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Facile Synthesis of the Trans-Fused Azabicyclo[3.3.0]octane Core of the Palau'amines and the Tricyclic Core of the Axinellamines from a Common Intermediate

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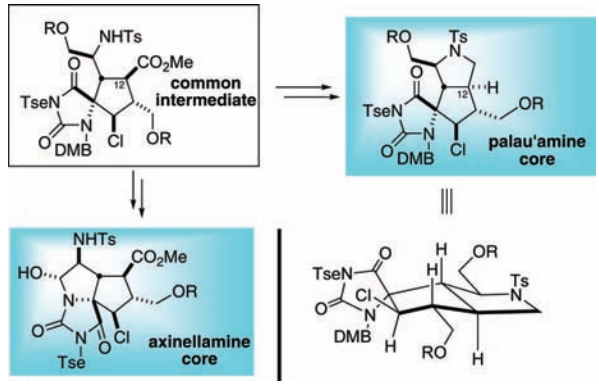
ABSTRACT



A facile synthesis of the trans-fused azabicyclo[3.3.0]octane core of palau'amine and related pyrrole-imidazole alkaloids is described. Following γ-lactam cleavage with concomitant epimerization at C12 of a previously reported tricycle, a facile intramolecular Mitsunobu reaction delivered the fully functionalized tricyclic core common to several members of the oroidin-derived alkaloids including palau'amine. An alternative cyclization of a related intermediate provides the tricyclic "aza-angular triquinane" core of the axinellamines.

The pyrrole-imidazole family of marine alkaloids features a variety of structurally diverse and complex natural products, e.g. **1**−**4**.[1] Because of their intriguing molecular architecture and, in some cases, enticing biological activities, these natural products have attracted much synthetic interest. While a racemic synthesis of axinellamine A and B was recently described,[2] other dimeric bis-guanidine alkaloids in this family, e.g. palau'amine, have not been synthesized despite the efforts of several groups.[3] The synthetic challenge of a number of these dimeric pyrrole-imidazole alkaloids was seemingly made more daunting after several recent independent reports revealed that the common, azabicyclo[3.3.0]-

(1) For recent reviews on this family of natural products, see: (a) Hoffman, H.; Lindel, T. *Synthesis* **2003**, *12*, 1753. (b) Jacquot, D. E. N.; Lindel, T. *Curr. Org. Chem.* **2005**, *9*, 1551.

(2) O'Malley, D. P.; Yamaguchi, J.; Young, I. S.; Seiple, I. B.; Baran, P. S. *Angew. Chem., Int. Ed.* **2008**, *47*, 3581.

(3) For recent advances toward oroidin alkaloids not cited in ref 1 see: (a) Sivappa, R.; Hernandez, N. M.; He, Y.; Lovely, C. *J. Org. Lett.* **2007**, *9*, 3861–3864. (b) Lanman, B. A.; Overman, L. E.; Paulini, R.; White, N. S. *J. Am. Chem. Soc.* **2007**, *129*, 12896. (c) O'Malley, D. P.; Li, K.; Maue, M.; Zografos, A. L.; Baran, P. S. *J. Am. Chem. Soc.* **2007**, *129*, 4762. (d) Tan, X.; Chen, C. *Angew. Chem., Int. Ed.* **2006**, *45*, 4345. (e) Wang, S.; Dilley, A. S.; Poullennec, K. G.; Romo, D. *Tetrahedron* **2006**, *62*, 7155. (f) Garrido-Hernandez, H.; Nakadai, M.; Vimolratana, M.; Li, Q.; Doundoulakis, T.; Harran, P. G. *Angew. Chem., Int. Ed.* **2005**, *44*, 765.

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octane moiety was in fact trans-fused[4] and not cis-fused as originally reported (Figure 1).[5]

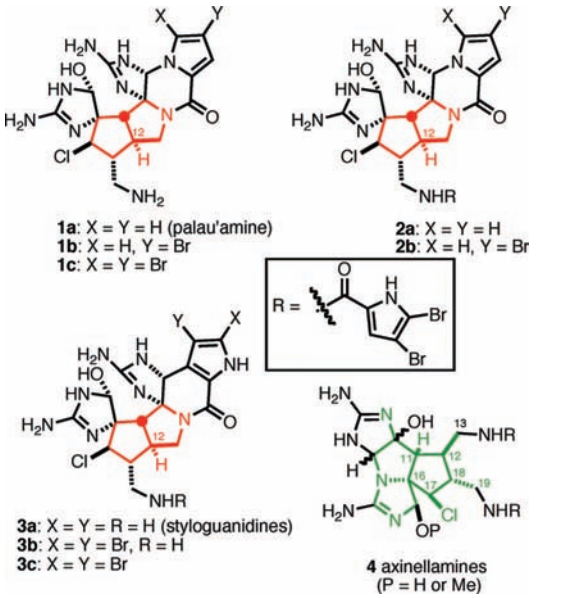


Figure 1. Structures of the palau'amines (**1**), konbu'acidins (**2**), and styloguanidines (**3**). The common *trans*-azabicyclo[3.3.0]octane core is highlighted in red. Structure of the axinellamines (**4**). The tricyclic carbon core synthesized in this work is highlighted in green (vide infra).

Although *trans*-bicyclo[3.3.0]octane systems are known and several strategies for their synthesis have been reported,[6] analogous systems containing a nitrogen atom are rare.[7] This bicyclic structure is even more scarce in the context of natural products.[4c] As described by Baran and Köck, of the >2000 known bicyclo[3.3.0]octane structures, only 10 feature a trans junction, and even more significantly, only a single crystal structure out of the 121 reported containing an azabicyclo[3.3.0]octane moiety is trans-fused. Furthermore, calculations suggest that a cis-fused system is significantly (~27 kJ/mol) favored energetically over the trans-fused counterpart.[8]

In our ongoing synthetic investigations of the pyrrole-imidazole alkaloids, we recently described an unusual oxidative cyclization that provided the first enantioselective synthesis of (+)-phakellin starting from L-prolinol (Figure 2a).[9] We envisioned the application of such phakellin

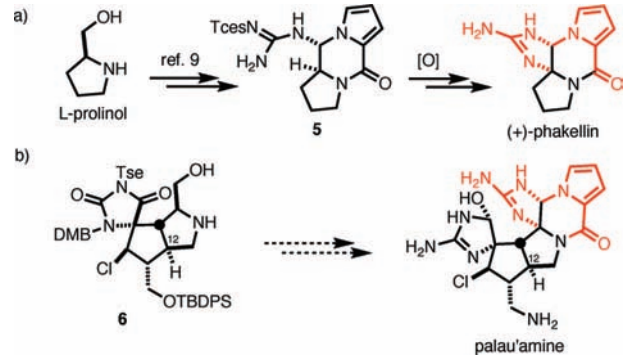


Figure 2. (a) Enantioselective synthesis of (+)-phakellin (Tces = 2,2,2-trichloroethoxysulfonyl) via an oxidative cyclization of a Tces-guanidine **5**. (b) Proposed application of this phakellin annulation strategy to palau'amine synthesis from aminoalcohol **6**.

annulation strategies to an eventual synthesis of palau'amine, which encompasses this substructure (Figure 2b).

Building on early biosynthetic proposals of Kinnel and Scheuer[5] and subsequently Al Mourabit and Potier,[10] we previously described concise entries to the spirocyclic chlorocyclopentane **7** via a sequential Diels−Alder/oxidation/chlorination/ring contraction process.[11] Herein, we describe an entry into the *trans*-azabicyclo[3.3.0]octane core (e.g., **6**, Figure 2b) of palau'amine and related pyrrole-imidazole marine alkaloids by a facile Mitsunobu process. In addition, a synthesis of the tricyclic carbon core of the axinellamines from the same intermediate is described.

We began our studies toward the *trans*-azabicyclo[3.3.0] core of palau'amine from *anti*-substituted cyclopentyl ester **8**, obtained from known tricyclic γ-lactam **7a**[11a] by selective deprotection followed by simultaneous ring cleavage/epimerization of alcohol **7b** with freshly prepared sodium methoxide.[12] The inversion of stereochemistry at C12 was confirmed by X-ray crystallographic analysis of the *p*-bromobenzoate derivative **9** (Scheme 1). The single-crystal X-ray structure of ester **9** verifies the *all-trans*-stereochemistry of the cyclopentane and also the relative stereochemistry of the spiro quaternary carbon, which is now common to various members of this alkaloid family.

In preparation for cyclization to the *trans*-azabicyclo[3.3.0] core of palau'amine, the primary alcohol of ester **8** was protected and then reduction of the methyl ester gave amino

(4) (a) Buchanan, M. S.; Carroll, R.; Quinn, R. J. *Tetrahedron Lett.* **2007**, *48*, 4573. (b) Buchanan, M. S.; Carroll, R.; Addepalli, R.; Avery, V. M.; Hooper, J. N. A.; Quinn, R. J. *J. Org. Chem.* **2007**, *72*, 2309. (c) Grube, A.; Köck, M. *Angew. Chem., Int. Ed.* **2007**, *46*, 2320. (d) Kobayashi, H.; Kitamura, K.; Nagai, K.; Nakao, Y.; Fusetani, N.; van Soest, R. W. M.; Matsunaga, S. *Tetrahedron Lett.* **2007**, *48*, 2127.

(5) (a) Kinnel, R. B.; Gehrken, H-P.; Swali, R.; Skoropowski, G.; Scheuer, P. J. *J. Org. Chem.* **1998**, *63*, 3281. (b) Kinnel, R. B.; Gehrken, H-P.; Scheuer, P. J. *J. Am. Chem. Soc.* **1993**, *115*, 3376.

(6) (a) Grieco, P. A.; Brandes, E. B.; McCann, S.; Clark, J. D. *J. Org. Chem.* **1989**, *54*, 5849. (b) Grieco, P. A.; Clark, J. D.; Jagoe, C. T. *J. Am. Chem. Soc.* **1991**, *113*, 5488. (c) Keese, R. *Angew. Chem., Int. Ed.* **1992**, *31*, 344, and references cited therein. (d) J-Gregoire, B.; Brosse, N.; Ianelli, S.; Nardelli, M.; Caubere, P. *J. Org. Chem.* **1993**, *58*, 4572. (e) Paquette, L. A.; Morwick, T. M. *J. Am. Chem. Soc.* **1997**, *119*, 1230. (f) Paquette, L. A.; Hamme, A. T.; Kuo, L. H.; Doyon, J.; Kreuzholz, R. *J. Am. Chem. Soc.* **1997**, *119*, 1242. (g) Molander, G. A.; Nichols, P. J.; Noll, B. C. *J. Org. Chem.* **1998**, *63*, 2292.

(7) To the best of our knowledge Mori was the first to report the synthesis of this system, see: Mori, M.; Saitoh, F.; Uesaka, N.; Okamura, K.; Date, T. *J. Org. Chem.* **1994**, *59*, 4993.

(8) Köck, M.; Grube, A.; Seiple, I. B.; Baran, P. S. *Angew. Chem., Int. Ed.* **2007**, *46*, 6586.

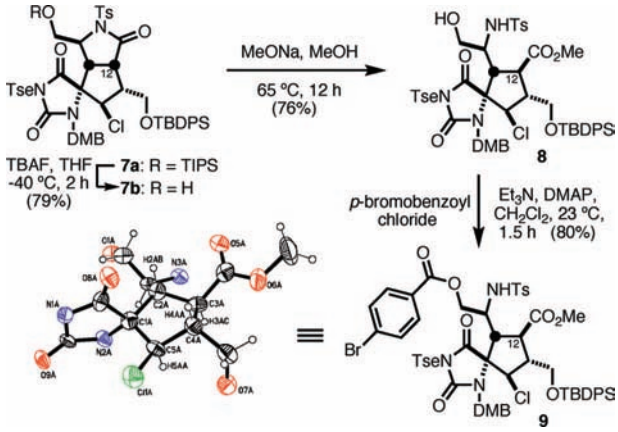
(9) Wang, S.; Romo, D. *Angew. Chem., Int. Ed.* **2008**, *47*, 1284.

(10) Al Mourabit, A.; Potier, P. *Eur. J. Org. Chem.* **2001**, 237.

(11) (a) Dransfield, P. J.; Dilley, A. S.; Wang, S.; Romo, D. *Tetrahedron* **2006**, *62*, 5223. (b) Dilley, A. S.; Romo, D. *Org. Lett.* **2001**, *3*, 1535.

(12) Full details of the extensive studies leading to optimization of this ring cleavage/epimerization of β-lactam **7** to deliver ester **8** will be described in a separate report.

Scheme 1. Simultaneous Ring Cleavage/C12 Epimerization of γ-Lactam **7** and Structural Verification by X-ray Analysis (Protecting Groups Are Removed for Clarity) of *p*-Bromobenzoate Derivative **9**



alcohol **11**.[13] For reasons indicated above, it was not clear how facile the cyclization to the trans-fused system might be; however, models indicated that a bis-envelope conformation was readily accessible in such an intermediate. Indeed, intramolecular displacement of the activated alcohol by the pendant sulfonamide under Mitsunobu conditions proceeded efficiently at ambient temperature to generate the desired *trans*-azabicyclooctane **12** in 74% yield (Scheme 2). Evidence for the stereochemistry of this bicyclic intermediate was garnered by comparison of the coupling constants of several key protons of pyrrolidine **12** with those reported for palau'amine by Quinn[14] (Table 1). The coupling constants indeed correlate well further confirming the revised stereochemistry of palau'amine, i.e. the *trans*-azabicyclo[3.3.0]-octane core. In addition, selected NOE enhancements for tricycle **12** also corroborate the relative stereochemistry and the conformation of this rather rigid, spirotricyclic system (Figure 3).

Scheme 2. Synthesis of *trans*-Azabicyclo[3.3.0]octane **12**

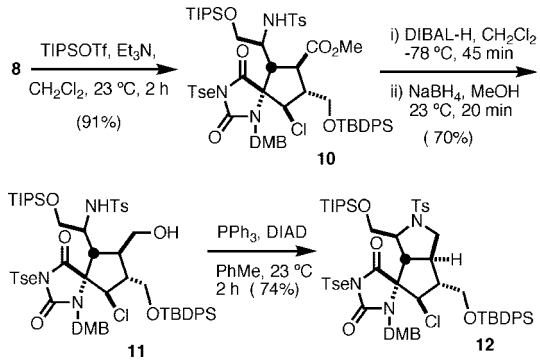
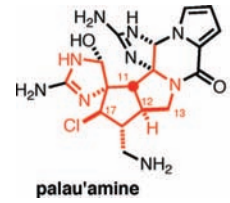
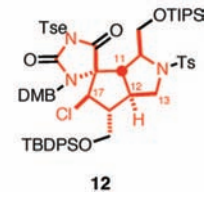


Table 1. Coupling Constant Comparison between Common Tricyclic Core of palau'amine and *trans*-Azabicyclo[3.3.0]octane **12**[a]


palau'amine


12

proton	palau'amine[b] mult (*J*)[c]	12 mult (*J*)[c]
11	d (14.4)	dd (14.5. 10.0)
12	dddd (14.6, 10.2, 9.0, 7.2)	dddd (14.5, 11.0, 10.5, 6.5)
13α	dd (10.2, 7.2)	dd (11.0, 6.5)
13β	t (10.2)	t (11.0)
17	d (9.0)	d (10.5)

[a] Obtained in DMSO-d_6. [b] Values from ref 14. [c] All *J* values are expressed in Hz.

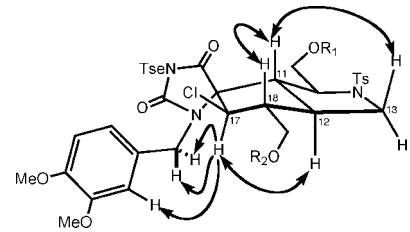


Figure 3. Selected NOE correlations for spirocycle **12** (R_1 = TIPS, R_2 = TBDPS) identified by 1D (single-headed arrows) and 2D (double-headed arrows) NOE experiments.

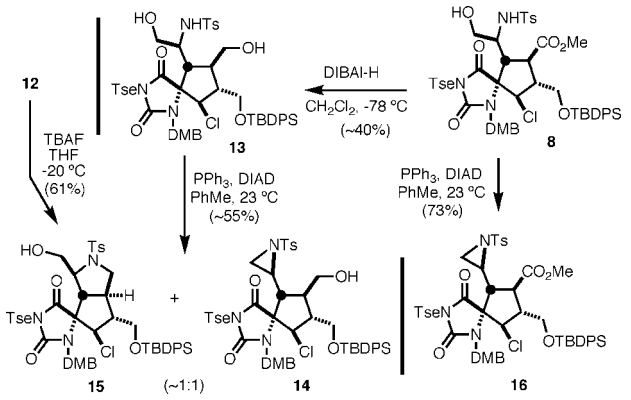
Further studies were conducted to determine the relative ease of cyclization to the *trans*-azabicyclo[3.3.0]octane core in comparison to other potential modes of intramolecular ring formation. In particular, we were interested in assessing the competition between formation of an aziridine and the *trans*-azabicyclo[3.3.0]octane when both modes of cyclization are possible. When aminodiol **13**, obtained by DIBAL reduction of ester **8**, was subjected to Mitsunobu conditions, nearly equal amounts of aziridine **14** and tricycle **15** were obtained (Scheme 3). The structure of tricycle **15** was verified by TIPS deprotection of tricycle **12** obtained previously, which gave the same compound. The structure of aziridine **14** was correlated to a related aziridine **16**, prepared by Mitsunobu reaction of alcohol **8**, by comparison of diagnostic signals in the ^{1}H NMR spectrum. It is noteworthy that this reaction leading to the aziridine required an excess amount of reagents and prolonged reaction time compared to formation of the pyrrolidine **12**.

We were also interested in studying the facility of a related intramolecular cyclization from the same intermediate ester

(13) Likely due to coordination of the aluminum reagent with the Lewis basic sulfonamide, a mixture of the desired alcohol and corresponding aldehyde was isolated after the first step. Treatment of the crude mixture with $NaBH_4$ enabled complete conversion to the desired alcohol.

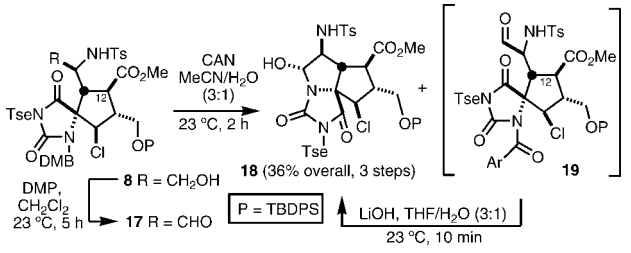
(14) Buchanan, M. S.; Carroll, A. R.; Quinn, R. J. *Tetrahedron Lett.* **2007**, *48*, 4573.

Scheme 3. Competition between Aziridine **14** and Azabicyclo[3.3.0]octane **15** Formation and Structural Correlations



8, which can serve as a precursor to the axinellamines. Following Dess−Martin oxidation of the primary alcohol, exposure to ceric ammonium nitrate (CAN) not only promoted the desired deprotection but also led to facile intramolecular cyclization generating the stable carbinolamine **18** under the slightly acidic conditions of this process (Scheme 4). A presumed overoxidation[15] of the DMB group to a benzoyl derivative **19** was observed; however, this intermediate was not fully characterized given that it was readily converted to the same carbinolamine **18** by basic hydrolysis. Thus, intramolecular cyclization to the tricyclic, "angular triquinane-type" core of the axinellamines (Figure 1, highlighted in green) is also quite facile.[16]

Scheme 4. Alternative Cyclization Mode of Cyclopentane **8** Leading to the Axinellamine Tricyclic Core



In summary, we have described facile modes of intramolecular cyclization from a common spiro hydantoin cyclopentane intermediate that efficiently delivers the core substructures of the palau'amines and the axinellamines. The facility of these cyclizations is consistent with a proposed biogenesis involving the synthesis of the various ring systems found in these natural products from a common cyclopentane intermediate. The relative configuration of the *anti*-chlorocyclopentane core has been verified crystallographically, firmly establishing the relative stereochemistry, including the spiro quaternary carbon. The tricyclic prolinol derivative **12** is a viable substrate for phakellin annulation employing our previously described oxidative cyclization from prolinol[9] and results of these studies will be described in due course.

Acknowledgment. This work was made possible by funding from the NIH (GM 52964) and the Welch Foundation (A-1280). We thank Dr. Joseph Reibenspies (TAMU) for solving the X-ray crystal structure of benzoate **9**.

Supporting Information Available: Experimental procedures and ^{1}H and ^{13}C NMR spectra for compounds **7b**, **8**, **10**−**12**, **15**, **16**, and **18**, crystal structure of **9**, and two-dimensional NMR spectra for **12**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(15) For a related example of over-oxidation during PMB removal, see: Ohfune, Y.; Demura, T.; Iwama, S.; Matsuda, H.; Namba, K.; Shimamoto, K.; Shinada, T. *Tetrahedron Lett.* **2003**, *44*, 5431.

(16) While our work was in progress, Baran and co-workers also reported the facility of this cyclization in the course of their studies leading to axinellamine (see ref 2).