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Total synthesis of the acetyl derivatives of *lyxo*-(2*R*,3*R*,4*R*)-phytosphingosine and (−)-jaspine B

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ABSTRACT

The total synthesis of acetyl derivatives of *lyxo*-(2*R*,3*R*,4*R*)-phytosphingosine and (−)-jaspine B using a Grignard reaction on sugar-imine and a Wittig reaction as the key steps.

1. Introduction

Sphingoids are the characteristic structural unit of sphingolipids and are basically long-chain amino-diol and amino-triol bases. Sphingoids are important membrane constituents and play an important role in cell regulation as well as signal transduction.[1] Furthermore, glycosphingolipids show important biological activities such as antitumor,[2a] antiviral,[2b] antifungal,[2c] and cytotoxic properties.[2d] Phytosphingosines, one of the major classes of sphingoids, have been isolated and identified either separately or as parts of sphingolipids from plants,[3a] marine organisms,[3b–c] fungi,[3d] yeasts,[3e] and even mammalian tissues[3f–k] of the kidney,[3g] liver,[3h] uterus,[3i] intestine,[3j] and skin.[3k] Phytosphingosines are one of the most important and common species of the naturally occurring sphingoid bases.[4] Phytosphingosines themselves have also been found to be bioactive lipids. For example, *ribo*-phytosphingosine 1 is a potential heat stress signal in yeast cells.[5] It has also been confirmed that various diastereomers of phytosphingosines **1**–**4** exhibit different activities and metabolisms (Fig. 1).[1b,6]

Much effort has been devoted toward the synthesis of these molecules for their use in biological studies. All of the diastereomers of the phytosphingosines have been synthesized since they have shown noticeable variation in their bioactivity.[7] However, all *lyxo*-phytosphingosines **2** and **3** have attracted much less attention from the synthetic community.[8]

In 2002, pachastrissamine **5** (jaspine B) (Fig. 2), the first naturally occurring anhydrophytosphingosine derivative, was isolated from the Okinawan marine sponge *Pachastrissa* sp. by Higa et al.[9] In 2003, Debitus et al. isolated the same compound from a different marine sponge, *Jaspis* sp. and named it jaspine B **5**.[10] This marine natural product exhibited high cytotoxic activity against various tumor cell lines in vitro.[9,10] Delgado et al. reported that the potency of the cytotoxicity is dependent on the stereochemistry of the tetrahydrofuran moiety.[11] Jaspine B **5** has an *erythro*-amino alcohol moiety in the tetrahydrofuran ring, which may be a key structural feature for its biological activity. Our group reported that (−)-jaspine B **8** showed promising results on MCF7 cells maybe because of the *cis*-configuration of its amino and hydroxy groups (*erythro* configuration).[12a] It has also shown better activity compared to the *trans*-configuration.

The novel structural features and interesting biological activities of pachastrissamine have prompted chemists to develop several syntheses for jaspine B **5,** its stereoisomers **6**–**9,** and its analogues.[13,14] Our group published the first total synthesis of jaspine B **5** and its C2 epimer **6**.[15] We also reported the synthesis of *ent*-4-*epi*-jaspine B **7** and (−)-jaspine B **8** and their biological activities in comparison to jaspine B **5**,[12a] and also synthesised 3-*epi*-jaspine B **9**.[12b] Recently we developed a common strategy for the synthesis of D-*ribo*-phytosphingosine **1** and 2-*epi*-jaspine B **6** from D-ribose,[7s] jaspine B **5** and D-*lyxo*-phytosphingosine **2** from L-ascorbicacid.[8i]

In continuation of our efforts in the stereoselective synthesis of bioactive azasugars,[16] and carbasugars[17] by using Grignard addition reactions on sugar-imines, we herein report the application of the above strategy for the development of efficient and common methods for the synthesis of *N*,*O*,*O*,*O*-tetra-acetyl *lyxo*-(2*R*,3*R*,4*R*)-phytosphingosine **10** and *N*,*O*-diacetyl-(−)-jaspine B **11**. The starting material for our approach was D-glucose, which is an inexpensive sugar and possesses the desired chirality.

The retro-synthetic analysis of **10** and **11** is depicted in Scheme 1. Compound **12** is a common intermediate for the synthesis of **10** and **11** and it can be obtained from compound **13** after appropriate manipulation. The amino group can be introduced by nucleophilic addition on sugar-imine **14** and the required lipid chain can be added by a Wittig olefination. Sugar-imine **14** can be obtained from D-glucose.

2. Results and discussions

Our synthesis of **10** and **11** started from **13**, which can be prepared from commercially available D-glucose using our earlier

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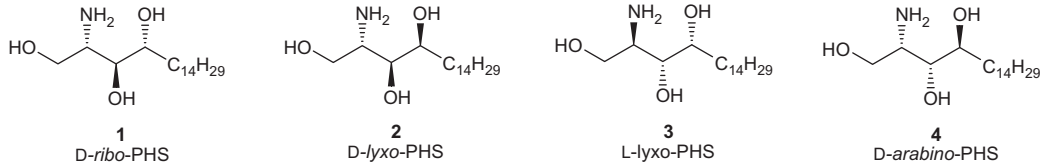


Figure 1. Structures of the phytophingosines.

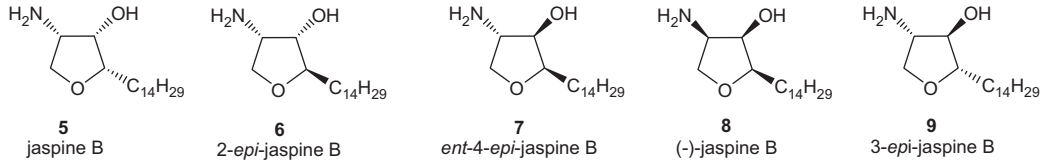
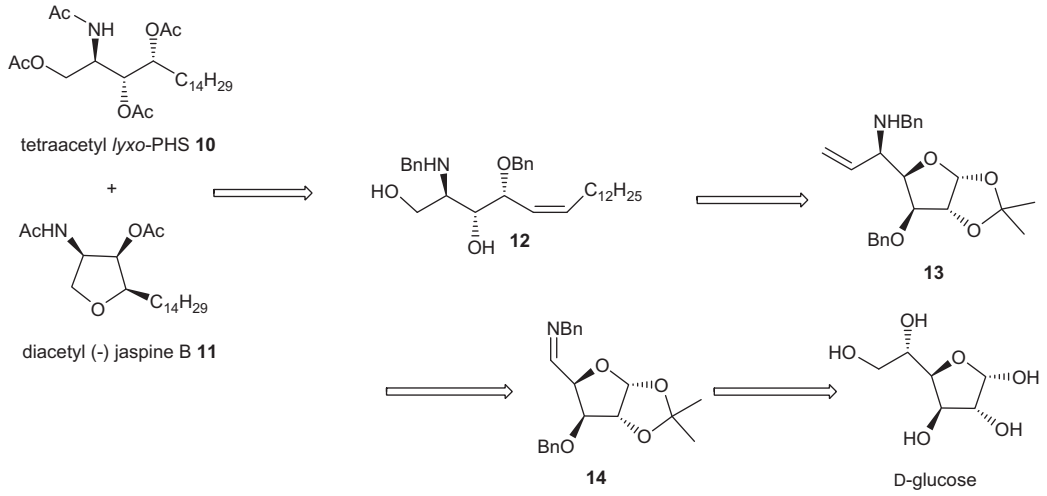
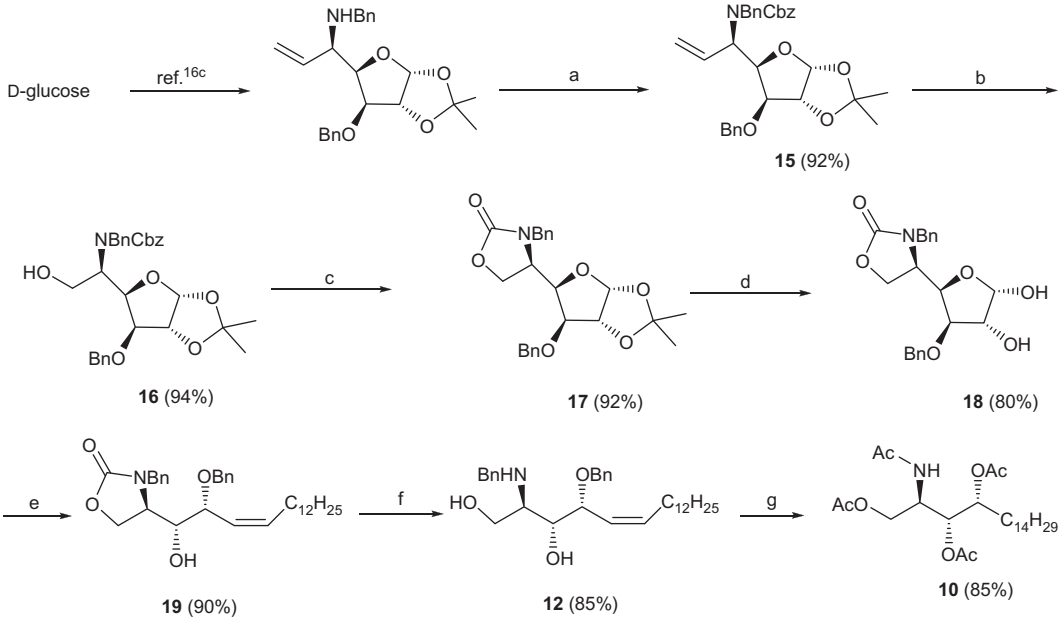


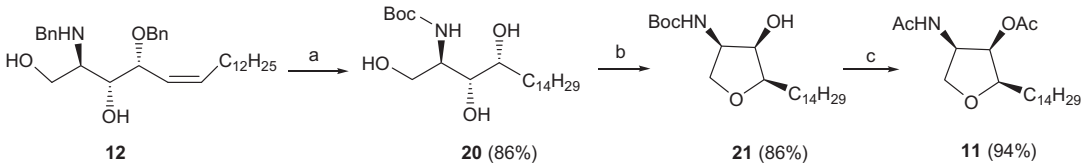
Figure 2. Structures of jaspine B and its structural isomers.



Scheme 1. Retro-synthetic analysis of acetyl derivatives of L-*lyxo*-phytosphingosine **10** and (−)-jaspine B **11**.



Scheme 2. Synthesis of the acetyl derivative of *lyxo*-phytosphingosine **10**: Reagents and conditions: (a) Cbz-Cl, $NaHCO_3$, MeOH, 1 h; (b) (i) O_3, CH_2Cl_2, −78 °C, 30 min then DMS, −78 °C to rt, 30 min; (ii) $NaBH_4$, MeOH, 1 h; (c) NaH, THF, 30 min; (d) TFA–H_2O, 0 °C to rt, 4 h; (e) (i) $NaIO_4$, MeOH, H_2O, rt, 1 h, (ii) $C_{13}H_{27}Ph_3P^+Br^-$, *n*-BuLi, THF, 0 °C, 1 h; (f) 4 M NaOH, EtOH, reflux, 6 h; (g) (i) H_2, Pd/C, MeOH, 6 h, (ii) Ac_2O, Et_3N, CH_2Cl_2, 6 h.



12 **20** (86%) **21** (86%) **11** (94%)

Scheme 3. Synthesis of diacetyl (−)-jaspine B **11**: Reagents and conditions: (a) (i) H_2, Pd/C, MeOH, 6 h, (ii) $(Boc)_2O$, Et_3N, CH_2Cl_2, 2 h; (b) TsCl, Et_3N, DMAP, CH_2Cl_2; (c) (i) TFA, CH_2Cl_2, 2 h; (ii) $(Ac)_2O$, Et_3N, CH_2Cl_2, 4 h.

procedure (Scheme 2).[16c] The allylamine **13** was treated with CbzCl in the presence of $NaHCO_3$ in dry MeOH to afford compound **15**. Oxidative cleavage of terminal double bond in **15** with O_3 in CH_2Cl_2 at −78 °C produced the aldehyde, which upon treatment with $NaBH_4$ in dry MeOH gave **16** in 94% yield. In order to protect the primary hydroxyl group, compound **16** was treated with sodium hydride to give the cyclic carbamate **17**. Deprotection of the 2,3-*O*-isopropylidene group in **17** was achieved using TFA·H_2O to afford hemiacetal **18**. Oxidative cleavage of **18** with $NaIO_4$ in MeOH·H_2O gave the aldehyde, which upon treatment with excess Wittig reagent ($C_{12}H_{25}P^+Ph_3Br^-$ in dry THF) at 0 °C, gave **19**. Deprotection of the carbamate in **19** was achieved with 4 M NaOH to give **12**; the stereochemistry of the double bond was confirmed as the *Z*-isomer by ^{1}H NMR coupling constants. Hydrogenation of compound **12** in the presence of Pd/C in MeOH under a hydrogen atmosphere gave L-*lyxo*-phytosphingosine **3**. For the sake of characterization, this was converted into acetyl derivative **10** by using Ac_2O in the presence of Et_3N. The spectroscopic data of **10** were in good agreement with the reported values.[18]

For the synthesis of the acetyl derivative of (−)-jaspine B **11**, the following reactions were carried out (Scheme 3). Hydrogenation of compound **12** using Pd/C in MeOH followed by protection of the resultant amino functionality with $(Boc)_2O$ in the presence of Et_3N afforded carbamate **20**. Regioselective tosylation of the primary hydroxy group of **20** prompted spontaneous cyclization to give tetrahydrofuran derivative **21** (Scheme 3).[13b] Deprotection of the Boc group in **21** with TFA/CH_2Cl_2 provided the (−)-jaspine B **8**, which upon acetylation using Ac_2O in the presence of excess Et_3N gave the acetyl derivative of (−)-jaspine B **11**. The physical properties of Boc protected (−)-jaspine B **21** and its diacetyl derivative **11** were in good agreement with the reported values.[13e]

3. Conclusions

In conclusion we have successfully demonstrated a common strategy for the synthesis of the acetyl derivatives of L-*lyxo*-phytosphingosine and (−)-jaspine B with good overall yields (16.8% and 13.7% respectively), from inexpensive and commercially available D-glucose by using Grignard addition on a chiral sugar-imine and a Wittig olefination. This strategy is also useful for making some other analogues and isomers of phytosphingosine and jaspine B with high stereoselectivity in order to study their activity.

4. Experimental

TLC was performed on Merck Kiesel gel 60, F254 plates (layer thickness 0.25 mm). Column chromatography was performed on silica gel (60–120 mesh) using ethyl acetate and hexane mixture as the eluent. Melting points were determined on a Fisher John's melting point apparatus and are uncorrected. IR spectra were recorded on a Perkin–Elmer RX-1 FT-IR system. ^{1}H NMR and ^{13}C NMR spectra were recorded using Varian Gemini-200 MHz, Bruker Avance-300 MHz, and Varian Inova-500 MHz spectrometer. ^{1}H NMR data are expressed as chemical shifts in ppm followed by multiplicity (s–singlet; d–doublet; t–triplet; q–quartet; m–multiplet), number of proton(s), and coupling constant(s) *J* (Hz). ^{13}C NMR chemical shifts are expressed in ppm. Optical rotations were measured with JASCO digital polarimeter. Accurate mass measurement was performed on Q STAR mass spectrometer (Applied Biosystems, USA).

4.1. Benzyl benzyl((*R*)-1-((3a*R*,5*R*,6*S*,6a*R*)-6-(benzyloxy)-2,2-dimethyltetrahydro-furo[2,3-*d*][1,3]dioxol-5-yl)allyl)carbamate 15

To a stirred solution of **13** (2.4 g, 6.1 mmol) in dry MeOH (20 mL) was added sodium bicarbonate (1.02 g, 12.2 mmol) followed by CbzCl (1.52 mL, 9.15 mmol) at 0 °C. The mixture was stirred at rt for 3 h. Next, MeOH was evaporated under reduced pressure and reaction mixture was extracted with EtOAc and water. The combined organic layers were washed with water and brine, and dried over anhydrous Na_2SO_4. The solvent was removed on a rotary evaporator and the resulting crude material was purified by column chromatography on silica gel by eluting with ethyl acetate:hexane (1:9) to give **15** (2.96 g, 92%) as a colorless liquid. $[\alpha]_D^{26} = -49.2$ (*c* 2.0, $CHCl_3$); IR ν_{max}: 2985, 2932, 1695, 1455, 1413, 1374, 1247, 1215, 1074, 1024, 740, 699 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.00–7.41(m, 15H), 5.81–6.20 (m, 2H), 4.73–5.31 (m, 5H), 4.32–4.66 (m, 5H), 4.02 (m, 1H), 3.59 (m, 1H), 1.17–1.42 (m, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 156.9, 138.3, 137.1, 136.1, 134.5, 128.2, 128.1, 127.8, 127.7, 127.6, 127.1, 116.9, 111.2, 104.7, 81.7, 81.2, 79.6, 71.5, 67.2, 57.7, 50.7, 26.4, 26.0 (because of the rotamers multiple peaks are observed in NMR); ESIMS *m*/*z*: 530 [M+H]$^+$; HRMS (ESI): Calcd for $C_{32}H_{36}NO_6$ [M+H]$^+$ 530.2542, found 530.2528.

4.2. Benzyl benzyl((*R*)-1-((3a*R*,5*R*,6*S*,6a*R*)-6-(benzyloxy)-2,2-dimethyltetrahydro-furo[2,3-*d*][1,3]dioxol-5-yl)-2-hydroxyethyl)carbamate 16

To a solution of compound **15** (2.0 g, 3.78 mmol) in CH_2Cl_2 (20 mL) at −78 °C, ozone gas was passed for 30 min (until the solution turns to a light blue color) and the reaction mixture was quenched with dimethyl sulfide (1.0 mL, 7.56 mmol), stirred for 30 min, and the reaction mixture was washed with CH_2Cl_2 (2 × 20 mL). The combined organic layers were washed with water and brine, and dried over anhydrous Na_2SO_4. The solvent was removed on a rotary evaporator and the resulting crude aldehyde was used in the next step without further purification.

To the solution of the resulting crude aldehyde in dry MeOH (20 mL) at 0 °C was added $NaBH_4$ (142 mg, 3.78 mmol) and the reaction mixture stirred for 2 h. The reaction mixture was quenched with a saturated NH_4Cl solution and the solvents were removed in vacuo. The crude compound was partitioned between CH_2Cl_2 and H_2O. The aqueous layer was washed with CH_2Cl_2 (2 × 20 mL). The combined organic layers were washed with brine and dried over anhydrous Na_2SO_4. The solvent was removed on a rotary evaporator and the resulting crude material was purified by column chromatography on silica gel by eluting with ethyl acetate:hexane (1:4) to give compound **16** (1.91 g, 94% for two steps)

as a colorless oil. $[\alpha]_D^{26} = -59.3$ (*c* 1.5, $CHCl_3$); IR ν_{max}: 3469, 2929, 1692, 1454, 1412, 1374, 1247, 1215, 1074, 1024, 740, 699 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 7.00–7.42 (m, 15H), 5.88 (br s, 1H), 5.00–5.30 (m, 2H), 4.30–5.00 (m, 6H), 4.17 (br d, 1H, *J* = 15.5 Hz), 3.94 (dd, 1H, *J* = 4.2 and 11.5 Hz), 3.55–3.85 (m, 2H), 1.67 (br s, 1H), 1.18–1.44 (m, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 156.9, 138.3, 137.0, 136.1, 128.5, 128.0, 127.8, 127.4, 111.8, 104.8, 82.1, 81.2, 78.8, 71.7, 67.6, 63.4, 58.1, 51.0, 29.6, 26.6, 26.2 (because of the rotamers multiple peaks are observed in NMR); ESIMS *m*/*z*: 534 $[M+H]^+$; HRMS (ESI): Calcd for $C_{31}H_{35}NO_7Na$ $[M+Na]^+$ 556.2311, found 556.2288.

4.3. (*R*)-3-Benzyl-4-((3a*R*,5*R*,6*S*,6a*R*)-6-(benzyloxy)-2,2-dimethyltetrahydrofuro[2,3-*d*][1,3]dioxol-5-yl)oxazolidin-2-one 17

To an ice cooled, stirred solution of compound **16** (1.7 g, 3.18 mmol) in dry THF (15 mL), was slowly added NaH (0.26 g, 60% w/v dispersion in mineral oil, 6.37 mmol) over 5 min (portionwise). Then the reaction was allowed to return to room temperature and stirred for 2 h. The reaction mixture was quenched with crushed ice and extracted with ethyl acetate (3 × 100 mL). The combined organic extracts were washed with water and brine, and dried over Na_2SO_4. The solvent was removed on a rotary evaporator and the residue was purified by column chromatography on silica gel using ethyl acetate:hexane (1:4) as the eluent to give pure compound **17** (1.24 g, 92%) as a colorless liquid. $[\alpha]_D^{26} = -39.7$ (*c* 1.0, $CHCl_3$); IR ν_{max}: 2924, 1742, 1427, 1371, 1217, 1074, 1023, 744, 700 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.12–7.36 (m, 10H), 5.88 (d, 1H, *J* = 3.8 Hz), 4.64 (d, 1H, *J* = 16.1 Hz), 4.60 (d, 1H, *J* = 11.7 Hz), 4.52 (d, 1H, *J* = 3.8 Hz), 4.43 (dd, 1H, *J* = 6.7 and 9.2 Hz), 4.33 (d, 1H, *J* = 11.7 Hz), 4.28 (t, 1H, *J* = 3.3 Hz), 4.16–4.26 (m, 2H), 3.83 (td, 1H, *J* = 3.3 and 9.2 Hz), 3.74 (d, 1H, *J* = 3.4 Hz), 1.34 (s, 3H), 1.28 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 158.5, 136.6, 136.0, 128.8, 128.6, 128.2, 127.7, 127.5, 112.0, 105.0, 82.4, 81.6, 77.0, 71.7, 63.8, 54.5, 46.5, 26.8, 26.3; ESIMS *m*/*z*: 426 $[M+H]^+$; HRMS (ESI): Calcd for $C_{24}H_{28}NO_6$ $[M+H]^+$ 426.1916, found 426.1903.

4.4. (*R*)-3-Benzyl-4-((2*R*,3*R*,4*R*,5*S*)-3-(benzyloxy)-4,5-dihydroxytetrahydrofuran-2-yl)oxazolidin-2-one 18

Compound **17** (1.2 g, 2.82 mmol) was treated with 20 mL of TFA:H_2O (3:2) at 0 °C then the reaction mixture was warmed to room temperature and stirred for 3 h. Solvents were removed by three coevaporations with toluene (10 mL), and the residue was purified by column chromatography on silica gel using ethyl acetate:hexane (2:3) as the eluent to give pure compound **18** (0.87 g, 80%) as a colorless liquid. $[\alpha]_D^{26} = -18.9$ (*c* 1.0, $CHCl_3$); IR ν_{max}: 3389, 2924, 1720, 1443, 1241, 1105, 1073, 1026, 746, 701 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.13–7.40 (m, 10H), 5.55 (d, 1H, *J* = 3.8 Hz), 4.84 (d, 1H, *J* = 15.5 Hz), 4.66 (d, 1H, *J* = 11.7 Hz), 4.60 (dd, 1H, *J* = 2.0 and 5.5 Hz), 4.32–4.42 (m, 2H), 4.08–4.24 (m, 3H), 3.92 (dd, 1H, *J* = 2.0 and 5.5 Hz), 3.81 (m, 1H), 3.05 (br s, 1H); ^{13}C-NMR ($CDCl_3$, 75 MHz): δ 159.1, 137.1, 135.4, 128.9, 128.5, 128.0, 2 x 127.9, 127.5, 96.3, 84.0, 76.1, 74.3, 71.7, 64.3, 54.5, 45.7; ESIMS *m*/*z*: 386 $[M+H]^+$; HRMS (ESI): Calcd for $C_{21}H_{24}NO_6$ $[M+H]^+$ 386.1603, found 386.1588.

4.5. (*R*)-3-Benzyl-4-((1*R*,2*R*,*Z*)-2-(benzyloxy)-1-hydroxyhexadec-3-enyl)oxazolidin-2-one 19

To a stirred solution of compound **18** (0.70 g, 1.82 mmol) in MeOH/H_2O (15 mL, 2:1 v/v) were added $NaIO_4$ (0.78 g, 3.64 mmol) and saturated $NaHCO_3$ solution (0.2 mL) at 0 °C. Stirring was continued for 2 h; after consumption of the starting material, methanol was removed under reduced pressure, and the resulting residue was diluted with H_2O and washed with CH_2Cl_2 (2 × 10 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ and brine, and dried over anhydrous Na_2SO_4. The solvent was removed on a rotary evaporator and the resulting crude aldehyde was used in the next step without any purification.

To a precooled solution of Wittig salt $C_{13}H_{27}Ph_3P^+Br^-$ (2.86 g, 5.46 mmol) in THF (30 mL) was slowly added *n*-BuLi (2.5 M in hexane, 1.45 mL, 3.64 mmol) under N_2 protection. The orange solution was stirred for about 30 min, after which a solution of the above crude aldehyde in dry THF (10 mL) was added dropwise under N_2 protection. The mixture was stirred at this temperature for another 30 min, and quenched by saturated NH_4Cl solution. The mixture was diluted with water and extracted with EtOAc (3 × 20 mL). The combined organic layer was washed with brine, and dried over Na_2SO_4. The solvent was removed on a rotary evaporator and the residue was purified by column chromatography on silica gel using ethyl acetate:hexane (1:9) as the eluent to give pure compound **19** (0.85 g, 90% for two steps) as a colorless oil. $[\alpha]_D^{26} = -28.5$ (*c* 1.0, $CHCl_3$); IR ν_{max}: 2923, 2853, 1748, 1426, 1376, 1256, 1210, 1070, 1038, 880, 702; ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 7.09–7.30 (m, 10H), 5.57(m, 1H), 5.03 (dd, 1H, *J* = 10.3 Hz), 4.70 (d, 1H, *J* = 15.6 Hz), 4.46 (d, 1H, *J* = 11.2 Hz), 4.28 (m, 1H), 4.15 (d, 1H, *J* = 11.2 Hz), 3.95–4.05 (m, 2H), 3.82 (m, 1H), 3.72 (d, 1H, *J* = 6.8 Hz), 3.53 (m, 1H), 1.70–2.06 (m, 4H), 1.05–1.25 (m, 20H), 0.78 (t, 1H, *J* = 6.6 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 158.6, 137.6, 137.5, 135.7, 128.7, 128.4, 128.0, 127.8, 124.9, 74.4, 70.0, 69.7, 62.01, 55.8, 45.9, 31.8, 29.6, 29.4, 29.2, 29.1, 28.7, 27.9, 22.6, 14.0; ESIMS *m*/*z*: 522 $[M+H]^+$; HRMS (ESI): Calcd for $C_{33}H_{48}NO_4$ $[M+H]^+$ 522.3583, found 522.3598.

4.6. (2*R*,3*R*,4*R*,*Z*)-2-(Benzylamino)-4-(benzyloxy)octadec-5-ene-1,3-diol 12

Compound **19** (0.50 g, 0.95 mmol) was taken in EtOH (20 ml); to this solution at room temperature was added aq 4 M NaOH (1.5 mL), then it was heated at reflux for 12 h. After completion of the reaction, it was neutralized with 1 M aq. HCl (6 mL) and extracted with EtOAc (2 × 20 mL). The combined organic layer was washed with brine and dried over Na_2SO_4. The solvent was removed on a rotary evaporator and the residue was purified by column chromatography on silica gel using ethyl acetate:hexane (2:3) as the eluent to give pure compound **12** (0.40 g, 85% for two steps) as a colorless oil. $[\alpha]_D^{26} = -53.4$ (*c* 1.0, $CHCl_3$); IR ν_{max}: 3342, 2923, 2853, 1728, 1457, 1062, 735, 699 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 7.21–7.38 (m, 10H), 5.77 (m, 1H), 5.30 (dd, 1H, *J* = 9.4 and 10.4 Hz), 4.60 (d, 1H, *J* = 11.4 Hz), 4.29 (d, 1H, *J* = 11.4 Hz), 4.23 (m, 1H), 3.74–3.85 (m, 3H), 3.68 (m, 1H), 3.63 (m, 1H), 2.62–2.74 (m, 4H), 1.98–2.17 (m, 2H), 1.21–1.41 (m, 18H), 0.88 (t, 1H, *J* = 7.2 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 137.3, 128.4. 128.3, 127.9, 127.8, 127.2, 125.4, 75.1, 73.9, 70.0, 60.1, 58.3, 50.9, 31.9, 29.6, 2 × 29.5, 29.4, 29.3, 28.1, 22.6, 14.1; ESIMS *m*/*z*: 496 $[M+H]^+$; HRMS (ESI): Calcd for $C_{32}H_{50}NO_3$ $[M+H]^+$ 496.3790, found 496.3802.

4.7. (2*R*,3*R*,4*R*)-2-Acetamidooctadecane-1,3,4-triyl triacetate 10

Compound **12** (0.2 g, 0.40 mmol) was taken in dry EtOH (5 mL) and to it 1:1 Pd/C and $Pd(OH)_2$ (20 mg) were added. The flask was then purged with hydrogen and hydrogenated at room temperature for 24 h. The reaction mixture was filtered and the filtrate was concentrated under reduced pressure to give a syrup, which was acetylated as such with Et_3N (0.17 mL, 1.2 mmol), Ac_2O

(0.18 mL, 0.72 mmol), and DMAP (5 mg) in CH_2Cl_2 (5 mL). The reaction mixture was diluted with CH_2Cl_2 (25 mL) and washed with saturated NH_4Cl solution, brine, dried over anhydrous Na_2SO_4, and the solvent was concentrated in vacuo to give the residue, which was purified by column chromatography on silica gel by eluting with ethyl acetate:hexane (3:7) to give tetraacetate derivative **10** (0.17 g, 85%, for two steps) as a yellow syrup. $[\alpha]_D^{26} = +3.8$ (*c* 0.62, $CHCl_3$), {lit.[18] $[\alpha]_D^{26} = +4.3$ (*c* 0.5, $CHCl_3$)}; IR ν_{max}: 2924, 2854, 1741, 1659, 1543, 1370, 1221, 1044 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 5.72 (d, 1H, *J* = 9.4 Hz), 5.09 (m, 2H), 4.53 (m, 1H), 4.22 (dd, 1H, *J* = 4.7 and 11.5 Hz), 3.94 (dd, 1H, *J* = 3.0 and 11.5 Hz), 2.12 (s, 3H), 2.09 (s, 3H), 2.06 (s, 3H), 1.97 (s, 3H), 1.42–1.66 (m, 2H), 1.18–1.34 (m, 24H), 0.88 (t, 3H, *J* = 6.6 Hz); ^{13}C MR ($CDCl_3$, 75 MHz): δ 170.8, 170.6, 170.3, 169.6, 71.9, 71.2, 63.1, 47.4, 31.9, 30.9, 29.7, 29.5, 2 × 29.4, 29.3, 25.2, 23.3, 22.7, 21.0, 20.8, 14.1; ESIMS *m*/*z*: 486 $[M+H]^+$; HRMS (ESI): Calcd for $C_{26}H_{48}NO_7$ $[M+H]^+$ 486.3420, found 486.3441.

4.8. *tert*-Butyl (2*R*,3*R*,4*R*)-1,3,4-trihydroxyoctadecan-2-ylcarbamate 20

Compound **12** (0.15 g, 0.30 mmol) was taken in dry EtOH (5 mL) and to it 1:1 Pd/C and $Pd(OH)_2$ (20 mg) were added. The flask was then purged with hydrogen and hydrogenated at room temperature for 24 h. The reaction mixture was filtered and the filtrate was concentrated under reduced pressure to give a syrup, which was treated with $(Boc)_2O$ (0.02 mL, 0.27 mmol), Et_3N (0.13 mL, 0.90 mmol) in CH_2Cl_2 (5 mL) and stirred at 0 °C to rt for 2 h. The reaction mixture was diluted with CH_2Cl_2 (10 mL) and washed with saturated NH_4Cl solution, brine, and dried over anhydrous Na_2SO_4. The solvent was concentrated in vacuo to give a residue, which was purified by column chromatography on silica gel by eluting with ethyl acetate:hexane (3:7) to afford the protected aminotriol **20** (0.11 g, 86%) (over two steps) as a syrup. $[\alpha]_D^{26} = +6.2$ (*c* 1.5, $CHCl_3$); ^1H-NMR ($CDCl_3$, 300 MHz): δ 5.21 (d, 1H, *J* = 9.0 Hz), 4.06 (d, 1H, *J* = 11.0 Hz), 3.76 (dd, 1H, *J* = 4.0 and 11.0 Hz), 3.62 (m, 1H), 3.52 (m, 1H), 3.39 (d, 1H, *J* = 8.0 Hz), 1.52–1.67 (m, 2H), 1.46 (s, 9H), 1.22–1.34 (m, 26H), 0.88 (t, 3H, *J* = 7 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 157.2, 80.4, 72.8, 69.6, 62.0, 53.5, 32.8, 31.9, 29.7, 29.6, 29.4, 28.3, 26.1, 22.7, 14.1; ESIMS *m*/*z*: 418 $[M+H]^+$; HRMS (ESI): Calcd for $C_{23}H_{47}NO_5$ $[M+H]^+$ 440.3351, found 440.3342.

4.9. *tert*-Butyl (3*R*,4*R*,5*R*)-4-hydroxy-5-tetradecyltetrahydrofuran-3-ylcarbamate 21

To a solution of **20** (0.30 g, 0.58 mmol) in pyridine/CH_2Cl_2 (4 mL, 1:1 v/v) was added *p*-toluenesulfonyl chloride (0.12 g, 0.63 mmol). The mixture was stirred for 18 h at rt. Next, MeOH (0.5 mL) and EtOH (30 mL) were added to the mixture, and the solution was extensively washed with an aqueous saturated $CuSO_4$ solution (3 × 10 mL) and dried over anhydrous Na_2SO_4. The solvent was removed on a rotary evaporator and the resulting residue was purified by column chromatography on silica gel by eluting with ethyl acetate:hexane (1:4) to give **21** (0.2 g, 86%) as a white solid. mp 82–84 °C; $[\alpha]_D^{26} = -7.1$ (*c* 1.5, $CHCl_3$) {lit.[13e] $[\alpha]_D = +6.8$ (*c* 1.0, $CHCl_3$) for the enantiomer}; IR ν_{max}: 3363, 2919, 2849, 1686, 1543, 1251, 1171 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 5.05 (d, 1H, *J* = 4.5 Hz), 4.26 (m, 1H), 3.96–4.04 (m, 2H), 3.74 (dt, 1H, *J* = 3.0 Hz and 6.8 Hz), 3.52 (t, 3H, *J* = 8.3 Hz); 1.86 (br s, 1H), 1.53–1.61 (m, 2H), 1.44 (s, 9H), 1.21–1.36 (m, 24H), 0.88 (t, 3H, *J* = 7 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 155.7, 82.2, 79.9, 71.9, 70.2, 54.3, 31.9, 29.6, 29.5, 29.3, 29.0, 28.3, 26.1, 22.7, 14.1; ESIMS (*m*/*z*): 422 $[M+Na]^+$; HRMS (ESI): Calcd for $C_{23}H_{45}NO_4Na$ $[M+Na]^+$ 422.3246, found 422.3249.

4.10. (2*R*,3*R*,4*R*)-4-Acetamido-2-tetradecyltetrahydrofuran-3-yl acetate 11

To an ice cooled, stirred solution of compound **21** (0.08 g, 0.2 mmol) in dry CH_2Cl_2 (2 mL), was added TFA (2 mL). The reaction was allowed to room temperature and stirred for 2 h. The volatiles were removed on a rotary evaporator to give the residue, which was then taken in dry CH_2Cl_2 (4 mL) and to it were added Et_3N (0.09 mL, 0.6 mmol), Ac_2O (0.03 mL, 0.3 mmol) and DMAP (2 mg). After the completion of addition, the reaction was allowed to return to room temperature and stirred for 4 h. The reaction mixture was diluted with CH_2Cl_2 (30 mL) and the organic layer was washed with saturated aq.NH_4Cl solution, water and brine, and dried over anhydrous Na_2SO_4. The solvent was removed on a rotary evaporator and the residue was purified by column chromatography on silica gel using ethyl acetate:hexane (1:2) as the eluent to afford the diacetate derivative of (−)-jaspine B **11** (0.08 g, 94%) as a syrup. $[\alpha]_D^{26} = +26.8$ (*c* 1.2, $CHCl_3$), {lit., [13e] $[\alpha]_D^{26} = -28.4$ (*c* 1.0, $CHCl_3$) for the enantiomer}; IR ν_{max}: 3298, 2920, 2851, 1740, 1658, 1557, 1376, 1232, 1072 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 5.56 (d, 1H, *J* = 8.3 Hz), 5.33 (dd, 1H, *J* = 3.4 and 5.2 Hz), 4.75 (ddd, 1H, *J* = 5.6, 7.8 and 8.0 Hz), 4.04 (t, 1H, *J* = 8.0 Hz), 3.87 (m, 1H), 3.53 (t, 1H, *J* = 8.2 Hz), 2.15 (s, 3H), 1.97 (s, 3H), 1.40–1.46 (m, 2H), 1.21–1.33 (m, 24H), 0.88 (t, 3H, *J* = 6.8 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 169.8, 169.7, 81.2, 73.6, 70.0, 51.4, 31.9, 29.7, 29.6, 29.5, 29.4, 29.3, 29.2, 26.0, 23.1, 22.6, 20.6, 14.0; ESIMS *m*/*z*: 406 $[M+H]^+$; HRMS (ESI): Calcd for $C_{22}H_{41}NO_4Na$ $[M+Na]^+$ 406.2933, found 406.2933.

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