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Synthesis of 2-Hydroxy-6-{[(16*R*)-β-D-mannopyranosyloxy]heptadecyl}benzoic Acid, a Fungal Metabolite with $GABA_A$ Ion Channel Receptor Inhibiting Properties

Alois Fürstner* and Ingo Konetzki

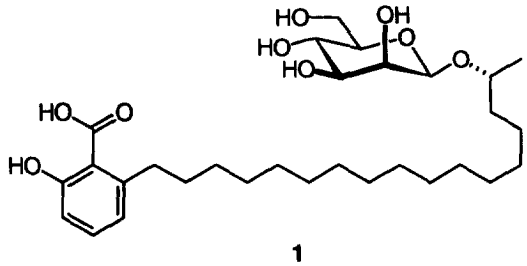
Max-Planck-Institut für Kohlenforschung

Kaiser-Wilhelm-Platz 1, D-45470 Mülheim/Ruhr, Germany

Abstract: An expeditious total synthesis of the physiologically active fungal metabolite **1** is described. The stereoselective formation of its β-D-mannopyranosidic linkage is achieved in two steps upon reaction of the hexopyranos-2-ulosyl bromide **15** with the glycosyl acceptor **13**, followed by reduction of the resulting β-D-glycos-2-uloside **16**. Alcohol **13** was efficiently prepared via a Suzuki reaction of the aryltriflate **11** with the 9-alkyl-9-BBN derivative **10**.

INTRODUCTION

Bioassay-guided fractionation of extracts of a culture broth of the fungus HA 137-89 has recently led to the discovery of two unnamed salicylic acid derivatives **1** and **2** which exhibit interesting properties as $GABA_A$/benzodiazepine chloride channel receptor complex inhibitors.[1] Almost simultaneously, the isolation of caloporoside **3** from *Caloporus dichrous* has been reported which acts as a strong and selective inhibitor of phospholipase C.[2]



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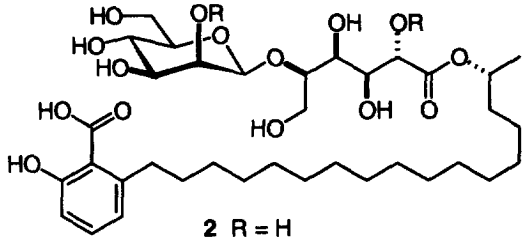
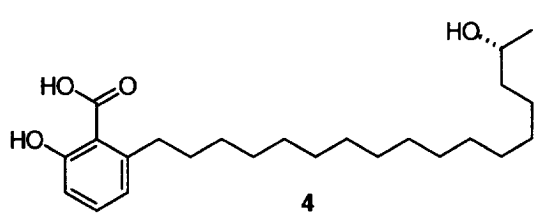


2 R = H

3 R = Ac ("*Caloporoside*")

The promising and diverse pharmacological profile of these closely related metabolites merits further biological evaluation. They share a common substructure **4** which may account to a large extend for their physiological activities. It belongs to the fairly large family of the so-called „anacardic acids", naturally occurring salicylic acid derivatives substituted at the 6-position, many of which exhibit interesting biological properties.[4] Specifically, **4** can be regarded as the dihydro derivative of merulinic acid B (**5**) previously discovered in the fruiting bodies of the mushrooms *Merulius tremellosus* and *Phlebia radiata*.[4a]



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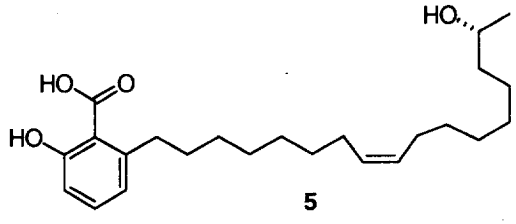

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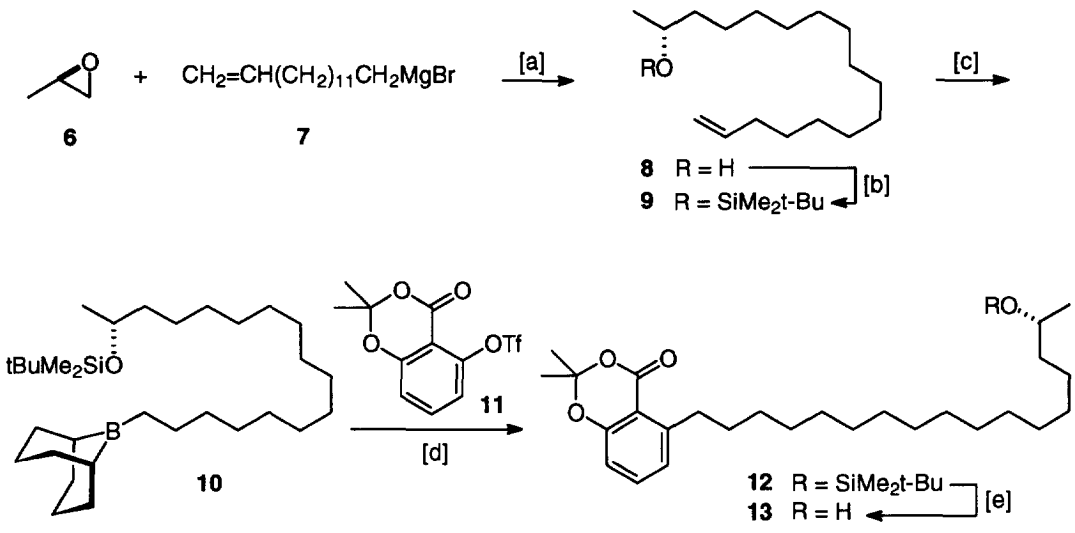
Therefore we were prompted to develop an expeditious entry into this new class of fungal metabolites which does not only lead to the natural products themselves but is flexible enough to allow the synthesis of analogues for screening purposes. We now describe our approach to their common 6-alkylated salicylic acid „aglycon" **4**, as well as the total synthesis of compound **1** as the elementary member of this series of target molecules.[3]

RESULTS AND DISCUSSION

Our synthesis of the suitably protected salicylic acid derivative **13** as the key-component (Scheme 1) starts with a CuCl(COD)-catalyzed [5] ring-opening of the commercially available (*R*)-(+)-propenoxide **6** with tetradec-13-enylmagnesium bromide **7** affording the unsaturated secondary alcohol **8** in enantiomerically pure form. Silylation of its OH group followed by hydroboration of the terminal alkene with 9-H-9-BBN dimer under standard conditions provides the functionalized 9-alkyl-9-BBN derivative **10**, which is cross-coupled with aryl triflate **11** (obtained from cheap 2,6-dihydroxybenzoic acid in two simple steps)[6] via a Suzuki reaction.[7,8] Specifically, the borate complex (^{11}B NMR δ -2.4 ppm) formed on addition of NaOMe to borane **10** (^{11}B NMR δ +82.4 ppm) readily transfers its alkyl group to the arylpalladium species prepared *in situ* from triflate **11** and catalytic amounts of $PdCl_2$(dppf) (dppf = 1,1'-bis(diphenylphosphino)ferrocene)[15] as the preferred pre-catalyst in the presence of KBr as a stabilizing agent. Thus, the salicylic acid derivative **13** bearing the properly (*R*)-configurated 16-hydroxy-heptadecenyl side chain was obtained in good overall yield after cleavage of the silyl ether. Both a Me_3Si-group and a t-$BuMe_2Si$-group may serve as the temporary protecting group R, with the latter being favored for its higher stability. Moreover it is obvious that this strategy based on a Suzuki-cross coupling reaction as the key step is flexible enough to provide a range of salicylic acid analogues which, when linked to an appropriate saccharide unit, may allow to fine tune the hydro-/lipophilicity of the drug.

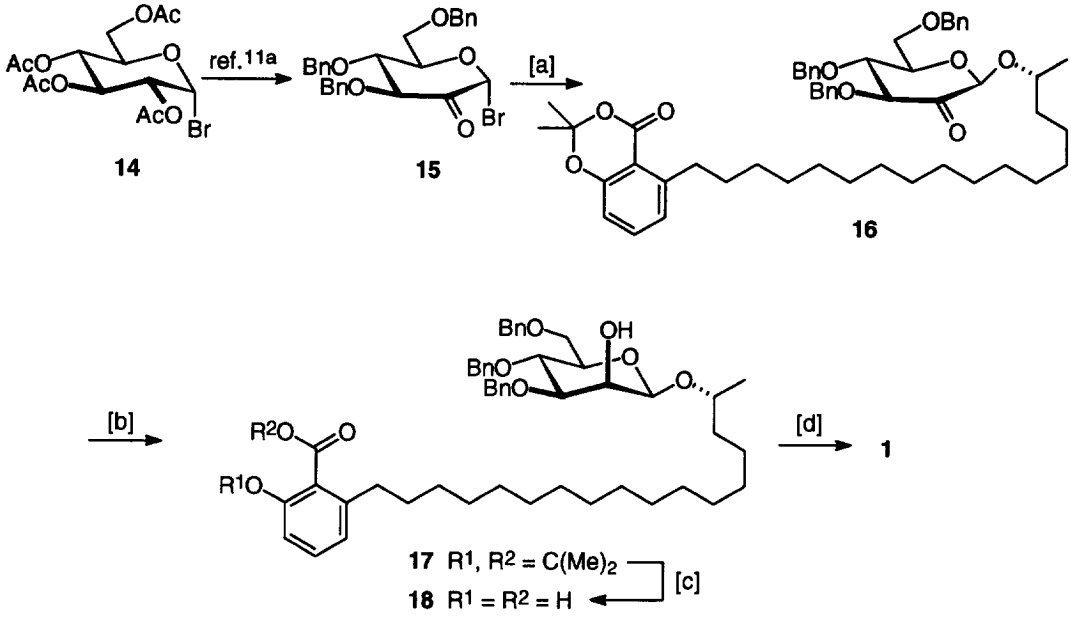


Scheme 1. [a] CuCl(COD) (10 mol%), THF, -78°C→r.t., overnight, 86%; [b] TBDMSCl, imidazole, DMF, r.t., 94%; [c] $[9\text{-H-9-BBN}]_2$, THF; [d] NaOMe (1 eq.), KBr (1.1 eq.), $PdCl_2(dppf)$ (2.5 mol%), THF, reflux, overnight, 86%; [e] TBAF, THF/H_20, r.t., 92%.

The formation of β-D-mannopyranosides in general is a formidable challenge because this particular 1,2-*cis* arrangement is highly disfavored both by the anomeric effect and by the eventual anchimeric assistance of protecting groups at O-2.[9] Only recently, some new concepts have evolved which hold the promise of providing practical solutions for this old problem;[9-11] they still await, however, a detailed evaluation by the synthesis of relevant target molecules. For our approach to antibiotic **1** we have chosen the „ulosyl bromide strategy" developed by *Lichtenthaler* [11] for its practicability and for the encouraging precedence provided by its successful application to the synthesis of a fairly complex trisaccharide unit of a glycosphingolipid.[11b]

For this very purpose 3,4,6-tri-O-benzyl-α-D-*arabino*-hexopyranos-2-ulosyl bromide **15** as an „indirect" mannosyl donor was prepared in 4 steps from acetobromoglucose (**14**) in good yield closely following the published procedure.[11a] As depicted in Scheme 2, the reaction of this ulosyl bromide with alcohol **13** as the glycosyl acceptor in CH_2Cl_2 in the presence of silver silicate on alumina as promotor [12] provided glycosuloside **16** which was reduced without further purification with $NaBH_4$ in $MeOH/CH_2Cl_2$. Thus, mannopyranoside **17** was obtained in 78% yield over two steps with excellent stereoselectivity.[13] Cleavage of its acylal-like isopropylidene group with aq. KOH in DMSO/i-PrOH, followed by hydrogenolysis of the benzyl ethers over Perlman's catalyst proceeded smoothly, affording the desired title compound **1** as a waxy solid, the analytical and spectroscopic data of which perfectly match those reported in the literature.[1] In particular, the $^3J_{C\text{-}1,H\text{-}1}$ of 155.2 Hz unequivocally indicates the desired β-D-*manno* configuration of the product which is difficult to ascertain solely on the basis of ^1H NMR data.[14]

The synthesis of other closely related compounds as well as the biological evaluation of these antibiotics is currently in progress and will be reported in due course.



Scheme 2. [a] **13**, Ag-silicate on alumina (≈ 3 eq.)[12], -10°C, 30 min, CH_2Cl_2, MS 3Å; [b] $NaBH_4$, CH_2Cl_2/MeOH (1:1), -78°C→r.t., 4h, 78% over both steps; [c] KOH (48% in water), DMSO/i-PrOH (1:1), 60°C, 4h, 84%; [d] H_2 (1atm), $Pd(OH)_2$ on charcoal (20% w/w), MeOH, overnight, 90%.

EXPERIMENTAL

General. All reactions were carried out under Ar using Schlenk techniques. Melting points: Gallenkamp apparatus, corrected. NMR: Spectra were recorded on a Bruker WH 400, AMX 300 or AC 200 spectrometer at 400.1, 300.1 or 200.1 MHz (^1H) and 100.6, 75.5 or 50.3 MHz (^{13}C), respectively, in $CDCl_3$ unless stated otherwise. Chemical shifts (δ) are given in ppm relative to TMS, coupling constants (J) in Hz. The multiplicity in the ^{13}C NMR spectra refers to the geminal protons (DEPT). IR: Nicolet FT-7199, KBr, wavenumbers in cm^{-1}. MS: Varian CH-5 (70 eV). Specific optical rotations: Perkin Elmer 241. Elemental analysis: Dornis and Kolbe, Mülheim. Flash chromatography: Merck silica gel 60 (230-400 mesh) with hexane/ethyl acetate as eluent in the proportions indicated. The solvents were dried by distillation over the following drying agents and were transferred under Ar: THF (Mg-anthracene), CH_2Cl_2 (P_2O_5), pyridine (KOH), DMF (CaH_2). Alumina (Degussa, product of flame pyrolysis, ∅ 13 nm) was employed for the preparation of the silver silicate/alumina glycosidation catalyst (loading: 3 mmol Ag(+1)/g).[12] The following compounds have been purchased and were used as received: CuCl(COD) (Fluka), *(R)*-1,2-epoxypropane (Merck), $PdCl_2$(dppf)[15] (Aldrich), TBAF (1.0 M in THF, Aldrich).

(2*R*)-Heptadec-16-enol (8). Magnesium (680 mg, 24 mmol) was activated overnight with a crystal of iodine and then suspended in THF (4 ml). 1-Bromotetradec-13-ene (4.0 g, 14.5 mmol) dissolved in THF (8 ml) was slowly dropped into this suspension and the resulting mixture was refluxed for 2 h. The Grignard reagent

thus obtained was added slowly via syringe to a solution of CuCl(COD) (290 mg, 1.4 mmol) and *(R)*-1,2-epoxypropane (1.4 ml, 21 mmol) in THF (50 ml) at -78 °C. The mixture was allowed to warm to ambient temperature and stirring was continued for 18 h. The reaction was quenched with 30 ml sat. aqueous NH_4Cl, extracted with ether and the combined organic phases were dried (Na_2SO_4). After evaporation of the solvents, the residue was chromatographed with hexane/ethyl acetate (10/1→4/1) as the eluent affording **8** as a colorless solid (3.18 g, 86 %). mp = 35-36 °C. $[\alpha]_D^{20}$ +3.6 (c 1, $CHCl_3$). IR: 3397, 3079, 2917, 2850, 1643, 1471, 1372, 993, 912. ^1H NMR (200 MHz): δ 5.82 (ddt, J = 6.7, 10.2, 17.0, 1H), 4.97 (m, 1H), 4.96 (m, 1H) 3.78 (m, 1H), 2.04 (m, 2H), 1.53 (d, J = 3.3, 1H, OH), 1.22-1.47 (br, 24H), 1.18 (d, J = 6.2, 3H). ^{13}C NMR (50 MHz): δ 139.2, 114.1, 68.2, 39.4, 33.8, 29.6, 29.5, 29.1, 28.9, 25.8, 23.5. MS (70 eV): *m/z* (rel. intensity): 254 (1, $[M^+]$), 236 (13), 96 (61), 82 (65), 69 (54), 55 (79), 45 (100).- $C_{17}H_{34}O$ (254.5): *calcd.* C 80.24, H 13.47; *found* C 80.13, H 13.01.

(16*R*)-(*tert*-Butyldimethylsilyloxy)heptadec-1-ene (9). A solution of **8** (2.80 g, 11.0 mmol), imidazole (898 mg, 13.2 mmol) and TBDMSCl (1.99 g, 13.2 mmol) was stirred in DMF (30 ml) at room temperature overnight. After quenching with sat. aqueous $NaHCO_3$, the aqueous layer was separated and extracted with CH_2Cl_2. The combined organic fractions were dried (Na_2SO_4), the solvent was evaporated and the remaining residue chromatographed with hexane/ethyl acetate (15/1) as the eluent to afford **9** (2.81 g, 94 %) as a colorless syrup. $[\alpha]_D^{22}$ = -8.0 (c 20, $CHCl_3$). IR: 3078, 2927, 2855, 1641, 1255, 1134, 909, 836, 774. ^1H NMR (200 MHz): δ 5.79 (ddt, J = 17.0, 10.3, 6.6, 1H), 4.98 (m, 1H), 4.90 (m, 1H), 3.75 (m, 1H), 2.03 (m, 2H), 1.19-1.49 (br, 24H), 1.11 (d, J = 6.0, 3H), 0.89 (s, 9H), 0.04 (s, 6H). ^{13}C NMR (50 MHz): δ 139.1, 114.1, 68.7, 39.8, 33.9, 29.8, 29.6, 29.2, 29.0, 25.9, 25.8, 23.9, 18.2, -4.4, -4.7. MS (70 eV): *m/z* (rel. intensity): 368 (0.1, $[M^+]$), 353 (2), 311 (44), 293 (2), 159 (7), 103 (3), 75 (100), 69 (2), 55 (4), 41 (3).- $C_{23}H_{48}OSi$ (368.7): *calcd.* C 74.92, H 13.12; *found* C 74.89, H 13.06.

2,2-Dimethyl-5-(trifluoromethanesulfonyl)-benzo[1,3]dioxin-4-one (11). To a solution of 2,2-dimethyl-5-hydroxy-4-oxo-benzo-1,3-dioxin (5.0 g, 25.8 mmol)[6a] in pyridine (50 ml) was added triflic anhydride (5.1 ml, 31.0 mmol) at such a rate that the temperature was maintained at 0 °C. Stirring was continued at that temperature for 10 min until TLC showed complete conversion. The reaction was quenched with sat. aqueous $NaHCO_3$ (30 ml), repeatedly extracted with ether, the combined organic layers were washed with water and dried (Na_2SO_4), the solvents were evaporated and the residue chromatographed with toluene/ethyl acetate (3/2) as the eluent. Recrystallization of the product thus obtained from ethyl acetate/hexane at -18 °C afforded the title compound as colorless needles (7.07 g, 84 %). mp = 114-115 °C. IR: 3094, 2997, 1746, 1622, 1476, 1439, 1218, 1207, 1141. ^1H NMR (200 MHz): δ 7.65 (t, J = 8.3, 1H), 7.14 (dd, J = 8.4, 0.9, 1H), 7.02 (d, J = 8.2, 1H), 1.77 (s, 6H). ^{13}C NMR (50 MHz): δ 157.1, 156.7, 148.3, 135.9, 118.4 (q, $^3J_{CF}$ = 325), 117.6, 116.2, 107.9, 106.5, 25.1. MS (70 eV): *m/z* (rel. intensity): 326 (12, $[M^+]$), 268 (100), 176 (20), 138 (17), 107 (39), 69 (12), 43 (10).- $C_{11}H_9F_3O_6S$ (326.2): *calcd.* C 40.50, H 2.78; *found* 40.57, H 2.78.

5-{[(16*R*)-*tert*-Butyldimethylsilanyloxy]heptadecyl}-2,2-dimethyl-benzo[1,3]dioxin-4-one (12). Alkene **9** (2.77 g, 8.5 mmol) was added to a solution of 9-BBN dimer (1.04 g, 8.5 mmol) in THF (10 ml) and the resulting mixture was stirred overnight at ambient temperature. The borane thus obtained (^{11}B-NMR: δ 82.4 ppm) was transferred via syringe to a Schlenk tube containing NaOMe (459 mg, 8.5 mmol). After stirring for 2 h at room temperature, triflate **11** (2.93 g, 9.0 mmol), KBr (1.11 g, 9.35 mmol), $PdCl_2$(dppf) (184 mg, 2.5 mol%) and THF (20 ml) were added and the mixture was refluxed for 4 h. For work-up, hexane (30 ml), 2 M NaOH (5

ml) and H_2O_2 (30 % in water, 5 ml) were introduced at room temperature and stirring continued for 1h. The aqueous phase was separated and extracted with ether, the combined organic layers were washed with sat. aqueous $NaHCO_3$ and water, dried (Na_2SO_4) and the solvents were evaporated. The crude product was purified by flash chromatography with hexane/ethyl acetate (15/1) as the eluent affording **12** as a colorless solid (4.00 g, 86 %). mp = 42-43 °C. $[\alpha]_D^{25}$ -5.4 (c 5, $CHCl_3$). IR: 2919, 2852, 1730, 1605, 1472, 1313, 1043, 834, 772. ^1H NMR (200 MHz): δ 7.38 (t, J = 8.0, 1H), 6.92 (d, J = 7.6, 1H), 6.81 (dd, J = 8.2, 1.0, 1H), 3.75 (m, 1H) , 3.08 (m, 2H), 1.69 (s, 6H), 1.22-1.64 (br, 28H), 1.11 (d, J = 6.0, 3H), 0.88 (s, 9H), 0.04 (s, 6H). ^{13}C NMR (50 MHz): δ 160.1, 157.1, 148.5, 135.0, 125.0, 115.0, 112.1, 104.9, 68.6, 39.7, 34.3, 31.2, 29.6, 29.5, 25.9, 25.8, 25.6, 23.8, 18.1, -4.4, -4.7. MS (70 eV): *m/z* (rel. intensity): 531 (3, $[M^+]$-CH_3), 489 (68), 431 (100), 357 (8), 221 (13), 207 (33), 159 (11), 133 (14), 75 (28), 55 (12).- $C_{33}H_{58}O_4Si$ (546.9): *calcd.* C 72.47, H 10.69; *found* C 72.49, H 10.59.

5-[(16*R*)-Hydroxyheptadecyl]-2,2-dimethyl-benzo[1,3]dioxin-4-one (13). A solution of **12** (3.76 g, 6.88 mmol) and Bu_4NF (8.26 mL, 8.26 mmol) in THF (30 ml) was stirred overnight at ambient temperature. A standard extractive work-up followed by flash chromatography of the crude product with hexane/ethyl acetate (10/1→4/1) as the eluent gave compound **13** (2.73 g, 92 %) as a colorless solid. mp = 51-52 °C. $[\alpha]_D^{20}$ -2.8 (c 5.0, $CHCl_3$). IR: 3379, 2918, 2849, 1743, 1607, 1538, 1477, 1313, 1266, 1208. ^1H NMR (200 MHz): δ 7.39 (t, J = 8.0, 1H), 6.93 (dd, J =7.7, 1.1, 1H), 6.80 (dd, J = 8.2, 1.1, 1H), 3.78 (m, 1H), 3.09 (m, 2H), 1.89 (br, 1H, OH), 1.70 (s, 6H), 1.22-1.63 (br, 28H), 1.18 (d, J = 6.2, 3H). ^{13}C NMR (50 MHz): δ 160.1, 157.0, 148.4, 135.0, 125.0, 115.0, 112.0, 104.9, 68.0, 39.3, 34.3, 31.1, 29.6, 29.4, 25.7, 25.6, 23.4. MS (70 eV): *m/z* (rel. intensity): 432 (23, $[M^+]$), 374 (88), 356 (100), 338 (54), 161 (60), 152 (63), 147 (59), 69 (27), 55 (47).- $C_{27}H_{44}O_4$ (432.6): *calcd.* C 74.96, H 10.25, *found* C 74.78, H 10.15.

2,2-Dimethyl-5-{[(16*R*)-β-D-(3,4,6-tri-O-benzyl)mannopyranosyloxy]heptadecyl}-benzo[1,3]dioxin-4-one (17). A suspension of alcohol **13** (172 mg, 0.4 mmol), silver silicate on alumina (400 mg, 3 mmol Ag(+1)/g catalyst)[12] and powdered MS 3 Å in CH_2Cl_2 (6 ml) was stirred for 10 min at room temperature. After cooling to 0 °C a solution of ulosyl bromide **15** (305 mg, 0.6 mmol)[11a] in CH_2Cl_2 (2 ml) was slowly added. After stirring for 30 min at that temperature the reaction mixture was filtered through Celite, the insoluble residues were thoroughly washed with CH_2Cl_2, the filtrate was evaporated, and the crude product purified by flash chromatography using hexane/ethyl acetate (4/1→2/1) as the eluent. Since compound **16** exists in its keto and its hydrated form, fractions with R_f-values between 0.71-0.81 (hexane/ethyl acetate 2/1) were collected to give 350 mg of a colorless syrup ($[\alpha]_D^{20}$ -21.3 (c 5, $CHCl_3$)). The product was directly used for the next step without further characterization. To a solution of this product in CH_2Cl_2 (5 ml) and MeOH (5 ml) was added $NaBH_4$ (300 mg) at -78°C and the resulting mixture was allowed to warm to room temperature during a period of 4 h. After diluting with CH_2Cl_2 (15 ml) the organic phase was washed with 3 % aqueous citric acid and water, dried (Na_2SO_4), the solvents were evaporated, and the residue chromatographed using hexane/ethyl acetate (4/1→2/1) as the eluent affording product **17** as a colorless syrup (270 mg, 78 % over both steps). $[\alpha]_D^{25}$ -11.2 (c 5, $CHCl_3$). IR: 3470, 3030, 2925, 2853, 1738, 1313, 1270, 1108, 736, 698. ^1H NMR (400 MHz): δ 7.22-7.43 (m, 16H), 6.92 (dd, J = 7.6, 1.1, 1H), 6.79 (dd, J = 8.2, 1.1, 1H), 4.90 and 4.56 (AB, J = 10.9, 2H, $PhCH_2$), 4.78 and 4.67 (AB, J = 12.0, 2H, $PhCH_2$), 4.63 and 4.56 (AB, J = 12.2, 2H, $PhCH_2$), 4.49 (s, 1H, H-1'), 4.05 (d, J = 3.0, 1H, H-2'), 3.91 (m, 1H), 3.86 (t, J = 9.4, 1H, H-4'), 3.77 (dd, J = 2.0, 11.0, 1H, H-6a'), 3.71 (dd, J = 5.3, 10.9, 1H, H-6b'), 3.57 (dd, J = 3.0, 9.1, 1H, H-3'), 3.41 (ddd, J = 2.0, 5.4, 9.7, 1H,

H-5'), 3.09 (t, 2H), 2.28 (br, 1H, OH), 1.68 (s, 6H), 1.57 (m, 2H), 1.23-1.48 (br, 26H), 1.13 (d, J = 6.2, 3H). This assignment was confirmed by ^{1}H-^{1}H-COSY spectra (400 MHz). ^{13}C NMR (100 MHz): δ 160.1, 157.0, 148.5, 138.4, 138.3, 137.9, 135.0, 128.4, 128.3, 128.2, 128.0, 127.8, 127.7, 127. 6, 127.4, 125.0, 115.0, 112.0, 104.8, 96.9, 81.8, 75.4, 75.1, 74.3, 73.9, 73.5, 71.2, 69.4, 68.9, 37.1, 34.3, 31.1, 29.6, 29.6, 29.4, 25.6, 25.5, 19.2. $^3J_{C\text{-}1,H\text{-}1}$ = 156.4 Hz (gated spectrum). MS (ESI): 1767 ([M]$_2$ + K$^+$), 1751 ([M]$_2$ + Na$^+$), 903 ([M]+K$^+$), 887 ([M]+ Na$^+$).- $C_{54}H_{71}O_9$ (865.2): *calcd.* C 74.97, H 8.39; *found* C 74.76, H 8.46.

2-Hydroxy-6-{[(16*R*)-β-D-(3,4,6-tri-O-benzyl)mannopyranosyloxy]heptadecyl}benzoic acid (18). A solution of **17** in DMSO (3 ml), i-PrOH (3 ml) and 48 % aqueous KOH (1.5 ml) was stirred for 4 h at 60 °C. After neutralization with 1 M HCl the mixture was extracted with CH_2Cl_2, the combined organic layers were dried (Na_2SO_4), the solvent was evaporated and the crude product purified by flash chromatography using hexane/ethyl acetate/HOAc (20/2/1→8/2/1) as the eluent. This afforded compound **18** as an colorless syrup (187 mg, 84 %). $[\alpha]_D^{20}$ = -21.4 (c 3.5, EtOH). IR: 3443, 3031, 2925, 2853, 1659, 1607, 1453, 1105, 736, 698. ^{1}H NMR (aceton-d_6, 400 MHz): δ 7.23 -7.44 (m, 16H), 6.79 (d, J = 8.2, 1H), 6.78 (d, J = 7.4, 1H), 4.91 (A-part of AB, J = 11.1, 1H, $PhCH_2$), 4.80 (A-part of AB, J = 11.9, 1H, $PhCH_2$), 4.58-4.67 (m, J = 12.1, 4H, $PhCH_2$), 4.65 (s, 1H, H-1'), 4.14 (d, J = 3.0, 1H, H-2'), 3.91 (m, 1H), 3.86 (t, J = 9.5, H-4'), 3.80 (dA-part of AB, J = 2.0, 11.1, 1H, H-6a'), 3.74 (dB-part of AB, J = 5.2, 11.1, H-6b'), 3.67 (dd, J = 3.1, 9.2, 1H, H-3'), 3.48 (ddd, J = 2.0, 5.1, 9.7, 1H, H-5'), 2.98 (t, J = 7.7, 2H), 1.55 -1.63 (m, 3H), 1.22 -1.47 (m, 26H), 1.13 (d, J = 6.2, 3 H). The assignment was confirmed by ^{1}H-^{1}H-COSY spectra. ^{13}C NMR (aceton-d_6, 100 MHz): δ 173.4, 163.3, 147.1, 140.0, 139.9, 139.9, 134.7, 129.0, 128.9, 128.6, 128.4, 128.3, 128.1, 128.1, 128.0, 122.9, 115.90, 113.2, 98.5, 83.3, 76.3, 75.4, 75.3, 74.0, 73.8, 71.0, 70.5, 69.1, 38.1, 36.7, 32.9, 30.2-30.5 (overlapping signals), 26.2, 19.9. $^3J_{C\text{-}1,H\text{-}1}$ = 156.4 Hz (gated spectrum). MS (ESI): 847 = ([M] + Na$^+$), 1671 ([M]$_2$ + Na$^+$).- $C_{51}H_{68}O_9$ (825.1): *calcd.* C 74.24, H 8.31, *found* C 74.29, H 8.42.

2-Hydroxy-6-{[(16*R*)-β-D-mannopyranosyloxy)heptadecyl]}benzoic acid (1). A mixture of compound **18** (79 mg, 0.96 mmol) and Pd(OH)$_2$ on charcoal (Perlman-catalyst, 20% w/w, 30 mg) in MeOH (5 ml) was stirred under an atmosphere of H_2 (1 atm) for 20 h at ambient temperature. The hydrogen uptake was monitored by a gas burette. The catalyst was filtered off and thoroughly washed with MeOH, the combined filtrate was evaporated and the residue dried *in vacuo* (10^{-3} torr) to yield analytically pure **1** as a colorless waxy solid, the data of which match those reported in ref.[1] in all respects. $[\alpha]_D^{20}$ = -29.0 (c 2, MeOH). IR: 3397, 2921, 2849, 1660, 1606, 1452, 1378, 1244, 1071. ^{1}H NMR (CD_3OD, 400 MHz): δ 7.18 (t, J = 8.2, 1H), 6.68 (d, J = 8.3, 1H), 6.66 (d, J = 7.6, 1H), 4.60 (s, 1H, H-1'), 3.84 (m, 1H, H-16), 3.81 (dd, J = 2.3, 11.7, 1H, H-6a'), 3.74 (d, J = 3.1, 1H, H-2'), 3.69 (dd, J = 5,3, 11.8, 1H, H-6b'), 3.54 (m, 1H, H-4'), 3.42 (dd, J = 3.2, 9.4, 1H, H-3'), 3.15 (ddd, J = 2.3, 5.2, 9.5, 1H, H-5'), 2.83 (m, 2H), 1.60-1.20 (m, 28H), 1.08 (d, J = 5.6, 3H). ^{13}C NMR (CD_3OD, 100 MHz): δ 162.4 (s), 147.0 (s), 134.3 (d), 123.2 (d),116.2 (d), 116.0 (s), 99.4 (d), 78.3 (d), 75.7 (d), 75.5 (d), 73.5 (d), 68.8 (d), 63.1(t), 38.6 (t), 36.9 (t), 33.5 (t), 30.8-31.1 (t, overlapping signals), 26.8 (t), 19.9 (q). $^3J_{C\text{-}1,H\text{-}1}$ = 155.15 Hz (gated spectrum). MS (70 eV): *m/z* (rel. intensity): 510 (1, [M$^+$] -44), 330 (52), 234 (11), 147 (9), 120 (21), 108 (100), 73 (22), 55 (14), 43 (13).- $C_{30}H_{50}O_9$ (554.7): *calcd.* C 64.96, H 9.09; *found* C 64.78, H 9.08.

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