Total Syntheses of KS-501, KS-502, and Their Enantiomers

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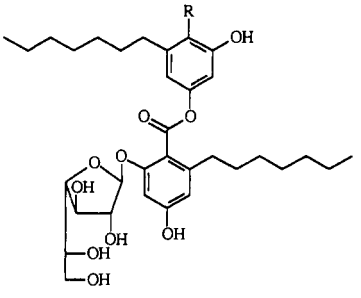
Abstract: The total syntheses of the title compounds are described. The key step involves the coupling of the anhydrofuranose **18** (as well as its enantiomer) with salicylate derivative **17** under the influence of potassium carbonate. Both the epoxidation of **7** (achieved with 2,2-dimethyldioxirane) and the glycosylation of **17** appear to be stereospecific.

KS-501 (**1**) and KS-502 (**2**) were isolated from the culture broth of *Sporothrix* sp. KAC-1985 by scientists at Kyowa Hakko Kogyo.[1a] The protocol which led to the identification of **1** and **2** involved screening for inhibition of calcium- and calmodulin-dependent cyclic-nucleotide phosphodiesterase (CaM-PDE) activity. Inhibitory concentrations causing 50% inhibition (IC_{50}) of bovine brain CaM-PDE for **1** and **2** occurred in the 1–5 μM range. By contrast, each compound displayed weak activity against calmodulin-independant phosphodiesterases and had no effect at all upon protein kinase C, another important Ca^{2+}-dependent enzyme. Since calmodulin dependency of PDE is quite tissue variable, this type of agent is of interest as a potential site-selective inhibitor of phosphodiesterase activity. Furthermore, both KS-501 and KS-502 may prove to be valuable biochemical tools for studying the function of CaM and CaM-PDE in cultured cells as well as in living systems.[1a]

Structure determinations of **1** and **2** were performed by a combination of chemical and spectroscopic means which relied heavily upon ^1H NMR NOE studies, ^{13}C NMR, and MS fragmentation data.[1b] KS-501 and KS-502 are structurally related to the so-called "TPI-series" of compounds,[2] and differ only in the sugar content of the molecules. The TPI compounds are isolates of *Nodulisporium* sp. M5220, and these also displayed some inhibitory activity against phosphodiesterases,[2] although it is not currently known whether these compounds inhibit the Ca^{2+}- and CaM-dependent enzymes.

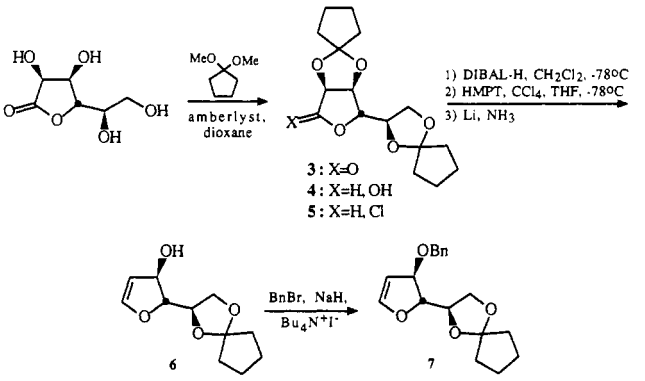
In earlier work we described the facile synthesis of β-aryl glucopyranosides[3] via epoxides derived from glycals. Our strategy for the synthesis of **1** and **2** envisioned extension and this methodology to the furanose series. Herein we report the first total synthesis of **1** and **2** and their antipodes. This work confirms the structures of these two compounds and provides a means to prepare them in considerable quantity. By extension, this work would allow for the laboratory syntheses of the TPI compounds and other analogues.



1: KS-501 R=H
2: KS-502 R=CO2H

Our approach envisioned the intermediacy of furanose glycal **7**, which was easily prepared through application of the methods of Ireland and co-workers.[4] Thus, D-talonic acid lactone[5] was

Scheme I



protected as its bis(cyclopentylidene) acetal **3** and then reduced with DIBAH in methylene chloride to give hemiacetal **4**. Treatment of **4** with hexamethylphosphorous triamide–carbon tetrachloride gave anomeric chloride **5**, which upon reduction with lithium in ammonia[4] followed by benzylation of the resultant **6** (NaH, BnBr, THF) provided a 50–60% yield of the protected furanose glycal **7** (Scheme I).

The aromatic coupling partners were synthesized from a common starting material, 2,4,6-trihydroxybenzoic acid (**8**). Reaction of **8** with acetone in the presence of trifluoroacetic acid–trifluoroacetic anhydride afforded the 1,3-benzodioxin **9**. Specific protection of the 4-hydroxyl group was accomplished by a Mitsunobu protocol.[6] Compound **10**, thus obtained in 92% yield, was converted to aryl triflate **11** through the agency of triflic anhydride–pyridine.[7] Cross coupling of **11** with 1-heptyne (bis(triphenylphosphine)palladium(II) chloride, triethylamine–DMF)[8] afforded a 68% yield of **12**.

Compound **12** lent itself to conversion to a variety of useful intermediates. Thus, hydrogenation of its triple bond gave **13** (~100%), which upon reaction with KOH–DMSO at 120 °C resulted in the expected decarboxylation with the formation of 5-heptylresorcinol[9] (**14**) (90% from **12**). Treatment of **13** with lithium benzyl oxide in THF afforded the dihydroxybenzyl ester **15**. The acylal-like linkage of **12** could also be opened with KOH–DMSO at 60 °C without concurrent decarboxylation. Dihydroxy acid **16** was esterified with β-(trimethylsilyl)ethanol to produce ester **17** (80% yield from **12**) (**Scheme** II).

The program for combining these building blocks commenced with epoxidation of glycal **7** (1 equiv of 2,2-dimethyldioxirane in methylene chloride–acetone).[10] Reaction of **17** with epoxide **18** (K_2CO_3, 18-crown-6, acetone) afforded an 81% yield of aryl glycoside **19**. The secondary alcohol function of **19** was benzylated

(1) Isolation: (a) Nakanishi, S.; Ando, K.; Kawamoto, I.; Kase, H. *J. Antibiot.* **1989**, *42*, 1049. Structure determination: (b) Yasuzawa, T.; Saitoh, Y.; Sano, H. *J. Antibiot.* **1990**, *43*, 336.
(2) Yaginuma, S.; Awata, M.; Takada, M.; Kinoshita, K. *Jpn. Kokai Tokkyo Koho* 87 215551, Sept 22, 1987.
(3) Dushin, R. G.; Danishefsky, S. J. Manuscript in preparation.
(4) (a) Ireland, R. E.; Wilcox, C. S.; Thaisrivongs, S. *J. Org. Chem.* **1978**, *43*, 786. (b) Ireland, R. E.; Thaisrivongs, S.; Vanier, N.; Wilcox, C. S. *J. Org. Chem.* **1980**, *45*, 48.
(5) Block, K.; Lundt, I.; Pedersen, C.; Refn, S. *Acta Chem. Scand., Ser. B* **1986**, *B40*, 740.
(6) Mitsunobu, O. *Synthesis* **1981**, 1.
(7) Subramanian, L. R.; Hanack, M.; Chang, L. W. K.; Imhoff, M. A.; Schleyer, P.; Effenberger, F.; Kurtz, W.; Stang, P. J.; Dueber, T. E. *J. Org. Chem.* **1976**, *41*, 4099.
(8) Chen, Q. Y.; Yang, Z. Y. *Tetrahedron Lett.* **1986**, *27*, 1171.
(9) Asahina, Y; Hashimoto, A. *Ber. Dtsch. Chem. Ges. B* **1934**, *67B*, 416.
(10) Chow, K.; Danishefsky, S. J. *J. Org. Chem.* **1990**, *55*, 4211.

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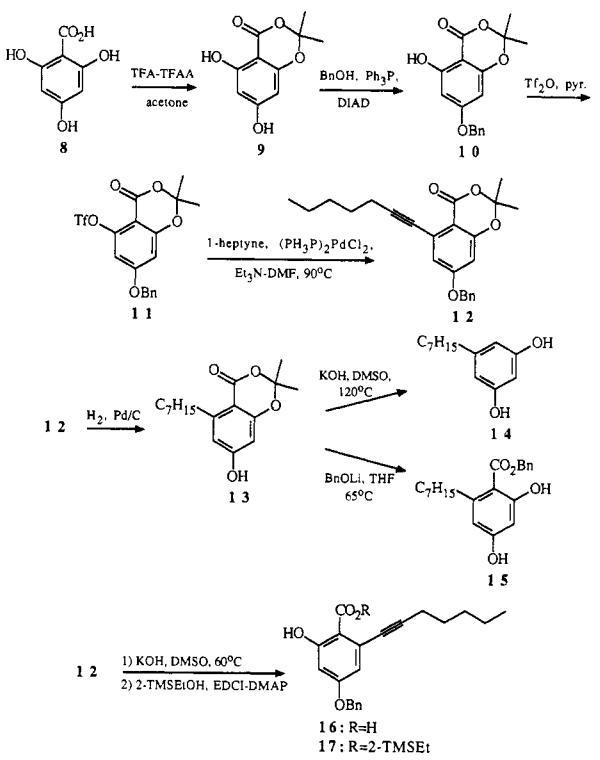
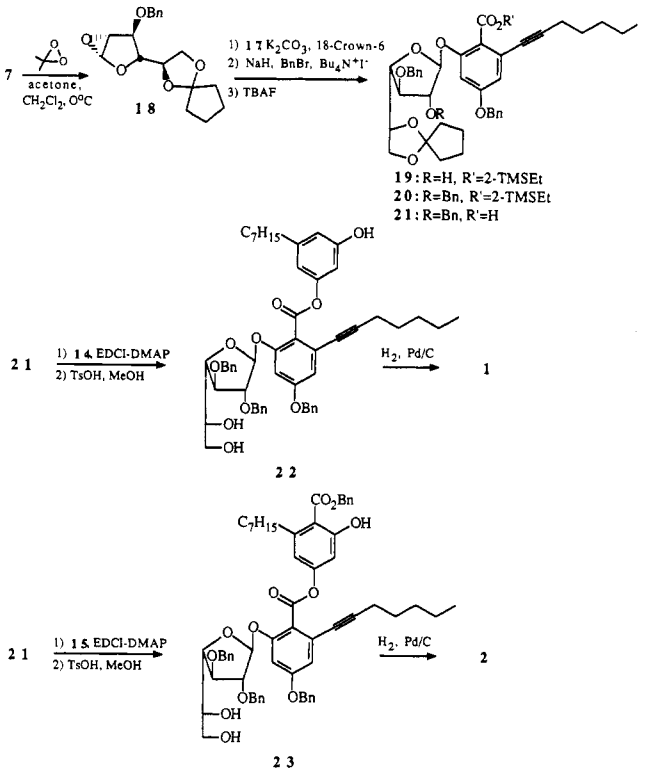
Scheme II



Scheme III



under the usual conditions to provide **20**. Unveiling of the carboxylic acid (TBAF, THF) led to **21** (86% yield from **19**). Coupling of **21** with **14** (EDCI–DMAP)[11] followed by hydrolysis of the 5,6-cyclopentylidene acetal (TsOH–MeOH) afforded a 49% yield of **22**. Exposure of this compound to the action of hydrogen (Pd/C) in ethanol resulted in hydrogenation of the triple bond and concurrent hydrogenolytic cleavage of all three benzyl protecting groups with the formation of KS-501. Fortunately, acylation of **15** with **21** (EDCI, DMAP)[11] occurred specifically at *p*-hydroxyl group. Cleavage of the cyclopentylidene group was again accomplished through the action of TsOH in methanol. Finally, hydrogenation of **23** over Pd/C resulted in reduction of the triple bond and cleavage of the four benzyl protecting groups with the formation of KS-502 (Scheme III). The ^{1}H NMR and UV data for our fully synthetic materials were identical with those of the natural materials.[1b] The optical rotations were in close accord (see Experimental Section) with the literature values reported for the natural products. The TLC mobilities were identical in all solvent systems which were studied. The total syntheses of both KS-501 and KS-502 have thus been accomplished.

Prior to carrying out the syntheses described in Scheme III, which began with commercially available, but costly, D-talose, all of the steps were executed in the enantiomeric L series. For this purpose, we took advantage of the recent work of Poss and Smyth,[12] who reported that L-ascorbic acid can be easily converted into L-talonic acid lactone. By the methodology described above, L-talonic acid lactone was converted to *ent*-KS-501 and *ent*-KS-502. Evaluation of the biological properties of these *ent* compounds is expected to provide insights as to the region of the molecule responsible for activity.

Experimental Section

2,3:5,6-Dicyclopentylidene-D-talonic Acid γ-Lactone (3). Using the method of Block,[5] a solution of D-talose (500 mg, 2.78 mmol) in water (3.3 mL) was treated with $CaCO_3$ (380 mg, 3.8 mmol) and Br_2 (165 μL, 510 mg, 3.2 mmol, 1.15 equiv), and the mixture was stirred for 24 h at room temperature. The solution was then filtered, passed through a 0.5 × 5 in. column of Amberlite IR-120 with methanol, and concentrated to give 590 mg of crude talonic acid γ-lactone as a brown gum. A solution of this crude material (2.78 mmol) in dioxane (7 mL) was treated with 1,1-dimethoxycyclopentane (4.5 mL) and Amberlyst-15 (30 mg). After stirring overnight, the solution was filtered, diluted with EtOAc, washed with water, saturated aqueous $NaHCO_3$, water, and brine, and dried over $MgSO_4$. Concentration, chromatography over silica gel (eluted with 18% EtOAc–hexanes), and crystallization gave 494 mg (57%) of **3** as white needles: mp 129–130 °C; $[\alpha]^{22}_D$ = +33.0° (*c* 1.09, $CHCl_3$); IR ($CHCl_3$) 3020, 2960, 1790, 1340, 1185, 1120, 975 cm^{-1}; ^{1}H NMR ($CDCl_3$, 250 MHz) δ 4.77 (d, 1 H, *J* = 5.7 Hz, H2), 4.70 (d, 1 H, *J* = 5.7 Hz, H3), 4.57 (d, 1 H, *J* = 1 Hz, H4), 4.22 (ddd, 1 H, *J* = 6.9, 6.8, 1 Hz, H5), 4.07 (dd, 1 H, *J* = 8.3, 6.8 Hz, H6), 3.95 (dd, 1 H, *J* = 8.3, 6.8 Hz, H6′), 1.58–1.98 (m, 16 H).

2,3:5,6-Dicyclopentylidene-L-talonic Acid γ-Lactone (*ent*-3). A solution of L-talonic acid γ-lactone[12] (356 mg, 2 mmol) in dioxane (5 mL) was treated with 1,1-dimethoxycyclopentane (5 mL) and Amberlyst-15 (30 mg), and the solution was stirred at room temperature for 12 h. The mixture was then filtered, diluted with EtOAc, washed with water, saturated aqueous $NaHCO_3$, water, and brine, and dried over $MgSO_4$. Concentration and crystallization from a minimal amount of EtOAc in hexanes gave 355 mg of fine needles. Chromatography of the mother liquor over silica gel (eluted with 18% EtOAc–hexanes) yielded an additional 255 mg (610 mg total, 98%) of product as white solids: mp 129–130 °C; $[\alpha]^{22}_D$ = −28.4° (*c* 1.08, $CHCl_3$); MS *m/e* (relative intensity) 310 (22.2), 281 (100), 253 (8.1), 153 (17.6), 139 (9.3), 97 (10.6), 69 (19.3), 55 (35.5). Anal. Calcd for $C_{16}H_{22}O_6$: C, 61.92; H, 7.15. Found: C, 61.63; H, 7.03.

1,4-Anhydro-5,6-cyclopentylidene-2-deoxy-D-*lyxo*-hex-1-enofuranose (6). A solution of lactone **3** (250 mg, 0.80 mmol) in CH_2Cl_2 (8 mL) at −78 °C was treated with DIBAH (1 M in CH_2Cl_2, 1.05 mL, 1.05 mmol, 1.3 equiv). After stirring 1 h the reaction was quenched with MeOH (0.5 mL), saturated aqueous Na/K tartrate (5 mL) was added, and the solution was allowed to stir at 0 °C for 1 h. The mixture was filtered through Celite, and the filtrate was washed twice with water and with brine, and dried over $MgSO_4$. Concentration left 250 mg (100%) of nearly pure hemiacetal **4** as a colorless oil: IR ($CHCl_3$) 3200–3600, 2970, 2880, 1440, 1345, 1115, 1055, 990 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 5.45 (dd, 1 H, *J* = 4.1, 11.1 Hz, H1, α-anomer), 5.37 (d, 1 H, *J* = 10.1 Hz, H1, β-anomer), 4.73 (m, 1 H, H2, α- and β-anomers), 4.57 (dd, 1 H, *J* = 4.1, 6.3 Hz, H3, α-anomer), 4.49 (d, 1 H, *J* = 6.0 Hz, H3, β-anomer), 4.31 (dd, 1 H, *J* = 1.3, 3.0 Hz, H4, β-anomer), 4.18 (dd, 1 H, *J* = 1.2, 3.0 Hz, H4, α-anomer), 4.10–4.16 (m, 1 H, H5, α- and β-anomers), 3.83–4.07 (m, 2 H, H6, α- and β-anomers), 1.67–2.04 (m, 16 H).

The aforementioned hemiacetal (0.80 mmol) in THF (8 mL) at −78

(11) Neises, B.; Steglich, W. *Angew. Chem., Int. Ed. Engl.* **1978**, *17* (7), 522.

(12) Poss, A. J.; Smyth, M. S. *Tetrahedron Lett.* **1989**, *30*, 5201.

°C was treated with CCl_4 (150 μL) and HMPT (85%, 180 μL, 137 mg, 0.83 mmol, 1.04 equiv). After 10 min the resulting crude anomeric chloride **5** was cannulated into a cooled (−78 °C) solution of Li metal (370 mg, 52.9 mmol, 66 equiv) in ammonia (30 mL). The mixture was refluxed for 2.5 h, and then the reaction was quenched with the careful addition of solid NH_4Cl (2.7 g) and 2-PrOH (5 mL). The resulting slurry was partitioned between Et_2O and water, and the aqueous layer was extracted three times with Et_2O. Pooled organic fractions were washed with brine, dried ($MgSO_4$), evaporated to dryness, and rapidly chromatographed over silica gel (eluted with 30% EtOAc in hexanes) to give 116 mg (68%) of **6** as a clear colorless oil: $[\alpha]^{23}_D = -232.5°$ (*c* 1.14, $CHCl_3$); IR ($CHCl_3$) 3300–3600, 3010, 2985, 1615, 1340, 1150, 1110, 1080 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 6.58 (dd, 1 H, *J* = 0.8 Hz, 2.6 Hz, H1), 5.20 (t, 1 H, *J* = 2.6 Hz, H2), 4.73 (br m, 1 H, H3), 4.30 (dd, 1 H, *J* = 3.2, 6.4 Hz, H4), 4.13 (ddd, 1 H, *J* = 6.0, 6.4, 6.7 Hz, H5), 4.00 (dd 1 H, *J* = 6.7, 8.4 Hz, H6), 3.87 (dd, 1 H, *J* = 6.0, 8.4 Hz, H6′).

1,4-Anhydro-5,6-cyclopentylidene-2-deoxy-L-*lyxo*-hex-1-enofuranose (*ent*-6). ***ent*-6** was prepared on a 0.77-mmol scale in 61% yield from ***ent*-3** as described above for the D-antipode. For ***ent*-6**: $[\alpha]^{23}_D$ = +212.6° (*c* 1.03, $CHCl_3$); MS *m/e* (relative intensity) 212 (13.5), 183 (100), 144 (10.6), 128 (17.8), 127 (14.8), 111 (70.5), 84 (30.4), 83 (39.2), 69 (30.7), 55 (89.1). Anal. Calcd for $C_{11}H_{16}O_4$: C, 62.25; H, 7.60. Found: C, 62.50; H, 7.41.

1,4-Anhydro-3-*O*-benzyl-5,6-cyclopentylidene-2-deoxy-D-*lyxo*-hex-1-enofuranose (7). A solution of furanose glycal **6** (64 mg, 0.30 mmol) in THF (2 mL) at 0 °C was treated with NaH (60% in oil, 18 mg, 0.45 mmol, 1.5 equiv), benzyl bromide (45 μL, 65 mg, 0.38 mmol, 1.27 equiv), and tetrabutylammonium iodide (5 mg). After warming to room temperature and stirring for 8 h, the mixture was diluted with water and extracted three times with EtOAc. Pooled extracts were washed with water and brine, dried ($MgSO_4$), and evaporated. Chromatography over silica gel (eluted with 5% EtOAc in hexanes) gave 78 mg (86%) of **7** as a clear colorless oil: $[\alpha]^{23}_D = -233.4°$ (*c* 1.06, $CHCl_3$); IR ($CHCl_3$) 3010, 2985, 2880, 1615, 1460, 1360, 1340, 1155, 1110, 1080, 1050, 975 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 7.29–7.37 (m, 5 H, ArH), 6.61 (dd, 1 H, *J* = 1.0, 2.7 Hz, H1), 5.23 (t, 1 H, *J* = 2.7 Hz, H2), 4.65 (ddd, 1 H, *J* = 1.0, 2.7, 3.3 Hz, H3), 4.53 (s, 2 H, $ROCH_2Ph$), 4.47 (dd, 1 H, *J* = 3.3, 6.1 Hz, H4), 4.15 (ddd, 1 H, *J* = 5.9, 6.1, 6.9 Hz, H5), 3.93 (dd, 1 H, *J* = 6.9, 8.4 Hz, H6), 3.79 (dd, 1 H, *J* = 5.9, 8.4 Hz, H6′), 1.64–1.90 (m, 16 H).

1,4-Anhydro-3-*O*-benzyl-5,6-cyclopentylidene-2-deoxy-L-*lyxo*-hex-1-enofuranose (*ent*-7). This compound was prepared on the 0.26-mmol scale in 94% yield from hydroxy glycal ***ent*-6** as described above for the D-antipode **7**: $[\alpha]^{22}_D$ = +220.9° (*c* 0.83, $CHCl_3$). Anal. Calcd for $C_{18}H_{22}O_4$: C, 71.50; H, 7.33. Found: C, 71.45; H, 7.09.

5,7-Dihydroxy-2,2-dimethyl-4*H*-1,3-benzodioxin-4-one (9). To an ice-cold suspension of 2,4,6-trihydroxybenzoic acid monohydrate (**8**) (5.0 g, 27 mmol) in trifluoroacetic acid (40 mL) were added trifluoroacetic anhydride (25 mL) and acetone (5 mL). The mixture was warmed slowly to room temperature and then stirred for 24 h. The slightly yellow homogeneous mixture was then concentrated on the rotary evaporator, poured into a saturated solution of aqueous $NaHCO_3$, and extracted with three portions of ethyl acetate. Pooled extracts were washed with water and brine, dried ($MgSO_4$), and concentrated to leave yellow solids. Chromatography over silica using 35% EtOAc in hexanes as the eluant left 1.88 g (34%) of white solids: mp 203–204 °C; IR ($CHCl_3$) 3200, 3020, 1680, 1640, 1595, 1490, 1275, 1165, 1100 cm^{-1}; ^1H NMR (acetone-d_6 250 MHz) δ 10.44 (br s, 1 H, *o*-OH), 6.06 (d, 1 H, *J* = 2.2 Hz, ArH), 5.98 (d, 1 H, *J* = 2.2 Hz, ArH), 3.02 (br s, 1 H, *p*-OH), 1.70 (s, 6 H, CH_3). Anal. Calcd for $C_8H_{10}O_5$: C, 57.14; H, 4.80. Found: C, 56.87; H, 4.63.

7-(Benzyloxy)-2,2-dimethyl-5-hydroxy-4*H*-1,3-benzodioxin-4-one (10). To a solution of diol **9** (1.88 g, 8.95 mmol) and benzyl alcohol (960 μL, 1.01 g, 9.40 mmol, 1.05 equiv) in THF (45 mL) in 0 °C were added triphenylphosphine (2.48 g, 9.40 mmol, 1.05 equiv) and DIAD (1.86 mL, 1.90 g, 9.40 mmol, 1.05 equiv), and the mixture was warmed to room temperature over 2 h. The solution was then diluted with EtOAc, washed thrice with water and brine, dried ($MgSO_4$), concentrated, and chromatographed over silica (eluted with 10% EtOAc–hexanes) to give 2.48 g (92%) of **10** as white solids: mp 80 °C; IR ($CHCl_3$) 3200, 3020, 1685, 1640, 1585, 1500, 1275, 100, 1160, 1100 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 10.46 (s, 1 H, *o*-OH), 7.39–7.42 (m, 5 H, ArH), 6.24 (d, 1 H, *J* = 2.2 Hz, ArH), 6.09 (d, 1 H, *J* = 2.2 Hz, ArH), 5.07 (s, 2 H, OCH_2Ph), 1.74 (s, 6 H, CH_3). Anal. Calcd for $C_{17}H_{16}O_5$: C, 67.99; H, 5.37. Found: C, 67.77; H, 5.39.

7-(Benzyloxy)-2,2-dimethyl-5-[(trifluoromethyl)sulfonyl]-4*H*-1,3-benzodioxin-4-one (11). A solution of alcohol **10** (2.4 g, 8.0 mmol) in pyridine (40 mL) at 0 °C was treated dropwise with trifluoromethanesulfonic anhydride (1.48 mL, 2.48 g, 8.8 mmol, 1.1 equiv), and the mixture was maintained at 0 °C for 12 h. The solution was then concentrated on the rotary evaporator, diluted with 4:1 Et_2O–EtOAc (200 mL), washed thrice with water and brine, dried ($MgSO_4$), and then evaporated to leave a dark oil. Chromatography over silica gel (eluted with 12.5% EtOAc–hexanes) gave 2.94 g (85%) of white solids: mp 86–88 °C; IR ($CHCl_3$) 3020, 1690, 1630, 1575, 1435, 1385, 1160, 1060 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 7.42–7.50 (m, 5 H, ArH), 6.61 (d, 1 H, *J* = 2.3 Hz), 6.57 (d, 1 H, *J* = 2.3 Hz), 5.11 (s, 2 H, OCH_2Ph), 1.75 (s, 6 H, CH_3). Anal. Calcd for $C_{18}H_{15}F_3O_7S$: C, 50.00; H, 3.50. Found: C, 50.19; H, 3.57.

7-(Benzyloxy)-2,2-dimethyl-5-(1-heptyn-1-yl)-4*H*-1,3-benzodioxin-4-one (12). A solution of triflate **11** (2.78 g, 6.4 mmol), 1-heptyne (1.18 mL, 864 mg, 9.0 mmol, 1.4 equiv), and bis(triphenylphosphine)palladium(II) chloride (105 mg, 0.150 mmol, 0.02 equiv) in DMF–Et_3N (5:1, 20 mL) was heated to 90 °C for 12 h. The solution was then cooled, diluted with Et_2O (200 mL), washed thrice with water and brine, dried ($MgSO_4$), and concentrated to leave a yellow oil. Chromatography over silica gel (eluted with 12% EtOAc–hexanes) gave 2.11 g (87%) of pale yellow solids. An analytical sample recrystallized from EtOAc–hexanes gave mp 104 °C; IR ($CHCl_3$) 3010, 3000, 2930, 2230, 1725, 1600, 1570, 1280, 1170 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 7.36–7.43 (m, 5 H, ArH), 6.84 (d, 1 H, *J* = 2.5 Hz, ArH), 6.45 (d, 1 H, *J* = 2.5 Hz, ArH), 5.08 (s, 2 H, OCH_2Ph), 2.52 (br t, 2 H, *J* = 7.0 Hz, CH_2), 1.70 (s, 6 H, CH_3), 1.32–1.68 (m, 6 H), 0.93 (t, 3 H, *J* = 7.2 Hz, CH_3). Anal. Calcd for $C_{24}H_{26}O_4$: C, 76.17; H, 6.92. Found: C, 76.04; H, 6.95.

2,2-Dimethyl-5-(1-heptyl)-7-hydroxy-4*H*-1,3-benzodioxin-4-one (13). Compound **12** (500 mg, 1.32 mmol) was hydrogenated over $Pd(OH)_2$ (20%, 95 mg, ca. 0.1 equiv) in EtOH (15 mL) at atmospheric pressure for 12 h. Filtration through Celite and concentration left 387 mg (100%) of white solids: mp 100–102 °C; IR ($CHCl_3$) 3100–3400, 3020, 2930, 1715, 1615, 1590, 1450, 1390, 1295, 1170, 1050 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 6.42 (d, 1 H, *J* = 2.4 Hz, ArH), 6.27 (d, 1 H, *J* = 2.4 Hz, ArH), 5.50 (br s, 1 H, OH), 3.04 (br t, 2 H, *J* = 7.7 Hz), 1.69 (s, 6 H, CH_3), 1.20–1.65 (m, 10 H), 0.88 (t, 3 H, *J* = 7.2 Hz, CH_3).

5-Heptylresorcinol (14). Compound **13** (383 mg, 1.31 mmol) in DMSO (6 mL) was treated with 48% aqueous KOH (1.5 mL) and the mixture was heated to 115 °C under a gentle stream of N_2 for 4.5 h. Upon cooling, the solution was diluted with water, acidified (10% HCl), and extracted three times with EtOAc. Pooled extracts were washed with three portions of water and brine, dried ($MgSO_4$), and concentrated. Chromatography of the resulting yellow oil over silica gel (eluted with 17–20% EtOAc–hexanes) gave 270 mg (99%) of the known[9] 5-heptylresorcinol as a pale yellow oil.

Benzyl 2,4-Dihydroxy-6-(1-heptyl)benzoate (15). To a solution of compound **13** (200 mg, 0.685 mmol) in THF (10 mL) was added BnOLi (0.5 M in THF, 6.8 mL, 3.4 mmol, 5 equiv), and the mixture was heated to reflux for 65 h. Upon cooling, the mixture was diluted with water and extracted with EtOAc. Pooled extracts were washed with aqueous HCl (10%), twice with water, and with brine, and the dried ($MgSO_4$). Concentration and chromatography over silica gel (using 8% EtOAc–hexanes as eluant) gave 214 mg (91%) of **15** as slightly pale solids. An analytical sample crystallized from a minimum of EtOAc in hexanes gave mp 104 °C; IR ($CHCl_3$) 3580, 3030, 2980, 2930, 1655, 1620, 1450, 1395, 1320, 1270, 1175, 1110 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 11.79 (s, 1 H, *o*-OH), 7.38–7.47 (m, 5 H, ArH), 6.29 (d, 1 H, *J* = 2.6 Hz, ArH), 6.21 (d, 1 H, *J* = 2.6 Hz, ArH), 5.36 (s, 2 H, OCH_2Ph), 5.34 (br s, 1 H, *p*-OH), 2.76 (br t, 2 H, *J* = 7.9 Hz), 1.07–1.47 (m, 10 H), 0.88 (t, 3 H, *J* = 7.2 Hz, CH_3). Anal. Calcd for $C_{21}H_{26}O_4$: C, 73.66; H, 7.65. Found: C, 73.58; H, 7.63.

β-(Trimethylsilyl)ethyl 4-(Benzyloxy)-6-(1-heptyn-1-yl)-2-hydroxybenzoate (17). Compound **12** (250 mg, 0.661 mmol) in DMSO (3 mL) was treated with 48% aqueous KOH (0.5 mL) and the mixture was heated at 60 °C for 30 min. Upon cooling, the solution was acidified (10% HCl) and extracted three times with EtOAc, and these extracts were washed with water and brine and dried over Na_2SO_4. Filtration and concentration left 248 mg of the crude acid **16** as yellow solids. IR ($CHCl_3$) 3200–3340, 3030, 2960, 2930, 2230, 1680, 1600, 1575, 1360, 1260, 1215, 1180, 1030 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 12.26 (s, 1 H, *o*-OH), 7.34–7.42 (m, 5 H, ArH), 6.70 (d, 1 H, *J* = 2.6 Hz, ArH), 6.56 (d, 1 H, *J* = 2.6 Hz, ArH), 5.11 (s, 2 H, OCH_2Ph), 2.56 (br t, 2 H, *J* = 7.1 Hz, CH_2), 1.61–1.73 (m, 2 H), 1.27–1.50 (m, 4 H), 0.94 (t, 3 H, *J* = 7.1 Hz, CH_3).

The foregoing crude acid and 2-(trimethylsilyl)ethanol (0.95 mL, 782 mg, 6.61 mmol, 10 equiv) were taken up in CH_2Cl_2 (6 mL) and treated at room temperature with 4-DMAP (89 mg, 0.723 mmol, 1.1 equiv) and EDCI (279 mg, 1.46 mmol, 2.2 equiv). The mixture was stirred for 5 h, then diluted with EtOAc, washed with aqueous NH_4Cl, twice with water and brine, and dried over $MgSO_4$. Concentration and chromatography over silica gel (eluted with 2% EtOAc–hexanes) left 254 mg (88%) of **17** as a clear colorless oil: IR ($CHCl_3$) 3020, 2940, 2840, 2220, 1650, 1600, 1570, 1330, 1265, 1210, 1170, 1030, 840 cm^{-1}; ^1H NMR

($CDCl_3$, 250 MHz) δ 11.77 (s, 1 H, o-OH), 7.34–7.43 (m, 5 H, ArH), 6.71 (d, 1 H, J = 2.6 Hz, ArH), 6.50 (d, 1 H, J = 2.6 Hz, ArH), 5.07 (s, 2 H, OCH_2Ph), 4.45 (m, 2 H, CO_2CH_2), 2.44 (br t, 2 H, J = 7.1 Hz, CH_2), 1.55–1.69 (m, 2 H), 1.30–1.51 (m, 4 H), 1.20 (m, 2 H, CH_2TMS), 1.94 (t, 3 H, 7.0 Hz, CH_3), 0.10 (s, 9 H, TMS). Anal. Calcd for $C_{26}H_{34}O_4Si$: C, 71.19; H, 7.81. Found: C, 71.08; H, 7.58.

3′-(Benzyloxy)-6′-[[β-(trimethylsilyl)ethoxy]carbonyl]-5′-(1-heptyn-1-yl)phenyl 3-*O*-Benzyl-5,6-cyclopentylidene-D-galactofuranoside (19). An ice-cold solution of glycal **7** (96 mg, 0.32 mmol) in CH_2Cl_2 (4 mL) was treated dropwise with 2,2-dimethyldioxirane (0.08 M in acetone, 4 mL, 1 equiv). After 10 min the solvent was evaporated under a gentle stream of dry N_2 and the flask was then evacuated under reduced pressure for 10 min. The resulting crude 1α,2α-anhydrosugar (**18**) was taken up in dry acetone (5 mL) and added to a refluxing solution of aryl alcohol **17** (139 mg, 0.32 mmol), K_2CO_3 (440 mg, 3.2 mmol, 10 equiv), and 18-crown-6 (10 mg) in acetone (5 mL). After refluxing for 8 h, the solution was cooled, diluted with saturated aqueous NH_4Cl, and extracted twice with EtOAc. Combined extracts were washed with water and brine, dried ($MgSO_4$), evaporated, and chromatographed over silica gel (eluted with 18% EtOAc in hexanes) to give 195 mg (81%) of **19** as a clear colorless oil: $[\alpha]^{20}_D$ = −48.6° (*c* 0.96, $CHCl_3$); IR ($CHCl_3$) 3230–3500, 3010, 2980, 2880, 1720, 1600, 1500, 1460, 1275, 1175, 1110, 1035, 850 cm^{-1}; ^1H NMR ($CDCl_3$, 490 MHz) δ 7.28–7.433 (m, 10 H, ArH), 6.77 (d, 1 H, J = 2.3 Hz, ArH), 6.73 (d, 1 H, J = 2.3 Hz, ArH), 5.55 (s, 1 H, H1) 5.05 (s, 2 H, $ArOCH_2Ph$), 4.74 (d, 1 H, J = 12.0 Hz, $ROCH_2Ph$), 4.56 (d, 1 H, J = 12.0 Hz, OCH_2Ph), 4.38 (br d, 1 H, J = 9.8 Hz, H2), 4.23–4.33 (overlapping m, 3 H), 4.13 (ddd, 1 H, J = 2.1, 6.8, 7.8 Hz, H5), 3.99 (m, 1 H, H3), 3.97 (dd, 1 H, J = 6.8, 8.1 Hz, H6), 3.92 (dd, 1 H, J = 7.8, 8.1 Hz, H6′), 3.68 (d, 1 H, J = 9.8 Hz, OH), 2.37 (t, 2 H, J = 7.1 Hz, CH_2), 1.32–1.85 (m, 14 H), 1.08 (t, 2 H, J = 8.8 Hz, $TMSCH_2R$), 0.93 (t, 3 H, J = 7.2 Hz, CH_3), 0.11 (s, 9 H, TMS).

3′-(Benzyloxy)-6′-[[β-(trimethylsilyl)ethoxy]carbonyl]-5′-(1-heptyn-1-yl)phenyl 3-*O*-Benzyl-5,6-cyclopentylidene-L-galactofuranoside (*ent*-19). This compound was prepared on a 0.28-mmol scale in 82% yield from L-glycal ***ent*-7** as described above for the D-antipode **19**: $[\alpha]^{22}_D$ = +51.3° (*c* 0.90, $CHCl_3$); FABLRMS (NOBA + NaI) *m/e* (rel intensity) 780 (22.7), 779 (40.0), 729 (17.0), 411 (58.2), 410 (56.0), 320 (25.6), 319 (100); FABHRMS calcd for $C_{44}H_{56}O_9SiNa$ 779.3591, found 779.3599. Anal. Calcd for $C_{44}H_{56}O_9Si$: C, 69.81; H, 7.46. Found: C, 69.66; H, 7.19.

3′-(Benzyloxy)-6′-[[β-(trimethylsilyl)ethoxy]carbonyl]-5′-(1-heptyn-1-yl)phenyl 2,3-Di-*O*-benzyl-5,6-cyclopentylidene-D-galactofuranoside (20). To an ice-cold solution of hydroxy aryl glycoside **19** (162 mg, 0.21 mmol) in THF (4 mL) were added NaH (60% in oil, 21 mg, 0.54 mmol, 2.5 equiv), benzyl bromide (33 μL, 47 mg, 0.28 mmol, 1.3 equiv), and tetrabutylammonium iodide (10 mg), and the solution was allowed to warm to room temperature and was then stirred for 6 h. The reaction was the diluted with saturated aqueous NH_4Cl and extracted twice with EtOAc. The extracts were washed with water and brine, dried ($MgSO_4$), and evaporated. Chromatography over silica gel (eluted with 10% EtOAc in hexanes) gave 164 mg (90%) of **20** as a clear colorless oil: $[\alpha]^{26}_D$ = −54.9° (*c* 0.79, $CHCl_3$); IR ($CHCl_3$), 3010, 2980, 2890, 1720, 1600, 1310, 1280, 1175, 1115 cm^{-1}; ^1H NMR ($CDCl_3$, 490 MHz) δ 7.28–7.43 (m, 15 H, ArH), 6.79 (d, 1 H, J = 2.1 Hz, ArH), 6.74 (d, 1 H, J = 2.1 Hz, ArH), 5.62 (s, 1 H, H1), 5.04 (s, 2 H, $ArOCH_2Ph$), 4.64 (d, 1 H, J = 11.8 Hz, $ROCH_2Ph$), 4.59 (d, 1 H, J = 11.8 Hz, $ROCH_2Ph$), 4.59 (d, 1 H, J = 11.8 Hz, $ROCH_2Ph$), 4.51 (d, 1 H, J = 11.8 Hz, $ROCH_2Ph$), 4.34 (m, 2 H, $ArCO_2CH_2R$), 4.28 (m, 1 H, H2), 4.21 (dd, J = 6.0, 6.6 Hz, H4) 4.18 (ddd, J = 6.0, 6.6, 6.6 Hz, H5), 4.00 (dd, J = 3.4, 6.6 Hz, H3), 3.86 (d, 2 H, J = 6.6 Hz, H6, H6′), 2.38 (t, 2 H, J = 7.2 Hz, CH_2), 1.33–1.87 (m, 14 H), 1.09 (m, 2 H, $TMSCH_2R$), 0.93 (t, 3 H, J = 7.1 Hz, CH_3), 0.02 (s, 9 H, TMS).

3′-(Benzyloxy)-6′-[[β-(trimethylsilyl)ethoxy]carbonyl]-5′-(1-heptyn-1-yl)phenyl 2,3-Di-*O*-benzyl-5,6-cyclopentylidene-L-galactofuranoside (*ent*-20). This compound was prepared on a 0.28-mmol scale in 98% yield from hydroxy aryl glycoside ***ent*-19** as described above for the D-antipode **20**: $[\alpha]^{23}_D$ = +65.5° (*c* 0.92, $CHCl_3$); FABLRMS (NOBA + NaI) *m/e* (relative intensity) 870 (68.2), 869 (95.5), 819 (26.2), 411 (65.8), 321 (100); FABHRMS calcd for $C_{51}H_{62}O_9SiNa$ 869.4061, found 869.4051. Anal. Calcd for $C_{51}H_{62}O_9Si$: C, 72.31; H, 7.38. Found: C, 72.09; H, 7.06.

3′-(Benzyloxy)-6′-carboxy-5′-(1-heptyn-1-yl)phenyl 2,3-Di-*O*-benzyl-5,6-cyclopentylidene-D-galactofuranoside (21). A solution of aryl glycoside **20** (160 mg, 0.19 mmol) in THF (5 mL) was treated at room temperature with TBAF (1.0 M in THF, 567 μL, 0.57 mmol, 3 equiv), and the mixture was allowed to stir for 4 h. Saturated aqueous NH_4Cl was the added and the mixture was diluted with EtOAc. This solution was washed with cold dilute HCl (0.5%), water, and brine and dried over Na_2SO_4. Evaporation and chromatography over silica gel (eluted with 0.25% AcOH in 25% EtOAc in hexanes) gave 135 mg (96%) of acid **21** as a clear colorless oil: $[\alpha]^{26}_D$ = −66.2° (*c* 1.35, $CHCl_3$); IR ($CHCl_3$) 3220–3600, 3010, 2980, 2970, 2890, 1730, 1600, 1580, 1455, 1340, 1325, 1175, 1110 cm^{-1}; ^1H NMR ($CDCl_3$, 490 MHz) δ 7.26–7.41 (m, 15 H, ArH), 6.80 (d, 1 H, J = 2.3 Hz, ArH), 6.74 (d, 1 H, J = 2.3 Hz, ArH), 5.72 (s, 1 H, H1), 5.04 (s, 2 H, $ArOCH_2Ph$), 4.58 (d, 1 H, J = 12.1 Hz, $ROCH_2Ph$), 4.54 (d, 1 H, J = 11.8 Hz, $ROCH_2Ph$), 4.51 (d, 1 H, J = 11.8 Hz, $ROCH_2Ph$), 4.49 (d, 1 H, J = 12.1 Hz, $ROCH_2Ph$), 4.24 (m, 1 H, H2), 4.22 (dd, 1 H, J = 4.6, 5.9 Hz, H4), 4.14 (ddd, J = 5.9, 6.3, 6.3 Hz, H5), 3.91 (dd, J = 1.8, 4.6 Hz, H3), 3.76 (overlapping m, 2 H, H6, H6′), 2.40 (t, 2 H, J = 7.2 Hz, CH_2), 1.30–1.81 (m, 14 H), 0.89 (t, 3 H, J = 7.2 Hz, CH_3).

3′-(Benzyloxy)-6′-carboxy-5′-(1-heptyn-1-yl)phenyl 2,3-Di-*O*-benzyl-5,6-cyclopentylidene-L-galactofuranoside (*ent*-21). This compound was prepared on a 0.092-mmol scale in 92% yield from aryl glycoside ***ent*-20** as described above for the D-antipode **21**: $[\alpha]^{23}_D$ = +68.1° (*c* 1.07, $CHCl_3$); FABLRMS (NOBA + NaI) *m/e* (relative intensity) 770 (11.4), 769 (25.3), 409 (23.7), 321 (50.6), 307 (58.4), 289 (41.5), 217 (31.9), 181 (100); FABHRMS calcd for $C_{46}H_{50}O_9Na$ 769.3352, found 769.3380.

3′-(Benzyloxy)-6′-[[5″-(1-heptyl)-3″-hydroxyphenoxy]carbonyl]-5′-(1-heptyn-1-yl)phenyl 2,3-Di-*O*-benzyl-D-galactofuranoside (22). A solution of acid **21** (30 mg, 0.04 mmol) and 5-heptylresorcinol (83 mg, 0.40 mmol, 10 equiv) in CH_2Cl_2 (2 mL) was treated at room temperature with 4-DMAP (6.3 mg, 0.052 mmol, 1.3 equiv) and EDCI (33.0 mg, 0.17 mmol, 4.3 equiv). After 6 h the solution was diluted with saturated aqueous NH_4Cl and extracted twice with EtOAc. Extracts were then washed with water and brine, dried ($MgSO_4$), and evaporated. Partial purification was performed by passage through a short column of silica gel (eluted with 15% EtOAc in hexanes) to provide recovered 5-heptylresorcinol (67 mg) and impure esterified arylfuranoside (18 mg). This material was stirred for 30 min at room temperature in TsOH–MeOH (0.025 M, 4 mL). The solution was then diluted with aqueous $NaHCO_3$ and EtOAc, and the organic layer was washed with water and brine and then dried over $MgSO_4$. Evaporation and chromatography over silica gel (eluted with 50% EtOAc in hexanes) gave 14.4 mg (41% from acid **21**) of pure **22** as a clear colorless oil: $[\alpha]^{26}_D$ = −69.7° (*c* 1.03, $CHCl_3$); IR ($CHCl_3$) 3150–3600, 3010, 2980, 2880, 1745, 1600, 1455, 1260, 1170, 1135, 1035 cm^{-1}; ^1H NMR ($CDCl_3$, 490 MHz) δ 7.24–7.40 (m, 15 H, ArH), 6.77 (d, 1 H, J = 2.2 Hz, ArH), 6.63 (d, 1 H, J = 2.2 Hz, ArH), 6.59 (br t, 1 H, J = <2 Hz, ArH), 6.50 (overlapping m, 2 H, ArH), 5.63 (s, 1 H, H1), 5.03 (s, 2 H, $ArOCH_2Ph$), 4.56 (d, 1 H, J = 11.9 Hz, $ROCH_2Ph$), 4.55 (d, 1 H, J = 11.7 Hz, $ROCH_2Ph$), 4.49 (d, 1 H, J = 11.7 Hz, $ROCH_2Ph$), 4.48 (d, 1 H, J = 11.9 Hz, $ROCH_2Ph$), 4.28–4.30 (overlapping m, 2 H, H2, H4), 4.11 (dd, 1 H, J = 2.9, 6.7 Hz, H3), 3.73 (br ddd, J = 6.7, 5.0, 5.0 Hz, H5), 3.61 (d, 2 H, J = 5.0 Hz, H6, H6′), 2.49 (t, 2 H, J = 7.8 Hz, $ArCH_2R$), 2.39 (t, 2 H, J = 7.2 Hz, CH_2), 1.23–1.64 (m, 16 H), 0.84–0.87 (overlapping t, 6 H, CH_3).

3′-(Benzyloxy)-6′-[[5″-(1-heptyl)-3″-hydroxyphenoxy]carbonyl]-5′-(1-heptyn-1-yl)phenyl 2,3-Di-*O*-benzyl-L-galactofuranoside (*ent*-22). This compound was prepared on a 0.04-mmol scale in 49% yield from acid ***ent*-21** as described above for the D-antipode **22**: $[\alpha]^{22}_D$ = +69.1° (*c* 0.65, $CHCl_3$); FABLRMS (NOBA + NaI) *m/e* (relative intensity) 893 (4.9), 663 (4.9), 5.29 (13.4), 321 (100); FABHRMS calcd for $C_{54}H_{62}O_{10}Na$ 893.4241, found 893.4268. Anal. Calcd for $C_{54}H_{62}O_{10}$: C, 74.46; H, 7.17. Found: C, 74.70; H, 6.98.

3′-(Benzyloxy)-6′-[[4″-[(benzyloxy)carbonyl]-5″-(1-heptyl)-3″-hydroxyphenoxy]carbonyl]-5′-(1-heptyn-1-yl)phenyl 2,3-Di-*O*-benzyl-D-galactofuranoside (23). A solution of acid **21** (135 mg, 0.18 mmol) and aryl alcohol **15** (62 mg, 0.18 mmol, 1 equiv) in CH_2Cl_2 (5 mL) was treated at room temperature with 4-DMAP (24 mg, 0.20 mmol, 1.1 equiv) and EDCI (69 mg, 0.36 mmol, 2 equiv). After 4 h the solution was diluted with saturated aqueous NH_4Cl and extracted twice with EtOAc. Extracts were then washed with water and brine, dried ($MgSO_4$), and evaporated. Partial purification was performed by passage through a short column of silica gel (eluted with 10% EtOAc in hexanes) to provide the desired esterified arylfuranoside contaminated with starting aryl alcohol **15** (190 mg, ca. 2.2:1 by ^1H NMR). This material was stirred for 30 min at room temperature in TsOH–MeOH (0.025 M, 10 mL). The solution was then diluted with aqueous $NaHCO_3$ and EtOAc, and the organic layer was washed with water and brine and then dried over $MgSO_4$. Evaporation and chromatography over silica gel (eluted with 40% EtOAc in hexanes) gave 123 mg (68% from acid **21**) of pure **23** as a clear colorless oil: $[\alpha]^{26}_D$ = −60.4° (*c* 1.08, $CHCl_3$); IR ($CHCl_3$) 3300–3600, 3010, 2980, 2970, 2885, 1750, 1715, 1660, 1600, 1460, 1365, 1320, 1250, 1145, 1035 cm^{-1}; ^1H NMR ($CDCl_3$, 490 MHz) δ 11.39 (s, 1 H, o-OH), 7.22–7.43 (m, 20 H, ArH), 6.81 (d, 1 H, J = 2.3 Hz, ArH), 6.77 (d, 1 H, J = 2.2 Hz ArH), 6.66 (d, 1 H, J = 2.2 Hz, ArH), 6.58 (d, 1 H, J = 2.3 Hz, ArH), 5.61 (s, 1 H, H1), 5.37 (s, 2 H, $ArCO_2CH_2Ph$), 5.04 (s, 2 H, $ArOCH_2Ph$), 4.58 (d, 1 H, J = 12.0 Hz,

$ROCH_2Ph$), 4.51 (d, 1 H, J = 11.7 Hz, $ROCH_2Ph$), 4.47 (d, 1 H, J = 12.0 Hz, $ROCH_2Ph$), 4.46 (d, 1 H, J = 11.7 Hz, $ROCH_2Ph$), 4.25 (m, 1 H, H2), 4.24 (dd, 1 H, J = 3.6, 6.5 Hz, H4), 4.09 (dd, 1 H, J = 2.9, 6.5 Hz, H3), 3.70 (m, 1 H, H5), 3.58-3.60 (overlapping m, 2 H, H6, H6'), 2.75 (t, 2 H, J = 8.0 Hz, $ArCH_2R$), 2.37 (t, 2 H, J = 7.2 Hz, CH_2), 1.00-1.57 (m, 16 H), 0.82-0.86 (overlapping t, 6 H, CH_3).

3'-(Benzyloxy)-6'-[[4''-[(benzyloxy)carbonyl]-5''-(1-heptyl)-3''-hydroxyphenoxy]carbonyl]-5'-(1-heptyn-1-yl)phenyl 2,3-Di-*O*-benzyl-L-galactofuranoside (*ent*-23). This compound was prepared on a 0.04-mmol scale in 69% yield from acid ***ent*-21** as described above for the D-antipode **23**: $[\alpha]^{22}_D$ = +58.0° (*c* 1.07, $CHCl_3$); FABLRMS (NOBA + NaI) *m/e* (relative intensity) 1027 (2.6), 663 (6.3), 411 (6.24), 321 (100); FABHRMS calcd for $C_{62}H_{68}O_2Na$ 1027.4608, found 1027.4668. Anal. Calcd for $C_{62}H_{68}O_{12}$: C, 74.08; H, 6.82. Found: C, 73.79; H, 6.56.

KS-501 (1). Compound **22** (14 mg, 0.016 mmol) was hydrogenated over 10% Pd/C (15 mg) under 1 atm of H_2 in EtOH (3 mL) for 36 h. The mixture was filtered, evaporated, and passed through a short pad of silica gel (eluted with 15% MeOH in $CHCl_3$) to leave 10.4 mg (100%) of pure **1** as a clear oil that solidified on standing: $[\alpha]^{23}_D$ = -54.3° (*c* 0.67, MeOH) (lit.[1] $[\alpha]^{23}_D$ = -53° (*c* 0.3, MeOH)); identical by TLC mobility, UV, and ^1H NMR spectra to the natural material.

***ent*-KS-501 (*ent*-1).** Compound ***ent*-22** (17 mg, 0.02 mmol) was hydrogenated over 10% Pd/C (20 mg) under 1 atm of H_2 in EtOH (4 mL) for 36 h. The mixture was filtered, evaporated, and passed through a short pad of silica gel (eluted with 15% MeOH in $CHCl_3$) to leave 10.4 mg (88%) of pure ***ent*-1** as a clear oil that solidified on standing: $[\alpha]^{23}_D$ = +53.5° (*c* 0.68, MeOH); identical by TLC mobility, UV, and ^1H NMR spectra to the natural isomer.

KS-502 (2). Compound **23** (120 mg, 0.12 mmol) was hydrogenated over 10% Pd/C (100 mg) under 1 atm of H_2 in EtOH (10 mL) for 14 h. The mixture was filtered, evaporated, and passed through a short pad of LiChroprep RP-18 (eluted with MeOH) to leave 77 mg (100%) to pure **2** as a clear oil that solidified on standing: $[\alpha]^{22}_D$ = -42.8° (*c* 0.54, MeOH) (lit.[1] $[\alpha]^{23}_D$ = -45° (*c* 0.3, MeOH)); identical by TLC mobility, UV, and ^1H NMR spectra to the natural material.

***ent*-KS-502 (*ent*-2).** Compound ***ent*-23** (19 mg, 0.019 mmol) was hydrogenated over 10% Pd/C (15 mg) under 1 atm of H_2 in EtOH (3 mL) for 24 h. The mixture was filtered, evaporated, and passed through a short pad of LiChroprep RP-18 (eluted with MeOH) to leave 13 mg (100%) of pure ***ent*-2** as a clear oil that solidified on standing: $[\alpha]^{22}_D$ = +42.0° (*c* 0.40, MeOH); identical by TLC mobility, UV, and ^1H NMR spectra to the natural isomer.

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Synthesis of a Cyanobacterial Sulfolipid: Confirmation of Its Structure, Stereochemistry, and Anti-HIV-1 Activity

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Abstract: The total synthesis of a cyanobacterial sulfolipid is described. The key steps involve the epoxidation of a glycal followed by conversion to a 1β-fluoro-2α-hydroxy moiety. After protection of the alcohol, the anomeric β-fluoro substituent is used to fashion an α-glycoside of a glycerol. A sulfonic acid is introduced at the 6-position by oxidation of a thioacetate with Oxone in the presence of a triene subunit.

By taking advantage of a newly developed soluble formazan assay to screen for the cytopathic effects of HIV-1 and for inhibitors of these effects,[1] scientists at the National Cancer Institute (NCI) were able to identify active principles from various cyanobacterial (blue-green algae) media.[2] From these cultures were isolated a series of related sulfolipids. Painstaking chromatographic separation provided four homogeneous compounds, which were tentatively assigned as structures **1-4**. The formulation of the sites of the nonidentical side chains in the diacylglycerol moiety followed from the analysis of mass spectrometric fragmentation data.[2] The *S* configuration at C_2 of the glycerol was presumed from the similarity of the optical rotation of the bis-deacylated product with that of material of known configuration.[3,4]

In light of their activity (EC_{50} 0.1-1 μg/mL depending upon the target cell line) and their undetermined mechanism of action, the sulfolipids were selected by the NCI for further preclinical investigation and for evaluation as to their possible clinical usefulness against AIDS.[2] In particular, questions regarding both the administration of the sulfolipids and their stability as well as efficacy in vivo require immediate attention. Unfortunately, progress toward these goals has been impeded by difficulties in the fermentation process and by the complexities of separating the closely related components of the mixture.[5]

In addition to the relevance of the compounds to issues of current medical concern, the development of a synthetic route to the cyanobacterial sulfolipid series was seen as providing an opportunity to implement strategies which our laboratory has been devising in the field of carbohydrate synthesis. Since we had developed concise methodology for the total synthesis of glycals using the LACDAC reaction,[6] it was our intention to reach compound **1** via a glycal. The use of a glycal starting material was clearly not the only way to reach any of the compounds of

(1) Weislow, O. S.; Kiser, R.; Fine, D. L.; Bader, J.; Shoemaker, R. H.; Boyd, M. R. *J. Natl. Cancer Inst.* **1989**, *81*, 577.

(2) Gustafson, K. R.; Cardellina, J. H., II; Fuller, R. W.; Weislow, O. S.; Kiser, R. F.; Snader, K. M.; Patterson, G. M. L.; Boyd, M. R. *J. Natl. Cancer Inst.* **1989**, *81*, 1254.

(3) Lepage, M.; Daniel, H.; Benson, A. A. *J. Am. Chem. Soc.* **1961**, *83*, 157.

(4) Okaya, Y. *Acta Crystallogr.* **1964**, *17*, 1276.

(5) (a) Cardellina, J. H., II The National Cancer Institute, Frederick, MD, Personal communication, 1991. (b) Acton, E. The National Cancer Institute, Frederick, MD, Personal communication, 1991.

(6) (a) Danishefsky, S. J. *Chemtracts: Org. Chem.* **1989**, *2*, 273. (b) Danishefsky, S. J.; DeNinno, M. P. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 15. (c) Danishefsky, S. J. *Aldrichimica Acta* **1986**, *19*, 59.

0002-7863/92/1514-659$03.00/0