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Highly efficient stereoselective synthesis of D-*erythro*-sphingosine and D-*lyxo*-phytosphingosine

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Abstract—Starting from a single suitable functionalised epoxide, a highly efficient stereoselective synthesis of D-*erythro*-sphingosine and D-*lyxo*-phytosphingosine is described. The approach allows the formal preparation of all stereoisomers of these sphingoid structures.

1. Introduction

Sphingolipids such as ceramides, cerebrosides and gangliosides are ubiquitous components of cell membranes, where they are involved in various processes based on recognition phenomena.[1] Common to this diverse group of natural products is a sphingoid base scaffold with a polar 2-amino alcohol head and a long aliphatic chain with a 4,5-trans double bond as in sphingosines (Fig. 1) or an 2-amino-1,3,4 triol head group without unsaturation as in phytosphingosines (Fig. 2).[2] The hydrophilic moiety, located on the external surface of the membrane, determines the specificity of interactions, whereas the lipophilic portion, anchored on the outer-leaflet, contributes primarily to the structural rigidity of the membrane.[3]

The wide spectrum of the biological activity of these molecules justifies the efforts towards the synthesis of them as well as of their stereoisomers and various analogues. Although the most commonly employed strategies are those which make use of carbohydrates[4] and serine[5] as source of chirality, many approaches are also based on asymmetric reactions, such as aldol condensation[6] as well as Sharpless asymmetric dihydroxylation[7] and asymmetric epoxidation (using Shi's catalyst[8] or Sharpless protocol[9]).

However, using the above-mentioned asymmetric reactions, the required introduction of the amino group often suffered from low regio- and stereoselectivity and therefore these approaches were scarcely utilised compared to those of natural products from the chiral pool. Furthermore, rarely a single

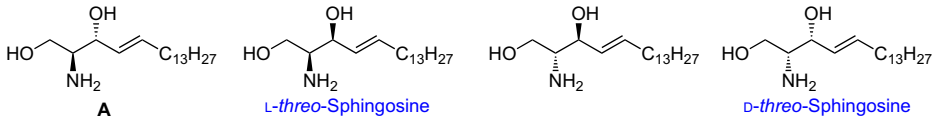

Figure 1.

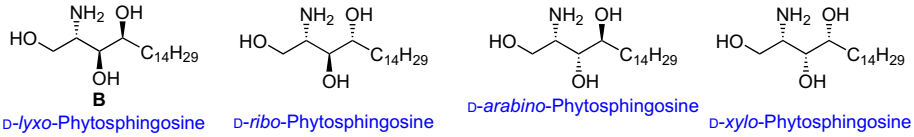

Figure 2.

Keywords: Functionalised epoxides; Amino alcohols; Sphingosines; Phytosphingosines.
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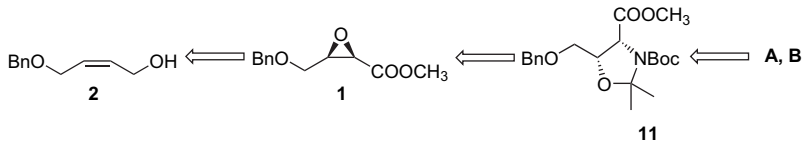


Scheme 1.

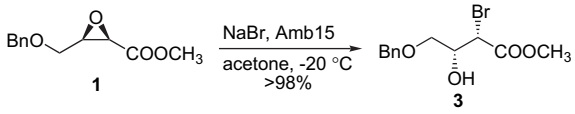
strategic approach has been designed to both sphingosines and phytosphingosines classes, due to the differences in their structure.

2. Results and discussion

In this regard, our approach to both classes of sphingoid structures is based on a stereoselective route from an easily prepared chiral epoxide **1**, obtained by the Sharpless AE of commercial allylic alcohol **2** (Scheme 1).

The introduction of the amino group to the common key oxazolidine **11** could be easily achieved based on the results obtained in the regio- and stereoselective opening of bifunctionalised epoxides with metal halides,[10] a route which can be considered very attractive for its generality.

Our synthesis started with known α,β-epoxy ester **1**, derived from the commercially available *Z*-4-benzyloxy-2-buten-1-ol **2**. Treatment with the NaBr/Amberlyst 15 system, already utilised for the regioselective opening of differently substituted α,β-epoxy esters,[11] furnished, with excellent stereoselectivity and chemical yield, the bromohydrin **3** (Scheme 2).



Scheme 2.

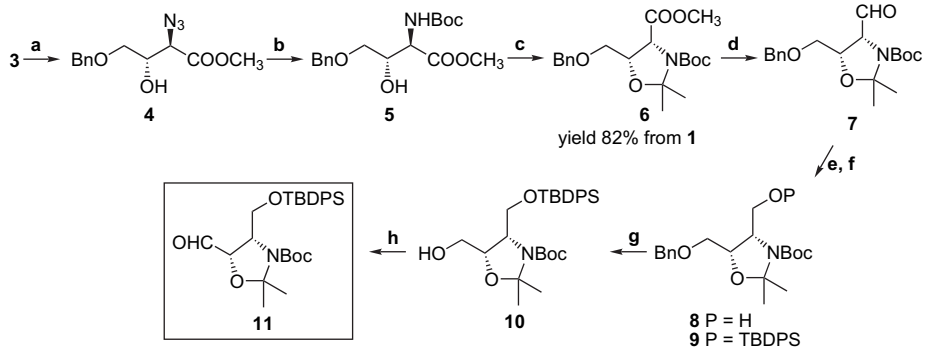
The polar 2-amino alcohol head was then easily obtained by subsequent transformation of the halide into an amino group: thus stereoselective azide nucleophilic substitution furnished the corresponding azido alcohol **4** in nearly quantitative yield (Scheme 3). The subsequent hydrogenation of **4** afforded the vicinal *anti* amino alcohol **5**, which was easily transformed into **6**. Worthy of note is that the key oxazolidine **6** was obtained from **1** with an overall yield of 82% without any purification of the previous intermediates.

Successively, **6** was converted into **11**, a suitable common precursor for the synthesis of sphingosine and phytosphingosine, through a few high-yielding steps. As shown in Scheme 3, the transformation of **6** into the alcohol **8** was performed by first reducing **6** with DIBAL to the aldehyde **7** and then with $NaBH_4$ to **8**.[12] After protection of the hydroxyl function of **8** as silyl ether, **9** was debenzylated and then the free alcohol group of **10** was oxidised to the aldehyde with the Py/SO_3 complex in a high-yielding sequence.

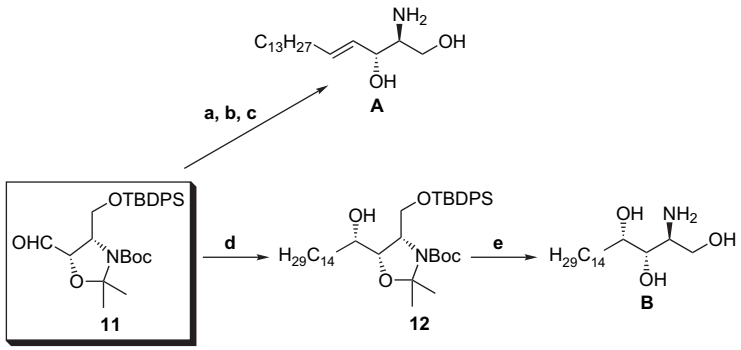
Multifunctional aldehyde **11** represents the key intermediate for the final transformation into different sphingoid structures, such as the D-*erythro*-sphingosine **A** and D-*lyxo*-phytosphingosine **B**. Although its preparation was already known starting from isoascorbic acid, our route is shorter (11 steps) and with higher overall yield. Furthermore, starting from *ent*-epoxy ester **2** the opposite enantiomer of **11** can be prepared.

Finally, aldehyde **11** was transformed into the D-*erythro*-sphingosine **A** following the already reported synthetic sequence[13] (Scheme 4). On the other hand, the D-*lyxo*-phytosphingosine **B** was finally prepared through the stereoselective addition of the required lithium cuprate, obtained from tetradecyl bromide, as clearly demonstrated by the value of the coupling constant of the diol system of **12** (J~4 Hz), which confirms its *syn* stereochemistry.[14] Subsequent deprotection afforded the phytosphingosine **B**, with its tetraacetate derivative resulting identical to the data reported in literature.[5a,c,7b]

In summary, through stereocontrolled, facile and high-yield reactions, we have developed a general highly efficient route, starting from the easily accessible *Z*-4-benzyloxy-2-buten-1-ol, to the preparation of both enantiomers D- and L-*erythro*-sphingosines. Starting from the known *E*-4-benzyloxy-2-buten-1-ol and following the same synthetic scheme it would be possible to have access to the D- and



Scheme 3. (a) NaN_3, DMF, rt; (b) H_2/Pd, Boc_2O, EtOAc, rt; (c) 2,2-DMP, *p*-TsOH, CH_2Cl_2, rt; (d) DIBAL, toluene, −78 °C, >95%; (e) $NaBH_4$, *i*-PrOH/THF, rt, >95%; (f) TBDPSCl, Et_3N, DMAP, rt, 93%; (g) H_2/Pd, MeOH, rt, 93%; (h) Py/SO_3, DMSO, 0 °C, 85%.



Scheme 4. (a) nC$_{14}$H$_{29}$PPh$_3$Br, nBuLi, THF, −78 °C to rt, 95%; (b) hν, PhSSPh cat., c-hexane, 91% (*Z*/*E*, 30/70); (c) TFA/H$_2$O 1:1, rt, 75%; (d) (nC$_{14}$H$_{29}$)$_2$CuLi, Et$_2$O, −20 °C, 65%; (e) TFA/H$_2$O 1:1, rt, 75%.

L-*threo*-diastereoisomers of sphingosine. Preliminary studies have shown in fact for this substrate the same aptitude for the formation of the corresponding oxazolidine (Scheme 5).

On the other hand, we have also prepared the D-*lyxo* phytosphingosine as well as, formally, the L-*lyxo*-phytosphingosine, throughout the *syn* diastereoselective addition of tetradecyl lithium cuprate to the aldehyde **11**.[14] Starting from the *E*-4-benzyloxy-2-buten-1-ol, the same diastereoselective reaction would give access to the D- or L-*xylo*-phytosphingosine. Moreover, the use of a diastereoselective organometallic *anti* addition to the aldehyde **11**[14] could be, in principle, adaptable even for the synthesis of D-*ribo*-phytosphingosine starting from the *Z*-4-benzyloxy-2-buten-1-ol and of D-*arabino*-phytosphingosine starting from the *E*-4-benzyloxy-2-buten-1-ol (Scheme 6).

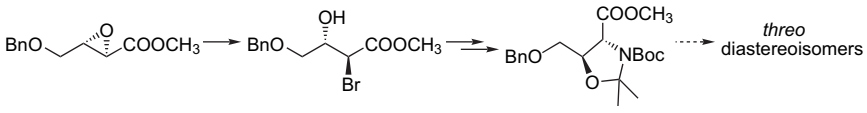
3. Experimental

3.1. General

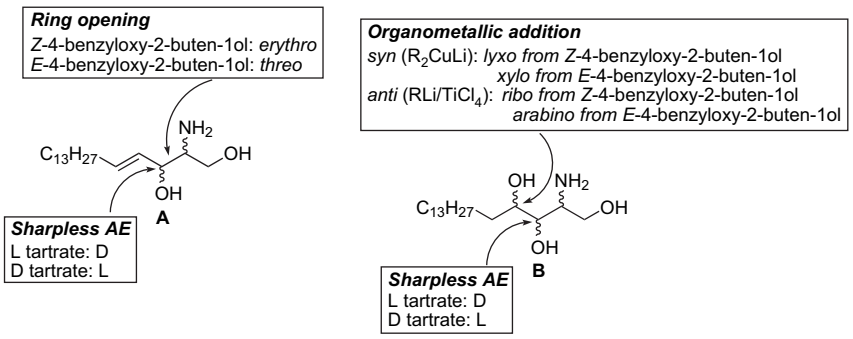
^{1}H and ^{13}C NMR spectra were recorded at 200 and 50.3 MHz, respectively. Reactions were monitored by TLC using Merck silica gel 60 F$_{254}$ plates with UV indicator or/and visualised with phosphomolybdic acid (10% solution in EtOH). Flash column chromatography on silica gel was normally used for purification of the reaction mixtures. All solvents were purified before use with standard drying procedures, unless otherwise specified. Elemental analyses for C and H were performed by the Servizio Microanalisi of the Dip. Chimica of the Università of Roma 'La Sapienza'.

Compounds **A** and **B** and its tetraacetyl derivative are known.[5a,c,13]

3.1.1. (2*R*,3*R*)-*Z*-4-Benzyloxy-2,3-epoxybutanoic acid methyl ester 1. To 2 mL of a 0.5 M solution of the (2*R*,3*R*)-*Z*-4-benzyloxy-2,3-epoxybutanal[15](192 mg, 1 mmol) in alcohol/water (9:1) buffered with NaHCO$_3$ (1682 mg, 20 mmol) was added 2 M solution of bromine (3 mmol) in MeOH/water (9:1 by volume). After stirring for 5 h, solid sodium thiosulfate was added to quench excess bromine and dilution with water (2 mL) was followed by extraction with 8 mL of diethylether (three times). Combined organic layers were dried (Na$_2$SO$_4$), filtered and the solvent was evaporated in vacuo, giving **1** as yellow pale oil (210 mg, 95%). No chromatographic purification was necessary. R_f (20% EtOAc/petroleum ether) 0.82. $[\alpha]_D^{20}$ −12.7 (*c* 5.0, CHCl$_3$); ν_{max} (liquid film) 3010, 1735, 1060, 830 cm^{-1}; δ_H (200 MHz, CDCl$_3$) 7.39–7.27 (5H, m, Ph), 4.85 (1H, d, *J* 11.5 Hz, C*H*$_a$Ph), 4.74 (1H, d, *J* 11.5 Hz, C*H*$_b$Ph), 3.73 (3H, s, O*Me*), 3.82–3.65 (2H, m, OC*H*$_2$), 3.56



Scheme 5.



Scheme 6.

(1H, d, *J* 4.4 Hz, OC*H*), 3.43 (1H, dd, *J* 4.4, 9.9 Hz, OC*H*); δ_C (50 MHz, $CDCl_3$) 167.9, 137.5, 128.3, 127.6, 73.2, 66.9, 55.5, 52.2, 51.2. Anal. Calcd for $C_{12}H_{14}O_4$ (222.09): C 64.85; H 6.35. Found: C 65.1; H 6.5.

3.1.2. (2*S*,3*R*)-4-Benzyloxy-2-bromo-3-hydroxybutanoic acid methyl ester 3. To a solution of **1** (222 mg, 1 mmol) in acetone (10 mL) was added NaBr (416 mg, 4 mmol) and Amberlyst 15 (240 mg). The solution was stirred at −20 °C for 6 h (TLC monitoring), then was filtered through a Celite pad and the solvent evaporated in vacuo affording **3** as yellow oil in almost quantitative yield (300 mg, >98%). R_f (20% EtOAc/petroleum ether) 0.23. $[\alpha]_D^{20}$ −23.7 (*c* 3.5, $CHCl_3$); ν_{max} (liquid film) 3200, 3010, 1740, 1260, 1060, 550 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 7.43–7.27 (5H, m, Ph), 4.59 (1H, d, *J* 3.7 Hz, C*H*Br), 4.55 (2H, s, CH_2Bn), 4.21–4.09 (1H, m, C*H*OH), 3.71 (3H, s, O*Me*), 3.70–3.49 (2H, m, CH_2OBn), 2.89 (1H, br s, O*H*); δ_C (50 MHz, $CDCl_3$) 169.1, 137.2, 128.2, 127.6, 73.3, 70.2, 69.7, 53.2, 48.8. Anal. Calcd for $C_{12}H_{15}BrO_4$ (303.02): C 47.54; H 4.99. Found: C 47.8; H 5.1.

3.1.3. (2*R*,3*S*)-2-Azido-4-benzyloxy-3-hydroxybutanoic acid methyl ester 4. To a solution of **3** (303 mg, 1 mmol) in 4 mL of DMF (or DMSO, 4 mL), NaN_3 (260 mg, 4 mmol) was added and the mixture was stirred at room temperature for 24 h. Then the reaction was diluted with EtOAc (8 mL) and washed several times with water and brine. The combined organic extracts were dried over Na_2SO_4 and concentrated in vacuo affording quantitatively **4** as yellow pale oil (265 mg, >98%). R_f (20% EtOAc/petroleum ether) 0.20. $[\alpha]_D^{20}$ +10.7 (*c* 3.5, $CHCl_3$); ν_{max} (liquid film) 3200, 3010, 2235, 1740, 1250, 1050 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 7.41–7.26 (5H, m, Ph), 4.53 (2H, s, CH_2Ph), 4.20–4.02 (1H, m, C*H*OH), 3.85–3.65 (2H, m, CH_2OBn), 3.74 (3H, s, O*Me*), 3.61 (1H, d, *J* 4.4 Hz, C*H*N_3), 3.13 (1H, br s, O*H*); δ_C (50 MHz, $CDCl_3$) 168.9, 137.3, 128.2, 127.6, 73.3, 70.6, 69.8, 63.2, 52.4. Anal. Calcd for $C_{12}H_{15}N_3O_4$ (265.11): C 54.33; H 5.70; N 15.84. Found: C 54.7; H 5.3; N 16.1.

3.1.4. (2*R*,3*S*)-4-Benzyloxy-2-*tert*-butoxycarbonylamino-3-hydroxybutanoic acid methyl ester 5. A solution of **4** (281 mg, 1 mmol) in EtOAc (2 mL) was hydrogenated at atmospheric pressure over 10% Pd/C (51 mg) in the presence of Boc_2O (231 mg, 1.2 mmol) for 1.5 h at room temperature. The solution was then filtered on a Celite pad and concentrated in vacuo affording **5** in almost quantitative yield as yellow pale oil (335 mg, >98%). R_f (30% EtOAc/petroleum ether) 0.25. $[\alpha]_D^{20}$ −14.3 (*c* 2.5, $CHCl_3$); ν_{max} (liquid film) 3250, 3010, 2950, 1740, 1630, 1200, 1060 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 7.44–7.27 (5H, m, Ph), 5.5 (1H, br d, *J* 7.3 Hz, CHN*H*), 4.69–4.41 (1H, m, C*H*OH), 4.50 (2H, s, CH_2Ph), 4.17 (1H, dd, *J* 7.3, 4.5 Hz, C*H*NH), 3.67 (3H, s, O*Me*), 3.55 (1H, d, *J* 5.9 Hz, CH_2OBn), 3.24 (1H, br s, O*H*), 1.44 (s, 9H, C(CH_3)$_3$); δ_C (50 MHz, $CDCl_3$) 170.5, 146.6, 137.5, 128.2, 127.6, 80.2, 73.4, 71.0, 70.5, 56.5, 52.2, 24.2. Anal. Calcd for $C_{17}H_{25}NO_6$ (339.17): C 60.16; H 7.42; N 4.13. Found: C 60.5; H 7.6; N 4.3.

3.1.5. (4*R*,5*S*)-5-Benzyloxymethyl-3-*N*-*tert*-butoxycarbonyl-2,2-dimethyl-1,3-oxazolidine-4-carboxylic acid methyl ester 6. A solution of **5** (338 mg, 1 mmol), DMP (1.3 mL, 10 mmol) and *p*-TsOH (cat.) in CH_2Cl_2 (1 mL) was stirred at room temperature; after 3 h (TLC monitoring) the mixture was diluted with CH_2Cl_2 (10 mL) and washed with $NaHCO_3$ (15 mL, satd aq). The organic extract was dried over Na_2SO_4 and concentrated in vacuo. The residue was chromatographed on silica gel (hexane/Et_2OAc, 8:2) affording **6** (348 mg, 0.91 mmol) (yield 82% from **1**). ν_{max} (liquid film) 3010, 2950, 1730, 1310 (br), 1200, 1060 cm^{-1}; δ_H [$(CD_3)_2SO$, 80 °C] 7.39–7.23 (5H, m, Ph), 4.58–4.34 (3H, m, C*H*OH+CH_2Ph), 3.75–3.47 (3H, m, CHN+CH_2OBn), 3.65 (3H, s, O*Me*), 1.72 (3H, s, CH_3), 1.55 (3H, s, CH_3), 1.43 (9H, s, C(CH_3)$_3$); δ_C [$(CD_3)_2SO$, 80 °C] 169.3, 150.9, 137.4, 127.5, 126.9, 126.8, 93.4, 78.9, 74.3, 72.3, 67.5, 60.1, 51.1, 27.5, 25.0, 23.8. Anal. Calcd for $C_{20}H_{29}NO_6$ (379.20): C 63.31; H 7.70; N 3.69. Found: C 63.7; H 7.9; N 3.9.

3.1.6. (4*R*,5*S*)-5-Benzyloxymethyl-3-*N*-*tert*-butoxycarbonyl-4-formyl-2,2-dimethyl-1,3-oxazolidine 7. To a stirred solution of **6** (379 mg, 1 mmol) in toluene (2 mL) at −78 °C was added DIBAL (0.8 mL of a solution of 1.5 M in toluene, 1.2 mmol) dropwise. The reaction mixture was stirred for 2 h (TLC monitoring) and then was quenched by slowly adding, at −78 °C, cold MeOH (0.38 mL). The resulting white emulsion was slowly poured into 6.5 mL of HCl 1 N with stirring over 15 min and the aqueous mixture was then extracted with EtOAc (3×15 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated in vacuo without further purification, affording **7** (340 mg, 97%) as colourless oil. ν_{max} (liquid film) 3010, 2950, 1720, 1390, 1200, 1060 cm^{-1}; δ_H [$(CD_3)_2SO$, 80 °C] 9.60 (1H, d, *J* 2.9 Hz, C*H*O), 7.51–7.29 (5H, m, Ph), 4.73–4.49 (1H, m, C*H*OCH_2OBn), 4.59 (2H, s, CH_2Ph), 4.46 (1H, dd, *J* 7.3, 2.9 Hz, C*H*N), 3.78 (1H, dd, *J* 10.9, 4.4 Hz, CH_aOBn), 3.66 (1H, dd, *J* 10.9, 3.6 Hz, CH_bOBn), 1.8 (3H, s, CH_3), 1.6 (3H, s, CH_3), 1.5 (9H, s, C(CH_3)$_3$); δ_C [$(CD_3)_2SO$, 80 °C] 198.7, 151.3, 137.3, 128.4, 128.3, 127.7, 94.9, 80.8, 75.7, 73.5, 67.0, 66.2, 28.1, 26.3, 23.8. Anal. Calcd for $C_{19}H_{27}NO_5$ (349.19): C 65.31; H 7.79; N 4.01. Found: C 65.7; H 7.9; N 4.3.

3.1.7. (4*S*,5*S*)-5-Benzyloxymethyl-3-*N*-*tert*-butoxycarbonyl-2,2-dimethyl-4-hydroxymethyl-1,3-oxazolidine 8. To an ice-cold solution of **7** (336 mg, 1 mmol) in 12 mL of isopropyl alcohol/THF (1:1) was added $NaBH_4$ (110 mg, 3 mmol). After the mixture was stirred for 2 h (TLC monitoring) and then was portioned between HCl 1 N and EtOAc until neutrality. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated in vacuo without further purification, affording **8** (446 mg, 96%) as colourless oil. ν_{max} (liquid film) 3200, 3010, 2950, 1260, 1200, 1060 cm^{-1}; δ_H [$(CD_3)_2SO$, 80 °C] 7.49–7.28 (5H, m, Ph), 4.59 (2H, s, CH_2Ph), 4.34 (1H, ddd, *J* 5.8, 5.1 Hz, C*H*OCH_2OBn), 4.15–4.02 (1H, m, C*H*N), 3.89–3.05 (5H, m, CH_2OBn+CH_2OH+OH), 1.59 (3H, s, CH_3), 1.53 (3H, s, CH_3), 1.47 (9H, s, C(CH_3)$_3$); δ_C [$(CD_3)_2SO$, 80 °C] 151.5, 137.3, 128.4, 127.9, 127.6, 93.2, 80.8, 74.4, 73.8, 67.4, 61.6, 60.4, 28.3, 27.4, 24.6. Anal. Calcd for $C_{19}H_{29}NO_5$ (351.2): C 64.93; H 8.32; N 3.99. Found: C 65.2; H 8.5; N 3.6.

3.1.8. (4*S*,5*S*)-5-Benzyloxymethyl-3-*N*-*tert*-butoxycarbonyl-4-(*tert*-butyl-diphenyl-silyloxyl-methyl)-2,2-dimethyl-1,3-oxazolidine 9. To a solution of **8** (338 mg,

1 mmol) dissolved in 5 mL of CH_2Cl_2 at 0 °C, Et_3N (0.27 mL, 1.1 mmol) and cat. DMAP were added. After 5 min TBDPSCl (180 mg, 1.5 mmol) was added; the mixture was stirred at room temperature for 24 h. After TLC monitoring, the mixture was quenched with $NaHCO_3$ (10 mL, satd aq). Aqueous layer was extracted with CH_2Cl_2 and organic layer was dried over Na_2SO_4 and concentrated in vacuo. The crude mixture was purified by flash chromatography (petroleum ether/EtOAc, 9:1) affording **9** (547 mg, yield 93%). ν_{max} (liquid film) 3010, 2950, 1200, 1090, 1060, 970 cm^{-1}; δ_H [$(CD_3)_2SO$, 80 °C] 7.85–7.55 (5H, m, Ph), 7.51–7.24 (10H, m, 2Ph), 4.71–4.33 (3H, m, C*H*OCH_2OBn+CH_2Ph), 4.11–3.49 (5H, m, C*H*N+CH_2OBn+CH_2OTBDPS), 1.52 (6H, s, C(CH_3)$_2$), 1.11 (9H, s, OC(CH_3)$_3$), 1.03 (9H, s, SiC(CH_3)$_3$); δ_C [$(CD_3)_2SO$, 80 °C] 150.8, 137.4, 135.0, 134.9, 134.7, 134.1, 129.1, 128.9, 127.7, 92.8, 79.1, 75.2, 72.8, 68.2, 60.8, 58.8, 26.0, 24.5, 22.8, 18.4. Anal. Calcd for $C_{35}H_{47}NO_5Si$ (589.32): C 71.27; H 8.03; N 2.37. Found: C 71.4; H 8.2; N 2.4.

3.1.9. (4*S*,5*S*)-3-*N*-*tert*-Butoxycarbonyl-4-(*tert*-butyl-diphenyl-silyloxyl-methyl)-2,2-dimethyl-5-hydroxymethyl-1,3-oxazolidine 10. A solution of **9** (589 mg, 1 mmol) in MeOH (2 mL) was hydrogenated at atmospheric pressure over 10% Pd/C (51 mg) for 3 h at room temperature; then the solution was filtered on a Celite pad and concentrated in vacuo affording **10** (474 mg, 95%) as colourless oil. ν_{max} (liquid film) 3200, 3010, 2950, 1260, 1090, 1060, 970 cm^{-1}; δ_H [$(CD_3)_2SO$, 80 °C] 7.81–7.61 (5H, m, Ph), 7.55–7.31 (5H, m, Ph), 4.42–4.21 (1H, m, C*H*OCH_2OH), 4.19–3.82 (3H, m, C*H*N+CH_2OH), 3.80–3.51 (2H, m, CH_2OTBDPS), 2.97 (1H, br t, OH), 1.53 (3H, s, CH_3), 1.47 (3H, s, CH_3), 1.25 (9H, s, OC(CH_3)$_3$), 1.07 (9H, s, SiC(CH_3)$_3$); δ_C [$(CD_3)_2SO$, 80 °C] 151.4, 135.6, 135.3, 134.8, 127.8, 127.6, 93.4, 80.0, 75.8, 61.5, 60.8, 59.4, 26.9, 24.6, 23.3, 19.1. Anal. Calcd for $C_{28}H_{41}NO_5Si$ (499.28): C 67.30; H 8.27; N 2.80. Found: C 67.7; H 8.4; N 3.0.

3.1.10. (4*S*,5*S*)-3-*N*-*tert*-Butoxycarbonyl-4-(*tert*-butyl-diphenyl-silyloxyl-methyl)-5-formyl-2,2-dimethyl-1,3-oxazolidine 11. To a solution of **10** (499 mg, 1 mmol) in 7.5 mL of CH_2Cl_2, Et_3N (0.56 mL, 4 mmol) was added and then the mixture was stirred at 0 °C. After 10 min, a solution of pyridine/SO_3 (477 mg, 3 mmol) in 3 mL of DMSO was poured into the reaction mixture. After 2 h TLC monitoring, the mixture was diluted with 20 mL of Et_2O and 41 mL of hexane and washed with 19 mL of aq $NaHCO_3$. The combined organic layers were washed with 39 mL of NaH_2PO_4 1 M and then with brine, dried over Na_2SO_4, filtered and concentrated in vacuo. Flash chromatography (petroleum ether/Et_2O, 8:2) afforded **11** as colourless oil (462 mg, yield 93%). ν_{max} (liquid film) 3010, 2950, 1720, 1090, 1060, 980 cm^{-1}; δ_H [$(CD_3)_2SO$, 80 °C] 9.93 (1H, d, *J* 2.1 Hz, C*H*O), 7.79–7.54 (5H, m, Ph), 7.52–7.30 (5H, m, Ph), 4.64–4.51 (1H, m, C*H*O), 4.49–4.25 (1H, m, C*H*N), 3.76 (1H, dd, *J* 10.4, 7.4 Hz, CH_aOTBDPS), 3.64 (1H, dd, *J* 10.4, 3.7 Hz, CH_bOTBDPS), 1.81 (3H, s, CH_3), 1.72 (3H, s, CH_3), 1.32 (9H, s, OC(CH_3)$_3$), 1.12 (9H, s, SiC(CH_3)$_3$); δ_C [$(CD_3)_2SO$, 80 °C] 197.1, 149.3, 136.2, 134.8, 129.4, 127.7, 127.6, 94.8, 79.7, 79.1, 60.8, 60.3, 28.2, 26.5, 24.7, 23.5, 19.0. Anal. Calcd for $C_{28}H_{39}NO_5Si$ (497.26): C 67.57; H 7.90; N 2.81. Found: C 67.8; H 8.1; N 3.1.

3.1.11. (4*S*,5*S*,1′*S*)-3-*N*-*tert*-Butoxycarbonyl-4-(*tert*-butyl-diphenyl-silyloxyl-methyl)-5-(1′-hydroxypentadecyl)-2,2-dimethyl-1,3-oxazolidine 12. To a solution of ($nC_{14}H_{29}$)$_2$CuLi freshly prepared in Et_2O (10 mL) at −20 °C, **11** (497 mg, 1 mmol) was added. The resulting solution was stirred for 5 h and after TLC monitoring, the reaction was quenched with saturated NH_4Cl solution and extracted with Et_2O; the combined organic extracts were dried over Na_2SO_4 and then evaporated to dryness in vacuo. The crude mixture was purified by flash chromatography (hexane/EtOAc, 6:4) affording **12** (323 mg, yield 63%). ν_{max} (liquid film) 3200, 3010, 2950, 1260, 1090, 1060, 990 cm^{-1}; δ_H [$(CD_3)_2SO$, 80 °C] 7.84–7.58 (5H, m, Ph), 7.53–7.32 (5H, m, Ph), 4.26–4.07 (1H, m, C*H*OH), 3.83 (1H, dd, *J* 4.8, 4 Hz, C*H*O), 3.87–3.41 (3H, m, C*H*N+CH_2OTBDPS), 2.73 (1H, br d, *J* 7.3 Hz, OH), 1.52 (3H, s, CH_3), 1.45 (3H, s, CH_3), 1.48–1.19 (m, 26H), 1.25 (9H, s, OC(CH_3)$_3$), 1.06 (9H, s, SiC(CH_3)$_3$), 0.88 (3H, t, *J* 6.0 Hz); δ_C (50 MHz, $CDCl_3$) 147.3, 135.2, 134.6, 129.2, 127.7, 126.7, 93.7, 79.5, 76.3, 72.4, 61.3, 60.9, 32.5, 32.0, 30.6, 30.3, 30.1, 28.5, 26.5, 24.7, 24.2, 23.5, 22.5, 19.0, 13.5. Anal. Calcd for $C_{42}H_{69}NO_5Si$ (695.49): C 72.47; H 9.99; N 2.01. Found: C 72.7; H 10.1; N 3.3.

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Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2006.08.049.

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