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

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Abstract: An expeditious total synthesis of the physiologically active furgal 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. Copyright © 1996 Elsevier Science Ltd

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



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}



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 (¹¹B NMR δ -2.4 ppm) formed on addition of NaOMe to borane **10** (¹¹B NMR δ +82.4 ppm) readily transfers its alkyl group to the arylpalladium species prepared *in situ* from triflate **11** and catalytic amounts of PdCl₂(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 Me₃Si-group and a t-BuMe₂Si-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 \rightarrow r.t., overnight, 86%; [b] TBDMSCl, imidazole, DMF, r.t., 94%; [c] [9-H-9-BBN]₂, THF; [d] NaOMe (1 eq.), KBr (1.1 eq.), PdCl₂(dppf) (2.5 mol%), THF, reflux, overnight, 86%; [e] TBAF, THF/H₂0, 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 CH₂Cl₂ in the presence of silver silicate on alumina as promotor ¹² provided glycosuloside 16 which was reduced without further purification with NaBH₄ in MeOH/CH₂Cl₂. 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-1,H-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 ($\approx 3 \text{ eq.}$)¹², -10°C, 30 min, CH₂Cl₂, MS 3Å; [b] NaBH₄, CH₂Cl₂/MeOH (1:1), -78°C \rightarrow r.t., 4h, 78% over both steps; [c] KOH (48% in water), DMSO/i-PrOH (1:1), 60°C, 4h, 84%; [d] H₂ (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 (¹³C), respectively, in CDCl₃ unless stated otherwise. Chemical shifts (δ) are given in ppm relative to TMS, coupling constants (J) in Hz. The multiplicity in the ¹³C 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), CH₂Cl₂ (P₂O₅), pyridine (KOH), DMF (CaH₂). Alumina (Degussa, product of flame pyrolysis, Ø 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), PdCl₂(dppf)¹⁵ (Aldrich), TBAF (1.0 M in THF, Aldrich).

(2R)-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*)-1,2epoxypropane (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 NH4Cl, extracted with ether and the combined organic phases were dried (Na₂SO₄). After evaporation of the solvents, the residue was chromatographed with hexane/ethyl acetate (10/1 \rightarrow 4/1) as the eluent affording **8** as a colorless solid (3.18 g, 86 %). mp = 35-36 °C. [α]D²⁰ +3.6 (c 1, CHCl₃). 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). ¹³C 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).- C₁₇H₃₄O (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 TBDMSCI (1.99 g, 13.2 mmol) was stirred in DMF (30 ml) at room temperature overnight. After quenching with sat. aqueous NaHCO₃, the aqueous layer was separated and extracted with CH₂Cl₂. The combined organic fractions were dried (Na₂SO₄), 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. [α]D²² = -8.0 (c 20, CHCl₃). 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). ¹³C 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).- C₂₃H48OSi (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 NaHCO3 (30 ml), repeatedly extracted with ether, the combined organic layers were washed with water and dried (Na₂SO₄), 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). ¹³C 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).- C₁₁H9F₃O₆S (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), PdCl2(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 H₂O₂ (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 NaHCO₃ and water, dried (Na₂SO₄) 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, CHCl₃). 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). ¹³C 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⁺]-CH₃), 489 (68), 431 (100), 357 (8), 221 (13), 207 (33), 159 (11), 133 (14), 75 (28), 55 (12).- C₃₃H₅₈O₄Si (546.9): *calcd*. C 72.47, H 10.69; *found* C 72.49, H 10.59.

5-[(16R)-Hydroxyheptadecyl]-2,2-dimethyl-benzo[1,3]dioxin-4-one (13). A solution of 12 (3.76 g, 6.88 mmol) and Bu4NF (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, CHCl3). 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). ¹³C 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).-C27H44O4 (432.6): calcd. C 74.96, H 10.25, found C 74.78, H 10.15.

2,2-Dimethyl-5-{[(16R)-B-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 CH₂Cl₂ (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 CH₂Cl₂ (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 CH₂Cl₂, the filtrate was evaporated, and the crude product purified by flash chromatography using hexane/ethyl acetate $(4/1 \rightarrow 2/1)$ as the eluent. Since compound 16 exists in its keto and its hydrated form, fractions with Rf-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, CHCl₃)). The product was directly used for the next step without further characterization. To a solution of this product in CH₂Cl₂ (5 ml) and MeOH (5 ml) was added NaBH4 (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 CH₂Cl₂ (15 ml) the organic phase was washed with 3 % aqueous citric acid and water, dried (Na2SO4), the solvents were evaporated, and the residue chromatographed using hexane/ethyl acetate $(4/1 \rightarrow 2/1)$ as the eluent affording product 17 as a colorless syrup (270 mg, 78 % over both steps). [α]D²⁵ -11.2 (c 5, CHCl3). 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, PhCH₂), 4.78 and 4.67 (AB, J = 12.0, 2H, PhCH₂), 4.63 and 4.56 (AB, J = 12.2, 2H, PhCH₂), 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, 1.0, 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 ¹H-¹H-COSY spectra (400 MHz). ¹³C 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-1,H-1} = 156.4 Hz (gated spectrum). MS (ESI): 1767 ([M]₂ + K⁺), 1751 ([M]₂ + Na⁺), 903 ([M]+K⁺), 887 ([M]+ Na⁺).- C54H7109 (865.2): *calcd.* C 74.97, H 8.39; *found* C 74.76, H 8.46.

2-Hydroxy-6-{[(16R)-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 CH₂Cl₂, the combined organic layers were dried (Na2SO4), the solvent was evaporated and the crude product purified by flash chromatography using hexane/ethyl acetate/HOAc $(20/2/1 \rightarrow 8/2/1)$ 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. ¹H NMR (aceton-d6, 400 MHz): \$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, PhCH₂), 4.80 (A-part of AB, J = 11.9, 1H, PhCH₂), 4.58-4.67 (m, J = 12.1, 4H, PhCH₂), 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 = 3.02.0, 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 ¹H-¹H-COSY spectra. ¹³C NMR (aceton-d6, 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. ${}^{3}J_{C-1 H-1} = 156.4 \text{ Hz}$ (gated spectrum). MS (ESI): $847 = ([M] + Na^{+}), 1671 ([M]_{2} + Na^{+}), -C51H68O9$ (825.1): calcd. C 74.24, H 8.31, found C 74.29, H 8.42.

2-Hydroxy-6-{[(16R)-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 H₂ (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. [α]D²⁰ = -29.0 (c 2, MeOH). IR: 3397, 2921, 2849, 1660, 1606, 1452, 1378, 1244, 1071. ¹H NMR (CD₃OD, 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). ¹³C NMR (CD₃OD, 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-1,H-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).- C₃₀H₅₀O9 (554.7): *calcd*. C 64.96, H 9.09; *found* C 64.78, H 9.08.

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