AN APPROACH TO THE TOTAL SYNTHESIS OF POLYETHER ANTIBIOTICS

Thesis by

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to Sharon

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ABSTRACT

Part I. The use of the ester enolate Claisen rearrangement in an approach to polyether antibiotics was investigated. The [3,3] sigmatropic rearrangement of O-silyl ketene acetals derived from the propanoate esters of 1,5-anhydro-hex-1-enitols (pyranoid glycals) provided α-methyl-5,6-dihydro-2H-pyran-2-acetic acid derivatives. Similarly, 1,4-anhydro-pent-1-enitols provided 2,5-dihydrofuran-2-acetic acid derivatives. The tetrahydro-2-furoate esters of pyranoid glycals provided glycol diethers. The products are models of key structural elements which are present in polyether antibiotics and in other acetogenous natural products of potential medicinal value. The furanoid and pyranoid glycals were conveniently prepared by reductive fragmentation of 2,3-O-(1-methylethylidene)-glycosyl chlorides.

Part II. The preparation of 6-deoxy-L-gulose from D-glucuronic acid is described. Three approaches to the deoxy sugar were explored, and the relative merits of each approach were considered. Several furanoid and pyranoid derivatives of 6-deoxy-L-gulose were described.

"I had indeed accomplished enough
when I had succeeded once, but I found
great pleasure in seeing and contemplating
the admirable works of Nature within
the vessels..."

--Nicholas Flamel (1330-1418)

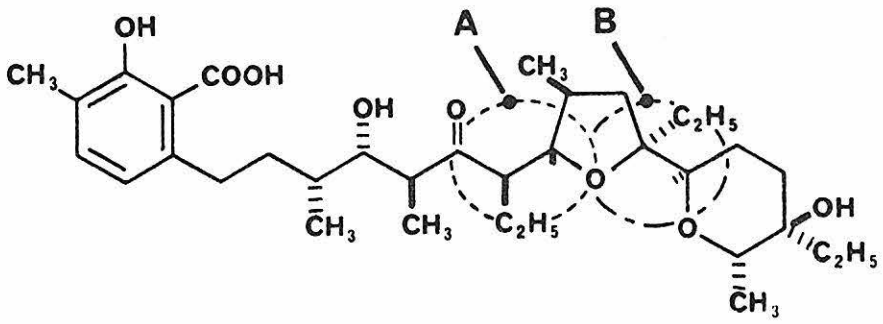
Part I

The Enolate Claisen Rearrangement of Esters from Furanoid and Pyranoid Glycals[1]

The total synthesis of polyether antibiotics constitutes a provocative challenge to the ingenuity of the organic chemist. These antibiotics are important representatives of a relatively new and rapidly expanding class of molecules known as ionophores.[2] The importance of these molecules is derived from their unique capacity to facilitate the transfer of cations across biological membranes. Among the most interesting examples of the polyether antibiotics is lasalocid A (I),[3] which has been shown[3] to form lipid soluble complexes with divalent calcium cations and with metabolically essential amines (e.g. catecholamines). In addition, lasalocid A, as well as several other polyether antibiotics, exerts a profound positive effect upon the contractility of heart muscle,[3a] and, in in vivo experiments, causes dramatic increases in coronary flow and cardiac output.[4] These observations have resulted in considerable interest in the potential application of these molecules as cardiovascular drugs, and the development of efficient, versatile syntheses of analogues of the polyethers could expedite the discovery of more efficacious cardiotonic agents. This investigation was undertaken to evaluate one synthetic approach to the polyether molecules.[5]

The two structural units encircled in structure I are characteristic features which are present in nearly all of the polyether antibiotics. They are similar in that both are created (in effect, but not in the accepted biogenetic

scheme) by the stereospecific attachment of a chiral carbon residue to the C-1 position of a saturated oxygen heterocycle. They are dissimilar in regard to the nature of the attached carbon residue. In one case (A), the attachment

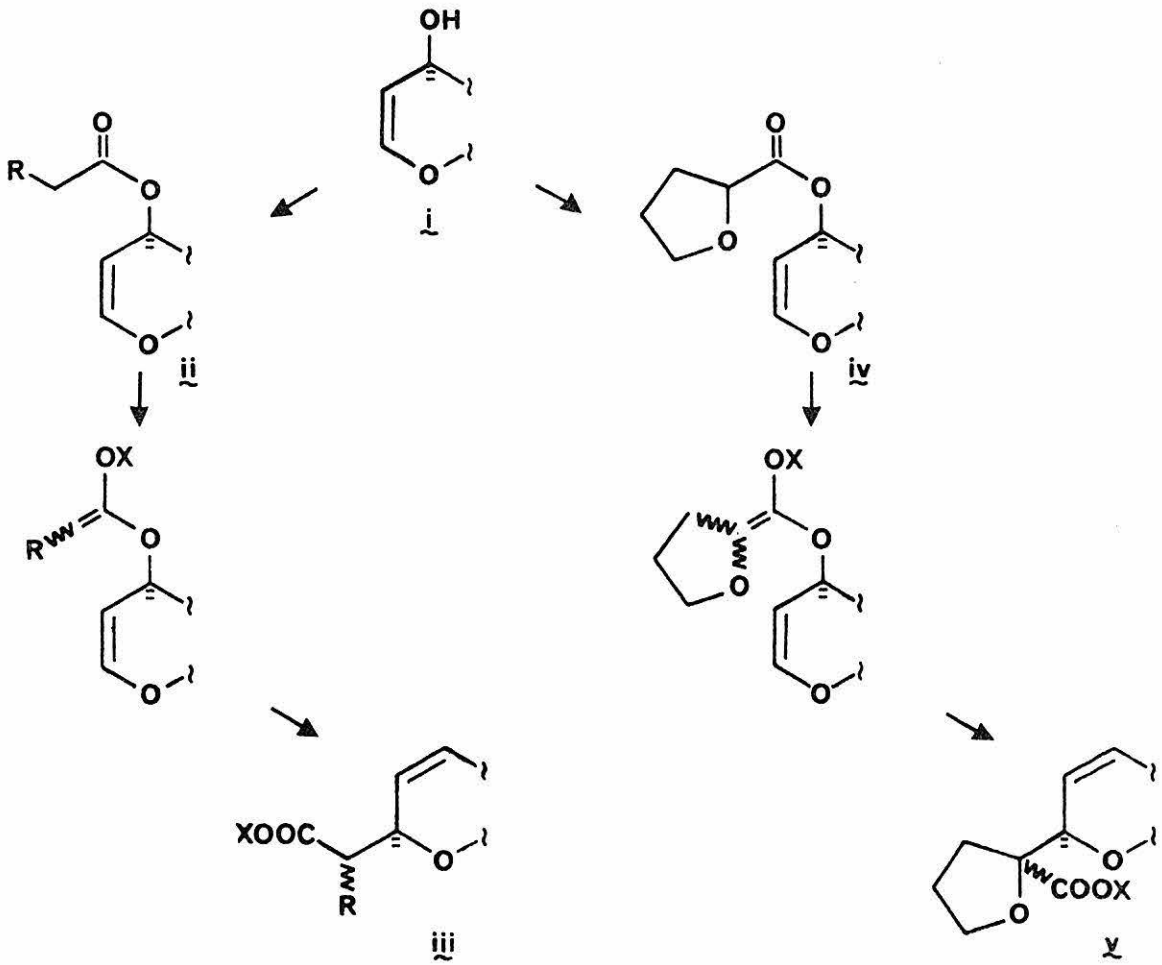


Lasalocid A (I)

results in an aldol-type structure, and a 1,3 relationship of carbon-oxygen bonds. In the second case (B), the attachment results in a 1,2 relationship of carbon-oxygen bonds, and provides a glycol diether. The prevalence of these structural units in all polyether antibiotics suggested that a practical preliminary goal in a program directed toward the preparation of synthetic analogues of these ionophores would be the development of efficient methods for generating these systems.

One means of potentially general utility for the attainment of this goal is a scheme which incorporates the ester enolate Claisen rearrangement as a key carbon-carbon bond forming reaction. In such an approach (outlined in Scheme I, where the partial structures are meant to denote

Scheme 1



both furanoid and pyranoid rings) a heterocyclic allylic alcohol i is used to provide either the aliphatic ester ii or the α-alkoxy ester iv, and these esters, in turn, by [3,3] sigmatropic rearrangement generate, respectively, the desired aldol-type structural unit iii, and the glycol diether congener v. Since the clinically and biologically interesting molecule lasalocid A contains both of these structural units and is one of the least complex of the

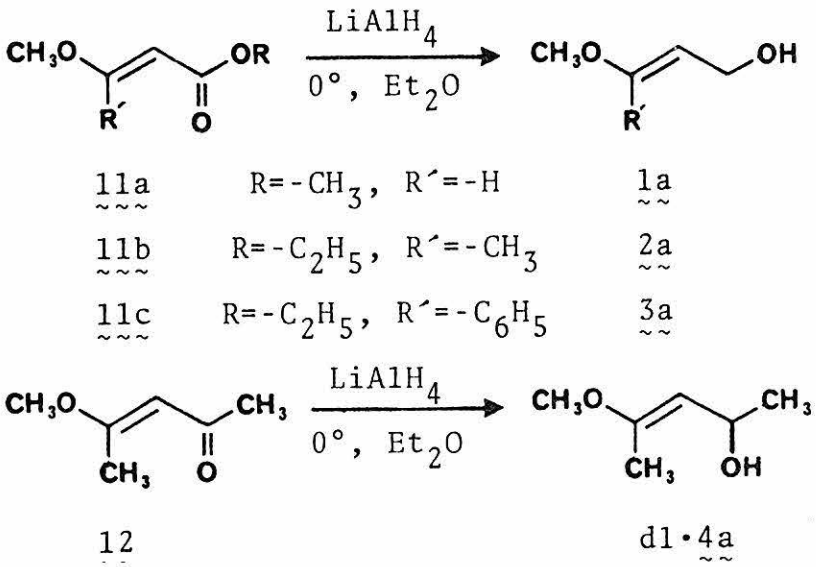
polyether antibiotics, the total synthesis of this system is an attractive and practical goal that would serve to evaluate this proposed approach. To begin this project and to test the applicability of the enolate Claisen rearrangement in as convenient a manner as possible, it was necessary first to develop a convenient method for the preparation of furanoid and pyranoid alcohols of type i, and then to establish that models of the required structural units can be constructed by sigmatropic rearrangements of ester enolates derived from those alcohols.[6]

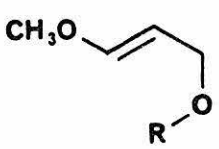
In the initial phase of this investigation the γ-methoxy allylic alcohols 1a-d1·4a were prepared and the Claisen rearrangements of ester enolates derived from these alcohols were examined. These alcohols are the most readily available and least sterically hindered analogues of the more complex heterocyclic alcohols which would be required for the total synthesis of lasalocid A. Previous experience established that the ester enolate Claisen rearrangement could be successfully applied to derivatives of β-methoxy allylic alcohols[7] and thereby demonstrated the compatibility of the reaction conditions with enol ether functional groups. Alcohols 1a-d1·4a were convenient models for revealing any special characteristics which would need to be dealt with in the reactions of γ-alkoxy allylic alcohols and their esters.

The desired alcohols were prepared by hydride

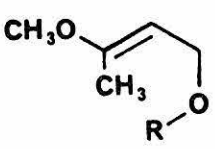
reduction of the corresponding carbonyl compounds. (Scheme 2) Reduction of ester 11a, which can be conveniently prepared by the addition of methyl alcohol to methyl propiolate,[8] afforded the sensitive alcohol 1a in 36% yield. Distillation of this alcohol was accomplished only with low recovery and was accompanied by the formation of nonvolatile, apparently polymeric material. Attempts to prepare ester 1b by acylation of alcohol 1a using propionic anhydride and pyridine in dichloromethane also resulted in polymer formation, and provided only low yields of impure ester. Ester 1b was prepared, however, in 70% yield under aprotic conditions by treatment of a solution of the alcohol in tetrahydrofuran with one equivalent of

Scheme 2

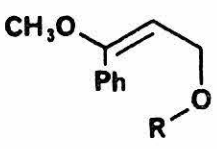




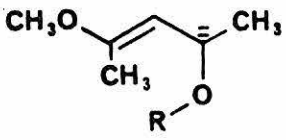
1x



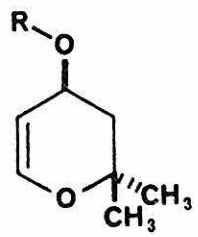
2x



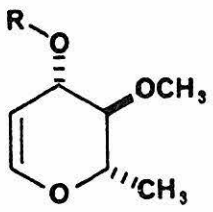
3x



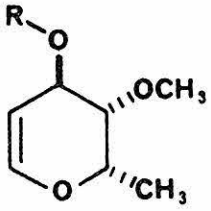
d1·4x



d1·5x



6x



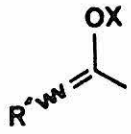
7x

1x-9x: x=a, R=-H

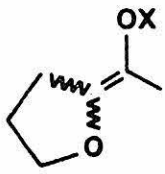
x=b, R=-$COCH_2CH_3$

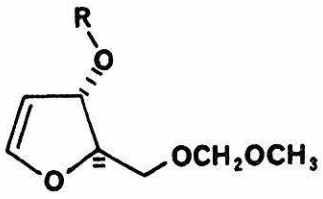
x=c, R=-$\overline{COCH(CH_2)_3O}$

x=d, R=



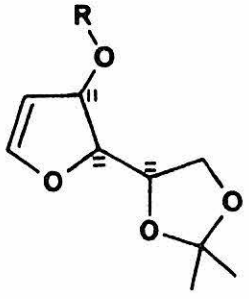
x=e, R=





8a, R=-H

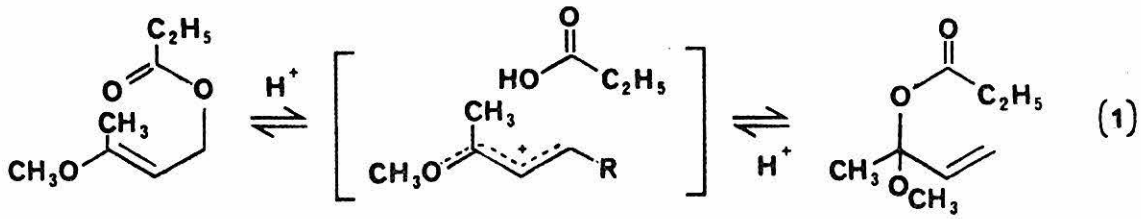
8b, R=-$COCH_2CH_2CH_3$



9x

n-butyllithium, followed by reaction of the resulting lithium alkoxide with propionic anhydride. The alcohols 2a and 3a were obtained in 60-70% yield by reduction of the esters 1b and 1c[10,11] with lithium aluminum hydride. In contrast to alcohol 1a, the more substituted alcohols 2a and 3a could be distilled without significant decomposition. Furthermore, alcohol 2a did provide up to 66% yields of ester 2b by acylation with propionic-anhydride in pyridine. However, esters 2b and 3b were obtained in higher and more consistent yields by the reaction of alkoxides with propionic anhydride, as described for 1b.

Initial attempts at acylation of 2a were complicated by the production of a by-product believed to be 13 on the basis of nuclear magnetic resonance and infrared spectral data. The production of this compound could be suppressed



(1)

2b vi 13

by thorough washing of the crude ester with base prior to distillation. The nuclear magnetic resonance spectrum of a sample of 2b showed no change after heating the sample for 60 minutes at 110°C. The formation of 13, as inferred by the appearance of typical terminal olefin spectral

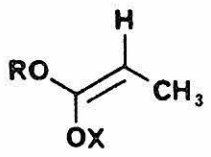
characteristics and corresponding shifts in the methyl and ethyl group resonances, was observed immediately following the addition of a catalytic amount of acid to this sample. This type of allylic rearrangement has been well documented in the carbohydrate literature for the acetate derivatives of the pyranoid enol ethers known as glycals.[17] Acid catalysis of this process has been demonstrated previously.[18] The appearance of this by-product illustrates the sensitivity of these esters toward heterolytic cleavage of the carbon-oxygen bond adjacent to the enol ether. The singular stability of the oxygen substituted allylic cation $\underset{\sim}{\text{vi}}$ (R=-H) undoubtedly contributes to the facility of this bond scission.

The secondary alcohol dl·$\underset{\sim}{4}\underset{\sim}{a}$ was prepared in 89% yield from the β-methoxy pentenone $\underset{\sim}{12}$[12,13] by reduction with lithium aluminum hydride. Attempts to isolate ester dl·$\underset{\sim}{4}\underset{\sim}{b}$ were uniformly unsuccessful. However, treatment of a solution of alcohol dl·$\underset{\sim}{4}\underset{\sim}{a}$ in tetrahydrofuran at -78° first with a small excess of n-butyllithium to form the lithium alcoholate, and then with propanoyl chloride, generated an equimolar solution of the ester, dl·$\underset{\sim}{4}\underset{\sim}{b}$, and lithium chloride. The high yield formation of the ester by this process is inferred by the successful utilization of this solution in the ester enolate Claisen rearrangement (vide infra). The decreased stability of ester $\underset{\sim}{4}\underset{\sim}{b}$ relative to ester $\underset{\sim}{2}\underset{\sim}{b}$ can be attributed to the increased stability of the allylic

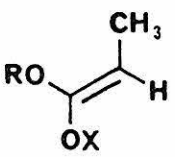
cation yi (R=-CH_3) and the concomitant ease of carbon-oxygen bond cleavage in the secondary versus the primary alkyl ester.

With the preparation of these acyclic models thus completed, attention turned toward the investigation of the [3,3] sigmatropic rearrangements of the silyl ketene acetals derived from these esters. In each case the ester was first deprotonated at -78° by lithium diisopropylamide (LDA), tert-butyldimethylchlorosilane (TBSCL) was then added, and after cooling was discontinued the mixture warmed to room temperature. In this manner the ketene acetals 1d-dl·4d (x=t-Bu$(CH_3)_2$Si-) were produced.

Previously obtained results from this laboratory[7] demonstrate that under these conditions, and dependent upon the solvent employed during the deprotonation, variable proportions of the two geometrically isomeric ketene acetals will be obtained. Specifically, it was shown that when the deprotonation is effected by LDA in a 23 vol % mixture of hexamethylphosphoric triamide (HMPA) in tetrahydrofuran (THF), the E-type enolate anion A is preferentially formed



A



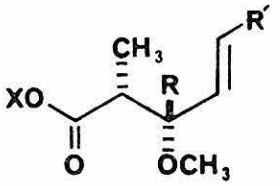
B

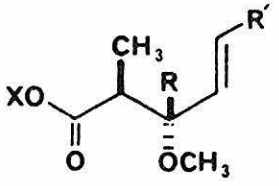
X= Li-, t-Bu$(CH_3)_2$Si-

and silylated. When LDA is used with THF in the absence of HMPA the predominant product was shown to be derived by silylation of the Z-type enolate anion, 8.

Subsequent sigmatropic rearrangement of these ketene acetals generated a mixture of diastereomeric γ,δ-unsaturated silyl esters. These esters provided the products dl·23a,b-dl·26a,b. The relative quantities of the diastereomers were determined by NMR analysis of the product mixtures. Ester 1b afforded, after hydrolysis of the resultant silyl ester with dilute aqueous acid, the acids dl·23a and dl·23b (X=-H). In the same manner ester 2b yielded dl·24a and dl·24b (X=-H). In the case of ester 3b the derived silyl esters were cleaved with potassium fluoride in HMPA,[31] and the resultant carboxylate salts were alkylated with methyl iodide[31] to yield esters dl·25a and dl·25b (X=-CH_3). A mixture of ester dl·4b and lithium chloride in THF was prepared (vide supra) and added to a solution of LDA in the desired solvent. Completion of the experiment in the usual manner yielded acids dl·26a and dl·26b (X=-H). The yields and ratios obtained in these experiments are collected in Table 1.

The stereochemistry indicated for the products is based upon the following reasoning. In the absence of any unusual steric constraints and in accordance with prior experimental observations[7,14] these rearrangements are assumed to occur via a chair-like transition state. In this





dl-23a R,X=-H; R'=-H dl-23b

dl-24a R=-H; R', X=-H dl-24b

dl-25a R=-C_6H_5; R'=H, X=-CH_3 dl-25b

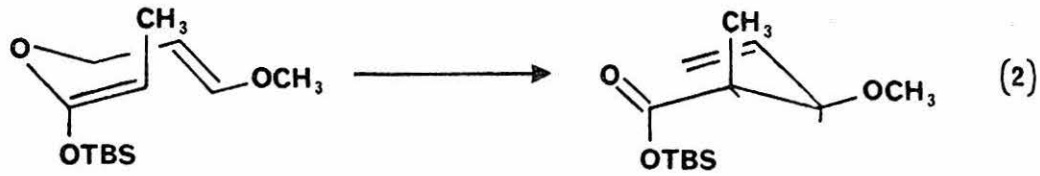
dl-26a R,R'=-CH_3; X=-H dl-26b

Table 1. Products Obtained from Esters 1b-dl-4b.

Reactant	Solvent[a]	Products[b]	Yield	a/b[d]	$\tau_{1/2}$,[e]
1b	THF	23a,23b	80%	1/5	<5
1b	HMPA-THF	23a,23b	75%	4/1	<5
2b	THF	24a,24b	76%	1/4	9±2
2b	HMPA-THF	24a,24b	80%	3/1	9±2
3b	THF	25a,25b[c]	67%	1/1	42±8
3b	HMPA-THF	25a,25b[c]	72%	1/1	42±8
4a[f]	THF	26a,26b	60%	3/7	10±2
4a[f]	HMPA-THF	26a,26b	59%	4/1	10±2

[a]Solvent employed during deprotonation of allylic ester. THF=100% THF, HMPA-THF=23% (v./v.) HMPA/THF. [b]Isolated as the carboxylic acids (X=-H), except: [c]Isolated as the methyl esters (X=-CH_3). [d]Ratio of diastereomers (XXa/XXb) as determined by NMR. [e]Half-life at 35°C for the sigmatropic rearranged as determined by NMR (see ref 7b). [f]The required ester was prepared from this alcohol just prior to deprotonation and was not isolated.

event, and based upon the preferential formation and silylation of isomeric enolate anions as described above, the configurational assignments indicated may be readily predicted. As an example of this, deprotonation and silylation of ester 1b is expected, based upon previous results with propanoate esters,[7] to yield a mixture of silyl ketene acetals 1d wherein the predominant geometrical isomer is of type B. Rearrangement of these isomeric acetals through a

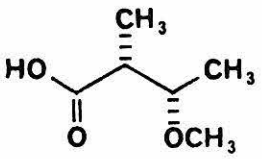


1d d1•23b (2)

chair-like transition state will produce a mixture of diastereomeric silyl esters in which d1•23b is the major component. This transformation is illustrated for the major isomer in eq 2. Based upon analogous reasoning, the products in the remaining examples were assigned the given relative configurations.

Tentative support for the proposed assignments was obtained from the nuclear magnetic resonance spectral data. It was observed that the doublet assigned to the α-methyl group of products d1•23-26a was consistently at lower field than was the corresponding doublet in the isomeric compounds, d1•23-26b. This is consistent with the work of Maskens and Polgar, who found that the α-methyl group in

erythro-3-methoxy-2-methylbutyric acid (vii) resonates at lower field than the corresponding methyl group in the threo isomer.[15] In addition, it is known from the work of Gerlach and Prelog that the α-methyl group of nonactic acid [(viii), R=-$CH_2CH(OH)CH_3$] resonates at higher field than does the α-methyl group of 2-epi-nonactic acid.[16] While these observations cannot be considered as proof of the proposed relative stereochemistries, a reassuring



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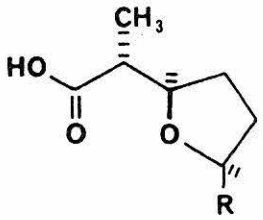


viii

consistency is nevertheless recognized.

Results from this preliminary investigation indicated that the ester enolate Claisen rearrangement could be successfully applied to esters of γ-methoxy allylic alcohols. The reactions proceed in good overall yield and the experimental evidence indicates that diastereomeric β-methoxy carboxylic acids or esters are obtained in proportions dependent upon the solvent employed during deprotonation. Furthermore, experimental procedures were developed which allow the enolate Claisen rearrangement to be applied to esters which are too unstable to be isolated under aqueous conditions.

With these encouraging results in hand, attention was turned toward a search for efficient methods for the preparation of heterocyclic alcohols of the type required for the synthesis of lasalocid A. Alcohol dl·5a was readily available by reduction of the corresponding enone,[17] and therefore constituted a practical starting point for these investigations. However, for the efficient use of alcohols of this type in a convergent plan of synthesis such as the scheme proposed for lasalocid A, a convenient preparation of optically active congeners of dl·5a was required. For this purpose, the carbohydrates appeared to be ideal starting materials.

The alcohols 6a-9a are representative of the class of carbohydrate derivatives known as pyranoid and furanoid glycals.[18] The pyranoid representatives of this group have long been recognized as valuable intermediates for carbohydrate synthesis. However, because of the logical emphasis of carbohydrate synthesis upon functional group manipulation, scant use has been made of these substrates in carbon-carbon bond forming reactions.[19] In the past, the preparation of these pyranoid glycals has been accomplished most often by some modification of the method of Fischer and Zach.[20,21] This method involves the reduction of peracetylated pyranosyl bromides by elemental zinc in acetic acid, and invariably yields the acetylated allylic alcohol derivative. Acylated glycals are known to undergo acid

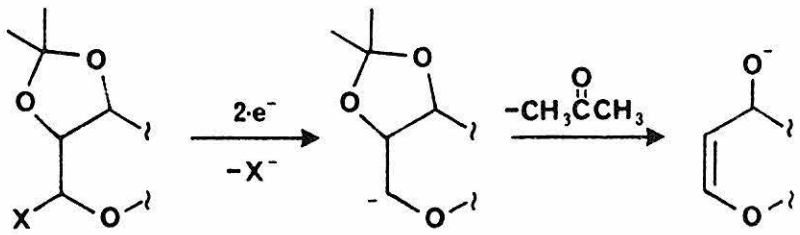
catalyzed rearrangements analogous to the reaction observed with ester 2b.[18] The furanoid glycals are particularly susceptible to this undesirable reaction, and therefore the classical technique, incorporating acidic reduction media, is inapplicable for the preparation of all but the most stable of furanoid glycal derivatives.[22] Results from the single previous successful preparation of furanoid glycal esters suggest that the lability of glycal derivatives is related, not unexpectedly, to the nature of the leaving group on C-3.[23,24]

For the purposes at hand, a synthesis of glycals with an unsubstituted C-3 hydroxyl group, suitable for acylation with any one of several reagents, was desired. In addition to being a requisite of efficiency and convenience, this specification was a practical necessity for the successful isolation of the furanoid substrates. By analogy with ester dl·4b, and in consideration of prior reports upon furanoid glycal esters, these alcohols were expected to be more stable than their corresponding esters, and therefore more easily isolated, purified, and stored. No known general technique met this requirement.

The fragmentation of β-alkoxyethyl halides on treatment with metals in inert solvent suggested that the reaction generalized in eq 3 could provide a solution to this problem. While the technique is essentially equivalent to the successful classical method, the use of an inert or

basic reduction medium offered the advantage that the acid catalyzed destruction of these sensitive products could be avoided. Furthermore, the use of a ketal or acetal for protection of both the C-2 and C-3 hydroxyl groups provides for the direct generation of the desired, unprotected allylic alcohol, in efficient fulfillment of our requirements.

To evaluate these possibilities, the furanosyl chloride



(3)

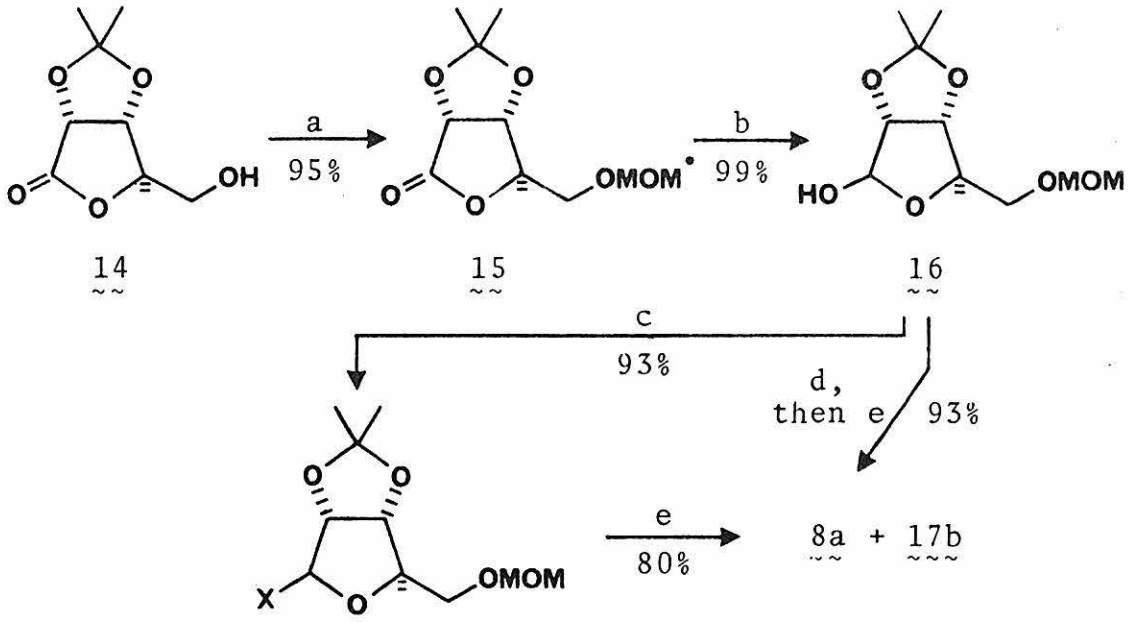
ix

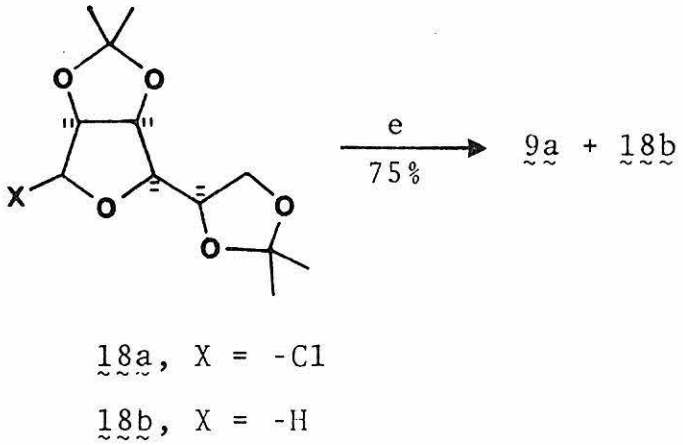
17a was prepared for an investigation of reductive fragmentation methods. (Scheme 3) Lactone 14, prepared from ribonic acid γ-lactone in 95% yield,[25] afforded the protected lactone 15 by alkylation with chloromethyl methyl ether in the presence of diisopropylethylamine. Reduction of the protected lactone 15 with diisobutylaluminum hydride at -78° provided the lactol 16 which was converted to chloride 17a with triphenylphosphine and carbon tetrachloride in tetrahydrofuran.

After trying several unsuccessful methods for the reduction of this chloride (including metal-halogen exchange

Scheme 3

Preparation of Furanoid Glycals 8a and 9a[a]





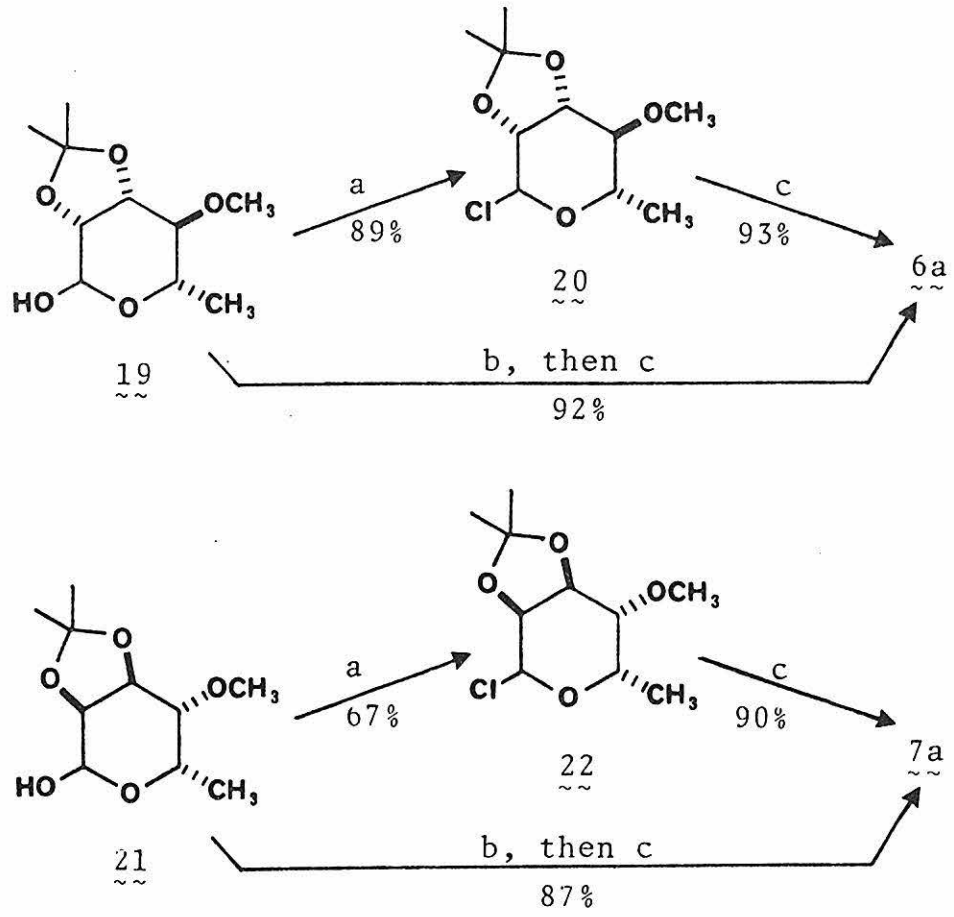
[a] a, $ClCH_2OCH_3$, $C_2H_5N(i\text{-}C_3H_7)_2$, H_2CCl_2; b, DIBAL, Et_2O, -78°; c, $Ph_3P\text{-}CCl_4$, THF, 67°; d, $P(NMe_2)_3\text{-}CCl_4$, -78°-0°; e, xs Li-NH_3, 2 hours, then NH_4Cl.

using zinc or magnesium, and transmetalation with organolithium reagents) a satisfactory technique was developed. Addition of a solution of the chloride to an excess of lithium in liquid ammonia at -78°, and isolation of the reduction products under anhydrous conditions following acidification of the reaction mixture with solid ammonium chloride, afforded a 93% yield of a 6:1 mixture of gycal 8a and tetrahydrofuran 17b. By-product 17b is most likely produced by protonation of the intermediate carbanion (ix, eq 3) prior to fragmentation. Reduction of furanosyl chloride 18a[26] afforded the alcohol 9a in 75% yield, together with a 9% yield of the tetrahydrofuran derivative 18b. Glycals 8a and 9a could be purified by chromatography on silica gel with 90% and 95% recoveries, respectively. Despite the lability of these products which results in only moderate recovery after purification, pure furanoid glycals are available by this procedure, and given the relatively inert nature of the by-product, for preparative purposes the mixture of products could be used without adverse effect in subsequent synthetic transformations.

The utilization of this methodology for preparation of pyranoid glycals was even more rewarding. Reaction of lactol 19[27] with triphenylphosphine and carbon tetrachloride afforded the pyranosyl chloride 20. Reduction of this chloride with lithium in ammonia produced the glycal 6a in 90% yield. Lactol 21, the preparation of which is

Scheme 4

Preparation of Pyranoid Glycals 6a and 7a[a]

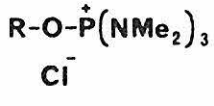


[a] a, Ph_3P-CCl_4, THF, 67°; b, $P(NMe_2)_3$-CCl_4, THF, -78°; c, Li-NH_3, 2 hours, then NH_4Cl.

described in Part II of this thesis, provided the chloride 22, an unstable liquid, in 67% yield. This chloride was converted in 90% yield to glycal 7a. In the reductions of 20 and 22 the glycals 6a and 7a were the only detectable products. No by-product analogous to 17b or 18b could be detected.

In light of the instability of the intermediate chlorides formed in this process, an alternative method for the transformation of these lactols to glycals was examined. It is known that hexamethylphosphorus triamide (trisdimethylaminophosphine, TDAP) reacts at very low temperatures with carbon tetrachloride in the presence of alcohols to form adducts of type xi.[27] Warming of these adducts leads to the formation of alkyl chlorides and HMPA at temperatures and rates determined by the nature of the alkyl portion. Addition of TDAP to a solution of lactol 18 and carbontetrachloride in tetrahydrofuran at -78°, then warming this mixture to 0° and immediately adding it to a solution of excess lithium in liquid ammonia yielded a mixture of glycal 6a and HMPA in equimolar amounts. The HMPA is easily removed by filtration of the crude product through silica gel. By this technique, the glycal 6a was obtained in 92% yield from lactol 19. In the same manner lactol 21 afforded glycal 7a in 87% yield, and lactol 16 was converted in 93% yield to a 6:1 mixture of 8a and 17b. Apparently, the high reactivity of

TDAP relative to triphenylphosphine obviates the need for destructively high temperatures during the preparation of the sensitive chlorides. Alternatively, in analogy with the dissolving metal reductions of tetramethylphosphorodiamidates developed in this laboratory,[28] reduction of adduct xi may lead directly to carbanion formation.



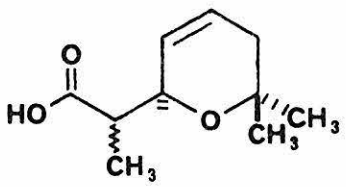
xi

These experiments resulted in the ready availability of optically active heterocyclic alcohols of the type required for the successful realization of the proposed approach to X-537A and analogues of the polyether antibiotics. The next phase of this work required the acylation of these alcohols, and the [3,3] sigmatropic rearrangements of the silyl ketene acetals obtained from the resulting esters. The preparations and reactions of the simple aliphatic esters were examined first.

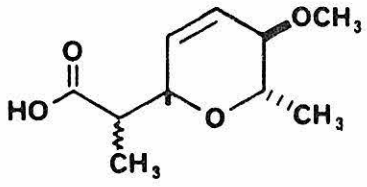
With some minor modifications, the experimental techniques applied to these reactions were the same as those used for their acyclic counterparts, as described above. Esters dl·5b and 6b were obtained from their corresponding alcohols by acylation with propanoyl chloride and pyridine in dichloromethane. In contrast to the acyclic ester

dl·4b these conformationally more restricted esters could be isolated in high yield. These esters were converted to silyl ketene acetals dl·5d and 6d by the action of LDA and TBSCl as described for ester 2b. Hydrolysis of the silyl esters obtained by rearrangement of these acetals afforded the acids dl·27a,b and 28a,b. Change of the solvent employed during deprotonation resulted in the expected variation of side chain stereochemistry (Table 2). The rates of rearrangement of the silyl ketene acetals dl·5d and 6d (X-=t-Bu$(CH_3)_2$Si-) at 35° were determined by NMR analysis to be 100±15 minutes and 30±5 minutes, respectively. For preparative purposes, these reactions were expedited by heating of the acetals at 67°C.

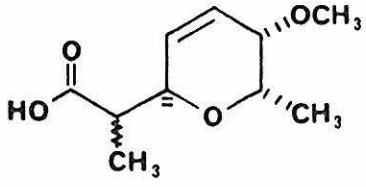
While esters could be obtained in good yield from dl·5a and 6a, the esters derived from 7a, and especially the esters of furanoid glycals 8a and 9a, were too unstable to allow isolation in acceptable yields. Therefore each of these esters was prepared by the reaction of a lithium alcoholate with the appropriate acyl chloride, and the resulting solution of ester was used immediately for the Claisen rearrangement. Ketene acetals derived from the furanoid glycal esters rearranged very quickly at 35° ($\tau_{1/2} \leq 5$ minutes). The products obtained from the furanoid glycal esters were produced in higher yield by silylation of the enolate anions with trimethylchlorosilane rather than with tert-butyldimethylchlorosilane. The results of



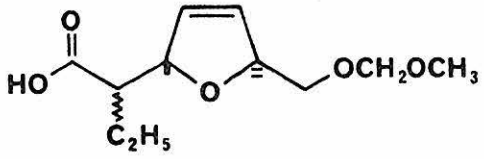
dl-27a,b



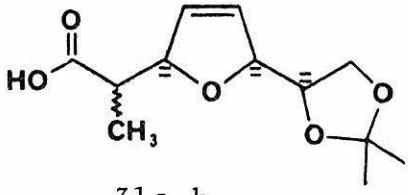
28a,b



29a,b



30a,b



31a,b

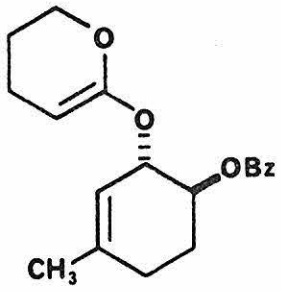
Table 2. Products Obtained from Furanoid and Pyranoid Glycals.

Reactant	Solvent[a]	Product	Yield	a/b[b]
dl-5b	HMPA-THF	dl-27a,b	79%	1/11
6b	THF	28a,b	73%	4/1
6c	HMPA-THF	28a,b	71%	1/4
6a[c]	THF	28a,b	79%	4/1
7a	THF	29a,b	69%	4/1
7a	HMPA-THF	29a,b	74%	1/4
8a	THF	30a,b	73%	4/1[d]
8a	HMPA-THF	30a,b	60%	1/4[d]
9a	THF	31a,b	52%	4/1
9a	HMPA-THF	31a,b	54%	1/1

[a]Solvent employed during deprotonation of allylic ester. THF=100% THF, HMPA-THF=23% (v./v.) HMPA/THF. [b]Ratio of diastereomers (XXa/XXb) determined by NMR. See discussion in text. [c]In this case, and in those listed below, the required ester was prepared just prior to use and was not isolated. [d]Ratio determined by GC analysis of hydrogenated methyl esters (see experimental section).

these reactions are collected in Table 2.

The prediction of the stereochemical outcome in these reactions, or assignment of relative stereochemistry to the major product in each reaction, is more complicated here than in the acyclic examples discussed above. Of

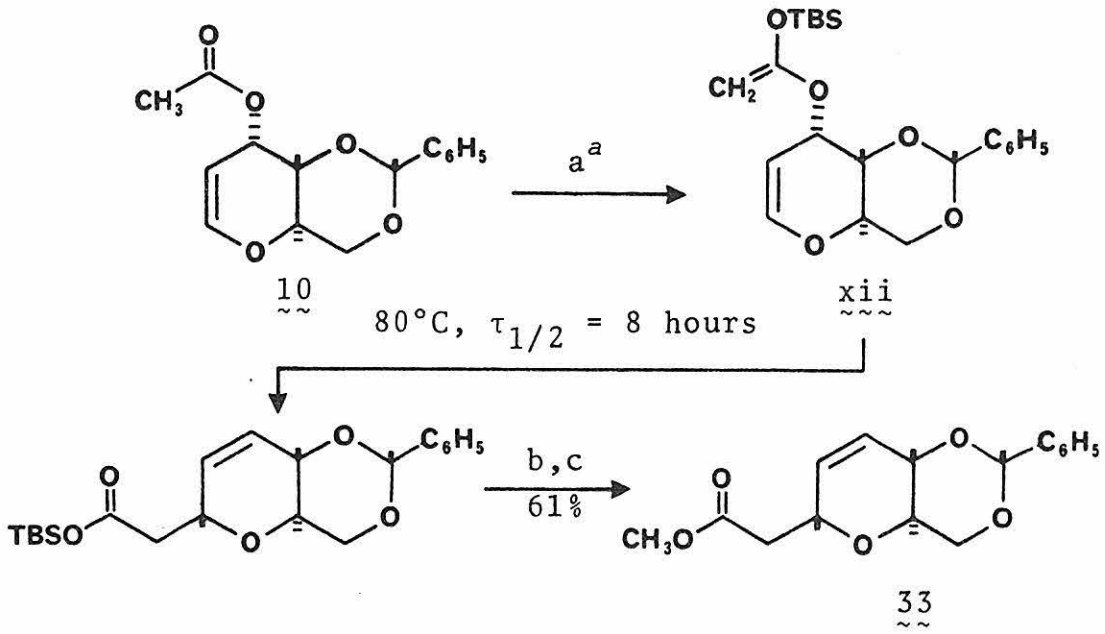


dl·32

course, the orientation of the new carbon-carbon bond at C-1 in these heterocycles is specified with certainty by the disposition of the allylic carbon-oxygen bond prior to rearrangement. However, although enolization and silylation of these esters is expected to exhibit the same selectivity found earlier, and solvent variation does provide the expected control of stereoisomer ratios, ill-defined non-bonded interactions between the substituents on the heterocyclic ring and the silyl ketene acetal must cast doubt upon the favorable nature of a chair-like transition state for these rearrangements. This doubt is further amplified by a report from Lythgoe[30] that the intermediate cyclohexenyl ketene acetal dl·32 rearranges exclusively

through a boat-like transition state. In the light of this uncertainty the configuration of the carbon alpha to the carbonyl in products dl·27-31 is not specified. In lieu of this assignment the ratio of diastereomers (Table 2) is based solely upon the NMR spectra of the products. Of the two diastereomer, XXa and XXb, the isomer in which the doublet attributed to the α-methyl group appears at higher field is defined as XXa. The isomer having the lower field methyl group resonance is designated XXb. It is interesting to note that enolization and silylation in 100% THF consistently afforded a mixture of final products in which the isomer with the higher field doublet predominates.

The last glycal we investigated was the acetate 10, generously provided to us for this purpose by Professor B. Fraser-Reid, Waterloo, Ontario. The ketene acetal xii was prepared by deprotonation of the acetate with potassium hexamethyldisilazide in tetrahydrofuran at -78° followed by silylation of the enolate anion with TBSCl. The ketene acetal xii rearranges very slowly relative to the monocyclic intermediates described above. The restricted conformational mobility inherent to the bicyclic framework no doubt contributes to this difference. The rearrangement is completed by heating the silyl ketene acetal for 23 hours at 100°, and the resultant silyl ester is converted to methyl ester 33 by treatment with potassium fluoride followed by methyl iodide in HMPA.[31] The overall yield of ester 33

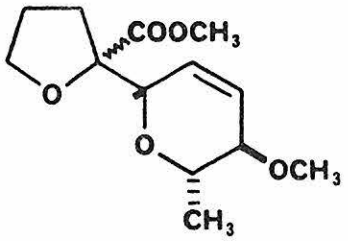


[a]a, KH, TBSCl; b, KF, HMPA; c, MeI, HMPA.

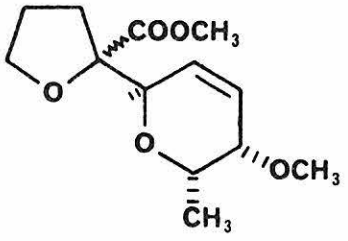
is 61%.

The successful preparation of the carboxylic acids dl·27a,b through 31 and ester 33 demonstrated that the ester enolate Claisen rearrangement could be usefully applied to esters of both furanoid and pyranoid glycals. The technique allows for the stereospecific attachment of sidechains to the C-1 position of saturated furanoid and pyranoid rings. The final stage of this developmental project called for the production of the tetrahydro-2-furoyl esters of pyranoid alcohols of type i, and the utilization of these products in the Claisen rearrangement.

The ester 6c was prepared and isolated in 90% yield by the reaction of tetrahydro-2-furoyl chloride with glycal



34a,b



35a,b

6a and pyridine in diethyl ether. A solution of this ester in tetrahydrofuran was treated first with LDA, and then with trimethylchlorosilane, to yield the silyl ketene acetal, 6e. Subsequent rearrangement of this acetal afforded, after esterification of the resultant carboxylic acid with diazomethane, the isomeric methyl esters 34a and 34b in a combined yield of 62%. The ester 7c, prepared immediately prior to use and not isolated, afforded, by the same process, the isomeric esters 35a and 35b in 67% yield. These isomers, and those obtained from glycal 6c, could be separated by chromatography on silica gel.

The effects of a few variations of solvent and base upon the ratios of products obtained have been investigated (Table 3). These effects are not as dramatic as those found with the simple aliphatic esters. Nevertheless, a synthetically useful preponderance of one diastereomer of the interesting products 34 and 35 is readily obtained. The successful preparation of these products is suggestive of

Table 3. The Preparation of Glycol Ethers 34a,b and 35a,b.

Reactant	Solvent[a]	Products	Yield[b]	a/b[c]
6c	THF	34a,b	76%	5/1
6c	THF-HMPA	34a,b	56%	1/1
6c	THF[d]	34a,b	67%	7/1
6a[e]	THF	34a,b	80%	5/1
7a[e]	THF	35a,b	73%	5/1
7a[e]	THF-HMPA	35a,b	67%	1/1

[a]Solvent employed during deprotonation of allylic ester. THF = 100% THF, HMPA-THF = 23% (v./v.) HMPA/THF. [b]Yield of carboxylic acid obtained upon hydrolysis of silyl ester. [c]Ratio of diastereomers obtained by NMR analysis of unfractionated product. [d]Potassium hexamethyldisilazide used as base. [e]The required ester was generated just prior to deprotonation and was not isolated.

the practical value of this reaction for the preparation of polyether antibiotics.

In summary, this investigation demonstrates that the ester enolate Claisen rearrangement, as applied in Scheme 1, is a useful and stereoselective method for the attachment of chiral side chains to the C-1 position of oxygen heterocycles. An efficient new method for the preparation of optically active furanoid and pyranoid glycals was developed, and chiral oxygen heterocycles of interest as models

or intermediates for the synthesis of lasalocid A were derived from those alcohols. This method has potential application in the field of C-glycoside synthesis. The ubiquitous occurrence of furanoid and pyranoid rings among the abundant acetogenous fungal metabolites, and the unique properties of heterocyclic ethers as chelating ligands in ionophores in general, further emphasize the value of the synthetic methods described in this report. Based upon this investigation work has been undertaken in this laboratory toward enantiospecific total syntheses of lasalocid A, nonactic acid, furanomycin, and other heterocyclic natural products. Reports upon these endeavors will be forthcoming.

Experimental Section[32]

(E)-3-Methoxy-2-propen-1-ol (1a). A solution of 1.16 g (0.01 mol) of ester 11a in 5 mL of dry ether was added dropwise, over a period of 15 minutes, to a stirred, argon protected, ice cooled solution of 0.38 g (0.01 mol) of lithium aluminum hydride in 40 mL of dry ether. After 5 minutes at 0°C, this mixture was hydrolysed,[34] and the resulting white precipitate was removed by filtration and washed with 50 mL of ether. The combined filtrates were dried (K_2CO_3) and removal of solvent under reduced pressure afforded 915 mg of a colorless liquid. Distillation [kugelrohr, 100°C (30 mmHg)] of this liquid provided 0.32 g (36%) of alcohol 1a: IR (CCl_4) 3600 cm^{-1} (OH), 1665 cm^{-1} (C=C); ^{1}H-NMR (CCl_4) δ 3.1 (bs, 1H, OH), 3.48 (s, 3H, OCH_3), 3.93 (d, 2H, J=7 Hz, CH_2O), 4.83 (m, 1H, C=CH-C), 6.42 (d, 1H, J=12.5 Hz, O-CH=C).

Anal. Calcd for $C_4H_8O_2$: C, 54.52; H, 9.15. Found: C, 54.50; H, 9.08.

(E)-3-Methoxy-2-buten-1-ol (2a). In the manner described for the preparation of alcohol 1a, 4.32 g (0.03 mol) of ester 11b,[10] in 10 mL of ether, with 1.14 g (0.03 mol) of lithium aluminum hydride in 100 mL of ether, afforded, after distillation [kugelrohr, 100°C (10 mmHg)], 2.52 g (82%) of alcohol 2a, a colorless, clear liquid: IR (neat)

3500-3200 cm^{-1} (OH), 1660 cm^{-1} (C=C); ^{1}H-NMR (CCl_4) 1.70 (s, 3H, C=CH_3), 3.40 (s, 3H, OCH_3), 4.47 (t, 1H, C=CH).

Anal. Calcd for $C_5H_{10}O_2$: C, 58.79; H, 9.87. Found: C, 58.75; H, 9.81.

(E)-3-Methoxy-3-phenyl-2-buten-1-ol (3a). A mixture of 19.2 g (0.10 mol) of ethyl benzoylacetate, 10.6 g (0.10 mol) of trimethylorthoformate and 6 drops of concentrated sulfuric acid was stirred at room temperature for 36 hours. After the addition of 0.5 mL of quinoline, distillation of the dark red reaction mixture, first at atmospheric pressure (removal of methyl formate and methanol) and then under reduced pressure provided 16.4 g (80%) of a colorless liquid, bp 122-124°C (1.3 mmHg). Analysis of this product by ^{1}H-NMR indicated the presence of two geometrical isomers of the β-methoxy ester 11c. Integration of the vinylic protons indicated that the major isomer (δ5.1) and the minor isomer (δ5.5) were present in a (4:1) ratio.[35]

A solution of 10.3 g of the above mixture in 10 mL of dry ether was added to a stirred solution of 1.9 g (0.05 mmol) of lithium aluminum hydride in 220 mL of dry ether. The ester was added at such a rate as to cause the ether to boil mildly. After one hour at room temperature, work up of this mixture as described for the isolation of alcohol 1a provided the crude product, distillation of which provided three fractions: A, 2.5 g, bp 82-85°C (0.6 mmHg); B, 2.0 g,

bp 85-92°C (0.6 mmHg); and C, 2.7 g, bp 92-94°C (0.6 mmHg). Fractions A and B were mixtures of the desired alcohol (~50%) with several byproducts, and were discarded. Fraction C was the alcohol 3a (26% yield, based on ethyl benzoylacetate): bp 92-94°C (0.6 mmHg); IR (CCl_4) 3600 cm^{-1} (OH), 1640 cm^{-1} (C=C); ^{1}H-NMR (CCl_4) δ 3.57 (s, 3H, OCH_3), 4.00 (d, 2H, J=8 Hz, CH_2-O), 4.87 (t, 1H, J=8 Hz, C=CH), 7.3 (bs, 5H, ArH).

Anal. Calcd for $C_{10}H_{12}O_2$: C, 73.14, H, 7.37. Found: C, 73.09; H, 7.32.

(E)-2-Methoxy-2-penten-4-ol (4a). In the manner described for the preparation of alcohol 1a from ester 11a, 3.68 g (0.03 mol) of enone 12,[12] in 15 mL of dry ether, with 1.22 g (0.03 mol) of lithium aluminum hydride in 100 mL of dry ether, afforded, after distillation, 3.3 g of the alcohol 4a: bp 51-53°C (3.1 mmHg); IR (neat) 3600-3200 cm^{-1} (OH), 1665 cm^{-1} (C=C); ^{1}H-NMR (CCl_4) δ 1.20 (d, 3H, J=6 Hz, CCH_3), 1.77 (s, 3H, $C=CCH_3$), 3.43 (s, 3H, OCH_3), 4.45 (m, 2H, C=CH and OCH).

m/e: Calcd for $C_6H_{10}O$ (M^+-18): 98.073. Found: 98.074.

(E)-3-Methoxy-2-propen-1-yl propanote (1b). To a stirred, argon protected solution of 0.32 g (3.6 mmol) of alcohol 1a in 25 mL of dry THF at -78°C was added 1.42 mL (3.6 mmol) of a 2.52 M solution of n-butyllithium in hexane.

After 3 minutes, 0.46 mL (3.6 mmol) of propionic anhydride was added rapidly, and the mixture was allowed to warm to room temperature. After 40 minutes, n-pentane extraction (Na_2SO_4),[33] followed by distillation [kugelrohr, 80°C (1.5 mmHg)] afforded 0.36 g (70%) of ester 1b, a colorless liquid: IR (CCl_4) 1735 cm^{-1} (C=O), 1655 cm^{-1} (C=C); ^{1}H-NMR (CCl_4) δ 1.10 (t, 3H, J=7 Hz, CCH_3), 2.23 (q, 2H, J=7 Hz, CH_2C), 3.52 (s, 3H, OCH_3), 6.52 (d, 1H, J=12 Hz, O-CH=C).

Anal. Calcd for $C_7H_{12}O_3$: C, 58.31; H, 8.39. Found: C, 58.42; H, 8.36.

(E)-3-Methoxy-2-buten-1-yl propanoate (2b). In the manner described for the preparation of ester 1b, 1.20 g (0.012 mol) of alcohol 2a, in 40 mL of dry THF, with 4.7 mL (0.012 mol) of 2.52 M n-butyllithium in hexane and 1.51 mL (0.012 mol) of propionic anhydride provided, after distillation [kugelrohr, 95-100°C (2.0 mmHg)], 1.55 g (84%) of the ester 2b: IR (CCl_4) 1735 cm^{-1} (C=O), 1660 cm^{-1} (C=C); ^{1}H-NMR (CCl_4) δ 1.10 (t, 3H, J=7 Hz, CH_3) 1.83 (s, 3H, $C=CH_3$), 3.48 (s, 3H, OCH_3) 4.50 (s, 3H, OCH_2 and C=CH).

Anal. Calcd for $C_8H_{14}O_3$: C, 60.74; H, 8.92. Found: C, 60.79; H, 8.80.

(E)-3-Methoxy-3-phenyl-2-buten-1-yl propanoate (3b). In the manner described for the preparation of ester 1b, 0.33 g (2.0 mmol) of alcohol 3a, in 10 mL of dry THF, with

0.79 mL (2.0 mmol) of 2.52 M n-butyllithium in hexane and 1.51 mL (2.0 mmol) of propionic anhydride provided, after distillation [kugelrohr, 120°C (0.6 mmHg)], 320 mg (73%) of the ester 3b: IR (CCl_4) 1735 cm^{-1} (C=O), 1648 cm^{-1} (C=C); ^{1}H-NMR (CCl_4) δ 1.10 (t, 3H, J=7 Hz, CCH_3), 2.28 (q, 2H, J=7 Hz, CCH_2), 3.67 (s, 3H, OCH_3), 4.90 (dd, 1H, J=6.5 Hz, J´=9.8 Hz, C=CH), 7.27 (s, 5H, ArH).

Anal. Calcd for $C_{13}H_{16}O_3$: C, 70.88; H, 7.32. Found: C, 70.80; H, 7.36.

(±)-3,4-Dihydro-2,2-dimethyl-2H-pyran-4-yl propanoate (dl·5b). To a stirred solution of 1.02 g (8.0 mmol) of alcohol 5a[17] in 30 mL of dry tetrahydrofuran under argon at 0°C was added 3.17 mL (8.0 mmol) of a 2.52 M solution of n-butyllithium in hexane. After 3 minutes, cooling was discontinued and 1.04 mL (8.0 mmol) of propionic anhydride was added. After 20 minutes at room temperature, during which time a flocculent white precipitate appeared, the product was isolated by ether extraction (K_2CO_3),[33] and distillation [kugelrohr, 100°C (4.2 mmHg)] afforded 1.19 g (85%) of the ester, 5b, a colorless liquid: R_f=0.35 (silica gel, 10% ether-petroleum ether); IR (CCl_4) 1730 cm^{-1} (C=O), 1640 cm^{-1} (C=C), 1185 cm^{-1} (C-O); ^{1}H-NMR (CCl_4) δ 1.10 (t, 3H, J=7 Hz, CH_3), 1.31 (s, 6H, 2xCH_3), 4.70 (dd, 1H, J=4Hz, J´=6 Hz, C=CH-C), 5.08 (m, 1H, OCH), 6.27 (dd, 1H, J=1 Hz, J´=6 Hz, O-CH=C).

Anal. Calcd for $C_{10}H_{16}O_3$: C, 65.19; H, 8.75. Found: C, 65.22; H, 8.82.

1,5-Anhydro-2,6-dideoxy-4-O-methyl-L-arabino-hex-1-enitol (6a). A. From Reduction of Chloride 20. To a stirred solution of 38 mg (5.4 mmol) of lithium wire in 15 mL of anhydrous liquid ammonia under an argon atmosphere at -78°C was added a solution of 210 mg (0.89 mmol) of the pyranosyl chloride 20 in 1 mL of dry THF. Cooling was then discontinued (ammonia reflux) and after 120 minutes 380 mg (7.0 mmol) of anhydrous ammonium chloride was cautiously added to the blue reaction mixture. The resulting colorless mixture was diluted with 15 mL of ether, the ammonia was allowed to evaporate, and ~0.5 g of anhydrous magnesium sulfate was added. The ethereal suspension was filtered and the solid was washed by trituration with five 3 mL portions of ether. Removal of solvent from these filtrates and drying of the residue under vacuum (1 mmHg) afforded 122 mg (95%) of a crystalline product, mp 76-77°C. This product was homogeneous by TLC (silica gel, 40% ethyl acetate-benzene). The analytical sample was obtained by recrystallization from n-hexane, and melted at 76-77°C: R_f=0.27 (40% ethyl acetate-benzene); IR (CCl_4) 3600 cm^{-1} (OH), 1640 cm^{-1} (C=C); ^{1}H-NMR (CCl_4) δ 1.35 (d, 3H, J=7 Hz, $CHCH_3$), 2.20 (bs, 1H, OH), 3.01 (dd, 1H, J=9 Hz, J´=6 Hz, OCH), 3.57 (s, 3H, OCH_3), 4.62 (dd, 1H, J=6Hz, J´=2 Hz, C=CH-C), 6.23

(d, 1H, J=6 Hz, O-CH=C); $[\alpha]_D^{24}$=-0.2° (c 1.2; $HCCl_3$).

Anal. Calcd for $C_7H_{12}O_3$: C, 58.31; H, 8.39. Found: C, 58.32; H, 8.30.

B. From Lactol 19, via Phosphonium Chloride Adduct. To a stirred solution of 300 mg (1.36 mmol) of lactol 19 and 0.20 mL (2.0 mmol) of carbon tetrachloride in 3 mL of dry THF at -78°C under an argon atmosphere was added 0.27 mL (1.5 mmol) of trisdimethylaminophosphine. After 30 minutes, the mixture was warmed in an ice-water bath and after 3 minutes at 0°C, the entire reaction mixture was taken up in an argon flushed syringe and added rapidly to a cold (-78°C) stirred solution of 116 mg (16.7 mmol) of lithium wire in 40 mL of anhydrous liquid ammonia. Two 1 mL rinses with dry THF sufficed to complete the transfer. Cooling was discontinued (ammonia reflux) and after 120 minutes, 1.2 g (22 mmol) of anhydrous ammonium chloride was added to the blue reaction mixture. The resulting colorless mixture was diluted with a total of 40 mL of ether as the ammonia was allowed to evaporate, and ~1 g of anhydrous magnesium sulfate was added. The ethereal suspension was filtered, and the solids were washed with ether. The combined filtrates were concentrated under reduced pressure to ~4 mL in volume. This concentrate was transferred to a column of silica gel (3 cm high and 2 cm in diameter) and eluted with 100 mL of 40% ethyl acetate-benzene. Removal of solvents from the

eluate and drying of the residue under vacuum (1 mmHg) afforded 187 mg (95%) of fine white crystals, mp 76-77°C. This product was spectrally identical to the product obtained in A, above.

1,5-Anhydro-2,6-dideoxy-4-O-methyl-3-O-propionyl-L-arabino-hex-1-enitol (6b). To a stirred solution of 149 mg (1.03 mmol) of glycal 6a and 97 μL (1.20 mmol) of dry pyridine in 2.0 mL of dry dichloromethane at 0°C under an argon atmosphere was added 104 μL (1.20 mmol) of propanoyl chloride. Cooling was then discontinued, and after 90 minutes at room temperature the product was isolated by pentane extraction ($MgSO_4$).[33] Distillation [kugelrohr, 90°C (0.7 mmHg)] afforded 190 mg (92%) of the ester 6b: R_f=0.58 (silica gel, 40% ethyl acetate-benzene); IR ($CHCl_3$) 1720 cm^{-1} (C=O), 1640 cm^{-1} (C=C); ^{1}H-NMR ($CDCl_3$) δ 1.14 (t, 3H, J=7 Hz, CH_2CH_3), 1.35 (d, 3H, J=7 Hz, $CHCH_3$), 2.32 (q, 2H, J=7 Hz, CH_2CH_3), 3.25 (dd, 1H, J=8.0 Hz, J′=5.5 Hz, $HCOCH_3$), 3.50 (s, 3H, OCH_3), 3.98 (dq, 1H, J=7 Hz, J′=8 Hz, $CHCH_3$), 4.69 (dd, 1H, J=6 Hz, J′=3Hz, C=CH-C), 5.27 (m, 1H, C=C-CH), 6.32 (dd, 1H, J=6 Hz, J′=1.2 Hz, O-CH=C); $[\alpha]_D^{23}$= +125° (c 1.1, $CHCl_3$).

Anal. Calcd for $C_{10}H_{16}O_4$: C, 59.98; H, 8.05. Found: C, 60.00; H, 8.06.

(±)-Tetrahydro-2-furancarboxylic acid. Adam's catalyst, freshly prepared from 500 mg of platinum oxide, was added to a stirred solution of 4.0 g (39 mmol) of tetrahydrofurfuryl alcohol and 3.2 g (39 mmol) of sodium bicarbonate in 200 mL of water at 60°C, and dry air was bubbled through this mixture. After 48 hours, analytical TLC (silica gel, 40% ethyl acetate-benzene) indicated no starting material (R_f=0.12) remained. The catalyst was removed from the cooled reaction mixture by filtration, and washed with 20 mL of water. The combined filtrates were acidified (pH ~2.5) with concentrated HCl, saturated with sodium chloride (80 g) and extracted with fifteen 100 mL portions of ether. The combined extracts were dried ($MgSO_4$) and the ether was removed under reduced pressure. Distillation of the residue [kugelrohr, 80°C (13 mmHg)] afforded 3.92 g (87%) of the carboxylic acid. Lit.[37] bp 131-132° (14 mmHg).

(±)-Tetrahydro-2-furancarbonyl chloride. A mixture of 232 mg (2.0 mmol) of tetrahydro-2-furancarboxylic acid and 0.45 mL (5.0 mmol) of oxalyl chloride was stirred under argon for 14 hours. Excess oxalyl chloride was then removed under reduced pressure (50-100 mmHg) and distillation of the residue [kugelrohr, 95-100°C (33 mmHg)] afforded 233 mg (87%) of tetrahydro-2-furancarbonyl chloride, a colorless liquid: IR ($CHCl_3$) 1780 cm^{-1} (C=O), 1080 cm^{-1}

(C-O).

m/e Calcd for C_4H_7O (M^+-COCl): 71.050. Found: 71.047.

This product effervesces very slowly at room temperature and was stored under an argon atmosphere at -20°C for up to three weeks.

1,5-Anhydro-2,6-dideoxy-4-O-methyl-3-O-[(±)-tetrahydro-2-furoyl]-L-arabino-hex-1-enitol (6c). A stirred solution of 200 mg (1.4 mmol) of glycal 6a and 0.27 mL (3.3 mmol) of dry pyridine in 3 mL of dry ether under an argon atmosphere at -5±2°C was treated with 0.19 mL (0.22 g, 1.54 mmol) of (±)-tetrahydro-2-furancarbonyl chloride. After 30 minutes, pentane extraction ($MgSO_4$)[33] followed by distillation [kugelrohr, 110°C (0.7 mmHg)] afforded 300 mg (89%) of the ester 6c: R_f=0.31 (50% ether-petroleum ether); IR (CCl_4) 1740, 1760 cm^{-1} (C=O), 1655 cm^{-1} (C=C); ^{1}H-NMR (CCl_4) δ 1.33 (d, 3H, J=6 Hz, $CHCH_3$), 3.17, 3.20 (2xdd, 1H, J=6 Hz, J´=8 Hz), 3.42 (s, 3H, OCH_3), 4.17-4.35 (m, 1H, α-OCH), 5.17 (bd, 1H, J=6 Hz), 6.26 (d, 1H, J=6 Hz, O-CH=C).

Anal. Calcd for $C_{12}H_{18}O_5$: C, 59.49; H, 7.49. Found: C, 59.52; H, 7.34.

1,5-Anhydro-2,6-dideoxy-4-O-methyl-L-xylo-hex-1-enitol (7a). A. From Reduction of Chloride 22. By procedure A described for the preparation of glycal 6a, 73 mg

(0.31 mmol) of freshly prepared chloride 22 in 2 mL of dry THF with 21 mg (3.0 mmol) of lithium metal in 10 mL of anhydrous liquid ammonia and 240 mg (4.5 mmol) of anhydrous ammonium chloride provided, after distillation [kugelrohr, 95°C (1.0 mmHg)] 41 mg (92%) of the pyranoid glycal 7a, a colorless liquid: R_f=0.17 (silica gel, 40% ethyl acetate-benzene); IR (CCl_4) 3600 cm^{-1} (OH), 1632 cm^{-1} (C=C); ^{1}H-NMR ($CDCl_3$) δ 1.38 (d, 3H, J=6 Hz, $HCCH_3$), 3.49 (s, 3H, OCH_3), 4.92 (dd, 1H, J=6 Hz, J´=1.5 Hz, C=CH-C), 6.50 (d, 1H, J=6 Hz, O-CH=C); $[\alpha]_D^{23}$=-121.5° (c 1.4, $CHCl_3$).

Anal. Calcd for $C_7H_{12}O_3$: C, 58.31; H, 8.39. Found: C, 58.37; H, 8.35.

B. From Lactol 21, via Phosphonium Chloride Adduct. By a procedure identical to process B described for the preparation of glycal 6a, 220 mg (1.0 mmol) of lactol 21 with 0.14 mL (1.5 mmol) of carbon tetrachloride and 0.20 mL (1.1 mmol) of trisdimethylaminophosphine in 2 mL of dry THF, and 83 mg (12 mmol) of lithium metal in 30 mL of anhydrous liquid ammonia with 870 mg (16 mmol) of anhydrous ammonium chloride, provided, after distillation, 125 mg (87%) of a colorless, clear oil. This product was identical (IR, NMR, $[\alpha]_D$) to the material obtained in part A, above.

1,5-Anhydro-2,6-dideoxy-4-O-methyl-3-O-propionyl-L-xylo-hex-1-enitol (7b). To a stirred solution of 63 mg

(0.44 mmol) of glycal 7a and 42 μL (0.52 mmol) of dry pyridine in 2 mL of dry dichloromethane at 0°C under an argon atmosphere was added 46 μL (0.52 mmol) of propanoyl chloride. The mixture was stirred at room temperature for 90 minutes, after which the product was isolated by pentane extraction ($MgSO_4$).[33] Distillation [kugelrohr, 90°C (0.8 mmHg)] afforded 67 mg (76%) of the ester 7b: R_f=0.52 (silica gel, 40% ethyl acetate-benzene); IR ($CHCl_3$) 1720 cm^{-1} (C=O), 1640 cm^{-1} (C=C); ^{1}H-NMR (CCl_4) δ 1.12 (t, 3H, J=7 Hz, CH_2CH_3), 1.30 (d, 3H, J=6 Hz, $CHCH_3$), 2.22 (q, 2H, J=7 Hz, CH_2CH_3), 3.00 (dd, 1H, J=1.5 Hz, J′=1 Hz, $CHOCH_3$), 3.43 (s, 3H, OCH_3), 3.83 (q, 1H, J=6 Hz, J′=1.5 Hz, $CHCH_3$), 5.00 (dd, J=5 Hz, J′=2 Hz), 6.41 (d, 1H, J=6 Hz, OCH=C); $[\alpha]_D^{22}$=-200° (c 0.7, $CHCl_3$).

Anal. Calcd for $C_{10}H_{16}O_4$: C, 59.98; H, 8.05. Found: C, 59.85; H, 8.13.

1,4-Anhydro-2-deoxy-5-O-methoxymethyl-D-erythro-pent-1-enitol (8a). A. From Reduction of Chloride 17a. By procedure A described for the preparation of glycal 6a, 178 mg (0.70 mmol) of freshly prepared chloride 17a in 2 mL of dry THF with 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 (0.005 mmHg)] 105 mg of a mixture of glycal 8a and the simple reduction product 17b. Analysis of this mixture by

NMR revealed these products were obtained in a 6:1 (8a:17b) ratio. Chromatography of this mixture on Florisil with 75% ether-petroleum ether provided pure products for analysis. Fraction I, 17b: R_f=0.52 (silica gel, 75% ether-petroleum ether); IR ($CHCl_3$) 1030 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.35 (s, 3H, CH_3), 1.52 (S, 3H, CH_3), 3.37 (s, 3H, OCH_3), 3.58 (d, 2H, J=5 Hz, $CHCH_2OMOM$), 3.95 (s, 1H, OCH,H), 4.00 (s, 1H, OCH,H), 4.60 (s, 2H, OCH_2O); $[\alpha]_D^{24}$=+36° (c 0.94, $CHCl_3$).

Anal. Calcd for $C_{10}H_{18}O_5$: C, 55.03; H, 8.31. Found: C, 55.16; H, 8.23.

Fraction II, 8a: R_f=0.25 (silica gel, 75% ether-petroleum ether); IR ($CHCl_3$) 3570 cm^{-1} (OH), 1610 cm^{-1} (C=C); ^{1}H-NMR ($CDCl_3$) 2.57 (d, 1H, J=6 Hz, OH), 3.37 (s, 3H, OCH_3), 4.63 (s, 2H, OCH_2O), 5.13 (dd, 1H, J=J´=3 Hz, C=CH-C), 6.52 (d, 1H, J=3 Hz, O-CH=C); $[\alpha]_D^{24}$=+259° (c 0.91, $CHCl_3$).

Anal. Calcd for $C_7H_{12}O_4$: C, 52.49; H, 7.55. Found: C, 52.41; H, 7.65.

B. From Lactol 16, via Phosphonium Chloride Adduct. To a stirred solution of 15 g (64 mmol) of lactol 16 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 minutes the mixture was warmed to 0°C (ice-water bath) and then taken up in an

argon flushed syringe and added rapidly to a cold (-78°C) stirred solution of 5.5 g (0.78 mol) of lithium metal in 800 mL of anhydrous liquid ammonia. Cooling was then discontinued (ammonia reflux) and after 150 minutes 42 g (0.79 mol) of anhydrous ammonium chloride was added to the blue reaction mixture. The resulting colorless mixture was diluted slowly with ether (750 mL) as the ammonia was allowed to evaporate and ~10 g of anhydrous magnesium sulfate was added. The resulting ethereal suspension was filtered, and concentration of the filtrates under reduced pressure afforded a crude mixture of glycal 8a, by-product 17b, and HMPA. This mixture was placed on a 100 g column of silica gel and eluted with 700 mL of 75% ether-petroleum ether. Concentration of the eluate afforded, after distillation [kugelrohr, 110°C (0.01 mmHg)], 10.1 g of a colorless mixture of glycal 8a and by-product 17b. This mixture is identical to the mixture obtained in part A, above, and the ratio of components is 6:1 (8a:17b). Based upon this ratio, the yield of glycal 8a is 80%. This mixture was used without further purification for the enolate Claisen rearrangements described below.

1,4-Anhydro-2-deoxy-5,6-O-isopropylidene-D-arabino-hex-1-enitol (9a). To a mechanically stirred solution of 3.48 g (0.48 mol) of lithium wire in 800 mL of anhydrous liquid ammonia under an argon atmosphere at -78°C was added

a solution of 22.5 g (0.081 mol) of the furanosyl chloride 18a[26] in 225 mL of dry THF. Cooling was then discontinued (ammonia reflux) and after 135 minutes 39 g (0.73 mol) of anhydrous ammonium chloride was cautiously added. The colorless, heterogeneous mixture was diluted with 800 mL of ether and the ammonia was allowed to evaporate. The resulting ethereal suspension was filtered and the filter cake was washed with ether. Concentration of the combined filtrates under reduced pressure, and distillation [kugelrohr, 70-110°C (0.06 mmHg)] provided 13.0 g (86%) of a colorless oil, a mixture of glycal 9a and by-product 18b.

A portion of this oil (421 mg) was chromatographed on 42 g of silica gel. Elution with 60% ether-petroleum ether provided 37 mg of the by-product 18b, which was characterized by IR and NMR spectra and was not further purified. Continued elution provided 69 mg glycal 9a contaminated with a small amount of by-product, followed by 300 mg of pure glycal 9a. Based on this result the yield of 9a from the furanosyl chloride is calculated to be 75%. For the pure glycal 9a: R_f=0.40 (silica gel, 60% ether-petroleum ether); IR (neat) 3600-3000 cm^{-1} (OH), 1605 cm^{-1} (C=C); ^{1}H-NMR ($CDCl_3$) δ 1.37 (s, 3H, CH_3), 1.45 (s, 3H, CH_3), 2.07 (bs, 1H, OH), 4.77-5.07 (m, 1H, C=C-CH), 5.24 (dd, 1H, J≈J´=3 Hz, C=CH-C), 6.57 (d, 1H, J=3 Hz, O-CH=C); $[\alpha]_D^{23}$=-100° (c 1.0, $CHCl_3$).

Anal. Calcd for $C_9H_{14}O_4$: C, 58.05; H, 7.58.

Found: C, 57.97; H, 7.48.

Methyl (E)-3-methoxy-2-propenoate (11a). The ester 11a was prepared according to Winterfeldt and Preuss,[8] except that heating of the reaction mixture under argon at atmospheric pressure at 120°C for 5 minutes prior to distillation of the product was followed by isolation of only the (E) isomer, 11a: bp 64-65°C (12 mmHg); IR (CCl_4) 1720 cm^{-1} (C=O), 1630 cm^{-1} (C=C); ^{1}H-NMR (CCl_4) δ 3.62 (s, 3H, OCH_3), 3.68 (s, 3H, OCH_3), 5.10 (d, H, J=12.5 Hz, C=CH-C), 7.52 (d, 1H, J=12.5 Hz, C=CH-O). [lit.[8] bp 80°C (16 mmHg)].

2,3-O-(1-Methylethylidene)-5-O-methoxymethyl-D-ribonic acid, γ-lactone (15). To a stirred, ice cooled solution of 18.5 g (98 mmol) of hydroxy lactone 14[25] in 200 mL of dry dichloromethane was added 68.5 mL (0.39 mol) of diisopropylethylamine and 29.9 mL (0.39 mol) 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 washed with five 400 mL portions of saturated aqueous $NaHCO_3$ and 400 mL of saturated aqueous NaCl. The combined aqueous extracts were washed with three 400 mL portions of ether, and the combined organic extracts

were dried ($MgSO_4$) and concentrated to afford 21.7 g (95%) of the methoxymethyl ether 15. Chromatography of a portion of this product on silica gel with 40% ethyl acetate-benzene afforded the analytical sample: R_f=0.40 (40% ethyl acetate-benzene); IR ($CHCl_3$) 1780 cm^{-1} (C=O); ^{1}H-NMR ($CDCl_3$) δ 1.38 (s, 3H, CH_3) 1.47 (s, 3H, CH_3), 3.33 (s, 3H, OCH_3), 3.78 (d, 2H, J=2 Hz, CCH_2O), 4.77 (s, 2H, OCH_2O); $[\alpha]_D^{25}$=-55° (c 0.90, $CHCl_3$).

Anal. Calcd for $C_{10}H_{10}O_6$: C, 51.72; H, 6.94. Found: C, 51.76; H, 6.94.

2,3-O-(1-Methylethylidene)-5-O-methoxymethyl-D-ribose (16). To a stirred solution of 21.7 g (93 mmol) of lactone 15 in 600 mL of dry ether under argon at -78°C was added, dropwise, over one hour, a solution of 24 mL (130 mmol) of diisobutylaluminum hydride in 75 mL of dry ether. After 1.5 hours the reaction mixture was cautiously treated with 26 mL of methanol, warmed to room temperature, and diluted with 1.5 L of ether. This solution was washed with three 400 mL portions of 0.5 M aqueous sodium potassium tartrate, 300 mL of saturated NaCl, and dried ($MgSO_4$). After removal of solvent under reduced pressure, chromatography of the residue on 250 g of silica gel with 60% ether-petroleum ether, provided 21.9 g (95%) of the lactol 16, as a mixture of anomers: R_f=0.20 (60% ether-petroleum ether); IR ($CHCl_3$) 3400 cm^{-1} (OH); ^{1}H-NMR ($CDCl_3$) δ (major

anomer, minor anomer) 1.32, 1.38 (s, 3H, CH_3), 1.47, 1.55 (s, 3H, CH_3), 3.38 (s, 3H, OCH_3), 3.63, 3.60 (d, 2H, J=5 Hz, CCH_2O), 4.65 (s, 2H, OCH_2O), 5.32, 5.37 (d, 1H, J_{major}=9 Hz, J_{minor}=7 Hz, OCHO); $[\alpha]_D^{25}$=+0.90° (c 0.89, $CHCl_3$).

Anal. Calcd for $C_{10}H_{18}O_6$: C, 51.27; H, 7.75. Found: C, 51.15; H, 7.64.

2,3-O-(1-Methylethylidene)-5-O-methoxymethyl-β-D-ribofuranosyl chloride (17a). By the procedure described for the preparation of pyranosyl chloride 20, 169 mg (0.72 mmol) of lactol 16, in 3.6 mL of dry THF with 350 μL of carbon tetrachloride and 380 mg of triphenylphosphine afforded, after distillation [kugelrohr, 70-80°C (0.005 mmHg)], 170 mg (93%) of the chloride 17a as a mixture of anomers, (ratio ~1:10): IR ($CHCl_3$) 690 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ (major isomer, minor isomer) 1.33, 1.37 (s, 3H, CH_3), 1.47, 1.65 (s, 3H, CH_3), 3.38 (s, 3H, OCH_3), 4.63 (s, 2H, OCH_2O), 6.13, 6.18 (s, 1H, OCHCl); $[\alpha]_D^{25}$=-45° (c 1.14, $CHCl_3$).

Anal. Calcd for $C_{10}H_{17}ClO_5$: C, 47.53; H, 6.78. Found: C, 47.46; H, 6.75.

6-Deoxy-2,3-O-(1-methylethylidene)-4-O-methyl-α,β-L-mannopyranosyl chloride (20). To a stirred solution of 220 mg (1.0 mmol) of lactol 19[27] and 0.48 mL (5.0 mmol) of carbon tetrachloride in 5 mL of dry THF under an argon

atmosphere was added 525 mg (2.0 mmol) of triphenylphosphine. The mixture was heated at reflux for 3 hours, then cooled to room temperature, and concentrated under reduced pressure (~20 mmHg) to a thick paste. This residue was extracted by trituration with six 2 mL portions of dry ether and discarded. Removal of solvents from the ethereal extract, and distillation [kugelrohr, 60°C (0.005 mmHg)] afforded 210 mg (89%) of the chloride 20, a colorless oil: IR (neat) 1375, 1112, 860, 700 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.31 (d, 3H, J=6 Hz, $CHCH_3$), 1.36 (s, 3H, CH_3), 1.54 (s, 3H, CH_3), 3.53 (s, 3H, OCH_3), 6.19 (s, 1H, OCHCl); $[\alpha]_D^{25}$=-114° (c 1.61, $CHCl_3$).

Anal. Calcd for $C_{10}H_{17}O_4Cl$: C, 50.74; H, 7.24. Found: C, 50.55; H, 7.28.

6-Deoxy-2,3-O-(1-methylethylidene)-4-O-methyl-α,β-L-gulopyranosyl chloride (22). By the procedure described above for the preparation of pyranosyl chloride 20, 190 mg (0.88 mmol) of the lactol 21, with 458 mg (1.76 mmol) of triphenylphosphine and 0.42 mL (4.4 mmol) of carbon tetrachloride in 6 mL of dry THF provided, after distillation [kugelrohr, 85°C (0.05 mmHg)], 146 mg (70%) of the pyranosyl chloride 22. This chloride was quite labile and was stored under argon at -20°C for brief periods only: IR (neat) 1380, 910, 850 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.35 (d, 3H, J=6 Hz, $CHCH_3$), 1.37 (s, 3H, CCH_3), 1.52 (s, 3H, CCH_3),

3.50 (s, 3H, OCH_3), 5.32 (d, 1H, J=6 Hz, OCHCl).

[(R*,S*) and (S*,S*)]-(±)-3-Methoxy-2-methyl-4-pentenoic acid [(dl·23a) and dl·23b)]. A. Deprotonation in THF. To a stirred solution of 1.1 mmol of LDA in 3.4 mL of dry THF,[7b] prepared under argon and cooled to -78°C, was added, over a two minute period, 144 mg (1.0 mmol) of ester 1b. After 3 minutes at -78°C, 0.66 mL (1.1 mmol) of a 1.66 M solution of tert-butyldimethylchlorosilane in dry HMPA was added, the mixture was allowed to warm to 0°, and, after 30 minutes, worked up by pentane extraction ($NaSO_4$).[33] The resulting crude silyl ester was hydrolysed in 30 mL of THF with 2 mL of 10% aqueous hydrochloric acid. After stirring at room temperature for 80 minutes, the mixture was diluted with 80 mL of ether, washed with four 30 mL portions of water, and then extracted with three 15 mL portions of 1 N aqueous sodium hydroxide. The combined basic extract was washed with two 15 mL portions of ether, cooled in ice, and acidified (pH ≈2.5) with 6N hydrochloric acid. The product which separated was isolated by dichloromethane extraction ($NaSO_4$).[33] Drying of the resulting residue for several hours under vacuum (1 mmHg) afforded 115 mg (80%) of a mixture of the acids dl·23a and dl·23b. The ^{1}H-NMR spectrum of a solution of this mixture in carbon tetrachloride revealed two doublets of unequal intensity, assigned to the α-methyl groups of the diastereomeric

products. The major doublet (δ 0.97, J=7 Hz) and the minor (δ 1.17, J=7 Hz) appeared in a ratio of (5:1). This mixture, without further purification, provided the following analytical data: IR (CCl_4) 3600-2400 cm^{-1} (CO_2H), 1710 cm^{-1} (C=O), 930 cm^{-1}, (C=C); ^{1}H-NMR (CCl_4) 0.97, 1.17 (two doublets, 5:1 ratio, 3H, J=7 Hz, α-CH_3), 3.23 (s, 3H, OCH_3), 4.95-5.7 (m, 3H, C-CH=CH_2).

Anal. Calcd for $C_7H_{12}O_3$: C, 58.31; H, 8.39. Found: C, 58.10; H, 8.47.

B. Deprotonation in 23% HMPA-THF. To a solution of 1.1 mmol of LDA in 2.6 mL of dry THF at -78°C,[7b] was added 0.8 mL of dry HMPA. The heterogeneous mixture was stirred for 5 minutes, and then 144 mg (1.0 mmol) of ester 1b was added, followed after 3 minutes by 0.37 mL (1.1 mmol) of a 2.99 M solution of tert-butyldimethylchlorosilane in dry hexane. The mixture was allowed to warm to 0°C and stirred for 30 minutes. Completion of this experiment as described in A, above, gave 108 mg (75%) of a mixture of dl·23a and dl·23b. The ^{1}H-NMR spectrum of a solution of this mixture in carbon tetrachloride revealed two doublets of unequal intensity. The major doublet (δ 1.17, J=7 Hz) and the minor doublet (δ 0.97, J=7 Hz) appeared in a ratio of (4:1). Except for the change in relative magnitudes for these doublets, the spectral data for this mixture were exactly as described in A.

Anal. Calcd for $C_7H_{12}O_3$: C, 58.31; H, 8.39. Found: C, 58.17; H, 8.49.

[(R*,S*) and (S*,S*)]-(±)-2,3-Dimethyl-3-methoxy-4-pentenoic acid [(dl·24a) and (dl·24b)]. A. Deprotonation in THF. In the manner described for the preparation of dl·23a and dl·23b from ester 1b, 158 mg (1 mmol) of ester 2b in 0.5 mL of dry THF was added to 1.1 mmol of LDA in 3.6 mL of dry THF at -78°, under argon, and this mixture was treated with 0.77 mL of 1.42 M tert-butyldimethylchlorosilane in dry hexamethylphosphoramide, warmed, and stirred at 0°C for 1.0 hour, then at 67°C for 0.5 hour. After cooling this mixture, completion of this experiment as described for the isolation of dl·23a,b, above, provided 119 mg (76%) of a mixture of acids dl·24a and dl·24b. The ^{1}H-NMR spectrum of a solution of this mixture in carbon tetrachloride revealed two doublets of unequal intensity, assigned to the α-methyl groups of the diastereomeric products. The major doublet (δ 1.07, J=7 Hz) and the minor (δ 1.14, J=7 Hz) appeared in a ratio of (4:1). This mixture, after distillation [kugelrohr, 90°C (0.5 mmHg)], provided 115 mg (73%) of material which was spectrally identical to the undistilled product: IR (CCl_4) 3600-2500 cm^{-1} (CO_2H), 1710 cm^{-1} (C=O); ^{1}H-NMR (CCl_4) δ 1.07, 1.14 (two doublets, 4:1 ratio, 3H, J=7 Hz, α-CH_3), 1.32 (s, 3H, β-CH_3), 3.12 (s, 3H, OCH_3), 5.0-5.4 (m, 2H, CH=CH_2), 5.93

(dd, 1H, J=11 Hz, J´=16 Hz, $\underset{\sim}{CH}=CH_2$).

Anal. Calcd for $C_8H_{14}O_3$: C, 60.74; H, 8.92. Found: C, 60.71; H, 9.02.

B. Deprotonation in 23% HMPA-THF. In the manner described for the preparation of dl·23a and dl·23b, 158 mg (1.0 mmol) of the ester 2b, dissolved in 0.4 mL of dry THF, added to 1.1 mmol of LDA in a mixture of 2.8 mL of dry THF and 0.8 mL of dry HMPA, and treated with 0.37 mL (1.1 mmol) of a 2.99 M solution of tert-butyldimethylchlorosilane in hexane, provided, after completion of the experiment as described in part A, 127 mg (80%) of a mixture of acids dl·24a and dl·24b. The ^{1}H-NMR spectrum of a solution of this mixture in carbon tetrachloride revealed two doublets of unequal intensity. The major (δ 1.14, J=7 Hz) and the minor doublet (δ 1.07, J=7 Hz) appeared in a ratio of (1:3). Without further purification, this mixture provided the following spectral data: IR (CCl_4) 3500-2700 cm^{-1} (CO_2H), 1710 cm^{-1} (C=O); ^{1}H-NMR (CCl_4) δ 1.07, 1.14 (two doublets, 3:1 ratio, 3H, J=7 Hz, α-CH_3), 1.32 (s, 3H, β-CH_3), 3.12 (s, 3H, OCH_3), 5.0-5.4 (m, 2H, $CH=\underset{\sim}{CH_2}$), 5.93 (dd, 1H, J=11 Hz, J´=16 Hz, $\underset{\sim}{CH}=CH_2$).

Anal. Calcd for $C_8H_{14}O_3$: C, 60.74; H, 8.92. Found: C, 60.86; H, 8.96.

Methyl [(R*,S*) and S*,S*)]-(±)-3-methoxy-2-methyl-3-phenyl-4-pentenoate [(d1·25a) and (d1·25b)]. A. Deprotonation in THF. To a stirred solution of 1.1 mmol of LDA in 3.4 mL of dry THF prepared under argon and cooled to -78°C, was added, over a 2 minute period, a solution of 220 mg (1.0 mmol) of ester 3b in 0.4 mL of dry THF. After 3 minutes at -78°C, 0.66 mL (1.1 mmol) of a 1.66 M solution of tert-butyldimethylchlorosilane in dry HMPA was added, the mixture was allowed to warm to 0°C, and, after 30 minutes, worked up by ether extraction (Na_2SO_4).[33] The residue was dissolved in 5 mL of dry THF and heated at 67°C for 3 hours. After cooling and removal of THF under reduced pressure, the residue was dissolved in 4 mL of dry HMPA and stirred for 18 hours at room temperature with 188 mg (2 mmol) of $KF \cdot 2H_2O$ and 250 mg (2.5 mmol) of $KHCO_3$. Then 0.19 mL (3 mmol) of methyl iodide was added, and after 3 hours at room temperature, the products were isolated by ether extraction (Na_2SO_4), including a base wash.[33] Spectral analysis (^{1}H-NMR) of the residue indicated the presence of two diastereomeric products in a (47:53) ratio. Chromatography on silica gel with 5% ethyl ether-petroleum ether provided, in addition to 10 mg of mixed fractions, the following pure products: Fraction I: 76 mg, R_f=0.24 (silica gel, 10% ether-petroleum ether); IR (CCl_4) 1740 cm^{-1} (C=O), 1080, 940 cm^{-1}; ^{1}H-NMR (CCl_4) δ 1.11 (d, 3H, J=7 Hz, α-CH_3), 2.90 (s, 3H, OCH_3), 3.32 (s, 3H, OCH_3), 5.23 (dd,

1H, J=11.1 Hz, J′=2.6 Hz, HC=CHH) 5.40 (dd, 1H, J=18.2 Hz, J′=2.6 Hz, HC=CHH), 6.23 (dd, 1H, J=11.1 Hz, J′=18.2 Hz, HC=CH_2), 7.23 (bs, 5H, ArH).

Anal. Calcd for $C_{14}H_{18}O_3$: C, 71.77; H, 7.74. Found: C, 71.63; H, 7.73.

Fraction II: 70 mg; R_f=0.20 (silica gel, 10% ether-petroleum ether); IR (CCl_4) 1732 cm^{-1} (C=O), 1080, 930 cm^{-1}; ^{1}H-NMR (CCl_4) δ 0.97 (d, 3H, J=7 Hz, α-CH_3), 2.97 (s, 3H, OCH_3), 3.55 (s, 3H, OCH_3), 5.08 (dd, 1H, J=11.1 Hz, J′=2.1 Hz, HC=CH,H), 5.35 (dd, 1H, J=18.2 Hz, J′=2.1 Hz, HC=CH,H), 6.18 (dd, 1H, J=11.1 Hz, J′=18.2 Hz, HC=CH_2), 7.23 (bs, 5H, ArH).

Anal. Calcd for $C_{14}H_{18}O_3$: C, 71.77; H, 7.74. Found: C, 71.74; H, 7.79.

Comparison of these data with spectra obtained before chromatography indicated that the product obtained as Fraction II predominated prior to separation. The total yield of dl·25a and dl·25b was 156 mg (67%).

B. Deprotonation in 23% HMPA-THF. This experiment was performed exactly as in A, above, except 1.1 mmol of LDA was dissolved in 2.6 mL of dry THF and after cooling to -78°C, before ester 3b (1.0 mmol) was added, 0.8 mL of dry HMPA was added. After 10 minutes, completion of the experiment as in A provided 86 mg of Fraction I, 80 mg of Fraction II, and 5 mg of mixed fractions. Spectral analysis (^{1}H-NMR) of the crude methyl esters prior to chromatography indicated

that the product obtained as Fraction I predominated (48:52) prior to separation. The total yield of dl·25a and dl·25b was 171 mg (72%).

[(R*,S*) and (S*,S*)]-(±)-(E)-2,3-Dimethyl-3-methoxy-4-hexenoic acid [(dl·26a) and (dl·26b)]. A. Deprotonation in THF. To a stirred solution of 174 mg (1.5 mmol) of alcohol dl·4a in 3 mL of dry THF at -78°C under an argon atmosphere was added 0.48 mL (1.65 mmol) of a 3.4 M solution of n-butyllithium in hexane, and, after 3 minutes, 0.14 mL (1.65 mmol) of propanoyl chloride. The mixture was warmed and stirred at 0°C for 5 minutes, then cooled again to -78°C, and 3 mL (1.5 mmol) of a 0.5 M solution of LDA in dry THF at 0°C was rapidly added. After 3 minutes, 1.61 mL (1.8 mmol) of a 1.13 M solution of tert-butyldimethylchlorosilane in HMPA was added, cooling was discontinued, and the mixture stirred for one hour at room temperature. Completion of this experiment in the manner described for the isolation of dl·23a and dl·23b provided 155 mg (60%) of a colorless oil, a mixture of dl·26a and dl·26b. The ^{1}H-NMR spectrum of a solution of this mixture in carbon tetrachloride revealed two doublets of unequal intensity, assigned to the α-methyl groups of the diastereomeric products. The major doublet (δ 1.08, J=7 Hz), and the minor (δ 1.13, J=7 Hz) appeared in a ratio of (7:3). Chromatography of this mixture on acidic silica gel with 20% ether-petroleum ether

afforded a pure sample of each diastereomer. The minor isomer was eluted first: IR (CCl_4) 3600-2500 cm^{-1} (CO_2H), 1710 cm^{-1} (C=O); ^{1}H-NMR (CCl_4) δ 1.13 (d, 3H, J=7 Hz, α-CH_3), 1.34 (s, 3H, CCH_3), 1.76 (d, 3H, J=5 Hz, C=$CHCH_3$), 3.22 (s, 3H, OCH_3), 10.1 (s, 1H, CO_2H).

Anal. Calcd for $C_9H_{16}O_3$: C, 62.76; H, 9.36. Found: C, 62.73; H, 9.35.

Continued elution provided the more polar isomer: IR (CCl_4) 3500-2600 cm^{-1} (CO_2H); 1710 cm^{-1} (C=O); ^{1}H-NMR (CCl_4) δ 1.08 (d, 3H, J=7 Hz, α-CH_3), 1.30 (s, 3H, CCH_3), 1.76 (d, 3H, J=5 Hz, C=$CHCH_3$), 3.21 (s, 3H, OCH_3), 10.4 (s, 1H, CO_2H).

Anal. Calcd for $C_9H_{12}O_3$: C, 62.76; H, 9.36. Found: C, 62.73; H, 9.35.

B. Deprotonation in 23% HMPA-THF. This experiment was performed exactly as in A, above, except 1.65 mmol of LDA was dissolved in 3.9 mL of a 23% (v./v.) solution of HMPA in THF and to this solution was added the solution of ester in THF described in A. Completion of this experiment as described above afforded a 4:1 mixture of the diastereomers described above, dl·?6a and dl·26b. The isomer having the lower field doublet (δ=1.13, α-CH_3) was the major product.

[(αR*,2R*) and (αS*,2R*)]-(±)-5,6-Dihydro-α,6,6-trimethyl-2H-pyran-2-acetic acid [(dl·27a) and (dl·27b)].

To a stirred solution of 1.19 mmol of LDA in 5.6 mL of dry THF under an argon atmosphere at -78°C was added 1.7 mL of dry HMPA. After 5 minutes, a solution of 200 mg (1.08 mmol) of ester dl-5b in 0.4 mL of dry THF was added dropwise over a 2 minute period, and after 3 additional minutes, 0.40 mL (1.19 mmol) of a 2.44 M solution of tert-butyldimethyl-chlorosilane in hexane was added. This mixture was stirred for 30 minutes at 0°C, and then diluted with 100 mL of ice-cold n-pentane and washed with 3x33 mL of ice-cold water. The organic phase was dried ($MgSO_4$) and pentane was removed at 15-20°C under reduced pressure. Spectral analysis of this residue indicated the product at hand was the silyl ketene acetal 5d: IR (CCl_4) 1675 cm^{-1} (C=C, acetal), 1640 cm^{-1} (C=C, enol ether); ^{1}H-NMR (CCl_4) δ 0.24 [s, 6H, $Si(CH_3)_2$], 6.42 (d, 1H, J=6 Hz, O-CH=CH). The rearrangement of this acetal at 35°C to afford the tert-butyldimethyl-silyl ester was evidenced by a gradual, and synchronous disappearance of the singlet at δ 0.24 and the doublet at δ 6.42 and the simultaneous appearance and growth of a singlet at δ 0.33 (attributed to the $Si(CH_3)_2$ of the silyl ester) and a multiplet at δ≈5.8. The half-life at 35°C was 100±10 minutes. When no acetal remained the silyl ester was hydrolysed in 10 mL of THF with 1.8 mL of 10% aqueous hydrochloric acid. The hydrolysis mixture was diluted with 100 mL of ether, washed with 4x30 mL of water, and extracted with 4x8 mL of 1N aqueous NaOH. The combined

extracts were washed with 4x10 mL of n-pentane and acidified (pH ≈2) with 10% aqueous hydrochloric acid. The product was isolated by dichloromethane extraction (Na_2SO_4).[33] Drying of the residue for several hours under vacuum afforded 158 mg (79%) of a mixture of dl·27a and dl·27b. The ^{1}H-NMR spectrum of a solution of this mixture in carbon tetrachloride revealed two doublets of unequal intensity. The major doublet (δ 1.16, J=7 Hz) and the minor (δ 1.12, J=7 Hz) appeared in a ratio of (11:1) and represent the two diastereomeric products. The analytical sample was prepared by distillation [kugelrohr, 100°C (0.7 mmHg)]: IR (CCl_4) 3500-2400 cm^{-1} (CO_2H), 1710 cm^{-1} (C=O), 1200 cm^{-1} (C-O); ^{1}H-NMR (CCl_4) δ 1.12, 1.16 (overlapping doublets, 11:1 ratio, 3H, J=7 Hz, α-CH_3), 1.20 (s, 6H, 2xCH_3), 4.2-4.45 (m, 1H, β-CH) 5.5-5.9 (m, 2H, CH=CH).

Anal. Calcd for $C_{10}H_{16}O_3$: C, 65.19; H, 8.75. Found: C, 65.16; H, 8.78.

[2S-[2α(S* and R*),5β,6α]]-5,6-Dihydro-α,6-dimethyl-5-methoxy-2H-pyran-2-acetic acid [(28a) and (28b)]. A. From Ester 6b by Deprotonation in THF. By the procedure described for the preparation of 27a,b, 100 mg (0.50 mmol) of ester 6b in 0.5 mL of dry THF, added to 0.55 mmol of LDA dissolved in 1.5 mL of dry THF, and treated with 0.38 mL of a 1.45 M solution of tert-butyldimethylchlorosilane in HMPA, provided the silyl ketene acetal 6d: ^{1}H-NMR (CCl_4) δ 0.19

(s, 6H, 2xSiCH_3), 1.45 (d, 3H, J=6 Hz, C=CH$\underset{\sim}{CH_3}$), 3.50 (s, 3H, OCH_3). Rearrangement at 35°C ($\tau_{1/2}$=30±5 minutes) afforded the silyl ester: ^{1}H-NMR (CCl_4) δ 0.25 (s, 6H, 2 x SiCH_3), 3.33 (s, 3H, OCH_3). After hydrolysis there was obtained 73 mg (73%) of a mixture of the diastereomeric acids, 28a and 28b. The ^{1}H-NMR spectrum of a solution of this mixture in carbon tetrachloride revealed two overlapping doublets. The major doublet (δ 1.07, J=7 Hz) and the minor (δ 1.12, J=7 Hz) appeared in a ratio of (4:1). Distillation [kugelrohr, 120°C (0.5 mmHg)] of this mixture afforded the analytical sample: IR ($HCCl_3$) 3600-2500 cm^{-1} (CO_2H), 1700 cm^{-1} (C=O); ^{1}H-NMR (CCl_4 δ 1.07, 1.12 [two doublets, (4:1) ratio, 3H, J=7 Hz, α-CH_3], 1.21 (d, 3H, J=6 Hz, CH$\underset{\sim}{CH_3}$), 3.32 (s, 3H, OCH_3), 5.5-6.0 (m, 2H, CH=CH).

Anal. Calcd for $C_{10}H_{12}O_4$: C, 59.98; H, 8.05. Found: C, 59.99; H, 8.03.

B. From Ester 6b by Deprotonation in 23% HMPA-THF. A solution of 0.55 mmol of LDA in 1.7 mL of 23% (by volume) HMPA-THF, with 100 mg (0.5 mmol) of ester 6b dissolved in 0.2 mL of dry THF, and 0.24 mL (0.55 mmol) of a 2.3 M solution of tert-butyldimethylchlorosilane in dry hexane provided the ketene acetal 6d. Rearrangement at 35° ($\tau_{1/2}$= 30±5 minutes) afforded the silyl ester, from which there was obtained 71 mg (71%) of a mixture of the diastereomeric acids 28a and 28b. Analysis of this mixture by NMR spectroscopy as described in A indicated that the ratio of

diastereomers was (1:4), and that the isomer having the lower field doublet (δ 1.12) was the major product. Distillation [kugelrohr, 120° (0.5 mmHg)] afforded an analytical sample, spectrally identical (except as noted) with the product obtained in A.

C. From Glycal 6a by Deprotonation in THF. To a stirred solution of 51 mg (0.35 mmol) of glycal 6a in 0.7 mL of dry THF under an atmosphere of argon at -78°C was added 0.16 mL (0.38 mmol) of a 3.45 M solution of n-butyllithium in hexane followed by 34 μL (0.38 mmol) of propanoyl chloride. After 30 minutes at -78°C and 10 minutes at 0°C, the entire reaction mixture was added to a cold (-78°C), stirred, argon protected solution of 0.77 mmol of LDA in 2.2 mL of dry THF. After 5 minutes, this mixture was treated with 0.53 mL (0.77 mmol) of a solution of tert-butyldimethylchlorosilane in dry HMPA. Completion of this experiment exactly as described in A (except the rearrangement was completed by heating a solution of the silyl ketene acetal in carbon tetrachloride at 75°C for 40 minutes) afforded 56 mg (79%) of a product identical (NMR, IR) to the product obtained in A.

[2R-[2α(S*andR*),5β,6β]]-5,6-Dihydro-α,6-dimethyl-5-methoxy-2H-pyran-2-acetic acid [(29a) and (29b)]. A. From Glycal 7a by Deprotonation in THF. By the procedure described for the preparation of 28a,b from glycal 6a, a

solution of 62 mg (0.43 mmol) of glycal 7a in 0.7 mL of dry THF with 0.19 mL (0.46 mmol) of a 2.45 M solution of n-butyllithium in hexane, treated with 41 μL (0.47 mmol) of propanoyl chloride, added to 0.95 mmol of LDA dissolved in 2.7 mL of dry THF and treated with 0.65 mL (0.96 mmol) of a 1.45 M solution of tert-butyldimethylchlorosilane in dry HMPA provided 59 mg (69%) of a mixture of the acids 29a and 29b. Analysis of this mixture (^{1}H-NMR), as described in previous examples, indicated the two products were present in a ratio of (4:1). Distillation [kugelrohr, 120°C (0.5 mmHg)] of this mixture provided the analytical sample: IR ($CHCl_3$) 3600-2400 cm^{-1} (CO_2H), 1705 cm^{-1} (C=O); ^{1}H-NMR (CCl_4) δ 1.14, 1.18 (two doublets, 4:1 ratio, 3H, J=7 Hz, α-CH_3), 1.14 (d, 3H, J=6 Hz, $CHCH_3$), 3.30 (s, 3H, OCH_3), 5.81 (s, 2H, CH=CH).

Anal. Calcd for $C_{10}H_{16}O_4$: C, 59.98; H, 8.05. Found: C, 59.96; H, 8.05.

B. From Glycal 7a by Deprotonation in 23% HMPA-THF. By the procedure described in A, 62 mg (0.43 mmol) of glycal 7a in 0.8 mL of dry THF with 0.19 mL (0.46 mmol) of a 2.45 M solution of n-butyllithium in hexane, treated with 41 μL (0.47 mmol) of propanoyl chloride, added to 0.95 mmol of LDA dissolved in 3.0 mL of 23% (by volume) HMPA-THF and treated with a solution of 143 mg (0.95 mmol) of tert-butyldimethylchlorosilane in 0.7 mL of dry hexane afforded 64 mg (74%) of a mixture of acids 29a and 29b. The ^{1}H-NMR

spectrum of a solution of this mixture in carbon tetrachloride revealed two doublets (major, δ1.18; minor, δ1.14) in a ratio of (4:1). Except for the inversion of relative magnitude for these doublets, the product was the same as described in A.

[2R-[2α(S*andR*),5β]]-2,5-Dihydro-α-ethyl-5-methoxymethylenoxymethyl-furan-2-acetic acid [(30a) and (30b)]. A. From Glycal 8a by Deprotonation in THF. To a stirred solution of 138 mg (0.70 mmol 8a) of the 6:1 mixture of 8a and 17b (described above) in 2.8 mL of dry THF at -78°C under argon was added 0.35 mL (0.84 mmol) of a 2.41 M solution of n-butyllithium in hexane, followed after 5 minutes by 87 μL (0.84 mmol) of n-butanoyl chloride. After 5 minutes at 0°C the entire reaction mixture was taken up in an argon flushed syringe and added, dropwise, to a stirred solution of 0.94 mmol of LDA in 3 mL of dry THF at -78°C under argon. After 10 minutes, the reaction mixture was treated with 0.24 mL (1.4 mmol TMSCl) of the supernatant centrifugate from a mixture of 0.36 mL of trimethylchlorosilane and 0.12 mL of dry triethylamine. After 10 minutes, at -78°C and one hour at room temperature, the reaction mixture was diluted with 10 mL of 0.5 N aqueous NaOH and washed with 2 mL of ether. The organic phase was extracted with three 10 mL portions of 0.5 N NaOH, and the combined aqueous extracts were washed with 20 mL of ether, and

acidified (pH ≈2). Ether extraction ($MgSO_4$)[33] afforded 118 mg (73%) of a mixture of the diastereomeric acids, 30a and 30b. 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: R_f=0.29 (40% ether-petroleum ether); IR ($CHCl_3$) 1720 cm^{-1} (C=O), 740 cm^{-1} (C=C); ^{1}H-NMR ($CDCl_3$) δ 6.90 (t, 3H, J=6 Hz, CH_3CH_2, 1.52 (m, 2H, CH_3CH_2), 3.33 (s, 3H, OCH_3), 3.53 (d, 2H, J=5 Hz, CCH_2O), 3.72 (s, 3H, OCH_3), 4.62 (s, 2H, OCH_2O), 5.92 (m, 2H, CH=CH).

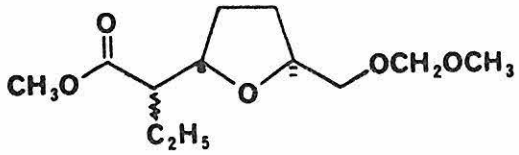
Anal. Calcd for $C_{12}H_{20}O_5$: C, 59.00; H, 8.25. Found: C, 58.92; H, 8.21.

A separate portion of the mixture of isomeric acids 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 esters 36a and 36b in a ratio of 4:1, 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. Fraction I (minor isomer): R_f=0.40 (50% ether-petroleum ether); IR ($CHCl_3$) 1720 cm^{-1} (C=O); ^{1}H-NMR ($CDCl_3$) δ 0.88 (t, 3H, J=7 Hz, CH_3CH_2), 3.33 (s, 3H, OCH_3), 3.46 (d, 2H, J=6 Hz, CCH_2O), 3.65 (s, 3H, OCH_3), 4.60 (s, 2H, OCH_2O); $[\alpha]_D^{25}$=-17° (c 0.90, $CHCl_3$).

Anal. Calcd for $C_{12}H_{22}O_5$: C, 58.52; H, 9.00. Found: C, 58.47; H, 8.97.

Fraction II (major isomer): R_f=0.25 (50% ether-petroleum ether); IR ($CHCl_3$) 1720 cm^{-1} (C=O); ^{1}H-NMR ($CDCl_3$) δ 0.89 (t, 3H, J=7 Hz, CH_3CH_2), 3.33 (s, 3H, OCH_3) 3.46 (d, 2H, J=6 Hz, CCH_2O), 3.69 (s, 3H, OCH_3), 4.60 (s, 2H, OCH_2O); $[\alpha]_D^{27}$=+3.4° (c 1.15, $CHCl_3$).

Anal. Calcd for $C_{12}H_{22}O_5$: C, 58.52; H, 9.00. Found: C, 58.58; H, 9.05.



36a,b

B. From Glycal 8b by Deprotonation in 23% 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 THF at -78°C, there was obtained 97 mg (60%) of a mixture of the isomeric acids 30a and 30b. The ratio of diastereomers (determined, as described above, by VPC analysis of the hydrogenated methyl esters) was found to be 1:4, with the major isomer having the higher R_f [R_f=0.40 (50% ether-petroleum ether)].

[2S-[2α(S*andR*),5α,5αR]-2,5-Dihydro-5-(2,2-dimethyl-1,3-dioxolan-4-yl)-α-methyl-furan-2-acetic acid [(31a) and (31b)]. A. From Glycal 9a by Deprotonation in THF. By the procedure described for the preparation of acids 30a,b from glycal 8a, 194 mg (1.04 mmol) of glycal 9a, with 0.45 mL (1.09 mmol) of n-butyllithium and 95 μL (1.09 mmol) of propanoyl chloride in 3 mL of dry THF, added to 2.18 mmol of LDA in 5 mL of dry THF afforded, following work-up and distillation [kugelrohr, 110-140°C (0.01 mmHg)], 132 mg (52%) of a mixture of diastereomeric acids, 31a and 31b. The ^{1}H-NMR spectrum of a solution of this mixture in carbon tetrachloride revealed two doublets of unequal intensity, attributed to the α-methyl groups of the diastereomeric acids. The major doublet (δ 1.18, J=7 Hz) and the minor (δ 1.13, J=7 Hz) appeared in a ratio of (4:1): IR ($CDCl_3$) 3600-2400 cm^{-1} (CO_2H), 1705 cm^{-1} (C=O); ^{1}H-NMR ($CDCl_3$) δ 1.13, 1.18 (overlapping doublets, 4:1 ratio, 3H, J=7 Hz, α-CH_3), 1.33 (s, 3H, CCH_3), 1.40 (s, 3H, CCH_3), 5.8-6.1 (m, 2H, CH=CH). A portion of this material was hydrogenated at 50 psi over 5% rhodium on carbon in THF for 5 hours. After removal of solvent under reduced pressure, chromatography of the residue on silica gel with 1% acetic acid in 50% ether-n-hexane afforded a saturated derivative of a single isomer of the title compound in 56% yield. For the saturated acid: IR ($CDCl_3$) 1705 cm^{-1} (C=O); ^{1}H-NMR ($CDCl_3$) δ 1.22 (d, 3H, J=7 Hz, α-CH_3), 1.35 (s, 3H CCH_3), 1.41

(s, 3H, CCH_3), 9.8 (s, 1H, OH); $[\alpha]_D^{23}$=+33° (c 1.2, $CHCl_3$).

Anal. Calcd for $C_{12}H_{20}O_5$: C, 59.00; H, 8.25. Found: C, 59.10; H, 8.24.

B. From Glycal 9a by Deprotonation in 23% HMPA-THF. By the procedure described for the preparation of acids 30a and 30b (part B), 342 mg (1.84 mmol) of glycal 9a with 0.79 mL (2.05 mmol) of 2.45 M n-butyllithium in hexane and 0.18 mL of propanoyl chloride in 3.5 mL of dry THF, added to 3.86 mmol of LDA in 13 mL of 23% HMPA-THF and treated with 5.79 mmol of trimethylchlorosilane, afforded, after distillation [kugelrohr, 110-135°C (0.08 mmHg)], 242 mg (54%) of a mixture of diastereomeric acids, 31a and 31b. The ^{1}H-NMR spectrum of a solution of this mixture in carbon tetrachloride revealed two doublets, as described in part A, and the ratio of isomers was 1:1.

[2R,5α,6β]-Methyl 5,6-dihydro-5-hydroxy-6-hydroxymethyl-2H-pyran-2-acetate, benzylidene acetal (33). To a stirred suspension of 80 mg (2.0 mmol) of potassium hydride (oil free) in 7 mL of dry THF at 23°C under argon was added 0.48 mL (2.2 mmol) of dry hexamethyldisilazane. After one hour at room temperature the resulting solution was cooled to -78°C and treated dropwise with a solution of 276 mg (1.0 mmol) of acetate 10 in 1 mL of dry THF. After 10 minutes at -78°C this mixture was treated with 1.38 mL (2.0 mmol) of 1.45 M tert-butylidimethylchlorosilane in

HMPA. Cooling was then discontinued and after standing 30 minutes at room temperature the solution afforded, following n-pentane extraction,[33] 532 mg of a colorless oil, the ketene acetal, xii: ^{1}H-NMR (CCl_4) δ 0.17 (s, 3H, $SiCH_3$), 0.23 (s, 3H, $SiCH_3$), 3.15 (d, 1H, J=2 Hz, C=C$\underset{\sim}{H}$,H), 3.32 (d, 1H, J=2Hz, C=CH,$\underset{\sim}{H}$), 6.43 (d, 1H, J=6 Hz, O-CH=C). This oil was taken up in 20 mL of n-pentane, dried ($MgSO_4$) and filtered through a fine frit. The filtrate was concentrated and the residue was dissolved in 7 mL of dry toluene and heated at 100°C for 22 hours. After cooling, toluene was removed under reduced pressure and the residue was dissolved in 3 mL of dry HMPA and treated with 282 mg (3 mmol) of $KF \cdot 2H_2O$ and 300 mg (3 mmol) of $KHCO_3$. The resulting mixture was stirred for 12 hours, and then 0.25 mL (4.0 mmol) of dry MeI was added. After 2 hours, n-pentane extraction ($MgSO_4$)[33] afforded 265 mg (91%) of a crystalline solid, crude ester $\underset{\sim}{33}$. Recrystallization from hexane, followed by chromatography of the mother liquor on silica gel with 10% ethyl acetate-benzene provided 32 mg of a 1:1 mixture of starting material and product, and 151 mg of ester $\underset{\sim}{33}$, mp 95-95.5°C. The yield based on unrecovered starting material is therefore 61%. The analytical sample was obtained by recrystallization from n-hexane: mp 95-95.5°C; R_f=0.30 (10% ethyl acetate-benzene); IR ($CHCl_3$) 1730 cm^{-1} (C=O), 690 cm^{-1} (C=C); ^{1}H-NMR ($CDCl_3$) δ 2.50 (dd, 1H, J=16 Hz, J′=6 Hz, α-CH_2), 2.74 (dd, 1H, J=16 Hz,

J´=9 Hz, α-CH_2), 3.71 (s, 3H, OCH_3), 5.55 (s, 1H, ArCH), 6.04 (bd, 1H, J=10 Hz, C=CH), 7.2-7.6 (m, 5H, ArH); $[\alpha]_D^{23}$= +67° (c 1.2, $CHCl_3$).

Anal. Calcd for $C_{16}H_{18}O_5$: C, 66.19; H, 6.25. Found: C, 66.23; H, 6.28.

Methyl[(2S)and(2R),2´S,5R,6S]-2-(5,6-dihydro-5-methoxy-6-methyl-2´H-pyran-2´-yl)-tetrahydro-2-furancarboxylate [(34a) and (34b)]. A. From Ester 6c by Deprotonation in THF. To a stirred solution of 2.7 mmol of LDA in 3 mL of dry THF at -78°C under an argon atmosphere was added a solution of 300 mg (1.24 mmol) of ester 6c in 1 mL of dry THF and, after 6 minutes, 0.62 mL (3.7 mmol TMSCl) of the supernatant centrifugate from a mixture of 0.94 mL of trimethylchlorosilane (TMSCl) with 0.30 mL of dry triethylamine. After 20 minutes at 0°C and 2.5 hours at room temperature the reaction mixture was diluted with 30 mL of ice-cold 0.5 N aqueous NaOH and washed with four 20 mL portions of ether. The aqueous solution was acidified (pH ≈2) and, after the addition of 18 g of sodium chloride, dichloromethane extraction ($MgSO_4$)[33] provided 247 mg (82%) of a mixture of diastereomeric carboxylic acids. This mixture was methylated with diazomethane in ether and chromatography of the product on 28 g of silica gel with 50% ether-petroleum ether afforded pure samples of each diastereomeric methyl ester, 34a and 34b. Fraction I: 25 mg;

R_f=0.30 (50% ether-petroleum ether); IR ($HCCl_3$) 1735 cm^{-1} (C=O); ^{1}H-NMR (CCl_4) δ 1.24 (d, 3H, J=6 Hz, $CHCH_3$), 3.33 (s, 3H, OCH_3), 3.69 (s, 3H, OCH_3), 4.43 (bs, 1H, H-2´), 5.6-6.0 (m, 2H, CH=CH); $[\alpha]_D^{24}$=-110° (c 0.84, $HCCl_3$).

Anal. Calcd for $C_{13}H_{20}O_5$: C, 60.92; H, 7.87. Found: C, 60.76; H, 7.89.

Fraction II: 150 mg, R_f=0.28 (50% ether-petroleum ether); IR ($HCCl_3$) 1735 cm^{-1} (C=O); ^{1}H-NMR (CCl_4) δ 1.24 (d, 3H, J=6 Hz, $CHCH_3$), 3.33 (s, 3H, OCH_3), 3.64 (s, 3H, OCH_3), 4.21 (bs, 1H, H-2´), 5.6-6.0 (m, 2H, CH=CH); $[\alpha]_D^{24}$=-134° (c 0.96, $HCCl_3$).

Anal. Calcd for $C_{13}H_{20}O_5$: C, 60.92; H, 7.87. Found: C, 60.97; H, 7.77.

The overall yield, including 22 mg of mixed fractions, was 62%. Comparison of the above spectral data with ^{1}H-NMR data obtained for the unfractionated acids and esters indicated the two isomers were produced in a ratio of (5:1).

B. From Ester 6c by Deprotonation in 23% HMPA-THF. In the manner described in A, a solution of 0.77 mmol of LDA in 2.0 mL of 23% (by volume) HMPA-THF with 85 mg (0.35 mmol) of ester 6c in 0.5 mL of dry THF and 1.05 mmol of TMSCl (treated with triethylamine as in A) provided, after rearrangement and hydrolysis, 48 mg (56%) of a colorless oil, which contained (by ^{1}H-NMR) a mixture of the two diastereomeric carboxylic acids in a ratio of (1:1).

C. From Ester 6c by Deprotonation in THF with Lithium Hexamethyldisilazide. By the procedure described in B, 0.77 mmol of hexamethyldisilazide in 2 mL of dry THF with 85 mg of ester 6c provided 57 mg (67%) of a clear, colorless oil, which contained (by ^{1}H-NMR analysis) a mixture of the two diastereomeric acids in a ratio of (7:1). The predominant isomer in this case was the same as the major isomer obtained in part A.

D. From Glycal 6a by Deprotonation in THF. To a stirred solution of 100 mg (0.69 mmol) of glycal 6a in 1.4 mL of dry THF at -78°C under an argon atmosphere was added 0.45 mL (0.73 mmol) of a 1.64 M solution of n-butyllithium in hexane, followed, after 5 minutes, by 85 µL (0.76 mmol) of (±)-tetrahydro-2-furancarbonyl chloride. This mixture was stirred for 10 minutes at 0°C and then taken up in a dry syringe and added dropwise to a solution of 1.52 mmol of LDA in 4 mL of dry THF. After 12 minutes, 4.56 mmol of TMSCl (pre-treated with dry triethylamine) was added. After 20 minutes at -78°C and 2.5 hours at room temperature, hydrolysis of this reaction mixture and isolation of the product as described in A provided 133 mg (80%) of a mixture of the diastereomeric carboxylic acids. The isomer ratio, as determined by ^{1}H-NMR, was (5:1). The mixture was identical to the mixture of acids obtained in A.

Methyl[(2S)and(2R),2αR,5S,6S]·2-(5,6-Dihydro-5-methoxy-6-methyl-2′H-pyran-2′-yl)-tetrahydro-2-furancarboxylate [(35a) and (35b)]. A. From Glycal 7a by Deprotonation in THF. A solution of 110 mg (0.76 mmol) of glycal 7a in 1.5 mL of dry THF at -78°C under an argon atmosphere was treated with 0.49 mL (0.80 mmol) of a 1.64 M solution of n-butyllithium in hexane and, after 5 minutes, 94 μL (0.83 mmol) of (±)-tetrahydro-2-furancarbonyl chloride. The resulting mixture, after 10 minutes at 0°C, was added to a solution of 1.67 mmol of LDA in 4.3 mL of dry THF at -78°C under an argon atmosphere, and, after 10 minutes at -78°C, the reaction was quenched with 2.5 mmol of TMSCl (pre-treated with dry triethylamine). After 2.5 hours at room temperature, treatment of this reaction mixture as described above (A) for the preparation of 34a and 34b afforded 135 mg (75%) of a mixture of diastereomeric acids, 35a and 35b. This mixture was methylated with diazomethane in ether and chromatography of the products on silica gel with 50% ether-petroleum ether afforded pure samples of each of the diastereomeric methyl esters.

Fraction I: 25 mg; R_f=0.20 (50% ether-petroleum ether); IR (CCl_4) 1740 cm^{-1} (C=O); ^{1}H-NMR (CCl_4) δ 1.10 (d, 3H, J=6 Hz, $CHCH_3$), 3.26 (s, 3H, OCH_3), 3.65 (s, 3H, OCH_3), 4.35-4.43 (m, 1H, 2′-H), 5.6-6.0 (m, 2H, HC=CH); $[\alpha]_D^{22}$=+188° (c 0.9, $HCCl_3$).

Anal. Calcd for $C_{12}H_{20}O_5$: C, 60.90; H, 7.87. Found: C, 60.87; H, 7.82.

Fraction II: 101 mg; R_f=0.15 (50% ether-petroleum ether); IR (CCl_4) 1760, 1740 cm^{-1} (C=O); ^{1}H-NMR (CCl_4) δ 1.06 (d, 3H, J=6 Hz, $CHCH_3$), 3.27 (s, 3H, OCH_3), 3.64 (s, 3H, OCH_3), 4.16-4.29 (m, 1H, 2′-H), 5.79-5.89 (m, 2H, CH=CH); $[\alpha]_D^{22}$=+199° (c 1.1, $HCCl_3$).

Anal. Calcd for $C_{12}H_{20}O_5$: C, 60.90; H, 7.87. Found: C, 61.01; H, 7.83.

The combined yield of the pure methyl esters was 65%. Comparison of the above spectral data with ^{1}H-NMR data obtained for the unfractionated acids and esters indicated the two isomers were produced in a ratio of (5:1).

B. From Glycal 7a by Deprotonation in 23% HMPA-THF. By the procedure described in A, 65 mg (0.45 mmol) of glycal 7a with 0.20 mL (0.47 mmol) of 2.38 M n-butyllithium in hexane and 55 μL (0.49 mmol) of (±)-tetrahydro-2-furancarbonyl chloride with 0.99 mmol of LDA in 2.6 mL of 23% (by volume) HMPA-THF and 1.45 mmol of TMSCl (pre-treated with dry triethylamine) afforded 75 mg (67%) of a mixture of the acids 35a and 35b, and 69 mg (60%) of the purified methyl esters. The two isomers, which were identical (NMR, IR, TLC) with the products obtained in A, were produced in approximately equimolar quantities.

References and Notes

(1) (a) Grateful acknowledgment is made for the support of this investigation through Public Health Service Research Grant No. HL 21367-01 from the National Heart and Lung Institute.

(b) The preparation of glycal 8a and the acids 30a,b from D-ribonic acid γ-lactone was performed by Suvit Thaisrivongs. The glycal 9a, and the acids 31a,b were prepared by Noel Vanier.

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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 or for IR spectra, 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. Acidic silica gel refers to Silicar CC-4 Special "for column chromatography", sold by Mallinckrodt Chemical Works, St. Louis, MO.

"Dry" solvents were distilled shortly before use from an appropriate drying agent. Ether, tetrahydrofuran (THF), and dimethoxyethane were distilled under dry argon from sodium metal in the presence of benzophenone. Benzene and toluene were distilled from calcium hydride. Hexane and dichloromethane were 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, hexamethyldisilazane, and dimethyl hydrazine 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 and n-propanoyl chloride were 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.

Mass spectral analyses were performed by Dr. Kai Feng, UCLA, Los Angeles, CA. Elemental combustion analyses were performed by Spang Microanalytical Laboratory, Eagle Harbor, MI.

(33) In cases where reaction intermediates or products were isolated "by solvent extraction (Na_2SO_4)", the procedure followed was to dilute the reaction mixture with the indicated solvent or to extract the aqueous solution with several portions of the indicated solvent; then the combined organic extracts were washed first with several portions of water, then with saturated sodium chloride, and dried over anhydrous sodium sulfate. Drying over anhydrous magnesium sulfate ($MgSO_4$) or anhydrous potassium carbonate (K_2CO_3) is indicated by the appropriate parenthetical substitution. After drying, the solution was filtered and the solvent was evaporated from the filtrate under reduced pressure (water aspirator) using a rotary evaporator. The use of the terms "base wash" or "acid wash" indicates washing of the organic solution with saturated aqueous sodium bicarbonate solution or with 10% aqueous hydrochloric acid, respectively, prior to the aforementioned washing with water.

(34) Reaction mixtures obtained in reductions with lithium aluminum hydride were hydrolysed by the method of Fieser and Fieser: L. F. Fieser and M. Fieser, "Reagents for Organic Synthesis", Wiley-Interscience, New York, N. Y., 1967, p. 584.

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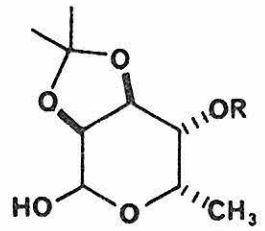
Part II

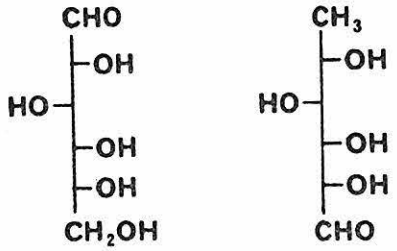
A New Synthesis of 6-Deoxy-L-Gulose[1]

In connection with an ongoing project in this laboratory, a synthetic approach to 4-O-(alkyl)-6-deoxy-2,3-O-(1-methylethylidene)-L-gulopyranose derivatives (I) was required. The first preparation of 6-deoxy-L-gulose was accomplished by Müller and Reichstein and began with



I

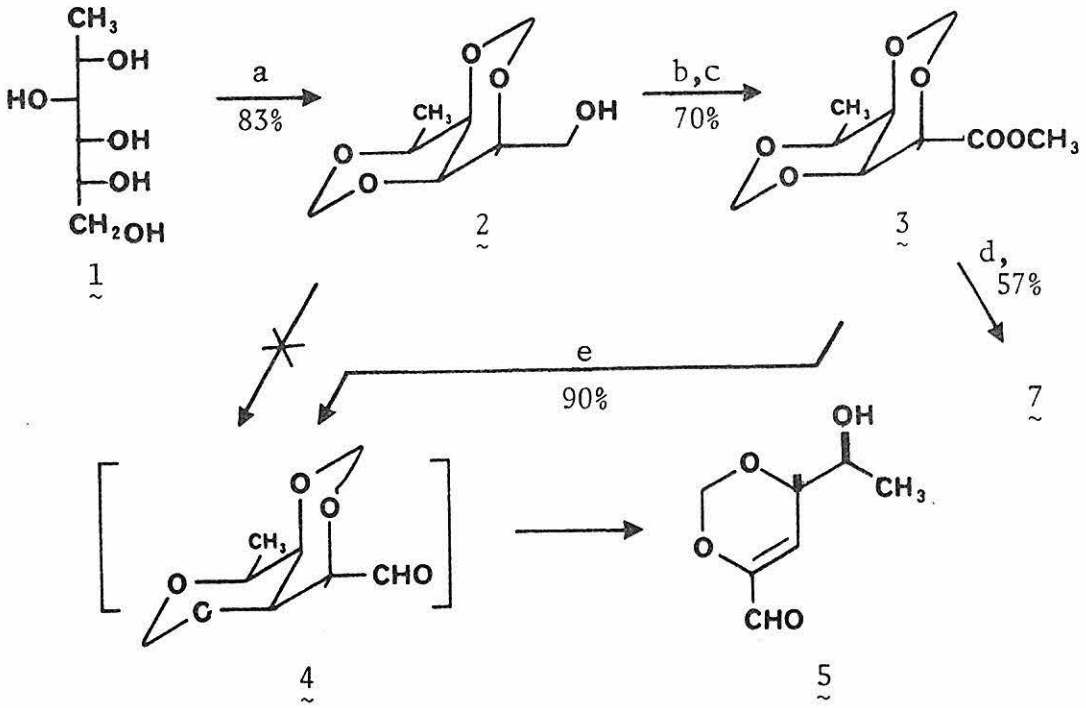
L-xylose.[2] The stereochemical correspondence between 6-deoxy-L-gulose and D-glucose (Figure 1) suggested that the abundant and inexpensive D-glucose could serve as a practical starting material for the preparation of derivatives related to I. The following experiments were undertaken to evaluate this possibility.



A B

Figure 1. Fisher-type formulae illustrating the relationship between D-glucose (A) and 6-deoxy-L-gulose (B).

Chart 1 [a]



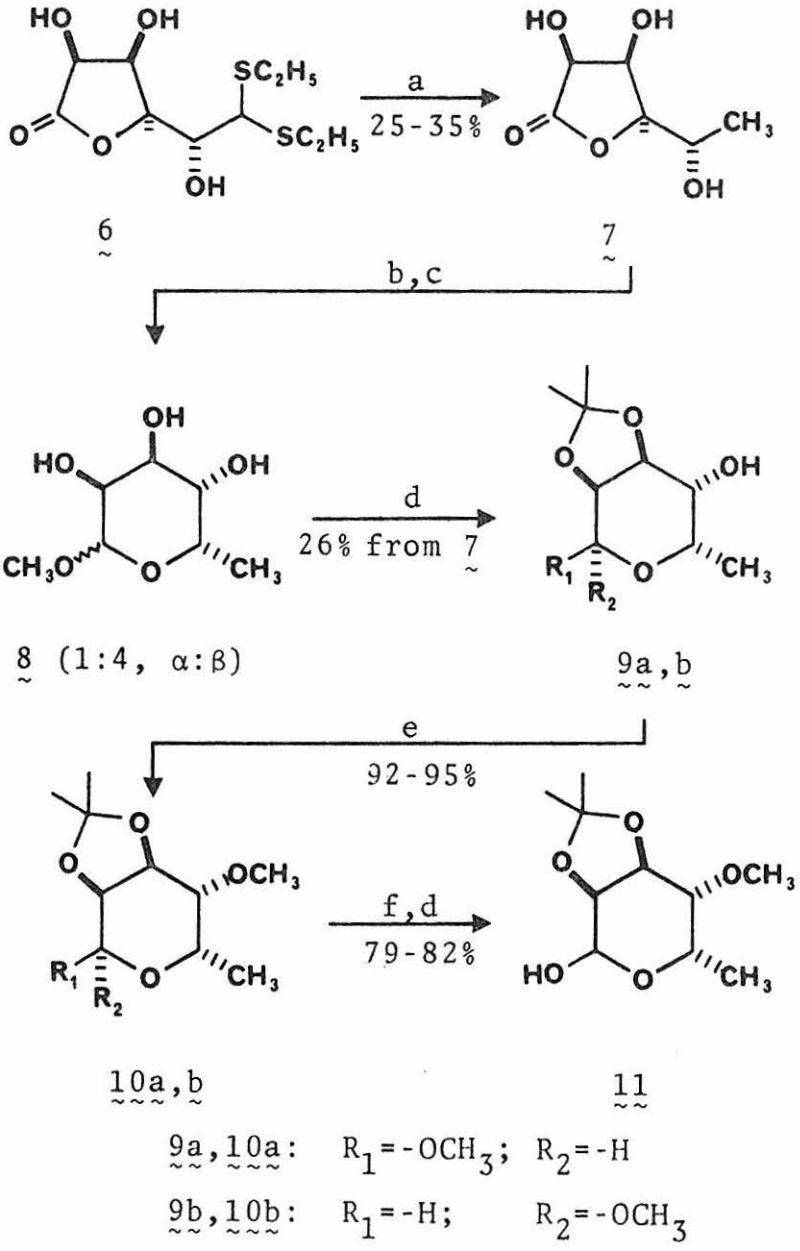
[a] a, H_2CO-H_2O, HCl; b, CrO_3-AcOH; c, CH_2N_2, Et_2O; d, BCl_3, CH_2Cl_2; e, DIBAL, OH^-.

The first approach (Chart 1) began with 1-deoxy-D-glucitol (1)[2] which was prepared in 51% from D-glucose via reductive desulfurization[3] of the diethylmercaptal.[4] Treatment of this pentitol with aqueous formaldehyde and hydrogen chloride afforded the primary alcohol 2[5] in 83% yield, based on unrecovered starting material. The initial plan entailed conversion of this alcohol to aldehyde 4, and removal of the methylene protecting groups to provide the desired 6-deoxy-L-gulose. However, several attempts at partial oxidation, including Collin's reagent,[6] pyridinium chlorochromate,[7]

and several variations of the Pfitzner-Moffatt process,[8] failed to provide any of the desired aldehyde. Successful oxidation of alcohol 2 was effected, however, with chromium trioxide in acetic acid, and methylation of the product with diazomethane provided ester 3 in 70% overall yield. Deprotection of this ester with excess boron trichloride afforded the known[2] compound, 6-deoxy-L-gulonolactone (7). Reduction of ester 3 with di-iso-butylaluminum hydride (DIBAL) afforded, when excess hydride and the intermediate aluminates were hydrolysed with anhydrous methanol, a 3:1 mixture of aldehyde 4 and enone 5. The proportion of enone 5 (as determined by NMR) steadily increased following dissolution of a portion of this mixture in deuteriochloroform. By treatment of ester 3 with DIBAL and hydrolysis of the reaction mixture with aqueous sodium hydroxide, enone 5 was prepared in 90% yield. The instability of aldehyde 4 precluded the isolation of this key intermediate and caused the abandonment of this approach to 6-deoxy-L-gulose.

An alternative approach to the desired pyranoid derivatives (Chart 2) began with the thioacetal 6,[9] derived from D-glucurono-γ-lactone. Desulfurization of this thioacetal with Raney nickel catalyst afforded 6-deoxy-L-gulonolactone (7) in 25-35% yield, based on D-glucuronolactone. Reduction of lactone 7 with sodium amalgam and treatment of the crude product with methanol and hydrogen chloride afforded a mixture (1:4, α:β)[10] of the isomeric

Chart 2[a]



6 7

8 (1:4, α:β) 9a,b

10a,b 11

9a,10a: R_1=-OCH_3; R_2=-H

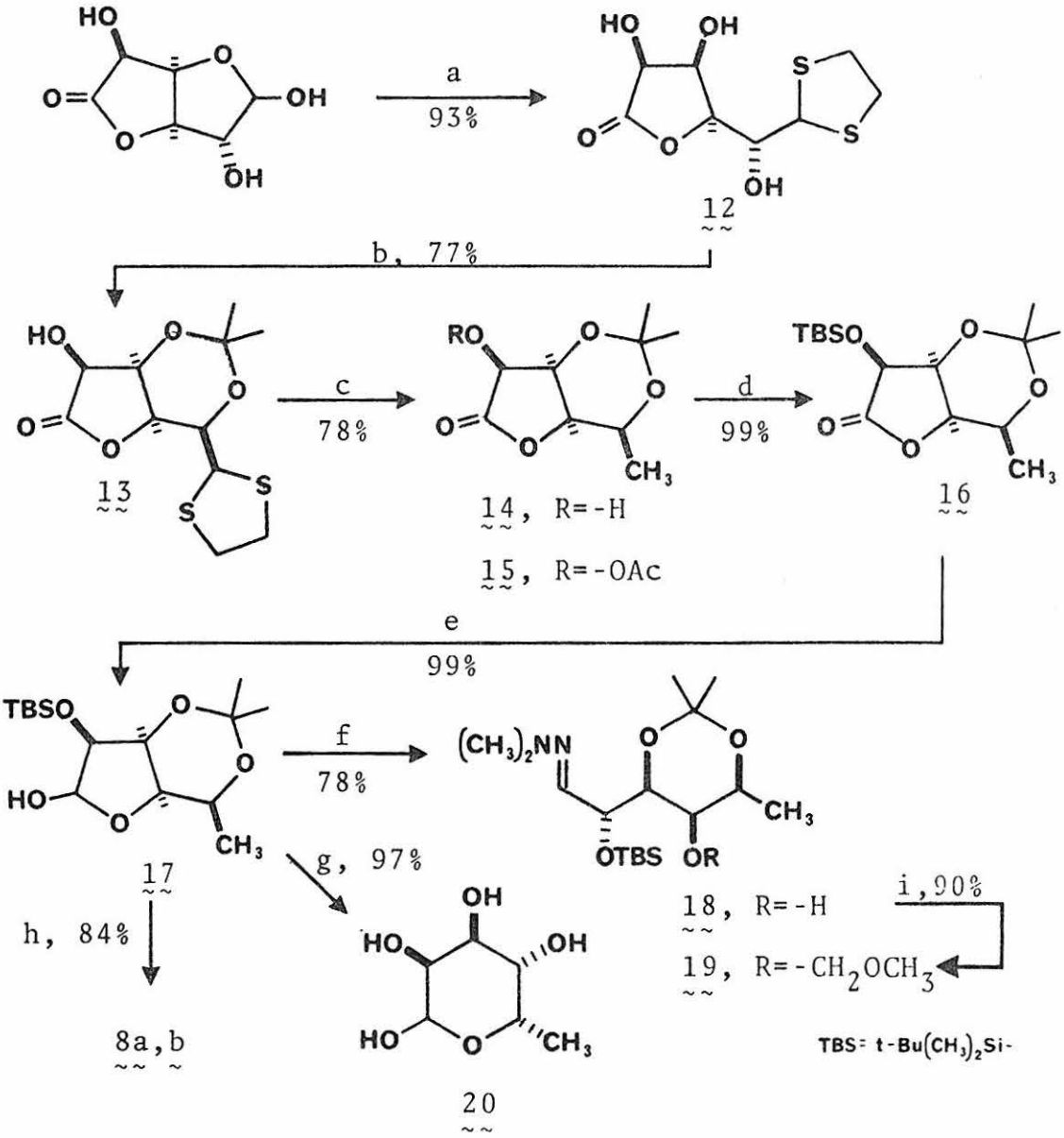
9b,10b: R_1=-H; R_2=-OCH_3

[a] a, Ni(R), 80% Et_2O-H_2O; b, Na(Hg), H_3O^+; c, CH_3OH,H^+; d, $CH_3C(OCH_3)_2CH_3$, H^+, acetone; e, KH, MeI, THF; f, H_3O^+.

methyl gulopyranosides 8. Treatment of this mixture with 2,2-dimethoxypropane and a trace of acid in acetone afforded the isopropylidene derivatives 9a and 9b. These isomers were separated by chromatography on silica gel and were isolated in 22% yield, overall, from lactone 7. Methylation of these anomeric alcohols afforded the gulopyranosides 10a and 10b. Lactol 11 was prepared in 79-82% yield from either 10a or 10b by hydrolysis with aqueous acid and treatment of the hydrolysate with dimethoxypropane and a trace of acid in acetone. The overall yield of this lactol from D-glucurono-γ-lactone is between four and six per cent.

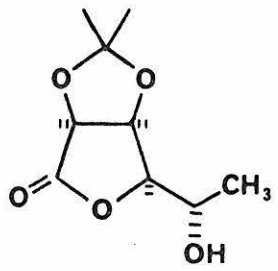
While providing the first samples of a derivative of the desired type, the scheme outlined above suffered from several technical deficiencies. Specifically, the amorphous nature of thioacetal 6 prevented convenient large-scale purification of this starting material. Also, the polarity of the triols 6 and 7 required the use of large volumes of polar solvent during the desulfurization, and, by adsorbence of these polar molecules onto the catalyst, adversely affected the material balance in this reaction. Furthermore, the reduction of aldonolactones with sodium amalgam requires careful control of pH and temperature and is further complicated by the difficulties encountered in separating water soluble products from aqueous solutions of inorganic salts.

Chart 3[a]

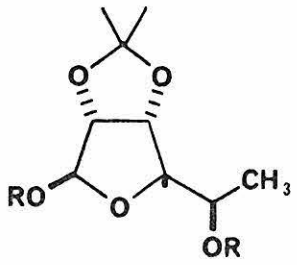


[a] a, $(CH_2SH)_2$, H_3O^+; b, $CH_3C(OCH_3)_2CH_3$, acetone, H^+; c, Ni(R), EtOH-THF; d, t-$C_4H_9(CH_3)_2SiCl$, DMF; e, DIBAL, THF; f, $CCl_4/P(NMe_2)_3$, $(CH_3)_2NNH_2$, THF; g, H_3O^+, 60°C; h, H^+, CH_3OH, 60°C; i, LDA, $ClCH_2OCH_3$.

To overcome these problems, a third approach (Chart 3) was developed. The acid catalysed reaction of ethanedithiol with D-glucurono-γ-lactone provided the crystalline thioacetal 12 in 93% yield. This acetal is a more tractable intermediate than is its amorphous analogue, 6. The acetal 12 afforded ketal 13 in 77% yield by treatment with acetone, dimethoxypropane, and sulfuric acid. Desulfurization of ketal 13 with Raney nickel catalyst generated, in 78% yield, the deoxylactone 14, which was silylated in 99% yield to provide silyl ether 16. Reduction of lactone 16 with DIBAL



i



ii, R=-H

iii, R=-OAc

afforded lactol 17 in 99% yield.

In principle, ketalization of triol 12 could have generated the 2,3-O-isopropylidene isomer of 13, which would provide, after desulfurization with Raney nickel, the isomeric hydroxy lactone i. That lactone 14 is indeed the 3,5-O-isopropylidene isomer could be shown by acetylation of the free hydroxyl group. The ^{1}H-NMR spectrum of the

resulting acetate, 15, was found to be similar to that of the hydroxy lactone 14, except that a doublet (1H, J=4 Hz) had shifted downfield 1.1 ppm. This is consistent with acetylation of the hydroxy group in the proposed structure for lactone 14, and inconsistent with the results expected in the event the alternative product, i, had been obtained. The quartet attributed to H-5 in lactone 14 (δ 4.10) moved downfield only 0.07 ppm upon acetylation of the hydroxyl group. This may be compared to the results reported for the hydroxy lactol ii, where acetylation to generate iii results in a 1.1 ppm downfield change in the H-5 quartet resonance.[11]

Several products of value in our investigations may be obtained from lactol 17. Treatment of lactol 17 with methanolic hydrogen chloride provided, in 80% yield, the mixture of methyl gulopyranosides (8a,b) described in Chart 2. The overall yield of these glycosides from 6-deoxy-D-glucurono-γ-lactone is 44% – a significant improvement over the 6-8% yield obtained in Chart 2. Alternatively, treatment of lactol 17 with trisdimethylaminophosphine and carbon tetrachloride, followed by dimethylhydrazine, provided hydrazone 18 in 78% yield. This product is of interest because it offers a method for introducing specific protecting groups on the C-4 hydroxyl group, as illustrated by the preparation of the 4-O-methoxymethyl ether, 19.

Finally, aqueous hydrolysis of lactol 17 provided 6-deoxy-L-gulose (20) as an amorphous solid, $[\alpha]_D^{22}$=+40.3° (c 1.60, H_2O) [lit.[2] $[\alpha]_D^{21}$=+40.8° (c 1.615, H_2O], which was further identified by conversion to the p-bromophenylhydrazone, mp 135-136°C (lit.[2] mp 136°C), $[\alpha]_D^{23}$=+14.5° (c 1.08, EtOH) [lit.[12] $[\alpha]_D^{25}$=+13±2° (c 1, EtOH)]. The overall yield of 6-deoxy-L-gulose from D-glucuronolactone is 52%.

In summary, methods have been developed for the synthesis of furanoid and pyranoid derivatives of 6-deoxy-L-gulose from D-glucurono-γ-lactone. In particular, the last approach is presented as a useful and high yield route to 6-deoxy-L-gulose, recently reported to be a constituent of antibiotic YA-56.[12]

Experimental Section.[13]

1-Deoxy-D-glucitol(6-deoxy-L-gulitol) (1). A solution of 15.0 g (54 mmol) of glucose diethylmercaptal[3] in 200 mL of 70% ethanol-water was added to a suspension of 120 g of Raney nickel catalyst in 900 mL of 70% ethanol-water at 45°C and this mixture was stirred for 7.5 hours. The catalyst was then removed by filtration through Celite, and washed with ten 100 mL portions of hot (~80°C) 80% ethanol-water. Concentration of the combined filtrates at 45-50°C under reduced pressure afforded a viscous oil which was taken up in 500 mL of absolute ethanol. Removal of ethanol from

this solution under reduced pressure, followed by drying of the residue under vacuum (0.4 mmHg, 18 hours), and recrystallization from ethanol, afforded 6.45 g (74%) of pentitol 1, a colorless, crystalline solid: mp 124-126°C; lit.[5] mp 127-128°C.

6-Deoxy-2,4:3,5-dimethylene-L-gulitol (2). A solution of 9 g (54 mmol) of pentitol 1 in 27 mL of 37% formaldehyde-water at 0-2°C was treated with 25 g of dry HCl. The mixture was then warmed to 75°C over a 1.6 hour period, and stirred for one hour. The cooled reaction mixture was neutralized with solid $NaHCO_3$ and concentrated. Extraction of the residue by trituration with several 100 mL portions of chloroform afforded, after drying ($MgSO_4$) of the combined extracts and removal of solvent under reduced pressure, 10.9 g of a viscous syrup. Chromatography of this syrup on 300 g of silica gel with 100% ethyl acetate provided 6.49 g (63%) of alcohol 2, as colorless crystals: R_f=0.27 (silica gel, 100% EtOAc); mp 116-117°C; IR ($HCCl_3$) 3600 cm^{-1} (OH), 1180, 1090, 1050 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.30 (d, 3H, J=7 Hz, $CHCH_3$), 3.5-4.3 (m, 6H), 4.76 (d, 1H, J=6 Hz, $OCH(H)O$), 5.06 (s, 2H, OCH_2O), 5.14 (d, 1H, J=6 Hz, $OCH(H)O$); $[\alpha]_D^{24}$=+17° (c 1.0, $HCCl_3$). Lit.[5] mp 117-118°C.

Anal. Calcd for $C_8H_{14}O_5$: C, 50.52; H, 7.42. Found: C, 50.45; H, 7.36.

In addition to 2, the chromatography gave 3.2 g of a

a mixture of unidentified by-products. This mixture was dissolved in a solution of 6.8 g of phloroglucinol in 150 mL of 5% hydrochloric acid, and the resulting solution was heated at reflux for 5 hours, and then set aside for 18 hours at room temperature. The resulting red precipitate was removed by filtration and the filtrate was washed with three 50 mL portions of ether and treated with excess silver carbonate. Removal of the silver salts from this solution by filtration and concentration of the filtrate afforded, after recrystallization of the residue from ethanol with decolorizing carbon, 2.2 g of slightly yellow, crystalline starting material (1), mp 113-118°C. Based on this recovered material, the overall yield of 2 is 83%.

Methyl 6-deoxy-2,4:3,5-dimethylene-L-gulonate (3). A stirred solution of 1.1 g (5.8 mmol) of alcohol 2 in 45 mL of acetone (freshly distilled from $KMnO_4$) at 0°C was treated dropwise with 3.19 mL (10% excess) of Jones reagent (8 N e^-). After 3.5 hours 1.0 mL of isopropanol was added, and the precipitated salts were removed by filtration through celite and washed with 100 mL of acetone and 50 mL of dichloromethane. The filtrate was concentrated to ~6 mL volume, taken up in 300 mL of dichloromethane, and treated with excess ethereal diazomethane. After removal of excess diazomethane under reduced pressure, the solution was dried ($MgSO_4$) and solvents were removed under reduced

pressure. Chromatography of the residue on 100 g of silica gel with 100% ethyl acetate afforded 0.87 g (70%) of ester 3, mp 94-95°C: R_f=0.54 (silica gel, 100% EtOAc); IR ($HCCl_3$) 1740 cm^{-1} (C=O); ^{1}H-NMR ($CDCl_3$) δ 1.30 (d, 3H, J=7 Hz, $CHCH_3$), 3.83 (s, 3H, OCH_3), 4.82 (d, 1H, J=6.5 Hz, OCH(H)O); $[\alpha]_D^{20}$=-18° (c 1.12, $HCCl_3$).

Anal. Calcd for $C_9H_{14}O_6$: C, 49.54; H, 6.47. Found: C, 49.47; H, 6.40.

[4S,4α5]-4-[1-Hydroxyethyl]-4H-1,3-dioxin-6-carbaldehyde (5). To a solution of 163 mg (0.75 mmol) of ester 3 in 9 mL of dry dichloromethane at -78°C under an argon atmosphere was added 2.2 mL of a 1M solution of diisobutylaluminum hydride in hexane. After one hour, 0.5 mL of anhydrous methanol was added, followed by 0.5 mL of 1N aqueous NaOH. After 30 minutes at room temperature, the mixture was treated with 1.0 g of anhydrous $MgSO_4$, filtered through celite, and the filtrate was dried over $MgSO_4$. Removal of solvent under reduced pressure and chromatography of the residue on 15 g of silica gel with 100% ethyl acetate afforded 106 mg (90%) of the enone 5. The analytical sample was provided by distillation [kugelrohr, 85-95°C (0.001 mmHg)] of a portion of this product: R_f=0.40 (silica gel, 100% EtOAc); IR ($HCCl_3$) 3600 cm^{-1} (OH), 1700 cm^{-1} (C=O), 1630 cm^{-1} (C=C); ^{1}H-NMR ($CDCl_3$) δ 1.28 (d, 3H, J=7 Hz, $CHCH_3$), 3.87 (dq, 1H, J=J´=7 Hz, $CHCH_3$), 4.32 (dd, 1H, J=7 Hz, J´=2 Hz, C=C-CH), 5.03 (d, 1H, J=6 Hz, OCH(H)O),

5.90 (d, 1H, J=2 Hz, C=CH), 9.17 (s, 1H, O=CH); $[\alpha]_D^{22}$=-80° (c 0.84, $HCCl_3$).

Anal. Calcd for $C_7H_{10}O_4$: C, 53.16; H, 6.37. Found: C, 53.10; H, 6.43.

6-Deoxy-L-gulono-1,4-lactone (7). A. By Deprotection of Ester 3. To a stirred solution of 100 mg (0.46 mmol) of ester 3 in 4 mL of dry dichloromethane at -78°C under an argon atmosphere was added 4.25 mL (3.7 mmol) of a 0.9 M solution of boron trichloride in dichloromethane. After 5 minutes the reaction mixture was warmed to 30-35°C and the solvent was removed under reduced pressure. Traces of solvent and excess boron trichloride were removed at 0.2 mmHg and the residual glass foam was heated at 40°C in a water bath for 15 minutes. A solution of the cooled residue in 4 mL of 90% methanol-water was stirred for 20 minutes at room temperature and concentrated to a viscous syrup. Traces of boron were removed from this syrup by several additions and evaporations of dry methanol. Recrystallization from ethanol afforded 45 mg (57%) of the lactone 7, mp 179-183°C. (lit.[2] mp 184-185°C). The analytical sample, obtained by two recrystallizations from ethanol, melted at 183-184°C.

Anal. Calcd for $C_6H_{10}O_5$: C, 44.44; H, 6.22. Found: C, 44.50; H, 6.17.

B. By Desulfurization of Thioacetal 6. The thioacetal 6 was first prepared by Zinner.[9] The process presented here is a modification of that procedure. A mixture of 14.1 g (0.08 mol) of D-glucurono-γ-lactone, 14.4 mL (0.20 mol) of ethanethiol, and 13.6 mL of concentrated hydrochloric acid, in a tightly stoppered 250 mL round bottomed flask, was shaken vigorously for 10 minutes and then cooled and stirred in an ice bath while 52 mL of 3 N aqueous NaOH was slowly added. Stirring was then discontinued, and after 20 minutes the oil which separated was removed by pipette and dissolved in 200 mL of dichloromethane. The remaining aqueous layer was extracted with two 50 mL portions of dichloromethane and discarded. The combined dichloromethane solutions were washed with 20 mL of saturated aqueous $NaHCO_3$ and 20 mL of saturated aqueous NaCl, dried (Na_2SO_4), and filtered. Concentration of the filtrate under reduced pressure afforded 20 g of a white foam, the crude thioacetal 6.

A solution of 20 g of crude thioacetal 6 in 300 mL of 60% ethanol-water was added to a stirred suspension of 200 g of freshly prepared Raney nickel catalyst (W-4) in 1800 mL of 60% ethanol-water. After 3 hours at room temperature, the catalyst was removed by filtration through powdered cellulose and washed with ten 200 mL portions of hot (~80°C) 60% ethanol-water. Concentration of the combined filtrates under reduced pressure at 45-50°C, and

recrystallization of the residue from ethanol, afforded 5.5 g (42%) of the lactone 7 (mp 170-179°C), suitable for reduction. Further purification by recrystallization provided 4.7 g (38%) of lactone 7, melting at 180-182°C. (lit.[2] mp 184-185°C).

Reduction of 6-Deoxy-L-gulonolactone (7). To a stirred solution of 5.9 g (36 mmol) of lactone 7 in 140 mL of deionized water at 5-10°C was added 120 g of 2.5% sodium amalgam (4-8 mesh) while at the same time 20% sulfuric acid was added, as required, to maintain the pH at 3.0-3.5. When no sodium remained, the supernatant was separated from the mercury, filtered, concentrated at 45°C under reduced pressure to ~50 mL, and then diluted with 1000 mL of absolute ethanol. The precipitated inorganic salts were removed by filtration and washed with absolute ethanol, and the ethanol was removed from the combined filtrates under reduced pressure. The residue was dissolved in 50 mL of water and treated with a saturated solution of barium hydroxide until basic to phenolphthalein. The mixture was diluted with 1000 mL of absolute ethanol, treated with decolorizing charcoal, and filtered. Evaporation of ethanol from the filtrate at reduced pressure gave 3.6 g of a cream colored, glassy foam, crude 6-deoxy-L-gulose.

Methyl-6-deoxy-2,3-O-(1-methylethylidene)-(αandβ)-L-gulopyranoside (9a and 9b). To a stirred solution of

0.8 g of the crude 6-deoxy-L-gulose in 10 mL of dry methanol was added 20 mL of 1% methanolic HCl. After 5 hours at room temperature, the reaction was quenched with excess silver carbonate and after filtration, removal of methanol under reduced pressure and chromatography of the residue on 40 g of silica gel afforded 270 mg of 8, as a colorless, water soluble oil: R_f=0.30 (silica gel, 5:1 chloroform-methanol). A solution of this oil in 10 mL of dry acetone with 0.2 mL of 2,2-dimethoxypropane and 5 mg of p-toluenesulfonic acid was stirred for 16 hours at room temperature, neutralized with solid $BaCO_3$, and filtered. Removal of solvent under reduced pressure and chromatography of the residue on 30 g of silica gel with 50% ethyl acetate-toluene afforded the two isomeric products.

Fraction I, 9b: 225 mg; R_f=0.45 (50% EtOAc-toluene); IR ($CHCl_3$) 3600 cm^{-1} (OH), 1375, 1065, 1040 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.32 (d, 3H, J=7 Hz, $CHCH_3$), 1.35 (s, 3H, CCH_3), 1.51 (s, 3H, CCH_3), 3.50 (s, 3H, OCH_3), 4.40 (dd, 1H, J=2 Hz, J'=6 Hz), 4.59 (d, 1H, J=3.5 Hz); $[\alpha]_D^{23}$=+54° (c 1.0, $HCCl_3$).

Anal. Calcd for $C_{10}H_{18}O_5$: C, 55.03; H, 8.31. Found: C, 54.88; H, 8.31.

Fraction II, 9a: 55 mg; R_f=0.27 (50% EtOAc-toluene); IR ($CHCl_3$) 3600 cm^{-1} (OH), 1375, 1060, 1030 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.24 (d, 3H, J=7 Hz, $CHCH_3$), 1.36 (s, 3H, CCH_3), 1.53 (s, 3H, CCH_3), 3.42 (s, 3H, OCH_3), 4.71 (dd, 1H,

J=2 Hz, J′=4 Hz); $[\alpha]_D^{23}$=-57° (c 0.8, $HCCl_3$).

Anal. Calcd for $C_{10}H_{18}O_5$: C, 55.03; H, 8.31. Found: C, 54.89; H, 8.21.

The combined overall yield of these alcohols from lactone 7 was 16%. For preparative purposes, a modified procedure which omitted the chromatographic purification of 8 was used. Thus, a solution of 2.5 g of crude 6-deoxy-L-gulose in 25 mL of 1.5% methanolic hydrogen chloride was heated at reflux for 80 minutes and then cooled. Neutralization with excess silver carbonate, filtration of the resulting mixture and evaporation of the methanol from the filtrate under reduced pressure gave 2.4 g of a brown oil. A solution of this oil in 50 mL of dry acetone with 3.3 mL of 2,2-dimethoxypropane and 20 μL of sulfuric acid was stirred for 16 hours at room temperature and then treated with excess barium carbonate and filtered. The crude product which remained after evaporation of acetone from the filtrate under reduced pressure was purified by chromatography on 200 g of silica gel with 40% ethyl acetate-benzene and gave 950 mg of 9b (R_f=0.31) and 242 mg of 9a (R_f=0.18). The combined overall yield from lactone 7 was 22%, and the products were identical (IR, NMR, TLC) to the products obtained above.

Methyl 6-deoxy-2,3-O-(1-methylethylidene)-4-O-methyl-α-L-gulopyranoside (10a). To a stirred suspension of 50 mg

(1.25 mmol) of potassium hydride in 7 mL of dry THF at 0°C under an argon atmosphere was added 0.44 mL (7.0 mmol) of dry methyl iodide, followed immediately by a solution of 218 mg (1.0 mmol) of alcohol 9a in 3 mL of dry THF, and the resulting mixture was stirred for 30 minutes at room temperature. Isolation of the product by dichloromethane extraction ($MgSO_4$), including a base wash,[14] gave 221 mg (95%) of methyl ether 10a, homogeneous by TLC. Distillation [kugelrohr, 95°C (1.0 mmHg)] of a portion of this product gave the analytical sample: R_f=0.33 (40% EtOAc-benzene); IR ($CHCl_3$) 1375, 1040 cm^{-1}; ^{1}H-NMR ($CDCl_3$) 1.22 (d, 3H, J=7 Hz, $CHCH_3$), 1.36 (s, 3H, CCH_3), 1.52 (s, 3H, CCH_3), 2.29, 2.31 (2s, 2 x 3H, 2 x OCH_3); $[\alpha]_D^{23}$=-42° (c 0.87, $CHCl_3$).

Anal. Calcd for $C_{11}H_{20}O_5$: C, 56.88; H, 8.68. Found: C, 56.77; H, 8.72.

Methyl 6-deoxy-2,3-O-(1-methylethylidene)-4-O-methyl-β-L-gulopyranoside (10b). By the procedure described for the preparation of 10a, 795 mg (3.42 mmol) of alcohol 9b in 5 mL of dry THF, with 172 mg (4.28 mmol) of potassium hydride and 1.5 mL (24 mmol) of methyl iodide in 13 mL of dry THF provided 816 mg (96%) of methyl ether 10b. Distillation [kugelrohr, 95°C (1.0 mmHg)] of a portion of this product gave the analytical sample: R_f=0.42 (40% EtOAc-benzene); IR ($CHCl_3$) 1375, 1160, 1040 cm^{-1}; ^{1}H-NMR ($CDCl_3$)

δ 1.32 (d, 3H, J=7 Hz, $CHCH_3$), 1.39 (s, 3H, CCH_3), 1.52 (s, 3H, CCH_3), 3.50 (s, 6H, 2 x OCH_3); $[\alpha]_D^{23}$=+127° (c 0.81, $CHCl_3$).

Anal. Calcd for $C_{11}H_{20}O_5$: C, 56.88; H, 8.68. Found: C, 56.94; H, 8.75.

6-Deoxy-2,3-O-(1-methylethylidene)-4-O-methyl-L-gulopyranose (11). A stirred solution of 195 mg (0.84 mmol) of guloside 10b in 30 mL of 2% aqueous sulfuric acid was heated at reflux for 16 hours and then cooled and treated with 2.4 g of barium carbonate. After 2 hours the solution was filtered and the water was removed from the filtrate under reduced pressure at 45-50°C. After drying under vacuum (1 mmHg), the residue was triturated with 10 mL of dry acetone, the resulting mixture was filtered, and the solids were washed with two 10 mL portions of dry acetone. The combined filtrates were stirred for 2 hours with 0.16 mL of 2,2-dimethoxypropane and 1 μL of sulfuric acid, and then treated with excess silver carbonate. Filtration of this reaction mixture and evaporation of acetone from the filtrate under reduced pressure gave 140 mg (77%) of 11, a crystalline solid, mp 93-96°C. Recrystallization of a portion of this product from n-hexane afforded the analytical sample: mp 97-98°C; R_f=0.19 (40% EtOAc-benzene); IR (CCl_4) 3600 cm^{-1} (OH); 1380, 1050, 1030 cm^{-1}; ^{1}H-NMR (CCl_4) δ 1.20 (d, 3H, J=6 Hz, $CHCH_3$), 1.29 (s, 3H, CCH_3), 1.40

(s, 3H, CCH_3), 3.47 (s, 3H, OCH_3); $[\alpha]_D^{23}$=+27° (c 0.92, $CHCl_3$).

Anal. Calcd for $C_{10}H_{18}O_5$: C, 55.03; H, 8.31. Found: C, 55.08; H, 8.35.

By the process described above, 250 mg (1.08 mmol) of glycoside 10a with 30 mL of 2% aqueous sulfuric acid, 2.4 g of barium carbonate, 30 mL of dry acetone and 0.2 mL (1.6 mmol) of 2,2-dimethoxypropane afforded 195 mg (83%) of 11, indistinguishable (mp, IR, NMR, TLC) from that obtained from glycoside 10b.

D-Glucurono-γ-lactone,ethylene mercaptal (12). A solution of 40 g (0.23 mol) of D-glucurono-γ-lactone in 60 mL of hot water was cooled to room temperature and then shaken vigorously for 20 minutes in a sealed flask with 40 mL (0.48 mol) of 1,2-ethanedithiol and 40 mL of concentrated hydrochloric acid. The mixture was shaken intermittently for 2 hours, and then set aside for 12 hours, while the product separated as a white crystalline solid. After dilution of the reaction mixture with 200 mL of ice cold water, the solid was collected by filtration, washed with four 100 mL portions of cold water and four 100 mL portions of ether, and dried under vacuum (1 mmHg) over P_2O_5 to give 53.7 g (93%) of thioacetal 12, mp 189-190°C. A portion of this material was recrystallized twice from 3:2 water-ethanol and dried under vacuum at 80°C to give

analytically pure material: mp 190-191°C; IR (nujol) 1740 cm^{-1} (C=O), 1160, 1000 cm^{-1}; ^{1}H-NMR (d_6-DMSO) δ 3.0-3.5 (m, 4H, SCH_2CH_2S), 4.56 (dd, 1H, J=7 Hz, J =4 Hz), 5.77 (d, 1H, J=7 Hz, SCHS); $[\alpha]_D^{22}$=+14°(c 0.95, H_2O).

Anal. Calcd for $C_8H_{12}O_5S_2$: C, 38.08; H, 4.79. Found: C, 38.09; H, 4.78.

2,4-O-(1-Methylethylidene)-D-glucurono-γ-lactone, ethylene dithioacetal (13). To a stirred suspension of 10.0 g (0.04 mmol) of finely ground triol 12 and 6.1 mL (0.05 mmol) of 2,2-dimethoxypropane in 1.0 L of acetone at room temperature was added 4 mL of concentrated sulfuricccc acid. After 10 hours the mixture was treated with excess $BaCO_3$ and filtered. Removal of solvent from the filtrate and recrystallization of the residue from acetone-hexane afforded 8.9 g (77%) of ketal 13, a white, crystalline solid: mp 238-239°C; IR (Nujol) 3540 cm^{-1} (OH), 1780 cm^{-1} (C=O); ^{1}H-NMR (d_6-DMSO) δ 1.28 (s, 3H, CH_3), 1.41 (s, 3H, CH_3), 3.15 (s, 4H, SCH_2CH_2S), 5.78 (d, 1H, J=7 Hz, SCHS); $[\alpha]_D^{22}$=+48° (c 0.65, CH_2Cl_2).

Anal. Calcd for $C_{11}H_{16}O_5S_2$: C, 45.19; H, 5.52. Found: C, 45.24; H, 5.48.

6-Deoxy-3,5-O-(1-methylethylidene)-L-gulono-γ-lactone (14). A solution of 7.8 g (27 mmol) of dithioacetal 13 in a mixture of 200 mL of acetone and 100 mL of dry THF at 60°C was added to a slurry of 160 mL of Raney

nickel (W-4) in 300 mL of absolute ethanol and stirred without external heating for 14 hours. The catalyst was then removed by filtration and washed with six 150 mL portions of 60% ethanol-acetone. Removal of solvents from the combined filtrates under reduced pressure afforded a glass foam, which was taken up in 200 mL of CH_2Cl_2. This solution was dried ($MgSO_4$), filtered, and solvent was removed to afford 4.2 g (78%) of lactone 14, mp 101-104°C. VPC analysis (4% SE-30, 140°C) indicated >99% purity. The analytical sample was obtained by recrystallization from ethyl acetate-hexane: mp 107-107.5°C; IR ($CHCl_3$) 3600 cm^{-1} (OH), 1805 cm^{-1} (C=O); ^{1}H-NMR ($CDCl_3$) δ 1.33 (d, 3H, J=7 Hz, CH_3), 1.43 (s, 3H, CH_3), 1.52 (s, 3H, CH_3), 4.10 (dq, 1H, J=7 Hz, J =2 Hz, H-5), 4.51 (d, 1H, J=2 Hz, H-2); $[\alpha]_D^{23}$= +76° (c 1.0, $CHCl_3$).

Anal. Calcd for $C_9H_{14}O_5$: C, 53.46; H, 6.98. Found: C, 53.47; H, 6.92.

2-O-(tert-Butyldimethylsilyl)-6-deoxy-3,5-O-(1-methylethylidene)-L-gulono-γ-lactone (16). To a solution of 5.12 g (25.3 mmol) of hydroxylactone 14 and 6.88 g (102 mmol) of imidazole (sublimed) in 10.0 mL of dry dimethylformamide at room temperature was added 7.6 g (51 mmol) of tert-butyldimethylchlorosilane. The resulting homogeneous solution was stirred for 29 hours, during which time it solidified to a colorless, crystalline mass. The

solid was then partially dissolved in 350 mL of ether, washed with four 80 mL portions of water, and dried ($MgSO_4$). Removal of ether under reduced pressure afforded a crystalline residue from which disiloxane was removed by evaporative transfer under vacuum (~1 mmHg) at 40°C for 14 hours. There remained 7.95 g (99%) of siloxy lactone 16 as a white, crystalline solid, mp 108-112°C. Recrystallization of a portion of this product from n-hexane afforded the analytical sample: mp 113.5-114.5°C; IR ($CHCl_3$) 1800 cm^{-1} (C=O); ^{1}H-NMR ($CDCl_3$) δ 0.17 (s, 6H, 2 x $SiCH_3$), 0.94 (s, 9H, t-butyl), 1.33 (d, 3H, J=7 Hz, CH_3), 1.39 (s, 3H, CH_3), 1.45 (s, 3H, CH_3), 4.12 (dq, 1H, J=7 Hz, J =2 Hz, H-5), 4.45 (bs, 2H, H-2 and H-4); $[\alpha]_D^{22}$=+88° (c 1.1, $CHCl_3$).

Anal. Calcd for $C_{13}H_{28}O_5Si$: C, 56.93; H, 8.92. Found: C, 56.78; H, 8.97.

2-O-(tert-Butyldimethylsilyl)-6-deoxy-3,5-O-(1-methylethylidene)-L-gulofuranose (17). To a stirred solution of 3.24 g (10.2 mmol) of siloxy lactone 16 in 150 mL of dry dichloromethane under an argon atmosphere at -78°C was added 30 mL (30 mmol) of a 1 M solution of di-iso-butylaluminum hydride in hexane. After 60 minutes, the reaction mixture was treated cautiously with 10 mL of methanol and allowed to warm to room temperature. After 30 minutes, the reaction mixture was diluted with 200 mL of dichloromethane and washed with 100 mL of 1 M sodium

potassium tartrate, three 100 mL portions of H_2O, and 50 mL of saturated NaCl. After drying ($MgSO_4$), removal of solvent under reduced pressure afforded 3.21 g (98%) of lactol 17, a crystalline solid, mp 108-110°C. Recrystallization from ethyl acetate-hexane provided the analytical sample: mp 110.5-111.5°C; IR ($CHCl_3$) 3600 cm^{-1} (OH); ^{1}H-NMR ($CDCl_3$) 0.10 (s, 6H, 2 x $SiCH_3$), 0.92 (s, 9H, t-butyl), 1.20 (d, 3H, J=7 Hz, CH_3), 1.39 (s, 6H, 2 x CH_3), 3.28 (dd, 1H, J=J´=2 Hz, H-3), 3.56 (d, 1H, J=12 Hz, OH), 4.81 (dd, J=12 Hz, J´=4 Hz, H-1); $[\alpha]_D^{23}$=+62° (c 1.33, $CHCl_3$).

Anal. Calcd for $C_{15}H_{30}O_5Si$: C, 56.57; H, 9.49. Found: C, 56.53; H, 9.48.

2-O-Acetyl-6-deoxy-3,5-O-(1-methylethylidene)-L-gulono-γ-lactone (15). To a stirred solution of 202 mg (1.0 mmol) of hydroxy lactone 14 in 2 mL of dry pyridine at room temperature, under an argon atmosphere was added 0.4 mL (4.0 mmol) of acetic anhydride. After 28 hours the reaction mixture was diluted with 10 mL of H_2O and extracted with two 30 mL portions of dichloromethane. The combined extracts were washed with 30 mL of 10% HCl, 20 mL of 1 N $CuSO_4$, and 20 mL of saturated $NaHCO_3$, and dried ($MgSO_4$). Removal of solvent under reduced pressure, and recrystallization of the residue from ethyl acetate-hexane, provided 238 mg (97%) of acetate 15: mp 130.5-131.5°C; IR ($CHCl_3$)

1750, 1800 cm^{-1} (C=O); ^{1}H-NMR ($CDCl_3$) 1.32 (d, 3H, J=7 Hz, CH_3), 1.38 (s, 3H, CH_3), 1.47 (s, 3H, CH_3), 4.17 (dq, 1H, J=7 Hz, J´=2 Hz, H-5), 5.38 (d, 1H, J=4 Hz, H-2); $[\alpha]_D^{22}$= +156° (c 1.14, $CHCl_3$).

Anal. Calcd for $C_{11}H_{16}O_6$: C, 54.09; H, 6.60. Found: C, 54.14; H, 6.53.

2-O-(tert-Butyldimethylsilyl)-6-deoxy-3,5-O-(1-methylethylidene)-L-gulose,N,N-dimethylhydrazone (18). To a stirred solution of 2.7 g (8.5 mmol) of lactol 17 and 1.23 mL (12.8 mmol) of carbon tetrachloride in 18 mL of dry THF at -78°C under an argon atmosphere was added 1.70 mL (9.35 mmol) of trisdimethylaminophosphine and, after 30 minutes, 5.2 mL (68 mmol) of unsym-dimethylhydrazine. Cooling was then discontinued, and, after 4 hours at room temperature, ether extraction ($MgSO_4$)[14] and chromatography of the crude product on 100 g of silica gel with 50% ether-petroleum ether provided 2.4 g (78%) of hydrazone 18, a colorless oil. Distillation [kugelrohr, 110-120°C (0.01 mmHg)] of a portion of this product afforded the analytical sample: IR ($CHCl_3$) 3600 cm^{-1} (OH), 1620 cm^{-1} (C=N), 840 cm^{-1} (O-Si); ^{1}H-NMR (CCl_4) 0.03 (s, 3H, $SiCH_3$), 0.10 (s, 3H, $SiCH_3$), 0.87 (s, 9H, t-butyl) 1.13 (d, 3H, J=7 Hz, CCH_3), 1.32 (s, 3H, CH_3), 1.35 (s, 3H, CH_3), 2.72 (s, 6H, CH_3NCH_3), 6.20 (d, 1H, N=CH); m/e, calcd 360.2444, found 360.2439 ± 0.0018; $[\alpha]_D^{22}$=+11° (c 1.1, $CHCl_3$).

Anal. Calcd for $C_{17}H_{36}O_4N_2Si$: C, 56.63; H, 10.06. Found: C, 56.83; H, 10.22.

2-O-(tert-Butyldimethylsilyl)-6-deoxy-4-O-methoxymethyl-3,5-O-(1-methylethylidene-L-gulose,N,N-dimethylhydrazone (19). To a solution of 1.25 g (3.5 mmol) of hydroxy hydrazone 18 in 7 mL of dry THF at -78°C under an argon atmosphere was added 5.8 mL (3.9 mmol) of a 0.66 M solution of lithium diisopropylamide in THF, followed by 4 mL of dry hexamethylphosphoramide and 0.60 mL (7.8 mmol) of dry chloromethyl methyl ether. Cooling was then discontinued, and after 2 hours at room temperature ether extraction ($MgSO_4$), including a base wash[14] afforded the crude product, which was further purified by filtration through 15 g of silica gel and elution with 100 mL of 70% ethyl acetate-hexane. Removal of solvents from the eluate provided 1.27 g (90%) of 19, a colorless oil. Distillation [kugelrohr, 120-130°C (0.005 mmHg)] of a portion of this product afforded the analytical sample: IR ($CHCl_3$) 1620 cm^{-1} (C=N), 840 cm^{-1} (O-Si); ^{1}H-NMR (CCl_4) 0.03, 0.11 (two singlets, 6H, 2 x $SiCH_3$), 0.90 (s, 9H, t-butyl), 1.21 (d, 3H, J=7 Hz, CCH_3), 1.33, 1.36 (two singlets, 6H, CH_3CCH_3), 2.78 (s, 6H, CH_3NCH_3), 3.40 (s, 3H, OCH_3), 4.56 (d, 1H, J=7 Hz, OCH(H)O), 4.73 (d, 1H, J=7 Hz, OCH(H)O), 6.23 (d, 1H, J=7 Hz, N=CH); $[\alpha]_D^{23}$=+23° (c 0.90, $CHCl_3$).

Anal. Calcd for $C_{19}H_{40}O_5N_2Si$: C, 56.40; H, 9.96.

Found: C, 56.46; H, 10.00.

Methanolysis of Lactol 17. Methyl 6-deoxy-(αandβ)-L-gulopyranoside (8a,b). A solution of 318 mg (1.0 mmol) of lactol 17 in 10 mL of 3% dry methanolic hydrogen chloride was heated at reflux under argon for 20 hours. The reaction mixture was then treated with excess silver carbonate and filtered. Removal of methanol from the filtrate afforded a residue, chromatography of which on 20 g of silica gel with 9% methanol-chloroform provided 150 mg (84%) of a mixture of pyranosides 8a and 8b, as described above. The ratio of anomers could be determined by ^{1}H-NMR: (D_2O) δ 1.3 (d, 3H, J=7 Hz, CH_3), 3.47 and 3.63 (two singlets, 1:4 ratio, 3H, α-OCH_3:β-OCH_3).

Hydrolysis of Lactol 17. 6-Deoxy-L-gulose (20). A suspension of 1.2 g (3.8 mmol) of lactol 17 in 10 mL of 2% aqueous sulfuric acid was heated at 60°C for 4 hours, during which time the mixture first became homogeneous and then tert-butyldimethyldisiloxane separated. The aqueous reaction mixture was then cooled, washed with two 15 mL portions of ether, and neutralized with excess $BaCO_3$. The resulting suspension was then filtered, and removal of water from the filtrate by lyophilization provided 658 mg (105%) of a fluffy white solid. A portion of this material (55 mg) was converted to the p-bromophenylhydrazone as described by Reichstein.[2] The hydrazone was recrystallized

from ethanol, and melted at 135-136°C. [(lit.[2] mp 136°C) (lit.[12] mp 135-137°C)]. $[\alpha]_D^{23}$=+14.5° (c 1.1, EtOH) [lit.[12] $[\alpha]_D^{25}$=+13±2° (c 1, EtOH)]. The remainder of the product was dissolved in 5 mL of water, and a small amount of insoluble material was removed by filtration through a fine glass frit. Removal of water from the filtrate by lyophilization provided 555 mg (97%, corrected) of 6-deoxy-L-gulose, $[\alpha]_D^{22}$=+40.3° (c 1.60, H_2O) [lit.[2] $[\alpha]_D^{21}$=+40.8° (c 1.615, H_2O)].

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(1) Grateful acknowledgment is made to the National Institutes of Health for the support of this work.

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(10) The anomeric configuration of these products is based upon the known preference for formation of the β-anomer and can be verified by comparison of the optical properties of alcohols 9a and 9b with the known rotation for the enantiomorph of 9a, methyl 6-deoxy-2,3-O-(1-methylethylidene)-α-D-gulopyranoside.[11]

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(13) 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 or for IR spectra, 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. Acidic silica gel refers to Silicar CC-4 Special "for column chromatography", sold by Mallinckrodt Chemical Works, St. Louis, MO.

"Dry" solvents were distilled shortly before use from an appropriate drying agent. Ether, tetrahydrofuran (THF), and dimethoxyethane were distilled under dry argon from sodium metal in the presence of benzophenone. Benzene and toluene were distilled from calcium hydride. Hexane and dichloromethane were 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, hexamethyldisilazane, and dimethyl hydrazine 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 and n-propanoyl chloride were 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.

Mass spectral analyses were performed by Dr. Kai Feng, UCLA, Los Angeles, CA. Elemental combustion analyses were performed by Spang Microanalytical Laboratory, Eagle Harbor, MI.

(14) In cases where reaction intermediates or products were isolated "by solvent extraction (Na_2SO_4)", the procedure followed was to dilute the reaction mixture with the indicated solvent or to extract the aqueous solution with several portions of the indicated solvent; then the combined organic extracts were washed first with several portions of water, then with saturated sodium chloride, and dried over anhydrous sodium sulfate. Drying over anhydrous magnesium sulfate ($MgSO_4$) or anhydrous potassium carbonate (K_2CO_3) is indicated by the appropriate parenthetical substitution. After drying, the solution was filtered and the solvent was evaporated from the filtrate under reduced pressure (water aspirator) using a rotary evaporator. The use of the terms "base wash" or "acid wash" indicates washing of the organic solution with saturated aqueous sodium bicarbonate solution or with 10% aqueous hydrochloric acid, respectively, prior to the aforementioned washing with water.

PROPOSITIONS

Abstracts of Propositions

I. The application of N-haloaziridines to the total synthesis of alkaloids is proposed. Based upon this concept, a synthetic approach to the pavine-type alkaloid (±)-argemonine is outlined.

II. An enantiospecific approach to chiral 1,4-dihydropyridine derivatives is described. An enantiospecific synthesis of an isotopically labelled 1,4-dihydronicotinate is proposed.

III. Based upon the transient formation of tertiary oxonium ions, a ring expansion approach to medium ring lactones is proposed.

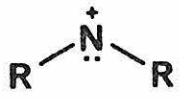
IV. Experiments designed to detect special differences in the nature of carbanions next to heteroatoms as compared to carbanions next to methylene units are described. The limitations on the conclusions which may be drawn from such experiments are discussed.

V. A new route to 1,3-dioxolan-4-one is suggested. The synthesis of verrucarinic acid *via* the Claisen rearrangement of a 4-allyloxy-1,3-dioxole is proposed.

PROPOSITION 1

(The utilization of N-haloaziridines in alkaloid synthesis is suggested and a synthesis of (±)-argemonine is proposed.)

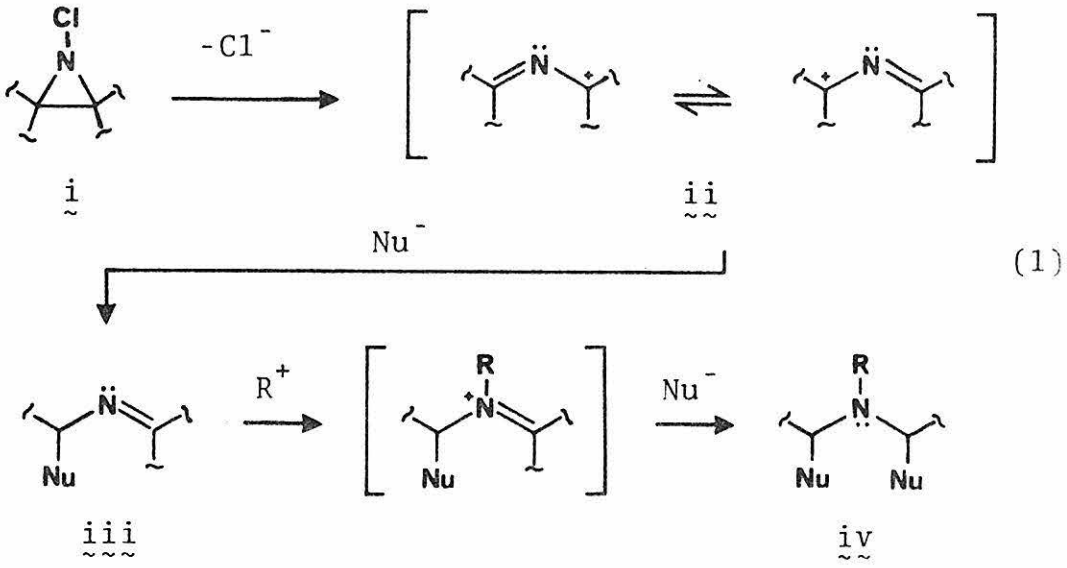
During the last fifteen years, knowledge of the chemistry of nitrenium ions (I) has grown from simple speculation to the well founded establishment of the reality of such divalent nitrogen intermediates.[1,2] Due, principally, to the investigations of Gassman, a firm experimental foundation is now available in the preparation and reactivity of these ions. The contributions of carbonium ion chemistry



I

to the total synthesis of natural products suggest the potential value of nitrenium ions in synthetic endeavors. While the direct use of nitrenium ions in the laboratory preparation of alkaloids is, of itself, a fertile area for speculation, one particular reaction of these ions is proposed as a potential route to a not readily obtained reactive intermediate.

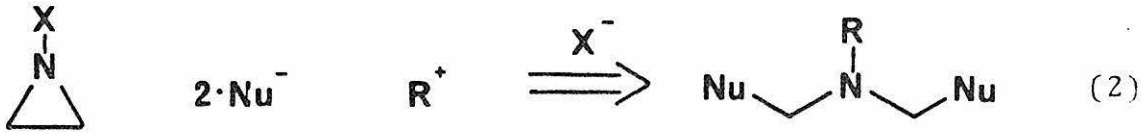
The solvolysis of N-haloaziridines (equation 1) has been shown to result in carbon-carbon bond cleavage and to yield the 2-aza-allylic cation ii in a manner analogous to the solvolyses of cyclopropyl halides.[3] The subsequent fate of this



(1)

novel electrophile will be determined by the nature of the substituents and the environment in which the cation is generated. It may be generalized, however, that a nucleophile (Nu^-) will trap this intermediate to provide the Schiff base iii. Alkylation or protonation of this azomethine would provide, ultimately, the product iv. The

overall process may be schematized as shown in equation 2, and the N-haloaziridine is recognized as equivalent to the hypothetical dication, II. Several applications for these



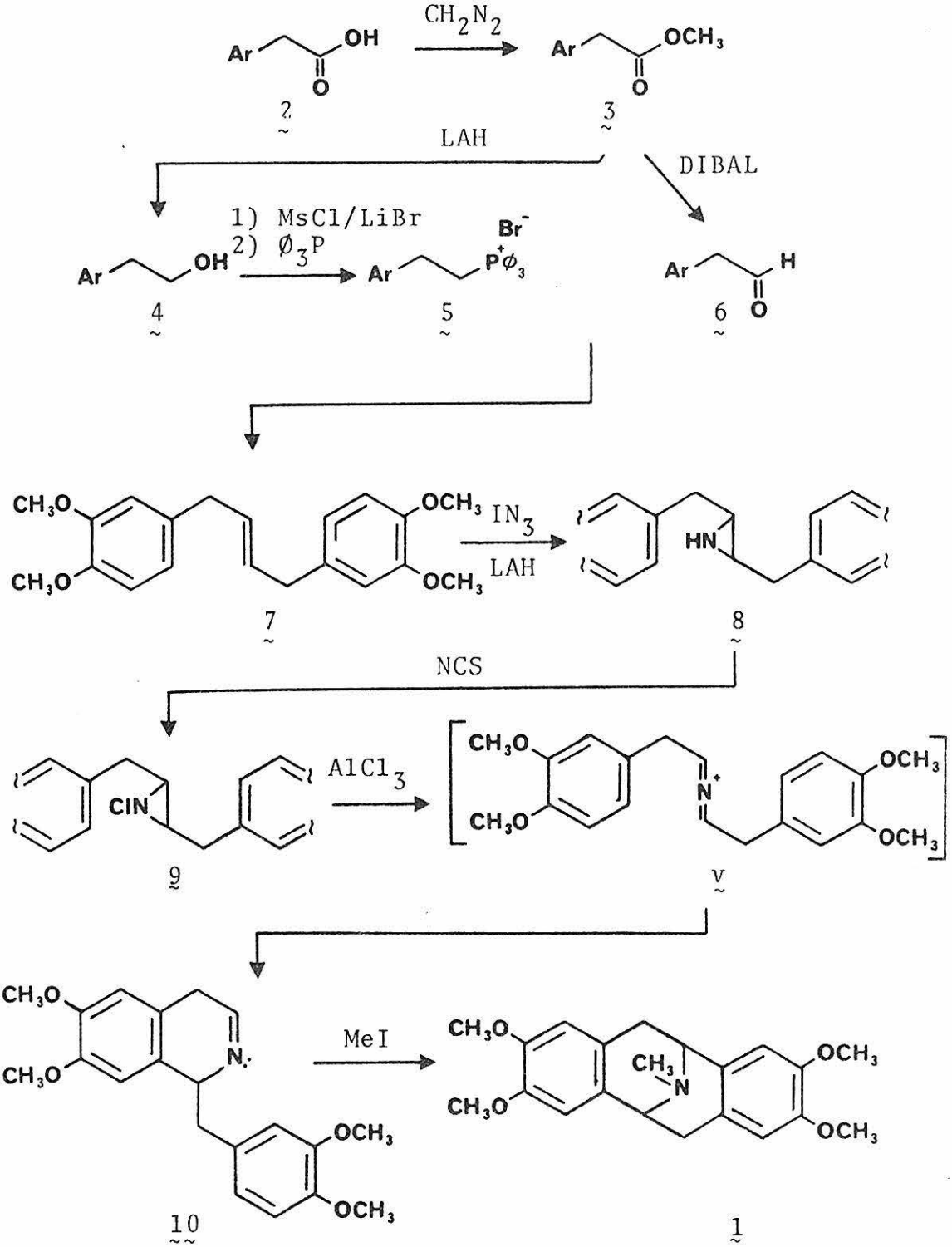
(2)

II

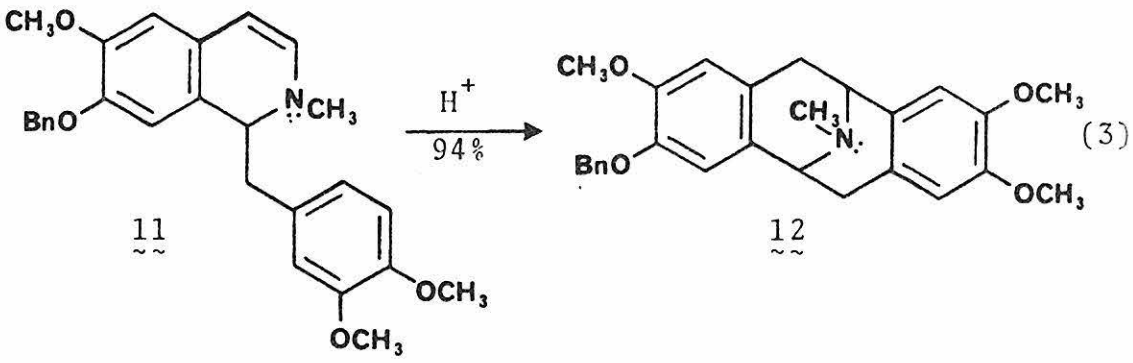
intermediates (ii-iv) may be imagined. Among these, the total synthesis of the pavine-type alkaloid (±)-argemonine (1),[4] is proposed as an interesting yet most straightforward demonstration of the general concept.

The approach to (±)-argemonine (Chart 1) begins with homoveratric acid (2). Although other methods are conceivable for the preparation of the dibenzylolefin, 7, the symmetrical approach suggested here is especially attractive. Treatment of olefin 7 with iodonium azide followed by lithium aluminum hydride provides aziridine 8, after the work of Hassner.[5,6] Either tert-butylhypochlorite[7] or

Chart 1


Ar
OH
O
CH_2N_2
OCH$_3$
2
3
LAH
DIBAL
1) MsCl/LiBr
2) ϕ_3P
Br$^-$
P$^+\phi_3$
H
4
5
6
CH$_3$O
OCH$_3$
IN_3
LAH
HN
7
8
NCS
CIN
$AlCl_3$
N$^+$
9
V
N
MeI
CH$_3$
10
1

N-chlorosuccinimide[8] should convert aziridine 8 to the N-chloro compound 9. Reaction of N-chloroaziridine 9 with aluminum trichloride will provide the ion v, which is expected to lead to the dihydroisoquinoline 10. Finally, methylation of 10 is expected to provide (±)-argemonine (1) in good yield. This expectation is based upon a previous preparation of (±)-norargemonine, wherein treatment of the dihydroisoquinoline 11 with phosphoric acid (equation 3) provided the product 12 in 94% yield.[9]



11 12 (3)

The preparation of (±)-argemonine outlined above provides a practical beginning project in the exploration of the synthetic utility of N-haloaziridines.

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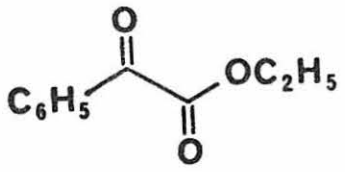
PROPOSITION 2

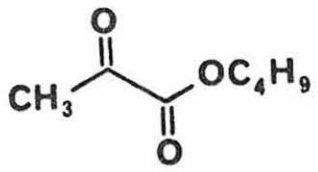
(An enantiospecific synthesis of a chiral, isotopically labelled 1,4-dihydronicotinate is proposed.)

The pyridine nucleotides NAD^+ and NADH, and the O-phosphorylated derivatives of these nucleotides ($NADP^+$ and NADPH) are essential coenzyme factors in many enzymically mediated oxidations and reductions.[1] Since the elucidation of the structure of NADH by Colowick,[2] several investigations have attempted to model these enzymic reactions. These models have been based upon the ability of N-alkyl-1,4-dihydronicotinamide derivatives to transfer a hydride ion to a suitable "acceptor" molecule. Most interesting among these models are the reductions of α-ketoesters.[3,4] These reductions model the reaction catalysed by lactate dehydrogenase. Wallenfels and Hofmann reported the reduction of pyruvic acid to DL-lactic acid by an N-benzyl-1,4-dihydronicotinamide in 1959.[4]

Recently, Ohnishi has reported significant asymmetric induction in the reductions of ethyl benzoylformate (1) and n-butyl pyruvate (2) by the alkylated (R)-(-)-N-α-methylbenzyl-1,4-dihydronicotinamide (3) in the presence of magnesium ion.[5] It was found that reduction of benzoylformate 1 with the chiral dihydropyridine 3 provided ethyl R-(-)-mandelate (4) with an optical purity of 20% (e.e.). Similarly, the reduction of n-butyl pyruvate provided



1



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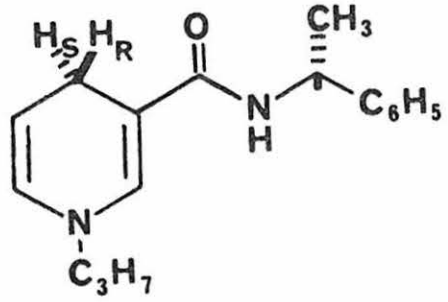

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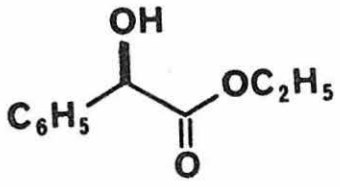

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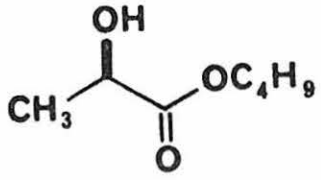

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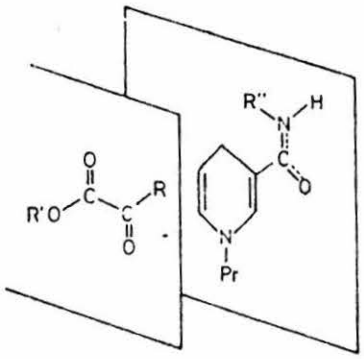
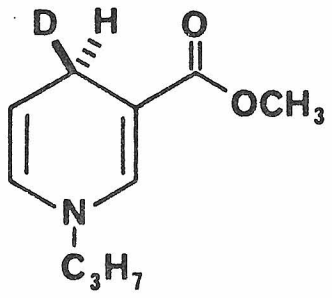


Figure 1 (reproduced from ref. 6)

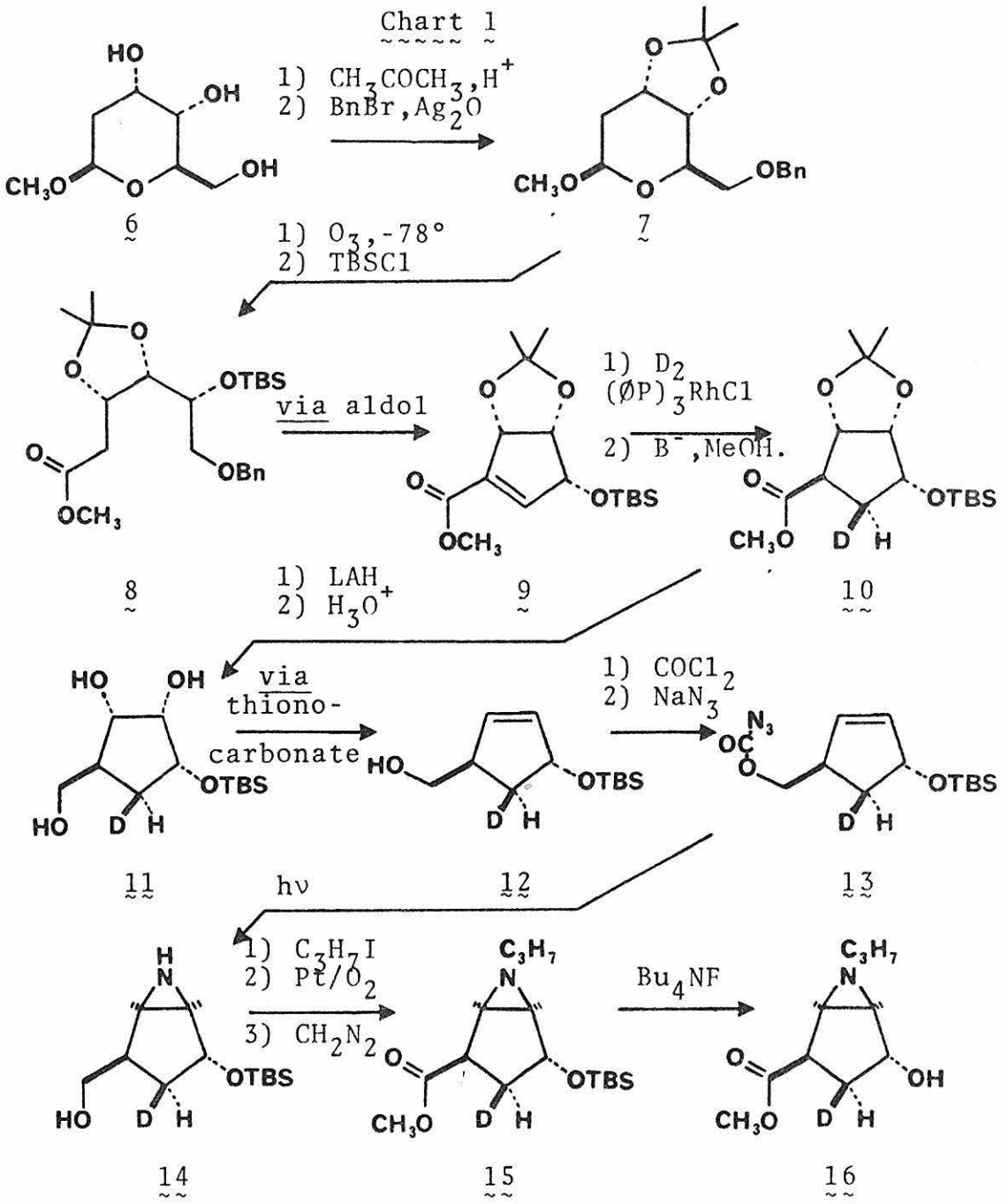
n-butyl (R)-(+)-lactate (5) with an optical purity of 38% (e.e.). These observations have led the authors to propose[5,6] that the asymmetric center in 3 results in an enhanced reactivity of the "pro-R" hydrogen (H_R in structure 3) via a transition state approximating the molecular arrangement illustrated in Figure 1.

The availability of a chiral, isotopically labelled analogue of the dihydronicotinamide 3 would provide a direct means of testing the hypothesis of Ohnishi and, furthermore, would make possible experiments which would unambiguously identify which and if either of the hydrogen atoms (pro-R or pro-S, structure 3) is preferentially transferred during these reductions. Therefore, the enantiospecific preparation of methyl (4R)-N-propyl-1,4-dideuteronicotinate (I) is proposed (Chart 1).



I

Chart 1

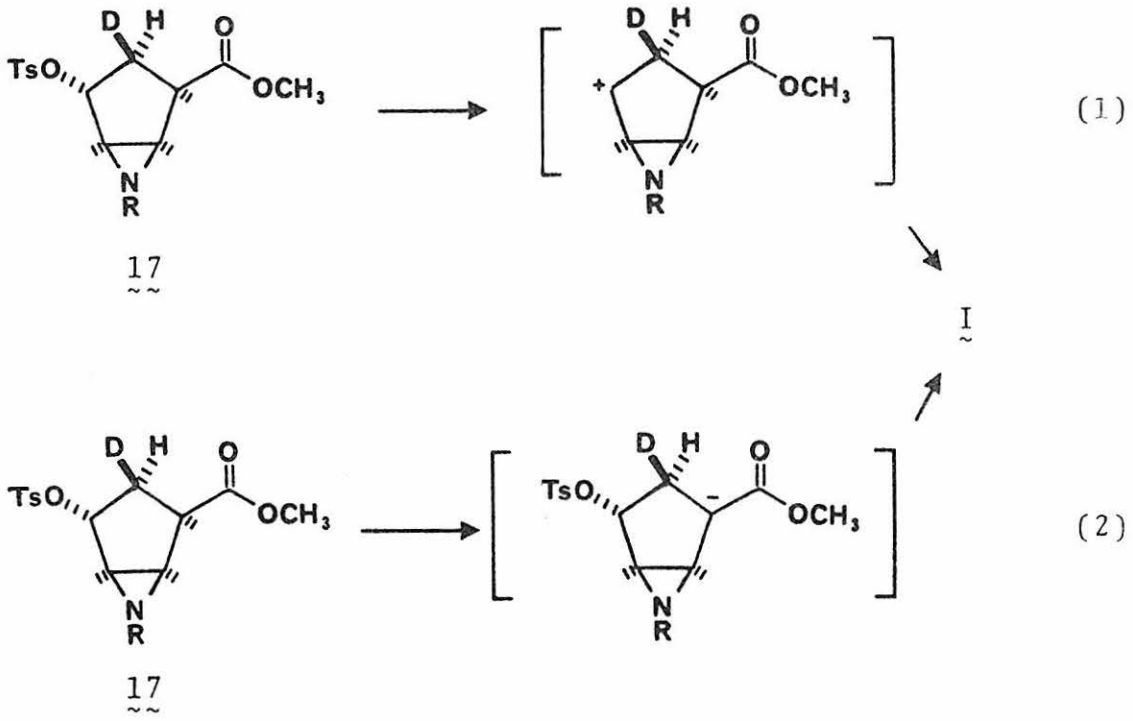

1) CH_3COCH_3, H^+
2) BnBr, Ag_2O
1) O_3, -78°
2) TBSCl
via aldol
1) D_2
$(\phi P)_3RhCl$
2) B^-, MeOH.
1) LAH
2) H_3O^+
via thiono-carbonate
1) $COCl_2$
2) NaN_3
hν
1) C_3H_7I
2) Pt/O_2
3) CH_2N_2
Bu_4NF
6
7
8
9
10
11
12
13
14
15
16

The synthesis begins with methyl 2-deoxy-β-D-allopyranoside 6, which is available in quantity as described by Zorbach.[7] Protection of the free hydroxyl groups provides 7, ozonolysis[8] of which generates, after silylation of the resulting hydroxy ester, the silyloxy ester 8. Debenzylation and oxidation is followed by an intramolecular aldol reaction to provide the α,β-unsaturated ester 9. Deuteration of this enone, catalysed by tris-(triphenylphosphino)-rhodium chloride (Wilkinson's catalyst)[9] is expected to provide the α,β-dideuterio isomer with both deuterium atoms oriented on the exocyclic side of this hindered [3.3.0] bicyclic system.[10] Subsequent equilibration of this product will provide 10, which can be converted to 11 by lithium aluminum hydride reduction followed by mild aqueous hydrolysis. The conversion of the vicinal diol in 11 to the olefin 12 follows the procedure of Winter and Corey,[11] and provides for the formation of aziridine 14 via azido formate 13, as described by Lwowski.[12] Finally, aziridine alkylation, oxidation of the primary alcohol, and deprotection of the secondary alcohol provides the key intermediate, the N-propyl aziridine 16.

The conversion of the N-propyl aziridine 16 to the 1,4-dihydronicotinate I would constitute the completion of the synthesis. Several methods may be imagined for effecting cleavage of the C_1-C_5 bond in this 6-azabicyclo[3.1.0]hexane derivative. In essence, the

methods explored would be cationic, radical, and anionic. Thus, formation of the p-toluenesulfonate 17, followed by solvolysis, could provide the target I directly, or after β-elimination (Equation 1). Alternatively, the p-toluenesulfonate might provide I under basic conditions (Equation 2). Precedent is available which suggests that the cationic process is promising. Friedrich and Winstein reported that the acetolysis of exo-2-bicyclo[3.1.0]hexyl p-toluenesulfonate provided a 48% yield of 4-cyclohexenyl acetate, and the only by-products consisted of simple displacement products (retention and inversion).[13] The total yield was reported to be close to theoretical. In addition, these authors note that samples of exo- or endo-2-bicyclo[3.1.0]hexyl p-toluenesulfonate rearrange "after a few days . . . to tan solids which were shown in both cases to consist entirely of cyclohexen-4-yl p-toluenesulfonate."[13] Fortunately, 6-methylazabicyclo[3.1.0]hex-3-en-2-exo-ol is readily available, and should therefore provide a convenient source of material for model solvolyses.

The availability of chiral isotopically labelled 1,4-dihydropyridine derivatives is expected to contribute to current investigations in bioorganic chemistry. On a different note, the availability of specific enantiomers of 4-substituted 1,4-dihydropyridine derivatives promises to be of value in the field of medicinal chemistry. Racemic mixtures of 1,4-dihydropyridine derivatives are



known to possess analgesic,[14] hypotensive,[15] and aporphyrial[16] properties. The use of chiral analogues of these molecules might help to define the nature, or identify the presence, of a receptor site for these drugs.

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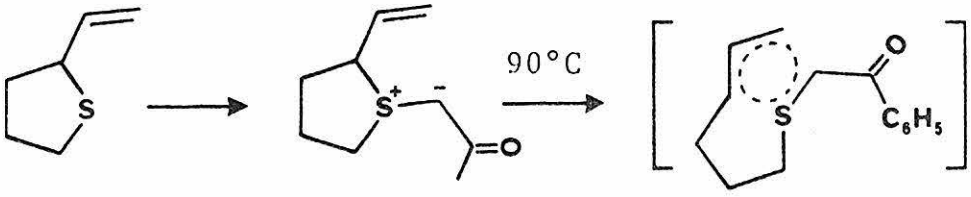
PROPOSITION 3

(Based upon the transient formation of tertiary oxonium ions, a ring expansion approach to medium ring lactones is proposed.)

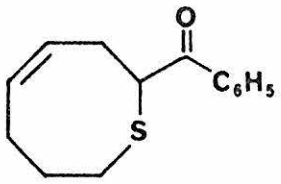
The preparation of macrocyclic lactones has received considerable attention in the past and this interest continues to grow, stimulated by the continual discovery of new macrocycles of promising biological activity. Many techniques have been developed for the preparation of large-ring lactones and excellent reviews are available which describe the positive and negative aspects of these techniques.[1-3]

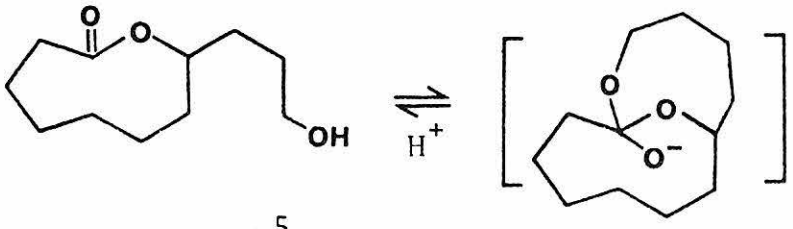
The available methods may be divided among two broad categories. In one group are reactions which allow direct cyclization of a bifunctional acyclic molecule to provide the desired large ring. In the other group may be collected those techniques which incorporate a ring expansion strategy, whereby the macrocycle is derived from a multicyclic intermediate by "core bond" cleavage. Within this second category are included those processes that have been described as "ring growing" reactions. Two illustrations of ring growing processes are provided in Figure 1. These examples constitute special cases of the second category wherein cleavage of the core bond is in close temporal proximity with formation of a bicyclic intermediate. The bicyclic

Figure 1



Vedejs (1975)[4]





Corey (1977)[5]

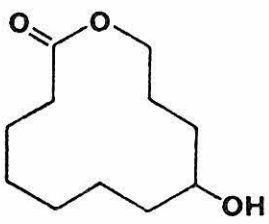
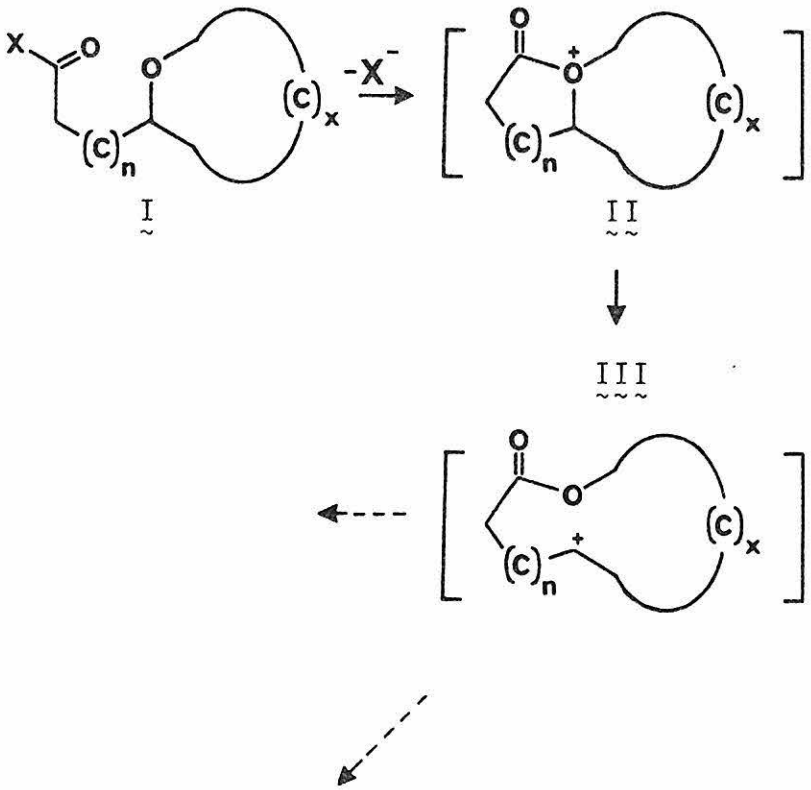


Figure 2

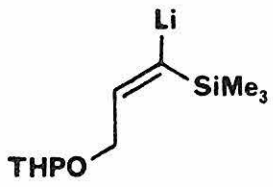


nature of the strategy is readily recognized upon consideration of the reactive intermediates, or transition states, for these processes.

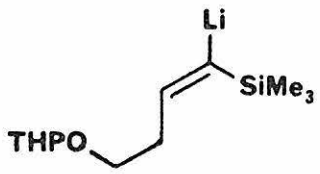
The well known ability of acyl halides (in the presence of suitable catalysts) to cleave aliphatic ethers suggests that the reaction schematized in Figure 2 may be of practical value for the preparation of medium to large ring lactones.[6,7] It is expected that activation of a suitably designed acylium ion precursor (I) will afford the acyl oxonium ion II, and this intermediate will fragment via core bond cleavage to afford lactone III. Of course the resultant cation (III) must be of such a design that subsequent reactions are well controlled. Furthermore, starting material I must be so designed that the carbon-oxygen bond which constitutes the core bond is selectively cleaved.

The preparation of a simple system for the examination of this concept is illustrated in Figure 3. Alkylation of 2-chlorotetrahydrofuran and 2-chlorotetrahydropyran with the readily available[8] α-lithio silanes 1 and 2 will provide, after hydrogenation of the olefin and oxidation of the alcohol function, the carboxylic acids 3a-6a. Two methods can be examined for the activation of these acids. The first method would entail the conversion of these acids to the acyl chlorides (3b-6b) and treatment of these chlorides with either $SnCl_4$ or $ZnCl_2$. Alternatively,

Figure 3



1



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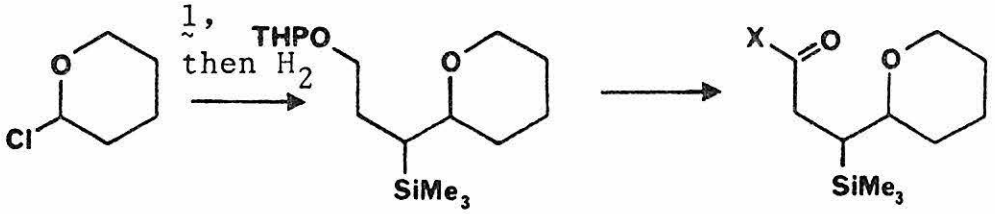
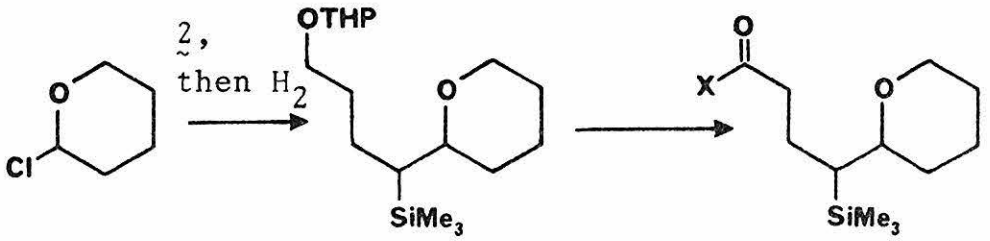
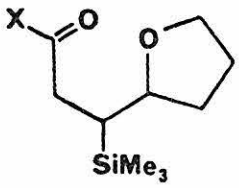


3a,b,c.



4a,b,c.



5a,b,c.

6a,b,c.

3-6,a: x = -OH.

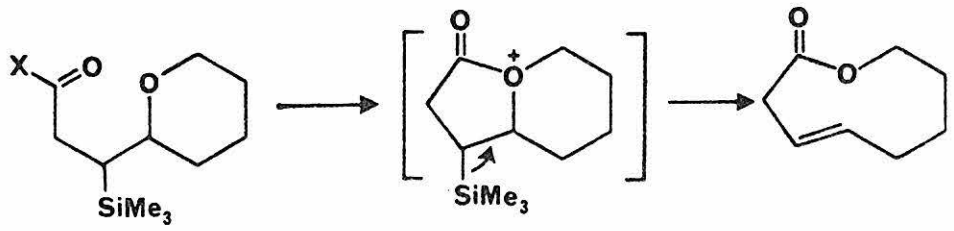
b: x = -Cl.

c: x = -S-t-Bu.

these chlorides can be converted to tert-butyl thiolate esters (3c-6c) which can be activated by treatment with thiophilic transition metal ions [i.e. Hg(II), Ag(I)] after the method of Masamune.[9] Either method of activation is expected to initiate the reactions illustrated in Figure 4. The intermediate acyl oxonium ions obtained from these molecules will fragment to provide the unsaturated lactones 7-10. This expectation is based upon the many examples of cleavage of mixed ethers by acetyl chloride wherein the alkyl-oxygen bond cleaved is that which affords the most stable cation.[5] The ability of silicon-carbon bonds to stabilize carbonium ions in an adjacent position[10] further increases the probability of core bond cleavage. The formation of olefin by carbon-silicon bond scission is analogous to the acid catalysed elimination of β-alkoxy silanes to afford carbon-carbon double bonds.[10]

It is proposed that an investigation of the above reaction be undertaken in an effort to reduce to practice the concept illustrated in Figure 2. While the concept is not necessarily restricted to medium rings, the method appears particularly well suited to the synthesis of eight and nine membered ring lactones, both of which are notoriously difficult to obtain by direct lactonization.

Figure 4



3b or 3c

7

Similarly:

4b or 4c → 8

5b or 5c → 9

6b or 6c → 10

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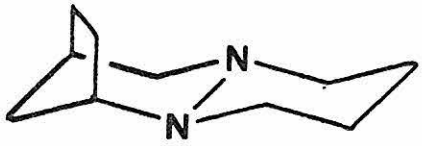
PROPOSITION 4

(Two types of experiments designed to detect special differences in the nature of carbanions next to heteroatoms as compared to carbanions next to methylene units are described. The limitations on the conclusions which may be drawn from such experiments are discussed.)

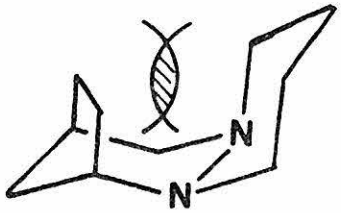
Based upon the consideration of potential energy surfaces calculable by the application of the quantum mechanical theory of matter, it has been suggested by Wolfe that "When electron pairs or polar bonds are placed on adjacent pyramidal atoms, syn- or anti-periplanar orientations are disfavored energetically with respect to that structure which contains the maximum number of gauche interactions."[1] In a less general statement, founded in similar logic, Lehn and Wipff state that "a C-H bond anti-periplanar to an electronic lone pair on an α-heteroatom should be much less acidic (and the corresponding carbanion much less stable) than its gauche rotamer."[2]

It would seem reasonable to ask what experimental evidence is available which will prove the validity of these statements. Further reflection, however, reveals that neither of these statements is of sufficient rigor that it might be proven or disproven by experiment. This is because the contribution of a lone pair-lone pair interaction to the total energy of a molecule cannot be

rigorously separated from the contributions of other electronic and steric effects upon the total energy of that molecule. As an example, consider the two conformations of the diazadecalin shown here (i, ii). While the conformation shown in ii certainly contains more gauche lone



i



ii

pair interactions than does i, it seems highly improbable that i is disfavored energetically with respect to ii. To the extent that lone pair-lone pair or polar bond-lone pair interactions cannot be separated from the other contributions to the relative stabilities of two molecules, the statements quoted in the opening paragraph appear to lack meaning.

While it would seem that absolute proof for those statements cannot be obtained, many observations may be cited which lend credence to the conclusions of Wolfe. Thus the preference for the gauche conformation in dimethoxymethane,[3] the long recognized preference for axial over equatorial electronegative substituents at the C-1 position of the tetrahydropyran ring,[4] and, conversely, the

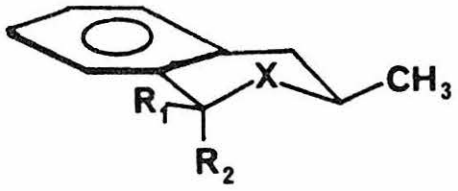
preference for equatorial electropositive substituents[5] at that position, the rapid ozonolysis of β-glycosides under conditions where α-glycosides are inert,[6] and the preference for one axial methyl group in N,N-dimethyl-hexahydro-1,3-diazene[7] and for two axial methyl groups in N,N,N,N-tetramethyl-hexahydrotetrazene[8] are all indicative of the special nature of molecular orbitals on nuclei adjacent to heteroatoms. But these observations are only given significance when compared to similar systems wherein the heteroatom is replaced by a carbon atom (usually methylene will suffice). For example, the preference of a chlorine atom for the axial position in 2-chlorotetrahydropyran is meaningful only because it is known that the equatorial conformer of chlorocyclohexane is more stable than the axial.

For the case of carbanions next to heteratoms, however, even such limited support is not available. Eliel, et. al., have found that deprotonation of conformationally fixed meta-dithiane and subsequent deuteration results in the isolation of only the equatorially deuterated isomer.[9] In addition, the same group discovered that the equatorially oriented 2-alkyl-1,3-dithianes deprotonate more slowly than the isomeric axially alkylated analogs. On a different front, Corey has shown that decarboxylation of optically active α-sulfonyl carboxylates occurs with 100% retention.[10] Also, Ireland et. al. have observed that

reduction of 2-chlorotetrahydrofuranyl substrates by lithium metal in liquid ammonia generates a greater proportion of the product arising by protonation of the (presumably intermediate) carbanion than does reduction of 2-chlorotetrahydropyranyl analogues.[11]

While it is tempting to interpret each of the above experimental observations in terms of current theories on the configurationally dependent stabilities of carbanions adjacent to heteroatoms, to do so would be meaningless, because of the possibility that additional factors may influence the outcome of these experiments. In fact, only in cases where the inversion barrier is significantly greater than the transition state energy for subsequent reactions will product analysis allow an inference to be made concerning the relative stabilities of carbanions adjacent to heteroatoms. These observations therefore are not of use in deciding what effects a heteroatom has upon a carbanion.

Two alternative methods which will provide suggestive evidence of the effect of α-heteroatoms upon carbanions are proposed here. First, consider the base catalysed cleavage of the benzyltrimethysilane congeners Ia and Ie. Eaborn, et. al., have determined, by analysing the effect of substituents upon the rate of "desilylation" of benzyltrimethylsilanes, that substantial negative charge is developed upon the benzylic carbon in the transition



Ia, X=-O-, R_1=-H, R_2=-TMS.

Ie, X=-O-, R_1=-TMS, R_2=-H.

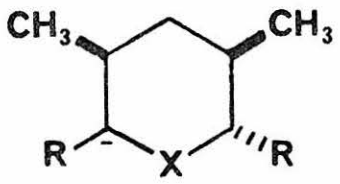
IIa, X=-CH_2-, R_1=-H, R_2=-TMS.

IIe, X=-CH_2-, R_1=-TMS, R_2=-H.

state for these reactions.[12] A similar effect was found in the reactions of phenyltrimethylsilanes, and Eaborn used this phenomenon to obtain evidence upon the relative stabilities of the 3- and 4-carbanions in 1,2-dihydro-benzocyclobutene. Focusing attention on the effect of the heteroatom in I, it seems likely that base catalysed cleavage of Ia, where the incipient "carbanion" is destabilized by the antiperiplanar lone pair on oxygen, will be slower than cleavage of the equatorial isomer, Ie, where the carbanion is probably stabilized, to some extent, by the inductive effect of oxygen.[2] However, other factors will be involved in the rate determining step. In particular, overlap of the incipient "carbanion" with the aromatic ring will be better for isomer Ia than Ie, and the effect on the rate of reaction will be opposite to that expected due to the heteroatom. Other more obscure effects will also play a role in this rate change. The total magnitude of these effects may be estimated by a

a comparison of the relative rates of cleavage of IIa and IIe. The difference in the rate of reaction of IIa and IIe will depend on steric and electronic factors which, in the simplest analysis, may be assumed to be equivalent to the factors which contribute, in addition to the effects (both steric and electronic) of the oxygen atom, to the difference in the rates of reaction of Ia and Ie. Based on this assumption, it is suggested that the difference in the rate of reaction of Ia compared to IIa will be due to the difference in stability of a carbanion antiperiplanar (app) to a lone pair, as compared to a carbanion app to a C-H bond. Similar conclusions could be drawn concerning Ie and IIe.

The discussion above illustrates the complications which accrue in the attempt to determine, by a kinetic analysis, the effect of a α-heteroatom upon a carbanion. As a less complicated approach to this problem it is proposed to generate the anions III, IV, and V and to examine



III, X=-SO_2-, R=H, CH_3

IV, X=-SO-, R=H, CH_3

V, X=-$\ddot{N}$-, R=H, CH_3

the NMR spectrum of each one, in order to determine the preferred orientation of the carbanion lone pair in each. In these experiments, several solvents and bases should be utilized, in an effort to evaluate the effect of the cation and the effect of differential solvation upon the two possible epimers. The results could be compared to the observations of Glaze and Selman, whose investigations indicate a preference for the equatorially oriented carbanion in cyclohexyl systems.[13]

The above experiments cannot provide rigorous proof of the alleged conformationally dependent effect of heteroatoms upon carbanions,[2] but they may provide some needed information in this currently rather confusing area.

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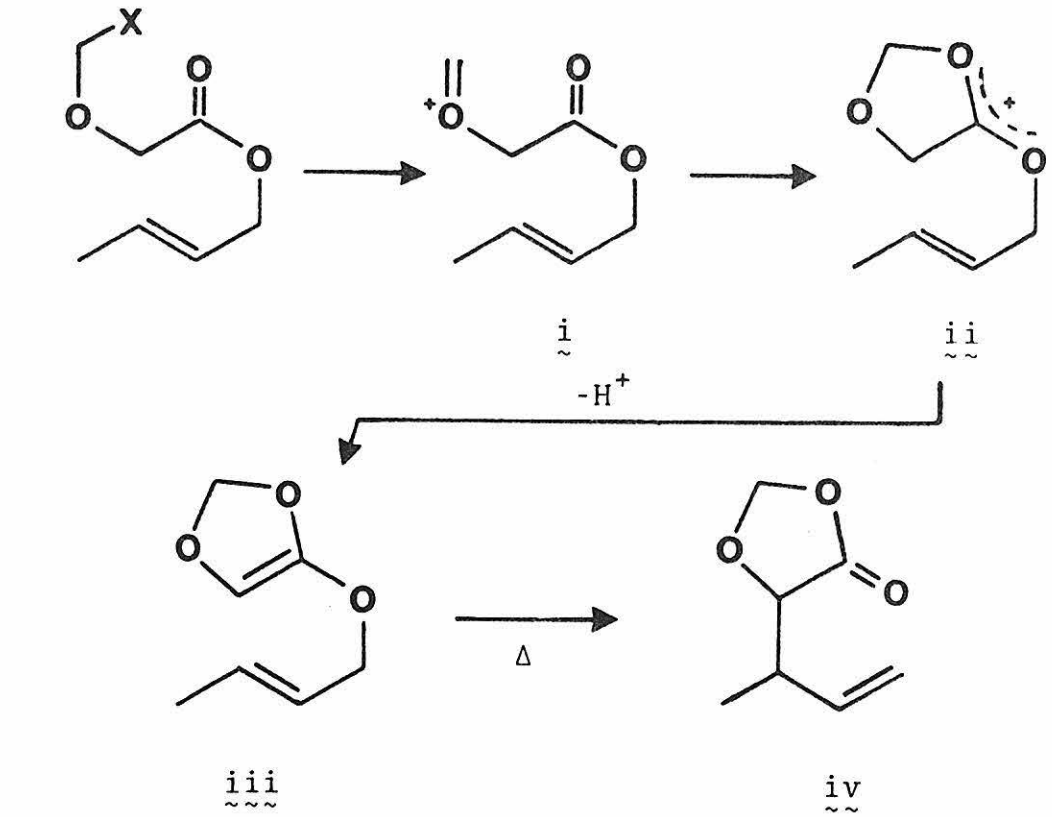
PROPOSITION 5

(A new route to 1,3-dioxolan-4-ones is suggested. The synthesis of verrucarinic acid *via* the Claisen rearrangement of a 4-allyloxy-1,3-dioxole is proposed.)

Consideration of positive and negative aspects concerning the applicability, efficiency and stereospecificity of both the ester enolate Claisen rearrangement[1] and the orthoester[2] syntheses of γ,δ-unsaturated acids suggests that an exploration of alternative methods for the synthesis of *O*-allyl ketene acetals be undertaken. One such method is illustrated in a generalized form in Figure 1. In this plan, generation of the oxocarbonium ion i results, by participation of the allylic ester carbonyl, in formation of the dioxocarbonium ion ii. Deprotonation of ion ii will provide the 4-allyloxy-1,3-dioxole iii. It is expected that this dioxole will undergo thermal rearrangement to provide the (protected) α-hydroxy-γ,δ-unsaturated acid iv. A similar process, resulting in formation of a dihydrodioxin, is also illustrated.

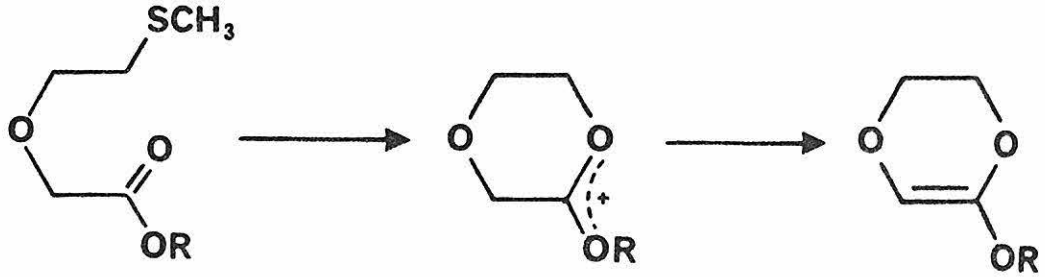
It is proposed that the reactions illustrated in equation 1 and equation 2 be investigated in an attempt to effect the hypothetical transformations suggested in Figure 1. The starting materials 1 and 5 would be prepared from crotyl glycolate. Allyl glycolate has been prepared in good yield from allyl alcohol and glycolic

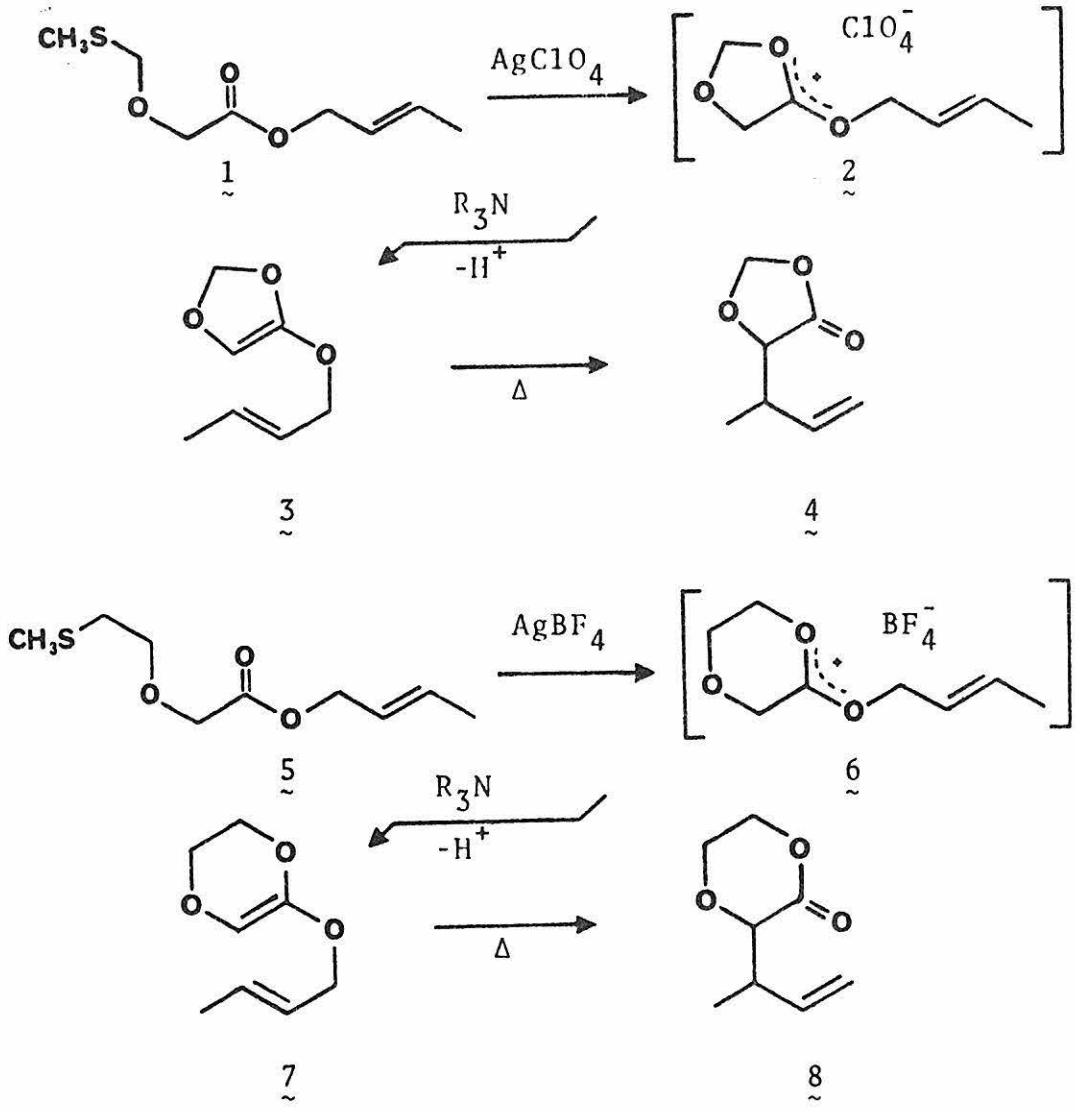
Figure 1



i ii

iii iv

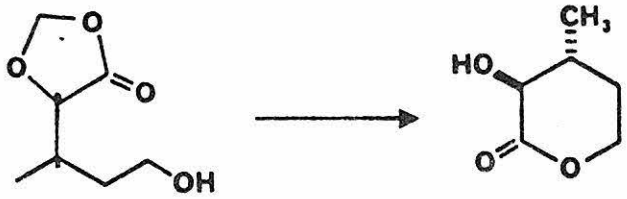




acid.[3] The use of silver fluoroborate or silver perchlorate to provide the dioxocarbonium ions 2 or 6 eliminates the possibility of X^- (Figure 1) entering into displacement reactions.[4] Other methods, such as Hg(II) salts, or even Meerwein salts, should also be effective.

After rearrangement, the resulting 1,3-dioxolan-4-one 4 may be converted, via hydroboration-oxidation, to

the alcohol 9, which, after deprotection, would provide



and/or epi-10.

9 dl·10

verrucarinolactone 10, or its isomer. The availability of spectral data for verrucarinolactone[5] would allow verification of the transition state geometry attained in the rearrangement step. Verrucarinic acid occurs in nature in the antibiotics Verrucarin A[5] and Roridin A.[6]

This approach to O-allyl ketene acetals 3 and 7 is attractive because of the mild conditions employed. No acid catalysis is required, as in the orthoester Claisen, and the strong bases necessary for the ester enolate Claisen rearrangement are also not required, because no enolate anion is formed. Furthermore, the ketene acetals 3 and 7 can be generated with only one possible geometry. Thus the reaction promises to afford single diastereomers of the rearrangement products.

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