# Improved, gram scale synthesis of *N*,*O*,*O*-triacetyl-*erythro*- and *threo*-$C_{18}$-sphingosines from serine

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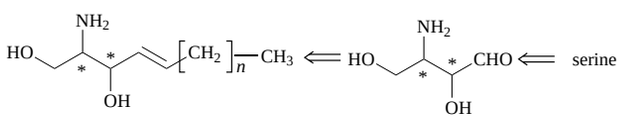
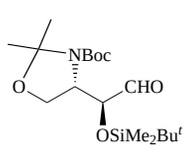
**A formal total synthesis of all four (*E*)-$C_{18}$-sphingosine stereoisomers from serine has been carried out. This involves the thiazole-based homologation of the amino acid into a chiral 3-amino-2,4-dihydroxybutanal 1 and the Wittig olefination of 1 with the ylide from the $C_{14}$ alkyl phosphonium salt 2. The photoisomerization of the resulting mixture of *Z*- and *E*-alkenes affords the target sphingosine. Thus, *N*,*O*,*O*-triacetyl-D-*erythro* $C_{18}$-sphingosine 5 and the L-*threo* isomer 10 were prepared in 43–44% overall yield from the aldehyde (*S*,*S*)-1a and (2*R*,3*S*)-1b, respectively. The corresponding antipodal L-*erythro* and D-*threo* isomers can be prepared in the same way starting from aldehydes *ent*-1a and *ent*-1b, respectively. Conversion of the above acetyl sphingosines into the free sphingoid bases has been reported in the literature.**

Because of the role exerted by sphingosines and their derivatives glycosphingolipids, ceramides and cerebrosides, in cell biology and protein kinase-C regulation,[1] there is an increasing demand for these compounds for biological studies and pharmaceutical applications. For instance, sphingosines have been recently considered as precursors of the biosynthesis of substances with sleep-inducing properties,[2] and a glycosphingolipid antigen associated with human breast cancer has been recently prepared by total synthesis.[3] Sphingosines have been immobilized on solid supports for the isolation and purification of the enzyme sphingosine kinase.[4] Various syntheses of sphingosines and analogues have been reported employing different methods and starting materials.[5] However the most straightforward route still appears to be that employing serine as starting material since this α-amino acid encompasses a part of the chiral moiety that is present in the final product. Starting from this amino acid, four independent research groups[6] reported in the same year similar synthetic approaches to sphingosines. These involved the stereoselective addition of a metal acetylene to the so called Garner serine derived amino aldehyde, *N*-Boc serinal acetonide (NBSA), followed by the stereoselective reduction of the triple to the *E*-double bond. The yield of the isolated sphingosine derivatives were in the range 25–81%. A recent method employing the direct alkenylation of NBSA by an (*E*)-alkenylzinc reagent in the presence of chiral amino alcohols gives mixtures of *anti* and *syn* adducts in good overall yield (*ca.* 50%).[7] Almost at the same time as reports from the above four research groups appeared, we reported[8] the synthesis of a D-*erythro* $C_{20}$-sphingosine involving first the conversion of NBSA into the α-hydroxy one-carbon higher homologue and then coupling of this with the appropriate alkylphosphorane. The phosphorus ylide was generated *in situ* from the phosphonium salt and phenyllithium as the base in the presence of lithium bromide to ensure *trans*-selectivity (Wittig–Schlosser olefination).[9] The yield of isolated (*E*)-olefin was modest (31%) and barely reproducible. Therefore, we report here the synthesis of the natural and unnatural D-*erythro*-$C_{18}$ and L-*threo*-$C_{18}$-sphingosines ($n = 12$) in much higher overall yield (43–44%) by an improved Wittig olefination of chiral 3-amino-2,4-dihydroxybutanal derivatives **1** and photoisomerization of the reaction mixture. The procedure requires only one separation of (*E*)- and (*Z*)-alkenes by chromatography or crystallization and is amenable for gram-scale preparations. The method is of potential generality because the use of the appropriate chirality set in **1** should permit the preparation of the other two $C_{18}$-sphingosine isomers with L-*erythro* and D-*threo* configuration.

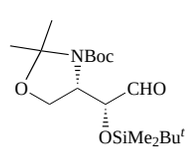



## Results and discussion

In recent work from this laboratory we have described methods for the multigram-scale synthesis of *N*- and *O*-protected 3-amino-2,4-dihydroxybutanals **1a** and **1b**, epimeric at C-2, from L-serine. The methods rely on the use of the thiazole ring as an equivalent of the formyl group.[10] In the route leading to **1a**, *N*-Boc-methyl-L-serinate acetonide was reduced to an aldehyde which was then treated with 2-(trimethylsilyl)thiazole to give an *anti* amino alcohol.[11] In the other route leading to **1b**, the same amino ester was first converted into a thiazolyl ketone that was then reduced to a *syn* amino alcohol.[12] After protection of the hydroxy group as a silyl ether, the aldehydes **1a** and **1b** were obtained by conversion of the thiazole ring into a formyl group *via* a simple deblocking protocol.[13] Evidently, the antipodes *ent*-**1a** and *ent*-**1b** (not shown) can be prepared in the same way starting from D-serine.



**1a**



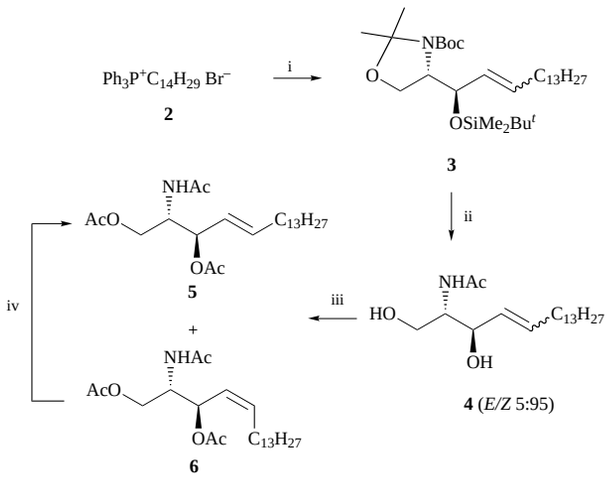
**1b**

Guided by literature precedents,[14] suitable conditions were sought to achieve a high yield olefination of the aldehyde **1a** with the ylide derived from tetradecanyl(triphenyl)phosphonium bromide **2** (Scheme 1). Thus, addition of this salt at room temperature to a solution of lithium hexamethyldisilazide (LHMDS) in tetrahydrofuran and then treatment with **1a** at the same temperature followed by work-up after 10–15 min, gave the olefin **3** mainly as the *Z*-isomer. While the *E*/*Z* ratio could not be determined by $^1$H NMR analysis because the signals overlapped at room temperature, the spectrum at 120 °C showed the overwhelming presence of the *Z*-isomer. A 3.2:2.8:1 ratio between **2**, LHMDS, and **1a** was employed in order to achieve complete consumption of the latter as the most expensive starting material. Under these optimized

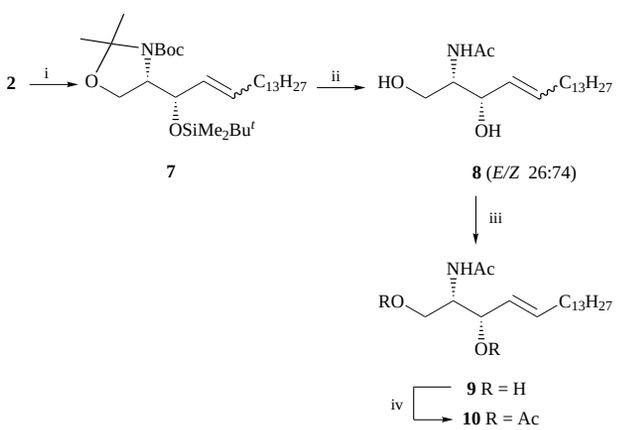
conditions, compound **3** was isolated in 80–84% yield in experiments carried out with variable amounts of **1a** in the range 60 mg–1 g. The use of freshly prepared LHMDS [from BuLi and $NH(SiMe_3)_2$] as the base employed for the ylide generation from **2** appeared quite crucial since other bases (BuLi, LDA) gave lower yields of the olefin **3**.

While the overall yield of the olefin **3** was satisfactory and set the basis for an improved synthesis of the target sphingosine, the unfavourable *E*/*Z* selectivity called for a *cis* to *trans* isomerization. A photochemical approach under the conditions recently described by Hudlicky and co-workers[15] in their chemoenzymatic synthesis of $C_{18}$-sphingosines appeared quite appropriate although we wondered whether this method could be employed on a preparative scale. To this aim all protective groups of **3** were removed by acid treatment in dioxane and the resulting unsaturated amino 1,3-diol was converted into the *N*-acetyl derivative **4** in almost quantitative yield. The $^1$H NMR analysis of this product showed the presence of (*E*)- and (*Z*)-alkenes in 5:95 ratio. These isomers were identified through the vinyl proton coupling constant values ($J_{cis}$ = 11.7 and $J_{trans}$ = 16 Hz) and the *E*/*Z* ratio determined from the intensity of the corresponding signals. The photoisomerization of this mixture was carried out by means of a water-cooled Hanovia 700 W lamp in a Pyrex apparatus and diphenyl disulfide as the sensitizer. The solution of **4** (0.2–0.5 g) in a 1:3 mixture of dioxane and cyclohexane was irradiated over a 6 h period while 1 equiv. of the sensitizer was added in three equal portions at 2 h intervals. Work-up of the resulting slightly coloured but limpid solution and acetylation showed the presence of (*E*)- and (*Z*)-alkenes in a 75:25 ratio by $^1$H NMR analysis. A lower *E*/*Z* ratio was obtained when 1 equiv. of the sensitizer was employed and added in one portion over the same irradiation time. The separation of these products by medium-pressure column chromatography afforded *N*,*O*,*O*-triacetyl D-*erythro*-$C_{18}$-sphingosine **5** and the *cis* isomer **6** in 58 and 22% yield, respectively. The photoisomerization of **6** under the above conditions gave an additional amount of **5**, thus leading to a combined yield of 43% from **1a**. Physical and spectroscopic properties of compound **5** were in agreement with literature data (see Experimental section). It is worth noting that the whole procedure is amenable to the preparation of gram quantities of **5** since the Wittig olefination of **1a** can be carried out at multigram levels and the photoisomerization of the mixture of alkenes can be conducted in various Pyrex flasks positioned around the irradiation lamp. The deacetylation of **5** to the natural sphingoid base has been reported.[16]

Having paved the way for a satisfactory gram-scale synthesis of the triacetyl sphingosine **5**, the same route was followed for the preparation of the L-*threo* isomer.† Among the various syntheses of L-*threo*-$C_{18}$-sphingosine from serine derivatives,[6] noteworthy is that of Herold *via* chelation-controlled *syn* addition of lithium pentadecyne to the Garner amino aldehyde NBSA.[6d] In other cases the *syn* configuration of the amino alcohol was achieved, although less efficiently, by alkenylalane addition[6a] or Mitsunobu inversion of the *anti* isomer.[6b] This problem does not exist in our method since the proper stereochemistry has been already set up in the construction of the aldehyde **1b**. Thus, following the same steps and under the same conditions described in Scheme 1, the aldehyde **1b** was converted into the *N*-acetyl-L-*threo*-$C_{18}$-sphingosine **9** in 47% overall yield (Scheme 2). Also in this synthesis, experiments were carried out with various amounts of materials in the range 0.2–1.5 g in the Wittig olefination and 0.2–0.5 g in the photoisomerization. The optimized yields of each reaction were close to those of Scheme 1. Quite rewardingly, photoisomerization of the mixture of (*E*)- and (*Z*)-alkenes **8** (26:74 ratio) produced an effective inversion of the ratio of the isomers (*E*/*Z*, 85:15) and the (*E*)-sphingosine **9** was isolated by simple crystallization. The physical and spectroscopic properties of this compound and of the triacetyl derivative **10** were in agreement with those reported in the literature (see Experimental section). The deacetylation of **9** to the unnatural sphingoid base has been reported.[16]




**Scheme 1** *Reagents and conditions*: i, LHMDS, **1a**, THF, 15 min (**3**, 80%); ii, HCl–dioxane (4.8 M), $H_2O$, overnight, then aq. $NaHCO_3$, MeOH, $Ac_2O$, 30 min (**4**, 81%); iii, *hv*, PhSSPh, cyclohexane–dioxane, 6 h, then $Ac_2O$, DMAP, pyridine, 1 h (**5**, 58%) (**6**, 22%); iv, *hv*, PhSSPh, cyclohexane–1,4-dioxane, 6 h (**5**, 40%) (**6**, 40%)




**Scheme 2** *Reagents and conditions*: i, LHMDS, **1b**, THF, 15 min (**7**, 74%); ii, HCl–dioxane (4.8 M), $H_2O$, overnight, then aq. $NaHCO_3$, MeOH, $Ac_2O$, 30 min (**8**, 81%); iii, *hv*, PhSSPh, cyclohexane–dioxane, 6 h (**9**, 79%); iv, $Ac_2O$, DMAP, pyridine, 1 h (**10**, 93%)

In conclusion, we have described the synthesis of *N*,*O*,*O*-triacetyl D-*erythro* and L-*threo* (*E*)-$C_{18}$-sphingosines **5** and **10** from L-serine *via* the aldehydes **1a** and **1b**. The availability of *ent*-**1a** and *ent*-**1b** from D-serine makes possible the synthesis of the two antipodal triacetyl D-*threo* and L-*erythro* (*E*)-$C_{18}$-sphingosines. Since the conversion of these acetyl sphingosines to the free sphingoid bases has been described,[16] a formal total synthesis of the four possible (*E*)-$C_{18}$-sphingosine stereoisomers appears to have been achieved. Given the high *Z*-selectivity of the Wittig olefination of the aldehydes **1** with the ylide from the phosphonium salt **2**, the method is even more suitable for the synthesis of (*Z*)-sphingosines which also are attracting interest for their presence in new cerebrosides.[17] In addition to being operatively simple, this method is amenable to gram-scale syntheses of sphingosines.

† Using the classical annotation of sphingosines [(*a*) *Natural Products Chemistry*, vol. 3, ed. K. Nakanishi, T. Goto, S. Ito, S. Natori, S. Nozoc, Kodansha LTD, Tokyo, 1983, p. 584; (*b*) H. Newman, *J. Am. Chem. Soc.*, 1973, **95**, 4098], L-*threo* sphingosines have been in some cases referred to as D-*threo* isomers. See ref. 6*a* and 6*d*.

## Experimental

### General details

All moisture-sensitive reactions were performed under a nitrogen atmosphere using oven-dried glassware. Solvents were dried over standard drying agents[18] and freshly distilled prior to use. Flash column chromatography[19] was performed on silica gel 60 (230–400 mesh), under positive pressure from a compressed air line. Medium-pressure chromatography was performed on silica gel 60 (230 mesh) using a chromatospac Prep 100. Reactions were monitored by TLC on silica gel 60 $F_{254}$ with detection by charring with alcoholic solutions of ninhydrin or sulfuric acid. Organic solutions after extractive work-up were dried over $Na_2SO_4$, filtered through a cotton plug and evaporated under reduced pressure. Melting points were determined with a capillary apparatus and are uncorrected. Optical rotations were measured at 20±2 °C and are recorded in units of $10^{-1}$ deg cm$^2$ g$^{-1}$. IR spectra were recorded using a Perkin-Elmer 1310 spectrometer. $^1$H (300 MHz) and $^{13}$C (75 MHz) NMR spectra were recorded at room temperature for $CDCl_3$ solutions, unless otherwise specified. Dioxane refers to 1,4-dioxane. The aldehyde **1a** was prepared as described below starting from the previously reported (*S*,*S*)-2-[(*tert*-butoxycarbonyl)amino]-3-hydroxy-2-*N*,3-*O*-isopropylidene-1-(1,3-thiazol-2-yl)propan-1-ol.[11] The aldehyde **1b** was obtained as described for *ent*-**1b**[20] starting from L-serine. Yield and physical data of **1b** were identical with those of *ent*-**1b** except for the optical rotation which had the opposite sign.

### 3-(*tert*-Butoxycarbonylamino)-2-*O*-(*tert*-butyldimethylsilyl)-3-deoxy-3-*N*,4-*O*-isopropylidene-L-erythrose 1a

To a stirred solution of (*S*,*S*)-thiazolyl alcohol[11] (2.0 g, 6.3 mmol) in DMF (12 cm$^3$) were added *tert*-butyldimethylsilyl trifluoromethanesulfonate (2.2 cm$^3$, 9.5 mmol) and DMAP (cat.). After being stirred for 1 h at room temperature, the solution was diluted with MeOH (2 cm$^3$), stirred for an additional 30 min and then concentrated. The residue was washed with water and extracted with $Et_2O$ (3 × 40 cm$^3$). The combined organic phases were dried and concentrated to give the crude silylated alcohol (2.6 g, 97%, pure by $^1$H NMR analysis) as a colourless syrup, $[\alpha]_D$ −46 (*c* 0.65, $CHCl_3$). A mixture of the silyl derivative (2.0 g, 4.7 mmol), activated 4 Å powdered molecular sieves (9.4 g) and anhydrous MeCN (46 cm$^3$) was stirred at room temperature for 10 min after which methyl triflate (0.6 cm$^3$, 5.6 mmol) was added to it. The suspension was stirred for 15 min and then concentrated to dryness. The residue was suspended in MeOH (46 cm$^3$), cooled to 0 °C, and treated with $NaBH_4$ (0.4 g, 10.2 mmol). The mixture was stirred at room temperature for 10 min, diluted with acetone (4 cm$^3$), filtered through Celite and concentrated. To a solution of the residue in MeCN–$H_2O$ (10:1; 46 cm$^3$), were added CuO (3.0 g, 37.3 mmol) and then $CuCl_2 \cdot H_2O$ (0.8 g, 4.7 mmol) portionwise and with vigorous stirring. After the mixture had been stirred for 15 min it was filtered through Celite and evaporated (bath temperature <40 °C). The brown syrup was sonicated with five (46 cm$^3$) portions of $Et_2O$ by an ultrasonic cleaning bath. The liquid layer was pipetted and filtered through a Florisil pad. The filtrate was concentrated to give crude **1a** (1.5 g, 86%) as a clear yellow syrup which was utilized for the Wittig olefination without purification. Analysis of this crude product by $^1$H NMR spectroscopy indicated a chemical purity of 90%. An analytical sample of **1a** was obtained by column chromatography with EtOAc–cyclohexane (1:9) as eluent, $[\alpha]_D$ −40.7 (*c* 0.6, $CHCl_3$) (Found: C, 57.7; H, 9.4; N, 3.7. $C_{18}H_{35}O_5NSi$ requires C, 57.9; H, 9.4; N, 3.7%); $\delta_H$([$^2H_6$]-DMSO, 120 °C) 0.1 (6 H, s, $SiMe_2$), 0.95 (9 H, s, $SiBu^t$), 1.44 (9 H, s, NBoc), 1.49 (3 H, s, CMe), 1.54 (3 H, s, CMe), 3.88 (1 H, dd, *J* 2.5 and 9.0, 4-H$^a$), 3.95 (1 H, dd, *J* 5.9 and 9.0, 4-H$^b$), 4.07 (1 H, dt, *J* 2.5 and 6.0, 3-H), 4.26 (1 H, dd, *J* 2.0 and 6.0, 2-H) and 9.55 (1 H, d, *J* 2.0, 1-H); $\nu_{max}$($CHCl_3$)/cm$^{-1}$ 1740, 1712 and 1690.

### Tetradecanyl(triphenyl)phosphonium bromide 2

A mixture of 1-bromotetradecane (9.8 cm$^3$, 36.1 mmol) and triphenylphosphine (10.4 g, 39.7 mmol) in toluene (30 cm$^3$) was stirred at 120 °C overnight. The solution was concentrated and the residue was treated with cold $Et_2O$ and filtered *in vacuo* to give the white *phosphonium salt* **2** (14.0 g, 72%), mp 83–84 °C; $\delta_H$ 0.84 (3 H, t, *J* 7, 14-$H_3$), 1.12–1.34 (20 H, m, 4- to 10-$H_2$), 1.52–1.70 (4 H, m, 2- to 3-$H_2$), 3.75–3.92 (2 H, m, 1-$H_2$) and 7.62–7.97 (15 H, m, 3 Ph).

### Wittig olefination of the aldehyde 1a with tetradecanylidene-(triphenyl)phosphorane

To a solution of lithium hexamethyldisilazide (LHMDS) (1.3 g, 7.6 mmol) in THF (8 cm$^3$) was added tetradecanyl(triphenyl)phosphonium bromide **2** (4.6 g, 8.6 mmol) at room temperature. The mixture was stirred at room temperature for 15 min, after which a solution of the aldehyde **1a** (1.0 g, 2.7 mmol) in THF (8 cm$^3$) was added dropwise to it in 1 min. The solution was vigorously stirred for 10 min and then treated with aqueous phosphate buffer (pH 7; 20 cm$^3$) and extracted with $CH_2Cl_2$ (3 × 30 cm$^3$). The combined organic layers were dried and concentrated to give a syrup which was subjected to column chromatography with toluene as eluent to afford a mixture of the *Z* and *E* olefins **3** (1.2 g, 80%) (Found: C, 69.6; H, 11.4; N, 2.5. $C_{32}H_{63}NO_4Si$ requires C, 69.5; H, 11.5; N, 2.5%); $R_f$ 0.48 (toluene); $\delta_H$($C_2D_2Cl_4$, 120 °C) 0.10 (3 H, s, SiMe), 0.12 (3 H, s, SiMe), 0.90–1.00 (12 H, m, $SiBu^t$, 18-$H_3$), 1.30–1.48 (22 H, m, 7- to 17-$H_2$), 1.45 (3 H, s, CMe), 1.57 (9 H, s, NBoc), 1.60 (3 H, s, CMe), 2.10–2.24 (2 H, m, 6-$H_2$), 3.76–3.86 (1 H, m, 2-H), 3.93 (1 H, dd, *J* 6.5 and 9, 1-H$^a$), 4.13 (1 H, dd, *J* 4 and 9, 1-H$^b$), 4.88 (1 H, dd, *J* 5 and 8.5, 3-H), 5.34 (1 H, dd, *J* 8.5 and 10, 4-H) and 5.40–5.52 (1 H, m, 5-H); $\nu_{max}$($CHCl_3$)/cm$^{-1}$ 2924, 2848, 1745, 1356 and 1352.

### (2*S*,3*R*)-2-*N*-Acetylamino-1,3-dihydroxyoctadec-4-(*Z* and *E*)-ene 4

A solution of HCl–dioxane (4.8 M; 5 cm$^3$) and water (0.5 cm$^3$) was added to the (*Z*) and (*E*) mixture of the olefins **3** (1.1 g, 2.0 mmol) at room temperature. The solution was stirred overnight and then concentrated. The resulting white salt was dissolved in saturated aqueous $NaHCO_3$ (5 cm$^3$) and MeOH (15 cm$^3$), and treated with acetic anhydride (0.5 cm$^3$). The mixture was stirred for 30 min and then concentrated. The residue was dissolved in saturated aqueous $NaHCO_3$ and extracted with EtOAc (3 × 30 cm$^3$). The combined organic layers were dried and concentrated. Chromatography of the residue with acetone–$CH_2Cl_2$ (2:3) as eluent gave a mixture of the (*Z*)- and (*E*)-*N*-acetyl olefins **4** (0.55 g, 81%) in a 95:5 ratio. Crystallization of a sample of this from diisopropyl ether gave pure (Z)-N-*acetyl-olefin* **4**, mp 72–75 °C; $[\alpha]_D$ −20 (*c* 0.52, $CHCl_3$) (Found: C, 70.2; H, 11.5; N, 4.1. $C_{20}H_{39}NO_3$ requires C, 70.3; H, 11.5; N, 4.1%); $\delta_H$ 0.81–0.95 (3 H, m, 18-$H_3$), 1.20–1.45 (22 H, m, 7- to 17-$H_2$), 2.00–2.20 (2 H, m, 6-$H_2$), 2.05 (3 H, s, Ac), 2.55 (1 H, d, *J* 4.7, 3-OH), 2.70 (1 H, dd, *J* 3.8 and 7.5, 1-OH), 3.74 (1 H, ddd, *J* 3.2, 7.5 and 11.7, 1-H$^a$), 3.86 (1 H, ddd, *J* 3.2, 6.8 and 8.8, 2-H), 4.02 (1 H, ddd, *J* 3.2, 3.8 and 11.7, 1-H$^b$), 4.7 (1 H, ddd, *J* 4.0, 4.7 and 8.8, 3-H), 5.46–5.68 (2 H, m, 4- to 5-H) and 6.29 (1 H, d, *J* 6.8, NH); $\nu_{max}$($CHCl_3$)/cm$^{-1}$ 3440, 2930, 2860, 1700 and 1530.

### Photoisomerization of the mixture of (*Z*)- and (*E*)-olefins 4

A solution of the olefins **4** (0.5 g, 1.5 mmol) and diphenyl disulfide (110 mg, 0.5 mmol) in cyclohexane–dioxane (3:1, 75 cm$^3$) in a Pyrex flask (100 cm$^3$), was degassed under nitrogen. The solution was irradiated by a water-cooled Hanovia 700-W high-pressure mercury lamp through a Pyrex filter for 2 h. The slightly yellow solution was treated twice with diphenyl disulfide (2 × 110 mg, 2 × 0.5 mmol) and irradiated over a total period of 4 h (2 × 2 h). The reaction mixture was then concentrated and the residue was treated with acetic anhydride

(8.4 $cm^3$), pyridine (8.4 $cm^3$) and DMAP (cat.). After being stirred for 1 h at room temperature, the mixture was concentrated to give a residue containing the (*E*)- and (*Z*)-olefins **5** and **6** in a 75:25 ratio (by $^1$H NMR analysis). Purification of the mixture by medium-pressure chromatography (6 atm) with acetone–$CH_2Cl_2$ (1:9) as eluent furnished the N,O,O,-*triacetyl*-D-erythro-$C_{18}$-*sphingosine* **5** (0.3 g, 58%) and the (*Z*)-*isomer* **6** (110 mg, 22%).

**Compound 5.** Mp 102–103 °C; $[\alpha]_D$ −11.7 (*c* 0.56, $CHCl_3$) {lit., 105–106 °C, $[\alpha]_D$ −12.9 (*c* 1.0, $CHCl_3$),[5] mp 101–102 °C, $[\alpha]_D$ −11.4 ($CHCl_3$)[16]} (Found: C, 67.5; H, 10.2; N, 3.28. $C_{24}H_{43}NO_5$ requires C, 67.7; H, 10.2; N, 3.3%); $\delta_H$ 0.88 (3 H, t, *J* 7, 18-$H_3$), 1.20–1.40 (22 H, m, 7- to 17-$H_2$), 1.99 (3 H, s, Ac), 2.07 (3 H, s, Ac), 2.08 (3 H, s, Ac), 2.00–2.10 (2 H, m, 6-$H_2$), 4.04 (1 H, dd, *J* 4 and 11.5, 1-H$^a$), 4.31 (1 H, dd, *J* 6 and 11.5, 1-H$^b$), 4.39–4.48 (1 H, m, 2-H), 5.27 (1 H, dd, *J* 7 and 7.5, 3-H), 5.39 (1 H, dd, *J* 7.5 and 15, 4-H), 5.64 (1 H, d, *J* 9, NH) and 5.80 (1 H, dt, *J* 7.5 and 15, 5-H); $\delta_C$ 13.15, 19.85, 20.17, 21.72, 22.41, 27.92, 28.06, 28.19, 28.38, 28.63, 28.69, 30.95, 31.31, 49.66, 61.62, 72.84, 123.14, 136.49, 168.69, 169.02 and 170.01; $\nu_{max}(CHCl_3)/cm^{-1}$ 3450, 2930, 2850, 1730, 1670 and 1368.

**Compound 6.** Mp 90–91 °C; $[\alpha]_D$ +4.8 (*c* 0.52, $CHCl_3$) (Found: C, 67.85; H, 10.2; N, 3.3. $C_{24}H_{43}NO_5$ requires C, 67.7; H, 10.2; N, 3.3%); $\delta_H$ 0.87 (3 H, t, *J* 7, 18-$H_3$), 1.15–1.45 (22 H, m, 7- to 17-$H_2$), 1.98 (3 H, s, Ac), 2.05 (3 H, s, Ac), 2.08 (3 H, s, Ac), 2.00–2.30 (2 H, m, 6-$H_2$), 4.03 (1 H, dd, *J* 3.6 and 11.6, 1-H$^a$), 4.33 (1 H, dd, *J* 6.5 and 11.6, 1-H$^b$), 4.35–4.47 (1 H, m, 2-H), 5.31 (1 H, dd, *J* 8.6 and 12.3, 3-H) and 5.55–5.75 (3 H, m, 4- to 5-H, NH); $\delta_C$ 13.15, 19.86, 20.12, 21.71, 22.38, 27.05, 28.33, 28.38, 28.45, 28.56, 28.70, 30.95, 50.10, 61.59, 68.65, 122.83, 136.05, 168.81, 169.01 and 170.08; $\nu_{max}(CHCl_3)/cm^{-1}$ 3445, 2925, 2860, 1730, 1670 and 1369.

A solution of the (*Z*)-*isomer* **6** (0.1 g, 0.2 mmol) and diphenyl disulfide (3 × 22 mg, 3 × 0.1 mmol) in cyclohexane–dioxane (3:1; 15 $cm^3$) was irradiated as described above for *Z/E* **4** to give a mixture of the olefins **5** and **6** in a 1:1 ratio (by $^1$H NMR analysis). Purification by medium-pressure chromatography furnished **5** (40 mg, 40%) and **6** (40 mg, 40%).

### Wittig olefination of the aldehyde 1b with tetradecanylidene-(triphenyl)phosphorane

The reaction was carried out as described above for **3** starting from crude **1b** (1.5 g, 4.0 mmol). Flash chromatography of the crude product using toluene as eluent gave a mixture of (*Z*)- and (*E*)-olefins **7** (1.65 g, 74 %) (Found: C, 71.8; H, 11.9; N, 2.6. $C_{32}H_{63}NO_4Si$ requires C, 72.0; H, 11.9; N, 2.6%); $R_f$ 0.48 (toluene); $\delta_H(C_2D_2Cl_4$, 120 °C, *Z* predominant isomer, selected data) 0.11 (3 H, s, SiMe), 0.14 (3 H, s, SiMe), 0.90–1.05 (12 H, m, SiBu$^t$, 18-$H_3$), 1.98–2.15 (2 H, m, 6-$H_2$), 4.96 (1 H, dd, *J* 4.5 and 9, 3-H) and 5.45 (1 H, dd, *J* 9 and 11.5, 4-H); $\nu_{max}(CHCl_3)/cm^{-1}$ 2930, 2860, 1654, 1356 and 1352.

### (*S,S*)-2-*N*-Acetylamino-1,3-dihydroxyoctadec-4-(*Z* and *E*)-ene 8

The same procedure as described above for **4** was applied to the mixture **7** (1.5 g, 2.7 mmol). Flash chromatography of the crude product with MeOH–$CH_2Cl_2$ (5%) as eluent gave (*Z*)- and (*E*)-*N*-acetyl olefins **8** (0.75 g, 81%) in 74:26 ratio (by $^1$H NMR analysis), $R_f$ 1.8 [MeOH–$CH_2Cl_2$ (5%)]; $\delta_H$(*Z* predominant isomer, selected data) 2.08 (3 H, s, Ac), 4.71 (1 H, dd, *J* 4 and 8, 3-H), 5.45 (1 H, dd, *J* 8 and 11, 4-H), 5.60 (1 H, dt, *J* 8 and 11, 5-H) and 6.28 (1 H, d, *J* 7, NH).

### Photoisomerization of the mixture of (*Z*)- and (*E*)-olefins 8

The photoisomerization was carried out as described above starting from a mixture of (*Z*)- and (*E*)-olefins **8** (0.5 g, 1.5 mmol). The reaction mixture was concentrated and purified by flash chromatography with acetone–$CH_2Cl_2$ (1:9) as eluent to give a mixture of **9** and its (*Z*)-isomer in 85:15 ratio (by $^1$H NMR analysis). Crystallization of the mixture afforded the *sphingosine* **9** (0.4 g, 79%) from diisopropyl ether, mp 69–70 °C; $[\alpha]_D$ −10.6 (*c* 0.79, $CHCl_3$) {lit.,[16] mp 65–66 °C, $[\alpha]_D$ −11.0 (*c* 0.6, $CHCl_3$)} (Found: C, 70.5; H, 11.5; N, 4.1. $C_{20}H_{39}NO_3$ requires C, 70.3; H, 11.5; N, 4.1%); $\delta_H$ 0.82–0.98 (3 H, m, 18-$H_3$), 1.20–1.45 (22 H, m, 7- to 17-$H_2$), 2.04 (3 H, s, Ac), 1.96–2.15 (2 H, m, 6-$H_2$), 2.47 (1 H, d, *J* 3.2, 3-OH), 2.59 (1 H, t, *J* 5.3, 1-OH), 3.78–3.84 (2 H, m, 1-$H_2$), 3.83–3.88 (1 H, m, 2-H), 4.35–4.43 (1 H, m, 3-H), 5.45 (1 H, dd, *J* 7.2 and 15.6, 4-H), 5.76 (1 H, dt, *J* 6 and 15.6, 5-H) and 6.13 (1 H, d, *J* 8.4, NH); $\delta_C$ 14.10, 22.66, 29.11, 29.45, 29.66, 31.89, 32.25, 54.88, 63.69, 72.53, 128.85, 133.87 and 171.24; $\nu_{max}(CHCl_3)/cm^{-1}$ 3430, 2920, 2850, 1700 and 1365.

### *N,O,O*-Triacetyl-L-*threo*-$C_{18}$-sphingosine 10

To a solution of **9** (0.25 g, 0.7 mmol) in pyridine (4.0 $cm^3$) was added acetic anhydride (4.0 $cm^3$) and DMAP (cat.). The solution was stirred for 1 h at room temperature and then concentrated. The residue was purified by flash chromatography with acetone–$CH_2Cl_2$ (1:9) as eluent to give the L-threo-*sphingosine* **10** (0.3 g, 93%), mp 47–48 °C; $[\alpha]_D$ +10.1 (*c* 0.63, $CHCl_3$) {lit.,[6d] $[\alpha]_D$ +10.4 (*c* 1.0, $CHCl_3$), lit.,[16] mp 41–42 °C, $[\alpha]_D$ +8.5 (*c* 1.0, $CHCl_3$)} (Found: C, 67.8; H, 10.2; N, 3.3. $C_{24}H_{43}NO_5$ requires C, 67.7; H, 10.2; N, 3.3%); $R_f$ 0.45 [acetone–$CH_2Cl_2$ (1:9)]; $\delta_H$ 0.88 (3 H, t, *J* 7, 18-$H_3$), 1.20–1.40 (22 H, m, 7- to 17-$H_2$), 2.00 (3 H, s, Ac), 2.06 (3 H, s, Ac), 2.08 (3 H, s, Ac), 2.00–2.10 (2 H, m, 6-$H_2$), 4.06 (1 H, dd, *J* 5.4 and 11, 1-H$^a$), 4.10 (1 H, dd, *J* 5.4 and 11, 1-H$^b$), 4.35–4.45 (1 H, m, 2-H), 5.29–5.44 (2 H, m, 3- to 4-H), 5.65 (1 H, d, *J* 9.3, NH) and 5.77 (1 H, dt, *J* 6.7 and 14.6, 5-H); $\delta_C$ 13.11, 19.75, 20.07, 21.85, 22.22, 27.50, 27.79, 28.13, 28.42, 28.57, 28.65, 30.91, 31.26, 49.82, 62.08, 72.05, 123.09, 136.29, 168.88, 169.07 and 169.65; $\nu_{max}(CHCl_3)/cm^{-1}$ 3440, 2922, 2855, 1730, 1670 and 1370.

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