Total Synthesis of (+)-*erythro*-*N*-Lauroyldocosasphinga-4,8-dienine from *Anemonia sulcata* and Determination of the Absolute Configuration

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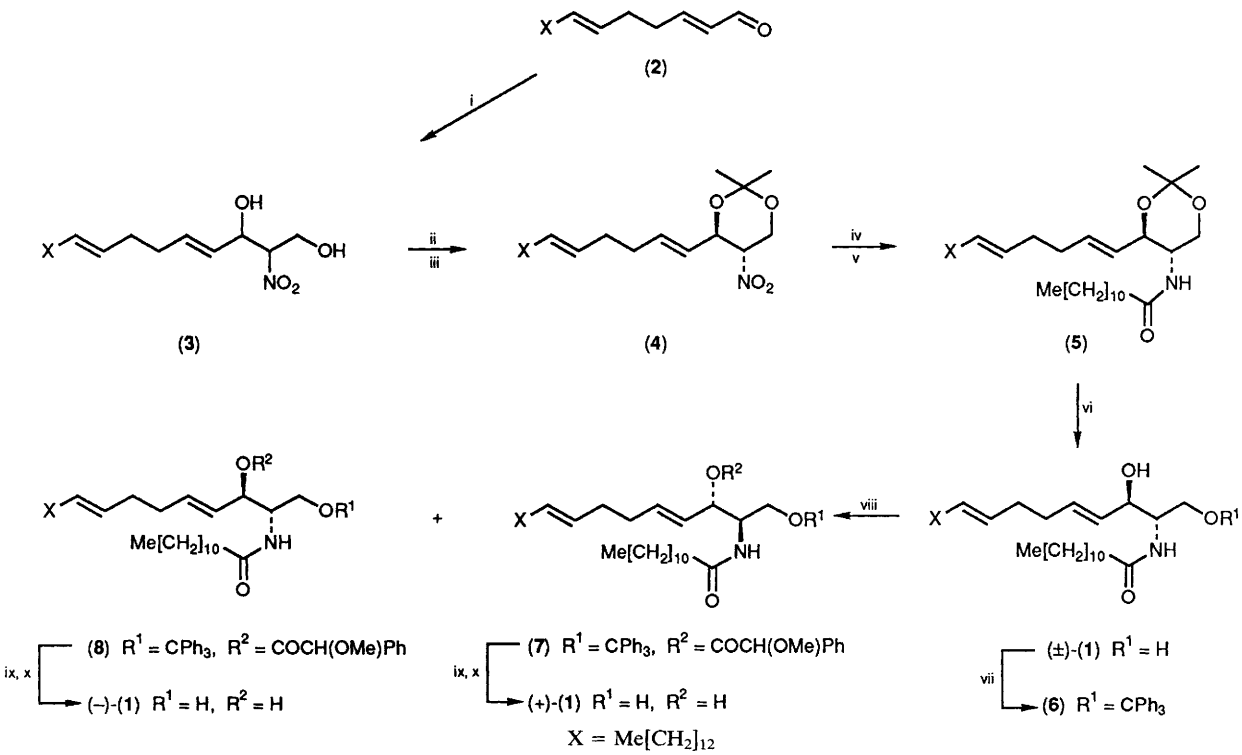
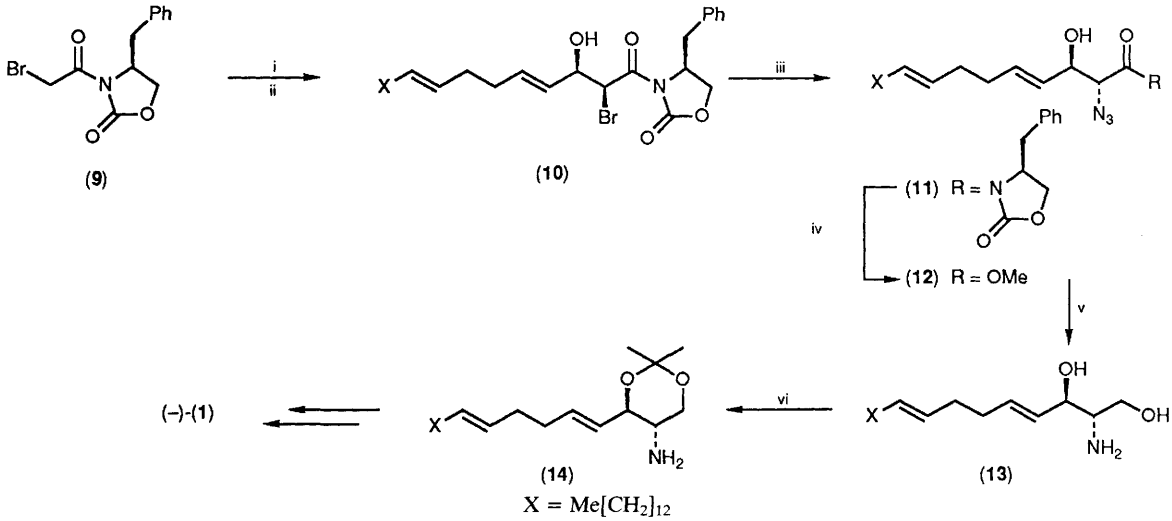
A new sphingosine derivative (**1**) from *Anemonia sulcata* has been synthesized and the L-*erythro* configuration determined.

Several reports of the occurrence of the dienic long-chain base, sphingadienine, have appeared in recent years.[1] A new sphingosine derivative, *erythro*-docosasphinga-4,8-dienine, has recently been isolated and characterized as an *N*-lauroyl derivative from *Anemonia sulcata* collected near Sousse; its structure was reported to be (**1**).[2] However, the absolute configuration of (**1**) has not been determined yet, although the relative stereochemistry at C-2 and C-3 has been determined to be *erythro* by the coupling constants between H-2 and H-3.

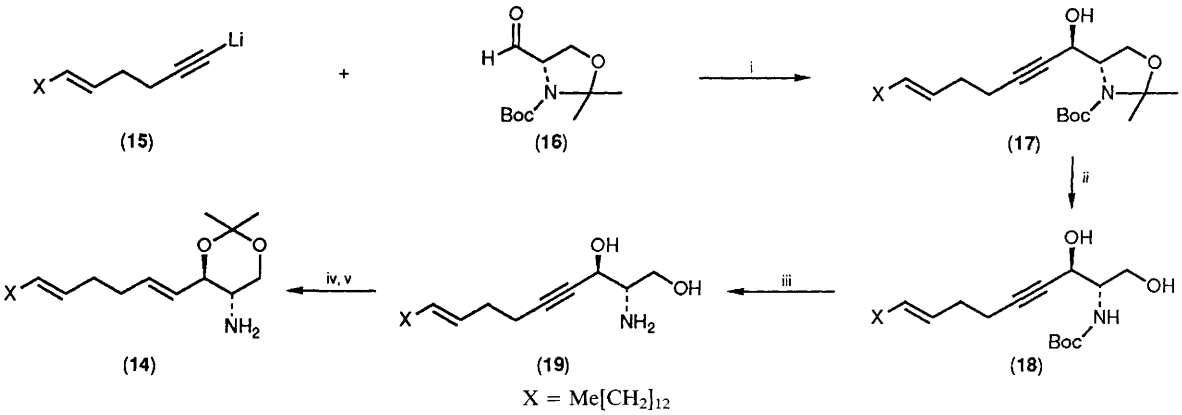
We have reported a simple method for preparation of



Scheme 1. *Reagents and conditions*: i, $HO[CH_2]_2NO_2$ (3.5 equiv.), Et_3N, 4 °C, 4 days; ii, $Me_2C(OMe)_2$–acetone, PPTS (0.1 equiv.), reflux, 16 h; iii, Et_3N, reflux, 5 h; iv, Al–Hg, tetrahydrofuran (THF)–H_2O, room temp., 1 h; v, $Me[CH_2]_{10}COCl$ (1 equiv.), Et_3N, CH_2Cl_2, room temp., 12 h; vi, pyridinium toluene-*p*-sulphonate (PPTS) (1.0 equiv.), MeOH, room temp., 2 days; vii, Ph_3CCl (2 equiv.), dimethylaminopyridine (DMAP) (3 quiv.), pyridine, 100 °C, 1.5 h; viii, (*S*)-*O*-methylmandelyl chloride, pyridine, benzene, room temp., 40 min, separation; ix, *p*-$MeC_6H_4SO_3H$ (1.3 equiv.), MeOH, room temp.; x, MeONa (4 equiv.), MeOH, room temp.



Scheme 2. *Reagents and conditions*: i, $Bu^n_2BOSO_2CF_3$ (1.1 equiv.), Et_3N (1.4 equiv.), Et_2O, −78 °C, then room temp., 1.5 h; ii, (**2**), −78 °C, 30 min, then 0 °C, 2 h; iii, NaN_3 (2 equiv.), dimethylformamide (DMF), room temp., 2.5 h; iv, MeOMgBr (1.1 equiv.), MeOH, 0 °C, 5 min; v, $LiAlH_4$ (3 equiv.), Et_2O, 0 °C, 15 min, then room temp., 1 h; vi, camphorsulphonic acid (CSA; 1 equiv.), $Me_2C(OMe)_2$, reflux, 1 h.



Scheme 3. *Reagents and conditions*: i, THF, −23 °C, 1.5 h; ii, *p*-$MeC_6H_4SO_3H$ (0.1 equiv.), MeOH, room temp., 6.5 h; iii, conc. HCl, AcOEt, room temp., 50 min; iv, $LiAlH_4$ (excess), $MeO[CH_2]_2OMe$, reflux, 10 h; v, $Me_2C(OMe)_2$, CSA (1 equiv.), reflux, 1 h.

erythro-sphingosine[3] which was applied to the total synthesis of cerebroside B_{1b}.[4] We now report the total synthesis of (**1**) by three different approaches and the determination of its absolute configuration.

The first approach to (**1**) involved the optical resolution of the racemic *erythro*-ceramide (±)-(**1**), obtained by our method which included the 1,2-addition reaction of nitroethanol to the dienal (**2**)[3,4] (Scheme 1). Treatment of the dienal (**2**) with nitroethanol gave the nitrodiol (±)-(**3**) (71%) as a mixture of *erythro*- and *threo*-isomers which was converted to the *erythro*-acetonide (±)-(**4**) [66% from (**3**)]. Reduction of (±)-(**4**), followed by acylation with lauroyl chloride, gave (±)-(**5**). Deprotection of (±)-(**5**) provided the *erythro*-*N*-lauroyldocosasphinga-4,8-dienine (±)-(**1**), m.p. 75.5 °C [54% from (**4**)].

Tritylation of (±)-(**1**), followed by esterification with (*S*)-*O*-methylmandelyl chloride[5] afforded a mixture of diastereoisomers (**7**) and (**8**),† separable by column chromatography. Detritylation and hydrolysis of the mandelates (**7**) and (**8**) afforded the corresponding enantiomeric alcohols (+)-(**1**) {m.p. 79.0—80.5 °C; $[\alpha]_D$ +2.25° (*c* 0.844, $CHCl_3$); 18% from (±)-(**1**)} and (−)-(**1**) {m.p. 79.0—82.0 °C; $[\alpha]_D$ −2.47° (*c* 1.094, $CHCl_3$); 14% from (±)-(**1**)},‡ respectively. The spectral data (IR, NMR, mass) of the synthetic (+)-(**1**) and (−)-(**1**) were identical with those of the natural product (lit. m.p. reported[2] as 297—298 °C; the m.p. of the natural products kindly given by Dr. Guyot was ~74 °C in our hands).

With the optically active (**1**) thus available by resolution, we then attempted two different chiral syntheses of (−)-(**1**) by unequivocal methods in order to determine the absolute configuration of the natural product (+)-(**1**).

The first approach involved the stereoselective aldol addi-

† The absolute configuration of the *O*-methylmandelate esters (**7**) [δ_H 3.45 (2-H) and 5.42 (4-H)] and (**8**) [δ_H 3.41 (2-H) and 5.43 (4-H)] was estimated to be (2*R*,3*S*) and (2*S*,3*R*), respectively.[5]

‡ (−)-(**1**): $\nu_{max.}$(KBr) 3280, 1635, and 960 cm^{-1}; δ_H 5.78 (1H, m, 5-H), 5.55 (1H, dd, *J* 15.4 and 6.3 Hz, 4-H), 5.45—5.34 (2H, m, 8- and 9-H), 4.32 (1H, m, 3-H), 3.95 (1H, dt, *J* 11.3 and 3.9 Hz, 1-H), 3.91 (1H, m, 2-H), 3.70 (1H, ddd, *J* 11, 7.7, and 3.3 Hz, 1-H), 2.73 (1H, d, *J* 5.0 Hz, CHO*H*, exch.), and 2.68 (1H, dd, *J* 7.4 and 3.9 Hz, CH_2O*H*, exch.); *m/z* 535 (0.76, M^+), 517 (2.09, $M^+ - H_2O$), 225 (52.19), and 60 (100%); satisfactory elemental analyses were obtained.

tion of (**2**) with Evans' chiral haloacetate enolate,[6] prepared from the bromoacetyloxazolidin-2-one (**9**), di-n-butylboryl trifluoromethanesulphonate (1.1 equiv.), and Et_3N, which afforded the bromo aldol adduct (**10**) {89%, $[\alpha]_D$ +43° (*c* 1.025, $CHCl_3$)} with >92% diastereoisomeric purity. Treatment of (**10**) with sodium azide in dimethylformamide (DMF) gave the corresponding azide (**11**) (99%). Methanolysis of (**11**) with methoxymagnesium bromide afforded the enantiomerically pure α-azido ester (**12**) (70%). $LiAlH_4$ reduction of (**12**) gave sphingadienine (**13**) which was immediately converted to the acetonide (**14**) [31% from (**12**)]. Acylation of (**14**) with lauroyl chloride yielded the *N*-lauroyl derivative (**5**) (95%), which was deprotected to give (2*S*,3*R*)-(−)-(**1**) {93%, m.p. 80—81.5 °C, $[\alpha]_D$ −3.20° (*c* 1.769, $CHCl_3$)} (Scheme 2).

In order rigorously to confirm the stereochemistry of (−)-(**1**), another approach to (−)-(**1**) by a stereoselective synthesis from L-serine[7] was carried out (Scheme 3). Reaction of the protected L-serinal (**16**) with nonadec-5-en-1-ynyllithium (**15**) provided the *erythro*-alkynol (**17**) {47%, $[\alpha]_D$ −38.1° (*c* 1.000, $CHCl_3$)} together with the *threo*-isomer (2%). Treatment of (**17**) with *p*-$MeC_6H_4SO_3H$ in MeOH resulted in selective cleavage of the acetal moiety, leading to the 1,3-diol (**18**). Acid hydrolysis of (**18**) to give (**19**) followed by selective $LiAlH_4$ reduction[8] gave (**13**) which was converted to (**14**) without purification. Acylation of (**14**) followed by deprotection gave the crystalline (2*S*,3*R*)-(−)-(**1**) {m.p. 78—80 °C, $[\alpha]_D$ −3.47° (*c* 0.336, $CHCl_3$); lit.[2] m.p. 297—298 °C, $[\alpha]_D$ +2.94° ($CHCl_3$)}.

Compound (**1**) was unambiguously shown by ^1H NMR analysis of (**14**) to have the *erythro*-relative configuration. Since the natural product (**1**) has been reported to have a positive optical rotation {$[\alpha]_D$ +2.94° ($CHCl_3$)}; the present synthesis allows the absolute configuration of the natural product to be assigned as L-*erythro* [(2*R*,3*S*)-(+)-*erythro*-*N*-lauroyldocosasphinga-4,8-dienine].

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