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Asymmetric total syntheses of spisulosine, its diastereo- and regio-isomers

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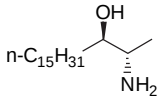
ABSTRACT

Starting from palmityl alcohol, divergent stereoselective syntheses of spisulosine and its diastereo- and regio-isomers have been achieved. In the Sharpless asymmetric dihydroxylation-based approach, the key step is the synthesis of monoprotected diol, whereas Miyashita's boron-directed C-2 regioselective azidolysis of enantiomerically pure epoxy alcohol is the vital step in the Sharpless asymmetric epoxidation-based route. The latter approach involves the first protecting-group-free synthesis of spisulosine.

1. Introduction

Long-chain 2-amino-3-alkanols, which are commonly found in tunicates and some sponges, comprise an important class of bioactive molecules. The structures are generally related to the widely distributed amphiphilic sphingosines and their carbon-chain length varies from C_{12} to C_{30} and their polyunsaturated variants have also been reported. Ascidians from *Pseudodistoma* and *Clavelina* genera have been prolific in the production of 2-amino-3-alkanols. Examples are crucigasterins 277, 275, and 225,[1] obscuraminols A–F,[2] clavaminols A–F,[3] and (2*S*,3*R*)-2-aminododecan-3-ol.[4] Researchers from PharmaMar reported an initial studies with a molecule known as ES-285 or spisulosine **1** (Fig. 1), isolated from the marine clam *Spisula polynyma*.[5] This compound caused a loss of actin stress fibers[5] and inhibited cell proliferation with an IC_{50} of 1 μM in the prostate tumor PC-3 and LNCaP cell lines.[6]



Spisulosine 1

Fig. 1. Structure of spisulosine.

The promising anticancer agent spisulosine is currently in clinical trial.[7] Consequently, a practical route providing the title compound should be highly desirable. However, despite its structural simplicity, spisulosine **1** has been less encountered in terms of its total synthesis.[8,9] The chemistry of **1** and the corresponding *syn*-diastereomer dates back to 1957 when Croatian researchers synthesized these two molecules for the first time in the determination of absolute configurations of lipid bases with two or more asymmetric carbon atoms.[8a] In this context it is important to mention that in the above synthesis, **1** was known as a purely synthetic molecule as its isolation as a natural product became known afterwards.[5] In recent time, efficient synthesis of spisulosine **1** and related compounds were achieved by a diastereoselective addition reaction of appropriate long alkyl chain Grignard reagents on L-alanine derived *N*-protected amino aldehyde derivative.[9] Lee and co-workers reported asymmetric synthesis of *N*-Boc-spisulosine from an enantiomerically pure 2-acylaziridine derivative.[8b] Very recently, Galvez and co-workers reported asymmetric synthesis of the hydrochloride salt of spisulosine from D-mannitol.[8c] Another recent report of synthesis of 1 involved the stereoselective addition of a racemic 3-alkoxy allenylzinc to enantiopure *N*-*tert*-butylsulfinyl imines and a cross-metathesis reaction as the key steps.[8d] In this paper, we report a divergent stereoselective and first protecting group-free syntheses of spisulosine **1** and its diastereo- and regio-isomers employing Sharpless asymmetric dihydroxylation and epoxidation reactions as the source of chirality.

2. Results and discussion

Our envisioned retrosynthetic analysis for the enantioselective preparation of spisulosine is depicted in Scheme 1. The target molecule **1** was anticipated to be accesible from monoprotected diol **2**, which, in turn, could be derived from epoxy alcohol **3**. Allylic chloride **4**, which could be derived from alcohol **5**.

On the basis of the above retrosynthetic analysis, the first target for the synthesis of **1** was to synthesize enantiomerically pure epoxy alcohol **3**. Our synthesis of **1** started with commercially available palmityl alcohol **5** (Scheme 2). Swern oxidation of **5** provided 1-hexadecanal, which was used directly in the subsequent Wittig

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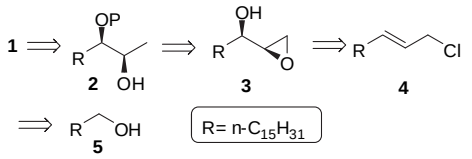
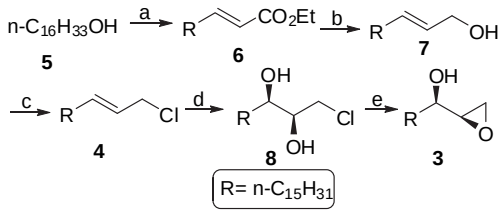


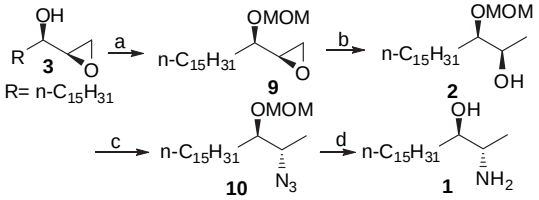
Scheme 1. Retrosynthetic analysis of spisulosine **1**.

reaction without further purification to avoid decomposition. Thus, reaction of the above crude aldehyde with $Ph_3P{=}CHCO_2Et$ in dry CH_2Cl_2 furnished the desired *trans*-α,β-unsaturated ester **6** in high yield (80% from **5**). Next, DIBAL-H reduction of **6** in dry toluene furnished the corresponding *trans*-α,β-unsaturated alcohol **7** in excellent yield. Compound **7** was then converted into allylic chloride **4** in 94% yield. Compound **4** was then subjected to Sharpless asymmetric dihydroxylation[10] with AD mix β in ^{t}BuOH-H_2O (1:1) at 0 °C for 24 h furnishing dihydroxyl derivatives **8** in good yield. It is important to mention that the reaction was carried out under 'buffered' conditions (with 3 equiv of $NaHCO_3$) to minimize the epoxide formation.[11,12] Next, treatment of diol **8** with powdered NaOH in THF at 0 °C afforded the epoxide **3** in good yield.



Scheme 2. Reagents and conditions: (a) (i) $(COCl)_2$, DMSO, anhyd. Et_3N, CH_2Cl_2, −78 °C, 2 h (ii) $Ph_3P{=}CHCO_2Et$, CH_2Cl_2, 8 h, 80% (for two steps). (b) DIBAL-H (1 M in toluene), toluene, 0 °C-rt, 1 h, 95%. (c) NCS, PPh_3, CH_2Cl_2, 0 °C-rt, 3 h, 94%. (d) AD mix β, $MeSO_2NH_2$, $NaHCO_3$, ^{t}BuOH-H_2O (1:1), 0 °C, 24 h, 88%. (e) NaOH, THF, 0 °C-rt, 3 h, 92%.

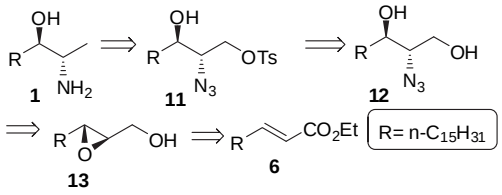
With the enantiomerically pure epoxy alcohol **3** in hand, our next target was to convert it into **1**. Toward that objective, hydroxyl group of **3** was protected as methoxymethyl ether with MOM-Cl in CH_2Cl_2 in the presence of *N*,*N*-diisopropylethylamine to give compound **9** in 98% yield (Scheme 3). Next, regioselective reductive ring opening of **9** with $LiAlH_4$ in THF at 0 °C provided **2** in 95% yield. Subsequent tosylation of alcohol **2** with tosyl chloride in the presence of triethylamine and a catalytic amount of DMAP furnished the corresponding tosylate, which was used for the next step without further purification. Thus, the above crude tosylate on refluxing with NaN_3 in dry DMF gave the azide **10** in good yield.



Scheme 3. Reagents and conditions: (a) MOMCl, *i*-Pr_2EtN, CH_2Cl_2, 0 °C-rt, 12 h, 95%. (b) $LiAlH_4$, THF, 0 °C-rt, 5 h, 95%. (c) (i) TsCl, CH_2Cl_2, anhyd. Et_3N, DMAP (cat.), 0 °C-rt, 48 h (ii) NaN_3, DMF, 90 °C, 5 h, 70% (for two steps). (d) (i) H_2, 10% Pd-C, methanol, 6 h, rt. (ii) conc. HCl, methanol, 80% (for two steps).

Finally, reduction of the azido group of **10** by hydrogen in the presence of 10% Pd-C in methanol followed by deprotection of MOM group of the resulting amine derivative with conc. HCl furnished spisulosine **1**. The physical and spectral data of **1** were in agreement with the literature data.[9] Thus, spisulosine **1** was synthesized from commercially available palmityl alcohol in 12 steps and 22.5% overall yield. However, the above synthetic route required a protecting group.

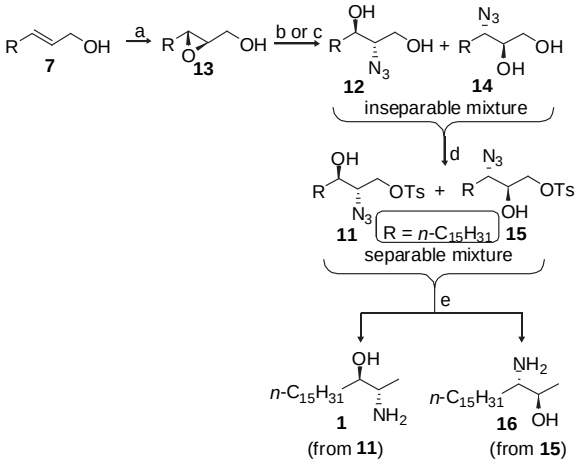
In an alternative way, we decided to synthesize spisulosine **1** without using any protecting group. Total synthesis of natural or synthetic biologically important molecules employing a protecting group-free strategy has been an important challenge in organic chemistry.[13] Our envisioned retrosynthetic analysis for the protecting group-free enantioselective preparation of spisulosine is depicted in Scheme 4.



Scheme 4. Protecting group-free retrosynthetic analysis of spisulosine **1**.

The target molecule **1** was anticipated to be prepared by one-pot reduction of azido tosylate **11**, which, in turn, could be derived from azido diol **12**. The compound **12** could be obtained from epoxy alcohol **13** by the trialkyl borate mediated C-2 selective azidolysis under Miyashita's condition.[14] Although Miyashita's pioneering C-2 selective nucleophilic substitution reactions including the azidolysis have been utilized for natural product synthesis,[15] it has never been employed in protecting-group-free synthesis of a target molecule.

We started by Sharpless asymmetric epoxidation[16] of **7** with D-(−)-diethyl tartrate to get epoxy alcohol **13** in 85% yield, which showed >98% ee by ^{1}H NMR analysis of the corresponding Mosher ester derivative (Scheme 5).



Scheme 5. Reagents and conditions: (a) D-(−)-DET, Ti(O*i*-Pr)$_4$, TBHP, CH_2Cl_2, −25 °C, 24 h, 85%.(b) NaN_3, $(MeO)_3B$, DMF, 50 °C, 5 h (c) NaN_3, NH_4Cl, MeOH/H_2O(8:1), 80 °C, 18 h (d) TsCl (1.1 equiv), CH_2Cl_2, anhyd. Et_3N, 0 °C, 6 h, 65% (for **11**, using reaction condition 'b'), 67% (for **15**, using reaction condition 'c'); for combined two steps. (e) $LiAlH_4$, THF, 0 °C-rt, 5 h, 70% (**1**), 62% (**16**).

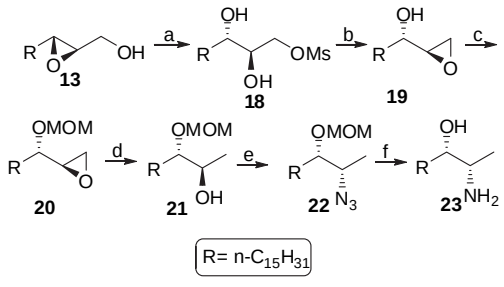
Next, C-2 selective azidolysis of enantiomerically pure epoxide **13** by sodium azide in dry DMF in the presence of trimethylborate furnished mixture of azidodiols **12** (major) and **14** (minor). Unfortunately, these two regioisomers did not show any separation

on TLC, and an attempt to purify by column chromatography was also unsuccessful. Miyashita and co-workers isolated the regioselective C-2 substituted products by $NaIO_4$-mediated oxidative cleavage of the corresponding C-3 substituted minor product (thus, removing the minor azido diol as one-carbon degraded less polar aldehydes). However, we were also interested in synthesizing the regioisomer of **1**, in which case compound **14** was needed as an intermediate. Thus, utilization of the $NaIO_4$-mediated oxidative cleavage reaction in a mixture of **12** and **14** was not a desired option for us. We were delighted to see that the corresponding tosylates **11** and **15**, which were obtained by tosylation of a mixture of **12** and **14** with 1.1 equiv of tosyl chloride in dry CH_2Cl_2 in the presence of triethylamine at 0 °C, were completely separable by silica gel column chromatography.

Amounts of isolated **11** and **15** suggested that in the azidolysis reaction compounds **12** and **14** were formed in 85:15 ratio. Subsequently, compound **11** was treated with $LiAlH_4$ in THF to get spisulosine **1** in 70% yield. Thus, this synthetic route of spisulosine did not require any protecting group and involved five fewer steps as compared to the other one already described in this paper.

Since the above synthetic route allowed to access compound **15** only in minor amount, it was necessary to search for an alternative route for getting sufficient amount of **15**, which could allow the synthesis of the regioisomer of **1**. Toward that objective, epoxide **13** was subjected to the standard azidolysis ring opening reaction[17] carried out with NaN_3/NH_4Cl in an 8:1 MeOH and H_2O solution to get **14** (major) and **12** (minor amount), Scheme 5. Next, tosylate **15** was isolated in pure form in the similar way as, that is, described for **11**. Treatment of compound **15** with $LiAlH_4$ in THF furnished amino alcohol **16** in 62% yield.

Next, we turned our attention toward the synthesis of a diastereoisomer **23** of spisulosine with the (2*S*, 3*S*) configuration. Toward that objective, the hydroxyl group of epoxide **13** was mesylated and the resulting epoxy mesylate was then treated with perchloric acid to afford dihydroxy mesylate **18**.[18] Treatment of **18** with anhyd. K_2CO_3 in dry methanol gave epoxy alcohol **19** in 89% yield. Next, compound **19** was converted into **23** in the similar way as that has been described for the synthesis of **1** from **3** (Scheme 6).



Scheme 6. Reagents and conditions: (a) (i) MsCl, Et_3N, CH_2Cl_2, 0 °C; (ii) $HClO_4$, DMSO, 60 °C, 87% (for two steps). (b) K_2CO_3, MeOH, rt, 89%. (c) MOMCl, *i*-Pr_2EtN, CH_2Cl_2, 0 °C-rt, 12 h, 96%. (d) $LiAlH_4$, THF, 0 °C-rt, 5 h, 94%. (e) (i) TsCl, CH_2Cl_2, anhyd Et_3N, DMAP (cat.), 0 °C-rt, 48 h (ii) NaN_3, DMF, 90 °C, 5 h, 71% (for both steps). (f) (i) H_2, 10% Pd-C, methanol, 6 h, rt. (ii) conc. HCl, methanol, 75% (for both steps).

3. Conclusion

In conclusion, starting from commercially available palmityl alcohol, new asymmetric total syntheses of spisulosine **1** and its regio- and diastereomers have been developed. Notable features of this approach include the use of Sharpless asymmetric dihydroxylation and epoxidation reactions to synthesize the enantiomerically pure epoxy alcohols and regioselective epoxide azidolysis for the first protecting-group-free synthesis of **1**. The other merits of this synthesis are high-yielding reaction steps, high enantioselectivity and various possibilities available for structural modification and thus it might be considered as a general synthetic strategy to enantiomerically pure 2-amino-3-alkanols.

4. Experimental

4.1. General methods

All dry reactions were carried out under nitrogen in oven-dried glassware using standard gas-light syringes, cannulas, and septa. All reagents and solvents were dried prior to use according to the standard methods. Commercial reagents were used without further purification unless otherwise stated. Reactions were monitored on silica gel TLC plates (coated with TLC grade silica gel, obtained from Merck). Detecting agents used (for TLC) were iodine vapors and/or spraying with an aqueous solution of vanillin in 10% sulfuric acid followed by heating at 150 °C. Column chromatography was performed over silica gel (100–200 mesh) procured from Qualigens (India) using freshly distilled solvents. Mass spectra were recorded using electron spray ionization (ESI-MS) on a JEOL SX 102 spectrometer using argon/xenon as the FAB gas. Elemental analyses were done on Varian EL-III C H N analyzer. IR spectra were recorded on a Perkin–Elmer FT-IR RXI spectrometer. ^1H NMR and ^{13}C NMR spectra were recorded on Brucker DPX-300 (operating at 300 MHz for ^1H and 75 MHz for ^{13}C) spectrometer using $CDCl_3$. Tetramethylsilane (0.00 ppm) served as an internal standard in ^1H NMR and $CDCl_3$ (77.0 ppm) in ^{13}C NMR. All spectra were recorded at 25 °C. Coupling constants (*J* values) are given in hertz (Hz). Chemical shifts were expressed in parts per million. Optical rotations were measured at the sodium D-line at ambient temperature with a Perkin–Elmer 141 polarimeter.

*4.1.1. (2E)-Octadec-2-enoate (**6**).* To a stirring solution of oxalyl chloride (4.53 g, 35.69 mmol) in dry CH_2Cl_2 (50 mL) at −78 °C was added dropwise dry DMSO (5.6 mL, 71.35 mmol) in CH_2Cl_2 (20 mL). After 30 min, alcohol **5** (5.76 g, 23.76 mmol) in CH_2Cl_2 (20 mL) was added over 10 min giving copious white precipitate. After stirring for 1 h at −78 °C the reaction mixture was brought to −60 °C and anhyd. Et_3N (13.26 mL, 95.12 mmol) was added slowly and stirred for 30 min allowing the reaction mixture to warm to rt. The reaction mixture was then diluted with water (75 mL) and CH_2Cl_2. The organic layer was separated and washed with water and brine, dried (Na_2SO_4), and passed through short pad of Celite. The filtrate was concentrated to give the aldehyde as a pale yellow oil, which was used as such for the next step without purification.

To a stirring solution of the above crude aldehyde in dry CH_2Cl_2 was added (ethoxycarbonylmethylene)-triphenylphosphorane (9.25 g, 26.54 mmol) and the reaction mixture was stirred for 8 h at rt. It was then concentrated and purification of the crude product by silica gel column chromatography (2% ethyl acetate in hexane) afforded **6** (5.90 g, 80%) as a colorless liquid. *Rf*: 0.54 (5% ethyl acetate in hexane). IR (neat): 1716, 1654 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.01–6.91 (m, 1H, H_3), 5.80 (d, 1H, J=15.4, H_2), 4.17 (q, 2H, J=7.2, CH_2), 2.18 (br q, 2H, J=6.9, H_4), 1.47–1.26 (m, 29H), 0.87 (t, 3H, J=6.5, CH_3). MS (ESI): *m*/*z* 311 $[M]^+$. Anal. Calcd for $C_{20}H_{38}O_2$: C, 77.36; H, 12.33. Found: C, 77.51; H, 12.47. The above spectroscopic data are in consistence with the literature data.[19]

*4.1.2. (2E)-Octadec-2-en-l-o1 (**7**).* To a stirring solution of 3.62 g (11.66 mmol) of **6** in 40 mL of dry toluene was added dropwise 35 mL (35.0 mmol) of DIBAL-H (1 M in toluene) at 0 °C. The resulting mixture was allowed to warm to rt over 1 h, then quenched by adding water (50 mL). The resulting gel was dissolved by dropwise addition of 6 N HC1. The organic layer was separated, and the aqueous phase was extracted with ethyl acetate (2×50 mL). The combined organic extracts were washed with saturated

aqueous $NaHCO_3$ solution (75 mL), then dried over dried over anhyd. Na_2SO_4, filtered, and then concentrated under reduced pressure. Purification of the crude product by silica gel column chromatography (8% ethyl acetate in hexane) afforded 7 (2.97 g, 95%) as a colorless solid. Mp: 46–48 °C. R_f: 0.54 (20% ethyl acetate in hexane). IR (neat): 3420, 2926, 2854, 1637, 1463, 1216, 972, 766 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 5.75–5.55 (m, 2H, $H_{2,3}$), 4.08 (d, 2H, J=4.9, H_1), 2.04 (br q, 2H, J=6.3, H_4), 1.48–1.25 (m, 27H), 0.86 (t, 3H, J=6.5, CH_3). ^{13}C NMR (50 MHz, $CDCl_3$): δ 133.5, 128.8, 63.8, 32.2, 31.9, 29.7, 29.6, 29.4, 29.3, 29.1, 22.7, 14.1. MS (ESI): m/z 268 $[M]^+$. Anal. Calcd for $C_{18}H_{36}O$: C, 80.53; H, 13.52. Found: C, 80.42; H, 13.66. The above spectroscopic data are in consistence with the literature data.[20]

*4.1.3. (2E)-1-Chloro-octadec-2-ene (**4**).* To a stirring solution of alcohol **7** (2.5 g, 9.31 mmol), and Ph_3P (2.68 g, 10.21 mmol) in 30 mL of dry CH_2Cl_2 was added NCS (1.50 g, 11.23 mmol) at 0 °C under nitrogen. The reaction mixture was stirred at 0 °C for 1 h, then allowed to warm to rt, and stirred for 2 h. It was then concentrated and purification of the crude product by silica gel column chromatography (2% ethyl acetate in hexane) afforded **4** (2.52 g, 94%) as a colorless liquid. R_f: 0.58 (5% ethyl acetate in hexane). IR (neat): 3350, 3000, 2950, 2860, 1480, 1200, 1050 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 5.78–5.68 (m, 2H), 4.01 (d, 2H, J=6.6), 2.05–2.02 (m, 2H), 1.28–1.43 (m, 26H), 0.89 (t, 3H, J=6.7). MS (ESI): m/z 289, 287 $[M]^+$. Anal. Calcd for $C_{18}H_{35}Cl$: C, 75.35; H, 12.30. Found: C, 75.39; H, 12.25.

*4.1.4. (2R,3R)-1-Chlorooctadecane-2,3-diol (**8**).* To a mixture of AD mix β (4.88 g) and $NaHCO_3$ (0.88 g, 10.45 mmol) in ^tBuOH-H_2O (1:1, 35 mL) cooled at 0 °C was added methanesulfonamide (0.33 g, 3.48 mmol). After being stirred for 10 min at 0 °C, allylic chloride **4** (1.0 g, 3.48 mmol) was added in one portion. The reaction mixture was vigorously stirred at 0 °C for 24 h and then quenched with solid sodium sulfite (25 g). The stirring was continued for 45 min and the solution was extracted with ethyl acetate (3×50 mL). The combined extracts were dried (Na_2SO_4) and concentrated under reduced pressure. Purification of the crude product by silica gel column chromatography (20% ethyl acetate in hexane) afforded **8** (0.98 g, 88%) as a colorless solid. Mp: 91–93 °C. R_f: 0.45 (30% ethyl acetate in hexane). $[\alpha]_D^{25}$ +8.7 (c 1.15, MeOH). IR (KBr): 3330, 2928, 1230, 563 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 3.99–3.62 (m, 2H), 3.62–3.53 (m, 2H), 2.65 (br s, 1H), 2.25 (br s, 1H), 1.62–1.52 (m, 2H), 1.40–1.15 (m, 26H), 0.90 (t, 3H, J=7.0). MS (ESI): m/z 323, 321 $[M]^+$. Anal. Calcd for $C_{18}H_{37}ClO_2$: C, 67.36; H, 11.62. Found: C, 67.49; H, 11.44.

*4.1.5. (2R,3R)-1,2-Epoxyoctadecan-3-ol (**3**).* To a stirring solution of diol **8** (0.82 g, 2.55 mmol) in THF (15 mL) was added pulverized NaOH (0.21 g, 5.25 mmol) at 0 °C and reaction mixture was stirred at rt for 3 h. It was quenched by addition of water (10 mL) and then extracted with diethyl ether (3×20 mL). The combined extracts were dried over Na_2SO_4, and concentrated under reduced pressure. Purification of the crude product by silica gel column chromatography (10% ethyl acetate in hexane) afforded **3** (0.667 g, 92%) as a colorless solid. Mp: 62–63 °C. R_f: 0.48 (20% ethyl acetate in hexane). $[\alpha]_D^{25}$ +0.19 (c 1.76, $CHCl_3$). IR (KBr): 3337, 2959, 2916, 2850, 1466, 1125, 959, 871, 755, 720 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 3.47–3.35 (m, 1H), 3.01–2.95 (m, 1H), 2.85–2.80 (m, 1H), 2.73–2.69 (m, 1H), 2.59–2.56 (m, 1H), 1.67–1.27 (m, 28H), 0.88 (t, 3H, J=6.7). ^{13}C NMR (75 MHz, $CDCl_3$): δ 71.7, 55.5, 45.0, 34.1, 31.8, 29.6, 29.4, 29.2, 25.2, 22.6, 14.0. MS (ESI): m/z 285 $[M]^+$. Anal. Calcd for $C_{18}H_{36}O_2$: C, 76.00; H, 12.76. Found: C, 6.18; H, 12.64.

*4.1.6. (2R,3R)-1,2-Epoxy-3-methoxymethoxyoctadecane (**9**).* To a stirring solution of alcohol **3** (0.45 g, 1.58 mmol), and i-Pr_2EtN (0.53 mL, 3.16 mmol) in CH_2Cl_2 (10 mL) was added MOMCl (0.21 mL, 2.37 mmol) at 0 °C. The mixture was stirred for 12 h at rt. The reaction was quenched with saturated aqueous NH_4Cl (10 mL) and the mixture was extracted with CH_2Cl_2 (2×20 mL). The organic layer was washed with brine (20 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (10% ethyl acetate in hexane) to give **9** (0.508 g, 98%) as a colorless oil. R_f: 0.5 (35% ethyl acetate in hexane). $[\alpha]_D^{25}$ +25.2 (c 1.5, $CHCl_3$). IR (neat): 2925, 2853, 1467, 1401, 1377, 1257, 1216, 1152, 1102, 1036, 920, 721 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 4.88 (d, 1H, J=6.6), 4.66 (d, 1H, J=6.7), 3.40 (s, 3H), 3.29–3.22 (m, 1H), 3.00–2.96 (m, 1H), 2.78 (t, 1H, J=4.6), 2.54–2.52 (m, 1H), 1.65–1.25 (m, 28H), 0.88 (t, 3H, J=6.9). ^{13}C NMR (75 MHz, $CDCl_3$): δ 95.4, 78.0, 55.5, 54.7, 43.8, 32.3, 31.9, 29.67, 29.63, 29.62, 29.56, 29.51, 29.34, 25.4, 22.6, 14.1. MS (ESI): m/z 329 $[M]^+$. Anal. Calcd for $C_{20}H_{40}O_3$: C, 73.12; H, 12.27. Found: C, 73.19; H, 12.37.

*4.1.7. (2R,3R)-3-Methoxymethoxyoctadecan-2-ol (**2**).* To a stirring suspension of $LiAlH_4$ (50 mg, 1.33 mmol) in dry THF (8 mL) was dropwise added a solution of epoxide **9** (0.35 g, 1.06 mmol) in dry THF (7 mL) at 0 °C. The reaction mixture was allowed to warm to rt, and stirred for 5 h. The reaction was quenched by the addition of water (5 mL). The mixture was extracted with ethyl acetate (3×15 mL), washed with water (15 mL), brine (15 mL), and dried over Na_2SO_4. It was then filtered and concentrated under reduced pressure. Purification of the crude product by silica gel column chromatography (15% ethyl acetate in hexane) afforded **2** (332 mg, 95%) as a colorless liquid. R_f: 0.41 (35% ethyl acetate in hexane). $[\alpha]_D^{25}$ +12.7 (c 1.5, $CHCl_3$). IR (neat): 3450, 2925, 2857, 1467, 1400, 1257, 1221, 1159, 1102, 1039, 921, 722 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 4.74–4.68 (m, 2H), 3.73–3.65 (m, 1H), 3.42 (s, 3H), 3.29–3.23 (m, 1H), 3.04 (br s, 1H), 1.59–1.25 (m, 28H), 1.15 (d, 3H, J=6.3), 0.88 (t, 3H, J=6.3). ^{13}C NMR (75 MHz, $CDCl_3$): δ 97.3, 85.4, 69.2, 55.7, 31.9, 31.1, 29.8, 29.6, 29.3, 25.0, 22.6, 19.0, 14.0. MS (ESI): m/z 331 $[M]^+$. Anal. Calcd for $C_{20}H_{42}O_3$: C, 72.67; H, 12.81. Found: C, 72.74; H, 12.89.

*4.1.8. (2S,3R)-2-Azido-3-methoxymethoxyoctadecane(**10**).* To an ice-cooled solution of alcohol **2** (325 mg, 0.98 mmol), anhyd. triethylamine (0.29 mL, 1.96 mmol), and DMAP (10 mg) in dry CH_2Cl_2 (10 mL) was added TsCl (200 mg, 1.05 mmol). After being stirred for 1 h in an ice bath and then 48 h at rt, the mixture was diluted with CH_2Cl_2 (30 mL) and water (20 mL). The organic layer was separated, washed with brine (15 mL), and dried over Na_2SO_4. It was then filtered and the filtrate was concentrated under reduced pressure to get the crude tosylate, which was used for the next step without further purification.

To a solution of the above crude tosylate in dry DMF (10 mL) was added NaN_3 (0.34 g, 5.25 mmol). After being stirred for 5 h at 90 °C, the mixture was diluted with ethyl acetate (20 mL) and water (10 mL). The organic layer was separated, washed with brine (15 mL), and dried over Na_2SO_4. It was then filtered and the filtrate was concentrated under reduced pressure. Purification of the crude product by silica gel column chromatography (4% ethyl acetate in hexane) afforded **10** (243 mg, 70%) as a colorless liquid. R_f: 0.58 (10% ethyl acetate in hexane). $[\alpha]_D^{25}$ +17.2 (c 1.5, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ 4.73–4.64 (m, 2H), 3.62–3.51 (m, 2H), 3.39 (s, 3H), 1.61–1.19 (m, 31H), 0.86 (t, 3H, J=6.9). ^{13}C NMR (75 MHz, $CDCl_3$): δ 96.4, 80.3, 59.6, 55.6, 31.8, 30.4, 29.62, 29.60, 29.52, 29.48, 29.3, 25.4, 22.6, 14.2, 14.0. MS (ESI): m/z 356 $[M]^+$, 342 $[M-N_2]^+$. Anal. Calcd for $C_{20}H_{41}N_3O_2$: C, 67.56; H, 11.62; N, 11.82. Found: C, 67.51; H, 11.77; N, 11.98.

*4.1.9. (2S,3R)-2-Aminooctadecan-3-ol (**1**).* To a stirred solution of **10** (100 mg, 0.28 mmol) in methanol (10 mL) was added 10% Pd-C (20 mg). After stirring for 4 h at rt under pressure of a hydrogen

balloon, the reaction mixture was filtered through a pad of Celite® and the filtrate was concentrated under reduced pressure to get the corresponding amine derivative as a colorless semi-solid, which was used for the next step without further purification.

To a solution of the above crude amine in methanol (5 mL) was added two drops of conc. HCl. After being stirred for 12 h at rt, the mixture was concentrated under reduced pressure. The residue was redissolved in $CHCl_3$ (10 mL) and the resulting solution was treated with saturated aqueous $NaHCO_3$ solution (10 mL). The organic layer was separated, washed with brine (15 mL), and dried over Na_2SO_4. It was then filtered and the filtrate was concentrated under reduced pressure. Purification of the crude product by silica gel column chromatography (50% methanol in $CHCl_3$) afforded **1** (64 mg, 80%) as a white solid. Mp: 67–68 °C. R_f: 0.48 (20% methanol in chloroform). $[\alpha]_D^{25}$ +21.4 (*c* 0.5, $CHCl_3$). IR (KBr): 3408 (OH), 3345–3200 (NH), 2922, 2854, 1652, 1468, 1257, 1190, 1070, 1044, 744, 621 cm^{-1}. ^1H NMR (300 MHz, CD_3OD): δ 3.68 (m, 1H, CH-3), 3.34–3.22 (m, 1H, CH-2), 1.49–1.27 (m, 31H), 1.20 (d, 3H, *J*=6.7, CH_3-1), 0.89 (t, 3H, *J*=6.2, CH_3-18). ^{13}C NMR (75 MHz, $CDCl_3$): δ 74.9, 50.5, 32.6, 32.1, 30.1, 29.9, 29.8, 26.4, 22.9, 17.1, 14.3. MS (ESI): *m*/*z* 287 $[M+1]^+$. Anal. Calcd for $C_{18}H_{39}NO$: C, 75.72; H, 13.77; N, 4.91. Found: C, 75.79; H, 13.88; N, 5.07. The physical and spectral data were in agreement with the literature data.[9]

*4.1.10. {(2R,3R)-3-Pentadecyloxiran-2-yl}methanol (**13**).* Freshly distilled $Ti(O^iPr)_4$ (3.9 mL, 13.1 mmol) was added to CH_2Cl_2 and the resulting solution was cooled to −25 °C. D-(−)-DET (3.0 mL, 17.4 mmol) was then added. The resulting mixture was then stirred for 20 min, and then a solution of **7** (2.92 g, 10.9 mmol) in CH_2Cl_2 (20 mL) was added. 20 min later TBHP (5.6 M in *n*-decane, 5.8 mL, 32.7 mmol) was added and then the reaction mixture was stored in the −20 °C refrigerator for 24 h. The reaction was then quenched by addition of Me_2S (3.2 mL, 43.6 mmol). The resulting mixture was stirred for 30 min at −20 °C and then saturated aqueous Na_2SO_4 (15 mL) was added. This suspension was allowed to warm to rt, then filtered through a pad of Celite, washed with diethyl ether, and purification of the crude product by silica gel column chromatography (6% ethyl acetate in hexane) afforded **13** (2.64 g, 85%) as a colorless solid. Mp: 67–68 °C. R_f: 0.53 (5% ethyl acetate in hexane). $[\alpha]_D^{25}$ +22.7 (*c* 0.93, MeOH). IR (neat): 3428, 2923, 1216, 762 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 3.95–3.89 (m, 1H, H_{1a}), 3.66–3.58 (m, 1H, H_{1b}), 2.98–2.91 (m, 2H, $H_{2,3}$), 1.61–1.14 (m, 28H), 0.86 (t, 3H, *J*=6.5, CH_3). ^{13}C NMR (50 MHz, $CDCl_3$): δ 61.7, 58.4, 56.0, 31.9, 31.5, 29.7, 29.5, 29.4, 25.9, 22.7, 14.1. MS (ESI): *m*/*z* 284 $[M]^+$. Anal. Calcd for $C_{18}H_{36}O_2$: C, 76.00; H, 12.76. Found: C, 75.96; H, 12.84. The above spectroscopic data are in consistence with the literature data.[20]

*4.1.11. (2S,3R)-2-Azido-3-hydroxyoctadecyl-4-methyl benzenesulfonate (**11**).* A solution of the epoxide **13** (1.3 g, 4.57 mmol), $(MeO)_3B$ (1.05 mL, 9.14 mmol), and NaN_3 (0.6 g, 9.14 mmol) in DMF was stirred at 50 °C for 3 h. After cooling to 0 °C, a saturated aqueous solution of $NaHCO_3$ was added, and the mixture was stirred for 30 min. The mixture was separated, and the aqueous layer was extracted with ethyl acetate. The combined organic layer was successively washed with water, a saturated aqueous solution of $NaHCO_3$, brine, and dried over Na_2SO_4. Concentration under reduced pressure followed by column chromagraphy affored 4.34 g (95%) of the azido diol as an 84:16 mixture of regioisomers.

To an ice-cooled solution of the above regioisomeric azido diol in dry CH_2Cl_2 (10 mL) was added anhyd. Et_3N (1.16 mL, 8.31 mmol) followed by TsCl (0.91 g, 4.75 mmol) and the mixture was kept overnight at 0 °C. The mixture was diluted with H_2O (25 mL) and extracted with CH_2Cl_2 (2×30 mL). The combined organic layers were washed with H_2O (25 mL), brine (25 mL), and dried (Na_2SO_4). The solvent was removed under reduced pressure and purification of the crude product by silica gel flash column chromatography (20% EtOAc in *n*-hexane) afforded **11** (1.43 g, 65%) as a colorless gum. R_f: 0.48 (30% ethyl acetate in hexane). $[\alpha]_D^{25}$ −3.22 (*c* 2.58, MeOH). IR (neat): 3431, 3021, 2928, 2364, 1636, 1216, 1102, 765, 669 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.82 (d, 2H, *J*=8.3, ArH), 7.37 (d, 2H, *J*=8.4, ArH), 4.34 (dd, 1H, J_1=3.17, J_2=3.13), 3.64–3.51 (m, 2H), 2.69 (d, 1H, *J*=5.18), 2.46 (s, 3H, $ArCH_3$), 1.48–1.23 (m, 28H), 0.88 (t, 3H, *J*=6.4, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ 145.2, 132.5, 130.0, 128.0, 71.0, 69.0, 64.6, 33.2, 31.9, 29.6, 29.5, 29.4, 29.3, 25.4, 22.7, 21.7, 14.1. MS (ESI): *m*/*z* 482 $[M]^+$. Anal. Calcd for $C_{25}H_{43}N_3O_4S$: C, 62.34; H, 9.00; N, 8.72. Found: C, 62.52; H, 9.21; N, 8.46.

*4.1.12. (2S,3S)-3-Azido-2-hydroxyoctadecyl-4-methylbenzenesulfonate (**15**).* A solution of the epoxy alcohol **13** (1.2 g, 4.21 mmol) in an 8:l $MeOH/H_2O$ mixture (18.0 mL) was treated with NaN_3 (1.26 g, 19.37 mmol) and NH_4Cl (0.45 g, 8.40 mmol) and the resulting reaction mixture was stirred at 80 °C for 18 h. Dilution with ether and evaporation of the solution afforded a crude reaction product. This crude mixture containing regiomeric azidodiols was treated in the same way as that described for **11**. The solvent was removed under reduced pressure and purification of the crude product by silica gel flash column chromatography (20% EtOAc in *n*-hexane) afforded **15** (1.42 g, 67%) as a colorless gum. R_f: 0.48 (30% ethyl acetate in hexane). $[\alpha]_D^{25}$ −4.53 (*c* 1.74, MeOH). IR (neat): 3428, 2927, 2366, 1635, 1218, 769 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.82 (d, 2H, *J*=8.3, ArH), 7.37 (d, 2H, *J*=8.4, ArH), 4.34 (dd, 1H, J_1=3.2, J_2=3.1), 3.64–3.51 (m, 2H), 2.69 (d, 1H, *J*=5.18), 2.46 (s, 3H, $ArCH_3$), 1.48–1.23 (m, 28H), 0.88 (t, 3H, *J*=6.4, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ 145.2, 132.5, 130.0, 128.0, 71.0, 69.0, 64.7, 33.2, 31.9, 29.6, 29.5, 29.4, 29.3, 25.4, 22.7, 21.7, 14.1. MS (ESI): *m*/*z* 482 $[M]^+$. Anal. Calcd for $C_{25}H_{43}N_3O_4S$: C, 62.34; H, 9.00; N, 8.72. Found: C, 62.52; H, 9.21; N, 8.46.

*4.1.13. (2R,3S)-3-Aminooctadecan-2-ol (**16**).* To a stirring suspension of $LiAlH_4$ (76 mg, 2.0 mmol) in dry THF (8 mL) was dropwise added a solution of tosylate **15** (0.12 g, 0.25 mmol) in dry THF (3 mL) at 0 °C. The reaction mixture was allowed to warm to rt, and stirred for 8 h. The reaction was quenched by the addition of water (5 mL). The mixture was extracted with ethyl acetate (3×10 mL), washed with water (10 mL), brine (10 mL), and dried over Na_2SO_4. It was then filtered and concentrated under reduced pressure. Purification of the crude product by silica gel column chromatography (50% methanol in $CHCl_3$) afforded **16** (44 mg, 62%) as a white solid. Mp: 61–63 °C. R_f: 0.48 (20% methanol in chloroform). $[\alpha]_D^{25}$ +7.3 (*c* 1.7, MeOH). IR (KBr): 3408, 3022, 2925, 2855, 1628, 1464, 1257, 1216, 1041, 762, 670 cm^{-1}. ^1H NMR (300 MHz, CD_3OD): δ 3.78–3.75 (m, 1H, CH-2), 2.81 (m, 1H, CH-3), 1.45–1.26 (m, 28H), 1.10 (d, 3H, *J*=6.4, CH_3-1), 0.88 (t, 3H, *J*=6.2, CH_3-18). ^{13}C NMR (75 MHz, $CDCl_3$): δ 70.2, 56.3, 33.3, 32.3, 30.2–29.7 (10×CH_2), 26.5, 23.0, 17.2, 14.2. MS (ESI): *m*/*z* 287 $[M+1]^+$. Anal. Calcd for $C_{18}H_{39}NO$: C, 75.72; H, 13.77; N, 4.91. Found: C, 75.63; H, 13.91; N, 5.02.

Spisulosine **1** was prepared (yield 70%) in the similar way from tosylate **11**.

*4.1.14. (2R,3S)-2,3-Dihydroxyoctadecyl methanesulfonate (**18**).* A solution of **13** (1.82 g, 6.39 mmol) in CH_2Cl_2 (40 mL) was treated with MsCl (0.75 mL, 9.6 mmol), and Et_3N (1.8 mL, 12.8 mmol) at 0 °C. Upon being stirred for 15 min, the reaction mixture was diluted with diethyl ether, washed with saturated NH_4Cl, water, and concentrated. The resulting mixture was dissolved in 60% DMSO (40 mL) solution, being treated with 70% $HClO_4$ (0.2 mL). After being stirred for 6 h at 50 °C, the mixture was diluted with EtOAc, washed with saturated $NaHCO_3$, and water, dried over Na_2SO_4, and concentrated. Purification by silica gel column chromatagraphy (hexane: EtOAc=7:3 to 1:1) gave 1**8** (2.12 g, 87%) as a colorless solid. Mp: 91–93 °C. R_f: 0.45 (30% ethyl acetate in hexane). $[\alpha]_D^{25}$ +5.1 (*c*

1.07, MeOH). IR (KBr): 3387, 3322, 2920, 2362, 1339, 1173 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 5.38–5.32 (m, 1H), 4.45–4.29 (m, 2H), 3.83–3.73 (m, 2H), 3.08 (s, 3H), 2.78 (d, 1H, J=6.7), 1.85–1.13 (m, 28H), 0.88 (t, 3H, J=6.6). ^{13}C NMR (50 MHz, $CDCl_3$): δ 72.5, 72.2, 71.0, 37.5, 32.7, 31.9, 31.8, 29.8, 29.6, 29.5, 29.4, 29.3, 29.2, 27.2, 25.7, 22.6, 14.1. MS (ESI): m/z 380 $[M]^+$, 403 $[M+Na]^+$. Anal. Calcd for $C_{19}H_{40}O_5S$: C, 59.96; H, 10.59. Found: C, 59.74; H, 9.87.

*4.1.15. (2R,3S)-1,2-Epoxyoctadecan-3-ol (**19**).* A solution of compound **18** (o.80 g, 2.1 mmol) in dry MeOH (30 mL) was treated with K_2CO_3 (0.44 g, 3.15 mmol), and the mixture was stirred for 45 min at rt. After completion of the reaction, the mixture was concentrated and extracted with diethyl ether, washed with water, and brine. The organic layer was dried over Na_2SO_4 and concentrated. The residue was purified by silica gel column chromatography (10% ethyl acetate in hexane) gave **19** (0.53 g, 89%) as a colorless solid. Mp: 69–72 °C. R_f: 0.48 (20% ethyl acetate in hexane). $[\alpha]_D^{25}$ +0.23 (c 1.54, MeOH). IR (KBr): 3328, 2963, 2838, 1446, 963, 852, 718 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 3.39–3.27 (m, 1H), 2.93–2.87 (m, 1H), 2.77–2.72 (m, 1H), 2.65–2.61 (m, 1H), 2.51–2.49 (m, 1H), 1.59–1.19 (m, 28H), 0.81 (t, 3H, J=6.5). ^{13}C NMR (75 MHz, $CDCl_3$): δ 71.6, 55.4, 45.0, 34.0, 31.6, 29.6, 29.5, 29.3, 25.1, 22.6, 14.0. MS (ESI): m/z 285 $[M]^+$. Anal. Calcd for $C_{18}H_{36}O_2$: C, 76.00; H, 12.76. Found: C, 76.09; H, 12.83.

*4.1.16. (2R,3S)-1,2-Epoxy-3-methoxymethoxyocta-decane (**20**).* From **19** (0.51 g, 1.79 mmol), the title compound was prepared in the same manner as that described for **9**. Purification of the crude product by silica gel column chromatography (10% ethyl acetate in hexane) afforded **20** (0.564 g, 96%) as a colorless oil. R_f: 0.5 (35% ethyl acetate in hexane). $[\alpha]_D^{25}$ +18.4 (c 1.2, MeOH). IR (neat): 2917, 2843, 1408, 1369, 1249, 1220, 1141, 1043, 724 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 4.88 (d, 1H, J=6.6, OCH_aH_bO), 4.66 (d, 1H, J=6.7, OCH_aH_bO), 3.40 (s, 3H, OCH_3), 3.29–3.22 (m, 1H, H_3), 3.00–2.96 (m, 1H, H_2), 2.78 (t, 1H, J=4.6, CH_aH_b-1), 2.54–2.52 (m, 1H, CH_aH_b-1), 1.65–1.25 (m, 28H), 0.88 (t, 3H, J=6.9). ^{13}C NMR (75 MHz, $CDCl_3$): δ 95.4, 78.0, 55.5, 54.7, 43.8, 32.3, 31.9, 29.67, 29.63, 29.62, 29.56, 29.51, 29.34, 25.4, 22.6, 14.1. MS (ESI): m/z 329 $[M]^+$. Anal. Calcd for $C_{20}H_{40}O_3$: C, 73.12; H, 12.27. Found: C, 73.28; H, 12.46.

*4.1.17. (2R,3S)-3-Methoxymethoxyoctadecan-2-ol (**21**).* From **20** (0.540 g, 1.64 mmol), the title compound was prepared in the same manner as that described for **2**. Purification of the crude product by silica gel column chromatography (15% ethyl acetate in hexane) afforded **21** (509 mg, 94%) as a colorless liquid. R_f: 0.41 (35% ethyl acetate in hexane). $[\alpha]_D^{25}$ +17.3 (c 1.3, MeOH). IR (neat): 3443, 2913, 2839, 1461, 1244, 1204, 1140, 1028, 913, 712 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 4.74–4.68 (m, 2H), 3.73–3.65 (m, 1H), 3.42 (s, 3H), 3.29–3.23 (m, 1H), 3.04 (br s, 1H), 1.59–1.25 (m, 28H), 1.15 (d, 3H, J=6.3), 0.88 (t, 3H, J=6.3). ^{13}C NMR (75 MHz, $CDCl_3$): δ 97.3, 85.4, 69.2, 55.7, 31.9, 31.1, 29.8, 29.6, 29.3, 25.0, 22.6, 19.0, 14.0. MS (ESI): m/z 331 $[M]^+$. Anal. Calcd for $C_{20}H_{42}O_3$: C, 72.67; H, 12.81. Found: C, 72.81; H, 12.94.

*4.1.18. (2S,3S)-2-Azido-3-methoxymethoxyoctadecane (**22**).* From **21** (410 mg, 1.24 mmol), the title compound was prepared in the same manner as that described for **10**. Purification of the crude product by silica gel column chromatography (4% ethyl acetate in hexane) afforded **22** (313 mg, 71%) as a colorless liquid. R_f: 0.58 (10% ethyl acetate in hexane). $[\alpha]_D^{25}$ +11.3 (c 1.7, MeOH). ^1H NMR (300 MHz, $CDCl_3$): δ 4.73–4.64 (m, 2H), 3.62–3.51 (m, 2H), 3.39 (s, 3H), 1.61–1.19 (m, 31H), 0.86 (t, 3H, J=6.9). ^{13}C NMR (75 MHz, $CDCl_3$): δ 96.4, 80.3, 59.6, 55.6, 31.8, 30.4, 29.62, 29.60, 29.52, 29.48, 29.3, 25.4, 22.6, 14.2, 14.0. MS (ESI): m/z 356 $[M]^+$, 342 $[M-N_2]^+$. Anal. Calcd for $C_{20}H_{41}N_3O_2$: C, 67.56; H, 11.62; N, 11.82. Found: C, 67.71; H, 11.83; N, 12.02.

*4.1.19. (2S,3S)-2-Aminooctadecan-3-ol (**23**).* From **22** (95 mg, 0.27 mmol), the title compound was prepared in the same manner as that described for **1** from **10**. Purification of the crude product by silica gel column chromatography (50% methanol in $CHCl_3$) afforded **23** (58 mg, 75%) as a white solid. Mp: 73–75 °C. R_f: 0.48 (20% methanol in chloroform). $[\alpha]_D^{25}$ +3.4 (c 1.8, MeOH). IR (KBr): 3408, 3345–3200, 2922, 2854, 1652, 1468, 1257, 1190, 1070, 1044, 744, 621 cm^{-1}. ^1H NMR (300 MHz, CD_3OD): δ 3.68 (m, 1H, CH-3), 3.26–3.22 (m, 1H, CH-2), 1.49–1.27 (m, 31H), 1.20 (d, 3H, J=6.7, CH_3-1), 0.89 (t, 3H, J=6.2, CH_3-18). ^{13}C NMR (75 MHz, $CDCl_3$): δ 75.0, 50.6, 32.7, 32.2, 30.1, 29.5, 26.3, 22.9, 17.1, 14.2. MS (ESI): m/z 287 $[M+1]^+$. Anal. Calcd for $C_{18}H_{39}NO$: C, 75.72; H, 13.77; N, 4.91. Found: C, 75.77; H, 13.92; N, 5.11.

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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.2010.09.018. These data include MOL files and InChIKeys of the most important compounds described in this article.

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