

Efficient stereocontrolled synthesis of *D*-erythro-sphingosine from *N*-benzoyl-*D*-glucosamine¹

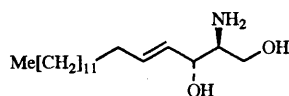
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D-erythro-Sphingosine is synthesized from *N*-benzoyl-*D*-glucosamine **2** in a highly regio- and stereo-controlled manner. The key features in the synthesis involve the efficient conversion of compound **2** into the vinyl epoxide **10** and the subsequent *S_N2'*-type reaction with a Grignard reagent in the presence of CuCN to afford the 1-*O*,2-*N*-protected sphingosine **11**.

Introduction

Sphingosines are long-chain amino alcohols found in the hydrophobic moiety of glycosphingolipids and sphingomyelins. In recent years, a great deal of research has been directed toward better understanding of the biological roles of these cell membrane constituents. These studies have shown that glycosphingolipids are involved in such processes as cell growth, cell-cell recognition and adhesion, oncogenesis, and neuronal repair.² In addition, sphingosine itself was found to be a potent inhibitor of protein kinase C, an essential enzyme in cell regulation and signal transduction.³ Owing to the biological significance as well as the inhomogeneities of sphingolipids in nature, *D*-erythro-*C*₁₈-sphingosine [(2*S*,3*R*,4*E*)-2-amino-octadec-4-ene-1,3-diol] **1**, the most widely occur-



D-erythro-*C*₁₈-sphingosine **1**

ring of the sphingoid bases, has been an important synthetic target. A variety of synthetic approaches to optically active **1** have been developed either by starting from natural chiral pools⁴ such as carbohydrates,⁵⁻⁸ L-serine,⁹ and others,¹⁰ or by using asymmetric reactions.¹¹⁻¹³

We have recently reported^{8b,c} the syntheses of sphingosine derivatives starting from *D*-glucosamine (2-amino-2-deoxy-*D*-glucose), the most abundant and inexpensive amino sugar. In order to introduce the long-chain alkyl group, either Wittig olefination with a non-stabilized ylide or *S_N2* reaction with an organocopper reagent was employed. However, the former 'Wittig strategy'^{8a,b} required two-carbon (C-5, -6) degradation and the subsequent olefination gave predominantly unnatural (4*Z*)-sphingosine derivative. The latter approach^{8c} required multi-(12) steps to sphingosine **1** from *N*-benzoyl-*D*-glucosamine **2**.

Herein we report a convenient stereocontrolled synthesis of sphingosine **1** from the glucosamine **2**, utilizing an *S_N2'*-type reaction of a vinyl epoxide derived from compound **2** with a copper(I)-catalysed Grignard reagent for the key carbon-carbon bond formation.

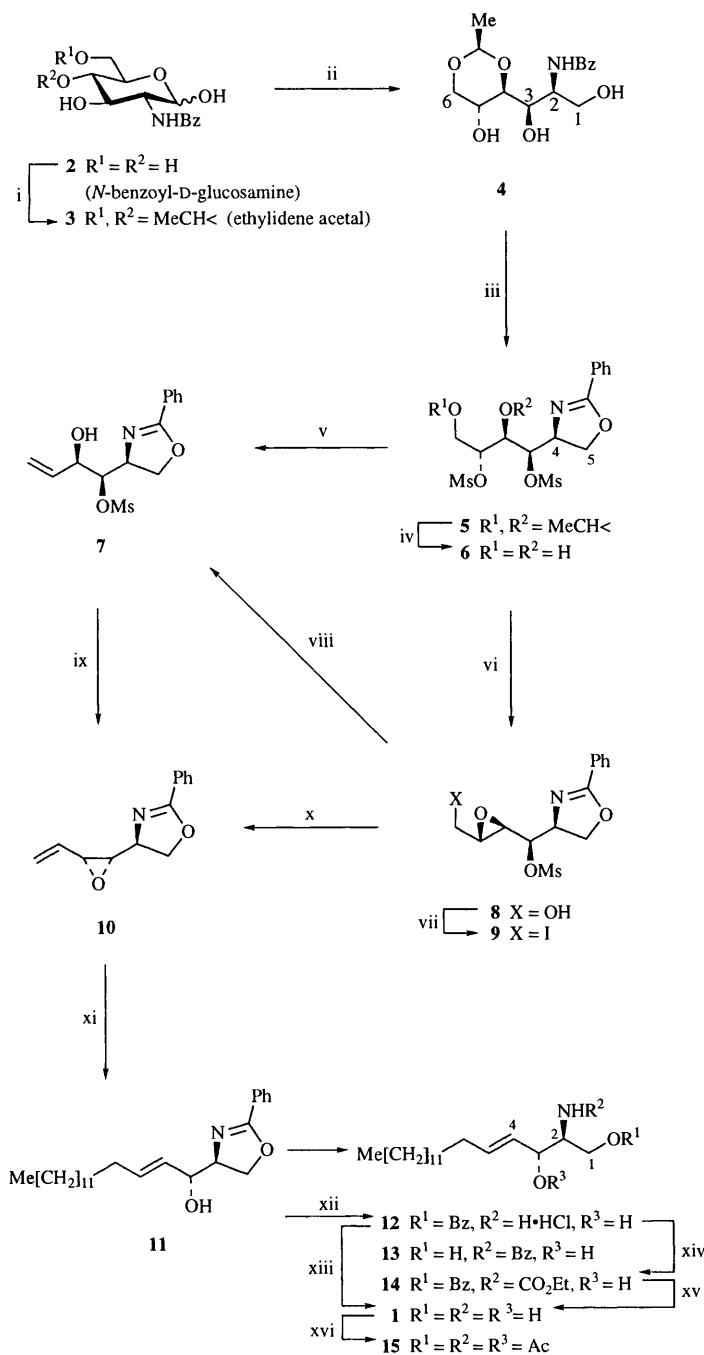
Results and discussion

Our approach is outlined in Scheme 1. Thus, *N*-benzoyl-*D*-glucosamine **2** was treated with paraldehyde in the presence of conc. sulfuric acid¹⁴ to give the 4,6-*O*-ethylidene derivative **3** selectively. The C-1 hemiacetal of compound **3** was reduced

with NaBH₄ in aq. PrⁱOH¹⁵ to give the 1,3,5-triol **4** in high yield. The reduction in MeOH or MeOH-tetrahydrofuran (THF) mixture often stopped before completion, and tedious separation of compounds **3** and **4** was required. Treatment of triol **4** with methanesulfonyl chloride (3.8 mol equiv.) and triethylamine in CH₂Cl₂ at -10 °C immediately gave the 1,3,5-tri-*O*-mesyl ester, whose primary mesyloxy group was readily eliminated at 20 °C to form the 2-phenyl-4,5-dihydrooxazole derivative **5**. The ethylidene acetal group of compound **5** was successfully removed by TiCl₄ and PhSH in CH₂Cl₂ to give the diol **6** as a labile solid.

When the diol **6** (40-100 mg) was treated with iodine (2 mol equiv.) and triphenylphosphine (3 mol equiv.) in the presence of pyridine in toluene¹⁶ at 60-70 °C, its primary hydroxy group was selectively converted into the corresponding iodide, which was reductively eliminated by iodide anion¹⁷ generated *in situ* to afford the terminal olefin **7** in 60-70% yield. This convenient process, however, was not effective for quantities >200 mg, giving compound **7** in only modest (30-50%) yield, presumably due to the instability of diol **6** and heterogeneity of the reaction mixture. Carrying out the reaction in CH₂Cl₂, in which iodine is soluble, did not improve the yield of compound **7** (40-60% yield). On the other hand, treatment of diol **6** with K₂CO₃ in MeOH at 0 °C produced only the 2',3'-*trans*-epoxide **8** as a kinetic product under these conditions.¹⁸ The remaining primary hydroxy group smoothly reacted with iodine and Ph₃P in CH₂Cl₂ at 0-10 °C¹⁹ to give the iodide **9** in 79% yield from **6**. Reductive elimination of the epoxy iodide was achieved by BuLi (3 mol equiv.) at -70 °C²⁰ to give the allylic alcohol **7** in ~70% overall yield from compound **6**. Thus the 3-step conversion (**6** → **8** → **9** → **7**) would be more reliable and suitable for large-scale synthesis than the former one-pot process. Treatment of compound **7** with K₂CO₃ in MeOH afforded the 1',2'-*cis*-epoxide **10** in 93% yield. The lithium alkoxide of **7**, formed *in situ* by the treatment of compound **9** with BuLi, spontaneously cyclized to the epoxide **10**, but the reaction proceeded slowly below 0 °C. In order to avoid side-reactions involving the excess of BuLi, AcOH (0.5 mol equiv. to compound **9**) in PrⁱOH was added to the reaction mixture before it was allowed to warm up.

Vinylepoxides have been reported to react with organocopper reagents to give predominantly *S_N2'*-type γ -alkylation (1,4-addition) products.²¹ Also in our case, the vinyl epoxide **10** smoothly reacted with dodecylmagnesium bromide in the presence of CuCN (10 mol%) in THF at -70 to -50 °C to afford the *S_N2'*-type coupling product **11** in high yield. Its ¹H NMR spectrum showed the characteristic *E*-olefinic proton signals at δ 5.44 (2'-H) and 5.83 (3'-H, *J*_{H2',3'} 15.4 Hz), which were identical with the reported values of the compound



Scheme 1 Reagents and conditions: i, $(CH_3CHO)_3, H_2SO_4$ (12 mol %), room temp., 20 h (94%); ii, $NaBH_4$ (1.4 mol equiv.), Pr^iOH -water (6:1), 0 °C, 1 h (93%); iii, CH_3SO_2Cl (3.8 mol equiv.), Et_3N (10 mol equiv.), CH_2Cl_2 , -10 °C to room temp., 12 h (93%); iv, $TiCl_4$ (3 mol equiv.), $PhSH$ (8 mol equiv.), CH_2Cl_2 , 0 °C, 2 h (83%); v, I_2 (2 mol equiv.), Ph_3P (3 mol equiv.), pyridine (5 mol equiv.), toluene, 65 °C, 1 h; vi, K_2CO_3 (1.3 mol equiv.), $MeOH$, 0–10 °C, 2 h; vii, I_2 (1.8 mol equiv.), Ph_3P (2 mol equiv.), pyridine (5 mol equiv.), CH_2Cl_2 , 0–10 °C, 2 h (79% from 6); viii, Bu^iLi (3 mol equiv.), THF, -70 °C, 15 min; then quench with aq. NH_4Cl (90%); ix, K_2CO_3 (1.5 mol equiv.), $MeOH$, 0 °C to room temp., 5 h (93%); x, $BuLi$ (3 mol equiv.), THF, -70 °C, 15 min; then $AcOH$ (0.5 mol equiv.), Pr^iOH (excess), THF, -60 °C to room temp., 1 h (78%); xi, $C_{12}H_{25}MgBr$ (2 mol equiv.), $CuCN$ (10 mol %), THF, -70 °C, 20 min to -20 °C (94%); xii, 2 mol dm^{-3} aq. HCl -THF (1:9), room temp., 16 h; xiii, 20% $NaOH$ in $MeOH$ -water (1:1), reflux, 30 min, (85% from 11); xiv, $ClCO_2Et$ (1.7 mol equiv.), Et_3N (2.7 mol equiv.), THF, 0 °C; xv, $NaOH$, water-EtOH-THF, 90 °C, 2 h (75% from 11); xvi, Ac_2O , pyridine, DMAP, CH_2Cl_2 (91%) (Bz = $PhCO$; Ms = CH_3SO_2 ; THF = tetrahydrofuran)

synthesized from L-serine.^{9b} The corresponding *Z*-isomer† was not detected by spectroscopic means. By using other copper(I) salts, compound 11 was also obtained without formation of the *Z*-isomer, but in slightly lower yields (CuI: 81%; CuBr: 87%).

Acidic hydrolysis of oxazoline 11 gave 1-*O*-benzoylsphingosine derivative 12 which can be readily converted into ceramides (*N*-acylsphingosines) and galactocerebroside as previously reported.^{9b} The benzoyl group of compound 12 migrated onto the amino group under neutral to basic conditions to give *N*-benzoylsphingosine 13. Removal of the benzoyl group was achieved by treatment of benzoate 12 with 20% $NaOH$ in $MeOH$ -water (1:1) at reflux²² to afford sphingosine 1 in 85% yield from the oxazoline 11. The drastic reaction conditions for the hydrolysis of the benzamide could be avoided by protecting the amino group of compound 12 temporarily by an ethoxycarbonyl group. The resulting carbamate 14 was hydrolysed under milder conditions (~1 mol dm^{-3} $NaOH$ in water-EtOH-THF; 90 °C; 2 h) to afford sphingosine 1. The structure of compound 1 was further confirmed by its conversion into the known *N,O,O*-triacylsphingosine 15, whose physical data were almost identical with those reported.⁵⁻¹³

In summary, *D-erythro*-sphingosine 1 was synthesized from the glucosamine 2 in a remarkably regio- and stereo-controlled manner, by utilizing the participation of the neighbouring functional groups of D-glucosamine. This approach will provide natural sphingosines and sphingolipids in gram quantities.

Experimental

Mps were determined with a Yanagimoto melting point apparatus and are uncorrected. Optical rotations were measured with a JASCO DIP-140 polarimeter and $[\alpha]_D$ -values are given in 10^{-1} deg cm^2 g^{-1} . 1H and ^{13}C NMR spectra were measured for solutions in $CDCl_3$ unless otherwise specified and chemical shifts (δ_H , δ_C) are given in parts per million (ppm) downfield relative to internal tetramethylsilane (TMS). 1H NMR spectra were recorded at 360 MHz on a Nicolet NT-360 spectrometer and *J*-values are given in Hz. ^{13}C NMR spectra were recorded at 67.8 MHz on a JEOL JNM-GSX-270 spectrometer. IR spectra were measured for samples as KBr pellets with a Perkin-Elmer paragon 1000 FT-IR spectrometer. Elemental analyses were performed by the analytical centre in this Institute (NIMC). High-resolution mass spectra (HRMS) were obtained on a Hitachi M-80B mass spectrometer. TLC was performed on Merck pre-coated silica gel 60F₂₅₄ plates. Column chromatography was performed on silica gel (Wako gel C-200). Organic solutions after extractive work-up were dried over Na_2SO_4 , filtered through a cotton plug, and evaporated under reduced pressure. Dodecylmagnesium bromide (1.0 mol dm^{-3} solution in diethyl ether) was purchased from Aldrich Chemical Co.

N-Benzoyl-4,6-*O*-ethylidene-D-glucosamine 3

To an ice-cooled, stirred suspension of 2-benzamido-2-deoxy-D-glucose 2 (4.0 g, 14.1 mmol) in paraldehyde (40 cm^3 , containing max. 20% acetaldehyde) was added conc. sulfuric acid (0.1 cm^3 , 1.8 mmol). The mixture was stirred for 20 h at room temperature, and was then neutralized with Et_3N (1 cm^3) and diluted with Et_2O (40 cm^3). The precipitate was filtered off, and washed thoroughly with Et_2O and dried *in vacuo* to give the acetal 3 (4.10 g, 94%) as a solid, mp 225–228 °C (decomp.) (needles from $AcOEt$ - $MeOH$) (Found: C, 58.0; H, 6.1; N, 4.5. $C_{15}H_{19}NO_6$ requires C, 58.25; H, 6.2; N, 4.5%); R_f 0.50 ($AcOEt$); δ_H ($CDCl_3$ - CD_3OD , α -anomer predominant) 1.39 (3 H, d, *J* 5.0, $CHCH_3$), 3.40 (1 H, t, *J* 9.5, 6- H^a), 3.57 (1 H, t, *J* 10.2, 4-H), 3.95 (1 H, dt, *J* 4.8 and 9.5, 5-H), 3.97 (1 H, t, *J* 9.8,

† The *Z*-isomer of 11 was alternatively synthesized from compound 3 via 2-*N*,3-*O*-protected (*Z*)-sphingosine as previously reported.^{8b} Although both isomers had almost the same R_f -values on TLC [R_f 0.28 [hexane- $AcOEt$ (3:1)]], the *Z*-olefinic proton signals [δ_H 5.39 (2'-H) and 5.63 (3'-H) $J_{2',3'}$ 10.9] were not detected in the 1H NMR spectrum of the coupling product after chromatographic purification.

3-H), 4.09 (1 H, dd, J 4.8 and 9.5, 6-H^{eq}), 4.22 (1 H, dd, J 3.7 and 10.1, 2-H), 4.80 (1 H, q, J 5.0, CHCH₃), 5.25 (1 H, d, J 3.6, 1-H), 7.30 (1 H, d, J 8.4, NH), 7.44 (2 H, m, Ph), 7.51 (1 H, m, Ph) and 7.83 (2 H, m, Ph); $\nu_{\max}/\text{cm}^{-1}$ 3417, 3270, 2994, 2932, 2865, 1632, 1547, 1380, 1329, 1129, 1031, 976 and 691.

2-Benzamido-2-deoxy-4,6-O-ethylidene-D-glucitol 4

To an ice-cooled solution of compound **3** (930 mg, 3.0 mmol) in a mixture of PrⁱOH (24 cm³) and water (4 cm³) was added NaBH₄ (180 mg, 4.7 mmol) in several portions. The ice-cooled reaction mixture was stirred for 1 h and was then quenched with 1 mol dm⁻³ aq. HCl (3 cm³). Evaporation off of the solvent under reduced pressure gave a solid, which was dissolved in a minimum quantity of CH₂Cl₂-MeOH mixture and subjected to column chromatography with CH₂Cl₂-MeOH (7:1, then 5:1) to give the *triol* **4** (870 mg, 93%) as a solid, mp 165–167 °C (needles from AcOEt-MeOH) (Found: C, 57.6; H, 6.5; N, 4.5. C₁₅H₂₁NO₆ requires C, 57.9; H, 6.8; N, 4.5%); R_f 0.35 [CH₂Cl₂-MeOH (7:1)]; $[\alpha]_D^{23} -13.3$ [c 1.0, CHCl₃-MeOH (1:1)]; δ_H (CDCl₃-CD₃OD) 1.17 (3 H, d, J 4.9, CHCH₃), 3.39 (1 H, t, J 10.8, 6-H^{ax}), 3.48 (1 H, dd, J 1.5 and 9.3, 4-H), 3.76–3.81 (3 H, m, 1-H₂ and 5-H), 4.11 (1 H, dd, J 5.3 and 10.8, 6-H^{eq}), 4.22 (1 H, m, 3-H), 4.29 (1 H, m, 2-H), 4.65 (1 H, q, J 4.9, CHCH₃), 7.44 (2 H, m, Ph), 7.51 (1 H, m, Ph) and 7.82 (2 H, m, Ph); δ_C (CDCl₃-CD₃OD) 20.1 (CH₃), 54.3 (C-2), 60.9, 61.8, 67.0, 70.6, 82.1, 98.8 (CHCH₃), 127.0, 128.3, 131.6, 133.8 and 168.7 (C=O); $\nu_{\max}/\text{cm}^{-1}$ 3354, 2855, 1632, 1556, 1411, 1307, 1162, 1078, 1043, 848 and 723.

(4S,1'R,2'S,3'R,1''R)-4-[2',4'-(Ethane-1,1-diylidioxy)-1',3'-bis(methylsulfonyloxy)butyl]-2-phenyl-4,5-dihydrooxazole 5

A solution of methanesulfonyl chloride (870 mg, 7.5 mmol) in CH₂Cl₂ (5 cm³) was added dropwise to a stirred solution of the *triol* **4** (620 mg, 2.0 mmol) and Et₃N (2.5 cm³, 17.3 mmol) in CH₂Cl₂ (10 cm³) at -15 °C (under nitrogen) over a period of 10 min. After being stirred for 2 h in an ice-bath, the mixture was allowed to warm to room temperature and the resulting yellow-orange solution was stirred for an additional 12 h. To this solution were added CH₂Cl₂ (30 cm³) and cold aq. NaHCO₃ (20 cm³), and the layers were separated. The aqueous phase was extracted with CH₂Cl₂ (2 × 20 cm³) and the combined organic layers were successively washed with water and brine, and then dried. Evaporation off of the solvent gave an orange solid (~1 g), which was purified by column chromatography with CH₂Cl₂-AcOEt (3:1) as eluent to give the *oxazoline* **5** (840 mg, 93%), mp 161–164 °C (decomp.) (colourless needles from AcOEt-hexane) (Found: C, 45.5; H, 4.9; N, 3.1; S, 14.2. C₁₇H₂₃NO₉S₂ requires C, 45.4; H, 5.15; N, 3.1; S, 14.3%); R_f 0.42 [hexane-AcOEt (1:1)]; $[\alpha]_D^{23} -19.8$ (c 0.65, CHCl₃); δ_H 1.30 (3 H, d, J 5.0, CH₃CH), 3.13 (3 H, s, CH₃SO₂), 3.34 (3 H, s, CH₃SO₂), 3.63 (1 H, dd, J 10.3 and 10.8, 4'-H^{ax}), 3.90 (1 H, dd, J 2.2 and 9.6, 2'-H), 4.48–4.56 (4 H, m, 5-H₂, 4'-H^{eq} and CHCH₃), 4.85 (1 H, dt, J 5.3 and 9.7, 3'-H), 4.93 (1 H, dt, J 2.2 and 7.1, 4-H), 5.05 (1 H, dd, J 2.2 and 7.1, 1'-H), 7.43 (2 H, m, Ph), 7.52 (1 H, m, Ph) and 7.92 (2 H, m, Ph); δ_C 20.0, 38.7 (CH₃SO₂), 39.0 (CH₃SO₂), 66.6, 67.6, 68.9, 76.4, 77.6, 99.7, 127.1, 128.3, 128.5, 131.9 and 166.0 (C=N); $\nu_{\max}/\text{cm}^{-1}$ 3033, 2871, 1650, 1453, 1414, 1347, 1254, 1177, 1114, 982, 948, 848 and 700.

(2'R,3'S,4'R,4S)-2',4'-Bis(methylsulfonyloxy)-4'-(2-phenyl-4,5-dihydrooxazol-4-yl)butane-1',3'-diol 6

To an ice-cooled solution of compound **5** (360 mg, 0.8 mmol) and thiophenol (0.7 cm³, 6.8 mmol) in CH₂Cl₂ (8 cm³) under nitrogen was added dropwise a 1.0 mol dm⁻³ solution of TiCl₄ in CH₂Cl₂ (2.4 cm³, 2.4 mmol) over a period of 10 min, and the mixture was stirred for 2 h at 0 °C. The resulting brown suspension was diluted with CHCl₃ (5 cm³) and quenched by the addition of a cooled solution of saturated aq. NaHCO₃ (10

cm³) while being vigorously stirred. The mixture was poured into a separatory funnel containing CHCl₃ (5 cm³), MeOH (2 cm³) and dilute aq. NaHCO₃ (10 cm³), and the organic layer was extracted. The aqueous phase was extracted with an azeotropic mixture of CHCl₃-MeOH (87:13) (3 × 20 cm³). The combined organic layers were dried and evaporated to give a pale-yellow solid, which was triturated and washed thoroughly with hexane-AcOEt (4:1) (40 cm³) to afford the *diol* **6** (280 mg, 83%) as a solid. This compound **6** was used in the next step without further purification since it decomposed upon heating in AcOEt-MeOH at 60 °C for recrystallization; mp > 150 °C (decomp.); R_f 0.62 (AcOEt); δ_H (CDCl₃-CD₃OD) 3.20 (3 H, s, CH₃SO₂), 3.26 (3 H, s, CH₃SO₂), 3.99 (1 H, dd, J 3.9 and 13.0, 1'-H^a), 4.12 (1 H, dd, J 3.6 and 13.0, 1'-H^b), 4.29 (1 H, dd, J 2.5 and 6.8, 3'-H), 4.57 (1 H, d, J 2.4, 5-H^a), 4.59 (1 H, s, 5-H^b), 4.76–4.82 (2 H, m, 4- and 2'-H), 4.99 (1 H, dd, J 2.7 and 4.4, 4'-H), 7.43 (2 H, m, Ph), 7.52 (1 H, m, Ph) and 7.91 (2 H, m, Ph); $\nu_{\max}/\text{cm}^{-1}$ 3320, 1650, 1342, 1173, 1086, 990, 950 and 697.

(1'R,2'R,4S)-1'-Methylsulfonyloxy-1'-(2-phenyl-4,5-dihydrooxazol-4-yl)but-3-en-2'-ol 7

To a stirred solution of compound **6** (85 mg, 0.2 mmol), triphenylphosphine (160 mg, 0.6 mmol) and pyridine (0.1 cm³, 1.2 mmol) in toluene (6 cm³) under nitrogen was added iodine (102 mg, 0.4 mmol) in three portions at room temperature, and the mixture was stirred at 60–70 °C for 1 h. After being cooled to room temperature, the resulting brown slurry was diluted with AcOEt (10 cm³), and treated with 5% aq. Na₂S₂O₃ (10 cm³) and vigorously stirred to give a colourless organic layer. The layers were separated and the aqueous layer was extracted with AcOEt (2 × 10 cm³). The combined organic extracts were successively washed with water and brine, and dried. Evaporation of the mixture gave a yellow solid, which was chromatographed on silica gel with hexane-AcOEt (3:2) as eluent to give the *allylic alcohol* **7** (41 mg, 66%), mp 130–132 °C (needles from hexane-AcOEt) (Found: C, 54.2; H, 5.4; N, 4.5; S, 10.3%; M⁺, 311.0825. C₁₄H₁₇NO₅S requires C, 54.0; H, 5.5; N, 4.5; S, 10.3%; M, 311.0826); R_f 0.38 [hexane-AcOEt (1:1)]; $[\alpha]_D^{26} +35.1$ (c 0.90, CHCl₃); δ_H 3.14 (3 H, s, CH₃SO₂), 3.90 (1 H, broad, OH), 4.53 (2 H, m, 5-H₂), 4.67 (2 H, m, 4- and 2'-H), 4.76 (1 H, t, J 3.8, 1'-H), 5.36 (1 H, dt, J 1.4 and 10.5, 4'-H^a), 5.56 (1 H, dt, J 1.5 and 17.1, 4'-H^b), 6.02 (1 H, ddd, J 5.2, 10.6 and 17.1, 3'-H), 7.41 (2 H, m, Ph), 7.50 (1 H, m, Ph) and 7.93 (2 H, m, Ph); δ_C 39.0, 68.0, 69.1, 72.9, 83.9 (C-1'), 117.9 (C-4'), 126.8, 128.4, 128.5, 131.9, 136.0 (C-3') and 165.9; $\nu_{\max}/\text{cm}^{-1}$ 3240, 1642, 1454, 1372, 1347, 1256, 1172, 1071, 958, 918, 901, 854, 783 and 703.

(2'S,3'R,4'R,4S)-2',3'-Epoxy-4'-(methylsulfonyloxy)-4'-(2-phenyl-4,5-dihydrooxazol-4-yl)butan-1'-ol 8

K₂CO₃ (180 mg, 1.3 mmol) was added to a stirred, ice-cooled solution of compound **6** (425 mg, 1.0 mmol) in MeOH (12 cm³) and the mixture was stirred for 2 h at 5–10 °C. To this suspension was added saturated aq. NH₄Cl (3 cm³), followed by AcOEt (30 cm³) and half-saturated brine (20 cm³). The layers were separated and the aqueous layer was extracted with AcOEt (2 × 20 cm³). The combined organic layers were washed successively with water and brine (20 cm³ each), dried, and concentrated under reduced pressure to give crude epoxide **8** as a foam (316 mg, 97%), which could be used in the next reaction without further purification. An analytical sample of the *epoxide* **8** was obtained as colourless plates by recrystallization from hexane-AcOEt, mp 130–132 °C (Found: C, 51.4; H, 5.0; N, 4.3; S, 10.0. C₁₄H₁₇NO₆S requires C, 51.4; H, 5.2; N, 4.3; S, 9.8%); R_f 0.40 (AcOEt); δ_H 2.96 (1 H, br s, OH), 3.19 (3 H, s, CH₃SO₂), 3.24 (1 H, m, 2'-H), 3.50 (1 H, dd, J 2.1 and 7.5, 3'-H), 3.65 (1 H, dd, J 3.8 and 12.9, 1'-H^a), 3.78 (1 H, dd, J 3.2 and 12.8, 1'-H^b), 4.47 (1 H, dd, J 3.6 and 7.6, 4'-H), 4.51 (1 H, dd, J 9.0 and 10.1, 5-H^a), 4.56 (1 H, dd, J 6.4 and 9.0, 5-H^b), 4.66 (1 H, ddd, J 3.8, 6.3 and 10.1, 4-H), 7.42 (2 H, m, Ph), 7.52 (1 H,

m, Ph) and 7.93 (2 H, m, Ph); δ_C 38.8, 54.0, 56.8, 60.7, 67.6, 68.5, 83.5, 126.6, 128.48, 128.55, 132.2 and 166.7; $\nu_{\max}/\text{cm}^{-1}$ 3476, 2934, 1650, 1579, 1453, 1359, 1169, 1093, 1073, 934, 851, 790 and 709.

(4S,1'R,2'R,3'R)-4-[2',3'-Epoxy-4'-iodo-1'-(methylsulfonyloxy)butyl]-2-phenyl-4,5-dihydrooxazole 9

To an ice-cooled solution of crude epoxide **8** (266 mg, 0.81 mmol), triphenylphosphine (420 mg, 1.60 mmol) and pyridine (0.4 cm³, 4.95 mmol) in CH₂Cl₂ (12 cm³) under nitrogen was added iodine (380 mg, 1.50 mmol) in five portions, and the resulting yellow suspension was stirred at 5–10 °C for 2 h. The mixture was diluted with AcOEt (40 cm³), and treated with 5% aq. Na₂S₂O₃ (30 cm³) while being vigorously stirred. The layers were separated and the aqueous layer was extracted with AcOEt (2 × 30 cm³). The combined organic extracts were successively washed with water and brine, and dried. Filtration, and evaporation off of the solvent, gave a yellow residue (850 mg), which was subjected to column chromatography with hexane–AcOEt (2:1) to give the *iodide* **9** (290 mg, 79% from diol **6**) as a solid, mp 109–111 °C (needles from hexane–AcOEt) (Found: C, 38.5; H, 3.8; N, 3.2; S, 7.3; I, 28.8. C₁₄H₁₆INO₅S requires C, 38.5; H, 3.7; N, 3.2; S, 7.3; I, 29.0%); R_f 0.37 [hexane–AcOEt (2:1)]; $[\alpha]_D^{25} + 62.8$ (*c* 1.0, CHCl₃); δ_H 3.10 (1 H, dd, *J* 6.0 and 10.1, 4'-H^a), 3.16 (1 H, dd, *J* 6.4 and 10.4, 4'-H^b), 3.18 (3 H, s, CH₃SO₂), 3.37 (1 H, dt, *J* 1.9 and 6.2, 3'-H), 3.44 (1 H, dd, *J* 1.9 and 7.3, 2'-H), 4.48 (1 H, dd, *J* 3.9 and 7.3, 1'-H), 4.52 (2 H, d, *J* 8.5, 5-H₂), 4.67 (1 H, dt, *J* 3.9 and 8.5, 4-H), 7.43 (2 H, m, Ph), 7.52 (1 H, m, Ph) and 7.96 (2 H, m, Ph); δ_C 2.4 (C-4'), 38.9, 57.1, 60.2, 67.9, 68.4, 82.7, 127.0, 128.5, 128.6, 132.0 and 166.3; $\nu_{\max}/\text{cm}^{-1}$ 1656, 1341, 1178, 1086, 977, 925 and 698.

(4S,1'S,2'R)-4-(1',2'-Epoxybut-3'-enyl)-2-phenyl-4,5-dihydrooxazole 10

K₂CO₃ (55 mg, 0.40 mmol) was added to a stirred, ice-cooled suspension of allylic alcohol **7** (84 mg, 0.27 mmol) in MeOH (3 cm³). The mixture was stirred for 30 min at 0 °C and then for 5 h at room temperature. To this suspension was added saturated aq. NH₄Cl (1 cm³), followed by AcOEt (10 cm³) and half-saturated brine (10 cm³). The layers were separated and the aqueous layer was extracted with AcOEt (2 × 10 cm³). The combined organic layers were washed successively with water and brine (10 cm³ each), dried, and concentrated under reduced pressure to give a pale yellow oil. Purification by chromatography with hexane–AcOEt (5:2) as eluent afforded the *vinyl epoxide* **10** (54 mg, 93%) as a solid, mp 38–40 °C; R_f 0.34 [hexane–AcOEt (3:1)]; $[\alpha]_D^{26} + 159.6$ (*c* 0.67, CHCl₃); δ_H 3.15 (1 H, dd, *J* 4.1 and 8.3, 1'-H), 3.63 (1 H, dd, *J* 4.2 and 6.3, 2'-H), 4.19 (1 H, dt, *J* 7.8 and 9.6, 4-H), 4.53 (2 H, m, 5-H₂), 5.46 (1 H, dt, *J* 1.4 and 10.5, 4'-H^a), 5.55 (1 H, dt, *J* 1.0 and 17.1, 4'-H^b), 5.93 (1 H, ddd, *J* 6.4, 10.6 and 17.1, 3'-H), 7.41 (2 H, m, Ph), 7.50 (1 H, m, Ph) and 7.96 (2 H, m, Ph); δ_C 57.5, 60.5, 64.3, 71.2 (C-5), 121.1 (C-4'), 127.2, 128.3(6), 128.4(5), 131.4, 131.7 and 165.7; $\nu_{\max}/\text{cm}^{-1}$ 1643, 1580, 1452, 1367, 1294, 1084, 1027, 965, 944, 818 and 687 (Found: M⁺, 215.0932. C₁₃H₁₃NO₂ requires M, 215.0946).

Alkene 10 from iodide 9

A 1.5 mol dm⁻³ solution of BuLi in hexane (1.3 cm³, 1.95 mmol) was added dropwise over a period of 5 min to a stirred solution of iodide **9** (280 mg, 0.64 mmol) in THF (6 cm³) at –70 °C under nitrogen. After 10 min, a solution of AcOH (20 mg, 0.33 mmol) in PrⁱOH (0.5 cm³) was added at –70 °C; the mixture was allowed to warm to room temperature, and was then stirred for an additional 1 h. To the reaction mixture was added saturated aq. NH₄Cl (1 cm³), followed by AcOEt (10 cm³) and water (10 cm³). The layers were separated and the aqueous layer was extracted with AcOEt (2 × 10 cm³). The combined organic layers were treated as described above to give the vinyl epoxide **10** (107 mg, 78%) as a solid.

(1'R,2'E,4S)-1'-(2-Phenyl-4,5-dihydrooxazol-4-yl)hexadec-2'-en-1'-ol 11

To a mixture of the vinyl epoxide **10** (43 mg, 0.20 mmol) and CuCN (2 mg, 0.02 mmol) under nitrogen was added dry THF (4 cm³), and the resulting suspension was stirred and cooled to –70 °C. To this was added dropwise a 1.0 mol dm⁻³ solution of dodecylmagnesium bromide in diethyl ether (0.4 cm³, 0.4 mmol) over a period of 5 min, and the resulting pale yellow solution was stirred at –70 to –50 °C for 30 min and was then allowed to warm. At ~ –20 °C this solution was treated with saturated aq. NH₄Cl (2 cm³), followed by AcOEt (15 cm³) and water (5 cm³). The layers were separated and the aqueous phase was extracted with AcOEt (2 × 15 cm³). The organic layer was washed successively with water and brine, dried and evaporated. The residue was chromatographed on a column with hexane–AcOEt (7:2) as eluent to afford the *2'E-olefin* **11** (72 mg, 93.5%) as a solid, mp 91–93 °C (colourless needles from hexane–AcOEt) (lit.,^{9b} 89–90 °C) (Found: C, 77.8; H, 10.4; N, 3.6. C₂₅H₃₉NO₂ requires C, 77.9; H, 10.2; N, 3.6%); R_f 0.28 [hexane–AcOEt (3:1)]; $[\alpha]_D^{26} - 1.8$ (*c* 1.0, CHCl₃); δ_H 0.88 (3 H, t, *J* 6.7, 16'-H₃), 1.26 (20 H, s-like, 6'- to 15'-H₂), 1.38 (2 H, m, 5'-H₂), 2.06 (2 H, q, *J* 6.9, 4'-H₂), 4.38 (3 H, m, 4-H and 5-H₂), 4.55 (1 H, d-like, *J* 4.9, 1'-H), 5.44 (1 H, dd, *J* 5.6 and 15.4, 2'-H), 5.83 (1 H, dt, *J* 6.9 and 15.4, 3'-H), 7.36 (2 H, m, Ph), 7.45 (1 H, m, Ph) and 7.86 (2 H, m, Ph); δ_C 14.1, 22.7, 29.2, 29.4, 29.5, 29.7, 31.9, 32.4, 67.5, 71.3, 71.6, 127.1, 128.1, 128.2, 131.3, 133.2 and 165.6; $\nu_{\max}/\text{cm}^{-1}$ 3160, 2919, 2850, 1650, 1469, 1366, 1108, 968 and 693.

N-Benzoyl-D-erythro-C₁₈-sphingosine 13

To a stirred solution of compound **11** (68 mg, 0.175 mmol) in THF (3.6 cm³) was added 2 mol dm⁻³ aq. HCl (0.4 cm³) and the mixture was stirred for 16 h at room temperature. Then, cooled in an ice-bath, the mixture was treated with aq. NaOH (80 mg, 2.0 mmol in 2 cm³) dropwise, and the mixture was stirred at 0 °C for 30 min and then at room temperature for 2 h. The reaction mixture was neutralized with 1 mol dm⁻³ aq. HCl, and extracted with AcOEt (3 × 10 cm³). The combined organic layers were dried and concentrated to give a solid, which was purified by chromatography with hexane–AcOEt (1:2) to give *N-benzoylsphingosine* **13** (60 mg, 84%) as a colourless solid, mp 89–91 °C (needles from hexane–CHCl₃) (Found: C, 74.5; H, 10.2; N, 3.4. C₂₅H₄₁NO₃ requires C, 74.4; H, 10.2; N, 3.5%); R_f 0.30 [hexane–AcOEt (1:2)]; δ_H 0.88 (3 H, t, *J* 6.8, 18-H₃), 1.25 (20 H, s-like, 8- to 17-H₂), 1.31 (2 H, m, 7-H₂), 2.06 (2 H, q, *J* 7.0, 6-H₂), 3.00 (2 H, br s, OH), 3.80 (1 H, dd, *J* 3.2 and 11.2, 1-H^a), 4.05 (1 H, dd, *J* 3.9 and 11.3, 1-H^b), 4.10 (1 H, dq, *J* 3.9 and 7.8, 2-H), 4.44 (1 H, t-like, *J* 5.0, 3-H), 5.58 (1 H, dd, *J* 6.3 and 15.4, 4-H), 5.82 (1 H, dt, *J* 7.2 and 15.3, 5-H), 7.02 (1 H, d, *J* 7.3, NH), 7.43 (2 H, m, Ph), 7.51 (1 H, m, Ph) and 7.80 (2 H, m, Ph); δ_C 14.1, 22.7, 29.2, 29.3, 29.4, 29.5, 29.6, 29.68, 29.70, 31.9, 32.3, 55.0, 62.2, 74.3, 127.1, 128.6, 128.8, 131.7, 134.1, 134.2 and 168.1; $\nu_{\max}/\text{cm}^{-1}$ 3330, 2918, 2849, 1621, 1537, 1462, 1315, 1103, 1053, 980 and 718.

D-erythro-C₁₈-Sphingosine[(2S,3R,4E)-2-aminooctadec-4-ene-1,3-diol] 1

To a stirred solution of compound **11** (77 mg, 0.20 mmol) in THF (3.6 cm³) was added 2 mol dm⁻³ aq. HCl (0.4 cm³) and the mixture was stirred for 16 h at room temperature. To this solution were added CHCl₃–MeOH (87:13) (20 cm³) and water (10 cm³). The layers were separated and the aqueous phase was extracted with an azeotropic mixture of CHCl₃–MeOH (87:13) (2 × 10 cm³). The combined organic extracts were dried, and concentrated under reduced pressure to give *1-O-benzoylsphingosine hydrochloride* **12** (81 mg) as a solid.

To a solution of the crude salt **12** in MeOH (0.5 cm³) was added aq. NaOH (200 mg, 5.0 mmol in 0.4 cm³), and the mixture was heated at 100 °C for 30 min. The cooled reaction mixture was diluted with water (10 cm³) and extracted with

Et₂O (3 × 10 cm³). The organic layer was dried and concentrated to give a solid, which was subjected to column chromatography, with CH₂Cl₂-MeOH (9:1), then with CH₂Cl₂-MeOH-2 mol dm⁻³ aq. NH₄OH (40:10:1) as eluent, to afford **sphingosine 1** (51 mg, 85%) as a waxy, air-sensitive solid, mp 70–74 °C (lit., 68–72.^{8a} 72–75.^{9c,f} and 81–82 °C^{12b}), *R*_f 0.36 [CH₂Cl₂-MeOH-2 mol dm⁻³ aq. NH₄OH (40:10:1)]; [α]_D²⁴ -1.2 (c 1.0, CHCl₃) {lit., [α]_D²¹ -1.3 (c 3.5, CHCl₃),^{9c} [α]_D -0.58 (c 1.67, CHCl₃)^{9f} and [α]_D²⁴ -2.8 (CHCl₃)^{12b}}; δ_H 0.88 (3 H, t, *J* 6.8, 18-H₃), 1.25 (20 H, s-like, 8- to 17-H₂), 1.36 (2 H, m, 7-H₂), 2.06 (2 H, q, *J* 6.8, 6-H₂), 2.87 (1 H, m, 2-H), 3.67 (2 H, m, 1-H₂), 4.07 (1 H, m, 3-H), 5.45 (1 H, dd, *J* 6.9 and 15.0, 4-H) and 5.75 (1 H, dt, *J* 7.5 and 15.0, 5-H); δ_C 14.1 (C-18), 22.7, 29.3, 29.4, 29.6, 29.69, 29.73, 32.0, 32.4, 56.3 (br, C-2), 63.1 (br, C-1), 74.7 (br, C-3), 129.0 (C-4) and 134.6 (C-5); ν_{max}/cm⁻¹ 3366, 3250, 2919, 2850, 1586, 1469, 1047, 1032, 970 and 720 [Found: (M + H)⁺, 300.2938. C₁₈H₃₈NO₂ requires *m/z*, 300.2904].

Sphingosine 1 from the oxazoline 11 via the carbamate 14

Compound **11** (58 mg, 0.15 mmol) was converted into compound **12** in a similar manner to that described above. The resulting crude salt **12** was dissolved in THF (3 cm³) and treated with ethyl chloroformate (28 mg, 0.25 mmol), followed by Et₃N (40 mg, 0.40 mmol) in THF (0.5 cm³) at 0 °C. After 10 min, aq. NaOH (120 mg, 3.0 mmol in 1.0 cm³)-EtOH (1.0 cm³) was added at 0 °C, and the mixture was heated at 90 °C for 2 h. The cooled reaction mixture was diluted with water (10 cm³) and extracted with Et₂O (3 × 10 cm³). The combined extracts were treated as described above to give sphingosine **1** (34 mg, 75%).

N,O,O-Triacetyl-D-erythro-C₁₈-sphingosine 15

To an ice-cooled solution of sphingosine **1** (21 mg, 0.07 mmol) in CH₂Cl₂ (2 cm³) was added pyridine (0.1 cm³) followed by acetic anhydride (0.1 cm³), and the mixture was stirred at room temperature. After 2 h, 4-(dimethylamino)pyridine (DMAP) (2 mg) was added to the mixture to complete the acetylation. After extractive work-up, the organic layer was dried and concentrated to give a solid, which was purified by chromatography to afford **triacetylsphingosine 15** (27 mg, 91%) as a solid, mp 105–106 °C (lit., 105–106,⁶ 103.5–104.5^{8a,9b} and 104.5–105 °C^{9e}) (Found: C, 67.7; H, 10.4; N, 3.3. C₂₄H₄₃NO₅ requires C, 67.7; H, 10.2; N, 3.35%); *R*_f 0.25 [hexane-AcOEt (1:2)]; [α]_D²⁴ -12.9 (c 1.0, CHCl₃) {lit., [α]_D²⁵ -12.9 (c 1.0, CHCl₃),^{9e} [α]_D -13.0 (c 1.08, CHCl₃)^{9f} and [α]_D²⁵ -12.8 (c 1, CHCl₃)^{12a}}; δ_H 0.88 (3 H, t, *J* 6.8, 18-H₃), 1.25 (20 H, s-like, 8- to 17-H₂), 1.33 (2 H, m, 7-H₂), 1.98, 2.06 and 2.07 (each 3 H, each s, Ac), 2.02 (2 H, m, 6-H₂), 4.04 (1 H, dd, *J* 3.9 and 11.6, 1-H^a), 4.30 (1 H, dd, *J* 6.0 and 11.6, 1-H^b), 4.43 (1 H, m, 2-H), 5.28 (1 H, t-like, *J* 6.7, 3-H), 5.39 (1 H, dd, *J* 7.4 and 15.3, 4-H), 5.70 (1 H, d, *J* 9.1, NH) and 5.79 (1 H, dt, *J* 6.8 and 15.3, 5-H); ν_{max}/cm⁻¹ 3287, 2921, 2851, 1737, 1658, 1555, 1374, 1268 and 1233.

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