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Stereoselective total synthesis of pachastrissamine (jaspine B)

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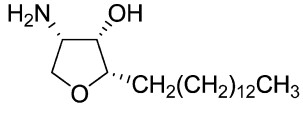
Abstract

A short total synthesis of the cytotoxic natural product pachastrissamine is described. The synthesis includes eight steps starting from Garner's aldehyde and proceeds in 20% overall yield. Pd(0)-mediated intramolecular cyclisation and Ru-mediated cross-metathesis are the key reactions in this sequence.

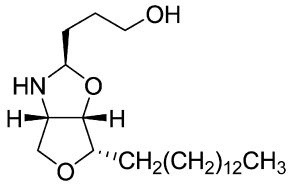
Keywords: Natural products; Enantioselective synthesis; Pachastrissamine; Cross metathesis; Cyclization

Natural products remain a rich source of leads for new drugs.[1] The structural diversity of natural compounds outmatches that of purely synthetic ones, and more closely matches those of drug-like structures than, for example, chemical libraries produced by combinatorial chemistry.[2] These often astounding structures continue to provide challenges for the development of new strategies for the formation of structural skeleta, although sometimes the sheer excitement of the endeavour of total synthesis has motivated many groups in the search for new chemistry.[3] Total synthesis is still an important tool for confirming the absolute structure of a compound.[4] Nature's ways of producing this structural diversity markedly differ from current synthetic practices, and this has recurrently led to endeavours in biomimetic synthesis,[5] protecting group-free strategies[6] and organocatalysis.[7]

In 2002, pachastrissamine **1**, an anhydrophytosphingosine, was isolated from the marine sponge *Pachastrissa* sp. (family Calthropellidae) found around the Okinawan islands.[8] Almost simultaneously a French group working on the ethanolic extracts of a Vanuatuan marine sponge, *Jaspis* sp.[9] isolated two bioactive compounds, jaspines A and B, the latter being identical to pachastrissamine. The structure of pachastrissamine consists of a 14-carbon alkyl chain attached to an all *S* (2*S*,3*S*,4*S*) configured 2-amino-3-hydroxytetrahydrofuran ring (Fig. 1).



Pachastrissamine (Jaspine B), 1



Jaspine A

Fig. 1. Structures of pachastrissamine (jaspine B) **1** and jaspine A.

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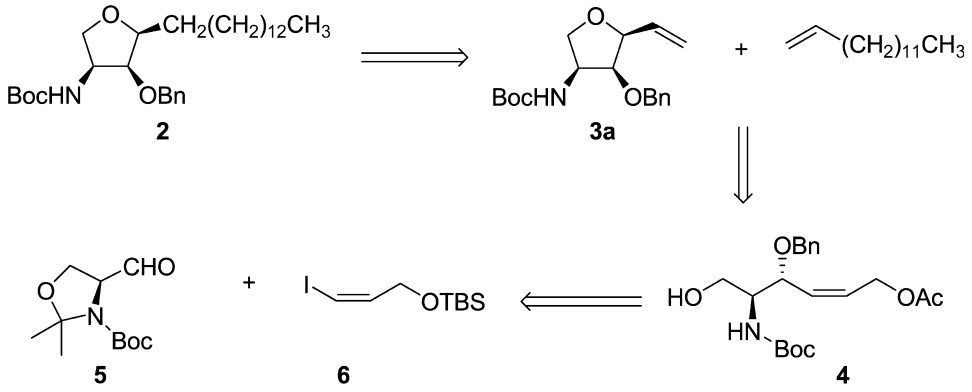
The hydrochloride salt of pachastrissamine displayed marked submicromolar cytotoxicity against the P388, HT29 and MEL28 cell lines. It has proved to be the most potent compound yet isolated from the genus *Jaspis* on the A549 human lung carcinoma cell line (IC_{50} 0.24 μM). Recently, several total syntheses of pachastrissamine **1** have been reported.[10]

We have a long interest in the use of amino acids as chiral adducts for the synthesis of nitrogen- containing natural products.[11] We envisioned that our previous experience as well as new methodology could be used in the synthesis of pachastrissamine **1**. Retrosynthetically (Scheme 1), **2** can be assembled via a cross-metathesis reaction of the vinylic tetrahydrofuran derivative **3a** and the commercial 1-tetradecene. The tetrahydrofuran ring **3a** can be derived from a Pd-mediated intramolecular 1,5-ring closure of the acyclic hydroxyalkene **4**. This in turn can easily be prepared from a stereoselective coupling of Garner's aldehyde **5** and vinylic iodide **6**.

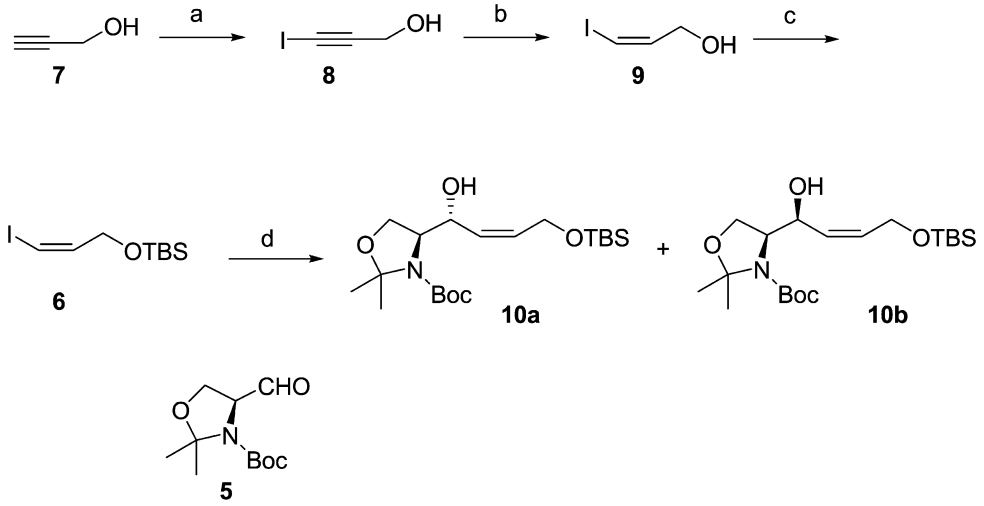
Our synthesis commenced with the preparation of the vinyl iodide **6**. Iodination of propargyl alcohol **7** under basic conditions in MeOH and diimide reduction of the triple bond followed by TBS protection of the free alcohol gave the vinyl iodide **6** (Scheme 2) in high yield (51% over three steps) with a single purification process (Kugelrohr distillation at <0.2 mmHg).

Iodide **6** was then coupled with Garner's aldehyde (*n*-BuLi in toluene). Without additives the *anti*/*syn*-selectivity was 4:1. Better selectivities were achieved with either HMPA (*anti*/*syn* 12:1) or DMPU (*anti*/*syn* up to 17:1) as an additive. Yields varied between 55% with DMPU and 63% without any additives. Stereoisomers **10a** and **10b** were easily separated by MPLC.

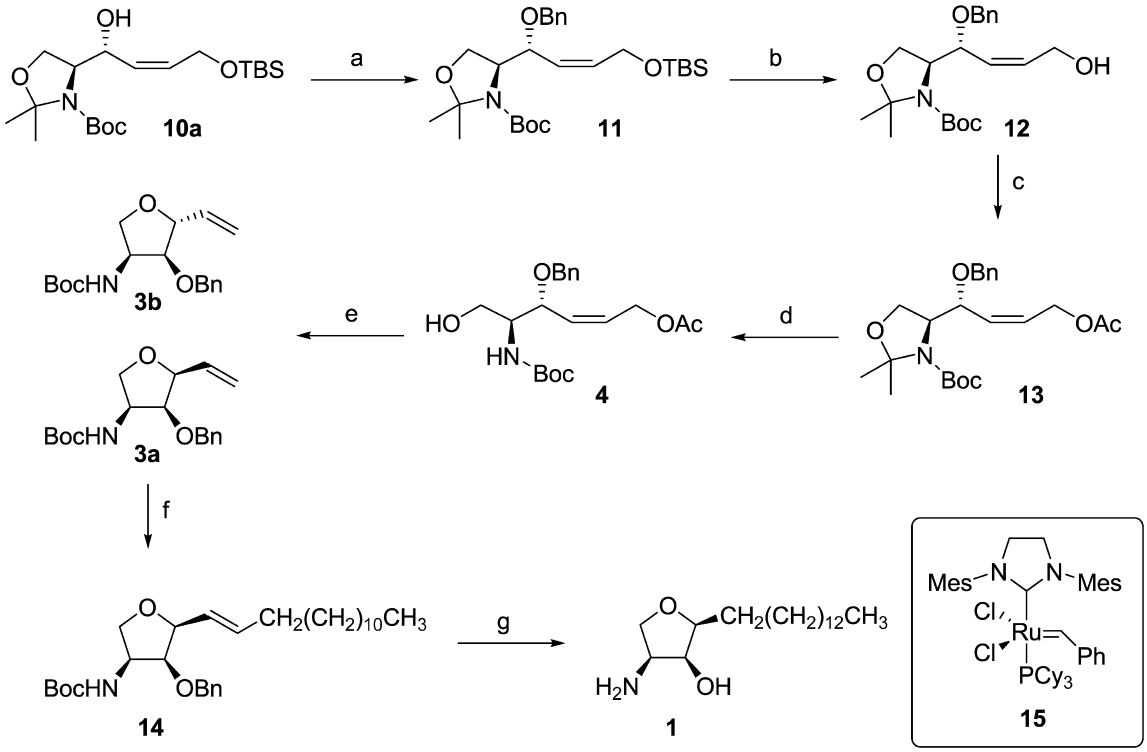
The *anti*-alcohol **10a** (Scheme 3) was protected as the benzyl ether **11** (NaH, in situ formed BnI in refluxing THF).[12] Removal of the TBS group (TBAF) followed by acetylation of the free alcohol **12** gave acetate **13**. Deprotection of the N,O-acetal with $FeCl_3$ adsorbed on silica gel[13] provided the primary alcohol **4**[14] in 94% yield. This reaction could also be performed with 80% aqueous AcOH at 55 °C,[11b] but depending on the scale, acetylation of the primary alcohol becomes a problem. With the free alcohol **4** to hand the stage was set for the key cyclisation step. Pd(0)-mediated intramolecular 1,5-cyclisation provided



Scheme 1. Retrosynthesis of pachastrissamine, **1**.



Scheme 2. Reagents and conditions: (a) I_2, KOH, MeOH, (82%); (b) $KO_2CN{=}NCO_2K$, AcOH, MeOH, (65%); (c) TBSCl, imidazole, DMF (96%); (d) (i) 6, *n*-BuLi, additive (HMPA or DMPU), toluene, −78 °C, (ii) 5, toluene, −95 °C.



Scheme 3. Reagents and conditions: (a) BnBr, TBAI, NaH, THF, 0 °C→reflux; (b) TBAF, CH_2Cl_2, rt (85% from **10a**); (c) Ac_2O, DMAP, Et_3N, CH_2Cl_2, rt (95%); (d) $FeCl_3$–SiO_2, $CHCl_3$, rt (94%); (e) cat. $Pd(PPh_3)_4$, PPh_3, THF, 55 °C (95%); (f) **15**, 1-tetradecane, CH_2Cl_2, 40 °C (87%); (g) (i) H_2 (g), $Pd(OH)_2$, MeOH/EtOAc (1:1), rt, (ii) HCl (g) MeOH/EtOAc (1:1) (76%).

the desired separable tetrahydrofuran diastereomers **3a** and **3b** in excellent yield (95%, 2:1 dr).[15,16]

Coupling of the alkyl chain to the furan derivative **3a** was effected using Grubbs' cross-metathesis reaction.[17] Cross- metathesis has been used in the synthesis of ceramide derivatives[18] as well as in the synthesis of nucleic acids.[19] Reaction of **3a** with Grubbs' 2nd generation catalyst **15** and an excess of 1-tetradecene (1000 mol %) provided the desired alkene **14**[20] in excellent yield (87%). According to ^1H NMR the alkene was produced only in the *E*-configuration. Finally, hydrogenation (H_2 gas with $Pd(OH)_2$ as the catalyst in (1:1) MeOH/EtOAc) effected the removal of both the double bond and benzyl protecting group. After filtration of the reaction mixture through a pad of Celite®, the solution was treated with HCl gas at 0 °C to cleave the Boc-protection to afford pachastrissamine (jaspine B) **1** as the hydrochloride salt (76%).

In conclusion, we have described a total synthesis of the cytotoxic natural product pachastrissamine **1** in eight steps and 20% overall yield starting from Garner's aldehyde. We have demonstrated the utility of the Pd(0)-mediated intramolecular cyclisation in forming tetrahydrofuran rings and cross-metathesis reaction in preparing the natural product.

Acknowledgements

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References and notes

1. (a) Newman, D. J.; Cragg, G. M. *J. Nat. Prod.* **2007**, *70*, 461–477; (b) Chin, Y.-W.; Balunas, M. J.; Chai, H. B.; Kinghorn, A. D. *AAPS J.* **2006**, *28*, E239–E253; (c) Lesney, M. S. *Today's Chemist at Work* **2004**, *July*, 26–32.
2. Feher, M.; Schmidt, J. M. *J. Chem. Inf. Comput. Sci.* **2003**, *43*, 218–227.
3. (a) Nicolaou, K. C.; Yue, E. W. *Pure Appl. Chem.* **1997**, *69*, 413–418; (b) Nicolaou, K. C. *J. Org. Chem.* **2005**, *70*, 7007–7027; (c) Nicolaou, K. C. *J. Med. Chem.* **2005**, *48*, 5613–5638.
4. Nicolaou, K. C.; Snyder, S. A. *Angew. Chem., Int. Ed.* **2005**, *44*, 1012–1044.
5. (a) Breslow, R. *Chem. Soc. Rev.* **1972**, *1*, 553–580; (b) Faulkner, D. J. *Pure Appl. Chem.* **1976**, *48*, 25–28; (c) Johnson, W. S. *Bioorg. Chem.* **1976**, *5*, 51–98; (d) Van Tamelen, E. E. *Pure Appl. Chem.* **1981**, *53*, 1259–1270; (e) McDonald, F. E.; Towne, T. B.; Schultz, C. C. *Pure Appl. Chem.* **1998**, *70*, 355–358; (f) Nicolaou, K. C.; Montagnon, T.; Snyder, S. A. *Chem. Commun.* **2003**, 551–564; (g) Valentine, J. C.; McDonald, F. E. *Synlett* **2006**, 1816–1828; (h) McDonald, F. E.; Tong, R.; Valentine, J. C.; Bravo, F. *Pure Appl. Chem.* **2007**, *79*, 281–291.
6. (a) Hoffmann, R. W. *Synthesis* **2006**, 3531–3541; (b) Forke, R.; Krahl, M. P.; Krause, T.; Schlechtingen, G.; Knölker, H.-J. *Synlett* **2007**, 268–272; (c) Schmidt, A. W.; Olpp, T.; Schmid, S.; Goutal, S.; Jäger, A.; Knölker, H.-J. *Synlett* **2007**, 1549–1552; (d) Baran, P. S.; Maimone, T. J.; Richter, J. M. *Nature* **2007**, *446*, 404–408.
7. (a) Dalko, P. I.; Moisan, L. *Angew. Chem., Int. Ed.* **2001**, *40*, 3726–3748; (b) Schreiner, P. R. *Chem. Soc. Rev.* **2003**, *32*, 289–296; (c) Dalko, P. I.; Moisan, L. *Angew. Chem., Int. Ed.* **2004**, *43*, 5138–5175; (d) de Figueiredo, R. M.; Christmann, M. *Eur. J. Org. Chem.* **2007**, *16*, 2575–2600; (e) *Organocatalysis in Organic Synthesis*; Kocovsky, P., Malkov, A. V., Eds.; Elsevier B.V.: Amsterdam, Netherlands, 2005; p 260.

8. Kuroda, I.; Musman, M.; Ohtani, I.; Ichiba, T.; Tanaka, J.; Garcia Gravalos, D.; Higa, T. *J. Nat. Prod.* **2002**, *65*, 1505–1506.
9. Ledroit, V.; Debitus, C.; Lavaud, C.; Massiot, G. *Tetrahedron Lett.* **2003**, *44*, 225–228.
10. (a) Sudhakar, N.; Ravi Kumar, A.; Prabhakar, A.; Jagadeesh, B.; Venkateswara Rao, B. *Tetrahedron Lett.* **2005**, *46*, 325–327; (b) Bhaket, P.; Morris, K.; Stauffer, C.; Datta, A. *Org. Lett.* **2005**, *7*, 875–876; (c) Du, Y.; Liu, J.; Linhardt, R. *J. Org. Chem.* **2006**, *71*, 1251–1253; (d) van den Berg, R.; Boltje, T.; Verhagen, C.; Litjens, R.; Van der Marel, G.; Overkleeft, H. *J. Org. Chem.* **2006**, *71*, 836–839; (e) Ribes, C.; Falomir, E.; Carda, M.; Marco, J. *Tetrahedron* **2006**, *62*, 5421–5425; (f) Chandrasekhar, S.; Tiwari, B.; Prakash, S. J. *ARKIVOC* **2006**, *xi*, 155–161; (g) Lee, T.; Lee, S.; Kwak, Y. S.; Kim, D.; Kim, S. *Org. Lett.* **2007**, *9*, 429–432; (h) Reddy, L. V. R.; Reddy, P. V.; Shaw, A. K. *Tetrahedron: Asymmetry* **2007**, *18*, 542–546; (i) Génisson, Y.; Lamandé, L.; Andrieu-Abadie, N.; Chantal, A.; Baltas, M. *Tetrahedron: Asymmetry* **2007**, *18*, 857–864; (j) Prasad, K. R.; Chandrakumar, A. *J. Org. Chem.* **2007**, *72*, 6312–6315.
11. (a) Koskinen, A. M. P.; Koskinen, P. M. *Tetrahedron Lett.* **1993**, *34*, 6765–6768; (b) Koskinen, A. M. P.; Otsomaa, L. A. *Tetrahedron* **1997**, *53*, 6473–6484; (c) Koskinen, A. M. P.; Kallatsa, O. *Tetrahedron* **2003**, *59*, 6947–6954.
12. Czernecki, S.; Georgoulis, C.; Provelenghiou, C. *Tetrahedron Lett.* **1976**, 3535–3536.
13. Kim, K.; Song, Y.; Lee, B.; Hahn, C. *J. Org. Chem.* **1986**, *51*, 404–407.
14. Compound **4**: ^{1}H NMR (400 MHz, $CDCl_3$) ppm: 1.42 (s, 9H), 2.07 (s, 3H), 2.33 (br s, 1H), 3.63 (m, 1H), 3.67 (dd, $J = 3.6$, 11.4 Hz, 1H), 3.95 (dd, $J = 3.1$, 11.2 Hz, 1H), 4.34 (d, $J = 11.7$ Hz, 1H), 4.42 (dd, $J = 5.2$, 8.7 Hz, 1H), 4.58 (dd, $J = 5.9$, 12.5 Hz, 1H), 4.61 (d, $J = 11.9$ Hz, 1H), 4.68 (dd, $J = 7.5$, 13.2 Hz, 1H), 5.22 (br s, 1H), 5.67 (tdd, $J = 1.1$, 9.3, 11.1 Hz, 1H), 5.84 (dddd, $J = 0.8$, 6.3, 7.2, 11.3 Hz, 1H), 7.31 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$) ppm: 20.9, 28.3, 54.8, 60.0, 62.3, 71.0, 75.8, 79.5, 127.8, 128.0, 128.5, 129.1, 132.0, 137.5, 155.7, 170.8. HRMS calcd for ($C_{20}H_{29}NO_6Na$) [M+Na] 402.1893, obsd: 402.1884.
15. (a) Hara, O.; Fujii, K.; Hamada, Y.; Sakagami, Y. *Heterocycles* **2001**, *54*, 419–424; (b) Burke, S.; Jiang, L. *Org. Lett.* **2001**, *3*, 1953–1955; (c) Jiang, L.; Burke, S. *Org. Lett.* **2002**, *4*, 3411–3414.
16. Compound **3a**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.43 (s, 9H), 3.70 (dd, $J = 7.3$, 8.6 Hz, 1H), 4.02 (dd, $J = 7.2$, 8.5 Hz, 1H), 4.02 (m, 1H), 4.38 (m, 1H), 4.52 (d, $J = 11.7$ Hz, 1H), 4.65 (d, $J = 11.7$ Hz, 1H), 5.03 (br d, $J = 7.7$ Hz, 1H), 5.29 (ddd, $J = 1.1$, 1.7, 10.3 Hz, 1H), 5.40 (ddd, $J = 1.3$, 1.6, 17.2 Hz, 1H), 6.03 (ddd, $J = 7.0$, 10.3, 17.2 Hz, 1H), 7.36 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.3, 52.8, 70.8, 73.6, 79.63, 79.67, 82.3, 118.2, 127.8, 128.0, 128.5, 134.2, 137.6, 155.5. HRMS calcd for ($C_{18}H_{25}NO_4Na$) [M+Na] 342.1681, obsd: 342.1689.
17. Blackwell, H.; O'Leary, D.; Chatterjee, A.; Washenfelder, R.; Bussman, D. A.; Grubbs, R. *J. Am. Chem. Soc.* **2000**, *122*, 58–71.
18. (a) Rai, A.; Basu, A. *Org. Lett.* **2004**, *6*, 2861–2863; (b) Rai, A.; Basu, A. *J. Org. Chem.* **2005**, *70*, 8228–8230.
19. Lera, M.; Hayes, C. *Org. Lett.* **2001**, *3*, 2765–2768.
20. Compound **14**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.88 (t, $J = 7.0$ Hz, 3H), 1.25 (m, 20H), 1.43 (s, 9H), 2.07 (m, 2H), 3.65 (t, $J = 8.1$ Hz, 1H), 3.95 (t, $J = 4.7$ Hz, 1H), 3.99 (dd, $J = 7.7$, 8.2 Hz, 1H), 4.32 (dd, $J = 4.2$, 7.7 Hz, 1H), 4.36 (m, 1H), 4.51 (d, $J = 11.7$ Hz, 1H), 4.66 (d, $J = 11.7$ Hz, 1H), 5.04 (d, $J = 7.7$ Hz, 1H), 5.65 (tdd, $J = 1.1$, 7.7, 15.5 Hz, 1H), 5.80 (td, $J = 6.7$, 15.4 Hz, 1H), 7.33 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.5, 23.1, 28.8., 29.4, 29.7, 29.8, 29.9, 30.00, 30.04, 30.1, 32.3, 32.8, 53.4, 70.9, 74.1, 80.0, 80.3, 83.0, 125.9, 128.2, 128.3, 128.9, 136.2, 138.1, 156.0. HRMS calcd for ($C_{30}H_{49}NO_4Na$) [M+Na] 510.3559, obsd: 510.3580.