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Studies toward the total synthesis of the hirsutellones

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ABSTRACT

A strategy of tandem ketene-trapping/IMDA toward the total synthesis of the hirsutellones was attempted. The AB ring moiety of the hirsutellones was constructed with the proper stereochemistry.

In 2005, a family of interesting natural products named as hirsutellones A–E was isolated from the insect pathogenic fungus *Hirsutella nivea* BCC 2594, showing strong antimycobacterial activities.[1] One year later, hirsutellone F, with a unique dimer structure, was isolated from the seed fungus *Trichoderma* sp. BCC 7579, also displaying antitubercular activity.[2] Structurally, these novel alkaloids were similar to GKK1032,[3] pyrrocidines,[4] and pyrrospirones.[5] All of these four families have a similar polycyclic core structure which consists of a tricyclic polyketide system, a γ-lactam or succinimide ring, a substituted phenyl ether, and a strained 12- or 13-membered ring (Fig. 1). The complex molecular skeleton and diverse bioactivities of these families make them very attractive target molecules for the synthetic community; however, few synthetic efforts were reported besides Kuwajima group's[6] and Katoh group's[7] work on the fragment synthesis of GKK1032s, as well as Sorensen group's very recent research on the synthesis of the decahydrofluorene core of the hirsutellones.[8] Herein, we describe our synthesis of AB ring of the hirsutellones and the efforts to realize the cyclization of the strained phenyl-ether-containing ring.

The most unique and challenging motif of the hirsutellones to a synthetic chemist is the highly strained 12- or 13-membered ring containing a γ-lactam or succinimide ring and a phenyl ether substructure. We envisioned that the lactam bond might be constructed via the amine trapping of a reactive intermediate, which would help to overcome the ring strain. As illustrated in Scheme 1, an ambitious tandem intramolecular ketene trapping/Diels–Alder strategy was designed, in which the highly reactive ketene generated in situ acts as such an important intermediate. This strategy is very similar to that of Sorensen's group.[8] To probe the feasibility of this strategy, a model substrate, simplified by omitting ring C of the hirsutellones, was proposed, which would be prepared by installation of the triene segment with sequential Takai reaction and Stille coupling, and subsequent installation of the 1,3-dioxinone via HWE reaction. The stereochemistry of the phenyl ether could be ensured by using a Pd-catalyzed allylic substitution. According to the above retrosynthetic analysis, the known compound **12**[9] was prepared following a routine synthetic sequence,[10,11] and then coupled with compound **17**[12] using O'Doherty's allylic phenoxylation reaction[9,13] (Scheme 2). The stereochemistry of compound **18** was confirmed by NOESY correlation of its derivative **21**. DIBAL-H reduction of **18**, followed by Lüch reduction, afforded alcohol **22,** whose primary allylic alcohol was selectively protected with TES at low temperature. While hydrogenation of **23** with Pd/C proved sluggish, the use of $Pd(OH)_2/C$ saturated the double bond and removed benzyl protection simultaneously in 62% yield, though a certain amount of triol **25** was also isolated in 20% yield.

Oxidative cleavage of diol **24** afforded an aldehyde intermediate, which was directly coupled with HWE reagent **26.**[14] In spite of many trials, the concomitant deprotection of TES ether could not be circumvented; thus a major THP-type cyclization product **27** was obtained, along with the desired alcohol **28**. All attempts to transform **27** to **28** failed, leading to either no reaction or decomposition of **27**. It is probably caused by the labile 2,2-dimethyl-1,3-dioxinone segment in **27**, and is consistent with a reported example of ring opening of tetrahydropyranyl ketone.[15] In order to furnish the key substrate **31,** a three-step procedure was applied, including Dess–Martin oxidation,[16] Takai reaction,[17] and Stille coupling[18] of **29** with (*E*)-buta-1,3-dienyltributylstannane **30**[19] at room temperature. As for Stille coupling to form triene **31**, different Pd catalysts, such as $Pd_2(dba)_3/PPh_3$, and $Pd_2(dba)_3/AsPh_3$, $Pd(PPh_3)_4$, were screened, and $PdCl_2(MeCN)_2$ afforded the best result among them. Inspired by the reported successful intermolecular capture of ketene by oxazolidinone[20] and amide,[21] we then tried the intramolecular ketene trapping/Diels–Alder tandem strategy. Interestingly, heating a highly diluted solution of **31** at 115 °C in a sealed tube did not achieve the desired product, but afforded bicycle **32** as an isolatable major product. The relative stereochemistry of **32** was confirmed to fortunately match that of the hirsutellones by NOESY (Scheme 3).[22]

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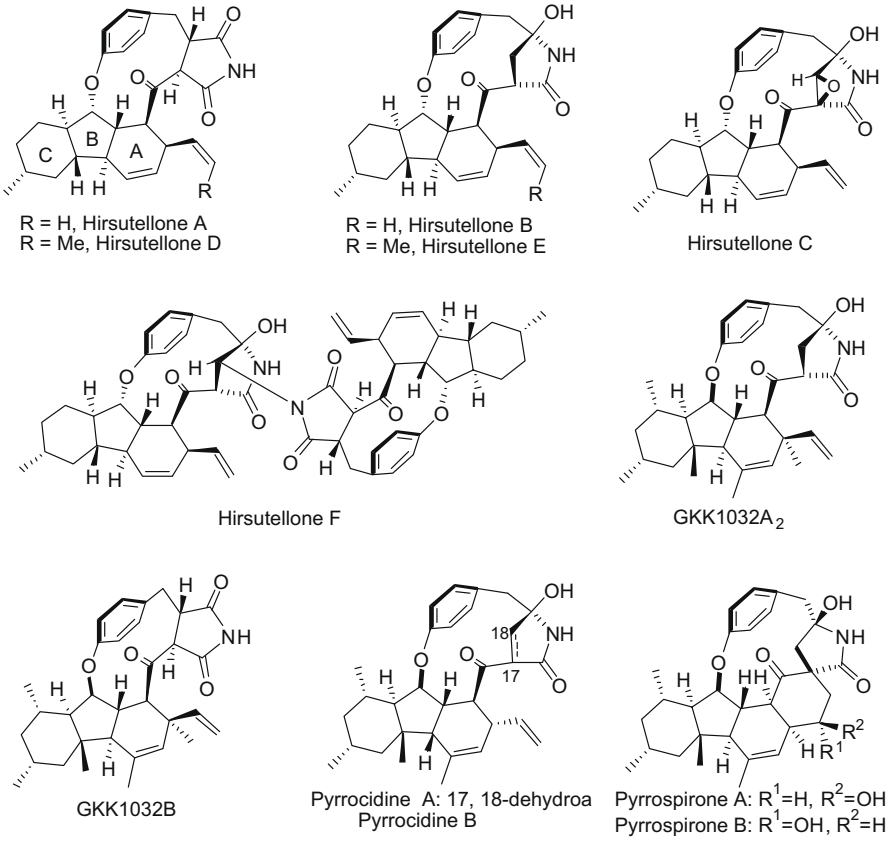
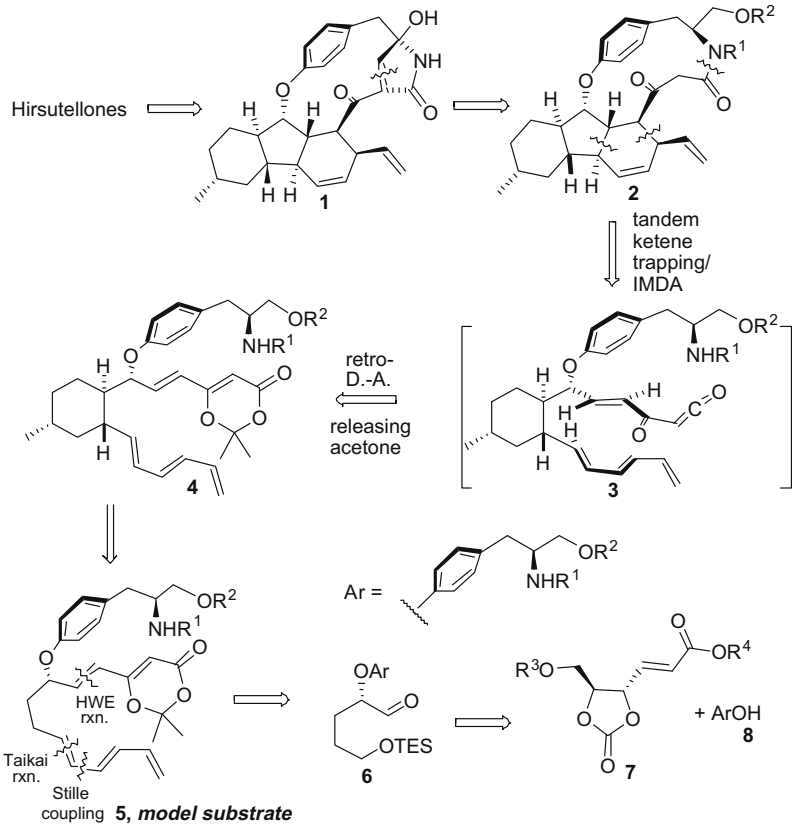


Figure 1. Molecular structures of hirsutellone, GKK1032, pyrrocidine, and pyrrospirone families.



Scheme 1. Synthetic strategy and retrosynthetic analysis of model substrate.