The Convergent Synthesis of Polyether Ionophore Antibiotics: The Synthesis of the Monensin Bis(tetrahydrofuran) via the Claisen Rearrangement of an Ester Enolate with a β-Leaving Group[1]

Robert E. Ireland* and Daniel W. Norbeck[2]

Contribution No. 7075 from the Chemical Laboratories, California Institute of Technology, Pasadena, California 91125. *Received September 28, 1984*

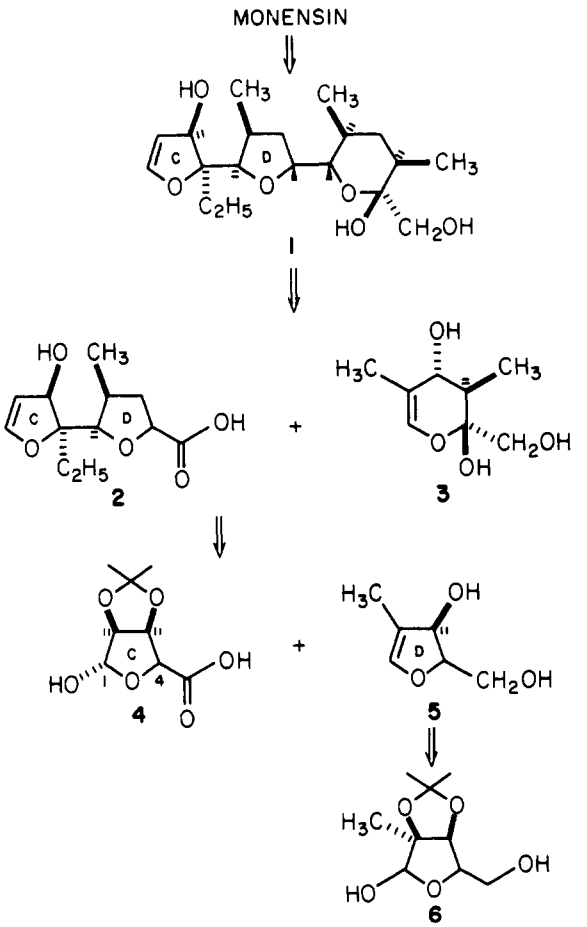
Abstract: The monensin bis(tetrahydrofuran) **25**, a versatile intermediate for the synthesis of polyether ionophore antibiotics, is prepared from D-xylose and D-mannose. In the key step, in situ silylation of an ester enolate with a β-leaving group allows the tetrahydrofuran rings to be joined by Claisen rearrangement.

The preceding article in this issue emphasizes the many structural identities among the polyether ionophore antibiotics. From a preparative point of view, convergency can be achieved on two levels by treatment of the recurring fragments as discrete synthetic subunits. One such subunit, derived from application of an ester enolate Claisen transform to monensin, is depicted in Scheme I.[3] Further application of this disconnection process generates the pyranoid glycal **3** and the topic of this report, the bifunctional building block **2**. Incorporating both the carboxylic acid and allylic alcohol components of the ester enolate Claisen rearrangement, this subunit can serve as a highly versatile, convergent link between a wide variety of other polyether fragments.

Reductive fragmentation of the lactol acetonide functional group array has proven to be a uniquely reliable route to furanoid glycals,[4] and this consideration dominated the retrosynthetic analysis of the bis(tetrahydrofuran) subunit **2** outlined in Scheme I. Utilization of the D ring first as the glycal and second as the carboxylic acid partner in sequential ester enolate Claisen rearrangements is straightforward. However, the reverse process with the similarly functionalized C ring poses a challenging dilemma: glycal formation requires β-elimination from a Cl carbanion; Claisen rearrangement forbids the same β-elimination from a C4 enolate.

To test the hypothesis that deprotonation and O-silylation of an ester with a β-leaving group can be executed without fragmentation, the model Claisen substrate **9** was prepared from D-mannose (**7**) via the known diol **8**[5] (Scheme II). The literature precedent for enolizations of this type was not encouraging. An alkoxide lacks the thermodynamic barrier to elimination imposed by dialkylamide[6] and lithium oxide[7] β-leaving groups, and in this instance fragmentation would be rendered irreversible by expulsion of acetone. Although a thermodynamically favored elimination can be kinetically impeded if the incipient π-bond is orthogonal to the breaking σ-bond,[8] the β-oxygen in ester **9** can easily assume a pseudoaxial orientation. We were thus disappointed but not

Scheme I. Retrosynthetic Analysis for the Bis(tetrahydrofuran) Polyether Building Block **2**



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(2) National Science Foundation Research Fellow, 1981–1984.

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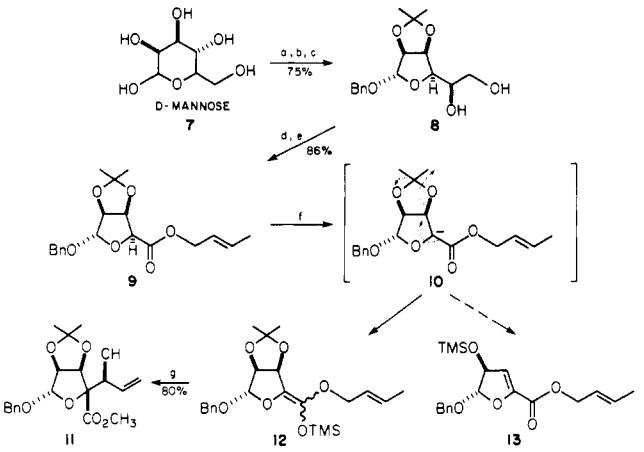
Scheme II. Ester Enolate Claisen Rearrangement in the Presence of a β-Leaving Group[aa]

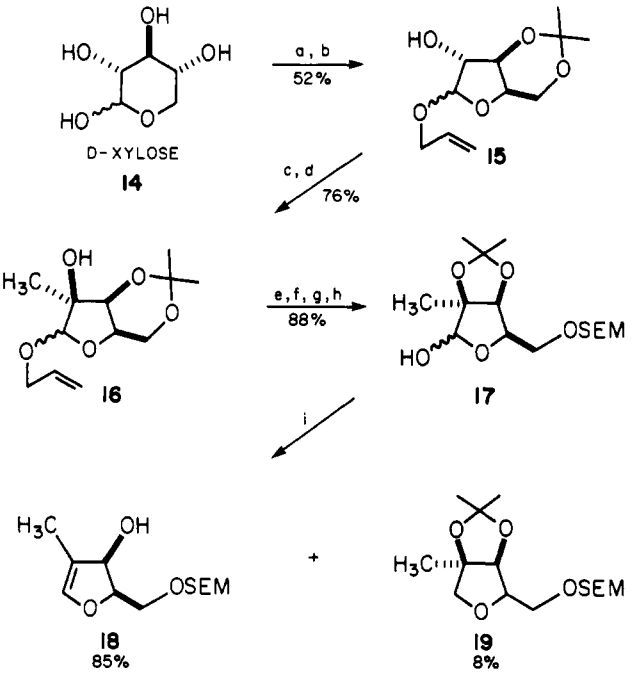


[a] (a) H_2SO_4, $(CH_3)_2CO$; (b) BnBr, NaH, DMF; (c) HCl, MeOH, H_2O; (d) $NaIO_4$, MeOH, H_2O; $AgNO_3$, KOH, H_2O, EtOH; (e) $(COCl)_2$, C_6H_6, DMF (catalytic); $CH_3CHCHCH_2OH$, DMAP, CH_2Cl_2; (f) LDA, TMSCl, THF/HMPA; (g) room temperature; H_3O^+; CH_2N_2, Et_2O.

surprised to find that enolization of the crotyl ester **9** with LDA in THF at −100 °C for 4 min followed by addition of excess TMSCl/TEA/HMPA in THF precooled to −78 °C consumed all of the starting material but, on warming to room temperature, afforded no products of Claisen rearrangement. While this experiment demonstrated that β-elimination of an ether oxygen from an ester enolate is indeed a fast process, we recognized that no conclusions could be drawn regarding the *relative* rates of fragmentation and O-silylation. To probe this question more incisively, it would be necessary to add another unknown to the experimental equation, namely, the relative rates of N-silylation and enolization. In the event, addition of the crotyl ester **9** to a *premixed* solution of LDA and TMSCl in 10% HMPA/THF cooled to −100 °C produced, after thermal rearrangement at room temperature, desilylation and treatment with diazomethane, a remarkable 80% yield of the diastereomeric methyl esters **11**. This three-component competition experiment, taken together with the previous result, indicates that enolization by LDA was considerably faster than its condensation with TMSCl,[9] that O-silylation was at least 4 times as fast as β-elimination, and that all these processes occurred on a subminute time scale at −100 °C.[10]

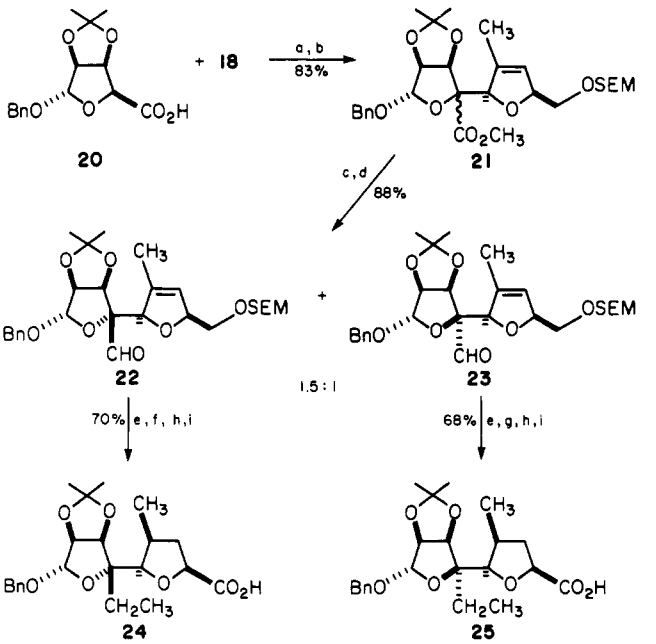
Having defined these crucial experimental conditions for the carboxylic acid partner of the ester enolate Claisen rearrangement, we next turned our attention to the preparation of the glycal component **18** (Scheme III). Inexpensive D-xylose (**14**) proved to be an ideal starting material for this subunit. Although this monosaccharide is appreciably soluble in allyl alcohol only at elevated temperatures, kinetically controlled[11] formation of the allyl furanosides could be realized by use of the weak acid pyridinium *p*-toluenesulfonate.[12] Replacement of the solvent with acetone then gave a 1:1 mixture of the C2 differentiated alcohols **15** as the only ether-soluble, water-insoluble products in an overall

Scheme III. Synthesis of the Furanoid Glycal 18[a]



[a] (a) $C_6H_5NH^+$-*p*-TsO^-, CH_2CHCH_2OH; (b) $C_6H_5NH^+$-*p*-TsO^-, $(CH_3)_2CO$; (c) $(COCl)_2$, Me_2SO, THF; Et_3N; (d) MeMgBr, Et_2O; (e) *p*-$TsOH{\cdot}H_2O$, $CuSO_4$, $(CH_3)_2CO$; (f) *t*-BuOK, Me_2SO; (g) $Me_3SiCH_2CH_2OCH_2Cl$, $(i\text{-}Pr)_2NEt$, CH_2Cl_2; (h) $Hg(OAc)_2$), THF, H_2O; (i) $P(NMe_2)_3$, CCl_4, THF; Li, NH_3; NH_4Cl.

Scheme IV. Synthesis of the Bis(tetrahydrofuran) Subunits 24 and 25[a]



[a] (a) **20**, $(COCl)_2$, C_6H_6, DMF (catalytic); **18**, *n*-BuLi, DMAP, THF; then acid chloride; (b) LDA, $(CH_3)SiCl$, THF/HMPA; room temperature; H_3O^+; CH_2N_2, Et_2O; (c) LAH, Et_2O; (d) $(COCl)_2$, $(CH_3)_2SO$, CH_2Cl_2; Et_3N; (e) Ph_3PCH_2, THF; (f) H_2, W-2 Ra-Ni, EtOAc; (g) H_2, 5% Pt/C, EtOAc; (h) CsF, HMPA; (i) $(COCl)_2$, $(CH_3)_2SO$, CH_2Cl_2; Et_3N; $AgNO_3$, KOH, H_2O, EtOH.

yield of 52%. Swern oxidation[13] in THF followed by the direct addition of excess methyl magnesium bromide to the crude reaction mixture circumvented the formation of a tenacious 2-keto-furanoside hydrate[14] and produced the tertiary alcohols **16** as the

(9) After completion of this work, similar in situ silylations were reported. Krizan, T. D.; Martin, J. C. *J. Am. Chem. Soc.* **1983**, *105*, 6155. Corey, E. J.; Gross, A. *Tetrahedron Lett.* **1984**, 495–498.

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exclusive diastereomers.[15] *p*-Toluenesulfonic acid promoted migration of the 3,5 acetonide to the thermodynamically preferred 2,3 position,[16] and standard protecting group manipulations[17] furnished the lactol **17** in excellent overall yield. Reduction of the corresponding furanosyl chloride with lithium in liquid ammonia[4] generated the acid labile glycal **18** in 85% yield along with 8% of the tetrahydrofuran **19**.

The extreme lability of the ester between this glycal and the acid **20** (Scheme IV) added yet another dimension of difficulty to the ester enolate Claisen rearrangement. Indeed, only obtention of the Claisen product itself confirmed that this ester had been formed. Nonetheless, addition of the solution prepared by mixing the acid chloride of **20** with the lithium alcoholate of the glycal **18** and a catalytic amount of DMAP in THF at −78 °C for 20 min to a premixed solution of LDA/TMSCl/HMPA in THF cooled to −110 °C reproducibly affords, even on multigram scale, a 1.5:1 mixture of diastereomeric Claisen prducts **21** in 83% yield. Attempts to alter the diastereomeric ratio were not successful. Omission of HMPA[18] from the enolization mixture caused the rate of O-silylation to plunge far below the rate of β-elimination; no Claisen products were detected. With the model crotyl ester **9**, substitution of either lithium or potassium hexamethyldisilylazide for LDA led to quantitative recovery of starting material. So far, the LDA/TMSCl/HMPA ensemble appears to be unique for enolization *and* O-silylation in the presence of a β-leaving group.

At this point, we were unable to confidently predict or unambiguously determine the stereochemistry of the methyl esters **21**, and we were therefore compelled to carry both diastereomers forward. Eventually, X-ray crystallography on an advanced intermediate[19] established the relative stereochemistry shown in Scheme IV. The derived epimeric aldehydes **22** and **23** were readily separated by flash chromatography[20] and then individually subjected to Wittig methylenation. Hydrogenation of the resulting vinyl dihydrofurans showed good (~8:1) stereoselectivity. Ultimately secured by X-ray crystallography,[19] the initial assignment of stereochemistry followed precedent from our lasalocid A synthesis[21] and from consideration of the steric bias of the *cis*-2,5-dialkyl substitution pattern. After purification by chromatography on silica gel, conversion to the bis(tetrahydrofurans) **24** and **25** required only deprotection and oxidation[13,22] of the primary alcohols to carboxylic acids.

Since the lactol acetonide is a latent furanoid glycal, the bifunctional nature of these intermediates potentiates the ester enolate Claisen rearrangement for the formation of carbon–carbon bonds at either terminus. In this vein, utilization of the carboxylic acids **24** and **25** as polyether building blocks is reported in the following article in this issue.

Experimental Section

Melting points are uncorrected. Proton nuclear resonance (^{1}H NMR) spectra were recorded at 90 MHz except where designated "500 MHz". Data reported as follows: chemical shift (multiplicity, integrated intensity, coupling constants, assignment). Optical rotations were measured in 1-dm cells of 1-mL capacity; chloroform, when used as a solvent for optical rotations, was filtered through neutral alumina (Activity I) immediately prior to use. Reaction solvents and liquid reagents were purified by distillation or drying shortly before use. 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. Reported temperatures were measured externally. Syringes and reaction flasks were dried at least 12 h in an oven (120–140 °C) and cooled in a dessicator over anhydrous $CaSO_4$ prior to use. If feasible reaction flasks were also flame-dried in vacuo.

Benzyl 2,3-*O*-(1-Methylethylidene)-α-D-lyxofuranosiduronic Acid, Methyl Ester. To a stirred solution of 50.0 g (0.161 mmol) of the diol **8**[5] in 850 mL of methanol was added dropwise over 1 h a solution of 37.9 g (0.177 mol) of $NaIO_4$ in 260 mL of water. After 75 min, most of the methanol was evaporated under reduced pressure, 600 mL of water was added, and then the resulting mixture was extracted with three 500-mL portions of ether. Each extract was washed with 150 mL of saturated aqueous NaCl, and then the combined organic phases were dried ($MgSO_4$) and concentrated under reduced pressure. To a stirred solution of the residue in 815 mL of ethanol was added a solution of 62.9 g (0.371 mol) of $AgNO_3$ in 86 mL of water, and then, dropwise over 1.5 h, a solution of 48.9 g (0.741 mol) of 85% KOH in 815 mL of water was added. After 8 h, the solution was filtered, and the precipitate was washed with three 50-mL portions of 6% aqueous KOH. Most of the ethanol was evaporated from the combined filtrates under reduced pressure. The resulting solution was washed with three 250-mL portions of ether and cooled to 0 °C. After the addition of 500 mL of ether, the stirred mixture was carefully acidified to pH 2 with concentrated aqueous HCl. The ether phase was separated and the aqueous phase was extracted with two additional 500-mL portions of ether. The combined organic extracts were washed with 150 mL of saturated aqueous NaCl, combined, dried ($MgSO_4$), and then concentrated under reduced pressure. Crystallization of the residue from ether/petroleum ether afforded 36.0 g of the acid **20** as a tan solid (mp 99–101 °C). Concentration of the mother liquors afforded 8.1 g of semicrystalline acid of at least 95% purity as judged by ^{1}H NMR, representing a total yield of 93%. ^{1}H NMR ($CDCl_3$) δ 1.36, 1.45 (2 s, 6 H, $(CH_3)_2C$), 4.48, 4.72 (2 d, 2 H, J = 12 Hz, $C_6H_5CH_2$), 4.68, 4.68 (2 d, 2 H, J = 6, 5 Hz, C(2)–H and C(4)–H), 5.05 (dd, 1 H, J = 6, J' = 5 Hz, C(3)–H), 5.28 (s, 1 H, OCHO), 7.33 (s, 5 H, C_6H_5). A portion of this acid was treated with ethereal diazomethane and chromatographed on silica gel with 3:7 ether/petroleum ether to afford the corresponding methyl ester as a colorless oil: R_f = 0.28 (silica gel, 3:7 ether/petroleum ether); evaporative distillation 120 °C (0.005 mmHg); $[\alpha]^{22}_D$ +46.4 (c 0.99, $CHCl_3$); IR ($CHCl_3$) 3040, 3000, 2960, 1760, 1740, 1455, 1440, 1390, 1380, 1220, 1080, 865 cm^{-1}; ^{1}H NMR ($CDCl_3$) 1.30, 1.43 (2 s, 6 H, $(CH_3)_2C$), 3.82 (s, 3 H, OCH_3), 4.50, 4.72 (2 d, 2 H, J = 12 Hz, $C_6H_5CH_2$), 4.65, 4.65 (2 d, 2 H, J = 5, Hz, C(2)–H and C(4)–H), 5.02 (dd, 1 H, J = 5, J' = 6 Hz, C(3)–H), 5.27 (s, 1 H, OCHO), 7.32 (s, 5 H, C_6H_5). Anal. Calcd for $C_{16}H_{20}O_6$: C, 62.33; H, 6.54. Found: C, 62.36; H, 6.46.

Benzyl 2,3-*O*-(1-Methylethylidene)-α-D-lyxofuranosiduronic Acid Chloride. To a stirred solution of 4.30 g (14.6 mmol) of the above acid **20** in 35 mL of benzene cooled in an ice bath were added 2.55 mL (29.5 mmol) of oxalyl chloride and then 3 drops of *N,N*-dimethylformamide. After 2 h at room temperature, the solvent was evaporated at reduced pressure. To the residue were added three 10-mL portions of benzene which were successively evaporated at reduced pressure. The residue was then dissolved in 40 mL of ether, filtered through a pad of celite, and recrystallized from ether/hexane at −20 °C to afford 4.10 g of the acid chloride as light yellow crystals: mp 65–67 °C; IR ($CHCl_3$) 3040, 3000, 2940, 1810, 1450, 1380, 1370, 1080, 1010, 860 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.32, 1.43 (2 s, 6 H, $(CH_3)_2C$), 4.48, 4.70 (2 d, 2 H, J = 12 Hz, $C_6H_5CH_2$), 4.67 (d, 1 H, J = 6 Hz), 4.87 (d, 1 H, J = 5 Hz), 5.17 (dd, 1 H, J = 5, J' = 6 Hz, C(3)–H), 5.27 (s, 1 H, OCHO), 7.30 s, 5 H, C_6H_5).

Benzyl 2,3-*O*-(1-Methylethylidene)-α-D-lyxofuranosiduronic Acid, *trans*-Crotyl Ester (9). To a stirred solution of 1.24 g (3.96 mmol) of the above acid chloride (used without crystallization) in 20 mL of dichloromethane at 0 °C were added 0.41 mL (4.75 mmol) of *trans*-crotyl alcohol and 580 mg (4.75 mmol) of 4-(dimethylamino)pyridine. The solution was allowed to warm to room temperature, diluted with 200 mL of ether, and then washed with 75 mL of saturated aqueous NaCl. The organic phase was dried ($MgSO_4$) and then concentrated under reduced pressure. Chromatography of the residue on 130 g of silica gel with 2:8 ether/petroleum ether afforded 1.35 g (98%) of the crotyl ester **9** as a colorless oil: R_f = 0.34 (silica gel, 3:7 ether/petroleum ether); evaporative distillation 150–155 °C (0.005 mmHg); $[\alpha]^{21}_D$ +36.7 (c 1.42, $CHCl_3$); IR ($CHCl_3$) 3040, 3000, 2950, 1760, 1730, 1455, 1385, 1375, 1195, 1085, 970, 860 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.27, 1.40 (2 s, 6 H, $(CH_3)_2C$), 1.67 (d, 3 H, J = 6 Hz, CH_3C=CH), 5.0 (dd, 1 H, J = 6,

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(15) The stereochemical assignment was based on the smooth equilibration of the acetonide to the 2,3 position. Inversion at C2 via a carbonium ion is not likely under the mild conditions used. Halford, M. H.; Ball, D. H.; Long, L., Jr. *Carbohydr. Res.* **1968**, *8*, 363–365.

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(22) Silver oxide: Shamma, M.; Rodriguez, H. R. *Tetrahedron* **1968**, *24*, 6583–6589. No epimerization was detected under these conditions. Reduction of the methyl esters of **24** and **25** with LAH gave the starting alcohols.

5 Hz, C(3)–H), 5.27 (s, 1 H, OCHO), 7.30 (s, 5 H, C_6H_5). Anal. Calcd for $C_{19}H_{24}O_6$: C, 65.50; H, 6.94. Found: C, 65.44; H, 6.82.

2(*R*)- and 2(*S*)-Carbomethoxy-2-(3(*R*)- and 3(*S*)-1-buten-3-yl)-3(*R*),4(*S*)-(dimethylmethylenedioxy)-5(*S*)-(benzyloxy)tetrahydrofuran (11). To a stirred solution of 1.75 mmol of LDA in 5.0 mL of THF and 0.7 mL of HMPA at −100 °C was added, over 3 min, a solution of 0.72 mL (4.14 mmol of trimethylchlorosilane) of the supernatant centrifugate from a 3:1 mixture of trimethylchlorosilane and triethylamine in 2.8 mL of THF at −78 °C. Within 5 min, to this mixture was then added dropwise over 2 min a solution of 435 mg (1.25 mmol) of the ester **9** in 2.0 mL of THF at −78 °C. After 8 min at −100 °C and then 8 min at −78 °C, the solution was allowed to warm to room temperature. After 2 h, the solution was treated for 30 min with 4.0 mL (4.0 mmol) of a 1 M solution of tetra-*n*-butylammonium fluoride in THF, diluted with 200 mL of ether, and then washed with 70 mL of saturated aqueous NaCl acidified to pH 2 with dilute aqueous HCl. The aqueous phase was extracted with three additional 150-mL portions of ether, the combined organic extracts dried ($MgSO_4$), concentrated to 100 mL, and then treated with excess ethereal diazomethane. The solvent was evaporated under reduced pressure and chromatography of the residue on 100 g of silica gel with 1:9 and then 2:8 ether/petroleum ether afforded first 155.0 mg (34.2%) of an inseparable 1:1 mixture of the methyl esters **11a** as a colorless oil: R_f = 0.48 (silica gel, 2:8 ether/petroleum ether); evaporative distillation 135 °C (0.005 mmHg); IR ($CHCl_3$) 3040, 3000, 2960, 1725, 1455, 1385, 1375, 1240, 1080, 870 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.03 (d, "1.5 H", J = 7 Hz, CH_3CH), 1.20 (d, "1.5 H", J = 7 Hz, CH_3CH), 1.32, 1.47 (2 s, 6 H, $(CH_3)_2C$), 3.02 (br q, 1 H, J = 7 Hz, CH_3CH), 3.50 (s, 3 H, OCH_3), 7.30 (s, 5 H, C_6H_5). Anal. Calcd for $C_{20}H_{26}O_6$: C, 66.28; H, 7.23. Found: C, 66.31; H, 7.22.

There was then eluted 119.5 mg (26.4%) of a methyl ester **11b** as a colorless oil: R_f = 0.28 (silica gel, 2:8 ether/petroleum ether); evaporative distillation 135 °C (0.005 mmHg); $[\alpha]^{21}_D$ +45.1 (*c* 1.10, $CHCl_3$); IR ($CHCl_3$) 3040, 2995, 2960, 1750, 1455, 1440, 1390, 1380, 1250, 1080, 1020, 870 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.08 (d, 3 H, J = 7 Hz, CH_3CH), 1.30, 1.40 (2 s, 6 H, $(CH_3)_2C$), 3.43 (s, 3 H, OCH_3), 7.33 (s, 5 H, C_6H_5). Anal. Calcd for $C_{20}H_{26}O_6$: C, 66.28; H, 7.23. Found: C, 66.33; H, 7.20.

There was then eluted 85.6 mg (18.9%) of a methyl ester **11c** as a colorless oil: R_f = 0.26 (silica gel, 2:8 ether/petroleum ether); evaporative distillation 135 °C (0.005 mmHg); $[\alpha]^{21}_D$ +43 (*c* 0.74, $CHCl_3$); IR ($CHCl_3$) 3040, 3000, 2960, 1750, 1460, 1440, 1390, 1380, 1240, 1080, 1005, 870 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.12 (d, 3 H, J = 7 Hz, CH_3CH), 1.27, 1.40 (2 s, 6 H, $(CH_3)_2C$), 3.77 (s, 3 H, OCH_3), 7.33 (s, 5 H, C_6H_5). Anal. Calcd for $C_{20}H_{26}O_6$: C, 66.28; H, 7.23. Found: C, 66.22; H, 7.16.

Allyl 3,5-*O*-(1-Methylethylidene)-α- and β-D-xylofuranoside (15). To a stirred solution of 75.0 g (0.500 mol) of D-xylose in 1.0 L of refluxing allyl alcohol was added 3.00 g (11.9 mmol) of pyridinium *p*-toluenesulfonate. The solution was gradually allowed to cool to 75 °C over a 4-h period. After 48 h at this temperature, the cooled solution was concentrated under reduced pressure, and the residue was then repetitively concentrated under reduced pressure from five 150-mL portions of benzene. To a stirred solution of the residue in 1.75 L of acetone (0.004% H_2O assay) was added 150 g of anhydrous copper sulfate. After 30 h at room temperature, the mixture was filtered, concentrated under reduced pressure, and then diluted with 500 mL of ether and 1 L of water. The organic phase was separated, and the aqueous phase was extracted with four additional 300-mL portions of ether. The combined organic extracts were dried ($MgSO_4$) and then concentrated under reduced pressure. Bulb-to-bulb distillation (110 °C, 0.001 mmHg) of the residue afforded 60.0 g (52%) of a 1:1 mixture of allyl furanosides **15** as a colorless oil of >95% purity according to TLC and NMR analyses. A portion of this material was chromatographed on silica gel with 1:1 ether/petroleum ether to afford first the α-anomer **15** as a white, low-melting solid: mp 40–41 °C, R_f = 0.34 (silica gel, 1:1 ether/petroleum ether); evaporative distillation 95–100 °C (0.001 mmHg); $[\alpha]^{22}_D$ +87.8° (*c* 2.67, $CHCl_3$); IR ($CHCl_3$) 3540, 3000, 2940, 1450, 1385, 1375, 1120, 1065, 1040, 850 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.37, 1.43 (2 s, 6 H, $(CH_3)_2C$), 2.97 (d, 1 H, J = 4 Hz, CHO*H*), 3.93–4.50 (m, 7 H), 5.33 (d, 1 H, J = 4 Hz, OCHO), 5.70–6.13 (m, 1 H, CH_2=C*H*). Anal. Calcd for $C_{11}H_{18}O_5$: C, 57.38; H, 7.89. Found: C, 57.46; H, 7.88.

There was then eluted the β-anomer **15** as a colorless oil: R_f = 0.13 (silica gel, 1:1 ether/petroleum ether); evaporative distillation 110 °C (0.001 mmHg); $[\alpha]^{22}_D$ 94.6° (*c* 2.63, $CHCl_3$); IR ($CHCl_3$) 3600, 3420, 3000, 2940, 1450, 1385, 1375, 1150, 990, 840 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.37 (s, 6 H, $(CH_3)_2C$), 2.30 (d, 1 H, J = 4 Hz, CHOH), 3.67–4.33 (m, 7 H), 5.00 (s, 1 H, OCHO). Anal. Calcd for $C_{11}H_{18}O_5$: C, 57.38; H, 7.89. Found: C, 57.41; H, 7.95.

Allyl 3,5-*O*-(1-Methylethylidene)-2-*C*-methyl-α- and β-D-lyxofuranoside (16). To a stirred solution of 19.9 mL (0.228 mol) of oxalyl chloride in 530 mL of THF cooled to −78 °C was added, over 15 min, a solution of 17.0 mL (0.239 mol) of dimethyl sulfoxide in 105 mL of THF. Following this addition, the internal temperature was allowed to rise to −40 °C, and after 15 min, the solution was recooled to −78 °C. To this mixture was added, over 20 min, a solution of 50.0 g (0.217 mol) of a 1:1 mixture of the above alcohols **15** in 150 mL of THF. The internal temperature was maintained between −65 and −70 °C during this addition and then allowed to increase to −40 °C. After 5 min, 151 mL (1.09 mol) of triethylamine was added over 5 min. The solution was then allowed to warm to 0 °C, and after 5 min was recooled to −78 °C. A 2.8 M solution of methyl magnesium bromide (390 mL 1.09 mol) in ether was then added over 25 min, during which time the internal temperature of the reaction was maintained below −60 °C. After 2 h at −78 °C, the reaction mixture was allowed to warm to −35 °C for 20 min, recooled to −78 °C, and then quenched by the addition of 60 mL of absolute ethanol. The warmed reaction was diluted with 3 L of ether and washed with 1.5 L of saturated aqueous NH_4Cl. The aqueous phase was extracted with two additional 200-mL portions of ether, and the combined organic extracts were dried ($MgSO_4$) and then concentrated under reduced pressure. Chromatography of the residue on 1 kg of silica gel with 2:8 and then 1:1 ether/petroleum ether afforded 40.1 g (76%) of the tertiary alcohols **16** as an oil of >95% purity as judged by TLC and NMR. By the procedure described above, the α-anomer **15** afforded on millimolar scale 85% of the α-anomer of **16** as a colorless oil: R_f = 0.28 (silica gel, 4:6 ether/petroleum ether); evaporative distillation 100 °C (0.005 mmHg); $[\alpha]^{22}_D$ +105° (*c* 1.80, $CHCl_3$); IR ($CHCl_3$) 3550, 3000, 2920, 1450, 1385, 1375, 1165, 1050, 1010, 840 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.30, 1.42, 1.42 (3 s, 9 H, 3 CH_3C), 3.27 (s, 1 H, OH), 3.63–4.40 (m, 6 H), 4.93 (s, 1 H, OCHO). Anal. Calcd for $C_{12}H_{20}O_5$: C, 59.00; H, 8.25. Found: C, 58.95; H, 8.19. By the procedure described above, the β-anomer of **15** afforded on 10 mM scale 75% of the β-anomer of **16** as a colorless oil: R_f = 0.28 nsilica gel, 4:6 ether/petroleum ether); evaporative distillation 100 °C (0.005 mmHg); $[\alpha]^{22}_D$ −97.4° (*c* 1.77, $CHCl_3$); IR ($CHCl_3$) 3560, 2960, 2820, 1450, 1380, 1370, 1170, 1120, 1050, 850, 840 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.32, 1.38, 1.38 (3 s, 9 H, 3 CH_3C), 3.40 (s, 1 H, OH), 3.55–4.40 (m, 6 H), 4.58 (s, 1 H, OCHO). Anal. Calcd for $C_{12}H_{20}O_5$: C, 59.00; H, 8.25. Found: C, 58.82; H, 8.17.

Allyl 2,3-*O*-(1-Methylethylidene)-2-*C*-Methyl-α- and β-D-lyxofuranoside. To a stirred solution of 40.1 g (0.164 mol) of the alcohols **16** in 1.1 L of acetone (0.1% H_2O assay) was added 100 g of anhydrous $CuSO_4$ and 340 mg (1.79 mmol) of *p*-toluenesulfonic acid. After 36 h at room temperature, the solution was neutralized with concentrated aqueous ammonia and then filtered. The solution was concentrated under reduced pressure, and the residue was dissolved in 1 L of 1:1 ether/petroleum ether and dried ($MgSO_4$). Evaporation of the solvent under reduced pressure afforded 40.1 g (100%) of the primary alcohols as an oil of >95% purity as judged by TLC and NMR. By the procedure described above, the α-anomer of **16** afforded on millimolar scale, after chromatography on silica gel with 1:1 ether/petroleum ether, 99% of the α-anomer of the primary alcohol as a colorless oil: R_f = 0.28 (silica gel, 6:4 ether/petroleum ether); evaporative distillation 90–95 °C (0.005 mmHg); $[\alpha]^{21}_D$ +87.2 (*c* 1.15, $CHCl_3$); IR ($CHCl_3$) 3500, 3000, 2940, 1455, 1380, 1250, 1095, 1020, 870 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.43, 1.47, 1.50 (3 s, 9 H, 3CH_3C), 2.20 (t, 1 H, J = 5 Hz, CH_2OH), 4.36 (d, 1 H, J = 3 Hz, C(3)–H), 4.90 (s, 1 H, OCHO). Anal. Calcd for $C_{12}H_{20}O^5$: C, 59.00; H, 8.25. Found: C, 59.05; H, 8.26.

By the procedure described above, the β-anomer of **16** afforded on millimolar scale, after chromatography on silica gel with 7:3 ether/petroleum ether, 98% of the β-anomer of the primary alcohol as a colorless oil: R_f = 0.11 (silica gel, 6:4 ether/petroleum ether); evaporative distillation 90–95 °C (0.005 mmHg); $[\alpha]^{21}_D$ −74.2° (*c* 1.52, $CHCl_3$); IR ($CHCl_3$) 3540, 3000, 2980, 2940, 1455, 1370, 1195, 1100, 1020, 870 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.40, 1.47, 1.55 (3 s, 9 H, 3CH_3C), 2.20 (t, 1 H, J = 6 Hz, CH_2OH), 4.35 (d, 1 H, J = 4 Hz, C(3)–H), 4.50 (s, 1 H, OCHO). Anal. Calcd for $C_{12}H_{20}O_5$: C, 59.00; H, 8.25. Found: C, 59.10; H, 8.26.

***cis*-Prop-1-enyl 2,3-*O*-(1-Methylethylidene)-2-*C*-methyl-α- and β-D-lyxofuranoside.** To a stirred solution of 40.1 g (0.164 mol) of the above primary alcohols in 330 mL of Me_2SO at 80 °C was added 36.7 g (0.327 mol) of potassium *tert*-butoxide. After 10 min, the solution was allowed to cool to room temperature, diluted with 1.5 L of ether, and then washed with two 300-mL portions of 50% saturated aqueous NaCl. The combined aqueous phases were extracted with 300 mL of ether, and the combined organic extracts were dried ($MgSO_4$) and then concentrated under reduced pressure. Chromatography of the residue on 1 kg of silica gel with 6:4 and then 7:3 ether/petroleum ether afforded 39.4 g (98%) of the propenyl ethers as a colorless oil of >95% purity as judged by TLC and ^1H NMR. By the procedure described above, the α-anomer of the primary alcohol afforded on millimolar scale, after chromatography on silica gel with 4:6 ether/petroleum ether, the α-propenyl ether in quantitative yield as a colorless oil: R_f = 0.20 (silica gel, 4:6 ether/petroleum ether); evaporative distillation 85 °C (0.005 mmHg); $[\alpha]^{21}_D$ +38.9 (*c*

1.33, $CHCl_3$); IR ($CHCl_3$) 3500, 3000, 2940, 1670, 1450, 1380, 1370, 1245, 1025, 870, 830 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.43, 1.50, 1.53 (3 s, 9 H, $3CH_3C$), 1.54 (dd, 3 H, J = 2, J' = 5 Hz, $CH_3CH{=}CH$), 2.17 (t, 1 H, J = 6 Hz, CH_2OH), 4.37 (d, 1 H, J = 3 Hz, C(3)–H), 5.03 (s, 1 H, OCHO). Anal. Calcd for $C_{12}H_{20}O_5$: C, 59.00; H, 8.25. Found: C, 59.09; H, 8.24. By the procedure described above, the β-anomer of the primary alcohol afforded on millimolar scale, after chromatography on silica gel with 8:2 ether/petroleum ether, the β-propenyl ether in quantitative yield as a colorless oil: R_f = 0.22 (silica gel, 7:3 ether/petroleum ether); evaporative distillation 85–90 °C (0.005 mmHg); $[\alpha]^{23}_D$ −24.0° (c 1.34, $CHCl_3$); IR ($CHCl_3$) 3600, 3500, 2985, 2940, 1670, 1450, 1370, 1355, 1250, 1020, 870 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.40, 1.50, 1.60 (3 s, 9 H, $3CH_3C$), 1.61 (dd, 3 H, J = 2, J' = 5 Hz, $CH_3CH{=}CH$), 2.06 (t, 1 H, J = 6 Hz, CH_2OH), 4.40 (d, 1 H, J = 4.5 Hz, C(3)–H), 4.67 (s, 1 H, OCHO). Anal. Calcd for $C_{12}H_{20}O_5$: C, 59.00; H, 8.25. Found: C, 58.96; H, 8.21.

2,3-*O*-(1-Methylethylidene)-5-*O*-[2-(trimethylsilyl)ethoxymethyl]-2-*C*-methyl-D-lyxose (17). To a stirred solution of 39.4 g (0.161 mol) of the above alcohols in 420 mL of dichloromethane was added 36.5 mL (0.210 mol) of *N,N*-diisopropylethylamine and then 31.1 mL (0.176 mol) of 2-(trimethylsilyl)ethoxymethyl chloride.[17] After 24 h at room temperature, the reaction was diluted with 1.5 L of ether, washed with two 300-mL portions of 50% saturated aqueous NaCl, dried ($MgSO_4$), and then concentrated under reduced pressure. Chromatography of the residue on 2 kg of silica gel with 2:8 ether/petroleum ether afforded 56.7 g (94%) of a 1:1 mixture of ethers as an oil: R_f = 0.45, 0.64 (silica gel, 1:1 ether/petroleum ether). To a rapidly stirred solution of 50.0 g (0.133 mol) of these ethers in 240 mL of THF and 78 mL of water was rapidly added a solution of 46.8 g (0.147 mol) of mercuric acetate in 110 mL of water. After 20 min at room temperature, the reaction mixture was diluted with 1 L of ether, and the organic phase was washed with 200 mL of saturated aqueous NaCl and then dried ($MgSO_4$). The solvent was evaporated at reduced pressure, and chromatography of the residue on 2 kg of silica gel with 4:6 and then 1:1 ether/petroleum ether afforded 42.8 g (96%) of the lactol **17** as a colorless oil. By the procedure described above, both the α- and β-anomer of the ether afforded on millimolar scale the lactol **17** in quantitative yield: R_f = 0.23 (silica gel, 4:6 ether/petroleum ether); evaporative distillation 95 °C (0.005 mmHg); $[\alpha]^{23}_D$ −21.0° (c 1.30, $CHCl_3$); IR ($CHCl_3$) 3600, 3500, 3000, 2960, 2900, 1450, 1420, 1380, 1250, 1110, 1060, 860, 840 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.37, 1.42, 1.53 (3 s, 9 H, $3CH_3C$), 4.66 (s, 2 H, OCH_2O), 5.17 (s, 1 H, OCHO). Anal. Calcd for $C_{15}H_{30}O_6Si$: C, 53.86; H, 9.04. Found: C, 53.97; H, 9.10.

1,4-Anhydro-2-deoxy-2-methyl-5-*O*-[2-(trimethylsilyl)ethoxymethyl]-D-*threo*-pent-1-enitol (18). To a stirred solution of 1.408 g (4.209 mmol) of the lactol **17** and 0.49 mL (5.08 mmol) of carbon tetrachloride in 21 mL of THF at −78 °C was added 0.80 mL (4.40 mmol) of tris(dimethylamino)phosphine. After 25 min, the reaction mixture was allowed to warm to room temperature and after 15 min was then added, via a cannula over 5 min, to a stirred solution of 18.9 cm (115 mmol) of lithium in 200 mL of anhydrous liquid ammonia at −78 °C. After 35 min, 6.2 g (116 mmol) of dry ammonium chloride was cautiously added to the reaction mixture. The resulting colorless mixture was diluted with 250 mL of ether and the ammonia allowed to evaporate. The resulting ethereal suspension was filtered and concentrated under reduced pressure. Flash chromatography of the residue on 120 g of silica gel with 1:1 ether/petroleum ether afforded first 113 mg (8.4%) of the tetrahydrofuran **19** as a colorless oil: R_f = 0.39 (silica gel, 1:1 ether/petroleum ether); evaporative distillation 90 °C (0.005 mmHg); IR ($CHCl_3$) 2995, 2960, 2940, 1450, 1385, 1255, 1120, 1065, 1045, 865, 845 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.05 (s, 9 H, $(CH_3)_3Si$), 1.40, 1.47, 1.48 (3 s, 9 H, $3CH_3C$), 3.35, 3.98 (2 d, 2 H, J = 10 Hz, OCH_2C), 4.28 (d, 1 H, J = 3 Hz, C(3)–H), 4.72 (s, 2 H, OCH_2O). Anal. Calcd for $C_{15}H_{30}O_5Si$: C, 56.57; H, 9.49. Found: C, 56.50; H, 9.41. There was then eluted 929 mg (85%) of the glycal **18** as a colorless oil: R_f = 0.22 (silica gel, 1:1 ether/petroleum ether); evaporative distillation 100 °C (0.005 mmHg); $[\alpha]^{22}_D$ −35.9° (c 1.19, $CHCl_3$); IR ($CHCl_3$) 3600, 3520, 3015, 2960, 2880, 1665, 1450, 1255, 1100, 870, 845 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.05 (s, 9 H, $(CH_3)_3Si$), 1.75 (s, 3 H, $CH{=}CH_3$), 2.20 (d, 1 H, J = 7 Hz, CHO*H*), 4.73 (s, 2 H, OCH_2O), 6.25 (br s, 1 H, $CH{=}CCH_3$). Anal. Calcd for $C_{12}H_{24}O_4Si$: C, 55.35; H, 9.29. Found: C, 55.49; H, 9.43.

2(*R*)- and 2(*S*)-Carbomethoxy-2-[2,5-dihydro-5(*S*)-([2-(trimethylsilyl)ethoxymethoxy]methyl)-3-methyl-2(*R*)-furyl]-3(*R*),4(*S*)-(dimethylmethylenedioxy)-5(*S*)-(benzyloxy)tetrahydrofuran (21). To a stirred solution of 4.27 g (16.37 mmol) of the glycal **18**, 190 mg (1.55 mmol) of 4-(dimethylamino)pyridine, and a crystal of 1,10 phenanthroline in 53 mL of THF at −78 °C was added dropwise 7.80 mL (16.37 mmol) of a 2.10 M solution of *n*-butyllithium in hexane. To this solution was then added over 5 min a solution of 5.12 g (16.37 mmol) of the crystallized acid chloride of **20** in 35 mL of THF at −78 °C. After 15 min, this solution was added over 5 min via a cannula to a rapidly stirred solution of LDA, trimethylchlorosilane, and HMPA in THF at −110 to −115 °C. [The latter solution was prepared by the addition of 27 mL of HMPA to 22.92 mmol of LDA in 143 mL of THF at −78 °C. This solution was then cooled to −110 to −115 °C, and then a solution of 10.0 mL (57.29 mmol of Me_3SiCl) of the supernatant centrifugate from a 3:1 mixture of trimethylchlorosilane and triethylamine in 33 mL of THF at −78 °C was added over 3 min. The external temperature ($MeOH/N_2$ taffylike slush) was maintained at −115 to −120 °C, and the THF mixture appeared to be viscous and heterogeneous. Five minutes after the addition of the Me_3SiCl was complete, the addition of the ester solution was begun, and the external temperature was maintained between −115 and −120 °C.] The resulting solution was then stirred 7 min at −100 °C, 7 min at −78 °C, and then allowed to warm to room temperature. After 15 h, the solution was cooled to 0 °C, treated with 40 mL of 1% aqueous HCl for 20 min, and then diluted with 1 L of ether and washed with 400 mL of saturated aqueous NaCl acidified to ~pH 2. The aqueous phase was extracted with an additional 250 mL of ether, and the combined organic extracts were dried ($MgSO_4$), concentrated under reduced pressure, dissolved in 300 mL of ether, and treated with excess ethereal diazomethane. Removal of the solvent under reduced pressure and chromatography of the residue on 700 g of silica gel with 3:7 ether/petroleum ether afforded 7.48 g (83%) of an unseparated 1:1.5 (^1H NMR) mixture of the methyl esters **21** as a light yellow oil: R_f = 0.32, 0.31 (silica gel, 4:6 ether/petroleum ether); evaporative distillation 195 °C (0.001 mmHg). Anal. Calcd for $C_{28}H_{42}O_9Si$: C, 61.07; H, 7.69. Found: C, 61.19; H, 7.57. Rechromatography of a portion of this material afforded first the minor diastereomer (the precursor to the aldehyde **23**) as a colorless oil: R_f = 0.32 (silica gel, 4:6 ether/petroleum ether); ^1H NMR (500 MHz, $CDCl_3$) 0.02 (s, 9 H, $(CH_3)_3Si$), 0.91 (m, 2 H, $TMSCH_2$), 1.35, 1.49 (2 s, 6 H, $(CH_3)_2C$), 1.99 (br s, 3 H, $CH_3C{=}C$ h), 3.25, 3.46 (2 dd, 2 H, J = 11.5, J' = 6 Hz, $CHCH_2O$), 3.50 (s, 3 H, OCH_3), 3.56 (m, 2 H, $TMSCH_2CH_2O$), 4.42, 4.66 (2 d, 2 H, J = 12 Hz, $C_6H_5CH_2$), 4.61, 4.64 (2 d, 2 H, J = 6.5 Hz, OCH_2O), 4.63 (d, 1 H, J = 6 Hz, C(14)–H), 4.85 (m, 1 H, $OCHCH_2$), 5.04 (br s, 1 H, C(17)—H), 5.10 (s, 1 H, OCHO), 5.49 (q, 1 H, J = 2 Hz, $CH_3C{=}CH$), 5.52 (d, 1 H, J = 6 Hz, C(15)—H), 7.23–7.33 (m, 5 H, C_6H_5).

There was then eluted the major diastereomer (the precursor to the aldehyde **22**) as a colorless oil: R_f = 0.31 (silica gel, 4:6 ether/petroleum ether); ^1H NMR (500 MHz, $CDCl_3$) δ 0.00 (s, 9 H, $(CH_3)_3Si$), 0.89 (m, 2 H, $TMSCH_2$), 1.31, 1.43 (2 s, 6 H, $(CH_3)_2C$), 1.69 (br s, 3 H, $CH_3C{=}CH$), 3.41 (d, 1 H, J = 10, J' = 4.5 Hz, $OCHCHHO$), 3.55 (m, 2 H, $TMSCH_2CH_2$), 3.61 (d, 1 H, J = 10, J' = 8 Hz, $OCHCHHO$), 3.80 (s, 3 H, OCH_3), 4.50, 4.54 (2 d, 2 H, J = 7 Hz, OCH_2O), 4.59, 4.78 (2 d, 2 H, J = 12 Hz, $C_6H_5CH_2$), 4.64 (dd, 1 H, J = 6, J' = 3 Hz, C(14)—H), 4.81 (m, 1 H, $OCHCH_2O$), 5.07 (d, 1 H, J = 6 Hz, C-(15)—H), 5.28 (br s, 1 H, C(17)—H), 5.38 (d, 1 H, J = 3 Hz, OCHO), 5.46 (q, 1 H, J = 2 Hz, $CH_3C{=}CH$), 7.25–7.36 (m, 5 H, C_6H_5).

2(*R*)- and 2(*S*)-(Hydroxymethyl)-2-[2,5-dihydro-5(*S*)-([2-(trimethylsilyl)ethoxymethoxy]methyl)-3-methyl-2(*R*)-furyl]-3(*R*),4(*S*)-(dimethylmethylenedioxy)-5(*S*)-(benzyloxy)tetrahydrofuran. To a stirred solution of 14.34 g (26.03 mmol) of a 1.5:1 mixture of the methyl esters **21** in 250 mL of ether at 0 °C was cautiously added 800 mg (21.1 mmol) of lithium tetrahydridoaluminate. After 1 h, the reaction mixture was sequentially treated with 0.8 mL of water, 0.8 mL of 15% aqueous sodium hydroxide, 2.4 mL of water, and then 5 g of $MgSO_4$. Filtration and then evaporation of the solvent at reduced pressure gave 13.04 g (96%) of a mixture of the primary alcohols as a colorless oil. Chromatography of a portion of this material on silica gel with 1:1 ether/petroleum ether afforded first the minor diastereomer (the precursor to the aldehyde **23**) as a colorless oil: R_f = 0.21 (silica gel, 1:1 ether/petroleum ether); evaporative distillation 190–195 °C (0.005 mmHg); $[\alpha]^{22}_D$ +16.3 (c 1.80, $CHCl_3$); IR ($CHCl_3$) 3440, 3000, 2950, 2870, 1450, 1380, 1370, 1250, 1160, 1070, 860, 840 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.05 (s, 9 H, $(CH_3)_3Si$), 1.38, 1.53 (2 s, 6 H, $(CH_3)_2C$), 1.88 (br s, 3 H, $CH_3C{=}CH$), 5.17 (s, 1 H, OCHO), 5.52 (br s, 1 H, $CH_3C{=}CH$), 7.32 (s, 5 H, C_6H_5). Anal. Calcd for $C_{27}H_{42}O_8Si$: C, 62.04; H, 8.10. Found: C, 62.05; H, 8.03.

There was then eluted the major diastereomer (precursor to the aldehyde **22**) as a colorless oil: R_f = 0.15 (silica gel, 1:1 ether/petroleum ether); evaporative distillation 185–190 °C (0.001 mmHg); $[\alpha]^{22}_D$ +8.6 (c 1.19, $CHCl_3$); IR ($CHCl_3$) 3500, 3000, 2950, 2860, 1450, 1380, 1370, 1250, 1160, 1025, 860, 845 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.00 (s, 9 H, $(CH_3)_3Si$), 1.30, 1.50 (2 s, 6 H, $(CH_3)_2C$), 1.88 (br s, 3 H, $CH_3C{=}CH$), 2.77 (t, 1 H, J = 7 Hz, CH_2OH), 5.20 (s, 1 H, OCHO), 5.47 (br s, 1 H, $CH_3C{=}CH$). Anal. Calcd for $C_{27}H_{42}O_8Si$: C, 62.04; H, 8.10. Found: C, 62.17; H, 8.13.

2(*R*)- and 2(*S*)-Formyl-2-[2,5-dihydro-5-(*S*)-([2-(trimethylsilyl)-ethoxymethoxy]methyl)-3-methyl-2(*R*)-furyl]-3(*R*),4(*S*)-(dimethyl-

methylenedioxy)-5(*S*)-(benzyloxy)tetrahdrofuran (22 and 23). To a stirred solution of 2.87 mL (32.9 mmol) of oxalyl chloride in 230 mL of dichloromethane at −78 °C was added over 5 min a solution of 2.92 mL (41.1 mmol) of Me_2SO in 23 mL of dichloromethane. After 15 min, a solution of 14.30 g (27.38 mmol) of a 1.5:1 mixture of the above alcohols in 70 mL of dichloromethane was added over 5 min to the reaction mixture. After 20 min, the reaction mixture was treated with 19.1 mL (137 mmol) of triethylamine, allowed to warm to room temperature, and then poured into 100 mL of saturated aqueous NaCl. The resulting mixture was extracted with two 200-mL portions of ether. The combined organic extracts were dried ($MgSO_4$) and then concentrated under reduced pressure. Flash chromatography of the residue on 700 g of silica gel with 3:7 ether/petroleum ether afforded first 7.80 g (54.7%) of the major aldehyde **22** as a colorless oil: R_f = 0.33 (silica gel, 3:7 ether/petroleum ether); evaporative distillation 190–195 °C (0.001 mmHg); $[\alpha]^{22}_D$ +58.5 (*c* 1.03, $CHCl_3$); IR ($CHCl_3$) 3000, 2960, 2870, 1735, 1455, 1485, 1475, 1250, 1155, 1085, 990, 860, 830 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.03 (s, 9 H, $(CH_3)_3Si$), 1.30, 1.45 (2 s, 6 H, $(CH_3)_2C$), 1.70 (br s, 3 H, $CH_3C{=}CH$), 4.67 (dd, 1 H, J = 6, J' = 2 Hz, C(14)—H), 5.09 (d, 1 H, J = 6 Hz, C(15)—H), 5.37 (d, 1 H, J = 2 Hz, OCHO), 5.52 (br s, 1 H, $CH_3C{=}CH$), 7.33 (s, 5 H, C_6H_5), 9.62 (s, 1 H, C(0)H). Anal. Calcd for $C_{27}H_{40}O_8Si$: C, 62.28; H, 7.74. Found: C, 62.34; H, 7.64.

There was then eluted 5.29 g (37.1%) of the minor aldehyde **23** as a colorless oil: R_f = 0.18 (silica gel, 3:7 ether/petroleum ether); evaporative distillation; 190–195 °C (0.001 mmHg); $[\alpha]^{23}_D$ +27.2° (*c* 1.66, $CHCl_3$); IR ($CHCl_3$) 3000, 2950, 2870, 1730, 1455, 1385, 1375, 1240, 1160, 1020, 865, 840 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.03 (s, 9 H, $(CH_3)_2Si$), 1.37, 1.50 (2 s, 6 H, $(CH_3)_2C$), 2.00 (br s, 3 H, $CH_3C{=}CH$), 5.15 (s, 1 H, OCHO), 5.30 (d, 1 H, J = 6 Hz, C(15)—H), 5.57 (br s, 1 H, $CH_3C{=}CH$), 7.30 (s, 5 H, C_6H_5), 9.42 (s, 1 H, C(0)H). Anal. Calcd for $C_{27}H_{40}O_8Si$: C, 62.28; H, 7.74. Found: C, 62.36; H, 7.70.

2(*R*)-Vinyl-2-[2,5-dihydro-5(*S*)-([2-(trimethylsilyl)ethoxymethoxy]methyl)-3-methyl-2(*R*)-furyl]-3(*R*),4(*S*)-(dimethylmethylenedioxy)-5-(*S*)-(benzyloxy)tetrahydrofuran. To a stirred suspension of 3.765 g (10.54 mmol) of methyltriphenylphosphonium bromide in 77 mL of THF at −78 °C was added 4.79 mL (10.06 mmol) of a 2.10 M solution of *n*-butyllithium in hexane. The resulting mixture was stirred 1 h at room temperature and then recooled to −78 °C. A solution of 4.989 g (9.582 mmol) of the aldehyde **23** in 30 mL of THF was then added, and the resulting mixture was stirred at room temperature for 9 h and then quenched by the addition of 40 mL of saturated aqueous $NaHCO_3$. The reaction mixture was then poured into 100 mL of saturated aqueous NaCl and extracted with two 200-mL portions of ether. The combined organic extracts were dried ($MgSO_4$) and then concentrated under reduced pressure. Chromatography of the residue in 250 g of silica gel with 3:7 ether/petroleum ether afforded 4.76 g (95%) of the olefin as a colorless oil: R_f = 0.21 (silica gel, 3:7 ether/petroleum ether); evaporative distillation 220 °C (0.001 mmHg); $[\alpha]^{23}_D$ +51.7° (*c* 1.96, $CHCl_3$); IR ($CHCl_3$) 3000, 2950, 2870, 1385, 1375, 1250, 1160, 1080, 1020, 870, 840 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.05 (s, 9 H, $(CH_3)_3Si$), 1.40, 1.55 (2 s, 6 H, $(CH_3)_2C$), 1.85 (br s, 3 H, $CH_3C{=}CH$), 5.17 (s, 1 H, OCHO), 5.52 (br s, 1 H, $CH_3C{=}CH$), 7.30 (s, 5 H, C_6H_5). Anal. Calcd for $C_{28}H_{42}O_7Si$: C, 64.83; H, 8.16. Found: C, 64.87; H, 8.04.

2(*S*)-Vinyl-2-[2,5-dihydro-5(*S*)-([2-(trimethylsilyl)ethoxymethoxy]methyl)-3-methyl-2(*R*)-furyl]-3(*R*),4(*S*)-(dimethylmethylenedioxy)-5-(*S*)-(benzyloxy)tetrahydrofuran. By the procedure described above, 1.28 g (3.59 mmol) of methyltriphenylphosphonium bromide in 26 mL of THF and 1.63 mL (3.42 mmol) of a 2.10 M solution of *n*-butyllithium in hexane, and then 1.70 g (3.26 mmol) of the aldehyde **22** in 10 mL of THF afforded, after chromatography on 120 g of silica gel with 3:7 ether/petroleum ether, 1.62 g (95%) of the olefin as a colorless oil: R_f = 0.14 (silica gel, 2:8 ether/petroleum ether); evaporative distillation 210 °C (0.001 mmHg); $[\alpha]^{23}_D$ −17° (*c* 0.86, $CHCl_3$); IR ($CHCl_3$) 3000, 2960, 2880, 1450, 1385, 1375, 1250, 1090, 1030, 870, 840 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.03 (s, 9 H, $(CH_3)_3Si$), 1.32, 1.43 (2 s, 6 H, $(CH_3)_2C$), 1.83 (br s, 3 H, $CH_3C{=}CH$), 5.22 (s, 1 H, OCHO), 7.32 (s, 5 H, C_6H_5). Anal. Calcd for $C_{28}H_{42}O_7Si$: C, 64.83; H, 8.16. Found: C, 64.54; H, 7.79.

2(*R*)-Ethyl-2-[5(*S*)-([2-(trimethylsilyl)ethoxymethoxy]methyl)-3(*R*)-and 3(*S*)-methyl-2(*R*)-tetrahydrofuryl]-3(*R*),4(*S*)-(dimethylmethylenedioxy)-5(*S*)-(benzyloxy)tetrahydrofuran. To a stirred solution of 546 mg (1.05 mmol) of the olefin derived from aldehyde **23** was added 100 mg of 5% platinum on carbon (Alfa). The reaction mixture was stirred at room temperature under 1 atm of hydrogen for 10 h. The catalyst was then removed by filtration and washed with five 20-mL portions of dichloromethane. The combined filtrates were concentrated under reduced pressure, and chromatography of the residue on 120 g of silica gel with 75:425 and then 3:7 ether/petroleum ether afforded first 412 mg (76%) of an alkane (the precursor to the acid **25**) as a colorless oil: R_f = 0.20 (silica gel, 2:8 ether/petroleum ether); $[\alpha]^{22}_D$ +52.1° (*c* 0.995, $CHCl_3$); IR ($CHCl_3$) 3000, 2940, 2880, 1455, 1385, 1375, 1250, 1030, 860, 830 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.01 (s, 9 H, $(CH_2)_3C$), 1.00 (t, 3 H, J = 6 Hz, CH_3CH_2), 1.10 (d, 3 H, J = 7 Hz, CH_3CH), 1.30, 1.48 (2 s, 6 H, $(CH_3)_2C$), 2.50 (m, 1 H, CH_3CH), 3.83 (d, 1 H, J = 4.5 Hz, C(17)–H), 5.10 (s, 1 H, OCHO), 7.33 (s, 5 H, C_6H_5). Anal. Calcd for $C_{28}H_{46}O_7Si$: C, 64.33; H, 8.87. Found: C, 64.20; H, 8.82.

There was then eluted 51 mg (9.4%) of an epimeric alkane: R_f = 0.17 (silica gel, 2:8 ether/petroleum ether); ^1H NMR ($CDCl_3$) δ 0.05 (s, 9 H, $(CH_3)_3Si$), 1.02 (t, 3 H, J = 6 Hz, CH_3CH_2), 1.21 (d, 3 H, J = 7 Hz, CH_3CH), 1.35, 1.52 (2 s, 6 H, $(CH_3)_2C$), 4.02 (d, 1 H, J = 6 Hz, C(17)–H), 5.12 (s, 1 H, OCHO), 7.33 (s, 5 H, C_6H_5).

2(*S*)-Ethyl-2-[5(*S*)-([2-(trimethylsilyl)ethoxymethoxy]methyl)-3(*R*)-and 3(*S*)-methyl-2(*R*)-tetrahydrofuryl]-3(*R*),4(*S*)-(dimethylmethylenedioxy)-5(*S*)-(benzyloxy)tetrahydrofuran. A suspension of W-2 Raney nickel in ethanol was allowed to settle in a centrifuge tube. The catalyst occupied 2 mL before centrifugation. After centrifugation, it occupied 1.5 mL. The supernatant ethanol was removed, the catalyst resuspended in 8.0 mL of ethyl acetate and centrifuged, and the supernatant then removed. The catalyst was washed 2 more times in this manner and was then added as a suspension in 3.5 mL of ethyl acetate to a solution of 1.15 g (2.22 mmol) of the olefin derived from the aldehyde **22** in 20 mL of ethyl acetate. The reaction mixture was stirred at room temperature under 1 atm of hydrogen for 12 h. The catalyst was then removed by filtration and washed with three 25-mL portions of ethyl acetate. The combined filtrates were concentrated under reduced pressure, and chromatography of the residue on 200 g of silica gel with 1:9 and then 2:8 ether/petroleum ether afforded first 110 mg (9.5%) of the minor epimer as a colorless oil: R_f = 0.28 (silica gel, 2:8 ether/petroleum ether); ^1H NMR ($CDCl_3$) δ 0.05 (s, 9 H, $(CH_3)_3Si$), 1.02 t 3 H, J = 7 Hz, CH_3CH_2), 1.12 (d, 3 H, J = 7 Hz, CH_3CH), 1.33, 1.48 (2 s, 6 H, $(CH_3)_2C$), 3.72 (d, 1 H, J = 5 Hz, C(17)–H), 5.08 (s, 1 H, OCHO), 7.32 (s, 5 H, C_6H_5). There was then eluted 931 mg (80%) of the major epimer (the precursor to the acid **24**) as a colorless oil: R_f = 0.23 (2:8 ether/petroleum ether); $[\alpha]^{23}_D$ +48.2° (*c* 1.18, $CHCl_3$); IR ($CHCl_3$) 3000, 2950, 2880, 1460, 1450, 1380, 1370, 1240, 865, 835, cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.03 (s, 9 H, $(CH_3)_3Si$), 1.00 (t, 3 H, J = 7 Hz, CH_3CH_2), 1.22 (d, 3 H, J = 7 Hz, CH_3CH), 1.33, 1.50 (2 s, 6 H, $(CH_3)_2C$), 3.87 (d, 1 H, J = 6 Hz, C(17)–H), 5.13 (d, 1 H, J = 2 Hz, OCHO), 7.32 (s, 5 H, C_{H5}). Anal. Calcd for $C_{28}H_{46}O_7Si$: C, 64.33; H, 8.87. Found: C, 64.31; H, 8.83. Hydrogenation under similar conditions using 5% platinum on carbon produced a 1:3 mixture of the above alkanes.

2(*R*)-Ethyl-2-[5(*S*)-(hydroxymethyl)-3(*S*)-methyl-2(*R*)-tetrahydrofuryl]-3(*R*),4(*S*)-(dimethylmethylenedioxy)-5(*S*)-(benzyloxy)tetrahydrofuran. A stirred solution of 3.20 g (6.12 mmol) of the above alkane (the precursor to the acid **25**) and 7.1 g (47 mmol) of dry CsF in 31 mL of HMPA was heated at 125 °C for 24 h. The cooled reaction mixture was poured into 100 mL of water, extracted with 200 mL of ether, and then washed with 100 mL of saturated aqueous NaCl. The organic phase was dried ($MgSO_4$) and then concentrated under reduced pressure. Flash chromatography of the residue on 200 g of silica gel with 6:4 ether/petroleum ether afforded 2.38 g (99%) of the alcohol as a colorless oil: R_f = 0.17 (silica gel, 1:1 ether/petroleum ether); $[\alpha]^{22}_D$ +65.8° (*c* 0.880, $CHCl_3$); IR ($CHCl_3$) 3500, 3000, 2950, 2880, 1455, 1385, 1375, 1270, 1010, 870 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.98 (t, 3 H, J = 7 Hz, CH_3CH_2), 1.10 (d, 3 H, J = 7 Hz, CH_3CH), 1.28, 1.48 (2 s, 6 H, $(CH_3)_2C$), 3.83 (d, 1 H, J = 4 Hz, C(17)–H), 5.12 (s, 1 H, OCHO), 7.32 (s, 5 H, C_6H_5). Anal. Calcd for $C_{22}H_{32}O_6$: C, 67.32; H, 8.21. Found: C, 67.29; H, 8.15.

2(*S*)-Ethyl-2-[5(*S*)-(hydroxymethyl)-3(*S*)-methyl-2(*R*)-tetrahydrofuryl]-3(*R*),4(*S*)-(dimethylmethylenedioxy)-5(*S*)-(benzyloxy)tetrahydrofuran. A stirred solution of 5.65 g (10.8 mmol) of the above alkane (the precursor to the acid **24**) and 12.5 g (82.2 mmol) of dry CsF in 555 mL of HMPA was heated at 125 °C for 27 h. The cooled solution was poured into 100 mL of water and extracted with two 200-mL portions of ether. The combined organic extracts were washed with 100 mL of saturated aqueous NaCl, dried ($MgSO_4$), and then concentrated under reduced pressure. Flash chromatography of the residue on 250 g of silica gel with 1:1 ether/petroleum ether afforded 4.20 g (99%) of the alcohol as a colorless oil: R_f = 0.26 (silica gel, 1:1 ether/petroleum ether); evaporative distillation 160 °C (0.005 mmHg); $[\alpha]_D$ +124° (*c* 0.935, $CHCl_3$); IR ($CHCl_3$) 3450, 3000, 2940, 2880, 1460, 1450, 1380, 1370, 1240, 1205, 1015, 875, 830 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.98 (t, 3 H, J = 7 Hz, CH_3CH_2), 1.18 (d, 3 H, J = 6 Hz, CH_3CH), 1.32, 1.45 (2 s, 6 H, $(CH_3)_2C$), 3.80 (d, 1 H, J = 5 Hz, C(17)–H), 5.12 (d, 1 H, J = 2 Hz, OCHO), 7.32 (s, 5 H, C_6H_5). Anal. Calcd for $C_{22}H_{32}O_6$: C, 67.32; H, 8.21. Found: C, 67.24; H, 8.22.

2(*R*)-Ethyl-2-[5(*S*)-carboxy-3(*S*)-methyl-2(*R*)-tetrahydrofuryl]-3-(*R*),4(*S*)-(dimethylmethylenedioxy)-5(*S*)-(benzyloxy)tetrahydrofuran (25) and Methyl Ester. To a stirred solution of 0.33 mL (3.8 mmol) of oxalyl chloride in 17 mL of dichloromethane at −78 °C was added a

solution of 0.36 mL (5.1 mmol) of dimethyl sulfoxide in 5 mL of dichloromethane. After 15 min, a solution of 1.00 g (2.55 mmol) of the above alcohol (the precursor to the acid **25**) in 8.5 mL of dichloromethane was added to the reaction mixture. After 20 min, the reaction mixture was treated with 1.78 mL (12.7 mmol) of trimethylamine, allowed to warm to room temperature, and then poured into 100 mL of 50% saturated aqueous NaCl. The resulting mixture was extracted with two 150-mL portions of ether, and the combined organic extracts were dried ($MgSO_4$) and then concentrated under reduced pressure. To a stirred solution of the residue in 17 mL of ethanol and 1.30 g (7.64 mmol) of $AgNO_3$ in 1.80 mL of water was added, over 15 min, a solution of 1.01 g (15.28 mmol) of 85% KOH in 16.8 mL of water. After 30 min at room temperature, the solution was filtered and the precipitate was washed with three 10-mL portions of 6% aqueous KOH. The combined filtrates were cooled to 0 °C, 200 mL of ether was added, and the stirred mixture was carefully acidified to pH 2 with concentrated aqueous HCl. The ether phase was separated and the aqueous phase was extracted with two 200-mL portions of ether. The combined organic extracts were dried ($MgSO_4$) and then concentrated under reduced pressure. Chromatography of the residue on 50 g of silica gel with ether afforded 984 mg (95%) of the acid **25** as a viscous, light-yellow oil: $R_f = 0.06$ (silica gel, 4:6 ether/petroleum ether). A portion of this material was treated with excess ethereal diazomethane. Evaporation of solvent at reduced pressure and chromatography of the residue on silica gel with 3:7 ether/petroleum ether afforded the methyl ester of **25** as a colorless oil: $R_f = 0.36$ (silica gel, 4:6 ether/petroleum ether); evaporative distillation 170 °C (0.005 mmHg); $[\alpha]^{27}_D$ +57.6° (*c* 1.83, $CHCl_3$); IR ($CHCl_3$) 3000, 2950, 2880, 1750, 1460, 1385, 1375, 1100, 1070, 1015, 870 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.03 (t, 3 H, CH_3CH_2), 1.12 (d, 3 H, CH_3CH), 1.33, 1.50 (2 s, 6 H, $(CH_3)_2C$), 3.73 (s, 3 H, OCH_3), 3.92 (d, 1 H, $J = 4$ Hz, C(17)–H), 5.07 (s, 1 H, OCHO), 7.33 (s, 5 H, C_6H_5). Anal. Calcd for $C_{23}H_{27}O_7$: C, 65.70; H, 7.67. Found: C, 65.77; H, 7.65. Treatment of this ester with lithium tetrahydridoaluminate in ether at 0 °C produced the starting alcohol.

2(*S*)-Ethyl-2-[5(*S*)-carboxy-3(*S*)-methyl-2(*R*)-tetrahydrofuryl]-3-(*R*),4(*S*)-(dimethylmethylenedioxy)-5(*S*)-(benzloxy)tetrahydrofuran (24) and Methyl Ester. By the procedure described above for the acid **25**, 195 μL (2.24 mmol) of oxalyl chloride in 10 mL of dichloromethane, 211 μL (2.98 mmol) of dimethylsulfoxide in 5.0 mL of dichloromethane, 585 mg (1.49 mmol) of the alcohol (the precursor to the acid **24**), and then dissolution of the crude aldehyde in 10 mL of ethanol, 0.76 g (4.47 mmol) of $AgNO_3$ in 1.1 mL of water, and addition of 0.59 g (8.95 mmol) of 85% KOH in 9.8 mL of water, afforded, after chromatography on 40 g of silica gel with ether, 567 mg (93%) of the acid **24** as a viscous, colorless oil: $R_f = 0.10$ (silica gel, 4:6 ether/petroleum ether). A portion of this material was treated with excess ethereal diazomethane. Evaporation of the solvent at reduced pressure and chromatography of the residue on silica gel with 3:7 ether/petroleum ether afforded the methyl ester of the acid **24** as a colorless oil: $R_f = 0.27$ (silica gel, 4:6 ether/petroleum ether); evaporative distillation 170 °C (0.005 mmHg); $[\alpha]^{23}_D$ +61.9° (*c* 1.46, $CHCl_3$); IR ($CHCl_3$) 3000, 2950, 2880, 1730, 1450, 1440, 1385, 1375, 1270, 1075, 875 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.00 (t, 3 H, $J = 7$ Hz, CH_3CH_2), 1.23 (d, 3 H, $J = 6$ Hz, CH_3CH), 1.33, 1.48 (2 s, 6 H, $(CH_3)_2C$), 3.47 (s, 3 H, OCH_3), 3.98 (d, 1 H, $J = 6$ Hz, C(17)–H), 5.12 (d, 1 H, $J = 2$ Hz, OCHO), 7.32 (s, 5 H, C_6H_5). Anal. Calcd for $C_{23}H_{32}O_7$: C, 65.70; H, 7.67. Found: C, 65.73; H, 7.72. Treatment of this ester with lithium tetrahydridoaluminate in ether at 0 °C produced the starting alcohol.

The Convergent Synthesis of Polyether Ionophore Antibiotics: An Approach to the Synthesis of the Monensin Tetrahydropyran–Bis(tetrahydrofuran) via the Ester Enolate Claisen Rearrangement and Reductive Decarboxylation[1]

Robert E. Ireland,* Daniel W. Norbeck,[2] Gretchen S. Mandel, and Neil S. Mandel[1b]

Contribution No. 7076 from the Chemical Laboratories, California Institute of Technology, Pasadena, California 91125, and the Department of Medicine, Medical College of Wisconsin, Research Services, Veterans Administration Hospital, Wood, Wisconsin 53193.
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Abstract: The monensin tetrahydropyran equivalent **22** is prepared from D-fructose and then joined to the monensin bis(tetrahydrofuran) equivalent **24a** via the ester enolate Claisen rearrangement. Methodology for the radical induced, reductive decarboxylation of the resulting acid **26a** is described. Anomeric stabilization of the intermediate tetrahydrofuran-2-yl radical is an important factor in the stereochemical outcome of this process. Reduction of 1-chloro-2,3-*O*-isopropylidene furanoid and pyranoid carbohydrate derivatives with lithium di-*tert*-butylbiphenyl affords the corresponding glycals in high yield.

Through the ester enolate Claisen rearrangement, difficult carbon–carbon bond constructions can be realized intramolecularly after the two reaction partners have been joined intermolecularly in a relatively easy esterification. Application of this inherently convergent process to furanoid and pyranoid carboxylic acids and glycals has led to a toal synthesis of lasalocid A[3] and its enantiomer[4] in sufficient quantities for biological testing. In order to explore this strategy further, we have developed routes ot additional subunits for polyether synthesis as reported in the preceding two papers in this issue. In general, the substitution pattern of the ionophore framework nicely accommodates the functionality engendered by the ester enolate Claisen rearrangement. The resulting olefin can, for example, be hydrogenated or hydroborated, and the carboxyl residue can usually be reduced to a methyl or ethyl group. When this is not the case, the convergent union of

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