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Enantiopure Aminotriol from D-Isoascorbic Acid Synthesis of D-*Threo*-C-18-Sphingosine.[1]

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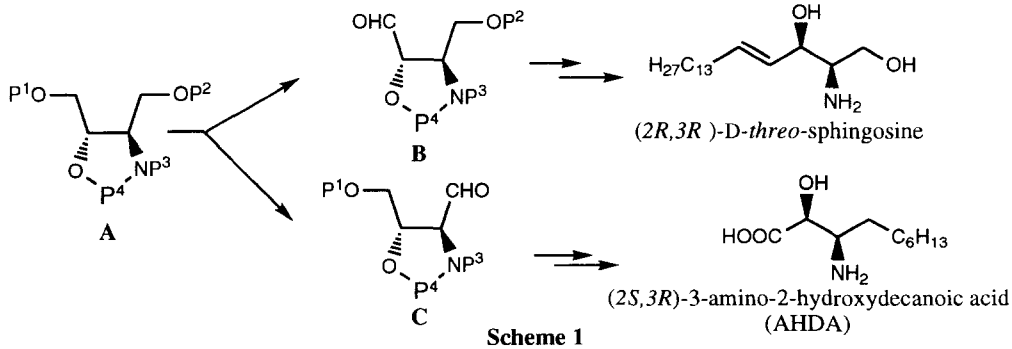
Abstract : Enantiopure suitably *N,O*-protected aminotriol has been prepared from D-isoascorbic acid. The utility of this homochiral building block in the synthesis of (*2R,3R*)-D-*threo*-C_{18}-sphingosine is described *via* a Wittig reaction on a *N,O*-protected β-amino-α-hydroxyaldehyde.

When suitably protected, enantiopure aminotriols **A** are interesting chiral building blocks. They can be converted into 3-deoxy-3-amino-tetrose **B** as well as 2-deoxy-2-amino-tetrose **C**,[2] versatile precursors for the synthesis of biologically active compounds such as (Scheme 1) :

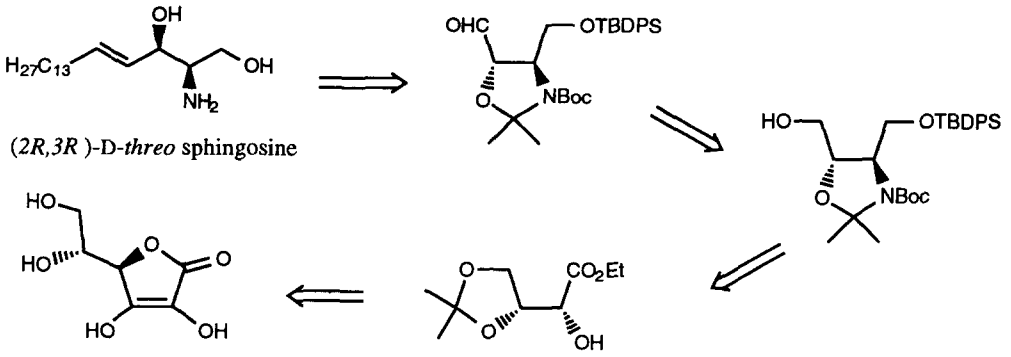
- sphingosine or phytosphingosine,[3,4] major backbone components of glycosphingolipids which play an important role in biological processes on cell surfaces.
- 3-amino-2-hydroxyacid (AHDA) which is the *N*-terminal moiety of microginin,[5] a linear pentapeptide isolated from the freshwater blue-green alga *Microcystis aeruginosa*.



Scheme 1

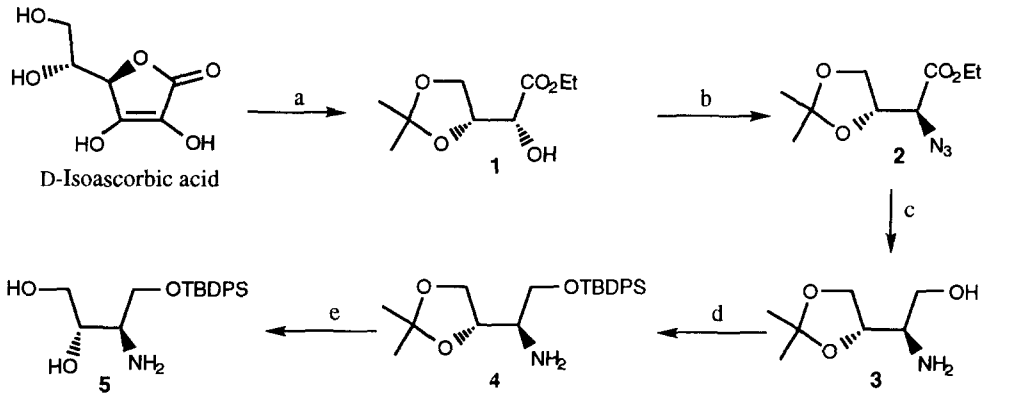
In this paper, we would like to report, firstly the synthesis of the enantiopure aminotriol **A** suitably protected from D-isoascorbic acid, and secondly its transformation into D-*threo*-sphingosine.

For the aminotriol **A** we have selected the following protecting groups : P^2 *tert*-butyldiphenylsilyl (TBDPS), P^3 *tert*-butoxycarbonyl (Boc), and P^4 *N,O*-methylethylidene. The chirality emarges from the D-isoascorbic acid in which the nitrogen atom was introduced with an inversion of configuration (Scheme 2).



Scheme 2

As previously described,[6] the D-isoascorbic acid can be converted in three steps (Scheme 3) into ethyl-3,4-*O*-methylethylidene-D-erythronate **1** by ketalisation, oxidative cleavage of the butenolide moiety and esterification with an overall yield of 67%. Activation of the hydroxyl group of **1** was carried out by trifluoromethanesulfonylation (Tf_2O, $CHCl_3$, - 60°C); the triflate was then converted *in situ* into the ethyl (*2S,3S*)-2-azido-3,4-isopropylidenedioxy-butanoate **2** (95% yield) upon treatment with tetramethylguanidinium azide (TMGA).[7] The reduction of **2** by $LiAlH_4$ in THF produced the aminoalcohol **3** in quantitative yield, then the latter was protected as *tert*-butyldiphenylsilyl ether **4** (TBDPSCl, Et_3N, 4-DMAP cat, CH_2Cl_2, 20°C, 90%). Acidic hydrolysis of **4** (TFA, H_2O, - 5°C) gave the aminodiol **5**.



a) *i*- $(CH_3)_2C(OCH_3)_2$, $CuSO_4$, $(CH_3)_2CO$; *ii*- K_2CO_3, H_2O_2, H_2O; *iii*- C_2H_5I, CH_3CN reflux, 67% overall yield. b) *i*- $(CF_3SO_2)_2O$, 2,6-lutidine, $CHCl_3$, -60°C; *ii*- TMGA, -60°C to 20°C, 95%. c) $LiAlH_4$, THF reflux, 2h. 100% d) TBDPSCl, NEt_3, 4-DMAP cat, CH_2Cl_2, 24h, 20°C, 90%. e) TFA/H_2O 1/1, 5h, -5°C.

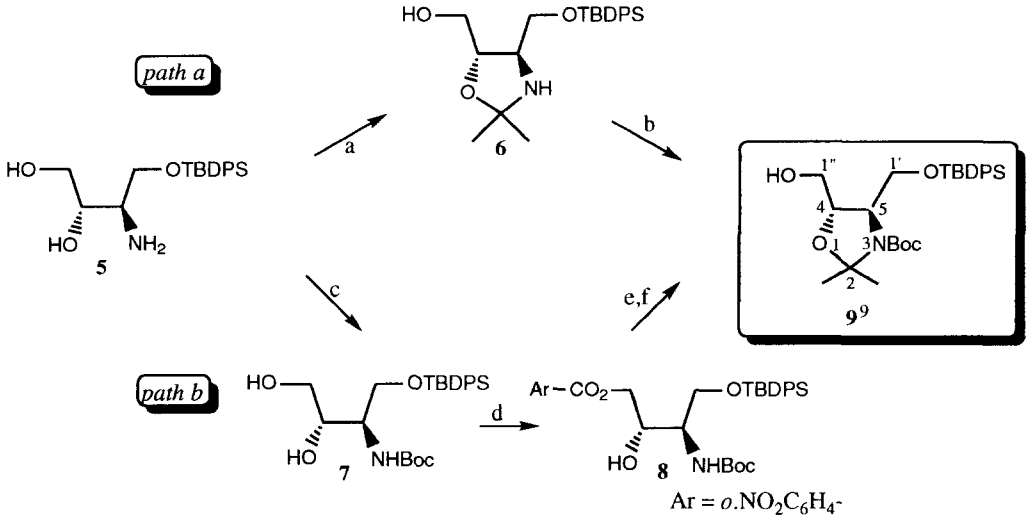
Scheme 3

To access to D-*threo*-sphingosine from **5** we have to transform the primary alcohol function into an alkenyl chain; for this, the other functionnal groups must be concealed. Two approaches (*path a* and *b*) have been investigated to obtain the *N*-Boc-oxazolidine **9** (Scheme 4), which differ only by the order of introduction of the two protecting groups :

path a : Condensation of the aminotriol **5** with dimethoxypropane in acetone in the presence of *p*-toluenesulfonic acid resulted in the clean formation of oxazolidine **6** (72% yield), then reaction with di-*tert*-butoxycarbonyl oxide afforded the *N*-Boc-oxazolidine **9** (35% yield).

path b : Treatment of the aminotriol **5** with 2-*tert*-butoxycarbonyloximino-2-phenylacetonitrile (Boc-ON)[8] in the presence of triethylamine in dioxane-water led to the *N*-Boc aminotriol **7** (83% yield). Its transformation into the *N*-Boc-oxazolidine **9** required successivly the selective *o*-nitrobenzoylation of the primary alcohol function (*o*-$NO_2C_6H_4COCl$, pyr, CH_2Cl_2, 97%),[10] the oxazolidine formation [$(CH_3)_2C(OCH_3)_2$, $(CH_3)_2CO$, BF_3-Et_2O cat, 87%] and the methanolysis of the benzoate protecting group (CH_3OH/THF, K_2CO_3, 95%).

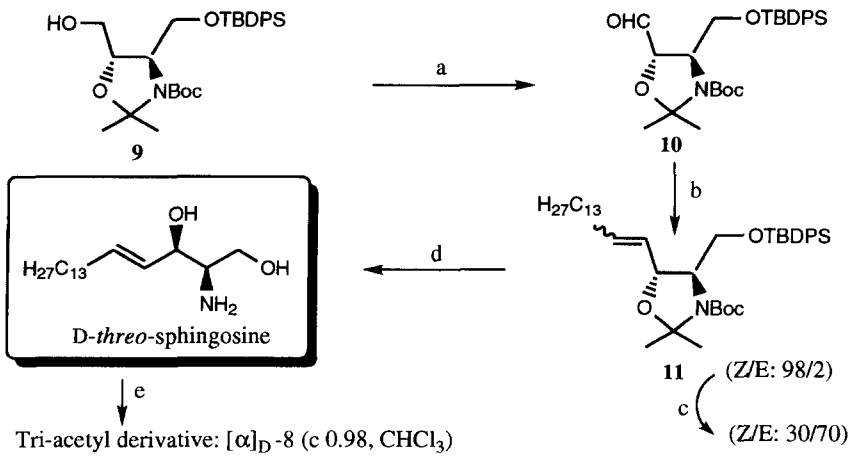
Although *path a* is shorter than *path b*, it is less effective (25% and 67% overall yield, respectively for *path a* and *b)*.



a) $(CH_3)_2C(OCH_3)_2$, $(CH_3)_2CO$, TsOH, 5 days, 20°C, 72%. b) Boc_2O, NEt_3, CH_2Cl_2, 3 days, 20°C, 35%.
c) Boc-ON, NEt_3, dioxane/H_2O 1/1, 83% from **4**. d) *o*.$NO_2C_6H_4COCl$, pyridine, CH_2Cl_2, 4 days, 20°C, 97%.
e) $(CH_3)_2C(OCH_3)_2$, $(CH_3)_2CO$, BF_3-Et_2O cat, 5 days, 20°C, 87% f) K_2CO_3, CH_3OH/THF 1/1, 24h, 20°C, 95%.

Scheme 4

Swern oxidation[11] of the primary alcohol function of **9** (Scheme 5) led to the crude aldehyde **10** which was immediately condensed with the required ylide, obtained from the tetradecyltriphenylphosphonium bromide, to reach **11** as an isomer mixture (*Z/E* 98/2; 95% yield). An isomerisation reaction is brought about by irradiation of **11** in the presence of phenyl sulfide[12] leading to an isomer mixture (*Z/E* 30/70; 91% yield), from which the desired E-isomer **E-11** was easily separated. Finally, acidic hydrolysis (TFA, H_2O, 75%) of **E-11** resulted in the D-*threo*-sphingosine which was characterized by its triacetyl derivative. The specific rotation, melting point and ^1H and ^{13}C NMR spectra were fully in agreement with the literature data,[13] thus confirming that no epimerisation had occurred during this procedure.



a) $(COCl)_2$, DMSO, NEt_3, CH_2Cl_2. b) $C_{13}H_{27}CH_2\overset{+}{P}Ph_3$ Br^-, nBuLi, THF, -78°C to 20°C, 3 days, 95% from **9** (Z/E : 98/2). c) hν, PhSSPh cat, cyclohexane, 91%, (Z/E 30/70). d) TFA/H_2O 1/1, 24h, 20°C, 75%. e) Ac_2O, pyr, 20°C, 12h, 60%.

Scheme 5

In conclusion, a suitably *N,O*-protected enantiopure aminotriol, a precursor of 2-deoxy-2-amino or 3-deoxy-3-amino-threoses, has been prepared from D-isoascorbic acid. The utility of this homochiral building block was demonstrated by the total synthesis of D-*threo*-sphingosine. Further utilization of this flexible methodology in the synthesis of other biologically active compounds will be reported in due course.

EXPERIMENTAL SECTION

Prior to use, tetrahydrofuran (THF) and diethylether (Et_2O) were distilled from sodium-benzophenone and dichloromethane (CH_2Cl_2) from P_2O_5. CH_2Cl_2 and ethyl acetate (EtOAc) were filtered on K_2CO_3 prior to use. ^1H NMR (250 MHz) and ^{13}C NMR (62,9 MHz) spectra were recorded in $CDCl_3$ at room temperature (unless indicated) on a Bruker AM 250. Chemical shifts are reported in δ (ppm) and coupling constants are given in Hertz. High Resolution Mass Spectra were recorded in Service de Spectrométrie de Masse, Université Pierre et Marie Curie. Optical rotations were measured on a Perkin Elmer 241C polarimeter with sodium (589 nm) lamp at 20°C. All reactions were recorded under argon atmosphere, and were monitored by thin-layer chromatography with Merck 60F-254 precoated silica (0.2 mm) on glass. Chromatography was performed with Merck Kieselgel 60 (200-500 μm) or 60H (5-40 μm). Spectroscopic (^1H and ^{13}C NMR, MS) and/or analytical data were obtained using chromatographically homogeneous samples.

Ethyl *(2S,3S)*-2-azido-3,4-isopropylidenedioxy-butanoate (2)

To a stirred solution of ethyl 3,4-*O*-methylethylidene-D-erythronate **1**[6] (30 g, 147.7 mmol) in $CHCl_3$ (350 mL) at -60°C, trifluoromethanesulfonic anhydride (30 mL, 177.2 mmol) and 2,6-lutidine (20.6 mL, 177.2 mmol) were successively added. After 30 min stirring at -60°C, the tetramethylguanidinium azide[14] (70 g, 443 mmol) was slowly added (30 min). Then the reaction mixture was slowly warmed to 20°C and was stirred for 12 h. Flash chromatography on a thin pad of silicagel (cyclohexane/EtOAc 1/1; Rf 0.5) afforded 31.80 g (95%) of **2** as a colorless oil. $[\alpha]_D$ -44 (c 1.05, CH_2Cl_2). IR (neat) 2100, 1740 cm^{-1}. ^1H NMR δ : 4.46 (1H, ddd, H-3, $J_{2,3}$ = 5Hz, $J_{3,4}$ = $J_{3,4'}$ = 6.5Hz), 4.24 (2H, q, OEt, J = 7.5Hz), 4.06, 3.89 (2H, 2dd, H-4,4', $J_{4,4'}$ = 8.5Hz, $J_{3,4}$ = $J_{3,4'}$ = 6.5Hz), 3.68 (1H, d, H-2, $J_{2,3}$ = 5Hz), 1.44, 1.30 (6H, 2s, CMe_2), 1.27 (3H, t, OEt, J = 7.5Hz). ^{13}C NMR δ : 167.8 (C-1), 110.2 ($\underline{C}Me_2$), 75.6 (C-3), 66.1 (C-4), 62.4 (C-2), 61.9 ($O\underline{C}H_2CH_3$), 25.7, 24.6, ($C\underline{Me}_2$), 13.8, ($OCH_2\underline{C}H_3$). Anal. Calcd. for $C_9H_{15}N_3O_4$: C, 47.16; H, 6.60, Found : C, 47.17; H, 6.49.

***(2S,3R)*-3-Amino-1,2-isopropylidenedioxy-butan-4-ol (3)**

To a stirred mixture of $LiAlH_4$ (6.7 g, 176.5 mmol) in dry THF (60 mL), at 0°C, was added dropwise the azidoester **2** (10.1 g, 44.1 mmol) in dry THF (60 mL). After stirring for 30 min at 20°C, the mixture was refluxed for 2.5 h, then H_2O (6.7 mL), 15% aqueous NaOH (6.7 mL) and H_2O (20.1 mL) were successively added to the cooled mixture. The precipitate was filtered and washed successively with diethylether and hot chloroform; the filtrate was then dried (Na_2SO_4). Concentration *in vacuo* afforded 7 g of **3** as a colorless oil in quantitative yield. $[\alpha]_D$ -2.7 (c 1.24, CH_2Cl_2). IR (neat) 3360, 3300 cm^{-1}. ^1H NMR δ : 4.08-3.90 (2H, m, H-1',2), 3.75-3.65 (1H, m, H-1), 3.53 (1H, dd, H-4, $J_{4,4'}$ = 11Hz, $J_{3,4}$ = 5Hz), 3.41 (1H, dd, H-4', $J_{4,4'}$ = 11Hz, $J_{3,4'}$ = 6Hz), 2.80 (1H, m, H-3), 1.39, 1.30 (6H, 2s, CMe_2). ^{13}C NMR δ : 108.2 ($\underline{C}Me_2$), 76.9 (C-3), 65.9 (C-4), 62.7 (C-1), 54.6 (C-2), 25.9, 24.6 ($C\underline{Me}_2$). Anal. Calcd. for $C_7H_{15}NO_3$: C, 52.16; H, 9.38; N, 8.69, Found : C, 52.31; H, 9.49; N, 8.68.

***(2S,3R)*-3-Amino-4-*tert*-butyldiphenylsilyloxy-1,2-isopropylidenedioxy-butane (4)**

To a stirred solution of **3** (1 g, 6.2 mmol) and triethylamine (863 µL, 6.21 mmol) in CH_2Cl_2 (40 mL) was added dropwise *tert*-butylchlorodiphenylsilane (1.6 mL, 6.2 mmol) then 4-dimethylaminopyridine (46 mg, 0.37 mmol). After stirring for 24 h, the reaction mixture was poured into water and extracted with CH_2Cl_2 (3x50 mL) and the combined organic layers were dried (Na_2SO_4), filtered and concentred *in vacuo*. Flash chromatography of the residue (cyclohexane/EtOAc 1/1; Rf 0.3) afforded 2.2 g (89%) of **4.** $[\alpha]_D$ -6 (c 1.15, CH_2Cl_2).^1H NMR δ : 7.62, 7.40 (10H, 2m, Ph), 4.05 (1H, q, H-2, $J_{1,2}$ = $J_{1',2}$ = 6Hz), 3.91 (1H, dd, H-1, $J_{1,1'}$ = 8Hz, $J_{1,2}$ = 6Hz), 3.69 (1H, dd, H-1', $J_{1,1'}$ = 8Hz, $J_{1',2}$ = 6Hz), 3.60 (1H, dd, H-4, $J_{4,4'}$ = 10Hz, $J_{3,4}$ = 6Hz), 3.52 (1H, dd, H-4', $J_{4,4'}$ = 10Hz, $J_{3,4'}$ = 6Hz), 2.83 (1H, q, H-3, $J_{3,2}$ = 6Hz), 1.38, 1.33 (6H, 2s, CMe_2), 1.04 (9H, s, *t*Bu). ^{13}C NMR δ : 135.2, 132.9, 129.4, 127.4 (Ph), 108.2 ($\underline{C}Me_2$), 77.0 (C-3), 66.3, 66.0 (C-1,4), 54.8 (C-2), 26.5 ($\underline{Me}_3C$), 26.3, 25.0 ($C\underline{Me}_2$), 18.8 ($Me_3\underline{C}$). MS (EI, %) 400 $(M+1)^{\cdot+}$, 384 (10), 342 (45), 298 (60), 240 (80), 199 (80). HMRS for $C_{23}H_{33}NO_3Si$ (M^+), calcd 399.2230, found 399.2228. Anal. Calcd. for $C_{23}H_{33}NO_3Si$: C, 69.13; H, 8.32; N, 3.51, Found : C, 69.26; H, 8.39; N, 3.49.

(*2S,3R*)-3-Amino-4-*tert*-butyldiphenylsilyloxy-butane-1,2-diol (5)

To a stirred mixture of **4** (9.67 g, 24.23 mmol) in water (121 mL) at -5°C was added dropwise trifluoroacetic acid (121 mL). After 5 h stirring, aqueous ammonia solution (33%) was added until pH 8-9, then the resulting mixture was extracted with CH_2Cl_2. The combined organic extracts were dried (Na_2SO_4), filtered and concentrated *in vacuo*. The crude product was used in the next step without further purification.

(*4R,5S*)-4-*tert*-Butyldiphenylsilyloxymethyl-5-hydroxymethyl-2,2-dimethyl-1,3-oxazolidine (6)

To a stirred solution of the aminodiol **5** (35 mg, 0.097 mmol) in acetone (500 µL) in presence of a catalytic amount of *p*-toluenesulfonic acid was added 2,2-dimethoxypropane (24 µL, 0.195 mmol) at 20°C. After 5 days stirring, the mixture was concentrated *in vacuo,* then water (3 mL) was added. After extraction with CH_2Cl_2 (3x5mL), the combined organic extracts were washed with saturated aqueous $NaHCO_3$, then dried (Na_2SO_4), filtered and concentrated *in vacuo*. Flash chromatography of the residue ($MeOH/CH_2Cl_2/NEt_3$ 1/9/1‰; Rf 0.3) afforded 28 mg (72%) of **6**. $[\alpha]_D$ -3 (c 1.06, CH_2Cl_2). ^1H NMR δ : 7.60,7.38 (10H, 2m, Ph), 3.82-3.90 (2H, m, H-1",5), 3.72 (1H, dd, H-1", $J_{1",5}$ = 4Hz, $J_{1",1"}$ = 11Hz), 3.67 (1H, dd, H-1', $J_{1',1'}$ = 11.5Hz, $J_{1',4}$ = 3.5Hz), 3.47 (1H, dd, H-1', $J_{1',1'}$ = 11.5Hz, $J_{1',4}$ = 4.5Hz), 3.3-3.2 (1H, m, H-4), 1.44, 1.34 (6H, 2s, CMe_2), 1.05 (9H, s, *t*Bu). ^{13}C NMR δ : 135.4, 132.7, 129.9, 127.7 (Ph), 94.9 ($\underline{C}Me_2$), 78.9 (C-5), 62.8, 61.6 ($\underline{C}H_2OH$, $\underline{C}H_2OTBDPS$), 60.2 (C-4), 28.2, 28.0 ($C\underline{Me}2$), 26.8 ($\underline{Me}_3C$), 14.1 ($Me_3\underline{C}$). MS (EI, %) 384 (10), 342 (45), 206 (25), 199 (77), 188 (25), 181 (30), 162 (28), 130 (100). MS (CI,NH_3) : 400 $(M+1)^{\cdot+}$(100).

(*2S,3R*)-3-*N*-*tert*-Butoxycarbonylamino-4-*tert*-butyldiphenylsilyloxy-butan-1,2-diol (7)

To the amine **5** (8.7 g, 24.23 mmol) in a 50% aqueous solution of 1,4-dioxane (100 mL) was successively added Et_3N (5.05 mL, 36.35 mmol) and 2-*tert*-butoxycarbonyloximino-2-phenylacetonitrile (6.56 g, 26.65 mmol) at 20°C. After 4.5 h stirring, and extraction with CH_2Cl_2 (3x100 mL), the organic layers were dried (Na_2SO_4), filtered and concentrated *in vacuo*. Flash chromatography of the residue (EtOAc/cyclohexane 4/6; Rf 0.4) afforded 9.2 g (83%) of **7** (yellow oil). $[\alpha]_D$ +1 (c 1.1, CH_2Cl_2).^1H NMR δ : 7.60, 7.40 (10H, m, Ph), 4.97 (1H, d, NH, $J_{3,NH}$ = 8.6 Hz), 4.00 (1H, m, H-2), 3.90-3.70 (3H, m, H-3,4,4'), 3.65-3.40 (2H, 2m, H-1,1'), 1.40 (9H, s, O*t*Bu), 1.06 (9H, s, Si*t*Bu). ^{13}C NMR δ : 156.6 ($N\underline{C}O_2$) 135.4, 132.7, 129.7, 127.7 (Ph), 79.6 ($O\underline{C}Me_3$), 71.4 (C-2), 64.6 (C-1), 63.3 (C-4), 52.2 (C-3), 28.2 ($OC\underline{Me}_3$), 26.7 ($\underline{Me}_3CSi$) .

(*2S,3R*)-3-*N*-*tert*-Butoxycarbonylamino-4-*tert*-butyldiphenylsilyloxy-1-(*o*-nitrobenzoyloxy)-butan-2-ol (8)

To the diol **7** (9.2 g, 20.1 mmol) in CH_2Cl_2 (70 mL) at 20°C was successively added pyridine (1.76 mL, 22.1 mmol) and 2-nitrobenzoyl chloride (2.64 mL, 20.1 mmol) in CH_2Cl_2 (10 mL) . After 4 days stirring, an 2% aqueous solution of H_2SO_4 (70 mL) was added, and the mixture was extracted with CH_2Cl_2 (3x100 mL). The organic layers were dried (Na_2SO_4), filtered and concentrated *in vacuo*. Flash chromatography of the

residue (EtOAc/cyclohexane 3/7; Rf 0.4) afforded 11.8 g (97%) of **8**. $[\alpha]_D$ +1 (c 1.1, CH_2Cl_2). ^1H NMR δ : 7.90, 7.40, (14H, 4m, Ar), 5.04 (1H, d, NH, $J_{NH,3}$ = 7.2Hz), 4.45-4.35 (3H, m, H-1,1',2), 3.90-3.70 (3H, m, H-3,4,4'), 1.40 (9H, s, O*t*Bu), 1.00 (9H, s, Si*t*Bu). ^{13}C NMR δ : 165.1 (Ar<u>C</u>O_2), 155.8 (N<u>C</u>O_2), 148.1, 135.5, 133.0, 131.8, 130.0, 127.8, 123.8 (Ar), 79.7 (O<u>C</u>Me_3), 69.3 (C-2), 67.7 (C-1), 64.8 (C-4), 52.3 (C-3), 28.3 (OC<u>Me</u>$_3$), 26.8 ($\underline{Me}_3$CSi), 19.1(Me_3<u>C</u>Si).

(4R,5S)-3-*N*-*tert*-Butoxycarbonyl-4-*tert*-butyldiphenylsilyloxymethyl-5-hydroxymethyl-2,2-dimethyl-1,3-oxazolidine (9)

From **6** :

To the oxazolidine **6** (4.57 g, 11.45 mmol) in CH_2Cl_2 (35 mL) at 0°C was successively added di-*tert*-butyl dicarbonate (2.75 g, 12.59 mmol) and NEt_3 (2.38 mL, 17.18 mmol). After 3 days at 20°C, the reaction was quenched with water (50 mL). Extraction with (3x50 mL), drying (Na_2SO_4), filtration, concentration *in vacuo* and flash chromatography (EtOAc/cyclohexane 2/8; Rf 0.4) afforded 2 g (35%) of **9** as a colorless oil.

From the benzoate **8** :

A solution of **8** (11.8 g, 19.4 mmol) in acetone (97 mL) at 20°C was successively added 2,2-dimethoxypropane (9.5 mL, 77.63 mmol) and BF_3-Et_2O (48 µL, 0.38 mmol). After 5 days at 20°C, concentration, and addition of water (50 mL), the combined organic extracts (CH_2Cl_2, 3x50 mL) were washed, with a saturated aqueous solution of $NaHCO_3$, dried (Na_2SO_4), filtered and concentred *in vacuo*. Flash chromatography of the residue (EtOAc/cyclohexane 2/8; Rf 0.4) afforded 10.9 g (87%) of the oxazolidine. m.p. 125-126°C. $[\alpha]_D$ +5 (c 1.05, CH_2Cl_2). ^1H NMR (C_6D_6, 70°C) δ : 7.80, 6.60 (14H, 4m, Ar), 4.71 (1H, m, H-5), 4.53 (1H, dd, H-1", $J_{1",5}$ = 4Hz, $J_{1",1"}$ = 11Hz), 4.39 (1H, dd, H-1", $J_{1",1"}$ = 11Hz, $J_{1",5}$ = 6Hz), 4.05-4.00 (2H,m, H-1'), 3.96 (1H, ddd, H-4, $J_{4,5}$ = 9Hz, $J_{1',4} = J_{1',4}$ = 5Hz), 1.60, 1.58 (6H, 2s, CMe_2), 1.35 (9H, s, O*t*Bu), 1.15 (9H, s, Si*t*Bu). ^{13}C NMR (C_6D_6, 70°C) δ : 164.9 (Ar<u>C</u>O_2), 158.4 (N<u>C</u>O_2), 149.2, 136.1, 133.9, 131.6, 131.4, 130.0, 123.8 (Ar), 95.5 (C-2), 79.8 (O<u>C</u>Me_3), 76.0 (C-5), 67.4 (C-1"), 63.5 (C-1'), 60.8 (C-4), 28.5 (OC<u>Me</u>$_3$), 28.0, 27.0 (C<u>Me</u>$_2$), 27.2 ($\underline{Me}_3$CSi), 19.5 (Me_3<u>C</u>Si). MS (EI, %) 633 (1), 535 (90), 491 (20). MS (CI, NH_3) : 649 $(M+1)^{\cdot+}$(100). Anal. Calcd. for $C_{35}H_{44}N_2O_8Si$: C, 64.79; H, 6.84; N, 4.32, Found : C, 64.80; H, 6.89; N, 4.41.

A solution of the previous oxazolidine in a 1/1 mixture of THF/MeOH (168 mL) in presence of K_2CO_3 (194 mg, 1.40 mmol) was stirred during 24 h at 20°C. After concentration *in vacuo*, water (50 mL) was added, and the CH_2Cl_2 extracts (3x70 mL) were dried (Na_2SO_4) and concentrated *in vacuo*. Flash chromatography of the residue ($PhCH_3$/acetone 95/5; Rf 0.3) afforded 6.70 g (95%) of **9**.

9 : $[\alpha]_D$ -15 (c 1.25, CH_2Cl_2). IR (neat) 1700 cm^{-1}. ^1H NMR (C_6D_6, 70°C) δ : 7.70-7.20 (10H, 2m, Ph), 4.40 (1H, m, H-5), 4.1-3.9 (2H, m, H-1',4), 3.92 (1H, dd, H-1', $J_{1',5}$ = 6Hz, $J_{1',1'}$ = 11Hz), 3.70-3.50 (2H, m, H-1"), 1.66, 1.58 (6H, 2s, CMe_2), 1.32 (9H, s, O*t*Bu), 1.13 (9H, s, Si*t*Bu). ^{13}C NMR (C_6D_6, 70°C) δ : 152.0 (N<u>C</u>O_2), 136.0, 133.9, 129.7 (Ph), 95.0 (C-2), 79.8 (O<u>C</u>Me_3), 78.9 (C-5), 64.0 (C-1"), 63.7 (C-1'), 60.1 (C-4), 28.5 (OC<u>Me</u>$_3$), 28.1, 26.9 (C<u>Me</u>$_2$), 27.2 ($\underline{Me}_3$CSi), 19.5 (Me_3<u>C</u>Si). MS (EI, %) 484 (10), 442 (75), 426 (40), 386 (90), 306 (40), 264 (20), 240 (25), 199 (85), 135 (100) . MS (CI, NH_3) : 500 $(M+1)^{\cdot+}$(100).

(4R,5S)-3-*N*-*tert*-Butoxycarbonyl-4-*tert*-butyldiphenylsilyloxymethyl-5-formyl-2,2-dimethyl-1,3-oxazolidine (10)

To a stirred solution of oxalyl chloride (126 µL, 1.47 mmol) in CH_2Cl_2 (2 mL) at -78°C was slowly added DMSO (208 µL, 2.93 mmol). The resulting complex was stirred for 15 min at -78°C prior to the addition of alcohol **9** (488 mg, 0.98 mmol) in CH_2Cl_2 (5 mL). After 45 min at -65°C, Et_3N (815 µL, 5.87 mmol) was added and, then after 1.5 h, Et_2O (30 mL) was added into the reaction mixture. The salt (Et_3NHCl) was removed by filtration, and the filtrate was concentred *in vacuo* to give **10** (colorless oil) which was used without further purification in the next step.

(4R,5R)-3-*N*-*tert*-Butoxycarbonyl-4-*tert*-butyldiphenylsilyloxymethyl-2,2-dimethyl-5-[(E)-1-pentadecenyl]-1,3-oxazolidine (E-11) and its stereoisomer (Z-11)

To the suspension of the tetradecyltriphenylphosphonium bromide (1.58 g, 2.93 mmol.) in THF (12 mL), at -78°C, was added dropwise n-butylithium (1.5 M in hexane, 1.9 mL, 2.88 mmol.); after 4 h stirring, a solution of the crude aldehyde **10** in THF (10 mL) was added. The temperature was then raised to 20°C for 3 days to achieve the Wittig reaction. Finally the mixture was concentrated *in vacuo* and poured into water (30 mL) and extracted with CH_2Cl_2 (3x60 mL). The organic extracts were dried (Na_2SO_4), filtered, concentrated *in vacuo*, and the residue was purified by flash chromatography (cyclohexane/EtOAc 96/4) to give 622 mg of **11** as an isomer mixture (Z/E 98/2, 95%).

A cyclohexane solution (3.5 mL) of **11** (47 mg, 0.069 mmol) and phenylsulfide (4 mg) was irradied with 100-W high pressure mercury lamp under argon for 2h. The solution was concentrated and chromatographed (EtOAc/cyclohexane 3.5/96.5) to give **(Z-11)** (Rf 0.3, 13 mg, 27%) and **(E-11)** (Rf 0.4, 30 mg, 64%).

(E-11) : $[\alpha]_D$ -11 (c 1.2, CH_2Cl_2). ^1H NMR (C_6D_6, 65°C) δ : 7.77, 7.24 (10H, 2m, Ph), 5.82 (1H, m, H-2"), 5.62 (1H, dd, H-1", $J_{1",5}$ = 6.4Hz, $J_{1",2"}$ = 15.5Hz), 4.89 (1H, dd, H-5, $J_{5,4}$ = $J_{1",5}$ = 6.4Hz), 4.41-4.20 (1H, m, H-1'a), 3.90 (1H, *br* d, H-1'b, $J_{1',1'}$ = 10Hz), 3.79 (1H, ddd, H-4, $J_{4,5}$ = 6.4Hz, $J_{1',4}$ = 2.8Hz and 3.6Hz), 1.96, (2H, m, H-3"), 1.78, 1.70 (6H, 2s, CMe_2), 1.41 (9H, s, O*t*Bu) 1.39-1.31 (22H, *br* s, H4"-14") , 1.18 (9H, s, Si*t*Bu), 0.89 (3H, t, CH_3, J = 6.8Hz). ^{13}C NMR (C_6D_6, 65°C) δ : 152.1 ($N\underline{C}O_2$), 136.1, 130.0, 120.1 (Ph), 134.8 (C-1") 128.3 (C-2") 94.6 (C-2), 79.4 ($O\underline{C}Me_3$), 78.3 (C-5), 64.3 (C-4), 62.1 (C-1'), 32.6 (C-3"), 30.1, 29.9, 29.7, 29.5, 29.4, 23.0 (C-4"-C14"), 28.5 ($OC\underline{Me}_3$), 28.1, 27.0 ($C\underline{Me}_2$), 27.2 ($\underline{Me}_3CSi$), 19.5 ($Me_3\underline{C}Si$), 14.2 (C-15").

(Z-11) : $[\alpha]_D$ -37 (c 1.27, CH_2Cl_2). ^1H NMR (C_6D_6, 65°C) δ : 7.80, 7.23 (10H, 2m, Ph), 5.56 (2H, m, H-1",2"), 5.33 (1H, dd, H-5, $J_{5,1"}$ = 7Hz, $J_{5,4}$ = 5.2Hz), 4.29 (1H, m, H-1'a), 3.84 (2H, m, H-1'b,4), 2.34 (1H, m, H-3"a), 2.14 (1H, m, H-3"b), 1.78, 1.70 (6H, 2s, CMe_2), 1.37 (9H, s, O*t*Bu), 1.31 (22H, *br* s, H4"-14"), 1.20 (9H, s, Si*t*Bu), 0.90 (3H, t, CH_3, J = 6.8Hz). ^{13}C NMR (C_6D_6, 65°C) δ : 152.1 ($N\underline{C}O_2$), 136.1, 135.3, 130.0, 128.1 (Ph), 135.3 (C-1"), 129.4 (C-2"), 94.6 (C-2), 79.4 ($O\underline{C}Me_3$), 72.8 (C-5), 65.0 (C-4), 62.1 (C-1'), 32.3 (C-3"), 30.1, 30.0, 29.9, 29.7, 29.6, 28.2, (C-4"-14"), 28.5 ($OC\underline{Me}_3$), 28.2, 27.2 ($C\underline{Me}_2$), 27.3 ($\underline{Me}_3CSi$), 19.6 ($Me_3\underline{C}Si$), 14.2 (C-15"). HMRS for $C_{34}H_{45}NO_4Si$: (M^+- 2 *t*Bu), calcd

563.3431, found 563.3431. Anal. Calcd. for $C_{42}H_{67}NO_4Si$: C, 74.40; H, 9.96; N, 2.07, Found : C, 74.39; H, 9.59; N, 2.05.

D-*threo*-Sphingosine

A solution of **E-11** (287 mg, 0.423 mmol) in trifluoroacetic acid/H_2O (v/v : 3/1, 9.3 mL) was stirred at room temperature for 24 h. Aqueous ammonia solution (33%) was then added until pH 8-9, and the resulting mixture was extracted with CH_2Cl_2. The combined organic extracts were dried (Na_2SO_4), filtered, and concentrated *in vacuo* and chromatographed (MeOH/CH_2Cl_2/NEt_3 1/9/1‰, Rf 0.1, then MeOH) to give 95 mg of sphingosine (75%).

$[\alpha]_D$ +4 (c 0.56, $CHCl_3$). ^1H NMR (pyridine d_5) δ : 5.96 (1H, dt, H-5, $J_{5,4}$ = 15Hz, $J_{5,6}$ = 6Hz), 5.83 (1H, dd, H-4, $J_{3,4}$ = 7Hz, $J_{5,4}$ = 15Hz), 4.91 (1H, t, H-3, $J_{3,4}$ = $J_{2,3}$ = 7Hz), 4.43 (1H, dd, H-1a, $J_{1a,1b}$ = 12Hz, $J_{1a,2}$ = 4Hz), 4.30 (1H, dd, H-1b, $J_{1a,1b}$ = 12Hz, $J_{1b,2}$ = 6Hz), 3.73 (1H, *br* s, H-2), 2.01 (2H, q, H-6, $J_{6,5}$ = $J_{6,7}$ = 7Hz), 1.23 (22H, *br* s, H7-17), 0.90 (3H, t, CH_3, J = 6.8Hz). ^{13}C NMR (pyridine d_5) δ : 134.5 (C-4), 130.4 (C-5), 70.5 (C-3), 60.2 (C-1), 59.2 (C-2), 32.8 (C-6), 32.2 (C-16), 29.8, 29.7, 29.5, 29.3, 29.2, (C-7-C15), 22.8 (C-17), 14.2 (C-18).

Acetylation of D-*threo*-sphingosine

To a solution of sphingosine (45 mg, 0.15 mmol) in pyridine (1.2 mL) was added acetic anhydride (1.4 mL) at 20°C. After stirring for 12 h, concentration, addition of a saturated aqueous solution of $NaHCO_3$, the combined organic extracts (CH_2Cl_2, 3x10 mL) were dried (Na_2SO_4), filtered and concentred *in vacuo*. Flash chromatography of the residue (EtOAc/cyclohexane 6/4; Rf 0.3) and recrystallization (EtOAc/hexane) afforded 38 mg (60%) of the triacetyl derivative of sphingosine. m.p. 43-44°C. $[\alpha]_D$ -8 (c 0.98, $CHCl_3$). ^1H NMR (pyridine d_5) δ : 5.75 (1H, m, H-5, $J_{5,4}$ = 15Hz), 5.60 (1H, d, NH, $J_{NH,2}$ = 8.8Hz), 5.39 (1H, m, H-3), 5.36 (1H, m, H-4), 4.38(1H, m, H-2), 4.05 (2H, m, H-1), 2.05, 2.04, 1.96 (9H, 3s, CH_3CO), 2.02 (22H, s, H-6-17), 0.85 (3H, t, CH_3, J = 6.8Hz). ^{13}C NMR δ : 170.6, 170.1, 169.8 ($CH_3\underline{C}O$), 137.3 (C-4), 124.1 (C-5), 73.0 (C-3), 63.1 (C-1), 50.9 (C-2), 32.2, 31.9, 29.7, 29.4, 29.3, 29.1, 28.8, 22.7 (C-6-17), 23.2, 21.0, 20.7,($\underline{C}H_3$), 14.1 (C-18). Anal. Calcd. for $C_{24}H_{43}NO_5$: C, 67.73; H, 10.18; N, 3.29, Found : C, 67.74; H, 10.11; N, 3.24.

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