Communication

Concise Total Synthesis of Herqulines B and C

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J. Am. Chem. Soc., **Just Accepted Manuscript** • Publication Date (Web): 21 Dec 2018

Concise Total Synthesis of Herqulines B and C

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Supporting Information Placeholder

ABSTRACT: A simple total synthesis of herqulines B and C is reported, modeled on the reductive biosynthesis reported by Tang and co-workers. Commencing from tyrosine, these alkaloids were fashioned through a dimerization, macrocyclization, and four consecutive reductions. Emerging from these studies are strategic insights on the synthesis of these strained alkaloids, as well as mild conditions for the exhaustive reduction of diketopiperizines.

From morphine to vancomycin, tyrosine-based natural products comprise some of the most fascinating and biologically significant structures ever isolated.[1] As a particularly redox-active amino acid, most biosyntheses of isolates originating from tyrosine involve key oxidative manipulations of the phenol moiety, leading to remarkable diversity.[2] Early studies from Barton[3] cemented the logic of how oxidized phenols prefer to react, and decades of biosynthetic studies have revealed the enzymatic machinery responsible for initiating such events.[2] Our own studies in the area of tyrosine-based natural products have focused on peculiar frameworks notable for their strained cyclophane cores (Figure 1A), such as haouamine (**1**) and arylomycin (**2**). In both instances, strain was introduced through oxidative events; the former relying on a late-stage unsaturation[4] and the latter on a specific Cu-based oxidant.[5] The herquline family, first isolated by Ōmura in 1979 from *Penicillium herquei*,[6] of which herquline B (**3**) is a representative member,[7] was of particular appeal due to its extensively reduced framework. A landmark study by the Tang group[8] recently revealed its unusual reductive biosynthesis, while the Wood group demystified the stereochemistry of **3** in their elegant synthesis.[9] The difficulty of assembling such structures is well documented and is described in detail below. This Communication outlines a concise entry into the herquline family that strategically mirrors the biosynthesis by employing a carefully choreographed sequence of chemical reductions from a simple tyrosine-based starting material.

Despite the apparent simplicity of its 2-D depiction and the direct nature of the approach described below, the journey towards the herqulines was far from straightforward. Indeed, this small, strained alkaloid has confounded several others as documented by the impressive collection of approaches found in the dissertation literature.[10] Structurally, the herqulines contain an unsymmetrical basic diamine wrapped within a bowl-shaped macrocycle containing two β,γ-unsaturated enones. From a strategic standpoint, several others[10] have recounted efforts to these structures based on unsuccessful phenol-oxidative coupling, iodoenone-reductive coupling, and Birch reduction of a biaryl macrocycle or linear precursor (Figure 1B). Such knowledge influenced our first forays and thus numerous pathways were explored before returning to the current approach outlined herein. From a tactical standpoint, it is worth mentioning that, in accordance with most total synthesis endeavors,[11] puzzling stability features of each intermediate dictated a specific sequence of events leading to the final route.

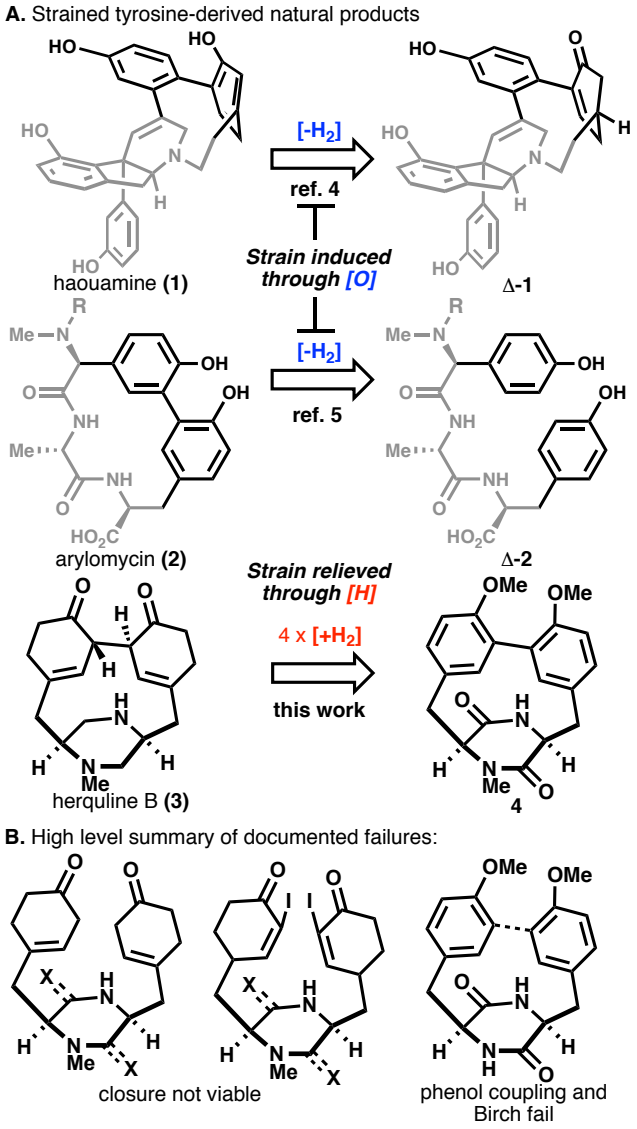
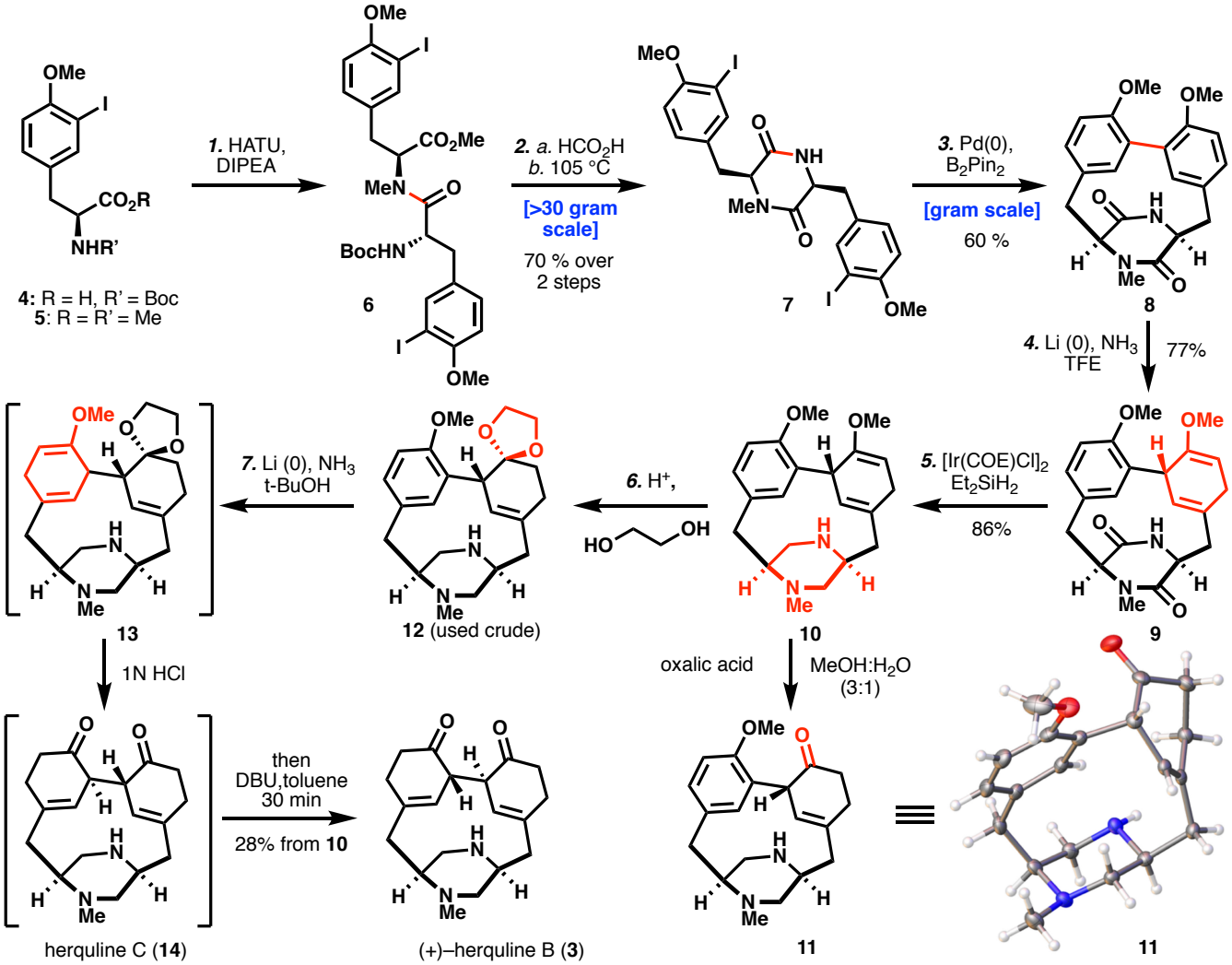


Figure 1. (A) Strained tyrosine-derived natural products are generally prepared through oxidation events with herquline as a notable outlier; (B) Summary of selected failed routes.

Scheme 1. Total Synthesis of Herqulines B (**3**) and C (**9**).[a]



[a]Reagents and conditions: **(1)** HATU (1.2 eq), DIPEA (1.5 eq), DMF, rt, overnight. **(2)** Formic acid, then *s*BuOH:PhMe (3:1), 105 ºC (70% yield over 2 steps). **(3)** $Pd(dppf)Cl_2$ (20 mol%), B_2Pin_2 (4.0 eq), K_2CO_3 (6.0 eq), DMSO:H_2O (100:1, 20 mM), 90 ºC, overnight (60% yield). **(4)** Li(0) (15 eq), NH_3, F_3CCH_2OH (8.0 eq), THF, -78 ºC, 1 h (77% yield). **(5)** $[Ir(COE)_2Cl]_2$ (20 mol%), Et_2SiH_2 (10 eq), PhMe, 2 h reflux (86% yield). **(6)** PTSA (0.5 eq), ethylene glycol (15 eq), benzene, Dean-Stark trap, reflux. **(7)** Li(0) (15 eq), NH_3, *t*BuOH:THF (1:10), -78 ºC, 2 h; THF/MeOH:1N HCl (3:1); DBU, PhMe, 30 min, rt (28% over 3 steps). HATU = 1-[Bis-(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxide hexafluorophosphate; DIPEA = *N,N*-diisopropylethylamine; DMF = *N,N*-dimethylformamide; PhMe = toluene; dppf = 1,1'-Bis(diphenylphosphino)ferrocene; DMSO = dimethylsulfoxide; *s*BuOH = *sec*-butyl alcohol; THF = tetrahydrofuran; COE = cyclooctene; PTSA = *p*-toluenesulfonic acid; DBU = 1,8-Diazobicyclo(5.4.0)undec-7-ene.

The synthesis of **3** commenced (Scheme 1) from known tyrosine-derived building blocks **4** and **5**.[12] Amide bond formation mediated by HATU delivered dipeptide **6** which was subjected to standard diketopiperazine (DKP) ring-forming conditions (HCO_2H followed by heat)[13] to furnish **7** in 70% overall yield from **4**/**5**. The ensuing Pd-catalyzed macrocyclization to **8** was accomplished by adopting a procedure initially reported by Hutton[14] and further improved by Schindler.[15] In order to increase the yield further and perform the reaction on a larger scale (4.6 gram), increasing the concentration (20 mM) proved helpful.

To convert **8** to the herquline core, no less than four reductions needed to be achieved. The precise order of events that appears in Scheme 1 was thus dictated empirically as a function of intermediate stability and reactivity. The first reduction was achieved using a venerable Birch reduction[16] to deliver enol ether **9** in 77% yield. The proton source (TFE) was essential to deliver the regiochemical outcome observed to deliver the 1,2/4,5 unsaturation (vs. the isomeric 3,4/1,6 diene that was observed when employing a range of other alcoholic proton sources). At this juncture the mechanistic basis of this empirical observation is unclear. The substituents on the DKP also appear to play a role in governing selectivity as the *N,N*-dimethyl congener delivered exclusively the wrong selectivity. The next two reductions required chemoselective excision of the DKP oxygens, a maneuver historically accomplished using DIBAL or LAH.[17] Exposure of **9** to either of these strong reducing agents led to monoreduction of the tertiary amide or de-

composition, respectively. Ultimately, Brookhart's Ir-based reduction protocol[18] provided a mild and reliable means to accomplish both reductions, thereby delivering **10** in 86% yield. To the best of our knowledge, this is the first use of such conditions to achieve exhaustive DKP reduction and will likely be useful in other contexts. The complete stereochemistry and structural assignments thus far were confirmed by X-ray crystallography of enone **11** after mild acidic hydrolysis.

The final reduction of **10** to access the herqulines proved extremely challenging, in accord with reports from others. All Birch reduction conditions screened on this substrate either cleanly returned **10** or led to reduction of the homobenzylic positions (4,5 and/or 1,2) before reducing the final aromatic ring. Such a result is not surprising given that Birch reductions of biaryls[16] without overreduction of one of the arenes is rare. It was reasoned that introducing two additional sp^3 carbon centers would both alleviate strain and prevent overreduction from occurring. Thus, exposure to ethylene glycol in the presence of PTSA led to clean conversion to ketal **12** which was taken forward in crude form to a final Birch reduction. Again, the proton source (TFE provided no observed product, whereas *t*BuOH was clean) proved pivotal in delivering reduced macrocycle **13**. This ketal-enol ether containing structure was then hydrolyzed with 1N HCl to deliver herquline C (**14**) and B (**3**) as an isolated 5:1 mixture. It should be noted that the crude reaction mixture was enriched in **14** but over time we noticed that it slowly converted to (–)-**3**.[19] To complete the synthesis of **3**, the mixture of isomers was simply treated with DBU in toluene for 30 minutes (28% overall yield from **10**). In contrast to prior reports,[8,9] **3** appears to be thermodynamically stable when using the above conditions as no change was observed even at 90 °C with excess DBU after 10 h. It is worth emphasizing that our initial target was **3** (not **14**) and that Wood's inaugural synthesis[9] allowed for rapid assignment of the **3**/**14** mixture.

A number of strategic and tactical challenges needed to be overcome to access the strained, reduced cyclophane architecture of the herqulines. The peculiar selectivity of late-stage Birch reductions in highly complex settings as a function of subtle structural changes and differing proton sources is notable. The chemoselective complete reduction of DKPs using an Ir/silane system is a useful observation that enabled this route. The syntheses reported here are another reminder of the role of careful experimentation to overcome tactical hurdles in the pursuit of a strategically concise (7-8 steps from iodotyrosine building blocks) pathway.

ASSOCIATED CONTENT

Supporting Information. Experimental procedures, analytical data (^{1}H and ^{13}C NMR, MS) for all new compounds. This material is available free of charge *via* the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

Author Contributions

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ACKNOWLEDGMENTS

We are grateful to Professor John L. Wood for sharing a copy of ref. 9 prior to publication. Financial support for this work was provided by NIH (GM-118176). We thank Dr. D.-H. Huang and Dr. L. Pasternack for NMR spectroscopic assistance, Prof. A. L. Rheingold and Dr. C. E. Moore for X-ray crystallographic analysis, and Dr. Jason Chen for helpful discussions.

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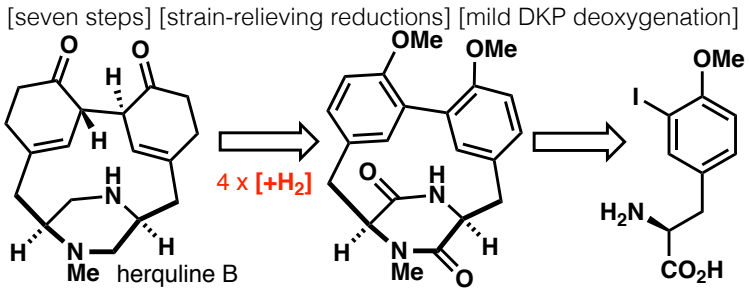

The herqulines: a decades-old challenge for synthesis