THE TOTAL SYNTHESIS OF LASALOCID A

Thesis by

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To my parents and all of my teachers

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ABSTRACT

A total asymmetric synthesis of the "right half ketone" of the stereo-complex polyether antibiotic, lasalocid A, is described. The [3,3] sigmatropic rearrangements of O-silyl-ketene acetals derived from esters of 1,4-anhydro-pent-1-enitols (furanoid glycals) and 1,5-anhydro-hex-1-enitols (pyranoid glycals) provided α-substituted-2,5-dihydrofuran-2-acetic acid and α-substituted-5,6-dihydro-2H-pyran-2-acetic acid derivatives. The products are key structural elements which are present in polyether antibiotics. The furanoid and pyranoid glycals were conveniently prepared by reductive fragmentation of 2,3-O-(1-methylethylidene)-furanosyl and pyranosyl chlorides. The synthetic scheme is highly convergent, utilizing a building-block approach with stereo- and regioselective carbon-carbon bond formation between the subunits.

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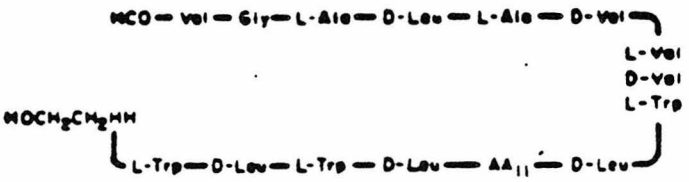
INTRODUCTION

An ionophore, as named by Pressman[1], is a molecule capable of complexing an ion and assisting in the transport of this ion through a lipophilic interface. Ions which can be involved in this complexation-transport process are, for example, alkali or alkali earth metals and protonated organic substances such as biogenic amines. An essential feature for all ionophores is the presence of heteroatoms, capable of acting as ligands for an ion, arranged on the interior of a three-dimensional conformation which exposes a relatively lipophilic exterior. The most well-known synthetic examples are the crown ethers.[2] Naturally occurring ionophores were classified by Westley[3] into the following four structural classes: 1)the peptide ionophores, 2)the cyclodepsipeptides, 3)the macrotetrolides and 4)the polyether antibiotics. (Illustrations were reproduced from Reference 3).

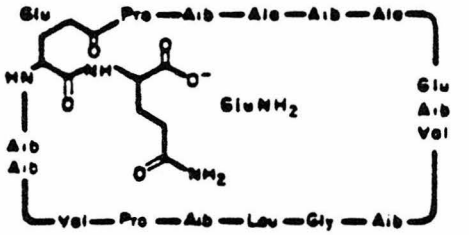
The peptide ionophores are composed entirely of amino acids; some examples are gramicidins A, B, C[4] and alamethicin.[5] The depsipeptides are composed of alternating hydroxy acids and amino acids and valinomycin[6] is a familiar example of this class. The macrotetrolides are constructed from a pair of dextro-rotatory and a pair of leavo-rotatory tetrahydrofuranyl hydroxy acids connected via ester linkages in such a way that the individual units have alternating absolute configurations. Nonactin and its homologs represent ionophores of this class. The polyether

PEPTIDE IONOPHORES

VALINE-GRAMICIDIN A | AA_{11} = Trp
B | AA_{11} = Phe
C | AA_{11} = Tyr

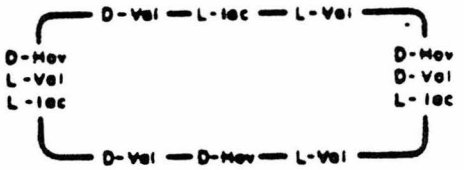


ALAMETHICIN

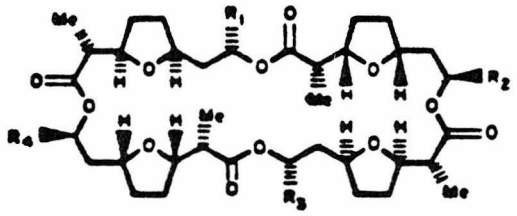


DEPSIPEPTIDE IONOPHORES

VALINOMYCIN

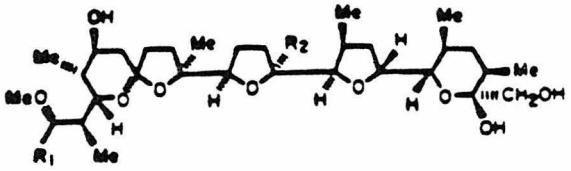


MACROTETROLIDE IONOPHORES

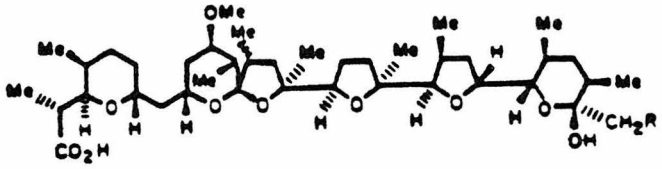


NONACTIN $R_1 = R_2 = R_3 = R_4 = Me$

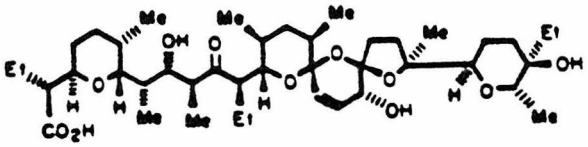
MONOVALENT POLYETHER ANTIBIOTICS



MONENSIN $R_1 = CH(Me)CO_2H$, $R_2 = Et$

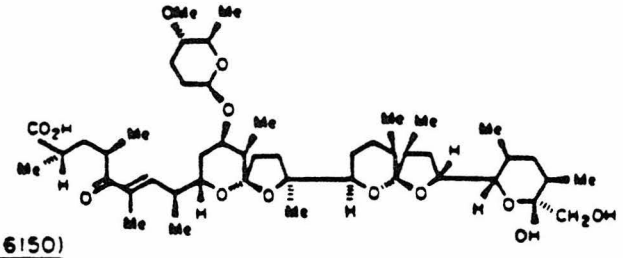


NIGERICIN $R = OH$

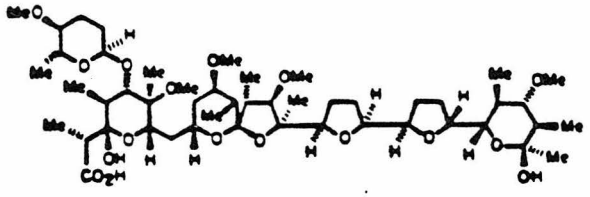


SALINOMYCIN

MONOVALENT MONOGLYCOSIDE POLYETHERS



LENOREMYCIN (Ro21-6150)



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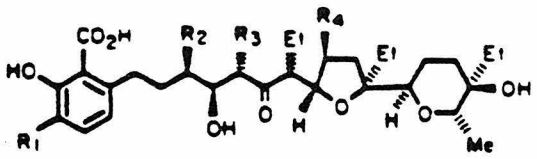
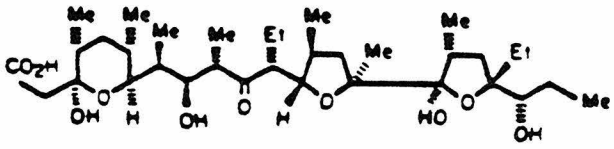
DIVALENT POLYETHER ANTIBIOTICS



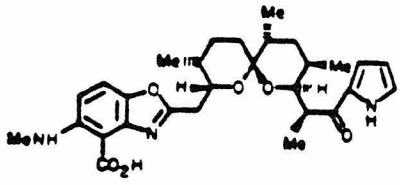
LASALOCID A

$R_1 = R_2 = R_3 = R_4 = Me$

LYSOCELLIN



DIVALENT PYRROLE-ETHER ANTIBIOTIC



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antibiotics are a highly diverse class of tetrahydrofuran and tetrahydropyran ring systems in a linear array that terminates in a carboxylic acid grouping. This large class of ionophores can be further subdivided into the following four sub-classes: 1) monovalent polyethers (e.g.monensin[8], nigericin[9], salinomycin[10]), 2) monovalent monoglycoside polyethers (e.g. lenoremycin,[11] antibiotic A204A[12]), 3)divalent polyethers (e.g. lasalocid A[13] and lysocellin[14]), and 4)divalent pyrrole ethers (e.g. calcimycin (A23187)[15]).

Ionophores were also subdivided by Pressman[16] into the following three groups according to their transport modes; 1)neutral ionophores, such as valinomycin, which are devoid of ionizable functional groups, 2)carboxylic ionophores, such as nigericin, monensin, and lasalocid A, which form rings via head-to-tail hydrogen bonding, and 3)channel-forming quasi-ionophores, which insert themselves into membranes as stationary ion-conducting channels; an example is alamethecin which has a voltage-dependent permeability induction for cations across cell membranes.

Initial interest in polyether antibiotics was the result of the discovery of the coccidiostatic activity of monensin, nigericin, dianemycin, and antibiotic X-206. Coccidia are parasitic protozoa which can cause infection in birds and mammals by invasion of their intestinal tracts. Coccidiostats are agents that control these protozoa. Several polyether antibiotics, including lasalocid A[18], have selective toxicity against coccidia in the intestinal tracts of chickens, while being poorly absorbed by

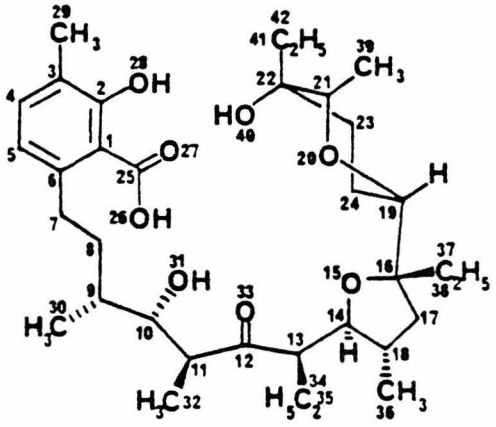
the host. This activity against cocci, Gram-positive bacilli, and filamentous microorganisms and inactivity against Gram-negative bacilli, is ascribed by *in vitro* testing[3] to losses of essential monovalent cations such as K^+.

Cellulose, which is the major component of the diet of most ruminants, is degraded into volatile fatty acids by microorganism fermentation. One of the major inefficiencies of this fermentation process is the production of acetate and butyrate by degradation of pyruvate. This metabolic pathway results in the loss of methane and therefore a loss of associated energy. An agent which tends to direct the fermentation towards propionate instead of acetate and butyrate will effect a more efficient utilization of dietary carbohydrates. It has been claimed that several polyether antibiotics exhibit the ability to increase the level of propionate production relative to acetate, as determined by *in vitro* fermentations of rumen fluid from steers.[19]

The divalent cation polyethers are very potent inotropic agents as they cause stimulation of myocardial contractility. The reason for this inotropic effect has been ascribed to the release of myocardial Ca^{2+} ions.[20] Unfortunately there are a number of problems with this simple Ca^{2+}-polyether-mediated release mechanism. Calcimycin, which has proven to be selective towards divalent cations[22] such as Ca^{2+}, should be an excellent inotropic agent. However, anomalous effects were obtained when it was administered to animals, often depressing

cardiovascular functions.[21] A number of lasalocid derivations have been shown to transport biogenic amines, such as serotonin, dopamine, norepinephrine, and epinephrine, across artificial lipid bilayers.[23] There is an excellent correlation between the observed inotropic effects and the catecholamine permeability coefficients of the membrane induced by these ionophore derivatives.[24] These results tend to favor a mechanism of catecholamine mobilization as the major factor in lasalocid polyether inotropic effects. Moreover, a number of monovalent cationic polyether antibiotics have been found to be active inotropic agents.[25] Monensin, which transports neither Ca^{2+} nor catecholamines across membranes in vitro, is also an active inotropic agent. It is therefore obvious that the mode of action is more complex than had been hypothesized earlier.

These observations have, however, resulted in considerable interest in the potential application of polyether ionophores as cardiovascular drugs. The development of efficient and versatile syntheses of these substances not only constitutes a provocative challenge to the ingenuity of organic chemists but could also accelerate the discovery of more efficacious cardiotonic agents as many synthetic analogues of these polyethers become readily available. Recently, successful synthetic approaches have been completed with three representatives: lasalocid[26,27], monensin[28,29] and calcimycin.[30]

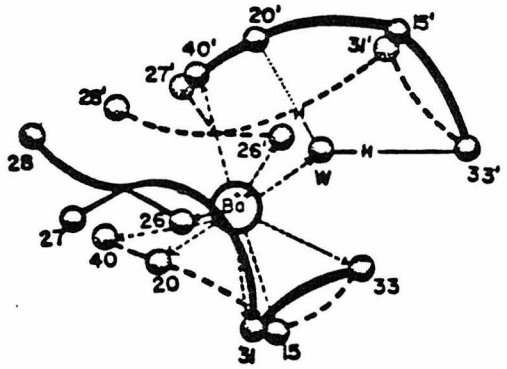


LASALOCID A

(X537A)

RESULTS AND DISCUSSION

Lasalocid was co-isolated with X-206 and nigericin from Streptomyces in 1951.[13] The structure of lasalocid A was elucidated with the aid of X-ray analysis in 1970.[31] It was the first ionophore of the polyether class shown to contain an aromatic chromophore. Biogenetically, lasalocid is derived from acetate, propionate, and butyrate units.[3] Four homologs have also been identified as minor components of the lasalocid complex (4-16%).[32] In the crystalline state, lasalocid A exists in a cyclic conformation with hydrogen bonding between the carboxyl end and the tertiary hydroxyl at the opposite end. It gives an unsymmetrical 2:1 complex with Ba^{2+} (reproduced here from Reference 31) wherein one lasalocid donates the carbonyl oxygen and the terminal hydroxyl, together with a molecule of water for coordination, and the other lasalocid employs all six "internal" oxygens.[31] This also appears to be preferred conformation in solution, as determined by NMR studies.[33] Lasalocid does not exhibit high ion specificity; it complexes all alkali and alkali earth metals, lanthanides and organic animes.[23,34] Lasalocid A



Schematic drawing of the co-ordination of barium. Only the oxygen atoms of the antibiotic molecules are shown.

has been modified substantially in the aromatic ring portion[24,35] and variable amounts of activity have resulted.

Of particular importance in the chemical degradation of lasalocid A is the ready cleavage of the molecule by base or heat in a reverse aldol-type reaction,[24] as illustrated in Figure 1. While the aldehyde B was unstable and underwent further degradation, the ketone C was readily available.

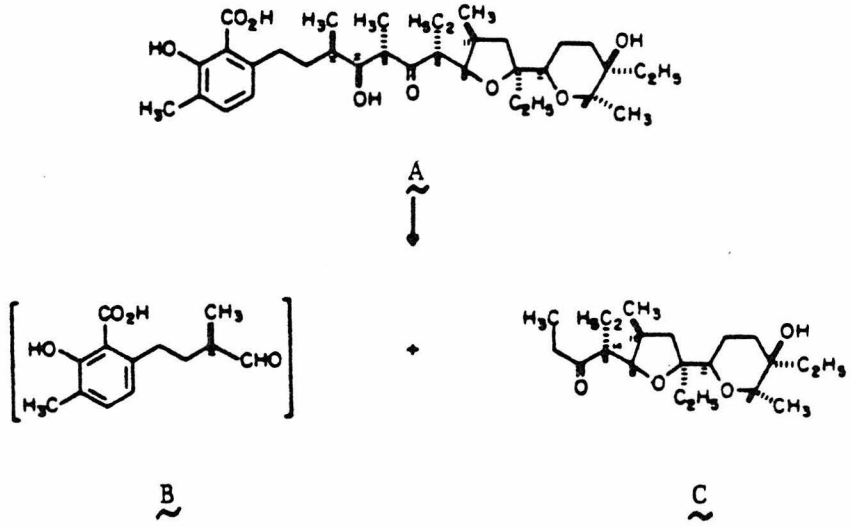
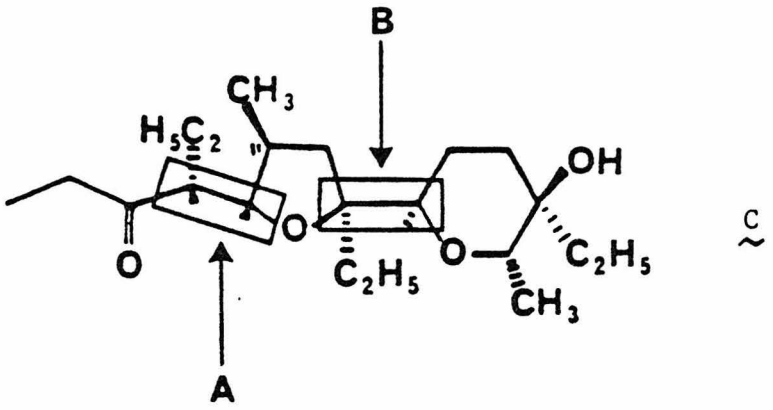


Figure 1

In analogy to this degradation, a key feature of the present synthesis is to effect an aldol-type condensation between two synthetic partners. The synthesis of the stereochemically more demanding polyether ketone C is reported in this work, and the complementary synthesis of the benzyl ester of the acid aldehyde B from this laboratory, together with an aldol condensation between the two halves to give synthetic lasalocid A, will be reported elsewhere.[36]



C

Figure 2

The two structural units encircled as A and B in the ketone C shown in Figure 2 are characteristic features which are present in nearly all of the polyether antibiotics. They are similar in that both can be created by the stereospecific attachment of a chiral

carbon residue to the C-1 position of a saturated oxygen heterocycle. In the A case, the attachment results in a 1,5-oxygen, oxygen relationship or an aldol-type structure. However, in the B case, the resulting attachment is a 1,4-oxygen,oxygen relationship or a glycol diether.

For this work, the ketone C was schematically envisaged as arising from the three subunits I, II, and III (Figure 3).

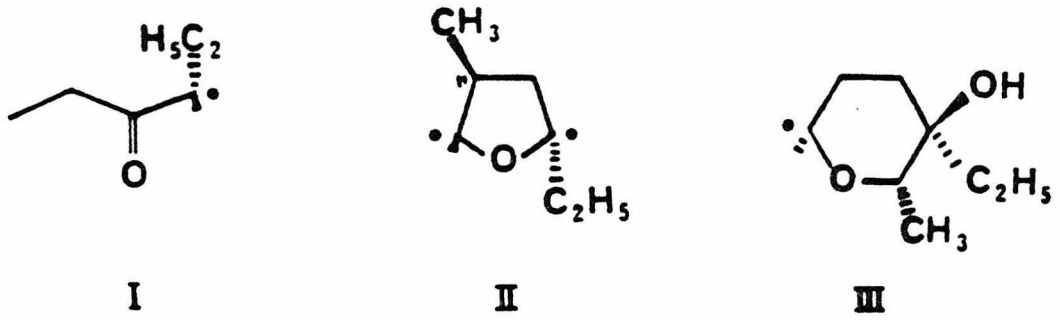
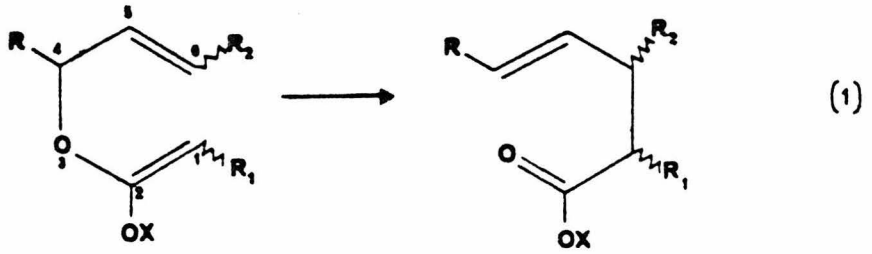


Figure 3

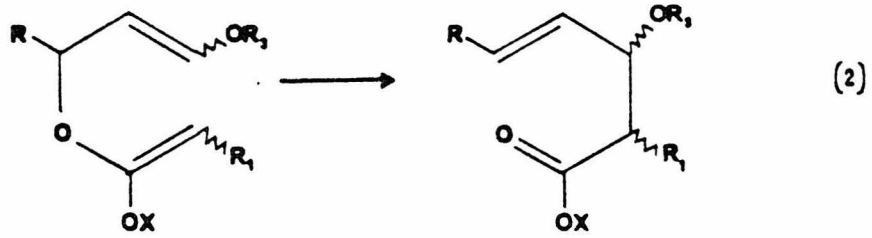
The plan called for the initial union of parts I and II, and the subsequent joining of the resulting product to the remaining subunit III. This approach has the advantage of not only being highly convergent, but also amenable to extensive variation of the subunits used. This basic design allows the construction of the ring systems of many polyether ionophores by utilizing furan

and pyran subunits as building blocks much as a polypeptide is built by the union of α-amino acids.

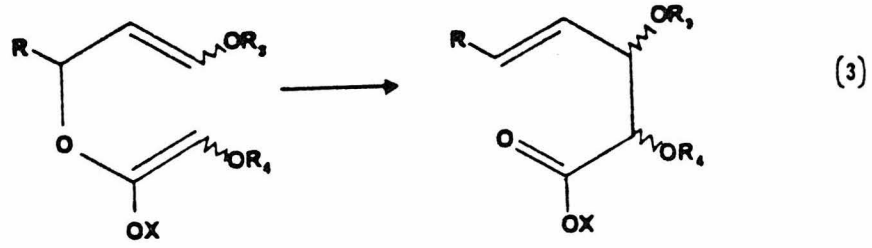
One means of potentially general utility for the attainment of this objective is a scheme which incorporates the recently developed ester enolate Claisen rearrangement and the attending stereochemical control demonstrated in the enolization stage of this rearrangement as a key carbon-carbon bond forming reaction.



(1)



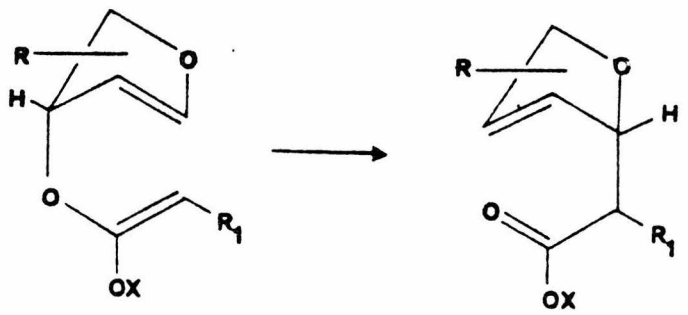
(2)



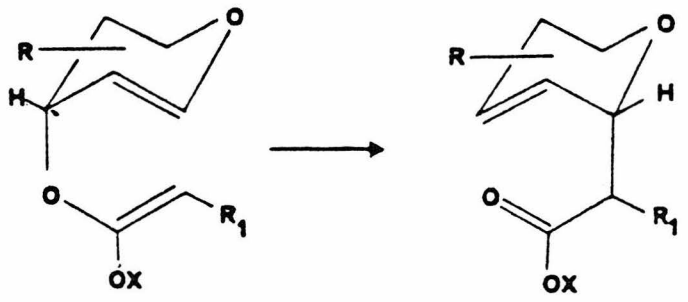
(3)

As can be seen in equation 1, the ester enolate Claisen rearrangement provides a means of fixing the geometry about the newly-formed carbon-carbon bond (between C-1 and C-6) when there is a preferred chair-like or boat-like transition state for the[3,3]sigmatropic rearrangement. When the substrate can be derived from an optically-active allylic alcohol, the chirality at C-4 can then be transferred to the newly-formed center.

When C-6 (equation 1) has an oxygen substitution, as shown in equation 2, this rearrangement offers a stereoselective route to aldol-type products.[37] Moreover, this approach then offers a means for the union of subunits I and II (Figure 3) or a solution to the structural unit A in compound C when the method is applied to an appropriately-substituted heterocyclic allylic alcohol to provide the aliphatic ester substrate as shown in equations 4 and 5.[38]

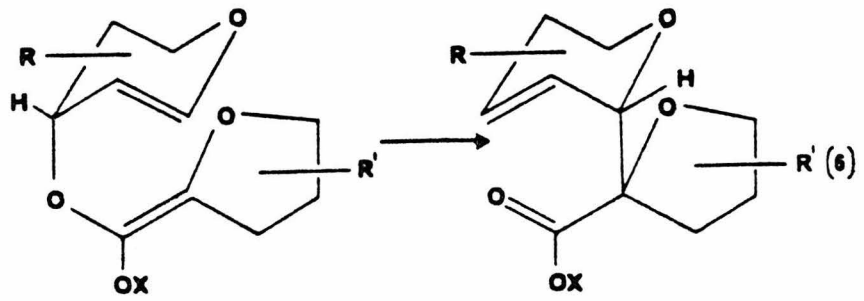


(4)



(5)

When both C-1 and C-6 (equation 1) have oxygen substitutions, as shown in equation 3, the resulting product from the ester enolate Claisen rearrangement has a glycol-diether structural unit,[38] the relative stereochemistry of which can be pre-selected. This is precisely the technology needed for joining the product from subunits I and II to the remaining subunit III (Figure 3) or a solution to the structural unit B in compound C. This is schematically shown in equation 6, below.



It is also apparent that the stereo-controlled connection between these heterocycle subunits shown above would be a general method in the construction of linear sequence of furans and pyrans found in many ionophores.

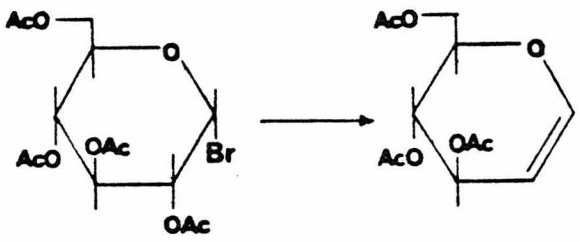
Subunits II and III can be derived from simple monosaccharides[39] which represent cheap chiral starting materials for the furan and pyran units. One simply has to choose sugars with the right constitutions of hydroxyl functions which would serve as appropriate frameworks and to transfer correct chiralities to

the carbon-carbon bonds formed from the [3,3]-sigmatropic rearrangements.

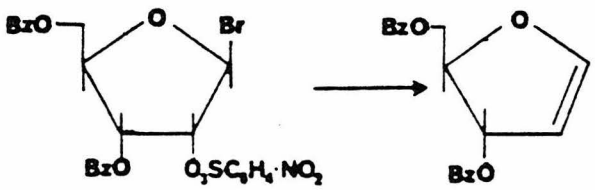
METHODOLOGY FOR GLYCAL FORMATION AND SUBSEQUENT REARRANGEMENT

Two immediate subgoals became apparent in order to test the applicability of the enolate Claisen rearrangement for union of the individual building blocks. It was necessary first to develop a convenient method for the preparation of furanoid and pyranoid allylic alcohol portions which could be esterified to provide substrates for rearrangements as shown in equations 4 and 5. Then it had to be established that these relatively labile allylic esters would smoothly undergo the requisite [3,3]-sigmatropic rearrangements.

The furanoid and pyranoid allylic alcohols are representatives of the class of carbohydrate compounds known as glycals.[40] The pyranoid members of this group have long been recognized as valuable intermediates for carbohydrate synthesis. They are most commonly prepared by some modification of the method of Fischer and Zach.[41,42] This method involves the reduction of peracetylated pyranosyl bromides, such as 2,3,4,6-tetra-O-acetyl α-D-glucopyranosyl bromide, by elemental zinc in acetic acid to give the peracetylated pyranoid glycals (equation 7).



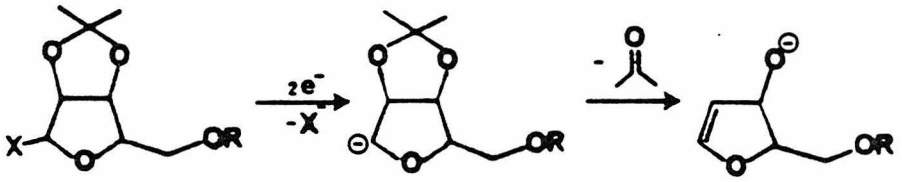
(7)



(8)

However, acetylated furanoid glycals are particularly susceptible to a facile acid-catalyzed allylic rearrangement because the C3 carbon-oxygen bond of either epimer is coplanar with the π cloud of the enol ether double bond. This consideration precludes the use of the classical Fischer and Zach method.[43] Results from the single previous successful preparation of furanoid glycal esters suggested that the lability of furanoid glycal derivatives was related, not surprisingly, to the nature of the leaving group at C-3. A successful preparation of a furanoid glycal was carried out by treating 3,5-di-O-benzoyl-2-O-p-nitrophenylsulfonyl-β-D-ribosyl bromide with sodium iodide in acetone[44] (equation 8). However, for the purposes at hand, a synthesis of glycals with an unsubstituted C-3 hydroxyl group, suitable for acylation with other acidic portions, was desired. In consideration of prior reports on furanoid glycal esters, the free allylic alcohols were expected to be more stable than their corresponding esters. This specification was then a practical necessity for the successful isolation of the furanoid glycals. There are no general methods known to provide these highly desirable substrates.

The fragmentation of β-alkoxyethyl halides on treatment with metals in inert solvents suggested that a scheme generalized in

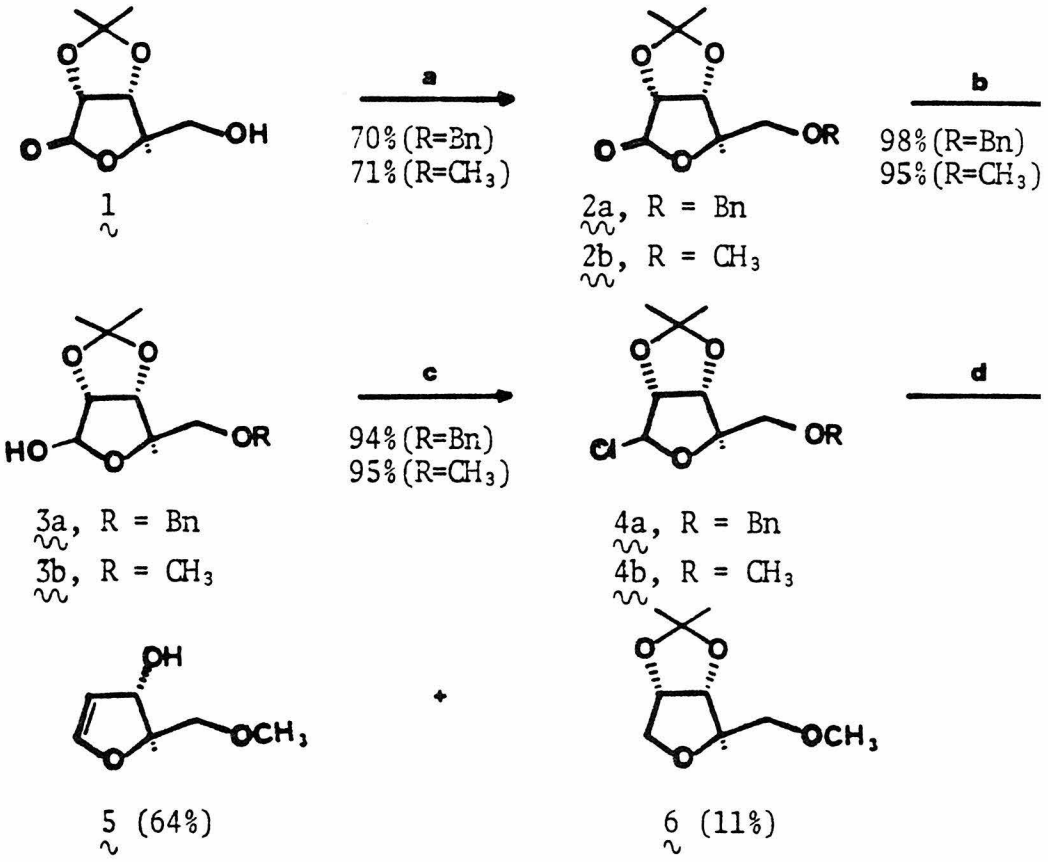


(9)

equation 9 could provide a solution to this problem. While the concept is equivalent to the classical method of Fischer and Zach, an approach utilizing non-acidic reduction conditions would offer the advantage that destruction of the glycals would be avoided. Furthermore, utilization of a 2,3-O-isopropylidene unit would not only provide selective initial protection of the 2,3-vicinal diol system but would also result in the generation of the desired 3-hydroxy glycal upon reductive elimination.

To evaluate this possibility, the furanosyl chloride 4a (Chart 1) was prepared for an investigation of reductive fragmentation methods. The hydroxy lactone 1, available from D-(+)-ribonic acid γ-lactone in 95% yield[45], afforded the benzyl ether 2a by alkylation with benzyl bromide in the presence of silver (I) oxide. Reduction of the protected lactone 2a with diisobutylaluminium hydride in ether at -78°C provided the lactol 3a which was converted to the furanosyl chloride 4a with triphenylphosphine and carbon tetrachloride in refluxing tetrahydrofuran.[46] The corresponding furanosyl bromide could be isolated by using carbon tetrabromide in place of carbon tetrachloride although, as expected, it was much more labile and decomposed on attempted distillation at reduced pressure. Metal-halogen exchanges using zinc, magnesium,[47] and sodium in aprotic solvents led to the isolation of starting materials and/or a collection of non-identified materials. A slightly encouraging result, however, appeared when attempted

Chart 1



1

2a, R = Bn

2b, R = CH_3

3a, R = Bn

3b, R = CH_3

4a, R = Bn

4b, R = CH_3

5 (64%)

6 (11%)

a) Ag_2O, $C_6H_5CH_2Br$ or CH_3I, DMF; b) DIBAL, ether, -78°C;

c) $(C_6H_5)_3P$, CCl_4, THF, reflux; d) Li, liq NH_3, then NH_4Cl

transmetalation with t-butyl lithium at low temperature provided a very small amount (less than 10%) of the desired product together with a de-halogenated material and a di-alkyl coupled product. Dissolving metal reductions then seemed promising, except that a benzyl ether at C-5 would not be compatible. As an alternate blocking group, a simple methyl ether was chosen for its stability and the simplicity of its signal in the ^{1}H-NMR spectrum. The furanosyl chloride 4b (Chart 1) was prepared in a manner analogous to the preparation of the furanosyl chloride 4a. Addition of a solution of the chloride 4b to an excess of lithium metal in liquid ammonia, and isolation of the reduction products under anhydrous condition by neutralization of the reaction mixture with solid anhydrous ammonium chloride, afforded a 75% yield of a 6:1 mixture (^{1}H-NMR) of the desired glycal 5 and the simple reduction product 6. The methyl ether 6 is most likely produced by protonation of the intermediate cabanion prior to fragmentation. The glycal 5 could be purified by chromatography on Florisil or silica gel with about 90% recovery. Due to the lability of this product and given the inert nature of the by-product, for preparative purposes the mixture of products was used without adverse effect in subsequent synthetic transformations.[48]

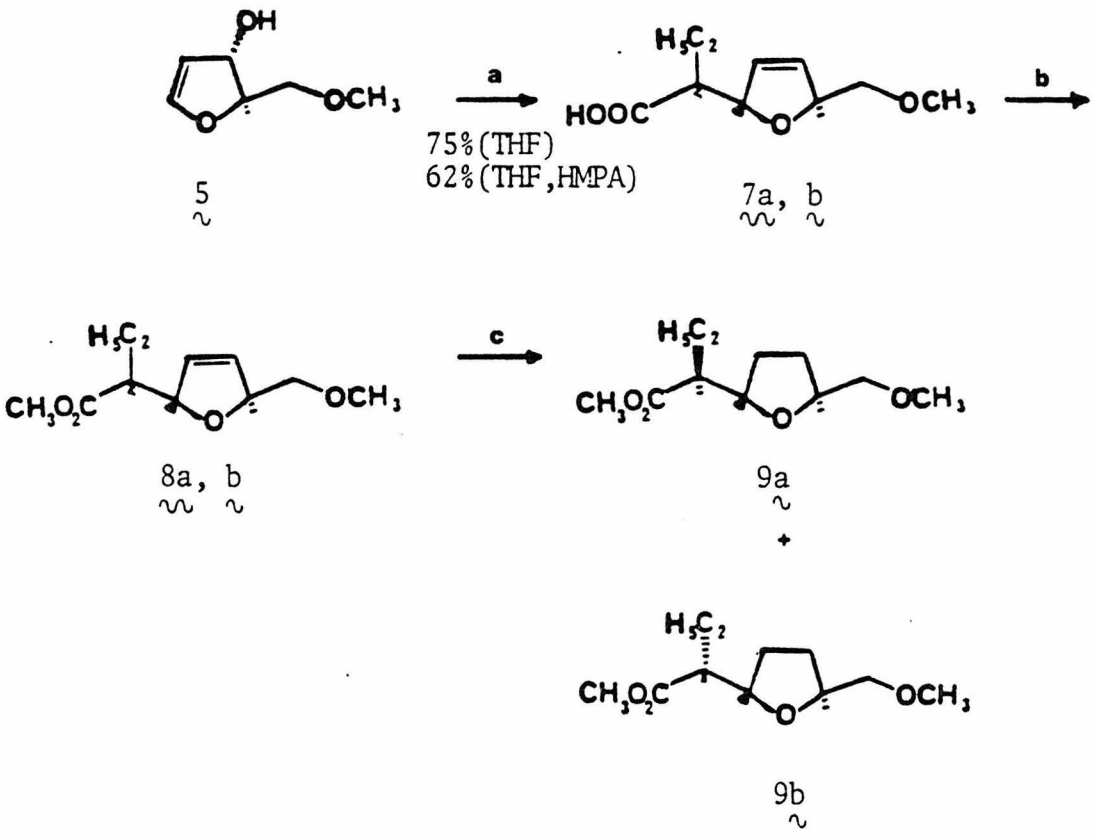
Results from previous investigations in this laboratory[37] indicated that the ester enolate Claisen rearrangement could be successfully applied to esters of γ-methoxy allylic alcohols. The reactions proceeded in good yields and the experimental evidence indicated that diastereomeric β-methoxy carboxylic acids were obtained in proportions dependent upon the solvents employed during

deprotonation. Furthermore, experimental procedures had been developed which allowed the enolate Claisen rearrangement to be applied to esters which were too unstable to be isolated.

Given these precedences, we turned our attention to the Claisen rearrangement of the ester derived from the newly obtained glycal 5. Not surprisingly, the butanoyl ester of this glycal could not be purified by column chromatography or reduced pressure distillation. A solution of this ester (Chart 2) prepared in tetrahydrofuran was then used directly for the preparation of the silylated ketene acetals, the [3,3]-sigmatropic rearrangement precursor. The ensuing rearrangement was extremely facile. Complete reaction had occurred within a few minutes at ambient temperature as evidenced by ^{1}H-NMR. Two diastereomeric acids, 7a and b were isolated after aqueous hydrolysis. The corresponding hydrogenated methyl esters 9a,b could be readily separated by column chromatography on silica gel or vapor phase chromatography and their ratios were thereby easily determined.

The ratio of these diastereomeric methyl esters (9a:9b) was 79:21 when the enolization was carried out in THF and 9:91 in 23% HMPA in THF. The prediction of the stereochemical outcome in these reactions or assignment of relative stereochemistry to the products was more complicated than in acyclic examples.[37] The orientation of the new carbon-carbon bond at C-1 in these heterocycles could be assigned with certainty by consideration of the cyclic transition state and the disposition of the allylic carbon-oxygen bond at C-3. However, although enolization and silylation of these esters were tentatively expected to exhibit the same stereoselectivity found

Chart 2



5

7a, b

8a, b

9a

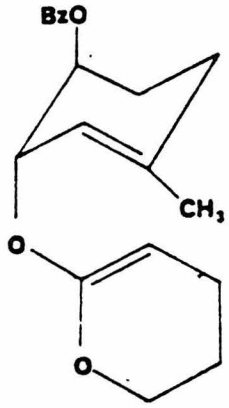
9b

9a: 9b = 79:21 (LDA); 9:91 (LDA, HMPA)

a) n-BuLi, n-C_3H_7COCl; LDA, THF (HMPA); TMSCl; ^-OH;

b) CH_2N_2, ether; c) H_2, 5% Rh on C

earlier,[37] ill-defined stereoelectronic considerations and non-bonded interactions between the substituents on the heterocyclic rings and the silyl ketene acetals cast doubt upon the favorable nature of chair-like transition states for these rearrangements. This doubt was further amplified by a report from Lythgoe[49] that the cyclohexyl ketene acetal dl.D rearranged through a boat-like transition state.



dl·D

The assignment of the stereochemistry at the α-carbon was made with certainty later in the synthetic route when a direct comparison to the natural material was possible. The configurations of the α-carbons as assigned to 9a and 9b then implied a preferred boat-like transition state for the [3,3]-sigmatropic rearrangement of these systems. This conclusion was based upon the assumption that the ratio of the enolates was similar to that observed previously.[37]

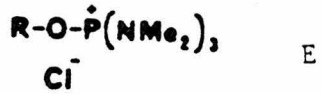
Further work from this laboratory, with more relevant examples, had established an efficient and general method for the preparation of furanoid and pyranoid glycals.[50] The corresponding esters underwent facile and smooth ester enolate Claisen rearrangements to afford C-1 glycosides with complete chirality transfer from C-3 to

to C-1. The stereochemistry at the α-carbon could be pre-selected without regard to relative thermodynamic stabilities.[38]

CONSTRUCTION OF THE SUBSTITUTED FURANOIC ACID

With this technology now in hand, it was possible to connect subunits I and II stereoselectively to give the acidic portion for the second critical[3,3]sigmatropic rearrangement as exemplified previously in equation 6. The furanosyl chloride 12 (Chart 3), readily available in a manner analogous to the preparation of furanosyl chlorides 4a and 4b (Chart 1), was treated with lithium in liquid ammonia to give a 6:1 mixture of the glycal 13 and the by-product 14.

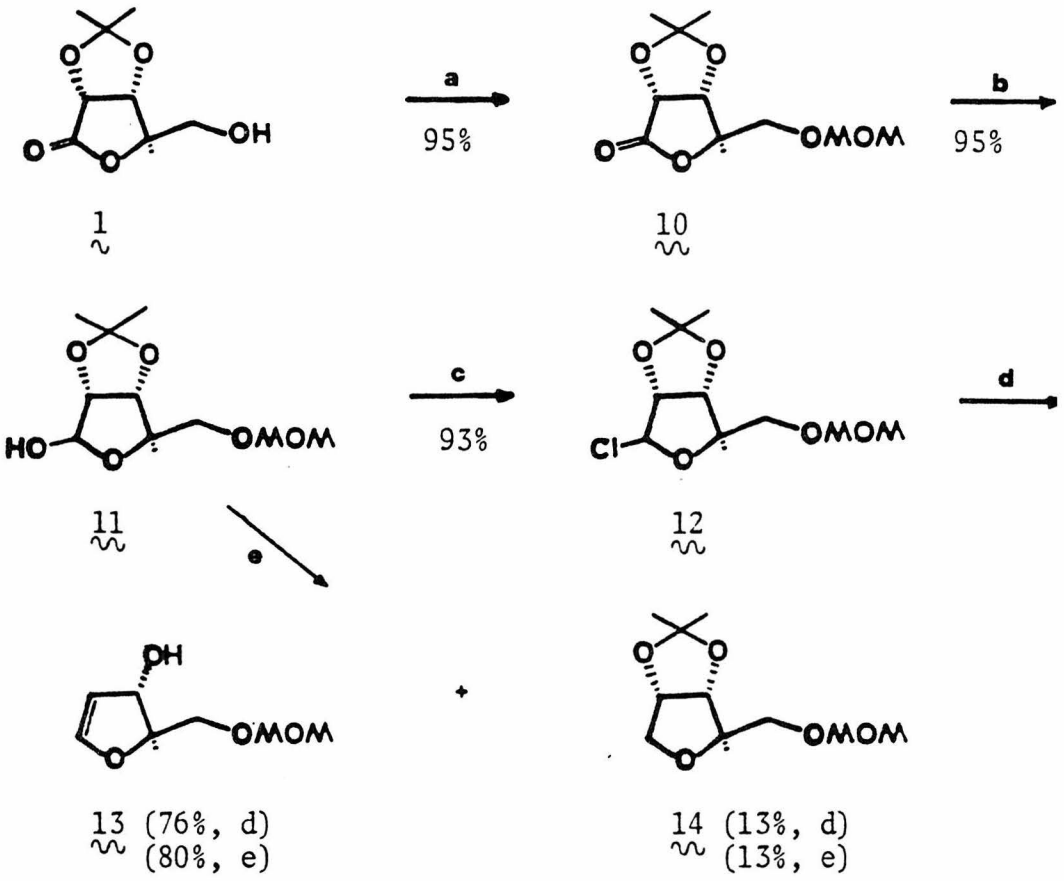
In light of the instability of the furanosyl and pyranosyl chlorides, an alternative method for the transformation of the lactols to glycals was examined. It was known that hexamethylphosphorus triamide reacted at low temperature with carbon tetrachloride in the presence of alcohols to form adducts of type E.



E

Warming of these adducts led to the formation of alkyl chlorides and HMPA.[51] Addition of hexamethylphosphorus triamide to a solution of the lactol 11 (Chart 3) and carbon tetrachloride in THF at -78°C, warming the solution to 0°C, and subsequent addition of the solution to lithium in liquid ammonia, yielded a mixture of

Chart 3



1 10 11 12 13 (76%, d) (80%, e) 14 (13%, d) (13%, e)

a) $ClCH_2OCH_3$, (i-Pr)$_2$NEt, CH_2Cl_2; b) DIBAL, ether, -78°C;

c) $(C_6H_5)_3P$, CCl_4, THF, reflux; d) Li, liq NH_3, then NH_4Cl;

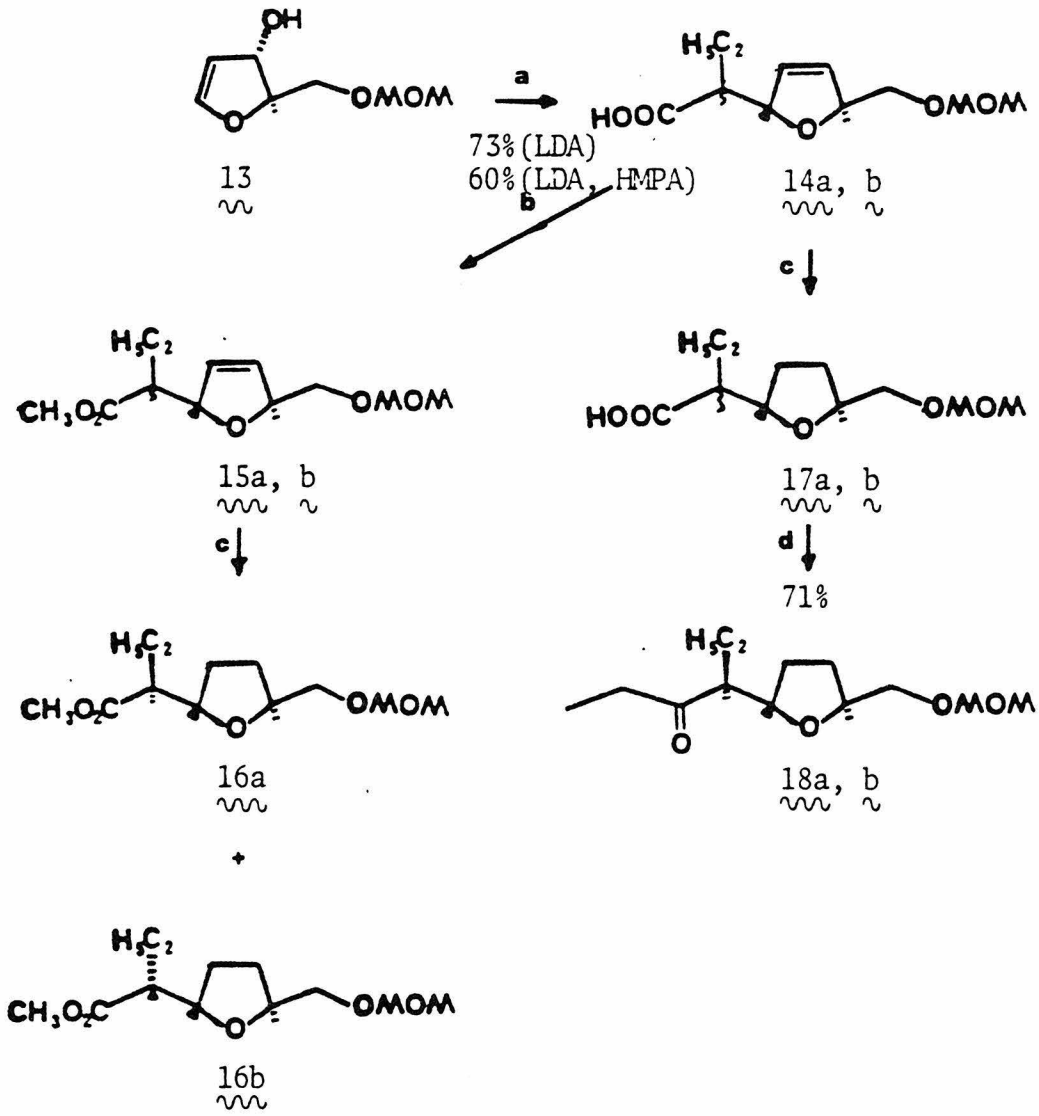
e) $P(NMe_2)_3$, CCl_4, THF, 0°C; Li, Liq NH_3, then NH_4Cl

HMPA, the glycal 13 and the by-product 14. Rapid filtration of the crude reaction product through a pad of silica gel removed the HMPA. The same 6:1 ratio of products 13 and 14 was obtained but in higher overall yield and without isolation of the furanosyl chloride 12.

The butanoyl ester of the glycal 13 was converted into silyl ketene acetals (Chart 4) by the action of LDA and TMSCl. Hydrolysis of the silyl esters obtained from the rearrangement of these acetals afforded the acids 14a, b. Again, the hydrogenated methyl esters 16a, b could be separated by column chromatography on silica gel. The ratios, determined by vapor phase chromatography, were 81:19 when the enolization was carried out in THF and 21:79 in 23% HMPA in THF.

Although lacking the C-18 (lasalocid numbering) methyl group of lasalocid A, it was felt that the esters 16a, b could be effectively utilized as model systems with a possibility of late incorporation of the methyl group. Accordingly, the hydrogenated acids 17a, b were converted to the ethyl ketones 18a, b by the action of lithium diethyl cuprate on the corresponding acid chlorides.[52] However, attempted protection of the ketone with ethylene glycol under acidic conditions led to the production of several materials with presumed scrambling of the stereochemistry of the α and β centers of the ketone. It was then decided to postpone the introduction of the ethyl ketone to a later stage or to protect the ketone as an alcohol with the resulting inconvenience of having a mixture of diastereomeric secondary alcohols.

Chart 4



16a: 16b = 81:19 (LDA); 21:79 (LDA, HMPA)

a) n-BuLi, n-C_3H_7COCl; LDA, THF (HMPA); TMSCl; ^-OH;

b) CH_2N_2, ether; c) H_2, 5% Rh on C; d) $(COCl)_2$; $LiEt_2Cu$, ether

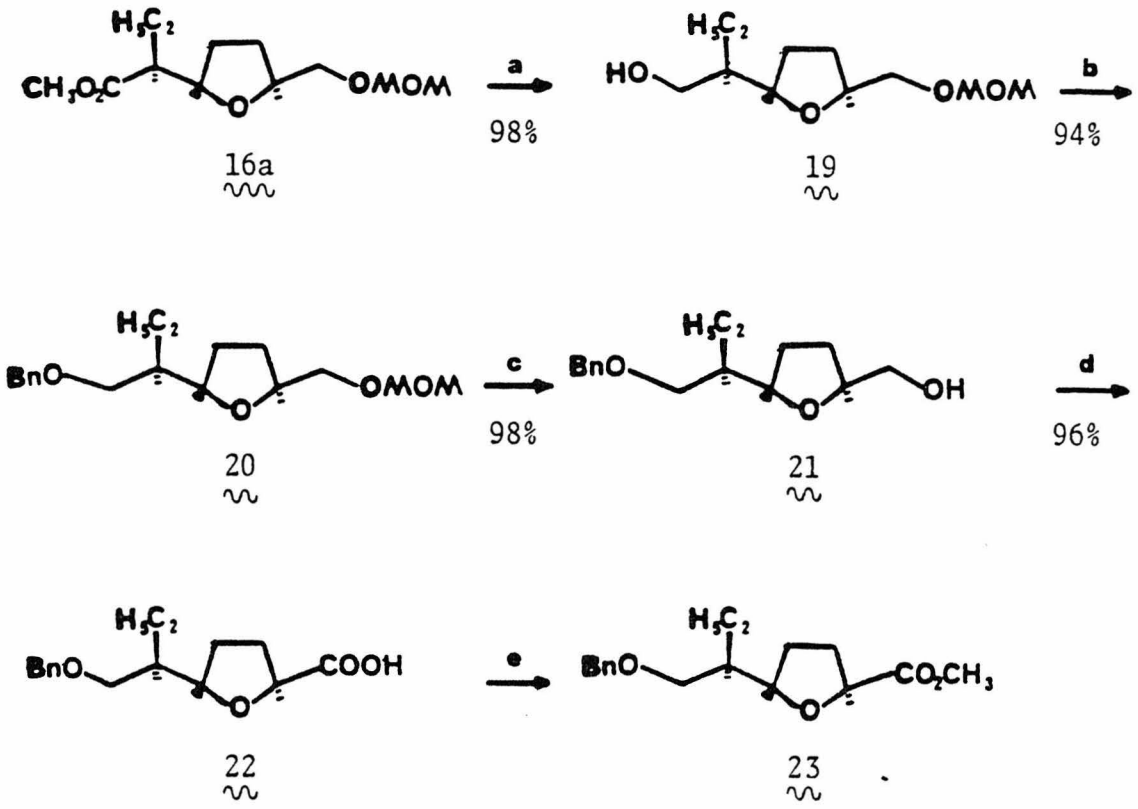
Therefore, the alcohol 19 (Chart 5), obtained from the methyl ester 16a by lithium aluminum hydride reduction, was converted to the benzyl ether 20 by alkylation of the potassium alkoxide with benzyl bromide. Hydrolysis of the methoxymethyl ether 20 gave the primary alcohol 21 which was smoothly oxidized to the carboxylic acid 22 with Adam's catalyst[53] and molecular oxygen. This material was fully characterized as its methyl ester 23.

Alternatively, the aldehyde 24 (Chart 6), available from the methyl ester 16a, could be treated with ethyl magnesium bromide to provide the diastereomeric alcohols 25a,b which were protected as the benzyl ethers 26a,b. Hydrolysis and oxidation then afforded the diastereomeric acids 28a,b which were characterized as the methyl esters 29a,b.

INCORPORATION OF A METHYL GROUP AT C-18 (LASALOCID A NUMBERING)

Attention was turned to the introduction of the methyl group at C-2 (C-18 lasalocid A numbering). The plan was to displace an α-oriented leaving group at C-2, and along this line of thought a hydroxyl function was introduced with the correct orientation by an iodolactonization[54] of the acids 14a,b (Chart 7). The resulting iodide was reduced with tri-n-butyltin hydride to give the lactones 30a,b, which were then treated with dimethyl-N-pyrrolidyl aluminum[55] to provide the hydroxy amides 31a,b. Alternatively, the lactones[56] 30a,b could be reduced with lithium aluminum hydride and the resulting diols could be selectively silylated[57] at the primary hydroxyl function to give the alcohols 32 a,b. Attempted displacement of alcohol derivatives[58] obtainable from compounds 31a,b

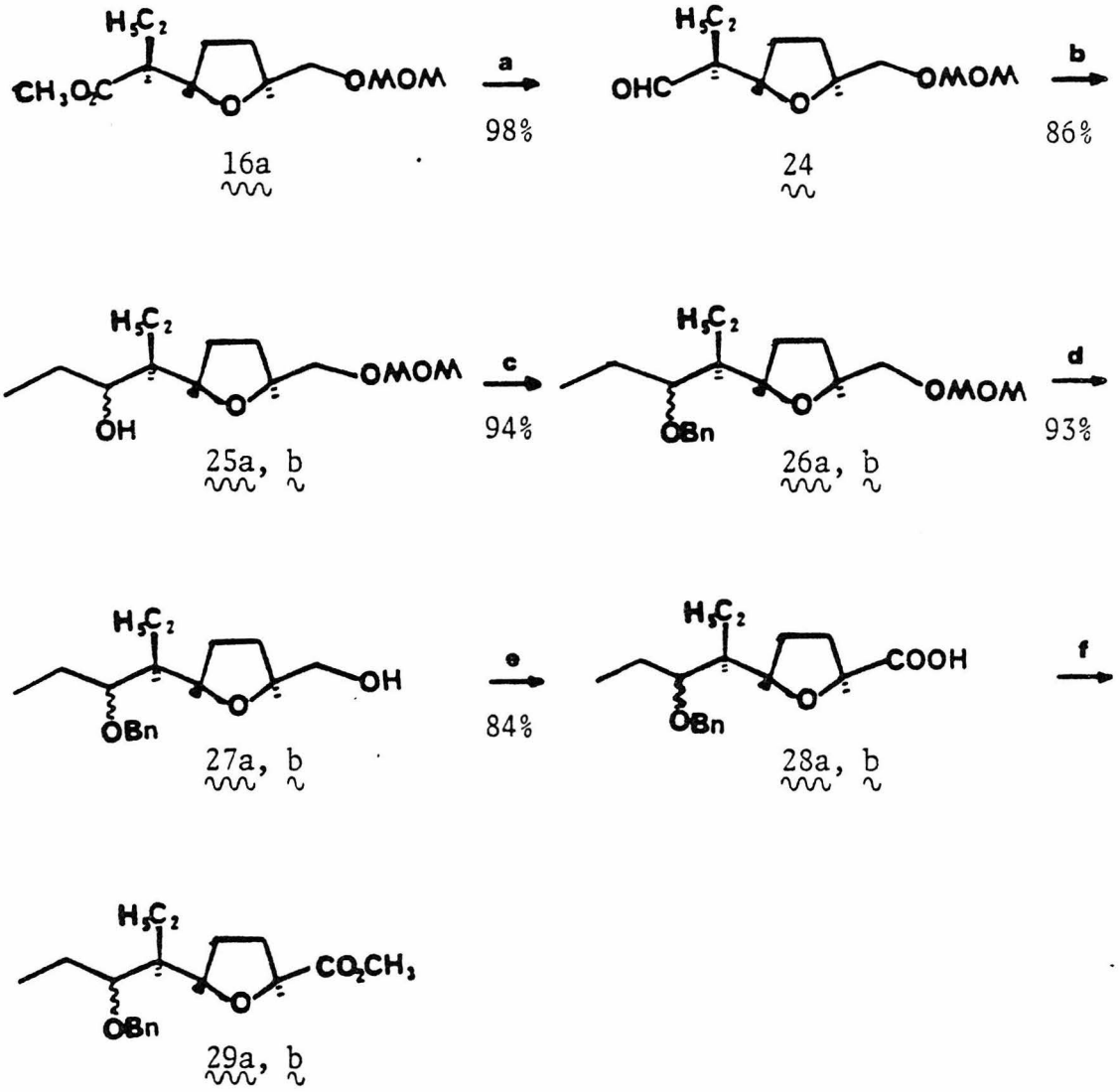
Chart 5



a) $LiAlH_4$, ether; b) KH, $C_6H_5CH_2Br$, THF; c) 10% aqHCl, THF;

d) Pt, O_2, $aqNaHCO_3$; e) CH_2N_2, ether

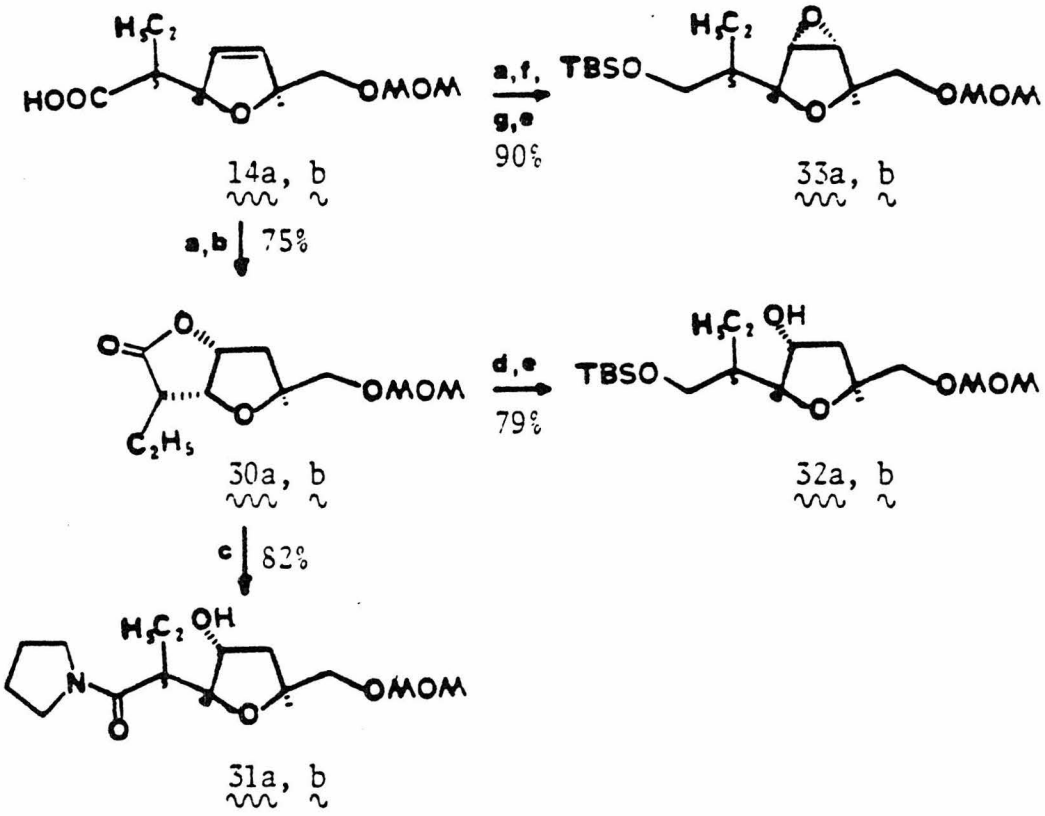
Chart 6



a) DIBAL, ether, -78°C; b) EtMgBr, THF; c) KH, $C_6H_5CH_2Br$, THF; d) 10% aqHCl, THF; e) Pt, O_2, aq $NaHCO_3$;

f) CH_2N_2, ether

Chart 7

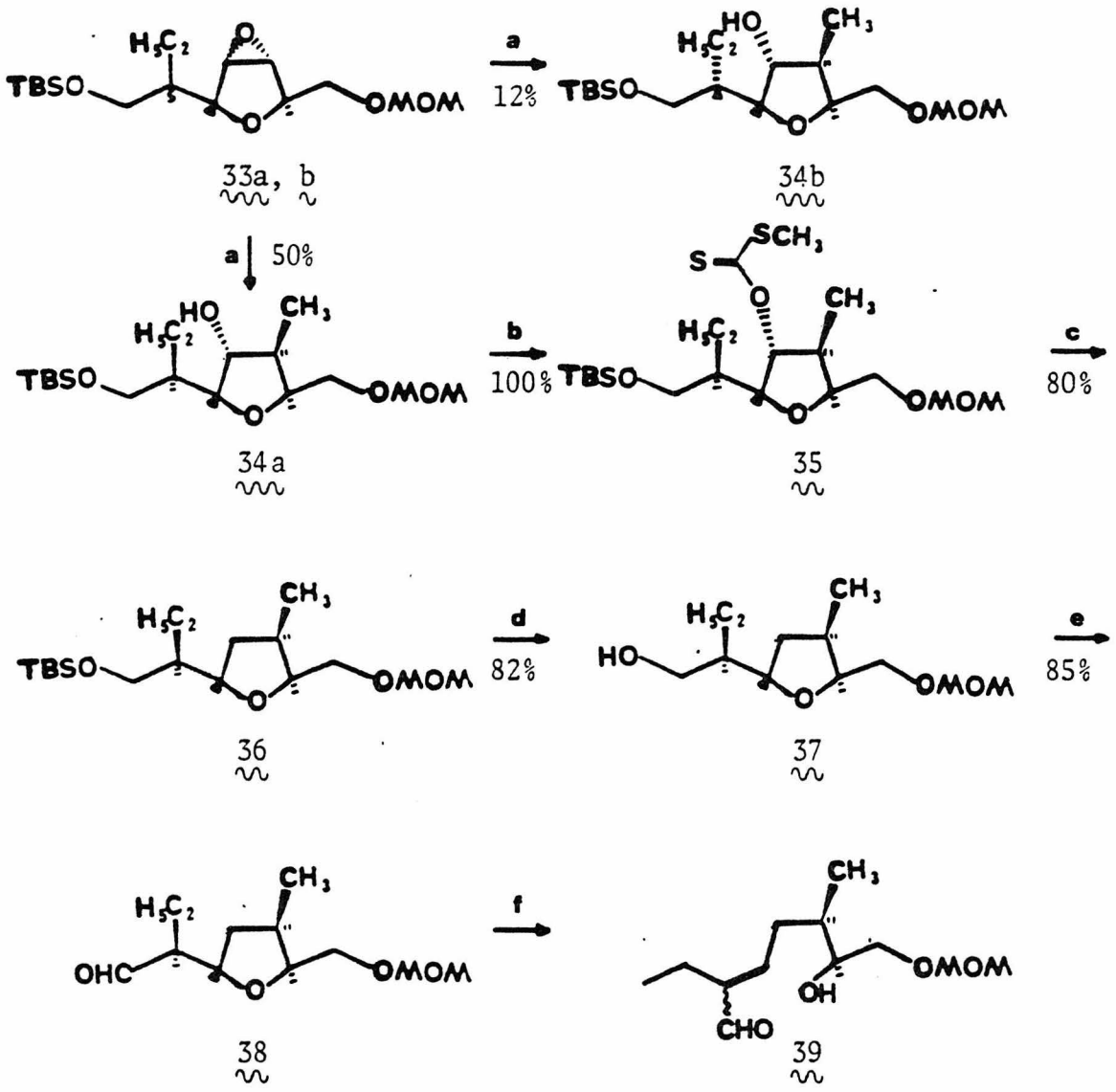


a) KI, I_2, aq $NaHCO_3$; b) n-Bu_3SnCl, $NaBH_4$, EtOH, hν; c) $Me_2AlN(CH_2)_4$, CH_2Cl_2; d) $LiAlH_4$, ether; e) TBSCl, imidazole, DMF; f) AlH_3, THF; g) Na_2CO_3, CH_3OH

and 32a,b with lithium dimethyl cuprate[59] was unsuccessful. It was then envisaged that a nucleophilic ring opening of a strained epoxide[60] at C-2 and C-3 could be carried out with less difficulty. The required epoxides 33a,b were obtained from the corresponding iodolactones of compounds 14a,b by reduction with alane[61], base-induced epoxide formation of the resulting iodohydrin, and protection of the primary hydroxyl function as a silyl ether.[56]

Treatment of the epoxides 33a,b (Chart 8) with lithium dimethyl cuprate in ether-pentane[62] indeed gave epoxide opening products. Unfortunately the electrophilic site proved to be at the unexpected C-3 position, adjacent to the β-oriented side-chain at C-4, resulting in the production of the alcohols 34a,b. This was tentatively rationalized by realization of the possibility of coordination of the incoming reagent to the methoxymethyl ether. The position of methylation was rigorously established by deprotonation of compound 34a with sodium hydride, acylated with carbon disulfide, and alkylation with methyl iodide. The resulting xanthate 35 was reduced with tri-n-butyltin hydride[63] to give compound 36 which was desilylated with tetra-n-butyl ammonium fluoride[56] to give the alcohol 37. The aldehyde 38, obtained by oxidation[64] of the alcohol 37, was induced to undergo β-elimination with potassium t-butoxide to yield the unsaturated aldehyde 39. Examination of the ^{1}H-NMR spectrum of compound 39 revealed that the signal due to the olefinic proton was a triplet and not a doublet. Methylation at C-2 would have given rise to a doublet whereas methylation at C-3 gives rise to the observed triplet. The possibility of the

Chart 8



33a, b 34b 34a 35 36 37 38 39

a) $LiMe_2Cu$, ether-pentane; b) NaH, CS_2, CH_3I, THF;

c) n-Bu_3SnH, toluene, reflux; d) n-Bu_4NF, THF;

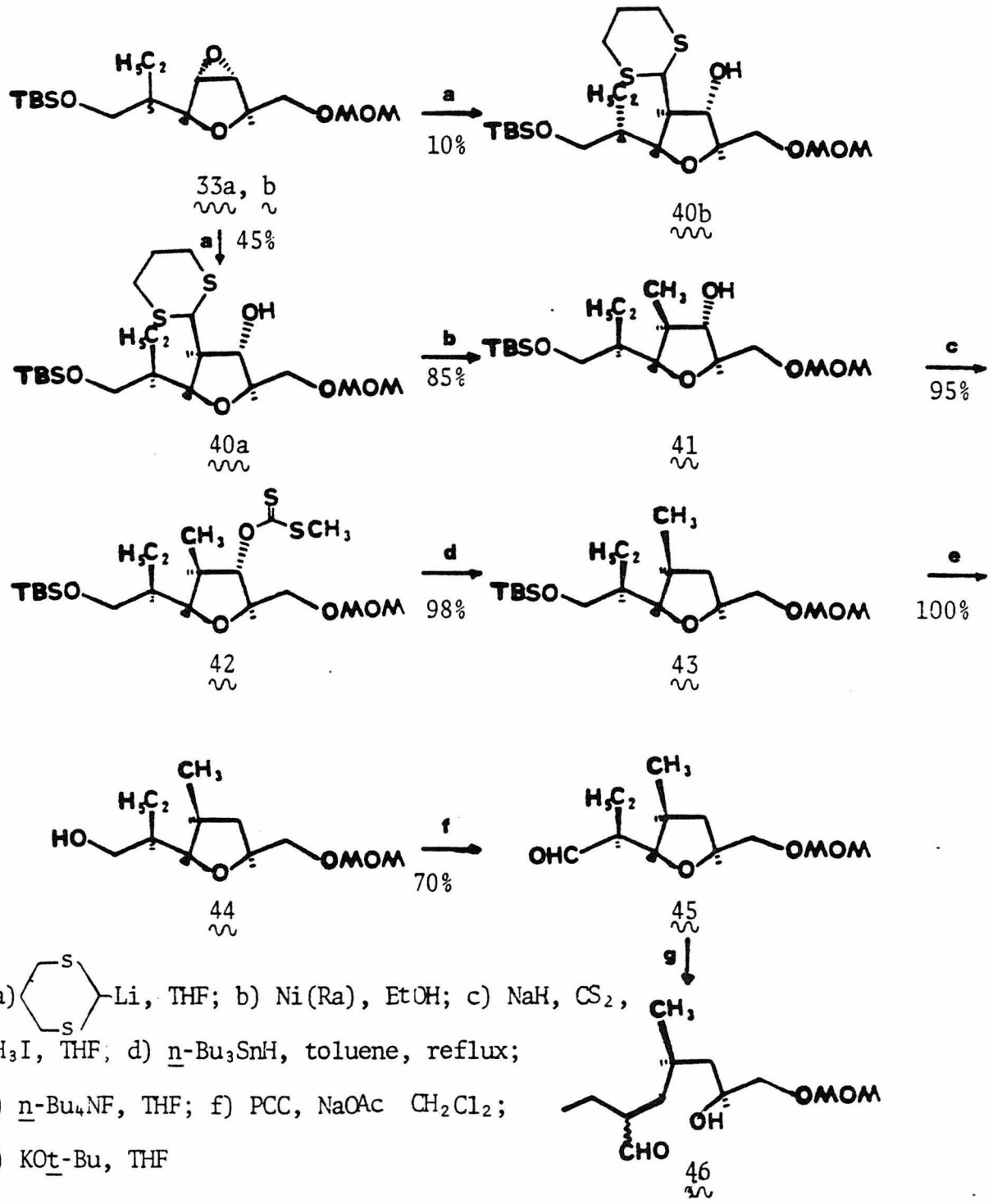
e) PCC, NaOAc, CH_2Cl_2; f) KOt-Bu, THF

signal being a pair of doublets, which would certainly be probable due to the possibility of olefin isomers, has also been ruled out by examination of the spectrum at different field strengths.

It is known that an epoxide in a sugar molecule can be opened by lithiated 1,3-dithiane.[65] Compounds 33a,b were subjected to this reaction (Chart 9) and two compounds, 40a and 40b, were isolated and determined to be epimeric from the previous ester enolate Claisen rearrangement. Compound 40a was desulfurized with Raney nickel[66] to give compound 41 which was distinct from the previously obtained compound 34a. Using the same sequence of chemical transformations utilized for the conversion of compound 34a into compound 39, compound 41 was converted into the unsaturated aldehyde 46. The ^{1}H-NMR spectrum indicated that the introduced methyl group was at C-2, the signal due to the olefinic proton being a clear doublet. For this reaction, the electrophilic site of the epoxide is at C-2, as was expected from purely steric arguments.

The substituted acid needed for the rearrangement depicted in equation 6 could now be secured from the alcohol 44 by utilization of the chemistry developed for the conversion of the alcohol 19 into the acid 22 (Chart 5). This is illustrated in Chart 10. The furanoic acid 49 was fully characterized as its methyl ester 50. Alternatively, the diastereomeric acids 54a,b (Chart 11) could be obtained from the aldehyde 45 in complete analogy to the production of the acids 28a,b from the aldehyde 24 (Chart 6). The acidic mixture 54a,b was characterized as the methyl ester mixture

Chart 9

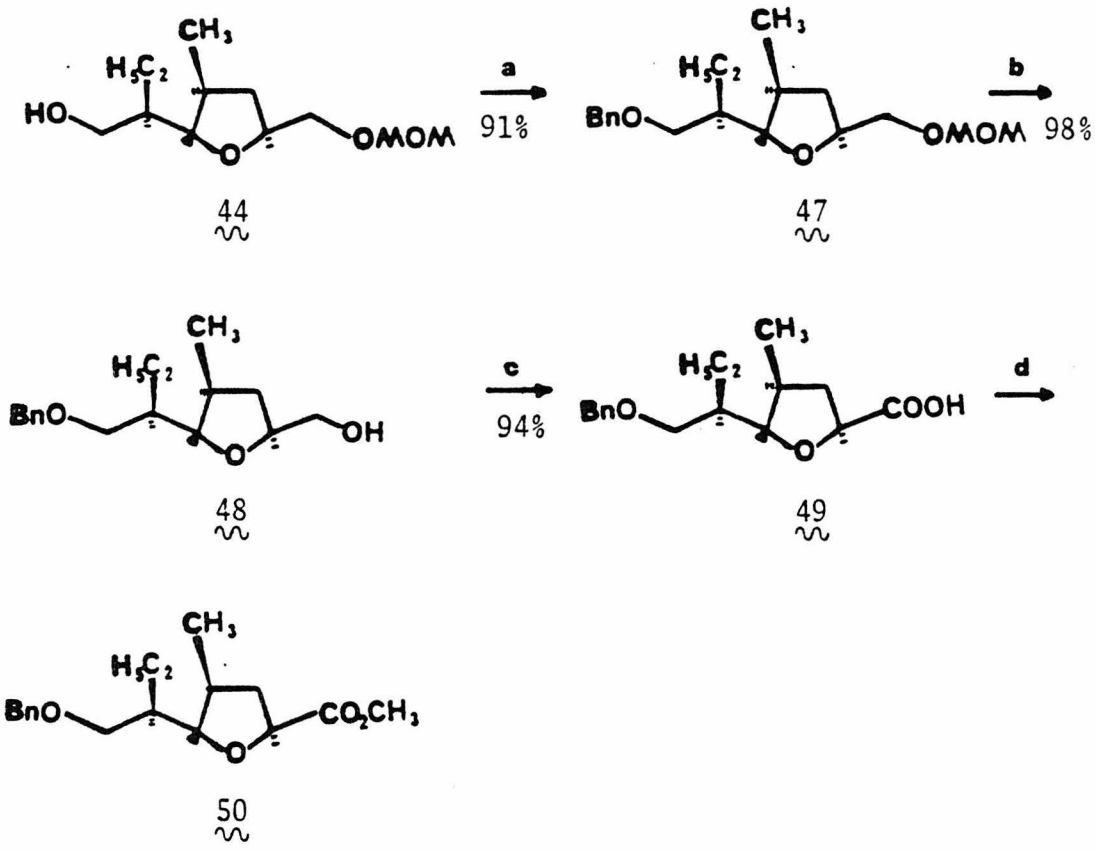


a)
Li, THF; b) Ni(Ra), EtOH; c) NaH, CS_2, CH_3I, THF; d) n-Bu_3SnH, toluene, reflux;

e) n-Bu_4NF, THF; f) PCC, NaOAc CH_2Cl_2;

g) KOt-Bu, THF

Chart 10

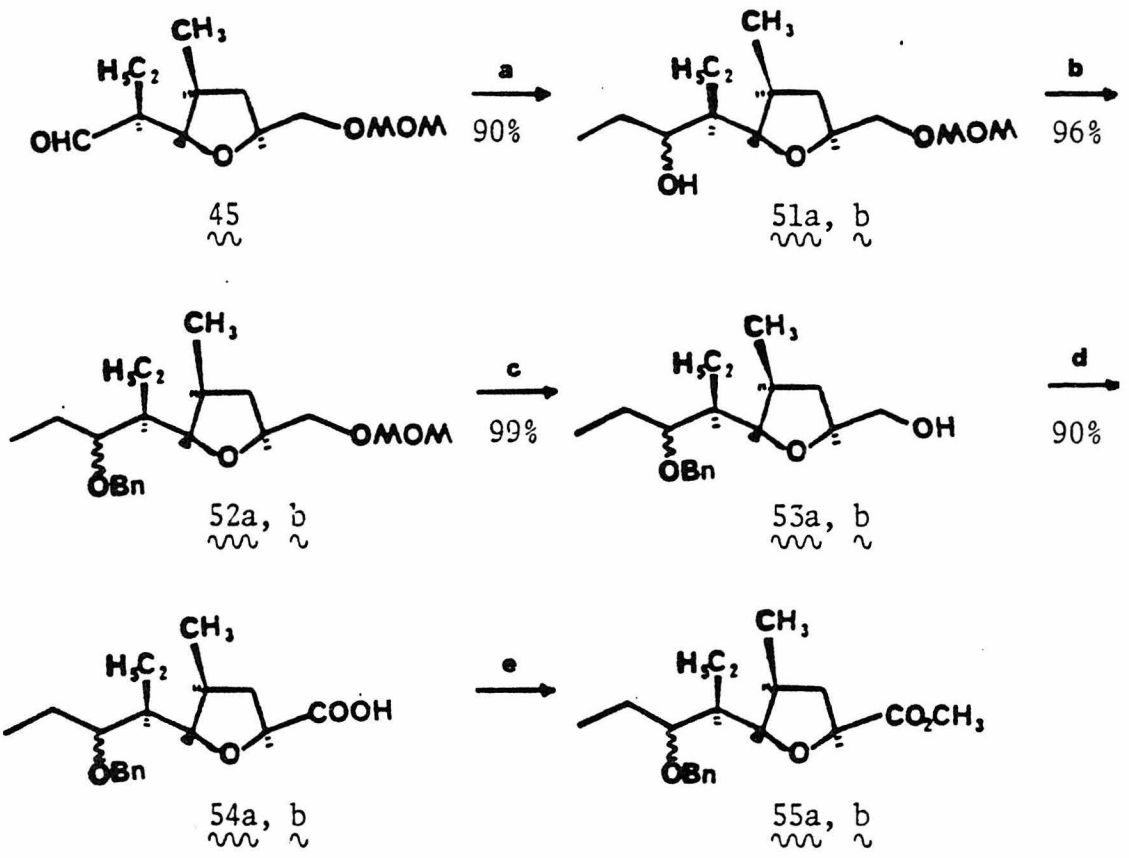


44 47 48 49 50

a) KH, $C_6H_5CH_2Br$, THF; b) 10% aq HCl, THF;

c) Pt, O_2, aq $NaHCO_3$; d) CH_2N_2, ether

Chart 11



45 → 51a, b → 52a, b → 53a, b → 54a, b → 55a, b

a) EtMgBr, THF; b) KH, $C_6H_5CH_2Br$, THF;

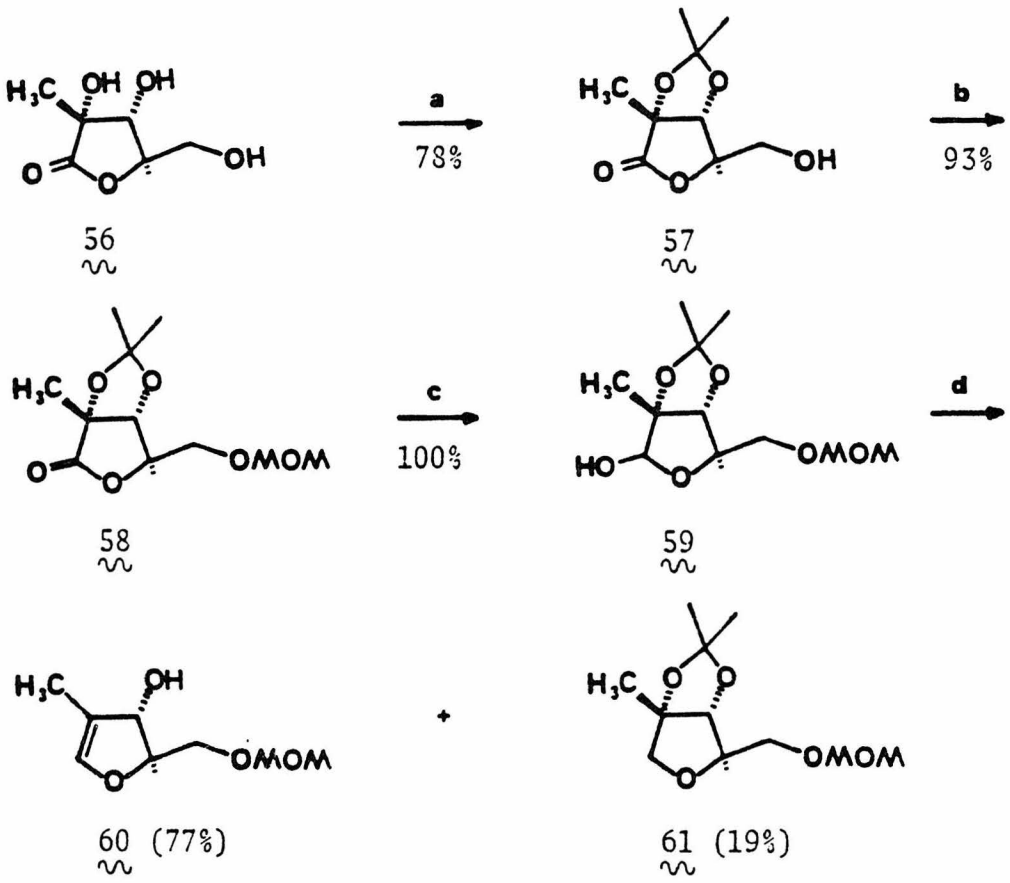
c) 10% aq HCl, THF; d) Pt, O_2, aq $NaHCO_3$;

e) CH_2N_2, ether

55a,b. With authentic compounds containing the correctly oriented methyl group at C-2 now in hand, we turned our attention to the possibility of utilizing a carbohydrate derivative that already contained a methyl group with the proper regiochemistry. The ester enolate Claisen rearrangement unfortunately places a double bond between C-2 and C-3 with the result that any stereointegrity at C-2 is destroyed. It was therefore essential that the asymmetry at this center be subsequently regenerated in a highly stereoselective manner and that the stereodisposition of the group be unambiguously assignable.

"α"-D-glucosaccharinic acid γ-lactone (56)[67] (Chart 12) was available by barium hydroxide treatment of hydrolyzed sucrose, a mixture of glucose and fructose trivially called invert sugar. The lactol 59 was obtained using the same sequence of manipulations as described previously for the preparation of the lactol 11 (Chart 3). Compound 59 was subjected to the glycal formation procedure to give compounds 60 and 61 in a ratio of 4:1. The ester enolate Claisen rearrangement of substrate 60 (Chart 13) gave a mixture of diastereomeric acids 62a,b and the corresponding hydrogenated methyl esters 64a and 64b were readily separable by column chromatography on silica gel. The ratios (64a:64b) were 9:1 for enolization in THF and 1:3 in HMPA/THF. The stereochemistry of the methyl group at C-2 was assigned as shown since reduction of the methyl ester 64a with lithium aluminum hydride gave an alcohol which proved identical in all respects to the alcohol 44 described in Chart 9. Hydrogenation of compounds 63a,b occurred in a highly stereoselective manner,

Chart 12

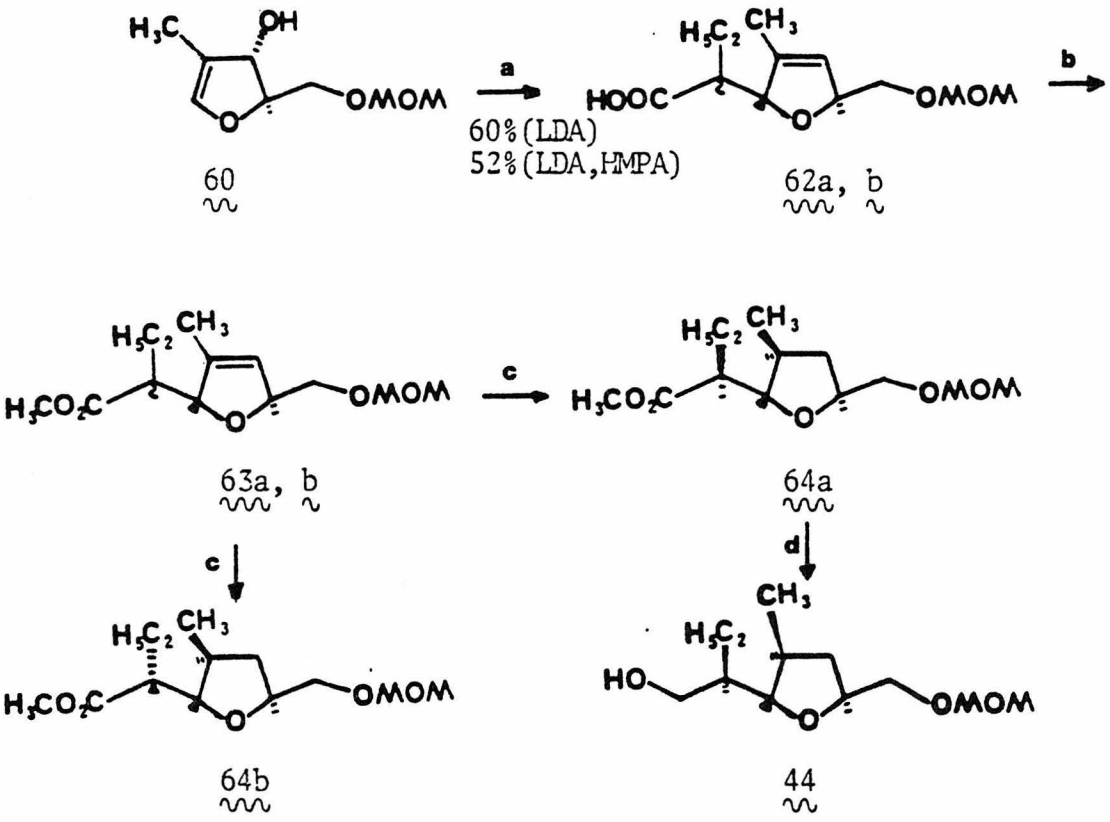


a) CH_3COCH_3, p-TSA; b) KH, $ClCH_2OCH_3$, THF;

c) DIBAL, ether, -78°C; d) $P(NMe_2)_3$, CCl_4, THF, 0°C;

Li, liq NH_3, then NH_4Cl

Chart 13



60 62a, b 63a, b 64a 64b 44

64a: 64b = 9:1 (LDA); 1:3 (LDA, HMPA)

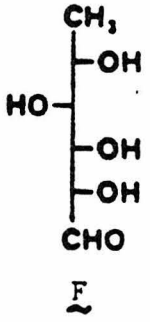
a) n-BuLi, n-C_3H_7COCl; LDA, THF (HMPA); TMSCl; ^-OH;

b) CH_2N_2, ether; c) H_2, 10% Pt on C, EtOAc; d) $LiAlH_4$, ether

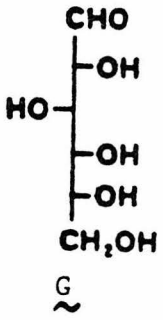
probably reflecting the importance of the steric environment around C-3 in the coordination of the π-bond to the metal surface[68] and the fact that the double bond is di-substituted at C-2 and mono-substituted at C-3. The carboxylic acid 68 (Chart 14), which is epimeric to the acid 50, could be obtained from the alcohol 65 in the same manner which produced the acid 50 from the alcohol 44 (Chart 10). The isolated acid 68 was characterized as its methyl ester 69.

CONSTRUCTION OF THE GULAL SEGMENT

For the remaining subunit III (Figure 3), the required starting material is 6-deoxy-L-gulose (F). The stereochemical relationship between this sugar and D-glucose (G) suggested that the abundant and inexpensive D-glucose could serve as a practical starting point.



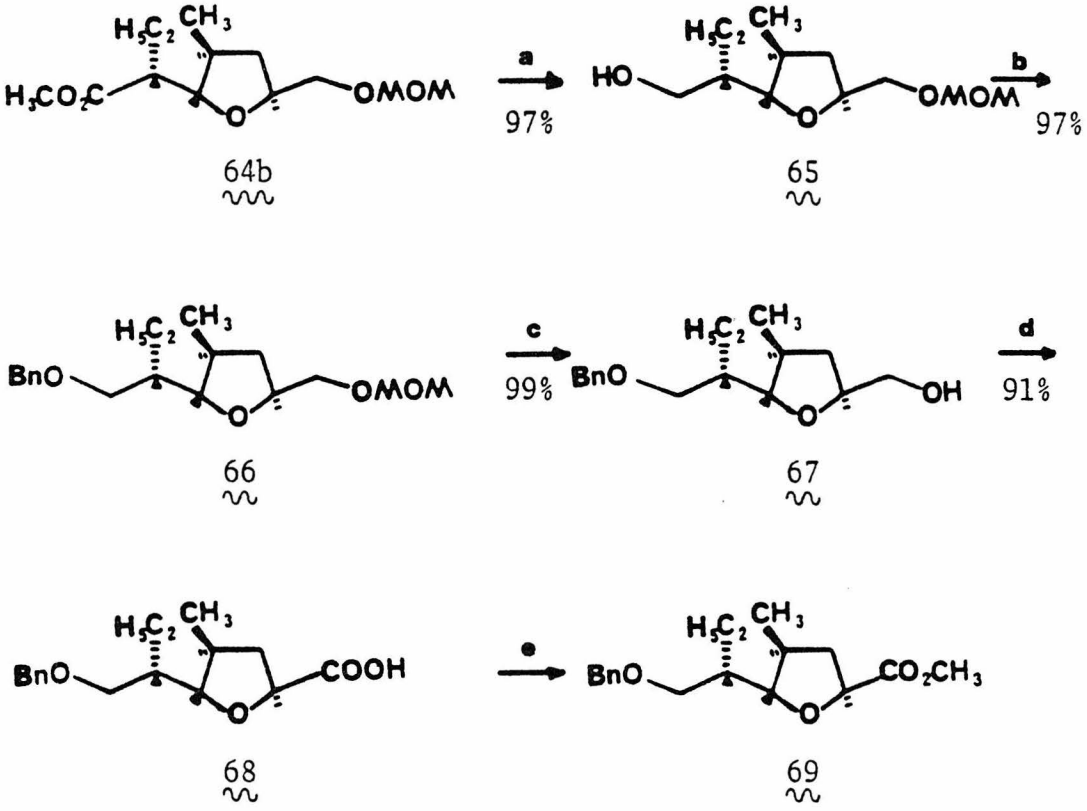
F



G

This transformation was successfully carried out in this laboratory[69] starting with D-glucurono-γ-lactone which is commercially available. With 6-deoxy-L-gulose readily available (52% overall yield), subunit III (Figure 3) was within reach. As shown

Chart 14



a) $LiAlH_4$, ether; b) KH, $C_6H_5CH_2Br$, THF;

c) 10% aq HCl, THF; d) Pt, O_2, aq $NaHCO_3$;

e) CH_2N_2, ether

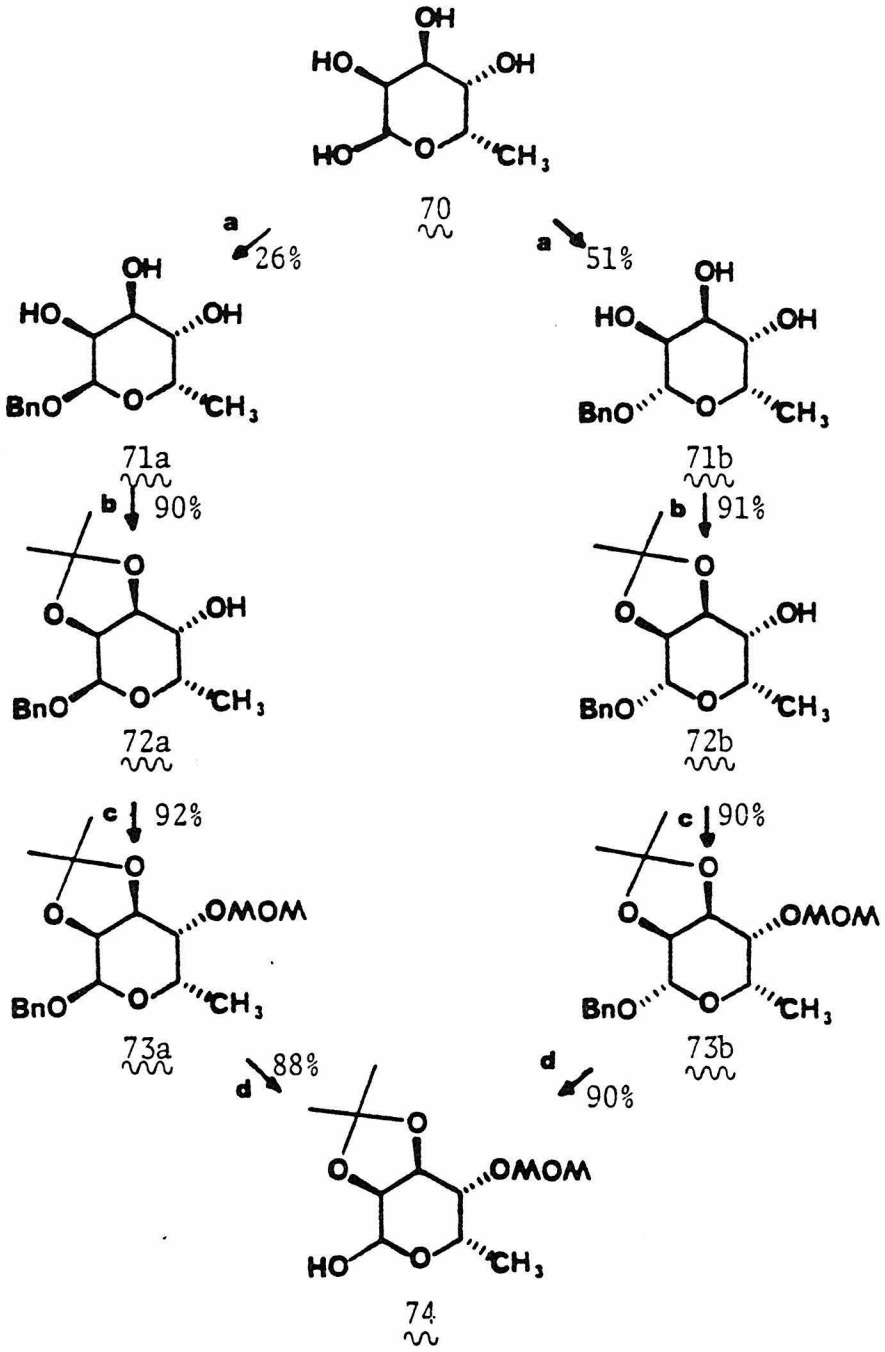
in Chart 15, 6-deoxy-L-gulose(70)was first converted into the glycosides 71a and 71b by the action of acidic benzyl alcohol, thereby securing the pyranose forms of the sugar. The hydroxyl groups at C-2 and C-3 readily and selectively formed a 2,3-O-isopropylidene unit thereby providing an opportunity to incorporate the C-22 (lasalocid numbering) ethyl group of lasalocid A at this stage.[70] However, we anticipated difficulties arising from the generation of a tertiary allylic ether, from the ester enolate Claisen rearrangement, which would be unstable to the acidic conditions from which it would need to be isolated. For the present work, the C-4 hydroxyl group was merely protected as a methoxymethyl ether, the incorporation of the ethyl group being postponed to a later stage.

The benzyl glycosides 73a and 73b were hydrogenolized to the lactol 74 using 10% palladium on carbon as catalyst. For preparative purposes, the benzyl glycosides 71a,b were carried through this sequence as a mixture (Chart 16). On a large scale operation, removal of the benzyl group from compound 73a,b using lithium in liquid ammonia was found to be simpler and more consistent than heterogeneous catalysis using palladium and gaseous hydrogen. The gulal derivative 75 was then derived from the lactol 74 according to the previously described procedures (see Chart 3).

MODEL EXAMINATION OF THE FURAN-PYRAN CONNECTION

It was deemed prudent to examine model systems for the rearrangement exemplified in equation 6. To this end the readily available acid 22 and the known rhamnal derivative, allylic alco-

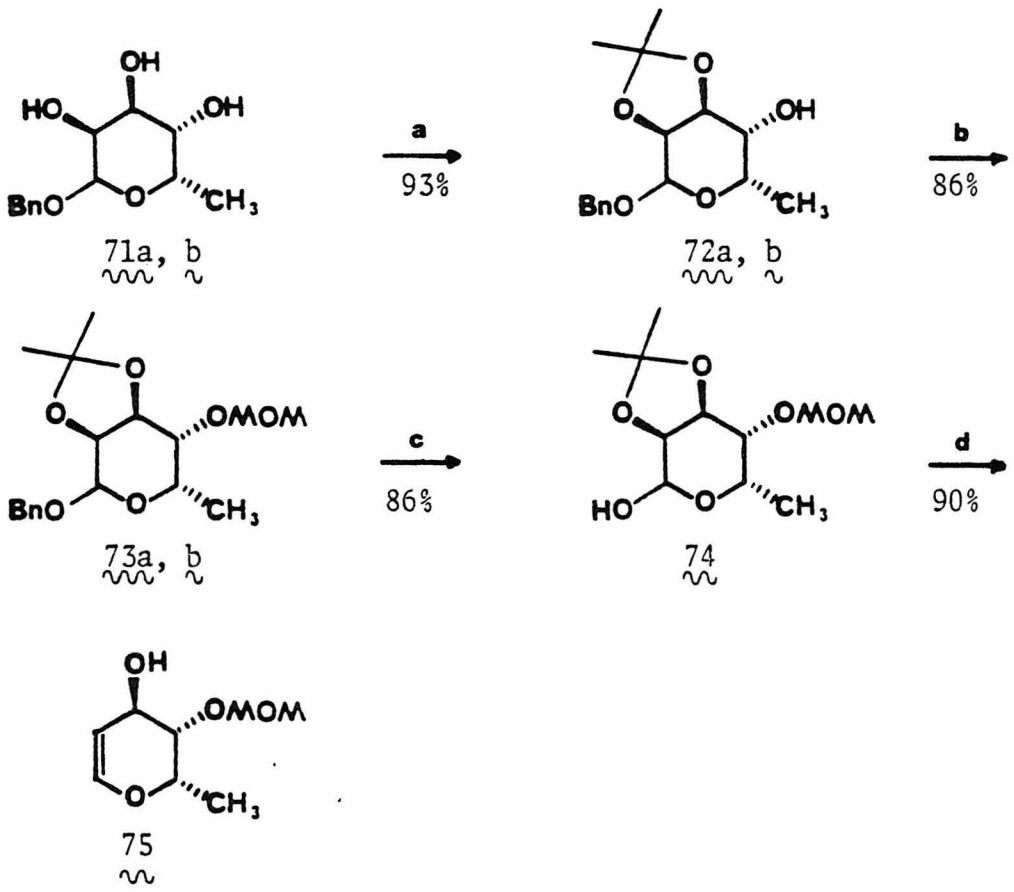
Chart 15



a) BnOH, CH_3COCl; b) CH_3COCH_3, p-TSA;

c) KH, $C_6H_5CH_2Br$, THF; d) H_2, 10% Pd on C, EtOAc

Chart 16



71a, b 72a, b 73a, b 74 75

a) CH_3COCH_3, p- TSA; b) KH, $C_6H_5CH_2Br$, THF;

c) Li, liq NH_3, then NH_4Cl; d) $P(NMe_2)_3$, CCl_4, THF;

Li, liq NH_3, then NH_4Cl

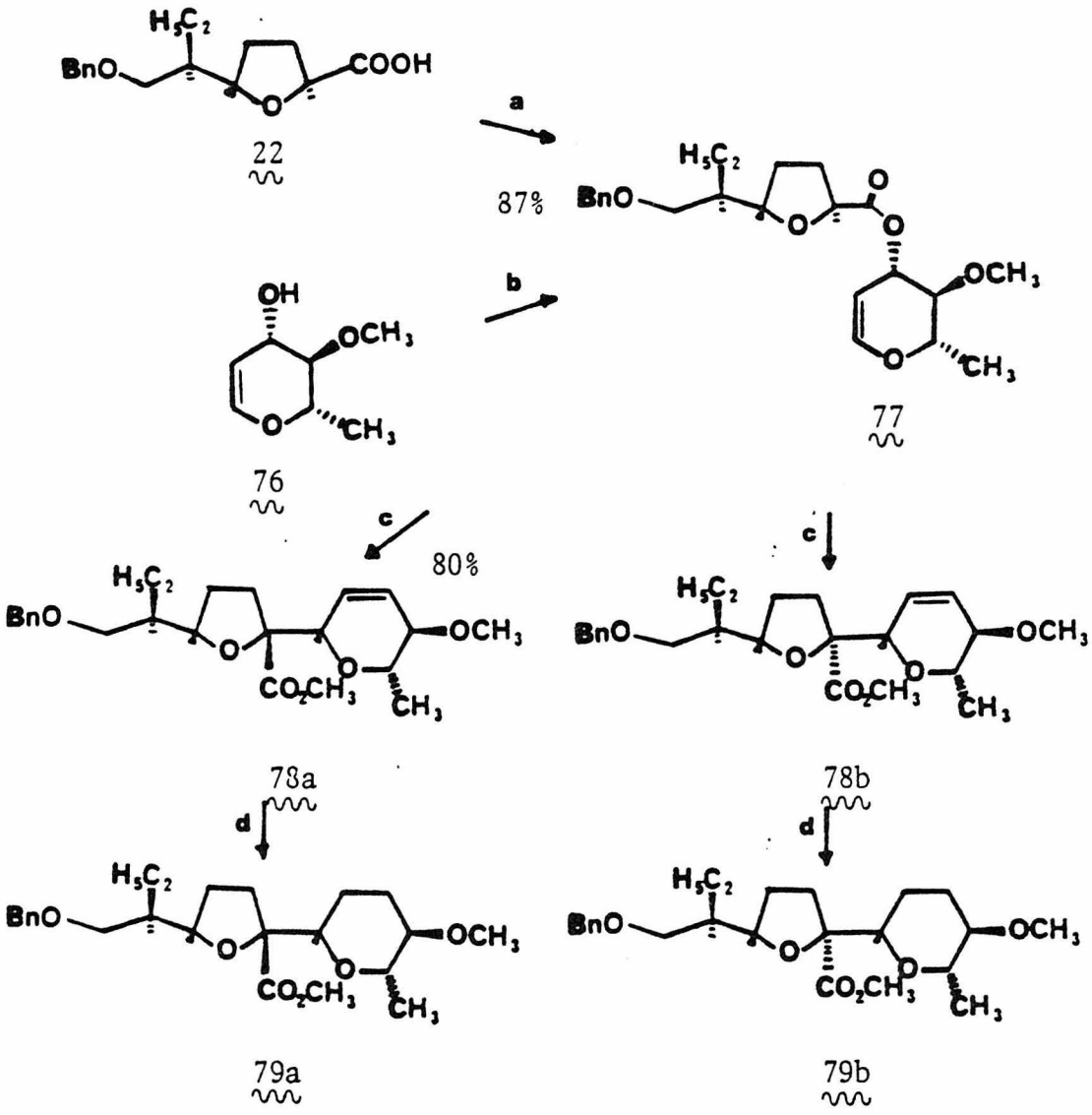
hol 76[71], were prepared. As expected (Chart 17), ester 77 was obtained when the alcohol 76 was treated with the acid chloride derived from the acid 22 in the presence of N,N-dimethylamino-pyridine.[72] After enolization of the ester 77 with LDA, silation of the enolates with TMSCl, isolation of rearrangement products and esterification with diazomethane, the methyl esters 78a,b were isolated and shown to be in a ratio of 77:23 when enolization was carried out in THF and 68:32 in HMPA/THF. The esters 78a,b were readily separated by silica gel chromatography and their stereochemistries were assigned as shown after it was possible to compare the synthetic materials to natural materials, *via infra*. The methyl esters 78a and 78b were then successfully saturated, with a minor amount of hydrogenolysis at allylic positions, to give compounds 79a and 79b respectively.

DEGRADATIVE STUDIES[73]

To facilitate an early unambiguous stereochemical assignment of the two centers of the ketone C resulting from enolate Claisen rearrangements, compound 87 (Chart 19) was elected as a common point for direct comparison of synthetic and natural materials.

As shown in Chart 18, the authentic ketone C was treated with potassium hexamethyldisilazide[74] followed by excess TMSCl, to provide the silylenol ether 80. Treatment of compound 80 with excess ozone gave an acidic material which was esterified with ethereal diazomethane. The resulting methyl ester 81 was then reduced to the alcohol 82 with lithium aluminum hydride. Removal of the silyl ether in compound 82 with tetra-*n*-butylammonium fluoride, followed

Chart 17



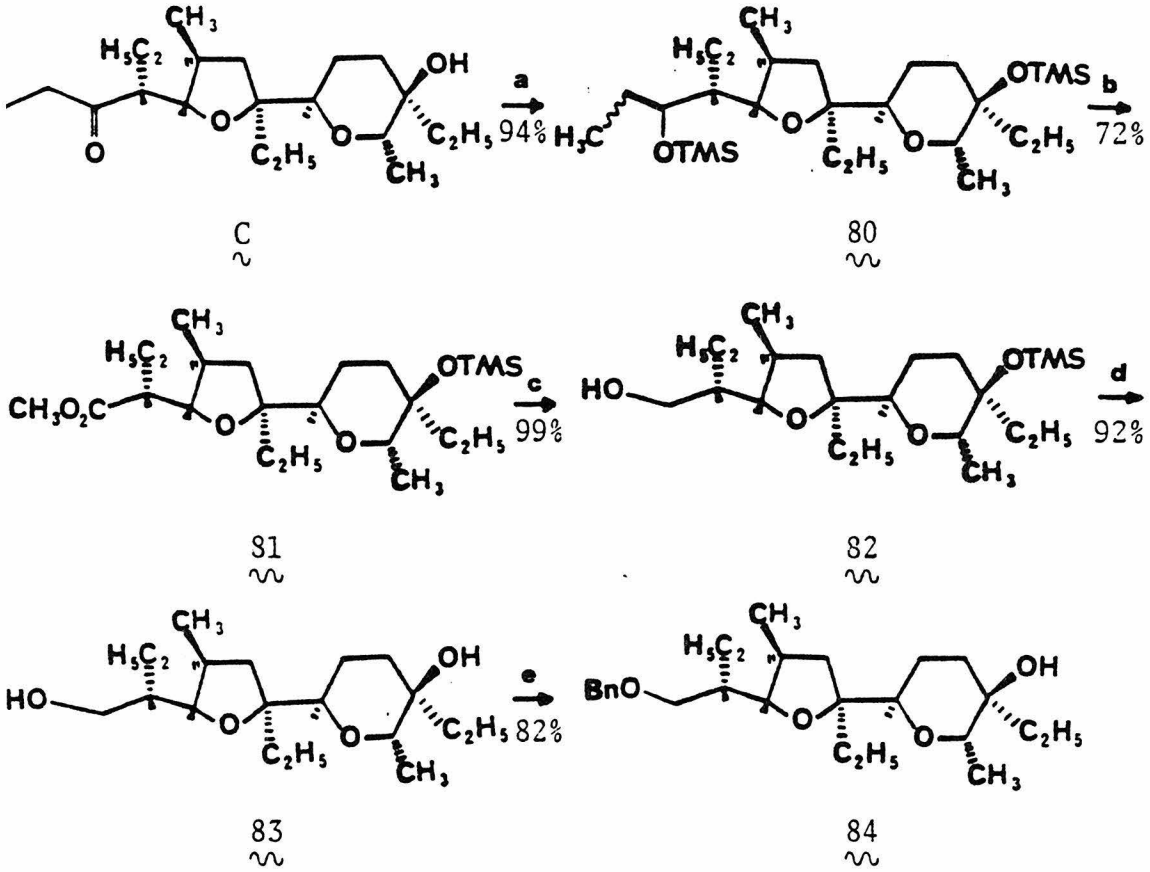
79a: 79b = 77:23 (LDA); 68:32 (LDA, HMPA)

a) $(COCl)_2$, benzene; b) DMAP, CH_2Cl_2;

c) LDA, THF (HMPA) ; TMSCl; ^-OH;

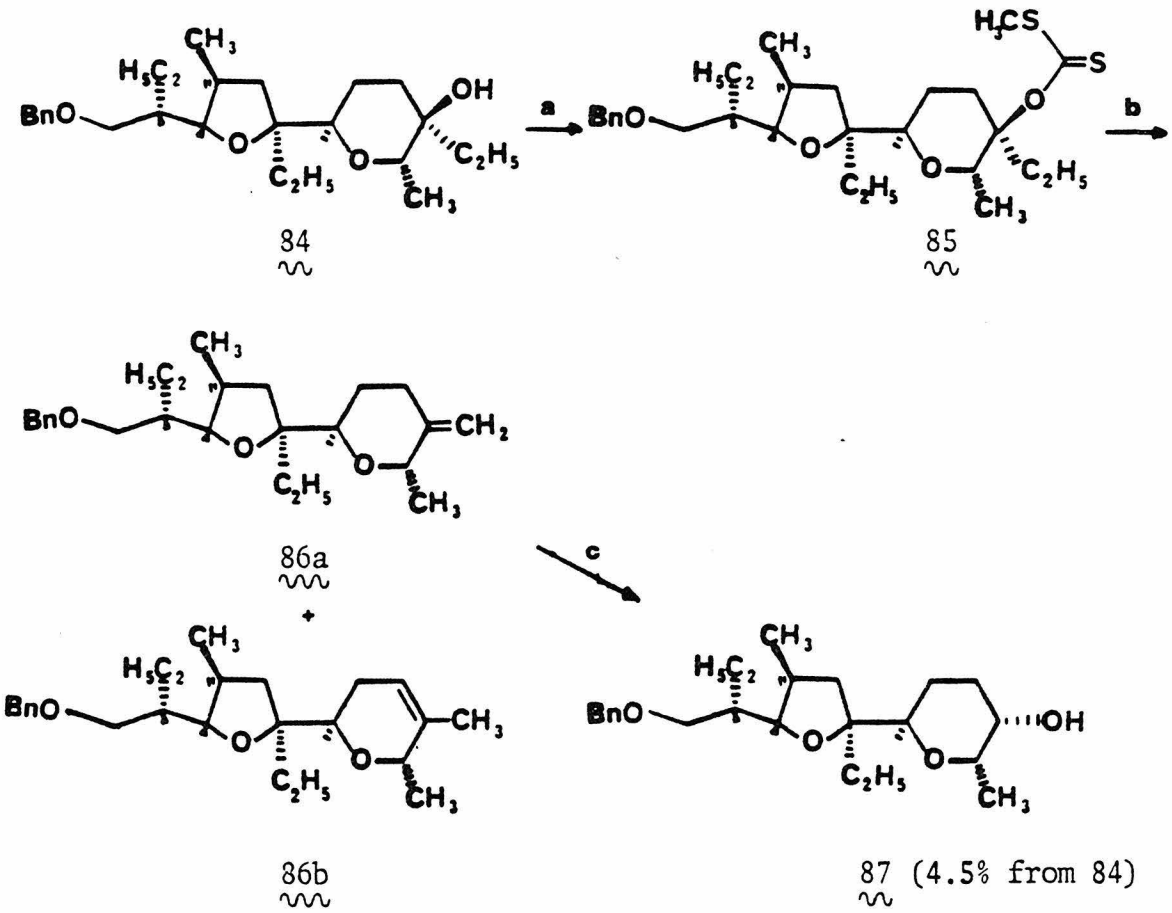
d) H_2, 10% Pt on C, EtOAc

Chart 18



a) $KNTMS_2$, THF; TMSCl; b) O_3, CH_3OH-CH_2Cl_2; $NaBH_4$; CH_2N_2, ether; c) $LiAlH_4$, ether; d) n-Bu_4NF, THF; e) KH, $C_6H_5CH_2Br$, THF

Chart 19



84 85

86a + 86b

87 (4.5% from 84)

a) KH, CS_2, CH_3I, THF; b) Δ

c) O_3, CH_3OH-CH_2Cl_2; $NaBH_4$

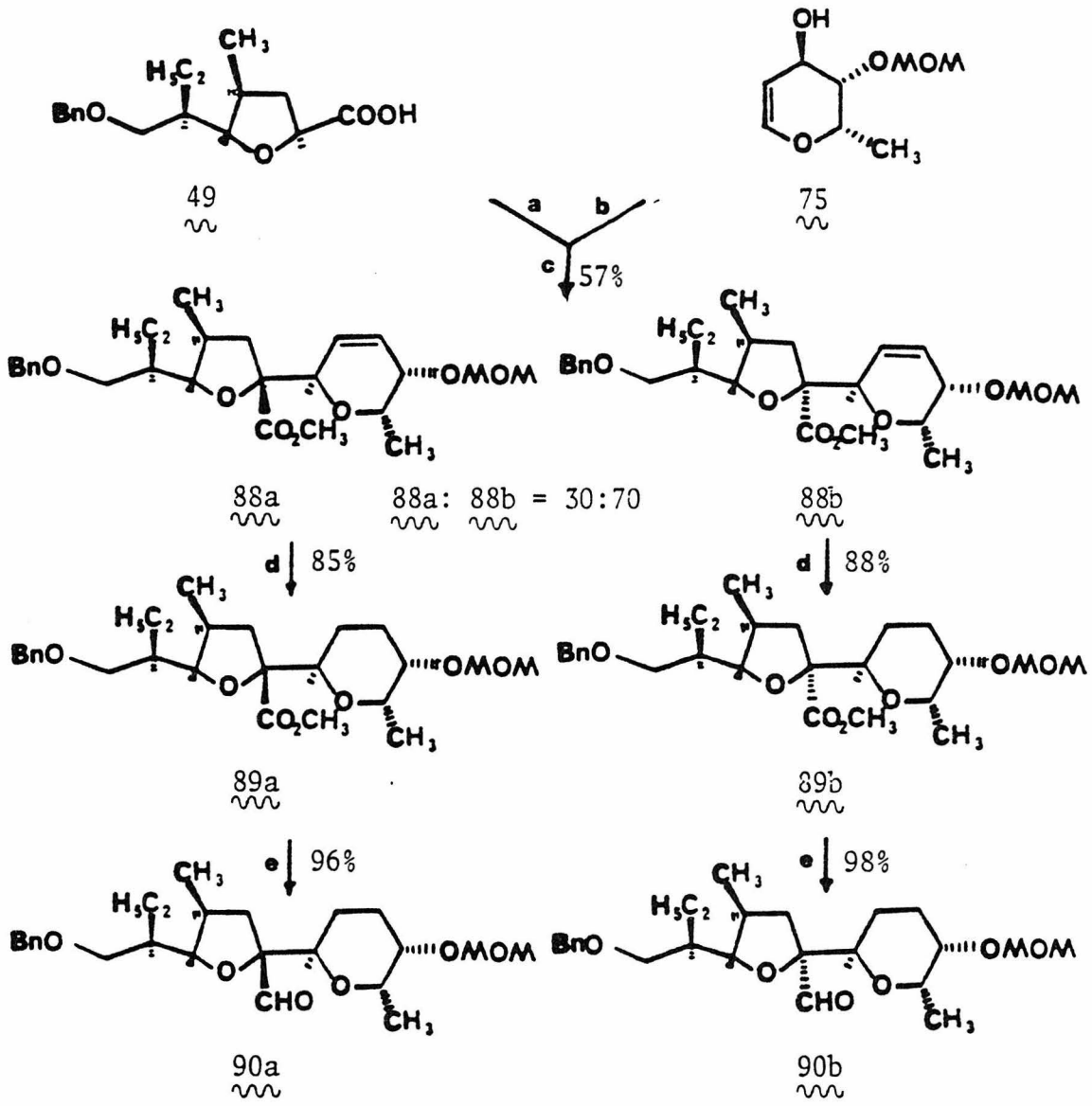
by selective protection of the primary hydroxyl group as a benzyl ether, provided compound 84. Attempted dehydration of the secondary alcohol of compound 84 with thionyl chloride[75] gave almost exclusively the undesired endocyclic olefin. The tertiary alcohol 84 was therefore converted into the corresponding xanthate 85 (Chart 19) which upon pyrolysis gave a 1:5 mixture of exocyclic and endocyclic olefins 86a and 86b respectively.[76] Treatment of the olefin mixture with ozone followed by sodium borohydride reduction afforded the desired alcohol 87.

SYNTHESIS OF THE KETONE C

We now had in hand the furan and pyran subunits, compounds 49, 68 and 75 respectively, the necessary technology for their union, and a point of comparison between synthetic and natural materials. It was now our intention to generate all four possible diastereomers obtainable from the union of the pyran subunit to both epimers of the furan subunit and to chemically and physically correlate the resultant stereoisomers with the natural degradation product 87.

A solution of the lithium salt of the glycal 75 in THF was treated with the acid chloride derived from the acid 49 (Chart 20) and the resulting ester was enolized with LDA, followed by quenching with TMSCl. Hydrolysis of the rearranged material and treatment of the residue with ethereal diazomethane gave two epimeric methyl esters 88a and 88b in a ratio of 30:70. These were readily separable by column chromatography on silica gel. In the same manner, the pair of compounds 68 and 75 (Chart 22) gave two epimeric methyl esters 88c and 88d in a ratio of 26:74.

Chart 20

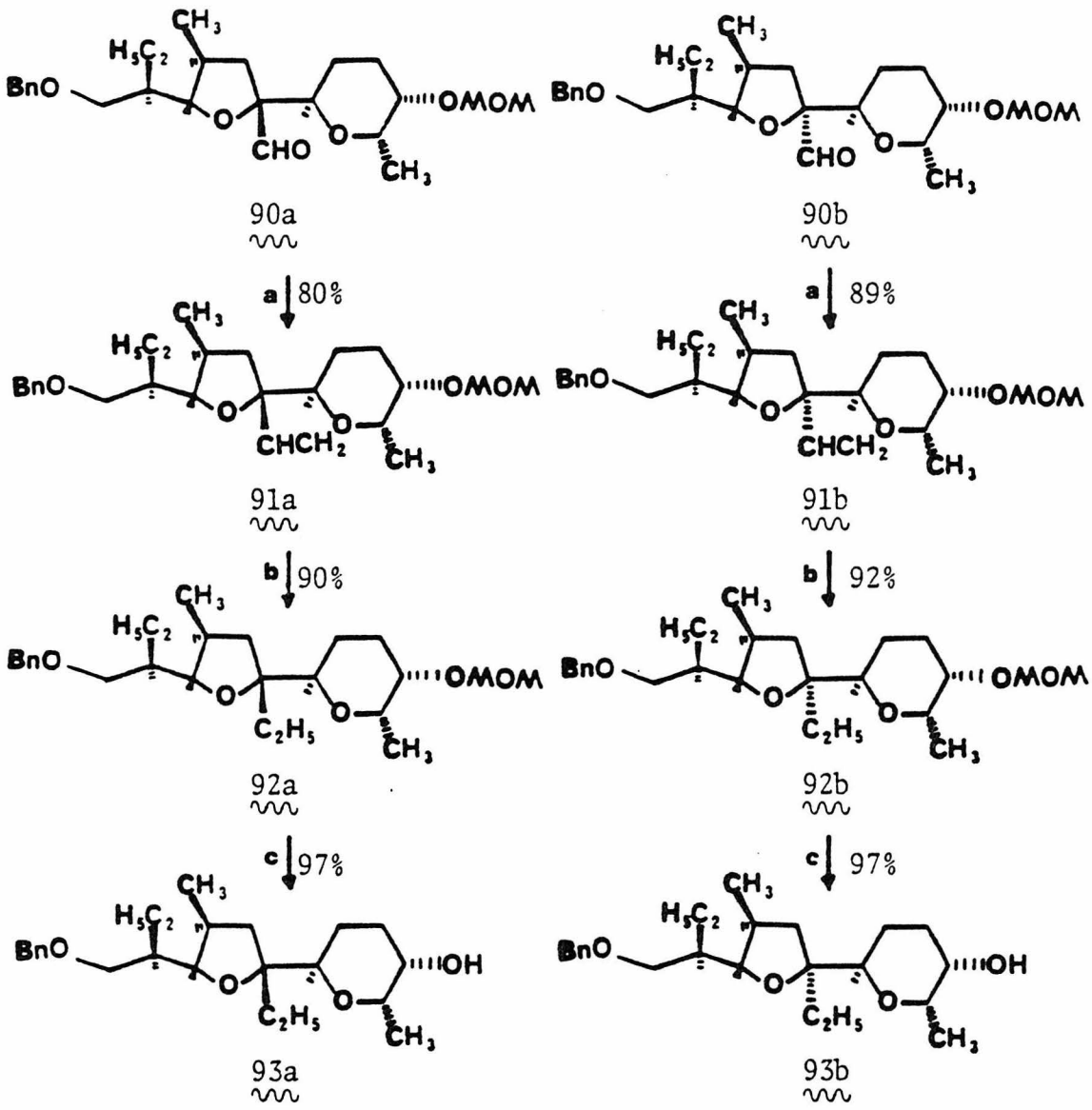


a) $(COCl)_2$, benzene, DMF (cat.); b) n-BuLi, THF;

c) LDA, THF; TMSCl; ^-OH; CH_2N_2, ether; d) H_2, Ni(Ra), EtOAc;

e) DIBAL, ether, -78°C

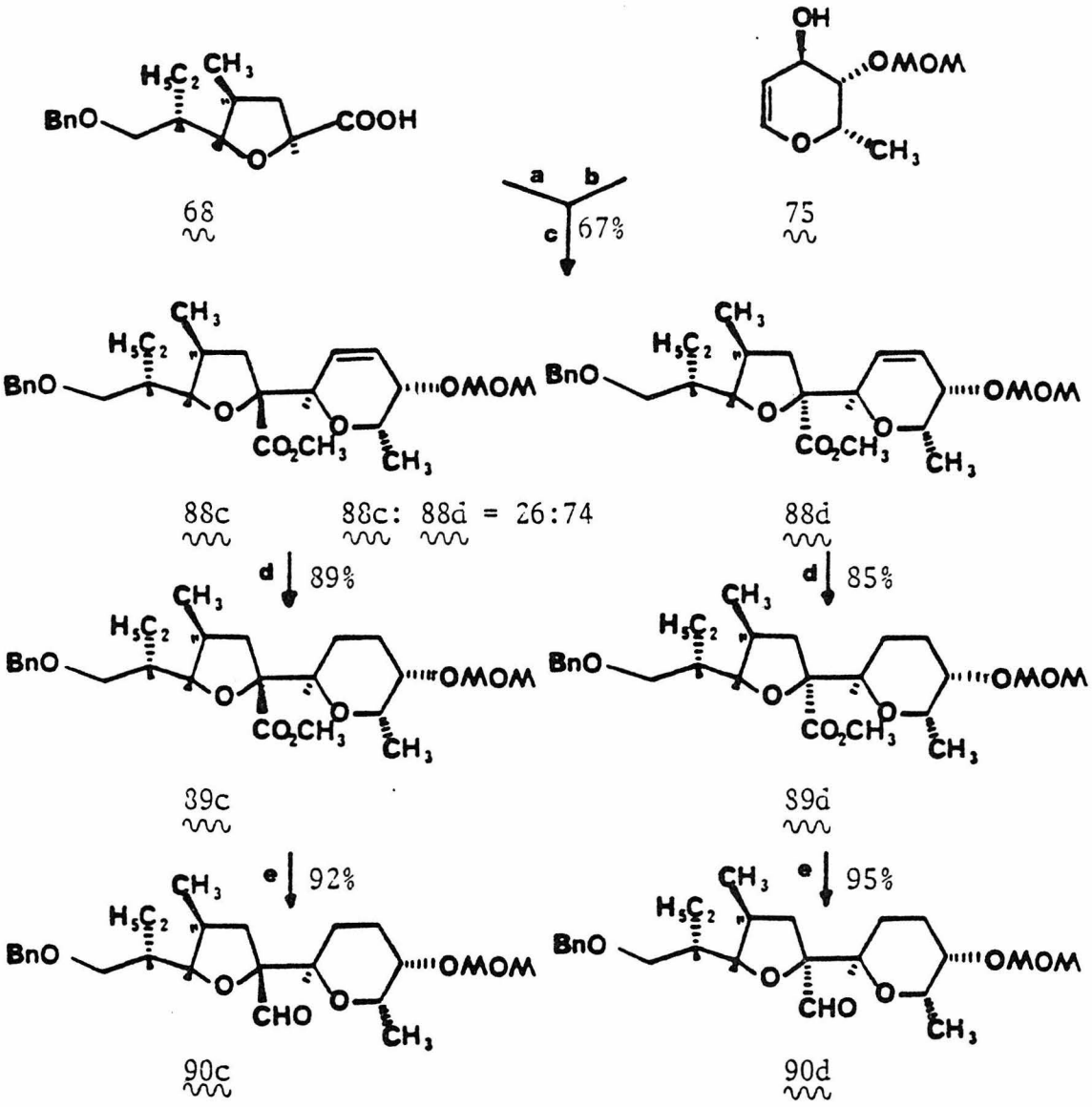
Chart 21



a) $(C_6H_5)_3PCH_2$, THF; b) H_2, Ni(Ra), EtOAc

c) 10% aq HCl, THF

Chart 22

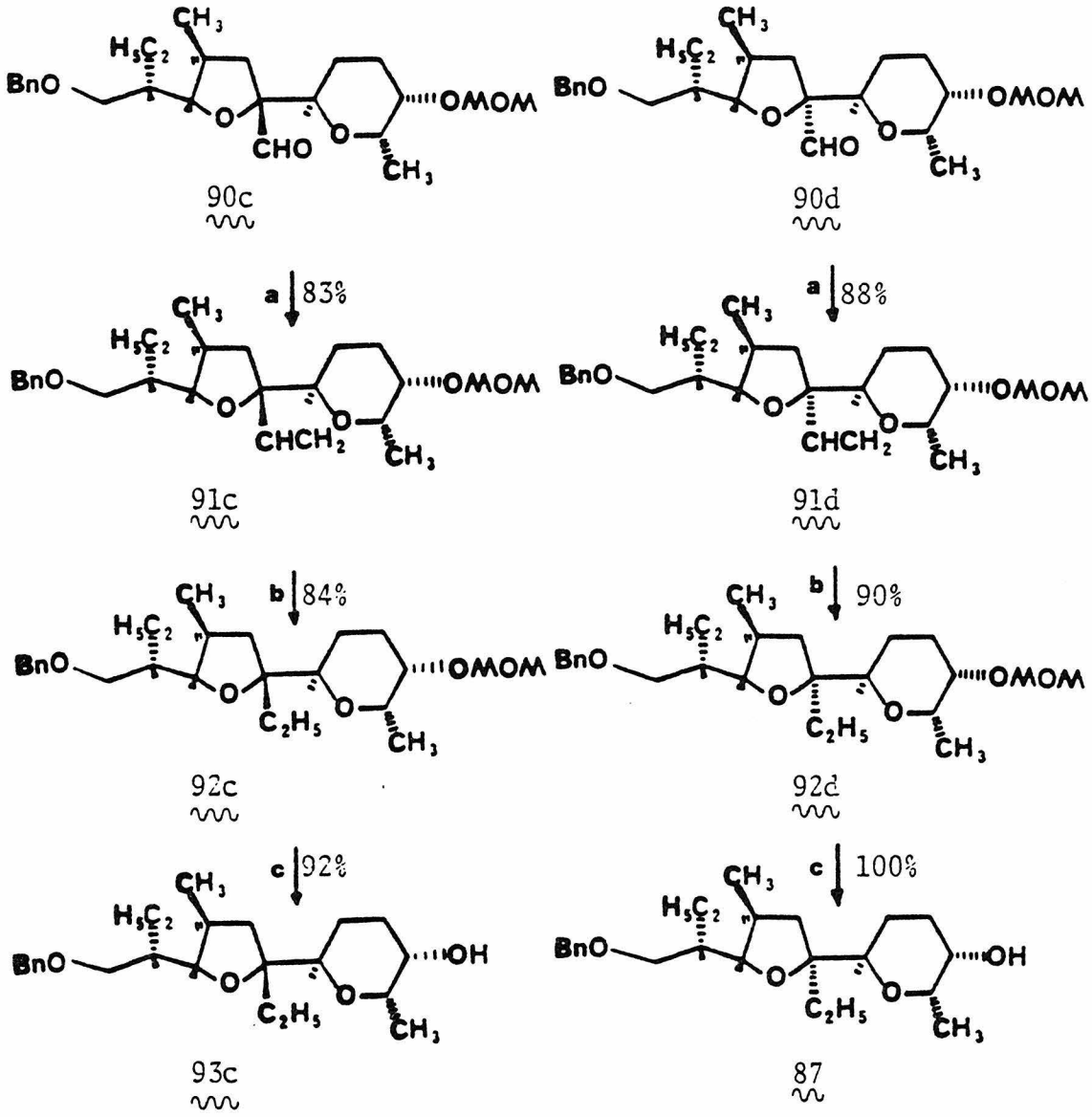


a) $(COCl)_2$, benzene, DMF(cat.); b) n-BuLi, THF;

c) LDA, THF; TMSCl; ^-OH; CH_2N_2, ether;

d) H_2, Ni(Ra), EtOAc; e) DIBAL ether, -78°C

Chart 23



a) $(C_6H_5)_3PCH_2$, THF; b) H_2, Ni(Ra), EtOAc;

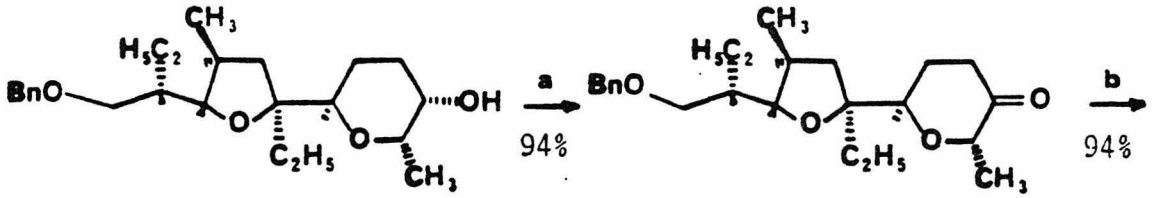
c) 10% aq HCl, THF

Each of compounds 88 was hydrogenated, and the resulting compound 89 was partially reduced with diisobutylaluminum hydride to give the aldehyde 90. The unsaturated compound 91, which resulted from Wittig olefination of the aldehyde 90, was hydrogenated and the methoxymethyl ether removed by acidic hydrolysis. All four diastereomers 93 were then compared with the natural degradation product 87 and it was determined that the desired stereoisomer arose from enolate Claisen product 88d, thereby confirming all the stereochemical assignments reported herein. This result implied a preferred boat-like transition state for the[3,3]-sigmatropic rearrangement of these heterocycles. The conclusion was based upon the assumption that the ratio of the enolates was similar to that observed previously.[37]

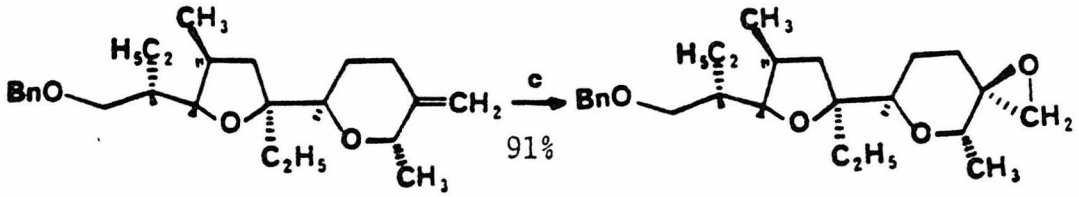
We were now faced with the introduction of two ethyl groups for the completion of the total synthesis of the ketone C. The synthetic compound 87 was oxidized[77] to the ketone 94 (Chart 24) and Wittig olefination led to the exocyclic methylene compound 95. Epoxidation with m-chloroperbenzoic acid[78] gave two diastereomeric epoxides, 96a and 96b, in a ratio of 3.5:1. It was anticipated that compound 95 would be preferentially epoxidized from the β-face because of the α-disposition of an adjacent methyl group. The stereochemistry of compounds 96a and 96b were assigned accordingly.

The epoxide 96a was opened with lithium dimethylcuprate (Chart 25) to give the tertiary alcohol 84 which was identical to that previously obtained from degradative work (Chart 18). The

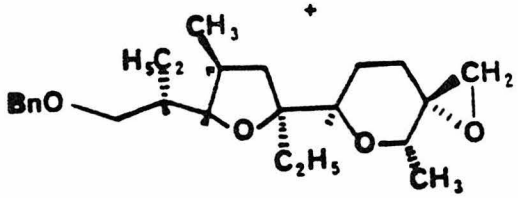
Chart 24



87 94



95 96a



+

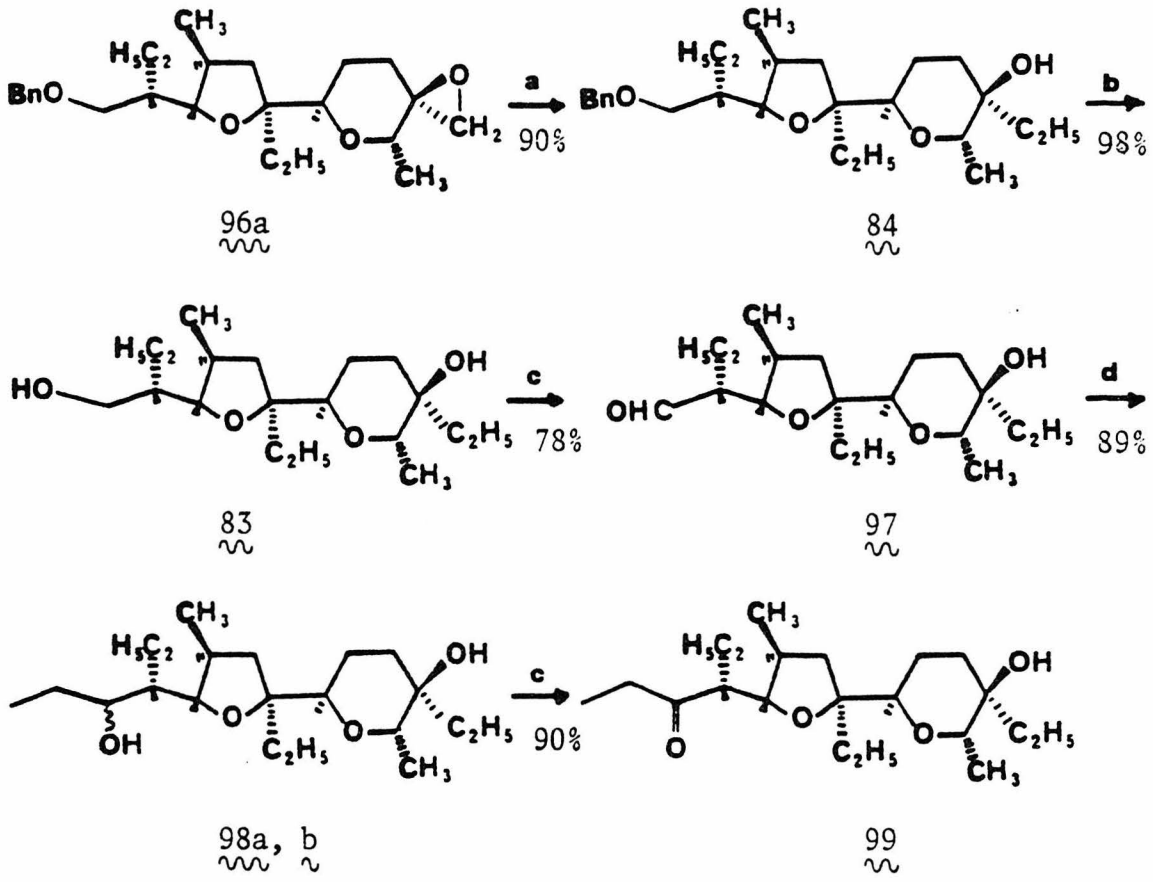
96b

96a: 96b = 3.5: 1

a) DMSO, $(COCl)_2$, Et_3N, CH_2Cl_2; b) $(C_6H_5)_3PCH_2$, THF;

c) MCPBA, CH_2Cl_2

Chart 25



96a 84 83 97 98a, b 99

a) $LiMe_2Cu$, ether-pentane; b) Li, liq NH_3, then NH_4Cl;

c) PCC, NaOAc, CH_2Cl_2; d) EtMgBr, THF;

protective benzyl group was then removed by dissolving metal reduction to give the crystalline compound 83, identical to that acquired from the degradative sequence. Ketone 99 was then produced by the oxidation[64] of the alcohol 83 to the aldehyde 97, addition of excess ethylmagnesium bromide to the aldehyde to produce the epimeric alcohols 98a,b, and finally, oxidation[64] of the alcohols to a single ketone. Ketone 99 was identical to the ketone C obtained from degradation of lasalocid A.[31] This therefore marks the completion of the total synthesis of the "right half" of this stereo-complex polyether antibiotic, and, when taken in conjunction with other work to be reported from this laboratory,[36] it also represents a total asymmetric synthesis of the entire (-) lasalocid A system.

EXPERIMENTAL

Boiling points are uncorrected. Melting points were determined using a Hoover capillary melting point apparatus and are uncorrected. Infrared (IR) spectra were determined on a Perkin-Elmer 237B or 737B, or a Beckmann 4210 infrared spectrometer. Proton nuclear magnetic resonance (^{1}H-NMR) spectra were recorded on Varian T-60 or EM-390 spectrometers. Chemical shifts are reported as δ values in parts per million relative to tetramethylsilane (δ 0.0) as an internal standard. Optical rotations were measured in 1 dm cells of 1 mL capacity using a Perkin-Elmer Model 141 polarimeter. Chloroform, when used as a solvent for optical rotation determinations, was filtered through neutral alumina immediately prior to use.

Vapor phase chromatographic (VPC) analyses were performed on a Hewlett-Packard 5750 gas chromatograph, equipped with a flame ionization detector, using helium carrier gas at a flow rate of 60 mL/min. The indicated liquid phase was absorbed on 60-80 mesh Chromosorb W AW DMCS.

Analytical thin layer chromatography (TLC) was conducted on 2.5 x 10 cm precoated TLC plates, silica gel 60 F-254, layer thickness 0.25 mm, manufactured by E. Merck and Co., Darmstadt, Germany. Preparative TLC was conducted on 20 x 20 cm glass plates coated in this laboratory with a 0.6 mm thickness of silica gel G "for TLC acc. to Stahl" (5-25 μ) manufactured by E. Merck and Co., Darmstadt, Germany. Silica gel columns for chromatography utilized

E. Merck "Silica Gel 60", 70-230 mesh ASTM.

"Dry" solvents were distilled shortly before use from an appropriate drying agent. Ether and tetrahydrofuran (THF) were distilled under dry argon from sodium metal in the presence of benzophenone. N-Pentane was distilled from sodium metal under argon. Benzene and toluene were distilled from calcium hydride. Dichloromethane was distilled from phosphorus pentoxide. Methanol was distilled from magnesium methoxide. Hexamethylphosphoramide (HMPA) was distilled at ~1.0 mmHg from pulverized calcium hydride. Triethylamine was distilled under argon from sodium-benzophenone immediately prior to use. Diisopropylamine, pyridine, and hexamethyldisilazane were all distilled before use from calcium hydride. Ammonia was distilled from the tank and then from a blue lithium solution.

Other reagents were purified as follows: oxalyl chloride was distilled under argon; n-butanoyl chloride was heated at reflux for 3 hours with phosphorus pentachloride, then distilled, and the distillate was treated with quinoline and redistilled; methyl iodide was distilled from phosphorus pentoxide immediately before use; tris-dimethylaminophosphine (TDAP) was distilled under argon before use; chloromethyl methyl ether was dried for several hours over anhydrous calcium chloride, decanted and stirred briefly with anhydrous potassium carbonate, and then distilled under argon from anhydrous calcium chloride. Ammonium chloride was dried at 75°C under vacuum (1 mmHg) over phosphorus pentoxide for at least 12 hours.

All other reactants and solvents were "Reagent Grade" unless described otherwise. "Ether" refers to anhydrous diethyl ether which is supplied by Mallinckrodt and Baker. "Petroleum ether" refers to the Analyzed Reagent grade hydrocarbon fraction, bp 35-60°C, which is supplied by J. T. Baker Co., Phillipsburg, NJ, and was not further purified.

Reactions were run under an argon atmosphere arranged with a mercury bubbler so that the system could be alternately evacuated and filled with argon and left under a positive pressure. Syringes and reaction flasks were dried at least 12 hours in an oven (at 120° to 140°C) and cooled in a desiccator over anhydrous $CaSO_4$ prior to use.

Mass spectral analyses were performed by Dr. Kai Fang, UCLA, Los Angeles, CA or Susan Rottschaefer, CalTech, Pasadena, CA. Elemental combustion analyses were performed by Spang Microanalytical Laboratory, Eagle Harbor, MI., or Jan Mitchell, CalTech, Pasadena, CA.

NOTE: Thin layer chromatographic mobility, physical constants, optical rotations, infrared and proton magnetic resonance spectra, and elemental combustion analyses of all compounds are collected in the Appendix.

2,3,-O-(1-Methylethylidene)-5-O-benzyl-D-ribonic acid, γ-lactone (2a)

To a stirred solution of 4.84 g (25.7 mmol) of the hydroxy lactone 1 and 17.9 g (77.3 mmol) of silver (I) oxide in 90 mL of N, N-dimethylforamide was added 18.5 mL (155.5 mmol) of benzyl bromide. The mixture was heated at 60°C for two days. It was allowed to cool to room temperature, then poured into 1 L of chloroform and filtered through a pad of Cellulose Cellex N-1. The filtrate was washed with three 250 mL portions of a 1 M solution of potassium cyanide and dried ($MgSO_4$). After removal of the solvents under reduced pressure, chromatography of the residue on 200 g of silica gel with 10% ethyl acetate-benzene provided 5.0 g (70%) of the lactone 2a as a colorless oil.

2,3-O-(1-Methylethylidene)-5-O-benzyl-D-ribose (3a)

To a stirred solution of 5.03 g (18.0 mmol) of the lactone 2a in 100 mL of dry ether under argon at -78°C was added, dropwise over 30 min., 20 mL of a 1 M solution of di-iso-butylaluminum hydride in hexane. After one hour, the reaction mixture was cautiously treated with 2 mL of methanol, allowed to warm to room temperature, and then diluted with 500 mL of ether. This solution was washed with three 70 mL portions of saturated aqueous sodium potassium tartrate, 70 mL of saturated aqueous NaCl, and then dried ($MgSO_4$). After removal of the solvent under reduced pressure, chromatography of the residue on 200 g of silica gel with 20% ethyl acetate-benzene provided 5.0 g (98%) of the lactol 3a

as a mixture of anomers.

2,3-O-(1-Methylethylidene)-5-O-benzyl-α and β-D-ribofuranosyl chloride (4a). To a stirred solution of 263.8 mg (0.94 mmol) of the lactol 3a, and 0.5 mL of carbon tetrachloride in 5 mL of dry THF under argon, was added 494 mg (1.88 mmol) of triphenylphosphine. The mixture was heated at reflux for 3 hours, cooled to room temperature, and concentrated under reduced pressure (ca 20 mm Hg) to yield a thick paste. This residue was extracted by trituration with three 10 mL portions of dry n-pentane and discarded. Removal of the solvent from the combined n-pentane extracts and subsequent distillation [kugelrohr, 120°C (0.02 mm Hg)] afforded 263.5 mg (94%) of the chloride 4a as a mixture of anomers.

2,3-O-(1-Methylethylidene)-5-O-methyl-D-ribose (3b).

By the procedure described for the preparation of the lactol 3a, 5.40 g (23.3 mmol) of the lactone 2b in 125 mL of dry ether and 25 mL of 1 M solution of di-iso-butylaluminum hydride in hexane, afforded, after chromatography on 200 g of silica gel with 40% ethyl acetate-benzene, 4.52 g (95%) of the lactol 3b as a mixture of anomers.

2,3-O-(1-Methylethylidene)-5-O-methyl-α and β-D-ribofuranosyl chloride (4b). By the procedure described for the preparation of the chloride 4a, 3.40 g (16.6 mmol) of the lactol 3b in 90 mL of dry THF, 9 mL of carbon tetrachloride and 8.7 g (33.2 mmol) of triphenylphosphine, afforded, after distillation [kugelrohr,

80°C (0.05 mmHg)], 3.53 g (95%) of the chloride 4b as a mixture of anomers.

1,4-Anhydro-2-deoxy-5-O-methyl-D-erythro-pent-1-enitol (5).

To a stirred solution of 10 cm (61 mmol) of lithium wire in 80 mL of anhydrous liquid ammonia under argon at -78°C was added a solution of 3.40 g (15.3 mmol) of the furanosyl chloride 4b in 15 mL of dry THF. Cooling was then discontinued (ammonia reflux) and after two hours 5 g of anhydrous ammonium chloride was cautiously added to the reaction mixture. The resulting colorless mixture was diluted with 80 mL of ether and the ammonia was allowed to evaporate. The ethereal suspension was filtered and the solid was washed by trituration with four 20 mL portions of ether. Removal of the solvent from these filtrates and distillation [kugelrohr, 80°C (0.2 mmHg)] afforded 1.57 g of a mixture of the glycal 5 and the by-product 6. Analysis of this mixture by ^{1}H-NMR revealed that these products were obtained in a 6:1 (5:6) ratio. Chromatography of this mixture on Florisil with 75% ether-petroleum ether provided pure products for analysis.

Methyl-2R and 2S-(2,5-dihydro-5S-methoxymethyl,-2S-furyl)-butanoate (8a and 8b) and Methyl-2S and 2R-(5S-methoxymethyl, 2S-tetrahydrofuryl)-butanoate (9a and 9b).

A. From the glycal 5 by deprotonation in THF. To a stirred solution of 125.3 mg (0.776 mmol of 5) of the 6:1 mixture of the glycal 5 and the by-product 6 in 2.6 mL of dry THF at -78°C under argon was added 0.34 mL (0.82 mmol) of a 2.41 M solution of n-butyl-

lithium in hexane, followed after 5 minutes by 0.085 mL (0.82 mmol) of n-butanoyl chloride. After 10 minutes at 0°C the reaction mixture was taken up in an argon flushed syringe and then added dropwise to a stirred solution of 0.87 mmol of LDA in 2.9 mL of dry THF at -78°C under argon. After 10 min, the reaction mixture was treated with 0.22 mL (1.3 mmol TMSCl) of the supernatant centrifugate from a mixture of 0.75 mL of trimethylchlorosilane and 0.25 mL of dry triethylamine. After two hours at room temperature, the reaction mixture was diluted with 5 mL of 1N aqueous NaOH and stirred for 15 min. The organic phase was extracted with three 10 mL portions of 1N aqueous NaOH and the combined aqueous phases were washed with 20 mL of ether, acidified (pH~2), then extracted with four 20 mL portions of ether. The combined ethereal extracts were washed with 20 mL of saturated aqueous NaCl and then dried ($MgSO_4$). Removal of the solvent under reduced pressure afforded 116.5 mg (75%) of a mixture of the diastereomeric acids 7a and 7b. A portion of this material was treated with diazomethane in ether and chromatography of the resulting methyl esters 8a and 8b on silica gel with 50% ether-petroleum ether provided the analytical sample.

A separate portion of the mixture of isomeric acids 7a and 7b was hydrogenated over 5% rhodium on carbon at 50 psi for 2 hours and the resulting saturated acids were treated with diazomethane in ether to provide a mixture of the diastereomeric methyl esters 9a and 9b in a ratio of 79:21 as determined by VPC analysis (4% SE-30, 105°C) chromatography of this mixture on silica gel with

50% ether-petroleum ether provided analytical samples of each isomer.

B. From the glycal 5 by deprotonation in HMPA-THF.

By the same procedure and with the same quantities of reactants as described in A above with the exception that 0.6 mL of dry HMPA was added to the solution of ester in THF at 0°C and 0.66 mL of dry HMPA was added to the solution of LDA in dry THF at -78°C, there was obtained 96.3 mg (62%) of a mixture of the diastereomeric acids 7a and 7b. The ratio of the diastereomers (determined by VPC analysis of the hydrogenated methyl esters) was found to be 9:91 (9a:9b).

2,3-O-(1-Methylethylidene)-5-O-methoxymethyl-D-ribonic acid,γ-lactone (10). To a stirred ice cooled solution of 18.5 g (98 mmol) of the hydroxy lactone 1 in 200 mL of dry dichloromethane was added 68.5 mL (390 mmol) of diisopropylethylamine and 29.9 mL (390 mmol) of chloromethyl methyl ether. Cooling was then discontinued and after 5 hours at room temperature an additional 17 ml (98 mmol) of diisopropylethylamine was added followed by 7.5 mL (98 mmol) of chloromethyl methyl ether. After 4 hours at room temperature the reaction mixture was diluted with 2 L of ether and then washed with five 400 mL portions of saturated aqueous $NaHCO_3$ and 400 mL of saturated aqueous NaCl. The combined aqueous washes were extracted with three 400 mL portions of ether and the combined organic extracts were dried ($MgSO_4$) and then concentrated under reduced pressure to afford 21.7 g (95%) of the methoxymethyl ether 10.

2,3-O-(1-Methylethylidene)-5-O-methoxymethyl-D-ribose (11).

By the procedure described for the preparation of the lactol 3a, 21.7 g (93 mmol) of the lactone 10 in 600 mL of dry ether with 24 mL of a 1M solution of di-isobutyl-aluminum hydride in hexane afforded, after chromatography on 250 g of silica gel with 60% ether-petroleum ether, 21.9 g (95%) of the lactol 11, as a mixture of anomers.

2,3-O-(1-Methylethylidene)-5-O-methoxymethyl-α and β-D-ribofuranosyl chloride (12). By the procedure described for the preparation of the chloride 4a, 169 mg (0.72 mmol) of the lactol 11 in 3.6 mL of dry THF with 0.35 mL of carbon tetrachloride and 380 mg (1.45 mmol) of triphenylphosphine, afforded after distillation [kugelrohr, 70-80°C (0.05 mmHg)], 170 mg (93%) of the chloride 12 as a mixture of anomers.

1,4-Anhydro-2-deoxy-5-O-methoxymethyl-D-erythro-pent-1-enitol (13).

A. From reduction of the chloride 12

By the procedure described for the preparation of the glycal 5, 178 mg (0.70 mmol) of the freshly prepared chloride 12 in 2 mL of dry THF, 22 mg (3 mmol) of lithium wire in 25 mL of anhydrous liquid ammonia and 240 mg of anhydrous ammonium chloride provided, after distillation [kugelrohr, 70-80°C (0.05 mmHg)], 105 mg of a mixture of the glycal 13 and the simple reduction product 14. Analysis of this mixture by ^{1}H-NMR revealed a ratio of 6:1 (13:14). Chromatography of this mixture on Florisil with 75% ether-petroleum

ether provided pure products for analysis.

B. From the lactol 11 via a phosponium chloride adduct.

To a stirred solution of 15 g (64 mmol) of the lactol 11 and 7.5 mL (78 mmol) of carbon tetrachloride in 200 mL of dry THF at -78°C under argon was added 12.2 mL (67 mmol) of trisdimethylaminophosphine. After 45 min. the reaction mixture was allowed to warm to 0°C and was then added, via a double-tipped needle, to a stirred solution of 127 cm (780 mmol) of lithium wire in 800 mL of anhydrous liquid ammonia at -78°C under argon. Cooling was then discontinued (ammonia reflux) and after two hours 42 g (790 mmol) of anhydrous ammonium chloride was cautiously added to the reaction mixture. The resulting colorless mixture was diluted with 750 mL of ether and the ammonia was allowed to evaporate. The resulting ethereal suspension was filtered and then concentrated under reduced pressure to afford a crude mixture of the glycal 13, the by-product 14 and HMPA. This mixture was applied onto a 100 g column of silica gel and rapidly eluted with 700 mL of 75% ether-petroleum ether. Concentration of the eluate under reduced pressure afforded, after distillation [kugelrohr, 110°C (0.01 mmHg)], 10.1 g of a mixture of the glycal 13 and the by-product 14. This mixture was identical (^{1}H-NMR analysis) to the mixture obtained in Part A.

Methyl-2R and 2S-(2,5-dihydro-5S-methoxymethylenoxymethyl-2S-furyl)-butanoate (15a and 15b) and Methyl-2S and 2R-5S-methoxymethylenoxymethyl-2S-tetrahydrofuryl)-butanoate (16a and 16b).

A. From the glycal 13 by deprotonation in THF.

By procedure A, described for the preparation of the methyl esters 8a,b, 138 mg (0.70 mmol of 13) of the 6:1 mixture of 13 and 14 with 0.35 mL (0.84 mmol) of n-butyllithium and 0.087 mL (0.84 mmol) of n-butanoyl chloride in 2.8 mL of dry THF was added to 0.94 mmol of LDA in 3 mL of dry THF, followed by 1.4 mmol of trimethylchlorosilane, affording 118 mg (73%) of a mixture of the diastereomeric acids 14a and 14b. A portion of this material was treated with diazomethane in ether and chromatography of the resulting methyl esters on silica gel with 40% ether-petroleum ether provided the analytical sample as a mixture of isomers (15a and 15b).

A separate portion of these isomeric acids was hydrogenated in THF over 5% rhodium on carbon at 50 psi for 2 hours and the resulting saturated acids were treated with diazomethane in ether to provide a mixture of the diastereomeric esters 16a and 16b in a ratio of 81:19, as determined by VPC analysis (4% SE-30, 110°C). Chromatography of this mixture on silica gel with 50% ether-petroleum ether provided analytical samples of each isomer.

B. From the glycal 13 by deprotonation in HMPA-THF.

By the same procedure and with the same quantities of reactants as described in A above, with the exception that 0.64 mL of dry HMPA was added to the solution of ester in THF at 0°C and 0.69 mL of dry HMPA was added to the solution of LDA in dry THF at -78°C, there was obtained 97 mg (60%) of a mixture of the diastereomeric acids 14a and 14b. The ratio of the diastereomers

(determined by VPC analysis of the hydrogenated methyl esters) was found to be 21:79 (16a and 16b).

4R and 4S-(5S-Methoxymethylenoxymethyl-2S-tetrahydrofuryl)-hexan-3-one (18a and 18b). A solution of 1.22 g (5.27 mmol) of the acids 17a,b in 5 mL of oxalyl chloride was stirred at room temperature for one hour and then concentrated under reduced pressure. To a stirred ice-cooled solution of 38 mmol of ethyllithium in 76 mL of dry ether under argon was added 3.8 g (20 mmol) of cuprous iodide. After 5 min., the resulting reaction mixture was cooled to -78°C and the above acid chloride in 5 mL of dry ether was added. After 30 min. the reaction mixture was cautiously treated with 3.1 mL of methanol and then allowed to warm to room temperature. This mixture was washed with three 200 mL portions of saturated aqueous NH_4Cl, 200 mL of saturated aqueous NaCl, and then dried ($MgSO_4$). After removal of the solvent under reduced pressure, chromatography of the residue on 75 g of silica gel with ether provided 479 mg (37%) of the ketones 18a,b and 361 mg (34%) of the ketones 18a,b with the methoxymethyl ether cleaved.

2R-(5S-Methoxymethylenoxymethyl-2S-tetrahydrofuryl)-butan-1-ol (19). To a stirred ice-cooled solution of 3.0 g (12.2 mmol) of the methyl ester 16a in 60 mL of dry ether under argon was added 470 mg of lithium tetrahydridoaluminate (50 mmol of hydride). After one hour the reaction mixture was cautiously treated with 0.47 mL of water, 0.47 mL of 15% aqueous NaOH, 1.41 mL of water, and then filtered. Removal of the solvent under reduced pressure gave 2.6 g (98%) of the alcohol 19.

Benzyl 2R-(5S-methoxymethylenoxymethyl-2S-tetrahydrofuryl)-butyl ether (20). To a stirred suspension of 56 mg (1.4 mmol) of potassium hydride in 3 mL of dry THF at 0°C under argon was added a solution of 250 mg (1.15 mmol) of the alcohol 19 in 1 mL of dry THF followed by 0.2 mL (1.68 mmol) of benzyl bromide. The resulting mixture was stirred for 2 hours at room temperature, then treated with 5 mL of saturated aqueous $NaHCO_3$, and diluted with 60 mL of ether. The organic phase was washed with two 20 mL portions of saturated aqueous $NaHCO_3$, 20 mL of saturated aqueous NaCl, and then dried ($MgSO_4$). After removal of the solvents under reduced pressure, chromatography of the residue on 25 g of silica gel with 20% ethyl acetate-cyclohexane provided 331.4 mg (94%) of the benzyl ether 20.

Benzyl 2R-(5S-hydroxymethyl-2S-tetrahydrofuryl)-butyl ether (21). To a stirred solution of 260.7 mg of the methoxy methyl ether 20 in 7 mL of THF was added 1.75 mL of 10% aqueous HCl. The resulting solution was heated at 50°C for 16 hours and then cooled to room temperature and diluted with 50 mL of ether. The organic phase was washed with 20 mL of water, 20 mL of saturated aqueous $NaHCO_3$, 20 mL of saturated aqueous NaCl, and then dried ($MgSO_4$). After removal of the solvent under reduced pressure, chromatography of the residue on 15 g of silica gel with 35% ethyl acetate-cyclohexane provided 220 mg (98%) of the alcohol 21.

Benzyl 2R-(5S-carbomethoxy-2S-tetrahydrofuryl)-butyl ether (23). To a stirred 10 mL aqueous solution of Adam's catalyst, freshly prepared from 500 mg of 84% platinum oxide, was added

84 mg (1 mmol) of solid $NaHCO_3$ followed by a solution of 206.3 mg (0.78 mmol) of the alcohol 21 in 1 mL of acetone. After complete addition, oxygen was bubbled through this mixture at 50°C for 4 hours. The catalyst was then removed from the cooled reaction mixture by filtration and subsequently washed with 2 x 20 mL of 0.2 M aqueous Na_2HPO_4. The combined filtrates were washed with 20 mL of ether and then acidified (pH≈2). The aqueous phase was extracted with four 20 mL portions of ether and the combined ethereal extracts were washed with 20 mL of saturated aqueous NaCl, and then dried ($MgSO_4$). Removal of the solvent under reduced pressure gave 208.4 mg (96%) of the acid 22. A portion of this material was treated with diazomethane in ether and chromatography of the resulting methyl ester on silica gel with 15% ethyl acetate-cyclohexane provided the analytical sample of the methyl ester 23.

2R-(5S-Methoxymethylenoxymethyl-2S-tetrahydrofuryl)-butanal (24). By the procedure described for the preparation of the lactol 3a, 477.8 mg (1.94 mmol) of the methyl ester 16a in 15 mL of dry ether with 4 mL of a 1 M solution of di-isobutylaluminum hydride in hexane afforded 410 mg (98%) of the aldehyde 24.

4R-(5S-Methoxymethylenoxymethyl-2S-tetrahydrofuryl)-hexan-3-ol (25a and 25b). To a stirred solution of 410 mg (1.90 mmol) of the aldehyde 24 in 15 mL of dry THF at -78°C under argon was added 3 mL of a 1 M solution of ethylmagnesium bromide in THF. The resulting solution was stirred at 0°C for 30 min. then treated with 10 mL of saturated aqueous NH_4Cl, and diluted with 50 mL

of ether. The organic phase was washed with 20 mL of saturated aqueous NH_4Cl, 20 mL of saturated aqueous NaCl, and then dried ($MgSO_4$). After removal of the solvents under reduced pressure, chromatography of the residue on 30 g of silica gel with 50% ether-petroleum ether provided 401.3 mg (86%) of the alcohols 25a,b as a mixture of diastereomers.

Benzyl 4R-(5S-methoxymethylenoxymethyl-2S-tetrahydrofuryl)-3-hexyl ether (26a and 26b). By the procedure described for the preparation of the benzyl ether 20, 138 mg (0.56 mmol) of the alcohols 25a,b with 30 mg (0.75 mmol) of potassium hydride and 0.11 mL (0.92 mmol) of benzyl bromide in 4 mL of dry THF afforded, after chromatography on 20 g of silica gel with 15% ethyl acetate-cyclohexane, 178 mg (94%) of the benzyl ethers 26a,b as a mixture of diastereomers.

Benzyl 4R-(5S-hydroxymethyl-2S-tetrafuryl)-3-hexyl ether (27a and 27b). By the procedure described for the preparation of the alcohol 21, 160 mg (0.48 mmol) of the methoxy methyl ethers 26a,b in 4 mL of THF and 1 mL of 10% aqueous HCl afforded, after chromatography on 10 g of silica gel with 30% ethyl acetate-cyclohexane, 129 mg (93%) of the alcohols 27a,b as a mixture of diastereomers.

Benzyl 4R-(5S-carbomethoxy-2S-tetrahydrofuryl)-3-hexyl ether (29a and 29b). By the procedure described for the preparation of the methyl ester 23, 119 mg (0.41 mmol) of the alcohols 27a,b in 5 mL of water with 43 mg (0.51 mmol) of solid $NaHCO_3$ and

freshly prepared Adam's catalyst (from 200 mg of 84% platinum oxide) afforded 105 mg (84%) of the acids 28a,b as a mixture of diastereomers. A portion of this material was treated with diazomethane in ether and chromatography of the resulting methyl ester on silica gel with 15% ethyl acetate-cyclohexane provided the analytical sample of the methyl esters 29a,b.

1R,5R-4R and 4S-Ethyl-3-oxo-7S-methoxymethylenoxymethyl-2,6-dioxa-bicyclo [3.3.0] octane (30a and 30b). To a stirred solution of 1.17 g (5.07 mmol) of the acids 14a,b in 50 mL of 0.5M aqueous $NaHCO_3$ was added a 25-mL aqueous solution of 8.4 g (50.6 mmol) of potassium iodide and 3.85 g (15.2 mmol) of iodine. The resulting mixture was stirred at room temperature in the dark for 12 hours, then treated with 100 mL of 10% aqueous Na_2SO_3, and then extracted with 3 x 60 mL portions of dichloromethane. The combined organic phases were washed with 40 mL of saturated aqueous $NaHCO_3$, and then dried ($MgSO_4$). Removal of the solvent under reduced pressure then gave the crude iodolactones. To a stirred solution of this residue in 50 mL of ethanol (previously purged with argon) at 0°C under argon was added 0.41 mL (1.5 mmol) of tri-n-butyltin chloride followed by a solution of 287 mg (7.6 mmol) of sodium borohydride in 25 mL of ethanol. The resulting solution was illuminated with a 275-w sunlamp for 30 min. and then treated with 40 mg (0.32 mmol) of oxalic acid dihydrate. After 5 min. the mixture was diluted with 300 mL of dichloromethane and the organic phase was washed with two 100 mL portions of saturated aqueous $NaHCO_3$, 100 mL of saturated aqueous NaCl, and then dried ($MgSO_4$). Removal of the

solvents under reduced pressure and chromatography of the residue on 100 g of silica gel with 50% ethyl acetate-cyclohexane afforded 865 mg (75%) of the lactones 30a,b as a mixture of diastereomers.

N,N-1,4-Butylidene 2R and 2S-(3R-hydroxy-5S-methoxymethyl-enoxymethyl-2R-tetrahydrofuryl)-butanoic amide (31a and 31b). To a stirred solution of 865 mg (3.76 mmol) of the lactones 30a,b in 7.5 mL of dry dichloromethane at 0°C under argon was added 9.5 mL of a 1 M solution of Dimethyl-N-pyrrolidyl-aluminum in dichloromethane. The resulting mixture was stirred at room temperature for 12 hours, then treated with 2 mL of 10% aqueous HCl, and diluted with 70 mL of dichloromethane. The organic phase was washed with 25 mL of water, two 25 mL portions of saturated aqueous $NaHCO_3$, 25 mL of saturated aqueous NaCl, and then dried ($MgSO_4$). Removal of the solvent under reduced pressure and chromatography of the residue on 80 g of silica gel with 50% acetone-ethyl acetate afforded 932 mg (82%) of the hydroxy amides 31a,b as a mixture of diastereomers.

t-Butyldimethylsilyl 2R and 2 S-(3R-hydroxy-5S-methoxymethylenoxymethyl-2R-tetrahydrofuryl)-butyl ether (32a and 32b). To a stirred solution of 440.6 mg (1.91 mmol) of the lactones 30a, b in 10 mL of dry ether at 0°C under argon was added 73 mg (1.9 mmol) of lithium tetrahydridoaluminate. After one hour the reaction mixture was treated with 0.075 mL of water, 0.075 mL of 15% aqueous NaOH, and 0.22 mL of water. After 15 min., the suspension was filtered and then concentrated under reduced pressure.

To a stirred solution of the residue in 3.7 mL of dry dichloromethane was added 0.63 mL (7.6 mmol) of dry pyridine and 293 mg (1.94 mmol) of t-butyldimethyl-chlorosilane. After 9 hours the reaction mixture was diluted with 60 mL of dichloromethane, then washed with 20 mL of saturated aqueous $NaHCO_3$, 20 mL of saturated aqueous $CuSO_4$, 20 mL of saturated aqueous NaCl, and then dried ($MgSO_4$). Removal of the solvent under reduced pressure and chromatography of the residue on 60 g of silica gel with 35% ethyl acetate-cyclohexane afforded 510 mg (79%) of the silyl ethers 32a,b as a mixture of diastereomers.

t-Butyldimethylsilyl 2R and 2S-(3R, 4S-epoxy-5S-methoxymethylenoxymethyl-2R-tetrahydrofuryl)-butyl ether (33a and 33b). To a stirred solution of 108 mg (2.85 mmol) of lithium tetrahydridoaluminate in 4 mL of dry THF at 0°C under argon was added 0.08 mL of 90% sulfuric acid. After one hour a solution of 746 mg (2.09 mmol) of the iodolactones from the acids 14a,b in 3 mL of dry THF was added to the reaction mixture. After one more hour the mixture was treated with 0.08 mL of water, 0.08 mL of 15% aqueous NaOH, 0.24 mL of water. After another 15 min. the suspension was filtered and then concentrated under reduced pressure. To a stirred solution of the residue in 10 mL of methanol was added 443 mg (4.18 mmol) of sodium carbonate. After 24 hours, the mixture was concentrated under reduced pressure and then taken up in 20 mL of saturated aqueous $NaHCO_3$ and 60 mL of dichloromethane. The organic phase was then washed with 20 mL of saturated aqueous

NaCl and then dried (K_2CO_3, Na_2SO_4). Removal of the solvents under reduced pressure gave the crude epoxy alcohol. To a stirred solution of this residue in 4 ml of dry DMF was added 427 mg (6.3 mmol) of imidazole and 472 mg (3.1 mmol) of t-butyldimethylchlorosilane. After 16 hours, the reaction mixture was diluted with 60 mL of ether, then washed with 20 mL of saturated aqueous $NaHCO_3$, 20 mL of saturated aqueous NaCl, and then dried (K_2CO_3, Na_2SO_4). Removal of the solvent and chromatography of the residue on 60 g of silica gel with 10% ethyl acetate-cyclohexane afforded 631.1 mg (90%) of the epoxy silyl ethers 33a,b as a mixture of diastereomers.

t-Butyldimethylsilyl 2R and 2S-(3R-hydroxy-5S-methoxy-methyl-enoxymethyl-4S-methyl-2R-tetrahydrofuryl)-butyl ether (34a and 34b). To a stirred suspension of 1.8 g (9.45 mmol) of cuprous iodide in 20 mL of dry n-pentane at 0°C under argon was added 10 mL of a 1.8 M solution of methyllithium in ether. After 15 min. a solution of 631 mg (1.8 mmol) of the epoxides 33a,b in 4 mL of n-pentane was added to the reaction mixture. After 3 hours, the mixture was treated with 10 mL of saturated aqueous NH_4Cl, diluted with 60 mL of ether, then washed with two 20 mL portions of saturated aqueous NH_4Cl, 20 mL of saturated aqueous NaCl, and then dried ($MgSO_4$). Removal of the solvents under reduced pressure and chromatography of the residue on 50 g of silica gel with 25% ethyl acetate-cyclohexane afforded 334 mg (50%) of the alcohol 34a and 80 mg (12%) of the alcohol 34b.

t-Butyldimethylsilyl 2R-(5S-methoxymethylenoxymethyl-4S-methyl-3R-methylthiothiocarbonyloxy-2R-tetrahydrofuryl)-butyl ether (35). To a stirred suspension of 26.5 mg (1.1 mmol) of sodium hydride in 1 mL of dry THF at 0°C under argon was added a solution of 334 mg (0.92 mmol) of the alcohol 34a in 1 mL of dry THF. After one hour, 0.28 mL (4.7 mmol) of carbon disulfide was added and, after an additional hour, 0.12 mL (1.93 mmol) of methyl iodide was added. The mixture was stirred for 3 hours, then diluted with 70 mL of ether. It was then washed with two 30 mL portions of saturated aqueous $NaHCO_3$, 20 mL of saturated aqueous NaCl, and then dried ($MgSO_4$). Removal of the solvents gave 425 mg (100%) of the xanthate 35.

t-Butyldimethylsilyl 2R-(5S-methoxymethylenoxymethyl-4R-methyl-2S-tetrahydrofuryl)-butyl ether (36). To a stirred solution of 425 mg (0.92 mmol) of the xanthate 35 in 9 mL of dry toluene at reflux under argon was added 0.3 mL (1.14 mmol) of tri-n-butyltin hydride. After 24 hours the reaction mixture was concentrated under reduced pressure and the residue chromatographed on 30 g of silica gel with 5% ethyl acetate-cyclohexane to afford 255 mg (80%) of the silyl ether 36.

2R-(5S-Methoxymethylenoxymethyl-4R-methyl-2S-tetrahydrofuryl)-butan-1-ol (37). To a stirred solution of 223.5 mg (0.645 mmol) of the silyl ether 36 in 3.2 mL of dry THF was added a solution of 430 mg (1.64 mmol) of tetra-n-butylammonium fluoride in 3.2 ml of dry THF. After 4 hrs. the reaction mixture was diluted with 70 mL of

ether, then washed with two 30 mL portions of saturated aqueous $NaHCO_3$, 30 mL of saturated aqueous NaCl, and then dried ($MgSO_4$). Removal of the solvents and chromatography of the residue on 10 g of silica gel with 35% ethyl acetate-cyclohexane afforded 123 mg (82%) of the alcohol 37.

2S-(5S-Methoxymethylenoxymethyl-4R-methyl-2S-tetrahydrofuryl)-butanal (38). To a stirred solution of 78 mg (0.336 mmol) of the alcohol 37 in 1.7 mL of dry dichloromethane was added 11 mg (0.134 mmol) of anhydrous sodium acetate and 145 mg (0.673 mmol) of pyridinium chlorochromate. After 2 hours the reaction mixture was diluted with 20 mL of dry ether and then stirred for 15 min. The resultant suspension was filtered and the solid was washed by trituration with three 20 mL portions of ether. Removal of the solvents and chromatography of the residue on 7 g of silica gel with 25% ethyl acetate-cyclohexane afforded 67 mg (85%) of the aldehyde 38.

2-Ethyl-6S-hydroxy-7-methoxymethylenoxy-5R-methyl-hept-2-en-al (39). To a stirred solution of 50 mg (0.217 mmol) of the aldehyde 38 in 4.4 mL of dry THF was added 5 mg of potassium t-butoxide. The suspension was heated at 70°C for 20 hours, then allowed to cool to room temperature and diluted with 30 mL of ether. The ethereal phase was washed with 2 x 10 mL portions of saturated aqueous $NaHCO_3$, 10 mL of saturated aqueous NaCl, and then dried ($MgSO_4$). Removal of solvents and chromatography of the residue on a TLC plate with 35% ethyl acetate-cyclohexane gave 25 mg of the β-elimination product 39.

t-Butyldimethylsilyl 2R and 2S-[3S-(2-1,3-dithianyl)-4S-hydroxy-5R-methoxymethylenoxymethyl-2R-tetrahydrofuryl]-butyl ether (40a and 40b). To a stirred solution of 1.46 g (12.2 mmol) of 1,3 dithiane in 12 mL of dry THF at -20°C under argon was added, dropwise, 4.8 mL (12 mmol) of a 2.5 M solution of n-butyllithium in n-hexane. After 90 min. a solution of 840 mg (2.42 mmol) of the epoxides 33a,b in 4.5 mL of dry THF was slowly added into the reaction mixture, which was then kept at 5°C for two days. The mixture was diluted with 60 mL of ether then washed with two 25 mL portions of water, 25 mL of saturated aqueous $NaHCO_3$, 25 mL of saturated aqueous NaCl, and then dried ($MgSO_4$). Removal of the solvents under reduced pressure and chromatography of the residue on 50 g of silica gel with 25% ethyl acetate-cyclohexane afforded 509 mg (45%) of the dithioacetal of 40a and 110 mg (10%) of the dithioacetal 40b.

t-Butyldimethylsilyl 2R-(4S-hydroxy-5R-methoxymethylenoxymethyl-3S-methyl-2S-tetrahydrofuryl)-butyl ether (41). A solution of 640 mg (1.37 mmol) of the dithioacetal 40a in 20 mL of ethanol was added to a slurry of W-4 Raney nickel (freshly-made from 20 g of Ni alloy) in 50 mL of ethanol at 90°C and stirred for 5 hours. The catalyst was then removed by filtration and washed with three 20 mL portions of ethanol. Removal of the solvent from the combined filtrates under reduced pressure and chromatography of the residue on 30 g of silica gel with 30% ethyl acetate-cyclohexane afforded 421 mg (85%) of the desulfurized compound 41.

t-Butyldimethylsilyl 2R-(5R-methoxymethylenoxymethyl-3S-methyl-4S-methylthiothiocarbonyloxy-2S-tetrahydrofuryl)-butyl ether (42). By the procedure described for the preparation of the xanthate 35, 421 mg (1.16 mmol) of the alcohol 41, 41.8 mg (1.74 mmol) of sodium hydride in 9 mL of dry THF, 0.35 mL (5.82 mmol) of carbon disulfide, and 0.18 mL (2.89 mmol) of methyl iodide afforded, after chromatography on 40 g of silica gel with 5% ethyl acetate-cyclohexane, 496 mg (95%) of the xanthate 42.

t-Butyldimethylsilyl 2R-(5S-methoxymethylenoxymethyl-3S-methyl-2S-tetrahydrofuryl)-butyl ether (43). By the procedure described for the preparation of the silyl ether 36, 470 mg (1.04 mmol) of the xanthate 42 in 10.4 mL of dry toluene with 0.41 mL (1.55 mmol) of tri-n-butyltin hydride afforded, after chromatography on 30 g of silica gel with 5% ethyl acetate-cyclohexane, 353 mg (98%) of the silyl ether 43.

2R-(5S-Methoxymethylenoxymethyl-3S-methyl-2S-tetrahydrofuryl)-butan-1-ol (44). By the procedure described for the preparation of the alcohol 37, 340 mg. (1.01 mmol) of the silyl ether 43 in 5 mL of dry THF with 530 mg (2 mmol) of tetra-n-butylammonium fluoride afforded, after chromatography on 20 g of silica gel with 35% ethyl acetate-cyclohexane, 236 mg (100%) of the alcohol 44.

2S-(5S-Methoxymethylenoxymethyl-3S-methyl-2S-tetrahydrofuryl)-butanal (45). By the procedure described for the preparation of the aldehyde 38, 130 mg (0.56 mmol) of the alcohol 44 in 3 mL of dry dichloromethane, 18 mg (0.22 mmol) of anhydrous

sodium acetate and 240 mg (1.11 mmol) of pyridinium chlorochromate afforded, after chromatography on 10 g of silica gel with 25% ethyl acetate-cyclohexane, 90 mg (70%) of the aldehyde 45.

2-Ethyl-6S-hydroxy-7-methoxymethylenoxy-4S-methyl-hept-2-en-al (46). By the procedure described for the preparation of the β-elimination product 39, 62 mg (0.27 mmol) of the aldehyde 45 in 2.5 mL of dry THF and 8 mg of potassium t-butoxide afforded, after preparative TLC with 35% ethyl acetate-cyclohexane, 25 mg of the β-elimination product 46.

Benzyl 2R-(5S-methoxymethylenoxymethyl-3S-methyl-2S-tetrahydrofuryl)-butyl ether (47). By the procedure described for the preparation of the benzyl ether 20, 97.9 mg (0.42 mmol) of the alcohol 44, 20 mg (0.5 mmol) of potassium hydride and 0.075 mL (0.6 mmol) of benzyl bromide in 4 mL of dry THF afforded, after chromatography on 10 g of silica gel with 15% ethyl acetate-cyclohexane, 122.8 mg (91%) of the benzyl ether 47.

Benzyl 2R-(5S-hydroxymethyl-3S-methyl-2S-tetrahydrofuryl)-butyl ether (48). By the procedure described for the preparation of the alcohol 21, 82.8 mg (0.26 mmol) of the methoxy methyl ether 47 in 4 mL of THF and 1 mL of 10% aqueous HCl afforded, after chromatography on 10 g of silica gel with 35% ethyl acetate-cyclohexane, 70 mg (98%) of the alcohol 48.

Benzyl 2R(5S-carbomethoxy-3S-methyl-2S-tetrahydrofuryl)-butyl ether (50). By the procedure described for the preparation of the methyl ester 23, 70 mg (0.25 mmol) of the alcohol 48 in

5 mL of water with 30 mg (0.36 mmol) of solid $NaHCO_3$ and freshly-prepared Adam's catalyst (from 200 mg of 84% platinum oxide) afforded 68.8 mg (94%) of the acid 49. A portion of this material was treated with diazomethane in ether and chromatography of the resulting methyl ester on silica gel with 10% ethyl acetate-cyclohexane provided the analytical sample of the methyl ester 50.

4R-(5S-Methoxymethylenoxymethyl-3S-methyl-2S-tetrahydrofuryl)-hexan-3-ol (51a and 51b). By the procedure described for the preparation of the alcohols 25a,b, 78.7 mg (0.34 mmol) of the aldehyde 45 in 3 mL of dry THF with 0.4 mL of a 1.29 M solution of ethylmagnesium bromide in THF afforded, after chromatography on 10 g of silica gel with 35% ethyl acetate-cyclohexane, 79.3 mg (90%) of the alcohols 51a,b as a mixture of diastereomers.

Benzyl 4R-(5S-methoxymethylenoxymethyl-3S-methyl-2S-tetrahydrofuryl)-3-hexyl ether (52a and 52b). By the procedure described for the preparation of the benzyl ether 20, 70 mg (0.27 mmol) of the alcohols 51a,b with 14 mg (0.35 mmol) of potassium hydride and 0.05 mL (0.42 mmol) of benzyl bromide in 2 mL of dry THF afforded, after chromatography on 10 g silica gel with 10% ethyl acetate-cyclohexane, 86 mg (96%) of the benzyl ethers 52a,b as a mixture of diastereomers.

Benzyl 4R(5S-hydroxymethyl-3S-methyl-2S-tetrahydrofuryl)-3-hexyl ether (53a and 53b). By the procedure described for the preparation of the alcohol 21, 80 mg (0.23 mmol) of the methoxy methyl ethers 52a,b in 4 mL of THF and 1 mL of 10% aqueous HCl

afforded, after chromatography on 10 g of silica gel with 30% ethyl acetate-cyclohexane, 70 mg (99%) of the alcohols 53a,b as a mixture of diastereomers.

Benzyl 4R-(5S-carbomethoxy-3S-methyl-2S-tetrahydrofuryl)-3-hexyl ether (55a and 55b). By the procedure described for the preparation of the methyl ester 23, 50 mg (0.16 mmol) of the alcohols 53a,b in 5 mL of water with 25 mg (0.3 mmol) of solid $NaHCO_3$ and freshly-prepared Adam's catalyst (from 200 mg of 84% platinum oxide) afforded 47 mg (90%) of the acids 54a,b as a mixture of diastereomers. A portion of this material was treated with diazomethane in ether and chromatography of the resulting methyl ester on silica gel with 10% ethyl acetate-cyclohexane provided the analytical sample of the methyl esters 55a,b.

2-Methyl-2,3-O-(1-methylethylidene)-5-O-methoxymethyl-D-ribonic acid, γ-lactone (58). To a stirred suspension of 1.3 g (32.4 mmol) of potassium hydride in 90 mL of dry THF at 0°C under argon was added a solution of 5.03 g (24.86 mmol) of the alcohol 57 in 20 mL of dry THF followed by 3 mL (39.5 mmol) of chloromethyl methyl ether. The resulting mixture was stirred at room temperature for 8 hours, then treated with 20 mL of saturated aqueous $NaHCO_3$, and then diluted with 400 mL of ether. The organic phase was washed with two 200 mL portions of saturated aqueous $NaHCO_3$, 200 mL of saturated aqueous NaCl, and then dried ($MgSO_4$). After removal of solvents under reduced pressure, chromatography of the residue on 200 g of silica gel with 50% ether-petroleum ether provided 5.70 g (93%) of the methoxy methyl ether 58.

2-Methyl-2,3-O-(1-methylethylidene)-5-O-methoxymethyl-D-ribose (59). By the procedure described for the preparation of the lactol 3a, 5.70 g (23.1 mmol) of the lactone 58 in 100 mL of dry ether with 35 mL of a 1 M solution of di-iso-butyl-aluminum hydride in hexane afforded, after chromatography on 200 g of silica gel with 75% ether-petroleum ether, 5.76 g (100%) of the lactol 59 as a mixture of anomers.

1,4-Anhydro-2-deoxy-2-methyl-5-O-methoxymethyl-D-erythro-pent-1-enitol (60). By the procedure described for the preparation of the glycal 13 part B, 6.52 g (26.26 mmol) of the lactol 59, 3.1 mL (32 mmol) of carbon tetrachloride, 5.1 mL (28 mmol) of tris-dimethylaminophosphine in 100 mL of dry THF with 52 cm (317 mmol) of lithium wire in 400 mL of anhydrous ammonia and 18.7 g (350 mmol) of anhydrous ammonium chloride afforded, after a rapid passage through 50 g of silica gel with 75% ether-petroleum ether, 4.694 g of a mixture of the glycal 60 and the by-product 61. Analysis of this mixture by ^{1}H-NMR revealed a ratio of 4:1 (60:61). Chromatography of a small portion on silica gel with 75% ether-petroleum ether provided pure products for analysis.

Methyl 2R and 2S-(2,5-dihydro-5S-methoxymethylenoxymethyl-3-methyl-2R-furyl)-butanoate (63a and 63b).

A. From the glycal 60 by deprotonation in THF.

By procedure A described for the preparation of the methyl esters 8a,b, 4.6 g (19.8 mmol of the glycal 60) of the 4:1 mixture of the glycal 60 and the by-product 61 with 8 mL (19.8 mmol) of

2.48 M solution of n-butyllithium in hexane and 2.1 mL (20.2 mmol) of n-butanoyl chloride in 57 mL of dry THF, added to 24.8 mmol of LDA in 57 mL of dry THF followed by 37.8 mmol of trimethyl-chlorosilane, afforded, after treating the diastereomeric acids with ethereal diazomethane and chromatography of the resulting methyl esters on 300 g of silica gel with 30% ether-petroleum ether, 3.07 g (60%) of the methyl esters 63a,b. ^{1}H-NMR analysis revealed a ratio of 9:1 for the two diastereomeric methyl esters.

B. From the glycal 60 by deprotonation in HMPA-THF.

By the same procedure as described in A, above, 17.87 mmol of the glycal 60 with 10.5 mL (24.15 mmol) of 2.3 M solution of n-butyllithium in hexane and 2.6 mL (25 mmol) of n-butanoyl chloride in 70 mL of dry THF and 10 mL of dry HMPA, added to 28.5 mmol of LDA in 64 mL of dry THF and 16 mL of dry HMPA, followed by 59 mmol of trimethylchlorosilane afforded, after treating the diastereomeric acids with ethereal diazomethane and chromatography of the resulting methyl esters on 200 g of silica gel with 30% ether-petroleum ether, 2.4 g (52%) of the methyl esters 63a,b. ^{1}H-NMR analysis revealed a ratio of 1:3 for the two diastereomeric methyl esters.

Methyl 2R and 2S-(5S-methoxymethylenoxymethyl-3S-methyl-2S-tetrahydrofuryl)-butanoate (64a and 64b). To a stirred solution of 2.4 g (9.3 mmol) of the diastereomeric methyl esters 63a,b (from HMPA/THF reaction) in 93 mL of ethyl acetate was added 240 mg of 10% platinum on carbon. The reaction mixture was stirred at room temperature under a hydrogen atmosphere for 3 hours. The

catalyst was then removed by filtration and washed with 3 x 25 mL portions of ethyl acetate. Removal of the solvent from the combined filtrates and chromatography of the residue on 200 g of silica gel with 25% ethyl acetate-cyclohexane afforded 1.6 g (66% of the methyl ester 64b and 0.53 g (21%) of the epimeric methyl ester 64a.

2S(5S-Methoxymethylenoxymethyl-3S-methyl-2S-tetrahydrofuryl)-butan-1-ol (65). By the procedure described for the preparation of the alcohol 19, 1.67 g (6.4 mmol) of the methyl ester 64b in 32 mL of dry ether with 243 mg of lithium tetrahydridoaluminate (25.6 mmol of hydride) afforded, after chromatography on 100 g of silica gel with 50% ethyl acetate-cyclohexane, 1.45 g (97%) of the alcohol 65.

Benzyl 2S(5S-methoxymethylenoxymethyl-3S-methyl-2S-tetrahydrofuryl)-butyl ether (66). By the procedure described for the preparation of the benzyl ether 20, 1.45 g (6.22 mmol) of the alcohol 65 with 300 mg (7.48 mmol) of potassium hydride and 1.2 mL (9.6 mmol) of benzyl bromide in 30 mL of dry THF afforded, after chromatography on 100 g of silica gel with 15% ethyl acetate-cyclohexane, 2.0 g (97%) of the benzyl ether 66.

Benzyl 2S-(5S-hydroxymethyl-3S-methyl-2S-tetrahydrofuryl)-butyl ether (67). By the procedure described for the preparation of the alcohol 21, 2.0 g (6.2 mmol) of the methoxy methyl ether 66 in 48 mL of THF and 12 mL of 10% aqueous HCl afforded, after chromatography on 100 g of silica gel with 35% ethyl acetate-cyclohexane, 1.7 g (99%) of the alcohol 67.

Benzyl 2S(5S-carbomethoxy-3S-methyl-2S-tetrahydrofuryl)-butyl ether (69). By the procedure described for the preparation of the methyl ester 23, 1.7 g (6.12 mmol) of the alcohol 67 in 60 mL of water with 643 mg (7.7 mmol) of solid $NaHCO_3$ and freshly prepared Adam's catalyst (from 2 g of 88% platinum oxide) afforded 1.63 g (91%) of the acid 68. A portion of this material was treated with diazomethane in ether and chromatography of the resulting methyl ester on silica gel with 10% ethyl acetate-cyclohexane provided the analytical sample of the methyl ester 69.

Benzyl-6-deoxy-α and β-L-gulose (71a and 71b).

To a stirred solution of 1.5 g (9.14 mmol) of 6-deoxy-L-gulose in 18 mL of benzyl alcohol was added 0.35 mL of acetyl chloride. After two days the reaction mixture was diluted with 40 mL of chloroform and then neutralized with 10 g of barium carbonate. The resulting suspension was filtered and the solid residue washed with 3 x 25 mL portions of chloroform. The combined filtrates were concentrated at 50°C, .01 mmHg and the residue was chromatographed on 200 g of silica gel with ethyl acetate to give 1.8 g (77%) of the benzyl glycosides 71a and 71b (α:β=1:2).

Benzyl-6-deoxy-2,3-O-(1-methylethylidene)-α-L-gulose (72a). To a stirred solution of 50 mg (0.197 mmol) of the benzyl glycoside 71a in 5 mL of dry acetone was added 9.5 mg (0.05 mmol) of p-toluenesulfonic acid monohydrate. After 12 hours the reaction mixture was neutralized with barium carbonate. The resulting suspension was filtered and the solid residue then washed with 3 x 5 mL por-

tions of acetone. The combined filtrates were concentrated under reduced pressure and the residue chromatographed on 10 g of silica gel with 35% ethyl acetate-petroleum ether to give 51.6 mg (90%) of the ketal 72a.

Benzyl-6-deoxy-2,3-O-(1-methylethylidene)-β-L-gulose (72b). By the procedure described for the preparation of the ketal 72a, 200 mg (0.79 mmol) of the benzyl glycoside 71b in 10 mL of dry acetone and 19 mg (0.1 mmol) of p-toluenesulfonic acid monohydrate afforded, after chromatography on 20 g of silica gel with 25% ethyl acetate-petroleum ether, 208.7 mg (91%) of the ketal 72b.

Benzyl-6-deoxy-2,3-O-(1-methylethylidene)-4-O-methoxymethyl-α-L-gulose (73a). By the procedure described for the preparation of the methoxymethyl ether 58, 43.5 mg (0.15 mmol) of the alcohol 72a with 8 mg (0.20 mmol) of potassium hydride and 0.03 mL (0.40 mmol) of chloromethyl methyl ether in 2 mL of dry THF afforded, after chromatography on 10 g of silica gel with 25% ethyl acetate-petroleum ether, 46 mg (92%) of the fully-protected sugar 73a.

Benzyl-6-deoxy-2,3-O-(1-methylethylidene)-4-O-methoxymethyl-β-L-gulose (73b). By the procedure described for the preparation of the methoxymethyl ether 58, 198.2 mg (0.67 mmol) of the alcohol 72b with 35 mg (0.87 mmol) of potassium hydride and 0.1 mL (1.3 mmol) of chloromethyl methyl ether in 6 mL of dry THF afforded, after chromatography on 20 g of silica gel with 30% ethyl acetate-petroleum ether, 205 mg (90%) of the fully-protected sugar 73b.

6-Deoxy-2,3-O-(1-methylethylidene)-4-O-methoxymethyl-L-gulose (74). A. From debenzylation of 73a.

To a stirred solution of 96 mg (0.28 mmol) of the benzyl glycoside 73a in 3 mL of ethyl acetate was added 20 mg of 10% palladium on carbon. The resulting suspension was stirred vigorously under an atmosphere of hydrogen. After 3 hrs. the catalyst was removed by filtration and then washed with three 5 mL portions of ethyl acetate. The combined filtrates were concentrated under reduced pressure and the residue chromatographed on 10 g of silica gel with 50% ethyl acetate-petroleum ether to give 62 mg (88%) of the lactol 74 as a mixture of anomers.

B. From debenzylation of 73b. By the procedure described in A, 114.7 mg (0.34 mmol) of the benzyl glycoside 73b in 4 mL of ethyl acetate with 20 mg of 10% palladium on carbon afforded, after chromatography on 10 g of silica gel with 50% ethyl acetate-petroleum ether, 76 mg (90%) of the lactol 74.

Benzyl-6-deoxy-2,3-O-(1-methylethylidene)-α and β-L-gulose (72a and 72b). By the procedure described for the preparation of the ketal 72a, 1.8 g (7.08 mmol) of a mixture of the benzyl glycosides 71a and 71b in 70 mL of dry acetone, 1.1 mL (8.9 mmol) of 2,2-dimethoxypropane, and 70 mg (0.37 mmol) of p-toluenesulfonic acid monohydrate afforded, after chromatography on 100 g of silica gel with 25% ethyl acetate-petroleum ether, 1.94 g (93%) of the ketals 72a and 72b.

Benzyl-6-deoxy-2,3-O-(1-methylethylidene)-4-O-methoxymethyl-α and β-L-gulose (73a and 73b). By the procedure described for the preparation of the methoxymethyl ether 58, 1.94 g (6.6 mmol) of a mixture of the alcohols 72a and 72b, 0.34 g (8.5 mmol) of potassium hydride and 1 mL (13.2 mmol) of chloromethyl methyl ether in 22 mL of dry THF afforded, after chromatography on 100 g of silica gel with 25% ethyl acetate-petroleum ether, 1.91 g (86%) of the mixture of the methoxymethyl ethers 73a and 73b.

6-Deoxy-2,3,-O-(1-methylethylidene)-4-O-methoxymethyl-L-gulose (74). To a stirred solution of 3 cm (18.3 mmol) of lithium wire in 50 mL of anhydrous ammonia at -78°C under argon was added a solution of 1.91 g (5.64 mmol) of the mixture of benzyl glycosides 73a and 73b in 10 mL of dry THF. Cooling was then discontinued (ammonia reflux) and after one hour 1.1 g (20.6 mmol) of anhydrous ammonium chloride was cautiously added to the reaction mixture. The resulting mixture was then diluted with 50 mL of ether and the ammonia was allowed to evaporate. The resulting suspension was filtered and the solid was then washed by trituration with four 20 mL portions of ether. Removal of the solvent from the combined filtrates gave 1.2 g (86%) of the crystalline lactol 74.

1,5-Anhydro-2,6-dideoxy-4-O-methoxymethyl-L-xylo-hex-1-enitol (75). By the procedure described for the preparation of the glycal 13, part B, 437.4 mg (1.76 mmol) of the lactol 74, 0.22 mL (2.28 mmol) of carbon tetrachloride, 0.34 mL (1.87 mmol)

of trisdimethylaminophosphine in 7 mL of dry THF with 3.5 cm (21.3 mmol) of lithium wire in 30 mL of anhydrous ammonia and 1.4 g (26.2 mmol) of anhydrous ammonium chloride afforded, after passage through 5 g of silica gel with 50% ethyl acetate-petroleum ether and distillation [kugelrohr, 60°C (0.1 mmHg)], 280 mg (90%) of the glycal 75.

1,5-Anhydro-2,6-dideoxy-4-O-methyl-3-O-2R-[5S(2S-1-benzyloxy-butyl)tetrahydrofuroyl]-L-arabino-hex-1-enitol (77).

To a stirred solution of 127.6 mg (0.425 mmol) of the sodium salt of the acid 22 in 1.7 mL of dry benzene under argon was added 0.74 mL (8.5 mmol) of oxalyl chloride. After 30 min. the reaction mixture was concentrated under reduced pressure, taken up in 2.1 mL of ether, and then added to a stirred solution of 61.4 mg (0.426 mmol) of 1,5-anhydro-2,6-dideoxy-4-O-methyl-L-arabino-hex-1-enitol and 63.4 mg (0.52 mmol) of N,N-dimethyl-4-aminopyridine in 1.1 mL of dichloromethane. After 45 min. the reaction mixture was diluted with 70 mL of ether, then washed with 20 mL of water, 20 mL of saturated aqueous $NaHCO_3$, 20 mL of saturated aqueous $CuSO_4$, 20 mL of saturated aqueous NaCl, and then dried ($MgSO_4$). Removal of the solvents under reduced pressure and chromatography of the residue on 10 g of silica gel with 15% ethyl acetate-cyclohexane afforded 150 mg (87%) of the ester 77.

Benzyl 2R-[5R and 5S-carbomethoxy-5-(5,6-dihydro-5R-methoxy-6S-methyl-2S-pyranyl)-2S-tetrahydrofuryl]-butyl ether (78a and 78b) and Benzyl 2R-[5R and 5S-carbomethoxy-5-(5R-methoxy-6S-methyl-2S-tetrahydropyranyl)-2S-tetrahydrofuryl]-butyl ether (79a and 79b).

A. From the ester 77 by deprotonation in THF.

To a stirred solution of 0.28 mmol of LDA in 0.5 mL of dry THF at -78°C was added a solution of 89.1 mg (0.22 mmol) of the ester 77 in 0.5 mL of dry THF. After 15 min. the reaction mixture was treated with 0.07 mL (0.41 mmol TMSCl) of the supernatant centrifugate from a mixture of 0.75 mL of trimethylchlorosilane and 0.25 mL of dry triethylamine. After two hours at room temperature 71.4 mg (80%) of a mixture of diastereomeric acids 78a,b were isolated from the reaction mixture using the procedure described for the preparation of the methyl esters 8a,b. This mixture was treated with diazomethane in ether and then hydrogenated in ethyl acetate over 5% platinum on carbon at atmospheric pressure to provide a mixture of the diastereomeric methyl esters 79a and 79b in a ratio of 77:23, as determined by VPC analysis (4% SE-30, 225°C). Chromatography of the mixtures of unsaturated and saturated methyl esters on silica gel with 10% ethyl acetate-cyclohexane provided analytical samples of each isomer.

B. From the ester 77 by deprotonation in HMPA-THF.

By the same procedure as described in A, above, 92.8 mg (0.23 mmol) of the ester 77 in 0.5 mL of dry THF and 0.115 mL of

dry HMPA, added to 0.29 mmol of LDA in 0.5 mL of dry THF and 0.115 mL of dry HMPA, followed by 0.44 mmol of trimethylchlorosilane, afforded 74.4 mg (80%) of the two diastereomeric acids. This mixture was transformed into a mixture of saturated methyl esters as described in A. VPC analysis (4% SE-30, 225°C) revealed a ratio of 68:32 (79a:79b).

4R-[5S-Ethyl-3S-methyl-5-(5R-ethyl-5-trimethylsiloxy-6S-methyl-2R-tetrahydropyranyl)-2S-tetrahydrofuryl]-3-trimethylsiloxy-hex-2-ene (80). To a stirred solution of 11.22 mmol of potassium hexamethyldisilazide in 20 mL of dry THF at -78°C under argon was added a solution of 1.325 g (3.74 mmol) of the ketone C in 3 mL of dry THF. After 10 min. the reaction mixture was treated with 2.8 mL (11.2 mmol of TMSCl) of the supernatant centrifugate from a mixture of 4.2 mL of trimethylchlorosilane and 1.4 mL of dry triethylamine. Cooling was then discontinued and the resulting mixture was stirred at room temperature for 90 min. then diluted with 300 mL of ether, washed with two 80 mL portions of water, 40 mL of saturated aqueous NaCl, and then dried (Na_2SO_4). Removal of the solvents under reduced pressure and distillation of the residue [kugelrohr, 180°C (0.05 mmHg)] afforded 1.76 g (94%) of the silylenol ether 80.

Methyl-2R-[5S-ethyl-3S-methyl-5-(5R-ethyl-5-trimethylsiloxy-6S-methyl-2R-tetrahydropyranyl)-2S-tetrahydrofuryl]-butanoate (81). A solution of 0.96 g (1.92 mmol) of the silylenol ether 80 in 25 mL of dry methanol and 4 mL of dry dichloromethane at -78°C was treated

with ozone until it was faintly blue. The reaction mixture was then treated with two 1.2 g (31.7 mmol) portions of sodium borohydride. Cooling was then discontinued and the resulting suspension was stirred at room temperature for two hours and then concentrated under reduced pressure. The residue was taken up in 50 mL of saturated aqueous NH_4Cl and then acidified (pH≅ 2) with 10% aqueous HCl. The aqueous phase was extracted with four 40 mL portions of dichloromethane and the combined organic extracts were dried (Na_2SO_4) and then concentrated under reduced pressure. The residue was treated with diazomethane in ether, then concentrated under reduced pressure and then chromatographed on 50 g of silica gel with 10% ether-petroleum ether to give 599 mg (72%) of the methyl ester 81.

2S-[5S-Ethyl-3S-methyl-5-(5R-ethyl-5-trimethylsiloxy-6S-methyl-2R-tetrahydropyranyl)-2S-tetrahydrofuryl]-butan-1-ol (82). By the procedure described for the preparation of the alcohol 19, 600 mg (1.4 mmol) of the methyl ester 81 in 4 mL of dry ether with 160 mg (16.8 mmol of hydride) afforded 557 mg (99%) of the alcohol 82

2S-[5S-Ethyl-3S-methyl-5-(5R-ethyl-5-hydroxy-6S-methyl-2R-tetrahydropyranyl)-2S-tetrahydrofuryl]-butan-1-ol (83). By the procedure described for the preparation of the alcohol 37, 264 mg (0.66 mmol) of the silyl ether 82 in 8 mL of dry THF with 430 mg (1.65 mmol) of tetra-n-butylammonium fluoride afforded 196 mg (92%) of the alcohol 83.

Benzyl 2S-[5S-ethyl-3S-methyl-5-(5R-ethyl-5-hydroxy-6S-methyl-2R-tetrahydropyranyl)-2S-tetrahydrofuryl]-butyl ether (84). By the procedure described for the preparation of the benzyl ether 20, 164 mg (0.5 mmol) of the alcohol 83 with 22 mg (0.6 mmol) of potassium hydride and 0.09 mL (0.75 mmol) of benzyl bromide in 2 mL of dry THF afforded, after chromatography on 20 g of silica gel with 35% ether-petroleum ether, 172 mg (82%) of the monobenzyl ether 84.

Benzyl 2S-[5S-ethyl-3S-methyl-5-(5S-hydroxy-6S-methyl-2R-tetrahydropyranyl)-2S-tetrahydrofuryl]-butyl ether (87). To a stirred solution of 60 mg (0.30 mmol) of potassium hydride in 0.5 mL of dry THF under argon was added a solution of 85 mg (0.20 mmol) of the alcohol 84 in 0.5 mL of dry THF, followed by 0.06 mL (1.0 mmol) of carbon disulfide. After 5 hours the reaction mixture was treated with 0.025 mL (0.4 mmol) of methyl iodide and after an additional 30 min., the mixture was diluted with 40 mL of ether and then washed with three 15 mL of water, 15 mL of saturated aqueous NaCl, and then dried ($MgSO_4$). Removal of the solvents gave a yellow oil which was then injected into a preparative GC column (4% SE-30, 0.25 in x 6 ft, 220°C, injector part 300°C) as a 50% solution in ether to give 38 mg of an olefin mixture (exo: endo=1:5).

A solution of the above residue in 20 mL of dry methanol and 2 mL of dry dichloromethane at -78°C was treated with ozone until it was faintly blue. The reaction mixture was then treated

with two 100 mg (2.6 mmol) portions of sodium borohydride. Cooling was then discontinued and the resulting suspension was stirred at room temperature for ten hours and then concentrated under reduced pressure. The residue was taken up in 30 mL of saturated aqueous NH_4Cl. The aqueous phase was then extracted with three 15 mL portions of ether. The combined ethereal phases were washed with 15 mL of saturated aqueous NaCl and then dried ($MgSO_4$). Removal of the solvent and chromatography of the residue on 10 g of silica gel with 25% ethyl acetate-petroleum ether provided 3.5 mg of the alcohol 87.

Benzyl 2R-[5R and 5S-carbomethoxy-3S-methyl-5-(5,6-dihydro-5S-methoxymethylenoxy-6S-methyl-2R-pyranyl)-2S-tetrahydrofuryl]-butyl ether (88a and 88b). By the procedure described for the preparation of the methyl esters 8a,b, part A, 272 mg (1.56 mmol) of the glycal 75 with 0.71 mL (1.63 mmol) of 2.3 M solution of n-butyllithium in hexane and 1.61 mmol of the acid chloride of the acid 49 in 6 mL of dry THF, added to 3.45 mmol of LDA in 7 mL of dry THF, followed by 5.1 mmol of trimethylchlorosilane afforded, after treatment with ethereal diazomethane and chromatography on silica gel with 20% ethyl acetate-cyclohexane, 125.7 mg of the methyl ester 88a and 283.4 mg of the methyl ester 88b, or a 30:70 ratio of a 57% combined yield.

Benzyl 2S-[5R and 5S-carbomethoxy-3S-methyl-5-(5,6-dihydro-5S-methoxymethylenoxy-6S-methyl-2R-pyranyl)-2S-tetrahydrofuryl]-butyl ether (88c and 88d). By the procedure described for the

preparation of the methyl esters 8a,b, part A, 381 mg (2.18 mmol) of the glycal 75 with 1 mL (2.3 mmol) of 2.3 M solution of n-butyllithium in hexane and 2.45 mmol of the acid chloride of the acid 68 in 5 mL of dry THF, added to 4.6 mmol of LDA in 5 mL of dry THF, followed by 9.5 mmol of trimethylchlorosilane afforded, after treatment with ethereal diazomethane and chromatography on silica gel with 20% ethyl acetate-cyclohexane, 178 mg of the methyl ester 88c and 504 mg of the methyl ester 88d, or a 26:74 ratio of a 67% combined yield.

Benzyl 2R-[5R-carbomethoxy-3S-methyl-5-(5S-methoxymethyl-enoxy-6S-methyl-2R-tetrahydropyranyl)-2S-tetrahydrofuryl]-butyl ether (89a). To a stirred solution of 140 mg (0.30 mmol) of the methyl ester 88a in 5 mL of ethyl acetate was added 0.1 mL of Raney nickel. The reaction mixture was stirred at room temperature under hydrogen atmosphere for 3 hours. The catalyst was then removed by filtration and washed with 3 x 5 mL portions of ethyl acetate. The combined filtrates were concentrated under reduced pressure and the resulting residue was chromatographed on 10 g of silica gel with 15% ethyl acetate in petroleum ether to give 120 mg (85%) of the methyl ester 89a.

Benzyl 2R-[5S-carbomethoxy-3S-methyl-5-(5S-methoxymethyl-enoxy-6S-methyl-2R-tetrahydropyranyl)-2S-tetrahydrofuryl]-butyl ether (89b). By the procedure described for the preparation of the methyl ester 89a, 340 mg (0.74 mmol) of the methyl ester 88b in 5 mL of ethyl acetate with 0.2 mL of Raney nickel afforded,

after chromatography on 30 g of silica gel with 20% ethyl acetate-petroleum ether, 300 mg (88%) of the methyl ester 89b.

Benzyl 2S-[5R-carbomethoxy-3S-methyl-5-(5S-methoxymethylenoxy-6S-methyl-2R-tetrahydropyranyl)-2S-tetrahydrofuryl]-butyl ether (89c). By the procedure described for the preparation of the methyl ester 89a, 168 mg (0.36 mmol) of the methyl ester 88c in 5 mL of ethyl acetate with 0.1 mL of Raney nickel afforded, after chromatography on 20 g of silica gel with 15% ethyl acetate-cyclohexane, 150 mg (89%) of the methyl ester 89c.

Benzyl 2S-[5S-carbomethoxy-3S-methyl-5-(5S-methoxymethylenoxy-6S-methyl-2R-tetrahydropyranyl)-2S-tetrahydrofuryl]-butyl ether (89d). By the procedure described for the preparation of the methyl ester 89a, 494 mg (1.07 mmol) of the methyl ester 88d in 8 mL of ethyl acetate with 0.3 mL of Raney nickel afforded, after chromatography on 40 g of silica gel with 20% ethyl acetate-cyclohexane, 420 mg (85%) of the methyl ester 89d.

Benzyl 2R-[5R-formyl-3S-methyl-5-(5S-methoxymethylenoxy-6S-methyl-2R-tetrahydropyranyl)-2S-tetrahydrofuryl]-butyl ether (90a). By the procedure described for the preparation of the lactol 3a, 100 mg (0.22 mmol) of the methyl ester 89a in 2 mL of dry ether with 0.7 mL of 1 M solution of di-isobutylaluminum hydride in hexane afforded, after chromatography on 10 g of silica gel with 20% ethyl acetate-petroleum ether, 90 mg (96%) of the aldehyde 90a.

Benzyl 2R-[5S-formyl-3S-methyl-5-(5S-methoxymethylenoxy-6S-methyl-2R-tetrahydropyranyl)-2S-tetrahydrofuryl]-butyl ether (90b). By the procedure described for the preparation of the lactol 3a, 206 mg (0.44 mmol) of the methyl ester 89b in 4 mL of dry ether with 1.4 mL of 1 M solution of di-iso-butylaluminum hydride in hexane afforded, after chromatography on 20 g of silica gel with 20% ethyl acetate-petroleum ether, 190 mg (98%) of the aldehyde 90b.

Benzyl 2S-[5R-formyl-3S-methyl-5-(5S-methoxymethylenoxy-6S-methyl-2R-tetrahydropyranyl)-2S-tetrahydrofuryl]-butyl ether (90c). By the procedure described for the preparation of the lactol 3a, 139 mg (0.30 mmol) of the methyl ester 89c in 3 mL of dry ether with 0.9 mL of 1 M solution of di-iso-butylaluminum hydride in hexane afforded, after chromatography on 20 g of silica gel with 20% ethyl acetate-cyclohexane, 120 mg (92%) of the aldehyde 90c.

Benzyl 2S-[5S-formyl-3S-methyl-5-(5S-methoxymethylenoxy-6S-methyl-2R-tetrahydropyranyl)-2S-tetrahydrofuryl]-butyl ether (90d). By the procedure described for the preparation of the lactol 3a, 407 mg (0.88 mmol) of the methyl ester 89d in 5 mL of dry ether with 2.7 mL of 1 M solution of di-iso-butylaluminum hydride in hexane afforded, after chromatography on 30 g of silica gel with 20% ethyl acetate-cyclohexane, 363 mg (95%) of the aldehyde 90d.

Benzyl 2R-[5S-vinyl-3S-methyl-5-(5S-methoxymethylenoxy-6S-methyl-2R-tetrahydropyranyl)-2S-tetrahydrofuryl]-butyl ether (91a). To a stirred solution of 161 mg (0.45 mmol) of methyltriphenylphosphonium bromide in 1 mL of dry THF at -78°C under argon was added 0.185 mL (0.43 mmol) of a 2.3 M solution of n-butyllithium in hexane. Cooling was then discontinued and the reaction mixture was stirred at room temperature for one hour, then cooled to -78°C and a solution of 80 mg (0.18 mmol) of the aldehyde 90a in 1 mL of dry THF was added. After 10 hours the reaction mixture was treated with 1 mL of saturated aqueous $NaHCO_3$, diluted with 40 mL of ether, then washed with 20 mL of saturated aqueous $NaHCO_3$, 20 mL of saturated aqueous NaCl, and then dried ($MgSO_4$). Removal of the solvents and chromatography of the residue on 10 g of silica gel with 8% ethyl acetate-petroleum ether afforded 64 mg (80%) of the adduct 91a.

Benzyl 2R[5R-vinyl-3S-methyl-5-(5S-methoxymethylenoxy-6S-methyl-2R-tetrahydropyranyl)-2S-tetrahydrofuryl]-butyl ether (91b). By the procedure described for the preparation of the adduct 91a, 180 mg (0.41 mmol) of the aldehyde 90b in 4 mL of dry THF with 0.85 mmol of methylenetriphenylphosphorane afforded, after chromatography on 20 g of silica gel with 8% ethyl acetate-petroleum ether, 160 mg (89%) of the adduct 91b.

Benzyl 2S-[5S-vinyl-3S-methyl-5-(5S-methoxymethylenoxy-6S-methyl-2R-tetrahydropyranyl)-2S-tetrahydrofuryl]-butyl ether (91c). By the procedure described for the preparation of the adduct 91a,

109.5 mg (0.25 mmol) of the aldehyde 90c in 2 mL of dry THF with 0.57 mmol of methylenetriphenylphosphorane afforded, after chromatography on 10 g of silica gel with 7% ethyl acetate-cyclohexane, 90 mg (83%) of the adduct 91c.

Benzyl 2S-[5R-vinyl-3S-methyl-5-(5S-methoxymethylenoxy-6S-methyl-2R-tetrahydropyranyl)-2S-tetrahydrofuryl]-butyl ether (91d). By the procedure described for the preparation of the adduct 91a, 353.4 mg (0.81 mmol) of the aldehyde 90d in 5 mL of dry THF with 1.72 mmol of methylenetriphenylphosphorane afforded, after chromatography on 30 g of silica gel with 7% ethyl acetate-cyclohexane, 310 mg (88%) of the adduct 91d.

Benzyl 2R-[5R-ethyl-3S-methyl-5-(5S-methoxymethylenoxy-6S-methyl-2R-tetrahydropyranyl)-2S-tetrahydrofuryl]-butyl ether (92a). By the procedure described for the preparation of the saturated compound 89a, 55 mg (0.13 mmol) of the adduct 91a in 2 mL of ethyl acetate with 0.05 mL of Raney nickel afforded, after chromatography on 10 g of silica gel with 7% ethyl acetate-petroleum ether, 49.5 mg (90%) of the saturated compound 92a.

Benzyl 2R[5S-ethyl-3S-methyl-5-(5S-methoxymethylenoxy-6S-methyl-2R-tetrahydropyranyl)-2S-tetrahydrofuryl]-butyl ether (92b). By the procedure described for the preparation of the saturated compound 89a, 141 mg (0.33 mmol) of the adduct 91b in 3 mL of ethyl acetate with 0.1 mL of Raney nickel afforded, after chromatography on 15 g of silica gel with 7% ethyl acetate-petroleum ether, 130 mg (92%) of the saturated compound 92b.

Benzyl 2S-[5R-ethyl-3S-methyl-5-(5S-methoxymethylenoxy-6S-methyl-2R-tetrahydropyranyl)-2S-tetrahydrofuryl]-butyl ether (92c). By the procedure described for the preparation of the saturated compound 89a, 77.4 mg (0.18 mmol) of the adduct 91c in 3 mL of ethyl acetate with 0.1 mL of Raney nickel afforded, after chromatography on 10 g of silica gel with 7% ethyl acetate-cyclohexane, 65 mg (84%) of the saturated compound 92c.

Benzyl 2S-[5S-ethyl-3S-methyl-5-(5S-methoxymethylenoxy-6S-methyl-2R-tetrahydropyranyl)-2S-tetrahydrofuryl]-butyl ether (92d). By the procedure described for the preparation of the saturated compound 89a, 300 mg (0.69 mmol) of the adduct 91d in 5 mL of ethyl acetate with 0.1 mL of Raney nickel afforded, after chromatography on 25 g of silica gel with 7% ethyl acetate-cyclohexane, 270 mg (90%) of the saturated compound 92d.

Benzyl 2R-[5R-ethyl-3S-methyl-5-(5S-hydroxy-6S-methyl-2R-tetrahydropyranyl)-2S-tetrahydrofuryl]-butyl ether (93a). By the procedure described for the preparation of the alcohol 21, 40 mg (0.09 mmol) of the methoxymethyl ether 92a in 3 mL of THF and 0.75 mL of 10% aqueous HCl afforded, after chromatography on 7 g of silica gel with 25% ethyl acetate-petroleum ether, 35 mg (97%) of the alcohol 93a.

Benzyl 2R-[5S-ethyl-3S-methyl-5-(5S-hydroxy-6S-methyl-2R-tetrahydropyranyl)-2S-tetrahydrofuryl]-butyl ether (93b). By the procedure described for the preparation of the alcohol 21, 120 mg

(0.28 mmol) of the methoxymethyl ether 92b in 4 mL of THF and 1 mL of 10% aqueous HCl afforded, after chromatography on 10 g of silica gel with 25% ethyl acetate-petroleum ether, 105 mg (97%) of the alcohol 93b.

Benzyl 2S-[5R-ethyl-3S-methyl-5-(5S-hydroxy-6S-methyl-2R-tetrahydropyranyl)-2S-tetrahydrofuryl]-butyl ether (93c). By the procedure described for the preparation of the alcohol 21, 54.8 mg (0.13 mmol) of the methoxymethyl ether 92c in 4 mL of THF and 1 mL of 10% aqueous HCl afforded, after chromatography on 10 g of silica gel with 20% ethyl acetate-cyclohexane, 45 mg (92%) of the alcohol 93c.

Benzyl 2S-[5S-ethyl-3S-methyl-5-(5S-hydroxy-6S-methyl-2R-tetrahydropyranyl)-2S-tetrahydrofuryl]-butyl ether (87). By the procedure described for the preparation of the alcohol 21, 265 mg of 10% aqueous HCl afforded, after chromatography on 20 g of silica gel with 25% ethyl acetate-petroleum ether, 240 mg (100%) of the alcohol 87.

Benzyl 2S-[5S-ethyl-3S-methyl-5-(6S-methyl-5-oxo-2R-tetrahydropyranyl)-2S-tetrahydrofuryl]-butyl ether (94). To a stirred solution of 0.06 mL of oxalyl chloride (0.69 mmol) in 2 mL of dry dichloromethane at -60°C under argon was added 0.11 mL (1.55 mmol) of dimethylsulfoxide. After 10 min. a solution of 240 mg (0.61 mmol) of the alcohol 87 in 1.5 mL of dry dichloromethane was added to the reaction mixture. After 15 min. the reaction mixture was treated with 0.44 mL (3.16 mmol) of dry triethylamine,

then allowed to warm to room temperature and diluted with 40 mL of ether. It was subsequently washed with 15 mL of water, 15 mL of saturated aqueous $NaHCO_3$, 15 mL of saturated NaCl, and then dried ($MgSO_4$). Removal of the solvents and chromatography of the residue on 20 g of silica gel with 10% ethyl acetate-cyclohexane afforded 225 mg (94%) of the ketone 94.

Benzyl 2S-[5S-ethyl-3S-methyl-5-(6S-methyl-5-methylene-2R-tetrahydropyranyl)-2S-tetrahydrofuryl]-butyl ether (95). By the procedure described for the preparation of the adduct 91a, 214.5 mg (0.55 mmol) of the ketone 94 in 4 mL of dry THF with 1.38 mmol of methylenetriphenylphosphorane afforded, after chromatography on 20 g of silica gel with 4% ethyl acetate-cyclohexane, 200 mg (94%) of the adduct 95.

Benzyl 2S-[5S-ethyl-3S-methyl-5-(3R and 3S-1,5-dioxo-4S-methyl-spiro[2.5]-6R-octyl)-2S-tetrahydrofuryl]-butyl ether (96a and 96b). To a stirred solution of 191 mg (0.49 mmol) of the adduct 95 in 5 mL of dry dichloromethane at 0°C under argon was added 160 mg (1.9 mmol) of solid $NaHCO_3$ and 160 mg (0.74-0.83 mmol) of 80-90% m-chloroperbenzoic acid. Cooling was then discontinued and the reaction mixture was stirred at room temperature for 3 hours and then treated with 2 mL of 10% aqueous Na_2SO_3. The resulting mixture was diluted with 60 mL of ether, then washed with two 20 mL portions of saturated aqueous $NaHCO_3$, 20 mL of saturated aqueous NaCl, and then dried ($MgSO_4$). Removal of the solvents and chromatography of the residue on 20 g of silica gel with 10% ethyl acetate-

petroleum ether afforded 40 mg of the epoxide 96a and 141 mg of the epoxide 96b, or a ratio of 3.5:1 of 91% combined yield.

Benzyl 2S-[5S-ethyl-3S-methyl-5-(5R-ethyl-5-hydroxy-6S-methyl-2R-tetrahydropyranyl)-2S-tetrahydrofuryl]-butyl ether (84). By the procedure described for the preparation of the alcohol 34a,b, 120 mg (0.30 mmol) of the epoxide 96a in 3 mL of dry n-pentane with 320 mg (1.56 mmol) of copper (I) bromide dimethylsulfide complex and 1.4 mL (3.08 mmol) of 2.2 M methyllithium in ether afforded, after chromatography on 10 g of silica gel column with 15% ethyl acetate-petroleum ether, 120 mg (90%) of the alcohol 84.

2S-[5S-Ethyl-3S-methyl-5-(5R-ethyl-5-hydroxy-6S-methyl-2R-tetrahydropyranyl)-2S-tetrahydrofuryl]-butan-1-ol (83). By the procedure described for the preparation of the lactol 74 from a mixture of the benzyl glycosides 73a and 73b, 53.8 mg (0.13 mmol) of the monobenzyl ether 84 in 1 mL of dry THF with 0.5 cm (3 mmol) of lithium wire in 10 mL of anhydrous ammonia and 250 mg (4.7 mmol) of anhydrous ammonium chloride afforded, after chromatography on 10 g of silica gel with 40% ethyl acetate-petroleum ether, 41.5 mg (98%) of the diol 83.

2R-[5S-Ethyl-3S-methyl-5-(5R-ethyl-5-hydroxy-6S-methyl-2R-tetrahydropyranyl)-2S-tetrahydrofuryl]-butanal (97). By the procedure described for the preparation of the aldehyde 38, 80 mg (0.24 mmol) of the diol 83 in 3 mL of dry dichloromethane with 10 mg (0.12 mmol) of anhydrous sodium acetate and 133 mg (0.62 mmol)

of pyridinium chlorochromate afforded, after chromatography on 10 g of silica gel with 40% ether-petroleum ether, 62 mg (78%) of the aldehyde 97.

4S-[5S-Ethyl-3S-methyl-5-(5R-ethyl-5-hydroxy-6S-methyl-2R-tetrahydropyranyl)-2S-tetrahydrofuryl]-hexan-3-ol (98). By the procedure described for the preparation of the alcohols 25a,b, 62 mg (0.19 mmol) of the aldehyde 97 in 4 mL of dry THF with 0.72 mL (0.58 mmol) of 0.8 M solution of ethylmagnesium bromide in THF afforded, after chromatography on 10 g of silica gel with 50% ether-petroleum ether, 60 mg (89%) of the alcohols 98a,b as a mixture of diastereomers.

4R-[5S-Ethyl-3S-methyl-5-(5R-ethyl-5-hydroxy-6S-methyl-2R-tetrahydropyranyl)-2S-tetrahydrofuryl]-hexan-3-one (99). By the procedure described for the preparation of the aldehyde 38, 35 mg (0.10 mmol) of the alcohols 98a,b in 1 mL of dry dichloromethane with 50 mg (0.23 mmol) of pyridinium chlorochromate afforded, after chromatography on 10 g of silica gel with 35% ether-petroleum ether, 31.4 mg (90%) of the ketone 99.

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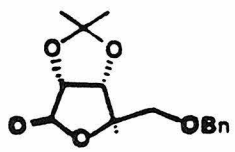
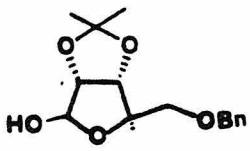
APPENDIX

Physical properties of all isolated intermediates.



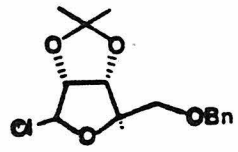
2a

R_f = 0.33 (10% ethyl acetate in benzene)
evap. dis. 120°-130°C, 0.03 mmHg
$[\alpha]_D^{25}$ = -42.9° (C = 1.40,$CHCl_3$)
IR($CHCl_3$) 1780, 1450, 1380, 1370, 1220, 1100, 1025, 970, 930, 850, 700 cm^{-1}
^{1}H-NMR($CDCl_3$) δ 1.37, 1.47 (s,6H,$(CH_3)_2C$), 3.50 (d,2H,J=2Hz,CCH_2O), 4.52 (bs,2H,$C_6H_5\underline{CH_2}$), 4.63 (t,1H,J=2Hz,H4), 4.65 (d,1H,J=2Hz,H3), 4.78 (d,1H,J=2Hz,H2), 7.30 (bs,5H,C_6H_5)
Anal. calcd. for $C_{15}H_{18}O_5$: C, 64.74; H, 6.52.
Found: C, 64.81; H, 6.53.



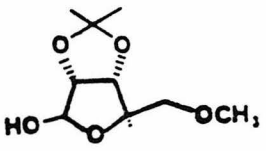
3a

R_f = 0.28 (20% ethyl acetate in benzene)
evap. dis. 120°-130°C, 0.04 mmHg
$[\alpha]_D^{25}$ = -0.5° (C=0.82,$CHCl_3$)
IR($CHCl_3$) 3600, 3400, 1380, 1370, 1210, 1160, 1090, 870, 700 cm^{-1}
^{1}H-NMR($CDCl_3$) δ (major, minor) 1.30, 1.37 (s,3H,$\underline{CH_3}CCH_3$), 1.47, 1.53 (s,3H,$\underline{CH_3}CCH_3$), 3.47 (d,2H,J=4Hz,CCH_2O), 5.13 (d,1H, J=11Hz,H1), 7.30 (bs,5H,C_6H_5)
Anal. calcd. for $C_{15}H_{20}O_5$: C, 64.27; H, 7.19.
Found: C, 64.24; H, 7.09.



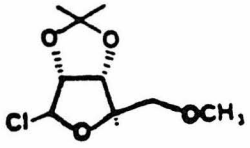
4a

evap. dis. 120°-125°C, 0.02 mmHg
$[\alpha]_D^{24}$= -41.7° (C = 1.155,$CHCl_3$)
IR($CHCl_3$) 1490, 1375, 1370, 1210, 1150, 1090, 860, 690 cm^{-1}
^{1}H-NMR($CDCl_3$) δ (major, minor) 1.30, 1.33 (s,3H,$\underline{CH_3}CCH_3$), 1.43, 1.62 (s,3H,$\underline{CH_3}CCH_3$), 3.65, 3.70 (d,2H,J=7Hz,CCH_2O), 6.10 (s,1H,H1), 7.27 (bs,5H,C_6H_5)
Anal. calcd. for $C_{15}H_{19}O_4Cl$: C, 60.30; H, 6.41.
Found: C, 60.23; H, 6.38.



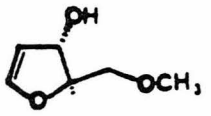
3b

R_f = 0.3 (35% ethyl acetate in benzene)
evap. dis. 60°-70°C, 0.04 mmHg
$[\alpha]_D^{26}$ = -18.8° (C = 1.68,$CHCl_3$)
IR($CHCl_3$) 3380, 1440, 1370, 1230, 1060, 900, 560 cm^{-1}
^{1}H-NMR($CDCl_3$) δ (major, minor) 1.32, 1.40 (s,3H,CH_3CCH_3), 1.47, 1.57 (s,3H,CH_3CCH_3), 3.43, 3.33 (s,3H,OCH_3), 3.53 (d,2H,CCH_2O), 5.28, 5.35 (d,1H,J=10Hz,H1)
Anal. calcd. for $C_9H_{16}O_5$: C, 52.93; H, 7.90.
Found: C, 52.84; H. 7.75.



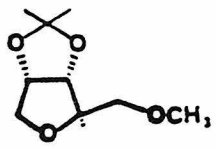
4b

evap. dis. 70°-80°C, 0.2 mmHg
$[\alpha]_D^{27}$= -71.0° (C = 1.80,$CHCl_3$)
IR($CHCl_3$) 1380, 1210, 1160, 1100, 1060, 870, 700 cm^{-1}
^{1}H-NMR($CDCl_3$) δ 1.33, 1.47 (s,6H,$(CH_3)_2C$), 3.40 (s,3H,OCH_3), 3.62 (d,2H,J=7Hz,CCH_2O), 4.47 (dt,1H,J=2Hz,7Hz,H4), 4.82 (dd,1H, J=2Hz,6Hz,H3), 5.05 (d,1H,J=6Hz,H2), 6.15 (s,1H,H])
Anal. calcd. for $C_9H_{15}O_4Cl$: C, 48.55; H, 6.79.
Found: C, 48.64, H, 6.72.



5

R_f = 0.22 (50% ethyl acetate in benzene)
evap. dis. 80°-90°C, 0.2 mmHg
$[\alpha]_D^{27}$= +318.1° (C = 0.83,$CHCl_3$)
IR($CHCl_3$) 3580, 3420, 1605, 1380, 1190, 1140, 1070, 1000, 920, 850 cm^{-1}
^{1}H-NMR($CDCl_3$) δ 3.38 (s,3H,OCH), 5.10 (dd,1H,J=3Hz,3Hz,H2), 6.45 (bd,1H, J=3Hz,H1)
Anal. calcd. for $C_6H_{10}O_3$: C, 55.37; H, 7.74.
Found: C, 55.42; H, 7.78.

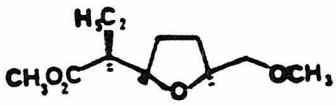


6

R_f = 0.23 (20% ethyl acetate in benzene)
evap. dis. 50° 60°C, 0.2 mmHg
$[\alpha]_D^{25}$ = +34.1° (C = 1.07, $CHCl_3$)
IR($CHCl_3$) 1450, 1375, 1225, 1085, 850 cm^{-1}
^{1}H-NMR($CDCl_3$) δ 1.33, 1.50 (s,6H,$(CH_3)_2C$), 3.33 (s,3H,OCH_3), 3.43 (d,2H,J=4Hz,CCH_2O)
Anal. calcd. for $C_9H_{16}O_4$: C, 57.43; H, 8.57.
Found: C, 57.49; H, 8.58.

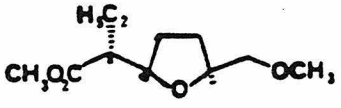
8a,b

R_f = 0.29 (50% ether in petroleum ether)
evap. dis. 50°-60°C, 0.005 mmHg
IR($CHCl_3$) 1720, 1450, 1430, 1190, 1165, 1070 cm^{-1}
^{1}H-NMR($CDCl_3$) δ 0.90 (t,3H,J=6Hz,CH_3CH_2), 3.40 (s,3H,OCH_3), 3.70 (s,3H,CO_2CH_3), 5.90 (m,2H,HC=CH)
Anal. calcd. for $C_{11}H_{18}O_4$: C, 61.66; H, 8.47.
Found: C, 61.79; H, 8.60.



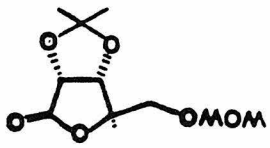
9a

R_f = 0.10 (35% ether in petroleum ether)
evap. dis. 50°-60°C, 0.005 mmHg
$[\alpha]_D^{27}$ = +7.4° (C = 0.78, $CHCl_3$)
IR($CHCl_3$) 1720, 1450, 1380, 1230, 1080, 990 cm^{-1}
^{1}H-NMR($CDCl_3$) δ 0.90 (t,3H,J=7Hz,CH_3CH_2), 3.33 (s,3H,OCH_3), 3.68 (s,3H,CO_2CH_3)
Anal. calcd. for $C_{11}H_{20}O_4$: C, 61.09; H, 9.32.
Found: C, 61.13; H, 9.35.



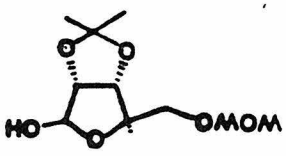
9b

R_f = 0.18 (35% ether in petroleum ether)
evap. dis. 50°-60°C, 0.005 mmHg
$[\alpha]_D^{23}$ = + 2.6° (C , 0.96, $CHCl_3$)
IR($CHCl_3$) 1720, 1460, 1270, 1200, 1160, 1080, 1000 cm^{-1}
^{1}H-NMR($CDCl_3$) δ 0.89 (t,3H,J=7Hz,CH_3CH_2), 3.34 (s,3H,OCH_3), 3.63 (s,3H,CO_2CH_3)
Anal. calcd. for $C_{11}H_{20}O_4$: C, 61.09; H, 9.32.
Found: C, 61.05, H, 9.39.



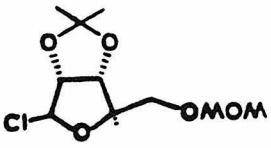
10

R_f = 0.45 (40% ethyl acetate in benzene)
evap. dis. 90°-100:C, 0.005 mmHg
$[\alpha]_D^{25}$ = -54.7° (C = 0.90, $CHCl_3$)
IR($CHCl_3$) 1780, 1380, 1370, 1150, 1020
^{1}H-NMR($CDCl_3$) δ 1.40, 1.48 (s,6H,$C(CH_3)_2$), 3.33 (s,3H,OCH_3), 3.75 (d,2H,J=3Hz,CCH_2O), 4.58 (s,2H,H2 and H3), 4.67 (t,1H,J=3Hz, H4), 4.77 (bs,2H,OCH_2O)
Anal. calcd. for $C_{10}H_{16}O_6$: C, 51.72; H, 6.94.
Found: C, 51.76; H, 6.94.



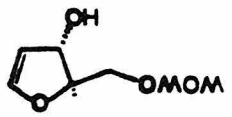
11

R_f = 0.20 (60% ether in petroleum ether)
evap. dis. 80°-90°C, 0.005 mmHg
$[\alpha]_D^{25}$ = +0.9° (C = 0.89, $CHCl_3$)
IR($CHCl_3$) 3400, 1450. 1440, 1380, 1370, 1220, 1150, 1060, 1020, 920, 860 cm^{-1}
^{1}H-NMR($CDCl_3$) δ (major, minor) 1.32, 1.42 (s,3H,H_3CCCH_3), 1.47, 1.53 (s,3H,H_3CCCH_3), 3.37 (s,3H,OCH_3), 3.63, 3.60 (d,2H,J=5Hz, CCH_2O), 4.65 (bs,2H,OCH_2O), 5.32, 5.37 (d,1H,J_{major} = 9Hz, J_{minor} = 7Hz, OCHOC)
Anal. calcd. for: $C_{10}H_{18}O_6$:C,51.27; H,7.75
Found: C, 51.15; H, 7.64.



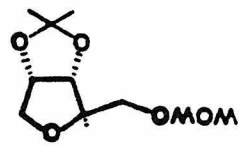
12

evap. dis. 70°-80°C, 0.005 mmHg
$[\alpha]_D^{25}$ = -45.4° (C = 1.14,$CHCl_3$)
IR($CHCl_3$) 1450, 1380, 1370, 1210, 1140, 1060, 910, 870, 690 cm^{-1}
^{1}H-NMR($CDCl_3$) δ (major, minor) 1.33, 1.37 (s,3H,H_3CCCH_3), 1.47, 1.65 (s,3H, H_3CCH_3), 3.38 (s,3H,OCH_3), 4.63 (s,2H, OCH_2O), 6.13, 6.18 (s,1H,ClCHOC)
Anal. calcd. for $C_{10}H_{17}ClO_5$: C, 47.53; H, 6.78.
Found: C, 47.46; H, 6.75



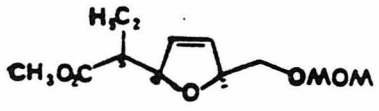
13

R_f = 0.25 (75% ether in petroleum ether)
evap. dis. 70°-80°C, 0.005 mmHg
$[\alpha]_D^{24}$ = +258.8° (C = 0.91, $CHCl_3$)
IR($CHCl_3$) 3560, 3450, 1605, 1380, 1150, 1040, 920 cm^{-1}
^{1}H-NMR($CDCl_3$) δ 3.37 (s,3H,OCH_3), 3.55 (d,2H,J=6Hz, CCH_2O), 4.63 (s,2H,OCH_2O), 5.13 (dd,1H,J=3Hz,3Hz, C=CHC). 6.52 (d,1H,J=3Hz,OCH=C)
Anal. calcd. for $C_7H_{12}O_4$: C, 52.49; H, 7.55.
Found: C, 52.41; H, 7.65



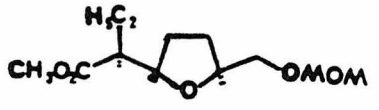
14

R_f = 0.52 (75% ether in petroleum ether)
evap. dis. 70°-80°C, 0.005 mmHg
$[\alpha]_D^{24}$ = +36.4° (C = 0.94,$CHCl_3$)
IR($CHCl_3$) 1380, 1370, 1210, 1150, 1100, 1030, 910, 850 cm^{-1}
^{1}H-NMR($CDCl_3$) δ 1.35, 1.52 (s,6H,$C(CH_3)_2$), 3.37 (s,3H,OCH_3), 3.58 (d,2H,J=5Hz,CCH_2O), 3.95, 4.00 (s,2H,OCHHC), 4.60 (s,2H,OCH_2O)
Anal. calcd. for $C_{10}H_{18}O_5$: C, 55.03; H, 8.31.
Found: C, 55.16; H. 8.23.



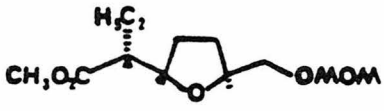
15a,b

R_f = 0.29 (40% ether in petroleum ether)
evap. dis. 60°-70°C, .005 mmHg
IR($CHCl_3$) 1720, 1460, 1430, 1140, 1030 cm^{-1}
^{1}H-NMR($CDCl_3$) δ 0.90 (t,3H,J=6Hz,CH_3CH_2), 3.33 (s,3H,OCH_3), 3.53 (d,2H,J=5Hz,CCH_2O), 3.72 (s,3H,CO_2CH_3), 4.62 (s,2H,OCH_2O), 5.92 (m,2H,HC=CH)
Anal. calcd. for $C_{12}H_{20}O_5$: C, 59.00; H, 8.25.
Found: C, 58.92; H, 8.21.



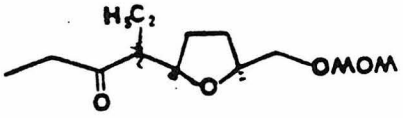
16a

R_f = 0.25 (50% ether in petroleum ether)
evap. dis. 70°-80°C, 0.005 mmHg
$[\alpha]_D^{27}$ = +3.4° (C = 1.145,$CHCl_3$)
IR($CHCl_3$) 1730, 1460, 1430, 1040 cm^{-1}
^{1}H-NMR($CDCl_3$) δ 0.89 (t,3H,J=7Hz,CH_3CH_2), 3.33 (s,3H,OCH_3), 3.46 (d,2H,J=6Hz,CCH_2O), 3.69 (s,3H,CO_2CH_3), 4.60 (s,2H,OCH_2O)
Anal. calcd. for $C_{12}H_{22}O_5$: C, 58.52; H, 9.00
Found: C, 58.58; H, 9.05.



16b

R_f = 0.40 (50% ether in petroleum ether)
evap. dis. 70°-80°C, .005 mmHg
$[\alpha]_D^{25}$ = -17.1° (C = 0.90, $CHCl_3$)
IR($CHCl_3$) 1740, 1470, 1160, 1040 cm^{-1}
^{1}H-NMR($CDCl_3$) δ 0.88 (t,3H,J=7Hz,CH_3CH_2), 3.33 (s,3H,OCH_3), 3.46 (d,2H,J=6Hz,CCH_2O), 3.65 (s,3H,CO_2CH_3), 4.60 (s,2H,OCH_2O)
Anal. calcd. for $C_{12}H_{22}O_5$: C, 58.52; H, 9.00.
Found: C, 58.47; H, 8.97.

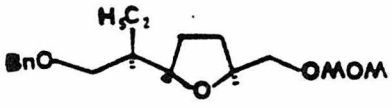


18a,b

R_f = 0.15 (20% ethyl acetate in benzene)
evap. dis. 110°-120°C, 0.005 mmHg
IR($CHCl_3$) 1705, 1220, 1040, 930, 750, 670 cm^{-1}
^{1}H-NMR($CDCl_3$) δ 0.80 (t,J=7Hz,3H,CH_3CH_2), 1.00 (t,J=7Hz,3H,CH_3CH_2CO), 3.30 (s,3H, OCH_3), 3.41 (d,J=6Hz,2H,CCH_2O), 4.56 (s,2H,OCH_2O)
Anal. calcd. for $C_{13}H_{24}O_4$: C, 63.91; H, 9.90.
Found: C, 63.92; J, 9.79.

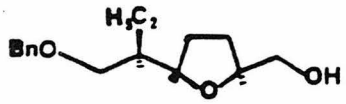
19

R_f = 0.13 (50% ethyl aceyate in cyclohexane)
evap. dis. 70°-80°C, 0.005 mmHg
$[\alpha]_D^{22}$ = -19.9° (C = 0.96,$CHCl_3$)
IR($CHCl_3$) 3500, 1470, 1150, 1110, 1040 cm^{-1}
^{1}H-NMR($CDCl_3$) δ 0.90 (t,3H,J=6Hz,CH_3CH_2), 3.33 (s,3H,OCH_3), 4.60 (s,2H,OCH_2O)
Anal. calcd. for $C_{11}H_{22}O_4$: C, 60.52; H, 10.16.
Found: C, 60.47; H, 10.21.



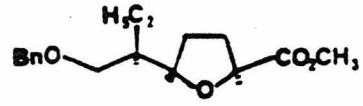
20

R_f = 0.20 (20% ethyl acetate in cyclohexane)
evap. dis. 110°-120°C, 0.005 mmHg
$[\alpha]_D^{23}$ = -13.2° (C = 1.455,$CHCl_3$)
IR($CHCl_3$) 1460, 1370, 1150, 1100, 1080, 1040 cm^{-1}
^{1}H-NMR($CDCl_3$) δ 0.87 (t,3H,J=6Hz,CH_3CH_2), 3.33 (s,3H,OCH_3), 4.43 (s,2H,$C_6H_5CH_2$), 4.67 (s,2H,OCH_2O), 7.37 (s,5H,C_6H_5)
Anal. calcd. for $C_{18}H_{28}O_4$: C, 70.10; H, 9.15.
Found: C, 69.98; H, 9.06.



21

R_f = 0.19 (35% ethyl acetate in cyclohexane)
evap. dis. 110°-120°C, .005 mmHg
$[\alpha]_D^{23}$ = +4.5° (C = 1.215,$CHCl_3$)
IR($CHCl_3$) 3580, 3450, 1460, 1360, 1100, 1030 cm^{-1}
^{1}H-NMR($CDCl_3$) δ 0.90 (t,3H,J=6Hz,CH_3CH_2), 3.50 (d,2H,J=6Hz,CCH_2OC), 4.45 (s,2H, $C_6H_5CH_2$), 7.30 (bs,5H,C_6H_5)
Anal. calcd. for $C_{16}H_{24}O_3$: C, 72.69; H, 9.15.
Found: C, 72.74; H, 9.20.

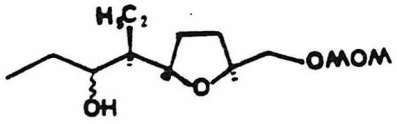


23

R_f = 0.24 (15% ethyl acetate in cyclohexane)
evap. dis. 110°-120°C, 0.005 mmHg
IR($CHCl_3$) 1740, 1460, 1440, 1220, 1085 cm^{-1}
^{1}H-NMR($CDCl_3$) δ 0.92 (t,3H,J=6Hz,CH_3CH_2), 3.50 (d,2H,J=6Hz,OCH_2C), 3.70 (s,3H,CO_2CH_3), 4.47 (s,2H,$C_6H_5CH_2$), 7.30 (s,5H,C_6H_5)
Anal. calcd.for $C_{17}H_{24}O_4$: C, 69.84; H, 8.27.
Found: C, 69.76; H, 8.30.

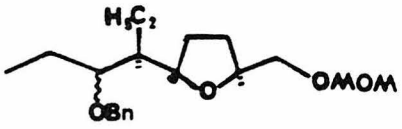
24

R_f = 0.18 (25% ethyl acetate in cyclohexane)
evap. dis. 70°-80°C, 0.005 mmHg
$[\alpha]_D^{25}$ = +21.0°)C = 1.26, $CHCl_3$)
IR($CHCl_3$) 1715, 1450, 1150, 1100, 1040 cm^{-1}
^{1}H-NMR($CDCl_3$) δ 0.90 (t,3H,J=7Hz,CH_3CH_2), 3.33 (s,3H,OCH_3), 3.47 (d,2H,J=4Hz,CCH_2O), 4.60 (bs,2H,OCH_2O), 9.70 (d,1H,J=4Hz,CHO)
Anal. calcd. for $C_{11}H_{20}O_4$: C, 61.09; H, 9.32.
Found: C, 61.07; H, 9.28



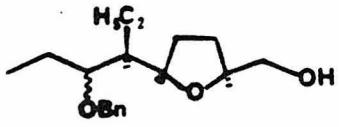
25a,b

R_f = 0.14 (50% ether in petroleum ether)
evap. dis. 80°-90°C, 0.005 mmHg
IR($CHCl_3$) 3450, 1460, 1140, 1110, 1040, 910 cm^{-1}
^{1}H-NMR($CDCl_3$) δ 3.33 (s,3H,OCH_3), 3.47 (d,2H,J=4Hz,CCH_2O), 4.60 (s,2H,OCH_2O)
Anal. calcd. for $C_{13}H_{26}O_4$: C, 63.38; H, 10.64.
Found: C, 63.44; H, 10.53.



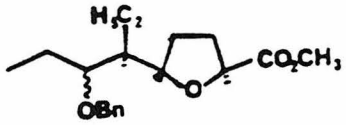
26a,b

R_f = 0.31 (20% ethyl acetate in cyclohexane)
evap. dis. 100°-110°C, 0.005 mmHg
IR($CHCl_3$) 1470, 1160, 1120, 1090, 1040 cm^{-1}
^{1}H-NMR($CDCl_3$) δ 3.33 (s,3H,OCH_3), 3.47 (d,2H,J=4Hz,CCH_2O), 4.48 (s,2H,$C_6H_5CH_2$), 4.62 (s,2H,OCH_2O), 7.31 (bs,5H,C_6H_5)
Anal. calcd. for $C_{20}H_{32}O_4$: C, 71.39; H, 9.59.
Found: C, 71.35; H, 9.58.



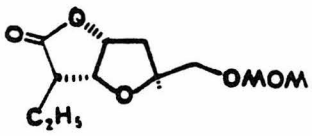
27a,b

R_f = 0.17 (30% ethyl acetate in cyclohexane)
evap. dis. 90°-100°C, 0.005 mmHg
IR($CHCl_3$) 3600, 3450, 1460, 1090, 1060, 1020 cm^{-1}
^{1}H-NMR($CDCl_3$) δ 0.93, 0.97 (t,6H,J=7Hz, CH_3CH_2), 4.50, 4.56 (s,2H,$C_6H_5CH_2$), 7.33 (bs,5H,C_6H_5)
Anal. calcd. for $C_{18}H_{28}O_3$: C, 73.93; H, 9.65.
Found: C, 73.74; H, 9.57.



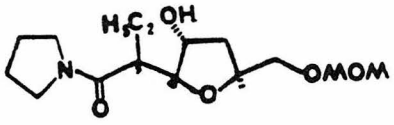
29a,b

R_f = 0.27. 0.31 (15% ethyl acetate in cyclohexane)
evap. dis. 100°-110°C, 0.005 mmHg
IR($CHCl_3$) 1740, 1460, 1220, 1080 cm^{-1}
^{1}H-NMR($CDCl_3$) δ 3.64, 3.69 (s,3H,CO_2CH_3), 4.50 (s,2H,$C_6H_5CH_2$), 7.30 (bs,5H,C_6H_5)
Anal. calcd. for $C_{19}H_{28}O_4$: C, 71.22; H, 8.81.
Found: C, 71.18; H, 8.82.



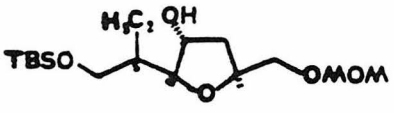
30a,b

R_f = 0.10 (50% ethyl acetate in cyclohexane)
evap. dis. 90°-100°C, 0.005 mmHg
IR($CHCl_3$) 1770, 1160, 1040 cm^{-1}
^{1}H-NMR($CDCl_3$) δ (minor,major) 1.04, 1.07 (t,3H,J=6Hz,CH_3CH_2), 3.33 (s,3H,OCH_3), 3.57, 3.62 (d,2H,J=4Hz,CCH_2O), 4.60 (s,2H, OCH_2O), 4.72 (dd,1H,J=4Hz,5Hz,CO_2CH), 5.00 (dd,1H,J=5Hz,5Hz,CO_2CCH)
Anal. calcd. for $C_{11}H_{18}O_5$: C, 57.38; H, 7.88.
Found: C, 57.25; H, 7.86.



31a,b

R_f = 0.20 (40% acetone in ethyl acetate)
amorphous white solid
IR($CHCl_3$) 3600, 3380, 1640, 1450, 1150, 1030 cm^{-1}
^{1}H-NMR($CDCl_3$) δ 0.87 (t,3H,J=7Hz,CH_3CH_2), 3.33 (s,3H,OCH_3), 3.50 (d,2H,J=5Hz,CCH_2O), 4.00 (dd,1H,J=3Hz,7Hz,$OCHCHOH$) 4.61 (s,2H,OCH_2O)
Anal. calcd. for $C_{15}H_{27}O_5N$: C, 59.78; H, 9.03; N, 4.65.
Found: C, 59.76; H, 9.05; N, 4.57.

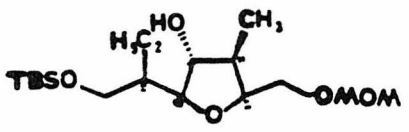


32a,b

R_f=0.21 (35% ethyl acetate in cyclohexane)
evap. dis. 100°-110° C, .005 mmHg.
IR($CHCl_3$) 3350,1475,1485,1260,1045,840 cm^{-1}
^{1}H-NMR($CDCl_3$)δ 0.08(s,6H,$(CH_3)_2Si$), 0.91 (s,9H,$(CH_3)_3C$), 3.33 (s,3H,OCH_3),3.52 (d, 2H,J=5 Hz,CCH_2O), 4.63 (s,2H,OCH_2O)
Anal. calcd. for $C_{17}H_{36}O_5Si$: C,58.58; H,10.41
Found: C, 58.53; H, 10.34.

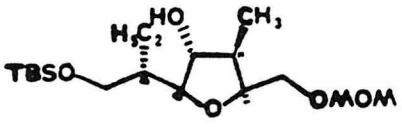
33a,b

R_f=0.15 (10% ethyl acetate in cyclohexane)
evap. dis. 95°-105°C, .005 mmHg
IR($CHCl_3$)1485,1475,1260,1160,1120,1040,840 cm^{-1}
^{1}H-NMR($CDCl_3$)δ 0.02(s,6H,$(CH_3)_2Si$), 0.87 (s, 9H,$(CH_3)_3C$), 3.30 (s,3H,OCH_3), 3.53 (d,2H, J=5Hz,CCH_2O), 4.57 (s,2H,OCH_2O).
Anal. calcd. for $C_{17}H_{34}O_5Si$: C, 58.92; H, 9.89
Found: C, 58.98; H, 9.88.



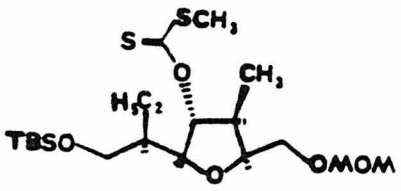
34a

R_f=0.17 (25% ethyl acetate in cyclohexane)
evap. dis. 110°-120°C, .005 mmHg
$[\alpha]_D^{22}$=+4.0° (C=0.93,$CHCl_3$)
IR($CHCl_3$)3360,1480,1470,1260,1040,840 cm^{-1}
^{1}H-NMR($CDCl_3$)δ0.08(s,6H,$(CH_3)_2Si$),0.90 (s, 9H,$(CH_3)_3C$), 0.94(d,3H,J=8 Hz,$CHCH_3$),3.30 (s,3H,OCH_3),4.57(s,2H,OCH_2O).
Anal. calcd. for $C_{18}H_{38}O_5Si$: C, 59.63; H, 10.56
Found: C, 59.65; H, 10.62



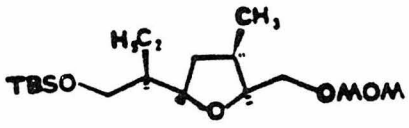
34b

R_f = 0.23 (25% ethyl acetate in cyclohexane)
evap. dis. 100°-120°C, 0.005 mmHg
$[\alpha]_D^{23}$ = +11.7° (C = 1.02,$CHCl_3$)
IR($CHCl_3$) 3430, 1460, 1260, 1040, 840 cm^{-1}
^{1}H-NMR($CDCl_3$) δ 0.10 (s,6H,$(CH_3)_2Si$), 0.93 (s,9H,$(CH_3)_3C$), 3.33 (s,3H,OCH_3), 4.62 (s,2H,OCH_2O)
Anal. calcd. for $C_{18}H_{38}O_5Si$: C, 59.63; H, 10.56.
Found: C, 59.64; H, 10.50.



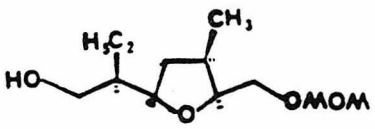
35

R_f = 0.21 (5% ethyl acetate in cyclohexane)
evap. dis. 130°-140°C, 0.005 mmHg
$[\alpha]_D^{22}$ = -3.5° (C = 1.50,$CHCl_3$)
IR($CHCl_3$) 1480, 1230, 1070, 1050, 850 cm^{-1}
^{1}H-NMR($CDCl_3$) δ 0.03 (s,6H,$(CH_3)_2Si$), 0.87 (s,9H,$(CH_3)_3C$), 1.05 (d,3H, J = 7Hz,$CHCH_3$), 2.53 (s,3H,SCH_3), 3.35 (s,3H,OCH_3), 4.63 (s,2H,OCH_2O), 5.67 (d,1H,J=4Hz,S_2COCH)
Anal. calcd. for $C_{20}H_{40}O_5Si$: C, 53.06; H, 8.91; S, 14.16.
Found: C, 53.27; H, 8.91; S, 14.11.



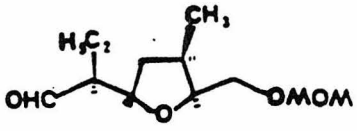
36

R_f = 0.19 (5% ethyl acetate in cyclohexane)
evap. dis. 75°-85°C, 0.005 mmHg
$[\alpha]_D^{24}$ = -11.1° (C = 1.055,$CHCl_3$)
IR($CHCl_3$) 1480, 1260, 1100, 1040, 840 cm^{-1}
^{1}H-NMR($CDCl_3$) δ 0.03 (s,6H,$(CH_3)_2Si$), 0.89 (s,9H,$(CH_3)_3C$), 0.95 (d,3H,J=7Hz, $CHCH_3$), 3.33 (s,3H,OCH_3), 3.52 (d,2H, J=6Hz,CCH_2O), 3.63 (d,2H,J=5Hz,$SiOCH_2$), 4.60 (s,2H,OCH_2O).
Anal. calcd. for $C_{18}H_{38}O_4Si$: C, 62.38; H, 11.05.
Found: C, 62.26; H, 11.05.



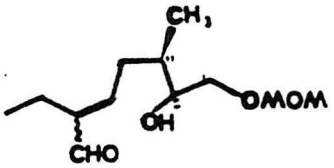
37

R_f = 0.13 (35% ethyl acetate in cyclohexane)
evap. dis. 60°-70°C, 0.005 mmHg
$[\alpha]_D^{23}$ = -21.0° (C = 1.405,$CHCl_3$)
IR($CHCl_3$) 3460, 1470, 1160, 1110, 1050 cm^{-1}
^{1}H-NMR($CDCl_3$) δ 0.96 (d,3H,J=7Hz,$CHCH_3$), 3.33 (s,3H,OCH_3), 3.53 (d,2H,J=6Hz, CCH_2OC), 4.60 (s,2H,OCH_2O)
Anal. calcd. for $C_{12}H_{24}O_4$: C, 62.04; H, 10.41.
Found: C, 62.16; H, 10.48.



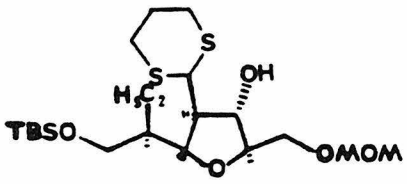
38

R_f = 0.20 (25% ethyl acetate in cyclohexane)
evap. dis. 60°-70°C, 0.005 mmHg
$[\alpha]_D^{23}$ = +22.5° (C = 1.11,$CHCl_3$)
IR($CHCl_3$) 2750, 1725, 1475, 1260, 1220, 1040, 920 cm^{-1}
^{1}H-NMR($CDCl_3$) δ 0.91 (t,3H,J=6Hz,CH_3CH_2), 1.00 (d,3H,J=7Hz,$CHCH_3$), 3.33 (s,3H, OCH_3), 3.53 (d,2H,J=6Hz,CCH_2OC), 4.07 (dd,1H,J=6Hz,12Hz,OCHCC), 4.33 (dd,1H, J=7Hz,14Hz,OCHCC), 4.60 (s,2H,OCH_2O), 9.72 (d,1H,J=4Hz,CHO)
Anal. calcd. for $C_{12}H_{22}O_4$: C, 62.58; H, 9.63.
Found: C, 62.56; H, 9.66.



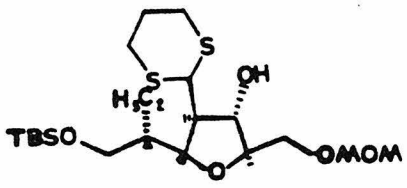
39

R_f = 0.13 (35% ethyl acetate in cyclohexane)
evap. dis. 80°-90°C, 0.005 mmHg
IR($CHCl_3$) 3600, 3450, 1680, 1460, 1160, 1120, 1040 cm^{-1}
^{1}H-NMR($CDCl_3$) δ 0.93 (t,3H,J=6Hz,CH_3CH_2), 0.96 (d,3H,J=7Hz,$CHCH_3$), 3.33 (s,3H,OCH_3), 4.61 (s,2H,OCH_2O), 6.42 (t,1H,J=8Hz, C=CH), 9.40 (s,1H,CHO)
Anal. calcd. for $C_{12}H_{22}O_4$: C, 62.58; H, 9.63.
Found: C, 62.24; H, 9.71.



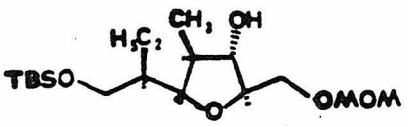
40a

R_f = 0.13 (25% ethyl acetate in cyclohexane)
evap. dis. 160°-170°C, 0.005 mmHg
$[\alpha]_D^{23}$ = +18.0° (C = 0.255,$CHCl_3$)
IR($CHCl_3$) 3600, 3450, 1480, 1470, 1260, 1040, 840 cm^{-1}
^{1}H-NMR($CDCl_3$) δ 0.09 (s,6H,$(CH_3)_2Si$), 0.92 (s,9H,$(CH_3)_3C$), 3.33 (s,3H,OCH_3), 4.63 (s,2H,OCH_2O)
Anal. calcd. for $C_{21}H_{42}O_5S_2Si$: C, 54.04; H, 9.07; S, 13.74.
Found: C, 54.26; H, 9.08; S, 13.78.



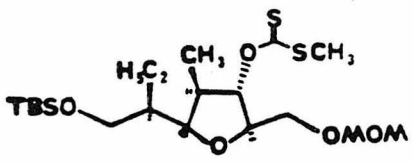
40b

R_f = 0.20 (35% ethyl acetate in cyclohexane)
evap. dis. 160°-;70°C, 0.005 mmHg
$[\alpha]_D^{22}$ = +22.1° (C = 1.095,$CHCl_3$)
IR($CHCl_3$) 3450, 1480, 1470, 1260, 1080, 840 cm^{-1}
^{1}H-NMR($CDCl_3$) δ 0.13 (s,6H,$(CH_3)_2Si$), 0.93 (s,9H,$(CH_3)_3C$), 3.33 (s,3H,OCH_3), 4.60 (s,2H,OCH_2O)
Anal. cald. for $C_{21}H_{42}O_5S_2Si$: C, 54.04; H, 9.07; S, 13.74.
Found: C, 53.86; H, 8.92; S, 13.54.



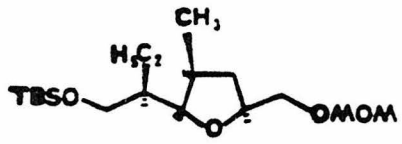
41

R_f = 0.16 (30% ethyl acetate in cyclohexane)
evap. dis. 110°-120°C, 0.005 mmHg
$[\alpha]_D^{23}$ = +9.4° (C = 1.04,$CHCl_3$)
IR($CHCl_3$) 3350, 1480, 1260, 1040, 840 cm^{-1}
^{1}H-NMR($CDCl_3$) δ 0.07 (s,6H,$(CH_3)_3Si$), 0.90 (s,9H,$(CH_3)_3C$), 1.10 (d,3H,J=7Hz, $CHCH_3$), 3.38 (s,3H,OCH_3), 4.67 (s,2H, OCH_2O)
Anal. calcd. for $C_{18}H_{38}O_5Si$: C, 59.63; H, 10.56.
Found: C, 59.71; H, 10.57.



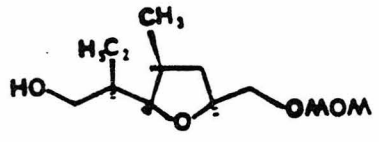
42

R_f = 0.21 (5% ethyl acetate in cyclohexane)
evap. dis. 130°-140°, 0.005 mmHg
$[\alpha]_D^{22}$ = +1.1° (C = 1.32, $CHCl_3$)
IR($CHCl_3$) 1475, 1465, 1220, 1060, 840 cm^{-1}
^{1}H-NMR($CDCl_3$) δ 0.04 (s,6H,$(CH_3)_2Si$), 0.90 (s,9H,$(CH_3)_3C$), 2.53 (s,3H,SCH_3), 3.33 (s,3H,OCH_3), 4.63 (s,2H,OCH_2O), 5.67 (dd,1H,J=4Hz,4Hz,S_2COCH)
Anal. calcd. for $C_{20}H_{40}O_5Si$: C, 53.06, H, 8.91; S, 14.61.
Found: C, 53.00; H, 8.89; S, 13.99.



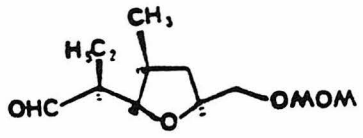
43

R_f = 0.19 (5% ethyl acetate in cyclohexane)
evap. dis. 70°-80°C, 0.005 mmHg
$[\alpha]_D^{23}$ = +10.4° (C = 1.15, $CHCl_3$)
IR($CHCl_3$) 1470, 1460, 1260, 1100, 1040, 840 cm^{-1}
^{1}H-NMR($CDCl_3$) δ 0.03 (s,6H,$(CH_3)_2Si$), 0.88 (s,9H,$(CH_3)_3C$), 3.33 (s,3H,OCH_3), 4.63 (s,2H,OCH_2O)
Anal. calcd. for $C_{18}H_{38}O_4Si$: C, 62.38; H, 11.05.
Found: C, 62.46; H, 11.07.



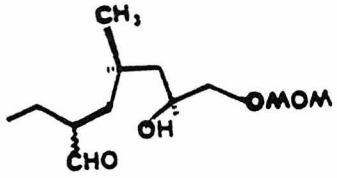
44

R_f = 0.13 (35% ethyl acetate in cyclohexane)
evap. dis. 60°-70°C, 0.005 mmHg
$[\alpha]_D^{22}$ = +5.4° (C = 1.025, $CHCl_3$)
IR($CHCl_3$)3490, 1460, 1110, 1040 cm^{-1}
^{1}H-NMR($CDCl_3$) δ 0.96 (t,3H,J=6Hz, CH_3CH_2), 1.05 (d,3H,J=6Hz,CH_3CHCC), 3.34 (s,3H,OCH_3), 4.62 (s,2H,OCH_2O)
Anal calcd. for $C_{12}H_{24}O_4$: C, 62.04; H, 10.41.
Found: C, 62.12; H, 10.32.



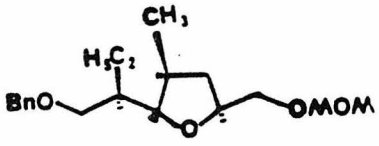
45

R_f = 0.15 (25% ethyl acetate in cyclohexane)
evap. dis. 60°-70°C, 0.005 mmHg
$[\alpha]_D^{22}$ = +19.5° (C = 1.435,$CHCl_3$)
IR($CHCl_3$) 1720, 1480, 1110, 1040, 920 cm^{-1}
^{1}H-NMR($CDCl_3$) δ 0.93 (t,3H,J=6Hz,CH_3CH_2), 1.05 (d,3H,J=6Hz,CHCH), 3.36 (s,3H,OCH_3), 3.52 (d,2H,J=5Hz,CCH_2OC), 3.70 (dd,1H, J=4Hz,8Hz,O=C-C-CH), 4.62 (s,2H,OCH_2O), 9.77 (d,1H,J=6Hz,CHO)
Anal.calcd. for $C_{12}H_{22}O_4$: C, 62.58; H, 9.63.
Found: C, 62.67; H, 9.68.



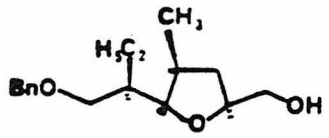
46

R_f = 0.12 (35% ethyl acetate in cyclohexane)
evap. dis. 80°-90°C, 0.005 mmHg
IR($CHCl_3$) 3500, 1680, 1460, 1150, 1040 cm^{-1}
^{1}H-NMR($CDCl_3$) δ 1.00 (t,3H,J=7Hz, CH_3CH_2), 1.12 (d,3H,J=6Hz,$CHCH_3$), 3.40 (s,3H,OCH_3), 4.67 (s,2H,OCH_2O), 6.27 (d,1H,J=10Hz, C=CH), 9.36 (s,1H,CHO)
Anal. calcd. for $C_{12}H_{22}O_4$:C, 62.58; H, 9.63.
Found: C, 62.65; H, 9.53.



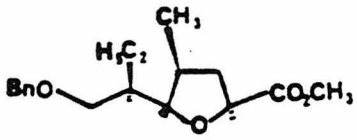
47

R_f = 0.19 (15% ethyl acetate in cyclohexane)
evap. dis. 100°-110°C, 0.005 mmHg
$[\alpha]_D^{21}$ = +9.9° (C = 0.97,$CHCl_3$)
IR($CHCl_3$) 1450, 1380, 1365, 1120, 1100, 1030 cm^{-1}
^{1}H-NMR($CDCl_3$) δ 0.90 (t,3H,J=6Hz,CH_3CH_2), 1.01 (d,3H,J=6Hz,CH_3CHCC), 3.33 (s,3H, OCH_3), 4.43 (s,2H,$C_6H_5CH_2$), 4.61 (s,2H, OCH_2O), 7.30 (bs,5H,C_6H_5)
Anal. calcd. for $C_{19}H_{30}O_4$: C, 70.77; H, 9.38.
Found: C, 70.61; H, 9.15.



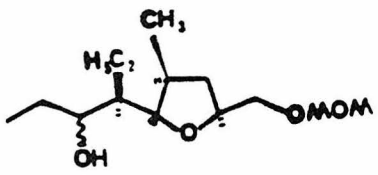
48

R_f = 0.19 (35% ethyl acetate in cyclohexane)
evap. dis. 100°-110°C, 0.005 mmHg
$[\alpha]_D^{21}$ = +26.9° (C = 1.005,$CHCl_3$)
IR($CHCl_3$) 3600, 3460, 1460, 1385, 1370, 1100, 1030 cm^{-1}
^{1}H-NMR($CDCl_3$) δ 0.94 (t,3H,J=6Hz,CH_3CH_2), 1.04 (d,3H,J=6Hz,CH_3CHCC), 4.49 (s,2H, $C_6H_5CH_2$), 7.36 (bs,5H,C_6H_5)
Anal. calcd. for $C_{17}H_{26}O_3$: C, 73.35; H, 9.41
Found: C, 73.42; H, 9.40.



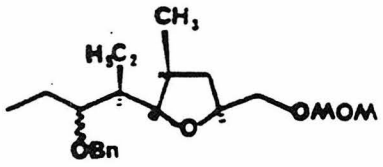
50

R_f = 0.18 (10% ethyl acetate in cyclohexane)
evap. dis. 100°-110° C, 0.005 mmHg
IR($CHCl_3$) 1740, 1460, 1385, 1370, 1100 cm^{-1}
^{1}H-NMR($CDCl_3$) δ 0.93 (t,3H,J=6Hz,CH_3CH_2), 1.00 (d,3H,J=6Hz,CH_3CHCC), 3.70 (s,3H, CO_2CH_3), 4.43 (s,2H,$C_6H_5CH_2$), 7.31 (s, 5H,C_6H_5)
Anal. calcd. for $C_{18}H_{26}O_4$: C, 70.56; H, 8.55.
Found: C, 70.58; H, 8.45.



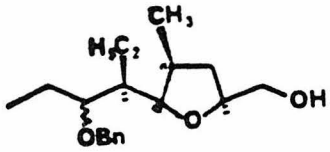
51a,b

R_f = 0.20 (35% ethyl acetate in cyclohexane)
evap. dis. 60°-70°C, 0.005 mmHg
IR($CHCl_3$) 3450, 1460, 1110, 1040 cm^{-1}
^{1}H-NMR($CDCl_3$) δ 3.33 (s,3H,OCH_3), 3.47 (d,2H,J=4Hz,CCH_2O), 4.73 (s,2H,OCH_2O)
Anal. calcd. for $C_{14}H_{28}O_4$: C, 64.58; H, 10.84.
Found: C, 64.53; H, 10.69.



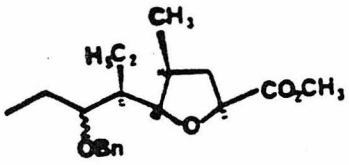
52a,b

R_f = 0.18 (10% ethyl acetate in cyclohexane)
evap. dis. 100°-110°C, 0.005 mmHg
IR($CHCl_3$) 1460, 1170, 1110, 1040 cm^{-1}
^{1}H-NMR($CDCl_3$) δ 3.33 (s,3H,OCH_3), 4.47 (s,2H for one isomer, $C_6H_5CH_2$), 4.50, 4.59 (d, 2H for another isomer,J=13Hz), 4.62 (s,2H,OCH_2O), 7.30 (bs,5H,C_6H_5)
Anal. calcd. for $C_{21}H_{34}O_4$: C, 71.96; H, 9.78.
Found: C, 71.83; H, 9.72.



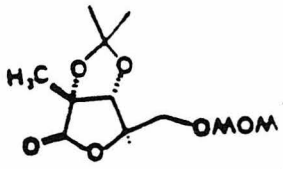
53a,b

R_f = 0.23, 0.24 (30% ethyl acetate in cyclohexane)
evap. dis. 90°-100°C, 0.005 mmHg
IR($CHCl_3$) 3600, 3450, 1460, 1380, 1100, 1060, 1030 cm^{-1}
^{1}H-NMR($CDCl_3$) δ 4.47, 4.52 (s,2H,$C_6H_5CH_2$), 7.30 (bs,5H,C_6H_5)
Anal. calcd. for $C_{19}H_{30}O_3$: C, 74.47; H, 9.87.
Found: C, 74.32; H, 9.77.



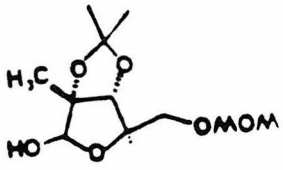
55a,b

R_f = 0.23 (10% ethyl acetate in cyclohexane)
evap. dis. 100°-110°C, 0.005 mmHg
IR($CHCl_3$) 1740, 1460, 1380, 1100, 1060, 1030 cm^{-1}
^{1}H-NMR($CDCl_3$) δ 3.70, 3.72 (s,3H,CO_2CH_3), 7.30 (bs,5H,C_6H_5)
Anal. calcd. for $C_{20}H_{30}O_4$: C, 71.82; H, 9.04.
Found: C, 71.77; H, 9.10



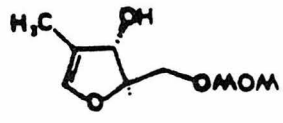
58

R_f = 0.2 (30% ethyl acetate in cyclohexane)
evap. dis. 90°-100°C, 0.005 mmHg
$[\alpha]_D^{22}$ = -22.4° (C = 1.32,$CHCl_3$)
IR ($CHCl_3$) 1780, 1380, 1220, 1160, 1105, 1060, 1020 cm^{-1}
^{1}H-NMR ($CDCl_3$) δ1.42 (s, 6H, C $(CH_3)_2$), 1.62 (s, 3H, CH_3), 3.33 (s, 3H, OCH_3), 3.74 (d, 2H, J= 3 Hz, CCH_2O), 4.47 (s, 1H, H3), 4.59 (bs, 2H, OCH_2O)
Anal. calcd. for $C_{11}H_{18}O_6$:C, 53.65; H. 7.37.
Found: C, 53.67; H, 7.25.



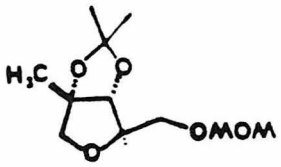
59

R_f= 0.15 (50% ether in petroleum ether)
evap. dis. 90°-100° C, 0.005 mm Hg
$[\alpha]_D^{22}$= +17.9° (C=1.17, $CHCl_3$)
IR($CHCl_3$) 3600, 3450, 1460, 1380, 1210, 1160, 1105, 1060, 1030 cm^{-1}
^{1}H-NMR($CDCl_3$) δ (minor anomer, major anomer) 3.31, 3.34 (s, 3H, OCH_3), 3.59, 3.63 (d, 2H, J= 2 Hz,CCH_2O), 4.58, 4.64 (s, 2H, OCH_2O), 5.00, 5.17 (d, 1H, J= 11 Hz, H1)
Anal. calcd. for $C_{11}H_{20}O_6$: C, 53.22; H, 8.12.
Found: C, 53.06; H 8.05.



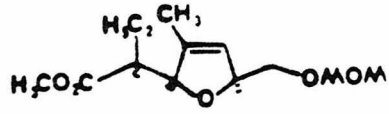
60

R_f= 0.16 (75% ether in petroleum ether)
evap. dis. 60°-70° C, 0.005 mm Hg
$[\alpha]_D^{23}$ = + 206.1° (C = 1.11, $CHCl_3$)
IR($CHCl_3$) 3590, 3450, 1675, 1460, 1380, 1210, 1150, 1100, 1020 cm^{-1}
^{1}H-NMR ($CDCl_3$) δ1.69 (d, 3H, J=2 Hz, CH_3), 3.37 (s, 3H, OCH_3), 3.56 (d, 2H, J=6 Hz, CCH_2O), 5.08 (s, 2H, OCH_2O), 6.22 (bs, 1H, HC=C)
Anal. calcd. for $C_8H_{14}O_4$: C, 55.16; H, 8.10.
Found: C, 55.11; H, 8.03.



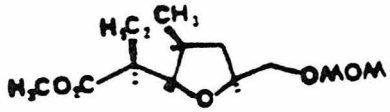
61

R_f= 0.35 (75% ether in petroleum ether)
evap. dis. 40° C, 0.005 mm Hg
$[\alpha]_D^{21}$ = +28.5° (C=1.36, $CHCl_3$)
IR ($CHCl_3$) 1460, 1385, 1220, 1160, 1040 cm^{-1}
^{1}H-NMR ($CDCl_3$) δ1.38 (s, 3H,CH_3), 1.50 (s,6H,$C(CH_3)_2$), 3.33 (s,3H,OCH_3),3.60 (d,2H,J=6Hz, CCH_2O), 3.62 (d,1H, J=9Hz, $H1_a$), 3.79 (d,1H,J=9Hz,$H1_b$), 4.17 (dt,1H, J=3Hz,6Hz,H4), 4.27 (d,1H,J=3Hz,H3), 4.59 (s,2H,OCH_2O)
Anal. calcd. for $C_{11}H_{20}O_5$: C, 56.88; H, 8.68.
Found: C, 56.84; H, 8.73.



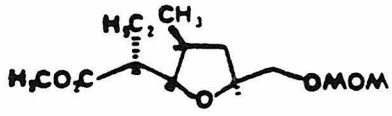
63a,b

R_f= 0.12 (30% ether in petroleum ether)
evap. dis. 60°-70° C, 0.005 mm Hg
IR ($CHCl_3$) 1730, 1460, 1440, 1150, 1110, 1080, 1030 cm^{-1}
^{1}H-NMR ($CDCl_3$) δ3.33 (s,3H,OCH_3), 3.49 (d,2H, J=4Hz,CCH_2O), 3.60, 3.68 (s,3H,CO_2CH_3), 4.60 (s,2H,OCH_2O),5.50 (bs,1H,C=CH)
Anal. calcd. for $C_{13}H_{22}O_5$: C, 60.45; H,8.58.
Found: C,60.47; H, 8.49.



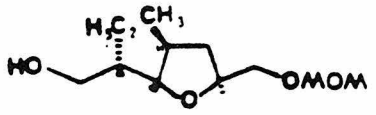
64a

R_f= 0.16 (25% ethyl acetate in cyclohexane)
evap. dis. 80°-90° C, 0.005 mm Hg
$[\alpha]_D^{25}$ = +16.2° (c=1.01, $CHCl_3$)
IR ($CHCl_3$) 1730,1460,1390,1110,1040 cm^{-1}
^{1}H-NMR ($CDCl_3$) δ0.90 (t,3H,J=6Hz,CH_3CH_2), 1.06 (d, 3H,J=6Hz,CH_3CHCC), 3.36 (s,3H,OCH_3), 3.52 (d,2H,J=5Hz, CCH_2O),3.69 (s,3H,CO_2CH_3), 4.61 (s,2H,OCH_2O)
Anal. calcd. for $C_{13}H_{24}O_5$: C, 59.98; H, 9.29.
Found: C, 59.92; H, 9.31.



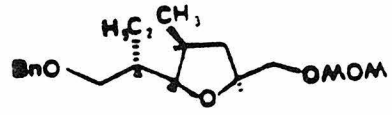
64b

R_f = 0.24 (25% ethyl acetate in cyclohexane)
evap. dis. 80°-90° C, 0.005 mm Hg
$[\alpha]_D^{25}$ = +5.4° (c=1.16, $CHCl_3$)
IR ($CHCl_3$) 1730, 1460, 1275, 1220, 1160, 1105, 1040 cm^{-1}
^{1}H-NMR ($CDCl_3$) δ0.88 (t,3H,J=6Hz,CH_3CH_2), 0.99 (d,3H,J=6Hz,CH_3), 3.36 (s,3H,OCH_3), 3.51 (d,2H,J=5Hz, CCH_2O) 3.68 (s,3H,CO_2CH_3),4.62, (s,2H,OCH_2O)
Anal. calcd. for $C_{13}H_{24}O_5$: C, 59.98; H, 9.29.
Found: C, 59.93; H. 9.12.



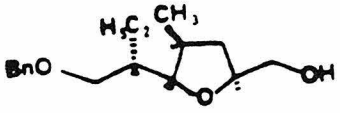
65

R_f = 0.15 (35% ethyl acetate in cyclohexane)
evap. dis. 60°-70° C, 0.005 mm Hg
$[\alpha]_D^{25}$ = +27.4° (C=1.265, $CHCl_3$)
IR ($CHCl_3$) 3650, 3500, 1460, 1230, 1150, 1105, 1040 cm^{-1}
^{1}H-NMR ($CDCl_3$) δ0.93 (t,3H,J=6Hz,CH_3CH_2), 1.01 (d,3H,J=6Hz,CH_3), 2.67 (dd, 1H,J=5Hz, 6Hz,CH CH_3), 3.33 (s,3H,OCH_3), 3.47 (d,2H, J=5Hz,CCH_2O), 4.60 (s,2H,OCH_2O)
Anal. calcd. for $C_{12}H_{24}O_4$: C, 62.04; H,10.41.
Found: C, 62.01; H, 10.32.



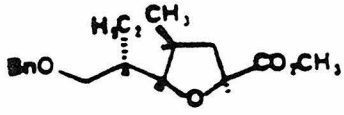
66

R_f = 0.19 (15% ethyl acetate in cyclohexane)
evap. dis. 100°-110°C,0.005 mm Hg
$[\alpha]_D^{25}$ = +18.7° (C=1.71,$CHCl_3$)
IR($CHCl_3$) 1460, 1380, 1120, 1040 cm^{-1}
^{1}H NMR ($CDCl_3$) δ0.92 (t,3H,J=6Hz,CH_3CH_2), 1.02 (d,3H,J=6Hz,CH_3), 3.33 (s,3H,OCH_3), 3.47 (d,4H,J=5Hz,CCH_2O) 4.43 (s,2H,$C_6H_5CH_2$), 4.60 (s,2H,OCH_2O), 7.28 (bs,5H,C_6H_5)
Anal. calcd. for $C_{19}H_{30}O_4$: C, 70.77; H, 9.38.
Found: C, 70.58; H, 9.22.



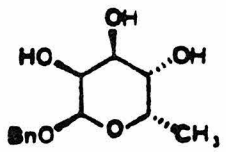
67

R_f = 0.19 (35% ethyl acetate in cyclohexane)
evap. dis. 100°-110°C, 0.005 mmHg
$[\alpha]_D^{25}$ = +49.3° (C = 1.07, $CHCl_3$)
IR($CHCl_3$) 3600, 3450, 1460, 1380, 1220, 1100, 1080, 1040 cm^{-1}
^{1}H-NMR ($CDCl_3$) δ0.93 (t,3H,J=6Hz,CH_3CH_2), 1.02 (d,3H,J=6Hz,CH_3), 3.47 (d,2H,J=6Hz, CCH_2O), 4.48 (s,2H,$C_6H_5CH_2$), 7.33 (bs,5H, C_6H_5)
Anal. calcd.for $C_{17}H_{26}O_3$: C, 73.35; H, 9.41.
Found: C, 73.46; H, 9.36.



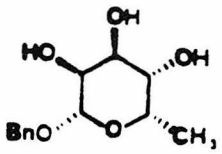
69

R_f = 0.18 (10% ethyl acetate in cyclohexane)
evap. dis. 100°-110°C, 0.005 mmHg
$[\alpha]_D^{24}$ = +1.4° (C = 1.11, $CHCl_3$)
IR($CHCl_3$) 1740, 1460, 1370, 1220, 1100, 1040 cm^{-1}
^{1}H-NMR ($CDCl_3$) δ0.93 (t,3H,J=6Hz,CH_3CH_2), 1.01 (d,3H,J=6Hz,CH_3),3.49 (d,2H,J=6Hz, CCH_2O), 3.70 (s,3H,CO_2CH_3), 3.80 (dd,1H, J=5Hz,8Hz,OCHCC),4.38 (t,1H,J=7Hz,$CHCO_2CH_3$), 4.47 (s,2H,$C_6H_5CH_2$), 7.32 (bs,5H,C_6H_5)
Anal. calcd.for $C_{18}H_{26}O_4$: C,70.56; H, 8.55.
Found: C, 70.54; H, 8.52.



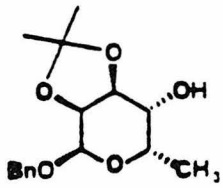
71a

R_f = 0.17 (ethyl acetate)
mp 134.5°-135.5°C (ethyl acetate-hexane)
$[\alpha]_D^{23}$ = -118.1° (C = 1.135, $CHCl_3$)
IR($CHCl_3$) 3600, 3500, 1220, 1105, 1080, 1040, 1000 cm^{-1}
^{1}H-NMR ($CDCl_3$) δ1.23 (d,3H,J=6Hz,CH_3), 4.54 (d,1H,J=12Hz,C_6H_5CHH), 4.73 (d,1H,J=12Hz, C_6H_5CHH), 4.93 (bs,1H,H1), 7.38 (bs,5H,C_6H_5)
Anal. calcd. for $C_{13}H_{18}O_5$: C, 61.41; H, 7.14.
Found: C, 61.33; H, 7.18.



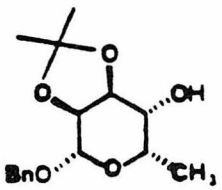
71b

R_f = 0.24 (ethyl acetate)
evap. dis. 130°-140°C, 0.005 mmHg
$[\alpha]_D^{25}$ = +117.9° (C = 0.585, $CHCl_3$)
IR($CHCl_3$) 3600, 3450, 1220, 1175, 1080, 1060, 1000 cm^{-1}
IR ($CHCl_3$) 3600,3450,1220,1175,1080,1060,1000 cm^{-1}
^{1}H-NMR ($CDCl_3$) δ1.27 (d,3H,J=6Hz,CH_3), 4.53 (d,1H,J=11Hz,C_6H_5CHH), 4.62 (d,1H,J=8Hz,H1), 4.89 (d,1H,J=11Hz,C_6H_5CHH), 7.34 (bs,5H,C_6H_5)
Anal. calcd. for $C_{13}H_{18}O_5$: C, 61.41; H, 7.14.
Found: C, 61.39; H, 7.18.



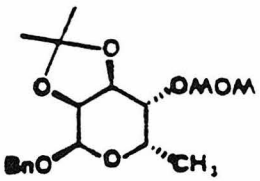
72a

R_f = 0.19 (35% ethyl acetate in petroleum ether)
mp 79°-80°C (hexane)
$[\alpha]_D^{23}$ = -62.8° (C = 0.955, $CHCl_3$)
IR($CHCl_3$) 3970,3460,1380,1240,1160,1100, 1030 cm^{-1}
^{1}H-NMR ($CDCl_3$) δ1.19 (d,3H,J=6Hz,CH_3), 1.36, 1.50 (s,6H,C $(CH_3)_2$), 4.56 (d,1H, J=12Hz,C_6H_5CHH), 4.71 (d,1H,J=12Hz,C_6H_5CHH), 4.87 (bs,1H,H1), 7.33 (bs,5H,C_6H_5)
Anal. calcd. for $C_{16}H_{22}O_5$: C, 65.29; H,7.53.
Found: C, 65.26; H,7.51.



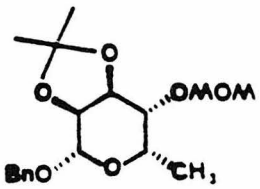
72b

R_f = 0.21 (25% ethyl acetate in petroleum ether)
evap. dis. 100°-110°C, 0.005 mmHg
$[\alpha]_D^{23}$ = +105.5° (C = 0.55, $CHCl_3$)
IR($CHCl_3$) 3560, 3350, 1390, 1230, 1180, 1120, 1060 cm^{-1}
^{1}H-NMR ($CDCl_3$) δ1.30 (d,3H,J=6Hz,CH_3), 1.31, 1.40 (s,6H,C $(CH_3)_2$), 4.73 (d,1H, J=4Hz,H1), 4.58 (d,1H,J=12Hz,C_6H_5CHH), 4.84 (d,1H,J=12Hz,C_6H_5CHH), 7.33 (bs,5H, C_6H_5)
Anal. calcd. for $C_{16}H_{22}O_5$: C, 65.29; H, 7.53.
Found: C, 65.31; H, 7.48.



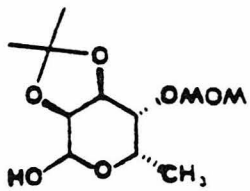
73a

R_f = 0.25 (25% ethyl acetate in petroleum ether)
evap. dis. 120°-130°C, 0.005 mmHg
$[\alpha]_D^{24}$ = -41.3° (C=0.75, $CHCl_3$)
IR ($CHCl_3$) 1380,1240,1150,1100,1020 cm^{-1}
^{1}H-NMR ($CDCl_3$) δ1.20 (d,3H,J=6Hz,CH_3), 1.36, 1.51 (s,6H,$C(CH_3)_2$), 3.40 (s,3H, OCH_3), 4.57 (bs,1H,H1), 7.34 (bs,5H,C_6H_5)
Anal. calcd. for $C_{18}H_{26}O_6$: C, 63.89; H, 7.74.
Found: C, 64.03; H, 7.75.



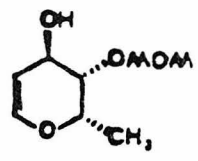
73b

R_f = 0.29 (25% ethyl acetate in petroleum ether)
evap. dis. 100°-110°C, 0.005 mmHg
$[\alpha]_D^{24}$ = +147.8° (C = 0.565, $CHCl_3$)
IR($CHCl_3$) 1390, 1230, 1155, 1040 cm^{-1}
^{1}H-NMR ($CDCl_3$) δ3.40 (s,3H, OCH_3),4.57 (d,1H,J=12Hz,H1), 7.30 (bs,5H,C_6H_5)
Anal. calcd. for $C_{18}H_{26}O_6$: C, 63.89; H, 7.74.
Found: C, 63.83; H, 7.57.



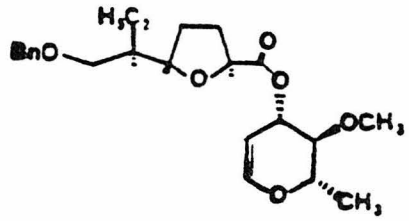
74

R_f = 0.22 (50% ethyl acetate in petroleum ether)
mp 139°C (ethyl acetate-hexane)
$[\alpha]_D^{23}$ = +61.7° (C = 1.215, $CHCl_3$)
IR($CHCl_3$) 3600, 3460, 1390, 1230, 1160, 1100, 1040 cm^{-1}
^{1}H-NMR ($CDCl_3$) δ1.27 (d,3H,J=6Hz,CH_3), 1.33, 1.47 (s,6H,$C(CH_3)_2$), 3.40 (s,3H,OCH_3), 3.57 (d,1H, J=6Hz,OH), 3.63 (dd,1H,J=3Hz,3Hz,H4), 4.00 (dq,1H, J=3Hz,6Hz,H5) 4.03 (dd,1H,J=6Hz,6Hz,H2), 4.33 (dd, 1H,J=3Hz,6Hz,H3) 4.63 (d,1H,J=6Hz, OCHHO), 4.77 (d,1H,J=6Hz, OCHHO), 4.87 (dd,1H,J=6Hz,6Hz,H1)
Anal. calcd. for $C_{11}H_{20}O_6$: C, 53.22; H, 8.12.
Found: C, 53.12; H, 8.21.



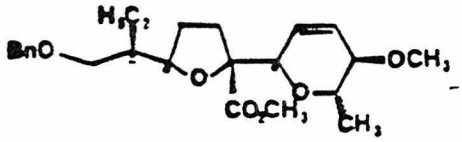
75

R_f=0.21 (50% ethyl acetate in petroleum ether)
evap. dis. 45°-55°C, .005 mmHg
$[\alpha]_D^{23}$= -206.4° (C=0.59, $CHCl_3$)
IR($CHCl_3$)3620,3450,1640,1240,1150,1090,1030,940 cm^{-1}
^{1}H-NMR ($CDCl_3$) δ1.36 (d,3H,J=6Hz,CH_3), 3.40 (s,3H, OCH_3), 3.56 (m,1H,H4), 4.10 (m,2H,H3 and H5), 4.66 (d,1H,J=6Hz, OCHHO),4.73 (d,1H,J=6Hz, OCHHO), 4.89 (m,1H,H2), 6.50 (d,1H,J=6Hz,H1)
Anal.calcd. for $C_8H_{14}O_4$: C, 55.16; H, 8.10.
Found: C, 55.27; H, 8.20.



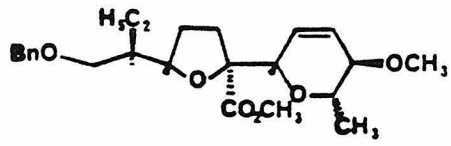
77

R_f= 0.11 (10% ethyl acetate in cyclohexane)
evap. dis. 130°-150°C, .005 mmHg
$[\alpha]_D^{23}$= +47.5° (C=1.07, $CHCl_3$)
IR($CHCl_3$) 1740,1650,1455,1390,1370,1230,1090 cm^{-1}
^{1}H-NMR ($CDCl_3$)δ 0.92 (t,3H,J=6Hz,CH_3CH_2), 1.37 (d,3H,J=6Hz,CH_3CHOC), 3.47 (s,3H,OCH_3), 3.53 (d,2H,J=6Hz,OCH_2C), 4.47 (s,2H,$C_6H_5CH_2$), 4.71 (dd,1H,J=3Hz,3Hz,=HCCHOC), 5.31 (dd,1H,J=3Hz, 6Hz,HC=CHC), 6.37 (bd,1H,J=6Hz,OCH=C), 7.33 (bs,5H,C_6H_5).
Anal. Calcd. for $C_{23}H_{32}O_6$: C,68.29; H,7.97.
Found: C,68.22; H,7.98.



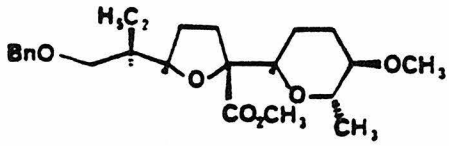
78a

R_f= 0.29 (20% ethyl acetate in cyclohexane)
evap. dis. 140°-150°C, .005 mmHg
$[\alpha]_D^{22}$= -104.1° (C=0.70,$CHCl_3$)
IR($CHCL_3$)1730,1455,1380,1240,1100,900 cm^{-1}
^{1}H-NMR($CDCl_3$) δ0.90 (t,3H=6Hz,CH_3CH_2), 1.25 (d,3H,J=6Hz,CH_3CHOC), 3.37 (s,3H,OCH_3), 3.52 (d,2H,J=5Hz,OCH_2C), 3.70 (s,3H,CO_2CH_3), 4.47 (s,2H,$C_6H_5CH_2$), 4.57 (bs,1H,OCHC=), 5.70-6.10 (bq,2H,HC=CH), 7.33 (bs,5H,C_6H_5).
Anal. Calcd for $C_{24}H_{34}O_6$: C,68.88; H,8.19.
Found: C,68.82; H,8.11.



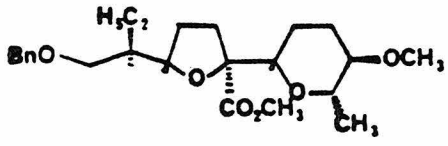
78b

R_f= 0.25 (20% ethyl acetate in cyclohexane)
evap. dis. 140°-150°C, .005 mmHg
$[\alpha]_D^{22}$= -102.9° (C=0.625,$CHCl_3$)
IR($CHCl_3$) 1730,1460,1240,1100 cm^{-1}
^{1}H-NMR($CDCl_3$) δ0.90 (t,3H,J=6Hz,CH_3CH_2),1.20 (d,3H,J=6Hz,CH_3CHOC), 3.37 (s,3H,OCH_3), 3.50 (d,2H,J=5Hz,OCH_2C), 3.69 (s,3H,CO_2CH_3), 4.33 (bs,1H,OCHC=), 4.47 (s,2H,$C_6H_5CH_2$),5.70-6.03 (bq,2H,HC=CH), 7.30 (bs,5H,C_6H_5)
Anal.Calcd. for $C_{24}H_{34}O_6$: C,68.88; H,8.19.
Found: C,68.94; H,8.19.



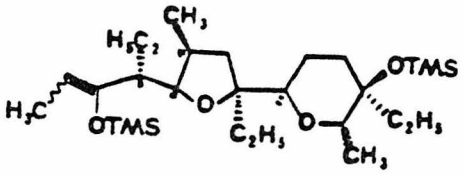
79a

R_f= 0.27 (20% ethyl acetate in cyclohexane)
evap. dis. 140°-150°C, .005 mmHg
$[\alpha]_D^{21}$= -31.1° (C=0.675, $CHCl_3$)
IR($CHCl_3$)1735,1450,1365,1270,1100,1000 cm^{-1}
^{1}H-NMR($CDCl_3$) δ0.90 (t,3H,J=6Hz,CH_3CH_2), 1.20 (d,3H,J=6Hz,CH_3CHOC),3.33 (s,3H,OCH_3), 3.57 (d,2H,J=5Hz,OCH_2C), 3.67 (s,3H,CO_2CH_3), 4.48 (s,2H,$C_6H_5CH_2$), 7.32 (bs,5H,C_6H_5)
Anal. Calcd. for $C_{24}H_{36}O_6$: C,68.55; H,8.63
Found: C,68.46; H,8.55.



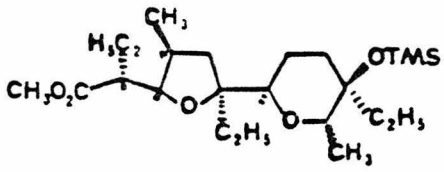
79b

R_f= 0.20 (20% ethyl acetate in cyclohexane)
evap. dis. 140°-150°C, .005 mmHg
$[\alpha]_D^{21}$= -47.4° (C=0.88,$CHCl_3$)
IR($CHCl_3$)1730,1460,1370,1270,1100,1000 cm^{-1}
^{1}H-NMR($CDCl_3$) δ 0.95(t,3H,J=6Hz,CH_3CH_2), 1.20 (d,3H,J=6Hz,CH_3CHOC), 3.33 (s,3H,OCH_3), 3.70 (s,3H,CO_2CH_3), 4.48 (s,2H,$C_6H_5CH_2$), 7.33 (bs,5H,C_6H_5)
Anal. Calcd. for $C_{24}H_{36}O_6$: C,68.55; H,8.63
Found: C,68.57; H,8.66.



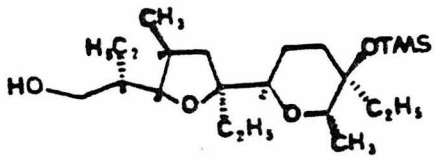
80

R_f= 0.30 (2% ethyl acetate in petroleum ether)
evap. dis. 190°C, .05 mmHg
$[\alpha]_D^{22}$=+13.0° (C=1.30,$CHCl_3$)
IR($CHCl_3$) 1680,1465,1255,1060,845 cm^{-1}
^{1}H-NMR($CDCl_3$) δ 0.15(s,9.H,$(CH_3)_3SiOC$=), 0.20 (s,9H,$(CH_3)_3SiOCC_3$), 0.87 (bt,J=7Hz,9H,CH_3CH_2), 0.92 (d,J=7Hz,3H,CH_3CHCC), 1.15 (d,J=7Hz,3H, CH_3CHOC), 1.50 (d,J=7Hz,3H,CH_3CH=), 3.83 (q,J= 7Hz,1H,CH_3CHOC), 4.57 (q,J=7Hz,1H,CH_3CH=)
Anal. Calcd. for $C_{27}H_{54}O_4Si_2$:C,65.00; H,10.91
Found: C,64.93; H,10.85.



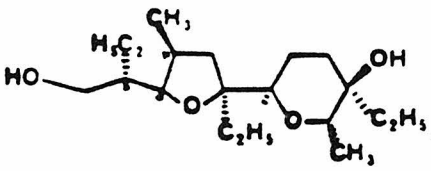
81

R_f= 0.27 (10% ether in petroleum ether)
evap. dis. 140°-145°C, .001 mmHg
$[\alpha]_D^{22}$= -6.3° (C=1.01,$CHCl_3$)
IR($CHCl_3$) 1730,1460,1260,1060,840 cm^{-1}
^{1}H-NMR($CDCl_3$) δ0.020 (s,9H,$(CH_3)_3Si$), 0.83 (bt,J=7Hz,9H,CH_3CH_2), 0.90 (d,J=6Hz,3H,CH_3CHCC), 1.15 (d,J=7Hz,3H,CH_3CHOC), 3.67 (s,3H,CO_2CH_3), 3.83 (q,J=7Hz,1H,CH_3CHOC)
Anal.Calcd. for $C_{23}H_{44}O_5Si$: C,64.44; H,10.35.
Found: C,64.40; H,10.26.



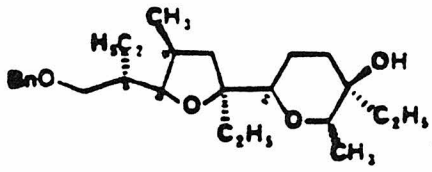
82

R_f= 0.19 (20% ether in petroleum ether)
evap. dis. 150°-155°C, .001 mmHg
$[\alpha]_D^{22}$= +7.83° (C=1.06,$CHCl_3$)
IR($CHCl_3$) 3520,1460,1255,1100,1050,840 cm^{-1}
^{1}H-NMR($CDCl_3$) δ 0.13 (s,9H,$(CH_3)_3Si$), 0.87 (bt,J=7Hz,9H,CH_3CH_2), 0.93 (d,J=6Hz,3H,CH_3CHCC), 1.17 (d,J=7Hz,3H,CH_3CHOC), 3.80 (q,J=7Hz,1H,CH_3CHOC)
Anal. Calcd for $C_{22}H_{44}O_4Si$: C,65.95; H,11.07
Found: C,66.00; H,11.06



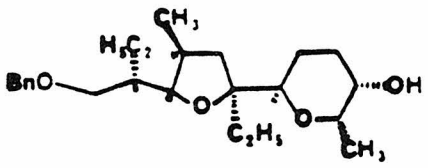
83

R_f= 0.17 (40% ethyl acetate in petroleum ether) mp 74°-75° C (hexane)
$[\alpha]_D^{24}$= +14.2° (C=1.16, $CHCl_3$)
IR ($CHCl_3$) 3600,3500,1460,1380,1100,1050, 950 cm^{-1}
^{1}H-NMR ($CDCl_3$) δ0.96 (d,3H,J=6Hz,CH_3CHCC), 1.22 (d,3H,J=6Hz,CH_3CHOC)
Anal. calcd. for $C_{19}H_{36}O_4$: C, 69.47; H, 11.05.
Found: C, 69.37; H, 10.96.



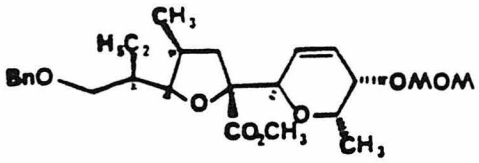
84

R_f= 0.17 (15% ethyl acetate in petroleum ether) evap. dis. 180°-190° C, 0.005 mm Hg
$[\alpha]_D^{22}$ = +21.8° (C=1.40,$CHCl_3$)
IR ($CHCl_3$) 3580,1460,1380,1120,1100,1050,960 cm^{-1}
^{1}H-NMR ($CDCl_3$) δ 0.96 (d,3H,J=6Hz,CH_3CHCC), 1.18 (d,3H,J=6Hz,CH_3CHOC), 3.76 (q,1H,J=6Hz, $CHCH_3OC$), 4.47 (s,2H,$C_6H_5CH_2$), 7.33 (bs,5H,C_6H_5)
Anal. calcd. for $C_{26}H_{42}O_4$: C, 74.60; H, 10.11.
Found: C, 74.50; H, 10.01.



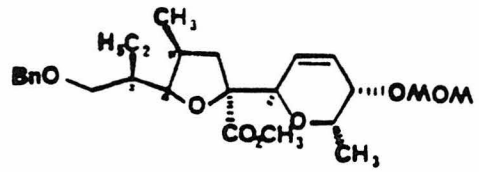
87

R_f= 0.13 (25% ethyl acetate in petroleum ether) evap. dis. 140°-150°C, .005 mmHg
$[\alpha]_D^{24}$= +25.8° (C=0.96,$CHCl_3$)
IR ($CHCl_3$) 3650, 3480, 1470, 1400,1120,1080 cm^{-1}
^{1}H-NMR ($CDCl_3$) δ 0.83, 0.92 (t,6H, J=6Hz,CH_3CH_2), 0.97(d,3H,J=6Hz,CH_3CHCC), 1.17 (d,3H,J=6Hz,CH_3CHOC),4.46 (s,2H, $C_6H_5CH_2$), 7.32 (bs,5H,C_6H_5)
Anal. calcd. for $C_{24}H_{38}O_4$: C, 73.81; H, 9.81.
Found: C, 73.76; H, 9.79.



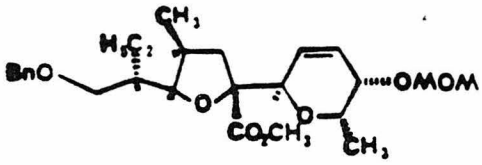
88a

R_f= 0.20 (20% ethyl acetate in cyclohexane)
evap. dis. 150°-160°C, .005 mmHg
$[\alpha]_D^{24}$= +135.7° (C=1.915,$CHCl_3$)
IR($CHCl_3$) 1740,1460,1390,1160,1100,1040 cm^{-1}
^{1}H-NMR($CDCl_3$) δ 0.93 (t,3H,J=6Hz,$C\underline{H}_3CH_2$), 0.97 (d,3H,J=6Hz,CH_3CHCC), 1.20 (d,3H,J=6Hz,CH_3CHOC), 3.37 (s,3H,OCH_3), 3.73 (s,3H,CO_2CH_3), 4.44 (bs,3H,$C_6H_5C\underline{H}_2$), 4.60 (d,1H,J=7Hz,$OCHHO$), 4.71 (d,1H,J=7Hz,$OCHHO$), 5.63-6.13 (m,2H,HC=CH), 7.33(bs,5H,C_6H_5)
Anal. Calcd for $C_{26}H_{38}O_7$: C,67.51; H,8.28
Found: C,67.70; H,8.33.



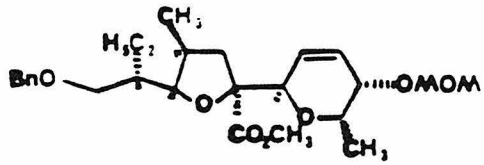
88b

R_f= 0.14 (20% ethyl acetate in cyclohexane)
evap. dis. 150°-160°C, .005 mmHg
$[\alpha]_D^{24}$= +159.5° (C=0.845, $CHCl_3$)
IR($CHCl_3$)1745,1730,1460,1380,1140,1090,1040 cm^{-1}
^{1}H-NMR($CDCl_3$) δ0.87 (t,3H,J=6Hz,$C\underline{H}_3CH_2$), 0.96 (d,3H,J=6Hz,CH_3CHCC), 1.13 (d,3H,J=6Hz,CH_3CHOC), 3.33 (s,3H,OCH_3), 3.64 (s,3H,CO_2CH_3), 4.41 (bs, 2H,$C_6H_5C\underline{H}_2$), 4.57 (d,1H,J=6Hz,$OCHHO$), 4.70 (d, 1H,J=6Hz,$OCHHO$), 6.0 (m,2H,HC=CH), 7.30 (bs,5H, C_6H_5)
Anal. Calcd. for $C_{26}H_{38}O_7$: C,67.51; H,8.28
Found: C,67.61; H,8.35.



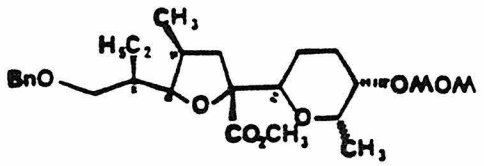
88c

R_f= 0.18 (20% ethyl acetate in cyclohexane)
evap. dis. 150°-160° C, 0.005 mm Hg
$[\alpha]_D^{23}$= +148.6° (C=1.22, CHCl3)
IR ($CHCl_3$) 1740,1460,1215,1160,1100,1040 cm^{-1}
^{1}H-NMR ($CDCl_3$) δ0.92 (t,3H,J=6Hz,$C\underline{H}_3CH_2$), 0.97 (d,3H,J=6Hz,$C\underline{H}_3CHCC$), 1.18 (d,3H, J=6Hz,$C\underline{H}_3CHOC$), 3.34 (s,3H,OCH_3), 3.73 (s,3H,CO_2CH_3), 4.47 (bs,2H,$C_6H_5C\underline{H}_2$), 4.62 (d,1H,J=7Hz,$OCHHO$), 4.71 (d,1H,J=7Hz, $OCHHO$), 5.67-6.17 (m,2H,HC=CH), 7.33 (bs,5H,C_6H_5)
Anal. calcd. for $C_{26}H_{38}O_7$: C, 67.51; H, 8.28.
Found: C, 67.70; H, 8.39.



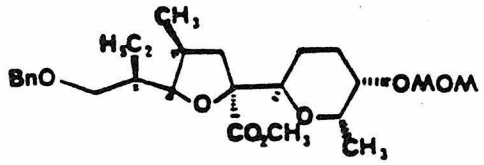
88d

R_f= 0.13 (20% ethyl acetate in cyclohexane)
evap. dis. 150°-160°C, .005 mmHg
$[\alpha]_D^{23}$= +178.8° (C=1.30,$CHCl_3$)
IR ($CHCl_3$) 1750, 1730, 1460, 1385, 1155, 1100, 1040 cm^{-1}
^{1}H-NMR ($CDCl_3$) δ0.90 (t,3H,J=6Hz, CH_3CH_2), 0.97 (d,3H,J=6Hz,CH_3CHCC) 1.16 (d,3H,J=6Hz,CH_3CHOC), 2.50 (q,1H,J=6Hz, CH_3CHCC), 3.34 (s,3H, OCH_3), 3.68 (s,3H,CO_2CH_3), 4.43 (s,2H, $C_6H_5CH_2$), 4.57 (d,1H,J=6Hz, OCHHO), 4.70 (d,1H,J=6Hz,OCHHO), 5.31 (bs,2H,HC=CH), 7.32 (bs,5H, C_6H_5)
Anal.calcd. for $C_{26}H_{38}O_7$: C, 67.51; H, 8.28.
Found: C, 67.43; H, 8.27.



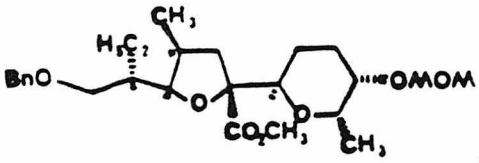
89a

R_f= 0.18 (15% ethyl acetate in petroleum ether)
evap. dis. 150°-160°C, .005 mmHg
$[\alpha]_D^{26}$= +3.4° (C=0.83, $CHCl_3$)
IR($CHCl_3$)1730,1460,1380,1100,1040 cm^{-1}
^{1}H-NMR($CDCl_3$)δ 0.93 (t,3H,J=6Hz,CH_3CH_2), 0.94 (d,3H,J=6Hz,CH_3CHCC), 1.20 (d,3H,J=6Hz,CH_3 CHOC), 3.31 (s,3H,OCH_3), 3.69 (s,3H,CO_2CH_3), 4.43 (bs,3H,$C_6H_5CH_2$), 4.58 (bs,3H,OCH_2O), 7.30 (bs,5H,C_6H_5)
Anal. Calcd. for $C_{26}H_{40}O_7$: C,67.22; H,8.68
Found: C,67.46; H,8.67.



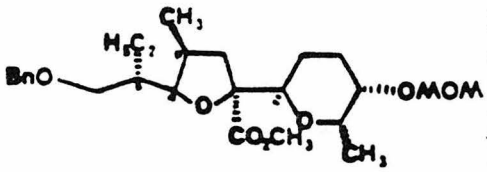
89b

R_f= 0.17 (20% ethyl acetate in petroleum ether)
evap. dis. 150°-160°C, .005 mmHg
$[\alpha]_D^{25}$= +19.3° (C=0.56, $CHCl_3$)
IR($CHCl_3$) 1745,1730,1460,1385,1210,1140, 1105,1030 cm^{-1}
^{1}H-NMR($CDCl_3$)δ 0.93 (t,3H,J=6Hz,CH_3CH_2), 0.97 (d,3H,J=6Hz,CH_3CHCC), 1.12 (d,3H,J=6Hz, CH_3CHOC), 3.30 (s,3H,OCH_3), 3.63 (s,3H,CO_2CH_3), 4.40 (bs,2H,$C_6H_5CH_2$), 4.57 (bs,2H,OCH_2O), 7.30 (s,5H,C_6H_5)
Anal.Calcd. for $C_{26}H_{40}O_7$:C,67.22; H,8.68
Found: C,67.23; H,8.69.



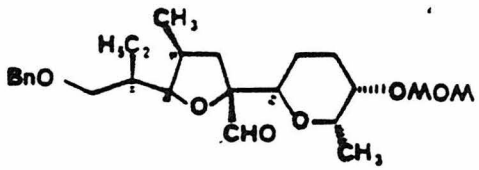
89c

R_f= 0.23 (20% ethyl acetate in cyclohexane)
evap. dis. 150°-160° C, 0.005 mm Hg
$[\alpha]_D^{24}$ = +3.5° (C=1.255, $CHCl_3$)
IR ($CHCl_3$) 1730,1460,1380,1110,1040 cm^{-1}
^{1}H-NMR ($CDCl_3$) δ0.93 (t,3H,J=6Hz,CH_3CH_2), 0.95 (d,3H,J=6Hz, CH_3CHCC), 1.17 (d,3H, J=6Hz, CH_3CHOC), 3.33 (s,3H,OCH_3), 3.70 (s,3H,CO_2CH_3), 4.47 (bs,2H,$C_6H_5CH_2$), 4.59 (bs,2H,OCH_2O), 7.33 (bs,5H,C_6H_5)
Anal. calcd. for $C_{26}H_{40}O_7$: C, 67.22; H, 8.68.
Found: C, 67.02; H, 8.69.



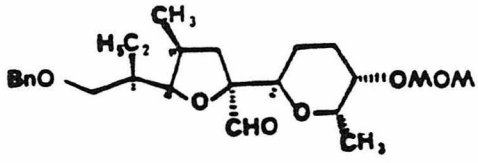
89d

R_f= 0.18 (20% ethyl acetate in cyclohexane)
evap. dis. 150°-160° C, 0.005 mm Hg
$[\alpha]_D^{23}$= +33.0° (C=1.03, $CHCl_3$)
IR ($CHCl_3$) 1750,1730,1460,1390,1110, 1040 cm^{-1}
^{1}H-NMR ($CDCl_3$) δ0.90 (t,3H,J=6Hz,CH_3CH_2), 0.94 (d,3H,J=6Hz, CH_3CHCC),1.12 (d,3H, J=6Hz,CH_3CHOC), 2.39 (q,1H,J=6Hz,CH_3CHCC), 3.32 (s,3H,OCH_3), 3.67 (s,3H,CO_2CH_3), 4.47 (bs,2H,$C_6H_5CH_2$), 4.60 (bs,2H,OCH_2O), 7.33 (bs,5H,C_6H_5)
Anal. calcd. for $C_{26}H_{40}O_7$: C, 67.22; H, 8.68.
Found: C, 67.31; H, 8.72.



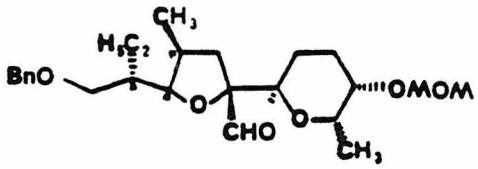
90a

R_f= 0.20 (20% ethyl acetate in petroleum ether)
evap. dis. 150°-160°C, .005 mmHg
$[\alpha]_D^{24}$= +6.2° (C=1.015, $CHCl_3$)
IR($CHCl_3$) 1735,1460,1385,1110,1040 cm^{-1}
^{1}H-NMR($CDCl_3$) δ 0.93 (t,3H,J=6Hz,CH_3CH_2), 0.94 (d,3H,J=6Hz,CH_3CHCC), 1.17 (d,3H,J=6Hz,CH_3CHOC), 3.33 (s,3H,OCH_3), 4.46 (bs,2H,$C_6H_5CH_2$), 4.60 (bs,2H,OCH_2O), 7.33 (bs,5H,C_6H_5), 9.57 (s,1H,CHO)
Anal. Calcd for $C_{25}H_{38}O_6$: C,69.10; H,8.81
Found: C,69.06; H,8.78.



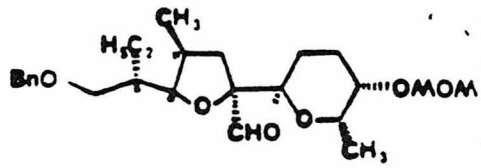
90b

R_f= 0.22 (20% ethyl acetate in petroleum ether)
evap. dis. 150°-160°, .005 mmHg
$[\alpha]_D^{24}$= + 30.7° (C=0.95, $CHCl_3$)
IR($CHCl_3$) 1740,1460,1390,1220,1110,1040 cm^{-1}
^{1}H-NMR($CDCl_3$) δ 0.92 (t,3H,J=6Hz,$C\underline{H}_3CH_2$),δ 0.96 (d,3H,J=6Hz,$C\underline{H}_3CHCC$), 1.13 (d,3H,J=6Hz,$C\underline{H}_3CHOC$), 3.32 (s,3H,OCH_3), 4.41 (bs,2H,$C_6H_5C\underline{H}_2$), 4.59 (bs, 2H,OCH_2O), 7.30 (bs,5H,C_6H_5), 9.67 (s,1H,CHO)
Anal. Calcd. for $C_{25}H_{38}O_6$: C,69.10; H,8.81.
Found: C,69.11; H,8.91.



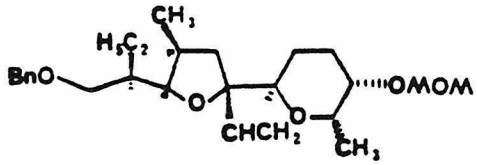
90c

R_f= 0.22 (20% ethyl acetate in cyclohexane)
evap. dis. 150°-160°C, .005 mmHg
$[\alpha]_D^{23}$= + 18.7° (C=1.55, $CHCl_3$)
IR($CHCl_3$) 1730,1460,1390,1100,1040 cm^{-1}
^{1}H-NMR($CDCl_3$) δ 0.93 (t,3H,J=6Hz,$C\underline{H}_3CH_2$), 0.93 (d,3H,J=6Hz,$C\underline{H}_3CHCC$), 1.17 (d,3H,J=6Hz,$C\underline{H}_3CHOC$), 3.33 (s,3H,OCH_3), 4.47 (bs,2H,$C_6H_5C\underline{H}_2$), 4.60 (bs,2H,OCH_2O), 7.33 (bs,5H,C_6H_5), 9.6 (s,1H,CHO)
Anal.Calcd. for $C_{25}H_{38}O_6$: C,69.10; H,8.81
Found: C,69.08; H,8.73.



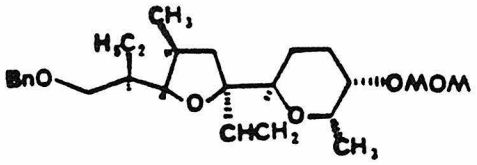
90d

R_f= 0.21 (20% ethyl acetate in cyclohexane)
evap. dis. 150°-160° C, 0.005 mm Hg
$[\alpha]_D^{23}$ = +50.8° (C=1.00, $CHCl_3$)
IR ($CHCl_3$) 1735,1460,1380,1110,1040 cm^{-1}
^{1}H-NMR ($CDCl_3$) δ0.90 (t,3H,J=6Hz,$C\underline{H}_3CH_2$), 0.94 (d,3H,J=6Hz,$C\underline{H}_3CHCC$), 1.12 (d,3H, J=6Hz,$C\underline{H}_3CHOC$), 2.33 (q,1H,J=6Hz,$CH_3C\underline{H}CC$), 3.30 (s,3H,OCH_3), 4.46 (bs,2H,$C_6H_5C\underline{H}_2$), 4.57 (bs,2H,OCH_2O), 7.30 (bs,5H,C_6H_5), 9.67 (s,1H, CHO)
Anal. calcd. for $C_{25}H_{38}O_6$: C, 69.10; H, 8.81.
Found: C, 69.06; H, 8.80.



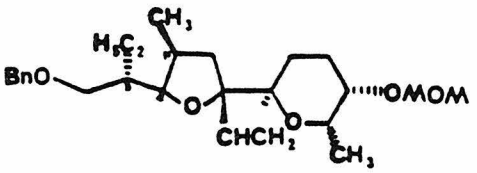
91a

R_f=0.20 (8% ethyl acetate in petroleum ether)
evap. dis. 140°-150°C, .005 mmHg
$[\alpha]_D^{26}$= -2.8° (C=1.04, $CHCl_3$)
IR ($CHCl_3$)1470,1390,1110,1040 cm^{-1}
^{1}H-NMR($CDCl_3$)δ 0.92 (t,3H,J=6Hz,CH_3CH_2),0.93 (d,3H,J=6Hz,CH_3CHCC), 1.13 (d,3H,J=6Hz,CH_3CHOC), 3.31 (s,3H,OCH_3), 4.44 (bs,2H,$C_6H_5CH_2$) 4.58 (bs,2H,OCH_2O), 4.96 (dd,1H,J=3Hz, 11 Hz,HC=CHH(c)), 5.19 (dd,1H,J=3Hz,18Hz, HC=CHH(t)), 5.87 (dd,J=11 Hz,18Hz,HC=CH_2), 7.31 (bs,5H,C_6H_5)
Anal. Calcd. for $C_{26}H_{40}O_5$= C,72.19; H,9.32
Found: C,72.11; H,9.20.



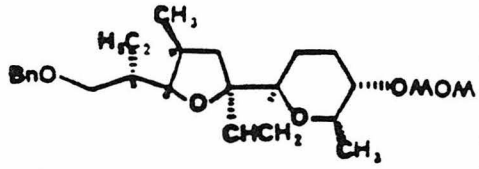
91b

R_f= 0.18 (8% ethyl acetate in petroleum ether)
evap. dis. 140°-150°C, .005 mmHg
$[\alpha]_D^{26}$= +42.1° (C=0.96, $CHCl_3$)
IR ($CHCl_3$)1460,1380,1100,1030 CM^{-1}
^{1}H-NMR($CDCl_3$)δ 0.93 (t,3H,J=6Hz,CH_3CH_2), δ 0.97 (d,3H,J=6Hz,CH_3CHCC), 1.20 (d,3H, J=6Hz,CH_3CHOC), 3.33 (s,3H,OCH_3), 4.44 (bs, 2H,$C_6H_5CH_2$), 4.59 (bs,2H,OCH_2O), 5.0 (dd, 1H,J=3Hz, 11 Hz,HC=CHH(c)), 5.13 (dd,1H,J= 3Hz,18Hz,HC=CHH(t)), 5.87 (dd,1H,J=11 Hz, 18Hz,HC=CH_2), 7.30 (bs,5H,C_6H_5)
Anal. Calcd. for $C_{26}H_{40}O_5$: C,72.19; H,9.32
Found: C,72.01; H,9.20.



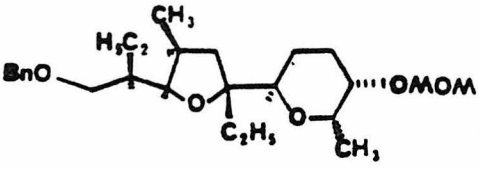
91c

R_f= 0.26 (10% ethyl acetate in cyclohexane)
evap. dis. 140°-150°C, .005 mmHg
$[\alpha]_D^{23}$= +2.8° (C=0.905,$CHCl_3$)
IR ($CHCl_3$)1460,1380,1205,1110,1040 cm^{-1}
^{1}H-NMR ($CDCl_3$)δ 0.93 (t,3H,J=6Hz,CH_3CH_2), 0.93 (d,3H,J=6Hz,CH_3CHCC), 1.14 (d,3H,J=6Hz, CH_3CHOC), 3.33 (s,3H,OCH_3), 4.44 (bs,2H, $C_6H_5CH_2$), 4.61 (bs,2H,OCH_2O), 4.93 (dd,1H, J=3Hz,11 Hz,HC=CHH(c)), 5.13 (dd,1H,J=3Hz, 18Hz,HC=CHH(t)), 5.90 (dd,1H,J=11 Hz,18Hz, HC=CH_2), 7.33 (bs,5H,C_6H_5)
Anal. Calcd. for $C_{26}H_{40}O_5$: C,72.19; H,9.32
Found: C,72.10; H,9.29.



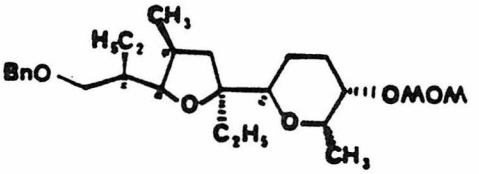
91d

R_f= 0.16 (7% ethyl acetate in cyclohexane)
evap. dis. 140°-150°C, 0.005 mm Hg
$[\alpha]_D^{23}$ = +51.4° (C=0.97, $CHCl_3$)
IR($CHC\ell_3$) 1460, 1380, 1100, 1030 cm^{-1}
^{1}H-NMR ($CDCl_3$) δ 0.91 (t,3H,J=6Hz,CH_3CH_2), 0.94 (d,3H,J=6Hz,CH_3CHCC), 1.20 (d,3H, J=6Hz,CH_3CHOC), 3.32 (s,3H,OCH_3), 4.47 (bs,2H,$C_6H_5CH_2$), 4.59 (bs,2H,OCH_2O), 5.02 (dd,1H,J=3Hz,10Hz, HC=CHH (c)), 5.20 (dd, 1H,J=3Hz,18Hz,HC=CHH (t)), 5.87 (dd,1H, J=10Hz,18Hz,$HC=CH_2$), 7.32 (bs,5H,C_6H_5)
Anal. calcd. for $C_{26}H_{40}O_5$: C, 72.19; H, 9.32.
Found: C, 72.26; H, 9.15.



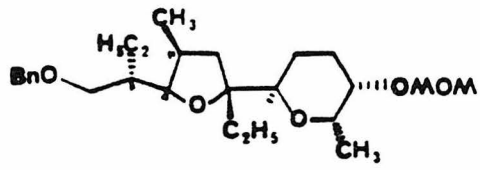
92a

R_f=0.19 (7% ethyl acetate in petroleum ether)
evap. dis. 140°-150°C, .005 mmHg
$[\alpha]_D^{25}$= +14.0° (C=0.97, $CHC\ell_3$)
IR ($CHC\ell_3$) 1460,1380,1100,1035 cm^{-1}
^{1}H-NMR ($CDC\ell_3$)δ 1.20 (d,3H,J=6Hz,CH_3CHOC), 3.33 (s,3H,OCH_3), 4.52 (bs,2H,$C_6H_5CH_2$), 4.61 (bs,2H,OCH_2O), 7.33 (bs,5H,C_6H_5)
Anal. Calcd. for $C_{26}H_{42}O_5$: C,71.85; H,9.74
Found: C,71.88; H,9.74.



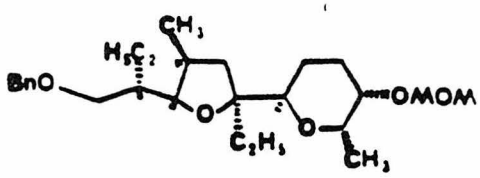
92b

R_f= 0.16 (7% ethyl acetate in petroleum ether)
evap. dis. 140°-150°C, .005 mmHg
$[\alpha]_D^{25}$= +14.3° (C=0.955, $CHC\ell_3$)
IR($CHC\ell_3$)1460,1385,1105,1040 cm^{-1}
^{1}H-NMR($CDC\ell_3$)δ 1.20 (d,3H,J=6Hz,CH_3CHOC), 3.33 (s,3H,OCH_3), 4.43 (bs,2H,$C_6H_5CH_2$), 4.60 (bs,2H,OCH_2O), 7.30 (bs,5H,C_6H_5)
Anal. Calcd. for $C_{26}H_{42}O_5$: C,71.85; H,9.74
Found: C,71.82; H,9.88.



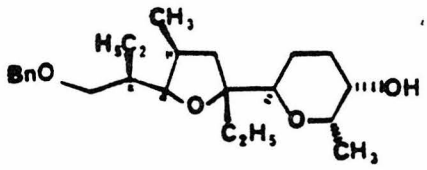
92c

R_f= 0.19 (7% ethyl acetate in cyclohexane)
evap. dis. 140°-150°C, .005 mmHg
$[\alpha]_D^{23}$= +27.0° (C=1.565,$CHCl_3$)
IR($CHCl_3$)1460,1380,1210,1110,1040 cm^{-1}
^{1}H-NMR($CDCl_3$)δ 1.17 (d,3H,J=6Hz,CH_3CHOC), 3.33 (s,3H,OCH_3), 4.44 (bs,2H,$C_6H_5CH_2$), 4.57 (bs,2H,OCH_2O), 7.33 (bs,5H,C_6H_5)
Anal. Calcd. for $C_{26}H_{42}O_5$: C,71.85; H,9.74
Found: C,71.68; H,9.58.



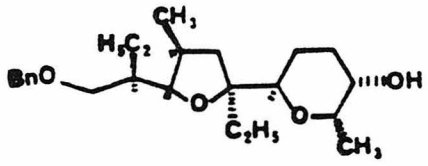
92d

R_f= 0.15 (7% ethyl acetate in cyclohexane)
evap. dis. 140°-150° C, 0.005 mm Hg
$[\alpha]_D^{24}$ = +28.3° (C=1.03, $CHCl_3$)
IR($CHCl_3$) 1460,1390,1100,1040 cm^{-1}
^{1}H-NMR ($CDCl_3$) δ 0.82, 0.90 (t,6H, J=6Hz,CH_3CH_2), 0.94 (d,3H,J=6Hz,CH_3CHCC), 1.18 (d,3H,J=6Hz,CH_3CHOC), 3.32 (s,3H,OCH_3), 4.46 (bs,2H,$C_6H_5CH_2$), 4.59 (bs,2H,OCH_2O), 7.30 (bs,5H,C_6H_5)
Anal. calcd. for $C_{26}H_{42}O_5$: C, 71.85; H, 9.74.
Found: C, 71.88; H, 9.59.



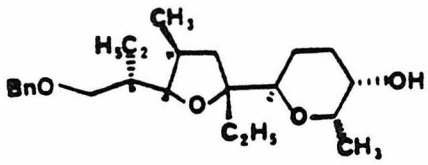
93a

R_f= 0.19 (25% ethyl acetate in petroleum ether)
evap. dis. 140°-150°C, .005 mmHg
$[\alpha]_D^{25}$= +11.6° (C=0.93,$CHCl_3$)
IR($CHCl_3$)3620,3450,1460,1380,1100,1070 cm^{-1}
^{1}H-NMR($CDCl_3$) δ1.14 (d,3H,J=6Hz,CH_3CHOC), 4.44 (s,2H,$C_6H_5CH_2$), 7.32 (bs,5H,C_6H_5)
Anal. Calcd. for $C_{24}H_{38}O_4$: C,73.81; H,9.81
Found: C,73.79; H,9.70.



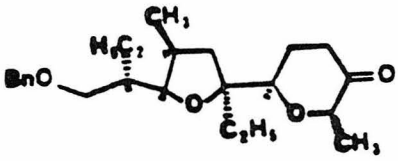
93b

R_f= 0.18 (25% ethyl acetate in petroleum ether)
evap. dis. 140°-150° C, .005 mmHg
$[\alpha]_D^{25}$= +9.7° (C=0.96, $CHCl_3$)
IR($CHCl_3$)3640,3450,1460,1380,1105,1070 cm^{-1}
^{1}H-NMR($CDCl_3$)δ 0.96 (d,3H,J=6Hz,CH_3CHCC), 1.17 (d,3H,J=6Hz,CH_3CHOC), 4.42 (s,2H,$C_6H_5CH_2$), 7.32 (bs,5H,C_6H_5)
Anal. calcd.for $C_{24}H_{38}O_4$:C,73.81; H,9.81
Found: C,73.91; H,9.73.



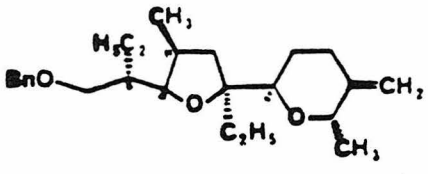
93c

R_f= 0.10 (20% ethyl acetate in cyclohexane)
evap. dis. 140°-150°C, .005 mmHg
$[\alpha]_D^{23}$= +19.8° (C=2.0,$CHCl_3$)
IR($CHCl_3$) 3650,3450,1460,1380,1100,1070 cm^{-1}
^{1}H-NMR($CDCl_3$)δ 1.17 (d,3H,J=6Hz,CH_3CHOC), 4.47 (s,2H,$C_6H_5CH_2$), 7.33 (bs,5H,C_6H_5)
Anal. Calcd. for $C_{24}H_{38}O_4$:C,73.81; H,9.81
Found: C,73.72; H,9.72.



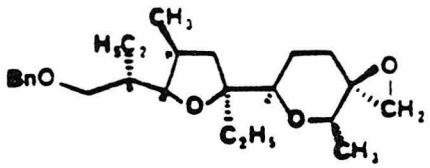
94

R_f = 0.2 (10% ethyl acetate in cyclohexane)
evap. dis. 120°-130° C, 0.005 mm Hg
$[\alpha]_D^{24}$= -5.9° (C=0.95, $CHCl_3$)
IR ($CHCl_3$) 1720,1460,1380,1110 cm^{-1}
^{1}H-NMR ($CDCl_3$) δ 1.27 (d,3H,J=6Hz,CH_3CHOC), 4.30 (q,1H,J=6Hz,CHCO), 4.44 (s,2H,$C_6H_5CH_2$), 7.33 (bs,5H,C_6H_5)
Anal. calcd. for $C_{24}H_{36}O_4$: C, 74.19; H, 9.34.
Found: C, 74.02; H, 9.35.



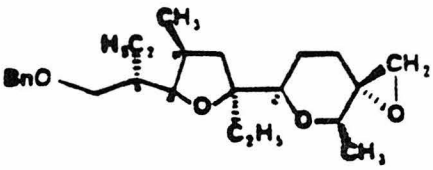
95

R_f= 0.25 (4% ethyl acetate in cyclohexane)
evap. dis. 120°-130° C, 0.005 mm Hg
$[\alpha]_D^{24}$= +7.9° (C=1.205, $CHCl_3$)
IR ($CHCl_3$) 1460,1380,1120,1080 cm^{-1}
^{1}H-NMR ($CDCl_3$) δ0.83, 0.93 (t,6H,J=6Hz, $C\underline{H}_3CH_2$), 0.97 (d,3H,J=6Hz,$C\underline{H}_3CHCC$), 1.30 (d,3H, J=6Hz,$C\underline{H}_3CHOC$), 4.43 (q,1H,J=6Hz,$C\underline{H}C$=C), 4.47 (s,2H,$C_6H_5C\underline{H}_2$), 4.67 (bs,2H,C=CH_2), 7.31 (bs,5H,C_6H_5)
Anal. calcd. for $C_{25}H_{38}O_3$: C, 77.68; H, 9.91.
Found: C, 77.64; H, 10.03.



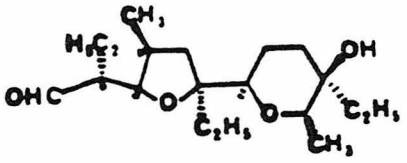
96a

R_f= 0.16 (10% ethyl acetate in petroleum ether)
evap. dis. 130°-140°C, 0.005 mm Hg
$[\alpha]_D^{24}$= -4.4° (C=1.03, $CHCl_3$)
IR ($CHCl_3$) 1460,1380,1120,1080 cm^{-1}
^{1}H-NMR ($CDCl_3$) δ 0.86, 0.93 (t,6H, J=6Hz,$C\underline{H}_3CH_2$), 0.97 (d,3H, J=6Hz, $C\underline{H}_3CHCC$), 1.27 (d,3H,J=6Hz,$C\underline{H}_3CHOC$), 2.52 (d,1H,J=4Hz,CC$\underline{H}$HO), 2.59 (d,1H, J=4Hz,CC$\underline{H}$HO), 4.47 (s,2H,$C_6H_5C\underline{H}_2$), 7.33 (bs,5H,C_6H_5)
Anal. calcd. for $C_{25}H_{38}O_4$: C, 74.59; H, 9.51.
Found: C, 74.50; H, 9.46.



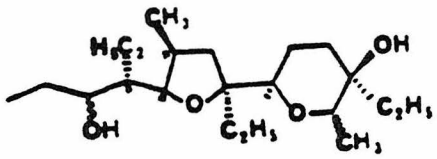
96b

R_f= 0.26 (10% ethyl acetate in petroleum ether)
evap. dis. 130°-140° C, 0.005 mm Hg
$[\alpha]_D^{24}$= +7.8° (C=1.02,$CHCl_3$)
IR($CHCl_3$) 1460,1380,1120,1080 cm^{-1}
^{1}H-NMR ($CDCl_3$) δ 0.86, 0.93 (t,6H,J=6Hz, $C\underline{H}_3CH_2$), 0.97 (d,3H,J=6Hz,$C\underline{H}_3CHCC$), 1.24 (d,3H,J=6Hz,$C\underline{H}_3CHOC$), 2.58 (d,1H,J=5Hz, CC$\underline{H}$HO), 2.71 (d,1H,J=5Hz,CC$\underline{H}$HO), 4.47 (s,2H,$C_6H_5C\underline{H}_2$), 7.31 (bs,5H,C_6H_5)
Anal. calcd. for $C_{25}H_{38}O_4$: C, 74.59; H, 9.51.
Found: C, 74.39; H, 9.36.



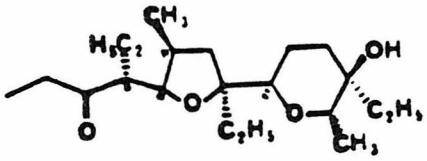
97

R_f= 0.17 (40% ether in petroleum ether)
evap. dis. 130°-140° C, 0.005 mm Hg
$[\alpha]_D^{22}$ = -2.5° (C=1.1, $CHCl_3$)
IR ($CHCl_3$) 3600,3450,2750,1720,1460,1390,1230, 1130,1100,1060,960 cm^{-1}
^{1}H-NMR ($CDCl_3$) δ 0.97 (d,3H,J=6Hz,CH_3CHCC), 1.18 (d,3H,J=6Hz,CH_3CHOC), 9.64 (d,1H,J=3Hz, CHO)
Anal. calcd. for $C_{19}H_{34}O_4$: C, 69.90; H, 10.50.
Found: C, 69.77; H, 10.44.



98

R_f= 0.12, 0.17 (50% ether in petroleum ether)
evap. dis. 120°-130° C, 0.005 mm Hg
IR ($CHCl_3$) 3600,3500,1460,1380, 1130,1100,1060,960 cm^{-1}
^{1}H-NMR ($CDCl_3$) δ 1.20 (d,3H, J=6Hz,CH_3CHOC)



99

R_f= 0.18 (35% ether in petroleum ether)
evap. dis. 110°-120° C, 0.005 mm Hg
$[\alpha]_D^{24}$= -19.2° (C=0.755, $CHCl_3$)
IR ($CHCl_3$) 3600,1710,1460,1385,1135, 1100,1060,960 cm^{-1}
^{1}H-NMR ($CDCl_3$) δ 1.20 (d,3H,J=6Hz, CH_3CHOC), 3.74 (q,1H,J=6Hz,$CH$$CH_3$OC)
Anal. calcd. for $C_{21}H_{38}O_4$: C, 71.15; H, 10.80.
Found: C, 71.14; H, 10.71.

Abstracts of Propositions

PROPOSITION 1

An approach to the synthesis of an alkaloid of the pumiliotoxin A class, isolated from the Ecuadorian frog, Denbrobates tricolor, is proposed using [3,3] and [2,3] sigmatropic rearrangements to control all relative stereochemical centers.

PROPOSITION 2

An approach to the synthesis of croomine, isolated from the roots and rhizomes of Croomia heterosepala Okuyama (Stemonaceae), is proposed using ester enolate Claisen rearrangements and halolactonizations to transfer chirality from the starting material D-galactose.

PROPOSITION 3

Two enantiomeric diols, each of which can be obtained in optically pure form from a monosaccharide, are proposed as ligands for boron in the reaction of crotyl boronates with optically-active aldehydes. The resulting aldol-type condensation product has the structural unit R_1-$CHCH_3$-CHOH-$CHCH_3$-R_2, which can be found in numerous natural products. Each of the eight possible diastereomers can be obtained by this procedure.

PROPOSITION 4

An investigation into the existence and possible synthesis of [2.2] (1,3) cyclobutadienophane and the corresponding bis-iron tricarbonyl complex is proposed, utilizing photo-α-pyrone for the preparation of the cyclobutadiene complex.

PROPOSITION 5

An investigation which will reveal the basic amino acid residues at the active sites of phosphoglucose and phosphomannose isomerases is proposed, using 1-chloro-1-deoxy-D-glucitol-6-phosphate and 1-chloro-1-deoxy-D-mannitol-6-phosphate as active-site-directed inhibitors which would label the bases involved in the "enediol" isomerization mechanism.

PROPOSITION 1

An approach to the synthesis of an alkaloid of the pumiliotoxin A class, isolated from the Ecuadorian frog, Denbrobates tricolor, is proposed using [3,3] and [2,3] sigmatropic rearrangements to control all relative stereochemical centers.

A large number of alkaloids have been isolated from the neotropical frogs of the family Dendrobatidae.[1] The skin of these brightly colored frogs contains alkaloids which serve as chemical defense against predators and, consequently, possess high pharmacological activity on nerve and muscle.[2] These dendrobatid alkaloids have been isolated in only minute quantities from a large number of frogs; therefore, efficient syntheses of these substances are highly desirable. A synthetic route which could be modified to incorporate structural variety would provide access to synthetic analogs in larger quantities. These modified alkaloids would then provide biochemists with material with which they could study the mechanism of action of this unique family of alkaloids on nerve-muscle synapses.

A relatively simple member of the indolizidine alkaloids has recently been isolated from an Ecuadorian frog, Denbrobates tricolor.[3] Extraction of the skins of 750 frogs provided 80 mg of a compound which was converted into its hydrochloride salt and subjected to X-ray analysis. This structural determination resulted in the unveiling (see figure 1) of the first structurally defined member of the pumiliotoxin A class of alkaloids.

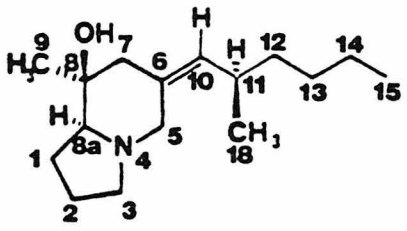


Figure 1

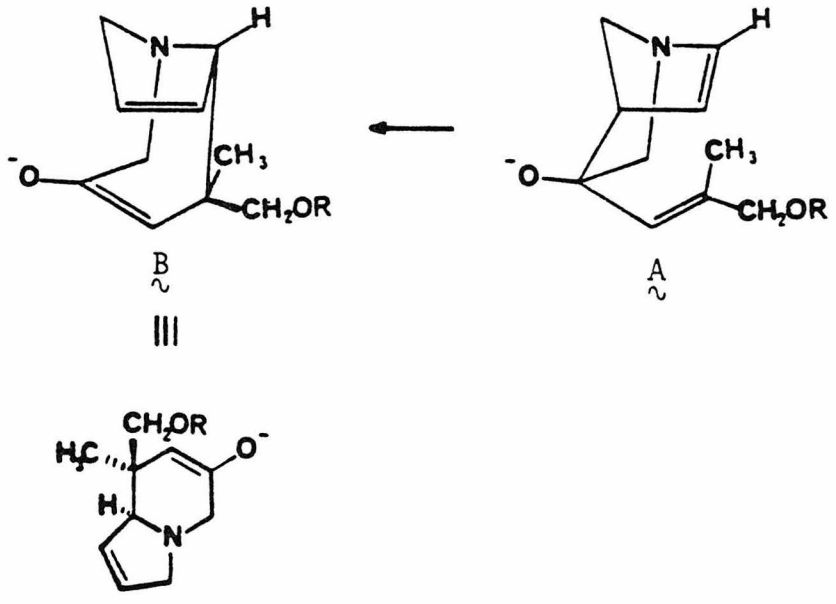


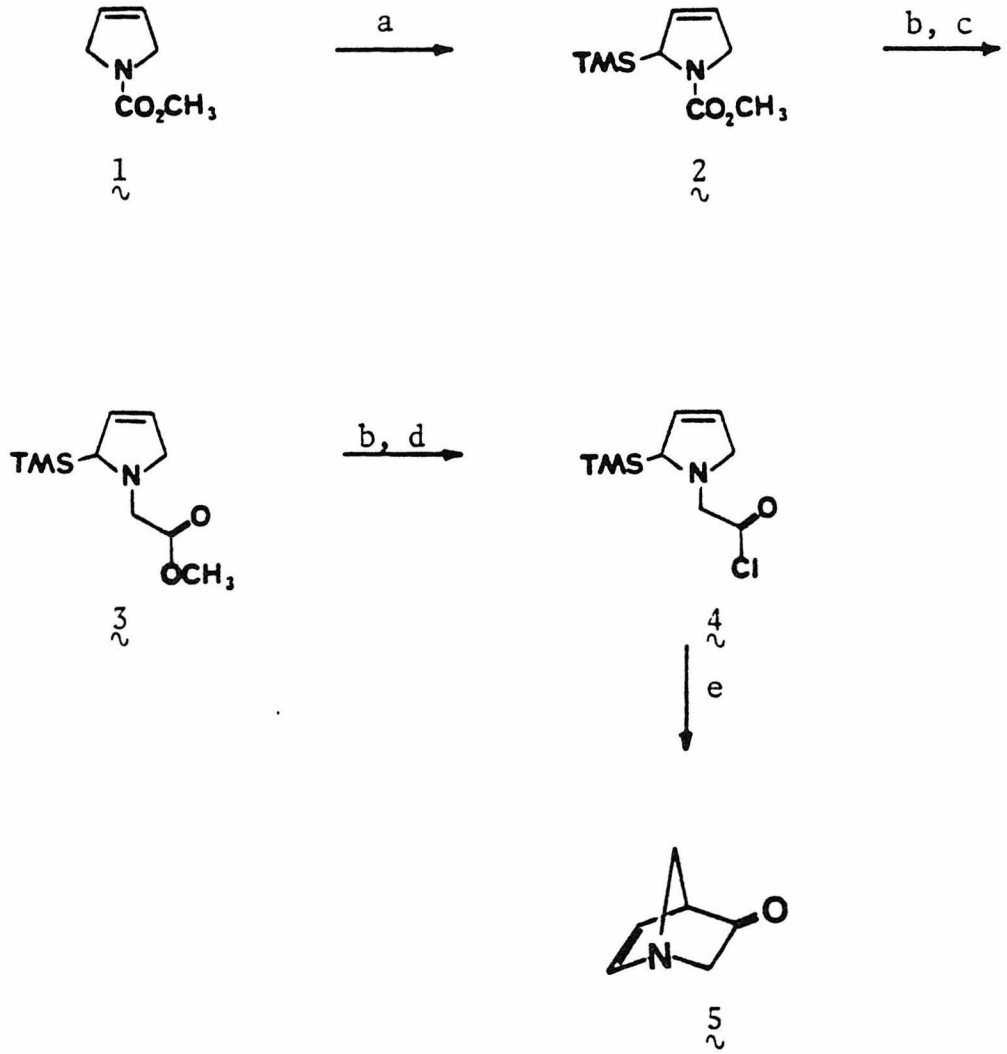
Figure 2

It was reasoned that the oxy-Cope rearrangement[4] of the bicyclo [2.2.1] system A, as shown in figure 2, would provide the indolizidine structure B with the correct relative stereochemistry at C-8 and C-8a being derived from the obligatory boat-like transition state of the sigmatropic rearrangement. This rearrangement would also provide a ketone function at C-6 which would serve as a functional center for the elaboration of the alkyl side chain. The substrate for this crucial transformation could be made available as shown in Chart 1. Silylation of the anion derived from deprotonation of N-carbomethoxy-2,5-dihydropyrrole (1)[5] should provide compound 2 which could be alkylated with methyl α-chloroacetate after basic hydrolysis. Compound 3 would then be saponified and converted into the transient acid chloride 4. Addition of aluminum chloride to the acid chloride solution[6] would then provide the bicyclic ketone 5.

The di-substituted vinyl Grignard reagent 7 could be prepared stereospecifically[7] from the protected propargylic alcohol 6, as shown in figure 3. Addition of this Grignard reagent to the ketone 5 will provide a mixture of tertiary alcohols, one of which (substrate A) is rearranged to give the oxy-Cope product.

Hydrogenation of the rearranged product should provide the ketone 8 which will be further elaborated into the frog toxin as outlined in Chart 2. Addition of a cis-vinyl Grignard reagent to the ketone 8 should occur from the α-face due to the axial MEM-ether grouping at C-8. The alcohol 9 would then be alkylated

Chart 1



1 2 3 4 5

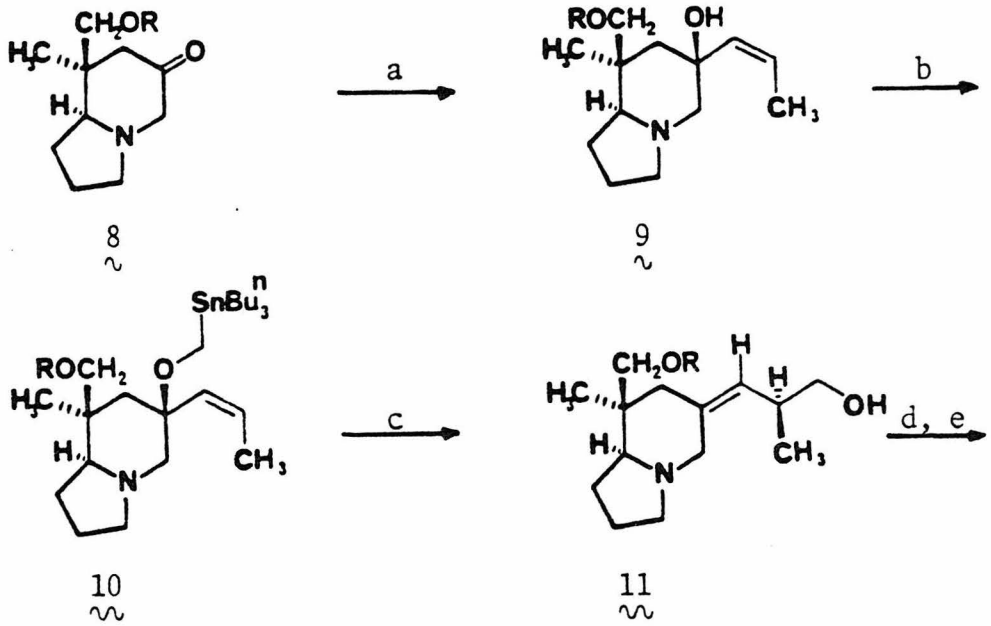
a) LDA; TMSCℓ; b) KOH, H_2O; c) $ClCH_2CO_2CH_3$, K_2CO_3; d) $(COCl)_2$; e) $AlCl_3$

Reagent: $CH_3MgBr \cdot DMS \cdot CuBr$; I_2; Mg

6 7

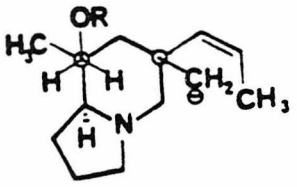
Figure 3 (R = MEM)

Chart 2



a) CH_3 (cyclopropyl) MgI; b) KH, $ICH_2SnBu^n_3$; c) n-BuLi;

d) TsCl, pyr; e) $LiPr_2Cu$; f) $ZnCl_2$, H_2O; g) Pt, O_2



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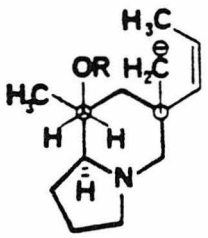

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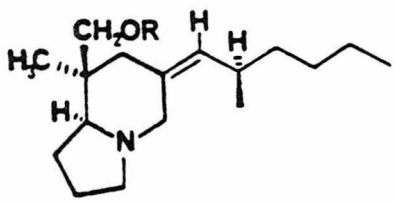
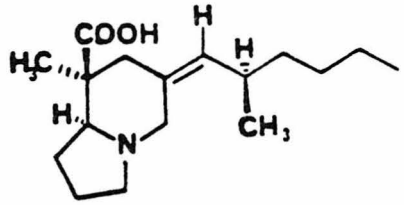


12

f, g



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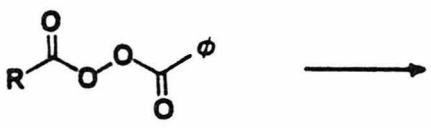

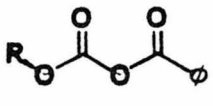

Figure 4

according to the procedure of Still[8] to give the derivative 10. Low temperature tin-lithium exchange would provide a substrate which will undergo a [2,3] sigmatropic rearrangement, leading to the γ,δ-unsaturated alcohol 11. As illustrated, conformer C should be lower in energy than the corresponding conformer D. Therefore, this rearrangement should proceed through transition state C, thereby affording the desired exocyclic olefin with the geometry as shown in compound 11. Homologation of compound 11 would then provide compound 12 and removal of an extra carbon from compound 12 would then afford the desired target melecule. A proposed plan for the final transformation relies on the instability of an acyl aroyl peroxide which undergoes a 1,2-alkyl migration to give a mixed carbonate, as shown in figure 4. This carboxy-inversion reaction can be carried out at -30°C for a tertiary acid chloride[9] and at this temperature there should not be any complications arising from oxidation of either the olefin or the nitrogen.

This therefore completes the proposed total synthesis of the first structurally defined indolizidine alkaloid of the pumiliotoxin A class.

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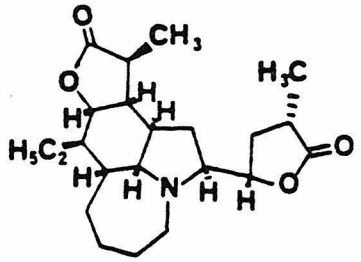
PROPOSITION 2

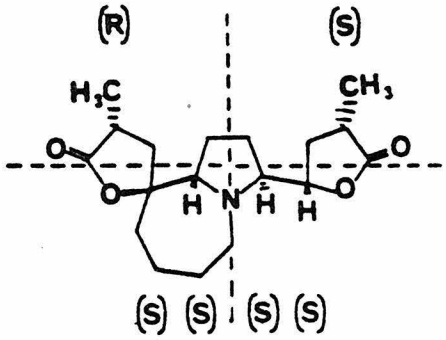
An approach to the synthesis of croomine, isolated from the roots and rhizomes of Croomia heterosepala Okuyama (Stemonaceae), is proposed using ester enolate Claisen rearrangements and halolactonizations to transfer chirality from the starting material D-galactose.

Stemona and Croomia are the two known genera of Stemonaceae. Various alkaloids from Stemona have been isolated and the structure of tuberostemonine (I)[1], shown in figure 1, is representative of this group. Recently, a new alkaloid, croomine, was isolated from the roots and rhizomes of Croomia heterosepala Okuyama (Stemonaceae)[2] and its structure was determined by single crystal X-ray analysis to be that as shown in II.

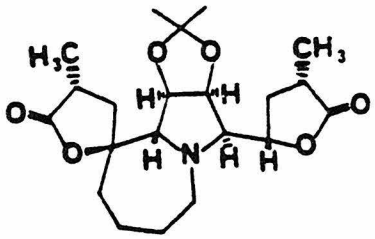
A synthetic approach to croomine should take advantage of the apparent symmetry elements present in its structure. If the structure of croomine is divided into four quadrants as shown, the top two quadrants are mirror images while the bottom two quadrants have a C_2 axis of symmetry (assuming that the methylene chain is viewed as equivalent to a proton.) If an optically active compound with latent meso properties is chosen as the starting material, two chirality transfer operations can be envisaged. Firstly, a functionality from one side of the starting material can transfer its chirality to one of the top quadrants, and, by the same operation, an analogous functionality from the mirror image side of the starting material would transfer chirality to the other top quadrant. Secondly, analogous functionalities from the two



I



II



III

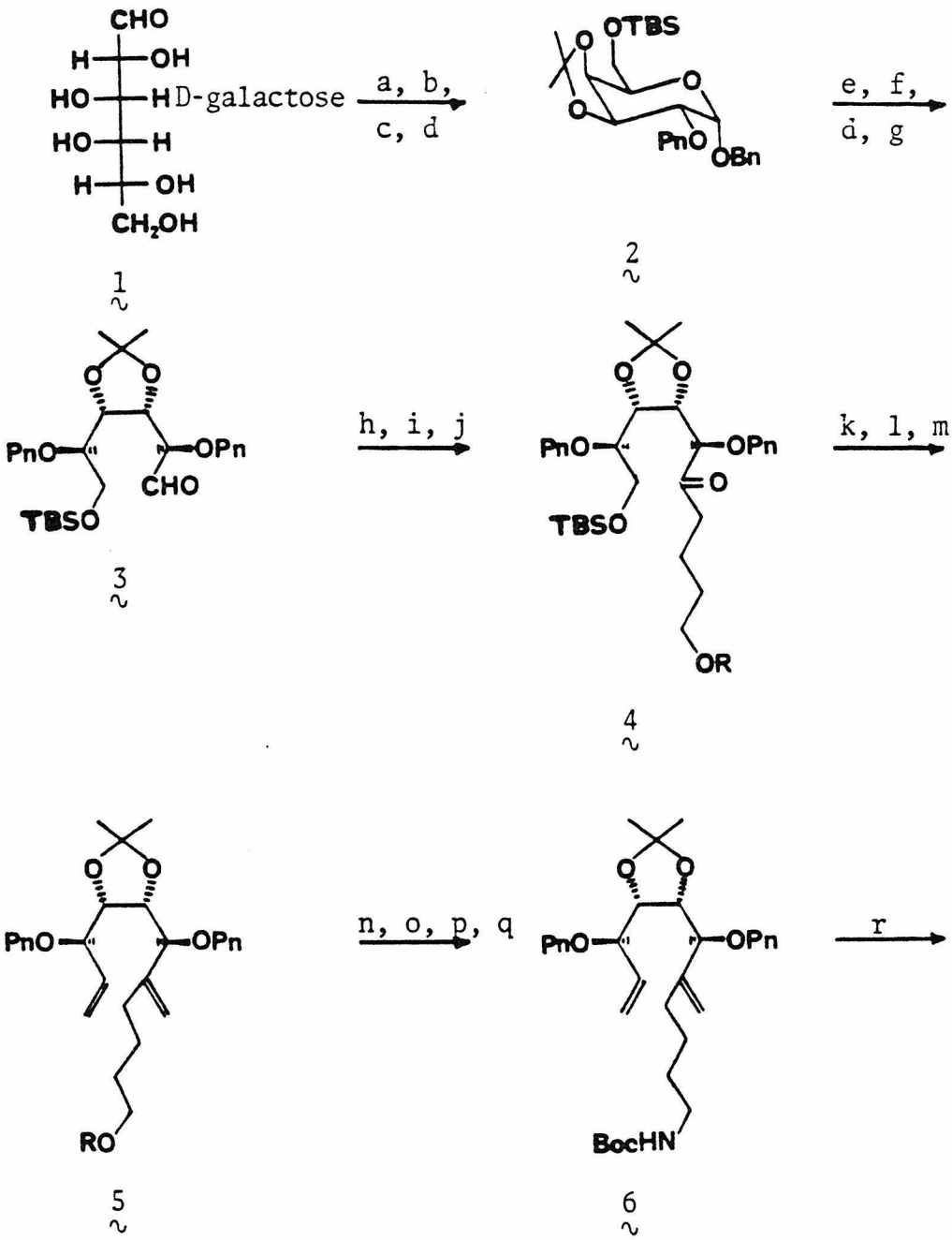
Figure 1

mirror-image halves of the starting material could transfer chirality to the bottom two quadrants, by operations which are mirror-image equivalent, in order to generate a C_2 axis of symmetry. This scheme will become apparent when the following synthetic route to compound III is examined.

The chosen starting material is D-galactose (1), Chart 1, which is a latent meso compound that suits the present purpose. It is optically active only when the two end functional groups are distinguishable. Glycosidation with benzyl alcohol[3] fixes the sugar as a pyrano-glycoside. Acetonide formation is expected to be selective[4] at C-3 and C-4 and subsequent selective protection of the primary alcohol, followed by acylation of the remaining hydroxyl group, would afford compound 2. Hydrogenolysis of the benzyl glycoside[5] would provide a lactol which can be opened by N,N-dimethylhydrazine. The released hydroxyl group can then be acylated and the aldehyde 3 can be generated by hydrolysis with cupric chloride.[6] Oxidation with silver (I) oxide[7], followed by treatment with oxalyl chloride, gives the corresponding acid chloride.

Addition of a manganese reagent[8] to the acid chloride, derived from the aldehyde 3, would give the ketone 4. Desilylation and oxidation[9] then affords a keto-aldehyde which then provides the allylic ester 5 upon Wittig olefination. The oxygen in compound 5 can be replaced with nitrogen by removal of the MEM-protecting group[10] and by utilizing the method of Mitsunobu.[11] The amino function is then protected[12] to give compound 6.

Chart 1



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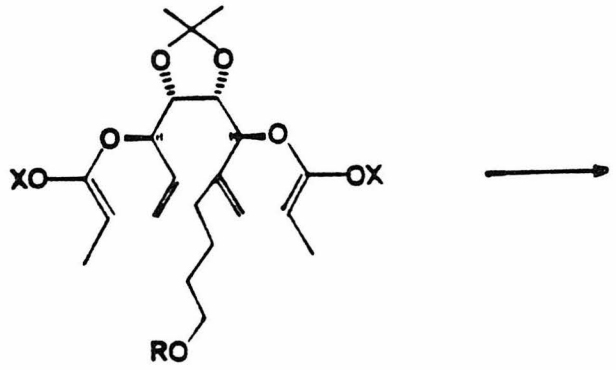

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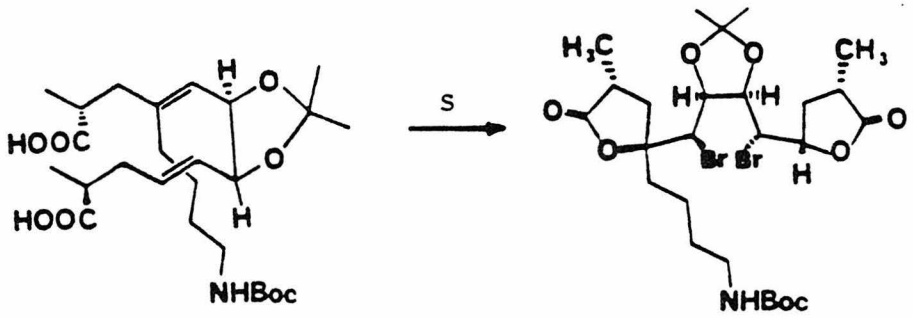


8 9

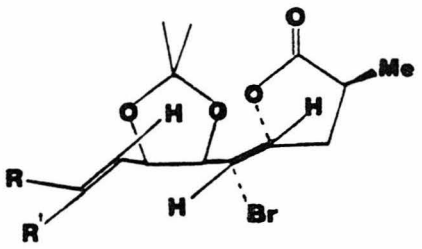
a) BnOH, H^+; b) $(MeO)_2CMe_2$, H^+; c) TBSCl, imidazole; d) C_2H_5COCl, pyr;

e) Pd, H_2; f) H_2NNMe_2; g) $CuCl_2$, H_2O; h) Ag_2O, EtOH; i) $(COCl)_2$;

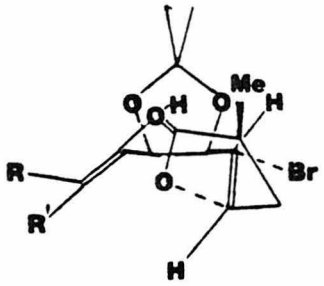
j) MEMO $(CH_2)_4MnI$; k) n-Bu_4NF; l) PCC; m) $(C_6H_5)_3PCH_2$; n) $ZnBr_2$;

o) $EtO_2CN = NCO_2Et$, $(C_6H_5)_3P$, Phthalimide; p) H_2NNH_2; q) Boc-anhydride

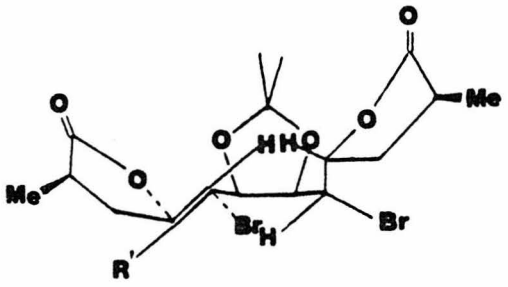
r) LDA, HMPA/THF; TMSCl; s) NBS, DMF



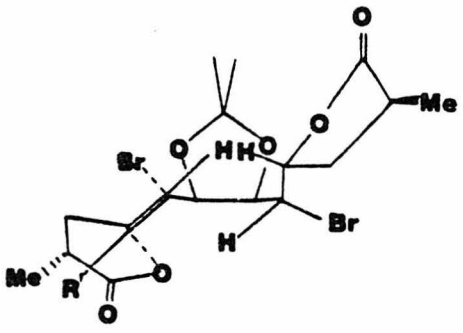
IV



V



VI



VII

Figure 2

The first chirality transfer operation is accomplished by an ester enolate Claisen rearrangement[13] whereby the stereochemistries of the resulting methyl groups have been predetermined by the chiralities of the two allylic esters.[13] Halolactonization[14] of compound 8 represents the second chirality transfer operation. It is proposed that one diastereomeric product should predominate over the other possible three diastereomers. As illustrated in figure 2, the di-substituted olefin will probably have a faster rate of halolactonization due to fewer steric interactions. Of the two possible transition states IV and V, which lead to two diastereomeric products, the former should be lower in energy on steric grounds. The subsequent halolactonization of the tri-substituted olefin has VI and VII as the two possible transition states leading to two diastereomeric products, and, since transition state VII is clearly lower in energy, this would lead to the desired diastereomeric product 9 (Chart 1).

After removal of the nitrogen-protecting group, compound 9 should cyclilize to give compound III (figure 1) with all stereocenters correctly oriented. Hydrolysis followed by removal of the vicinal diol[15] then completes the proposed total asymmetric synthesis of natural croomine.

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PROPOSITION 3

Two enantiomeric diols, each of which can be obtained in optically pure form from a monosaccharide, are proposed as ligands for boron in the reaction of crotyl boronates with optically-active aldehydes. The resulting aldol-type condensation product has the structural unit R_1-$CHCH_3$-CHOH-$CHCH_3$-R_2, which can be found in numerous natural products. Each of the eight possible diastereomers can be obtained by this procedure.

The structural unit R_1-$CHCH_3$-CHOH-$CHCH_3$-R_2 can be found in numerous natural products, such as polyether[1], ansamycin[2], and macrolide[3] antibiotics. Recently, Kishi and co-workers[4] have developed stereo- and regioselective methods for the synthesis of such structural units by a combination of Wittig olefination, epoxidation and hydroboration. The resulting transformations are summarized in figure 1.

A direct way of obtaining this structural unit is an aldol-type condensation which establishes the relative stereochemistry of the vicinal centers about the newly formed carbon-carbon bond. Work in this area has led to the stereochemical control of these two stereocenters in the kinetically controlled aldol processes[5,6,7,8,9]; however, the relative stereochemistry arising from addition to an aldehyde with an α-chiral center, resulting in a mixture of Cram and anti-Cram products, cannot be adequately controlled.

It is envisaged that an aldol-type condensation of an optically active aldehyde and a chiral reagent could result in either epimer at the carbon bearing the hydroxyl group without regard to the α-chiral center of the starting aldehyde. This is equivalent to controlling Cram or anti-Cram stereochemistry. Coupled with the ability to control the relative stereochemistry of the newly

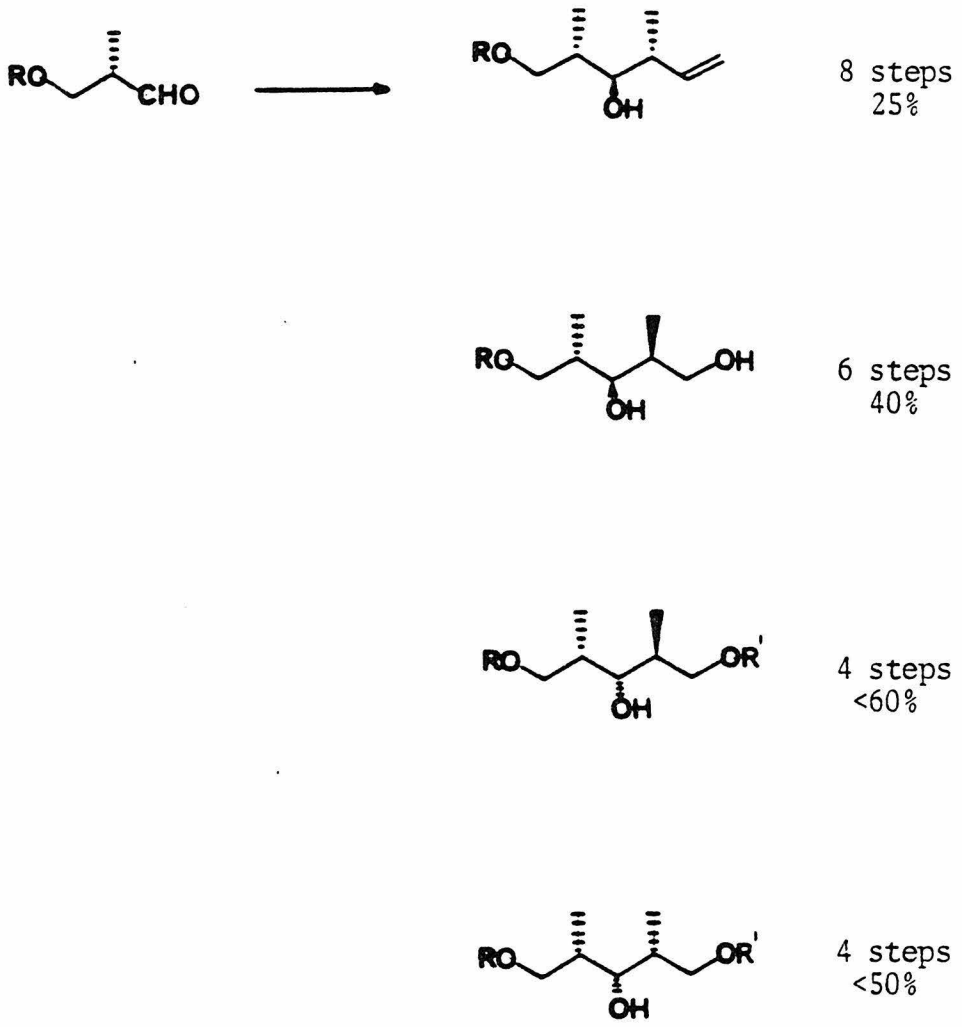

RO
CHO
RO
OH
8 steps
25%
RO
OH
OH
6 steps
40%
RO
OH
OR'
4 steps
<60%
RO
OH
OR'
4 steps
<50%

Figure 1

formed carbon-carbon bond from the aldol-type condensation, this approach would lead to the structural unit R^1-$CHCH_3$-CHOH-$CHCH_3$-R^2 in one step with all three consecutive asymmetric centers controlled.

Recently Hoffman published a diastereoselective synthesis of β-methyl homoallyl alcohols *via* crotylboronates[10], as shown in figure 2. The reaction of allylboronates modified by the diol i (figure 3) resulted in enantioselectivity of 65-75%.[11] It was also implied that the *trans* crotylboronates would give predominantly the threo products.

It is proposed that various diols with the structure shown as in compound ii (figure 3) could serve as a chiral ligands for these crotylboronate reactions. The side chain R projects into the transition state conformation of the condensation and should result in excellent control of enantioselectivity. Various R groups would be tested for optimum chiral induction.

The four possible diastereotopic transition states are shown in figure 4 for *cis* crotyl boronate and one enantiomer of the boron ligand. The non-bonded interactions are least severe in transition state B and this would result in chirality transfer from the boron ligand to the aldol product. Moreover, these diols could be prepared in enantiomerically pure forms by synthesis from either enantiomer of the readily available simple sugars,[12,13] 3a and 3b (figure 5). The synthesis for the diol ii is straightforward as shown in Chart 1.

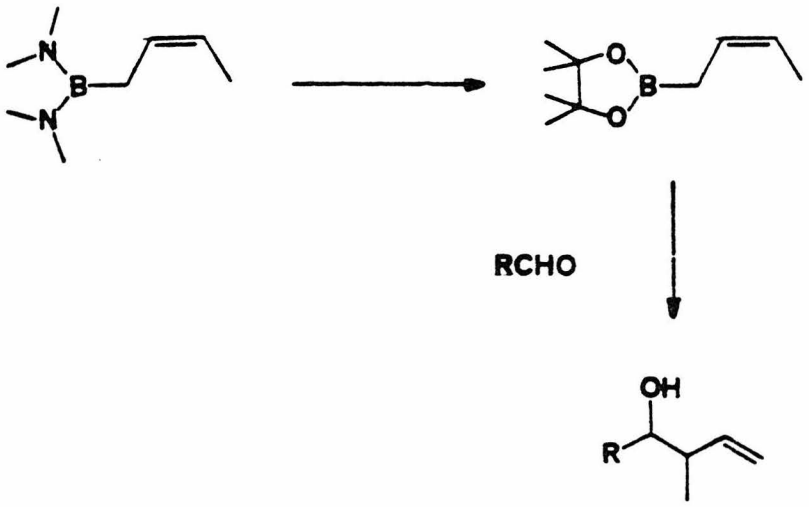
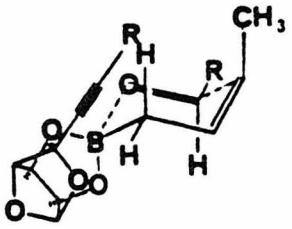


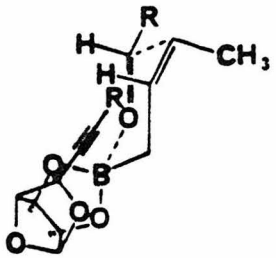
Figure 2

i ii

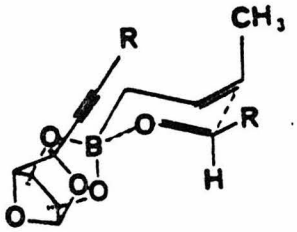
Figure 3



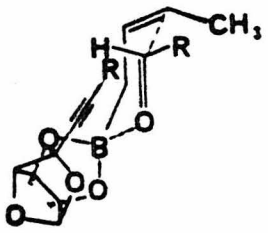
A



C



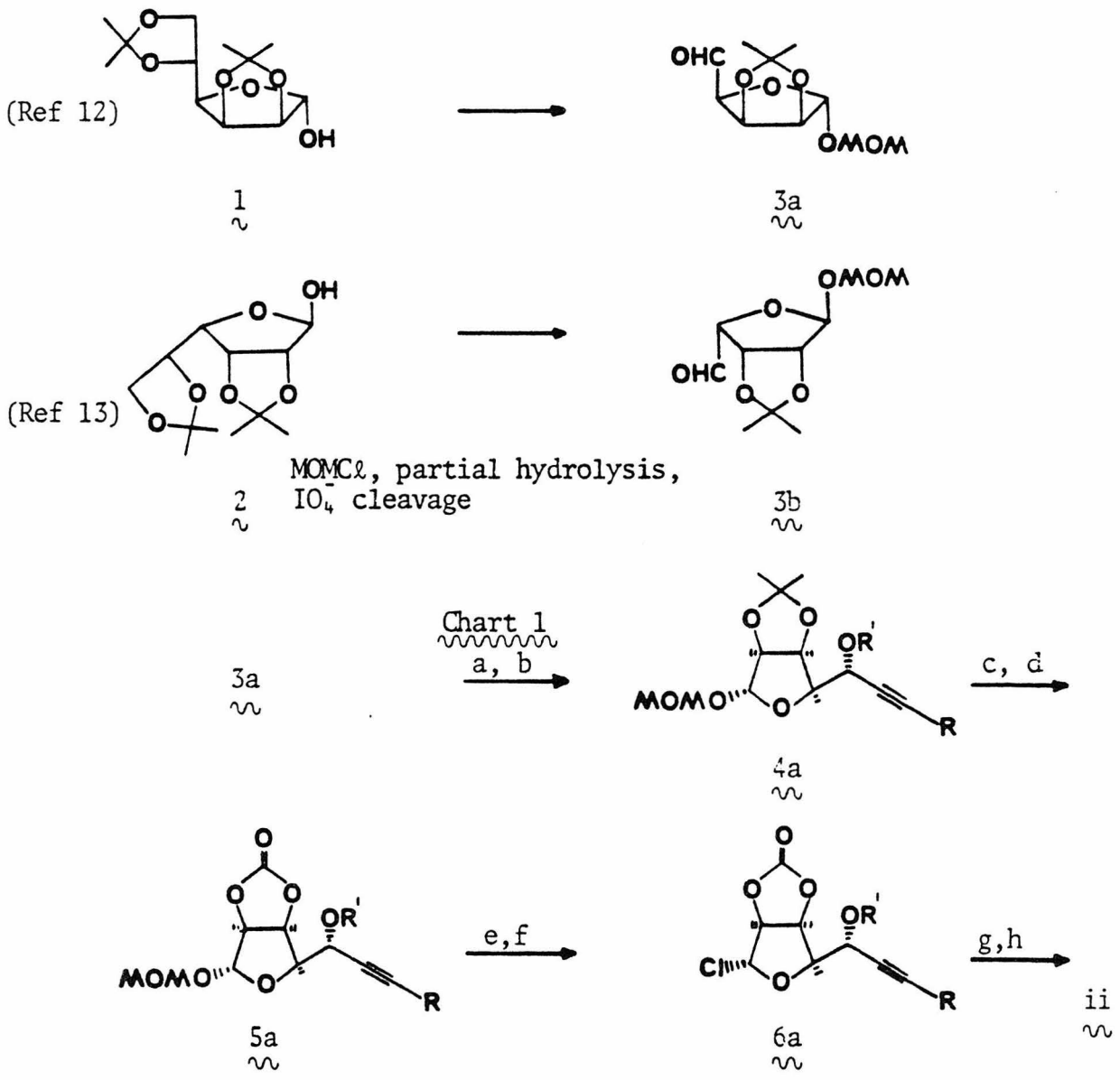
B



D

Figure 4

Figure 5



a) RC ≡ CMgX; b) t-Bu $(C_6H_5)_2SiC\ell$, imidazole; c) AcOH, H_2O;

d) $(imid.)_2$ C=O; e) $TrBF_4$; f) $CC\ell_4$, $P(NMe_2)_3$; g) AgF;

h) $NaOCH_3$

With both enantiomers of the diols available, utilizing the *cis* or the *trans* crotylboronate would result in the selective generation of any single one of the four possible products as shown in figure 6. The resulting olefin may be cleaved to a new aldehyde and this sequence can be repeated to give a methylene chain with alternate substitutions of methyl and hydroxyl groups, each center absolutely controlled.

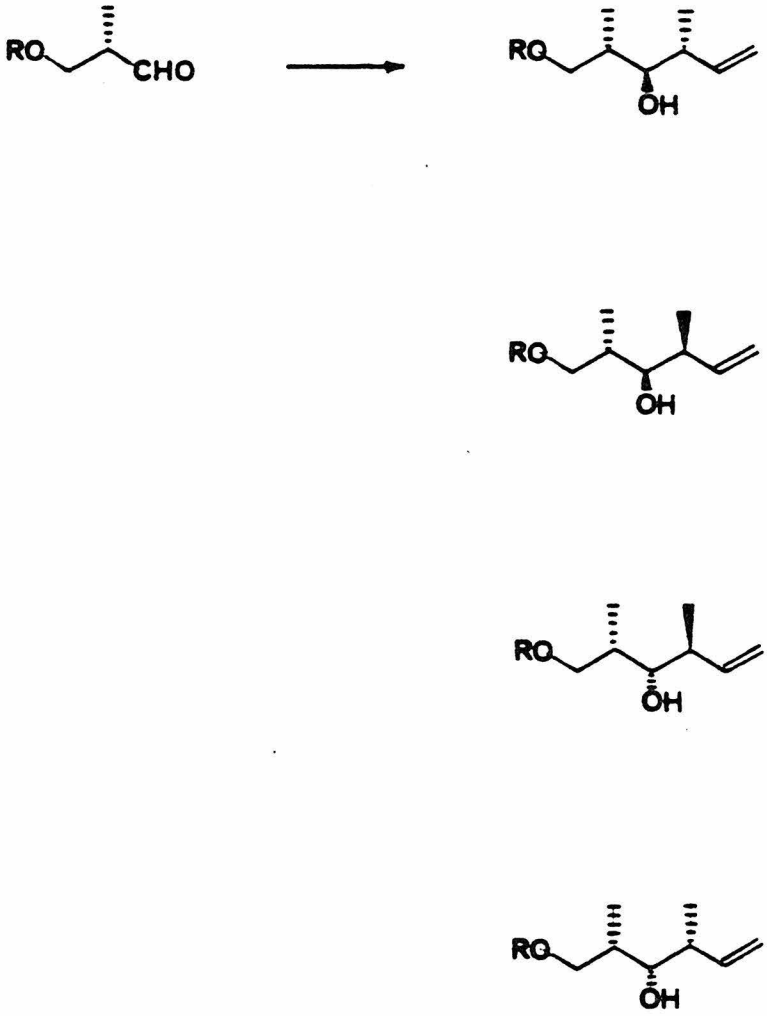


Figure 6

References:

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PROPOSITION 4

An investigation into the existence and possible synthesis of [2.2] (1,3) cyclobutadienophane and the corresponding bis-iron tricarbonyl complex is proposed, utilizing photo-α-pyrone for the preparation of the cyclobutadiene complex.

Hückel's rule of 4n+2 π-electrons[1] as a criterion for aromaticity provided a theoretical basis for cyclobutadiene as a member of the 4n π-electron class of molecules which exhibit no particular stabilization in spite of the conjugated arrangement of double bonds. In 1965, Petitt and coworkers reported the first successful generation and trapping of cyclobutadiene[2] from its iron tricarbonyl complex.[3] A notable method for obtaining this type of compound is the utilization of photo-α-pyrone in the preparation of cyclobutadiene complexes reported by Rosenblum.[4] Direct observation of cyclobutadiene became possible due to the refinement of matrix-isolation techniques which led to the recording of the infrared spectrum of cyclobutadiene by Krantz[5] and Chapman.[6] Examination of the infrared spectrum led to the interpretation that cyclobutadiene had a square geometry (D_4h). However, subsequent theoretical calculations[7] indicated that the square geometry represented a minimum energy of a triplet state which was a transition state between two rectangular geometries (D_2h) of singlet ground states. This ground state rectangular geometry had been indicated[8] or established[9] for substituted cyclobutadienes. A vicinal diphenyl derivative of cyclobutadiene appeared to exist

as two valence tautomers separated by a high activation energy barrier.[10]

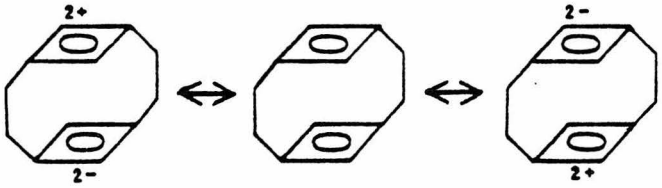
Cyclobutadiene dication and cyclobutadiene dianion formally have two and six π-electrons respectively and they would comply to the 4n+2 π-electron rule of aromaticity. Tetramethyl cyclobutadiene dication[11] and tetraphenyl cyclobutadiene dication[12] have been generated and there is also evidence for cyclobutadiene dianion.[13] These ions are understandably destabilized by electrostatic strain. It is proposed that [2.2] (1,3) cyclobutadienophane 1 would have some contribution to its stability by intramolecular charge transfer between the two parallel rings as exemplified by the two extreme resonance structures shown in figure 1.

Phanes are compounds that contain at least one aromatic nucleus and at least one bridge.[14] Compounds with two aromatic nuclei containing two bridges and two atoms per bridge are classified as [2.2] phanes. As a result of the shortness of the bridges, [2.2] phanes show large ring strain and rigid molecular framework. This presents interesting aspects of the resulting intramolecular steric and electronic interactions.[15,16] One of the most interesting [2.2] phanes is [2.2] paracyclophane which has two benzene rings bridged at the para-positions.[17] This highly-strained molecule has its aromatic rings in boat shapes and the two rings are skewed with respect to each other, as determined by an X-ray analysis.[18] It was rationalized that the structure reflected the coulombic repulsion between the two benzene rings. There are

several syntheses of derivatives of the [2.2] paracyclophane systems[19] in which one electron-rich benzene ring and an electron-poor one form a donor-acceptor pair. There are also calculations[20] made of several intramolecular charge transfer systems of this type. It is then hoped that [2.2] (1,3) cyclobutadienophane 1 would exist as a stable intramolecular charge transfer complex.

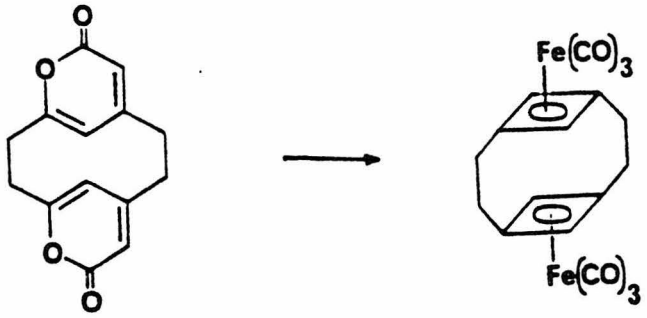
Based on the isolation of a cyclobutadiene irontricarbonyl complex when α-pyrone underwent photodecarboxylation in the presence of iron pentacarbonyl[4], the analogous transformation shown in figure 2 is proposed. An oxidizing agent[21] such as ceric ammonium nitrate or iron trichloride might free [2.2] (1,3) cyclobutadienophane 1 from its irontricarbonyl complex 3.

A proposed synthesis of compound 2 is outlined in chart 1, starting from the Diels-Alder adduct between trans, trans-1,4-diacetoxy-butadiene[22] and maleic anhydride. A Diels-Alder reaction between compound 8 and 2-chloro-1,1-dimethoxyethylene should lead to compound 2 according to the substituted α-pyrone synthesis of Bélanger and Brassard.[23]



1

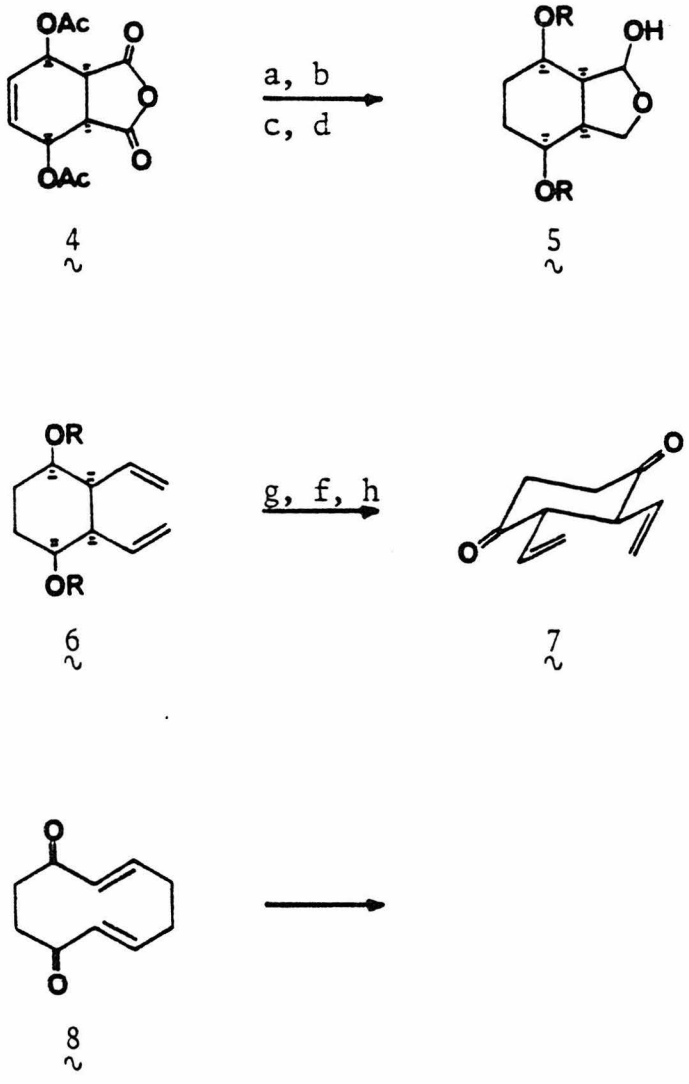
Figure 1



2 3

Figure 2

Chart 1



4 5 6 7 8

a) H_2, Rh on $A\ell_2O_3$ b) $NaBH_4$ c)TBSCℓ, imidazole d) DIBAL

e) ϕ_3PCH_2 f) PCC g) nBu_4NF h) $NaOCH_3$, CH_3OH i) Δ

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PROPOSITION 5

An investigation which will reveal the basic amino acid residues at the active sites of phosphoglucose and phosphomannose isomerases is proposed, using 1-chloro-1-deoxy-D-glucitol-6-phosphate and 1-chloro-1-deoxy-D-mannitol-6-phosphate as active-site-directed inhibitors which would label the bases involved in the "enediol" isomerization mechanism.

Phosphoglucose isomerase and phosphomannose isomerase are two glycolytic enzymes that function as aldose-ketose isomerases. Phosphoglucose isomerase interconverts D-glucose-6-phosphate and D-fructose-6-phosphate;whereas phosphomannose isomerase interconverts D-mannose-6-phosphate and D-fructose-6-phosphate.[1] The reaction sequence is more complicated than that of triosephosphate isomerase due to the existence of sugars in solution as the cyclic hemiacetals which are mixtures of α and β anomers. The actual substrate for the isomerization reaction is the acyclic form and it had been shown that phosphoglucose isomerase has a greater affinity for the opened chain form than it has for cyclic structurally related compounds.[2] Very little of the acyclic sugar exists in solution and so the first step of the reaction is the enzyme catalysed opening of the hemiacetal. Phosphoglucose isomerase has a 20-fold preference for the α-anomer over the β-anomer of D-glucose-6-phosphate[3]; whereas phosphomannose isomerase is highly specific for the β-anomer of D-mannose-6-phosphate.[4] These anomeric specificities agree well with a proposed mechanism of the isomerization reaction based on stereochemical arguments, vide-infra.

Phosphoglucose isomerase had been subjected to X-ray analysis

with a resolution of 3.5Å.[5] However, the enzyme has not yet been sequenced and so the amino acid side chains cannot be identified. Study on the kinetic parameters of phosphoglucose isomerase led to the tentatively assigned involvement of an imidazole group of histidine and an ε-amino group of lysine in the active site.[6] The protonated amino group is involved in the opening of the pyranose ring to yield the acyclic form and the imidazole base is involved in the isomerization step *via* formation of an enediol intermediate. Moreover, the affinity label,1,2-anhydro-D-mannitol-6-phosphate, labels a glutanic residue in phosphoglucose isomerase.[7] It shows saturation kinetics, competitive inhibition by substrates and 1:1 stoichiometry.

These observations led to the following proposed mechanism of phosphoglucose isomerase[6] as shown in figure 1. The enzyme has binding sites for the hydroxyl groups at C-3 and C-4 and for the phosphate group at C-6. There is an acidic residue, probably lysine, close to the oxygen at C-5. There are two basic residues, one of which is close to the protons at C-1 and C-2 (B' is probably histidine) and the other residue is close to the hydroxyl groups at C-1 and C-2 (B'' is probably glutamate). The ring-opening step occurs when the ring oxygen of compound 1 is protonated and the hydroxyl group at C-1 is deprotonated by B''. Protonation of the aldehyde 2 by the conjugated acid of B'' and deprotonation of C-2 by B' gives an intermediate *cis*-enediol 3. Deprotonation of the hydroxyl group at C-2 of compound 3 by B'' and protonation of C-1 by the conjugated

Phosphoglucose isomerase

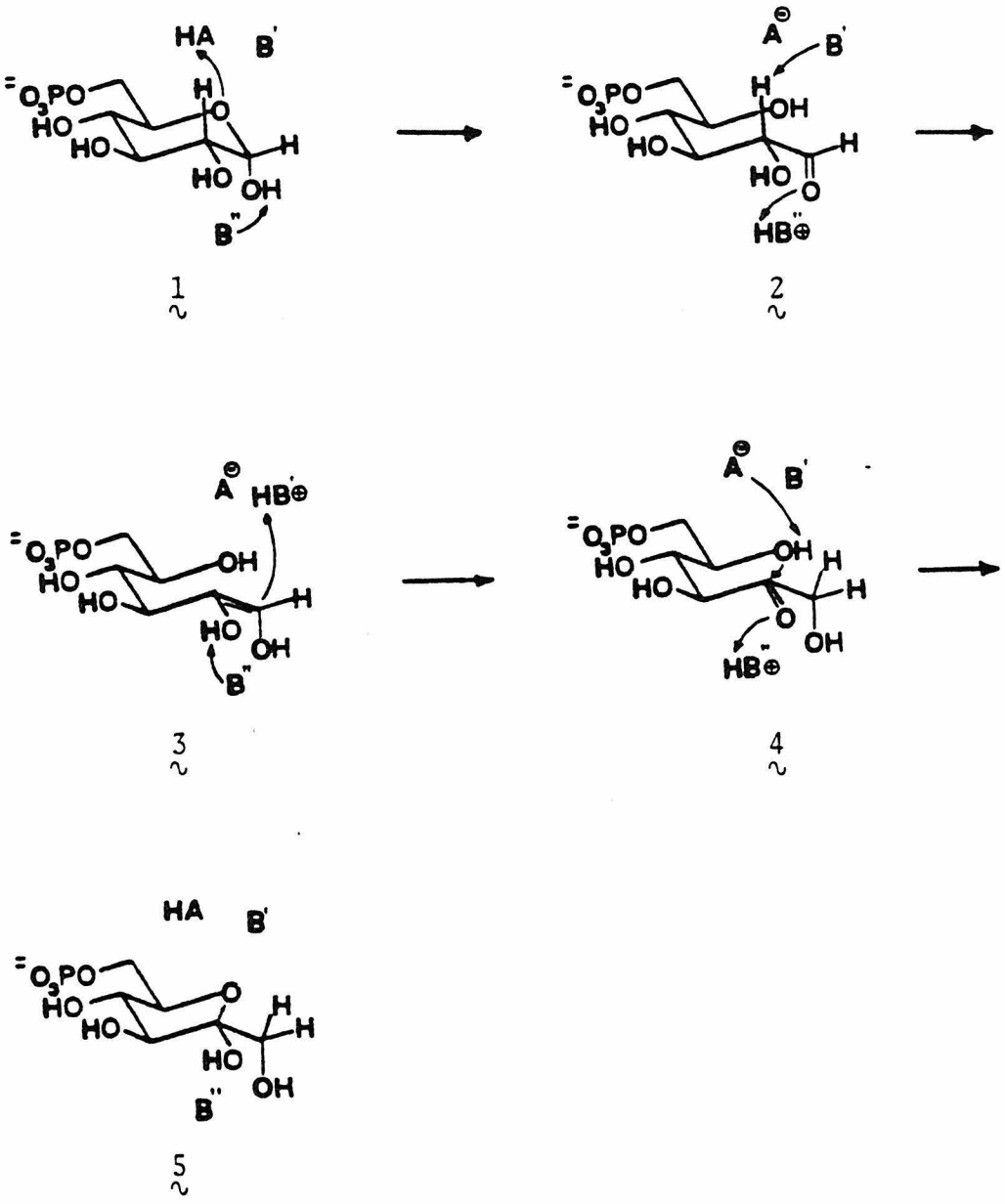


Figure 1

Phosphomannose isomerase

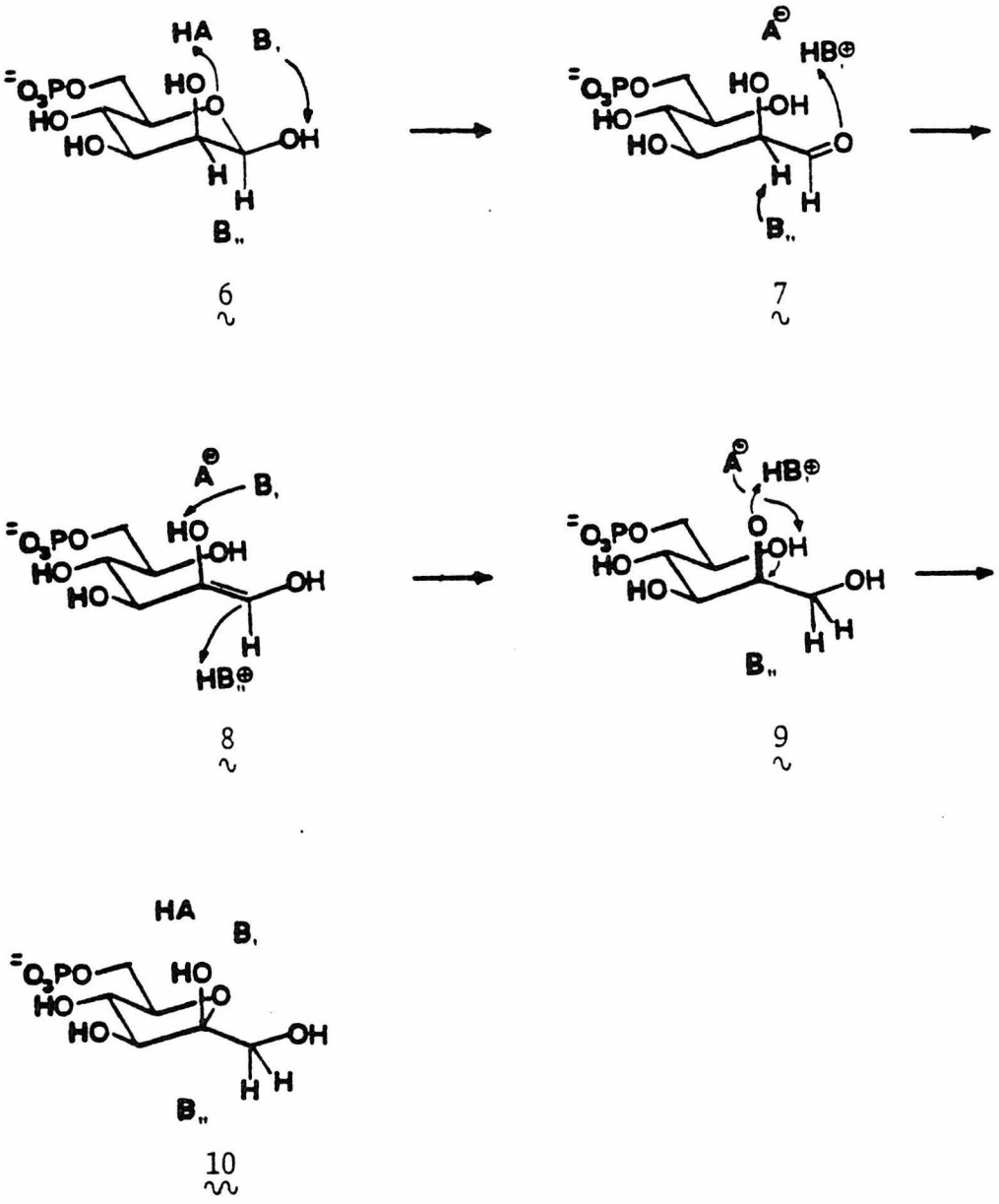


Figure 2

acid of B' gives the acyclic form of D-fructose-6-phosphate(4). Deprotonation of the hydroxyl group at C-5 by the conjugated base of HA and protonation of the carbonyl oxygen at C-2 by the conjugated acid of B'' gives α-D-fructose-6-phosphate (5).

This mechanism rationalizes the anomeric specifity of phosphoglucose isomerase due to the proposed intermediate cis-enediol and the disposition of the two bases involved in transferring protons between C-1 and C-2. An analogous mechanism for phosphomannose isomerase is shown on figure 2. This would lead to the prediction that β-D-mannose-6-phosphate (6) would be the substrate for this enzyme and that it would be converted into β-D-fructose-6-phosphate(10). There are numerous experimental evidences in support of the "enediol" mechanism. Interconversion of D-glucose-6-phosphate and D-fructose-6-phosphate by phosphoglucose isomerase in tritiated water resulted in the incorporation of 1 atom of tritium into each of the two compounds.[8] D-fructose-6-phosphate-1-T formed a considerable amount of D-glucose-6-phosphate-2-T[8]; this indicated a fast apparent intramolecular transfer of hydrogen. Phosphoglucose and phosphomannose isomerases are able to distinguish between the two diastereotopic hydrogen atoms at C-1 of D-fructose-6-phosphate. One enzyme removes a pro-R proton while the other removes a pro-S proton.[9] The absolute configuration of the monotritiated D-fructose-6-phosphate formed by the reaction with phosphoglucose isomerase in tritiated water has been determined by degradation studies[10] and agrees with the proposed mechanism.

Finally, 5-phosphoarabinoate is the strongest known competitive inhibitor of phosphoglucose isomerase.[11] This is a stable analogue of the enediolate anion believed to occur transiently in the reaction of phosphoglucose isomerase.

In order to offer more evidence for the "enediol" mechanism, specifically to locate the two bases that are involved in proton transfers of the substrate at each of the active sites of these two enzymes, it is proposed that active-site-directed inhibitors be used in identifying the functional groups involved. Conversion of the inhibitors into their reactive forms depends upon the specific catalytic capabilities of the active site after the binding of the substrates. The concept of substrate-induced irreversible inhibition of enzymes has been recognized as a promising approach to highly specific therapeutic agents and the study of the mechanistic aspects and biochemical actions of these suicide enzyme inactivators has contributed to an understanding of enzymatic functions.[12] In this proposed study, 1-chloro-1-deoxy-D-glucitol-6-phosphate (11) and 1-chloro-1-deoxy-D-mannitol-6-phosphate (12) are considered as potential substrates for the two enzymes.

As shown in figure 3, for phosphoglucose isomerase, B" would deprotonate the hydroxyl group at C-2 of 1-chloro-1-deoxy-D-glucitol-6-phosphate (11) and lead to an intermediate 1,2-anhydro sugar 13 which would be alkylated at C-1 by B' to give compound 14. In the same manner, 1-chloro-1-deoxy-D-mannitol-6-phosphate (12) would be alkylated at C-1 by B" to give compound 16. Figure 4 shows the

Phosphoglucose isomerase

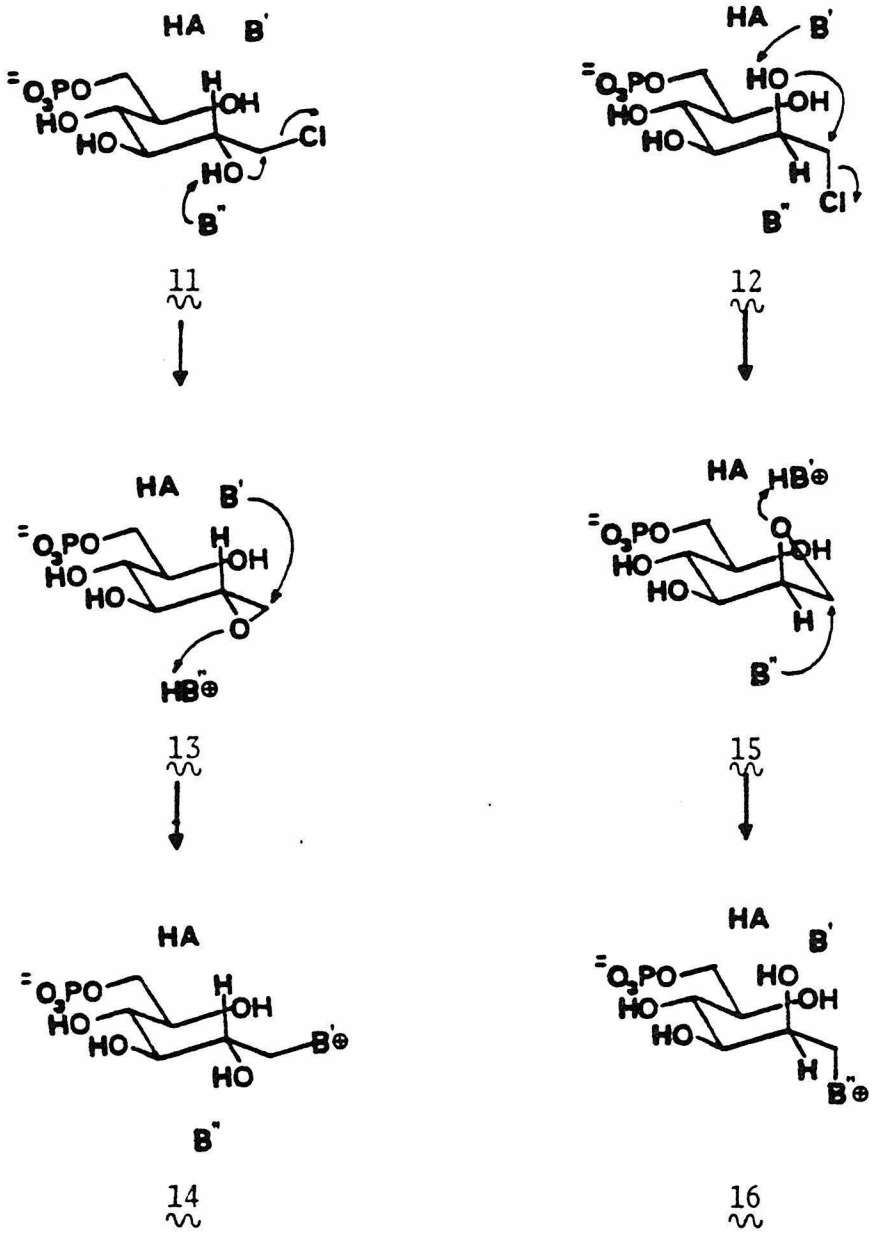


Figure 3

Phosphomannose isomerase

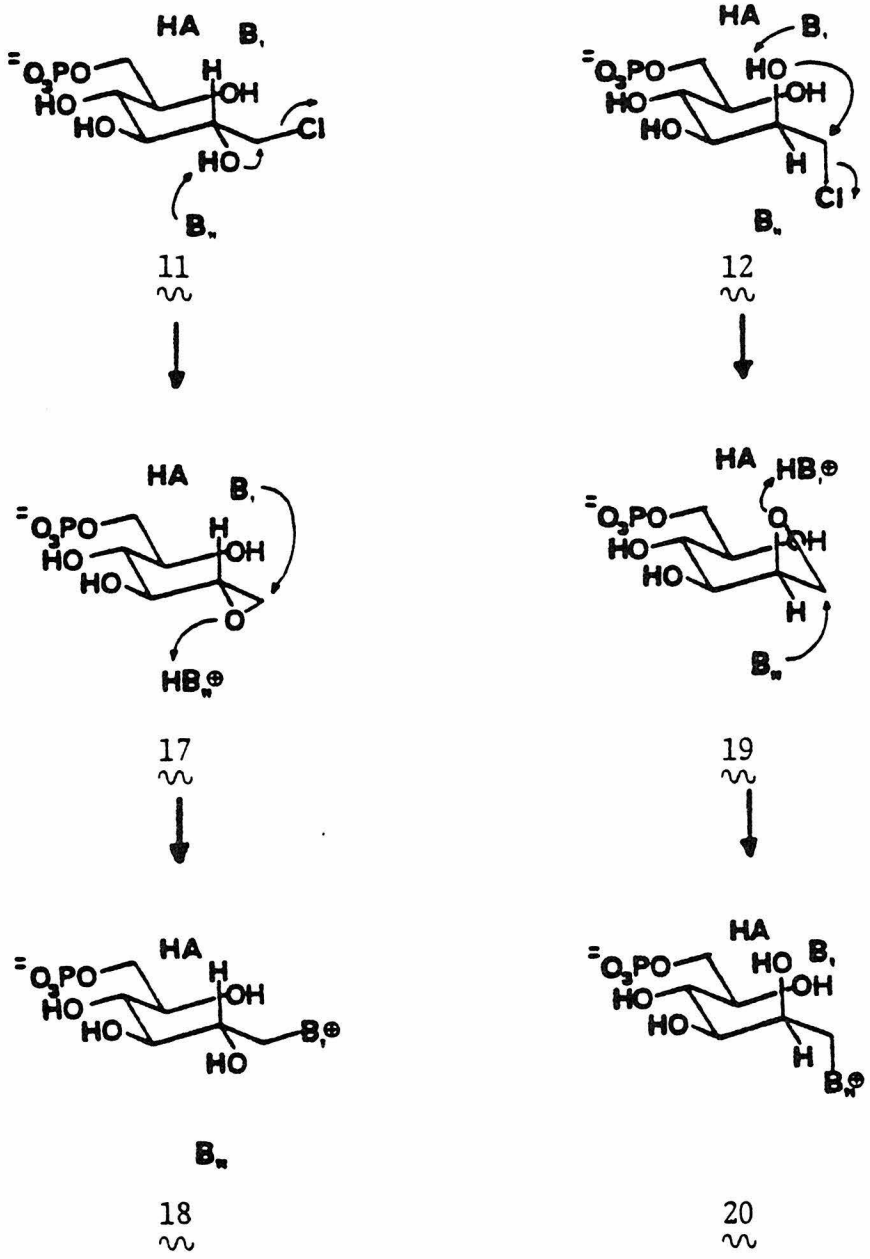
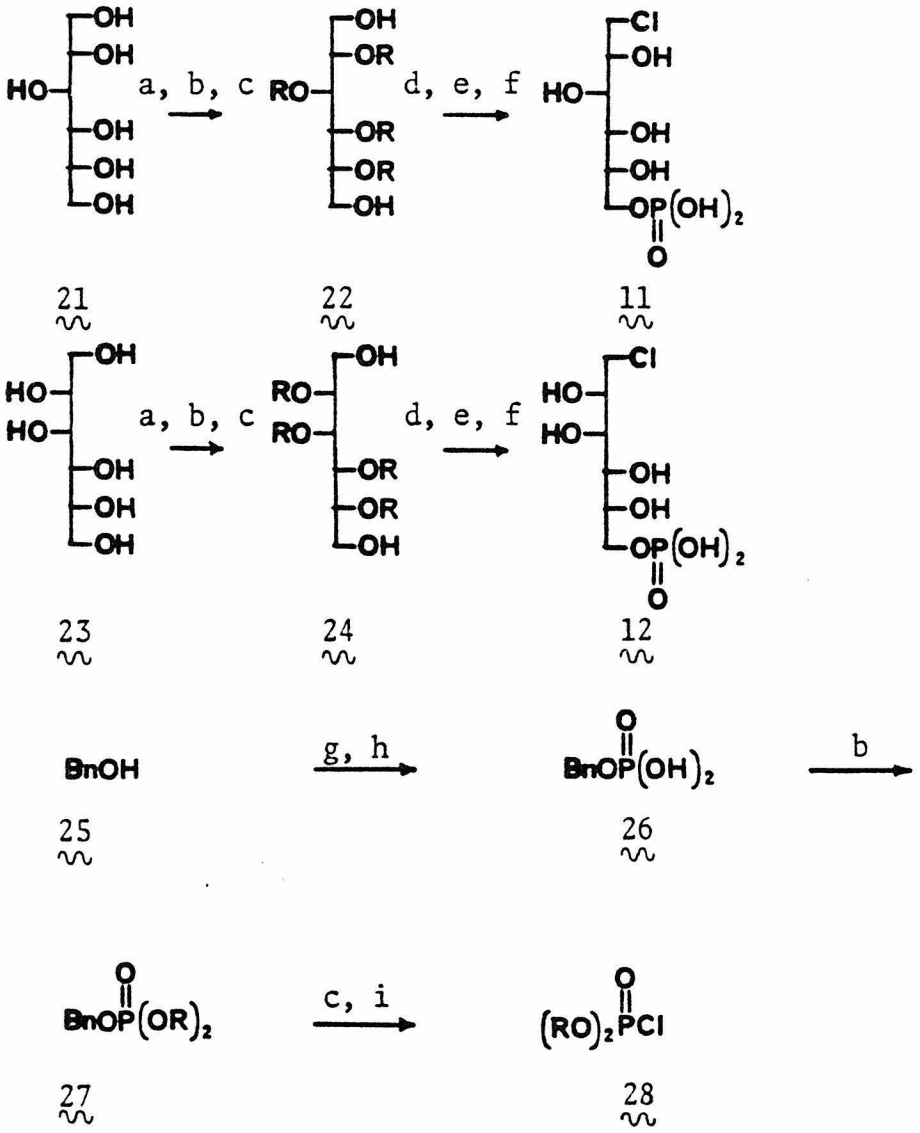


Figure 4

the situation for phosphomannose isomerase. 1-Chloro-1-deoxy-D-glucitol-6-phosphate (11) would be alkylated at C-1 by B_I to give compound 18 and 1-chloro-1-deoxy-D-mannitol-6-phosphate (12) would be alkylated at C-1 by B_{II} to give compound 20. All four cases should lead to inactivation of the enzymes. The resulting polypeptides with covalently-bound inhibitors can be hydrolysed and the amino acid residues involved in the catalysis at the active sites can then be identified.

1-Chloro-1-deoxy-D-glucitol-6-phosphate (11) can be synthesized as shown in Chart 1. The two primary hydroxyl groups of D-glucitol (21) can be selectively protected as their trityl ethers. The remaining hydroxyl groups would then be protected as MEM-ethers. Hydrogenolysis should lead to the removal of the trityl protecting groups to give compound 22. Treatment of the resulting di-hydroxy compound with a limited amount of dialkyl phosphoryl chloride would lead to a mixture, one component of which is the desired C-6 phosphorylated compound. Chlorination at C-1 and removal of the MEM-protecting groups would give the desired substrate 11. 1-Chloro-1-deoxy-D-mannitol-6-phosphate (12) can be prepared from D-mannitol (23) in an analogous manner. The required dialkyl phosphoryl chloride 28 can be prepared as outlined. Pyrophosphoryl chloride reacts with benzyl alcohol (25) to give benzyl phosphorodichloridate which gives benzyl phosphoric acid (26) upon aqueous hydrolysis.[13] Alkylation with β-methoxyethoxymethyl chloride in the presence of diisopropylethyl amine followed by hydrogenolysis would give the di-

Chart 1 (R = MEM)



a) 2 eq. TrCℓ, pyr ; b) MEMCℓ, i-Pr_2NEt; c) H_2, Pd/C;

d) $(RO)_2$ POCℓ; e) $CCℓ_4$, P $(NMe_2)_3$; f) $ZnCℓ_2$, H_2O;

g) $(Cℓ_2PO)_2O$; h) H_2O; i) $SOCℓ_2$, Na_2CO_3

alkyl phosphoric acid.[14] Treatment of the acid with thionyl chloride[15] or phosphorous pentachloride[16] in the presence of base should then give the corresponding phosphoryl chloride 28.

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