From 2,2′-Methylenedifuran to All Stereomeric Pentadecane-1,3,5,7,9,11,13,15-octols

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A great variety of natural products of biological interest includes polyketides (1,3-polyoxo, 1,3-polyols, aldols).[1] Several approaches for their synthesis have been proposed.[2,3] Inspired by the work of Lautens[4] and Hoffmann and co-workers,[5] who have converted 8-oxabicyclo[3.2.1]-oct-6-en-3-one into 7-carbon-1,3-polyols and analogues,[6] and by that of Kaku et al.,[7] who have transformed cyclohept-3-ene-1,6-diol into 1,3-polyols, we have proposed a new, noniterative asymmetric synthesis of long-chain 1,3-polyols starting from the now readily available 2,2′-methylenedifuran (**1**).[8] The method imployed the double [3+4]-cycloaddition of the 1,1,3-trichloro-2-oxyallyl cation to **1**. After reductive workup, a 45:55 mixture of *meso*-**2** and (±)-*threo*-**2** was obtained in 55% yield and separated by fractional crystallizations. The meso compound was converted into *meso*-**3**, which was desymmetrized into diol (−)-**4** by means of the Sharpless asymmetric dihydroxylation.[9] Further transformations imploying the combinations of Evans' anti[10] and Nasaraka's syn[11] aldol reductions with Mitsunobu reaction[12] allow to prepare, in principle, 16 diastereomeric pentadecane-1,3,5,7,9,11,13,15-octols (e.g., (−)-**5**) and analogues (Scheme 1). If the syn relationship between the 4-methoxybenzoates at C-3 and C-13 (atom numbering of (−)-**5**) could be changed into an anti relative configuration, all possible stereomeric pentadecane-1,3,5,7,9,11,13,15-octols could be reached in both enantiomeric forms. We report here a solution to that problem.

As already described,[8] diol (−)-**4** was converted (Scheme 2) into tetrol (−)-**6** in 75% overall yield. Treatment of (−)-**6** with $(MeO)_2CMe_2$ in acetone under acidic conditions (pyridinium paratoluenesulfonate) gave acetonide (−)-**7** in 92% yield. Heating (−)-**7** in acetonitrile in the presence of 12 equiv of DBU (1,8-diazabicyclo[5.4.0]undec-7-ene) induced the isomerization of (−)-**7** into the primary paramethoxybenzoate (−)-**8**. Equilibrium ([(−)-**8**]/[(−)-**7**] = 3.0) was reached after 4 h at 80 °C, and (−)-**8** could be isolated in 70% yield (Scheme 2). This result can be interpreted in terms of acyl group migration from the C-3 to the C-1 position (atom numbering of (−)-**5**; IUPAC numbering: 2‴,4‴, see (−)-**8**), the primary ester (−)-**8** being more stable than (−)-**7** for steric reasons. Also for steric reasons, the intramolecular migration of the paramethoxybenzoyl group from the 1-oxy position to the 6-hydroxy group of the cycloheptenol moiety is forbidden. Attempts to displace the acyclic secondary alcohol at C-3 (atom numbering of (−)-**5**; IUPAC: 2‴) using the Mitsunobu reaction ($(EtOOC)_2N_2$, PPh_3, 4-$NO_2C_6H_4COOH$)[12] were not met with success. They led to complex mixtures. Selective sulfonylation of the acyclic alcohol at C-3 (IUPAC: 2‴) with CH_3SO_2Cl and *p*-TsCl (pyridine, Et_3N) also led to intractable mixtures.

Selective methanolysis of the acyclic paramethoxybenzoate at C-3 (IUPAC: 6′) was possible on treating (−)-**7** in MeOH containing 7.2 equiv of $Mg(OMe)_2$ (40 °C, 8 h). This furnished triol (−)-**9** in 68% yield, together with 12% of (−)-**8**. Dihydroxylation of the cycloheptene moiety of (−)-**9** with (*N*-methylmorpholine *N*-oxide, cat. OsO_4, CCl_4) followed by oxidative cleavage of the vicinal diol with $Pb(OAc)_4$ provided (+)-**10** (3:2 mixture of anomers) in 92% yield. Treatment of (+)-**10** with $(i\text{-prop})_3SiCl$ and imidazole (DMF, 20 °C, 48 h) led to selective double silylation of the pyranose and primary alcoholic functions, leaving the secondary alcohol at C-3 (IUPAC: 2‴) unprotected. This provided (+)-**11** in 73% yield as a single β-pyranoside.[13] Sulfonylation of the secondary alcohol (+)-**11** with CH_3SO_2Cl (pyridine, DMAP cat.) gave the corresponding mesylate that was not purified but used directly in the next step. Heating this mesylate in benzene containing anhydrous CsOAc and 18-crown-6 ether led to a 3:2 mixture of the product of S_N2 substitution (+)-**12** and of unreacted mesylate. This could not been pushed to completion as decomposition completed with the substitution. Acetate (+)-**12** was isolated in 63% yield, together with unreacted mesylate (32%), after column flash chro-

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(13) Structure confirmed by ^3J(H-6,H-5) = 7.4 Hz.

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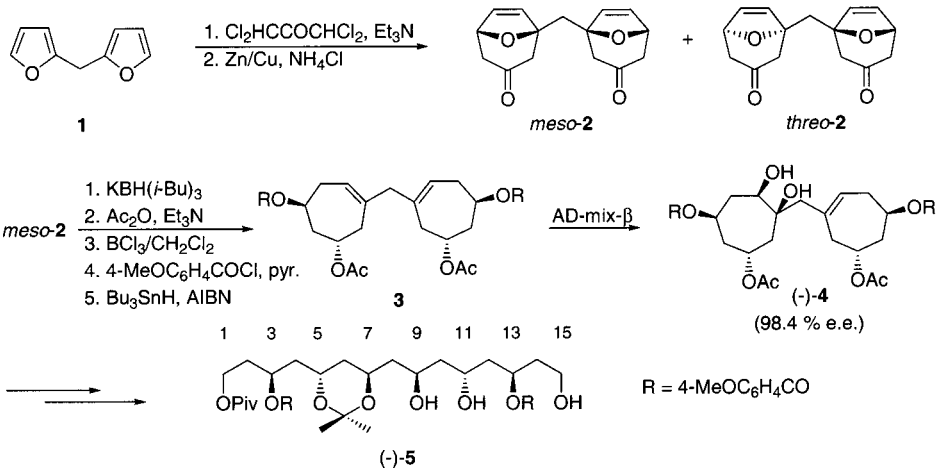
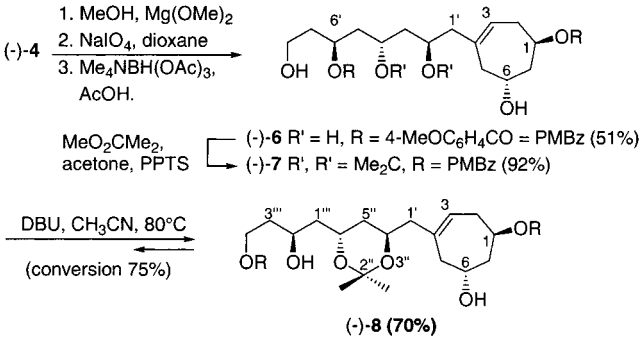
Scheme 1



Scheme 2



matography on silica gel. According to the NMR data, it was a different product than that of acetylation of (+)-**10** with Ac_2O/pyr./DMAP.

Selective monodesilylation of (+)-**12** with Bu_4NF (THF, −78 to −50 °C) liberated the pyranose without desilylation of the primary alcoholic moiety. This furnished (+)-**13** in 85% yield. Reduction of (+)-**13** under Evans' conditions[10] ($Me_4NBH(OAc)_3$/AcOH/CH_3CN, 0−2 °C, 15 h) provided triol (−)-**14** isolated in 44% yield. Its structure was confirmed by the ^{13}C NMR spectra[14] of the corresponding tetraacetonide (−)-**15** obtained by desilylation of (−)-**14** with Bu_4NF (THF, 20 °C), followed by methanolysis of the ester (MeOH/MeOK) and treatment with $(MeO)_2CMe_2$/acetone under acidic conditions.

This paper together with our previous report[8] demonstrates that *meso*-1,1′-methylenedi[(1*R*,1′*S*,5*S*,5′*R*)-3-oxo-8-oxabicyclo[3.2.1]oct-6-ene] (*meso*-**2**) obtained readily from furan and furfuryl alcohol can be converted, in principle, into all possible stereomeric pentadecane-1,3,5,7,9,11,13,15-octols with high stereoselectivity and enantiomeric purity. This realizes a flexible, noniterative approach to the total asymmetric synthesis of long-chain polyketides. The success of this approach relies on well-established reactions such as Evans' anti[10] and Nasaraka's syn[11] reductions of aldols, S_N2 substitution[12] and on our ability to differentiate between the reactivity of alcohols on aliphatic and on cycloheptene or tetrahydropyran rings. The method permits the synthesis of polyketides bearing various protective groups, thus enhancing its flexibility.

Experimental Section

General Remarks. See ref 15. Flash column chromatography (FC) was performed on Merck silica gel (230−400 mesh, no. 9385). Thin-layer chromatography (TLC) was carried out on silica gel (Merck aluminum foils). ^1H NMR signals assignments were confirmed by double irradiation experiments and, when required, by 2D NOESY and COSY spectra. *J* values are given in hertz.

(−)-(1*R*,6*R*)-6-Hydroxy-4-[[(4*R*,6*S*)-6-[(2*S*)-4-hydroxy-2-[(4-methoxybenzoyl)oxy]butyl]-2,2-dimethyl-1,3-dioxan-4-yl]methyl]cyclohept-3-en-1-yl 4-Methoxybenzoate ((−)-7). A mixture of (−)-**6**[8] (0.95 g, 1.66 mmol), acetone (20 mL), 2,2-dimethoxypropane (9.5 mL), and pyridinium paratoluenesulfonate (45 mg) was stirred at 0 °C for 4 h. The solvent was evaporated to dryness and the residue taken in CH_2Cl_2 (20 mL). After the temperature was maintained at 20 °C for 2 h with pyridinium paratoluenesulfonate (5 mg), $NaHCO_3$ (100 mg) was added under vigorous stirring. The solvent was evaporated and the residue purified by FC (CH_2Cl_2/MeOH 97:3) giving 935 mg (92%) of (−)-**7**, colorless, amorphous solid: $[\alpha]^{25}_D = -17$ (*c* = 0.94, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 8.01−7.94 (m, 4H), 6.94−6.88 (m, 4H), 5.63 (t, 1H, *J* = 6.6 Hz), 5.46 (dddd, 1H, *J* = 9.8, 9.7, 3.2, 3.1 Hz), 5.16 (dddd, 1H, *J* = 9.7, 9.6, 3.9, 3.8 Hz), 4.06 (m, 1H), 3.99 (m, 1H), 3.91 (m, 1H), 3.86 (s, 3H), 3.84 (s, 3H), 3.79−3.55 (m, 2H), 2.91 (br.s, 1H), 2.53 (br.s, 1H), 2.51−2.42 (m, 4H), 2.26−2.09 (m, 4H), 1.98−1.87 (m, 2H), 1.81−1.72 (m, 2H), 1.64 (ddd, 1H, *J* = 21.7, 12.8, 8.9 Hz), 1.63 (ddd, 1H, *J* = 21.7, 12.8, 9.0 Hz), 1.31 (s, 3H), 1.14 (s, 3H). Anal. Calcd for $C_{34}H_{44}O_{10}$ (612.716): C, 66.65; H, 7.24. Found: C, 66.51; H, 7.36.

(−)-(1*R*,6*R*)-6-Hydroxy-4-[[(4*R*,6*S*)-6-[(2*S*)-4-[(4-methoxybenzoyl)oxy]-2-hydroxybutyl]-2,2-dimethyl-1,3-dioxan-4-yl]methyl]cyclohept-3-en-1-yl 4-Methoxybenzoate ((−)-8). A mixture of (−)-**7** (0.1 g, 0.16 mmol), anhyd CH_3CN (4 mL), and DBU (0.3 g, 1.97 mmol) was heated to 80 °C for 4 h. After being cooled to −78 °C, the solution was poured dropwise into 1% aqueous HCl solution, cooled to 0 °C under vigorous stirring, and extracted with EtOAc (10 mL, three times). The combined organic extracts were dried ($MgSO_4$). After filtration (Celite), $NaHCO_3$ (20 mg) was added and the solvent evaporated to dryness. FC (CH_2Cl_2/MeOH 98:2, R_f ((−)-**7**) = 0.22, R_f ((−)-**8**) = 0.27) gave (−)-**7** (22 mg, 22%) and (−)-**8** (70 mg, 70%): colorless oil; $[\alpha]^{25}_D = -51$ (*c* = 1.10, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 8.01−7.95 (m, 4H), 6.94−6.89 (m, 4H), 5.67 (t, 1H, *J* = 6.8 Hz), 5.18 (m, 1H), 4.53 (ddd, 1H, *J* = 11.1, 8.2, 5.5 Hz), 4.40 (ddd, 1H, *J* = 11.1, 5.7, 5.6 Hz), 4.18 (m, 1H), 4.11 (m, 1H), 4.03 (m, 2H), 3.86 (s, 6H), 2.53−2.48 (m, 4H), 2.27−2.15 (m, 4H), 1.69 (t, 2H, *J* = 5.8 Hz), 1.75−1.68 (m, 1H), 1.61 (ddd, 1H, *J* = 13.0, 9.1, 6.0 Hz), 1.37 (s, 3H), 1.36 (s, 3H). Anal. Calcd for $C_{43}H_{44}O_{10}$ (612.72): C, 66.65; H, 7.24. Found: C, 66.52; H, 7.24.

(−)-(1*R*,6*R*)-6-Hydroxy-4-[[(4*R*,6*R*)-6-[(2*S*)-2,4-dihydroxybutyl]-2,2-dimethyl-1,3-dioxan-4-yl]methyl]cyclohept-3-en-

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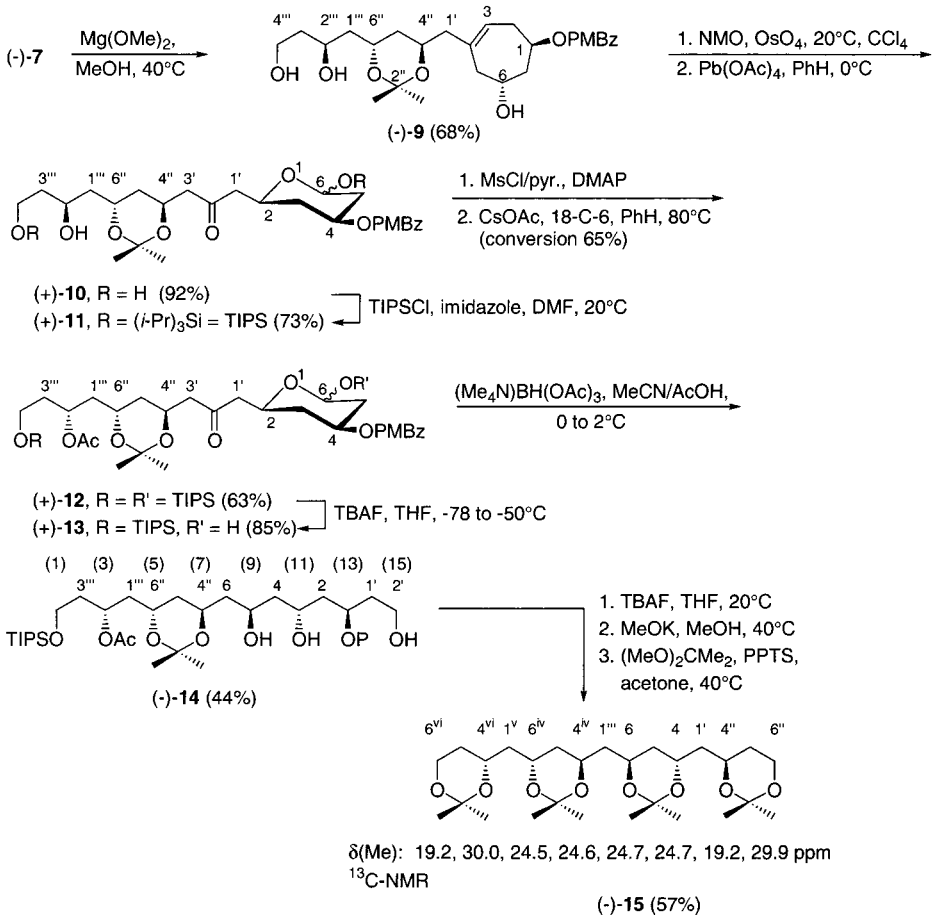
Scheme 3



1-yl 4-Methoxybenzoate ((−)-9). A 0.6 M solution of $Mg(OMe)_2$ in anhyd MeOH (6 mL, 3.6 mmol) was added dropwise to a stirred solution of (−)-**7** (305 mg, 0.5 mmol) in anhyd MeOH (10 mL). The mixture was stirred at 40 °C for 8 h (TLC, SiO_2, CH_2Cl_2/MeOH 95:5, R_f ((−)-7) = 0.35, R_f ((−)-8) = 0.40, R_f ((−)-9) = 0.19). After being cooled to 0 °C, the mixture was neutralized with 0.5 M anhyd oxalic acid solution in MeOH. The solvent was evaporated and the residue purified by FC (CH_2Cl_2/MeOH 95:5) giving (−)-**8** (37 mg, 12%) and (−)-**9** (162 mg, 68%): colorless oil; $[\alpha]^{25}_D = -52$ (c = 1.05, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (m, 2H), 6.90 (m, 2H), 5.66 (t, 1H, J = 6.8 Hz), 5.17 (tt, 1H, J = 8.4, 3.5 Hz), 4.22−4.00 (m, 4H), 3.89−3.80 (m, 2H), 3.86 (s, 3H, OMe), 2.50 (m, 4H), 2.24 (m, 3H), 2.14 (ddd, 1H, J = 13.6, 8.8, 3.2 Hz), 1.80−1.59 (m, 6H), 1.38, 1.37 (2s, 6H). Anal. Calcd for $C_{26}H_{38}O_8$ (478.58): C, 65.25; H, 8.00; found: C, 65.19; H, 8.03.

(+)-(2*S*,4*S*,6*S* and 6*R*)-2-[3-[(4*S*,6*S*)-6-[(2*S*)-2,4-Dihydroxybutyl]2,2-dimethyl-1,3-dioxan-4-yl]-2-oxopropyl]tetrahydro-6-hydroxy-2*H*-pyran-4-yl 4-Methoxybenzoate ((+)-10). A mixture of (−)-**9** (135 mg, 0.28 mmol), acetone (1.3 mL), H_2O (0.2 mL), *N*-methylmorpholine *N*-oxide (65 mg, 0.48 mmol), and a 0.1 M solution of OsO_4 in CCl_4 (0.13 mL) was stirred at 20 °C for 15 h. $Na_2S_2O_5$ (0.1 g) was added and the mixture stirred at 20 °C for 30 min and extracted with EtOAc (2 mL, five times); the combined extracts were dried ($MgSO_4$) and the solvent evaporated to dryness. The residue was taken in dioxane (2 mL). Benzene (5 mL) was added and the solution cooled to 0 °C. $Pb(OAc)_4$ (dried under vacuum, 10^{-3} Torr, 20 °C) was added (185 mg, 0.42 mmol) portionwise under stirring. Stirring was continued at 0 °C for 15 min (TLC, SiO_2, CH_2Cl_2/MeOH 9:1, R_f (intermediate diol) = 0.12, R_f ((+)-**10**) = 0.26) and a saturated aqueous solution of $NaHCO_3$ (2 mL) was added under vigorous stirring. The mixture was extracted with EtOAc (3 mL, five times). The combined extracts were dried ($MgSO_4$), the solvent was evaporated, and the residue was purified by FC (CH_2Cl_2/MeOH 95:5) yielding (+)-**10** (132 mg, 92%) as a colorless oil: $[\alpha]^{25}_D = +8$ (c = 0.51, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (m, 2H), 6.92 (m, 2H), 5.48 (tt, 0.6H, J = 11.4, 4.9 Hz), 5.44 (br.s, 0.6H), 5.31 (tt, 0.4H, J = 11.4, 4.9 Hz), 4.87 (br d, 0.4H, J = 8.6 Hz), 4.65 (m, 0.6H), 4.34 (m, 1H), 4.16 (m, 2H), 4.04 (m, 0.4H), 3.87 (m, 2H), 3.86 (s, 3H), 2.88 (dd, 0.4H, J = 16.5, 8.3 Hz), 2.74, 2.54 (2m, 3.6H), 2.45−2.07 (m, 2H), 1.85−1.38 (m, 8H), 1.36 (s, 6H). Anal. Calcd for $C_{26}H_{38}O_{10}$ (510.78): C, 61.16; H, 7.50. Found: C, 61.22; H, 7.56.

(+)-(2*S*,4*S*,6*S*)-2-[3-[(4*S*,6*S*)-6-[(2*S*)-2-Hydroxy-4-[(triisopropylsilyl)oxy]butyl]-2,2-dimethyl-1,3-dioxan-4-yl]-2-oxopropyl]tetrahydro-6-[(triisopropylsilyl)oxy]-2*H*-pyran-4-yl 4-Methoxybenzoate ((+)-11). A mixture of (+)-**10** (124 mg, 0.24 mmol), anhyd DMF (6 mL), imidazole (185 mg, 2.72 mmol), and $(i\text{-Pr})_3SiCl$ (0.25 mL, 227 mg, 1.18 mmol) was stirred at 20 °C for 48 h (TLC, SiO_2, CH_2Cl_2/MeOH 95:5, R_f ((+)-**11**) = 0.50). The mixture was neutralized by addition of a saturated aqueous solution of $NaHCO_3$ (15 mL) and extracted with EtOAc (5 mL, three times). The combined organic extracts were dried ($MgSO_4$), and the solvent was removed. FC (Et_2O/light petroleum ether 3:2) yielded (+)-**11** (146 mg, 73%) as a colorless oil: $[\alpha]^{25}_D = +5$ (c = 1.20, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (m, 2H), 6.90 (m, 2H), 5.14 (tt, 1H, J = 11.4, 4.7 Hz), 4.86 (dd, 1H, J = 7.4, 1.9 Hz), 4.27 (m, 1H), 4.12 (m, 1H), 4.07−3.87 (m, 4H), 3.86 (s, 3H), 3.62 (br d, 1H, J = 2.3 Hz), 2.85 (dd, 1H, J = 16.5, 7.6 Hz), 2.72 (br dd, 1H, J = 16.4, 8.2 Hz), 2.53 (br dd, 1H, J = 16.5, 4.8 Hz), 2.47 (br dd, 1H, J = 16.4, 4.5 Hz), 2.32 (br d, 1H, J = 9.0 Hz), 2.08 (br d, 1H, J = 12.1 Hz), 1.73−1.45 (m, 7H), 1.41 (br d, 1H, J = 11.8 Hz), 1.34, 1.33 (2s, 6H), 1.15−0.97 (m, 42H). Anal. calcd for $C_{44}H_{78}O_{10}Si_2$ (823.26): C, 64.19; H, 9.55. Found: C, 64.22; H, 9.61.

(+)-(2*S*,4*S*,6*S*)-2-[3-[(4*S*,6*S*)-6-[(2*R*)-2-Acetoxy-4-[(triisopropyl)oxy]butyl]-2,2-dimethyl-1,3-dioxan-4-yl]-2-oxopropyl]tetrahydro-6-[(triisopropylsilyl)oxy]-2*H*-pyran-4-yl 4-Methoxybenzoate ((+)-12). A mixture of (+)-**11** (140 mg, 0.17 mmol), CH_2Cl_2 (4 mL), anhyd pyridine (0.4 mL), $MeSO_2Cl$ (0.2 mL, 295 mg, 2.57 mmol), and 4-(dimethylamino)pyridine (10 mg) was stirred at 20 °C for 4 h. A saturated aqueous solution of $NaHCO_3$ (4 mL) was added and the mixture stirred

at 20 °C for 30 min. The mixture was extracted with CH_2Cl_2 (5 mL, three times). The combined organic extracts were dried ($MgSO_4$) and evaporated to dryness (20 °C, 10^{-3} Torr). The residue was taken in anhyd benzene (4 mL). Cesium acetate (520 mg, 2.7 mmol) and 18-crown-6 ether (160 mg, 0.6 mmol) were added, and the mixture was heated to 80 °C for 6 h. After the mixture was heated to 20 °C, a saturated aqueous solution of $NaHCO_3$ (2 mL) was added and the mixture extracted with EtOAc (2 mL, twice). The combined organic extracts were dried ($MgSO_4$), and the solvent was evaporated. FC (Et_2O/light petroleum ether 3:2) yielded (+)-**12** (94 mg, 63%) as a colorless oil (R_f = 0.52) and 35 mg of the intermediate mesylate (22%) that can be used in a second batch for the displacement reaction. Data for (+)-**12**: $[\alpha]^{25}_D$ = +5 (c = 0.95, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 (m, 2H), 6.91 (m, 2H), 5.15 (m, 1H), 4.86 (br dd, J = 9.1, 1.8, 1H), 4.26 (m, 1H), 3.98 (m, 1H), 3.89 (m, 1H), 3.86 (s, 3H), 3.72 (t, 2H, J = 6.5 Hz), 2.85 (dd, 1H, J = 16.5, 7.6 Hz), 2.71 (dd, 1H, J = 16.4, 8.4 Hz), 2.53 (dd, 1H, J = 16.5, 4.8 Hz), 2.46 (dd, 1H, J = 16.4, 4.3 Hz), 2.33 (br d, 1H, J = 11.0 Hz), 2.08 (m, 1H), 2.03 (s, 3H), 1.90−1.80 (m, 3H), 1.74−1.56 (m, 4H), 1.46−1.30 (m, 1H), 1.33, 1.29 (2s, 6H), 1.05 (m, 42H). Anal. Calcd for $C_{46}H_{80}O_{11}Si_2$ (865.30): C, 63.85; H, 9.32. Found: C, 63.85; H, 9.27.

(+)-(2*S*,4*S*,6*S* and 6*R*)-Tetrahydro-6-hydroxy-2-[3-[(4*S*,6*R*)-6-[(2*S*)-2-acetoxy-4-[(triisopropylsilyl)oxy]butyl]-2,2-dimethyl-1,3-dioxan-4-yl]-2-oxopropyl]-2*H*-pyran-4-yl 4-Methoxybenzoate ((+)-13). A 0.1 M solution of Bu_4NF in anhyd THF (0.4 mL) was added dropwise to a stirred solution of (+)-**12** (35 mg, 0.04 mmol) in anhyd THF (6 mL) cooled to −78 °C. The mixture was stirred at −50 °C for 1 h and was poured into an ice-cold, saturated aqueous solution of NH_4Cl (1 mL) under vigorous stirring. Stirring at 20 °C was continued for 30 min, and the mixture was extracted with EtOAc (3 mL, three times). The combined organic extracts were dried ($MgSO_4$), and the solvent was evaporated. FC (CH_2Cl_2/MeOH 97:3) yielded (+)-**13** (24 mg, 85%) as colorless oil: $[\alpha]^{25}_D$ = +8 (c = 1.10, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 (m, 2H), 6.91 (m, 2H), 5.48 (tt, 0.6H, J = 11.3, 4.9 Hz), 5.43 (br.s, 0.6H), 5.16 (m, 1.4 + 0.4H), 4.88 (ddd, 0.4H, J = 9.6, 5.5, 1.8 Hz), 4.60 (m, 0.6H), 4.29 (m, 1H), 3.97 (m, 0.4H), 3.86 (s, 6H), 3.77 (m, 1H), 3.70 (m, 2H), 2.83 (dd, 0.4H, J = 14.9, 9.1 Hz), 2.78−2.64 (m, 2H), 2.57−2.39 (m, 2H), 2.38−2.07 (m, 2H), 2.05, 2.03 (2s, 6H), 1.95−1.35 (m, 8H), 1.33, 1.32, 1.30, 1.29 (4s, 6H), 1.05 (m, 21H). Anal. Calcd for $C_{37}H_{60}O_{11}Si$ (708.96): C, 62.68; H, 8.53. Found: C, 62.56; H, 8.62.

(−)-(1*R*,3*R*,5*R*)-3,5-Dihydroxy-1-(2-hydroxymethyl)-6-[(4*R*,6*R*)-6-[(2*R*)-2-acetoxy-4-[(triisopropyl)oxy]-butyl]-2,2-dimethyl-1,3-dioxan-4-yl]hexyl 4-Methoxybenzoate ((−)-14) (or 3-*O*-Acetyl-5,7-*O*-diisopropylidene-13-*O*-(4-methoxybenzoyl)-1-*O*-(triisopropylsilyl)-(3*R*,5*S*,7*R*,9*R*,11*R*,13*R*)-pentadecane-1,3,5,7,9,11,13,15-octol). A 9:1 mixture of AcOH/CH_3CN (1.35 mL) was added dropwise to a stirred solution of (+)-**13** (23 mg, 0.032 mmol) and Me_4NBH_4 (440 mg) cooled to 0 °C. After the mixture was stirred at 2 °C for 15 h (TLC, SiO_2, CH_2Cl_2/MeOH 9:1, R_f ((+)-**13**) = 0.64, R_f ((−)-**14**) = 0.47), the solvent was evaporated to dryness (10^{-3} Torr, 20 °C), and a saturated aqueous solution of $NaHCO_3$ (3 mL) was added. After the mixture was stirred at 20 °C for 10 min, more $NaHCO_3$ was added until neutralization. The mixture was extracted with EtOAc (3 mL, five times). The combined organic extracts were dried ($MgSO_4$), and the solvent was evaporated. FC (CH_2Cl_2/MeOH 97:3) yielded (−)-**14** (10 mg, 44%) as a colorless oil: $[\alpha]^{25}_D$ = −14 (c = 0.60, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.99 (m, 2H), 6.92 (m, 2H), 5.51 (tt, 1H, J = 8.4, 4.2 Hz), 5.14 (quint, 1H, J = 6.7 Hz), 4.09 (m, 2H), 3.92 (m, 2H), 3.87 (s, 3H), 3.71 (t, 2H, J = 6.5 Hz), 3.67 (m, 2H), 2.02 (s, 3H), 2.05−1.40 (m, 14H), 1.36, 1.31 (2s, 6H), 1.05 (m, 21H). Anal. Calcd for $C_{37}H_{64}O_{11}Si$ (712.99): C, 62.33; H, 9.05. Found: C, 62.22; H, 9.09.

(−)-(4*S*,6*R*)-4-[[(4*R*)-2,2-Dimethyl-1,3-dioxan-4-yl]methyl]-6-[[(4*S*,6*R*)-6-[[(4*R*)-2,2-dimethyl-1,3-dioxan-4-yl]methyl]-2,2-dimethyl-1,3-dioxan-4-yl]methyl]-2,2-dimethyl-1,3-dioxan ((−)-15) (or 1,3:5,7:9,11:13,15-Tetra-*O*-isopropylidene-(3*R*,5*R*,7*S*,9*R*,11*S*,13*R*)-pentadecane-1,3,5,7,9,11,13,15-octol). A mixture of (−)-**14** (10 mg, 0.014 mmol), anhyd THF (1 mL), and 1 M Bu_4NF in anhyd THF (0.03 mL) was stirred at 20 °C for 2.5 h. The solvent was evaporated to dryness (10^{-3} Torr, 20 °C) and the residue taken in anhyd MeOH (2 mL). After the addition of MeOK (20 mg), the solution was stirred at 20 °C for 15 h. AcOH was added until neutralization (bromothymol blue), and SiO_2 (200 mg) was added. The solvent was evaporated and the residue purified by FC (CH_2Cl_2/MeOH 9:1, then 7:3). The main fraction was dissolved in acetone (3 mL), and 2,2-dimethoxypropane (2 mL), pyridinium paratoluenesulfonate (3 mg), and anh. $CuSO_4$ (50 mg) were added. The mixture was stirred at 40 °C for 15 h (TLC, SiO_2, Et_2O/light petroleum ether 3:2, R_f ((−)-**15**) = 0.32). A saturated aqueous solution of $NaHCO_3$ (0.5 mL) was added, and the solvent was evaporated to dryness (10^{-3} Torr, 20 °C). The residue was taken with H_2O (2 mL) and extracted with EtOAc (2 mL, five times). The combined organic extracts were dried ($MgSO_4$), and the solvent was evaporated. FC (Et_2O/light petroleum ether 1:1) yielded (−)-**15** (4 mg, 57%): colorless oil; $[\alpha]^{25}_D$ = −19 (c = 0.35, $CHCl_3$); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 100.4, 100.2 (2s), 98.3, 98.2 (2s), 65.6, 64.9, 63.3, 63.1, 62.7, 62.1 (6d), 60.1, 59.9 (2t), 42.3, 41.8, 38.6, 38.3, 31.7, 30.8 (6t), 30.0, 29.9 (2q), 24.7, 24.7, 24.6, 24.5 (4q), 19.2 (q). Anal. Calcd for $C_{27}H_{48}O_8$ (500.67): C, 64.77; H, 9.66. Found: C, 64.81; H, 9.67.

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Supporting Information Available: Detailed ^{1}H and ^{13}C NMR spectra and signal assignments and UV, IR, and MS spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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