THE TOTAL SYNTHESIS OF THE ENANTIOMER OF LASALOCID A

Thesis by

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To my wife, Mary Ann and my daughter, Victoria

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ABSTRACT

A convergent total synthesis of the enantiomer of the naturally occurring polyether antibiotic Lasalocid A (X-537A) and preliminary results of the biological testing of this compound are reported.

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Chapter 1.

BACKGROUND

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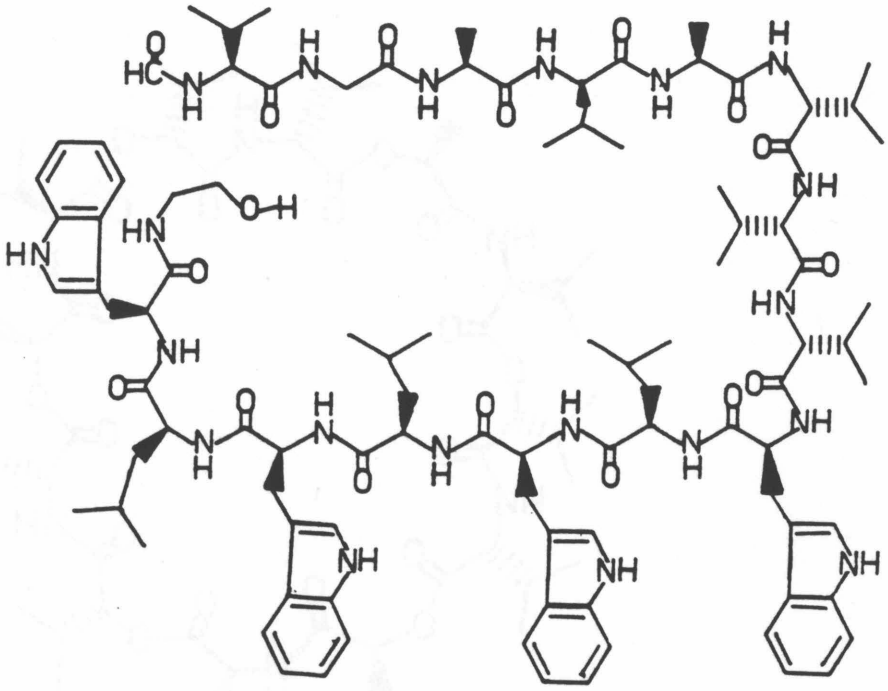
An ionophore was defined, by Pressman[1,2] in 1964, as a molecule that aids the transport of ions through a lipophilic interface through prior complexation. Although the ion transported is most often that of an alkali or alkali earth metal, cases of iron(III), proton and biogenic amines have also been reported.

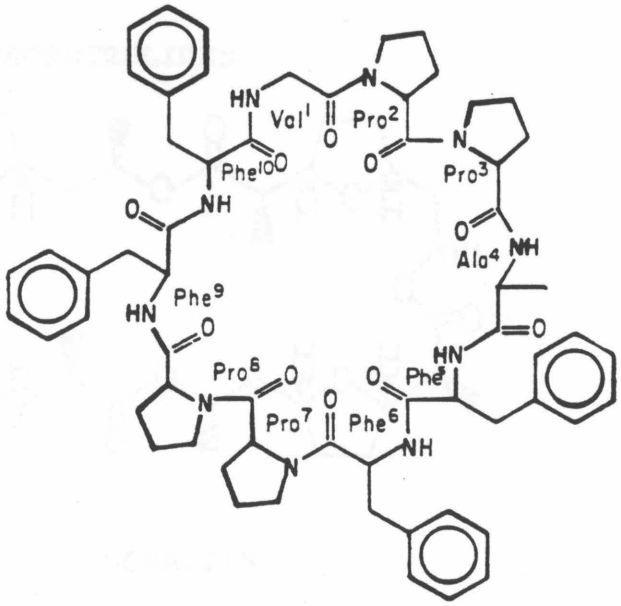
The ionophores are a very broad class of molecules that encompass a wide diversity of structural types and biological properties. A common feature of all ionophores is the presence of heteroatoms. These heteroatoms, usually oxygen or nitrogen, are arranged in such a manner to allow their 3-dimensional inward orientation in the proper geometry to complex the ion, and the outward orientation of the ionophore's lipophilic substituents. This property allows the ions to appear greasy to the lipophilic interace, and thus their passage is at least partially facilitated through the membrane. Westley has divided the naturally occurring ionophores into four classes based on their structure[3]: 1) peptide ionophores, 2) cyclodepsipeptides, 3) macrotetrolides, and 4) polyether antibiotics. Examples of these classes are shown on the following pages.

The peptide ionophores, such as the gramicidins,[4] consist entirely of a linear or cyclic arrangement of amino acids. The cyclodepsipeptides, of which valinomycin[5] is the best known example, are composed of alternating amino and

PEPTIDE IONOPHORES

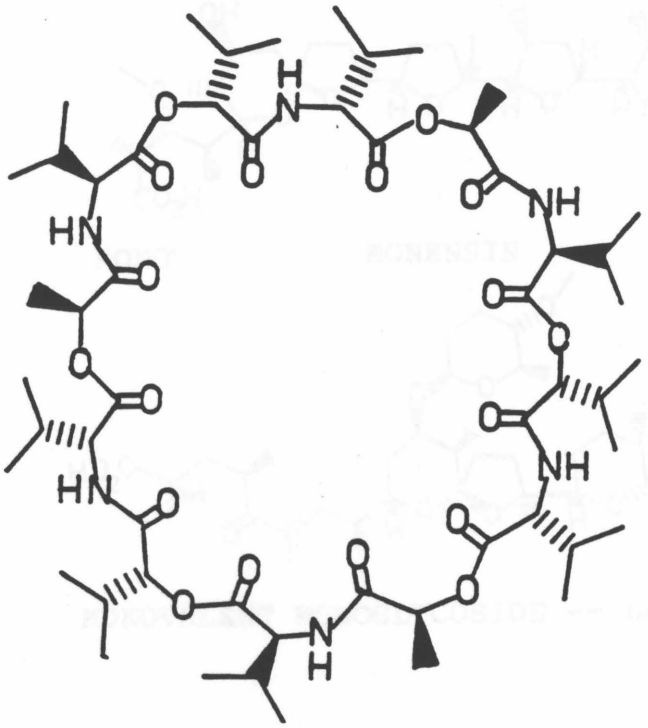


Val-GRAMICIDIN A



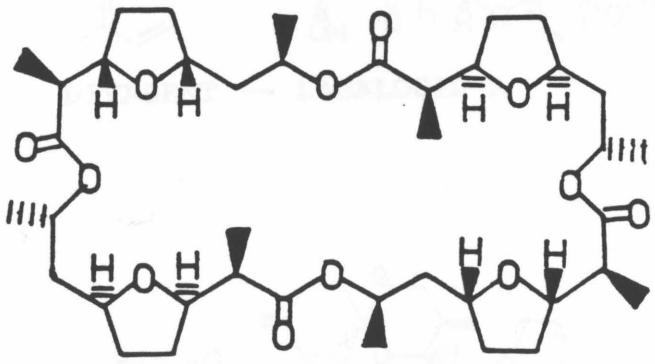
ANTAMANIDE

CYCLODEPSIPEPTIDES



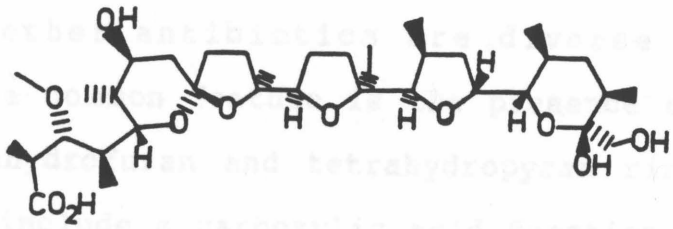
VALINOMYCIN

MACROTETROLIDES

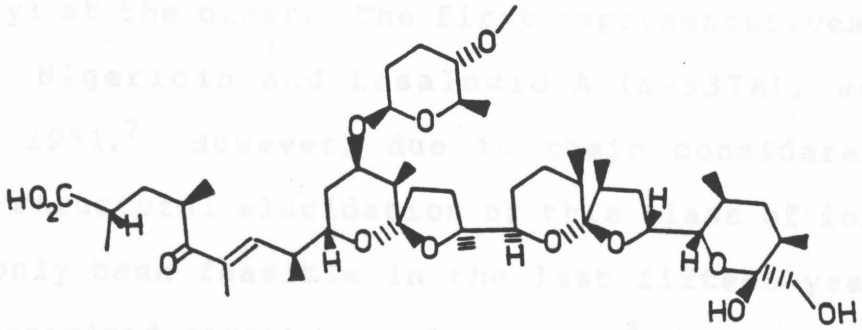


NONACTIN

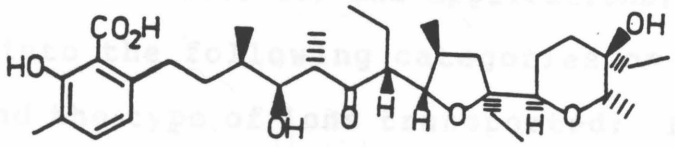
POLYETHER ANTIBIOTICS



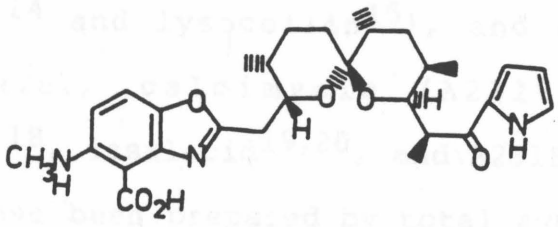
MONOVALENT -- MONENSIN



MONOVALENT MONOGLYCOSIDE -- LENORMYCIN



DIVALENT -- LASALOCID A



DIVALENT PYRROLE ETHERS -- CALCIMYCIN

hydroxy acid units. The macrotetrolides, such as nonactin, are meso compounds consisting of an alternating sequence of (+) and (-) tetrahydrofuranyl hydroxy acids.

The polyether antibiotics are diverse groups of compounds whose common feature is the presence of a linear chain of tetrahydrofuran and tetrahydropyran ring systems. These systems include a carboxylic acid function at one end and a hydroxyl at the other. The first representatives of this class, Nigericin and Lasalocid A (X-537A), were isolated in 1951.[7] However, due to their considerable complexity, structural elucidation of this class of ionophores has only been feasible in the last fifteen years. The X-ray determined structures of monensin[8] and Lasalocid A[9] were not published until 1967 and 1970, respectively. Although a relatively new class, it has been growing rapidly in both numbers (now over 57) and applications, and has been subdivided into the following categories on the basis of structure and the type of ions transported: 1) monovalent polyethers (i.e. monensin,[8], nigericin[10] and salinomycin[11]); 2) monovalent monoglycoside polyethers (i.e. lenormycin[12] and antibiotic A-204A[13]); 3) divalent polyethers (i.e., the lasalocids[14] and lysocellin[15]), and 4) divalent pyrrole ethers (i.e., calcimycin (A23187)[16]). Of these monensin[17,18], lasalocid[19,20], and A23187,[21] salinomycin and narasin, have been prepared by total synthesis.

Pressman[22] has proposed an alternate classification that is based on the ionophore's mode of ion transport: 1) neutral ionophores, such as valinomycin; 2) carboxylic ionophores like monensin and lasalocid A; and 3) channel forming quasi-ionophores such as alamethecin, which simply cause holes in the membrane and thus facilitate the diffusion of ions.

Of all the classes of ionophores, the polyethers have shown the greatest promise of utility. The only commercial application of their biological activity has been the marketing of monensin in 1971 and Lasalocid A (X-537A) in 1976[3] as coccidiostats and feed utilization enhancers. The polyether antibiotics also show cardiotonic properties[23,24] which make them very interesting from a pharmacological standpoint.

The effect of the polyether antibiotics on heart action has been studied extensively by Pressman et al.[22,25] Pressman first demonstrated that lasalocid A stimulates isolated rabbit heart and then that a single dose (2mg/kg) of lasalocid A administrated intravenously to an intact sedated dog causes: 1) a two to three fold increase in contractility, i.e. an "inotropic" effect; 2) a doubling of cardiac output; 3) a small rise in aortic pressure and heart rate; 4) a drop in peripheral resistance; and 5) a large decrease in coronary resistance leading to as much as a tenfold increase in blood flow through the coronary arteries

of the left ventricle[25]. Since oxygen consumption remains virtually constant, except for a small transient initial rise, the latter two effects translate into a large increase in the pumping efficiency of the heart.

The stimulation of the pumping characteristics of the heart without dramatic changes in pressure or rate may be useful during pathological cardiovascular conditions, such as those that occur in acute pump failure or shock. The latter use was confirmed with dogs that had been sent into shock by incision and ligation of their intestines.[25] Increasing the efficiency of the heart may prove valuable under conditions of limited oxygen supply, such as occurs in coronary vessel disease (often accompanied by angina) or in selected regions of the heart following an infarction. These effects are in sharp contrast to those of the catecholamines (i.e. epinephrine) which although they increase cardiac work also increase oxygen consumption, which is undesirable under conditions with accompanying ischemia. This difference is interesting since lasalocid A has been shown to transport catecholamines[26], and its vaseodilatory effects are inhibited by β-blockers. This inhibition indicates the participation of catecholamines.[27] However, since the other physiological properties of lasalocid A are not affected, the mechanism of its action must be multi-pronged.

The initial driving force for the testing of lasalocid A was its ability to complex and transport Ca^{2+} and biogenic amines. It was this ability that formed the basis of the initial explanation of lasalocid A's physiological effects. This has proven to be, at best, an oversimplification since ionophores that cannot transport Ca^{2+} or catecholamines were shown to be more effective at bringing about many of the same effects as lasalocid A. Also, the Ca^{2+} specific ionophore A23187's *in vitro* effects could only be sporadically reproduced in anesthetized dogs. Since the monovalent ionophores (i.e., monensin, X-204) are more ion specific and their various effects can be differentiated on the basis of dosage, the prevailing opinion is that they are more suitable candidates for pharmacological development.[28]

Although the mode of action of the polyether antibiotics is not clearly understood, it is believed that the monovalent ionophores cause an influx of Na^{+} into the cells activating either a passive release of Ca^{2+} from sequestered pools in the cell or the influx of extracellular Ca^{2+} via an exchange diffusion carrier, the so called "Baker pump".[29,30] An increase in intracellular Ca^{2+} is also postulated as the mode of action of the cardiac glycosides (i.e., digitalis) which are believed to increase intracellular Na^{+} by blocking the cells K^{+}-Na^{+} pump.[31] Since Ca^{2+} specific ionophores can mimic physiological Ca^{2+} mediated cell activation by increasing the permeability of

the cell's membrane to extracellular Ca^{2+}, and lasalocid A is able to transport both Na^{+} and Ca^{2+}, its mode of action may be a combination of the above pathways.

Monensin, a highly selective monovalent ionophore, has been shown to cause the release of catecholamines from adrenal cells in the absence of extracellular Ca^{2+}.[29] This result indicates that an ionophore need not be able to transport catecholamines in order to cause their release. Monensin is believed to cause this release by freeing intracellular Ca^{2+}, by increasing intracellular Na^{+}, which in turn stimulates the release of catecholamines. Again, this mechanism is possible for lasalocid A as well as the more direct pathway of increasing membrane permeability to catecholamines.

Lasalocid A's ability to transport Ca^{2+} also lead to studies on its effect on numerous other Ca^{2+} dependent processes. In addition to stimulating the release of catecholamines[32] and its cardiotonic properties, lasalocid A has been found to modify insulin release,[33] inhibit Ca^{2+} uptake by brain mitochondria in cats and in mice,[34] and stimulate the release of acetyl choline.[35] Recent reviews[30,36-37] of the physiological properties of the various polyether antibiotics are available.

The biological importance of the polyether antibiotics has also led to numerous studies into the mechanism of their complexation and decomplexation of ions and their

relationship with cell membranes. The conformations of complexed and "free" ionophores have been studied utilizing their C.D., N.M.R., I.R. and fluorescence spectra both in solutions of various polarity and with membranes of varying phospholipid composition.[38]

These studies have led to the following proposed model. At physiological PH (7.4), the carboxyl function of the ionophores exists in its deprotonated state and is complexed to the polar face of the membrane via the ammonium functionalities present on the membrane face. When a complexable cation O^{m+} comes close enough, complexation begins by the formation of a solvated ion pair. The ionophore now wraps around the cation displacing the molecules of the cation's primary solvation sphere with its internally facing liganding functionalities. The complex thus formed is capable of passively diffusing across the lipophilic interior of the membrane where at the inside interface it can release the cation by the reverse of the complexation procedure. The ionophore is now held on the inside of the membrane and can combine with a different cation I^{n+} and by the above sequence of events transport it to the outside interface and release it. The net result is an exchange of O^{m+} and I^{n+} across the membrane with maintenance of electrical neutrality. Therefore, the polyether antibiotics act as passive exchange carriers, possibly similar to the previously mentioned "Baker pump". Since an

ionophore does not complex and transport all cations equally, the exchange may not be on a one-for-one basis. An example of this is monensin which transports Na^+ in and a mixture of K^+ and H^+ out. The ability to transport protons is very important physiologically. This transport is possible since the protonated ionophore is neutral and favors a conformation similar to that obtained when complexing a cation. This has been demonstrated by the X-ray determined structures of the free acids of monensin[40] and a derivative of lasalocid A.[41]

The above mechanism assumes that the ionophores interact only with the phospholipids of the membrane and not with the membrane imbedded proteins, which compose up to 70% of the membrane. The observed tissue selectivity of the ionophores is, therefore, ascribed to differences in their phospholipid composition. It should be noted that the cation complexing selectivity of the ionophores in bulk solvents is substantially different than the cation transport selectivity observed with membranes. This is thought to be due to two factors; first that the ionophore interacts with the membrane in such a way as to modify its selectivity; second, in order to transport cations, the ionophore must complex and release the cations. Therefore, a fine balance of complexation strength must be obtained in order to transport cations. Too weak a complexation would lead to the cation never forming a tight enough complex to

enter the membrane, while too strong a complexation would diminish the ionophore's ability to release the translocated cation. In light of this, the nature of the ionophores interaction with the membrane both in its "free" form and as a complex assumes an important role in understanding the effects of these compounds.

Lasalocid A, as stated previously, has too wide an activity spectrum to be useful as a therapeutic agent. However, this non-specificity may make it useful as a probe into the importance of its various transporting abilities. One of the most interesting properties of lasalocid A is its ability not only to transport biogenic amines but also to distinguish between the enantiomers of those with asymmetric centers. Lasalocid has been shown to preferentially complex the natural (R) enantiomer.[42] Lasalocid is sufficiently effective at enantiodiscrimination to warrant its being patented as a resolving agent[43] and its marketing as such by Aldrich. It should, therefore, be possible to dissect out the various ion transporting abilities of lasalocid A and elucidate the nature of its interaction with cell membranes by the synthesis of modified versions of this ionophore.

To this end, it was felt that the synthesis of the enantiomer of lasalocid A (enantio-X537A) to study the enantiodependence of its various physiological effects would be a logical first step.

If lasalocid A transports cations by simply forming a lipophilic complex which then diffuses across the membrane, the transport of metal cation and the effects due to this transport should be unchanged with enantio-X537A. However, if the transport involves interaction with membrane proteins or phospholipids, both of which contain asymmetric centers, some alteration of transport and physiological properties should occur. While the transport of biogenic amines that lack an asymmetric center (i.e., dopamine) should behave similar to that of metal cations, the transport of those with asymmetric centers should be affected to a noticeable extent. Since lasalocid A complexes preferentially with the natural R enantiomer of these amines, enantio-X537A should not complex these amines as well. Therefore, the effects elicited by the transport of these amines should be accentuated or reduced.

A synthesis of enantio-X537A was designed and sufficient quantities of enantio-X537A prepared to allow for *in vitro* and *in vivo* testing of its properties. The synthesis and the preliminary results of the tests are presented in the next section.

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Chapter 2.

THE TOTAL SYNTHESIS OF POLYETHER ANTIBIOTICS. THE SYNTHESIS OF THE ENANTIOMER OF LASALOCID A (X-537A)

The Total Synthesis of Polyether Antibiotics. The Synthesis of the Enantiomer of Lasalocid A (X-537A).[1]

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Contribution No. 6859 from the Chemical Laboratories, California Institute of Technology, Pasadena, California 91125

Abstract: A convergent total synthesis of the enantiomer of Lasalocid A (X-537A) and the preliminary results of the biological testing of this compound are reported.

In a previous report[3] from these laboratories, the total synthesis of the antibiotic ionophore lasalocid A was presented. The basic design of this synthesis was predicated on a desire to define a synthetic strategy that could be applied to the construction of other polyether antibiotics, both natural and non-natural. An example of the use of this strategy for the construction of a synthetic lasalocid analog--enantio-X537A--is reported here.

Lasalocid A is among the least ion selective of the polyether ionophores, for it complexes and transports the cations of all alkali/alkaline earth metals, the lanthanides, thallium and organic amines. The ability of lasalocid A to transport Ca^{2+} and biogenic amines led to numerous studies of its physiological effects.[4] Among many other effects lasalocid A was shown to be a powerful cardiotonic agent.[5] These effects were initially attributed to the transport of Ca^{2+} and biogenic amines; however, later evidence proved that hypothesis to be, at best, overly simplistic. The contrary evidence arose from studies involving polyether antibiotics which were able to transport neither Ca^{2+} nor biogenic amines (i.e., monensin and antibiotic X-204).[5] These compounds were found to elicit many of the same effects as lasalocid A. The physiological effects of the polyether antibiotics are now believed to be primarily due to Ca^{2+} and biogenic amine release induced by disruption of the Na^+/K^+ gradient across the cell

membrane.[6,7] The polyether antibiotics are thought to bring about this translocation of cations by acting as passive exchange diffusion carriers.[8]

The potential importance of the physiological properties of the polyether antibiotics has generated considerable interest in the synthesis of their non-natural analogs.[9] Such analogs may be designed to exhibit specific properties or to provide information concerning the mechanism by which these antibiotics act. An analog that would test the dependence of the physiological activity of the polyether antibiotics on their chirality would be the enantiomer of the natural product.

If the transport of cations across a membrane by lasalocid A is affected only by the gross physical properties (ρ, viscosity, μ) of that membrane, <u>enantio-X537A</u> should exhibit properties identical to those of the natural ionophore. Since lasalocid A preferentially complexes the natural R enantiomer of asymmetric biogenic amines,[10] <u>enantio-X537A</u> should not complex these amines as well. Therefore, the activity of <u>enantio-X537A</u> should reflect this diminished capacity for natural amine complexation and allow a determination of the contribution the transport of these amines makes to the overall effect of lasalocid A. Therefore, a synthesis of the enantiomer of lasalocid A (<u>enantio X-537A</u>) was devised and sufficient material

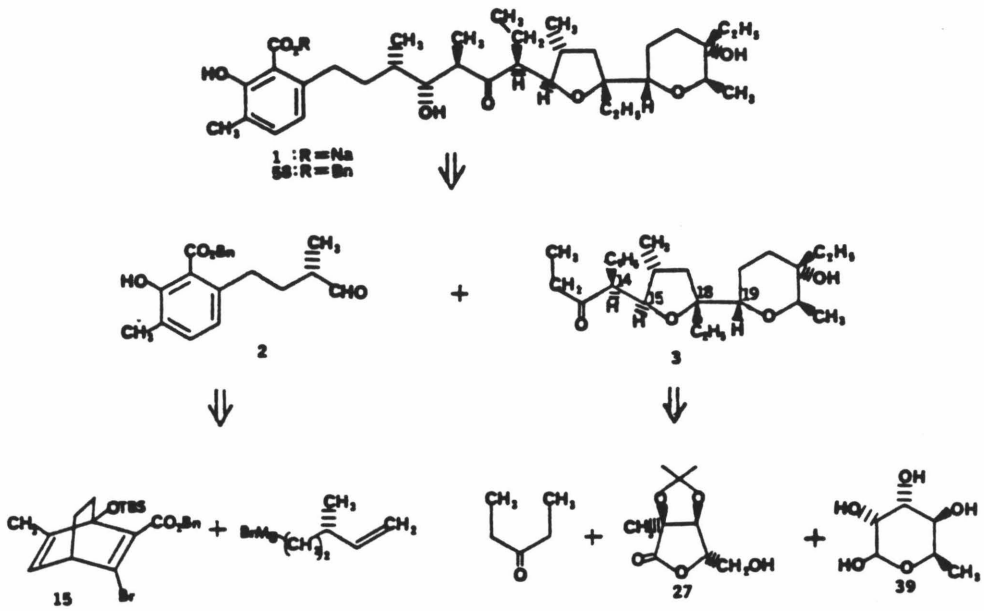
prepared to allow for comprehensive testing of the associated physiological properties.

The critical feature of the current synthetic scheme was the development of syntheses for the enantiomers of key subunits used in the earlier synthesis[3] of the natural ionophore. While it was expected that much of the previously developed synthetic strategy,[3] could be utilized, efforts were made to improve and modify the technology involved so as to provide an even more efficient overall process.

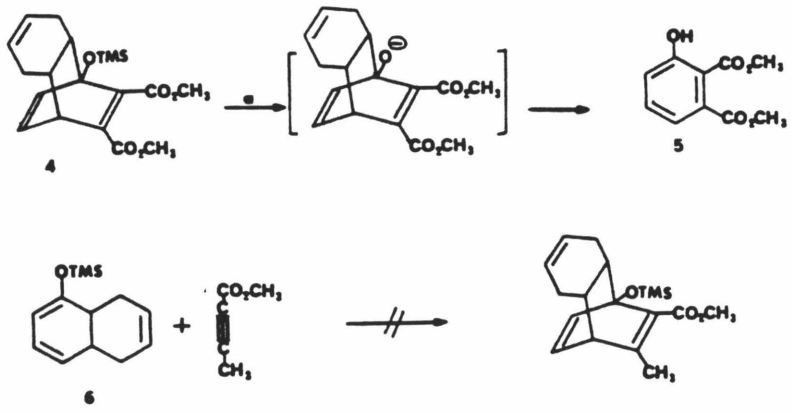
A structural feature common to the polyether antibiotics is the aldol-type linkage, and this assemblage can be used antithetically to divide enantio-X537A into the aldehyde 2 and the ketone 3 (Scheme I). Technology used in the synthesis of lasalocid A[3] that re-established this aldol-type linkage was then available for the condensation of "enantio left-aldehyde" 2 and "enantio right-half ketone" 3.

The pivotal point of this synthesis of "enantio right-half ketone" 3 is the use of ester enolate Claisen rearrangements for the formation of the C(14)-C(15) and C(18)-C(19) bonds. This convergent building block approach allows the use of preformed tetrahydrofuranoid and tetrahydropyranoid intermediates derived from readily available monosaccharides.

SCHEME I



SCHEME II



(a) NBu_4NF, THF, r.t.

The synthesis of the "left-half aldehyde" 2 was envisaged as proceeding through the addition of an appropriate asymmetric side chain to a non-aromatic precursor, and then the conversion of this adduct into the desired tetrasubstituted aromatic moiety. Ideally, this method would allow for the preparation of further analogs by simple variation of the precursors utilized. The route used to prepare left-half aldehyde in the synthesis of the natural ionophore[3] suffered from several shortcomings, the most serious of which was its length. The length of the previous route made it less flexible than desired and would make a relatively large throughput of material difficult. These problems made this first route unattractive for the current work, and a new, more flexible and efficient synthesis for the enantio-left half aldehyde 2 was developed.

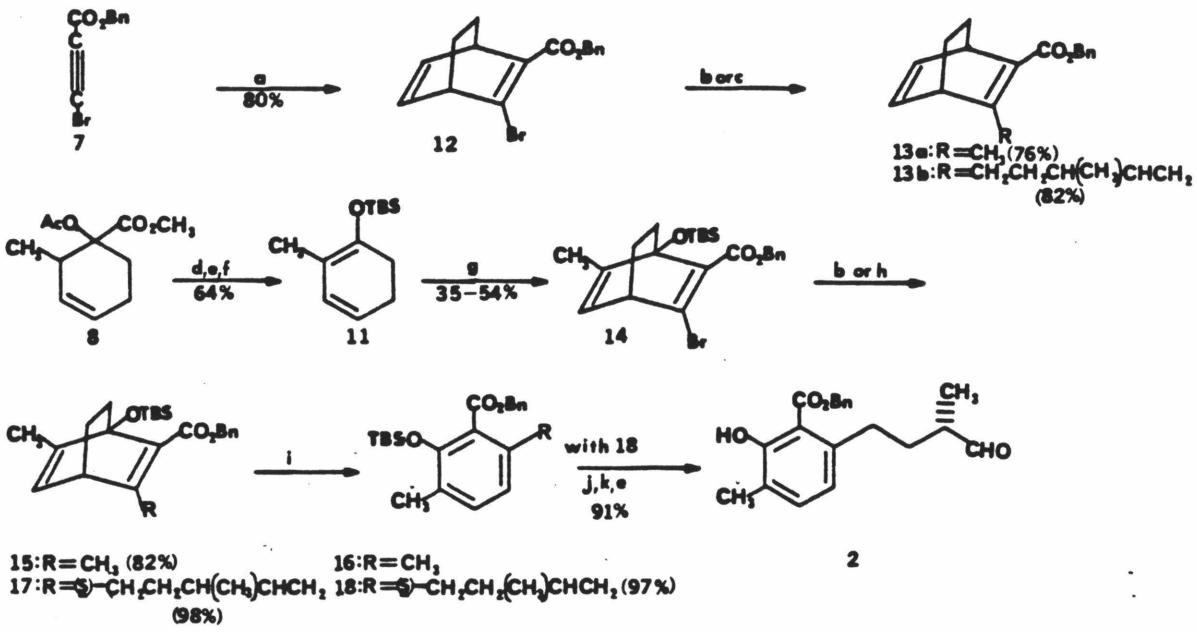
Synthesis of Enantio-Left Half 2. The genesis of the approach used to prepare aldehyde 2 was a report by Grimme and Papies that the cycloadduct 4 upon treatment with tetra n-butylammonium fluoride (TBAF) gave the aromatic ester 5 by facile alkoxide accelerated cycloreversion at room temperature[11] (Scheme II). In order to make direct usage of this reaction, the synthesis of the aldehyde 2 would require a 3-alkyl propiolate. However, Grimme also reported that the Diels-Alder cycloaddition of the diene 6 and methyl 3-butynoate could not be realized.[12]

The preparation of the aldehyde **2** by such a strategy would therefore require: 1) a dienophile that would undergo the desired Diels-Alder condensation and allow for the subsequent attachment of the alkyl side chain; and 2) a 2-methyl-1-silyloxy-1,3-cyclohexadiene derivative as the diene.

Benzyl 3-bromopropiolate **7** appeared to be a suitable candidate for the dienophile. The methyl ester has been reported as a good dienophile[13] and the bromo functionality would provide the necessary means to attach the alkyl chain. The ester **7** was prepared from the known 3-bromopropiolic acid,[14] and used in a cycloaddition with 1,3-cyclohexadiene. The model bicycloadduct **12** formed was used to test the viability of the subsequent addition of the alkyl side chain. The presence of an absorption band for the α,β unsaturated ester at λ_{max}=248 nm in the ultraviolet spectrum of this adduct **12** indicated that conjugate addition to this molecule should be possible, and indeed it was found that the bromo substituent was readily replaced when the bicycloadduct **12** was treated with homoalkylcuprate or copper catalysed Grignard reagents (**Scheme III**).

Although the preparation of the desired diene initially appeared to be a simple matter, this did not prove to be the case in practice. Treatment of 2 methylcyclohex-2-en-1-one under a variety of conditions[15,16,17,18] led to the 3-methyl-2-oxy-1,3-cyclohexadiene and/or intractable tars.

Scheme III



(a) 1,3 cyclohexadiene, PhH, reflux; (b) Me_2CuLi, ether, 0°C; (c) CH_2=CHCH(CH_3)CH_2CH_2MgBr/CuBr-DMS, ether, r.t.; (d) $LiAlH_4$, ether, r.t.; (e) $NaIO_4$, MeOH/H_2O, r.t.; (f) KH/TBSCl, THF, r.t.; (g) **6**:**10** = 1:1.3, r.t.; (h) (S) CH_2 = CHCH(CH_3)CH_2CH_2MgBr/$Cu(OAc)_2$, ether, 0°C; (i) 160°C, sealed tube; (j) nBu_4NF, THF, r.t.; (k) OsO_4/NMO, THF/H_2O, r.t.

Only minor amounts (<5%) of the desired dienic product could be detected. After the failure of other more direct schemes, a less direct approach was utilized (Scheme III). Hydride reduction of the Diels-Alder adduct of trans-piperylene and methyl 2-acetoxypropenoate 8, and then sodium metaperiodate cleavage of the resulting diol 9 afforded 2-methyl-cyclohex-3-en-1-one 10[19] in good yield. Addition of a solution of this β,γ enone 9 to a suspension of potassium hydride in a THF solution of tert-butylchlorodimethylsilane at room temperature provided the desired diene 11 in excellent yield.[20]

When a mixture of this diene 11 and the dienophile 7 (1:1.3) was allowed to stand at room temperature under an argon atmosphere for 12 h, a moderate yield[21] of the desired 1-silyloxy-bicyclo[2.2.2]octadiene 14 was obtained as the only Diels-Alder cycloadduct detected. The ultraviolet spectrum of this cycloadduct 14 exhibited a complete lack of an absorption band due to the α,β unsaturated ester (λmax 248 nm). This is possibly due to the buttressing effects of the bromine and silyloxy substituents on the carboxylate forcing it out of the plane of the adjacent double bond. While this apparent lack of conjugation cast some doubt on the outcome of the subsequent copper catalysed addition reaction, bromine displacement still proved to be quite facile, for treatment of the cycloadduct 14 with lithiodimethylcuprate afforded the adduct 15 in excellent yield.

The bicyclo[2.2.2]octadiene 15 provided both a means for ascertaining the regiochemistry of the cycloaddition by ^{1}H-NMR spectroscopy. Irradiation of the bridgehead proton led to Nuclear Overhauser Enhancements (N.O.E.'s) of approximately 25% and 10% of the signals due to the lone olefinic proton and the protons of the C - 3 methyl substituent, respectively. No N.O.E. was detected for the benzylic protons of the ester in this experiment.

The bicycloadduct 15 also provided a model compound for testing the cycloreversion reaction. Treatment of a solution of 15 in THF with TBAF led to the deep burgundy color described by Grimme,[11] but no trace of the desired aromatic compound could be detected. In an effort to study the alkoxide assisted cycloreversion directly, the silyl ether of the adduct 15 was cleaved selectively with lithium tetrafluoroborate in acetonitrile and the alkoxide from resulting alcohol formed with potassium hydride. This alkoxide also failed to generate a phenol by cycloreversion even after a period of several days at room temperature; indeed, the only discernable reaction was a slow decomposition of the starting material. Although the reported accelerated cycloreversion could not be realized in this system, pyrolysis the adduct 15 at 160^{o} for 20 h did afford benzyl 3,6-dimethyl-2-silyloxybenzoate 16 in quantitative yield.

The alkyl chain of enantio left half aldehyde 2 was derived from 5-bromo-3S-methyl-1-pentene.[3] Copper(I)-

catalysed addition of the Grignard reagent derived from this bromopentene to the cycloadduct 14 again proceeded smoothly and gave the alkylated product 17 in excellent yield. When this adduct 17 was pyrolysed in a sealed tube at 160° for 22h, an excellent yield of the desired tetrasubstituted aromatic system 18 resulted. The ester 18 had physical and spectral properties (R_f, elemental analysis, ^{1}H-NMR, IR) that were entirely consistent with those of the enantiomeric material derived from natural lasalocid A, except that the optical rotation was equal in magnitude but opposite in sign. Cleavage of the silyl ether of the ester 18 with TBAF, and then osmium tetroxide oxidation of the olefin 19, afforded the diol 20. Treatment of this diol 20 with sodium metaperiodate provided the desired enantio left half aldehyde 2, which exhibited physical and spectral properties (R_f, elemental analysis, ^{1}H-NMR, IR) that were in excellent agreement with those obtained for the aldehyde derived from the natural ionophore.[3] As expected, the optical rotation was equal in magnitude but opposite in sign.

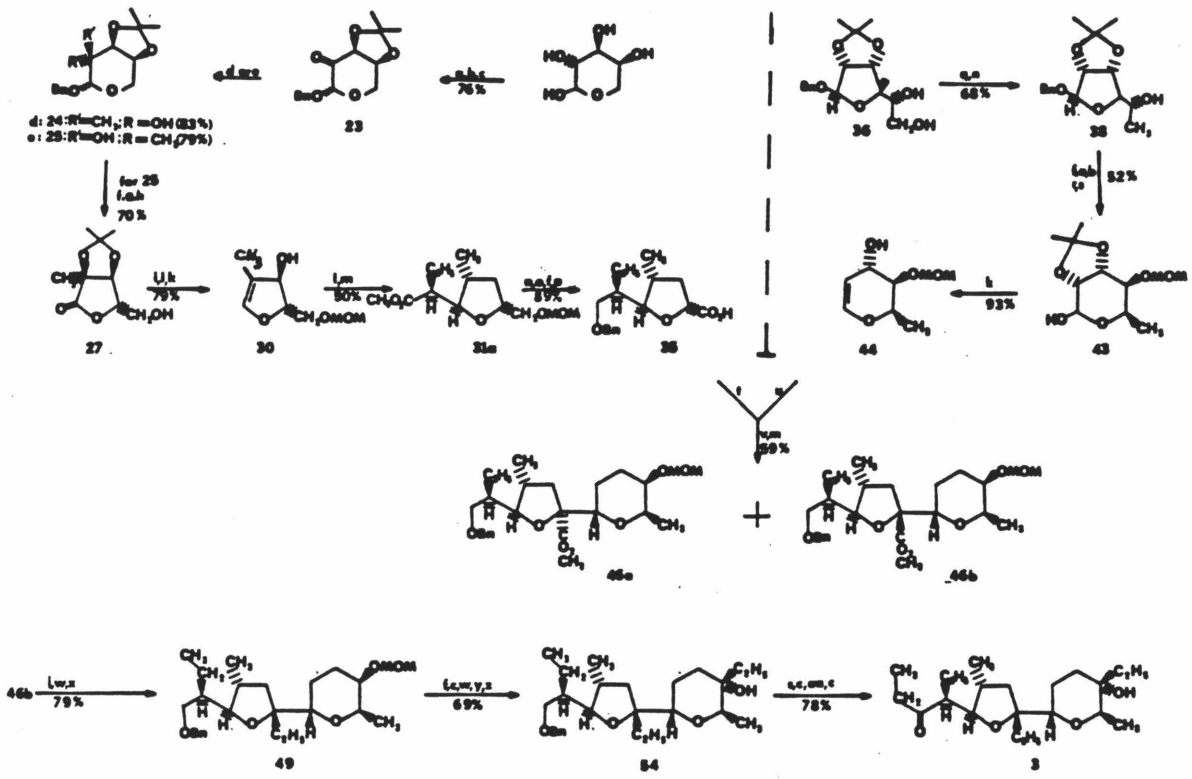
From commercially available starting materials, this new scheme provided a 31% yield of left half aldehyde in 10 steps versus a 7% yield in 14 steps for the scheme used previously.[3] This new scheme is also more convergent and provides for the incorporation of the alkyl side chain only 5 steps from the end versus 11 steps for the previous

scheme.[3]. The above synthetic scheme should not only allow preparation of analogs of the aldehyde 2, but also other substituted benzoates by variation of either the diene component for the Diels-Alder condensation or the Grignard reagent used to introduce the side chain.

Synthesis of Enantio Right Half 3. In order to take advantage of as much of the synthetic methodology and strategy developed for the synthesis of lasalocid A[1] as possible, the carbohydrate derivatives 27 and 39 (Scheme IV) which are enantiomeric to intermediates in the synthesis of lasalocid A[3] were set as initial targets. The lactone 27 is an L-carbohydrate derivative, and as such is not generally readily available. However, the lactone 27 is a 2-C-methyl-L-pentose derivative and a suitable precursor, L-arabinose, is both available and inexpensive. The sugar 39 is 6-deoxy-D-gulose and is a known compound.[22]

The synthesis of the lactone 27 was carried out as shown in Scheme IV. The glycoside 22 was prepared by a modification of the procedure of Fletcher,[23] and the remaining hydroxyl group was oxidized with oxalyl chloride/DMSO in dichloromethane.[24] Due to the anomeric effect, the resultant ketone 23 should exist predominantly in the chair conformation with the benzyloxy substituent axial. Examination of molecular models of this conformer indicate that sterically controlled nucleophilic attack should occur from the α-face. However, addition of methyl

Scheme IV



(a) BnOH/AcCl; 50°; (b) 2,2-Dimethoxymethane/H^+, acetone; (c) Swern; (d) MeMgBr, ether; (e) low halide MeLi, ether, -78°; (f) $H_3{}^+O$; (g) $Br_2/CaCO_3$, H_2O; (h) acetone/H^+; (i) $(CH_3O)_2CH_2/P_2O_5$, CH_2Cl_2; (j) DIBAL-H, ether; (k) $(Me_2N)_3P/CCl_4$, THF; then Li/NH_3; (l) nBuLi (1.0 eq); nPrCOCl; DA, THF/HMPA; TMSCl; ^-OH; CH_2N_2; (m) H_2/50% Pt-c, ethyl acetate; (n) $LiAlH_4$, ether; (o) KH/BnBr, THF; (p) Swern; then Ag_2O/OH, H_2O; (q) NaH/Ts(imid), THF; (r) KH/CH_3OCH_2Cl, THF; (s) Li/NH_3, THF; (t) oxalyl chloride/DMF (cat), benzene; (u) n-BuLi (1.0 eq), THF; (v) LDA, THF; TMSCl; OH; CH_2N_2; (w) $\phi_3P{=}CH_2$, THF; (x) Raney Ni, ethyl acetate; (y) MCPBA, CH_2Cl_2; (z) $LiMe_2Cu$, pentane; (aa) EtMgBr, THF.

magnesium bromide to the ketone **23** occurred exclusively from the β-face and gave the alcohol **24**. However, addition of methyl lithium at -78° gave a 1:8 mixture of the alcohols **24** and **25**, respectively.[25] Molecular mechanics calculations were employed[26] in order to understand better this interesting reversal of face selectivity between the methyl magnesium bromide and the methyl lithium addition. MM2 calculations indicated that the chair conformer with the benzyloxy substituent axial was only 0.8 kcal/mole lower in energy than the alternate chair conformer with the benzyloxy substituent equatorial. Therefore, the face selectivity of the methyllithium addition may simply reflect the distribution of these two chair conformers. Still[27] has suggested that the face selectivity of the addition of methylmagnesium bromide may be the result of the formation of an intermediate in which the carbonyl and glycosidic oxygen of a ketone such as **23** are complexed by magnesium. This complexation is then followed by nucleophilic attack of the organometallic reagent from the face opposite the complexing alkoxyl functionality. This is similar to the mechanism for the addition of Grignard reagents to simple α-alkoxy ketones also proposed by Still.[28]

Hydrolysis of the adduct **25** with aqueous acid removed the benzyl glycoside and acetonide and afforded 2-C-methyl-L-ribose **24** in good yield.[29] Oxidation of the free sugar **26** with excess aqueous bromine and calcium carbonate (1.1 eq)

and then treatment of the resultant calcium salt with sulfuric acid in acetone gave the desired lactone 27. Lactone 27 exhibited physical and spectral properties (m.p., R_f, ^{1}H-NMR, IR, $[\alpha]_D$) consistent with its being enantiomeric with the corresponding intermediate utilized in the synthesis of lasalocid A.[3]

As stated previously, 6-deoxy-D-gulose 39 is a known compound. However, a new, although conceptually similar, route to the sugar 39 was developed (Scheme IV) in order to improve the overall efficiency of the process. Addition of a solution of the diol 36[30] in THF to a mixture of sodium hydride and tosylimidazolide[31] in THF afforded the epoxide 37. Treatment of this epoxide 37 with excess lithium tetrahydridoaluminate in ether led cleanly to the 6-deoxy sugar 38. Hydrolysis of this 6-deoxy sugar 38 removed the benzyl glycoside and the acetonide and afforded 6-deoxy-D-gulose 34 in good yield.

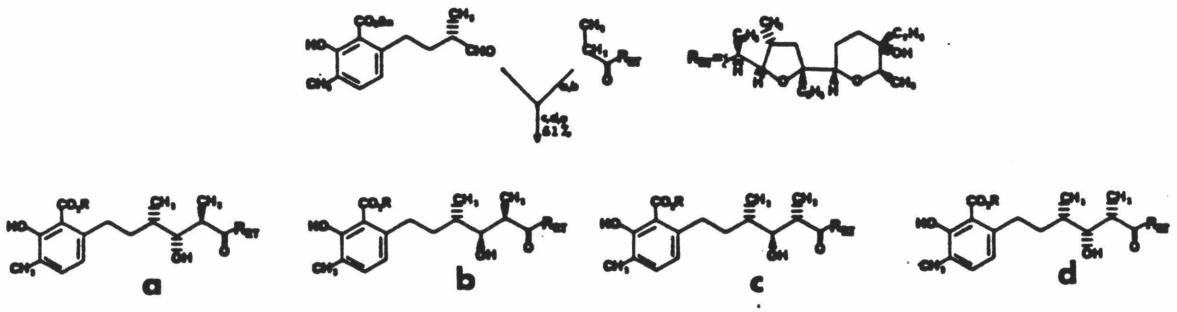
The methodology developed for the synthesis of the natural isomer was applied to the completion of the synthesis of enantio right half 3 with one notable exception as shown in SchemeIV. The enolization of the glycal butanoate utilized in the ester enolate Claisen rearrangement that converted the glycal 30 into the ester 31 was performed at -100° rather than at -78°. This led to an increased yield (67% vs. 54%) of the Claisen products 31a and 31b and to a more favorable ratio of diasteriomers (6:1

vs. 3:1). This reaction could be performed routinely on a 15 mmole scale.

The enantio right half ketone 3 that resulted from the indicated operations (Scheme IV) exhibited physical and spectral properties (R_f, elemental analysis, ^{1}H-NMR, IR) consistent with material derived from Lasalocid A, except that the optical rotation ($[\alpha]_D$ = +23.6° (c=1.705, $CHCl_3$); lit for enantiomer[3], $[\alpha]_D^{24}$ = -19.6° (c=1.02, $CHCl_3$)) is equal in magnitude, but opposite in sign.

Synthesis of Enantio X-537A - Sodium Salt 1. Since the conditions employed for the aldol condensation in the synthesis of lasalocid A[3] gave what were believed to be less than optimum results, this reaction was reinvestigated. These new experiments confirmed the previous results and also led to an improved procedure for the aldol condensation (Scheme V). Reaction of the zinc enolate of 3 with the aldehyde 2 (2:1) in benzene at 0° gave a 64% yield of isolated aldol products (98% based on recovered 3). Chromatographic separation of the diasteriomers gave the four products in a ratio of 61:20:11:7, of which the major component represents a 39% yield of the desired diasteriomer 58a. The benzyl ester 58a and its diasteriomers were separately converted to their corresponding sodium salts as described in the synthesis of lasalocid A.[3] An interesting difference between the ^{1}H-NMR chemical shifts of the

Scheme V



a:b:c:d = 61:20:11:7.

R=	Diasteriomer	δ aromatic H's
Bn	a	6.67; 7.18
	b	6.65; 7.14
	c	6.65; 7.15
	d	6.60; 7.17
H	a	6.43; 6.95
	b	6.67; 7.22
	c	6.69; 7.23
	d	6.63; 7.21
Na	a	6.40; 6.92
	b	6.43; 6.98
	c	6.43; 6.96
	d	6.42; 6.98

(a) LDA (2.05 eq), ØH, 0^{o} C; (b) $ZnCl_2$ (1.1 eq), ether;
(c) H_2/10% Pd-C, ethanol; (d) Na_2CO_3, CH_2Cl_2.

aromatic protons of the desired diasteriomer and the other diasteriomers (Scheme V) has become apparent. The ^{1}H-NMR signals due to aromatic protons of the desired diasteriomer 58a shifted upfield by approximately 0.2 ppm on hydrogenolysis of the benzyl ester, while the signals due to the same protons of the other diasteriomers did not. The shift of the ^{1}H-NMR signals of the aromatic protons of the desired diasteriomer on formation of the acid may be due to a head to tail cyclic conformation with a hydrogen bond between the carboxylic acid and the tertiary hydroxyl group[33]. The lack of this shift on the formation of the acids of the other diasteriomers indicated that the added steric interactions along the backbone in these acids prevents the formation of the cyclic conformation. Although the other diasteriomers should not complex cations as well as enantio-X537A, they do form complexes with Na^+ as indicated by the upfield shift of the ^{1}H-NMR signals due to their aromatic protons on formation of their sodium salts.

This synthesis of enantio-X537A by virtue of its efficiency and convergency has led to the preparation of more than 1 gram of the salt 1, and this fulfilled the objective of preparing sufficient quantities of salt 1 for physiological testing of its properties.

Preliminary results of the biological testing[32] of enantio-X537A indicate that both the cardiotonic and the antimicrobial activity of enantio-X537A are very similar to

those of the natural ionophore. These data indicate that the aforementioned effects are probably due to a passive disruption of inter/intracelular ion gradients. These results are entirely consistent with the model of ionophore mediated ion transport proposed by Painter and Pressman.[8] A detailed account of the biological testing of enantio-X537A will be reported elsewhere.

EXPERIMENTAL SECTION[34]

4-Acetoxy-4-carbomethoxy-3-methylcyclohexene (8).[19] A degassed mixture of 5.0733 g (74.48 mmol), of trans-1,3-pentadiene, 4.6974 g (32.59 mmol) of methyl-2-acetoxypropenoate[35] and 0.4 g of pyrogallol in a sealed evacuated, thick walled Pyrex® ampule was heated to 160° C. After 20 h, the reaction mixture was cooled to room temperature; the ampule was then opened and the excess 1,3 pentadiene was removed under reduced pressure. Flash chromatography of the residue on 500 g of silica gel with 10% ethyl acetate in petroleum ether and then evaporative distillation of the chromatographed material at 110° C (0.5 mmHg) gave 6.71 g (97%) of the adduct 8: evaporative distillation 150° C (8 mmHg); ^{1}H NMR ($CDCl_3$) δ 0.89 and 1.03 (2 doublets, 3H total, J=8 Hz diasteriotopic CH_3's), 2.05 (s, 3H, CH_3, CO), 3.72 (s, 3H, CH_3O), 5.60 (m, 2H, CH=CH).

4-Hydroxy-4-hydroxymethyl-3-methylcyclohexene (9).[19] To a stirred suspension of 4.0 g (105 mmol) of lithium tetrahydridoaluminate in 100 mL of dry ether at 0° C under argon was added a solution of 6.71 g (31.6 mmol) of the ester 8 in 25 mL of dry ether over a period of 15 min. After 1 h, the reaction mixture was cautiously treated with 4.0 mL of water, 4.0 mL of a 15% aqueous NaOH and then 12 mL of water. The resulting suspension was stirred vigorously for 15 min, dried ($MgSO_4$) and filtered. Removal of the

solvent under reduced pressure and flash chromatography of the residue on 200 g of silica gel with 75% ethyl acetate in petroleum ether gave 3.947 g (96%) of the desired diol **9**: evaporative distillation 110° C (5 mm Hg); IR (neat) 3380, 3010, 2975, 2962, 2935, 1450, 1095, 1045, 690 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.93 and 1.05 (2 doublets, 3H-total, J=7.5 Hz, diasteriotopic CH_3's), 3.43 (bs, 2H, CH_2O), 6.63 (m, 2H, CH=CH).

2-methylcyclohex-3-en-1-one (10).[19] To a stirred solution of 3.947 g (30.32 mmol) of the diol **9** in 40 mL of methanol was slowly added a solution of 12 g (56.1 mmol) of sodium metaperiodate in 40 mL of water. The resulting mixture was stirred at room temperature for 1 h then extracted with three 150mL portions of ether . The combined organic extracts were dried ($MgSO_4$) and the solvent was removed under reduced pressure. Flash chromatography of the residue on 150 g of silica gel with 10% ether in petroleum ether and then evaporative distillation of the chromatographed material at 100° C (25 mmHg) gave 2.469 gm (74%) of the desired enone **10**: evaporative distillation 100° C (20 mmHg); ^1H NMR ($CDCl_3$) δ 1.16 (d, 3H, J=7.5 Hz, CH_3), 2.47 (bs, 4H, $=CCH_2CH_2CO$), 2.88 (m, 1H, $CHCH_3$), 5.678 (ABX, 2H, CH=CH).

1-tert-Butyldimethylsilyloxy-2-methyl-1,3-cyclohexadiene (11). To a stirred suspension of 1.74 g (43.5 mmol) of potassium hydride in a solution of 6.502 g (43.1 mmol) of

tert-butylchlorodimethylsilane in 25 mL of THF under argon was added a solution of 1.582 g (14.36 mmol) of the enone **10** in 25 mL dry THF at a rate such that the temperature of the reaction mixture was maintained at less than 35° C. The resulting mixture was stirred at room temperature for 5 min, then diluted to 400 mL with ether and the excess potassium hydride destroyed by the careful addition of 2 mL of water. The organic phase was washed with three 250 mL portions of water, dried ($MgSO_4$) and the solvent removed under reduced pressure. Flash chromatography of the residue on 100 g of silica gel with petroleum ether and then evaporative distillation of the chromatographed material at 100° C (0.5 mmHg) gave 2.888 g (90%) of the desired diene **11**: evaporative distillation 100°C (0.5 mmHg); ^1H NMR ($CDCl_3$) δ 0.14 (s, 6H, $(CH_3)_2Si$), 0.95 (s, 9H, $(CH_3)_3C$), 1.63 (bs, 3H, $CH_3C=$), 2.20 (bs, 4H, CH_2CH_2), 5.07 (m, 1H, $=CHCH_2$), 5.70 (d, 1H, J=6 Hz, $CH=CH-CH_2$).

Benzyl 3-bromopropiolate (7). To a solution of 4.377 g (29.4 mmol) of 3-bromopropiolic acid in 20 mL of benzene was added 7 mL of benzyl alcohol and 20 mg of p-toluenesulfonic acid monohydrate. The flask was then fitted with a Dean-Stark trap and a condensor and the resulting mixture was heated under reflux. After 21 h, the reaction mixture was cooled to room temperature and diluted with 50 mL of ether. The organic phase was then washed with two 50 mL portions of saturated aqueous $NaHCO_3$, dried ($MgSO_4$) and the solvent was

removed under reduced pressure. Chromatography of the residue on 400 g of silica gel with 5% ether in petroleum ether and then evaporative distillation of the chromatographed material at 70° C (0.001 mmHg) gave 5.145 g (73%) of the desired ester 7: evaporative distillation 70° C (0.001 mmHg); IR (neat) 3025, 2200, 1705, 1215, 1000, 740, 695 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.17 (s, 2H, $ArCH_2O$), 7.38 (s, 5H, Ar); Anal. Calcd. for $C_{10}H_7O_2Br$: C 50.24; H 2.95; Br 33.42. Found: C 50.15; H, 3.01; Br 33.51.

3-Bromo-2-carbobenzyloxybicyclo[2.2.2]octadiene(12). A solution of 0.84 mL (0.84 mmol) of 1,3 cyclohexadiene and 0.85 g (0.42 mmol) of benzyl 3-bromopropiolate 7 in 10 mL of dry benzene was heated to reflux under argon. After 5 days, the resulting solution was cooled to room temperature and the solvent was removed under reduced pressure. Column chromatography of the residue on 79 g of silica gel with 4% ethyl acetate in petroleum ether gave 913 mg (80%) of the desired adduct 12 as a white solid: evaporative distillation 70° C (0.005 mmHg); IR ($CHCl_3$) 2950, 1700, 1590, 1265, 1245, 1220, 1070 cm^{-1}; UV (C_6H_{12}) max. 215 nm (19,500, Ar), λ_{max} 248 nm ($\varepsilon \sim 12{,}300$, α,β unsaturated ester); ^1H NMR ($CDCl_3$) δ 1.15-1.70 (m, 4H, CH_2CH_2), 3.86 (m, 1H, CHCBr=), 4.30 (m, 1H, $CHC(CO_2Bn)$=), 5.20 (s, 2H, $ArCH_2O$), 6.27 (m, 2H, CH=CH), 7.35 (bs, 5H, ArH). Anal. Calcd. for $C_{16}H_{15}O_2Br$: C 60.21; H 4.74; Br 25.03. Found: C 60.04; H 4.64; Br 24.97.

2-Carbobenzyloxy-3-methylbicyclo[2.2.2]octadiene (13a). To a stirred suspension of 24 mg (0.59 mmol) of cuprous bromide-dimethyl sulfide complex in 5 mL of dry ether at 0° C under argon was slowly added 0.29mL (0.58mmol) of 2.0M methyllithium in ether. After 15 min, a solution of 119 mg (0.373 mmol) of the β-bromo ester **12** (0.373 mmol) in 5 mL of ether was added and the resulting dark red solution was stirred at 0° C. After 25 min, the reaction mixture was quenched by the addition of 1 mL of water and then diluted to 50 mL with ether. The organic phase was washed successively with two 50 mL portions of saturated aqueous NH_4Cl and one 50 mL portion of brine, dried ($MgSO_4$) and then the solvent was removed under reduced pressure. Column chromatography of the residue on 10 g of silica gel with 5% ethyl acetate in petroleum ether gave 72.1 mg (76%) of the alkylated adduct **13a**: evaporative distillation 60° C (0.005 mmHg); IR ($CHCl_3$) 2970, 1695, 1390, 1355, 1270, 1260, 1075 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.33 (bs, 4H, CH_2CH_2), 2.23 (s, 3H, CH_3), 3.45 (m, 1H, CHC(Me)=), 4.2 (m, 1H, CHC(CO_2Bn)=), 5.17 (s, 2H, $ArCH_2O$), 6.30 (m, 2H, CH=CH), 7.37 (bs, 5H, ArH); Anal. Calcd. for $C_{17}H_{18}O_2$: C 80.24; H 7.13. Found: C 80.12; H 7.01.

2-Carbobenzyloxy-3-(3-methyl-4-pentenyl)bicyclo-[2.2.2]-octadiene (13b). To a stirred solution of 240 mg (0.746 mmol) of the β-bromo ester **12** in 8 mL of dry ether under argon was added a deep purple solution of the Grignard

reagent derived from 5-bromo-3-methyl-1-pentene[3] (1.2 mmol) and 24 mg (0.12 mmol) of cuprous bromide-dimethylsulfide complex (0.12 mmol) in 10 mL of ether. The resulting suspension was stirred at room temperature. After 1 h, the reaction mixture was quenched with 1 mL of water and then diluted to 50 mL with ether. The organic phase was washed successively with two 50 mL portions of saturated aqueous NH_4Cl and one 50 mL portion of brine, dried ($MgSO_4$) and then the solvent was removed under reduced pressure. Column chromatography of the residue on 10 g of silica gel with 5% ethyl acetate in petroleum ether afforded 99 mg (41%) of the desired adduct **13b** and 98 mg (41%) of the starting material **12**: For **13b**: evaporative distillation 75° C (0.005 mmHg); IR ($CHCl_3$) 2980, 1695, 1645, 1605, 1460, 1390, 1360, 1270, 1260 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.93 (d, 3H, J=6 Hz, CH_3), 1.32 (bs, 4H, CH_2CH_2), 1.43 (m, 2H, CH_2CH_2CH), 2.02-2.96 (m, 3H, CH_2CH), 3.50 (m, 1H, CHC(R)=), 4.17 (m, 1H, $CHC(CO_2Bn)$=), 4.85 (m, 2H, $=CH_2$), 5.16 (s, 2H, $ArCH_2O$), 5.62 (m, 1H, CHCH=), 6.26 (m, 2H, CH=CH), 7.38 (bs, 5H, ArH); Anal. Calcd. for $C_{22}H_{26}O_2$: C 81.95; H 8.13. Found: C 81.86; H 8.07.

3-Bromo-1-tert-butyldimethylsilyloxy-2-carbobenzyloxy-6-methyl-bicyclo[2.2.2]octadiene (14). To a stirred mixture of 310 mg of the diene **11** (1.38 mmol) and 50 mg pyrogallol under argon was added 0.36 mL (506 mg, 2.12 mmol) of benzyl 3-bromopropiolate **7**. The resulting mixture was stirred at

room temperature for 12 h. Column chromatography of the reaction mixture on 80 gm of silica gel with 2% ether in petroleum ether provided 343 mg (54%) of the cycloadduct **14**: IR ($CHCl_3$) 2960, 1740, 1260, 1170, 950, 950, 840 cm^{-1}; U.V. (C_6H_{12}) λ_{max} 212 nm (ε~10,500, Ar); ^{1}H-NMR δ 0.20 (s, 3H, CH_3Si), 0.23 (s, 3H, CH_3Si), 0.92 (s, 9H, $(CH_3)_3C$), 1.78 (d, 3H, J=1.5 Hz, CH_3C=), 3.46 (dm, 1H, J=7.2 Hz, CHCH=), 5.15 (s, 2H, $ArCH_2O$), 5.83 (dm, 1H, J=7.2 Hz, CH=), 7.30 (m, 5H, ArH). Anal. Calcd. for $C_{23}H_{31}O_3BrSi$: C 59.60; H 6.74; Br 17.24. Found: C 59.75; H 6.70; Br 17.15. The yield of the above Diels-Alder cycloaddition varied from 35 to 54%.

1-tert-Butyldimethylsilyloxy-2-carbobenzyloxy-3,6-dimethyl-bicyclo[2.2.2]octadiene (15). By the procedure described for the preparation of the adduct **13a**, 30 mg (0.065 mmol) of the β-bromoester **14** in 2 mL of dry ether, 80 mg (0.39 mmol) of cuprous bromide-dimethyl sulfide complex, 0.19 mL (0.38 mmol) of 2.0 M methyllithium in ether afforded, after chromatography of the residue on 5 g of silica gel with 2% ether in petroleum ether, 21.1 mg (82%) of the dimethyl adduct **15**: evaporative distillation 130° C (0.001 mm); IR ($CHCl_3$) 2975, 2960, 2925, 1712, 1458, 1260, 1065, 1055, 835 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.17 (s, 3H, CH_3Si), 0.20 (s, 3H, CH_3Si), 0.95 (s, 9H, $(CH_3)_3Si$), 1.73 (s, 3H, CH_3C=C(CO_2Bn)), 1.77 (d, 3H, J=1.5 Hz, CH_3C=CH), 3.08 (dm, 1H, J=6.6 Hz, CHCH=), 5.14 (bs, 2H, $ArCH_2O$), 5.77 (dm, 1H,

J=6.6 Hz, CHCH=), 7.30 (bs, 5H, ArH); Anal. Calcd. for $C_{24}H_{34}O_3Si$: C 72.32; H 8.60. Found: C 72.45; H 6.70; Br 17.15.

1-tert-Butyldimethylsilyloxy-2-carbobenzyloxy-6-methyl-3-(3(S)-methyl-4-pentenyl)bicyclo[2.2.2]octadiene (17). To 165 mg (0.81 mmol) of cupric acetate monohydrate in a stirred solution of 1.501 gm (3.24 mmol) of the β-bromoester **14** in 125 mL of dry ether at -35°C under argon was added dropwise 12.95 mL of a 0.5M solution of 3(S)-methyl-5-pentenyl magnesium bromide in ether. The resulting mixture was stirred at -35° to -25° C for 30 min, allowed to warm to room temperature for 30 min and then the reaction was quenched by the careful addition of 10 mL of saturated aqueous NH_4Cl. The organic phase was diluted to 250 mL with ether and washed with three 100 mL portions of saturated aqueous NH_4Cl, dried ($MgSO_4$) and then the solvent was removed under reduced pressure. Flash chromatography of the residue on 200 g of silica gel with 2% ether in petroleum ether afforded 2.274 gm (90%) of the alkylated adduct **17**. On a 50 mg scale the yield was 98%. IR ($CHCl_3$) 2970, 1740, 1645, 1610, 1465, 1260 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.18 (s, 3H, CH_3Si), 0.21 (s, 3H, CH_3Si), 0.84 (d, 3H, J=6.2 Hz, CH_3CH), 0.90 (s, 9H, $(CH_3)_3C$), 1.75 (d, 3H, J=1.5 Hz, CH_3C=), 1.2-2.3 (m, 9H, $2CH_2CH_2$ and $CHCH_3$), 3.13 (dm, 1H, J=6.3 Hz, =CCHC=), 4.8 (m, 2H, $CH=CH_2$), 5.07 (s, 2H, $ArCH_2O$), 5.47 (m,

1H, C<u>H</u>=CH_2), 5.74 (dd, 1H, J=6.2 Hz, J'=1.5 Hz, C<u>H</u>=C(CH_3)), 7.27 (bs, 5H, Ar<u>H</u>).

Benzyl 2-<u>tert</u>-butyldimethylsilyloxy-3-methyl-6-(3(<u>S</u>)-methyl-4-pentenyl)benzoate (18). In an evacuated sealed, thick walled Pyrex® ampule 2.624 g (5.622 mmol) of the degassed bicyclo[2.2.2]octadiene **17** was heated in a 160°C oil bath for 12 h, then allowed to cool to room temperature. Column chromatography of the residue on 200 g of silica gel with 2% ether in petroleum ether afforded 2.3816 gm (97%) of the desired tetrasubstituted aromatic **18**: evaporative distillation 120° C (0.01 mmHg); $[\alpha]_D^{23}$ -2.34° (neat, l=0.1 dm). IR ($CHCl_3$) 2965, 2940, 2870, 1720, 1482, 1418, 1275, 1138, 845 cm^{-1}; ^1H NMR ($CDCl_3$) 0.15 (s, 6H, $(CH_3)_2Si$), 0.87 (d, 3H, J=6.9 Hz), 0.98 (s, 9H, $(CH_3)_3C$), 1.42 (m, 2H, Ar C<u>H</u>C<u>H</u>$_2$), 1.97 (m, 1H, C<u>H</u>(CH_3)C=), 2.17 (s, 3H, Ar<u>CH</u>$_3$), 2.45 (m, 2H, Ar<u>CH</u>$_2$<u>CH</u>$_2$), 4.83 (m, 2H, CH=C<u>H</u>$_2$), 5.24 (s, 2H, Ar<u>CH</u>$_2$O), 5.57 (m, 1H, C<u>H</u>=CH_2), 6.67 (d, 1H, J=8.1 Hz, Ar<u>H</u>), 7.05 (d, 1H, J=8.1 Hz, Ar<u>H</u>), 7.35 (m, 5H, Ar<u>H</u>). Anal. Calcd. for $C_{27}H_{38}O_3Si$: C 73.95; H 8.73. Found: C 74.06; H 8.57.

Benzyl 2-hydroxy-3-methyl-6-(3(<u>S</u>)methyl-4-pentenyl)-benzoate (19). To a stirred solution of 2.348 gm (5.35 mmol) of the silyl ether **18** in 25 mL THF under argon was added 2.5 gm (9.7 mmol) of tetra n-butylammonium fluoride and the resulting mixture was stirred at room temperature. The reaction mixture was diluted with 150 mL

of ether and the resultant organic phase was washed with two 100 mL portions of saturated aqueous $NaNCO_3$, dried ($MgSO_4$) and the solvent was removed under reduced pressure. Flash chromatography of the residue on 120 g of silica gel with 5% ether in petroleum ether afforded 1.725 gm (99%) of the desired phenol **19**: evaporative distillation 110° C (0.01 mmHg); IR ($CHCl_3$) 3230, 2970, 1715, 1488, 1425, 1140 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.84 (d, 3H, J=6.6 Hz, CH_3CH), 1.41 (m, 2H, $ArCH_2CH_2CH$), 1.89 (m, 1H, $CH(CH_3)C=$), 2.19 (s, 3H, $ArCH_3$), 2.75 (m, 2H, $ArCH_2CH_2$), 4.83 (m, 2H, $CH=CH_2$), 5.33 (s, 2H, $ArCH_2O$), 5.53 (m, 1H, $CH=CH_2$), 6.52 (d, 1H, J=8.4 Hz, ArH), 7.00 (d, 1H, J=8.4 Hz, ArH), 7.34 (bs, 5H, ArH).

Benzyl 2-hydroxy-3-methyl-6-(4,5 dihydroxy-3(S)methyl-pentyl)benzoate (20). To a stirred solution of 1.725 gm (5.32 mmol) of the olefin **19** in 1.4 mL THF under argon was consecutively added 920 mg (6.81 mmol) of 4-methyl morpholine 4-oxide, 2.5 mL water and 0.2 mL of 0.1 M osmium tetroxide in tert-butanol and the resulting mixture was stirred at room temperature overnight. The reaction mixture was then quenched by stirring with 50 mL of 15% aqueous $Na_2S_2O_4$ for 30 min and diluted with 50 mL of water. The resulting mixture was extracted with three 100 mL portions of dichloromethane, the combined organic extracts were then dried ($MgSO_4$) and the solvent was removed under reduced pressure. Flash chromatography of the residue on 120 g of silica gel with ethyl acetate afforded 1.857 gm

(98%) of the diasteriomeric diols **20** as a white solid: evaporative distillation 165-180° C (0.001 mmHg); IR($CHCl_3$) 3610, 1670, 1430, 1260, 1160 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.78 (bd, 3H, J=6 Hz, $CHCH_3$), 2.20 (s, 3H, $ArCH_3$), 5.38 (s, 2H, CO_2CH_2Ph), 6.60 (d, 1H, J=7.5 Hz, ArH), 7.17 (d, 1H, J=7.5 Hz, ArH), 7.42 (bs, 5H, CO_2CH_2Ph), 11.38 (bs, 1H, ArOH). Anal. Calcd. for $C_{21}H_{26}O_5$: C, 70.37; H, 7.31. Found: C, 70.51; H, 7.30.

Benzyl 2-hydroxy-3-methyl-6-(3(S)-formylbutyl)benzoate (2). To a stirred solution of 430.7 mg (1.20 mmol) of the above diols **18** in 18 mL of methanol was added 342 mg (1.60 mmol) of sodium metaperiodate in 7.0 mL of water. The reaction was stirred for 30 min at room temperature and then diluted with 50 mL of water and extracted with four 50 mL portions of dichloromethane. The organic extracts were combined and dried ($MgSO_4$). Removal of the solvent under reduced pressure and flash chromatography of the residue on 30 g of silica gel with 5% ethyl acetate in petroleum ether gave 368.0 mg (94%) of the desired "enantio left-half" aldehyde **2**: evaporative distillation 140° C (0.01 mmHg); $[\alpha]_D^{23}$ +16.26° (c 1.175, $CHCl_3$); IR ($CHCl_3$) 2990, 2970, 2935, 2260(d), 1715, 1660, 1620, 1465, 1420, 1390, 1300, 1250, 1150 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.92 (d, 3H, J=7 Hz, CH_3), 2.20 (s, 3H, $ArCH_3$), 2.81 (bt, 2H, J=7 Hz, $ArCH_2C$), 5.36 (s, 3H, CO_2CH_2), 6.56, 7.14 (2d, 2H, J=7.5 Hz, 2 ArH), 9.37 (d, 1H, J=1.5 Hz, CHO), 11.43 (s, 1H, OH).

Anal. Calcd. for $C_{20}H_{22}O_4$: C, 73.60; H, 6.79.

Found: C, 73.62; H, 6.78.

Benzyl-β-L-arabinopryanoside (21).[23] To a mixture 250 mL of benzyl alcohol and 10 mL of acetyl chloride at 0° C under argon was added 50 g (0.333 mol) of L-arabinose and the resulting mixture warmed to 50°C. After 24 h the reaction mixture was cooled to room temperature and poured slowly into 500 mL of ether with stirring. The product was allowed to crystallize at room temperature for 4 h, then the mixture was cooled to 0° C overnight, to complete the crystallization. Collection of the product by filtration gave 65.4 g (82%) of the glycoside **21**.

Benzyl 3,4-O-(1-methylethlidene)-β-L-arabinopyranoside (22).[23] To a stirred suspension of 65.4 g (0.272 mol) of the glycoside (**21**) in 1.25 L of dry acetone was added 15 mg p-toluenesulfonic acid (0.08 mmol) and 62.5 mL (0.510 mol) of 2,2-dimethoxypropane and the resulting mixture was stirred at room temperature. After 36 h, the reaction mixture was neutralized with aqueous NH_4OH and concentrated under reduced pressure. The residue was dissolved in 750 mL of dichloromethane and the resulting solution was washed with saturated aqueous $NaHCO_3$ (2x250 mL) dried ($MgSO_4$) and the solvent was removed under reduced pressure. Evaporative distillation of the residue at 135° C (0.1 mmHg) gave 76.2 g (99.8%) of the alcohol **22** as a clear syrup which slowly crystallized.

Benzyl 3,4-O-(1-methylethylidene)-β-L-erythro-pent-2-ulosyl-pyranoside (23). To a stirred solution of 13.5 mL (0.155 mol) of oxalyl chloride in 400 mL of dichloromethane at -60°C under argon was added 27.1 mL (0.382 mol) of dimethylsulfoxide. After 30 min, a solution of 33.1 g (0.118 mol) of the alcohol 22 in 100 mL of dichloromethane was added to the reaction mixture. After 2 h, the reaction mixture mixture was treated with 81.0 mL (0.581 mol) of dry triethylamine, allowed to warm to room temperature and then 134 mL of water was added. After 15 min, the resulting mixture was poured into 650 mL saturated aqueous $NaHCO_3$, the organic phase was separated, and the aqueous phase was extracted with 300 mL of dichloromethane. The combined organic phases were dried ($MgSO_4$) and the solvent was removed under reduced pressure. Flash chromatography of the residue on a 10x26 cm column of silica gel with 20% ethyl acetate in petroleum ether and then evaporative distillation of the chromatographed material at 100° C (0.05 mmHg) afforded 30.6 gm (93%) of the ketone 23: evaporative distillation 100° C (0.005 mmHg); $[\alpha]_D^{25}$ +191.2 (c0.94, $CHCl_3$); IR ($CHCl_3$) 2980, 1755, 1260, 1080 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.32 (s, 3H, CH_3), 1.43 (s, 3H, CH_3), 3.9-4.5 (m, 4H, H-3, -4, -5's), 4.72 (d, 2H, J=7.5 Hz, Ph-CH_2), 4.87 (s, 1H, H-1), 7.4 (s, 1H, Ph). Anal. Calcd. for $C_{15}H_{18}O_5$: C, 64.73; H, 6.52. Found: C, 64.68; H, 6.59.

Benzyl-3,4-O-(1-methylethylidene)2-C-methyl-β-L-arabinopyranoside (24). A solution of 5.100 g (18.46 mmol) of the ketone **23** in 90 mL of dry ether was added slowly to a stirred solution of methyl magnesium iodide (110.76 mmol) in 210 mL of dry ether at 0° under argon, and the resulting solution was allowed to warm to room temperature. After 1 h the reaction was quenched by the careful addition of 200 mL saturated aqueous NH_4Cl, the ether phase was separated, dried ($MgSO_4$) and the solvent was removed under reduced pressure. Column chromatography of the residue on 200 g of silica gel with 20% ethyl acetate in petroleum ether gave 4.190 gm (83%) of the adduct **24** : evaporative distillation 100°C (0.005 mmHg); $[\alpha]_D^{25}$ +129.1 (c1.2, $CHCl_3$); IR ($CHCl_3$) 3350, 2960, 1610, 1270, 1060 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.26 (s, 6H, $2CH_3$), 1.41 (s, 3H, CH_3), 3.1 (bs, 1H, OH), 3.3-4.3 (m, 4H, H-3, 4, 5's), 4.55 (s, 1H, H-1), 4.69 (AB, 2H, $PhCH_2$), 7.3 (s, 5H, Ph). Anal. Calcd. for $C_{16}H_{20}O_5$: C, 65.29; H, 7.53. Found: C, 65.23; H, 7.37.

Benzyl-3,4-O-(1-methylethylidene)2-C-methyl-β-L-ribo and arabinopyranosides (25) and (24). To a stirred solution of 12.806 g (46.0 mmol) of the ketone **23** in 300 mL of dry ether at -78°C under argon was added 23.4 mL (46.0 mmol) of 1.97 M methyllithium in ether and the resulting solution was stirred at -78° C. After 30 min, 5.4 mL (9.4 mmol ethanol) of 10% ethanol in ether was added. After 15 min, 9.4 mL (18.4 mmol) of 1.97 M methyllithium was added, and

the resulting mixture was allowed to warm to room temperature. After 1 hr, the reaction mixture was quenched by the careful addition of 100 mL of saturated aqueous NH_4Cl. The organic phase was separated, dried ($MgSO_4$), and the solvent was removed under reduced pressure. Medium pressure liquid chromatography of the residue on a Lobar C column with 10% ethyl acetate in petroleum ether afforded 10.472 g (80%) of the adduct **25** and 1.131 g (9%) of the adduct **24**: For **25**: evaporative distillation 100°C (0.005 mmHg); $[\alpha]_D^{23}$ +186.5° (c 1.0, $CHCl_3$); IR ($CHCl_3$) b 3350, 2980, 1605, 1280, 1070 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.23 (s, 3H, CH_3), 1.37 (s, 3H, CH_3), 1.59 (s, 3H, CH_3), 2.55 (s, 1H, OH), 4.0 (d, 2H, J=3.0 Hz, H-5's), 4.1 (d, 1H, J=11.5 Hz, H-3), 4.2 (dt, 1H, J_1=3.0 Hz, J_2=11.5 Hz, H-4), 4.62 (s, 1H, H-1), 4.63 (AB, 2H, Ph-CH_2), 7.32 (m, 5H, Ph). Anal. Calcd. for $C_{16}H_{20}O_5$: C, 65.29; H, 7.53. Found: C, 65.49; H, 7.71.

2-C-Methyl-L-ribose (26). To a stirred solution of 39.0 g (133.4 mmol) of the glycoside **25** in 50 mL of methanol was added 1 L of 4% aqueous H_2SO_4 over a period of 1 h and the resulting mixture was heated under reflux at atmospheric pressure. After 22 h, the reaction mixture was neutralized with concentrated aqueous NH_4OH and the solvent was removed under reduced pressure. The residue was taken up in 1 L of methanol, filtered and then the solvent was removed under reduced pressure. Flash chromatography of the

residue on 800 g of silica with 30% methanol in dichloromethane afforded 17.05 g (78%) of the free sugar **26**.

2,3-O-(1-methylethylidene)-2-C-methyl-L-ribono-1,4-lactone (27). To a stirred solution of 6.388 g (38.91 mmol) of the lactol **26** in 220 mL of deionized water was added 3.45 mL (66.92 mmol) of bromine and 4.47 g (44.66 mmol) of calcium carbonate, and the resulting mixture was stirred at room temperature. After 30 min the excess bromine was removed by aeration and the water was removed under reduced pressure. The residue was dried under vacuum (0.005 mmHg) for 12 h, slurried in 300 mL of dry acetone with 10 g anhydrous Na_2SO_4, sufficient concentrated sulfuric acid was then added to adjust the pH to approximately 0.5 (moist test strip). The resulting mixture was stirred at room temperature for 1h, neutralized with concentrated aqueous NH_4OH, filtered washing with two 100 mL portions of dichloromethane, and then the solvent was removed under reduced pressure. Column chromatography of the residue on 500 g of silica gel with 30% ethyl acetate in petroleum ether gave 6.450 g (82%) of the lactone **27**. The yield on a 2 mmol scale was 90%. Recrystalization from ether/hexane afforded an analytical sample: MP 62-62.5° C (lit. for the antipode 62°-63°C[36]; $[\alpha]_D^{22}$ +39.15° (c 1.51, $CHCl_3$) lit for the antipode -38.4 [36]; IR ($CHCl_3$) b 3450, 3000, 2950, 1780, 1180, 1225, 1025 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.42 (s, 6H, $(CH_3)_2C$), 1.63 (s, 3H, CH_3C), 3.33 (bs, 1H, O<u>H</u>), 3.87 (m,

2H, H-5's), 4.52 (s+m, 2H, s=H-3, m=H-4). Anal. Calcd. for $C_9H_{14}O_5$: C, 53.46, H, 6.98. Found: C, 53.55; H, 6.84.

2,3-O-(1-methylethylidene)-5-O-methoxymethyl-2-C-methyl-L-ribono-1,4-lactone (28). To a stirred solution of 22.296 g of the lactone **27** (0.110 mol) in 250 mL of chloroform at 0°C was added 59 mL(0.667 mol) of dimethoxymethane and 49 g of P_2O_5:Celite (1:1), and the resulting mixture was stirred at room temperature. After 1 h, the reaction mixture was poured into iced aqueous saturated $NaHCO_3$ with stirring and the resultant mixture was filtered. The organic phase was separated, and the aqueous phase was extracted with two 150 mL portions of chloroform. The combined organic phases were dried ($MgSO_4$) and then the solvent was removed under reduced pressure. Evaporative distillation of the residue at 100 °C (0.005 mmHg) gave 26.896 g (99%) of the methoxymethyl ether **28**: evaporative distillation 90-100°C, (0.005 mmHg); $[\alpha]_D^{22}$ +26.05° (*c* 1.97, $CHCl_3$); IR ($CHCl_3$) 1780, 1380, 1220, 1160, 1105, 1060, 1020 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.42 (s, 6H, $C(CH_3)_2$), 1.62 (s, 3H, CH_3), 3.33 (s, 3H, OCH_3), 3.74 (d, 2H, J=3 Hz, CCH_2O). Anal. Calcd. for $C_{11}HHH_{18}O_6$: C, 53.65; H, 7.37. Found: C, 53.71; H, 7.42.

2,3-O-(1-methylethylidene)-5-O-methoxymethyl-2-C-methyl-L-ribose (29). To a stirred solution of 26.859 g (0.109 mol) of the lactone **28** in 500 mL of dry ether at -78°C under argon was added 153 mL (0.153 mol) of 1 M diisobutylaluminum hydride in hexane (0.153 mol) over a period of

30 min, and the resulting mixture was stirred at -78°C. After 1 h, 36 mL of dry methanol was cautiously added, the reaction mixture was allowed to warm to room temperature, and then 650 mL of 0.5 M aqueous potassium sodium tartrate was added with stirring. When two distinct phases could be noticed (approx. 2 h), the organic phase was separated and the aqueous phase was extracted with two 500 mL portions of dichloromethane. The combined organic phases were dried ($MgSO_4$), and the solvent was removed under reduced pressure. Evaporative distillation of the residue at 110°C (0.005 mmHg) yielded 27.072 g (99.7%) of the desired lactol **29**: evaporative distillation 90-100°C (0.005 mmHg); $[\alpha]_D^{22}$ -18.36° (c 4.48, $CHCl_3$); IR ($CHCl_3$) 3600, 3450, 1460, 1380, 1210, 1160, 1105, 1060, 1030 cm^{-1}; ^1H NMR ($CDCl_3$) (minor anomer, major anomer) 3.31, 3.34 (s, 3H, OCH_3), 3.59, 3.63 (d, 2H, J=2 Hz, CCH_2O), 4.58, 4.64 (s, 2H, OCH_2O), 5.00, 5.17 (d, 1H, J=11 Hz, H1). Anal. Calcd. for $C_{11}H_{20}O_6$: C, 53.22; H, 8.12. Found: C, 53.36; H, 8.12.

1,4-Anhydro-2-deoxy-2-methyl-5-O-methoxymethyl-L-erythro-pent-1-enitol (30). To a stirred solution of 6.559 g (26.42 mmol) of the lactol **29** in 80 mL of dry THF at -78°C was sequentially added 3.15 mL (29.9 mmol) of carbon tetrachloride and 5.2 mL (28.6 mmol) of trisdimethylamino-phosphine, and the resulting mixture was stirred at -78°C. After 30 min the reaction mixture became opaque and was allowed to warm to room temperature with stirring until it

became clear. The resulting solution was canulated into a stirred solution of 53 cm (approx. 0.3 mol) of lithium wire in 400 mL dry ammonia at -78°C rinsing with two 10 mL portions of dry THF, cooling was then discontinued (ammonia reflux). After 2h, 18.8 gm of dry ammonium chloride was cautiously added, the resulting colorous mixture was diluted with 200 mL ether, and the ammonia was allowed to evaporate. The resulting suspension was filtered, washing with four 50 mL portions of ether, and the solvent was removed under reduced pressure. Flash chromatography of the residue on 200 gm of silica with ether and then evaporative distillation of the chromatographed material at 80°C (0.005 mmHg) gave 9.053 g of a 4:1 mixture (^{1}H-NMR) of the desired glycal **30** (79%) and the deschloro compound **60** (20%). Chromatography of this mixture on silica gel with 20% ethyl acetate in petroleum ether provided pure samples for analysis: For **30** - evaporative distillation 60-70°C (0.005 mmHg); $[\alpha]_D^{23}$ -190.7° (c2.0, $CHCl_3$); IR ($CHCl_3$) 3590, 3450, 1675, 1460, 1380,, 1210, 1150, 1100, 1020 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.69 (d, 3H, J=2 Hz, CH_3), 3.37 (s, 3H, OCH_3), 3.56 (d, 2H, J=6 Hz, CCH_2O), 5.08 (s, 2H, OCH_2O), 6.22 (bs, 1H, HC=C). Anal. Calcd. for $C_8H_{14}O_4$: C, 55.16; H, 8.10. Found: C, 54.89; H, 8.00. For **60** - evaporative distillation 40°C (0.005 mmHg); $[\alpha]_D^{21}$ -26.58 (c2.25, $CHCl_3$); IR ($CHCl_3$) 1460, 1385, 1220, 1160, 1040 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.38 (s, 3H, CH_3), 1.50 (s, 6H, $C(CH_3)_2$), 3.33 (s, 3H, OCH_3), 3.60 (d,

2H, J=6 Hz, CCH_2O), 3.62 (d, 1H, J=9 Hz, $H1_a$), 3.79 (d, 1H, J=9 Hz, $H1_b$), 4.17 (dt, 1H, J-3 Hz, 6 Hz, H4), 4.27 (d, 1H, J=3 Hz, H3), 4.59 (s, 2H, OCH_2O). Anal. Calcd. for $C_{11}H_{20}O_5$: C, 56.88; H, 8.68. Found: C, 56.71; H, 8.58.

Methyl 2(S)-and 2(R)-5(S)-Methoxymethylenoxymethyl)-3-(R)-methyl-2(R)-tetrahydrofuryl)butanoate (31a) and (31b). To a stirred solution of 2.931 g (15.1 mmol) of the glycal **30** as a 4:1 mixture with the byproduct **60** in 49 mL of dry THF and 11.3 mL of dry HMPA at -78° C under argon was added 6.69 mL (15.1 mmol) of 2.26 M n-butyllithium in hexane, and then after 5 min, 1.7 mL of n-butanoyl chloride (16.4 mmol) was added. After 10 min the reaction mixture was canulated dropwise into a stirred solution of 22.3 mmol of LDA in 53.5 mL of dry THF and 15.4 mL of dry HMPA at -100° C rinsing with two 5 mL portions of dry THF. After 10 min, the reaction mixture was treated with 7.5 mL of the supernatant centrifugate from a 3:1 mixture of chlorotrimethylsilane and triethylamine (44.3 mmol of TMSCl). After 2 h at room temperature, the reaction mixture was treated with 100 mL 1 N of aqueous NaOH and the resulting mixture was stirred for 15 min. The aqueous phase was then saturated with NaCl and acidified (PH2) with concentrated sulfuric acid. The organic phase was separated and the aqueous phase was extracted with three 100 mL portions of ether. The combined organic phases were dried ($MgSO_4$) and the solvent was removed under reduced pressure. Ester-

ification of the residue with ethereal diazomethane and then flash chromatography of the resultant esters on 200 g of silica gel with 25% ethyl acetate in petroleum ether afforded 2.621 gm (67%) of a 6:1 (^{1}H-NMR) mixture of the diasteriomeric esters. The yield of the above ester enolate Claisen reaction varied from 54 to 67% using 1 to 20 mmol of the glycal **30**.

The above mixture was dissolved in 125 mL of ethyl acetate, 500 mg of 5% Pt/C was added and the resulting mixture was stirred under an atmosphere of hydrogen. After 12 h, the catalyst was removed by filtration and the solvent was removed under reduced pressure. Medium pressure liquid chromatography of the residue on a Lobar C column with 20% ethyl acetate in petroleum ether, gave 1.9713 g (75%) of the desired 2S ester **31a** and 297 mg (11%) of the 2R ester **31b**: For **31a** - evaporative distillation 80-90°C (0.005 mmHg); $[\alpha]_D^{25}$ -8.04° (c2.64, $CHCl_3$); IR ($CHCl_3$) 1730, 1460, 1275, 1220, 1160, 1105, 1040 cm $^{-1}$; ^{1}H NMR ($CDCl_3$) δ 0.88 (t, 3H, J=6 Hz, CH_3CH_2), 0.99 (d, 3H, J=6 Hz, CH_3), 3.36 (s, 3H, OCH_3), 3.51 (d, 2H, J=5 Hz, CCH_2O), 3.68 (s, 3H, CO_2CH_3), 4.62 (s, 2H, OCH_2O). Anal. Calcd. for $C_{13}H_{24}O_5$: C, 59.98; H, 9.29. Found: C, 59.84; H, 9.16. For **31b** - evaporative distillation 80-90°C (0.005 mmHg); $[\alpha]_D^{25}$ -15.07° (c2.48, $CHCl_3$); IR ($CHCl_3$) 1730, 1460, 1390, 1110, 1040 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.90 (t, 3H, J=6 Hz, CH_3CH_2), 1.06 (d, 3H, J=6 Hz, CH_3CHCC), 3.36 (s, 3H, OCH_3), 3.52 (d, 2H, J=5 Hz, CCH_2O),

3.69 (s, 3H, CO_2CH_3), 4.61 (s, 2H, OCH_2O). Anal. Calcd. for $C_{13}H_{24}O_5$: C, 59.98; H, 9.29. Found: C, 60.06; H, 9.26.

2(R)-5(R)-(Methoxymethylenoxymethyl)-3(R)-methyl-2(R)-tetrahydrofuryl)-butan-1-ol (32). By the procedure described for the preparation of the alcohol **8**, 5.8337 g (22.41 mmol) of the 2S methyl ester **31a** in 110 mL of dry ether with 850 mg (21.7 mmol) of lithium tetrahydridoaluminate afforded, after column chromatography on 300 g silica gel with 30% ethyl acetate in petroleum ether, 4.9391 g (95%) of the alcohol **32**: evaporative distillation 60-70° C (0.005 mmHg); $[\alpha]_D^{24}$ -24.7° (c0.45, $CHCl_3$); IR ($CHCl_3$) 3650, 3500, 1460, 1230, 1150, 1105, 1030 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.93 (t, 3H, J=6 Hz, CH_3CH_2), 1.01 d, 3H, J=6 Hz, CH_3), 2.67 (dd, 1H, J=5 Hz, 6 Hz, $CHCH_3$), 3.33 (s, 3H, OCH_3), 3.47 (d, 2H, J=5 Hz, CCH_2O), 4.60 (s, 2H, OCH_2O). Anal. Calcd. for $C_{12}H_{24}O_4$: C, 62.04; H, 10.41. Found: C, 62.12; H, 10.42.

Benzyl 2(R)-5(R)-(Methoxymethylenoxymethyl)-3(R)-methyl-2(R)-(tetrahydrofurfyl)butyl ether (33). To a suspension of 1.02 gm (24.5 mmol) of potassium hydride in 50 mL of dry THF and 4.1 mL (34.5 mmol) of benzyl bromide under argon was added a solution of 4.937 g of the alcohol **32** (21.3 mmol) in 50 mL dry THF was added over a period of 30 min. The resulting mixture was stirred at room temperature for 1 h, then 75 mL of saturated aqueous $NaHCO_3$ was cautiously added with stirring. After 1 h, the mixture was

diluted with 600 mL of ether, the organic phase was separated, washed with two 200 mL portions of saturated aqueous $NaHCO_3$, dried ($MgSO_4$), and then the solvent was removed under reduced pressure. Column chromatography of the residue on 400 g of silica gel with 15% ethyl acetate in petroleum ether afforded 6.7732 g (99%) of the benzyl ether **33**: evaporative distillation 100-110° C (0.005 mmHg); $[\alpha]_D^{24}$ -17.8° (c1.00, $CHCl_3$); IR ($CHCl_3$) 1460, 1380, 1120, 1040 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.92 (t, 3H, J=6 Hz, CH_3CH_2), 1.02 (d, 3H, J=6 Hz, CH_3), 3.33 (s, 3H, OCH_3), 3.47 (d, 4H, J=5 Hz, CCH_2O), 4.43 (s, 2H, $C_6H_5CH_2$), 4.60 (s, 2H, OCH_2O), 7.28 (bs, 5H, C_6H_5). Anal. Calcd. for $C_{19}H_{30}O_4$: C, 70.77; H, 9.38. Found: C,70.74; H9.34.

Benzyl 2(R)-5(R)-(Hydroxymethyl)-3(R)-methyl-2(S)-tetrahydrofuryl)-butyl ether (34). To a solution of 21.70 g (67.3 mmol) of the methoxymethylether **33** in 520 mL of THF was added 150 mL of aqueous 10% HCl and the resulting mixture warmed to 50° C. After 12 h, the reaction mixture was cooled to room temperature, neutralized by the careful addition of saturated aqueous $NaHCO_3$ and extracted with three 500 mL portions of ether. The combined extracts were dried ($MgSO_4$) and the solvent was removed under reduced pressure. Flash chromatography of the residue on 500 g of silica gel with 50% ethyl acetate in petroleum ether afforded 18.74 g (100%) of the alcohol **34**: evaporative distillation 100-110°C (0.005 mmHg); $[\alpha]_D^{21}$ - 51.8 (c2.57,

$CHCl_3$); IR ($CHCl_3$) 3600, 3450, 1460, 1380, 1220, 1100, 1080, 1040 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.93 (t, 3H, J=6 Hz, CH_3CH_2), 1.02 (d, 3H, J=6 Hz, CH_3), 3.47 (d, 2H, J=6 Hz, CCH_2O), 4.48 (s, 2H, $C_6H_5CH_2$), 7.33 (bs, 5H, C_6H_5). Anal. Calcd. for $C_{17}H_{26}O_3$: C, 73.35; H, 9.41. Found: C, 73.38; H, 9.37.

Benzyl 2(R)-5(R)-Carbomethoxy-3(R)-methyl-2(R)-tetrahydro-furyl)-butyl ether (35a). By the procedure described for the preparation of the ketone **23**, 16.25 g of the alcohol **34** (58.37 mmol) was treated with 9.9 mL (139.7 mmol) of DMSO activated with 6.6 mL of oxalyl chloride (75.9 mmol) then 24.6 mL of triethylamine (excess) in 220 mL of dichloromethane. The resultant aldehyde was dissolved in 440 mL of absolute ethanol and a solution of 28.7 g (1676 mmol) of silver nitrate in 44.0 mL of water was added. To the resulting mixture 364 mL of 0.93 M potassium hydroxide was added over 30 min and the resulting mixture was stirred at room temperature for 5 min then filtered. The filtrate was concentrated under reduced pressure to approximately 400 mL, washed with two 300 mL portions of ether, acidified (PH 2) and extracted with five 300 mL portions of dichloromethane. The combined dichloromethane extracts were dried ($MgSO_4$) and the solvent was removed under reduced pressure to give 16.26 gm (95%) of the acid **35**. A portion of this material was treated with diazomethane in ether and chromatography of the resulting methyl ester **35a** on silica gel with 10% ethyl acetate in petroleum

ether afforded an analytical sample: evaporative distillation 100-110° C (0.005 mmHg); $[\alpha]_D^{20}$ -1.28° (c1.08, $CHCl_3$); IR ($CHCl_3$) 1740, 1460, 1370, 1220, 1100, 1040 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.93 (t, 3H, J=6 Hz, CH_3CH_2), 1.01 (d, 3H, J=6 Hz, CH_3), 3.49 (d, 2H, J=6 Hz, CCH_2O), 3.70 (s, 3H, CO_2CH_3), 3.80 (dd, 1H, J=5 Hz, 8 Hz, OCHCC), 4.38 (t, 1H, J=7 Hz,, $CHCO_2CH_3$), 4.47 (s, 2H, $C_6H_5CH_2$), 7.32 (bs, 5H, C_6H_5). Anal. Calcd. for $C_{18}H_{26}O_4$: C, 70.56; H, 8.55. Found: C, 70.75; H, 8.54.

Benzyl 5,6-anhydro-2,3-O-(1-methylethylidene)-β-D-gulofurranoside (37). To a stirred suspension of 8.9 g (370.9 mmol) of sodium hydride in 300 mL of dry THF at 0° C was cautiously added a solution of 51.2 gm (165.0 mmol) of the gulonoside diol **36** in 300 mL of dry THF and the resulting mixture was stirred at 0° C. After 15 min a solution of 41.0 g (1.84 mmole) of p-toluenesulfonylimidazolide[25] in 400 mL of dry THF was added over 1 h and the resulting mixture was stirred at 0°C. After 45 min the excess sodium hydride was destroyed by the careful addition of 50 mL of water and the reaction mixture was diluted with 4 L of ether. The organic phase was washed with two 1.5 L portions of water, dried ($MgSO_4$) and then the solvent was removed under reduced pressure. Crystallization of the residue from dichloromethane/petroleum ether afforded 34.0 gm of the desired epoxide **37** and flash chromatography of the mother liqueurs on 500 g of silica gel with 20% ethyl

acetate in petroleum ether gave a further 8.1 g of the epoxide 37. The total yield of the epoxide 37 was 42.1 g (87%): MP 87.5-88.0° C; $[\alpha]_D^{22}$ -86.95° (c 2.28, $CHCl_3$); IR ($CHCl_3$) 2995, 2930, 1448, 1380, 1370, 1102, 1075, 1015, 850, 695 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.31 and 1.50 (s, 6H, $(CH_3)_2C$), 2.65 (dd, 1H, $J_{6a,6b}$=4.5 Hz, $J_{5,6a}$=3.0 Hz, H-6a), 2.90 (dd, 1H, $J_{5,6b}$ $J_{6a,6b}$=4.5 Hz, H-6b), 3.30 (ddd, 1H, $J_{5,6a}$=3.0 Hz, $J_{5,6b}$=4.5 Hz, $J_{4,5}$=6.6 Hz, H-5), 3.58 (dd, 1H, $J_{4,5}$=6.6 Hz, $J_{3,4}$=3.5 Hz, H-4), 4.60 (AB quartet, 2H, $PhCH_2O$), 4.72 (m, 2H, H-2 and H-3), 5.16 (bs, 1H, H-1), 7.31 (bs, 5H, PhH). Anal. Calcd. for $C_{16}H_{20}O_5$: C, 65.74; H, 6.90. Found: C, 65.75; H, 6.86.

Benzyl 6-deoxy-2,3-O-(1-methylethylidene)-β-D-gulofuranoside (38). By the procedure described for the preparation of the alcohol **32**, 14.370 g (49.16 mmol) of the epoxide **37**, 2.5 gm (65.9 mmol) of lithium tetrahydroaluminate and 200 mL of dry ether afforded, after crystallization from dichloromethane/pentane and flash chromatography of the mother liqueurs on silica gel with 20% ethyl acetate in petroleum ether, 11.487g of the desired alcohol **38** (79%). The yield on a 5 mmol scale was 91%: MP 111-112.5° C; $[\alpha]_D^{22}$ -99.83 (c 1.6, $CHCl_3$); IR($CHCl_3$) 3600 (sharp), 3520 (broad), 2995, 2940, 1455, 1385, 1375, 1105, 1075, 1015, 855, 695 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.26 (d, 3H, $J_{5,6}$=6.2 Hz, H-6's), 1.27 and 1.44 (s, 6H, $(CH_3)_2$)C), 2.7 (bs, 1H, OH), 3.76 (dd, 1H, J_4=6.2 Hz, $J_{3,4}$=2 Hz, H-4), 4.13

(dt, 1H, $J_{5,6}$ $J_{4,5}$=6.2 Hz, H-5), 4.57 (AB quartet, 2H, PhC$\underline{H}_2$O), 4.65 (bs, 2H, H-2 and H-3), 5.10 (s, 1H, H-1), 7.30 (s, 5H, Ph$\underline{H}$). Anal. Calcd. for $C_{16}H_{22}O_5$: C, 65.29; H, 7.53. Found: C, 65.24; H, 7.49.

6-deoxy-$\underline{D}$-gulose (39). A solution of 11.473 gm (39.0 mmol) of the glycoside **38** in 300 mL of 4:1 acetic acid/water was heated under reflux under argon. After 12h the reaction mixture was cooled to room temperature and the solvent was removed under reduced pressure. Passage of the residue through a 10x20 cm pad of silica gel, eluting with ethyl acetate, afforded 5.224 gm (86%) of the free sugar **39**.

Benzyl-6-deoxy-αandβ-$\underline{D}$-gulopyranoside (40a&b). To a stirred solution of 9.316 g (56.7 mmol) of 6-deoxy-$\underline{D}$-gulose **39** in 100 mL of benzyl alcohol was added 2.5 mL of acetyl chloride and the resulting mixture warmed to 50° C. After one day, the reaction mixture was diluted with 100 mL of chloroform and then neutralized with 100 g of barium carbonate. The resulting suspension was filtered and the solid residue was washed with three 100 mL portions of chloroform. The combined filtrates were concentrated at 50°C (0.01 mmHg). Flash chromatography of the residue on 1000 g of silica gel with ethyl acetate gave 11.231 g (78%) of the benzyl glycosides (α:β=1:2) **40 a&b**: α-glycoside: mp 134.5°-135.5° C (ethyl acetate-hexane); $[\alpha]_D^{21}$ +117.8° ($\underline{c}$0.863, $CHCl_3$); IR ($CHCl_3$) 3600, 3450, 1220, 1175, 1080,

1040, 1000 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.23 (d, 3H, J=6 Hz, CH_3), 4.54 (d, 1H, J=12 Hz, $C_6H_5CH\underline{H}$), 4.73 (d, 1H, J=12 Hz, $C_6H_5C\underline{H}H$), 4.93 (bs, 1H, H1), 7.38 (bs, 5H, C_6H_5). Anal. Calcd. for $C_{13}H_{18}O_5$: C, 61.41; H, 7.14. Found: C, 61.79; H, 7.14. β-glycoside: evaporative distillation 130-140°C (0.005 mmHg); $[\alpha]_D^{25}$ -117.8 (c1.133, $CHCl_3$); IR ($CHCl_3$) 3600, 3450, 1220, 1175,, 1080, 1060, 1000 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.27 (d, 3H, J=6 Hz, CH_3), 4.53 (d, 1H, J=11 Hz, $C_6H_5CH\underline{H}$), 4.62 (d, 1H, J=8 Hz, H1), 4.89 (d, 1H, J=11 Hz, $C_6H_5C\underline{H}H$), 7.34 (bs, 5H, C_6H_5). Anal. Calcd. for $C_{13}H_{18}O_5$: C, 61.41; H, 7.14. Found: C, 61.31; H, 7.22.

Benzyl-6-deoxy-2,3-O-(1-methylethylidene)-α and β-D-gulopyranosides (41 a&b). To a stirred solution of 11.231 g (44.17 mmol) of the benzyl glycosides **40 a&b** in 500 mL of dry acetone was added 70 mg (0.37 mmol) of p-toluenesulfonic acid monohydrate and 9.5 mL (76.7 mmol) of 2,2-dimethoxypropane. After 12 h, the reaction mixture was neutralized with concentrated aqueous NH_4OH. The resulting suspension was filtered and the filtrate was concentrated under reduced pressure. Flash chromatography of the residue on 500 g of silica gel with 25% ethyl acetate-petroleum ether gave 12.74 g (98%) of the corresponding ketals. α-glycoside: mp 79-80°C (hexane); $[\alpha]_D^{21}$ +62.1 (c0.965, $CHCl_3$); IR ($CHCl_3$) 3970, 3460, 1380, 1240, 1160, 1100, 1030 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.19 (d, 3H, J=6 Hz, CH_3), 1.36, 1.50 (s, 6H, $C(CH_3)_2$), 4.56 (d, 1H, J=12 Hz, $C_6H_5CH\underline{H}$), 4.71

(d, 1H, J=12 Hz, C_6H_5CHH), 4.87 (bs, 1H, H1), 7.33 (bs, 5H, CH_5). Anal. Calcd. for $C_{16}H_{22}O_5$: C, 65.29; H, 7.53. Found: C, 65.36; H, 7.46. β-glycoside: evaporative distillation 100-110°C, 0.005 mmHg; $[\alpha]_D^{21}$ -106.2 (c1.206, $CHCl_3$); IR ($CHCl_3$) 3560, 3350, 1390, 1230, 1180, 1120, 1060 cm^{-1}; ^1H NMR ($CDCl_3$) 1.30 (d, 3H, J=6 Hz, CH_3), 1.31, 1.40 (s, 6H, $C(CH_3)_2$), 4.73 (d, 1H, J=4 Hz, H1), 4.58 (d, 1H, J=12 Hz, C_6H_5CHH), 4.84 (d, 1H, J=12 Hz, C_6H_5CHH), 7.33 (bs, 5H, C_6H_5). Anal. Calcd. for $C_{16}H_{22}O_5$: C, 65.29; H, 7.53. Found: C, 65.21; H, 7.50.

Benzyl-6-deoxy-2,3-O-(1-methylethylidene)-4-O-methoxymethyl-α and β-D-gulopyranoside 42 a and b. To a suspension of 5.15 gm (128.5 mmol) of potassium hydride in 160 mL of dry THF at 0° C was cautiously added a solution of 29.41 g (99.9 mmol) the alcohols **41 a and b** in 80 mL dry THF and the resulting mixture was stirred at 0° C. After 15 min, 15.1 mL (200 mmol) of chloromethylmethyl ether was added and the resulting mixture was stirred at room temperature. After 12 h, the excess potassium hydride was quenched by the cautious addition of 10 mL of water and the mixture was diluted with 750 mL of ether. The organic phase was washed with two 300 mL portions of water and one 300 mL portion of brine, dried ($MgSO_4$) and the solvent was removed under reduced pressure. Flash chromatography of the residue on 350 g of silica gel with 25% ethyl acetate in petroleum ether afforded 28.37 gm of the methoxymethyl ethers **42 a and**

b (84%): α -glycoside: evaporative distillation 120-130° C (0.005 mmHg); $[\alpha]_D^{21}$ +41.0° (c0.80, $CHCl_3$); IR ($CHCl_3$) 1380, 1240, 1150, 1100, 1020 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.20 (d, 3H, J=6 Hz, CH_3), 1.36, 1.51 (s, 6H, $C(CH_3)_2$), 3.40 (s, 3H, OCH_3), 4.57 (bs, 1H, H1), 7.34 (bs, 5H, C_6H_5). Anal. Calcd. for $C_{18}H_{26}O_6$: C, 63.89; H, 7.74. Found: C, 63.90; H, 7.64. β -glycoside: evaporative distillation 100-110° C (0.005 mmHg); $[\alpha]_D^{21}$ = -148° (c0.904, $CHCl_3$); IR ($CHCl_3$) 1390, 1230, 1155, 1040 cm^{-1}; ^1H NMR ($CDCl_3$) 3.40 (s, 3H, OCH_3), 4.57 (d, 1H, J=12 Hz, H1), 7.30 (bs, 5H, C_6H_5). Anal. Calcd. for $C_{18}H_{26}O_6$: C, 63.89; H, 7.74. Found: C, 63.82; H, 7.75.

6-Deoxy-2,3-O-(1-methylethylidene)-4-O-methoxymethyl-D-gulose (43). To a stirred solution of 21 cm (128 mmol) of lithium wire in 200 mL of anhydrous ammonia at -78° C under argon was added a solution of 14.68 g (43.38 mmol) of the mixture of benzyl glycosides **42a** and **b** in 40 mL of dry THF. Cooling was then discontinued (ammonia reflux) and after 1 h, 8.0 g (150 mmol) of anhydrous ammonium chloride was cautiously added to the reaction mixture. The resulting mixture was then diluted with 300 mL of ether and the ammonia was allowed to evaporate. The resulting suspension was filtered, and the solid was then washed by trituration with four 100 mL portions of ether. Removal of the solvent from the combined filtrates gave 10.2 g (95%) of the crystalline lactol **43**: mp 139° C (ethyl acetate-hexane):

$[\alpha]_D^{22}$ -62.5° (c1.201, $CHCl_3$); IR ($CHCl_3$) 3600, 3460, 1390, 1230, 1160, 1100, 1040 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.27 (d, 3H, J=6 Hz, CH_3), 1.33, 1.47 (s, 6H, $C(CH_3)_2$), 3.40 (s, 3H, OCH_3), 3.57 (d, 1H, J=6 Hz, OH), 3.63 (dd, 1H, J=3 Hz, 3 Hz, H4), 4.00 (dq, 1H, J=3 Hz, 6 Hz, H3), 4.63 (d, 1H, J=6 Hz, OCHHO), 4.77 (d, 1H, J=6 Hz, OCHHO), 4.87 (dd, 1H, J=6 Hz, 6 Hz, H1). Anal. Calcd. for $C_{11}H_{20}O_6$: C, 53.22; H, 8.12. Found: C, 53.35; H, 8.06.

1,5-Anhydro-2,6-dideoxy-4-O-methoxymethyl-D-xylo-hex-1-enitol (44). By the procedure described for the preparation of the glycal **30**, 8.74 g (35.2 mmol) of the lactol **43**, 4.4 mL (45.6 mmol) of carbon tetrachloride, 6.8 mL (37.4 mmol) of trisdimethylaminophosphine in 140 mL of dry THF with 71 cm (432 mmol) of lithium wire in 600 mL of anhydrous ammonia and 25 g (468 mmol) of anhydrous ammonium chloride afforded, after passage through 100 g of silica gel with 50% ethyl acetate-petroleum ether and evaporative distillation at 60° C (0.1 mmHg), 5.73 mg (93%) of the glycal **44**: $[\alpha]_D^{22}$ +199.8° (c0.65, $CHCl_3$); IR ($CHCl_3$) 3620,, 3450, 1640, 1240, 1150, 1090, 1030, 940 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.36 (d, 3H, J=6 Hz, CH_3), 3.40 (s, 3H, OCH_3), 3.56 (m, 1H, H4), 4.10 (m, 2H, H3 and H5), 4.66 (d, 1H, J=6 Hz, OCHHO), 4.73 (d, 1H, J=6 Hz, OCHHO), 4.89 (m, 1H, H2), 6.50 (d, 1H, J=6 Hz, H1). Anal. Calcd. for $C_8H_{14}O_4$: C, 55.16; H, 8.10. Found: C, 55.19; H, 8.23.

Benzyl 2(R)-[5(S) and 5(R)-carbomethoxy-3(S)-methyl-5-(5,6-dihydro-5(R)-methoxymethylenoxy-6(R)-methyl-2(S)-pyranyl)-2(R)-tetrahydrofuryl]-butyl ether (45a&b). By the procedure described for the preparation of the methyl esters **31a&b**, 660 mg (3.48 mmol) of the glycal **44**, with 1.62 mL (3.48 mmol) of 2.17 M solution of n-butyllithium in hexane and 3.98 mmol of the acid chloride of the acid **35** in 9 mL of dry THF, added to 7.0 mmol of LDA in 9 mL of dry THF, followed by 21.0 mmol of trimethylchlorosilane afforded, after treatment with ethereal diazomethane and chromatography on 200 g of silica gel with 20% ethyl acetate in petroleum ether, 226 mg of the methyl ester **45a** and 817 mg of the methyl ester **45b**, or a 22:78 ratio of a 65% combined yield. Methyl ester **45a**: evaporative distillation 150-160° C (0.005 mmHg); $[\alpha]_D^{22}$ -149.2 (c1.256, $CHCl_3$); IR ($CHCl_3$) 1740, 1460, 1215, 1160, 1100, 1040 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.92 (t, 3H, J=6 Hz, CH_3CH_2), 0.97 (d, 3H, J=6 Hz, CH_3CHCC), 1.18 (d, 3H, J=6 Hz, CH_3CHOC), 3.34 (s, 3H, OCH_3), 3.73 (s, 3H, CO_2CH_3), 4.47 (bs, 2H, $C_6H_5CH_2$), 4.62 (d, 1H, J=7 Hz, OCHHO), 4.71 (d, 1H, J=7 Hz, OCHHO), 5.67-6.17 (m, 2H, HCCH), 7.33 (bs, 5H, C_6H_5). Anal. Calcd. for $C_{26}H_{38}O_7$: C, 67.51; H, 8.28. Found: C, 67.64, H, 8.26. Methyl ester **45b**: evaporative distillation 150-160° C (0.005 mmHg); $[\alpha]_D^{22}$ -177.1° (c0.552, $CHCl_3$); IR ($CHCl_3$) 1750, 1730, 1460, 1385, 1155, 1100, 1040 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.90 (t, 3H, J=6 Hz, CH_3CH_2), 0.97 (d, 3H, J=6 Hz, CH_3CHCC), 1.16 (d,

3H, J=6 Hz, CH_3CHOC), 2.50 (q, 1H, J=6 Hz, CH_3CHCC), 3.34 (s, 3H, OCH_3), 3.68 (s, 3H, CO_2CH_3), 4.43 (s, 2H, $C_6H_5CH_2$), 4.57 (d, 1H, J=6 Hz, $OCHHO$), 4.70 (d, 1H, J=6 Hz, $OCHHO$), 5.31 (bs, 2H, $HC=CH$), 7.32 (bs, 5H, C_6H_5). Anal. Calcd. for $C_{26}H_{38}O_7$: C, 67.51; H, 8.28. Found: C, 67.48; H, 8.41. The yield of the above ester enolate Claisen varied from 59 to 69% on a 0.5 to 5.0 mmole scale.

Benzyl 2(R)-[5(S)-Carbomethoxy-3(R)-methyl-5-(5(S)-methoxymethylenoxy-6(R)-methyl-2(S)-tetrahydropyranyl)-2(R)-tetrahydrofuryl]butyl Ether (46a). By the procedure described for preparation of **31a&b**, 203 mg (0.44 mmol) of the methyl ester **45a** in 5 mL of ethyl acetate with 20mg of 5% platinum on carbon catalyst afforded, after chromatography on 20 g of silica gel with 15% ethyl acetate-cyclohexane, 181 mg (89%) of the saturated methyl ester **46a**: evaporative distillation 150-160° C (0.005 mmHg); $[\alpha]_D^{22}$ -5.1° (c1.118, $CHCl_3$); IR ($CHCl_3$) 1730, 1460, 1380, 1110, 1040 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.93 (t, 3H, J=6 Hz, CH_3CH_2), 0.95 (d, 3H, J=6 Hz, CH_3CHCC), 1.17 (d, 3H, J=6 Hz, CH_3CHOC), 3.33 (s, 3H, OCH_3), 3.70 (s, 3H, CO_2CH_3), 4.47 (bs, 2H, $C_6H_5CH_2$), 4.59 (bs, 2H, OCH_2O), 7.33 (bs, 5H, C_6H_5). Anal. Calcd. for $C_{26}H_{40}O_7$: C, 67.22; H, 8.68. Found: C, 67.47; H, 8.75.

Benzyl 2(R)-[5(R)-Carbomethoxy-3(R)-methyl-5-(5(S)-methoxymethylenoxy-6(R)-methyl-2(S)-tetrahydropyranyl)-2(R)-tetrahydrofuryl]butyl Ether (46b). By the above procedure, 8.347 g (18.0 mmol) of the methyl ester **45b** in 165 mL of ethyl acetate with 220 mg of 5% platinum on carbon catalyst afforded, after flash chromatography on 400 g of silica gel with 20% ethyl acetatecyclohexane), 7.51 g (90%) of the saturated methyl ester **46b**: evaporative distillation 150-160° C (0.005 mmHg); $[\alpha]_D$ -34.0° (c0.662, $CHCl_3$); IR ($CHCl_3$) 1750, 1730, 1460, 1390, 1110, 1040 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.90 (t, 3H, J=6 Hz, CH_3CH_2), 0.94 (d, 3H, J=6 Hz, CH_3CHCC), 1.12 (d, 3H, J=6 Hz, CH_3CHOC), 2.39 (q, 1H, J=6 Hz, CH_3CHCC), 3.32 (s, 3H, OCH_3), 3.67 (s, 3H, CO_2CH_3), 4.47 (bs, 2H, $C_6H_5CH_2$), 4.60 (bs, 2H, OCH_2O), 7.33 (bs, 5H, C_6H_5). Anal. Calcd. for $C_{26}H_{40}O_7$: C, 67.22; H, 8.68. Found: C, 67.40; H, 8.88.

Benzyl 2(R)[5(R)-Formyl-3(R)-methyl-5-(5(R)-methoxymethylenoxy-6R-methyl-2(S)-tetrahydropyranyl]-2(R)-tetrahydrofurylbutyl Ether (47). By the procedure described for the preparation of the lactol **29**, 8.801 gm (20.25 mmol) of ester **46b**, 29.1 mL (29.1 mmol) of 1 M Diisobutylaluminum hydride, 110 mL of dry ether, 3.0 mL of methanol and 200 mL 0.5 M potassium sodium tartrate afforded, after chromatography on 400 gm of silica gel with 20% ethyl acetate petroleum ether, 7.312 g (89%) of the aldehyde **47**: evaporative distillation 150-160° C

(0.005 mmHg); $[\alpha]_D$ -51.8° (c0.541, $CHCl_3$); IR ($CHCl_3$) 1735, 1460, 1380, 1110, 1040 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.90 (t, 3H, J=6 Hz, CH_3CH_2), 0.94 (d, 3H, J=6 Hz, CH_3CHCC), 1.12 (d, 3H, J=6 Hz, CH_3CHOC), 2.33 (q, 1H, J=6 Hz, CH_3CHCC), 3.30 (s, 3H, OCH_3), 4.46 (bs, 2H, $C_6H_5CH_2$), 4.57 (bs, 2H, OCH_2O), 7.30 (bs, 5H, C_6H_5), 9.67 (s, 1H, CHO). Anal. Calcd. for $C_{25}H_{38}O_6$: C, 69.10; H, 8.81. Found: C, 68.85; H, 8.75.

Benzyl 2(R)-[5(S)-Vinyl-3(R)-methyl-5-(5(R)-methoxymethylenoxy-6R-methyl-2(S)-tetrahydropyranyl)-2(R)-tetrahydrofuryl]-butyl Ether (48). To a stirred suspension of 14.86 gm (41.43 mmol) of methyltriphenyphosphonium bromide in 150 mL of dry THF at -78° C under argon was added 14.9 mL (39.18 mmol) of a 2.63 M solution of n-butyllithium in hexane. Cooling was then discontinued and the reaction mixture was stirred at room temperature for one hour, then cooled to -78° C. A solution of 7.285 g (16.76 mmol) of the aldehyde 47 in 50 mL of dry THF was added, and the cooling was discontinued. After 10 h, the reaction mixture was treated with 20 mL of saturated aqueous $NaHCO_3$, diluted with 600 mL of ether, washed with 200 mL of saturated aqueous $NaHCO_3$, 200 mL of saturated aqueous NaCl, and then dried ($MgSO_4$). Removal of the solvents at reduced pressure and flash chromatography of the residue on 500 g of silica gel with 8% ethyl acetate in petroleum ether afforded 6.71 g (92%) of the adduct 48: evaporative distillation 140-150° C

(0.005 mmHg); $[\alpha]_D$ -50.9° (c1.065, $CHCl_3$); IR ($CHCl_3$) 1460, 1380, 1100, 1030 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.91 (t, 3H, J=6 Hz, CH_3CH_2), 0.94 (d, 3H, J=6 Hz, CH_3CHCC), 1.20 (d, 3H, J=6 Hz, CH_3CHOC), 3.32 (s, 3H, OCH_3), 4.47 (bs, 2H, $C_6H_5CH_2$), 4.59 (bs, 2H, OCH_2O), 5.02 (dd, 1H, J=3 Hz, 10 Hz, HC=CHH(c)), 5.20 (dd, 1H, J=3 Hz, 18 Hz, HC=CHH(t)), 5.87 (dd, 1H, J=10 Hz, 18 Hz, HC=CH_2), 7.32 (bs, 5H, C_6H_5). Anal. Calcd. for $C_{26}H_{40}O_5$: C, 72.19; H, 9.32. Found: C, 72.04; H, 9.32.

Benzyl 2(R)-[5(R)-Ethyl-3(R)-methyl-5-(5(R)-methoxymethylenoxy-6(R)-methyl-2(S)-tetrahydropyranyl)-2(R)-tetrahydrofuryl]butyl Ether (49). To a solution of 6.71 gm (15.4 mmol) of the olefin **48** in 200 mL of ethyl acetate was added approximately 20 mL of W-2 Raney Nickel catalyst and the resulting suspension stirred under a hydrogen atmosphere. After 12 h, the catalyst was removed by filtration and then the solvent was removed under reduced pressure. Flash chromatography of the residue on 300 g of silica gel with 8% ethyl acetate in petroleum ether afforded 6.509 g (97%) of the saturated material **49**: evaporative distillation 140-150° C (0.005 mmHg); $[\alpha]_D^{21}$ -27.8° (c1.011, $CHCl_3$); IR ($CHCl_3$) 1460, 1380, 1210, 1110, 1040 cm^{-1} ; ^1H NMR ($CDCl_3$) δ 1.17 (d, 3H, J=6 Hz, CH_3CHOC), 3.33 (s, 3H, OCh_3), 4.44 (bs, 2H, $C_6H_5CH_2$), 4.57 (bs, 2H, OCH_2O), 7.33 (bs, 5H, C_6H_5). Anal. Calcd. for $C_{26}H_{42}O_5$: C, 71.85; H, 9.74. Found: C, 71.89; H, 9.64.

Benzyl 2(R)-[5(R)-Ethyl-3(R)-methyl-5-(5(R)-hydroxy-6(R)-methyl-2(S)-tetrahydropyranyl)-2(R)-tetrahydrofuryl]-butyl Ether (50). By the procedure described for the preparation of the alcohol **34**, 6.509 g (14.98 mmol) of the methoxymethyl ether **49** in 80 mL of THF and 20 mL of 10% aqueous HCl afforded, after flash chromatography on 200 g of silica gel with 25% ethyl acetate in petroleum ether, 5.85 mg (100%) of the alcohol **50**: evaporative distillation 140-150° C (0.005 mmHg); $[\alpha]_D$ -26.3 (c 0.681, $CHCl_3$); IR ($CHCl_3$) 3650, 3480, 1470, 1400, 1120, 1080 cm^{-1}; ^1H NMR ($CDCl_3$) δ0.83, 0.92 (2t, 6H, J=6 Hz, $2CH_3CH_2$), 0.97 (d, 3H, J=6 Hz, CH_3CHCC), 1.17 (d, 3H, J=6 Hz, CH_3CHOC), 4.46 (s, 2H, $PhCH_20$), 7.32 (bs, 5H, Ph-H). Anal. Calcd. for $C_{24}H_{38}O_4$: C, 73.81; H, 9.81. Found: C, 74.02; H, 10.03.

Benzyl 2(R)-[5(R)-Ethyl-3(R)-methyl-5-(6(R)-methyl-5-oxo-2(S)-tetrahydro-pyranyl)-2(R)-tetrahydrofuryl]-butyl Ether (51). To a stirred solution of 1.7 mL (19.55 mmol) of oxalyl chloride in 50 mL of dry dichloromethane at -60° C under argon was added 3.12 mL (44.0 mmol) of dimethyl-sulfoxide. After 10 min, a solution of 5.85 g (14.98 mmol) of the alcohol **50** in 50 mL of dry dichloromethane was added to the reaction mixture. After 15 min, the reaction mixture was treated with 12.5 mL (89.7 mmol) of dry triethylamine, allowed to warm to room temperature and then diluted with 350 mL of ether. This mixture was washed with 200 mL of water, 200 mL of saturated aqueous $NaHCO_3$, 200 mL of

saturated aqueous NaCl, and then dried ($MgSO_4$). Removal of the solvents at reduced pressure, and flash chromatography of the residue (10% ethyl acetate in petroleum ether), afforded 5.753 g (99%) of the ketone **51**: evaporative distillation 120-130° C(0.005 mmHg); $[\alpha]_D^{21}$ +61.1° (c0.570, $CHCl_3$); IR ($CHCl_3$) 1720, 1460, 1380, 1110 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.27 (d, 3H,, J=6 Hz, CH_3CHOC), 4.30 (q, 1H, J=6 Hz, CHCO), 4.44 (s, 2H, $C_6H_5CH_2$), 7.33 (bs, 5H, C_6H_5). Anal. Calcd. for $C_{24}H_{36}O_4$: C, 74.19; H, 9.34. Found: C, 74.26; H, 9.47.

Benzyl 2(R)-[5(R)-Ethyl-3(R)-methyl-5-(6(R)-methyl-5-methylene-2(S)-tetrahydropyranyl)-2(R)-tetrahydrofuryl]-butyl Ether (52). By the procedure described for the preparation of the adduct **48** 2.850 g (7.33 mmol) of the ketone **51** in 53 mL of dry THF with 18.33 mmol of methylene-triphenylphosphorane afforded, after flash chromatography on 150 g of silica gel with 4% ethyl acetate in petroleum ether 2.764 g (97%) of the corresponding olefin **52**: evaporative distillation 120-130° C (0.005 mmHg); $[\alpha]_D^{24}$ -8.2° (c1.203, $CHCl_3$); IR ($CHCl_3$) 1460, 1380, 1120, 1080 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.83, 0.93 (2t, 6H, J=6 Hz, CH_3CH_2), 0.97 (d, 3H, J=6 Hz, CH_3CHCC), 1.30 (d, 3H, J=6 Hz, CH_3CHOC), 4.43 (q, 1H, J=6 Hz, CHC=C), 4.47 (s, 2H, $C_6H_5CH_2$), 4.67 (bs, 2H, $C=CH_2$), 7.31 (bs, 5H, C_6H_5). Anal. Calcd. for $C_{25}H_{38}O_3$: C, 77.68; H, 9.91. Found: C, 77.81; H, 10.00.

Benzyl 2(R)-[5(R)-Ethyl-3(R)-methyl-5-(3(S)-1,5-dioxo-4(R)-methyl-spiro-[2.5]-6(S)-octyl)-2(R)-tetrahydrofuryl]-butyl Ether (53). To a stirred solution of 2.612 g (6.76 mmol) of the olefin **52** in 70 mL of dry dichloromethane at 0° C under argon was added 2.3 g (27.4 mmol) of solid $NaHCO_3$ and 2.3 g (10.6-11.9 mmol) of 80-90% m-chloroperbenzoic acid. Cooling was then discontinued, and the reaction mixture was stirred at room temperature for 3 h. After treatment of this mixture with 30 mL of 10% aqueous Na_2SO_3, the resulting mixture was diluted with 300 mL of ether, washed with two 100 mL portions of saturated aqueous $NaHCO_3$, 100 mL of saturated aqueous NaCl, and then dried ($MgSO_4$). Removal of the solvents and chromatography of the residue on 300 g of silica gel with 10% ethyl acetate in petroleum ether afforded 1.950 g of the epoxide **53** and 568 mg of the epimeric epoxide (ratio of 3.4:1 of 93% combined yield). Epoxide **53**: evaporative distillation 130-140° C (0.005 mmHg); $[\alpha]_D^{24}$ +4.8° (c 1.025, $CHCl_3$); IR ($CHCl_3$) 1460, 1380, 1120, 1080 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.86, 0.93 (2t, 6H, J=6 Hz, CH_3CH_2), 0.97 (d, 3H, J=6 Hz, CH_3CHCC), 1.27 (d, 3H, J=6 Hz, CH_3CHOC), 2.52 (d, 1H, J=4 Hz, $CCHHO$), 2.59 (d, 1H, J=4 Hz, $CCHHO$), 4.47 (s, 2H, $C_6H_5CH_2$), 7.33 (bs, 5H,, C_6H_5). Anal. Calcd. for $C_{25}H_{38}O_4$: C, 74.59; H, 9.51. Found: C, 74.70; H, 9.60. Epi-epoxide **53**: evaporative distillation 130-140° C (0.005 mmHg); IR ($CHCl_3$) 1460, 1380, 1120, 1080 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.86,

0.93 (2t, 6H, J=6 Hz, CH_3CH_2), 0.97 (d, 3H, J=6 Hz, CH_3CHCC), 1.24 (d, 3H, J=6 Hz, CH_3CHOC), 2.58 (d, 1H, J=5 Hz, CCHHO), 2.71 (d, 1H, J=5 Hz, CCHHO), 4.47 (s, 2H, $C_6H_5CH_2$), 7.31 (bs, 5H, C_6H_5).

Benzyl 2(R)[5(R)-Ethyl-3(R)-methyl-5-(5(S)-ethyl-5-hydroxy-6(R)-methyl-2(S)-tetrahydropyranyl)-2(S)-tetrahydrofuryl]-butyl ether (54). To a stirred suspension of 5.1 g (24.9 mmol) of cupric bromide-dimethyl sulfide complex in 36 mL of dry pentane at 0° C was slowly added 32 mL (49.2 mmol) of 1.54 M low halide methyl lithium in ether and the resulting white suspension was stirred at 0° C. After 30 min a solution of 1.901 g (4.72 mmol) of the epoxide 53 in 12 mL of dry pentane was added slowly. After 2 h, the reaction mixture was treated with 40 mL of saturated aqueous NH_4Cl and diluted with 200 mL of ether. The organic phase was separated and washed with two 200 mL portions of saturated aqueous NH_4Cl and one 200 mL portion of brine, then dried ($MgSO_4$) and then the solvent was removed under reduced pressure. Flash chromatography of the residue on 150 g of silica gel with 15% ethyl acetate in petroleum ether afforded 1.975 g (99.9%) of the alcohol 54: evaporative distillation 180-190° C (0.005 mmHg); $[\alpha]_D^{24}$ -21.3° (c1.320, $CHCl_3$); IR ($CHCl_3$) δ 3580, 1460, 1380, 1120, 1100, 1050, 960 cm^{-1}; ^1H NMR ($CDCl_3$) 0.96 (d, 3H, J=6 Hz, CH_3CHCC), 1.18 (d, 3H, J=6 Hz, CH_3CHOC), 3.76 (q, 1H,

J=6 Hz, $CH_3C\underline{H}OC$), 4.47 (s, 2H, $PhC\underline{H}_2O$), 7.33 (bs, 5H, $Ph\underline{H}$). Anal. Calcd. for $C_{26}H_{42}O_4$: C, 74.60; H, 10.11. Found: C, 74.70; H, 10.18.

2(R)-[5(R)-Ethyl-3(R)-methyl-5-(5(S)-ethyl-5-hydroxy-6(R)-methyl-2(S)-tetrahydropyranyl)-2(R)-tetrahydrofuryl]-butan-1-ol (55). To a stirred solution of 3.5 cm (21 mmol) of lithium wire in 80 mL of anhydrous liquid ammonia at -78° C under argon was added a solution of 1.975 g (4.72 mmol) of the monobenzyl ether 54 in 20 mL of dry THF. Cooling was then discontinued (ammonia reflux) and after 1 h, 1.75 g (33 mmol) of anhydrous ammonium chloride was cautiously added to the reaction mixture. The resulting mixture was then diluted with 100 mL of ether and the ammonia was allowed to evaporate. The resulting suspension was filtered and the solid was washed by trituration with four 50 mL portions of ether. Removal of the solvent at reduced pressure from the combined filtrates and then chromatography of the residue on 120 g of silica gel with 40% ethyl acetate in petroleum ether afforded 1.507 g (97%) of the diol 55: mp 74-75° C (hexane); $[\alpha]_D^{21}$ -14.5° (c 1.16, $CHCl_3$); IR ($CHCl_3$) 3600, 3500, 1460, 1380, 1100, 1050, 950 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.96 (d, 3H, J=6 Hz, $C\underline{H}_3CHCC$), 1.22 (d, 3H, J=6 Hz, $C\underline{H}_3CHOC$), 3.73 (q, 1H, J=6 Hz, $CH_3C\underline{H}OC$). Anal. Calcd. for $C_{19}H_{36}O_4$: C, 69.47; H, 11.05. Found: C, 69.55; H, 10.97.

2(S)-[5(R)-Ethyl-3(R)-methyl-5-(5(S)-ethyl-5-hydroxy-6(R)-methyl-2(S)-tetrahydropyranyl)-2(R)-tetrahydrofuryl]-butanal (56). By the procedure described for preparation of the ketone 23, treatment of 1.5070 g (4.588 mmol) of the alcohol 55 with 0.81 mL (6.0 mmol) of DMSO, 0.45 mL (5.05 mmol) of oxalyl chloride, 1.6 mL of dry triethyl amine in 20 mL of dry dichloromethane afforded, after flash chromatography on 120 g of silica gel with 15% ethyl acetate in petroleum ether 1.499 g (100%) of the aldehyde 56: evaporative distillation 130-140° C (0.005 mmHg); $[\alpha]_D^{21}$ +2.4° (0.971, $CHCl_3$); IR ($CHCl_3$) 3600, 3450, 2750(d), 1720, 1460, 1390, 1230, 1130, 1100, 1060, 960 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.97 (d, 3H, J=6 Hz, CH_3CHCC), 1.18 (d, 3H, J=6 Hz, CH_3CHOC), 9.64 (d, 1H, J=3 Hz, CHO).

4(R)[5(R)-Ethyl-3(R)-methyl-5-(5(S)-ethyl-5-hydroxy-6(R)-methyl-2(S)-tetrahydropyranyl)-2(R)-tetrahydrofuryl]-hexan-3-ol (57). To a stirred solution of 1.499 g (4.589 mmol) of the aldehyde 56 in 35 mL of dry THF at -78° C under argon was added 8 mL (16 mmol) of a 2.0 M solution of ethylmagnesium bromide in THF. The resulting solution was stirred at room temperature for 12 h, cautiously treated with 10 mL of saturated aqueous NH_4Cl and then diluted with 200 mL of ether. The organic phase was separated and washed with 200 mL of saturated aqueous NH_4Cl and 100 mL of saturated aqueous NaCl, then dried ($MgSO_4$). Removal of the solvent at reduced pressure and then flash

chromatography of the residue on 230 g of silica gel with a gradient of 30 to 50% ethyl acetate in petroleum ether afforded 98.4 mg (6%) of the alcohols **55** and 1.502 g (92%) of the diastereoisomeric mixture of alcohols **57**: evaporative distillation 120-130° C (0.005 mmHg); IR ($CHCl_3$) 3600, 3500, 1460, 1380, 1130, 1100, 1060, 960 cm^{-1}; ^1H NMR ($CDCl_3$) 1.20 (d, 3H, J=6 Hz, CH_3CHOC).

4(S)-[5(R)-Ethyl-3(R)-methyl-5-(5(S)-ethyl-5-hydroxy-6(R)-methyl-2(S)-tetrahydropyranyl)-2(R)-tetrahydrofuryl]-hexan-3-one (3). By the procedure described for the preparation of ketone **23**, treatment 1.502 g of the alcohol **56** (4.213 mmol) with 0.81 mL of DMSO (6.0 mmol), 0.45 mL oxalyl chloride (5.05 mmol), 2.5 mL of triethylamine in 20 mL of dry dichloromethane afforded, after flash chromatography on 120 g of silica gel with 15% ethyl acetate in petroleum ether, 1.286 g (87%) of the enantio-right half ketone **3**: evaporative distillation 200°C (0.001 mmHg); $[\alpha]_D^{25}$ +23.6° (c 1.705, $CHCl_3$); IR ($CHCl_3$) 3600, 1710, 1460, 1385, 1135, 1100, 1060, 960 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.20 (d, 3H, J=6 Hz, CH_3CHOC), 3.74 (q, 1H, J=6 Hz, CH_3CHOC). Anal. Calcd. for $C_{21}H_{38}O_4$: C, 71.15; H, 10.80. Found: C, 71.20; H, 10.81.

Enantio-Benzyl Lasalocid A (58a). To a solution of 1.799 mmol of LDA in 2 mL of dry benzene at 0° C a solution of 303.6 mg (0.856 mmol) of the ketone **3** in 3 mL of dry benzene was added over 10 min and the resulting solution

stirred at 0° C. After 10 min, 1.43 mL (0.88 mmol) of 0.66 M zinc chloride in ether[37] was added to the reaction mixture. After 20 min a solution of 142.8 mg (0.438 mmol) of aldehyde **2** in 2 mL of dry benzene was added rapidly and the resulting mixture was stirred at 0° C. After 4 min, the reaction mixture was poured into 50 mL of vigorously stirred saturated aqueous NH_4Cl, and the resulting mixture was extracted with two 50 mL portions of ether.The combined organic extracts were dried ($MgSO_4$) and then the solvent was removed under reduced pressure. Flash chromatography of the residue on a 2.7x24 cm column of silica gel with 300 mL of 10%, 500 mL of 15%, 500 mL of 20% and 500 mL of 30% ethyl acetate in petroleum ether and then high pressure liquid chromatography of the mixed fractions with 15% ethyl acetate in hexane afforded 116.1 mg (39%) of the desired diasteriomer **58a**, 38.2 mg (13%) of the aldol product **58b** , 22.0 mg (7%) of the aldol product **58c** and 13.7 mg (4.6%) of the aldol product **58d** or a 64% combined yield in a ratio of 61:20:11:7: Compound **58a** exhibited ^1H NMR and IR spectra that were in agreement to those obtained from Benzyl Lasalocid A.[9] Aldol 2 **58b** (Erythro-Cram): $[\alpha]_D^{22}$ +20.60° (c1.19, $CHCl_3$); IR ($CHCl_3$) 3450vb, 2980, 2950, 2895, 1685b, 1605, 1460, 1385, 1250, 1150, 955 cm^{-1}; ^1H-NMR ($CDCl_3$) δ 2.20 (s, 3H, $ArCH_3$), 5.41 (s, 2H, $PhCH_2$-O), 6.65 (d, 1H, J=7.5 Hz, ArH), 7.18 (d, 1H, J=7.5 Hz, ArH), 7.40 (m, 5H, PhH).

Aldol 3 58c (Threo-Anti Cram): $[\alpha]_D^{22}$ +0.11° (c1.135, $CHCl_3$); IR ($CHCl_3$) 3400b, 2970, 2940, 2885, 1700, 1655, 1460, 1385, 1250, 1148, 955 cm^{-1}; ^1H NMR ($CDCl_3$) 2.25 (s, 3H, $ArCH_3$), 5.40 (s, 2H, $PhCH_2O$), 6.65 (d, 1H, J=7.5 Hz, ArH), 7.15 (d, 1H, J=7.5 Hz, ArH), 7.38 (m, 5H, PhH).
Aldol 4 58d (Erythro-Anti Cram): $[\alpha]_D^{22}$ +8.81° (c1.84, $CHCl_3$); IR ($CHCl_3$) 3500vb, 2970, 2940, 2880, 1695, 1655, 1455, 1382, 1265, 1145, 955, 700 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.20 (s, 3H, $ArCH_3$), 5.40 (m(AB), 2H, $PhCH_2O$), 6.60 (d, 1H, J=7.0 Hz, ArH), 7.17 (d, 1H, J=7.0 Hz, ArH), 7.40 (bs, 5H, PhH).

Enantio Lasalocid A-sodium salt (1). A solution of 774 mg (1.147 mmol) of the ester **58** in 12 mL of absolute ethanol containing 70 mg of 5% palladium on carbon was stirred under an atmosphere of hydrogen for 12 h. The catalyst was then removed by filtration and then the solvent was removed under reduced pressure. Flash chromatography on a 3.0x24 cm column of silica gel eluting successively with 200 mL of each 20%, 30%, 40% and 50% ethyl acetate in petroleum ether afforded 641.2 mg (96%) of the corresponding acid: $[\alpha]_D^{22}$ +40.1° (c0.565, $CHCl_3$); IR ($CHCl_3$) 3300 vb, 2940, 2880, 2860, 1705, 1655, 1460, 1385, 1100 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.16 (bs, 3H, $ArCH_3$), 2.85 (m, 2H, CHCOCH), 3.3-4.4 (complex multiplets, 4H, CHOC's), 6.43 (d, 1H, J=6.5 Hz, Ar), 6.95 (d, 1H, J=6.5 Hz, ArH).

To a solution of 616.6 mg (1.04 mmol) of the above acid

in 15 mL of dichloromethane was added 0.7 g (8.3 mmol) of anhydrous sodium carbonate and the resulting mixture was stirred at room temperature under argon. After 10 h, the mixture was diluted with 35 mL of benzene and filtered. Removal of the solvent under reduced pressure gave 663.1 mg (99.7%) of enantio Lasalocid A-sodium salt: mp 169-172° C (benzene/cyclohexane, 1:20); $[\alpha]_D^{22}$ +84.0° (c0.96, $CHCl_3$); $[\ ]_D^{22}$ +31.4° (c0.89, MeOH); IR ($CHCl_3$); 3530 b, 2980, 1710, 1600, 1460, 1385, 1170 b, 1105, 1050 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.18 (s, 3H, $ArCH_3$), 6.40 (d, 1H, J=6.6 Hz, ArH), 6.92 (d, 1H, J=6.6 Hz, ArH), 14.3 (bs, 1H, ArOH). The IR and ^1H-NMR spectra were in excellent agreement with those obtained from natural lasalocid A-sodium salt. Anal. Calcd. for $C_{34}H_{53}O_8Na$: C, 66.64; H, 8.72. Found: C, 66.77; H, 8.61.

Enantio-epilasalocid A-sodium salts. The undesired diasteriomers from the above aldol were transformed into their respective acids then sodium salts by the above procedure for the preparation of **1**. Their physical data follows: Aldol 2 acid (Erythro-Cram): $[\alpha]_D^{22}$ +13.27° (c1.605, $CHCl_3$) 3460b, 2970, 2940, 2880, 1700, 1655, 1458, 1415, 1382, 1230b, 1160, 1100, 1040, 950 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.28 (m, 3H, $ArCH_3$), 6.67 (d, 1H, J-8.0 Hz, ArH), 7.22 (d, 1H, J=8.0 Hz, ArH).

Aldol 3 acid (Threo-Anti Cram): $[\alpha]_D^{22}$ +13.10° (c1.43, $CHCl_3$); IR ($CHCl_3$) 3440b, 2970, 2940, 2880, 1695, 1655, 1460, 1415, 1385, 1230vb, 1165, 1095, 1045b, 965b cm^{-1};

^{1}H NMR ($CDCl_3$) δ 2.23 (s, 3H, $ArCH_3$), 6.69 (d, 1H, J=8.0 Hz, ArH), 7.23 (d, 1H, J=8 Hz, ArH).

Aldol 4 acid (Erythro-Anti Cram): $[\alpha]_D^{22}$ +81.67° (c1.10, $CHCl_3$); IR ($CHCl_3$) 3520b, 2970, 2940, 2880, 1698, 1652, 1460, 1410, 1380, 1230vb, 1155, 960 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.23 (s, 3H, $ArCH_3$), 6.63 (d, 1H, J=8.0 Hz, ArH), 7.21 (d, 1H, J=8.0 Hz, ArH).

Aldol 2-sodium salt (Erythro-Cram): $[\alpha]_D^{22}$ -35.52° (c0.855, $CHCl_3$); IR ($CHCl_3$) 3300b, 2960, 2920, 2870, 1695, 1588, 1452, 1378, 1100, 1025, 960, 940, 905 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.20 (s, 3H, $ArCH_3$), 6.47 (d, 1H, J=6.5 Hz, ArH), 6.98 (d, 1H, J=6.5 Hz, ArH).

Aldol 3-sodium salt (Threo-Anti Cram): $[\alpha]_D^{2}$ -26.14° (c2.025, $CHCl_3$); IR ($CHCl_3$) 3300b, 2960, 2920, 2870, 1685, 1590, 1455, 1380, 1100, 960, 945, 905 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 2.18 (bs, 3H, $ArCH_3$), 6.43 (bd, 1H, J=6.5 Hz, ArH), 6.96 (d, 1H, J=6.5 Hz, ArH).

Aldol 4-sodium salt (Erythro-Anti Cram): $[\alpha]_D^{22}$ -36.18° (c1.345, $CHCl_3$); IR ($CHCl_3$) 3250vb, 2960, 2920, 2870, 1690, 1595, 1455, 1378, 1310, 1095, 945, 905 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.20 (bs, 3H, $ArCH_3$), 6.42 (d, 1H, J=7.0 Hz, ArH), 6.98 (d, 1H, J=7.0 Hz, ArH).

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use. Analytical 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 2 mL/min, preparative VPC on a Varian 930, equipped with a thermal conductivity detector, at a flow rate of 60 mL/min. The indicated liquid phase was absorbed on 60-80 mesh Chromosorb W AM 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, flash chromatography used 230-400 mesh ASTM. Alumina refers to the Brockmann Activity I-Neutral material manufactured by M. Woelm.

Analytical high pressure liquid chromatographic (HPLC) analyses were performed on a Perkin-Elmer Series 2 HPLC equipped with a Perkin-Elmer analytical silica column and a variable wavelength ultraviolet absorption detector using the indicated solvent at a flow rate of 1.9 mL/min. Preparative HPLC was performed on the

above system except that a Perkin-Elmer preparative silica column and a flow rate of 23 mL/min were used.

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

Other reagents were purified as follows: oxalyl chloride was distilled under argon; n-butanoyl chloride was heated at reflux for 3 hours with phosphorus pentachloride, then distilled, and the distillate was treated with quinoline and redistilled; methyl iodide was distilled from phosphorus pentoxide immediate before use; trisdimethylaminophosphine (TDAP) was distilled under argon before use; chloromethyl methyl

ether was dried for several hours over anhydrous calcium chloride, decanted and stirred briefly with anhydrous potassium carbonate, and then distilled under argon from anhydrous calcium chloride. Ammonium chloride was dried at 75° C under vacuum (1 mmHg) over phosphorus pentoxide for at least 12 hours.

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

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

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APPENDIX

The Total Synthesis of Polyether Antibiotics. The Synthesis of Lasalocid A (X-537A)

The Total Synthesis of Ionophore Antibiotics. A Convergent Synthesis of Lasalocid A (X537A)[1]

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Abstract: The construction of both the left-side aldehyde 2 and the right-side ketone 3 available from the reverse aldol reaction with lasalocid A (X537A) is described. For each synthesis chiral starting materials are used. For the aldehyde 2, (*R*)-(−)-citronellene is the source of the lone asymmetric center and the aromatic ring is prepared by a Diels–Alder reaction between the pyrone 22 and 1-(dibenzylamino)-1-propyne. For the ketone 3, carbohydrate precursors serve as the source of the furanoid and pyranoid subunits. These subunits are then joined through the use of the ester enolate Claisen rearrangement. Details for the aldol condensation between the aldehyde 2 and the zinc enolate of the ketone 3 are presented, and the formation of the natural ionophore from this process completes the highly convergent total synthesis.

The recently characterized[7] polyether ionophore antibiotics[8] represent a broad new class of biologically potent compounds that have rapidly found commercial value as coccidiostats[9] and anabolic agents[10] in animal medicine. In addition, the demonstration of their powerful cardiotonic activity[11] and apparent tissue selectivity[11] in mammalian systems holds promise for their use in human pharmacology. In light of these results, it is not surprising that the synthesis of these molecules has attracted the concern of numerous research groups, and several representatives of this class have yielded to total synthesis.[12] One such effort resulting in the total synthesis of lasalocid A (X537A) (1) is described herein.[13]

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The basic design for this synthesis was predicated on a desire to define a synthetic strategy that could be generally applied to the construction of numerous members of the polyether ionophore class as well as to potentially important nonnatural analogues. Due to the structural complexity and chemical sensitivity of the naturally occurring polyether ionophores, it may only be through efficient total syntheses that a wider range of biologically informative structural variants will become available in useful quantities for evaluation. This total synthesis of lasalocid A (X537A) then represents not only an important objective in its own right, but also a reasonable milieu in which to evaluate the potential generality of the overall synthetic scheme.

A striking structural feature of most of the polyether ionophores is the chain of substituted tetrahydrofuran and tetrahydropyran rings. One of the simplest member of this group is lasalocid A (X537A) which contains one tetrahydrofuran and one tetrahydropyran ring in sequence. It was the objective of this work to develop a methodology to generate the polyether skeleton in a building block manner by joining individually performed tetrahydrofuran and/or tetrahydropyran rings. Not only is such a convergent approach potentially logistically efficient, but it also offers the opportunity for a flexible combination of the oxygen-heterocyclic building blocks with possible wide structural variation.

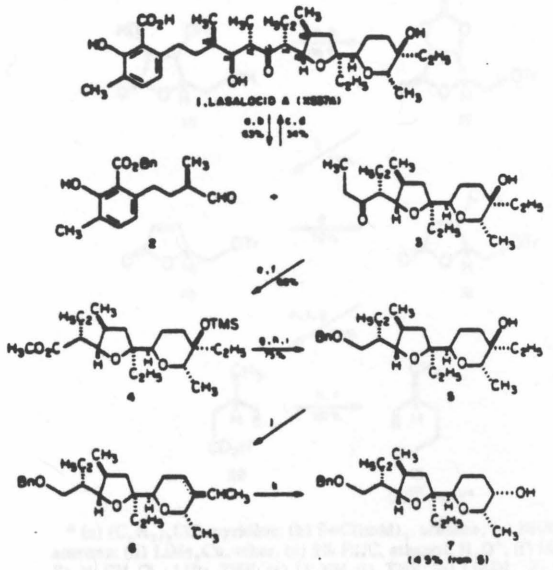
Another structural feature that is prevalent in these polyether ionophores and also central to lasalocid A (X537A) is the aldol-type linkage. In the antithetic sense, the C10,11 bond of lasalocid A (X537A) becomes the ideal point at which to divide the molecule. Technology gained through a process in which this particular aldol-type linkage can be reestablished from condensation of the left-side aldehyde 2 and the right-side ketone 3 should apply directly to other members of this class.

These objectives and basic concepts then form the basis of a broad synthetic program directed toward polyether ionophores, the first achievement in which is the total synthesis of lasalocid A (X537A). The current effort may be divided into three distinct segments. First, degradative work with the natural product itself[14] led quickly to the realization that the aldol-type condensation was indeed a viable approach for the construction of lasalocid A (X537A), and several key structures for comparison were also prepared from the right-side ketone 3. Second, a synthesis of the chiral left-side aldehyde 2 from the readily available terpenoid precursor (*R*)-(−)-citronellene 8 and nonaromatic substrates was developed. Third, a strategy for the convergent synthesis of the right-side ketone 3 was realized through the application of the ester enolate Claisen rearrangement to appropriate tetrahydrofuranoid and tetrahydropyranoid intermediates derived from readily available monosaccharides.

I. Degradation and Aldol-Type Reconstitution of Lasalocid A (X537A) (1). The initial degradation of lasalocid A (X537A) (1) (Scheme I) through the reverse aldol-type reaction followed previously reported[14] conditions. After formation of the benzyl ester of the ionophore, pyrolysis led to the aldehyde 2 and the ketone 3 in good yield. This reverse aldol-type reaction provided optically pure samples of both partners in contrast to a previous report,[13] which indicated that the right-side ketone 3 was epimerized at C14.[16] In the present investigation, only a single diastereomer was observed in the ^{13}C NMR spectrum of compound 3. For this purpose the pyrolytic process is obviously superior to the basic condition which also will effect the cleavage but leads to racemization of the aldehyde 2 and epimerization of the ketone 3.

After much experimentation with a variety of conditions, it was found that the reconstruction of lasalocid A (X537A) (1) as its

Scheme I. Degradation and Aldol-Type Reconstitution of Lasalocid A (X537A)[a]



[a] (a) Na salt of lasalocid A (X537A), BnBr, dioxane; (b) 230 °C (0.01 mmHg); (c) LDA, ether, −78 °C; $ZnCl_2$, 0 °C; RCHO, 0 °C, 5 min; (d) H_2, Pd/C, EtOH; (e) $KN(Me_3Si)_2$, THF; $(Me_3Si)Cl$; (f) O_3, CH_3OH–CH_2Cl_2; $NaBH_4$; CH_2N_2, Et_2O; (g) $LiAlH_4$, Et_2O; (h) *n*-Bu_4NF, THF; (i) KH, THF, BnBr; (j) KH, CS_2, CH_3I, THF; heat; (k) O_3, CH_3OH–CH_2Cl_2; $NaBH_4$.

benzyl ester could be accomplished through the aldol-type reaction between 2 equiv of the aldehyde 2 and one of the zinc enolate[17] of the ketone 3. The isomeric composition of the products obtained in 62% yield based on the ketone 3 used (95% based on unrecovered ketone 3) was 54:32:10:4. No conditions were found that would duplicate the previously reported[12b] results in which aldehyde 2 of significantly lower optical purity was used. Chromatography of this isomeric mixture resulted in the isolation of the desired benzyl ester in isomerically pure form in a 34% yield, and hydrogenolysis then freed the natural product itself.

While this aldol-type condensation effects the desired reconstitution of the ionophore and thereby assures the success of any synthetic scheme that can generate the two partners, the efficiency of the process is less than ideal, and further modifications are in order. However, the current results are sufficient to warrant a shift of attention to syntheses of the aldehyde 2 and the ketone 3. In this connection, intermediate comparison samples were desired for the stereochemically more demanding synthesis of the ketone 3. Particularly useful would be a naturally derived system representative of a stage in the synthesis shortly after the union of the tetrahydrofuran and tetrahydropyran rings. The degradation of the ketone 3 outlined in Scheme I was explored.

From the previous aldol-type reaction experiments, it was known that kinetic enolization of the ketone 3 generated the less substituted enolate. This was trapped with trimethylchlorosilane and then the resulting silyl enol ether was ozonized. Esterification of the acid formed led to the ester 4, which was subsequently converted to the benzyl ether 5. Since the planned synthetic scheme left the introduction of the tertiary alcohol in the tetrahydropyran ring until last, it would be advantageous to remove this substitution in the current degradation. Unfortunately, this could only be accomplished in poor yield, since dehydration of this tertiary alcohol invariably led to predominate formation of the endocyclic olefin. Only the described xanthate pyrolysis formed small but workable amount of the exocyclic olefin 6.

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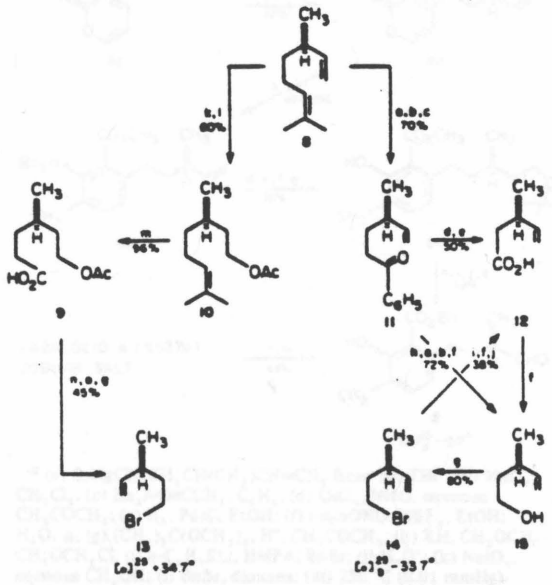
(17) Original conditions of House et al. (House, H. O.; Crumrine, D. S.; Teranishi, A. Y.; Olmstead, H. D. *J. Am. Chem. Soc.* **1973**, *95*, 3310–3324).

Scheme II. Synthesis of the Enantiomeric Bromopentenes 13 and 14[a]



[a] (a) MCPBA, CH_2Cl_2; (b) H_5IO_6, Et_2O; C_6H_5MgBr, Et_2O; (c) PCC, CH_2Cl_2; (d) $HCO_2C_2H_5$, $NaOCH_3$; (e) $NaIO_4$, aqueous CH_3OH; (f) $LiAlH_4$, Et_2O; (g) MsCl, Et_3N, CH_2Cl_2; LiBr, acetone; (h) LDA, THF, -78 °C; Me_3SiCl; (i) $AgBF_4$, Me_2SO; (j) 8 N H_2CrO_4, acetone; (k) 9-BBN, THF; H_2O_2, OH^-; (l) AcCl, Et_3N; (m) O_3; 8 N H_2CrO_4, acetone; (n) $Pb(OAc)_4$, $Cu(OAc)_2$, C_6H_6-pyr.; (o) $NaOCH_3$, CH_3OH.

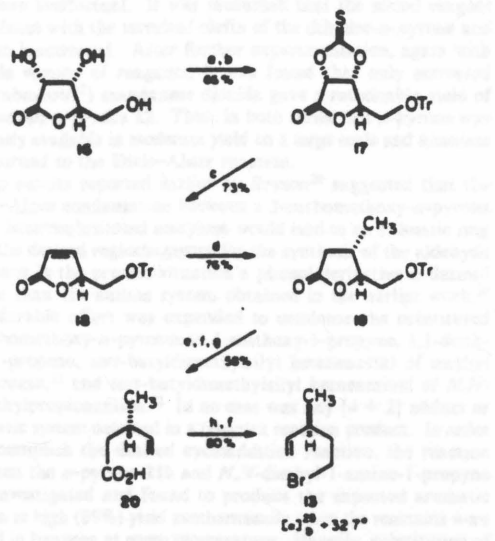
Ozonolysis, reduction, and then chromatography of the mixture of these olefins led to the isolation of the alcohol 7. The physical and spectral constants of this alcohol proved to be invaluable in the definition of the stereochemical outcome of the ensuing synthetic effort.

II. Synthesis of the Chiral Left-Side Aldehyde 2. For the synthesis of the aldehyde 2, an approach was chosen that entailed the construction of the aromatic ring system from aliphatic precursors. The more apparent approach that relied on the substitution of a preformed aromatic ring seemed fraught with difficulty by virtue of the tetrasubstituted pattern. The first focus for this scheme is the generation of a suitable side-chain unit that can serve as a latent aldehyde and carries the lone asymmetric center of the system. While initial successful exploration of this synthesis was done in a racemic model series, this report is confined to a discussion of the results with enantiomerically pure compounds.

The chiral unit chosen as starting material for this work was the monoterpene (*R*)-(−)-citronellene 8 (Scheme II). By suitable modification of the reaction sequences, it was possible to convert *either* olefinic arm of this terpene to the required bromoethyl residue *at will*. Thus, operation first by peracid oxidation resulted in preferential attack at the trisubstituted olefin and thence ultimate conversion to the bromopentane 14 required for the synthesis of the aldehyde 2 from naturally occurring lasalocid A (X537A) (1). In this work two procedures were developed for the degradative cleavage of the phenylketone 11; one leads through the acid 12 to the alcohol 15 and the other provides the same alcohol 15 directly. The bromide 14 obtained from the latter approach was then reoxidized to the acid 12 for comparison purposes. In each case, when the enantiomeric purity of the acid 12 was checked by analysis of its ^1H NMR spectrum with a chiral shift reagent,[18] only one enantiomer could be detected (>95%).

(18) Tris[3-(heptafluoropropylhydroxymethylene)-*d*-camphorato]europium(III).

Scheme III. Alternate Synthesis of the Bromopentene 13[a]

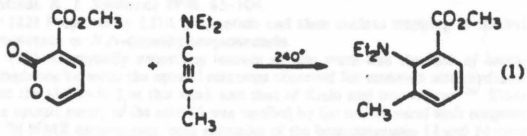


[a] (a) $(C_6H_5)_3CCl$, pyridine; (b) S=C(imid)$_2$, acetone; (c) Ni(Ra), acetone; (d) $LiMe_2Cu$, ether; (e) 5% Pd/C, ethanol, H_3O^+; (f) MsCl, Et_3N, CH_2Cl_2; LiBr, THF; (g) Li, NH_3(l), THF; (h) $LiAlH_4$, Et_2O.

As an alternative means to check this point and as well to provide access to the enantiomeric aldehyde 2, initial hydroboration of (*R*)-(−)-citronellene 8 was investigated as a means to modify the less substituted olefinic arm (Scheme II). After conversion of the hydroboration product to the acid 9 by ozonization with an oxidative workup, Kochi decarboxylative oxidation[19] converted the carboxyl-bearing arm to the vinyl group, and ultimately the enantiomeric bromide 13 became available. The optical rotation of this bromide was equal in magnitude, but opposite in sign, to that of the bromide 14. This result clearly demonstrated that no partial racemization had occurred during these reaction sequences and was a satisfying classical support for the optical purity of the two enantiomers. Thus, from the same chiral starting material, *both* enantiomers of the aliphatic side chain of the aldehyde 2 are readily available.

In contrast to material obtained elsewhere[12b] through attempted resolution of racemic acid 12, the high enantiomeric purity of the bromide 14 in this investigation was confirmed *independently* from another synthesis of the bromide 13 from D-(+)-ribonic acid, γ-lactone (16), as shown in Scheme III. A single isomer resulted from addition of lithium dimethyl cuprate to the unsaturated lactone 18. The acid 20, which is enantiomeric to the acid 12, was obtained via a reductive fragmentation of the bromide derivative of the lactone 19. The specific rotation of the bromide 13 secured from this synthetic route was in excellent agreement with that derived from (*R*)-(−)-citronellene.

For the construction of the aromatic ring, the Diels–Alder reaction between a carbomethoxy-α-pyrone and an acetylenic reagent was chosen. Such an aromatic ring synthesis was reported earlier by Bryson[20] (eq 1) for the parent α-pyrone, and the sub-

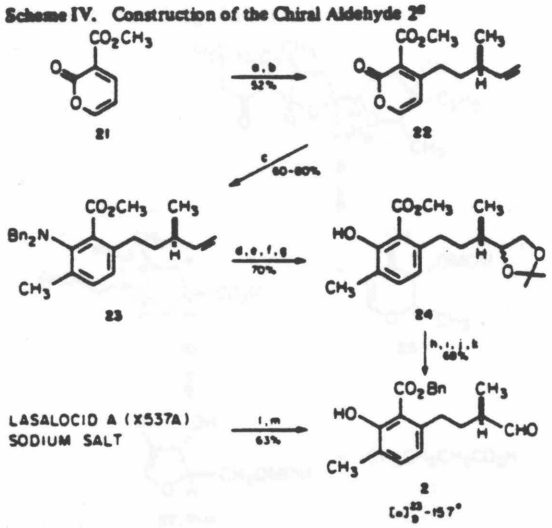


(1)

stitution pattern of the resulting aromatic ring was attractively similar to that of the desired aldehyde 2. For the case at hand, it was first necessary to construct an α-pyrone that bore the alkyl side chain prepared above and then to explore the possibility that

(19) Bacha, J. D.; Kochi, J. K. *Tetrahedron* **1968**, *24*, 2215–2226.
(20) Bryson, T. A.; Dennison, D. M. *J. Org. Chem.* **1977**, *42*, 2930–2931.

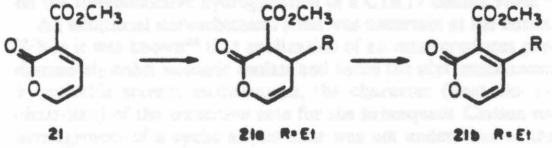
Scheme IV. Construction of the Chiral Aldehyde 2[a]



[a] (a) $BrMgCH_2CH_2CH(CH_3)CH{=}CH_2$ from 14, THF; (b) MnO_2, CH_2Cl_2; (c) $Bn_2NC{\equiv}CCH_3$, C_6H_6; (d) OsO_4, NMO, aqueous CH_3COCH_3; (e) H_2, Pd/C, EtOH; (f) *i*-AmONO, HBF_4, EtOH; H_2O, Δ; (g) $(CH_3)_2C(OCH_3)_2$, H^+, CH_3COCH_3; (h) KH, CH_3OCH_2-CH_2OCH_2Cl; (i) *n*-C_4H_9SLi, HMPA; BnBr; (j) H_3O^+; (k) $NaIO_4$, aqueous CH_3OH; (l) BnBr, dioxane; (m) 230 °C (0.01 mmHg).

an oxygen-substituted rather than nitrogen-substituted acetylenic system could be used in the Diels–Alder reaction. A solution to the former problem was readily found, but an extensive search for oxygen-substituted dienophiles proved fruitless. As a result, a synthesis of the aldehyde **2** was built around the utilization of an ynamine in the Diels–Alder reaction with the substituted α-pyrone (Scheme IV).

A noteworthy facet of this synthesis was the initial transformation of the α-pyrone **21** to its substituted derivative **22**. It was proposed that the preferred mode of organometallic conjugate addition to the α-pyrone **21** would be 1,4-addition rather than 1,6-addition by virtue of the deactivation of the 6-position by the ether oxygen. Rearomatization of the resulting 1,4 adduct was then to be accomplished by dehydrogenation. In model experiments, on addition of the α-pyrone **21** to lithium dimethyl cuprate



or cupric acetate/ethylmagnesium bromide solution, the reaction mixture turned purple, and after varying reaction times and temperatures, workup led to *no* desired adduct. On the premise that these results were the consequences of initial electron transfer from an incipient cuprate to the aromatic α-pyrone, the addition of ethylmagnesium bromide itself in the absence of copper salt was investigated. It was gratifying to find that the yield of the 1,4 adduct **21a** under these conditions was 90%. This result underscores the difference in character between these two organometallic reagents.

The dehydrogenation of the 1,4 adduct **21a** also proved to be an initial obstacle. Several standard reagents, such as sulfur, DDQ, and chloranil, were ineffective, and activated manganese dioxide, while effective, was capricious. In this model series, dehydrogenation was most efficiently (65% yield) effected by nickel peroxide which gave the model substituted α-pyrone **21b**.

When these experiences were applied to the preparation of the desired α-pyrone **22** in which both the racemic and optically active bromopentenes **14** were used, the conjugated 1,4-addition was similarly observed in good yield with the derived organomagnesium reagent. The nickel peroxide dehydrogenation procedure, however, was now ineffectual. It was presumed that the nickel reagent complexes with the terminal olefin of the dihydro-α-pyrone and is then inactivated. After further experimentation, again with a wide variety of reagents, it was found that only activated (Attenburrow[21]) manganese dioxide gave a reasonable yield of the desired α-pyrone **22**. Thus, in both series this α-pyrone was routinely available in moderate yield on a large scale and attention was turned to the Diels–Alder reaction.

The results reported earlier by Bryson[20] suggested that the Diels–Alder condensation between a 3-carbomethoxy-α-pyrone and a heterosubstituted acetylene would lead to an aromatic ring with the desired regiochemistry for the synthesis of the aldehyde **2**. Since in the present situation a phenol derivative is desired rather than the aniline system obtained in the earlier work,[20] considerable effort was expended to condense the substituted 3-carbomethoxy-α-pyrones to 1-methoxy-1-propyne, 1,1-diethoxy-1-propene, *tert*-butyldimethylsilyl keteneacetal of methyl propionate,[22] and *tert*-butyldimethylsilyl ketneaminal of *N,N*-dimethylpropionamide.[22] In no case was any [4 + 2] adduct or aromatic system detected in a complex reaction product. In order to accomplish the desired cycloaddition reaction, the reaction between the α-pyrone **21b** and *N,N*-diethyl-1-amino-1-propyne was investigated and found to produce the expected aromatic system in high (89%) yield exothermically when the reactants were mixed in benzene at room temperature. Happily, substitution of either the racemic or optically active substituted α-pyrone **22** and *N,N*-dibenzyl-1-amino-1-propyne did not alter these results, and in each case the aniline derivative **23** was obtained in high yield.

The choice of the *N,N*-dibenzyl-1-amino-1-propyne was predicated by the necessity to replace the nitrogen by oxygen through diazotization of the aniline derivative obtainable after hydrogenolysis of the initial aromatic product **23**. This process was efficiently accomplished as shown in Scheme IV, and the major skeletal and functional synthetic problems presented by the aldehyde **2** were solved. Further cosmetic work to exchange the methyl for a benzyl ester and to ummask the aldehyde function led to the desired aldehyde **2**. The necessity to exchange the methyl for the benzyl ester was dictated by the observation that the methyl ester was highly resistant to hydrolysis, and particularly after aldol-type condensation with the right-side ketone **3**, the methyl ester could not be removed without severe degradation of the system.

The identity of the chiral synthetic aldehyde **2** was established by comparison of its physical and spectral data with those observed on sample of the aldehyde **2** derived from natural lasalocid A (X537A) (**1**). A reliable (20% from α-pyrone **21** and 8% from (*R*)-(−)-citronellene (**8**)) synthesis of the chiral aldehyde **2** was thus available[23] and construction of the polyether ketone **3** was pursued.

III. Construction of the Polyether Right-Side Ketone 3. The basic concept for the synthesis of the right-side ketone **3** is presented in Scheme V. The heart of this highly convergent approach is the union of the furanoid acid **25** to the pyranoid glycal **26** through application of the ester enolate Claisen rearrangement.[24] Such an approach allows for the stereochemical control

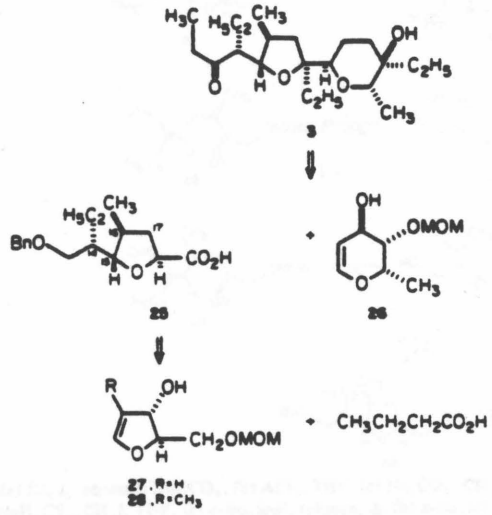
(21) Attenburrow, J.; Cameron, A. F. B.; Chapman, J. H.; Evans, R. M.; Hems, B. A.; Jansen, A. B. A.; Walker, T. *J. Chem. Soc.* **1952**, 1094–1111. Fatiadi, A. J. *Synthesis* **1976**, 65–104.

(22) Prepared by LDA enolization and then enolate trapping of methyl propionate or *N,N*-dimethylpropionamide.

(23) An initially unsettling feature of this work was the lack of correspondence between the optical rotations observed for common intermediates and the aldehyde **2** in this work and that of Kishi and co-workers.[12b] Since the optical purity of the acid **12** was verified by the use of chiral shift reagents in ^1H NMR experiments, both antipodes of the bromopentenes **13** and **14** were prepared, and the optical rotation of both synthetic and naturally derived aldehyde **2** was identical, the optical purity of the systems reported here is believed to be on a firm basis. The previously reported[12b] values for these systems seem, therefore, to represent the observations made on partially racemic material.

(24) Ireland, R. E.; Mueller, R. H.; Willard, A. K. *J. Am. Chem. Soc.* **1976**, *98*, 2868–2877.

Scheme V. Basic Design for Synthesis of Ketone 3



of the formation of the central carbon–carbon bond in an *intramolecular* reaction after the two partners have been joined in an efficient *intermolecular* esterification process. The known potential for stereochemical control during the Claisen rearrangement[25] is augmented in the ester enolate version through the possibility that either the *erythro* or *threo* product is accessible from the same precursor[26,27] by choice of enolization conditions.

Carbohydrate precursors were especially suitable for the construction of the chiral furanoid **25** and pyranoid **26** subunits. In an earlier report, the preparation[28] of various glycals and subsequent model studies[29] for ester enolate Claisen rearrangement were presented. For this synthesis, the pyranoid subunit **26** could be secured with minor modification of the existing sequence.[29,30] It remained to prepare the furanoid subunit **25** in order to explore the remaining features of this synthetic scheme.

The basic strategy for the construction of this subunit entailed the application of the ester enolate Claisen rearrangement technology to the butyrate of either glycal **27** or **28**. In the former case, it would then be necessary to introduce the C16 methyl group,[16] while in the latter situation, synthetic success depends on the stereoselective hydrogenation of a C16,17 double bond.[16]

An additional stereochemical point was uncertain at the outset. While it was known[24] that enolization of an ester produces predominately either isomeric enolate and hence the silyl keteneacetal by suitable solvent modification, the character (boat-like vs. chair-like) of the transition sate for the subsequent Claisen rearrangement of a cyclic allylic ester was not understood at the time.[31] Therefore, it was not possible to predict in advance which enolate geometry would lead to the desired *S* configuration at C14[16] in subunit **25**. On the other hand, the correct chirality at C15[16] was assured by the choice of furanoid glycal. Thus, while synthetic success was certain by virtue of the availability of both the 14*R* and 14*S* configurations[16] from the appropriate enolates, the correct conditions could not be defined until the four diastereomers **7** and **56–58** were prepared and compared with material obtained from degradation of the natural product itself. On the assumption that the stereochemical result of the enolization of the butyrate of the glycals **27** and **28** is the same as that for acyclic esters established earlier,[24] the later comparison revealed that the preferred transition state for this Claisen rearrangement was boat-like. Therefore, the 14*S* configuration[16] in subunit **25** would be derived from the (*Z*)-ketene acetal via enolization in 23% HMPA in THF.

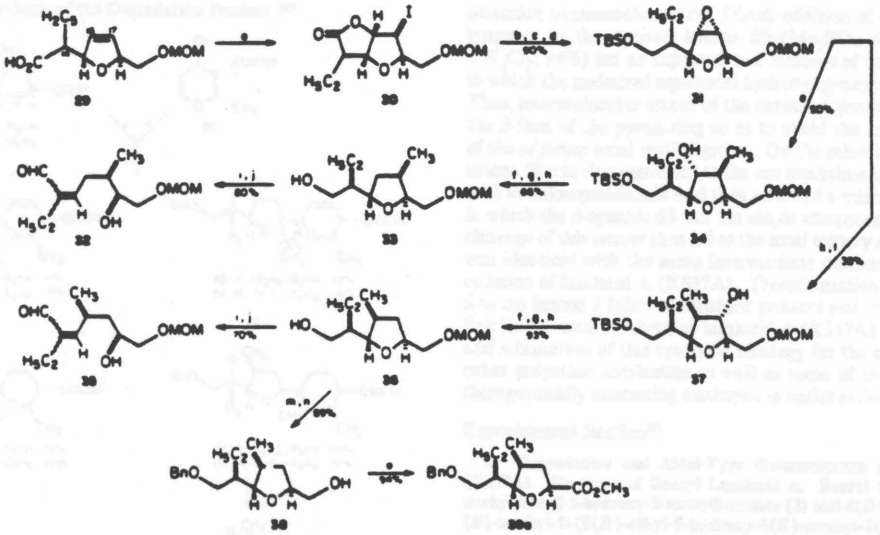
The construction of the acid **25** was first approached through the glycal **27**[29] from which the acid **29** was prepared (Scheme VI) as a mixture of C14 isomers[16] (LDA/THF: 73%; ratio[32] 81:19 and LDA/HMPA–THF: 60%; ratio[32] 21:79) as described earlier.[29] The problem was now the introduction of the C16 methyl group,[16] and for this exploration the more conveniently available LDA/THF isomeric mixture **29** was used. This acid mixture was converted to the α-oriented epoxides **31** in 90% overall yield through the intermediate iodolactone **30**. Reaction of this α-epoxide mixture with lithium dimethyl cuprate in ether/pentane resulted in the introduction of a β-oriented methyl group, and after chromatographic separation, the alcohol **34**, along with 12% of its C14 epimer,[16] was obtained. Removal of the hydroxyl group and silyl ether cleavage led to the isomerically pure primary alcohol **33**. In order to ascertain the location of the newly introduced ring methyl group, this alcohol was converted to the unsaturated aldehyde **32**. The ^{1}H NMR spectrum of this aldehyde revealed that the resonance due to the olefinic hydrogen was a triplet. Methylation at the desired C16 position[16] should give rise to an unsaturated aldehyde in which this olefinic hydrogen is only a doublet. The possibility of this signal being a pair of doublets, due to the possible formation of olefin isomers during base elimination, was ruled out by examination of the spectrum at different field strengths. This result showed that cuprate cleavage had occurred at the undesired C17 position.[16]

Since the methylation had taken place at the more hindered C17 position[16] with lithium dimethyl cuprate, it was hypothesized that the cleavage entailed prior complexation of the organometallic reagent with the adjacent methoxymethylene blocking group. To avoid this effect, the α-epoxide mixture **31** was treated with lithiated 1,3-dithiane.[33] Desulfurization of the resulting products then provided a new methylated alcohol **37** in moderate yield. In order to verify that this new alcohol was indeed the result of epoxide cleavage at the C16 position,[16] it was converted to the unsaturated aldehyde **35**, using the same sequence as described above. In this instance, the resonance due to the olefinic hydrogen in the ^{1}H NMR spectrum was the expected doublet. With the assurance that the structure of the furan ring was now correct, the intermediate primary alcohol **36** was converted to the anticipated furanoid subunit as its methyl ester **39a**.

The overall yield of this construction was disappointing and prompted an exploration into an alternate approach through a branched-chain carbohydrate precursor. For this purose, "α"-D-glucosaccharinic acid, γ-lactone (**40**),[34] was the ideal substrate. Available on large scale by the treatment of invert sugar with aqueous calcium hydroxide,[34] this branched-chain sugar fit the previously described technology (Scheme VII). Systematic application of the previous sequence[29] led in good yield to the mixture of unsaturated esters **43** in which either the *R* or *S* epimer at C14[16] could be made to predominate. It was somewhat surprising, but gratifying, to discover that catalytic hydrogenation of C16,17 double bond[16] in esters **43** gave a readily separable mixture of two saturated esters that were *only* epimeric at the earlier C14 pos-

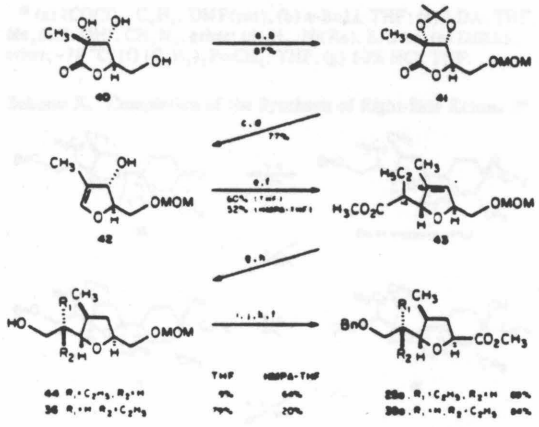
(25) von E. Doering, W.; Roth, W. R. *Tetrahedron* **1962**, *18*, 67–74.
(26) Ireland, R. E.; Wilcox, C. S. *Tetrahedron Lett.* **1977**, 2839–2842.
(27) In the ester enolate Claisen rearrangement, two factors determine the stereochemical outcome of the single carbon–carbon bond formation: the geometry of the enolate and the chair/boat character of the transition state. Enolate formation of straight chain esters can be readily controlled and predicted;[24] however, such is not the case with α-substituted esters. In the latter situation, the geometry of the enolate formed may be specific, but experimental reversal of the enolate geometry may not be possible. Moreover, reasonably accurate prediction of enolate geometry is possible only in the case of most α-heterosubstituted esters.
(28) Ireland, R. E.; Wilcox, C. S.; Thaisrivongs, S. *J. Org. Chem.* **1978**, *43*, 786–787.
(29) Ireland, R. E.; Thaisrivongs, S.; Vanier, N.; Wilcox, C. S. *J. Org. Chem.* **1980**, *45*, 48–61.
(30) Ireland, R. E.; Wilcox, C. S. *J. Org. Chem.* **1980**, *45*, 197–202.
(31) Subsequent to the current work, a definitive determination for the boat-like character for the transition state for rearrangement of glycal silyl ketene acetals was made through the synthesis of the (+)- and (−)-eonectic acids (Ireland, R. E.; Vevert, J.-P. *Can. J. Chem.* **1981**, *59*, 572–583).
(32) Ratios were determined from the corresponding hydrogenated methyl esters by GLPC (4% SE-30, 120 °C, $^1/_4$ in. × 6 ft).
(33) Yamashita, A.; Rosowsky, A. *J. Org. Chem.* **1976**, *41*, 3422–3425.
(34) Whistler, R. L.; BeMiller, J. N. *Meth. Carbohydr. Chem.* **1963**, *2*, 484–485.

Scheme VI. Synthesis of Epimeric Furanoid Subunit 39[a]



[a] (a) KI, I_2, aqueous $NaHCO_3$; (b) AlH_3, THF; (c) Na_2CO_3, CH_3OH; (d) TBSCl, imidazole, DMF; (e) $LiMe_2Cu$, ether–pentane; (f) NaH, CS_2, CH_3I, THF; (g) *n*-Bu_3SnH, toluene, Δ; (h) *n*-Bu_4NF, THF; (i) PCC, NaOAc, CH_2Cl_2; (j) KO-*t*-Bu, THF; (k) $C_6H_5S_2Li$, THF, (l) Ni(Ra), EtOH; (m) KH, $C_6H_5CH_2Br$, THF; (n) 10% HCl, THF; (o) Pt, O_2, aqueous $NaHCO_3$; CH_2N_2.

Scheme VII. Synthesis of Furanoid Subunit 25a[a]



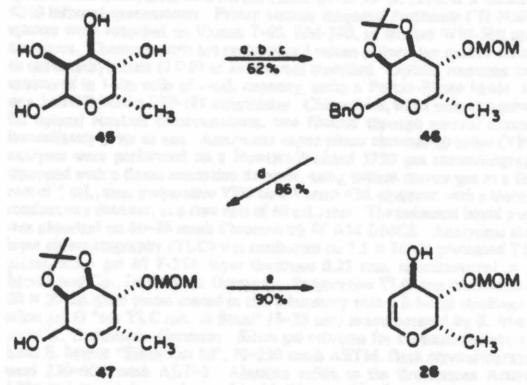
[a] (a) CH_3COCH_3, H_2SO_4; (b) KH, $ClCH_2OCH_3$, THF; (c), DIBAL, ether, −78 °C. (d) $P(NMe_2)_3$, CCl_4, THF, 0 °C; Li, NH_3(l), then NH_4Cl; (e) *n*-C_3H_7COCl; LDA, THF (HMPA); Me_3SiCl; OH^-. (f) CH_2N_2, ether; (g) H_2, 10% Pt/C, EtOAc; (h) $LiAlH_4$, ether; (i) KH, $C_6H_5CH_2Br$, THF; (j) 10% HCl, THF, (k) Pt, O_2, aqueous $NaHCO_3$.

ition.[16] Hydrogenation had taken place in a highly stereoselective manner and in the desired α sense. Hydride reduction of the 14*S* ester[16] led to the previously formed (Scheme VI) alcohol **36**, while reduction of the 14*R* ester[16] gave the alcohol **44**. Both alcohols were readily transformed to the esters **25a** and **39a**. While the basis for the stereoselectivity of the catalytic hydrogenation of the esters **43** is not obvious, the outcome greatly increased the efficiency of the synthetic route for these furanoid subunits.

The construction of the alcohol **26** started with 6-deoxy-L-gulose (**45**)[30] as shown in Scheme VIII. The hydroxyl groups were differentiated as benzyl glycoside, *O*-isopropylidene, and methoxymethyl ether in compound **46**. Removal of the benzyl ether then led to the lactol **47** which was converted to the desired glycal **26** by the previously described procedure.[29]

The building blocks (acids **25** and **39** and the glycal **26**) of the right-side ketone **3** were now in hand, together with the necessary technology for their union.[29] It was the intention to generate all

Scheme VIII. Synthesis of the Glycal 26[a]

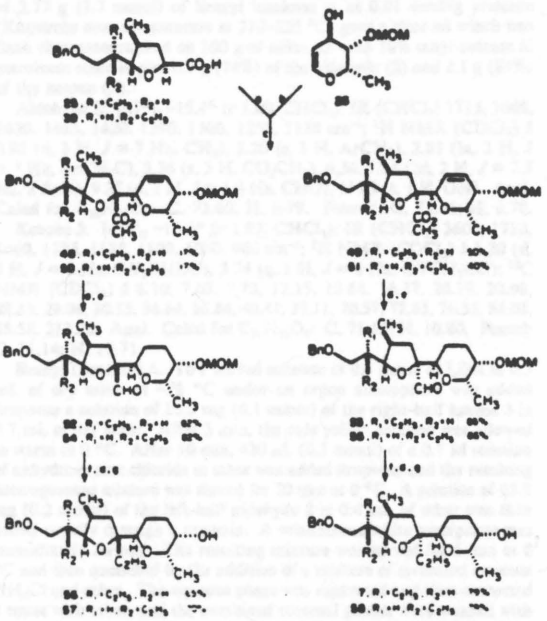


[a] (a) BnOH, AcCl, (b) $(CH_3)_2C(OCH_3)_2$, H^+, acetone; (c) KH, $ClCH_2OCH_3$, THF; (d) Li, NH_3(l), THF; (e) $P(NMe_2)_3$, CCl_4, THF; 0 °C; Li, NH_3(l), then NH_4Cl.

four possible diastereoisomers **7** and **56–58** from the connection of the pyranoid subunit **26** to both epimers of the furanoid acids **25** and **39** and to correlate the resultant stereoisomers with the natural degradation product **7**.

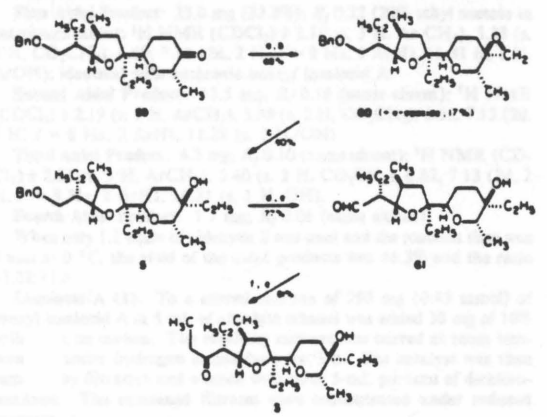
As described previously,[29] it was not possible to alter dramatically the stereochemical outcome of the enolization of α-heterosubstituted esters, and hence the more convenient THF conditions were used in these ester enolate Claisen rearrangements (Scheme IX). In this manner, the acid **25** resulted in the formation of the readily separable isomeric esters **48** and **49**, while the C14 epimer **39**[16] afforded the isomeric esters **50** and **51**. Although the yields of even the major diastereoisomers **49** and **51** were modest, this crucial step lent credability to the convergent synthetic scheme. Subsequent transformation of these esters individually to the projected alcohols **7** and **56–58** proceeded in excellent yields. With all four of the diastereoisomers in hand, it was now possible, through comparison to the natural degradation product **7**, to define completely their stereochemistry. The synthetic stereoisomer that was identical with the degradation product **7** is that derived from the major Claisen isomer **49** from the furanoid acid **25** which itself was the major Claisen isomer when

Scheme IX. Synthesis of the Degradation Product 7[a]



[a] (a) $(COCl)_2$, C_6H_6, DMF(cat); (b) *n*-BuLi, THF; (c) LDA, THF, Me_3SiCl; OH^-; CH_2N_2, ether; (d) H_2, Ni(Ra), EtOAc; (e) DIBAL, ether; -78 °C; (f) $(C_6H_5)_3P{=}CH_2$, THF; (g) 10% HCl, THF.

Scheme X. Completion of the Synthesis of Right-Side Ketone 3[a]



[a] (a) $(C_6H_5)_3P{=}CH_2$, THF; (b) MCPBA, CH_2Cl_2; (c) $LiMe_2Cu$, ether–pentane; (d) Li, NH_3(l); NH_4Cl; (e) PCC, NaOAc, CH_2Cl_2; (f) C_2H_5MgBr, THF.

the glycal **42** butyrate was enolized in HMPA/THF. Since the naturally derived material **7** is the syn isomer, its minor companion **56** must be from the anti series, as shown. The materials derived from the acid **39** which is formed by ester enolate Claisen rearrangement of the glycal **42** butyrate in THF will be epimeric with those from the acid **25** at C14[16] only, and thus, the major isomer must be the syn alcohol **58** and the minor is the anti alcohol **57**. This correlation served to assign the stereochemical outcome of all of these synthetic transformations and also defined the desired pathway for the construction of intermediate alcohol **7** for use in the completion of the synthesis of the ketone **3**.

The final stages of the ketone **3** synthesis (Scheme X) entailed essentially the introduction of two ethyl groups. The first of these, which transformed the secondary alcohol of the pyran ring of the intermediate **7** to the designated tertiary alcohol, required some attention to stereochemistry. Direct addition of organometallic reagents to the derived ketone **59** (Me_2SO, $(COCl)_2$, Et_3N, CH_2Cl_2; 94%) led as expected to a mixture of tertiary alcohols in which the undesired equatorial hydroxyl group predominated.[35] Thus, intermolecular attack of the carbonyl group takes place on the β-face of the pyran ring so as to avoid the steric hindrance of the adjacent axial methyl group. On the other hand, when the ketone **59** was first converted to the exo methylene olefin, oxidation with *m*-chloroperbenzoic acid then afforded a mixture of epoxides in which the β-epoxide **60** was the major component. Subsequent cleavage of this isomer then led to the axial tertiary alcohol **5** which was identical with the same intermediate obtained during degradation of lasalocid A (X537A). Transformation of this alcohol **5** to the ketone **3** followed standard protocol and provided the last link for the total synthesis of lasalocid A (X537A). Modification and adaptation of this synthetic strategy for the construction of other polyether antibiotics as well as some of their potentially therapeutically interesting analogues is under active investigation.

Experimental Section[36]

I. Degradation and Aldol-Type Reconstitution of Lasalocid A (X537A). Pyrolysis of Benzyl Lasalocid A. Benzyl 6-[(4-exo-3(*R*)-methyl)butyl]-2-hydroxy-3-methylbenzoate (2) and 4(*R*)-[5(*S*)-Ethyl-3-(*S*)-methyl-5-(5(*R*)-ethyl-5-hydroxy-6(*S*)-methyl-2(*R*)-tetrahydro-

(35) Unpublished results from this laboratory by L. Courtney.

(36) Boiling points are uncorrected. Melting points were determined with a Hoover capillary melting point apparatus and are uncorrected. Infrared (IR) spectra were determined on a Perkin-Elmer 237B, 737B, 1310, or a Beckman 4210 infrared spectrometer. Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded on Varian T-60, EM-390, or Bruker WM-500 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 or a JASCO Model DIP-181 polarimeter. Chloroform, when used as a solvent for optical rotation determinations, was filtered through neutral alumina immediately prior to use. Analytical 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 2 mL/min, preparative VPC on a Varian 930, equipped with a thermal conductivity detector, at a flow rate of 60 mL/min. The indicated liquid phase was absorbed on 60–80 mesh Chromosorb W AM DMCS. Analytical thin-layer chromatography (TLC) was conducted on 2.5 × 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 × 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 μm) manufactured by E. Merck and Co., Darmstadt, Germany. Silica gel columns for chromatography utilized E. Merck "Silica Gel 60", 70–230 mesh ASTM; flash chromatography used 230–400 mesh ASTM. Alumina refers to the Brockmann Activity I-Neutral material manufactured by M. Woelm. "Dry" solvents were distilled shortly before use from an appropriate drying agent. Ether and tetrahydrofuran (THF) were distilled under dry argon from sodium metal in the presence of benzophenone. *n*-Pentane was distilled from sodium metal under argon. Benzene and toluene were distilled from phosphorus pentoxide. Methanol was distilled from magnesium methoxide. Hexamethylphosphoramide (HMPA) was distilled at ~1.0 mm of Hg from pulverized calcium hydride. Triethylamine and diisopropylamine were distilled under argon from sodium benzophenone immediately prior to use. Pyridine and hexamethyldisilazane were all distilled before use from calcium hydride. Ammonia was distilled from the tank and then from a blue lithium solution. Other reagents were purified as follows: oxalyl chloride was distilled under argon; *n*-butanoyl chloride was heated at reflux for 3 h with phosphorus pentachloride and then distilled, and the distillate was treated with quinoline and redistilled; methyl iodide was distilled from phosphorus pentoxide immediately before use; tris(dimethylamino)phosphine (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 h. All other reactants and solvents were "Reagent Grade" unless described otherwise. "Ether" refers to anhydrous diethyl ether which is supplied by Mallinckrodt and Baker. "Petroleum ether" refers to the Analyzed Reagent grade hydrocarbon fraction, bp 35–60 °C, which is supplied by J. T. Baker Co., Phillipsburg, NJ, and was not further purified. Reactions were run under an argon atmosphere arranged with a mercury bubbler so that the system could be alternately evacuated and filled with argon and left under a positive pressure. Syringes and reaction flasks were dried at least 12 h in an oven (at 120–140 °C) and cooled in a desiccator over anhydrous $CaSO_4$ prior to use. Mass spectral analyses were performed by Dr. Kai Fang, UCLA, Los Angeles, CA, or Susan Rotschaefer, Caltech, Pasadena, CA. Elemental combustion analyses were performed by Spang Microanalytical Laboratory, Eagle Harbor, MI, or Jan Mitchell, Caltech, Pasadena, CA.

pyranyl)-2(*S*)-tetrahydrofuryl]hexan-3-one (3). Evaporative distillation of 2.77 g (3.7 mmol) of benzyl lasalocid A at 0.01 mmHg pressure (Kugelrohr oven temperature at 210–220 °C) gave a clear oil which was flash chromatographed on 100 g of silica gel with 10% ethyl acetate in petroleum ether to give 0.9 g (74%) of the aldehyde (2) and 1.1 g (84%) of the ketone (3).

Aldehyde 2: $[\alpha]^{22}_D$ −15.4° (*c* 1.00, $CHCl_3$); IR ($CHCl_3$) 1715, 1660, 1620, 1465, 1420, 1390, 1300, 1250, 1150 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.92 (d, 3 H, *J* = 7 Hz, CH_3), 2.20 (s, 3 H, $ArCH_3$), 2.81 (bt, 2 H, *J* = 7 Hz, $ArCH_2C$), 5.36 (s, 3 H, CO_2CH_2), 6.56, 7.14 (2d, 2 H, *J* = 7.5 Hz, 2 ArH), 9.37 (d, 1 H, *J* = 1.5 Hz, CHO), 11.43 (s, 1 H, OH). Anal. Calcd for $C_{20}H_{22}O_4$: C, 73.60; H, 6.79. Found: C, 73.56; H, 6.70.

Ketone 3: $[\alpha]^{24}_D$ −19.6° (*c* 1.02, $CHCl_3$); IR ($CHCl_3$) 3600, 1710, 1460, 1385, 1135, 1100, 1060, 960 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.20 (d, 3 H, *J* = 6 Hz, CH_3CHOC), 3.74 (q, 1 H, *J* = 6 Hz, $CHCH_3OC$); ^{13}C NMR ($CDCl_3$) δ 6.10, 7.08, 7.73, 12.15, 13.84, 16.37, 20.79, 20.98, 28.33, 29.04, 30.15, 36.64, 36.84, 40.41, 57.11, 70.57, 72.65, 76.55, 84.08, 85.58, 213.28. Anal. Calcd for $C_{21}H_{36}O_4$: C, 71.15; H, 10.80. Found: C, 71.14; H, 10.71.

Benzyl Lasalocid A. To a stirred solution of 0.3 mmol of LDA in 0.5 mL of dry ether at −78 °C under an argon atmosphere was added dropwise a solution of 35.5 mg (0.1 mmol) of the right-half ketone 3 in 0.7 mL of dry ether. After 5 min, the pale yellow solution was allowed to warm to 0 °C. After 10 min, 430 μL (0.3 mmol) of a 0.7 M solution of anhydrous zinc chloride in ether was added dropwise and the resulting heterogeneous mixture was stirred for 20 min at 0 °C. A solution of 65.3 mg (0.2 mmol) of the left-half aldehyde 2 in 0.4 mL of ether was then added rapidly through a cannula. A voluminous white precipitate was immediately formed. The resulting mixture was stirred for 5 min at 0 °C and then quenched by the addition of a mixture of saturated aqueous NH_4Cl and ether. The aqueous phase was separated and then extracted 3 times with ether, and the combined ethereal phases were washed with saturated aqueous NaCl and dried ($MgSO_4$). Removal of the solvent under reduced pressure and high-pressure liquid chromatography of the residue on silica gel with a solvent gradient of 5–10% ethyl acetate in petroleum ether allowed the separation of four aldol products in a combined yield of 62.4% (95% based on unrecovered ketone 3) and a ratio of 54:32:10:4.

First Aldol Product: 23.0 mg (33.8%); R_f 0.22 (20% ethyl acetate in petroleum ether); ^1H NMR ($CDCl_3$) δ 2.19 (s, 3 H, Ar CH_3), 5.38 (s, 2 H, CO_2CH_2), 6.60, 7.11 (2d, 2 H, *J* = 8 Hz, 2 ArH), 11.31 (s, 1 H, ArOH); identical with authentic benzyl lasalocid A.

Second Aldol Product: 13.5 mg; R_f 0.16 (same eluent); ^1H NMR ($CDCl_3$) δ 2.19 (s, 3 H, $ArCH_3$), 5.39 (s, 2 H, CO_2CH_2), 6.62, 7.13 (2d, 2 H, *J* = 8 Hz, 2 ArH), 11.28 (s, 1 H, OH).

Third Aldol Product: 4.3 mg; R_f 0.10 (same eluent); ^1H NMR ($CDCl_3$) δ 2.21 (s, 3 H, $ArCH_3$), 5.40 (s, 2 H, CO_2CH_2), 6.62, 7.13 (2d, 2 H, *J* = 8 Hz, 2 ArH), 11.31 (s, 1 H, OH).

Fourth Aldol Product: 1.7 mg; R_f 0.06 (same eluent).

When only 1.1 equiv of aldehyde 2 was used and the reaction time was 4 min at 0 °C, the yield of the aldol products was 46.3% and the ratio 53:28:12:6.

Lasalocid A (1). To a stirred solution of 290 mg (0.43 mmol) of benzyl lasalocid A in 5 mL of absolute ethanol was added 30 mg of 10% palladium on carbon. The resulting mixture was stirred at room temperature under hydrogen atmosphere for 3 h. The catalyst was then removed by filtration and washed with three 5-mL portions of dichloromethane. The combined filtrates were concentrated under reduced pressure.

The above residue was dissolved in 5 mL of dichloromethane and 300 mg of solid Na_2CO_3 was added. The resulting mixture was stirred at room temperature for 10 h and then filtered. Concentration of the filtrate under reduced pressure gave 260 mg (100%) of the sodium salt of lasalocid A.

The spectral properties of this compound were identical with those of the authentic sodium salt of lasalocid A.

4(*R*)-[5(*S*)-Ethyl-3(*S*)-methyl-5-(5(*R*)-ethyl-5-(trimethylsiloxy)-6(*S*)-methyl-2(*R*)-tetrahydropyranyl)-2(*S*)-tetrahydrofuryl]-3-(trimethylsiloxy)hex-2-ene. To a stirred solution of 11.22 mmol of potassium hexamethyldisilazide in 20 mL of dry THF at −78 °C under argon was added a solution of 1.325 g (3.74 mmol) of the ketone 3 in 3 mL of dry THF. After 10 min the reaction mixture was treated with 2.8 mL (11.2 mmol of Me_3SiCl) of the supernatant centrifugate from a mixture of 4.2 mL of trimethylchlorosilane and 1.4 mL of dry triethylamine. Cooling was then discontinued and the resulting mixture was stirred at room temperature for 90 min, diluted with 300 mL of ether, washed with two 80-mL portions of water and 40 mL of saturated aqueous NaCl, and then dried (Na_2SO_4). Removal of the solvents under reduced pressure and evaporative distillation of the residue afforded 1.76 g (94%) of the silyl enol ether: evaporative distillation 190 °C (0.05 mmHg); $[\alpha]^{22}_D$ +13.0° (*c* 1.30, $CHCl_3$); IR ($CHCl_3$) 1680, 1465, 1255, 1060, 845 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.15 (s, 9 H, $(CH_3)_3SiOC$=), 0.20 (s, 9 H, $(CH_3)_3SiOCC_2$), 0.87 (bt, 9 H, *J* = 7 Hz, CH_3CH_2), 0.92 (d, 3 H, *J* = 7 Hz, CH_3CHCC), 1.15 (d, 3 H, *J* = 7 Hz, CH_3CHOC), 1.50 (d, 3 H, *J* = 7 Hz, CH_3CH=), 3.83 (q, 1 H, *J* = 7 Hz, CH_3CHOC), 4.57 (q, 1 H, *J* = 7 Hz, CH_3CH=). Anal. Calcd for $C_{27}H_{54}O_5Si_2$: C, 65.00; H, 10.91. Found: C, 64.93; H, 10.85.

Methyl 2(*R*)-[5(*S*)-ethyl-3(*S*)-methyl-5-(5(*R*)-ethyl-5-(trimethylsiloxy)-6(*S*)-methyl-2(*R*)-tetrahydropyranyl)-2(*S*)-tetrahydrofuryl]butanoate (4). A solution of 0.96 g (1.92 mmol) of the above silyl enol ether in 25 mL of dry methanol and 4 mL of dry dichloromethane at −78 °C was treated with ozone until it was faintly blue. The reaction mixture was then treated with two 1.2-g (31.7 mmol) portions of sodium borohydride. Cooling was then discontinued, and the resulting suspension was stirred at room temperature for 2 h and then concentrated under reduced pressure. The residue was taken up in 50 mL of saturated aqueous NH_4Cl and then acidified (pH ≃ 2) with 10% aqueous HCl. The aqueous phase was extracted with four 40-mL portions of dichloromethane and the combined organic extracts were dried (Na_2SO_4) and then concentrated under reduced pressure. Treatment of the residue with diazomethane in ether, and then chromatography of the resulting ester on 50 g of silica gel with 10% ether–petroleum ether gave 599 mg (72%) of the methyl ester 4: evaporative distillation 140–145 °C (0.001 mmHg); $[\alpha]^{22}_D$ −6.3° (*c* 1.01, $CHCl_3$) δ 0.020 (s, 9 H, $(CH_3)_3Si$), 0.83 (bt, 9 H, *J* = 7 Hz, CH_3CH_2), 0.90 (d, 3 H, *J* = 6 Hz, CH_3CHCC), 1.15 (d, 3 H, *J* = 7 Hz, CH_3CHOC), 3.67 (s, 3 H, CO_2CH_3), 3.83 (q, 1 H, *J* = 7 Hz, CH_3CHOC). Anal. Calcd for $C_{28}H_{56}O_5Si$: C, 64.44; H, 10.35. Found: C, 64.40; H, 10.26.

2(*S*)-[5(*S*)-Ethyl-3(*S*)-methyl-5-(5(*R*)-ethyl-5-(trimethylsiloxy)-6(*S*)-methyl-2(*R*)-tetrahydropyranyl)-2(*S*)-tetrahydrofuryl]butan-1-ol. To a stirred ice-cooled solution of 600 mg (1.4 mmol) of the methyl ester 4 in 4 mL of dry ether under argon was added 160 mg (16.8 mmol of hydride) of lithium tetrahydridoaluminate. After 1 h the reaction mixture was cautiously treated with 0.16 mL of water, 0.16 mL of 15% aqueous NaOH, and then 0.48 mL of water, stirred for 0.5 h and then filtered. Removal of the solvent under reduced pressure afforded 557 mg (99%) of the corresponding primary alcohol: evaporative distillation 150–155 °C (0.001 mmHg); $[\alpha]^{22}_D$ +7.83° (*c* 1.06, $CHCl_3$); IR ($CHCl_3$) 3520, 1460, 1255, 1100, 1050, 840 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.13 (s, 9 H, $(CH_3)_3Si$), 0.87 (bt, 9 H, *J* = 7 Hz, CH_3CH_2), 0.93 (d, 3 H, *J* = 6 Hz, CH_3CHCC), 1.17 (d, 3 H, *J* = 7 Hz, CH_3CHOC), 3.80 (q, 1 H, *J* = 7 Hz, CH_3CHOC). Anal. Calcd for $C_{27}H_{56}O_4Si$: C, 65.95; H, 11.07. Found: C, 66.00; H, 11.06.

2(*S*)-[5(*S*)-Ethyl-3(*S*)-methyl-5-(5(*R*)-ethyl-5-hydroxy-6(*S*)-methyl-2(*R*)-tetrahydropyranyl)-2(*S*)-tetrahydrofuryl]butan-1-ol. To a stirred solution of 264 mg (0.66 mmol) of the above alcohol in 8 mL of dry THF was added a solution of 430 mg (1.64 mmol) of tetra-*n*-butylammonium fluoride in 3.2 mL of dry THF. After 4 h, the reaction mixture was diluted with 70 mL of ether, then washed with two 30-mL portions of saturated aqueous $NaHCO_3$ and 30 mL of saturated aqueous NaCl, and then dried ($MgSO_4$). Removal of the solvents and chromatography of the residue on 10 g of silica gel with 35% ethyl acetate in cyclohexane afforded 196 mg (92%) of the corresponding diol: mp 74–75 °C (hexane); $[\alpha]^{24}_D$ +14.2° (*c* 1.16, $CHCl_3$); IR ($CHCl_3$) 3600, 3500, 1460, 1380, 1100, 1050, 950 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.96 (d, 3 H, *J* = 6 Hz, CH_3CHCC), 1.22 (d, 3 H, *J* = 6 Hz, CH_3CHOC). Anal. Calcd for $C_{19}H_{36}O_4$: C, 69.47; H, 11.05. Found: C, 69.37; H, 10.96.

Benzyl 2(*S*)-[5(*S*)-Ethyl-3(*S*)-methyl-5-(5(*R*)-ethyl-5-hydroxy-6(*S*)-methyl-2(*R*)-tetrahydropyranyl)-2(*S*)-tetrahydrofuryl]butyl Ether (5). To a stirred suspension of 22 mg (0.6 mmol) of potassium hydride in 2 mL of dry THF at 0 °C under argon was added a solution of 164 mg (0.5 mmol) of the above diol in 1 mL of dry THF and then 0.09 mL (0.75 mmol) of benzyl bromide. The resulting mixture was stirred for 2 h at room temperature, treated with 5 mL of saturated aqueous $NaHCO_3$, and then diluted with 60 mL of ether. The organic phase was separated and washed with two 20-mL portions of saturated aqueous $NaHCO_3$ and 20 mL of saturated aqueous NaCl and then dried ($MgSO_4$). After removal of the solvents at reduced pressure, chromatography of the residue on 20 g of silica gel with 35% ether–petroleum ether provided 172 mg (82%) of the monobenzyl ether 5: evaporative distillation 180–190 °C (0.005 mmHg); $[\alpha]^{22}_D$ +21.8° (*c* 1.40, $CHCl_3$); IR ($CHCl_3$) 3580, 1460, 1380, 1120, 1100, 1050, 960 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.96 (d, 3 H, *J* = 6 Hz, CH_3CHCC), 1.18 (d, 3 H, *J* = 6 Hz, CH_3CHOC), 3.76 (q, 1 H, *J* = 6 Hz, $CHCH_3OC$), 4.47 (s, 2 H, $C_6H_5CH_2$), 7.33 (b s, 5 H, C_6H_5). Anal. Calcd for $C_{26}H_{42}O_4$: C, 74.60; H, 10.11. Found: C, 74.50; H, 10.01.

Benzyl 2(*S*)-[5(*S*)-Ethyl-3(*S*)-methyl-5-(5(*S*)-hydroxy-6(*S*)-methyl-2(*R*)-tetrahydropyranyl)-2(*S*)-tetrahydrofuryl]butyl Ether (7). To a stirred solution of 60 mg (0.30 mmol) of potassium hydride in 0.5 mL of dry THF under argon was added a solution of 85 mg (0.20 mmol)

of the alcohol 5 in 0.5 mL of dry THF, followed by 0.06 mL (1.0 mmol) of carbon disulfide. After 5 h, the reaction mixture was treated with 0.025 mL (0.4 mmol) of methyl iodide and after an additional 30 min, the mixture was diluted with 40 mL of ether, washed with three 15-mL portions of water and 15 mL of saturated aqueous NaCl, and then dried ($MgSO_4$). Removal of the solvents gave a yellow oil which on preparative gas chromatography (column: 4%, SE-30, 0.25 in. × 6 ft, 220 °C, injector port 300 °C) as a 50% solution in ether gave 38 mg of the olefin mixture (exo:endo = 1:5) 6.

A solution of the above residue in 20 mL of dry methanol and 2 mL of dry dichloromethane at −78 °C was treated with ozone until it was faintly blue. The reaction mixture was then treated with two 100-mg (2.6 mmol) portions of sodium borohydride. Cooling was then discontinued and the resulting suspension was stirred at room temperature for 10 h and then concentrated under reduced pressure. The residue was taken up in 30 mL of saturated aqueous NH_4Cl. The aqueous phase was separated and then extracted with three 15-mL portions of ether. The combined ethereal phases were washed with 15 mL of saturated aqueous NaCl and then dried ($MgSO_4$). Removal of the solvent and chromatography of the residue on 10 g of silica gel with 25% ethyl acetate–petroleum ether provided 3.5 mg (4.5%) of the alcohol 7: evaporative distillation 140–150 °C (0.005 mmHg); $[\alpha]^{24}_D$ +25.8° (*c* 0.96, $CHCl_3$); IR ($CHCl_3$) 3650, 3480, 1470, 1400, 1120, 1080 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.83, 0.92 (2t, 6 H, J = 6 Hz, CH_3CH_2), 0.97 (d, 3 H, J = 6 Hz, CH_3CHCC), 1.17 (d, 3 H, J = 6 Hz, CH_3CHOC), 4.46 (s, 2 H, $C_6H_5CH_2$), 7.32 (b s, 5 H, C_6H_5). Anal. Calcd for $C_{26}H_{32}O_4$: C, 73.81; H, 9.81. Found: C, 73.76; H, 9.79.

II. Synthesis of the Left-Side Aldehyde 2. Citronellyl Acetate (10). To a stirred solution of 435 mL of 0.5 M 9-BBN in THF (0.2175 mol) at 0 °C was added 30.0 g (0.217 mol) of (*R*)-(−)-citronellene over 45 min. The resulting solution was allowed to warm to room temperature; after 2 h, 130 mL of absolute ethanol and 43.5 mL of 6 N aqueous NaOH were added. The resulting mixture was cooled to 0 °C and 84 mL of 30% H_2O_2 added over 30 min. The resulting mixture was refluxed for 1 h and then cooled to 0 °C, and the aqueous phase saturated with 200 g of K_2CO_3. The organic phase was separated and then dried ($MgSO_4$). Removal of solvent under reduced pressure, gave a residue which upon distillation (110–115 °C (25 mmHg)) gave 24.1 g of a mixture of citronellol and 1,5-cyclooctadiol.

The above mixture was dissolved in 600 mL of dry dichloromethane, and the resulting solution cooled to 0 °C. To this stirred solution was added 25.9 mL of triethylamine and 13.1 mL of acetyl chloride. After 1 h, 400 mL of saturated aqueous $NaHCO_3$ was added, and the organic phase separated and then dried ($MgSO_4$). Removal of solvent under reduced pressure and flash chromatography of the residue with 10% ethyl acetate in petroleum ether gave a residue which upon evaporative distillation (150 °C (25 mmHg)) gave 23.6 g of citronellyl acetate 10 (54% from citronellene): ^1H NMR ($CDCl_3$) δ 0.91 (d, 3 H, J = 5.5 Hz, CH_3CH); 1.62 and 1.68 (2s, 3 H (2×), $=C(CH_3)_2$), 2.03 (s, 3 H, CH_3CO_2), 4.10 (t, 2 H, J = 6 Hz, CH_2OAc), 5.10 (m, 1 H, $=CH$).

6-Acetoxy-4(*R*)-methyl Hexanoic Acid (9). A solution of 10.0 g (50 mmol) of citronellyl acetate (10) in 500 mL of dichloromethane was cooled to −78 °C and a stream of ozone in oxygen bubbled in until the solution remained blue for 10 min. The solution was then purged with a stream of nitrogen to remove excess ozone and the solvent removed under reduced pressure. The residual ozonide was dissolved in 250 mL of acetone and the resulting solution cooled to 0 °C. A solution of 8 N H_2CrO_4 in acetone was then added slowly until the solution remained brown. The reaction mixture was then poured into 800 mL of water and the resulting mixture extracted with 500-, 300-, and 200-mL portions of dichloromethane. The combined organic phases were dried ($MgSO_4$) and concentrated under reduced pressure. Evaporative distillation of the residue (160 °C (0.5 mmHg)) gave 7.4 g (78%) of the title acid. The yield on a 5-mmol scale was 96%: evaporative distillation 150–160 °C (0.5 mmHg); $[\alpha]^{25}_D$ +2.61° (c 3.52, $CHCl_3$); IR (neat) 3200, 1740, 1710, 1380, 1250 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.93 (s, 3 H, J = 5 Hz, CH_3CH), 1.2–1.9 (m, 5 H, CH_2CHCH_2), 2.01 (s, 3 H, CH_3CO), 2.37 (t (dd), 2 H, J = 7 Hz, CH_2CO_2H), 4.10 (t (dd), 2 H, J = 6 Hz, CH_2OAc). Anal. Calcd for $C_9H_{16}O_4$: C, 57.43; H, 8.57. Found: C, 57.45; H, 8.62.

3(*S*)-Methyl-4-pentenyl Acetate. To a solution of 3.002 g (15.94 mmol) of the acid 9 in 105 mL of benzene and 0.47 mL of pyridine were added 710 mg (3.56 mmol) of cupric acetate monohydrate and 12.84 g (28.96 mmol) of lead tetraacetate. The resulting mixture was refluxed for 16 h, and 6.0 g (13.53 mmol) of lead tetraacetate was then added and refluxing continued. After 6 h, the reaction mixture was cooled to room temperature and then poured into 150 mL of water. The organic phase was then separated, washed with three 150-mL portions of water, extracted with two 100-mL portions of saturated aqueous $NaHCO_3$, and then dried ($MgSO_4$). Removal of solvent at atmospheric pressure through a 30-cm Vigreux column gave a residue which was fractionally distilled (100–105 °C (25 mmHg)) to give 1.518 g (67%) of the 3(S)-methyl-4-pentenyl acetate: $[\alpha]^{25}_D$ +19.9° (*c* 1.18, $CHCl_3$); IR (neat) 2990, 1742, 1380, 1245, 1080, 920 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.00 (d, 3 H, J = 6.5 Hz, CH_3CH), 1.63 (d t, 2 H, J = J' = 5.5 Hz, $HCHCH_2CH_2O$), 2.00 (s, 3 H, CH_3CO), 2.25 (m (dtq), 1 H, $=CHCH(CH_3)CH_2$), 4.07 (t, 2 H, J = 6 Hz, CH_2CH_2O), 4.95 (m, 2 H, $CH=CH_aH_b$), 5.70 (m, 1 H, $HCCH=CH_aH_b$). Anal. Calcd for $C_9H_{14}O_2$: C, 67.57; H, 9.92. Found: C, 67.63; H, 9.89.

The bicarbonate extracts were acidified to pH 2 and extracted with two 100-mL portions of dichloromethane. The combined extracts were dried ($MgSO_4$) and concentrated under reduced pressure. Evaporative distillation of the residue (100 °C (0.005 mmHg)) gave 759 mg (26%) of the acid 9.

3(*S*)-Methyl-4-penten-1-ol. To a stirred solution of 4.69 g (33 mmol) of the above acetate in 28 mL of methanol was added 30 mg of sodium methoxide, and the resulting solution stirred at room temperature. After 8 h, the reaction mixture was poured into 150 mL of ether and the resulting mixture washed with two 50-mL portions of water and then dried ($MgSO_4$). Removal of solvent by distillation at atmospheric pressure through a 30-cm Vigreux column gave a residue which upon evaporative distillation (80 °C (25 mmHg)) gave 3.26 g (99%) of the corresponding alcohol: $[\alpha]^{25}_D$ +29.22° (*c* 1 54, $CHCl_3$); IR (neat) 3350, 1655, 1060, 1005, 920 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.01 (d, 3 H, J = 4.5 Hz, CH_3), 1.53 (dt, 2 H, J = J' = 4.5 Hz, $HCCH_2CH_2$), 2.28 (m, 1 H, $=CH=CH(CH_3)CH_2$), 4.97 (m, 2 H, $CH=CH_aH_b$), 5.70 (m, 1 H, $CH=CH_aH_b$).

5-Bromo-3(*S*)-methyl-1-pentene (13). To a stirred solution of 4.504 g (44.97 mmol) of the above alcohol in 100 mL of dichloromethane at 0 °C were added 3.8 mL (49.1 mmol) of methanesulfonyl chloride and 6.91 mL (49.6 mmol) of triethylamine sequentially, and the resulting mixture stirred at 0 °C for 15 min. The reaction mixture was then poured into 100 mL of saturated aqueous $NaHCO_3$ and the resulting mixture stirred vigorously for 10 min. The organic phase was separated, dried ($MgSO_4$), and then concentrated under reduced pressure. The residue was dissolved in 130 mL of dry THF and 5.87 g (67.6 mmol) of anhydrous lithium bromide was added. The resulting mixture was refluxed for 4 h and then cooled to room temperature. It was poured into 300 mL of pentane, and the organic phase washed with two 100-mL portions of saturated $NaHCO_3$ and five 100-mL portions of water and then dried ($MgSO_4$). Solvent was removed by distillation through a 30-cm Vigreux column at atmospheric pressure. Evaporative distillation of the residue (70 °C (80 mmHg)) gave 6.28 g (86%) of the bromide 13: $[\alpha]^{25}_D$ +32.7° (*c* 2.74, CH_3OH); IR (neat) 1655, 1470, 1435, 1270, 1015, 925 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.01 (d, 3 H, J = 5 Hz, CH_3), 1.80 (dt, 2 H, J = J' = 5 Hz, CH_2CH_2Br), 2.35 (m, 1 H, J = 5 Hz, $=CHCH(CH_3)CH_2$), 3.36 (t, 2 H, J = 5 Hz, CH_2CH_2Br), 5.02 (m, 2 H, $HC=CH_aH_b$), 5.64 (m, 1 H, $HCCH=CH_aH_b$).

1,1-Dimethyl-2-(3(*R*)-methyl-4-pentenyl)oxirane. To a stirred mixture of 18.99 g (110 mmol) of *m*-chloroperbenzoic acid and 15.19 g (180 mmol) of sodium bicarbonate in 450 mL of CH_2Cl_2 at 0 °C was added, in one portion, 12.5 g (90.4 mmol) of (*R*)-(−)-citronellene. The reaction mixture was stirred for 1.5 h at 0 °C and was then quenched by the addition of 150 mL of 10% aqueous Na_2SO_3. The resulting mixture was stirred for 15 min and then 25 g of $NaHCO_3$ in 50 mL of water was added. The organic layer was separated and then washed with two 200-mL portions of water and then dried ($MgSO_4$). The solvent was removed under reduced pressure to give a residue which was evaporatively distilled (150 °C (25 mmHg)) to give 11.2 g (80%) of the oxiranes: ^1H NMR ($CDCl_3$) δ 1.00 (d, 3 H, J = 6 Hz, $CHCH_3$), 1.25 (s, 3 H, CH_3), 1.30 (s, 3 H, CH_3), 1.47 (m, 4 H, $CHCH_2CH_2CHO$), 2.15 (m, 1 H, $H_2C=CHCH$), 2.80 (m, 1 H, CH_2CHO), 4.93 (m, 2 H, $H_2C=CH$), 5.70 (m, 1 H, $H_2C=CHCH$). Anal. Calcd for $C_{10}H_{18}O$: C, 77.87; H, 11.76. Found: C, 77.81; H, 11.65.

1-Oxo-1-phenyl-4(*R*)-methyl-5-hexene (11). To a stirred solution of 15.0 g (97.24 mmol) of the above epoxides in 450 mL of ether at 0 °C was added, in portions over 1.5 h, 26.6 g (116.7 mmol) of paraperiodic acid. The reaction mixture was then allowed to warm to room temperature. After 5 h, 23 g of $NaHCO_3$ was added and the mixture was stirred for 2 h. The reaction mixture was then dried ($MgSO_4$) and filtered.

The ethereal solution obtained above was cooled to 0 °C, and 200 mL of a 2.0 M solution of phenylmagnesium bromide in ether was slowly added. The reaction mixture was stirred at 0 °C for 1 h and then at room temperature overnight. It was then quenched by the careful addition of 50 mL of saturated aqueous NH_4Cl solution, followed by 300 mL of water and enough 3 N aqueous HCl to dissolve all the precipitated salts. The ethereal layer was separated and then washed consecutively with a 200-mL portion of each of the following: saturated aqueous NH_4Cl solution, saturated aqueous $NaHCO_3$ solution, saturated aqueous NaCl.

The organic layer was dried ($MgSO_4$) and then the solvent was removed under reduced pressure to give an oily residue.

To a stirred solution of the above oily residue in 450 mL of CH_2Cl_2 were added 2.6 g of sodium acetate and 74 g of a 1:1 (w/w) mixture of Celite and pyridinium chlorochromate. The reaction mixture was stirred at room temperature for 5 h, poured into 1.2 L of dry ether, and then filtered through Celite. Removal of the solvent under reduced pressure and flash chromatography of the residue on 100 g of silica gel with 10% ether in pentane gave 12.2 g (67%) of the phenyl ketone 11: evaporative distillation 60 °C (1 mmHg); $[\alpha]^{25}_D$ +10.1° (*c* 1.76, $CHCl_3$); IR ($CHCl_3$) 1690, 1610, 1590, 1460, 920 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.05 (d, 3 H, J = 7.5 Hz, $CHCH_3$), 1.73 (m, 2 H, $CHCH_2CH_2$), 2.16 (m, 1 H, H_2C=$CHCH$), 2.90 (t, 2 H, J = 7.5 Hz, $COCH_2CH_2$), 4.92 (m, 2 H, H_2C=CH), 5.67 (m, 1 H, H_2C=$CHCH$), 7.4 (m, 3 H, ArH), 7.92 (m, 2 H, ArH). Anal. Calcd for $C_{13}H_{16}O$: C, 82.94; H, 8.57. Found: C, 83.08; H, 8.45.

3(*R*)-Methyl-4-pentan-1-ol (15) (Method A). A solution of 8.0 g (42.5 mmol) of the ketone 11 and 8.5 g (157 mmol) of sodium methoxide in 250 mL of dry ethyl formate was stirred at room temperature overnight and then acidified to pH 4 with acetic acid. The reaction mixture was diluted with 1 L of ether and then extracted with two 400-mL portions of a 5% aqueous NaOH solution. The combined aqueous extracts were acidified to pH 2 with 6 N aqueous HCl and then extracted with two 400-mL portions of ether. The solvent was then removed under reduced pressure to give an oily residue.

The above residue was dissolved in 175 mL of methanol and 175 mL of pH 4 buffer and then 24.5 g (115 mmol) of sodium metaperiodate was added. The reaction mixture was stirred at room temperature for 7 days and then extracted with three 100-mL portions of dichloromethane. The organic extracts were combined and then washed with three 100-mL portions of 5% aqueous NaOH solution. The combined aqueous extracts were acidified to pH 2 with 6 N aqueous HCl and then extracted with three 100-mL portions of dichloromethane. These final organic extracts were dried ($MgSO_4$), and then the solvent was removed under reduced pressure to afford a residue containing the desired acid and benzoic acid.

The mixture of acids was dissolved in 400 mL of dry ether and 2 g (52.7 mmol) of lithium tetrahydridoaluminate was added. The reaction mixture was stirred at room temperature for 24 h and then 2 mL of water, 2 mL of 15% aqueous NaOH, and 6 mL of water were added successively. After being stirred vigorously for 20 min, the reaction mixture was dried ($MgSO_4$) and then the solvent was removed by atmospheric distillation through a Vigreux column. The residue was then fractionally distilled (60 °C (30 mmHg)) to give 2.107 g (49%) of the alcohol 15: $[\alpha]^{25}_D$ −28.92° (*c* 2.5, $CHCl_3$); IR (neat) 3350, 1655, 1060, 1005, 920 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.01 (d, 3 H, J = 4.5 Hz, $CHCH_3$), 1.53 (dt, 2 H, J = 4.5 Hz, 4.5 Hz, $CHCH_2CH_2$), 2.28 (m, 1 H, $CHCH_3$), 4.97 (m, 2 H, H_2C=CH), 5.70 (m, 1 H, H_2C=CH). Anal. Calcd for $C_6H_{12}O$: C, 71.95; H, 12.08. Found: C, 71.83; H, 12.00.

3(*R*)-Methyl-4-pentan-1-ol (15) (Method B). To a stirred solution of 90.51 mmol of LDA in 300 mL of dry THF at −78 °C was added 14.20 g (75.42 mmol) of the ketone 11 in 40 mL of dry THF. The reaction mixture was stirred at −78 °C for 0.5 h and then 19.2 mL of the centrifugate obtained from 30 mL of trimethylsilyl chloride and 10 mL of dry triethylamine were added. After the mixture was stirred at room temperature for 2 h, the reaction mixture was diluted with 1 L of pentane and then washed with two 500-mL portions of water and 500 mL of saturated aqueous NaCl. The organic layer was dried (K_2CO_3, Na_2SO_4), and then the solvent was removed under reduced pressure to give a colorless residue.

The above residue was dissolved in 300 mL of CH_2Cl_2 and cooled to 0 °C. To this solution was added 14.3 g (82.96 mmol) of *m*-chloroperbenzoic acid and 12.6 g (150.84 mmol) of $NaHCO_3$. The resulting mixture was stirred for 1 h at 0 °C and then for 3 h at room temperature. At this time, 1.4 g (8.2 mmol) of *m*-chloroperbenzoic acid was added. The reaction mixture was stirred at room temperature for another 3 h and then quenched by the addition of 100 mL of 10% aqueous Na_2SO_3 and 100 mL of a saturated $NaHCO_3$ solution. The organic layer was separated, washed with two 150-mL portions of water, and then dried ($MgSO_4$). Removal of solvent under reduced pressure gave a colorless residue.

The above residue was dissolved in 350 mL of cold ether and 22.4 g (98.05 mmol) of paraperiodic acid was added. The reaction mixture was stirred at 0 °C for 1 h and then at room temperature for 3 h. The ethereal solution was then washed with two 200-mL portions of a saturated $NaHCO_3$ solution and 200 mL of saturated aqueous NaCl and then dried ($MgSO_4$).

The above ethereal solution was cooled to 0 °C, and then 5.7 g (150.8 mmol) of lithium tetrahydridoaluminate was carefully added. The resulting mixture was stirred at 0 °C for 1 h and was then treated consecutively with 5.7 mL of water, 5.7 mL of a 15% aqueous NaOH solution, and 18 mL of water. The mixture was stirred vigorously for 15 min and then dried ($MgSO_4$). The solvent was removed by atmospheric distillation through a 15-cm Vigreux column, and the resulting residue was evaporatively distilled (up to 120 °C (27 mmHg)) to give 5.44 g (72%) of the alcohol (15).

5-Bromo-3(*R*)-methyl-1-pentene (14). To a stirred solution of 21.85 g (218 mmol) of the alcohol 15 and 45.58 mL of dry triethylamine in 520 mL of dry CH_2Cl_2 at 0° was added dropwise 18.56 mL (240 mmol) of methanesulfonyl chloride over a 10–15-min period. The reaction mixture was then stirred for 15 min at 0 °C and then poured into 500 mL of water. The aqueous layer was separated and then extracted with three 250-mL portions of dichloromethane. The organic fractions were dried ($MgSO_4$) and concentrated under reduced pressure to give an oily residue.

The above residue was dissolved in 600 mL of dry THF and then 26.06 g (300 mmol) of lithium bromide was added. The reaction mixture was heated at reflux for 4 h and then poured into 500 mL of water. This was extracted with three 250-mL portions of ether which were then combined and washed with 250 mL of saturated aqueous NaCl. The ethereal layer was dried ($MgSO_4$), and then the solvent was removed by atmospheric distillation through a 25-cm Vigreux column. The residue was then distilled under reduced pressure (68–69 °C (60 mmHg)) to give 25.72 g (77%) of the colorless bromide 14: $[\alpha]^{25}_D$ −33.7° (*c* 2.76, CH_3OH); IR (neat) 1655, 1470, 1435, 1270, 1015, 925 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.01 (d, 3 H, J = 5 Hz, $CHCH_3$), 1.80 (dt, 2 H, J = 5 Hz, 5 Hz, CH_2CH_2Br), 2.35 (m, 1 H, J = 5 Hz, $CHCH_3$), 3.36 (t, 2 H, J = 5 Hz, CH_2Br), 5.02 (m, 2 H, H_2C=CH), 5.64 (m, 1 H, H_2C=CH).

3(*R*)-Methyl-4-pentenoic Acid (12). To a solution of 164 mg (0.84 mmol) of silver tetrafluoroborate in 0.8 mL of Me_2SO was added 123 mg (0.70 mmol) of the bromide 14. The reaction mixture was stirred at room temperature for 24 h and then 80 μL of dry triethylamine was added. This was stirred for 1 h and then diluted with 20 mL of ether. The mixture was filtered through Celite and the filtrate was washed with three 10-mL portions of water and 10 mL of saturated aqueous NaCl. The organic layer was dried ($MgSO_4$) and then the volume was brought up to 30 mL by the addition of dry ether. To this ethereal solution at 0 °C was added 261 mg (6.9 mmol) of lithium tetrahydridoaluminate. The reaction mixture was stirred at 0 °C for 1.5 h and then 261 μL of water, 261 μL of a 15% aqueous NaOH solution, and 783 μL of water were added consecutively. The mixture was stirred vigorously for 20 min and then dried ($MgSO_4$). Solvent was removed by atmospheric distillation through a Vigreux column to give an oily residue.

The above residue was dissolved in 10 mL of acetone, and then enough Jones reagent was added to give the solution a brown tinge which persisted for longer than 15 min. The reaction mixture was then treated with 20% aqueous NaOH to pH 14 and then diluted with 20 mL of water. The aqueous layer was washed with three 10-mL portions of dichloromethane and then acidified with 6 N aqueous HCl to pH 2. The aqueous layer was extracted with three 10-mL portions of dichloromethane, and then the extracts were combined and dried ($MgSO_4$). The solvent was removed by atmospheric distillation through a Vigreux column and then the residue was evaporatively distilled (80–100 °C (27 mmHg)) to give 30 mg (38%) of the acid 12: $[\alpha]^{25}_D$ −13.97° (*c* 2.90, $CHCl_3$); IR ($CHCl_3$) 3200, 1710, 1410, 1300, 930 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.12 (d, 3 H, J = 7 Hz, $CHCH_3$), 2.37 (ABXM, 2 H, CH_2CO_2H), 2.6 (m, 1 H, $CHCH_3$), 5.02 (m, 2 H, H_2C=CH), 5.80 (m, 1 H, H_2C=CH). Anal. Calcd for $C_6H_{10}O_2$: C, 63.14; H, 8.83. Found: C, 63.21; H, 8.85.

5-*O*-(Triphenylmethyl)-D-ribono-1,4-lactone. To a stirred solution of 8.15 g (55 mmol) of D-ribonic acid, γ-lactone in 400 mL of dry pyridine was added 18.6 g (66.7 mmol) of chlorotriphenylmethane. The resulting solution was heated at 70 °C for 16 h. The cooled reaction mixture was diluted with 600 mL of dichloromethane, washed with three 300-mL portions of 10% aqueous HCl and two 100-mL portions of saturated aqueous $NaHCO_3$, and then dried ($MgSO_4$). Removal of the solvents and chromatography of the residue on 300 g of silica gel with 50% ethyl acetate in petroleum ether afforded 18 g (84%) of the triphenylmethyl ether: IR ($CHCl_3$) 3590, 3020, 1790, 1490, 1450, 1125, 1095 cm^{-1}; ^1H NMR (CD_3COCD_3) δ 3.40 (ABX (ddd), 2 H, $J_{4,5} \simeq J_{4,5'}$ = 3 Hz), 4.27 (d, 1 H, J = 5 Hz, H-3), 4.47 (dd, 1 H, $J \simeq J'$ = 3 Hz, H-4), 4.77 (d, 1 H, J = 5 Hz, H-2), 7.33 (m, 15 H, Ph_3).

2,3-*O*-(Thiocarbonyl)-5-*O*-(triphenylmethyl)-D-ribono-1,4-lactone (17). To a stirred solution of 4 g (10 mmol) of the above diol in 500 mL of dry acetone was added 2.74 g (15.4 mmol) of *N,N'*-thiocarbonyldiimidazole. The resulting solution was heated to reflux for 3.5 h. The cooled reaction mixture was concentrated under reduced pressure to half the original volume and then poured into 500 mL of water. The resulting mixture was extracted with three 200-mL portions of dichloromethane. The combined organic phases were washed with two 200-mL portions of saturated aqueous $NaHCO_3$ and two 200-mL portions of water and then dried ($MgSO_4$). Removal of solvents and chromatography of the residue

on 200 g of silica gel with 20% ethyl acetate in petroleum ether afforded 3.5 g (79%) of compound 17: mp 189–190 °C; $[\alpha]^{25}_D$ −8.9° (*c* 1.7, $CHCl_3$); IR ($CHCl_3$) 1820, 1505, 1460, 1315, 1190, 1010 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.2 (d, 1 H, *J* = 13 Hz, H-2), 3.85 (dd, 1 H, J_1 = 13 Hz, J_2 = 2 Hz, H-3), 4.8 (m, 1 H, H-4), 5.3 (ABX, 2 H, H-5's), 7.3 (s, 15 H, Ph_3). Anal. Calcd for $C_{25}H_{22}O_3S$: C, 69.43; H, 4.66; S, 7.41. Found: C, 69.41; H, 4.71; S, 7.43.

4(*S*)-Hydroxy-5-(triphenylmethoxy)-2-pentenoic Acid 1,4-Lactone (18). A suspension of 25 g of W-4 Raney nickel in 125 mL of acetone was heated to reflux overnight. The solid obtained was resuspended in 300 mL of tetrahydrofuran and 3.08 g (7.1 mmol) of the thiocarbonate 17 was added. The vigorously stirred mixture was heated to reflux for 24 h. The cooled mixture was then filtered and the solid residue washed with two 50-mL portions of tetrahydrofuran. The combined filtrates were concentrated under reduced pressure to give a solid residue which was crystallized from ethyl acetate–hexane to give 1.8 g (73%) of compound 18: mp 151–153 °C; $[\alpha]^{25}_D$ −50.2° (*c* 1.0, $CHCl_3$); IR ($CHCl_3$) 1510, 1465, 1180, 1105 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.3 (d, 2 H, *J* = 5 Hz, H-5's), 4.55 (m, 1 H, H-4), 4.95 (m, 1 H, H-3), 6.1 (dd, 1 H, J_1 = 9 Hz, J_2 = 2.5 Hz, H-2), 7.3 (m, 15 H, Ph_3). Anal. Calcd for $C_{24}H_{20}O_2$: C, 80.88; H, 5.66. Found: C, 80.69; H, 5.69.

4(*S*)-Hydroxy-3(*S*)-methyl-5-(triphenylmethoxy)pentanoic Acid 1,4-Lactone (19). To a stirred suspension of 4.97 g (23.5 mmol) of cuprous bromide–dimethyl sulfide complex in 150 mL of ether at 0 °C under argon was slowly added 21.85 mL (40.2 mmol) of a 1.84 M solution of methyllithium in ether. After 15 min, a solution of 1.19 g (3.35 mmol) of the butenolide 18 in 30 mL of benzene was added. After 1 h, the reaction mixture was washed with three 100-mL portions of NH_4Cl/NH_4OH pH 8 buffer and two 100-mL portions of water. The organic layer was dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue on 75 g of silica gel with 20% ethyl acetate in petroleum ether afforded 0.94 g (76%) of the lactone 19: $[\alpha]^{25}_D$ +22.3° (*c* 2.8, $CHCl_3$); IR ($CHCl_3$) 2950, 1770, 1500, 1450, 1160, 1100 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.98 (d, 3 H, *J* = 6 Hz, CH_3), 2.1 (dd, 1 H, J_1 = 6 Hz, J_2 = 17 Hz, H-2), 2.35 (m, 1 H, H-3), 2.75 (dd, 1 H, J_1 = 5 Hz, J_2 = 17 Hz, H-2a), 4.1 (m, 1 H, H-5), 7.3 (m, 15 H, Ph_3). Anal. Calcd for $C_{25}H_{26}O_2$: C, 80.62; H, 6.49. Found: C, 80.73; H, 6.39.

4(*S*),5-Dihydroxy-3(*S*)-methylpentanoic Acid 1,4-Lactone. To a stirred solution of 0.94 g (2.5 mmol) of the triphenylmethyl ether 19 in 50 mL of ethanol was added 20 mg of 5% palladium on carbon and 2 drops of concentrated sulfuric acid. The resulting suspension was stirred at room temperature under a hydrogen atmosphere for 24 h, and then 0.5 g of solid $NaHCO_3$ was added. The mixture was filtered and the filtrate concentrated under reduced pressure. Chromatography of the residue on 20 g of silica gel with 50% ethyl acetate in petroleum ether afforded 0.25 g (76%) of the corresponding alcohol: evaporative distillation 90 °C (0.01 mmHg); $[\alpha]^{25}_D$ +81.7° (*c* 0.3, $CHCl_3$); IR ($CHCl_3$) 3600, 2950, 1790, 1470, 1170, 1110, 1030 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.05 (d, 3 H, *J* = 6 Hz, CH_3), 2.0–3.0 (m, 3 H, H-2's, H-3), 3.35 (b s, 1 H, OH), 3.75 (m, 2 H, H-5's), 4.15 (m, 1 H, H-4). Anal. Calcd for $C_5H_8O_3$: C, 55.37; H, 7.75. Found: C, 55.50; H, 7.72.

5-Bromo-4(*S*)-hydroxy-3(*S*)-methylpentanoic Acid 1,4-Lactone. By the procedure described for the preparation of the bromide 14, 525 mg (4.03 mmol) of the above alcohol in 25 mL of dichloromethane with 1.56 mL (20 mmol) of methanesulfonyl chloride and 2.79 mL (20 mmol) of triethylamine gave the corresponding mesylate. This intermediate in 25 mL of tetrahydrofuran with 5 g of lithium bromide gave 685 mg (88%) of the desired bromide after evaporative distillation at 105 °C (0.025 mmHg): ^1H NMR ($CDCl_3$) δ 1.2 (d, 3 H, *J* = 6 Hz, CH_3), 2.1–3.0 (m, 3 H, H-2's, H-3), 3.05 (m, 2 H, H-5's), 4.3 (m, 1 H, H-4).

3(*S*)-Methyl-4-pentenoic Acid (20). To a solution of 0.1 g (14 mmol) of lithium in 40 mL of liquid ammonia at −78 °C was added a solution of 275 mg (1.4 mmol) of the above bromide in 10 mL of dry tetrahydrofuran. After 2 h, excess dry NH_4Cl was added and ammonia allowed to evaporate. The residue was diluted with 100 mL of water and the resulting aqueous phase was acidified and then extracted with three 20-mL portions of ether. The combined organic phases were dried ($MgSO_4$) and then concentrated under reduced pressure. Evaporative distillation of the residue at 90 °C (0.01 mmHg) gave 140 mg (86%) of the acid 20: $[\alpha]^{24}_D$ +13.55° (*c* 3.3, $CHCl_3$); IR ($CHCl_3$) 3200, 1710, 1410, 1300, 930 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.12 (d, 3 H, *J* = 7 Hz, C*H*$_3$), 2.37 (ABX m, 2 H, HCC*H*$_a$*H*$_b$CO$_2$H), 2.6 (m, 1 H, =CHC*H*-(CH$_3$)CH$_2$), 5.02 (m, 2 H, CH=C*H*$_a$H$_b$), 5.80 (m, 1 H, CHC*H*=CH$_a$H$_b$). Anal. Calcd for $C_6H_{10}O_2$: C, 63.14; H, 8.83. Found: C, 63.21; H, 8.85.

3-Carbomethoxy-4-(3(*R*)-methyl-5-pentenyl)-3,4-dihydro-2*H*-pyran-2-one. To 33 mL of 0.80 M THF solution (26.4 mmol) of the Grignard reagent derived from the bromide 14 was added 3.699 g (24 mmol) of α-pyrone 21 in 20 mL of dry THF over a period of 10 min. The resulting red-orange solution was stirred for 15 min at 0 °C and then poured into 250 mL of cold 10% aqueous HCl with vigorous stirring. The layers were separated and the aqueous layer was extracted with three 100-mL portions of dichloromethane. The combined organic layers were dried ($MgSO_4$), and then the solvent was removed under reduced pressure. The residue was evaporatively distilled (110–120 °C (1 mmHg)) to afford 4.956 g (87%) of the pale yellow adducts: IR (neat) 1775, 1745, 1660, 1215 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.98 (d, 3 H, *J* = 4 Hz, CHC*H*$_3$), 2.11 (m, 1 H, C*H*CH$_3$), 2.94 (m, 1 H, C*H*CH=CHO), 3.44 (d, 1 H, *J* = 5 Hz, C*H*CO$_2$CH$_3$), 3.74 (s, 3 H, CO$_2$C*H*$_3$), 4.95 (2 b s, 2 H, CH=C*H*$_2$), 5.28 (dd, 1 H, *J* = 3, 4 Hz, C*H*=CHO), 5.40–5.85 (m, 1 H, C*H*=CH$_2$), 6.49 (dd, 1 H, *J* = 1, 4 Hz, CH=C*H*O). Anal. Calcd for $C_{13}H_{18}O_4$: C, 65.53; H, 7.61. Found: C, 65.56; H, 7.60.

3-Carbomethoxy-4-(3(*R*)-methyl-5-pentyl)-2*H*-pyran-2-one (22). To a solution of 5.00 g (21 mmol) of the above dihydropyrones in 1 L of dichloromethane was added 100 g of activated MnO_2. The reaction mixture was stirred vigorously at room temperature for 3 h. The mixture was filtered through a pad of Celite which was then thoroughly washed with fresh dichloromethane. The filtrate was dried ($MgSO_4$) and the solvent was subsequently removed under reduced pressure to give 2.979 g (60%) of the α-pyrone 22: evaporative distillation 105–110 °C (0.5 mmHg); $[\alpha]^{22}_D$ +3.3° (*c* 1.00, $CHCl_3$); IR (neat) 1730, 1640, 1555, 1250 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.00 (d, 3 H, *J* = 4 Hz, CHC*H*$_3$), 3.86 (s, 3 H, CO$_2$C*H*$_3$), 4.86 (b s, 1 H, CH=CH*H*), 5.03 (b s, 1 H, CH=CH*H*), 5.64 (ddd, 1 H, *J* = 5, 6, 12 Hz, CH$_2$=C*H*), 6.11 (d, 1 H, *J* = 3.5 Hz, C*H*=CHO), 7.42 (d, 1 H, *J* = 3.5 Hz, CH=C*H*O). Anal. Calcd for $C_{13}H_{16}O_4$: C, 66.09; H, 6.83. Found: C, 66.25; H, 6.74.

1-(Dibenzylamino)-2-propyne. To a solution of 17.0 mL (88.3 mmol) of freshly distilled *N*,*N*-dibenzylamine in 75 mL of ether was added 21.0 g (176.51 mmol) of freshly distilled propargyl bromide. The reaction mixture was stirred at room temperature for 15 min, heated at 40 °C for 12 h, and then cooled to room temperature and treated with 11.5 g of KOH in 50 mL of water. After the resulting mixture was vigorously stirred until all of the solids had dissolved, the layers were separated and the aqueous phase was extracted with 100 mL of ether. The ethereal fractions were washed with 100 mL of saturated aqueous NaCl and then dried (K_2CO_3). Removal of the solvent under reduced pressure and flash chromatography on 100 g of silica gel with 10% ethyl acetate in petroleum ether of the residue gave 13.0 g (63%) of the crystalline propyne: mp 42–43.5 °C; IR ($CHCl_3$) 3300, 1600, 1490, 1450, 1330, 1120 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.22 (t, 1 H, C≡CH), 3.23 (d, 2 H, C≡CCH$_2$), 3.67 (s, 4 H, 2×NC*H*$_2$Ph), 7.30 (m, 10 H, 2×N*Ph*). Anal. Calcd for $C_{17}H_{17}N$: C, 86.77; H, 7.28; N, 5.95. Found: C, 86.74; H, 7.26; N, 5.85.

1-(Dibenzylamino)-1-propyne. To a solution of 5.0 g (21.25 mmol) of the above propyne in 3 mL of dry Me_2SO was added a solution of 100 mg (0.91 mmol) of potassium *tert*-butoxide in 0.75 mL of dry Me_2SO. The reaction mixture was stirred at room temperature for 1 h and then the solvent was removed by evaporative distillation under reduced pressure (0.01 mmHg) with the oven temperature being increased rapidly to 100 °C. The residue was then rapidly evaporatively distilled (130–190 °C (0.01 mmHg)) to give the desired ynamine. This ynamine could be stored in a freezer for up to 2 weeks if protected from moisture but was always evaporatively redistilled immediately before use: ^1H NMR ($CDCl_3$) δ 1.80 (s, 3 H, CH_3), 3.95 (s, 4 H, 2×NC*H*$_2$Ph), 7.28 (m, 10 H, 2×N*Ph*).

2-(Dibenzylamino)-3-methyl-6-(3(*R*)-methyl-4-pentenyl)benzoic Acid, Methyl Ester (23). To a solution of 503.3 mg (2.13 mmol) of the α-pyrone 22 in 5 mL of dry benzene was added 551.4 mg (2.34 mmol) of the freshly distilled ynamine in 2 mL of dry benzene. The reaction mixture was heated at reflux for 1 h and then cooled to room temperature and poured into 15 mL of water. The resultant mixture was extracted with two 25-mL portions of dichloromethane, and the organic fractions were dried ($MgSO_4$). Removal of the solvents under reduced pressure and column chromatography of the residue on 30 g of silica gel with 2.5% ether in petroleum ether afforded 542.2 mg (60%) of the aromatic ester 23: evaporative distillation 165–175 °C (0.005 mmHg); $[\alpha]^{22}_D$ +4.1° (*c* 1.18, $CHCl_3$); IR (neat) 1715, 1275, 1135, 750, 695 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.00 (d, 3 H, *J* = 4 Hz, CHC*H*$_3$), 1.93 (s, 3 H, ArC*H*$_3$), 3.78 (s, 3 H, CO$_2$C*H*$_3$), 4.10 (s, 4 H, 2×NC*H*$_2$Ph), 5.00 (m, 2 H, CH=C*H*$_2$), 5.70 (ddd, 1 H, *J* = 5, 6, 12 Hz, C*H*=CH$_2$), 6.94 (dd, 2 H, *J* = 5 Hz, 5 Hz, Ar*H*), 7.23 (s, 10 H, 2×NCH$_2$*Ph*). Anal. Calcd for $C_{29}H_{33}NO_2$: C, 81.46; H, 7.78; N, 3.28. Found: C, 81.41; H, 7.65; N, 3.27.

2-(Dibenzylamino)-3-methyl-6-(3(*R*)-methyl-4,5-*O*-isopropylidene-pentyl)benzoic Acid, Methyl Ester. To a solution of 4.233 g (9.92 mmol) of the aromatic olefin 23 and 1.676 g (12.4 mmol) of 4-methylmorpholine 4-oxide in 4.41 mL of water and 2.20 mL of acetone was added 1.9 mL (0.019 mmol) of a solution of 0.01 M osmium tetroxide in *tert*-butyl alcohol. The reaction mixture was stirred for 24 h at room temperature and then quenched by the addition of a slurry of 50 mg of $Na_2S_2O_4$ and 2 g of Florisil in 1 mL of water. After being stirred for 5 min, the mixture was filtered through a pad of Celite with thorough washing of

the filter pad with acetone. The volume of the filtrate was brought to about 200 mL by the addition of acetone, and to this was added 150 mL of 10% aqueous HCl and the resulting solution was allowed to stand at room temperature for 15 min. The solution was then extracted with three 200-mL portions of dichloromethane, and the combined organic extracts were dried ($MgSO_4$). The solvent was removed under reduced pressure to give a residue which was flash chromatographed on 100 g of silica gel with 20% ethyl acetate in petroleum ether to afford 4.510 g (91%) of an inseparable mixture of the desired aromatic compounds: evaporative distillation 180–195 °C (0.005 mmHg); IR (neat) 1735, 1280, 1230, 1145, 1065, 710 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.84, 1.00 (2d, 3 H, J = 4 Hz, $CHCH_3$), 1.30, 1.35 (2s, 6 H, $C(CH_3)_2$), 1.90 (s, 3 H, $ArCH_3$), 3.77 (s, 3 H, CO_2CH_3), 4.09 (s, 4 H, $2\times NCH_2Ph$), 6.91 (m, 2 H, Ar*H*), 7.19 (s, 10 H, $2\times NCH_2Ph$). Anal. Calcd for $C_{22}H_{29}NO_4$: C, 76.61; H, 7.84; N, 2.79. Found: C, 76.82; H, 7.83; N, 2.74.

2-Amino-3-methyl-6-(3(*R*)-methyl-4,5-*O*-isopropylidenepentyl)benzoic Acid, Methyl Ester. A mixture of 5.156 g (10.3 mmol) of the above dibenzylamino compounds and 516 mg of 10% palladium on carbon in 103 mL of absolute ethanol was shaken under a 50 psi atmosphere of hydrogen on a Parr hydrogenator for 10 h. The reaction mixture was then filtered and the filtrate was diluted with 300 mL of water. This mixture was extracted with three 150-mL portions of dichloromethane which were then combined and dried ($MgSO_4$). Removal of the solvents under reduced pressure gave a resident containing the desired amines and the vicinal diols. This mixture could be conveniently used in the subsequent reactions or separated by flash chromatography on 100 g of silica gel with ethyl acetate to give 518 mg of the aminodiols and 2.489 g of the amines (93% corrected total yield): evaporative distillation 135–140 °C (0.008 mmHg); IR (neat) 3490, 3390, 1690, 1615, 860, 805 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.90, 1.02 (2d, 3 H, J = 4 Hz, $CHCH_3$), 1.30, 1.35 (2s, 6 H, $C(CH_3)_2$), 2.02 (s, 3 H, $ArCH_3$), 3.82 (s, 3 H, CO_2CH_3), 4.90 (b s, 2 H, NH_2), 6.47 (dd, 1 H, J = 5.5 Hz, 5.5 Hz, Ar*H*), 6.97 (d, 1 H, J = 5.5 Hz, Ar*H*). Anal. Calcd for $C_{18}H_{27}NO_4$: C, 67.26; H, 8.47; N, 4.36. Found: C, 67.12; H, 8.37; N, 4.27.

3-Methyl-6-(3(*R*)-methyl-4,5-dihydroxypentyl)salicylic Acid, Methyl Ester. To a stirred solution of 2.389 g (7.45 mmol) of the above amines and 7.45 mL of 48–50% tetrafluoroboric acid in 74.5 mL of absolute ethanol at 0 °C was added, in a dropwise manner, 1.50 mL (11.2 mmol) of isoamyl nitrite, and the resulting colorless solution was stirred for 30 min at 0 °C. At this time the reaction mixture was concentrated under reduced pressure and then the concentrate was dissolved in 125 mL of water. The resulting solution was then heated at 80 °C until 15 min past the cessation of gas evolution as monitored by a bubbler. The reaction mixture was then extracted with three 100-mL portions of dichloromethane and the combined extracts were then dried ($MgSO_4$). Removal of the solvent under reduced pressure gave a residue which afforded 1.779 g (85%) of the phenols after column chromatography on 100 g of silica gel with ethyl acetate: evaporative distillation 165–170 °C (0.01 mmHg); IR (neat) 3500, 1665, 1420, 1255, 1155, 1040 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.97 (2d, 3 H, J = 4 Hz, $CHCH_3$), 2.19 (s, 3 H, $ArCH_3$), 3.93 (s, 3 H, CO_2CH_3), 6.62, 7.16 (2d, 2 H, J = 5.5 Hz, 5.5 Hz, Ar*H*), 11.24 (bs, 1 H, ArO*H*). Anal. Calcd for $C_{15}H_{22}O_5$: C, 63.81; H, 7.85. Found: C, 63.82; H, 7.90.

3-Methyl-6-(3(*R*)-methyl-4,5-*O*-isopropylidenepentyl)salicylic Acid, Methyl Ester (24). A mixture of 2 mL of 2,2-dimethoxypropane, 2 mL of acetone, 179.7 mg (0.636 mmol) of the above diols, and a catalytic amount of *p*-toluenesulphonic acid was stirred at room temperature for 15 min. The reaction mixture was then taken up in 40 mL of ether, and this was washed with two 20-mL portions of a saturated $NaHCO_3$ solution and 20 mL of saturated aqueous NaCl and then dried ($MgSO_4$). Removal of the solvent under reduced pressure gave 201.5 mg (98%) of the essentially pure acetonides 24: evaporative distillation 95–105 °C (0.003 mmHg); IR (neat) 1660, 1255, 1150, 1075, 870, 810 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.87, 1.03 (2d, 3 H, J = 6 Hz, $CHCH_3$), 1.33, 1.34 (2s, 6 H, $C(CH_3)_2$), 2.18 (s, 3 H, $ArCH_3$), 3.95 (s, 3 H, CO_2CH_3), 6.63 (dd, 1 H, J = 2.2, 7.5 Hz, Ar*H*), 7.18 (d, 1 H, J = 7.5 Hz, Ar*H*), 11.53 (s, 1 H, ArO*H*). Anal. Calcd for $C_{18}H_{26}O_5$: C, 67.06; H, 8.13. Found: C, 67.17; H, 7.93.

2-(β-Methoxyethoxymethyl)-3-methyl-6-(3(*R*)-methyl-4,5-*O*-isopropylidenepentyl)salicylic Acid, Methyl Ester. To a stirred suspension of 2.88 mmol of potassium hydride in 5 mL of dry THF at 0 °C was added 93.0 mg (0.288 mmol) of the phenols 24 in 1 mL of dry THF. The reaction mixture was stirred for 20 min at 0 °C and then 0.33 mL (2.88 mmol) of β-methoxyethoxymethyl chloride was added. The resulting mixture was stirred at 0 °C for 1 h and then at room temperature for 0.5 h. The reaction mixture was carefully quenched by the addition of a few drops of water and then diluted with 30 mL of ether which was then washed with two 10-mL portions of water and 10 mL of saturated aqueous NaCl. The organic layer was dried ($MgSO_4$) and then solvents were removed under reduced pressure to give quantitatively the essentially pure methyl esters: evaporative distillation 135–155 °C (0.003 mmHg); IR ($CHCl_3$) 1730, 1250, 1220, 1040 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.88, 1.01 (2d, 3 H, $CHCH_3$), 1.33, 1.38 (2s, 6 H, $C(CH_3)_2$), 2.27 (s, 3 H, $ArCH_3$), 3.40 (s, 3 H, CH_2OCH_3), 3.92 (s, 3 H, CO_2CH_3), 5.07 (s, 2 H, OCH_2O), 6.90 (dd, 1 H, J = 3, 7.5 Hz, Ar*H*), 7.18 (d, 1 H, J = 7.5 Hz, Ar*H*). Anal. Calcd for $C_{20}H_{30}O_7$: C, 64.37; H, 8.35. Found: C, 64.52; H, 8.32.

2-(β-Methoxyethoxymethyl)-3-methyl-6-(3(*R*)-methyl-4,5-*O*-isopropylidenepentyl)salicylic Acid, Benzyl Ester. To a stirred solution of 0.52 mL (5.76 mmol) of *n*-propanethiol in 5 mL of dry pentane at 0 °C was added 1.25 mL (2.88 mmol) of a solution of 2.3 M butyllithium in hexane. The mixture was stirred at 0 °C for 15 min and then concentrated under reduced pressure. The resultant salt was dissolved in 4 mL of dry HMPA and this was cooled to 0 °C. To this solution 118.4 mg (0.288 mmol) of the above methyl esters in 2 mL of dry HMPA was added and the reaction mixture was stirred at 0 °C for 10 min and then at room temperature for 45 min. At this time, 0.69 mL (5.76 mmol) of benzyl bromide was added and the reaction mixture was stirred at room temperature for 2 h and then quenched by the addition of 4 mL of 10% aqueous HCl and 40 mL of ether. The ethereal layer was then consecutively washed with three 20-mL portions of 10% aqueous HCl, 20 mL of a saturated aqueous $NaHCO_3$, and 20 mL of saturated aqueous NaCl. The organic phase was then dried ($MgSO_4$). Removal of the solvent under reduced pressure gave a residue that was chromatographed on 10 g of silica gel with 20% ethyl acetate in petroleum ether to give 119.0 mg (85%) of the benzyl esters: evaporative distillation 180–195 °C (0.001 mmHg); IR (neat) 1738, 1250, 1140, 1040, 740 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.75, 0.90 (2d, 3 H, $CHCH_3$), 1.32, 1.35 (2s, 6 H, $C(CH_3)_2$), 2.27 (s, 3 H, $ArCH_3$), 3.33 (s, 3 H, OCH_3), 4.97 (s, 2 H, OCH_2O), 5.33 (s, 2 H, OCH_2Ph), 6.87 (dd, 1 H, J = 3.7, 7.5 Hz, Ar*H*), 7.13 (d, 1 H, J = 7.5 Hz, ar*H*), 7.38 (m, 5 H, OCH_2Ph). Anal. Calcd for $C_{28}H_{38}O_7$: C, 69.11; H, 7.87. Found: C, 69.17; H, 7.94.

3-Methyl-6-(3(*R*)-methyl-4,5-dihydroxypentyl)salicylic Acid, Benzyl Ester. A mixture of 0.75 mL of 10% aqueous HCl, 3 mL of THF, and 89.5 mg (0.184 mmol) of the above benzyl esters was stirred at room temperature for 4 h and then heated at 50 °C for 7 h. The reaction mixture was diluted with 30 mL of ethyl acetate which was then washed with three 15-mL portions of saturated aqueous NaCl and dried ($MgSO_4$). Removal of the solvent under reduced pressure gave quantitatively the desired dihydroxy phenols: evaporative distillation 165–185 °C (0.003 mmHg); IR ($CHCl_3$) 3610, 1670, 1430, 1260, 1160 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.78 (b d, 3 H, J = 6 Hz, $CHCH_3$), 1.32, 1.35 (2s, 6 H, $C(CH_3)_2$), 2.20 (s, 3 H, $ArCH_3$), 5.38 (s, 2 H, CO_2CH_2Ph), 6.60 (d, 1 H, J = 7.5 Hz, Ar*H*), 7.17 (d, 1 H, J = 7.5 Hz, Ar*H*), 7.42 (b s, 5 H, CO_2CH_2Ph), 11.33 (b s, 1 H, ArO*H*). Anal. Calcd for $C_{21}H_{26}O_5$: C, 70.37; H, 7.31. Found: C, 70.28; H, 7.27.

3-Methyl-6-(3(*R*)-formylbutyl)salicylic Acid, Benzyl Ester (2). To a solution of 66.0 mg (0.184 mmol) of the above diols in 4 mL of methanol was added 47.2 mg (0.221 mmol) of sodium metaperiodate in 1.5 mL of water. The reaction mixture was stirred for 2 h at room temperature and then diluted with 15 mL of water and extracted with two 15-mL portions of dichloromethane. The organic extracts were combined and dried ($MgSO_4$). Removal of the solvent under reduced pressure and chromatography of the residue on 10 g of silica gel with 5% ethyl acetate in petroleum ether gave 48.0 mg (80%) of the desired "left-half" aldehyde 2.

***tert*-Butyldimethylsilyl-2(*R*)- and -2(*S*)-(3(*R*),4(*S*)-epoxy-5(*S*)-(methoxymethylenoxymethyl)-2(*R*)-tetrahydrofuryl)butyl Ether (31).** To a stirred solution of 1.17 g (5.07 mmol) of the acids 29 in 50 mL of 0.5 M aqueous $NaHCO_3$ was added a 25 mL aqueous solution of 8.4 g (50.6 mmol) of potassium iodide and 3.85 g (15.2 mmol) of iodine. The resulting mixture was stirred at room temperature in the dark for 12 h, then treated with 100 mL of 10% aqueous Na_2SO_3, and then extracted with three 60-mL portions of dichloromethane. The combined organic phases were washed with 40 mL of saturated aqueous $NaHCO_3$ and then dried ($MgSO_4$). Removal of the solvent under reduced pressure gave the crude iodolactones 30.

To a stirred solution of 108 mg (2.85 mmol) of lithium tetrahydridoaluminate in 4 mL of dry THF at 0 °C under argon was added 0.08 mL of 90% sulfuric acid. After 1 h, a solution of 746 mg (2.09 mmol) of the above iodolactones 30 in 3 mL of dry THF was added to the reaction mixture. After an additional hour, the mixture was treated successively with 0.08 mL of water, 0.08 mL of 15% aqueous NaOH, and 0.24 mL of water. After another 15 min, the suspension was filtered and the filtrate concentrated under reduced pressure.

To a stirred solution of this residue in 10 mL of methanol was added 443 mg (4.18 mmol) of Na_2CO_3. After 24 h, the mixture was concentrated under reduced pressure and then taken up in 20 mL of saturated aqueous $NaHCO_3$ and 60 mL of dichloromethane. The organic phase was then washed with 20 mL of saturated aqueous NaCl and then dried

(K_2CO_3 and Na_2SO_4). Removal of the solvents under reduced pressure gave the crude epoxy alcohols.

To a stirred solution of this residue in 4 mL of dry DMF was added 427 mg (6.3 mmol) of imidazole and 472 mg (3.1 mmol) of *tert*-butyldimethylchlorosilane. After 16 h, the reaction mixture was diluted with 60 mL of ether, washed with 20 mL of saturated aqueous $NaHCO_3$ and 20 mL of saturated aqueous NaCl, and then dried (K_2CO_3 and Na_2SO_4). Removal of the solvent and chromatography of the residue on 60 g of silica gel with 10% ethyl acetate–cyclohexane afforded 631.1 mg (90%) of the epoxy silyl ethers 31 as a mixture of diastereomers: evaporative distillation 95–105 °C (0.005 mmHg); IR ($CHCl_3$) 1485, 1475, 1260, 1160, 1120, 1040, 840 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.02 (s, 6 H, $(CH_3)_2Si$), 0.87 (s, 9 H, $(CH_3)_3C$), 3.30 (s, 3 H, OCH_3), 3.53 (d, 2 H, J = 5 Hz, CCH_2O), 4.57 (s, 2 H, OCH_2O). Anal. Calcd for $C_{17}H_{34}O_5Si$: C, 58.92; H, 9.89. Found: C, 58.98; H, 9.88.

tert-Butyldimethylsilyl-2(*R*)- and -2(*S*)-(3(*R*)-hydroxy-5(*S*)-methoxymethyleneoxymethyl-4(*S*)-methyl-2(*R*)-tetrahydrofuryl)butyl Ether (34 and Epi-34). To a stirred suspension of 1.8 g (9.45 mmol) of cuprous iodide in 20 mL of dry *n*-pentane at 0 °C under argon was 10 mL of a 1.8 M solution of methyllithium in ether. After 15 min, a solution of 631 mg (1.8 mmol) of the epoxides 31 in 4 mL of *n*-pentane was added to the reaction mixture. After 3 h, the mixture was treated with 10 mL of saturated aqueous NH_4Cl, diluted with 60 mL of ether, washed with two 20-mL portions of saturated aqueous NH_4Cl and 20 mL of saturated aqueous NaCl, and then dried ($MgSO_4$). Removal of the solvents under reduced pressure and chromatography of the residue on 50 g of silica gel with 25% ethyl acetate–cyclohexane afforded 334 mg (50%) of the alcohol 34 and 80 mg (12%) of the alcohol epi-34. Alcohol 34: evaporative distillation 110–120 °C (0.005 mmHg); $[\alpha]^{22}_D$ +4.0° (*c* 0.93, $CHCl_3$); IR ($CHCl_3$) 3360, 1480, 1470, 1260, 1040, 840 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.08 (s, 6 H, $(CH_3)_2Si$), 0.90 (s, 9 H, $(CH_3)_3C$), 0.94 (d, 3 H, J = 8 Hz, $CHCH_3$), 3.30 (s, 3 H, OCH_3), 4.57 (s, 2 H, OCH_2O). Anal. Calcd for $C_{18}H_{38}O_5Si$: C, 59.63; H, 10.56. Found: C, 59.65; H, 10.62. Alcohol epi-34: evaporative distillation 100–120 °C (0.005 mmHg); $[\alpha]^{22}_D$ +11.7° (*c* 1.02, $CHCl_3$); IR ($CHCl_3$) 3430, 1460, 1260, 1040, 840 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.10 (s, 6 H, $(CH_3)_2Si$), 0.93 (s, 9 H, $(CH_3)_3C$), 3.33 (s, 3 H, OCH_3), 4.62 (s, 2 H, OCH_2O). Anal. Calcd for $C_{18}H_{38}O_5Si$: C, 59.63; H, 10.56. Found: C, 59.64; H, 10.50.

tert-Butyldimethylsilyl-2(*R*)-(5(*S*)-(methoxymethyleneoxymethyl)-4-(*S*)-methyl-3(*R*)-(methylthiothiocarbonyloxy)-2(*R*)-tetrahydrofuryl)butyl Ether. To a stirred suspension of 26.5 mg (1.1 mmol) of sodium hydride in 1 mL of dry THF at 0 °C under argon was added a solution of 334 mg (0.92 mmol) of the alcohol 34 in 1 mL of dry THF. After 1 h, 0.28 mL (4.7 mmol) of carbon disulfide was added, and after an additional hour, 0.12 mL (1.93 mmol) of methyl iodide was added. The mixture was stirred for 3 h and then diluted with 70 mL of ether. It was then washed with two 30-mL portions of saturated aqueous $NaHCO_3$, 20 mL of saturated aqueous NaCl, and then dried ($MgSO_4$). Removal of the solvents gave 425 mg (100%) of the corresponding xanthate: evaporative distillation 130–140 °C (0.005 mmHg); $[\alpha]^{22}_D$ −3.5° (*c* 1.50, $CHCl_3$); IR ($CHCl_3$) 1480, 1230, 1070, 1050, 850 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.03 (s, 6 H, $(CH_3)_2Si$), 0.87 (s, 9 H, $(CH_3)_3C$), 1.05 (d, 3 H, J = 7 Hz, $CHCH_3$), 2.53 (s, 3 H, SCH_3), 3.35 (s, 3 H, OCH_3), 4.63 (s, 2 H, OCH_2O), 5.67 (d, 1 H, J = 4 Hz, S_2COCH). Anal. Calcd for $C_{20}H_{40}O_5S_2Si$: C, 53.06; H, 8.91; S, 14.16. Found: C, 53.27; H, 8.91; S, 14.11.

tert-Butyldimethylsilyl-2(*R*)-(5(*S*)-(methoxymethyleneoxymethyl)-4-(*R*)-methyl-2(*S*)-tetrahydrofuryl)butyl Ether. To a stirred solution of 425 mg (0.92 mmol) of the above xanthate in 9 mL of dry toluene at reflux under argon was added 0.3 mL (1.14 mmol) of tri-*n*-butyltin hydride. After 24 h, the reaction mixture was concentrated under reduced pressure and chromatography of the residue on 30 g of silica gel with 5% ethyl acetate–cyclohexane afforded 255 mg (80%) of the deoxysilyl ether: evaporative distillation 75–85 °C (0.005 mmHg); $[\alpha]^{24}_D$ −11.91° (*c* 1.055, $CHCl_3$); IR ($CHCl_3$) 1480, 1260, 1100, 1040, 840 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.03 (s, 6 H, $(CH_3)_2Si$), 0.89 (s, 9 H, $(CH_3)_3C$), 0.95 (d, 3 H, J = 7 Hz, $CHCH_3$), 3.33 (s, 3 H, OCH_3), 3.52 (d, 2 H, J = 6 Hz, CCH_2O), 3.63 (d, 2 H, J = 5 Hz, $SiOCH_2$), 4.60 (s, 2 H, OCH_2O). Anal. Calcd for $C_{19}H_{38}O_4Si$: C, 62.38; H, 11.05. Found: C, 62.26; H, 11.05.

2(*R*)-(5(*S*)-(Methoxymethyleneoxymethyl)-4(*R*)-methyl-2(*S*)-tetrahydrofuryl)butan-1-ol (33). To a stirred solution of 223.5 mg (0.645 mmol) of the above silyl ether in 3.2 mL of dry THF was added a solution of 430 mg (1.64 mmol) of tetra-*n*-butylammonium fluoride in 3.2 mL of dry THF. After 4 h, the reaction mixture was diluted with 70 mL of ether, washed with two 30-mL portions of saturated aqueous $NaHCO_3$ and 30 mL of saturated aqueous NaCl, and then dried ($MgSO_4$). Removal of the solvents and chromatography of the residue on 10 g of silica gel with 35% ethyl acetate–cyclohexane afforded 123 mg (82%) of the alcohol 33: evaporative distillation 60–70 °C (0.005 mmHg); $[\alpha]^{23}_D$ −21.0° (*c* 1.405, $CHCl_3$); IR ($CHCl_3$) 3460, 1470, 1160, 1110, 1050 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.96 (d, 3 H, J = 7 Hz, $CHCH_3$), 3.33 (s, 3 H, OCH_3), 3.53 (d, 2 H, J = 6 Hz, CCH_2OC), 4.60 (s, 2 H, OCH_2O). Anal. Calcd for $C_{12}H_{24}O_4$: C, 62.04; H, 10.41. Found: C, 62.16; H, 10.48.

2(*S*)-(5(*S*)-(Methoxymethyleneoxymethyl)-4(*R*)-methyl-2(*S*)-tetrahydrofuryl)butanal. To a stirred solution of 78 mg (0.336 mmol) of the alcohol 33 in 1.7 mL of dry dichloromethane was added 11 mg (0.134 mmol) of anhydrous sodium acetate and 145 mg (0.673 mmol) of pyridinium chlorochromate. After 2 h, the reaction mixture was diluted with 20 mL of dry ether and then stirred for 15 min. the resultant suspension was filtered and the solid was washed by trituration with three 20-mL portions of ether. Removal of the solvents and chromatography of the residue on 7 g of silica gel with 25% ethyl acetate–cyclohexane afforded 67 mg (85%) of the corresponding aldehyde: evaporative distillation 60–70 °C (0.005 mmHg); $[\alpha]^{23}_D$ +22.5° (*c* 1.11, $CHCl_3$); IR ($CHCl_3$) 2750, 1725, 1475, 1260, 1220, 1040, 920 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.91 (t, 3 H, J = 6 Hz, CH_3CH_2), 1.00 (d, 3 H, J = 7 Hz, $CHCH_3$), 3.33 (s, 3 H, OCH_3), 3.53 (d, 2 H, J = 6 Hz, CCH_2OC), 4.07 (dd, 1 H, J = 6, 12 Hz, $OCHCC$), 4.33 (dd, 1 H, J = 7, 14 Hz, $OCHCC$), 4.60 (s, 2 H, OCH_2O), 9.72 (d, 1 H, J = 4 Hz, CHO). Anal. Calcd for $C_{12}H_{22}O_4$: C, 62.58; H, 9.63. Found: C, 62.56; H, 9.66.

2-Ethyl-6(*S*)-hydroxy-7-(methoxymethyleneoxy)-5(*R*)-methylhept-2-enal (32). To a stirred solution of 50 mg (0.217 mmol) of the above aldehyde in 4.4 mL of dry THF was added 5 mg of potassium *tert*-butoxide. The suspension was heated at 70 °C for 20 h, allowed to cool to room temperature, and then diluted with 30 mL of ether. The ethereal phase was washed with two 10-mL portions of saturated aqueous $NaHCO_3$ and 10 mL of saturated aqueous NaCl, and then dried ($MgSO_4$). Removal of solvents and chromatography of the residue on a silica gel TLC plate with 35% ethyl acetate–cyclohexane gave 25 mg of the β-elimination product 32: evaporative distillation 80–90 °C (0.005 mmHg); IR ($CHCl_3$) 3600, 3450, 1680, 1460, 1160, 1120, 1040 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.93 (t, 3 H, J = 6 Hz, CH_3CH_2), 0.96 (d, 3 H, J = 7 Hz, $CHCH_3$), 3.33 (s, 3 H, OCH_3), 4.61 (s, 2 H, OCH_2O), 6.42 (t, 1 H, J = 8 Hz, C=CH), 9.40 (s, 1 H, CHO). Anal. Calcd for $C_{12}H_{22}O_4$: C, 62.58; H, 9.63. Found: C, 62.24; H, 9.71.

tert-Butyldimethylsilyl-2(*R*)- and -2(*S*)-[3(*S*)-(1,3-dithian-2-yl)-4-(*S*)-hydroxy-5(*R*)-(methoxymethyleneoxymethyl)-2(*R*)-tetrahydrofuryl]butyl Ether. To a stirred solution of 1.46 g (12.2 mmol) of 1,3 dithiane in 12 mL of dry THF at −20 °C under argon was added, dropwise, 4.8 mL (12 mmol) of a 2.5 M solution of *n*-butyllithium in *n*-hexane. After 90 min, a solution of 840 mg (2.42 mmol) of the epoxides 26 in 4.5 mL of dry THF was slowly added into the reaction mixture, which was then kept at 5 °C for 2 days. The mixture was diluted with 60 mL of ether, washed with two 25-mL portions of water, 25 mL of saturated aqueous $NaHCO_3$, and 25 mL of saturated aqueous NaCl, and then dried ($MgSO_4$). Removal of the solvents under reduced pressure and chromatography of the residue on 50 g of silica gel with 25% ethyl acetate–cyclohexane afforded 509 mg (45%) of the dithioacetal of the 2*R*-isomer and 110 mg (10%) of the dithioacetal of the 2*S*-isomer. 2*R*-Isomer: evaporative distillation 160–170 °C (0.005 mmHg); $[\alpha]^{23}_D$ +18.0° (*c* 0.255, $CHCl_3$); IR ($CHCl_3$) 3600, 3450, 1480, 1470, 1260, 1040, 840 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.09 (s, 6 H, $(CH_3)_2Si$), 0.92 (s, 9 H, $(CH_3)_3C$), 3.33 (s, 3 H, OCH_3), 4.63 (s, 2 H, OCH_2O). Anal. Calcd for $C_{21}H_{42}O_5S_2Si$: C, 54.04; H, 9.07; S, 13.74. Found: C, 54.26; H, 9.08; S, 13.78. 2*S*-Isomer: evaporative distillation 160–170 °C (0.005 mmHg); $[\alpha]^{22}_D$ +22.1° (*c* 1.095, $CHCl_3$); IR ($CHCl_3$) 3450, 1480, 1470, 1260, 1080, 840 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.13 (s, 6 H, $(CH_3)_2Si$), 0.93 (s, 9 H, $(CH_3)_3C$), 3.33 (s, 3 H, OCH_3), 4.60 (s, 2 H, OCH_2O). Anal. Calcd for $C_{21}H_{42}O_5S_2Si$: C, 54.04; H, 9.07; S, 13.74. Found: C, 53.86; H, 8.92; S, 13.54.

(*tert*-Butyldimethylsilyl)-2(*R*)-(4(*S*)-hydroxy-5(*R*)-(methoxymethyleneoxymethyl)-3(*S*)-methyl-2(*S*)-tetrahydrofuryl)butyl Ether (37). A solution of 640 mg (1.37 mmol) of the 2*R*-dithioacetal in 20 mL of ethanol was added to a slurry of W-4 Raney nickel (freshly made[37] from 20 g of Ni alloy) in 50 mL of ethanol at 90 °C and stirred for 5 h. The catalyst was then removed by filtration and washed with three 20-mL portions of ethanol. Removal of the solvent from the combined filtrates under reduced pressure and chromatography of the residue on 30 g of silica gel with 30% ethyl acetate–cyclohexane afforded 421 mg (85%) of the desulfurized compound 37: evaporative distillation 110–120 °C (0.005 mmHg); $[\alpha]^{23}_D$ +9.4° (*c* 1.04, $CHCl_3$); IR ($CHCl_3$) 3350, 1480, 1260, 1040, 840 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.07 (s, 6 H, $(CH_3)_2Si$), 0.90 (s, 9 H, $(CH_3)_3C$), 1.10 (d, 3 H, J = 7 Hz, $CHCH_3$), 3.38 (s, 3 H, OCH_3), 4.67 (s, 2 H, OCH_2O). Anal. Calcd for $C_{18}H_{38}O_5Si$: C, 59.63;

(37) W-4: Adkins, H.; Pavlic, A. A. *J. Am. Chem. Soc.* **1946**, *68*, 1471; **1947**, *69*, 3039–3041.

H, 10.56. Found: C, 59.71; H, 10.57.

***tert*-Butyldimethylsilyl-2(*R*)-(5(*R*)-(methoxymethyleneoxymethyl)-3-(*S*)-methyl-4(*S*)-(methylthiothiocarbonyloxy)-2(*S*)-tetrahydrofuryl)butyl Ether.** By the procedure described for the preparation of the xanthate of the 4*R*-methyl series, 421 mg (1.16 mmol) of the alcohol 37, 41.8 mg (1.74 mmol) of sodium hydride in 9 mL of dry THF, 0.35 mL (5.82 mmol) of carbon disulfide, and 0.18 mL (2.89 mmol) of methyl iodide afforded, after chromatography on 40 g of silica gel with 5% ethyl acetate–cyclohexane, 496 mg (95%) of the corresponding xanthate: evaporative distillation 130–140 °C (0.005 mmHg); $[\alpha]^{21}_D$ +1.1° (*c* 1.32, $CHCl_3$); IR ($CHCl_3$) 1475, 1465, 1220, 1060, 840 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.04 (s, 6 H, $(CH_3)_2Si$), 0.90 (s, 9 H, $(CH_3)_3C$), 2.53 (s, 3 H, SCH_3), 3.33 (s, 3 H, OCH_3), 4.63 (s, 2 H, OCH_2O), 5.67 (dd, 1 H, J = 4 Hz, 4 Hz, S_2COCH). Anal. Calcd for $C_{20}H_{40}O_5S_2Si$: C, 53.06; H, 8.91; S, 14.61. Found: C, 53.00; H, 8.89; S, 13.99.

***tert*-Butyldimethylsilyl-2(*R*)-(5(*S*)-(methoxymethyleneoxymethyl)-3-(*S*)-methyl-2(*S*)-tetrahydrofuryl)butyl Ether.** By the procedure described for the preparation of the silyl ether of the 4*R*-methyl series, 470 mg (1.04 mmol) of the above xanthate in 10.4 mL of dry toluene with 0.41 mL (1.55 mmol) of tri-*n*-butyltin hydride afforded, after chromatography on 30 g of silica gel with 5% ethyl acetate–cyclohexane, 353 mg (98%) of the corresponding silyl ether: evaporative distillation 70–80 °C (0.005 mmHg); $[\alpha]^{23}_D$ +10.4° (*c* 1.15, $CHCl_3$); IR ($CHCl_3$) 1470, 1460, 1260, 1100, 1040, 840 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.03 (s, 6 H, $(CH_3)_2Si$), 0.88 (s, 9 H, $(CH_3)_3C$), 3.33 (s, 3 H, OCH_3), 4.63 (s, 2 H, OCH_2O). Anal. Calcd for $C_{19}H_{38}O_4Si$: C, 62.38; H, 11.05. Found: C, 62.46; H, 11.07.

2(*R*)-(5(*S*)-(Methoxymethyleneoxymethyl)-3(*S*)-methyl-2(*S*)-tetrahydrofuryl)butan-1-ol (36). By the procedure described for the preparation of the alcohol 33, 340 mg (1.01 mmol) of the above silyl ether in 5 mL of dry THF with 530 mg (2 mmol) of tetra-*n*-butylammonium fluoride afforded, after chromatography on 20 g of silica gel with 35% ethyl acetate–cyclohexane, 236 mg (100%) of the alcohol 36: evaporative distillation 60–70 °C (0.005 mmHg); $[\alpha]^{22}_D$ +5.4° (*c* 1.025, $CHCl_3$); IR ($CHCl_3$) 3490, 1460, 1110, 1040 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.96 (t, 3 H, J = 6 Hz, CH_3CH_2), 1.05 (d, 3 H, J = 6 Hz, CH_3CHCC), 3.34 (s, 3 H, OCH_3), 4.62 (s, 2 H, OCH_2O). Anal. Calcd for $C_{12}H_{24}O_4$: C, 62.04; H, 10.41. Found: C, 62.12; H, 10.32.

2(*S*)-(5(*S*)-(Methoxymethyleneoxymethyl)-3(*S*)-methyl-2(*S*)-tetrahydrofuryl)butanal. By the procedure described for the preparation of the aldehyde of the 4*R*-methyl series, 130 mg (0.56 mmol) of the alcohol 36 in 3 mL of dry dichloromethane, 18 mg (0.22 mmol) of anhydrous sodium acetate, and 240 mg (1.11 mmol) of pyridinium chlorochromate afforded, after chromatography on 10 g of silica gel with 25% ethyl acetate–cyclohexane, 90 mg (70%) of the corresponding aldehyde: evaporative distillation 60–70 °C (0.005 mmHg); $[\alpha]^{22}_D$ +19.5° (*c* 1.435, $CHCl_3$); IR ($CHCl_3$) 1720, 1480, 1110, 1040, 920 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.93 (t, 3 H, J = 6 Hz, CH_3CH_2), 1.05 (d, 3 H, J = 6 Hz, $CHCH$), 3.36 (s, 3 H, OCH_3), 3.52 (d, 2 H, J = 5 Hz, CCH_2OC), 3.70 (dd, 1 H, J = 4 Hz, 8 Hz, O=CCCH), 4.62 (s, 2 H, OCH_2O), 9.77 (d, 1 H, J = 6 Hz, CHO). Anal. Calcd for $C_{12}H_{22}O_4$: C, 62.58; H, 9.63. Found: C, 62.67; H, 9.68.

2-Ethyl-6(*S*)-hydroxy-7-(methoxymethyleneoxy)-4(*S*)-methylhept-2-enal (35). By the procedure described for the preparation of the β-elimination product 32, 62 mg (0.27 mmol) of the above aldehyde in 2.5 mL of dry THF and 8 mg of potassium *tert*-butoxide afforded, after preparative silica gel TLC with 35% ethyl acetate–cyclohexane, 25 mg of the β-elimination product 35: evaporative distillation 80–90 °C (0.005 mmHg); IR ($CHCl_3$) 3500, 1680, 1460, 1150, 1040 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.00 (t, 3 H, J = 7 Hz, CH_3CH_2), 1.12 (d, 3 H, J = 6 Hz, $CHCH_3$), 3.40 (s, 3 H, OCH_3), 4.67 (s, 2 H, OCH_2O), 6.27 (d, 1 H, J = 10 Hz, C=CH), 9.36 (s, 1 H, CHO). Anal. Calcd for $C_{12}H_{22}O_4$: C, 62.58; H, 9.63. Found: C, 62.65; H, 9.53.

Benzyl 2(*R*)-(5(*S*)-(Methoxymethyleneoxymethyl)-3(*S*)-methyl-2-(*S*)-tetrahydrofuryl)butyl Ether. By the procedure described for the preparation of the benzyl ether 5, 97.9 mg (0.42 mmol) of the alcohol 31, 20 mg (0.5 mmol) of potassium hydride, and 0.075 mL (0.6 mmol) of benzyl bromide in 4 mL of dry THF afforded, after chromatography on 10 g of silica gel with 15% ethyl acetate–cyclohexane, 122.8 mg (91%) of the corresponding benzyl ether: evaporative distillation 100–110 °C (0.005 mmHg); $[\alpha]^{21}_D$ +9.9° (*c* 0.97, $CHCl_3$); IR ($CHCl_3$) 1450, 1380, 1365, 1120, 1100, 1030 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.90 (t, 3 H, J = 6 Hz, CH_3CH_2), 1.01 (d, 3 H, J = 6 Hz, CH_3CHCC), 3.33 (s, 3 H, OCH_3), 4.43 (s, 2 H, $C_6H_5CH_2$), 4.61 (s, 2 H, OCH_2O), 7.30 (b s, 5 H, C_6H_5). Anal. Calcd for $C_{19}H_{30}O_4$: C, 70.77; H, 9.38. Found: C, 70.61; H, 9.15.

Benzyl 2(*R*)-(5(*S*)-(Hydroxymethyl)-3(*S*)-methyl-2(*S*)-tetrahydrofuryl)butyl Ether (38). To a stirred solution of 82.8 mg (0.26 mmol) of the methoxymethyl ether above in 4 mL of THF was added 1 mL of 10% aqueous HCl. The resulting solution was heated at 50 °C for 16 h, cooled to room temperature and then diluted with 50 mL of ether. The organic phase was washed with 20 mL of water, 20 mL of saturated aqueous $NaHCO_3$, and 20 mL of saturated aqueous NaCl and then dried ($MgSO_4$). After removal of the solvent at reduced pressure, chromatography of the residue on 10 g of silica gel with 35% ethyl acetate–cyclohexane afforded 70 mg (98%) of the alcohol 38: evaporative distillation 100–110 °C (0.005 mmHg); $[\alpha]^{21}_D$ +26.9° (*c* 1.005, $CHCl_3$); IR ($CHCl_3$) 3600, 3460, 1460, 1385, 1370, 1100, 1030 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.94 (t, 3 H, J = 6 Hz, CH_3CH_2), 1.04 (d, 3 H, J = 6 Hz, CH_3CHCC), 4.49 (s, 2 H, $C_6H_5CH_2$), 7.36 (b s, 5 H, C_6H_5). Anal. Calcd for $C_{17}H_{26}O_3$: C, 73.35; H, 9.41. Found: C, 73.42; H, 9.40.

Benzyl 2(*R*)-(5(*S*)-Carboxmethoxy-3(*S*)-methyl-2(*S*)-tetrahydrofuryl)butyl Ether (39a). To a stirred 5 mL aqueous solution of Adam's catalyst (freshly prepared from 200 mg of 84% platinum oxide) was added 30 mg (0.36 mmol) of solid $NaHCO_3$ and then a solution of 70 mg (0.25 mmol) of the alcohol 38 in 1 mL of acetone. After complete addition, oxygen was bubbled through this mixture at 50 °C for 4 h. The catalyst was then removed from the cooled reaction mixture by filtration and subsequently washed with two 20-mL portions of 0.2 M aqueous Na_2HPO_4. The combined filtrates were washed with 20 mL of ether and then acidified to pH ~2. The aqueous phase was extracted with four 20-mL portions of ether, and the combined ethereal extracts were washed with 20 mL of saturated aqueous NaCl and then dried ($MgSO_4$). Removal of the solvent at reduced pressure gave 68.8 mg (94%) of the corresponding acid epi-25.

A portion of this material was treated with diazomethane in ether and then chromatography of the resulting methyl ester 39a on silica gel with 10% ethyl acetate–cyclohexane provided the analytical sample: evaporative distillation 100–110 °C (0.005 mmHg); IR ($CHCl_3$) 1740, 1460, 1385, 1370, 1100 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.93 (t, 3 H, J = 6 Hz, CH_3CH_2), 1.00 (d, 3 H, J = 6 Hz, CH_3CHCC), 3.70 (s, 3 H, CO_2CH_3), 4.43 (s, 2 H, $C_6H_5CH_2$), 7.31 (s, 5 H, C_6H_5). Anal. Calcd for $C_{19}H_{28}O_4$: C, 70.56; H, 8.55. Found: C, 70.58; H, 8.45.

2-Methyl-2,3-*O*-(1-methylethylidene)-D-ribonic Acid, γ-Lactone. To a stirred suspension of 67.0 mg (0.41 mol) of D-glucosaccharinic acid, γ-lactone[34] (40) in 815 mL of dry acetone at room temperature was added 8.15 mL of 96% sulfuric acid. After 30 h, the reaction mixture was adjusted to pH ~8 with aqueous ammonia. The resulting mixture was filtered and the filtrate concentrated under reduced pressure. The residual oil was dissolved in 800 mL of ether and washed with 500 mL of water. The aqueous layer was then extracted with three 100-mL portions of ether. The combined organic phases were washed with 300 mL of saturated aqueous NaCl and then dried ($MgSO_4$). Removal of solvent under reduced pressure and flash chromatography of the residue on 800 g of silica gel with 85% ether in petroleum ether afforded 77.9 g (94%) of the corresponding ketal, mp 60–61 °C (lit.[38] mp 61–61.5 °C).

2-Methyl-2,3-*O*-(1-methylethylidene)-5-*O*-(methoxymethyl)-D-ribonic Acid, γ-Lactone (41). To a stirred suspension of 1.3 g (32.4 mmol) of potassium hydride in 90 mL of dry THF at 0 °C under argon was added a solution of 5.03 g (24.86 mmol) of the 2,3-acetonide of D-glucosaccharinic acid, γ-lactone in 20 mL of dry THF, and then 3 mL (39.5 mmol) of chloromethyl methyl ether was added. The resulting mixture was stirred at room temperature for 8 h, treated with 20 mL of saturated aqueous $NaHCO_3$, and then diluted with 400 mL of ether. The organic phase was separated and then washed with two 200-mL portions of saturated aqueous $NaHCO_3$, 200 mL of saturated aqueous NaCl, and then dried ($MgSO_4$). After removal of solvents under reduced pressure, chromatography of the residue on 200 g of silica gel with 50% ether in petroleum ether provided 5.70 g (93%) of the methoxymethyl ether 41: evaporative distillation 90–100 °C (0.005 mmHg); $[\alpha]^{22}_D$ −22.4° (*c* 1.32, $CHCl_3$); IR ($CHCl_3$) 1780, 1380, 1220, 1160, 1105, 1060, 1020 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.42 (s, 6 H, $C(CH_3)_2$), 1.62 (s, 3 H, CH_3), 3.33 (s, 3 H, OCH_3), 3.74 (d, 2 H, J = 3 Hz, CCH_2O), 4.47 (s, 1 H, H3), 4.59 (b s, 2 H, OCH_2O). Anal. Calcd for $C_{11}H_{18}O_6$: C, 53.65; H, 7.37. Found: C, 53.67; H, 7.25.

2-Methyl-2,3-*O*-(1-methylethylidene)-5-*O*-(methoxymethyl)-D-ribose. To a stirred solution of 5.70 g (23.1 mmol) of the lactone 41 in 100 mL of dry ether under argon at −78 °C was added, dropwise over 30 min, 35 mL of a 1 M solution of diisobutylaluminum hydride in hexane. After 1 h, the reaction mixture was cautiously treated with 2 mL of methanol, allowed to warm to room temperature, and then diluted with 500 mL of ether. This solution was washed with three 70-mL portions of saturated aqueous sodium potassium tartarate solution and 70 mL of saturated aqueous NaCl and then dried ($MgSO_4$). After removal of the solvent under reduced pressure, chromatography of the residue on 200 g of silica gel with 75% ether in petroleum ether afforded 5.76 g (100%) of the

(38) Utkin, L. M.; Grabilina, G. O. *Dokl. Akad. Nauk SSSR* **1953**, *93*, 301. Sowden, J. C.; Blair, M. G.; Kuzuna, D. J. *J. Am. Chem. Soc.* **1957**, *79*, 6450–6454.

corresponding lactol as a mixture of anomers: evaporative distillation 90–100 °C (0.005 mmHg); $[\alpha]^{22}_D$ +17.9° (*c* 1.17, $CHCl_3$); IR ($CHCl_3$) 3600, 3450, 1460, 1380, 1210, 1160, 1105, 1060, 1030 cm^{-1}; ^1H NMR ($CDCl_3$) δ (minor anomer, major anomer) 3.31, 3.34 (s, 3 H, OCH_3), 3.59, 3.63 (d, 2 H, J = 2 Hz, CCH_2O), 4.58, 4.64 (s, 2 H, OCH_2O), 5.00, 5.17 (d, 1 H, J = 11 Hz, H-1). Anal. Calcd for $C_{11}H_{20}O_5$: C, 53.22; H, 8.12. Found: C, 53.06; H, 8.05.

1,4-Anhydro-2-deoxy-2-methyl-5-*O*-(methoxymethyl)-D-erythropent-1-enitol (42). To a stirred solution of 6.52 g (26.26 mmol) of the above lactol and 3.1 mL (32 mmol) of carbon tetrachloride in 100 mL of dry THF at −78 °C under argon was added 5.1 mL (28 mmol) of tris(dimethylamino)phosphine. After 45 min, the reaction mixture was allowed to warm to 0 °C and was then added, via a double-tipped needle, to a stirred solution of 52 cm (317 mmol) of lithium wire in 400 mL of anhydrous liquid ammonia at −78 °C under argon. Cooling was then discontinued (ammonia reflux), and after 2 h, 18.7 g (350 mmol) of anhydrous ammonium chloride was cautiously added to the reaction mixture. The resulting colorless mixture was diluted with 500 mL of ether and the ammonia was allowed to evaporate. The resulting ethereal suspension was filtered, and then concentration of the filtrate under reduced pressure afforded a crude mixture of the glycal 42, the tetrahydrofuran reduction byproduct[28,29] and HMPA. After rapid passage of this crude product through 50 g of silica gel with 75% ether in petroleum ether, concentration of the eluate at reduced pressure and then distillation [Kugelrohr, 110 °C (0.01 mmHg)] of the residue gave 4.694 g of a mixture of the glycal 42 and the byproduct. Analysis of this mixture by ^1H NMR spectroscopy revealed a ratio of 4:1 for glycal to byproduct. Chromatography of a small portion of this mixture on silica gel with 75% ether–petroleum ether provided pure product for analysis: evaporative distillation 60–70 °C (0.005 mmHg); $[\alpha]^{25}_D$ +206.1° *c* 1.11, $CHCl_3$); IR ($CHCl_3$) 3590, 3450, 1675, 1460, 1380, 1210, 1150, 1100, 1020 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.69 (d, 3 H, J = 2 Hz, CH_3), 3.37 (s, 3 H, OCH_3), 3.56 (d, 2 H, J = 6 Hz, CCH_2O), 5.08 (s, 2 H, OCH_2O), 6.22 (b s, 1 H, HC=C). Anal. Calcd for $C_8H_{14}O_4$: C, 55.16; H, 8.10. Found: C, 55.11; H, 8.03.

Methyl 2(*R*)- and 2(*S*)-(2,5-dihydro-5(*S*)-(methoxymethyleneoxymethyl)-3-methyl-2(*R*)-furyl)butanoates (43). A. From the Glycal 42 by Deprotonation in THF. To a stirred solution of 4.6 g (19.8 mmol of the glycal 42) of the 4:1 mixture of the glycal 42 and the byproduct in 57 mL of dry THF at −78 °C under argon was added 8 mL (19.8 mmol) of a 2.48 M solution of *n*-butyllithium in hexane, and then after 5 min, 2.1 mL (20.2 mmol) of *n*-butyryl chloride was added. After 10 min at 0 °C, the reaction mixture was taken up in an argon flushed syringe and added dropwise to a stirred solution of 24.8 mmol of LDA in 57 mL of dry THF at −78 °C under argon. After 10 min, the reaction mixture was treated with 6.4 mL (37.8 mmol of Me_3SiCl) of the supernatant centrifugate from a 3:1 mixture of trimethylchlorosilane and triethylamine. After 2 h at room temperature, the reaction mixture was diluted with 100 mL of 1 N aqueous NaOH and stirred for 15 min. The organic phase was separated and extracted with three 50-mL portions of 1 N aqueous NaOH, and then the combined aqueous base phases were washed with 50 mL of ether, acidified (pH ~2) and extracted with four 100-mL portions of ether. The combined ethereal extracts were washed with 50 mL of saturated aqueous NaCl and then dried ($MgSO_4$). Removal of the solvent under reduced pressure afforded a mixture of the diastereomeric acids which was esterified with ethereal diazomethane. Chromatography of the resulting methyl esters on 300 g of silica gel with 30% ether in petroleum ether afforded 3.07 g (60%) of the methyl esters 43. ^1H NMR analysis revealed a ratio of 9:1 for the two diastereomeric methyl esters: evaporative distillation 60–70 °C (0.005 mmHg); IR ($CHCl_3$) 1730, 1460, 1440, 1150, 1110, 1080, 1030 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.33 (s, 3 H, OCH_3), 3.49 (d, 2 H, J = 4 Hz, CCH_2O), 3.60, 3.68 (s, 3 H, CO_2CH_3), 4.60 (s, 2 H, OCH_2O), 5.50 (b s, 1 H, C=CH). Anal. Calcd for $C_{13}H_{22}O_5$: C, 60.45; H, 8.58. Found: C, 60.47; H, 8.49.

B. From the Glycal 42 by Deprotonation in HMPA–THF. By the same procedure as described in part A above, 17.87 mmol of the glycal 42 with 10.5 mL (24.15 mmol) of 2.3 M solution of *n*-butyllithium in hexane, 2.6 mL (25 mmol) of *n*-butyryl chloride in 70 mL of dry THF, and 10 mL of dry HMPA, added to 28.5 mmol of LDA in 64 mL of dry THF and 16 mL of dry HMPA, followed by 59 mmol of trimethylchlorosilane, afforded, after treating the diastereomeric acids with ethereal diazomethane and chromatography of the resulting methyl esters on 200 g of silica gel with 30% ether in petroleum ether, 2.4 g (52%) of the isomeric methyl esters 43. ^1H NMR analysis revealed a ratio of 1:3 for the two diastereomeric methyl esters.

Methyl 2(*R*)- and 2(*S*)-(5(*S*)-(Methoxymethyleneoxymethyl)-3(*S*)-methyl-2(*S*)-tetrahydrofuryl)butanoate. To a stirred solution of 2.4 g (9.3 mmol) of the diastereomeric methyl esters 43 (from HMPA/THF reaction) in 93 mL of ethyl acetate was added 240 mg of 10% platinum on carbon. The reaction mixture was stirred at room temperature under a hydrogen atmosphere for 3 h. The catalyst was then removed by filtration and washed with three 25-mL portions of ethyl acetate. Removal of the solvent from the combined filtrates and chromatography of the residue on 200 g of silica gel with 25% ethyl acetate in cyclohexane afforded 1.6 g (66%) of the 2*R* methyl ester and 0.53 g (21%) of the epimeric 2*S* methyl ester. 2*S* Methyl ester: evaporative distillation 80–90 °C (0.005 mmHg); $[\alpha]^{25}_D$ +16.2° (*c* 1.01, $CHCl_3$); IR ($CHCl_3$) 1730, 1460, 1390, 1110, 1040 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.90 (t, 3 H, J = 6 Hz, CH_3CH_2), 1.06 (d, 3 H, J = 6 Hz, CH_3CHCC), 3.36 (s, 3 H, OCH_3), 3.52 (d, 2 H, J = 5 Hz, CCH_2O), 3.69 (s, 3 H, CO_2CH_3), 4.61 (s, 2 H, OCH_2O). Anal. Calcd for $C_{13}H_{24}O_5$: C, 59.98; H, 9.29. Found: C, 59.92; H, 9.31. 2*R* Methyl ester: evaporative distillation 80–90 °C (0.005 mmHg); $[\alpha]^{25}_D$ +5.4° (*c* 1.16, $CHCl_3$); IR ($CHCl_3$) 1730, 1460, 1275, 1220, 1160, 1105, 1040 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.88 (t, 3 H, J = 6 Hz, CH_3CH_2), 0.99 (d, 3 H, J = 6 Hz, CH_3), 3.36 (s, 3 H, OCH_3), 3.51 (d, 2 H, J = 5 Hz, CCH_2O), 3.68 (s, 3 H, CO_2CH_3), 4.62 (s, 2 H, OCH_2O). Anal. Calcd for $C_{13}H_{24}O_5$: C, 59.98; H, 9.29. Found: C, 59.93; H, 9.12.

2(*R*)-(5(*S*)-(Methoxymethyleneoxymethyl)-3(*S*)-methyl-2(*S*)-tetrahydrofuryl)butan-1-ol (36). By the procedure described for the preparation of the corresponding alcohol of compound 4, 530 mg (2.0 mmol) of the 2*S* methyl ester above in 10 mL of dry ether with 80 mg of lithium tetrahydridoaluminate (8.4 mmol of hydride) afforded, after chromatography on 40 g of silica gel with 40% ethyl acetate in cyclohexane, 440 mg (95%) of an alcohol, the ^1H NMR spectrum of which was identical with that of compound 36.

2(*S*)-(5(*S*)-(Methoxymethyleneoxymethyl)-3(*S*)-methyl-2(*S*)-tetrahydrofuryl)butan-1-ol (44). By the procedure described for the preparation of the corresponding alcohol of compound 4, 1.67 g (6.4 mmol) of the 2*R* methyl ester above in 32 mL of dry ether with 240 mg of lithium tetrahydridoaluminate (25.6 mmol of hydride) afforded, after chromatography on 100 g of silica gel with 50% ethyl acetate in cyclohexane, 1.45 g (97%) of the alcohol 44: evaporative distillation 60–70 °C (0.005 mmHg); $[\alpha]^{25}_D$ +27.4° (*c* 1.265, $CHCl_3$); IR ($CHCl_3$) 3650, 3500, 1460, 1230, 1150, 1105, 1040 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.93 (t, 3 H, J = 6 Hz, CH_3CH_2), 1.01 (d, 3 H, J = 6 Hz, CH_3), 2.67 (dd, 1 H, J = 5, 6 Hz, $CHCH_3$), 3.33 (s, 3 H, OCH_3), 3.47 (d, 2 H, J = 5 Hz, CCH_2O), 4.60 (s, 2 H, OCH_2O). Anal. Calcd for $C_{12}H_{24}O_4$: C, 62.04; H, 10.41. Found: C, 62.01; H, 10.32.

Benzyl 2(*S*)-(5(*S*)-(Methoxymethyleneoxymethyl)-3(*S*)-methyl-2(*S*)-tetrahydrofuryl)butyl Ether. By the procedure described for the preparation of the benzyl ether 5, 1.45 g (6.22 mmol) of the alcohol 44 with 300 mg (7.48 mmol) of potassium hydride and 1.2 mL (9.6 mmol) of benzyl bromide in 30 mL of dry THF afforded, after chromatography on 100 g of silica gel with 15% ethyl acetate in cyclohexane, 2.0 g (97%) of the corresponding benzyl ether: evaporative distillation 100–110 °C (0.005 mmHg); $[\alpha]^{25}_D$ +18.7° (*c* 1.71, $CHCl_3$); IR ($CHCl_3$) 1460, 1380, 1120, 1040 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.92 (t, 3 H, J = 6 Hz, CH_3CH_2), 1.02 (d, 3 H, J = 6 Hz, CH_3), 3.33 (s, 3 H, OCH_3), 3.47 (d, 4 H, J = 5 Hz, CCH_2O), 4.43 (s, 2 H, $C_6H_5CH_2$), 4.60 (s, 2 H, OCH_2O), 7.28 (b s, 5 H, C_6H_5). Anal. Calcd for $C_{19}H_{30}O_4$: C, 70.77; H, 9.38. Found: C, 70.58; H, 9.22.

Benzyl 2(*S*)-(5(*S*)-(Hydroxymethyl)-3(*S*)-methyl-2(*S*)-tetrahydrofuryl)butyl Ether. By the procedure described for the preparation of the alcohol 38, 2.0 g (6.2 mmol) of the above methoxy methyl ether in 48 mL of THF and 12 mL of 10% aqueous HCl afforded, after chromatography on 100 g of silica gel with 35% ethyl acetate in cyclohexane, 1.7 g (99%) of the corresponding alcohol: evaporative distillation 100–110 °C (0.005 mmHg); $[\alpha]^{25}_D$ +49.3° (*c* 1.07, $CHCl_3$); IR ($CHCl_3$) 3600, 3450, 1460, 1380, 1220, 1100, 1080, 1040 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.93 (t, 3 H, J = 6 Hz, CH_3CH_2), 1.02 (d, 3 H, J = 6 Hz, CH_3), 3.47 (d, 2 H, J = 6 Hz, CCH_2O), 4.48 (s, 2 H, $C_6H_5CH_2$), 7.33 (b s, 5 H, C_6H_5). Anal. Calcd for $C_{17}H_{26}O_3$: C, 73.35; H, 9.41. Found: C, 73.46; H, 9.36.

Benzyl 2(*S*)-(5(*S*)-Carbomethoxy-3(*S*)-methyl-2(*S*)-tetrahydrofuryl)butyl Ether (25a). By the procedure described for the preparation of the methyl ester 34a, 1.7 g (6.12 mmol) of the above alcohol in 60 mL of water with 643 mg (7.7 mmol) of solid $NaHCO_3$ and freshly prepared Adam's catalyst (from 2 g of 88% platinum oxide) afforded 1.63 g (91%) of the acid 25. A portion of this material was treated with diazomethane in ether and chromatography of the resulting methyl ester on silica gel with 10% ethyl acetate in cyclohexane provided the analytical sample of the methyl ester 25a: evaporative distillation 100–110 °C (0.005 mmHg); $[\alpha]^{24}_D$ +1.4° (*c* 1.11, $CHCl_3$); IR ($CHCl_3$) 1740, 1460, 1370, 1220, 1100, 1040 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.93 (t, 3 H, J = 6 Hz, CH_3CH_2), 1.01 (d, 3 H, J = 6 Hz, CH_3), 3.49 (d, 2 H, J = 6 Hz, CCH_2O), 3.70 (s, 3 H, CO_2CH_3), 3.80 (dd, 1 H, J = 5, 8 Hz, OCHCC), 4.38 (t, 1 H, J = 7 Hz, $CHCO_2CH_3$), 4.47 (s, 2 H, $C_6H_5CH_2$), 7.32 (b s, 5 H, C_6H_5). Anal. Calcd for $C_{18}H_{26}O_4$: C, 70.56; H, 8.55. Found: C, 70.54; H, 8.52.

Benzyl 6-deoxy-α- and -β-L-gulose. To a stirred solution of 1.5 g (9.14 mmol) of 6-deoxy-L-gulose (45) in 18 mL of benzyl alcohol was added 0.35 mL of acetyl chloride. After 2 days, the reaction mixture was diluted with 40 mL of chloroform and then neutralized with 10 g of barium carbonate. The resulting suspension was filtered and the solid residue washed with three 25-mL portions of chloroform. The combined filtrates were concentrated at 50 °C (0.01 mmHg) and the residue was chromatographed on 200 g of silica gel with ethyl acetate to give 1.8 g (77%) of the benzyl glycosides (α:β = 1:2). α-Glycoside: mp 134.5–135.5 °C (ethyl acetate–hexane); $[\alpha]^{23}_D$ −118.1° (*c* 1.135, $CHCl_3$); IR ($CHCl_3$) 3600, 3500, 1220, 1105, 1080, 1040, 1000 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.23 (d, 3 H, *J* = 6 Hz, CH_3), 4.54 (d, 1 H, *J* = 12 Hz, C_6H_5CHH), 4.73 (d, 1 H, *J* = 12 Hz, C_6H_5CHH), 4.93 (b s, 1 H, H-1), 7.38 (b s, 5 H, C_6H_5). Anal. Calcd for $C_{13}H_{18}O_5$: C, 61.41; H, 7.14. Found: C, 61.33; H, 7.18. β-Glycoside: evaporative distillation 130–140 °C (0.005 mmHg); $[\alpha]^{23}_D$ +117.9° (*c* 0.585, $CHCl_3$); IR ($CHCl_3$) 3600, 3450, 1220, 1175, 1080, 1060, 1000 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.27 (d, 3 H, *J* = 6 Hz, CH_3), 4.53 (d, 1 H, *J* = 11 Hz, C_6H_5CHH), 4.62 (d, 1 H, *J* = 8 Hz, H-1), 4.89 (d, 1 H, *J* = 11 Hz, C_6H_5CHH), 7.34 (b s, 5 H, C_6H_5). Anal. Calcd for $C_{13}H_{18}O_5$: C, 61.41; H, 7.14. Found: C, 61.39; H, 7.18.

Benzyl 6-deoxy-2,3-*O*-(1-methylethylidene)-α- and -β-L-gulose. To a stirred solution of 1.8 g (7.08 mmol) of the above benzyl glycosides in 70 mL of dry acetone was added 70 mg (0.37 mmol) of *p*-toluenesulfonic acid monohydrate and 1.1 mL (8.9 mmol) of 2,2-dimethoxypropane. After 12 h, the reaction mixture was neutralized with barium carbonate. The resulting suspension was filtered and the solid residue then washed with three 50-mL portions of acetone. The combined filtrates were concentrated under reduced pressure and the residue chromatographed on 100 g of silica gel with 25% ethyl acetate–petroleum ether to give 1.94 g (93%) of the corresponding ketals. α-Glycoside: mp 79–80 °C (hexane); $[\alpha]^{23}_D$ −62.8 °C (*c* 0.955, $CHCl_3$); IR ($CHCl_3$) 3970, 3460, 1380, 1240, 1160, 1100, 1030 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.19 (d, 3 H, *J* = 6 Hz, CH_3), 1.36, 1.50 (s, 6 H, $C(CH_3)_2$), 4.56 (d, 1 H, *J* = 12 Hz, C_6H_5CHH), 4.71 (d, 1 H, *J* = 12 Hz, C_6H_5CHH), 4.87 (b s, 1 H, H1), 7.33 (b s, 5 H, C_6H_5). Anal. Calcd for $C_{16}H_{22}O_5$: C, 65.29; H, 7.53. Found: C, 65.26; H, 7.51. β-Glycoside: evaporative distillation 100–110 °C (0.005 mmHg); $[\alpha]^{23}_D$ +105.5° (*c* 0.55, $CHCl_3$); IR ($CHCl_3$) 3560, 3350, 1390, 1230, 1180, 1120, 1060 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.30 (d, 3 H, *J* = 6 Hz, CH_3), 1.31, 1.40 (s, 6 H, $C(CH_3)_2$), 4.73 (d, 1 H, *J* = 4 Hz, H-1), 4.58 (d, 1 H, *J* = 12 Hz, C_6H_5CHH), 4.84 (d, 1 H, *J* = 12 Hz, C_6H_5CHH), 7.33 (b s, 5 H, C_6H_5). Anal. Calcd for $C_{16}H_{22}O_5$: C, 65.29; H, 7.53. Found: C, 65.31; H, 7.48.

Benzyl 6-deoxy-2,3-*O*-(1-methylethylidene)-4-*O*-(methoxymethyl)-α- and -β-L-gulose (46). By the procedure described for the preparation of the methoxymethyl ether 41, 1.94 g (6.6 mmol) of a mixture of the above alcohols, 0.34 g (8.5 mmol) of potassium hydride and 1 mL (13.2 mmol) of chloromethyl methyl ether in 22 mL of dry THF afforded, after chromatography on 100 g of silica gel with 25% ethyl acetate–petroleum ether, 1.91 g (86%) of the methoxymethyl ethers 46. α-Glycoside: evaporative distillation 120–130 °C (0.005 mmHg); $[\alpha]^{24}_D$ −41.3° (*c* 0.75, $CHCl_3$); IR ($CHCl_3$) 1380, 1240, 1150, 1100, 1020 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.20 (d, 3 H, *J* = 6 Hz, CH_3), 1.36, 1.51 (s, 6 H, $C(CH_3)_2$), 3.40 (s, 3 H, OCH_3), 4.57 (b s, 1 H, H-1), 7.34 (b s, 5 H, C_6H_5). Anal. Calcd for $C_{18}H_{26}O_6$: C, 63.89; H, 7.74. Found: C, 64.03; H, 7.75. β-Glycoside: evaporative distillation 100–110 °C (0.005 mmHg); $[\alpha]^{24}_D$ +147.8° (*c* 0.565, $CHCl_3$); IR ($CHCl_3$) 1390, 1230, 1155, 1040 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.40 (s, 3 H, OCH_3), 4.57 (d, 1 H, *J* = 12 Hz, H-1), 7.30 (b s, 5 H, C_6H_5). Anal. Calcd for $C_{18}H_{26}O_6$: C, 63.89; H, 7.74. Found: C, 63.83; H, 7.57.

6-Deoxy-2,3-*O*-(1-methylethylidene)-4-*O*-(methoxymethyl)-L-gulose (47). To a stirred solution of 3 cm (18.3 mmol) of lithium wire in 50 mL of anhydrous ammonia at −78 °C under argon was added a solution of 1.91 g (5.64 mmol) of the mixture of benzyl glycosides 46 in 10 mL of dry THF. Cooling was then discontinued (ammonia reflux), and after 1 h, 1.1 g (20.6 mmol) of anhydrous ammonium chloride was cautiously added to the reaction mixture. The resulting mixture was then diluted with 50 mL of ether and the ammonia was allowed to evaporate. The resulting suspension was filtered, and the solid was then washed by trituration with four 20-mL portions of ether. Removal of the solvent from the combined filtrates gave 1.2 g (86%) of the crystalline lactol 47: mp 139 °C (ethyl acetate–hexane); $[\alpha]^{23}_D$ +61.7° (*c* 1.215, $CHCl_3$); IR ($CHCl_3$) 3600, 3460, 1390, 1230, 1160, 1100, 1040 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.27 (d, 3 H, *J* = 6 Hz, CH_3), 1.33, 1.47 (s, 6 H, $C(CH_3)_2$), 3.40 (s, 3 H, OCH_3), 3.57 (d, 1 H, *J* = 6 Hz, OH), 3.63 (dd, 1 H, *J* = 3 Hz, 3 Hz, H-4), 4.00 (dq, 1 H, *J* = 3 Hz, 6 Hz, H-5), 4.03 (dd, 1 H, *J* = 6 Hz, 6 Hz, H-2), 4.33 (dd, 1 H, *J* = 3 Hz, 6 Hz, H-3), 4.63 (d, 1 H, *J* = 6 Hz, $OCHHO$), 4.77 (d, 1 H, *J* = 6 Hz, $OCHHO$), 4.87 (dd, 1 H, *J* = 6 Hz, 6 Hz, H-1). Anal. Calcd for $C_{11}H_{20}O_6$: C, 53.22; H, 8.12. Found: C, 53.12; H, 8.21.

1,5-Anhydro-2,6-dideoxy-4-*O*-(methoxymethyl)-L-xylo-hex-1-enitol (26). By the procedure described for the preparation of the glycal 42, 437.4 mg (1.76 mmol) of the lactol 47, 0.22 mL (2.28 mmol) of carbon tetrachloride, 0.34 mL (1.87 mmol) of tris(dimethylamino)phosphine in 7 mL of dry THF with 3.5 cm (21.3 mmol) of lithium wire in 30 mL of anhydrous ammonia and 1.4 g (26.2 mmol) of anhydrous ammonium chloride afforded, after passage through 5 g of silica gel with 50% ethyl acetate–petroleum ether and distillation [Kugelrohr, 60 °C (0.1 mmHg)], 280 mg (90%) of the glycal 26: $[\alpha]^{23}_D$ −206.4° (*c* 0.59, $CHCl_3$); IR ($CHCl_3$) 3620, 3450, 1640, 1240, 1150, 1090, 1030, 940 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.36 (d, 3 H, *J* = 6 Hz, CH_3), 3.40 (s, 3 H, OCH_3), 3.56 (m, 1 H, H-4), 4.10 (m, 2 H, H-3 and H-5), 4.66 (d, 1 H, *J* = 6 Hz, $OCHHO$), 4.73 (d, 1 H, *J* = 6 Hz, $OCHHO$), 4.89 (m, 1 H, H-2), 6.50 (d, 1 H, *J* = 6 Hz, H-1). Anal. Calcd for $C_8H_{14}O_4$: C, 55.16; H, 8.10. Found: C, 55.27; H, 8.20.

Benzyl 2(*R*)-[5(*R*)- and 5(*S*)-Carbomethoxy-3(*S*)-methyl-5-(5,6-dihydro-5(*S*)-(methoxymethyloxy)-6(*S*)-methyl-2(*R*)-pyranyl)-2(*S*)-tetrahydrofuryl]butyl Ether (50 and 51). By the part A procedure described for the preparation of the methyl esters 43, 272 mg (1.56 mmol) of the glycal 26 with 0.71 mL (1.63 mmol) of 2.3 M solution of *n*-butyllithium in hexane and 1.61 mmol of the acid chloride of the acid 39 in 6 mL of dry THF, added to 3.45 mmol of LDA in 7 mL of dry THF, followed by 5.1 mmol of trimethylchlorosilane, afforded, after treatment with ethereal diazomethane and chromatography on 30 g of silica gel with 20% ethyl acetate–cyclohexane, 125.7 mg of the methyl ester 50 and 283.4 mg of the methyl ester 51, or a 30:70 ratio of a 57% combined yield. Methyl ester 50: evaporative distillation 150–160 °C (0.005 mmHg); $[\alpha]^{24}_D$ +135.7° (*c* 1.915, $CHCl_3$); IR ($CHCl_3$) 1740, 1460, 1390, 1160, 1100, 1040 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.93 (t, 3 H, *J* = 6 Hz, CH_3CH_2), 0.97 (d, 3 H, *J* = 6 Hz, CH_3CHCC), 1.20 (d, 3 H, *J* = 6 Hz, CH_3CHOC), 3.37 (s, 3 H, OCH_3), 3.73 (s, 3 H, CO_2CH_3), 4.44 (b s, 2 H, $C_6H_5CH_2$), 4.60 (d, 1 H, *J* = 7 Hz, $OCHHO$), 4.71 (d, 1 H, *J* = 7 Hz, $OCHHO$), 5.63–6.13 (m, 2 H, HC=CH), 7.33 (b s, 5 H, C_6H_5). Anal. Calcd for $C_{28}H_{36}O_7$: C, 67.51; H, 8.28. Found: C, 67.70; H, 8.33. Methyl ester 51: evaporative distillation 150–160 °C (0.005 mmHg); $[\alpha]^{24}_D$ +159.5° (*c* 0.845, $CHCl_3$); IR ($CHCl_3$) 1745, 1730, 1460, 1380, 1140, 1090, 1040 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.87 (t, 3 H, *J* = 6 Hz, CH_3CH_2), 0.96 (d, 3 H, *J* = 6 Hz, CH_3CHCC), 1.13 (d, 3 H, *J* = 6 Hz, CH_3CHOC), 3.33 (s, 3 H, OCH_3), 3.64 (s, 3 H, CO_2CH_3), 4.41 (b s, 2 H, $C_6H_5CH_2$), 4.57 (d, 1 H, *J* = 6 Hz, $OCHHO$), 4.70 (d, 1 H, *J* = 6 Hz, $OCHHO$), 6.00 (m, 2 H, HC=CH), 7.30 (b s, 5 H, C_6H_5). Anal. Calcd for $C_{28}H_{36}O_7$: C, 67.51; H, 8.28. Found: C, 67.61; H, 8.35.

Benzyl 2(*S*)-[5(*R*)- and 5(*S*)-Carbomethoxy-3(*S*)-methyl-5-(5,6-dihydro-5(*S*)-(methoxymethyloxy)-6(*S*)-methyl-2(*R*)-pyranyl)-2(*S*)-tetrahydrofuryl]butyl Ether (48 and 49). By the part A procedure described for the preparation of the methyl esters 43, 381 mg (2.18 mmol) of the glycal 26 with 1 mL (2.3 mmol) of 2.3 M solution of *n*-butyllithium in hexane and 2.45 mmol of the acid chloride of the acid 25 in 5 mL of dry THF, added to 4.6 mmol of LDA in 5 mL of dry THF, followed by 9.5 mmol of trimethylchlorosilane, afforded, after treatment with ethereal diazomethane and chromatography on 50 g of silica gel with 20% ethyl acetate–cyclohexane, 178 mg of the methyl ester 48 and 504 mg of the methyl ester 49, or a 26:74 ratio of a 67% combined yield. Methyl ester 48: evaporative distillation 150–160 °C (0.005 mmHg); $[\alpha]^{23}_D$ +148.6° (*c* 1.22, $CHCl_3$); IR ($CHCl_3$) 1740, 1460, 1215, 1160, 1100, 1040 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.92 (t, 3 H, *J* = 6 Hz, CH_3CH_2), 0.97 (d, 3 H, *J* = 6 Hz, CH_3CHCC), 1.18 (d, 3 H, *J* = 6 Hz, CH_3CHOC), 3.34 (s, 3 H, OCH_3), 3.73 (s, 3 H, CO_2CH_3), 4.47 (b s, 2 H, $C_6H_5CH_2$), 4.62 (d, 1 H, *J* = 7 Hz, $OCHHO$), 4.71 (d, 1 H, *J* = 7 Hz, $OCHHO$), 5.67–6.17 (m, 2 H, HC=CH), 7.33 (b s, 5 H, C_6H_5). Anal. Calcd for $C_{28}H_{36}O_7$: C, 67.51; H, 8.28. Found: C, 67.70; H, 8.39. Methyl ester 49: evaporative distillation 150–160 °C (0.005 mmHg); $[\alpha]^{23}_D$ +178.8° (*c* 1.30, $CHCl_3$); IR ($CHCl_3$) 1750, 1730, 1460, 1385, 1155, 1100, 1040 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.90 (t, 3 H, *J* = 6 Hz, CH_3CH_2), 0.97 (d, 3 H, *J* = 6 Hz, CH_3CHCC), 1.16 (d, 3 H, *J* = 6 Hz, CH_3CHOC), 2.50 (q, 1 H, *J* = 6 Hz, CH_3CHCC), 3.34 (s, 3 H, OCH_3), 3.68 (s, 3 H, CO_2CH_3), 4.43 (s, 2 H, $C_6H_5CH_2$), 4.57 (d, 1 H, *J* = 6 Hz, $OCHHO$), 4.70 (d, 1 H, *J* = 6 Hz, $OCHHO$), 5.31 (b s, 2 H, HC=CH), 7.32 (b s, 5 H, C_6H_5). Anal. Calcd for $C_{28}H_{36}O_7$: C, 67.51; H, 8.28. Found: C, 67.43; H, 8.27.

Benzyl 2(*R*)-[5(*R*)-Carbomethoxy-3(*S*)-methyl-5-(5(*S*)-(methoxymethyloxy)-6(*S*)-methyl-2(*R*)-tetrahydropyranyl)-2(*S*)-tetrahydrofuryl]butyl Ether. To a stirred solution of 140 mg (0.30 mmol) of the methyl ester 50 in 5 mL of ethyl acetate was added 0.1 mL of Raney nickel catalyst suspension.[27] The reaction mixture was stirred at room temperature under hydrogen atmosphere for 3 h. The catalyst was then removed by filtration and washed with three 5-mL portions of ethyl acetate. The combined filtrates were concentrated under reduced pressure, and chromatography of the resulting residue on 10 g of silica gel

with 15% ethyl acetate in petroleum ether gave 120 mg (85%) of the saturated methyl ester: evaporative distillation 150–160 °C (0.005 mmHg); $[\alpha]^{26}_D$ +3.4° (*c* 0.83, $CHCl_3$); IR ($CHCl_3$) 1730, 1460, 1380, 1100, 1040 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.93 (t, 3 H, J = 6 Hz, CH_3CH_2), 0.94 (d, 3 H, J = 6 Hz, CH_3CHCC), 1.20 (d, 3 H, J = 6 Hz, CH_3CHOC), 3.31 (s, 3 H, OCH_3), 3.69 (s, 3 H, CO_2CH_3), 4.43 (b s, 3 H, $C_6H_5CH_2$), 4.58 (b s, 2 H, OCH_2O), 7.30 (b s, 5 H, C_6H_5). Anal. Calcd for $C_{28}H_{46}O_7$: C, 67.22; H, 8.68. Found: C, 67.46; H, 8.67.

Benzyl 2(*R*)-[5(*S*)-Carbomethoxy-3(*S*)-methyl-5-(5(*S*)-(methoxymethyleneoxy)-6(*S*)-methyl-2(*R*)-tetrahydropyranyl)-2(*S*)-tetrahydrofuryl]butyl Ether. By the procedure described above, 340 mg (0.74 mmol) of the methyl ester 51 in 5 mL of ethyl acetate with 0.2 mL of Raney nickel catalyst suspension[27] afforded, after chromatography on 30 g of silica gel with 20% ethyl acetate in petroleum ether, 300 mg (88%) of the saturated methyl ester: evaporative distillation 150–160 °C (0.005 mmHg); $[\alpha]^{23}_D$ +19.3° (*c* 0.56, $CHCl_3$); IR ($CHCl_3$) 1745, 1730, 1460, 1385, 1210, 1140, 1105, 1030 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.93 (t, 3 H, J = 6 Hz, CH_3CH_2), 0.97 (d, 3 H, J = 6 Hz, CH_3CHCC), 1.12 (d, 3 H, J = 6 Hz, CH_3CHOC), 3.30 (s, 3 H, OCH_3), 3.63 (s, 3 H, CO_2CH_3), 4.40 (b s, 2 H, $C_6H_5CH_2$), 4.57 (b s, 2 H, OCH_2O), 7.30 (s, 5 H, C_6H_5). Anal. Calcd for $C_{28}H_{46}O_7$: C, 67.22; H, 8.68. Found: C, 67.23; H, 8.69.

Benzyl 2(*S*)-[5(*R*)-Carbomethoxy-3(*S*)-methyl-5-(5(*S*)-(methoxymethyleneoxy)-6(*S*)-methyl-2(*R*)-tetrahydropyranyl)-2(*S*)-tetrahydrofuryl]butyl Ether. By the same hydrogenation procedure, 168 mg (0.36 mmol) of the methyl ester 48 in 5 mL of ether acetate with 0.1 mL of Raney nickel catalyst suspension[27] afforded, after chromatography on 20 g of silica gel with 15% ethyl acetate–cyclohexane, 150 mg (89%) of the saturated methyl ester: evaporative distillation 150–160 °C (0.005 mmHg); $[\alpha]^{24}_D$ +3.5° (*c* 1.255, $CHCl_3$); IR ($CHCl_3$) 1730, 1460, 1380, 1110, 1040 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.93 (t, 3 H, J = 6 Hz, CH_3CH_2), 0.95 (d, 3 H, J = 6 Hz, CH_3CHCC), 1.17 (d, 3 H, J = 6 Hz, CH_3CHOC), 3.33 (s, 3 H, OCH_3), 3.70 (s, 3 H, CO_2CH_3), 4.47 (b s, 2 H, $C_6H_5CH_2$), 4.59 (b s, 2 H, OCH_2O), 7.33 (b s, 5 H, C_6H_5). Anal. Calcd for $C_{28}H_{46}O_7$: C, 67.22; H, 8.68. Found: C, 67.02; H, 8.69.

Benzyl 2(*S*)-[5(*S*)-Carbomethoxy-3(*S*)-methyl-5-(5(*S*)-(methoxymethyleneoxy)-6(*S*)-methyl-2(*R*)-tetrahydropyranyl)-2(*S*)-tetrahydrofuryl]butyl Ether. By the above procedure, 494 mg (1.07 mmol) of the methyl ester 49 in 8 mL of ethyl acetate with 0.3 mL of Raney nickel catalyst suspension[27] afforded, after chromatography on 40 g of silica gel with 20% ethyl acetate–cyclohexane, 420 mg (85%) of the saturated methyl ester: evaporative distillation 150–160 °C (0.005 mmHg); $[\alpha]^{23}_D$ +33.0° (*c* 1.03, $CHCl_3$); IR ($CHCl_3$) 1750, 1730, 1460, 1390, 1110, 1040 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.90 (t, 3 H, J = 6 Hz, CH_3CH_2), 0.94 (d, 3 H, J = 6 Hz, CH_3CHCC), 1.12 (d, 3 H, J = 6 Hz, CH_3CHOC), 2.39 (q, 1 H, J = 6 Hz, CH_3CHCC), 3.32 (s, 3 H, OCH_3), 3.67 (s, 3 H, CO_2CH_3), 4.47 (b s, 2 H, $C_6H_5CH_2$), 4.60 (b s, 2 H, OCH_2O), 7.33 (b s, 5 H, C_6H_5). Anal. Calcd for $C_{28}H_{46}O_7$: C, 67.22; H, 8.68. Found: C, 67.31; H, 8.72.

Benzyl 2(*R*)-[5(*R*)-Formyl-3(*S*)-methyl-5-(5(*S*)-(methoxymethyleneoxy)-6(*S*)-methyl-2(*R*)-tetrahydropyranyl)-2(*S*)-tetrahydrofuryl]butyl Ether (54). To a stirred solution of 100 mg (0.22 mmol) of the saturated methyl ester from the ester 50 in 2 mL of dry ether under argon at −78 °C was added dropwise over 10 min 0.7 mL of a 1 M hexane solution of diisobutylaluminum hydride. After 1 h, the reaction mixture was cautiously treated with 0.1 mL of methanol, allowed to warm to room temperature, and then diluted with 30 mL of ether. This solution was washed with three 10-mL portions of saturated aqueous sodium tartarate and 10 mL of saturated aqueous NaCl and then dried ($MgSO_4$). After removal of the solvent under reduced pressure, chromatography of the residue on 10 g of silica gel with 20% ethyl acetate in petroleum ether gave 90 mg (96%) of the aldehyde 54: evaporative distillation 150–160 °C (0.005 mmHg); $[\alpha]^{24}_D$ +6.2° (*c* 1.015, $CHCl_3$); IR ($CHCl_3$) 1735, 1460, 1385, 1110, 1040 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.93 (t, 3 H, J = 6 Hz, CH_3CH_2), 0.94 (d, 3 H, J = 6 Hz, CH_3CHCC), 1.17 (d, 3 H, J = 6 Hz, CH_3CHOC), 3.33 (s, 3 H, OCH_3), 4.46 (b s, 2 H, $C_6H_5CH_2$), 4.60 (b s, 2 H, OCH_2O), 7.33 (b s, 5 H, C_6H_5), 9.57 (s, 1 H, CHO). Anal. Calcd for $C_{28}H_{44}O_6$: C, 69.10; H, 8.81. Found: C, 69.06; H, 8.78.

Benzyl 2(*R*)-[5(*S*)-Formyl-3(*S*)-methyl-5-(5(*S*)-(methoxymethyleneoxy)-6(*S*)-methyl-2(*R*)-tetrahydropyranyl)-2(*S*)-tetrahydrofuryl]butyl Ether (55). By the procedure described above, 206 mg (0.44 mmol) of the saturated methyl ester from methyl ester 51 in 4 mL of dry ether with 1.4 mL of 1 M solution of diisobutylaluminum hydride in hexane afforded, after chromatography on 20 g of silica gel with 20% ethyl acetate in petroleum ether, 190 mg (98%) of the aldehyde 55: evaporative distillation 150–160 °C (0.005 mmHg); $[\alpha]^{24}_D$ +30.7° (*c* 0.95, $CHCl_3$); IR ($CHCl_3$) δ 0.92 (t, 3 H, J = 6 Hz, CH_3CH_2), 3.32 (s, 3 H, OCH_3), 4.41 (b s, 2 H, $C_6H_5CH_2$), 4.59 (b s, 2 H, OCH_2O), 7.30 (b s, 5 H, C_6H_5), 9.67 (s, 1 H, CHO). Anal. Calcd for $C_{28}H_{44}O_6$: C, 69.10; H, 8.81. Found: C, 69.11; H, 8.91.

Benzyl 2(*S*)-[5(*R*)-Formyl-3(*S*)-methyl-5-(5(*S*)-(methoxymethyleneoxy)-6(*S*)-methyl-2(*R*)-tetrahydropyranyl)-2(*S*)-tetrahydrofuryl]butyl Ether (52). By the procedure described above, 139 mg (0.30 mmol) of the saturated methyl ester from methyl ester 48 in 3 mL of dry ether with 0.9 mL of 1 M solution of diisobutylaluminum hydride in hexane afforded, after chromatography on 20 g of silica gel with 20% ethyl acetate in cyclohexane, 120 mg (92%) of the aldehyde 52: evaporative distillation 150–160 °C (0.005 mmHg); $[\alpha]^{23}_D$ +18.7° (*c* 1.55, $CHCl_3$); IR ($CHCl_3$) 1730, 1460, 1390, 1100, 1040 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.93 (t, 3 H, J = 6 Hz, CH_3CH_2), 0.93 (d, 3 H, J = 6 Hz, CH_3CHCC), 1.17 (d, 3 H, J = 6 Hz, CH_3CHOC), 3.33 (s, 3 H, OCH_3), 4.47 (b s, 2 H, $C_6H_5CH_2$), 4.60 (b s, 2 H, OCH_2O), 7.33 (b s, 5 H, C_6H_5), 9.60 (s, 1 H, CHO). Anal. Calcd for $C_{28}H_{44}O_6$: C, 69.10; H, 8.81. Found: C, 69.08; H, 8.73.

Benzyl 2(*S*)-[5(*S*)-Formyl-3(*S*)-methyl-5-(5(*S*)-(methoxymethyleneoxy)-6(*S*)-methyl-2(*R*)-tetrahydropyranyl)-2(*S*)-tetrahydrofuryl]butyl Ether (53). By the procedure described above, 407 mg (0.88 mmol) of the saturated methyl ester from methyl ester 49 in 5 mL of dry ether with 2.7 mL of 1 M solution of diisobutylaluminum hydride in hexane afforded, after chromatography on 30 g of silica gel with 20% ethyl acetate in cyclohexane, 363 mg (95%) of the aldehyde 53: evaporative distillation 150–160 °C (0.005 mmHg); $[\alpha]^{23}_D$ +50.8° (*c* 1.00, $CHCl_3$); IR ($CHCl_3$) 1735, 1460, 1380, 1110, 1040 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.90 (t, 3 H, J = 6 Hz, CH_3CH_2), 0.94 (d, 3 H, J = 6 Hz, CH_3CHCC), 1.12 (d, 3 H, J = 6 Hz, CH_3CHOC), 2.33 (q, 1 H, J = 6 Hz, CH_3CHCC), 3.30 (s, 3 H, OCH_3), 4.46 (b s, 2 H, $C_6H_5CH_2$), 4.57 (b s, 2 H, OCH_2O), 7.30 (b s, 5 H, C_6H_5), 9.67 (s, 1 H, CHO). Anal. Calcd for $C_{28}H_{44}O_6$: C, 69.10; H, 8.81. Found: C, 69.06; H, 8.80.

Benzyl 2(*R*)-[5(*S*)-Vinyl-3(*S*)-methyl-5-(5(*S*)-(methoxymethyleneoxy)-6(*S*)-methyl-2(*R*)-tetrahydropyranyl)-2(*S*)-tetrahydrofuryl]butyl Ether. To a stirred solution of 161 mg (0.45 mmol) of methyltriphenylphosphonium bromide in 1 mL of dry THF at −78 °C under argon was added 0.185 mL (0.43 mmol) of a 2.3 M solution of *n*-butyllithium in hexane. Cooling was then discontinued and the reaction mixture was stirred at room temperature for 1 h and then cooled to −78 °C. A solution of 80 mg (0.18 mmol) of the aldehyde 54 in 1 mL of dry THF was added and the reaction mixture allowed to warm to room temperature, after 10 h, the reaction mixture was treated with 1 mL of saturated aqueous $NaHCO_3$, diluted with 40 mL of ether, washed with 20 mL of saturated aqueous $NaHCO_3$ and 20 mL of saturated aqueous NaCl, and then dried ($MgSO_4$). Removal of the solvents at reduced pressure and chromatography of the residue on 10 g of silica gel with 8% ethyl acetate in petroleum ether afforded 64 mg (80%) of the adduct: evaporative distillation 140–150 °C (0.005 mmHg); $[\alpha]^{26}_D$ −2.8° (*c* 1.04, $CHCl_3$); IR ($CHCl_3$) 1470, 1390, 1110, 1040 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.92 (t, 3 H, J = 6 Hz, CH_3CH_2), 0.93 (d, 3 H, J = 6 Hz, CH_3CHCC), 1.13 (d, 3 H, J = 6 Hz, CH_3CHOC), 3.31 (s, 3 H, OCH_3), 4.44 (b s, 2 H, $C_6H_5CH_2$), 4.58 (b s, 2 H, OCH_2O), 4.96 (dd, 1 H, J = 3, 11 Hz, HC=CH*H*(c)), 5.19 (dd, 1 H, J = 3, 18 Hz, CH=C*H*H(t)), 5.87 (dd, J = 11, 18 Hz, *H*C=CH_2), 7.31 (b s, 5 H, C_6H_5). Anal. Calcd for $C_{28}H_{46}O_5$: C, 72.19; H, 9.32. Found: C, 72.11; H, 9.20.

Benzyl 2(*R*)-[5(*R*)-Vinyl-3(*S*)-methyl-5-(5(*S*)-(methoxymethyleneoxy)-6(*S*)-methyl-2(*R*)-tetrahydropyranyl)-2(*S*)-tetrahydrofuryl]butyl Ether. By the procedure described above, 180 mg (0.41 mmol) of the aldehyde 55 in 4 mL of dry THF with 0.85 mmol of methylenetriphenyiphospborane afforded, after chromatography on 20 g of silica gel with 8% ethyl acetate in petroleum ether, 160 mg (89%) of the adduct: evaporative distillation 140–150 °C (0.005 mmHg); $[\alpha]^{26}_D$ +42.1° (*c* 0.96, $CHCl_3$); IR ($CHCl_3$) 1460, 1380, 1100, 1030 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.93 (t, 3 H, J = 6 Hz, CH_3CH_2), 0.97 (d, 3 H, J = 6 Hz, CH_3CHCC), 1.20 (d, 3 H, J = 6 Hz, CH_3CHOC), 3.33 (s, 3 H, OCH_3), 4.44 (b s, 2 H, $C_6H_5CH_2$), 4.59 (b s, 2 H, OCH_2O), 5.00 (dd, 1 H, J = 3, 11 Hz, HC=CH*H*(c)), 5.13 (dd, 1 H, J = 3, 18 Hz, HC=CH*H*(t)), 5.87 (dd, 1 H, J = 11, 18 Hz, *H*C=CH_2), 7.30 (b s, 5 H, C_6H_5). Anal. Calcd for $C_{28}H_{46}O_5$: C, 72.19; H, 9.32. Found: C, 72.01; H, 9.20.

Benzyl 2(*S*)-[5(*S*)-Vinyl-3(*S*)-methyl-5-(5(*S*)-(methoxymethyleneoxy)-6(*S*)-methyl-2(*R*)-tetrahydropyranyl)-2(*S*)-tetrahydrofuryl]butyl Ether. By the procedure described above, 109.5 mg (0.25 mmol) of the aldehyde 52 in 2 mL of dry THF with 0.57 mmol of methylenetriphenyiphosphorane afforded, after chromatography on 10 g of silica gel with 7% ethyl acetate in cyclohexane, 90 mg (83%) of the adduct: evaporative distillation 140–150 °C (0.005 mmHg); $[\alpha]^{23}_D$ +2.8° (*c* 0.905, $CHCl_3$); IR ($CHCl_3$) 1460, 1380, 1205, 1110, 1040 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.93 (t, 3 H, J = 6 Hz, CH_3CH_2), 0.93 (d, 3 H, J = 6 Hz, CH_3CHCC), 1.14 (d, 3 H, J = 6 Hz, CH_3CHOC), 3.33 (s, 3 H, OCH_3), 4.44 (b s, 2 H, $C_6H_5CH_2$), 4.61 (b s, 2 H, OCH_2O), 4.93 (dd, 1 H, J = 3, 11 Hz, HC=CH*H*(c)), 5.13 (dd, 1 H, J = 3, 18 Hz, HC=CH*H*(t)), 5.90 (dd, 1 H, J = 11, 18 Hz, *H*C=CH_2), 7.33 (b s, 5 H, C_6H_5). Anal. Calcd for $C_{28}H_{46}O_5$: C, 72.19; H, 9.32. Found: C, 72.10; H, 9.29.

Benzyl 2(*S*)-[5(*R*)-Vinyl-3(*S*)-methyl-5-(5(*S*)-(methoxymethyleneoxy)-6(*S*)-methyl-2(*R*)-tetrahydropyranyl)-2(*S*)-tetrahydrofuryl]butyl Ether. By the procedure described above, 353.4 mg (0.81 mmol) of the aldehyde **53** in 5 mL of dry THF with 1.72 mmol of methylenetriphenylphosphorane afforded, after chromatography on 30 g of silica gel with 7% ethyl acetate in cyclohexane, 310 mg (88%) of the adduct: evaporative distillation 140–150 °C (0.005 mmHg); $[\alpha]^{25}_D$ +51.4° (*c* 0.97, $CHCl_3$); IR ($CHCl_3$) 1460, 1380, 1100, 1030 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.91 (t, 3 H, J = 6 Hz, CH_3CH_2), 0.94 (d, 3 H, J = 6 Hz, CH_3CHCC), 1.20 (d, 3 H, J = 6 Hz, CH_3CHOC), 3.32 (s, 3 H, OCH_3), 4.47 (b s, 2 H, $C_6H_5CH_2$), 4.59 (b s, 2 H, OCH_2O), 5.02 (dd, 1 H, J = 3, 10 Hz, HC=CH*H*(c)), 5.20 (dd, 1 H, J = 3, 18 Hz, HC=CH*H*(t)), 5.87 (dd, 1 H, J = 10, 18 Hz, *H*C=CH_2), 7.32 (b s, 5 H, C_6H_5). Anal. Calcd for $C_{26}H_{40}O_5$: C, 72.19; H, 9.32. Found: C, 72.26; H, 9.15.

Benzyl 2(*R*)-[5(*R*)-Ethyl-3(*S*)-methyl-5-(5(*S*)-(methoxymethyleneoxy)-6(*S*)-methyl-2(*R*)-tetrahydropyranyl)-2(*S*)-tetrahydrofuryl]butyl Ether. By the procedure described for the hydrogenation of ester **48**, 55 mg (0.13 mmol) of the adduct from aldehyde **54** in 2 mL of ethyl acetate with 0.05 mL of Raney nickel catalyst suspension[27] afforded, after chromatography on 10 g of silica gel with 7% ethyl acetate in petroleum ether, 49.5 mg (90%) of the saturated compound: evaporative distillation 140–150 °C (0.005 mmHg); $[\alpha]^{25}_D$ +14.0° (*c* 0.97, $CHCl_3$); IR ($CHCl_3$) 1460, 1380, 1100, 1035 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.20 (d, 3 H, J = 6 Hz, CH_3CHOC), 3.33 (s, 3 H, OCH_3), 4.52 (b s, 2 H, $C_6H_5CH_2$), 4.61 (b s, 2 H, OCH_2O), 7.33 (b s, 5 H, C_6H_5). Anal. Calcd for $C_{26}H_{42}O_5$: C, 71.85; H, 9.74. Found: C, 71.88; H, 9.74.

Benzyl 2(*R*)-[5(*S*)-Ethyl-3(*S*)-methyl-5-(5(*S*)-(methoxymethyleneoxy)-6(*S*)-methyl-2(*R*)-tetrahydropyranyl)-2(*S*)-tetrahydrofuryl]butyl Ether. By the procedure described for the hydrogenation of ester **48**, 141 mg (0.33 mmol) of the adduct from aldehyde **55** in 3 mL of ethyl acetate with 0.1 mL of Raney nickel catalyst suspension[27] afforded, after chromatography on 15 g of silica gel with 7% ethyl acetate in petroleum ether, 130 mg (92%) of the saturated compound: evaporative distillation 140–150 °C (0.005 mmHg); $[\alpha]^{25}_D$ +14.3° (*c* 0.955, $CHCl_3$); IR ($CHCl_3$) 1460, 1385, 1105, 1040 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.20 (d, 3 H, J = 6 Hz, CH_3CHOC), 3.33 (s, 3 H, OCH_3), 4.43 (b s, 2 H, $C_6H_5CH_2$), 4.60 (b s, 2 H, OCH_2O), 7.30 (b s, 5 H, C_6H_5). Anal. Calcd for $C_{26}H_{42}O_5$: C, 71.85; H, 9.74. Found: C, 71.82; H, 9.88.

Benzyl 2(*S*)-[5(*R*)-Ethyl-3(*S*)-methyl-5-(5(*S*)-(methoxymethyleneoxy)-6(*S*)-methyl-2(*R*)-tetrahydropyranyl)-2(*S*)-tetrahydrofuryl]butyl Ether. By the procedure described for the hydrogenation of ester **48**, 77.4 mg (0.18 mmol) of the adduct from aldehyde **52** in 3 mL of ethyl acetate with 0.1 mL of Raney nickel catalyst suspension[27] afforded, after chromatography on 10 g of silica gel with 7% ethyl acetate in cyclohexane, 65 mg (84%) of the saturated compound: evaporative distillation 140–150 °C (0.005 mmHg); $[\alpha]^{25}_D$ +27.0° (*c* 1.565, $CHCl_3$); IR ($CHCl_3$) 1460, 1380, 1210, 1110, 1040 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.17 (d, 3 H, J = 6 Hz, CH_3CHOC), 3.33 (s, 3 H, OCH_3), 4.44 (b s, 2 H, $C_6H_5CH_2$), 4.57 (b s, 2 H, OCH_2O), 7.33 (b s, 5 H, C_6H_5). Anal. Calcd for $C_{26}H_{42}O_5$: C, 71.85; H, 9.74. Found: C, 71.68; H, 9.58.

Benzyl 2(*S*)-[5(*S*)-Ethyl-3(*S*)-methyl-5-(5(*S*)-(methoxymethyleneoxy)-6(*S*)-methyl-2(*R*)-tetrahydropyranyl)-2(*S*)-tetrahydrofuryl]butyl Ether. By the procedure described for the hydrogenation of ester **48**, 300 mg (0.69 mmol) of the adduct from aldehyde **53** in 5 mL of ethyl acetate with 0.1 mL of Raney nickel catalyst suspension[27] afforded, after chromatography on 25 g of silica gel with 7% ethyl acetate in cyclohexane, 270 mg (90%) of the saturated compound: evaporative distillation 140–150 °C (0.005 mmHg); $[\alpha]^{25}_D$ +28.3° (*c* 1.03, $CHCl_3$); IR ($CHCl_3$) 1460, 1390, 1100, 1040 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.82, 0.90 (2t, 6 H, J = 6 Hz, CH_3CH_2), 0.94 (d, 3 H, J = 6 Hz, CH_3CHCC), 1.18 (d, 3 H, J = 6 Hz, CH_3CHOC), 3.32 (s, 3 H, OCH_3), 4.46 (b s, 2 H, $C_6H_5CH_2$), 4.59 (b s, 2 H, OCH_2O), 7.30 (b s, 5 H, C_6H_5). Anal. Calcd for $C_{26}H_{42}O_5$: C, 71.85; H, 9.74. Found: C, 71.88; H, 9.59.

Benzyl 2(*R*)-[5(*R*)-Ethyl-3(*S*)-methyl-5-(5(*S*)-hydroxy-6(*S*)-methyl-2(*R*)-tetrahydropyranyl)-2(*S*)-tetrahydrofuryl]butyl Ether (57). By the procedure described for the preparation of the alcohol **38**, 40 mg (0.09 mmol) of the methoxymethyl ether from aldehyde **54** in 3 mL of THF and 0.75 mL of 10% aqueous HCl afforded, after chromatography on 7 g of silica gel with 25% ethyl acetate in petroleum ether, 35 mg (97%) of the alcohol **57**: evaporative distillation 140–150 °C (0.005 mmHg); $[\alpha]^{25}_D$ +11.6° (*c* 0.93, $CHCl_3$); IR ($CHCl_3$) 3620, 3450, 1460, 1380, 1100, 1070 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.14 (d, 3 H, J = 6 Hz, CH_3CHOC), 4.44 (s, 2 H, $C_6H_5CH_2$), 7.32 (b s, 5 H, C_6H_5). Anal. Calcd for $C_{24}H_{36}O_4$: C, 73.81; H, 9.81. Found: C, 73.79; H, 9.70.

Benzyl 2(*R*)-[5(*S*)-Ethyl-3(*S*)-methyl-5-(5(*S*)-hydroxy-6(*S*)-methyl-2(*R*)-tetrahydropyranyl)-2(*S*)-tetrahydrofuryl]butyl Ether (58). By the procedure described for the preparation of the alcohol **38**, 120 mg (0.28 mmol) of the methoxymethyl ether from aldehyde **55** in 4 mL of THF and 1 mL of 10% aqueous HCl afforded, after chromatography on 10 g of silica gel with 25% ethyl acetate in petroleum ether, 105 mg (97%) of the alcohol **58**: evaporative distillation 140–150 °C (0.005 mmHg); $[\alpha]^{25}_D$ +9.7° (*c* 0.96, $CHCl_3$); IR ($CHCl_3$) 3640, 3450, 1460, 1380, 1105, 1070 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.96 (d, 3 H, J = 6 Hz, CH_3CHCC), 1.17 (d, 3 H, J = 6 Hz, CH_3CHOC), 4.42 (s, 2 H, $C_6H_5CH_2$), 7.32 (b s, 5 H, C_6H_5). Anal. Calcd for $C_{24}H_{36}O_4$: C, 73.81; H, 9.81. Found: C, 73.91; H, 9.73.

Benzyl 2(*S*)-[5(*R*)-Ethyl-3(*S*)-methyl-5-(5(*S*)-hydroxy-6(*S*)-methyl-2(*R*)-tetrahydropyranyl)-2(*S*)-tetrahydrofuryl]butyl Ether (56). By the procedure described for the preparation of the alcohol **38**, 54.8 mg (0.13 mmol) of the methoxymethyl ether from aldehyde **52** in 4 mL of THF and 1 mL of 10% aqueous HCl afforded, after chromatography on 10 g of silica gel with 20% ethyl acetate–cyclohexane, 45 mg (92%) of the alcohol **56**: evaporative distillation 140–150 °C (0.005 mmHg); $[\alpha]^{25}_D$ +19.8° (*c* 2.0, $CHCl_3$); IR ($CHCl_3$) 3650, 3450, 1460, 1380, 1100, 1070 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.17 (d, 3 H, J = 6 Hz, CH_3CHOC), 4.47 (s, 2 H, $C_6H_5CH_2$), 7.33 (b s, 5 H, C_6H_5). Anal. Calcd for $C_{24}H_{36}O_4$: C, 73.81; H, 9.81. Found: C, 73.72; H, 9.72.

Benzyl 2(*S*)-[5(*S*)-Ethyl-3(*S*)-methyl-5-(5(*S*)-hydroxy-6(*S*)-methyl-2(*R*)-tetrahydropyranyl)-2(*S*)-tetrahydrofuryl]butyl Ether (7). By the procedure described for the preparation of the alcohol **38**, 265 mg (0.62 mmol) of the methoxymethyl ether from aldehyde **53** in 8 mL of THF and 2 mL of 10% aqueous HCl afforded, after chromatography on 20 g of silica gel with 25% ethyl acetate in petroleum ether, 240 mg (100%) of the alcohol **7**. The spectral characteristics of this material were identical with those of the alcohol derived from degradation of lasalocid A.

Benzyl 2(*S*)-[5(*S*)-Ethyl-3(*S*)-methyl-5-(6(*S*)-methyl-5-exo-2(*R*)-tetrahydropyranyl)-2(*S*)-tetrahydrofuryl]butyl Ether (59). To a stirred solution of 0.06 mL of oxalyl chloride (0.69 mmol) in 2 mL of dry dichloromethane at −60 °C under argon was added 0.11 mL (1.55 mmol) of dimethyl sulfoxide. After 10 min, a solution of 240 mg (0.61 mmol) of the alcohol **7** in 1.5 mL of dry dichloromethane was added to the reaction mixture. After 15 min, the reaction mixture was treated with 0.44 mL (3.16 mmol) of dry triethylamine, allowed to warm to room temperature, and then diluted with 40 mL of ether. This mixture was washed with 15 mL of water, 15 mL of saturated aqueous $NaHCO_3$, and 15 mL of saturated aqueous NaCl, and then dried ($MgSO_4$). Removal of the solvents at reduced pressure and chromatography of the residue on 20 g of silica gel with 10% ethyl acetate in cyclohexane afforded 225 mg (94%) of the ketone **59**: evaporative distillation 120–130 °C (0.005 mmHg); $[\alpha]^{25}_D$ −5.9° (*c* 0.95, $CHCl_3$); IR ($CHCl_3$) 1720, 1460, 1380, 1110 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.27 (d, 3 H, J = 6 Hz, CH_3CHOC), 4.30 (q, 1 H, J = 6 Hz, $CHCO$), 4.44 (s, 2 H, $C_6H_5CH_2$), 7.33 (b s, 5 H, C_6H_5). Anal. Calcd for $C_{24}H_{36}O_4$: C, 74.19; H, 9.34. Found: C, 74.02; H, 9.35.

Benzyl 2(*S*)-[5(*S*)-Ethyl-3(*S*)-methyl-5-(6(*S*)-methyl-5-methylene-2(*R*)-tetrahydropyranyl)-2(*S*)-tetrahydrofuryl]butyl Ether. By the procedure described for the preparation of the adduct of aldehyde **54**, 214.5 mg (0.55 mmol) of the ketone **59** in 4 mL of dry THF with 1.38 mmol of methylenetriphenylphosphorane afforded, after chromatography on 20 g of silica gel with 4% ethyl acetate in cyclohexane, 200 mg (94%) of the corresponding exomethylene olefin: evaporative distillation 120–130 °C (0.005 mmHg); $[\alpha]^{24}_D$ +7.9° (*c* 1.205, $CHCl_3$); IR ($CHCl_3$) 1460, 1380, 1120, 1080 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.83, 0.93 (2t, 6 H, J = 6 Hz, CH_3CH_2), 0.97 (d, 3 H, J = 6 Hz, CH_3CHCC), 1.30 (d, 3 H, J = 6 Hz, CH_3CHOC), 4.43 (q, 1 H, J = 6 Hz, CHC=C), 4.47 (s, 2 H, $C_6H_5CH_2$), 4.67 (b s, 2 H, C=CH_2), 7.31 (b s, 5 H, C_6H_5). Anal. Calcd for $C_{25}H_{38}O_3$: C, 77.68; H, 9.91. Found: C, 77.64; H, 10.03.

Benzyl 2(*S*)-[5(*S*)-Ethyl-3(*S*)-methyl-5-(3(*R*)-1,5-dioxo-4(*S*)-methylspiro[2.5]-6(*R*)-octyl)-2(*S*)-tetrahydrofuryl]butyl Ether (60). To a stirred solution of 191 mg (0.49 mmol) of the above olefin in 5 mL of dry dichloromethane at 0 °C under argon were added 160 mg (1.9 mmol) of solid $NaHCO_3$ and 160 mg (0.74–0.83 mmol) of 80–90% *m*-chloroperbenzoic acid. Cooling was then discontinued, and the reaction mixture was stirred at room temperature for 3 h. After treatment of this mixture with 2 mL of 10% aqueous Na_2SO_3, the resulting mixture was diluted with 60 mL of ether, washed with two 20-mL portions of saturated aqueous $NaHCO_3$ and 20 mL of saturated aqueous NaCl, and then dried ($MgSO_4$). Removal of the solvents and chromatography of the residue on 20 g of silica gel with 10% ethyl acetate in petroleum ether afforded 141 mg of the epoxide **60** and 40 mg of the epimeric epoxide (ratio of 3.5:1 of 91% combined yield). Epoxide **60**: evaporative distillation 130–140 °C (0.005 mmHg); $[\alpha]^{24}_D$ −4.4° (*c* 1.03, $CHCl_3$); IR ($CHCl_3$) 1460, 1380, 1120, 1080 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.86, 0.93 (2t, 6 H, J = 6 Hz, CH_3CH_2), 0.97 (d, 3 H, J = 6 Hz, CH_3CHCC), 1.27 (d, 3 H, J = 6 Hz, CH_3CHOC), 2.52 (d, 1 H, J = 4 Hz, CCH*H*O), 2.59 (d, 1 H, J = 4 Hz, CC*H*HO), 4.47 (s, 2 H, $C_6H_5CH_2$), 7.33 (b s, 5 H, C_6H_5). Anal. Calcd for $C_{25}H_{38}O_4$: C, 74.59; H, 9.51. Found: C, 74.50; H, 9.46. Epi-epoxide **60**: evaporative distillation 130–140 °C (0.005 mmHg); $[\alpha]^{24}_D$ +7.8° (*c* 1.02, $CHCl_3$); IR ($CHCl_3$) 1460, 1380, 1120,

1080 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.86, 0.93 (2t, 6 H, J = 6 Hz, CH_3CH_2), 0.97 (d, 3 H, J = 6 Hz, CH_3CHCC), 1.24 (d, 3 H, J = 6 Hz, CH_3CHOC), 2.58 (d, 1 H, J = 5 Hz, $CCHHO$), 2.71 (d, 1 H, J = 5 Hz, $CCHHO$), 4.47 (s, 2 H, $C_6H_5CH_2$), 7.31 (b s, 5 H, C_6H_5). Anal. Calcd for $C_{25}H_{38}O_4$: C, 74.59; H, 9.51. Found: C, 74.39; H, 9.36.

Benzyl 2(*S*)-[5(*S*)-Ethyl-3(*S*)-methyl-5-(5(*R*)-ethyl-5-hydroxy-6-(*S*)-methyl-2(*R*)-tetrahydropyranyl)-2(*S*)-tetrahydrofuryl]butyl Ether (5). By the procedure described for the preparation of the alcohols 34, 120 mg (0.30 mmol) of the epoxide 60 in 3 mL of dry *n*-pentane with 320 mg (1.56 mmol) of copper(I) bromide–dimethyl sulfide complex and 1.4 mL (3.08 mmol) of 2.2 M methyllithium in ether afforded, after chromatography on 10 g of silica gel column with 15% ethyl acetate in petroleum ether, 120 mg (90%) of the alcohol 5. The spectral characteristics of this material were identical with those of the alcohol derived from degradation of lasalocid A.

2(*S*)-[5(*S*)-Ethyl-3(*S*)-methyl-5-(5(*R*)-ethyl-5-hydroxy-6(*S*)-methyl-2(*R*)-tetrahydropyranyl)-2(*S*)-tetrahydrofuryl]butan-1-ol. To a stirred solution of 0.5 cm (3 mmol) of lithium wire in 10 mL of anhydrous liquid ammonia at −78 °C under argon was added a solution of 54 mg (0.13 mmol) of the monobenzyl ether 5 in 1 mL of dry THF. Cooling was then discontinued (ammonia reflux) and after 1 h, 250 mg (4.7 mmol) of anhydrous ammonium chloride was cautiously added to the reaction mixture. The resulting mixture was then diluted with 20 mL of ether and the ammonia was allowed to evaporate. The resulting suspension was filtered and the solid was washed by trituration with four 10-mL portions of ether. Removal of the solvent at reduced pressure from the combined filtrates and then chromatography of the residue on 10 g of silica gel with 40% ethyl acetate in petroleum ether afforded 42 mg (98%) of the corresponding diol. The spectral characteristics of this material were identical with those of the diol derived from degradation of lasalocid A.

2(*R*)-[5(*S*)-Ethyl-3(*S*)-methyl-5-(5(*R*)-ethyl-5-hydroxy-6(*S*)-methyl-2(*R*)-tetrahydropyranyl)-2(*S*)-tetrahydrofuryl]butanal (61). By the procedure described for the oxidation of the alcohol 33, 80 mg (0.24 mmol) of the above diol in 3 mL of dry dichloromethane with 10 mg (0.12 mmol) of anhydrous sodium acetate and 133 mg (0.62 mmol) of pyridinium chlorochromate afforded, after chromatography on 10 g of silica gel with 40% ether in petroleum ether, 62 mg (78%) of the aldehyde 61: evaporative distillation 130–140 °C (0.005 mmHg); $[\alpha]^{22}_D$ −2.5° (c 1.1, $CHCl_3$); IR ($CHCl_3$) 3600, 3450, 2750, 1720, 1460, 1390, 1230, 1130, 1100, 1060, 960 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.97 (d, 3 H, J = 6 Hz, CH_3CHCC), 1.18 (d, 3 H, J = 6 Hz, CH_3CHOC), 9.64 (d, 1 H, J = 3 Hz, CHO). Anal. Calcd for $C_{19}H_{34}O_4$: C, 69.90; H, 10.50. Found: C, 69.77; H, 10.44.

4(*S*)-[5(*S*)-Ethyl-3(*S*)-methyl-5-(5(*R*)-ethyl-5-hydroxy-6(*S*)-methyl-2(*R*)-tetrahydropyranyl)-2(*S*)-tetrahydrofuryl]hexan-3-ol. To a stirred solution of 62 mg (0.19 mmol) of the aldehyde 61 in 4 mL of dry THF at −78 °C under argon was added 0.72 mL (0.58 mmol) of an 0.8 M solution of ethylmagnesium bromide in THF. The resulting solution was stirred at 0 °C for 30 min, treated with 5 mL of saturated aqueous NH_4Cl, and then diluted with 25 mL of ether. The organic phase was separated, washed with 10 mL of saturated aqueous NH_4Cl and 10 mL of saturated aqueous NaCl, and then dried ($MgSO_4$). After removal of the solvents at reduced pressure and chromatography of the residue on 10 g of silica gel with 50% ether in petroleum ether, there was obtained 60 mg (89%) of a diastereoisomeric mixture of the corresponding alcohols: evaporative distillation 120–130 °C (0.005 mmHg); IR ($CHCl_3$) 3600, 3500, 1460, 1380, 1130, 1100, 1060, 960 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.20 (d, 3 H, J = 6 Hz, CH_3CHOC).

4(*R*)-[5(*S*)-Ethyl-3(*S*)-methyl-5-(5(*R*)-ethyl-5-hydroxy-6(*S*)-methyl-2(*R*)-tetrahydropyranyl)-2(*S*)-tetrahydrofuryl]hexan-3-one (3). By the procedure described for the preparation of the aldehyde 61, 35 mg (0.10 mmol) of the above alcohols in 1 mL of dry dichloromethane with 50 mg (0.23 mmol) of pyridinium chlorochromate afforded, after chromatography on 10 g of silica gel with 35% ether in petroleum ether, 31.4 mg (90%) of the ketone 3. The spectral and physical data obtained on this ketone were identical with those of the same ketone obtained from the reverse aldol of lasalocid A (X537A).

PROPOSITIONS

ABSTRACTS OF PROPOSITIONS

Proposition 1. The design of a new class of suicide enzyme substrates for -lactamases and penicillin sensitive enzymes and general methods for their preparation are proposed.

Proposition 2. A systematic study of the effects of electron withdrawing substituents on the rate of the alkoxide accelerated cycloreversion of 1-hydroxy-bicyclo-[2.2.2]octadienes and the comparison of these effects with those predicted by a Huckel Molecular Orbital based model are proposed.

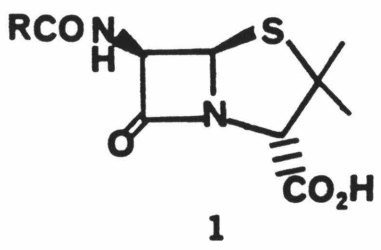
Proposition 3. The use of an asymmetric ene reaction to provide access to optically pure tetrahydrothiophenes and the conversion of these compounds into optically pure cyclobutene and cyclobutane derivatives are proposed.

Proposition 4. Syntheses of the antibiotic Amipurimycin and its C-6' epimer are proposed.

Proposition 5. A suicide substrate for S-Adenosylmethionine decarboxylase is proposed.

PROPOSITION 1.

The design of a new class of suicide enzyme substrates for β-lactamases and pencillin sensitive enzymes (PSE's)-(transpeptidases and D,D-carboxypeptidases) and general schemes for their preparation are proposed.



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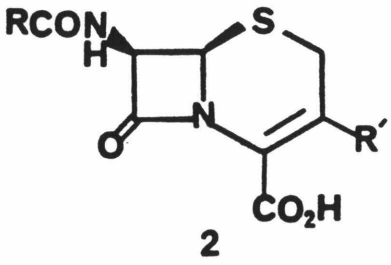

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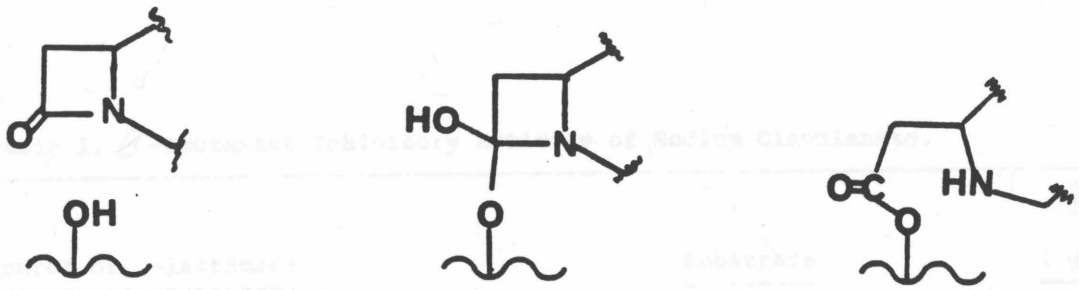
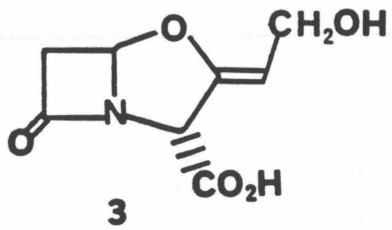
Pencillin **1** and cephalosporin **2** antibiotics and analogs thereof are medicinally very important. This is due to their ability to inactivate enzymes responsible for cell wall synthesis by irreversibly acylating a specific serine residue in the active site[1] (Figure 1). Unfortunately, many bacteria have acquired a gene which causes the production of an enzyme similar in composition and activity to the PSE's, in which the acylation is now reversible. These enzymes, termed β-lactamases, hydrolyse the β-lactam and therefore protect the PSE's from β-lactam antibiotics. This ability of bacteria to become resistant to pencillin and cephalosporins has led to a large amount of work aimed at producing β-lactamase resistant β-lactam antibiotics.

FIGURE 1.



More recently, a different approach has come to the fore, spurred on by the isolation of clavalate acid 3[2]. Although a poor antibiotic, clavalate inhibits β-lactamases (Table 1)[4] and therefore may be used in synergy with conventional β-lactam antibiotics[3] (Table 2)[4]. Pencillin sulfone CP-45,899[5] 4 closely duplicates the action of clavalanate in both inactivating β-lactamases[6] and its synergy with other β-lactam antibiotics.[7] The mechanism of the action of these β-lactamase inhibitors has been studied by Knowles[8] who has proposed the following suicide substrate mechanism (Scheme I).



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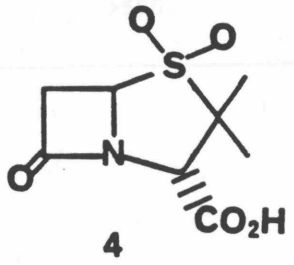

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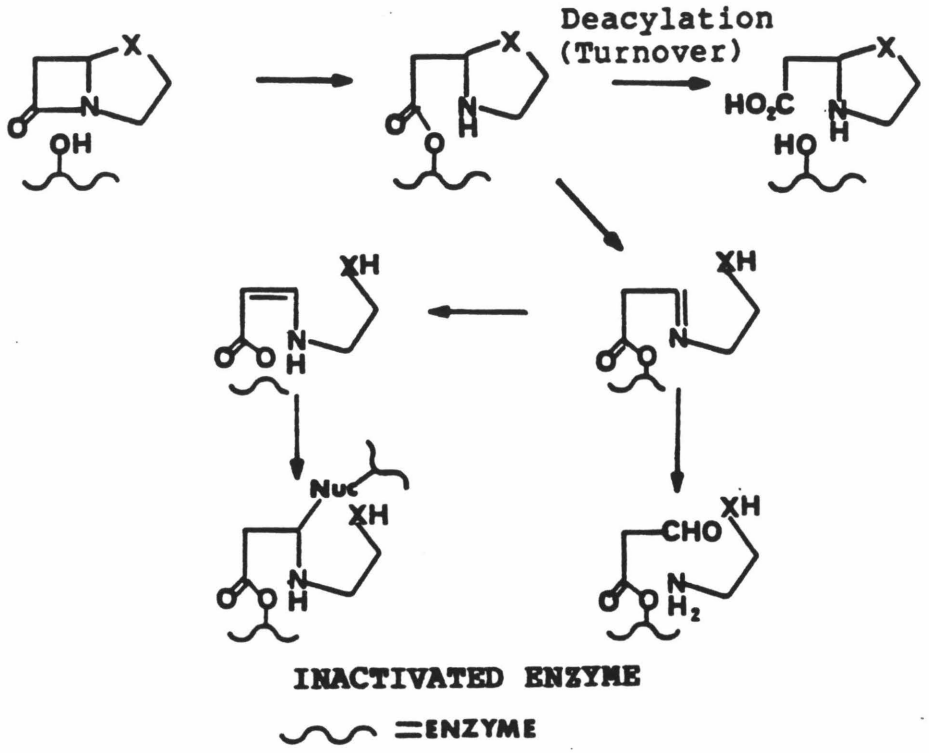
Table 1. β-Lactamase Inhibitory Activity of Sodium Clavulanate.

Source of -lactamase	Substrate	I_{50} (g/ml)
Staphylococcus aureus (Russell)	Benzylpenicillin	0.06
E. coli JT410 (chromosomally mediated)	Cephaloridine	56.00
E. coli JT4 (Rfactor mediated)	Benzylpenicillin	0.08
Proteus mirabilis C889	Benzylpenicillin	0.03
Enterobacter cloacae P99	Cephaloridine	10.00
Klebsiella aerogenes NCTC418	Benzylpenicillin	0.03
Pseudomonas aeruginosa (Sabbath type)	Cephaloridine	160.00
Pseudomonas aeruginosa Dalgleish	Benzylpenicillin	0.10

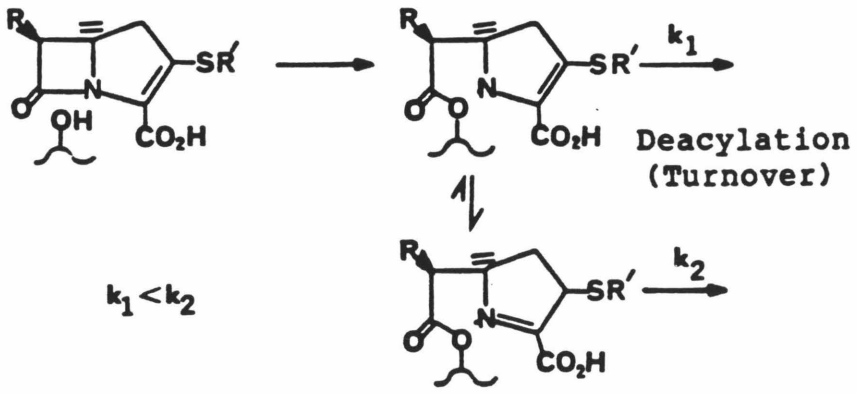
Table 2. Effect of sodium clavulanate upon the MICs of ampicillin against β-lactamase producing organisms.

	MICs (g/ml)		
Organism	Sodium Clavulanate	Ampicillin	Ampicillin + 1 g sodium clavulanate
Staphylococcus aureus (Russell)	15	500	<0.4
Staphylococcus aureus (Russell)	62	250	7.5
E. coli NCTC10418	31	1.8	<0.4
E. coli B11	62	125	<0.4
Klebsiella aerogenes A	31	125	<0.4
Klebsiella aerogenes sp62	31	125	<0.4
Enterobacter cloacae	62	250	62
Serratia marcescens	125	>500	62

SCHEME I



SCHEME II

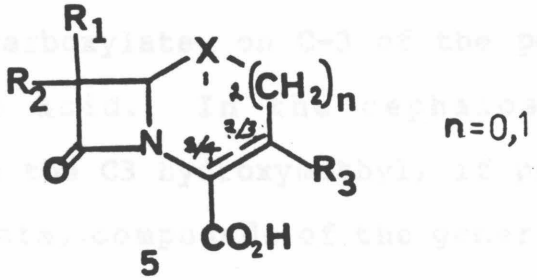


A second class of β-lactamase inhibitors are the carbopenams[9,10], which are reversible inhibitors. The proposed mechanism[10] for these compounds action is shown in Scheme II.

A third, totally synthetic class of β-lactamase inhibitors are pencillin analogs where the 6 amino group has been replaced by a good leaving group (i.e.: "bromo"), thus activating C-6 as an alkylating center.

Of these three classes of inhibitors, the suicide substrate approach is the most attractive, since it allows for the inactivation of a specific type of enzyme, based on its mode of action. This irreversibility of the inhibition allows the inhibitor to be used less often and often in lower doses. The ideal suicide substrate would not only inactivate β-lactamases, but also be a good antibiotic.

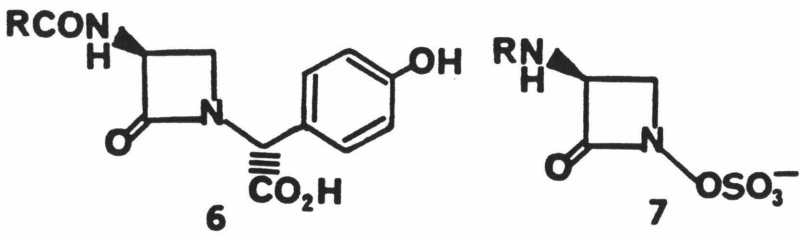
Although the relationship of structure to activity for β-lactam antibiotics and β-lactamase inhibitors hasbeen extensively studied,[12] the picture is far from clear. A summary of characteristic structural features of β-lactam antibiotics and β-lactamase substrates 5 is given below:



5

1) A β-lactam fused to another ring. This forces the nitrogen from its preferred planar conformation, thus destabilizing the β-lactam bond. Exceptions to this are

the nocardicinic acids 6[13] and monosulfactoms 7[14];



2) Non-planarity of the β-lactam ring;

3) If R_1 = R'-NH, it must be on the β-face of the lactam as drawn and R' should be an acyl group;

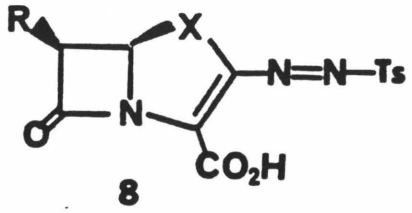
4) R_2 must be H or OCH_3;

5) In cephalosporins the presence of a good leaving group on the substituent at C3 generally increases its antibacterial activity and its ability to act as a substrate for β-lactamases. This is thought to be due to the further destabilization of the lactam bound due to the electronegativity of the substituent;

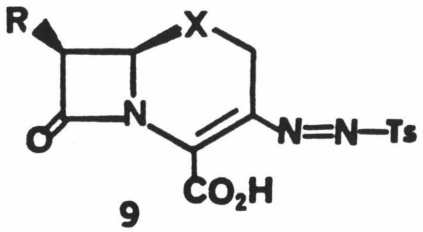
6) Extension of the conjugation of the double bond in cephalosporins should destabilize the lactam bond and thus may increase the activity of the compound[15];

7) The carboxylate on C-3 of the pencillin must exist as the free acid. In the cephalosporins it may be lactonized to the C3 hydroxymethyl, if present.

Given this data, compounds of the general formulae **8** and **9** appear to be good candidates as β-lactam antibiotics and/or β-lactamase inhibitors.



8



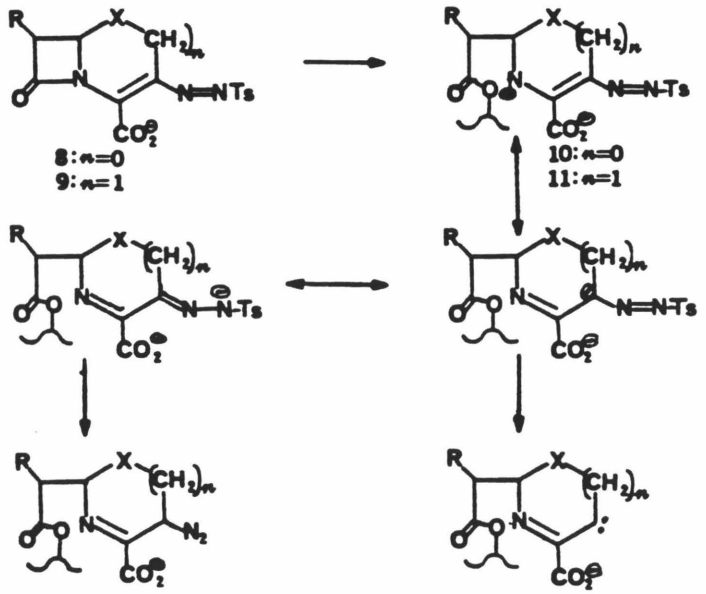
9

X=S,O,CH_2

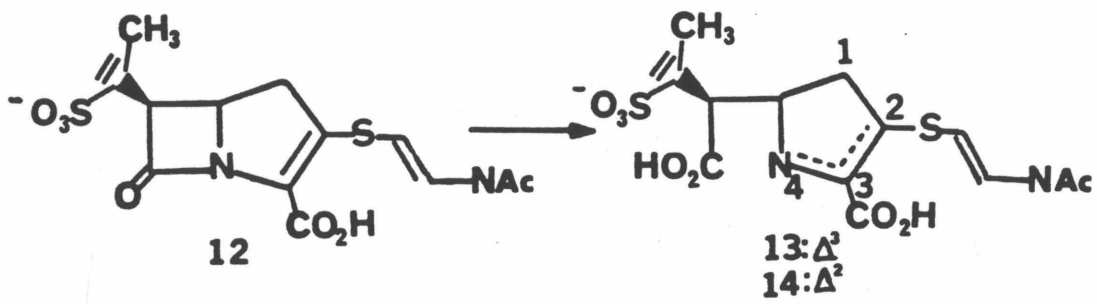
Both compounds **8** and **9** possess the necessary carboxylate and should not have a planar lactam nitrogen or lactam ring. In the simplest variants X=S and R= acyl N the structure of **9** would be very similar to that of the natural cephalosporins. Therefore, its binding to the active site should be similar. Compound **9** possess a good leaving group at C-3 that also extends the conjugation of the α,β unsaturated ester; therefore, the lactam bond should be doubly activated. This activation should also apply with compound **8** as well.

Both **8** and **9** should function as suicide enzyme substrates in a similar manner, as outlined below in Scheme III.

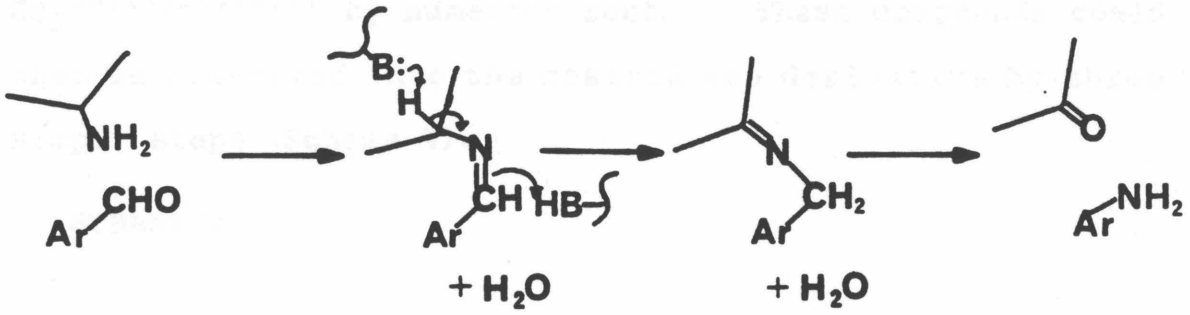
SCHEME III



The opening of the β-lactam ring would render **8** or **9** susceptible to the irreversible loss of nitrogen and the generation of the C-2/C-3 carbene or the loss of RSO_2^- and the generation of the C-2/C-3 diazo compound. Either of these moieties would then alkylate the enzyme on the active site. This would inhibit the enzyme irreversibly, thus removing it from the active pool. The viability of this approach is indicated in studies with carbapenem **12**[10] which is a potent β-lactamase inactivator and by studies on enzymes which have pyridoxal phosphate as a co-factor. Studies on **12** have shown that the product of its enzymatic hydrolysis is **13** with no trace of the double bond isomer **14** being found. This study also determined that the proton at C-2 could be completely exchanged for deuterium by incubation of **13** at neutral PH in D_2O. These results indicate that the resonance form of **10** or **11** with the negative charge on the substuent bearing carbon should contribute strongly to the overall character of the molecule, and that the proton at this center in the neutral form is very acidic. An example of increased acidity due to a -N= function is found in the action of pyridoxal phosphate in conjunction with transamines (Scheme IV).



SCHEME IV

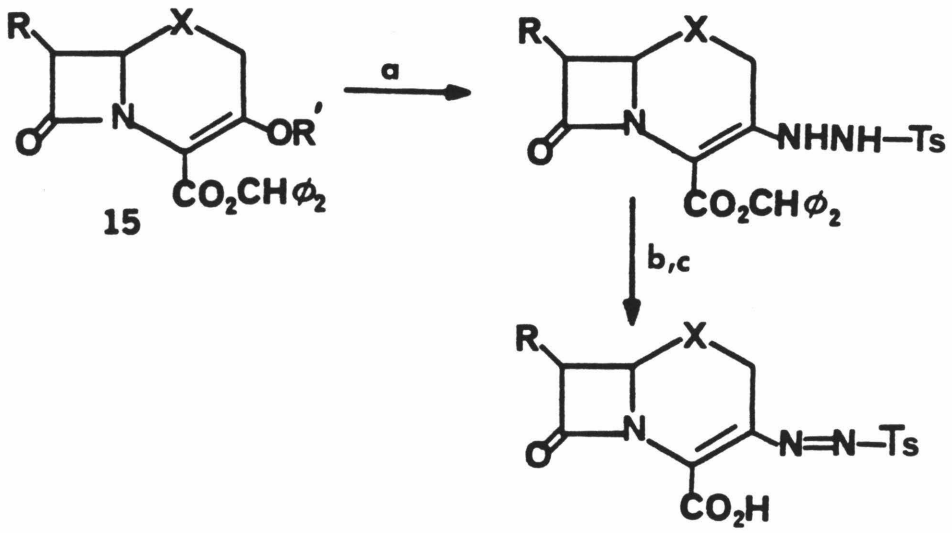


As with all compounds with physiological properties, the optimal type of R and X groups would have to be determined by testing. Therefore, the preparation of **8** and **9** will be discussed in general terms.

There are many methods to prepare pencillin and cephalosporin analogs. These involve either the incorporation of R into a starting material or the introduction of R at a late stage in the synthesis via the enolate of the β-lactam. For the purposes of this proposal, the latter method of introducing the desired R group would be preferred. This would allow the preparation of compounds with various R groups from an intermediate late in the synthetic scheme.

Preparations of compounds of type 15 are reported in the literature for a wide variety of R' and X=O, S or CH_2[16,17,18,19,20] by numerous routes. These compounds could then be converted into the desired azo derivative by three simple steps (Scheme V).

SCHEME V



(a) $TsNHNH_2$; (b) [O]; (c) CF_3CO_2H.

Addition of tosyl hydrazine to 15[16] followed by elimination of -OR would give the desired C-3 hydrazine. Air oxidation of the compound followed by deprotection of the acid would then afford the desired azo compounds.

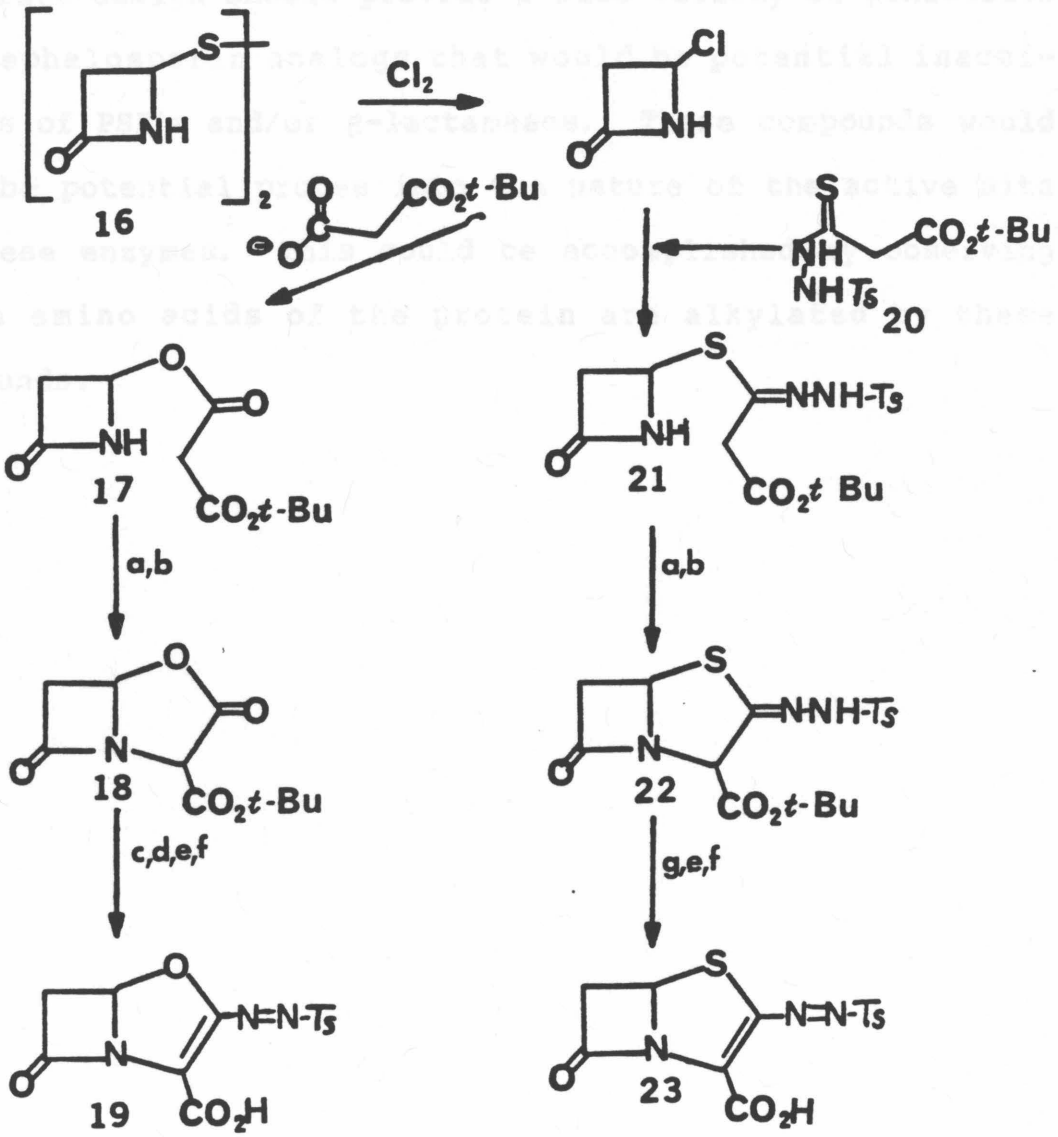
Since very little is known concerning the preparation of 2 heterosubstituted penem, the schemes proposed for their preparation do not possess direct precedent in the literature. Again here, it would be best for the purpose of generating numerous structural analogues for testing to introduce R late in the synthesis.

For X=O, the desired azo compound could be prepared from β-lactam **16**[16] (Scheme VI). Treatment of **16** with chlorine in carbon tetrachloride would give the corresponding chloride, which then could be displaced by the carboxylate salt of the half ester of malonic acid to give the ester **17**. The ester **17** could then be converted to the **18** by treatment with $HO_2CC_6H_4SO_2N_3$, then $Rh(OAc)_2$.[19] Compound **18** could then be converted to the desired azo compound **19** as outlined previously.

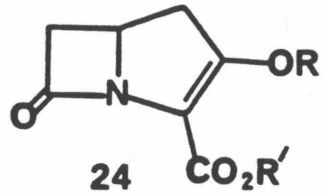
For X=S, treatment of the chloride from the disulfide **16** with the thioamide **20** would afford the ester **21**. Compound **21** could then be converted to the desired azo compound **23** by treatment with $HO_2CC_6H_4SO_2N_3$ then $Rh(OAc)_2$.[19] followed by isomerization, oxidation and removal of the ester protecting group.

For compounds where $X=CH_2$ intermediate **24** used in the synthesis of thienamycin[19] could be converted to the desired azo compound by addition of $TSNHNH_2$, analogous to the addition of HS-R in the thienamycin synthesis, followed by air oxidation and deprotection of the acid.

SCHEME IV



(a) $HO_2C-C_6H_4-SO_2N_3$; (b) $Rh(OAc)_2$; (c) base/Me_3OBF_4; (d) $TsNHNH_2$; (e) [O]; (f) CF_3CO_2H; (g) NaOMe.



In conclusion, the proposed strategy of suicide enzyme substrate design should provide a wide variety of penicillin- and cephalosporin analogs that would be potential inactivators of PSE's and/or β-lactamases. These compounds would also be potential probes into the nature of the active site of these enzymes. This could be accomplished by observing which amino acids of the protein are alkylated by these compounds.

PROPOSITION 2.

A systematic study of the effects of electron withdrawing substituents on the rate of the alkoxide accelerated cycloreversion of 1-hydroxybicyclo[2.2.2]octadienes and the comparison of these effects with those predicted by a Huckel Molecular Orbital (HMO) based model are proposed. A study of the mode of the cycloreversion is also proposed.

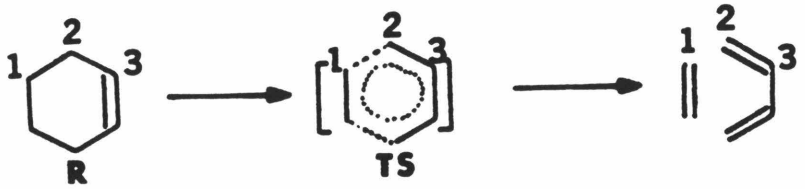
The effect of substituents on the rates of pericyclic reactions is of considerable theoretical[1,2,3] and synthetic interest[4,5,6,7]. To account for the effects of substituents on the rate of pericyclic reactions, Carpenter[2] has proposed a comprehensive theoretical model. Carpenter's model compares the effect of a substituent on the total π energy of the ground state (GS) of the reactant(s) with the effect it exerts on the total π energy of the transition state (TS) of the reaction. This model predicts that a substituent which increases the total π energy of the transition state more than it increases the π energy of the reactant(s) will increase the rate of the reaction. This model uses the tabulated HMO π energies[8,9] of analogous compounds to calculate the π energy of the reactants and of the transition state. Samples of the equivalences used are shown in Table 1.

Table 1.

Compound/TS	Equivalent	Energy (β)
x=Polarizing	allyl radical	2.838
x=Conjugating	butadiene	4.472
UNSUBSTITUTED	ethene	2.000
x=Polarizing	benzyl radical	8.720
x=Conjugating	styrene	10.425
UNSUBSTITUTED	benzene	8.000

Application of this model to the singularly substituted retro-Diels-Alder reaction yields the results shown in Table 2.[2] Since Δ is the effect of a substituent on the reactant(s) minus its effect on the transition state, a negative value for Δ indicates that the substituent should increase the rate of the reaction. Therefore, this model

Table 2.



SUBSTITUENT		ENERGY (β)		
Position	Type	R	TS	Δ
1 or 2	Polarizing	2.000	8.720	-0.721
	Conjugating	4.00	10.425	-0.425
3	Polarizing	2.838	8.720	+0.108
	Conjugating	4.472	10.425	+0.047
Unsubstituted		2.000	8.000	0.000

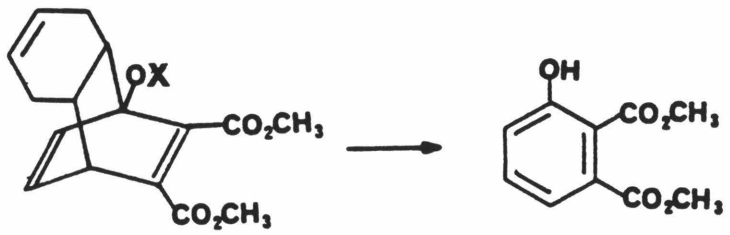
predicts that a substituent at position 1 or 2 will increase the rate of the retro-Diels-Alder reaction; while a substituent at position 3 will decrease the reaction rate. The above predictions are supported by the examples shown in Figure 1.

Figure 1.

Polar substituent at position 3.

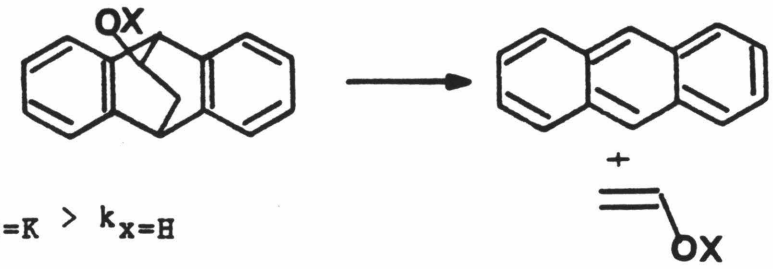
$k_{X=OLi} < k_{X=H}$

Polar substituent at position 2.



$k_{X=Bu\ N} > k_{X=TMS}$

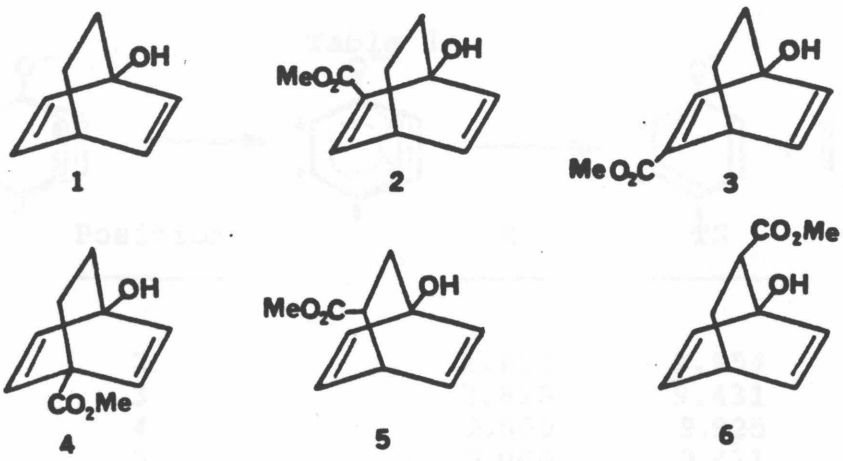
Polar substituent at position 1.



$k_{X=K} > k_{X=H}$

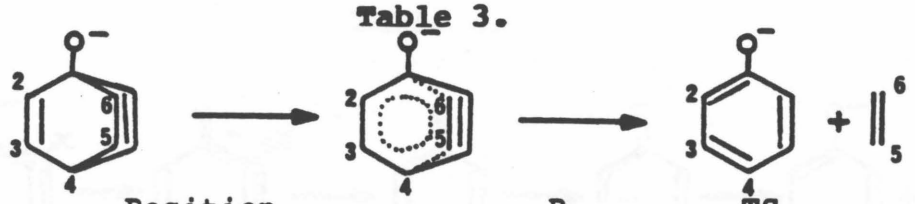
Although the alkoxide assisted cycloreversion of example **2** above is potentially synthetically useful, the presence of the two ester groups make determination of the effect of the alkoxide alone impossible. Therefore, in order to better understand the effects of an ester substituent on the above cycloreversion reaction, the preparation of the bicyclo[2.2.2] octadienes shown in Figure 2, and a study of the ratio of their alkoxide assisted cycloreversions are proposed.

Figure 2.



A comparison of the observed effect of the carbomethoxy functionality at the various positions and the effect predicted by an extension of Carpenter's model is also proposed. Application of the extended model to the above systems yields the results presented in Table 3. Since the carbomethoxyl moiety can act both as an electron accepting and as a conjugating substituent, its effect should lie between the effect predicted for the two types of substituents for a given position.

Table 3.

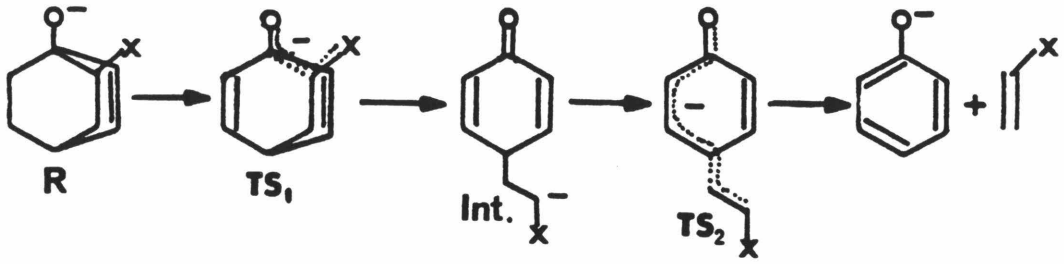


Type	Position	R	TS	Δ
Accepting	2	2.828	9.954	-0.405
	3	2.828	9.431	+0.118
	4	2.000	9.925	-1.204
	5	2.000	9.431	-0.710
	6	2.000	9.954	-1.233
	UNSUBSTITUTED	2.000	8.721	0.000
Conjugating	2	4.472	11.204	0.000
	3	4.472	11.142	+0.051
	4	4.000	11.190	-0.469
	5	4.000	11.142	-0.421
	6	4.000	11.204	-0.483
	UNSUBSTITUTED	2.000	8.721	0.000

The extended model, therefore, predicts that a carbomethoxy substituent in any position other than position 3 will increase the rate of the cycloreversion. Based on this model, the order of increasing rates for the esters **1** through **6** should be 3<1<2<5<4<6.

The results presented in Table 3 are based on the assumption that the cycloreversion is concerted. However, if the reaction is not concerted, then different transition states must be considered. Application of the extended model to the non-concerted cycloreversion of the bicyclo[2.2.2]octadiene **6** gives the results presented in Table **4**.

Table 4.



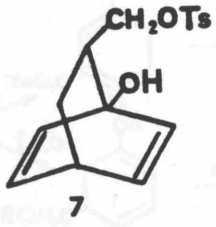
ENERGY (β)

X	R	TS_1	Δ_1	Int.	TS_2	Δ_2
Accepting	2.000	6.472	-1.644	6.472	9.518	+0.537
Conjugating	4.000	7.464	-0.636	7.300	10.628	+0.255
Unsubstituted	2.000	4.828	0.000	4.472	8.055	0.000

Therefore, the model predicts that the rate of the cleavage of the first bond (R -> Int.) of the ester **6** will be increased by the carbomethoxy substituent, while the rate of cleavage of the second bond will be decreased. If the cycloreversion is not concerted and the cleavage of the second bond is rate determining, then the rate of the cycloreversion should be reduced by the presence of a carbomethoxy substituent at position 6. However, if the cycloreversion is concerted or if the cleavage of the first bond in the stepwise pathway is rate determining, then the reaction rate should be increased by the presence of a carbomethoxy substituent at position 6.

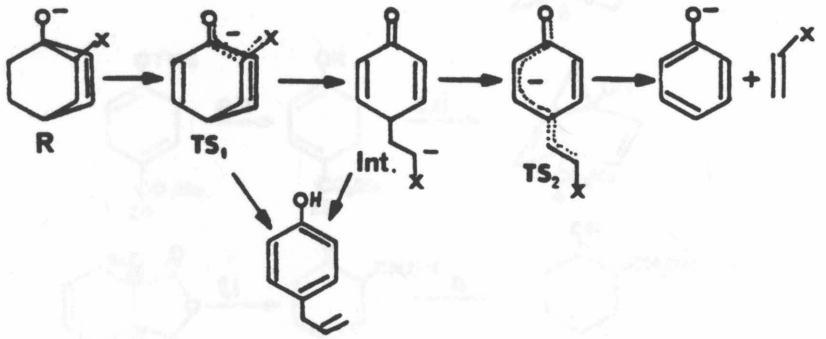
In order to test the concertedness of the cycloreversion further, the preparation and cycloreversion of the bicyclo[2.2.2]octadiene 7 is proposed.

If the cycloreversion is not concerted, then either TS_1 or the intermediate anion **Int.** should eliminate TsO^- thereby short circuiting the reaction pathway as shown in Scheme I.



7

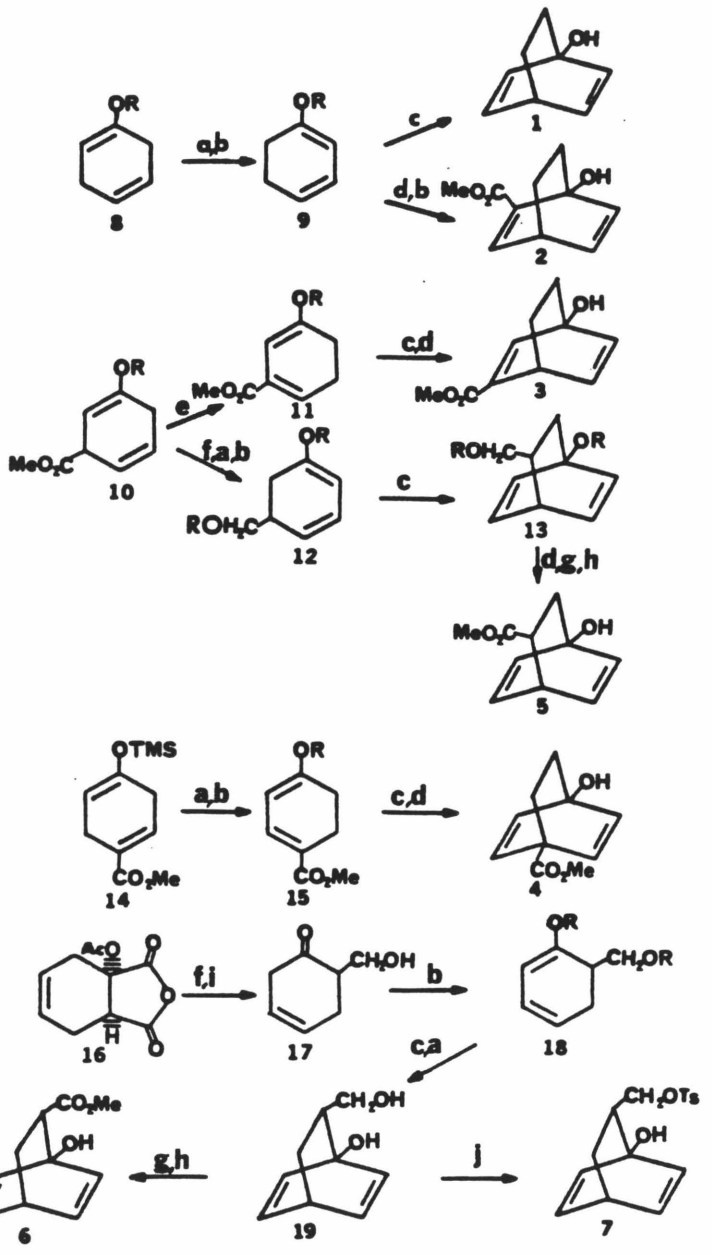
SCHEME I



Proposed synthetic schemes for the preparation of the desired bicyclo[2.2.2]octadienes 1 through 7 are presented in Scheme II.

Treatment of the 1,4 cyclohexadiene[12] 8 with lithium fluoroborate[13] would give the corresponding β, γ enone. This enone could then be enolized, and the enolate trapped with t-butylchlorodimethylsilane (TBSCl)[14] would give diene 9. Diels-Alder addition of the diene 9 to an acetylene

SCHEME II

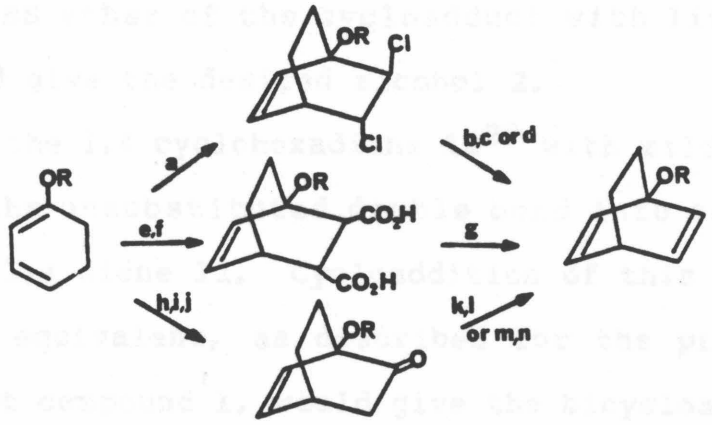


(a) $LiBF_4$, CH_3CN; (b) KH/TBSCl; (c) "HC CH" see Scheme III; (d) H-c C-CO_2Me; (e) NaOMe/MeOH; (f) $LiAlH_4$; (g) Swern, then Ag_2O; (h) CH_2N_2; (i) $NaIO_4$, $MeOH/H_2O$; (j) $CH_3C_6H_4SO_2Cl$.

equivalent, and then the generation of the second olefin would give the desired parent compound 1.

Three possible acetylene equivalents are shown in Scheme III.

SCHEME III



(a) trans ClHC=CHCl; (b) Na-anthracene; (c) Na/NH_3; (d) Mg; (e) maleic anhydride; (f) H_2O; (g) $Pb(OAc)_4$; (h) $CH_2=C(Cl)COCl$; (i) NaN_3; (j) H_3^+O; (k) LDA/$(Me_2N)_2P(O)Cl$; (l) $Na/CH_3CH_2NH_2$; (m) $TsNHNH_2$; (n) tBuLi.

Cycloaddition of 1,2 dichloroethene to the diene[15] would give the corresponding adduct. Treatment of this adduct with sodium anthracene[15], sodium in ammonia or magnesium, and then lithium fluoroborate would give the desired diene.

Addition of maleic anhydride to the cyclohexadiene and hydrolysis of the resulting anhydride would give the corresponding bicyclo[2.2.2]octene dicarboxylic acid. Treatment of the diacid with lead tetraacetate[16] would give the desired bicyclo[2.2.2]octadiene.

Addition of 2-chloropropenoyl chloride to the cyclohexadiene and conversion of the adduct into the corresponding ketone[17] would give the bicyclo[2.2.2]octenone. This ketone could then be converted to the desired olefin by

way of the corresponding tosylhydrazone[18] or by way of the phospho-diamidate derivative of the its enolate.[19]

Treatment of the diene **9** with methyl propiolate and cleavage of the TBS ether of the cycloadduct with lithium fluoroborate would give the desired alcohol **2**.

Treatment of the 1,4 cyclohexadiene **10**[20] with mild base would isomerize the unsubstituted double bond into conjugation giving the 1,3 diene **11**. Cycloaddition of this diene with an acetylene equivalent, as described for the preparation of the parent compound **1**, would give the bicycloadduct **3**.

Conversely, reduction of the ester **10** with lithium tetrahydridoaluminate and then treatment of the resultant alcohol as described for the conversion of the 1,4 diene **8** to the 1,3 diene **9** would give the diene **12**. Treatment of this diene with an acetylene equivalent, as described above, would give the 4 substituted bicyclooctadiene **13**. Removal of the TBS protecting groups, oxidation of the primary hydroxyl group, and esterification of the result acid with diozomethane would give the desired ester **5**.

Hydrolysis of the silyl enol ether of the 1,4 diene **4**[21] would give the corresponding ketone. Enolization of this ketone and trapping of the enolate with TBSCl would give the 1,3 diene **15**. Treatment of this diene with an acetylene equivalent, as described above, would give the desired cycloadduct **4**.

Treatment of the anhydride 6[22] with LAH and sodium metaperiodate cleavage of the resulting triol would give the β,γ enone 17. Enolization of the enone 16 and trapping of the enolate with TBSCl would give the 1,3 diene 18. Treatment of the diene with an acetylene equivalent and then removal of the protecting groups would provide the diol 19. Oxidation of the primary alcohol of the adduct 19 and then esterification with diazomethane would give the desired ester 6, while selective tosylation of the primary alcohol would yield the sulfonate 7.

The corresponding alkoxides of these alcohols could be generated by treatment with nBuLi, sodium or potassium hydride, and the cycloreversion rates of the alkoxides of alcohols 1 through 6 could then be determined by the observation of the time dependent appearance of the ultraviolet absorption band of the aromatic ester products. In the case of the tosylate 7, analysis of the products of the reaction would also be necessary to determine if any elimination had occurred.

In summary, the preparation of the bicyclo[2.2.2]-octadienes 1 through 7 and the study of their anion assisted cycloreversion will provide useful information about this interesting and potentially valuable reaction.

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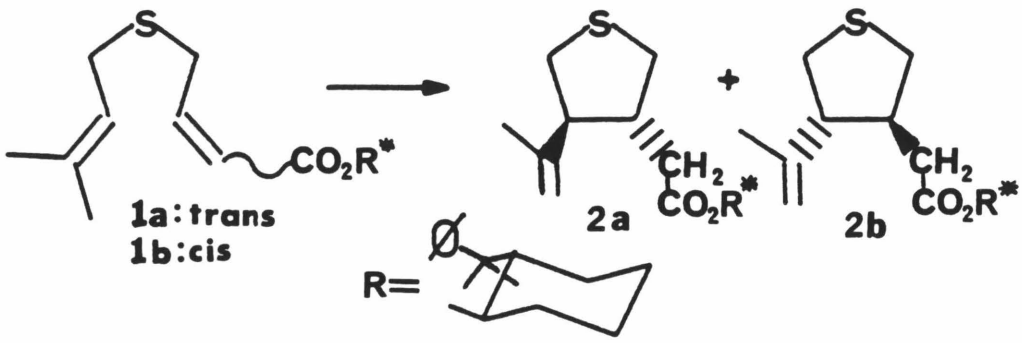
PROPOSITION 3.

The use of an asymmetric ene reaction to provide access to optically pure tetrahydrothiophenes and the conversion of these compounds into optically pure cyclobutene and cyclobutane derivatives is proposed.

Asymmetric induction in carbon-carbon bond formation has received substantial interest in recent years. The most common method of achieving asymmetric induction is the incorporation of a chiral auxillary into one of the reaction substrates. This method has been successfully applied to aldol condensations,[1,2] enolate alkylations[3] and acylations,[4] Diels-Alder cycloadditions,[5,6] the ene[7,8] reaction, and conjugate additions.[9] However, this method cannot be extended directly to 2+2 cyclo-additions due to the nature of the transition state of the reaction.

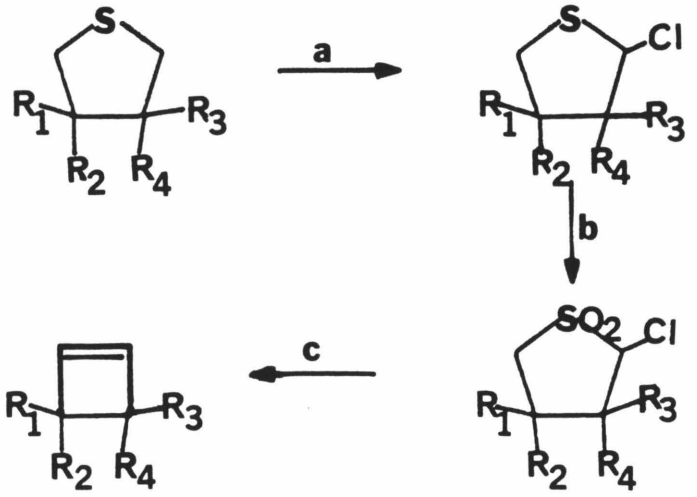
Therefore, the preparation of optically pure cyclobutenes and cyclobutanes requires the development of an alternate strategy. An alternate method for the preparation of four-membered rings is the contraction of a five membered ring by the extrusion of one of its members. A suitable candidate for such a process would be available through the thio analog of the asymmetric ene reaction reported by Oppolzer's group,[7] as shown in Scheme I. The tetrahydrothiophene **2** produced from the above ene reaction would be well suited for the preparation of optically pure cyclobutenes and cyclobutanes since both enantiomers would be

SCHEME I



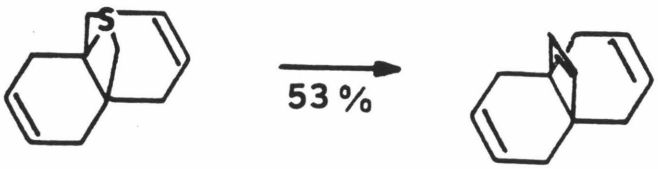
1a	minor	major
1b	major	minor

SCHEME II



(a) N-chlorosuccinimide; (b) MCPBA; (c) KOt-Bu, 0° C.

SCHEME III



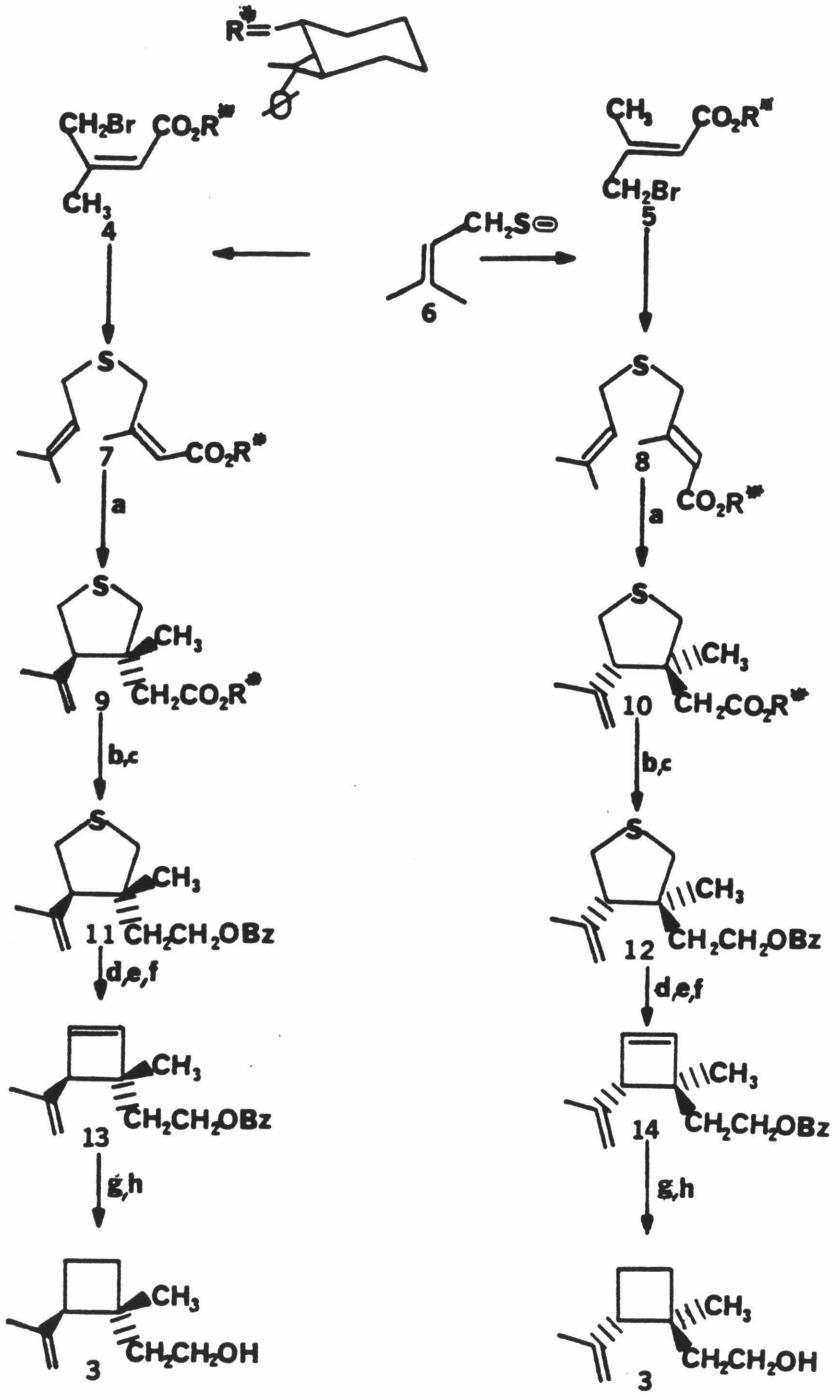
available by variation of the enoate portion of the 1,6 diene utilized in the ene reaction. In addition, there are numerous methods available for the contraction of rings by the extrusion of sulfur.

For the purpose of this proposal, the Ramberg-Backlumb rearrangement[10] (Scheme II) would be the method of choice since it has been successfully used to prepare cyclobutenes in good yield[11] (Scheme III) and does not involve the use of harsh reagents or reaction conditions. The cyclobutene thus prepared could be converted to the corresponding cyclobutane by hydrogenation of the highly strained endocyclic olefin. Conversely, the highly reactive olefin could be utilized for further functionalization of the ring (i.e.: cycloaddition, epoxidation, or hydroboration).

A proposed example of the use of this method is shown in Scheme II. Fragenol **3** is a terpene isolated from the roots of <u>Artemisia fragrans</u> Willd. The structure was assigned solely on the basis of ^{1}H-NMR data.

Treatment of the (Z) 4 bromo-3-methyl-2-butenoate **4**[13] with the anion of 3 methyl-2-buten-1-thiol **6** would give the 1,6 diene required for the preparation of one enatiomer of Fragenol **3**. Likewise, the (E) butenoate **5** would provide the 1,6 diene that would lead to the other enantiomer. Treatment of the butenoates **7** or **8** with Et_2AlCl as described by Oppolzer[7] should then lead to the enantiomeric tetrahydrothiophenes **9** and **10**. Reduction of the ester and then

SCHEME IV



(a) Et_2AlCl; (b) $LiAlH_4$; (c) BzCl; (d) N-chlorosuccinimide; (e) $NaIO_4$; (f) KO<u>t</u>-Bu; (g) $H_2/Pd\text{-}PbSO_4$; (h) NaOMe.

protection of the resulting alcohols would give the enantiomeric benzoates **11** and **12**. Treatment of the esters **11** and **12** successively with N-chloro-succinimide, sodium metaperiodate and potassium *t*-butoxide would effect the Ramberg-Backlumb rearrangement giving the enantiomeric cyclobutenes **13** and **14**. Selective hydrogenation of the highly strained endocyclic olefin would then provide both enantiomers of Fragenol **3**.

In summary, the asymmetric induction of the ene reaction could be utilized to provide access to optically pure cyclobutene and cyclobutane derivatives.

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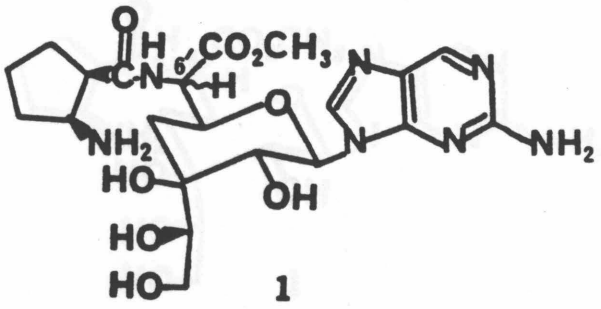
PROPOSITION 4.

A total synthesis of the nucleoside antibiotic Amipurimycin methyl ester 1 and its C-6' epimer is proposed.



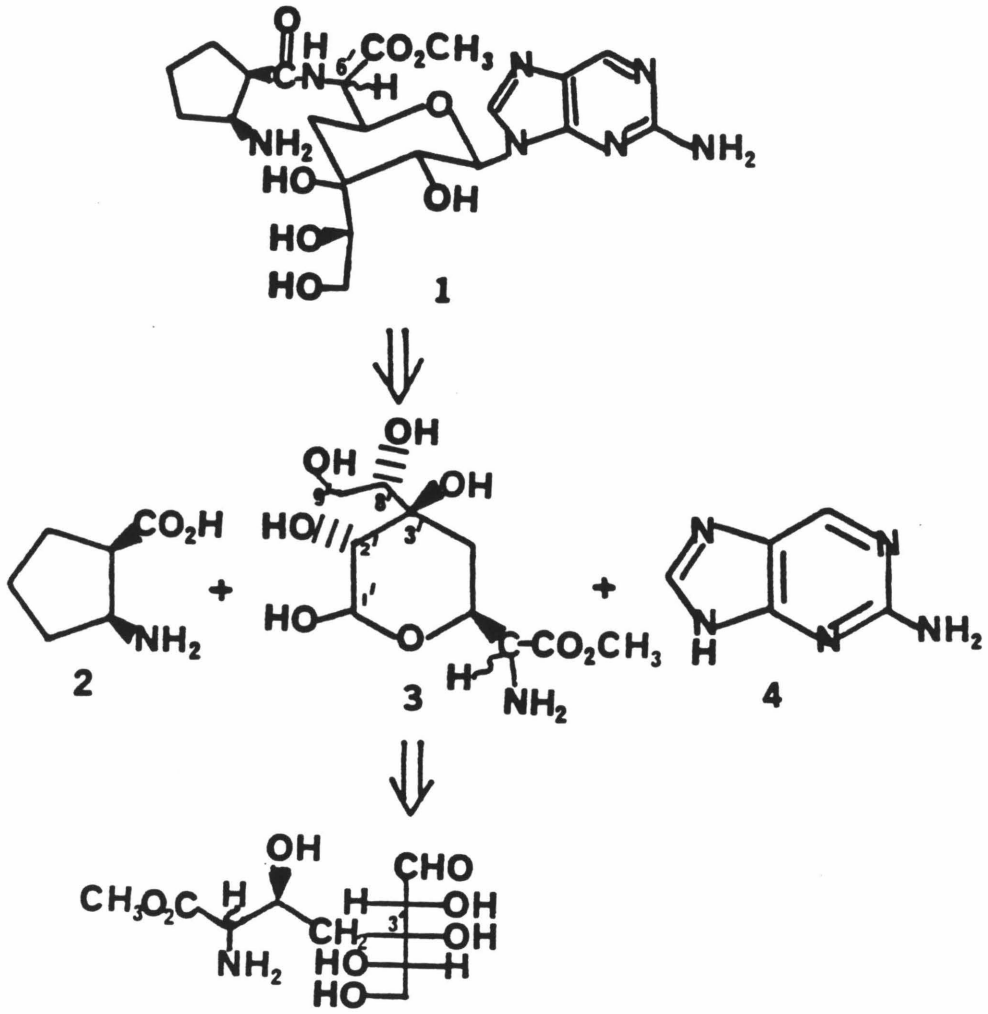
1

Amipurimycin is an antibiotic isolated from Streptomyces novoguineenis by Harada and Kishi.[1] Amipurimycin was shown to be active against various agricultural blasts in vitro and in vivo at low dosages[2] and therefore is potentially valuable as an agricultural antibiotic.

The structure for amipurimycin shown above was determined by Goto and coworkers[3] on the basis of chemical and spectral data. However, the relative stereochemistry of C-6' and the absolute stereochemistry of the antibiotic was not determined. Therefore, a total synthesis of both C-6' diasteriomers of one enantiomer of amipyrimyciin methyl ester would erase any ambiguity about the structure of amipurimycin.

Amipurimycin methyl ester 1 can be divided, in an antithetic sense, into three parts as shown in Scheme I:

SCHEME I

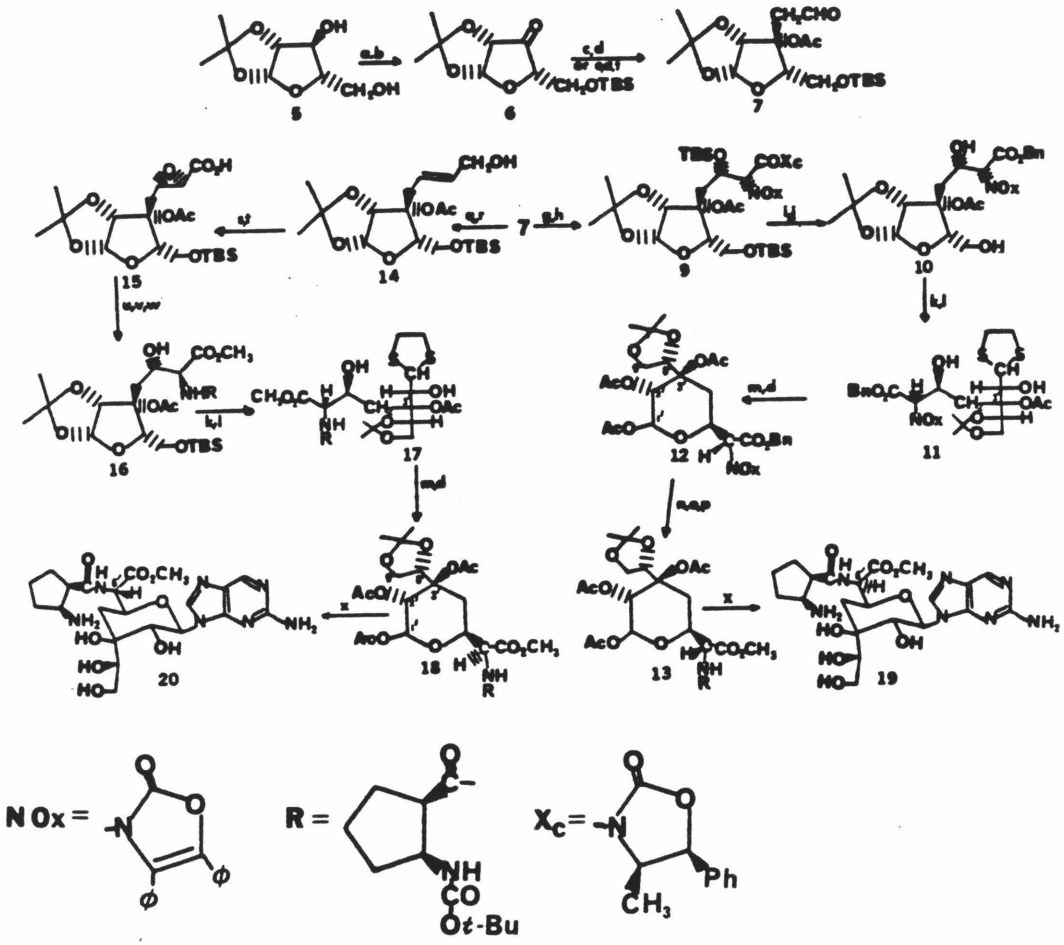


1) cis-2-aminocyclopentanecarboxylic acid **2**; 2) the novel branched carbohydrate moiety **3**; and 3) 9H-2-aminopurine **4**. Examination of the carbohydrate moiety **3** reveals it to be a L-pentose, C-1'-C-3', C-8' and C-9', branched at C-3'. Since both the R,S and the S,S diasteriomers of the amino alcohol side chain are required, an intermediate that would lead to both would be advantageous. This strategy has been employed in this proposed synthesis.

The proposed syntheses of amipurimycin methyl ester and its C-6' epimer are shown in Scheme II. Protection of the primary alcohol of the L-arabinose derivative **5**[4] as its tert-butyldimethylsilyl (TBS) ether and oxidation of the remaining hydroxyl group would provide the ketone **6**, required for the attachment of the amino alcohol chain. Addition of the enolate of acetaldehyde or an equivalent to the ketone **6** from the less hindered β-face and acetylation of the resulting alcohol would give the aldehyde **7** required for the generation of both C-6' epimers.

Aldol condensation of the boron enolate of the glycine derivative **8**[5] utilizing the conditions developed by Evan's group[6] would provide the erythro-amino alcohol **9**. Protection of the resulting alcohol **9** as its TBS ether, removal of the chiral auxillary and then removal of both TBS groups would afford the diol **10**. Treatment of the diol **10** with ethanedithiol and protection of the resulting vicinal hydroxyl groups as their acetonide derivative would provide

SCHEME II



(a) TBSCl; (b) Swern[o]; (c) $LiCH_2CHO$; (d) $AcCl/Et_3N$;(e) $CH_2=CH-CH_2Li$; (f) O_3; (g) R'BCH(NO_x)COXc (8);(h) TBSCl; (i) BnOLi; (j) n-Bu_4NF; (k) $HSCH_2CH_2SH/BF_3{\cdot}Et_2O$; (l) 2,2 Dimethoxypropane/H^+; (m) Hg^{2+}; (n) H_2/Pd; (o) RCl; (p) CH_2N_2; (q) $\phi_3P=CHCHO$; (r) $NaBH_4$; (s) RuO_4; (t) (+)diisopropyltartrate/Ti(OiPr)$_4$/tBuOOH; (u) NH_4OH; (v) RCl; (w) CH_2N_2; (x) $TiCl_4$/2-t-butoxycarbonylamino-9-chloro-mercuric purine.

the thioacetal **11**. Hydrolysis of the thioacetal **11** and acetylation of the resulting pyranose would give the pyranoside **12**. Hydrogenolysis of the benzyl ester and nitrogen protection group, N-acylation of the resulting amino acid with the acid chloride of N-tert-butoxycarbonyl cis-2-aminocyclopentanecarboxylic acid[12] and esterification with diazomethane would afford the pyranoside **13**.

Treatment of the aldehyde **7** with formylmethylene triphenylphosphorane[7] and reduction of the resulting aldehyde would provide the allylic alcohol **14**. Epoxidation of the alcohol **14** using the conditions described by Sharpless et al[8] and oxidation of the resulting epoxy alcohol[9] would give the epoxy acid **15**. Treatment of the epoxy acid **15** with ammonium hydroxide should open the epoxide α to the acid,[10] N-acylation of the resulting amino acid and esterification with diazomethane would give the threo-amino ester **16**. Removal of the TBS protecting group, opening of the furanoside **16** with ethanedithiol and boron-trifluoride etherate and protection of the resulting vicinal diol as its acetonide derivative would afford the thioacetal **17**. Hydrolysis of the thioacetal and acetylation of the resulting pyranose would provide the pyranoside **18**. This pyranoside would be epimeric at C-6' to the pyranose **13**.

Treatment of pyranoside **13** or **18** with titanium tetra-chloride and the chloromercuric salt of N-tertbutoxy-

carbonyl-2-aminopurine[11] and then removal of the protecting groups would afford amipurimycin or its C-6' epimer.

In summary, the syntheses described above would provide the information necessary for the determination of the relative and absolute stereochemistry of amipurimycin.

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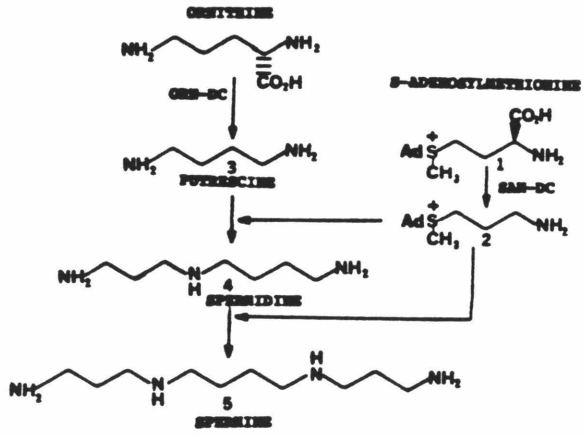
PROPOSITION 5.

The design and synthesis of a suicide enzyme substrate for S-adenosylmethionine decarboxylase is proposed.

S-adenosylmethionine decarboxylase (SAM-DC) converts its namesake **1** into S-adenosyl-S-methylhomocysteamine **2**, a propyl amine transfer compound utilized in the biosynthesis of spermidine **4** and spermine **5** (Scheme I). Spermidine **4** and spermine **5** have been implicated in cellular division and growth;[1] therefore, a potent inhibitor of their biosynthesis might be useful in controlling physiological disorders involving excessive cell proliferation.

Inhibitors of ornithine decarboxylase (Orn-DC) have been shown to retard the growth of a mouse sarcoma[2] lending credence to this proposal.

SCHEME I

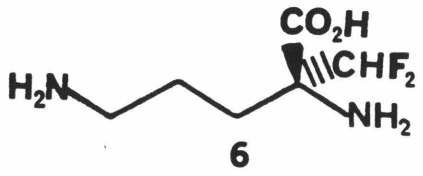


Competitive inhibitors of Orn-DC lead to an accumulation of the enzyme and thus a burst of putrescine **3** when the inhibitor is cleared from the organism. Therefore, irreversible suicide enzyme substrates for Orn-DC were

synthesized and tested for their ability to lower putrescine 3, spermidine 4 and spermine 5 concentrations.[3,4] One of these α-difluoromethylornithine 6 proved to be effective in blocking the testosterone induced increase of putrescine 3 and spermidine 4 and slows the accumulation of spermine 5 in castrated rats.[5] α-difluoromethylornithine also prolonged the survival time of mice innoculated with leukemia cells[6] and slows tumor growth in mice[7] combined with minimal toxicity. The proposed mechanism of action of 6 is shown in Scheme II.[8]

Unfortunately, Orn-DC is synthesized rapidly; therefore, adequate levels of any Orn-DC inhibitor must be constantly maintained in order to keep putrescine 3 synthesis to a minimum. Also, organisms can maintain or restore the spermine 5 pool, even when putrescine 3 concentrations are low. Therefore, in order to suppress the biosynthesis of spermidine 4 and spermine 5 effectively, the inhibition of another enzyme in the synthetic pathway must be inhibited, individually or in conjunction with an Orn-DC inhibitor.

The ideal enzyme to inhibit would seem to be SAM-DC since the S-adenosyl-S-methylhomocysteamine 2 it produces is used at two points in the biosynthesis of spermine. This would greatly accentuate the effect of any reduction in the activity of SAM-DC.



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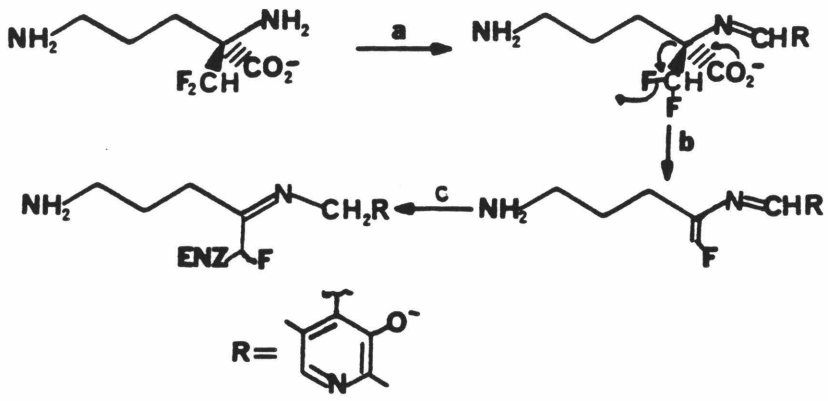
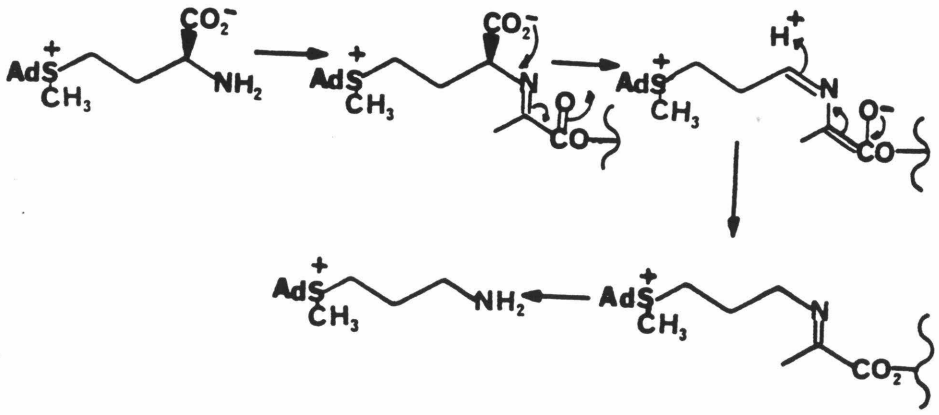
SCHEME II



(a) Binding to pyridoxal phosphate; (b) elimination; (c) Micheal addition of enzyme nucleophile.

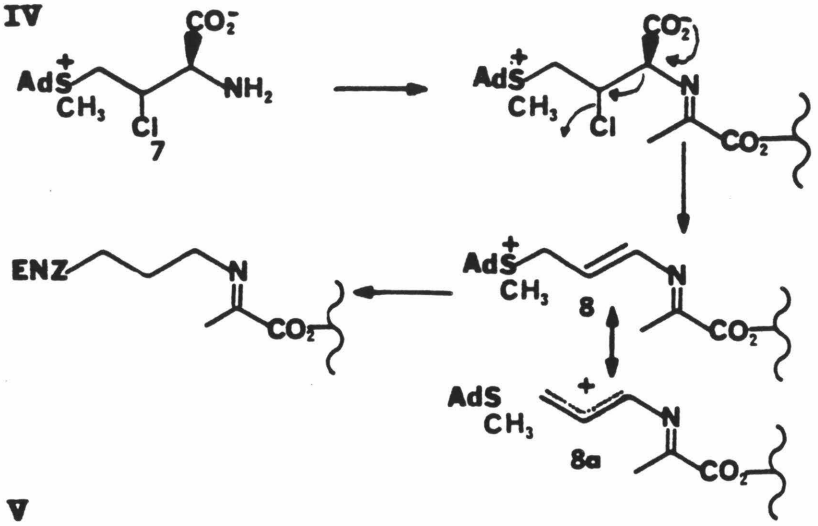
SCHEME III



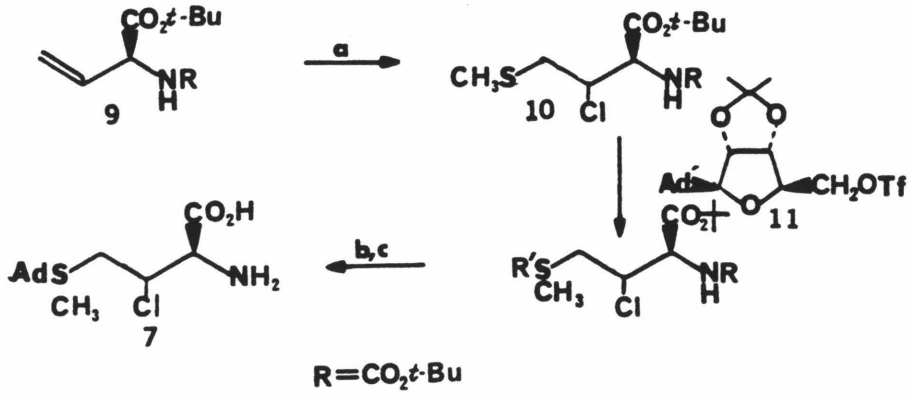
The proposed mechanism of SAM-DC's action is shown in Scheme III. It is important to note one major difference between the mechanisms for SAM-DC and most decarboxylases and transaminases (ex. Orn-DC, Scheme II). While Orn-DC utilizes pyridoxal phosphate, SAM-DC uses, evolutionally more primative, covalently bound pyruvate as an electron sink.[9] The use of this less effective electron sink not only raises the energy of the decarboxylation but also severely reduces the attractiveness of the traditional approach to suicide enzyme substrates. This approach (Scheme II) uses an enzyme mediated elimination to generate a Micheal acceptor which utilizes cofactor as its electron sink.

The use of 3-chloro SAM 7, as a suicide enzyme substrate for SAM-DC, and methods for its preparation are proposed. The preparation of both epimers at the chlorine bearing carbon and their use separately will be necessary, since the conformational rigidity imposed by the enzyme active site may lead to different results with each diasteriomer. The proposed mechanism of action of 7 is shown in Scheme IV. Decarboxylation would be accompanied by loss of an electro negative group as for Orn-DC inhibitor α-difluoromethyl ornithine; however, with 7, both a Micheal acceptor and more importantly a vinyl sulfonium moiety 8 which can act as a powerful alkylating agent would be generated. In order to fully appreciate the potential of 8

SCHEME IV

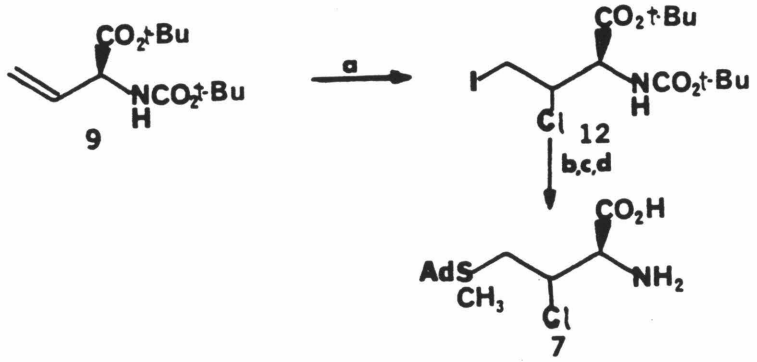


SCHEME V



(a) CH_3SCl; (b) $H_3{}^+O$; (c) CF_3CO_2H.

SCHEME IV



(a) ICl; (b) 2',3'-O-(1-methylethylidene)-5'-thiomethyladenosine; (c) $H_3{}^+O$; (d) CF_3CO_2H

as an alkylating agent, one only needs to consider its no bond resonance form **8a**.

Compound **7** should be available optically pure by several methods starting with protected L-vinyl glycine.[10] Two possible schemes (**V** and **VI**) are shown below.

Addition of methylsulfenylchloride to t-Butyl t-BOC-vinylglycine **9** would give the terminal sulfide **10**. Treatment of the sulfide **10** with 2',3'-O-(methylethylidene)-5'-trifluorosulfonate adenosine **11** followed by deprotection of the product would afford the desired SAM derivative **7**.[12,13]

Addition of ICl to **9** would yield the terminal iodide **12**. Treatment of the iodide **12** with 2',3'-O-(1-methylethylidene)-5'-thiomethyladenosine[14] followed by deprotection would also yield the desired SAM-derivative.

In summary, compound **7** should be a suicide enzyme substrate for SAM-DC by virtue of an enzyme mediated generation of an allyl sulfonium moiety.

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