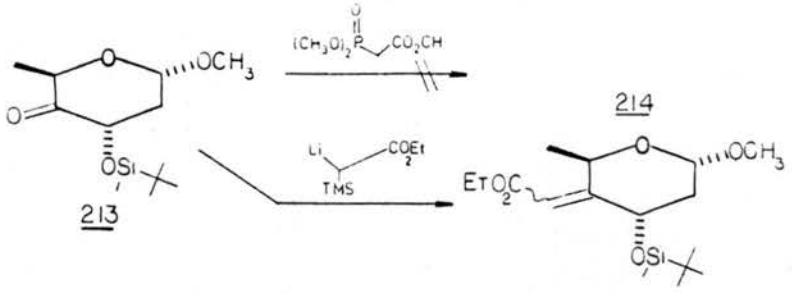
the labile ketone can be purified by direct recrystallization of the crude reaction mixture. Reduction of the ketone using L-selectride gave the desired axial alcohol in almost quantitative yield affording crystalline 204 in multigram quantities.

Similar to our work with the thienamycin arabino-hexose benzylidene derivative; we found that NBS oxidation of 209 followed by a Raney Ni reduction in isopropanol afforded a selectively protected 6-deoxy diol (211) (Scheme 69). Selective deprotection of the benzoate (211) and oxidation should yield the 4-ulose derivative (213). Homologation, accomplished by standard Wittig chemistry, followed by reduction would give 215. The work of Hanessian[53] indicated that the cis addition of hydrogen would occur from the desired face to give the ribo-configuration of 215. Compound 211 was chosen because the benzoate in principle could be removed under basic conditions leaving the C_3 silylether intact. The silylation of the very hindered C_3 alcohol proved very difficult. Significant steric constraints resulted from the 1,3-diaxial interaction with the α-methoxy aglycone. Refluxing alcohol 204 in DMF in the presence of silylchloride and two equivalents of DMAP for 48 hr resulted in only starting material. Silylation was achieved by use of t-butyldimethyl silyltriflate. Using this reagent the silylation proceeded in almost quantitative yield at room temperature in CH_2Cl_2 in the


204
SIOTF
209
OCH3
NBS
BR
RA NI
H2
CH3
BzO
211
210
NaOCH3
HO
212
DMSO
CICOCOCI
213
X
CO2R
H2
RO2C
215
214

SCHEME 69

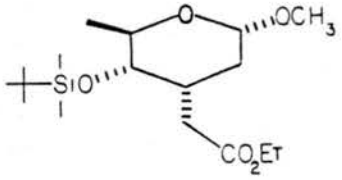
presence of 2,6-lutidine; the reaction was complete upon addition of the neat silyltriflate. Oxidation using NBS under conditions developed by Hanessian gave the C-6 bromo derivative (210) in high yield. Reduction using freshly prepared RaNi yielded the 6-deoxy protected diol (211) in excellent yield under conditions identical to those used to obtain the analogous arabino-hexose (30). Base solvolysis of benzoate 211 gave a new alcohol contaminated by a minor product. Oxidation of this alcohol using Swern conditions seemed straight-forward. Attempted homologation with the phosphonate reagent, as described for the corresponding C_3-benzoate-4-ulose, failed. The added steric hindrance of the adjacent t-butyl silyl derivative may have prevented the addition of this reagent. The poor reactivity of Wittig type reagents with hindered ketones of these branched sugar derivatives was well documented in Chapter One. Homologation was achieved using a Peterson olefination reagent prepared from α-trimethylsilyl ethyl acetate. This lithiated compound was found to add readily to ketone 213 at -78°C. A 3:1 mixture of α,β-unsaturated ethyl esters (214a,b) were obtained in almost 80% yield (Scheme 70). Hydrogenation using Pearlman's catalyst[53] in EtOH appeared to give the desired C_3-O-silyl-trideoxy-ribohexose (215). Careful examination of the proton spectrum of 215 revealed incorrect regiochemistry of the model compound prepared in this way. The product we obtained is assigned



213 214

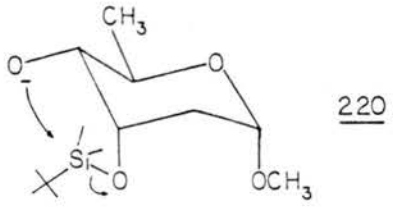
SCHEME 70

structure **216.** The error in regiochemistry was not

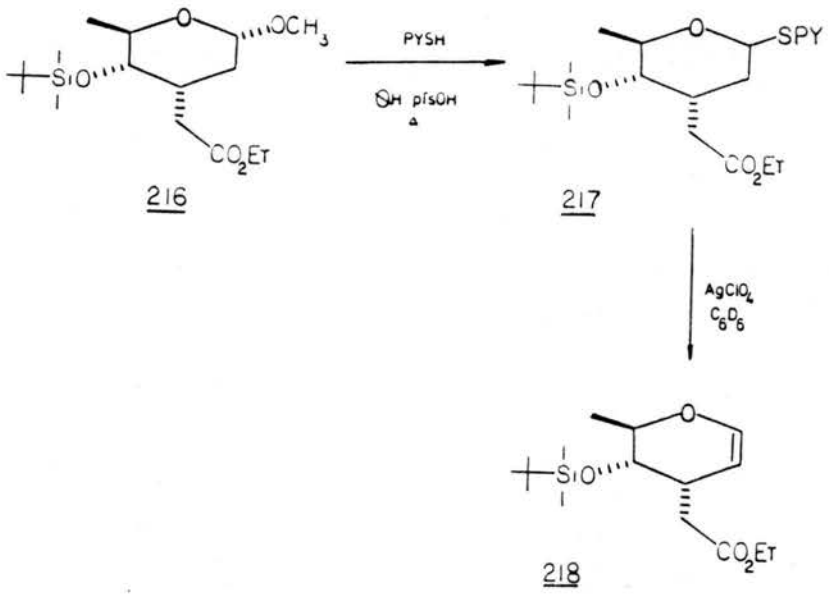


216

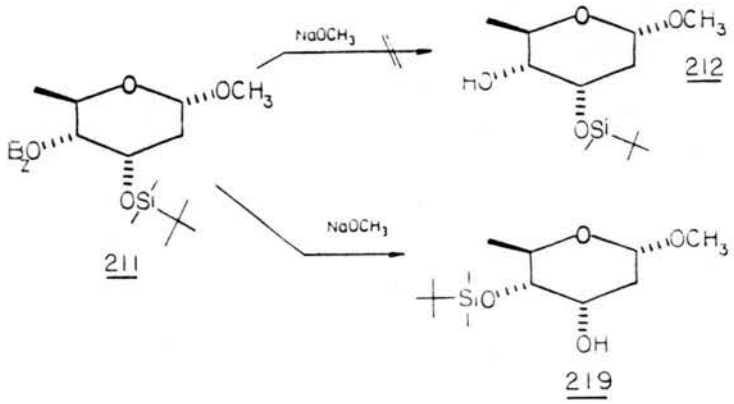
discovered until the thioacetal (217) had been prepared from 216. Reaction of 217 with silver(I)-perchlorate resulted in glycal (218) formation (Scheme 71). The



220

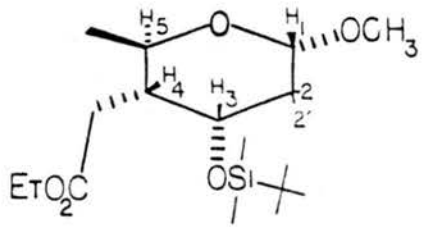


SCHEME 71

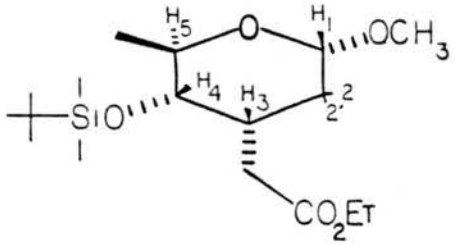


SCHEME 72

regiochemical problems encountered appear to result from silyl-migration during hydrolysis of the benzoate under basic conditions (Scheme 72). The desired 212 is probably the minor product observed in this reaction. Silyl migration can relieve the 1,3-diaxial strain between the C_1 aglycone and the C_3 t-butyl dimethyl silyl ether. Facile silyl transfer can be envisioned to occur from the alkoxide (220) generated from deprotection of the benzoate (211). Scheme 71 depicts the attempted cyclization of the 2,3,6-deoxy model system. This sequence was examined based on the premise that the 2,4,6-deoxy species (215) was in hand. The regiochemistry was not immediately identified primarily due to the unusual ^1H NMR spectrum of compound 216. The lowest field resonance exhibited in the proton spectrum is from H_4 (Fig. 5). The adjacent heteroatom combined with the deshielding cone of the C_3 ester cause H_4 to be downfield from H_1. H_4 of compound 216 was therefore assigned H_1 of compound 215. The true H_1 of structure 216



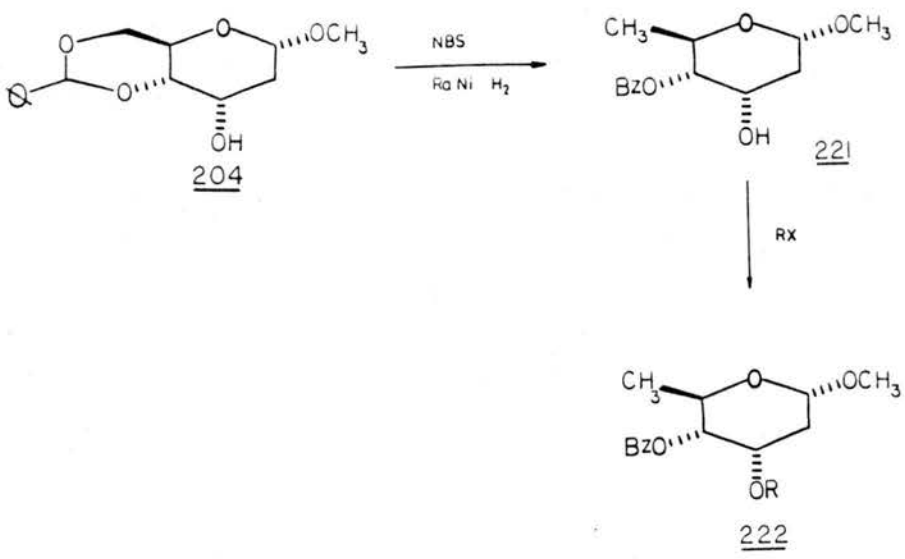
215



216

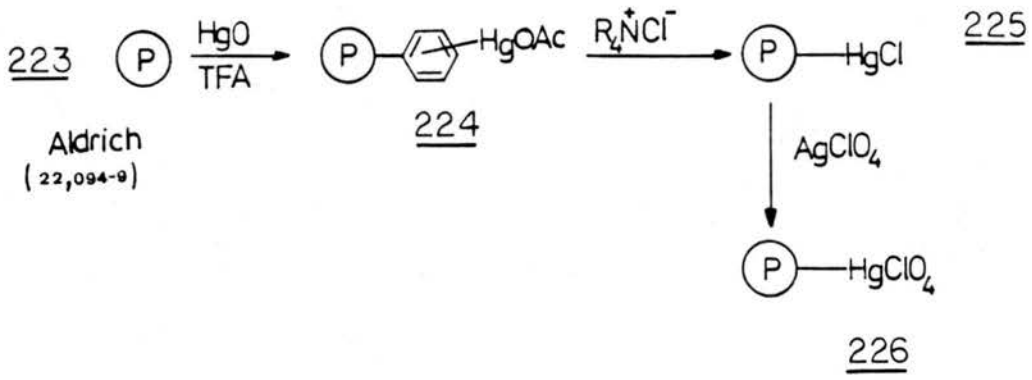
FIGURE 5

consequently was assigned H_3 of **215**. Irradiation of this signal (H_1, **216**), of course led to collapse of a coupling constant in the 2,2'-methylene and initially indicated structure **215**. The wrong regiochemistry combined with the misassignment of H_1 and H_4 strongly suggested the desired structure but more careful homo decoupling starting with the C_6 methyl doublet revealed the correct structure (**216**). Although the mistake was not detected before conversion to the thioacetal and attempted cyclization this sequence demonstrated: 1) the thiopyridyl acetal exchange could be performed on the methylglycoside by removal of methanol (**216** **217**). 2) Products from activating the C_1-thio compound could be observed directly in a non-polar deuterated solvent by NMR. In view of the facility of the silyl migration the use of a silicon protecting group on the C_3 axial alcohol did not seem feasible. An alternative triol manipulation might be achieved by NBS oxidation and reduction of the unprotected alcohol (**205**) (Scheme 73). Alcohol **221** could now be protected by some group not prone to migration. The Ra Ni reduction, however, gave a mixture of benzoates (**221**). The mixture was protected as the benzyl ether and further epimerization, presumably at the anomeric center gave a mixture of four compounds (**222**). The selective manipulation at the C_3, C_4 diol obtained from reductive deoxygenation of C_6 did not appear to be synthetically useful.

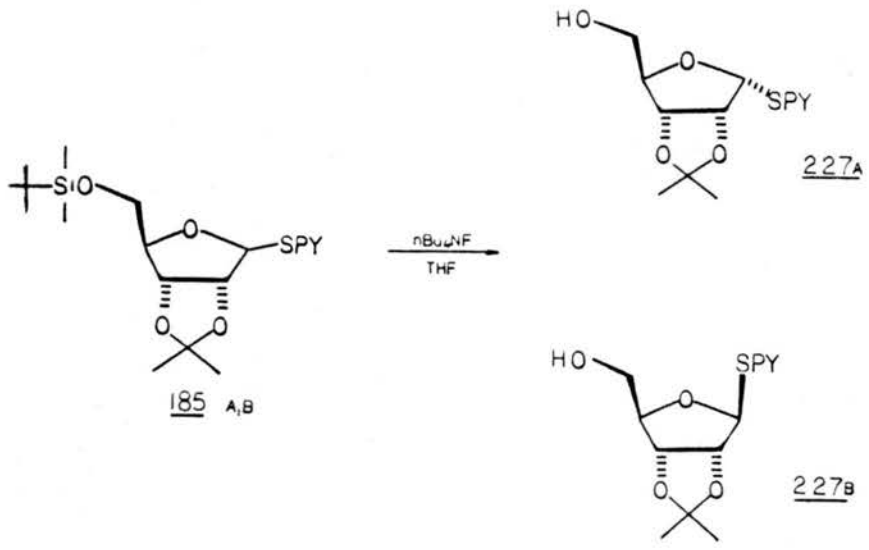


SCHEME 73

At the time we were encountering these difficulties it was decided to prepare the polymer reagent and examine its reactivity with other model systems. The polymer bound mercury(II) perchlorate was prepared by an alternative procedure than had previously been employed in the original report of this reagent from our laboratories. Direct mercuration of commercially available macroporous polystyrene beads (223)[54] was accomplished as reported by Taylor[55]. The resulting aryl mercuric acetate (224) was transformed to the corresponding perchlorate (226) by a similar ion exchange sequence (Scheme 74). Extensive THF washings after the final step afforded the light blue resin which was dried under vacuum to constant weight. The resin was stored in a dessicator under nitrogen until used. Until

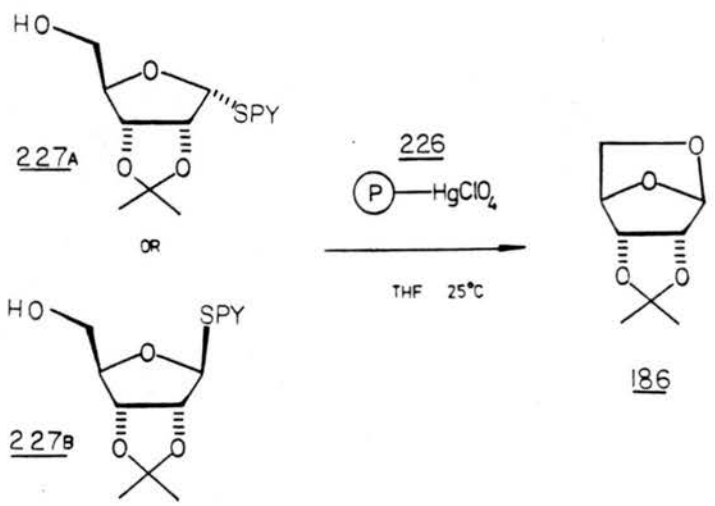


SCHEME 74



SCHEME 75

the correct pyranose substrate could be prepared, we considered the thioacetals (**186a,b**) as models to test the ability of the polymer reagent to activate the thiopyridyl acetal for intramolecular glycosidation. The mixture of anomers (**186a,b**) were treated with tetra-n-butylammonium fluoride trihydrate in THF to give the easily separated hydroxymethyl-thioacetals (**227a,b**) (Scheme 75). Stirring either anomer (**227a or b**) in THF with the functionalized polystyrene beads led to clean activation and intramolecular glycosidation to give the tricyclic 1,5-anhydro derivative **186** (Scheme 76).

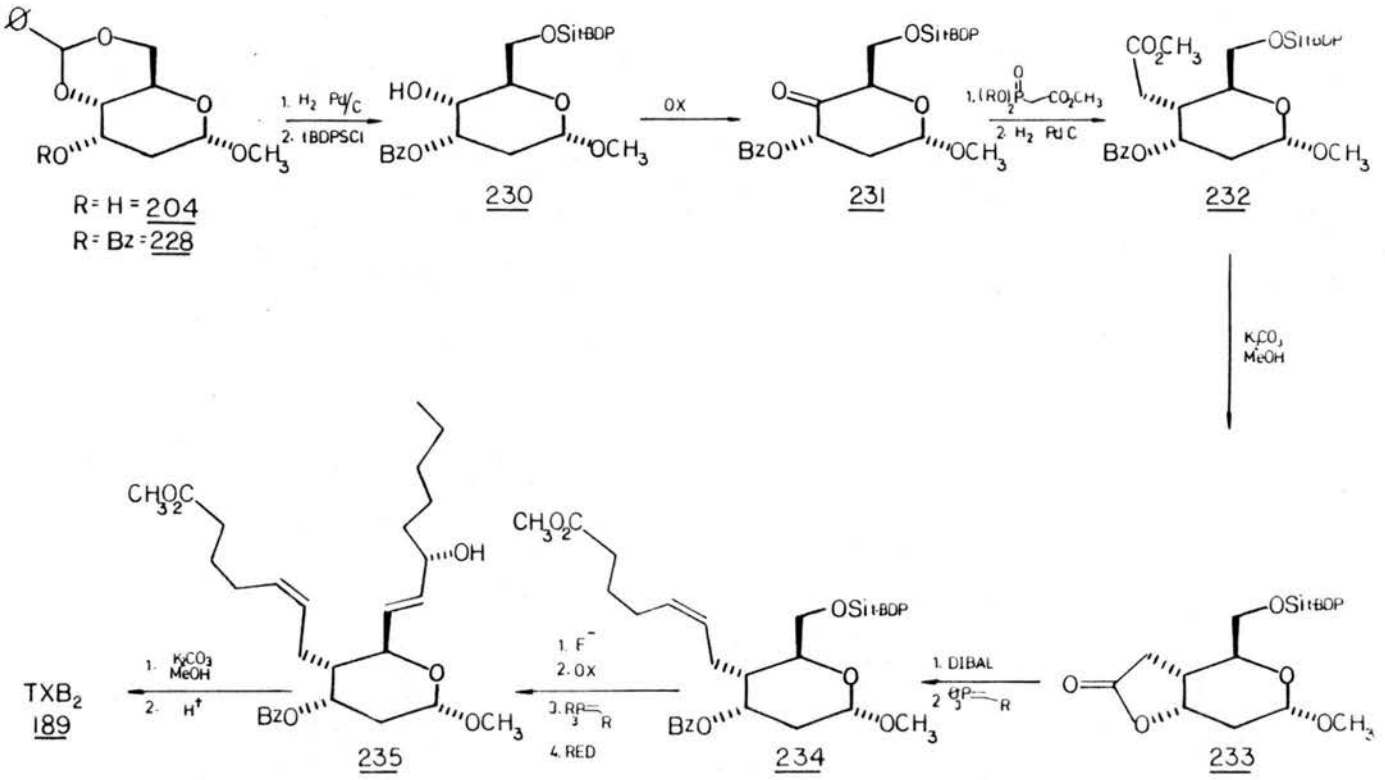


SCHEME 76

The isolated yield of the crystalline product[56] was only about 50% but there were amounts of starting material still present. This may represent problems in determining the loading of the polymer reagent. We had assigned a value of 1 mmol/gram based on combustion analysis of the polymer prepared by the procedure originally reported.

Interestingly, under identical conditions and concentrations, the β-isomer (**227b**) was found to react more rapidly than the α-isomer (**227a**). This certainly reveals the important stereoelectronic role of the ring oxygen; the geometry for a direct SN_2 displacement can only be achieved by the α-isomer. The reaction times were approximatley 24h for the β-isomer and 48h for the α-isomer. These slow reaction times indicated a slower diffusion rate than desired. It was felt that rapid reaction rates at moderate temperatures would simplify isolation of sensitive glycosides. A possible solution would involve low temperature incubation of the substrate with the polymer bound metal to complex all thiopyridyl residues with the active metal sites; followed by a temperature increase to overcome the activation barrier to cyclization. The use of a new polymer allowing higher diffusion rates might also be indicated.

The polymer activation of these model compounds was encouraging but the problem of preparing the 1-thio-2,4,6-trideoxy-ribo-hexose remained. We decided to follow the known route from alcohol **205** to TXB_2. Scheme 77 outlines

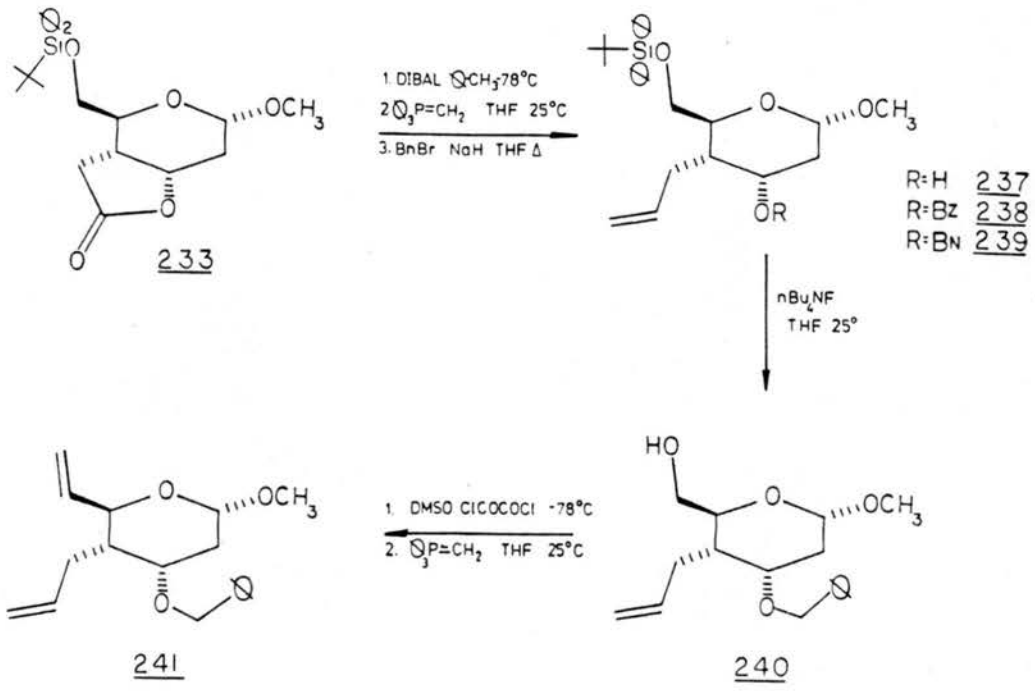


HANNESSIAN SYNTHESIS REF. 52

the elegant synthesis of Hanessian.[53] The benzylidene derivative 205 is protected as the C_3 benzoate (228) using pyridine as a solvent. Hydrogenation followed by selective tert-butyldiphenylsilyl ether formation at the C_6 hydroxyl affords the crystalline deprotected triol (230). The C_4 alcohol can now be oxidized to yield the crystalline C_4-ulose derivative (231). Homologation and reduction provide the C_4-two carbon homologated ester (232). This ester can be cyclized to give lactone (233). This lactone is easily transformed to the lactol using Dibal. This crude aldehyde is condensed with a Wittig type reagent corresponding to the desired prostoglandin side chain to yield 234. A similar oxidation homologation sequence is performed on the C_6 alcohol after desilylation to yield the protected form of TXB_2 (236). A two step hydrolysis of the methyl glycoside and the C_3 benzoate complete this remarkable synthesis of (+)-TXB_2. We decided to start our synthesis with the known lactone 233. The regio and stereochemistry could be confirmed at this stage by correlation to known physical data. Homologation using simpler Wittig reagents would not only provide an excellent model compound but one whose synthesis could easily be modified to provide the correct side-chains. The work by Hanessian, was unfortunately, a communication, and contained no experimental detail. However, this work outlines a route proven to be successful. In preparation of the lactone (233) it was found that the C_4-ulose derivative (231) could be

homologated with the Peterson reagent described for the 4-ulose compound (213) to give the ethyl ester or using the phosphonate reagent as described by Hanessian to provide the methyl ester. Both compounds clearly gave the same lactone. However, the methyl ester appeared to cyclize more easily. Under identical isolation conditions the methyl ester reaction mixture did not require an acidic treatment before chromotography to ensure the absence of ring-opened hydroxy-ester.

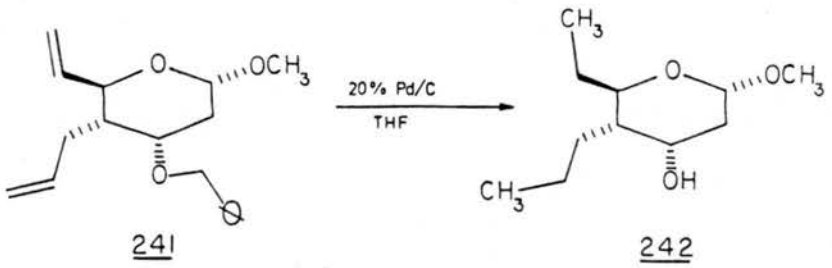
Scheme 78 depicts our route to the protected 2,4,6-trideoxy-ribo-hexose (241) containing the unsaturated side chains and protected C_3-alcohol. The Dibal reduction of lactone 233 gave the crude lactol in high yield by TLC. The crude lactol after work up was added directly to a solution of freshly generated ylide. The yield ranged from 35-70% after chromatographic purification. The resulting C_3-alcohol (237) was originally protected to give the benzoate (238). The use of the benzyl protecting group (239) was finally adopted since hydrogenation of the side chains would simultaneously yield the deprotected C_3-alcohol. The hydrogenation of the side chains was needed to ensure transparency of the region δ 4.0 - δ 6.0 in the NMR spectrum. The actual synthesis of TXA_2 would, of course, require unsaturated side-chains but characterization of the cyclized model would be greatly facilitated by this hydrogenation. The C_6 silyl ether was then removed and the corresponding C_6-aldehyde obtained by



233 241 240

SCHEME 78

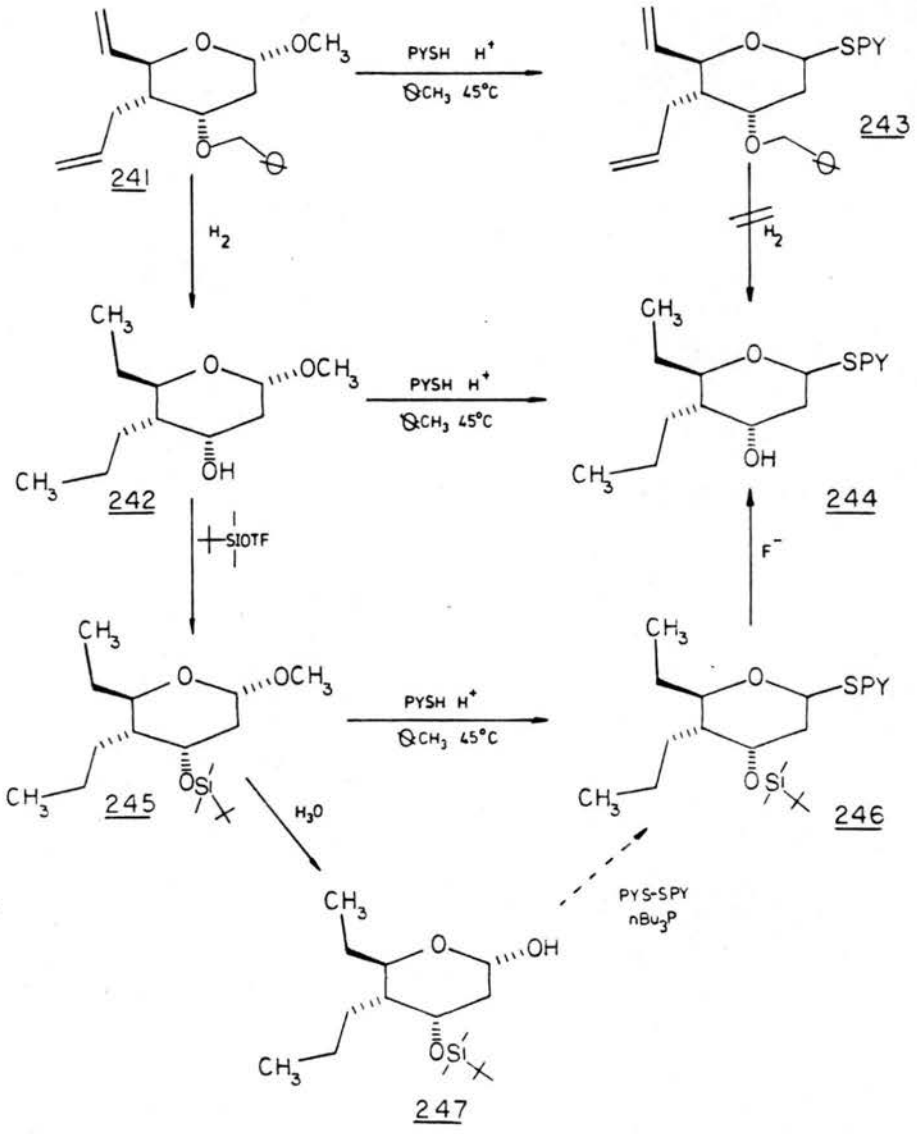
Swern oxidation. The crude aldehyde was treated with the simple methylene triphenyl phosphorane to yield the diallyl-benzylether (**241**). The diallyl-benzylether (**241**) was found to hydrogenate easily using 20% $Pd(OH)_2$ on carbon in THF at room temperature under one atmosphere of hydrogen. The hydrogenation was complete within 0.5h and gave a quantitative yield of alcohol **242** (Scheme 79). Alcohol **242** proved to be very labile, and appeared to decompose to volatile products. No identifiable mass or signal in the proton NMR spectrum remained after being stored at room temperature open to the air! The low



241 242

SCHEME 79

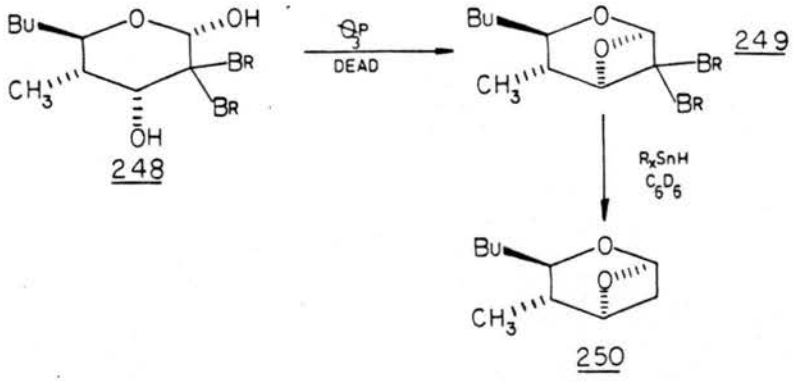
molecular weight of this alcohol (**242**) and the possibility of extrusion of methanol motivated immediate protection of the alcohol or conversion of the methylglycoside to the thioacetal. The strategies for obtaining the desired thioacetal (**244**) are outlined in Scheme 80. The clean hydrogenation of **241** to **242** followed by treatment in refluxing benzene with mercaptopyridine in the presence of p-toluene sulfonic acid gave a complex mixture of compounds but no desired **244** could be isolated or identified. Under milder conditions **241** could be converted to the thioacetals **243a,b**. Simply stirring in toluene at 45°C with a catalytic amount of p-toluene sulfonic acid and excess thiol produced a mixture of anomers (**243a,b**). Any attempt at cyclization of these compounds would require deprotection of the C_3 benzyl ether. Attempted hydrogenation of the benzyl ether in the presence of the thioacetal proved unsuccessful. Reaction with $Pd(OH)_2$ on carbon in THF yield a multicomponent mixture with no UV active material except


PYSH H+
CH3 45°C
241
243
H2
242
244
SIOTF
F-
245
246
H3O
PYS-SPY
nBu3P
247

SCHEME 80

starting thioacetal. The use of 5% Rh on carbon gave an extremely clean rapid reaction, however, the new compound displayed no UV activity. The UV activity of the thiopyridyl residue is very intense; the lack of UV activity in the hydrogenation indicated desulfurization had occurred. The preparation of these thioacetals (**243a,b**) from the methylglycoside **241** under milder conditions (45°, toluene) warranted reinvestigation of preparing **244** from **242**. Even under these conditions rapid consumption of starting material gave a multicomponent mixture in which no UV active product showed any sign of the characteristic sugar stain (TLC). Protection of **242** with a protecting group on the C_3 alcohol that could be removed after the thioacetal was generated was strongly indicated. Treatment of alcohol **242** with t-butyldimethylsilyl triflate produced the silyl ether **245**. It was planned to convert this material to the C_3 protected thioacetal **246**. This could be accomplished by hydrolysis to the hemiacetal **247** followed by the Arbuzov reaction or direct acid catalyzed acetal exchange to achieve compound **246**. Attempts to hydrolyze **245** under mild conditions (Dowex, 50W-8X) appeared to only effect anomerization of the methylglycoside. Direct acid catalyzed conversion of **245** to **246** proved surprisingly rapid in toluene as described above. Starting material was rapidly consumed and two new UV active compounds of appropriate R_f were cleanly formed in less than 0.5 h. Isolation proved to be difficult with significant loss of

mass and decomposition being observed after PTLC isolation. The crude reaction could be filtered through a silica gel pad, to remove excess mercaptan, and concentrated. The NMR spectrum of this crude residue seemed to reveal the H_1 protons of both anomers of thioacetals (**246a,b**). The crude thioacetals obtained in this way were treated in situ with with silver perchlorate; by NMR, starting material disappeared immediately but produced no identifiable cyclized product. The observed instability of these thioacetal precursors may be attributed to the acidic conditions of the exchange reaction under which they are produced. Crude **246** was neutralized with 0.1 N NaOH before passage through silica gel. This crude material was treated with fluoride in an attempt to produce **244** under basic conditions. Even under these conditions the desired thioacetal did not appear to be stable to isolation or characterization. The apparent instability of desired thioacetal (**244**) may indicate that the direct cyclization of a trideoxy substrate may not be feasible. Cyclization of a racemic compound containing bromine atoms in the 2,2' position has just been reported by Still[57]. A Mitsunobu-type reaction of the dibromide (**248**) provided the cyclized product (**249**) (Scheme 81). The strained 4-membered acetal with the adjacent electron withdrawing groups (**249**) proved stable enough for chromatographic isolation on silica gel. Final reduction of these electron withdrawing groups using a polymer bound tin hydride provided the desired 2,6-dioxa



SCHEME 81

(3.1.1) bicyclo nucleus of TXA_2 (250). The target compound (248) is characterized by a ^1H NMR spectrum in C_6D_6 and exhibits similar stability to hydrolysis as that of natural TXA_2. Stills work represents the first synthesis of the unique (3.1.1) oxetane nucleus of TXA_2.[57a] Using this approach Still has recently completed the synthesis of TXA_2 from natural TXB_2.[57b]

The stability of 249 may be attributed to the inductive effect of the adjacent electron withdrawing groups Still's successful strategy involves destabilization of the intermediate oxonium ion by which the four-membered bicyclic acetal can decompose. Our own unsuccessful approach also reveals the subtle effect that electron withdrawing groups have on the reactivity of the cyclic acetal of the pyranose ring. The reactivity of 2deoxy sugars is well known. The lack of an electronegative substitutent in the C_2 position dramatically affects the

reactivity. Stabilization of the electron deficient transition state lowers the activation energy of any reaction involving an electrophilic anomeric carbon. The proposed cyclization precursor **244** requires a mixed acetal of a trideoxy sugar. The lack of electron withdrawing substitutents on the pyranose ring contribute to the instability of this compound by stabilizing undesired reaction pathways. The added feature of the unprotected C_3 alcohol further stabilize the intermediate oxonium ion by neighboring group participation. With the C_3 hydroxyl group protected as the stable benzyl ether we apparently were able to prepare small quantities of thioacetal **249**. All thioacetals of the deoxyhexose derivatives prepared proved very labile to anomerization under nearly neutral conditions. The only reasonable mechanism for this anomerization would be ring opening to give a thionium ion followed by recyclization. The intermediate thionium ion in this epimerization would also be stabilized in the deoxy series relative to the stable β-glucose compound (**122**).

While the 1-thiocompounds do not appear to be suitable for direct cyclization of this particular deoxysubstrate, their efficient activation by thiophillic metals remain a valuable tool in glycosidations. The heterogeneous polymer bound mercury salt should prove an especially valuable complement to homogeneous metal salts in activation and subsequent application of these sugar derivatives to other complex and sensitive glycosidations.

CHAPTER 5

EXPERIMENTAL SECTION

GENERAL PROCEDURES

In most cases reaction progress was monitored by thin layer chromatography (TLC using 0.25 mm E. MERCK precoated silica gel plates (60F-254)). Development was accomplished using 5% phospho-molybdic acid in ethanol/heat and/or UV light. Preparative layer chromatography was performed on 20x20 cm glass plates described above or on a Harrison Res. Chromatotron. Woelm silica gel (32-63) was used for flash column chromatography. Flow rates of 10-100 ml/min, dependent on the column diameter/column height, were achieved under light pressure from a hand air pump. The R_f of the compound in the eluting solvent was generally one-half the relative value in an analytical system. Eluting solvents for each separation are given with the reaction scale and spectra.

Acid-sensitive reactions were carried out in glassware that had been flame dried on a vacuum pump (~0.5 mm) and nitrogen admitted through the vacuum adaptor via a balloon. The balloon on the stopcock maintains the positive pressure

of nitrogen in the reaction vessel. Reactions are stirred with teflon covered stir bars that are included during the drying process.

Reaction solvents and other liquid reagents were distilled before use under nitrogen using standard methods. The most commonly used were purified by distillation from the following: THF, benzophenone/sodium; CH_2Cl_2, P_2O_5; DMF, P_2O_5, stored over 3A sieves; CCl_4, P_2O_5; stored over 3 Å sieves; diisopropylamine, CaH_2; triethylamine, CaH_2; Et_2O, CaH_2; benzene, CaH_2; DMSO, CaH_2 , stored over 3 A sieves; trimethylsilylchloride - CaH_2, MeCN, P_2O_5, stored over 3 Å sieves; toluene, sodium; and oxalyl chloride, 0.5 mole % quinoline.

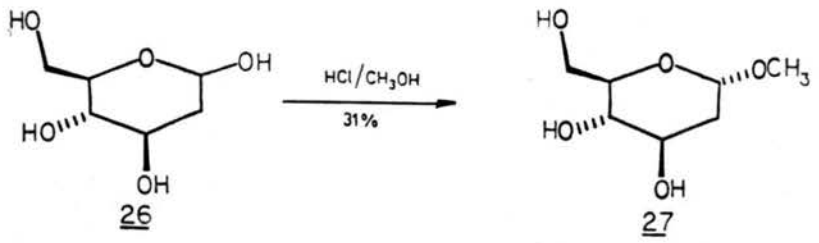
Silver(I) triflate was prepared fresh according to the method of Whitesides[62] and silyltriflates by the method of Corey[63]. 2,3,5-tri-O-benzyl[64a] and 2,3-isopropylidene-D-ribo-furanose[64b] were prepared from ribose by known methods. Trimethylsilyl derivatives of carbonyl compounds were prepared fresh. 2,3,4,6-tetra-O-benzyl-D-glucopyranose, 2-deoxy-glucose, and methyl-α-D-mannopyranoside were obtained commercially.

NMR spectrum were recorded on Varian T-60 (60 MHz), Varian EM 360 (60 MHz), Jeol JNM-FX100 (100 MHz), IBM Brucker WP-270SY (270 MHz) or Nicolet EM-360 (360 MHz) spectrometer and are reported in δ values relative to the reference indicated. IR spectra, unless indicated otherwise, were obtained on a Beckman 4240 spectrometer

from neat films obtained by evaporation of a concentrated CH_2Cl_2 solution onto NaCl plates. Melting points were recorded on a Mel-Temp instrument in open capillaries and are uncorrected. Microanalyses were performed on crystalline compounds by MHW Laboratories and are within $\pm$0.3% of the calculated values.

The following abbreviations are used throughout this section:

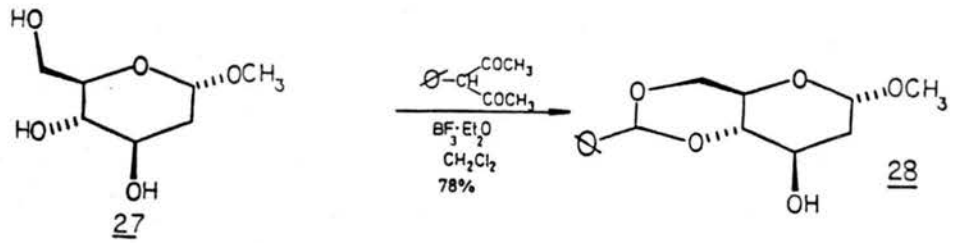
Ac_2O	acetic anhydride
CSA	camphor sulfonic acid
DMF	dimethyl formamide
DMSO	dimethyl sulfoxide
Dibal	diisobutyl aluminum hydride
EtOAc	ethyl acetate
EtOH	ethanol
LAH	lithium aluminum hydride
MeOH	methanol
NBS	n-bromosuccinamide
MS	methane sulfonyl
nBuLi	n-butyl lithium
TBMS	tert-butyldimethylsilyl
TBDPS	tert-butyldiphenylsilyl
Tf	trifluoromethylsulfonyl
TFFA	trifluoroacetic anhydride
TEA	triethylamine
DMAP	4-N,N-dimethylaminopyridine



26 27

Methyl 2-deoxy α-D-arabino-hexopyronoside (**27**)

2-deoxyglucose (**26**) (30 g, 0.186 mol) was dissolved in 1 N HCl/MeOH (200 ml) and stirred at room temperature overnight. The solution was neutralized with solid $NaHCO_3$ and filtered. The solution was concentrated to an oil, redissolved in dry THF and refiltered. After concentration the residue was dissolved in dry acetonitrile, an equal amount of toluene was added and the solution concentrated on a rotary evaporator with the bath temperature at $40^{o}C$. This was repeated two more times and the resulting syrup was recrystallized from dry acetonitrile. The first crop of white crystals were collected, ground, and dried in a desiccator overnight in the presence of P_2O_5, yielding 11.93 g (31%) of **27** as pure white crystals. The known methyl-glycoside[65] was used without further characterization.



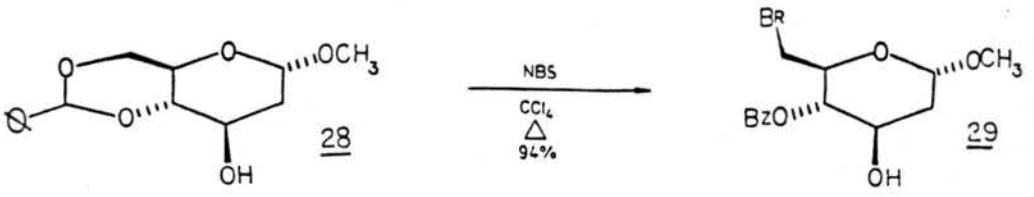
Methyl 4-6-O-benzylidene 2-deoxy-α-D-arabino-hexopyranoside (**28**)

To a stirred suspension of methylglycoside (**27**) (8.13 g, 45 mmol, 1.0 eq.) in dry CH_2Cl_2 (150 ml) was added benzaldehyde dimethylacetal (6.93 g, 45 mmol, 1.0 e.g.). A drop of $BF_3 \cdot Et_2O$ was added and the mixture stirred at room temperature for two hours. The solution was then diluted with CH_2Cl_2 (100 ml) and washed 2x25 ml 0.1 N NaOH. The organic phase was then dried (Na_2SO_4) and concentrated to give a white solid. The solid was recrystallized from CCl_4 to give 9.3 g (78%) of **28** as fine white needles.

mp 150-152°C

^1H NMR (60 MHz) ($CDCl_3$) δ (TMS): 1.78(M, 1H), 2.19(m, 1H), 2.28(BS, 1H), 3.26(S, 3H), 3.76(M, 5H), 4.69(m, 1H), 5.13(S, 1H), 7.35(m, 5H).

The known benzylidene derivative[9] was used without further characterization.

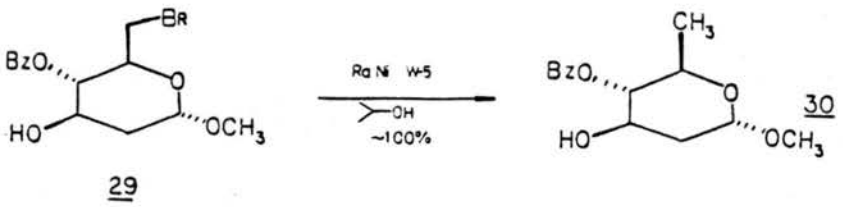


Methyl 4-O-benzoyl-6-bromo-2,6-dideoxy-α-D-arabino-hexopyranoside (**29**)

To a stirred solution of benzylidene derivative (**28**) (12.0 g, 45.1 mmol, 1.0 eg.) in CCl_4 (400 ml) was added NBS (8.83 g, 49.6 mmol, 1.1 eq) and $BaCO_3$ (5 g, excess). The mixture was refluxed for one hour, cooled, filtered, and concentrated. A small flash column was used to remove residual succinimide; eluting with 50% EtOAc/hexane yields 13.8 g (94%) of **29** as an off white solid.

^1H NMR (60 MHz) ($CDCl_3$) δ (TMS): 1.85(m, 1H), 2.27(m, 1H), 8.82(bs, 1H), 3.40(s, 3H), 3.46(d, 2H), 4.15 (m, 2H), 8.86(m, 2H), 7.13(m, 3H), 7.93(m, 2H).

The known bromide[9] was used without further characterization.



29 30

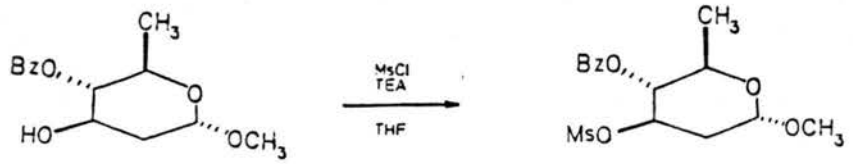
Methyl-4-O-benzoyl-2,6-dideoxy-α-D-arabino-hexopyranoside (30)

The bromo-benzoate (29) (13.8 g, 40 mmol) was dissolved in isopropanol (300 mL) at room temperature. To this solution was added a suspension of Raney-nickel W-5 in isopropanol (7 mL) and the mixture degassed. The mixture was then stirred vigorously under an atmosphere of H_2 for 12 h at room temperature. The suspension was filtered, concentrated, diluted with $CHCl_3$ and washed twice with H_2O. The organic layer was dried over anhydrous sodium sulfate, filtered, and evaporated to afford 10.6 g of the 2,6-dideoxy-benzoate (30) (100%) as a glass.

$[\alpha]_D^{25}$ = +121.5° (CH_2Cl_2)

^1H NMR (60 MHz, $CDCl_3$) δ TMS: 1.36(3H, d, J=6.2Hz); 1.65-2.60(2H, m); 2.85(1H, br s); 3.36(3H, s); 3.93(2H, m); 4.82(2H, m); 7.48(3H, m); 8.00(2H, m).

IR(NaCl, neat): 3460, 2930, 1740, 1265 cm^{-1}.

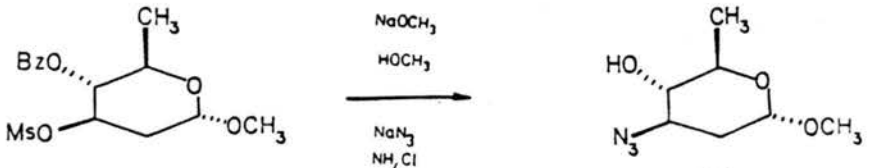


30 31

Methyl-3-azido-2,3,6-trideoxy-αD-arabino-hexopyranoside (33)

To a stirred solution of the benzoate (30) (5.30 g, 19.9 mmol, 1.0 equiv.) in THF (150 mL) at 0°C was added triethylamine (2.15 g, 21.2 mmol, 1.0 equiv.) and a solution of methanesulfonyl chloride (2.67 g, 23.3 mmol, 1.1 equiv.) in THF (2 mL) dropwise. The mixture was stirred 15 min at 0°C, 15 min at 25°C, filtered to remove $Et_3N°HCl$, and the solvent evaporated to afford 6.62 g (97%) of the 3-mesylate-4-benzoate derivative (31) as a white crystalline solid which was directly used for the next step without further purification.

^1H NMR (100 MHz, $CDCl_3$) δ TMS: 1.30(3H, d, J=6Hz); 1.75-2.70(2H, m); 2.80(3H, s); 3.35(3H, s); 3.80(1H, m); 4.75(1H, br s); 5.15(2H, m); 7.45(3H, m); 8.10(2H, m).



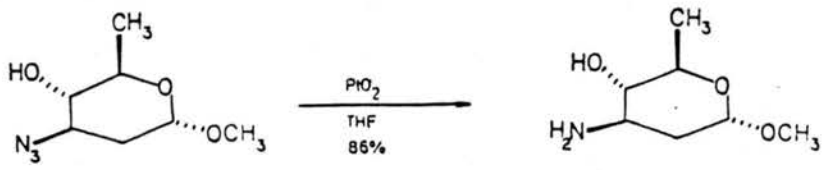
31 33

To a stirred solution of the crude mesylate (1.61 g, 4.68 mmol, 1.0 equiv.) in MeOH (50 mL) was added powdered sodium methoxide (1.51 g, 28 mmol, 5.7 equiv.) portionwise at room temperature. The mixture was stirred 5h at room temperature, 2 drops of ethnolic phenolphthalein solution was added and the mixture was neutralized with 0.5N HCl until a colorless solution persisted. To this solution was added sodium azide (0.91 g, 14 mmol, 2.85 equiv.), ammonium chloride (0.50 g, 9.3 mmol, 1.9 equiv.) and the mixture brought to reflux for 24h. The solution was then allowed to cool, diluted with H_2O (150 mL) and thoroughly extracted with $CHCl_3$. The combined extracts were dried over anhydrous sodium sulfate, filtered, evaporated, and separated on a silica gel column (eluted with 50% EtOAc in hexanes) to afford 0.55 g (63%) of pure azido alcohol (**33**) (oil).

$[\alpha]_D^{25}$ = +127.5° ($CHCl_3$). (Lit. L-series -131.8°; Lit. (D-series +125° ($CHCl_3$)).

^1H NMR (100 MHz, $CDCl_3$) δ $CHCl_3$: 1.30(3H, d, J=6.3Hz); 1.72(1H, m); 2.12(1H, m); 2.60(1H, br s, D_2O exch); 3.16 (1H, m); 3.34(3H, s); 3.69(2H, m); 4.74(1H, br s).

IR($CHCl_3$): 3440, 2920, 2100, 1125, 1045 cm^{-1}.



33 34

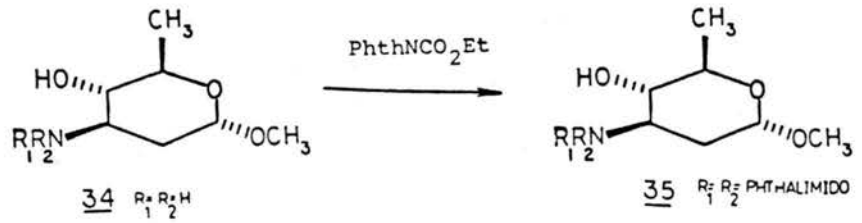
Methyl-3-amino-2,3,6-trideoxy-α-D-arabino-hexopyranoside (**34**)

A mixture of the azido alcohol (**33**) (3.93 g, 21 mmol) and PtO_2 (47 mg, 0.21 mmol, 0.01 mmol %) in THF (400 mL) was vigorously stirred under a hydrogen atmosphere for 6h at room temperature. Filtration, evaporation of the solvent, and filtration through a small plug of silica gel (50% MeOH in CH_2Cl_2) affords 2.92 g (86%) of amino alcohol (**34**).

mp 128.5-129.5°C (recryst. Et_2O/MeOH).

$[\alpha]_D^{25}$ = +142.8° [MeOH] (lit. in L-series = -145.1° in MeOH).

^1H NMR (100 MHz, $CDCl_3$) δ $CHCl_3$: 1.27(3H, d, J=6.3Hz); 1.43-2.17(5H, m); 2.71-3.09(2H, m); 3.60(3H, s); 3.69-3.80(1H, m); 4.67(1H, m). IR(NaCl, neat): 3340, 3110, 2875, 1060, 1045 cm^{-1}.



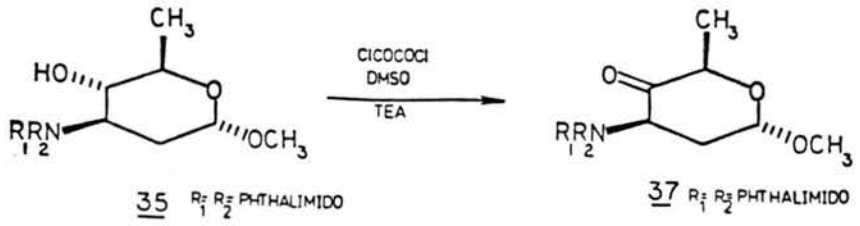
Methyl-3-phthalimido-2,3,6-trideoxy-α-D-arabino-hexopyranoside (35)

The amino-alcohol (**34**) (1.52 g, 9.44 mmol, 1.0 equiv) and N-carboethoxy phthalimide (2.28 g, 10.38 mmol, 1.1 equiv) were dissolved in toluene (75 mL) and stirred at reflux temperature for 4h. The mixture was allowed to cool to room temperature, washed with brine, dried over anhydrous sodium sulfate, filtered, concentrated, and separated on silica gel (4 mm chromatotron PTLC, eluted with 3:1, hexanes:EtOAc) to afford the phthalimide (**35**) 2.07 g (75%) as a white solid.

mp 111-113°C (recryst. Et_2O/hexanes) $[\alpha]_D^{25}$ = +81.2° ($CHCl_3$).

^1H NMR (100 MHz, $CDCl_3$ δ $CHCl_3$: 1.30(3H, d, J=6Hz); 1.85(1H, m); 2.60(1H, m); 3.00(1H, br s, D_2O exch); 3.32(3H, s); 3.84(3H, m); 4.72(1H, br s); 7.60(4H, m).

IR($CHCl_3$): 3450, 2920, 1740, 1690 cm^{-1}. Anal. Calcd. for ($C_{15}'H_{17}NO_5$) C, 61.84; H, 5.88; N, 4.81. Found: C, 61.45; H, 6.02; N, 4.79.



Phthalimido-Ketone (**37**)

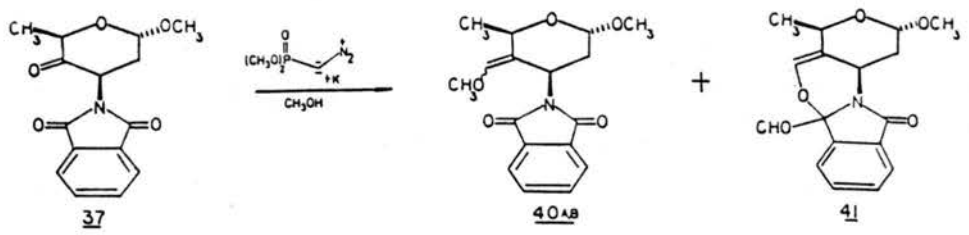
To a stirred solution of oxalyl chloride (0.99 g, 7.8 mmol, 1.1 equiv) in CH_2Cl_2 (70 mL) at -78°C was added DMSO (1.22 g, 15.6 mmol, 2.2 equiv) dropwise. After stirring the mixture 15 min at -78°C, a solution of the phthalimido-alcohol (**35**) (2.07 g, 7.1 mmol, 1.0 equiv) in CH_2Cl_2 (10 mL) was added dropwise and stirring continued an additional 30 min at -78°C. Triethylamine (3.58 g, 35.5 mmol, 5.0 equiv) was added and the mixture stirred 15 min at -78°C, 15 min at room temperature and the solvent removed under reduced pressure. The residue was triturated with THF, filtered to remove $Et_3N.HCl$, evaporated, and passed through a plug of silica gel (2:1, hexanes:EtOAc) to afford 1.78 g (79%) of the pure ketone (**37**).

mp 133-135°C (recryst. MeOH).

$[\alpha]_D^{25}$ = + 96.4° ($CHCl_3$).

^1H NMR (100 MHz, $CDCl_3$) δ $CHCl_3$: 1.37(3H, d, J=6.7Hz); 2.29(1H, m); 3.02(1H, m); 3.48(3H, s); 4.39(1H, q, J=6.7Hz); 4.96(1H, br s); 5.28(1H, dd, J=13Hz, J=7Hz); 7.75(4H, m).

IR($CHCl_3$): 2960, 1740, 1710, 1365, 1230 cm^{-1}.



Phthalimido Enol Ethers (**40, 41**)

To a stirred solution of potassium **tert**-butoxide (280 mg, 2.5 mmol, 2.0 equiv) in methanol (10 mL) was added a solution of dimethyl diazomethylphosphonate (373 mg, 2.5 mmol, 2.0 equiv) in methanol (3 mL) at room temperature. After the addition was complete, a solution of the ketone **37** (360 mg, 1.24 mmol, 1.0 equiv) in THF (2 mL) was added dropwise. After an initial, mild evolution of N_2, the mixture stirred, 1.5h at room temperature, was poured into H_2O and thoroughly extracted with CH_2Cl_2. The combined extracts were dried over anhydrous sodium sulfate, filtered, evaporated, and separated on PTLC silica gel (eluted with 25% EtOAc in hexanes) to afford 191 mg (49%) of the major isomer (**41**), 116 mg (30% of the minor isomers **40a,b** and unreacted starting material (**37**), (63 mg, 18%) (97% conversion).

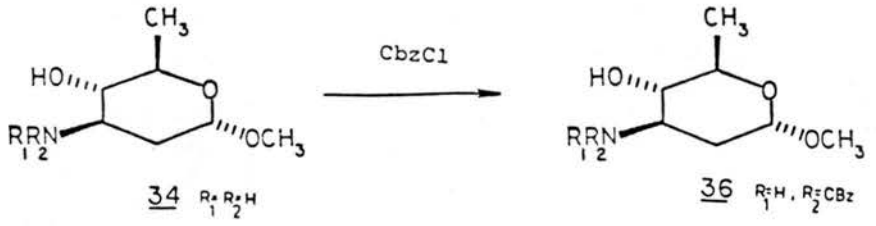
Major Diastereomer: ^1H NMR (100 MHz, $CDCl_3$) δ $CHCl_3$: 1.24(3H, d, J=6.5Hz); 1.85(1H, m); 2.22(1H, m); 3.33(3H, s); 3.83(3H, s); 4.41(1H, q, J-6.5Hz); 4.63(1H, m); 4.82(1H, m); 6.29(1H, m); 7.32-7.56(3H, m); 7.56-7.80(1H, m).

IR($CHCl_3$): 2960, 1720, 1700, 1260, 1045 cm^{-1}.

Mass spectrum, m/e = 317(0.8), 316(3.2), 286(2.8).

Minor Diastereomers Mixture: ^1H NMR (60 MHz, $CDCl_3$) δ $CHCl_3$: 1.41(3H, d, J=6.5Hz); 2.17(2H, m); 3.11(1.5H, s); 3.17(1.5H, s); 3.47(3H, s); 3.91-5.21(3H, m); 6.31(1H, m); 7.61(4H, m).

IR(Neat): 2965, 1715, 1700, 1370, 1190 cm^{-1}.



34 R_1=R_2=H

36 R_1=H, R_2=CBz

Methyl-3-(N-carbobenzyloxy)amino)-2,3,6-trideoxy-α-D-arabino-hexopyranoside (36)

To a vigorously stirred solution of amino alcohol (34) (140 mg, 0.87 mmol, 1.0 equiv) in CH_2Cl_2 (5 mL)/saturated

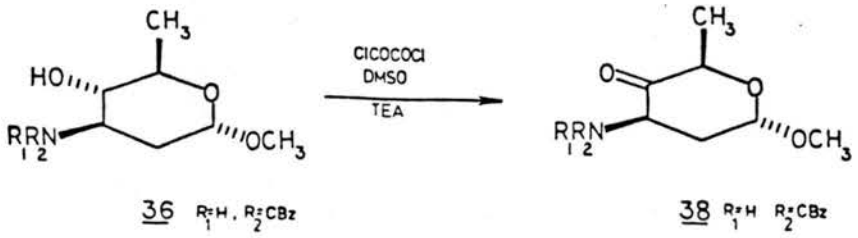
$NaHCO_3$ (5 mL) at 25°C was added benzylchloroformate (223 mg, 1.30 mmol, 1.5 equiv) dropwise. The mixture stirred for 30 min, was diluted with CH_2Cl_2, poured into H_2O and thoroughly extracted with CH_2Cl_2. The combined organic extracts were dried over anhydrous sodium sulfate, filtered, evaporated, and separated on a small silica gel column (eluted with 50% EtOAc/hexanes) to afford 165 mg (64%) of (**36**).

mp 128-130° (Et_2O/hexanes).

$[\alpha]_D^{25}$ = +125.5°C ($CHCl_3$).

^1H NMR (100 MHz, $CDCl_3$ δ TMS: 1.38(3H, d, J=6.1Hz); 1.37-1.74(2H, m); 2.03(1H, m); 3.03(1H, m): 3.33(3H, s); 3.46-4.14(2H, m); 4.58-4.90(2H, m); 5.10(2H, s); 7.34(5H, s).

IR(Neat): 3415, 3320, 2970, 1680, 1535 cm^{-1}.



<u>36</u> R_1=H, R_2=CBz <u>38</u> R_1=H R_2=CBz

<u>N-Carbobenzoxy Ketone</u> (**38**)

To a stirred solution of oxalyl chloride, (73.0 mg, 0.57 mmol, 1.1 equiv) in CH_2Cl_2 (10 mL) at -78°C was added

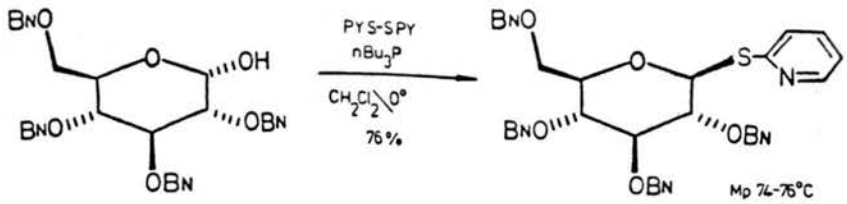
DMSO (90.0 mg, 1.15 mmol, 2.2 equiv) dropwise. After stirring the mixture for 15 min at -78°C, a solution of alcohol (**36**) (154 mg, 0.522 mmol, 1.0 equiv) in CH_2Cl_2 (2 mL) was added dropwise. After 15 min at -78°C, triethylamine (0.365 mL, 2.61 mmol, 5.0 equiv) was added and the resulting mixture allowed to warm to room temperature, and the solvent removed under reduced pressure. The residue was triturated with THF, filtered to remove $Et_3N \cdot HCl$, evaporated, diluted with CH_2Cl_2, and washed with H_2O. The organic extract was dried over anhydrous sodium sulfate, filtered, and evaporated to afford 105 mg (69%) of the ketone (**38**).

mp 73-75°C (Et_2O/hexane).

$[\alpha]_D^{25}$ = +88.5°C ($CHCl_3$).

^1H NMR (100 MHz, $CDCl_3$) δ $CHCl_3$: 1.28(3H, d, J=6.6Hz); 1.90(1H, m); 2.82(1H, m); 3.44(3H, s); 4.37(1H, q, J=6.5Hz); 4.61-4.93(2H, m); 5.09(2H, s); 5.51(1H, m, NH); 7.32(5H, s).

IR(Neat): 3328, 2920, 1745, 1715, 1700, 1515 cm^{-1}.



121 122

β-2,3,4,6-tetra-O-benzyl-1-(2-thiopyridyl)-D-glucopyranose (122)

To a stirred solution of 2,3,4,6-tetra-O-benzyl glucopyranose (121) (0.504 g, 0.93 mmol, 1.0 equiv) and 2,2'-dipyridyl disulfide (0.226 g, 1.03 mmol, 1.1 equiv) in CH_2Cl_2 (25 mL) at 0°C was added tri-n-butylphosphine (0.208 g, 1.03 mmol, 1.1 equiv) dropwise. After stirring for 5H at 0°C, 3 g of silica gel was added and the mixture evaporated to dryness. The silica gel powder containing the adsorbed reaction mixture was loaded on top of a silica gel flash column (eluted with 25% Et_2O in hexanes) to afford 0.406 g (69%) of 122 as a waxy solid.

$[\alpha]_D^{25}$ = +8.8° (CH_2Cl_2 c=2.0)

mp 74-76°C (recryst. Et_2O/hexanes).

^1H NMR (100 MHz)($CDCl_3$) δ TMS: 3.40-3.86(6H, m), 4.24-5.07(8H, m); 5.43(1H, d, J=9.6Hz); 6.50-7.60(23H, m); 7.41(1H, m). Anal. ($C_{39}H_{39}NO_5S$) C, H, N, S.

General Procedure for C-Glycosidation of (122)

To a stirred solution of **122** (1.0 equiv) in distilled, dry CH_2Cl_2 (0.16 M) was added the aromatic or TMS enol ether substrate (3.5 equiv) in one portion, followed by addition of silver(I) triflate (2.2 equiv). The mixture was stirred at room temperature for 2h (or until TLC analysis indicates disappearance of starting material), diluted with CH_2Cl_2, filtered, and washed with 0.1 N NaOH. The organic layer was separated, dried over anhydrous sodium sulfate, filtered, evaporated, and separated by silica gel chromatography. Solvent systems for separations are given with the reaction scale and spectral data for each compound. All reactions were carried out in CH_2Cl_2 unless otherwise stated under a nitrogen atmosphere.

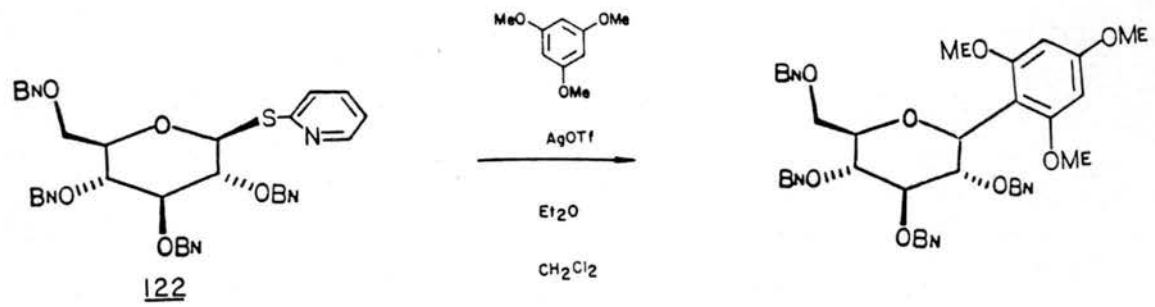
General Procedure for Hydrogenolysis of Benzyl Protecting Groups

To a stirred solution of the per-O-benzyl C-glycoside (1.0 equiv) in THF (0.01 M) at 25°C was added 10% Pd on Charcoal (0.1 mol equiv). The reaction vessel was evacuated using standard aspirator suction and the pressure relieved by introduction of H_2 gas. The evacuation/H_2flushing sequence is repeated four times and the mixture allowed to stir vigorously for 12h. The

suspension was filtered through a small plug of celite and separated by silica gel chromatography. The solvent systems for separation are given with the reaciton scale and spectral data for each poly-ol product. In some cases, the poly-ol was directly used for the subsequent acetylation or acetonization reaction without chromatographic isolation and spectroscopic characterization.

General Procedure for per-O-acetylation of C-Glycosides

To a stirred, room temperature solution of the poly-ol substrate (1.0 equiv) in CH_2Cl_2 (0.02 M), pyridine (50 equiv) and acetic anhydride (6.0 equiv) was added DMAP (0.1 equiv). The mxiture stirred at room temperature for 1h, was diluted with CH_2Cl_2 and washed twice with 0.1 N HCl. The organic layer was dried over anhydrous sodium sulfate, filtered, evaporated, and separated by PTLC silica gel. The solvent systems for separation are given with the reaction scale and spectral data for each product.



122

1-Deoxy-1-(C-2',4',6'-trimethoxyphenyl)-2,3,4,6-tetra-O-benzyl-D-glucopyranose (**126**)

From 25 mg (0.04 mmol) of **122**, 17 mg (0.1 mmol) of 1,3,5-trimethoxybenzene and 26 mg (0.1 mmol) of silver(I) triflate in CH_2Cl_2 (1.5 mL), 17.2 mg (63 %) of pure β-**126a** was obtained (isolated on PTLC silica gel, eluted with 50% ET_2O in hexanes)(oil).

$[\alpha]_D^{25}$ = +5.4° (c=0.4, $CHCl_3$), (lit[17e] +5.4°).

^1H NMR (100 MHz) ($CDCl_3$) δ TMF: 3.40-5.12(15H, m), 3.66(3H, s), 3.73(3H, s), 3.76(3H, s), 6.10(2H, m), 6.62-7.40(20H, m);

IR(NaCl, neat): 1605, 1585, 1450, 1200, 1150, 1115, 1090, 1060, 690 cm^{-1}.

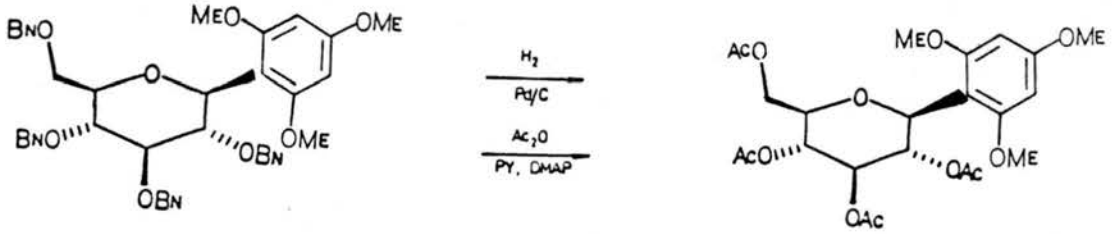
Mass spectrum m/z = 690(M^+, 1.0), 599(13.0), 287(68.2), 97(100).

Under identical conditions, except in Et_2O (1.5 mL) as reaction solvent, a 5:1 α:β ratio of product was obtained: α-**126**: (oil) $[\alpha]_D^{25}$ = +40.0° (c=0.2, $CHCl_3$).

^1H NMR (100 MHz) ($CDCl_3$) δ TMS: 3.30-4.96(14H, m), 3.72(6H, s), 3.81(3H, s), 5.88(1H, d, J=7.5Hz), 6.14(2H, s), 6.80-7.40(20H, m).

IR(NaCl, neat): 3050, 2920, 1610, 1455 cm^{-1}.

Mass spectrum m/e = 690(M^+, 0.4), 599 (18.4), 287(98.3), 91(100).



126B 127B

β-1-Deoxy-1-(2',4',6'-trimethoxyphenyl)-2,3,4,6-tetra-O-acetyl-D-glucopyranose (**127B**)

From 70.3 mg (0.1 mmol) of β-**126B**, 15 mg of 10% Pd/c in THF (10 mL), 26.7 mg (79%) of the tetra-ol was obtained by filtration of the catalyst and evaporation of the solvent. This material was directly acetylated without further purification. Acetylation using 0.8 mg DMAP, 43 mg Ac_2O and 276 mg pyridine in CH_2Cl_2 (3 mL) afforded 19.8 mg

(40%) of the tetra-acetate **127B** (chromatographed on PTLC silica gel, eluted with 50% EtOAc in hexanes) (oil).

$[\alpha]_D^{25}$ = -14.4° (c=1.2, CH_2Cl_2).

^1H NMR (100 MHz)($CDCl_3$) δ TMS: 1.73(3H, s), 2.01(3H, s), 2.05(6H, s), 3.80-4.28(3H, m), 3.78(6H, s), 3.83(3H, s), 4.80-5.40(3H, m), 5.70-6.20(3H, m).

^1H NMR (360 MHz)($CDCl_3$) δ TMS: 5.02(1H, d, $J_{1,2}$=10.5Hz).

IR(NaCl, neat): 2940, 1750, 1612, 1225 cm^{-1}.

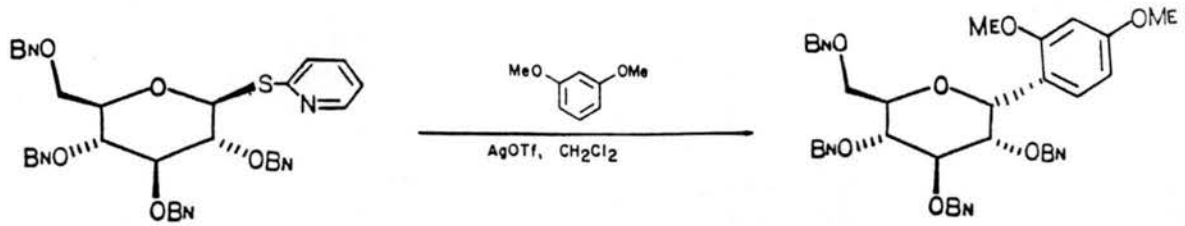
<u>α-1-Deoxy-1-(C-2'4',6'-trimethoxyphenyl)-2,3,4,6-tetra-O-acetyl-D-glucopyranose</u> (**127A**)

From 48 mg (0.07 mmol) of α-**126A**, 10 mg of 10% Pd/C in THF (8 mL), 16.2 mg (70%) of the tetra-ol was obtained by filtration of the catalyst and evaporation of the solvent. Direct acetylation of this material (10.6 mg, 0.03 mmol) using 20 mg Ac_2O, 0.4 mg DMAP and 126 mg pyridine in CH_2Cl_2 (1.5 mL) afforded 10.2 mg (64%) of tetra-acetate **127A** (oil).

$[\alpha]_D^{25}$ = +67.6° (c=0.8, CH_2Cl_2).

^{1}H NMR (100 MHz) ($CDCl_3$) δ TMS: 1.78(3H, s), 2.04(9H, s), 2.84(3H, s), 3.90(6H, s), 3.80-4.36(3H, m), 4.92-5.60(2H, m), 5.80-6.16(2H, m), 6.17(2H, s).

^{1}H NMR (360 MHz) ($CDCl_3$) δ TMS: 6.03(1H, d, J=7.6Hz).



122 128

<u>α-1-Deoxy-1-(C-2',4'-dimethoxyphenyl)-2,3,4,6-tetra-O-benzyl-D-glycopyranose</u> (**128**)

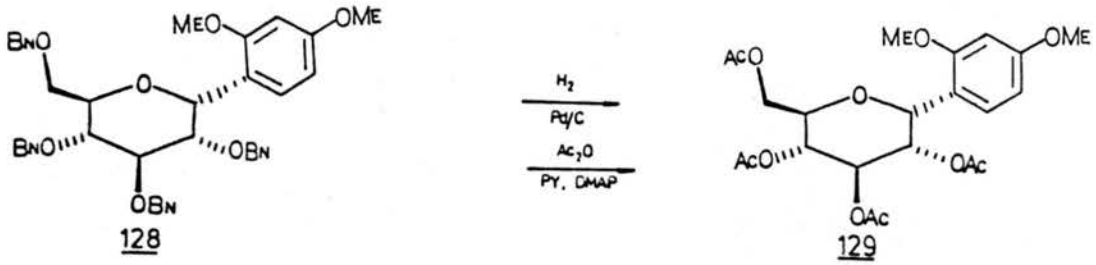
From 700 mg (1.11 mmol) of **122**, 534 mg (3.87 mmol) of <u>m</u>-dimethoxybenzene and 625 mg (2.43 mmol) of silver(I) triflate in CH_2Cl_2 (7 mL) 351 mg (48%) of C-glycosylated product was obtained (chromatographed on a silica gel column with 40% Et_2O in hexanes) (oil).

$[\alpha]_D^{25}$ = +22.7° ($CHCl_3$).

^{1}H NMR (100 MHz) ($CDCl_3$) δ TMS: 3.60-4.12(6H, m), 3.67(3H, s), 3.80(3H, s), 4.20-5.00(8H, m), 5.42(1H, d, J=3.4Hz), 6.29-6.57(2H, m), 6.83-7.43(20H, m), 7.62(1H, d, J=7.8Hz).

IR(NaCl, neat): 1610, 1580, 1500, 1460, 1450, 1205, 1085, 1065, 730, 690 cm^{-1}.

Mass spectrum m/z = 660(M^+, 0.3), 569(1.6), 257(51.6), 91(100).



128 129

α-1-Deoxy-1-C-2',4'-dimethoxyphenyl)-2,3,4,6-tetra-O-acetyl-D-glucopyranose (**129**)

From 170 mg (0.26 mmoL) of **128**, 20 mg of 10% Pd/C in THF (15 mL), the tetra-ol 66.5 mg (85%) was obtained by silica gel PTLC chromatography (10% MeOH in CH_2Cl_2) and was used directly for the acetylation reaction.

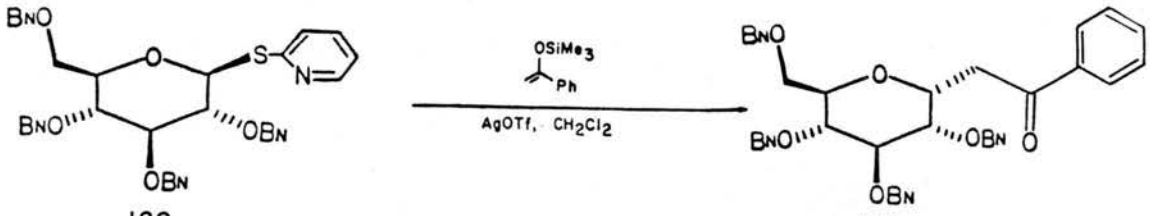
From 35.0 mg (0.12 mmol) of the tetra-ol, DMAP (2 mg, 0.011 mmol), 71.7 mg Ac_2O and 462 mg pyridine in CH_2Cl_2 (2 mL) was obtained 37.0 mg (66%) of tetra-acetate **129** (oil).

$[\alpha]_D^{25}$ = +26.1° (c=3.7, CH_2Cl_2).

^1H NMR (100 MHz) ($CDCl_3$) TMS: 1.84(3H, s), 2.06(3H, s), 2.06(3H, s), 2.12(3H, s), 3.80(3H, s), 3.80(3H, s),

3.90-4.50(3H, m), 5.00-5.60(4H, m), 6.45(2H, m), 7.42(1H, d, J=7.8Hz).

^1H NMR (360 MHz)($CDCl_3$) δ tMS: 5.51(1H, d, J_{1-2}= 4.14Hz).



122 130

<u>α-1-Deoxy-1-(C-phenacyl)-2,3,4,6-tetra-O-benzyl-D-glucopyranose</u> (130)

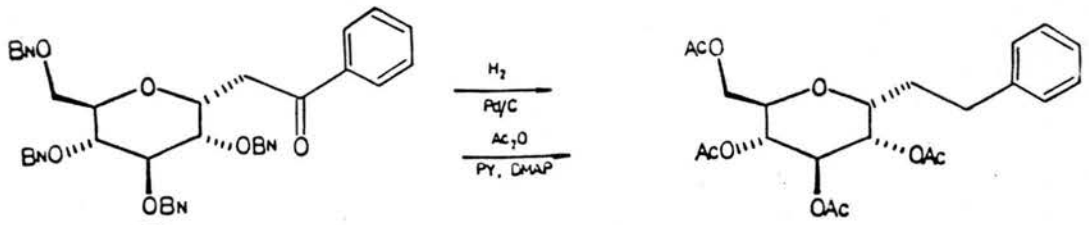
From 78 mg (0.12 mmol) of **122**, 118 mg (0.61 mmol) of the TMS enol-ether of acetophenone and 63 mg (0.24 mmol) of silver(I) triflate in CH_2Cl_2 (2.5 mL), 64.3 mg (81%) of the ketone (130) was obtained (chromatographed on PTLC silica gel, eluted with 33% Et_2O in hexanes).

mp 74.5-75°C (recryst. Et_2O/hexanes).

$[\alpha]_D^{25}$ = +48.2° ($CHCl_3$).

^1H NMR (100 MHz) ($CDCl_3$) δ TMS: 3.30(2H, m), 3.50-3.90(6H, m), 4.30-5.00(9H, m), 7.00-7.90(25H, m).

IR(NaCl, neat): 3015, 2860, 1680, 1080 cm^{-1}. Anal ($C_{42}H_{42}O_6$): C, H.



α-1-Deoxy-1-(C-1-phenethyl)-2,3,4,6-tetra-O-acetyl-D-glucopyranose (131)

From 40.3 mg (0.063 mmol) of (130), 10 mg of 10% Pd/C in THF (8 mL), the tetra-ol 16.6 mg (94%) was obtained (chromatographed on PTLC silica gel, eluted with 10% MeOH in CH_2Cl_2) as an amorphous solid.

Mass spectrum, m/e = 268(M^+, 1.0); 177(2.2); 91(100).

From 11.5 mg (0.04 mmol) of the tetra-ol, 1.0 mg DMAP, 25 mg Ac_2O and 161 mg pyridine in CH_2Cl_2 (2 mL) was obtained 9.6 mg (52%) of the tetra-acetate (131) (chromatographed by PTLC silica gel, eluted with 50% EtOAc in hexanes) (oil).

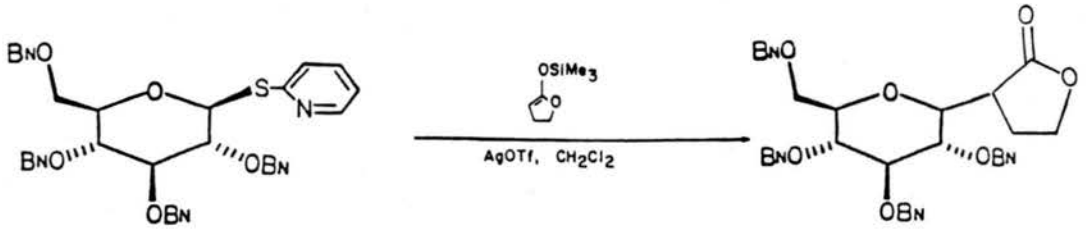
$[\alpha]_D^{25}$ = +56.5° (c=0.9, CH_2Cl_2).

^1H NMR (100 MHz) ($CDCl_3$) δ TMS: 1.60-2.38(2H, m), 2.01(3H, s), 2.03(3H, s), 2.04(3H, s), 2.10(3H, s), 2.40-3.00(2H, m), 3.70-4.00(1H, m), 4.00-4.36(3H, m), 4.75-5.40(3H, m), 7.18-7.40(5H, m).

^1H NMR (360 MHz) ($CDCl_3$) δ TMS: 5.10(1H, dd, $J_{1,2}$=5.5Hz).

IR(NaCl, neat): 3020, 2950, 1745, 1365, 1220 cm^{-1}.

Mass spectrum, m/z = 436(M^+, 5.1), 376(8.7, 316(3.7), 91(100).



122 136ABCD

1-Deoxy-1-(C-2'-butyrolactonyl)-2,3,4,6-tetra-O-benzyl-D-glucopyranose (136)

From 320 mg (0.5 mmol) of **122**, 194 mg (1.0 mmol) of the TMS enol-ether of γ-butyrolactone and 260 mg (1.0 mmol) of silver(I) triflate in CH_2Cl_2 (5 mL), 85 mg (28%) of one α-lactone and 96 mg (32%) of a faster 3 compound mixture which was rechromatographed (PTLC 12% Et_2O/toluene) (1:1.1(α):3.2(β) ratio) (overall α:β ratio = 4:1).

<u>β-isomer 136C</u>: $[\alpha]_D^{25}$ = +3° (c=0.79, CH_2Cl_2), R_f (0.34, 12% Et_2O/toluene)

^1H NMR (270 MHz) ($CDCl_3$) δ TMS: 2.27(1H, m), 2.44(1H, m), 3.01(1H, m), 3.40-3.75(6H, m), 4.09-4.40(3H, m), 4.45-5.05(8H, m), 7.10-7.55(20H, m).

IR(NaCl, neat): 3030, 2860, 1765, 1455, 1100 cm^{-1}.

Mass spectrum, m/z = 637(M^+ +29, CI, CH_4, 3.7), 609(M^+ + 1, 0.3), 517(7.5), 91(100).

<u>β-isomer 136D</u>: $[\alpha]_D^{25}$ = -43° (c=0.415, CH_2Cl_2), R_f (0.29, 12% Et_2O/toluene)

^1H NMR (270 MHz) ($CDCl_3$) δ TMS: 1.39(1H, m), 2.11(1H, m), 2.81(1H, m), 3.28(1H, m), 3.45(1H, m), 3.60-3.83(5H, m), 3.98(1H, m), 4.20(1H, m), 4.41-4.68(4H, m), 4.77-5.02(4H, m), 7.10-7.45(20H, m).

IR(NaCl, neat): 3030, 2900, 1775, 1090 cm^{-1}.

Mass spectrum, m/z = 637(M^+ +29, CI, CH_4, 0.7), 517(0.7), 91(100).

<u>α-isomer 136A</u>: $[\alpha]_D^{25}$ = +28.6° (c=1.32, CH_2Cl_2), R_f (0.25 12% Et_2O/toluene)

^1H NMR (270 MHz) ($CDCl_3$) δ TMS: 2.39(2H, m), 3.04(1H, m), 3.54-3.80(4H, m), 3.95-4.20(4H, m), 4.30(1H, m), 4.38-4.73(8H, m), 7.12-7.60(20H, m).

IR(NaCl, neat): 3030, 2860, 1770, 1090 cm^{-1}.

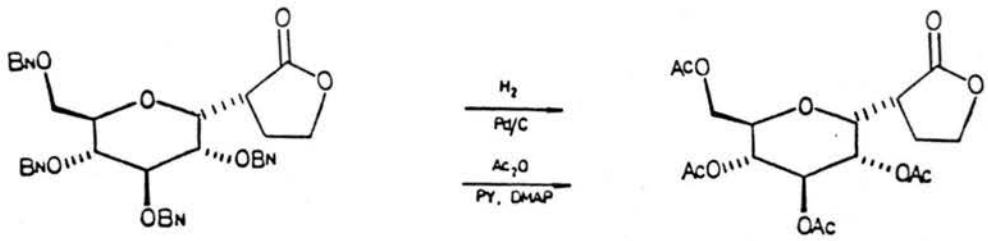
Mass spectrum, m/z = 517(M^+ -91, 5.1), 425(0.7), 411(5.1), 91(100).

<u>α-isomer 136B</u>: $[\alpha]_D^{25}$ =+44.4° (c=0,63, CH_2Cl_2), R_f (0.18 12% Et_2O/toluene)

^1H NMR (270 MHz) ($CDCl_3$) δ TMS: 2.44(2H, m), 3.01(1H, m), 3.60-3.95(6H, m), 4.07-4.28(2H, m), 4.36-3.90(9H, m), 7.08-7.45(20H, m).

IR(NaCl, neat): 3015, 2860, 1770, 1455, 1090 cm^{-1}.

Mass spectrum, m/z = 517(M^+ +29, CI, CH_4, 0.2), 517(0.7, 91(100). Anal. ($C_{38}H_{40}O_7$) C, H. mp = 94-96° (recryst, Et_2O/hexanes).



136AB 137A

α-1-Deoxy-(C-2'-butyrolactonyl)-2,3,4,6-tetra-O-acetyle-D-glucopyranose (**137A**)

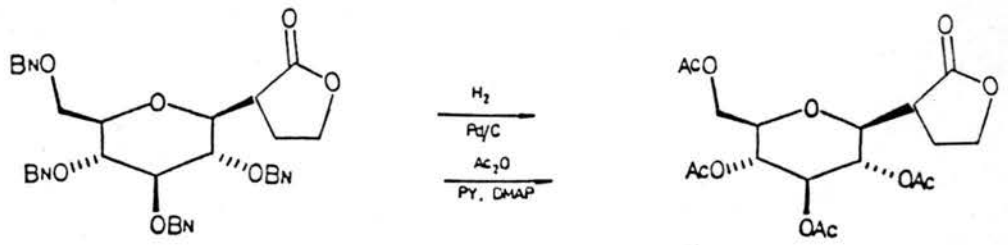
From 125 mg (0.206 mmol) of α-lactone (**136B**), 22 mg of 10% Pd/C in THF (15 mL0, 63.2 mg of crude tetra-ol (R=H, R_1=0, R_2=CH_2CH_2, X=0) was obtained by filtration of the catalyst and evaporation of the solvent. Direct acetylation of this material (33 mg, 0.133 mmol) using, 81 mg Ac_2O, 1.6 mg DMAP, 157 mg pyridine in CH_2Cl_2 (5 mL) afforded 12 mg (22%) of tetra-acetate (**137A**) (chromatographed on PTLC silica gel, eluted with 2% acetone in Et_2O) (oil).

$[\alpha]_D^{25}$ = +35.2° (c=0.92, CH_2Cl_2).

^1H NMR (100 MHz) ($CDCl_3$) δ TMS: 1.86-2.36(2H, m), 2.06(3H, s), 2.09(3H, s), 2.11(3H, s), 2.13(3H, s), 2.57-2.93(1H, m), 3.89-4.77(7H, m), 4.83-5.00(1H, m), 5.20-5.46(1H, m).

^1H NMR (360 MHz) ($CDCl_3$) δ TMS: 4.43(1H, dd, $J_{1,2}$=5.13Hz).

IR(NaCl, neat): 2950, 1780-1740, 1370 1220 cm^{-1}.



136CD 137B

α-1-Deoxy-1-(C-2'-butyrolactonyl)-2,3,4,6-tetra-O-acetyl-D-glucopyranose (**137B**)

From 60 mg (0.09 mmol) of β-lactone (**136C**), 11 mg of 10% Pd/C in THF (10 mL), 32.8 mg of crude tetra-ol was obtained by filtration of the catalyst and evaporation of the solvent. Direct acetylation of this material (20 mg, 0.08 mmol) using 49.4 mg Ac_2O, 1 mg DMAP, and 96 mg pyridine in CH_2Cl_2 (4 mL) afforded 4.0 mg (12%) of tetra-acetate **137B** (chromatographed on PTLC silica gel, eluted with Et_2O) (oil).

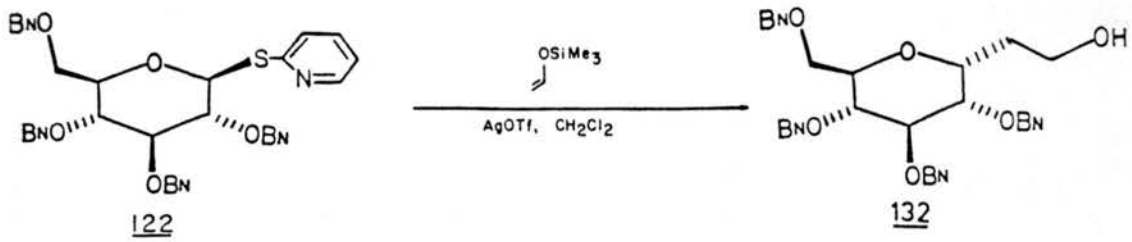
$[\alpha]_D^{25}$ = +79.2° (c=0.4, CH_2Cl_2).

^1H NMR (100 MHz) ($CDCl_3$) δ TMS: 1.70-2.10(2H, m), 2.05(3H, s), 2.08(3H, s), 2.10(6H, s), 2.76-3.10(1H, m), 3.72-4.70(6H, m), 4.80-5.48(3H, m).

^1H NMR (360 MHz) ($CDCl_3$) δ TMS: 4.61(1H, dd, $J_{1,2}$=7.6Hz).

IR(NaCl, neat): 2955, 1790-1740, 1370, 1220 cm^{-1}.

Mass spectrum m/z = 417(M^+, +1, 11.6), 357(80).



122 132

1-Deoxy-1-(C-2'-hydroxyethyl)-2,3,4,6-tetra-O-benzyl-D-glucopyranose (133)

From 80 mg (0.12 mmol) of **122**, 22 mg (0.19 mmol) of the TMS-enol-ether of acetaldehyde and 49 mg (0.19 mmol) of silver(I) triflate in CH_2Cl_2 (2 mL), the labile aldehyde product (**132**) (obtained crude from extractive work-up with 0.1 N NaOH/CH_2Cl_2) was directly subjected to $LiAlH_4$ (5 mg, 0.12 mmol) reduction in Et_2O (2 mL) at 0°C. The reaction was quenched with $Na_2SO_4 \cdot 10\ H_2O$, filtered and separated on PTLC silica gel (eluted with 33% EtOAc in hexanes) to afford 25.2 mg (36% overall) of the corresponding primary alcohol (oil).

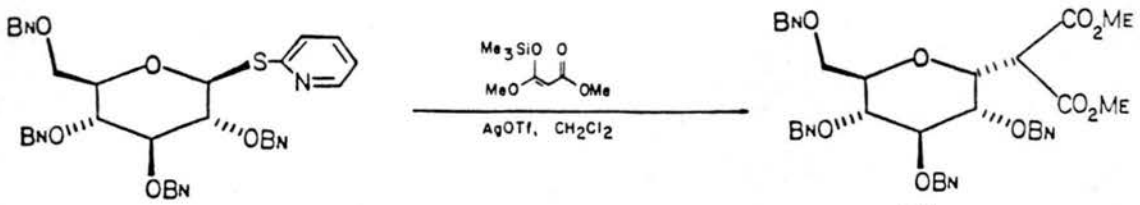
$[\alpha]_D^{25} = +29.7°$ (c=0.6, CH_2Cl_2).

^1H NMR (100 MHz)($CDCl_2$) δ TMS: 1.74-2.14(2H, m), 2.14-2.53(1H, broad s, D_2O exch.), 3.15-3.93(8H, m), 4.00-4.28(1H, m), 4.28-4.97(8H, m), 6.95-7.54(20H, m).

^1H NMR (360 MHz) ($CDCl_3$) δ TMS: 4.22(1H, dd, $J_{1,2}$ = 5.6Hz).

IR(NaCl, neat): 3470, 3015, 2865, 1500, 1455 cm^{-1}.

Mass spectrum m/z = 569(M^+ +1, 0.5), 477(0.5), 91(100).



122 134

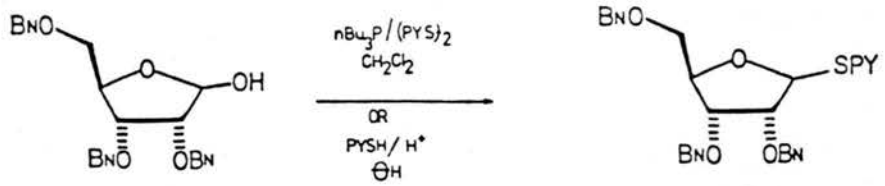
1-Deoxy-1-(C-diemthylmalonyl)-2,3,4,6-tetra-O-benzyl-D-glucopyranose (**134**)

From 193 mg (0.3 mmol) of **122**, 122 mg (0.6 mmol) of carbomethoxyketenemethyltrimethylsilyl acetal and 117 mg (0.46 mmol) of silver(I) triflate in CH_2Cl_2 (5 mL), 94 mg (48%) of pure α-**134** was obtained (isolated by PTLC silica gel, eluted with 50% Et_2O in hexanes). mp 100-101°C (Et_2O/hexane).

$[\alpha]_D^{25}$ = +58.74 (c=0.825, CH_2Cl_2).

^1H NMR (270 MHz)($CDCl_3$) δ TMS: 3.36(3H, s), 3.50-3.90(6H, m), 3.68(3H, s), 4.05(1H, d, J=11.1Hz), 4.30-4.90(8H, m), 5.00(1H, dd, J=4.7Hz, J=11.1Hz), 7.15-7.31(20H, m).

IR(NaCl, neat): 3025, 2860, 1765, 1735, 1500, 1445, 1085, 690. Anal. ($C_{39}H_{42}O_9$) C, H.



146 147AB

2,3,5-tri-O-benzyl-1-(2-thiopyridyl)-D-ribose (**147**)

Method A. To a stirred solution of 2,3,5-tri-O-benzyl (**146**) ribofuranose (98 mg, 0.23 mmol, 1.0 eq) and 2,2'-dipyridyl disulfide (77 mg, 0.35 mmol, 1.1 eq) in CH_2Cl_2 (7 mL) at 0°C was added tri-n-butylphosphine (69 mg, 0.31 mmol, 1.2 eq) dropwise. After stirring for 1h at 0°C, the solution was concentrated and separated on PTLC silica gel (eluted with 10% ET_2O in toluene) to afford the two diastereomeric thioglycosides **147** (47% combined). α anomer **147B**: 25.3 mg (21%); β-anomer **147A** 30.5 mg (26%).

β-anomer **147A**: ^1H NMR (100 MHz) ($CDCl_3$) δ TMS: 3.50-3.80(2H, m), 4.15-4.85(9H, m), 6.21(1H, d, J=2.69Hz), 6.9-7.70(18H, m), 8.40-8.50(1H, m).

$[\alpha]_D^{25}$ = -16.7° (CH_2Cl_2, c=1.1).

IR(NaCl, neat): 3065, 3030, 2830, 1580, 1452 cm^{-1}.

Anal. ($C_{31}H_{31}NO_4S$), C, H, N, S.

mp 87-89°C (recryst. Et_2O/hexanes).

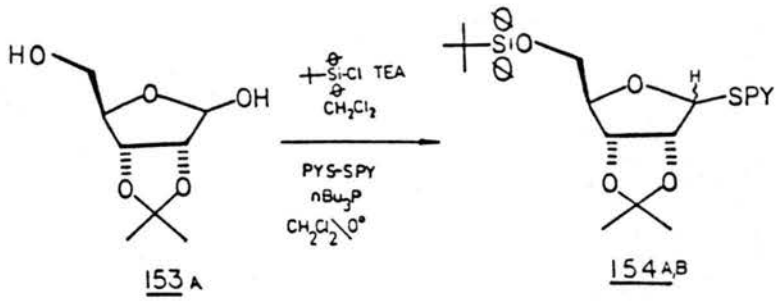
α-anomer **147B**: (oil) ^{1}H NMR (100 MHz) ($CDCl_3$) δ TMS: 3.40-3.60(2H, m), 3.90-4.85(9H, m), 6.72(1H, d, J=5.62Hz), 6.90-7.60(18H, m), 7.42-8.48(1H, m).

$[\alpha]_D^{25}$ = +147.3° (CH_2Cl_2, c=1.6).

IR(NaCl, neat): 3060, 3025, 2855, 1575, 1452 cm^{-1}.

Method B: For this particular substrate, this method was found to be preferred due to the difficult separation problems inherent in Method A and was found to be applicable to large scale.

A solution of 2,3,5-tri-O-benzylribofuranose (7.0 gm, 16.67 mmol, 1.0 equiv), 2-mercaptopyridine (7.20 gm, 64.7 mmol, 3.8 equiv), and p-toluenesulfonic acid (350 mg, 1.85 mmol, 0.1 equiv) in dry benzene (300 mL) was refluxed for 15h. The mixture was cooled to room temperature, washed twice with 75 mL portions of saturated $NaHCO_3$, concentrated, and separated on a silica gel flash column (eluted with 20% EtOAc in hexanes) to afford 2.76 gm of the α-anomer (**147B**), 3.83 gm of the β-anomer (**147A**) (77% combined or 92% based on unreacted starting material 1.05 gm (15%).



1-(2'-Thiopyridiyl)-2,3-O-isopropylidene-5-O-**tert**-butyldiphenyl)silyl]-D-ribofuranose (**154**)

To a stirred solution of ribofuranose-2,3-acetonide (4.67 gm, 24.5 mmol, 1.0 equiv) in CH_2Cl_2 (100 mL) was added Et_3N (2.73 gm, 27 mmol, 1.1 equiv), **tert**-butyldiphenylsilyl chloride (7.43 gm, 27 mmol, 1.1 equiv) and DMAP (300 mg, 2.45 mmol, 0.1 equiv) at 0°C. The cooling bath was removed, and the mixture was allowed to stir for 5h at ambient temperature. The solvent was removed under reduced pressure, the residue was triturated with THF and filtered to remove $Et_3N \cdot HCl$. The filtrate was concentrated, absorbed, onto 15 gm of silica gel, dried and loaded onto a flash column (silica gel, 150 gm, prepared in hexanes) and eluted with 20% Et_2O in hexane to afford 8.36 gm (79%) of the C-5 silyloxy derivative (α,β mixture) which was directly used for the following transformation.

To a stirred solution of the hemi-acetal obtained above (1.35 gm, 3.15 mmol), 1.0 equiv) in CH_2Cl_2 (30 mL) was added 2,2'-dipyridyl disulfide (830 mg, 3.77 mmol, 1.2 equiv) and tri-n-butylphosphine (762 mg, 3.77 mmol, 1.2 equiv) at 0°C. The reaction was allowed to stir for 30 min

at 0°C, poured onto silica gel (5 gm) containing 10 mL CH_2Cl_2, evaporated to dryness and loaded onto a flash column (silica gel, 50 gm, prepared in hexanes) and eluted with 10% Et_2O in $CHCl_3$ (500 mL) to afford 1.3 gm (79%) of thioacetal 3 which was a mixture of anomers ($\alpha:\beta$ = 3:1) (**154A, B**) (oil). Analytical samples of each were obtained by PTLC/silica gel (10% Et_2O in CCl_4). The mixture as obtained above was directly used for C-glycosidations.

<u>α-anomer (**154A**)</u>: (oil) $[\alpha]_D^{25}$ = +90.4° (c=1.3, CH_2Cl_2)

^1H NMR (370 MHz) ($CDCl_3$) δ TMS: 1.07(9H, s), 1.41(3H, s), 1.60(3H, s), 3.73-3.90(2H, m), 4.28(1H, br s), 4.94(1H, d, J=6.4Hz), 5.08(1H, m), 6.68(1H, d, J=4.4Hz), 7.09(1H, m), 7.26-7.75(12H, m), 8.38(1H, m).

IR(NaCl, neat): 2930, 1580, 1420, 1110, 700 cm^{-1}.

Mass spectrum m/z = 522(M^+, +1, 9.8), 464(5.2), 59(100).

<u>β-anomer (**154B**)</u>: (oil) $[\alpha]_D^{25}$ = -115.8° (c=1.3, CH_2Cl_2)

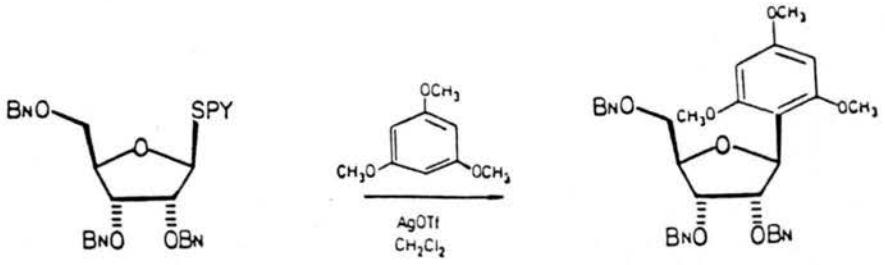
^1H NMR (270 MHz) ($CDCl_3$) δ TMS: 1.06(9H, s), 1.26(3H, s), 1.56(3H, s), 3.76-3.83(2H, m), 4.37(1H, m), 4.82(2H, m), 6.19(1H, d, J=1.4Hz), 7.0(1H, m), 7.19=7.70(12H, m), 8.46(1H, m).

IR(NaCl, neat): 2930, 1580, 1415, 1105, 1085, 700 cm^{-1}.

Mass spectrum, m/z = 522(M^+ +1, 46.1), 464(17.6), 59(100).

General Procedure for C-Glycosidation of **147** and **154**

To a stirred solution of (**147** or **154**) (1.0 equiv) in distilled, dry CH_2Cl_2 (0.05 M) was added the aromatic or TMS-enol ether substrate (1.5-2.0 equiv) followed by addition of silver(I) triflate (1.25-2.0 equiv). The mixture was stirred at room temperature for 0.5h (or until TLC analysis indicates disappearance of starting material), diluted with CH_2Cl_2, and washed with 0.1 N NaOH. The combined organic extracts were dried over anhydrous sodium sulfate, filtered, evaporated, and separated by silica gel chromatography. Solvent systems for separations are given with the reaction scale and spectral data for each compound.



147a 175

1-Deoxy-1-(C-2',4'-6'-triemthoxyphenyl)-2,3,5-tri-O-benzyl-D-ribofuranose (**175**)

From 540 mg (1.05 mmol) of **147A**, 194 mg (1.16 mmol) of 1,3,5-trimethoxybenzene and 405 mg (1.58 mmol) of silver(I) triflate in CH_2Cl_2 (10 mL), 293 mg (49%) of pure β-**175** was obtained (isolated on PTLC silica gel, eluted with 2% EtOAc/hexanes).

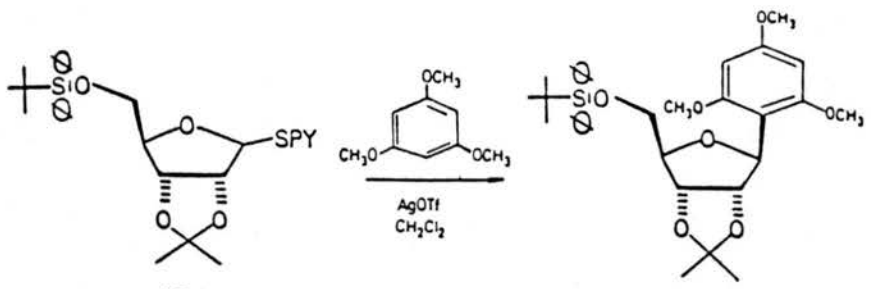
$[\alpha]_D^{25}$ = +18.0° (c=1.2, CH_2Cl_2)

mp 93-95°C (recryst. Et_2O/hexanes).

^1H NMR (270 MHz) ($CDCl_3$) δ TMS: 3.61(6H, s); 3.80(3H, s); 4.10-4.80(11H, m); 5.55(1H, d, J=4.4Hz); 6.06(2H, s); 7.15-7.45(15H, m).

Mass spectrum, m/z = 479(M^+ -91, 5.1), 463(4.0), 391(2.0), 107(100). Anal. ($C_{35}H_{38}O_7$), C, H.

* The same result was obtained from the β-isomer of **147** (**147B**).



154A,B 177

β-1-Deoxy-1-(C-2',4',6'-trimethoxyphyenyl)-2,3-O-isopropylidene-5-O-[tert-butyldiphenylsilyl]-D-ribofuranose (**177**)

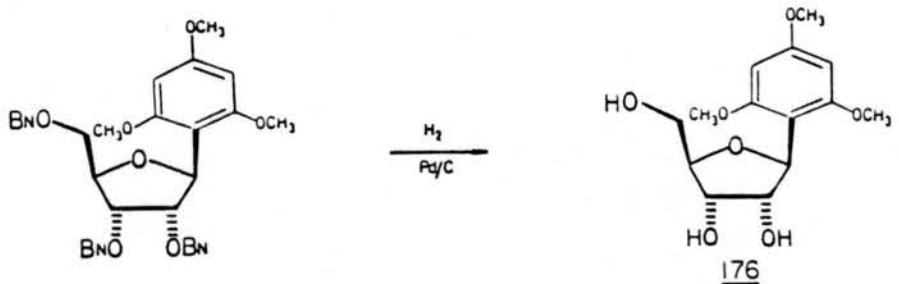
From 330 mg (0.63 mmol) of **154A,B** (α:β mixture 3:1), 160 mg (0.95 mmol) of 1,3,5-trimethoxybenzene and 244 mg (0.95 mmol) of silver(I) triflate in CH_2Cl_2 (15 mL), 227 mg (61%) of pure β-**177** was obtained (isolated on PTLC silica gel, eluted with 25% Et_2O in hexanes) (oil). $[\alpha]_D^{25}$ = +13.84° (c=1.3, CH_2Cl_2).

^1H NMR (270 mHz) ($CDCl_3$) δ TMS: 1.05(9H, s); 1.34(3H, s); 1.59(3H, s); 3.64(6H, s); 3.6-3.85(2H, m); 3.79(3H, s); 4.08(1H, m), 4.73(1H, m); 4.99(1H, m); 5.53(1H, d, J=2.93Hz); 6.06(2H, s); 7.24-7.75(10H, m).

^{13}C NMR (67.933 MHz) ($CDCl_3$) δ $CDCl_3$: 19.33; 25.84; 26.94; 27.89; 55.32; 55.59; 64.89; 77.65; 83.13; 84.78; 91.15; 108.33; 113.57; 127.53; 129.43; 133.71; 134.08; 135.75; 159.71; 161.51.

IR(NaCl, neat): 1615, 1595, 1470, 1430, 1220, 1210, 1155, 1135, 1110, 1065, 700 cm^{-1}.

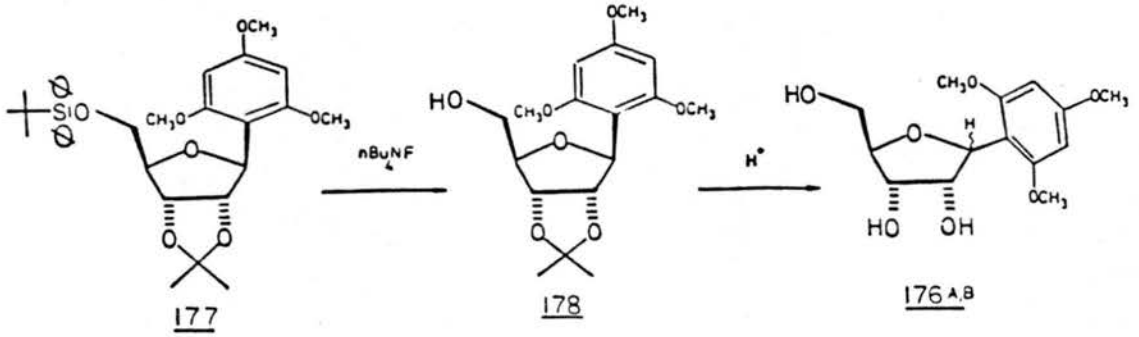
Mass spectrum, m/z = 579(M^+ + 1, 2.6); 563(0.9); 549(1.1); 521(9.0); 503(5.4); 463(15); 443(17.1); 181(100).



175 176

β-1-Deoxy-1-(C-2',4',6'-trimethoxyphenyl)-D-ribofuranose (176)

From 205 mg (0.36 mmol) of **175** 160 mg of 10% Pd/C in THF (50 mL), the triol **176B** (23 mg, 21%) was obtained.



177 178 176A,B

The same triol was obtained by the following two-step procedure: To a stirred solution of C-glycoside **177** (300 mg, 0.519 mmol, 1.0 equiv) in THF (10 mL) at 25°C was added

$Bu_4NF \cdot 3H_2O$ (196 mg, 0.62 mmol, 1.2 equiv). The mixture was allowed to stir 7h at ambient temperature, poured into H_2O and thoroughly extracted with CH_2Cl_2. The combined organic extracts were dried over anhydrous sodium sulfate, filtered, evaporated, and separated on PTLC silica gel (eluted with 50% EtOAc in hexanes) to afford 149 mg (85%) of the de-silylated alcohol **178** (oil).

$[\alpha]_D^{25} = -13.85°C$ (c=1.3, CH_2Cl_2).

^1H NMR (270 MHz) ($CDCl_3$) δ $CHCl_3$: 1.32(3H, s); 1.58(3H, s); 1.65(1H, br s, D_2O exch.); 3.72-3.88(2H, m); 3.78(9H, s); 4.06(1H, m); 4.86-4.97(2H, m); 5.54(1H, d, J=4.23Hz); 6.10(2H, s).

^{13}C NMR (67.933 MHz) ($CDCl_3$) δ $CDCl_3$: 25.67; 27.79; 55.33; 55.69; 62.41; 78.00; 81.59; 84.29; 85.03; 91.37; 107.49; 113.95; 159.61; 161.73.

IR(NaCl, neat): 3450, 1610, 1590, 1465, 1455, 1420, 1380, 1225, 1205, 1150, 1065 cm^{-1}. Mass spectrum, m/z = 340(M^+, 15.3); 323(10.1); 283(45.8); 181(100).

Treatment of the acetonide alcohol obtained above with camphorsulfonic acid (cat.) in MeOH afforded a mixture. The β-triol **176B** identical to that obtained above from hydrogenolysis of the corresponding tri-o-benzyl derivative (**175**) was separated by PTLC silica gel.

β-anomer (176B):

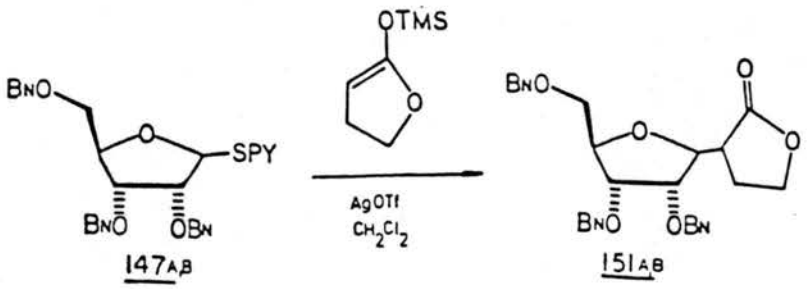
$[\alpha]_D^{25}$ = -32.7° (c=0.4, H_2O, lit.[10] -34°), mp 96-98°C (lit. 98-99°C).

^1H NMR (100 MHz) ($CDCl_3$) δ TMS: 260(1H, m), 2.84(1H, m), 3.65-3.85(3H, m), 3.77(6H, s), 3.80(3H, s), 4.25(1H, s), 4.25(1H, m), 4.50(1H, m), 5.36(1H, d, J=6.2Hz), 6.13(2H, s).

α-anomer (176A):

$[\alpha]_D^{25}$ = -15° (c=0.45, H_2O, lit.[10] = -18°).

^1H NMR (100 MHz) ($CDCl_3$) δ TMS: 2.10(1H, m), 2.50(1H, m), 2.84(1H, m), 3.5-4.0(3H, m), 3.8(9H, s), 4.36(2H, m), 5.03(1H, d, J=9.7Hz), 6.13(2H, s).



147A,B 151A,B

1-Deoxy-1-(C-2'-butyrolactonyl)-2,3,5-tri-O-benzyl-D-ribofuranose (151)

From 375 mg (0.73 mmol) of β-(**147a**), 230 mg (1.2 mmol) of the TMS-enol ether of γ-butyrolactone and 308 mg (1.2 mmol) of silver(I) triflate in CH_2Cl_2 (10 mL), 249 mg (70%

combined) of the α anomers (151) were obtained (isolated by chromatotron silica gel, eluted with 25% EtOAc in hexanes).

α-anomer 151A: (oil) $[\alpha]_D^{25}$ = 45.5° (c=1.3; CH_2Cl_2) (R_f=0.53, 50% EtOAc/hexanes).

^1H NMR (270 MHz) ($CDCl_3$) δ TMS: 2.30-2.44(2H, m); 2.95-3.14(1H, m); 3.44-3.69(2H, m); 4.05-4.95(12H, m); 7.33(15H, m).

IR(NaCl, neat): 1770, 1500, 1460, 1025, 740, 690 cm^{-1}.

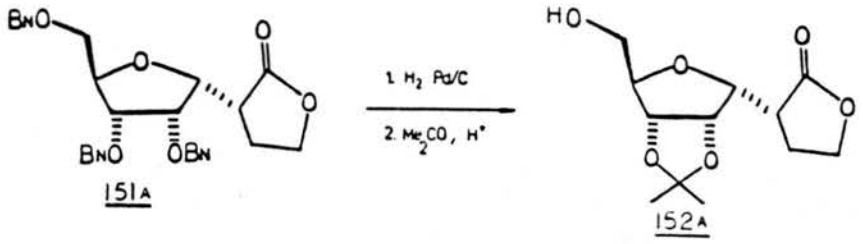
Mass spectrum, m/z = 489(M^+ + 1, 3.7); 398(3.0); 381(18); 91(100).

α-anomer 151B: (oil) $[\alpha]_D^{25}$ = +40.5° (c=1.1; CH_2Cl_2)(R_f=0.41, 50% EtOAc/hexanes).

^1H NMR (270 MHz) ($CDCl_3$) δ TMS: 2.07-2.26(1H, m); 2.46-2.64(1H, m); 3.06-3.24(1H, m); 3.45-3.72(2H, m); 3.90-4.86(12H, m); 7.31(15H, m).

IR(NaCl, neat): 1770, 1500, 1460, 1025, 735, 695 cm^{-1}.

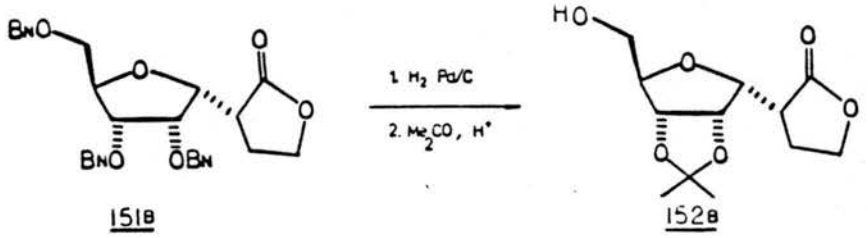
Mass spectrum, m/z = 489(M^+ + 1, 9.4); 397(19.5); 381(19.5); 381(1.9); 91(100).



151A 152A

α-1-Deoxy-1-(C-2'-butyrolactonyl)-2,3-O-isopropylidene-D-ribofuranose (**152A**)

From 130 mg (0.27 mmol) of the α-tri-O-benzyl butyrolactone derivative (**151A**) obtained above, 32 mg 10% Pd/C in THF (8 mL) was obtained 18 mg (31%) of the triol (isolated by PTLC silica gel, eluted with 10% MeOH in CH_2Cl_2) which was directly subjected to acetonide formation without further characterization. Treatment of the triol with dimethoxypropane (4 mL) and camphorsulfonic acid (3 mg) at room temperature for 12h followed by evaporation and PTLC isolation (silica gel, eluted with 10% hexanes/EtOAc) afforded 8.2 mg (38%) of the α-acetonide **152A** which was identical to that obtained from fluoride deprotection of the corresponding **tert**-butyldiphenylsilyl acetonide derivative (**155A**) prepared from **154**, (R_f = 0.47, 10% hexane/EtOAc).

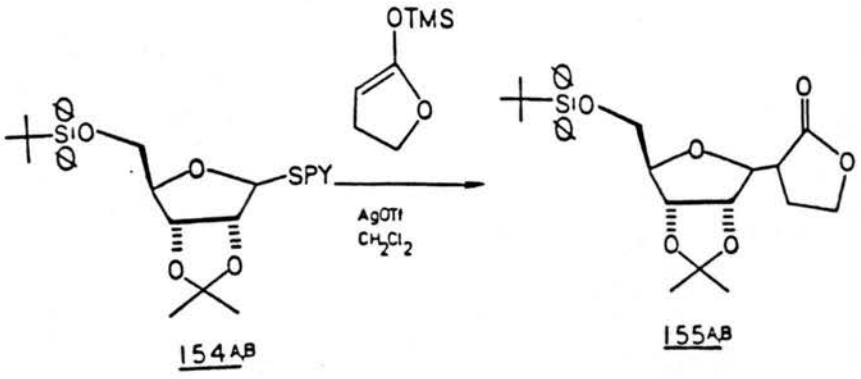


151B 152B

α-1-Deoxy-1-(C-2'-butyrolactonyl)-2,3-O-isopropylidene-D-ribofuranose (**152B**)

From 108 mg (0.22 mmol) of the α-tri-O-benzyl butyrolactone derivative (**151B**) obtained above, 26 mg 10% Pd/C in THF (10 mL) was obtained 20 mg (41%) of the triol (isolated by PTLC silica gel, eluted with 15% MeOH in CH_2Cl_2) which was directly subjected to acetonide formation without further characterization.

Treatment of the triol with acetone (2 mL) $CuSO_4$ (60 mg) and H_2SO_4 (0.2%, 0.04 mL) at room temperature for 5h followed by addition of solid $Ca(OH)_2$, filtration, evaporation, and isolation by PTLC (silica gel, 10% hexanes/EtOAc) afforded 16 mg (28%) of the α-acetonide **152B** which was identical to that obtained from HF·py deprotection of the corresponding **tert**-butyldiphenylsilyl acetonide derivative **155B** prepared from **154** (R_f = 0.24, 10% hexanes/EtOAc).



1-Deoxy-1-(C-2'-butyrolactonyl)-2,3-O-isopropylidene-5-O-(tert-butyldiphenylsilyl)-D-ribofuranose (**155**)

From 220 mg (0.42 mmol) of **154** (α:β, 3:1), 100 mg (0.65 mmol) of the TMS enol ether of γ-butyrolactone and 130 mg (0.5 mmol) of silver(I) triflate in CH_2Cl_2 (7 mL) at 25°C for 30 min afforded, after aqueous isolation and separation on PTLC silica gel (eluted with 25% EtOAc in hexanes), 117 mg (56% combined) of the α-configured lactones **155** (1:1 ratio).

Data for faster component on TLC **155A** (R_f=0.5 in 50% Et_2O/hexanes) (oil) $[\alpha]_D^{25}$=+7.3° (c=1.1, CH_2Cl_2)

^{1}H NMR (270 MHz) ($CDCl_3$) δ TMS: 1.05(9H, s); 1.36(3H, s); 1.5(3H, s); 2.35-2.5(2H, m); 2.05(1H, m); 3.63-3.81(2H, m); 4.14(1H, t, J=3.8Hz); 4.23(1H, q, J=8.3 Hz); 4.40(1H, m); 4.53(1H, dd, J=5.23, J=2.7Hz); 4.9(2H, m); 7.42(6H, m); 7.66(4H, m).

IR(NaCl, neat): 2910, 1775, 1425, 1380, 1110 cm^{-1}.

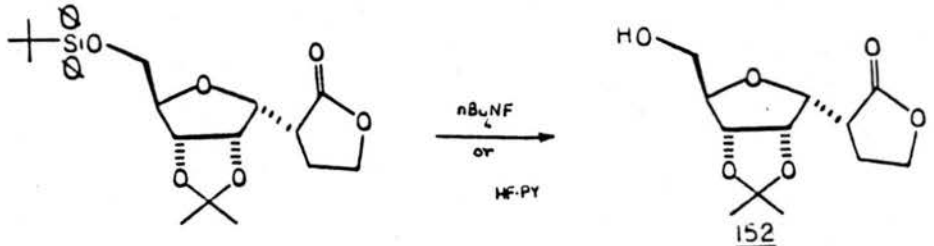
Mass spectrum, m/z (methane CI): 525(M^+ + 29, 8.2); 481(4.5); 419(100).

Data for slower component **155B** on TLC (R_f=0.42 in 50% Et_2O/hexanes) (oil) $[\alpha]_D^{25}$ = -3.5° (c=0.9, CH_2Cl_2)

^1H NMR (270 MHz) ($CDCl_3$) δ TMS: 1.05(9H, s); 1.34(3H, s); 1.50(3H, s); 2.13-2.32(1H, m); 2.35-2.55(1H, m); 3.05(1H, q, J=9.2Hz); 3.65-3.90(2H, m); 4.15-4.35(3H, m); 4.45(1H, dd, J=3.95, J=9.2Hz); 4.77(1H, dd, J=6.14, J=3.95Hz); 4.91(1H, d, J=6.14Hz); 7.416(6H, m); 7.63(4H, m).

IR(NaCl, neat): 2915, 1775, 1430, 1370, 1110 cm^{-1}.

Mass spectrum, m/z (methane CI): 525(M^+ + 29, 5.7); 481(3.9); 419(100).



155 152

α-1-Deoxy-1-(C-2'-butyrolactonyl)-2,3-O-isopropylidene-D-ribofuranose (**152A**)

From 62 mg (0.125 mmol) of the **tert**-butyldiphenylsilyl lactone (**155A**); (faster component on TLC obtained above

from **154A, B**) and 47 mg (0.15 mmol) of **tetra-n-butyl**-ammonium fluoride·$3H_2O$ in THF (10 mL), stirred at room temperature for 2h, evaporated, and separated on PTLC silica gel (eluted with 10% hexanes in EtOAc) was obtained 16.5 mg (51%) of a single hydroxymethyl lactone derivative (**152A**) (oil) (R_f=0.47, 10% hexanes in EtOAc).

^1H NMR (270 MHz) ($CDCl_3$) δ TMS: 1.35(3H, s); 1.50(3H, s); 2.05(1H, br s, D_2O exch.); 2.3502.63(2H, m); 3.02(1H, m); 3.65(2H, m); 4.10-4.30(2H, m); 4.30-4.48(2H, m); 4.70(1H, m); 4.87(1H, m).

^{13}C NMR (67.933 MHz) ($CDCl_3$) δ $CDCl_3$: 24.620; 42.772; 27.478; 40.101; 62.354; 67.388; 79.219; 81.838; 82.537; 84.612; 112.83.

IR(NaCl, neat): 3470, 2940, 1765, 1380, 1210, 1020 cm^{-1}.

Mass spectrum m/z = 259(M^+ + 1, 44.8); 243(38); 201(100).

$[\alpha]_D^{25}$=+14.0° (c=0.4, CH_2Cl_2).

Treatment of the epimeric lactone (**155B**) (slower component on TLC obtained above from **3**) under identical conditions ($Bu_4NF·3H_2O$/THF, 25°C) afforded exclusively, the same hydroxymethyl lactone **152A** obtained above from the faster component **155A**. Stereochemical integrity of this

material could be maintained by desilylating with the milder HF·pyridine complex as described below:

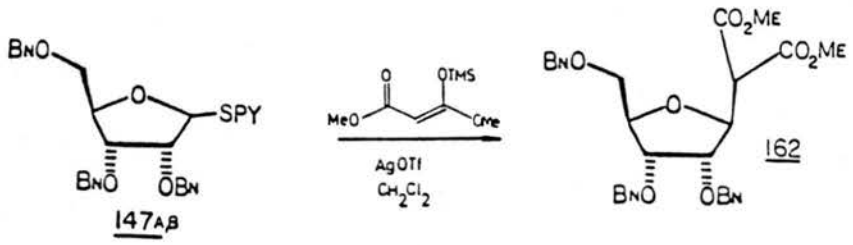
HF·pyridine complex was added to 83.0 mg (0.167 mmol) of the **tert**-butyldiphenylsilyl lactone (**155B**; slower component on TLC obtained above) in THF (7 mL) at room temperature and allowed to stir for 2.5h. The mixture was diluted with CH_2Cl_2, poured into H_2O and extracted with CH_2Cl_2. The combined extracts were dried over anhydrous sodium sulfate, filtered, concentrated, and separated on PTLC silica gel (eluted with 10% hexanes in EtOAc) to afford 21 mg (49%) of a single hydroxymethyl lactone (**152B**) which was distinct from that obtained from the faster component (**152A**) above (R_f=0.24, 10% EtOAc in hexanes).

^{1}H NMR (270 MHz) ($CDCl_3$) δ TMS: 1.32(3H, s); 1.50(3H, s); 2.19-2.55(2H, m); 3.0(1H, br s, D_2O exch.); 3.08(1H, q, J=9.4Hz); 3.65(2H, m); 4.14-4.47(4H, m); 4.66-4.78(2H, m).

^{13}C NMR (67.933 MHz) ($CDCl_3$) δ $CDCl_3$: 24.758; 25.196; 26.145; 40.208; 62.403; 66.858; 79.163; 8.19125; 82.277; 85.241; 112.882.

IR(NaCl, neat): 3470, 2940, 1765, 1380, 1210, 1020 cm^{-1}.

Mass spectrum, m/z = 259(M^+ + 1, 55.3), 243(17.6), 59(100).



β-1-Deoxy-1-(C-dimethylmalonyl)-2,3,5-tri-O-benzyl-D-ribofuranose (**162**)

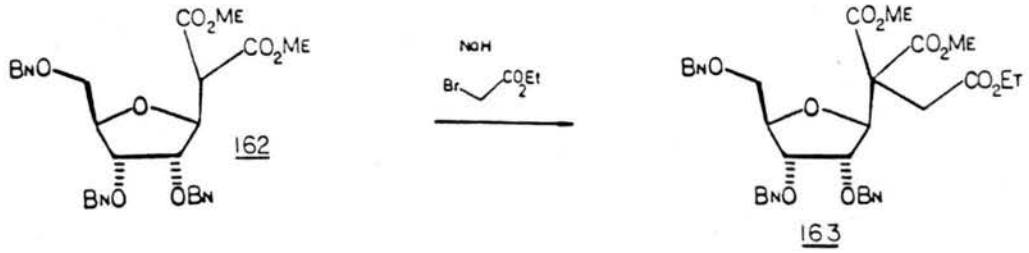
From 90 mg (0.175 mmol) of (**147a**), 186 mg (1.06 mmol) of carbomethoxyketenemethyltrimethylsilyl acetal and 163 mg (0.63 mmol) of silver(I) triflate in CH_2Cl_2 (4 mL), 67.2 mg (71%) of pure β-(**162**) was obtained (isolated on flash column silica gel, eluted with 15% EtOAc in hexanes) (oil).

$[\alpha]_D^{25}$ = +16.5° (c=2.0, CH_2Cl_2).

^1H NMR (360 MHz) ($CDCl_3$) δ TMS: 3.45-3.65(2H, m); 3.52(3H, s); 3.74(3H, s); 4.06-4.13(2H, m); 4.17-4.23(1H, m); 4.25-4.31(1H, m); 4.38-4.81(7H, m); 7.20-7.38(15H, m); J_{12} from decoupling = 5.6Hz).

IR(NaCl, neat): 3024, 2947, 1750, 1735, 1459 cm^{-1}.

Mass spectrum, m/z = 443(M^+ - 91, 0.7); 351(1.9); 122(1.4); 91(100).



162 163

1,1-Dimethyl-2-ethyl-2',3',5'-tri-O-benzyl-(β,D-ribofuranosyl)-1,1,2-ethanetricarboxylate (163)

To a stirred solution of (162) (840 mg, 1.57 mmol, 1.0 equiv) in THF (3 mL) was added a suspension of NaH (126 mg, 3.16 mmol, 2.0 equiv) in THF (20 mL). The mixture was allowed to stir for 2h at room temperature and bromo ethylacetate (792 mg, 4.75 mmol, 3.0 equiv) was added dropwise. After stirring for 12h at room temperature, the solvent was evaporated under reduced pressure, diluted with CH_2Cl_2, poured into H_2O, and thoroughly extracted with CH_2Cl_2. The combined organic extracts were dried over anhydrous sodium sulfate, filtered, concentrated, and separated by flash column silica gel (50 gm, loaded in hexanes) (eluted with 25% Et_2O in CCl_4) to afford 770 mg (79%) of the β-triester (163) (oil).

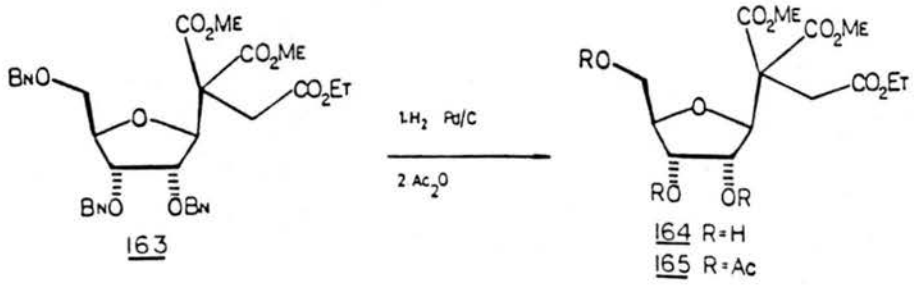
$[\alpha]_D^{25}$ = +16.1° (c=1.1, CH_2Cl_2).

^1H NMR (270 MHz) ($CDCl_3$) δ TMS: 1.19(3H, t, J=7.2Hz), 3.04(1H, 1/2ABq, J=17Hz), 3.10(1H, 1/2ABq, J=17Hz), 3.35-3.84(3H, m), 3.51(3H, s), 3.69(3H, s), 4.05(2H, q,

J=7.2Hz), 4.16(1H, m), 4.26(1H, m), 4.37-4.84(7H, m), 7.12-7.44(15H, m).

IR(NaCl, neat): 3030, 2950, 1745, 1450, 1200 cm^{-1}.

Mass spectrum, m/z = 529(M^+ - 91, 1.1), 423(25.4), 106(100).



163

164 R=H

165 R=Ac

1,1-Dimethyl-2-ethyl-2',3',5'-tri-O-acetyl-(β-D-ribofuranosyl)-1,1,2-ethane-tricarboxylate (165)

Hydrogenation of 163 (65 mg, 0.105 mmol) with 18% Pd/C (10 mg) in absolute ethanol under a H_2 atmosphere for 12h at room temperature afforded 25 mg (68%) of the corresponding triol (164) (isolated by PTLC silica gel, eluted with 16% MeOH in $CHCl_3$) (oil).

IR(NaCl, film): 3460, 2950, 1735, 1435 cm^{-1}.

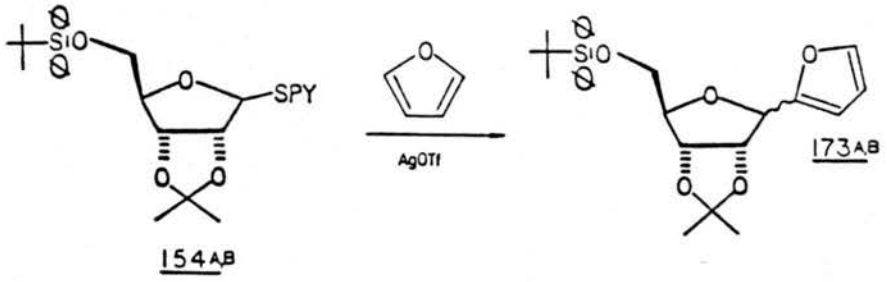
Mass spectrum, m/z = 319(M^+ - 31, 0.9), 305(1.5), 145(100). Exact mass calcd. M + 1 351.1291, found 351.1297.

Acetylation of this triol (**164**) (20 mg, 0.057 mmol) with acetic anhydride (1 ml), pyridine (2 mL), sodium acetate (5 mg) and DMAP (0.5 mg) afforded 18.8 mg (69%) of the 2',3',5'-triacetate (**164**) (oil).

$[\alpha]_D^{25}$ = +17.0° (c = 0.6, CH_2Cl_2).

^1H NMR (270 MHz) ($CDCl_3$) δ TMS: 1.25(3h, t, J=7.3Hz), 2.046(3H, s), 2.08(3H, s), 2.11(3H, s), 3.09(2H, s), 3.76(3H, s), 3.78(3H, s), 4.0-4.35(5H, m), 4.63(1H, d, J=4.8Hz), 5.10(1H, t, J=6Hz), 5.15(1H, t, J=5Hz).

IR(NaCl, neat): 2950, 1745, 1370, 1220 cm^{-1}.



154AB

2-[2-3-O-Isopropylidene-5-O-tert-butyldiphenylsilyl-β- and α-D-ribofuranosyl) furan (173)

From 125 mg (0.24 mmol) of **154** (α:β, 3:1) and 92 mg (0.36 mmol) of silver(I) triflate in furan (5 mL) at room temperature for 15 min was obtained 12.5 mg (11%) of the β-anomer (**173A**) and 60.1 mg (53%) of the α-anomer (**173B**) (isolated by PTLC silica gel, eluted with 10% EtOAc/hexanes).

<u>β-173</u> (oil) $[\alpha]_D^{25}$ = -7.15° (c=1.1, CH_2Cl_2)

^1H NMR (100 MHz) ($CDCl_3$) δ TMS: 1.07(9H, s), 1.40(3H, s), 1.60(3H, s), 3.75(2H, m), 4.20(1H, m), 4.80-4.95(3H, m), 6.31(2H, br s), 7.30-7.75(11H, m).

IR(NaCl, neat): 3070, 2930, 1455, 1430, 700 cm^{-1}.

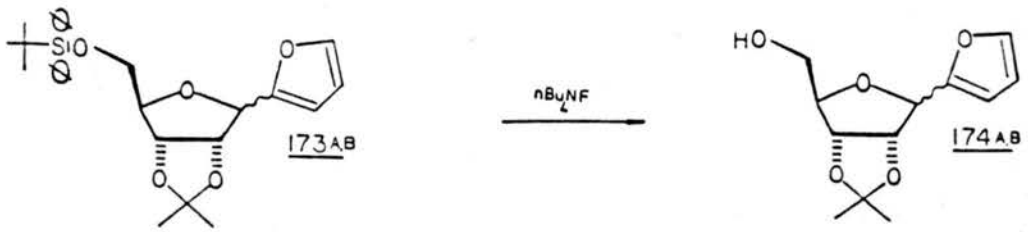
Mass spectrum, m/z = 463(M^+ - 15, 2.1), 421(3.5), 151(100).

<u>α-173B</u> (oil) $[\alpha]_D^{25}$ = -27.0° (c = 0.75, CH_2Cl_2)

^1H NMR (100 MHz) ($CDCl_3$) δ TMS: 1.08(9H, s), 1.35(3H, s), 1.50(3H, s), 3.80(2H, m), 4.21(1H, m), 4.95(2H, m), 5.33(1H, d, J=4Hz), 6.37(1H, m), 6.46(1H, m), 7.30-7.75(11H, m).

IR(NaCl, neat): 3070, 2930, 1430, 1110, 700 cm^{-1}.

Mass spectrum, m/z = 463(M^+ - 15, 2.2), 421(4.0), 129(100).



2-(2,3-O-Isopropylidene-β- and α-D-ribofuranosyl)furan (174A,B)

To a stirred solution of the β-**173A** (14.9 mg, 0.031 mmol) in THF (5 mL) was added $Bu_4NF \cdot 3H_2O$ (20 mg, 0.0625 mmol, 2.0 equiv) in one portion. The mixture was allowed to stir for 3h at ambient temperature, concentrated, and separated by PTLC silica gel (eluted with 20% Et_2O in $CHCl_3$) to afford 3.8 mg (50%) of the β-alcohol (**174A**) (oil).

$[\alpha]_D^{25} = -58.4°$ (c=0.19, CH_2Cl_2).

^1H NMR (270 MHz) ($CDCl_3$) δ TMS: 1.37(3H, s), 1.59(3H, s), 2.15(1H, br s), 3.75(2H, m), 4.21(1H, m), 4.71(1H, m), 4.91(2H, m), 6.36(2H, m), 7.42(1H, m).

^{13}C NMR (77 MHz) ($CDCl_3$): δ $CHCl_3$: 114.48, 27.47, 25.53, lit. (114.49, 27.37, 25.39).

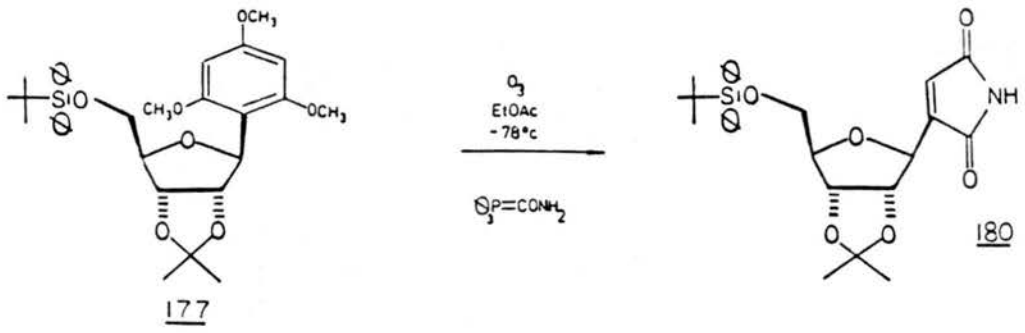
In the same manner, 15 mg of α-**173B** was converted into 4.7 mg (62%) of the corresponding α-alcohol **173A**.

mp 57-59°C (recryst Et_2O/hexanes).

$[\alpha]_D^{25}$ = -52.8° (c=0.24, CH_2Cl_2).

^1H NMR (270 MHz) ($CDCl_3$) δ TMS: 1.34(3H, s), 1.52(3H, s), 1.80(1H, br s), 3.77(2H, m), 4.28(1H, m), 4.75(1H, m), 4.86(1H, m), 5.11(1H, d, J=4.1Hz), 6.39(1H, m), 6.50(1H, m), 7.42(1H, m).

^{13}C NMR (77 MHz) ($CDCl_3$) δ $CHCl_3$: 113.48, 26.42 25.27, lit. (113.08, 26.20, 25.03). IR(NaCl, neat): 3440, 2930, 1380, 745 cm^{-1}.



177 180

Showdomycin (**56**)

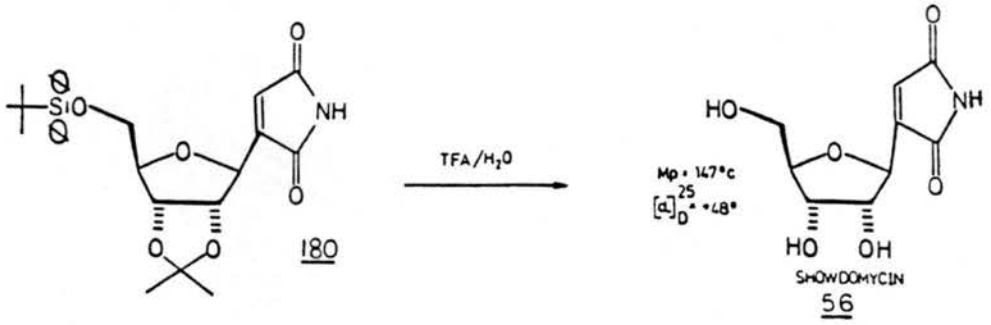
A stirred solution of **177** (98 mg, 0.15 mmol) in EtOAc (5 mL) at -78°C, was treated with ozone gas for 20 min. The resulting blue solution was stirred 1h at -78°C and dimethyl sulfide (0.28 mL, 30 equiv) was added. The mixture gradually warmed to room temperature over a 90-minute period and evaporated to dryness. The crude, labile α-keto methyl ester was then dissolved in $CHCl_3$ (10 mL) and treated with carbamoylmethylenetriphenylphosphorane (140 mg, 0.44 mmol, 3.0 equiv). The mixture was stirred for 45

min at ambient temperature, concentrated and separated by PTLC silica gel (eluted with 50% Et_2O/hexanes) to afford 15.4 mg (20% two steps) of the fully protected 2,3-O-isopropydiene-5-O-**tert**-butryldiphenylsilyl-showdowmycin derivative (**180**) (oil).

$[\alpha]^{25}$ = +8.9° (c=0.35, CH_2Cl_2).

^1H NMR (270 MHz) ($CDCl_3$) δ TMS: 1.05(9H, s), 1.36(3H, s), 1.60(3H, s). 3.70-3.85(2H, s), 4.22(1H, m) 4.61-4.80(2H, m), 4.85(1H, m), 6.49(1H, d, J= 1.9Hz), 7.30-7.75(10H, m).

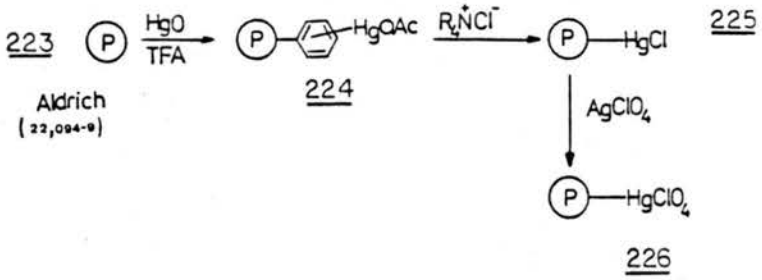
IR(NaCl, neat); 2900, 1720, 110 cm^{-1}.



180 56

The material obtained above (**180**) (18.5 mg, 0.036 mmol) was converted into showdomycin (**56**) by treatment with aqueous trifluoroacetic acid[15] (4:1, TFA:H_2O, 5 mL) for 1.25h at 25°C. The mixture was evaporated to dryness and chromatographed by PTLC silica gel (eluted with 30% THF in EtOAc) to afford 6.5 mg (78%) of showdomycin as a white solid, mp 146-147°C (recryst. acetone/benzene) (lit. 153°).

$[\alpha]_D^{25}$ = +48.0° (c = 0.05, H_2) (lit. +47.1 - 49.9°). The spectral properties (TLC, ^1H NMR, IR, and MS) of the natural and synthetic materials were identical. Comparison ^1H NMR spectra are in the text on page 84.

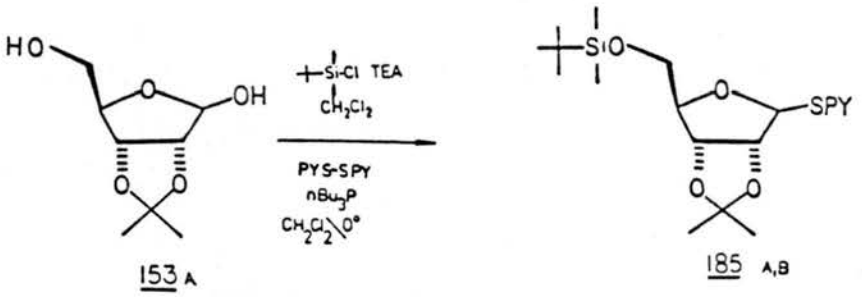


Resin-Bound $Hg^{II}ClO_4$ (**266**)

A suspension of macroporous polystyrene (2.6 g, Aldrich 22,094-9) was stirred gently in CH_2Cl_2 (35 ml) at 0°C. Via a dropping funnel was added a solution of HgO (2.7 g, 12.5 mmol) and TFAA (19.3 g, 169 mmol) in CH_2Cl_2 (15 ml). The mixture was gently stirred for 24h at room temperature. The suspension was then filtered, loaded onto a column and washed 4 x 100 ml MeOH. The resin was then transferred to a 100 ml flask, MeOH (50 ml) and Me_4NCl (3.9 g, azeotropically dried with benzene) were added and the suspension stirred slowly for 12h. The resin was then washed with MeOH (100 ml) and placed in a soxhlet extractor and washed with MeOH for 24h. Collection and high vacuum drying afford 5.4 g of functionalized resin (**225**). The resin was suspended in 50 ml THF and solid $AgClO_4$ (4.47 g)

was added and the mixture stirred for 0.5h. A series of decantings and adding fresh THF was conducted, initially at 0.25h intervals (X5) then at 1.0h intervals (X5). The resin was then placed in a soxhlet extractor and washed with THF for 4 days, changing the THF daily. The light blue resin was then transferred to a 100 ml flask, the THF was removed by rotary evaporator and then placed under high vacuum. Drying to constant weight affords 6.41 g of the light bluish gray resin (**226**).

IR (KBr): 2920, 1490, 1450, 1080, 690 cm^{-1}.



1-(2'-Thiopyridyl-2,3-O-isopropylidene-5-O-(tert-butyldimethyl-silyl)-D-ribofuranose (**185**)

To a stirred solution of ribofuranose 2,3-acetonide (4.75 g, 25 mmol, 1.0 equiv) in CH_2Cl_2 (75 ml) was added Et_3N (2.78 g, 27.5 mmol, 1.1 equiv), **tert**-butyldimethylsilyl chloride (4.14 g, 27.5 mmol, 1.1 equiv) and DMAP (305 mg, 2.50 mmol, 0.1 equiv) at room temperature. The mixture was alowed to stir for five

hours. The mixture was then concentrated, dissolved in THF and filtered. The concentrated crude reaction mixture was then purified by flash column chromatography. Eluting with 20% Et_2O/hexanes affords 4.61 g (60.4%) of the C-5 siloxy-derivative (α, β mixture ~1:8) which was directly used in the following procedure.

To a stirred solution of the hemiacetals obtained above (3.41 g, 11.2 mmol, 1.0 equiv) in CH_2Cl_2 (50 ml) was added 2,2'-dipyridyldisulfide (2.98 g, 13.5 mmol, 1.2 equiv) and tri-n-butyl phosphine (2.72 g, 13.5 mmol, 1.2 equiv) at 0°C. After 0.5 h the reaction was poured onto 20 g silica containing 100 ml CH_2Cl_2, loaded onto a flash column and eluted with 10% EtOAc/hexanes to afford 3.12 g (77%) of thioacetals (**185**) which were a mixture of anomers (α/β = 4:1)(oil).

<u>α anomer (oil) **185A**:</u> <u>$[\alpha]_D^{25}$ = +24° (c=1.05, CH_2Cl_2)</u>

^{1}H NMR (270 MHz)($CDCl_3$) δ (TMS): 0.09(s, 3H), 0.12(s, 3H), 0.91(s, 9H), 1.40(s, 3H), 1.60(s, 3H), 3.77(dd, J=11Hz, 3Hz, 1H), 4.28(m, 1H), 4.87(d, J=6Hz, 1H), 4.98(m, 1H), 6.45(d, J=4.4Hz, 1H, 7.00(m, 1H), 7.32(m, 1H), 7.49(m, 1H), 8.40(m, 1H).

IR (NaCl, neat): 2930, 2855, 1575, 1115 cm^{-1} m/z: 398(M^+ - 122) (61.0), 287(80.1), 112(100).

β anomer (oil) **185B:** $[\alpha]_D^{25} = -160°$ (c=1.21 CH_2Cl_2)

^1H NMR (270 MHz)($CDCl_3$) δ (TMS): 0.06(s, 3h), 0.08(s, 3H), 0.90(s, 9H), 1.37(s, 3H), 1.57(s, 3H), 3.84(m, 2H), 4.33(m, 1H), 4.86(m, 2H), 6.21(d, J=2.1Hz, 1H), 7.02(m, 1H), 7.27(m, 1H), 7.50(m, 1H), 8.48(m, 1H).

IR (NaCl, neat): 2930, 2855, 1575, 1065 cm^{-1} m/z.

185 A,B 227 A,B

1-(2'-Thiopyridyl)-2,3-O-isopropylidene-D-ribofuranose (**227**)

To a stirred solution of thioacetals (**185**) (3.42 g, 8.61 mmol, 1.0 equiv) in THF (50 ml) was added $nBu_4NF\cdot(H_2O)_3$ (3.26 g, 10.31 mmol, 1.2 equiv). The mixture was stirred for 12h, concentrated and separated by flash column. Eluting with 2:1 hexane/EtOAc easily separates the two anomers, affording α (**227A**) (1.5 g, 61%) and β (**227B**) (0.5 g, 20%) thioacetals.

α anomer (**227A**)

$[\alpha]_D^{25}$ = +184° (c=1.5, CH_2Cl_2)

^1H NMR (270 MHz)($CDCl_3$) δ (TMS): 1.40(s, 3H), 1.63(s, 3H), 2.65(bs, 1H), 3.72(m, 1H), 3.85(m, 1H), 4.28(m, 1H), 4.81(m, 1H), 5.05(m, 1H), 5.60(d, J=4.9Hz, 1H), 7.05(m, 1H), 7.27(m, 1H), 7.52(m, 1H), 8.45(m, 1H).

IR (NaCl, neat): 3380, 2930, 1580, 1420, 1095 cm^{-1}.

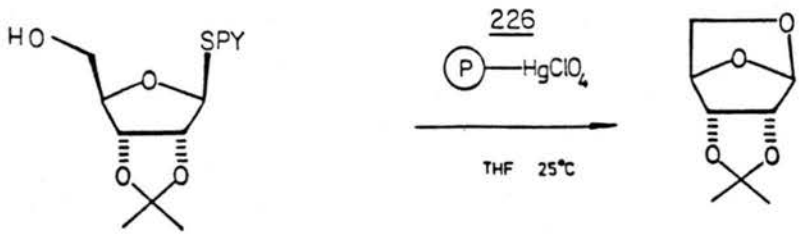
mp = 118-120°C (Et_2O/hexanes). Anal. ($C_{13}H_{17}O_4NS$) C, H, N, S. m/z: 283(M^+, 1.3), 226(2.4), 173(15.3), 112(100).

β anomer (**227B**)

$[\alpha]_D^{25}$ = -188.5° (c=1.12 CH_2Cl_2)(oil)

^1H NMR (270 MHz)($CDCl_3$) δ (TMS): 1.38(s, 3H), 1.67(s, 3H), 3.66-3.92(m, 3H), 4.45(m, 1H), 4.80(m, 1H), 4.91(m, 1H), 5.95(d, J=3.0Hz, 1H), 7.15(m, 1H), 7.40(m, 1H), 7.63(m, 1H), 8.54(m, 1H).

IR (NaCl, neat): 3380, 2930, 1580, 1420, 110 cm^{-1}. m/z: 284(M^+ + 1)(1.6), 226(0.6), 173(15), 112(100).



227B 186

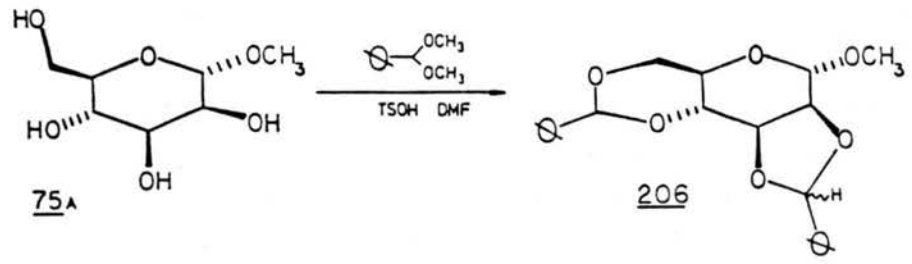
1,5-anhydro-2,3-O-isopropylidene-D-ribofuranoside (**186**)

To a stirred solution of β-thioacetal (**227B**) (22.4 mg, 0.094 mmol, 1.0 equiv) in THF (5 ml) was added mercurated resin (**226**)(94 mg). The mixture was gently stirred for 24h. The reaction mixture was filtered, the resin washed with THF and the combined THF solution concentrated. PTLC eluting with 50% EtOAc/hexanes yields 8.5 mg (53%) of crystalline 1,5-anhydroribose derivative (**186**).

$[\alpha]_D^{25}$ = -6.6° (c=0.5 MeOH) (lit. -6.0° c=.78 MeOH).

mp = 56-58°C (lit. 61°C).

^{1}H NMR (270 MHz)($CDCl_3$) δ (7.24, $CHCl_3$): 1.27(s, 3H), 1.44(s, 3H), 3.28(d, J=7.2Hz, 1H), 3.42(dd, J=7.2Hz, 3.8Hz, 1H), 4.28(d, J=13.5Hz, 1H), 4.30(d, J=13.5Hz, 1H), 4.68(d, J=3.8Hz, 1H), 5.43(s, 1H).



75A 206

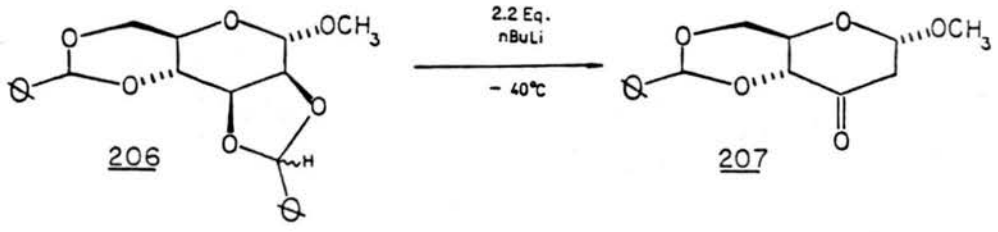
Methyl 2,3:4,6-di-O-benzylidene-α-D-Mannopyranoside (**206**)

To a stirred suspension of methyl-α-D-mannopyranoside (**75A**) (33.1 g, 170.5 mmol, 1.0 equiv) in DMF (200 ml) was added p-toluenesulfonic acid (0.66 g, anhydrous, dried by azeotropic removal of water with benzene), and benzaldehyde dimethylacetal (61.0 g, 398 mmol, 2.3 equiv). The flask was fitted with a reflux condenser and the mixture was heated at 75°C for 3h. The mixture was then cooled and poured into a 0.7 l mixture of ice and water containing $NaHCO_3$ (20 g). The solid was filtered, collected, resuspended in ice/H_2O, recollected and air dried to give 35 g of a crude white solid. The crude solid was dissolved in 0.5 l hot isopropanol; cooling and scratching produced a first crop of **206** (13.65 g) as white crystals. Concentration of the mother liquor yield an additional 4.0 g (total 17.65 g, 47 mmol, 28%). Proton NMR shows the product to be mainly one isomer. A second recrystallization gives almost a pure isomer.

mp = 174-178°C (lit. 176-177°C).

$[\alpha]_D^{25}$ = -6.6° (c=1.05 $CHCl_3$) (lit. +0.03 ($CHCl_3$));

^1H NMR (270 MHz)($CDCl_3$) δ (TMS): 3.40(s, 3H), 3.75-3.97(m, 3H), 4.14(d, J=5.4Hz, 1H), 4.37(m, 1H), 4.64(m, 1H), 5.02(s, 1H), 5.64(s, 1H), 6.29(s, 1H), 7.28-7.63(m, 10H).



206 207

Methyl 4,6-O-benzylidene-2-deoxy-α-D-erythrohexopyranosid-3-ulose (207)

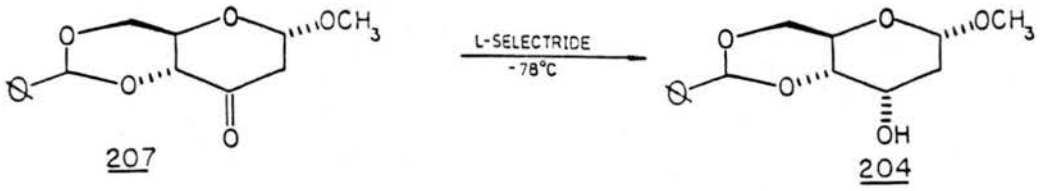
In a 1 l 3-necked flask equipped with a dropping funnel and thermometer was stirred a solution of the dibenzylidene derivative (206) (13.45 g, 36.31 mmol, 1.0 equiv) in THF (300 ml). The stirred solution was cooled to -40°C and the dropping funnel charged with nBuLi (47 ml, 1.7 M/hexane, 80 mmol, 2.2 equiv). The nBuLi solution was slowly added not allowing the reaction to rise above -35°C. The mixture was stirred an additional 0.75 h at -35°C then poured into a vigorously stirred mixture of ice/H_2O (300 ml) and NH_4Cl (25 g). The THF was removed by rotary evaporator leaving a white solid suspended in water. The solid

was collected, dissolved in CH_2Cl_2 (200 ml) and washed with 50 ml water. The organic layer was dried (Na_2SO_4) and concentrated to give 12.2 g of white solid. The crude solid was recrystallized using EtOAc/hexane (100/300 ml) yielding a first crop of pure (**207**) 6.31 (70%).

mp = 163-166°C (lit. 170-171°C).

$[\alpha]_D^{25}$ = +135° (c=0.9, $CHCl_3$) (lit. +150°, c=1.0, $CHCl_3$).

^1H NMR (270 MHz), ($CDCl_3$) δ (TMS): 2.66(d, J=14Hz, 1H), 2.84(m, 1H), 3.37(s, 3H), 3.91(dd, J=10.2Hz, 1H), 4.14(m, 1H), 4.25-4.42(m, 2H), 5.14(d, J=4.5Hz, 1H), 5.58(s, 1H), 7.36(m, 3H), 7.52(m, 2H).



207 204

Methyl 4,6-O-benzylidene-2-deoxy-α-D-ribo-hexopyranoside (**204**)

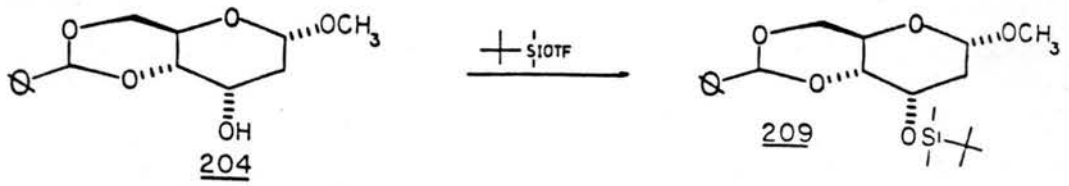
To a -78°C L-selectride solution (139 ml, 139 mmol, 1M in THF, 1.5 equiv) was added via a dropping funnel a THF solution (0.7 l) of ketone (**207**) (23.0 g, 92.4 mmol, 1.0

equiv). The ketone solution added dropwise and after the addition was complete the reaction was stirred 0.5h at -78°C. Water (15 ml) was then added cautiously through the addition funnel. The ice bath was removed and the reaction was warmed to room temperature. The mixture was diluted with THF (300 ml) and transferred to a 3 l flask. While stirring a 0°C 3 N NaOH (300 ml) was added followed by careful addition of 30% H_2O_2 (300 ml). The mixture was stirred 0.5h diluted with 0.5 l EtOAc and the layers separated. The organic layer was washed with water 6 x 250 ml. The combined aqueous layer was washed 3 x 200 ml EtOAc and the organics combined, dried ($MgSO_4$), and concentrated to give an oil that spontaneously crystallizes (22.5 g). Recrystallization from (EtOAc hexane (200/600 ml)) gives a first crop of colorless crystals of pure **204** ((14.3 g). Concentration of the mother liquor yields an additional 5.52 g. (Total 19.82 g, 86%).

mp 121-124°C (lit. 125-127°C).

$[\alpha]_D^{25}$ = +143° (c=1.1 $CHCl_3$).

^1H NMR (270 MHz) ($CDCl_3$): 1.97(m, 1H), 2.18(m, 1H), 3.01(d, J=6.7Hz, 1h), 3.39(s, 3H), 3.59(dd, J=2.7Hz, 9.4Hz, 1H), 3.77(m, 1H), 4.12-4.35(m, 3H), 4.77(d, J=3.8Hz, 1H), 5.60(s, 1H), 7.33(m, 3H), 7.50(m, 2H).

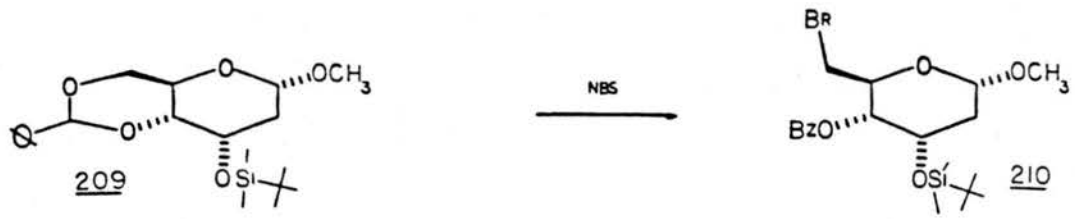


204 209

Methyl 3-O-(tert-butyldimethylsilyl)-4,6-O-benzilidene-2-deoxy-α-D-ribo-hexopyranoside (**209**)

To a stirred solution of alcohol (**204**) (230 mg, 0.92 mmol, 1.0 equiv) in CH_2Cl_2 (25 ml) was added 2,6-lutidine (196 mg, 1.83 mmol, 2.0 equiv) and tert-butyl-dimethyl-silyltriflate (362 mg, 1.38 mmol, 1.5 equiv). The solution was stirred for 0.25 h, diluted with CH_2Cl_2 and washed 2 x 50 ml 0.2 N HCl and 1 x 50 ml at $NaHCO_3$, dried (Na_2SO_4) concentrated to give 270 mg (78%) of (**209**) as a semisolid.

^1H NMR (60 MHz) ($CDCl_3$) δ (7.24, $CHCl_3$): 0.05(s, 3H), 6.0(s, 3H), 0.93(s, 9H), 1.98(m, 2H), 3.30(s, 3H), 3.30-3.88(m, 3H), 4.03-4.50(m, 2H), 2.64(m, 1H), 5.52(s, 1H), 7.24-7.79(m, 5H).

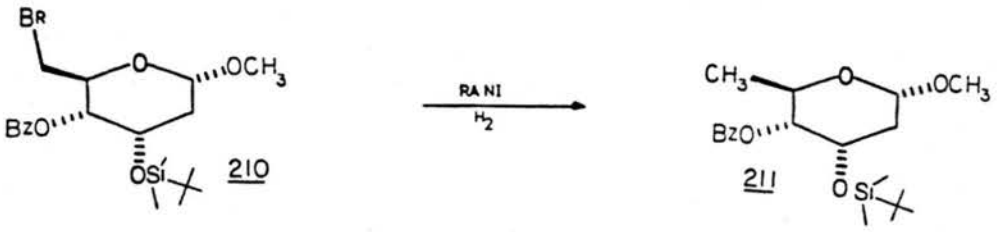


209 210

Methyl 6-bromo-4-O-benzoyl-3-O-(tert-butyldimethylsilyl)-2,6-dideoxy-α-D-ribo-hexopyranoside (**210**)

To a stirred solution of benzylidene derivative (**209**) (200 mg, 0.5 mmol, 1.0 equiv) in CCl_4 (5 ml) was added NBS (103 mg, 0.58 mmol, 1.1 equiv) and $BaCO_3$ (0.5 g, 2.5 mmol, 5.0 equiv). The mixture was refluxed for 0.5h and cooled. Filtering through a silica plug with 50% Et_2O/hexanes yields 180 mg (80%) of **210** as an oil.

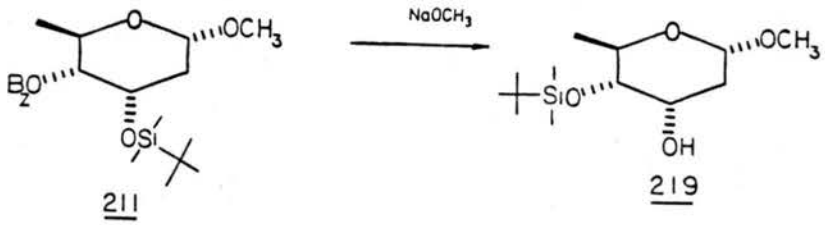
^1H NMR (60 MHz)($CDCl_3$) δ (7.24, $CHCl_3$): -0.23(s, 3H), -0.08(s, 3H), 0.85(s, 9H), 1.95(m, 2H), 3.37(s, 3H), 3.57(m, 2H), 4.27-5.0(m, 4H), 7.49(m, 3H), 8.0(m, 2H).



Methyl 3-O-(tert-butyldimethylsilyl)-4-O-benzoyl-7,6-dideoxy-α-D-ribo-hexopyranoside (211)

To a solution of bromide (210) (6.8 g, 14.8 mmol, 1.0 equiv) in isopropanol (100 ml) was added RaNi (2-5) (15 ml settled material) and diethylamine (1.5 ml). The mixture was degassed and stirred under a balloon of hydrogen overnight. The solution was then passed through a short silica column and eluted with $CHCl_3$. The resulting liquid was concentrated to give 4.85 g (86%) of 211 as a clear oil.

^1H NMR (60 MHz) ($CDCl_3$): 0.0(s, 3H), 0.10(s, 3H), 0.89(s, 9H), 1.33(d, J=6Hz, 3H), 2.16(m, 2H), 2.90(BS, 1H), 3.35(s, 3H), 4.17(m, 1H), 4.74(m, 1H), 5.34(m, 1H), 7.34-7.62(m, 3H), 7.87-8.13(m, 2H).

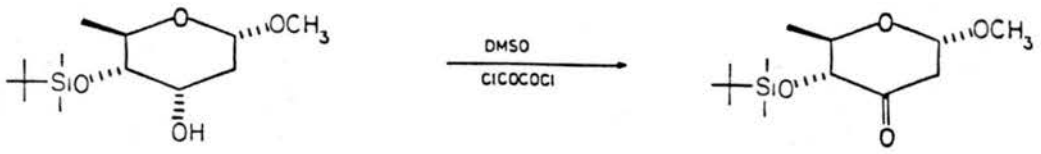


211 219

Methyl 4-O-(tert-butyldimethylsilyl)-2,6-dideoxy-α-D-ribo-hexopyranoside (219)

To a stirred solution of benzoate (211) (4.85 g, 12.7 mmol, 1.0 equiv) in MeOH (100 ml) was added sodium methoxide (2.75 g, 51.05 mmol, 4.0 equiv). The mixture was stirred for 24h, methanolic phenolphthaline was added and the mixture neutralized with 2H HCl. The mixture was concentrated, diluted with CH_2Cl_2 and washed with saturated $NaHCO_3$. The concentrated residue was purified by flash column; eluting with 25% Et_2O/hexanes yield 2.45 g (70%) of (219) as a clear oil.

^1H NMR (270 MHz)($CDCl_3$) δ (7.24, $CHCl_3$): 0.10(s, 6H), 0.89(s, 9H), 1.23(d, J=6Hz, 3H), 1.88(m, 1H), 2.13(m, 1H), 3.04(bs, 1H), 3.31(m, 1H), 3.35(s, 3H), 3.91(m, 2H), 4.69(m, 1H).

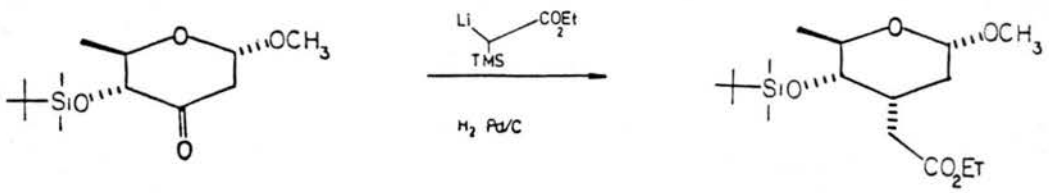


219 213B

Methyl 4-O-(tert-butyldimethylsilyl)-2,6-dideoxy-α-D-erythro-hexopyranosid-3-ulose (213B)

To a stirred -78°C solution of oxalyl chloride (476 mg, 3.75 mmol, 1.5 equiv), in CH_2Cl_2 (50 ml) was added DMSO (586 mg, 7.5 mmol, 3.0 equiv). The reaction was stirred 0.25h at -78°C and a CH_2Cl_2 (10 ml) solution of alcohol (219) (690 mg, 2.5 mmol, 1.0 equiv) was added dropwise. After stirring 0.5h at -78°C triethylamine (1.52 g, 15 mmol, 5.0 equiv) was added neat via syringe; the ice bath was removed and the mixture stirred 0.45h. The mixture was then concentrated, the residue dissolved in THF, filtered and reconcentrated. Flash column chromatography, eluting with 25% Et_2O/hexane affords 460 mg (67%) of C-3 ketone as an oil.

^1H NMR (270 MHz) ($CDCl_3$) δ (7.24, $CHCl_3$): 0.00(s, 3H), 0.14(s, 3H), 0.89(s, 9H), 1.38(d, J=5.8Hz, 3H), 2.56(m, 1H), 2.71(m, 1H), 3.30(s, 3H), 3.80-3.94(m, 2H), 5.00(d, J=4.2Hz, 1H).



213B 216

Methyl 3-O-(tert-butyldimethylsilyl)-3-(carboethoxymethyl)-2,3,6-trideoxy-α-D-ribo-hexopyranoside (**216**)

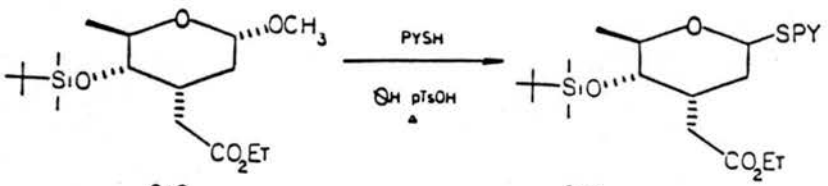
To a stirred -78°C solution of diisopropylamine (265 mg, 2.53 mmol, 1.1 equiv) in THF (10 ml) was added nBuLi (1.05 ml, 2.53 mmol, 2.4M/hexane, 1.1 equiv). The mixture was warmed to 0°C for 0.25h and recooled to -78°C. α-trimethylsilyl ethylacetate (410 mg, 2.53 mmol, 1.1 equiv) was added neat via syringe and the mixture stirred 0.25h. A THF (5 ml) solution of C-3 ketone (**213B**) (63 mg, 2.30 mmol, 1.0 equiv) was added by syringe and the mixture stirred an additional 0.5h. The reaction was then poured into saturated aqueous NH_4Cl. After CH_2Cl_2 extraction the organic layer was dried (Na_2SO_4) and concentrated. Isolation on a 4-mm chromatotron plate eluting with 15% Et_2O/hexane affords 550 mg of a major isomer and 52 mg of a minor isomer of α, β-unsaturated esters (76%) as oils.

A mixture of isomers (525 mg, 1.52 mmol) obtained in this manner were dissolved in 25 ml absolute ethanol and to this solution was added 20% $Pd(OH)_2$ on carbon (162 mg). The mixture was thoroughly degassed and flushed with

hydrogen. The reaction was stirred vigorously overnight under a balloon of hydrogen, the catalyst removed by filtration and the mixture concentrated. The residue was purified by flash column chromatography; eluting with 60% Et_2O/hexane yields 235 mg (45%) of saturated ester (**216**) as an oil.

^1H NMR (270 MHz) ($CDCl_3$) δ (7.24 $CHCl_3$): 0.31(s, 3H), 0.50(s, 3H), 0.86(s, 9H), 32.31(d, J=6.3Hz, 3H), 1.25(t, J=7.3Hz, 3H), 1.75-1.94(m, 2H), 2.39(m, 1H), 2.67(dd, J=17Hz, 3.5Hz, 1H), 3.81(dd, J=17Hz, 10.4Hz, 1H), 3.27(s, 3H), 4.44(m, 1H), 4.64(m, 2H), 4.10(q, J=7.0Hz, 2H), 4.59(m, 1H).

IR (NaCl, neat): 2430, 1735, 1090 cm^{-1}.



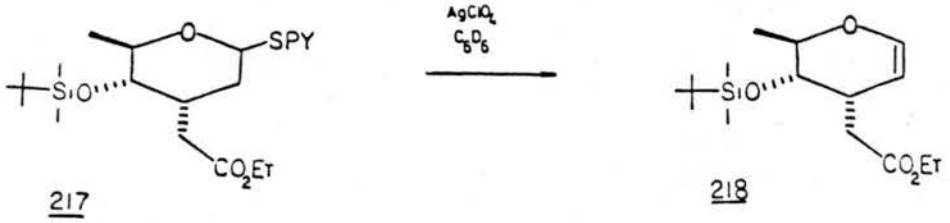
216 217

1-(2-Thiopyridyl)-4-O-(tert-butyldimethylsilyl)-4-(carboethoxymethyl)-2,3,6-trideoxy-D-ribo-hexopyranoside (**217**)

To a stirred solution of methylglycoside (**216**) (32 mg, 0.09 mmol, 1.0 equiv) in benzene (7 ml) are added

mercaptopyridine (31 mg, 0.27 mmol, 3.0 equiv) and p-toluenesulfonic acid (3.5 mg, 0.02 mmol, 0.2 equiv). The mixture was brought to reflux and benzene distilled. More benzene was added as necessary until 10 ml had been distilled. The mixture was then concentrated and separated by PTLC. Eluting with 25% Et_2O/hexane affords 10.0 mg of the major β isomer (**217**) as an oil.

^1H NMR (270 MHz) (C_6D_6) δ (7.15, C_6H_6): -0.06(s, 3H), 0.01(s, 3H), 0.89(s, 9H), 0.93(t, J=7Hz, 3H), 1.18(d, J=5.7Hz, 3H), 3.12(m, 1H), 2.29(m, 1H), 2.50(m, 1H), 2.69(m, 1H), 2.85(m, 1H), 3.46(m, 2H), 3.93(m, 2H), 6.12(dd, J=12Hz, 2.4Hz, 1H), 6.39(m, 1H), 6.79(m, 1H), 6.93(m, 1H), 8.30(m, 1H).

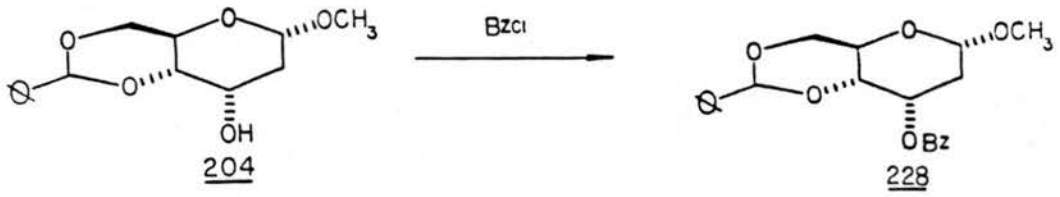


217 218

Trideoxy-D-ribo-glycal Derivative (**218**)

To a solution of thioacetal (**217**) (9.5 mg, 0.023 mmol, 1.0 equiv) in dry C_6D_6 (0.5 ml), in a 5mm NMR tube, was added silver perchlorate (4.7 mg, 0.025 mmol, 1.0 equiv). PTLC, eluting with 25% Et_2O/hexane, affords 3.2 mg of (**218**), corresponding to the major component by crude NMR.

^1H NMR (270 MHz) ($CdCl_3$) δ (7.24, $CHCl_3$): 0.07(s, 3H), 0.07(s, 3H), 0.88(s, 9H), 1.23(m, 6H), 2.11(m, 1H), 2.75(m, 2H), 3.74(m, 2H), 4.12(q, J=7Hz, 2H), 4.66(m, 1H), 6.22(d, J=5.2Hz, 1H). IR(NaCl, neat): 2920, 1740, 1645, 1073 cm^{-1}.



204 228

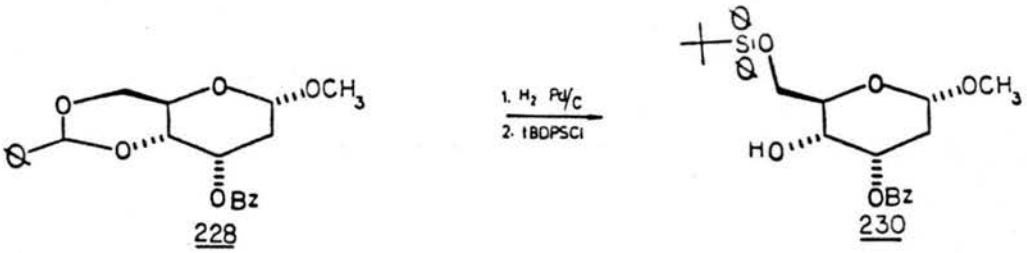
Methyl 3-O-benzoyl-4,6-O-benzylidene-2-deoxy-α-D-ribo-hexopyranoside (228)

To a 0° stirred solution of alcohol (**204**) (18.59 g, 74.1 mmol, 1.0 equiv) in dry pyridine (150 ml) was added benzyl chloride (12.0 g, 85.2 mmol, 1.15 equiv) by syringe. The reaction was stirred 1.5 h at 0°C and poured into 2 l Et_2O. The organic phase was washed 3 x 700 ml cold 3 N HCl. The combined aqueous layers are washed with Et_2O and the organics combined and dried ($MgSO_4$). A slightly yellow oil was obtained by concentration and dissolved in 300 ml hot 95% EtOH. This solution was concentrated and cooled, scratching produces a first crop of 13.5 g white crystals. Concentration of the mother liquor yields an additional 5.4 g of crystalline (**228**) (total 18.9 g, 72%).

mp 94-96°C (lit.[52] 100-102°C).

$[\alpha]_D^{25}$ = +185° (c=1.3 $CHCl_3$)(lit. +183°, c=1.2 $CHCl_3$).

^1H NMR (270 MHz) ($CDCl_3$) δ (TMS): 2.13(m, 1H), 2.39(dd, J=15Hz, 3Hz, 1H), 3.38(s, 3H), 3.80(m, 2H), 4.36(m, 1H), 4.48(m, 1H), 4.78(d, J=4.2Hz, 1H), 5.55(m, 1H), 5.62(s, 1H), 7.24-7.60(m, 8H), 8.14(m, 2H).



228 230

Methyl 5-O-(tert-butyldiphenylsilyl)-3-O-benzoyl-2-deoxy-α-D-ribo-hexopyranoside (230)

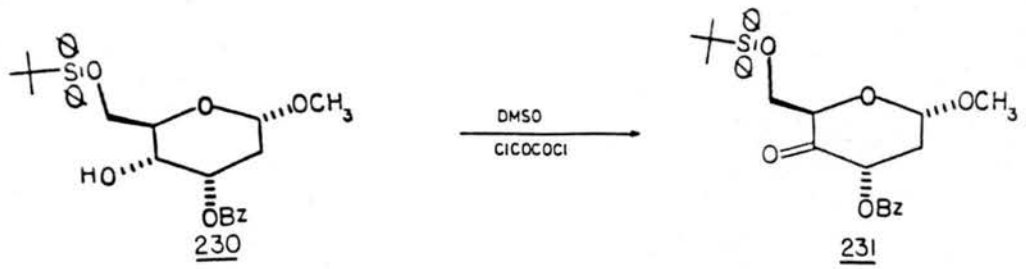
Freshly prepared 20% $Pd(OH)_2$ on carbon (1.5 g) was added to an absolute EtOH (500 ml) solution of the benzylidene derivative (228) (17.4 g, 49 mmol). The mixture was degassed and placed in a Parr shaker overnight at 60 p.s.i. hydrogen. The catalyst was removed by filtration, washed with ethanol and the solution concentrated. The residue was dissolved in EtOAc and reconcentrated to give an oil that was placed under the high vacuum for 4h. The crude diol obtained in this manner was dissolved in 800 ml freshly distilled CH_2Cl_2. The solution was cooled to 0°C

and tert-butyldiphenylchlorosilane (17.5 g, 63.8 mmol, 1.1 equiv) was added neat via syringe. Triethyl amine (5.9 g, 58 mmol, 1.0 equiv) and DMAP (700 mg) were added and the mixture placed in a -30°C freezer for 18h. After concentration at room temperature on a rotary evaporator the residue was dissolved in 0.5 l EtOAc and filtered. The EtOAc was washed with water, the aqueous layer was washed with EtOAc and the organic extracts were combined and dried (Na_2SO_4). The organics are concentrated and the residue dissolved in 250 ml hot MeOH, which was concentrated to 150 ml. Cooling and scratching induce crystallization, yielding a first crop of pure (**230**) (12.4 g). Concentration of the mother liquor afford on additional 6.1 g (total 18.5 g, 61.4%).

mp 107-109°C (lit. 116-117°C).

$[\alpha]_D^{25}$ = +88.3° (c=1.2 $CHCl_3$) (lit.[52] +90.2, c=1.1 $CHCl_3$).

^1H NMR (270 MHz) ($CDCl_3$) δ (TMS): 1.08(s, 9H), 2.02(m, 1H), 2.28(m, 1H), 2.48(d, J=6.0Hz, 1H), 3.34(s, 3H), 3.82-4.12(m, 4H), 4.76(d, J=4.2Hz, 1H), 5.44(d, J=3.2Hz, 1H), 7.30-7.63(m, 9H), 7.73(m, 4H), 8.09(m, 2H).



230 231

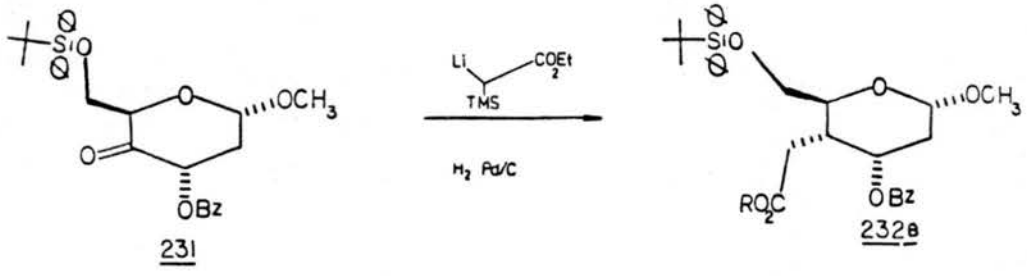
Methyl 5-O-(tert-butyldiphenylsilyl)-3-O-benzoyl-α-D-hexopyranosid-4-ulose derivative (231)

To a stirred -78°C solution of oxalylchloride (1.16 g, 9.2 mmol, 1.5 equiv) in CH_2Cl_2 (200 ml) was added DMSO (1.43 g, 18.35 mmol, 3.0 equiv) via syringe. After stirring the solution for 0.25h at -70°C a CH_2Cl_2 (50 ml) solution of alcohol (230) (3.18 g, 6.12 mmol, 1.0 equiv) was added via cannula. After stirring for 0.75h triethylamine (3.1 g, 30.6 mmol, 5.0 equiv) was added dropwise, the ice bath removed and the reaction allowed to warm to room temperature. The mixture was concentrated and the residue dissolved in THF, filtered, and concentrated. The residue was purified by a short flash column; eluting with 10% EtOAc/hexane affords ketone (231) 2.96 g (93%). Crystals could be obtained by dissolving in hot EtOH and cooling. mp 78-80°C (lit. 86-88°C).

$[\alpha]_D^{25}$ = +144 (c=0.9 $CHCl_3$) (lit.[52] +148°, C=1.2 $CHCl_3$).

^{1}H NMR (270 MHz) ($CDCl_3$) δ (7.24 $CHCl_3$): 1.04(s, 9H), 2.10(m, 1H), 2.91(m, 1H), 3.41(s, 3H), 3.95(dd, J=11Hz, 2.5Hz, 1H), 4.07(dd, J=11Hz, 4.5Hz, 1H), 5.18(m, 1H), 5.84(m, 1H), 7.30-7.61(m, 9H), 7.70(m, 4H), 8.09(m, 2H).

IR (NaCl, neat): 3070, 2920, 1758, 1730, 1725 cm^{-1}.



231 232a

Methyl 5-O-(tert-butyldiphenyl-3-O-benzoyl-4-(carboethoxy-methyl)-3,4-dideoxy-α-D-ribo-hexopyranoside (**232**)

To a stirred -78°C THF (25 ml) solution of diisopropylamine (0.37 g, 3.68 mmol, 1.5 equiv) was added nBuLi (2.2 ml, 3.68 mmol, 1.5 equiv, 1.7 M/hexane). The solution was warmed to 0°C for 0.25h and recooled to -78°C. To this cold stirred solution was added α-trimethylsilylethylacetate (0.59 g, 3.68 mmol, 1.5 equiv) as a THF solution (2 ml). The reaction was stirred for 0.25h at -78° and a THF solution of ketone (**231**) (1.27 g, 2.45 mmol, 1.0 equiv) was added via syringe. The reaction was stirred 0.25h at -78°C, 0.25h at -40°C and then diluted with EtOAc (50 ml) and poured into ice water containing NH_4Cl (50 ml/1

g). The layers are separated, the aqueous layer washed 1 x 25 ml EtOAc and the organics combined, dried (Na_2SO_4) and concentrated. The residue was purified by column chromatography on silica. Eluting with 15% Et_2O/hexanes affords a 1.21 g (84%) of a clear oil shown to be a mixture of 2 isomers of the α,β-unsaturated esters.

The mixture was used directly for catalytic hydrogenation. The oil obtained in the above manner 1.21 g, 2.05 mmol, 1.0 equiv) was dissolved in 75 ml absolute EtOH and 20% $Pd(OH)_2$ on carbon (650 mg, ~1,25 mmol, 0.5 equiv) was added. The mixture was thoroughly degassed and stirred vigorously under 1 atm of hydrogen overnight. After 12h the catalyst was filtered and the mixture concentrated. The residue was separated by flash column chromatography. Eluting with 5% Et_2O/hexane affords 812 mg (56%) of (**232**) as a clear oil.

$[\alpha]_D^{25}$ = +105 (c=1.7, CH_2Cl_2).

^1H NMR (270 MHz)($CDCl_3$) δ (TMS): 1.09(s, 9H), 1.12(t, J=7Hz, 3H), 1.95-2.65(m, 5H), 3.30(s, 3H), 3.84(m, 1H), 3.93-4.14(m, 3H), 4.84(m, 1H), 5.38(m, 1H), 7.30-7.63(m, 9H), 7.76(m, 4H), 8.09(m, 2H).

IR (NaCl, neat): 3070, 2930, 1735, 1720, 1280 cm^{-1}.

m/z: 619(M^+ + 29(3.9), 559(4.1), 533(14.3), 513(11.4), 437(92), 360(100).

Methyl 4-(carboxymethyl)-6-O-(tert-butyldiphenylsilyl)-2,4-dideoxy-γ-lactone-α-D-ribo-hexopyranoside (233)

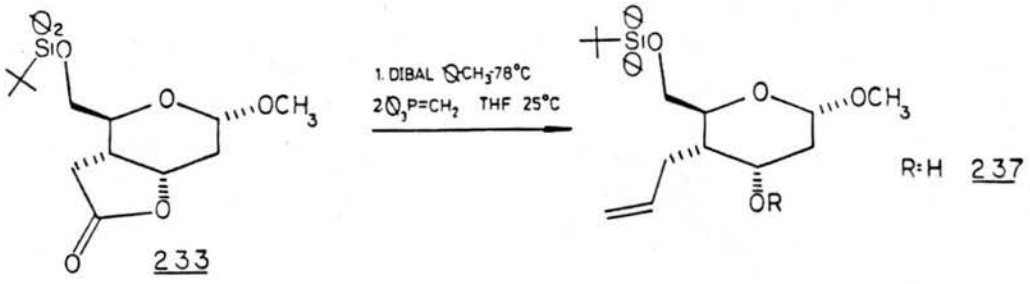
To a stirred solution of diester (232) (750 mg, 1.27 mmol, 1.0 equiv) in MeOH (25 ml) was added sodium methoxide (70 mg, 1.27 mmol, 1.0 equiv). The mixture was stirred for 48h at room temperature. Several drops of methanolic phenolphthaline are added and the reaction neutralized with 3 N HCl. The reaction mixture was concentrated, dissolved in CH_2Cl_2 and washed with water. The mixture was dried (Na_2SO_4) concentrated and dissolved in EtOAc (50 ml). Twenty-five mg of p-toluenesulfonic acid was added and the mixture evaporated to dryness using a bath tempèrature of 40°C. This procedure was repeated two more times and the resulting residue loaded onto a flash column. Eluting with 10% EtOAc/hexanes affords 230 mg (41%) of lactone (233) as a clear oil.

$[\alpha]_D^{25}$ = +45° (c=1.85 $CHCl_3$). (lit:[52] mp 80-81°C,

$[\alpha]_D^{25}$ = +42° (c=1.05 $CHCl_3$).

^{1}H NMR (270 MHz)($CDCl_3$) δ (7.24, $CHCl_3$): 1.05(s, 9H), 2.05-2.20(m, 3H), 2.48(m, 2H), 3.33(s, 3H), 3.71(m, 3H), 4.60(m, 1H), 4.85(m, 1H), 7.40(m, 6H), 7.77(m, 4H).

IR (NaCl, neat): 3080, 2920, 1780, 1425, 1105 cm^{-1}.



Methyl 4-(allyl)-6-O-(tert-butyldiphenylsilyl)-2,5-dideoxy-α-D-ribo-hexopyranoside (237)

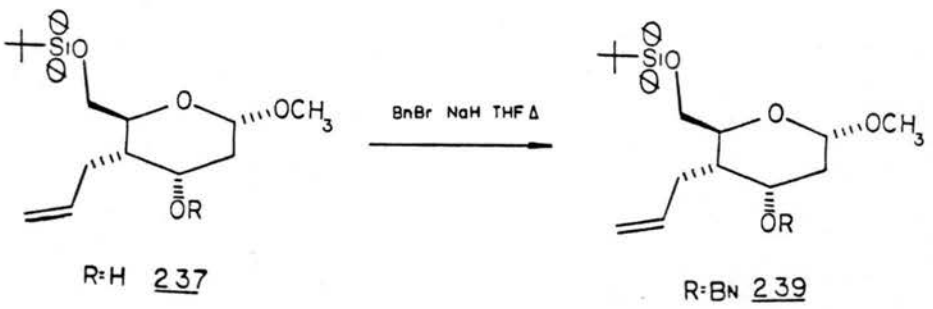
To a stirred solution of lactone (233) (164 mg, 0.373 mmol, 1.0 equiv) in toluene (4 ml) at -78°C was added Dibal (0.41 ml, 0.41 mmol, 1.1 equiv, 1 M/toluene) via syringe. The mixture was stirred 0.5h at -78°C and poured into 30 ml Et_2O and 25 ml 0.1 N NaOH. The layers are separated and the aqueous layer washed 3 x 25 ml Et_2O. The organics are combined, dried (Na_2SO_4) and concentrated. The residue was transferred to a dry flask and dissolved in THF (5 ml). The stirred solution was cooled to 0° and the preformed ylide was added dropwise. The ylide was prepared in the following manner: to a stirred solution of (methyl)triphenylphosphonium bromide (213 mg, 0.65 mmol, 1.7 equiv) in

dry THF (5 ml) was added nBuLi (0.3 ml, 0.56 mmol, 1.5 eqiv). The yellow solution was stirred for 5 min. at room temperature and used directly for the above procedure. The crude lactol and ylide are stirred at 0°C for 0.5h and ylide were stirred at 0°C for 0.5h and 5 ml acetone added. The mixture was concentrated, diluted with Et_2O, filtered, the ether washed with water, dried (Na_2SO_4), and concentrated. A small flask column eluted with 25% Et_2O/hexane affords 90 mg (52%) of alcohol (**237**) as a clear oil.

$[\alpha]_D^{25}$ = +74 (c=0.4, CH_2Cl_2)

^1H NMR (270 MHz)($CDCl_3$) δ (7.24 $CHCl_3$): 1.04(s, 9H), 1.68-2.20(m, 5H), 3.29(d, J=9.3Hz, 1H), 3.34(s, 3H), 3.64-3.97(m, 4H), 4.83-5.08(m, 3H), 5.78(m, 1H), 7.39(m, 6H), 7.71(m, 4H).

IR (NaCl, neat): 3540, 3080, 2935, 1640, 1430, 1110 cm^{-1}. m/z: 409 (M - 31)(3.7), 351(6.9), 331(10.7), 241(42.4), 221(66.6), 153(100).



Methyl 4-(allyl)-6-O-(tert-butyldiphenylsilyl)-3-O-benzyl-2,4-dideoxy-α-D-ribo-hexopyranoside (**239**)

To a stirred solution of alcohol (**237**) (70 mg, 0.15 mmol, 1.0 equiv) in THF (10 ml) was added NaH (9.1 mg, 0.23 mmol, 1.5 equiv) and the mixture stirred 0.5h. Benzylbromide (52 mg, 0.302 mmol, 2.0 equiv), and nBu_4NI (24 mg, 0.08 mmol, 0.5 equiv) are added and the mixture heated to reflux for 24h, after which time the reaction was concentrated to approximately 2 ml. The mixture was cooled, concentrated to dryness, dissolved in CH_2Cl_2, washed with water and dried (Na_2SO_4). Concentration followed by flash column chromatography eluting with 15% Et_2O/hexanes affords 53.1 mg (66%) of the benzyl ether (**239**) as an oil.

$[\alpha]_D^{25} = +23°$ (c=0.88 CH_2Cl_2)

^1H NMR (270 MHz)($CDCl_3$) δ (7.24, $CHCl_3$): 1.05(s, 9H), 1.65-228(m, 5H), 3.34(s, 3H), 3.78(m, 3H), 3.97(m, 1H),

4.33(d, J=11.7Hz, 1H), 4.68(d, J=11.7Hz, 1H), 4.79(m, 1H), 4.97(m, 2H), 5.68(m, 1H), 7.34(m, 11H), 7.73(m, 4H).

IR (NaCl, neat): 3060, 2920, 1110 cm^{-1}. m/z: 499(M^+ - 31(2.8), 441(4.5), 421(5.6), 391(7.9), 221(33.4), 91(100).

R=Bn 239 240

Methyl 4-(allyl)-3-O-benzyl-2,4-dideoxy-α-D-ribo-hexo-pyranoside (240)

To a stirred solution of silylether (239) (142 mg, 0.27 mmol, 1.0 equiv) in THF (20 ml) was added tetra-n-butylammonium fluoride trihydrate (127 mg, 0.4 mmol, 1.5 equiv). The solution was stirred for 24 h, evaporated to dryness and loaded onto a small flash column. The column was eluted with 30% Et_2O/hexanes and affords 74 mg (94%) of alcohol (240) as a clear oil.

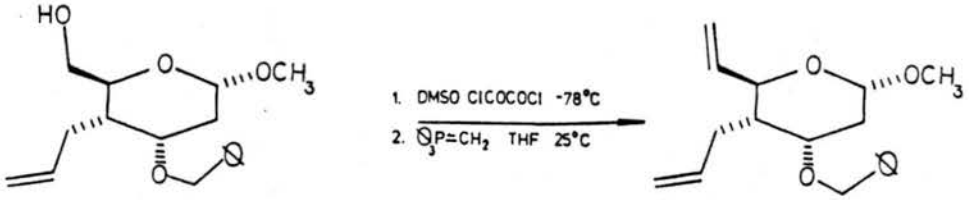
$[\alpha]_D^{25}$ = +173° (c=1.06 CH_2Cl_2)

^1H NMR (270 MHz)($CDCl_3$) δ (TMS): 1.80(m, 1H), 1.95-2.34(m, 4H), 3.35(s, 3H), 3.57-3.84(m, 3H), 4.04(m, 1H),

4.30(d, J=11.5Hz, 1H), 4.71(d, J=11.5Hz, 1H), 4.79(d, J=4.2Hz, 1H), 5.03(m, 2H), 5.83(m, 1H), 7.24-7.41(m, 5H).

IR (NaCl, neat): 3450, 3060, 2820, 1645, 1130 cm^{-1}.

m/z: 261(M^+ - 31)(8.8), 197(13.8), 91(100).



240 241

Methyl 4-(allyl)-6-(vinyl)-3-O-benzyl-2,4,6-trideoxy-α-D-ribo-hexopyranoside (**241**)

To a stirred solution of oxalylchloride (48 mg, 0.38 mmol, 1.5 equiv) in CH_2Cl_2 (7 ml) at -78°C was added DMSO (60 mg, 0.76 mmol, 3.0 equiv). After stirring for 0.25h at -78°C a CH_2Cl_2 (5 ml) solution of alcohol (**240**) (74 mg, 0.253 mmol, 1.0 equiv) was added by syringe and the mixture stirred 0.75h. Triethylamine (130 mg, 1.27 mmol, 5.0 equiv) was added neat via syringe and the ice bath removed. After 1h the mixture was concentrated and placed under high vacuum. The residue was dissolved in THF and filtered. The resulting liquid was concentrated and placed under high vacuum. After 0.5h the above residue was transferred to a dry flask and dissolved in THF (10 ml). To this stirred

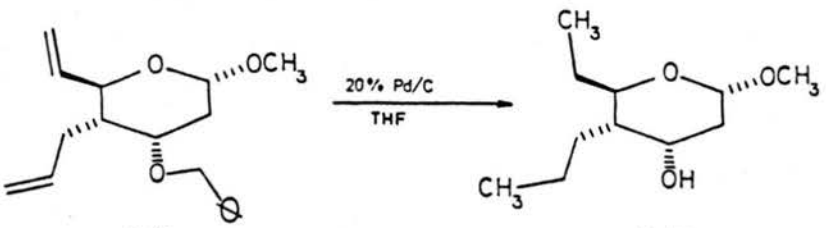
0°C solution of crude aldehyde was added the preformed ylide via syringe. The ylide was prepared by the following: To a stirred suspension of methyltri-phenyl-phosphonium-bromide (145 mg, 0.44 mmol, 1.75 equiv) was added nBuLi(0.2 ml, 1.9M/hexane, 0.38 mmol, 1.50 equiv), the resulting yellow solution was stirred 5 min at room temperature and used directly for the above procedure. The crude aldehyde and ylide reaction mixture was stirred for 0.5h and concentrated to dryness. The residue was dissolved in Et_2O filtered and concentrated. PTLC, eluting with 10% EtOAc/hexane yields 29.5 mg (41%) of (**241**) as a clear oil.

$[\alpha]_D^{25}$ = +180° (c=0.5 CH_2Cl_2)

^1H NMR (270 MHz)($CDCl_3$) δ (7.24, $CHCl_3$): 1.55-1.73(m, 2H), 1.98-2.29(m, 3H), 3.35(s, 3H), 3.71(m, 1H), 4.33(m, 2H), 4.73(m, 2H), 4.97(m, 2H), 5.24(m, 2H), 5.75(m, 2H), 7.24-7.40(m, 5H).

IR(NaCl, neat): 3170, 2880, 1640, 1115 cm^{-1}.

m/z: 256(M^+-32)(7.1), 91(100).

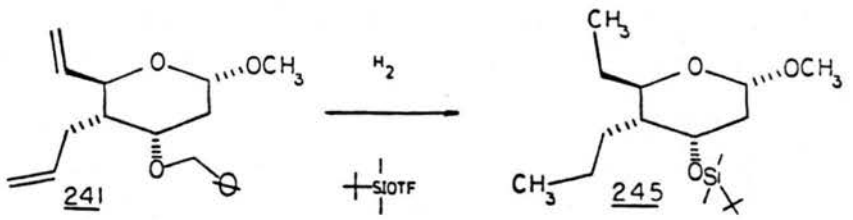


241 242

Methyl 4-(propyl)-6-(ethyl)-2,4,6-trideoxy-α-D-ribo-hexapyranoside (242)

To a stirred suspension of 18% Pd/C (10 mg) in THF (3 mls) was added a THF solution (0.5 mol) of the benzyl ether (241) (15.2 mg, 0.053 mmol). The stirred mixture was degassed and stirred vigorously under an atmosphere of hydrogen for 0.75 hr. The mixture was then filtered through celite and concentrated to give 12 mg of a residue shown by NMR to be almost quantitative production of the unstable alcohol 242.

^1H NMR (270 MHz) ($CDCl_3$) δ(7.24, $CHCl_3$): 0.88(t, J=7Hz, 3H), 0.97(t, J=7Hz, 3H), 1.05-2.10(m, 9H), 3.25(d, J=9.9Hz, 1H), D_2O exchangeable, 3.34(s, 3H), 3.57(m, 1H), 3.88(m, 1H), 4.82(d, J=3.5Hz, 1H).



Methyl 4-(propyl)-6-(ethyl)-3-O-(t-butyldimethylsilyl)-2,4,6-tridoxy-α-D-ribo-hexopyranoside (**245**)

To a stirred solution of benzyl ether **241** (16.78 mg, 0.058 mmol) in THF (1mls) was added 18% Pd/C (10 mg). The mixture was degassed and stirred vigorously under a hydrogen atmosphere for 0.75 hr. The mixture was filtered and concentrated. The resulting residue was dissolved in dry methylene nitrogen. To this solution was added 2,6-lutidiene (19 mg, 0.175 mmol) and t-butylsilyltriflate (32 mg, 0.12 mmol). The mixture was stirred for 0.25 hr and concentrated to dryness. PTLC (eluting with 10% EtOAc/hexane) afforded 3.1 mg (17%) of the silyl ether **245**.

$[\alpha]_D^{25} = +113°$ (C = 0.3, CH_2Cl_2)

IR (NaCl, neat) 2940, 2860, 1460, 1250, 1120, 1085 cm^{-1}

^1H NMR (270 MHz) ($CDCl_3$) δ(7.24 $CHCl_3$): -0.10(s, 3HO, 0.04(s, 3H), 0.87(s, 9H), 0.75-1.90(m, 12HO, 0.95(t, J-7.3Hz, 3H), 3.28(s, 3H), 3.75(m, 1H), 3.95(m, 1H), 4.65(m, 1H).

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