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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.

Graphical abstract

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

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Supporting Information **Available** Experimental procedures and ¹H and ¹³C 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>.

several recent independent reports revealed that the common, azabicyclo [3.3.0] octane moiety was in fact *trans*-fused⁴ and not *cis*-fused as originally reported (Figure 1).⁵

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

Building on early biosynthetic proposals of Kinnel and Scheuer⁵ 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 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. 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 Quinn¹⁴ (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).

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 aziridine formation and the *trans*-azabicyclo[3.3.0]octane.

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 ¹H NMR spectrum. It is noteworthy that this reaction leading to the aziridine required 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 **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. A presumed over-oxidation¹⁵ of the DMB group to a benzoyl derivative **19** was observed, however it 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 red) is also quite facile.¹⁶

In summary, we have described facile modes of intramolecular cyclization from a common spiro hydantoin cyclopentane intermediate that efficiently delivers the core sub-structures 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 prolinol⁹ and results of these studies will be described in due course.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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

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*).

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**.

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.

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**.

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

Scheme 3.

Competition between aziridine **14** and azabicyclo[3.3.0] octane **15** formation and structural correlations

Scheme 4.

Alternative cyclization mode of cyclopentane **8** leading to the axinellamine tricyclic core.

Table 1

Coupling constant comparison between common tricyclic core of palau'amine and *trans*-azabicyclo[3.3.0]octane **12**^a

proton	palau'amine ^b mult (<i>J</i>) ^c	12 mult (<i>J</i>) ^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)
13 α	dd (10.2, 7.2)	dd (11.0, 6.5)
13 β	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.