Naural Product Synthesis

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Total Synthesis of the Marine Alkaloid Palau'amine**

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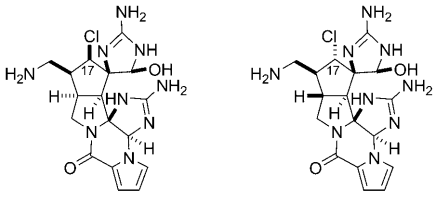
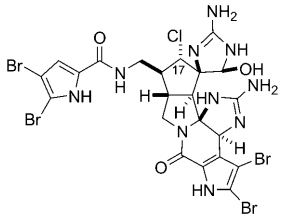
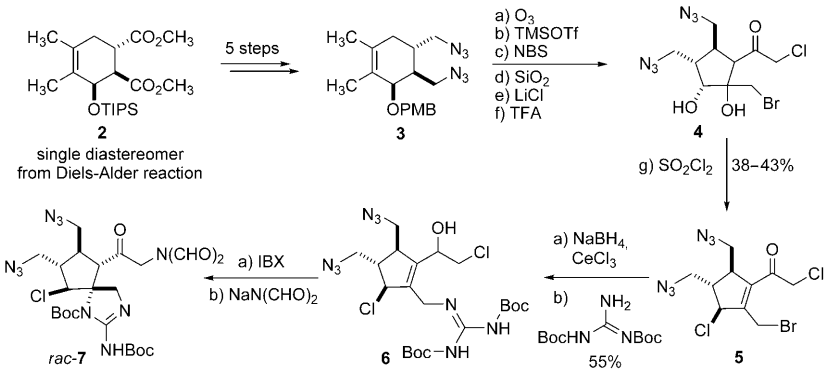
alkaloids · cascade reactions · palau'amine · synthetic methods · total synthesis

The architecturally intriguing marine alkaloid palau'amine (**1**) posed an inspiring structural and synthetic challenge to chemists since its first isolation in 1993 by Scheuer and co-workers.[1] The structure that was originally proposed for palau'amine—involving a *cis*-fused azabicyclo[3.3.0]octane structure and epimeric at C17—lured many synthetic groups into despair.[2] Although this structure was certainly chemically reasonable, the isolation of additional congeners combined with detailed NMR and computational analyses suggested a structural revision of palau'amine to the structure shown for **1**.[3] In a recent Communication,[4] Baran and co-workers described the successful preparation of the revised structure of palau'amine (**1**) in totally synthetic form, and thus delivered further evidence for the revised structure. Therefore, the endeavors of many research groups towards the first total synthesis of this unique natural product have now culminated in this achievement.





The reaction sequence commenced with the single diastereoisomer **2**, which was readily obtained in multi-gram amounts from a Diels–Alder reaction (Scheme 1).[5] The cyclohexane diazide **3** (obtained after a five-step sequence) was subsequently contracted to the cyclopentane **4**: Ozonolytic scission of the olefin in **3** to a bis(methyl ketone) was followed by immediate conversion into its bis(enol) ether, dibromination, and cyclization by an intramolecular aldol reaction on dry silica. The more reactive bromo group was then exchanged by a chloro group, thus attenuating the halogen reactivity for later-stage conversions. Cleavage of the protecting group then furnished diol **4**. At this stage, exposure of **4** to thionyl chloride initiated an interesting cascade reaction,



Scheme 1. Preparation of the cyclopentane core **7** of palau'amine. Boc = *tert*-butoxycarbonyl, IBX = *o*-iodoxybenzoic acid, NBS = *N*-bromosuccinimide, OTf = trifluoromethanesulfonate, PMB = *p*-methoxybenzyl, TFA = trifluoroacetic acid, TIPS = triisopropylsilyl, TMS = trimethylsilyl.

which facilitated direct access of enone **5** on a multigram scale. This conversion was speculated to proceed by a cyclic sulfate or bis(chlorosulfonate) ester, which are prone to elimination and chloride inversion. Luche reduction of chloroketone **5** and a selective displacement of the allylic bromide with *N*,*N*′-bis(Boc) guanidine furnished allylic alcohol **6**, which was then spirocyclized by intramolecular aza annulation[6] reaction after oxidation with IBX. Final elaboration with sodium diformylamide gave rise to the desired diastereomer *rac*-**7** in slight excess (1.3:1). Some ambiguity concerning the position of the Boc groups in **7** remained

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between the original report of its preparation[5] and later studies documenting the use of **7** (see Schemes 1 and 2).[7] The spirocycle **7** has the cyclopentane core related to many alkaloids of this family, such as massadine, axinellamine and palau'amine.

Spirocycle **7** was transformed into palau'amine (**1**) in an impressively small number of steps, combining a highly chemoselective late-stage oxidation, cascade reactions, and by utilizing the intrinsic bipolar reactivity of heterocycles in a C–N bond forming process and a daring cyclization event, giving the unprecedented *trans*-azabicyclo[3.3.0]octane substructure.

After deprotection of *rac*-**7** under acidic conditions, Baran and co-workers developed a protocol using silver(II)-picolinate to obtain hemiaminal **8** with outstanding regio- and stereoselectivity in a one-pot procedure. It should be pointed out that that this hemiaminal functionality remains untouched in subsequent steps, which underlines the detailed and subtle understanding of Baran et al. of the inherent reactivity of functional groups leading[8] to highly efficient processes.

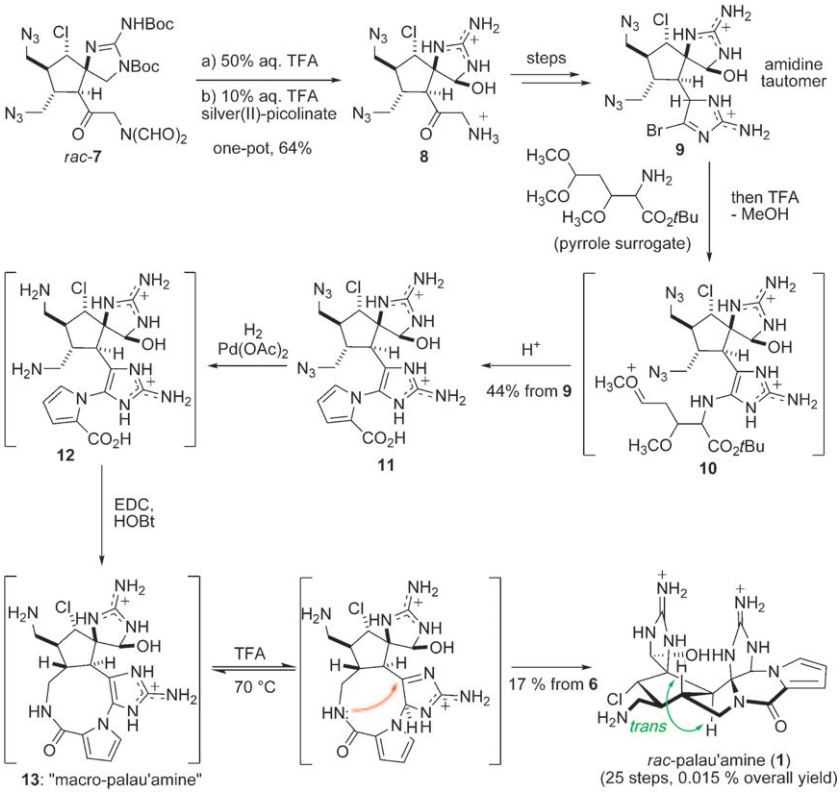
Two further steps converted the α-amino ketone **8** into its 2-amino-4-bromoimidazole derivative, of which the amidine tautomer **9** is shown in Scheme 2. As transition-metal-catalyzed reactions failed to produce any of the desired product, Baran et al. switched to an unconventional method of introducing the pyrrole moiety by uncatalyzed nucleophilic displacement. The direct introduction of, for example, pyrrole was unsuccessful, which stimulated the Baran group to developing a cascade reaction to give the desired pyrrole **11**.

This cascade process combines acid-catalyzed methanol eliminations (proceeding by oxonium ion **10**) with a cyclization and a deprotection reaction to tie up no less than five chemical transformations in a one-pot reaction with a yield of 44%.

The final elaboration was carried out by another cascade sequence: Reduction of both azido groups followed by EDC mediated coupling gave the nine-membered macrolactone **13**. Again, the inherent ambiphilic nature of the imidazole–amidine system was successfully exploited to cause formation of the strained *trans*-fused 5,5-ring system by a transannular attack.

With synthetic palau'amine now in hand, the remaining questions about its bioactivity and biogenesis can be addressed. It will certainly be interesting to see whether the ring closure of macropalau'amine **13** to the target **1** is a synthetic reflection of the underlying reactivity enshrined in the natural product or its biogenetic precursors. As several hypotheses for the biosynthesis of palau'amine and congeners have been put forth,[2] it is worth noting that a process conceptually similar to the "macro-palau'amine" to palau'amine ring closure was initially proposed by Al Mourabit and Potier for dibromocantharellin.[9]

On top of the structurally complex hexacyclic ring system containing eight contiguous stereogenic centers, the Baran group had to struggle with highly polar intermediates with dreadful physical properties concerning their purification and dissolution. Their elegant solution to these synthetic challenges combines cascade reactions and one-pot transformations to obtain palau'amine **1** in an impressively small number of steps. This total synthesis will certainly stand as a new hallmark in organic synthesis.



Scheme 2. Total synthesis of racemic palau'amine. EDC = *N*′-(3-dimethylaminopropyl)-*N*-ethylcarbodiimide, HOBt = 1-hydroxy-1*H*-benzotriazole.

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