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Biomimetically Inspired Short Access to the 2-Aminoimidazole-Fused Tetracyclic Core of (±)-Dibromoagelaspongin†

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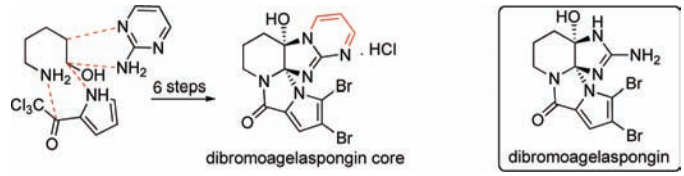
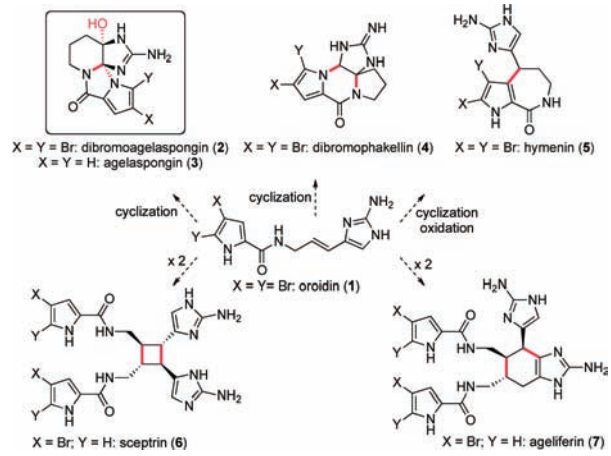
ABSTRACT



A six-step synthesis of the tetracyclic core of the natural compound (±)-dibromoagelaspongin, isolated from *Agelas* sp. Sponge, was achieved from the commercially available 5-aminopentan-1-ol, 2-trichloroacetylpyrrole, and 2-aminopyrimidine. Following a biomimetic inspired approach, successive oxidative reactions including the final DMDO biomimetic oxidation gave the interesting triaminomethane-fused core.

Pyrrole-2-aminoimidazoles (P-2-AIs) constitute a growing family of marine alkaloids, mainly isolated from Agelasidae and Axinellidae families of sponges.[1] Except the single preliminary experiment published by Kerr,[2] their biosynthesis remains unknown to date. Few hypotheses have been proposed that enlighten the central role of the linear monomeric P-2-AIs like oroidin (**1**) and the chemical pathways relating various cyclized members of this family.[3] The variety of intramolecular cyclization modes exhibited by oroidin (**1**) and congeners is sufficient to overcome various assemblies of the complex monomeric and dimeric P-2-AI metabolites. Scheme 1 shows a few examples (**2**−**7**) of the cyclization modes that we proposed in 2001.[3b] Since we last

Scheme 1. Some Oroidin (**1**) P-2-AI Polycyclic Derivatives Generated through Various Tautomers



† Dedicated to the memory of Christian Marazano.

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(1) (a) Braeckman, J.-C.; Daloze, D.; Stoller, C.; Van Soest, R. W. M. *Biochem. Syst. Ecol.* **1992**, *20*, 417–431. (b) Erpenbeck, D.; Van Soest, R. W. M. *Mar. Biotechnol.* **2007**, *9*, 2–19.

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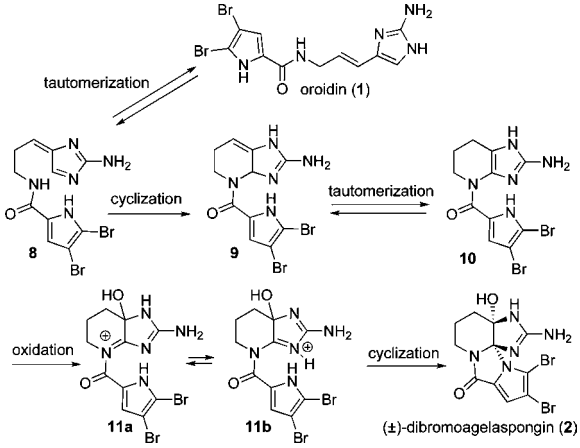
proposed the crucial role of the ambivalent reactivity of the oroidin precursor, considerable progress on the chemistry of pyrrole-2-aminoimidazole metabolites has been accomplished by several groups.[3e,4]

The oroidin motif can be easily identified in the dibromoagelaspongin (**2**), an intricate tetracyclic P-2-AI member with two adjacent quaternary carbons exhibiting a cis stereochemistry of the ring fusion. The racemic dibromoagelaspongin (**2**) was isolated from *Agelas* sp. sponge in 1989.[5] Biosynthetically, tautomerization of oroidin (**1**) into the isomer form **8** followed by the sequence of cyclization oxidation reactions **8** → **9** would give the fused piperidine-2-aminoimidazole derivative **10**. Oxidation would provide an acyl iminium **11a** or **11b** species that could undergo spontaneous intramolecular ring closure to yield dibromoagelaspongin (**2**) (Scheme 2). While finishing this work, the

Scheme 2. Proposed (±)-Dibromoagelaspongin (**2**) Biosynthesis from Oroidin (**1**)

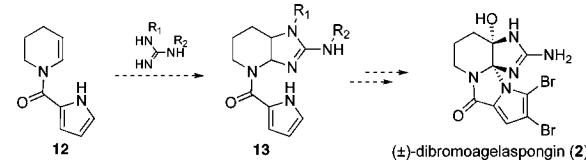


total synthesis of dibromoagelaspongin was published by Feldman et al. in 15 steps from imidazole, in 4.7% yield from an advanced imidazole sulfoxide intermediate.[6]

The likely biosynthetic oroidin cyclization turned out to be quite difficult to accomplish biomimetically. The cyclization of **8** into **9** is only one of the huge possibilities offered by the subtle reactivity of various dual tautomers of oroidin.[3b,7]

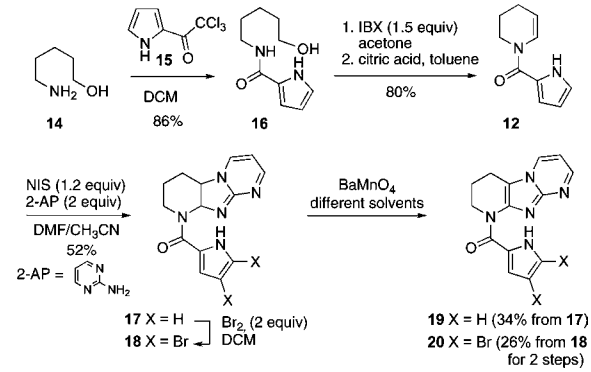
To test this approach experimentally, we targeted a synthetic equivalent of the hypothetical cyclized oroidin derivative **10** using a more expedient method than the preparation of the oroidin itself. The proximity between oroidin (**1**) and dibromoagelaspongin (**2**) structures led us to propose a common chemical approach via the chemistry of the oxidative addition of guanidine derivatives to olefins developed in our laboratory.[8] The synthesis was envisaged through the intermediates **13** by the addition of a protected guanidine or 2-aminopyrimidine (2-AP) to the appropriate tetrahydropyridine **12** in oxidative conditions.[9] Further oxidation, cyclization, and deprotection would give the dibromoagelaspongin (**2**) or other fused tetrahydropyridin-2-aminoimidazole analogues (Scheme 3).

Scheme 3. Synthetic Scheme Forward (±)-Dibromoagelaspongin



The new tetrahydropyridine **12** was readily available from the commercially available 5-aminopentanol (**14**) and the 2-trichloroacetylpyrrole (**15**). The acylation of **14** with **15** followed by IBX oxidation[10] and carbinolamine dehydration[11] was achieved in 69% overall yield on a multigram scale (Scheme 4). The guanidine equivalent 2-aminopyri-

Scheme 4. Synthesis of the 6-5-6 Fused Tricycle



midine reacted with the *N*-acylpyrrole tetrahydropyridine **12** in the presence of *N*-iodosuccinimide to afford the coupling product **17** in 52% yield. Bromination of the pyrrole moiety was best accomplished at this stage, with bromine in CH_2Cl_2, to give the dibrominated compound **18**, which was further engaged without purification. The following steps were conducted in parallel on the two substrates **17** and **18**. We

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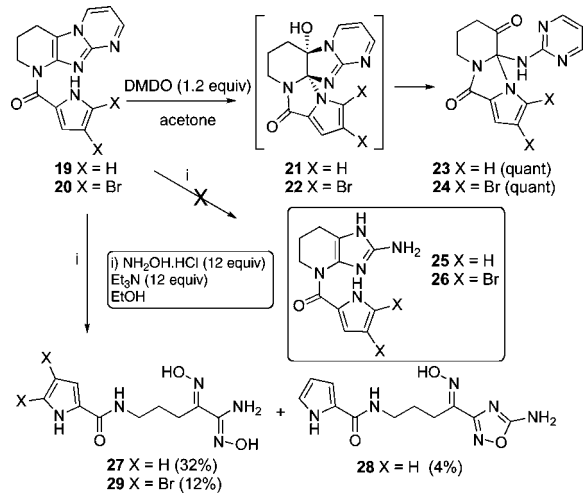
next examined the oxidation of the latter compounds into **19** and **20**, respectively. This reaction was found to be problematic: several oxidants were investigated (MnO_2,[12] $BaMnO_4$,[13] DDQ,[14] Pd/C-cyclohexene,[15] IBX,[16] DIB,[17] TCCA[18]), and among them, $BaMnO_4$ gave the best yield albeit modest. Attempts to further optimize the reaction were conducted on the nonbrominated compound **17**. After many experiments including the survey of solvents, reaction time, and temperature, the desired compound **19** was obtained in 34% yield, together with 35% of the recovered starting material. The dibrominated derivative **18** required longer reaction time in CH_2Cl_2, to give the targeted protected cyclic dibrominated derivative **20** in 26% overall yield.

With the key intermediates in hand, we investigated the biomimetic oxidative cyclization (Scheme 5). Treatment of

Scheme 5. Oxidation of the Protected Cyclic Oroidin

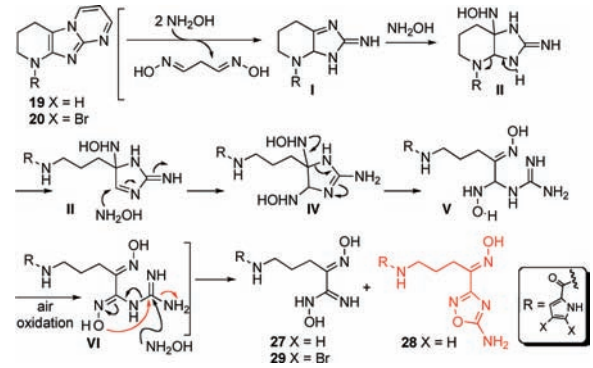


compounds **19** and **20** with a slight excess of dimethyldioxirane (DMDO)[19] provided the 3-piperidone derivatives **23** and **24**, respectively, in quantitative yield. As expected, the pyrrole moiety cyclized spontaneously via the acyliminium intermediates.[7,20] Unluckily, the obtained pentacycles **21** and **22** showed instability due to the driving force leading to the aromatic 2-aminopyrimidine part in the 3-piperidone derivatives **23** and **24**.

To circumvent this difficulty, we explored the deprotection of the guanidine moiety of the intermediates **19** and **20**, before the oxidative cyclization step. The standard deprotection procedure using $NH_2OH{\cdot}HCl$, NEt_3,[21] for the transformation of 2-AP part into 2-aminoimidazoles **25** and **26** was applied, but the expected products were not obtained. The only identifiable products isolated from the complex reaction mixture are the linear compounds **27** and **29**. The rearrangement compound oxadiazolamine **28** was also isolated in the case of the nonbrominated derivative.

The formation of the linear compounds **27** and **29** could be explained by the sensitivity of the intermediates **19** and **20** to the hydroxylamine nucleophilicity that leads to their decomposition. A possible mechanism leading to the isolated compounds is given in Scheme 6. It is noteworthy that when

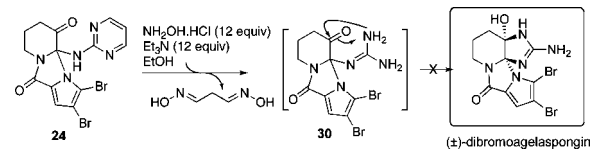
Scheme 6. Plausible Mechanism for the Formation of the Linear Compounds **27** + **28** and the Oxadiazolamine **28**



the reaction was run with only 2 equiv of hydroxylamine we noticed no progress of the reaction. The deprotection reaction needs a large excess of the reagent.

We next examined if guanidine deprotection of the 3-piperidone **24** would lead to further cyclization of the expected guanidine-free derivative **30** (Scheme 7) to furnish

Scheme 7. Deprotection/Cyclization Tentative of **24** into **2**



the natural compound **2**. Exposure of **24** to the standard deprotecting reagents caused only degradation.

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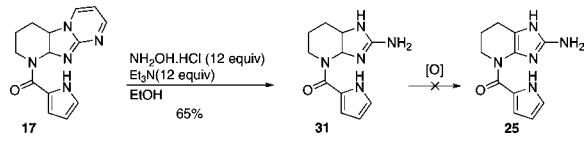
Considering the instability of the functionalized compounds **21**−**22** and **24** regarding the final deprotection step, we returned to the tetrahydropyridine derivative **17** for an early deprotection. Treatment of **17** with a hydroxylamine furnished the desired compound **31** in the reasonable yield of 65% (Scheme 8). None of the previously tested oxidants

Scheme 8. Deprotection of **17**

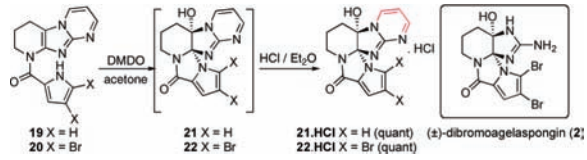


allowed the transformation of the imidazoline moiety of **31** into the desired 2-aminoimidazole **25**, the starting material being recovered in most cases.

To overcome all the difficulties related to the 2-aminopyrimidine as protected guanidine, we explored the use of Boc-guanidine or Cbz-guanidine instead of the 2-aminopyrimidine from the beginning of the synthesis. Unfortunately, all the attempts of the oxidative addition of the Boc-guanidine to the starting tetrahydropyridine **12** in the presence of bromine or NIS were not successful in a reasonable yield. The presence of the pyrrole section on the tetrahydropyridine together with the Boc-guanidine seems to be unfavorable to the construction of the tricycle of type **13** (Scheme 3).

Nevertheless, validation of the outcome of our biomimetic approach was achieved by the preparation of the intricate tetracyclic compound **22** as its HCl salt (Scheme 9).

Scheme 9. Isolation of the Tetracyclic Core of Dibromoagelaspongin

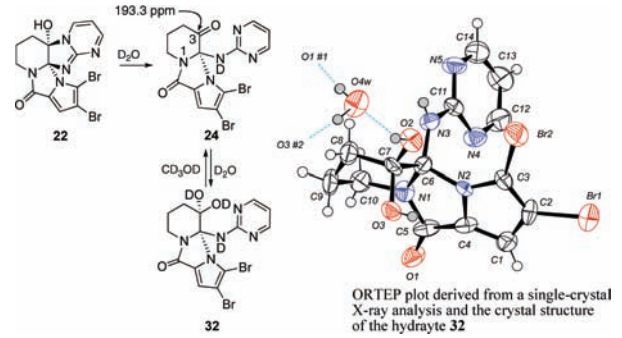


Performing the oxidation key step of the protected cyclic oroidin-type compounds **19** and **20**, with DMDO at room temperature, followed by the stabilization of the reaction products with diethyl ether HCl solution at −78 °C, allowed the isolation of the HCl salts of **21** and **22** in quantitative yield without any purification. The nonbrominated derivative **21** was prone to degradation even as a salt. The compound **22** corresponds to the protected dibromoagelaspongin (**2**).

Obtaining the non-natural derivatives **21** and **22** raises the problem of the stereoselectivity of the intramolecular ring closure, i.e., how to ascertain the ring junction stereochemistry. It is clear that the quaternary carbons on the ring junction render the task very difficult. NMR NOESY studies did not permit the confirmation of the very probable *cis* ring junction. The difference between the relative energies (>30 kcal/mol) of the *cis* and *trans* stereoisomers obtained by ab initio calculations with the 6-31G(d,p) basis set[22] showed that the natural *cis* configuration is by far the thermodynamically favored one.[23]

Interestingly, by the solubilization of HCl salt of **22** in D_2O for NMR spectra record, the hydrated derivative **32** crystallizes nicely. X-ray analysis gave the ORTEP crystal structure shown in Scheme 10. The solubilized crystals of

Scheme 10. Hydrated **32** from **24-*d*** Separated by Precipitation



32 in CD_3OD gave immediately the ketone **24-*d*** indicated by the ^1H and ^{13}C NMR spectra comparison. The chemical shift showed by the C-3 of the ketone is at δ 193.9 ppm.

In summary, the tetracyclic core of dibromoagelaspongin (**2**) was synthesized in quantitative yield from the protected cyclic oroidin type **20** in one pot. Oxidative cyclization of **20** afforded the key acyliminium intermediate, which underwent spontaneous ring closure by intramolecular nucleophilic attack of the pyrrole moiety with complete diastereocontrol, to yield the protected dibromoagelaspongin **22**. This short and straightforward sequence supports a plausible biosynthetic connection between oroidin (**1**) and complex cyclized derivatives such as dibromoagelaspongin (**2**).

Supporting Information Available: Experimental procedures, full spectral data for compounds **12**, **16**−**24**, and **27**−**29**, and a CIF file. This material is available free of charge via the Internet at http://pubs.acs.org.

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(23) See Supporting Information for the details.