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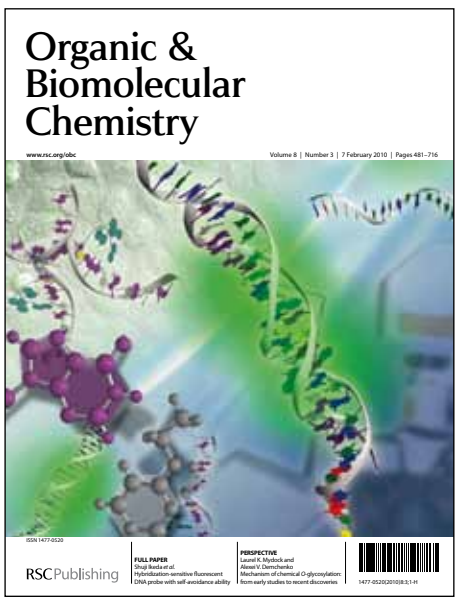

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Communication

Total syntheses of oroidin, hymenidin and clathrodin

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The total syntheses of oroidin, hymenidin and clathrodin are reported *via* the intermediacy of an imidazo[1,2-*a*]pyrimidine derivative. The chemistry described herein obviates the need for expensive guanidine reagents, multiply protected pre-functionalized 2-aminoimidazole synthons, or the need for laborious olefinations thereby achieving synthetic efficiency amenable to scale-up. The approach outlined in this manuscript provides the opportunity for further functionalizations through the imidazo[1,2-*a*]pyrimidine core and through functional groups placed strategically on the side chain.

Pyrrole-imidazole alkaloids (PIAs), a class of nitrogen rich natural products,[1] have attracted considerable attention from synthetic chemists due largely to their intricate structural complexity and the wide range of potential biological activities.[2] Marine sponges, specifically the *Agelasidae* and *Leucetta* families, are the primary sources for a plethora of fascinating, structurally diverse secondary metabolites, usually containing a 2-aminoimidazole, that are rarely found in terrestrial flora and fauna. In many cases, they appear to serve as anti-feedants in the hosts to deter predators.[3] Since the discovery of the first member of this alkaloid family, oroidin (**1**) in 1971,[4] nearly 150 additional natural products have been isolated. The astonishing complexity of this family ranging from simple acylic monomers to incredibly complex cyclic tetramers of oroidin has been proposed[5] to be derived biosynthetically from three building blocks, oroidin (**1**), hymenidin (**2**)[6] and clathrodin (**3**).[7] Some representative members of this family are shown in Figure 1. This group of alkaloids represents a classical example of combinatorial and diversity oriented synthesis of which Nature is capable. Oroidin (**1**) has been shown to possess anti-biofouling properties through inhibition of biofilm development in the marine α-proteobacterium *R. salexigens*.[8, 9] Oroidin-free base is known to potently inhibit the malaria etiological agent *Plasmodium falciparum*[10] and to interfere with membrane depolarization and calcium metabolism.[11] Very recently, it has also been shown to inhibit the activity and function of Pdr5p, an enzyme responsible for the multidrug resistance phenotype in *Saccharomyces cerevisiae*.[12]

Oroidin (**1**) and its congeners have rekindled interest in heterocyclic chemistry by providing stimuli for new chemical developments and elegant methodologies.[13] The discovery of facile and general synthetic routes to simple acyclic oroidin monomers would pave the way to establish routes to the more complex congeners and as a result ten research groups have described the synthesis of the monomers.[14] The approaches adopted in these reports can be broadly grouped into three categories, as shown in Scheme 1: (1) approaches that involve olefinations; (2) approaches that involve Pd-mediated C-C bond formation with alkynes/alkenes; (3) approaches that depend on the natural resources. The first two approaches require suitably functionalized and protected imidazoles or guanidines as starting materials, making these otherwise attractive routes less suitable for scale-up. The third approach includes two routes that utilize

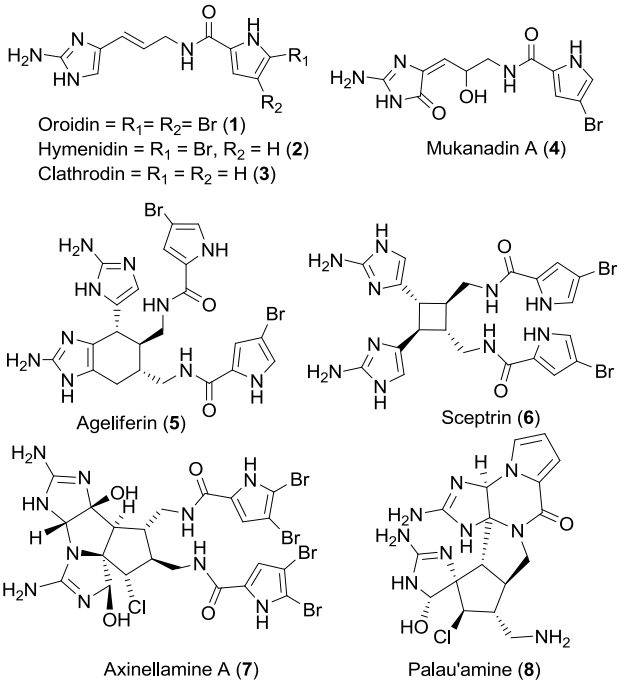

Figure 1 Oroidin and its congeners

natural synthons i.e., urocanic acid[14h] and ornithine.[14t] These methods suffer from cost effectiveness or involve operations that require the use of Na/Hg amalgam, though the problem with the former approach has been alleviated to some extent by the development of a method to convert histidine into urocanic acid.[9s] Thus, despite impressive progress achieved over the years, there is still an evident need for novel routes for the preparation of oroidin (**1**) and its congeners that are facile and amenable to scale-up. Our ongoing interest to identify novel anti-bacterial and anti-biofilm compounds[15] led us to develop a research program to explore the potential of the oroidin family. As part of this effort, we initiated a program to develop a synthesis route for oroidin (**1**) and its congeners. Our retrosynthetic analysis of oroidin (**1**) and its congeners, hymenidin (**2**) and clathrodin (**3**) is depicted in Scheme 1.

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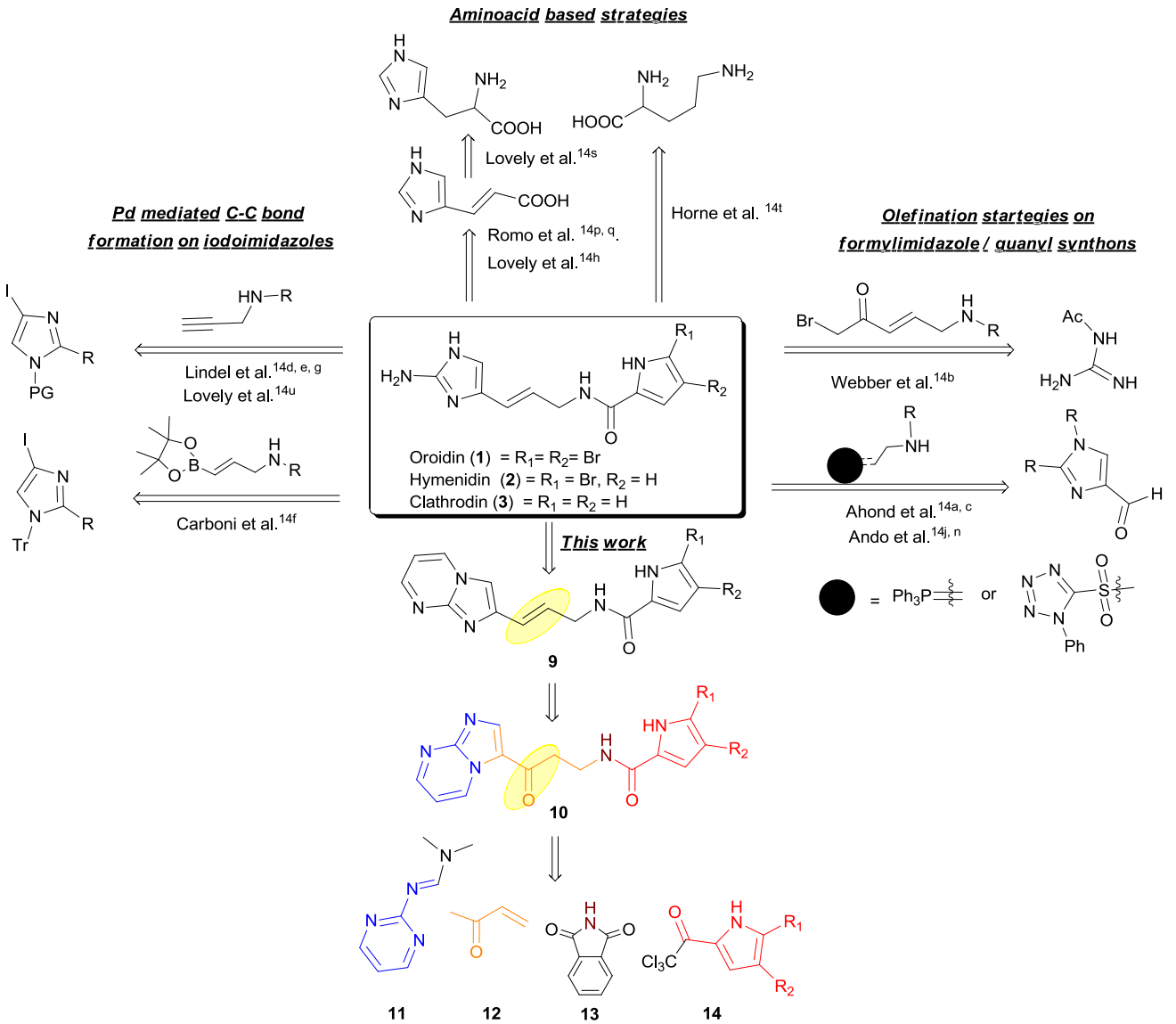

Scheme 1: Retrosynthetic analysis of oroidin monomers

At the outset, we aimed to dispense the drawbacks of the earlier approaches associated with the installation of the 2-amino moiety and the unsaturation of the targets under consideration. With longer term goals in mind, we wanted to develop the synthesis of an intermediate that would serve as a linchpin towards the synthesis of other acyclic monomers such as stevensine,[16] agelanine A[17] and possibly acyclic dimers such as the nagelamides[18] in a divergent fashion. Hence, we identified the acyl imidazole precursor **10** and planned to install the unsaturation in the side chain through hitherto unexplored acyl imidazole chemistry. Keeping the sensitivity of 2-aminoimidazole moiety[2b] and the need for multiple protections of the active hydrogens on guanidine in mind, we decided to employ a masked 2-aminoimidazole in our synthetic approach towards these alkaloids. Imidazo[1,2-*a*]pyrimidine[19] as a heterocyclic surrogate for polysubstituted 2-amino-1*H*-imidazoles has not been explored fully in total synthesis[14m, 20] despite its ease of formation and subsequent facile cleavage to produce substituted 2-aminoimidazoles. It is worth noting that Al Mourabit et al., have employed similar heterocycles in conjunction with pyridine chemistry.[21] We chose to construct imidazo[1,2-*a*]pyrimidine via a suitably functionalized haloketone[22] in our efforts. The electron deficient nature of its pyrimidine ring allows nucleophilic attack by amine-based deprotection reagents, whereas the electron-rich nature of the imidazole ring facilitates its participation in reactions such as Friedel-Crafts acylations,[23] brominations,[24] and Pd-mediated coupling reactions,[25] critical for our future ventures to prepare non-natural guanidines. We also proposed to evaluate the imidazo[1,2-*a*]pyrimidine framework as a pharmacophore,[26] and thereby elucidate the role and importance of a free 2-aminoimidazole for antibacterial activity of the targets under consideration.[27] Herein, we describe the synthesis and elaboration of imidazo[1,2-*a*]pyrimidine **10** in the total synthesis of oroidin (**1**), hymenidin (**2**) and clathrodin (**3**).

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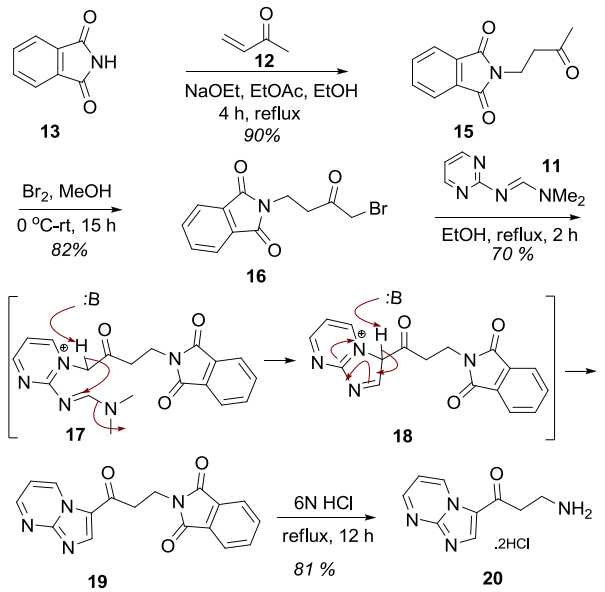
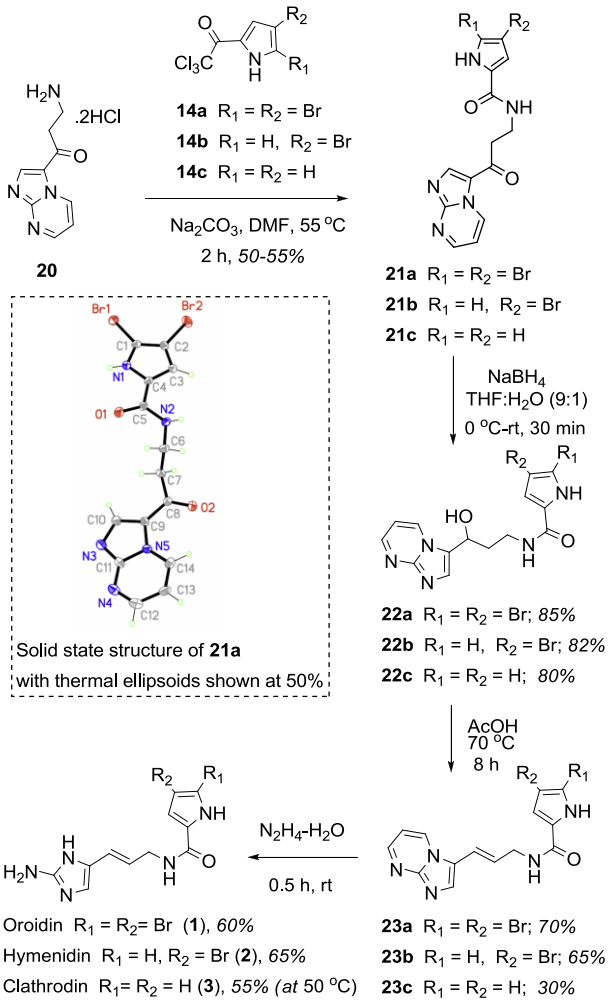
Our synthesis efforts commenced with the synthesis of α-haloketone **16** for the construction of imidazo[1,2-*a*]pyrimidinyl substrates, as shown in Scheme 2. The required bromoketone **16** was accessed following the reported procedures.[28] Briefly, the conjugate addition of phthalimide **13** to methyl vinyl ketone **12** afforded the ketone **15** which was subjected to bromination with Br_2/MeOH to obtain the bromide **16**. The reactions are clean and high yielding. However, the α-ketobromide **16** was unstable and converts readily into its hydrate form upon exposure to the atmosphere and accordingly it was utilized in the next step immediately. Condensation of the bromide **16** with *N*,*N*-dimethyl-*N'*-2-pyrimidinyl-(*E*)-methanimidamide **11**[29] furnished imidazo[1,2-*a*]pyrimidine compound **19** in good yield in a regioselective fashion.[30] We have designed this chemistry not only to gain access to acyl imidazoles, but also for accessing the iminium intermediate **18** for further bond formations in the context of synthesis of other natural and unnatural heterocyclic scaffolds. The next task en route to the title compounds was to



Scheme 2: Synthesis of acyl imidazo[1,2-*a*]pyrimidine

access the aliphatic amine **20** for preparation of pyrrolylamides. However, the selective deprotection of the phthalimido group of **19** to primary amine **20** proved difficult under standard hydrazinolysis and other basic conditions due to competing attack on the imidazopyrimidine core. After an extensive investigation, we succeeded in selectively removing the phthaloyl moiety with refluxing 6N HCl to obtain the amine **20** as the hydrochloride salt after the simple filtration of the phthalic acid by-product followed by the concentration of the aqueous layer. Thus, we have successfully developed facile chemistry suitable for the multigram (*ca* 500g) synthesis of acyclic amine **20** without recourse to expensive protected guanidine reagents or involving laborious chromatographic purifications. The thus obtained amine hydrochloride **20** was subjected to acylation in presence of excess base with various pyrrolyl trichloromethyl ketones **14a-c** which in turn were prepared from pyrrole to provide compounds **21a-c**, as shown in Scheme 3. Structural proof for the structures has been obtained through NMR and X-ray crystallography of **21a** (Scheme 3 inset). Partial reduction of the carbonyl functionality of **21** with $NaBH_4$ provided benzylic alcohols **22a-c**. Dehydration in the presence of acetic acid delivered unsaturated compounds **23a-c**. All that remained to complete the synthesis of oroidin (**1**), hymenidin (**2**), and clathrodin (**3**) was unmasking of 2-aminoimidazole. We were aware of the problems that were faced with deprotection on elaborated base sensitive systems[20a] and as expected, the final deprotection was not straightforward. After some experimentation with conditions and bases, we were delighted to find clean deprotection occurred with neat hydrazine hydrate to afford the 2-aminoimidazole core, providing the natural products **1, 2** and **3** in good yields. It is pertinent to mention that the dehydration of the unsubstituted pyrrole amide **22c** was problematic and gave a lower yield than the bromopyrrolyl compounds **22a** and **22b**.



Scheme 3: Synthesis of Oroidin, Hymenidin and Clathrodin

Conclusions

In summary, we have developed facile imidazo[1,2-*a*]pyrimidine-based chemistry for the total synthesis of oroidin (**1**), hymenidin (**2**) and clathrodin (**3**) that obviates the need for the *de novo* construction of the 2-aminoimidazole using expensive reagents thereby achieving the synthetic efficiency. Of further note is that the functional groups and diversity points available in **21a-c** and **22a-c** render them suitable as intermediates for the synthesis of other members of this family including the cyclic monomers *e.g.* stevensine,[19] hymenin[31] and agelanine A[20] and acyclic dimers such as members of the nagelamide family.[21]

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Notes and references

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*†Electronic Supplementary Information (ESI) available: [Complete experimental procedures are provided, including copies of 1H and ^{13}C NMR spectra of all new compounds and HRMS analysis. X-ray data (CIF) for **21a** is also provided.]. See DOI: 10.1039/b000000x/*

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