Studies toward the total synthesis of the oroidin dimers†

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A Diels–Alder/rearrangement sequence is described for the construction of the core ring systems of several oroidin dimers, including ageliferin and palau'amine.

Palau'amine (**1**, Fig. 1), a hexacyclic bisguanidine-containing alkaloid isolated from the marine sponge *Styllotella aurantium* found off the Western Caroline Islands, is a member of the oroidin family of alkaloids.[1,2] This molecule has engendered significant attention from the synthetic community, in large part, as a consequence of the intricate and complex structure, and its potent immunosuppressive activity. Of the six rings in this natural product, only one is carbocyclic (E-ring), and it contains five of the eight contiguous chiral centers present in this molecule, all of which originally were reported to possess a *syn* relationship (**3**, Fig. 1). However, recently, the original structure reported by Scheuer and Kinnel has been revised to an all-*trans* relative stereochemistry (**1**, Fig. 1), which is now consistent with several other related oroidin dimers, suggesting that they have a common biogenesis.[3,4] As is often the case with structurally unusual natural products, several imaginative approaches towards this alkaloid have been reported, although no total synthesis has appeared yet. Our own approach was guided by a biosynthetic proposal that was suggested in the Scheuer and Kinnel report[1] which involved a Diels–Alder (DA)-rearrangement sequence.[5] We[6] and the Romo[7] group have reported the successful execution of this strategy in which an *inter*molecular DA reaction plays a prominent role employing imidazoles and imidazolones respectively; in our version leading to the construction of **4** (Fig. 1) containing the DEF-ring substructure of the originally assigned structure of palau'amine (**3**).[8,9] Baran has also reported a ring contraction strategy for the construction of the spiro fused bicycle system found in the related family members axinellamine and massadine.[10] In this report, we disclose the evolution of our strategy in which the key steps are an *intra*molecular DA reaction of a bis imidazole-containing substrate,[11] and its subsequent stereo- and chemoselective oxidative rearrangement to provide the all *trans*-substituted cyclopentane ring common to several members of the oroidin family of alkaloids. This change in strategy permits the incorporation of the whole contiguous carbon skeleton at an early stage.

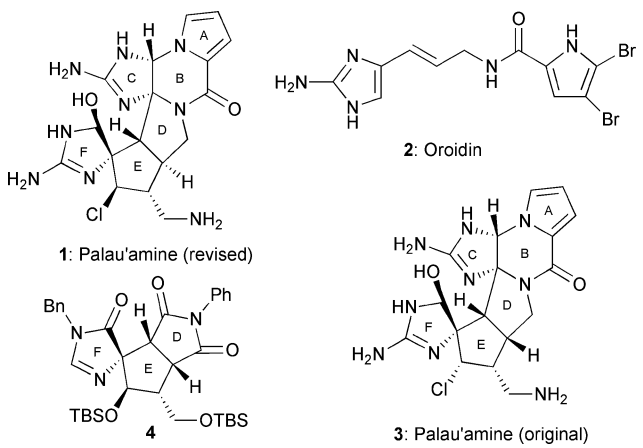
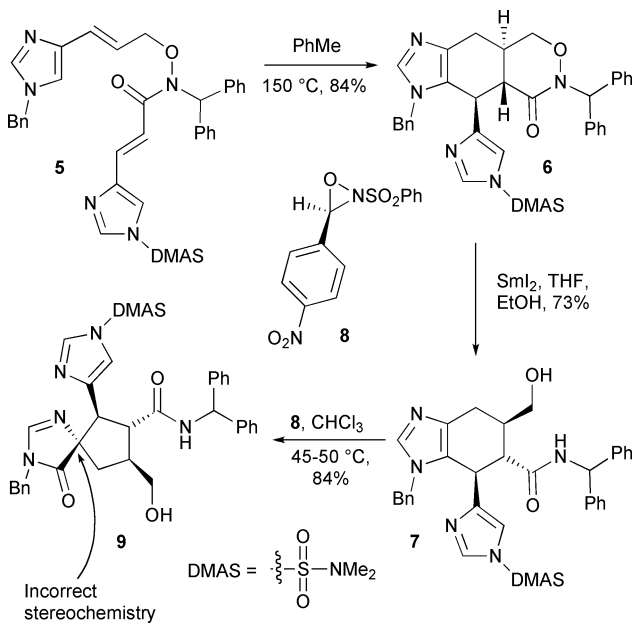


Fig. 1 Palau'amine and related molecules.

Our first generation plan focused on the construction of the ABC rings of palau'amine through elaboration of the succinimide-containing substrates related to **4** (Fig. 1), which were to be assembled *via* an *inter*molecular DA reaction between a vinylimidazole and subsequent oxidative rearrangement.[6,12] However, several aspects of this approach became less attractive in light of developments in a parallel investigation in our lab on the *intra*molecular DA reaction. It was found in the course of these studies that fairly elaborate systems, *e.g.*, **5** (Scheme 1) could be assembled extremely rapidly and these substrates would



Scheme 1

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† Electronic supplementary information (ESI) available: Experimental and characterization data for all new compounds. CCDC reference numbers 732270 (**22a**) and 734669 (**22b**). For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/b909482b

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engage in cycloadditions with reasonable efficiencies. Most notable were systems that potentially allowed access into the ageliferin[13] and axinellamine[7,14] families through the cyclization of pseudo dimeric substrates such as **5** which afford the all *trans* substituted tetrahydrobenzimidazoles **6** on IMDA reaction (Scheme 1). Subsequent reductive cleavage of the hydroxamate and oxidative rearrangement with an *N*-sulfonyloxaziridine **8** provided the spiro fused imidazolone **9**. Unfortunately, the rearranged product was epimeric at the spiro fused center preventing the further use of this particular intermediate en route to axinellamine A or palau'amine (**1**). However, if the stereochemical issue could be corrected, a concise approach for the construction of the key EF-ring system of palau'amine would be possible.

At the time that these studies were initiated they were directed toward the original structure of palau'amine, *i.e.*, **3** (Fig. 2). As indicated above, the use of bis imidazole substrates potentially increase convergency, and would provide substrates that could utilize chemistries related to those used for the construction of the monomeric oroidin alkaloid phakellin for the formation of the BD-rings (**10**→**3**, Fig. 2).[15] Thus, if an all *cis* analog of **9**, *i.e.*, **10** could be constructed, access to a palau'amine-like precursor could be envisioned. However, rather than use a *cis* substituted dienophile in our bis-imidazole approach delineated in Scheme 1, we chose to employ a propiolic acid derivative in the cycloaddition and perform a diastereocontrolled hydrogenation on the resulting cycloalkene to establish the relative stereochemistry (**13**→**12**→**11**).[16] At the outset, this strategy had several advantages over the chemistry depicted in Scheme 1; first it would preclude the normal/inverse-electron demand selectivity issue that complicates the dimer cycloadditions with amide and hydroxamate derivatives. Second, it obviates concerns associated with base-induced isomerization of the *cis*-double bond prior to cycloaddition or epimerization at the carbon adjacent to the carbonyl in the cycloadduct under the thermal reaction conditions. We also had encouraging preliminary success[17] with propiolate

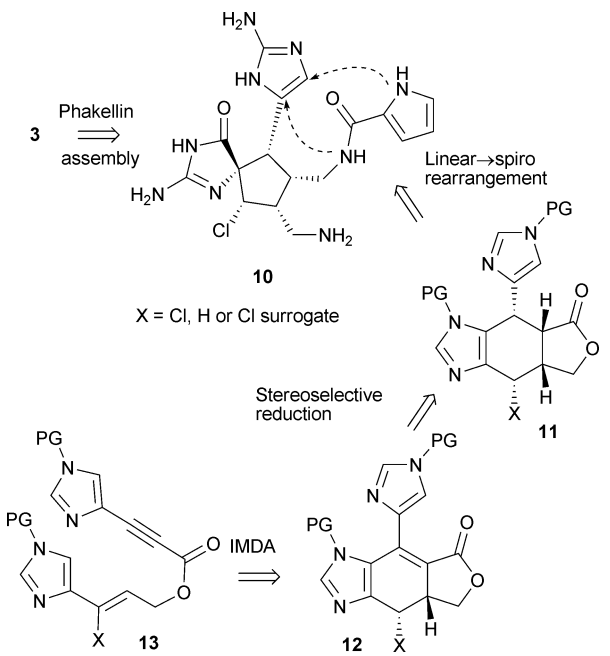
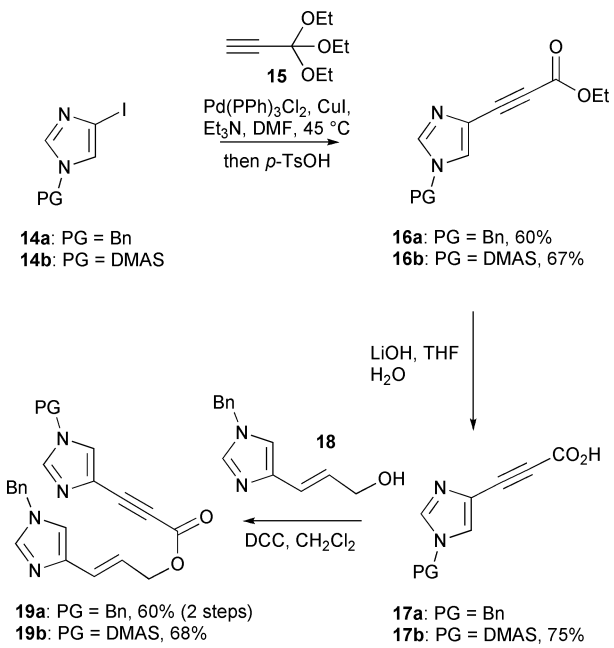


Fig. 2

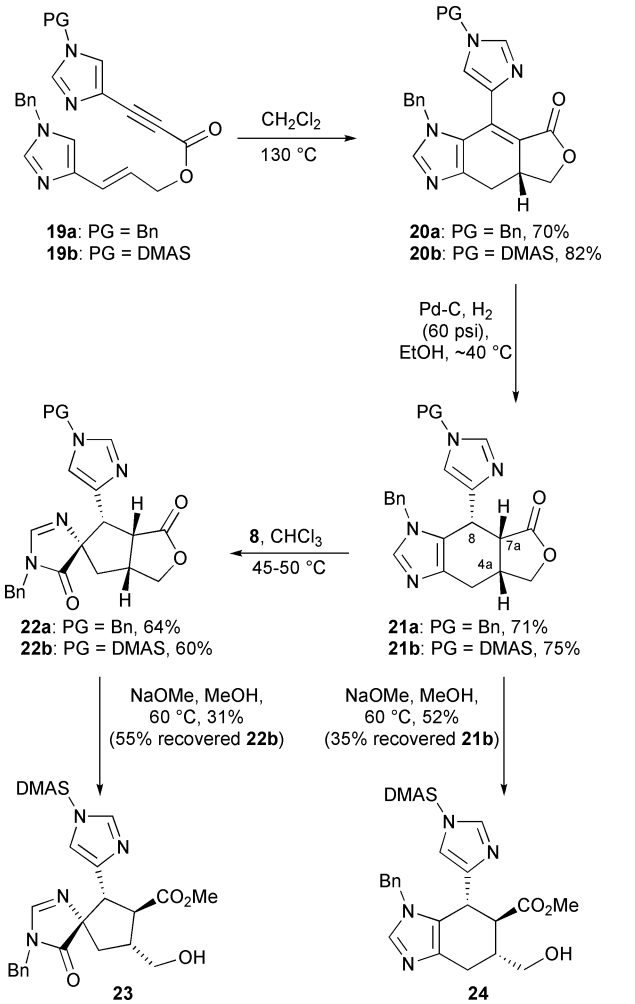
derivatives in the IMDA reaction providing the more readily elaborated lactone moiety to undertake the bis imidazole enyne IMDA approach.

The first target in evaluating this strategy became the construction of the corresponding imidazolyl propiolic acid derivatives **17a–b**, of which there were no previous reports. There are a several examples of Sonogashira reactions involving haloimidazole derivatives in the literature with propargyl alcohol or amine derivatives, and so initially this pathway was followed.[18] Although the cross-coupling reaction with protected propargyl alcohol derivatives works very well, the approach was thwarted by our inability to transform the alcohol to the corresponding acid derivative. Attempts to employ methyl propiolate directly in a Sonogashira cross coupling were partially successful on a small scale, but unfortunately this route was compromised by poor scalability (< 1 g).[19] However, the use of the ortho ester derivative **15** provided a successful synthesis of the ethyl ester **16a–b** after in situ hydrolysis of the cross-coupled product.[20] Subsequent ester hydrolysis with LiOH provided the acid **17a–b**, which upon activation with DCC in the presence of camphorsulfonic acid and DMAP,[21] and coupling with the known allylic alcohol **18**[8] provided the key cyclization precursors **19a–b** in good yield (Scheme 2).



Scheme 2

Heating a deoxygenated dichloromethane solution of the enynes **19a–b** at 130 °C in a sealed tube for 16 h led to smooth cycloaddition and provision of the expected cycloadducts **20a–b** in good yield (Scheme 3). Subsequent controlled catalytic hydrogenation at 60 psi and 40 °C over 10% Pd-C provided the all-*cis* lactones **21a–b**. Notably, this reaction was not accompanied by significant reductive debenzylation, and the corresponding tetrahydrobenzimidazoles **21a–b** were obtained in 70–75% yield. The initial assignment of the relative stereochemistry of the reduction product was obtained by examination of the relevant coupling constants of the bridgehead and benzylic protons. It has been determined that $J_{4a,7a}$ = 8.7 Hz and $J_{7a,8}$ = 8.7 Hz, which are completely consistent with the indicated stereochemistry. We



Scheme 3 §

have prepared a large number of cycloadducts related to **21a–b**, with the exception that they are all *trans* substituted, and in these cases the corresponding coupling constants are substantially larger $J_{4a,7a}$ = 12.8–13.6 Hz, and $J_{7a,8}$ = 10.1–10.8 Hz.[11] Further, in several cases the relative configurations of these derivatives have been rigorously established by X-ray crystallography. We have found that the reduction product undergoes ring opening with epimerization at the center adjacent to the ester providing the all *trans* diastereomer **24** in 51% yield (35% recovered starting materials). This product now possesses the correct stereochemistry for use in an approach to the ageliferin family of natural products.[22]

With the all-*cis* cycloadducts **21a–b** in hand, our next task involved its elaboration, including its rearrangement into the spiro fused system. We have shown previously that this can be accomplished through an oxidative rearrangement using dimethyldioxirane,[6] and while this works well in many cases, aspects of this chemistry were unattractive, in particular the need to prepare isolated reagent.[23] It has recently been found that this same rearrangement can be performed using Davis' reagents (*N*-sulfonyloxaziridines)[24] in comparable, and in many cases, with improved efficiencies.[25] Accordingly, when **21a–b** were treated with two equivalents of Davis reagent in $CHCl_3$ at 40 °C, it undergoes a smooth oxidative rearrangement providing a single spiro imidazolone **22a–b** in good yield. The exquisite chemoselectivity for the more substituted (and presumably more electron rich) imidazole in this reaction is noteworthy. We were also fortunate that both **22a** and **b** were well-behaved crystalline solids, which gave crystals suitable for X-ray crystallography (see Supporting Information for details).¶ This not only confirms the stereochemical sense of the spiro fusion, but also that the catalytic hydrogenation leads to an all-*cis* fusion. Of particular note is the stereochemical outcome of this rearrangement. Our previously reported studies with all *trans* substituted systems[14] and also one related substrate reported by Baran and coworkers[10] gives rise to an imidazolone with the opposite stereochemistry, and this seemingly subtle change in the relative stereochemistry of the substrate leads to a complete changeover in selectivity. After some experimentation it was found that the lactone underwent ring opening-epimerization on treatment with NaOMe in MeOH at 60 °C, providing the hydroxy ester in a modest 35% yield, with 55% recovered starting material.[7] Although both ring opening/epimerization reactions, require further optimization, access to the spiro fused core of palau'amine and related compounds has been developed. In addition, the cycloadducts **21a–b** provide an entry to the ageliferin and potentially the related nagelamide family[26] of natural products by suitable adjustments of the stereochemistry, and these efforts are underway.

In summary, we have developed a concise entry into the all *trans*-substituted spiro cyclopentyl imidazolone system found in palau'amine and related natural products *via* an IMDA reaction of an enyne followed by an oxidative rearrangement. Initial experiments aimed at elaborating this intermediate have demonstrated that precursors suitable for investigating various end-game strategies can be constructed by differentiating the two one-carbon sidechains. Currently we are investigating methods for the stereoselective incorporation of the chloro moiety, and for the construction of the remaining rings.

Acknowledgements

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Notes and references

§ Compounds **20a–b**, **21a–b**, **22a–b**, **23** and **24** were prepared as racemic mixtures, of which one enantiomer is depicted in Scheme 3 and in the Figures S1 and S2 illustrating the X-ray crystal structures (ESI section).

¶ X-Ray data for compound **22a**: Chemical formula, $C_{26}H_{24}N_4O_3$; FW, 440.49; Monoclinic, Space group = $P2_1/n$; a = 11.5704(8) (Å), b = 14.5997(10), c = 12.5793(9), α = 90°, β = 95.664(1)°, γ = 90°; V = 2114.6(3) Å^3; Z = 4; Mo Kα radiation, Temp. = 100(2) K; reflections, 4144 independent (R_{int} = 0.0272); R_1 and wR_2 (I = 2σ(I)) = 0.0338, 0.1009; R_1 and wR_2 (all data) = 0.0448, 0.1066.

X-Ray data for compound **22b**: Chemical formula, $C_{21}H_{23}N_5O_5S$; FW, 457.50; Monoclinic, Space group = $P2_1/n$; a = 10.6504(12) (Å), b = 19.300(2), c = 11.4094(13), α = 90°, β = 115.389(2)°, γ = 90°; V = 2118.7(4) Å^3; Z = 4; Mo Kα radiation, Temp. = 100(2) K; reflections, 5092 independent (R_{int} = 0.0794); R_1 and wR_2 (I = 2σ(I)) = 0.0508, 0.1380; R_1 and wR_2 (all data) = 0.0628, 0.1468.

1 R. B. Kinnel, H. P. Gehrken and P. J. Scheuer, *J. Am. Chem. Soc.*, 1993, **115**, 3376; R. B. Kinnel, H.-P. Gehrken, R. Swali, G. Skoropowski and P. J. Scheuer, *J. Org. Chem.*, 1998, **63**, 3281.

2 For a general overview of synthetic studies toward the oroidin alkaloids see: H. Hoffmann and T. Lindel, *Synthesis*, 2003, 1753; For current reviews of synthetic approaches toward palau'amine and other dimers:; M. Koeck, A. Grube, I. B. Seiple and P. S. Baran, *Angew. Chem., Int. Ed.*, 2007, **46**, 6586; H.-D. Arndt and M. Riedrich, *Angew. Chem., Int. Ed.*, 2008, **47**, 4785; B. Heasley, *Eur. J. Org. Chem.*, 2009, 1477.

3 H. Kobayashi, K. Kitamura, K. Nagai, Y. Nakao, N. Fusetani, R. W. M. van Soest and S. Matsunaga, *Tetrahedron Lett.*, 2007, **48**, 2127; M. S. Buchanan, A. R. Carroll, R. Addepalli, V. M. Avery, J. N. A. Hooper and R. J. Quinn, *J. Org. Chem.*, 2007, **72**, 2309; M. S. Buchanan, A. R. Carroll and R. J. Quinn, *Tetrahedron Lett.*, 2007, **48**, 4573.

4 A. Grube, S. Immel, P. S. Baran and M. Koeck, *Angew. Chem., Int. Ed.*, 2007, **46**, 6721.

5 Other biosynthetic pathways have been suggested A. Al-Mourabit and P. Potier, *Eur. J. Org. Chem.*, 2001, 237; P. S. Baran, D. P. O'Malley and A. L. Zografos, *Angew. Chem., Int. Ed.*, 2004, **43**, 2674. See also ref. 4.

6 C. J. Lovely, H. Du, Y. He and H. V. R. Dias, *Org. Lett.*, 2004, **6**, 735.

7 M. A. Zancanella and D. Romo, *Org. Lett.*, 2008, **10**, 3685.

8 C. J. Lovely, H. Du, R. Sivappa, M. K. Bhandari, Y. He and H. V. R. Dias, *J. Org. Chem.*, 2007, **72**, 3741.

9 Y. He, H. Du, R. Sivappa and C. J. Lovely, *Synlett*, 2006, 965.

10 D. P. O'Malley, K. Li, M. Maue, A. L. Zografos and P. S. Baran, *J. Am. Chem. Soc.*, 2007, **129**, 4762. For related studies see: X. Tan and C. Chen, *Angew. Chem., Int. Ed.*, 2006, **45**, 4345.

11 Y. He, Y. Chen, H. Wu and C. J. Lovely, *Org. Lett.*, 2003, **5**, 3623.

12 A diastereomeric *endo* spiro 5-imidazolone was obtained in the oxidative the rearrangement as a minor product.

13 P. Krishnamoorthy, Y. He, R. Sivappa, H. V. R. Dias and C. J. Lovely, unpublished results; See ref. 10, see also I. Kawasaki, N. Sakaguchi, A. Khadeer, M. Yamashita and S. Ohta, *Tetrahedron*, 2006, **62**, 10182.

14 R. Sivappa, N. M. Hernandez, Y. He and C. J. Lovely, *Org. Lett.*, 2007, **9**, 3861 and references cited therein; See also, J. Yamaguchi, I. B. Seiple, I. S. Young, D. P. O'Malley, M. Maue and P. S. Baran, *Angew. Chem., Int. Ed.*, 2008, **47**, 3578; D. P. O'Malley, J. Yamaguchi, I. S. Young, I. B. Seiple and P. S. Baran, *Angew. Chem., Int. Ed.*, 2008, **47**, 3581.

15 K. J. Weise, K. Yakushijin and D. A. Horne, *Tetrahedron Lett.*, 2002, **43**, 5135; K. S. Feldman and A. Skoumbourdis, *Org. Lett.*, 2005, **7**, 929.

16 Lindel and co-workers have used an alkyne based approach to access some of the simple monomeric members of the oroidin family of alkaloids, see: T. Lindel and M. Hochguertel, *J. Org. Chem.*, 2000, **65**, 2806.

17 C. J. Lovely, Y. He, Y. Chen, P. Krishnamoorthy, H. M. Fenton, R. Sivappa, H. Wu and H. V. R. Dias, unpublished results.

18 M. D. Cliff and S. G. Pyne, *Tetrahedron*, 1996, **52**, 13703.

19 M. R. Dobler, *Tetrahedron Lett.*, 2003, **44**, 7115.

20 P. G. Gassman and S. P. Chavan, *J. Org. Chem.*, 1988, **53**, 2392; T. Sakamoto, F. Shiga, A. Yasuhara, D. Uchiyama, Y. Kondo, Y. and H. Yamanaka, *Synthesis*, 1992, 746.

21 T. Sunazuka, T. Hirose, Y. Harigaya, S. Takamatsu, M. Hayashi, K. Komiyama, S. Mura, P. A. Sprengeler and A. B. Smith, *J. Am. Chem. Soc.*, 1997, **119**, 10247.

22 J. Kobayashi, M. Tsuda, T. Murayama, H. Nakamura, Y. Ohizumi, M. Ishibashi, M. Iwamura, T. Ohta and S. Nozoe, *Tetrahedron*, 1990, **46**, 5579; P. A. Keifer, R. E. Schwartz, M. E. S. Koker, R. G. Hughes, Jr., D. Rittschof and K. L. Rinehart, *J. Org. Chem.*, 1991, **56**, 2965.

23 Attempts to effect the rearrangement reaction by using *in situ* generated dimethyldioxirane were unsuccessful.

24 F. A. Davis and A. C. Sheppard, *Tetrahedron*, 1989, **45**, 5703.

25 R. Sivappa, P. Koswatta and C. J. Lovely, *Tetrahedron Lett.*, 2007, **48**, 5771.

26 T. Endo, M. Tsuda, T. Okada, S. Mitsuhashi, H. Shima, K. Kikuchi, Y. Mikami, J. Fromont and J. Kobayashi, *J. Nat. Prod.*, 2004, **67**, 1262.

