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Construction of the Cyclophane Core of the Hirsutellones via a RCM Strategy§

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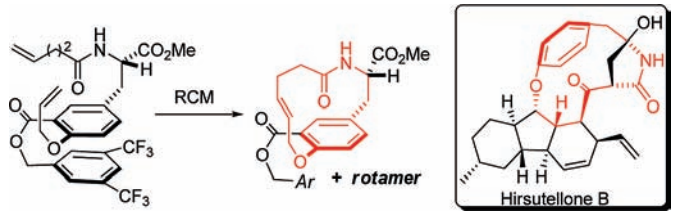
ABSTRACT



Construction of the highly strained [10]-paracyclophane core of the hirsutellones has been completed via an effective RCM strategy.

Despite that cyclophanes have been extensively synthesized and evaluated due to their unique physical and chemical properties for decades,[1] examples on isolation and total synthesis of cyclophane-containing natural products are rare, which include haouamines A,[2] sanjoinine G1,[3] acerogenin A,[4] longithorone A,[5] cylindrocyclophane A,[6] etc. Recently, a family of natural products named hirsutellones A−F were reported, some of which show antimycobacterial activity.[7] Their novel structures (Figure 1) are very similar to those of GKK1032s,[8] pyrrocidines,[9] and pyrrospirones.[10] Interestingly, all of them contain a highly stained paracyclophane core embracing a *bent* benzene ring.

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§ Dedicated to Prof. Wei-Shan Zhou on the occasion of his 87th birthday.

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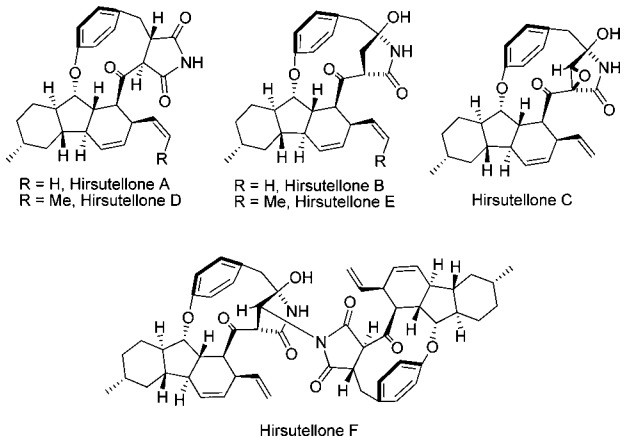
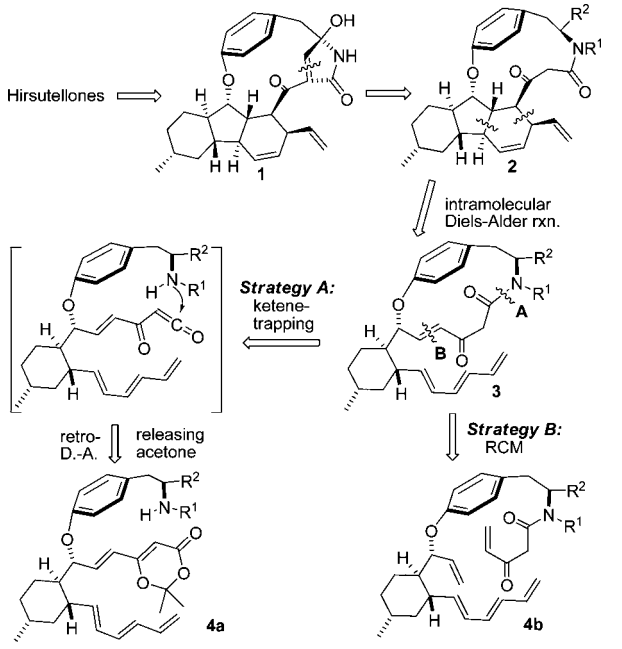


Figure 1. Structures of the hirsutellones.

The structural novelty and interesting bioactivity of the hirsutellones have attracted the attention of synthetic chemists. The Nicoloau group achieved an elegant total synthesis of hirsutellone B in 2009, which featured an epoxide opening/Diels−Alder cascade to form the 6−5−6 fused tricyclic motif and the construction of a cyclophane core through a Ramberg−Bäcklund reaction.[11] In addition, the Sorensen group and our group proposed a very similar ketene-trapping/IMDA cascade strategy independently (Scheme 1).[12] From

Scheme 1. Retrosynthetic Analysis toward the Hirsutellones



a biogenic viewpoint,[13,7b] the hirsutellones are able to be transformed from a key intermediate **1**, which could be obtained from compound **2** following Snider's methodology.[14] The 5−6 fused ring substructure can be constructed by an intramolecular Diels−Alder reaction (IMDA) from **3**. One of the key steps is to constitute the paracyclophane core effectively, which might be realized through two strategies. On one hand, an ambitious ketene-trapping/IMDA tandem strategy (strategy A) was devised to install three rings in one step, in which the highly reactive ketene generated in situ acts as an important reaction intermediate from **4a**. On the other hand, cleavage at the *trans*- double bond in the cyclophane core of **3** would give the ring closing metathesis (RCM) precursor **4b** (strategy B). Following the retrosynthetic analysis, we evaluated these synthetic strategies, respectively, with simplified model substrates.

In our previous communication, to promptly test the feasibility of the tandem reaction (strategy A), we applied a model substrate by omitting one six-membered ring; however, the desired ketene trapping toward formation of paracyclophane did not work, although the intramolecular Diels−Alder reaction occurred smoothly.[12b] It suggested that the formation of the strained paracyclophane core be the most important and difficult puzzle. To fully address the possibility of a current ketene-trapping strategy, we synthesized compounds **9a**−**9d** from the known compound **5** via routine procedures (Scheme 2).[15] Theoretically, compounds **9a**−**9d**, with sufficient rotational flexibility, might show different reactivity in the intramolecular ketene-trapping step based on their different steric and electric properties. In fact, to our disappointment, no desired [10]-paracyclophane could be detected by heating the cyclization precursors **9a**−**9d** either in a sealed tube or with a Dean−Stark trap. We speculated that such failure be ascribed to the ring strain of [10]-paracyclophane since a less strained [14]-paracyclophane with similar structure was successfully constructed by employing the same ketene-trapping tactic in a recent total synthesis of macrocidin A.[16]

To circumvent this obstacle, we turned our attention to the RCM protocol, which has been employed to construct the [16]-paracyclophane core of the turrianes by the Fürstner group[17] and to make a [12]-paracyclphane of longithorone A by the Zhu group.[4] Thus, compounds **11a** and **11b** were prepared conveniently from the known compound **5**, and both were subsequently subjected to the RCM conditions in a highly diluted solution of DCM or toluene, with Grubbs first or second generation catalysts or Hoveyda−Grubbs second generation catalyst.[18] However, very low conversion was

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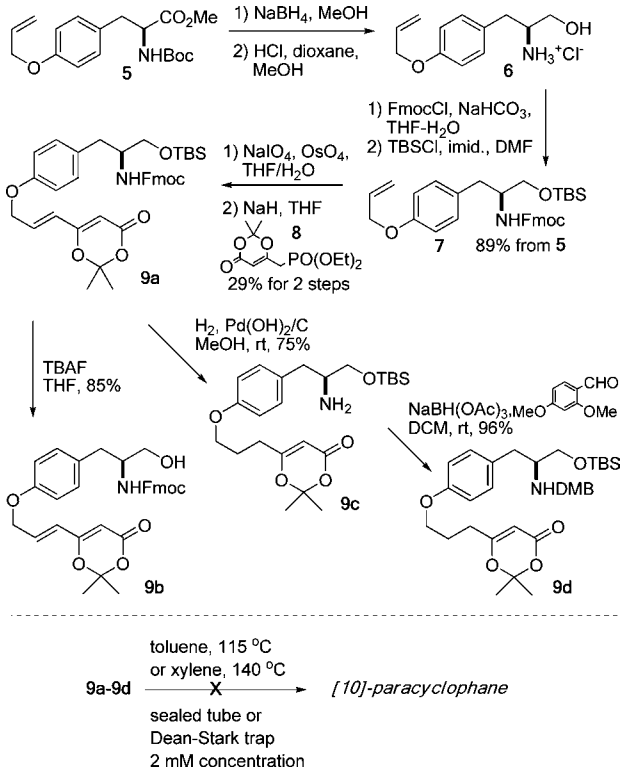
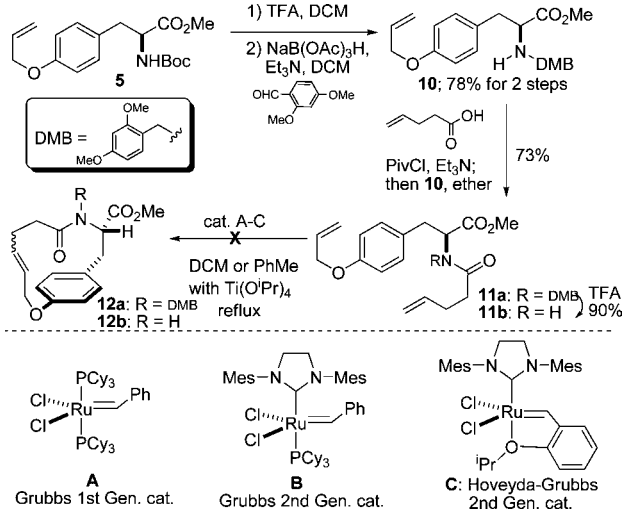
Scheme 2. Ketene-Trapping Strategy to Construct the [10]-Paracyclophane Core



observed, and paracyclophane **12** could not be detected, even though titanium(IV) isopropoxide was applied to mediate the basic nitrogen atom of amides **11a** and **11b** and supposedly to assist RCM (Scheme 3).[19] We surmised that the abortion

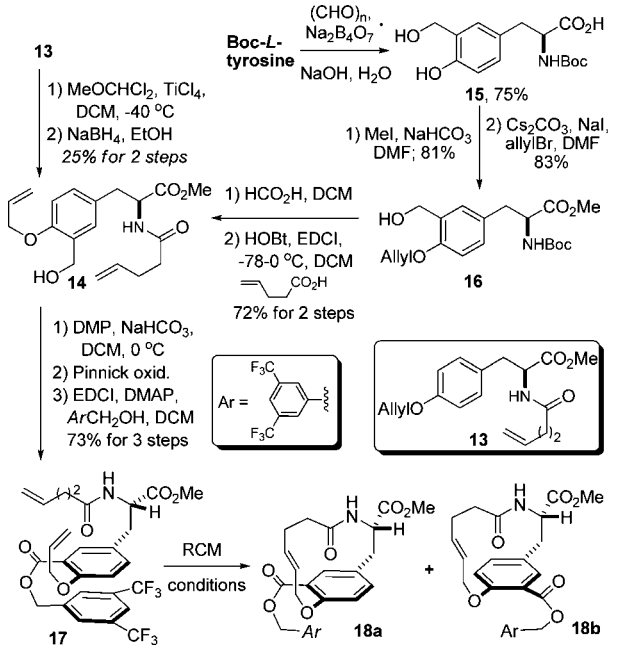
Scheme 3. First Generation of the RCM Strategy to Construct the [10]-Paracyclophane Core



of this direct RCM method should result from two vital factors. One is that the lone electron pair on *sp*^{2}*-hybrided* ethereal oxygen in **11** is conjugated with a π-orbital on the benzene ring, making the two double bonds far away from each other. The other is that excess enthalpy is required to overcome the energy barrier for contorting the flat benzene ring to a *bent* ring, a necessary conformation in the transition state.

Enlightened by the Collins group's pioneering work on exploitation of fluorophenyl−phenyl interactions for macrocyclizations by metathesis,[20] we anticipated that the above-mentioned problems from direct RCM might be solved by introducing an electron-deficient benzyl gearing element. On one hand, steric repulsion between ester substitution at the *ortho* position and the phenyl ether, as well as lp$-\pi$ interaction between ethereal oxygen and an electron-deficient aryl ring, can break up the conjugation between ethereal oxygen and the benzene ring. On the other hand, the flat benzene structure might be partially distorted by $\pi-\pi$ stacking between *electron-rich* and *electron-deficient* aryl rings in both the ground state and transition state. To access the desired RCM precursor **17** from compound **13**, various formylation methods, such as the Vilsmeier−Haack reaction[21] and DMF/^{n}BuLi,[22] were tried, but did not work. In fact, an important intermediate **14** toward the precursor of RCM was prepared through titanium-mediated formylation,[23] followed by reduction with sodium borohydride to faciliate column chromatography (Scheme 4).[24] However, since the

Scheme 4. Second Generation of RCM Strategy to Construct the [10]-Paracyclophane Core



RCM conditions: Grubbs 2nd Generation catalyst (20 mol %), DCM, reflux, 24 h
69% combined yield;**18a:18b** *ca.* 1:1

25% yield of this transformation is quite unsatisfactory, we developed a second synthetic route. Commercially available Boc-L-tyrosine was treated by paraformaldehyde and borax to afford compound **15**, which was then selectively converted to methyl ester and allyl phenyl ether in turn. After removal

of Boc protection, the free amine was transformed to amide **14** by coupling 4-pentenoic acid. The RCM precursor **17** was thus obtained by converting the hydroxylmethyl group in **14** to an acid and then esterifying it with 3,5-di(trifluoromethyl) benzyl alcohol. While application of Grubbs first generation catalyst did not result in any conversion, using 20 mol % loading of Grubbs second generation catalyst smoothly promoted the formation of [10]-paracyclophanes **18a** and **18b**,[25] by refluxing **17** in dichloromethane for 24 h. It is worth noting that compounds **18a** and **18b** are a pair of rotamers since the small cavity of [10]-paracyclophanes restricts free rotation along the central axis across the benzene ring. The geometric configuration of the double bond in these two rotamers was determined to be *E*-form from the coupling constants, which is crucial for the following intramolecular Diels−Alder reaction to install the proper stereocenters in total synthesis of the hirsutellones.

In summary, a synthetic method to construct the [10]-paracyclophane skeleton of hirsutellones via RCM was established successfully. Total synthesis of the hirsutellones with this strategy is underway in our laboratory.

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Supporting Information Available: Experimental procedures, characterization data for new compounds, and selected copies of NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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