Asymmetric Synthesis of Jaspine B (Pachastrissamine) via an Organocatalytic Aldol Reaction as Key Step

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Dedicated to Professor R. W. Hoffmann on the occasion of his 75th birthday

Abstract: The asymmetric synthesis of jaspine B (pachastrissamine) using a (*R*)-proline-catalyzed enantioselective aldol reaction as key step is described. Jaspine B was synthesized from the commercially available and inexpensive 1-pentadecanal and the dihydroxyacetone equivalent 2,2-dimethyl-1,3-dioxan-5-one in nine steps, good overall yield (23.6%) and excellent stereoselectivity (de >98%, ee = 95%).

Key words: pachastrissamine (jaspine B), asymmetric synthesis, aldol reaction, organocatalysis, proline

The naturally occurring, cyclic anhydrophytosphingosine derivative jaspine B (pachastrissamine, **1**) was first isolated from the Okinawan marine sponge *Pachastrissa sp.* (family Calthropellidae) in 2002 by Higa et al.[1] and later from a different marine sponge, *Jaspis sp.*, by Debitus and co-workers.[2]

Due to the significant cytotoxic activity of jaspine B (IC_{50} 0.01 μg/mL against P388, A549, HT29 and MEL28 tumour cell lines), there is increasing interest within the chemical community regarding its total synthesis.[1]

Indeed, several stereoselective syntheses of jaspine B have been reported. Most of these routes are based on chiral pool strategies and use L-serine,[3] Garner's aldehyde,[4,5] D-xylose,[6] L-xylose[7] (to obtain a truncated pachastrissamine), D-glucose,[8] D-galactal[9] and D-tartaric acid as starting materials.[10] The synthesis of jaspine B (**1**) derived from the chiral substrates (*R*)-glycidol[11] or other epoxides,[12] generated by asymmetric Sharpless epoxidation, have also been described. The research groups of Yakura[13] and Srinivasan[14] have independently disclosed the synthesis of **1** using the asymmetric Sharpless dihydroxylation as a key step. Very recently Davies et al. described an elegant asymmetric synthesis via an aza-Michael addition/enolate oxidation sequence.[15]

As a cyclic anhydrophytosphingosine derivative, the structure of jaspine B is similar to that of phytosphingosines, e.g. D-*ribo*-phytosphingosine (**2**), with characteristic sub-units present in the ubiquitous sphingolipids. Both **1** and **2** possess common structural elements, namely, 18 carbon atoms, three contiguous stereogenic centers,

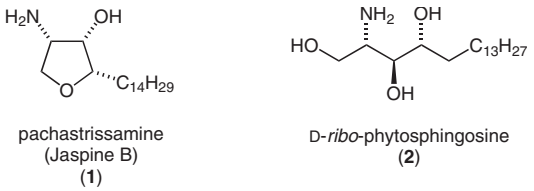

Figure 1 Jaspine B (**1**) and D-*ribo*-phytosphingosine (**2**)

a non-polar aliphatic 'tail' and a polar aminoalcohol 'head' (Figure 1).

Recently reported syntheses of **1** and its analogues by the groups of Overkleeft[16] und Kim[17] have taken advantage of this structural similarity and transformed phytosphingosine (**2**) into jaspine B.

Our research group has developed a proline-catalyzed aldol reaction that allows access to D- and L-phytosphingosines (e.g **2**) in a highly enantioselective manner.[18] Herein we report an efficient asymmetric synthesis of jaspine B, which employs this diastereo- and enantioselective aldol reaction as a key step. Retrosynthetically, we envisaged the preparation of the title compound by reduction of the cyclic azide **12**, which could be traced back to the tosylate **11** via a one-pot acid-catalyzed deprotection/intramolecular nucleophilic substitution reaction (Scheme 1). In turn, the tosylate **11** could be obtained from the known acetonide and TBS-protected triol **7** in an azidation/tosylation sequence. The asymmetric aldol reaction of dioxanone **3** with 1-pentadecanal, catalyzed by proline, would give access to the protected chiral *anti*-diol **5** that contains two of the required stereocenters of jaspine B (**1**).[18] Furthermore, the asymmetric organocatalytic aldol reaction of dioxanone **3** and 1-pentadecanal would assemble all 18 carbons of jaspine B in one synthetic step.

To commence the synthesis of the jaspine B target, the silyl ether **7** was prepared from dioxanone **3**[19] using (*R*)-proline for the organocatalytic aldol reaction (Scheme 2). This five-step procedure is similar to that reported previously which used (*S*)-proline.[18,20] Thus, the aldol product **5** was prepared using the diastereo- and enantio-selective (*R*)-proline-catalyzed aldol reaction of dioxanone **3** and 1-pentadecanal (**4**). Next, protection of the alcohol as a *tert*-butyldimethylsilyl (TBS) ether to form **6** and subsequent diastereoselective reduction with L-Selectride afforded the protected *anti*-1,3-diol **7** in multi-gram quantities. The free hydroxy group of alcohol **7** was then transformed into

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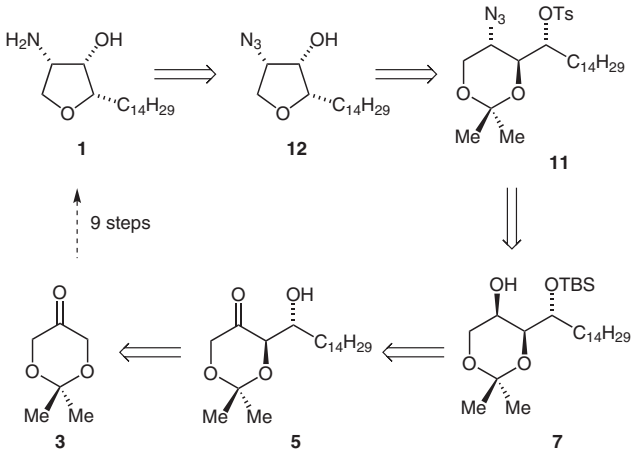
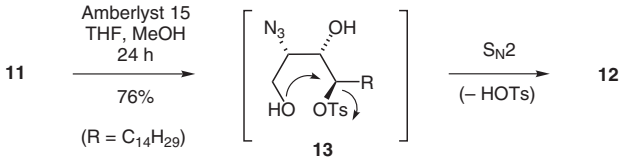


Scheme 1 Retrosynthetic analysis of jaspine B (**1**)

the mesylate **8** in 98% yield. Reaction of **8** with sodium azide in the presence of 18-crown-6 proceeded with virtually complete inversion of configuration and gave the desired TBS-protected *syn*-1,3-azido alcohol **9** in 79% yield (de > 98% by NMR and GC). After deprotection of the silyl ether **9** with *tetra*-butylammonium fluoride (TBAF), the secondary alcohol of the *syn*-1,3-azido alcohol **10** was tosylated to afford **11** in 81% yield. Treatment of this tosylate in a methanol/tetrahydrofuran solution with an acidic resin (Amberlyst 15) at room temperature installed the tetrahydrofuran ring present in jaspine B. Mechanistically, the one-pot, acid-catalyzed formation of tetrahydrofuran **12** likely involves an initial acid-catalyzed acetal solvolysis reaction within tosylate **11** to form the transient diol intermediate **13** (Scheme 3). A subsequent intramolecular nucleophilic displacement reaction of intermediate **13** then affords the tetrahydrofuran **12** and sets the appropriate relative and absolute stereochemistry. To complete

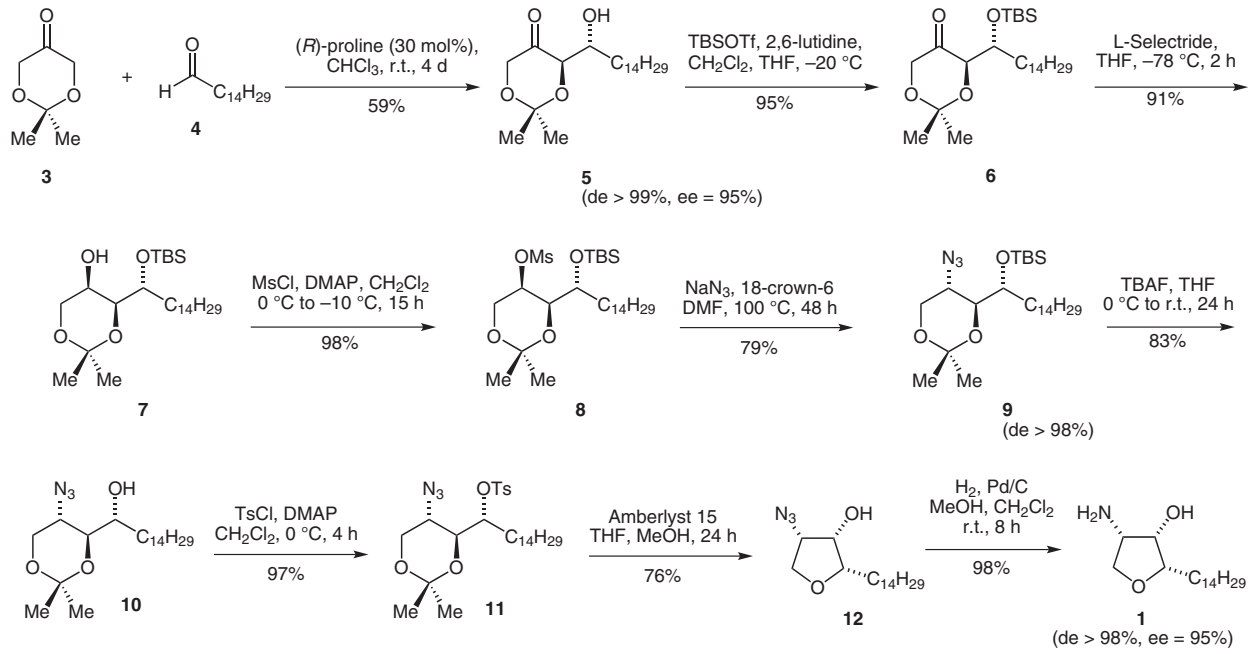


Scheme 3 Acid-catalyzed intramolecular cyclization

the synthesis, the azide group of the tetrahydrofuran **12** was subjected to a catalytic hydrogenation reaction, which afforded jaspine B (**1**) in 98% yield.

In summary, we have developed an efficient asymmetric synthesis of jaspine B (pachastrissamine, **1**) using an organocatalytic aldol reaction as a key step. The title compound was obtained in nine steps with a good overall yield (23.6%) starting from the readily available achiral precursors dioxanone **3** and 1-pentadecanal (**4**), in excellent diastereo- and enantiomeric excesses (de >98%, ee = 95%). This method allows access to both enantiomers of jaspine B depending on whether (*R*)- or (*S*)-proline is used as catalyst. Furthermore, the pro-chiral ketone function of **6** can be easily functionalized into epimeric amino groups.[18] In theory, this route allows access to various stereoisomers of jaspine B, which is the subject of current investigations in our laboratories.

All solvents were dried by conventional methods. Starting materials and reagents were purchased from commercial suppliers and used without further purification. THF was freshly distilled from Na–Pb alloy under argon. CH_2Cl_2 was freshly distilled from CaH under argon. Preparative column chromatography was performed using silica gel 60, particle size 0.040–0.063 mm (230–240 mesh, flash). Analytical TLC was carried out employing silica gel 60 F_{254} plates from Merck, Darmstadt. Visualization of the developed chromatograms was performed by staining with phosphomolybdic acid solution in EtOH. Optical rotation values were measured on a Perkin–



Scheme 2 Asymmetric synthesis of jaspine B (pachastrissamine; **1**)

Elmer P241 polarimeter. Microanalyses were obtained with a Vario EL element analyzer. Mass spectra were acquired on a Finnigan SSQ7000 spectrometer (CI 100 eV; EI 70 eV). HRMS data were recorded on a Finnigan MAT95 spectrometer. IR spectra were measured on a Perkin–Elmer FT-IR 1760 spectrophotometer. ^{1}H and ^{13}C NMR spectra were recorded on Varian Mercury 300, Gemini 300 or Inova 400 spectrometers with TMS as the internal standard. Analytical HPLC was performed on Hewlett–Packard 1100 Series chromatographs.

(*R*,*R*)-4-(1-Hydroxypentadecyl)-2,2-dimethyl-1,3-dioxan-5-one (5)

A suspension of the dioxanone **3** (1.00 g, 7.68 mmol) and 30 mol% (*R*)-proline (0.27 g, 2.3 mmol) in $CHCl_3$ (5 mL) was stirred for 30 min before aldehyde **4** (1.74 g, 7.7 mmol) was added in one portion. The resulting mixture was stirred at r.t. under argon for 4 d. The reaction mixture was quenched with sat. NH_4Cl (10 mL), extracted with Et_2O (3 × 20 mL) and the combined organic phases were dried over $MgSO_4$, concentrated and the crude product was purified by column chromatography (silica gel, CH_2Cl_2–Et_2O, 9:1) to give the aldol product **5**.

Yield: 1.62 g (59%); colourless oil; de >99% (NMR, GC, HPLC); ee = 95% (HPLC, Daicel IA, *n*-heptane–*i*-PrOH, 95: 5; major isomer 10.4 min, minor isomer 11.0 min); $[\alpha]_D^{22}$ +112.8 (*c* 1.1, $CHCl_3$).

IR ($CHCl_3$): 3540, 2925, 2855, 1741, 1463, 1378, 1223, 1092, 722 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.88 (t, *J* = 6.9 Hz, 3 H, CH_3), 1.28 (m, 26 H, 13 × CH_2), 1.44 (s, 3 H, CH_3), 1.48 (s, 3 H, CH_3), 2.97 (br s, 1 H, OH), 3.89 (m, 1 H, CH), 4.02 (d, *J* = 17.3 Hz, 1 H, CH_2), 4.09 (dd, *J* = 6.9, 1.4 Hz, 1 H, CH), 4.27 (dd, *J* = 17.3, 1.4 Hz, 1 H, CH_2).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.1 (CH_3), 22.7 (CH_2), 23.5 (CH_3), 23.9 (CH_3), 25.0 (CH_2), 29.4 (CH_2), 29.6 (3 × CH_2), 29.7 (2 × CH_2), 29.8 (3 × CH_2), 31.9 (CH_2), 32.3 (CH_2), 66.7 (CH_2), 70.6 (CH), 76.0 (CH), 100.9 (C), 211.2 (C=O).

MS (CI): *m*/*z* (%) = 340 (22) [M$^+$ – 16], 339 (100) [M$^+$ – 17], 338 (8).

Anal. Calcd for $C_{21}H_{40}O_4$: C, 70.74; H, 11.31. Found: C, 71.02; H, 11.36.

(*R*,*R*)-4-[1-(*tert*-Butyldimethylsilyloxy)pentadecyl]-2,2-dimethyl-1,3-dioxan-5-one (6)

To a solution of the aldol product **5** (1.50 g, 4.21 mmol) in CH_2Cl_2 (15 mL) at –20 °C was added sequentially, 2,6-lutidine (2.0 mL, 16.8 mmol) and TBSOTf (2.9 mL, 12.6 mmol) dropwise via syringe. After 2 h the reaction mixture was quenched with sat. $NaHCO_3$ solution (10 mL) and warmed to r.t. The aqueous phase was extracted with CH_2Cl_2 (3 × 30 mL) and the combined organic layers were dried over $MgSO_4$ and the solvent was removed under reduced pressure. Purification by flash chromatography (silica gel, *n*-pentane–CH_2Cl_2, 1:1) afforded the desired product **6**.

Yield: 1.88 g (95%); colourless oil; de >99% (NMR); $[\alpha]_D^{21}$ +88.5 (*c* 2.4, $CHCl_3$).

IR ($CHCl_3$): 2926, 2856, 1750, 1465, 1378, 1252, 1225, 1096, 838, 763 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.08 (s, 3 H, CH_3Si), 0.10 (s, 3 H, CH_3Si), 0.88 (t, *J* = 6.9 Hz, 3 H, CH_3), 0.89 [s, 9 H, $(CH_3)_3CSi$], 1.26 (m, 24 H, 12 × CH_2), 1.29 (m, 2 H, CH_2), 1.45 (s, 3 H, CH_3), 1.46 (s, 3 H, CH_3), 3.91 (d, *J* = 15.8 Hz, 1 H, CH_2), 4.07 (m, 1 H, CH), 4.20 (dd, *J* = 15.8, 1.5 Hz, 1 H, CH_2), 4.23 (m, 1 H, CH).

^{13}C NMR (100 MHz, $CDCl_3$): δ = –4.6 (CH_3), –4.4 (CH_3), 14.1 (CH_3), 18.1 (C), 22.7 (CH_2), 23.4 (CH_3), 24.5 (CH_3), 25.9 (CH_3), 26.0 (CH_2), 29.4 (CH_2), 29.6 (2 × CH_2), 29.65 (2 × CH_2), 29.7 (4 × CH_2), 32.0 (CH_2), 32.7 (CH_2), 67.3 (CH_2), 72.2 (CH), 78.5 (CH), 100.5 (C), 207.9 (C=O).

MS (CI): *m*/*z* (%) = 471 (2.1) [M$^+$ + 1], 470 (0.5) [M$^+$], 413 (10), 343 (7), 342 (27), 341 (100), 339 (7), 129 (18).

Anal. Calcd for $C_{27}H_{54}O_4Si$: C, 68.88; H, 11.56. Found: C, 68.88; H, 11.32.

(4*S*,5*R*)-4-[(*R*)-1-(*tert*-Butyldimethylsilyloxy)pentadecyl]-2,2-dimethyl-1,3-dioxan-5-ol (7)

To a solution of **6** (1.00 g, 2.12 mmol) in anhydrous THF (30 mL) was added, dropwise, a solution of L-Selectride in THF (1 M, 2.3 mL, 2.34 mmol) at –78 °C. After 2 h the reaction mixture was warmed to r.t. then quenched with aq NH_4Cl (20 mL) and extracted with Et_2O (3 × 30 mL). The combined organic layers were washed with brine (20 mL), dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by flash chromatography (silica gel, CH_2Cl_2–Et_2O, 9:1) to afford the alcohol **7**.

Yield: 0.91 g (91%); colourless oil; de >98% (NMR); $[\alpha]_D^{22}$ –7.9 (*c* 1.1, $CHCl_3$).

IR ($CHCl_3$): 3582, 3499, 2927, 2855, 1465, 1381, 1255, 1200, 1116, 1070, 836, 776 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.08 (s, 3 H, CH_3Si), 0.09 (s, 3 H, CH_3Si), 0.85 (t, *J* = 6.9 Hz, 3 H, CH_3), 0.92 [s, 9 H, $(CH_3)_3CSi$], 1.27 (m, 24 H, 12 × CH_2), 1.43 (s, 3 H, CH_3), 1.44 (s, 3 H, CH_3), 1.58 (m, 2 H, CH_2), 3.45 (br s, 1 H, OH), 3.65 (m, 2 H, 2 × CH), 3.85 (dd, *J* = 12.2, 1.7 Hz, 1 H, CH_2), 3.91 (m, 1 H, CH), 3.98 (dd, *J* = 12.2, 1.0 Hz, 1 H, CH_2).

^{13}C NMR (100 MHz, $CDCl_3$): δ = –4.7 (CH_3), –4.6 (CH_3), 14.1 (CH_3), 18.1 (C), 18.5 (CH_3), 22.7 (CH_2), 24.1 (CH_2), 25.2 (2 × CH_3), 29.4 (CH_2), 29.6 (3 × CH_2), 29.7 (4 × CH_2), 29.9 (CH_2), 32.1 (CH_2), 33.1 (CH_2), 63.3 (CH), 66.1 (CH_2), 72.2 (CH), 72.3 (CH), 98.7 (C).

MS (CI): *m*/*z* (%) = 473 (100) [M$^+$ + 1], 472 (2) [M$^+$], 471 (4) [M$^+$ – 1], 416 (13).

Anal. Calcd for $C_{27}H_{56}O_4Si$: C, 68.59; H, 11.94. Found: C, 68.45; H, 11.43.

(4*R*,5*R*)-4-[(*R*)-1-(*tert*-Butyldimethylsilyloxy)pentadecyl]-2,2-dimethyl-1,3-dioxan-5-yl Methanesulfonate (8)

To a stirred solution of **7** (0.90 g, 1.90 mmol) in CH_2Cl_2 (20 mL) was added DMAP (2.32 g, 19.0 mmol) at 0 °C. After 10 min the reaction mixture was cooled to –10 °C and methanesulfonyl chloride (1.09 g, 9.50 mmol) was added dropwise. After 4 h the reaction mixture was warmed to r.t. and stirred for an additional 11 h then poured into H_2O (18 mL) and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were washed with brine (15 mL) and dried over $MgSO_4$. Evaporation of the solvent followed by column chromatography (silica gel, *n*-pentane–Et_2O, 3:1) of the crude product afforded **8**.

Yield: 1.03 g (98%); colourless oil; de >98% (NMR); $[\alpha]_D^{23}$ –26.4 (*c* 1.25, $CHCl_3$).

IR ($CHCl_3$): 2927, 2856, 1465, 1357, 1258, 1176, 1119, 962, 906, 836, 778, 528 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.10 (s, 3 H, CH_3Si), 0.14 (s, 3 H, CH_3Si), 0.88 (t, *J* = 6.9 Hz, 3 H, CH_3), 0.90 [s, 9 H, $(CH_3)_3CSi$], 1.26 (m, 24 H, 12 × CH_2), 1.43 (s, 3 H, CH_3), 1.46 (s, 3 H, CH_3), 1.64 (m, 2 H, CH_2), 3.13 (s, 3 H, OSO_2CH_3), 3.77 (dd, *J* = 1.0, 8.7 Hz, 1 H, CH), 3.97 (m, 1 H, CH), 4.00 (dd, *J* = 13.9, 1.0 Hz, 1 H, CH_2), 4.37 (dd, *J* = 13.9, 1.8 Hz, 1 H, CH_2), 4.64 (m, 1 H, CH).

^{13}C NMR (100 MHz, $CDCl_3$): δ = –4.8 (CH_3), –4.2 (CH_3), 14.1 (CH_3), 18.1 (C), 18.5 (CH_3), 21.7 (CH_2), 22.7 (CH_2), 26.0 (CH_3), 29.2 (CH_3), 29.4 (CH_2), 29.5 (CH_2), 29.6 (CH_2), 29.7 (CH_2), 29.8

(4 × CH_2), 29.9 (CH_2), 31.9 (CH_2), 32.0 (CH_2), 40.2 (OSO_2CH_3), 62.3 (CH_2), 68.7 (CH), 72.0 (CH), 72.9 (CH), 99.1 (C).

MS (CI): *m/z* (%) = 551 (100) [M^+ + 1], 493 (25), 419 (21), 341 (19).

Anal. Calcd for $C_{28}H_{58}O_6SSi$: C, 61.05; H, 10.61. Found: C, 60.76; H, 10.69.

(*R*)-1-[(4*S*,5*S*)-5-Azido-2,2-dimethyl-1,3-dioxan-4-yl)pentadecyloxy]-*tert*-butyldimethylsilane (9)

To a solution of **8** (1.00 g, 1.81 mmol) in DMF (20 mL) were added 18-crown-6 (0.95 g, 3.62 mmol) and NaN_3 (1.17 g, 18.1 mmol). The reaction mixture was heated to 100 °C and stirred under argon for 48 h then DMF was distilled off and the crude residue was dissolved in H_2O–Et_2O (1:1, 70 mL). The aqueous phase was extracted with Et_2O (3 × 25 mL) and the combined organic layers were dried over $MgSO_4$. Evaporation of the solvent followed by column chromatography (silica gel, *n*-pentane–Et_2O, 9:1) of the crude residue afforded **9**.

Yield: 0.71 g (79%); colourless oil; de >98% (NMR); $[\alpha]_D^{23}$ +24.9 (*c* 1.0, $CHCl_3$).

IR ($CHCl_3$): 2927, 2856, 2109, 1465, 1380, 1258, 1224, 1100, 1029, 836, 777 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 0.08 (s, 3 H, CH_3Si), 0.10 (s, 3 H, CH_3Si), 0.88 (t, *J* = 6.9 Hz, 3 H, CH_3), 0.92 [s, 9 H, $(CH_3)_3CSi$], 1.26 (m, 24 H, 12 × CH_2), 1.35 (s, 3 H, CH_3), 1.40 (s, 3 H, CH_3), 1.58 (m, 2 H, CH_2), 3.57 (d, *J* = 7.2 Hz, 1 H, CH), 3.68 (dd, *J* = 14.1, 6.9 Hz, 1 H, CH_2), 3.73 (m, 2 H, 2 × CH), 3.92 (dd, *J* = 14.5, 7.9 Hz, 1 H, CH_2).

^{13}C NMR (100 MHz, $CDCl_3$): δ = –4.9 (CH_3), –4.1 (CH_3), 14.0 (CH_3), 18.1 (C), 20.3 (CH_3), 22.6 (CH_2), 25.8 (CH_3), 26.1 (CH_2), 27.15 (CH_3), 29.2 (CH_2), 29.4 (3 × CH_2), 29.5 (2 × CH_2), 29.55 (3 × CH_2), 31.8 (CH_2), 33.9 (CH_2), 55.1 (CH), 62.4 (CH_2), 73.9 (CH), 74.4 (CH), 99.3 (C).

MS (ESI): *m/z* (%) = 471 (33) [M^+ – 26], 470 (100) [M^+ – 27].

Anal. Calcd for $C_{27}H_{55}N_3O_3Si$: C, 65.14; H, 11.14; N, 8.44. Found: C, 64.90; H, 10.96; N, 8.74.

(*R*)-1-[(4*S*,5*S*)-5-Azido-2,2-dimethyl-1,3-dioxan-4-yl]pentadecan-1-ol (10)

To a solution of **9** (0.70 g, 1.41 mmol) in THF (30 mL) was added TBAF (1 M in THF, 2.8 mL, 2.80 mmol) at 0 °C. The reaction was stirred at r.t. for 24 h then the solvent was removed under reduced pressure followed by filtration through a short pad of silica gel using Et_2O (20 mL) as eluent to give **10**.

Yield: 0.45 g (83%); colourless oil; de >98% (NMR); $[\alpha]_D^{21}$ +22.7 (*c* 1.9, $CHCl_3$).

IR (film): 3531, 2925, 2856, 2106, 1461, 1377, 1265, 1220, 1163, 1098, 866, 771 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 0.88 (t, *J* = 6.9 Hz, 3 H, aliph. CH_3), 1.26 (m, 24 H, 12 × CH_2), 1.37 (s, 3 H, CH_3), 1.43 (s, 3 H, CH_3), 1.53 (m, 2 H, CH_2), 2.22 (d, *J* = 4.4 Hz, 1 H, OH), 3.62 (m, 1 H, CH), 3.72 (m, 1 H, CH), 3.75 (m, 1 H, CH_2), 3.95 (t, *J* = 2.4 Hz, 1 H, CH), 3.97 (dd, *J* = 11.8, 4.4 Hz, 1 H, CH_2).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.1 (CH_3), 20.4 (CH_3), 22.7 (CH_2), 25.6 (CH_3), 25.9 (CH_2), 27.4 (CH_3), 29.35, 29.4, 29.57, 29.59, 29.6, 29.7 (6 × CH_2), 31.6 (CH_2), 31.9 (CH_2), 55.1 (CH), 62.3 (CH_2), 72.3 (CH), 74.1 (CH), 99.3 (C).

MS (EI): *m/z* (%) = 368 (17) [M^+ – 15], 156 (7), 114 (8), 99 (9), 84 (47), 72 (24), 71 (22), 69 (79), 59 (100), 57 (31).

HRMS: *m/z* [$C_{21}H_{41}N_3O_3$ – CH_3] calcd for: 368.2913; found: 368.2915.

(*R*)-1-[(4*S*,5*S*)-5-Azido-2,2-dimethyl-1,3-dioxan-4-yl]pentadecyl *p*-Toluenesulfonate (11)

To a solution of **10** (0.20 g, 0.52 mmol) in CH_2Cl_2 (5 mL) was added DMAP (127 mg, 1.04 mmol) and *p*-toluenesulfonyl chloride (148 mg, 0.78 mmol) at 0 °C. The reaction was stirred at r.t. for 4 h then quenched with H_2O (5 mL), extracted with CH_2Cl_2 (3 × 10 mL) and dried over $MgSO_4$. Evaporation of the solvent gave the crude product, which was purified by flash chromatography (silica gel, CH_2Cl_2–Et_2O, 9:1) to give **11**.

Yield: 0.27 g (97%); de >98% (NMR); $[\alpha]_D^{22}$ +30.0 (*c* 2.4, $CHCl_3$).

IR (film): 2925, 2856, 2106, 1598, 1461, 1370, 1269, 1180, 1099, 920, 814, 766, 672, 557 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 0.88 (t, *J* = 6.8 Hz, 3 H, CH_3-18), 1.26 (m, 24 H, 12 × CH_2), 1.32 (s, 6 H, 2 × CH_3), 1.55 (m, 1 H, CH_2-5a), 1.78 (m, 1 H, CH_2-5b), 2.44 (s, 3 H, Ar-CH_3), 3.37 (m, 1 H, CH-2), 3.69 (dd, *J* = 11.8, 7.8 Hz, 1 H, CH_2-1a), 3.80 (dd, *J* = 9.4, 2.5 Hz, 1 H, CH-3), 3.92 (dd, *J* = 11.6, 5.2 Hz, 1 H, CH_2-1b), 4.67 (m, 1 H, TsOC*H*), 7.34 (d, *J* = 8.0 Hz, 2 H, ArH), 7.81 (d, *J* = 8.2 Hz, 2 H, ArH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.1 (CH_3), 19.7 (Ar-*C*H_3), 21.6 (CH_3), 22.7 (CH_2), 25.1 (CH_2), 27.4 (CH_3), 29.2, 29.4, 29.5, 29.6, 29.69, 29.7 (9 × CH_2), 31.9 (2 × CH_2), 55.1 (CH), 62.1 (CH_2), 72.6 (CH), 82.6 (CH), 99.6 (C), 128.0 (CH_{Ar}), 129.7 (CH_{Ar}), 134.4 (C_{Ar}), 144.7 ($C_{Ar}CH_3$).

MS (EI): *m/z* (%) = 522 (23) [M^+ – 15], 239 (11), 173 (29), 156 (28), 155 (100), 137 (13), 123 (23), 109 (38), 98 (52), 97 (40), 95 (60), 91 (86), 84 (64), 72 (41), 69 (57), 57 (62).

HRMS: *m/z* calcd for [$C_{28}H_{47}N_3O_5S$ – CH_3]: 522.3001; found: 522.3002.

(2*S*,3*S*,4*S*)-4-Azido-2-tetradecyltetrahydrofuran-3-ol (12)

To a solution of **11** (0.16 g, 0.30 mmol) in THF (2 mL) and MeOH (2 mL) was added Amberlyst 15 (0.15 g) and the mixture was stirred for 24 h. After filtration of the resin, the solvent was removed under reduced pressure. Purification by flash chromatography (silica gel, CH_2Cl_2–Et_2O, 9:1) afforded the desired product **12**.

Yield: 74 mg (76%); colourless solid; de >98% (NMR); $[\alpha]_D^{23}$ +15.9 (*c* 1.1, $CHCl_3$) {Lit.[17] $[\alpha]_D$ +16.7 (*c* 1.0, $CHCl_3$), Lit.[10] $[\alpha]_D$ +17 (*c* 1.0, $CHCl_3$)}.

IR ($CHCl_3$): 3332, 2920, 2852, 2106, 1467, 1340, 1261, 1121, 759 cm^{-1}.

^1H NMR ($CDCl_3$, 400 MHz,): δ = 0.88 (t, *J* = 6.9 Hz, 3 H, CH_3), 1.25–1.44 (m, 24 H, 12 × CH_2), 1.64 (m, 2 H, CH_2-5), 2.04 (d, *J* = 5.2 Hz, 1 H, OH), 3.76 (ddd, *J* = 3.6, 6.9, 6.9 Hz, 1 H, H-4), 3.85 (dd, *J* = 6.6, 9.1 Hz, 1 H, H-1a), 3.98 (dd, *J* = 7.4, 9.1 Hz, 1 H, H-1b), 4.11 (ddd, *J* = 4.9, 6.6, 7.1 Hz, 1 H, H-2), 4.21 (dd, *J* = 4.4, 4.7 Hz, 1 H, H-3).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.1 (CH_3), 22.7, 26.0, 28.8, 29.3, 29.49, 29.53, 29.61, 29.64 (CH_2, C6-17), 31.9 (CH_2, C-5), 63.6 (CH, C-2), 68.3 (CH_2, C-1), 72.4 (CH, C-3), 82.0 (CH, C-4).

MS (EI): *m/z* (%) = 268 (7) [M^+ – 57], 250 (5), 97 (11), 85 (8), 83 (14), 72 (16), 71 (100), 69 (29), 57 (66), 55 (28).

Anal. Calcd for $C_{18}H_{35}N_3O_2$: C, 66.42; H, 10.84; N, 12.91. Found: C, 66.56; H, 11.03; N, 12.89.

Jaspine B (Pachastrissamine; 1)

To a solution of **12** (158 mg, 0.48 mmol) in MeOH (5 mL) and CH_2Cl_2 (6 mL) were added 5% Pd/C (158 mg). The reaction mixture was stirred for 8 h under an H_2 atmosphere at r.t. then filtered through a short pad of Celite and washed with CH_2Cl_2–MeOH (1:1, 20 mL). Evaporation of the solvent followed by flash chromatography (silica gel, CH_2Cl_2–MeOH, 9:1, including 1% NH_4OH), afforded the title compound **1**.

Yield: 144 mg (98%); de >98% (NMR); ee = 95%; $[\alpha]_D^{23}$ +20.2 (*c* 0.55, MeOH) {Lit.[1] $[\alpha]_D$ +18 (*c* 0.1, EtOH), Lit.[10] $[\alpha]_D$ +17.5 (*c* 0.4, EtOH), Lit.[15] $[\alpha]_D^{23}$ +17.5 (*c* 0.3, EtOH)}.

IR (KBr): 3343, 3284, 2923, 2852, 2742, 1584, 1471, 1383, 1037, 719 cm^{-1}.

^1H NMR ($CDCl_3$, 300 MHz): δ = 0.88 (t, *J* = 6.8 Hz, 3 H, CH_3), 1.25 (m, 24 H, 12 × CH_2), 1.65 (m, 2 H, CH_2-5), 2.08 (br s, 3 H, NH_2, OH), 3.51 (dd, *J* = 8.4, 6.7 Hz, 1 H, H-1a), 3.61–3.68 (br m, 1 H, H-2), 3.74 (ddd, *J* = 3.7, 6.9, 6.9 Hz, 1 H, H-4), 3.85–3.96 (m, 2 H, H-3, H-1b).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.1 (CH_3), 22.7, 26.3, 29.3, 29.4, 29.6, 29.7, 29.8 (CH_2, C6-17), 31.9 (CH_2, C-5), 54.4 (CH, C-2), 71.8 (CH, C-3), 72.4 (CH_2, C-1), 83.2 (CH, C-4).

MS (EI): *m*/*z* (%) = 299 (5) [M^+], 252 (2), 226 (4), 83 (4), 71 (6), 60 (100), 59 (46), 57 (9).

HRMS: *m*/*z* calcd for $C_{18}H_{37}NO_2$: 299.2824; found: 299.2826.

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References

(1) Kuroda, I.; Musman, M.; Ohtani, I. I.; Ichiba, T.; Tanaka, J.; Garcia-Gravalos, D.; Higa, T. *J. Nat. Prod.* **2002**, *65*, 1505.
(2) Ledroit, V.; Debitus, C.; Lavaud, C.; Massiot, G. *Tetrahedron Lett.* **2003**, *44*, 225.
(3) Bhaket, P.; Morris, K.; Stauffer, C. S.; Datta, A. *Org. Lett.* **2005**, *7*, 875.
(4) Sudhakar, N.; Ravi Kumar, A.; Prabhakar, A.; Jagadeesh, B.; Venkateswara Rao, B. *Tetrahedron Lett.* **2005**, *46*, 325.
(5) Passiniemi, M.; Koskinen, A. M. P. *Tetrahedron Lett.* **2008**, *49*, 980.
(6) (a) Du, Y.; Liu, J.; Linhardt, R. J. *J. Org. Chem.* **2006**, *71*, 1251. (b) Liu, J.; Du, Y.; Dong, X.; Meng, S.; Xiao, J.; Cheng, L. *Carbohydr. Res.* **2006**, *341*, 2653.
(7) Chandrasekhar, S.; Tiwari, B.; Prakash, S. J. *ARKIVOC* **2006**, *(xi)*, 155.
(8) Ramana, C. V.; Giri, A. G.; Suryawanshi, S. B.; Gonnade, R. G. *Tetrahedron Lett.* **2007**, *48*, 265.
(9) Reddy, L. V. R.; Reddy, P. V.; Shaw, A. K. *Tetrahedron: Asymmetry* **2007**, *18*, 542.
(10) Prasad, K. R.; Chandrakumar, A. *J. Org. Chem.* **2007**, *72*, 6312.
(11) Ribes, C.; Falomir, E.; Carda, M.; Marco, J. A. *Tetrahedron* **2006**, *62*, 5421.
(12) Génisson, Y.; Lamandé, L.; Salma, Y.; Andrieu-Abadie, N.; André, C.; Baltas, M. *Tetrahedron: Asymmetry* **2007**, *18*, 857.
(13) Yakura, T.; Sato, S.; Yoshimoto, Y. *Chem. Pharm. Bull.* **2007**, *55*, 1284.
(14) Venkatesan, K.; Srinivasan, K. V. *Tetrahedron: Asymmetry* **2008**, *19*, 209.
(15) Abraham, E.; Candela-Lena, J. I.; Davies, S. G.; Georgiou, M.; Nicholson, R. L.; Roberts, P. M.; Russell, A. J.; Sánchez-Fernández, E. M.; Smith, A. D.; Thomson, J. E. *Tetrahedron: Asymmetry* **2007**, *18*, 2510.
(16) van den Berg, R. J. B. H. N.; Boltje, T. J.; Verhagen, C. P.; Litjens, R. E. J. N.; van der Marel, G. A.; Overkleeft, H. S. *J. Org. Chem.* **2006**, *71*, 836.
(17) Lee, T.; Lee, S.; Kwak, Y. S.; Kim, D.; Kim, S. *Org. Lett.* **2007**, *9*, 429.
(18) Enders, D.; Paleček, J.; Grondal, C. *Chem. Commun.* **2006**, 655.
(19) 2,2-Dimethyl-1,3-dioxan-5-one was prepared in two steps from tris(hydroxymethyl)aminomethane hydrochloride, see: (a) For a review: Enders, D.; Voith, M.; Lenzen, A. *Angew. Chem. Int. Ed.* **2005**, *44*, 1304; *Angew. Chem.* **2005**, *117*, 1330. (b) Enders, D.; Voith, M.; Ince, S. J. *Synthesis* **2002**, 1775. (c) Enders, D.; Whitehouse, D. L.; Runsink, J. *Chem. Eur. J.* **1995**, *1*, 382.
(20) (a) Enders, D.; Grondal, C. *Angew. Chem. Int. Ed.* **2005**, *44*, 1210; *Angew. Chem.* **2005**, *117*, 1235. (b) Enders, D.; Grondal, C.; Vrettou, M.; Raabe, G. *Angew. Chem. Int. Ed.* **2005**, *44*, 4079; *Angew. Chem.* **2005**, *117*, 4147. (c) Grondal, C.; Enders, D. *Tetrahedron* **2006**, *62*, 329.. (d) Enders, D.; Vrettou, M. *Synthesis* **2006**, 2155. (e) Enders, D.; Grondal, C.; Vrettou, M. *Synthesis* **2006**, 3597. (f) Grondal, C.; Enders, D. *Synlett* **2006**, 3507. (g) Grondal, C.; Enders, D. *Adv. Synth. Catal.* **2007**, *349*, 694. For related publications, see: (h) Westermann, B.; Neuhaus, C. *Angew. Chem. Int. Ed.* **2005**, *44*, 4077; *Angew. Chem.* **2005**, *117*, 4145. (i) Suri, J. T.; Ramachary, D. B.; Barbas, C. F. III *Org. Lett.* **2005**, *7*, 1383. (j) Suri, J. T.; Mitsumori, S.; Albertshofer, K.; Tanaka, F.; Barbas, C. F. III *J. Org. Chem.* **2006**, *71*, 3822. (k) Ibrahem, I.; Córdova, A. *Tetrahedron Lett.* **2005**, *46*, 3363. (l) Ibrahem, I.; Zou, W.; Casas, J.; Sundén, H.; Córdova, A. *Tetrahedron* **2006**, *62*, 357. (m) Ibrahem, I.; Zou, W.; Xu, Y.; Córdova, A. *Adv. Synth. Catal.* **2006**, *348*, 211. (n) Majewski, M.; Niewczas, I.; Palyam, N. *Synlett* **2006**, 2387.