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ENANTIOSELECTIVE SYNTHESES OF D- AND L-RIBO- AND ARABINO-C_{18}-PHYTOSPHINGOSINE FROM (R)-2,3-O-ISOPROPYLIDENE GLYCERALDEHYDE

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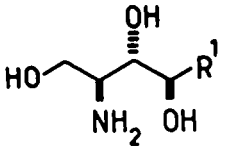
Abstract. Practical syntheses of homochiral D- and L-ribo- and arabino-C_{18}-phytosphingosine 1 and 2 from (R)-2,3-O-isopropylidene glyceraldehyde (3) are described (Scheme 1), the key steps being: (1) the (Z)-selective olefination of 3 (→5) (2) the selective monobenzoylation of the diol 6 (→7); (3) the Mitsunobu-type introduction of the nitrogen (7→9); (4) the osmylation of 9 (→10/11).

D-ribo-C_{18}-Phytosphingosine ((2S,3S,4R)-2-amino-octadecane-1,3-4-triol) (1) and similarly, its C_{20}-homologue, are widely distributed as amides of α-hydroxy long chain acids in plant sphingolipids[1]. The presence of phytosphingosines in human brain and kidney lipids has also been reported[2]. Owing to the biological importance of the compound, several syntheses of 1 have been described, both of the racemic[3] and the optically active[4,5,6] material. By contrast, the D-arabino-isomer 2 apparently has not yet been prepared in enantiomerically pure form.



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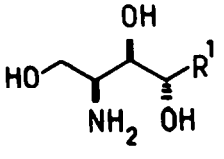


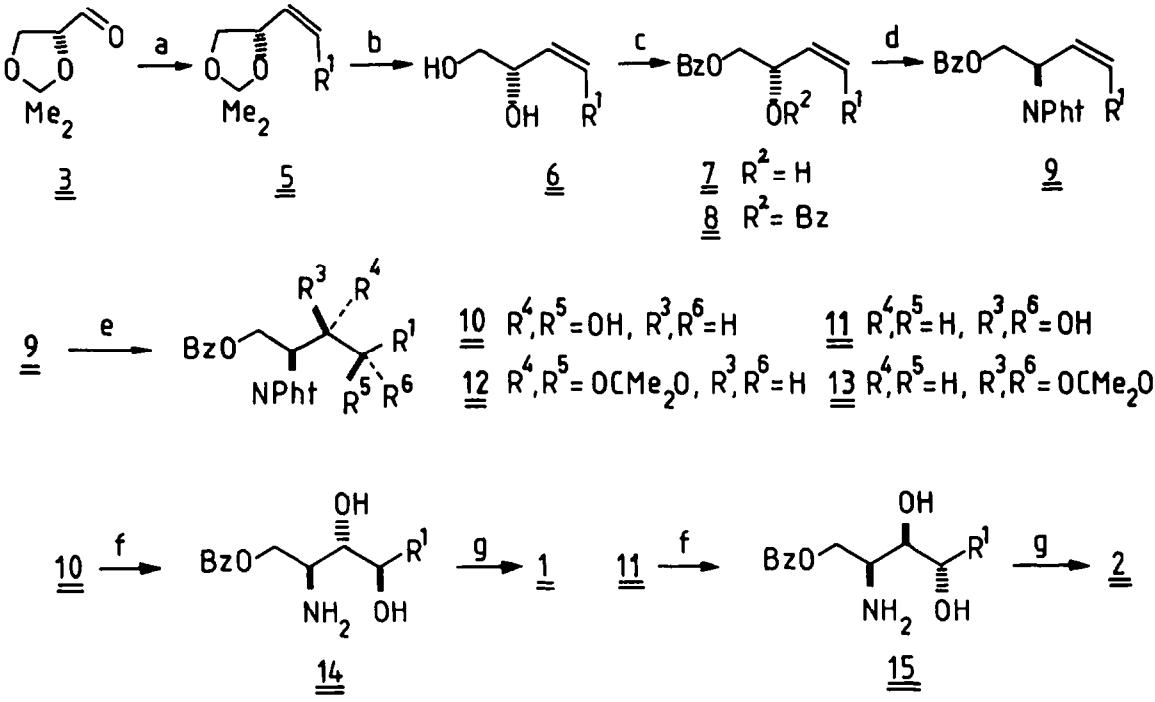
2

$R^1 = C_{14}H_{29}$

Our approach to 1 and 2 (Scheme 1) is based on the ready availability of (R)-2,3-O-isopropylidene glyceraldehyde (3) from inexpensive D-mannitol in multigram quantities[7]. Wittig condensation between 3 and phosphorane 4 stereoselectively (>98% according to ^{13}C NMR analysis) furnished the (Z)-olefin 5 which after acidic

hydrolysis of the acetonide moiety gave the crystalline diol 6 ($[\alpha]_D^{20}$ = -11.8 (c 1, pyridine)). Monobenzoylation at the primary position led to 7 with high selectivity; no secondary benzoate could be detected and the formation of the di-benzoate 8 ($[\alpha]_D^{20}$ = -38.2 (c 3.3, $CHCl_3$)) did not exceed a maximum of ca. 7%[8]. 7 was subjected to a Mitsunobu reaction[9] with triphenylphosphine, diethyl azodicarboxylate and phthalimide to give the phthalimido olefin 9 under clean inversion of configuration. Cis-hydroxylation with OsO_4/N-methyl-morpholine-N-oxide converted 9 into a 2:1-mixture of the diols 10/11, which were quantitatively separated via their acetonides 12/13 by simple gravity column chromatography on a multigram scale.

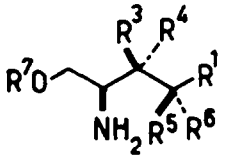
SCHEME 1 (R^1 = $C_{14}H_{29}$, Bz = COPh)



a. Ph_3P = CHR^1 (4; from the phosphonium bromide + nBuLi), THF, -78°C, 2 hrs, 80%. b. 60% HOAc/H_2O + 2N H_2SO_4, THF, 20°C, 24 hrs, 94%. c. 1 mole equiv. benzoyl chloride in ether added dropwise to 6 in pyridine at 0°C, 2 hrs, 87%. d. triphenylphosphine, diethylazodicarboxylate, phthalimide, THF, 20°, 20 hrs, 77%. e. i. 9→10: 1 mole equiv. N-methyl-morpholine-N-oxide-hydrate, 2 mole % OsO_4, acetone-H_2O, 20°C, 20 hrs, 90% - ii. 10,11→12,13: acetone, sulfuric acid, 22°C, 48 hrs, 92%, LC-separation on silica gel ethylacetate-hexane 1:6, R_F(12) 0.45, R_F(13) 0.37. - iii. 12→10, 13→11: 60% HOAc-H_2O + 2N H_2SO_4, CH_3CN, 20°C, 72 hrs, 78%. f. $N_2H_4 \cdot H_2O$ (10 mole equiv.), ethanol, 60°C, 2 hrs, 79%. g. KOH in methanol, 12 hrs 20°C, 3 hrs 60°C, 85%.

The stereochemical outcome of the hydroxylation does confirm Kishi's rule[10], although the stereoselectivity appears to be considerably lower for allylic phthalimides than for analogous alcohols and ethers. The pure crystalline diols 10 and 11 were transformed into 1 and 2 by successive removal of the protecting groups.

Specifically, 10 and 11 gave the mono-benzoates 14 and 15 on treatment with hydrazine, and with strong alkali, 14 and 15 were saponified to afford 1 and 2. The identity of 1 with the natural product described clearly followed from the congruence of the melting point and the optical rotation of our material with the reported data[4,11]. The ^{13}C NMR spectrum of 1 was superimposable with that of a racemic authentic sample[12]. Finally, we prepared the "acetone compound"[13] and the tetra-acetate[14] from 1 as known derivatives. En route, additional crystalline derivatives of 1 and 2 were obtained. For instance, the acetonides 12 and 13 were N-deprotected with hydrazine to give 16 and 17. 16 was converted into 3,4-O-isopropylidene phytosphingosine 18, which yielded 1 on acidic hydrolysis.



16 $R^4,R^5 = OCMe_2O, R^3,R^6 = H, R^7 = Bz$

17 $R^4,R^5 = H, R^3,R^6 = OCMe_2O, R^7 = Bz$

18 $R^4,R^5 = OCMe_2O, R^3,R^6 = H, R^7 = H$

To gain access to the opposite series of enantiomers, 7 was inverted under Mitsunobu conditions[9] (triphenylphosphine, diethylazodicarboxylate, benzoic acid, THF, 22°C) to give a di-benzoate identical in all respects with 8 but showing $([\alpha]_D^{20}$ = 38.0 (c 3.3, $CHCl_3$). Similarly, the diol obtained on saponification was identical with 6 except for the sign of the specific rotation ($[\alpha]_D^{20}$ = 11.5 (c 1, pyridine)). The optical purity of our compounds was checked by esterifying 7 with (-)-methoxytrifluoromethyl-phenyl-acetyl chloride (MTPA chloride, Mosher's reagent)[15] and analyzing the resulting MTPA ester by ^{13}C NMR spectroscopy. A comparison with the MTPA ester prepared from racemic 7 revealed an ee value of >97%.

In conclusion, we have presented practical syntheses of the homochiral C_{18}-phytosphingosines (+)- and (-)-1/2 from D-mannitol. Our method uses inexpensive reagents and simple conditions, and is suitable for the gram scale. Moreover, it involves the preparation of N- and O-protected derivatives, which may be useful for incorporating 1/2 into biologically active ceramide and cerebroside structures[1]. Work aiming in this direction is under way in our laboratory.

EXPERIMENTAL

NMR: Bruker WH 270, AC 250, TMS as internal standard. IR: Perkin Elmer IR 580B. Polarimeter Perkin Elmer 121. All reactions were monitored by TLC. Preparative column chromatography on silicagel Merck 60 (230-400 mesh) with ethyl acetate/hexane (ea/h) mixtures as eluent.

1. (2S)-1,2-Di-O-isopropylidene-3-octadecene-1,2-diol (5)

To pentadecyltriphenylphosphonium bromide (100.0g, 180.64 mmol) in THF (400 ml) n-butyllithium (110 ml of a 1.6 M solution in hexane, 176.0 mmol) was added slowly within 10 min. The dark red solution of phosphorane 4 was treated dropwise with 3 (30.0g, 230.8 mmol) in THF (80 ml) at -78°. After 2 hrs at -78° and 14 hrs at 22° the mixture was concentrated under reduced pressure, diluted with water (200 ml) and extracted with pentane. The organic phase was washed with water, dried ($MgSO_4$) and evaporated to give after chromatography (ea/h 1/4) 47.4g (80%) of pure 5.

^1H NMR (270 MHz, $CDCl_3$): δ = 0.88 (t, J=7.5 Hz, 3H, $(CH_2)_{12}CH_3$); 1.26 (s,24H, $(CH_2)_{12}CH_3$); 1.40 (s, CH_3); 1.42 (s, CH_3); 2.10 (m, 2H, $CH_2(CH_2)_{12}CH_3$); 3.50 (t, J=8Hz, 1H, 1-H); 4.04 (dd, J=8Hz, J=6Hz, 1H, 1-H, CH_2-O); 4.82 (q, J=6Hz, J=8Hz, 1H, 2-H);

5.38 (dd, J=9Hz, J=8Hz, 1H, 4-H); 5.62 (dt, J=8Hz, J=9Hz, 1H, 3-H). ^{13}C NMR (62.88 MHz, $CDCl_3$): δ =13.98, 22.60, 25.90, 26.70, 27.69, 29.11, 29.29, 29.39, 29.53, 29.59 31.86, 69.42, 71.99, 108.88, 127.21, 134.85.- IR (film): 3000, 2930, 2860 s (br., C-H), 1662 w (C=C), 1470 s (C-H def.), 1380 s, 1370 s, 1298 w, 1248 m, 1215 m, 1160 s, 1065 s (C-O), 1035 w, 990 w, 970 w, 865 s, 800 w, 725 s, 515 s cm^{-1}.- $[\alpha]_D^{20}$ = 4.0 (c 5.72, $CHCl_3$). Anal. calcd. for $C_{21}H_{40}O_2$: C 77.72, H 12.42. Found: C 77.78, H 12.56.

2. (2S)-3-Octadecene-1,2-diol (6)

5 (40.0g, 140.6 mmol) was stirred with a mixture of acetic acid (250 ml), water (150 ml), THF (45 ml) and 2N sulfuric acid (10 ml) at room temperature for 24 hrs. After neutralization with potassium carbonate and extraction with ethyl acetate, the organic phase was dried ($MgSO_4$) and evaporated to give 6 (32.0g, 94%) as colorless platelets (mp. 56-57°) after recrystallization from hexane.- ^{1}H NMR (270 MHz, $CDCl_3$): δ = 0.88 (t, J=7.5Hz, 3H, $(CH_2)_{12}CH_3$); 1.28 (s, 24H, $(CH_2)_{12}CH_3$); 2.11 (m, 2H, $CH_2(CH_2)_{12}CH_3$); 2.40 (s, 2H, OH); 3.50 (dd, ABX, J=12Hz, J=8Hz, 1H, CH_2OH); 3.59 (dd, ABX, J=12Hz, J=4Hz, 1H, CH_2OH); 4.57 (mc, ABX, J=8Hz, J=4Hz, J=11Hz, 1H, CH-OH); 5.37 (t, J=9Hz, J=11Hz, 1H, 4-H); 5.61 (dt, J=11Hz, J=9Hz, 1H, 3-H).- ^{13}C NMR (62.88 MHz, $CDCl_3$): δ = 14.00, 22.62, 27.91, 29.29, 29.50, 29.64, 31.87, 66.33, 68.68, 127.85, 134.24.- IR (KBr): 3240 (br., OH), 2960, 2920 and 2855 s (C-H), 1468 s (C-H def.), 1415 w, 1370 w (CH_3), 1317 w, 1275 w, 1260 w, 1210 m, 1140 w, 1092 s, 1070 s (C-O), 1025 s, 950 w, 885 s, 770 w, 740 w, 720 s (C-H), 682 m, 540 w cm^{-1}.- $[\alpha]_D^{20}$ = 8.1 (c 3.23, $CHCl_3$), -11.8 (c 1.0, pyridine).- Anal. calcd. for $C_{18}H_{36}O_2$: C 76.00, H 12.76. Found: C 76.04, H 12.51.

3. (2S)-1-Benzoyloxy-3-octadecene-2-ol (7) and (2S)-1,2-Dibenzoyloxy-3-octadecene (8)

6 (30.0g, 105.5 mmol) in pyridine (150 ml) was treated dropwise with benzoyl chloride (15.6g, 110.8 mmol) in ether (50 ml) at 0°. The mixture was stirred for 2 hrs at 0° and for 24 hrs at 22°, concentrated under reduced pressure, diluted with water and extracted with ether. The organic phase was washed with 2N sulfuric acid and water, dried ($MgSO_4$) and evaporated to give 43.0g of crude product which was chromatographed (ee/h 1/4) to give 7 (35.38g, 87%) (R_f = 0.28) and the dibenzoate 8 (2.31g, 6%) (R_f = 0.52). Analytical data of 7: ^{1}H NMR (270 MHz, $CDCl_3$): δ = 0.88 (t, J=7.5Hz, 3H, $(CH_2)_{12}CH_3$); 1.28 (s, 24H, $(CH_2)_{12}CH_3$); 2.14 (m, 2H, $CH_2(CH_2)_{12}(CH_3)$; 2.36 (s, 1H, CH-OH); 4.28 (dd, ABX, J=12Hz, J=8Hz, 1H, CH_2OBz); 4.34 (dd, ABX, J=12Hz, J=4Hz, 1H, CH_2OH); 4.84 (m, br., ABX, 1H, CH-OH); 5.46 (t, J=9Hz, J=11Hz, 1H, 4-H); 5.64 (dt, J=12Hz, J=9Hz, 1H, 3-H); 7.44 and 7.56 (2xm, 3H, arom-H); 8.06 (d, J=8Hz, 2H, arom.-H).- ^{13}C NMR (62.88 MHz, $CDCl_3$): δ = 14.06, 22.65, 27.95, 29.24, 29.32, 29.46, 29.55, 29.64, 31.89, 66.39, 68.42, 127.37, 128.35, 129.66 and 133.08, 135.13, 167.10.- IR (film): 3410 m (br., OH), 3040 and 2990 w (arom. C-H), 2900 and 2840 vs (aliph. C-H), 1710 s (C=O), 1595 and 1575 w (arom. C-H), 1445 m (C-H def.), 1365 w, 1310 w, 1265 s (C-O), 1170 w, 1110 m, 1060 m, 1020 m, 963 w, 705 vs, 680 w cm^{-1}.- $[\alpha]_D^{20}$ = 11.6 (c 2.2, pyridine).- Anal. calcd. for $C_{25}H_{40}O_3$: C 77.27, H 10.38. Found: C 76.95, H 10.30.- 8: ^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.88 (t, J=7.5 Hz, $(CH_2)_{12}CH_3$); 1.28 (s, 24H, $(CH_2)_{12}CH_3$) 2.29 (m, 2H, $CH_2(CH_2)_{12}CH_3$); 4.56 (d, J=7Hz, J=0.5Hz, 2H, CH_2-OBz); 5.54 (dd, J=11Hz, J=9Hz, 1H, 3-H); 5.76 (dt, J=11Hz, J=7.5Hz, J=0.5Hz, 1H, CH-OBz); 6.22 (dt, J=9Hz, J=6Hz, 1H, 4-H); 7.44 and 7.56 (2xm, 6H, arom.-H); 8.08 (mc, 4H, arom.-H).- ^{13}C NMR (62.88 MHz, $CDCl_3$): δ = 14.04, 22.62, 28.16, 29.22, 29.30, 29.40, 29.53, 29.61, 30.27, 31.87, 65.54, 68.72, 123.43, 128.25, 129.62, 132.86, 137.10 (C-3), 165.56, 166.13.- IR (film): 3040, 2990 w (arom. C-H), 2900 and 2840 vs (aliph. C-H), 1710 s (C=O), 1590, 1575 m (arom. C-H), 1443 s (C-H def.), 1370 w, 1310 w, 1265 vs (C-O), 1170 m, 1090 s, 1060 m, 1020 m, 960 w, 871 w, 840 w, 795 w, 703 vs, 680 w cm^{-1}.- $[\alpha]_D^{20}$ = -38.2 (c 3.25, $CHCl_3$).- Anal. calcd. for $C_{32}H_{44}O_4$: C 78.01, H 9.00. Found: C 78.15, H 9.27.

4. (2R)-1-Benzoyloxy-2-phthalimido-3-octadecene (9)

A mixture of 7 (37.10g, 95.5 mmol), triphenylphosphine (37.56g, 143.2 mmol) and phthalimide (16.86g, 114.6 mmol) in THF (500 ml) was treated dropwise at 22° under vigorous stirring with diethylazodicarboxylate (24.94g, 143.2 mmol) in THF (100 ml). After stirring overnight the mixture was concentrated and triturated with ether. The crystalline precipitate was removed by filtration and the filtrate was evaporated to give 44g of crude product which after chromatography (ee/h 1/4) afforded 38.04g (77%) of pure 9 (R_f = 0.27) as a viscous oil.- ^{1}H NMR (270 MHz, $CDCl_3$): δ = 0.88 (t, J=7.5Hz, 3H, $(CH_2)_{12}CH_3$); 1.28 (s, 24H, $(CH_2)_{12}CH_3$); 2.22 (m, 2H, $CH_2(CH_2)_{12}CH_3$); 4.56 (dd, J=12Hz, J=6Hz, 1H, CH_2OBz); 4.82 (dd, J=12Hz, J=10Hz, 1H, CH_2OBz); 5.54 (ddd, J=6Hz, J=10Hz, J=9Hz, 1H, CH-NPhth); 5.72 (dt, J=11Hz, J=8Hz, 1H, 4-H); 5.98 (dd, J=11Hz, J=9Hz, 1H, 3-H); 7.36 and 7.48 (m, 3H, arom.-H); 7.68 and 7.82 (2xmc, 4H, arom.-H); 7.90 and 8.02 (2xm, 2H, arom-H).- IR (film): 3080 and 3040 w (arom. C-H), 2930 and 2860 s (aliph. C-H), 1775 s, 1720 vs (C=O), 1605

and 1588 w (arom. C-H), 1540 w, 1470 and 1455 m (doubl., C-H def.), 1425 w, 1387 s, 1360 m, 1336 m, 1317 m, 1270 s (C-O), 1180 m, 1110 s, 1070 m, 1030 m (C-O), 990 w, 877 w, 760 w, 713 vs, 533 m cm^{-1}.- $[\alpha]_D^{20}$ = 9.5 (c 4.15, $CHCl_3$). Anal. calcd. for $C_{33}H_{43}NO_4$: C 76.56, H 8.37, N 2.71. Found: C 76.43, H 8.20, N 2.59.

5. (2S,3S,4R)- and (2S,3R,4S)-1-Benzoyloxy-2-phthalimido-octadecane-3,4-diol (10 and 11)

A solution of N-methylmorpholine N-oxide hydrate (9.10g, 67.36 mmol) in water (140 ml) and acetone (60 ml) was treated with 200 mg of osmium tetroxide in t-butanol (20 ml). After 15 min at 22° 9 (31.70g, 61.24 mmol) in acetone (20 ml) was added dropwise over 15 min. After stirring the mixture for 24 hrs at 22° a slurry of sodium hydrosulphite (5g) and celite (20g) in water (100 ml) was added and the stirring was continued for a further 2 hrs. Filtration and concentration under reduced pressure furnished an aqueous solution which was acidified with 2N sulfuric acid to pH 2 and extracted with ethyl acetate. The organic phase was dried ($MgSO_4$) and evaporated to afford 30.4g crude material, which was purified by chromatography (ee/h 1/2) to give 30.0g (89%) of a spectroscopically pure mixture of 10 and 11 in a ratio (^{13}C NMR analysis) of 2:1, which were converted into the acetonides 12/13 without diastereomer separation.

(2S,3S,4R)- and (2S,3R,4S)-1-Benzoyloxy-3,4-O-isopropylidene-2-phthalimido-octadecane-3,4-diol (12 and 13)

30.0g (54.38 mmol) of the abovementioned 10/11-mixture were stirred with 2.5 ml conc. sulfuric acid in acetone (700 ml) at 22° for 48 hrs. Then potassium carbonate (50g) was added and stirring was continued for a further 30 min. Filtration and evaporation of the solvent left 29.5g (92%) of a yellow oil which was chromatographed (ee/h 1/6) to furnish 12 (R_f = 0.45) (17.5g) and 13 (R_f = 0.37) (8.77g) both diastereomerically pure according to ^1H NMR analysis. 12: ^1H NMR (270 MHz, $CDCl_3$): δ = 0.88 (t, J=7.5Hz, 3H, $(CH_2)_{12}CH_3$); 1.24 (br., 24H, $(CH_2)_{12}CH_3$); 1.40 (s, 3H, CH_3); 1.54 (s, 3H, CH_3-H); 1.62 (m, 2H, $CH_2(CH_2)_{12}CH_3$); 4.10 (dd, J=5Hz, J=10 Hz, 1H, CH-NPhth); 4.80 (m, 3H, 1-H and 4-H); 5.14 (dd, J=5Hz, J=10Hz, 1H, 3-H); 7.32, 7.46 (2xm, 3H, arom.-H); 7.70 (mc, 2H, arom.-H); 7.84 (m, 4H, arom.-H).- $[\alpha]_D^{20}$ = -33.2 (c 1.38, $CHCl_3$). Anal. calcd. for $C_{36}H_{49}NO_6$: C 73.08, H 8.35, N 2.37. Found: C 73.38, H 8.50, N 2.30.- 13: ^1H NMR (270 MHz, $CDCl_3$): δ = 0.88 (t, J=7.5Hz, 3H, $(CH_2)_{12}CH_3$); 1.26 (s, 24H, $(CH_2)_{12}CH_3$); 1.30 and 1.32 (2x5, CH_3); 1.66 (m, 2H, $CH_2(CH_2)_{12}CH_3$); 4.24 (mc, 1H, CH-NPhth); 4.50 (mc, 1H, 4-H); 4.80 (m, 3H, CH_2OBz and 3-H); 7.36 and 7.50 (2xm, 3H, arom.-H); 7.70 (mc, 2H, arom.-H); 7.82 (mc, 2H, arom.-H); 7.90 (m, 2H, arom.-H).- $[\alpha]_D^{20}$ = -12.6 (c 1.35, $CHCl_3$).

Acidic hydrolysis as described in 2. converted 12 (16.50g, 27.78 mmol) into 10 (13.30g, 80%) and 13 (7.50g, 14.37 mmol) into 11 (6.18g, 78%). 10: mp. 73-74°. ^1H NMR (250 MHz, $CDCl_3$): δ = 0.88 (t, J=7.5Hz, 3H, $(CH_2)_{12}CH_3$); 1.28 (s, 24H, $(CH_2)_{12}CH_3$); 2.16 (m, br., $CH_2(CH_2)_{12}CH_3$); 2.23 (d, J=5Hz, 1H, CH-OH); 3.82 (m, 1H, 4-H); 4.02 (dd, J=3Hz, J=8Hz, 1H, 3-H); 4.33 (d, J=3Hz, 1H, CH-OH); 4.84 (d, J=8Hz, 2H, CH_2OBz); 5.08 (dd, J=3Hz, J=8Hz, 1H, CH-NPhth); 7.37 and 7.51 (2xm, 3H, arom.-H); 7.76 (mc, 2H, arom.-H); 7.88 (m, 4H, arom.-H).- ^{13}C NMR (62.88 MHz, $CDCl_3$): δ = 14.04, 22.64, 25.56, 29.31, 29.52, 29.64, 31.88, 32.64, 51.96, 62.56, 72.52, 75.10, 123.61, 128.27, 129.60, 131.59, 132.95, 134.36, 166.41, 168.99. IR (KBr): 3480 m (OH), 3040 and 3082 w (arom. C-H), 2920 and 2850 vs (aliph. C-H), 1777 s (C=O), 1720 and 1700 vs (C=O), 1600 and 1585 w (arom. C-H), 1468 and 1450 m (C-H def.), 1403 m, 1388 m, 1318 w, 1273 s (C-O), 1175 m, 1150 m, 1118 m, 1070 m, 1040 and 1028 m (C-O), 880 w, 800 w, 723 and 710 s, 533 w cm^{-1}. $[\alpha]_D^{20}$ = -49.5 (c 2.0, $CHCl_3$). Anal. calcd. for $C_{33}H_{45}NO_6$: C 71.84, H 8.22, N 2.54. Found: C 71.73, H 8.30, N 2.39.- 11: mp. 76-77°. ^1H NMR (250 MHz, $CDCl_3$): δ = 0.88 (t, J=7.5Hz, 3H, $(CH_2)_{12}CH_3$); 1.28 (s, 24H, $(CH_2)_{12}CH_3$); 1.80 (m, 2H, $CH_2(CH_2)_{12}CH_3$); 1.82 (d, J=5Hz, 1H, CH-OH); 3.46 (m, 1H, 4-H); 3.91 (m, 1H, 3-H); 4.32 (d, J=10Hz, 1H, CH-OH); 4.77 (dd, J=12Hz, J=6Hz, 1H, CH_2OBz); 4.88 (t, J=12Hz, J=10Hz, 1H, CH_2OBz); 5.12 (dd, J=6Hz, J=10Hz, 1H, CH-NPhth); 7.38 and 7.54 (2xm, 3H, arom.-H); 7.77 (mc, 2H, arom. H); 7.89 (m, 4H, arom.-H).- ^{13}C NMR (62.88 MHz, $CDCl_3$): δ = 14.06, 22.65, 25.62, 29.32, 29.55, 29.62, 31.89, 33.13, 51.95, 63.10, 73.04, 73.89, 123.75, 128.33, 129.62, 131.62, 133.06, 134.44, 169.80.- IR (KBr): 3560 s (OH), 3420 and 3310 (OH) 3060 and 3038 w (arom. C-H), 2918 and 2850 vs (aliph. C-H), 1775 s (C=O), 1702 vs (C=O), 1610, 1600 and 1582 w (arom. C-C), 1465 and 1450 m (C-H def.), 1380 m, 1363 m, 1328 w, 1312 w, 1287 and 1270 s (C-O), 1178 w, 1110 m, 1095 w, 1070 m, 1020 s (C-O), 885 w, 875 w, 860 w, 840 w, 755 m, 720, 710 s, 592 w, 535 m cm^{-1}.- $[\alpha]_D^{20}$ = -51.0 (c 2.0, $CHCl_3$). Anal. Found: C 71.48, H 8.36, N 2.51.

6. (2S,3S,4R)- and (2S,3R,4S)-2-Amino-1-benzoyloxy-octadecane-3,4-diol (14 and 15)

Diol 10 (12.00g, 21.72 mmol) was heated with hydrazine hydrate (12.0 ml, 247.2 mmol) in ethanol (600 ml) to 60° for 2 hrs. The solution was concentrated under reduced pressure, diluted with ethyl acetate (500 ml), washed with 2N sodium hydroxide and water, dried ($MgSO_4$) and evaporated to furnish 14 (7.24g, 79%) as colorless prisms (mp. 126-127°) after recrystallization from acetonitrile. Likewise, 15 (3.84g, 84%) was obtained from 11 (6.00g, 10.92 mmol) as colorless crystals of

mp. 80-81° (acetonitrile). 14: ^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.88 (t, J=7.5Hz, 3H, $(CH_2)_{12}CH_3$, 1.28 (mc, 24H, $(CH_2)_{12}CH_3$); 1.52 (mc, 2H, $CH_2(CH_2)_{12}CH_3$); 3.72 (mc, 2H, 2-H and 4-H); 3.88 (dd, J=12Hz, J=6Hz, 1H, CH_2OBz); 4.05 (dd, J=12Hz, J=3Hz, 1H, CH_2OBz); 4.39 (m, 1H, CH-NH_2); 7.13 (d, J=7.5Hz, 1H, CH-NH_2); 7.50 (mc, 3H, arom.-H); 7.83 (d, J=7.5Hz, 2H, arom.-H).- $[\alpha]_D^{20}$ = 4.2 (c 1.0, pyridine).- Anal. calcd. for $C_{25}H_{43}NO_4$: C 71.22, H 10.28, N 3.32. Found: C 70.55, H 10.30, N 3.25.- 15: ^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.88 (t, J=7.5Hz, 3H, $(CH_2)_{12}CH_3$); 1.28 (s, 24H, $(CH_2)_{12}CH_3$); 1.64 (m, br., 2H, $CH_2(CH_2)_{12}CH_3$); 2.78 (m, br., 1H, CH-OH); 3.00 (m, br., 1H, CH-OH); 3.38 (mc, br., 1H, CH-OH); 3.79 (d, J=9Hz, 1H, CH-OH); 3.98 and 4.13 (2xmc, 2H, CH_2OBz); 4.38 (d similar mc, 1H, CH-NH_2); 4.49 (mc, 1H, CH-NH_2); 7.15 (d, J=9Hz, 1H, CH-NH_2); 7.52 (mc, 3H, arom.-H); 7.88 (d, J=7.5Hz, 2H, arom.-H). After D_2O-exchange: δ = 3.38 (t, J=9Hz, 1H, CH-OH, 4-H); 3.95 (dd, J=12Hz, J=6Hz, 1H, CH_2OBz); 4.10 (dd, J=12Hz, J=3Hz, 1H, CH_2OBz).- $[\alpha]_D^{20}$ = -33.3 (c 1.0, pyridine). Anal. found: C 70.75, H 10.10, N 3.15.

7. (2S,3S,4R)- and (2S,3R,4S)-2-Amino-octadecane-1,3,4-triol (D-ribo- and D-arabino-C_{18}-Phyto-sphingosine) (1 and 2)

14 (6.70g, 15.84 mmol) was stirred with 50 ml of satur. aqueous KOH in methanol (1000 ml) at 22° for 12 hrs and at 60° for 3 hrs. Then the mixture was concentrated under reduced pressure, diluted with water and left in the refrigerator for crystallization. The precipitate was filtrated under suction, washed with water and recrystallized from acetonitrile to afford 1 (4.26g, 85%) as a colorless crystalline powder of mp. 103° and $[\alpha]_D^{20}$ = 7.9 (c 1.0, pyridine). (Lit. data: mp. 95-97° [4a], 97-101° [4b], 104-108° [11]; $[\alpha]_D^{20}$ = 7.7 (c 1.0, pyridine), 7.9 (c 1.2, pyridine), 8.05 (c 1.0, pyridine) [4a]; 8.2 (c 1.2, pyridine) [11].- ^{1}H NMR (250 MHz, [D_6] DMSO): δ = 0.88 (t, J=7.5Hz, 3H, $(CH_2)_{12}CH_3$); 1.28 (mc, 24H, $(CH_2)_{12}CH_3$); 1.60 (mc, 2H, $CH_2(CH_2)_{12}CH_3$); 2.68 (dd, J=10Hz, J=7.5Hz, 1H, CH-OH, 4-H); 3.06 (t, J=7.5 Hz, 1H, CH-OH, 3-H); 3.38 (br., dd, J=10Hz, J=7Hz, 1H, CH_2OH); 3.52 (dd, J=10Hz, J=4Hz, CH_2OH); 4.50 (br., 1H, OH); 8.32 (s, 2H, CH-NH_2).- ^{13}C NMR (62.88 MHz, [D_6] DMSO): δ = 13.77, 21.96, 24.89, 28.59, 28.95, 29.11, 29.31, 31.18, 33.21, 55.79, 63.24, 73.23, 78.96.- IR (KBr): 3380 m (br., OH), 2920 and 2850 s (C-H), 1750 w, 1560 w (N-H def.), 1470 s (O-H def.), 1380 w, 1240 w, 1065 m (br., C-O), 940 w, 850 w, 800 w, 720 m (C-H) cm^{-1}. Anal. calcd. for $C_{18}H_{39}NO_3$: C 68.09, H 12.38, N 4.41. Found: C 67.50, H 12.13, N 4.21.-

Likewise, 2 (3.07g, 82%) was prepared from 15 (5.00g, 11.82 mmol) Crystalline powder of mp. 75°. ^{1}H NMR (270 MHz, [D_6] DMSO): δ = 0.88 (t, J=7.5Hz, 3H, $(CH_2)_{12}CH_3$); 1.28 (mc, 24H, $(CH_2)_{12}CH_3$); 1.56 (m, 2H, $CH_2(CH_2)_{12}CH_3$); 3.08 (mc, 1H, CH-OH, 4-H); 3.24 (t, J=8Hz, 1H, CH-OH, 3-H); 3.42 (dd, J=11Hz, J=7Hz, 1H, CH_2OH); 3.54 (d, J=5Hz, 1H, CH_2OH); 4.80 (br., 1H, OH); 8.72 (mc, 2H, CH-NH_2).- $[\alpha]_D^{20}$ = -12.3 (c 0.6, pyridine). Anal. found: C 67.82, H 12.10, N 4.30.

8. (2S,3S,4R)-1,3,4-Trisacetoxy-2-acetamido-octadecane (1- Tetraacetate)

1 (350 mg, 1.10 mmol) and 4-N,N-dimethylaminopyridine (50 mg, 4.10 mmol) in pyridine (10 ml) were treated with acetic anhydride (500 mg, 3.73 mmol) for 3 hrs at 22°. Workup as described in 3. including chromatography (ee/h 1/1) gave 450 mg (84%) of the crystalline tetra-acetate. Mp. 48°, $[\alpha]_D^{20}$ = 4.9 (c 1, DMF), 26.3 (c 2, $CHCl_3$) (ref. [14]: mp. 48°, $[\alpha]_D^{20}$ = 5 (c 4.8, DMF)).- ^{1}H NMR (270 MHz, $CDCl_3$): δ = 0.88 (t, J=7.5Hz, $(CH_2)_{12}CH_3$); 1.28 (s, 24H, $(CH_2)_{12}CH_3$); 1.64 (mc, 2H, $CH_2(CH_2)_{12}CH_3$); 2.04, 2.06, 2.08 (4xs, 12H, acetyl-CH_3); 4.04 (dd, J=12Hz, J=3Hz, 1H, CH_2OAc) 4.32 (dd, J=12Hz, J=5.5Hz, 1H, CH_2OAc); 4.48 (mc, J=3Hz, J=5.5Hz, 1H, CH-NHAc, 2-H) 4.69 (dt, J=8Hz, J=3Hz, 1H, CH-OAc, 4-H); 5.12 (dd, J=8Hz, J=3Hz, 1H, CH-OAc, 3-H); 6.08 (d, J=9.5Hz, 1H, CH-NHAc).- ^{13}C NMR (62.88 MHz, $CDCl_3$): δ = 14.04, 20.67, 20.96, 22.63, 23.21, 25.45, 28.24, 29.25, 29.30, 29.44, 29.54, 29.63, 31.87, 47.67, 62.83, 72.14, 72.94, 169.64, 170.00, 170.76, 171.03.- IR (KBr): 3450 w, 3320 s (N-H), 2930 and 2862 s (C-H), 1733 vs (C=O), 1690 w, 1662 m, 1553, 1470 w, 1377 m, 1230 s, 1050 m (C-O), 890 w, 745 w, 612 w cm^{-1}.- Anal. calcd. for $C_{26}H_{47}NO_7$: C 64.30, H 9.75, N 2.88. Found: C 64.60, H 9.95, N 3.00.

9. "Acetone-Compound" of 1

1 (300 mg, 9.46 mmol) was briefly heated in acetone (200 ml) and left for crystallization to give 280 mg (83%) of the acetone compound as colorless crystals of mp. 110-111° and $[\alpha]_D^{20}$ = 15.3 (c 1.0, $CHCl_3$), 21.0 (c 1.0, pyridine). (Lit. data [6]: mp. 108-109°, $[\alpha]_D^{20}$ = 15.4 (c 1, $CHCl_3$), 21 (c 1, pyridine)).- ^{1}H NMR (250 MHz, $CDCl_3$) δ = 0.88 (t, J=7.5Hz, 3H, $(CH_2)_{12}CH_3$); 1.28 (mc, 24H, $(CH_2)_{12}CH_3$); 1.39 and 1.40 (2xs, 3H, acetonide-CH_3); 1.42 and 1.45 (2xs, 3H, acetonide-CH); 1.80 (mc, 2H, $CH_2(CH_2)_{12}CH_3$); 2.27 (br., 3H, OH, NH); 3.00 (mc, J=10Hz, J=5Hz, 1H, CH_2OH); 3.14 (t, J=10Hz, 1H, CH_2OH); 3.55 (dt, J=5Hz, J=6Hz, 1H, CH-NH, 2-H); 3.75 (dd, J=11Hz, J=5Hz, 1H, CH-OH, 4-H); 3.86 (dd, J=11Hz, J=6Hz, 1H, CH-OH, 3-H).- Anal. calcd. for $C_{21}H_{43}NO_3$: C 70.53, H 12.12, N 3.92. Found: C 69.69, H 11.70, N 3.91.

10. (2S,3S,4R)- and (2S,3R,4S)-2-Amino-1-benzoyloxy-3,4-O-isopropylidene-octadecane-3,4-diol (16 and 17)

12 (1.88g, 3.18 mmol) and 13 (830 mg, 1.40 mmol) were reacted with hydrazine hydrate as described in 6. to afford 16 (1.25g, 85%) and 17 (570 mg, 88%), respectively. 16: mp. 100-101°. $[\alpha]_D^{20}$ = 19.5 (c 1.0, $CHCl_3$).- ^{1}H NMR (270 MHz, $CDCl_3$): δ = 0.88 (t, J=7.5Hz, 3H, $(CH_2)_{12}CH_3$); 1.26 (mc, 24H, $(CH_2)_{12}CH_3$); 1.36 and 1.50 (2xs, 3H, acetonide-CH_3); 1.61 (mc, 2H, $CH_2(CH_2)_{12}CH_3$); 2.61 (br., 1H, CH-NH); 3.78 (dd, J=12Hz, J=3Hz, 1H, CH_2OBz); 4.00 (dd, J=12Hz, J=3Hz, 1H, CH_2OBz); 4.24-4.28 (m, 3H, 2-H, 3-H and 4-H); 6.73 (d, J=8Hz, 1H, CH-NH); 7.44 (mc, 3H, arom.-H); 7.76 (d, J=8Hz, 2H, arom.-H).- Anal. calcd. for $C_{28}H_{47}NO_4$: C 72.84, H 10.26, N 3.03. Found: C 73.03, H 10.47, N 2.80.- 17: mp. 59-60°. $[\alpha]_D^{20}$ = 23.0 (c 1.0, $CHCl_3$).- ^{1}H NMR (270 MHz, $CDCl_3$): δ = 0.88 (t, J=7.5Hz, 3H, $(CH_2)_{12}CH_3$); 1.26 (mc, 24H, $(CH_2)_{12}CH_3$); 1.41, 1.57 (2xs, 3H, acetonide-CH_3); 1.60 (mc, 2H, $CH_2(CH_2)_{12}CH_3$); 3.75 and 3.84 (2xdd, J=12Hz, J=6Hz, 1H, CH_2OBz); 4.16 (mc, 1H, 4-H); 4.28 (mc, 1H, 2-H); 4.39 (dd, J=8 and 2Hz, 1H, 3-H); 6.74 (d, J=7.5Hz, 1H, CH-NH); 7.45 (mc, 3H, arom.-H); 7.75 (d, J=8Hz, 2H, arom.-H).

11. (2S,3S,4R)-2-Amino-3,4-O-isopropylidene-octadecane-1,3,4-triol (18)

16 (1.10g, 2.38 mmol) was saponified as described in 7. to give 18 (840 mg, 98%) as colorless needles with mp. 62-63° (hexane).- ^{1}H NMR (270 MHz, $CDCl_3$): δ = 0.88 (t, J=7.5Hz, $(CH_2)_{12}CH_3$); 1.28 (mc, 24H, $(CH_2)_{12}CH_3$); 1.33 and 1.42 (2xs, 3H, acetonide CH_3); 1.56 (mc, 2H, $CH_2(CH_2)_{12}CH_3$); 1.73 (br., 3H, CH_2OH and CH-NH_2); 2.95 (mc, 1H, 4-H); 3.57 (dd, J=12Hz, J=6Hz, 1H, CH_2OH); 3.73 (dd, J=12Hz, J=4Hz, 1H, CH_2OH); 3.84 (dd, J=8Hz, J=5Hz, 1H, 3-H); 4.16 (mc, J=5Hz, 1H, 2-H).- $[\alpha]_D^{20}$ = 21.0 (c 2.0, $CHCl_3$). Anal. calcd. for $C_{21}H_{43}NO_3$: C 70.54, H 12.12, N 3.92. Found: C 70.34, H 12.12, N 3.72.- Under the conditions described in 6. for the conversion of 12/13 into 10/11, 18 furnished a quantitative yield of impure 1.

12. (2R)-1,2-Dibenzoyloxy-3-octadecane (ent-8)

A mixture of 7 (1.41g, 3.63 mmol), triphenylphosphine (1.43g, 5.45 mmol) and benzoic acid (440 mg, 3.63 mmol) in THF (50 ml) was treated dropwise with diethylazodicarboxylate (950 mg, 5.45 mmol) at 22° and stirred overnight. Workup as described in 4. and chromatography (ee/h 1/4) afforded ent-8 (1.67g, 93%), identical in the ^{1}H NMR spectrum with 8 and showing $[\alpha]_D^{20}$ = 38.0 (c 3.25, $CHCl_3$).-

13. (2R)-3-Octadecane-1,2-diol (ent-6)

Ent-8 (1.40g, 2.84 mmol) was saponified as described in 7. to furnish after chromatography (ee/h 1/1) and crystallization from hexane ent-6 (570 mg, 71%) as colorless crystals with mp. 56-57° and $[\alpha]_D^{20}$ = -7.5 (c 2.0, $CHCl_3$), 11.5 (c 1.0, pyridine). The ^{1}H NMR spectrum was identical with that of 6. Anal. calcd. for $C_{18}H_{36}O_2$: C 76.00, H 12.76. Found: C 76.28, H 12.76.

14. MTPA-ester of 7 (Mosher analysis)

7 (100 mg, 0.26 mmol) was treated with (-)-MTPA-chloride (70.0 mg, 0.28 mmol) in pyridine (5 ml) for 12 hrs at 22°. Workup as described in 3. afforded 140 mg (90%) of the crude MTPA-ester, diastereomerically pure according to ^{1}H and ^{13}C NMR analysis.- ^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.88 (t, J=7.5Hz, 3H, $(CH_2)_{12}CH_3$); 1.28 (s, 24H, $(CH_2)_{12}CH_3$); 2.28 (m, 2H, $CH_2(CH_2)_{12}CH_3$); 3.52 (d, J=7.5Hz, 3H, OCH_3); 4.44 (dd, J=7Hz, J=7.5Hz, J=4Hz, 2H, CH_2OBz); 5.36 (dd, J=11.3Hz, J=10Hz, 3H); 5.76 (dt, J=11.3Hz, J=10Hz, 1H, 4-H); 6.20 (mc, J=10Hz, J=4Hz, 1H, 2-H); 7.28 (mc, 3H, arom.-H); 7.48 (mc, 5H, arom.-H); 8.00 (mc, 2H, arom.-H).- ^{13}C NMR (62.88 MHz, $CDCl_3$): δ = 14.06, 22.66, 28.17, 29.25, 29.34, 29.47, 29.57, 29.66, 30.34, 31.91, 55.37, 65.21, 70.69, 121.68, 127.31, 128.28, 128.43, 129.48, 129.69, 133.23, 138.47, 165.50, 165.90.- $[\alpha]_D^{20}$ = -42.0 (c 1.95, $CHCl_3$). Anal. calcd. for $C_{35}H_{47}F_3O_5$: C 69.51, H 7.83, Found: C 70.03, H 8.13. Likewise the MTPA-ester of racem. 7 was prepared. The ^{1}H and ^{13}C NMR spectrum showed two distinguishable sets of signals.

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