Literature Review of Total Syntheses of Herqulines: June 2004 to February 2019

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*Note that this is a literature review written by an undergrad for the purpose of learning more about natural product chemistry. I do also add some computations that I myself perform. Overall, take this with two grains of salt.

ABSTRACT: The Herquline family of natural products is a group of macrocyclic piperazines that display inhibition of influenza virus replication (Herquline A) and platelet aggregation (Herquline B). The central difficulties, and opportunities, of their synthesis are the formation of a strained biaryl C-C bond and the selective reductions of the dityrosine aromatic rings and amides. This literature review will focus on relevant PhD theses as well as the recently published work of the Wood group, the Baran group, and Schindler group (2018-2019) detailing the total synthesis of Herqulines B & C.

Herqulines are a family of natural products isolated from *Penicillium herquei* consisting of the pentacyclic Herquline A and the tetracyclic Herqulines B & C.[1] The phenolic oxidative coupling and dearomatizing reductions that compose their synthesis from tyrosine have been a field of active study since 2004.[2]

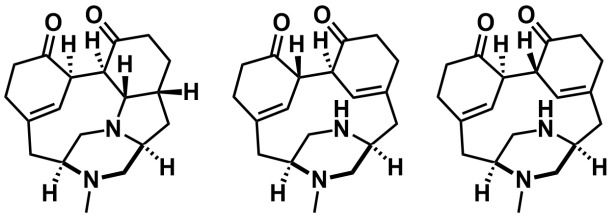


Figure 1: The Herquline family of natural products.

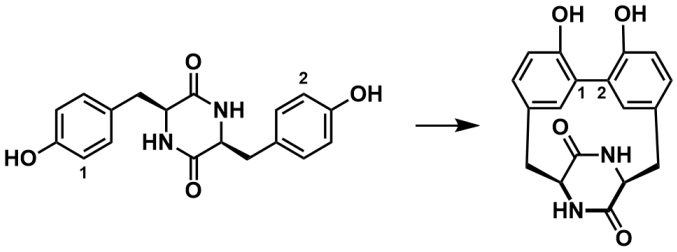
At the time of writing (April [], 2019) there were three articles published independently and in quick succession by the Wood group[3] (2018/12/18), Baran group[4] (2018/12/21), and Schindler group[5] (2019/2/14) detailing the total syntheses of Herqulines B & C from tyrosine. In this literature review, I discuss the key transformations in the total synthesis of Herqulines and the development of the strategies employed to finally reach the target.

Ortho-Ortho Phenol Coupling

All three of the above publications refer to a paper by the Tang group (2016) in which the biosynthesis of the Herqulines is thoroughly investigated.[6] In this work, the Tang group confirms that these molecules are synthesized from two tyrosines and proposes a mechanism for the oxidative, radical coupling of the phenols. Thus a biomimetic retrosynthesis of the 1,4 diketone suggests the use of a phenolic coupling reaction to form the biaryl C-C bond. Even before this work by the Tang group, however, organic chemists were already working toward this goal.

Synthetic efforts on this front began in the 2000s with the PhD work of J. M. Hart. Her initial efforts focused on the use of various oxidative coupling reagents for the formation of phenol-phenol C-C bonds.

Table 1: Reagents screened by Hart for ortho-ortho phenol coupling.



Reagent	Result
VOF_3, TFA	No product observed
$FeCl_3$	No conversion
$Pb(OAc)_2$	No conversion

However, this initial screen was not successful in finding conditions for the formation of the key C-C bond. Some reagents did have mild success in test systems but no conditions led to product for tyrosine derived substrates.

Hart then moved to coupling reactions, attempting palladium and nickel catalyzed Ullmann Couplings on protected, iodinated Tyr-Tyr peptides. But these either gave no results (Pd) or resulted in dehalogenation (Ni). The only coupling that yielded this difficult C-C bond was the Bowman Coupling.[7]

[1] (a) Ōmura, S.; Hirano, A.; Iwai, Y.; Masuma, R. *J. Antibiot.* 1979, 32, 786. (b) Furusaki, A.; Matsumoto, T.; Ogura, H.; Takayanagi, H.; Hirano, A.; Ōmura, S. *J. Chem. Soc., Chem. Commun.* 1980, 698.

[2] Hart, J. M. Ph.D. Thesis. University of Leeds, Jun 2004.

[3] Cox, J. B.; Kimishima, A.; Wood, J. L. *J. Am. Chem. Soc.* 2019, 141 (1), 25–28.

[4] He, C.; Stratton, T. P.; Baran, P. S. *J. Am. Chem. Soc.* 2019, 141 (1), 29–32.

[5] Zhu, X.; McAtee, C. C.; Schindler, C. S. *J. Am. Chem. Soc.* 2019, 141 (8), 3409–3413.

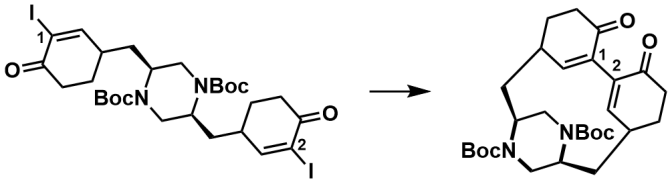
[6] Yu, X.; Liu, F.; Zou, Y.; Tang, M. C.; Hang, L.; Houk, K. N.; Tang, Y. *J. Am. Chem. Soc.* 2016, 138 (41), 13529–13532.

[7] Bell, N. V.; Bowman, R.; Coe, P.; Turner, A. T.; Whybrow, D. *Tetrahedron Lett.* 1997, 38 (14), 2581–2584.

This little known reaction worked in intermolecular reactions between protected 3,5-diiodotyrosines but failed to yield any product for the intramolecular coupling of protected, diiodinated Tyr-Tyr peptides (Fig. 2). Ultimately, Hart's PhD ended before the discovery of a robust methodology that could form this key bond.

Stawski continued work on this frontier in his PhD thesis.[8] Unlike Hart who started the synthesis from tyrosine, Stawski planned a synthesis starting from pyroglutamate. He successfully synthesized a piperazine intermediate that preceded the strained, biaryl C-C bond forming step. A diverse array of reaction conditions were attempted that included nickel, nickel/zinc, copper, and palladium catalyzed couplings. However, none were successful.

Table 2: A selection of the methodologies attempted by Stawski.



Conditions	Result
$Ni(PPh_3)_2Cl_2$, Zn, PPh_3 NaH, THF, 90 °C	decomposition
$Ni(COD)_2$, THF, -78 °C to RT	complex mixture
$Ni(COD)_2$, P(*n*-Bu)$_3$, DMF, RT to 40 °C	complex mixture
Cu (activated), RT to 130 °C	decomposition
n-Bu_6Sn_2, $Pd(PPh_3)_4$, THF, 50 °C	dehalogenation
$(BPin)_2$, $Pd(dppf)_2Cl_2$, KOAc, DMSO, 80 °C	decomposition

Frustratingly, Stawski was very close to the "correct" answer. He attempts a two-step, one-pot procedure utilizing Pd^0, $(BPin)_2$, and a base in DMSO at 80 °C. This is essentially identical to the methodology used by the Wood group to form the biaryl C-C bond. If Stawski had started his route from tyrosine rather than pyroglutamate, he likely would have stumbled upon the prize. Ultimately, as with Hart, his work on the topic ended before finding a robust methodology.

The final relevant PhD thesis was completed by Yang. Yang, like Hart, starts with a screening of oxidative couplings.

Before discussion of the recent synthetic successes, this is a good point to consider the differences of reactivity between the 2,5-diketopiperazine and the reduced piperazine. The Wood paper mentions this issue, citing it as the rationale for their late installation of the piperazine ring.

Modern syntheses utilize a one-pot Miyaura Borylation and Suzuki-Miyaura Coupling of a 3-iodo-L-tyrosine derivative in order to access

■ CONCLUSIONS

In conclusion, I am a cat.

■ METHODS

Ab initio density functional theory calculations were used to calculate minimum geometries for various intermediates along the route of the synthesis. Gas phase geometries original to this work were calculated using B3LYP-D3(BJ)/6-31G(d) in the 2018-R1 version of GAMESS. Geometries for the radical anion intermediates original to this work were calculated using RO-B3LYP-D3(BJ)/6-31+G(d). As this is not a real publication, frequency calculations were not carried out to confirm minima because they take a long time.

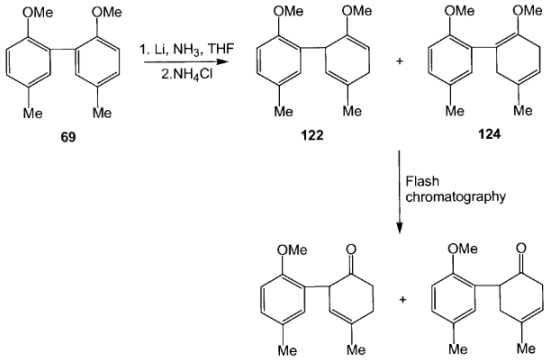
[8] Stawski, P. S. Ph.D. Thesis. Ludwig-Maximilians-Universität München, Dec 2012.

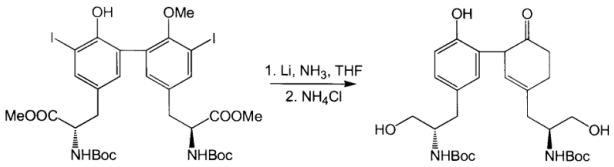
Writing Scraps

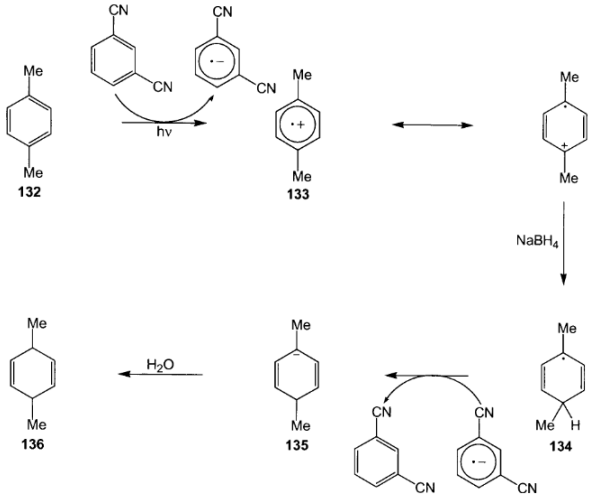
Initial Efforts

Preliminary work toward the synthesis of the Herqulines was first done at KAIST by G. T. Kim.[9] The proposed retrosynthesis was very different compared to the modern retrosynthesis as it focused on first synthesizing Herquline A, and then eliminating to yield Herqulines B & C. In general, the proposed transformations were not in line with modern approaches to the synthesis and the efforts ended before reaching the first key intermediate of the synthesis.

[9] Kim, G. T. Ph.D. Thesis, Korea Advanced Institute of Science and Technology, November 1997

- The Birch Reduction
  - Occurs by radical anion (Li in NH_3)
  - Regioselectivity is questionable
  - Tested in diaryls first
  - 

    - Desired regioisomer (left) was the major product
    - Aryl stabilization of anion is key
  - 

    - The first Birch reduction goes as desired, yielding the correct regioisomer
    - The esters were also reduced
  - Attempts with the photo-Birch
    - Use of initial charge-transfer to dicyanobenzene (form radical cation), attack of hydride from $NaBH_4$, then return of electron to form anion
    - 

    - Difficult to work-up due to dilute conditions
    - Previous reaction scope was limited to xylenes, no applications to phenols
  - Attempts of Birch with intramolecular alcohols

Stawski, P. S. Ph.D. Thesis. Ludwig-Maximilians-Universität München, Dec 2012.

Yang, H. Ph.D Thesis. University of Birmingham, Aug 2015.