VIP Natural Products

DOI: 10.1002/ange.200801138

Total Synthesis of (±)-Axinellamines A and B**

*Daniel P. O'Malley, Junichiro Yamaguchi, Ian S. Young, Ian B. Seiple, and Phil S. Baran**

The axinellamines (**1**,**2**, Figure 1), isolated by Quinn and co-workers in 1999, are among the most complex marine natural products isolated to date.[1] The intricate architecture of these molecules includes a tetracyclic bisguanidine core with eight contiguous stereocenters. The highly polar nature of the two guanidine units present in **1** and **2** further complicate the practical aspects of dealing with such molecules. Indeed, together with the massadines and palau'amines (see Figure 1 in the preceeding communication for structures),[2] these molecules represent a complexity frontier for chemical synthesis. Despite extensive efforts by many groups, a solution to this puzzle has thus far remained elusive.[3,4] Herein, we present the first total synthesis of axinellamines A (**1**) and B (**2**).

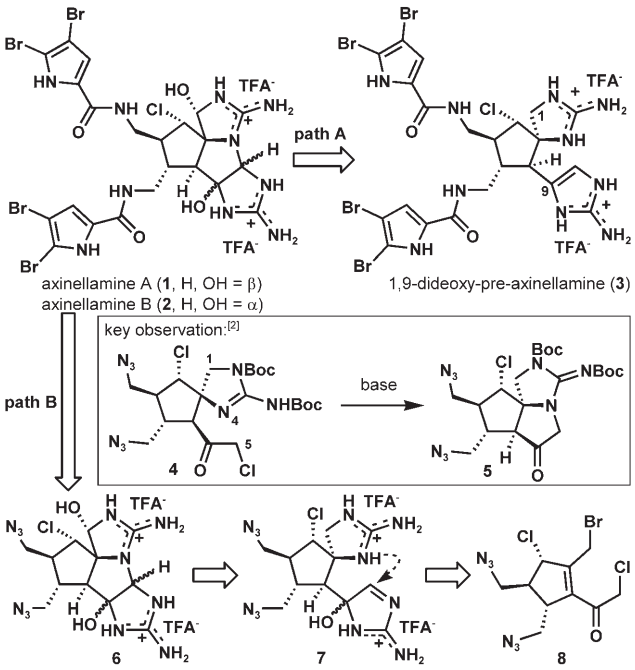


Figure 1. Retrosynthetic analysis of the axinellamines A (**1**) and B (**2**) inspired by a key observation made in reference [2].

The preceding communication reported the synthesis of 1,9-dideoxy-pre-axinellamine (**3**),[2] a pivotal first step towards empirically testing the "pre-axinellamine"-biogenetic hypothesis (Path A, Figure 1) for the formation of complex dimeric pyrrole-imidazole alkaloids (PIA).[3] During the course of that work, it was found that the spirocyclic guanidine unit in intermediates such as **4** (Figure 1) would readily displace leaving groups at C-5 (axinellamine numbering) to form **5**, thereby establishing the N-4–C-5 bond found in the axinellamines. Although the formation of compound **5** represented a hurdle that had to be overcome during the synthesis of 1,9-dideoxy-pre-axinellamine (**3**), it was recognized that the facility of this ring closure provided an opportunity to target the axinellamine family selectively via **6** (Path B, , Figure 1); by forging the N-4–C-5 connection by way of an intermediate such as imine **7**, interference by massadine, palau'amine, or styloguanidine type ring closures could be avoided. Elaboration of the tetracyclic core of the axinellamines prior to attachment of the pyrrole side chains and oxidation at C-1 proved to be a successful strategy, as demonstrated in Scheme 1.

Accordingly, intermediate **9** (obtained from **8**, see preceding communication[2]) was deprotected with TFA/DCM to give free aminoimidazole **10** (Scheme 1). Exposure to dimethyldioxirane (DMDO) at 0 °C in acetone/water then afforded diol **11** as a mixture of two major diastereomers, along with minor amounts of closed product **12**.[5] Although other oxidants such as *N*-bromosuccinimide also formed **11**, the use of DMDO allowed the removal of excess reagent by simple evaporation.[6] The crude mixture of diastereomers was then subjected to cyclization with TFA/DCM to give two diastereomers of **12**, which possess the tetracyclic core of the axinellamines. This reaction presumably proceeds by dehydration of **11** to form imine **7**, which undergoes intramolecular attack by the spiro guanidine subunit. Although this mixture of diastereomeric hemiaminals (**11**) could be separated by preparative HPLC, it was routinely carried forward to the next step without purification.

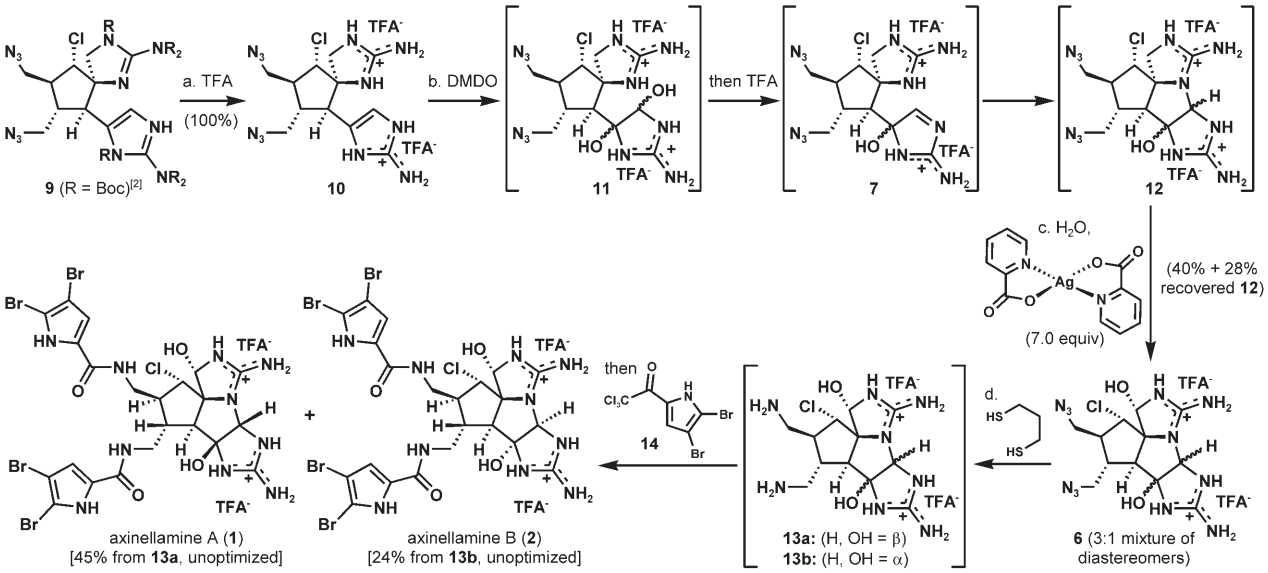
At this point, the stage was set for the key oxidation of the spiro methylene unit at C-1. Although there is ample precedent for the oxidation of amines to imines[7] and amides to *N*-acylimines,[8] there are no previous reports of similar oxidations of unactivated guanidines. Of the oxidants evaluated for this transformation, silver(II) picolinate[9] and $K_2S_2O_8$ gave the most promising results. In the event, heating intermediate **12** to 50 °C with silver(II) picolinate in H_2O gave

[*] D. P. O'Malley, Dr. J. Yamaguchi, Dr. I. S. Young,[+] I. B. Seiple,[+] Prof. Dr. P. S. Baran
Department of Chemistry
The Scripps Research Institute
10650 North Torrey Pines Road, La Jolla, CA 92037 (USA)
Fax: (+1) 858-784-7375
E-mail: pbaran@scripps.edu

[+] Both authors contributed equally to this paper.

[**] We thank Prof. R. J. Quinn for a sample of authentic **1**. Financial support for this work was provided by the NIH/NIGMS (GM-073949), Bristol–Myers Squibb, Eli Lilly, Merck, the Japan Society for the Promotion of Science (JSPS) for a postdoctoral fellowship to J.Y., the Natural Sciences and Engineering Research Council of Canada (NSERC) for a postdoctoral fellowship to I.S.Y., and the U.S. Department of Defense and the Hertz Foundation for predoctoral fellowships to D.P.O.

Supporting information for this article is available on the WWW under http://www.angewandte.org or from the author.



Scheme 1. Total synthesis of axinellamines A (**1**) and B (**2**). Reagents and conditions: a) TFA/DCM (2/1), 23 °C, 3 h, quantitative; b) DMDO (1.4 equiv), H_2O, 0 °C, 5 h; then TFA/DCM (2/1), 23 °C, 13 h; c) silver(II) picolinate (7.0 equiv), H_2O, 50 °C, 19 h, 30% one diastereomer, 10% other diastereomer (+28% RSM for minor diastereomer); d) 1,3-propanedithiol (15–20 equiv), triethylamine (11–14 equiv), methanol, 23 °C, 2 h; then **14** (3.0 equiv), diisopropylethylamine (3.0 equiv), DMF, 45 °C, 6–11 h, **1** = 45%, **2** = 24%. TFA = trifluoroacetic acid, DCM = dichloromethane, DMDO = dimethyldioxirane, DMF = *N*,*N*-dimethylformamide, RSM = recovered starting material.

two diastereomers of tetracycle **6** in 40% yield from **9**, along with 28% of one recovered diastereomer of **12**. Given the six amines and the free hemiaminal in compound **12**, it is rather remarkable that this protocol could achieve the necessary chemo- and regio- selectivity necessary to oxidize C-1 and avoid overoxidation to an imidazolidinone. Strategically, the success of this reaction validates the underlying logic of a retrosynthetic plan that emphasizes a gradual linear increase in oxidation state (as opposed to the reduction of an imidazolidinone to set the C-1 oxidation level).[10]

Completion of the total synthesis relied on the ability to reduce the azides present in **6** and selectively acylate the resulting primary amines in the presence of two unprotected guanidines and the two potentially sensitive hemiaminal functionalities. Ultimately, each diastereomer of **6** was elaborated to axinellamine by reduction of the azides with 1,3-propanedithiol[11] and triethylamine followed by acylation of the crude diamine (**13a**,**b**) with trichloro ketone **14**[12] and Hünig's base in DMF, which furnished axinellamines A (**1**) and B (**2**) in 45 and 24% yield (both unoptimized), respectively, from **6**. Monitoring the above reactions (azide reduction and acylation) by LC-MS and crude ^{1}H NMR spectroscopy suggest that they are fairly efficient (>80%), and the diminished overall yield for the two-step sequence may be a result of the purification process. The spectroscopic and physical properties of synthetic **1** and **2** were identical to those reported by Quinn and co-workers[1,13] (for ^{1}H NMR comparison, see Figure 2).

In conclusion, we report a concise synthesis of axinellamines A and B that requires only two purification events from previously reported intermediate **9**. Representing the first total synthesis of any member of the palau'amine/axinellamine/massadine family, this synthesis is a culmination

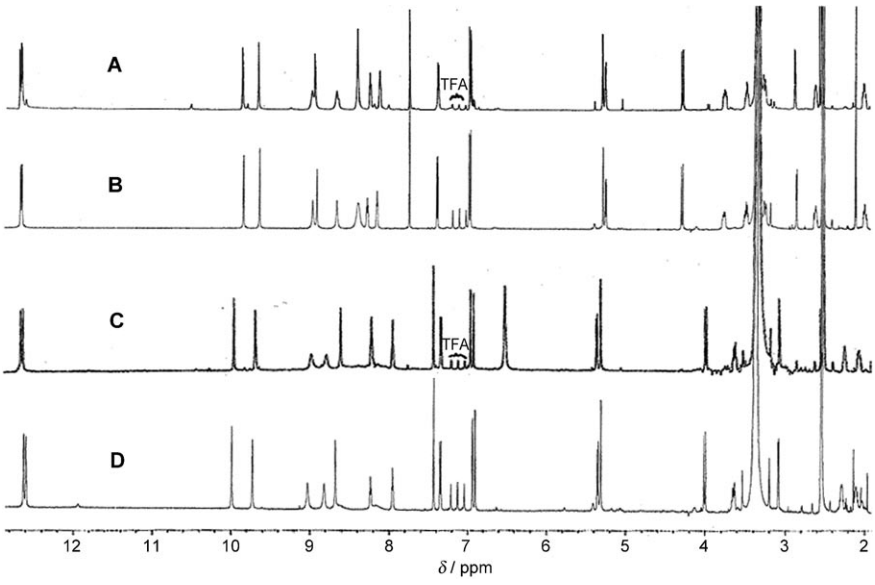


Figure 2. Spectroscopic comparison of natural axinellamine A (panel A) and axinellamine B (panel C) with synthetic versions (panels B and D respectively). See Supporting Information for a more detailed image.

of efforts to understand the fundamental chemical reactivity of complex pyrrole-imidazole alkaloids, beginning with sceptrin and ageliferin.[5,14] Of particular note in the present report is the development of protocols with striking chemoselectivity for the oxidation and acylation of highly complex unprotected[10] polyamines and the recognition that the N-4–C-5 connection could profitably be formed in an intermediate such as **7**. Much more remains to be learned in the study of this fascinating marine natural product family.[13]

Received: March 9, 2008
Published online: March 20, 2008

Keywords: alkaloids · axinellamine · natural products · oxidation · palau'amine · total synthesis

[1] S. Urban, P. de A. Leone, A. R. Carroll, G. A. Fechner, J. Smith, J. N. A. Hooper, R. J. Quinn, *J. Org. Chem.* **1999**, *64*, 731 – 735.
[2] J. Yamaguchi, I. B. Seiple, I. S. Young, D. P. O'Malley, M. Maue, P. S. Baran, *Angew. Chem.* **2008**, *120*, DOI: 10.1002/ange.200705913; *Angew. Chem. Int. Ed.* **2008**, *47*, DOI: 10.1002/anie.200705913, see preceding paper.
[3] For a review, see: M. Köck, A. Grube, I. B. Seiple, P. S. Baran, *Angew. Chem.* **2007**, *119*, 6706 – 6714; *Angew. Chem. Int. Ed.* **2007**, *46*, 6586 – 6594.
[4] For a summary of approaches to the pyrrole-imidazole alkaloids, see ref. [2,4], references therein, and the following recent reports: a) B. A. Lanman, L. E. Overman, R. Paulini, N. S. White, *J. Am. Chem. Soc.* **2007**, *129*, 12896 – 12900; b) R. Sivappa, N. M. Hernandez, Y. He, C. J. Lovely, *Org. Lett.* **2007**, *9*, 3861 – 3864; c) L. Tang, D. Romo, *Heterocycles* **2007**, *74*, 999 – 1007; d) T. A. Cernak, J. L. Gleason, *J. Org. Chem.* **2008**, *73*, 702 – 710; e) S. Wang, D. Romo, *Angew. Chem. Int. Ed.* **2008**, *47*, 1284 – 1286.
[5] D. P. O'Malley, K. Li, M. Maue, A. L. Zografos, P. S. Baran, *J. Am. Chem. Soc.* **2007**, *129*, 4762 – 4775.
[6] Oxidation of 2-aminoimidazoles with intra- and intermolecular nucleophilic capture is precedented, see ref. [5] and: a) L. H. Foley, G. Büchi, *J. Am. Chem. Soc.* **1982**, *104*, 1776 – 1777; b) A. Olofson, K. Yakushijin, D. A. Horne, *J. Org. Chem.* **1998**, *63*, 1248 – 1253; c) A. C. B. Sosa, K. Yakushijin, D. A. Horne, *Org. Lett.* **2000**, *2*, 3443 – 3444; d) K. J. Wiese, K. Yakushijin, D. A. Horne, *Tetrahedron Lett.* **2002**, *43*, 5135 – 5136; e) K. S. Feldman, A. P. Skoumbourdis, M. D. Fodor, *J. Org. Chem.* **2007**, *72*, 8076 – 8086; f) H. Garrido-Hernandez, M. Nakadai, M. Vimolratana, Q. Li, T. Doundoulakis, P. G. Harran, *Angew. Chem.* **2005**, *117*, 775 – 779; *Angew. Chem. Int. Ed.* **2005**, *44*, 765 – 769; g) M. Nakadai, P. G. Harran, *Tetrahedron Lett.* **2006**, *47*, 3933 – 3935.
[7] a) S.-I. Murahashi, T. Naota, H. Taki, *J. Chem. Soc. Chem. Commun.* **1985**, 613 – 614; b) R. M. Moriarty, R. K. Vaid, M. P. Duncan, *Tetrahedron Lett.* **1988**, *29*, 6913 – 6916; c) A. Goti, M. Romani, *Tetrahedron Lett.* **1994**, *35*, 6567 – 6570; d) K. C. Nicolaou, C. J. N. Matheson, T. Montagnon, *J. Am. Chem. Soc.* **2004**, *126*, 5192 – 5201; e) H. Choi, M. P. Doyle, *Chem. Commun.* **2007**, *7*, 745 – 747.
[8] a) S.-I. Murahashi, T. Naota, T. Kuwabara, T. Saito, H. Kumobayashi, S. Akutagawa, *J. Am. Chem. Soc.* **1990**, *112*, 7820 – 7822; b) T. Nagamatsu, H. Yamasaki, *J. Chem. Soc. Chem. Commun.* **1995**, 2041 – 2043; c) G. Han, M. G. Laporte, J. J. Folmer, K. M. Werner, S. M. Weinreb, *J. Org. Chem.* **2000**, *65*, 6293 – 6306; d) X.-L. Qui, F.-L. Qing, *J. Org. Chem.* **2005**, *70*, 3826 – 3837; e) C. J. N. Matheson, Ph.D. Thesis, The Scripps Research Institute, **2007**.
[9] a) G. W. A. Fowles, R. W. Matthews, R. A. Walton, *J. Chem. Soc. A* **1968**, 1108 – 1113; b) T. G. Clarke, N. A. Hampson, J. B. Lee, J. R. Morley, B. Scanlon, *Can. J. Chem.* **1969**, *47*, 1649 – 1654; c) T. G. Clarke, N. A. Hampson, J. B. Lee, J. R. Morley, B. Scanlon, *J. Chem. Soc. C* **1970**, 815 – 817; d) J. B. Lee, C. Parkin, M. J. Shaw, *Tetrahedron* **1973**, *29*, 751 – 752.
[10] P. S. Baran, T. J. Maimone, J. M. Richter, *Nature* **2007**, *446*, 404 – 408.
[11] H. Bayley, D. N. Stardring, J. R. Knowles, *Tetrahedron Lett.* **1978**, *19*, 3633 – 3634.
[12] D. M. Bailey, R. E. Johnson, *J. Med. Chem.* **1973**, *16*, 1300 – 1302.
[13] See Supporting information for full characterization and copies of spectra for all isolated intermediates.
[14] a) P. S. Baran, A. L. Zografos, D. P. O'Malley, *J. Am. Chem. Soc.* **2004**, *126*, 3726 – 3727; b) P. S. Baran, D. P. O'Malley, A. L. Zografos, *Angew. Chem.* **2004**, *116*, 2728 – 2731; *Angew. Chem. Int. Ed.* **2004**, *43*, 2674 – 2677; c) P. S. Baran, K. Li, D. P. O'Malley, C. Mistos, *Angew. Chem.* **2006**, *118*, 255 – 258; *Angew. Chem. Int. Ed.* **2006**, *45*, 249 – 252; d) B. H. Northrop, D. P. O'Malley, A. L. Zografos, P. S. Baran, K. N. Houk, *Angew. Chem.* **2006**, *118*, 4232 – 4236; *Angew. Chem. Int. Ed.* **2006**, *45*, 4126 – 4130.

