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Synthetic studies on palau'amine. Construction of the cyclopentane core via an asymmetric 1,3-dipolar cycloaddition

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ABSTRACT

The cyclopentane core of palau'amine has been constructed in optically pure form through the use of an asymmetric azomethine ylid [1,3]-dipolar cycloaddition reaction.

Palau'amine is a dauntingly complex hexacyclic *bis*-guanidine antibiotic obtained from the sponge *Stylotella agminata* that displays potent cytotoxic and immunosuppressive activities (Fig. 1).[1a,b] This substance has attracted considerable attention from the synthetic community[2] and a recent, brilliant total synthesis of racemic palau'amine by the Baran laboratory is particularly noteworthy.[3] The relative stereochemistry of palau'amine was recently revised independently by Quinn[4] and Köck[5] to the stereostructure depicted in Figure 1 and turned out to be a fortuitous stereochemical array for the approach described herein. The related alkaloids, the styloguanidines, were isolated from the marine sponge *Stylotella aurantium* and have been shown to be inhibitors of chitinase, an important enzyme in the molting of crustaceans.[6] The axinellamines, isolated from the marine sponge *Axinella* sp., display moderate bactericidal activity against *Helicobacter pylori*.[7]

All of these substances share a structurally related cyclopentane core and thus far, only the Baran laboratory has been successful in total synthesis efforts in this family of alkaloids.[8,9] The relative stereochemistry of the cyclopentane core of palau'amine and the styloguanidines is the same while the axinellamines dispose the aminomethyl substituent adjacent to the chlorine atom in an *anti*-relationship.

It should be noted that the absolute stereochemistry of these natural products has not been rigorously assigned, although based on CD similarities with monobromophakellin hydrochloride, Scheuer and co-workers, have postulated the absolute stereostructure shown.[1] All of these agents represent an unusually challenging density of functionality and stereochemistry and provides perhaps an extreme test of suitable synthetic methodologies. While the landmark accomplishment by Baran and co-workers on the first total synthesis of palau'amine represents an important milestone in the chemistry of this fascinating family of alkaloids, the asymmetric synthesis of palau'amine remains an important synthetic objective.

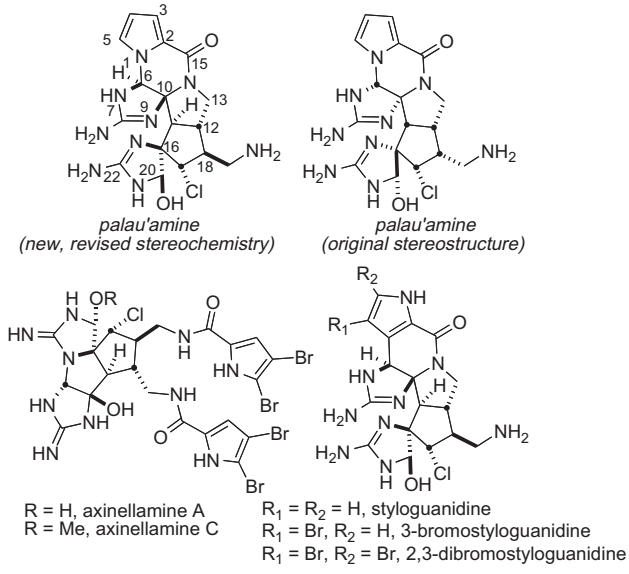

Figure 1. Structures of palau'amine and congeners.

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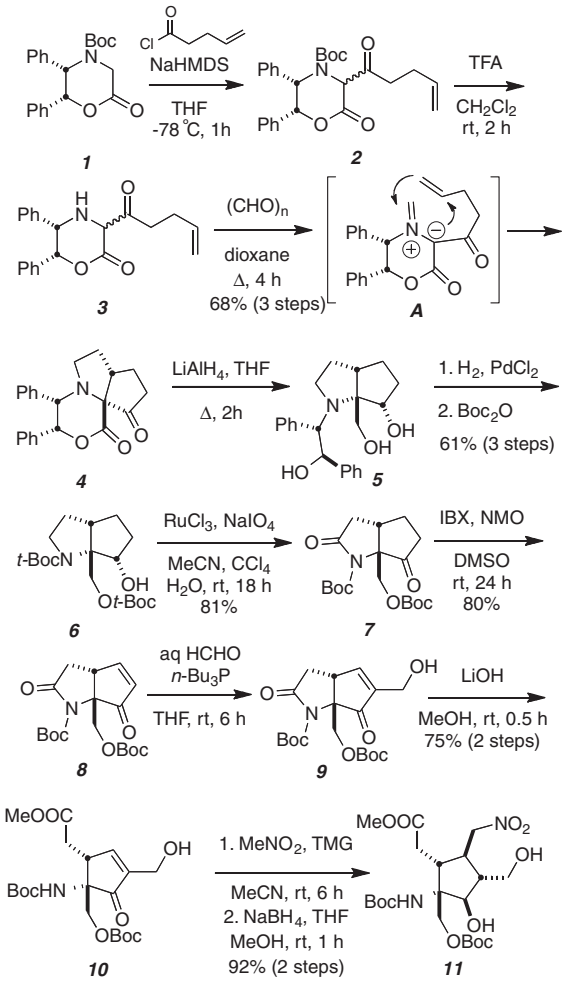

Scheme 1. Asymmetric synthesis of cyclopentane **11**.

We have devised an efficient, stereocontrolled entry to the highly functionalized cyclopentane core of palau'amine by an asymmetric intramolecular azomethine ylide dipolar cycloaddition[10,11] as the key step and report these preliminary studies herein (Scheme 1).

Our synthesis commences with the enolate acylation of commercially available oxazinone **1**[11] to provide **2** (relative stereochemistry unassigned and inconsequential). Removal of the *t*-Boc group furnishes aminoketone **3** which was condensed with formaldehyde to generate the incipient azomethine ylid (**A**) that produced tricyclic intramolecular cycloaddition product **4** as a single diastereomer in 63% overall yield for the three steps. The intrinsic facial bias of this intramolecular cycloaddition remains unclear and constitutes the subject of ongoing studies.

This substance was reduced with $LiAlH_4$ to triol **5**, followed by catalytic hydrogenation and *t*-Boc-protection to give **6** in 61% overall yield from **4**. Ruthenium-mediated oxidation cleanly afforded ketoamide **7** in 81% yield that was converted into the unsaturated ketone by exposure to IBX and *N*-methylmorpholine *N*-oxide in DMSO delivering enone **8** in 80% yield.[12]

Stereoselective installation of the two one-carbon arms to enone **8** was accomplished in two stages beginning with a Morita–Baylis–Hillman type of hydroxymethylation that deployed aqueous formaldehyde and *tri*-*N*-butyl phosphine providing **9** in good yield.[13] Methanolic lithium hydroxide treatment of **9** gave the monocyclic methyl ester **10** in 75% overall yield from **9**. For the second stage, enone **10** was then treated with nitromethane and tetramethyl guanidine in acetonitrile at room temperature to give exclusively, the 1,2-*anti* product. Reduction of the ketone gave diol **11** which was subjected to extensive ^1H NMR NOE experiments to secure the relative stereochemistry of this substance. The relative stereochemistry of the vicinal hydroxymethyl and nitromethyl substituents in **11** are set with the correct relative stereochemistry as per the newly reassigned stereochemistry of palau'amine.

Cyclopentane **11** embodies the stereochemistry and relevant functionality to constitute a viable intermediate for the asymmetric synthesis of palau'amine and congeners. Efforts to complete an asymmetric total synthesis of palau'amine from cyclopentane **11** are currently under investigation in these laboratories.

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Supplementary data

Supplementary data (complete experimental details and spectroscopic characterization of all new compounds) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.10.037.

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