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Revisiting the Kinnel–Scheuer hypothesis for the biosynthesis of palau'amine†‡

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Received 29th June 2010, Accepted 3rd September 2010
DOI: 10.1039/c0cc02214d

We propose herein an alternative biosynthetic pathway for palau'amine in order to resolve the stereochemical issue from the original Kinnel–Scheuer hypothesis. Furthermore, we use this revised hypothesis as a guide toward the laboratory synthesis of palau'amine.

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Dimeric pyrrole-imidazole alkaloids[1] form a class of structurally unique marine natural products that have, over the past decades, inspired chemists to develop numerous synthetic strategies and methods.[2,3] In particular, the recent completion of the syntheses of the [3 + 2] dimers axinellamines,[4] massadines,[5] and palau'amine[6] by the Baran group stands as a landmark in modern synthesis. The biosynthetic pathway of these pyrrole-imidazole dimers has also been proposed.[7] We present herein a plausible biosynthetic pathway of palau'amine (**1**), and use it as a strategy for the laboratory synthesis of **1**.

Kinnel, Scheuer, and co-workers have suggested in their isolation paper that "palau'amine" (**2**) may arise from a [4 + 2] cycloaddition of 3-amino-1-(2-aminoimidazolyl)prop-1-ene (**3**) and 11,12-dehydrophakellin (**4**), followed by a chloroperoxidase-mediated chlorination and ring contraction (Scheme 1).[7c]§ However, the structure of palau'amine was recently revised from **2** to **1**.[8] The C-11/C-12 *anti* stereochemistry in **1** cannot easily be explained by this proposed pathway. The thermal Diels–Alder reaction pathway will result in a *syn* stereochemistry, and the photo Diels–Alder reaction pathway is not likely considering the lack of sufficient UV-light to the sponges.[7a] Meanwhile, the difficulty in constructing the piperazine moiety of **1** at a late stage[6,9] indicates that this transformation is highly endothermic, and requires significant energy input. We therefore suspected that the ring strain of **1** may be introduced stepwise, both biosynthetically and synthetically.

In addition to Baran's macrocycle strategy,[6] we consider the original Kinnel–Scheuer hypothesis a viable pathway. To reconcile the stereochemical issue of the [4 + 2] cycloaddition, we propose the intermediacy of ageliferin analog **7** (Scheme 1). Specifically, a [4 + 2] cycloaddition reaction of **3** and clathrodin (**6**) would give rise to **7**, and set the *anti* C-11/C-12 stereochemistry. An oxidative bicyclization would then provide the modified Kinnel–Scheuer intermediate **8**, which could undergo a chlorinative ring contraction to afford **1**. We have synthesized **9**, a close analog of **8**, in its protected form as a step toward the laboratory synthesis of **1**.

Central to our synthetic strategy is a Mn(III)-mediated oxidative radical cyclization reaction,[10,11] that, in an intramolecular way, resembles the biogenic [4 + 2] dimerization to construct the cyclohexenyl core of **7** (Scheme 2). Specifically, oxidation of β-ketoester **15** with $Mn(OAc)_3$ initiated a cascade radical cyclization sequence to deliver **16** that bears the ageliferin skeleton. Two C–C bonds (C-11/C-20 and C-12/C-18) and three stereogenic centers (C-11, C-12, and C-18) were established in this single transformation.

To construct **15**, we used a convergent approach that comprises an aldol reaction between aldehyde **11** and ester **14** (LiHMDS, THF; 79% over three steps), and an alcohol oxidation (Dess–Martin periodinane, H_2O, CH_2Cl_2). Aldehyde **11** was prepared in one-pot from imidazole (**10**) (NaH, BOMCl, DMF, then NaH, $CuCl_2$, O_2, then $POCl_3$; 68%). Ester **14** was prepared from coupling (DCC, CH_2Cl_2) of Cbz-β-Ala-OH with the known alcohol **13**, which was in turn synthesized in two steps from Garner's aldehyde (**12**) ((i) $Ph_3P{=}CHCOOMe$, benzene; (ii) DIBAL, THF) according to the literature.[12]

Treating β-ketoester **15** with $Mn(OAc)_3$ in warm acetic acid results in a quite clean transformation. The ageliferin core skeleton **16** was obtained as the only diastereomer in 36% yield over two steps from the aldol product of **11** and **14**.[13] The stereochemical course of this reaction was controlled by the C-10 stereogenic center through an $A^{1,3}$ strain.[10] The ester tether, used for the intramolecular Mn(III) oxidation reaction, was then removed. The decarboxylation (LiOH, THF, H_2O) of **16** gave rise to a product with *cis*-C-12/C-18 stereochemistry as the thermodynamic product. The N-14 nitrogen atom was then introduced as an azide by a Mitsunobu reaction ($(PhO)_2P(O)N_3$, DEAD, PPh_3, THF; 42% for two steps). The C-18 stereocenter was subsequently epimerized through kinetic protonation of the corresponding enolate (LiHMDS, THF, then HOAc) and the C-17 carbonyl group was deoxygenated ($Ca(BH_4)_2$, THF,[14] then $NaBH_3CN$, HOAc) to afford **17**.

In order to implement the oxidative bicyclization strategy to install the piperazine ring, we converted the C-11 side chain of **17** to an imidazolinone group by a three-pot procedure. The acetonide protecting group was first removed (TFA, CH_2Cl_2) and the resulting alcohol was oxidized (Dess–Martin periodinane, H_2O, CH_2Cl_2). The Boc protecting group was next removed under acidic conditions, followed by *in situ* treatment of the amino aldehyde with potassium cyanate at pH 4 to afford **18** (HCl, MeOH, H_2O, then *o*-$(HO_2C)C_6H_4(CO_2K)$, NaOH, KOCN).[15] It is noteworthy that Myers and co-workers have previously reported that amino aldehydes are stable in

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† This article is part of the 'Emerging Investigators' themed issue for ChemComm.

‡ Electronic supplementary information (ESI) available: Experimental procedures and characterization data. See DOI: 10.1039/c0cc02214d

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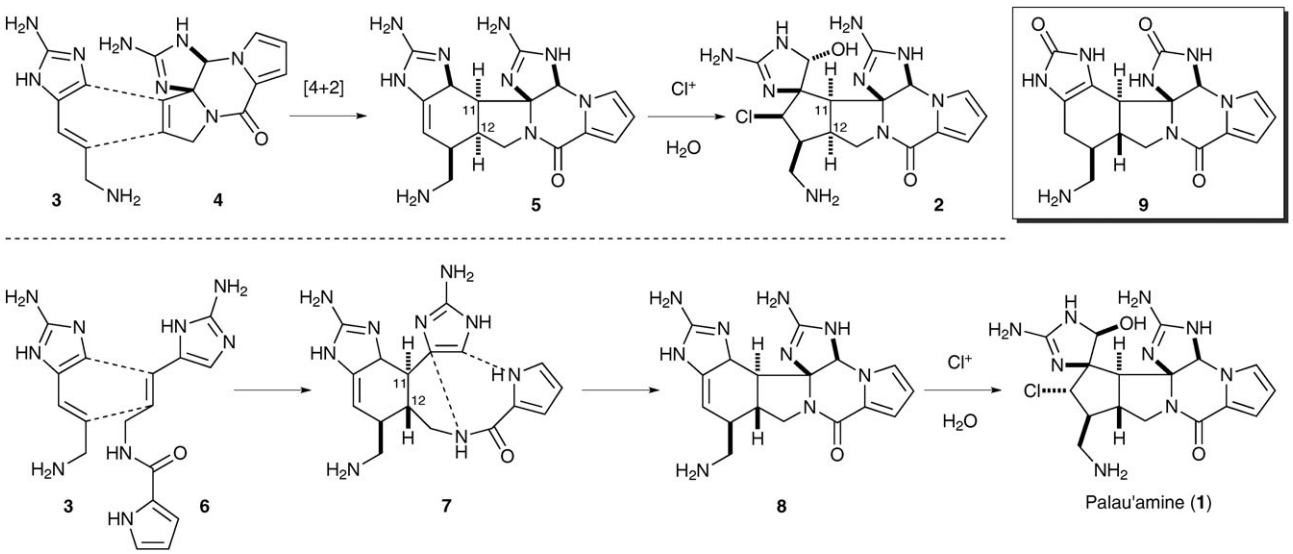
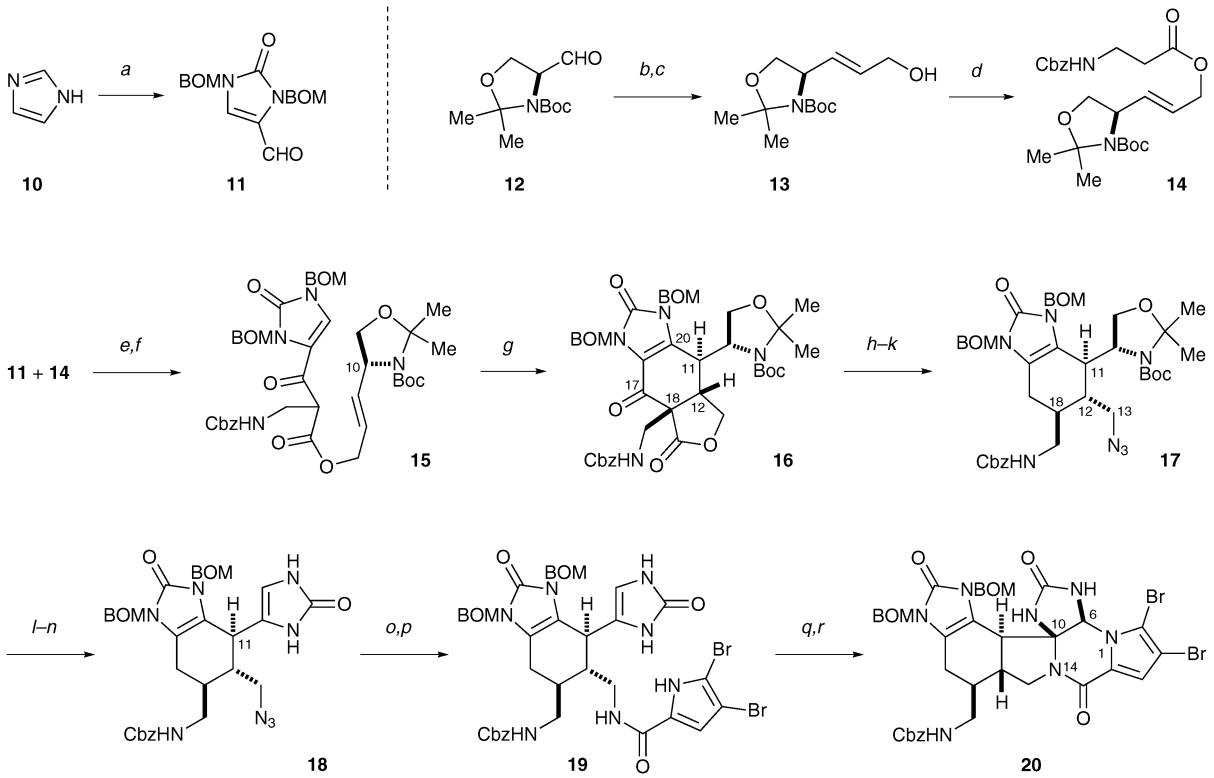


Scheme 1 The original (top) and revised (bottom) Kinnel–Scheuer biosynthesis of palau'amine.



Scheme 2 The synthesis of **20**, a close analog of the Kinnel–Scheuer intermediate. (a) NaH, BOMCl, DMF, 23 °C, then NaH, $CuCl_2$, O_2, 23 °C, then $POCl_3$, 23 °C; 68%. (b) $Ph_3P{=}CHCOOMe$, benzene, 23 °C; 95%. (c) DIBAL, THF, 0 °C. (d) Cbz-β-Ala-OH, DCC, CH_2Cl_2, 23 °C. (e) LiHMDS, THF, −78 °C; 79% over three steps. (f) Dess–Martin periodinane, H_2O, CH_2Cl_2, 23 °C. (g) $Mn(OAc)_3$, HOAc, 60 °C; 36% over two steps. (h) LiOH, THF, H_2O, 23 °C. (i) $(PhO)_2P(O)N_3$, DEAD, PPh_3, THF, 23 °C; 42% over two steps. (j) LiHMDS, THF, then HOAc, −78→0 °C. (k) $Ca(BH_4)_2$, THF, 0 °C, then $NaBH_3CN$, HOAc, 50 °C. (l) TFA, CH_2Cl_2, 0 °C. (m) Dess–Martin periodinane, H_2O, CH_2Cl_2, 23 °C. (n) HCl, MeOH, H_2O, 40 °C, then *o*-$(HO_2C)C_6H_4(CO_2K)$, NaOH, KOCN, 110 °C. (o) PPh_3, H_2O, THF, 80 °C; 7–10% over 6 steps. (p) $(Br_2$-Pyrrole$)COCCl_3$, NEt_3, DMF, 70 °C; 33%. (q) PhIO, Na_2CO_3, TFE, 23 °C. (r) DMSO, 50 °C; 20% over two steps.

aqueous media below pH 5, with the aldehyde group existing in its hydrate form.[16] In our hands, buffering the aqueous methanol solution of the amino aldehyde with potassium hydrogen phthalate gave the best results.

With **18** in hand, we next sought to introduce the pyrrole group and set the stage for the oxidative bicyclization. The azido group was reduced by a Staudinger reduction (PPh_3, H_2O, THF) and the product was obtained in 7–10% yield over

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6 steps after HPLC purification. The pyrrole group was then installed ((Br$_2$-Pyrrole)COCCl$_3$, NEt$_3$, DMF; 33%). Use of a less pure amine for this reaction resulted in significantly less or no product.

We previously reported a hypervalent iodine(III)-mediated oxidative bicyclization reaction of dihydro-14-oxo-oroidin to give dibromophakellstatin in quantitative yield.[17] Pleasingly, use of the same reaction conditions (PhI(OAc)$_2$, Na$_2$CO$_3$, TFE) to oxidize **19** did afford **20**, though inconsistently in 0–5% yield. After extensive optimization, we found PhIO to be a better oxidant, which gave rise to an unstable product that slowly converted to the Kinnel–Scheuer intermediate analog **20** at elevated temperature in DMSO in 20% yield over two steps. A similar unstable intermediate, which was suspected to be the monocyclized product, was also observed by Büchi and co-workers when oxidizing dihydrooroidin with bromine to form dibromophakellin.[15b,18]

In summary, as part of our palau'amine synthesis project, we have synthesized a close analog of the modified Kinnel–Scheuer intermediate from their biosynthesis proposal. The stereochemistry of this advanced synthetic intermediate is consistent with the revised structure of palau'amine. The biomimetic oxidative ring contraction of the Kinnel–Scheuer intermediate has previously been realized in model systems in the laboratory by Romo,[3d] Lovely,[3c] Baran[19] and us.[10] In particular, the method developed by Romo allowed for the introduction of the chlorine atom. We are currently examining the practicality of these methods in converting advanced synthetic intermediates such as **20** into palau'amine (**1**).

We thank the NIH (Grant NIGMS R01-GM079554), the Welch Foundation (I-1596), and UT Southwestern for financial support, and Prof. Joseph Fox (University of Delaware) for the suggestion of the use of ethyltrichlorosilane-deactivated silica gel.

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