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

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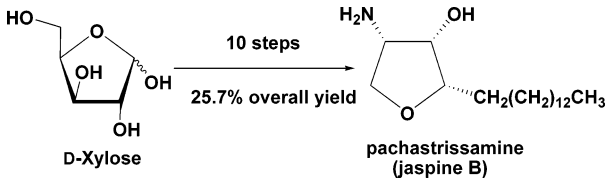

The first naturally occurring anhydrophytosphingosine, pachastrissamine (jaspine B), a marine compound cytotoxic toward P388, A549, HT29, and MEL28 cell lines at IC_{50} = 0.01 μg/mL level, has been stereoselectively synthesized from D-xylose in 10 linear steps with 25.7% overall yield.

Pachastrissamine (**1**, Figure 1) is a natural occurring anhydrophytosphingosine derivative, first isolated in 2002 by Higa and co-workers[1] 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 μg/mL against P388, A549, HT29, and MEL28 cell lines. Almost at the same time, Debitus and co-workers[2] investigated the cytotoxicity of ethanolic extract (IC_{95} = 10 μg/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 μM) 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 derivatization studies suggested that the structure of pachastrissamine and jaspine B were identical, i.e., an all-syn trisubstituted tetrahedrofuran framework and the (2*S*,3*S*,4*S*) absolute configuration.

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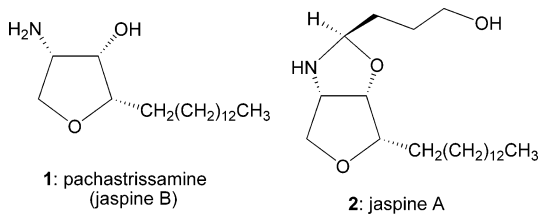
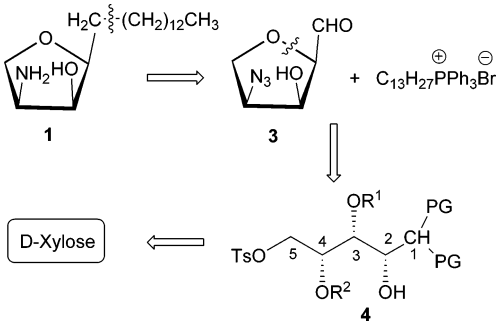


FIGURE 1. Structure of natural anhydrophytosphingosine pachastrissamine (jaspine B).

SCHEME 1. Retrosynthetic Analysis of Pachastrissamine (1)



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 H_2SO_4 in acetone[6] gave 1,2-acetal **5** in 82% yield (Scheme 2). Regioselective tosylation of **5** on the primary alcohol with tosylimidazolide, MeOTf, and *N*-methylimidazole in THF at 0 °C afforded **6** in excellent yield.[7]

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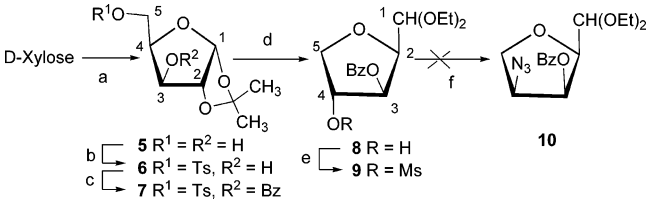
SCHEME 2. Attempted Synthesis toward Pachastrissamine (1)[a]



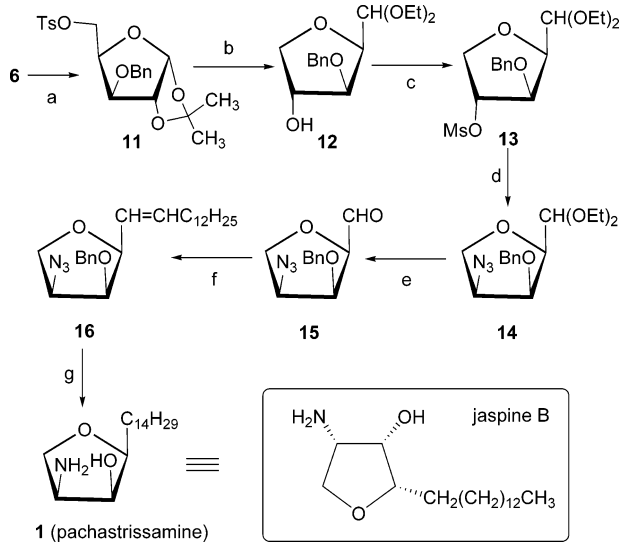
[a] Reagents and conditions: (a) concd H_2SO_4, acetone, then Na_2CO_3, 82%; (b) tosylimidazolide, MeOTf, *N*-methylimidazole, THF, 93%; (c) BzCl, pyridine, rt, 5 h, 96%; (d) 5% hydrochloric acid in ethanol (v/v), reflux, 3 h, 90%; (e) MsCl, pyridine, rt, 4 h, 99.4%; (f) NaN_3, NH_4Cl, dry DMF, 60−120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

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 ^{1}H−^{1}H 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 ^{1}H 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 NaN_3 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 trifluroacetic 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 ^{1}H 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

SCHEME 3. Total Synthesis of Pachastrissamine (1)[a]



[a] Reagents and conditions: (a) benzyl trichloroacetimidate, 1 mol % of TMSOTf, dry CH_2Cl_2, −40 °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 °C, 20 h, 71% for two steps; (e) aqueous 50% trifluroacetic acid, CH_2Cl_2, room temperature, 30 min, 90%; (f) $C_{13}H_{27}Ph_3P^+Br^-$, BuLi, dry THF, − 40 °C, 86%, *Z*/*E* > 10/1; (g) $Pd(OH)_2$/C, H_2, MeOH/EtOAc, 5 h, 92%.

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: $[\alpha]^{25}_D$ − 21 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz,

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$CDCl_3$) δ 1.25, 1.43 (2s, 2 × 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 $C_{22}H_{26}O_7S$: 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 × 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%): $[\alpha]^{25}_D$ + 77 (*c* 0.7, $CHCl_3$); ^{1}H 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, $CDCl_3$) 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 $C_{16}H_{24}O_5$: 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 μL, 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**: $[\alpha]^{25}_D$ + 80 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) 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); ^{13}C NMR (100 MHz, $CDCl_3$) 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 $C_{17}H_{26}O_7S$: 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 NaN_3 (91 mg, 1.41 mmol) and anhydrous NH_4Cl (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 × 10 mL). The organic phase was dried over anhydrous Na_2SO_4 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: $[\alpha]^{25}_D$ + 106 (*c* 1.3, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) 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); ^{13}C NMR (100 MHz, $CDCl_3$) 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 $C_{16}H_{23}N_3O_4$ 321.1689, found 322.1660 (M + H)$^+$. Anal. Calcd for $C_{16}H_{23}N_3O_4$: 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 CH_2Cl_2 (3 mL), and aqueous 50% trifluroacetic 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 CH_2Cl_2 (3 × 20 mL), and the combined organic layer was washed with brine, dried over Na_2SO_4, 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: $[\alpha]^{25}_D$ + 25 (*c* 0.2, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) 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, 5 H), 9.66 (br d, 1H, J = 4.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) 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 °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 × 20 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: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.88 (t, 3H, J = 7.1 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 Hz), 4.62, 4.70 (2d, 2H, J = 11.8 Hz), 4.71−4.72 (m, 1H), 5.65−5.73 (m, 2H, J = 11.0 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: $[\alpha]^{25}_D$ +7 (*c* 0.2, $CHCl_3$); ^{1}H NMR (400 MHz, CD_3OD) δ 0.89 (t, 3H, J = 7.0 Hz), 1.26−1.45 (m, 24H), 1.60−1.65 (m, 2H), 3.70 (dt, 1H, J = 3.5, 6.8 Hz), 3.79 (dd, 1H, J = 4.8, 7.9 Hz), 3.82−3.93 (m, 2H), 4.23 (dd, 1H, J = 3.5, 4.8 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)$^+$.

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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.

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