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Enantioselective Strategy to the Spirocyclic Core of Palau'amine and Related Bisguanidine Marine Alkaloids

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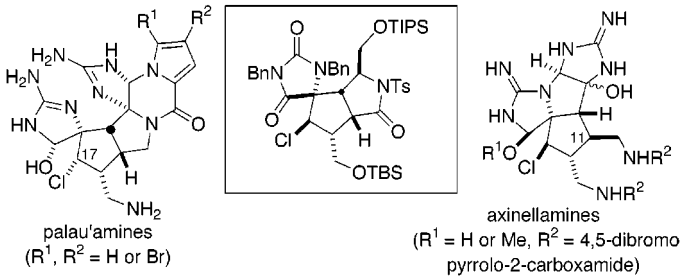
ABSTRACT



An enantioselective strategy to the spirocyclic core found in the oroidin-derived family of bisguanidine marine alkaloids has been devised, premised on a biosynthetic proposal. Herein, we describe the successful implementation of this strategy, which entails a Diels–Alder reaction and a chlorination/ring contraction sequence that delivers the fully functionalized spirocyclic core. In this initial report, an intermolecular chlorination delivers a cyclopentane that is epimeric at C17 relative to the palau'amines and epimeric at C11 relative to the axinellamines.

The remarkable structural diversity of guanidine-containing marine natural products makes them attractive synthetic targets.[1] In addition, many of these compounds possess potent biological activity that renders them potentially useful as biochemical probes. In this regard, the class of bioactive marine natural products that includes the palau'amines (**1**),[2] the styloguanidines (**2**),[3] and the axinellamines (**3**)[4] possess a common, highly complex cyclopentane that is stereogenic at every carbon including one quaternary spiro center (Figure 1).[5] These alkaloids also include two cyclic guanidines within their structure. Biosynthetically, these metabolites are thought to be derived from a common precursor, oroidin. Our interest in these natural products stems from their challenging structure coupled with the potent immunosuppressive activity of palau'amine.[6] Two approaches to these metabolites that have been described are a concise route to an abbreviated tetracyclic core structure by Overman[7a] and a desymmetrization strategy to the axinellamine cyclopentane described by Carreira.[7b] Herein, we describe our synthetic approach to this class of bisguanidine alkaloids that is premised on the biosynthetic proposal of Kinnel and Scheuer.[2a,8] This

(1) (a) Berlinck, R. G. S. *Nat. Prod. Rep.* **1999**, *16*, 339−365. (b) Faulkner, D. J. *Nat. Prod. Rep.* **2000**, *17*, 7−55.

(2) (a) Kinnel, R. B.; Gehrken, H.-P.; Scheuer, P. J. *J. Am. Chem. Soc.* **1993**, *115*, 3376−3377. (b) Kinnel, R. B.; Gehrken, H.-P.; Swali, R.; Skoropowski, G.; Scheuer, P. J. *J. Org. Chem.* **1998**, *63*, 3281−3286.

(3) Kato, T.; Shizuri, Y.; Izumida, H.; Yokoyama, A.; Endo, M. *Tetrahedron Lett.* **1995**, *36*, 2133−2136.

(4) (a) Urban, S.; Leone, P. D. A.; Carroll, A. R.; Fechner, G. A.; Smith, J.; Hooper, J. N. A.; Quinn, R. J. *J. Org. Chem.* **1999**, *64*, 731−735. (b) It should be noted that the same name was previously given to related, simpler pyrrole alkaloids; see: Bascombe, K. C.; Peter, S. R.; Tinto, W. F.; Bissada, S. M.; McLean, S.; Reynolds, W. F. *Heterocycles* **1998**, *48*, 1461−1464.

(5) The absolute configuration of these natural products has not been determined unambiguously; however, the absolute stereochemistry of palau'amine (as shown in Figure 1) has been tenatively assigned on the basis of similarities of its CD spectrum with monobromophakellin hydrochoride (see ref 2a).

(6) Palau'amine has an IC_{50} of 42.8 nM in the mixed lymphocyte reaction (ref 2a).

(7) (a) Overman, L. E.; Rogers, B. N.; Tellew, J. E.; Trenkle, W. C. *J. Am. Chem. Soc.* **1997**, *119*, 7159−7160. (b) Starr, J. T.; Koch, G.; Carreira, E. M. *J. Am. Chem. Soc.* **2000**, *122*, 8793−8794.

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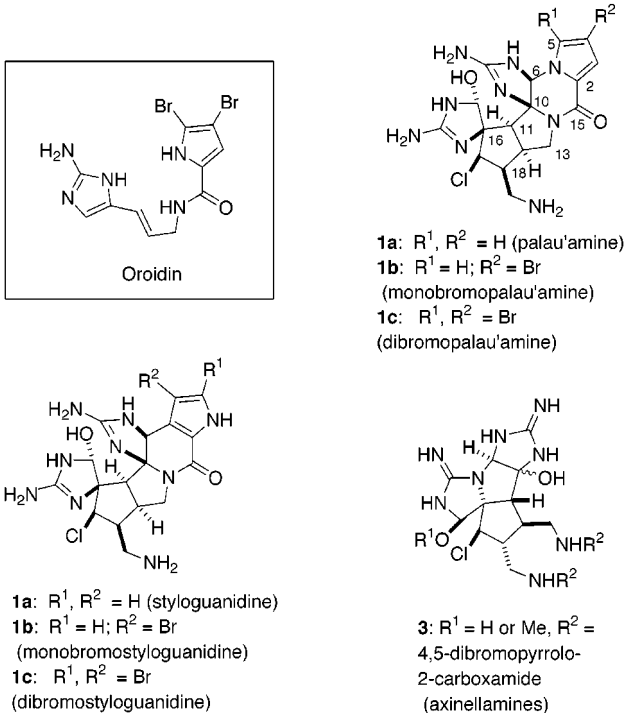
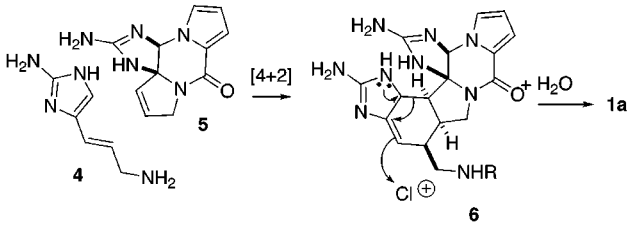


Figure 1. Structure of oroidin and oroidin-derived sponge alkaloids.

strategy provides a rapid entry into the complex spirocycle of these compounds and includes a Diels−Alder reaction of a vinyl imidazolone and a chlorination-induced 1,2-alkyl migration as key steps.[9]

The biosynthetic proposal of Kinnel and Scheuer invokes a Diels−Alder reaction between dehydrophakellin **5**, an unknown metabolite related to the known mono- and dibromophakellins,[10] and the known metabolite 2-amino-1-(2-aminoimidazolyl)prop-1-ene (**4**, AAPE) (Scheme 1).[11] A

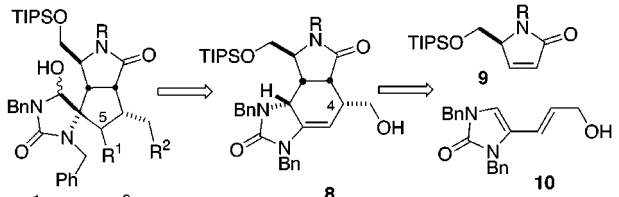
Scheme 1. Proposed Biosynthesis of Palau'amine



subsequent chlorination, presumably involving a chloroperoxidase, is proposed to initiate a pinacol-like 1,2-shift/ring contraction to deliver the spirocycle found in the palau'amines and styloguanidines after capture of the resulting iminium ion by water.

Initially, to validate this approach, we envisioned a 1,2-alkyl shift induced by a *nondirected, intermolecular* chlorination of cyclohexene **8** followed by trapping of the resulting iminium ion with water (Scheme 2). This would

Scheme 2. Retrosynthetic Analysis of the Palau'amine Spirocyclic Core **7**

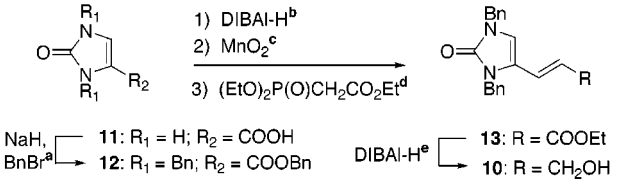


7a: R^1 = β-Cl, R^2 = OTBS
7b: R^1 = α-Cl, R^2 = directing group

deliver spirocyclic lactam **7a**, which is epimeric at C5 (C17, palau'amine numbering) relative to the cyclopentane of palau'amine. Ultimately, to access the stereochemistry found in palau'amine, we anticipated the use of the pendant group at C4 to perform a *directed* or *intramolecular* chlorination. A Diels−Alder reaction involving the pyroglutamic acid derived lactam **9**[12] and vinyl imidazolone **10** would furnish the tricyclic scaffold **8**.[13] Notably, all relative and absolute stereochemistry in palau'amine would be derived from the single stereogenic center of pyroglutamic acid. We expected high facial and *endo* selectivity on the basis of Diels−Alder reactions with related dienophiles;[14] however, the extent of regiocontrol was less secure. Support for the proposed chlorination-induced 1,2-shift was garnered from recently described, related ring contractions in synthetic studies of the paraherquamides and the spirotryprostatins.[15]

The synthesis of diene **10** was initiated by perbenzylation of the known imidazolone **11** (Scheme 3).[16] Reduction of

Scheme 3. Synthesis of the Diene[a]



[a] (a) DMF, 80 °C (41%); (b) CH_2Cl_2, −78 °C (84%); (c) CH_2Cl_2, 25 °C (98%); (d) NaH, THF, 0 → 25 °C; (e) CH_2Cl_2, −78 °C (78%, two steps).

the benzyl ester **12** with DIBAl-H to the alcohol followed by oxidation with MnO_2 gave the corresponding aldehyde.

(8) (a) This biosynthetic proposal was suggested by a reviewer of the publication by Kinnel and Scheuer (see footnote 23, ref 2b). (b) For a recently described unifying biosynthetic proposal of oroidin-derived metabolites, see: Mourabit, A. A.; Potier, P. *Eur. J. Org. Chem.* **2001**, 237−243.

(9) For related Diels−Alder reactions of vinyl imidazoles, see: Lovely, C.; Du, H.; Rasika Dias, H. V. *Org. Lett.* **2001**, *3*, 1319−1322.

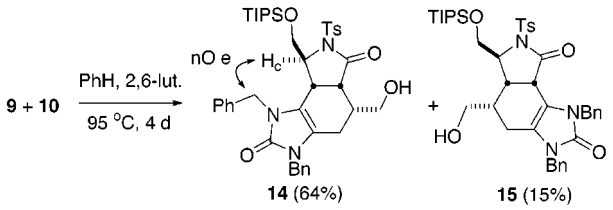
(10) Sharma, G.; Magdoff-Fairchild, B. *J. Org. Chem.* **1977**, *42*, 4118−4124.

(11) Wright, A. E.; Chiles, S. A.; Cross, S. S. *J. Nat. Prod.* **1991**, *54*, 1694−1686.

A subsequent olefination gave ester **13**, which was reduced to furnish alcohol **10**. Because of the pronounced acid sensitivity of this alcohol it was used without purification, and subsequent Diels−Alder reactions could only be performed under thermal conditions with added base.

Upon heating dienophile **9** and diene **10** in benzene in a sealed tube at 95 °C for 4 days, we were pleased to find that the desired cycloadduct **14** could be isolated as the major adduct (64%) along with the expected regioisomer **15** (15%) (Scheme 4). However, the double bond migrates to regenerate

Scheme 4. Diels-Alder Reaction

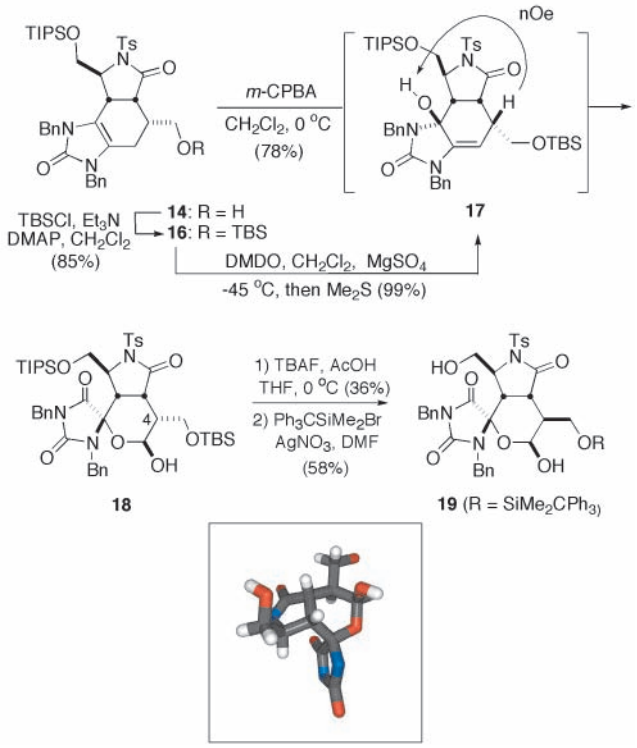


the imidazolone ring under the conditions of the Diels−Alder reaction. Stereochemical proof of the major cycloadduct was based upon NMR studies including a critical GOESY experiment[17] that showed an NOE correlation between a benzylic proton and H_c, which would only be possible in regioisomer **14** (Scheme 4). Mosher ester analysis of Diels−Alder adduct **14** indicated an enantiomeric excess of >95%.[18] Structural confirmation of the minor Diels−Alder regioisomer was secured by X-ray analysis.

Despite isomerization of the double bond in the Diels−Alder reaction, we proceeded to study the viability of the 1,2-shift/ring-contraction sequence. We reasoned that epoxidation of imidazolone **14** would furnish a rearranged deschloro spirohydantoin analogous to **7**. However, after silyl protection of alcohol **14**, treatment of imidazolone **16** with *m*-CPBA rapidly (<5 min) led to what we initially believed to be allylic alcohol **17** (Scheme 5). This structure was quickly excluded since mass spectral analysis indicated the incorporation of three oxygen atoms.

Although extensive spectral analysis was performed on the overoxidation product, complete structure elucidation was only possible following X-ray analysis of a derivative obtained after deprotection and silylation with trityldimeth-

Scheme 5. Oxidation Chemistry of Imidazolone **16** and X-ray Structure of Overoxidation Product **19**; POVchem Rendering; Nitrogen and Oxygen Protecting Groups Are Omitted for Clarity



ylsilylbromide.[19] This suggested the structure of the overoxidation product to be hemiacetal **18** (Scheme 5).

Our current mechanistic proposal for this overoxidation involves an initial epoxidation of alkene **16** with *m*-CPBA, followed by epoxide ring opening via presumed iminium ion formation and deprotonation to give carbinol **17**. A second epoxidation/ring opening sequence was followed by a proposed Baeyer−Villiger-type oxidation of the resulting iminium intermediate.[20] Furthermore, subsequent rearrangement to the spirocyclic hydantoin **18** spontaneously ensued. The stereochemistry of the quaternary center of **18** suggests that epimerization of the proposed intermediate **17** occurs under the acidic conditions of the epoxidation. We determined that epimerization at C4 occurs under the basic conditions of the TBAF deprotection of lactol **18**. While not useful for our synthesis, the formation of this rearrangement product did suggest the viability of the proposed 1,2-shift leading to a spirocyclic hydantoin.

At this stage, we recognized the potential of alcohol **17** as an ideal substrate for the projected chlorination/rearrangement sequence since it possesses an alkene in the desired position and also provides the driving force of C=O bond formation during the rearrangement. Ultimately, we were able to generate alcohol **17** in a highly diastereoselective manner and in high yield by careful treatment of imidazolone **16** with dimethyldioxirane (DMDO) at −45 °C. The structure and stereochemical proof of carbinolurea **17** was provided

(12) Dienophile **9** was synthesized from (*S*)-pyroglutamic acid (five steps) in analogy to reported procedures for related dienophiles; see: (a) Ohfune, Y.; Tomita, M. *J. Am. Chem. Soc.* **1982**, *104*, 3511−3513. (b) Ackermann, J.; Matthes, M.; Tamm, C. *Helv. Chim. Acta* **1990**, *73*, 122−132.

(13) Current efforts are directed toward the presumed enantiomeric tricyclic core structure in order to utilize the less expensive (*S*)-pyroglutamic acid.

(14) Sauter, R.; Thomas, E. J.; Watts, J. P. *J. Chem. Soc., Perkin Trans. 1* **1989**, 519−523. See also ref 12b.

(15) (a) Cushing, T. D.; Sanz-Cervera, J. F.; Williams, R. M. *J. Am. Chem. Soc.* **1996**, *118*, 557−579. (b) Edmondson, S.; Danishefsky, S. J.; Sepp-Lorenzino, L.; Rosen, N. *J. Am. Chem. Soc.* **1999**, *121*, 2147−2155. (c) Ganesan, A.; Wang, H. *J. Org. Chem.* **2000**, *65*, 4685−4693.

(16) Baxter, R. L.; Camp, D. J.; Coutts, A.; Shaw, N. *J. Chem. Soc., Perkin Trans. 1* **1992**, 255−258.

(17) Stonehouse, J.; Adell, P.; Keeler, J.; Shaka, A. J. *J. Am. Chem. Soc.* **1994**, *116*, 6037−6038.

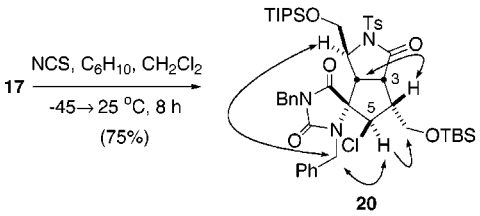
(18) See Supporting Information for details.

(19) Ager, D. J.; Fleming, I. *J. Chem. Res.* **1977**, 6−7.

by detailed spectral analysis including COSY and HMQC spectra. Key data included the presence of a carbinolurea carbon in the ^{13}C spectra (δ 86.5, d_6-acetone)[21] and a GOESY[22] experiment that showed a NOE between the carbinol hydroxyl proton and the C4 proton (Scheme 5). This hydroxyl proton appears as a sharp singlet at δ 5.57 and is exchangeable with D_2O. In support of the mechanism proposed above, treatment of alcohol **17** with *m*-CPBA also led to acetal **18**.

With a suitable substrate in hand, we studied a nondirected, intermolecular chlorination. Pleasingly, treatment of carbinolurea **17** with *N*-chlorosuccinimide (NCS) in the presence of cyclohexene[23] delivered the chlorinated spirocyclic hydantoin **20** in 75% yield (Scheme 6). The stereochemistry of the spirohydantoin was determined by GOESY experiments (Scheme 6) and is consistent with mechanistic considerations involving initial intermolecular chlorination from the convex face of alcohol **17** followed by a suprafacial 1,2-alkyl shift.

Scheme 6. Chlorination/Ring Contraction Sequence Leading to Spirocyclic Hydantoin **20**; Observed NOE's Indicated with Arrows



In summary, we have developed a concise, enantioselective approach to the spirocyclic core of the bisguanidine family of marine natural products. Spirocycle **20** possesses the full complement of cyclopentane functionality found in palau'amine but is epimeric at the chlorine-bearing atom C5 (C17 in palau'amine, see Figure 1). Epimerization at C3 would also provide the cyclopentane stereochemistry of the axinellamines. Studies toward a substrate-directed or intramolecular chlorination by the pendant C4 substituent to access the cyclopentane stereochemistry of palau'amine are in progress.

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Supporting Information Available: Selected experimental procedures and characterization data (including ^1H, GOESY, and ^{13}C NMR spectra) for compounds **9**, **12**−**14**, **17**, and **20**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(20) For a Baeyer−Villiger oxidation of an oxocarbenium ion, see: Hunt, K. W.; Grieco, P. A. *Org. Lett.* **2000**, *2*, 1717−1719. We thank Dr. Eric Moher (Eli Lilly) for bringing this related work to our attention.

(21) This chemical shift correlates well with related carbinolurea carbons found in: (a) agelastatin A (δ 93.3, CD_3OD): D'Ambrosio, M.; Guerriero, A.; Debitus, C.; Ribes, O.; Pusset, J.; Leroy, S.; Pietra, F. *J. Chem. Soc., Chem. Commun.* **1993**, 1305−1306. (b) slagenin A (δ 93.3, d_6-DMSO): Tsuda, M.; Uemota, H.; Kobayashi, J. *Tetrahedron Lett.* **1999**, *40*, 5709−5712.

(22) GOESY experiments shown were performed on spirocycle **20** and a deprotected derivative. See Supporting Information for details.

(23) Substantial quantities of aromatized byproducts were produced unless cyclohexene was added as an "alkene buffer". An example of this concept (unpublished results of J. J. Hans) was described to us recently by Professor T. R. Hoye.