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

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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 nonnatural. An example of the use of this strategy for the construction of a synthetic lasalocid analogue, *ent*-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 a 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 nonnatural analogues.[9] Such analogues may be designed to exhibit specific properties or to provide information concerning the mechanism by which these antibiotics act. An analogue 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, *ent*-X537A should exhibit properties identical with those of the natural ionophore. Since lasalocid A preferentially complexes the natural *R* enantiomer of asymmetric biogenic amines,[10] *ent*-X537A should not complex these amines as well. Therefore, the activity of *ent*-X537A should reflect this diminished capacity for natural amine complexation and allow a determination of the contribution the transport of these amines make to the overall effect of lasalocid A. Therefore, a synthesis of the enantiomer of lasalocid A (*ent*-X-537A) 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 *ent*-X537A into the aldehyde **2** and the ketone **3** (Scheme I). Technology used in the synthesis of lasalocid A[3] that reestablished 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.

The synthesis of the "left-half aldehyde" **2** was envisaged as proceeding through the addition of an appropriate asymmetric side chain to a nonaromatic precursor and then the conversion of this adduct into the desired tetrasubstituted aromatic moiety. Ideally, this method would allow for the preparation of further analogues by simple variation of the precursors utilized. The route used to prepare the 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 rel-

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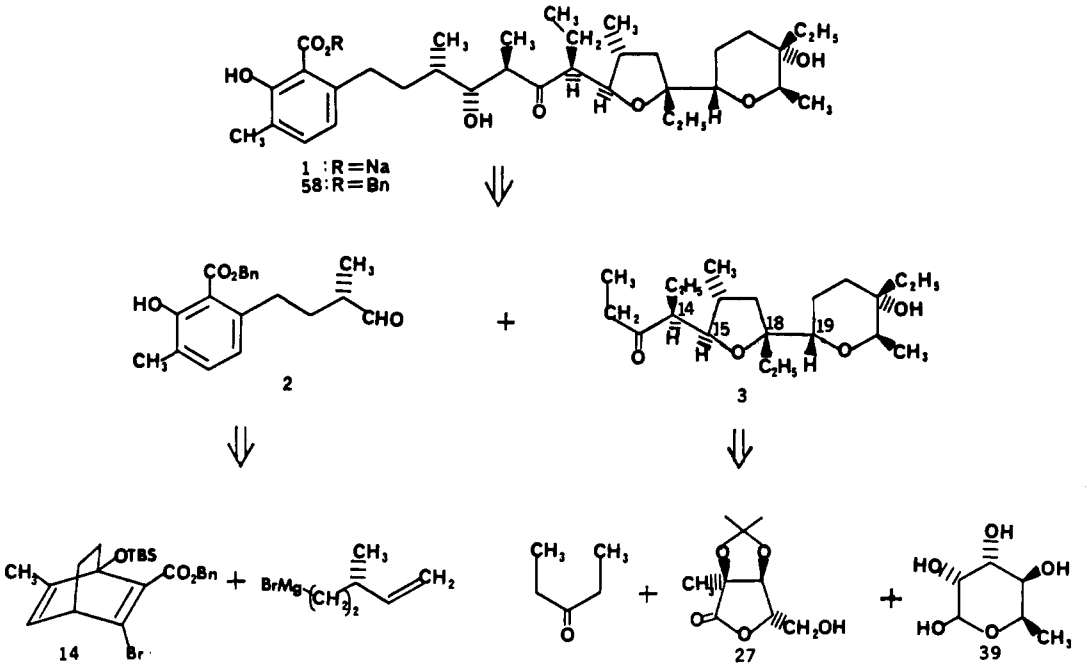
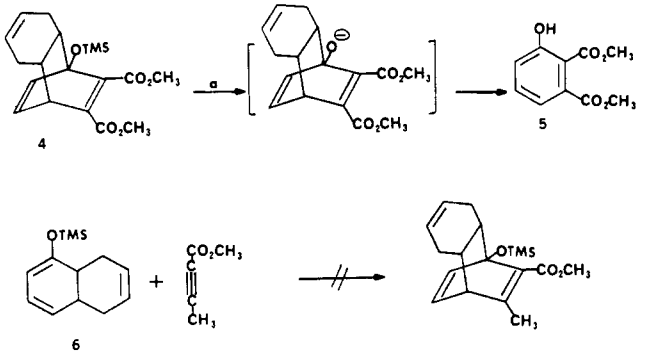
Scheme I. Retrosynthetic Analysis



Scheme II. Alkoxide Accelerated Cycloreversion[a]



[a] (a) n-Bu_4NF, THF, room temperature.

atively 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 homoalkyl cuprate or copper-catalyzed 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[15-18] led to the 3-methyl-2-oxy-1,3-cyclohexadiene and/or intractable tars. 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-methylcyclohex-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]

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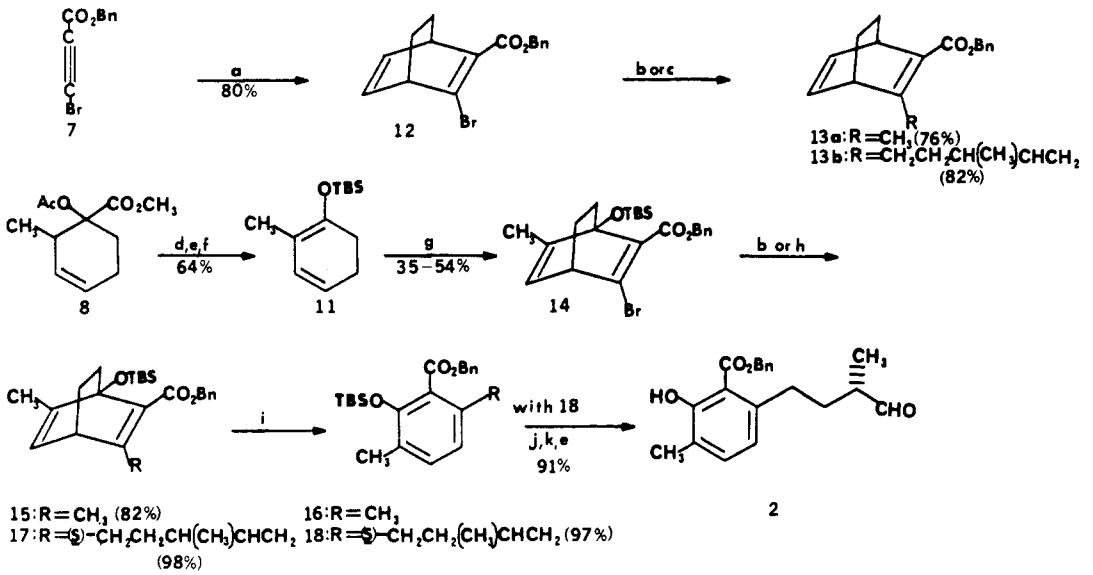
Scheme III. Synthesis of "Enantio-Left Half" Aldehyde 2[a]



[a] (a) 1,3-Cyclohexadiene, PhH, reflux; (b) Me_2CuLi, ether, 0 °C; (c) CH_2=CHCH(CH_3)CH_2CH_2MgBr/CuBr-DMS, ether, room temperature; (d) $LiAlH_4$, ether, room temperature; (e) $NaIO_4$, MeOH/H_2O, room temperature; (f) KH/TBSCl, THF, room temperature; (g) **6**/**10** = 1:1.3, room temperature; (h) (*S*)-CH_2=CHCH(CH_3)CH_2CH_2MgBr/Cu($OAc)_2$, ether, 0 °C; (i) 160 °C, sealed tube; (j) *n*-Bu_4NF, THF, room temperature; (k) OsO_4/NMO, THF/H_2O, room temperature.

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 (λ_{max} 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-catalyzed addition reaction, bromine displacement still proved to be quite facile, for treatment of the cycloadduct **14** with lithium dimethylcuprate afforded the adduct **15** in excellent yield.

The bicyclo[2.2.2]octadiene **15** provided a means for ascertaining the regiochemistry of the cycloaddition by ^1H NMR spectroscopy. Irradiation of the bridgehead proton led to nuclear Overhauser enhancements (NOEs) 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 NOE 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,[6] 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 the resulting alcohol was 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 discernible 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 °C for 20 h did afford benzyl 3,6-dimethyl-2-(silyloxy)benzoate **16** in quantitative yield.

The alkyl chain of enantio left-half aldehyde **2** was derived from 5-bromo-3(*S*)-methyl-1-pentene.[3] Copper(I)-catalyzed 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 pyrolyzed in a sealed tube at 160 °C for 22 h, an excellent yield of the desired tetrasubstituted aromatic system **18** resulted. The ester **18** had physical and spectral properties (R_f, elemental analysis, ^1H 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 tetraoxide 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, ^1H 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 vs. 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 vs. 11 steps for the previous scheme.[3] The above synthetic scheme should allow preparation not only of analogues of the aldehyde **2** but also of 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, we set the carbohydrate derivatives **27** and **39** (Scheme IV), which are enantiomeric to intermediates in

(21) The yield of the cycloaddition could not be improved by the addition of radical inhibitors or insoluble bases, while addition of soluble nitrogen-containing bases led to immediate decomposition of the dienophile.

the synthesis of lasalocid A[3], 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/Me_2SO in dichloromethane.[24] Due to the anomeric effect, the resultant ketone **23** should exist predominately in the chair conformation with the benzyloxy substituent axial. Examination of molecular models of this conformer indicates that sterically controlled nucleophilic attack should occur from the α face. However, addition of methylmagnesium bromide to the ketone **23** occurred exclusively from the β face and gave the alcohol **24**. However, addition of methyllithium at −78 °C gave a 1:8 mixture of the alcohols **24** and **25**, respectively.[25] Molecular mechanics calculations were employed[26] order to understand better this interesting reversal of face selectivity between the methylmagnesium bromide and the methyllithium addition. MM2 calculations indicated that the chair conformer with the benzyloxy substituent axial was only 0.8 kcal/mol 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 the 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 equiv) 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 (melting point, R_f, ^1H NMR, IR, $[\alpha]_D$) consistent with its being enantiomeric with the corresponding intermediate utilized in the synthesis of lasalocid A.[3]

As stated previously, the 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 **39** 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 Scheme IV. 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 °C rather than at −78 °C. 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-mmol scale.

The enantio right-half ketone **3** that resulted from the indicated operations (Scheme IV) exhibited physical and spectral properties (R_f, elemental analysis, ^1H NMR, IR) consistent with those of material derived from lasalocid A, except that the optical rotation ($[\alpha]^{22}_D$ +23.6° (*c* 1.705, $CHCl_3$); lit.[3] (for enantiomer) $[\alpha]^{24}_D$ −19.6° (*c* = 1.02, $CHCl_3$)) is equal in magnitude but opposite in sign.

Synthesis of *ent*-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 °C 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 ^1H NMR chemical shifts of the aromatic protons of the desired diasteriomer and the other diasteriomers (Scheme V) has become apparent. The ^1H 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 ^1H 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 in the formation of the acids of the other diasteriomers indicated that the added steric interactions along the backbone in these acids prevent the formation of the cyclic conformation. Although the other diasteriomers should not complex cations as well as *ent*-X537A, they do form complexes with Na^+ as indicated by the upfield shift of the ^1H NMR signals due to their aromatic protons on formation of their sodium salts.

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

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(28) Still, W. C. and McDonald, J. H., III. *Tetrahedron Lett.* **1980**, *21*, 1031–1034.
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Preliminary results of the biological testing[32] of *ent*-X537A indicate that both the cardiotonic and the antimicrobial activities of *ent*-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 *ent*-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 d, 3 H total, J = 8 Hz diasteriotopic CH_3's), 2.05 (s, 3 H, CH_3CO), 3.72 (s, 3 H, CH_3O), 5.60 (m, 2 H, C*H*=C*H*).

4-Hydroxy-4-(hydroxymethyl)-3-methylcyclohexene (9).[19] To a stirred suspension of 4.0 g (105 mmol) of lithium tetrahydroaluminate 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 mmHg); IR (neat) 3380, 3010, 2975, 2962, 2935, 1450, 1095, 1045, 690 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.93 and 1.05 (2 d, 3 H total, J = 7.5 Hz, diasteriotopic CH_3's), 3.43 (br s, 2 H, CH_2O), 6.63 (m, 2 H, C*H*=C*H*).

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 and then extracted with three 150 mL 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 g (74%) of the desired enone **10**: evaporative distillation 100 °C (20 mmHg); ^{1}H NMR ($CDCl_3$) δ 1.16 (d, 3 H, J = 7.5 Hz, CH_3), 2.47 (br s, 4 H, =CC*H*$_2$C*H*$_2$CO), 2.88 (m, 1 H, C*H*CH$_3$), 5.678 (ABX, 2 H, C*H*=C*H*).

1-[(*tert*-Butyldimethylsilyl)oxy]-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 and then diluted to 400 mL with ether, and the excess potassium hydride was destroyed by the careful addition of 2 mL of water. The organic phase was washed with three 250-mL portions of water and dried ($MgSO_4$), and the solvent was 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); ^{1}H NMR ($CDCl_3$) δ 0.14 (s, 6 H, $(CH_3)_2Si$), 0.95 (s, 9 H, $(CH_3)_3C$), 1.63 (br s, 3 H, CH_3C=), 2.20 (br s, 4 H, C*H*$_2$C*H*$_2$), 5.07 (m, 1 H, =C*H*CH$_2$), 5.70 (d, 1 H, J = 6 Hz, C*H*=CHCH$_2$).

Benzyl 3-Bromopropiolate (7). To a solution of 4.377 g (29.4 mmol) of 3-bromopropiolic acid in 20 mL of benzene were 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 $NaHCO_3$ and dried ($MgSO_4$), and the solvent was removed under

(34) Boiling points are uncorrected. Melting points were determined by using a Hoover capillary melting point apparatus and are uncorrected. Infrared (IR) spectra were determined on a Perkin-Elmer 237B or other infrared spectrometers. Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded on Varian EM-390 and Bruker WM-500 spectrometers. Chemical shifts are reported as values in parts per million relative to tetramethylsilane (δ 0.00) as an internal standard. Optical rotations were measured in 1-dm cells of 1-mL capacity by 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, and 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.

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 by 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 dyring agent. Ether and tetrahydrofuran (THF) were distilled under dry argon from sodium metal in the presence of benzophenone. *n*-Pentane was distilled from sodium metal under argon. Benzene and toluene were distilled from calcium hydride. Dichloromethane was distilled from phosphorus pentoxide. Methanol was distilled from magnesium methoxide. Hexamethylphosphoramide (HMPA) was distilled at ~1.0 mmHg from pulverized calcium hydride. Triethylamine and diisopropylamine were distilled under argon from sodium–benzophenone immediately prior to use. Pyridine and hexamethyldisilazane were 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 immediate 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, 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.

Elemental combustion analyses were performed by Spang Microanalytical Laboratory, Eagle Harbor, MI.

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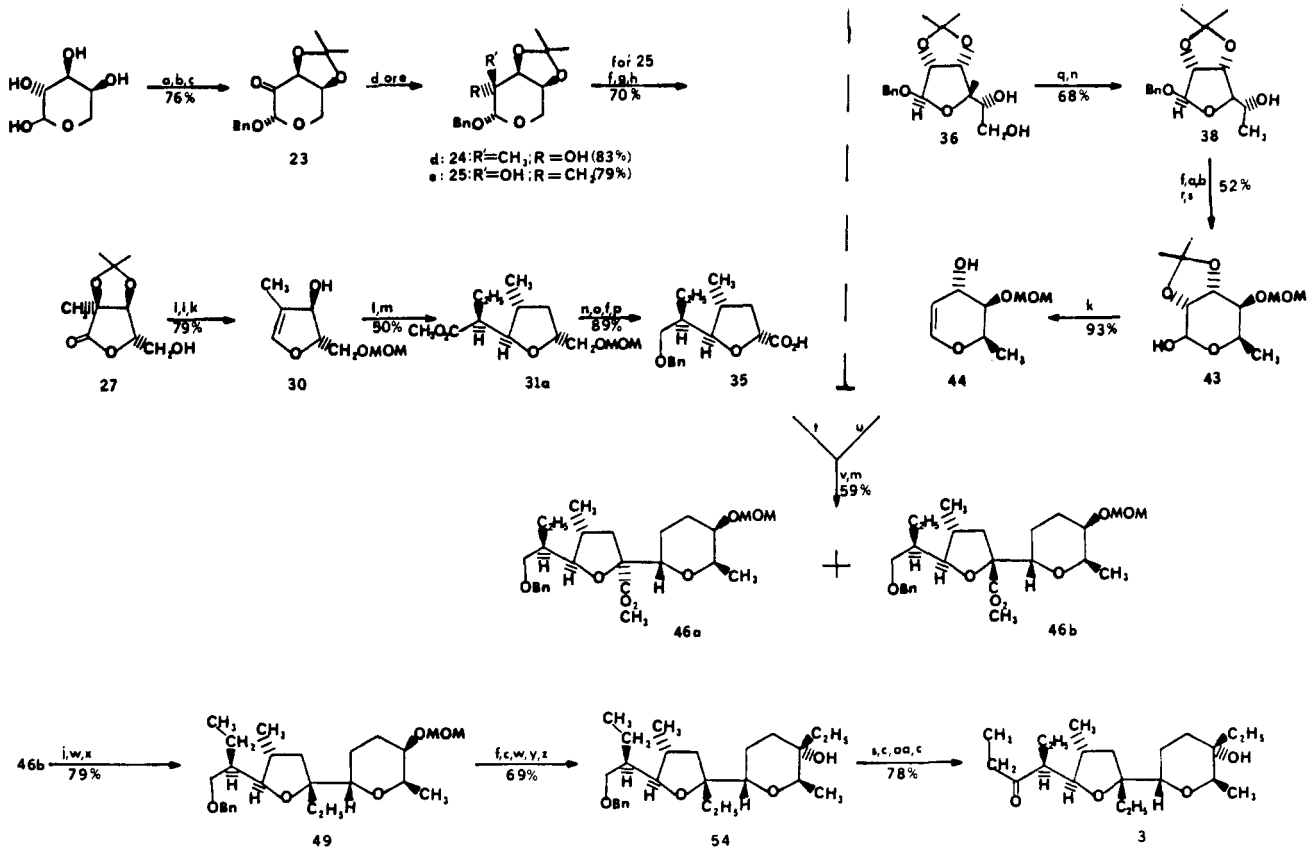
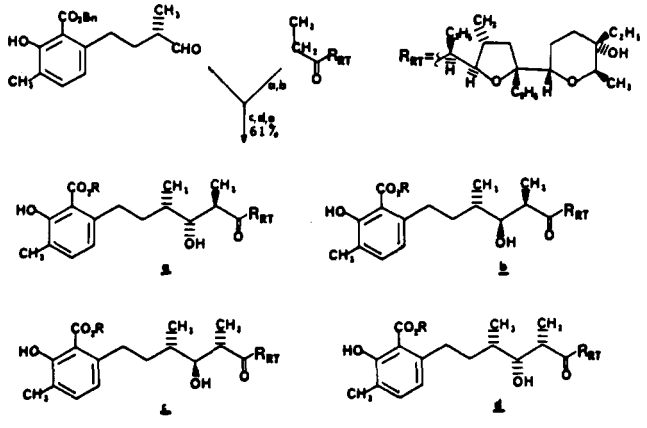
Scheme IV. Synthesis of "Enantio-Right Half" Ketone 3[a]



[a] (a) BnOH/AcCl, 50 °C; (b) 2,2-dimethoxypropane/H^+, acetone; (c) Swern; (d) MeMgBr, ether; (e) low-halide MeLi, ether, −78 °C; (f) H_3O^+; (g) Br_2CaCO_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) *n*-BuLi (1.0 equiv, *n*-PrCOCl, LDA, THF/HMPA, Me_3SiCl, ^-OH, CH_2N_2; (m) H_2–5% 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 (catalyst), benzene; (u) *n*-BuLi (1.0 equiv), THF; (v) LDA, THF; Me_3SiCl; ^-OH; CH_2N_2; (w) $Ph_3P{=}CH_2$, THF; (x) Raney Ni, ethyl acetate; (y) MCPBA, CH_2Cl_2; (z) $LiMe_2Cu$, pentane; (aa) EtMgBr, THF.

Scheme V. Completion of the Synthesis of *ent*-X537A Na^+ Salt 1[a]



[a] (a) LDA (2.05 equiv, PhH, 0 °C; (b) $ZnCl_2$ (1.1 equiv), ether; (c) H_2–10% Pd/C, ethanol; (d) Na_2CO_3, CH_2Cl_2.

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, 2 H, $ArCH_2O$), 7.38 (s, 5 H, 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-(carbobenzyloxy)bicyclo[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 max (C_6H_{12}) 215 nm (ε 19 500, Ar), 248 (~12 300, α,β-unsaturated ester); ^1H NMR ($CDCl_3$) δ 1.15–1.70 (m, 4 H, CH_2CH_2), 3.86 (m, 1 H, CHCBr=), 4.30 (m, 1 H, $CHC(CO_2Bn)$=), 5.20 (s, 2 H, $ArCH_2O$), 6.27 (m, 2 H, CH=CH), 7.35 (br s, 5 H, Ar H). 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 0.29 mL (0.58 mmol) of 2.0 M 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 and 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 (br s, 4 H, CH_2CH_2), 2.23 (s, 3 H, CH_3), 3.45 (m, 1 H, CHC(Me)=), 4.2 (m, 1 H, $CHC(CO_2Bn)$=), 5.17 (s, 2 H, $ArCH_2O$), 6.30 (m, 2 H, CH=CH), 7.37 (br s, 5 H, Ar H). 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–dimethyl sulfide 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 and 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 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, 3 H, J = 6 Hz, CH_3), 1.32 (br s, 4 H, CH_2CH_2), 1.43 (m, 2 H, CH_2CH_2CH), 2.02–2.96 (m, 3 H, CH_2CH), 3.50 (m, 1 H, CHC(R)=), 4.17 (m, 1 H, CHC(CO_2Bn)=), 4.85 (m, 2 H, $=CH_2$), 5.16 (s, 2 H, $ArCH_2O$), 5.62 (m, 1 H, CHCH=), 6.26 (m, 2 H, CH=CH), 7.38 (br s, 5 H, Ar H). 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*-butyldimethylsilyl)oxy]-2-(carbobenzyloxy)-6-methylbicyclo[2.2.2]octadiene (14). To a stirred mixture of 310 mg of the diene **11** (1.38 mmol) and 50 mg of 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 g 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}; UV (C_6H_{12}) λ_{max} 212 nm (ε ~10 500, Ar); ^1H NMR δ 0.20 (s, 3 H, CH_3Si), 0.23 (s, 3 H, CH_3Si), 0.92 (s, 9 H, $(CH_3)_3C$), 1.78 (d, 3 H, J = 1.5 Hz, CH_3C=), 3.46 (dm, 1 H, J = 7.2 Hz, CHCH=), 5.15 (s, 2 H, $ArCH_2O$), 5.83 (dm, 1 H, J = 7.2 Hz, CH=), 7.30 (m, 5 H, Ar H). 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*-Butyldimethylsilyl)oxy]-2-(carbobenzyloxy)-3,6-dimethylbicyclo[2.2.2]octadiene (15). By the procedure described for the preparation of the adduct **13a**, 30 mg (0.065 mmol) of the β-bromo ester **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}; ^1H NMR ($CDCl_3$) δ 0.17 (s, 3 H, CH_3Si), 0.20 (s, 3 H, CH_3Si), 0.95 (s, 9 H, $(CH_3)_3Si$), 1.73 (s, 3 H, CH_3C=C(CO_2Bn)), 1.77 (d, 3 H, J = 1.5 Hz, CH_3C=CH), 3.08 (dm, 1 H, J = 6.6 Hz, CHCH=), 5.14 (br s, 2 H, $ArCH_2O$), 5.77 (dm, 1 H, J = 6.6 Hz, CHCH=), 7.30 (br s, 5 H, Ar H). 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*-Butyldimethylsilyl)oxy]-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 g (3.24 mmol) of the β-bromo ester **14** in 125 mL of dry ether at −35 °C under argon was added dropwise 12.95 mL of a 0.5 M solution of 3(*S*)-methyl-5-pentenylmagnesium bromide in ether. The resulting mixture was stirred at −35 to −25 °C for 30 min and 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, washed with three 100-mL portions of saturated aqueous NH_4Cl, and 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 g (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, 3 H, CH_3Si), 0.21 (s, 3 H, CH_3Si), 0.84 (d, 3 H, J = 6.2 Hz, CH_3CH), 0.90 (s, 9 H, $(CH_3)_3C$), 1.75 (d, 3 H, J = 1.5 Hz, CH_3C=), 1.2–2.3 (m, 9 H, $2CH_2CH_2$ and $CHCH_3$), 3.13 (dm, 1 H, J = 6.3 Hz, =CCHC=), 4.8 (m, 2 H, CH=CH_2), 5.07 (s, 2 H, $ArCH_2O$), 5.47 (m, 1 H, CH=CH_2), 5.74 (dd, 1 H, J = 6.2 Hz, J' = 1.5 Hz, CH=C(CH_3)), 7.27 (br s, 5 H, Ar H).

Benzyl 2-[(*tert*-Butyldimethylsilyl)oxy]-3-methyl-6-[3-(*S*)-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 and 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 g (97%) of the desired tetrasubstituted aromatic **18**: evaporative distillation 120 °C (0.01 mmHg); $[\alpha]^{23}_D$ −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, 6 H, $(CH_3)_2Si$), 0.87 (d, 3 H, J = 6.9 Hz), 0.98 (s, 9 H, $(CH_3)_3C$), 1.42 (m, 2 H, $ArCHCH_2$), 1.97 (m, 1 H, $CH(CH_3)C$=), 2.17 (s, 3 H, $ArCH_3$), 2.45 (m, 2 H, $ArCH_2CH_2$), 4.83 (m, 2 H, CH=CH_2), 5.24 (s, 2 H, $ArCH_2O$), 5.57 (m, 1 H, CH=CH_2), 6.67 (d, 1 H, J = 8.1 Hz, Ar H), 7.05 (d, 1 H, J = 8.1 Hz, Ar H), 7.35 (m, 5 H, Ar H). 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(*S*)-methyl-4-pentenyl]-benzoate (19). To a stirred solution of 2.348 g (5.35 mmol) of the silyl ether **18** in 25 mL of THF under argon was added 2.5 g (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, the resultant organic phase was washed with two 100-mL portions of saturated aqueous $NaNCO_3$ and 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 g (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, 3 H, J = 6.6 Hz, CH_3CH), 1.41 (m, 2 H, $ArCH_2CH_2CH$), 1.89 (m, 1 H, $CH(CH_3)C$=), 2.19 (s, 3 H, $ArCH_3$), 2.75 (m, 2 H, $ArCH_2CH_2$), 4.83 (m, 2 H, CH=CH_2), 5.33 (s, 2 H, $ArCH_2O$), 5.53 (m, 1 H, CH=CH_2), 6.52 (d, 1 H, J = 8.4 Hz, Ar H), 7.00 (d, 1 H, J = 8.4 Hz, Ar H), 7.34 (br s, 5 H, Ar H).

Benzyl 2-Hydroxy-3-methyl-6-[4,5-dihydroxy-3(*S*)-methylpentyl]benzoate (20). To a stirred solution of 1.725 g (5.32 mmol) of the olefin **19** in 1.4 mL of THF under argon were consecutively added 920 mg (6.81 mmol) of 4-methylmorpholine 4-oxide, 2.5 mL of water, and 0.2 mL of 0.1 M osmium tetraoxide in *tert*-butyl alcohol, 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 g (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 (br d, 3 H, J = 6 Hz, $CHCH_3$), 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 (br s, 5 H, CO_2CH_2Ph), 11.38 (br s, 1 H, 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); $[\alpha]^{23}_D$ +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, 3 H, J = 7 Hz, CH_3), 2.20 (s, 3 H, $ArCH_3$), 2.81 (br t, 2 H, J = 7 Hz, $ArCH_2C$), 5.36 (s, 3 H, CO_2CH_2), 6.56, 7.14 (2 d, 2 H, J = 7.5 Hz, 2 Ar H), 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, 73.62; H, 6.78.

Benzyl β-L-Arabinopyranoside (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-Methylethylidene)-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, the resulting solution was washed with saturated aqueous $NaHCO_3$ (2 × 250 mL) and 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-ulosylpyranoside (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 dimethyl sulfoxide. 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 and 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 of 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 10 × 26 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 g (93%) of the ketone **23**: evaporative distillation 100 °C (0.005 mmHg); $[\alpha]^{25}_D$ +191.2 (*c* 0.94, $CHCl_3$); IR ($CHCl_3$) 2980, 1755, 1260, 1080 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.32 (s, 3 H, CH_3), 1.43 (s, 3 H, CH_3), 3.9–4.5 (m, 4 H, H-3, -4, -5's), 4.72 (d, 2 H, *J* = 7.5 Hz, PhCH_2), 4.87 (s, 1 H, H-1), 7.4 (s, 1 H, 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 methylmagnesium iodide (110.76 mmol) in 210 mL of dry ether at 0 °C 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 of saturated aqueous NH_4Cl, the ether phase was separated and 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 g (83%) of the adduct **24**: evaporative distillation 100 °C (0.005 mmHg); $[\alpha]^{25}_D$ +129.1 (*c* 1.2, $CHCl_3$); IR ($CHCl_3$) 3350, 2960, 1610, 1270, 1060 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.26 (s, 6 H, $2CH_3$), 1.41 (s, 3 H, CH_3), 3.1 (br s, 1 H, OH), 3.3–4.3 (m, 4 H, H-3, H-4, H-5's), 4.55 (s, 1 H, H-1), 4.69 (AB, 2 H, PhCH_2), 7.3 (s, 5 H, Ph). Anal. Calcd for $C_{16}H_{22}O_5$: 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).[38] 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 h, the reaction mixture was quenched by the careful addition of 100 mL of saturated aqueous NH_4Cl. The organic phase was separated and 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); $[\alpha]^{23}_D$ +186.5° (*c* 1.0, $CHCl_3$); IR ($CHCl_3$) 3350, 2980, 1605, 1280, 1070 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.23 (s, 3 H, CH_3), 1.37 (s, 3 H, CH_3), 1.59 (s, 3 H, CH_3), 2.55 (s, 1 H, OH), 4.0 (d, 2 H, *J* = 3.0 Hz, H-5's), 4.1 (d, 1 H, *J* = 11.5 Hz, H-3), 4.2 (dt, 1 H, J_1 = 3.0 Hz, J_2 = 11.5 Hz, H-4), 4.62 (s, 1 H, H-1), 4.63 (AB, 2 H, PhCH_2), 7.32 (m, 5 H, Ph). Anal. Calcd for $C_{16}H_{22}O_5$: 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 and 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 and slurried in 300 mL of dry acetone with 10 g of anhydrous Na_2SO_4, and 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 1 h, neutralized with concentrated aqueous NH_4OH, and 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%. Recrystallization from ether/hexane afforded an analytical sample: mp 62–62.5 °C [lit.[36] (for the antipode) mp 62–63 °C]; $[\alpha]^{22}_D$ +39.15° (*c* 1.51, $CHCl_3$) [lit.[36] (for the antipode) −38.4]; IR ($CHCl_3$) 3450, 3000, 2950, 1780, 1180, 1225, 1025 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.42 (s, 6 H, $(CH_3)_2C$), 1.63 (s, 3 H, CH_3C), 3.33 (br s, 1 H, OH), 3.87 (m, 2 H, H-5's), 4.52 (s + m, 2 H, 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); $[\alpha]^{22}_D$ +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, 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). Anal. Calcd for $C_{11}H_{18}O_6$: 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 (approximately 2 h), the organic phase was separated, and the aqueous phase was extracted with

(38) Multiple addition of methyllithium was used to overcome partial ketone enolization.

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); $[\alpha]^{22}_D$ −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, 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, 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 were sequentially added 3.15 mL (29.9 mmol) of carbon tetrachloride and 5.2 mL (28.6 mmol) of tris(dimethylamino)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 (approximately 0.3 mol) of lithium wire in 400 mL of dry ammonia at −78 °C, rinsing with two 10-mL portions of dry THF, and cooling was then discontinued (ammonia reflux). After 2 h, 18.8 g of dry ammonium chloride was cautiously added, the resulting colorless mixture was diluted with 200 mL of 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 g 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 (^1H NMR) of the desired glycal **30** (79%) and the dechloro 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); $[\alpha]^{23}_D$ −190.7° (*c* 2.0, $CHCl_3$); 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 (br s, 1 H, 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); $[\alpha]^{21}_D$ −26.58 (*c* 2.25, $CHCl_3$); IR ($CHCl_3$) 1460, 1385, 1220, 1160, 1040 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.38 (s, 3 H, CH_3), 1.50 (s, 6 H, $C(CH_3)_2$), 3.33 (s, 3 H, OCH_3), 3.60 (d, 2 H, J = 6 Hz, CCH_2O), 3.62 (d, 1 H, J = 9 Hz, $H1_a$), 3.79 (d, 1 H, J = 9 Hz, $H1_b$), 4.17 (dt, 1 H, J = 3 Hz, 6 Hz, H4), 4.27 (d, 1 H, J = 3 Hz, H3), 4.59 (s, 2 H, 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*)-[(Methoxymethoxy)-methyl]-3(*R*)-methyl-2(*R*)-tetrahydrofuryl]butanoate (31a,b). 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 Me_3SiCl). 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 (pH 2) 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. Esterification 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 g (67%) of a 6:1 (^1H NMR) mixture of the diasteriomeric esters. The yield of the above ester enolate Claisen reaction varied from 54% to 67% on using 1–20 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 1 atm 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 2*S* ester **31a** and 297 mg (11%) of the 2*R* ester **31b**. For 31a: evaporative distillation 80–90 °C (0.005 mmHg); $[\alpha]^{25}_D$ −8.04° (*c* 2.64, $CHCl_3$); 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, 59.84; H, 9.16. For **31b**: evaporative distillation 80–90 °C (0.005 mmHg); $[\alpha]^{25}_D$ −15.07° (*c* 2.48, $CHCl_3$); 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, 60.06; H, 9.26.

2(*R*)-[5(*R*)-[(Methoxymethoxy)methyl]-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 2*S* 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); $[\alpha]^{24}_D$ −24.7° (*c* 0.45, $CHCl_3$); IR ($CHCl_3$) 3650, 3500, 1460, 1230, 1150, 1105, 1030 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 Hz, 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, 62.12; H, 10.42.

Benzyl 2(*R*)-[5(*R*)-[(Methoxymethoxy)methyl]-3(*R*)-methyl-2(*R*)-tetrahydrofuryl]butyl Ether (33). To a suspension of 1.02 g (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 over a period of 30 min. The resulting mixture was stirred at room temperature for 1 h, and 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 $NaHCO_3$, and 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); $[\alpha]^{24}_D$ −17.8° (*c* 1.00, $CHCl_3$); 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 (br s, 5 H, C_6H_5). Anal. Calcd for $C_{19}H_{30}O_4$: C, 70.77; H, 9.38. Found: C, 70.74; H, 9.34.

Benzyl 2(*R*)-[5(*R*)-(Hydroxymethyl)-3(*R*)-methyl-2-(*R*)-tetrahydrofuryl]butyl Ether (34). To a solution of 21.70 g (67.3 mmol) of the methoxymethyl ether **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); $[\alpha]^{21}_D$ −51.8 (*c* 2.57, $CHCl_3$); 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 (br s, 5 H, 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*)-tetrahydrofuryl]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 Me_2SO activated with 6.6 mL of oxalyl chloride (75.9 mmol) and then 24.6 mL of triethylamine (excess) in 220 mL of dichloromethane. The re-

sultant 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 was added 364 mL of 0.93 M potassium hydroxide over 30 min, and the resulting mixture was stirred at room temperature for 5 min and 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 g (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); $[\alpha]^{20}_D$ −1.28° (*c* 1.08, $CHCl_3$); 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 Hz, 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 (br s, 5 H, 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-gulofuranoside (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 g (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 mmol) of *p*-tolylsulfonyl)imidazolide[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 and 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**: total yield of the epoxide **37** 42.1 g (87%); mp 87.5–88.0 °C; $[\alpha]^{22}_D$ −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, 6 H, $(CH_3)_2C$), 2.65 (dd, 1 H, $J_{6a,6b}$ = 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, 1 H, $J_{5,6a}$ = 3.0 Hz, $J_{5,6b}$ = 4.5 Hz, $J_{4,5}$ = 6.6 Hz, H-5), 3.58 (dd, 1 H, $J_{4,5}$ = 6.6 Hz, $J_{3,4}$ = 3.5 Hz, H-4), 4.60 (AB q, 2 H, $PhCH_2O$), 4.72 (m, 2 H, H-2 and H-3), 5.16 (br s, 1 H, H-1), 7.31 (br s, 5 H, Ph*H*). 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 g (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, 11.478 g (79%) of the desired alcohol **38**. The yield on a 5-mmol scale was 91: mp 111-112.5 °C; $[\alpha]^{22}_D$ −99.83 (*c* 1.6, $CHCl_3$); IR ($CHCl_3$) 3600 (sharp), 3520 (br), 2995, 2940, 1455, 1385, 1375, 1105, 107,5 1015, 855, 695 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.26 (d, 3 H, $J_{5,6}$ = 6.2 Hz, H-6's), 1.27 and 1.44 (s, 6 H, $(CH_3)_2C$), 2.7 (br s, 1 H, OH), 3.76 (dd, 1 H, J_4 = 6.2 Hz, $J_{3,4}$ = 2 Hz, H-4), 4.13 (dt, 1 H, $J_{5,6}$ = $J_{4,5}$ = 6.2 Hz, H-5), 4.57 (AB q, 2 H, $PhCH_2O$), 4.65 (br s, 2 H, H-2 and H-3), 5.10 (s, 1 H, H-1), 7.30 (s, 5 H, Ph*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-D-gulose (39). A solution of 11.473 g (39.0 mmol) of the glycoside **38** in 300 mL of 4:1 acetic acid/water was heated under reflux under argon. After 12 h the reaction mixture was cooled to room temperature, and the solvent was removed under reduced pressure. Passage of the residue through a 10 × 20 cm pad of silica gel, eluting with ethyl acetate, afforded 5.224 g (86%) of the free sugar **39**.

Benzyl 6-Deoxy-α- and -β-D-gulopyranosides (40a,b). To a stirred solution of 9.316 g (56.7 mmol) of 6-deoxy-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 1 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 ratio of 1:2) **40a,b**. α-Glycoside: mp 134.5–135.5 °C (ethyl acetate–hexane); $[\alpha]^{21}_D$ +117.8° (*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, 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 (br s, 1 H, H1), 7.38 (br s, 5 H, 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); $[\alpha]^{25}_D$ −117.8 (*c* 1.133, $CHCl_3$); 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, H1), 4.89 (d, 1 H, *J* = 11 Hz, C_6H_5CHH), 7.34 (br s, 5 H, 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 (41a,b). To a stirred solution of 11.231 g (44.17 mmol) of the benzyl glycosides **40a,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); $[\alpha]^{21}_D$ +62.1° (*c* 0.965, $CHCl_3$); 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 (br s, 1 H, H1), 7.33 (br s, 5 H, 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); $[\alpha]^{21}_D$ −106.2 (*c* 1.206, $CHCl_3$); IR ($CHCl_3$) 3560, 3350, 1390, 1230, 1180, 1120, 1060 cm^{-1}; ^1H NMR ($CDCl_3$) 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, H1), 4.58 (d, 1 H, *J* = 12 Hz, C_6H_5CHH), 4.84 (d, 1 H, *J* = 12 Hz, C_6H_5CHH), 7.33 (br s, 5 H, 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-gulopyranosides (42a,b). To a suspension of 5.15 g (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 **41a,b** in 80 mL of dry THF, and the resulting mixture was stirred at 0 °C. After 15 min, 15.1 mL (200 mmol) of chloromethyl methyl 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 and 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 g (84%) of the methoxymethyl ethers **42a,b**. α-Glycoside: evaporative distillation 120–130 °C (0.005 mmHg); $[\alpha]^{21}_D$ +41.0° (*c* 0.80, $CHCl_3$); 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 (br s, 1 H, H1), 7.34 (br s, 5 H, 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); $[\alpha]^{21}_D$ −148° (*c* 0.904, $CHCl_3$); IR ($CHCl_3$) 1390, 1230, 1155, 1040 cm^{-1}; ^1H NMR ($CDCl_3$) 3.40 (s, 3 H, OCH_3), 4.57 (d, 1 H, *J* = 12 Hz, H1), 7.30 (br s, 5 H, 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,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); $[\alpha]^{22}_D$ –62.5° (*c* 1.201, $CHCl_3$); 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, H4), 4.00 (dq, 1 H, *J* = 3 Hz, 6 Hz, H3), 4.63 (d, 1 H, *J* = 6 Hz, OCH*H*O), 4.77 (d, 1 H, *J* = 6 Hz, OC*H*HO), 4.87 (dd, 1 H, *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 tris(dimethylamino)phosphine 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**: $[\alpha]^{22}_D$ +199.8° (*c* 0.65, $CHCl_3$); 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, H4), 4.10 (m, 2 H, H3 and H5), 4.66 (d, 1 H, *J* = 6 Hz, OCH*H*O), 4.73 (d, 1 H, *J* = 6 Hz, OC*H*HO), 4.89 (m, 1 H, H2), 6.50 (d, 1 H, *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(*R*)-methyl-5-[5,6-dihydro-5(*R*)-(methoxymethoxy)-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**, 600 mg (3.48 mmol) of the glycal **44**, 1.62 mL (3.48 mmol) of a 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 were added to 7.0 mmol of LDA in 9 mL of dry THF, followed by 21.0 mmol of trimethylchlorosilane, and 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); $[\alpha]^{22}_D$ –149.2° (*c* 1.256, $CHCl_3$); 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 (br s, 2 H, $C_6H_5CH_2$), 4.62 (d, 1 H, *J* = 7 Hz, OCH*H*O), 4.71 (d, 1 H, *J* = 7 Hz, OC*H*HO), 5.67–6.17 (m, 2 H, H_cCH), 7.33 (br s, 5 H, 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); $[\alpha]^{22}_D$ –177.1° (*c* 0.552, $CHCl_3$); 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, OCH*H*O), 4.70 (d, 1 H, *J* = 6 Hz, OC*H*HO), 5.31 (br s, 2 H, *HC*=C*H*), 7.32 (br s, 5 H, 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 reaction varied from 59% to 69% on a 0.5–5.0-mmol scale.

Benzyl 2(*R*)-[5(*S*)-Carbomethoxy-3(*R*)-methyl-5-[5(*R*)-(methoxymethoxy)-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 20 mg 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); $[\alpha]^{22}_D$ –5.1° (*c* 1.118, $CHCl_3$); 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 (br s, 2 H, $C_6H_5CH_2$), 4.59 (br s, 2 H, OCH_2O), 7.33 (br s, 5 H, 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(*R*)-(methoxymethoxy)-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 acetate–cyclohexane), 7.51 g (90%) of the saturated methyl ester **46b**: evaporative distillation 150–160 °C (0.005 mmHg); $[\alpha]_D$ –34.0° (*c* 0.662, $CHCl_3$); 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 (br s, 2 H, $C_6H_5CH_2$), 4.60 (br s, 2 H, OCH_2O), 7.33 (br s, 5 H, 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*)-(methoxymethoxy)-6(*R*)-methyl-2(*S*)-tetrahydropyranyl]-2(*R*)-tetrahydrofuryl]butyl Ether (47). By the procedure described for the preparation of the lactol **29**, 8.801 g (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 g 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° (*c* 0.541, $CHCl_3$); 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 (br s, 2 H, $C_6H_5CH_2$), 4.57 (br s, 2 H, OCH_2O), 7.30 (br s, 5 H, C_6H_5), 9.67 (s, 1 H, 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*)-(methoxymethoxy)-6(*R*)-methyl-2(*S*)-tetrahydropyranyl]-2(*R*)-tetrahydrofuryl]butyl Ether (48). To a stirred suspension of 14.86 g (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 1 h and 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 $NaHCO_3$ and 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° (*c* 1.065, $CHCl_3$); 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 (br s, 2 H, $C_6H_5CH_2$), 4.59 (br s, 2 H, OCH_2O), 5.02 (dd, 1 H, *J* = 3 Hz, 10 Hz, HC=C*H*H(c)), 5.20 (dd, 1 H, *J* = 3 Hz, 18 Hz, HC=CH*H*(t)), 5.87 (dd, 1 H, *J* = 10, 18 Hz, *H*C=CH_2), 7.32 (br s, 5 H, 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*)-(methoxymethoxy)-6(*R*)-methyl-2(*S*)-tetrahydropyranyl]-2(*R*)-tetrahydrofuryl]butyl Ether (49). To a solution of 6.71 g (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); $[\alpha]^{21}_D$ –27.8° (*c* 1.011, $CHCl_3$); 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 (br s, 2 H, $C_6H_5CH_2$), 4.57 (br s, 2 H, OCH_2O), 7.33 (br s, 5 H, 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 g (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 ($CDCl_3$) δ 0.83, 0.92 (2 t, 6 H, *J* = 6 Hz, $2CH_3CH_2$), 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, $PhCH_2O$), 7.32 (br s, 5 H, 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*)-tetrahydropyranyl]-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 $NaHCO_3$, and 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); $[\alpha]^{21}_D$ +61.1° (*c* 0.570, $CHCl_3$); 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 (br s, 5 H, 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 methylenetriphenylphosphorane 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); $[\alpha]^{24}_D$ −8.2° (*c* 1.203, $CHCl_3$); IR ($CHCl_3$) 1460, 1380, 1120, 1080 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.83, 0.93 (2 t, 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, *CH*C=C), 4.47 (s, 2 H, $C_6H_5CH_2$), 4.67 (br s, 2 H, C=CH_2), 7.31 (br s, 5 H, 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(*R*)-1,5-dioxa-4(*R*)-methylspiro[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 were 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 $NaHCO_3$ and 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); $[\alpha]^{24}_D$ +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 (2 t, 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 (br s, 5 H, 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. Epiepoxide **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 (2 t, 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, CCH*H*O), 2.71 (d, 1 H, *J* = 5 Hz, CC*H*HO), 4.47 (s, 2 H, $C_6H_5CH_2$), 7.31 (br s, 5 H, 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(*R*)-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 methyllithium 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, washed with two 200-mL portions of saturated aqueous NH_4Cl and one 200-mL portion of brine, and 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); $[\alpha]^{24}_D$ −21.3° (*c* 1.320, $CHCl_3$); IR ($CHCl_3$) δ 3580, 1460, 1380, 1120, 1100, 1050, 960 cm^{-1}; ^1H NMR ($CDCl_3$) 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, CH_3CHOC), 4.47 (s, 2 H, $PhCH_2O$), 7.33 (br s, 5 H, Ph*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); $[\alpha]^{21}_D$ −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, 3 H, *J* = 6 Hz, CH_3CHCC), 1.22 (d, 3 H, *J* = 6 Hz, CH_3CHOC), 3.73 (q, 1 H, *J* = 6 Hz, CH_3CHOC). 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 Me_2SO, 0.45 mL (5.05 mmol) of oxalyl chloride, and 1.6 mL of dry triethylamine in 20 mL of dry dichloromethane afforded, after flash chromatography on 120 g of silica gel with 15% ethyl acetate in petroleum ether, 1.499 g (100%) of the aldehyde **56**: evaporative distillation 130–140 °C (0.005 mmHg); $[\alpha]^{21}_D$ +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, 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, *CH*O).

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, washed with 200 mL of saturated aqueous NH_4Cl and 100 mL of saturated aqueous NaCl, and 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 30–50% 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 ($CDCl_3$) δ 1.20 (d, 3 H, *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 Me_2SO (6.0 mmol), 0.45 mL of oxalyl

chloride (5.05 mmol), and 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); $[\alpha]^{25}_D$ +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, 3 H, *J* = 6 Hz, CH_3CHOC), 3.74 (q, 1 H, *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.

***ent*-Benzyl Lasalocid A (58a).** To a solution of 1.799 mmol of LDA in 2 mL of dry benzene at 0 °C was added a solution of 303.6 mg (0.856 mmol) of the ketone **3** in 3 mL of dry benzene over 10 min, and the resulting solution was 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 2.7 × 24 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, respectively. Compound **58a** exhibited ^1H NMR and IR spectra that were in agreement to those obtained from benzyl lasalocid A.[9] Aldo 2 (**58b**, erythro Cram): $[\alpha]^{22}_D$ +20.60° (*c* 1.19, $CHCl_3$); IR ($CHCl_3$) 3450 (vbr), 2980, 2950, 2895, 1685 (br), 1605, 1460, 1385, 1250, 1150, 955 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.20 (s, 3 H, $ArCH_3$), 5.41 (s, 2 H, $PhCH_2O$), 6.65 (d, 1 H, *J* = 7.5 Hz, Ar H), 7.18 (d, 1 H, *J* = 7.5 Hz, Ar H), 7.40 (m, 5 H, PhH). Aldol 3 (**58c**, threo-anti Cram): $[\alpha]^{22}_D$ +0.11° (*c* 1.135, $CHCl_3$); IR ($CHCl_3$) 3400 (br), 2970, 2940, 2885, 1700, 1655, 1460, 1385, 1250, 1148, 955 cm^{-1}; ^1H NMR ($CDCl_3$) 2.25 (s, 3 H, $ArCH_3$), 5.40 (s, 2 H, $PhCH_2O$), 6.65 (d, 1 H, *J* = 7.5 Hz, Ar*H*), 7.15 (d, 1 H, *J* = 7.5 Hz, Ar H), 7.38 (m, 5 H, Ph*H*). Aldol 4 (**58d**, erythro-anti Cram): $[\alpha]^{22}_D$ +8.81° (*c* 1.84, $CHCl_3$); IR ($CHCl_3$) 3500 (vbr), 2970, 2940, 2880, 1695, 1655, 1455, 1382, 1265, 1145, 955, 700 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.20 (s, 3 H, $ArCH_3$), 5.40 (m (AB), 2 H, $PhCH_2O$), 6.60 (d, 1 H, *J* = 7.0 Hz, Ar H), 7.17 (d, 1 H, *J* = 7.0 Hz, Ar H), 7.40 (br s, 5 H, Ph*H*).

***ent*-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 3.0 × 24 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: $[\alpha]^{22}_D$ +40.1° (*c* 0.565, $CHCl_3$); IR ($CHCl_3$) 3300 (vbr), 2940, 2880, 2860, 1705, 1655, 1460, 1385, 1100 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.16 (br s, 3 H, $ArCH_3$), 2.85 (m, 2 H, $CHCOCH$), 3.3–4.4 (complex multiplets, 4 H, $CHOC$'s), 6.43 (d, 1 H, *J* = 6.5 Hz, Ar), 6.95 (d, 1 H, *J* = 6.5 Hz, Ar H).

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 *ent*-lasalocid A sodium salt: mp 169–172 °C (benzene/cyclohexane, 1:20); $[\alpha]^{22}_D$ +84.0° (*c* 0.96, $CHCl_3$); $[\alpha]^{22}_D$ +31.4° (*c* 0.89, MeOH); IR ($CHCl_3$) 3530 (br), 2980, 1710, 1600, 1460, 1385, 1170 (br), 1105, 1050 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.18 (s, 3 H, $ArCH_3$), 6.40 (d, 1 H, *J* = 6.6 Hz, Ar *H*), 6.92 (d, 1 H, *J* = 6.6 Hz, Ar H), 14.3 (br s, 1 H, ArO*H*). 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.

***ent*-Epilasalocid A Sodium Salts.** The undesired diasteriomers from the above aldol were transformed into their respective acids and then into their sodium salts by the above procedure for the preparation of **1**. Their physical data are as follows.

Aldol 2 acid (erythro Cram): $[\alpha]^{22}_D$ +13.27° (*c* 1.605, $CHCl_3$) 3460 br), 2970, 2940, 2880, 1700, 1655, 1458, 1415, 1382, 1230 (br), 1160, 1100, 1040, 950 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.28 (m, 3 H, $ArCH_3$), 6.67 (d, 1 H, *J* = 8.0 Hz, Ar H), 7.22 (d, 1 H, *J* = 8.0 Hz, Ar H).

Aldol 3 acid (threo-anti Cram): $[\alpha]^{22}_D$ +13.10° (*c* 1.43, $CHCl_3$); IR ($CHCl_3$) 3440 (br), 2970, 2940, 2880, 1695, 1655, 1460, 1415, 1385, 1230 (vbr), 1165, 1095, 1045 (br), 965b cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.23 (s, 3 H, $ArCH_3$), 6.69 (d, 1 H, *J* = 8.0 Hz, Ar H), 7.23 (d, 1 H, *J* = 8 Hz, Ar H).

Aldol 4 acid (erythro-anti Cram): $[\alpha]^{22}_D$ +81.67° (*c* 1.10, $CHCl_3$); IR ($CHCl_3$) 3520 (br), 2970, 2940, 2880, 1698, 1652, 1460, 1410, 1380, 1230 (vbr), 1155, 960 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.23 (s, 3 H, $ArCH_3$), 6.63 (d, 1 H, *J* = 8.0 Hz, Ar H), 7.21 (d, 1 H, *J* = 8.0 Hz, Ar H).

Aldol 2 sodium salt (erythro Cram): $[\alpha]^{22}_D$ −35.52° (*c* 0.855, $CHCl_3$); IR ($CHCl_3$) 3300 (br), 2960, 2920, 2870, 1695, 1588, 1452, 1378, 1100, 1025, 960, 940, 905 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.20 (s, 3 H, $ArCH_3$), 6.47 (d, 1 H, *J* = 6.5 Hz, Ar H), 6.98 (d, 1 H, *J* = 6.5 Hz, Ar H).

Aldol 3 sodium salt (threo-anti Cram): $[\alpha]^{2}_D$ −26.14° (*c* 2.025, $CHCl_3$); IR ($CHCl_3$) 3300 (br), 2960, 2920, 2870, 1685, 1590, 1455, 1380, 1100, 960, 945, 905 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.18 (br s, 3 H, $ArCH_3$), 6.43 (br d, 1 H, *J* = 6.5 Hz, Ar H), 6.96 (d, 1 H, *J* = 6.5 Hz, Ar H).

Aldol 4 sodium salt (erythro-anti Cram): $[\alpha]^{22}_D$ −36.18° (*c* 1.345, $CHCl_3$); IR ($CHCl_3$) 3250 (vbr), 2960, 2920, 2870, 1690, 1595, 1455, 1378, 1310, 1095, 945, 905 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.20 (br s, 3 H, $ArCH_3$), 6.42 (d, 1 H, *J* = 7.0 Hz, Ar H), 6.98 (d, 1 H, *J* = 7.0 Hz, Ar H).

Registry No. **1**, 87678-17-9; **1** (R = H), 87725-61-9; **2**, 87598-75-2; **3**, 87678-18-0; **7**, 87598-76-3; **8**, 70291-20-2; **9**, 70291-22-4; **10**, 4982-22-3; **11**, 87598-77-4; **12**, 87598-78-5; **13a**, 87598-79-6; **13b**, 87598-80-9; **14**, 87598-81-0; **15**, 87598-82-1; **17**, 87598-83-2; **18**, 87598-84-3; **19**, 87598-85-4; (*S*,*S*)-**20**, 87598-86-5; (*R*,*S*)-**20**, 87599-04-0; **21**, 7473-38-3; **22**, 18403-22-0; **23**, 65247-32-7; **24**, 87598-87-6; **25**, 87598-88-7; **26**, 87598-89-8; **27**, 87598-90-1; **28**, 87598-91-2; **29**, 87725-62-0; **30**, 87678-19-1; **31a**, 87598-92-3; **31b**, 87598-93-4; **32**, 87678-20-4; **33**, 87678-21-5; **34**, 87678-22-6; **34** (aldehyde), 87599-03-9; **35**, 87598-94-5; **35** (acid chloride), 87598-96-7; **35a**, 87598-95-6; **36**, 74912-02-0; **37**, 87598-97-8; **38**, 87598-98-9; **39**, 643-17-4; α-**40a**, 87598-99-0; β-**40b**, 87599-00-6; α-**41a**, 87678-23-7; β-**41b**, 87678-24-8; α-**42a**, 87678-25-9; β-**42b**, 87678-26-0; **43**, 87599-01-7; **44**, 87678-27-1; **45a**, 87678-28-2; **45b**, 87678-29-3; **46a**, 87678-30-6; **46b**, 87678-31-7; **47**, 87678-32-8; **48**, 87678-33-9; **49**, 87678-34-0; **50**, 87678-35-1; **51**, 87678-36-2; **52**, 87678-37-3; **53**, 87678-38-4; *epi*-**53**, 87678-39-5; **54**, 87678-40-8; **55**, 87678-41-9; **56**, 87678-42-0; **57** (isomer 1), 87678-43-1; **57** (isomer 2), 87678-51-1; **58a**, 87678-44-2; **58b**, 87678-45-3; **58c**, 87678-47-5; **58d**, 87678-49-7; **60**, 87599-02-8; aldol **2** acid, 87678-46-4; aldol **2** sodium salt, 87725-63-1; aldol **3** acid, 87678-48-6; aldol **3** sodium salt, 87725-64-2; aldol **4** acid, 87678-50-0; aldol **4** sodium salt, 87725-65-3; methyl 2-acetoxypropenoate, 686-46-4; 3-bromopropiolic acid, 16900-53-1; 1,3-cyclohexadiene, 592-57-4; L-arabinose, 5328-37-0; *n*-butanoyl chloride, 141-75-3; *trans*-1,3-pentadiene, 2004-70-8.