A microwave-assisted stereoselective synthesis of polyandrocarpamines A and B

Author

Davis, Rohan A, Baron, Paul S, Neve, Juliette E, Cullinane, Carleen

Published

2009

Journal Title

Tetrahedron Letters

DOI

10.1016/j.tetlet.2008.12.010

Rights statement

Downloaded from

Griffith Research Online

A microwave-assisted stereoselective synthesis of polyandrocarpamines A and B

Rohan A. Davis,[a,*] Paul S. Baron,[a] Juliette E. Neve,[a] Carleen Cullinane[b]

[a] *Eskitis Institute, Griffith University, Brisbane, QLD 4111, Australia*
[b] *Peter MacCallum Cancer Centre, St. Andrew's Place, East Melbourne, VIC 3002, Australia*

Abstract

A stereoselective synthesis of the marine natural products, polyandrocarpamines A and B, has been achieved using a high-yielding one-step aldol condensation reaction under microwave conditions. The structures of both synthetic compounds were confirmed following 1D and 2D NMR, UV, IR and MS spectral analysis, and by comparison with literature data. Both synthetic natural products were assigned *Z* geometry about their exocyclic double bond on the basis of $^{13}C/^{1}H$ long-range coupling constants, which were measured using a gHSQMBC experiment. Polyandrocarpamines A and B were evaluated for their cytotoxicity towards the tumour cell lines, MCF-7 (breast), H460 (lung) and SF268 (central nervous system). Polyandrocarpamine A displayed selective cytotoxicity towards the SF268 cell line with a GI_{50} value of 65 μM.

---

[*] Corresponding author. Tel.:+61-7-3735-6043; fax: +61-7-3735-6001; e-mail: r.davis@griffith.edu.au.

Introduction

Marine organisms have proven to be a rich source of novel, and structurally diverse metabolites that display a wide variety of biologically significant activities.[1-3] Examples include the anti-fouling oroidin dimer, mauritiamine,[4] the MEK-1 inhibitor, hymenialdisine,[5] the EGF inhibitor, purealidin K[6] and the histaminergic antagonist, dispacamide A **3**.[7] All the marine metabolites listed above all belong to the 2-aminoimidazolone class of compounds, and all have been isolated from marine sponges. Other marine organisms, such as ascidians, have also yielded a small number of alkaloids belonging to this structure class, although no bioactivity has been reported.[8] Polyandrocarpamines A **1** and B **2** are examples of ascidian-derived 2-aminoimidazolones. These simple alkaloids were first isolated and synthesized in 2002,[9] although sufficient quantities of these molecules were obtained by total synthesis, no biological activity was reported. Due to our interest in the synthesis of bioactive natural products and their structural analogues,[10-15] we wished to obtain polyandrocarpamines A **1** and B **2** in sufficient quantities in order to undertake biological evaluations. Herein, we report an alternative synthesis for polyandrocarpamines A and B, along with their cytotoxicity profile against three different tumour cell lines.

The previous synthesis of polyandrocarpamines A **1** and B **2** (Scheme 1),[9] along with the related marine-derived imidazolones dispacamide A **3**,[16] and leucettamine B **4**,[17] have all been reported using the same methodology for the construction of the 2-aminoimidazolone moiety (Figure 1).[9,16,17]

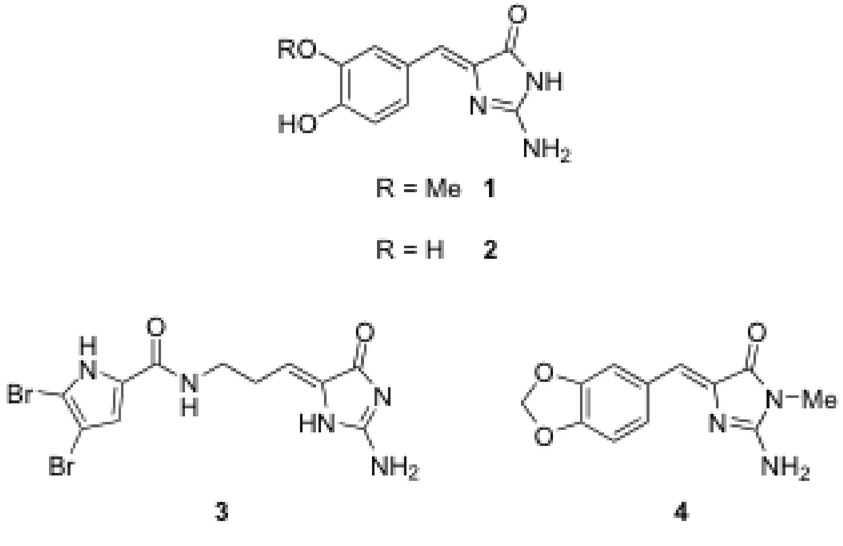
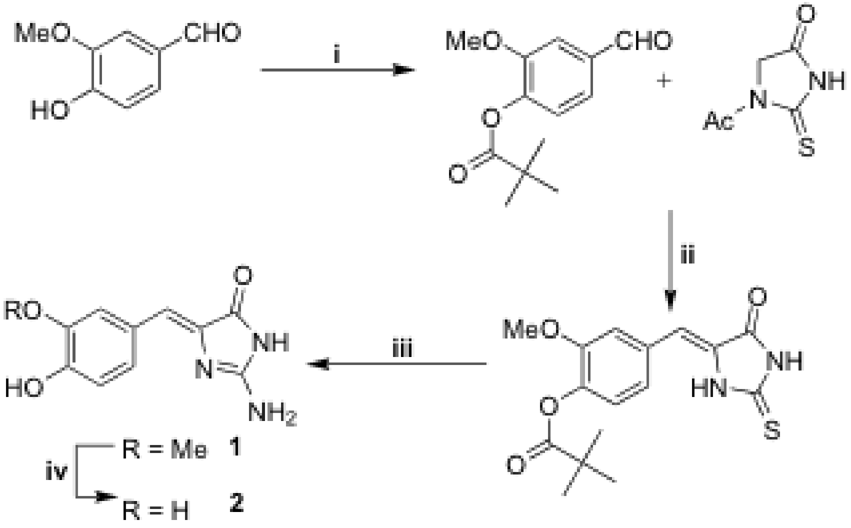


Figure 1. Chemical structures of marine natural products **1**-**4**.

The synthesis of the 2-aminoimidazolone component for **1**-**4** involved the generation of an alkyl- or aryl-thiohydantoin, followed by the facile conversion of the thiohydantoin to the corresponding 2-aminoimidazolones using *tert*-butyl hydroperoxide as an oxidant in the presence of aqueous ammonia (Scheme 1).[9,16,17] This method generally requires the protection of reactive groups (e.g., -OH) and long reaction times (up to 72 h), which often result in variable yields.[9]

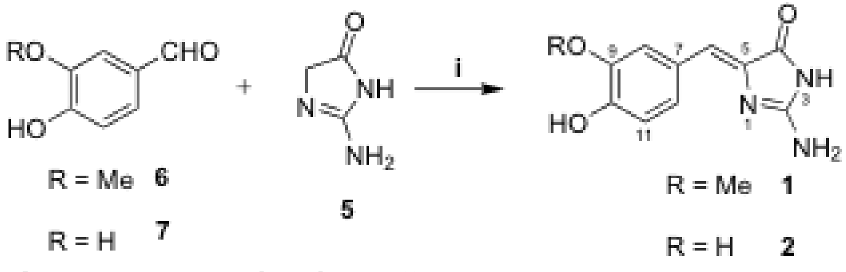


Scheme 1. Reagents and conditions for the original synthesis of polyandrocarpamines A and B[9]: (i) Pivaloyl chloride, pyridine, Ar, rt, 7 h (ii) NaOAc, AcOH, reflux, 2 h (iii) *tert*-Butyl hydroperoxide, aq. NH_4OH, MeOH, rt, 72 h (iv) $BBr_3.S(Me)_2$, DCE, reflux, 15 min.

An alternative synthetic route for the synthesis of 2-aminoimidazolones has been reported using glycocyamidine **5**, or a glycocyamidine derivative, in the presence of an aldehyde, NaOAc and AcOH.[17-19] This method uses a readily synthesized reagent (i.e. **5**), requires no protection chemistry and involves a one-step condensation reaction that we thought might be suitable for microwave chemistry. The sponge metabolite, leucettamine B **4** has been successfully synthesized using this glycocyamidine methodology under reflux conditions, although the reaction generated a *Z/E* mixture (9.5:0.5) of **4**.[17]

In our laboratory, the HCl salt of glycocyamidine **5** was synthesized using a microwave-modified literature preparation.[20] This involved the addition of glycocyamine to a solution of H_2O/32% aqueous HCl (3:1) followed by heating under microwave conditions at 160 °C for 30 min. Following purification by recrystallisation, the HCl salt of glycocyamidine **5** was condensed with 3-methoxy-4-hydroxybenzaldehyde **6** or 3,4-dihydroxybenzaldehye **7** in a NaOAc/AcOH slurry under microwave conditions of 160 °C for 30 min (Scheme 2). Purification of each separate reaction mixture using C_{18} flash chromatography yielded the TFA salts of polyandrocarpamines A[21] **1** (193 mg, 56%) and B[22] **2** (267 mg, 80%) in high-yields.

By comparing the overall yields for both **1** (31% v.s. 56%), and **2** (6% v.s. 80%) from the two different synthetic routes outlined in Schemes 1 and 2, we showed that the new, faster and simpler methodology also resulted in substantial yield improvements.



Scheme 2. Reagents and conditions: (i) NaOAc, AcOH, µw, 160 °C, 20 min.

The structural confirmation and $^1H/^{13}C$ NMR assignments of compounds **1** and **2** were performed following extensive 1D and 2D NMR spectroscopy (gCOSY, gHSQC, gHMBC, ROESY). The geometry about the exocyclic double bonds of **1** and **2** was determined on the basis of $^{13}C/^1H$ long range coupling constants, which were measured using a gHSQMBC experiment.[23] Analysis of each gHSQMBC experiment identified that the coupling constant between the exocyclic protons [δ 6.81 (H-6) for **1**; δ 6.79 (H-6) for **2**] and the imidazolone carbonyl [165.2 ppm (C-4) for **1**; 165.7 ppm (C-4) for **2**] was 5.4 Hz for both molecules, which is consistent with the *Z* geometry.[24,25] Both synthetic **1** and **2** were obtained solely as their *Z* isomers and no isomerisation about the exocyclic double bond was observed during our studies.

Interestingly, several chemical shift values for the TFA salts of **1** and **2** differed compared to the original data reported for the natural products and synthetics.[9] In particular, the ^{13}C NMR data for the 2-aminoimidazolone moiety of **1** and **2** reported in this letter showed some differences (Δ 5.2 - 8.7 ppm for C-2; Δ 11.1 - 13.0 ppm for C-4; Δ 8.4 - 8.8 ppm for C-5) with that published in the original isolation and synthesis paper of polyandrocarpamines A and B.[9] These differences were postulated to arise since the isolated natural products were purified as their free bases.[9] In order to confirm this hypothesis, a small amount of polyandrocarpamine A TFA salt was purified on a base-stable C_{18} HPLC column using aqueous NH_4OH/MeOH. The free base of polyandrocarpamine A was obtained, and NMR assignments were made following analysis of the 1D and 2D NMR spectra, and were shown to be essentially identical to those of the natural product originally reported.[9]

Polyandrocarpamines A and B were tested for their cytotoxic activity against the tumour cell lines, H460 (lung), MCF-7 (breast), and SF268 (central nervous system).[26,27] Initial dosing at 10 μM for 72 h for both alkaloids showed no growth inhibition towards H460 and MCF-7; however, moderate cytotoxicity was identified towards the cancer cell line, SF268. Further biological testing revealed that **1** and **2** showed cytotoxicity towards this cell line with GI_{50} values of 65 and >80 μM, respectively.

In conclusion, we have successfully synthesized polyandrocarpamines A and B stereoselectively in high-yield using a microwave reactor, and shown that both natural products have selective cytotoxicity towards the SF268 tumour cell line. With the synthesis of large quantities of **1** and **2**, these molecules will now be added to the Queensland compound library (QCL)[28] at the Eskitis Institute, where they will be available for further biological evaluations. This new synthetic route to polyandrocarpamines has substantially reduced synthesis time, by up to 80 h, and uses less reagents compared to the original procedure.[9] This method makes this class of marine alkaloids now more amenable to natural product-based combinatorial synthesis.

Acknowledgements

The authors acknowledge financial support of this work by Griffith University and the Eskitis Institute. We thank H. T. Vu from Griffith University for acquiring the HRESIMS measurements. One of us (P. B.) thanks Griffith University for an Honours scholarship. A. Slater is acknowledged for technical assistance in performing the cell culture assays.

References and notes

1. Hill, R. A. *Annu. Rep. Prog. Chem., Sect. B: Org. Chem.* **2007**, *103*, 125.
2. Blunt, J. W.; Copp, B. R.; Hu, W.-P.; Munro, M. H. G.; Northcote, P. T.; Prinsep, M. R. *Nat. Prod, Rep*. **2007**, *24*, 31.
3. Blunt, J. W.; Copp, B. R.; Hu, W.-P.; Munro, M. H. G.; Northcote, P. T.; Prinsep, M. R. *Nat. Prod, Rep*. **2008**, *25*, 35.
4. Tsukamoto, S.; Kato, H.; Hirota, H.; Fusetani, N. *J. Nat. Prod*. **1996**, *59*, 501.
5. Tasdemir, D.; Mallon, R.; Greenstein, M.; Feldberg, L. R.; Kim, S. C.; Collins, K.; Wojciechowicz, D.; Mangalindan, G. C.; Concepcion, G. P.; Harper, M. K.; Ireland, C. M. *J. Med. Chem.* **2002**, *45*, 529.
6. Kobayashi, J. I.; Honma, K.; Sasaki, T.; Tsuda, M. *Chem. Pharm. Bull.* **1995**, *43*, 403-7.
7. Cafieri, F.; Gattorusso, E.; Mangoni, A.; Taglialatela-Scafati, O. *Tetrahedron Lett.* **1996**, *37*, 3587.
8. *Dictionary of Natural Products on CD-ROM*, 16.2 ed.; Chapman and Hall Electronic Publishing Division: 2008.
9. Davis, R. A.; Aalbersberg, W.; Meo, S.; Moreira da Rocha, R.; Ireland, C. M. *Tetrahedron* **2002**, *58*, 3263.
10. Davis, R. A.; Carroll, A. R.; Quinn, R. J. *Aust. J. Chem*. **2001**, *54*, 355.
11. Davis, R. A. *J. Nat. Prod.* **2005**, *68*, 769.
12. Davis, R. A.; Watters, D.; Healy, P. C. *Tetrahedron Lett.* **2005**, *46*, 919.
13. Davis, R. A.; Kotiw, M. *Tetrahedron Lett*. **2005**, *46*, 5199.
14. Davis, R. A.; Pierens, G. K.; Parsons, P. G. *Magn. Reson. Chem*. **2007**, *45*, 442.
15. Poulsen, S.-A.; Davis, R. A.; Keys, T. G. *Bioorg. Med. Chem.* **2006**, *14*, 510.
16. Lindel, T.; Hoffmann, H. *Tetrahedron Lett.* **1997**, *38*, 8935.
17. Roue, N.; Bergman, J. *Tetrahedron* **1999**, *55*, 14729.
18. Johnson, T. B.; Nicolet, B. H. *J. Am. Chem. Soc*. **1915**, *37*, 2416.
19. Prager, R. H.; Tsopelas, C. *Aust. J. Chem.* **1990**, 43, 367.
20. Bengelsdorf, I. S. *J. Am. Chem. Soc.* **1953**, *75*, 3138.
21. Yellow amorphous solid; mp 182-186 ºC; UV (MeOH) λ_{max} (log ε) 216 (3.66), 240 (2.55), 357 (2.76) nm; IR ν_{max} (KBr) 3500-2800, 1712, 1667, 1592, 1519, 1436, 1395, 1291, 1201, 1136, 1055, 1029, 840, 802, 723 cm^{-1}; ^1H NMR (500 MHz, CD_3OD) δ 3.91 (3H, s, 9-OCH_3), 6.81 (1H, s, H-6), 6.87 (1H, d, *J* = 8.5 Hz, H-11), 7.10 (1H, dd, *J* = 8.5, 1.5 Hz, H-12), 7.12 (1H, d, *J* = 1.5 Hz, H-8); ^{13}C NMR (125 MHz, CD_3OD) δ 56.8 (9-OCH_3), 114.3 (C-8), 116.9 (C-11), 119.7 (C-6), 123.6 (C-5), 124.8 (C-7), 125.8 (C-12), 149.5 (C-9), 150.6 (C-10), 157.6 (C-2), 165.2 (C-4); (+)-LRESIMS *m/z* (rel. int.) 234 (100) $[M-CF_3COO]^+$; (+)-HRESIMS *m/z* 234.08709 ($C_{11}H_{12}N_3O_3$ $[M-CF_3COO]^+$ requires 234.08732).
22. Yellow amorphous solid; mp >250 ºC (decomp.); UV (MeOH) λ_{max} (log ε) 218 (2.98), 250 (2.73), 359 (3.00) nm; IR ν_{max} (KBr) 3500-2800, 1704, 1655, 1594, 1438, 1396, 1270, 1191, 1135, 841, 797, 722, 669 cm^{-1}; ^1H NMR (500 MHz, CD_3OD) δ 6.79 (1H, s, H-6), 6.86 (1H, d, *J* = 8.0 Hz, H-11), 7.01 (1H, d, *J* = 8.0 Hz, H-12), 7.02 (1H, s, H-8); ^{13}C NMR (125 MHz, CD_3OD) δ 117.0 (C-11), 118.0 (C-8), 119.8 (C-6), 124.0 (C-5), 124.1 (C-12), 125.0 (C-7), 147.1 (C-9), 149.5 (C-10), 157.9 (C-2), 165.7 (C-4); (+)-LRESIMS *m/z* (rel. int.) 220 (100) $[M-CF_3COO]^+$; (+)-HRESIMS *m/z* 220.07273 ($C_{10}H_{10}N_3O_3$ $[M-CF_3COO]^+$ requires 220.07167).

23. Williamson, R. T.; Marquez, B. L.; Gerwick, W. H.; Kover, K. E. *Magn. Reson. Chem*. **2000**, *38*, 265.
24. Guella, G.; Mancini, I.; Zibrowius, H.; Pietra, F. *Helv. Chim. Acta* **1988**, *71*, 773.
25. Chan, G. W.; Mong, S.; Hemling, M. E.; Freyer, A. J.; Offen, P. H.; DeBrosse, C. W.; Sarau, H. M.; Westley, J. W. *J. Nat. Prod.* **1993**, *56*, 116.
26. Skehan, P.; Storeng, R.; Scudiero, D.; Monks, A.; McMahon, J.; Vistica, D.; Warren, J. T.; Bokesch, H.; Kenney, S.; Boyd, M. R. *J. Natl. Cancer Inst.* **1990**, *82*, 1107.
27. Monks, A.; Scudiero, D.; Skehan, P.; Shoemaker, R.; Paull, K.; Vistica, D.; Hose, C.; Langley, J.; Cronise, P.; Vaigro-Wolff, A. *J. Natl. Cancer Inst.* **1991**, *83*, 757.
28. www.griffith.edu.au/science/queensland-compound-library

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.12.010.