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A flexible approach to construct three contiguous chiral centers of sphingolipids, and asymmetric synthesis of D-*ribo*-phytosphingosine and its derivatives

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ABSTRACT

An efficient approach to build the three contiguous stereogenic centers of sphingosine unit starting from cheap glutamic acid is described. The key step of this approach is the SmI_2-mediated cross-coupling of chiral *N*-*tert*-butanesulfinyl imine **11** with sterically hindered aliphatic aldehyde **9** or **21** to construct hydroxymethyl β-amino alcohol **10** or **22** in high diastereoselectivity (>99%, de). The utility of this flexible method has been demonstrated in the synthesis of D-*ribo*-phytosphingosine **1**, its two derivatives **18** and **29**. Moreover, a practicable synthetic route for synthesis of various sphingolipids, ceramides, α-galactosylceramides and their derivatives is also described.

1. Introduction

Sphingosine and phytosphingosine are two most important long-chain constituents of cell members (Fig. 1).[1] They are widely distributed in mammalian cells, bacteria and fungi, yeasts, plants, and marine organisms.[2] Their structural function of a small positive change at neutral pH as a consequence of intermolecular hydrogen bonding enable them as an unusual class of sphingolipids, which serve as an essential components of all eukaryotic cell membranes together with glycerolipids and sterols.[3] Sphingosine and phytosphingosine **1** play critical roles in many physiological processes, which include cellular recognition, modulation of immune response, adhesion and apoptosis.[4] In addition, they can effectively inhibit the protein kinase C, and their ceramide derivatives are also potent stimulators of the mammalian immune system.[5] Phytosphingosine or its derivatives are one essential core fragment of several ceramides, which possess diverse bioactivities, such as controlling cell growth, maturity, survival and death, and inhibiting or activating certain enzymes, and lead to promising efficacies for the control of cancer and other cell proliferation.[6] As a prime instance, modification of marine natural product agelasphine-9b **4** led to an anticancer drug candidate KRN7000,[7] which can regulate immune system through interaction with CD1d protein located on the surface of antigen-presenting cells.[8] Recent studies revealed that some of sphingolipids analogues could inhibit the diabetes, cancers, infection by microorganisms, Alzheimer's disease, heart disease of human body.[9] In nature, among of eight possible

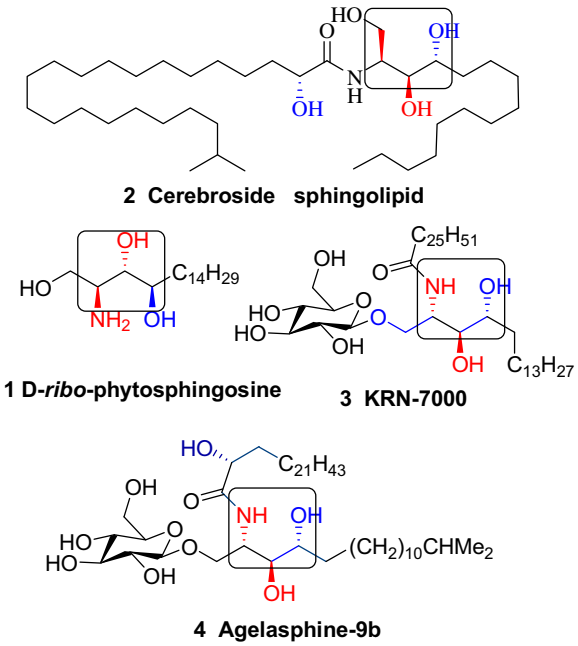

Fig. 1. The structure of several bioactive molecules.

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stereoisomers of phytosphingosines, D-*ribo*-phytosphingosine **1** is the most predominant one. Due to their biological activities and intriguing structures, the D-*ribo*-phytosphingosine **1**, agelasphine-9b **4** or their derivative KRN7000 **3** have attracted more attention of many chemists and several approaches to the asymmetric synthesis of them have been reported recently.[10] From the practical point of view, the most challenging work is the construction of three contiguous chiral centers in optically active sphingosine.

In continuation of our tremendous efforts to explore some multifunctional building blocks based on the cheap resources and utilizing them in the asymmetric synthesis of some natural products[11] including asymmetric synthesis of ceramide sphingolipid **2**, a sex pheromone of hair crab, based on the chiral lactam derived from the cheap glutamic acid.[12] As part of this program, we focus on developing efficient asymmetric methods to build the three chiral centers unit of sphingosine and using them in the asymmetric synthesis of D-*ribo*-phytosphingosine **1** and its ceramides, α-galactosylceramide derivatives. Herein we describe a flexible method for the construction two chiral centers of the D-*ribo*-phytosphingosine **1** promoted by SmI_2 and its utility in the diverse synthesis of the derivatives.

Chiral *N*-*tert*-butanesulfinamide, as pioneered by Ellman and Davis, is undoubtedly one of the most efficient auxiliaries occurring in modern organic synthesis,[13] and Lin group has achieved a powerful method for the synthesis of unsymmetrical vicinal β-amino alcohols based on it.[14] Later, our group used it to study the chemical selectivity of the imine[15b] with aldehydes in the presence of ester or ketone, and those results have been applied in the total synthesis of (−)-deoxoprosophylline **5** (Fig. 2).[15a] As shown in Fig. 2, in this work our purpose is to study the stereoselective cross-coupling reaction of imine with high sterically hindered long-chain aliphatic aldehydes derived from the glutamic acid, and to build a flexible method for synthesis of bioactive D-*ribo*-phytosphingosine **1**, agelasphine-9b **4** and their analogues.

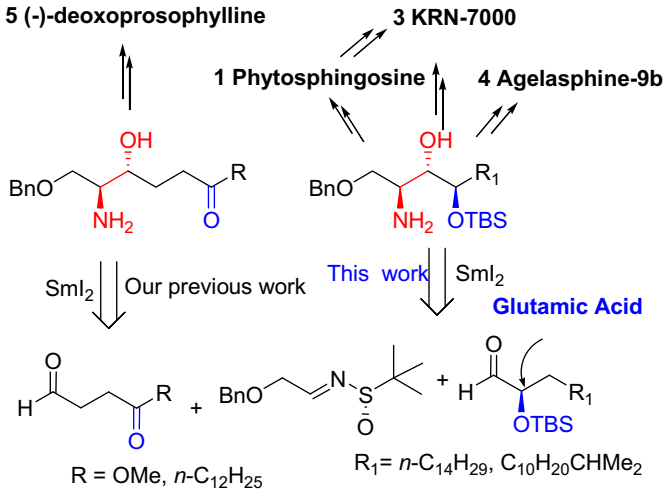
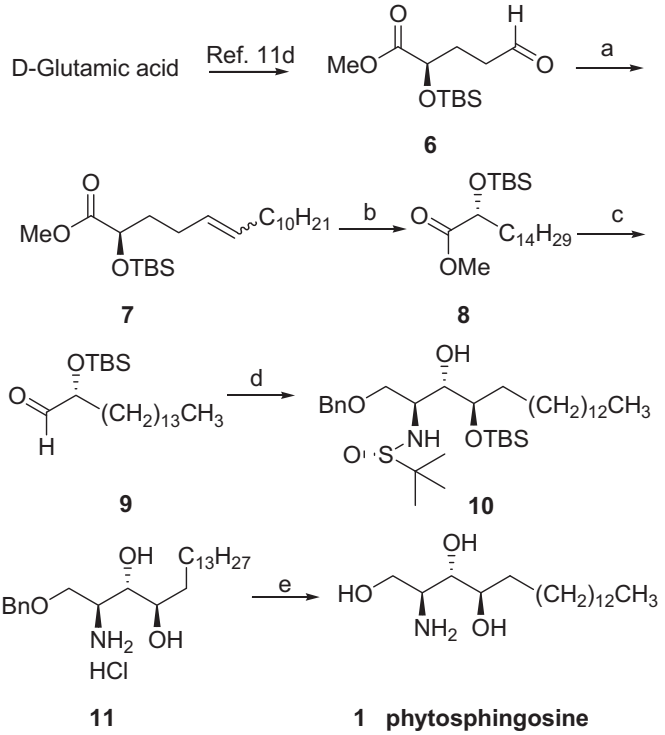


Fig. 2. The synthetic strategy of this work.

2. Results and discussion

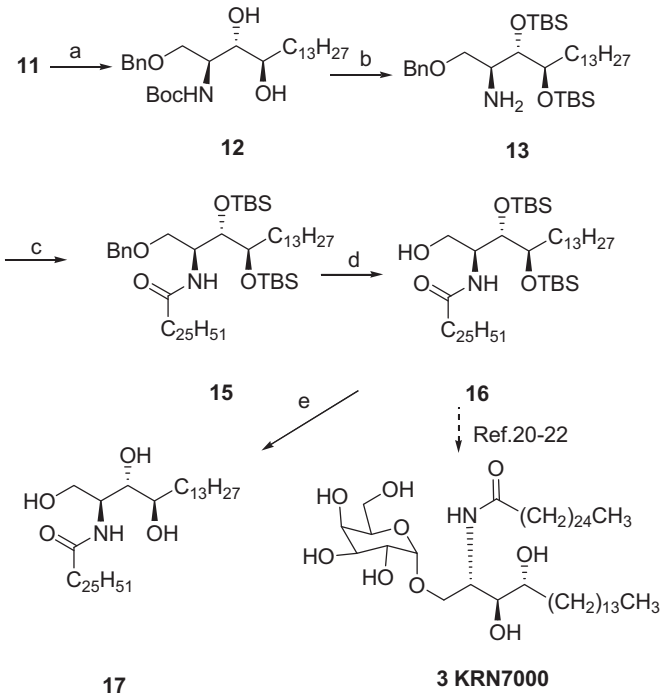
Firstly, D-glutamic acid was selected as a starting material to prepare the aldehyde *R*-**6** for the cross-coupling reaction in our plan according to our previous method.[11d] Then the unpurified aldehyde **6** was directly subjected to the Wittig reaction with undecanetriphenylphosphonium bromide in the presence of *n*-BuLi to afford the *E* and *Z* mixture of the olefin in 89% combined yield (Scheme 1). Hydrogenation (10% Pd/C, MeOH) of the olefin afforded the ester **8** in 95% yield. Treatment of ester **8** with DIBAL-H[16] in toluene at −78 °C for 3 h gave aldehyde **9** in 85% yield. Although the cross-coupling reaction of (*S*)-*N*-*tert*-butanesulfinyl imine with aromatic aldehydes is a robust method to build the unit of β-amino alcohol, it often need 4 equiv amounts of aldehydes for the aliphatic reactants.[14a] Considering the difficulty of preparation for **9** through the multi-steps reaction, we started to screen the ratio of sterically hindered aliphatic aldehyde **9** with (*S*)-*N*-*tert*-butanesulfinyl imine[17] **11**. Fortunately, when the equivalent amount aldehydes **9** was used, the cross-coupling reaction was smoothly occurred in 5 h, and generated protective hydroxymethyl β-amino alcohol **10** with high diastereoselectivity (>99%, de) in 68% yield. Then, compound **10** was treated with dry HCl in MeOH for 4 h, the chiral auxiliary[14a] and *tert*-butyldimethylsilyl group of secondary hydroxyl was removed in one-pot. Then transfer hydrogenation[18] (HCOOH/MeOH) of the concentrated crude salt **11** in the presence of stoichiometric catalyst (10% Pd/C) at room temperature for 12 h produced crude **1**, which was purified by chromatography on silica gel (DCM/MeOH) to give D-*ribo*-phytosphingosine **1** {$[\alpha]_D^{25}$ +7.9 (*c* 0.2, C_6H_5N); lit.[19] $[\alpha]_D^{23}$ +7.0 (*c* 0.09, C_6H_5N); lit.[10g] $[\alpha]_D^{23}$ +8.0 (*c* 0.8, C_6H_5N)} in 54% overall yield. The spectroscopic and physical data of the synthetic D-*ribo*-phytosphingosine **1** were identical with the reported data.[10g]



Scheme 1. Synthesis of D-*ribo*-phytosphingosine **1**. a. *n*-$C_{11}H_{23}PPh_3Br$, *n*-BuLi, THF, −78 °C, rt, 6 h, 89%; b. H_2, 10% Pd/C, MeOH, rt, 1 h, 95%; c. DIBAL-H, toluene, −78 °C, 3 h, 88%; d. 2-benzoxyl ethyl (*S*)-*N*-*tert*-butanesulfinyl imine, SmI_2, *t*-BuOH, −78 °C, 5 h, 68%; e. (i) HCl/MeOH, 4 h; (ii) 10% Pd/C, HOOH, MeOH, 12 h, 54%.

To explore an efficient method for the synthesis of KRN7000 **3**, The crude salt **11** was treated with di-*tert*-butyl dicarbonate in the presence of 1 M NaOH to afford compound **12** in 75% yield (Scheme 2). When compound **12** was treated with TBSOTf and 2,6-Lutidine in DCM, the hydroxyl were protected, simultaneously, the deprotection of amino group was occurred in one-pot to afford amine **13** in 78% overall yield. Then compound **13** was treated with the commercial active ester **14** in the presence of DMAP to afford amide **15** in 45% yield. Hydrogenation (20% $Pd(OH)_2$−10% Pd/C, H_2) of amide **15** gave alcohol **16** {$[\alpha]_D^{25}$ −9.2 (*c* 1.0, $CHCl_3$); lit.[20] $[\alpha]_D^{16}$ −9.5 (*c* 6.2, $CHCl_3$); lit.[21]

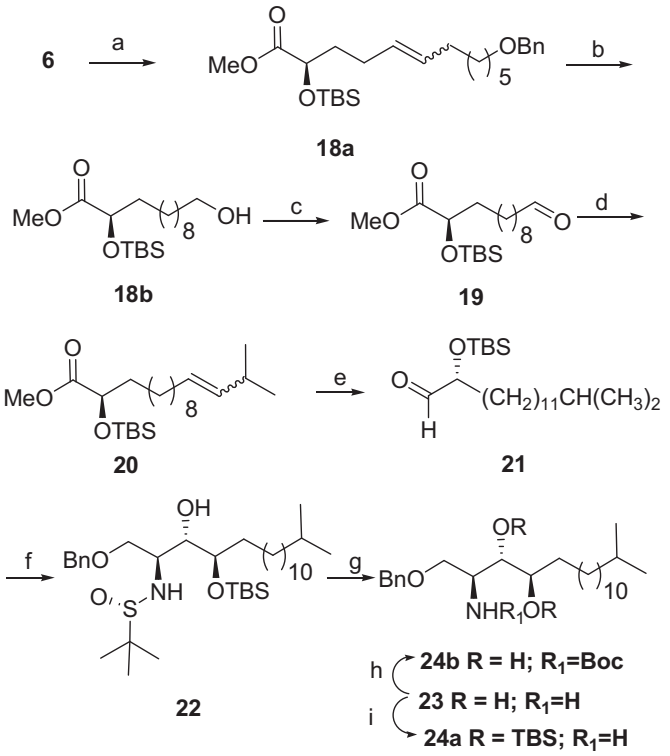
$[\alpha]_D^{26}$ −10.9 (*c* 1.0, $CHCl_3$)} in 82% yield, which can be easily converted to KRN7000 **3** by known method.[20–22] Conveniently, when the alcohol **16** was treated with dry HCl in MeOH, a new derivative **17** of cerebroside was produced {$[\alpha]_D^{20}$ −5.3(*c* 1.0, $CHCl_3$)} in 52% yield. The spectroscopic and physical data of the compound **16**[20,21] and **17** were identical with the reported data.



Scheme 2. Reagents and conditions: a. Boc_2O, 1 M NaOH, dioxane/H_2O (1:1), 48 h, 75%; b: TBSOTf, 2,6-Lutidine, 0 °C, rt, 12 h, 78%; c. (i) hexacosanoic acid, NMM, Ethyl chloroformate, THF, −20 °C, rt, 1 h; (ii) $C_2H_5OCO_2C_{26}H_{53}$ **14**, NMM, DMAP, THF, 45%; d. H_2, 10% Pd/C, 20% $Pd(OH)_2$, MeOH, rt, 12 h, 82%; e. HCl/MeOH, 4 h, 52%.

Encouraged by the convenient method for synthesis of D-*ribo*-phytosphingosine **1**, we then started to investigate the synthesis of agelasphine-9b **4** and its derivatives. The Wittig reaction of aldehyde **6** with 7-(benzyloxy)heptan-1-triphenylphosphonium bromide in the presence of *n*-BuLi gave the mixture of *E* and *Z*-olefin **18a** in 72% yield (Scheme 3). Hydrogenation [20% $Pd(OH)_2$–10% Pd/C, H_2] of a mixture of olefin **18a** gave alcohol 19 in 78% yield. Upon Swern oxidation [$(COCl)_2$, DMSO] of compound **18a**, the resulting crude aldehyde **19** was directly treated with 2-methylpropanetriphenylphosphonium bromide in the presence of *n*-BuLi to generate the mixture of *E* and *Z*-olefin **20** in 84% overall yield. Reduction (10% Pd/C, H_2) of the olefin **20** and subsequent reaction with DIBAL-H in dry tetrahydrofuran at −78 °C gave aldehyde **21** in 82% overall yield. Then the SmI_2-induced cross-coupling of **21** with (*S*)-*N*-*tert*-butanesulfinyl imine generated hydroxymethyl β-amino alcohol **22** with high diastereoselectivity (>99%, de) in 67% yield. After removal (HCl/MeOH) of the chiral auxiliary and protective group of secondary alcohol, the crude amide **23** was obtained without further purification, which was directly subject to react with di-*tert*-butyl dicarbonate and followed by TBSOTf to produce the key intermediate amide **24a** in 59% overall yield from compound **22** (Scheme 3).

To build an effective method for preparation of the side chain in agelasphine-9b **4** and its derivatives, the numerous material *S*-**18b** derived from L-glutamic acid was considered.[12] Thus, Swern oxidation [$(COCl)_2$, DMSO] of compound *S*-**18b** and the resulted crude aldehyde was directly subjected to the Wittig reaction with dodecanetriphenylphosphonium bromide in the presence of *n*-BuLi

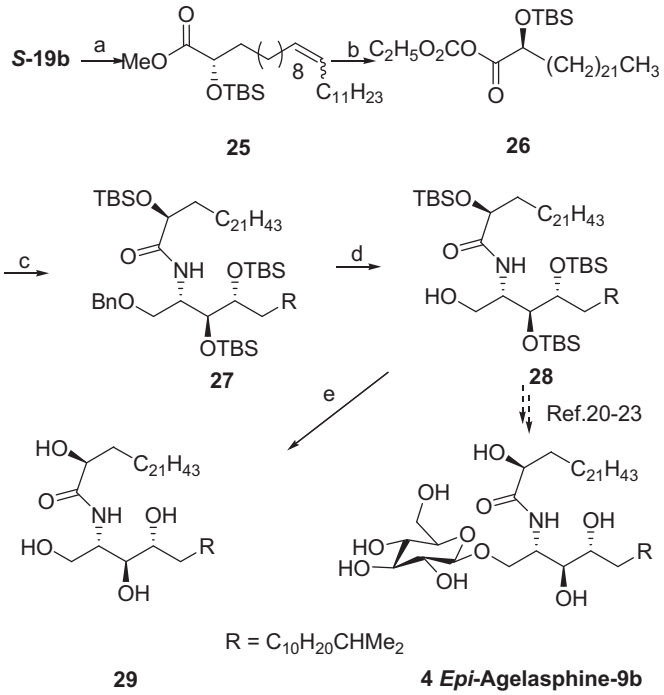


Scheme 3. Reagents and conditions: a. $BnOC_7H_{14}PPh_3Br$ *n*-BuLi, THF, −78 °C, rt, 6 h, 72%; b. H_2, 10% Pd/C, 20% $Pd(OH)_2$, MeOH, rt, 12 h, 78%; c. DMSO, $(COCl)_2$, TEA, −78 °C, 3.5 h, 82%; d. isobutanenetriphenylphosphonium bromide, *n*-BuLi, THF, −78 °C, rt, 6 h, 84%; e. (i) H_2, 10% Pd/C, MeOH, rt, 1 h, 96%; (ii) DIBAL-H, toluene, −78 °C, 3 h, 85%; f. 2-benzoxyl ethyl (*S*)-*N*-*tert*-butanesulfinyl imine, SmI_2, *t*-BuOH, −78 °C, 5 h, 67%; g. HCl/MeOH, 4 h; h. Boc_2O, 1M NaOH, dioxane/H_2O (1:1), 48 h, 75%; i. TBSOTf, 2,6-Lutidine, 0 °C, rt, 12 h, 78%.

to afford the *E* and *Z* mixture of the olefin **25** in 85% combined yield. Hydrogenation (10% Pd/C, H_2) of the olefin **25** and subsequent reaction with LiOH in mixture solvent of MeOH and water (MeOH/THF/H_2O=5:3:3) generated crude intermediate acid, which was directly treated with ethyl carbonochloridate in the presence of NMM to give crude compound **26** in quantitative yield. When the compound **24** was treated with the active ester **26** in the presence of DMAP, amide **27** was produced in overall 27% yield from olefin **25**. Although several conditions were conducted to improve the yield of amide **27**, all the results were not significantly improved. Hydrogenation (20% $Pd(OH)_2$–10% Pd/C, H_2) of amide **27** generated alcohol **28** in 65% yield. The compound **28**, an important protective isomer of cerebrosides, was easily converted to the epimer of agelasphine-9b **4** by resemble reported method.[7,20–22] Simultaneously, the alcohol **28** was treated with a solution of saturated hydrogen chloride in 1,4-dioxane to afford an epimer of ceramide **29** {$[\alpha]_D^{20}$ 7.7 (*c* 0.2, $CHCl_3$)} in 60% yield (Scheme 4). The structure of **29** was readily determined by all spectroscopic and physical data.

3. Conclusions

In summary, an efficient approach by SmI_2-induced cross-coupling of *N*-*tert*-butanesulfinyl imine with sterically hindered aliphatic aldehydes derived from cheap glutamic acid for building the three chiral centers of sphingosine unit has been developed. D-*ribo*-phytosphingosine **1** and its two derivatives **18** and **29** have been synthesized by this approach. Simultaneously, a practicable approach for synthesis of agelasphine-9b **4** and its derivative KRN7000 **3** has also been achieved. Furthermore, this flexible approach might be generally applicable in the synthesis of various



Scheme 4. Reagents and conditions: a. (i) DMSO, $(COCl)_2$, TEA, −78 °C, 3.5 h; (ii) *n*-$C_{12}H_{25}PPh_3Br$, *n*-BuLi, THF, −78 °C, rt, 6 h, two steps 85%; b. (i) H_2, 10% Pd/C, MeOH, rt, 1 h, 95%; (ii) LiOH·H_2O, MeOH, THF, H_2O, 85%; (iii) NMM, Ethyl chloroformate, THF, −20 °C, rt, 1 h; c. **24a**, NMM, DMAP, THF, in four steps 27%; d. H_2, 10% Pd/C, 20% $Pd(OH)_2$, MeOH, rt, 12 h, 65%; e. HCl/MeOH, 4 h, 60%.

sphingolipids, ceramides, α-galactosylceramides and their derivatives with important structural and biological.

4. Experimental section

4.1. General

THF was distilled from sodium/benzophenone. All reactions were monitored by thin layer chromatography (TLC) on glass plates coated with silica gel with fluorescent indicator (Huanghai HSGF254). Flash chromatography was performed on silica gel (Huanghai 300–400) with Petroleum/EtOAc as eluent. Melting points were recorded on a Mel-Temp apparatus and uncorrected. Optical rotations were measured on a JASCO P-1030 polarimeter with a sodium lamp. Mass spectra were recorded on a HP-5989 instrument and HRMS (MALDI/DHB) were measured on a LCMS-IT-TOF (Shimazu Corporation) apparatus. IR spectra were recorded using KBr disks or film, on a Fourier Transform Infrared Spectrometer, Type: Avatar 360 E.S.P, manufactured by Thermo Nicolet Corporation, USA. NMR spectra were recorded on a Varian or a Bruker spectrometer (300 or 400 MHz), and chemical shifts are reported in *d* (parts per million) referenced to an internal TMS standard for ^{1}H NMR and $CDCl_3$ (77.0 ppm) for ^{13}C NMR.

4.2. (*R*)-Methyl 2-(*tert*-butyldimethylsilyloxy)hexadec-5-enoate (7)

To a solution of *n*-undecanetriphenylphosphonium bromide (9.3 g, 18.7 mmol) in dry THF (60 mL) was treated with a solution of *n*-BuLi (11.3 mL, 18.1 mmol, 1.6 in THF) to 0 °C under argon atmosphere for 2 h. Then, the resulted mixture was cooled to −78 °C and a solution of crude aldehyde **6** (3.24 g, 12.4 mmol) in dry THF was slowly dropped. After being stirred for 1 h, the mixture was allowed to worm to room temperature within 2 h and stirred for another 3 h at room temperature. The reaction was quenched with an aqueous solution of saturated $NaHCO_3$ (10 mL) and diluted with water (10 mL) and ethyl acetate (20 mL). The resulted mixture was separated and the aqueous phase was extracted with ethyl acetate for three times. The combined organic layers were washed with brine for three times and dried over anhydrous Na_2SO_4. Filtered and concentrated, the residue was purified by chromatography on silica gel to give **7** (4.4 g, 89%) as a colorless oil. $[\alpha]_D^{25}$ +17.4 (*c* 1.0, $CHCl_3$): IR (film); ν_{max} 2926, 1758, 1461, 1257, 1216, 1139, 1039 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 5.38–5.44 (m, 2H), 4.26–4.23 (m, 1H), 3.75 (s, 3H), 2.22–2.10 (m, 2H), 2.08–1.96 (m, 2H), 1.81–1.75 (m, 2H), 1.38–1.30 (m, 16H), 0.94 (s, 9H), 0.92 (t, *J*=6.8 Hz, 3H), 0.11 (s, 3H), 0.08 (s, 3H) ppm; ^{13}C NMR ($CDCl_3$, 100 Hz): *δ*=174.2, 131.0, 128.3, 71.9, 51.6, 35.4, 31.9, 29.7, 29.6, 29.5, 29.3, 27.3, 25.7, 22.8, 22.6, 18.3, 14.1, −4.9, −5.3 ppm; MS (ESI): 399 ($M+H^+$); HRMS (ESI) calcd for ($C_{23}H_{46}O_3Si+H^+$): 399.3294, found: 399.3276.

4.3. (*S*)-Methyl 2-(*tert*-butyldimethylsilyloxy)hexadecanoate (8)

To a suspension of 10% Pd/C (450 mg) in methanol (20 mL) was dropped to a solution of **7** (4.3 g, 15.04 mmol) in methanol (100 mL) under H_2 atmosphere. After stirring for 1 h, the mixture was filtered and concentrated under reduced pressure. The residue was purified by chromatography on silica gel to give **8** (4.11 g, 95%), as a colorless oil. $[\alpha]_D^{25}$ +15.5 (*c* 1.0, $CDCl_3$); IR (film): ν_{max} 3416, 2927, 2855, 2283, 1591, 1467, 1216, 1121 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 4.23–4.20 (m, 1H), 3.74 (s, 3H), 1.74–1.69 (m, 2H), 1.46–1.38 (m, 2H), 1.37–1.29 (m, 24H), 0.94 (s, 9H), 0.91–0.90 (m, 3H), 0.11 (s, 3H), 0.08 (s, 3H) ppm; ^{13}C NMR ($CDCl_3$, 100 Hz): *δ*=174.5, 72.3, 51.7, 35.2, 31.9, 29.7, 29.6, 29.5, 29.4, 29.3, 25.7, 25.1, 22.7, 18.3, 14.1, −5.0, −5.3 ppm; MS (ESI): 401 ($M+H^+$); HRMS (ESI) calcd for ($C_{23}H_{48}NO_3Si+H^+$): 401.3451, found: 401.3434.

4.4. (*S*)-2-(*tert*-Butyldimethylsilyloxy)hexadecanal (9)

To a solution of compound **8** (4.0 g, 9.99 mmol) in dry toluene (50 mL) was slowly dropped a solution of DIBAL-H (9.7 mL, 9.99 mmol, 20% in toluene) at −78 °C under argon atmosphere. After stirring for 3 h at the same temperature, the reaction mixture was quenched with an aqueous solution of saturated potassium sodium tartrate and stirred for another four 4 h at room temperature. The organic layer was separated and aqueous layer was extracted with ethyl acetate for three times (40mL×3). The combined organic layers were washed with brine for three times (20mL×3) and dried over anhydrous Na_2SO_4. Filtered and concentrated under reduced pressure, the residue was purified by chromatography on silica gel to give **9** (3.36 g, 88%), as a colorless oil. $[\alpha]_D^{25}$ +10.8 (*c* 1.0, $CDCl_3$); IR (film): ν_{max} 3426, 2926, 2855, 1738, 1467, 1468, 1115, 838, 778 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 9.61 (d, *J*=2.0 Hz, 1H), 4.00–3.97 (m, 1H), 1.69–1.61 (m, 2H), 1.45–1.36 (m, 2H), 1.35–1.29 (m, 22H), 0.95 (s, 9H), 0.91 (t, *J*=6.8 Hz, 3H), 0.11 (s, 3H), 0.10 (s, 3H) ppm; ^{13}C NMR ($CDCl_3$, 100 Hz): *δ*=204.3, 77.7, 32.6, 31.9, 29.7, 29.6, 29.5, 29.4,29.3, 25.7, 24.6, 22.7, 18.2, 14.1, −4.6, −4.9 ppm; MS (ESI): 371 ($M+H^+$); HRMS (ESI) calcd for ($C_{22}H_{46}NO_2Si+H^+$): 371.3345, found: 371.3321.

4.5. *N*-((2*S*,3*S*,4*R*)-1-(Benzyloxy)-4-(*tert*-butyldimethylsilyloxy)-3-hydroxyoctadecan-2-yl)-2-methylpropane-2-sulfinamide (10)

The mixture of compound **9** (3.10 g, 8.36 mmol), *t*-BuOH (2.45 mL, 25.80 mmol) and 2-benzoxyl ethyl (*S*)-*N*-*tert*-butanesulfinyl imine (2.16 g, 8.36 mol) in the dry THF (30 mL) was stirred at −78 °C under argon atmosphere. Then a freshly solution of SmI_2 (25.80 mmol, 20 mL) in dry THF was dropped. After stirred for 5 h, the reaction mixture was quenched with an aqueous solution of

saturated $Na_2S_2O_3$ (10 mL) and warmed to room temperature. The mixture was diluted with ethyl acetate (30 mL) and the organic layer was separated. The aqueous layer was extracted with ethyl acetate for three times (40mL×3) and the combined organic layers were washed with brine for three times. Dried, filtered and concentrated, the residue was purified by chromatography on silica gel to give **10** (3.36, 68%), as a colorless oil. $[\alpha]_D^{25}$ +1.2 (*c* 1.0, $CDCl_3$); IR (film): ν_{max} 3409, 2924, 1739, 1598, 1467, 1119, 1077, 776 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 7.40–7.30 (m, 5H), 4.63 (d *J*=11.6 Hz, H), 4.58 (d *J*=11.6 Hz, H), 4.09–4.06 (m, 2H), 3.94 (dd, *J*=4.2, 9.0 Hz, 1H), 3.78 (dd, *J*=3.2, 8.8 Hz, 1H), 3.46–3.44 (m, 1H), 3.28–3.23 (m, 1H), 2.63 (d, *J*=9.2 Hz, 1H), 1.73–1.69 (m, 1H), 1.62–1.57 (m, 1H), 1.49–1.44 (m, 1H), 1.41–1.38 (m, 1H), 1.26 (s, 9H), 1.31–1.27 (m, 22H), 0.91 (s, 9H), 0.92–0.89 (m, 3H), 0.13 (m, 6H) ppm; ^{13}C NMR ($CDCl_3$, 100 Hz): δ=138.3, 128.3, 127.8, 127.6, 73.3, 71.1, 70.8, 70.1, 58.0, 56.1, 34.6, 31.9, 29.7, 29.6, 29.3, 25.9, 25.3, 22.8, 22.7, 18.1, 14.1, −3.8, −4.1 ppm; MS (ESI): 626 ($M+H^+$); HRMS (ESI) calcd for ($C_{35}H_{67}NO_4SSi+H^+$): 626.4638, found: 626.4616.

4.6. (2*S*,3*S*,4*R*)-2-Aminooctadecane-1,3,4-triol phytosphingosine (1)

To a solution of **10** (130 mg, 0.21 mmol) in absolute MeOH (3 mL) was treated with a solution of HCl/MeOH (4 M, 3 mL) at room temperature. After stirring for 4 h, the mixture was concentrated under reduced pressure to afford crude intermediate salt **11** without further purification. A suspension of 10% Pd/C (85 mg) in methanol (3 mL) was dropped to a solution of above crude salt **11** (85 mg, 0.21 mmol) in methanol (4 mL) under argon atmosphere. Then a solution of HCOOH (1 mL) was slowly dropped and the mixture was stirred for 12 h. The mixture was directly concentrated and the residue was purified by chromatography on silica gel to give **1** (36 mg, 54% for two steps), as a white solid. {$[\alpha]_D^{25}$ +7.9 (*c* 0.2, C_6H_5N); lit.[19] $[\alpha]_D^{23}$ +7.0 (*c* 0.09, C_6H_5N); lit.[10g] $[\alpha]_D^{23}$ +8.0 (*c* 0.8, C_6H_5N)}; IR (film): ν_{max} 3361, 2918, 2495, 1592, 1468, 1320, 1076, 1028 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 3.78 (dd, *J*=4.2, 10.7 Hz, 1H), 3.60–3.53 (m, 2H), 3.39–3.34 (m, 1H), 3.67–3.66 (dd, *J*=6.0, 10.4 Hz, 1H), 1.80–1.75 (m, 1H), 1.60–1.58 (m, 1H), 1.46–1.36 (m, 2H), 1.35–1.26 (m, 22H), 0.93 (t, *J*=6.8 Hz, 3H), ppm; ^{13}C NMR ($CDCl_3$, 100 Hz): δ=75.2, 73.1, 62.9, 54.5, 33.4, 31.7, 29.6, 29.4, 29.1, 25.3, 22.3, 13.0 ppm: MS (ESI): 308 ($M+H^+$); HRMS (ESI) calcd for ($C_{18}H_{39}NO_3+H^+$): 318.3008, found: 318.3008.

4.7. *tert*-Butyl (2*S*,3*S*,4*R*)-1-(benzyloxy)-3,4-dihydroxyoctadecan-2-ylcarbamate (12)

To a solution of **11** (2.10 g, 5.43 mmol) in 1,4-dioxane and water (30 mL, v/v=1:1) was treated with a solution of 1 M NaOH (5 mL) and stirred for 2 h. Then a solution of Boc_2O (1.77 g, 8.16 mmol) in 1,4-dioxane (5 mL) was dropped and the resulted mixture was stirred for 48 h at room temperature. The reaction mixture was quenched with a solution of HCl (5 mL, 1 M), and the mixture was extracted with ethyl acetate for three times (30 mL×3). The combined organic layers were washed with saturated $NaHCO_3$ aqueous solution (30 mL) and brine (20 mL×3). Dried, filtered and concentrated, the residue was purified by chromatography on silica gel to give **12** (2.06, 75%), as a white solid. $[\alpha]_D^{25}$ −6.4 (*c* 1.0, $CDCl_3$); IR (film): ν_{max} 3378, 2928, 1710, 1502, 1463, 1377, 1169, cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 7.42–7.30 (m, 5H), 5.27 (d, *J*=8.4 Hz, 1H), 4.59 (d, *J*=11.6 Hz, 1H), 4.54 (d, *J*=11.6 Hz, 2H), 3.9 (dd, *J*=1.8, 9.0 Hz, 1H), 3.84 (d, *J*=4.0 Hz, 1H), 3.68–3.66 (m, 1H), 3.64–3.58 (m, 2H), 3.49–3.45 (m, 1H), 2.34 (d, *J*=10.0 Hz, 1H), 1.70–1.68 (m, 1H), 1.51–1.46 (m, 1H), 1.48 (s, 9H), 1.32–1.28 (m, 24H), 0.92 (t, *J*=6.4 Hz, 3H), ppm; ^{13}C NMR ($CDCl_3$, 100 Hz): δ=157.2, 137.5, 128.5, 127.9, 127.8, 80.3, 73.6, 72.7, 69.5, 69.1, 52.5, 35.1, 32.7, 30.0, 29.7, 29.6, 28.3, 28.0, 27.4, 26.1, 22.7, 14.1 ppm: MS (ESI): 508 ($M+H^+$); HRMS (ESI) calcd for ($C_{30}H_{53}NO_5+H^+$): 508.4002, found: 508.4000.

4.8. (2*S*,3*S*,4*R*)-1-(Benzyloxy)-3,4-bis(*tert*-butyldimethylsilyloxy)octadecan-2-amine (13)

To a solution of **12** (1.9 g, 3.85 mmol) and 2.6-luditine (1.31 mL, 11.24 mmol) in dry DCM (20 mL) was stirred for 15 min at 0 °C under argon atmosphere. Then, a solution of TBSOTf (2.58 mL, 11.24 mmol) was slowly dropped and the mixture was stirred for over night at room temperature, the reaction mixture was quenched with H_2O, and the resulted mixture was extracted with DCM for three times (50 mL×3). The combined organic layers were washed with saturated $NaHCO_3$ aqueous solution (40 mL) and brine (20 mL×3), dried over anhydrous Na_2SO_4. Filtered and concentrated under reduced pressure, the residue was purified by chromatography on silica gel to give to **13** (1.91 g, 78%), as a colorless oil. $[\alpha]_D^{25}$ +18.1 (*c* 1.0, $CDCl_3$); IR (film): ν_{max} 3379, 2928, 1702, 1502, 1464, 1377, 1179, 772 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 7.37–7.28 (m, 5H), 4.59 (d, *J*=12.0 Hz, 1H), 4.51 (d, *J*=12.0 Hz, 1H), 3.70 (dd, *J*=2.6, 9.0 Hz, 1H), 3.66–3.65 (m, 1H), 3.64–3.63 (m, 1H), 3.54–3.50 (m, 1H), 3.21–3.17 (m, 1H), 2.09–2.04 (m, 2H), 1.77–1.69 (m, 1H), 1.57–1.50 (m, 1H), 1.42–1.28 (m, 24H), 0.93 (s, 9H), 0.92–0.90 (m, 3H), 0.89 (s, 9H), 0.15 (s, 3H), 0.11 (s, 3H), 0.09 (s, 3H), 0.06 (s, 3H) ppm; ^{13}C NMR ($CDCl_3$, 100 Hz): δ=138.6, 128.3, 127.6, 127.4, 76.5, 74.5, 73.2, 72.6, 52.9, 31.2, 30.9, 29.7, 29.6, 29.4, 26.7, 26.0, 25.8, 22.7, 18.0, 14.1, −3.8, −4.1, −4.8, −4.9 ppm; MS (ESI): 636 ($M+H^+$); HRMS (ESI) calcd for ($C_{37}H_{73}NO_3Si_2+H^+$): 636.5207, found: 636.5199.

4.9. (2*S*,3*S*,4*R*)-Benzyl-3,4-bis-*tert*-butyldimethylsilyloxy-2-hexacosanoyl-amide-4-octadecanol (15)

To a solution of hexacosanoic acid (627 mg, 1.58 mmol) and NMM (0.52 mL, 4.74 mmol) was stirred at −20 °C under argon atmosphere. Then a solution of ethyl chloroformate (0.15 mL, 1.58 mmol) in dry THF was dropped and the reaction mixture was stirred for 1 h at the same temperature to prepare a fresh solution of **14**. A mixture of NMM (0.52 mL, 4.74 mmol) and catalytic amount of DMAP in THF (3 mL) was dropped, then, a solution of **13** (1 g, 1.58 mmol) in dry THF (8 mL) was dropped. The reaction mixture was allowed to warm to room temperature and stirred for 5 h. The reaction was quenched with water and extracted with ethyl acetate for three times (50 mL×3). The combined organic layers were washed with saturated $NaHCO_3$ aqueous solution (40 mL) and brine (40 mL×3), dried over anhydrous Na_2SO_4. Filtered and concentrated under reduced pressure, the residue was purified by chromatography on silica gel to give **15** (720 mg, 45%), as a colorless oil. $[\alpha]_D^{25}$ −12.1 (*c* 1.0, $CDCl_3$); IR (film): ν_{max} 3415, 2924, 2854, 1678, 1466, 1258, 1097, 836, 778 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 7.34–7.28 (m, 5H), 6.78 (d, *J*=5.6 Hz, 1H), 4.54 (d, *J*=12.0 Hz, 1H), 4.48 (d, *J*=12.0 Hz, 1H), 4.11 (dd, *J*=2.8, 8.4 Hz, 1H), 3.99–3.92 (m, 1H), 3.78–3.72 (m, 2H), 3.70–3.67 (m, 1H), 2.15–2.11 (m, 2H), 1.73–1.70 (m, 2H), 1.66–1.62 (m, 2H), 1.30 (m, 68H), 0.96 (s, 9H), 0.90 (s, 9H), 0.94–0.92 (m, 6H), 0.14 (s, 3H), 0.12 (s, 3H), 0.10 (s, 3H), 0.07 (s, 3H) ppm; ^{13}C NMR ($CDCl_3$, 100 Hz): δ=172.6, 138.7, 128.2, 127.3, 76.3, 73.1, 70.2, 68.4, 53.4, 37.3, 31.9, 31.5, 31.4, 30.2, 29.7, 26.0, 25.8, 22.7, 18.0, −4.2, −4.9 ppm; MS (ESI): 1014 ($M+H^+$); HRMS (ESI) calcd for ($C_{63}H_{123}NO_4Si_2+H^+$): 1014.9069, found: 1014.9066.

4.10. (2*S*,3*S*,4*R*)-3,4-Bis-*tert*-butyldimethylsilyloxy-2-hexacosanoyl-amide-4-octadecanol (16)

To a suspension of 10% Pd/C (90 mg) and 20% $Pd(OH)_2$ (90 mg) in methanol (90 mL) was dropped a solution of **15** (600 mg,

0.59 mmol) in methanol (20 mL) under H_2 atmosphere. After being stirred for 12 h, the mixture was filtered and concentrated under reduced pressure and the residue was purified by chromatography on silica gel to give **16** (447 mg, 82%), as a colorless oil. {$[\alpha]_D^{25}$ −9.2 (*c* 1.0, $CHCl_3$); lit.[20] $[\alpha]_D^{16}$ −9.5 (*c* 6.2, $CHCl_3$); lit.[21] $[\alpha]_D^{26}$ −10.9 (*c* 1.0, $CHCl_3$)}; IR (film): ν_{max} 3415, 2925, 2853, 1655, 1529, 1467, 1256, 1095 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 7.22 (d, *J*=4.0 Hz, 1H), 3.97–3.88 (m, 2H), 3.75–3.69 (m, 2H), 3.70–3.67 (m, 1H), 3.65–3.61 (m, 1H), 2.21–2.17 (m, 2H), 1.80–1.71 (m, 2H), 1.70–1.61 (m, 2H), 1.35–1.24 (m, 68H), 0.99 (s, 9H), 095 (s, 9H), 0.92–0.89 (m, 6H), 0.15 (s, 3H), 0.13 (s, 3H), 0.12 (s, 3H), 0.10 (s, 3H) ppm; ^{13}C NMR ($CDCl_3$, 100 Hz): δ=174.9, 76.6, 71.8, 65.0, 56.9, 37.0, 31.9, 30.8, 29.7, 25.8, 22.7, 18.0, 14.1, −4.1, −4.5, −4.9 ppm; MS (ESI): 924 ($M+H^+$); HRMS (ESI) calcd for ($C_{56}H_{117}NO_4Si_2+H^+$): 924.8599 found: 924.8596.

4.11. (2*S*,3*S*,4*R*)-3,4-Diol-2-hexacosanoyl-2-amino-4-actadecanol (17)

To a solution of **16** (100 mg, 0.108 mmol) in MeOH (2 mL) was dropped to solution of HCl/MeOH (4 M, 1 mL) at room temperature. After stirring for 4 h, the mixture was concentrated under reduced pressure to afford crude intermediate product, which was diluted with water and extracted with ethyl acetate for three times (10 mL×5). The combined organic layers were washed with brine (10mL×2) and dried over anhydrous Na_2SO_4. Filtered and concentrated under reduced pressure, the residue was purified by chromatography on silica gel to give **17** (40 mg, 52%), as a white solid. $[\alpha]_D^{25}$ −5.3 (*c* 1.0, $CDCl_3$); IR (film): ν_{max} 3500, 2956, 1739, 1456, 1261, 1216, 1164, 1107 cm^{-1}; ^1H NMR (400 MHz, C_6H_5N) δ; 8.01 (d, *J*=8.8 Hz, 1H), 5.10 (br s, 3H), 4.78–4.72 (m, 1H), 4.39–4.34 (m, 2H), 4.19–4.16 (m, 1H), 2.52–2.48 (m, 2H), 2.11–2.05 (m, 2H), 1.86–1.83 (m, 2H), 1.69–1.60 (m, 64H), 0.87–0.82 (m, 6H) ppm; ^{13}C NMR ($CDCl_3$, 100 Hz): δ=176.1, 74.8, 72.3, 63.1, 55.9, 37.9, 36.4, 35.8, 35.2, 33.4, 32.7, 31.1, 30.3, 28.1, 27.5, 24.1, 20.5, 15.4, 14.8 ppm; MS (ESI): 696 ($M+Na^+$); HRMS (ESI) calcd for ($C_{44}H_{89}NO_4+Na^+$): 696.6870, found: 696.6843.

4.12. (*R*)-Methyl 2-(*tert*-butyldimethylsilyloxy)-7-methyloct-5-enoate (20)

To a solution of isobutanenetriphenylphosphonium bromide (9.29 g, 22.5 mmol) in dry THF (60 mL) was treated with a solution of *n*-BuLi (13.4 mL, 18.1 mmol, 1.6 in THF) at 0 °C under argon atmosphere. After stirring for 2 h, the mixture was cooled to −78 °C and a solution of crude aldehyde derived from compound **18b** (5.37 g, 15 mmol) in dry THF was slowly dropped. The reaction was stirred for another 1 h at the same temperature and warmed to room temperature within 2 h. After being stirred for 3 h at room temperature. The mixture was quenched with an aqueous solution of saturated $NaHCO_3$ (10 mL) and diluted with water (10 mL) and ethyl acetate (20 mL). The resulted mixture was separated and the aqueous phase was extracted with ethyl acetate for there times. The combined organic layers were washed with brine. Dried, filtered and concentrated, the residue was purified by chromatography on silica gel to give **20** (5.0 g, 84%) as a colorless oil. $[\alpha]_D^{25}$ +17.5 (*c* 1.0, $CHCl_3$): IR (film): ν_{max} 3416, 2926, 2283, 1758, 1590, 1467, 1257, 1216, 1120, 1039 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 5.39–5.20 (m, 2H), 4.22 (t, *J*=6.0 Hz, 1H), 3.74 (s, 3H), 2.59–2.47 (m, 1H), 2.08–2.03 (m, 2H), 1.75–1.69 (m, 2H), 1.43–1.30 (m, 14H), 1.00–0.96 (m, 6H), 0.96 (s, 9H), 0.11 (s, 3H), 0.08 (s, 3H) ppm; ^{13}C NMR ($CDCl_3$,100 Hz): δ=174.4, 137.5, 127.5, 72.3, 51.7, 35.3, 29.9, 29.5, 29.4, 29.3, 27.3, 25.7, 26.4, 25.7, 25.1, 23.2, 22.7, 18.3, −4.9, −5.3 ppm; MS (ESI): 399 ($M+Na^+$); HRMS (ESI) calcd for ($C_{23}H_{46}O_3Si+H^+$): 399.3294, found: 399.3270.

4.13. (*R*)-2-(*tert*-Butyldimethylsilyloxy)-14-methylpentadecanal (21)

To a suspension of 10% Pd/C (490 mg) in methanol (20 mL) was dropped to a solution of **20** (4.9 g, 12.31 mmol) in methanol (100 mL) under H_2 atmosphere. After stirring for 1 h, the mixture was filtered and concentrated to give **21** (4.68 g, 95%) without further purification. To a solution of above crude compound (4.6 g, 11.5 mmol) in dry toluene (50 mL) was slowly dropped a solution of DIBAL-H (11.2 ml, 11.5 mmol 0.73, 20%) at −78 °C under argon atmosphere. After stirring for 3 h, the reaction mixture was quenched with an aqueous solution of saturated potassium sodium tartrate and stirred for another four 4 h at room temperature. The organic layer was separated and aqueous layer was extracted with ethyl acetate for three times (40mL×3). The combined organic layers were washed with brine for three times (20mL×3) and dried over anhydrous Na_2SO_4. Filtered and concentrated under reduced pressure, the residue was purified by chromatography on silica gel to give **21** (3.62 g, 85%), as a colorless oil. $[\alpha]_D^{25}$ +3.4 (*c* 1.0, $CDCl_3$); IR (film): ν_{max} 3451, 2926, 2855, 1738, 1467, 1468, 1115, 838, 778 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 9.62 (d, *J*=2.0 Hz, 1H), 4.01–3.97 (m, 1H), 1.66–1.63 (m, 2H), 1.62–1.61 (m, 1H), 1.44–1.36 (m, 2H), 1.33–1.26 (m, 16H), 1.19–1.17 (m, 2H), 0.93 (s, 9H), 0.90–0.88 (m, 6H), 0.11 (s, 3H), 0.10 (s, 3H) ppm; ^{13}C NMR ($CDCl_3$, 100 Hz): δ=203.3, 77.7, 39.1, 32.6, 31.9, 29.7, 29.6, 29.5, 29.4, 25.7, 24.6, 22.7, 18.2, 14.1, −4.6, −4.9 ppm; MS (ESI): 371 ($M+Na^+$); HRMS (ESI) calcd for ($C_{22}H_{46}NO_2Si+H^+$): 371.3345, found: 371.3305.

4.14. *N*-((2*S*,3*S*,4*R*)-1-(Benzyloxy)-4-(*tert*-butyldimethylsilyloxy)-3-hydroxy-16-methylheptadecan-2-yl)-2-methylpropane-2-sulfinamide (22)

The mixture of compound **21** (3.5 g, 9.46 mmol), *t*-BuOH (3.6 ml, 28.4 mmol) and 2-benzoxyl ethyl (*S*)-*N*-*tert*-butanesulfinyl imine (2.4 g, 9.46 mmol) was stirred in dry THF (30 mL) at −78 °C under argon atmosphere. Then a freshly solution of SmI_2 (28.4 mmol, 20 mL) in dry THF was dropped and the resulted mixture was stirred for 5 h the reaction was quenched with an aqueous solution of saturated $Na_2S_2O_3$ (10 mL) and warmed to room temperature. The mixture was diluted with ethyl acetate (30 mL) and the organic layer was separated. The aqueous layer was extracted with ethyl acetate for three times (40mL×3) and the combined organic layers were washed with brine for three times. Dried, filtered and concentrated, the residue was purified by chromatography on silica gel to give **22** (3.96, 67%), as a colorless oil. $[\alpha]_D^{25}$ +0.34 (*c* 1.0, $CDCl_3$); IR (film): ν_{max} 3436, 2926, 1739, 1631, 1598, 1467, 1119, 1077, 776 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 7.40–7.29 (m, 5H), 4.63 (d, *J*=11.6 Hz 1H), 4.58 (d, *J*=11.6 Hz 1H), 4.08–4.06 (m, 2H), 3.94 (dd, *J*=4.0, 8.6 Hz 1H), 3.79 (dd, *J*=3.2, 8.8 Hz 1H), 3.50–3.45 (m, 1H), 3.28–3.24 (m, 1H), 2.62 (d, *J*=9.6 Hz, 1H), 1.77–1.69 (m, 1H), 1.58–1.51 (m, 1H), 1.50–1.41 (m, 1H), 1.31–1.27 (m, 18H), 1.26 (s, 9H), 1.21–1.16 (m, 2H), 0.93 (s, 9H), 0.90 (d, *J*=6.8 Hz, 6H), 0.13 (s, 6H) ppm; ^{13}C NMR ($CDCl_3$, 100 Hz): δ=138.3, 128.4, 127.9, 127.6, 73.4, 71.1, 70.8, 70.1, 58.0, 56.1, 39.1, 34.6, 31.9, 29.7, 29.6, 29.3, 25.9, 25.3, 22.8, 22.7, 22.6 18.1, −3.8, −4.1 ppm; MS (ESI): 626 ($M+H^+$); HRMS (ESI) calcd for ($C_{35}H_{67}NO_4SSi+H^+$): 626.4638, found: 626.4613.

4.15. *tert*-Butyl (2*S*,3*S*,4*R*)-1-(benzyloxy)-3,4-dihydroxy-16-methylheptadecan-2-ylcarbamate (24b)

To a solution of **12** (2.47 g, 6.07 mmol) in 1,4-dioxane and water (30 mL, v/v=1:1) was treated with a solution of 1 M NaOH (5 mL) and stirred for 2 h at rt °C. Then a solution of Boc_2O (1.98 g, 9.11 mmol) in 1,4-dioxane (5 mL) was dropped and the resulted mixture was stirred for 48 h at room temperature. The reaction was

quenched with a solution of HCl (5 mL 1 M), and the mixture was extracted with ethyl acetate for three times (30 mL×3). The combined organic layers were washed with saturated $NaHCO_3$ aqueous solution (30 mL) and brine (20 mL×3). Dried, filtered and concentrated, the residue was purified by chromatography on silica gel to give **24b** (2.31, 75%), as a white solid. $[\alpha]_D^{25}$ −6.3 (*c* 1.0, $CDCl_3$); IR (film): ν_{max} 3378, 2928, 1710, 1502, 1463, 1377, 1169, 722.3, 696.3 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 7.41–7.30 (m, 5H), 5.28 (d, *J*=8.0 Hz, 1H), 4.60 (d, *J*=11.6 Hz, 1H), 4.55 (d, *J*=11.6 Hz, 1H), 3.97 (d, *J*=7.6 Hz, 1H), 3.84 (s, 1H), 3.67–3.64 (m, 1H), 3.62–3.59 (m, 2H), 3.49–3.44 (m, 1H), 2.46–2.40 (m, 1H), 1.73–1.65 (m, 1H), 1.60–1.52 (m, 1H), 1.48 (s, 9H), 1.34–1.27 (m, 18H), 1.20–1.16 (m, 2H), 0.90 (d, *J*=6.8 Hz 6H) ppm; ^{13}C NMR ($CDCl_3$, 100 Hz): δ=157.2, 137.8, 128.5, 127.9, 127.8, 80.3, 73.6, 72.7, 69.5, 69.1,52.6,, 32.7, 32.0, 30.0, 29.7, 29.6, 29.3, 28.3, 26.1, 22.7, 14.1 ppm: MS (ESI): 508 ($M+H^+$); HRMS (ESI) calcd for ($C_{30}H_{53}NO_5+H^+$): 508.4002, found: 508.4000.

4.16. (2*S*,3*S*,4*R*)-1-(Benzyloxy)-3,4-bis(*tert*-butyldimethylsilyloxy)-16-methylheptadecan-2-amine (24a)

To a solution of **24b** (2.2 g, 4.34 mmol) and 2.6-luditine (1.55 mL, 13.29 mmol) was stirred in dry DCM (20 mL) for 15 min at 0 °C under argon atmosphere, then a solution of TMSOTf (3.05 mL, 13.29 mmol) was slowly dropped and the mixture was stirred for over night at room temperature. The reaction mixture was quenched with H_2O and extracted with CH_2Cl_2 for three times (50 mL×3). The combined organic layers were washed with saturated $NaHCO_3$ aqueous solution (40 mL) and brine (20 mL×3). Dried, filtered and concentrated, the residue was purified by chromatography on silica gel to give to **24a** (2.15 g, 78%), as a colorless oil. $[\alpha]_D^{25}$ +19.3 (*c* 1.0, $CDCl_3$); IR (film): ν_{max} 3379, 2928, 1702, 1502, 1464, 1377, 1179, 772 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 7.37–7.329 (m, 5H), 4.60 (d, *J*=12.4 Hz, 1H), 4.51 (d, *J*=12.4 Hz, 1H), 3.72–3.69 (m, 1H), 3.66–3.63 (m, 2H), 3.53–3.50 (m, 1H), 3.21–3.16 (m, 1H), 2.01 (s, 2H), 1.74–1.70 (m, 1H), 1.57–1.50 (m, 2H), 1.44–1.30 (m, 2H), 1.35–1.26 (m, 16H), 1.20–1.17 (m, 2H), 0.93 (s, 9H), 0.92–0.90 (m, 6H), 0.89 (s, 9H), 0.15 (s, 3H), 0.11 (s, 3H), 0.09 (s, 3H), 0.06 (s, 3H) ppm; ^{13}C NMR ($CDCl_3$, 100 Hz): δ=138.6, 128.3, 127.6, 127.4, 76.5, 74.5, 73.2, 72.7, 52.9, 39.1, 30.9, 29.9, 29.7, 29.6, 29.5, 27.9, 27.4, 26.7, 25.9, 25.8, 22.7, 18.0, 14.1, −3.8, −4.1, −4.8, −4.9 ppm; MS (ESI): 635 ($M+H^+$); HRMS (ESI) calcd for ($C_{37}H_{70}NO_3Si_2+H^+$): 635.5207, found: 635.5190.

4.17. (*R*)-*N*-((2*S*,3*S*,4*R*)-1-(Benzyloxy)-3,4-bis(*tert*-butyldimethylsilyloxy)-16-methylheptadecan-2-yl)-2-(*tert*-butyldimethylsilyloxy)tetracosanamide (27)

To a mixture of compound **26** (3.15 mmol, 10 mL), NMM (0.7 mL 6.31 mmol) and catalytic amount of DMAP was stirred in THF (3 mL), then a solution of **24a** (2.0 g, 3.15 mmol) in dry THF (4 mL) was dropped. The reaction mixture was warmed to room temperature and stirred for 5 h. The mixture was quenched with water and extracted with ethyl acetate for three times (50 mL×3). The combined organic layers were washed with saturated $NaHCO_3$ aqueous solution (40 mL) and brine (40 mL×3), dried over anhydrous Na_2SO_4. Filtered and concentrated under reduced pressure, the residue was purified by chromatography on silica gel to give **27** (912 mg, 27%). $[\alpha]_D^{25}$ −8.5 (*c* 1.0, $CDCl_3$); IR (film): ν_{max} 3415, 2924, 2854, 1678, 1466, 1258, 1097, 836, 778 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 7.35–7.29 (m, 5H), 6.95 (d, *J*=8.8 Hz, 1H), 4.55–4.47 (m, 2H), 4.23–4.19 (m, 2H), 4.09–4.00 (m, 1H) 3.70–3.68 (m, 1H), 3.57–3.55 (m, 2H), 1.78–1.72 (m, 2H), 1.59–1.52 (m, 1H), 1.47–1.41 (m, 2H), 1.32–1.26 (m, 56H), 1.23–1.18 (m, 4H), 0.97–0.95 (m, 12H), 0.92–0.89 (m, 19H), 0.84–0.83 (m, 5H), 0.15–0.02 (m, 18H) ppm; ^{13}C NMR ($CDCl_3$, 100 Hz): δ=177.7, 138.7, 128.2, 127.3, 124.5, 123.8, 76.0, 73.1, 70.6, 68.9, 60.2, 54.2, 39.1, 34.9, 31.4, 30.9, 30.2, 29.9, 29.7, 29.6, 29.7, 27.9, 27.4, 26.5, 25.8, 22.7, 18.0, 14.6, −4.0, −4.3, −4.5, −4.9 ppm; MS (ESI): 1116 ($M+H^+$); HRMS (ESI) calcd for ($C_{67}H_{133}NO_5Si_3+H^+$): 1116.9570, found: 1116.9541.

4.18. (*R*)-*N*-((2*S*,3*S*,4*R*)-3,4-Bis(*tert*-butyldimethylsilyloxy)-1-hydroxy-16-methylheptadecan-2-yl)-2-(*tert*-butyldimethylsilyloxy)tetracosanamide (28)

To a suspension of 10% Pd/C (22.5 mg) and 20% $Pd(OH)_2$ (22.5 mg) in methanol (20 mL) was dropped to a solution of **26** (150 mg, 0.14 mmol) in methanol (5 mL) under H_2 atmosphere. After being stirred for 12 h, the mixture was filtered and concentrated under reduced pressure, the residue was purified by chromatography on silica gel to give **28** (89 mg, 65%), as a colorless oil. $[\alpha]_D^{25}$ −0.9 (*c* 1.0, $CDCl_3$); IR (film): ν_{max} 3428, 2925, 2853, 1658, 1461, 1377,1257, 1093, 836, 778 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 7.27 (d, *J*=8.8 Hz, 1H), 4.32–4.25 (m, 1H), 4.24–4.14 (m, 1H), 3.90–3.87 (m, 1H), 3.87–3.83 (m, 1H), 3.69–3.66 (m, 2H), 1.83–1.81 (m, 1H), 1.78–1.68 (m, 2H), 1.58–1.50 (m, 2H), 1.48–1.40 (m, 2H), 1.31–1.27 (m, 56H), 0.98–0.95 (m, 18H), 0.94–0.88 (m, 18H), 0.16–0.12 (m, 18H) ppm; ^{13}C NMR ($CDCl_3$, 100 Hz): δ=174.9, 76.4, 76.2, 74.2, 71.8, 65.0, 56.9, 37.0, 31.9, 30.8, 29.7, 25.8, 22.7, 18.0, 14.1, −4.1, −4.9 ppm; MS (ESI): 1048 ($M+Na^+$); HRMS (ESI) calcd for ($C_{60}H_{127}NO_5Si_3+Na^+$): 1048.8920 found: 1048.8885.

4.19. (*R*)-2-Hydroxy-*N*-((2*S*,3*S*,4*R*)-1,3,4-trihydroxy-16-methylheptadecan-2-yl)tetracosanamide (29)

To a solution of **28** (60 mg, 0.038 mmol) in MeOH (2 mL) was dropped to solution of HCl/1.4-dioxane (4 M, 1 mL) at room temperature. After stirring for 4 h, the mixture was concentrated under reduced pressure to afford crude intermediate product, which was diluted with water and extracted with ethyl acetate for three times (10 mL×5). The combined organic layers were washed with brine (10mL×2) and dried over anhydrous Na_2SO_4. Filtered and concentrated under reduced pressure, the residue was purified by chromatography on silica gel to give **29** (25 mg, 60%), as a white solid. $[\alpha]_D^{25}$ +7.7 (*c* 0.2, $CDCl_3$); IR (film): ν_{max} 3338, 2953, 2850, 1733, 1650, 1469, 1417, 1279, 1217, 1125, 1103 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ; 5.05–4.95 (m, 1H), 4.48–4.39 (m, 1H), 4.36–4.27 (m, 1H), 4.03–3.88 (m, 1H), 3.82–3.70 (m, 1H), 1.83–1.70 (m, 1H), 1.55–1.51 (m, 2H), 1.43–1.41 (m, 2H), 1.37–1.25 (br m, 58H), 1.24–1.19 (m, 2H), 0.93–0.89 (m, 9H) ppm; ^{13}C NMR ($CDCl_3$, 100 Hz): δ=173.9, 77.3, 75.2, 72.9, 60.3, 53.4, 38.9, 33.7, 31.8, 29.7, 27.8, 26.8, 22.7, 14.0 ppm; MS (ESI): 684 ($M+H^+$); HRMS (ESI) calcd for ($C_{42}H_{85}NO_5+H^+$): 684.6506, found: 684.6498.

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