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Total Synthesis of (±)-2-Debromohymenin via Gold-Catalyzed Intramolecular Alkyne Hydroarylation

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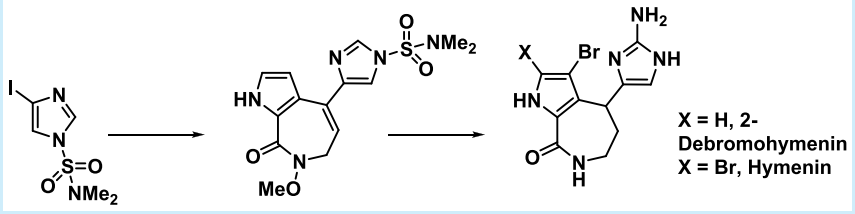

ABSTRACT: An intramolecular, gold-catalyzed alkyne hydroarylation results in the formation of the core pyrroloazepinone framework of the hymenin group of oroidin alkaloids. Elaboration of the cyclic adduct via C2-azidation, bromination of the pyrrole, and deprotection set the stage for global reduction with $Mo(CO)_6$ resulting in the formation 2-debromohymenin.

The pyrrole-imidazole alkaloids (PIAs) are a family of sponge-derived secondary metabolites that exhibit a remarkable array of structural diversity.[1−7] These alkaloids are formally derived from oroidin (**1a**) (or congeners **1b**−**d**)[8] and are often characterized by the number of oroidin units found in their framework, giving rise to a series of monomers, dimers, and even tetramers. The monomeric derivatives display a range of different constitutions, possessing annulated five to seven membered rings and up to two additional rings (**2**−**7**, Figure 1).[9−12] While the precise details of their biosyntheses remain to be fully elucidated,[13,14] the origin of these natural products can be formulated in terms of electrophilic or oxidative reactions of oroidin.[15] In the course of our studies toward a number of oroidin dimers,[16] we have used propargylic imidazole[17−20] precursors and recognized that they may function as precursors to several monomeric derivatives in their own right. Specifically, we described the use of imidazolyl propargylamides for the synthesis of various frameworks found in the oroidin monomers and completed the formal total synthesis of cyclooroidin (**4**).[21] Herein, we report the construction of the pyrroloazepinone skeleton common to hymenin[22,23] and congeners[24−27] via an intramolecular, gold-catalyzed hydroarylation[28] and an investigation of its elaboration into hymenin (**6**)[22,29] and 2-debromohymenin (**7**).[25] Hymenin was isolated by Kobayashi and co-workers from a sample of *Hymeniacidon sp.* found off Ishigaki,[22,29] whereas the 2-debromo congener was obtained from an Indonesian sponge, *Stylissa carteri* (syn. *Axinella carteri*), and described by the Proksch lab.[25] Hymenin and hymenialdisine (**3**)[9,30] have been shown to protect cortical neurons against oxidative stress at low nanomolar concentrations (1−10 nM in cell viability and MTT assays after treatment with H_2O_2).[31]

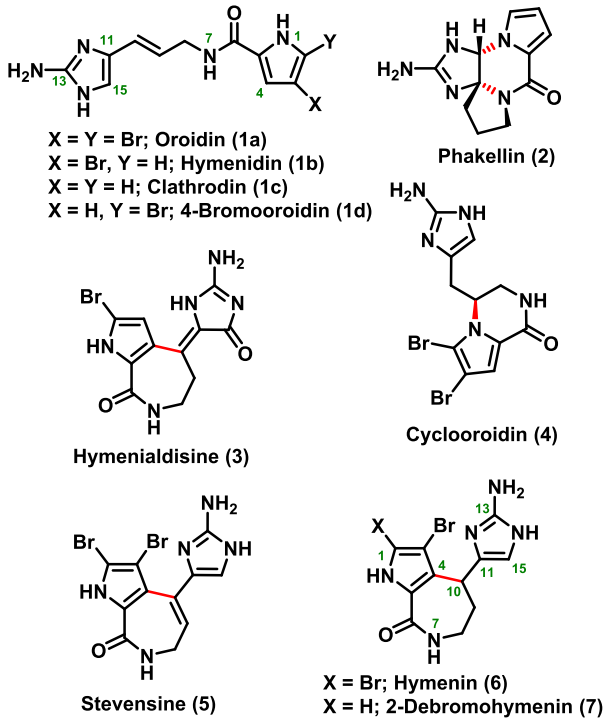

Figure 1. Structures of several oroidin monomers.

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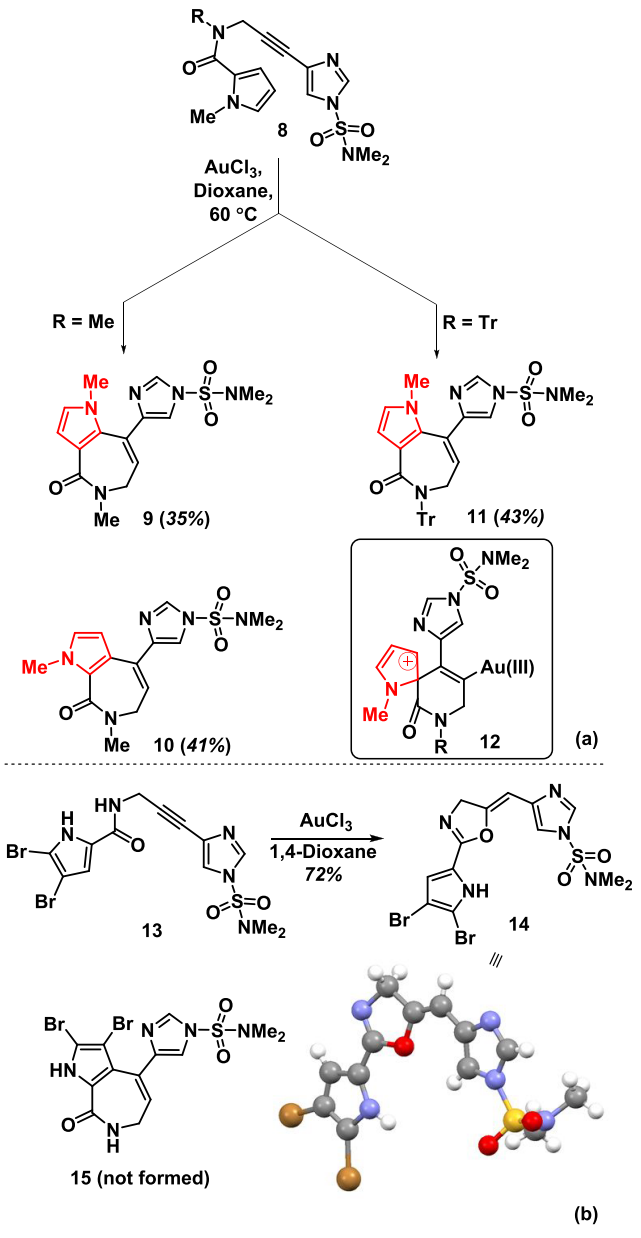
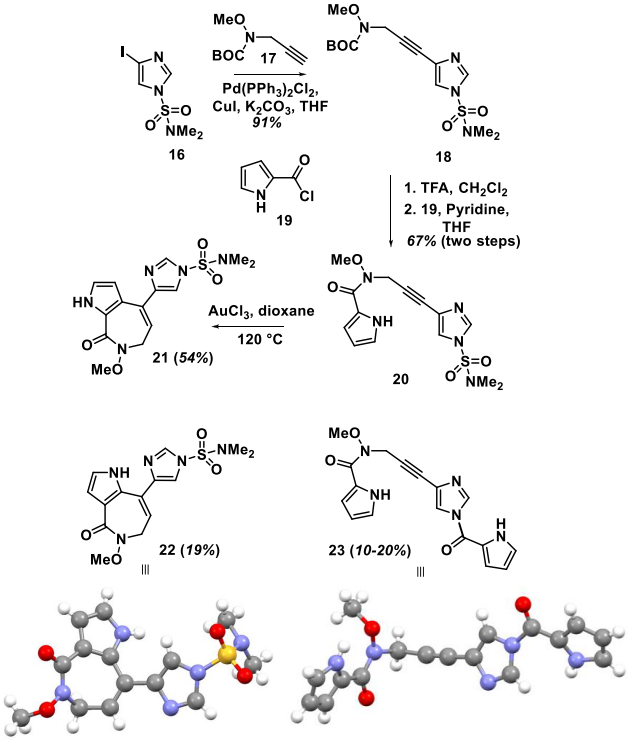
However, both hymenin and 2-debromohymenin were reported to be inactive against human monocytic leukemia cells.

The only prior synthetic approach to this family of natural products has been reported by the Horne lab which involves the initial construction of the pyrroloazepinone core and a subsequent Friedel–Crafts-like arylation with 2-aminoimidazole.[27,32,33] Our work[21] in this area was inspired by a report by Beller and co-workers who demonstrated that both Pt- and Au-catalysts result in the formation of pyrroloazepinones upon cyclization of aryl substituted *N*-propargyl pyrrolecarboxamides via hydroarylation. Pt-Catalysts delivered rearranged products predominantly (cf. **9** in Scheme 1) whereas Au-catalysts produced mixtures of the required product (cf. **10** in Scheme 1) in addition to the rearranged product; the ratio of the two was dependent on the reaction temperature.[34,35] The formation of rearrangement products was rationalized via the intermediacy of the spiro fused derivative **12** derived from *ipso* addition to the pyrrole (Scheme 1).[36] The nonrearranged pyrroloazepinone skeleton was required in order to apply this chemistry to a total synthesis of stevensine or hymenin. Our preliminary work on Au-catalyzed hydroarylations[34,35] of imidazolyl alkynes with pyrroles showed that there was some substituent sensitivity in the reaction with respect to the fusion of the pyrrole ring.[21] Large amide *N*-substituents appeared to favor the rearranged product (Scheme 1, **8** (R = Tr) → **11**),[37] whereas smaller substituents resulted in the formation of two pyrroloazepinones in comparable amounts (Scheme 1, **8** (R = Me) → **9** + **10**). In order to apply this chemistry to stevensine (**5**) or hymenin (**6**), the use of an *N*-methyl substituent on either the pyrrole nitrogen or amide nitrogen was not likely to be synthetically viable. Although Beller's studies suggested that the use of an NH-pyrrole and a secondary amide was not likely to be productive, an attempt to cyclize the dibrominated pyrrole carboxamide **13** was investigated anyway. A high yielding cyclization was observed, but oxazolidine **14** rather than the pyrroloazepine **15** was obtained in good yield and confirmed through X-ray crystallography (Scheme 1b). Given this observation, it was determined that protection of the amide nitrogen was necessary,[35] therefore we sought to identify a small, but readily removable substituent for the amide nitrogen. The use of an *N*-OMe group was appealing, as it appeared to meet the criterion of a small (A-values Me = 1.7; Et = 1.8; MeO = 0.6 kcal mol^{-1})[38] yet removable substituent and we had some prior experience with reductive cleavage of N–O bonds in other contexts with imidazole-containing substrates; thus, we constructed the appropriate substrate **17** to test the hypothesis (Scheme 2).[39] It was also determined that using the brominated pyrrole was unattractive, as this renders the ring less nucleophilic and increases the steric crowding in

Scheme 1. Gold-Catalyzed Hydroarylation of Imidazolyl Pyrrole Carboxamides



Scheme 2. Construction and Cyclization of the Pyrrole-Substituted Propargylimidazole



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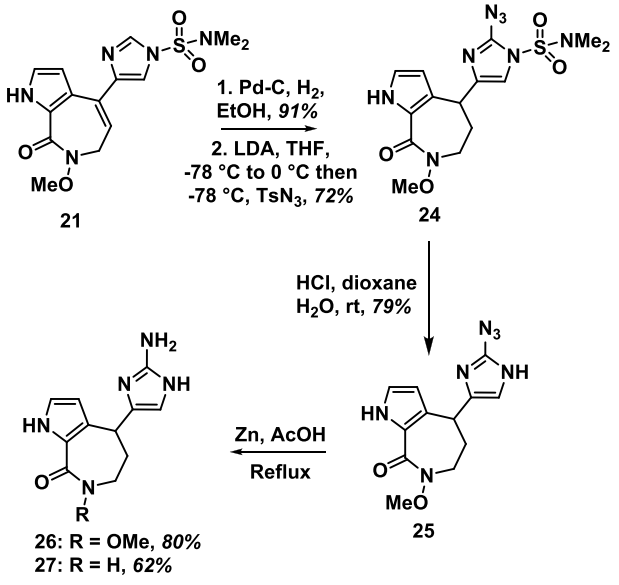
the desired ring fusion thus reducing the selectivity of the cyclization.

The known propargyl amine derivative **17**[40] was coupled with 4-iodoimidazole **16**[41] through a Sonogashira reaction (Scheme 2). Exposure of **18** to TFA removed the carbonate moiety and the resulting *N*-methoxyamine was acylated with the pyrrolecarbonyl chloride **19**, affording pyrrole amide **20**. Treatment of the pyrrole carboxamide **20** with $AuCl_3$ in dioxane led to the formation of two pyrroloazepinones **21** and **22** (X-ray), of which the major product **21** (2,3-fusion) had the correct orientation of the ring fusion for application to the synthesis of hymenin and stevensine. In addition to the cyclization products, a small amount of the *trans* acylated derivative **23** (X-ray) and ca. 10−20% of unreacted starting material **20** were recovered. Our initial plan was to employ the nonrearranged adduct en route to stevensine via bromination of the pyrrole ring; however, exposure of **21** to NBS resulted in competitive bromination of the azepinone double bond and thus these advanced intermediates were better configured for a pursuit of hymenin.

The major 2,3-isomer **21** was subjected to catalytic hydrogenation to deliver the saturated congener, which upon lithiation with LDA (3.9 equiv) and exposure of the resulting organolithium to TsN_3 resulted in the formation of the 2-azido derivative **24** (Scheme 3).[18,42−45] Deprotection of the

Scheme 3. Elaboration of the Pyrroloazepinone Core



sulfonylurea afforded the free imidazole **25** (confirmed by X-ray structure; see Supporting Information) which upon reduction with Zn/AcOH afforded desbromohymenin (**27**) in good overall yield.[7,19] Through careful control of the stoichiometry and the reaction time (for **26** Zn = 10 equiv, 1 h; for **27** Zn = 25 equiv, 6 h), the azide can be reduced chemoselectively to afford **26**. Attempts were made to effect bromination of **27** to generate hymenin (or debromohymenin) with little success, presumably due to competitive reaction of the imidazole at C5; therefore, bromination was explored earlier in the sequence.

Gratifyingly, monobromination of **24** occurred readily at C4 on the pyrrole using 1.0 equiv of NBS in THF/H_2O at −60 °C affording **28** in 80% (Scheme 4); the location of the bromine and the overall connectivity of the hymenin framework was confirmed by X-ray crystallography. Dibromination of the pyrrole was achieved by exposure to 2.2 equiv of NBS at low temperature to deliver **31**, again confirmed by X-ray crystallography (Scheme 4). This was a more challenging transformation as bromination also occurred on the imidazole ring (C5) leading to **32** and thus the reaction had to be monitored carefully by NMR spectroscopy to maximize the yield of the dibromide ∼50%. Bromination at C5 on the imidazole moiety began to impinge as the degree of conversion increased and thus reaction was terminated once over bromination was observed. The monobromide **28** was deprotected by acid-catalyzed hydrolysis of the sulfonyl urea to provide the corresponding free imidazole **29** (Scheme 4). Completion of the synthesis of **7** simply required conversion of the azide to the amine and removal of the *O*-methyl group. Finding a suitable reductant to effect both conversions while retaining the bromide(s) was challenging. As expected, Zn/HOAc was effective in the required reductions (*cf.* **25** → **27**, Scheme 4), but also resulted in reductive debromination. At this point, we explored using a two-step reduction sequence by converting the azide to the amine by treatment with Lindlar catalyst and hydrogen which delivered the corresponding amines **30** (and **33**) in accordance with prior experience.[18,42−45] SmI_2, which we have employed in related but less advanced intermediates to cleave an N−O bond reductively was investigated.[39] However, upon reaction of either **30** or **33** to SmI_2, reductive cleavage was accompanied by partial reductive debromination, which in the case of **33** delivered debromohymenin (**7**) in good yield. Harran and coworkers have observed similar reductive debromination on pyrroles during their synthesis of advanced axinellamine derivatives.[46] At this point, we sought reagents with different mechanisms for N−O bond cleavage, whereupon the use of $Mo(CO)_6$ in wet acetonitrile for cleavage of isoxazolidines was identified as a possibility.[47] Gratifyingly, treatment of **30** under these conditions resulted in a clean reduction of the N−O bond which upon purification provided 2-debromohymenin (**7**). We also found that reaction of the azide-containing precursor **29** with four equivalents of $Mo(CO)_6$ delivered **7** in good yield and thus telescoping the last two steps (Scheme 4).[48] Dibrominated intermediate **33** was subjected to the same sequence of reactions, unfortunately clean hymenin (**6**) was not obtained from this sequence giving rise to inseparable mixtures of products (Scheme 4).

In summary, we have developed a convenient 9-step synthesis of pyrroloazepinone-containing natural product 2-debromohymenin (**7**) from a commercially available iodoimidazole via a key gold-catalyzed hydroarylation. Critical to the success of this chemistry was the use of an N-OMe group as a protecting group to facilitate the selectivity of the pyrrole ring fusion. Elaboration of the pyrroloazepinone through reduction, C2-azidation and bromination delivered key late stage intermediates. Chemoselective reduction of the C2-azide and reductive cleavage of the *N*-methoxy group with $Mo(CO)_6$ delivered the debromohymenin congener in good yield. This synthesis is longer than the previously reported approach from the Horne group, but it is potentially more flexible and avoids the use of extremely long reaction times (2 × 7 days). Efforts are ongoing to find an alternative endgame solution to afford higher brominated congener, hymenin as well as addressing the issues of a stevensine synthesis.

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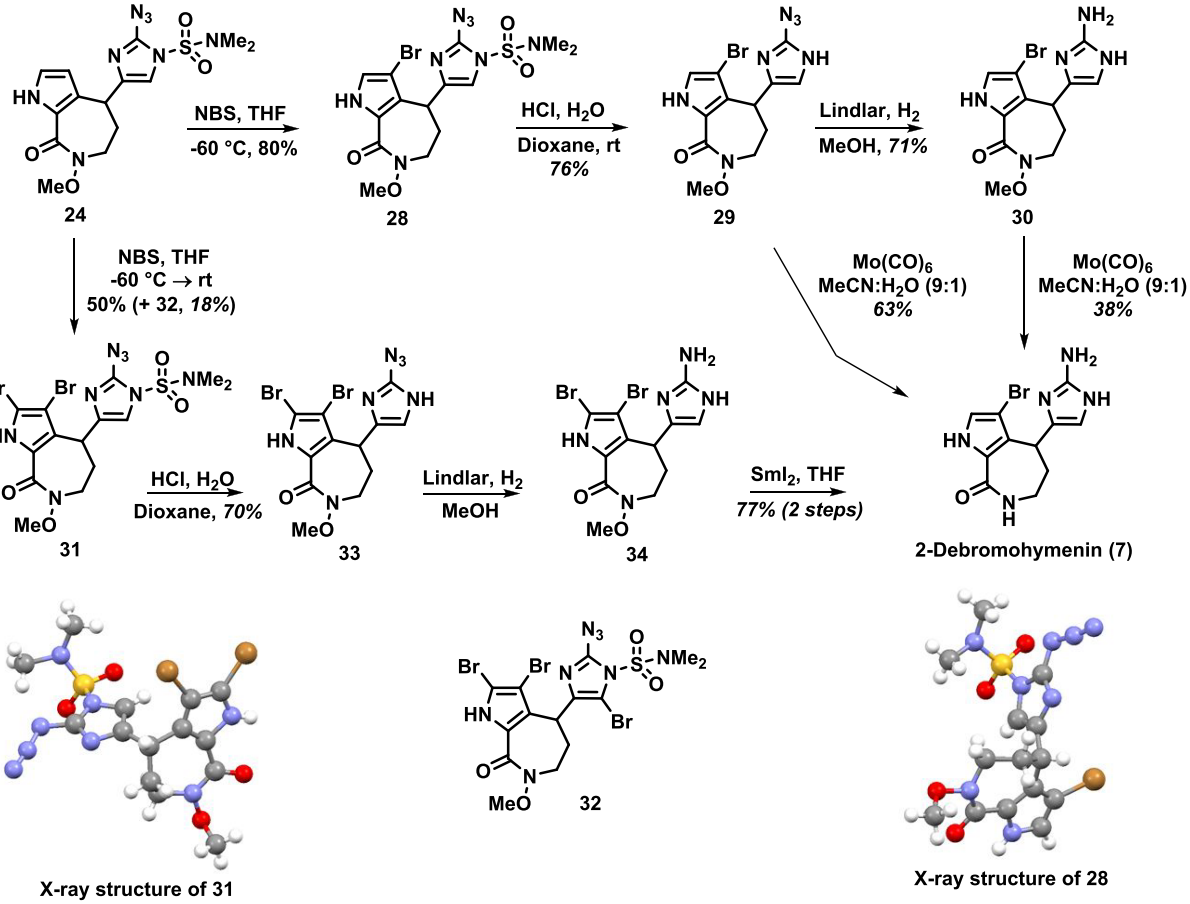
Scheme 4. Completion of the Synthesis of 2-Debromohymenin (X-ray Structures of Bromination Products 28 and 31)



■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c00883.

Experimental procedures, characterization data, and NMR spectra for all new compounds (PDF)

Accession Codes

CCDC 1908138 (**14**), 1909373 (**22**), 1910290 (**23**)−1910291 (**25**), 1910608 (**28**), and 1913850 (**31**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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