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Total synthesis of pachastrissamine (jaspine B) enantiomers from D-glucose

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Abstract—Synthesis of both enantiomers of pachastrissamine is described from a common chiral template. The stereoselective construction of the central tetrahydrofuran units was based on the pseudodesymmetrization of a pentodialdo-1,4-furanose derivative taking advantage of the latent symmetry present.

Pachastrissamine (**1**, Fig. 1), isolated and characterized by Higa and co-workers in 2002 from the Okinawa marine sponge *Pachastrissa* sp. (family Calthropellidae) is a novel anhydrophytosphingosine with important bioactivity.[1] It was later (in 2003) isolated from another marine sponge, genus *Jaspis* by Debitus and co-workers and named as jaspine B.[2] The structure of **1** and the all-cis geometry of the THF ring was assigned by spectroscopy, largely NMR, and the (2*S*,3*S*,4*S*) configuration of the ring carbon atoms was determined on the basis of (*S*)- and (*R*)-MTPA derivatization on the N-monoacetylated pachastrissamine. This was reported to exhibit promising cytotoxic activity in the submicromolar range against P388, A549, HT29, and MEL28 ($IC_{50} = 0.001$ μg/mL) cell lines. Its simple structure and this promising biological activity have stimulated substantial synthetic work, culminating in several total syntheses.[3–7] In this letter we wish to report a chiral pool synthesis of both **1** and its antipode **2** starting from a single chiron.

As shown in Figure 1, our intended strategy exploited the pseudosymmetry present in pentodialdo-1,4-furanose **9**[8] to derive enantiomeric azidoalkynes **3** and **4**, which upon alkylation and hydrogenation should result

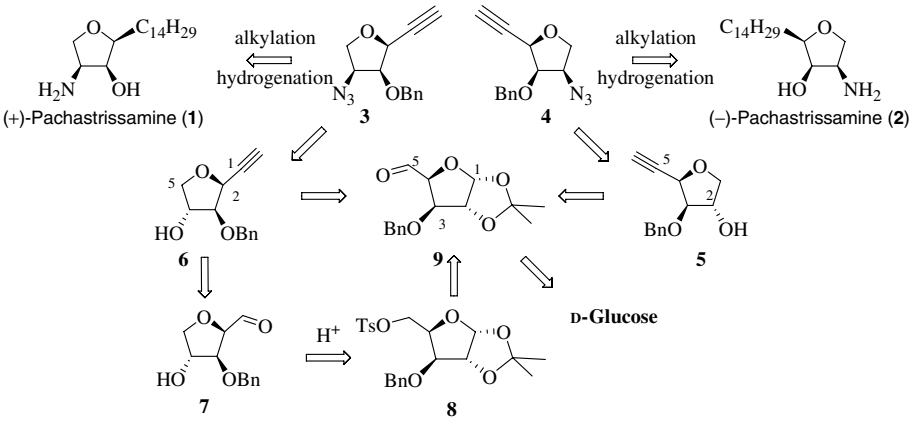

Figure 1. The key pseudodesymmetrization strategy for (+)- and (−)-pachastrissamine.

Keywords: Chiron approach; Pachastrissamine/jaspine B; Pentodialdo-1,4-furanose; Ohira–Bestmann reaction; Ring isomerization.
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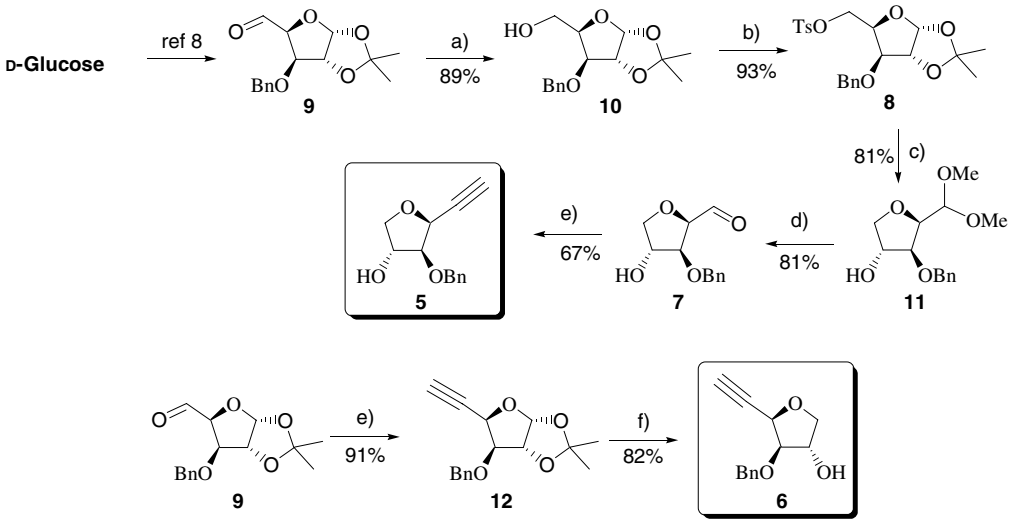
in the synthesis of **1** and **2**, respectively.[9] We anticipated that the two enantiomeric furan systems **5** and **6** could be fashioned efficiently by employing selective Ohira–Bestmann alkynylation at either end of **9**. The Ohira–Bestmann alkynylation at C(5) is a direct proposition, whereas for the Ohira–Bestmann alkynylation at C(1), we were interested in the acid mediated ring isomerization of **8**.

Prior to the discussion on the synthesis of enantiomeric alkynols **5** and **6**, it is pertinent to mention that while our work was in progress furanoaldehyde **7** was prepared and used by Linhardt and co-workers[5] for the synthesis of natural pachastrissamine (**1**). The synthesis of alkynol **5** started with reduction of the easily available dialdofuranose **9** (prepared from D-glucose following the literature procedure, Scheme 1) with $NaBH_4$.[10] Tosylation of **10** using *p*-TsCl in pyridine followed by acid mediated acetonide deprotection with concomitant 2,5-ring closure gave dimethylacetal **11** in a good yield. The following acetal hydrolysis reaction proceeded with 2 N sulfuric acid in acetic acid and the resulting aldehyde **7** was subjected to Ohira–Bestmann alkynylation under standard conditions.[11]

Alkynol **6** was prepared in two steps from **9** by first subjecting it to the Ohira–Bestmann alkynylation and then reductive deketalization[12] of the resulting alkyne **12**[13] using excess triethylsilane in the presence of $BF_3{\cdot}Et_2O$. The spectral data of **6** were comparable with its antipode **5**.[14]

Once we had easy access to enantiomeric alkynols **5** and **6**, the stage was set for the synthesis of the mirror isomers of pachastrissamine. Thus, alkynols **5** and **6** were transformed to the corresponding azidoalkynes **3** and **4** by treatment with Tf_2O in pyridine followed by reacting the intermediate triflates with LiN_3 in DMF. The spectral and analytical data of compounds **3** and **4** were in agreement with the proposed structures.[15] After examining a set of bases and reaction conditions, we concluded that the alkylation of azidoalkynes **3**, **4** with 1-bromododecane was facile using *n*-BuLi in THF-HMPA and the alkylated products **13** and **14** were obtained in 61% and 57% yields, respectively.[16] Hydrogenolysis of **13** and **14** was effected by refluxing in methanol in the presence of ammonium formate and cat. 10% Pd/C. The requisite pachastrissamine enantiomers were characterized either after chromatographic purification or as their diacetates **15** and **16**, respectively (Scheme 2). The spectral and analytical data of the **1** and its diacetate **15**[17] were in agreement with the reported values and the structure of **15** was further established by single crystal X-ray analysis (Fig. 2).[18–20]



Scheme 1. Reagents and conditions: (a) $NaBH_4$, MeOH, 0 °C, 2 h; (b) *p*-TsCl, pyridine, DMAP, CH_2Cl_2, 5 h; (c) PTSA, methanol, reflux, 6 h; (d) 2 N, H_2SO_4, 50% AcOH, 9 °C, 2 h; (e) $(MeO)_2P(=O)C(=N_2)COCH_3$, methanol, K_2CO_3, rt, 7–9 h; (f) $BF_2{\cdot}Et_2O$, Et_3SiH, CH_2Cl_2, −20 °C − rt, 6 h.

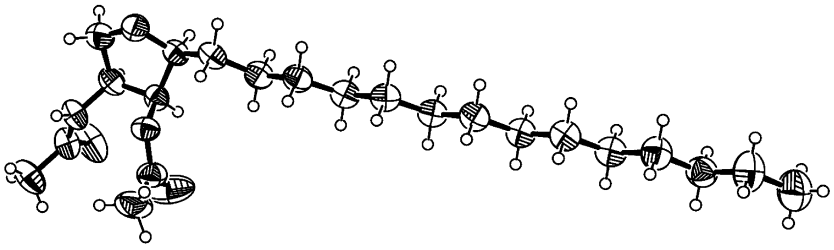
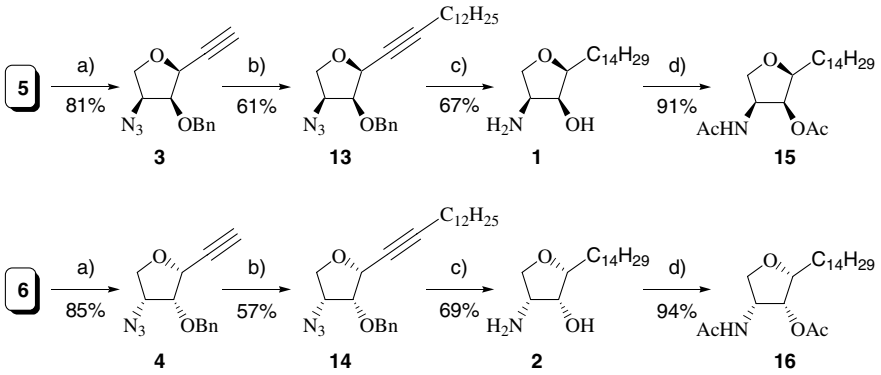


Figure 2. ORTEP structure of compound **15**.



Scheme 2. Reagents and conditions: (a) (i) Tf_2O, pyridine, CH_2Cl_2, 0 °C, 6 h; (ii) LiN_3, DMF, rt, 12 h; (b) *n*-BuLi, THF:HMPA (7:1), $C_{12}H_{25}Br$, −78 to −40 °C, 1 h; (c) 10% Pd/C, ammonium formate, MeOH, reflux, 10 h; (d) Ac_2O, Et_3N, DMAP, CH_2Cl_2, rt, 6 h.

In summary, we have reported a simple chiral pool strategy for the synthesis of both enantiomers of pachastrissamine starting with D-glucose. The synthesis is sufficiently flexible to allow substitution or variation in the length of the side chain to synthesize analogues.

Acknowledgements

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14. *Spectral data of* **5**. $[\alpha]_D^{25}$ −57.9 (*c* 1, $CHCl_3$). IR ($CHCl_3$) *v*: 3403, 3290, 3065, 2942, 2120, 1598, 1496, 1218, 1069, 754, 698, 666 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) *δ*: 2.15 (br s, 1H), 2.57 (d, $J = 2.3$ Hz, 1H), 3.67 (dd, $J = 2.2$, 9.8 Hz, 1H), 3.91 (dd, $J = 2.3$, 4.7 Hz, 1H), 4.18 (dd, $J = 4.7$, 9.8 Hz, 1H), 4.32–4.34 (dt, $J = 2.3$, 4.7 Hz, 1H), 4.64 (d, $J = 11.9$ Hz, 1H), 4.77 (dd, $J = 2.2$, 4.7 Hz, 1H), 4.78 (d, $J = 11.9$ Hz, 1H), 7.27–7.38 (m, 5H). ^{13}C NMR (50 MHz, $CDCl_3$) *δ*: 70.6 (d), 72.7 (t), 73.1 (t), 75.5 (d), 76.4 (d), 78.9 (s), 84.9 (d), 127.8 (d), 127.9 (d), 128.5 (d), 137.5 (s) ppm. ESI-MS: *m/z* 219.1 (23%, $[M+1]^+$), 236.2 (38%, $[M+NH_4]^+$), 241.2 (100%, $[M+Na]^+$), 257.1 (18%, $[M+K]^+$). Anal. calcd for $C_{13}H_{14}O_3$: C, 71.54; H, 6.47. Found: C, 71.44; H, 6.59. *Spectral data of* **6**. $[\alpha]_D^{25}$ 56 (*c* 0.9, $CHCl_3$). ESI-MS: *m/z* 241.3 (100%, $[M+Na]^+$), 257.3 (24%, $[M+K]^+$); Anal. calcd for $C_{13}H_{14}O_3$: C, 71.54; H, 6.47. Found: C, 71.49; H, 6.39.
15. *Spectral data of* **3**. $[\alpha]_D^{25}$ −69 (*c* 1.3, $CHCl_3$). IR ($CHCl_3$) *v*: 3304, 3020, 2125, 2110, 1603, 1585, 1216, 759, 698, 638 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) *δ*: 2.64 (d, $J = 2.3$ Hz, 1H), 3.92–4.04 (m, 3H), 4.16 (br dd, $J = 5.0$, 6.1 Hz, 1H), 4.71 (dd, $J = 2.3$, 6.1 Hz, 1H), 4.74 (d, $J = 11.8$ Hz, 1H), 4.83 (d, $J = 11.8$ Hz, 1H), 7.31–7.46 (m, 5H). ^{13}C NMR (50 MHz, $CDCl_3$) *δ*: 59.9 (d), 69.4 (t), 69.7 (d), 73.2 (t), 76.9 (d), 78.8 (s) 79.4 (d), 127.9 (d), 128.0 (d), 128.5 (d), 137.0 (s). Anal. calcd for $C_{13}H_{13}N_3O_2$: C, 64.19; H, 5.39, N, 17.27. Found: C, 64.29; H, 5.21, N, 17.18. *Spectral data of* **4**. $[\alpha]_D^{25}$ 70.1 (*c* 1.3, $CHCl_3$). ESI-MS: *m/z* 267.3 (27%), 283.4 (40%, $[M+K]^+$). Anal. calcd for $C_{13}H_{13}N_3O_2$: C, 64.19; H, 5.39, N, 17.27. Found: C, 64.01; H, 5.61, N, 17.24.
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17. *Spectral data of* **15**. Mp: 110 °C; $[\alpha]_D^{25}$ −34.6 (*c* 1, $CHCl_3$), lit.[7] {$[\alpha]_D^{25}$ −28.4 (*c* 1, $CHCl_3$)}. IR ($CHCl_3$) *v*: 3019, 2927, 2855, 1743, 1676, 1550, 1467, 1374, 1215, 1049, 757 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) *δ*: 0.86 (t, $J = 6.8$ Hz, 3H), 1.23 (br s, 24H), 1.40–1.48 (m, 2H), 1.97 (s, 3H), 2.15 (s, 3H), 3.58 (dd, $J = 7.9$, 8.6 Hz, 1H), 3.85–3.93 (m, 1H), 4.06

(dd, $J = 8.1$, 8.6 Hz, 1H), 4.80 (dq, $J = 5.4$, 8.0 Hz, 1H), 5.37 (dd, $J = 3.4$, 5.5 Hz, 1H), 5.61 (d, $J = 8.2$ Hz, 1H). ^{13}C NMR (50 MHz, $CDCl_3$) δ: 14.1 (q), 20.6 (q), 22.6 (t) 23.1 (q), 26.0 (t), 29.3 (2t), 29.4 (t), 29.5 (2t), 29.6 (2t), 31.9 (t), 51.3 (d), 69.9 (t), 73.5 (d), 81.20 (d). ESI-MS: *m/z* 384.2 (82%, $[M+1]^+$), 406.3 (100%, $[M+Na]^+$). *Spectral data of* **16**. Mp: 108 °C; $[\alpha]_D^{25}$ 29 (*c* 1, $CHCl_3$). ESI-MS: *m/z* 384.4 (23%, $[M+1]^+$), 406 (100%, $[M+Na]^+$), 422.3 (20% $[M+K]^+$).

18. X-ray intensity data was collected on a Bruker SMART APEX CCD diffractometer with graphite-monochromatized (Mo K$\alpha = 0.71073$ Å) radiation at room temperature. All the data were corrected for Lorentzian, polarization, and absorption effects using Bruker's SAINT and SADABS programs. SHELX-97 (G.M. Sheldrick, SHELX-97 program for crystal structure solution and refinement, University of Gottingen, Germany, 1997)[19] was used for structure solution and full-matrix least-squares refinement on F^2. Hydrogen atoms were included in the refinement as per the riding model.
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20. The crystallographic data has been deposited with the Cambridge Crystallographic Data Centre as deposition No. CCDC 617243 (**15**). Copies of the data can be obtained, free of charge, on application to the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44 (1223) 336033; e-mail: deposit@ccdc.cam.ac.uk].