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Synthesis of Bis-γ-Butyrolactones Containing Conformationally Constrained (*S*)- and (*R*)-Diacylglycerol Structures

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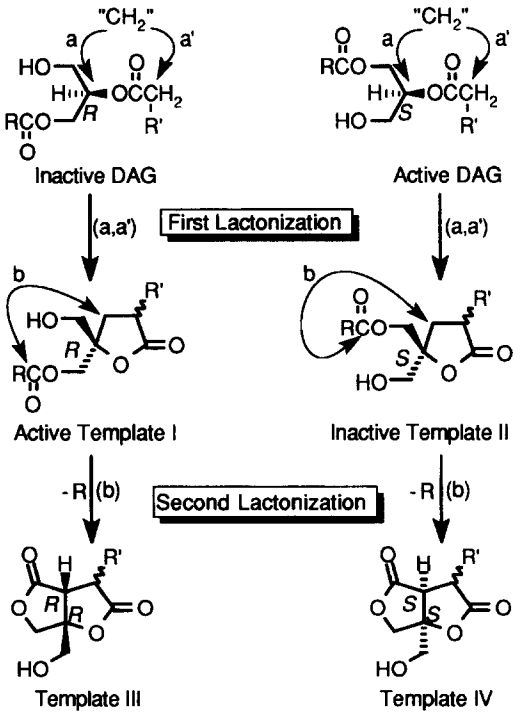
Abstract—The synthesis of two sets of rigid diacylglycerol (DAG) analogues with either the (*S*)-DAG or (*R*)-DAG enantiomer embedded into a bis-γ-butyrolactone template was accomplished stereoselectively from di-*O*-isopropylidene-α-D-apiose. The key step in both syntheses was the assemblage of the bicyclic perhydrofuro[3,4-*b*]furan ring system via a radical *exo-dig* intramolecular cyclization. A lipophilic undecanyl alkyl chain attached at C-3 of the fully assembled perhydrofuro[3,4-*b*]furan-2,4-dione (bis-γ-butyrolactone) template can adopt two orientations with the one directed away from the concave face of the bicyclic system favored by a 4 to 1 ratio in each case. Evaluation of the final target pairs of enantiomers as PK-Cα ligands revealed that the template containing an embedded (*R*)-DAG structure was more effective. The difference in binding affinity was also modulated by the direction of the alkyl chain. Published by Elsevier Science Ltd

Introduction

The basal activity of protein kinase C (PK-C) is stimulated by the release of diacylglycerol (DAG), a product of hydrolysis of membrane-resident phosphatidylinositol 4,5-diphosphate.[1] The binding of DAG to the regulatory domain of PK-C is stereospecific with only the (*S*)-enantiomer functioning as an effective ligand and stimulator of the enzyme.[2] In contrast, enantiomeric 4,4-disubstituted-γ-lactones,[3,4] which contain an embedded DAG structure, showed a stereochemical reversal in their preference for the enzyme relative to DAG. Hence, lactones constructed with an embedded (*R*)-DAG enantiomeric structure (Active Template I, Scheme 1) functioned as extremely potent PK-C ligands, whereas those containing the (*S*)-DAG enantiomer (Inactive Template II, Scheme 1) were ineffective. An explanation of this phenomenon was found after comparing the energies (enthalpy) of each enantiomer of DAG and γ-lactone in their optimal fit to a hypothetical pharmacophore receptor model.[4,5]

Separately, we have also attempted to place additional restrictions on some DAG-embedded lactones by extending the glycerol backbone (Second Lactonization, Scheme 1) into two fused γ-lactone rings.[6-9] Before this change in stereochemical preference between DAG and lactone was known, the first compounds made with the bis-γ-lactone template were designed to contain an embedded (*S*)-DAG structure [(*S,S*)-Template IV, Scheme 1].[6] In light of the new findings mentioned above, we set out to prepare the optical antipode of this template which contains, instead, an embedded (*R*)-DAG structure [(*R,R*)-Template III, Scheme 1]. The present work describes a detailed synthesis of the first set of (*S*)-DAG-containing bis-γ-lactones, which was already communicated in brief,[6] and the synthesis of a new set of (*R*)-DAG-containing bis-γ-lactones. The determination of PK-C binding affinities with PK-Cα confirmed that for these restricted bis-γ-lactones, the template containing an embedded (*R*)-DAG structure was also the more effective template.



Scheme 1.

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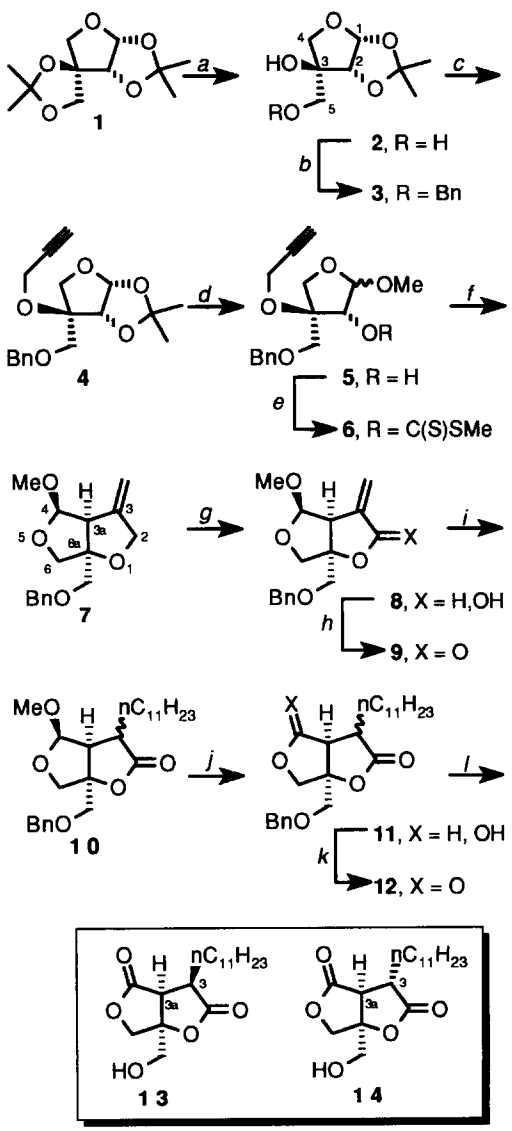
Results

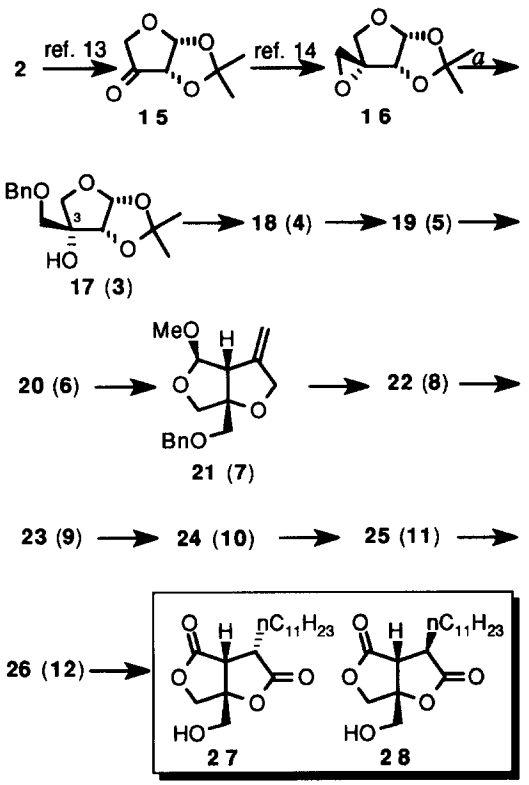
1,2:3,5-di-*O*-isopropylidene-α-D-*threo*-apiofuranose[10] was hydrolysed under mild conditions to remove selectively the 3,5-*O*-isopropylidene group (Scheme 2). Selective monobenzylation of the primary alcohol in **2** via the 3,5-*O*-(dibutylstannylene)-intermediate gave 1,2-*O*-isopropylidene-3-*C*-[(benzyloxy)methyl]-α-D-*threo*-furanose (**3**) in quantitative yield, and alkylation of the free hydroxyl group in **3** with propargyl bromide provided the propargyl ether **4** in excellent yield. Methanolysis of this compound produced an equal mixture of anomeric methyl glycosides (**5**) which were converted to the xanthate ester **6**. An ensuing *exo-dig* intramolecular radical cyclization provided the key bicyclic intermediate **7** in modest yield (40%). When this reaction was performed separately with each diastereoisomer, the results indicated that the α-anomer reacted poorly, while the β-anomer gave a comparable yield to that of the mixture (ca. 48%). It is of interest to note that upon cyclization to **7**, only a single anomer at C-4 was observed. Although the stereochemistry at this site is of no relevance to the outcome of the synthesis, we have tentatively assigned the β-stereochemistry to this center based on the value of the coupling constant of the anomeric hydrogen ($J_{3a,4}=5.8$ Hz) to the bridgehead proton. Several oxidation methods were tried to obtain **9**. Under refluxing conditions, pyridinium chlorochromate (PCC) produced extensive decomposition, while Collins reagent over-oxidized the substrate giving a mixture of **9** and a product with an extra carbonyl function at C-6 that was difficult to separate. The problem was solved by performing the oxidation in two stages: first, conversion of **7** to the lactol **8** through the action of SeO_2, and then oxidation to the lactone stage (**9**) by MnO_2. The introduction of the long alkyl chain was performed via a copper-catalysed 1,4-addition of $C_{10}H_{21}Mg$ Br which, as expected, generated a mixture of diastereoisomers. ^1H NMR analysis revealed that **10** was a 4:1 mixture in favor of the C-3 α-isomer, but separation was postponed until the end of the synthesis for fear of isomerization during the subsequent steps. Hydrolysis of the acetal function in **10** and oxidation of the intermediate lactol **11** with PDC gave the penultimate intermediate **12**. Removal of the benzyl protection by catalytic hydrogenation gave a 4:1 mixture of **14**/**13** which was then separated by silica gel column chromatography. The 4:1 ratio in favor of the C-3α-isomer remained unchanged from the time when side chain was introduced (compound **10**) suggesting that this bulky substituent prefers to be away from the concave face of this fused bicyclic system. The characteristic $J_{3,3a}$ couplings of 10.3 and 3.3 Hz, respectively for compounds **13** and **14**, helped corroborate the assignments.

Syntheses of the optical antipodes of **13** (**27**) and **14** (**28**) were performed from intermediate **17** in essentially the same manner as described in Scheme 2. The required inversion at C-3 in 1,2-*O*-isopropylidene-3-*C*-[(benzyloxy)methyl]-α-D-*threo*-furanose (**3**, Scheme 2) to the diastereoisomeric 1,2-*O*-isopropylidene-3-*C*-[(benzyloxy)methyl]-α-D-*erythro*-furanose (**17**, Scheme 3) was accomplished via the corresponding 3-ulose **15** obtained from 1,2-isopropylidene-α-D-apio-L-furanose (**2**). Stereoselective formation of the C-3 oxirane **16**, followed by ring opening with sodium benzylate gave the desired intermediate **17**. From this point onward, compounds **18**–**20** in Scheme 3 correspond to the structures shown in parentheses from Scheme 2, except for the inversion of stereochemistry at C-3. Compounds **21** through the final targets **27** and **28**, correspond to those from Scheme 2 (in parentheses) having the opposite *R,R*-ring fusion. As expected, the [α] values for **27** and **28** were equal in value, but opposite in sign, to the corresponding enantiomers **13** and **14** (Table 1).

The affinities of these ligands for PK-C were assessed in terms of their ability to displace bound [^{3}H-20]-

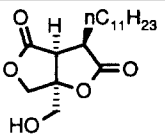
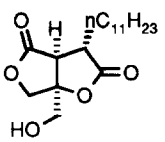
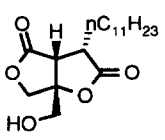
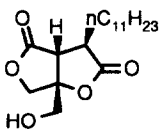


Scheme 2. Reagents and conditions: a. ref 13. b. $(Bu_3Sn)_2O$/BnBr (99%). c. Propargyl bromide/NaH (95%). d. MeOH/H^+ (92%). e. CS_2, NaH/MeI (93%). f. Bu_3SnH/AIBN (40%). g. SeO_2 (72%). h. MnO_2 (100%). i. $C_{10}H_{21}MgBr$/CuCl (70%). j. H^+/THF/H_2O (85%). k. PDC (81%). l. H_2/Pd/C (95%).



Scheme 3. Reagents and conditions: a. ref 13. b. ref 14. c. $PhCH_2OH/NaH$ (96%). Compounds **18–20** correspond to structures shown in Scheme 2 (parentheses) with opposite stereochemistry at C-3. Compounds **21–28** correspond to structures shown in Scheme 2 (parentheses) with opposite *R,R*-ring fusion. Yields and conditions are similar to those in Scheme 2.

Table 1. Apparent K_i values for ligands as inhibitors of PDBU binding to PK-Cα

Compound	Structure	$[\alpha]_D$	K_i (μM)
13		+20.0°	30.70 ± 7.4
14		+24.8°	81.60 ± 4.06
27		−21.7°	7.70 ± 0.51
28		−25.0°	15.83 ± 2.35

phorbol-12,13-dibutyrate (PDBU) from a recombinant single isozyme PK-Cα (Table 1). The ID_{50} values were determined by fit of the data points to the theoretical non-cooperative competition curve.[11] The K_i's for inhibition of binding were calculated from the ID_{50} values. A comparison between the two types of templates indicated that bis-γ-lactones containing an embedded (*R*)-DAG (compounds **27** and **28**) are more effective PK-C ligands than those containing the opposite (*S*)-DAG enantiomer (compounds **13** and **14**). Additionally, the results from this assay support the concept that the orientation of the side chain of the ligand is important. Indeed, in both groups a different alkyl chain orientation corresponded to a 2.1–2.6-fold difference in binding affinity.

Experimental

General

All chemical reagents were commercially available. Melting points were determined on a Mel-Temp II apparatus (Laboratory Devices, U.S.A.) and are uncorrected. Silica gel column chromatography was performed on silica gel 60 (E. Merck, 230–400 mesh). IR, specific rotations, and $^1H/^{13}C$ NMR spectra were recorded in standard laboratory instruments. Positive-ion fast-atom bombardment mass spectra (FABMS) were obtained by using samples dissolved in a glycerol matrix, and ionization was effected by a beam of xenon atoms derived by neutralizing xenon ions accelerated through 8.6 kV. Elemental analyses were performed by Atlantic Microlab Inc. (Atlanta, GA).

Analysis of inhibition of [^{3}H]PDBU binding by non-radioactive ligands

Enzyme–ligand interactions were analysed by competition with [^{3}H]PDBU binding essentially as described in our previous work,[11] except that the PK-C preparation used here was the single isozyme PK-Cα. This recombinant PK-Cα was expressed in the baculovirus system and was isolated as described in ref 12. The ID_{50} values were determined from the competition curves, and the corresponding K_i values for the ligands were calculated from the ID_{50} values as described before.[11,12] Values represent the mean ± standard error (three determinations).

1,2-*O*-isopropylidene-α-D-apio-L-furanose (2). This compound was prepared from di-*O*-isopropylidene-α-D-apiose (Pfanstiehl Laboratories, Inc.) by the literature procedure of Carey et al.[13]

1,2-*O*-Isopropylidene-3-*C*-[(benzyloxy)methyl]-α-D-*threo*-furanose (3). A soln of the diol **2** (3.8 g, 20 mmol) and $(Bu_3Sn)_2O$ (7.6 mL, 15 mmol) in toluene (300 mL) was refluxed for 4 h in a flask connected to a Dean–Stark trap. The temperature was lowered to 80 °C, and the 3,5-*O*-(dibutylstannylene) intermediate formed was treated with benzyl bromide (4.8 mL, 40 mmol) and

tetra-*n*-butylammonium bromide (3.2 g, 10 mmol). After 16 h, the mixture was allowed to reach room temperature, it was diluted with Et_2O (400 mL), and the organic layer was washed with 10% $NaHCO_3$, brine, and dried ($MgSO_4$). The residue obtained after evapn of the solvent was purified by flash column chromatography with EtOAc:hexane (1:1) as eluant to give **3** (5.54 g, 99%) as a white solid: mp 61–62 °C; $[\alpha]_D$ +33.47° (*c* 3.57; $CHCl_3$); IR ν^{KBr} cm^{-1}: 3450; ^1H NMR ($CDCl_3$): δ 7.25–7.40 (m, 5H), 5.97 (d, 1H, *J*=3.6 Hz), 4.63 (d, 1H, *J*=11.9 Hz), 4.57 (d, 1H, *J*=11.9 Hz), 4.35 (d, 1H, *J*=3.6 Hz), 3.84 (m, 2 H), 3.79 (d, 1H, *J*=9.4 Hz), 3.53 (d, 1H, *J*=9.4 Hz), 2.77 (s, 1H), 1.47 (s, 3H), 1.31 (s, 3Hs); ^{13}C NMR: δ 137.69, 128.43, 127.79, 112.33, 106.22, 84.26, 81.35, 73.77, 73.63, 69.78, 27.03, 26.46; Anal. calcd for $C_{15}H_{20}O_5$: C, 64.27; H, 7.19. Found: C, 64.32; H, 7.21.

1,2-*O*-Isopropylidene-3-*O*-propargyl-3-*C*-[(benzyloxy)-methyl]-α-D-*threo*-furanose (4). A stirred soln of **3** (4.20 g, 15 mmol) in DMF (75 mL) was treated with NaH (60% in mineral oil, 1.2 g, 30 mmol) at room temperature for 15 min. Propargyl bromide (80% in toluene, 3.34 mL, 30 mmol) was added and after 16 h the reaction mixture was diluted with ether (300 mL), washed with satd NH_4Cl soln and H_2O. The organic layer was dried ($MgSO_4$), concd, and the residue was purified by flash column chromatography with EtOAc:hexane (1:5) as eluant to give **4** (4.53 g, 95%) as a yellow syrup: $[\alpha]_D$ +39.62° (c 2.13, $CHCl_3$); IR ν^{neat} cm^{-1}: 3283, 2125; ^1H NMR ($CDCl_3$): δ 7.25–7.35 (m, 5H), 5.95 (d, 1H, *J*=3.6 Hz), 4.57 (d, 1H, *J*=12.0 Hz), 4.52 (d, 1H, *J*=12.0 Hz), 4.41 (d, 1H, *J*=3.6 Hz), 4.33 (ddd, 2H, *J*=15.3, 2.4, 2.4 Hz), 4.16 (d, 1H, *J*=10.7 Hz), 3.73–3.88 (m, 3H), 2.42 (t, 1H, *J*=2.4 Hz), 1.46 (s, 3H), 1.30 (s, 3H); ^{13}C NMR: δ 137.76, 128.35, 127.66, 112.22, 106.13, 87.25, 83.11, 80.52, 74.10, 73.50, 69.69, 69.02, 52.90, 26.92, 26.39. Anal. calcd for $C_{18}H_{22}O_5$: C, 67.90; H, 6.97. Found: C, 67.84; H, 6.92.

Methyl 3-*O*-propargyl-3-*C*-[(benzyloxy)methyl]-2-*O*-[(*S*-methylthio)thio-carbonyl]-α,β-D-*threo*-furanose (6). A soln of **4** (3.18 g, 10 mmol) in MeOH (100 mL) was treated with Dowex H^+-resin (4 g, prewashed with MeOH before use) and refluxed for 3 h. The mixture was cooled, filtered and washed with MeOH. The filtrate was concd under vacuum to give **5** (anomeric mixture) as a white solid which was used immediately for the following step. Thus, a solution of **5** in THF (60 mL) was treated with NaH (60%, 0.8 g, 20 mmol) at 0 °C, and stirred for 30 min at room temperature. The mixture was cooled to 0 °C, treated with CS_2 (6 mL, 100 mmol), and stirred for 2 h more. Iodomethane (5 mL, 80 mmol) was added to the mixture and stirred for 30 min. The mixture was diluted with ether (200 mL) and washed successively with a satd NH_4Cl solution and brine. The ether layer was dried ($MgSO_4$) and concentrated. The residue was purified by flash column chromatography with EtOAc:hexane (1:5) as eluant to give both anomers of **6** as yellow oils (3.3 g, 86% combined yield from **4**).

α-Anomer (first fraction). $[\alpha]_D$ +91.82° (*c* 1.76; $CHCl_3$); IR ν^{neat} cm^{-1}: 3286, 2118, 1496, 1453, 1365; ^1H NMR ($CDCl_3$): δ 7.25–7.35 (m, 5H), 5.79 (d, 1H, *J*=4.5 Hz), 5.31 (d, 1H, *J*=4.5 Hz), 4.61 (d, 1H, *J*=12.0 Hz), 4.55 (d, 1H, *J*=12.0 Hz), 4.22 (d, 2 H, *J*=2.35 Hz), 4.15 (d, 1H, *J*=10.3 Hz), 4.04 (d, 1H, *J*=10.3 Hz), 3.89 (d, 1H, *J*=11.0 Hz), 3.78 (d, 1H, *J*=11.0 Hz), 3.30 (s, 3H), 2.53 (s, 3H), 2.39 (t, 1H, *J*=2.5 Hz); ^{13}C NMR ($CDCl_3$): δ 214.52, 137.68, 128.33, 127.71, 127.67, 101.24, 85.62, 84.82, 79.96, 74.11, 73.61, 72.13, 69.49, 55.36, 52.85, 19.21. Anal. calcd for $C_{18}H_{22}O_5S_2$: C, 56.37; H, 5.78; S, 16.72. Found: C, 56.60; H, 5.85; S, 16.67.

β-Anomer (second fraction). $[\alpha]_D$ −59.86° (*c* 1.45; $CHCl_3$); IR ν^{neat} cm^{-1}: 3287, 2118, 1496, 1453, 1362; ^1H NMR ($CDCl_3$): δ 7.25–7.35 (m, 5 H), 6.07 (s, 1H), 4.88 (s, 1H), 4.60 (d, 1H, *J*=12.0 Hz), 4.53 (d, 1H, *J*=12.0 Hz), 4.31 (d, 2H, *J*=2.45 Hz), 4.19 (d, 1H, *J*=9.6 Hz), 4.03 (dd, 1H, *J*=9.6, 1.2 Hz), 3.77 (dd, 1H, *J*=11.0, 4 Hz), 3.66 (d, 1H, *J*=11.0 Hz), 3.37 (s, 3H), 2.51 (s, 3H), 2.39 (t, 1H, *J*=2.4 Hz); ^{13}C NMR ($CDCl_3$): δ 214.24, 137.43, 128.26, 127.66, 127.59, 107.64, 88.64, 86.23, 79.87, 74.39, 73.52, 72.83, 68.09, 54.89, 53.55, 19.17. Anal. calcd for $C_{18}H_{22}O_5S_2$: C, 56.37; H, 5.78; S, 16.72. Found: C, 56.60; H, 5.85; S, 16.67.

[3a*S*,4*R*,6a*S*]-3-Methylidene-4-methoxy-6a-[(benzyl-oxy)methyl]perhydrofuro-[3,4-*b*]furan (7). A soln of **6** (3.07 g, 8.0 mmol) and azobis(isobutyronitrile) (AIBN, 0.26 g, 1.6 mmol) in toluene (80 mL) was heated to 80 °C and treated with *n*-Bu_3SnH (2.58 mL, 9.6 mmol). After 1 h, the mixture was concd and the residue was purified by flash column chromatography with EtOAc:hexane (1:5) as eluant to give **7** as a clear oil (0.884 g, 40%): $[\alpha]_D$ −95.07° (*c* 3.00; $CHCl_3$); IR ν^{neat} cm^{-1}: 1671, 1496, 1453, 1362, 1315, 1287; ^1H NMR ($CDCl_3$): δ 7.25–7.40 (m, 5 H), 4.90–5.10 (m, 2H), 5.01 (d, 1H, *J*=5.8 Hz), 4.50–4.65 (m, 3H), 4.41 (dt, 1H, *J*=12.2, 1.8 Hz), 3.95 (br s, 2H), 3.51 (d, 1H, *J*=9.7 Hz), 3.46 (d, 1H, *J*=9.7 Hz), 3.38 (s, 3H), 3.21 (m, 1H); ^{13}C NMR ($CDCl_3$): δ 145.72, 138.06, 128.39, 127.66, 127.57, 107.44, 105.93, 93.23, 74.44, 73.50, 73.16, 72.27, 56.43, 55.35. Anal. calcd for $C_{16}H_{20}O_4$: C, 69.54; H, 7.30; Found: C, 69.28; H, 7.23.

[3a*S*,4*R*,6a*S*]-3-Methylidene-4-methoxy-6a-[(benzyl-oxy)methyl]perhydrofuro-[3,4-*b*]furan-2-one (9). A soln of **7** (0.829 g, 3.0 mmol) in dioxane (30 mL) was treated with SeO_2 (0.4 g, 3.6 mmol) and refluxed for 30 min. The mixture was filtered, diluted with CH_2Cl_2 (150 mL), washed with water, dried (Na_2SO_4), and concd. The residue was purified by flash column chromatography with EtOAc:hexane (1:2) as eluant to give an isomeric mixture of **8** as a clear oil. This compound was dissolved in CH_2Cl_2 (30 mL) and stirred with MnO_2 (5.22 g, 60 mmol) for 2 h at room temperature. The mixture was filtered and concd, and the residue was purified by flash column chromatography with EtOAc:hexane (1:2) as eluant to give **9** (0.627 g, 72% from **7**) as a clear oil: $[\alpha]_D$ −12.92° (*c* 1.00; $CHCl_3$); IR ν^{neat} cm^{-1}: 1769, 1664, 1453, 1364, 1283; ^1H NMR

($CDCl_3$): δ 7.25–7.40 (m, 5H), 6.31 (d, 1H, J=1.8 Hz), 5.63 (d, 1H, J=1.6 Hz), 5.09 (d, 1H, J=5.4 Hz), 4.58 (d, 1H, J=12.2 Hz), 4.51 (d, 1H, J=12.2 Hz), 4.03 (d, 1H, J=10.2 Hz), 3.96 (d, 1H, J=10.2 Hz), 3.64 (d, 1H, J=10.3 Hz), 3.52 (d, 1H, J=10.3 Hz), 3.44 (dt, 1H, J=5.4, 1.8 Hz), 3.32 (s, 3 H); ^{13}C NMR ($CDCl_3$): δ 169.67, 137.25, 133.54, 128.46, 127.86, 127.50, 123.52, 104.77, 89.80, 73.56, 71.83, 71.76, 55.08, 51.31. Anal. calcd for $C_{16}H_{18}O_5$: C, 66.19; H, 6.25; Found: C, 66.02; H, 6.28.

[3*S*,3a*S*,6a*S*]-3-Undecanyl-6a-(hydroxymethyl)perhydrofuro[3,4-*b*]furan-2,4-dione (14) and [3*R*,3a*S*,6a*S*]-3-undecanyl-6a-(hydroxymethyl)perhydrofuro-[3,4-*b*]furan-2,4-dione (13). A flask containing ether (18 mL) was cooled to −40 °C. After the temperature of the solution reached −40 °C, 6 mL of a 1 M ether soln of decylmagnesium bromide and CuCl (0.02 g, 0.2 mmol) was added. After stirring for 5 min, a solution of **9** (0.58 g, 2.0 mmol) in ether (10 mL) was slowly added during the course of 1 h. The mixture was quenched with aq satd NH_4Cl (5 mL) and diluted with ether (100 mL). The ether layer was washed with water, dried ($MgSO_4$), and concd. The residue obtained was purified by flash column chromatography over silica gel with EtOAc:hexane (1:4) to give **10** (0.606 g, 70%) of an oily mixture of diastereosiomers.

A soln of **10** (0.52 g, 1.2 mmol) was dissolved in a (1:1:1) mixture of AcOH:H_2O:THF (30 mL), treated with concd HCl (0.8 mL) and maintained at 80 °C for 18 h. The mixture was cooled, neutralized with solid $NaHCO_3$ and extracted with ether. The organic layer was washed with water and brine, dried ($MgSO_4$), and concentrated. The residue was purified by flash column chromatography over silica gel with EtOAc:hexane (1:3) as eluant to give **11** as a mixture of hemiacetals. This mixture was immediately dissolved in CH_2Cl_2 (20 mL) and treated with pyridinium dichromate (PDC, 1.35 g, 3.6 mmol), 4 Å molecular sieves (ca. 1 g) and AcOH (0.12 mL, 2.16 mmol). After stirring for 2 h at room temperature, the mixture was diluted with ether (100 mL), treated with Celite and stirred for 30 min more. The mixture was then filtered through a short pad of silical gel and the filtrate was concd. The residue obtained was purified by flash column chromatography over silica gel with EtOAc:hexane (1:3) as eluant to give **12** (0.405 g, 81%) as an oily mixture of diastereoisomers. A soln of **12** (0.4 g, 0.96 mmol) in MeOH (20 mL) was treated with 10% palladium (0.4 g) on charcoal and AcOH (2 drops), and hydrogenated under a balloon of hydrogen for 6 h. The mixture was filtered and concd. The residue was purified by flash column chromatography with EtOAc:hexane (1:1) as eluant to give **14** (0.238 g, 76%) and **13** (0.06 g, 19%), respectively, as white solids.

Compound 14. Mp 95–95.5 °C; $[\alpha]_D$ +24.8° (*c* 1.6; $CHCl_3$); IR ν^{KBr} cm^{-1}: 3427, 1782, 1750; ^{1}H NMR ($CDCl_3$): δ 4.49 (d, 1H, J=11.2 Hz), 4.39 (d, 1H, J=11.2 Hz), 3.91 (br d, 1H, J=11.0 Hz), 3.79 (br d, 1H, J=11.0 Hz), 3.12 (d, 1H, J=3.3 Hz), 2.89 (m, 1H), 2.70 (br s, 1H), 1.20–2.05 (m, 20 H), 0.88 (t, 3H); ^{13}C NMR ($CDCl_3$): δ 176.6 (s), 175.7 (s), 88.4 (s), 73.1 (t), 63.9 (t), 46.9 (d), 44.8 (d), 31.9 (t), 31.6 (t), 29.6 (t), 29.5 (t), 29.4 (t), 28.9 (t), 27.4 (t), 22.7 (t), 14.1 (q); FABMS *m/z* (relative intensity) 327 (MH^+, 100). Anal. calcd for $C_{18}H_{30}O_5$: C, 66.23; H, 9.26; Found: C, 66.13; H, 9.22.

Compound 13. Mp 65–65.5 °C; $[\alpha]_D$ +20.0° (*c* 0.45; $CHCl_3$); IR ν^{KBr} cm^{-1}: 3448, 1794, 1747; ^{1}H NMR ($CDCl_3$): δ 4.47 (d, 1H, J=11.1 Hz), 4.29 (d, 1H, J=11.1 Hz), 3.95 (d, 1H, J=12.0 Hz), 3.84 (d, 1H, J=12.0 Hz), 3.42 (d, 1H, J=10.3 Hz), 3.11 (m, 1H), 2.18 (br s, 1H), 1.20–1.90 (m, 20 H), 0.88 (t, 3H); ^{13}C NMR ($CDCl_3$): δ 175.9 (s), 172.2 (s), 87.8 (s), 71.5 (t), 63.6 (t), 44.5 (d), 42.6 (d), 31.9 (t), 29.6 (t), 29.5 (t), 29.4 (t), 29.3 (t), 28.1 (t), 26.2 (t), 22.7 (t), 14.1 (q); FABMS *m/z* (relative intensity) 327 (MH^+, 100). Anal. calcd for $C_{18}H_{30}O_5$: C, 66.23; H, 9.26; Found: C, 66.53; H, 9.13.

1,2-*O*-Isopropylidene-D-*glycero*-tetros-3-ulose (15). This compound was prepd from **2** by the literature procedure of Carey et al.[13]

1,2-*O*-isopropylidene-3,5-anhydro-α-D-apio-D-furanose (16). This compound was prepared from **15** by the literature procedure of Ezekiel et al.[14]

1,2-*O*-Isopropylidene-3-*C*-[(benzyloxy)methyl]-α-D-*erythro*-furanose (17). A soln of benzyl alcohol (6.2 mL, 60 mmol) in THF (150 mL) was treated with NaH (2.4 g, 60% dispersion, 60 mmol) at 0 °C and stirred for 1 h at room temperature. The mixture was treated with **16** (3.44 g, 20 mmol) in THF (20 mL) and refluxed for 4 h. The reaction mixture was concd to a small vol, diluted with ether, washed with H_2O and brine, dried ($MgSO_4$), and concd. The residue was purified by flash column chromatography with EtOAc:hexane (1:2) as eluant to give **17** (5.38 g, 96%), which was crystallized from hexane as white needles: mp 71–72 °C; $[\alpha]_D$ +24.5° (*c* 1.0; $CHCl_3$); IR ν^{KBr} cm^{-1}: 3464; ^{1}H NMR ($CDCl_3$): δ 7.25–7.40 (m, 5H), 5.75 (d, 1H, J=3.9 Hz), 4.65 (d, 1H, J= 12.1 Hz), 4.57 (d, 1H, J=12.1 Hz), 4.37 (d, 1H, J=3.9 Hz), 3.79 (d, 1H, J=9.1 Hz), 3.69 (d, 1H, J=9.1 Hz), 3.55 (d, 1H, J=10.3 Hz), 3.44 (d, 1H, J=10.3 Hz), 2.83 (s, 1H), 1.57 (s, 3H), 1.35 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 137.68, 128.44, 127.81, 127.73, 112.60, 105.41, 79.38, 78.77, 73.77, 71.64, 71.52, 26.59. Anal. calcd for $C_{15}H_{20}O_5$: C, 64.27; H, 7.19. Found C, 64.25; 7.20.

1,2-*O*-Isopropylidene-3-*O*-propargyl-3-*C*-[(benzyloxy)-methyl]-α-D-*erythro*-furanose (18). This compound was prepared from **17** by the same procedure described above for the preparation of **4**. It was obtained in 88% yield as a white solid: mp =84–85 °C; $[\alpha]_D$ +72.2° (*c* 1.0; $CHCl_3$); IR ν^{KBr} cm^{-1}: 3282, 2125; ^{1}H NMR ($CDCl_3$): δ 7.25–7.35 (m, 5H), 5.67 (d, 1H, J=3.8 Hz), 4.60 (d, 1H, J=11.9 Hz), 4.51 (d, 1H, J=11.9 Hz), 4.50

(d, 1H, J=3.8 Hz), 4.40 (AB, 2H, J=2.6 Hz), 3.93 (d, 1H, J= 8.6 Hz), 3.81 (d, 1H, J=8.6 Hz), 3.64 (d, 1H, J= 10.9 Hz), 3.56 (d, 1H, J=10.9 Hz), 2.41 (t, 1H, J=2.3Hz), 1.57 (s, 3H), 1.32 (s, 3H); ^{13}C NMR: δ 137.48, 128.47, 127.90, 127.71, 112.90, 105.41, 84.02, 80.73, 78.89, 73.90, 73.61, 70.68, 70.10, 54.49, 26.72, 26.63. Anal. calcd for $C_{18}H_{22}O_5$: C, 67.90; H, 6.97. Found: C, 68.00; H, 6.95

Methyl 3-*O*-propargyl-3-*C*-[(benzyloxy)methyl]-2-*O*-[(*S*-methylthio)thiocarbonyl-α,β-D-*erythro*-furanose (20). This compound was prepared from **18** by the same procedure described above for the preparation of **6**. It was obtained in 85% yield as an oily mixture of anomers which was separated by flash column chromatography with EtOAc:hexane (1:5) as eluant.

β-Anomer. $[\alpha]_D$ −52.32° (*c* 2.24; $CHCl_3$); IR ν^{neat} cm^{-1}: 3286, 2120, 1496, 1453, 1363; ^{1}H NMR ($CDCl_3$): δ 7.25–7.35 (m, 5H), 5.86 (d, 1H, J=0.84 Hz), 5.03 (d, 1H, J=0.84 Hz), 4.60 (d, 1H, J=12.0 Hz), 4.53 (d, 1H, J=12.0 Hz), 4.33 (dd, 1H, J=15.6, 2.5 Hz), 4.23 (dd, 1H, J=15.6, 2.5 Hz) 4.19 (d, 1H, J=10.25 Hz), 4.07 (d, 1H, J=10.25 Hz), 3.82 (d, 1H, J=10.6 Hz), 3.73 (d, 1H, J=10.6 Hz), 3.32 (s, 3H), 2.59 (s, 3H), 2.40 (t, 1H, J=2.35 Hz); ^{13}C NMR ($CDCl_3$): δ 215.12, 137.66, 128.33, 127.69, 107.43, 84.80, 84.70, 80.36, 73.92, 73.56, 72.58, 71.73, 55.19, 54.33, 19.20. Anal. calcd for $C_{18}H_{22}O_5S_2$: C, 56.37; H, 5.78; S, 16.72. Found: C, 56.46; H, 5.79; S, 16.69.

α-Anomer. $[\alpha]_D$ +82.07° (*c* 1.74; $CHCl_3$); IR ν^{neat} cm^{-1}: 3285, 2120, 1496, 1453, 1365; ^{1}H NMR ($CDCl_3$): δ 7.25–7.35 (m, 5H), 5.62 (d, 1H, J=4.8 Hz), 5.15 (d, 1H, J=4.8 Hz), 4.60 (d, 1H, J=12.2 Hz), 4.54 (d, 1H, J=12.2 Hz), 4.41 (m, 2H) 4.09 (d, 1H, J=9.9 Hz), 3.92 (d, 1H, J=9.9 Hz), 3.64 (d, 1H, J=10.2 Hz), 3.58 (d, 1H, J=10.2 Hz), 3.38 (s, $3H_3$), 2.59 (s, 3H), 2.41 (t, 1H, J=2.35 Hz); ^{13}C NMR ($CDCl_3$): δ 215.42, 137.40, 128.31, 127.70, 127.66, 101.01, 81.68, 80.86, 79.64, 73.87, 73.40, 72.05, 69.25, 55.45, 53.98, 19.16. Anal. calcd for $C_{18}H_{22}O_5S_2$: C, 56.37; H, 5.78; S, 16.72. Found: C, 56.51; H, 5.83; S, 16.68.

[3a*R*,4*R*,6a*R*]-3-Methylidene-4-methoxy-6a-[(benzyloxy)methyl]perhydrofuro-[3,4-*b*]furan (21). This compound was prepd from **20** by the same procedure described for the preparation of **7**, and was obtained in 36% yield as a clear oil: $[\alpha]_D$ +15.22° (*c* 2.68, $CHCl_3$); IR ν^{neat} cm^{-1}: 1668, 1496, 1453, 1361, 1311, 1287, 1097; ^{1}H NMR ($CDCl_3$): δ 7.25–7.40 (m, 5H), 5.06 (m, 2H), 4.89 (s, 1H), 4.61 (d, 1H, J=12.4 Hz), 4.55 (d, 1H, J=12.4 Hz), 4.43 (m, 2H), 4.00 (d, 1H, J=10.0 Hz), 3.91 (d, 1H, J=10.0 Hz), 3.65 (d, 1H, J=10.1 Hz), 3.60 (d, 1H, J=10.1 Hz), 3.30 (s, 3H), 3.05 (br s, 1H); ^{13}C NMR ($CDCl_3$): δ 148.29, 138.09, 128.30, 127.56, 127.43, 111.07, 106.57, 93.81, 74.33, 73.53, 72.61, 72.43, 57.47, 54.51. Anal. calcd for $C_{16}H_{20}O_4$: C, 69.54; H, 7.30; Found: C, 69.48; H, 7.28.

[3a*R*,4*R*,6a*R*]-3-Methylidene-4-methoxy-6a-[(benzyloxy)methyl]perhydrofuro-[3,4-*b*]furan-2-one (23). This compound was prepared from **21** by the same procedure described for the preparation of **9**, and was obtained in 72% yield: $[\alpha]_D$ −63.67° (*c* 2.56; $CHCl_3$); IR ν^{neat} cm^{-1}: 1769, 1664, 1453, 1364, 1287; ^{1}H NMR ($CDCl_3$): δ 7.25–7.40 (m, 5H), 6.36 (d, 1H, J=2.5 Hz), 5.79 (d, 1H, J=2.2 Hz), 4.86 (s, 1H), 4.56 (s, 2H), 4.05 (d, 1H, J=10.5 Hz), 3.88 (d, 1H, J=10.5 Hz), 3.73 (d, 1H, J=10.5 Hz), 3.63 (d, 1H, J=10.5 Hz), 3.39 (distorted t, 1H), 3.32 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 168.91, 137.36, 135.48, 128.36, 127.71, 127.39, 124.66, 110.50, 91.41, 73.55, 71.46, 71.03, 54.53, 52.99. Anal. calcd for $C_{16}H_{18}O_5$: C, 66.19; H, 6.25; Found: C, 66.08; H, 6.27.

[3*R*,3a*R*,6a*R*]-3-Undecanyl-6a-(hydroxymethyl)perhydrofuro[3,4-*b*]furan-2,4-dione (28) and [3*S*,3a*R*,6a*R*]-3-undecanyl-6a-(hydroxymethyl)perhydrofuro-[3,4-*b*]-furan-2,4-dione (27). These compounds were obtained from **23** following a similar sequence of four steps used for the preparation of **14** and **13** from **9**. The combined yield was 53%.

Compound 28. Mp 96 °C; $[\alpha]_D$ −25.0° (*c* 1.0; $CHCl_3$); the IR, ^{1}H and ^{13}C NMR spectra were indentical to those of its optical antipode **14**. FABMS *m/z* (relative intensity) 327 (MH^+, 100). Anal. calcd for $C_{18}H_{30}O_5$: C, 66.23; H, 9.26; Found: C, 66.32; H, 9.24.

Compound 27. Mp 65 °C; $[\alpha]_D$ −21.7° (*c* 0.82; $CHCl_3$); the IR, ^{1}H and ^{13}C NMR spectra were indentical to those of its optical antipode **13**. FABMS *m/z* (relative intensity) 327 (MH^+, 100). Anal. calcd for $C_{18}H_{30}O_5$: C, 66.23; H, 9.26; Found: C, 66.24; H, 9.25.

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