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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 total synthesis. Send me criticism or feedback at therealsam@berkeley.edu.

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 syntheses 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 discuss relevant PhD theses as well as the recently published work of the Wood, Baran, and Schindler groups detailing the total syntheses 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]

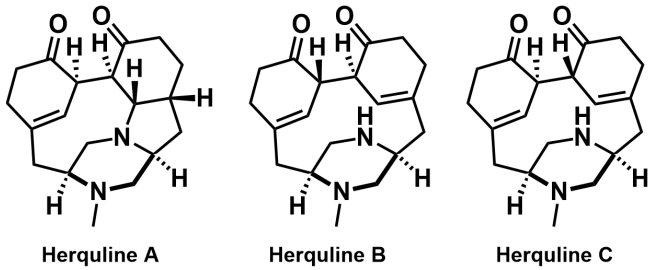


Figure 1: The herquline family of natural products.

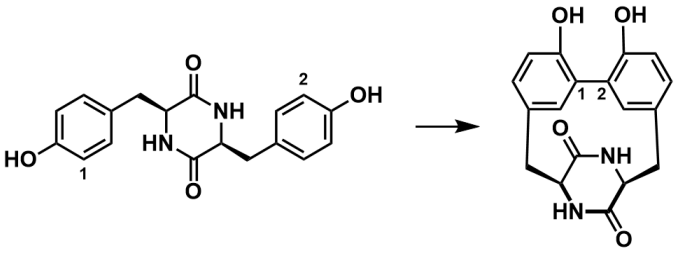
At the time of writing there were three articles published independently and in quick succession by the Wood group[3], Baran group[4], and Schindler group[5] detailing the total syntheses of herqulines B & C from tyrosine. In this literature review, I discuss the key transformations in the total synthesis of herquline B and the development of the strategies employed to finally reach the target.

Ortho-Ortho Phenol Coupling

All three of the publications refer to a paper by the Tang group (2016) in which the biosynthesis of the herqulines is thoroughly investigated.[6] 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 working toward this goal.

Synthetic efforts on this front began in the 2000s with the PhD work of J. M. Hart.[2] 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. Yang, in his PhD work performed in the 2010s, would also attempt oxidative couplings and again fail to find any conditions that facilitated this transformation.[7]

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

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

Bowman Coupling.[8] This little known reaction worked in *intermolecular* reactions between protected 3,5-diiodotyrosines but failed to yield any product for the desired *intramolecular* coupling of protected, diiodinated Tyr-Tyr dipeptides (Fig. 2).

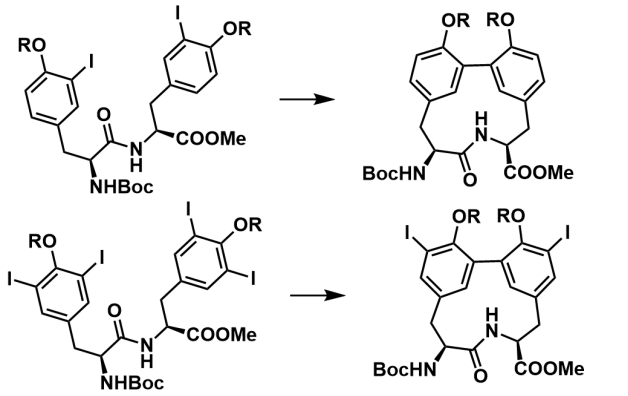
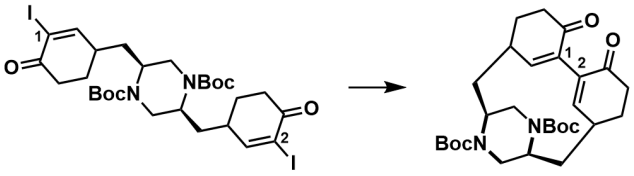


Figure 2: The cross-coupling transformations attempted by Hart. Above is the Ullmann Coupling and below is the Bowman Coupling..

Stawski continued work on this frontier in his PhD thesis.[9] Unlike Hart who started the synthesis from tyrosine, however, Stawski planned a synthesis starting from pyroglutamate. He successfully synthesized a piperazine intermediate that preceded the formation of the strained, biaryl C-C bond. A diverse array of reaction conditions was then attempted that included nickel-, 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
$(BPin)_2$, $Pd(dppf)Cl_2$, KOAc, DMSO, 80 °C	decomposition

Stawski was actually very close to the "correct" answer. The two-step, one-pot procedure utilizing Pd^0, $(BPin)_2$, and a base in DMSO at 80 °C is nearly identical to the methodology used by the Wood group to form the biaryl C-C bond in their total synthesis.[3] If Stawski had started his route from tyrosine rather than pyroglutamate, he likely would have stumbled upon the prize.

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

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

The proof-of-concept reaction for the formation of this biaryl C-C bond came out of a total synthesis performed by the Hutton group of a biologically unrelated natural product, mycocyclosin.[10] A dityrosine produced by *Mycobacterium tuberculosis*, it bears a striking resemblance to the herqulines.

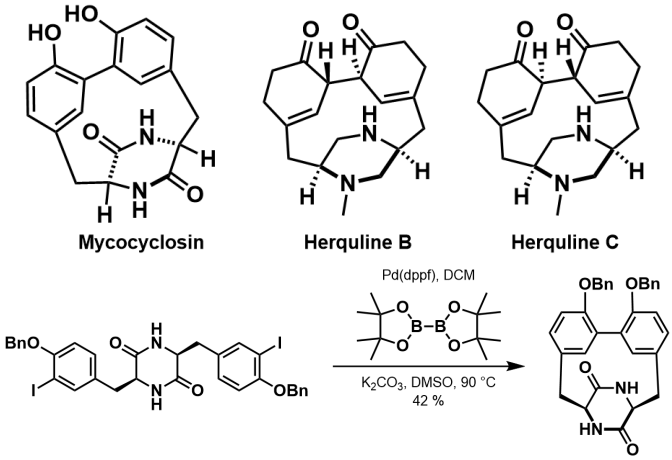


Figure 3: (above) Mycocyclosin compared to herqulines B & C. (below) The conditions used by Hutton to form the strained, biaryl bond.

This molecule, so tantalizingly close to the desired product, seems to only be a few reductions away. The Hutton group's synthetic efforts solved the question of the biaryl C-C bond. However, much work was still required to complete the synthesis.

Dearomatization and Reduction

In contrast to the ortho-ortho phenol coupling reaction, there was much less work done concerning the reduction of the aryl rings. This is likely because dearomatization conditions are already commonly available in modern total synthesis.

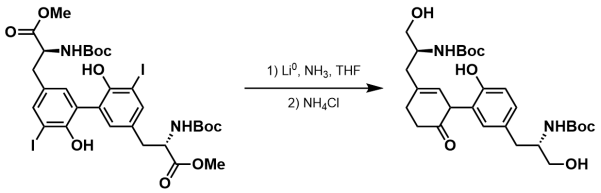


Figure 4: The Birch Reduction as run by Hart on a dityrosine derivative.

In her PhD work, Hart performs an important study on the Birch Reduction in relation to protected dityrosines. The substrate (product from an intermolecular Bowman Coupling) is only partially reduced when subjected to the Birch Reduction. However, the major isomer obtained from this reaction crucially yields the correct alkene regioselectivity. This is relevant to the synthesis performed by the Baran group which utilizes this reaction for their first reduction.

[10] Cochrane, J. R.; White, J. M.; Wille, U.; Hutton, C. A. *Org. Lett.* 2012, 14 (9), 2402–2405. https://doi.org/10.1021/ol300831t.

In order to push the reaction to completion, Hart attempts an interesting intramolecular alcohol-based strategy that the Schindler group also utilizes in their total synthesis. The Birch Reduction normally relies on an external proton source to protonate the carbanion that is formed *in situ*. Previous studies showed that intramolecular alcohols can affect the regioselectivity of the Birch Reduction. Unfortunately for the test compound Hart used, the attempted reduction did not reach completion.

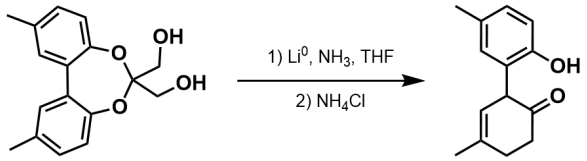


Figure 5: A Birch Reduction on a test compound involving intramolecular proton donation.

While the Birch Reduction involves a reductive dearomatization, reactions involving PIDA (PhenylIodine(III) DiAcetate) can induce oxidative dearomatizations. The Wood group and Schindler group both use PIDA oxidations in conjunction with reducing agents in order to obtain the desired oxidation state and regioselectivity.

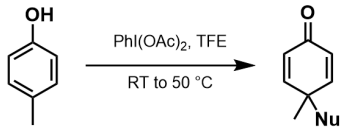


Figure 6: A dearomatization induced by PIDA.

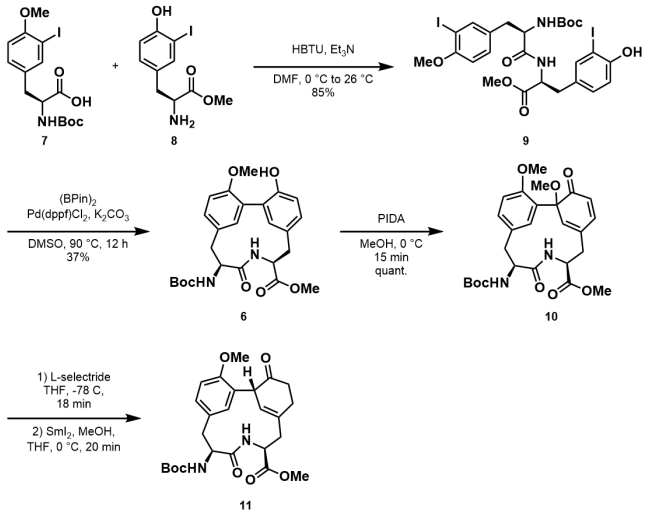
With the key synthetic steps introduced we move on to the total syntheses.

■ Total Synthesis: The Wood Route

The Wood group was chronologically the first to synthesize herqulines B & C and has the distinction of determining the stereochemistry of herquline B. Thus we'll start with their work and see how later syntheses improve upon it. The first step in their synthesis was the formation of a dipeptide (**9**) from derivatives of tyrosine (**7** & **8**) using a HBTU coupling. Next was the formation of the biaryl C-C bond using the aforementioned tandem Miyaura Borylation - Suzuki-Miyaura Coupling which yielded the dityrosine (**6**). PIDA was used to oxidatively dearomatize the unprotected phenol to generate the α-methoxyketone (**10**). L-selectride was then used to selectively reduce the β-position of the enone. This was followed by SmI_2 which reduced the α-methoxyketone to a ketone (**11**).

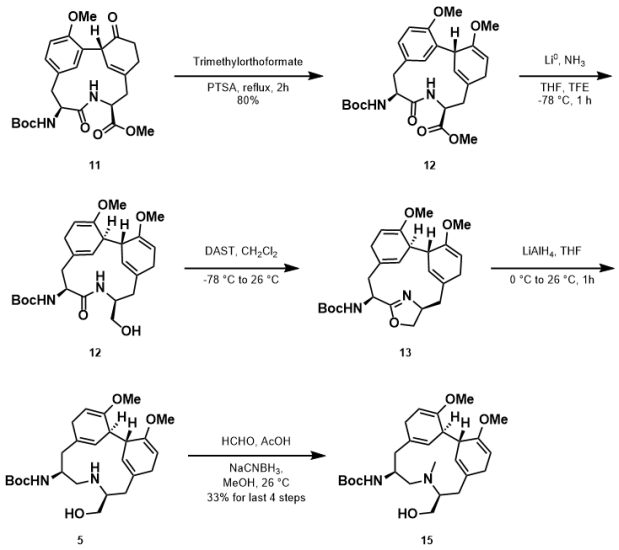
The unique feature of this synthesis is that the Wood group does not close the dipeptide into a cyclic 2,5-diketopiperazine immediately as the Baran and Schindler groups do. Because the previous work done by Stawski demonstrated the negative effects of the piperazine ring on the biaryl coupling step, the Wood group elected to install the piperazine ring at the very end of the synthesis.

Scheme 1: Peptide coupling, biaryl C-C bond formation, and oxidative dearomatization followed by reduction.



The Wood group continues, protecting the ketone by converting it to a methyl enol ether (**12**) using trimethyl orthoformate. The Birch Reduction dearomatizes the other ring, yielding the desired olefin (**13**). Curiously, Hart was not able to induce dearomatization of the second ring with the Birch Reduction. This is possibly due to the presence of the ketone which was protected in the Wood route.

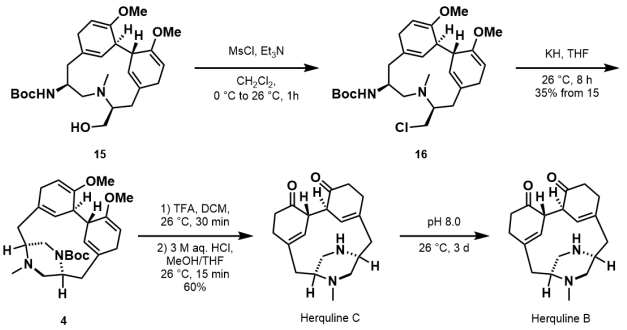
Scheme 2: Continued reduction of the biaryl system and the amide.



In order to reduce the amide, it was necessary to first convert it to a oxazoline (**14**) with DAST before reducing to an amine (**5**) with $LiAlH_4$. The secondary amine was then methylated by reductive amination (**15**). At this juncture, all the necessary reductions had been completed and all that remained was the ring closure to form the piperazine.

The primary alcohol was substituted using MsCl to form the alkyl halide (**16**). The piperazine was then cyclized using KH to yield **4**. Following a TFA deprotection, herquline C was epimerized to yield herquline B.

Scheme 3: Ring closing to yield the piperazine.

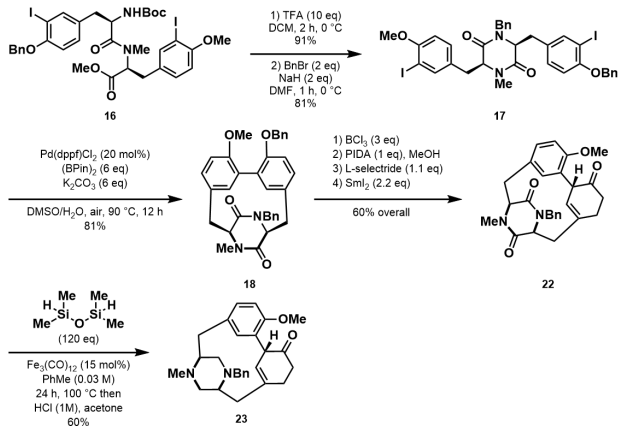


Overall, this is a 13 step synthesis with an overall yield of 1.2%. While this yield is quite low relative to the Baran and Schindler syntheses, it should be noted that the Wood route was originally pursuing herquline A. However, the strategic decision that lead to this low yield was the late installation of the piperazine ring. This conservative decision not only added steps to the overall synthesis, it required low-yielding, late-stage modifications to be made to the final carbon skeleton. In all, the Wood group deserves the credit for being the first to synthesize herquline B. However, there were many improvements to be made.

■ Total Synthesis: The Schindler Route

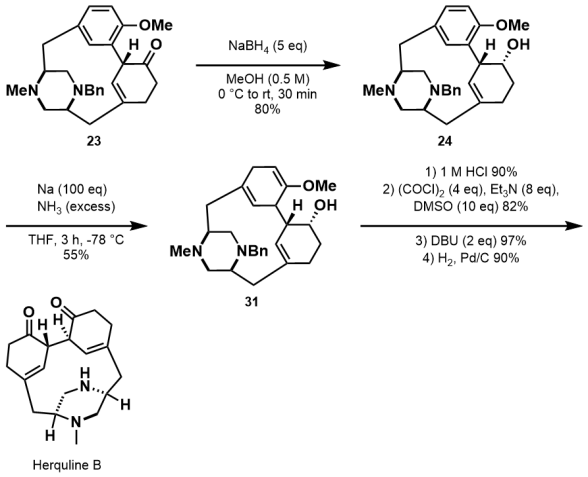
The most recent total synthesis was performed by the Schindler group and it makes major improvements to the Wood route.

Scheme 4: Diketopiperazine synthesis followed by formation of the biaryl bond and first dearomatization.



After an initial HBTU coupling (not shown), they deprotect the amine and cyclize to form the diketopiperazine. They then protect the amide to yield the protected diketopiperazine (**17**). The use of an improved tandem Miyaura Borylation - Suzuki-Miyaura Coupling yields a protected mycocyclosin derivative (**18**). After a phenol deprotection, they follow a sequence borrowed from the Wood synthesis to yield a singly reduced mycocyclosin derivative (**22**). The diketopiperazine is then reduced to a piperazine (**23**) using an iron-catalyzed reduction.

Scheme 5: Formation of an intramolecular proton source followed by the Birch Reduction, global deprotection, oxidation, and epimerization.



Their substrate unfortunately did not yield the desired reduction under Birch conditions. This required a more circuitous route involving the reduction of the ketone to the alcohol (**24**). This intramolecular proton source yielded the desired olefin (**31**) via the Birch Reduction. Following deprotection of the methyl enol ether to the ketone, oxidation of the alcohol to the ketone, and epimerization, the Schindler group successfully synthesized herquline B.

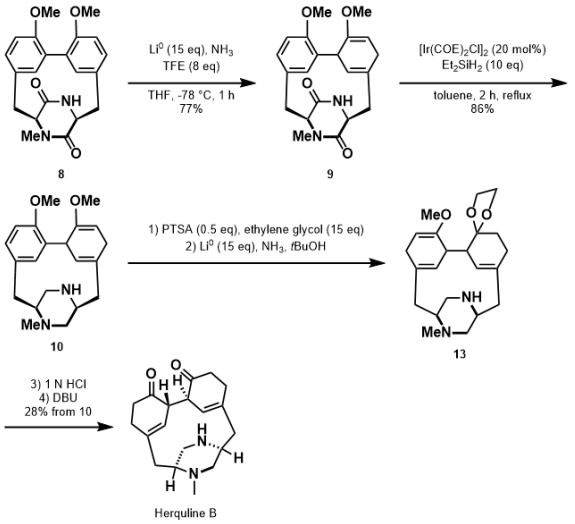
Overall this is a 14 step synthesis with an overall yield of 7.2%. While the synthesis slightly longer than the Wood route, the yield increases 6-fold. There are two main reasons. The first is that the tandem Miyaura Borylation - Suzuki-Miyaura Coupling the Schindler route uses provides roughly a 2-fold increase in yield. The second is that the Schindler group closes the diketopiperazine early and accomplishes its reduction in one step. The drawback to this decision is seen in the Birch Reduction; where the Wood group easily accomplishes this transformation, the Schindler route requires the formation of an intramolecular proton source. However, the yield improves greatly by avoiding low-yielding, late-stage modifications to the piperazine.

■ Total Synthesis: The Baran Route

The most straightforward and elegant of the three routes is by far the Baran group. It is even evident in the titles of the papers. Where the Wood and Schindler groups title their publications *Total Synthesis of Herqulines B and C*, only the Baran group dares to title their publication *Concise Total Synthesis of Herqulines B and C*. The Baran route starts as the Schindler route does with a peptide coupling, cyclization to form a diketopiperazine. and a tandem Miyaura Borylation -

Suzuki-Miyaura Coupling to yield a mycocyclosin derivative (**8**). However, they sidestep the PIDA, L-selectride, SmI_2 dearomatization sequence and simply apply the Birch Reduction to access the singly reduced mycocyclosin (**9**). Following an iridium-catalyzed reduction of the diketopiperazine to synthesize the piperazine (**10**), they protect the ketone as an acetal and perform a second Birch Reduction to obtain the fully reduced mycocyclosin (**13**). Acidic workup yields herquline C which is epimerized to herquline B.

Scheme 6: The initial Birch Reduction followed by reduction of the diketopiperazine. The methyl enol ether is transformed to an acetal to mediate the second Birch Reduction



Overall this an 8 step synthesis with an overall yield of 7.8%. The Baran route owes its strategic strength to its avoidance of oxidizing agents. Herquline is reduced relative to tyrosine and thus, any oxidations will necessarily add steps. The Baran route avoids the PIDA/L-selectride/SmI_2 oxidative dearomatization sequence and applies a Birch Reduction instead. Utilizing two Birch Reductions allows the Baran group to access the Herqulines in an incredibly direct manner.

■ CONCLUSIONS

The herqulines as a synthetic target have been a subject of interest for decades. This deceptively simple dityrosine molecule evaded synthesis, in part due to the difficulty of forming the strained, biaryl C-C bond that nature so effortlessly oxidatively couples. Ultimately a concise synthetic route, itself deceptively simple, was accomplished by the Baran group. These syntheses highlight the power of modern cross-coupling chemistry, the challenges and opportunities posed by late-stage Birch Reductions, and the strategic difficulties that come with pursuing strained macrocycles.