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ASYMMETRIC SYNTHESIS OF D-erythro-SPHINGOSINE [1]

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Abstract - D-erythro-Sphingosine **9** is a building block of cerebrosides and glycosphingolipids and was synthesized in 5 steps via an asymmetric aldol addition of the lithiated bislactim ether of cyclo-(L-Val-Gly) **4** to (2E)-hexadecenal (**3**) in an overall yield of 21 %.

I. Introduction

Glycosphingolipids, which are major constituents of outer cell membranes, are of great synthetic importance since these compounds are of interest for biological and medical studies.[2] The glycosphingolipids with a varying structure of their oligosaccharide chain are assumed to play an important role as antigenes.

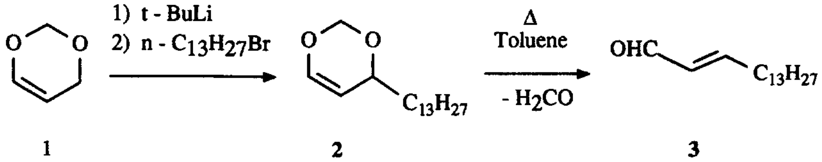
In this communication we present a synthesis of D-erythro-sphingosine **9**, the main component of glycosphingolipids, via an asymmetric aldol addition. Within the last five years several asymmetric syntheses of D-erythro-sphingosine **9** have been reported. Vasella et al.[3] described a seven-step synthesis via Katsuki-Sharpless epoxidation starting from pent-2-en-4-in-1-ol. Rapoport and Boutin[4] used a five-step synthesis which yielded D-erythro-sphingosine **9** from N-benzyloxycarbonyl-L-serine. Schmidt and Zimmermann[5] converted 4,6-O-benzyliden-D-galactose into **9** in five steps. Independently Herold[6] and Radunz et al.[7] reported syntheses of **9** using an asymmetric aldol addition to a derivative of L-serinal. Recently Hayashi, Ito et al.[8] obtained in a catalytic asymmetric aldol addition D-threo-sphingosine, which was converted into D-erythro-sphingosine **9** by a Mitsunobu reaction.

The enantioselective synthesis of anti-amino alcohols or anti-α-amino-β-hydroxy acids by aldol addition remains a challenging problem. Almost all of the known methods for asymmetric aldol additions predominantly deliver syn-diastereomers.

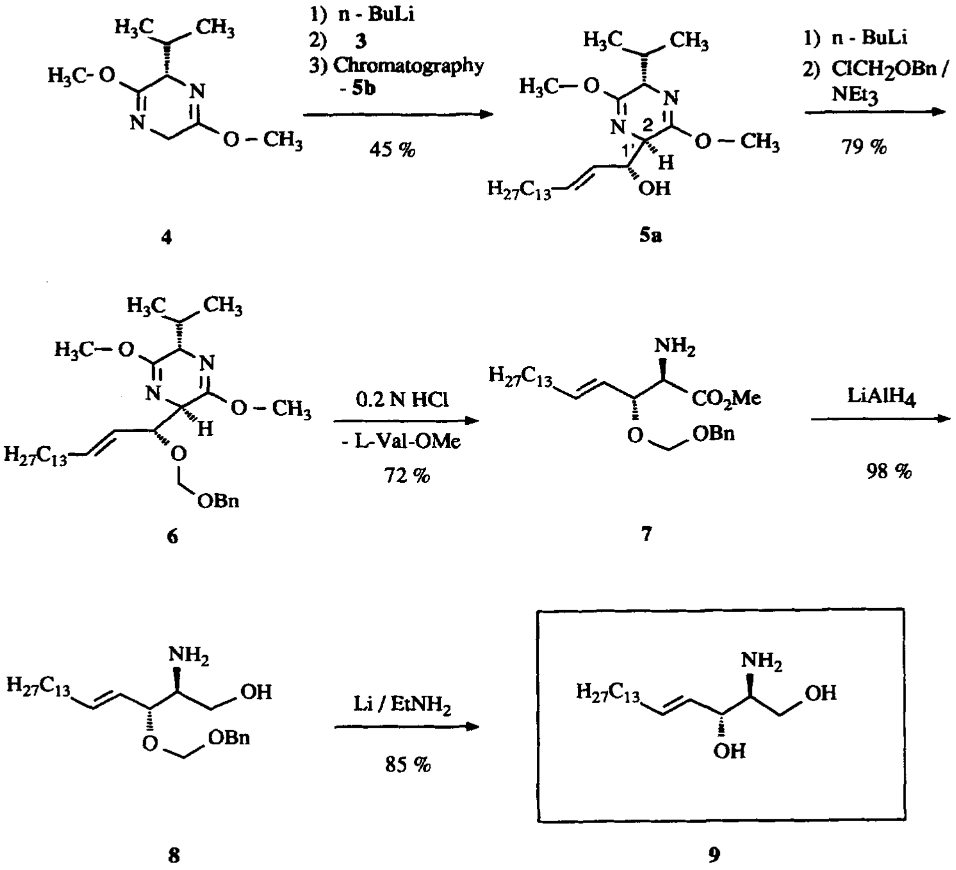
In our sphingosine-synthesis the target molecule was built up using the bislactim ether method.[9]

II. Results and Discussion

As reported recently[10], the titanated bislactim ether of cyclo-(L-Val-Gly) **4** reacts with α,β-unsaturated aldehydes in a 1,2-fashion with very high diastereoselectivity, giving almost exclusively the syn-addition products. The reaction of the lithiated derivative of bislactim ether **4** with α,β-unsaturated aldehydes affords an almost 1:1 mixture of the syn/anti-aldol adducts.[10,11] Since the syn/anti-isomers are separable by chromatography, the anti-aldol adducts are obtainable by the bislactim ether method. Hydrolysis of these aldol adducts would yield erythro-serine methyl esters.



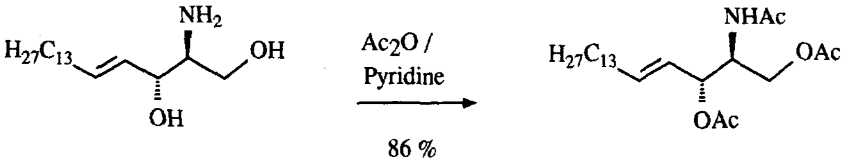
Therefore, (2E)-hexadecenal (**3**) was prepared on a multigram scale by a procedure reported by Funk and Bolton.[12] The dioxene **1** was lithiated with t-butyllithium and alkylated with 1-bromotridecane to afford the dioxene **2**. Heating up of **2** in toluene provided hexadecenal **3** in an almost quantitative yield by a retro-Diels-Alder reaction.



The aldol addition of the lithiated bislactim ether of cyclo-(L-Val-Gly) **4** to (2E)-hexadecenal (**3**) afforded a 1:1 mixture of the diastereomers **5a,b** epimeric at C-1' in 91% yield. Products with the (2S)-configuration were not observed. The diastereomers **5a,b** were easily separated by flash chromatography even on a multigram scale. Since the syn-adduct **5b** could be oxidized under Swern conditions and subsequently reduced with sodium borohydride yielding again a 1:1 mixture of the syn/anti-isomers **5a,b**, the undesired syn-adduct could be converted stepwise into the anti-adduct **5a**.

Upon hydrolysis of **5a** (two equivalents of 0.2 N HCl, room temperature) the corresponding substituted serine ester was obtained in only 23% yield. Predominantly a dipeptide ester was formed by partial cleavage of the bislactim ether ring. Therefore the hydroxy group of the aldol adduct **5a** has to be protected in order to achieve a clean hydrolysis of both imino ether groups. We found that the BOM group (benzyloxy-methyl group) was suitable for this purpose. Interestingly, the addition of triethylamine to the mixture of the lithiated aldol adduct of **5a** and benzyl chloromethyl ether increased the yield of the protected aldol adduct **6** considerably.

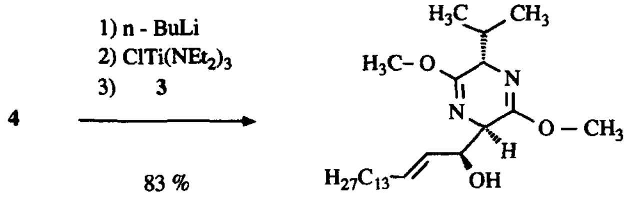
Acidic hydrolysis of **6** yielded methyl L-valinate (81%) - the chiral auxiliary in this synthesis - and the protected erythro-serine methyl ester **7** (72%), which were separated by flash chromatography. Subsequent reduction of the serine ester **7** to the amino alcohol **8** and deprotection of **8** with lithium in ethylamine afforded D-erythro-sphingosine **9** in an overall yield of 21% for the five-step synthesis. To confirm the stereochemistry of **9** it was converted into the crystalline and more stable triacetate **10**.



9 **10**

This method offers access to all four stereoisomers of C_{18}-sphingosine - starting with bislactim ether **4** and ent-**4** - via the adducts **5a/b** and ent-**5a/b** and should be transferable to the synthesis of C_{20}-sphingosines.

Metal-metal-exchange of the lithiated derivative of bislactim ether **4** with tris-(diethylamido)-titanium chloride to the tris-(diethylamido)-titanium azaenolate of bislactim ether **4** and subsequent aldol addition to (2E)-hexadecenal (**3**) afforded the syn-isomer **5b** in 83% yield with a diastereomeric excess of > 98%. In order to avoid the separation of diastereomers **5a,b** we are testing the application of the Mitsunobu reaction to convert D-threo-sphingosine into D-erythro-sphingosine **9**, that was reported by Ito, Sawamura and Hayashi.[8] D-threo-sphingosine would be provided enantiomerically and diastereomerically pure from the syn-diastereomer **5b**.



5b

EXPERIMENTAL

NMR spectra were taken on Varian VXR 200 and XL 200 spectrometers. IR spectra were taken on a Perkin Elmer Mod. 298 spectrometer. Mass spectra were recorded on Varian MAT 731 and 311 A spectrometers. Optical rotations were measured on a Perkin Elmer Mod. 141 polarimeter. TLC analyses were performed on Polygram Sil G/UV$_{254}$ silica gel plates. Silica gel 60 (240-400 mesh) from E.Merck Darmstadt or aluminum oxide (Alumina Woelm, activity III) from Woelm Pharma Eschwege were used for flash chromatography. Combustion analyses were carried out by the microanalytical laboratory of the University of Göttingen. If required, reactions were carried out under dry argon. All reagents were purified and dried if necessary before using. The bislactim ether **4** was prepared according to lit.[13] or purchased from Merck-Schuchardt.[14]

Preparation of (2E)-Hexadecenal (3). 5-Tosyloxy-1,3-dioxane: To a solution of glycerol formal (50.0 g, 0.48 mol) and p-toluenesulfonyl chloride (95.0 g, 0.50 mol) in $CHCl_3$ (100 ml) pyridine (47.4 g, 48 ml, 0.60 mol) was added dropwise at 0°C. After stirring for 24 h at room temp. the reaction mixture was poured into water (100 ml) und extracted with chloroform (100 ml). The organic layer was dried over $MgSO_4$, the solvent evaporated and the oily residue crystallized from ether/petroleum ether. 5-Tosyloxy-1,3-dioxane (37.0 g, 0.14 mol, 40%) was obtained as white crystals.

1,3-Diox-4-ene (1): KOH (21.3 g, 0.38mol) was dissolved in triethyleneglycol (100 ml) at 100°C. The solution was allowed to cool down to 50°C and 5-tosyloxy-1,3-dioxane (37.0 g, 0.14 mol) was added. The mixture was slowly heated up to 190°C. The volatile products were collected in an ice-cooled trap, taken up in pentane (100 ml) and dried over $MgSO_4$. Fractional distillation yielded 7.2 g (84 mmol, 60%) **8**; b.p. 75°C.[12]

4-Tridecyl-1,3-diox-5-ene (2): To a solution of **1** (2.32 g, 27 mmol) in THF (50 ml) a solution of t-butyllithium in pentane (1.7N, 17.6 ml, 30 mmol) was slowly added at -78°C and after 1 h 1-bromotridecane (7.10 g, 27 mmol) in THF (10 ml) was added. The solution was allowed to warm up to room temperature within 16 h, was poured into phosphate buffer (20 ml, pH 7) and extracted with ether (3 portions of 50 ml). Solvent evaporation and silica gel filtration (petroleum ether) afforded **2** (5.44 g, 20 mmol, 75%).-**IR (KBr)**: 3060 (C-H/olefin), 1640 (C=C), 1215 (C-O), 720 cm^{-1} (γ-CH_2).-**^{1}H NMR ($CDCl_3$)**: δ = 0.8-1.5 (m; 27H, 1'-to 13'-H), 4.1-4.3 (m; 1H, 4-H), 4.8 (dd, J_1 = 10 Hz, J_2 = 3 Hz; 1H, 5-H), 5.0 (m; 2H, 2-H), 6.5 (dd J_1 = 10 Hz, $^4J_2$ = 3 Hz; 1H, 6-H).-**HRMS (70 eV)**: calculated for $C_{17}H_{23}O_2$ 268.2402, found 268.2402.

(2E)-Hexadecenal (3): A solution of **2** (5.44 g, 20 mmol) in toluene (150 ml) was heated under reflux for 12 h. The toluene was removed in vacuo and the residue purified by bulb-to-bulb distillation, yielding **3** (4.64 g, 19.5 mmol, 95%) as a white, waxy solid, m.p. 25°C, b.p. 130°C/0.01 Torr.-**IR (neat)**: 1690 (C=O), 1630 cm^{-1} (C=C).-**^1H NMR ($CDCl_3$)**: δ = 0.85-0.91 (m; 3H, 16-H), 1.1-1.6 (m; 22H, 5-to 15-H), 2.27-2.39 (m; 2H, 4-H), 6.12 (ddt, J_1 = 15.5 Hz, J_2 = 8 Hz, $^4J_3$ = 1.5 Hz; 1H, 2-H), 6.86 (dt, J_1 = 15.5 Hz, J_2 = 7 Hz; 1H, 3-H), 9.50 (d, J = 7 Hz; 1H, 1-H).-**^{13}C NMR ($CDCl_3$)**: δ = 14.14 (C-16), 22.74, 27.91, 29.21, 29.41, 29.42, 29.43, 29.57, 29.70, 29.72, 29.73, 31.98, 32.77 (C-4 to C-15), 133.03 (C-3), 158.87 (C-2), 193.95 (C-1).- **HRMS (70 eV)**: calculated for $C_{16}H_{30}O$ 238.2297, found 238.2297.

(2R,5S,1'R,2'E)-2,5-Dihydro-2-(1-hydroxy-hexadec-2'-en-1'-yl)-5-isopropyl-3,6-dimethoxy-pyrazine (5a): n-Butyllithium in hexane (1.7 N, 11.8 ml, 20.0 mmol) was added slowly to a solution of **4** (3.70 g, 20.0 mmol) in THF (150 ml) at -78°C. After 15 min **3** (4.64 g, 19.5 mmol) in THF (10 ml) was added dropwise, the mixture stirred at -78°C for 12 h and then quenched with acetic acid (1.26 g, 21.0 mmol) and H_2O (30 ml). Extraction with ether, evaporation of the solvent and flash chromatography on silica gel (ether/pentane 1:2) afforded **5a** (3.70 g, 8.8 mmol, 45%, R_F = 0.20) and **5b** (3.75 g, 8.9 mmol, 46%, R_F = 0.11).-**(5a)**: **IR (neat)**: 3100-3600 (O-H), 1690 cm^{-1} (C=N).-**^1H NMR ($CDCl_3$)**: δ = 0.70 and 1.03 (2d, J = 7Hz; 3H each, $CH(C\underline{H}_3)_2$), 0.85-0.91 (m; 3H, 16'H), 1.1-1.4 (m; 22H, 5'-to 15'-H), 1.91-2.01 (m; 2H, 4'-H), 2.24 (dsp, J_1 = 7 Hz, J_2 = 3.5 Hz; 1H, $C\underline{H}(CH_3)_2$), 3.19 (d, J = 10 Hz; 1H, OH), 3.68 and 3.70 (2s; je 3H, OCH_3), 3.93 (dd, J_1 = J_2 = 3.5 Hz; 1H, 5-H), 4.22 (dd, J_1 = J_2 = 3.5 Hz; 1H, 2-H), 4.5 (m; 1H, 1'-H), 5.17 (ddt, J_1 = 15 Hz, J_2 = 6.5 Hz, $^4J_3$ = 1.5 Hz; 1H, 2'-H), 5.64 (ddt, J_1 = 15 Hz, J_2 = 7 Hz, $^4J_3$ = 1 Hz; 1H, 3'-H).-**^{13}C NMR ($CDCl_3$)**: δ = 14.13 (C-16'), 16.68, 19.01 ($CH(\underline{C}H_3)_2$), 22.73 (C-15'), 29.00, 29.29, 29.41, 29.42, 29.58, 29.67, 29.71, 29.74, 29.83, 31.97, 32.36 (C-4' to C-14'), 32.06 ($\underline{C}H(CH_3)_2$), 52.30, 52.65 (OCH_3), 59.84, 61.07 (C-2 and C-5), 72.27 (C-1'), 127.79, 133.75 (C-2' and C-3'), 161.23, 164.95 (C-3 and C-6).- **MS (70 eV)**: 351 (1.6%, M^+-C_5H_{11}), 239 (0.3%, $C_{16}H_{30}OH$), 184 (44%, M^+-3), 141 (100%, M^+-3-$(CH_3)_2CH$).- **$C_{25}H_{46}N_2O_3$ (422.4)** calc. C,71.05;H,10.97, found C,71.15;H,11.02%.

(2R,5S,1'S,2'E)-2,5-Dihydro-2-(1-hydroxy-hexadec-2'-en-1'-yl)-5-isopropyl-3,6-dimethoxy-pyrazine (5b): To yield diastereomerically pure **5b** (7.05 g, 16.7 mmol, 83%), the aldol addition was performed as described above, but a solution of tris-(diethylamido)-titanium chloride[15] (6.0 g, 20 mmol) in hexane (20 ml) was added dropwise and the reaction mixture was stirred at -78°C for 1 h prior to addition of **3**.- **IR (neat)**: 3100-3600 (O-H), 1690 cm^{-1} (C=N).- **^1H NMR ($CDCl_3$)**: δ = 0.70 and 1.04 (2d, J = 7Hz; 3H each, $CH(C\underline{H}_3)_2$), 0.85-0.91 (m; 3H, 16'H), 1.2-1.4 (m; 22H, 5'- to 15'-H), 1.99-2.09 (m; 2H, 4'-H), 2.26 (dsp, J_1 = 7 Hz, J_2 = 3.5 Hz; 1H, $C\underline{H}(CH_3)_2$), 2.36 (d, J = 9 Hz; 1H, OH), 3.71 and 3.74 (2s; 3H each, OCH_3), 3.96 (dd, J_1 = J_2 = 3.5 Hz; 1H, 5-H), 4.05 (dd, J_1 = J_2 = 3.5 Hz; 1H, 2-H), 4.4 (m; 1H, 1'-H), 5.57 (ddt, J_1 = 15 Hz, J_2 = 6 Hz, $^4J_3$ < 1 Hz; 1H, 2'-H), 5.74 (ddt, J_1 = 15 Hz, J_2 = 6.5 Hz, $^4J_3$ < 1 Hz; 1H, 3'-H).- **^{13}C NMR ($CDCl_3$)**: δ = 14.14 (C-16'), 16.72, 19.08 ($CH(\underline{C}H_3)_2$), 22.74 (C-15'), 29.18, 29.30, 29.41, 29.43, 29.44, 29.60, 29.72, 29.75, 29.76, 31.98, 32.41 (C-4' to C-14'), 31.82 ($\underline{C}H(CH_3)_2$), 52.53, 52.57 (OCH_3), 60.40, 60.89 (C-2 and C-5), 73.74 (C-1'), 129.24, 133.43 (C-2' and C-3'), 161.76, 165.55 (C-3 and C-6).- **MS (70 eV)**: 351 (2.4%, M^+-C_5H_{11}), 184 (17%, M^+-3), 141 (100%, M^+-3-$(CH_3)_2CH$).- **$C_{25}H_{46}N_2O_3$ (422.4)** calc. C,71.05;H,10.97, found C,71.23;H,11.09%.

(2R,5S,1'R,2'E)-2-(1'-Benzyloxymethoxy-hexadec-2'-en-1'-yl)-2,5-dihydro-5-isopropyl-3,6-dimethoxy-pyrazine (6): The aldol adduct **5a** (1.27 g, 3.0 mmol) in THF (50 ml) was metallated with n-butyllithium (1.7N, 1.76 ml, 3.0 mmol) at -78°C. To this solution benzyl chloromethyl ether (0.47 g, 3.0 mmol) and triethylamine (0.41 ml, 3.6 mmol) were added. The reaction mixture was allowed to warm up to room temperature within 15 h, stirred for another 5 h at this temperature and then phosphate buffer (15 ml, pH 7) was added. Extraction with ether (3 portions of 50 ml) and solvent evaporation yielded crude **6** (1.28 g, 2.4 mmol, 79%), that was hydrolyzed without further purification.

Methyl (2R,3R,4E)-2-amino-3-benzyloxymethoxy-4-octadecenoate (7): To a solution of the obtained **6** in acetonitrile (8 ml) hydrochloric acid (0.5N, 9.5 ml, 4.8 mmol) was added and the mixture was stirred for 2 d at room temperature. Then the solution was saturated with NaCl, poured into 50 ml of ether and brought to pH 9-10 with conc. ammonia. Extraction with ether (3 portions of 50 ml), solvent evaporation and flash chromatography (aluminum oxide, ether/pentane 1:3) provided **7** (0.77 g, 1.73 mmol, 72%, $R_F = 0.12$) and methyl L-valinate (0.32 g, 2.4 mmol, 81%, based on **5a**, $R_F = 0.60$).- **IR (Film)**: 3380 (N-H), 3080, 3050, 3020 (C-H/ phenyl), 1735 cm^{-1} (C=O).-^{1}**H NMR ($CDCl_3$)**: δ = 0.82-0.92 (m; 3H, 18-H), 1.26 (m; 22H, 7-to 17-H), 1.6 (b; 2H, NH_2), 1.98-2.12 (m; 2H, 6-H), 3.65 (d, J = 5.5 Hz; 1H, 2-H), 3.74 (s; 3H, OCH_3), 4.32 (ddd, J_1 = 8 Hz, J_2 = 3.5 Hz, J_3 < 1 Hz; 1H, 3-H), 4.48 and 4.67 (AB-system, J_{AB} = 12 Hz; 2H, OCH_2phenyl), 4.71 and 4.80 (AB-system, J_{AB} = 7 Hz; 2H, OCH_2O), 5.34 (ddt, J_1 = 15.5 Hz, J_2 = 8.5 Hz, $^4J_3$ = 1 Hz; 1H, 4-H), 5.78 (ddd, J_1 = 15.5 Hz, J_2 = 7 Hz, $^4J_3$ < 1 Hz; 1H, 5-H), 7.30-7.42 (m; 5H, phenyl).- **MS (70 eV)**: 401 (0.2%, M^+-OCH_3/-CH_3), 388 (0.2%, M^+-CO_2CH_3), 329 (7%, $C_{22}H_{33}O_2$), 91 (100%, benzyl).

(2S,3R,4E)-2-Amino-3-benzyloxymethoxy-1-hydroxy-4-octadecene (8): A solution of **7** (0.66 g, 1.5 mmol) in ether (5 ml) was added dropwise to lithium aluminum hydride (114 mg, 3.0 mmol) in refluxing ether (50 ml). The mixture was heated under reflux for an additional 30 min, cooled down to 0°C and hydrolyzed with 3 ml of water in THF (15 ml). Precipitated aluminum hydroxide was filtered off, the solvent evaporated and the waxy residue purified by filtration on silica gel in ether ($R_F = 0.09$) yielding **8** (0.61 g, 1.45 mmol, 98%).- **IR (neat)**: 3600-3100 (N-H and O-H), 3080, 3050, 3020 (C-H/phenyl), 1660 (C=C), 1560-1610 cm^{-1} (NH_2).-^{1}**H NMR ($CDCl_3$)**: δ = 0.82-0.94 (m; 3H, 18-H), 1.25 (m; 22H, 7- to 17-H), 1.96-2.12 (m; 2H, 6-H), 2.1-2.5 (b; 3H, NH_2 and OH), 2.88 (ddd, $J_1 = J_2$ = 6 Hz, J_3 = 4.5 Hz; 1H, 2-H), 3.58 (A-part of ABM-system, J_{AB} = 11 Hz, J_{AM} = 6 Hz; 1H, 1-H), 3.73 (B-part of ABM-system, J_{AB} = 11 Hz, J_{BM} = 4.5 Hz; 1H, 1-H), 4.00 (m; 1H, 3-H), 4.52 and 4.70 (AB-system, J_{AB} = 11.5 Hz; 2H, OCH_2phenyl), 4.69 and 4.81 (AB-system, J_{AB} = 7 Hz; 2H, OCH_2O), 5.30 (ddt, J_1 = 15.5 Hz, J_2 = 8.5 Hz, $^4J_3$ < 1 Hz; 1H, 4-H), 5.68-5.86 (m; 1H, 5-H), 7.30-7.64 (m; 5H, phenyl).- **MS (70 eV)**: 419 (0.2%, M^+), 91 (100%, benzyl), 60 (100%, C_2H_6NO).

(2S,3R,4E)-2-Amino-1,3-dihydroxy-4-octadecene, D-erythro-Sphingosine (9): A solution of **8** (0.42 g, 1.0 mmol) in THF (5 ml) was slowly added to a darkblue solution of lithium (35 mg, 5.0 mmol, 5% sodium) in ethylamine (20 ml) at -78°C. The mixture was stirred at -78°C for 3 h and after addition of phosphate buffer (5 ml, pH 7) and ether (20 ml) it was allowed to warm up to room temperature. The solvents were evaporated and the residue extracted with $CHCl_3$ (50 ml). The $CHCl_3$ was removed in vacuo, the waxy product applied on silica gel in $CHCl_3$/methanol 9:1 and eluated with methanol. **9** (0.25 g, 0.85 mmol, 85%) was obtained as a white, air sensitive wax.- $[\alpha]_D^{20}$ = -6° (c = 0.84, $CHCl_3$), m.p. 75-80°C; lit[4]: $[\alpha]_D^{21}$ = -1.3° (c = 3.5, $CHCl_3$); lit[5]: $[\alpha]_D^{22}$ = -2.5° (c = 6, $CHCl_3$); lit. [16]: $[\alpha]_D$ = -3° ($CHCl_3$), m.p. 79-82°C.- The spectroscopic data are in accord with those in lit.[17].

(2S,3R,4E)-2-Acetamido-1,3-diacetoxy-4-octadecene (10): Acetic anhydride (0.50 g, 5.0 mmol) was added to a solution of **9** (0.15 g, 0.5 mmol), 4-dimethylamino pyridine (25 mg, 0.2 mmol) and pyridine (0.4 ml, 5.0 mmol) in $CHCl_3$ (20 ml). The mixture was stirred at room temperature for 12 h, washed with water (10 ml), the solvent evaporated and the residue recrystallized from ether. **10** (185 mg, 0.43 mmol, 86%) was obtained as white needles.- $[\alpha]_D^{20}$ = -11.4° (c = 1.02, $CHCl_3$), m.p. 102°C; lit.[6]: $[\alpha]_D^{25}$ = -12.9° (c = 1.0, $CHCl_3$); lit.[8]: $[\alpha]_D^{24}$ = -12.2° (c = 1.0, $CHCl_3$); lit.[18]: $[\alpha]_D^{24}$ = -12.8° (c = 1.0, $CHCl_3$), 103.5-104°C.- The spectroscopic data are in accord with those in lit.[17].- **$C_{24}H_{43}NO_5$ (425.6)** calc. C,67.73;H,10.18, found C,67.81;H,10.02%.

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