Efficient stereocontrolled synthesis of D-*erythro*-sphingosine from *N*-benzoyl-D-glucosamine [1]

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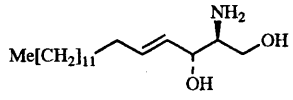
D-*erythro*-Sphingosine is synthesized from *N*-benzoyl-D-glucosamine 2 in a highly regio- and stereo-controlled manner. The key features in the synthesis involve the efficient conversion of compound 2 into the vinyl epoxide 10 and the subsequent S_N2'-type reaction with a Grignard reagent in the presence 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-aminooctadec-4-ene-1,3-diol] **1**, the most widely occurring 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 pools[4] such as carbohydrates,[5–8] L-serine,[9] and others,[10] or by using asymmetric reactions.[11–13]



D-*erythro*-C_{18}-sphingosine **1**

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**.

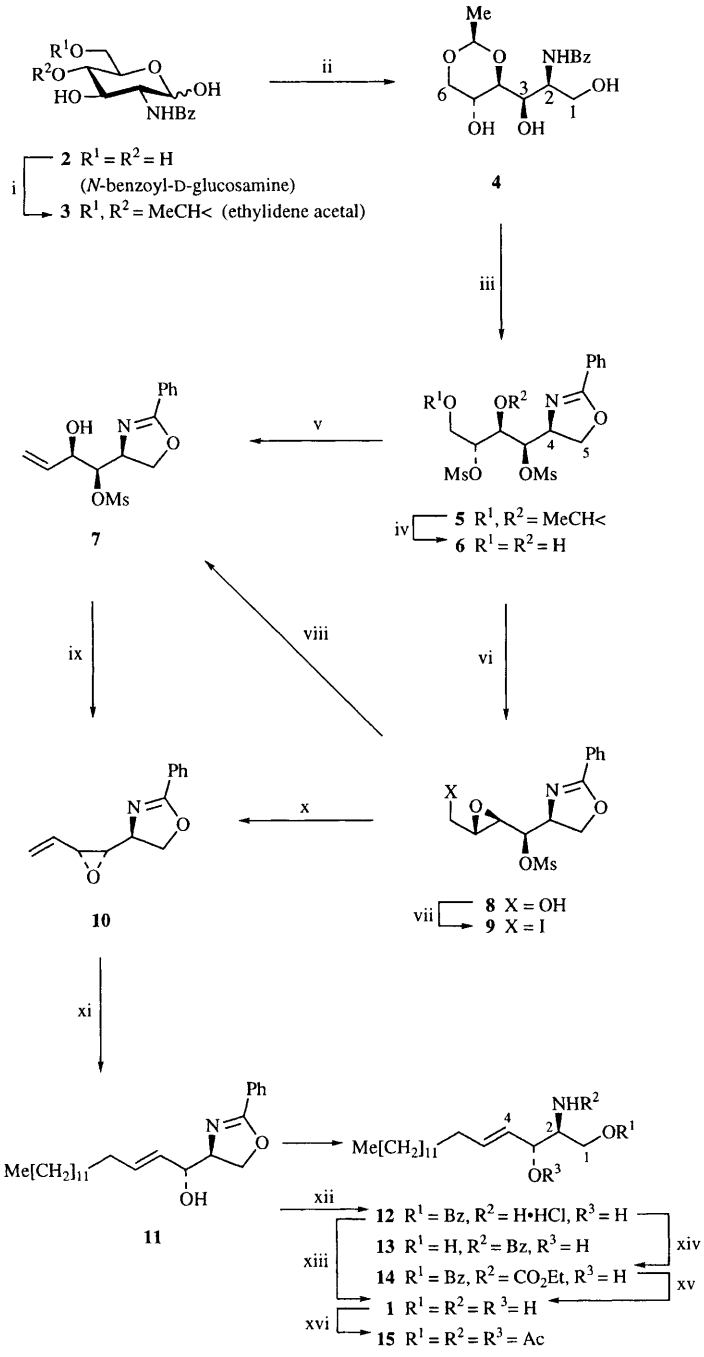
Herein we report a convenient stereocontrolled synthesis of sphingosine **1** from the glucosamine **2**, utilizing an S_N2'-type reaction of a vinyl epoxide derived from compound **2** with a copper(I)-catalysed Grignard reagent for the key carbon–carbon bond formation.

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 acid[14] to give the 4,6-*O*-ethylidene derivative **3** selectively. The C-1 hemiacetal of compound **3** was reduced with $NaBH_4$ in aq. Pr^iOH[15] 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 CH_2Cl_2 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 $TiCl_4$ and PhSH in CH_2Cl_2 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 toluene[16] at 60–70 °C, its primary hydroxy group was selectively converted into the corresponding iodide, which was reductively eliminated by iodide anion[17] 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 CH_2Cl_2, 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 K_2CO_3 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 Ph_3P in CH_2Cl_2 at 0–10 °C[19] 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 °C[20] 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 K_2CO_3 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 Pr^iOH was added to the reaction mixture before it was allowed to warm up.

Vinyl epoxides 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^nLi (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 reflux[22] 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*-triacetylsphingosine **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 $60F_{254}$ 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^{ax}), 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, C*H*CH$_3$), 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); ν_{max}/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 Pr^{i}OH (24 cm^3) and water (4 cm^3) was added $NaBH_4$ (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 cm^3). Evaporation off of the solvent under reduced pressure gave a solid, which was dissolved in a minimum quantity of CH_2Cl_2–MeOH mixture and subjected to column chromatography with CH_2Cl_2–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. $C_{15}H_{21}NO_6$ requires C, 57.9; H, 6.8; N, 4.5%); R_f 0.35 [CH_2Cl_2–MeOH (7:1)]; $[\alpha]_D^{23}$ −13.3 [*c* 1.0, $CHCl_3$–MeOH (1:1)]; δ_H($CDCl_3$–CD_3OD) 1.17 (3 H, d, *J* 4.9, CHC*H*$_3$), 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-H$_2$ 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, C*H*CH$_3$), 7.44 (2 H, m, Ph), 7.51 (1 H, m, Ph) and 7.82 (2 H, m, Ph); δ_C($CDCl_3$–CD_3OD) 20.1 (CH_3), 54.3 (C-2), 60.9, 61.8, 67.0, 70.6, 82.1, 98.8 (*C*HCH$_3$), 127.0, 128.3, 131.6, 133.8 and 168.7 (C=O); ν_{max}/cm^{-1} 3354, 2855, 1632, 1556, 1411, 1307, 1162, 1078, 1043, 848 and 723.

(4*S*,1′*R*,2′*S*,3′*R*,1″*R*)-4-[2′,4′-(Ethane-1,1-diyldioxy)-1′,3′-bis(methylsulfonyloxy)butyl]-2-phenyl-4,5-dihydrooxazole 5

A solution of methanesulfonyl chloride (870 mg, 7.5 mmol) in CH_2Cl_2 (5 cm^3) was added dropwise to a stirred solution of the triol **4** (620 mg, 2.0 mmol) and Et_3N (2.5 cm^3, 17.3 mmol) in CH_2Cl_2 (10 cm^3) 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 CH_2Cl_2 (30 cm^3) and cold aq. $NaHCO_3$ (20 cm^3), and the layers were separated. The aqueous phase was extracted with CH_2Cl_2 (2 × 20 cm^3) 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 CH_2Cl_2–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. $C_{17}H_{23}NO_9S_2$ 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, $CHCl_3$); δ_H 1.30 (3 H, d, *J* 5.0, C*H*$_3$CH), 3.13 (3 H, s, CH_3SO_2), 3.34 (3 H, s, CH_3SO_2), 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-H$_2$, 4′-H^{eq} and C*H*CH$_3$), 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 (CH_3SO_2), 39.0 (CH_3SO_2), 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); ν_{max}/cm^{-1} 3033, 2871, 1650, 1453, 1414, 1347, 1254, 1177, 1114, 982, 948, 848 and 700.

(2′*R*,3′*S*,4′*R*,4*S*)-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 cm^3, 6.8 mmol) in CH_2Cl_2 (8 cm^3) under nitrogen was added dropwise a 1.0 mol dm^{-3} solution of $TiCl_4$ in CH_2Cl_2 (2.4 cm^3, 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 $CHCl_3$ (5 cm^3) and quenched by the addition of a cooled solution of saturated aq. $NaHCO_3$ (10 cm^3) while being vigorously stirred. The mixture was poured into a separatory funnel containing $CHCl_3$ (5 cm^3), MeOH (2 cm^3) and dilute aq. $NaHCO_3$ (10 cm^3), and the organic layer was extracted. The aqueous phase was extracted with an azeotropic mixture of $CHCl_3$–MeOH (87:13) (3 × 20 cm^3). 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 cm^3) 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($CDCl_3$–CD_3OD) 3.20 (3 H, s, CH_3SO_2), 3.26 (3 H, s, CH_3SO_2), 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); ν_{max}/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 cm^3, 1.2 mmol) in toluene (6 cm^3) 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 cm^3), and treated with 5% aq. $Na_2S_2O_3$ (10 cm^3) and vigorously stirred to give a colourless organic layer. The layers were separated and the aqueous layer was extracted with AcOEt (2 × 10 cm^3). 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. $C_{14}H_{17}NO_5S$ 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, $CHCl_3$); δ_H 3.14 (3 H, s, CH_3SO_2), 3.90 (1 H, broad, OH), 4.53 (2 H, m, 5-H$_2$), 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; ν_{max}/cm^{-1} 3240, 1642, 1454, 1372, 1347, 1256, 1172, 1071, 958, 918, 901, 854, 783 and 703.

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

K_2CO_3 (180 mg, 1.3 mmol) was added to a stirred, ice-cooled solution of compound **6** (425 mg, 1.0 mmol) in MeOH (12 cm^3) and the mixture was stirred for 2 h at 5–10 °C. To this suspension was added saturated aq. NH_4Cl (3 cm^3), followed by AcOEt (30 cm^3) and half-saturated brine (20 cm^3). The layers were separated and the aqueous layer was extracted with AcOEt (2 × 20 cm^3). The combined organic layers were washed successively with water and brine (20 cm^3 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. $C_{14}H_{17}NO_6S$ 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, CH_3SO_2), 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; ν_{max}/cm^{-1} 3476, 2934, 1650, 1579, 1453, 1359, 1169, 1093, 1073, 934, 851, 790 and 709.

(4*S*,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 cm^3, 4.95 mmol) in CH_2Cl_2 (12 cm^3) 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 cm^3), and treated with 5% aq. $Na_2S_2O_3$ (30 cm^3) while being vigorously stirred. The layers were separated and the aqueous layer was extracted with AcOEt (2 × 30 cm^3). 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. $C_{14}H_{16}INO_5S$ 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, $CHCl_3$); 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, CH_3SO_2), 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-H_2), 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; ν_{max}/cm^{-1} 1656, 1341, 1178, 1086, 977, 925 and 698.

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

K_2CO_3 (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 cm^3). 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. NH_4Cl (1 cm^3), followed by AcOEt (10 cm^3) and half-saturated brine (10 cm^3). The layers were separated and the aqueous layer was extracted with AcOEt (2 × 10 cm^3). The combined organic layers were washed successively with water and brine (10 cm^3 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, $CHCl_3$); 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-H_2), 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; ν_{max}/cm^{-1} 1643, 1580, 1452, 1367, 1294, 1084, 1027, 965, 944, 818 and 687 (Found: M^+, 215.0932. $C_{13}H_{13}NO_2$ requires M, 215.0946).

Alkene 10 from iodide 9

A 1.5 mol dm^{-3} solution of BuLi in hexane (1.3 cm^3, 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 cm^3) at −70 °C under nitrogen. After 10 min, a solution of AcOH (20 mg, 0.33 mmol) in Pr^iOH (0.5 cm^3) 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. NH_4Cl (1 cm^3), followed by AcOEt (10 cm^3) and water (10 cm^3). The layers were separated and the aqueous layer was extracted with AcOEt (2 × 10 cm^3). 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*,4*S*)-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 cm^3), 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 cm^3, 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. NH_4Cl (2 cm^3), followed by AcOEt (15 cm^3) and water (5 cm^3). The layers were separated and the aqueous phase was extracted with AcOEt (2 × 15 cm^3). 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. $C_{25}H_{39}NO_2$ 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, $CHCl_3$); δ_H 0.88 (3 H, t, *J* 6.7, 16′-H_3), 1.26 (20 H, s-like, 6′- to 15′-H_2), 1.38 (2 H, m, 5′-H_2), 2.06 (2 H, q, *J* 6.9, 4′-H_2), 4.38 (3 H, m, 4-H and 5-H_2), 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; ν_{max}/cm^{-1} 3160, 2919, 2850, 1650, 1469, 1366, 1108, 968 and 693.

***N*-Benzoyl-D-*erythro*-C_{18}-sphingosine 13**

To a stirred solution of compound **11** (68 mg, 0.175 mmol) in THF (3.6 cm^3) was added 2 mol dm^{-3} aq. HCl (0.4 cm^3) 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 cm^3) 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 cm^3). 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–$CHCl_3$ (Found: C, 74.5; H, 10.2; N, 3.4. $C_{25}H_{41}NO_3$ 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-H_3), 1.25 (20 H, s-like, 8- to 17-H_2), 1.31 (2 H, m, 7-H_2), 2.06 (2 H, q, *J* 7.0, 6-H_2), 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; ν_{max}/cm^{-1} 3330, 2918, 2849, 1621, 1537, 1462, 1315, 1103, 1053, 980 and 718.

D-*erythro*-C_{18}-Sphingosine[(2*S*,3*R*,4*E*)-2-aminooctadec-4-ene-1,3-diol] 1

To a stirred solution of compound **11** (77 mg, 0.20 mmol) in THF (3.6 cm^3) was added 2 mol dm^{-3} aq. HCl (0.4 cm^3) and the mixture was stirred for 16 h at room temperature. To this solution were added $CHCl_3$–MeOH (87:13) (20 cm^3) and water (10 cm^3). The layers were separated and the aqueous phase was extracted with an azeotropic mixture of $CHCl_3$–MeOH (87:13) (2 × 10 cm^3). 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 cm^3) was added aq. NaOH (200 mg, 5.0 mmol in 0.4 cm^3), and the mixture was heated at 100 °C for 30 min. The cooled reaction mixture was diluted with water (10 cm^3) and extracted with

Et_2O (3 × 10 cm^3). The organic layer was dried and concentrated to give a solid, which was subjected to column chromatography, with CH_2Cl_2–MeOH (9:1), then with CH_2Cl_2–MeOH–2 mol dm^{-3} aq. NH_4OH (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 [CH_2Cl_2–MeOH–2 mol dm^{-3} aq. NH_4OH (40:10:1)]; $[\alpha]_D^{24}$ −1.2 (*c* 1.0, $CHCl_3$) {lit., $[\alpha]_D^{21}$ −1.3 (*c* 3.5, $CHCl_3$),[9c] $[\alpha]_D$ −0.58 (*c* 1.67, $CHCl_3$) [9f] and $[\alpha]_D^{24}$ −2.8 ($CHCl_3$) [12b]}; δ_H 0.88 (3 H, t, *J* 6.8, 18-H_3), 1.25 (20 H, s-like, 8- to 17-H_2), 1.36 (2 H, m, 7-H_2), 2.06 (2 H, q, *J* 6.8, 6-H_2), 2.87 (1 H, m, 2-H), 3.67 (2 H, m, 1-H_2), 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. $C_{18}H_{38}NO_2$ 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 cm^3) and treated with ethyl chloroformate (28 mg, 0.25 mmol), followed by Et_3N (40 mg, 0.40 mmol) in THF (0.5 cm^3) at 0 °C. After 10 min, aq. NaOH (120 mg, 3.0 mmol in 1.0 cm^3)–EtOH (1.0 cm^3) 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 cm^3) and extracted with Et_2O (3 × 10 cm^3). The combined extracts were treated as described above to give sphingosine **1** (34 mg, 75%).

***N,O,O*-Triacetyl-D-*erythro*-C_{18}-sphingosine 15**

To an ice-cooled solution of sphingosine **1** (21 mg, 0.07 mmol) in CH_2Cl_2 (2 cm^3) was added pyridine (0.1 cm^3) followed by acetic anhydride (0.1 cm^3), 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. $C_{24}H_{43}NO_5$ requires C, 67.7; H, 10.2; N, 3.35%); R_f 0.25 [hexane–AcOEt (1:2)]; $[\alpha]_D^{24}$ −12.9 (*c* 1.0, $CHCl_3$) {lit., $[\alpha]_D^{25}$ −12.9 (*c* 1.0, $CHCl_3$),[9e] $[\alpha]_D$ −13.0 (*c* 1.08, $CHCl_3$) [9f] and $[\alpha]_D^{25}$ −12.8 (*c* 1, $CHCl_3$) [12a]}; δ_H 0.88 (3 H, t, *J* 6.8, 18-H_3), 1.25 (20 H, s-like, 8- to 17-H_2), 1.33 (2 H, m, 7-H_2), 1.98, 2.06 and 2.07 (each 3 H, each s, Ac), 2.02 (2 H, m, 6-H_2), 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.

Acknowledgements

We thank Mr H. Minamikawa for helpful discussions.

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Paper 5/05691H
Received 29*th August* 1995
Accepted 13*th October* 1995