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Stitching together palau'amine

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Abstract

The long-awaited first total synthesis of the structurally intriguing natural product palau'amine has now been achieved. The synthesis features cascade reactions and an 'across-ring' stitching of a 'macropalau' amine', and sets the bar for future efforts towards an enantioselective variant.

Every so often, a complex natural product is isolated that deeply challenges and inspires a cadre of synthetic chemists to develop novel strategies and, in some cases, novel methods to achieve a chemical synthesis. What drives such endeavours varies with each target, but typically stems from the challenge of a fascinating molecular architecture, a novel juxtaposition of functionality, or proven bioactivity. Historically, this was the case with natural products such as penicillin, vitamin B12 and taxol. Indeed, these total-synthesis efforts led to the development of a number of creative synthetic strategies, new synthetic methods, and — in one case — important physical–organic principles^{1,2}.

Palau'amine, isolated by the Scheuer group³ from a marine sponge off the coast of Palau — a small island in the western Pacific ocean — was first described in 1993, and may fall into this category of strategy- and method-inspiring natural products. Arguably, the capstone member of the growing family (>100) of marine-derived pyrrole–imidazole alkaloids (PIAs), the initially reported structure of palau'amine was revised in 2007, revealing a *trans*-fused 5,5-azabicyclic ring system that was unprecedented in the realm of natural products and seemingly made the synthesis even more challenging (Fig. 1a). This alkaloid and other closely related PIAs have inspired over twelve research groups around the world to forge unique synthetic tactics and methods for its synthesis^{4,5}.

The high polarity of palau'amine — owing to its high nitrogen content and correspondingly high N/C ratio — along with its extremely compact stereochemical complexity, has made this a daunting target for total synthesis, but also an important one given its purported potent immunosuppressive activity (in a mixed lymphocyte reaction, the half-maximal inhibitory concentration (IC₅₀) is less than 40 nM)³. [Au: OK?] The interest is further heightened given that structural novelty often comes hand in hand with unique biological activity. A ground-breaking report in *Angewandte Chemie International Edition* by Baran and co-workers⁶ reveals some interesting methods and strategies — including cascade reactions and a transannular ('across-ring') stitching process — enabling the first synthesis of this complex and structurally intriguing PIA from simple starting materials (Fig. 1a).

As with many total-synthesis endeavours, the ability to ultimately find a solution to this complex target stemmed from a number of important precedents. The described synthesis clearly benefitted from the Baran group's long-standing interest and successful syntheses of

other PIAs. The most notable feature is the transannular or ‘across-ring’ bond stitching of a ‘macropalau'amine’ leading to the final two rings found in palau'amine (Fig. 1a,b). This tactic was reportedly taken to overcome the strain associated with the final 5,6 ring system, and was first proposed by Al Mourabit and coworkers in considering plausible biosynthetic pathways to phakellin and related tetracyclic PIAs⁷. The process is also highly reminiscent of one recently employed by the Du Bois group in their elegant synthesis of saxitoxin^{8,9}.

The ambiphilic reactivity of 2-aminoimidazoles enables them to participate as both nucleophiles and electrophiles through tautomerization (Fig. 1c). This reactivity had first been suggested by Potier and Al Mourabit in the context of a possible biosynthetic pathway to tetracyclic PIAs¹⁰. The Baran team made clever use of these precedents in postulating and implementing the successful transannular closure used to form the last two rings of palau'amine. Another highlight of the synthesis is the strategic use of a silver(ii) oxidant, methodology that was developed in the course of this group's previous synthetic studies toward the axinellamines, and one that minimizes redox adjustments and enabled installation of the labile carbinolamine late in the synthesis.

The laboratory synthesis of palau'amine also raises interesting questions regarding its biosynthesis. The reported failed attempts to directly form the final two rings using biomimetic oxidative cyclizations are provocative. Is it possible that strategies such as these — involving medium-sized ring formation followed by transannular ring closure — are common in natural product biosynthesis? Indeed, there are numerous postulated examples of such ring contractions involving transannular Diels–Alder processes of macrocycles^{1,2}. These questions will hopefully inspire chemists to explore the pathways and enzymes involved in the biosynthesis of these structurally complex alkaloids.

Although the first chemical synthesis of racemic palau'amine has been achieved (in 25 steps with an overall yield of 0.0015%), the story of palau'amine's synthesis and biological properties — as with similar structurally intriguing and challenging natural products — is just beginning. Certainly, the ability to access these compounds and, in particular, design derivatives in optically active form, will pave the way for broader and more detailed biological studies. Furthermore, palau'amine and related PIAs will undoubtedly continue to inspire novel synthetic strategies and synthetic methods in the future.

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Figure 1.

The total synthesis of palau'amine. **a**, The synthesis was achieved from several simple starting materials. The strategic bond disconnection used in the formation of the 5,6-fused ring system is highlighted in red, and the unusual *trans*-fused 5,5-ring junction in blue. **b**, Graphical representation of the transannular ('across-ring') stitching used in the synthesis via a 'macropalau'amine'. **c**, Ambiphilic reactivity of 2-aminoimidazoles exploited in the transannular ring stitching.