The Convergent Synthesis of Polyether Ionophore Antibiotics: The Synthesis of the Monensin Spiroketal

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Abstract: The monensin spiroketal 2, a versatile intermediate for the synthesis of polyether ionophore antibiotics, is prepared from D-fructose. Key steps include the ester enolate Claisen rearrangement of a glycal propionate, expansion of a furanoid to a pyranoïd ring, and the acid-catalyzed equilibration of a bicyclic ketal to a spiroketal. An alternative approach, entailing the hetero-Diels-Alder condensation of the exocyclic enol ether 15 with acrolein, is thwarted by facile isomerization to the endocyclic enol ether 18.

The complex chemistry and potent biological activity of the polyether antibiotics have engaged widespread interest. As ionophores, these compounds possess a striking ability to perturb ionic gradients by catalytically transporting cations across lipid barriers. While optimal membrane and ion selectivity remain elusive goals, the commercial use of monensin for control of poultry coccidiosis and enhancement of ruminant feed utilization have encouraged intensive efforts in the isolation and study of these compounds. Several have demonstrated potential in human medicine, particularly as cardiovascular agents. In addition to their diverse biological activity, these antibiotics display a formidable molecular complexity, and the attendant challenge of total synthesis has been taken up by numerous research groups.

Structurally, most of the polyether ionophores feature linear chains of substituted tetrahydropyranyl and tetrahydrofuran rings. Comparison reveals that nearly all these rings recur with high frequency, often in stereochemically indistinguishable sequences. The unified biosynthetic pathway proposed by Cane, Celmer, and Westley underscores the structural identities and combinatorial diversity of these antibiotics.

We have recently developed a versatile, building-block approach to the polyethers in which prefunctionalized furanoid and tetrahydrofuran rings are joined via the ester enolate Claisen rearrangement. This work has culminated in the total synthesis of lasalocid A and its enantiomer from readily available carbohydrates. In this and the following two papers in this issue, we report the preparation of several additional subunits for the synthesis of naturally occurring polyethers and potentially informative analogues.

Serving as rigid bands in the polyether backbone, spirotetals play a critical role in establishing the coordination geometry necessary for ion complexation. Since one of the spiro oxygens usually acts as a ligand as well, spirotetals are prominent features of the polyether class. Monensin spirotetal is a particularly attractive synthetic target, as it occurs in at least eight other ionophores. Disconnection of the C2,3 and C12,13 bonds of monensin generates the common structural subunit 2, and the results of an aldol and ester enolate Claisen transform are shown in Scheme I.

Our synthetic plan for this polyether building block developed out of model studies which demonstrated the value of the hetero-Diels-Alder condensation in the construction of spirotetals (Scheme II). Although the rigidity of the spirotetal system itself can mediate control of relative stereochemistry, in this...
instance we planned to use the bicyclic ketal 11 for this purpose. Conceptually, a 2,4-dideoxy-2-methyl pyranoid glycal is an appealing starting material for this modified C-glycoside. However, the problems associated with deoxygenating a hexopyranose at the 4 position and the rarity of branched carbohydrates precluded Simmons-Smith cyclopropanation, the incipient "4-deoxypyranose" carbon was introduced without complication into the carbon backbone at C7. At each step, we confronted three problems: expansion of a furanoid to a pyranoid ring; stereoselective oxygenation of the carbon backbone at C4; reduction of the ketone oxidation state at C9, and the standing in chloroform, 7 was quantitatively converted to the corresponding furan. The monensin numbering system is used throughout this discussion for clarity.

(24) Ireland, R. E.; et al., ref 8b.
(28) Cyclopropanes 9 and 10 were both obtained as a single diastereomer; carbene addition presumably occurred from the conformational face of bicyclooctanenes 7 and 8.
Monensin Spiroketal Synthesis

Scheme III. Synthesis of the Bicyclic Ketal 11

J. Am. Chem. Soc., Vol. 107, No. 11, 1985 3273

Scheme IV. Hetero-Diels-Alder Approach to the Spiroketal 2


(30) The conformation of the bicyclic ketal 11 depicted is supported by 90-MHz NMR. While the C4 proton occurs in the expected 2.1-2.4 ppm range as a multiplet, the C4 methyl group occurs as a doublet at 0.75 ppm. We attribute this upfield shift to shielding by the olefin. The effect is more dramatic in the C4 epimer 12. Here the C4 methyl group has the same chemical shift as the C4 hydrogen and occurs as a singlet at 1.37 ppm.

(31) Concentrated perchloric acid (62%) is essentially a tribromide, and the minimal amount of water present in the reaction no doubt enhances the effective acidity. Although ring expansion actually occurs faster than MOM removal under these conditions, the protecting group must be hydrolyzed prior to rearrangement by treatment with aqueous HCl in acetonitrile. Attempts to do so afterward resulted in decomposition. The presence of a nonucleophilic counterion also appeared to be essential, as concentrated HCl in acetonitrile caused degradation.


(36) The structure of 15 was confirmed by conversion to the aldehydes 19 via isomerization, hydroboration, acetylation, deborylation, and Swern oxidation. All compounds had satisfactory spectra and combustion analyses. Although the isomeric exocyclic enol ether 16 could not be consistently isolated, NMR analysis of the crude reaction mixture indicated a 3:1 mixture of 15 and 16.
Scheme V. Thermodynamic Equilibration to the Monensin Spiroketal

Two factors conspired to thwart the hetero-Diels-Alder reaction we had envisioned. First, isomerization to the endocyclic olefin 18 was incredibly facile, with a half-life of no more than 10 min in THF at 55 °C in base-washed glassware. Although no isomerization was detected at this temperature after several hours when either pyridine or triethylamine were used as a solvent, these and even the hindered base 4-hydroxy-2,2,6,6-tetramethylpiperidine polymerized acrolein at room temperature. Furthermore, although good yields of adduct were obtained by allowing 2 equiv of acrolein for a few days, the use of acrolein as a solvent for optical rotations, was filtered through neutral alumina as a solvent for optical rotations. Syringes and reaction flasks were dried at least 12 h in an over (120-140 °C) and cooled in a dessicator over anhydrous CaSO₄, prior to use. If feasible, reaction flasks were also flame-dried in vacuo.

Methyl 2(R)- and 2(S)-2,5-Dihydro-5-(S)-(methylthio)methyl)-3-methyl-2(R)-furylpropionate (5 and 6). To a stirred solution of 2.65 g (15.2 mmol) of the glycal 42 in 50 mL of THF at -78 °C was added 6.43 mmol of a 2.36 M solution of n-butyllithium in hexane, and then after 5 min, 1.37 mmol (15.8 mmol) of propionyl chloride was added. After 10 min at 0 °C, the solution was recooled to -78 °C and added dropwise to a stirred solution of 17.5 mmol of LDA in 27 mL of THF and 11 mL of HMPO at -78 °C. After 10 min, the reaction


(39) That the C723 hydrogen of bicyclic ketal


(43) In order of increasing polarity, the silyl ethers were obtained in a ratio of 7:4:2:1:1:1:1.0. As expected on the basis of these results, the major compound was shown to bear the same configuration at the carbethoxy carbon as the silyl ether from the ketal with pyridinium p-toluenesulfonate in chloroform. The silyl ethers of intermediate polarity were also interconvertible.


(45) Reference 8c.
mixture was treated with 4.57 mL (26.3 mmol of Me3SiCl) of the subsequent from a 3:1 mixture of trimethylchlorosilane and triethylamine. After 3 h at room temperature, the reaction mixture was diluted with 70 mL of 1 N aqueous NaOH and stirred for 15 min. The THF was evaporated at reduced pressure, and the aqueous layer was then washed with 100 mL of ether. The organic phase was counterextracted with five 20-mL portions of 1 N aqueous sodium hydroxide, and then the combined aqueous base was washed with five 20-mL portions of ether, acidified to pH 2 with concentrated aqueous HCl, and then extracted with six 50-mL portions of ether. The combined ethereal extracts were washed with 50 mL of saturated aqueous NaCl, dried (MgSO4), concentrated to 100 mL, and then treated with excess ethereal diazomethane. The solvent was removed under reduced pressure, and methyl ester 6 was obtained as a colorless oil: \( R_\text{f} = 0.26 \) (silica gel, 1:1 ether/petroleum ether); evaporative distillation 80–90 °C (0.005 mmHg); \( \delta_{\text{H}}^\text{1} = 7.33-7.36 \) (s, 2 H, CH3); \( \delta_{\text{H}}^\text{1} = 4.67-4.69 \) (2 H, OCH2). Anal. Calcd for C17H20O2: C, 70.17; H, 8.78. Found: C, 70.30; H, 8.95.

(5R,1R,4S)-1,4-Dimethyl-7-(((methoxymethyl)oxy) methyl)-2,6-dioxabicyclo[3.3.0]octane. To a stirred solution of 509 mg (1.80 mmol) of the methyl ester 5 in 12 mL of ether at 0 °C was added 68 mg (1.80 mmol) of lithium tetrahydridaluminate. After 1 h at room temperature, the mixture was cautiously treated with 70 mL of water, 70 mL of 15% aqueous NaOH, and then 210 mL of water. The mixture was filtered and then concentrated under reduced pressure. Chromatography of the residue on 20 g of silica gel with ether afforded 373 mg (96%) of the alcohol as a colorless oil: \( R_\text{f} = 0.23 \) (silica gel, 9:1 ether/petroleum ether); evaporative distillation 80–90 °C (0.005 mmHg); \( \delta_{\text{H}}^\text{1} = 7.33-7.36 \) (s, 2 H, CH3); \( \delta_{\text{H}}^\text{1} = 4.67-4.69 \) (2 H, OCH2). Anal. Calcd for C17H20O2: C, 70.17; H, 8.78. Found: C, 70.30; H, 8.95.

(5R,1R,4S)-1,4-Dimethyl-8(S)-ido-7-(((methoxymethyl)oxy)methyl)-2,6-dioxabicyclo[3.3.0]octane. To a stirred solution of 509 mg (1.80 mmol) of the alcohol described above, 7.06 g (30 mmol) of 1,5-diaza-7-azabicyclo[4.3.0]4-endo-5-ene was added, 50 mL of chloroform was added, and then 5 mL of cold water and 0.40 mL of aqueous NaOH were added. After 0.5 h at room temperature, the reaction mixture was vigorously stirred for 4 h at 0 °C and was then diluted with 60 mL of cold water and 100 mL of ether. The resulting mixture was filtered through celite. The organic layer was separated, washed with 60 mL of saturated aqueous NaCl, and dried (MgSO4). Removal of the solvent under reduced pressure and chromatography of the residue on 30 g of silica gel with 3:7 ether/petroleum ether afforded 997 mg (99% of the dichlorocyclopropane as a colorless oil: \( R_\text{f} = 0.40 \) (1:1 ether/petroleum ether); evaporative distillation 90–100 °C (0.005 mmHg); \( \delta_{\text{H}}^\text{1} = 7.33-7.36 \) (s, 2 H, CH3); \( \delta_{\text{H}}^\text{1} = 4.67-4.69 \) (2 H, OCH2). Anal. Calcd for C17H18Cl2O2: C, 49.58; H, 8.42. Found: C, 49.58; H, 8.41.

(5R,1R,4S)-1,4-Dimethyl-8(R)-ido-7-(((methoxymethyl)oxy)methyl)-2,6-dioxabicyclo[3.3.0]octane. To a stirred solution of 509 mg (1.80 mmol) of the alcohol described above, 7.06 g (30 mmol) of 1,5-diaza-7-azabicyclo[4.3.0]4-endo-5-ene was added, 50 mL of chloroform was added, and then 5 mL of cold water and 0.40 mL of aqueous NaOH were added. After 0.5 h at room temperature, the reaction mixture was vigorously stirred for 4 h at 0 °C and was then diluted with 60 mL of cold water and 100 mL of ether. The resulting mixture was filtered through celite. The organic layer was separated, washed with 60 mL of saturated aqueous NaCl, and dried (MgSO4). Removal of the solvent under reduced pressure and chromatography of the residue on 30 g of silica gel with 3:7 ether/petroleum ether afforded 997 mg (99% of the dichlorocyclopropane as a colorless oil: \( R_\text{f} = 0.40 \) (1:1 ether/petroleum ether); evaporative distillation 90–100 °C (0.005 mmHg); \( \delta_{\text{H}}^\text{1} = 7.33-7.36 \) (s, 2 H, CH3); \( \delta_{\text{H}}^\text{1} = 4.67-4.69 \) (2 H, OCH2). Anal. Calcd for C17H18Cl2O2: C, 49.58; H, 8.42. Found: C, 49.58; H, 8.41.

(5R,1R,4S)-1,4-Dimethyl-8(R)-ido-7-(((methoxymethyl)oxy)methyl)-2,6-dioxabicyclo[3.3.0]octane. To a stirred solution of 509 mg (1.80 mmol) of the alcohol described above, 7.06 g (30 mmol) of 1,5-diaza-7-azabicyclo[4.3.0]4-endo-5-ene was added, 50 mL of chloroform was added, and then 5 mL of cold water and 0.40 mL of aqueous NaOH were added. After 0.5 h at room temperature, the reaction mixture was vigorously stirred for 4 h at 0 °C and was then diluted with 60 mL of cold water and 100 mL of ether. The resulting mixture was filtered through celite. The organic layer was separated, washed with 60 mL of saturated aqueous NaCl, and dried (MgSO4). Removal of the solvent under reduced pressure and chromatography of the residue on 30 g of silica gel with 3:7 ether/petroleum ether afforded 997 mg (99% of the dichlorocyclopropane as a colorless oil: \( R_\text{f} = 0.40 \) (1:1 ether/petroleum ether); evaporative distillation 90–100 °C (0.005 mmHg); \( \delta_{\text{H}}^\text{1} = 7.33-7.36 \) (s, 2 H, CH3); \( \delta_{\text{H}}^\text{1} = 4.67-4.69 \) (2 H, OCH2). Anal. Calcd for C17H18Cl2O2: C, 49.58; H, 8.42. Found: C, 49.58; H, 8.41.

(5R,1R,4S)-1,4-Dimethyl-8(R)-ido-7-(((methoxymethyl)oxy)methyl)-2,6-dioxabicyclo[3.3.0]octane. To a stirred solution of 509 mg (1.80 mmol) of the alcohol described above, 7.06 g (30 mmol) of 1,5-diaza-7-azabicyclo[4.3.0]4-endo-5-ene was added, 50 mL of chloroform was added, and then 5 mL of cold water and 0.40 mL of aqueous NaOH were added. After 0.5 h at room temperature, the reaction mixture was vigorously stirred for 4 h at 0 °C and was then diluted with 60 mL of cold water and 100 mL of ether. The resulting mixture was filtered through celite. The organic layer was separated, washed with 60 mL of saturated aqueous NaCl, and dried (MgSO4). Removal of the solvent under reduced pressure and chromatography of the residue on 30 g of silica gel with 3:7 ether/petroleum ether afforded 997 mg (99% of the dichlorocyclopropane as a colorless oil: \( R_\text{f} = 0.40 \) (1:1 ether/petroleum ether); evaporative distillation 90–100 °C (0.005 mmHg); \( \delta_{\text{H}}^\text{1} = 7.33-7.36 \) (s, 2 H, CH3); \( \delta_{\text{H}}^\text{1} = 4.67-4.69 \) (2 H, OCH2). Anal. Calcd for C17H18Cl2O2: C, 49.58; H, 8.42. Found: C, 49.58; H, 8.41.
in 5.3 mL of HMPA was added 1.00 g (3.10 mmol) of tetra-n-
CH₂C=CH), 3.20, 4.12 (2 s, 2 H, CH₂CH₂OCH₂), 5.76 (br s, 1 H, CH₂C=CH). Anal. Calcd for C₂₁H₂₃O₄: C, 63.13; H, 8.83. Found: C, 63.21; H, 8.71.

(1R,2R,7S)-2,8-Dimethyl-5(S)-(hydroxymethyl)-6,9-dioxabicyclo-
[3.3.0]octane (13). To a stirred solution of 405 mg (1.77 mmol) of the alcohol in 6 mL of dichloromethane were added, every 2 h, 0.13 mL (1.14 mmol) of (2-chloroethyl)dimethylchlorosilane. After the mixture was heated at 45 °C for 9 h, it was allowed to cool and then poured into 75 mL of water. The resulting mixture was extracted with 200 mL of ether and then washed with 50 mL of saturated aqueous NaHCO₃. Although an analytical sample of the bromide could be stored safely at -20 °C.

(1R,2R,2S)-2,8-Dimethyl-5(S)-(hydroxymethyl)-6,9-dioxabicyclo-
[3.3.0]octane (14). To a stirred solution of 303 mg (1.14 mmol) of the above alcohol in 6 mL of dichloromethane were added, every 2 h, 0.13 mL (1.14 mmol) of (2-chloroethyl)dimethylchlorosilane and 0.20 mL (1.14 mmol) of N,N-diisopropylethylamine. After 10 h at room temperature, the reaction mixture was diluted with 200 mL of ether and then washed with 50 mL of saturated aqueous NaHCO₃. The combined aqueous phases were extracted with one 200-mL portion of ether and then four 70-mL portions of dichloromethane. The combined organic extracts were dried (MgSO₄) and then concentrated under reduced pressure. Chromatography of the residue on 20 g of silica gel with 2:3 ether/petroleum afforded 164 mg (62%) of the exocyclic enol ether as an oil. Rf = 0.11 (silica gel, 1:9 ether/petroleum ether); evaporative distillation 45-55 °C (0.005 mmHg); [α]D = +92.6° (c 2.32, CHCl₃); IR (CHCl₃) 2960, 2925, 2880, 1450, 1240, 1130, 1190, 990 cm⁻¹; 'H NMR (CDCl₃) 6 0.97, 1.12 (2 d, 6 H, CH₂CH₂), 1.67-2.07 (m, 2 H, 2CH₂CH₂), 3.33 (s, 3 H, OCH₃), 3.58, 3.65 (2 d, 2 H, CH₂Br), 3.85, 4.25 (2 s, 2 H, OCH₂), 7.13, 7.32 (2 s, 5 H, C₅H₅). In separate experiments, 'H NMR analysis of the crude reaction mixture indicated a 3:1 mixture of 13 and 14.

(2R)-1-(Benzylloxy)-2-(3-propyl)-3(R)-methyl-4(S)-(1-(2-methoxyethoxy)methyl)-6-methyleneoctahydropryan (15). To a stirred solution of 263 mg (0.745 mmol) of the bromide 14 in 20 mL of THF at -78 °C was added 0.59 mL (1.40 mmol) of a 2.38 M solution of n-butyllithium in hexane. After 3.5 h at -78 °C, 0.4 mL (3.36 mmol) of benzyl bromide (purified by filtration through alumina) was added, and then the solution was allowed to warm to 0 °C. One milliliter of HMPA was added to the mixture at 0 °C, and after 30 min the solution was concentrated under reduced pressure. Chromatography of the residue on 30 g of alumina (Activity III) with 1:3 ether/pentane afforded first 169 mg (62%) of the exocyclic enol ether 15 as a colorless oil: Rf = 0.07, 0.30 (silica gel, 1:1 ether/pentane ether). Silica gel causes isomerization to the endocyclic enol ether of the bromide 13 and is not useful in preparative work. 1H NMR (CDCl₃) 6 0.97, 1.12 (2 d, 6 H, J = 6 Hz, 2CH₂CH₂), 1.67-2.07 (m, 2 H, 2CH₂CH₂), 2.33 (m, 2 H, CH₂CH₂), 3.28 (s, 3 H, OCH₃), 3.89, 4.22 (2 s, 2 H, OCH₃), 4.42 (s, 2 H, CH₂OCH₂), 4.63 (s, 3 H, OCH₃), 7.13 (s, 5 H, C₅H₅).
169 mg (0.464 mmol) of the exocyclic enol ether 15 in 15 mL of THF was heated at 50 °C for 1 h. The cooled solution was then concentrated under reduced pressure, and chromatography of the residue on 20 g of alumina (Activity III) with 1:3 ether/petroleum ether afforded 169 mg (100%) of the endocyclic enol ether 18 as a colorless oil: \( R_f = 0.30 \) (silica gel, 1:3 ether/petroleum ether); evacuative distillation 145–155 °C (0.001 mmHg); \( [a]_D^0 = +142.2^\circ \) (c 0.79, CHCl₃); IR (CHCl₃) 3440, 3000, 2925, 2890, 1470, 1460, 1120, 1100, 1005, 835 cm⁻¹; \( ^1H \) NMR (CDCl₃) \( \delta = 0.97, 1.05, 1.63, 1.71 \) (4, 6, 3, 2 H, \( CH₂CH₃ \)); 3.43 (4, 7, 2 H, \( CH₂CH₂CH₃ \)); 4.34 (2, 1 H, \( CH=CH \)), 6.72 (2, 1 H, \( CH=CH \)). Anal. Calcd for \( C_{19}H_{22}O_4 \): C, 71.22; H, 8.81. Found: C, 71.25; H, 8.75. 'H NMR (cis isomer, CDCl₃) \( \delta = 0.90, 1.15 \) (2 d, 6 H, \( CH₂CH₂ \)), 3.43 (dd, 2 H, \( CH₂CH₂CH₂ \)), 4.02 (ddd, 1 H, \( CH=CH \)), 4.47 (2 d, 2 H, \( CH₂CH₂CH₂ \)), 7.34 (5, 5 H, \( CH₂CH₂CH₂ \)). Anal. Calcd for \( C_{19}H_{22}O_4 \): C, 69.29; H, 7.50. 'H NMR (trans isomer, CDCl₃) \( \delta = 0.88, 1.14 \) (2 d, 6 H, \( CH₂CH₂ \)), 3.38 (dd, 2 H, \( CH₂CH₂CH₂ \)), 4.02 (ddd, 1 H, \( CH=CH \)), 4.47 (2 d, 2 H, \( CH₂CH₂CH₂ \)), 7.31 (5, 5 H, \( CH₂CH₂CH₂ \)). Anal. Calcd for \( C_{19}H_{22}O_4 \): C, 70.12; H, 7.58.  

**Method 3** \( (5R, 5S, 6R)-4,6-Dimethyl-7-(S)-hydroxy-1-(S)-(1,1-dimethyl-ethyl)dihydroxilyloxy)-2,9-dioxabicyclo[3.3.1]nonane-3-one (23).** To a stirred solution of 21 mg (0.95 mmol) of the alcohol in 1 mL of ethyl acetate at 0 °C was added 69 mg (0.97 mmol) of dimethyl sulfoxide. After 10 min, a solution of 91 mg (0.404 mmol) of the alcohol 20 in 2 mL of dichloromethane was added to the reaction mixture. After 15 min, the reaction mixture was treated with 0.2 mL (2.0 mmol) of triethylamine and then allowed to warm to 0 °C. Methyl (triphenylphosphoranylidene) acetate (405 mg, 1.21 mmol) was then added, and after 10 min at room temperature, the reaction mixture was poured into 40 mL of saturated aqueous NaCl and extracted with two 100-mL portions of dichloromethane. The combined organic extracts were dried (MgSO₄) and then concentrated under reduced pressure. Chromatography of the residue on 25 g of silica gel with 1:1 ether/petroleum ether afforded 138 mg (99%) of a 9:5 trans/cis mixture (\( [a]_D^0 = -142.0^\circ \) (c 0.973, CHCl₃); IR (CHCl₃) 3000, 2925, 2890, 1470, 1460, 1120, 1100, 1005, 835 cm⁻¹; \( ^1H \) NMR (CDCl₃) \( \delta = 0.97, 1.05, 1.63, 1.71, 3.43 \) (4, 6, 3, 2 H, \( CH₂CH₂ \)), 3.47 (4, 7, 2 H, \( CH₂CH₂CH₃ \)), 4.34 (2, 1 H, \( CH=CH \)), 6.72 (2, 1 H, \( CH=CH \)). Anal. Calcd for \( C_{19}H_{22}O_4 \): C, 71.22; H, 8.81. Found: C, 71.25; H, 8.75.}

**J. Am. Chem. Soc., Vol. 107, No. 11, 1985** 3277
2CH₂CH₂), 4.40, 4.63 (2 d, 2 H, J = 12 Hz, C₅H₅CH₂), 7.32 (s, 3 H, C₆H₅), 7.5 (s, 5 H, C₆H₅). Anal. Caled for C₃₂H₅₂O₂Si: C, 66.37; H, 9.15. Found: C, 66.21; H, 9.16.

There was then eluted 8.5 mg (19%) of an isomeric spiroketal as a colorless oil: Rₚ = 0.12 (silica gel, 2:8 ether/petroleum ether); evaporation distillation 195°C (0.001 mmHg); IR (CHCl₃) 3560, 2960, 2940, 2860, 1745, 1460, 1260, 1100, 1035, 1010, 840 cm⁻¹; H NMR (500 MHz, CDCl₃) 8 0.02, 0.03 (s, 6 H, (CH₃)₂Si), 0.97, 0.98 (2 d, 2 H, J = 6 Hz, C₂H₅CH₂), 1.29 (s, 3 H, J = 7 Hz, CH₃CH₂), 1.67 (m, 1 H), 1.77 (m, 1 H), 1.83 (dd, 1 H, J₁ = 15 Hz, J₂ = 2 Hz, CH₂CH₂), 1.98 (m, 1 H), 2.15 (dd, 1 H, J₁ = 14 Hz, J₂ = 3 Hz, CH₂CH₂). Anal. Caled for C₁₂H₂₀O₂Si: C, 66.37; H, 9.15. Found: C, 66.21; H, 9.16.

To a stirred solution of 5.0 mg (0.0098 mmol) of the spiroketal 24 (Rₚ = 0.26, silica gel, 2:8 ether/petroleum ether) in 2 mL of ethanol was added 10 mg of 10% palladium on carbon. The reaction mixture was stirred at room temperature under a hydrogen atmosphere (1 atm) for 2h. The catalyst was then removed by filtration and washed with 2 mL of absolute ethanol. The combined filtrates were concentrated under reduced pressure to a solution of the residue in 0.5 mL of DCI₃, added 5 mg of pyridinium p-toluenesulfonate. After 24 h at room temperature, the solution was concentrated under reduced pressure.

By the procedure described above, a solution of 5.0 mg (0.0098 mmol) of the spiroketal 24 (Rₚ = 0.26, silica gel, 2:8 ether/petroleum ether) in 2 mL of ethanol with 10 mg of 10% palladium on carbon and then 5 mg of pyridinium p-toluenesulfonate in 0.5 mL of DCI₃, afforded, after chromatography on 5 g of silica gel with 7:3 ether/petroleum ether afforded 3.7 mg (90%) of the alcohol 25 as a colorless oil: Rₚ = 0.25 (silica gel, 7:3 ether/petroleum ether); IR (CCl₄) 3560, 2960, 2940, 2860, 1760, 1740, 1465, 1375, 1255, 1100, 1060, 1035, 840 cm⁻¹; H NMR (500 MHz, CDCl₃) 8 0.05, 0.07 (s, 6 H, (CH₃)₂Si), 0.98, 0.99 (2 d, 2 H, J = 6 Hz, C₂H₅CH₂), 1.29 (s, 3 H, J = 6 Hz, CH₃CH₂), 1.66 (m, 1 H), 1.70 (m, 1 H), 1.79 (m, 1 H), 1.84 (dd, 1 H, J₁ = 15 Hz, J₂ = 2 Hz, CH₂CH₂), 1.99 (m, 1 H), 2.17 (dd, 1 H, J₁ = 14 Hz, J₂ = 3 Hz, CH₂CH₂). Anal. Caled for C₁₂H₂₀O₂Si: C, 66.37; H, 9.15. Found: C, 66.26; H, 8.91.

The most and least polar of the spiroketal diastereomers were shown to bear the same configuration at the carboxethoxy center by equilibration of the spiroketal center with pyridinium p-toluenesulfonate in chloroform. The spiroketals of intermediate polarity were also interconverted by acid-catalyzed equilibration.
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

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Abstract: The monensin bis(tetrahydrofuran) 25, a versatile intermediate for the synthesis of polyether ionophore antibiotics, is prepared from D-xylene 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 glycales,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 carbon; 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 (Scheme II). The literature precedent for enolizations of this type was not encouraging. An alkoxide lacks the thermodynamic barrier to elimination imposed by dialkylamide⁶ and lithium oxide⁷ 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 α-bond is orthogonal to the breaking α-bond,¹ the β-oxygen in ester 9 can easily assume a pseudoeaxial orientation. We were thus disappointed but not...
surprised to find that enolization of the crotol ester \(9 \) with LDA in THF at \(-100^\circ C\) for 4 min followed by addition of excess TMSCl/TEA/HMPA in THF precooled to \(-78^\circ C\) consumed all of the starting material but, on warming to room temperature, afforded no products of Claisen rearrangement. While this experiment demonstrated that \(\beta\)-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 crotol ester \(9 \) to a premixed solution of LDA and TMSCl in 10\% HMPA/THF cooled to \(-100^\circ C\) 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, \(1,0\) that O-silylation was at least 4 times as fast as \(\beta\)-elimination, and that all these processes occurred on a subminute time scale at \(-100^\circ C\).

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

Completion of this work, similar in situ silylations were reported.


For other instances of the successful utilization of carbanions with good \(\beta\)-leaving groups, see: Seyferth, D.; Mueller, D. C.; Armbrecht, F. M. J. Org. Chem. 1980, 45, 52%.

Swern oxidation 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 \(15\) as the only ether-soluble, water-insoluble products in an overall 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

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(10) For other instances of the successful utilization of carbanions with good \(\beta\)-leaving groups, see: Seyferth, D.; Mueller, D. C.; Armbrecht, F. M. J. Org. Chem. 1980, 45, 52%.
exclusive diastereomers.\textsuperscript{15} \textit{p}-Toluenesulfonic acid promoted migration of the 3,5 acetonide to the thermodynamically preferred 2,3 acetonide, and we were therefore compelled to carry both diastereomers forward. Eventually, X-ray crystallography on an advanced intermediate\textsuperscript{19} established the relative stereochemistry shown in Scheme IV. The derived epimeric aldehydes 22 and 23 were readily separable by flash chromatography\textsuperscript{50} and then individually subjected to Wittig methylation. Hydrogenation of the resulting vinyl dihydrofurans showed good (~8:1) stereoselectivity. Ultimately secured by X-ray crystallography,\textsuperscript{19} the initial assignment of the cis-crotyl esters followed precedents from our laser-assisted cleavage\textsuperscript{17} 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(tetrahydrofuran) 24 and 25 required only deprotection and oxidation\textsuperscript{13,22} of the primary alcohols to carboxylic acids.

Since the lactol acetonide is a latent furanoid glycal, the bi-functional nature of these intermediates potentiates the ester bond 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**

Measurements are uncorrected. Proton nuclear resonance (\(\text{H NMR}\)) 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. Reactions were monitored occasionally by TLC. Reactions were carried to completion. Synergistically and reactivity of the ester enolate Claisen rearrangement. Indeed, only obtention of the Claisen product itself confirmed that this ester had been subjected to Wittig methylenation. Hydrogenation of the resulting crotyl ester 9 as a colorless oil: \(\text{2940, 1810, 1450, 1380, 1370, 1080, 1010, 860 cm}^{-1}\). ‘H NMR (\(\text{CDCl}_3\)) \(\delta 1.36, 1.45 (2\ H, (\text{CH})_2C)\), 4.48, 4.70 (2\ d, 2\ H, \text{J} = 12\ Hz, \text{C}(2)-\text{H}, \text{C}(4)-\text{H}), 5.05 (\text{dd}, 1\ H, \text{J} = 6, \text{J}' = 5\ Hz, C(2)-H and C(4)-H), 5.28 (\text{dd}, 1\ H, \text{J} = 6, \text{J}' = 5\ Hz, C(3)-H), 5.37 (\text{dd}, 1\ H, \text{J} = 6, \text{J}' = 5\ Hz, C(3)-H), 5.57 (\text{dd}, 1\ H, \text{J} = 6, \text{J}' = 5\ Hz, C(3)-H), 5.27 (1\ s, 1\ H, OCHO), 7.32 (1\ s, 5\ H, CH₅). Anal. Caled for \(\text{C}_{27}\text{H}_{32}\text{O}_{6}\): C 62.33; H 6.54. Found: C 62.36; H 6.46.

**References**

\begin{enumerate}
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\end{enumerate}
chloride in 530 mL of THF cooled to -78 °C was added, over 15 min, to furanoside (16). Anal. Calcd for C_{12}H_{20}O_{5}: C, 59.00; H, 8.25. Found: C, 58.82; H, 8.17.

To a stirred solution of 19.9 mL (0.228 mol) of oxalyl chloride in 150 mL of THF cooled to -78 °C, 15 mL (0.175 mol) of 1,1-dimethylethylene was added. The reaction mixture was allowed to warm to room temperature, and then quenched by the addition of 60 mL of absolute ethanol. The warm reaction mixture was diluted with 50 mL of saturated aqueous NaCl and acidified to pH 2 with dilute aqueous HCl. The aqueous phase was extracted with 3 additional 150 mL portions of ether, and the combined organic extracts were dried (MgSO_4) and then concentrated under reduced pressure. The residue was then eluted with 4.6 mL of methylene chloride and 0.28 mL of ether; evaporative distillation at 100 °C (0.005 mmHg); [a]_D^22 = +97.4° (c 1.77, CHCl_3); IR (CHCl_3) 3540, 3000, 2990, 2850, 1530, 1515, 1450, 1440, 1380, 1370, 1270, 1165, 1050, 840 cm⁻¹; 'H NMR (CDCl₃) δ 1.10, 1.42, 1.42 (3 s, 9 H, CH₃C), 1.30, 1.37, 1.40, 2.30 (s, 6 H, CH₃C), 3.27 (s, 3 H, CH₃), 3.55-4.40 (m, 6 H), 4.93 (s, 1 H, OCHO). Anal. Calcd for C_{12}H_{20}O₅C: 59.00; H, 8.25. Found: C, 59.85; H, 8.19.

By the procedure described above, the β-α-anomer of 15 afforded on millimolar scale 75% of the β-α-anomer of 16 as a colorless oil: Rf = 0.28 (silica gel, 6:4 ether/petroleum ether); evaporative distillation at 100 °C (0.005 mmHg); [a]_D^22 = -74.2° (c 1.52, CHCl₃); IR (CHCl₃) 3540, 2990, 2850, 1530, 1515, 1450, 1440, 1380, 1370, 1270, 1165, 1050, 840 cm⁻¹; 'H NMR (CDCl₃) δ 1.32, 1.38, 1.38, 3.55-4.40 (m, 6 H), 4.58 (s, 1 H, OCHO). Anal. Calcd for C_{12}H_{20}O₅C: 59.00; H, 8.25. Found: C, 58.82; H, 8.26.

Allyl 3,5-O-(1-Methylthiobenzylidene)-α- and β-α-xlyofuranoside (15). To a stirred solution of 75.0 g (0.500 mol) of oxo-butyraldehyde in 1 L of refluxing allyl alcohol was added 3.0 g (11.9 mmol) of pyridinium p-toluene-sulfonate. 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 5-150 mL portions of benzene. To 1.75 L of acetonitrile (0.004% H₂O assay) was added 150 g of anhydrous copper sulfate. After 30 min 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 (MgSO₄) 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-α-anomer 15 as a white, low-melting solid (mp 41 °C); Rf = 0.34 (silica gel, 1:1 ether/petroleum ether); evaporative distillation 95-100 °C (0.001 mmHg); [a]_D^22 = +87.8° (c 2.67, CHCl₃); IR (CHCl₃) 3540, 3000, 2940, 1450, 1385, 1170, 1065, 1040, 850 cm⁻¹; 'H NMR (CDCl₃) δ 1.37, 1.43 (2 s, 6 H, CH₃C), 2.97 (d, 1 H, J = 4 Hz, CHOH), 3.93-4.50 (m, 7.33 d, 1 H, J = 4 Hz, OCHO). Anal. Calcd for C_{12}H_{20}O₅C: 57.38; H, 7.89. Found: C, 57.46; H, 7.88.

There was then eluted the β-α-anomer 15 as a colorless oil: Rf = 0.13 (silica gel, 1:1 ether/petroleum ether); evaporative distillation 110 °C (0.001 mmHg); [a]_D^22 = +94.6° (c 2.63, CHCl₃); IR (CHCl₃) 3600, 3420, 3000, 2940, 1450, 1385, 1150, 1090, 1065, 1040, 850 cm⁻¹; 'H NMR (CDCl₃) δ 1.34, 1.44 (3 s, 6 H, CH₃C), 2.97 (d, 1 H, J = 4 Hz, CHOH), 3.93-4.50 (m, 7.33 d, 1 H, J = 4 Hz, OCHO). Anal. Calcd for C_{12}H_{20}O₅C: 57.38; H, 7.89. Found: C, 57.46; H, 7.88.

cis-Prop-1-ene 2,3-O-(1-Methylthiobenzylidene)-2-C-methyl-α- and β-α-xlyofuranoside. To a stirred solution of 40.1 g (0.164 mol) of the above primary alcohols in 330 mL of MeOH 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 50 mL of saturated aqueous NaCl. The combined aqueous phases were extracted with 300 mL of ether, and the combined organic extracts were dried (MgSO₄) and then concentrated under reduced pressure. Chromatography of the residue on 1 kg of silica gel with mixed ether/petroleum ether (1:9) as eluent afforded 250 mL of the propenyl ethers as a colorless oil of >95% purity as judged by TLC and 'H NMR. By the procedure described above, the α-α-anomer of 16 afforded on millimolar scale, after chromatography on silica gel with 1:1 ether/petroleum ether, 99% of the α-α-anomer of the primary alcohol as a colorless oil: Rf = 0.28 (silica gel, 6:4 ether/petroleum ether); evaporative distillation 90-95 °C (0.005 mmHg); [a]_D^22 = -74.2° (c 1.52, CHCl₃); IR (CHCl₃) 3540, 3000, 2940, 2850, 1530, 1515, 1450, 1440, 1380, 1370, 1270, 1165, 1050, 840 cm⁻¹; 'H NMR (CDCl₃) δ 1.43, 1.47, 1.50 (3 s, 9 H, 3 CH₃C), 2.92, 2.97, 3.85 (2 s, 6 H, CH₃), 7.33 (s, 1 H, OCHO). Anal. Calcd for C_{12}H_{20}O₅C: 59.00; H, 8.25. Found: C, 59.10; H, 8.26.

By the procedure described above, the β-α-anomer of 16 afforded on millimolar scale, after chromatography on silica gel with 7:3 ether/petroleum ether, 98% of the β-α-anomer of the primary alcohol as a colorless oil: Rf = 0.11 (silica gel, 6:4 ether/petroleum ether); evaporative distillation 90-95 °C (0.005 mmHg); [a]_D^22 = -74.2° (c 1.52, CHCl₃); IR (CHCl₃) 3540, 3000, 2940, 2850, 1540, 1380, 1250, 1095, 1020, 870 cm⁻¹; 'H NMR (CDCl₃) δ 1.43, 1.47, 1.50 (3 s, 9 H, 3 CH₃C), 3.85, 3.90, 3.97 (3 s, 6 H, CH₃), 7.33 (s, 1 H, OCHO). Anal. Calcd for C_{12}H_{20}O₅C: 59.00; H, 8.25. Found: C, 59.10; H, 8.26.
2.3-0-(1-Methylthioline)-5-O-[2-(trimethylsilyl)ethoxy]methyl-2-
C-methyl-0-xylene (17). To a stirred solution of 39.4 g (0.161 mol) of the above alkoxysilane in 430 mL of dichloromethane was added 36.5 mL (0.210 mol) of 1,3-dipolar cycloaddition. The reaction mixture was then diluted with 0.5 L of ether, washed with 200 mL of saturated aqueous NaCl, and then filtered and concentrated under reduced pressure. Chromatography of the residue on 2 kg of silica gel afforded first the minor diastereomer (the precursor to the aldohexose 22) as a colorless oil: 0.31 g (68%) of a mixture of the primary alcohols as a colorless oil. Chromatography of the residue on 700 g of silica gel with 8:2 ether/petroleum ether afforded first the minor diastereomer (the precursor to the aldohexose 22) as a colorless oil: 0.15 g (12%) of a mixture of the primary alcohols as a colorless oil.
methyleneoxy)-5(S)-(benzoxly)tetrahydrofuran (22 and 23). To a stirred solution of 2.87 mL (32.9 mmol) of octyl chloride in 230 mL of dichloromethane at -78 °C was added over 5 min a solution of 2.92 mL (34.76 mmol) of MeSO in 23 mL of dichloromethane. After 15 min, a solution of 14.30 g (27.8 mmol) of the mixed ester in 10 mL of dichloromethane was added to the reaction mixture. After 10 min, the reaction mixture was treated with 19.1 mL of 5% sodium hydroxide solution and then diluted with 100 mL of saturated aqueous NaCl. The resulting mixture was extracted with two 200-mL portions of ether. The combined organic extracts were dried (MgSO₄) and then concentrated under reduced pressure. Flash chromatography of the residue on 250 g of silica gel with 1:1 ether/petroleum ether afforded first 7.80 g (95%) of the olefin as a colorless oil: \[ R = 0.21 \text{ (silica gel, 3:7 ether/petroleum ether); IR (CHCl₃) 3450, 3000, 2940, 2880, 1455, 1385, 1370, 1240, 1100, 1050, 865, 840 cm}^{-1}; \] \[ 1 H NMR (CDCl₃) \delta 0.05 \text{ (s, 9 H, (CH₃)₂Si), 1.02} \text{ (d, 3 H, } J = 6 \text{ H, (CH₃)₂C)=CH, CH₃), 1.35, 1.52 (2 s, 6 H, (CH₃)₂C)=CH, CH₃}. \] Anal. Calcd for C₂₂H₃₂O₆: C, 67.24; H, 8.22.

There was then eluted 51 mg (9.4%) of an epimeric alkane: \[ R = 0.17 \text{ (silica gel, 3:7 ether/petroleum ether); IR (CHCl₃) 3450, 3000, 2940, 2880, 1455, 1385, 1370, 1240, 1100, 1050, 865, 840 cm}^{-1}; \] \[ 1 H NMR (CDCl₃) \delta 0.05 \text{ (s, 9 H, (CH₃)₂Si), 1.02} \text{ (d, 3 H, } J = 6 \text{ H, (CH₃)₂C)=CH, CH₃), 1.35, 1.52 (2 s, 6 H, (CH₃)₂C)=CH, CH₃}. \] Anal. Calcd for C₂₂H₃₂O₆: C, 67.24; H, 8.22.

2(S)-Ethyl-2-[S-(12-(trimethylsilyloxymethyl)ethylthio)methyl]-3(R)-methyl-2-[5(S)-carboxy-3(S)-methyl-2(R)-tetrahydrofuryl]-3(R),4(S)-(dimethylmethyleneoxy)-5(S)-(benzoxly)tetrahydrofuran. A stirred solution of 0.050 mmol of the alcohol derived from aldehyde (90%) of the alcohol to the acid (25) was added to a stirred solution of 0.050 mmol of the aldehyde in 10 mL of dichloromethane at -78 °C was added over 5 min a solution of 0.29 mL (2.10 M solution of n-butyllithium in hexane, and then 1.70 mL (3.26 mmol) of the aldehyde was added. The reaction mixture was stirred at room temperature for 12 h. The catalyst was then removed by filtration and washed with water. The organic layer was concentrated under reduced pressure. Evaporative distillation; 190-195 °C (0.001 mmHg); \[ [\alpha]_{22}^{D} = +58.5^0 \text{ (c 0.995, CHCl₃); IR (CHCl₃) 3000, 2960, 2870, 1735, 1455, 1385, 1375, 1240, 1150, 1085, 990, 860, 830 cm}^{-1}; \] \[ 1 H NMR (CDCl₃) \delta 1.37, 1.50 (2 s, 6 H, (CH₃)₂C)=CH, CH₃), 2.00 (br s, 3 H, CH₃C)=CH, CH₃), 2.50 (m, 1 H, CH₂CH₃), 3.83 (d, 1 H, } J = 4.5 H, CH(17)=CH, 7.33 (s, 5 H, CH₃C)=CH, CH₃). Anal. Calcd for C₃₆H₄₄O₈Si: C, 63.87; H, 8.43. Found: C, 64.20; H, 8.82.
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 (MgSO₄) 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 AgNO₃ in 1.80 mL of water was added, over 15 min, a solution of 1.01 g (15.28 mmol) of 85% KOH in 9.8 mL of water, afforded, after chromatography on 40 g of silica gel with 3:7 ether/petroleum ether, 984 mg (95%) of the acid 25 as a colorless oil; Rf = 0.06 (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 25 as a colorless oil; Rf = 0.27 (silica gel, 4:6 ether/petroleum ether); evaporative distillation 170 °C (0.005 mmHg); [α]D₂⁵ = +61.9° (c 1.46, CHCl₃); IR (CHCl₃) 3000, 2950, 2880, 1730, 1450, 1440, 1385, 1375, 1270, 1075, 875 cm⁻¹; ¹H NMR (CDCl₃) δ 1.03 (t, 3 H, CH₃CH₂), 1.12 (d, 3 H, CH₃CH), 1.33, 1.50 (2 x 6 H, (CH₃)₂C), 3.73 (s, 3 H, OCH₃), 3.92 (d, 1 H, J = 4 Hz, C(17)-H), 5.07 (s, 1 H, OCHO), 7.33 (s, 5 H, C₆H₅). Anal. Calcd for C₃₄H₃₂O₇: C, 65.70; H, 7.65. 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)-[dimethylmethyleneoxy]-5(S)-[benzoxyl]tetrahydroyran (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 μg (1.49 mmol) of the alcohol (the precursor to the acid 24), and then dissolution of the crude aldehyde in 10 mL of ether, 0.76 g (4.47 mmol) of AgNO₃ 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; Rf = 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; Rf = 0.27 (silica gel, 4:6 ether/petroleum ether); evaporative distillation 170 °C (0.005 mmHg); [α]D₂⁵ = +61.9° (c 1.46, CHCl₃); IR (CHCl₃) 3000, 2950, 2880, 1730, 1450, 1440, 1385, 1375, 1270, 1075, 875 cm⁻¹; ¹H NMR (CDCl₃) δ 1.00 (t, 3 H, J = 7 Hz, CH₂CH₃), 1.23 (d, 3 H, J = 6 Hz, CH₂CH), 1.33, 1.48 (2 x 6 H, (CH₃)₂C), 2.47 (s, 3 H, OCH₃), 3.98 (s, 1 H, J = 4 Hz, C(17)-H), 5.12 (d, 1 H, J = 2 Hz, OCHO), 7.32 (s, 5 H, C₆H₅). Anal. Calcd for C₃₄H₳O₇; 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 Decarboxylation¹

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Abstract: The monensin tetrahydropyran equivalent 22 is prepared from D-fructose and then joined to the monensin bis(tetrahydrofuran) equivalent 24 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-D-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 total synthesis of lasalocid A\(^2\) and its enantiomer\(^4\) in sufficient quantities for biological testing. In order to explore this strategy further, we have developed routes at 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 olenin 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

¹(1) (a) Grateful acknowledgment is made for support of this investigation by NIH (No. HL-23167). Acknowledgment is also made for the use of the Southern California Regional NMR Facility (National Science Foundation Grant CHE-79-16324). (b) The crystallographic analysis was supported in part by grants from the Veterans Administration (No. 5455-01P), the National Institute of Health (AM03579), and the Fannie E. Ripple Foundation. Neil Mandel is a Veterans Administration Associate Research Career Scientist. Acknowledgment: is also made for the use of the Southern California Regional NMR Facility (National Science Foundation Grant CHE-79-16324).

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


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 (2.35 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 (MgSO₄) 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 AgNO₃ 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 (MgSO₄) 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: Rf = 0.06 (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 25 as a colorless oil: Rf = 0.27 (silica gel, 4:6 ether/petroleum ether); evaporative distillation 170 °C (0.005 mmHg); [α]D = +61.9° (c 1.46, CHCl₃); IR (CHCl₃) 3000, 2950, 2880, 1750, 1460, 1385, 1375, 1100, 1070, 1015, 870 cm⁻¹; ¹H NMR (CDCl₃) δ 1.03 (t, 3 H, CH₂CH₃), 1.12 (d, 3 H, CH₃CH), 1.33, 1.50 (2 s, 6 H, (CH₃)₂C), 3.73 (s, 3 H, OCH₃), 3.92 (d, 1 H, J = 4 Hz, C(17)-H), 5.07 (s, 1 H, OCHO), 7.33 (s, 5 H, C₆H₅). Anal. Calcd for C₁₅H₁₇O₅: C, 65.70; H, 7.67. Found: C, 65.77; H, 7.72. Treatment of this ester with lithium tetrahydrodialuminolate 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)-(dimethylmethyleneoxy)-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 ether, 0.76 g (4.47 mmol) of AgNO₃ 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: Rf = 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: Rf = 0.27 (silica gel, 4:6 ether/petroleum ether); evaporative distillation 170 °C (0.005 mmHg): [α]D = +61.9° (c 1.46, CHCl₃); IR (CHCl₃) 3000, 2950, 2880, 1750, 1460, 1385, 1375, 1100, 1070, 1015, 870 cm⁻¹; ¹H NMR (CDCl₃) δ 1.03 (t, 3 H, CH₂CH₃), 1.12 (d, 3 H, CH₃CH), 1.33, 1.50 (2 s, 6 H, (CH₃)₂C), 3.97 (s, 3 H, OCH₃), 7.33 (s, 5 H, C₆H₅). Anal. Calcd for C₁₇H₁₈O₇: C, 65.70; H, 7.67. Found: C, 65.73; H, 7.72. Treatment of this ester with lithium tetrahydrodialuminolate 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

Robert E. Ireland, Daniel W. Norbeck, Gretchen S. Mandel, and Neil S. Mandel

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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-y1 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 glycalcs 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 glycalcs has led to a toal synthesis of lasalocid A² and its enantionomer⁴ in sufficient quantities for biological testing. In order to explore this strategy further, we have developed routes at 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 olenin 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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two subunits carries a price: removal of a surplus carbon. Indeed, the bond joining the terminal tetrahydrofuran and tetrahydrofuran rings of a large subclass of polyethers bears vicinal hydrogens. Reductive decarboxylation of γ,δ-unsaturated acids is thus an important goal of our program for polymer synthesis; broader implications exist for the expanded utility of the ester enolate as an important goal of our program for polyether synthesis; broader implications exist for the expanded utility of the ester enolate


(16) In fact, attempts to equilibrate the parallel 4-epi series from the aldehyde 13 demonstrated that elimination of alkyl alcohol from C5 is irreversible.
monensin tetrahydropyran synthesis

Table I. Reductive Fragmentation of the Model Furanosyl Chloride 23a

<table>
<thead>
<tr>
<th>reductant</th>
<th>yield of 23b</th>
<th>23b:23c</th>
</tr>
</thead>
<tbody>
<tr>
<td>Li/NH₃</td>
<td>75%</td>
<td>7.9:1</td>
</tr>
<tr>
<td>Na₂/NH₃</td>
<td>77%</td>
<td>10.7:1</td>
</tr>
<tr>
<td>K/NH₃</td>
<td>79%</td>
<td>15.0:1</td>
</tr>
<tr>
<td>SmI₃</td>
<td>0%</td>
<td></td>
</tr>
<tr>
<td>sodium naphthalene</td>
<td>82%</td>
<td>&gt;50:1</td>
</tr>
<tr>
<td>lithium benzophenone</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td>sodium anthracene</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td>sodium trimethylboronate</td>
<td></td>
<td>&gt;50:1</td>
</tr>
<tr>
<td>lithium 4,4-di-tert-butylbiphenyl</td>
<td>94%</td>
<td>&gt;50:1</td>
</tr>
</tbody>
</table>

*35 eq of metal, 0.5 M, 1:10 THF/NH₃, -78 °C, 30 min, then NH₄Cl. 2 eq, 0.07 M, THF, 25 °C, 3 h. 6 eq, 0.21 M THF, -35 °C, 20 min, then H₂O. 5 eq, 0.50 M THF, 25 °C. 5 eq, 0.025 M THF, 25 °C, 75 eq, 0.25 M THF, -20°C, 1 h, then H₂O. 5 eq, 0.20 M THF, -78 °C, 15 min, then H₂O. No reaction.

C7 methylene hydrogens indicated that these substituents were cis in the more polar ketal; the corresponding enhancement between the C7 and C5 hydrogens to the extent of 80% to 90% was not observed. If these byproducts arise from protonation of an intermediate carbanion by a relatively acidic lithium cation-anion pair, they would be expected to increase fragmentation to protonation ratios with decreasing counterion solvation. While this argument is admittedly oversimplified, the furanosyl chloride 23a did in fact display the expected trend (Table I). However, reduction of the pyranosyl chloride 20 with potassium in liquid ammonia gave results indistinguishable from those obtained with lithium in liquid ammonia (Table II). We therefore turned our attention to aprotic reducing media.

After an initial disappointment with samarium diiodide in THF, a series of radical anions gave promising results with the model furanosyl chloride 23a. Particularly encouraging was the absence of hydrodehalogenation products. Sodium naphthalene had been previously reported to give the glycal 23b in 52% yield, in our hands, lowering the reaction temperature to -53 °C raised the chromatographed yield to 82%. Use of Freeman's radical anion was even more rewarding, and

Table II. Reductive Fragmentation of the Pyranosyl Chloride 20

<table>
<thead>
<tr>
<th>reductant</th>
<th>yield of 22</th>
</tr>
</thead>
<tbody>
<tr>
<td>Li/NH₃</td>
<td>25%</td>
</tr>
<tr>
<td>K/NH₃</td>
<td>31%</td>
</tr>
<tr>
<td>sodium naphthalene</td>
<td>&gt;50:1</td>
</tr>
<tr>
<td>lithium 4,4-di-tert-butylbiphenyl</td>
<td>&gt;50:1</td>
</tr>
</tbody>
</table>

*50 eq of metal, 0.06 M, 1:10 THF/NH₃, -78 °C, 30 min, then NH₄Cl. 12 eq, 0.20 M THF, -78 °C, 30 min, then H₂O. 12 eq, 0.20 M THF, -78 °C, 15 min, then H₂O.

Scheme III. Union of Monensin's E and C + D Ring Subunits (a = α-C₅H₅, b = β-C₅H₅)

its striking superiority as an electron-transfer reagent became fully apparent with the pyranyl chloride 20 (Table II). While other base-induced elimination\(^{25}\) of an incipient aldehyde of fragmentation\(^{26}\) of the intermediate radical could conceivably be responsible for the poor mass balance observed with both lithium in liquid ammonia and sodium naphthalene, these or other nonproductive pathways are minimized by lithium di-tert-butylphenyl which reproducibly delivered the pyranal glycol 22 in 81% chromatographed yield.

With the subunits for monensin's C and D rings already in hand,\(^{27}\) the stage was now set for joining this E ring juncture, we attacked the major problem of reductive decarbonylation of 26b while the crystallographic investigation was still in progress.

Of all the methods available for removing unactivated carbonyl groups, only Wilkinson's catalyst,\(^{31}\) which uniquely avoids radical or carbonium ion intermediates, offers a mechanistically rational basis for achieving decarbonylation with retention of stereochemistry.\(^{32}\) However, sterically hindered aldehydes undergo the rate-determining oxidative addition to the rhodium center only with extreme difficulty,\(^{33}\) and the likelihood of side reactions\(^{34}\) under the forcing conditions anticipated dissuaded us from pursuing this approach. Although nonstereorational, the trialkylstannane-induced decarbonylation of phenyl seleno esters is an attractive alternative.\(^{35}\) This method would not only provide the noralkane directly, but its compatibility with olefin functionality\(^{36}\) would allow us to ascertain the configuration of the resulting stereocenter through chemical correlation.

Preparation of the required phenyl seleno ester 27b provided an unexpected challenge. The failure of lithium hydroxide in refluxing aqueous THF to saponify the methyl ester of the acid 26b had alerted us to the extraordinary steric hindrance to nucleophilic attack at the acyl carbon; not surprisingly, the carboxylic acid 26b was utterly impregnable to reagents which mechanistically rely on the intramolecular delivery of a nucleophile for carbonyl activation or phenyl seleno ester formation.\(^{37}\) Conceptually, an intramolecular esterification process provides an elegant way out of this difficulty. Experimental realization of this concept in preparatively acceptable yield was tortuous but ultimately gratifying, as numerous standard as well as recent procedures were carefully explored before the following reaction sequence was developed.

The hypothesis that nucleophilic displacement at phosphorus proceeds through a pentacovalent oxyphosphorane intermediate has been a fruitful concept in the interpretation of the chemical


\(^{28}\) The monensin numbering system is used here.


stereochemical behavior of organophosphorous compounds,\(^\text{(38)}\) We speculated that such an intermediate might have a lifetime of sufficient duration to allow for an intramolecular condensation between phenyl selenide and carboxylate ligands (see below).

Since alkyl phenylselenyl halophosphates have not been characterized,\(^\text{(40)}\) we elected to add selenolenone to the mixed anhydride between the carboxylic acid 26b and an alkyl dihalophosphate. In the event, treatment of the triethyamine salt of the acid with phenyl dichlorophosphate\(^\text{(41)}\) in THF at 0°C for 30 min, followed by the addition of excess triethyamine and selenolenone, produced within minutes an 80% yield of the phenyl seleno ester 27b and 12% recovered carboxylic acid. While we have no direct evidence for the intermediacy of an oxophosphate, this result stands in sharp contrast to the inefficacy of mixed anhydrides with relatively weak electrophilicity at phosphorus.

Decarboxylation of the phenyl seleno ester with tri-n-butyltin hydride and a trace of AIBN\(^\text{(35)}\) in refluxing benzene afforded the noralkane 28b in 74% yield. Intriguingly, 500-MHz NMR indicated that a single C20\(^\text{28}\) epimer had been obtained. Since the results of the X-ray crystal structure had denoted this work to model status, we were content to demonstrate the chemical fitness of the decarboxylation methodology and postponed resolution of the stereochemical issue until the correct C16\(^\text{28}\) epimer 26a was in hand.

Reinvestigation of the Claisen rearrangement of the model ester 25b revealed that the modest yield was due in part to C-silylation of the ester enolate. Enolization by potassium hexamethyldisilazide and trapping with TBSCl eliminated this problem, and use of this reagent combination to generate the silyl ketene acetal of the ester 25a provided, after thermal rearrangement at room temperature for 48 h, a 5:1 mixture of diastereomeric Claisen products in 65% yield.\(^\text{(42)}\) The mixed chlorophosphate anhydride method again met our expectations, and the resulting phenyl seleno esters were separated by chromatography and individually decarboxylated: significantly, each gave an identical 5:1 mixture of inseparable noralkane epimers. The stereochemical outcome of this process was determined by chemical degradation as outlined in Scheme IV.

Cleavage of the E ring gave a mixture of the diols 29, and the two major components were separated by chromatography and individually hydrolyzed to the diols 30. Periodate cleavage of these intermediates would give either aldehyde 31 or 32. Samples of these epimers were prepared from the alcohol 33.\(^\text{(37)}\) Reduction of the aldehyde 31 gave back the starting alcohol, and equilibration with potassium carbonate in methanol produced the epimeric aldehyde 32. In the event, periodate cleavage of the diols 30 gave in each case a product identical with aldheyde 31 and distinct from aldheyde 32 as judged by direct comparison by TLC and 500-MHz NMR. Therefore, the stereochemistry at C20\(^\text{28}\) was predominantly incorrect.

Since the intermediate alloy radical generated by decarboxylation is pyramidal and inverting rapidly,\(^\text{(43)}\) the product distribution is controlled, according to the Curtin–Hammett principle,\(^\text{(44)}\) only by the difference between the total free energy of activation for each pathway. It appeared to us that steric interactions between the tri-n-butylstannane and the cis-alkyl substituents on the tetrahydrofuranyl radical might produce the energy difference decisive against the desired steriosomer. To test this hypothesis, we prepared the phenyl seleno ester 38 via the known diol 34\(^\text{(45)}\) and the glycal 22 as outlined in Scheme V.

The steric bias of the bicyclic 1,2-O-isopropylideneuraneose system had been amply demonstrated.\(^\text{(46)}\) In the specific case of free radical reactions, treatment of the diisocarbonate 39 with tri-n-butyltin deuteride gave an 85:15 mixture of the deoxy isomers 40 and 41. Similar treatment of the diisocarbonate 42 gave only the deoxyfuraneose 43 from exclusive exo attack.\(^\text{(47)}\) Thus, if steric effects are indeed decisive in the stereochemical outcome of hydrocarbon abstraction by tetrahydrofuran-2-yl radicals, the all-cis-tetrahydrofuran 37 should predominate in the decarboxylation of phenyl seleno ester 38. In fact, we obtained 37 as a 1:1 mixture.

\[^{41}\text{Phenyl dichlorophosphate has been used for the preparation of unhindered thio esters: Liu, H.-J.; Sabesan, S. Y. Can. J. Chem. 1980, 58, 2645–2648.}\]
\[^{42}\text{Since the same ratio was obtained with LDA, the predominant epimer bears the same configuration at C20 as 26b.}\]
Considering the previous results, the relatively high proportion of hydrogen abstraction by the endo radical is surprising. This outcome can be explained by considering the contribution of a stereoelectronic effect to the total free energy of activation.

Both theoretical and experimental studies have demonstrated that carbon-centered radicals whose orbitals are antiperiplanar to a nonbonded electron pair on an \( \alpha \)-oxygen are significantly stabilized by conjugative delocalization.\(^{43,44}\) The stereoelectronic preference for axial bond formation and cleavage at such centers is a manifestation of this stabilization.\(^{49}\) Since the activation enthalpy for hydrogen abstraction is rather insensitive to radical stability,\(^{26}\) differences in the total free energy of activation will arise from the conformational influences, stereochemical effects, and steric interactions with the reagent. A pseudoequatorial exocyclic side chain and a pseudooxial C=O bond are important stabilizing factors in furanosides.\(^{51}\) In conformer 45 the radical is also quasi-axial, and this stereoelectronic stabilization apparently compensates for steric interactions with the trialkylstannane; the total free energy of activation is therefore competitive with that for unhindered hydrogen abstraction by the exo radical.\(^{52}\) Reconsidering the decarboxylation of ester 27a, we see that radical 44 enjoys a pseudoequatorial disposition of its most bulky substituents, a pseudooxial radical, and unhindered access to hydrogen abstraction. Since no other conformer meets all these criteria, the cis-3-tris-tetrahydrofuran predominates. We are currently exploring new avenues to reverse this stereoechemical outcome.

**Experimental Section**

Melting points are uncorrected. Proton nuclear magnetic resonance (\( \text{H} \) NMR) spectra were recorded at 90 MHz except where designated (\( \text{H} \) NMR) spectra were recorded at 90 MHz except where designated.**

**References**


6 H, (CH3)2Si), 0.88 (s, 9 H, (CH3)2C), 1.38 (s, 6 H, 2CH3C), 1.43 (s, 3 H, CH3CO), 1.80 (s, 3 H, CH3, C), 2.83-3.13 (m, 1 H, CH2CH2), 3.04 (m, 1 H, CH3), 3.27 (d, 1 H, J = 1.5 Hz, CH2CH), 3.72 (s, 1 H, CH3), 3.83 (d, 1 H, J = 11 Hz, CHO), 4.56 (s, 1 H, C=CH2). Anal. Calcd for C28H38O3Si: C, 60.72; H, 10.19. Found: C, 60.46; H, 10.07.

To a stirred solution of 0.32 mL (3.7 mmol) of oxalyl chloride in 10 mL of dichloromethane at -78 °C was added a solution of 0.28 mL (2.7 mmol) of trimethylsilyltetrahydrofuran (15). To a stirred solution of 0.32 mL (3.7 mmol) of oxalyl chloride in 10 mL of dichloromethane at -78 °C was added a solution of 0.85 mL (5.3 mmol) of dimethyl sulfoxide in 4 mL of dichloromethane. After 10 min, a solution of 3.35 and 2(S)-methyl-n-pentan-1-ol (12 and 13). To a stirred solution of 1.01 mL (11.6 mmol) of oxalyl chloride in 60 mL of dichloromethane at -78 °C was added over 5 min a solution of 0.97 mL (13.7 mmol) of dimethyl sulfoxide in 5 mL of dichloromethane. After 10 min, a solution of 3.35 and 2(S)-methyl-n-pentan-1-ol (12 and 13). To a stirred solution of 1.01 mL (11.6 mmol) of oxalyl chloride in 60 mL of dichloromethane at -78 °C was added over 5 min a solution of 0.97 mL (13.7 mmol) of dimethyl sulfoxide in 5 mL of dichloromethane. After 10 min, a solution of 3.35 and 2(S)-methyl-n-pentan-1-ol (12 and 13). To a stirred solution of 1.01 mL (11.6 mmol) of oxalyl chloride in 60 mL of dichloromethane at -78 °C was added over 5 min a solution of 0.97 mL (13.7 mmol) of dimethyl sulfoxide in 5 mL of dichloromethane. After 10 min, a solution of 3.35 and 2(S)-methyl-n-pentan-1-ol (12 and 13). To a stirred solution of 1.01 mL (11.6 mmol) of oxalyl chloride in 60 mL of dichloromethane at -78 °C was added over 5 min a solution of 0.97 mL (13.7 mmol) of dimethyl sulfoxide in 5 mL of dichloromethane. After 10 min, a solution of 3.35 and 2(S)-methyl-n-pentan-1-ol (12 and 13). To a stirred solution of 1.01 mL (11.6 mmol) of oxalyl chloride in 60 mL of dichloromethane at -78 °C was added over 5 min a solution of 0.97 mL (13.7 mmol) of dimethyl sulfoxide in 5 mL of dichloromethane. After 10 min, a solution of 3.35 and 2(S)-methyl-n-pentan-1-ol (12 and 13). To a stirred solution of 1.01 mL (11.6 mmol) of oxalyl chloride in 60 mL of dichloromethane at -78 °C was added over 5 min a solution of 0.97 mL (13.7 mmol) of dimethyl sulfoxide in 5 mL of dichloromethane. After 10 min, a solution of 3.35 and 2(S)-methyl-n-pentan-1-ol (12 and 13). To a stirred solution of 1.01 mL (11.6 mmol) of oxalyl chloride in 60 mL of dichloromethane at -78 °C was added over 5 min a solution of 0.97 mL (13.7 mmol) of dimethyl sulfoxide in 5 mL of dichloromethane. After 10 min, a solution of 3.35 and 2(S)-methyl-n-pentan-1-ol (12 and 13).
2-(Alloxy)-3R-(methyl)-3R-(dimethylenedioxy)-5R-methyl-6-(dimethyldimethylsiloxyl)tetrahydro-2H-pyran-2(2H)-one (16 and 17). To a stirred solution of 683 mg (1.63 mmol) of the ketals 16 in 25 mL of dry methanol was added 200 mg (0.22 mmol) of pyridinium p-toluenesulfonate, and the mixture was then heated 2 h at 45 °C. The reaction was allowed to cool and then concentrated under reduced pressure. Chromatography of the residue on 30 g of silica gel with 1:9 ether/petroleum ether afforded first recovered 4,4'-di-tert-butylbiphenyl and then 495 mg (81%) of the glycal 22 as a colorless oil.

To a stirred solution of 683 mg (1.63 mmol) of the ketals 16 in 25 mL of dry methanol was added 200 mg (0.22 mmol) of pyridinium p-toluenesulfonate, and the mixture was then heated 5 h at 45 °C. The reaction was allowed to cool and then concentrated under reduced pressure. Chromatography of the residue on 30 g of silica gel with 1:9 ether/petroleum ether afforded first 296 mg of the methyl ketal 5 and then 198 mg of the methyl ketal 7, as a colorless oil.

To a stirred solution of 683 mg (1.63 mmol) of the ketals 16 in 25 mL of dry methanol was added 50 mg (0.2 mmol) of pyridinium p-toluenesulfonate, and the mixture was then heated 5 h at 45 °C. The reaction was allowed to cool and then concentrated under reduced pressure. Chromatography of the residue on 30 g of silica gel with 1:9 ether/petroleum ether afforded first recovered 4,4'-di-tert-butylbiphenyl and then 495 mg (81%) of the glycal 22 as a colorless oil: Rf = 0.15 (silica gel, 1:9 ether/petroleum ether); evaporative distillation afforded 262 mg (0.718 mmol) of the allyl ether 18 in a manner similar to that described above provided 234 mg of additional methyl ketol 16 representing a total yield of 85%.

2-(1-Oxy-cis-propenyl)-3R-methyl-3,4(R)-(dimethylenedioxy)-5(R)-methyl-6(S)-methyldioxy)tetrahydropyran-2-ol (19). To a stirred solution of 392 mg (0.965 mmol) of the acid 22 in 2.5 mL of dichloromethane and 2.5 mL of saturated aqueous NaCl. The solution was stirred (MgSO₄) and then evaporated at reduced pressure. Chromatography of the residue on silica gel with 1:9 ether/petroleum ether afforded first recovered 4,4'-di-tert-butylbiphenyl and then 495 mg (81%) of the glycal 22 as a colorless oil: Rf = 0.15 (silica gel, 1:9 ether/petroleum ether); evaporative distillation afforded 1 mol (2.12 mmol) of distilled tri(dimethylamino)phosphine.

To 4,4'-di-tert-butylbiphenyl and then 495 mg (81%) of the glycal 22 as a colorless oil: Rf = 0.15 (silica gel, 1:9 ether/petroleum ether); evaporative distillation afforded 1 mol (2.12 mmol) of distilled tri(dimethylamino)phosphine.

To a stirred solution of 1.02 mmol of potassium hexamethyldisilazide in 2.5 mL of THF was added dropwise 0.39 mL (2.12 mmol) of distilled tri(dimethylamino)phosphine.

To a stirred solution of 392 mg (0.965 mmol) of the acid 22 in 2.5 mL of dichloromethane and 2.5 mL of saturated aqueous NaCl. The solution was stirred (MgSO₄) and then evaporated at reduced pressure. Chromatography of the residue on silica gel with 1:9 ether/petroleum ether afforded first recovered 4,4'-di-tert-butylbiphenyl and then 495 mg (81%) of the glycal 22 as a colorless oil: Rf = 0.15 (silica gel, 1:9 ether/petroleum ether); evaporative distillation afforded 1 mol (2.12 mmol) of distilled tri(dimethylamino)phosphine.

To a stirred solution of 1.02 mmol of potassium hexamethyldisilazide in 6.9 mL of THF at −78 °C was added dropwise 0.39 mL (2.12 mmol) of distilled tri(dimethylamino)phosphine. After 20 min, the solution was allowed to warm to room temperature and then stirred an additional 30 min. To 102 mL (25 mmol) of a stirred solution of lithium (18). Elution with 25 mg (0.655 mmol) of the allyl ether 18 in a manner similar to that described above provided 234 mg of additional methyl ketol 16 representing a total yield of 85%.

2-(1-Oxy-cis-propenyl)-3R-methyl-3,4(R)-(dimethylenedioxy)-5(R)-methyl-6(S)-methyldioxy)tetrahydropyran-2-ol (19). To a stirred solution of 392 mg (0.965 mmol) of the acid 22 in 2.5 mL of dichloromethane and 2.5 mL of saturated aqueous NaCl. The solution was stirred (MgSO₄) and then evaporated at reduced pressure. Chromatography of the residue on silica gel with 1:9 ether/petroleum ether afforded first recovered 4,4'-di-tert-butylbiphenyl and then 495 mg (81%) of the glycal 22 as a colorless oil: Rf = 0.15 (silica gel, 1:9 ether/petroleum ether); evaporative distillation afforded 1 mol (2.12 mmol) of distilled tri(dimethylamino)phosphine.

To a stirred solution of 1.02 mmol of potassium hexamethyldisilazide in 6.9 mL of THF at −78 °C was added dropwise 0.39 mL (2.12 mmol) of distilled tri(dimethylamino)phosphine. After 20 min, the solution was allowed to warm to room temperature and then stirred an additional 30 min. To 102 mL (25 mmol) of a stirred solution of lithium (18). Elution with 25 mg (0.655 mmol) of the allyl ether 18 in a manner similar to that described above provided 234 mg of additional methyl ketol 16 representing a total yield of 85%.

2-(1-Oxy-cis-propenyl)-3R-methyl-3,4(R)-(dimethylenedioxy)-5(R)-methyl-6(S)-methyldioxy)tetrahydropyran-2-ol (19). To a stirred solution of 392 mg (0.965 mmol) of the acid 22 in 2.5 mL of dichloromethane and 2.5 mL of saturated aqueous NaCl. The solution was stirred (MgSO₄) and then evaporated at reduced pressure. Chromatography of the residue on silica gel with 1:9 ether/petroleum ether afforded first recovered 4,4'-di-tert-butylbiphenyl and then 495 mg (81%) of the glycal 22 as a colorless oil: Rf = 0.15 (silica gel, 1:9 ether/petroleum ether); evaporative distillation afforded 1 mol (2.12 mmol) of distilled tri(dimethylamino)phosphine.

To a stirred solution of 1.02 mmol of potassium hexamethyldisilazide in 6.9 mL of THF at −78 °C was added dropwise 0.39 mL (2.12 mmol) of distilled tri(dimethylamino)phosphine. After 20 min, the solution was allowed to warm to room temperature and then stirred an additional 30 min. To 102 mL (25 mmol) of a stirred solution of lithium (18). Elution with 25 mg (0.655 mmol) of the allyl ether 18 in a manner similar to that described above provided 234 mg of additional methyl ketol 16 representing a total yield of 85%.
centred under reduced pressure. Chromatography of the residue on 15 g of silica gel (4:6 ether/petroleum ether) afforded 229 mg (65%) of an unseparable 5:1 diastereomeric mixture of the acids 26a as a colorless oil: \( R_f = 0.24 \) (major diastereomer), 0.21 (minor diastereomer) (silica gel, 4:6 ether/petroleum ether); IR (CHCl₃) 3200, 2930, 1715, 1630, 1570, 1460, 1385, 1375, 1260, 1210, 1095, 1015 cm⁻¹; 'H NMR (CDCl₃) 6 0.17 H, C₆H₅CHH), 5.09 (1 H, CH₂CH₂), 1.75 (s, 3 H, CH₃C=CH), 1.92 (dt, 1 H, J = 14, 7.5 Hz, CH₃CH=C), 1.75 (s, 3 H, CH₃C=CH), 1.92 (dt, 1 H, J = 14, 7.5 Hz, CH₃CH₂), 1.69 (dt, 1 H, J = 14, 7.5 Hz, CH₃CH=CH₂), 1.75 (s, 3 H, CH₃C=CH), 1.92 (dt, 1 H, J = 14, 7.5 Hz, CH₃CH₂); 1.59 (s, 3 H, CH₃C=CH), 1.92 (dt, 1 H, J = 14, 7.5 Hz, CH₃CH₂); 1.59 (s, 3 H, CH₃C=CH), 1.92 (dt, 1 H, J = 14, 7.5 Hz, CH₃CH₂); 1.59 (s, 3 H, CH₃C=CH), 1.92 (dt, 1 H, J = 14, 7.5 Hz, CH₃CH₂). Anal. Cald. for C₃₃H₃₀O₆S: C, 64.37; H, 8.34.

The residue on 10 g of silica gel with 1:1 ether/petroleum ether yielded 57 mg (5%) of the aldehyde 26b as a colorless oil: \( R_f = 0.06 \) (silica gel, 1:1 ether/petroleum ether); 'H NMR (CDCl₃) δ 0.15 (3 H, J = 7 Hz, CH₃CH₂), 1.13 (3 H, J = 7 Hz, CH₃CH₂), 1.33, 1.52 (2 s, 6 H, (CH₃)₂C), 0.86 (1 H, J = 4 Hz, C(7)-H), 0.69 (1 H, J = 4 Hz, C(8)-H), 1.63 (br s, 1 H, CH₂C=CH), 1.83 (d, 1 H, J = 11 Hz, CH₂C=CH), 2.34 (br s, 1 H, CH₂C=CH). Anal. Cald. for C₃₃H₃₀O₆S: C, 64.37; H, 8.34.

To a stirred solution of 22 mg of the aldehyde 26b in 1.1 mL of dry THF at 0 °C, was added 0.19 mL (1.07 mmol) Me₂SiCl. The reaction mixture was treated with 0.19 mL (1.07 mmol) of the ester 27a. There was then eluted 84 mg (70%) of a seleno ester 28b as a white solid. Recrystallization from 3:7 ether/petroleum ether afforded 71 mg (65%) of the seleno ester 28b as a white solid.

To a stirred solution of 34 mg (0.087 mmol) of the aldehyde 26a in 0.6 mL of dichloromethane, and then washed with 50 mL of saturated aqueous NaCl acidified to pH 2 with dilute aqueous HCl. The solution was concentrated under reduced pressure. Chromatography of the residue on 3:7 ether/petroleum ether afforded 12 mg (35%) of the aldehyde 26a as a colorless oil: \( R_f = 0.21 \) (silica gel, 3:7 ether/petroleum ether); IR (CHCl₃) 3200, 2930, 1715, 1630, 1570, 1460, 1385, 1375, 1255, 1140, 1095, 1010, 870, 840 cm⁻¹; 'H NMR (CDCl₃) δ 0.17 H, C₆H₅CHH), 5.13 (d, 1 H, J = 7 Hz, CH₂C=CH), 1.33, 1.52 (2 s, 6 H, (CH₃)₂C), 0.86 (1 H, J = 4 Hz, C(7)-H), 1.63 (br s, 1 H, CH₂C=CH), 2.34 (br s, 1 H, CH₂C=CH). Anal. Cald. for C₃₃H₃₀O₆S: C, 64.37; H, 8.34.

To a stirred solution of 34 mg (0.087 mmol) of the aldehyde 26a in 0.6 mL of dichloromethane, and then washed with 50 mL of saturated aqueous NaCl acidified to pH 2 with dilute aqueous HCl. The solution was concentrated under reduced pressure. Chromatography of the residue on 3:7 ether/petroleum ether afforded 12 mg (35%) of the aldehyde 26a as a colorless oil: \( R_f = 0.21 \) (silica gel, 3:7 ether/petroleum ether); IR (CHCl₃) 3200, 2930, 1715, 1630, 1570, 1460, 1385, 1375, 1255, 1140, 1095, 1010, 870, 840 cm⁻¹; 'H NMR (CDCl₃) δ 0.17 H, C₆H₅CHH), 5.13 (d, 1 H, J = 7 Hz, CH₂C=CH), 1.33, 1.52 (2 s, 6 H, (CH₃)₂C), 0.86 (1 H, J = 4 Hz, C(7)-H), 1.63 (br s, 1 H, CH₂C=CH), 2.34 (br s, 1 H, CH₂C=CH). Anal. Cald. for C₃₃H₃₀O₆S: C, 64.37; H, 8.34.

To a stirred solution of 34 mg (0.087 mmol) of the aldehyde 26a in 0.6 mL of dichloromethane, and then washed with 50 mL of saturated aqueous NaCl acidified to pH 2 with dilute aqueous HCl. The solution was concentrated under reduced pressure. Chromatography of the residue on 3:7 ether/petroleum ether afforded 12 mg (35%) of the aldehyde 26a as a colorless oil: \( R_f = 0.21 \) (silica gel, 3:7 ether/petroleum ether); IR (CHCl₃) 3200, 2930, 1715, 1630, 1570, 1460, 1385, 1375, 1255, 1140, 1095, 1010, 870, 840 cm⁻¹; 'H NMR (CDCl₃) δ 0.17 H, C₆H₅CHH), 5.13 (d, 1 H, J = 7 Hz, CH₂C=CH), 1.33, 1.52 (2 s, 6 H, (CH₃)₂C), 0.86 (1 H, J = 4 Hz, C(7)-H), 1.63 (br s, 1 H, CH₂C=CH), 2.34 (br s, 1 H, CH₂C=CH). Anal. Cald. for C₃₃H₃₀O₆S: C, 64.37; H, 8.34.

To a stirred solution of 34 mg (0.087 mmol) of the aldehyde 26a in 0.6 mL of dichloromethane, and then washed with 50 mL of saturated aqueous NaCl acidified to pH 2 with dilute aqueous HCl. The solution was concentrated under reduced pressure. Chromatography of the residue on 3:7 ether/petroleum ether afforded 12 mg (35%) of the aldehyde 26a as a colorless oil: \( R_f = 0.21 \) (silica gel, 3:7 ether/petroleum ether); IR (CHCl₃) 3200, 2930, 1715, 1630, 1570, 1460, 1385, 1375, 1255, 1140, 1095, 1010, 870, 840 cm⁻¹; 'H NMR (CDCl₃) δ 0.17 H, C₆H₅CHH), 5.13 (d, 1 H, J = 7 Hz, CH₂C=CH), 1.33, 1.52 (2 s, 6 H, (CH₃)₂C), 0.86 (1 H, J = 4 Hz, C(7)-H), 1.63 (br s, 1 H, CH₂C=CH), 2.34 (br s, 1 H, CH₂C=CH). Anal. Cald. for C₃₃H₃₀O₆S: C, 64.37; H, 8.34.
of the seleno ester 27b as a colorless oil: \( R_f = 0.16 \) (silica gel, 19 ether/petroleum ether); IR (CHCl\(_3\)): 3000, 2960, 2940, 2890, 2865, 1710, 1655, 1385, 1375, 1260, 1195, 1020, 845 cm\(^{-1}\); \(^1\)H NMR (CDCl\(_3\)) \( \delta 0.05 \) (2 s, 6 H, \( (CH_3)_2Si \)), 0.89 (s, 9 H, \( (CH_3)_3C \)), 0.97 (d, 3 H, \( CH_3 \)), 1.19 (d, 3 H, \( CH_3 \)), 1.28, 1.50 (2 s, 6 H, \( (CH_3)_2C \)), 1.57 (s, 3 H, \( CH_3=CH \)), 3.20 (s, 3 H, \( OCH_3 \)).

3-Deoxy-1,2-O-(1-methylthiobenzyloxy)-3-\( \beta \)-l-threo-pentofuranuronic Acid Ester with the Glycitol 22 (36). By the procedure described for the preparation of the noralkanes 23a, 140 mg (0.016 mmol) of the seleno ester 27b, 70 \( \mu \)L (0.26 mmol) of tri-n-butyltin hydride, and a solution of 469 mg (2.12 mmol) of \( (1\,1\text{-dimethylmethylene})\text{bis(2-hydroxyethyl)} \) pyran in 1.5 mL of dichloromethane afforded, after chromatography on 20 g of silica gel with 1:9 and then 2:8 ether/petroleum ether, 91 mg (61%) of the methyl ester of acid 33 as a colorless oil: \( R_f = 0.19 \) (silica gel, 19 ether/petroleum ether); IR (CHCl\(_3\)): 3000, 2960, 2940, 2890, 2865, 1710, 1655, 1385, 1375, 1260, 1195, 1020, 845 cm\(^{-1}\); \(^1\)H NMR (CDCl\(_3\)) \( \delta 0.04 \) (s, 6 H, \( (CH_3)_2Si \)), 0.89 (s, 9 H, \( (CH_3)_3C \)), 0.96 (d, 3 H, \( CH_3 \)), 2.72-3.30 (4 H, \( OCH_2CH_2 \)), 3.36, 3.43 (m, 4 H, \( OCH_2CH_2 \)), 3.73 (s, 3 H, \( OCH_3 \)), 5.33 (s, 1 H, \( CH=OCH \)), 5.60 (d, 1 H, \( J = 6 \) Hz, \( CH=OCH \)), 5.97 (s, 1 H, \( OCH_3 \)).

1,2-Deoxy-\( \beta \)-l-threo-pentofuranuronic Acid Ester with the Glycitol 22 (36). By the procedure described for the preparation of the ester 25a, 163 mg (0.009 mmol) of the acid 35 as an oil of >95% purity; \(^1\)H NMR (CDCl\(_3\)) \( \delta 0.03 \) (2 s, 6 H, \( (CH_3)_2Si \)), 0.87 (s, 9 H, \( (CH_3)_3C \)), 0.92 (d, 3 H, \( CH_3 \)), 7.50 (3 H, \( J = 7 \) Hz, \( CH=CH \)), 1.00 (t, 3 H, \( J = 7 \) Hz, \( CH_3 \)), 1.19 (d, 3 H, \( J = 11 \) Hz, \( CH_3 \)), 1.32, 1.49 (2 s, 6 H, \( (CH_3)_2C \)), 1.46 (s, 3 H, \( CH_3=CH \)), 3.34 (s, 3 H, \( OCH_3 \)), 3.56, 3.69 (2 d, 2 H, \( J = 6 \) Hz, \( CH=CH \)), 3.77 (t, 2 H, \( J = 6 \) Hz, \( CH=CH \)), 4.86, 4.89 (dd, 1 H, \( J = 6 \), \( J' = 2.5 \) Hz, \( OCH_3 \)), 5.15 (d, 1 H, \( J = 6 \) Hz, \( CH=OCH \)), 5.60 (d, 1 H, \( J = 6 \) Hz, \( CH=OCH \)).