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Stereoselective synthesis of pachastrissamine (jaspine B)

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Dedicated to Professor J. Barluenga, from the University of Oviedo, on the occasion of his 65th birthday

Abstract—A stereoselective synthesis in enantiopure form of the natural anhydrophytosphingosine pachastrissamine (jaspine B), a metabolite isolated from sponges, is described. The chiral epoxide (*R*)-glycidol was the starting material. Key steps of this synthesis are a Sharpless asymmetric epoxidation, an intramolecular stereospecific epoxide opening mediated by a trichloroacetimidate group, and the formation of a tetrahydrofuran ring via intramolecular nucleophilic displacement.

1. Introduction

Sponges of the genus *Jaspis* (family Coppatiidae) have received in recent times a considerable attention from scientists because of the interesting pharmacological properties of its chemical components. Among these, modified peptides[1] and nucleosides,[2] sterols and other triterpene derivatives,[3] unusual bisoxazoles,[4] cytotoxic macrolides,[5] styryl sulfates,[6] unusual terpenes of mixed biogenetic origin,[7] α-amino-ε-lactam derivatives (bengamides),[8] and brominated tyrosine derivatives[9] are particularly worth mentioning. Very recently, two cytotoxic anhydrophytosphingosine derivatives, named jaspine A **1** and B **2**, have been isolated from a new species of the aforementioned genus.[10] Compound **2** was found highly active against the A5409 human lung carcinoma cell line (IC_{50}=0.34 μM). Compound **2** had also been isolated shortly before from another sponge species of the *Pachastrissa* genus (family Calthropellidae) and received the name pachastrissamine.[11,12] It was assayed against the P388, HT29, MEL28 tumoral cell lines and found cytotoxic at the submicromolar level. The valuable pharmacological properties and novel structural features of **2**[13] have prompted us to undertake its total synthesis in enantiopure form (Fig. 1).

Very recently, total syntheses of **2** starting from the chiral pool have been reported.[14] As a part of our research program aimed at developing stereocontrolled syntheses of naturally occurring bioactive compounds in enantiopure form,[15] we here report our own synthesis of pachastrissamine (jaspine B) **2** from (*R*)-glycidol as the chiral starting material.[16]

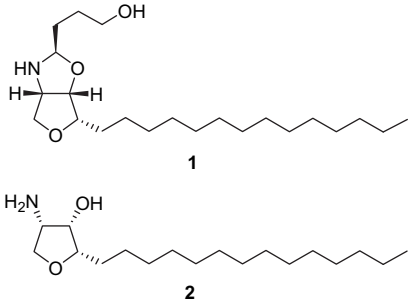
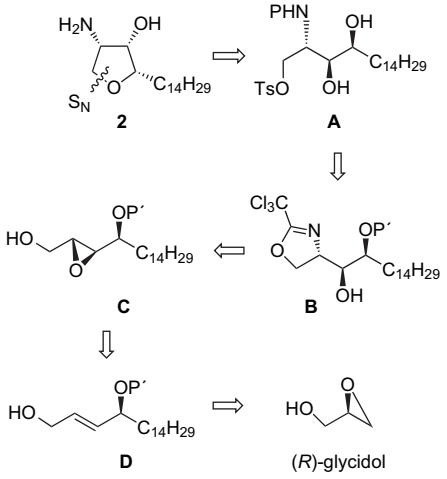


Figure 1. Structures of jaspines A and B.

The retrosynthetic strategy for the synthesis of **2** is outlined in Scheme 1 (P, P′=protecting groups). Retrocleavage of one of the C–O bonds in the tetrahydrofuran ring via



Scheme 1. Retrosynthetic plan for the synthesis of pachastrissamine (jaspine B) **2**.

Keywords: Pachastrissamine (jaspine B); (*R*)-Glycidol; Sharpless asymmetric epoxidation; Imidate epoxide opening.
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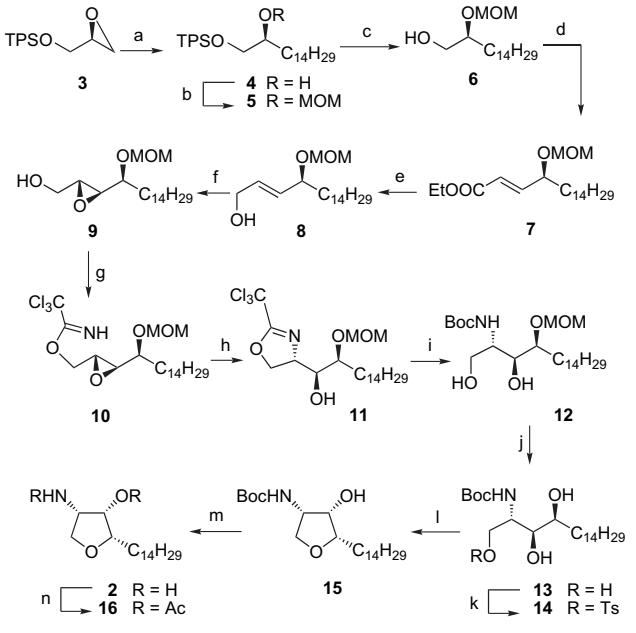
intramolecular nucleophilic displacement gives the open chain intermediate **A**. The nitrogen atom is then introduced (in the retrosynthetic sense) by means of another intramolecular nucleophilic displacement in epoxy alcohol **C** via oxazoline **B**. Compound **C** can be obtained through Sharpless epoxidation of (*E*)-allylic alcohol **D**, to be prepared in turn from (*R*)-glycidol.

2. Results and discussion

The synthesis of **2** is illustrated in Scheme 2. Commercial (*R*)-glycidol was transformed into its known[17] TPS ether **3** (for nonstandard acronyms, see Scheme 2). Epoxide opening in **3** with a *n*-tridecyl cuprate reagent[18] afforded alcohol **4**, which was then protected as its MOM derivative **5**.[19] Desilylation of the latter with TBAF furnished alcohol **6**, which was transformed into the (*E*)-unsaturated ester **7** as reported by sequential Swern oxidation and olefination.[20] DIBAL reduction of **7** to (*E*)-allylic alcohol **8** followed by Sharpless asymmetric epoxidation with *t*-BuO_2H in the presence of Ti(*i*PrO)$_4$ and (−)-diethyl tartrate[21] provided epoxy alcohol **9**. Upon reaction with trichloroacetonitrile in the presence of DBU, **9** furnished the corresponding imino ester derivative **10**.[22] The nucleophilic intramolecular epoxide opening in **10** was first attempted in the presence of catalytic amounts of $BF_3\cdot Et_2O$ but only decomposition was observed. Success was finally achieved through reaction of imidate **10** in the presence of Et_2AlCl to yield oxazoline **11**.[23] Acidic hydrolysis of **11** followed by *N*-Boc protection furnished diol **12**. Removal of the MOM group could be performed with TMSBr[24,25] to provide triol **13**, which was then selectively tosylated at the primary alcohol group. Basic treatment of monotosylate **14** with K_2CO_3 in MeOH caused intramolecular tosylate displacement and gave rise to tetrahydrofuran **15**. Cleavage of the *N*-Boc group in **15** with TFA yielded compound **2**, which had spectral properties identical to those reported in the bibliography for either pachastrissamine[11] or jaspine B.[10] Furthermore, acetylation of **2** provided the *O*,*N*-diacetyl derivative **16**, with spectral properties also identical to those reported in the bibliography.[10,11]



Scheme 2. Synthesis of pachastrissamine (jaspine B) **2**. Reaction conditions: (a) $CH_3(CH_2)_{12}MgBr$, CuI, THF, −10→0 °C, 82%; (b) MOMCl, EtN*i*Pr$_2$, CH_2Cl_2, 24 h, rt, 94%; (c) TBAF, THF, 3 h, rt, 94%; (d) Ref. 20; (e) DIBAL, hexane, 0 °C, 2.5 h, 95%; (f) *t*-BuO_2H, (−)-diethyl tartrate, Ti(*i*PrO)$_4$, CH_2Cl_2, −20 °C, 24 h, 89%; (g) Cl_3CCN, DBU, CH_2Cl_2, 30 min, 0 °C; (h) Et_2AlCl, CH_2Cl_2, 0 °C→rt, 5 h, 72% overall yield from **9**; (i) aq 1 M HCl, THF, 5 h, rt, then $NaHCO_3$, Boc_2O, 16 h, rt, 96% overall yield from **11**; (j) TMSBr, CH_2Cl_2, −78 °C, 30 min, 75%; (k) TsCl, Et_3N, DMAP, CH_2Cl_2, 20 min, rt; (l) K_2CO_3, MeOH, 16 h, rt, 70% overall from **13**; (m) TFA, CH_2Cl_2, 0 °C→rt, 45 min, 75%; (n) Ac_2O, Et_3N, DMAP, CH_2Cl_2, 16 h, rt (Acronyms: CSA=camphorsulfonic acid; TBAF=tetra-*n*-butyl ammonium fluoride hydrate; TPS=*tert*-butyldiphenylsilyl).

3. Conclusions

We have performed a stereoselective synthesis of the natural anhydrophytosphingosine pachastrissamine (jaspine B) with (*R*)-glycidol as the chiral starting material. Since both antipodes of glycidol as well of diethyl tartrate (for the Sharpless asymmetric epoxidation step) are available, our synthetic concept is flexible enough as to be adaptable to the preparation of the non-natural antipode of **2** or else diastereomers thereof. Furthermore, ring-opening of the protected glycidol with organocopper reagents of various structures would provide a library of pachastrissamine analogues for structure–activity studies.

4. Experimental

4.1. General

$^1H/^{13}C$ NMR spectra were measured at 500/125 MHz in $CDCl_3$ solution at 25 °C. The signals of the deuterated solvent ($CDCl_3$) were taken as the reference (the singlet at δ 7.25 for ^1H NMR and the triplet centered at 77.00 ppm for ^{13}C NMR data). Carbon atom types (C, CH, CH_2, CH_3) were determined with the DEPT pulse sequence. Mass spectra were run by the electron impact (EIMS, 70 eV) or the fast atom bombardment mode (FABMS, *m*-nitrobenzyl alcohol matrix) on a VG AutoSpec mass spectrometer. IR data are given only for compounds with relevant functions (OH, C=O) and were recorded as oily films on NaCl plates (oils) or as KBr pellets (solids). Optical rotations were measured at 25 °C. Reactions which required an inert atmosphere were carried out under N_2 with flame-dried glassware. Et_2O and THF were freshly distilled from sodium–benzophenone ketyl and transferred via syringe. Dichloromethane was freshly distilled from CaH_2. Tertiary amines were freshly distilled from KOH. Toluene was freshly distilled from sodium wire. Commercially available reagents were used as received. Unless detailed otherwise, 'work-up' means pouring the reaction mixture into brine, followed by extraction with the solvent indicated in parenthesis. If the reaction medium was acidic (basic), an additional washing with 5% aq $NaHCO_3$ (aq NH_4Cl) was performed. Drying over anhydrous Na_2SO_4 and elimination of the solvent under reduced pressure were followed by chromatography of the residue on a silica gel column (60–200 μm) with the indicated eluent. Where solutions were filtered through a Celite pad, the pad was additionally washed with the same solvent used, and the washings incorporated to

the main organic layer. Nonstandard acronyms are explained in the caption of Scheme 2.

4.1.1. (2*S*)-1-(*tert*-Butyldiphenylsilyloxy)hexadecan-2-ol (4). Magnesium turnings (365 mg, ca. 15 mmol) were suspended under N_2 in dry THF (10 mL) at room temperature. A few drops of 1,2-dibromoethane were added to the suspension via syringe until an effervescence started. A solution of *n*-tridecyl bromide (3.6 mL, 14 mmol) in THF (10 mL) was then added dropwise via syringe. The resulting mixture was stirred at 50 °C for 30 min.

Powdered CuI (1.33 g, 7 mmol) was gently heated in vacuo until the solid turned light yellow. The flask was then filled with Ar and cooled to −30 °C, followed by addition of dry THF (30 mL). The previously prepared solution of *n*-tridecylmagnesium bromide was then added dropwise via syringe. The mixture was then stirred for 15 min at −30 °C. The TPS derivative **3** of (*R*)-glycidol (1.1 g, ca. 3.5 mmol) was dissolved in dry THF (10 mL) and added dropwise to the solution of organocopper reagent. The reaction mixture was then stirred for 15 min at −10 °C and then for further 4 h at 0 °C. Work-up (Et_2O) and column chromatography on silica gel (hexane–EtOAc, 9:1) afforded pure **4** (1.42 g, 82%): oil; $[\alpha]_D$ +1.5 (*c* 1.4, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.70–7.60 (4H, m), 7.45–7.35 (6H, m), 3.72 (1H, m), 3.68 (1H, dd, *J*=10, 3.3 Hz), 3.52 (1H, dd, *J*=10, 7.5 Hz), 2.50 (1H, br s, OH), 1.50–1.20 (26H, br m), 1.08 (9H, s), 0.89 (3H, t, *J*=7 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 133.3, 133.2, 19.3 (C), 135.6, 135.5, 129.8, 127.8, 71.9 (CH), 68.0, 32.8, 32.0, 29.7 (several overlapped peaks), 25.5, 22.7 (CH_2), 26.9 (×3), 14.1 (CH_3); IR ν_{max} 3460 (br, OH) cm^{-1}; HREIMS *m/z* (rel int.) 439.3036 (M^+-tBu, 9), 199 (100), 139 (36). Calcd for $C_{32}H_{52}O_2Si-t$Bu, 439.3032. Anal. Calcd for $C_{32}H_{52}O_2Si$: C, 77.36; H, 10.55. Found: C, 77.37; H, 10.66.

4.1.2. (2*S*)-1-(*tert*-Butyldiphenylsilyloxy)-2-(methoxymethoxy)hexadecane (5). Alcohol **4** (1.24 g, 2.5 mmol) was dissolved in dry CH_2Cl_2 (25 mL) and treated with MOM chloride (570 μL, ca. 7.5 mmol), DMAP (12 mg, 0.1 mmol), and triethyl amine (1.26 mL, ca. 9 mmol). The resulting solution was stirred at room temperature for 24 h. Work-up (CH_2Cl_2) and column chromatography on silica gel (hexane–EtOAc, 19:1) provided compound **5** (1.27 g, 94%): oil; $[\alpha]_D$ −25.4 (*c* 1.4, $CHCl_3$); ^{1}H NMR (500 MHz) δ 7.70–7.60 (4H, m), 7.45–7.35 (6H, m), 4.78 (1H, d, *J*=6.8 Hz), 4.65 (1H, d, *J*=6.8 Hz), 3.70–3.60 (3H, m), 3.36 (3H, s), 1.650–1.20 (26H, br m), 1.07 (9H, s), 0.89 (3H, t, *J*=7 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 133.6 (×2), 19.2 (C), 135.7, 135.6, 129.7, 127.7, 78.0 (CH), 96.2, 66.5, 32.0, 31.8, 29.7 (several overlapped peaks), 25.4, 22.7 (CH_2), 55.5, 26.9 (×3), 14.1 (CH_3); HREIMS *m/z* (rel int.) 483.3266 (M^+-tBu, 1), 213 (96), 153 (32), 91(50), 71 (100). Calcd for $C_{34}H_{56}O_3Si-t$Bu, 483.3294. Anal. Calcd for $C_{34}H_{56}O_3Si$: C, 75.50; H, 10.44. Found: C, 75.27; H, 10.32.

4.1.3. (2*S*)-2-(Methoxymethoxy)hexadecan-1-ol (6). Silyl ether **5** (1.19 g, 2.2 mmol) was dissolved in dry THF (20 mL) and treated with a solution of TBAF (680 mg, 2.6 mmol) in dry THF (5 mL). The reaction mixture was stirred at room temperature until consumption of the starting material (about 3 h, TLC monitoring!). After removal of all volatiles in vacuo, the residue was chromatographed on silica gel (hexane–EtOAc, 4:1) to yield **6** (625 mg, 94%): solid; mp 39–40 °C, lit.[20] mp 36.9–38.1 °C; $[\alpha]_D$ +28.7 (*c* 1.6, $CHCl_3$), lit.[20] $[\alpha]_D$ +33.3 (*c* 2.3, $CHCl_3$); spectral data identical to those reported.[20]

4.1.4. Ethyl (2*E*,4*S*)-4-(methoxymethoxy)octadec-2-enoate (7). Prepared from **6** as reported.[20]

4.1.5. (2*E*,4*S*)-4-(Methoxymethoxy)octadec-2-en-1-ol (8). Ester **7** (650 mg, 1.75 mmol) was dissolved in dry hexane (5 mL) and cooled to 0 °C. Then DIBAL (4 mL, 1 M in hexane) was added and the reaction mixture was stirred at 0 °C for 2.5 h. Work-up (CH_2Cl_2) and column chromatography on silica gel (hexane–EtOAc, 19:1, then 4:1) furnished alcohol **8** (546 mg, 95%); solid; mp 44–45 °C; $[\alpha]_D$ −54.8 (*c* 2, $CHCl_3$); ^{1}H NMR (500 MHz) δ 5.80 (1H, dt, *J*=15.5, 5.3 Hz), 5.56 (1H, ddt, *J*=15.5, 8, 1.3 Hz), 4.69 (1H, d, *J*=6.8 Hz), 4.52 (1H, d, *J*=6.8 Hz), 4.15 (2H, d, *J*=4.5 Hz), 4.00 (1H, dt, *J*=8, 6.5 Hz), 3.36 (3H, s), 1.70–1.35 (6H, m), 1.35–1.20 (21H, s), 0.88 (3H, t, *J*=7 Hz); ^{13}C NMR (125 MHz) δ 131.9, 131.7, 76.4 (CH), 93.8, 62.9, 35.6, 31.9, 29.6 (several overlapped peaks), 25.5, 22.7 (CH_2), 55.4, 14.1 (CH_3); IR ν_{max} 3400 (br, OH) cm^{-1}; HREIMS *m/z* (rel int.) 297.2784 (M^+-CH_2OH, 1), 267 (4), 225 (7), 178 (25), 131 (100), 83 (20). Calcd for $C_{20}H_{40}O_3-CH_2OH$, 297.2793. Anal. Calcd for $C_{20}H_{40}O_3$: C, 73.12; H, 12.27. Found: C, 73.02; H, 12.24.

4.1.6. (2*R*,3*R*,4*S*)-2,3-Epoxy-4-(methoxymethoxy) octadecan-1-ol (9). Titanium tetraisopropoxide (0.6 mL, ca. 2 mmol) and D-(−)-diethyl tartrate (0.38 mL, ca. 2.2 mmol) were sequentially added at −20 °C to a stirred suspension of powdered 4 Å molecular sieves (250 mg) in dry CH_2Cl_2 (5 mL). After stirring for 5 min, a solution of allylic alcohol **8** (526 mg, 1.6 mmol) in dry CH_2Cl_2 (10 mL) was added, and the mixture was stirred for 30 min. After this, *tert*-butyl hydroperoxide (2.5 mL of a freshly prepared ≈4 M solution in toluene, 10 mmol) was added dropwise and the reaction mixture was further stirred at −20 °C for 24 h. Work-up (CH_2Cl_2) and column chromatography on silica gel (hexane–EtOAc, 7:3) afforded epoxy alcohol **9** (491 mg, 89%): solid; mp 40–41 °C; $[\alpha]_D$ −13.4 (*c* 1.1, $CHCl_3$); ^{1}H NMR (500 MHz) δ 4.83 (1H, d, *J*=6.8 Hz), 4.63 (1H, d, *J*=6.8 Hz), 3.92 (1H, dq, *J*=12.8, 2.2 Hz), 3.63 (1H, dq, *J*=12.8, 4.4 Hz), 3.38 (3H, s), 3.36 (1H, m), 3.02 (1H, dd, *J*=7, 2.2 Hz), 2.99 (1H, dt, *J*=4.4, 2.2 Hz), 2.10 (1H, br s, OH), 1.65–1.50 (2H, m), 1.40–1.20 (24H, br m), 0.87 (3H, t, *J*=7 Hz); ^{13}C NMR (125 MHz) δ 77.1, 58.0, 55.6 (CH), 95.5, 61.2, 32.3, 31.9, 29.6 (several overlapped peaks), 25.4, 22.7 (CH_2), 55.5, 14.1 (CH_3); IR ν_{max} 3450 (br, OH) cm^{-1}; HRFABMS *m/z* 345.3009 (M+H)$^+$. Calcd for $C_{20}H_{41}O_4$, 345.2999. Anal. Calcd for $C_{20}H_{40}O_4$: C, 69.72; H, 11.70. Found: C, 69.92; H, 11.88.

4.1.7. (1*S*,2*S*)-2-(Methoxymethoxy)-1-[(4*S*)-(2-trichloromethyl-4,5-dihydrooxazol-4-yl)]hexadecan-1-ol (11). A solution of epoxy alcohol **9** (482 mg, 1.4 mmol) in dry CH_2Cl_2 (5 mL) was cooled at 0 °C and treated dropwise with trichloroacetonitrile (200 μL, 2 mmol) and DBU (45 μL, 0.3 mmol). The mixture was then stirred for 30 min at 0 °C. Work-up (CH_2Cl_2) and rapid column chromatography on silica gel (hexane–EtOAc, 4:1) gave

trichloroacetimidate **10**, which was directly used in the following reaction.

A solution of the trichloroacetimidate from above in dry CH_2Cl_2 (10 ml) was cooled at 0 °C and treated with diethylaluminum chloride (1 mL of a 1 M solution in hexane, 1 mmol). The reaction mixture was stirred for 5 h at room temperature and then filtered through a pad of Celite. Solvent removal in vacuo and column chromatography on silica gel (hexane–EtOAc, 9:1) yielded **11** (493 mg, 72% overall yield from **9**): oil; $[\alpha]_D$ +32.7 (*c* 1.8, $CHCl_3$); ^1H NMR (500 MHz) δ 4.75–4.70 (3H, m), 4.64 (1H, t, *J*=9 Hz), 4.42 (1H, dt, *J*=9, 5.5 Hz), 3.75–3.65 (2H, m), 3.41 (s, 3H), 2.65 (1H, d, *J*=7 Hz, OH), 1.60 (2H, m), 1.35–1.20 (24H, br m), 0.88 (3H, t, *J*=7 Hz); ^{13}C NMR (125 MHz) δ 163.6 (C), 79.2, 73.6, 69.1 (CH), 96.7, 73.0, 32.0, 31.1, 29.7 (several overlapped peaks), 25.2, 22.7 (CH_2), 56.0, 14.1 (CH_3) (the quaternary carbon signal from the CCl_3 group was not detected); IR ν_{max} 3440 (br, OH), 1662 (C=N) cm^{-1}; HRFABMS *m/z* 488.2111 $(M+H)^+$. Calcd for $C_{22}H_{41}^{35}Cl_3NO_4$, 488.2101. Anal. Calcd for $C_{22}H_{40}Cl_3NO_4$: C, 54.05; H, 8.25. Found: C, 54.02; H, 8.11.

4.1.8. (2*S*,3*S*,4*S*)-4-(Methoxymethoxy)-2-(*tert*-butyloxycarbonylamino)octadecan-1,3-diol (12). Oxazoline **11** (489 mg, 1 mmol) was dissolved in THF (6 ml) and treated with 1 M aq HCl (1.2 mL). The reaction mixture was stirred at room temperature for 5 h. Solid $NaHCO_3$ (1 g) was then added, followed by addition of di-*tert*-butyl dicarbonate (3 mL of a 1 M solution in THF). The reaction mixture was then stirred for 16 h at room temperature. Work-up (EtOAc) and column chromatography on silica gel (hexanes–EtOAc, 1:1) furnished **12** (443 mg, 96%): oil; $[\alpha]_D$ +14.4 (*c* 1.1, $CHCl_3$); ^1H NMR (500 MHz) δ 5.40 (1H, br d, *J*=9 Hz), 4.76 (1H, d, *J*=6.7 Hz), 4.70 (1H, d, *J*=6.7 Hz), 3.90 (1H, m), 3.75–3.65 (3H, m), 3.55 (1H, m), 3.41 (s, 3H), 1.65–1.55 (2H, m), 1.44 (9H, s), 1.45–1.20 (26H, br m), 0.88 (3H, t, *J*=7 Hz); ^{13}C NMR (125 MHz) δ 156.0, 79.7 (C), 81.4, 74.6, 52.5 (CH), 97.7, 62.8, 32.0, 31.4, 29.7 (several overlapped peaks), 25.3, 22.7 (CH_2), 56.0, 28.4, 14.1 (CH_3); IR ν_{max} 3440 (br, OH), 1714 (C=O) cm^{-1}; HREIMS *m/z* (rel int.) 462.3781 ($M+H^+$, 1), 430 (2), 269 (34), 160 (37), 264 (100), 134 (52), 104 (44), 60 (76), 57 (100). Calcd for $C_{25}H_{52}NO_6$, 462.3794. Anal. Calcd for $C_{25}H_{51}NO_6$: C, 65.04; H, 11.13. Found: C, 65.02; H, 11.11.

4.1.9. (2*S*,3*S*,4*S*)-2-(*tert*-Butyloxycarbonylamino) octadecan-1,3,4-triol (13). A solution of diol **12** (438 mg, 0.95 mmol) in dry CH_2Cl_2 (10 mL) was cooled at −78 °C. Trimethylsilyl bromide (185 μL, 1.4 mmol) was then added dropwise. The reaction mixture was stirred for 30 min at −78 °C. Work-up (EtOAc) and column chromatography on silica gel (hexane–EtOAc, 1:1) afforded the protected aminotriol **13** (298 mg, 75%): oil; $[\alpha]_D$ −8.3 (*c* 1, $CHCl_3$); ^1H NMR (500 MHz) δ 5.25 (1H, br d, *J*=9 Hz), 4.05 (1H, br d, *J*=10.5 Hz), 3.76 (1H, dd, *J*=10.5, 4 Hz), 3.63 (1H, m), 3.53 (1H, m), 3.40 (1H, m), 2.50 (1H, br s, OH), 1.70–1.60 (2H, m), 1.45 (9H, s), 1.40–1.20 (26H, br m), 0.88 (3H, t, *J*=7 Hz); ^{13}C NMR (125 MHz) δ 157.2, 80.5 (C), 69.7, 62.1, 53.5 (CH), 73.0, 32.9, 31.9, 29.7 (several overlapped peaks), 26.1, 22.7 (CH_2), 28.4, 14.1 (CH_3); IR ν_{max} 3400 (br, OH), 3250 (br, NH), 1671 (C=O) cm^{-1}; HRFABMS *m/z* 418.3547 $(M+H)^+$. Calcd for $C_{23}H_{48}NO_5$, 418.3532. Anal. Calcd for $C_{23}H_{47}NO_5$: C, 66.15; H, 11.34. Found: C, 66.06; H, 11.40.

4.1.10. (2*S*,3*S*,4*S*)-4-(*tert*-Butyloxycarbonylamino)-2-(tetradecyl)tetrahydrofuran-3-ol (15). Triol **13** (250 mg, 0.6 mmol) was diluted in dry CH_2Cl_2 (20 mL), cooled to 0 °C and treated with Et_3N (420 μL, 3 mmol), DMAP (6 mg, 0.05 mmol), and tosyl chloride (343 mg, 1.8 mmol). The reaction mixture was then stirred at room temperature until consumption of the starting material (about 20–30 min). Work-up (CH_2Cl_2) provided the crude monotosylate **14**, which was used directly in the next step.

A solution of crude **14** in MeOH (8 mL) was cooled at 0 °C and treated with K_2CO_3 (415 mg, 3 mmol). The reaction mixture was stirred for 16 h at room temperature and then filtered through a pad of Celite. Solvent removal in vacuo and column chromatography on silica gel (hexane–EtOAc, 4:1) afforded **15** (168 mg, 70% overall yield from **13**): solid, mp 110–111 °C; $[\alpha]_D$ +6.8 (*c* 1.0, $CHCl_3$); ^1H NMR (500 MHz) δ 5.10 (1H, br d, *J*=8 Hz), 4.30 (1H, br s), 4.07 (1H, m), 4.04 (1H, t, *J*=8.5 Hz), 3.79 (1H, td, *J*=7, 2.8 Hz), 3.58 (1H, t, *J*=8.5 Hz), 2.00 (1H, br s, OH), 1.65–1.55 (2H, m), 1.45 (9H, s), 1.40–1.20 (24H, br m), 0.88 (3H, t, *J*=7 Hz); ^{13}C NMR (125 MHz) δ 155.7 (C), 82.2 ($+C_q$), 71.9, 54.3 (CH), 70.3, 31.9, 29.7 (several overlapped peaks), 26.1, 22.7 (CH_2), 28.4, 14.1 (CH_3); IR ν_{max} 3365 (br, OH, NH), 1688 (C=O) cm^{-1}; HRFABMS *m/z* 400.3463 $(M+H)^+$. Calcd for $C_{23}H_{46}NO_4$, 400.3426. Anal. Calcd for $C_{23}H_{45}NO_4$: C, 69.13; H, 11.35. Found: C, 69.20; H, 11.42.

4.1.11. Pachastrissamine (jaspine B) (2). A solution of **15** (120 mg, 0.3 mmol) in CH_2Cl_2 (5 mL) was cooled to 0 °C and treated with TFA (220 μL, ca. 3 mmol). The reaction mixture was then stirred for 45 min at room temperature. After this time, 2.5 M NaOH in MeOH (2 mL) was added and the stirring was continued for 5 min. Work-up (CH_2Cl_2) and column chromatography on silica gel ($CHCl_3$–MeOH–aq NH_4OH, 95:4:1) furnished **2** (67 mg, 75%): amorphous solid; $[\alpha]_D$ +9 (*c* 1.5, $CHCl_3$), lit.[10] $[\alpha]_D$ +7 (*c* 0.1, $CHCl_3$), lit.[11] $[\alpha]_D$ +18 (*c* 0.1, EtOH); ^1H NMR (500 MHz) δ 3.92 (1H, dd, *J*=8.5, 7.5 Hz), 3.86 (1H, dd, *J*=5, 3.5 Hz), 3.73 (1H, ddd, *J*=7.5, 7.5, 3.5 Hz), 3.65 (1H, m), 3.51 (1H, dd, *J*=8.5, 7 Hz), 2.00 (1H, br s, OH), 1.70–1.60 (2H, m), 1.45–1.20 (26H, br m), 0.88 (3H, t, *J*=7 Hz); ^{13}C NMR (125 MHz) δ 83.3, 71.8, 54.4 (CH), 72.4, 31.9, 29.7 (several overlapped peaks), 26.4, 22.7 (CH_2), 14.1 (CH_3); IR ν_{max} 3340 (br, OH, NH) cm^{-1}; HREIMS *m/z* (rel int.) 299.2774 (M^+, 9), 282 (26), 265 (21), 226 (17), 60 (100). Calcd for $C_{18}H_{37}NO_2$, 299.2824.

4.1.12. *N*,*O*-diacetylpachastrissamine (*N*,*O*-diacetyl-jaspine B) (16). Compound **2** was acetylated under the standard conditions (Ac_2O, Et_3N, DMAP, CH_2Cl_2, room temperature). Work-up (CH_2Cl_2) and column chromatography on silica gel (hexane–EtOAc, 1:1) yielded **16**[10,11]: amorphous solid; $[\alpha]_D$ −28.4 (*c* 1, $CHCl_3$); ^1H NMR (500 MHz) δ 5.60 (1H, br d, *J*=8.2 Hz), 5.40 (1H, dd, *J*=5.3, 3.5 Hz), 4.83 (1H, qd, *J*=8.2, 5.3 Hz), 4.09 (1H, t, *J*=8.2 Hz), 3.90 (1H, ddd, *J*=8.2, 5.3, 3.5 Hz), 3.60 (1H, t, *J*=8.2 Hz), 2.17 (3H, s), 2.00 (3H, s), 1.55–1.40 (2H, m), 1.35–1.20 (24H, br m), 0.88 (3H, t, *J*=7 Hz); ^{13}C NMR (125 MHz) δ 169.9,

169.8 (C), 81.2, 73.6, 51.4 (CH), 70.0, 31.9, 29.6 (several overlapped peaks), 26.0, 22.7 (CH_2), 23.2, 20.7, 14.1 (CH_3); IR ν_{max} 3215 (NH), 1741, 1642 (C=O) cm^{-1}; HREIMS *m/z* (rel int.) 384 ($M+H^+$, 14), 383.3034 (M^+, 4), 340 (14), 323 (27), 264 (100), 157 (30), 114 (44). Calcd for $C_{22}H_{41}NO_4$, 383.3035.

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