ORGANIC LETTERS

2010
Vol. 12, No. 20
4532−4535

Extending Pummerer Reaction Chemistry: Application to the Assembly of the Pentacyclic Core of Dibromopalau'amine

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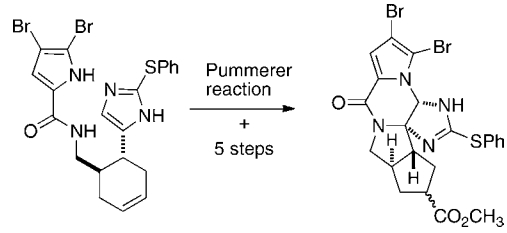
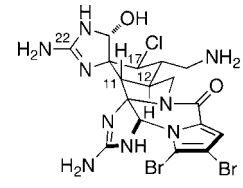
Received August 5, 2010

ABSTRACT



A pentacyclic model system featuring the trans azabicyclo[3.3.0]octane unit of dibromopalau'amine was prepared with complete diastereoselectivity in the polycyclic core from a tricyclic precursor. The key transformations of this sequence include (a) a Pummerer reaction-mediated oxidative bicyclization, and (b) a Wolff rearrangement-based ring contraction to deliver the strained azabicyclo[3.3.0]octane core.

Palau'amine[1] and its monobromo- and dibromo- congeners[2] have been the focus of numerous structural[3] and synthesis[3d,4] studies since the original disclosure by Scheuer and Kinnel, and for a long time these species stood at the pinnacle of structural complexity among the pyrrole-imidazole alkaloids. More recently, a structural revision (reversed stereochemistry at C(11) and C(17)) revealed palau'amine to possess a highly strained trans azabicyclo[3.3.0]octane core instead of the originally assigned cis fused configuration (Figure 1).[3] This revision derailed several ongoing approaches to the synthesis of the palau'amine skeleton and reset the synthesis clock. The synthesis challenges inherent



1 dibromopalau'amine

Figure 1. (Revised) structure of dibromopalau'amine.

in the revised palua'amine architecture recently were met by Baran et al., who described an elegant solution to the preparation of the trans azabicyclo[3.3.0]octane moiety en route to a concise assembly of the natural product target.[5]

Speculation about the biosynthesis of the palau'amine system has run in several directions,[2,3c,4g,6] but one line of thinking suggests that **1** may owe its origins to the simple precursor oroidin.[6] Oroidin also has been invoked as a

(1) Kinnel, R. B.; Gehrken, H.-P.; Scheuer, P. J. *J. Am. Chem. Soc.* **1993**, *115*, 3376–3377.

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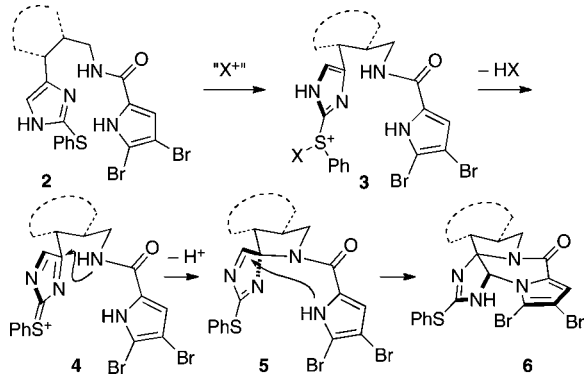
(3) (a) Grube, A.; Köck, M. *Angew. Chem., Int. Ed.* **2007**, *46*, 2320–2324. (b) Buchanan, M. S.; Carroll, A. R.; Quinn, R. J. *Tetrahedron Lett.* **2007**, *48*, 4573–4574. (c) Köck, M.; Grube, A.; Seiple, I. B.; Baran, P. S. *Angew. Chem., Int. Ed.* **2007**, *46*, 6586–6594. (d) Lanman, B. A.; Overman, L. E.; Paulini, R.; White, N. S. *J. Am. Chem. Soc.* **2007**, *129*, 12896–12900.

10.1021/ol1018322
Published on Web 09/14/2010

plausible precursor to simpler pyrrole-imidazole alkaloids of the phakellin family,[6] and several synthesis strategies directed toward these sponge alkaloids that were based upon this model have come to fruition.[7] In our laboratories, a possibly biomimetic oxidative cyclization of sulfur-containing dihydrooroidin derivatives has been developed for the construction of this phakellin-type structure, and this chemistry has been featured in total syntheses of the simple pyrrole-imidazole alkaloids dibromophakellstatin, dibromophakellin, and dibromoagelaspongin.[7c,d,f,g] The pivotal transform in this chemistry is a Pummerer reaction, which is utilized to transfer a unit of "oxidation" from sulfur to the imidazole nucleus, thus activating it for nucleophilic capture by the tethered nitrogens.[8]

The extension of this chemistry to the more demanding palau'amine system is illustrated in conceptual form in Scheme 1, where now a thiophenylated dihydrooroidin

Scheme 1. Pummerer-Reaction-Based Approach to the Pentacyclic Core of the Dibromopalau'amine Skeleton

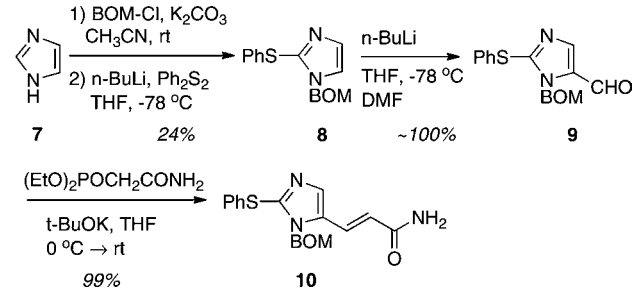


derivative **2** bearing a third ring of undefined dimensions (dotted line) can be activated by a sulfur-specific electrophile "X^+" to initiate the Pummerer cyclization cascade. Note that for simplicity of presentation, only the vinylogous Pummerer intermediate **4** (diazacyclopentadiene thionium ion) is illustrated; the additive mechanism may be operational as well.[8] The anticipated outcome of this process is the pentacyclic product **6**, which bears a greater or lesser resemblence to the palau'amine skeleton, depending upon the exact nature/stereochemistry of the appended ring.

The initial foray into this chemistry involved the synthesis of a Pummerer cyclization substrate **2** featuring the requisite trans cyclopentane ring in place of the dotted lines. Unfortunately, all attempts at achieving this cyclization met with failure.[9] These frustrated Pummerer bicyclization attempts led to a reevaluation of the synthesis plan, and as a result recourse was made to an alternative and indirect strategy for trans cyclopentane introduction. Specifically, the use of a less torsionally demanding cyclohexene ring with trans disposed substituents might both enable the Pummerer chemistry and provide a handle for the later ring contraction that ultimately is necessary to provide the requisite trans azabicyclo[3.3.0]octane moiety of the palau'amine structure.

This hypothesis was tested by first preparing a cyclohexene ring featuring vicinal and trans disposed imidazole and pyrrole moieties through Diels–Alder chemistry. The dienophile for this Diels–Alder reaction was prepared from imidazole in 4 steps as illustrated in Scheme 2. Standard functionalization

Scheme 2. Synthesis of the Imidazole-Based Diels–Alder Dienophile **10**



procedures utilizing imidazole metalation chemistry[10] furnished the aldehyde **9**, which was converted to the unsaturated primary amide **10** through Emmons-Horner chemistry.

Acquisition of dienophile **10** set the stage for the key Diels–Alder reaction,[11] which proceeded smoothly with butadiene at high temperature to afford the trans-substituted cyclohexene-containing product **11** in moderate yield, Scheme 3. The simple butadiene adduct **11** was an adequate starting point to test the further chemistry, and so the amide function

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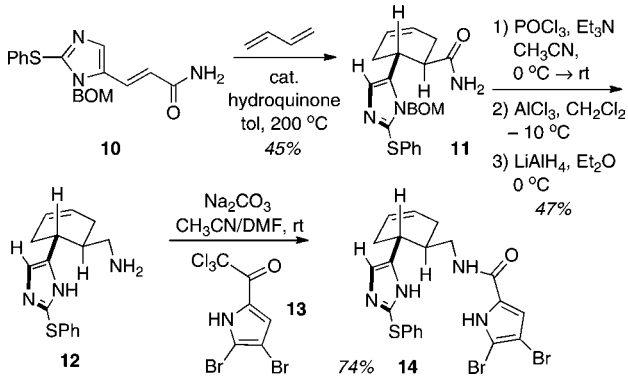
(11) For a related Diels–Alder reaction of a β-imidazole unsaturated ester, see: Kawasaki, I.; Sakaguchi, N.; Khadeer, A.; Yamashita, M.; Ohta, S. *Tetrahedron* **2006**, *62*, 10182–10192.

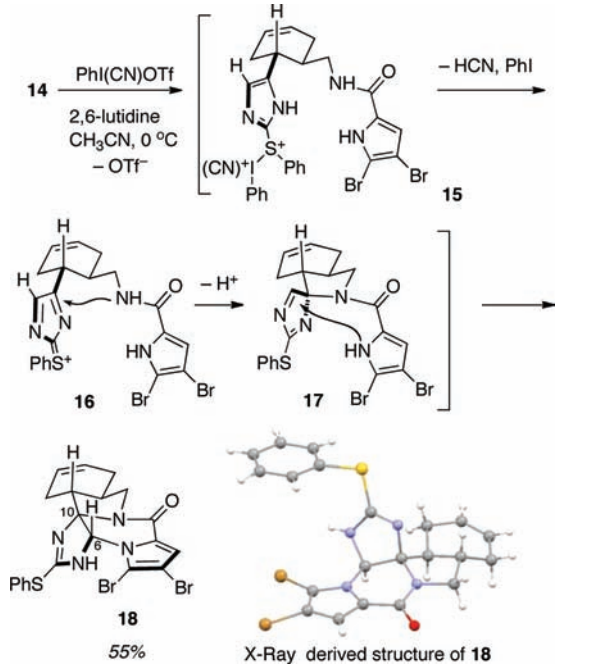
Scheme 3. Preparation of the Pummerer Reaction Substrate **14**



was reduced to the amine in **12** via an intermediate nitrile (direct reduction of **11** was capricious and low-yielding), and that amine was acylated with the dibromopyrrole **13** to deliver the Pummerer cyclization precursor **14** in good yield.

Treatment of sulfide **14** with PhI(CN)OTf (Stang's reagent[9]) followed procedures developed earlier for the synthesis of the simplier pyrrole-imidazole alkaloids,[7c,d,12] Scheme 4. Mechanistic speculation for this cyclization

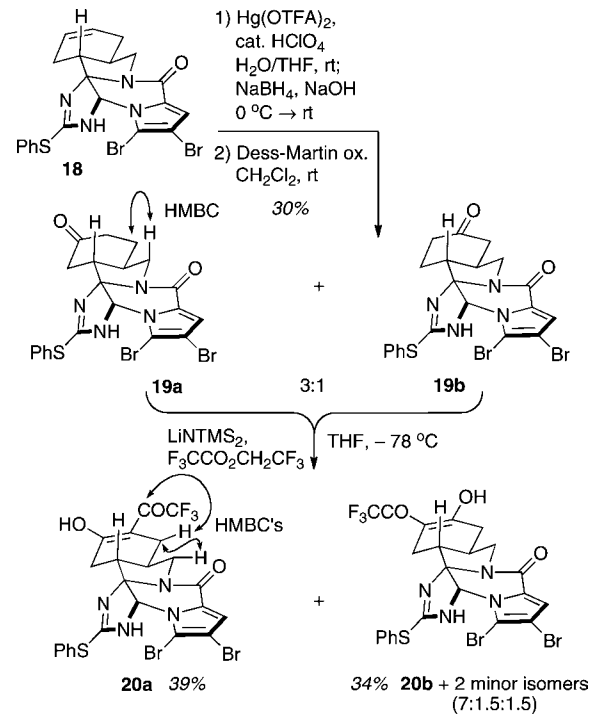
Scheme 4. Pummerer-Type Oxidative Cyclization of **14**, with Mechanistic Speculation, and Structural Characterization of the Pentacyclic Product **18**



extends to initial sulfur activation by the iodonium reagent to give **15**, which expels the elements of HCN and PhI to deliver the presumed key electrophilic intermediate **16** (or the additive Pumerer equivalent). Successive trapping of the two electrophilic sites within the diazacyclopentadiene thionium ion moiety then leads to the observed product, pentacycle **18**. The structure and stereochemistry of **18** was suggested by comparison of spectroscopic data (^{1}H NMR singlet at 5.37 ppm for H(6); ^{13}C NMR 71.8 ppm C(6), 92.6 ppm C(10)) with a related but simplier system[7c] and confirmed by single crystal X-ray analysis.[13] Cyclization product **18** was isolated as a single diastereomer whose relative stereochemistry can be rationalized by citing reaction through the conformer **16**. This conformation should minimize A^{1,3} strain along the imidazole-cyclohexene ring bond compared to the diasatereomeric alternative (not shown) in which the diazacyclopentadiene unit is rotated by 180° (i.e., $=S^+Ph$ pointing "up"). There are several interrelated biosynthesis proposals for palau'amine currently in play, and the conformational preference → desired stereochemical outcome implied in **16** is relevant to some of them.[3c,6]

Contracting the cyclohexene ring of the trans fused system **18** to a cyclopentane ring represents the final challenge to completing this model dibromopalau'amine system. The Wolff rearrangement of α-diazoketones seemed like a reasonable starting point for developing a ring contraction strategy, since (a) it has a long history of application to the formation of small strained rings, and (b) it does not involve a ring-opening/acyclic closure sequence.[14] The synthesis of an appropriate α-diazoketone from **18** commenced with an oxymercuration/oxidation sequence to introduce the ketone part, in this case as an inconsequential ~3:1 mixture of

Scheme 5. Formation of the Trifluoromethylacetyl Ketones **20a/b**

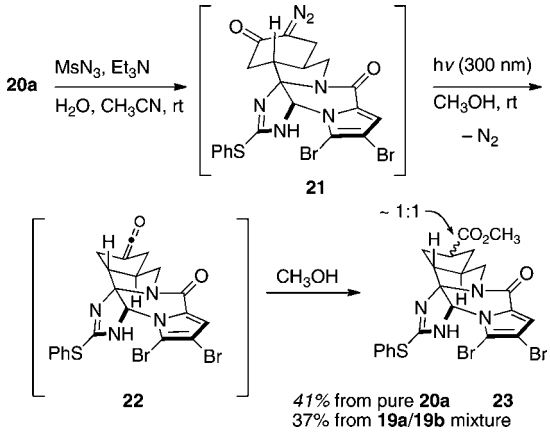


regioisomers **19a**/**19b**, Scheme 5. This mixture was processed on to the α-trifluoromethylacetyl ketones **20a**/**20b**, isolated

as enols, by the method of Danheiser[15] to set up diazo introduction. The regiochemical assigment of the isolable major isomer **20a** rests on the HMBC signals shown; three other regioisomers were isolated as a mixture, and the most prevalent of these three is assigned the regiochemistry shown as **20b** based upon mechanistic reasoning.

Purified major isomer **20a** was treated with mesyl azide to furnish the diazoketone **21**, but that species proved too reactive for isolation and purification, Scheme 6. Consequently, it was used crude in the Wolff rearrangement reaction. Irradiation of a sample of **21** prepared in this manner at 300 nm in methanol led to a single cyclopentane-containing regisomer as a mixture of epimers at C(17), pentacycle **23**. In a subsequent experiment, the mixture of all 4 regioisomers of the trifluoromethylacetyl ketones **20** was subjected to both diazo introduction and Wolff rearrangement, and the same mixture of diastereomeric cyclopentane methyl esters **23** as the major products resulted.

Scheme 6. Synthesis of the Pentacyclic Framework of Dibromopalau'amine via Wolff Rearrangement



The structural assigment of **23** stems from analysis of its HMBC signals, the most informative of which are shown in Figure 2. The critical coupling constant between H(11) and H(12) is 13.3 Hz for both diastereomers, similar to that reported for palau'amine itself (14.4 Hz).

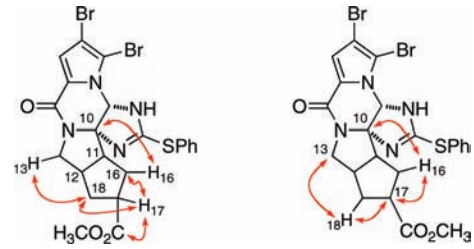


Figure 2. Key HMBC signals for the structural assignment of pentacycle **23**.

Thus, the highly strained trans-fused azabicyclo[3.3.0]octane-bearing pentacyclic skeleton of dibromopalau'amine has been prepared in a diastereoselective fashion in 15 overall steps from imidazole. The use of the Pummerer-initiated bicyclization reaction to assemble the target's framework extends this methodology to a more demanding context, and, when coupled to the Wolff ring contraction sequence, defines a new approach to the palau'amine system.

Acknowledgment. Support from the National Science Foundation via CHE 0808983 and CHE 0131112 (X-ray Crystallographic facility) is gratefully acknowledged. This paper is dedicated to my colleague and friend, Dr. Raymond Funk, on the occasion of his 60th birthday.

Supporting Information Available: Experimental procedures, full spectral data and copies of ^{1}H NMR and ^{13}C NMR spectra for **8**, **9**, **10**, **11**, **12**, **14**, **18**, **19a**, **20a**, and **23**; X-ray crystallographic data in CIF format for **18**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL1018322

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