# PROGRESS TOWARD THE TOTAL SYNTHESIS OF POLYETHER IONOPHORE ANTIBIOTICS

Thesis by

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To my parents

## ACKNOWLEDGMENTS

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**ABSTRACT**

Several subunits for the convergent synthesis of polyether ionophore antibiotics via the ester enolate Claisen rearrangement of furanoid and pyranoid carboxylic acids and glycals are prepared from carbohydrates. Key steps from D-fructose to the monensin spiroketal include the ester enolate Claisen rearrangement of a glycal propionate, expansion of a furanoid to a pyranoid ring, and the acid catalyzed equilibration of a bicyclic ketal to a spiroketal. An alternative approach, entailing the hetero-Diels-Alder condensation of a 2-methylenetetrahydropyran and acrolein is thwarted by facile isomerization to the endocyclic enol ether. The monensin bis-tetrahydrofuran is prepared from D-xylose and D-mannose. In the key step, *in situ* silylation of an ester enolate with a beta leaving group allows the tetrahydrofuran rings to be joined by Claisen rearrangement. The monensin tetrahydropyran is prepared from D-fructose and then joined to the bis-tetrahydrofuran by the ester enolate Claisen rearrangement. Methodology for the radical induced, reductive decarboxylation of the resulting acid via its phenyl selenoester is described. Anomeric stabilization of the intermediate tetrahydrofuran-2-yl radical is an important factor in the stereochemical outcome of this process. Reduction of 2,3-O-(1-methylethylidene)furanosyl and pyranosyl chloride with lithium 4,4'-di-*t*-butylbiphenyl affords the corresponding glycals in high yield. The direct addition of nucleophilic reagents to crude Swern oxidation reaction mixtures circumvents the deleterious side

reactions characteristic of highly reactive carbonyl compounds. Hexylglyoxal, produced by Swern oxidation of 1,2-octanediol, condenses with methyl (triphenylphosphoranylidene)acetate to give the γ-oxo- crotonate. Addition of methyl magnesium bromide to an unstable 2-ketofuranoside delivers the branched chain carbohydrate derivative. The transient existence of monomeric trimethylsilyl formaldehyde, generated at -78°C by Swern oxidation of trimethylsilylmethanol, is established by isolation of a Wittig condensation product.

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# CHAPTER 1

## The Synthesis of the Monensin Spiroketal

# THE CONVERGENT SYNTHESIS OF POLYETHER IONOPHORE ANTIBIOTICS: THE SYNTHESIS OF THE MONENSIN SPIROKETAL[1]

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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 pyranoid 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.[4] As ionophores, these compounds possess a striking ability to perturb ionic gradients by catalytically transporting cations across lipid barriers.[5] While optimal membrane and ion selectivity remain elusive goals, the commercial use of monensin for control of poultry coccidiosis[6] and enhancement of ruminant feed utilization[6] have encouraged intensive efforts in the isolation and study of these compounds. Several have demonstrated potential in human medicine, particularly as cardiovascular agents.[7] 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.[8] Structurally, most of the polyether ionophores feature linear chains of substituted tetrahydropyran and tetrahydrofuran rings. Comparison reveals that nearly all of 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.[9]

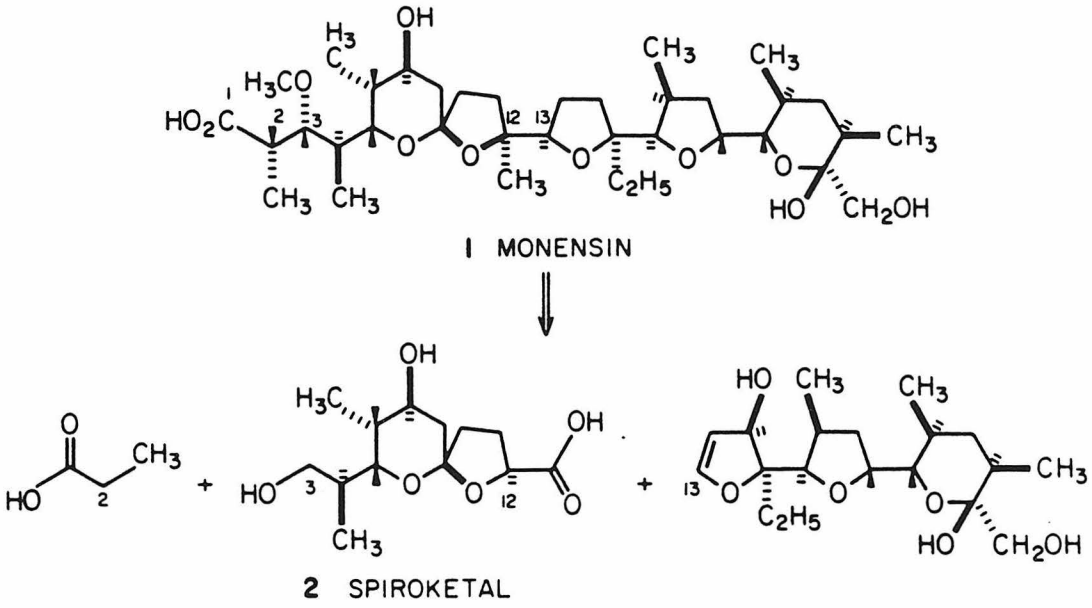
We have recently developed a versatile, building-block approach to the polyethers in which prefabricated tetrahydrofuran and tetrahydropyran rings are joined via the ester enolate Claisen rearrangement. This work has

culminated in the total synthesis of lasalocid A[8b] and its enantiomer[10] from readily available carbohydrates. In this and the following articles, we report the preparation of several additional subunits for the synthesis of naturally occurring polyethers and potentially informative analogues.

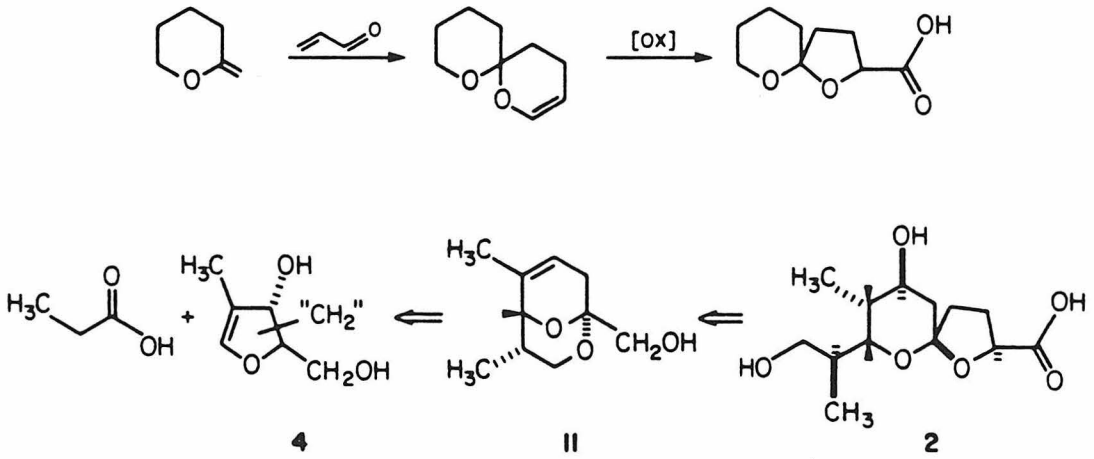
Serving as rigid bends in the polyether backbone, spiroketals play a critical role in establishing the coordination geometry necessary for ion complexation.[11] Since one of the spiro oxygens usually acts as a ligand as well, spiroketals are prominent features of the polyether class.[12] Monensin's[13] spiroketal 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 spiroketals (Scheme II).[14] Although the rigidity of the spiroketal system itself can mediate control of relative stereochemistry,[15] 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.[16] However, the problems associated with deoxygenating a hexopyranose at the

**SCHEME I** RETROSYNTHETIC ANALYSIS FOR MONENSIN




**SCHEME II** BASIC DESIGN FOR THE SYNTHESIS OF THE SPIROKETAL **2**

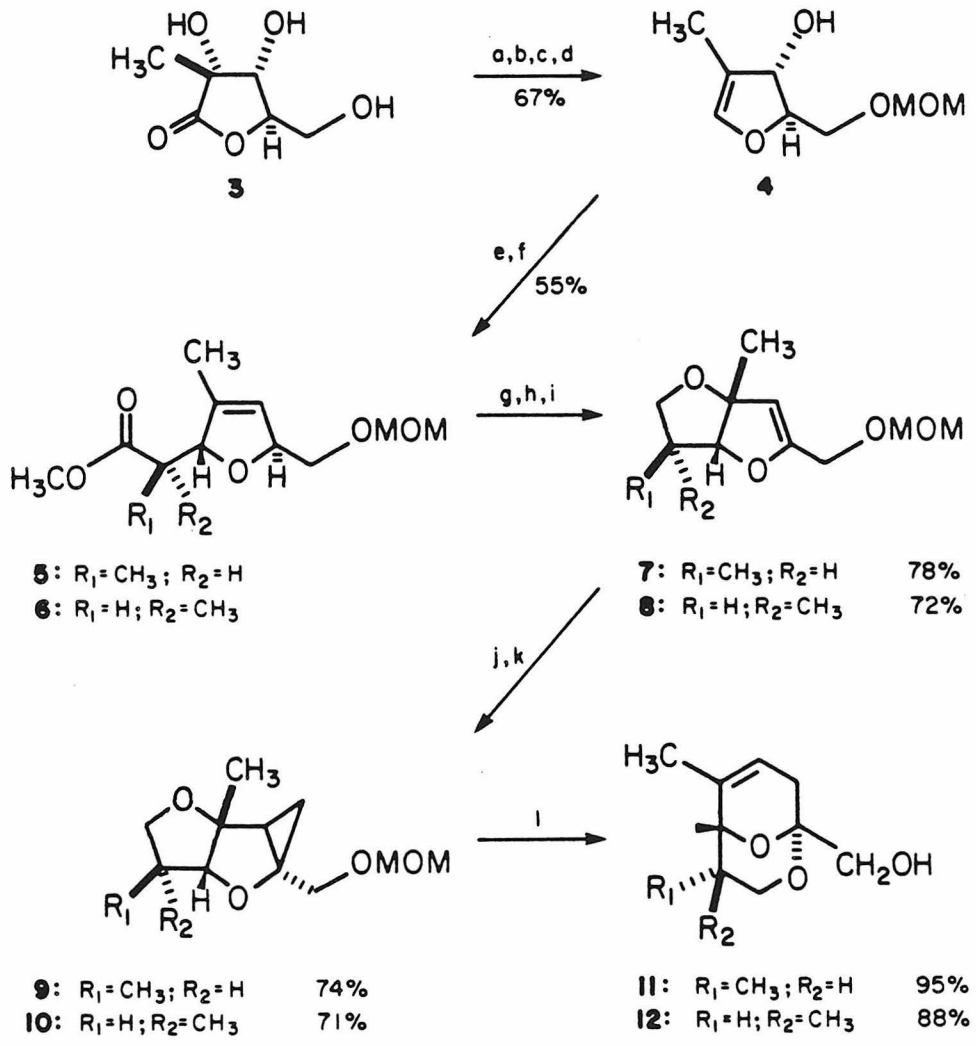


4 position[17] and the rarity of branched carbohydrates[18] prompted us to take a more subtle tack using the furanoid glycal **4** as a pyranoid equivalent.

Available on large scale by treatment of invert sugar with aqueous calcium hydroxide, the branched chain carbohydrate "α"-D-glucosaccharinic acid, γ-lactone (**3**),[19] has been converted previously to the required glycal **4**[20] (Scheme III). Application of the ester enolate Claisen rearrangement to the corresponding propionate provided a diastereomeric mixture of the esters **5** and **6**. As described earlier,[21] either isomer could be made to predominate by choice of enolization conditions (LDA/THF--**5**:**6**/20%:80%; LDA/THF, 23% HMPA--**5**:**6**/80%:20%). Ample precedent[22] allowed us to predict that rearrangement of the Z silyl ketene acetal through a preferred boat-like transition state would deliver the R configuration at C4,[23] and thus the major product obtained from enolization in the presence of HMPA was identified as the desired diastereomer and separated by chromatography.

Having attached the side chain at C5,[23] we now confronted three problems: expansion of a furanoid to a pyranoid ring; stereoselective oxygenation of the carbon backbone at C7;[23] and introduction of the ketone oxidation state at C9.[23] Reduction of the ester **5**, iodoetherification, and then elimination of HI overcame the latter problem and neatly set the stage for solving the remaining

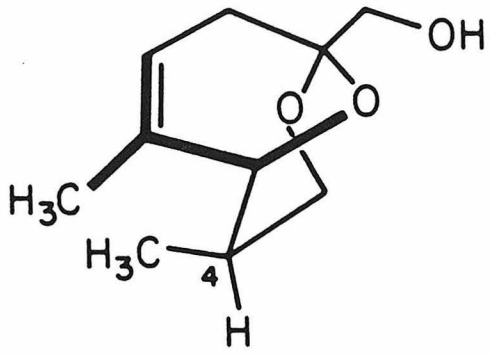
**SCHEME III** SYNTHESIS OF THE BICYCLIC KETAL **11**[a]




[a](a) $H_2SO_4$, $(CH_3)_2CO$; (b) KH, $ClCH_2OCH_3$, THF; (c) DIBAL, $Et_2O$, -78°C; (d) $P(NMe_2)_3$, $CCl_4$, THF; Li, $NH_3$; $NH_4Cl$; (e) n-BuLi, n-$C_2H_5COCl$, THF; LDA, THF/HMPA; $Me_3SiCl$; $OH^-$; (f) $CH_2N_2$, $Et_2O$; (g) LAH, $Et_2O$; (h) $I_2$, $Na_2CO_3$, $CH_3CN$; (i) DBU, $C_6H_6$; (j) 50% aqueous NaOH, $CHCl_3$, TEBAC; (k) LAH, $Et_2O$; (l) **11**: 62% $HClO_4$, $CH_3CN$; **12**: 10% HCl, THF.

two. While the acid sensitivity[24] of the furanoid glycal **7** precluded Simmons-Smith cyclopropanation,[25] the incipient "4-deoxypyranose" carbon was introduced without complication by phase transfer catalyzed dichlorocyclopropanation[26] followed by hydrodehalogenation.[27,28] When purification was carried out only at this point, the cyclopropane **9** was reproducibly obtained in 85% overall yield from the methyl ester **5**. Acid catalyzed rearrangement of this cyclopropyl ether[29] to the bicyclic ketal **11** completed the furanoid to pyranoid ring conversion and restored a double bond between C6 and C7[23] for future oxygenation.

The diastereomeric cyclopropanes **9** and **10** showed disparate reactivity in this transformation. Heating the α-methyl epimer **10** in 1:4/10% HCl:THF at 55°C for 17 hours induced rearrangement to the bicyclic ketal **12** in 88% yield. With the β-methyl epimer **9**, these conditions merely removed the MOM group to give the corresponding cyclopropyl carbinol. At higher temperatures and extended reaction times, TLC indicated that the bicyclic ketal **11** decomposed nearly as rapidly as it formed. Although the reason for the difference in rearrangement rate is not entirely clear, models show that the difference in product stabilities is a result of the severe steric congestion encountered by the C6[23] methyl group in bicyclic ketal **11**.[30] Choice of both solvent and acid proved to be crucial to the success of

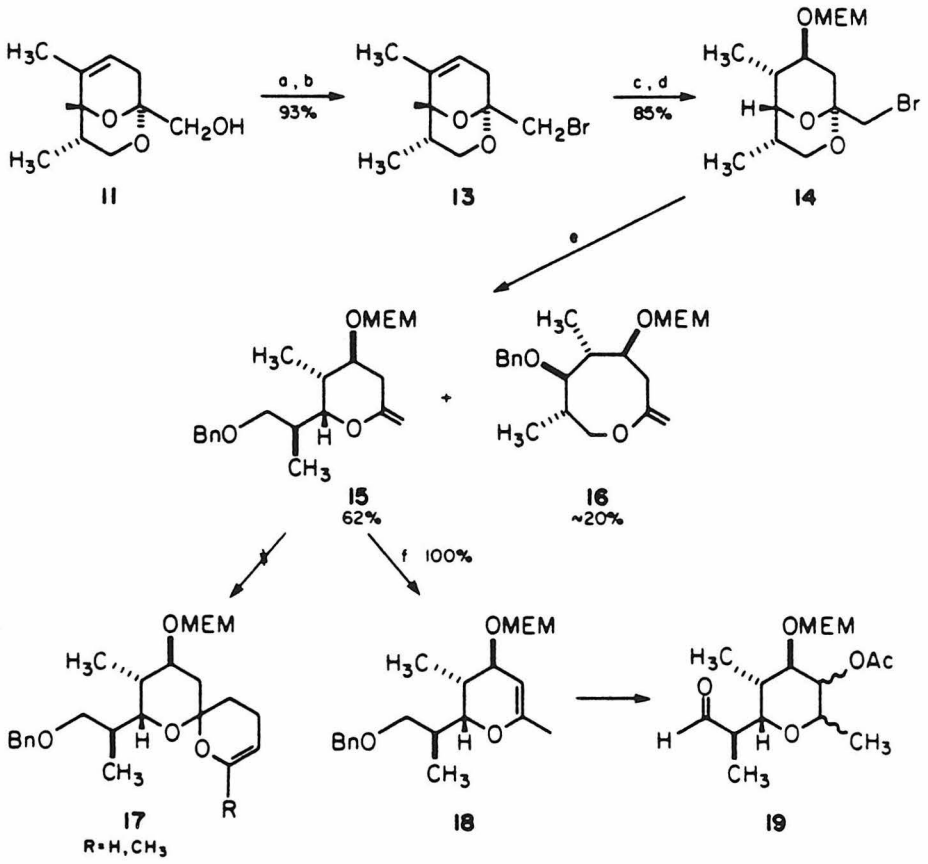



11

this reaction. While modest yields were obtained with two equivalents of $TiCl_4$ in benzene at 7°C, consideration of the ionic character of the transition state suggested that use of a more polar solvent might facilitate the rearrangement. To our delight, concentrated perchloric acid in acetonitrile at room temperature gave the bicyclic ketal **11** in 95% yield.[31]

Conversion of this intermediate to an exocylic enol ether required deoxygenation at a neopentyl center with <u>two</u> $\alpha$ oxygens (Scheme IV). Although $S_N2$ displacement at this center was expected to be difficult,[32] the triflate ester[33] of **11**, recovered quantitatively from excess lithium bromide in refluxing THF, was seemingly indestructible under $S_N2$ conditions. The surprising ease with which the triflate succumbed to tetra-<u>n</u>-butyl ammonium bromide in HMPA suggests

**SCHEME IV** THE HETERO-DIELS-ALDER APPROACH TO THE SPIROKETAL 2[a]




[a](a) $(CF_3SO_2)_2O$, $C_5H_5N$, $CH_2Cl_2$; (b) $(n\text{-Bu})_4NBr$, HMPA; (c) $BH_3$, THF; 10% NaOH, 30% $H_2O_2$; (d) $CH_3OCH_2CH_2OCH_2Cl$, $(i\text{-Pr})_2NEt$, $CH_2Cl_2$; (e) n-BuLi, THF; BnBr, HMPA; (f) $H^+$.

changeover to an $S_N1$ mechanism with anchimeric assistance from a ketal oxygen.[34] Hydroboration of the resulting bromo-olefin **13** occurred with complete regio and stereoselectivity from the convex face of the bicyclic ketal, which, having served its intended architectural role, was now expendable. Stereoelectronic considerations[35] led us to predict that the desired methylene pyran **15**, resulting from the fragmentation of an axial carbon--carbon bond, rather than its eight membered ring analogue **16**, should be the major product of a reductive elimination across C9 and C10.[23] An obstacle before, the steric hindrance about C10[23] now permitted clean metal-halogen exchange with n-butyllithium at -78°C. After the reaction was quenched with benzyl bromide, the protected methylene pyran **15** was reproducibly obtained in 62% yield after chromatography on alumina.[36]

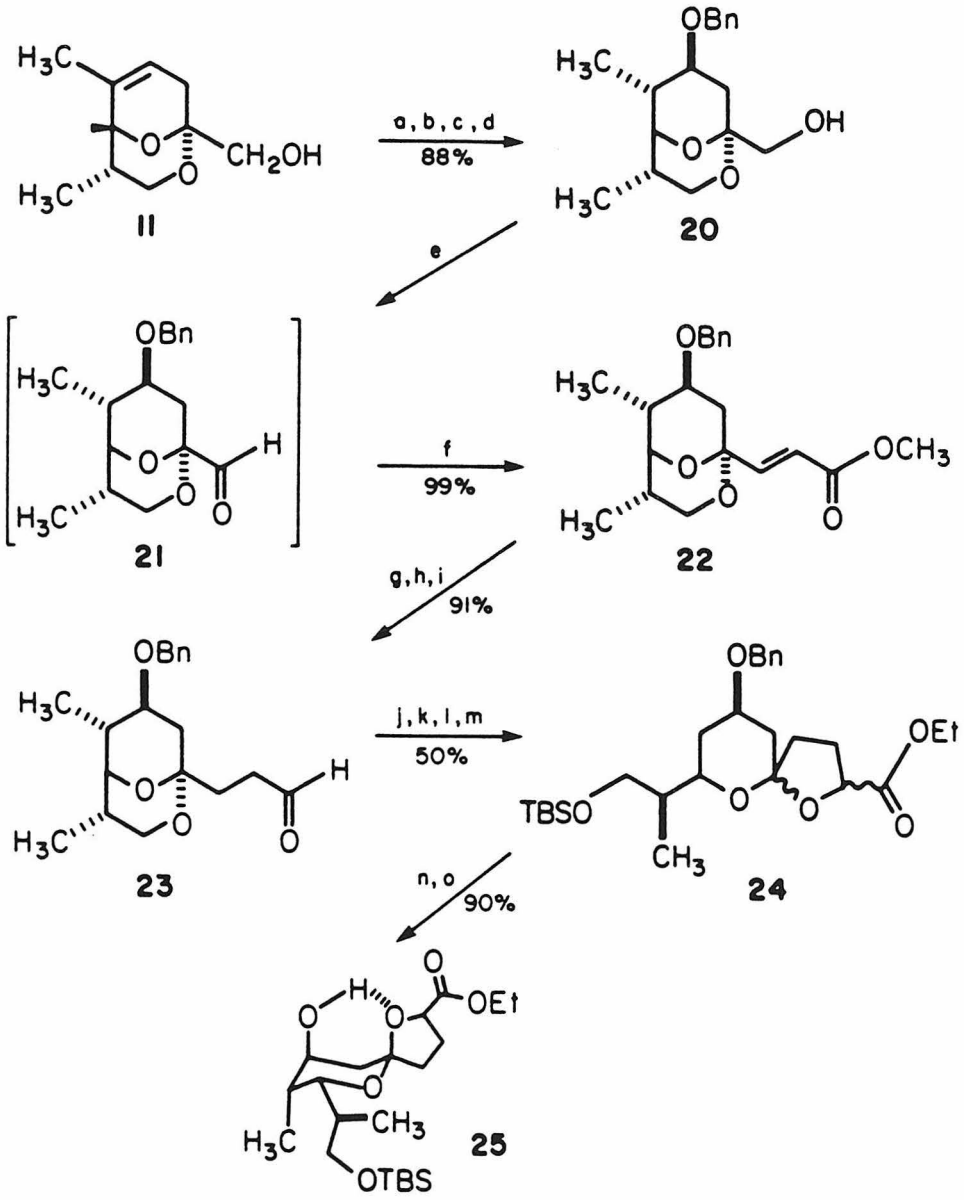
Two factors conspired to thwart the hetero-Diels-Alder reaction we had envisioned. First, isomerization to the endocylic olefin **18** was incredibly facile, with a half-life of no more than ten minutes in THF at 55°C in base washed glassware. Although no isomerization was detected at this temperature 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.[37] Furthermore, although good yields of adduct were obtained by allowing 2-

methylenetetrahydropyran to stand at room temperature with one equivalent of acrolein for a few days,[14] use of acrolein as solvent for the functionalized methylene pyran **15** led only to slow isomerization. It was this second factor, lack of reactivity, which finally forced us to abandon this route. For despite the fact that methyl vinyl ketone could be heated to reflux as a 1:1 mixture with either pyridine or triethylamine without undue polymerization, no adduct with the methylene pyran **15** could be detected at reaction temperatures below 70°C. At higher temperatures, isomerization was complete in a few hours.

Recognizing that the extremely severe steric congestion created by hydroboration of the bicyclic ketal **11** is relieved by cleavage of the axial carbon-oxygen bond, we envisioned an alternative, thermodynamic entry to the spiroketal system via acid catalyzed equilibration with an appropriately functionalized side chain. Fortunately, this new strategy could be implemented with an advanced intermediate in the hetero-Diels-Alder route (Scheme V).

Hydroboration of the silyl ether of olefin **11** was again completely selective, and a protection-deprotection[38] sequence gave the neopentyl alcohol **20**[39] in 88% overall yield from the bicyclic ketal. In light of our previous difficulties, this initially appeared to be an unlikely site for appending the spiroketal sidechain. However, the extreme steric demands of a pentagonal transition state are

**SCHEME V** THERMODYNAMIC EQUILIBRATION TO THE MONENSIN SPIROKETAL[a]




[a](a) TBSCl, $C_5H_5N$, $CH_2Cl_2$; (b) $BH_3$, THF; 10% NaOH, 30% $H_2O_2$; (c) t-BuOK, BnBr, THF; (d) $(n\text{-Bu})_4NF$, THF; (e) $(COCl)_2$, $Me_2SO$, $CH_2Cl_2$; $Et_3N$; (f) $\phi_3PCHCO_2Me$; (g) $H_2$, 5% Rh/C, $n\text{-}C_5H_{12}$; (h) LAH, $Et_2O$; (i) $(COCl)_2$, $Me_2SO$, $CH_2Cl_2$; $Et_3N$; (j) $CH_2C(OEt)Li$; (k) $O_3$, $CH_2Cl_2$, MeOH; $Me_2S$; (l) $C_6H_5NH^+ \cdot p\text{-}TsO^-$, $CHCl_3$; (m) TBSCl, $C_5H_5N$, $CH_2Cl_2$; (n) $H_2$, 10% Pd/C, EtOH: (o) $C_6H_5NH^+ \cdot p\text{-}TsO^-$, $CHCl_3$.

attenuated in the corresponding conversion from trigonal to tetrahedral hybridization, and the inductive effect of the ketal oxygens should activate an adjacent electrophilic center. In fact, special reaction conditions were required to overcome the propensity of the neopentyl aldehyde **21** toward hydration and decomposition. The Swern oxidation[40] is both mildly basic and completely anhydrous, and addition of methyl (triphenylphosphoranylidene)acetate to the crude reaction mixture provided the unsaturated ester **22** in nearly quantitative yield. After adjustment of the side chain oxidation state, the spiroketal carboxylate carbon was introduced by ozonization of the adduct with lithiated ethyl vinyl ether.[41]

Complete equilibration from the bicyclic to spirocylic ketal system was smoothly promoted by pyridinium p-toluenesulfonate, and protection[42] of the liberated primary hydroxyl group gave the four spiroketal diastereomers **24**[43] in an overall yield of 50% from the aldehyde **23**.[44] Easily separated by chromatography, each epimer at the carboethoxy center[43] gave a single spiroisomer **25** when debenzylated and subjected to equilibration with pyridinium p-toluenesulfonate. A sharp absorption at 3560 $cm^{-1}$ in the IR spectrum confirmed the presence of an intramolecular hydrogen bond between the $C7^{23}$ hydroxyl and axial spiroketal oxygen. Since the asymmetry at the carboethoxy center will be lost during enolization in the Claisen rearrangement

joining this subunit to the polyether backbone, each of the four diastereomers can, in principle, be converted to the thermodynamic[45] monensin spiroketal.

## EXPERIMENTAL SECTION

Melting points were determined using a Hoover capillary melting point apparatus and are uncorrected. Infrared (IR) spectra were determined on a Perkin-Elmer 727B or 1310 infrared spectrophotometer. Proton nuclear magnetic resonance ($^1$H NMR) spectra were recorded on a Varian EM-390 spectrometer, except where "500 MHz" denotes spectra recorded on a Bruker WM-500 spectrometer (Southern California Regional NMR Facility, Caltech, Pasadena, California). Chemical shifts are reported as $\delta$ values in parts per million relative to tetramethylsilane ($\delta$ 0.0) as an internal standard. Data are reported as follows: chemical shift (multiplicity, integrated intensity, coupling constants, assignment). Optical rotations were measured in 1 dm cells of 1 mL capacity using a JASCO Model DIP-181 polarimeter. Chloroform, when used as a solvent for optical rotations, was filtered through neutral alumina (Activity I) immediately prior to use. Analytical thin-layer chromatography (TLC) was conducted on 2.5 x 10 cm precoated TLC plates: silica gel 60 F-254, layer thickness 0.25 mm, manufactured by E. Merck and Co., Darmstadt, Germany. Silica gel columns for chromatography utilized E. Merck silica gel 60 (70-230 mesh ASTM). Flash chromatography was performed on E. Merck silica gel 60 (230-400 mesh ASTM) according to a published procedure (Still W. C.; Kahn, M.; Mitra, A. J. Org. Chem. **1978**, 43, 2923-2925). Acidic silica gel refers to Silicar CC-4 Special "for column chromatography," sold by

Mallinckrodt Chemical Works, St. Louis, MO. "Alumina" refers to the grade I neutral variety manufactured by M. Woelm, Eschwege, Germany, which was neutralized to the indicated grade by the addition of water. Reaction solvents and liquid reagents were purified by distillation or drying shortly before use. Benzene, pyridine, n-hexane, trimethylchlorosilane, oxalyl chloride, N,N-diisopropylethylamine, and dichloromethane were distilled from powdered calcium hydride. Dimethyl sulfoxide, dimethylformamide, and hexamethylphosphoramide were distilled under reduced pressure from powdered calcium hydride and stored over a mixture of 3A and 4A sieves. n-Pentane was distilled from sodium metal under argon. Hexamethyldisilazane was distilled under argon from powdered calcium hydride and stored over a mixture of 3A and 4A sieves. Ether, tetrahydrofuran, triethylamine and diisopropylamine were distilled under argon from sodium metal with sodium benzophenone ketyl as an indicator. Methanol was distilled from sodium methoxide and methyl benzoate. Acetonitrile was dried over a mixture of 3A and 4A sieves. Ammonia was distilled from the tank and then from a blue lithium solution. n-Propionyl chloride was heated at reflux for 3h with phosphorous pentachloride and then distilled, and the distillate was treated with quinonline and redistilled. Tris(dimethylamino)phosphine was distilled at reduced pressure under argon. Ammonium chloride was dried at 75°C under vacuum (1 mm Hg) over phosphorous pentoxide for at least 12h. All

other reactants and solvents were "reagent grade" unless described otherwise. "Ether" refers to anhydrous diethyl ether which is supplied by Mallinckrodt and Baker. "Petroleum ether" refers to the "analyzed reagent" grade hydrocarbon fraction (bp 35-60°C) which is supplied by J. T. Baker, Co., Phillipsburg, NJ. 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 12h 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*. Mass spectral analyses were performed by Larry Henling, Caltech, Pasadena, CA. Elemental combustion analyses were performed by Spang Microanalytical Laboratory, Eagle Harbor, MI.

**Methyl 2(*R*) and 2(*S*)-[2,5-dihydro-5(*S*)-(methoxymethylene-oxymethyl)-3-methyl-2(*R*)-furyl]propanoate (5 and 6).** To a stirred solution of 2.65 g (15.2 mmol) of the glycal **4**[20] in 50 mL of THF at -78°C was added 6.43 mL (15.2 mmol) of a 2.36 M solution of *n*-butyllithium in hexane, and then after 5 min, 1.37 mL (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 HMPA at -78°C. After 10 min, the

reaction mixture was treated with 4.57 mL (26.3 mmol of $Me_3SiCl$) of the supernatant centrifugate from a 3:1 mixture of trimethylchlorosilane and triethylamine. After 3h 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 solution 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 phases were washed with two 40 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 ($MgSO_4$), concentrated to 100 mL, and then treated with excess ethereal diazomethane. The solvent was removed under reduced pressure and medium-pressure liquid chromatography (Lobar prepacked column, size C, LiChroprep Si60, EM Reagents) of the residue with 24:76 ethyl acetate/cyclohexane afforded first 408 mg (11%) of the ester **6** as a colorless oil: $R_f$ = 0.26 (silica gel, 1:1 ether/petroleum ether); evaporative distillation 80-90°C (0.005 mm Hg); $[\alpha]_D^{23}$ -137° (c 1.66, $CHCl_3$); IR ($CHCl_3$) 2990, 1740, 1475, 1455, 1170, 1130, 1100, 1050 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 1.14 (d, 3H, J=8 Hz, $CH_3CH$), 1.67 (bs, 3H, $CH_3C=CH$), 3.33 (s, 3H, $OCH_3$), 3.67 (s, 3H, $CO_2CH_3$), 4.60 (s, 2H, $OCH_2O$), 5.47 (bs, 1H, $CH_3C=CH$).

There was then eluted 1.64 g (44%) of the ester **5** as a colorless oil: $R_f$ = 0.20 (silica gel, 1:1 ether/petroleum ether); evaporative distillation 80-90°C (0.005 mm Hg); $[\alpha]_D^{23}$ -87.3° (*c* 1.53, $CHCl_3$); IR ($CHCl_3$) 2990, 1740, 1455, 1145, 1130, 1100, 1050 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 1.04 (d, 3H, J=7 Hz, $CH_3CH$), 1.67 (bs, 3H, $CH_3C=CH$), 3.33 (s, 3H, $OCH_3$), 3.70 (s, 3H, $CO_2CH_3$), 4.49 (s, 2H, $OCH_2O$), 5.50 (bs, 1H, $CH_3C=CH$). Anal. Calcd for $C_{12}H_{20}O_5$ (mixture of **5** and **6**): C, 59.00; H, 8.25. Found: C, 58.91; H, 8.23.

**2(*S*)-[2,5-Dihydro-5(*S*)-(methoxymethyleneoxymethyl)-3-methyl-2(*R*)-furyl]propan-1-ol.** To a stirred solution of 439 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 tetrahydridoaluminate. After 1h at room temperature, the mixture was cautiously treated with 70 μL of water, 70 μL of 15% aqueous NaOH, and then 210 μL 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: $R_f$ = 0.23 (silica gel, 9:1 ether/petroleum ether); $[\alpha]_D^{22}$ -94° (*c* 1.33, $CHCl_3$); IR ($CHCl_3$) 3645, 3500, 1680, 1440, 1155, 1120, 1085, 1030 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 0.81 (d, 3H, J=7 Hz, $CH_3CH$); 1.67 (bs, 3H, $CH_3C=CH$), 3.33 (s, 3H, $OCH_3$), 4.60 (s, 2H, $OCH_2O$), 5.41 (bs, 1H, $CH_3C=CH$). Anal. Calcd for $C_{11}H_{20}O_4$: C, 61.09; H, 9.32. Found: C, 60.80; H, 9.30.

**2(R)-[2,5-Dihydro-5(S)-(methoxymethyleneoxymethyl)-3-methyl-2(R)-furyl]-propan-1-ol.** By the procedure described for the above alcohol, 3.87 g (15.8 mmol) of the methyl ester **6** and 0.6 g (15.8 mmol) of lithium tetrahydridoaluminate in 100 mL of ether afforded, after flash chromatography on 150 g of silica gel with ether, 3.25 g (95%) of the alcohol as a colorless oil: $R_f$ = 0.24 (silica gel, 9:1 ether/petroleum ether); evaporative distillation 70-80°C (0.004 mm Hg); IR ($CHCl_3$) 3630, 3480, 1670, 1445, 1145, 1110, 1020, 915 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 1.09 (d, 3H, J=7 Hz, $CH_3CH$), 1.75 (bs, 3H, $CH_3C=CH$), 3.33 (s, 3H, $OCH_3$), 4.62 (s, 2H, $OCH_2O$), 5.45 (bs, 1H, $CH_3C=CH$). Anal. Calcd for $C_{11}H_{20}O_4$: C, 61.09; H, 9.32. Found: C, 61.16; H, 9.34.

**5(R)-1(S),4(S)-Dimethyl-8(S)-iodo-7(R)-(methoxymethyleneoxymethyl)-2,6-dioxabicyclo[3.3.0]octane.** To a stirred solution of 509 mg (2.35 mmol) of the above alcohol (derived from ester **5**) in 26 mL of dry acetonitrile was added 2.49 g (23.5 mmol) of anhydrous sodium carbonate and 2.99 g (11.8 mmol) of iodine. The mixture was stirred in the dark for 2h at room temperature, diluted with 80 mL of ether and then treated with 40 mL of 10% aqueous $Na_2SO_3$. The organic layer was separated, washed with 50 mL of saturated aqueous NaCl and dried ($MgSO_4$). 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 732 mg (93%) of

the iodoether as a light yellow oil: $R_f$ = 0.20 (silica gel, 3:7 ether/petroleum ether); evaporative distillation 65-75°C (0.001 mm Hg); $[\alpha]_D^{22.5}$ +36.2 (*c* 1.64, $CHCl_3$); IR ($CHCl_3$) 1480, 1405, 1165, 1125, 1100, 1055, 938 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 1.08 (d, 3H, J=7.5 Hz, $CH_3CH$), 1.70 (s, 3H, $CH_3$), 3.37 (s, 3H, $OCH_3$), 4.40 (d, 1H, J=4 Hz, CHI), 4.63 (s, $OCH_2O$, 2H). Anal. Calcd for $C_{11}H_{19}IO_4$: C, 38.61; H, 5.60. Found: C, 38.62; H, 5.56.

**5(R)-1(S),4(R)-Dimethyl-8(S)-iodo-7(R)-(methoxymethylene-oxymethyl)-2,6-dioxabicyclo[3.3.0]octane.** By the procedure described for the preparation of the above iodoether, 3.25 g (15.0 mmol) of the above alcohol (derived from the ester 6), 19.07 g (75.1 mmol) of iodine, and 15.93 g (150 mmol) of anhydrous sodium carbonate in 150 mL of acetonitrile afforded, after flash chromatography on 150 g of silica gel with 3:7 ether/petroleum ether, 4.38 g (87%) of the iodoether as a light yellow oil: $R_f$ = 0.26 (silica gel, 3:7 ether/petroleum ether); evaporative distillation 70-80°C (0.005 mm Hg); $[\alpha]_D^{25}$ +10.8° (*c* 1.14, $CHCl_3$); IR ($CHCl_3$) 1460, 1385, 1135, 1110, 1020, 985, $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 1.08 (d, 3H, J=7.5 Hz, $CH_3CH$), 1.67 (s, 3H, $CH_3C$), 3.34 (s, 3H, $OCH_3$), 4.40 (d, 1H, J=3 Hz, CHI), 4.62 (s, 2H, $OCH_2O$). Anal. Calcd for $C_{11}H_{19}IO_4$: C, 38.61; H, 5.60. Found: C, 38.37; H, 5.35.

**5(R)-1(R),4(S)-Dimethyl-7-(methoxymethyleneoxymethyl-2,6-dioxabicyclo[3.3.0]oct-7-ene (7).** To a stirred solution of 5.90 g (17.6 mmol) of the above iodoether (derived from the ester **5**) in 52 mL of benzene was added 11.85 mL (79.2 mmol) of 1,5-diazabicyclo[5.4.0]undec-5-ene. After 12 h at room temperature, the solution was heated to reflux for 2 h, allowed to cool, and then poured into 300 mL of ether. The resulting mixture was washed with three 100 mL portions of saturated aqueous NaCl and then dried ($Na_2CO_3$). Removal of the solvent under reduced pressure and flash chromatography of the residue on 50 g of silica gel with 4:6 ether/petroleum ether afforded 3.28 g (87%) of the olefin **7** as a colorless oil: $R_f$ = 0.26 (silica gel, 4:6 ether/petroleum ether); evaporative distillation 60-65°C (0.004 mm Hg); $[\alpha]_D^{23}$ +0.014° (c 1.49, $CHCl_3$); IR ($CHCl_3$) 1675, 1470, 1385, 1150, 1105, 1040, 990, 960 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 1.07 (d, 3H, J=7 Hz, $CH_3CH$), 1.51 (s, 3H, $CH_3C$), 3.33 (s, 3H, $OCH_3$), 4.07 (s, 2H, $CCH_2O$), 4.63 (s, 2H, $OCH_2O$), 4.90 (s, 1H, C=CH). Anal. Calcd for $C_{11}H_{18}O_4$: C, 61.66; H, 8.47. Found: C, 61.49; H, 8.32.

**5(R)-1(R),4(R)-Dimethyl-7-(methoxymethyleneoxymethyl)-2,6-dioxabicyclo[3.3.0]oct-7-ene (8).** By the procedure described above for the preparation of the olefin **7**, a solution of 4.37 g (13.1 mmol) of the above iodoether (derived from the ester **6**) and 8.96 g (58.8 mmol) of 1,5-diazabicyclo[5.4.0]undec-5-ene in 38 mL of benzene afforded, after flash chromatography

on 50 g of silica gel with 3:7 ether/petroleum ether, 2.44 g (87%) of the olefin **8** as a colorless oil: $R_f$ = 0.26 (silica gel, 3:7 ether/petroleum ether); evaporative distillation 55-65°C (0.005 mm Hg); $[\alpha]_D^{25}$ +11.8° (*c* 1.19, $CHCl_3$); IR ($CHCl_3$) 1670, 1460, 1380, 1150, 1105, 1030, 980, 950 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 1.04 (d, 3H, J=7 Hz, $CH_3CH$), 1.42 (s, 3H, $CH_3C$), 3.34 (s, 3H, $OCH_3$), 4.07 (s, 2H, $CCH_2O$), 4.63 (s, 2H, $OCH_2O$), 4.84 (s, 1H, CH=C). Anal. Calcd for $C_{11}H_{18}O_4$: C, 61.66; H, 8.47. Found: C, 61.54; H, 8.44.

**1(R),5(R)-4,4-Dichloro-6(R),9(S)-dimethyl-3(R)-(methoxymethyleneoxymethyl)-2,7-dioxatricyclo[4.3.0.0$^{3,5}$]nonane.** To a stirred solution of 807 mg (3.76 mmol) of the olefin **7** in 16.5 mL of chloroform at 0°C was added 16.5 mL of cold 50% aqueous NaOH and 17 mg (0.075 mmol) of benzyltriethylammonium chloride. The reaction mixture was vigorously stirred for 6 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 ($MgSO_4$). 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 (89%) of the dichlorocyclopropane as a colorless oil: $R_f$ = 0.40 (1:1 ether/petroleum ether); evaporative distillation 90-100°C (0.005 mm Hg); $[\alpha]_D^{22}$ +90.4 (*c* 1.04, $CHCl_3$); IR ($CHCl_3$) 1465, 1390, 1150, 1105, 1038,

1000, 895, 845 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 0.99 (d, 3H, J=7 Hz, $CH_3CH$), 1.63 (s, 3H, $CH_3C$), 2.24 (s, 1H, $Cl_2CCH$), 3.40 (s, 3H, $OCH_3$), 4.78 (s, $OCH_2O$, 2H). Anal. Calcd for $C_{12}H_{18}Cl_2O_4$: C, 48.50; H, 6.11. Found: C, 47.31; H, 6.36.

**1(R),5(R)-4,4-Dichloro-6(R),9(R)-dimethyl-3(R)-(methoxymethyleneoxymethyl)-2,7-dioxatricyclo[4.3.0.$0^{3,5}$]nonane.** By the procedure described above for the dichlorocyclopropanation of the olefin **7**, 2.43 g (11.3 mmol) of the olefin **8**, 45 mL of chloroform, 45 mL of 50% aqueous NaOH, and 52 mg (0.226 mmol) of benzyltriethylammonium chloride afforded, after flash chromatography on 50 g of silica gel with 1:3 ether/petroleum ether, 3.05 g (91%) of the dichlorocyclopropane as a colorless oil: $R_f$ = 0.19 (silica gel, 1:4 ether/petroleum ether); evaporative distillation 75-80°C (0.005 mm Hg); $[\alpha]_D^{24}$ +83.3 (c 1.12, $CHCl_3$); IR ($CHCl_3$) 1455, 1385, 1150, 1105, 1030, 1010, 875, 840 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 1.07 (d, 3H, J=7.5 Hz, $CH_3CH$), 1.52 (s, 3H, $CH_3C$), 2.30 (s, 1H, $Cl_2CCH$), 3.39 (s, 3H, $OCH_3$), 4.70 (s, 2H, $OCH_2O$). Anal. Calcd for $C_{12}H_{18}Cl_2O_4$: C, 48.50; H, 6.11. Found: C, 48.64; H. 6.25.

**1(R),5(S)-6(R),9(S)-Dimethyl-3(R)-(methoxymethyleneoxymethyl)-2,7-dioxatricyclo[4.3.0.$0^{3,5}$]nonane (9).** To a stirred solution of 994 mg (3.34 mmol) of the above dichlorocyclopropane (derived from the olefin **7**) in 38 mL of ether was added 380 mg (10 mmol) of lithium tetrahydridoaluminate.

After 48 h at room temperature, the mixture was cautiously treated with 0.38 mL of water, 0.38 mL of 15% aqueous NaOH, and then 1.14 mL of water. The mixture was filtered and then concentrated under reduced pressure. Chromatography of the residue on 20 g of silica gel with 3:2 ether/petroleum ether afforded 630 mg (83%) of the cyclopropane **9** as a colorless oil: $R_f$ = 0.23 (silica gel, 1:1 ether/petroleum ether); evaporative distillation 55-65°C (0.005 mm Hg); $[\alpha]_D^{22}$ +97.2 (*c* 1.05, $CHCl_3$); IR ($CHCl_3$) 1465, 1390, 1240, 1150, 1105, 1040, 925 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 0.6-0.8 (m, 2H, cyclopropyl-$CH_2$), 1.00 (d, 3H, J=7.5 Hz, $CH_3CH$), 1.50 (s, 3H, $CH_3C$), 3.37 (s, 3H, $OCH_3$), 4.67 (s, 2H, $OCH_2O$). Anal. Calcd for $C_{12}H_{20}O_4$: C, 63.13; H, 8.83. Found: C, 63.34; H, 9.09.

**1(R),5(S)-6(R),9(R)-Dimethyl-3(R)-(methoxymethyleneoxymethyl)-2,3-dioxatricyclo[4.3.0.0$^{3,5}$]nonane (10).** By the procedure described above for the preparation of the cyclopropane **9**, a solution of 528 mg (1.78 mmol) of the above dichlorocyclopropane (derived from the olefin **8**) and 202 mg (5.33 mmol) of lithium tetrahydridoaluminate afforded, after chromatography on 20 g of silica gel with 2:3 ether/petroleum ether, 317 mg (78%) of the cyclopropane **10** as a colorless oil: $R_f$ = 0.24 (silica gel, 1:1 ether/petroleum ether); evaporative distillation 55-65°C (0.005 mm Hg); $[\alpha]_D^{22}$ +92.6° (*c* 1.01, $CHCl_3$); IR ($CHCl_3$) 1460, 1380, 1285, 1145, 1105, 1025, 1000, 915, 870 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 0.6-0.8 (m, 2H, cyclopropyl-

$CH_2$), 1.03 (d, 3H, J=7.5 Hz, $CH_3CH$), 1.40 (s, 3H, $CH_3C$), 3.37 (s, 3H, $OCH_3$), 4.67 (s, 2H, $OCH_2O$). Anal. Calcd for $C_{12}H_{20}O_4$: C, 63.13; H, 8.83. Found: C, 63.21; H, 8.71.

**1(R)-2,8(R)-Dimethyl-5-(S)-(hydroxymethyl)-6,9-dioxabicyclo-[3.3.1]non-2-ene (12).** To a stirred solution of 405 mg (1.77 mmol) of the cyclopropane **10** in 22.5 mL of THF at 55°C was added 5.5 mL of 10% aqueous HCl. After 17 h, the cooled reaction mixture was diluted with 70 mL of ether. The organic layer was separated, washed with four 20 mL portions of saturated aqueous NaCl and dried ($MgSO_4$). Removal of the solvent under reduced pressure and chromatography of the residue on 20 g of silica gel with 4:6 ether/petroleum ether afforded 288 mg (88%) of the alcohol **12** as a colorless oil: $R_f$ = 0.12 (silica gel, 4:6 ether/petroleum ether); evaporative distillation 55-65°C (0.008 mm Hg); $[\alpha]_D^{23}$ -75.0° (c 0.955, $CHCl_3$); IR ($CHCl_3$) 3580, 3470, 1350, 1365, 1100, 1055, 1030, 990, 930 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 1.37 (s, 3H, $CH_3CH$), 1.37 (m, 1H, $CH_3CH$), 1.70, (d, 3H, J=2 Hz, $CH_3C=CH$), 3.48 (d, 2H, J=6 Hz, $CH_2OH$), 3.91 (s, 1H, CHCHO), 4.22 (dd, 1H, J=12 Hz, J'=3 Hz, CHCHHO), 5.67 (bs, 1H, $CH_3C=CH$). Anal. Calcd for $C_{10}H_{16}O_3$: C, 65.19; H, 8.75. Found: C, 65.24; H, 8.71.

**1(R)-2,8(S)-Dimethyl-5(S)-(hydroxymethyl)-6,9-dioxabicyclo-[3.3.1]non-2-ene (11).** To a stirred solution of 448 mg (1.97 mmol) of the cyclopropane **9** in 24 mL of acetonitrile at

55°C was added 6 mL of 10% aqueous HCl. After 40 min, the reaction mixture was allowed to cool, diluted with 200 mL of ether, and then washed with 50 mL of saturated aqueous $NaHCO_3$. The organic phase was washed with 50 mL of saturated aqueous NaCl. The combined aqueous phases were extracted with four 70 mL portions of dichloromethane. The combined organic phases were dried ($MgSO_4$) and then concentrated under reduced pressure. To a stirred solution of the residue in 18 mL of dry acetonitrile was added 0.45 mL of 62% aqueous $HClO_4$. After 30 min at room temperature, the reaction mixture was poured into 50 mL of saturated aqueous $NaHCO_3$ and extracted with 200 mL of ether and then three 30 mL portions of dichloromethane. The combined organic extracts were dried ($MgSO_4$) and then concentrated under reduced pressure. Chromatography of the residue on 15 g of silica gel with 7:3 ether/petroleum ether afforded 344 mg (95%) of the alcohol **11** as an oil: $R_f$ = 0.36 (silica gel, ether); evaporative distillation 45-55°C (0.005 mm Hg); $[\alpha]_D^{24}$ -105° (c 1.69, $CHCl_3$); IR ($CHCl_3$) 3590, 3470, 1620, 1470, 1380, 1130, 1060, 940, 840 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 0.75 (d, 3H, J=7.5 Hz, $CH_3CH$), 1.77 (m, 3H, $CH_3C=CH$), 3.43 (d, 2H, J=5.5 Hz, $CH_2OH$), 3.63, 3.70 (2s, 2H, $CHCH_2O$), 4.17 (d, 1H, J=5 Hz, CHCHO), 5.76 (bs, 1H, $CH_3C=CH$). Anal. Calcd for $C_{10}H_{16}O_3$: C, 65.19; H, 8.75. Found: C, 65.01; H, 8.92.

**1(R)-2,8(S)-Dimethyl-5(S)-(trifluoromethanesulfonyloxymethyl)-6,9-dioxabicyclo[3.3.1]non-2-ene, and 1(R)-2,8(S)-dimethyl-5(S)-(bromomethyl)-6,9-dioxabicyclo[3.3.1]non-2-ene (13).** To a stirred solution of 176 mg (0.955 mmol) of the alcohol **11** and 0.13 mL (1.62 mmol) of pyridine in 9.2 mL of dichloromethane at -20°C was added 0.26 mL (1.53 mmol) of trifluoromethanesulfonic anhydride. After 1 h, the reaction was poured into 50 mL of ice-cold saturated aqueous $NaHCO_3$. The resulting mixture was extracted with 200 mL of dichloromethane and then washed with 20 mL of saturated aqueous $NaHCO_3$. The combined aqueous phases were extracted with three 20 mL portions of dichloromethane and dried over a mixture of $K_2CO_3$ and $MgSO_4$. The solvent was evaporated under reduced pressure to afford the triflate as a dark oil.

In a separate experiment, chromatography of the residue on silica gel with 1:9 ether/petroleum ether afforded the triflate in 81% yield as a colorless oil: $R_f$ = 0.23 (silica gel, 1:9 ether/petroleum ether); evaporative distillation 70-80°C (0.005 mm Hg); $[\alpha]_D^{21}$ -81.5° (c 1.209, $CHCl_3$); IR ($CHCl_3$) 1465, 1410, 1140, 1110, 1050, 1010, 985 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 0.75 (d, 3H, J=7.5 Hz, $CH_3CH$), 1.64 (m, 3H, $CH_3C=CH$), 3.20, 4.12 (2s, $CH_2OSO_2CF_3$), 3.48 (d, 1H, J=3 Hz, $CHCHHO$), 3.57 (s, 1H, $CHCHHO$), 4.05 (d, 1H, J=5 Hz, $CHCHO$), 5.60 (bs, 1H, $CH_3C=CH$). Anal. Calcd for $C_{11}H_{15}F_3O_3S$: C, 41.77; H, 4.78; S, 10.14. Found: C, 41.50; H, 5.08; S, 9.96.

To prepare the bromide **13**, to a stirred solution of the above crude triflate in 5.3 mL of HMPA was added 1.00 g (3.10 mmol) of tetra-n-butylammonium bromide. 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 one 200 mL portion and then four 25 mL portions of ether. The combined organic extracts were dried ($MgSO_4$) and then concentrated under reduced pressure. Chromatography of the residue on 20 g of silica gel with 35:465 ether/petroleum ether afforded 219 mg (93%) of the bromide **13** as a colorless white solid: mp 55-56°C; $R_f$ = 0.27 (silica gel, 1:9 ether/petroleum ether); evaporative distillation 50-60°C (0.005 mm Hg); $[\alpha]_D^{22}$ -92.9° (c 2.32, $CHCl_3$); IR ($CHCl_3$) 2960, 2925, 2880, 1450, 1240, 1130, 1190, 990 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$0.72 (d, 3H, J=7.5 Hz, $CH_3CH$), 1.77 (m, 3H, $CH_3C=CH$), 3.37 (s, 3H, $CH_2Br$), 3.63 (d, 1H, J=2.5 Hz, $CHCHHO$), 3.72 (s, 1H, $CHCHHO$), 4.22 (d, 1H, J=5 Hz, $CHCHO$), 5.75 (bs, 1H, $CH_3C=CH$). Anal. Calcd for $C_{10}H_{15}BrO_2$: C, 48.60; H, 6.12. Found: C, 48.61; H, 6.12.

**5(R)-4(S),6(R)-Dimethyl-7(S)-hydroxy-1(S)-(bromomethyl)-2,9-dioxabicyclo[3.3.1]nonane.** To a stirred solution of the olefin **13** in 5 mL of THF at 0°C was added 6.75 mL (6.75 mmol) of a 1M solution of borane in THF. After 1 h at room temperature, the solution was recooled to 0°C and cautiously treated with 0.5 mL of water. After the evolution of hydrogen

ceased (ca. 15 min), 0.60 mL of 10% aqueous NaOH and 0.15 mL of 30% aqueous $H_2O_2$ was added to the reaction mixture. After 1 h at 55°C, an additional 0.4 mL of 10% aqueous NaOH and 0.2 mL of 30% aqueous $H_2O_2$ were added. Heating was continued for 40 min, and then the cooled solution was poured into 40 mL of water and extracted with one 200 mL portion and three 35 mL portions of ether. The combined organic extracts were dried ($MgSO_4$) and then concentrated under reduced pressure. Chromatography of the residue on 35 g of silica gel with 1:1 ether/petroleum ether afforded 337 mg (94%) of the alcohol as a colorless oil: $R_f$ = 0.15 (silica gel, 1:1 ether/petroleum ether); evaporative distillation 80-90°C (0.001 mm Hg); $[\alpha]_D^{24}$ +31.3° (c 1.76, $CHCl_3$); IR ($CHCl_3$) 3560, 3300, 2975, 2920, 1470, 1370, 1175, 1120, 990, 905 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 0.93, 1.27 (2d, 6H, J=7.5 Hz, 2 $CH_3CH$), 3.32 (s, 2H, $CH_2Br$), 3.58, 3.85 (2d, 2H, J=12 Hz, $CHCH_2O$). Although an analytical sample of the bromide **13** decomposed on standing in a sealed tube at room temperature, the compound could be stored safely at -20°C.

**5(R)-4(S),6(R)-Dimethyl-7(S)-[(2-methoxyethoxy)methyleneoxy]-1(S)-(bromomethyl)-2,9-dioxabicyclo[3.3.1]nonane (14).** To a stirred solution of 303 mg (1.14 mmol) of the above alcohol in 6 mL of dichloromethane were added, every two hours, 0.13 mL (1.14 mmol) of 2-methoxyethoxymethyl chloride 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 dichloromethane and was washed with 40 mL of saturated aqueous $NaHCO_3$ and then 20 mL of saturated aqueous NaCl. The organic phase was dried ($MgSO_4$) and then concentrated under reduced pressure. Chromatography of the residue on 35 g of silica gel with 1:1 ether/petroleum afforded 363 mg (90%) of the ether **14** as a colorless oil: $R_f$ = 0.11 (silica gel, 4:6 ether/petroleum ether); evaporative distillation; 140-145°C (0.001 mm Hg); $[\alpha]_D^{23}$ +68° (c 0.50, $CHCl_3$); IR ($CHCl_3$) 2940, 2900, 1485, 1450, 1240, 1200, 1100, 1040, 910, 850 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 0.93, 1.13 (2d, 6H, J=7 Hz, 2 $CH_3CH$), 3.33 (s, 2H, $CH_2Br$), 3.38 (s, 3H, $OCH_3$), 4.70, 4.83 (2d, 2H, J=7 Hz, $OCH_2O$). Anal. Calcd. for $C_{14}H_{25}BrO_5$: C, 47.60; H, 7.13. Found: C, 47.69; H, 7.09.

**2(R)-[1-(Benzyloxy)-2(S)-propyl]-3(R)-methyl-4(S)-[(2-methoxyethoxy)methyleneoxy]-6-methylene-tetrahydropyran (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. 1.0 mL of HMPA was added, and, after 3.5 h at room temperature, the solution was concentrated at reduced pressure. Chromatography of the residue on 30 g of alumina (Activity III) with 1:3 ether/petroleum ether afforded

first 169 mg (62%) of the exocyclic enol ether **15** as colorless oil: $R_f$ = 0.07, 0.30 (silica gel, 1:1 ether/petroleum ether. Silica gel causes isomerization to the endocyclic enol ether **18**. The more polar compound is presumably the hydrate); $^1H$ NMR ($CCl_4$) $\delta$ 0.97, 1.12 (2d, 6H, J=6 Hz, 2 $CH_3CH$), 1.67-2.07 (m, 2H, 2 $CH_3CH$), 2.33 (m, 2H, $CH_2C=CH_2$), 3.28 (s, 3H, $OCH_3$), 3.89, 4.22 (2s, 2H, $OC=CH_2$), 4.42 (s, 2H, $C_6H_5CH_2$), 4.63 (s, 2H, $OCH_2O$), 7.23 (s, 5H, $C_6H_5$). There was then eluted 12 mg (4.4%) of the enol ether **16** as a colorless oil: $R_f$ = 0.00, 0.19 (silica gel, 1:1 ether/petroleum ether); $^1H$ NMR ($CCl_4$) $\delta$1.05, 1.12(2d, 6H, J=6 Hz, 2$CH_3CH$), 3.28 (s, 3H, $OCH_3$), 3.96, 4.25 (2s, 2H, $OC=CH_2$), 7.23 (s, 5H, $C_6H_5$). In separate experiments, $^1H$ NMR analysis of the crude reaction mixture indicated a 3:1 mixture of **15** and **16**.

**2(R)-[1-(Benzyloxy)-2(S)-propyl]-3(R)-methyl-4(S)-[2-(methoxyethoxy)methyleneoxy]-6-methyl-3,4-dihydro-2H-pyran (18).** A solution of 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, 1:1 ether/petroleum ether); evaporative distillation 145-155°C (0.001 mm Hg); $[\alpha]_D^{26}$ +142° (c 0.973,

$CHCl_3$); IR ($CHCl_3$) 3000, 2925, 1660, 1450, 1090, 1030, 910 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 0.77, 1.15 (2d, 6H, J=7 Hz, 2 $CH_3CH$), 1.77 (s, 3H, $CH_3C=CH$), 1.87-2.27 (m, 2H, 2 $CH_3CH$), 3.37 (s, 3H, $OCH_3$), 4.47 (s, 2H, $C_6H_5CH_2$), 4.73 (s, 2H, $OCH_2O$). Anal. Calcd for $C_{21}H_{32}O_5$: C, 69.20; H, 8.85. Found: C, 69.07; H, 8.87.

**1(R)-2,8(S)-Dimethyl-5(S)-[[(1,1-dimethylethyl)dimethylsilyl]-oxymethyl]-6,9-dioxabicyclo[3.3.1]non-2-ene.** To a stirred solution of 222 mg (1.21 mmol) of the alcohol **11** in 2.0 mL of dichloromethane were added 0.8 mL (9.64 mmol) of pyridine and 363 mg (2.41 mmol) of t-butyldimethylchlorosilane. After 16 h at room temperature, the reaction mixture was poured into 50 mL of saturated aqueous NaCl and extracted with two 100 mL portions of ether. The combined organic extracts were dried ($MgSO_4$) and then concentrated under reduced pressure. Chromatography of the residue on 30 g of silica gel with 1:9 ether/petroleum ether afforded 360 mg (100%) of the silyl ether as a colorless oil: $R_f$ = 0.30 (silica gel, 1:9 ether/petroleum ether); evaporative distillation 70-75°C (0.005 mm Hg); $[\alpha]_D^{21}$ -78.0° (c 1.75, $CHCl_3$); IR ($CHCl_3$) 2960, 2860, 1470, 1255, 1120, 1060, 840 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 0.07 (s, 6H, $(CH_3)_2Si$), 0.72 (d, 3H, J=7 Hz, $CH_3CH$), 0.90 (s, 9H, $(CH_3)_3C$), 1.77 (bs, 3H, $CH_3C=CH$), 3.52 (s, 2H, $CH_2OSi$), 3.60, 3.68 (2s, 2H, $CHCH_2O$), 4.15 (d, 1H, J=5 Hz, CHCHO), 5.77 (bs,

1H, $CH_3C=C\underline{H}$). Anal. Calcd for $C_{16}H_{30}O_3Si$: C, 64.38; H, 10.13. Found: C, 64.47; H, 10.20.

**5(R)-4(S),6(R)-Dimethyl-7(S)-hydroxy-1(S)-[[(1,1-dimethylethyl)dimethylsilyl]oxymethyl]-2,9-dioxabicyclo[3.3.1]nonane.** To a stirred solution of 340 mg (1.14 mmol) of the above silyl ether in 5.7 mL of THF at 0°C was added 5.7 mL (5.7 mmol) of a 1M solution of borane in THF. After 1 h at room temperature, the solution was recooled to 0°C and treated with 0.84 mL of 15% aqueous NaOH and then 0.25 mL of 30% aqueous $H_2O_2$. After 1 h at 55°C, the cooled solution was poured into 50 mL of saturated aqueous NaCl and extracted with two 100 mL portions of ether. The combined organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue on 25 g of silica gel with 6:4 ether/petroleum ether afforded 332 mg (92%) of the alcohol as a white solid: mp 183°C; $R_f$ = 0.23 (silica gel, 1:1 ether/petroleum ether); $[\alpha]_D^{22}$ +26.4° (c 1.94, $CHCl_3$); IR ($CHCl_3$) 3620, 3450, 1460, 1390, 1255, 1120, 1020, 840 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 0.07 (s, 6H, $(CH_3)_2Si$), 0.90 (s, 9H, $(CH_3)_3C$), 0.90 (d, 3H, J=7 Hz, $C\underline{H}_3CH$), 1.17 (d, 3H, J=7 Hz, $C\underline{H}_3CH$), 3.47 (s, 2H, $CH_2OSi$). Anal. Calcd for $C_{16}H_{32}O_4Si$: C, 60.72; H, 10.19. Found: C, 60.81; H, 10.25.

**5(R)-4(S),6(R)-Dimethyl-7(S)-(benzyloxy)-1(S)-[[(1,1-dimethylethyl)dimethylsilyl]oxymethyl]-2,9-dioxabicyclo-[3.3.1]nonane.** To a stirred solution of 62 mg (0.19 mmol) of the above alcohol in 4 mL of THF at 0°C were added 90 μL (0.76 mmol) of benzyl bromide (purified by filtration through alumina) and then 43 mg (0.38 mmol) of potassium t-butoxide. After 10 min, the reaction was poured into 30 mL of saturated aqueous NaCl and extracted with two 75 mL portions of ether. The combined organic extracts were dried ($MgSO_4$) and then concentrated under reduced pressure. Chromatography of the residue on 10 g of silica gel with 1:9 ether/petroleum ether afforded 77 mg (97%) of the benzyl ether as a colorless oil: $R_f$ = 0.19 (silica gel, 1:9 ether/petroleum ether); evaporative distillation 145-150°C (0.005 mm Hg); $[\alpha]_D^{22}$ +75.0° (c 2.56, $CHCl_3$); IR ($CHCl_3$) 2950, 2920, 2860, 1470, 1460, 1120, 1110, 1000, 835 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 0.07 (s, 6H, $(CH_3)_2Si$), 0.87 (d, 3H, $CH_3CH$), 0.90 (s, 9H, $(CH_3)_3C$), 1.12 (d, 3H, J=7 Hz, $CH_3CH$), 3.47 (s, 2H, $CH_2OSi$), 4.43, 4.67 (2d, 2H, J=12 Hz, $C_6H_5CH_2$), 7.31 (s, 5H, $C_6H_5$). Anal. Calcd for $C_{23}H_{38}O_4Si$: C, 67.94; H, 9.42. Found: C, 68.08; H, 9.39.

**5(R)-4(S),6(R)-Dimethyl-7(S)-(benzyloxy)-1(S)-(hydroxymethyl)-2,9-dioxabicyclo[3.3.1]nonane (20).** To a stirred solution of 166 mg (0.407 mmol)of the above silyl ether in 4.0 mL of THF was added 1.0 mL (1.0 mmol) of a 1M solution of tetra-n-butylammonium fluoride in THF. After 2 h at room

temperature, the solution was poured into 50 mL of 50% saturated aqueous NaCl and extracted with two 75 mL portions of ether. The combined organic extracts were dried ($MgSO_4$) and then concentrated under reduced pressure. Chromatography of the residue on 25 g of silica gel with ether afforded 118 mg (99%) of the alcohol **20** as a colorless oil: $R_f$ = 0.30 (silica gel, ether); evaporative distillation 145-150°C (0.005 mm Hg); $[\alpha]_D^{22}$ +98° (c 0.59, $CHCl_3$); IR ($CHCl_3$) 3580, 3500, 3000, 2920, 1475, 1450, 1190, 1130, 1065, 1005, 910 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$) $\delta$ 0.90 (d, 3H, J=7 Hz, $CH_3CH$), 1.16 (d, 3H, J=7 Hz, $CH_3CH$), 1.83 (dd, 1H, J=13 Hz, J'=9 Hz, C(8)-$\beta$H), 2.05 (dd, 1H, J=8 Hz, J'=5 Hz, $CH_2OH$), 2.27 (m, 1H, $CH_3CH$), 2.36 (dd, 1H, J=13 Hz, J'=6 Hz, C(8)-$\alpha$H), 2.53 (m, 1H, $CH_3CH$), 3.43 (dd, 1H, J=11 Hz, J'=8 Hz, $CHHOH$), 3.49 (dd, 1H, J=11 Hz, J'=5 Hz), 3.64 (dd, 1H, J=12 Hz, J'=12 Hz, $CHCHHO$), 3.84 (dd, 1H, J=12 Hz, J'=6 Hz, $CHCHHO$), 3.99 (dd, 1H, J=5 Hz, J'=5 Hz, $CHCHO$), 4.02 (ddd, 1H, J=10 Hz, J'=9 Hz, J''=6 Hz, $CH_2CHCHCH_3$), 4.47, 4.68 (2d, 2H, J=12 Hz, $C_6H_5CH_2$). Anal. Calcd for $C_{17}H_{24}O_4$: C, 69.84; H, 8.27. Found: C, 69.75; H, 8.18.

**Methyl 3-[5(R)-4(S),6(R)-dimethyl-7(S)-(benzyloxy)-2,9-dioxabicyclo[3.3.1]nonan-1-yl]cis and trans-propenoate (22).** To a stirred solution of 42 µL (0.49 mmol) of oxalyl chloride in 4.0 mL of dichloromethane at -60°C was added 69 µL (0.97 mmol) of dimethyl sulfoxide. After 10 min, a solution of 118 mg (0.404 mmol) of the alcohol **20** in 3 mL of dichloromethane

was added to the reaction mixture. After 15 min, the reaction mixture was treated with 0.28 mL (2.0 mmol) of triethylamine and then allowed to warm to 0°C. 405 mg (1.21 mmol) of methyl (triphenylphosphoranylidene)acetate 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 ($MgSO_4$) 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 95:5 trans:cis mixture ($^1H$ NMR) of $\alpha,\beta$-unsaturated esters as a colorless oil: $R_f$ = 0.67 (trans), 0.63 (cis) (silica gel, ether). The trans isomer had the following physical properties: evaporative distillation 165-170°C (0.005 mm Hg); $[\alpha]_D^{21}$ +92.9 (c 1.47, $CHCl_3$); IR ($CHCl_3$) 3000, 2950, 2885, 1715, 1430, 1305, 1275, 1125, 1070, 1000, 910 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 0.90, 1.15 (2d, 6H, J=7 Hz, 2 $CH_3CH$), 1.75 (dd, 1H, J=14 Hz, J'=9 Hz, $CCHHCH$), 2.42 (dd, H, J=14 Hz, J'=6 Hz, $CCHHCH$), 3.70 (s, 3H, $OCH_3$), 4.43, 4.65 (2d, 2H, J=12 Hz, $C_6H_5CH_2$), 6.10, 6.77 (2d, 2H, J=16 Hz, CH=CH), 7.31 (s, 5H, $C_6H_5$). Anal. Calcd for $C_{20}H_{26}O_5$: C, 69.34; H, 7.56. Found: C, 69.29; H, 7.50. $^1H$ NMR (cis isomer, $CDCl_3$) $\delta$ 0.88, 1.14 (2d, 6H, J=7 Hz, 2 $CH_3CH$), 3.37 (s, 3H, $OCH_3$), 5.83 (s, 2H, CH=CH), 7.32 (s, 5H, $C_6H_5$).

**Methyl 3-[5(R)-4(S),6(R)-dimethyl-7(S)-(benzyloxy)-2,9-dioxabicyclo[3.3.1]nonan-1-yl]propanoate.** To a stirred solution of 131 mg (0.378 mmol) of the above olefins **22** in 5 mL of n-pentane was added 35 mg of 5% rhodium on carbon. The reaction mixture was stirred at room temperature under a hydrogen atmosphere for 5 h. The catalyst was then removed by filtration and washed with three 10 mL portions of ethyl acetate. Removal of the solvent from the combined filtrates and chromatography of the residue on 25 g of silica gel with 4:6 ether/petroleum ether afforded 124 mg (94%) of the alkane as a colorless oil: $R_f$ = 0.28 (silica gel, 4:6 ether/petroleum ether); evaporative distillation 165-170°C (0.005 mm Hg); $[\alpha]_D^{21}$ +87.1° (c 2.03, $CHCl_3$); IR ($CHCl_3$) 3000, 2950, 1730, 1435, 1190, 1125, 1065, 1005, 960 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 0.88, 1.13 (2d, 6H, J=7 Hz, 2 $CH_3CH$), 3.68 (s, 3H, $OCH_3$), 4.48, 4.72 (2d, 2H, J=12 Hz, $C_6H_5CH_2$), 7.34 (s, 5H, $C_6H_5$). Anal. Calcd for $C_{20}H_{28}O_5$: C, 68.94; H, 8.10. Found: C, 68.80; H, 8.02.

**3-[5(R)-4(S),6(R)-Dimethyl-7(S)-benzyloxy)-2,9-dioxabicyclo[3.3.1]nonan-1-yl]propan-1-ol.** To a stirred solution of 115 mg (0.331 mmol) of the above methyl ester in 5 mL of ether at 0°C was added 36 mg (0.95 mmol) of lithium tetrahydridoaluminate. After 1 h, the reaction mixture was cautiously treated with 36 μL of water, 36 μL of 15% aqueous NaOH, and then 108 μL of water. The reaction mixture was

filtered and then concentrated under reduced pressure. Chromatography of the residue on 10 g of silica gel with ether afforded 106 mg (100%) of the alcohol as a colorless oil: $R_f$ = 0.21 (silica gel, ether); evaporative distillation 175°C (0.001 mm Hg); $[\alpha]_D^{21}$ +95.7° (c 2.03, $CHCl_3$); IR ($CHCl_3$) 3440, 3000, 2960, 2890, 1450, 1370, 1190, 1065, 1000, 910 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 0.87, 1.13 (2d, 6H, J=7 Hz, 2 $CH_3CH$), 4.43, 4.67 (2d, 2H, J=12 Hz, $C_6H_5CH_2$), 7.33 (s, 5H, $C_6H_5$). Anal. Calcd for $C_{19}H_{28}O_4$: C, 71.22; H, 8.81. Found: C, 71.25; H, 8.75.

**3-[5(R)-4(S),6(R)-Dimethyl-7(S)-(benzyloxy)-2,9-dioxabicyclo[3.3.1]nonan-1-yl]propanal (23).** To a stirred solution of 29 μL (0.33 mmol) of oxalyl chloride in 3 mL of dichloromethane at -60°C was added 47 μL (0.66 mmol) of dimethyl sulfoxide. After 10 min, a solution of 88 mg (0.27 mmol) of the above alcohol in 2 mL of dichloromethane was added to the reaction mixture. After 15 min, the reaction mixture was treated with 0.19 mL (1.4 mmol) of triethylamine, allowed to warm to room temperature, and then poured into 20 mL of brine. The resulting mixture was extracted with two 50 mL portions of ether. The combined organic extracts were dried ($MgSO_4$) and then concentrated under reduced pressure. Chromatography of the residue on 25 g of silica gel with 4:6 ether/petroleum ether afforded 86 mg (97%) of the aldehyde **23** as a colorless oil: $R_f$ = 0.30 (silica gel, 1:1 ether/petroleum ether);

evaporative distillation 170°C (0.005 mm Hg); $[\alpha]_D^{21}$ +89.7° (c 1.76, $CHCl_3$); IR ($CHCl_3$) 3000, 2960, 1720, 1450, 1370, 1190, 1090, 1080, 1010, 910 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 0.85, 1.12 (2d, 6H, J=7 Hz, 2 $CH_3CH$), 4.40, 4.63 (2d, 2H, J=12 Hz, $C_6H_5CH_2$), 7.32 (s, 5H, $C_6H_5$), 9.73 (t, 1H, J=1.5 Hz, C(O)H). Anal. Calcd for $C_{19}H_{26}O_4$: C, 71.67; H, 8.23. Found: C, 71.57; H, 8.29.

**Ethyl 4-[5(R)-4(S),6(R)-Dimethyl-7(S)-(benzyloxy)-2,9-dioxabicyclo[3.3.1]nonan-1-yl]-2(R) and 2(S)-hydroxybutanoate.** To a stirred solution of 0.25 mL (2.6 mmol) of ethyl vinyl ether in 2.5 mL of THF at -78°C was added 1.36 mL (1.63 mmol) of a 1.2M solution of t-butyllithium in pentane. The resulting mixture was placed in an ice bath, and after 10 min, 1.5 mL (~0.6 mmol) of the pale yellow solution was added all at once to a solution of 93 mg (0.29 mmol) of the aldehyde **23** in 4 mL of THF at -78°C. After 10 min, the solution was allowed to warm to 0°C and was then poured into 25 mL of a saturated aqueous solution of $NH_4Cl$ buffered to pH 8 with concentrated aqueous ammonia. The resulting mixture was extracted with two 50 mL portions of ether. The combined organic extracts were dried and then concentrated under reduced pressure. To a solution of the residue in 4 mL of dichloromethane at -78°C was added 1 mL of methanol. A stream of ozone was passed through this solution until the light blue color persisted (1 min). The solution was purged with a

stream of nitrogen, and then 0.4 mL of dimethylsulfide was added to the reaction mixture. After 1 h at room temperature, the solvent was removed under reduced pressure. Chromatography of the residue on 10 g of silica gel with 7:3 ether/petroleum ether afforded 71 mg (62%) of a ~1:1 mixture of ethyl esters as a colorless oil: $R_f$ = 0.26 (silica gel, 7:3 ether/petroleum ether); evaporative distillation 190°C (0.005 mm Hg); IR ($CHCl_3$) 3530, 3400, 3000, 2980, 1725, 1450, 1385, 1365, 1205, 1190, 1065, 1005 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 0.88, 1.13 (2d, 6H, J=7 Hz, 2 $C\underline{H}_3CH$), 1.30 (t, 3H, J=7 Hz, $C\underline{H}_3CH_2$), 4.18 (q, 2H, J=7 Hz, $CH_3C\underline{H}_2$), 4.43, 4.67 (2d, 2H, J=12 Hz, $C_6H_5C\underline{H}_2$), 7.33 (s, 5H, $C_6\underline{H}_5$). Anal. Calcd for $C_{22}H_{32}O_6$: C, 67.32; H, 8.22. Found: C, 67.40; H, 8.29.

**6(S) and 6(R)-2(R)-(1-hydroxy-2(S)-propyl)-3(R)-methyl-4(S)-(benzyloxy)-8(R) and 8(S)-carboethoxy-1,7-dioxaspiro-[5.4]decane.** To a solution of 56 mg (0.14 mmol) of the above alcohol in 1.0 mL of $CDCl_3$ in an NMR tube was added 19 mg (0.077 mmol) of pyridinium p-toluenesulfonate. The progress of the equilibration was monitored by the disappearance of the doublet ($C\underline{H}_3CH$) at 1.13 ppm. After 20 h, the reaction mixture was concentrated under reduced pressure. Chromatography of the residue on 10 g of silica gel with ether afforded 48 mg (85%) of an unseparated mixture of spiroketals as a colorless oil: $R_f$ = 0.48, 0.41, 0.36 (silica gel, ether); evaporative distillation 190-195°C (0.005 mm Hg); IR ($CHCl_3$) 3450, 3000, 2930, 1735, 1450, 1375, 1350, 1215, 1195, 1095, 1065, 1055,

1025. Anal. Calcd for $C_{22}H_{32}O_6$: C, 67.32; H, 8.22. Found: C, 67.27; H, 8.18.

**6(S) and 6(R)-2(R)-[[[1-(1,1-Dimethylethyl)dimethylsilyl]-oxy]-2-(S)-propyl]-3(R)-methyl-4(S)-(benzyloxy)-8(R) and 8(S)-carboethoxy-1,7-dioxaspiro[5.4]decane (24).** To a stirred solution of 34 mg (0.087 mmol) of the above alcohols in 2.0 mL of dichloromethane were added 0.5 mL of pyridine and 50 mg (0.33 mmol) of t-butyldimethylchlorosilane. After 4 h at room temperature, the reaction mixture was poured into 20 mL of saturated aqueous NaCl and extracted with 75 mL of ether. The organic phase was dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue on 10 g of silica gel with 2:8 ether/petroleum ether afforded first 19.9 mg (45%) of a spiroketal as a colorless oil: $R_f$ = 0.26 (silica gel, 2:8 ether/petroleum ether); evaporative distillation 195°C (0.001 mm Hg); IR ($CHCl_3$) 3000, 2960, 2930, 2860, 1740, 1460, 1380, 1350, 1250, 1100, 1050, 1030, 1010, 840 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$) $\delta$ 0.02 (s, 6H, $(CH_3)_2Si$), 0.87 (s, 9H, $(CH_3)_3C$), 0.88, 0.95 (2d, 6H, J=7 Hz, 2 $CH_3CH$), 1.26 (t, 3H, J=7 Hz, $CH_3CH_2$), 1.68-1.80 (m, 2H), 1.89 (dd, 1H, J=15 Hz, J'=4 Hz, CHHCHO), 1.89-1.98 (m, 3H), 2.12 (dd, 1H, J=15 Hz, J'=1 Hz, CHHCHO), 2.42. (m, 1H, $CH_3CH$), 3.35 (dd, 1H, J=10 Hz, J'=6.5 Hz, CHCHHOSi), 3.47 (m, $CH_2CHCH$), 3.52 (dd, 1H, J=10 Hz, J'=5 Hz, CHCHHOSi), 3.93 (dd, 1H, J=10 Hz, J'=2 Hz, CHCHCH), 4.17 (q, 2H, J=7 Hz, $CH_3CH_2$), 4.54, 4.69 (2d, 2H,

J=12.5 Hz, $C_6H_5C\underline{H}_2$), 4.59 (dd, 1H, J=9.5 Hz, J'=3.5 Hz, $CH_2C\underline{H}CO_2Et$). Anal. Calcd for $C_{28}H_{46}O_6Si$: C, 66.37; H, 9.15. Found: C, 66.45; H, 9.11.

There was then eluted 10.9 g (25%) of an isomeric spiroketal as a colorless oil: $R_f$ = 0.16 (silica gel, 1:1 ether/petroleum ether); evaporative distillation 195°C (0.001 mm Hg); IR ($CHCl_3$) 3000, 2970, 2940, 2860, 1755, 1725, 1460, 1260, 1100, 1160, 840 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$) δ 0.00 (s, 6H, $(CH_3)_2Si$), 0.85 (s, 9H, $(CH_3)_3C$), 0.85, 0.89 (2d, 6H, J=7 Hz, 2 $C\underline{H}_3CH$), 1.30 (t, 3H, J=7 Hz, $C\underline{H}_3CH_2$), 1.64-1.73 (m, 2H), 1.87 (dd, 1H, J=15 Hz, J'=2.5 Hz, $C\underline{H}HCHO$), 1.95 (dd, 1H, J=15 Hz, J'=4 Hz, $CH\underline{H}CHO$), 1.97-2.04 (m, 2H), 2.17-2.32 (m, 2H), 3.31 (dd, J=10 Hz, J'=6 Hz, $CHC\underline{H}HOSi$), 3.45 (dd, J=10 Hz, J'=5 Hz, $CHCH\underline{H}OSi$), 3.50 (m, 1H, $CH_2C\underline{H}CH$), 4.13 (dd, 1H, J=10 Hz, J'=2 Hz, $CHC\underline{H}CH$), 4.13, 4.25 (2dq, 2H, J=11 Hz, J'=7 Hz, $CH_3C\underline{H}_2$), 4.57, 4.64 (2d, 2H, J=13 Hz, $C_6H_5C\underline{H}_2$), 4.62 (dd, 1H, J=9.5 Hz, J'=8 Hz, $CH_2CHCO_2Et$). Anal. Calcd for $C_{28}H_{46}O_6Si$: 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: $R_f$ = 0.12 (silica gel, 2:8 ether/petroleum ether); evaporative distillation 195°C (0.001 mm Hg); IR ($CHCl_3$) 3000, 2970, 2940, 2860, 1745, 1460, 1260, 1150, 1100, 1030, 1000, 840 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$) δ 0.02, 0.03 (2s, 6H, $(CH_3)_2Si$), 0.86 (s, 9H, $(CH_3)_3C$), 0.98, 1.01 (2d, 6H, J=7 Hz, 2 $C\underline{H}_3CH$), 1.28 (t, 3H, J=7.5 Hz, $C\underline{H}_3CH_2$), 1.69 (m, 1H), 1.80 (m, 1H), 1.97-2.05 (m, 3H), 2.20

(dd, 1H, J=15 Hz, J'=3 Hz, CHHCHO), 2.37 (m, 1H), 2.46 (m, 1H), 3.49 (dd, 1H, J=11 Hz, J'=5 Hz, CHCHHOSi), 3.51 (dd, 1H, J=11 Hz, J'=5 Hz, CHCHHOSi), 3.64 (dd, 1H, J=6 Hz, J'=3 Hz, $CH_2CHCH$), 3.69 (dd, 1H, J=9.5 Hz, J'=2 Hz, CHCHCH), 4.19 (m, 2H, $CH_3CH_2$), 4.52, 4.55 (2d, 2H, J=12 Hz, $C_6H_5CH_2$), 4.68 (dd, 1H, J=9.5 Hz, 3 Hz, $CH_2CHCO_2Et$). Anal. Calcd for $C_{28}H_{46}O_6Si$: C, 66.37; H, 9.15. Found: C, 66.64; H, 9.15.

There was then eluted 2.7 mg (6%) of an isomeric spiroketal as a colorless oil: $R_f$ = 0.09 (silica gel, 2:8 ether/petroleum ether); evaporative distillation 195°C (0.001 mm Hg); IR ($CHCl_3$) 2960, 2940, 2860, 1725, 1460, 1150, 1100, 1070, 1030, 1010, 840 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$) $\delta$ 0.02, 0.03 (2s, 6H, $(CH_3)_2Si$), 0.97, 0.98 (2d, 6H, J=7 Hz, 2 $CH_3CH$), 1.28 (t, 3H, J=7 Hz, $CH_3CH_2$), 1.67 (m, 1H), 1.77 (m, 1H), 1.83 (dd, 1H, J=14 Hz, J'=2 Hz, CHHCHO), 1.98 (m, 1H), 2.15 (dd, 1H, J=14 Hz, J'=3 Hz, CHHCHO), 2.17-2.25 (m, 2H), 2.53 (m, 1H), 3.47 (d, 2H, J=4.5 Hz, $CHCH_2OSi$), 3.63 (ddd, 1H, J=6 Hz, J'=3 Hz, J''=2 Hz, $CH_2CHCH$), 3.66 (dd, 1H, J=9.5 Hz, J'=2 Hz, CHCHCH), 4.19, 4.25 (2m, 2H, $CH_3CH_2$), 4.48 (dd, 1H, J=8 Hz, J'=8 Hz, $CH_2CHCO_2Et$), 4.49, 4.55 (2d, 2H, J=12 Hz, $C_6H_5CH_2$). Anal. Calcd for $C_{28}H_{46}O_6Si$: 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 carboethoxy 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.

**6(R)-2(R)-[[[1-(1,1-dimethylethyl)dimethylsilyl]oxy]-2-(S)-propyl]-3(R)-4(S)-hydroxy-8-carboethoxy-1,7-dioxaspiro-[5.4]decane (25).** To a stirred solution of 5.0 mg (0.0098 mmol) of the spiroketal **24** ($R_f$ = 0.16, 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 for 22 h. The catalyst was then removed by filtration and washed with two 5 mL portions of ethyl acetate. The combined filtrates were concentrated under reduced pressure. To a solution of the residue in 0.5 mL of $CDCl_3$ was added 5 mg of pyridinium p-toluenesulfonate. After 24 h at room temperature, the solvent was removed under reduced pressure. Chromatography of the residue 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: $R_f$ = 0.25 (silica gel, 7:3 ether/petroleum ether); IR ($CCl_4$) 3560, 2960, 2940, 2860, 1760, 1740, 1465, 1375, 1255, 1100, 1060, 1035, 840 $cm^{-1}$; $^1H$ NMR (500 MHz, 9:1 $CCl_4/C_6D_6$) $\delta$ 0.03, 0.04 (2s, 6H, $(CH_3)_2Si$), 0.82, 0.89 (2d, 6H, J=7 Hz, 2 $CH_3CH$), 0.91 (s, 9H, $(CH_3)_3C$), 1.22 (t, 3H, J=7 Hz, $CH_3CH_2$), 1.54 (m, 1H), 1.56 (bd, 1H, J=12 Hz, CHHCHO), 1.69 (m, 1H), 1.79 (m, 1H), 1.94 (m, 1H), 1.96 (d, 1H, J=12 Hz, CHHCHO), 2.07-2.22 (m, 2H), 3.37 (dd, 1H, J=10 Hz, J'=6 Hz, CHCHHOSi), 3.41 (dd,

1H, J=10 Hz, J'=4 Hz, CHCH$\underline{H}$OSi), 3.62 (bm, 1H, $CH_2C\underline{H}CH$), 4.05 (dd, 1H, J=10 Hz, J'=2 Hz, CHC$\underline{H}$CH), 4.06 (dq, 1H, J=11 Hz, J'=7 Hz, $CH_3C\underline{H}H$), 4.14 (dq, 1H, J=11 Hz, J'=7 Hz, $CH_3CH\underline{H}$), 4.43 (dd, 1H, J=8.5 Hz, J'=8.5 Hz, $CH_2C\underline{H}CO_2Et$).

By the procedure described above, a solution of 5.0 mg (0.0098 mmol) of the spiroketal **24** ($R_f$ = 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 $CDCl_3$, afforded, after chromatography on 5 g of silica gel with 7:3 ether/petroleum ether, 3.7 mg (90%) of the alcohol **25** as a colorless oil: $R_f$ = 0.26 (silica gel, 7:3 ether/petroleum ether); evaporative distillation 190°C (0.005 mm Hg); IR ($CCl_4$) 3560, 2960, 2940, 2860, 1755, 1465, 1380, 1255, 1200, 1120, 1100, 1050, 1035, 840 $cm^{-1}$; $^1H$ NMR (500 MHz, 9:1 $CCl_4/C_6D_6$) $\delta$ 0.03, 0.04 (2s, 6H, $(CH_3)_2Si$), 0.83 (d, 3H, J=7 Hz, $C\underline{H}_3CH$), 0.90 (s, 9H, $(CH_3)_3C$), 0.96 (d, 3H, J=6.5 Hz, $C\underline{H}_3CH$), 1.21 (t, 3H, J=7 Hz, $C\underline{H}_3CH_2$), 1.63-1.74 (m, 2H), 1.78(dd, 1H, J=15 Hz, J'=2 Hz, C$\underline{H}$HCHO), 1.85-1.93 (m, 2H), 1.96 (dd, 1H, J=15 Hz, J'=3.5 Hz, CH$\underline{H}$CHO), 2.24-2.33 (m, 2H), 3.26 (bd, 1H, J=9 Hz, CHO$\underline{H}$), 3.36 (dd, 1H, J=10 Hz, J'=6 Hz, CHC$\underline{H}$HOSi), 3.48 (dd, 1H, J=10 Hz, J'=4 Hz), 3.65 (bm, 1H, $CH_2C\underline{H}CH$), 3.82 (dd, 1H, J=10 Hz, J'=2 Hz, CHC$\underline{H}$CH), 4.07, 4.08 (2q, 2H, J=7 Hz, $CH_3C\underline{H}_2$), 4.43 (dd, 1H, J=9 Hz, J'=4 Hz, $CH_2C\underline{H}CO_2Et$). Anal. Calcd for $C_{21}H_{40}O_6Si$: C, 60.54; H, 9.68. Found: C, 60.60; H, 9.57.

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30. The conformation of the bicyclic ketal **11** depicted is supported by 90 MHz NMR. While the $C4^{23}$ hydrogen 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 trihydrate, 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 non-nucleophilic counterion also appeared to be essential, as concentrated HCl in acetonitrile caused degradation.

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43. In order of increasing polarity, the spiroketals were obtained in a ratio of 7.4:4.0:3.1:1.0. As expected on the basis of these ratios, the most and least polar compounds were shown to bear the same configuration at the carboethoxy center by equilibration of the spiroketal center with pyridinium p-toluenesulfonate in chloroform. The spiroketals of intermediate polarity were also interconvertible.

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# CHAPTER 2

## The Synthesis of the Monensin Bis-Tetrahydrofuran via the Claisen Rearrangement of an Ester Enolate with a β-Leaving Group

# 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]

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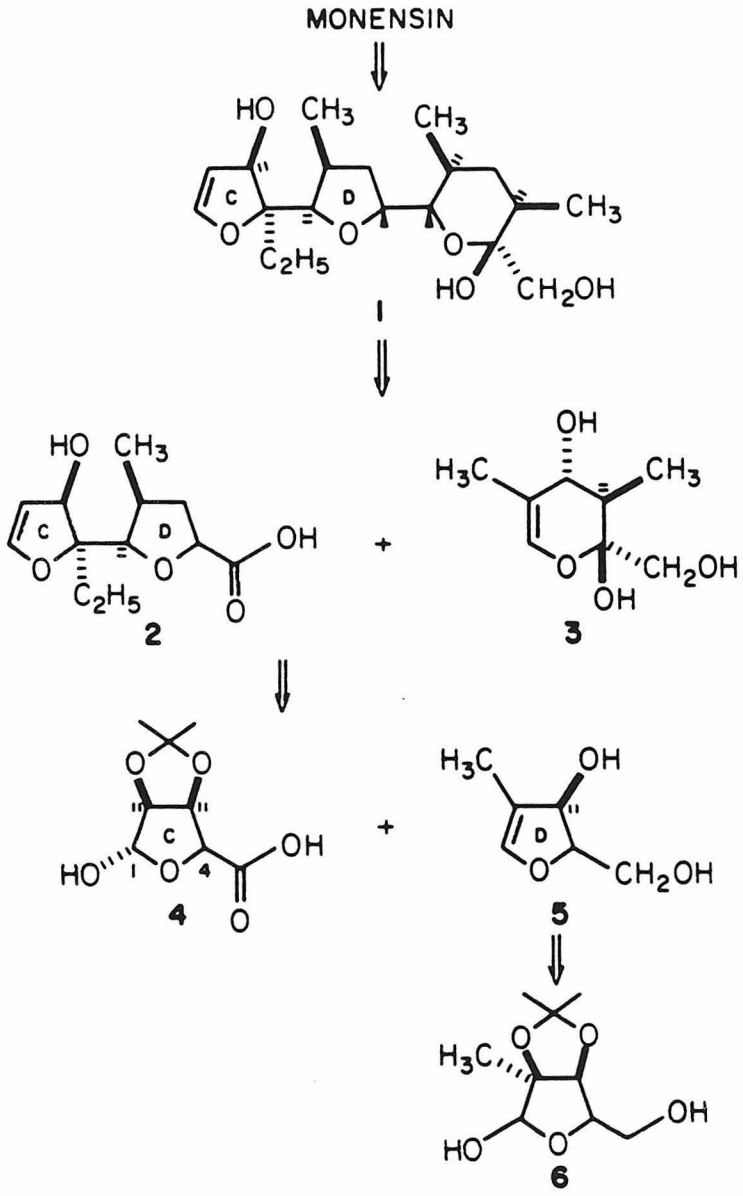
**Abstract:** The monensin bis-tetrahydrofuran **25**, a versatile intermediate for the synthesis of polyether ionophore antibiotics, is prepared from D-xylose and D-mannose. In the key step, *in situ* silylation of an ester enolate with a β-leaving group allows the tetrahydrofuran rings to be joined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

The preceding article 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.

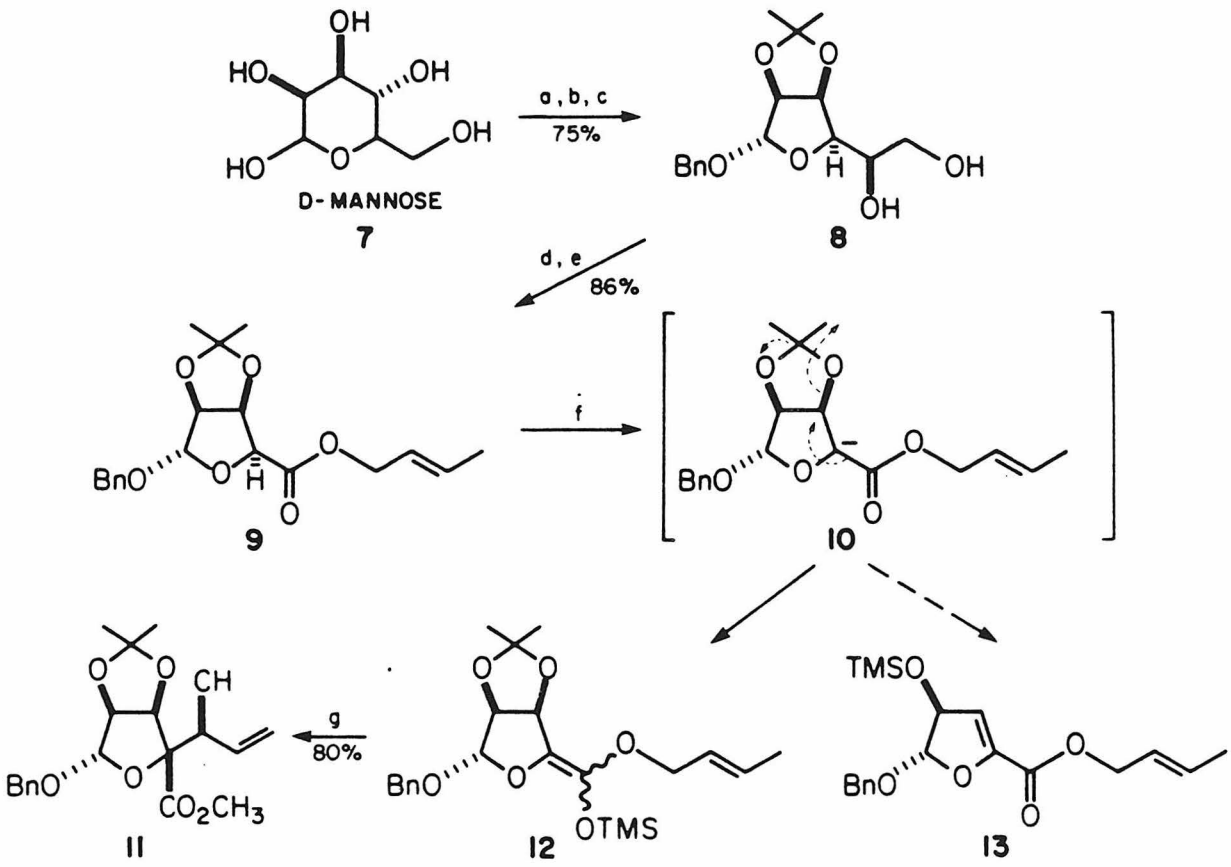
Reductive fragmentation of the lactol-acetonide functional group array has proven to be a uniquely reliable route to furanoid glycals,[4] and this consideration dominated the retrosynthetic analysis of the bis-tetrahydrofuran subunit **2** outlined in Scheme I. Utilization of the D ring first as the 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 C1 carbanion; Claisen rearrangement forbids the same β-elimination from a C4 enolate.

**SCHEME I** RETROSYNTHETIC ANALYSIS FOR THE BIS-TETRAHYDROFURAN POLYETHER BUILDING BLOCK **2**



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 pseudo-axial orientation. We were thus disappointed but not surprised to find that enolization of the crotyl ester **9** with LDA in THF at -100°C for four minutes 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

**SCHEME II** ESTER ENOLATE CLAISEN REARRANGEMENT IN THE PRESENCE OF A β- LEAVING GROUP[a]

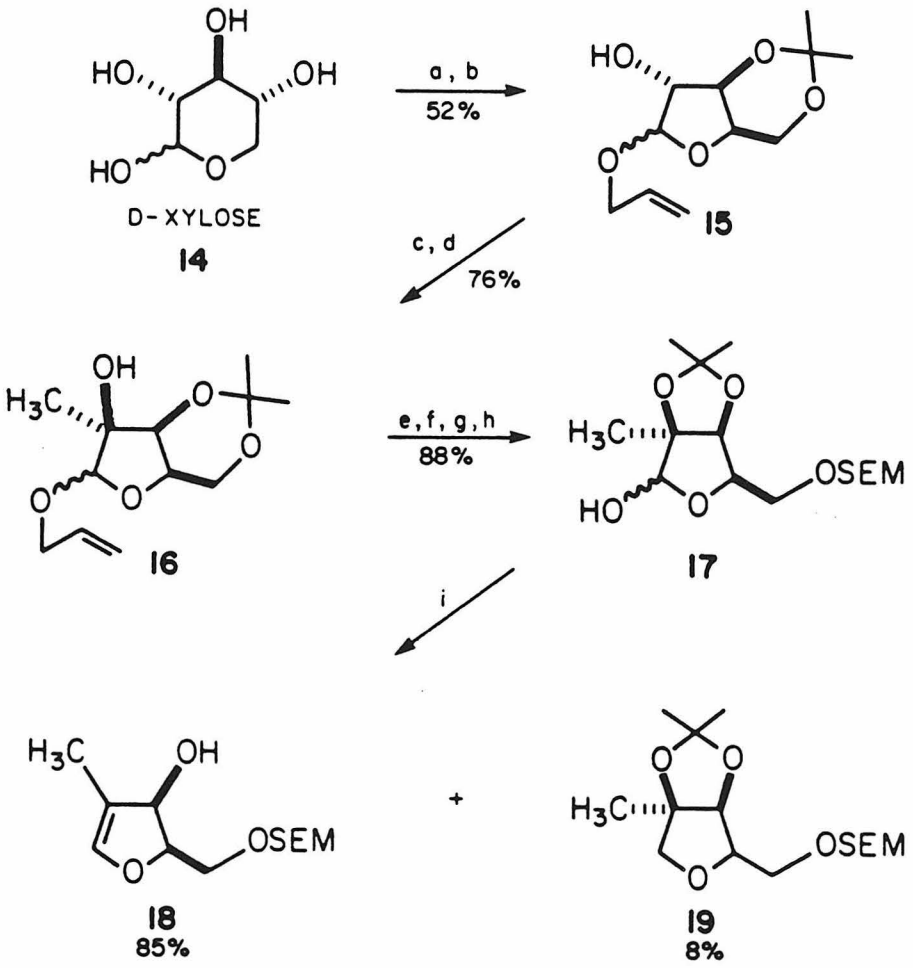



[a](a) $H_2SO_4$, $(CH_3)_2CO$; (b) BnBr, NaH, DMF; (c) HCl, MeOH, $H_2O$; (d) $NaIO_4$, MeOH, $H_2O$; $AgNO_3$, KOH, $H_2O$, EtOH; (e) $(COCl_2)$, $C_6H_6$, DMF (catalytic); $CH_3CHCHCH_2OH$, DMAP, $CH_2Cl_2$; (f) LDA, TMSCl, THF/HMPA; (g) room temperature; $H_3O^+$; $CH_2N_2$, $Et_2O$.

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 four times as fast as β-elimination, and that all of 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 yield of 52%. Swern oxidation[13] in THF followed by the direct addition of excess methyl magnesium bromide to the crude reaction mixture

**SCHEME III** SYNTHESIS OF THE FURANOID GLYCAL 18[a]

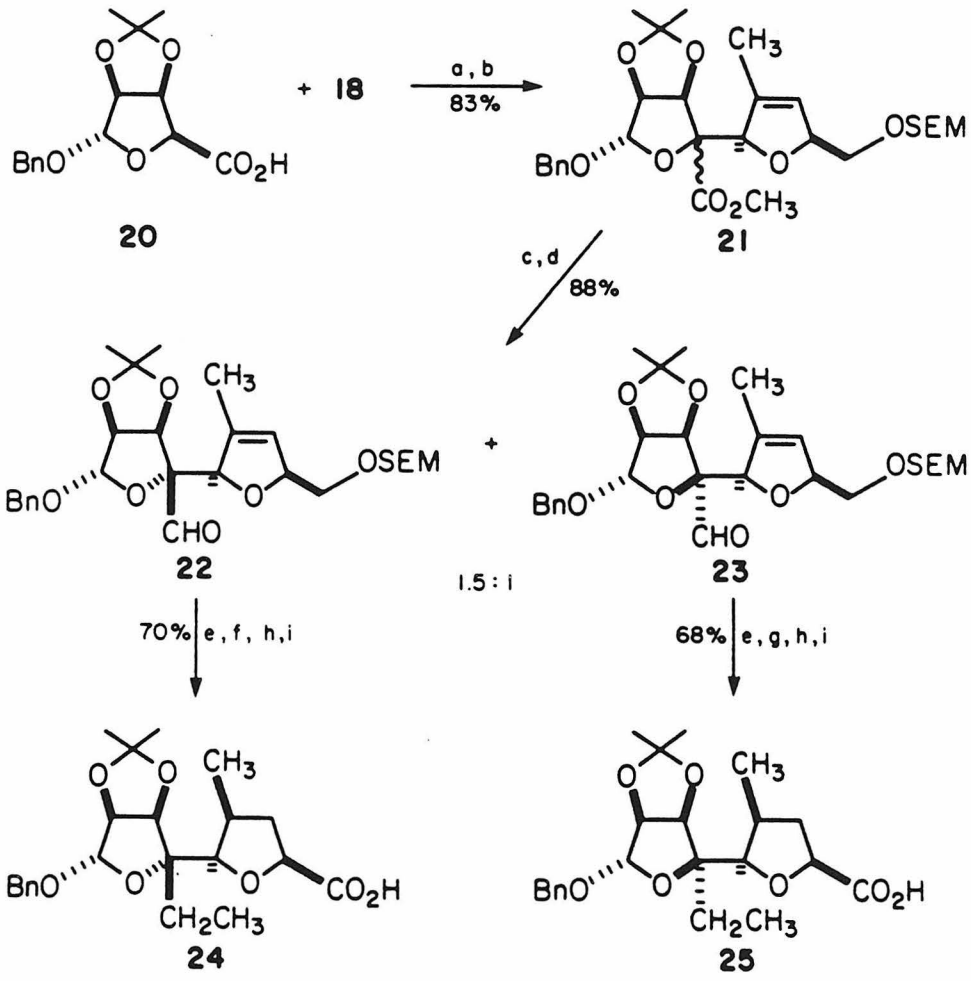



[a](a) $C_6H_5NH^+.p\text{-}TsO^-$, $CH_2CHCH_2OH$; (b) $C_6H_5NH^+.p\text{-}TsO^-$, $(CH_3)_2CO$; (c) $(COCl)_2$, $Me_2SO$, THF; $Et_3N$; (d) MeMgBr, $Et_2O$; (e) $p\text{-}TsOH\cdot H_2O$, $CuSO_4$, $(CH_3)_2CO$; (f) $t\text{-}BuOK$, DMSO; (g) $Me_3SiCH_2CH_2OCH_2Cl$, $(i\text{-}Pr)_2NEt$, $CH_2Cl_2$;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

circumvented the formation of a tenacious 2-ketofuranoside hydrate[14] and produced the tertiary alcohols **16** as the 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 twenty minutes 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 products **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**,

**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.

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 ( $\sim$ 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.

**EXPERIMENTAL SECTION**

Melting points were determined using a Hoover capillary melting point apparatus and are uncorrected. Infrared (IR) spectra were determined on a Perkin-Elmer 727B or 1310 infrared spectrophotometer. Proton nuclear magnetic resonance ($^1$H NMR) spectra were recorded on a Varian EM-390 spectrometer, except where "500 MHz" denotes spectra recorded on a Bruker WM-500 spectrometer (Southern California Regional NMR Facilty, Caltech, Pasadena, California). Chemical shifts are reported as $\delta$ values in parts per million relative to tetramethylsilane ($\delta$ 0.0) as an internal standard. Data are reported as follows: Chemical shift (multiplicity, integrated intensity, coupling constants, assignment). Optical rotations were measured on 1 dm cells of 1 mL capacity using a JASCO Model DIP-181 polarimeter. Chloroform, when used as a solvent for optical rotations, was filtered through neutral alumina (Activity I) immediately prior to use. Analytical thin-layer chromatography (TLC) was conducted on 2.5 x 10 cm precoated TLC plates: Silica gel 60 F-254, layer thickness 0.25 mm, manufactured by E. Merck and Co., Darmstadt, Germany. Silica gel columns for chromatography utilized E. Merck silica gel 60 (70-230 mesh ASTM). Flash chromatography was performed on E. Merck silica gel 60 (230-400 mesh ASTM) according to a published procedure (Still, W. C.; Kahn, M.; Mitra, A. J. Org. Chem. **1978**, 43, 2923-2925). Acidic

silica gel refers to Silicar CC-4 Special "for column chromatography," sold by Mallinckrodt Chemical Works, St. Louis, MO. "Alumina" refers to the grade I neutral variety manufactured by M. Woelm, Eschwege, Germany, which was neutralized to the indicated grade by the addition of water. Reaction solvents and liquid reagents were purified by distillation or drying shortly before use. Benzene, pyridine, n-hexane, trimethylchlorosilane, oxalyl chloride, N,N-diisopropylethyalmine and dichloromethane were distilled from powdered calcium hydride. Dimethyl sulfoxide, dimethylformamide, and hexamethylphosphoramide were distilled under reduced pressure from powdered calcium hydride and stored over a mixture of 3A and 4A sieves. n-Pentane was distilled from sodium metal under argon. Hexamethyldisilazane was distilled under argom from powdered calcium hydride and stored over a mixture of 3A and 4A sieves. Ether, tetrahydrofuran, triethylamine, and diisopropylamine were distilled under argon from sodium metal with sodium benzophenone ketyl as an indicator. Methanol was distilled from sodium methoxide and methyl benzoate. Acetonitrile was dried over a mixture of 3A and 4A sieves. Ammonia was distilled from the tank and then from a blue lithium solution. n-Propionyl chloride was heated at reflux for 3h with phosphorous pentachloride and then distilled, and the distillate was treated with quinoline and redistilled. Tris(dimethylamino)phosphine was distilled at

reduced pressure under argon. Ammonium chloride was dried at 75°C under vacuum (1 mm Hg) over phosphorous pentoxide for at least 12h. All other rectants and solvents were "reagent grade" unless described otherwise. "Ether" refers to anhydrous diethyl ether which is supplied by Mallinckrodt and Baker. "Petroleum ether" refers to the "analyzed reagent" grade hydrocarbon fraction (bp 35-60°C) which is supplied by J. T. Baker, Co., Phillipsburg, NJ. 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 12h 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*. Mass spectral analyses were performed by Larry Henling, Caltech, Pasadena, CA. Elemental combustion analyses were performed by Spang Microanalytical Laboratory, Eagle Harbor, MI.

**Benzyl 2,3-O-(1-methylethylidene)- -D-lyxofuranosiduronic acid, methyl ester.** To a mechanically 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 mechanically 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. 500 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 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 semi-crystalline acid of at least 95% purity as judged by $^1H$ NMR, representing a total yield of 93%. $^1H$ NMR ($CDCl_3$) $\delta$ 1.36, 1.45 (2s, 6H, $(CH_3)_2C$),

4.48, 4.72 (2d, 2H, J=12 Hz, $C_6H_5C\underline{H}_2$), 4.68, 4.68 (2d, 2H, J=6 Hz, J=5 Hz, C(2)-H and C(4)-H), 5.05 (dd, 1H, J=6 HJz, J'=5 Hz, C(3)-H), 5.28 (s, 1H, OCHO), 7.33 (s, 5H, $C_6H_5$). 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 mm Hg); $[\alpha]_D^{22}$ +46.4 (c 0.99, $CHCl_3$); IR ($CHCl_3$) 3040, 3000, 2960, 1760, 1740, 1455, 1440, 1390, 1380, 1220, 1080, 865 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) 1.30, 1.43 (2s, 6H, $(CH_3)_2C$), 3.82 (s, 3H, $OCH_3$), 4.50, 4.72 (2d, 2H, J=12 Hz, $C_6H_5C\underline{H}_2$), 4.65, 4.65 (2d, 2H, J=5 Hz, J=6 Hz, C(2)-H and C(4)-H), 5.02 (dd, 1H, J=5 Hz, J'=6 Hz, C(3)-H), 5.27 (s, 1H, OCHO), 7.32 (s, 5H, $C_6H_5$). 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 three 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 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 1.32, 1.43 (2s, 6H, $(CH_3)_2C$), 4.48, 4.70 (2d, 2H, J=12 Hz, $C_6H_5C\underline{H}_2$), 4.67 (d, 1H, J=6 Hz), 4.87 (d, 1H, J=5 Hz), 5.17 (dd, 1H, J=5 Hz, J'=6 Hz, C(3)-H), 5.27 (s, 1H, OCHO), 7.30 (s, 5H, $C_6H_5$).

**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-dimethylaminopyridine. 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 mm Hg); $[\alpha]_D^{21}$ +36.7 (c 1.42, $CHCl_3$); IR ($CHCl_3$) 3040, 3000, 2950, 1760, 1730, 1455, 1385, 1375, 1195, 1085, 970, 860 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 1.27, 1.40 (2s, 6H, $(CH_3)_2C$), 1.67 (d, 3H, J=6 Hz, $C\underline{H}_3C=CH$), 5.0 (dd,

1H, J=6 Hz, J=5 Hz, C(3)-H), 5.27 (s, 1H, OCHO), 7.30 (s, 5H, $C_6H_5$). 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)(dimethylmethoylenedioxy)-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 1M solution of tetra-n-butyl ammonium 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 mm Hg); IR ($CHCl_3$) 3040, 3000, 2960, 1725, 1455, 1385, 1375, 1240, 1080, 870 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 1.03 (d, "1.5H", J=7 Hz, $CH_3CH$), 1.20 (d, "1.5H", J=7 Hz, $CH_3CH$), 1.32, 1.47 (2s, 6H, $(CH_3)_2C$), 3.02 (bq, 1H, J=7 Hz, $CH_3CH$), 3.50 (s, 3H, $OCH_3$), 7.30 (s, 5H, $C_6H_5$). 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 mm Hg); $[\alpha]_D^{21}$ +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 ($CDCl_3$) $\delta$ 1.08 (d, 3H, J=7 Hz, $CH_3CH$), 1.30, 1.40 (2s, 6H, $(CH_3)_2C$), 3.43 (s, 3H, $OCH_3$), 7.33 (s, 5H, $C_6H_5$). 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 mm Hg); $[\alpha]_D^{21}$ +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 ($CDCl_3$) $\delta$ 1.12 (d, 3H, J=7 Hz, $CH_3CH$), 1.27, 1.40 (2s, 6H, $(CH_3)_2C$), 3.77 (s, 3H, $OCH_3$), 7.33 (s,

5H, $C_6H_5$). 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 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 mm Hg) 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 mm Hg); $[\alpha]_D^{22}$ +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 (2s, 6H, $(CH_3)_2C$), 2.97 (d, 1H, J=4 Hz, CHOH), 3.93-4.50 (m, 7H), 5.33 (d, 1H, J=4 Hz, OCHO), 5.70-6.13 (m, 1H, $CH_2$=CH). 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 mm Hg); $[\alpha]_D^{22}$ -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, 6H, $(CH_3)_2C$), 2.30 (d, 1H, J=4 Hz, CHOH), 3.67-4.33 (m, 7H), 5.00 (s, 1H, 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-methylethylidne)-2-C-methyl-α and β-D-lyxofuranoside (16).** To a mechanically 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 to -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°. 390 mL (1.09 mol) of a 2.8M solution of methyl magnesium bromide 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 mm Hg); $[\alpha]_D^{22}$ +105° (c 1.80, $CHCl_3$); IR ($CHCl_3$) 3550, 3000, 2920, 1450,

1385, 1375, 1165, 1050, 1010, 840 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 1.30, 1.42, 1.42 (3s, 9H, 3 $CH_3C$), 3.27 (s, 1H, OH), 3.63-4.40 (m, 6H), 4.93 (s, 1H, 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 millimolar scale 75% of the β-anomer of **16** as a colorless oil: $R_f$ = 0.28 (silica gel, 4:6 ether/petroleum ether); evaporative distillation 100°C (0.005 mm Hg); $[\alpha]_D^{22}$ -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 ($CDCl_3$) $\delta$ 1.32, 1.38, 1.38 (3s, 9H, 3 $CH_3C$), 3.40 (s, 1H, OH), 3.55-4.40 (m, 6H), 4.58 (s, 1H, 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, the residue dissolved in 1L 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 mm Hg); $[\alpha]_D^{21}$ +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 (3s, 9H, 3 $CH_3C$), 2.20 (t, 1H, J=5 Hz, $CH_2OH$), 4.36 (d, 1H, J=3 Hz, C(3)-H), 4.90 (s, 1H, 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 mm Hg); $[\alpha]_D^{21}$ -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 (3s, 9H, 3 $CH_3C$), 2.20 (t, 1H, J=6 Hz, $CH_2OH$), 4.35 (d, 1H, J=4 HJz, C(3)-H), 4.50 (s, 1H, 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-methylethylidne)-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 DMSO at 80°C was added 36.7 g (0.327 mol) of potassium *t*-

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 mm Hg); $[\alpha]_D^{21}$ +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 (3s, 9H, 3 $CH_3C$), 1.54 (dd, 3H, J=2 Hz, J'=5 Hz, $CH_3CH=CH$), 2.17 (t, 1H, J=6 Hz, $CH_2OH$), 4.37 (d, 1H, J=3 Hz, C(3)-H), 5.03 (s, 1H, 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 mm Hg); $[\alpha]_D^{23}$ -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 (3s, 9H, 3 $CH_3C$), 1.61 (dd, 3H, J=2 Hz, J'=5 Hz, $CH_3CH=CH$), 2.06 (t, 1H, J=6 Hz, $CH_2OH$), 4.40 (d, 1H, J=4.5 Hz, C(3)-H), 4.67 (s, 1H, 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 1L 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 mm Hg); $[\alpha]_D^{23}$ -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 (3s, 9H, 3 $CH_3C$), 4.66 (s, 2H, $OCH_2O$), 5.17 (s, 1H, 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 mm Hg); IR ($CHCl_3$) 2995, 2960, 2940, 1450, 1385, 1255, 1120, 1065, 1045, 865, 845 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 0.05 (s, 9H, $(CH_3)_3Si$), 1.40, 1.47, 1.48 (3s, 9H, $3CH_3C$), 3.35, 3.98 (2d, 2H, J=10 Hz, $OCH_2C$), 4.28 (d, 1H, J=3 Hz, C(3)-H), 4.72 (s, 2H, $OCH_2O$). 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° (0.005 mm Hg); $[\alpha]_D^{22}$ -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 ($CDCl_3$) $\delta$ 0.05 (s, 9H, $(CH_3)_3Si$), 1.75 (s, 3H, $CH=CH_3$), 2.20 (d, 1H, J=7 Hz, CHOH), 4.73 (s, 2H, $OCH_2O$), 6.25 (bs, 1H, $CH=CCH_3$). 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-(trimethylsily)ethoxymethyleneoxymethyl]-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) ofthe glycal **18**, 190 mg (1.55 mmol) of 4-dimethylaminopyridine, 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 ($MeOH/N_2$ taffy-like slush) was maintained at -115 to -120°C, and the THF mixture appeared to be viscous and heterogeneous. 5 min 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 to -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 15h, the solution was cooled to 0°C, treated with 40 mL of 1% aqueous HCl for 20 min, and then diluted with 1L 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 mm Hg). 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, 9H, $(CH_3)_3Si$), 0.91 (m, 2H, $TMSC\underline{H}_2$), 1.35, 1.49 (2s, 6H, $(CH_3)_2C$), 1.99 (bs, 3H, $C\underline{H}_3C=CH$), 3.25, 3.46 (2dd, 2H, J=11.5 Hz, J'=6 Hz, $CHC\underline{H}_2O$), 3.50 (s, 3H, $OCH_3$), 3.56 (m, 2H, $TMSCH_2C\underline{H}_2O$), 4.42, 4.66 (2d, 2H, J=12 Hz, $C_6H_5C\underline{H}_2$), 4.61, 4.64 (2d, 2H, J=6.5 Hz, $OCH_2O$), 4.63 (d, 1H, J=6 Hz, C(14)-H), 4.85 (m, 1H, $OC\underline{H}CH_2$), 5.04 (bs, 1H, C(17)-H), 5.10

(s, 1H, OCHO), 5.49 (q, 1H, J=2 Hz, $CH_3C=C\underline{H}$), 5.52 (d, 1H, J=6 Hz, C(15)-H), 7.23-7.33 (m, 5H, $C_6H_5$).

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, $CDCl_3$) $\delta$ 0.00 (s, 9H, $(CH_3)_3Si$), 0.89 (m, 2H, $TMSCH_2$), 1.31, 1.43 (2s, 6H, $(CH_3)_2C$), 1.69 (bs, 3H, $C\underline{H}_3C=CH$), 3.41 (d, 1H, J=10 Hz, J'=4.5 Hz, $OCHC\underline{H}HO$), 3.55 (m, 2H, $TMSCH_2C\underline{H}_2$), 3.61 (d, 1H, J=10 Hz, J'=8 Hz, $OCHCH\underline{H}O$), 3.80 (s, 3H, $OCH_3$), 4.50, 4.54 (2d, 2H, J=7 Hz, $OCH_2O$), 4.59, 4.78 (2d, 2H, J=12 Hz, $C_6H_5C\underline{H}_2$), 4.64 (dd, 1H, J=6 Hz, J'=3 Hz, C(14)-H), 4.81 (m, 1H, $OC\underline{H}CH_2O$), 5.07 (d, 1H, J=6 Hz, C(15)-H), 5.28 (bs, 1H, C(17)-H), 5.38 (d, 1H, J=3 Hz, OCHO), 5.46 (q, 1H, J=2 Hz, $CH_3C=C\underline{H}$), 7.25-7.36 (m, 5H, $C_6H_5$).

**2(R) and 2(S)-Hydroxymethyl-2-[2,5-dihydro-5(S)-[2-(trimethylsilyl)ethoxymethyleneoxymethyl]-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 1h, 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 mm Hg); $[\alpha]_D^{22}$ +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 ($CDCl_3$) $\delta$ 0.05 (s, 9H, $(CH_3)_3Si$), 1.38, 1.53 (2s, 6H, $(CH_3)_2C$), 1.88 (bs, 3H, $CH_3C=CH$), 5.17 (s, 1H, OCHO), 5.52 (bs, 1H, $CH_3C=CH$), 7.32 (s, 5H, $C_6H_5$). 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 mm Hg); $[\alpha]_D^{22}$ +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 ($CDCl_3$) $\delta$ 0.00 (s, 9H, $(CH_3)_3Si$), 1.30, 1.50 (2s, 6H, $(CH_3)_2C$), 1.88 (bs, 3H, $CH_3C=CH$), 2.77 (t, 1H, J=7 Hz, $CH_2OH$), 5.20 (s, 1H, OCHO), 5.47 (bs, 1H, $CH_3C=CH$). 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)ethoxymethyleneoxymethyl]-3-methyl-2(R)-furyl]-3(R),-4(S)-(dimethylmethylenedioxy)-5(S)-benzyloxy-tetrahydrofuran (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 DMSO 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 mm Hg); $[\alpha]_D^{22}$ +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 ($CDCl_3$) $\delta$ 0.03 (s, 9H, $(CH_3)_3Si$), 1.30, 1.45 (2s, 6H, $(CH_3)_2C$), 1.70 (bs, 3H, $CH_3C=CH$), 4.67 (dd, 1H, J=6 Hz, J'=2 Hz, C(14)-H), 5.09 (d, 1H, J=6 Hz, C(15)-H), 5.37 (d, 1H, J=2 Hz, OCHO), 5.52 (bs,

1H, $CH_3C=C\underline{H}$), 7.33 (s, 5H, $C_6H_5$), 9.62 (s, 1H, 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 mm Hg); $[\alpha]_D^{23}$ +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 ($CDCl_3$) $\delta$ 0.03 (s, 9H, $(CH_3)_2$)Si), 1.37, 1.50 (2s, 6H, $(CH_3)_2C$), 2.00 (bs, 3H, $C\underline{H}_3C=CH$), 5.15 (s, 1H, OCHO), 5.30 (d, 1H, J=6 Hz, C(15)-H), 5.57 (bs, 1H, $CH_3C=C\underline{H}$), 7.30 (s, 5H, $C_6H_5$), 9.42 (s, 1H, 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)ethoxymethyleneoxymethyl]-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 1h 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 9h 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° (0.001 mm Hg); $[\alpha]_D^{23}$ +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 ($CDCl_3$) $\delta$ 0.05 (s, 9H, $(CH_3)_3Si$), 1.40, 1.55 (2s, 6H, $(CH_3)_2C$), 1.85 (bs, 3H, $CH_3C=CH$), 5.17 (s, 1H, OCHO), 5.52 (bs, 1H, $CH_3C=CH$), 7.30 (s, 5H, $C_6H_5$). 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)ethoxymethyleneoxymethyl]-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 2.10M 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 mm Hg); $[\alpha]_D^{23}$ -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, 9H, $(CH_3)_3Si$), 1.32, 1.43 (2s, 6H, $(CH_3)_2C$), 1.83 (bs, 3H, $CH_3C=CH$), 5.22 (s, 1H, OCHO), 7.32 (s, 5H, $C_6H_5$). 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)ethoxymethyleneoxymethyl]-3(R) and 3(S)-methyl-2(R)-tetrahydrofuryl]-3(R), 4(S)-(dimethylmethylenedioxy)-5(S)-benzyloxytetrahydrofuran.** 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 atmosphere of hydrogen for 10h. 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); $[\alpha]_D^{22}$ +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, 9H, $(CH_3)_3C$), 1.00 (t, 3H, J=6 Hz, $CH_3CH_2$), 1.10 (d, 3H,

J=7 Hz, $CH_3CH$), 1.30, 1.48 (2s, 6H, $(CH_3)_2C$), 2.50 (m, 1H, $CH_3CH$), 3.83 (d, 1H, J=4.5 Hz, C(17)-H), 5.10 (s, 1H, OCHO), 7.33 (s, 5H, $C_6H_5$). 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 ($CDCl_3$) $\delta$ 0.05 (s, 9H, $(CH_3)_3Si$), 1.02 (t, 3H, J=6 Hz, $CH_3CH_2$), 1.21 (d, 3H, J=7 Hz, $CH_3CH$), 1.35, 1.52 (2s, 6H, $(CH_3)_2C$), 4.02 (d, 1H, J=6 Hz, C(17)-H), 5.12 (s, 1H, OCHO), 7.33 (s, 5H, $C_6H_5$).

**2(S)-Ethyl-2-[5-(S)-[2-(trimethylsilyl)ethoxymethyleneoxymethyl]-3(R) and 3(S)-methyl-2(R)-tetrahydrofuryl]-3(R), 4(S)-(dimethylmethylenedioxy)-5(S)-benzyloxytetrahydrofuran.** 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, centrifuged, and the supernatant then removed. The catalyst was washed two 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 atmosphere of hydrogen for 12h. 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 ($CDCl_3$) $\delta$ 0.05 (s, 9H, $(CH_3)_3Si$), 1.02 (t, 3H, J=7 Hz, $CH_3CH_2$), 1.12 (d, 3H, J=7 Hz, $CH_3CH$), 1.33, 1.48 (2s, 6H, $(CH_3)_2C$), 3.72 (d, 1H, J=5 Hz, C(17)-H), 5.08 (s, 1H, OCHO), 7.32 (s, 5H, $C_6H_5$). 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); $[\alpha]_D^{23}$ +48.2° (c 1.18, $CHCl_3$); IR ($CHCl_3$) 3000, 2950, 2880, 1460, 1450, 1380, 1370, 1240, 865, 835, $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 0.03 (s, 9H, $(CH_3)_3Si$), 1.00 (t, 3H, J=7 Hz, $CH_3CH_2$), 1.22 (d, 3H, J=7 Hz, $CH_3CH$), 1.33, 1.50 (2s, 6H, $(CH_3)_2C$), 3.87 (d, 1H, J=6 Hz, C(17)-H), 5.13 (d, 1H, J=2 Hz, OCHO), 7.32 (s, 5H, $C_6H_5$). 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 m of HMPA was heated at 125°C for 24h. 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); $[\alpha]_D^{22}$ +65.8° (c 0.880, $CHCl_3$); IR ($CHCl_3$) 3500, 3000, 2950, 2880, 1455, 1385, 1375, 1270, 1010, 870 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 0.98 (t, 3H, J=7 Hz, $CH_3CH_2$), 1.10 (d, 3H, J=7 Hz, $CH_3CH$), 1.28, 1.48 (2s, 6H, $(CH_3)_2C$), 3.83 (d, 1H, J=4 Hz, C(17)-H), 5.12 (s, 1H, OCHO), 7.32 (s, 5H, $C_6H_5$). 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 (8.22 mmol) of dry CsF in 555 mL of HMPA was heated at 125°C for 27h. 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 mm Hg); $[\alpha]_D$ +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, 3H, J=7 Hz, $CH_3CH_2$), 1.18 (d, 3H, J=6 Hz, $CH_3CH$), 1.32, 1.45 (2s, 6H, $(CH_3)_2C$), 3.80 (d, 1H, J=5 Hz, C(17)-H), 5.12 (d, 1H, J=2 Hz, OCHO), 7.32 (s, 5H, $C_6H_5$). 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)-benzyloxytetrahydrofuran (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 dimethylsulfoxide 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, 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 mm Hg); $[\alpha]_D^{27}$ +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 ($CDCl_3$) $\delta$ 1.03 (t, 3H, $CH_3CH_2$), 1.12 (d, 3H, $CH_3CH$), 1.33, 1.50 (2s, 6H, $(CH_3)_2C$), 3.73 (s, 3H, $OCH_3$), 3.92 (d, 1H, J=4 Hz,

C(17)-H), 5.07 (s, 1H, OCHO), 7.33 (s, 5H, $C_6H_5$). 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)-benzyloxytetrahydrofuran (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 mm Hg); $[\alpha]_D^{23}$ +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 ($CDCl_3$) $\delta$ 1.00 (t, 3H, J=7 Hz, $CH_3CH_2$), 1.23 (d, 3H, J=6 Hz, $CH_3CH$), 1.33, 1.48 (2s, 6H, $(CH_3)_2C$), 3.47 (s, 3H, $OCH_3$), 3.98 (d, 1H, J=6 Hz, C(17)-H), 5.12 (d, 1H, J=2 Hz, OCHO), 7.32 (s, 5H, $C_6H_5$). 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.

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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.

# CHAPTER 3

## An Approach to the Monensin Tetrahydropyran-Bis-Tetrahydrofuran via the Ester Enolate Claisen Rearrangement and Reductive Decarboxylation

# 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]

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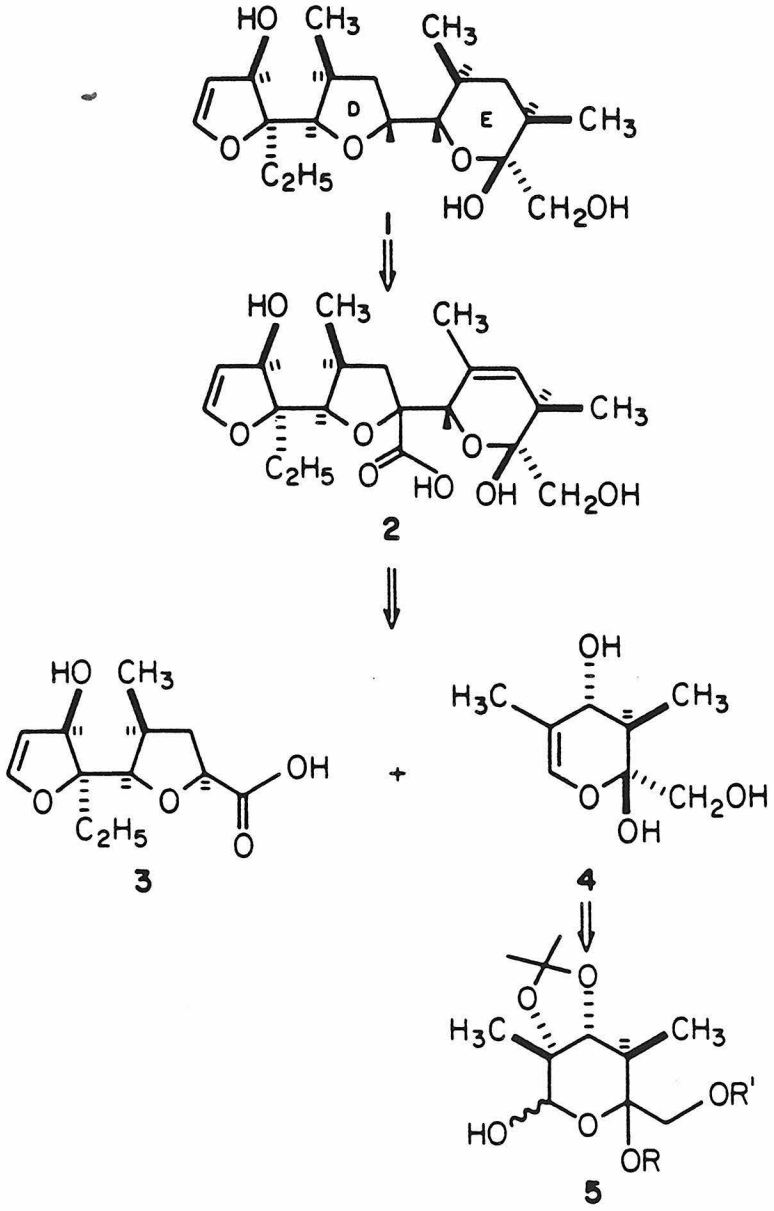
**Abstract:** The monensin tetrahydropyran equivalent **22** is prepared from D-fructose and then joined to the monensin bis-tetrahydrofuran equivalent **24a** via the ester enolate Claisen rearrangement. Methodology for the radical induced, reductive decarboxylation of the resulting acid **26a** is 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-t-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[3] and its enantiomer[4] in sufficient quantities for biological testing. In order to explore this strategy further, we have developed routes to additional subunits for polyether synthesis as reported in the preceding papers in this journal. In general, the substitution pattern of the ionophore framework nicely accommodates the functionality engendered by the ester enolate Claisen rearrangement. The resulting olfein 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 two subunits carries a price: removal of a surplus carbon. Indeed, the bond joining the terminal tetrahydropyran and tetrahydrofuran rings of a large subclass of polyethers bears vicinal hydrogens. Reductive decarboxylation of $\gamma,\delta$ unsaturated acids is thus an important goal of our program for polyether synthesis; broader implications exist for the expanded utility of the ester enolate Claisen rearrangement as well.

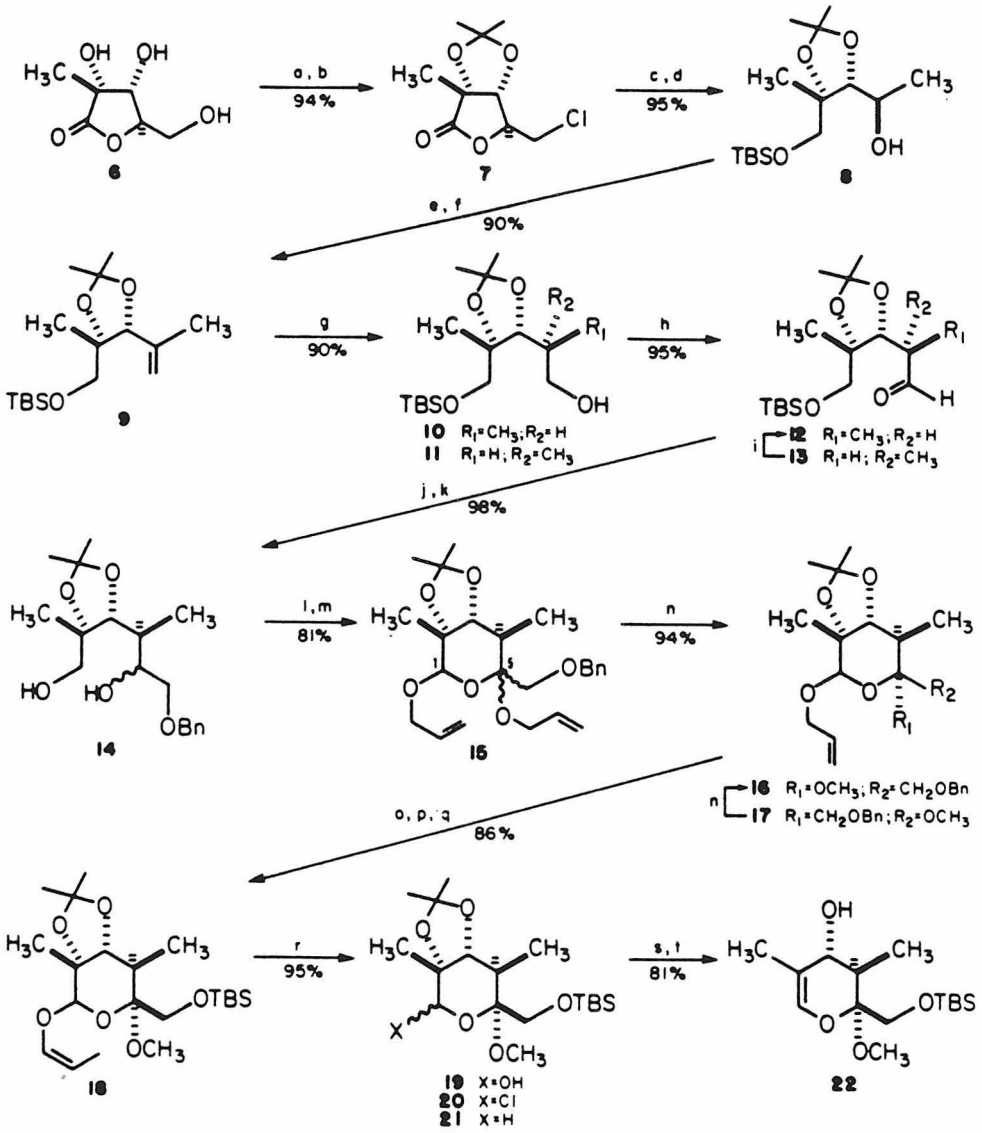
The connection of monensin's D and E rings depicted in Scheme I is an appropriate setting in which to evaluate this problem. In planning a route to the glycal **4**, our confidence in the procedure developed for the reductive fragmentation of lactol-acetonides[5]

**SCHEME I** RETROSYNTHETIC ANALYSIS FOR THE CONNECTION OF MONENSIN'S D AND E RINGS



outweighed our doubts concerning the stability of the hemiacetal-ketal **5**. "α"-D-glucosaccharinic acid, γ-lactone(**6**),[6] requiring introduction of an oxygenated two-carbon fragment at C4 and deoxygenation at C5, was therefore a suitable starting material for this subunit (Scheme II). Hydride reduction of the derived[7] chlorolactone **7** accomplished the latter objective, and selective protection[8] of the resulting diol[9] allowed for chain extension at C4 by oxidation to the ketone and Wittig methylenation. Hydroboration[10] of the olefin **9** was studied in some detail. While borane in THF produced a slight 2:1 excess of the desired 4S diastereomer **10**, dialkylboranes exhibited a marked preference for production of the 4R epimer **11** which increased with the steric bulk of the reagent (Table I).[11] Following completion of this work, Midland[12] reported a similar dependency, and the Felkin type transition state model he proposed can be used to rationalize our results as well. Fortunately, this less than satisfactory stereochemical outcome could be ameliorated by equilibration to a 1:1 mixture of the aldehydes **12** and **13** on silica gel, and after two recycles of the minor aldehyde **13** the desired aldehyde **12** was obtained in a total yield of 77% from the olefin **9**. The C6 carbon was then introduced in the form of benzyloxymethyllithium,[13] and fluoride[14] treatment of the resulting adduct gave a 1:1 mixture of the diols **14** which contain all the atoms of the seco-glycal core. Addition of the crude keto-aldehyde obtained from dual Swern oxidation[15] to p-toluenesulfonic acid in allyl alcohol caused ring closure to a 1:1 mixture of the tetrahydropyrans **15**. Selective ketal exchange in methanol

**SCHEME II** SYNTHESIS OF THE MONENSIN E RING EQUIVALENT, GLYCAL **22**[a]




[a](a) $H_2SO_4$, $(CH_3)_2CO$; (b) DMF, $(COCl)_2$, $CH_2Cl_2$; (c) LAH, $Et_2O$; (d) TBSCl, $C_5H_5N$, $CH_2Cl_2$; (e) $(i\text{-PrN})_2C$, $Cl_2CHCO_2H$, DMSO, $C_6H_6$; (f) $(Ph)_3PCH_2$, THF; (g) $BH_3$, THF; 10% NaOH, 30% $H_2O_2$; (h) $(COCl)_2$, DMSO, $Et_3N$; (i) $SiO_2$, petroleum ether, $Et_2O$; (j) $C_6H_5CH_2OCH_2Sn(n\text{-Bu})_3$, $n$-BuLi, THF; (k) $(n\text{-Bu})_4NF$, THF; (l) $(COCl)_2$, DMSO; $Et_3N$; (m) $p$-TsOH, $CH_2CHCH_2OH$: (n) $C_6H_5NH^+ \cdot p\text{-TsO}^-$, MeOH; (o) $t$-BuOK, DMSO; (p) $Li/NH_3$, THF; (q) TBSOTf, 2,6-lutidine, $CH_2Cl_2$; (r) $Hg(OAc)_2$, THF, $H_2O$; (s) $P(NMe_2)_3$, $CCl_4$, THF; (t) lithium 4,4'-di-$t$-butylbiphenyl, THF.

Table I. Hydroboration of Olefin **9**

| Reagent | **10:11** |
|---|---|
| $BH_3$-$Me_2S$[a] | 2:1 |
| 9-BBN[a] | 1:10 |
| thexylborane[a] | 1:15 |
| (-)-bis(isopinocampheyl)borane[b] | <1:50 |

[a] 0°C, THF. [b] 25°C, THF, 1h.

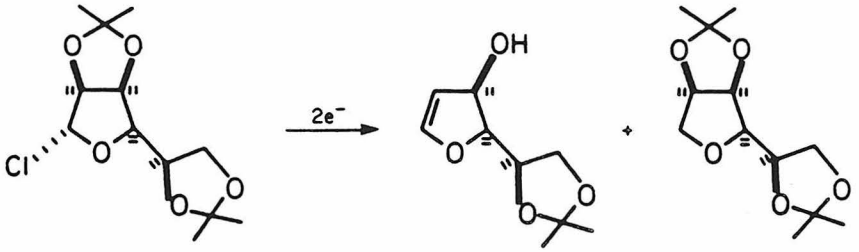
demonstrated that these products were epimeric only at C5 and operationally distinguished this center from the allyl acetal at C1. The proton NMR spectra of the easily separated mixture of methyl ketals **16** and **17** each showed a 9 Hz coupling between the C3 and C4 hydrogens. This confirmed that epimerization had not occurred at the C4 methyl group during either the cyclization or equilibration process.[16] Difference NOE spectra at 500 MHz then established the relative stereochemistry at C5: an enhancement between the C4 methyl group and the C6 methylene hydrogens indicated that these substitutents were cis in the more polar ketal **16**; the corresponding enhancement between the C6 and C4 hydrogens in the less polar ketal **17** corroborated this interpretation. Anticipating the need for stereochemical control in the hydrogenation of a future C2, 3 olefin, we elected to consolidate the C5 ketals through equilibration in methanol and carry forward the epimer with the benzyloxmethylene substituent axially disposed. The acid stable benzyl protecting group had served to prevent intramolecular acetalization at C1, but now its incompatability with the reducing conditions prescribed for glycal formation[5] called for its replacement. Base catalyzed isomerization of the allyl group,[17] Birch reduction, and low temperature silylation with TBS-triflate[18] delivered the modified tetrahydropyran **18** in excellent overall yield. Finally, treatment of the cis-propenyl ether with mercuric acetate in aqueous THF[17] unmasked the hemiacetal-ketal **19** under essentially neutral conditions. Although this lactol slowly unravelled to the corresponding keto-aldehyde on standing in deuterochloroform

(half-life: 12 hours), its remarkable stability to aqueous workup and chromatography on silica gel allowed the pure oil to be isolated in 95% yield and stored indefinitely at -20°C.

This straightforward resolution of the most dubious aspect of our synthetic plan casts an ironic light on the unforeseen difficulties we encountered in obtaining useful quantities of the glycal **22**. While proton NMR indicated that Castro's tris(dimethylamino)phosphine/carbon tetrachloride reagent[19] gave the pyranosyl chloride **20** without incident, addition of this material to excess lithium in liquid ammonia at -78°C according to our standard procedure[5] produced a disconcerting 1:1 ratio of the desired glycal **22** and the tetrahydropyran **21** in a combined yield of only 50%. Nearly quantitative recovery of the isolated glycal from the reducing medium ruled out product decomposition as a cause of the exceptionally low ratio and yield. Equally puzzling was the poor mass balance of the reaction, since TLC did not even show a hint of other byproducts. Frustrated by these results, we were constrained to reinvestigate basic methodology for glycal synthesis from lactol-acetonide precursors.

These experiments are summarized in Tables II and III. Products of hydrodehalogenation such as **21** had not be observed previously with pyranoid glycals, but the analagous byproducts (e.g., **23c**) usually accompany furanoid glycals to the extent of 10-20%.[5] If these byproducts arise from protonation of an intermediate carbanion by a relatively acidic lithium cation - ammonia complex, one would expect to observe increasing fragmentation to protonation ratios with

Table II. Reductive Fragmentation of the Model Furanosyl Chloride **23a**




**23a** **23b** **23c**

| Reductant | Yield of **23b** | **23b:23c** |
|---|---|---|
| $Li/NH_3$[a] | 75% | 7.9:1 |
| $Na/NH_3$[a] | 77% | 10.7:1 |
| $K/NH_3$[a] | 79% | 15.0:1 |
| $SmI_2$[b] | 0% | —— |
| sodium naphthalene[c] | 82% | > 50:1 |
| lithium benzophenone[d] | NR[h] | — |
| sodium anthracene[e] | NR | — |
| sodium trimesitylborane[f] | 70% | > 50:1 |
| lithium 4,4'-di-t-butyl-biphenyl[g] | 94% | > 50:1 |

[a] 35 eq metal, 0.5 M, 1:10/THF:$NH_3$, -78°C, 30 m, then $NH_4Cl$. [b] 2 eq, 0.07 M, THF, 25°C, 3h. [c] 6 eq, 0.21 M THF, -35°C, 20 m, then $H_2O$. [d] 5 eq, 0.50 M THF, 25°C. [e] 5 eq, 0.25 M THF, 25°C. [f] 5 eq, 0.25 M THF, -20 to 0°C, 1 h, then $H_2O$. [g] 5 eq, 0.20 M THF, -78°C, 15 m, then $H_2O$. [h] No reaction.

Table III. Reductive Fragmentation of the Pyranosyl Chloride **20**

| Reductant | Yield of **22** | **22:21** |
|---|---|---|
| $Li/NH_3$[a] | 25% | 1.05:1 |
| $K/NH_3$[a] | 27% | 1.07:1 |
| sodium napathalene[b] | 31% | > 50:1 |
| lithium 4,4'di-t-butyl-biphenyl[c] | 81% | > 50:1 |

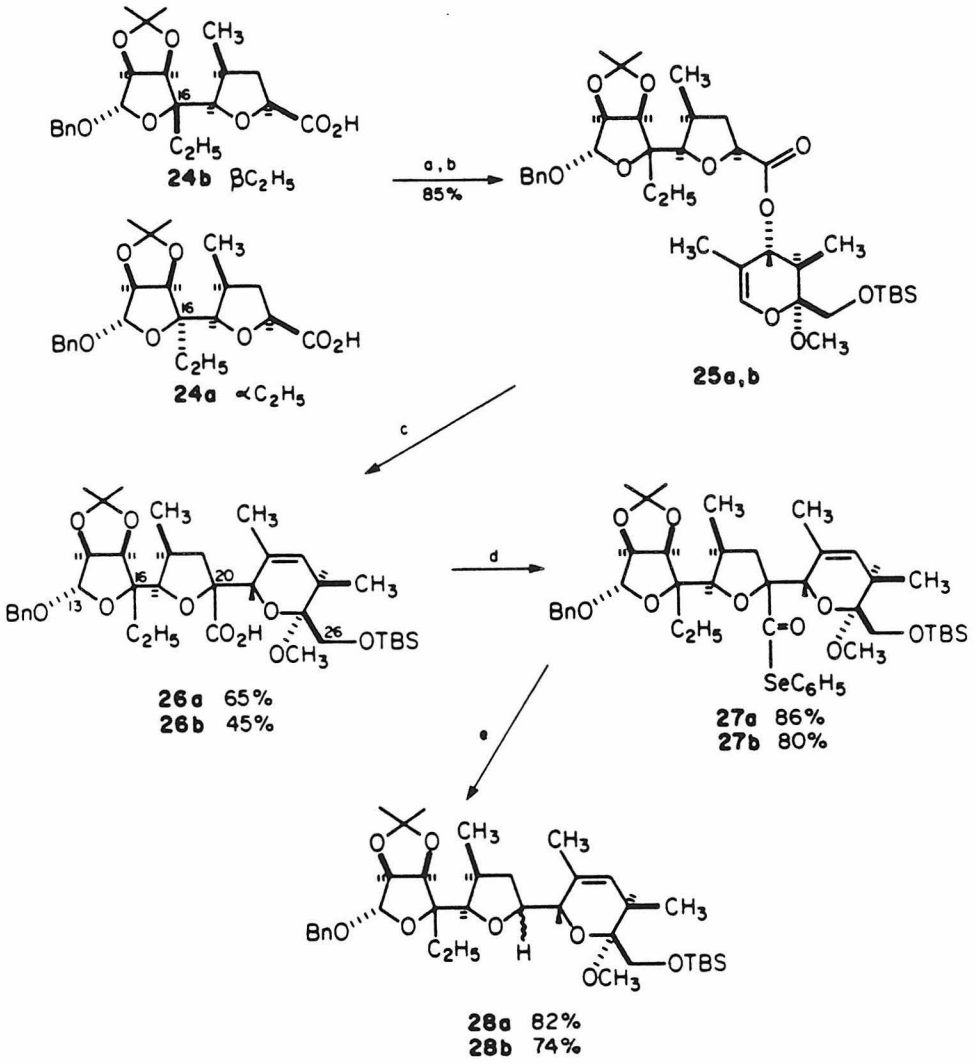
[a] 50 eq metal, 0.06 M, 1:10/THF:$NH_3$, -78°C, 30 m, then $NH_4Cl$. [b] 12 eq, 0.20 M THF, -78°C, 30 m, then $H_2O$. [c] 12 eq, 0.20 M THF, -78°C, 15 m, then $H_2O$.

decreasing counterion solvation. While this argument is admittedly oversimplified, the furanosyl chloride **23a**[20] did in fact display the expected trend (Table II). However, reduction of the pyranosyl chloride **20** with potassium in liquid ammonia gave results indistinguishable from those obtained with lithium in liquid ammonia (Table III). We therefore turned our attention to aprotic reducing media.

After an initial disappointment with samarium diiodide in THF,[21] a series of radical anions[22] gave promising results with the model furanosyl chloride **23a**. Particularly encouraging was the absence of hydrodehalogenation products. Sodium naphthelene had been previously reported to give the glycal **23b** in 59% yield;[23] in our hands, lowering the reaction temperature to -35°C raised the chromatographed yield to 82%. Use of Freeman's[24] di-<u>tert</u>-butylbiphenyl radical anion was even more rewarding, and its striking superiority as an electron transfer reagent became fully apparent with the pyranosyl chloride **20** (Table II). While either base induced elimination[25] of an incipient aldehyde or fragmentation[26] of the intermediate radical could conceivably be responsible for the poor mass balance observed with both lithium in liquid ammonia and sodium naphthelene, these or other nonproductive pathways are minimized by lithium di-<u>tert</u>-butylbiphenyl which reproducibly delivered the pyranoid glycal **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 equivalent to the polyether backbone (Scheme III). At this point we had been

**SCHEME III** UNION OF MONENSIN'S E AND C+D RING SUBUNITS ($a=\alpha C_2H_5$, $b=\beta C_2H_5$)[a]



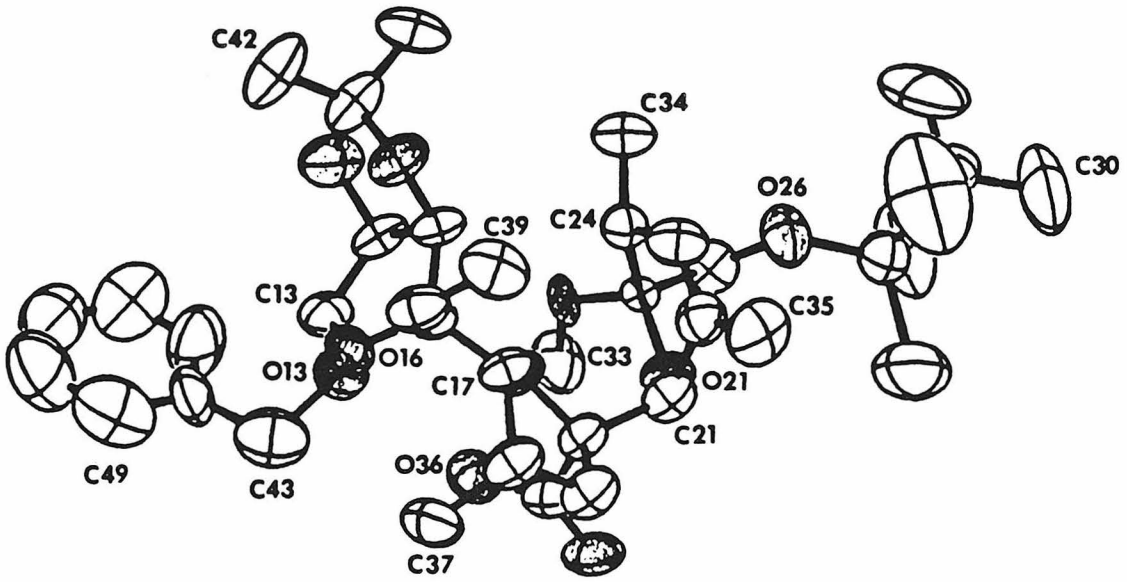

[a] (a) $(Ph)_3P$, $CCl_4$, $CH_2Cl_2$; (b) **22**, DMAP, $CH_2Cl_2$; (c) **25a**: $KN(TMS)_2$), TBSCl, THF; IN LiOH; **25b**: LDA, TMSCl, THF; $H_3O^+$; (d) $PhOP(O)Cl_2$, $C_6H_5SeH$, $Et_3N$, THF; (e) $(n\text{-}Bu)_3SnH$, AIBN, $C_6H_6$.

unable to determine the C16[28] configuration of the Claisen epimers **24a** and **24b**, so we planned to carry both carboxylic acids forward until we obtained a crystalline intermediate or derivative. Formation of the acid chlorides with triphenylphosphine/carbon tetrachloride[29] permitted direct addition of the glycal **22** and DMAP to the crude reaction mixtures, and in both cases the acid sensitive esters **25a** and **25b** could be isolated in 85% yield by chromatography on activity III alumina. Our initial study of the ester enolate Claisen rearrangement was carried out on the major epimer. Luckily, enolization with LDA and trapping with TMSCl provided, after thermal rearrangement at 50°C, a single crystalline carboxylic acid in 45% yield. The result of the X-ray structure analysis[30] depicted in Figure 1 confirmed the stereochemical assignments we had made[27] on the basis of spectroscopic or chemical inference and established that the minor Claisen epimer **24a** possessed the natural configuration at C16.[28]

Since the relative stereochemistry at this center was expected to have little bearing on the chemistry of the D-E ring juncture, we attacked the major problem of reductive decarboxylation 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

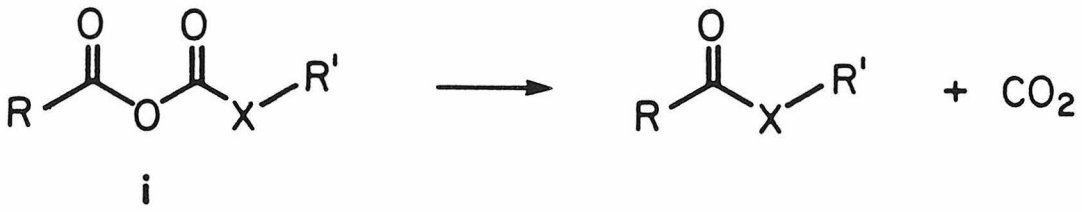
FIGURE I: X-RAY CRYSTAL STRUCTURE OF THE ACID 26b



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 non-stereorational, the trialkylstannane induced decarbonylation of phenyl selenoesters is an attractive alternative.[35] This method would not only provide the noralkane directly, but its compatability with olefin functionality[36] would allow us to ascertain the configuration of the resulting sterocenter through chemical correlation.

Preparation of the required phenyl selenoester **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 <u>intermolecular</u> delivery of a nucleophile for carbonyl activation or phenyl selenoester formation.[37]

Conceptually, an <u>intramolecular</u> esterification process provides an elegant way out of this difficulty. Experimental realization of this concept in preparatively acceptable yield was tortuous but ultimately gratifying. The decomposition of carbonate anhydrides (i) to esters is known to proceed intramolecularly, and

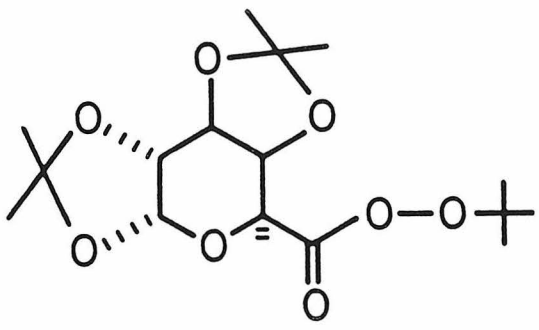


i

when X is a good nucleophile (e.g., RNH, RS, $RCO_2$), the expulsion of carbon dioxide is particularly facile.[38] With the frustrating intermolecular results as a background, we were delighted to find that addition of phosgene to the thallium carboxylate[39] of **26b** followed by addition of excess selenophenol[40] and triethylamine provided, within minutes at 0 °C, a 30% yield of the phenyl seleno-ester and recovered carboxylic acid. Our efforts to improve this reaction were not successful. In particular, chloroformate mixed anhydrides of simple acids are reported to disproportionate to the acid anhydride at -5 °C.[41] However, formation of the mixed anhydride

of **26b** with triethylamine and phosgene in THF at temperatures between -70 and -20°C, and addition of selenophenol with triethylamine or as its lithium salt invariably resulted in high recoveries of starting material and low yields of ester. In principle, condensation of the carboxylic acid with phenylselenyl chloroformate should give the intermediate phenylselenyl carbonate mixed anhydride directly. Unfortunately, rigorous attempts to prepare this reagent from excess phosgene, triethylamine, and selenophenol in THF produced only diphenyl diselenide.[42] At this point we digressed to another possible reagent for intramolecular carboxyl activation, t-butylperoxy chloroformate.[43]

For hindered peresters, radical chain decomposition via trialkylstannes[44] constitutes a mild alternative to the forbidding conditions and yields of a classical perester thermolysis.[45] Addition of tri-n-butyltin hydride to the relatively unhindered perester (ii) in refluxing benzene cleanly yielded a mixture of the

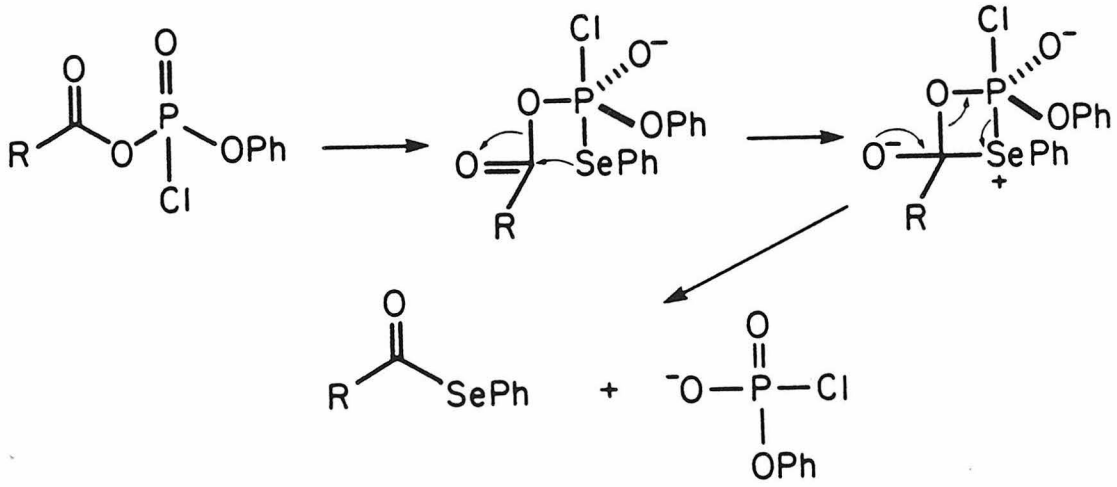


ii

corresponding noralkane[46] and acid. Although the triethylamine salt of this model acid smoothly condensed with t-butylperoxy chloroformate, intramolecular delivery of t-butylhydroperoxide did not materialize at room temperature - conditions where the t-butyl perester of the acid 26 would be expected to be reasonably stable.[47] Subsequent addition of DMAP to the reaction mixture did produce some rearrangement, but no doubt through an intermolecular process.[48] When treatment of the partially purified mixed anhydride with tri-n-butyltin hydride in refluxing benzene gave back starting acid,

we returned our attention to another approach to the phenyl selenoester **27b**.

The hypothesis that nucleophilic displacement at phosphorous proceeds though a pentacovalent oxyphosphorane intermediate has been a fruitful concept in the interpretation of the chemical and stereochemical behavior of organophosphorous compounds.[49,50] We speculated that such an intermediate might have a lifetime of sufficient duration to allow for an intramolecular condensation between phenylselenide and carboxylate ligands. The bond reorganization we envisioned is depicted below. Since alkyl phenylselenyl



halophosphates have not been characterized,[51] we elected to add selenophenol to the mixed anhydride between the carboxylic acid **26b** and an alkyl dihalophosphate. In the event, treatment of the triethylamine salt of the acid with phenyl dichlorophosphate[52] in THF at 0 °C for 30 minutes, followed by the addition of excess triethylamine and selenophenol, produced within minutes an 80% yield of the phenyl selenoester **27b** and 12% recovered carboxylic acid. While we have no direct evidence for the intermediacy of an oxyphosphorane, this result stands in sharp contrast to the inefficacy of mixed anhydrides with relatively weak electrophilicity at phosphorous.[37]

Decarbonylation of the phenyl selenoester with tri-*n*-butyltin hydride and a trace of AIBN[35] in refluxing benzene afforded the noralkane **28b** in 74% yield. Intriguingly, 500 MHz NMR indicated that a single C20[28] epimer had been obtained. Since the results of the X-ray crystal structure had demoted 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[28] epimer **26a** was in hand.

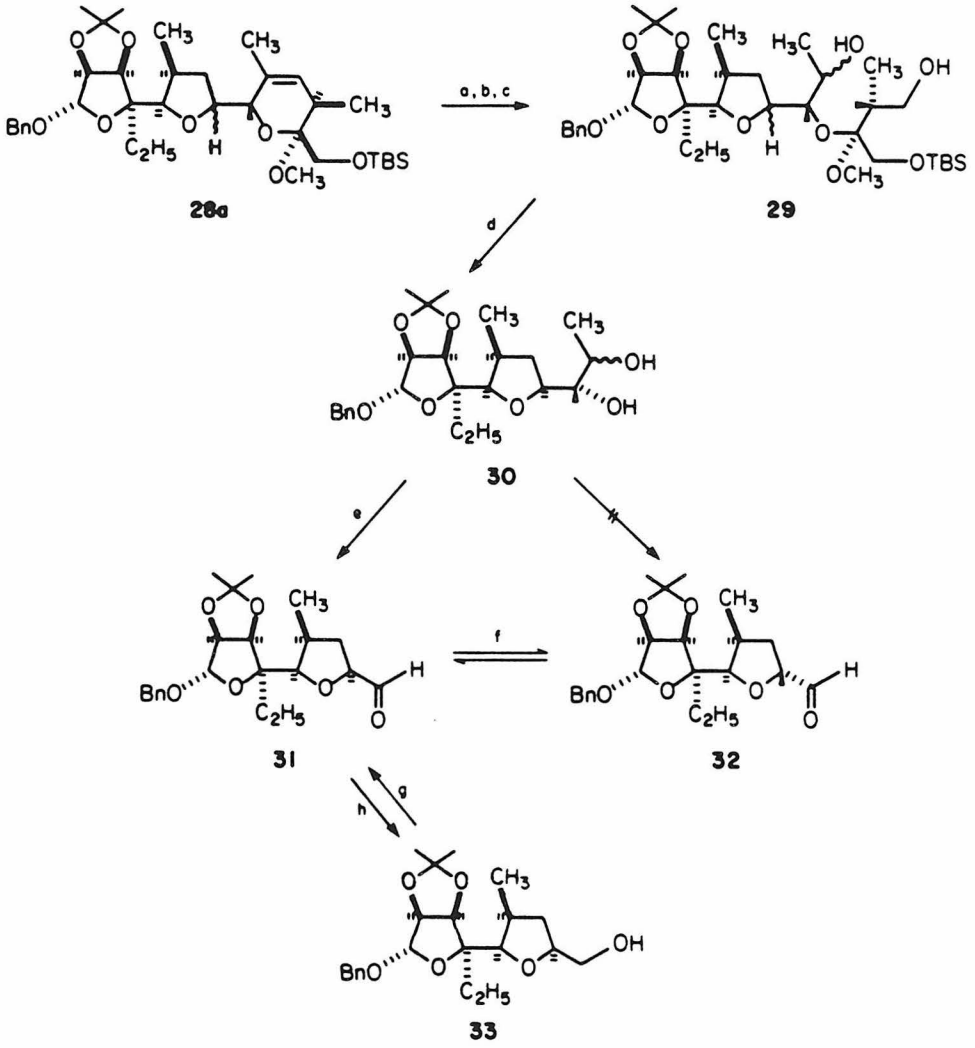
Reinvestigation of the Claisen rearrangement of the model ester **25b** revealed that the modest yield was due in part to C-silylation of the ester enolate. Enolization by potassium hexamethyldisilazide and trapping with TBSCl eliminated this problem, and use of this reagent combination to generate the silyl ketene acetal of the ester **25a** provided, after thermal rearrangement at room temperature for 48 hours, a 5:1 mixture of diastereomeric Claisen

products in 65% yield.[53] The mixed chlorophosphate anhydride method again met our expectations, and the resulting phenyl selenoesters were separated by chromatography and individually decarbonylated: 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**.[27] 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 to aldehyde **31** and distinct from aldehyde **32** as judged by direct comparison by TLC and 500 MHz NMR. Therefore, the stereochemistry at C20[28] was predominantly incorrect.

Since the intermediate alkoxy radical generated by decarbonylation is pyramidal and inverting rapidly,[54] the product distribution is controlled, according to the Curtin-Hammett principle,[55] 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 stereoisomer. To test this hypothesis, we prepared the phenyl selenoester **38** via the known

**SCHEME IV** DETERMINATION OF THE CONFIGURATION AT C20 RESULTING FROM THE DECARBOXYLATION OF THE ACID **26a**[a]



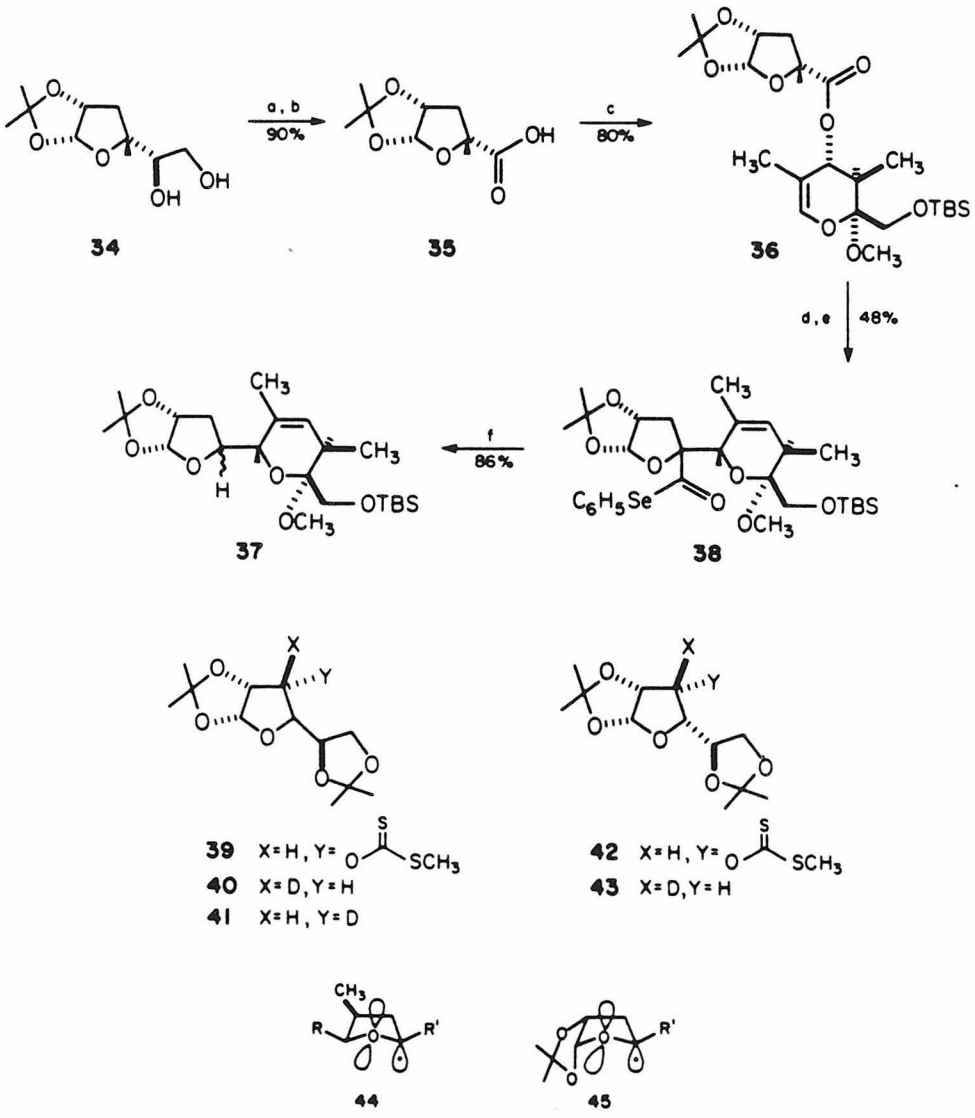

[a] (a) $OsO_4$, $C_5H_5N$; aqueous $NaHSO_3$, THF; (b) $NaIO_4$, $H_2O$, THF; (c) $NaBH_4$, EtOH; (d) 1% HCl, THF; (e) $NaIO_4$, $H_2O$, THF; (f) $k_2CO_3$, MeOH; (g) $(COCl_2)$, DMSO; $Et_3N$; (h) LAH, $Et_2O$.

diol **34**[56] and the glycal **22** as outlined in Scheme V.

The steric bias of the bicyclic 1,2-*O*-isopropylidene furanose system has been amply demonstrated.[57] In the specific case of free radical reactions, treatment of the dithiocarbonate **39** with tri-*n*-butyltin deuteride gave an 85:15 mixture of the deoxy isomers **40** and **41**.[58] Similar treatment of the dithiocarbonate **42** gave only the deoxyfuranose **43** from exclusive exo attack.[58] Thus, if steric effects are indeed decisive in the stereochemical outcome of hydrogen abstraction by tetrahydrofuran-2-yl radicals, the all cis tetrahydrofuran **37** should predominate in the decarbonylation of phenyl selenoester **38**. In fact, we obtained **37** as a 1:1 mixture. 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.[54,59] The stereoelectronic preference for axial bond formation and cleavage at such centers is a manifestation of this stabilization.[60] Since the activation enthalpy for hydrogen abstraction is rather insensitive to radical stability,[61] differences in the total free energy of activation will arise from the usual conformational factors, stereoelectronic effects, and steric interactions with the reagent. A pseudo-equatorial exocylic side chain and a pseudo-axial C1-O bond are

**SCHEME V** MODEL STUDY OF DECARBOXYLATION STEREOCHEMISTRY[a]




[a](a) $NaIO_4$, $H_2O$; (b) $AgNO_3$, KOH, $H_2O$, EtOH; (c) $(Ph_3)P$, $CCl_4$, $CH_2Cl_2$; 22, DMAP, $CH_2Cl_2$; (d) $KN(TMS)_2$, TBSCl, THF; IN LiOH; (e) $PhOP(O)Cl_2$, $C_6H_5SeH$, $Et_3N$, THF; (f) $(n\text{-}Bu)_3SnH$, AIBN, $C_6H_6$.

important stabilizing factors in furanosides.[62] 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 competetive with that for unhindered hydrogen abstraction by the exo radical.[63] Reconsidering the decarboxylation of ester **27a**, we see that radical **44** enjoys a pseudo-equatorial disposition of its most bulky substituents, a pseudo-axial radical, and unhindered access to hydrogen abstraction. Since no other conformer meets all these criteria, the all cis tetrahydrofuran predominates. We are currently exploring new avenues to reverse this stereochemical outcome.

## EXPERIMENTAL SECTION

Melting points were determined using a Hoover capillary melting point apparatus and are uncorrected. Infrared (IR) spectra were determined on a Perkin-Elmer 727B or 1310 infrared spectrophotometer. Proton nuclear magnetic resonance ($^1$H NMR) spectra were recorded on a Varian EM-390 spectrometer, except where "500 M Hz" denotes spectra recorded on a Bruker WM-500 spectrometer (Southern California Regional NMR Facility, Caltech, Pasadena, CA). Chemical shifts are reported as $\delta$ values in parts per million relative to tetramethylsilane ( $\delta$ 0.0) as an internal standard. Data are reported as follows: chemical shift (multiplicity, integrated intensity, coupling constants, assignment). Optical rotations were measured in 1 dm cells of 1 mL capacity using a JASCO Model DIP-181 polarimeter. Chloroform, when used as a solvent for optical rotations, was filtered through neutral alumina (activity I) immediately prior to use. Analytical thin-layer chromatography (TLC) was conducted on 2.5 x 10 cm precoated TLC plates: silica gel 60 F-254, layer thickness 0.25 mm, manufactured by E. Merck and Co., Darmstadt, Germany. Silica gel columns for chromatography utilized E. Merck silica gel 60 (70-230 mesh ASTM). Flash chromatography was performed on E. Merck silica gel 60 (230-400 mesh ASTM) according to a published procedure (Still, W.C.; Kahn, M.; Mitra, A., J. Org. Chem. 1978, 43, 2923-2925). Acidic silica gel refers to Silicar CC-4 Special "for column chromatography," sold by Mallinckrodt Chemical Works, St. Louis, MO. "Alumina" refers to the grade I neutral variety manufactured by M. Woelm, Eschwege, Germany, which was

neutralized to the indicated grade by the addition of water. Reaction solvents and liquid reagents were purified by distillation or drying shortly before use. Benzene, pyridine, n-hexane, trimethylchlorosiliane, oxalyl chloride, N,N-diisopropyl-ethylamine and dichloromethane were distilled from powdered calcium hydride. Dimethyl sulfoxide, dimethyl formamide, and hexamethyl phosphoramide were distilled under reduced pressure from powdered calcium hydride and stored over a mixture of 3A and 4A sieves. n-Pentane was distilled from sodium metal under argon. Hexamethyldisilazane was distilled under argon from powdered calcium hydride and stored over a mixture of 3A and 4A sieves. Ether, tetrahydrofuran, triethylamine, and diisopropylamine were distilled under argon from sodium metal with sodium benzophenone ketyl as an indicator. Methanol was distilled from sodium methoxide and methyl benzoate. Acetonitrile was dried over a mixture of 3A and 4A sieves. Ammonia was distilled from the tank and then from a blue lithium solution. n-Propionyl chloride was heated at reflux for 3 h with phosphorous pentachloride and then distilled, and the distillate was treated with quinoline and redistilled. Tris(dimethylamino)phosphine was distilled at reduced pressure under argon. Ammonium chloride was dried at 75°C under vacuum (1 mmHg) over phosphorous pentoxide for at least 12 h. All other reactants and solvents were "reagent grade" unless described otherwise. "Ether" refers to anhydrous diethyl ether which is supplied by Mallinckrodt and Baker. "Petroleum ether" refers to the "analyzed reagent" grade hydrocarbon fraction (bp 35–60°C) which is supplied by J. T. Baker, Co., Phillipsburg, NJ. 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*. Mass spectral analyses were performed by Larry Henling, Caltech, Pasadena, CA. Elemental combustion analyses were performed by Spang Microanalytical Laboratory, Eagle Harbor, MI.

**2,3-O-(1-Methylethylidene)-2-C-methyl-5-chloro-D-5-deoxyribono-1,4-lactone (7).** To a stirred solution of 0.28 mL (3.2 mmol) of oxalyl chloride in 10 mL of dichloromethane at 0 °C was added, dropwise over 3 min, 0.26 mL (3.3 mmol) of N,N-dimethylformamide. The resulting white suspension was allowed to warm to room temperature, and after 10 min was recooled to 0 °C and 606 mg (3.0 mmol) of crystalline 2-methyl-2,3-O-(1-methylethylidene)-D-ribonic acid, $\gamma$-lactone was then added in one portion. The resulting solution was heated at reflux for 4.5 h and then cooled to room temperature, poured into 75 ml of saturated aqueous NaCl, and then extracted with two 150 ml portions of ether. The organic extracts were combined and dried ($MgSO_4$). Removal of the solvent under reduced pressure and chromatography of the residue on 50 g of silica gel with 4:6 ether/petroleum ether afforded 660 mg (100%) of the lactone as a white, crystalline solid: mp 78-79 °C; $R_f$ = 0.18 (silica

gel, 3:7 ether/petroleum ether); evaporative distillation 70-75°C (0.001 mmHg); $[\alpha]^{23}_D$ -41.9° (c 1.51, $CHCl_3$); IR ($CHCl_3$) 3000, 2940, 1785, 1450, 1375, 1350, 1100, 1000 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 1.43 (s, 6H, $CH_3$), 1.65 (s, 3H, $CH_3$), 3.50-3.87 (m, 2H, $CH_2Cl$), 4.47 (s, 1H, C(3)-H), 4.70 (m, 1H, C(4)-H). Anal. Calcd for $C_9H_{13}O_4$: C, 48.99; H, 5.94. Found: C, 49.09; H, 5.99.

**2(S)-Methyl-2,3-(R)-(dimethylmethylenedioxy)-n-pentane-1,4(R)-diol.** To a stirred solution of 58.7 g (0.266 mol) of the lactone **7** in 1.0 L of ether cooled to 0°C was added, cautiously in several portions, 12.1 g (0.32 mol) of lithium tetrahydridolauminate. Cooling was then discontinued and the resulting mixture was stirred at room temperature for 7 h and then recooled to 0°C and sequentially treated with 12.1 ml of water, 12.1 ml of 15% aqueous sodium hydroxide, 36.3 ml of water, and then 20 g of $MgSO_4$. Filtration and evaporation of the solvent at reduced pressure afforded 50.8 g (100%) of the diol as a white solid, mp 103-104°C (Lit.[9] mp 103-104°C). Chromatography of a portion of this solid on silica gel with 8:2 ether/petroleum ether provided the analytical sample: mp 105-105.5°C; $R_f$ = 0.22 (silica gel, 8:2 ether/petroleum ether); $[\alpha]^{23}_D$ = -36.1° (c 1.56, $CHCl_3$), (Lit.[9] $[\alpha]_D$ = -36° (c 1.0, $CHCl_3$)); IR ($CHCl_3$) 3495, 3000, 2950, 1385, 1375, 1245, 1100, 1055 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 1.33 (d, 3H, J=7 Hz, $CH_3CH$), 1.37 (s, 6H, 2 $CH_3C$), 1.43 (s, 3H, $CH_3C$), 3.1-4.2 (m, 6H). Anal. Calcd for $C_9H_{18}O_4$: C, 56.82; H, 9.54. Found: C, 56.85; H, 9.62.

**5-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-4(S)-methyl-3(R),4-(dimethylmethylenedioxy)-n-pentan-2(R)-ol (8).** To a stirred solution of 50.8 g (0.266 mol) of the above diol in 530 mL of dichloromethane were added 86 mL (1.06 mol) of pyridine and then 48.1 g (0.319 mol) of tert-butyldimethylchlorosilane. After 36 h at room temperature, the reaction mixture was diluted with 1.5 L of ether and washed with 500 mL of water, two 500 mL portions of saturated aqueous NaCl, and then dried ($MgSO_4$). Removal of the solvent under reduced pressure and chromatography of the residue on 500 g of silica gel with 2:8 ether/petroleum ether afforded 76.9 g (95%) of the alcohol **8** as a colorless oil: $R_f$ = 0.35 (silica gel, 2:8 ether/petroleum ether); evaporative distillation 85-90 °C (0.005 mmHg); $[\alpha]^{23}_D = -19.7°$ (c 1.11, $CHCl_3$); IR ( $CHCl_3$) 3450, 3000, 2960, 2940, 2875, 1470, 1385, 1375, 1250, 1100, 1075, 840 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 0.13 (s, 6H, $(CH_3)_2Si$), 0.92 (s, 9H, $(CH_3)_3C$), 1.30 (d, 3H, J=7 Hz, $CH_3CH$), 1.35 (s, 6H, $2CH_3C$), 1.40 (s, 3H, $CH_3C$), 3.18-4.06 (m, 5H). Anal. Calcd for $C_{15}H_{32}O_4Si$: C, 59.17; H, 10.59. Found: C, 59.30; H, 10.58.

**5-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-4(S)-methyl-3(R),4-(dimethylmethylenedioxy)-n-pentan-2-one.** To a stirred solution of 6.13 g (20.1 mmol) of the above alcohol **8** in 11.9 mL of dimethyl sulfoxide and 11.9 mL of benzene at 0 °C were added 0.84 mL (10.1 mmol) of dichloroacetic acid and then, dropwise over 5 min, 6.33 mL (40:4

mmol) of diisopropylcarbodiimide. Cooling was discontinued, and the resulting mixture was stirred for 1.5 h at room temperature. The solution was then diluted with 900 mL of ether, and washed with 500 mL of 2% aqueous $H_2SO_4$ acid, 500 mL of 2% aqueous NaOH, 500 mL of saturated aqueous NaCl, and then dried ($MgSO_4$). The solvent was evaporated under reduced pressure and to the residue was added 200 ml of petroleum ether. The undissolved urea was removed by filtration. Evaporation of the solvent and flash chromatography of the residue on 250 g of silica gel with 1:9 ether/petroleum ether afforded 5.72 g (94%) of the ketone as a colorless oil: $R_f$ = 0.35 (silica gel, 2:8 ether/petroleum ether); evaporative distillation 75-80°C (0.005 mmHg); $[\alpha]^{24}_D = -39.3^\circ$ (c 1.47, $CHCl_3$); IR ($CHCl_3$) 3000, 2860, 1725, 1710, 1475, 1465, 1380, 1375, 1100, 1000, 925 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 0.03 (s, 6H, $(CH_3)_2Si$), 0.87 (s, 9H, $(CH_3)_3C$), 1.37 (s, 3H, $CH_3C$), 1.40 (s, 3H, $CH_3C$), 1.50 (s, 3H, $CH_3C$), 2.26 (s, 3H, $CH_3C(O)$), 3.33 (d, 1H, J=11 Hz, $CC\underline{H}HO$), 3.55 (s, 1H, J=11 Hz, $CCH\underline{H}O$), 4.17 (s, 1H, CCHC(O)). Anal. Calcd for $C_{15}H_{30}O_4Si$: C, 59.56; H, 10.00. Found: C, 59.58; H, 10.05.

**5-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-4(S)-methyl-3(R),4-(dimethylmethylenedioxy)-2-methyl-n-pent-1-ene (9).** To a stirred suspension of 2.43 g (6.81 mmol) of methyltriphenylphosphonium bromide in 20 mL of THF at 0°C was added dropwise 4.00 mL (6.24 mmol) of a 1.56 M solution of n-butyllithium in hexane. Cooling was then discontinued and the reaction mixture was stirred at room temperature

for 30 min and then cooled to -78°C. A solution of 1.72 g (5.68 mmol) of the above ketone in 8 mL of THF was added over 5 min and the reaction was then allowed to warm to room temperature. After 50 min the reaction mixture was cooled to -78°C, treated with 5 mL of saturated aqueous $NaHCO_3$, allowed to warm to room temperature, poured into 150 mL of saturated aqueous NaCl, and then extracted with three 200 mL portions of petroleum ether. The combined organic extracts were dried ($MgSO_4$) and then evaporated under reduced pressure. Chromatography of the residue on 100 g of silica gel with 1:9 ether/petroleum ether afforded 1.64 g (96%) of the olefin as an oil: $R_f$ = 0.66 (silica gel, 3:7 ether/petroleum ether); evaporative distillation 75-80°C (0.005 mmHg); $[\alpha]^{23}_D$ - 29.5° (c 1.84, $CHCl_3$); IR ($CHCl_3$) 3000, 2870, 1465, 1385, 1375, 1250, 1100, 1000, 850 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 0.03 (s, 6H, $(CH_3)_2Si$), 0.88 (s, 9H, $(CH_3)_3C$), 1.38 (s, 6H, 2 $CH_3C$), 1.43 (s, 3H, $CH_3C$), 1.80 (s, 3H, $CH_3C{=}C$), 3.21 (d, 1H, J=10 Hz, $CC\underline{H}HO$), 3.52 (d, 1H, J=10 Hz, $CCH\underline{H}O$), 4.20 (s, 1H, CCHC=C), 4.88 (bs, 1H, $C{=}C\underline{H}H$), 5.18 (bs, 1H, $C{=}CH\underline{H}$). Anal. Calcd for $C_{16}H_{32}O_3Si$: C, 63.95; H, 10.73. Found: C, 63.81; H, 10.72.

**5-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-4(S)-methyl-3(R),4-(dimethylmethylenedioxy)-2(R) and 2(S)-n-pentan-1-ol (10) and (11).** To a stirred solution of 440 mg (1.46 mmol) of the olefin **9** in 10 mL of THF at 0°C was added over 1 min 4.4 mL (4.40 mmol) of a 1.0 M solution of $BH_3$ in THF. After 1.5 h at 0°C, the reaction mixture was cautiously treated with 1.5 mL of 3M aqueous NaOH and then allowed to

warm to room temperature. When there was no further evidence of $H_2$ evolution (ca. 15 min), 1.1 mL of 30% aqueous $H_2O_2$ was added and the resulting mixture was heated in an oil bath at 50°C. After 1 h, the solution was allowed to cool, poured into 75 mL of saturated aqueous NaCl, and then extracted with two 150 mL portions of ether. The combined organic extracts were dried ($MgSO_4$), and the solvent was then evaporated under reduced pressure. $^1H$ NMR of the crude residue indicated the presence of a 2.0:1.0 mixture of diastereomeric alcohols **10** and **11**. Chromatography of this residue on 30 g of silica gel with 35:65 ether/petroleum ether afforded as a colorless oil 420 mg (90%) of the unseparated alcohols: $R_f$ (major diastereomer) = 0.32 (silica gel, 4:6 ether/petroleum ether); $R_f$ (minor diastereomer) = 0.29 (silica gel, 4:6 ether/petroleum ether); evaporative distillation 95-100°C (0.005 mmHg); IR ($CHCl_3$) 3530, 3400, 2990, 2860, 1470, 1460, 1380, 1370, 1250, 1080 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 0.08 (s, 6H, $(CH_3)_2Si$), 0.90 (s, 9H, $(CH_3)_3C$), 0.93 (d, "1H", J=7 Hz, $CHCH_3$, minor diastereometer), 1.09 (d, "2H", J=7 Hz, $CHCH_3$, major diastereomer), 1.33, 1.37 (2s, 9H, 3 $CH_3C$), 1.85-2.25 (bm, 1H, $CH_3CH$). Anal. Calcd for $C_{16}H_{34}O_4Si$: C, 60.33; H, 10.76. Found: C, 60.38; H, 10.77.

**5-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-4(S)-methyl-3(R),4-(dimethylmethylenedioxy)-2(R) and 2(S)-methyl-n-pentan-1-al (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 dimethylsulfoxide in 5 mL of dichloromethane. After 15 min, a solution of 3.35 g (10.5 mmol) of a 2:1 mixture of alcohols **10** and **11** in 20 mL of dichloromethane was added over 10 min to the reaction mixture. After 20 min at -78°C, the reaction mixture was treated with 7.3 mL (53 mmol) of triethylamine, allowed to warm to room temperature, and then poured into 100 mL of saturated aqueous NaCl. This mixture was extracted with two 200 mL portions of ether, and the combined organic extracts were dried ($MgSO_4$). Evaporation of the solvent under reduced pressure and chromatography of the residue on 300 g of silica gel with 20:280 ether/petroleum ether afforded first 2.12 g (64%) of the aldehyde **12** as a colorless oil: $R_f$ = 0.24 (silica gel, 20:280 ether/petroleum ether); evaporative distillation 65-70°C (0.001 mmHg); IR ($CHCl_3$) 3000, 2940, 1725, 1470, 1385, 1375, 1255, 1090 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 0.07 (s, 6H, $(CH_3)_2Si$), 0.89 (s, 9H, $(CH_3)_3C$), 1.22 (d, 3H, J=7 Hz, $CH_3CH$), 1.30 (s, 3H, $CH_3C$), 1.37 (s, 6H, 2 $CH_3C$), 2.73-3.13 (m, 1H, $CH_3CH$), 3.21 (d, 1H, J=10 Hz, $CCHHO$), 3.65 (d, 1H, J=10 Hz, $CCHHO$), 4.02 (d, 1H, J=10 Hz, $CCHCH$), 9.70 (d, 1H, J=1.5 Hz, CHO). Anal. (2:1 mixutre of **12** and **13**) Calcd for $C_{16}H_{32}O_4Si$: C, 60.72; H, 10.19. Found: C, 60.46; H, 10.07.

There was then eluted 1.04 g (31%) of the aldehyde **13** as a colorless oil: $R_f$ = 0.19 (silica gel, 20:280 ether/petroleum ether); evaporative distillation 65-70°C (0.001 mmHg); IR ($CHCl_3$) 3000, 1725, 1470, 1385, 1375, 1255, 1090 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 0.07 (s, 6H, $(CH_3)_2Si$), 0.90 (s, 9H, $(CH_3)_3C$), 1.15 (d, 3H, J=7 Hz, $CH_3CH$), 1.33 (s, 3H, $CH_3C$), 1.36 (s, 6H, 2 $CH_3C$), 2.68-3.00 (m, 1H, $CH_3CH$), 3.27

(d, 1H, J=11 Hz, CC$\underline{H}$HO), 3.76 (d, 1H, J=11 Hz, CCH$\underline{H}$O), 3.81 (d, 1H, J=10 Hz, CC$\underline{H}$CH), 9.75 (d, 1H, J=3 Hz, CHO). Anal. (2:1 mixture of **12** and **13**) Calcd for $C_{16}H_{32}O_4Si$: C, 60.72; H, 10.19. Found: C, 60.46; H, 10.07.

**Recycling of the Aldehyde 13.** To a stirred solution of 1.04 g (3.28 mmol) of the aldehyde **13** in 20 mL of petroleum ether and 1 mL of ether was added 9.4 g of silica gel and the resulting slurry was stirred under argon until TLC indicated that a 1:1 mixture of aldehydes **12** and **13** had been produced (ca. 36 h). The mixture was then filtered and the silica gel was thoroughly rinsed with ether. Evaporation of the solvent and chromatography of the residue on 150 g of silica gel with 20:280 ether/petroleum ether afforded 0.48 g of the aldehyde **12**. Repetition of the above process on the recovered aldehyde **13** afforded an additional 0.22 g of the aldehyde **12**, thus constituting an 85% overall yield from the alcohols **10** and **11**.

**6-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-5(S)-methyl-4(R),5-(dimethylmethylenedioxy)-3(S)-methyl-1-benzyloxy-n-hexan-2(R) and 2(S)-ol.** To a stirred solution of 3.27 g (9.04 mmol) of (benzyloxymethyl)tributylstannane in 55 mL of THF at -78°C was added 5.35 mL (8.34 mmol) of a 1.56 M solution of n-butyllithium in hexane. After 5 min, a solution of 2.20 g (6.95 mmol) of the aldehyde **12** in 9 mL of THF was added over 6 min. The resulting mixture was stirred 55

min at -78°C and then treated with 5 mL of saturated aqueous $NH_4Cl$. The solution was poured into 100 mL of saturated aqueous NaCl and extracted with two 250 mL portions of ether. The combined organic extracts were dried ($MgSO_4$) and the solvent was then evaporated under reduced pressure. Flash chromatography of the residue on 200 g of silica gel with 35:65 ether/petroleum ether afforded 3.01 g (98%) of an unseparated 1.4:1 mixture of the alcohols as a colorless oil: $R_f$ = 0.32 (silica gel, 4:6 ether/petroleum ether); evaporative distillation 145-150°C (0.005 mmHg); IR ($CHCl_3$) 3580, 2990, 2860, 1465, 1460, 1450, 1380, 1370, 1250, 1085 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 0.03 (s, 6H, $(CH_3)_2Si$), 0.87 (s, 9H, $(CH_3)_3C$), 0.98 (d, "1.25H", J=7 Hz, $CH_3CH$), 1.00 (d, "1.75H", J=7 Hz, $CH_3CH$), 1.30, 1.37 (2s, 9H, 3 $CH_3C$), 4.47, 4.49 (2s, 2H, $C_6H_5CH_2$), 7.29 (s, 5H, $C_6H_5$). Anal. Calcd for $C_{24}H_{42}O_5Si$: C, 65.71; H, 9.65. Found: C, 65.66; H, 9.60.

**2(S)-Methyl-2,3(R)-(dimethylmethylenedioxy)-4(S)-methyl-5(R) and 5(S)-hydroxy-6-benzyloxy-n-hexan-1-ol (14).** To a stirred solution of 3.01 g (6.86 mmol) of the above alcohol in 20 mL of THF at room temperature was added 8.0 mL (8.0 mmol) of a 1 M solution of tetra-n-butylammonium fluoride in THF. After 20 min, the reaction mixture was poured into 100 mL of 50% saturated aqueous NaCl and extracted with three 100 mL portions of ether. The combined organic extracts were dried ($MgSO_4$) and the solvent evaporated at reduced pressure. Chromatography of the residue on 200 g of silica gel with 8:2 ether/petroleum ether afforded first 751 mg of a single epimer of

the alcohol **14**: $R_f$ = 0.22 (silica gel, 8:2 ether/petroleum ether); evaporative distillation 145-150°C (0.005 mmHg); $[\alpha]^{23}_D$ = -1.7° (*c* 0.56, $CHCl_3$); IR ($CHCl_3$) 3570, 3450, 2980, 1450, 1375, 1365, 1230, 1100, 900 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 1.07 (d, 3H, J=7 Hz, $CH_3CH$), 1.40 (s, 6H, 2 $CH_3C$), 1.46 (s, 3H, $CH_3C$), 3.98 (d, 1H, J=8 Hz, $CCHCH$), 4.57 (s, 2H, $C_6H_5CH_2$), 7.37 (s, 5H, $C_6H_5$). Anal. Calcd for $C_{18}H_{28}O_5$: C, 66.64; H, 8.70. Found: C, 66.76; H, 8.72.

There were then eluted 736 mg of mixed fractions and then 743 mg of a single epimer of the alcohol **14**: $R_f$ = 0.14 (silica gel, 8:2 ether/petroleum ether); evaporative distillation 145-150°C (0.005 mmHg); $[\alpha]^{23}_D$ = -15° (*c* 0.52, $CHCl_3$); IR ($CHCl_3$) 3570, 3430, 2990, 1450, 1375, 1365, 1100, 1030, 925 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 0.97 (d, 3H, J=7 Hz, $CH_3CH$), 1.37 (s, 6H, 2 $CH_3C$), 1.43 (s, 3H, $CH_3C$), 3.83 (d, 1H, J=7 Hz, $CCHCH$), 4.56 (s, 2H, $C_6H_5CH_2$), 7.33 (s, 5H, $C_6H_5$). Anal. Calcd for $C_{18}H_{28}O_5$: C, 66.64; H, 8.70. Found: C, 66.68; H, 8.78. Total yield of diols **14**: 2.23 g (100%).

**2-(Allyloxy)-3(R)-methyl-3,4(R)-(dimethylmethylenedioxy)-5(R)-methyl-6(R) and 6(S)-(allyloxy)-6-(benzyloxymethyl)tetrahydropyran (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 0.28 mL (3.9 mmol) of dimethyl sulfoxide in 4 mL of dichloromethane. After 10 min, a solution of 573 mg (1.76 mmol) of the alcohols **14** in 4 mL of dichloromethane was added to the reaction

mixture. After 25 min, the reaction mixture was treated with 1.97 mL (14.1 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 150 mL portions of ether, dried ($MgSO_4$), and then evaporated under reduced pressure and then further dried under high vacuum for 30 min to afford 565 mg of an oil. To a stirred solution of this material in 5 mL of allyl alcohol and 0.5 mL of a mixture of 2,2-diallyloxypropane and 2-allyloxypropene (see below) was added 42 mg (0.22 mmol) of p-toluenesulfonic acid monohydrate. After 95 min at room temperature, 0.5 mL (3.6 mmol) of triethylamine was added and then the reaction was evaporated under reduced pressure. Chromatography of the residue on 60 g of silica gel with 2:8 ether/petroleum ether afforded 599 mg (81%) of an oil consisting of a 1:1 mixture of the allyl ketals **15** epimeric at C5: $R_f$ = 0.32, 0.36 (silica gel, 2:8 ether/petroleum ether); evaporative distillation 140-150°C (0.005 mmHg); IR ($CHCl_3$) 3000, 1450, 1380, 1225, 1110, 995, $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 1.15 (d, "1.5H", J=7 Hz, $CH_3CH$), 1.17 (d, "1.5H", J=7 Hz, $CH_3CH$), 1.37, 1.40, 1.43 (3s, 9H, 3 $CH_3C$), 3.52 (s, "1H", $CCH_2O$), 3.57 (s, "1H", $CCH_2O$), 4.73 (s, "0.5H", OCHO), 4.87 (s, "0.5H", OCHO), 7.33 (s, 5H, $C_6H_5$). Anal. Calcd for $C_{24}H_{34}O_6$: C, 68.88; H, 8.18. Found: C, 68.87; H, 8.16.

**2,2-Diallyloxypropane and 2-allyloxypropene** To a solution of 50 mL (0.41 mol) of dimethoxypropane and 58 mL (0.85 mol) of allyl alcohol was added 250 mg (1 mmol) of pyridinium p-toluenesulfonate, the resulting mixture was heated in an oil bath at 110°C, and methanol was distilled off through a Vigreaux column at 65-70°C. After 5 h,

the oil bath was allowed to cool to 60°C, and the pressure was gradually reduced to 75 mmHg. The material (25 mL) which distilled between 50-55°C at this pressure consisted of a ca. 1:2 mixture of 2,2-diallyloxypropane and 2-allyloxypropene and some allyl alcohol. No methanol or methyl ethers were present: IR ($CHCl_3$) 3620, 3480, 3000, 1655, 1610, 1380, 1275, 995 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 1.32 (s, $(CH_3)_2C$), 1.77 (s, $CH_3C=C$).

**2-(Allyloxy)-3(R)-methyl-3,4(R)-(dimethylmethylenedioxy)-5(R-methyl-6(R) and 6(S)-methoxy-6-(benzyloxymethyl)-tetrahydropyran (16) and (17).** To a stirred solution of 683 mg (1.63 mmol) of the ketals **15** 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 50 g of silica gel with 1:9 ether/petroleum ether afforded first 296 mg of the methyl ketal **17** as a colorless oil: $R_f$ = 0.22 (silica gel, 2:8 ether/petroleum ether); evaporative distillation 160-165°C (0.01 mmHg); $[\alpha]^{22}_D$ -2.7° (*c* 1.06, $CHCl_3$); IR ($CHCl_3$) 2990, 1455, 1380, 1370, 1260, 925, 870 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 1.07 (d, 3H, J=6 Hz, $CH_3CH$), 1.33 (s, 9H, 3 $CH_3C$), 2.10-2.47 (m, 1H, $CH_3CH$), 3.20 (s, 3H, $OCH_3$), 3.50 (s, 2H, $CCH_2O$), 3.82 (d, 1H, J=9 Hz, $CCHCH$), 4.53 (s, 2H, $C_6H_5CH_2$), 4.70 (s, 1H, OCHO), 7.33 (s, 5H, $C_6H_5$). Anal. Calcd for $C_{22}H_{32}O_6$: C, 67.32; H, 8.22. Found: C, 67.42; H, 8.19.

There was then eluted 304 mg of the methyl ketal **16** as a

colorless oil: $R_f$ = 0.16 (silica gel, 2:8 ether/petroleum ether); evaporative distillation 160-165°C (0.01 mmHg); $[\alpha]^{22}_D$ = -55.1° (*c* 0.88, $CHCl_3$); IR ($CHCl_3$) 2990, 1450, 1380, 1370, 940, 870 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 1.17 (d, 3H, J=6 Hz, $CH_3CH$), 1.37 (s, 3H, $CH_3C$), 1.43 (s, 6H, 2 $CH_3C$), 2.00-2.33 (m, 1H, $CH_3CH$), 3.33 (s, 3H, $OCH_3$), 3.53 (s, 2H, $CCH_2O$), 3.90 (d, 1H, J=9 Hz, CCHCH), 4.90 (s, 1H, OCHO), 7.33 (s, 5H, $C_6H_5$). Anal. Calcd for $C_{22}H_{32}O_6$: C, 67.32; H, 8.22. Found: C, 67.08; H, 8.13. Three recycles of the methyl ketal **17** in a manner similar to that described above provided 234 mg of additional methyl ketal **16** representing a total yield of 85%.

**2-(Cis-propenyl-1-oxy)-3(R)-methyl-3,4(R)-(dimethylmethylene-dioxy)-5(R)-methyl-6(S)-methoxy-6-(benzyloxymethyl)tetrahydropyran.** To a stirred solution of 282 mg (0.718 mmol) of the allyl ether **16** in 2.0 mL of DMSO was added in one portion 81 mg (0.72 mmol) of potassium *t*-butoxide and the resulting mixture was immediately immersed in an oil bath preheated to 80°C. After 20 min, the dark solution was allowed to cool, poured into 75 mL of brine, and then extracted with two 100 mL portions of ether. The combined organic extracts were dried ($MgSO_4$) and the solvent evaporated at reduced pressure. Chromatography of the residue on 30 g of silica gel with 1:9 ether/petroleum ether afforded 269 mg (95%) of the cis-propenyl ether as a colorless oil: $R_f$ = 0.29 (silica gel, 1:9 ether/petroleum ether); evaporative distillation 170°C (0.01 mmHg); $[\alpha]^{22}_D$ - 37.6° (*c* 1.24, $CHCl_3$); IR ($CHCl_3$) 3000, 2940, 1670, 1450, 1380, 1370, 1010,

870 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 1.18 (d, 3H, J=7 Hz, $CH_3CH$), 1.47 (s, 9H, 3 $CH_3C$), 1.67 (dd, 3H, J=7 Hz, J'=2 Hz, $CH_3CH=CH$), 2.00-2.37 (m, 1H, $CH_3CH$), 3.33 (s, 3H, $OCH_3$), 3.53 (s, 2H, $CCH_2O$), 5.00 (s, 1H, OCHO), 7.33 (s, 5H, $C_6H_5$). Anal. Calcd for $C_{22}H_{32}O_6$: C, 67.32; H, 8.22. Found: C, 67.22; H, 8.11.

**2-(Cis-propenyl-1-oxy)-3(R)-methyl-3,4(R)-(dimethylmethylene-dioxy)-5(R)-methyl-6(S)-methoxy-6-[[(1,1-dimethylethyl)dimethysilyl]-oxymethyl]tetrahydropyran (18).** To a stirred solution of 42 mg (6.1 mmol) of lithium in 30 mL of anhydrous liquid ammmonia at -78°C was added a solution of 257 mg (0.655 mmol) of the above benzyl ether in 3.5 mL of THF over 5 min. After an additional 10 min, 530 mg (10 mmol) of dry $NH_4Cl$ was cautiously added, and the resulting colorless mixture was diluted with 50 ml of ether and allowed to evaporate. The resulting ethereal suspension was treated briefly with $MgSO_4$, filtered, and then concentrated under reduced pressure. The residue was dried under high vacuum for 1 h, dissolved in 2.2 mL of dichloromethane, and cooled to -30°C. To the resulting, stirred solution were added 0.15 mL (1.31 mmol) of dry 2,6-lutidine and then 0.22 mL (0.98 mmol) of nearly colorless t-butyldimethylsilyl triflate. After 40 min, 0.5 mL of saturated aqueous $NaHCO_3$ was added, the reaction mixture poured into 50 ml of saturated aqueous $NaHCO_3$, and then extracted with two 75 mL portions of ether. The combined organic extracts were dried ($MgSO_4$), and the solvent was then evaporated under reduced pressure. Chromatography of the

residue on 30 g of silica gel with 1:9 ether/petroleum ether afforded 248 mg (91%) of the silyl ether **18** as a colorless oil: $R_f$ = 0.29 (silica gel, 1:9 ether/petroleum ether); evaporative distillation 120-130°C (0.005 mmHg); $[\alpha]^{22}_D$ - 36.6° (c 1.00, $CHCl_3$); IR ($CHCl_3$) 3990, 2860, 1670, 1460, 1380, 1250, 970, 840 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 0.10 (s, 6H, $(CH_3)_2Si$), 0.93 (s, 9H, $(CH_3)C$), 1.20 (d, 3H, J=7 Hz, $CH_3CH$), 1.47 (s, 9H, 3 $CH_3C$), 1.67 (dd, 3H, J=7 Hz, J'=2 Hz, $CH_3CH=CH$), 2.20 (dq, H, J=8 Hz, J'=7 Hz, $CH_3CHCH$), 3.33 (s, 3H, $OCH_3$), 3.95 (d, 1H, J=8 Hz, $CCHCH$), 4.57 (dq, 1H, J=7 Hz, J'=7 Hz, $CH_3CH=CH$), 5.00 (s, 1H, OCHO), 6.11 (dq, 1H, J=7 Hz, J'=2 Hz, $CH_3CH=CH$). Anal. Calcd for $C_{21}H_{40}O_6Si$: C, 60.54; H, 9.68. Found: C, 60.66; H, 9.53.

**3(R)-Methyl-3,4(R)-(dimethylmethylenedioxy)-5(R)-methyl-6(S)-methoxy-6-[[(1,1-dimethylethyl)dimethylsilyl]oxymethyl]tetrahydropyran-2-ol (19).** To a stirred solution of 936 mg (2.25 mmol) of the cis-propenyl ether **18** in 49.3 mL of THF and 12.4 mL of water was added 1.07 g (3.37 mmol) of mercuric acetate. After 30 min at room temperature, the reaction mixture was poured into 300 mL of ether and then washed with 100 mL of saturated aqueous NaCl. The aqueous washing was extracted with 100 mL of ether and the combined organic phases were dried briefly ($MgSO_4$). Evaporation of the solvent under reduced pressure and chromatography of the residue on 125 g of silica gel with 1:1 ether/petroleum ether afforded 805 mg (95%) of the lactol **19** as a homogeneous colorless oil. $R_f$ = 0.23 (silica gel, 1:1

ether/petroleum ether); $^1$H NMR ($CDCl_3$) $\delta$ 0.1 (s, 6H, $(CH_3)_2Si$); 0.93 (s, 9H, $(CH_3)_3C$), 1.17 (d, 3H, J=7 Hz, $CH_3CH$), 1.40 (s, 3H, $CH_3C$), 1.45 (s, 6H, 2 $CH_3C$), 3.0 (bs, 1H, OH), 3.32 (s, 3H, $OCH_3$), 3.93 (d, 1H, J=9 Hz), 5.13 (bs, 1H, HOCHO).

**3-Methyl-4(R)-hydroxy-4,5-dihydro-5(R)-methyl-6(S)-methoxy-6-[[(1,1-dimethylethyl)dimethylsilyl]oxymethyl]pyran (22).** To a stirred solution of 12.66 g (47.5 mmol) of 4,4'-di-t-butylbiphenyl in 173 mL of THF was added under a blanket of argon 300 mg (43.2 mmol) of lithium wire cut into 15 pieces. Before addition, each piece was dipped briefly in methanol, rinsed in ether, squeezed with forceps, and then added to the THF solution while still wet with ether. After the solution turned deep blue-green (ca. 2 min), the solution was cooled to 0°C and stirred for 6 h.

Then, to a stirred solution of 761 mg (2.02 mmol) of the lactol **19** and 0.23 mL (2.4 mmol) of $CCl_4$ in THF at -78°C was added dropwise 0.39 mL (2.12 mmol) of distilled tris(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 4,4'-di-t- butylbiphenyl at -78°C was then added over 5 m the above solution of the pyranosyl chloride **20** in THF. After 10 min, 5 ml of water was added to the reaction mixture. The solution was allowed to warm to room temperature, poured into 300 mL of ether, and then washed with 100 mL of saturated aqueous NaCl. The solution was dried

($MgSO_4$) 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-*t*-butylbiphenyl and then 495 mg (81%) of the glycal **22** as a colorless oil: $R_f$ = 0.15 (silica gel, 1:5 ether/petroleum ether); evaporative distillation 85-90 °C (0.001, mmHg); $[\alpha]^{23}_D$ = +9.8° (*c* 0.52, $CHCl_3$); IR ($CHCl_3$) 3520, 2990, 2850, 1670, 1470, 1460, 1250, 1135, 1000, 840 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 0.10 (s, 6H, $(CH_3)_2Si$), 0.88 (d, 3H, J=7 Hz, $CH_3CH$), 0.95 (s, 9H, $(CH_3)_3C$), 1.73 (d, 3H, J=1.5 Hz, $CH=CCH_3$), 2.45 (q, 1H, J=7 Hz), 3.23 (s, 3H, $OCH_3$), 3.40 (s, 2H, $CHOH$), 3.43 (d, 1H, J=11 Hz, $CCHHO$), 3.80 (d, 1H, J=11 Hz, $CCHHO$), 5.92 (d, 1H, J=1.5 Hz, $CH=CCH_3$). Anal. Calcd for $C_{15}H_{30}O_4Si$: C, 59.56; H, 10.00. Found: C, 59.79; H, 10.06.

**2(R)-Ethyl-2-[5-(S)-carboxy-3-(S)-methyl-2-(R)-tetrahydrofuryl]-3(R),4(S)-(dimethylmethylenedioxy)-5(S)-benzyloxytetrahydrofuran, ester with the glycal 22 (25a).** To a stirred solution of 392 mg (0.965 mmol) of the acid **24a** in 2.5 mL of dichloromethane and 2.5 mL of carbon tetrachloride was added 380 mg (1.44 mmol) of triphenylphosphine and the resulting mixture was heated in an oil bath at 50 °C. After 2 h, an additional 105 mg (0.40 mmol) of triphenylphosphine was added, heating was continued for 20 min, and then the solution was cooled to 0 °C. To this solution were added a solution of 278 mg (0.919 mmol) of the glycal **22** and 337 mg (2.76 mmol) of 4-dimethylaminopyridine in 2.0 mL of dichloromethane. The

resulting mixture was allowed to warm to room temperature, and after 20 min the reaction mixture was applied directly to a column of 40 g of alumina (activity III). Elution with 2:8 ether/petroleum ether afforded 541 mg of the ester **25a** as a colorless oil: $R_f$ = 0.20 (silica gel, 2:8 ether/petroleum ether); IR ($CHCl_3$), 2950, 1730, 1670, 1460, 1385, 1375, 1255, 1020, 910, 870, 840 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 0.11 (s, 6H, $(CH_3)_2Si$), 0.95 (s, 9H, $(CH_3)C$), 1.17 (d, 3H, $CH_3CH$), 1.38, 1.53 (2s, 6H, $(CH_3)_2C$), 1.65 (s, 3H, $CH_3C=CH$), 3.25 (s, 3H, $OCH_3$), 3.48 (d, 1H, J=12 Hz, $CCHHO$), 3.85 (d, 1H, J=12 Hz, $CCHHO$), 3.93 (d, 1H, J=5 Hz, C(17)-H), 5.12 (s, 1H, OCHO), 6.13 (s, 1H, J<0.5 Hz, $CH_3C=CH$), 7.32 (s, 5H, $C_6H_5$).

**2(S)-[5(R) And 5(S)-carboxy-3(S)-methyl-2(R)-[2(R)-ethyl-3(R),4(S)-(dimethylmethylenedioxy)-5-(S)-benzyloxy-2-tetrahydrofuryl]-5-tetrahydrofuryl]-3-methyl-5,6-dihydro-5(R)-methyl-6(S)-methoxy-6-[[(1,1-dimethylethyl)dimethylsilyl]oxymethyl]-2H-pyran (26a).** To a stirred solution of 1.02 mmol of potassium hexamethyldisilazide in 6.9 mL of THF at -78°C was added, dropwise over 5 min, a solution of 352 mg (0.509 mmol) of the ester **25a** in 3.5 mL of THF. After 15 min, 12.7 mL (1.27 mmol) of a 0.10 M solution of t-butyldimethylsilylchlorosilane in THF (this solution was stored over a mixture of 3A and 4A sieves) was added over 3 min. The resulting mixture was allowed to stand at room temperature for 48 h, treated wtih 5.0 mL of 1 M aqueous LiOH for 45 min, diluted with 150 mL of ether, and then washed with 50 mL of saturated aqueous NaCl

acidified to pH 2 with dilute aqueous HCl. The organic phase was dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue on 35 g of silica gel with 4:6 ether/petroleum ether afforded 229 mg (65%) of an unseparated 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 ($CHCl_3$) 3220, 2920, 1765, 1455, 1385, 1375, 1255, 1095, 1010, 875, 840 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 0.13 (s, 6H, $(CH_3)_2Si$), 0.97 (s, 9H, $(CH_3)_3C$ , 1.33, 1.47 (2s, "5H", $(CH_3)_2C$), 1.36, 1.53 (2s, "1H", $(CH_3)_2C$), 1.63 (bs "0.5H", $CH_3C=CH$), 1.78 (bs, "2.5H", $CH_3C=CH$), 3.47 (s, 3H, $OCH_3$), 5.23 (bs, "0.17H, $CH_3C=CH$), 5.30 (bs, "0.83H", $CH_3C=CH$), 7.33 (s, 5H, $C_6H_5$). Anal. Calcd for $C_{37}H_{58}O_{10}Si$: C, 64.32; H, 8.46. Found: C, 64.37; H, 8.34.

**2(S)-[5(R) and 5(S)-carboxy-3(S)-methyl-2(R)-[2(R)-ethyl-3(R),4(S)-(dimethylmethylenedioxy)-5-(S)-benzyloxy-2-tetrahydrofuryl]-5-tetrahydrofuryl]-3-methyl-5,6-dihydro-5(R)-methyl-6(S)-methoxy-6-[[(1,1-dimethylethyl)dimethylsilyl]oxymethyl]-2H-pyran, phenyl selenoester (27a).** To a stirred solution of 100 mg (0.145 mmol) of the acids **26a** in 1.8 mL of THF at 0°C were added 61 μL (0.43 mmol) of triethylamine and then 43 μL (0.29 mmol) of phenyl dichlorophosphate. After 30 min, 100 μL (0.72 mmol) of triethylamine and then 61 μL (0.58 mmol) of selenophenol were added. After 10 min at 0 °C, the mixture was allowed to warm to room temperature, diluted with 100 mL of ether, and then washed with 50 mL

of saturated aqueous NaCl. The solvent was dried ($MgSO_4$) and then evaporated under reduced pressure. Chromatography of the residue on 20 g of silica gel with 5:95 ether/petroleum ether afforded first 19 mg (16%) of a selenoester **27a**: $R_f$ = 0.20 (silica gel, 1:9 ether/petroleum ether); IR ($CHCl_3$) 2950, 2860, 1715, 1460, 1385, 1375, 1250, 1100, 1015, 845 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 0.00 (s, 6H, $(CH_3)_2Si$), 0.83 (s, 9H, $(CH_3)_3C$), 1.30, 1.48 (2s, 6H, $(CH_3)_2C$), 1.73 (bs, 3H, $CH_3C=CH$), 3.43 (s, 3H, $OCH_3$), 3.67 (s, 2H, $CCH_2O$), 5.10 (s, 1H, OCHO), 5.20 (bs, 1H, $CH_3C=CH$), 7.23-7.57 (m, 10H, 2 $C_6H_5$).

There was then eluted 84 mg (70%) of a selenoester **27a**: $R_f$ = 0.17 (silica gel, 1:9 ether/petroleum ether); IR ($CHCl_3$) 2950, 2860, 1715, 1460, 1385, 1250, 1100, 1015, 845 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 0.00 (s, 6H, $(CH_3)_2Si$), 0.88 (s, 9H, $(CH_3)_3C$), 1.27, 1.43 (2s, 6H, $(CH_3)_2C$), 1.88 (bs, 3H, $CH_3C=CH$), 3.30 (s, 3H, $CH_3O$), 5.13 (s, 1H, OCHO), 5.23 (bs, 1H, $CH_3C=CH$), 7.23-7.52 (m, 10H, 2 $C_6H_5$).

**2(S)-[3(S)-Methyl-2(R)-[2(R)-ethyl-3(R),4(S)-(dimethylmethylenedioxy)-5-(S)-benzyloxy-2-tetrahydrofuryl]-5(R) and 5(S)-tetrahydrofuryl]-3-methyl-5,6-dihydro-5(R)-methyl-6(S)-methoxy-6-[[(1,1-dimethyethyl)dimethylsilyl]oxymethyl]-2H-pyran (28a).** To a stirred solution of 103 mg (0.124 mmol) of the selenoesters **27a** and 200 µL (0.74 mmol) of freshly distilled tri-*n*-butyltin hydride in 6.0 mL of refluxing benzene was added a trace of AIBN. After 120 min, the reaction was allowed to cool to room temperature and the solvent was evaporated at reduced pressure. Chromatography of the residue on

15 g of silica gel with 1:9 ether/petroleum ether afforded 66 mg (82%) of an inseparable 5:1 ($^1$H NMR) mixture of noralkanes **28a** as a colorless oil: $R_f$ = 0.17 (silica gel, 1:9 ether/petroleum ether); IR 2960, 2940, 2890, 2860, 1460, 1385, 1375, 1260, 1210, 1095, 1015, 845 $cm^{-1}$; $^1$H NMR (500 MHz, $CDCl_3$) major diastereomer: $\delta$ 0.05 (s, 6H, $(CH_3)_2Si$), 0.88 (s, 9H, $(CH_3)C$), 0.95 (d, 3H, J=7 Hz, $CH_3CH$), 0.98 (t, 3H, J=7.5 Hz, $CH_3CH_2$), 1.07 (d, 3H, J=7 Hz, $CH_3CH$), 1.28, 1.46 (2s, 6H, $(CH_3)_2C$), 1.48 (ddd, 1H, J=12 Hz, J'=5.5 Hz, J"=2.5 Hz, C(19)- H), 1.69 (dt, 1H, J=14 Hz, J'=7.5 Hz, $CH_3CHH$), 1.75 (s, 3H, J<0.5 Hz, $CH_3C=CH$), 1.92 (dt, 1H, J=14 Hz, J'=7.5 Hz, $CH_3CHH$), 1.99 (dq, 1H, J=1.5 Hz, J'=7 Hz, $CH_3CHCH=C$), 2.40-2.48, 2.48-2.56 (2bm, 2H, C(18)-H, C(19)-$\alpha$H), 3.39 (s, 3H, $OCH_3$), 3.61 (d, 1H, J=11 Hz, $CCHHO$), 3.68 (d, 1H, J=4.5 Hz, C(17)-H), 3.73 (d, 1H, J=11 Hz, $CCHHO$), 4.10 (ddd, 1H, J=10 Hz, J'=5.5 Hz, J"=5 Hz, C(20)-H), 4.19 (bs, 1H, C(21)-H), 4.39 (d, 1H, J=12 Hz, $C_6H_5CHH$), 4.55, 4.71 (2d, 2H, J=6 Hz, $OCHCHO$), 4.68 (d, 1H, J=12 Hz, $C_6H_5CHH$), 5.09 (s, 1H, OCHO), 5.33 (bs, 1H, J=1.5 Hz, J'<0.5 Hz, $CH_3=CHCH$), 7.25-7.34 (m, 5H, $C_6H_5$); minor diastereomer: $\delta$ 0.06 (s, 6H, $(CH_3)_2Si$), 1.12 (d, 3H, $CH_3CH$), 1.77 (s, 3H, J<0.5 Hz, $CH_3C=CH$), 2.28 (m, 1H), 3.36 (s, 3H, $OCH_3$), 3.62 (d, 1H, J=11 Hz, $CCHHO$), 3.72 (d, 1H, J=11 Hz, $CCHHO$), 3.88 (d, 1H, J=5 Hz, C(17)-H), 4.40 (d, 1H, J=12 Hz, $C_6H_5CHHO$), 4.58 (d, 1H, J=6 Hz, $OCHCHO$), 5.01 (s, 1H, OCHO), 5.35 (bs, 1H, $CH_3C=CH$). Anal. Calcd for $C_{36}H_{58}O_8Si$: C, 66.84; H, 9.04. Found: C, 66.77; H, 8.88. Decarbonylation of the separated selenoesters **27a** under conditions similar to those described above gave in each case an identical 5:1 mixture of noralkanes.

**2(R)-Ethyl-2-[5-(S)-formyl-3-(S)-methyl-2-(R)-tetrahydrofuryl]-3(R),4(S)-(dimethylmethylenedioxy)-5(S)-benzyloxy-tetrahydrofuran (31).** To a stirred solution of 22 μL (0.26 mmol) of oxalyl chloride in 2 mL of dichloromethane at -78°C was added 24 μL (0.34 mmol) of dimethylsulfoxide. After 10 min, a solution of 67 mg (0.17 mmol) of the alcohol **33**[27] in 0.5 mL of dichloromethane was added to the reaction mixture. After 15 min, the solution was treated with 120 μL (0.85 mmol) of triethylamine, allowed to warm to room temperature, and then diluted with 50 mL of ether. This mixture was washed with 20 mL of 50% saturated aqueous NaCl, the organic phase was dried ($MgSO_4$), and then the solvent was evaporated under reduced pressure. Chromatography of the residue on 10 g of silica gel with 1:1 ether/petroleum ether 57 mg (85%) of the aldehyde **31** as a colorless oil: $R_f$ = 0.36 (silica gel, 1:1 ether/petroleum ether); $^1H$ NMR ($CDCl_3$) δ 1.03 (t, 3H, J=7 Hz, $CH_3CH_2$), 1.13 (d, 3H, J=7 Hz, $CH_3CH$), 1.33, 1.52 (2s, 6H $(CH_3)_2C$), 3.97 (d, 1H, J=4 Hz, C(17)-H), 5.10 (s, 1H, OCHO), 9.72 (d, 1H, J=2 Hz, C(O)H). Treatment of a portion of this aldehyde with LAH in ether at 0°C produced the alcohol **33** as identified by TLC and $^1H$ NMR.

**2(R)-Ethyl-2-[5-(R)-formyl-3-(S)-methyl-2-(R)-tetrahydrofuryl]-3(R),4(S)-(dimethylmethylenedioxy)-5(S)-benzyloxy-tetrahydrofuran (32).** To a stirred solution of 34 mg (0.087 mmol) of the aldehyde

**31** in 3.0 mL of dry methanol was added 200 mg of granular, anhydrous $K_2CO_3$ and the mixture was heated in an oil bath at 60°C. After 2 h, the cooled reaction mixture was diluted with 40 mL of ether, washed with 20 mL of water and then 20 mL of saturated aqueous NaCl. The organic phased was dried ($MgSO_4$), and the solution concentrated under reduced pressure. Chromatography of the residue with 3:7 ether/petroleum ether afforded first 12 mg (35%) of the aldehyde **31** and then 14 mg (41%) of the aldehyde **32** as a colorless oil: $R_f$ = 0.28 (silica gel, 1:1 ether/petroleum ether); $^1H$ NMR ($CDCl_3$) 1.03 (t, 3H, J=7 Hz, $CH_3CH_2$), 1.10 (d, 3H, J=6 Hz, $CH_3CH$), 1.33, 1.50 (2s, 6H, $(CH_3)_2C$), 4.02 (d, 1H, J=4 Hz, C(17)-H), 5.13 (s, 1H, OCHO), 9.75 (d, 1H, J=2 Hz, C(O)H).

**2(S)-Ethyl-2-[5-(S)-carboxy-3-(S)-methyl-2-(R)-tetrahydrofuryl]-3(R),4(S)-(dimethylmethylenedioxy)-5(S)-benzyloxy-tetrahydrofuran, ester with the glycal 22 (25b).** By the procedure described above for the preparation of ester **25a**, 310 mg (0.763 mmol) of the acid **24b** and 300 mg (1.14 mmol) of triphenylphosphine in 1.5 mL of carbon tetrachloride and 1.5 mL of dichloromethane, and a solution of 279 mg (2.28 mmol) of 4-dimethylaminopyridine and 226 mg (0.748 mmol) of the glycal **22** in 2.0 mL of dichloromethane afforded, after chromatography on 35 g of alumina (activity III) with 2:8 ether/petroleum ether, 439 mg (85%) of the ester **25b** as a colorless oil: $R_f$ = 0.27 (silica gel, 3:7 ether/petroleum ether); IR ($CHCl_3$) 3000, 2935, 2860, 1735, 1670, 1460, 1385, 1375, 1255, 1140, 1095, 1010, 870, 840 $cm^{-1}$; $^1H$ NMR

($CDCl_3$) $\delta$ 0.08 (s, 6H, $(CH_3)_2Si$), 0.90 (s, 9H, $(CH_3)_3C$), 1.32, 1.52 (2s, 6H, $(CH_3)_2C$), 1.55 (s, 3H, J<0.5 Hz, $CH_3C=CH$), 3.22 (s, 3H, $OCH_3$), 3.42 (d, 1H, J=14 Hz, $CCHHO$), 3.80 (d, 1H, J=14 Hz, $CCHHO$), 3.97 (d, 1H, J=5 Hz, C(17)-H), 5.15 (d, 1H, J=1.5 Hz, OCHO), 6.08 (s, 1H, J<0.5 Hz, $CH_3C=CH$), 7.32 (bs, 5H, $C_6H_5$).

**2(S)-Ethyl-[5-(R)-carboxy-3-(S)-methyl-2-(R)-[2(S)-ethyl-3(R), 4(S)-(dimethylmethylenedioxy)-5-(S)-benzyloxy-2-tetrahydrofuryl]-5-tetrahydrofuyl]-3-methyl-5,6-dihydro-5(R)-methyl-6(S)-methoxy-6-[[(1,1-dimethylethyl)dimethylsilyl]oxymethyl]-2H-pyran (26b).** To a stirred solution of 0.70 mmol of lilthium diisopropylamide in 4.0 mL of THF at -78°C was added, dropwise over 5 min, a solution of 373 mg (0.538 mmol) of the ester **25b** in 1.5 mL of THF. After 10 min, the reaction mixture was treated with 0.19 mL (1.07 mmol $Me_3SiCl$) of the supernatant centrifugate from a 3:1 mixture of trimethylchlorosilane and triethylamine. The reaction mixture was then heated at 50°C for 2 h, allowed to cool, diluted with 100 mL of ether, and washed with 40 mL of saturated aqueous NaCl acidified to $\sim$ pH 2 with dilute aqueous HCl. The organic phase was dried ($MgSO_4$), and the solvent evaporated under reduced pressure. Chromatography of the residue on 25 g of silica gel with 3:7 ether/petroleum ether afforded 170 mg (45%) of the acid **26b** as a white solid. Recrystallization of a portion of this material from methanol afforded the analytical sample as colorless plates: mp 167-168°C; $R_f$ = 0.38 (silica gel, 4:6 ether/petroleum ether); IR ($CHCl_3$) 3200, 2930, 2885, 2860, 1755,

1460, 1365, 1275, 1095, 1010, 840 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 0.08 (s, 6H, $(CH_3)_2Si$), 0.93 (s, 9H, $(CH_3)_3C$), 1.35, 1.47 (2s, 6H, $(CH_3)_2C$), 1.82 (bs, 3H, $CH_3$-C=CH), 3.42 (s, 3H, $OCH_3$), 3.95 (d, 1H, J=4 Hz, C(17)-H), 4.23 (bs, 1H, C(21)-H), 5.13 (d, 1H, J=1.5 Hz, OCHO), 5.40 (bs, 1H, $CH_3C$=CH). Anal. Calcd for $C_{37}H_{58}O_{10}Si$: C, 64.32; H, 8.46. Found: C, 64.37; H, 8.42.

**2(S)-Ethyl-[5-(R)-carboxy-3-(S)-methyl-2-(R)-[2(S)-ethyl-3(R), 4(S)-(dimethylmethylenedioxy)-5-(S)-benzyloxy-2-tetrahydrofuryl]-5-tetrahydrofuryl]-3-methyl-5,6-dihydro-5(R)-methyl-6(S)-methoxy-6-[[(1,1-dimethylethyl)dimethylsilyl]oxymethyl]-2H-pyran, phenyl selenoester (27b).** By the procedure described above for the preparation of selenoester **27a**, 20 mg (0.029 mmol) of the acid **26b**, 12 $\mu$L (0.086 mmol) of triethylamine, and 8.6 $\mu$L (0.058 mmol) of phenyl dichlorophosphate in 0.4 mL of THF, and then 20 L (0.14 mmol) of triethylamine and 12 $\mu$L (0.12 mmol) of selenophenol, afforded, after chromatography on 5 g of silica gel with 1:9 ether/petroleum ether 19 mg (80%) of the selenoester **27b** as a colorless oil: $R_f$ = 0.16 (silica gel, 1:9 ether/petroleum ether); IR ($CHCl_3$) 3000, 2960, 2940, 2890, 2865, 1710, 1465, 1385, 1375, 1260, 1195, 1020, 845 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 0.08 (s, 6H, $(CH_3)_2Si$), 0.90 (d, 3H, J=7 Hz, $CH_3CH$), 1.05 (t, 3H, J=7 Hz, $CH_3CH_2$), 1.18 (d, 3H, J=7 Hz, $CH_3CH$), 1.37, 1.55 (2s, 6H, $(CH_3)_2C$), 1.98 (bs, 3H, $CH_3C$=CH), 3.34 (s, 3H, $OCH_3$), 3.58 (s, 2H, $CCH_2O$), 4.07 (d, 1H, J=5 Hz, C(17)-H), 4.17 (bs, 1H, $CHC(CH_3)$), 4.57, 4.83 (2d, 2H, J=12 Hz, $C_6H_5CH_2$), 4.85 (bs, 2H,

OCHCHO), 5.18 (bs, 1H, OCHO), 5.30 (bs, 1H, $CH_3C=CH$).

**2(S)-[3(S)-Methyl-2-(R)-[2(S)-ethyl-3(R),4(S)-(dimethylmethylene-dioxy)-5-(S)-benzyloxy-2-tetrahydrofuryl]-5-tetrahydrofuryl]-3-methyl-5,6-dihydro-5(R)-methyl-6(S)-methoxy-6-[[(1,1-dimethylethyl)-dimethylsilyl]oxymethyl]-2H-pyran (28b).** By the procedure described for the preparation of the noralkanes **28a**, 14.0 mg (0.0169 mmol) of the selenoester **27b**, 70 μL (0.26 mmol) of tri-n-butyltin hydride, and a trace of AIBN in 5.0 mL of benzene afforded, after 1 h at reflux and chromatography on 7 g of silica gel with 1:9 ether/petroleum ether, 8.1 mg (74%) of a single noralkane **28b** as a colorless oil: $R_f$ = 0.19 (silica gel, 1:9 ether/petroleum ether); IR ($CHCl_3$) 2960, 2930, 2860, 1465, 1385, 1375, 1255, 1095, 1015, 845 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$) δ 0.03, 0.04 (2s, 6H, $(CH_3)_2Si$), 0.87 (s, 9H, $(CH_3)_3C$), 0.92 (d, 3H, J=7.5 Hz, $CH_3CH$), 1.00 (t, 3H, J=8 Hz, $CH_3CH_2$), 1.19 (d, 3H, J=7 Hz, $CH_3CH$), 1.32, 1.49, (2s, 6H, $(CH_3)_2C$), 1.46 (s, 3H, $CH_3C=CH$), 3.34 (s, 3H, $OCH_3$), 3.56, 3.69 (2d, 2H, J=11 Hz, $CCH_2O$), 3.77 (d, 1H, J=7 Hz, C(17)-H), 3.80 (m, 1H, C(20)-H), 4.17 (bd, 1H, J=6 Hz, $OCHC(CH_3)$), 4.52, 4.75 (2d, 2H, J=12 Hz, $C_6H_5CH_2$), 4.66 (d, 1H, J=6 Hz, OCHCHC), 4.85 (dd, 1H, J=6 Hz, J'=2.5 Hz, OCHCHC), 5.15 (d, 1H, J=6 Hz, OCHO), 5.30 (bs, 1H, $CH_3C=CH$).

**3-Deoxy-1,2-O-(1-methylethylidene)-β-L-threo-pentofuranuronic acid (35), and methyl ester.** To a stirred solution of 454 mg (2.22 mmol) of the diol **34** in 10.0 ml of water at room temperature was added 475 mg (2.22 mmol) of $NaIO_4$. After 30 min, the solution was extracted with two 100 mL portions of chloroform, the combined organic extracts dried ($MgSO_4$), and then concentrated under reduced pressure. The residue was dissolved in 8.7 ml (5.10 mmol) of 0.588 M aqueous silver nitrate, and to the stirred solution at room temperature was added, dropwise over 5 min, 11.2 ml (10.2 mmol) of 0.91 M aqueous KOH. After 20 min, the solution was filtered, and the precipitate was washed with two 10 mL portions of 0.91 M aqueous KOH. The filtrate was cooled to 0°C, carefully acidified to pH 2 with 6 M aqueous HCl, and then extracted with four 100 mL portions of chloroform. The combined organic extracts were dried ($MgSO_4$) and then concentrated under reduced pressure to afford 376 mg (90%) of the acid **35** as an oil of >95% ($^1H$ NMR) purity; $^1H$ NMR ($CDCl_3$) δ 1.30, 1.52 (2s, 6H, $(CH_3)_2$), 2.32 (ddd, 1H, J=14 Hz, J'=9 Hz, J"=5 Hz, OCHC<u>H</u>HCH, β-H), 2.72 (dd, 1H, J=14 Hz, J'=1 Hz, OCHCH<u>H</u>CH, α-H), 4.63 (dd, 1H, J=9 Hz, J'=1 Hz, OC<u>H</u>C(O)), 4.73 (dd, 1H, J=4.5 Hz, J'=5 Hz, OCHC<u>H</u>O), 5.88 (d, 1H, J=4.5 Hz, OC<u>H</u>O), 9.12 (bs, 1H, $CO_2$<u>H</u>). A portion of this oil was treated with ethereal diazomethane and the solvent evaporated under reduced pressure. Chromatography of the residue on silica gel with 7:3 ether/petroleum ether afforded the methyl ester of acid **35** as a colorless oil: $R_f$ = 0.20 (silica gel, 7:3 ether/petroleum ether); evaporative distillation 60°C (0.005 mmHg); $[\alpha]^{22}_D$ - 63.6° (c 1.12, $CHCl_3$); Lit.[64] $[\alpha]^{20}_D$ -67.1° (c 1, $CHCl_3$); IR ($CHCl_3$) 2990, 2950,

1750, 1735, 1440, 1385, 1375, 1260, 1160, 1105, 1070, 1035, 855 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 1.30, 1.47 (2s, 6H, $(CH_3)_2C$), 2.27 (ddd, 1H, J=14 Hz, J'=9 Hz, J"=5 Hz, OCHC$\underline{H}$HCH, $\beta$-H), 2.68 (d, 1H, J=14 Hz, J' 0.5 Hz, OCHCH$\underline{H}$CH, $\alpha$-H), 3.42 (s, 3H, $OCH_3$), 4.62 (dd, 1H, J=9 Hz, J' 0.5 Hz, OCHC(O)), 4.68 (dd, 1H, J=5 Hz, J'=4 Hz, OCHC$\underline{H}$O), 5.83 (d, 1H, J=4 Hz, OCHO). Anal. Calcd for $C_9H_{14}O_5$: C, 53.46; H, 6.99. Found: C, 53.59; H. 6.99.

**3-Deoxy-1,2-O-(1-methylethylidene)-β-L-threo-pentofuranuronic acid, ester with the glycal 22 (36).** By the procedure described for the preparation of ester **25a**, 133 mg (0.707 mmol) of the acid **35** and 370 mg (1.41 mmol) of triphenylphosphine in 1.5 mL of carbon tetrachloride and 1.5 mL of dichloromethane, and a solution of 259 mg (2.12 mmol) of 4-dimethylaminopyridine and 203 mg (0.673 mmol) of the glycal **22** in 2.0 ml of dichloromethane afforded, after chromatogrpahy on 20 g of alumina (activity III) with 4:6 ether/petroleum ether 254 mg (80%) of the ester **36** as a colorless oil: $R_f$ = 0.19 (silica gel, 1:1 ether/petroleum ether); IR ($CHCl_3$) 2970, 2950, 2860, 1750, 1680, 1465, 1385, 1375, 1260, 1140, 1030, 845 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 0.05 (s, 6H, $(CH_3)_2Si$), 0.88 (s, 9H, $(CH_3)C$), 1.28, 1.50 (2s, 6H, $(CH_3)_2C$), 1.57 (s, 3H, $CH_3C$=CH), 3.20 (s, 3H, $OCH_3$), 3.43 (d, 1H, J=14 Hz, CC$\underline{H}$HO), 3.83 (d, 1H, J=14 Hz, CCH$\underline{H}$O), 4.58 (dd, 1H, J=6 Hz, J'=2 Hz, OCHC(O)), 4.65 (dd, 1H, J=3 Hz, J'=3 Hz, OCHC$\underline{H}$O), 5.10 (d, 1H, OC$\underline{H}$CHCH$_3$), 5.83 (d, 1H, J=3 Hz, OCHO), 6.10 (s, 1H, OC$\underline{H}$=CCH$_3$, J$\sim$0.5 Hz).

**2-(S)-[2-Carboxy-4-(R),5(R)-(dimethylmethylenedioxy)-2-tetrahydrofuryl]-3-methyl-5,6-dihydro-5(R)-methyl-6(S)-methoxy-6-[[(1,1-dimethylethyl)dimethylsilyl]oxymethyl]-2H-pyran.** By the procedure described for the preparation of the acids **26a**, 0.22 mmol of potassium hexmethyldisilazide in 1.5 mL of THF, a solution of 67 mg (0.14 mmol) of the ester **36**, and 2.82 mL (0.282 mmol) of a 1 M solution of t-butyldimethylchlorosilane, provided, after treatment with 1.0 mL of 1 M aqueous LiOH and chromatography on 10 g of silica gel with 1:9 methanol/chloroform, 41 mg (61%) of a single acid as a colorless oil: $R_f$ = 0.27 (silica gel, 1:9 methanol/chloroform); IR ($CHCl_3$) 3400, 2960, 2930, 2860, 1765, 1465, 1380, 1255, 1110, 845 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 0.08 (s, 6H, $(CH_3)_2Si$), 0.92 (s, 9H, $(CH_3)_3C$), 0.96 (d, 3H, J=7 Hz, $CH_3CH$), 1.35, 1.57 (2s, 6H, $(CH_3)_2C$), 1.83 (s, 3H, $CH_3C=CH$), 3.47 (s, 3H, $OCH_3$), 3.73 (s, 2H, $CCH_2O$), 5.33 (s, 1H, $CH_3C=CH$), 6.05 (d, 1H, J=3 Hz, OCHO). Anal. Calcd for $C_{23}H_{40}O_8Si$: C, 58.45; H, 8.53. Found: C, 58.09; H, 8.43.

**2-(S)-[2-Carboxy-4-(R),5(R)-(dimethylmethylenedioxy)-2-tetrahydrofuryl]-3-methyl-5,6-dihydro-5(R)-methyl-6(S)-methoxy-6-[[(1,1-dimethylethyl)dimethylsilyl]oxymethyl]-2H-pyran, phenyl seleonester (38).** By the procedure described above for the preparation of selenoester **27a**, 40 mg (0.084 mmol) of the above acid in 1.0 mL of

THF, 25 μL (0.17 mmol) of phenyl dichlorophosphate, and 35 μL (0.25 mmol) of triethylamine, and then 36 μL (0.34 mmol) of selenophenol and 59 μL (0.42 mmol) of triethylamine, provided after chromatography on 10 g of alumina (activity III) with 1:9 and then 2:8 ether/petroleum ether, 41 mg (79%) of the selenoester **38** as a light yellow oil: $R_f$ = 0.29 (silica gel, 2:8 ether/petroleum ether); IR ($CHCl_3$) 2960, 1720, 1385, 1375, 1100, 845 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 0.05 (s, 6H, $(CH_3)_2Si$), 0.90 (s, 9H, $(CH_3)_3C$), 0.95 (d, 3H, J=7 Hz, $CH_3CH$), 1.35 (s, 3H, $CH_3C$), 1.74 (s, 6H, $CH_3C$, $CH_3C=CH$), 2.32 (dd, 1H, J=14 Hz, J'=2 Hz, $CHCHHC$, α-H), 2.52 (m, 1H, $CH_3CHCH$), 2.76 (dd, J=14 Hz, J'=6 Hz $CHCHHC$, β-H), 3.42 (s, 3H, $OCH_3$), 3.67 (s, 2H, $CCH_2O$), 4.58 (bs, 1H, $OCHC(CH_3)$), 4.85 (ddd, 1H, J=6 Hz, J'=4 Hz, J"=2 Hz, $OCHCHO$), 5.35 (bs, 1H, $CH_3=CH$), 5.97 (d, 1H, J=4.5 Hz, OCHO), 7.12-7.68 (m, 5H, $C_6H_5$).

**2-(S)-[4-(R),5(R)-(dimethylmethylenedioxy)-2(R) and 2(S)-tetrahydrofuryl]-3-methyl-5,6-dihydro-5(R)-methyl-6(S)-methoxy-6-[[(1,1-dimethylethyl)dimethylsilyl]oxymethyl]-2H-pyran (37).** By the procedure described above for the noralkanes **28a**, 30 mg (0.049 mmol) of the selenoester **38**, 50 L (0.19 mmol) of freshly distilled tri-n-butyltin hydride, and a trace of AIBN in 2.0 mL of benzene provided, after 50 min at reflux and chromatogaphy on silica gel with 1:9 and then 2:8 ether/petroleum ether, first 8.8 mg (42%) of a noralkane **37**: $R_f$ = 0.23 (silica gel, 2:8 ether/petroleum ether); IR ($CHCl_3$) 2960, 2860, 1460, 1485, 1475, 1255, 1110, 1030, 850 $cm^{-1}$; $^1H$

NMR (500 MHz, $CDCl_3$) $\delta$ 0.04, 0.05 (2s, 6H, $(CH_3)_2Si$), 0.89 (s, 9H, $(CH_3)_3C$), 0.97 (d, 3H, J=7 Hz, $CH_3CH$), 1.31, 1.56 (2s, 6H, $(CH_3)_2C$), 1.83 (s, 3H, $CH_3C=CH$), 2.11 (ddd, 1H, J=14 Hz, J'=7 Hz, J"=7 Hz, $CHCHHCH$, $\beta$-H), 2.38 (bm, 1H, $CH_3CH$), 2.61 (ddd, 1H, J=14 Hz, J'=2Hz, J"=1 Hz, $CHCHHCH$, $\alpha$-H), 3.28 (s, 3H, $OCH_3$), 3.59, 3.68 (2d, 2H, J=12 Hz, $CCH_2O$), 4.22 (ddd, 1H, J=11 Hz, J'=7 Hz, J"=2 Hz, $CH_2CHCH(CH_3)$), 4.26 (bd, 1H, J=11 Hz, $OCHCCH_3$), 4.73 (ddd, 1H, J=7 Hz, J'=5 Hz, J"=1 Hz, $OCHCHO$), 5.43 (bs, 1H, $CH_3C=CH$), 5.80 (d, 1H, J=5 Hz, OCHO); mass spectrum: m/e 428 ($M^+$).

There was then eluted 9.3 mg (44%) of a noralkane **37**: $R_f$ = 0.18 (silica gel, 2:8 ether/petroleum ether); IR ($CHCl_3$) 2940, 2870, 1465, 1385, 1375, 1260, 1170, 850 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$) $\delta$ 0.04, 0.05 (2s, 6H, $(CH_3)_2Si$), 0.87 (s, 9H, $(CH_3)_3C$), 0.92 (d, 3H, $CH_3CH$), 1.32, 1.48 (2s, 6H, $(CH_3)_2C$), 1.71 (s, 3H, $CH_3C=CH$), 2.01 (dd, 1H, J=14 Hz, J'=4 Hz, $CHCHHCH$, $\alpha$-H), 2.06 (ddd, 1H, J=14 Hz, J'=8 Hz, J"=4 Hz, $CHCHHCH$, $\beta$-H), 2.52 (bm, 1H, $CH_3CH$), 3.36 (s, 3H, $OCH_3$), 3.58, 3.76 (2d, 2H, J=11 Hz, $CCH_2O$), 4.12 (bs, 1H, $OCHCCH_3$), 4.45 (ddd, 1H, J=8 Hz, J'=4 Hz, J"=4Hz, $CH_2CHCHC(CH_3)$), 4.74 (dd, 1H, J=4 Hz, J'=3 Hz), 5.41 (bs, 1H, $CH_3C=CH$), 5.81 (d, 1H, J=3 Hz, OCHO); mass spectrum: m/e 428 ($M^+$).

**X-ray Crystallography of the Acid 26b.** $SiC_{34}O_9H_{57}$, crystallized by slow evaporation of methanol in the monoclinic space group $P2_1$. Crystal data are as follows: a = 15.983(10) A, b = 10.615(8) A, c = 11.537(8) A, $\beta$ = 98.63(5)°, Z = 2, $d_c$ = 1.057 g $cm^{-3}$, mol wt = 637.9, F(000) = 650, u (Mo K$\alpha$) = 1.10 $cm^{-1}$.

Diffraction data were collected on a Nicolet $P2_1$ automated diffractometer by the $\theta$-$2\theta$ scan technique at room temperature with graphite-monchromated Mo K$\alpha$ radiation. The scan rate varied from 2 to 15°/min, dependent on the intensity of the diffraction maxima. The basewidth was 1.8° and the sum of the background times was equal to half of the total scan time. No decay was noted in the three check reflections monitored every 50 reflections. A total of 5111 reflections were collected out to a maximum $2\theta$ of 45°. Duplicate reflections were averaged to give 2727 unique reflections with 1968 being considered observed with intensities >2.3 $\sigma$(I).

The structure was solved by direct methods using the program MULTAN[65] with the aide of a shell Patterson[66] which was used to determine the correct position for the Si atom. Only 13 atoms were located in the first E-Map; the remaining atoms were slowly located in Fourier and difference Fourier maps. This was, in part, due to the high thermal motion at both ends of the molecule. Hydrogen atom positions were calculated based on known geometry for the non-methyl

hydrogen atoms. Block-diagonal least-squares calculations, minimizing the function $\Sigma w(|F_o| - |F_c|)^2$ and refining the scale factor, secondary extinction parameter, and non-hydrogen atom coordinates and anisotropic temperature factors, converged at R = 0.076 and a goodness-of-fit of 3.06.

As suggested by the lack of tailing on silica gel thin layer chromatograpy and by the infrared spectrum, the molecule has a strong intramolecular hydrogen bond, 2.784(9) A, from the carboxylic acid, O(36B), to the benzyl oxygen, O(13). The bond distances near O(13) and O(16), i.e. O (13)-C(43) of 1.506(17), O(13)-C(13) of 1.385(13), C(13)-O(16) of 1.394(16), and O(16)-C(16) of 1.446(12), indicate that O(16) shares in the charge burden of this intramolecular bond. The ring containing O(16) is twisted with C(14) and C(15) being on either side of the plane of the other atoms. The ring containing O(14) and O(15) is an envelop with O(15) being out of the plane. The ring containing O(17) is also an envelop with C(18) being out of the plane. The ring containing O(21) is a flattened boat.

An ORTEP[30] drawing of the molecule is given in Figure 1. The relative rather than the absolute stereochemistry was determined in this structural determination.[67]

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# CHAPTER 4

## The Swern Oxidation - In Situ Condensation Combination: A Method for the Manipulation of Highly Reactive Carbonyl Compounds

# THE SWERN OXIDATION - IN SITU CONDENSATION COMBINATION: A METHOD FOR THE MANIPULATION OF HIGHLY REACTIVE CARBONYL COMPOUNDS[1]

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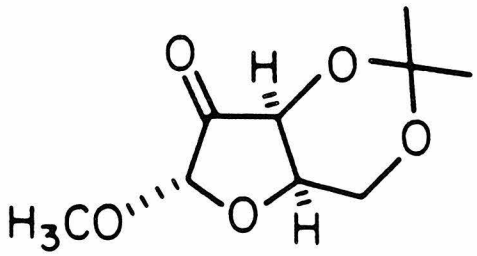
**Abstract:** The direct addition of nucleophilic reagents to crude Swern oxidation reaction mixtures circumvents the deleterious side reactions characteristic of highly reactive carbonyl compounds. Hexylglyoxal, produced by Swern oxidation of 1,2-octanediol, condenses with methyl (triphenylphosphoranylidene)acetate to give the $\gamma$-oxo-crotonate **10**. Addition of methyl magnesium bromide to the unstable 2-ketofuranoside **3** delivers the branched chain carbohydrate derivative **4**. The transient existence of monomeric trimethylsilyl formaldehyde, generated at -78 °C by Swern oxidation of trimethylsilylmethanol, is established by isolation of the Wittig condensation product **13**.

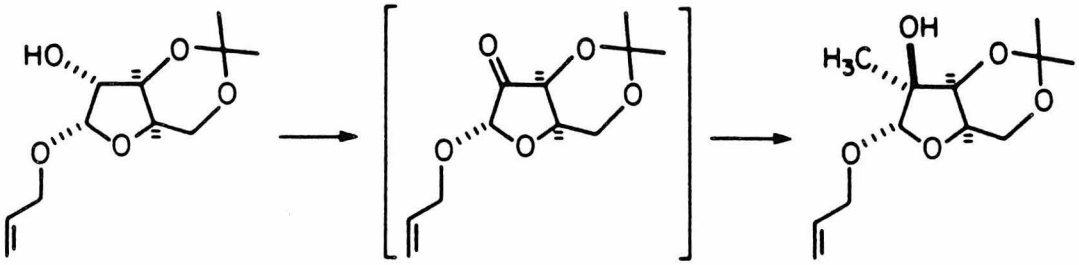
Aldehydes or ketones bearing strongly electronegative substituents are inductively destabilized toward addition reactions and decomposition.[3] In the course of synthetic studies toward the polyether ionophore antibiotics, we encountered several carbonyl containing intermediates which were troublesome in this regard. Here we report experimental modifications of the Swern oxidation[4] which have been exceptionally useful in handling extremely reactive carbonyl compounds.

2-Ketofuranosides are often intractable. For instance, the pentofuranosid-2-ulose **1**, obtained as its hydrate by ruthenium



**1**

tetraoxide oxidation in a crude yield of 57%, was unstable to chromatography on silica gel or alumina and could not be completely dehydrated by azeotropic distillation in toluene.[5] Our efforts to prepare the 2-methyl-tetrahydrofuran D ring of monensin[6] were thwarted by the similar behavior of the 2-ketofuranoside **3**. Of all

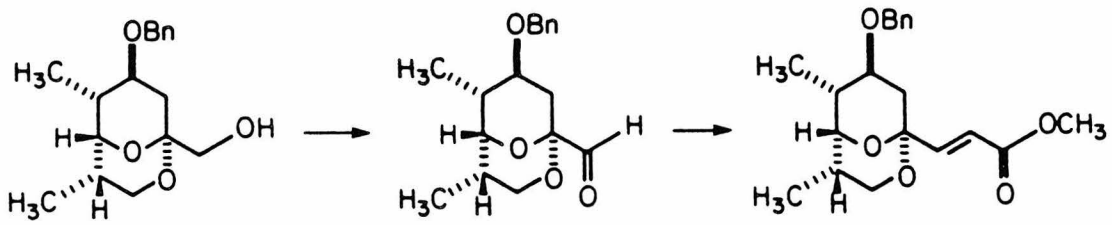



2 3 4

the methods available for oxidizing alcohols, the Swern procedure offers some unique advantages for highly reactive carbonyl compounds. The reaction is anhydrous, proceeds rapidly at low temperature, and produces relatively innocuous byproducts: carbon monoxide, carbon dioxide, dimethyl sulfide, and triethylamine hydrochloride.[7] These considerations led us to develop the following two step, one pot procedure for the synthesis of branched-chain carbohydrates.[8] Swern oxidation of the alcohol **2** in THF at -78°C gave the ketone **3** nearly quantitatively on warming to 0°C as indicated by TLC. After recooling the solution to -78°C, five equivalents of methyl magnesium bromide were added, and conventional workup provided the tertiary alcohol **4** as a single diastereomer in 85% chromatographed yield.[9]

Aldehyde **6**, an intermediate for monensin's spiroketal, was also prone to hydration and decomposition, and could not be isolated

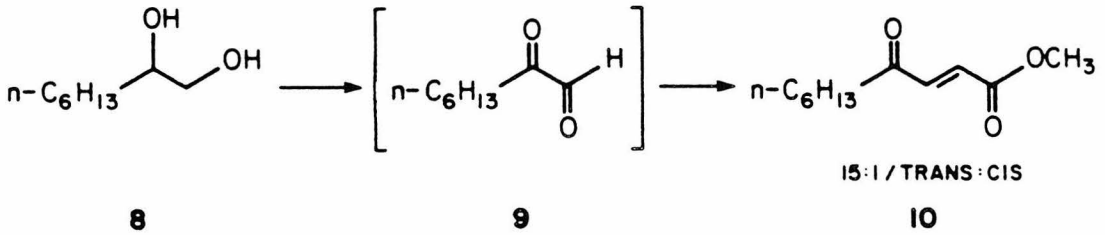
in good yield, even in an impure state. In this case, addition of




methyl (triphenylphosphoranylidene)acetate to the crude Swern oxidation mixture provided a remarkable 98% yield of the unsaturated esters 7.

Aliphatic α-ketoaldehydes are another class of hyperreactive carbonyl compounds and consequently have seen little use in organic synthesis.[10] Propylglyoxal, for example, is described as a fuming, green-brown liquid which polymerizes on storage in a sealed tube.[11] Similar tendencies are reported for other aliphatic α-ketoaldehydes,[12] and even the relatively hindered 1-adamantylglyoxal hydrates, spontaneously polymerizes, and eventually air oxidizes to 1-adamantanecarboxylic acid.[13] The Swern oxidation has been used previously to prepare vicinal diketones.[7,14] Addition of methyl (triphenylphosphoranylidene)acetate to the crude reaction

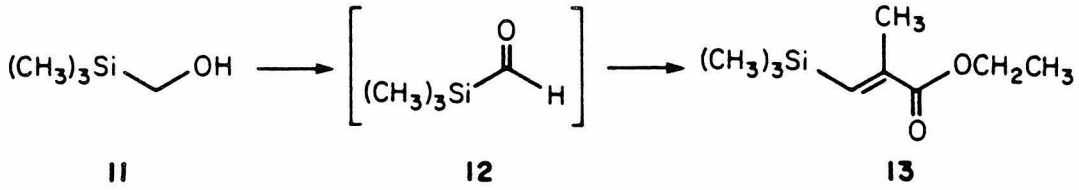
mixture from Swern oxidation of 1,2-octanediol quenched the bright yellow color characteristic of hexylglyoxal[10b] instantaneously, and the Wittig condensation product **10**[15] was isolated in 90% yield. This




**8** **9** **10**

constitutes a simple new method for the synthesis of γ-oxygenated crotonate esters. Due to its presence in several natural products,[16] preparation of this functional array has received considerable attention.[17]

As an even more demanding test of this protocol, we selected the hitherto unkown parent acylsilane, trimethylsilylformaldehyde. In this instance Swern oxidation of trimethylsilylmethanol[18] was



11 12 13

carried out entirely at -78°C, and the addition of triethylamine was followed five minutes later by the addition of ethyl 2-(triphenylphosphoranylidene)propionate. The solution was then allowed to warm to room temperature, and the novel silicon compound **13** was isolated by chromatography in 54% yield.[19] Attempts to characterize the putative trimethylsilylformaldehyde at room temperature were not successful. $^1$H NMR of a crude reaction aliquot showed no resonance between 9-10 ppm, and the infrared spectrum showed no absorption between 1500-2100 cm$^{-1}$. Since addition of the Wittig reagent to a crude reaction mixture which had been allowed to warm to 0°C produced no condensation product,we infer that polymerization occurs quite rapidly. Ethyl (E)-3-(trimethyl- silyl)methacrylate (**13**) is of potential interest as a synthetic building block.[20] More importantly, the low temperature viability of trimethylsilylformaldehyde suggests new possibilities for the incorporation of

silicon into organic molecules.[21]

## EXPERIMENTAL SECTION

Melting points were determined using a Hoover capillary melting point apparatus and are uncorrected. Infrared (IR) spectra were determined on a Perkin-Elmer 727B or 1310 infrared spectrophotometer. Proton Nuclear Magnetic Resonance ($^1$H NMR) spectra were recorded on a Varian EM-390 spectrometer. Chemical shifts are reported as $\delta$ values in parts per million relative to tetramethylsilane ( $\delta$ 0.0) as a internal standard. Data are reported as follows: chemical shift (multiplicity, integrated intensity, coupling constants, assignment). Optical rotations were measured in 1 dm cells of 1 mL capacity using a JASCO model DIP-181 polarimeter. Chloroform, when used as a solvent for optical rotations, was filtered through neutral alumina (activity I) immediately prior to use. Analytical thin-layer chromatography (TLC) was conducted on 2.5 x 10 cm precoated TLC plates: silica gel 60 F-2254, layer thickness 0.25 cm, manufactured by E. Merck and Co., Darmstadt, Germany. Silica gel columns for chromatography utilized E. Merck silica gel 60 (70-230 mesh ASTM). Reaction solvents and liquid reagents were purified by distillation or drying shortly before use. Tetrahydrofuran (THF) and triethylamine were distilled under argon from sodium metal with sodium benzophenone ketyl as an indicator. Dichloromethane and oxalyl chloride were distilled from powdered calcium hydride. Dimethyl sulfoxide was distilled under reduced pressure from powdered calcium hydride and stored over a mixture of 3A and 4A sieves. All other reactants and solvents were "reagent grade" unless described otherwise. "Ether" refers to anhydrous

diethyl ether which is supplied by Mallinckrodt and Baker. "Petroleum ether" refers to the "analyzed reagent" grade hydrocarbon fraction (bp 35-60 °C) which is supplied by J.T. Baker, Co., Phillipsburg, NJ. Reactions were run under an argon atmosphere arranged with a mercury bubbler so that the system could be alternatively 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*. Elemental combustion analyses were performed by Spang Microanalytical Laboratory, Eagle Harbor, MI.

**Ally 3,5-O-(1-methylethylidene)-2-C-methyl- -D-lyxofuranoside (4).** To a stirred solution of 67 μL (0.77 mmol) of oxalyl chloride in 2.0 mL of THF at -78°C was added 57 μL (0.81 mmol) of dimethyl sulfoxide. The solution was allowed to warm to -35°C for 3 min and was then recooled to -78°C. A solution of 169 mg (0.734 mmol) of the alcohol **2** in 1.0 mL of THF was then added to the reaction mixture. The resulting solution was allowed to warm to -35°C, and after 15 min was treated with 0.51 mL (3.7 mmol) of triethylamine. The reaction mixture was allowed to warm briefly to room temperature and was then recooled to -78°C. 1.31 mL (3.67 mmol) of a solution of methyl magnesium bromide was then added dropwise to the vigorously stirred reaction mixture. The temperature of the solution was allowed to

warm to -50 °C over 1 h, was recooled to -78 °C, and was then cautiously treated with 0.5 mL of ethanol and then 1.0 mL of a saturated aqueous solution of $NH_4Cl$ buffered to pH 8 with concentrated aqueous ammonia. The warmed reaction mixture was then poured into 75 mL of the above buffer and extracted with two 150 mL portions of ether. The combined organic extracts were dried ($MgSO_4$) and then concentrated under reduced pressure. Chromatography of the residue on 12 g of silica gel with 1:1 ether/petroleum ether afforded 153 mg (85%) of the alcohol **4** 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 ($CDCl_3$) 1.30, 1.42, 1.42 (3s, 9H, 3 $CH_3C$), 3.27 (s, 1H, OH), 2.63-4.40 (m, 6H), 4.93 (s, 1H, OCHO). Anal. Calcd for $C_{12}H_{20}O_5$: C, 59.00; H, 8.25. Found: C, 58.95; H, 8.19

**Methyl 3-[5(R)-4(S),6(R)-dimethyl-7(S)-(benzyloxy)-2,9-dioxabicyclo[3.3.1]nonan-1-yl]cis and trans-propenoate (7).** To a stirred solution of 42 μL (0.49 mmol) of oxalyl chloride in 4.0 mL of dichloromethane at -60 °C was added 69 μL (0.97 mmol) of dimethyl sulfoxide. After 10 min, a solution of 118 mg (0.404 mmol) of the alcohol **5** in 3 mL of dichloromethane was added to the reaction mixture. After 15 min, the reaction mixture was treated with 0.28 mL (2.0 mmol) of triethylamine and then allowed to warm to 0 °C. 405 mg (1.21 mmol) of methyl (triphenylphosphoranylidene)acetate 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 ($MgSO_4$) 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 95:5 trans:cis mixture ($^1H$ NMR) of $\alpha,\beta$-unsaturated esters as a colorless oil: $R_f$ = 0.67 (trans), 0.63 (cis) (silica gel, ether). The trans isomer had the following physical properties: evaporative distillation 165-170°C (0.005 mmHg); $[\alpha]^{21}_D$ + 92.9 (c 1.47, $CHCl_3$); IR ($CHCl_3$) 3000, 2950, 2885, 1715, 1430, 1305, 1275, 1125, 1070, 1000, 910 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 0.90, 1.15 (2d, 6H, J=7 Hz, 2 $CH_3CH$), 1.75 (dd, 1H, J=14 Hz, J'=9 Hz, $CCHHCH$), 2.42 (dd, 1H, J=14 Hz, J'=6 Hz, $CCHHCH$), 3.70 (s, 3H, $OCH_3$), 4.43 4.65 (2d, 2H, J=12 Hz, $C_6H_5CH_2$), 6.10, 6.77 (2d, 2H, J=16 Hz, CH=CH), 7.31 (s, 5H, $C_6H_5$). Anal. Calcd for $C_{20}H_{26}O_5$: C, 69.34; H, 7.56. Found: C, 69.29; H, 7.50. $^1H$ NMR (cis isomer, $CDCl_3$) $\delta$ 0.88, 1.14 (2d, 6H, J=7 Hz, 2 $CH_3CH$), 3.37 (s, 3H, $OCH_3$), 5.83 (s, 2H, CH=CH), 7.32 (s, 5H, $C_6H_5$).

**Methyl (E) and (Z)-4-oxo-2-decenoate (10).** To a stirred solution of 192 μL (2.20 mmol) of oxalyl chloride in 8 mL of dichloromethane at -78°C was added 184 μL (2.60 mmol) of dimethyl sulfoxide. After 10 min, a solution of 146 mg (1.00 mmol) of 1,2-octanediol in 2 mL of dichloromethane was added over 3 min to the reaction mixture. After 20 min, 0.84 mL (6.0 mmol) of triethylamine was added, and after 10

min at -78 °C, a solution of 501 mg (1.50 mmol) of methyl (triphenylphosphoranylidene)acetate in 2.0 mL of dichloromethane was added to the reaction mixture over 3 min. The reaction mixture was allowed to warm to room temperature, was poured into 50 mL of 50% saturated aqueous NaCl, and was then extracted with 100 mL of ether. The organic phase was dried ($MgSO_4$) and then concentrated under reduced pressure. Chromatography of the residue on 15 g of silica gel with 1:9 ether/petroleum ether afforded first 167 mg (84%) of the olefin **10** as a low melting white solid: mp 43-45°C (Lit.[15] mp 48-49°C); $R_f$ = 0.33 (silica gel, 2:8 ether/petroleum ether); IR ($CHCl_3$) 2960, 2940, 2860, 1720, 1700, 1630, 1460, 1435, 1305, 1180, 980, 910 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 0.85 (bt, 3H, J=6Hz, $CH_3CH_2$), 1.25 (bs, 6H), 1.40-1.80 (bm, 2H), 2.57 (t, 2H, J=7Hz, $CH_2CH_2C(O)$), 3.80 (s, 3H, $OCH_3$), 6.62, 7.05 (2d, 2H, J=17Hz, CH=CH). Anal. Calcd for $C_{11}H_{18}O_3$: C, 66.64; H, 9.15. Found: C, 66.45; H, 9.04. There was then eluted 11 mg (5.5%) of the cis isomer as a colorless oil: $R_f$ = 0.20 (silica gel, 2;8 ether/petroleum ether); evaporative distillation 85°C (0.5 mmHg); IR ($CHCl_3$) 2960, 2940, 2860, 1725, 1700, 1630, 1460, 1440, 1390, 1230, 1130, 1085, 1000 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 0.90 (bt, 3H, J=6Hz, $CH_3CH_2$), 1.30 (bs, 6H), 1.40-1.80 (bm, 2H), 2.63 (t, 2H, J=6Hz, $CH_2CH_2C(O)$), 3.70 (s, 3H, $OCH_3$), 6.00, 6.47 (2d, 2H, J=12Hz, CH=CH). Anal. Calcd for $C_{11}H_{18}O_3$: C, 66.64; H, 9.15. Found: C, 66.38; H, 9.03.

**Ethyl (E)-3-(trimethylsilyl)methacrylate (13).** To a stirred solution of 131 μL (1.50 mmol) of oxalyl chloride in 8.0 mL of dichloromethane at -78°C was added 121 μL (1.70 mmol) of dimethyl sulfoxide. After 10 min, a solution of 104 mg (1.00 mmol) of trimethylsilylmethanol in 2 mL of dichloromethane was added over 4 min to the reaction mixture. After 15 min, 0.52 mL (3.7 mmol) of triethylamine was added over 1 min. After 5 min at -78°C, a solution of 690 mg (1.9 mmol) of ethyl 2-(triphenylphosphoranylidene)propionate was added over 3 min. The reaction mixture was then allowed to warm to room temperature, was diluted with 70 mL of ether, and was then washed with 40 mL of water and then 40 mL of saturated aqueous NaCl. The organic phase was dried ($MgSO_4$) and then concentrated under reduced pressure. Chromatography of the residue on 10 g of silica gel with 3:97 ether/petroleum ether afforded 101 mg (54%) of the olefin **13** as a colorless oil: $R_f$ = 0.33 (silica gel, 5:95 ether/petroleum ether); IR ($CHCl_3$) 3000, 2960, 1700, 1610, 1370, 1330, 1320, 1210, 1100, 860, 840 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 0.17 (s, 9H, $(CH_3)_3Si$), 1.30 (t, 3H, J=7Hz, $CH_3CH_2$), 2.00 (s, 3H, $CH_3C$), 4.17 (q, 2H, J=7Hz, $CH_3CH_2$), 6.82 (s, 1H, $CH$=C). Mass spectrum: m/e (relative intensity, composition) 171 (100, $C_8H_{15}O_2Si$), 143 (46, $C_7H_{15}OSi$), 113 (5, $C_6H_{13}Si$), 75 (38, $C_3H_7O_2$), 73 (32, $C_3H_5O_2$, $C_3H_9Si$).

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