

Published in final edited form as:

J Org Chem. 2006 February 3; 71(3): 1251–1253. doi:10.1021/jo051644y.

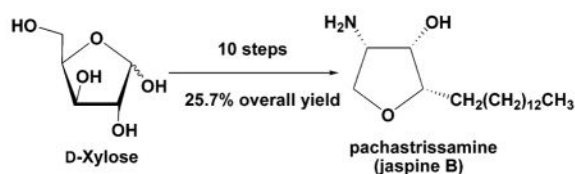
Stereoselective Synthesis of Cytotoxic Anhydrophytosphingosine Pachastrissamine (Jaspine B) from D-Xylose

 Yuguo Du[†], Jun Liu[†], and Robert J. Linhardt[‡]

State Key Laboratory of Environmental Chemistry and Ecotoxicology, Research Center for Eco-Environmental Sciences, Chinese Academy of Sciences, Beijing 100085, China, and Departments of Chemistry, Biology, and Chemical and Biological Engineering, Rensselaer Polytechnic Institute, Troy, New York 12180

Yuguo Du: duyuguo@mail.rcees.ac.cn

Abstract



The first naturally occurring anhydrophytosphingosine, pachastrissamine (jaspine B), a marine compound cytotoxic toward P388, A549, HT29, and MEL28 cell lines at $IC_{50} = 0.01 \mu\text{g/mL}$ level, has been stereoselectively synthesized from D-xylose in 10 linear steps with 25.7% overall yield.

Pachastrissamine (**1**, Figure 1) is a natural occurring anhydrophytosphingosine derivative, first isolated in 2002 by Higa and co-workers¹ from the Okinawa marine sponge *Pachastrissa* sp. (family Calthropellidae). Bioassay-guided separation of the sponge crude oil led to pure **1**, which exhibited a significant cytotoxicity of $0.01 \mu\text{g/mL}$ against P388, A549, HT29, and MEL28 cell lines. Almost at the same time, Debitus and coworkers² investigated the cytotoxicity of ethanolic extract ($IC_{95} = 10 \mu\text{g/mL}$, KB cell line) from a new species of *Jaspis*, a marine sponge collected in Vanuatu, and the bioguided fractionation of this extract using a brine shrimp bioassay led to two cytotoxic compounds, named as jaspine A (**2**, Figure 1) and jaspine B (**1**, Figure 1). Jaspine B hydrochloride displayed remarkable bioactivity ($IC_{50} = 0.24 \mu\text{M}$) against the A549 human lung carcinoma cell line using the ATPlite assay and represented the most potent anticancer agent on this cell line yet isolated from the *Jaspis* genus. High-resolution NMR, mass spectral analysis, and chemical

© 2006 American Chemical Society

Correspondence to: Yuguo Du, duyuguo@mail.rcees.ac.cn; Robert J. Linhardt.

[†]Chinese Academy of Sciences.

[‡]Rensselaer Polytechnic Institute.

 Supporting Information Available: Detailed experimental procedures and spectral data for compounds **1**, **7–9**, and **11–16**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

derivatization studies suggested that the structure of pachastrissamine and jaspine B were identical, i.e., an all-syn trisubstituted tetrahydrofuran framework and the (2*S*,3*S*,4*S*) absolute configuration.

It has been reported that sphingosine 1-phosphate induces a rapid and relevant release of arachidonic acid and increases phospholipase D activity in A549 cells.³ To improve our understanding of this anhydrosphingosine targeting to tumor cells and explore more potent analogues based on this novel structure, we launched a stereoselective total synthesis of natural pachastrissamine (jaspine B). During our efforts, two synthetic communications^{4,5} aimed to the total synthesis of pachastrissamine (jaspine B) using L-serine as starting material were published. In Rao's work,⁴ a diastereoisomeric mixture of **1** was formed, using a standard asymmetric synthesis, in 10 steps and 15.4% overall yield. In Datta's letter,⁵ enantiopure **1** was prepared through a bicyclic lactone intermediate in 14 steps and 15.5% overall yield from L-serine. Here, we report the stereoselective total synthesis of pachastrissamine (jaspine B).

Pachastrissamine **1** can be retrosynthetically disconnected into a formylfuran derivative **3** and a commercially available alkyl Wittig reagent. The furan structure of **3** can be derived from 2,5-ring closure of an acyclic intermediate **4**, which can be easily prepared from natural D-xylose through suitable functional group transformations (Scheme 1).

D-Xylose treated with concentrated H₂SO₄ in acetone⁶ gave 1,2-acetal **5** in 82% yield (Scheme 2). Regioselective tosylation of **5** on the primary alcohol with tosylimidazole, MeOTf, and *N*-methylimidazole in THF at 0 °C afforded **6** in excellent yield.⁷ Benzoylation of **6** (→ **7**), followed by acid-catalyzed furan ring reconstruction in ethanol under reflux conditions, afforded the key intermediate, 2,5-anhydro-3-*O*-benzoylxylose diethylacetal (**8**), in 81% yield over three steps. The structure of **8** was confirmed by FABMS [*m/z* 311 (M + H)⁺] and its ¹H-¹H COSY spectrum (chemical shift of H-1 moved upfield from 5.85 to 4.76 ppm). Derivatization of **8** with acetic anhydride in pyridine resulted in the downfield movement of the peak corresponding to H-4 (δ: 4.33 ppm → 5.22 ppm) in the ¹H NMR spectrum, further confirming the structure of **8** (see the Supporting Information). To obtain the *S*-configuration required for the 4-amino group, the 4-OH of **8** was mesylated with methanesulfonyl chloride in pyridine (→ **9**), followed by an S_N2 substitution using NaN₃ in DMF. Unfortunately, extensive efforts failed to produce a good yield of desired compound **10**, affording instead a rather complex mixture based on NMR analysis. A literature survey suggested that the 3,4-acyloxonium ion might be formed in our experiments leading to an inseparable mixture of 3*R*-, 4*R*-, and 4*S*-azido-displaced products.⁸

A high yield of C-4 azido-displacement can be accomplished by protecting the hydroxyl group at C-3 through alkylation (Scheme 3) as in **11**, instead of through acylation (Scheme 2) as in **9**. The xylose derivative **6** was benzylated with benzyl trichloroacetimidate in the presence of TMSOTf (→ **11**).⁹ Acid-catalyzed furan ring reconstruction afforded 2,5-anhydro compound **12** in a yield of 89%. Mesylation (→ **13**) and azido substitution using sodium azide afforded the key enantiopure acetal **14** in 71% isolated yield over two steps. The acetal protection of **14** was removed with aqueous trifluoroacetic acid to afford aldehyde **15**.¹⁰ Standard Wittig olefination of **15** with a C-13 alkyl donor resulted in the incorporation

of an inseparable mixture of *E*- and *Z*-isomers of the corresponding C-14 olefinic side chain. The *Z/E* ratio was determined to be greater than 10:1 on the basis of ^1H NMR but both could be further reduced to the desired alkyl side chain (Scheme 3). In a single step, hydrogenation of azido, benzyl, and the side chain double bond furnished target molecule **1** in an excellent yield of 92%.

In conclusion, the stereoselective total synthesis of a structurally unique bioactive anhydrosphingosine natural product has been achieved in 10 linear steps and 25.7% overall yield from an inexpensive natural product, D-xylose. This synthesis took advantage of D-xylose, a carbohydrate having a chiral template that could be modified through an acid-catalyzed 2,5-cyclization and C-3 azido-substitution to fit the required (2*S*,3*S*,4*S*) configuration of the pachastrissamine target. As exemplified in this study, carbohydrate moieties provide versatile synthons in asymmetric synthesis of natural products.¹¹ The present study should provide a valuable strategy for the preparation of other functionalized tetrahydrofuran derivatives, acyclic sphingosine analogues, carbasugars, and heterocyclic enzyme inhibitors.^{2,12}

Experimental Section

3-O-Benzyl-1,2-O-isopropylidene-5-O-*p*-toluenesulfonyl- α -D-xylofuranose (**11**)

To a solution of compound **6** (104 mg, 0.3 mmol) and benzyl trichloroacetimidate (142 mg, 0.6 mmol) in dry CH_2Cl_2 (2 mL) at -40°C was added TMSOTf (1.1 μL , 0.003 mmol) under N_2 protection. The reaction was monitored by TLC (2:1 EtOAc–petroleum ether) until all starting material was consumed and then quenched with Et_3N and concentrated to dryness. The residue was subjected to silica gel column chromatography (3:1 petroleum ether–EtOAc) to give **11** (97 mg, 75%) as a syrup: $[\alpha]_{\text{D}}^{25} - 21$ (*c* 1.0, CHCl_3); ^1H NMR (400 MHz, CDCl_3) δ 1.25, 1.43 (2s, 2 \times 3H), 2.41 (s, 3H), 3.95 (d, 1H, *J* = 3.3 Hz), 4.18 (dd, 1H, *J* = 6.1, 9.9 Hz), 4.30 (dd, 1H, *J* = 6.1, 9.9 Hz), 4.35 (dt, 1H, *J* = 3.3, 6.1 Hz), 4.45 (d, 1H, *J* = 11.8 Hz), 4.56 (d, 1H, *J* = 3.7 Hz), 4.60 (d, 1H, *J* = 11.8 Hz), 5.85 (d, 1H, *J* = 3.7 Hz), 7.23–7.25 (m, 2H), 7.28–7.35 (m, 5H), 7.76–7.78 (m, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 21.4, 26.1, 26.6, 66.9, 71.8, 77.4, 81.0, 81.8, 105.0, 111.9, 127.5, 127.8, 127.9, 128.3, 129.7, 132.5, 136.9, 144.8. Anal. Calcd for $\text{C}_{22}\text{H}_{26}\text{O}_7\text{S}$: C, 60.81; H, 6.03. Found: C, 61.09; H, 5.97.

2,5-Anhydro-3-O-benzyl- α -D-xylose Diethyl Acetal (**12**)

Compound **11** (217 mg, 0.5 mmol) was dissolved in anhydrous ethanol (10 mL) containing concentrated hydrochloric acid (0.5 mL). The mixture was stirred under reflux for 3 h and then neutralized with saturated aqueous sodium carbonate. The aqueous layer was extracted with EtOAc (3 \times 20 mL), and the combined organic phase was washed with brine, dried over Na_2SO_4 , and concentrated under vacuum. Purification of the residue by silica gel column chromatography (1:1 petroleum ether–EtOAc) gave **12** as a syrup (131 mg, 89%): $[\alpha]_{\text{D}}^{25} + 77$ (*c* 0.7, CHCl_3); ^1H NMR (400 MHz, CDCl_3) δ 1.18 (t, 3H, *J* = 7.0 Hz), 1.24 (t, 3H, *J* = 7.0 Hz), 1.67 (br s, 1H), 3.50–3.55 (m, 1H), 3.67–3.80 (m, 4H), 3.94 (d, 1H, *J* = 3.6 Hz), 4.12 (dd, 1H, *J* = 3.7, 7.7 Hz), 4.20 (dd, 1H, *J* = 4.0, 9.9 Hz), 4.33 (br d, 1H, *J* = 3.9 Hz), 4.60, 4.62 (2d, 2H, *J* = 11.8 Hz), 4.76 (d, 1H, *J* = 7.7 Hz), 7.26–7.37 (m, 5H); ^{13}C

NMR (100 MHz, CDCl₃) δ 15.2, 15.3, 61.5, 63.0, 72.2, 74.2, 74.4, 79.7, 84.2, 100.5, 127.4, 127.6, 128.3, 137.9. Anal. Calcd for C₁₆H₂₄O₅: C, 64.84; H, 8.16. Found: C, 65.09; H, 8.11.

2,5-Anhydro-3-O-benzyl-4-O-methanesulfonyl- α -D-xylose Diethyl Acetal (**13**)

To a solution of **12** (70 mg, 0.24 mmol) in pyridine (2 mL) was added methanesulfonyl chloride (37 μ L, 0.48 mmol). The mixture was stirred at room temperature for 4 h and then coevaporated with toluene. The crude mesylate **13** was directly used in the next step without further purification. A small sample was purified on a silica gel column to get the physical data of **13**: $[\alpha]_D^{25} + 80$ (c 1.0, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 1.16 (t, 3H, *J* = 7.0 Hz), 1.25 (t, 3H, *J* = 7.0 Hz), 2.97 (s, 3H), 3.46–3.52 (m, 1H), 3.67–3.79 (m, 3H), 3.98 (d, 1H, *J* = 11.0 Hz), 4.05 (dd, 1H, *J* = 3.7, 7.6 Hz), 4.25 (d, 1H, *J* = 3.6 Hz), 4.30 (dd, 1H, *J* = 4.4, 11.0 Hz), 4.62, 4.68 (d, 2H, *J* = 11.8 Hz), 4.75 (d, 1H, *J* = 7.6 Hz), 5.12 (d, 1H, *J* = 4.3 Hz), 7.31–7.38 (m, 5H); ¹³C NMR (100 MHz, CDCl₃) δ 15.1, 15.2, 38.3, 61.5, 63.0, 71.4, 72.5, 79.9, 81.1, 81.8, 100.0, 127.7, 127.9, 128.3, 137.1. Anal. Calcd for C₁₇H₂₆O₇S: C, 54.53; H, 7.00. Found: C, 54.76; H, 6.91.

2,5-Anhydro-4-azido-3-O-benzyl-4-deoxy- α -L-arabinose Diethyl Acetal (**14**)

To a solution of crude mesylate **13** (88 mg, 0.23 mmol) in dry DMF (3 mL) were added NaN₃ (91 mg, 1.41 mmol) and anhydrous NH₄Cl (23 mg, 0.44 mmol). The mixture was heated to 120 °C and stirred at these conditions for about 20 h in a dark room. The reaction was monitored by TLC (3:1 petroleum ether–EtOAc) until all starting material disappeared, and then the mixture was diluted with water and extracted with EtOAc (4 \times 10 mL). The organic phase was dried over anhydrous Na₂SO₄ and concentrated. Purification of the residue by silica gel column chromatography (3:1 petroleum ether–EtOAc) gave **14** (54 mg, 71% for two steps) as a syrup: $[\alpha]_D^{25} + 106$ (c 1.3, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 1.18 (t, 3H, *J* = 7.0 Hz), 1.24 (t, 3H, *J* = 7.0 Hz), 3.41–3.45 (m, 1H), 3.66–3.77 (m, 3H), 3.83 (dd, 1H, *J* = 4.5, 7.8 Hz), 3.90 (dd, 1H, *J* = 4.0, 7.7 Hz), 3.98 (dd, 1H, *J* = 7.7, 8.5 Hz), 4.04 (dd, 1H, *J* = 4.3, 8.5 Hz), 4.19 (t, 1H, *J* = 4.3 Hz), 4.66 (d, 1H, *J* = 11.2 Hz), 4.76 (d, 1H, *J* = 7.7 Hz), 4.82 (d, 1H, *J* = 11.2 Hz), 7.31–7.41 (m, 5H); ¹³C NMR (100 MHz, CDCl₃) δ 15.2, 15.3, 61.4, 62.0, 62.8, 68.4, 74.2, 79.7, 80.7, 100.4, 127.6, 127.7, 128.2, 137.6. HRFABMS calcd for C₁₆H₂₃N₃O₄ 321.1689, found 322.1660 (M + H)⁺. Anal. Calcd for C₁₆H₂₃N₃O₄: C, 59.80; H, 7.21. Found: C, 59.57; H, 7.29.

2,5-Anhydro-4-azido-3-O-benzyl-4-deoxy- α -L-arabinose (**15**)

The acetal **14** (310 mg, 0.96 mmol) was dissolved in CH₂Cl₂ (3 mL), and aqueous 50% trifluoroacetic acid (1 mL) was added. The reaction progress was monitored by TLC (2:1 petroleum ether–EtOAc) until all **14** was consumed, the mixture was neutralized with saturated aqueous sodium carbonate and further extracted with CH₂Cl₂ (3 \times 20 mL), and the combined organic layer was washed with brine, dried over Na₂SO₄, and concentrated to dryness. Purification of the residue by silica gel column chromatography (2:1 petroleum ether–EtOAc) gave aldehyde **15** (215 mg, 90%) as a syrup: $[\alpha]_D^{25} + 25$ (c 0.2, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 3.99–4.08 (m, 3H), 4.30 (dd, 1H, *J* = 2.5, 7.1 Hz), 4.50 (dd, 1H, *J* = 4.5, 7.1 Hz), 4.66, 4.70 (2d, 2H, *J* = 11.6 Hz), 7.31–7.39 (m, 5H), 9.66 (br d, 1H, *J* = 4.5 Hz); ¹³C NMR (100 MHz, CDCl₃) δ 60.9, 70.4, 73.6, 81.4, 82.3, 127.9, 128.2, 128.5, 136.5,

200.4; HRFABMS calcd for $C_{12}H_{13}N_3O_3$ 247.0957; found 248.0931 ($M + H$)⁺. Anal. Calcd for $C_{12}H_{13}N_3O_3$: C, 58.29; H, 5.30. Found: C, 58.51; H, 5.23.

Synthesis of Olefin 16

To a precooled ($-40\text{ }^{\circ}\text{C}$) solution of Wittig salt $C_{13}H_{27}Ph_3P^+Br^-$ (61 mg, 0.11 mmol) in THF (1.5 mL) was slowly added *n*-BuLi (2.5 M in hexane, 50 μL , 0.12 mmol) under N_2 protection. The orange solution was stirred at these conditions for about 20 min, at the end of which time, a solution of **15** (25 mg, 0.1 mmol) in dry THF (3 mL) was dropwise added under N_2 protection. The mixture was stirred at this temperature for another 30 min, then allowed to warm to room temperature and quenched by saturated NH_4Cl (0.2 mL). The mixture was diluted with water and extracted with EtOAc ($3 \times 20\text{ mL}$). The combined organic phase was dried over anhydrous Na_2SO_4 and concentrated to dryness. Purification of the residue by silica gel column chromatography (9:1 petroleum ether–EtOAc) gave **16** (36 mg, 86%, *Z/E* > 10:1) as a syrup. Selected *Z*-isomer: 1H NMR (400 MHz, $CDCl_3$) δ 0.88 (t, 3H, $J = 7.1\text{ Hz}$), 1.20 (br s, 20H), 2.07–2.09 (m, 2H), 3.88–3.97 (m, 3H), 4.11 (t, 1H, $J = 5.0\text{ Hz}$), 4.62, 4.70 (2d, 2H, $J = 11.8\text{ Hz}$), 4.71–4.72 (m, 1H), 5.65–5.73 (m, 2H, $J = 11.0\text{ Hz}$), 7.29–7.37 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.0, 22.6, 27.7, 29.2, 29.3, 29.4, 29.5, 29.6, 31.8, 61.5, 68.6, 73.3, 75.8, 80.4, 124.9, 127.7, 127.8, 128.3, 135.0, 137.4; HRFABMS calcd for $C_{25}H_{39}N_3O_2$ 413.3042, found 414.3068 ($M + H$)⁺. Anal. Calcd for $C_{25}H_{39}N_3O_2$: C, 72.60; H, 9.50. Found: C, 72.35; H, 9.42.

Synthesis of Pachastrissamine (Jaspine B) 1

A mixture of olefin **16** (42 mg, 0.1 mmol) and $Pd(OH)_2/C$ (10% content, 10 mg) in MeOH/EtOAc (1:1 v/v, 6 mL) was bubbled into H_2 at a flow rate of 100 mL/min at room temperature and 1 atm pressure. The hydrogenation was kept at these conditions for about 5 h, at the end of which time TLC (4:1 EtOAc/methanol) showed only one product generated. The $Pd(OH)_2/C$ was filtered, and the filtrate was concentrated. The residue was purified on a short silica gel column, which was pre-eluted with methanol containing 2% Et_3N (v/v) using 4:1 EtOAc/methanol as eluent to furnish target compound **1** (28 mg, 92%) as a white solid: $[\alpha]_D^{25} +7$ (c 0.2, $CHCl_3$); 1H NMR (400 MHz, CD_3OD) δ 0.89 (t, 3H, $J = 7.0\text{ Hz}$), 1.26–1.45 (m, 24H), 1.60–1.65 (m, 2H), 3.70 (dt, 1H, $J = 3.5, 6.8\text{ Hz}$), 3.79 (dd, 1H, $J = 4.8, 7.9\text{ Hz}$), 3.82–3.93 (m, 2H), 4.23 (dd, 1H, $J = 3.5, 4.8\text{ Hz}$); ^{13}C NMR (100 MHz, CD_3OD) δ 14.5, 23.7, 27.2, 29.7, 30.5, 30.7, 30.8, 30.9, 33.1, 54.3, 68.9, 70.9, 84.4. HRFABMS calcd for $C_{18}H_{37}NO_2$ 299.2824, found 300.2856 ($M + H$)⁺.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

This work was supported by National Basic Research Program of China (2003CB415001), NNSF of China (30330690), and NIH of the US (HL62244).

References

1. Kuroda I, Musman M, Ohtani II, Ichiba T, Tanaka J, Cravalos DC, Higa T. *J Nat Prod.* 2002; 65:1505–1506. [PubMed: 12398554]
2. Ledroit V, Debitus C, Lavaud C, Massiot G. *Tetrahedron Lett.* 2003; 44:225–228.
3. (a) Vasta V, Meacci E, Catarzi S, Donati C, Farnararo M, Bruni P. *Biochim Biophys Acta.* 2000; 1483:154–160. [PubMed: 10601704] (b) Meacci E, Vasta V, Moorman JP, Bobak DA, Bruni P, Moss J, Vaughan MJ. *Biol Chem.* 1999; 274:18605–18612.
4. Sudhakar N, Kumar AR, Prabhakar A, Jagadeesh B, Rao BV. *Tetrahedron Lett.* 2005; 46:325–327.
5. (a) Bhaket P, Morris K, Stauffer CS, Datta A. *Org Lett.* 2005; 7:875–876. [PubMed: 15727463] (b) Bhaket P, Stauffer CS, Datta A. *J Org Chem.* 2004; 69:8594–8601. [PubMed: 15575734]
6. Moravcova J, Capkova J, Stanek J. *Carbohydr Res.* 1994; 263:61–66.
7. Gerspacher M, Rapoport H. *J Org Chem.* 1991; 56:3700–3706.
8. Hill J, Hough L, Richardson AC. *Carbohydr Res.* 1968; 8:7–18.
9. Nakajima N, Horita K, Abe R, Yonemitsu O. *Tetrahedron Lett.* 1988; 29:4139–4142.
10. Ellison RA, Lukenbach ER, Chiu CW. *Tetrahedron Lett.* 1975; 29:499–502.
11. (a) Boons, G-J.; Hale, KJ. *Organic Synthesis with Carbohydrates.* Sheffield Academic Press; Sheffield, England: 2000. (b) Elliott MC, Williams E. *J Chem Soc, Perkin Trans.* 2001; 1:2303–2340. (c) Elliott MC. *J Chem Soc Perkin Trans.* 2002; 1:2301–2323. (d) Harmange JC, Figadere B. *Tetrahedron: Asymmetry.* 1993; 4:1711–1754. (e) Ziegler FE, Wang Y. *J Org Chem.* 1998; 63:426–427. [PubMed: 11672025] (f) Carda M, Rodriguez S, Segovia B, Marco JA. *J Org Chem.* 2002; 67:6560–6563. [PubMed: 12201784]
12. (a) Muralidhar P, Radhika P, Krishna N, Rao DV, Rao CB. *Nat Prod Sci.* 2003; 9:117–142. (b) O'Connell PW, Tsien SH. *Arch Biochem Biophys.* 1959; 80:289–294. (c) Sugiyama S, Honda M, Komori T. *Liebigs Ann Chem.* 1988:619–625. (d) Birk R, Sandhoff K, Schmidt RR. *Liebigs Ann Chem.* 1993:71–75. (e) Jo SY, Kim HC, Jeon DJ, Kim HR. *Heterocycles.* 2001; 55:1127–1132. (f) Bols M. *Acc Chem Res.* 1998; 31:1–8. (g) Asano N, Nash RJ, Molyneux RJ, Fleet GWJ. *Tetrahedron: Asymmetry.* 2000; 11:1645–1680. (h) Callam CS, Lowary TL. *J Org Chem.* 2001; 66:8961–8972. [PubMed: 11749629] (i) Bleriot Y, Giroult A, Mallet J-M, Rodriguez E, Vogel P, Sinaj P. *Tetrahedron: Asymmetry.* 2002; 13:2553–2565.

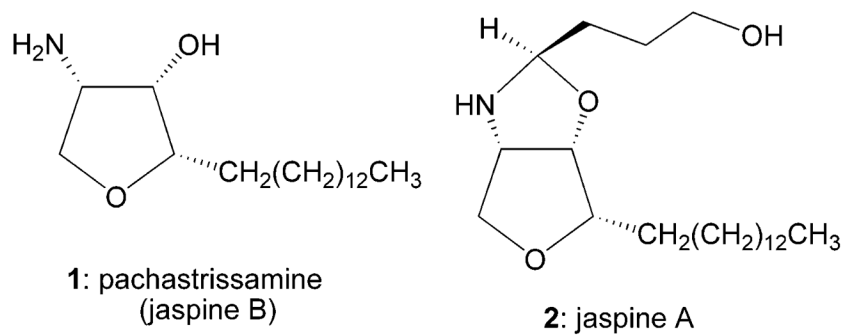
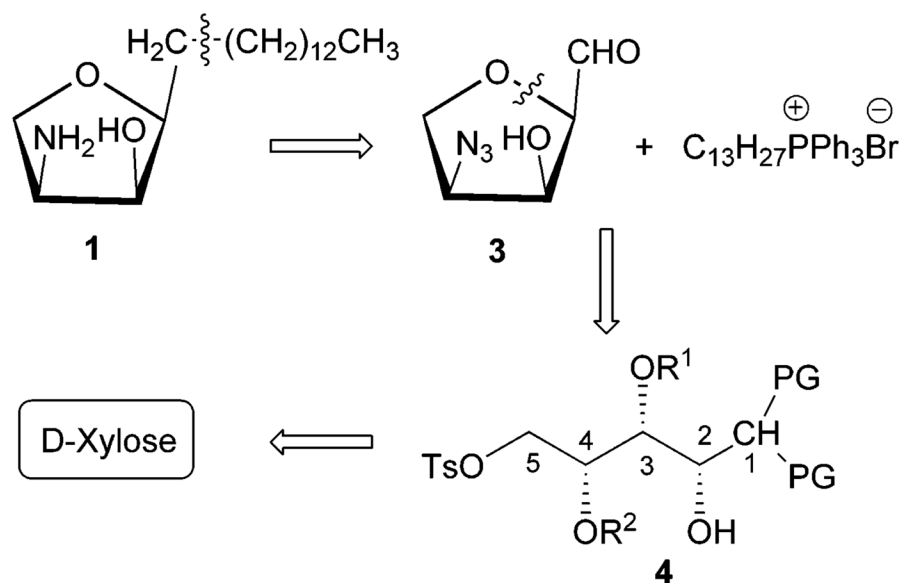
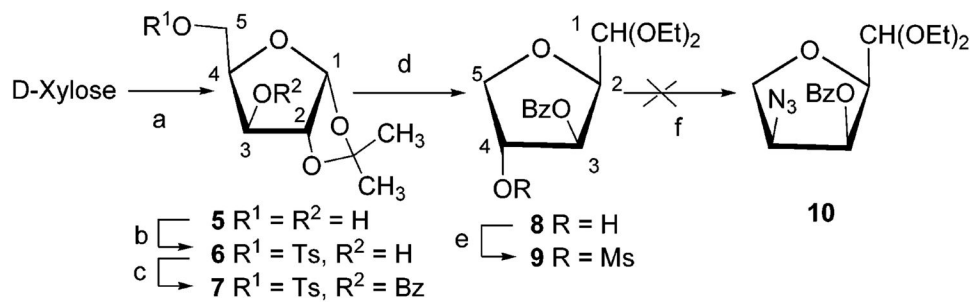


Figure 1.
Structure of natural anhydrophytosphingosine pachastrissamine (jaspine B).

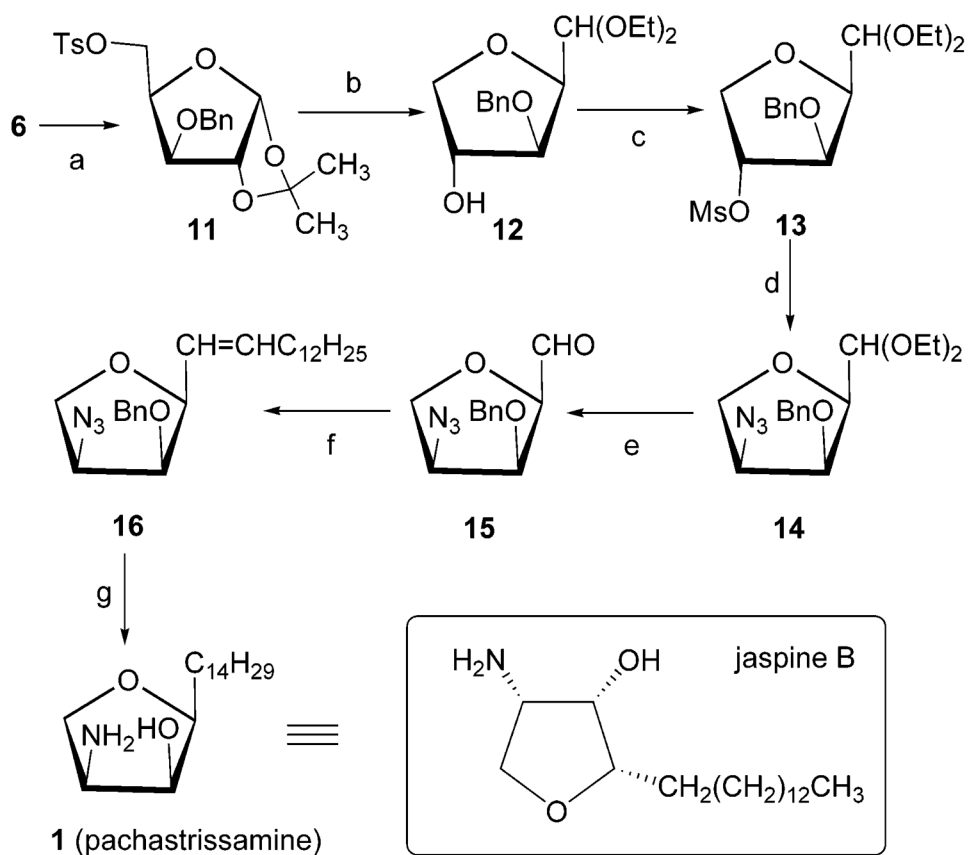


Scheme 1.
Retrosynthetic Analysis of Pachastrissamine (1)



Scheme 2. Attempted Synthesis toward Pachastrissamine (1)^a

^a Reagents and conditions: (a) concd H_2SO_4 , acetone, then Na_2CO_3 , 82%; (b) tosylimidazolide, MeOTf, *N*-methylimidazole, THF, 93%; (c) BzCl, pyridine, rt, 5 h, 96%; (d) 5% hydrochloric acid in ethanol (v/v), reflux, 3 h, 90%; (e) MsCl, pyridine, rt, 4 h, 99.4%; (f) NaN_3 , NH_4Cl , dry DMF, 60–120 °C, 5–15 h.



Scheme 3. Total Synthesis of Pachastrissamine (1)^a

^a Reagents and conditions: (a) benzyl trichloroacetimidate, 1 mol % of TMSOTf, dry CH_2Cl_2 , $-40\text{ }^\circ\text{C}$, 75%; (b) 5% hydrochloric acid in ethanol (v/v), reflux, 3 h, 89%; (c) MsCl, pyridine, rt, 4 h; (d) NaN_3 , NH_4Cl , dry DMF, $120\text{ }^\circ\text{C}$, 20 h, 71% for two steps; (e) aqueous 50% trifluoroacetic acid, CH_2Cl_2 , room temperature, 30 min, 90%; (f) $\text{C}_{13}\text{H}_{27}\text{Ph}_3\text{P}^+\text{Br}^-$, BuLi, dry THF, $-40\text{ }^\circ\text{C}$, 86%, $Z/E > 10/1$; (g) $\text{Pd}(\text{OH})_2/\text{C}$, H_2 , MeOH/EtOAc, 5 h, 92%.