Diastereo- and Enantioselective Synthesis of L-*threo*- and D-*erythro*-Sphingosine

Dieter Enders,* Darren L. Whitehouse and Jan Runsink

Dedicated to Professor Peter Paetzold on the occasion of his 60th birthday

Abstract: L-*threo*-sphingosine and its D-*erythro* isomer (**1**) are subunits of many glycosphingolipids, gangliosides and ceramides. This paper describes the highly diastereo- and enantioselective synthesis of both isomers (*de*, *ee* > 98%). The key steps in the synthesis are the aldol reaction of the SAMP hydrazone (*S*)-**2** with racemic α-phenylselenylpentadecanal **3**, the diastereoselective triacetoxyborohydride reduction of ketone **5** and exclusive (*E*) C=C double bond formation in the elimination of hydroxyl and selenyl moieties promoted by methanesulfonyl chloride. Mesylate **8** was then readily converted via the 1,3-*O*-acetonide-protected azidosphingosine **9** to L-*threo*-sphingosine. Conversion to the known 1-*O*,2-*N*-diacetyl-protected sphingosine **13** with subsequent Mitsunobu inversion of the C3–OH centre afforded the D-*erythro*-sphingosine epimer.

Keywords
asymmetric syntheses · alkenylations · SAMP/RAMP hydrazones · selenyl aldehydes · sphingosine

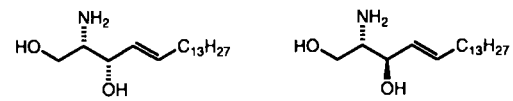
Introduction

The glycosphingolipids (e.g., ceramides, cerebrosides, sphingomyelins and gangliosides) are a broad class of compounds, which have aroused much scientific interest in recent years due to their important biological activities. The major constituent of these sphingolipids is the C_{18} base sphingosine, which is most commonly found as the D-*erythro* isomer (2*S*,3*R*,4*E*)-2-amino-1,3-dihydroxy-4-octadecene,[1] although longer chain (e.g., C_{20}) and phytosphingosine homologues have been detected in the gangliosides of the brain and in skin, respectively.[2]

Importantly, the glycosphingolipids have been shown to mediate cell recognition events.[3] Recently Merrill et al. have reported that sphingosine itself has potent inhibitor properties of protein kinase C (PKC) both in vivo and in vitro;[4] it thus plays a pivotal role in cell recognition, cell growth modulation and signal transduction. Spiegel has demonstrated that sphingosine stimulates DNA synthesis and cell proliferation at very low concentrations independently of the PKC pathway.[5] Harouse et al. have recently demonstrated that galactosyl ceramide acts as a receptor for HIV binding in cells lacking the CD4 receptor.[6]

Sphingosine has also been reported to inhibit insulin-stimulated hexose transport and glucose oxidation in rodent adipocytes.[7] Other reports have indicated the important role of the sphingosine bases as prophylactics against certain diseases in animals such as allergic encephalomyelitis in rabbits[8] and tetanus toxin in mice.[9] Abnormally high concentrations of these sphingolipids have also been found in cases of leukodystrophy,[10] cataracts,[11] Niemann-Pick and Tay-Sachs diseases.[12] Therefore, owing to their ever increasing importance in cell-membrane research, the synthesis and isolation of these sphingosine bases and related compounds (for example phytosphingosines) have received considerable attention.[13–16]

Although there are notable enantioselective syntheses of sphingosine (e.g., Weinreb's *N*-sulfinylcarbamate cycloaddition strategy,[13a] Kitagawa's and Vasella's Sharpless asymmetric epoxidation,[13b] Hayashi's chiral gold complex catalysed aldol reaction,[13c] Takano's anomalous Sharpless asymmetric epoxidation[13d] and Hudlicky's chemoenzymatic synthesis[13e]), most early strategies for the preparation of these sphingosine bases were syntheses of the racemic mixtures[14] or employed the vast array of naturally occurring building blocks as starting materials (ex-chiral pool syntheses).[15–16] Here we report a new highly diastereo- and enantioselective synthesis of both L-*threo*-sphingosine and its D-*erythro* isomer (**1**) from achiral starting materials employing our well-established SAMP/RAMP hydrazone methodology to create the C-2 and C-3 stereogenic centres.



(2*S*,3*S*,4*E*) [L-*threo*] (2*S*,3*R*,4*E*) [D-*erythro*]

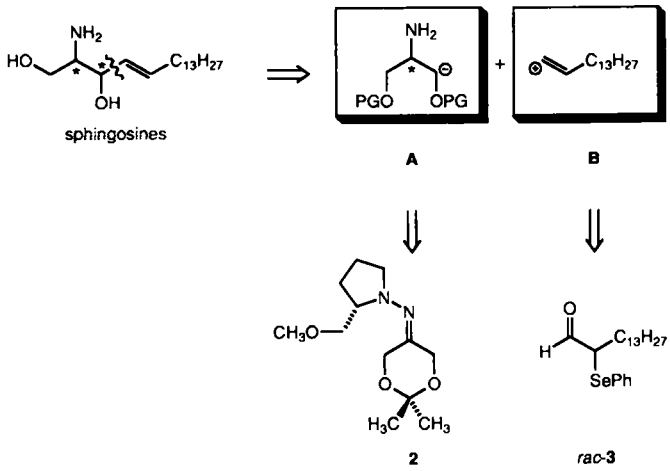
sphingosine (**1**)

Results and Discussion

The retrosynthetic analysis of sphingosine (Scheme 1) by heterolytic cleavage of the C-3/C-4 bond leads to the aminodiol anionic synthon **A** and the alkenyl cationic synthon **B**. Synthon **A** can clearly be derived from the known SAMP hydrazone

[*] Prof. Dr. D. Enders, Dr. D. L. Whitehouse, Dr. J. Runsink
Institut für Organische Chemie der Technischen Hochschule, Professor-Pirlet-Strasse-1, D-52074 Aachen (Germany)
Telefax: Int. code + (241)8888-127

0947-6539/95/0106-0382 $ 30.00+.25/0



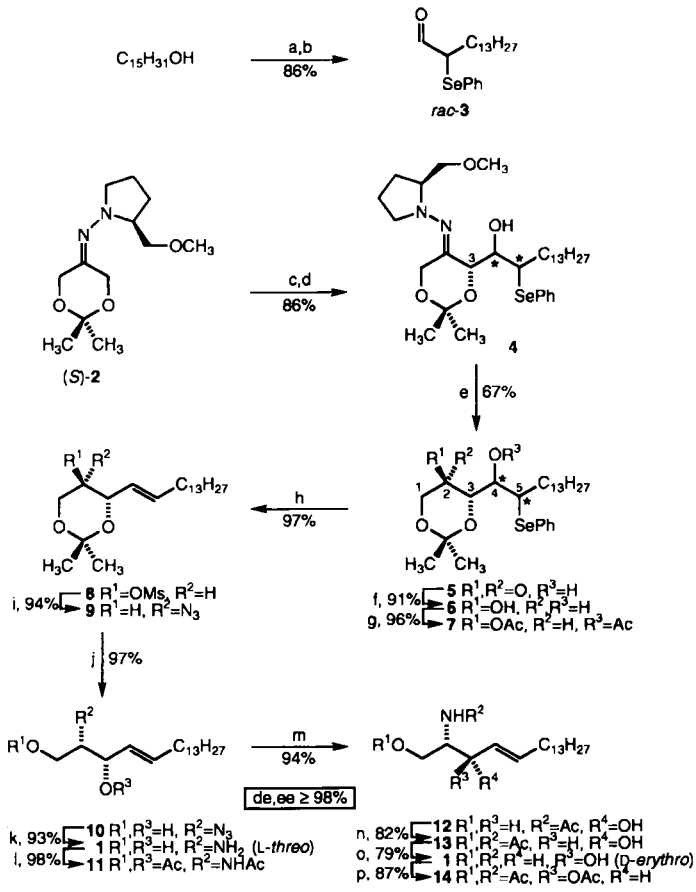
Scheme 1. Retrosynthetic analysis of sphingosine.

(*S*)-**2**.[17] Stereoselective α-alkenylation of the corresponding azaenolate, promoted by the chiral auxiliary, would then permit access to the sphingosine bases after functional group manipulation of the hydrazone unit.

It has been reported by Krief,[18] Clive[19] and Reich[20] that the facile non-oxidative elimination of β-hydroxyselenides proceeds by activation of the alcohol under mild conditions to afford olefins, although in many cases only poor double-bond geometry control has been observed. Thus, through the aldol reaction with hydrazone (*S*)-**2** and subsequent elimination of the hydroxyl and selenyl groups, the α-phenylselenyl aldehyde *rac*-**3** can serve as the alkenyl cationic synthon **B**.

Pentadecanal, prepared under modified Swern conditions from pentadecanol (Scheme 2),[21] was converted to the racemic α-phenylselenyl aldehyde *rac*-**3** by using the method described by Sonoda et al. [SeO_2, $(PhSe)_2$, cat. H_2SO_4].[22] Aldol reaction of the racemic aldehyde *rac*-**3** with the azaenolate of SAMP hydrazone (*S*)-**2** [*t*BuLi, THF, −100 °C] afforded a diastereomeric mixture of β-hydroxyselenides **4** with very high asymmetric induction with respect to the SAMP hydrazone C-3 centre (sphingosine numbering). The absolute configuration given for the new stereogenic centre at C-3 is based on the relative topicity detected for all electrophilic substitutions with SAMP/RAMP hydrazones.[23] In this "metallo-retentive" mechanism the lithium azaenolate is attacked by the corresponding electrophile (here the aldehyde **3**) predominantly *syn* to the intramolecular coordinated lithium, which is located below the C-3,C-2,N,N plane of the azaenolate.

By analogy with previous results of our research group, the C-3 and C-4 centres in the diasteromers **4** were assigned a *syn* or *anti* relationship from the H-3/H-4 coupling constants of 2.1 and 6.5 Hz, respectively, measured for the corresponding diacetates **7**. This was entirely consistent with the ^{13}C NMR chemical shifts $\delta = 207.98$ and 210.47 for the C-2 sp^2 carbons of ketones *syn*-**5** and *anti*-**5**, respectively.[17] The C-4/C-5 relationship could not be assigned unambiguously by NMR experiments. Since subsequent elimination would remove both C-4/C-5 centres, the stereochemistry of the C-5 centre was not investigated further. The stereochemistry at the important C-3 centre was established unambiguously by NOE studies, carried out on diacetates **7**, and by comparing data for the synthetic products with that of known natural products (vide supra). The diastereoselectivity for the newly formed C-3 centre was determined by gas chromatography and $^1H/^{13}C$ NMR studies, and proved to be greater than 96% for both isomers.



Scheme 2. Diastereo- and enantioselective synthesis of L-*threo*- and D-*erythro*-sphingosine. Reagents and conditions: a) $(COCl)_2$, DMSO, NEt_3, CH_2Cl_2, −20 °C; b) SeO_2, $(PhSe)_2$, H_2SO_4, CH_2Cl_2; c) *t*BuLi, THF, −80 °C; d) *rac*-**3**, THF, −100 °C; e) O_3, PPh_3, pentane, −70 °C; f) $MeN_4BH(OAc)_3$, THF; g) Ac_2O, NEt_3, DMAP, CH_2Cl_2; h) **6**, MsCl, NEt_3, CH_2Cl_2, 0 °C; i) NaN_3, 18-crown-6, DMF, 100 °C; j) 6N HCl, THF, H_2O; k) $LiAlH_4$, THF; l) Ac_2O, NEt_3, DMAP, CH_2Cl_2; m) K_2CO_3, MeOH; n) Ac_2O, NEt_3, CH_2Cl_2, −20 °C; o) DEAD, $PhCO_2H$, PPh_3, THF then 2N KOH, EtOH; p) Ac_2O, NEt_3, DMAP, CH_2Cl_2

Very recently the chemoselective oxidative cleavage of terminal double bonds in the presence of selenyl groups, with limited oxidative elimination of selenoxide, has been decribed.[24] Under similar conditions to those reported, oxidative cleavage of the hydrazone unit with reductive workup (ozone, PPh_3) afforded the ketones **5** with no observed oxidative elimination of selenium. As expected, no epimerisation of the α-centre was observed in the oxidative cleavage, as shown by $^1H/^{13}C$ NMR spectroscopy (*de* > 96%).

Reduction of the ketone group with tetramethylammonium triacetoxyborohydride according to Evans et al.[25] gave the diols **6** in excellent yield (91%) and with complete induction at the new C-2 hydroxyl centre. This is presumably due to the very high preference for axial attack of hydride to give the equatorial alcohol under nonchelating reduction conditions. To confirm the relative stereochemical assignments of the C-2 and C-3 centres, the diacetates **7** were prepared under standard conditions [Ac_2O, NEt_3, DMAP]. The axial attack of hydride was consistent with the observed C-2/C-3 axial–axial coupling constants of 10.1 and 8.6 Hz for the two isomers **7**, respectively. Further confirmation of this stereochemical assignment was given by H-COSY and NOE studies carried out on these diacetates; the fact that no observable enhancement was observed between the C-2 and C-3 protons indicates that they are in a *trans* relationship.

With diols **6** in hand, a method for the regioselective double bond formation was sought. Treatment of the diol mixture with methanesulfonyl chloride (NEt_3, CH_2Cl_2, 0°C) afforded the mesylate **8** as a single diastereoisomer with complete (*E*) geometry of the newly formed double bond (determined by $^1H/^{13}C$ NMR analysis). The mesylate **8** was then converted to the natural product L-*threo*-sphingosine (**1**) by using standard functional group manipulations: S_N2 displacement of the mesylate with sodium azide in DMF in the presence of 18-crown-6[15p] afforded the axial azide **9** as a single diastereoisomer (*de* > 98% by $^1H/^{13}C$ NMR). Reduction of azide **9** to the corresponding 1,3-*O*-acetonide-protected sphingosine with lithium aluminium hydride[26] and subsequent protic-acid hydrolysis of the acetonide group yielded L-*threo*-sphingosine (**1**) in modest yield (62% from azide **9**).

This problem with the yield was overcome by initial acid-catalysed deprotection of the acetonide (HCl, THF/H_2O) to give the azidosphingosine **10**, which was smoothly reduced with lithium aluminium hydride to L-*threo*-sphingosine (**1**) in excellent yield (90%). The product was identical in all spectroscopic detail to that reported.[13b, 15l] Further confirmation was given by conversion to the known triacetate **11** (Ac_2O, NEt_3, DMAP, CH_2Cl_2), whose analytical data once again agreed with literature values.[13c, 15e]

Hayashi[13c] has described the conversion of L-*threo*-sphingosine (**1**) to the D-*erythro* isomer by the Mitsunobu inversion method.[27] However, this reported inversion involved the selective diacetylation of the amino and primary hydroxyl groups in sphingosine (**1**), which was accomplished in only moderate yield (53%). This low-yielding step was avoided by selective deprotection of the triacetate **11** (K_2CO_3, MeOH, 94%) to the acetamide **12**. Subsequent monoacetylation was carried out under high-dilution conditions (Ac_2O, NEt_3, CH_2Cl_2, −20°C) to afford the known alcohol **13** in 77% yield from sphingosine **1**. Trace quantities of the triacetate **11** were produced (< 10%), but could be recycled via acetamide **12**. The alcohol **13**, identical in all spectroscopic detail to that reported by Hayashi,[13c] was converted to the D-*erythro* isomer **1** by Mitsunobu inversion (DEAD, $PhCO_2H$, PPh_3) with immediate alkaline hydrolysis (2N KOH, EtOH) and subsequent recrystallisation from hexane/dichloromethane (79% from **13**). The analytical data for synthetic D-*erythro*-sphingosine (**1**) were in accordance with those reported in the literature.[15l] Conversion to the known triacetate[15e, l] **14** under standard conditions further confirmed the structure of **1**.

In summary, an efficient highly diastereo- and enantioselective synthesis of both L-*threo*- and D-*erythro*-sphingosine from achiral starting materials to yield both isomers with *de*, *ee* > 98% and with complete (*E*) double bond control has been reported.

Experimental Procedure

Solvents were dried and purified prior to use. Tetrahydrofuran (THF) was freshly distilled from potassium under argon. Dichloromethane, dimethyl sulphoxide (DMSO), triethylamine and dimethylformamide (DMF) were distilled from CaH_2 and stored under argon. Methanol and ethanol were distilled from their corresponding magnesium alkoxides. Ether and pentane were distilled prior to use. Analytical glass-backed TLC plates (silica gel $60F_{254}$) and silica gel (230–400 mesh) were purchased from Merck, Darmstadt. Reagents of commercial quality were used from freshly opened containers unless otherwise stated. Melting points are uncorrected. Optical rotations were measured on a Perkin-Elmer P241 polarimeter and with solvents of Merck UVASOL quality. Microanalyses were obtained with a CHN-O-RAPID elemental analyser. ^1H and ^{13}C NMR spectra were obtained on a Varian *VXR 300*, *Gemini 300* (*300 and 75 MHz*) or *Varian Unity 500* (*500 and 125 MHz*) with TMS as internal standard. IR spectra were recorded on a Beckman Acculab4 and a Perkin-Elmer FT/IR 1750 spectrophotometer as evaporated films. Mass spectroscopic analyses were obtained on a Varian MAT212, EI 70 eV (relative intensities in parantheses). High-resolution mass spectra were recorded on a Finnigan MAT, MAT95. Melting points were recorded on a Büchi apparatus (system Dr. Tottoli) and are uncorrected.

Pentadecanal [21]: Dimethyl sulphoxide (3.02 g, 2.74 mL, 38.6 mmol, 2.2 equiv) in CH_2Cl_2 (15 mL) was added dropwise to a stirred solution of oxalyl chloride (2.45 g, 1.68 mL, 19.3 mmol, 1.1 equiv) in CH_2Cl_2 (25 mL) at −20°C under an atmosphere of argon. After 5 min a precooled solution (−20°C) of pentadecanol (4.01 g, 17.54 mmol) in CH_2Cl_2 (50 mL) was added through a cannula, and the resultant colourless suspension was stirred at −20°C for 30 min. Triethylamine (10.65 g, 14.67 mL, 105 mmol, 6.0 equiv) was added. The reaction mixture was allowed to warm to room temperature, then poured into sat. NH_4Cl solution, extracted with CH_2Cl_2, washed with brine, dried ($MgSO_4$) and concentrated in vacuo to give a colourless oil. Purification by flash column chromatography (silica gel, eluent: pentane/ether 10:1) afforded pentadecanal as a waxy colourless solid (3.86 g, 97%); M.p. 23–25°C (Lit. [28]: 24–25°C); ^1H NMR (300 MHz, $CDCl_3$, RT, TMS): δ = 9.76 (t, $^3J(H,H)$ = 2 Hz, 1H; H-1), 2.41 (dt, $^3J(H,H)$ = 7.4, $^3J(H,H)$ = 2.0 Hz, 2H; 2 × H-2), 1.63 (m, 2H; 2 × H-3), 1.26 (brs, 22H) and 0.88 (t, $^3J(H,H)$ = 6.9 Hz, 3H; C-15 Me); ^{13}C NMR (75 MHz, $CDCl_3$, RT, TMS): δ = 202.96 (C-1), 43.95 (C-2), 31.96 (C-13), 29.72 (3 × C), 29.68, 29.62, 29.47, 29.39 (2 × C), 29.21, 22.73, 22.13 (C-14) and 14.14 (C-15); IR (film): $\tilde{\nu}$ = 2922, 2917, 2945, 2705, 1718 (C=O), 1432 and 710 cm^{-1}; MS (70 eV, EI): *m/z* (%): 208 (5) [$M^+ - H_2O$], 57 (100) [$C_2H_4CHO^+$] and 43 (64) [CH_2CHO^+]; $C_{15}H_{30}O$ (226.4): calcd C 79.57, H 13.36; found C 79.08, H 13.41.

2-(Phenylselenyl)pentadecanal (*rac*-**3**): Pentadecanal (3.75 g, 16.59 mmol, 1.0 equiv) in CH_2Cl_2 (10 mL) was added dropwise to a stirred solution of diphenyl diselenide (3.11 g, 9.95 mmol, 0.6 equiv), selenium dioxide (1.10 g, 9.95 mmol, 0.6 equiv) and sulfuric acid (110 µL, 1.99 mmol, 0.12 equiv) in CH_2Cl_2 (20 mL) at room temperature. The resultant mixture was stirred overnight and then poured into sat. $NaHCO_3$ solution and extracted with CH_2Cl_2. The combined organic extracts were washed with water, dried ($MgSO_4$) and concentrated in vacuo to give a dark orange oil. Purification by flash column chromatography (silica gel, eluent: pentane then pentane/ether 20:1) afforded *rac*-**3** as a viscous yellow liquid (5.63 g, 89%); ^1H NMR (300 MHz, $CDCl_3$, RT, TMS): δ = 9.38 (d, $^3J(H,H)$ = 3.8 Hz, 1H; H-1), 7.48–7.52 (m, 2H; Ar-H), 7.26–7.34 (m, 3H; Ar-H), 3.60 (ddd, $^3J(H,H)$ = 8.0 Hz, $^3J(H,H)$ = 6.9 Hz, $^3J(H,H)$ = 3.6 Hz, 1H; H-2), 1.81 (m, 1H; H-3), 1.66 (m, 1H; H-3), 1.12–1.54 (m, 22H) and 0.88 (t, $^3J(H,H)$ = 6.9 Hz, 3H; C-15 Me); ^{13}C NMR (75 MHz, $CDCl_3$, RT, TMS): δ = 193.68 (C-1), 136.37 (2 × C, arom-C), 129.82 (2 × C, arom-C), 129.75 (arom-C), 129.38 (arom-C), 53.54 (C-2), 32.50 (C-13), 30.25 (2 × C), 30.22 (2 × C), 30.18, 30.08, 29.93, 29.81, 28.54, 28.22, 23.27 (C-14) and 14.08 (C-15); IR (film): $\tilde{\nu}$ = 3052, 2918, 2847, 2712, 1708 (C=O), 1579, 1478, 1437 and 738 cm^{-1}; MS (70 eV, EI): *m/z* (%): 382 (100) [M^+(^{80}Se)], 380 (56) [M^+(^{78}Se)], 353 (83) [M^+(^{80}Se)−CHO], 351 (42) [M^+(^{78}Se)−CHO], 225 (3) [M^+−PhSe]; $C_{21}H_{34}O^{80}Se$ (382.2) calcd 382.1775; found 382.1777; $C_{21}H_{34}O^{78}Se$ (380.2) calcd 380.1783; found 380.1779.

(1*R*,2*R*/*S*,2″*S*,4′*S*)- and (1*S*,2*R*/*S*,2″*S*,4′*S*)-1-[5-(2-Methoxymethylpyrrolidin-1-ylimino)-2,2-dimethyl-[1,3]dioxan-4-yl]-2-phenylselenyl-pentadecan-1-ol (**4**): To a stirred solution of hydrazone (*S*)-**2** (760 mg, 3.15 mmol, 1.0 equiv) in THF (15 mL) at −80°C under an atmosphere of argon was added *tert*-butyllithium (1.6M solution in hexane, 2.17 mL, 3.47 mmol, 1.1 equiv). The solution was stirred at this temperature for 30 min and then cooled to −100°C. A precooled solution (−70°C) of aldehyde *rac*-**3** (1.50 g, 3.94 mmol, 1.25 equiv) in THF (15 mL) was then added through a cannula to the deprotonated hydrazone solution. The reaction mixture was stirred at −100°C for 2 h, slowly allowed to warm to room temperature overnight, then poured into water and extracted with ether. The ethereal phase was washed with brine, dried ($MgSO_4$) and concentrated in vacuo to give a dark orange oil. Purification by flash column chromatography (silica gel, eluent: pentane/ether 2:1) afforded the β-hydroxy selenide (1*R*,4′*S*)-**4** as a pale yellow oil (824 mg, 42%) and (1*S*,4′*S*)-**4** as a colourless oil (863 mg, 44%).

(1*R*,4′*S*)-**4**: $[\alpha]_D^{24}$ = + 50.64 (*c* = 1 in chloroform); ^1H NMR (300 MHz, $CDCl_3$, RT, TMS): δ = 7.56–7.63 (m, 2H; Ar-H), 7.20–7.30 (m, 3H; Ar-H), 5.16 (brs, 1H; OH), 4.45 (d, $^2J(H,H)$ = 15.6 Hz, 1H; H-6′), 4.34 (dd, $^3J(H,H)$ = 8.8 Hz, $^3J(H,H)$ = 1.4 Hz, 1H; H-4′), 4.17 (m, 1H; H-1), 4.14 (dd, $^2J(H,H)$ = 15.6 Hz, $^4J(H,H)$ = 1.4 Hz, 1H; H-6′), 3.54 (m, 1H; H-2), 3.22–3.44 (m, 6H including δ = 3.32 (s, 3H; OMe)), 3.10 (m, 1H; NC*H*H), 2.46 (dd, $^2J(H,H)$ = 16.8 Hz, $^3J(H,H)$ = 8.0 Hz, 1H; NCH*H*), 1.59–2.04 (m, 7H), 1.34–1.46 (m, 7H including δ = 1.36 and 1.41 both (s, 3H; acetonide-Me)), 1.20–1.28 (m, 20H) and 0.88 (t, $^3J(H,H)$ = 6.9 Hz, 3H; C-15 Me); ^{13}C NMR (75 MHz, $CDCl_3$, RT, TMS): δ = 163.09 (C-5′), 133.26 (2 × C, arom-C), 131.50 (arom-C), 128.81 (2 × C, arom-C), 126.59 (arom-C), 100.67 (C-2′), 76.00 (C-4′), 75.21 (C-6′), 68.90, 66.82, 59.44, 59.16, 55.93, 48.52, 31.93 (C-13), 29.69 (3 × C), 29.65 (2 × C), 29.59, 29.52, 29.49, 29.36, 28.47, 26.59, 24.17, 23.64, 22.80, 22.69 (C-14) and 14.14 (C-15); IR (film): $\tilde{\nu}$ = 3460, 3036, 2899, 2814, 1568, 1445, 1422, 1206, 1061, 855 and 626 cm^{-1}; MS (70 eV, EI): *m/z* (%): 467 (4) [M^+−PhSe], 409 (5.4) [M^+−PhSe−$(CH_3)_2CO$]; $C_{33}H_{56}N_2O_4Se$ (623.8): calcd C 63.54, H 9.05, N 4.49; found C 63.80, H 9.43, N 4.39.

(1*S*,4′*S*)-**4**: $[\alpha]_D^{24}$ = +13.61 (*c* = 1 in chloroform); ^1H NMR (300 MHz, $CDCl_3$, RT, TMS): δ = 7.51–7.60 (m, 2H; Ar-H), 7.09–7.17 (m, 3H; Ar-H), 5.01 (dd,

0947-6539/95/0106-0384 $ 30.00+.25/0 Chem. Eur. J. 1995, 1, No. 6

$^3J(H,H) = 2.0$ Hz, $^4J(H,H) = 1.7$ Hz, 1H; H-4'), 4.75 (ddd, $^3J(H,H) = 9.9$ Hz, $^3J(H,H) = 7.5$ Hz and $^3J(H,H) = 2.0$ Hz, 1H, H-1), 4.46 (dd, $^2J(H,H) = 13.4$ Hz and $^4J(H,H) = 1.7$ Hz, 1H; H-6'), 4.12 (d, $^3J(H,H) = 7.5$ Hz, 1H, OH), 4.02 (d, $^2J(H,H) = 13.4$ Hz, 1H; H-6'), 3.22–3.44 (m, 7H including $\delta = 3.30$ (s, 3H; OMe)), 3.06 (ddd, $^2J(H,H) = 10.2$ Hz, $^3J(H,H) = 6.9$ Hz and $^3J(H,H) = 3.0$ Hz, 1H; NC*H*H), 2.58 (m, 1H, NCH*H*), 1.53–2.08 (m, 7H), 1.36–1.42 (m, 4H including $\delta = 1.40$ (s, 3H; acetonide-Me)), 1.16–1.28 (m, 23H including $\delta = 1.27$ (s, 3H; acetonide-Me)) and 0.88 (t, $^3J(H,H) = 6.9$ Hz, 3H; C-15 Me); ^{13}C NMR (75 MHz, $CDCl_3$, RT, TMS): $\delta = 166.26$ (C-5'), 134.36 (2 × C, arom-C), 129.75 (arom-C), 128.83 (2 × C, arom-C), 127.22 (arom-C), 100.16 (C-2'), 74.47 (C-4'), 72.86 (C-6'), 69.34 (C-1), 65.98, 64.13, 58.76, 54.16, 48.24, 31.94 (C-13), 29.67 (6 × C), 29.62 (2 × C), 29.55, 29.37, 27.44, 25.68 (2 × C), 22.70 (C-14), 22.46 and 14.14 (C-15); IR (film): $\tilde{\nu} = 3420$, 3036, 2898, 2822, 1568, 1444, 1361, 1211, 1050 and 726 cm^{-1}; MS (70 eV, EI): *m/z* (%): 467 (14) [M^+ −PhSe], 409 (20) [M^+ −PhSe−$(CH_3)_2CO$]; $C_{33}H_{56}N_2O_4Se$ (623.8) calcd C 63.54, H 9.05; found C 63.51, H 9.28.

(1′*R*,2′*R*/*S*,4*S*)- and (1′*S*,2′*R*/*S*,4*S*)-4-(1-Hydroxy-2-phenylselenylpentadecanyl)-2,2-dimethyl-[1,3]dioxan-5-one (5): Ozone was bubbled through a solution of hydrazone **4** (1.48 g, 2.38 mmol, 1.0 equiv) in pentane at −70 °C. The reaction was monitored by TLC. Upon complete consumption of the starting material, argon was bubbled through the solution at −70 °C to remove any excess ozone. Triphenylphosphine (1.87 g, 7.16 mmol, 3.0 equiv) was added in one portion and the reaction mixture was allowed to warm slowly with stirring to room temperature over 5 h. Filtration through Celite and removal of the solvent in vacuo gave the crude ketones as a colourless oil. Purification by flash column chromatography (silica gel, eluent: pentane/ether 6:1) afforded ketone (1′*R*,4*S*)-**5** as a colourless oil (390 mg, 32%) and ketone (1′*S*,4*S*)-**5** as a viscous colourless oil (427 mg, 35%).
(1′*R*,4*S*)-**5**: $[\alpha]_D^{24} = -63.87$ ($c = 1$ in chloroform); ^1H NMR (300 MHz, $CDCl_3$, RT, TMS): $\delta = 7.53-7.62$ (m, 2H; Ar-H), 7.23–7.30 (m, 3H; Ar-H), 4.44 (dd, $^3J(H,H) = 7.1$ Hz and $^4J(H,H) = 1.4$ Hz, 1H; H-4), 4.26 (dd, $^2J(H,H) = 17.3$ Hz and $^4J(H,H) = 1.4$ Hz, 1H; H-6), 4.15 (dd, $^3J(H,H) = 7.1$ Hz and $^3J(H,H) = 4.1$ Hz, 1H; H-1'), 4.00 (d, $^2J(H,H) = 17.3$ Hz, 1H; H-6), 3.45 (dt, $^3J(H,H) = 9.9$ Hz, $^3J(H,H) = 7.7$ Hz and $^3J(H,H) = 4.1$ Hz, 1H; H-2'), 3.16 (brs, 1H (exch. D_2O); OH), 1.62–1.80 (m, 2H; 2 × H-3'), 1.49 (s, 3H; acetonide-Me), 1.42 (s, 3H; acetonide-Me), 1.20–1.30 (brs, 22H) and 0.89 (t, $^3J(H,H) = 6.9$ Hz, 3H; C-15' Me); ^{13}C NMR (75 MHz, $CDCl_3$, RT, TMS): $\delta = 210.47$ (C=O), 134.10 (2 × C, arom-C), 130.13 (arom-C), 128.97 (2 × C, arom-C), 127.25 (arom-C), 101.10 (C-2), 74.71 (C-4), 73.29 (C-1'), 66.65 (C-6), 49.06 (C-2'), 31.93 (C-13'), 30.05, 29.69 (2 × C), 29.66 (2 × C), 29.58, 29.49, 29.42, 29.36, 28.14, 23.75 (2 × C, 2 × acetonide-Me), 22.69 (C-14') and 14.14 (C-15'); IR (film): $\tilde{\nu} = 3508$, 3059, 2920, 2851, 1740 (C=O), 1479, 1378, 1224 and 739 cm^{-1}; MS (70 eV, EI): *m/z* (%): 512 (2) [M^+(^{80}Se)], 454 (10) [M^+(^{80}Se)−$(CH_3)_2CO$] and 355 (9) [M^+−PhSe]; $C_{27}H_{44}O_4Se$ (511.6): calcd C 63.39, H 8.67; found C 63.36, H 8.92.
(1′*S*,4*S*)-**5**: $[\alpha]_D^{25} = -81.92$ ($c = 1$ in chloroform): ^1H NMR (300 MHz, $CDCl_3$, RT, TMS): $\delta = 7.53-7.58$ (m, 2H; Ar-H), 7.24–7.30 (m, 3H; Ar-H), 4.79, (brs, 1H; H-4), 4.27 (dd, $^2J(H,H) = 17.0$ Hz and $^4J(H,H) = 1.3$ Hz, 1H; H-6), 4.19 (m, 1H; H-1'), 4.03 (d, $^3J(H,H) = 17.0$ Hz, 1H; H-6), 3.29 (m, 1H; H-2'), 2.58 (brs, 1H (exch. D_2O); OH), 1.92 (m, 1H; H-3'), 1.65 (m, 1H; H-3'), 1.42–1.48 (m, 4H including $\delta = 1.46$ (s, 3H; acetonide-Me)), 1.30 (s, 3H; acetonide-Me), 1.20–1.28 (m, 21H) and 0.88 (t, $^3J(H,H) = 6.8$ Hz, 3H; C-15' Me); ^{13}C NMR (75 MHz, $CDCl_3$, RT, TMS): $\delta = 207.98$ (C=O), 134.48 (2 × C, arom-C), 129.69 (arom-C), 129.08 (2 × C, arom-C), 127.61 (arom-C), 100.63 (C-2), 76.08 (C-4), 71.73 (C-1'), 67.32 (C-6), 50.23 (C-2'), 32.17, 31.93 (C-13'), 29.69 (2 × C), 29.66 (3 × C), 29.58, 29.49, 29.36, 27.61, 24.64 (acetonide-Me), 23.21 (acetonide-Me), 22.70 (C-14') and 14.14 (C-15'); IR (film): $\tilde{\nu} = 3460$, 3062, 2920, 2850, 1751 (C=O), 1478, 1441, 1376, 1222 and 736 cm^{-1}; MS (70 eV, EI): *m/z* (%): 510 (1) [M^+(^{78}Se)], 454 (4) [M^+(^{80}Se)−$(CH_3)_2CO$], 353 (29) [$C_{14}H_{29}{}^{80}SePh^+$] and 183 (6) [$C_{13}H_{27}{}^+$]; $C_{27}H_{44}O_4Se$ (511.6) calcd C 63.39, H 8.67; found C 63.18, H 8.93.

(1′*R*,2′*R*/*S*,4*S*,5*R*)- and (1′*S*,2′*R*/*S*,4*S*,5*R*)-4-(1-Hydroxy-2-phenylselenylpentadecanyl)-2,2-dimethyl-[1,3]dioxan-5-ol (6): Tetramethylammonium triacetoxyborohydride (792 mg, 3.01 mmol, 4.5 equiv) was added portionwise over 5 min to a stirred solution of ketones **5** (320 mg, 6.26×10^{-4} mol, 1.0 equiv) in THF (10 mL) at room temperature under an atmosphere of argon. The resultant colourless suspension was stirred at this temperature for a further 36 h, then poured into water and extracted with CH_2Cl_2. The combined organic extracts were washed with brine, dried ($MgSO_4$) and concentrated in vacuo. Purification by flash column chromatography (silica gel, eluent: pentane/ether 1:1) afforded the diol (1′*R*,4*S*,5*S*)-**6** as a viscous colourless oil (141 mg, 44%) and the diol (1′*S*,4*S*,5*S*)-**6** as a colourless oil (151 mg, 47%).
(1′*R*,4*S*,5*S*)-**6**: $[\alpha]_D^{26} = -5.23$ ($c = 1$ in chloroform); ^1H NMR (300 MHz, $CDCl_3$, RT, TMS): $\delta = 7.48-7.58$ (m, 2H; Ar-H), 7.24–7.30 (m, 3H; Ar-H), 3.89 (dd, $^2J(H,H) = 15.6$ Hz and $^3J(H,H) = 9.9$ Hz, 1H; H-6), 3.58–3.78 (m, 6H, H-4, H-5, H-6, H-1',H-2' and OH), 3.05 (brs, 1H; OH), 1.40–1.82 (m, 7H including $\delta = 1.46$ (s, 3H; acetonide-Me)), 1.36 (s, 3H; acetonide-Me), 1.24–1.34 (m, 20H) and 0.88 (t, $^3J(H,H) = 6.9$ Hz, 3H; C-15' Me); ^{13}C NMR (75 MHz, $CDCl_3$, RT, TMS): $\delta = 133.79$ (2 × C, arom-C), 129.30 (2 × C, arom-C), 128.46 (arom-C), 127.62 (arom-C), 98.48 (C-2), 76.94 (C-4), 71.78 (C-1'), 67.63 (C-5), 63.73 (C-6), 49.92 (C-2'), 31.93 (C-13'), 29.68 (3 × C), 29.65 (2 × C), 29.62, 29.37, 29.32, 28.48 (acetonide-Me), 28.39, 27.33, 22.69 (C-14'), 19.17 (acetonide-Me) and 14.13 (C-15'); IR (film): $\tilde{\nu} = 3410$, 3060, 2918, 2844, 1580, 1461, 1376, 1220, 1201, 864 and 736 cm^{-1}; MS (70 eV, EI): *m/z* (%): 514 (18) [M^+(^{80}Se)], 512 (9) [M^+(^{78}Se)], 299 (23) [M^+−PhSe−$(CH_3)_2CO$] and 281 [M^+−PhSe−$(CH_3)_2CO-H_2O$]; $C_{27}H_{46}O_4Se$ (513.6) calcd C 63.14, H 9.03; found C 63.27, H 9.27.
(1′*S*,4*S*,5*S*)-**6**: $[\alpha]_D^{26} = -27.52$ ($c = 1$ in chloroform); ^1H NMR (300 MHz, $CDCl_3$, RT, TMS): $\delta = 7.53-7.60$ (m, 2H; Ar-H), 7.22–7.29 (m, 3H; Ar-H), 4.04 (d, $^3J(H,H) = 8.8$ Hz, 1H), 3.85–3.95 (m, 3H), 3.64 (dt, $^3J(H,H) = 11.2$ Hz and $^3J(H,H) = 1.6$ Hz, 1H), 3.26 (m, 1H; H-2'), 2.84 (brs, 1H (exch. D_2O); OH), 2.80 (brs, 1H (exch. D_2O); OH), 1.86–2.01 (m, 1H; H-3'), 1.59–1.72 (m, 1H; H-3'), 1.29–1.48 (m, 8H including $\delta = 1.31$ and 1.37 both (s, 3H; acetonide-Me)), 1.20–1.26 (m, 20H) and 0.89 (t, $^3J(H,H) = 6.9$ Hz, 3H; C-15' Me); ^{13}C NMR (75 MHz, $CDCl_3$, RT, TMS): $\delta = 134.24$ (2 × C, arom-C), 130.89 (arom-C), 128.97 (2 × C, arom-C), 127.32 (arom-C), 98.80 (C-2), 73.55 (C-4), 70.38 (C-1'), 64.56 (C-6), 62.42 (C-5), 51.97 (C-2'), 32.97, 31.93 (C-13'), 29.66 (3 × C), 29.61 (2 × C), 29.51, 29.45, 29.37, 28.50 (acetonide-Me), 27.71, 22.69 (C-14'), 19.08 (acetonide-Me) and 14.13 (C-15'); IR (film): $\tilde{\nu} = 3318$, 3070, 2918, 2846, 1579, 1476, 1382, 1070, 888 and 735 cm^{-1}; MS (70 eV, EI): *m/z* (%): 514 (6) [M^+(^{80}Se)], 512 (5) [M^+(^{78}Se)], 299 (16.5) [M^+−PhSe−$(CH_3)_2CO$], 281 (7) [M^+−PhSe−$(CH_3)_2CO-H_2O$] and 263 (2) [M^+−PhSe−$(CH_3)_2CO-2H_2O$]; $C_{27}H_{46}O_4Se$ (513.6) calcd C 63.14, H 9.03; found C 63.05, H 9.18.

(1′*S*,2′*R*/*S*,4*S*,5*R*)-4-(1-Acetoxy-2-phenylselenylpentadecanyl)-5-acetoxy-2,2-dimethyl-[1,3]dioxane (7): To a stirred solution of diol (1′*S*,2′*RS*,4*S*,5*S*)-**6** (12 mg, 2.34×10^{-5} mol, 1.0 equiv) in CH_2Cl_2 (0.5 mL) at 0 °C under an atmosphere of argon was added dropwise triethylamine (18.9 mg, 26 μL, 1.87×10^{-4} mol, 8.0 equiv) and then acetic anhydride (10.1 mg, 8.9 μL, 9.36×10^{-5} mol, 4.0 equiv). A catalytic amount of DMAP (< 1 mg) was added, and the reaction mixture was stirred at room temperature for 15 h, then poured into water and extracted with CH_2Cl_2. The combined CH_2Cl_2 extracts were washed with brine, dried ($MgSO_4$) and concentrated in vacuo. Purification by flash column chromatography (silica gel, eluent: pentane/ether 9:1) afforded the diacetate **7** as a colourless oil (13.7 mg, 98%); $[\alpha]_D^{27} = +37.82$ ($c = 1$ in chloroform); ^1H NMR (500 MHz, $CDCl_3$, RT, TMS): $\delta = 7.53-7.58$ (m, 2H; Ar-H), 7.22–7.30 (m, 3H; Ar-H), 5.16 (dd, $^3J(H,H) = 10.1$ Hz and $^3J(H,H) = 2.1$ Hz, 1H; H-1'), 4.72 (dd, $^3J(H,H) = 10.1$ Hz and $^3J(H,H) = 2.1$ Hz, 1H; H-4), 4.65 (ddd, $^3J(H,H) = 10.1$ Hz, $^3J(H,H) = 8.2$ Hz and $^3J(H,H) = 5.5$ Hz, 1H; H-5), 3.98 (dd, $^2J(H,H) = 11.3$ Hz and $^3J(H,H) = 5.5$ Hz, 1H, H-6), 3.64 (dd, $^2J(H,H) = 11.3$ Hz and $^3J(H,H) = 8.2$ Hz, 1H; H-6), 3.35 (dt, $^3J(H,H) = 10.1$ Hz and $^3J(H,H) = 3.4$ Hz, 1H, H-2'), 2.11 (s, 3H; CH_3CO), 2.03 (s, 3H; CH_3CO), 1.67 (m, 1H, H-3'), 1.36–1.46 (m, 4H including $\delta = 1.39$ (s, 3H; acetonide-Me)), 1.31 (s, 3H; acetonide-Me), 1.21–1.29 (m, 22H) and 0.88 (t, $^3J(H,H) = 7.0$ Hz, 3H; C-15' Me); ^{13}C NMR (75 MHz, $CDCl_3$, RT, TMS): $\delta = 170.06$ (acetate C=O), 169.86 (acetate C=O), 134.61 (2 × C, arom-C), 131.33 (arom-C), 128.99 (2 × C, arom-C), 127.72 (arom-C), 99.81 (C-2), 71.99 (C-4), 70.07 (C-5), 65.07 (C-1'), 61.87 (C-6), 44.16 (C-2'), 31.93 (C-13'), 31.25, 29.66 (4 × C), 29.58 (3 × C), 29.51, 29.36, 27.86 (acetonide-Me), 27.69 (acetonide-Me), 22.70 (C-14'), 20.79 (acetate-Me), 19.29 (acetate-Me) and 14.13 (C-15'); IR (film): $\tilde{\nu} = 3052$, 2918, 2842, 1746, 1578, 1436, 1369, 1232, 1048, 888, 737 and 691 cm^{-1}; MS (70 eV, MS): *m/z* (%): 598 (6) [M^+(^{80}Se)], 596 (4) [M^+(^{78}Se)], 441 (13) [M^+−PhSe]; $C_{31}H_{50}O_6Se$ (597.7) calcd C 62.30, H 8.43; found C 62.29, H 8.37.

(1′*R*,2′*R*/*S*,4*S*,5*R*)-4-(1-Acetoxy-2-phenylselenylpentadecanyl)-5-acetoxy-2,2-dimethyl-[1,3]dioxane (7) was prepared in an analogous fashion to that described above from diol (1′*R*,2′*RS*,4*S*,5*S*)-**6** (11 mg, 2.14×10^{-5} mol, 1.0 equiv), triethylamine (18.9 mg, 26 μL, 1.87×10^{-4} mol, 8.7 equiv), acetic anhydride (10.1 mg, 8.9 μL, 9.36×10^{-5} mol, 4.4 equiv) and DMAP (< 1 mg, cat.) in CH_2Cl_2 (0.5 mL) and was isolated as a colourless viscous oil (12.3 mg, 96%); $[\alpha]_D^{26} = -38.66$ ($c = 1$ in chloroform): ^1H NMR (500 MHz, $CDCl_3$, RT, TMS): $\delta = 7.55-7.61$ (m, 2H; Ar-H), 7.21–7.30 (m, 3H; Ar-H), 5.20 (dd, $^3J(H,H) = 6.4$ Hz and $^3J(H,H) = 4.0$ Hz, 1H; H-1'), 4.87 (dt, $^3J(H,H) = 8.6$ Hz and $^3J(H,H) = 4.6$ Hz, 1H; H-5), 4.23 (dd, $^3J(H,H) = 8.3$ Hz and $^3J(H,H) = 6.4$ Hz, 1H; H-4), 3.95 (dd, $^2J(H,H) = 12.5$ Hz and $^3J(H,H) = 4.6$ Hz, 1H; H-6), 3.57 (dd, $^2J(H,H) = 12.5$ Hz and $^3J(H,H) = 4.3$ Hz, 1H; H-6), 3.34 (dt, $^3J(H,H) = 10.0$ Hz and $^3J(H,H) = 4.0$ Hz, 1H, H-2'), 2.00 (s, 3H; CH_3CO), 1.90 (s, 3H; CH_3CO), 1.32–1.70 (m, 5H including $\delta = 1.45$ (s, 3H; acetonide-Me)), 1.31 (s, 3H; acetonide-Me), 1.23–1.29 (m, 22H) and 0.88 (t, $^3J(H,H) = 7.0$ Hz, 3H; C-15' Me); ^{13}C NMR (75 MHz, $CDCl_3$, RT, TMS): $\delta = 170.02$ (acetate C=O), 169.85 (acetate C=O), 134.98 (2 × C, arom-C), 129.45 (arom-C), 129.01 (2 × C, arom-C), 127.66 (arom-C), 100.04 (C-2), 76.01 (C-4), 70.15 (C-1'), 69.86 (C-5), 62.36 (C-6), 47.69 (C-2'), 31.93 (C-13'), 30.48, 29.71 (2 × C), 29.66 (2 × C), 29.62, 29.49, 29.36, 29.33, 28.18, 25.86 (acetonide-Me), 22.69 (C-14'), 21.74 (acetonide-Me), 20.95 (acetate-Me), 20.68 (acetate-Me) and 14.13 (C-15'); IR (film): $\tilde{\nu} = 3051$, 2918, 2845, 1748, 1578, 1456, 1368, 1221, 1045, 855 and 737 cm^{-1}; MS (70 eV, EI): *m/z* (%): 598 (23) [M^+(^{80}Se)], 596 (15) [M^+(^{78}Se)], 480 (4) [M^+(^{80}Se)−2AcO], 441 (21) [M^+−PhSe], 43 (100) [Ac^{+}]; $C_{31}H_{50}O_6Se$ (597.7) calcd C 62.30, H 8.43; found C 62.63, H 8.76.

(4*S*,5*R*,1′*E*)-2,2-Dimethyl-5-methanesulfonyloxy-4-pentadec-1′-enyl-[1,3]dioxane (8): To a stirred solution of diol mixture **6** (570 mg, 1.11 mmol, 1.0 equiv) in CH_2Cl_2 (10 mL) at 0 °C under an atmosphere of argon was added dropwise triethylamine (1.124 g, 1.55 mL, 11.11 mmol, 10.0 equiv), and then methanesulfonyl chloride (636 mg, 430 μL, 5.55 mmol, 5.0 equiv) was added dropwise. The resultant red solution was stirred at room temperature for 10 min, then poured into water and extracted with CH_2Cl_2. The combined CH_2Cl_2 extracts were washed with water,

brine, dried ($MgSO_4$) and concentrated in vacuo. Purification by flash column chromatography (silica gel, eluent: pentane/ether 4:1) afforded **8** as a pale yellow oil (452 mg, 97%); $[\alpha]_D^{27} = -14.21$ ($c = 1$ in chloroform); ^{1}H NMR (300 MHz, $CDCl_3$, RT, TMS): $\delta = 5.89$ (dtd, $^3J(H,H) = 15.4$ Hz, $^3J(H,H) = 6.6$ Hz and $^3J(H,H) = 1.0$ Hz, 1H; H-2'), 5.44 (ddt, $^3J(H,H) = 15.4$ Hz, $^3J(H,H) = 7.4$ Hz and $^4J(H,H) = 1.5$ Hz, 1H; H-1'), 4.38 (ddd, $^3J(H,H) = 9.0$ Hz, $^3J(H,H) = 8.2$ Hz and $^3J(H,H) = 5.3$ Hz, 1H; H-5), 4.20 (dd, $^3J(H,H) = 9.0$ Hz and $^3J(H,H) = 7.4$ Hz, 1H; H-4), 4.11 (dd, $^2J(H,H) = 11.8$ Hz and $^3J(H,H) = 5.3$ Hz, 1H; H-6), 3.89 (dd, $^3J(H,H) = 11.8$ Hz and $^3J(H,H) = 8.2$ Hz, 1H; H-6), 2.97 (s, 3H; SO_2Me), 2.06 (m, 2H; 2 × H-3'), 1.53 (s, 3H; acetonide-Me), 1.40–1.43 (m, 5H including $\delta = 1.42$ (s, 3H; acetonide-Me), 1.22–1.30 (brs, 20H) and 0.89 (t, $^3J(H,H) = 7.1$ Hz, 3H; C-15' Me); ^{13}C NMR (75 MHz, $CDCl_3$, RT, TMS): $\delta = 137.60$ (C-1'), 125.75 (C-2'), 99.45 (C-2), 75.51 (C-4), 72.24 (C-5), 62.37 (C-6), 38.45 ($MeSO_2-$), 32.41 (C-3'), 31.93 (C-13'), 29.66 (4 × C), 29.58, 29.48, 29.36, 29.31, 28.84, 27.82 (acetonide-Me), 22.69 (C-14'), 19.73 (acetonide-Me) and 14.13 (C-15'); IR (film): $\tilde{\nu} = 2990$, 2958, 2847, 1456, 1376 (S = O), 1178 (S = O), 964 and 849 cm^{-1}; MS (70 eV, EI): *m/z* (%): 403 (2) [$M^+ - Me$], 360 (2) [$M^+ - (CH_3)_2CO$], 281 (20) [$M^+ - SO_2Me - (CH_3)_2CO$]; $C_{22}H_{42}O_5S$ (418.6) calcd C 63.12, H 10.11; found C 62.90, H 10.13.

(4*S*,5*S*,1'*E*)-5-Azido-2,2-dimethyl-4-pentadec-1'-enyl-[1,3]dioxane (9): To a stirred solution of mesylate **8** (406 mg, 9.71×10^{-4} mol, 1.0 equiv) in DMF (20 mL) was added sodium azide (630 mg, 9.71 mmol, 10.0 equiv) and 18-crown-6 (256 mg, 9.71×10^{-4} mol, 1.0 equiv). This reaction mixture was then heated to 100 °C under an atmosphere of argon for 48 h. Upon cooling the reaction mixture was poured into water and extracted with ether. The combined ethereal extracts were washed with brine (3 ×), dried ($MgSO_4$) and concentrated in vacuo. Purification by flash column chromatography (silica gel, eluent: pentane/ether 4:1) afforded **9** as a colourless oil (334 mg, 94%); $[\alpha]_D^{27} = +106.59$ ($c = 1$ in chloroform); ^{1}H NMR (300 MHz, $CDCl_3$, RT, TMS): $\delta = 5.84$ (dtd, $^3J(H,H) = 15.4$ Hz, $^3J(H,H) = 6.6$ Hz and $^4J(H,H) = 1.0$ Hz, 1H; H-2'), 5.61 (ddt, $^3J(H,H) = 15.6$ Hz, $^3J(H,H) = 6.3$ Hz and $^4J(H,H) = 1.6$ Hz, 1H; H-1'), 4.53 (ddd, $^3J(H,H) = 6.3$ Hz, $^3J(H,H) = 2.0$ Hz and $^4J(H,H) = 1.0$ Hz, 1H; H-4), 4.23 (dd, $^2J(H,H) = 12.6$ Hz and $^3J(H,H) = 2.2$ Hz, 1H; H-6), 4.08 (dd, $^2J(H,H) = 12.6$ Hz and $^3J(H,H) = 1.9$ Hz, 1H; H-6), 2.77 (dd, $^3J(H,H) = 2.2$ Hz and $^3J(H,H) = 1.9$ Hz, 1H; H-5), 2.08 (m, 2H; 2 × H-3'), 1.52 (s, 3H; acetonide-Me), 1.47 (s, 3H; acetonide-Me), 1.32–1.45 (m, 2H; 2 × H-4'), 1.24–1.30 (brs, 20H) and 0.88 (t, $^3J(H,H) = 7.1$ Hz, 3H; C-15' Me); ^{13}C NMR (75 MHz, $CDCl_3$, RT, TMS): $\delta = 135.00$ (C-1'), 126.39 (C-2'), 99.41 (C-2), 72.96 (C-4), 64.27 (C-6), 56.84 (C-5), 32.39 (C-3'), 31.94 (C-13'), 29.67 (4 × C), 29.62, 29.50, 29.37, 29.24, 28.89, 28.75 (acetonide-Me), 22.70 (C-14'), 18.59 (acetonide-Me) and 14.13 (C-15'); IR (film): $\tilde{\nu} = 2990$, 2918, 2846, 2105 (N_3), 1456, 1380, 1196, 965 and 878 cm^{-1}; MS (70 eV, EI): *m/z* (%): 350 (3.4) [$M^+ - Me$], 265 (7) [$M^+ - (CH_3)_2CO - N_3$]; $C_{21}H_{39}N_3O_2$ (365.6) calcd C 68.99, H 10.75, N 11.49; found C 68.76, H 10.78, N 11.30.

(2*S*,3*S*,4*E*)-2-Azidooctadec-4-ene-1,3-diol (10): To a stirred solution of azide **9** (302 mg, 8.27×10^{-4} mol) in THF/H_2O (10 mL, 9:1) at room temperature was added dropwise 6 N hydrochloric acid (1 mL). The resultant solution was stirred for 6 h, then poured into sat. $NaHCO_3$ solution and extracted with chloroform. The combined chloroform extracts were washed with brine, dried ($MgSO_4$) and concentrated in vacuo. Purification by flash column chromatography (Silica gel, eluent: CH_2Cl_2/MeOH 20:1) afforded the azidosphingosine **10** as a colourless oil (261 mg, 97%); $[\alpha]_D^{26} = +0.87$ ($c = 1$ in chloroform); ^{1}H NMR (300 MHz, $CDCl_3$, RT, TMS): $\delta = 5.81$ (dtd, $^2J(H,H) = 15.4$ Hz, $^3J(H,H) = 6.6$ Hz and $^3J(H,H) = 1.0$ Hz, 1H; H-5), 5.52 (ddt, $^2J(H,H) = 15.4$ Hz, $^3J(H,H) = 7.1$ Hz and $^4J(H,H) = 1.5$ Hz, 1H; H-4), 4.22 (app. q, $^3J(H,H) = 6.0$ Hz, 1H; H-3), 3.81 (ddd, $^2J(H,H) = 11.5$ Hz, $^3J(H,H) = 6.0$ Hz and $^4J(H,H) = 1.5$ Hz, 1H; H-1), 3.70 (dt, $^2J(H,H) = 11.5$ Hz and $^3J(H,H) = 6.0$ Hz, 1H; H-1), 3.48 (m, 1H; H-2), 2.03 (m, 2H (exch. D_2O); OH), 2.06 (app. q, $^3J(H,H) = 6.6$ Hz, 2H; 2 × H-6), 1.15–1.45 (m, 22H) and 0.88 (t, $^3J(H,H) = 6.9$ Hz, 3H; C-18 Me); ^{13}C NMR (75 MHz, $CDCl_3$, RT, TMS): $\delta = 135.58$ (C-4), 128.21 (C-5), 73.54 (C-3), 67.58 (C-2), 62.89 (C-1), 32.29 (C-6), 31.94 (C-16), 29.68 (2 × C), 29.62 (2 × C), 29.48 (2 × C), 29.37, 29.21, 28.93, 22.70 (C-17) and 14.13 (C-18); IR (film): $\tilde{\nu} = 3352$, 2921, 2847, 2103 (N_3), 1463, 1262, 968 and 851 cm^{-1}; MS (70 eV, EI): *m/z* (%): 239 (24) [$M^+ - HOCH_2CHN_3$], 57 (100) [$C_4H_9^+$] and 43 (79) [$C_3H_7^+$]; $C_{18}H_{37}N_3O_2$ (325.5); $C_{16}H_{31}O$ (239.2) [$M^+ - HOCH_2CHN_3$] calcd 239.2375; found 239.2372.

(2*S*,3*S*,4*E*)-2-Aminooctadec-4-ene-1,3-diol [L-*threo*-sphingosine] (1): To a stirred slurry of lithium aluminium hydride (37.6 mg, 9.91×10^{-4} mol, 2.0 equiv) in THF (3 mL), at room temperature under an atmosphere of argon was added dropwise a solution of azidosphingosine **10** (161 mg, 4.95×10^{-4} mol, 1.0 equiv) in THF (2 mL). The reaction mixture was stirred for 20 min, and then 10% NaOH solution (720 µL, 1.80 mmol, 3.6 equiv) was added dropwise, followed by chloroform (10 mL). This two-phase system was stirred for 5 min and then separated, and the aqueous phase was further extracted with chloroform. The combined organic phases were washed with brine, dried (Na_2CO_3) and concentrated in vacuo to yield L-*threo*-sphingosine **1** as a colourless solid (138 mg, 93%); M.p. 86–87 °C (Lit. [15l]: 88.0–88.5 °C); $[\alpha]_D^{26} = -2.83$ ($c = 1$ in chloroform) (Lit. [15l]: −2.65 ($c = 1.13$, $CHCl_3$); [13b]: −2.70 ($c = 1$, $CHCl_3$)); ^{1}H NMR (300 MHz, $CDCl_3$, RT, TMS): $\delta = 5.69$ (dt, $^3J(H,H) = 15.6$ Hz and $^3J(H,H) = 6.7$ Hz, 1H; H-5), 5.41 (dd, $^3J(H,H) = 15.6$ Hz and $^3J(H,H) = 6.8$ Hz, 1H; H-4), 3.94 (t, $^3J(H,H) = 5.8$ Hz, 1H; H-3), 3.62 (dd, $^2J(H,H) = 10.9$ Hz and $^3J(H,H) = 4.5$ Hz, 1H; H-1), 3.48 (dd, $^2J(H,H) = 10.9$ Hz and $^3J(H,H) = 6.3$ Hz, 1H; H-1), 2.73 (m, 1H; H-2), 1.99 (app. q, $^3J(H,H) = 6.9$ Hz, 6H (collapses to q, $^3J(H,H) = 6.7$ Hz, 2H with D_2O); 2 × H-6, NH_2 and 2 × OH), 1.17–1.26 (m, 22H) and 0.88 (t, $^3J(H,H) = 6.8$ Hz, 3H; C-18 Me); ^{13}C NMR (75 MHz, $CDCl_3$, RT, TMS): $\delta = 134.77$ (C-4), 130.32 (C-5), 74.48 (C-3), 65.37 (C-1), 57.01 (C-2), 32.90 (C-6), 32.49 (C-16), 30.25 (4 × C), 30.18, 30.05, 29.93, 29.80, 29.73, 23.26 (C-17) and 14.70 (C-18); IR (film): $\tilde{\nu} = 3350$, 2958, 2920, 2845, 1592, 1465, 1262, 1041 and 871 cm^{-1}; MS (70 eV, EI): *m/z* (%): 263 (0.5) [$M^+ - CH_2OH$] and 60 (100) [$OCH_2CH_2NH_2^+$]; $C_{18}H_{37}NO_2$ (299.5) calcd C 72.19, H 12.45, N 4.68; found C 72.35, H 12.72, N 4.85.

(4*S*,5*S*,1'*E*)-2,2-Dimethyl-4-pentadec-1'-enyl-[1,3]dioxan-5-ylamine (1,3-*O*-acetonide-protected sphingosine): A solution of azide **9** (19.8 mg, 5.47×10^{-5} mol) in THF (1 mL) was added dropwise to a stirred slurry of lithium aluminium hydride (4.1 mg, 1.09×10^{-4} mol, 2.0 equiv) in THF (1 mL) at room temperature under an atmosphere of argon. After 30 min this slurry was quenched with 10% NaOH solution (88 µL, 2.19×10^{-4} mol, 4.0 equiv) and extracted with chloroform. The combined organic extracts were dried (Na_2CO_3) and concentrated in vacuo. Purification by flash column chromatography (silica gel, eluent: CH_2Cl_2/MeOH 20:1) afforded 1,3-*O*-acetonide-protected sphingosine (18.2 mg, 98%) as a colourless oil; $[\alpha]_D^{23} = +6.85$ ($c = 1$ in chloroform); ^{1}H NMR (300 MHz, $CDCl_3$, RT, TMS): $\delta = 5.75$ (dtd, $^3J(H,H) = 15.6$ Hz, $^3J(H,H) = 6.9$ Hz and $^3J(H,H) = 1.4$ Hz, 1H; H-2'), 5.46 (ddt, $^3J(H,H) = 15.6$ Hz, $^3J(H,H) = 5.5$ Hz and $^4J(H,H) = 1.4$ Hz, 1H; H-1'), 4.43 (d, $^3J(H,H) = 5.2$ Hz, 1H; H-4), 4.13 (dd, $^2J(H,H) = 11.8$ Hz and $^3J(H,H) = 2.2$ Hz, 1H; H-6), 3.81 (dd, $^2J(H,H) = 11.8$ Hz and $^3J(H,H) = 1.7$ Hz, 1H; H-6), 2.58 (dd, $^3J(H,H) = 2.2$ Hz and $^3J(H,H) = 1.7$ Hz, 1H; H-5), 2.24 (brs, 2H (exch. D_2O); NH_2), 2.07 (q, $^3J(H,H) = 6.9$ Hz, 2H; 2 × H-3'), 1.48 (s, 3H; acetonide-Me), 1.45 (s, 3H; acetonide-Me), 1.24–1.43 (m, 22H) and 0.88 (t, $^3J(H,H) = 6.9$ Hz, 3H; C-15' Me); ^{13}C NMR (75 MHz, $CDCl_3$, RT, TMS): $\delta = 133.89$ (C-1'), 127.34 (C-2'), 99.88 (C-2), 72.83 (C-4), 66.25 (C-6), 48.77 (C-5), 32.54 (C-3'), 31.94 (C-13'), 29.77 (acetonide-Me), 29.70 (4 × C), 29.63 (2 × C), 29.52, 29.38, 29.14, 22.72 (C-14'), 18.67 (acetonide-Me) and 14.14 (C-15'); IR (film): $\tilde{\nu} = 3380$, 2996, 2922, 2855, 1460, 1382, 1200, 972 and 865 cm^{-1}; MS (70 eV, EI): *m/z* (%): 324 (1.3) [$M^+ - Me$], 281 (1.4) [$M^+ - (CH_3)_2CO$] and 43 (100) [$C_3H_7^+$]; $C_{21}H_{41}NO_2$ (339.563) calcd C 74.28, H 12.17, N 4.12; found C 74.44, H 12.74, N 4.68; $C_{20}H_{39}NO_2$, [$M^+ - Me$], (324.3) calcd 324.2903; found 324.2905.

The acetonide group was then hydrolytically removed by stirring with 6 N hydrochloric acid (1 mL) in THF/H_2O (3 mL, 2:1) at room tempertature for 6 h. The solution was made alkaline by the addition of excess 2 N NaOH solution and extracted with chloroform (3 × 5 mL). The organic extracts were dried ($MgSO_4$) and concentrated. Recrystallisation from hexane/dichloromethane afforded L-*threo*-sphingosine (**1**) (62% from **9**) which was identical in all spectroscopic detail to that prepared earlier (vide infra).

L-*threo*-Sphingosine-*N*,*O*,*O*-triacetate (11): To a stirred solution of L-*threo*-sphingosine **1** (120 mg, 4.01×10^{-4} mol, 1.0 equiv) in CH_2Cl_2 (10 mL) were added consecutively triethylamine (325 mg, 448 µL, 3.21 mmol, 8.0 equiv), acetic anhydride (164 mg, 143 µL, 1.60 mmol, 4.0 equiv) and DMAP (1 mg, cat.) at 0 °C under an atmosphere of argon. The reaction mixture was stirred at room temperature for 2 h, then poured into water and extracted with CH_2Cl_2. The combined organic extracts were washed with brine, dried ($MgSO_4$) and concentrated in vacuo. Purification by flash column chromatography (silica gel, eluent: pentane/ethyl acetate 1:1) afforded **11** as a colourless solid (167 mg, 98%); M.p. 41–42 °C (Lit. [15e]: 43 °C); $[\alpha]_D^{26} = +6.92$ ($c = 1$ in chloroform) (Lit. [13c]: +8.78 ($c = 1.2$, $CHCl_3$)); ^{1}H NMR (300 MHz, $CDCl_3$, RT, TMS): $\delta = 5.77$ (dt, $^3J(H,H) = 14.0$ Hz and $^3J(H,H) = 6.9$ Hz, 1H; H-5), 5.66 (d, $^3J(H,H) = 9.3$ Hz, 1H; NH), 5.36–5.44 (m, 2H; H-4,H-3), 4.40 (m, 1H; H-2), 4.09 (dd, $^2J(H,H) = 12.0$ Hz and $^3J(H,H) = 6.5$ Hz, 1H; H-1), 4.06 (dd, $^2J(H,H) = 12.0$ Hz and $^3J(H,H) = 6.0$ Hz, 1H; H-1)1.97–2.08 (m, 11H including $\delta = 2.07$, 2.05 and 1.99 all (s, 3H; CH_3CO)), 1.25 (brs, 22H) and 0.88 (t, $^3J(H,H) = 6.8$ Hz, 3H; C-18 Me); ^{13}C NMR (75 MHz, $CDCl_3$, RT, TMS): $\delta = 171.25$ (acetate C=O), 170.68 (acetate C=O), 170.42 (acetate C=O), 138.38 (C-4), 124.61 (C-5), 73.62 (C-3), 63.66 (C-1), 51.42 (C-2), 32.83 (C-6), 32.48 (C-16), 30.23 (4 × C), 30.15, 29.99, 29.92, 29.71, 29.36, 23.83 (acetate-Me), 23.25 (C-17), 21.66 (acetate-Me), 21.33 (acetate-Me) and 14.68 (C-18); IR (film): $\tilde{\nu} = 3290$ (NH), 2921, 2850, 1751 (C=O ester), 1654 (C=O amide), 1467, 1369, 1046, 968 and 723 cm^{-1}; MS (70 eV, EI): *m/z* (%): 425 (0.5) [M^+], 366 (2.5) [$M^+ - OAc$], 264 (2.5) [$M^+ - 2AcO-Ac$], 43 (16.4) [Ac^+]; $C_{24}H_{43}NO_5$ (425.6) calcd. C 67.73, H 10.18, N 3.29; found C 67.42, H 10.34, N 3.57.

(2*S*,3*S*,4*E*)-*N*-Acetamidooctadec-4-ene-1,3-diol (12): Anhydrous potassium carbonate (26 mg, 1.38×10^{-4} mol, 2.0 equiv) was added portionwise to a solution of triacetate **11** (40 mg, 9.41×10^{-5} mol, 1.0 equiv) in MeOH (3 mL) at room temperature under an atmosphere of argon. The resultant suspension was stirred at room temperature for 1 h, then poured into water and extracted with chloroform. The combined organic extracts were washed with brine, dried ($MgSO_4$) and concentrated in vacuo. Purification by flash column chromatography (silica gel, eluent: CH_2Cl_2/MeOH 20:1) afforded **12** as a colourless oil (30.2 mg, 94%); $[\alpha]_D^{26} = -9.72$ ($c = 1$ in chloroform); ^{1}H NMR (300 MHz, $CDCl_3$, RT, TMS): $\delta = 6.25$ (d, $^3J(H,H) = 8.0$ Hz, 1H; NH), 5.75 (dtd, $^3J(H,H) = 15.4$ Hz, $^3J(H,H) = 6.8$ Hz and $^3J(H,H) = 0.8$ Hz, 1H; H-5), 5.47 (ddt, $^3J(H,H) = 15.4$ Hz, $^3J(H,H) = 6.6$ Hz and $^4J(H,H) = 1.0$ Hz, 1H; H-4), 4.38 (m, 1H; H-2), 3.90 (m, 1H; H-3),

0947-6539/95/0106-0386 $ 30.00+.25/0 Chem. Eur. J. 1995, 1, No. 6

3.79 (app. t, $^2J(H,H) = 5.0$ Hz, 2H; 2 × H-1), 3.15 (t, $^3J(H,H) = 5.2$ Hz, 1H (exch. D_2O); OH), 2.98 (d, $^3J(H,H) = 3.3$ Hz, 1H (exch. D_2O); OH), 1.98–2.10 (m, 5H including $\delta = 2.03$ (s, 3H; CH_3CO)), 1.18–1.42 (m, 22H) and 0.88 (t, $^3J(H,H) = 7.1$ Hz, 3H; C-18 Me); ^{13}C NMR (75 MHz, $CDCl_3$, RT, TMS): $\delta = 171.87$ (acetate C=O), 134.64 (C-4), 129.47 (C-5), 73.56 (C-3), 64.72 (C-1), 55.38 (C-2), 32.85 (C-6), 32.49 (C-16), 30.26 (3 × C), 30.23, 30.19, 30.08, 29.93, 29.80, 29.71, 23.90 (acetate-Me), 23.26 (C-17) and 14.69 (C-18); IR (film): $\tilde{\nu} = 3310$ (br, OH,NH), 2922, 2858, 1648 (C=O amide), 1379, 1060 and 966 cm^{-1}; MS (70 eV; EI): *m/z* (%): 323 (1) [$M^+ - H_2O$], 102 (18) [$HOCH_2CH(NH)CH(OH)CH^+$] and 43 (24) [Ac^+]; $C_{20}H_{39}NO_3$ (341.5) calcd C 70.34, H 11.51, N 4.10; found C 70.17, H 11.21, N 3.73.

(2*S*,3*S*,4*E*)-*N*-Acetamido-1-*O*-acetyloctadec-4-ene-1,3-diol (13): To a solution of acetamide **12** (22 mg, 6.45×10^{-5} mol, 1.0 equiv) in CH_2Cl_2 (2 mL) at −20 °C under an atmosphere of argon was added triethylamine (13 mg, 18 µL, 1.29×10^{-4} mol, 2.0 equiv) and then acetic anhydride (206 µL of a 0.313 M solution in CH_2Cl_2, 6.45×10^{-5} mol, 1.0 equiv). The reaction mixture was stored at −20 °C for 5 d (TLC control), then poured into water and extracted with CH_2Cl_2. The combined organic extracts were washed with brine, dried (Na_2CO_3) and concentrated in vacuo. Purification by flash column chromatography (Silica gel, eluent CH_2Cl_2/MeOH 40:1) afforded the alcohol **13** as a colourless oil (20.2 mg, 82%); $[\alpha]_D^{26} = -19.85$ (*c* = 1 in chloroform) (Lit. [13c] = −20.3, (*c* = 1.1, $CHCl_3$)); ^1H NMR (300 MHz, $CDCl_3$, RT, TMS): $\delta = 5.88$ (d; $^3J(H,H) = 7.5$ Hz, 1H; NH), 5.74 (dtd, $^3J(H,H) = 15.4$ Hz, $^3J(H,H) = 6.8$ Hz and $^3J(H,H) = 1.1$ Hz, 1H; H-5), 5.45 (dd, $^3J(H,H) = 15.4$ Hz and $^3J(H,H) = 6.3$ Hz, 1H; H-4), 4.06–4.30 (m, 4H; 2 × H-1, H-2 and H-3), 2.49 (brs, 1H (exch. D_2O); OH), 1.96–2.12 (m, 8H including $\delta = 2.09$ and 2.01 both (s, 3H; CH_3CO)), 1.18–1.40 (m, 22H) and 0.88 (t, $^3J(H,H) = 7.1$ Hz, 3H; C-18 Me); ^{13}C NMR (75 MHz, $CDCl_3$, RT, TMS): $\delta = 171.39$ (acetate C=O), 170.60 (acetate C=O), 134.40 (C-4), 128.38 (C-5), 71.02 (C-3), 63.24 (C-1), 52.51 (C-2), 32.28 (C-6), 31.93 (C-16), 29.68 (4 × C), 29.62, 29.50, 29.36, 29.21, 29.12, 23.29 (acetate-Me), 22.69 (C-17), 20.89 (acetate-Me) and 14.13 (C-18); IR (film): $\tilde{\nu} = 3391$ (OH), 3314 (NH), 2912, 2842, 1726 (C=O ester), 1636 (C=O amide) 1545 1266 and 1040 cm^{-1}; MS (70 eV, EI): *m/z* (%): 383 (0.1) [M^+], 366 (1.3) [$M^+ - OH$], 323 (1.6) [$M^+ - AcOH$], 264 (2.9) [$M^+ - AcOH - Ac - OH$], 144 (30) [$AcOCH_2CHNHAc^+$] 85 (100) [$CH_2CHNHAc^+$]; $C_{22}H_{41}NO_4$ (383.6) calcd C 68.89, H 10.77, N 3.65; found C 69.25, H 11.20, N 3.73.

(2*S*,3*R*,4*E*)-2-Aminooctadec-4-ene-1,3-diol [D-*erythro*-sphingosine] (1): Diethylazodicarboxylate (550 µL of a 0.534 M solution in THF, 2.94×10^{-4} mol, 3.0 equiv) was added dropwise to a stirred solution of alcohol **13** (28 mg, 9.72×10^{-5} mol, 1.0 equiv), benzoic acid (48 mg, 3.89×10^{-4} mol, 4.0 equiv) and triphenylphosphine (103 mg, 3.89×10^{-4} mol, 4.0 equiv) in THF (2 mL) at room temperature under an atmosphere of argon. The reaction mixture was stirred overnight at ambient temperature, then poured into water and extracted with ether. The ethereal phase was washed with water, then brine, dried ($MgSO_4$) and concentrated in vacuo. The crude reaction mixture was then redissolved in EtOH (3 mL) and 2 N KOH solution (0.5 mL, Xs) was added. This mixture was then heated at reflux for 6 h. Upon cooling the solution was poured into water and extracted with chloroform. The combined organic extracts were washed with brine, dried ($MgSO_4$) and then concentrated in vacuo to give a colourless solid. Recrystallisation from hexane/dichloromethane gave D-*erythro*-sphingosine **1** as a colourless solid (23 mg, 79%); M.p. 72–73 °C (Lit. [15p]: 72–74 °C); $[\alpha]_D^{25} = -1.23$ (*c* = 0.5 in chloroform) (Lit. [15p]: −2.8 (*c* = 1, $CHCl_3$)); ^1H NMR (300 MHz, $CDCl_3$, RT, TMS): $\delta = 5.75$ (dt; $^3J(H,H) = 15.5$ Hz and $^3J(H,H) = 7.1$ Hz, 1H), 5.47 (dd, $^3J(H,H) = 15.5$ Hz and $^3J(H,H) = 7.1$ Hz, 1H), 4.06 (t, $^3J(H,H) = 6.2$ Hz, 1H), 3.66 (m, 2H), 2.86 (m, 1H), 2.18 (brs, 4H, NH_2, 2 × OH), 2.05 (q, $^2J(H,H) = 6.2$ Hz, 2H), 1.18–1.42 (m, 22H) and 0.88 (t, $^3J(H,H) = 6.9$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, RT, TMS): $\delta = 134.85$ (C-4), 129.41 (C-5), 75.52 (C-3), 64.06 (C-1), 56.26 (C-2), 32.36 (C-6), 31.94 (C-16), 29.70, 29.64, 29.50, 29.38, 29.26, 29.17, 22.71 (C-17) and 14.14 (C-18); IR (film): $\tilde{\nu} = 3360$, 2908, 2838, 1592, 1467, 1045, 1031, 967 and 937 cm^{-1}; MS (70 eV, EI): *m/z* (%): 280 (0.5) [$M^+ - H - H_2O$], 87 (2.5) [$HOCH_2CH(NH_2)CH_2^+$], 60 (100) [$HOCH_2CHNH_2^+$], 43 (16) [$C_3H_7^+$]; $C_{18}H_{37}NO_2$ (299.5) calcd C 72.19, H 12.45, N 4.68; found C 72.23, H 12.13, N 4.48.

D-*erythro*-Sphingosine-*N*,*O*,*O*-triacetate (14): The triacetate **14** of D-*erythro*-sphingosine **1** was prepared in an analogous fashion to that of the L-*threo*-sphingosine isomer (vide infra) by using D-*erythro*-sphingosine **1** (12 mg, 4.01×10^{-5} mol, 1.0 equiv), triethylamine (41 mg, 56 µL, 4.0×10^{-4} mol, 10.0 equiv), acetic anhydride (21 mg, 20 µL, 2×10^{-4} mol, 5.0 equiv) and DMAP (< 1 mg, cat.) in CH_2Cl_2 (2 mL). The triacetate **14** was isolated, after flash column chromatography (silica gel, eluent: pentane/ethyl acetate 1:1), as a colourless solid (14.8 mg, 87%); M.p. 102–103 °C (Lit. [13c]: 103 °C); $[\alpha]_D^{23} = -12.16$ (*c* = 1 in chloroform) (Lit. [13c]: −13.0 (*c* = 1.08, $CHCl_3$); Lit. [15o]: −12.9 (*c* = 1, $CHCl_3$)); ^1H NMR (300 MHz, $CDCl_3$, RT, TMS): $\delta = 5.78$ (dt, $^3J(H,H) = 15.4$ Hz and $^3J(H,H) = 6.6$ Hz, 1H; H-5), 5.67 (d, $^3J(H,H) = 9.4$ Hz, 1H; NH), 5.39 (ddt, $^3J(H,H) = 15.4$ Hz, $^3J(H,H) = 7.4$ Hz and $^4J(H,H) = 1.4$ Hz, 1H; H-4), 5.27 (dd, $^3J(H,H) = 7.2$ Hz and $^3J(H,H) = 5.8$ Hz, 1H; H-3), 4.42 (m, 1H; H-2), 4.30 (dd, $^2J(H,H) = 11.5$ Hz and $^3J(H,H) = 6.0$ Hz, 1H; H-1), 4.04 (dd, $^2J(H,H) = 11.5$ Hz and $^3J(H,H) = 4.1$ Hz, 1H; H-1), 1.95–2.10 (m, 11H including $\delta = 2.06$, 2.05 and 1.98 all (s, 3H, CH_3CO)), 1.18–1.41 (m, 22H) and 0.88 (t, $^3J(H,H) = 6.8$ Hz, 3H; C-18 Me); ^{13}C NMR (75 MHz, $CDCl_3$, RT, TMS): $\delta = 170.99$ (acetate C=O), 170.00 (acetate C=O), 169.68 (acetate C=O), 137.47 (C-4), 124.12 (C-5), 73.83 (C-3), 62.60 (C-1), 50.66 (C-2), 32.29 (C-6), 31.93 (C-16), 29.68 (4 × C), 29.60, 29.46, 29.36, 29.18, 28.89, 23.39 (acetate-Me), 22.70 (C-17), 21.15 (acetate-Me), 20.83 (acetate-Me) and 14.13 (C-18); IR (film): $\tilde{\nu} = 3292$ (NH), 2918, 2848, 1737 (C=O ester), 1653 (C=O amide), 1554, 1376, 1234 and 1028 cm^{-1}; MS (70 eV, EI): *m/z* (%): 425 (0.8) [M^+], 366 (4) [$M^+ - AcO$], 264 (5) [$M^+ - 2AcO - Ac$], 43 (38) [Ac^+]; $C_{24}H_{43}NO_5$ (425.6) calcd. C 67.73, H 10.18, N 3.29; found C 67.29, H 10.56, N 3.70.

Acknowledgements: This work was supported by the Fonds der Chemischen Industrie and the Deutsche Forschungsgemeinschaft (Leibniz award, Sonderforschungsbereich 380). We thank Degussa AG, BASF AG, Bayer AG and Hoechst AG for the kind donation of chemicals.

Received: February 1, 1995 [F78]

[1] a) K. A. Karlsson, *Nature* **1960**, *188*, 312; b) H. E. Carter, F. J. Glick, W. P. Norris, G. E. Phillips, *J. Biol. Chem.* **1947**, *170*, 285; c) H. E. Carter, F. J. Glick, W. P. Norris, G. E. Phillips, *ibid.* **1942**, *142*, 449.

[2] a) P. W. Wertz, M. C. Miethke, S. A. Long, J. S. Stauss, D. T. Downing, *J. Invest. Dermatol.* **1985**, *84*, 410; b) H. Wakita, K. Nishimura, M. Takigawa, *ibid.* **1992**, *99*, 617.

[3] a) T. A. Springer, I. A. Lasky, *Nature* **1991**, *349*, 196; b) T. Feizi, *Trends Biochem. Sci.* **1991**, *16*, 84; c) K.-A. Karlsson, *Trends Pharm. Sci.* **1991**, *12*, 265.

[4] a) A. H. Merrill Jr., *J. Bioenerg. Biomembr.* **1991**, *23*, 83; b) Y. A. Hannun, R. M. Bell, A. H. Merrill Jr., *Science* **1989**, *243*, 500; c) A. H. Merrill Jr., V. L. Stevens, *Biochim. Biophys. Acta* **1989**, *1010*, 131; d) Y. A. Hannun, C. R. Loomis, A. H. Merrill Jr., R. M. Bell, *J. Biol. Chem.* **1986**, *261*, 12604; e) E. Wilson, M. C. Olcott, R. M. Bell, A. H. Merrill Jr., J. D. Lambeth, *J. Biol. Chem.* **1986**, *261*, 12616; f) A. H. Merrill, *Biochemistry*, **1989**, *28*, 3138; see also R. H. Weiss, H. C. Long, H. E. Ives, *J. Cell Physiol.* **1991**, *149*, 307.

[5] a) H. Zhang, N. E. Buckley, K. Gibson, S. Spiegel, *J. Biol. Chem.* **1990**, *265*, 76; b) A. Olivera, S. Spiegel, *Glycoconjugate J.* **1992**, *9*, 110.

[6] J. M. Harouse, S. Bhat, S. L. Spitalnik, M. Laughlin, K. Stefano, D. H. Silberberg, F. Gonzalez-Scarano, *Science* **1991**, *253*, 320.

[7] A. H. Merrill, *J. Biol. Chem.* **1989**, *264*, 6773.

[8] B. Niedieck, U. Kuck, *Z. Immunitaetsforsch. Allerg. Klin. Immunol.* **1967**, *133*, 43.

[9] J. Mellanby, H. Mellanby, D. Pope, W. E. Van Heyningen, *J. Gen. Microbiol.* **1969**, *54*, 161.

[10] M. Sakai, T. Tano, *Yokohama Med. Bull.* **1965**, *16*, 57; *Chem. Abstr.* **1965**, *63*, 16935h.

[11] G. L. Feldman, L. S. Feldman, *Invest. Ophthalmol.* **1965**, *4*, 162.

[12] G. Rouser, G. Feldman, G. Galli, *J. Amer. Oil Chem. Soc.* **1965**, *42*, 411.

[13] a) R. S. Garigipati, S. M. Weinreb, *J. Am. Chem. Soc.* **1983**, *105*, 4499; b) H. Shibuya, K. Kawashima, M. Ikeda, I. Kitagawa, *Tetrahedron Lett.* **1989**, *30*, 7205; B. Bernet, A. Vasella, *ibid.* **1983**, *24*, 5491; R. Julina, T. Herzog, B. Bernet, A. Vasella, *Helv. Chim. Acta.* **1986**, *69*, 368; c) Y. Ito, M. Sawamura, T. Hayashi, *Tetrahedron Lett.* **1988**, *29*, 239; d) S. Takano, Y. Iwabuchi, K. Ogasawara, *J. Chem. Soc. Chem. Commun.* **1991**, 820; e) T. Hudlicky, T. Nugent, W. Griffith, *J. Org. Chem.* **1994**, *59*, 7944; for further examples see: A. Bongini, G. Cardillo, M. Oreano, S. Sandri, G. Tomasini J. *Chem. Soc. Perkin Trans 1* **1986**, 1339; A. Bongini, G. Cardillo, M. Oreano, S. Sandri, G. Tomasini, *ibid.* **1986**, 1345; G. Cardillo, M. Oreano, S. Sandri, G. Tomasini, *Tetrahedron* **1986**, *42*, 917; K. C. Nicolaou, T. Caulfield, H. Kataoka, T. Kumazawa, *J. Am. Chem. Soc.* **1988**, *110*, 7910; U. Groth, U. Schöllkopf, T. Tiller, *Tetrahedron* **1991**, *47*, 2835;

[14] a) D. Shapiro, H. Segal, H. M. Flowers, *J. Am. Chem. Soc.* **1958**, *80*, 1194; b) R. R. Schmidt, R. Kläger, *Angew. Chem.* **1982**, *94*, 215; *Angew. Chem. Int. Ed. Engl.* **1982**, *21*, 210.

[15] a) E. J. Reist, P. H. Christie, *J. Org. Chem.* **1970**, *35*, 3521; b) E. J. Reist, P. H. Christie, *ibid.* **1970**, *35*, 4127; c) H. Newmann, *J. Am. Chem. Soc.* **1973**, *95*, 4098; d) R. Gigg, R. Conant, *J. Chem. Soc. Perkin Trans 1* **1977**, 2006; e) P. Tkaczuk, E. R. Thornton, *J. Org. Chem.* **1981**, *46*, 4393; f) K. Mori, Y. Funaki, *Tetrahedron* **1985**, *41*, 2379; g) R. R. Schmidt, P. Zimmermann, *Tetrahedron Lett.* **1986**, *27*, 481; h) R. H. Boutin, H. Rapoport, *J. Org. Chem.* **1986**, *51*, 5320; i) M. A. Findeis, G. M. Whitesides, *ibid.* **1987**, *52*, 2838; j) S. Nimkar, D. Menaldino, A. H. Merrill, D. Liotta, *Tetrahedron Lett.* **1988**, *29*, 3037; k) P. Zimmermann, R. R. Schmidt, *Liebigs. Ann. Chem.* **1988**, 663; l) P. Garner, J. M. Park, E. Malecki, *J. Org. Chem.* **1988**, *53*, 4395; m) A. Dondoni, G. Fantin, M. Fogagnolo, A. Medici, *J. Chem. Soc. Chem. Commun.* **1988**, 10; n) H.-E. Radunz, R. M. Devant, V. Eiermann, *Liebigs Ann. Chem.* **1988**, 1103; o) P. Herold, *Helv. Chim. Acta.* **1988**, *71*, 354; p) A. Dondoni, G. Fantin, M. Fogagnola, P. Pedrini, *J. Org. Chem.* **1990**, *55*, 1439; q) N. Hirata, Y. Yamagiwa, T. Kamikawa, *J. Chem. Soc. Perkin 1* **1991**, 2279. For a comprehensive review see R. M. Devant, *Kontakte* (Merck, Darmstadt) **1992**, *3*, 11.

[16] a) S. Sugiyama, M. Honda, T. Komori, *Liebigs Ann. Chem.* **1988**, 619; b) *ibid.* **1990**, 1069; c) R. Polt, M. A. Peterson, L. De Young, *J. Org. Chem.* **1992**, *57*, 5469; d) T. Bär, B. Kratzer, R. Wild, K. Sandhoff, R. R. Schmidt, *Liebigs Ann.*

Chem. **1993**, 419; e) J. S. Yadav, D. Vidyanad, D. Rajagopal, *Tetrahedron Lett.* **1993**, *34*, 1191; f) P. Somfai, R. Olsson, *Tetrahedron* **1993**, *49*, 6645; g) H. Suga, H. Fujieda, Y. Hirotsu, T. Ibata, *J. Org. Chem.* **1994**, *59*, 3359; h) R. Birk, K.-H. Jung, R. R. Schmidt, *Liebigs Ann. Chem.* **1994**, 83; i) G. R. Cook, L. G. Beholz, J. R. Stille, *J. Org. Chem.* **1994**, *59*, 3575; j) H.-S. Byun, R. K. Erukulla, R. Bittman, *ibid.* **1994**, *59*, 6495; k) R. Wild, R. R. Schmidt, *Tetrahedron: Asymmetry* **1994**, 2195; l) A. Solladie-Cavallo, J. L. Koessler, *J. Org. Chem.* **1994**, *59*, 3240.

[17] a) B. Bockstiegel, Dissertation, Technical University of Aachen, **1989**; b) D. Enders, B. Bockstiegel, *Synthesis* **1989**, 493; c) D. Enders, W. Gatzweiler, U. Jegelka, *Synthesis* **1991**, 1137; d) D. Enders, U. Jegelka, *Synlett.* **1992**, 999; e) D. Enders, B. Bockstiegel, H. Dyker, U. Jegelka, H. Kipphardt, D. Kownatka, H. Kuhlmann, D. Mannes, J. Tiebes, K. Papadopoulos, *Dechema—Monographien Band 129*, VCH, Weinheim, **1993**, p. 209; f) D. Enders, U. Jegelka, B. Dücker, *Angew. Chem.* **1993**, *105*, 423; *Angew. Chem. Int. Ed. Engl.* **1993**, *32*, 423; g) D. Enders, U. Jegelka, *Tetrahedron Lett.* **1993**, *34*, 2453; h) D. Enders in *Stereoselective Synthesis* (Eds.: E. Ottow, K. Schöllkopf, B.-G. Schulz), Springer, Berlin, **1994**, p. 63; i) D. Enders, W. Bettray, *Recent Advances in the Development of Highly Enantioselective Synthetic Methods, Proceedings of the Chiral Europe 1994 Symposium*, Spring Innovations, Stockport, **1994**, p. 51.

[18] J. Remion, W. Dumont, A. Krief, *Tetrahedron Lett.* **1976**, *17*, 1385, 3227, 3743.

[19] D. L. J. Clive, V. N. Kale, *J. Org. Chem.* **1981**, *46*, 231.

[20] H. J. Reich, F. Chow, *J. Chem. Soc. Chem. Commun.* **1975**, 790.

[21] A. J. Mancuso, S-L. Huang, D. Swern, *J. Org. Chem.* **1978**, *43*, 2480.

[22] N. Hiyoshi, N. Kambe, S. Murai, N. Sonoda, T. Yamamoto, *Tetrahedron Lett.* **1982**, 4813.

[23] a) D. Enders, *Chem. Scr.* **1985**, *25*, 139; b) D. Enders, G. Bachstädter, K. A. M. Kremer, M. Marsch, K. Harms, G. Boche, *Angew. Chem.* **1988**, *100*, 1580; *Angew. Chem. Int. Ed. Engl.* **1988**, *27*, 1522; c) K. G. Davenport, H. Eichenauer, D. Enders, M. Newcomb, D. E. Bergbreiter, *J. Am. Chem. Soc.* **1979**, *101*, 5654.

[24] M. H. D. Postema, D. L. J. Clive, *J. Chem. Soc. Chem. Commun.* **1994**, 235.

[25] D. A. Evans, K. T. Chapman, *Tetrahedron Lett.* **1986**, *27*, 5939.

[26] Z. Dukozovic, N. K. Roberts, J. F. Sawyer, J. Whelan, B. Bosnich, *J. Am. Chem. Soc.* **1986**, *108*, 2034; V. J. Gatto, K. A. Arnold, A. M. Viscariello, S. R. Miller, C. R. Morgan, G. W. Gokel, *J. Org. Chem.* **1986**, *51*, 5373.

[27] Review: O. Mitsunobu, *Synthesis* **1981**, 1.

[28] La Sueur, *J. Chem. Soc.* **1905**, *87*, 1896.

0947-6539/95/0106-0388 $ 30.00+.25/0