

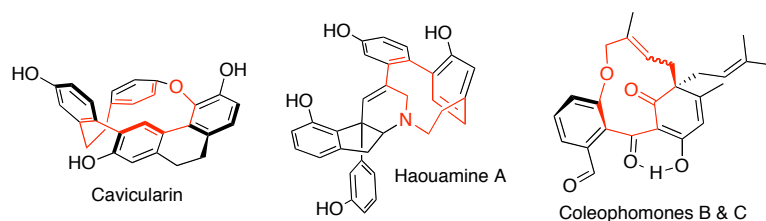
Recent Approaches to the Synthesis of Strained Macrocyclic Natural Products

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ABSTRACT



It is often said that for today's chemist it is not whether or not a natural compound can be synthesized, but how efficiently and selectively this can be accomplished. Highly strained molecules have challenged the synthetic community to apply and develop methodologies that are up to the daunting task of their synthesis and reminded those who accepted the challenge that nature is still the ultimate creative force.

Strain has been an intriguing aspect of organic synthesis for decades, both in relation to the synthesis of highly strained natural compounds and the use of strained molecules to elicit unusual reactivity. One of the most strained classes of compounds are $[n]$ paracyclophanes which have a long history dating to the first synthesis of [2.2]paracyclophane in 1949 and further exploration initiated by Cram.¹ Extensive synthetic and theoretical studies have demonstrated the bent nature of the benzene rings in highly strained paracyclophanes. The strain energy required for such a distortion of bond angles in these systems was thought to rule out their existence in nature; however, cavicularin (**1**) (isolated in 1996)² and haouamine A (**2**) and B (isolated in 2003)³ have demonstrated that biosynthetic pathways exist for their synthesis. These molecules, along with other highly strained macrocycles, have caught the attention of synthetic chemists and have shown that even robust reactions fail to perform effectively in their synthesis.

Cavicularin (**1**), isolated from the liverwort *Cavicularia densa*, is a naturally occurring paracyclophane that contains a benzene ring bent 15° out of the plane in its 14-membered macrocyclic architecture. A proposed biosynthesis was put forth that invoked an intramolecular phenolic oxidative coupling of the known natural product riccardin C.² Based on this pathway, Harrowven *et al.* developed a rapid synthesis of **1** which centered around a radical cyclization of the methyl-protected riccardin C intermediate **3** (Scheme 1).⁴ The kinetic barrier for a biaryl coupling in such a strained macrocycle would typically be prohibitive; however, it was postulated that the close proximity of the aryl radical enabled closure to the non-aromatized radical intermediate **4**. The remaining energy necessary for bending the newly formed aromatic ring of **1** could be realized by the energy gained via aromatization of this intermediate. This synthesis of the first naturally occurring paracyclophane demonstrates both the utility of radical induced ring contraction and the power of aromatization, even of bent rings, to provide enough energy to overcome large energy barriers in synthesis.

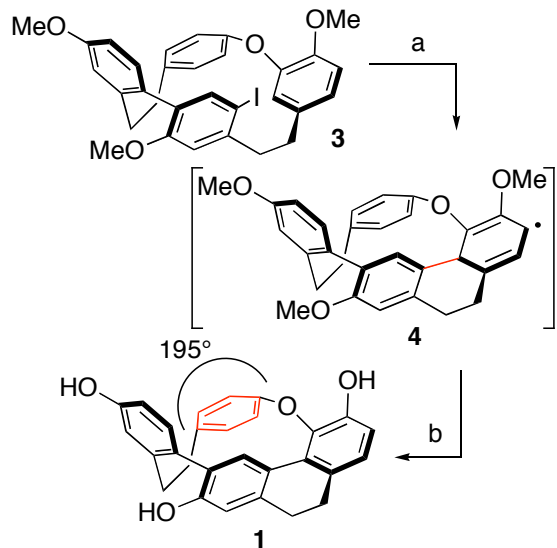
¹ (a) Brown, C. J.; Farthing, A. C. *Nature*, **1949**, *164*, 915. (b) Cram, D. J.; Bram, J. M. *Acc. Chem. Res.* **1971**, *4*, 204.

² Toyota, M.; Yoshida, T.; Kan, Y. Takaoka, S.; Asakawa, Y. *Tetrahedron. Lett.* **1996**, *37*, 4745.

³ Garrido, L.; Zubia, E.; Ortega, M. J.; Salva, J. J. *Org. Chem.* **2003**, *68*, 293.

⁴ Harrowven, D. C.; Woodcock, T.; Howes, P. D. *Angew. Chem. Int. Ed.* **2005**, *44*, 3899.

Scheme 1. Radical induced, trans-annular ring contraction for the synthesis of Cavicularin.



Reagents and Conditions: (a) TTMS, AIBN, PhMe, 90 °C (b) quench, then BBr₃, CH₂Cl₂, 0 °C

Although structurally intriguing, lack of impressive biological activity and possessing clear biosynthetic origins, cavicularin led to little interest in the synthetic community. In contrast, the isolation of haouamines A and B attracted immediate attention both for their novel 3-aza-[7]-paracyclophane moiety that contains a highly strained B ring (Figure 1) and impressive activity against human colon carcinoma HT-29 cell lines (IC₅₀ = 0.1 μg/mL).³ Several groups have recently published approaches to the

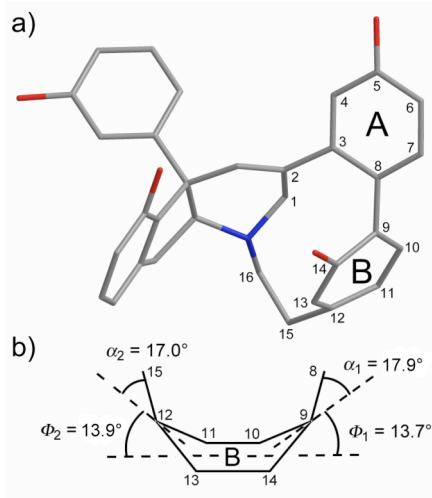
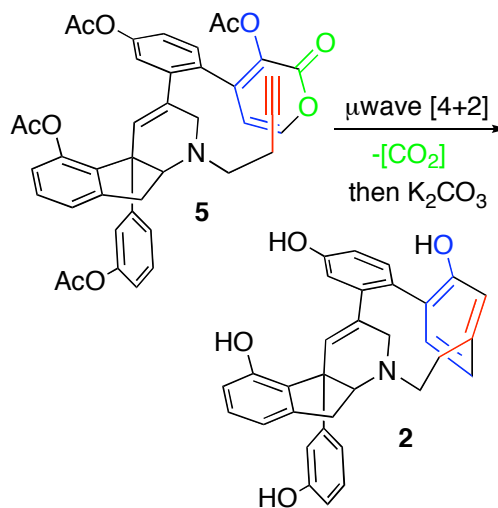


Figure 1. (a) X-ray structure of haouamine A; (b) deviations from planarity in ring B.

left-hand fragment of the haouamines,⁵ but it was not until Barran's total synthesis that a novel strategy for the highly strained paracyclophane was developed, quickly followed by an alternative approach presented by Wipf *et al.*⁶

After failing with such standard cyclization reactions as transition metal-based biaryl coupling, Witkop photocyclization and intramolecular alkylation, Baran proposed that a new strategy of generating a non-aromatic bent ring, followed by subsequent aromatization could prove successful. Indeed, the pyrone-alkyne Diels-Alder reaction worked beautifully and haouamine A (**2**) was isolated in 21% yield after basic acetate hydrolysis (Scheme 2). This use of such a Diels-Alder reaction for a macrocyclization was unprecedented in the literature. Fully acylated precursor **5** was required to prevent

Scheme 2. Key cyclization in Baran's Haouamine A synthesis.



decomposition during the extensive 250 °C, 10 h microwave heating. These reaction conditions generate an aromatic ring that is 27.6° out of the plane in the X-ray structure of **2** (Figure 1) – an estimated 32 kcal of strain in the benzene ring alone!

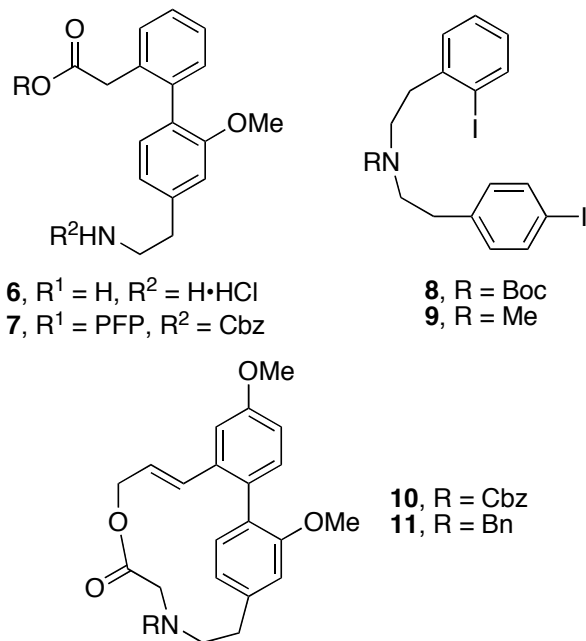
Wipf also quickly realized the difficulty in closing this strained macrocycle, even when employing typical reaction conditions to overcome kinetic barriers in ring closing reactions (Scheme 3). Approaching the problem from all angles, macrolactamization of **6** or **7** proved unsuccessful providing only dimer and unreacted material. Further attempts involving various biaryl couplings of **8** or **9** were not fruitful, including recently published organocuprate oxidation to form medium biaryl rings.⁷ In a last ditch

⁵ (a) Smith, N. D.; Hayashida, J.; Rawal, V. H. *Org. Lett.* **2005**, *7*, 4309. (b) Grundl, M. A.; Trauner, D. *Org. Lett.* **2006**, *8*, 23. (c) Jeong, J. H.; Weinreb, S. M. *Org. Lett.* **2006**, *8*, 2309.

⁶ (a) Baran, P. S.; Burns, N. Z. *J. Am. Chem. Soc.* **2006**, *128*, 3908. (b) Wipf, P.; Furegati, M. *Org. Lett.* **2006**, *8*, 1901.

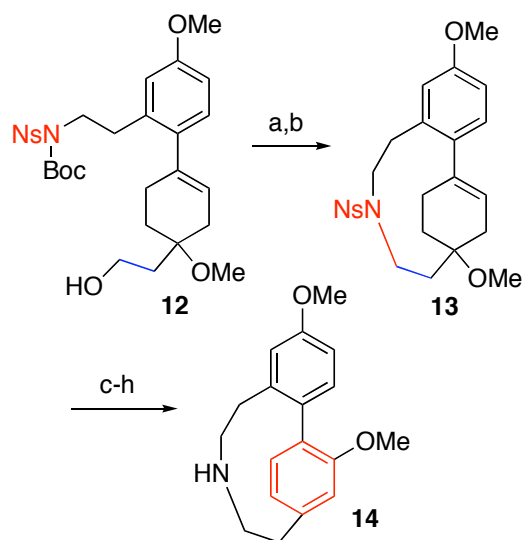
⁷ Surry, D. S.; Su, X.; Fox, D. J.; Franckevicius, V.; Macdonald, S. J. F.; Spring, D. R. *Angew. Chem. Int. Ed.* **2005**, *44*, 1870.

Scheme 3. Wipf's initial approaches to the cyclization of the 3-aza-[7]paracyclophane core of **2**.



attempt to construct this ring in a rapid fashion, a ring contraction strategy involving synthesis of macrocycles **10** and **11** followed by a [3,3] sigmatropic rearrangement was employed. Although formation of the necessary silyl

Scheme 4. Stepwise ring-closure/aromatization approach to **14**.



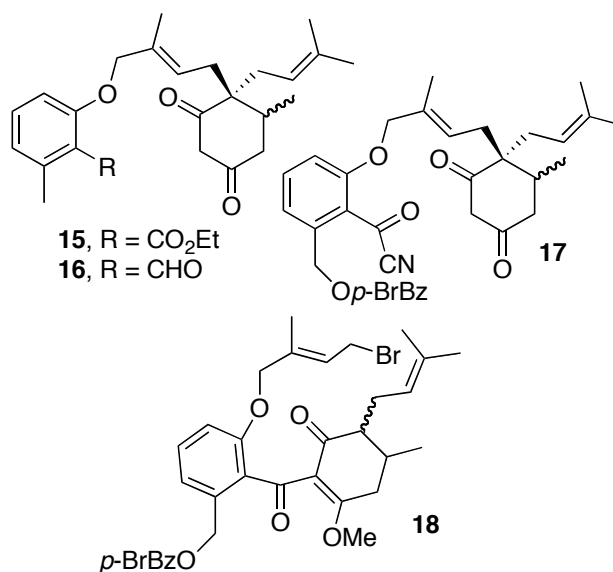
Reagents and Conditions: (a) 165 °C, neat 20 min (b) DEAD, PPh₃, toluene/THF, rt, 12 h (51%) (c) *m*CPBA, DCM, rt, 12 h (d) HBF₄, CHCl₃, rt, 22 h (e) DMP, DCM, rt, 1 h (63%) (f) DIPEA, 2,2,2-trifluoroethanol, 170 °C, 1 h (g) Me₂SO₄, acetone, K₂CO₃, reflux, 7 h (90%) (h) PhSH, K₂CO₃, DMF, rt, 2.5 h (61%)

ketene acetals was facile, subsequent heating up to 220 °C did not provide any of the desired 11-membered ring.

Similarly to Harrowven and Barran, an alternative approach involving the preparation of macrocycle **13** which could undergo hybridization from sp³ to sp² and subsequent tautomerization to the phenol that would generate **14** was explored (Scheme 4). The forward synthesis of **13** was straightforward via a Mitsunobu reaction, a result that highlights the negative effects of the bent aromatic rings in previous systems. Subsequent conversion of **13** to the desired paracyclophane **14** was high yielding, again highlighting the power of aromatization to overcome seemingly prohibitive energy barriers. Further extension of this novel approach to completing the total synthesis of **2** should provide an alternative to Baran's rapid synthesis of this intriguing molecule.

Distorted aromatic rings in medium macrocycles are certainly not the only functionality that can make for extremely difficult macrocyclizations. Coleophomones A-D, isolated by Shionogi Pharmaceutical Co. and later by Merck, demonstrate this in their compact 11-membered core.⁸ An already strained 11-membered macrocycle is further strained by the presence of 6 sp² carbons, an ethereal oxygen, fused aromatic ring, bridged 6-membered carbocycle and in the case of coleophomone B, an (*E*)-trisubstituted alkene. Intrigued by this complexity and strain, Nicolaou *et al.* began synthetic explorations toward the synthesis of this class of molecules which was met with remarkable resistance in the closure of the key macrocycle.⁹

Scheme 5. Attempted precursors to cyclization in Nicolaou's synthesis of coleophomones B and C.



⁸ Wilson, K. E.; Tsou, N. N.; Guan, Z.; Ruby, C. L.; Pelaez, F.; Gorrochategui, J.; Vicente, F.; Onishi, H. R. *Tetrahedron Lett.* **2000**, *41*, 8705.

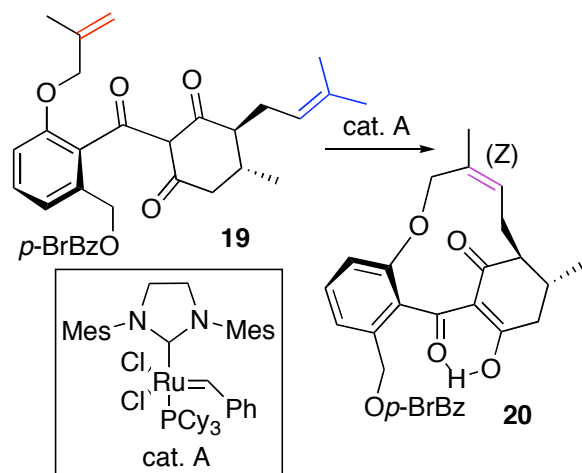
⁹ Nicolaou, K. C.; Montagnon, T.; Vassilikogiannakis, G.; Mathison, C. J. N. *J. Am. Chem. Soc.* **2005**, *127*, 8872.

Initial studies focused on the synthesis of advanced intermediates such as **15** to investigate the possibilities of a Claisen-type condensation (Scheme 5). It was quickly realized that although this reaction has typically been successful in complex systems, no desired product was formed under an array of conditions. The ester unit of **15** was then reduced to generate aldehyde **16** in order to examine the feasibility of an Aldol reaction to form the required carbon-carbon bond. Unfortunately, a variety of bases were unable to promote this aldol reaction.

A recent literature report describing the use of acyl cyanides to C-acylate 1,3-dicarbonyl compounds under mild (Et_3N) conditions were explored in this context and were very successful on simple, intermolecular model systems. Based on other attempts discussed previously it is not surprising that when these conditions were employed with **17**, no reaction was observed. A third generation approach to closing the macrocycle that centered around intramolecular alkylation of **18** also failed.

Olefin metathesis, having proved its robust nature in a variety of medium ring syntheses,¹⁰ was the Nicolaou groups final approach to the coleophomone skeleton. Gratifyingly, this approach would indeed prove successful, albeit after extensive experimentation and many unexpected results. The pivotal intermediate that provided hope for this proposed bond disconnection was **19**, which underwent smooth ring closing metathesis upon treatment with Grubbs II catalyst (cat. A) in refluxing CH_2Cl_2 (Scheme 6). Although the yield was a modest 30%, it was more intriguing that the product existed as a single olefin isomer. As though the facile nature of the strained ring closure were not enough, even better results were obtained serendipitously though a protecting group manipulation. Due to the lability of the tricarbonyl moiety, the authors

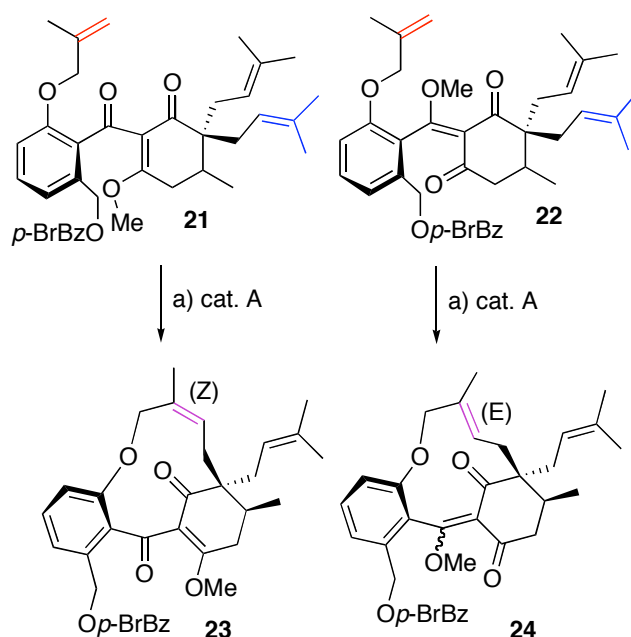
Scheme 6. Successful ring closing metathesis reaction on model substrate **19**.



¹⁰ For selected examples, see: (a) Wipf, P.; Stephenson, C. R. J.; Walczak, M, A, A. *Org. Lett.* **2004**, *6*, 3009. (b) Deiters, A.; Martin, S. F. *Chem. Rev.* **2004**, *104*, 2199 and references cited therein.

proposed protecting it as its methyl vinylogous ester using diazomethane since other protecting strategies would most likely prove unsuccessful in this complex, hindered system. With key intermediate **22** in hand, ring closing metathesis was attempted utilizing the previously mentioned conditions with Grubbs II (Scheme 7). Not only was the reaction successful, but to their astonishment it generated the (*E*)-alkene isomer as the only isolated product. To further their delight, subjecting **21** to the same conditions generated the (*Z*)-alkene isomer as a single product. In this fashion, a concise route to both coleophomones B and C had been developed from a common intermediate.

Scheme 7. Key ring closing metathesis reaction in the synthesis of Coleophomones B and C.



In conclusion, macrocyclization is an arduous task which has required the development of novel reactions and the modification of others to succeed. The addition of highly strained aromatic rings or compact rings with unsaturation makes the synthesis of these targets extremely difficult. Even reactions a chemist may consider robust often fail when the kinetic barrier for ring closure is high – requiring the development of novel methods and strategies to tackle these problems. The intriguing biological activity of haouamine A and the coleophomones makes this pursuit worthwhile. Molecules of this type demonstrate in a profound way that synthetic chemists still have a lot to learn about constructing complex natural products, with every achievement making the next more possible. Over the next decades nature should continue to provide complex macrocycles that intrigue the best chemical minds while furthering the innovation and creativity already present today.