4-Formylazetidin-2-one as a Useful Building Block for the Formal Synthesis of *xylo*-(2*S*,3*R*,4*R*)-Phytosphingosine and *threo*-(2*S*,3*S*)-Sphingosine

Ajaykumar S. Kale,[a] Prathmesh S. Sakle,[a] Vikas K. Gumaste,[a] Abdul Rakeeb A. S. Deshmukh*[b]

[a] Division of Organic Chemistry (Synthesis), National Chemical Laboratory, Pune 411008, Maharashtra, India

[b] Emcure Pharmaceuticals Limited, ARC-H, P-2, I.T.-B.T. Park, Phase-II, M.I.D.C., Hinjwadi, Pune 411057, Maharashtra, India
E-mail: Abdulrakeeb.Deshmukh@emcure.co.in

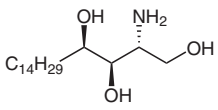
Received 28 March 2007; revised 23 May 2007

Abstract: Stereoselective formal synthesis of *xylo*-(2*S*,3*R*,4*R*)-phytosphingosine and *threo*-(2*S*,3*S*)-sphingosine is described starting from an enantiopure formyl-substituted β-lactam. Grignard reaction of the *N*-Boc-protected-β-lactam carbonyl group, followed by further transformations, provides a common intermediate for *xylo*-(2*S*,3*R*,4*R*)-phytosphingosine and *threo*-(2*S*,3*S*)-sphingosine.

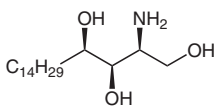
Keywords: β-lactam, Grignard reaction, sphingosine, phytosphingosine, azetidin-2-one

β-Lactams have a prominent position in medicinal chemistry as the most widely used antibiotics and continue to exhibit utility in newer applications.[1–3] Over the last few decades the scope and applications of the β-lactams has widened appreciably opening new avenues of research.[4] Amongst these applications the most important one, which has shown a staggering growth, has been their use as synthons for other biologically important products.[5] The ease of cleavage of the β-lactam bond, ascribable largely to ring strain, makes it amenable to various transformations. All four bonds of the β-lactam ring can be cleaved selectively, which renders it flexible for different transformations. Various natural products and intermediates have thus been synthesized using the β-lactam synthon method.[4d,5,6] It has been applied successfully to asymmetric synthesis of a variety of protein and nonprotein amino acids, peptides and peptidomimetics.[4d,6] Synthesis of the phenylisoserine side chain of taxol from enantiopure 3-hydroxy-β-lactams[7] has provided one of the most practical semisynthetic routes to taxol. The subject has been extensively reviewed[8c] and remains a field of constant activity. We have been engaged in the use of enantiopure β-lactams as synthons for biologically useful compounds and intermediates.[8,9] As a part of this research program, we now present our work on the synthesis of sphingolipids, *xylo*-(2*S*,3*R*,4*R*)-phytosphingosine (**2**) and *threo*-(2*S*,3*S*)-sphingosine (**5**) (Figure 1), from an optically pure formyl-substituted β-lactam.

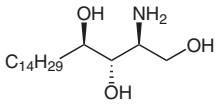
Sphingolipids are membrane components of all eukaryotic cells, plasma membranes and some intramolecular cell organelles.[10] It is known that sphingosines and ceramides play an important role in intracellular signaling, along with secondary messenger molecules.[11] Sphingosines are lipophilic components of glycosphingolipids and ceram-



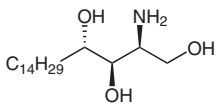
xylo-(2*R*,3*R*,4*R*)-phytosphingosine (**1**)



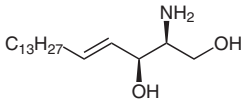
xylo-(2*S*,3*R*,4*R*)-phytosphingosine (**2**)



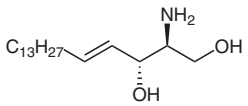
ribo-(2*S*,3*S*,4*R*)-phytosphingosine (**3**)



arabino-(2*S*,3*R*,4*S*)-phytosphingosine (**4**)



threo-(2*S*,3*S*)-sphingosine (**5**)



erythro-(2*S*,3*R*)-sphingosine (**6**)

Figure 1

SYNTHESIS 2007, No. 17, pp 2631–2636
Advanced online publication: 24.07.2007
DOI: 10.1055/s-2007-983815; Art ID: Z08107SS

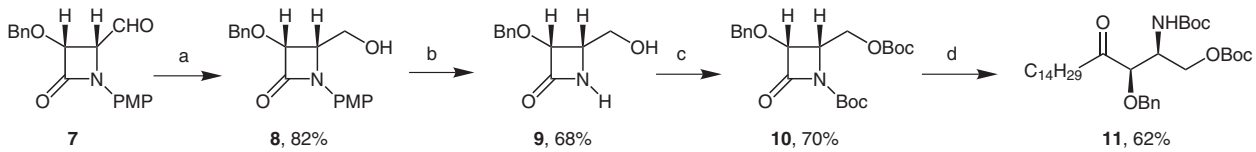
ides.[11b,12] Phytosphingosines (e.g., **1**–**4**) constitute the major base component of higher plants, protozoa, yeast and fungi.[13] They have also been found in human kidney cerebrosides and in some cancer cell types.[14] D-*erythro*-Sphingosine (**6**) shows promising protein kinase inhibitory activity.[11c,15] Moreover, it has been shown that diastereomers of ceramides, sphingosines and dihydrosphingosines exhibit different activities and metabolisms.[16] Thus, owing to the number of applications, this area has attracted a large number of synthetic chemists.[17] The subtle variations in biological activities over the range of diastereomers have inevitably led to synthesis of all diastereomers of sphingosines. This fact is reflected in a steep rise in the number of publications dealing with the synthesis of sphingosines.[13,14,17]

Since sphingosines are popular synthetic targets, many synthetic routes have been reported; however, a literature survey brought forth only two examples using β-lactams as synthons. In one of the reports the starting β-lactam was subjected to ring opening by a phosphonate-stabilized carbanion, followed by a Horner–Wadsworth–Emmons reaction to obtain unsaturated ketone, which on further elaboration yielded sphingosines.[17i] In another approach *n*-tetradecyl *p*-toluenesulfonate and *n*-butyllithium were used to open the β-lactam ring. Subsequent desulfonylation using lithium naphthalenide, and further synthetic manipulations, led to the corresponding sphingosines.[12g] While both reports present beautiful approaches to sphingosines, the installation of the tetradecyl chain essentially happens in a two-step process in both cases. In view of the above-mentioned facts, we envisaged that an attack of Grignard reagent would open the β-lactam ring and simultaneously bring into place the side chain in one step (Scheme 1).

The optically pure formyl-substituted β-lactam **7** can be easily prepared from commercially available D-glyceraldehyde acetonide via a Staudinger ketene–imine cycloaddition reaction, in excellent yield and high enantiopurity, by following a reported procedure.[6a] The aldehyde **7** was reduced in good yield to the corresponding alcohol **8** with sodium borohydride. Oxidative removal of the *p*-methoxyphenyl group was then carried out using cerium(IV) ammonium nitrate to provide N-deprotected β-lactam **9**. Subsequently, the β-lactam nitrogen and the hydroxy were protected as the *N*-Boc and *O*-Boc derivatives, respectively, giving compound **10**. Grignard reaction of **10** with *n*-tetradecylmagnesium bromide proceeded smoothly furnishing the required keto compound **11** in good yield. Attempts to deprotect the *N*-Boc and *O*-Boc groups using various conditions led to a complex mixture of products. Alternatively, it was decided to reduce the keto group first and then carry out the deprotection; however, to our dismay, the reduction reaction also gave a very complex reaction mixture. Therefore, the hydroxymethylene group at the C-4 position of azetidin-2-one **9** was protected as the *O*-*tert*-butyldimethylsilyl ether **12** (Scheme 2). This was followed by protection of the lactam nitrogen as the *tert*-butoxycarbonyl derivative **13**. Compound **13** was then subjected to Grignard reaction with *n*-tetradecylmagnesium bromide in tetrahydrofuran to obtain compound **14**. The benzyloxy group was successfully deprotected by transfer hydrogenation with ammonium formate and 10% Pd/C to give **15**. Compound **15** on treatment with *tert*-butyldimethylsilyl chloride yielded the protected (2*S*,3*R*)-2-(*tert*-butoxycarbonylamino)-1,3-bis(*tert*-butyldimethylsilyloxy)octadecan-4-one (**16**) in good yield. The transformation of **16** to *xylo*-(2*S*,3*R*,4*R*)-phytosphingosine (**2**) is a well-documented three-step synthetic protocol.[17i,j] Compound **16** is also an important intermediate in the synthesis of *threo*-(2*S*,3*S*)-sphingosine (**5**), via a well-established three-step synthetic sequence.[17i,j] Thus, (2*S*,3*R*)-2-(*tert*-butoxycarbonylamino)-1,3-bis(*tert*-butyldimethylsilyloxy)octadecan-4-one (**16**) is a common intermediate in the synthesis of *xylo*-(2*S*,3*R*,4*R*)-phytosphingosine (**2**) and *threo*-(2*S*,3*S*)-sphingosine (**5**).

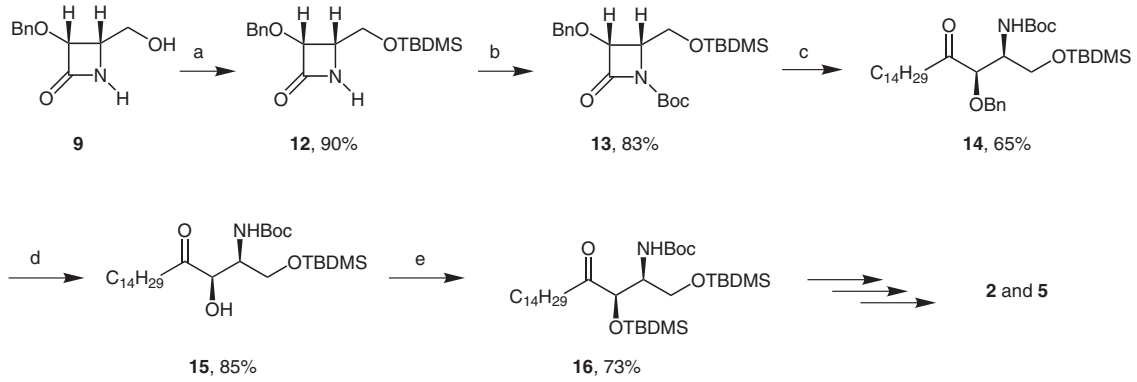
In conclusion, we have established a stereoselective synthesis of a common intermediate **16** for *xylo*-(2*S*,3*R*,4*R*)-phytosphingosine (**2**) and *threo*-(2*S*,3*S*)-sphingosine (**5**) starting from an enantiopure formyl-substituted β-lactam. A Grignard reaction on the β-lactam carbonyl, followed by further transformations, provided this crucial common precursor in good yield.

^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ solution on a Bruker AV200 or DRX500 spectrometer and the chemical shifts are reported in ppm downfield from TMS (for ^{1}H NMR spectra). IR spectra were recorded on a Shimadzu FTIR-8400 instrument using NaCl optics. Mass spectrometric measurements were carried out with electrospray ionization on an API QSTAR Pulsar mass spectrometer. Melting points were recorded on a Buchi Melting Point B 540 apparatus and are uncorrected. Optical rotations were recorded on a JASCO-181 digital polarimeter under standard conditions. The microanalyses were performed on a Carlo–Erba CHNS-O EA 1108 elemental analyzer. Petroleum ether refers to the fraction boiling at 60–80 °C.



7 **8**, 82% **9**, 68% **10**, 70% **11**, 62%

Scheme 1 Synthesis of keto compound **11**. *Reagents and conditions*: a) $NaBH_4$, MeOH, 8 h; b) CAN, MeCN–H_2O, 45 min; c) $(Boc)_2O$, DMAP, CH_2Cl_2, 12 h; d) $C_{14}H_{29}MgBr$, THF, –78 °C to –40 °C, 1 h.



Scheme 2 Synthesis of common intermediate **16**. *Reagents and conditions*: a) TBDMSCl, imidazole, DMF, 3 h; b) $(Boc)_2O$, DMAP, CH_2Cl_2, 5 h; c) $C_{14}H_{29}MgBr$, THF, –78 °C to –40 °C, 1 h; d) $HCOONH_4$, 10% Pd/C, MeOH, reflux, 1 h; e) TBDMSCl, imidazole, DMF, 35 °C, 12 h.

(3*R*,4*S*)-3-(Benzyloxy)-4-(hydroxymethyl)-1-(4-methoxyphenyl)azetidin-2-one (8)

To a cooled soln of the 4-formylazetidin-2-one[6a] **7** (3.11 g, 10 mmol) in MeOH (50 mL) at 0 °C was added $NaBH_4$ (1.85 g, 50 mmol) portionwise under an argon atmosphere. The mixture was allowed to warm to r.t. and stirred for 8 h. After completion of the reaction (TLC), H_2O (20 mL) was added carefully and the mixture was further stirred for 1 h. MeOH was removed under reduced pressure and the residue was extracted with EtOAc (2 × 80 mL). The combined organic layer was washed with brine (15 mL) and dried (anhyd Na_2SO_4). Removal of the solvent under reduced pressure gave the crude product, which was purified by column chromatography (acetone–petroleum ether, 25:75) to afford alcohol **8** (2.56 g, 82%) as a white crystalline solid; mp 119–120 °C; $[\alpha]_D^{30}$ +160 (*c* 1.0, $CHCl_3$).

IR ($CHCl_3$): 3337, 1743 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 2.38 (dd, *J* = 5.6 Hz, 1 H), 3.79 (s, 3 H), 3.99–4.08 (m, 2 H), 4.08–4.26 (m, 1 H), 4.78 (d, *J* = 11.6 Hz, 1 H), 4.87 (d, *J* = 5.1 Hz, 1 H), 5.03 (d, *J* = 11.6 Hz, 1 H), 6.87 (d, *J* = 9.1 Hz, 2 H), 7.36–7.42 (m, 7 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 55.3, 57.9, 59.2, 73.5, 80.7, 114.3, 118.7, 128, 128.2, 128.5, 130.4, 136.4, 156.7, 164.1.

MS: *m*/*z* = 314 [M + 1].

Anal. Calcd for $C_{18}H_{19}NO_4$: C, 68.99; H, 6.11; N, 4.47. Found: C, 68.93; H, 6.09; N, 4.38.

(3*R*,4*S*)-3-(Benzyloxy)-4-(hydroxymethyl)azetidin-2-one (9)

A soln of CAN (10.5 g, 19.2 mmol) in H_2O (65 mL) was added dropwise to a soln of (3*R*,4*S*)-3-(benzyloxy)-4-(hydroxymethyl)-1-(4-methoxyphenyl)azetidin-2-one (**8**) (2 g, 6.4 mmol) in MeCN (67 mL) at 0 °C. The mixture was stirred at 0 °C for 45 min. H_2O (50 mL) was added, and the mixture was extracted with EtOAc (3 × 125 mL) and washed with sat. aq $NaHCO_3$ (2 × 50 mL). The aqueous $NaHCO_3$ layer was extracted with EtOAc (1 × 25 mL), and the combined organic extracts were washed with 40% $NaHSO_3$ (3 × 60 mL) and brine (10 mL), and then dried (anhyd Na_2SO_4). The solvent was removed under reduced pressure to give crude product, which was purified by flash column chromatography (acetone–petroleum ether, 40:60) to furnish **9** (0.9 g, 68%) as a white solid; mp 80 °C; $[\alpha]_D^{25}$ –36 (*c* 1.0, $CHCl_3$).

IR ($CHCl_3$): 3373, 1753 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 3.51–3.9 (m, 5 H), 4.62 (d, *J* = 11.6 Hz, 1 H), 4.66 (d, *J* = 5.5 Hz, 1 H), 4.78 (d, *J* = 11.6 Hz, 1 H), 7.34–7.42 (m, 5 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 54.8, 61.5, 73.4, 82.1, 128, 128.2, 128.5, 136.5, 169.1.

MS: *m*/*z* = 208 [M + 1].

Anal. Calcd for $C_{11}H_{13}NO_3$: C, 63.76; H, 6.32; N, 6.76. Found: C, 63.62; H, 6.28; N, 6.68.

(3*R*,4*S*)-3-(Benzyloxy)-1-(*tert*-butoxycarbonyl)-4-[(*tert*-butoxycarbonyloxy)methyl]azetidin-2-one (10)

Boc_2O (3.8 mL, 16.9 mmol) and DMAP (0.77 g, 6.3 mmol) were added to a soln of azetidin-2-one **9** (1 g, 4.8 mmol) in CH_2Cl_2 (20 mL) at 0 °C, and the reaction mixture was stirred for 12 h. Then, CH_2Cl_2 (25 mL) was added, and the mixture was washed with sat. aq $NaHCO_3$ (20 mL) and brine (10 mL). The organic layer was dried (anhyd Na_2SO_4) and the solvent was removed under reduced pressure to give crude product, which was purified by column chromatography (acetone–petroleum ether, 5:95) to furnish the title β-lactam **10** (1.38 g, 70%) as a white solid; mp 98–99 °C; $[\alpha]_D^{25}$ +77 (*c* 1.0, $CHCl_3$).

IR ($CHCl_3$): 1812, 1741 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 1.44 (s, 9 H), 1.46 (s, 9 H), 4.26–4.33 (m, 2 H), 4.36–4.44 (m, 1 H), 4.63 (d, *J* = 5.1 Hz, 1 H), 4.72 (d, *J* = 11.7 Hz, 1 H), 4.79 (d, *J* = 11.7 Hz, 1 H), 7.27–7.37 (m, 5 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 27.6, 27.8, 55.5, 62.5, 73.4, 80.5, 82.2, 83.7, 127.8, 128.0, 128.3, 136.4, 147.5, 152.8, 164.1.

MS: *m*/*z* = 408 [M + 1].

Anal. Calcd for $C_{21}H_{29}NO_7$: C, 61.90; H, 7.17; N, 3.44. Found: C, 61.77; H, 7.12; N, 3.31.

(2*S*,3*R*)-3-(Benzyloxy)-2-(*tert*-butoxycarbonylamino)-1-(*tert*-butoxycarbonyloxy)octadecan-4-one (11)

n-Tetradecylmagnesium bromide (1 M in THF; 3.2 mL, 3.2 mmol) was added to a soln of the starting β-lactam **10** (1.2 g, 2.9 mmol) in THF (15 mL) at –78 °C (acetone–CO_2 bath). The reaction mixture was stirred at –40 °C (MeCN–CO_2 bath) for 1 h. After completion of the reaction (TLC), sat. NH_4Cl soln (4 mL) was poured into the mixture, which was then extracted with EtOAc (3 × 40 mL). The combined organic extracts were washed with brine (10 mL) and dried (anhyd Na_2SO_4). The solvent was removed under reduced pressure to yield the product. Purification by flash column chromatography (acetone–petroleum ether, 3:97) gave β-amino ketone **11** (1.1 g, 62%) as an oil; $[\alpha]_D^{25}$ +56 (*c* 0.8, $CHCl_3$).

IR ($CHCl_3$): 3438, 1739, 1722 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 0.86–0.92 (m, 3 H), 1.17–1.26 (m, 21 H), 1.35–1.43 (m, 3 H), 1.40 (s, 9 H), 1.49 (s, 9 H), 2.42–2.53

(m, 2 H), 3.56 (br s, 1 H), 4.07 (d, *J* = 6.3 Hz, 2 H), 4.41 (d, *J* = 11.4 Hz, 1 H), 4.67–4.73 (m, 2 H), 4.95 (d, *J* = 11.4 Hz, 1 H), 7.33–7.36 (m, 5 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 13.9, 22.5, 23.0, 27.6, 28.1, 28.2, 29.0, 29.2, 29.3, 29.4, 30.2, 31.7, 39.0, 50.3, 64.9, 72.8, 75.9, 81.3, 81.5, 81.9, 127.8, 128.1, 128.3, 136.9, 152.9, 154.9, 208.9.

MS: *m*/*z* = 606 [M + 1].

Anal. Calcd for $C_{35}H_{59}NO_7$: C, 69.39; H, 9.82; N, 2.31. Found: C, 69.28; H, 9.78; N, 2.24.

(3*R*,4*S*)-3-(Benzyloxy)-4-[(*tert*-butyldimethylsilyloxy)methyl]azetidin-2-one (12)

To a mixture of azetidin-2-one **9** (0.73 g, 3.5 mmol) and imidazole (0.6 g, 8.8 mmol) in anhyd DMF (1.2 mL) was added TBDMSCl (0.63 g, 4.2 mmol) at r.t. The reaction mixture was stirred at r.t. for 3 h. After completion of the reaction (TLC), the mixture was poured onto H_2O (5 mL) and extracted with EtOAc (3 × 15 mL). The combined organic extracts were successively washed with H_2O (3 × 5 mL) and brine (10 mL), then dried (anhyd Na_2SO_4). The solvent was removed under reduced pressure to afford crude product, which was purified by column chromatography (EtOAc–petroleum ether, 20:80) to furnish **12** (1.02 g, 90%) as a colorless oil; $[\alpha]_D^{25}$ +0.51 (*c* 1.0, $CHCl_3$).

IR (neat): 3259, 1762 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.05 (s, 3 H), 0.06 (s, 3 H), 0.88 (s, 9 H), 3.70–3.82 (m, 3 H), 4.67 (d, *J* = 11.9 Hz, 1 H), 4.71–4.74 (m, 1 H), 4.81 (d, *J* = 11.9 Hz, 1 H), 6.12 (br s, 1 H), 7.26–7.35 (m, 5 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = –5.4, 18.2, 25.8, 55.7, 62.8, 73.1, 82, 127.9, 128.3, 128.4, 137, 168.7.

MS: *m*/*z* = 322 [M + 1].

Anal. Calcd for $C_{17}H_{27}NO_3Si$: C, 63.51; H, 8.47; N, 4.36. Found: C, 63.40; H, 8.41; N, 4.22.

(3*R*,4*S*)-3-(Benzyloxy)-1-(*tert*-butoxycarbonyl)-4-[(*tert*-butyldimethylsilyloxy)methyl]azetidin-2-one (13)

Boc_2O (1.35 mL, 5.9 mmol) and DMAP (0.04 g, 0.3 mmol) were added to a soln of azetidin-2-one **12** (0.950 g, 2.9 mmol) in anhyd CH_2Cl_2 (10 mL) at 0 °C, and the mixture was stirred for 5 h. Then, CH_2Cl_2 (20 mL) was added, and the mixture was washed with sat. $NaHCO_3$ soln (20 mL) and sat. brine (10 mL). The organic layer was dried (anhyd Na_2SO_4) and the solvent was removed under reduced pressure to give crude product, which was purified by column chromatography (EtOAc–petroleum ether, 12:88) to furnish the title β-lactam **13** (1.03 g, 83%) as a colorless oil; $[\alpha]_D^{25}$ +51 (*c* 1.5, $CHCl_3$).

IR (neat): 1811, 1718 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.05 (s, 3 H), 0.06 (s, 3 H), 0.89 (s, 9 H), 1.51 (s, 9 H), 3.97–4.03 (m, 2 H), 4.04–4.09 (m, 1 H), 4.69 (d, *J* = 5.2 Hz, 1 H), 4.77 (s, 2 H), 7.31–7.36 (m, 5 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = –5.6, –5.5, 18.2, 25.7, 28, 58.2, 63.1, 73.3, 80.3, 83.3, 127.9, 128.2, 128.4, 136.8, 148, 164.9.

MS: *m*/*z* = 422 [M + 1].

Anal. Calcd for $C_{22}H_{35}NO_5Si$: C, 62.67; H, 8.37; N, 3.32. Found: C, 62.49; H, 8.29; N, 3.24.

(2*S*,3*R*)-3-(Benzyloxy)-2-(*tert*-butoxycarbonylamino)-1-(*tert*-butyldimethylsilyloxy)octadecan-4-one (14)

n-Tetradecylmagnesium bromide (1 M in THF; 2.2 mL, 2.2 mmol) was added to a soln of β-lactam **13** (0.84 g, 2 mmol) in THF (5 mL) at –78 °C (acetone–CO_2 bath). The reaction mixture was stirred at –40 °C (MeCN–CO_2 bath) for 1 h. After completion of the reaction (TLC), sat. NH_4Cl soln (4 mL) was poured into the mixture, which was then extracted with EtOAc (3 × 30 mL). The combined organic layer was washed with brine (10 mL) and dried (anhyd Na_2SO_4). The solvent was removed under reduced pressure to yield the product. Purification by flash column chromatography (EtOAc–petroleum ether, 1:99) gave β-amino ketone **14** (0.804 g, 65%) as an oil; $[\alpha]_D^{25}$ –4 (*c* 1.0, $CHCl_3$).

IR ($CHCl_3$): 3436, 1718, 1706 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.05 (s, 3 H), 0.07 (s, 3 H), 0.85–0.89 (m, 12 H), 1.20–1.30 (m, 22 H), 1.39 (s, 9 H), 1.55 (t, *J* = 6.8 Hz, 2 H), 2.48 (dd, *J* = 6.8, 14.4 Hz, 2 H), 3.51–3.69 (m, 2 H), 4.05–4.18 (m, 1 H), 4.26 (d, *J* = 2.9 Hz, 1 H), 4.40 (d, *J* = 11.2 Hz, 1 H), 4.68 (d, *J* = 11.2 Hz, 1 H), 4.91 (d, *J* = 9.6 Hz, 1 H), 7.29–7.39 (m, 5 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = –5.5, –5.4, 14.1, 18.1, 22.6, 23.4, 25.8, 28.2, 29.2, 29.3, 29.4, 29.6, 31.9, 39.1, 53.1, 61.4, 73.0, 81.3, 127.9, 128.1, 128.4, 137.4, 155.2, 210.3.

MS: *m*/*z* = 620 [M + 1].

Anal. Calcd for $C_{36}H_{65}NO_5Si$: C, 69.74; H, 10.57; N, 2.26. Found: C, 69.61; H, 10.48; N, 2.12.

(2*S*,3*R*)-2-(*tert*-Butoxycarbonylamino)-1-(*tert*-butyldimethylsilyloxy)-3-hydroxyoctadecan-4-one (15)

A mixture of β-amino ketone **14** (0.62 g, 1 mmol), ammonium formate (0.189 g, 3 mmol) and 10% Pd/C (0.07 g) in MeOH (10 mL) was refluxed for 1 h. The reaction mixture was filtered through a small pad of Celite® and washed with EtOAc (2 × 10 mL). The solvent was removed under reduced pressure. The residue was diluted with EtOAc (50 mL), and washed with H_2O (2 × 5 mL) and brine (5 mL). The organic layer was dried (anhyd Na_2SO_4) and concentrated to give crude product, which was purified by flash column chromatography (EtOAc–petroleum ether, 2:98) to afford **15** (0.45 g, 85%) as an oil; $[\alpha]_D^{25}$ –24 (*c* 1.0, $CHCl_3$).

IR ($CHCl_3$): 3442, 1712 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.09 (s, 3 H), 0.10 (s, 3 H), 0.79–0.97 (m, 13 H), 1.20–1.35 (m, 23 H), 1.39 (s, 9 H), 2.41–2.62 (m, 2 H), 3.61–3.73 (m, 3 H), 4.10–4.25 (m, 1 H), 4.30–4.50 (m, 1 H), 4.56–4.65 (m, 1 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = –5.5, –5.4, 14.1, 18.2, 22.7, 23.6, 25.8, 28.2, 29.1, 29.3, 29.4, 29.5, 29.6, 31.9, 37.7, 53.1, 62.3, 74.7, 79.7, 155.2, 211.5.

MS: *m*/*z* = 530 [M + 1].

Anal. Calcd for $C_{29}H_{59}NO_5Si$: C, 65.74; H, 11.22; N, 2.64. Found: C, 65.61; H, 11.18; N, 2.52.

(2*S*,3*R*)-2-(*tert*-Butoxycarbonylamino)-1,3-bis(*tert*-butyldimethylsilyloxy)octadecan-4-one (16)

To a mixture of hydroxy compound **15** (0.3 g, 0.56 mmol) and imidazole (0.096 g, 1.4 mmol) in anhyd DMF (1 mL) was added TBDMSCl (0.102 g, 0.68 mmol) at 35 °C. The reaction mixture was stirred at 35 °C for 12 h. After completion of the reaction (TLC), the mixture was poured onto H_2O (3 mL) and extracted with EtOAc (3 × 15 mL). The combined organic extracts were successively washed with H_2O (3 × 5 mL) and sat. brine (8 mL), then dried (anhyd Na_2SO_4). The solvent was removed under reduced pressure to give crude product, which was purified by column chromatography (EtOAc–petroleum ether, 1:99) to furnish **16** (0.26 g, 73%) as a colorless oil; $[\alpha]_D^{25}$ –9 (*c* 1.0, $CHCl_3$).

IR ($CHCl_3$): 3436, 1715 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.01 (s, 3 H), 0.04 (s, 3 H), 0.07 (s, 3 H), 0.10 (s, 3 H), 0.90 (s, 9 H), 0.94 (s, 9 H), 1.20–1.27 (m, 22 H), 1.41 (s, 9 H), 1.45–1.61 (m, 5 H), 2.42–2.53 (m, 2 H), 3.51 (t,

J = 8.5 Hz, 1 H), 3.62–3.67 (m, 1 H), 3.70 (br s, 1 H), 4.42–4.44 (m, 1 H), 4.90 (d, *J* = 9.1 Hz, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = –5.4, –5.3, –4.7, 14.1, 18.2, 18.3, 22.7, 23.5, 25.8, 28.3, 29.2, 29.4, 29.5, 29.6, 31.9, 38.6, 54.2, 61.0, 75.7, 77.2, 79.5, 155.2, 211.3.

MS: *m*/*z* = 645 [M + 1].

Anal. Calcd for $C_{35}H_{73}NO_5Si_2$: C, 65.26; H, 11.42; N, 2.17. Found: C, 65.14; H, 11.28; N, 2.10.

Acknowledgment

The authors thank the Department of Science and Technology New Delhi for financial support and CSIR New Delhi for a research fellowship to A.S.K.

References

(1) For reviews on β-lactam antibiotics, see: (a) Dürkheimer, W.; Blumbach, J.; Lattrell, R.; Scheunemann, K. H. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 180. (b) *Chemistry and Biology of β-Lactam Antibiotics*, Vol. 1-3; Morin, R. B.; Gorman, M., Eds.; Academic: New York, **1982**. (c) Coulton, S.; Hunt, E. In *Recent Progress in the Chemical Synthesis of Antibiotics and Related Microbial Products*, Vol. 2; Lukacs, G., Ed.; Springer-Verlag: Berlin, **1993**, 621. (d) Southgate, R. *Contemp. Org. Synth.* **1994**, *1*, 417. (e) Rothstein, J. D.; Patel, S.; Regan, M. R.; Haenggelli, C.; Huang, Y. H.; Bergles, D. E.; Jin, L.; Hoberg, M. D.; Vidensky, S.; Chung, D. S.; Toan, S. V.; Bruijn, L. I.; Su, Z.-z.; Gupta, P.; Fisher, P. B. *Nature (London)* **2005**, *433*, 73. (f) Burnett, D. A.; Caplen, M. A.; Davis, H. R. Jr.; Burrie, R. E.; Clader, J. W. *J. Med. Chem.* **1994**, *37*, 1733. (g) Dugar, S.; Yumibe, N.; Clader, J. W.; Vizziano, M.; Huie, K.; van Heek, M.; Compton, D. S.; Davis, H. R. Jr. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 1271.

(2) *The Chemistry of β-Lactams*; Page, M. I., Ed.; Chapman & Hall: London, **1992**.

(3) For comprehensive general reviews, see: (a) Koppel, G. A. In *Small Ring Heterocycles*, Vol. 42; Hasner, A., Ed.; Wiley & Sons: New York, **1983**, 219. (b) Backes, J. In *Houben–Weyl Methoden der organischen Chemie*, Vol. E 16b; Klamann, D., Ed.; Georg Thieme: Stuttgart, **1991**, 31. (c) De Kimpe, N. In *Comprehensive Heterocyclic Chemistry II*, Vol. 1B; Katritzky, A. R.; Rees, C. W.; Scriven, E. F. V.; Padwa, A., Eds.; Pergamon: Oxford, **1996**, 507. (d) Wu, G. G. *Org. Process Res. Dev.* **2000**, *4*, 298. (e) Han, W. T.; Trehan, A. K.; Wright, J. J. K.; Federici, M. E.; Seiler, S. M.; Meanwell, N. A. *Bioorg. Med. Chem.* **1995**, *3*, 1123. (f) Zhou, N. E.; Guo, D.; Thomas, G.; Reddy, A. V. N.; Kaleta, J.; Purisima, E.; Menard, R.; Micetich, R. G.; Singh, R. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 139.

(4) (a) Ojima, I.; Georg, G. I. *The Organic Chemistry of β-Lactams*; VCH: New York, **1993**, 197; and references cited therein. (b) Palomo, C.; Aizpurua, J.; Ganboa, I. In *Enantioselective Synthesis of β-Amino Acids*; Juaristi, E., Ed.; Wiley-VCH: New York, **1997**, 279–357; and references cited therein. (c) For a review on this subject, see: Ojima, I.; Delaloge, F. *Chem. Soc. Rev.* **1997**, *26*, 377. (d) Alcaide, B.; Almendros, P. *Chem. Soc. Rev.* **2001**, *30*, 226. (e) Alcaide, B.; Almendros, P. *Synlett* **2002**, 381.

(5) (a) Nagahara, T.; Kametani, T. *Heterocycles* **1987**, *25*, 729. (b) Thomas, R. C. In *Recent Progress in the Chemical Synthesis of Antibiotics*; Lukacs, G.; Ohno, M., Eds.; Springer-Verlag: Berlin, **1990**, 553. (c) Palomo, C. In *Recent Progress in the Chemical Synthesis of Antibiotics*; Lukacs, G.; Ohno, M., Eds.; Springer-Verlag: Berlin, **1990**, 565. (d) Palomo, C.; Arrieta, A.; Cossío, F. P.; Aizpurua, J. M.; Mielgo, A.; Aurrekoetxea, N. *Tetrahedron Lett.* **1990**, *31*, 6429. (e) Palomo, C.; Cabre, F.; Ontoria, J. M. *Tetrahedron Lett.* **1992**, *33*, 4819. (f) Annunziata, R.; Benaglia, M.; Cinquini, M.; Cozzi, F.; Ponzini, F. *J. Org. Chem.* **1993**, *58*, 4746.

(6) (a) Jayaraman, M.; Deshmukh, A. R. A. S.; Bhawal, B. M. *J. Org. Chem.* **1994**, *59*, 932. (b) Jayaraman, M.; Nandi, M.; Sathe, K. M.; Deshmukh, A. R. A. S.; Bhawal, B. M. *Tetrahedron: Asymmetry* **1993**, *4*, 609. (c) Jayaraman, M. J.; Deshmukh, A. R. A. S.; Bhawal, B. M. *Tetrahedron* **1996**, *52*, 8989. (d) Banik, B. K.; Mathur, C.; Wagle, D. R.; Manhas, M. S.; Bose, A. K. *Tetrahedron* **2000**, *56*, 5603.

(7) (a) Denis, J.-N.; Greene, A. E.; Guénard, D.; Guéritte-Voegelein, F.; Mangatal, L.; Potier, P. *J. Am. Chem. Soc.* **1988**, *110*, 5917. (b) Holton, R. A.; Liu, J. H. *Bioorg. Med. Chem. Lett.* **1993**, *3*, 2475. (c) Georg, G. I.; Cheruvallath, Z. S.; Harriman, G. C. B.; Hepperle, M.; Park, H. *Bioorg. Med. Chem. Lett.* **1993**, *3*, 2467.

(8) (a) Jayaraman, M.; Puranik, V. G.; Bhawal, B. M. *Tetrahedron* **1996**, *52*, 9005. (b) Srirajan, V.; Deshmukh, A. R. A. S.; Puranik, V. G.; Bhawal, B. M. *Tetrahedron: Asymmetry* **1996**, *7*, 2733. (c) Deshmukh, A. R. A. S.; Bhawal, B. M.; Krishnaswamy, D.; Govande, V. V.; Shinkre, B. A.; Jayanthi, A. *Curr. Med. Chem.* **2004**, *11*, 1889. (d) Shirode, N. M.; Kulkarni, K. C.; Gumaste, V. K.; Deshmukh, A. R. A. S. *ARKIVOC* **2005**, *(i)*, 53. (e) Tiwari, D. K.; Gumaste, V. K.; Deshmukh, A. R. A. S. *Synthesis* **2006**, 115.

(9) (a) Krishnaswamy, D.; Govande, V. V.; Deshmukh, A. R. A. S. *Synthesis* **2003**, 1903. (b) Kale, A. S.; Deshmukh, A. R. A. S. *Synlett* **2005**, 2370.

(10) (a) Thudichum, J. L. W. *A Treatise on the Chemical Constitution of the Brain*; Archon Books: Hamden, CT, **1962**. (b) Hakomori, S. *J. Biol. Chem.* **1990**, *265*, 18713. (c) van Meer, G.; Burger, K. N. J. *Trends Cell Biol.* **1992**, *2*, 338.

(11) (a) Merrill, A. H. Jr.; Sweeley, C. C. In *Biochemistry of Lipids, Lipoproteins and Membranes*; Vance, D. E.; Vance, J. E., Eds.; Elsevier: Amsterdam, **1996**, Chap. 12, 309. (b) Koskinen, P. M.; Koskinen, A. M. P. *Synthesis* **1998**, 1075. (c) Kolter, T.; Sandhoff, K. *Angew. Chem. Int. Ed.* **1999**, *38*, 1532.

(12) For recent studies of D-*erythro*-sphingosine synthesis, see: (a) Nugent, T. C.; Hudlicky, T. *J. Org. Chem.* **1998**, *63*, 510. (b) Hoffman, R. V.; Tao, J. *Tetrahedron Lett.* **1998**, *39*, 3953. (c) Hoffman, R. V.; Tao, J. *J. Org. Chem.* **1998**, *63*, 3979. (d) Yin, J.; Liu, H.; Pidgeon, C. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 179. (e) Khiar, N.; Singh, K.; Garcia, M.; Martin-Lomas, M. *Tetrahedron Lett.* **1999**, *40*, 5779. (f) Hertweck, C.; Boland, W. *J. Org. Chem.* **1999**, *64*, 4426. (g) Nakamura, T.; Shiozaki, M. *Tetrahedron Lett.* **1999**, *40*, 9063. (h) Azuma, H.; Tamagaki, S.; Ogino, K. *J. Org. Chem.* **2000**, *65*, 3538.

(13) For studies on the synthesis of phytosphingosine and its derivatives, see: (a) Sugiyama, S.; Honda, M.; Komori, T. *Liebigs Ann. Chem.* **1990**, 1069. (b) Dondoni, A.; Fantin, G.; Fogagnolo, M.; Pedrini, P. *J. Org. Chem.* **1990**, *55*, 439. (c) Wild, R.; Schmidt, R. R. *Tetrahedron: Asymmetry* **1994**, *5*, 2195. (d) Murakami, T.; Minamikawa, H.; Hato, M. *Tetrahedron Lett.* **1994**, *35*, 745. (e) Nakashima, H.; Hirata, N.; Iwamura, T.; Yamagiwa, Y.; Kamikawa, T. *J. Chem. Soc., Perkin Trans. 1* **1994**, 2849. (f) Kobayashi, S.; Hayashi, T.; Kawasuji, T. *Tetrahedron Lett.* **1994**, *35*, 9573. (g) Matsumoto, K.; Ebatu, T.; Matsushita, H. *Carbohydr. Res.* **1995**, *279*, 93. (h) Wild, R.; Schmidt, R. R. *Liebigs Ann.* **1995**, 755. (i) Li, Y. L.; Mao, X. H.; Wu, Y. L. *J. Chem. Soc., Perkin Trans. 1* **1995**, 1559. (j) Kemp, S. J.; Bao, J.; Pedersen, S. F. *J. Org. Chem.* **1996**, *61*, 7162. (k) Lin, G. Q.; Shi, Z. C. *Tetrahedron* **1996**, *52*, 2187. (l) Yoda, H.; Oguchi, T.; Takabe, K. *Tetrahedron: Asymmetry* **1996**, *7*, 2113. (m) Murakami, M.; Ito, H.; Ito, Y. *Chem. Lett.* **1996**, 185. (n) Wee, A. G. H.; Tang, F. *Tetrahedron Lett.* **1996**, *37*, 677. (o) Shimizu, M.; Wakioka, I.; Fujisawa, T. *Tetrahedron Lett.* **1997**, *38*, 6027. (p) Imashiro, R.; Sakurai, O.; Yamashita, T.; Horikawa, H. *Tetrahedron* **1998**, *54*, 10657. (q) Takikawa, H.; Muto, S.; Mori, K. *Tetrahedron* **1998**, *54*, 3141. (r) Li, S.; Pang, J.; Wilson, W. K.; Schroepfer, J. Jr. *Tetrahedron: Asymmetry* **1999**, *10*, 1697. (s) Murakami, T.; Toguchi, K. *Tetrahedron* **1999**, *55*, 989. (t) Shirota, O.; Nakanishi, K.; Berova, N. *Tetrahedron* **1999**, *55*, 13643. (u) Martin, C.; Prunck, W.; Bortolussi, M.; Bloch, R. *Tetrahedron: Asymmetry* **2000**, *11*, 1585.

(14) For recent reviews on sphingosines/ceramides, see: (a) Liao, J.; Tao, J.; Lin, G.; Liu, D. *Tetrahedron* **2005**, *61*, 4715. (b) Curfman, C.; Liotta, D. *Methods Enzymol.* **1999**, *311*, 391.

(15) (a) Karlsson, K.-A. *Trends Pharmacol. Sci.* **1991**, *12*, 265. (b) Hannun, Y.; Bell, R. M. *Science (Washington, D. C.)* **1989**, *243*, 500. (c) Hannun, Y. *Science (Washington, D. C.)* **1996**, *274*, 1855. (d) Vankar, Y. D.; Schmidt, R. R. *Chem. Soc. Rev.* **2000**, *29*, 201. (e) Brodesser, S.; Sawatzki, P.; Kolter, T. *Eur. J. Org. Chem.* **2003**, 2021.

(16) (a) Motoki, K.; Kobayashi, E.; Uchida, T.; Fukushima, H.; Koezuka, Y. *Bioorg. Med. Chem. Lett.* **1995**, *5*, 705. (b) Pushkareva, M.; Chao, R.; Bielawska, A.; Merrill, A. H.; Crane, H. M.; Lagu, B.; Liotta, D.; Hannun, Y. A. *Biochemistry* **1995**, *34*, 1885. (c) Inokuchi, J.-i.; Usuki, S.; Jimbo, M. *J. Biochem. (Tokyo)* **1995**, *117*, 766.

(17) (a) Olofsson, B.; Somfai, P. *J. Org. Chem.* **2003**, *68*, 2514. (b) Jeong, I.-Y.; Lee, J. H.; Lee, B. W.; Kim, J. H.; Park, K. H. *Bull. Korean Chem. Soc.* **2003**, *24*, 617. (c) Milne, J. E.; Jarowicki, K.; Kocienski, P. J.; Alonso, J. *Chem. Commun.* **2002**, 426. (d) Lees, W. J.; Gargano, J. M. *Tetrahedron Lett.* **2001**, *42*, 5845. (e) Duclos, R. I. *Chem. Phys. Lipids* **2001**, *111*, 111. (f) Lee, J.-M.; Lim, H.-S.; Chung, S.-K. *Tetrahedron: Asymmetry* **2002**, *13*, 343. (g) Bittman, R.; Chun, J.; Li, G.; Byun, H.-S. *Tetrahedron Lett.* **2002**, *43*, 375. (h) Chaudhari, V. D.; Ajish Kumar, K. S.; Dhavale, D. D. *Org. Lett.* **2005**, *7*, 5805. (i) Lee, K. H.; Kim, E.-K.; Pak, C. S. *Tetrahedron Lett.* **2002**, *43*, 9641. (j) Nakamura, T.; Shiozaki, M. *Tetrahedron* **2001**, *57*, 9087. (k) Raghavan, S.; Rajandar, A.; Yadav, J. S. *Tetrahedron: Asymmetry* **2003**, *14*, 2093. (l) van den Berg, R. J. B. H. N.; Korevaar, C. G. N.; Overkleeft, H. S.; van der Marel, G. A.; van Boom, J. H. *J. Org. Chem.* **2004**, *69*, 5699. (m) Lombardo, M.; Capdevila, M. G.; Pasi, F.; Trombini, C. *Org. Lett.* **2006**, *8*, 3303.