system. Thin-layer chromatography (TLC) was run with precoated silica gel plates (Merck, Art. No. 5554). Spot detection was carried out by UV light and/or staining with 0.1% 1,3-dihydroxynaphthalene in $EtOH/H_2O/H_2SO_4$ (200/157/43 (v/v/v)). The elution solvent for TLC was n-$C_3H_7OH/AcOEt/H_2O$ (7/7/5 (v/v/v)). Prepacked columns (Merck, Lobar column LiChroprep Rp18 and Rp8) were used for reverse-phase column chromatography. High-performance liquid chromatography (HPLC) was performed on a TSKgel-410 ODS SIL column (4 × 300 mm, 5 μm, Toyo Soda, Japan).

Preparation and Isolation of Unsymmetrically Disubstituted Cyclodextrins 1–6 and 7–12. These have been reported by us.[3,4]

Conversion of Disubstituted β-Cyclodextrins 3 and 4 to Oligosaccharides 15 and 16. A solution of **3** (50 mg) in 0.1 N aqueous NaOH (3 mL) was kept at 60 °C for 4.5 h. After neutralization by addition of diluted HCl, the mixture was concentrated in vacuo to dryness. The residue was dissolved in 5 mL of 0.2 M acetate buffer (pH 5.5) containing 0.01 M $CaCl_2$. After 50 mg of Taka amylase (Sigma, α-amylase type X-A) was added to the solution, the mixture was kept at 40 °C for 20 days. The enzyme was denatured by addition of 3 N ammonium hydroxide (2 mL), and the precipitated protein was separated by centrifugation. The supernatant was concentrated in vacuo to dryness, dissolved in water (50 mL), and applied on a reverse-phase column (Rp18). After elution with water (300 mL), a gradient elution from water (300 mL) to 30% aqueous ethanol (300 mL) was applied to give **15**, which was purified by reverse-phase HPLC. **13**: R_f 0.30. **15**: 14 mg (43.3%); R_f 0.42.

Similarly, **4** (50 mg) was converted to **16** via **14**. In the isolation of **16** by reverse-phase column chromatography, a gradient elution from water (300 mL) to 20% aqueous ethanol (300 mL) followed by an elution of 20% aqueous ethanol (500 mL) was used after an elution of water (250 mL). **14**: R_f 0.30. **16**: 20 mg (63.0%); R_f 0.43.

$NaBH_4$ Reduction of Modified Oligosaccharides 15 and 16. A solution of **15** (10 mg) in 1% aqueous $NaBH_4$ (2.7 mL) was kept at room temperature for 24 h. After neutralization, the mixture was adsorbed on a reverse-phase column (Rp18) and chromatographed with an elution of water (200 mL) and then a gradient elution from 10% aqueous ethanol (300 mL) to 30% aqueous ethanol (300 mL) to give **17**. **17**: 8.5 mg (85.1%); R_f 0.43; FABMS, m/z 905 ($M + H^+$), 927 ($M + Na^+$), 943 ($M + K^+$); ^{13}C NMR, Figure 1.

Similarly, **16** (10 mg) gave **18**. **18**: 8.3 mg (83.2%); R_f 0.37; FABMS, m/z 905 ($M + H^+$), 927 ($M + Na^+$), 943 ($M + K^+$); ^{13}C NMR, Figure 1.

Acetylation of Reduced Oligosaccharides 17 and 18. A mixture of **17** (5 mg), acetic anhydride (1.5 mL), and pyridine (1.5 mL) was kept at room temperature overnight and concentrated by evaporation of volatile materials together with a stream of nitrogen. After dry chloroform (0.5 mL) was added to the residue, the evaporation was repeated. This procedure was carried out two more times to give **19**. **19**: R_f 0.38; FDMS, m/z 1535 ($M + H^+$).

Similarly, **20** was prepared. **20**: R_f 0.52; FDMS, m/z 1535 ($M + H^+$).

Reaction of 6^A-*S*-Phenyl-6^X-*O*-(β-naphthylsulfonyl)-6^A-thio-β-cyclodextrins 1–6 with *tert*-Butyl Mercaptan. A solution of the sulfonate (20 mg), *tert*-butyl mercaptan (80 mg), and sodium hydride (13 mg) in dimethylformamide (0.5 mL) was kept at 80 °C overnight in a sealed tube. After evaporation of dimethylformamide and *tert*-butyl mercaptan, the residue was, in the case of the reaction of **1**, **3**, or **5**, recrystallized from water to give **21** (9 mg, 49%), **24** (8 mg, 44%), or **25** (6 mg, 33%), respectively, and in the case of the reaction of **2**, **4**, or **6**, chromatographed with a reverse-phase column to give **22** (6 mg, 33%), **23** (8 mg, 44%), or **26** (12 mg, 60%), respectively. ^1H NMR absorption of *tert*-butyl group (Me_2SO-d_6, δ): **21**, 1.18; **22**, 1.19; **23**, 1.22; **24**, 1.20; **25**, 1.20; **26**, 1.28.

Reaction of 6^A-*S*-(*tert*-Butyl)-6^X-(β-naphthylsulfonyl)-6^A-thio-β-cyclodextrins 7–12 with Thiophenol. A solution of **7** (20 mg), thiophenol (13 mg), and sodium carbonate (4 mg) in dimethylformamide (0.5 mL) was stirred at 80 °C for 5 h. After evaporation of dimethylformamide, the residue was dissolved in aqueous ethanol, acidified with HCl, and extracted with ether. The aqueous layer was neutralized with NaOH, concentrated in vacuo, and chromatographed with a reverse-phase column (Rp8) to give **22** (10 mg, 54%).

Similarly, **8** (15 mg), **9** (4 mg), **10** (20 mg), **11** (20 mg), or **12** (20 mg) gave **21** (8 mg, 58%), **23** (3 mg, 81%), **24** (10 mg, 54%), **26** (10 mg, 54%), or **25** (11 mg, 59%), respectively.

The ^1H NMR spectra were the same as those of the corresponding compounds prepared from 6^A-*S*-phenyl-6^X-(β-naphthylsulfonyl)-6^A-thio-β-cyclodextrins.

Acknowledgment. We are indebted to Japan Maize Products Co. Ltd. for a generous gift of β-cyclodextrin.

From Carbohydrates to Carbocycles. 2. A Free Radical Route to Corey Lactone and Other Prostanoid Intermediates[1]

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The hex-5-enyl radical cyclization methodology was applied for the synthesis of optically active Corey lactone (**7**) with readily available 3-deoxy-D-glucopyranose as starting material. The cyclic radical (**19**) generated from the 4,6-*O*-benzylidene-protected hexose derivative (**16**) cyclizes with high stereoselectivity, i.e., 1,5-trans ring closure, to give cyclopentane (**20**) with the correct absolute and relative configuration of Corey lactone. This unusual stereoselectivity is rationalized by invoking a boatlike transition state for the radical cyclization. Also described here are several chemical transformations of **20**, which are potentially useful for the synthesis of prostaglandin-like molecules. Degradations of a commercially available Corey lactone derivative, which were initially found useful for structural correlations with synthetic intermediates are also described.

The cyclization of hex-5-enyl radicals to cyclopentylmethyl radicals, "the radical clock reaction", has attracted considerable attention in synthetic and physical organic chemistry.[2] Kinetic parameters for the individual steps[3]

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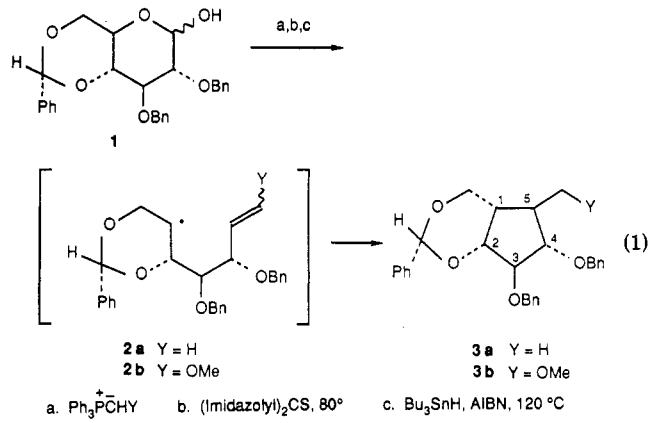
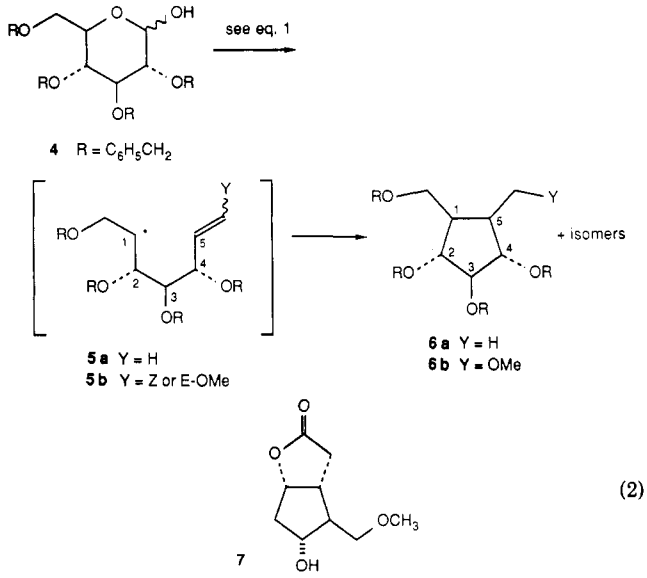
involved in the generation, rearrangement, subsequent trapping, and regeneration of the chain initiator as well as the stereochemistry of products[4] from prototypical alkyl-substituted hex-5-enyl radicals have been established. Several groups have exploited this reaction for the synthesis of complex natural products[5] and highly functionalized cyclopentanes also have been prepared from aldose sugar precursors.[6,7] We have developed a general synthetic protocol[7a,b] for generating hex-5-enyl radicals from hexopyranoses as shown in eq 1 and 2 and found that the open chain radicals cyclize predominantly to 1,5-cis products (eq 1) as in the case with many other analogous systems reported in the literature.[4,5a-e,7,8] In sharp contrast, however, the cyclic radicals derived from 4,6-*O*-benzylidene glucose derivatives, exhibited unprecedented and exclusive 1,5-trans selectivity (eq 2). A close examination of the results of this new stereochemical control reveals that cyclic, but not acyclic, hex-5-enyl radicals derived from 3-deoxy-D-*ribo*-hexopyranose (3-deoxy-D-glucopyranose) should give rise to oxygenated cyclopentanes having the relative and absolute configuration appropriate for prostaglandins. Thus, we have undertaken the synthesis of Corey lactone, **7**, a well-documented prostanoid synthon,[9]



(1)



(2)

to test the general applicability of the free radical cyclization reaction and to gain further information regarding the substituent effects on the product stereochemistry.

Results

Synthesis of Radical Precursor 17. The synthesis of radical precursor **16** is summarized in Scheme I. 3-Deoxyglucose **9** derived from readily available 3-deoxy-1,2:5,6-di-*O*-isopropylidene-α-D-*ribo*-hexofuranose 8[10] exists as a mixture of various furanose and pyranose forms.[11] This sugar may be converted to a highly crystalline tetraacetate **10**[11b] or can be directly treated with allyl alcohol in the presence of AG50W-X8 (acidic) resin with simultaneous removal of water to give a mixture of α- and β-allyl glycosides **12a** and **12b** (along with other furanose glycosides) in 80% overall yield after chromatography. Alternatively, tetraacetate **10** can be converted to an allyl glycoside triester **11** by treatment with allyl alcohol in the presence of anhydrous stannic chloride.[12] The α- and β-anomers **11a** and **11b** are readily identified by the cou-

(1) Contribution No. 4708 from Central Research and Development Department. Preliminary accounts of this work have appeared. RajanBabu, T. V. *Abstracts of Papers*, 193rd National Meeting of the American Chemical Society, Denver, Colorado; American Chemical Society: Washington, DC, 1987; ORGN 225; ref 7a.

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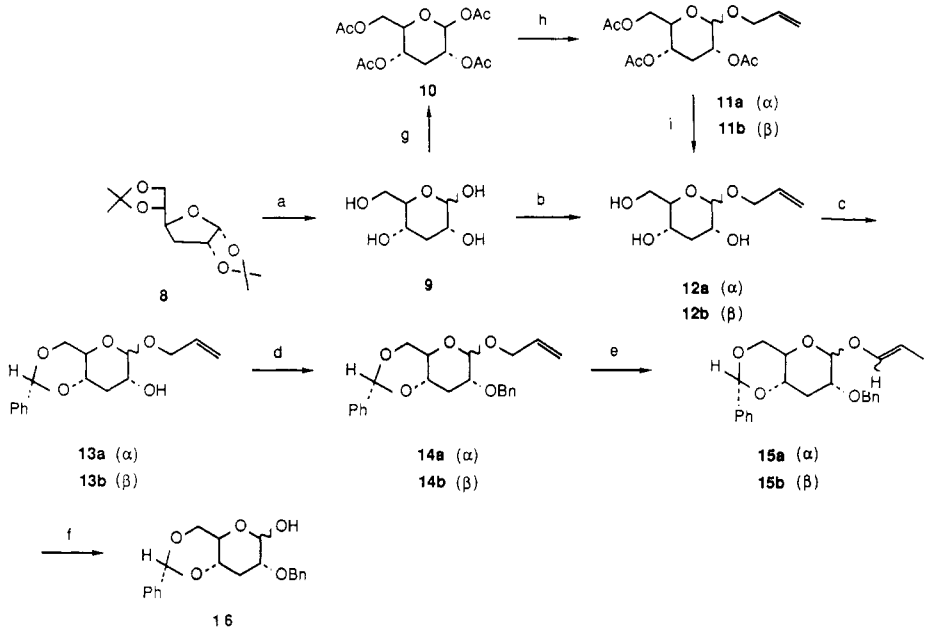
Scheme I. Synthesis of 2-*O*-(Phenylmethyl)-4,6-*O*-(phenylmethylene)-3-deoxy-D-*ribo*-hexopyranose (16)[a]

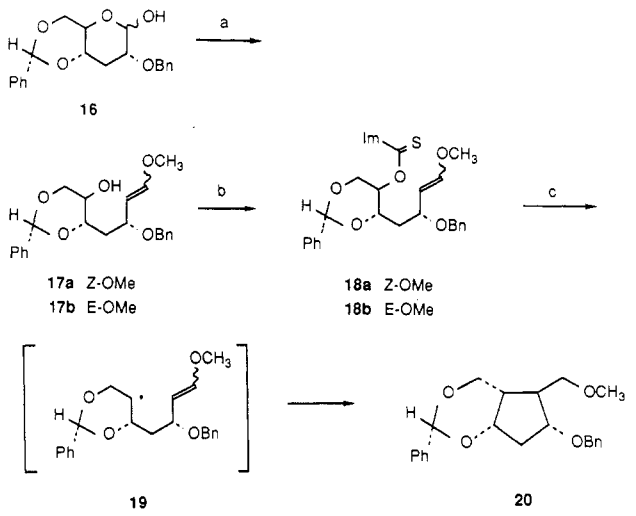


[a] (a) H^+, H_2O, EtOH; (b) H^+, allyl alcohol, PhH; (c) $PhCHBr_2$, py, Δ; (d) BnBr, NaH, DMF; (e) $[Ir(COD)(PPh_2Me)]^+PF_6^-/H_2$; (f) $HgCl_2$, HgO, H_2O, acetone; (g) Ac_2O, py; (h) allyl alcohol, $SnCl_4$; (i) AGMP-1(OH^-), MeOH.

pling constants of the anomeric protons; $J_{1,2}$ is 4.0 and 8.0 Hz in the α- and β-anomer, respectively. Although the anomers could be separated and independently processed, the mixture was used for further synthesis because in the last step free sugar is released and the stereochemistry at C-1 is of no consequence. The mixture, **11a** and **11b**, was hydrolyzed and converted to the 4,6-benzylidene derivative **13a** and **13b** by Garegg's procedure[13] by using benzal bromide in refluxing pyridine. As expected[13b,c] only the thermodynamic products with the equatorial phenyl orientation are observed. Protection of the C-2 hydroxy group under standard conditions as the benzyl ether sets the stage for deprotection of the allyl glycoside. Initial attempts to effect the allyl to propenyl ether isomerization with Wilkinson's catalyst[14] resulted in considerable amounts of reduction of the double bond under a variety of conditions. The use of $[Ir(COD)(PPh_2Me)_2]^+PF_6^-$ catalyst activated by molecular hydrogen[15] circumvented the problem, and the vinyl ether **15** was obtained in good yield. However, contrary to the observations in the literature where only trans products are reported to be formed, a mixture of cis and trans (1:6) propenyl ethers are produced. Hydrolysis of the vinyl ether mixture, **15a** and **15b**, with mercuric chloride and mercuric oxide in aqueous acetone afforded the 3-deoxyglucose derivative **16** as a mixture of anomers.

Free-Radical Cyclization. The free radical cyclization of 3-deoxyglucose derivative **16** follows the general scheme outlined in eq 2 and summarized in Scheme II. Treatment with (methoxymethylene)triphenylphosphorane in THF at −20 °C gives a mixture of the vinyl ethers **17a** and **17b** in a 40:60 ratio. The *Z* and *E* isomers, **17a** and **17b**, can be easily distinguished in the ^1H NMR spectrum, in which the C=C*H*OMe signals appear at δ 6.14 (dd, J = 6 and 1 Hz) and 6.53 (d, J = 12 Hz), respectively. We have also separated small amounts of the isomers by careful column chromatography and subjected them individually to the cyclization. However, since there appeared to be little differences in the yield and stereochemistry of these reactions, the mixture of the isomers **17a** and **17b** was used for the subsequent reactions. Treatment with a slight excess of thiocarbonylbis(imidazole) (99% pure, Fluka) in refluxing 1,2-dichloroethane followed by mild acid wash afforded a mixture of **18a** and **18b**, which was sufficiently pure for the crucial radical cyclization reaction. Treatment of **18** with tributyltin hydride and AIBN under Barton's deoxygenation conditions[16a] afforded **20** as the exclusive cyclization product, although 5–12% of alcohol **17** was consistently recovered in several runs. In other related

Scheme II. Generation and Cyclization of Radical 19[a]



[a] (a) $Ph_3P^+CH_2OCH_3Cl^-$, *n*-BuLi; (b) thiocarbonylbis(imidazole), CH_2ClCH_2Cl, Δ; (c) *n*-Bu_3SnH, AIBN, $PhCH_3$, Δ.

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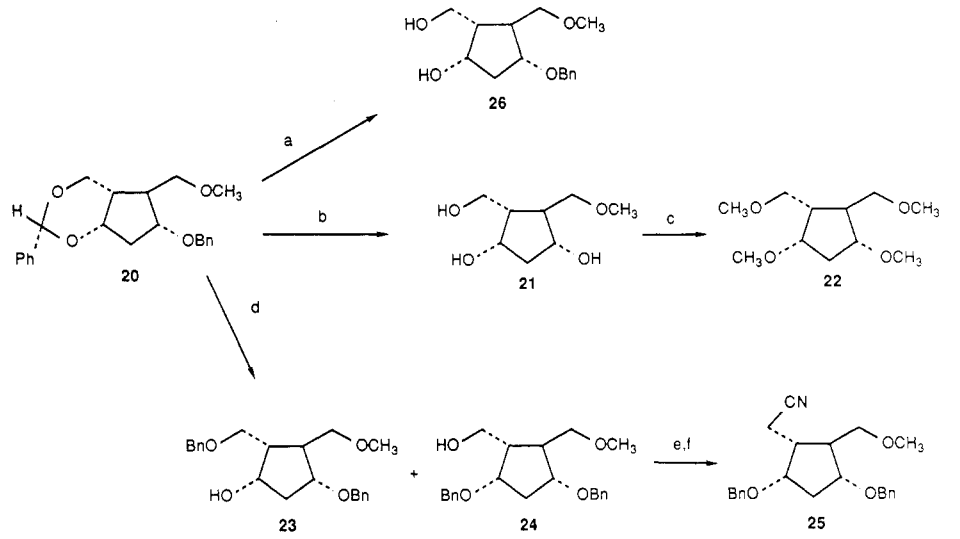
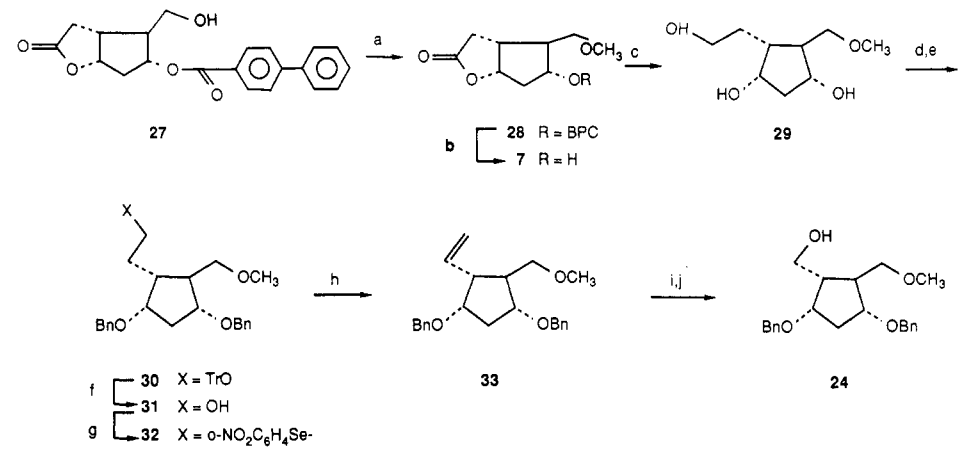
Scheme III. Reactions of the Adduct 20[a]



[a] (a) H^+; (b) H_2, Pd, H^+; (c) MeI, NaH, DMF; (d) LAH, $AlCl_3$; (e) TsCl, py; (f) NaCN, DMF, 83 °C.

Scheme IV. Preparation of Authentic 7 and 24 from 27[a]



[a] (a) NaH, MeI, DMF; (b) K_2CO_3, MeOH; (c) LAH, THF; (d) TrCl, py; (e) NaH, BnBr, DMF; (f) H^+; (g) o-$NO_2C_6H_4SeCN$, Bu_3P; (h) H_2O_2; (i) O_3, CH_3SCH_3; (j) $NaBH_4$.

systems, we have since found that the yield of cyclization can be markedly improved by the phenylthionocarbonate procedure developed by Robins.[16b]

Chemical Correlation. Since the assignment of the 1,5-trans structure, **20**, to cyclization product is crucial for its use in the subsequent synthesis and is unprecedented in terms of stereochemical outcome prior to our studies,[7] we sought to confirm it by chemical correlation and independent synthesis of one of its derivatives. For example, as shown in Scheme III, hydrogenolysis of **20** in acidic ethyl acetate to triol **21** followed by methylation afforded a tetramethyl ether **22** which showed four methyl singlets in the NMR spectrum. Since the 1,2-cis relationship is well precedented[7,8] in the cyclization of related systems, the lack of symmetry in the product is consistent only with the 1,5-trans relationship in **20**. Whereas acid treatment of **20** gives a diol **26**, regioselective unmasking of the benzylidene group in **20** can be carried out with LAH/$AlCl_3$.[17] Chain elongation at the primary alcohol center to the nitrile **25** illustrates the versatility of **20** as a synthetic intermediate. Other S_N2 type reactions and oxidation to the corresponding aldehyde followed by nucleophilic addition can also envisioned as possible routes for side-chain elaboration.

Before undertaking the synthesis of Corey lactone from the cyclization product, the commercially available Corey lactone **27** was transformed to the primary alcohol **24** to unequivocally confirm the structure. The transformation is summarized in Scheme IV. The methyl ether **28** was reduced with LAH to the triol **29**. The primary hydroxyl group was protected as a trityl ether and the secondary hydroxyls were converted to the benzyl ethers. Aqueous acid treatment of **30** to release the primary hydroxyl group followed by treatment with (*o*-nitrophenyl)selenocyanate[18] and tri-*n*-butylphosphine gave the phenylselenide **32**. Oxidation of **32** with 30% H_2O_2 and ozonolysis of the resulting olefin followed by borohydride reduction afforded an alcohol, which was identical in all respects ($[\alpha]^{25}_D$, IR, HRMS, and ^{13}C and ^1H NMR) with the alcohol **24** prepared by LAH/$AlCl_3$ cleavage of the benzylidene acetal **20**.

Finally, the conversion of **21** to Corey lactone was accomplished by procedures closely parallel to those pub-

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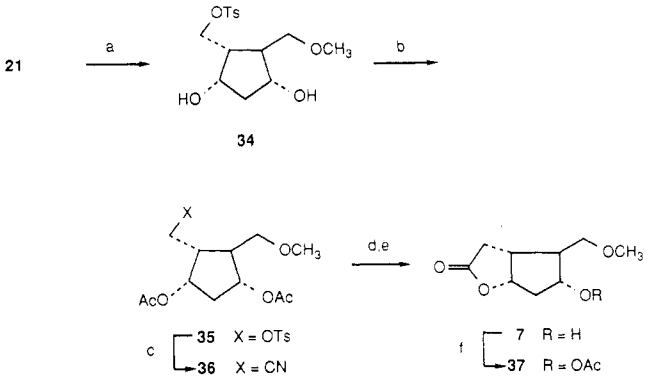
Scheme V. Synthesis of Corey Lactone[a]

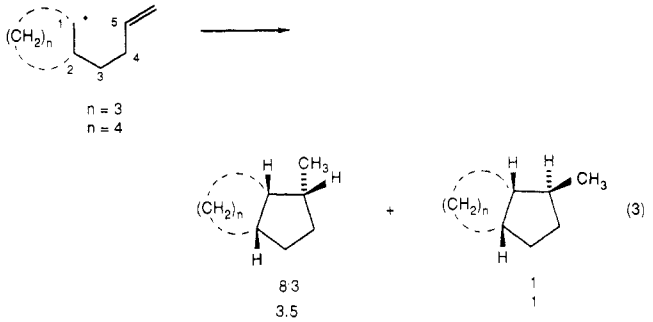


[a] (a) TsCl, py; (b) Ac_2O, py; (c) NaCN, DMF; (d) OH^-, H^+; (e) concentrated HCl; (f) Ac_2O, py.

lished earlier[19] as summarized in Scheme V. The structures of **7** and **37** were confirmed by the comparison of their spectral properties and optical rotations with those of authentic samples.[20]

Discussion

Stereochemistry of substituted hex-5-enyl radical cyclizations have been extensively studied by Beckwith, and general guidelines to predict product stereochemistry have been formulated[4] on the basis of the assumption that the cyclization proceeds through the transition state resembling the cyclohexane chairlike conformation. Accordingly, 1- and 3-substituted radicals give mostly 1,5- and 3,5-cis-disubstituted cyclopentanes, respectively, whereas 2- and 4-substituted systems give mainly 2,5- and 4,5-trans products, respectively. For C-1 substituted radicals the stereoselectivity is generally low, while it is quite high for 4-substituted radicals leading to trans products.[4c] The 1,5-cis/trans ratio for the cyclization of cyclic radicals, 2-(but-3-enyl)cyclohexyl[8a] and cyclopentyl[8b] radicals, are reported to be 3.5 and 8.3, respectively (eq 3). In these



and other related systems,[5,7,8] the 1,2-ring junction is almost exclusively cis. Beckwith also proposed[8a] that in the case of 2-(but-3-enyl)cyclohexyl radicals the cyclization proceeds via the cyclohexane chairlike transition state in which the butenyl group occupies an axial position and is attacked by a radical center oriented to the pseudoquatorial direction. Such a conformation is energetically unfavorable in the present case since it would force the bulky phenyl group also into an axial position. In light of these precedents, the exclusive 1,5-trans stereoselectivity we observed in the cyclization of **19** and related systems was quite unexpected.

The unexpected 1,5-trans ring closure can be rationalized, however, if one assumes a boatlike transition state (**38**) for the cyclization. In this transition-state model, the 1,3-dioxane ring is in the energetically most favorable chair conformation with both phenyl and but-3-enyl groups in the equatorial positions. It should also be noted that within the framework of a cyclohexane boatlike transition state, the allyl ether portion (C-3–C-6) is in the energetically most favorable[21,22] (for example figure 39) conformation and the benzyloxy group is in a favorable pseudoquatorial orientation. In this boatlike conformation the 1,3-allylic strain in the C-3–C-6 segment is also minimized by having the hydrogen rather than the benzyloxy group in the same plan as the olefinic hydrogens. Recent calculations[4e] show that a boatlike transition state for hex-5-enyl radical cyclizations is energetically accessible at temperatures at which these reactions are routinely carried out. We have since shown[7b] that if the C-4 configuration (radical numbering) is inverted (i.e. manno configuration), exclusive 1,5-cis selectivity may be achieved. Of course in this case it is the chairlike transition state that will have the favorable allylic conformation (Scheme VI).

Concluding Remarks

We have demonstrated that readily available pyranose sugars can be converted via free radical methodology into highly functionalized carbocycles such as prostaglandin intermediates. With proper choice of protecting groups, the conformation of the radicals and hence the stereoselectivity of the cyclizations can be controlled. Because a large number of sugars are readily available and their protection group chemistry is well developed, the free radical conversion of pyranose to cyclopentane should be quite versatile. Furthermore, the novel 1,5-trans stereoselectivity arises from a cyclohexane chairlike transition state and depends crucially on the stereochemical disposition of the oxy substituent at C-4.[22] Finally, elaborate Wittig reagents may be used in the synthetic strategy to allow for the direct introduction of functionalized side chains to the cyclopentanes.

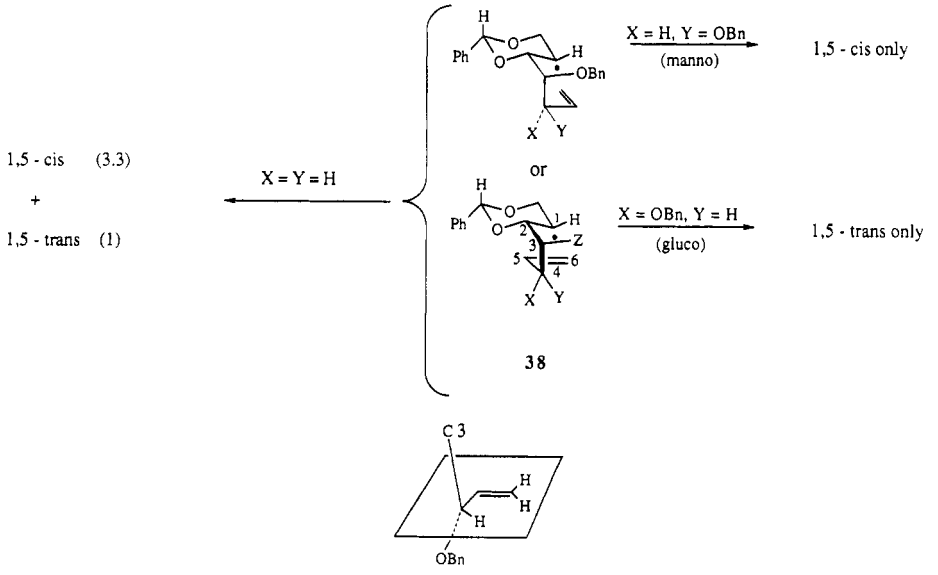
Experimental Section

Infrared spectra were determined on a Nicolet Model 7199 FT spectrometer. ^1H NMR spectra were measured at 300 or 360 MHz on GE QE300 or Nicolet 360WB spectrometers, respectively, and the chemical shifts are reported relative to tetramethylsilane. ^{13}C NMR spectra were measured at 75 MHz on a GE QE300 instrument and were calibrated against the 0.00 ppm line of TMS. High-resolution mass spectra were measured on a VG Analytical ZAB-SE mass spectrometer. Optical rotation measurements were done on a Perkin-Elmer 241 ME polarimeter.

All anhydrous reactions were carried out in oven-dried or flame-dried glassware under dry nitrogen atmosphere. All solvents were purified before use: THF was distilled from sodium benzophenone ketyl; pyridine and CH_2CL_2 were distilled from CaH_2 and stored over activated 3-Å sieves; DMF was distilled from toluene diisocyanate and was stored over activated 3-Å sieves. Column chromatography was performed according to the method described by Still.[23] Analytical and preparative thin-layer chromatography was done on E. Merck plates coated with 0.25 and 1 mm thicknesses of silica gel containing fluorescent indicator.

(19) Jones, G.; Raphael, R. A.; Wright, S. *J. Chem. Soc., Perkin Trans. 1* **1974**, 1676.
(20) Corey, E. J.; Schaaf, T. K.; Huber, W.; Koelliker, U.; Weinshenker, N. M. *J. Am. Chem. Soc.* **1970**, *92*, 397.
(21) (a) Karabatsos, G. J.; Fenglio, D. J. *Topics in Stereochemistry*; Eliel, E. L., Allinger, N. L., Eds.; Wiley-Interscience: New York, 1970; Vol. V. p 167. (b) Cha, J. K.; Christ, W. J.; Kishi, Y. *Tetrahedron* **1984**, *40*, 2247.
(22) Manno and galacto systems give almost exclusive 1,5-cis selectivity as would have been predicted by the most favorable C-3–C-6 conformation and its effect on the transition-state geometry. Likewise 4-deoxy system gives a mixture of 1,5-cis and 1,5-trans products in a ratio of 3.3 to 1.0 (Scheme VI). See ref 7 for a detailed discussion.
(23) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

Scheme VI



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The acidic (AG50W-X8) and basic (AG MP-1) resins used were purchased from Biorad. All reagents were purified prior to use either by recrystallization or distillation unless otherwise mentioned in the particular experiment. The melting points are uncorrected, and yields reported are for chromatographically pure isolated products. In general, the yields were not optimized.

Tetra-*O*-acetyl-3-deoxy-β-D-*ribo*-hexopyranose (10). A solution of 18.30 g (75.00 mmol) of 8[10] in 75 mL of ethanol and 240 mL of water was treated, at reflux, with 38 g of water-washed AG50W-X8 resin for 4 h. The resin was filtered off, and it was further washed with 40 mL of water. Excess water and ethanol were removed on the rotary evaporator and then on a high vacuum pump. The product was freeze-dried over 3 days until a white solid was obtained. By ^{13}C and ^{1}H NMR analyses this product was established to be a complex mixture of various furanose and pyranose isomers of the expected hexose, **9**.[11]

The crude product **9** was dissolved in 105 mL of dry pyridine, and to this cold solution was added 60 mL of acetic anhydride at 0 °C. The mixture was brought to room temperature and was further stirred overnight. The reaction mixture was added to 250 mL of saturated sodium bicarbonate, and the product was extracted into 300 mL of CH_2Cl_2. The combined CH_2Cl_2 layer was washed with ice-cold 3 N HCl, saturated sodium bicarbonate, and saturated sodium chloride (~100 mL each). Drying followed by concentration and recrystallization from 95% ethanol gave 9.0 g (36% from **8**) of **10**: $[\alpha]^{25}_D$ −12.4 ± 0.8° (*c* 1.03, $CHCl_3$) (lit.[11b] $[\alpha]^{25}_D$ −14° (*c*, 1, $CHCl_3$)]; ^{1}H NMR (360 MHz) inter alia δ 5.70 (d, $J_{1,2}$ = 8 Hz, 1 H). Anal. C, H.

Allyl 2,4,6-Tri-*O*-acetyl-3-deoxy-D-*ribo*-hexopyranosides (11a and 11b). A flame-dried single-necked flask fitted with a 15-mL dropping funnel was charged with 7.95 g (23.9 mmol) of **10** in 150 mL of dry CH_2Cl_2. By use of a gas-tight syringe with a Teflon plunger, 2.76 mL (23.9 mmol) of distilled stannic chloride was added to the reaction mixture, and it was stirred for 10 min at room temperature. To the stirred solution was added 1.71 mL (25.14 mmol) of allyl alcohol dissolved in 5 mL of CH_2Cl_2. The entire solution was stirred at room temperature for 2 h. After adding 100 mL of saturated sodium bicarbonate, the organic layer was separated. The aqueous layer was extracted with more CH_2Cl_2 (60 mL × 4), and the combined organic extracts were washed with saturated sodium chloride and water. It was further dried and concentrated. The products were isolated by column chromatography on silica gel with 40 to 50% ethyl acetate/hexane as the solvent. The first fractions gave 5.41 g (68%) of pure α-anomer (**11a**) and the second fractions, 1.46 g (19%), were a mixture of α- and β-anomers (**11a** and **11b**). Careful chromatography of a sample of the mixture yielded pure β-anomer. Typically, the mixtures were carried on for further transformations to **16**. The anomer ratios were ascertained by high-resolution ^{1}H NMR spectra. The anomeric proton in the α-anomer resonates at δ 4.98 (d, *J* = 4 Hz, 1 H) and in the β-anomer at δ 4.53 (d, *J* = 8 Hz, 1 H). **11a**: ^{1}H NMR (360 MHz) δ 1.15–1.35 (m, 2 H), 2.05–2.10 (3 s, 9 H), 3.90–3.60 (ddd, *J* = 8, 5, 2 Hz, 1 H), 4.05–4.30 (m, 4 H), 4.79–4.91 (m, 2 H), 4.98 (d, *J* = 4 Hz, 1 H), 5.23 (ddd, *J* = 10, 2, 2 Hz, 1 H), 5.34 (ddd, *J* = 17, 2, 1 Hz, 2 H), 5.93 (m, 1 H).

Allyl 3-Deoxy-D-*ribo*-hexopyranosides (12a and 12b) from 11a/11b. To a solution of 1.45 g of the triacetate anomers (**11a** and **11b**) in 20 mL of anhydrous methanol was added 0.40 g of methanol-washed AG MP-1 (OH^-) resin and the suspension was stirred for 1 h. An additional 0.20 g of the OH^- resin was added, and the stirring was continued for 30 more min. The resin was then filtered off, and the filter cake was washed with excess methanol. The solvent was removed under vacuum to give 0.90 g (~100%) of the desired allyl glycosides, which were also prepared more directly by the acid-catalyzed reaction of allyl alcohol with **9** as described below. No further purification was attempted before conversion to **13a** and **13b**.

From 9. A 500-mL flask connected to a Dean–Stark water remover was charged with **9** (from 24.40 g of **8**, vide supra), 2.50 g of methanol-washed (and dried) AG50W-X8 resin, 150 mL of allyl alcohol, and 200 mL of benzene. The mixture was refluxed for 2 h with removal of water and was further stirred overnight at room temperature. The resin was filtered off through a pad of anhydrous $MgSO_4$ and Celite. The filter cake was washed with excess ethyl acetate. Column chromatography with 5% methanol/CH_2Cl_2 as a solvent gave a mixture of 14.53 g (66%) of allyl 3-deoxy-D-*ribo*-hexanopyranosides (**12a** and **12b**), which were used without purification for further transformations to **13a** and **13b**.

(*R*)-Allyl 4,6-*O*-(Phenylmethylene)-3-deoxy-D-*ribo*-hexopyranosides (13a and 13b). A mixture of 17.54 g (0.09 mol) of allyl glycosides **12a** and **12b**, obtained directly from **9** and 16.55 mL (0.10 mol) of distilled benzal bromide was dissolved in 320 mL of dry pyridine and refluxed for 90 min. It was subsequently cooled to room temperature and 1 L of ether was added. After the mixture was stirred for 10 min, the precipitated solid was filtered off and the filter cake was washed with excess ether. The filtrate was washed with ice-cold 1 N HCl and then saturated sodium bicarbonate. It was further dried and concentrated. The last traces of pyridine were removed by azeotroping with toluene. Finally column chromatography on silica gel with 20–30% ethyl acetate/hexane gave the desired product as a mixture of α- and β-glycosides (7.70 g, 32% from **8**). The α-glycoside was separated by crystallization from acetone/hexane. The yield of **13a**/**13b** from **10** in three steps (Scheme I) was 47%. **13a**: mp 138–144 °C; IR (KBr) 3450, 3060, 1645, 755, 695 cm^{-1}; ^{1}H NMR (360 MHz) δ 1.90 (ddd, *J* = 12, 12, 12 Hz, H_{3a}, 1 H), 2.06 (d, *J* = 12 Hz, exch D_2O, 1 H), 2.32 (dt, *J* = 12, 5 Hz, H_{3e}, 1 H), 3.55 (ddd, *J* = 12, 8, 4 Hz, 1 H), 3.65–3.90 (m, 3 H), 4.07 (ddm, *J* = 12, 6 Hz, 1 H), 4.27 (m, 2 H), 4.85 (d, *J* = 4 Hz, H_1, 1 H), 5.24 (d, m, *J* = 10 Hz, 1 H), 5.34 (dm, *J* = 17 Hz, 1 H), 5.52 (s, 1 H), 5.90 (m, 1 H), 7.35

(m, 3 H), 7.49 (m, 2 H); HRMS 292.1315 (M^+), calcd for $C_{16}H_{20}O_5$ 292.1311. **13b** (deduced from the NMR of a mixture of **13a** and **13b**): inter alia δ 1.72 (dd, J = 12, 12, 11 Hz, H_{3a}, 1 H), 2.45 (dt, J = 11, 5 Hz, H_{3e}, 1 H), 4.37 (d, J = 8 Hz, H_1, 1 H), 5.52 (s, PhC*H*, 1 H).

Allyl 3-Deoxy-2-*O*-(phenylmethyl)-4,6-*O*-(phenylmethylene)-D-*ribo*-hexopyranosides (14a and 14b). In a flame-dried three-necked flask fitted with a thermocouple adapter, dropping funnel, and nitrogen inlet was dissolved 8.70 g (29.7 mmol) of **13** (mixture of anomers) in 90 mL of DMF. The mixture was cooled to 0 °C, and 3.21 g (133.6 mmol) of mineral oil free sodium hydride in small lots was added. The cold bath was removed, and the reaction mixture was stirred at room temperature for 1 h. The dropping funnel was charged with 21.2 mL of benzyl bromide. The reaction flask was cooled to −10 °C, and the benzyl bromide was added dropwise with good stirring at −10 to 0 °C. The mixture was stirred for 4 h. Sixty milliliters of methanol was slowly added to that the temperature is kept below 25 °C. The solvents were removed on the rotary evaporator and high vacuum pump, and the crude product was redissolved in 600 mL of CH_2Cl_2. The CH_2Cl_2 layer was washed with water (60 mL × 3), dried, and concentrated. Last traces of solvents and excess reagents were removed on a high vacuum pump at 45 °C. Column chromatography on silica gel with 5–10% ethyl acetate/hexane yielded 9.86 g (87%) of the benzyl ether **14** as a mixture of anomers. Small samples of pure anomers **14a** and **14b** were purified by column chromatography on silica gel with ethyl acetate/hexane as the solvent: mp 76–78 °C (α-anomer); $[\alpha]^{25}_D$ +62.6 ± 0.8 °C (*c* 1, MeOH); ^{1}H NMR (360 MHz) δ 2.10 (ddd, J = 12, 12, 12 Hz, 1 H), 2.28 (dt, J = 12, 4 Hz, 1 H), 3.50 (ddd, J = 12, 8, 4 Hz, 1 H), 3.55–3.70 (m, 2 H), 3.83 (m, 1 H), 4.08 (ddt, J = 13, 6, 2 Hz, 1 H), 4.25 (m, 2 H), 4.61 (AB q, J_{AB} = 12 Hz, $\Delta\nu_{AB}$ 21 Hz, 2 H), 4.86 (d, J = 4 Hz, H_1, 1 H), 5.24 (dm, J = 10 Hz, 1 H), 5.37 (dm, J = 17 Hz, 1 H), 5.50 (s, 1 H), 5.97 (m, 1 H, 7.25–7.51 (m, 10 H); HRMS 382.1776 (M^+), calcd for $C_{23}H_{26}O_5$ 382.1780. **14b**: ^{1}H NMR (360 MHz) δ 1.75 (ddd, J = 12, 12, 12 Hz, 1 H), 2.41 (d, t, J = 12, 5 Hz, 1 H) 3.30–3.55 (m, 3 H), 3.72 (t, J = 10 Hz, 1 H), 4.18 (ddm, J = 13, 6 Hz, 1 H), 4.30 (dd, J = 10, 5 Hz, 1 H), 4.41 (ddm, J = 13, 5 Hz, 1 H), 4.52 (d, J = 8 Hz, 1 H), 4.74 (AB q, J_{AB} = 12 Hz, 2 H), 5.22 (dm, J = 10 Hz, 1 H), 5.36(dm, J = 16 Hz, 1 H), 5.49 (s, 1 H), 5.90 (m, 1 H), 7.25–7.50 (m, 10 H); mass spectrum, m/e 382 (M^+).

Attempted Isomerization of the Allyl Ether 14a to 15a Using Wilkinson's Catalyst. To a solution of 0.17 g of **14a** in 3.50 mL of ethanol and 0.50 mL of water was added 0.10 g of Wilkinson's catalyst ($Rh(Cl)(PPh_3)_3$), and the mixture was refluxed for 2 h. Excess ether was added, and the organic layer was washed with saturated sodium chloride, dried, and concentrated. ^{1}H NMR studies (360 MHz) revealed that most of the starting material remained unreacted. Among the minor products obtained was small amounts of the desired enol ether **15a** (<10%) in addition to products tentatively identified as resulting from reduction of the allyl double bond.

(*Z*)- and (*E*)-Prop-1-enyl 3-Deoxy-2-*O*-(phenylmethyl)-4,6-*O*-(phenylmethylene)-D-*ribo*-hexopyranosides (15a and 15b). A mixture of 9.86 g of **14** and 0.20 g of (Ir (Cyclooctadiene) $(Ph_2PMe)_2)^+PF_6^-$[15] in 160 mL of freshly distilled THF was connected to a vacuum pump through a long condenser. The system was partially evacuated until THF barely began to boil over. The system was refilled with nitrogen. A Firestone valve was used for this operation, which was repeated four times. Then the catalyst was activated by attaching a balloon full of hydrogen to the top of the condenser and vigorously stirring the catalyst suspension. The original pink color of the iridium complex disappeared in 2–5 min. The balloon was replaced, and the system was evacuated three more times. In 2 h the starting material was completely consumed as determined by TLC. The solvent was removed on the rotary and then the high vacuum pump, and the crude product consisting of 6:1 mixture of trans to cis isomers (9.90 g, 100%) was used for the next step without further purification. A pure sample of **15a** was isolated by preparative TLC for analysis: IR (KBr) 3090, 3060, 3030, 2990, 2940, 2920, 2880, 1676, 1495, 1100, 750, 695 cm^{-1}; ^{1}H NMR (360 MHz) δ 1.56 (dd, J = 7, 2 Hz), 1.70 (dd, J = 7, 2 Hz) together 3 H, 2.00–2.30 (m, 2 H), 3.40–3.54 (m, 1 H), 3.55–3.70 (m, 2 H), 3.71–3.85 (m, 1 H), 4.22 (dd, J = 10, 5 Hz, 1 H), 4.50–4.70 (m, 2 H), 5.00 (m, 1 H), 5.46 (s), 5.47 (s) together 1 H, 6.08 (dm, J = 7 Hz, 1 H), 6.18 (dm, J = 12 Hz, 1 H), 7.25–7.50 (m, aromatic H); HRMS 382.1775 (M^+), calcd for $C_{23}H_{26}O_5$ 382.1780.

3-Deoxy-2-*O*-(phenylmethyl)-4,6-*O*-(phenylmethylene)-D-*ribo*-hexopyranose (16). Crude **15** obtained by the Ir^+-catalyzed 1,3-H-migration was dissolved in 90 mL of reagent grade acetone and 10 mL of water, and 6.99 g of yellow HgO was added. Separately 7.36 g of mercuric chloride was dissolved in 30 mL of 9:1 acetone/water. To the suspension of **15** and HgO was added the mercuric chloride solution dropwise over 5 min. After 5 min of vigorous stirring, the insoluble mercury salts were filtered off with the aid of Celite, and the filter cake was washed with excess ethyl acetate. The filtrate was evaporated to dryness, and the product was redissolved in 700 mL of ether. The ether solution was washed with half-saturated potassium iodide (~80 mL), water (~80 mL), and saturated sodium chloride (~80 mL). Drying and concentration of the ether layer gave the crude product, which after chromatography on silica gel yielded 8.70 g (98% from **14**) of **16**. An analytical sample was prepared by recrystallization from acetone/hexane: mp 125–129 °C; $[\alpha]^{25}_D$ −19.8 ± 0.8° (*c* 1, MeOH); IR (KBr) 3440, 2990, 2960, 2930, 750, 695 cm^{-1}; ^{1}H NMR (360 MHz) δ 1.70 (ddd, J = 12, 12, 12 Hz), 1.98 (ddd, J = 12, 12, 12 Hz) together 1 H, 2.32 (dt, J = 12, 4 Hz), 2.50 (dt, J = 12, 4 Hz) together 1 H, 2.98 (d, J = 4 Hz), 3.12 (d, J = 5 Hz) together 1 H exch D_2O 3.30–3.80 (m), 4.00 (m), together 4 H, 4.25–4.35 (m, 1 H), 4.58–4.82 (two AB q, J_{AB} = 12 Hz each, 2 H), 4.80 (dd, J = 7, 5 Hz), 5.21 (dd, J = 4, 3 Hz) together 1 H (anomeric H), 5.50 (s, 1 H), 7.25–7.50 (aromatic H); HRMS 252.0959 (M^+, C_7H_7), calcd for $C_{13}H_{16}O_5$ 252.0997. Anal. C, H.

(*Z*)- and (*E*)-2,4-Dideoxy-1-*O*-methyl-3-(phenylmethyl)-5,7-*O*-(phenylmethylene)-D-*ribo*-hept-1-enitol (17a and 17b). A three-necked flask fitted with a dropping funnel, thermocouple lead, and serum stopper was thoroughly flame-dried and was charged with 2.66 g (7.75 mmol) of (methoxymethyl)-triphenylphosphonium chloride (recrystallized from ethyl acetate/chloroform and dried at 100 °C (1 mm)) and 40 mL of anhydrous THF. The mixture was cooled to −20 °C, and from a dropping funnel was added 4.75 mL of 1.6 M *n*-butyllithium in hexane. After all the butyllithium was added, the dropping funnel was washed down with 5 mL of THF. The mixture was stirred at −20 °C to room temperature until all the solid disappeared (~1 h). The benzylidene sugar **16** (1.09 g, 3.09 mmol) dissolved in 8 mL of THF was added to the reaction mixture from the dropping funnel at −20 °C, and the reaction mixture was warmed to room temperature and was further stirred overnight (16 h). The flask was attached to a dry condenser and the mixture was maintained at 50 °C for 15 min. The mixture was cooled to room temperature, and 20 mL of reagent grade acetone was added. After the mixture was stirred for 5 min, 500 mL of ether was added and the precipitated solid was filtered off with the aid of Celite. The Celite pad was washed with 100 mL of ether. The combined ether portion was washed with 80 mL each of saturated sodium bicarbonate, sodium chloride, and water, dried, and concentrated. The product **17** was collected by chromatography on silica gel with 40–50% ethyl acetate/hexane as the solvent. It was dried by azeotropically using toluene. The last traces of the solvent were removed on a high vacuum pump to give 0.987 g (84%) of the desired products **17** as a mixture of *Z* and *E* isomers: ^{1}H NMR (360 MHz) inter alia δ 2.05–2.20 (m, 2 H), 2.62 (s, br, 1 H, exch D_2O), 3.60 s), 3.62 (s) together 3 H, 5.43 (s), 5.45 (s) together 1 H, 6.14 (dd, J = 6, 1 Hz), 6.53 (d, J = 12 Hz) together 1 H. Signals at δ 6.14 and 6.53 arises from =C(*H*)OMe of the *Z* and *E* isomers, respectively. From the intensities of those signals, a ratio of 60:40 was calculated for the *E* vs *Z* isomers.

[(2*R*)-(2α,4aβ,5β,6α,7aβ)]-Hexahydro-5-(methoxymethyl)-2-phenyl-6-(phenylmethoxy)cyclopenta-1,3-dioxin (20). A mixture of 3.72 g (20.8 mmol) of thiocarbonylbis(imidazole) and 6.44 g (17.4 mmol) of the enol ether **17a**/**17b** in 60 mL of 1,2-dichloroethane was refluxed for 3 h under nitrogen. An additional 0.93 g of thiocarbonylimidazole was added, and refluxing was continued for one more hour. A check of TLC (30% ethyl acetate/hexane, silica) indicated complete consumption of the starting material. Fifty milliliters of water and 500 mL of dichloromethane were added, and the mixture was shaken thoroughly for 2 min in a separatory funnel. The organic layer was quickly washed with 100 mL of water, dried ($MgSO_4$), and

concentrated. Filtration through a silica pad with 1:1 ethyl acetate/hexane followed by evaporation of the solvents yielded 6.13 g (74%) of the expected product **18**, which was used for the subsequent reaction.

A solution of 6.13 g (12.8 mmol) of **18**, 5.15 mL (19.1 mmol) of tributyltin hydride and 0.12 g of AIBN in 120 mL of dry toluene was refluxed for 1 h. Additional 0.5 equiv of Bu_3SnH and 60 mg of AIBN were added, and the refluxing was continued for one more hour. The reaction mixture was added to 400 mL of ether, and it was washed with 80 mL each of saturated KF, 1N HCl and saturated sodium bicarbonate. The organic layer was washed with three 50-mL portions of saturated potassium fluoride and dried over anhydrous $MgSO_4$. Concentration and chromatography of the crude mixture yielded 3.59 g (58% from **17**) of the desired product **20**. A more polar fraction (0.129 g, 2% from **17**) was identified as a mixture of compounds, at least one of which was an isomer of **20**, by high-resolution mass spectroscopy. No further characterization of this mixture was undertaken. Varying amounts 5–12% of the starting alcohol **17** was also isolated in some runs. Small samples of **17a** and **17b** were separated by column chromatography, and each was separately subjected to the reductive cyclization. Both isomers gave the same cyclic product **20** in comparable yields. $[\alpha]^{25}_D$ −23.8 ± 0.8°; ^{1}H NMR (360 MHz) δ 1.70 (ddd, J = 12.0, 3.5, 3.0 Hz, 1 H), 1.96 (dd, J = 14.0, 3.5 Hz, 1 H), 2.15 (ddd, J = 14.0, 7.0, 5.0 Hz, 1 H), 2.81 (ddt, J = 12.0, 9.0, 4.0 Hz, 1 H), 3.30 (s, 3 H), 3.54 (d, J = 4.0 Hz, 2 H), 4.00 (ddd, J = 9.0, 7.0, 3.5 Hz, 1 H), 4.16 (AB qd, J_{AB} = 13.0, 2.5 Hz, 2 H), 4.34 (dd, J = 5.0, 3.5 Hz, 1 H), 4.55 (AB q, J_{AB} = 10.0 Hz, 2 H), 5.45 (s, 1 H), 7.25–7.54 (aromatic H); ^{13}C NMR δ 38.21, 39.52, 44.81, 59.01, 66.09, 71.09, 71.42, 78.57, 80.48, 100.71; HRMS 354.1777 (M^+), calcd for $C_{22}H_{26}O_4$ 354.1831.

Preparation of [1*S*-(1α,2α,3β,4α)]-3-(Methoxymethyl)-4-(phenylmethoxy)-2-[(phenylmethoxy)methyl]cyclopentanol (23) and [1*S*-(1α,2β,3α,5α)]-2-(Methoxymethyl)-3,5-bis(phenylmethoxy)cyclopentanemethanol (24). To a solution of 0.074 g (0.2 mmol) of **20** in 1 mL of dry CH_2Cl_2 and 1 mL of dry ether was added 0.025 g (0.66 mmol) of LAH. To the suspension was added 0.035 g (0.3 mmol) of sublimed $AlCl_3$, and the mixture was stirred at room temperature for 1 h. TLC (30% ethyl acetate/hexane) indicate complete disappearance of starting material. A 3:3:1 mixture of sodium sulfate, Celite, and water (~2 g) was added, followed by 20 mL of THF. After the mixture was stirred for 15 min, the solids were filtered off through a bed of Celite and $MgSO_4$, and the filter cake was washed with THF. The products **23** (0.014 g, 19%) and **24** (0.048 g, 65%) were isolated by column chromatography on silica gel with 20–30% ethyl acetate/hexane as the solvent. **23**: ^{1}H NMR (360 MHz) δ 1.85–2.05 (m, 3 H), 2.20 (m, 1 H), 2.80 (d, J = 8 Hz, exch D_2O, 1 H), 3.23 (dd, J = 10, 7 Hz, 1 H), 3.30 (s, 3 H), 3.45 (dd, J = 10, 5 Hz, 1 H), 3.64 (dd, J = 8, 5 Hz, 1 H), 3.81 (dd, J = 8, 7 Hz, 1 H), 3.91 (m, 1 H), 4.28 (m, 1 H), 4.50 (s, 2 H), 4.55 (s, 2 H), 7.25–7.40 (aromatic H). **24**: $[\alpha]^{25}_D$ +5.2 ± 0.8° (*c* 1.00, $CHCl_3$); for ^{1}H NMR and FAB MS see under preparation of an authentic sample of **24**.

[1*S*-(1α,2α,3β,4α)]-1,4-Dimethoxy-2,3-bis(methoxymethyl)cyclopentane (22) from 21. To a solution of 0.017 g (0.1 mmol) of **21** (vide infra) in 2 mL of dry DMF was added 40 mg of mineral oil free sodium hydride. The mixture was stirred for 20 min and cooled to 0 °C. At 0 °C, 0.124 mL of methyl iodide was added, and the reaction mixture was warmed to room temperature and stirred at that temperature for 1 h. Five mL of methanol was added, and the solvents were removed on the rotary and high vacuum pump. The product was redissolved in CH_2Cl_2 and the CH_2Cl_2 layer was washed with water and brine. Drying, concentration and chromatography gave 0.019 g (90%) of the expected tetramethyl ether **22**: ^{1}H NMR (360 MHz) δ 1.85–1.97 (m, 2 H), 1.97–2.10 (m, 2 H), 3.305 (s, 3 H), 3.313 (s, 3 H), 3.333 (s, 3 H), 3.341 (s, 3 H), 3.30–3.40 (m, 1 H), 3.40–3.50 (m, 2 H), 3.60–3.68 (m, 2 H), 3.75 (m, 1 H); ^{13}C NMR δ 35.71, 45.56, 47.86, 57.08, 58.84, 58.91, 71.61, 73.86, 76.08, 77.61, 81.36, 83.38.

[1*R*-(1α,2β,3α,5α)]-2-(Methoxymethyl)-3,5-bis(phenylmethoxy)cyclopentaneacetonitrile (25). To a solution of 0.034 g of **24** in 1 mL of pyridine and 1 mL of methylene chloride was added 0.036 g of *p*-toluenesulfonyl chloride at 0 °C. The reaction mixture was stored in the refrigerator (0 °C) overnight and was added to 10 mL of water. The mixture was extracted with CH_2Cl_2 and washed with 1 N HCl, $NaHCO_3$, and water. The solution was dried and concentrated, and the tosylate was converted into **25** without further purification: ^{1}H NMR (360 MHz) δ 1.90 (m, 2 H), 2.18 (m, 2 H), 2.38 (s, 3 H), 3.26 (s, 3 H), 3.36 (m, 2 H), 3.81 (m, 1 H), 3.95 (m, 1 H), 4.20–4.57 (m, 6 H), 7.18–7.40, 7.75 (aromatic H).

A mixture of the tosylate of **24** (0.052 g) and 0.075 g of NaCN was heated in 1 mL of DMF to 83 °C and maintained at that temperature for 5 h. The solvent was evaporated, and the product was redissolved in CH_2Cl_2. The CH_2Cl_2 solution was washed with saturated sodium bicarbonate and water and then dried. Concentration and column chromatography with acetone/hexane yielded 0.029 g (84% from **24**) of **25**: ^{1}H NMR (360 MHz) δ 1.90–2.25 (m, 4 H), 2.60 (ABX, J_{AB} = 17 Hz, J_{AX} = 8 Hz, J_{BX} = 6 Hz, 2 H), 3.29 (s, 3 H), 3.42 (d ABX, J_{AB} = 10 Hz, J_{AX} = 5 Hz, J_{BX} = 3 Hz, 2 H), 3.81 (m, 1 H), 4.01 (m, 1 H), 4.42 (AB q, J_{AB} = 7 Hz, 2 H), 4.56 (AB q, J_{AB} = 10 Hz, 2 H), 7.20–7.40 (aromatic H); HRMS 365.1970 (M^+), calcd for $C_{23}H_{27}NO_3$ 365.1991.

(3aα,4α,5β,6aα)-(−)-Hexahydro-4-(methoxymethyl)-5-[(4-phenylphenyl)carboxy]-2*H*-cyclopenta[*b*]furan-2-one (28). To a solution of 1.0 g (2.8 mmol) of commercially available (Aldrich) Corey lactone 4-phenylbenzoate ester (**27**) and 0.70 g (1.1 mmol) of methyl iodide in 10 mL of anhydrous DMF was added at 0 °C 0.136 g of mineral oil free sodium hydride. The mixture was stirred for 30 min at 0 °C, and 5 mL of saturated NaH_2PO_4 was added. The entire solution was then added to 80 mL of CH_2Cl_2, and the organic solution was successively washed with saturated sodium bicarbonate, sodium chloride, and water. It was then dried and concentrated. Chromatography on silica gel using 30 to 40% ethyl acetate/hexane gave 0.39 g (36%) of the desired methyl ether **28** identified by its ^{1}H NMR spectrum: ^{1}H NMR (360 MHz) δ 2.35–2.61 (m, 4 H), 2.85–2.97 (m, 2 H), 3.34 (s, 3 H), 3.43 (d, J = 5 Hz, 2 H), 5.10 (t, br, J = 5 Hz, 1 H), 5.39 (ddd, J = 10, 5, 5 Hz, 1 H), 7.30–8.10 (aromatic H).

[1*S*-(1α,2α,3β,4α)]-4-Hydroxy-2-(2-hydroxyethyl)-3-(methoxymethyl)cyclopentanol (29). A solution of 0.387 g (1.063 mmol) of **28** in 10 mL of THF was cooled to 5 °C, and 2 mL of a 1 M solution of LAH in THF was added. The mixture was stirred for 1 h during which time the temperature rose to 25 °C. The reaction was quenched by addition of 4 g of a mixture of 3:3:1 sodium sulfate, Celite, and water. Stirring was continued for 15 min, and the solids were filtered off. The filter cake was washed with THF, and the filtrate was dried with anhydrous $MgSO_4$. Evaporation of the solvent and chromatography on silica gel yielded 0.079 g (40%) of the desired triol **29**: ^{1}H NMR (360 MHz) δ 1.40–2.20 (m, 6 H), 3.00–3.50 (m, 2 H), 3.36 (s, 3 H), 3.40 (ABX, J_{AB} = 18 Hz, J_{AX} = J_{BX} = 8 Hz, 2 H, CH_2OCH$_3$), 3.75 (dm, br, 3 H), 4.08 (s, br, 1 H), 4.32 (s, br, 1 H).

Tritylation of 29. A mixture of 0.299 g (1.570 mmol) of the triol **29**, 0.526 g (1.884 mmol) of trityl chloride, and 0.050 g of 4-(dimethylamino)pyridine in 5 mL pyridine was stirred at room temperature for 4 days. Twenty milliliters of ice-cold water was added, and the product was extracted into CH_2Cl_2. The combined CH_2Cl_2 layers were washed with ice-cold (−5 to 0 °C) 1 N HCl (20 mL × 2) and saturated sodium bicarbonate. Drying, concentration, and chromatography on silica gel using 50 to 100% ethyl acetate/hexane yielded the desired trityl ether, which was carried on to the next step.

Preparation of 30. The trityl ether obtained in the above experiment was dissolved in 10 mL of anhydrous DMF, and 0.220 g (9.166 mmol) of mineral oil free sodium hydride was added. The mixture was cooled to 0 °C, and 0.746 mL (6.280 mmol) of benzyl bromide was added. After the mixture was stirred for 90 min at 0 °C, 10 mL of anhydrous methanol was added and solvents were removed on the rotary evaporator and high vacuum pump. The residue was dissolved in CH_2Cl_2, and the CH_2Cl_2 layer was washed with brine. Concentration and column chromatography on silica gave 0.524 g (54% from **29**) of the bis(benzyl ether) **30**: ^{1}H NMR (300 MHz) δ 1.70–2.20 (m, 6 H), 3.00 (q, m, J = 8 Hz, 1 H), 3.22 (m, 1 H), 3.31 (s, 3 H), 3.41 (ABX, J_{AB} = 10 Hz, J_{AX} = 4 Hz, J_{BX} = 5 Hz, $\Delta\nu_{AB}$ = 41 Hz, 2 H), 3.64 (m, 1 H), 3.90 (m, 1 H), 4.31 (AB q, J_{AB} = 6 Hz, $\Delta\nu_{AB}$ = 91 Hz, 2 H), 4.54 (AB q, J_{AB} = 11 Hz, $\Delta\nu_{AB}$ = 18 Hz, 2 H), 7.20–7.70 (m, aromatic H).

Hydrolysis of the Trityl Ether 30: Preparation of 31. A solution of 0.345 g of the trityl ether **30** in 10 mL of acetic acid and 2 mL of water was stirred overnight at room temperature.

The solvents were evaporated, and the residue was chromatographed on silica gel with 50% ethyl acetate/hexane as the solvent, to give 0.153 g (73%) of the product (**31**), which was used for the next step: ^{1}H NMR (300 MHz) δ 1.70 (m, 1 H), 1.81–2.35 (m, 5 H), 2.41 (t, J = 6 Hz, exch D_2O, 1 H), 3.35 (s, 3 H), 3.46 (ABX, J_{AB} = 10 Hz, J_{AX} = J_{BX} = 5 Hz, 2 H), 3.70 (q, br, J = 6 Hz, 2 H), 3.83 (q, br, 1 H), 3.95 (q, br, 1 H), 4.50 (AB q, J_{AB} = 13 Hz, 2 H), 4.56 (AB q, J_{AB} = 13 Hz, 2 H), 7.20–7.60 (m, aromatic H).

Preparation of Authentic 24 from 31. A solution of 0.15 g (0.41 mmol) of **31** and 0.14 g (0.62 mmol) of (*o*-nitrophenyl)-selenocyanate in 2 mL of dry pyridine was cooled to 0 °C under nitrogen, and from a syringe was added 0.15 mL (0.62 mmol) of tri-*n*-butylphosphine. The cold bath was removed, and the mixture was stirred at room temperature for 90 min. The solvent was removed on the pump, and the product was redissolved in 3 mL of THF. On milliliter of 30% H_2O_2 was added, and the mixture was further stirred for 2 h. The olefin **33** was isolated by column chromatography on silica gel with use of 10% ethyl acetate/hexane as solvent. The olefin was dissolved in 1.5 mL of methanol and 4 mL of CH_2Cl_2 containing 5 mg of solid sodium bicarbonate, and ozone was passed through the solution at −78 °C until a blue color persisted. It was further stirred at −78 °C for 15 min, and then excess ozone was removed from the solution by bubbling argon through the solution. The reduction of the ozonides were carried out by addition of 0.50 mL of dimethyl sulfide at −78 °C followed by storage at 0 °C overnight in the refrigerator. The reaction mixture was cooled to −20 °C, and excess sodium borohydride was added. After warming to 0 °C, the mixture was treated with 5 mL of water. The product was extracted into CH_2Cl_2. Column chromatography on silica gel gave 0.040 g (27% from **31**) of **24**, identical in all respects (IR, ^{1}H NMR, ^{13}C NMR, MS, $[\alpha]^{25}_D$) with a sample prepared by LAH/$AlCl_3$ reductive cleavage of **20**. **24**: $[\alpha]^{25}_D$ +5.8 ± 0.8° (*c* 1, $CHCl_3$); ^{1}H NMR (360 MHz) δ 1.94 (m, 2 H), 2.16 (m, 1 H), 2.40 (m, 1 H), 3.24 (dd, J = 8, 5 Hz, exch D_2O, 1 H), 3.33 (s, 3 H), 3.38 (dd, J = 9, 6 Hz, 1 H), 3.51 (dd, J = 9, 4 Hz, 1 H), 3.74–3.85 (m, 3 H), 4.04 (m, 1 H), 4.49 (AB q, J_{AB} = 12 Hz, $\Delta\nu_{AB}$ = 79 Hz, 2 H), 4.52 (AB q, J_{AB} = 11 Hz, $\Delta\nu_{AB}$ = 33 Hz, 2 H), 7.25–7.35 (aromatic H); FABMS 357.00 (M^+ + H), calcd for $C_{22}H_{29}O_4$ 357.21.

[1*R*-(1α,2β,3α,5α)]-3,5-Diacetoxy-2-(methoxymethyl)-cyclopentaneacetonitrile (36). A solution of 0.560 g of **20** dissolved in 25 mL of 1:1 ethyl acetate/acetic acid containing 50 μL of concentrated HCl was hydrogenated on a Parr shaker with 100 mg of 10% Pd on C at 50 psi until all starting material disappeared. The catalyst was filtered off with the aid of Celite, and the crude triol **21** was used for the subsequent reaction without purification.

A mixture of 0.165 g (0.94 mmol) of the triol **21** and 0.193 g of TosCl (1.01 mmol) in 2 mL of dry CH_2Cl_2 and 2 mL of dry pyridine was stored at 0 to −5 °C for 4 days. Twenty milliliters of saturated sodium bicarbonate was added to the reaction mixture, and the product was extracted into CH_2Cl_2. The combined organic layer was dried and concentrated. The tosylate **34** was dissolved in 1 mL of pyridine and 0.5 mL of acetic anhydride, and 10 mg of 4-(dimethylamino)pyridine was added. After the mixture was stirred for 2 h at room temperature, the low boiling components were pumped off and the product **35** was isolated by column chromatography on silica gel with 40–50% ethyl acetate/hexanes as the solvent in >95% isolated yield: ^{1}H NMR (360 MHz) δ 1.85 (d, br, J = 17.0 Hz, 1 H), 1.91 (s, 3 H), 2.02 (s, 3 H), 2.00–2.40 (m, 3 H), 2.49 (s, 3 H), 3.31 (s, 3 H), 3.46 (m, 2 H), 4.21 (ABX, J_{AB} = 10.1 Hz, J_{AX} = 6.1 Hz, J_{BX} = 9.1 Hz, 2 H), 5.00 (m, br, 1 H), 5.16 (m, br, 1 H), 7.38 (d), 8.00 (d) (aromatic H). The tosylate **35** was directly converted into the nitrile.

A mixture of 0.187 g of **35** and 0.150 g of sodium cyanide was heated in 2 mL of DMF at 85 °C for 5 h under nitrogen. The solvent was removed on the rotary evaporator and high vacuum pump. The product **36** was collected by flash chromatography on silica gel with 40–50% ethyl acetate/hexanes as the solvent: yield 0.101 g (83%); ^{1}H NMR (300 MHz) δ 1.86 (dt, J = 16.0, 2.7 Hz, 1 H), 2.04 (s, 3 H), 2.11 (s, 3 H), 2.20–2.45 (m, 3 H), 2.59 (ABX, J_{AB} = 15.0 Hz, J_{AX} = 5.0 Hz, J_{BX} = 5.5 Hz, 2 H), 3.34 (s, 3 H), 3.52 (ABX, J_{AB} = 9.5 Hz, J_{AX} = 3.0 Hz, J_{BX} = 4.1 Hz, 2 H), 5.00 (m, 1 H), 5.20 (m, 1 H).

(3aα,4α,5β,6aα)-(−)-Hexahydro-5-hydroxy-4-(methoxymethyl)-2*H*-cyclopenta[*b*]furan-2-one (7).[19] To a solution of 0.101 g of the cyanoacetate **36** in 3 mL of anhydrous methanol was added 100 mg of powdered K_2CO_3, and the mixture was stirred at room temperature until all starting material disappeared. To this solution was added 10 mL of 1 N HCl, and the entire mixture was evaporated to dryness. The residue was heated with 1.5 mL of concentrated HCl on a water bath for 2 h. The solvent was evaporated, and the product was extracted into ethyl acetate. The ethyl acetate extract was dried ($MgSO_4$) and concentrated. Column chromatography on silica gel with 5% methanol in CH_2Cl_2 gave 0.024 g (38%) of the desired product (**7**), identical in all respects with a sample prepared from commercially available Corey lactone derivative **27** as described below.

Preparation of Authentic 7. A solution of 0.205 g of azeotropically dried **28** (vide supra) in 3 mL of anhydrous methanol was stirred with 0.078 g of anhydrous K_2CO_3 until all the starting material disappeared, as determined by TLC with 50% ethyl acetate/hexanes. The solvent was removed on the rotary evaporator, and the product was redissolved in 30 mL of CH_2Cl_2. Twenty milliliters of 1 N HCl was added, and the organic layer was separated. The aqueous layer was further extracted with CH_2Cl_2. The CH_2Cl_2 extracts were combined, dried, and concentrated. Chromatography on silica gel with 5% methanol/CH_2Cl_2 hexane as the solvent yielded the expected product, **7**:[24] $[\alpha]^{25}_D$ −24.3 ± 1.1° (*c* 0.7, $CHCl_3$); IR ($CHCl_3$) 1765 cm^{-1}; ^{1}H NMR (360 MHz, chemical shifts and coupling constants established by decoupling and 2D-NOE experiments) δ 2.03 (ddd, J = 15.0, 6.0, 2.7 Hz, 1 H, H_{6exo}), 2.06 (dddd, J = 6.5, 6.5, 6.5, 6.5 Hz, 1 H, H_4), 2.40 (ddd, J = 15.0, 6.5, 6.5 Hz, 1 H, H_{6endo}), 2.52 (dd, J = 18.0, 2.5 Hz, 1 H, H_3), 2.65 (dddd, J = 10.0, 9.7, 6.5, 2.5 Hz, 1 H, H_{3a}), 2.80 (dd, J = 18, 10 Hz, 1 H, H_3), 3.33 (s, 3 H, OCH_3), 3.40 (ABX, J_{AB} = 9.2, J_{AX} = 6.5, J_{BX} = 6.0 Hz, 2 H, CH_2OCH_3), 4.13 (ddd, J = 6.5, 6.5, 6.0 Hz, 1 H, H_5), 4.93 (ddd, J = 9.7, 6.5, 2.7 Hz, 1 H, H_{6a}); $J_{3,3'}$ = 18 Hz, $J_{3,3a}$ = 10 Hz, $J_{3',3a}$ = 2.5 Hz, $J_{3a,4}$ = 6.5 Hz, $J_{3a,6a}$ = 9.7 Hz, $J_{4,HA}$ = 6.8 Hz, $J_{4,HB}$ = 6.5 Hz, $J_{4,5}$ = 6.5 Hz, $J_{5,6exo}$ = 6.0 Hz, $J_{5,6endo}$ = 6.5 Hz, $J_{6exo,6endo}$ = 15 Hz, $J_{6exo,6a}$ = 2.7 Hz, $J_{6endo,6a}$ = 6.5 Hz; ^{13}C NMR δ 35.37, 39.94, 40.61, 53.51, 59.12, 73.57, 75.54, 83.78, 177.08.

(3aα,4α,5β,6aα)-(−)-5-Acetoxyhexahydro-4-(methoxymethyl)-2*H*-cyclopenta[*b*]furan-2-one (37). To a solution of 0.016 g of **7** dissolved in 1 mL of CH_2Cl_2 and 0.5 mL of pyridine was added 0.5 mg of (dimethylamino)pyridine and 33 μL of acetic anhydride at 0 °C. The mixture was stirred for 1 h, and the product was extracted into CH_2Cl_2 after adding excess water. Chromatography on silica gel using 30% ethyl acetate/hexane as the solvent yielded 0.016 g (90%) of acetate **37** identical in all respects (^{1}H NMR, ^{13}C NMR, IR, HRMS, TLC) with the compound reported in the literature: $[\alpha]^{25}_D$ −77.2 ± 1.6° (*c* 0.5, $CHCl_3$) (reported[20] $[\alpha]^{29}_D$ −70.3° (*c* 2.90)).

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(24) For a related compound, see: Collington, E. W.; Wallis, C. J.; Waterhouse, I. *Tetrahedron Lett.* **1983**, *24*, 3125.