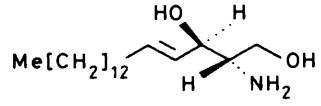
A New Route to Racemic *erythro*-Sphingosine and Ceramides. The 1,2- *versus* 1,4-Addition Reaction of Hexadec-2-enal with 2-Nitroethanol

Tohru Hino,* Kiyoshi Nakakyama, Mikio Taniguchi, and Masako Nakagawa
Faculty of Pharmaceutical Sciences, Chiba University, Yayoi-cho, Chiba-shi 260, Japan

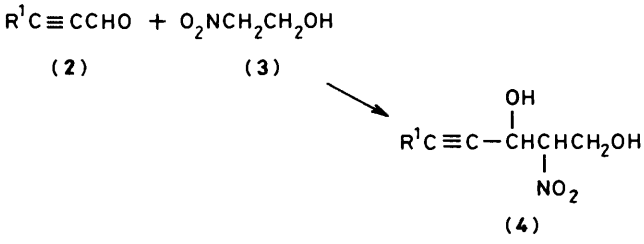
The reaction of hexadec-2-enal (**5**) with 2-nitroethanol (**3**) in triethylamine gave the 1,2-adducts (**8**) and (**9**), while the reaction in methanol–potassium carbonate gave the Michael adducts (**6**) and (**7**). Epimerization of the *threo*-acetonide (**10**) smoothly gave the *erythro*-acetonide (**11**), which gave the amino acetonide (**12**) on reduction. Phthaloylation, deacetalization, and deprotection of compound (**12**) gave *rac-erythro*-sphingosine (**1**). On the other hand, acylation and deacetalization of compound (**12**) gave the ceramide (**16**).

Increasing interest in the chemistry and biochemistry of sphingolipids in recent years has resulted in new developments of synthetic methods for *erythro*-sphingosine (**1**).[1] Grob has reported the reaction of hexadec-2-ynal (**2**) with 2-nitroethanol (**3**) to form a mixture of the *threo*- and the *erythro*-nitro diols (**4**) which was converted into *erythro*-sphingosine (**1**) by reduction.[1b] However, the reaction of hexadec-2-enal and 2-nitroethanol has not been reported. Therefore we examined this reaction and found a new route to racemic *erythro*-sphingosine.

The reaction of α,β-unsaturated aldehydes with a carbanion will be expected to give either a Michael-type adduct or/and a Knoevenagel-type adduct. The selective conditions for these two reaction pathways have not been well established, though it is well known that a weakly basic nucleophile prefers to undergo Michael reaction, and that a strongly basic nucleophile prefers the Knoevenagel reaction in general.

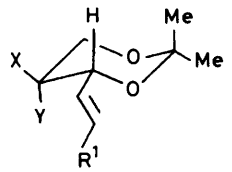


(**1**)

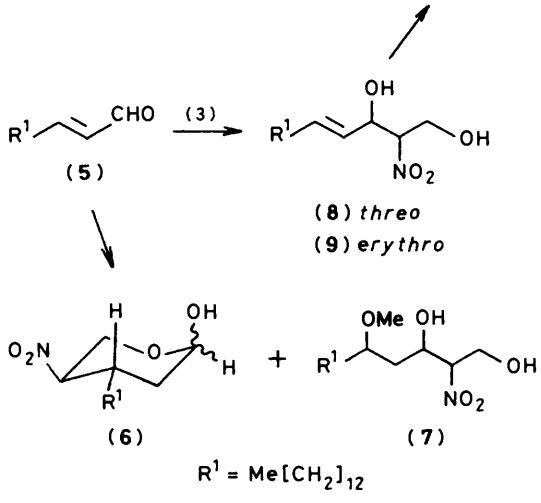


(**4**)

(*E*)-Hexadec-2-enal (**5**) has been prepared by the selective reduction of (*E*)-hexadec-2-enoic acid[1a] with dimethylformamide (DMF)–oxalyl chloride–lithium tri-(t-butoxy)aluminium hydride in excellent yield.[2] The reaction of (*E*)-hexadec-2-enal (**5**) with 2-nitroethanol (**3**) in methanol in the presence of potassium carbonate at room temperature, conditions under which compound (**2**) gave the adduct (**4**),[1b] did not give the desired nitro diols (**8**) and (**9**), but instead gave the pyranol (**6**) (50% yield), the acetal of the Michael adduct with nitroethanol, and methanol adduct (**7**) (12%). At 0 °C, the reaction gave the methanol adduct (**7**) (40%) as the major product. However, the 1,2-addition products (**8**) and (**9**) became the major product (70%) when the reaction was carried out in triethylamine at room temperature. The *threo*-isomer (**8**) was isolated as the major product (51%). Selective formation of the desired

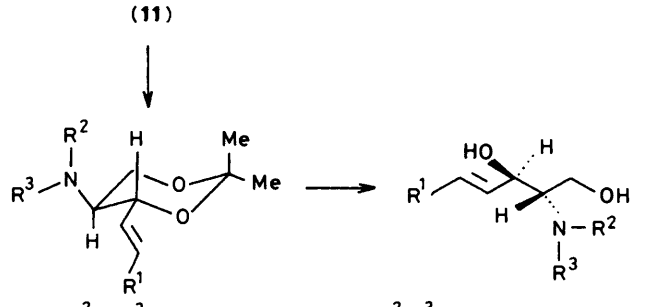


(**10**) X = H, Y = NO_2 (*threo*)
(**11**) X = NO_2, Y = H (*erythro*)



erythro-isomer (**9**) (19%) was unsatisfactory, but the *threo*-isomer could be converted into the *erythro*-isomer *via* the acetonide as follows. The mixture of compounds (**8**) and (**9**) was converted into the acetonides (**10**) and (**11**) in 2,2-dimethoxypropane in the presence of a catalytic amount of (±)-camphor-10-sulphonic acid (CSA) in excellent yield.[3] The *threo* (**10**) and *erythro* (**11**) isomers were separated in 58 and 41% yield, respectively. The isomerization of the *threo*-isomer (**10**) to the *erythro*-isomer (**11**) was readily accomplished by refluxing in triethylamine for 6 h (87% yield). Thus the *erythro*-isomer (**11**) was obtained in 71% yield from the mixture of the nitro diols (**8**) and (**9**). Reduction of the nitro group in compound (**11**) with aluminium amalgam or lithium aluminium hydride gave the *erythro*-amino derivative (**12**) in excellent yield. However, hydrolysis of the amino acetonide (**12**), under various acidic conditions, to obtain sphingosine (**1**) met with some difficulties due to the fact that the dienamine derivatives were produced by the dehydration of sphingosine (**1**) under the reaction conditions. This unfavourable situation was overcome by conversion of amine (**12**) into the phthalimide derivative (**13**),

followed by cleavage of the acetonide with toluene-*p*-sulphonic acid (PTSA) in methanol–methylene dichloride (1:1) at room temperature to give the phthaloylsphingosine (**15**) in over 90% yield. Removal of the phthaloyl group gave racemic *erythro*-sphingosine (**1**) in 89% yield, which was identified by its m.p. and n.m.r. spectrum.



(**12**) $R^2 = R^3 = H$ (**15**) R^2R^3 = phthaloyl

(**13**) R^2R^3 = phthaloyl (**16**) $R^2 = H, R^3 = Me[CH_2]_{14}CO$

(**14**) $R^2 = H, R^3 = Me[CH_2]_{14}CO$

Furthermore the amino acetonide (**12**) can be used as a precursor for the synthesis of ceramides (*N*-acyl sphingosines). Acylation of amine (**12**) with palmitoyl chloride in methylene dichloride–triethylamine gave the *N*-palmitoyl derivative (**14**) in 85% yield, which gave the ceramide (**16**), m.p. 89.5 °C, on removal of the acetonide function with PTSA as above, in 83% yield.

These methods are valuable for the preparation of racemic *erythro*-sphingosine and ceramides in gram quantities.

Experimental

M.p.s were determined on a Yamato MP-1 apparatus and are uncorrected. I.r. spectra were taken with Hitachi IR-295 and 260 spectrometers, n.m.r. spectra were recorded for $CDCl_3$ solutions on a JEOL FX-270 spectrometer, and mass spectra were run on a Hitachi M-60 instrument.

(E)-*Hexadec-2-enoic Acid.*—A mixture of malonic acid (14 g, 0.13 mol), myristaldehyde (22 g, 0.10 mol), and piperidine (0.8 ml) in anhydrous pyridine (28 ml) was stirred for 1 h at 50—60 °C and then refluxed for 4 h. The mixture was poured into chilled water and acidified with conc. hydrochloric acid to pH 2, and then extracted with methylene dichloride. The extracts were washed successively with water and brine, and dried over sodium sulphate. Evaporation of the solvent gave a wax (24 g), which was recrystallized from hexane to give plates (18 g). The mother liquor was distilled to give further crop of (*E*)-hexadec-2-enoic acid, b.p. 169 °C/1 mmHg (4.1 g; total 22.1 g, 83%), m.p. 48—49 °C (from hexane) (lit.,[1a] 48—49 °C); δ_H 0.88 (3 H, t, *J* 6.5 Hz, Me), 1.15—1.40 (20 H, m, CH_2), 1.47 (2 H, m, 5-H_2), 2.23 (2 H, m, 4-H_2), 5.82 (1 H, dt, *J* 16.0 and 1.5 Hz, 2-H), 7.09 (1 H, dt, *J* 16.0 and 7.0 Hz, 3-H), and 9.2 (1 H, br, CO_2H); *m/z* 255 (38, *M* + 1), 254 (25, M^+), and 84 (100%).

(E)-*Hexadec-2-enal* (**5**).—Oxalyl chloride (12 ml, 96 mmol) was added to a solution of anhydrous DMF (3.6 ml, 48 mmol) in methylene dichloride (120 ml) at 0 °C. The mixture was stirred for 1 h at 0 °C and the solvent was evaporated off to give a residue, which was dissolved in a mixture of acetonitrile (60 ml) and tetrahydrofuran (THF) (120 ml). A solution of (*E*)-hexadec-2-enoic acid (12 g, 47 mmol) in anhydrous THF (100 ml) containing pyridine (3.2 ml) was added to the solution at −30 °C, and the mixture was stirred at −30 °C for 1 h. Copper(I) iodide (912 mg, 4.8 mmol) and lithium tri-(t-butoxy)-aluminium hydride (24 g, 96 mmol) were added to the above solution at −78 °C, and the mixture was stirred for 5 h at the same temperature. The excess of the hydride was quenched with water, and the mixture was filtered. The filtrate was evaporated to give a residue, which was extracted with methylene dichloride. The extracts were washed successively with saturated aqueous $NaHCO_3$ and brine, and then dried. Evaporation of the solvent gave a residue (11.1 g), which was passed through a short silica gel column to remove a trace of copper compounds. The yellow residual oil (10.8 g) was distilled to give (*E*)-hexadec-2-enal (**5**), b.p. 135 °C/1 mmHg, as an oil (10.54 g, 94%); $\nu_{max.}$(neat) 2 940, 2 860, 1 695, 1 470, and 980 cm^{-1}; δ_H 0.88 (3 H, t, *J* 6.8 Hz, Me), 1.15—1.40 (20 H, m, CH_2), 1.40—1.60 (2 H, m, 5-H_2), 2.34 (2 H, qd, *J* 7.2 and 1.3 Hz, 4-H_2), 6.12 (1 H, ddt, *J* 15.6, 7.7, and 1.5 Hz, 2-H), 6.85 (1 H, dt, *J* 15.8 and 6.7 Hz, 3-H), and 9.51 (1 H, d, *J* 8.1 Hz, CHO); *m/z* 239 (16, *M* + 1), 238 (10, M^+), and 83 (100%).

The Reaction of Aldehyde (**5**) *with Nitroethanol* (**3**) *in Methanol-*K_2CO_3.—*5-Nitro-4-tridecyltetrahydropyran-2-ol* (**6**). To a solution of hexadec-2-enal (**5**) (6.9 g, 29 mmol) and 2-nitroethanol (2.9 g, 30 mmol) in methanol (60 ml) was added potassium carbonate (550 mg, 100 mmol). The mixture was stirred for 19 h at room temperature and then neutralized with 5% HCl solution. The mixture was filtered and the filtrate was diluted with methylene dichloride. The organic layer was washed with brine and dried. Evaporation of the solvent left a residue (10.5 g), which was chromatographed on a silica gel column (300 g) and eluted with benzene–ethyl acetate (9:1). The first eluate gave the starting aldehyde (**5**) (1.76 g) and the second eluate gave the tetrahydropyran-2-ol (**6**) (4.77 g, 50%) as a solid. The third eluate gave the methanol adduct (**7**) (1.31 g, 12%). The *tetrahydropyran* (**6**) was recrystallized from hexane to give a powder, m.p. 94—96.5 °C (Found: C, 65.65; H, 10.6; N, 4.2. $C_{18}H_{35}NO_4$ requires C, 65.61; H, 10.71; N, 4.25%); $\nu_{max.}$(KBr) 3 420, 2 925, 2 850, 1 540, 1 100, and 1 020 cm^{-1}; δ_H (β-anomer) 0.88 (3 H, t, *J* 6.9 Hz, Me), 1.1—1.5 (25 H, m, 3-H and CH_2), 2.10 (1 H, ddd, *J* 14.0, 4.3, and 1.7 Hz, 3-H), 2.50 (1 H, dd, *J* 2.3 and 3.3 Hz, OH), 2.60 (1 H, m, 4-H) 3.90 (1 H, dd, *J* 10 and 4.3 Hz, 6-H_{eq}), 4.30 (1 H, t, *J* 10, 6-H_{ax}), 4.40 (1 H, dt, *J* 10 and 4.3 Hz, 5-H), and 5.30 (1 H, br s, 2-H).

On addition of D_2O, a new peak, δ_H 4.91 (dd, *J* 8.9 and 2.6 Hz) appeared, and was assigned to the anomeric proton of the α-anomer.

The methanol adduct (**7**), a mixture of diastereoisomers, showed $\nu_{max.}$(neat) 3 500—3 200, 2 850, 2 830, 1 550, 1 380, and 1 070 cm^{-1}; δ_H 0.90 (3 H, t, *J* 6.8 Hz, CH_2*Me*), 1.1—1.8 (24 H, m, CH_2), 2.2—2.45 (2 H, m, 2 × OH), 3.37 (3 H, s, OMe), 3.50 (2 H, m, 4-H_2), 4.0—4.3 (3 H, m, 1- and 5-H), 4.3—4.6 (2 H, m, 2- and 3-H).

The Reaction of Hexadecenal (**5**) *with Nitroethanol* (**3**) in Triethylamine.—threo- *and* erythro-*2-nitro-octadec-*4(E)-*ene-1,3-diol* (**8**) *and* (**9**). Nitroethanol (**3**) (8.8 g, 96.7 mmol) was added to a solution of (*E*)-hexadec-2-enal (**5**) (11.0 g, 46.2 mmol) in triethylamine (80 ml). The mixture was stirred for 2 days at room temperature under argon, and then for 2 days at −20 °C. The solvent was removed to give a residue, which was dissolved in methylene dichloride. The solution was washed successively with 5% HCl and water, and then dried. Evaporation of the solvent gave an orange oil (14.91 g), which was chromatographed on a silica gel column (600 g). The first eluate, with benzene–ethyl acetate (7:3), gave the recovered aldehyde (**5**) with some impurities (2.4 g). The second eluate, with the same solvent, gave the Michael adduct (**6**) (1.19 g, 8%) as a solid. The third eluate gave the *threo*-nitro diol (**8**) (7.69 g,

51%) as a slightly yellow waxy solid, and the fourth eluate gave the *erythro*-nitro diol (**9**) (2.89 g, 19%) as a slightly yellow oil.

The *threo*-isomer (**8**) had $\nu_{max.}$(KBr) 3 400, 2 910, 2 840, 1 540, 1 460, 1 350, 1 240, 1 100, 1 020, and 970 cm^{-1}; δ_H 0.88 (3 H, t, Me), 1.26 (20 H, m, CH_2), 2.07 (2 H, m, 6-H_2), 2.1—2.4 (2 H, br, OH exchangeable), 4.05 (2 H, m, 1-H_2), 4.60 (2 H, m, 2- and 3-H), 5.45 (1 H, ddt, *J* 15.3, 7.1, and 1.3 Hz, 4-H), and 5.89 (1 H, dt, *J* 15.2 and 6.9 Hz, 5-H); δ_C 14.14 (q, C-18), 22.72 (t, C-17), 61.22 (t, C-1), 71.47 (d, C-3), 92.92 (d, C-2), 125.97 (d, C=C), and 137.41 (d, C=C).

The *erythro*-isomer (**9**) had $\nu_{max.}$(KBr) 3 360, 2 905, 2 830, 1 545, 1 460, 1 355, 1 050, and 970 cm^{-1}; δ_H 0.88 (3 H, t, Me), 1.26 (22 H, m CH_2), 2.06 (2 H, q, *J* 6.8 Hz, 6-H_2) 2.60 (2 H, m, 2 × OH), 4.13 (1 H, dd, *J* 12.5 and 3.3 Hz, 1-H), 4.25 (1 H, dd, *J* 12.9 and 6.6 Hz, 1-H), 4.52 (1 H, m, 2-H), 4.75 (1 H, t, *J* 5.8 Hz, 3-H), 5.47 (1 H, ddt, *J* 15.3, 6.6, and 1.7 Hz, 4-H), and 5.87 (1 H, dt, *J* 15.5 and 7.6 Hz, 5-H); δ_C 14.14 (q, C-18), 22.72 and 28.85 (each t, CH_2), 29.20—33.86 (CH_2), 60.38 (t, C-1), 72.07 (d, C-3), 91.31 (d, C-2), 126.03 (d, C=C), and 136.78 (d, C=C).

Reaction of nitroethanol (**3**) and the aldehyde (**5**) in ether in the presence of potassium carbonate (0.1 mol equiv.) for 68 h at room temperature gave a mixture of isomers (**8**) and (**9**) in 49% yield, and a small amount of the pyran (**6**) (4%), besides recovered aldehyde (**5**) (45%). The reaction of nitroethanol and aldehyde (**5**) in acetonitrile in the presence of KF and tetrabutylammonium bromide (or fluoride)[2] did not proceed, and aldehyde (**5**) was recovered.

threo- *and* erythro-2,2-*Dimethyl*-5-*nitro*-4-[(E)-*pentadec*-1-*enyl*]-1,3-*dioxane* (**10**) *and* (**11**).—A mixture of the nitro diols (**8**) and (**9**) (5.1 g, 15.5 mmol) and CSA (30 mg, 0.13 mmol) in 2,2-dimethoxypropane (100 ml) was refluxed for 15 h under argon. The mixture was poured into saturated aqueous $NaHCO_3$, extracted with methylene dichloride, and the extract was washed with brine, and dried. Evaporation of the solvent gave an orange oil (7.91 g), which was chromatographed on a silica gel column (250 g) and eluted with benzene. The first eluate gave the *erythro*-acetonide (**11**) (2.367 g, 41%) as an oil. The second eluate gave the *threo*-acetonide (**10**) (3.29 g, 57.5%) as an oil. The *erythro*-isomer (**11**) had $\nu_{max.}$(neat) 2 990, 2 920, 2 880, 1 550, 1 460, 1 380, 1 210, 1 110, and 970 cm^{-1}; δ_H 0.88 (3 H, t, *J* 6.6 Hz, CH_2*Me*), 1.1—1.4 (22 H, m, CH_2), 1.43 (3 H, s, 2-Me), 1.57 (3 H, s, 2-Me), 2.01 (2 H, m, CH_2C=C), 4.16 (1 H, dd, *J* 10.0 and 5.3 Hz, 6-H_{eq}), 4.25 (1 H, t, *J* 10.0 Hz, 6-H_{ax}), 4.50 (1 H td, *J* 9.6 and 5.6 Hz, 5-H), 4.66 (1 H, dd, *J* 9.6 and 7.3 Hz, 4-H), 5.42 (1 H, ddt, *J* 15.3, 7.5, and 1.3 Hz, 4-CH=C), and 5.80 (1 H dt, *J* 15.5 and 6.6 Hz, 4-C=CH).

The *threo*-isomer (**10**) had $\nu_{max.}$(neat) 2 990, 2 920, 2 880, 1 550, 1 460, 1 380, 1 200, 1 170, 1 080, and 980 cm^{-1}; δ_H 0.88 (3 H, t, *J* 6.4 Hz, CH_2*Me*), 1.1—1.4 (22 H, m, CH_2), 1.48 (3 H, s, 2-Me), 1.50 (3 H, s, 2-Me), 2.00 (2 H, m, CH_2C=C), 4.26 (1 H, dd, *J* 13.0 and 4.0 Hz, 6-H_{eq}), 4.36 (1 H, dd, *J* 13.0 and 2.6 Hz, 6-H_{ax}), 4.48 (1 H, m, 5-H), 4.61 (1 H, dd, *J* 6.4 and 3.0 Hz, 4-H), 5.50 (1 H, dd, *J* 15.6 and 6.4 Hz, 4-CH=C), 5.85 (1 H, dt, *J* 15.4 and 6.8 Hz, 4-C=CH).

Epimerization of threo-*Isomer* (**10**) *to* erythro-*Isomer* (**11**).—A solution of the *threo*-isomer (**10**) (2.3 g, 6.2 mmol) in triethylamine (20 ml) was refluxed for 6 h under argon. Evaporation of the solvent gave a residue, which was dissolved in methylene dichloride. The solution was washed successively with 5% HCl, water, and brine, and then dried. Evaporation of the solvent gave a yellow liquid (2.33 g), which was chromatographed on a silica gel column (70 g) and eluted with benzene. The first eluate gave the *erythro*-isomer (**11**) (2.0 g, 87%) as a yellow liquid. The second eluate gave a mixture of the *threo*- and *erythro*-isomers (**10**) and (**11**) (211 mg).

The *erythro*-isomer (**11**) was readily obtained from a mixture of the *threo*- and *erythro*-nitro diols (**8**) and (**9**) as follows. A mixture of compounds (**8**) and (**9**) (2.2 g, 6.7 mmol) in 2,2-dimethoxypropane (50 ml) in the presence of CSA (10 mg) was refluxed for 10 h, and then worked-up as above to give a mixture of the acetonides (**10**) and (**11**) (2.20 g). A solution of the acetonides (**10**) and (**11**) in benzene (50 ml) in the presence of silica gel (10 g) was refluxed for 7.5 h. Usual work-up and chromatography (silica gel) of the crude mixture gave the *erythro*-isomer (**11**) [1.76 g, 71% from (**8**) and (**9**)] and the *threo*-isomer (**10**) (43 mg, 2%).

erythro-5-*Amino*-2,2-*dimethyl*-4-[(E)-*pentadec*-1-*enyl*]-1,3-*dioxane* (**12**).—(i) *By aluminium amalgam reduction.* Aluminum amalgam [prepared from aluminium (2 g)] was gradually added to a solution of the *erythro*-acetonide (**11**) (650 mg, 1.9 mmol) in a mixture of ether (25 ml) and water (5 ml) at room temperature. The mixture was stirred for 25 h at room temperature and then filtered. The filtrate was passed through Celite 545, which was then washed with methanol. The filtrate and washings were evaporated to leave a residue, which was dissolved in methylene dichloride. The solution was washed with brine and dried. Evaporation of the solvent gave the title compound (**12**) as an oil (550 mg, 92%), $\nu_{max.}$(neat) 3 400, 3 000, 2 925, 2 850, 1 470, 1 380, and 970 cm^{-1}; δ_H 0.88 (3 H, t, *J* 6.6 Hz, CH_2*Me*), 1.2—1.4 (22 H, m, CH_2), 1.42 (3 H, s, 2-Me), 1.50 (3 H, s, 2-Me), 2.0—2.10 (4 H, m, C=CCH_2 and NH_2), 2.86 (1 H, td, *J* 9.5 and 5.3 Hz, 5-H), 3.93 (1 H, dd, *J* 9.9 and 9.2 Hz, 6-H_{ax}), 4.04 (1 H, dd, *J* 11.4 and 5.4 Hz, 6-H_{eq}), 4.20 (1 H, dd, *J* 9.2 and 8.2 Hz, 4-H), 5.42 (1 H, ddt, *J* 15.5, 7.9, and 1.3 Hz, 4-CH=C), and 5.82 (1 H, dt, *J* 15.5 and 6.6 Hz, 4-C=CH); *m/z* 340 (30.2, *M* + 1) and 43 (100%).

(ii) *By* $LiAlH_4$ *reduction.*—To a suspension of $LiAlH_4$ (250 mg, 6.6 mmol) in THF (10 ml) was added the *erythro* acetonide (**11**) (850 mg, 2—3 mmol) in THF (5 ml) at room temperature (an exothermic reaction was observed). The mixture was stirred for 2 h at room temperature, and then the excess of $LiAlH_4$ was quenched with water. The mixture was condensed under reduced pressure to a small volume and diluted with ethyl acetate. The mixture was filtered to remove insoluble material. The organic layer was separated, washed successively with water and brine, and dried. Evaporation of the solvent gave the title amine (**12**) as an oil (769 mg, 98.5%) which showed a single spot on t.l.c.

erythro-2,2-*Dimethyl*-4-[(E)-*pentadec*-1-*enyl*]-5-*phthalimido*-1,3-*dioxane* (**13**).—Ethoxycarbonylphthalimide (672 mg, 3.07 mmol) was added to a solution of amine (**12**) (800 mg, 2.36 mmol) in a mixture of methylene dichloride (10 ml) and triethylamine (2 ml) at room temperature under argon. The mixture was stirred for 10 h at room temperature, and then diluted with methylene dichloride. The solution was washed successively with 5% HCl, water, and brine, and then dried. Evaporation of the solvent left an oil, which was purified on a silica gel column to give the phthalimide (**13**) (1.01 g, 91%) as an oil, $\nu_{max.}$(neat) 3 000, 2 930, 2 860, 1 780, 1 720, 1 470, 1 385, 980, and 720 cm^{-1}; δ_H 0.88 (3 H, t, *J* 6.6 Hz, CH_2*Me*), 1.0—1.4 (22 H, m, CH_2), 1.48 (3 H, s, 2-Me), 1.69 (3 H, s, 2-Me), 1.86 (1 H, m, CH_2C=C), 3.76 (1 H, dd, *J* 10.9 and 5.6 Hz, 6-H_{eq}), 4.25 (1 H, td, *J* 10.8 and 5.6 Hz, 5-H), 4.60 (1 H, t, *J* 11.2 Hz, 6-H_{ax}), 5.05 (1 H, dd, *J* 10.2 and 8.2 Hz, 4-H), 5.34 (1 H, ddt, *J* 15.3, 8.2, and 1.3 Hz, 4-CH=C), 5.61 (1 H, dt, *J* 15.5 and 7.3, 4-C=CH), 7.73 (2 H, m, ArH), and 7.80 (2 H, m, ArH).

rac-N-*Phthaloylsphingosine* (**15**).—A mixture of the dioxane (**13**) (650 mg, 1.4 mmol) and PTSA hydrate (100 mg, 0.53 mmol) in a mixture of methanol (5 ml) and methylene dichloride (5 ml) was stirred for 12 h at room temperature under argon. The mixture was poured into saturated aqueous $NaHCO_3$ and extracted with methylene dichloride. The extract was washed

successively with water and brine, and then dried. Evaporation of the solvent gave a yellow residue (593 mg), which was chromatographed on a silica gel column (20 g) and eluted with benzene–ethyl acetate (9:1). The first eluate gave the starting material (25 mg) and the second eluate gave the diol (**15**) (564.9 mg, 95%) as an slightly yellow oil, $\nu_{max.}$(neat) 3 450, 2 935, 2 860, 1 780, 1 710, 1 470, 1 395, 980, and 730 cm^{-1}; δ_H 0.88 (3 H, t, *J* 6.6 Hz, Me), 1.08—1.40 (22 H, m, CH_2), 1.90 (2 H, m, 6-H_2), 2.98 (1 H, d, *J* 4.0 Hz, 3-OH, exchangeable), 3.20 (1 H, dd, *J* 8.9 and 4.0 Hz, 1-OH, exchangeable), 4.09—4.33 (3 H, m, 1-H_2 and 2-H), 4.70 (1 H, td, *J* 7.3 and 3.6 Hz, 3-H), 5.48 (1 H, dd, *J* 15.5 and 7.3 Hz, 4-H), 5.67 (1 H, td, *J* 15.2 and 7.3 Hz, 5-H), 7.74 (2 H, m, ArH), and 7.84 (2 H, m, ArH).

rac-*Sphingosine* (**1**).—A solution of compound (**15**) (260 mg, 0.59 mmol) in 10% ethanolic hydrazine hydrate (7 ml) was refluxed for 1.5 h. The mixture was diluted with water and basified with potassium hydroxide (pellets; 2.0 g) and then extracted with methylene dichloride. The extracts were dried and evaporated to give a white solid (240 mg). The residue was dissolved in ether and the solution was filtered to remove insoluble materials. The ether solution gave a white solid (188 mg) on evaporation of the solvent. The residue was recrystallized from ether to give sphingosine (**1**) (161 mg, 89%), m.p. 69—73 °C. Further recrystallization from ether gave a pure sample, m.p. 71—73 °C (lit.,[1b] 65—67 °C; lit.,[1a] 71—73 °C) (Found: C, 72.05; H, 12.1; N, 4.65. Calc. for $C_{18}H_{37}NO_2$: C, 72.19; H, 12.45; N, 4.68%); $\nu_{max.}$(KBr) 3 250—3 460, 2 960, 2 925, 2 850, 1 590, 1 470, 1 045, 1 035, and 975 cm^{-1}; δ_H 0.88 (3 H, t, *J* 6.6 Hz, Me), 1.18—1.35 (22 H, m, CH_2), 2.06 (2 H, q, *J* 6.9 Hz, 6-H_2), 2.18 (4 H, br s, NH_2, and 2 × OH), 2.87 (1 H, q, *J* 5.4 Hz, 2-H), 3.65 (2 H, m, 1-H_2), 4.04 (1 H, t, *J* 6.3 Hz, 3-H), 5.46 (1 H, dd, *J* 15.3 and 6.9 Hz, 4-H), and 5.76 (1 H, dt, *J* 15.5 and 6.6 Hz, 5-H); *m/z* 301 (3, *M* + 2), 300 (10, *M* + 1), and 60 (100%).

2,2-*Dimethyl*-5-*palmitamido*-4-[(E)-*pentadec*-1-*enyl*]-1,3-*dioxane* (**14**).—To an ice-cooled solution of amine (**12**) (204 mg, 0.60 mmol) and triethylamine (2 ml) in methylene dichloride (5 ml) was gradually added a solution of palmitoyl chloride (170 mg, 0.62 mmol) in methylene dichloride (5 ml) under argon during 20 min. The mixture was stirred for 3 h under ice-cooling, and then poured into water. The organic layer was washed successively with 5% HCl and brine, and then dried. Evaporation of the solvent gave a residue (660 mg), which was chromatographed on silica gel (20 g) and eluted with benzene–ethyl acetate (3:2). The first eluate gave the palmitoyl derivative (**14**) (296 mg, 85%) as a semi-solid. Recrystallization from ether–hexane gave crystals, m.p. 75—76.5 °C (Found: C, 76.6; H, 12.3; N, 2.4. $C_{37}H_{71}NO_3$ requires C, 76.89; H, 12.38; N, 2.42%); $\nu_{max.}$(KBr) 3 260, 3 000, 2 925, 1 640, 1 560, 1 470, 1 380, 1 200, and 980 cm^{-1}; δ_H 0.88 (6 H, t, 2 × CH_2*Me*), 1.2—1.4 (48 H, m, CH_2), 1.42 (3 H, s, 2-Me), 1.49 (3 H, s, 2-Me), 2.0—2.2 (4 H, m, C=CCH_2 and $COCH_2$), 3.65 (1 H, dd, *J* 10.9 and 9.2 Hz, 6-H_{ax}), 3.80 (1 H, m, 5-H), 4.00 (1 H, dd, *J* 11.0 and 5.1 Hz, 6-H_{eq}), 4.08 (1 H, dd, *J* 8.9 and 8.2 Hz, 4-H), 5.15 (1 H, d, *J* 7.9 Hz, HNCO), 5.42 (1 H, dd, *J* 15.3 and 7.8 Hz, 4-CH=C), and 5.75 (1 H, dt, *J* 15.5 and 6.6 Hz, 4-C=CH).

rac-erythro-N-*Palmitoylsphingosine* (**16**).—A solution of compound (**14**) (240 mg, 0.42 mmol) and PTSA hydrate (36 mg, 0.19 mmol) in a mixture of methanol (5 ml) and methylene dichloride (5 ml) was stirred for 21 h at room temperature under argon. The mixture was poured into saturated aqueous $NaHCO_3$ solution and extracted with methylene dichloride. The extracts were washed successively with water and brine, and then dried. Evaporation of the solvent gave crude product (**16**) (285 mg), which was recrystallized from ether to give crystals (156.4 mg). The mother liquor was chromatographed on a silica gel column (4 g) to give a further crop of compound (**16**) (30 mg; total 186.4 mg, 83%). Further recrystallization from ether gave a powder, m.p. 89.5 °C (Found: C, 75.85; H, 12.3; N, 2.7. $C_{34}H_{67}NO_3$ requires C, 75.93; H, 12.54; N, 2.60%); $\nu_{max.}$(KBr) 3 330, 2 960, 2 920, 2 850, 1 608, 1 555, 1 465, 1 100, 1 050, 985, and 718 cm^{-1}; δ_H 0.88 (6 H, t, 2 × Me), 1.17—1.40 (48 H, br s, CH_2), 2.05 (2 H, q, *J* 6.9 Hz, 6-H_2), 2.23 (2 H, t, *J* 7.6 Hz, $COCH_2$), 2.65 (2 H, br s, 2 × OH, exchangeable), 3.69 (1 H, m, 2-H), 3.90 (2 H, m, 1-H_2), 4.32 (1 H, m, 3-H), 5.53 (1 H, dd, *J* 15.3 and 6.4 Hz, 4-H), 5.78 (1 H, dt, *J* 15.4 and 6.6 Hz, 5-H), and 6.22 (1 H, d, *J* 7.6 Hz, NH, exchangeable); *m/z* 539 (3, *M* + 1), 538 (6, M^+), and 281 (100%).

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