An Expeditious, Non-Iterative, and Asymmetric Synthesis of 3,5,7,9,11,13,15-Heptahydroxypentadecanals

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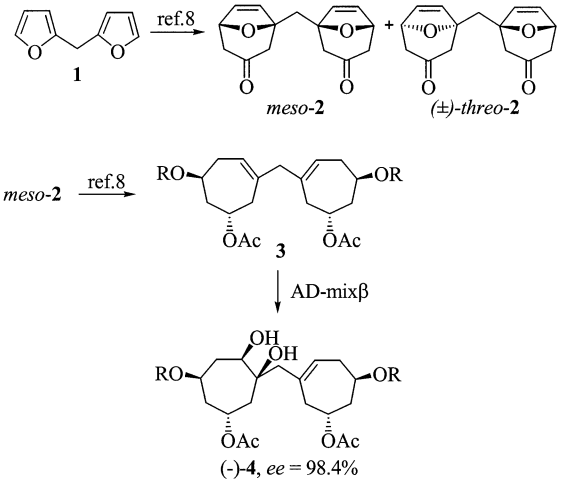
Ozonolysis of (1*R*,1′*R*,6*R*,6′*R*)-3,3′-methylenebis{6-[(benzyloxy)methoxy]cyclohept-3-en-1-ol} followed by the diastereoselective reduction of the resulting β-hydroxy ketone intermediates gives a rapid route to long-chain polyketides bearing unsymmetrical functions at their terminal positions. These can easily be converted into enantiomerically pure long-chain 1,3-polyol fragments.

Introduction

A great variety of natural products of biological interest include polyketide (1,3-polyoxo, 1,3-polyols, aldols) components,[1] and several approaches to their synthesis have been proposed.[2] Inspired by the work of Lautens[3] and Hoffmann and co-workers,[4] who have converted 8-oxabicyclo[3.2.1]oct-6-en-3-one into seven-carbon chain 1,3-polyols and analogues,[5] and by that of Kaku et al.,[6] who have transformed cyclohept-3-ene-1,6-diol into 1,3-polyols, we have proposed a new, non-iterative asymmetric synthesis of long-chain 1,3-polyols starting from the now readily available 2,2′-methylenebis(furan) (**1**).[7] This method involved a double [3+4] cycloaddition between the 1,1,3-trichloro-2-oxyallyl cation and **1** (Scheme 1). After reductive workup, a 45:55 mixture of *meso*-**2** and (±)-*threo*-**2** was obtained in 55% yield and separated by fractional crystallization. The *meso* compound was converted into *meso*-**3**, which was desymmetrized into diol (−)-**4** by Sharpless asymmetric dihydroxylation.[8] Further transformations allow one to prepare, in principle, all possible stereoisomers of pentadecane-1,3,5,7,9,11,13,15-octol.[9] In the meantime we have found a method to convert *threo*-**2** into diacetate (+)-**5** (40% yield, 98% *ee*).[10] We now present an efficient route for its conversion into a 3,5,7,9,11,13,15-heptahydroxypentadecanal derivative and into several pentadecane-1,3,5,7,9,11,13,15-octol derivatives, based on the double ozonolysis of (1*R*,1′*R*,6*R*,6′*R*)-3,3′-methylenebis{6-[(benzyloxy)methoxy]cyclohept-3-en-1-ol} [(−)-**8**]. Conditions for the generation of long-chain polyketides in which the two ends of the chain bear different functions (chemical desymmetrization) have been found. The chemistry disclosed here significantly reduces the number of steps necessary to convert **1** into enantiomerically pure long-chain polyketides.



Scheme 1. Strategy for polyketide synthesis by Sharpless desymmetrization

Results and Discussion

Diacetate (+)-**5** was treated with BCl_3 to give the corresponding double chloroborate, which was treated with $BnOCH_2Cl$ and $(iPr)_2NEt$ in the presence of a catalytic amount of tetrabutylammonium iodide to provide **6** in 60% yield (Scheme 2). Dechlorination with Bu_3SnH and AIBN (toluene, 80 °C) afforded (−)-**7** (70%), which was methanolyzed (anhydrous MeOH, K_2CO_3) to give diol (−)-**8** (97%). Ozonolysis of (−)-**8**, followed by reductive treatment with Me_2S and then with $NaBH_4$ (8 equiv.) under Nazaraka's conditions,[11] afforded a mixture of hemiacetals (−)-**9** in 65% yield. Concentrations, a reaction temperature (−10 °C), a reaction time (45 min), and workup conditions

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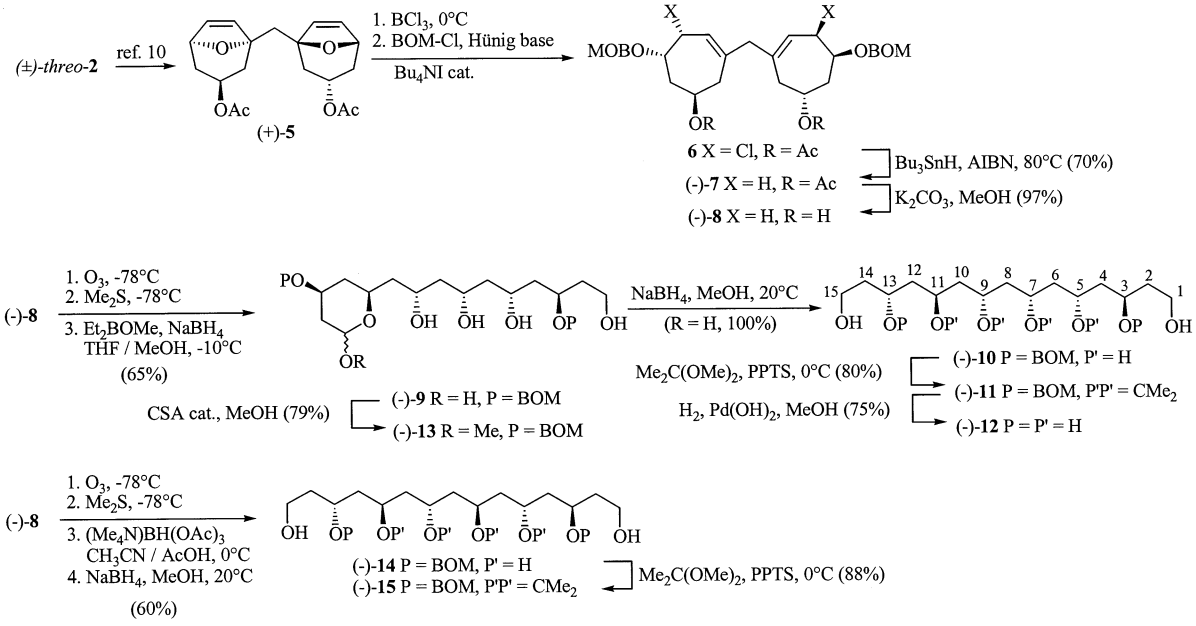
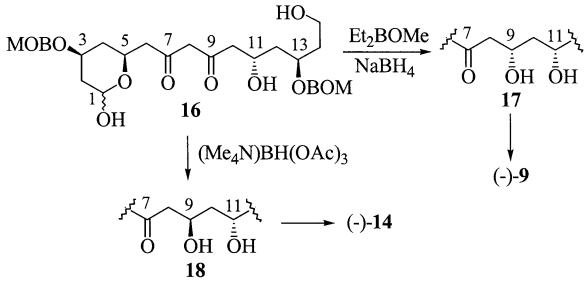


Scheme 2. New strategy for the expeditious preparation of long-chain polyketides; AIBN: $Me_2C(CN)N{=}NC(CN)Me_2$, BOM = $PhCH_2OCH_2$, CSA: camphorsulfonic acid, Hünig base: $(i\text{Pr})_2\text{NEt}$, PPTS: pyridinium *p*-toluenesulfonate

(AcOH, then $NaHCO_3$) suitable for avoiding the reduction of the hemiacetal moiety were found, thus providing an efficient chemical desymmetrization of the long-chain polyketide. Application of a similar reaction sequence to analogues of (−)-**8** in which the BOM protecting groups had been exchanged for other groups [Ac, benzyl, MOM, 4-Me-OC_6H_4CO, (tBu)Me_2Si] failed to give reasonable yields of derivatives of **9** or of the corresponding polyols, so the BOM groups in (−)-**8** appear to be crucial for the success of its conversion into **9**. The relative configuration of the diol at C-7 and C-9, resulting from the reduction of the corresponding pentadecane-7,9-dione intermediate, was determined by conversion of **9** into hexol (−)-**10**, which was then transformed into the corresponding bis(acetonide) (−)-**11**. Typical ^{13}C NMR signals[12] were observed for the acetonide at δ_{Me} = 30.3, 19.8 ppm (C-5, C-7) and for the acetonide at δ_{Me} = 25.0, 24.9 ppm (C-9, C-11). These results suggest that one of two hemiacetals is reduced first, giving the corresponding 11,15-diol **16**. The hydroxy group at C-11 controls the *syn*-diastereoselective reduction of the oxo moiety at C-9. The diastereoselective reduction of the carbonyl group at C-7 is not controlled by the hydroxy group at C-5 but by the newly generated alcohol group at C-9 (Scheme 3). Hydrogenolysis of hexol (−)-**10** [H_2, $Pd(OH)_2$, MeOH] provided the unprotected polyol (−)-**12** in 75% yield. Treatment of hemiacetal **9** with camphorsulfonic acid in anhydrous methanol afforded a 1:1 mixture of pyranosides (−)-**13**.

Ozonolysis of (−)-**8**, followed by reductive treatment with Me_2S under Evans conditions [$(Me_4N)BH(OAc)_3$],[13] gave (−)-**14** as the major product in 60% yield. The *anti*,*anti*,*anti* relative configuration of the tetrol at C-5, C-7, C-9, C-11 was established from the ^{13}C NMR spectrum of the corresponding bis(acetonide) (−)-**15** (δ_{Me} = 25.9, 25.4 ppm). It



Scheme 3. Possible intermediates in the reductions of the diketone **16** resulting from double ozonolysis of (−)-**8**

was expected that intermediate **16** should be reduced into **18**. The hydroxy group at C-9 thus controls the *anti*-stereoselective reduction of the carbonyl moiety at C-7.

Since the enantiomer of (+)-**5** is also available and the two acetoxy groups can be inverted, the chemistry disclosed here opens an expeditious route to the synthesis of a number of stereomeric long-chain polyketides containing six stereogenic centers.

Experimental Section

General: Commercial reagents (Fluka, Aldrich) were used without purification. Solvents were distilled prior to use: THF from Na and benzophenone, MeOH from Mg and I_2, DMF from P_2O_5, and CH_2Cl_2 from CaH_2. Light petroleum ether used refers to the fraction boiling at 40−60 °C. Solutions after reactions and extractions were concentrated in a rotary evaporator under reduced pressure. Liquid/solid flash chromatography (FC): columns of silica gel (0.040−0.63 mm, Merck No.9385 silica gel 60, 240−400 mesh). TLC for reaction monitoring: Merck $60F_{254}$ silica gel plates; detection by UV light; Pancaldi reagent [$(NH_4)_6MoO_4$, $Ce(SO_4)_2$,

H_2SO_4, H_2O] or $KMnO_4$. IR spectra: Perkin−Elmer 1420 spectrometer. ^1H NMR spectra: Bruker ARX 400 spectrometer (400 MHz); δ(H) in ppm relative to the solvent's residual ^1H signal [$CHCl_3$: δ(H) = 7.27 ppm; CH_3OD: δ(H) = 3.31 ppm; C_6H_6: δ(H) = 7.3 ppm] as internal reference; all ^1H assignments were confirmed by 2D-COSY-45 and 2D-NOESY spectra. ^{13}C NMR spectra: same instrument as above (100.6 MHz); δ(C) in ppm relative to solvent's C-signal [$CDCl_3$: δ(C) = 77.0 ppm; CD_3OD: δ(C) = 49.2 ppm; C_6D_6: δ(C) = 128.5 ppm] as internal reference; coupling constants *J* in Hz. MS: Nermag R-10-10C, chemical ionization (NH_3) mode *m*/*z* (amu) [% relative base peak (100%)]. Elemental analyses: Ilse Beetz, 96301 Kronach, Germany.

(1*R*,1′*R*,6*R*,6′*R*)-3,3′-Methylenebis{6-[(benzyloxy)methoxy]-cyclohept-3-en-1-yl} Diacetate [(−)-7]: A solution of BCl_3 in CH_2Cl_2 (1 M, 109 mL, 0.109 mol) was added dropwise at 0 °C to a solution of (−)-**5** (12.7 g, $3.647.10^{-2}$ mol) in CH_2Cl_2 (660 mL). After the mixture had been stirred at 0 °C for 30 min, a satd. aq. solution of $NaHCO_3$ (200 mL) was added and the mixture was stirred at 25 °C for 15 min. The mixture was extracted with CH_2Cl_2 (300 mL, twice). The combined organic extracts were dried ($MgSO_4$) and concentrated in vacuo. The residue was taken up in CH_2Cl_2 (600 mL) and treated with Hünig base (75 mL, 0.438 mol), BOMCl (40.6 mL, 0.292 mol), and Bu_4NI (1 g). The mixture was stirred at 25 °C for 13 h and then poured into an aq. solution of HCl (1 M, 800 mL). The solution was extracted with CH_2Cl_2 (800 mL, 3 times). The combined organic extracts were dried ($MgSO_4$) and concentrated in vacuo. Flash chromatography on silica gel (EtOAc/light petroleum ether, 1:5) afforded **6** as a colorless oil (14.4 g, 60%). Bu_3SnH (6 mL, $2.275.10-^2$ mol) and AIBN (250 mg) were added to a solution of **6** (4.3 g, 6.499 mmol) in toluene (25 mL). The mixture was stirred at 80 °C for 2 h. The solvent was evaporated, the residue was taken up in MeCN (80 mL), and the solution was washed with pentane (20 mL, twice) and concentrated in vacuo. Flash chromatography on silica gel (EtOAc/light petroleum ether, 1:3) afforded (−)-**7** as a colorless oil (2.7 g, 70%). R_f = 0.83 (EtOAc/light petroleum ether, 1:1). $[\alpha]_{589}^{20} = -60$, $[\alpha]_{577}^{20} = -60$, $[\alpha]_{546}^{20} = -66$, $[\alpha]_{435}^{20} = -73$, $[\alpha]_{405}^{20} = -92$ (*c* = 0.96, CH_2Cl_2). IR (film): $\tilde{\nu}$ = 3090, 3065, 3030, 2940, 1740, 1610, 1495, 1455, 1370, 1240, 1165, 1100, 1080, 1045, 975, 735, 700, 645 cm^{-1}. UV (MeCN): λ_{max} (ε) = 217, 205 (10710, 8205 $dm^3\ mol^{-1}\ cm^{-1}$) nm. ^1H NMR ($CDCl_3$, 400 MHz): δ = 7.39−7.28 (m, 10 H arom.), 5.51 (t, ^3J = 6.6 Hz, 2 H, H-4, H-4′), 5.00−5.05 (m, 2 H, H-1, H-1′), 4.79 [s, 4 H, 2 × CH_2(BOM)], 4.62 (s, 4 H, 2 × CH_2Ph), 3.95−3.89 (m, 2 H, H-6, H-6′), 2.68 (s, 2 H, H_2-8), 2.35−2.45 (m, 6 H, H-2, H-2′, H_2-5, H_2-5′), 2.26 (d, ^2J = 13.8 Hz, 2 H, H-2, H-2′), 2.10 (dd, ^3J = 5.8, 5.7 Hz, 4 H, H_2-7, H_2-7′), 2.01 (s, 6 H, 2 × OAc) ppm. ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ = 170.2 (s, 2 × C=O), 137.9 (s, 2 C arom.), 136.9 (s, C-3, C-3′), 128.4, 127.9, 127.7 (3 d, $^1J_{C,H}$ = 160, 159, 161 Hz, 10 C arom.), 124.0 (d, $^1J_{C,H}$ = 161 Hz, C-4, C-4′), 92.8 [t, $^1J_{C,H}$ = 163 Hz, CH_2(BOM)], 70.8 (d, $^1J_{C,H}$ = 142 Hz, C-1, C-1′), 69.5 (t, $^1J_{C,H}$ = 142 Hz, CH_2Ph), 68.8 (d, $^1J_{C,H}$ = 145 Hz, C-6, C-6′), 50.8 (t, $^1J_{C,H}$ = 127 Hz, C-8), 42.2 (t, $^1J_{C,H}$ = 126 Hz, C-7, C-7′), 35.7 (t, $^1J_{C,H}$ = 129 Hz, C-2, C-2′), 33.2 (t, $^1J_{C,H}$ = 128 Hz, C-5, C-5′), 21.4 (q, $^1J_{C,H}$ = 129 Hz, 2 × OAc) ppm. CI-MS: *m*/*z* = 610 (6) [M + NH_4^+], 273 (1), 213 (4), 133 (7), 91 (100) [$PhCH_2^+$]. $C_{35}H_{44}O_8$ (592.73): calcd. C 70.92, H 7.48; found C 70.90, H 7.39.

(1*R*,1′*R*,6*R*,6′*R*)-3,3′-Methylenebis{6-[(benzyloxy)methoxy]-cyclohept-3-en-1-ol} [(−)-8]: K_2CO_3 (1.1 g, 7.761 mmol) was added to a solution of (−)-**7** (4.6 g, 7.761 mmol) in MeOH (210 mL) and the mixture was vigorously stirred at 25 °C for 4 h. The solution was poured into water (300 mL) and extracted with $CHCl_3$ (300 mL, 3 times). The combined organic extracts were dried ($MgSO_4$) and concentrated in vacuo to afford (−)-**8** as a white solid (3.83 g, 97%). M.p. 95−97 °C. R_f = 0.38 (CH_2Cl_2/MeOH, 95:5). $[\alpha]_{589}^{20} = -46$, $[\alpha]_{577}^{20} = -50$, $[\alpha]_{546}^{20} = -57$, $[\alpha]_{435}^{20} = -102$, $[\alpha]_{405}^{20} = -126$ (*c* = 0.91, $CHCl_3$). IR (KBr): $\tilde{\nu}$ = 3365, 3090, 3035, 2920, 1655, 1455, 1380, 1265, 1185, 1165, 1090, 1040, 750, 700 cm^{-1}. UV (MeCN): λ_{max} (ε) = 208 (11570 $dm^3{\cdot}mol^{-1}{\cdot}cm^{-1}$) nm. ^1H NMR ($CDCl_3$, 400 MHz): δ = 7.39−7.28 (m, 10 H arom.), 5.23 (t, ^3J = 7.7 Hz, 2 H, H-4, H-4′), 4.32 [s, 4 H, 2 × CH_2(BOM)], 4.12 (s, 4 H, 2 × CH_2Ph), 3.37−3.27 (m, 4 H, H-1, H-1′, H-6, H-6′), 1.82 (s, 2 H, H_2-8), 1.44 (dd, ^3J = 7.7, 7.4 Hz, 4 H, H_2-5, H_2-5′), 1.42 (dd, ^2J = 14.9, ^3J = 4.1 Hz, 2 H, H-2, H-2′), 1.37 (d, ^2J = 14.9 Hz, 2 H, H-2, H-2′), 1.14−1.00 (m, 4 H, H_2-7, H_2-7′) ppm. ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ = 137.9 (s, 2 C arom.), 128.5, 127.9, 127.7 (3 d, $^1J_{C,H}$ = 160, 158, 162 Hz, 10 C arom.), 124.0 (d, $^1J_{C,H}$ = 150 Hz, C-4, C-4′), 93.0 [t, $^1J_{C,H}$ = 163 Hz, 2 × CH_2(BOM)], 71.3 (d, $^1J_{C,H}$ = 143 Hz, C-6, C-6′), 69.5 (t, $^1J_{C,H}$ = 142 Hz, 2 × CH_2Ph), 65.7 (d, $^1J_{C,H}$ = 145 Hz, C-1, C-1′), 51.5 (t, $^1J_{C,H}$ = 130 Hz, C-8), 45.6 (t, $^1J_{C,H}$ = 126 Hz, C-7, C-7′), 39.5 (t, $^1J_{C,H}$ = 128 Hz, C-2, C-2′), 33.3 (t, $^1J_{C,H}$ = 126 Hz, C-5, C-5′) ppm. CI-MS: *m*/*z* = 526 (100) [M + NH_4^+], 464 (5), 406 (13), 293 (6), 126 (82), 108 (92), 91 (91) [$PhCH_2^+$]. $C_{31}H_{40}O_6$ (508.65): calcd. C 73.20, H 7.93; found C 72.58, H 7.77.

(3*R*,5*R*,7*R*,9*S*,11*R*,13*R*)-3,13-Bis[(benzyloxy)methoxy]pentadecane-1,5,7,9,11,15-hexol [(−)-10]: A solution of (−)-**8** (0.35 g, 0.69 mmol) in anhydrous CH_2Cl_2 (12 mL) was ozonolyzed at −78 °C for 4 min. A stream of dry O_2 was then passed through the solution for 2 min, and Me_2S (0.2 mL, 2.75 mmol) was added dropwise. After the mixture had been stirred at −78 °C for 5 min, the solvent was evaporated at −20 °C. The residue was taken up in THF/MeOH (10:1, 8.8 mL) at −10 °C and a solution of Et_2BOMe in THF (1 M, 4.1 mL, 4.13 mmol) was added dropwise. After the mixture had been stirred at −10 °C for 45 min, $NaBH_4$ (0.2 g, 5.5 mmol) was added portionwise and the stirring was continued for an additional 15 min. AcOH (0.3 mL) was added and the solution was stirred at 25 °C for 2 min. After addition of a satd. aq. solution of $NaHCO_3$ (25 mL), the mixture was extracted with EtOAc (25 mL, 4 times). The combined organic extracts were dried ($MgSO_4$) and concentrated in vacuo. Flash chromatography on silica gel (CH_2Cl_2/MeOH, 12:1) afforded (−)-**9** (259 mg, 65%) as a colorless oil. A solution of **9** (100 mg, 0.173 mmol) in MeOH (4 mL) was treated with $NaBH_4$ (13 mg, 0.346 mmol) and the mixture was stirred at 25 °C for 30 min. After addition of a satd. aq. solution of $NaHCO_3$ (10 mL), the mixture was extracted with EtOAc (10 mL, 3 times). The combined organic extracts were dried ($MgSO_4$) and concentrated in vacuo. Flash chromatography on silica gel (CH_2Cl_2/MeOH, 11:1, 1% NEt_3) afforded (−)-**10** (100 mg, 100%) as a colorless oil. R_f = 0.23 (CH_2Cl_2/MeOH, 10:1). $[\alpha]_{589}^{20} = -22$, $[\alpha]_{577}^{20} = -30$, $[\alpha]_{546}^{20} = -31$, $[\alpha]_{435}^{20} = -31$, $[\alpha]_{405}^{20} = -171$ (*c* = 0.3, MeOH). IR (film): $\tilde{\nu}$ = 3385, 3065, 3030, 2940, 1560, 1460, 1380, 1210, 1165, 1035, 825, 740, 700, 670 cm^{-1}. UV (MeCN): λ_{max} (ε) = 209 (7905 $dm^3{\cdot}mol^{-1}{\cdot}cm^{-1}$) nm. ^1H NMR ([D$_4$]MeOH, 400 MHz): δ = 7.42−7.31 (m, 10 H arom.), 4.88 [s, 4 H, 2 × CH_2(BOM)], 4.69 (s, 4 H, 2 × CH_2Ph), 4.06−4.00 (m, 6 H, H-3, H-5, H-7, H-9, H-11, H-13), 3.71 (t, ^3J = 6.5 Hz, 4 H, H_2-1, H_2-15), 1.88−1.82 (m, 4 H, H_2-2, H_2-14), 1.72−1.54 (m, 10 H, H_2-4, H_2-6, H_2-8, H_2-10, H_2-12) ppm. ^{13}C NMR ([D$_4$]MeOH, 100.6 MHz): δ = 141.8 (s, 2 C arom.), 132.0, 131.6, 131.3 (3 d, $^1J_{C,H}$ = 160, 161, 159 Hz, 10 C arom.), 98.1 [t, $^1J_{C,H}$ = 158 Hz, 2 × CH_2(BOM)], 77.0, 76.8 (2 d, $^1J_{C,H}$ = 139, 140 Hz, C-3, C-13), 73.4 (t, $^1J_{C,H}$ = 142 Hz, 2 × CH_2Ph), 72.8, 70.7, 70.4, 68.4 (4 d, $^1J_{C,H}$ = 141, 139, 142, 138 Hz, C-5, C-7, C-9, C-11), 62.0 (t, $^1J_{C,H}$ = 141 Hz, C-1, C-15), 48.9, 48.5, 47.2, 46.8 (4 t, $^1J_{C,H}$ = 127,

126, 125, 128 Hz, C-4, C-6, C-8, C-10, C-12), 41.9 (t, $^1J_{C,H}$ = 127 Hz, C-2, C-14) ppm. MS (ES): *m*/*z* = 581 (100) [M + H$^+$]. $C_{31}H_{48}O_{10}$ (580.71): calcd. C 64.12, H 8.33; found C 64.26, H 8.29.

(3*R*,5*R*,7*S*,9*S*)-3-[(Benzyloxy)methoxy]-10-{(2*R*,4*S*)-4-[(benzyloxy)-methoxy]-6-methoxy-tetrahydro-2*H*-pyran-2-yl}decane-1,5,7,9-tetrol [(−)-13]: A solution of (−)-**9** (85 mg, 0.147 mmol) and camphorsulfonic acid (5 mg) in MeOH (4 mL) was stirred at 25 °C for 45 min. The mixture was neutralized with solid $NaHCO_3$, filtered, and concentrated in vacuo. Purification by flash chromatography (CH_2Cl_2/MeOH, 96:4) afforded (−)-**13** (68 mg, 79%, 1:1 mixture of isomers) as a colorless oil. R_f = 0.29 (CH_2Cl_2/MeOH, 96:4). $[\alpha]_{589}^{20}$ = −36 (*c* = 0.18, MeOH). IR (film): $\tilde{\nu}$ = 3470, 3065, 3030, 2935, 1605, 1495, 1455, 1385, 1200, 1115, 1025, 965 cm^{-1}. UV (MeCN): λ_{max} (ε) = 208 (4830 dm^3·mol^{-1}·cm^{-1}) nm. ^{1}H NMR ([D$_4$]MeOH, 400 MHz): δ = 7.37−7.29 (m, 10 H arom.), 4.83 [m, 4 H, 2 × CH_2(BOM)], 4.63, 4.62 (2 s, 4 H, 2 × CH_2Ph), 4.37 (m, 1 H, H-6′), 4.11 (dddd, ^3J = 7.2, 7.1, 3.4, 2.9 Hz, 1 H, H-4′), 4.08−4.01 (m, 4 H, H-3, H-5, H-7, H-9), 3.99 (m, 2 H, H_2-1), 3.86 (m, 1 H, H-2′), 3.37, 3.35 (2 s, 3 H, OMe-C-6′), 2.21−1.95 (m, 4 H, H_2-2, H_2-3), 1.72−1.51, 1.48−1.22 (2 m, 10 H, H_2-4, H_2-6, H_2-8, H_2-10, H_2-5′) ppm. ^{13}C NMR ([D$_4$]MeOH, 100.6 MHz): δ = 140.2 (s, C arom.), 130.3, 129.8, 129.5 (3 d, 10 C arom.), 101.4, 101.1 (2 d, C-6′), 94.8, 94.7 [2 t, 2 × CH_2(BOM)], 74.2, 74.1 (2 d, C-2′), 71.7, 71.5, 71.4 (3 d, C-3, C-4′), 71.3 (t, 2 × CH_2Ph), 69.7, 69.6, 68.6, 68.5, 67.9, 67.8 (3 d, C-5, C-7, C-9), 66.2 (t, C-1), 56.0, 55.9 (2 q, OMe-C-6′), 46.9, 46.7, 46.5, 45.7, 45.6, 45.3, 45.0 (7 t, C-4, C-6, C-8, C-10, C-5′), 40.6, 40.4 (2 t, C-3′), 38.9 (t, C-2) ppm. MS (ES): 593 (100) [M + H$^+$]. $C_{32}H_{48}O_{10}$ (592.721): calcd. C 64.84, H 8.16; found C 64.90, H 8.19.

(3*R*)-3-[(Benzyloxy)methoxy]-4-{(4*S*,6*S*)-6-[{(4*R*,6*S*)-6-{(2*R*)-2-[(benzyloxy)methoxy]-4-hydroxybutyl}-2,2-dimethyl-1,3-dioxan-4-yl}methyl]-2,2-dimethyl-1,3-dioxan-4-yl}butan-1-ol [(−)-11]: A solution of (−)-**10** (30 mg, 5.166.10^{-5} mol) in 2,2-dimethoxypropane/acetone (2 mL/0.2 mL) was stirred in the presence of *p*TsOH (4 mg) for 15 min at 0 °C. The mixture was neutralized with solid $NaHCO_3$ and filtered, and the solvents were evaporated in vacuo. The residual oil was taken up in CH_2Cl_2 (2 mL) with pyridinium *p*-toluenesulfonate (2 mg) and stirred at 25 °C. After 1 h, the solution was neutralized with solid $NaHCO_3$, filtered, and concentrated in vacuo. Purification by flash chromatography (CH_2Cl_2/MeOH, 97:3) afforded (−)-**11** (27 mg, 80%) as a colorless oil. R_f = 0.1 (CH_2Cl_2/MeOH, 95:5). $[\alpha]_{589}^{20}$ = −3, $[\alpha]_{577}^{20}$ = −20, $[\alpha]_{435}^{20}$ = −170, $[\alpha]_{405}^{20}$ = −298 (*c* = 0.3, MeOH). IR (film): $\tilde{\nu}$ = 3405, 2945, 2870, 1495, 1455, 1430, 1405, 1380, 1250, 1205, 1165, 1100, 1035, 740, 700 cm^{-1}. UV (MeCN): λ_{max} (ε) = 210 (6420 dm^3·mol^{-1}·cm^{-1}) nm. ^{1}H NMR (C_6D_6, 400 MHz): δ = 7.34−7.31, 7.19−7.06 (2 m, 10 H arom.), 4.74 [m, 4 H, 2 × CH_2(BOM)], 4.62, 4.49 (2 d, ^2J = 12.6 Hz, 2 H, CH_2Ph), 4.61, 4.52 (2 d, ^2J = 11.9 Hz, 2 H, CH_2Ph), 4.15 (m, 2 H, H-3, H-2^{IV}), 4.10−3.75 (m, 4 H, H-4′, H-6′, H-4′′′, H-6′′′), 3.71, 3.61 (2 dm, ^2J = 12.2 Hz, 4 H, H_2-1, H_2-4^{IV}), 2.02−1.81 (m, 4 H, H_2-2, H_2-3^{IV}), 1.72, 1.35 (m, 10 H, H_2-4, H_2-5′, H_2-1′′, H_2-5′′′, H_2-1^{IV}), 1.50, 1.46, 1.30, 1.24 (4 s, 12 H, 2 × Me-C-2′, 2 × Me-C-2′′′) ppm. ^{13}C NMR (C_6D_6, 100.6 MHz): δ = 140.1 (s, 2 C arom.), 129.3, 129.1, 128.6 (3 d, 10 C arom.), 100.1, 98.4 (2 s, C-2′, C-2′′′), 94.7, 94.6 [2 t, 2 × CH_2(BOM)], 74.4, 73.4 (2 d, C-3, C-2^{IV}), 69.6 (t, 2 × CH_2Ph), 65.8, 65.5, 64.8, 63.5 (4 d, C-4′, C-6′, C-4′′′, C-6′′′), 59.1 (t, C-1, C-4^{IV}), 43.4, 42.9 (2 t, C-5′, C-5′′′), 42.8 (t, C-1′′), 42.7, 42.3 (2 t, C-4, C-1^{IV}), 38.3, 38.2 (2 t, C-2, C-2^{IV}), 30.3, 19.8 (2 q, 2 × Me-C-2′), 25.0, 24.9 (2 q, 2 × Me-C-2′′′) ppm. CI-MS: 678 (10) [M + NH_4^+], 645 (21), 495 (10), 437 (30), 387 (5), 329 (10), 91 (100) [$PhCH_2^+$]. $C_{37}H_{56}O_{10}$ (660.84): calcd. C 67.25, H 8.54; found C 67.23, H 8.79.

(3*R*,5*S*,7*S*,9*R*,11*S*,13*R*)-Pentadecan-1,3,5,7,9,11,13,15-octol [(−)-12]: A solution of (−)-**10** (80 mg, 0.138 mmol) in MeOH (8 mL) was stirred at 25 °C, under 1 atm of H_2, in the presence of $Pd(OH)_2$/C (50 mg) for 19 h. The mixture was filtered through a pad of Celite (eluent: MeOH, 50 mL) and concentrated in vacuo. Purification by flash chromatography (MeCN/NH_4OH, 4:1) afforded a white foam (35 mg, 75%). R_f = 0.19 (MeCN/NH_4OH, 4:1). $[\alpha]_{589}^{20}$ = −30 (*c* = 0.4, H_2O). IR (film): $\tilde{\nu}$ = 3200, 2940, 1415, 1135, 1080, 940, 895, 820, 800 cm^{-1}. UV (MeCN): λ_{max} (ε) = 209 (5100 dm^3 mol^{-1} cm^{-1}) nm. ^{1}H NMR (D_2O, 400 MHz): δ = 3.98−3.89 (m, 6 H, H-3, H-5, H-7, H-9, H-11, H-13), 3.65 (t, ^3J = 6.6 Hz, 4 H, H_2-1, H_2-15), 1.69−1.51 (m, 14 H, H_2-2, H_2-4, H_2-6, H_2-8, H_2-10, H_2-12, H_2-14) ppm. ^{13}C NMR (D_2O, 100.6 MHz): δ = 70.2, 68.7, 68.6, 67.8, 67.6, 67.1 (6 d, C-3, C-5, C-7, C-9, C-11, C-13), 61.1 (t, C-1, C-15), 47.0, 46.8, 46.5, 46.1, 46.0 (5 t, C-4, C-6, C-8, C-10, C-12), 41.7, 41.6 (2 t, C-2, C-14) ppm. CI-MS: 341 (2, [M + H$^+$]), 309 (2), 211 (8), 141 (56), 127 (100), 111 (63) ppm.

(3*R*,5*S*,7*R*,3′*R*,5′*S*,7′*R*)-7,7′-Methylenebis{3-[(benzyloxy)methoxy]-heptane-1,5,7-triol} [(−)-14]: A solution of (−)-**8** (0.12 g, 0.236 mmol) in anhydrous CH_2Cl_2 (6 mL) was ozonolyzed at −78 °C for 2 min. A stream of dry O_2 was then passed through the solution for 2 min, and Me_2S (69 μL, 0.944 mmol) was added dropwise. After the mixture had been stirred at −78 °C for 5 min, the solvent was evaporated at −20 °C. The residue was taken up in MeCN/AcOH (3:1, 4 mL) at 0 °C, and $(Me_4N)BH(OAc)_3$ (1.1 g, 4.248 mmol) was added portionwise. After the mixture had been stirred at 0 °C for 40 min, the solvents were evaporated. The residue was taken up in EtOAc (10 mL) and poured onto ice (15 mL). The mixture was neutralized with solid $NaHCO_3$ and extracted with EtOAc (15 mL, 3 times). The combined organic extracts were dried ($MgSO_4$) and concentrated in vacuo. The crude hemiacetal was treated with $NaBH_4$ (54 mg, 1.416 mmol) in MeOH (4 mL) at 25 °C for 15 min. AcOH was added (150 μL), and after stirring at 25 °C for 2 min, the solution was poured into a satd. aq. solution of $NaHCO_3$ (15 mL). The mixture was extracted with EtOAc (15 mL, 3 times). The combined organic extracts were dried ($MgSO_4$) and concentrated in vacuo. Flash chromatography on silica gel (CH_2Cl_2/MeOH, 11:1, 1% NEt_3) afforded (−)-**14** (82 mg, 60%) as a colorless oil. R_f = 0.19 (CH_2Cl_2/MeOH, 10:1). $[\alpha]_{589}^{20}$ = −3 (*c* = 0.9, MeOH). IR (film): $\tilde{\nu}$ = 3390, 3055, 2940, 1605, 1550, 1425, 1380, 1265, 1205, 1160, 1025, 780, 710 cm^{-1}. UV (MeCN): λ_{max} (ε) = 209 (9080 dm^3·mol^{-1}·cm^{-1}) nm. ^{1}H NMR ([D$_4$]MeOH, 400 MHz): δ = 7.41−7.29 (m, 10 H arom.), 4.87 [s, 4 H, 2 × CH_2(BOM)], 4.68 (s, 4 H, 2 × CH_2Ph), 4.08−4.03 (m, 6 H, H-3, H-5, H-7, H-3′, H-5′, H-7′), 3.70 (t, ^3J = 6.7 Hz, 4 H, H_2-1, H_2-1′), 1.89−1.82 (m, 4 H, H_2-2, H_2-2′), 1.80−1.54 (m, 10 H, H_2-4, H_2-6, H_2-8, H_2-4′, H_2-6′) ppm. ^{13}C NMR ([D$_4$]MeOH, 100.6 MHz): δ = 140.1 (s, 2 C arom.), 130.3, 129.9, 129.6 (3 d, $^1J_{C,H}$ = 160, 158, 161 Hz, 10 C arom.), 96.4 [t, $^1J_{C,H}$ = 163 Hz, 2 × CH_2(BOM)], 75.1 (d, $^1J_{C,H}$ = 143 Hz, C-3, C-3′), 71.7 (t, $^1J_{C,H}$ = 143 Hz, 2 × CH_2Ph), 68.9, 68.8 (2 d, $^1J_{C,H}$ = 142, 141 Hz, C-5, C-7, C-5′, C-7′), 60.4 (t, $^1J_{C,H}$ = 141 Hz, C-1, C-1′), 47.4 (t, $^1J_{C,H}$ = 125 Hz, C-4, C-4′), 46.5 (t, $^1J_{C,H}$ = 126 Hz, C-8), 45.1 (t, $^1J_{C,H}$ = 125 Hz, C-6, C-6′), 40.2 (t, $^1J_{C,H}$ = 126 Hz, C-2, C-2′) ppm. MS (ES): *m*/*z* = 581 (100) [M + H$^+$]. $C_{31}H_{48}O_{10}$ (580.71): calcd. C 64.12, H 8.33; found C 64.02, H 8.25.

(3*R*)-3-[(Benzyloxy)methoxy]-4-{(4*S*,6*R*)-6-[{(4*R*,6*S*)-6-{(2*R*)-2-[(benzyloxy)methoxy]-4-hydroxybutyl}-2,2-dimethyl-1,3-dioxan-4-yl}methyl]-2,2-dimethyl-1,3-dioxan-4-yl}butan-1-ol [(−)-15]: A solution of (−)-**14** (30 mg, 5.166 × 10^{-5} mol) in 2,2-dimethoxypropane/acetone (2 mL/0.2 mL) was stirred in the presence of *p*TsOH (3 mg) at 0 °C for 1 h. The mixture was poured into a satd. aq. solution

of $NaHCO_3$ (10 mL) and extracted with EtOAc (10 mL, 3 times). The combined organic extracts were dried ($MgSO_4$) and concentrated in vacuo. Purification by flash chromatography (CH_2Cl_2/MeOH, 97:3) afforded (−)-**15** (30 mg, 88%) as a pale yellow oil. R_f = 0.29 (EtOAc/light petroleum, 3:1). $[\alpha]_{589}^{20}$ = −56 (c = 0.35, CH_2Cl_2). IR (film): $\tilde{\nu}$ = 3445, 3065, 3030, 2990, 2940, 1495, 1455, 1380, 1225, 1165, 1025, 940, 740, 700 cm^{-1}. UV (MeCN): λ_{max} (ε) = 206 (9890 $dm^3 \cdot mol^{-1} \cdot cm^{-1}$) nm. ^1H NMR (C_6D_6, 400 MHz): δ = 7.36−7.31 (m, 10 H arom.), 4.82 [m, 4 H, 2 × CH_2(BOM)], 4.73, 4.59 (2 d, ^2J = 11.9 Hz, 2 × CH_2Ph), 4.07−4.04 (m, 2 H, H-3, H-2^{IV}), 3.99−3.96 (m, 4 H, H-4′, H-6′, H-4′′′, H-6′′′), 3.84 (dm, ^2J = 11.2 Hz, 2 H, H-1, H-4^{IV}), 3.75 (dm, ^2J = 11.2, 2 H, H-1, H-4^{IV}), 1.90−1.84 (m, 4 H, H_2-2, H_2-4^{IV}), 1.78−1.51, 1.45−1.21 (2 m, 10 H, H_2-4, H_2-5′, H_2-1′′, H_2-5′′′, H_2-1^{IV}), 1.38, 1.37, 1.36, 1.34 (4 s, 12 H, 2 × Me-C-2′, 2 × Me-C-2′′′) ppm. ^{13}C NMR (C_6D_6, 100.6 MHz): δ = 137.4 (s, 2 C arom.), 128.5, 127.9, 127.8 (3 d, $^1J_{C,H}$ = 160, 161, 159 Hz, 10 C arom.), 100.1 (s, C-2′, C-2′′′), 95.04 [t, $^1J_{C,H}$ = 163 Hz, 2 × CH_2 (BOM)], 73.7 (d, $^1J_{C,H}$ = 143 Hz, C-3, C-2^{IV}), 70.0 (t, $^1J_{C,H}$ = 141 Hz, 2 × CH_2Ph), 65.4, 65.2 (2 d, $^1J_{C,H}$ = 140, 142 Hz, C-4′, C-6′, C-4′′′, C-6′′′), 59.4 (t, $^1J_{C,H}$ = 140, C-1, C-4^{IV}), 42.6 (t, $^1J_{C,H}$ = 125, C-1′′), 37.8, 35.4 (t, $^1J_{C,H}$ = 127, 126, C-4, C-5′, C-5′′′, C-1^{IV}), 37.1 (t, $^1J_{C,H}$ = 127, C-2, C-3^{IV}), 25.9, 25.4 (2 q, $^1J_{C,H}$ = 126, 124, 2 × Me-C-2′, 2 × Me-C-2′′′) ppm. CI-MS: m/z = 678 (1) [M + NH_4^+], 645 (2), 495 (7), 437 (10), 387 (5), 329 (7), 91 (100) [$PhCH_2^+$]. $C_{37}H_{56}O_{10}$ (660.84): calcd. C 67.25, H 8.54; found C 67.25, H 8.79.

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