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Studies toward the total synthesis of the hirsutellones

Mingzheng Huang, Chong Huang, Bo Liu *

Key Laboratory of Green Chemistry & Technology of Ministry of Education, College of Chemistry, Sichuan University, Chengdu 610064, PR China

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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]

* Corresponding author. Tel./fax: +86 28 8541 3712.
E-mail address: chembliu@scu.edu.cn (B. Liu).

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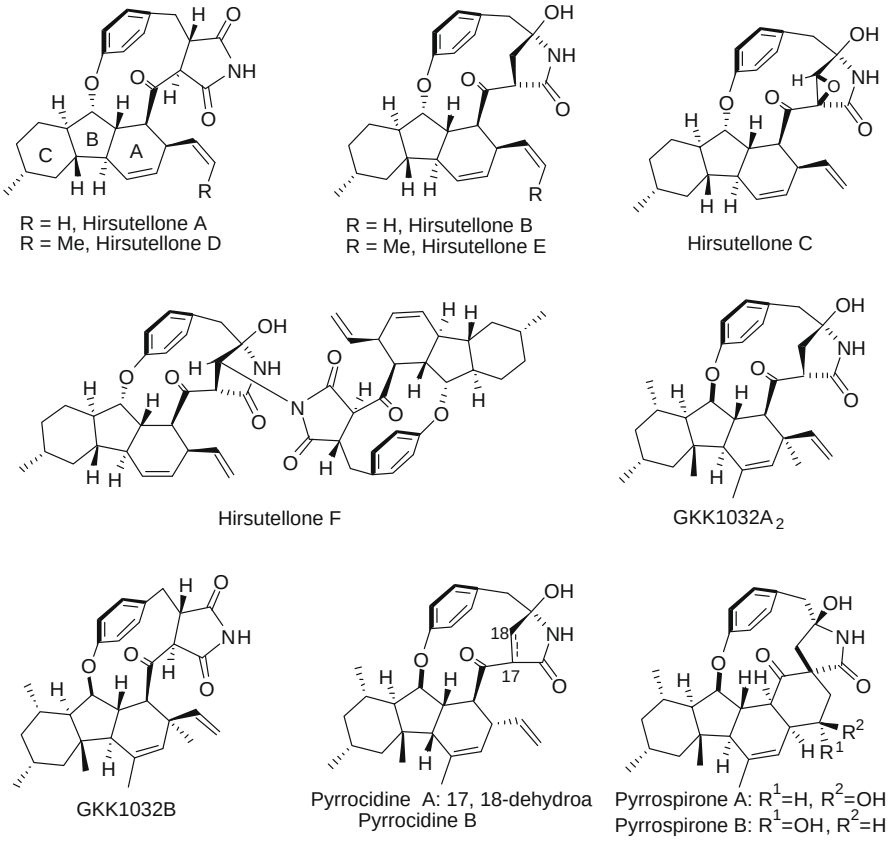
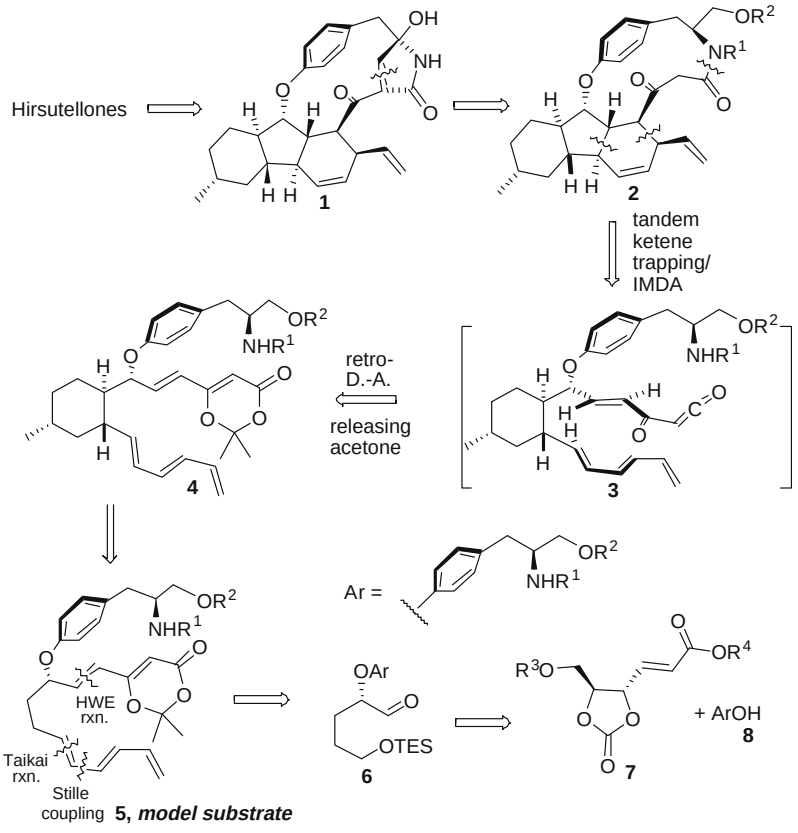
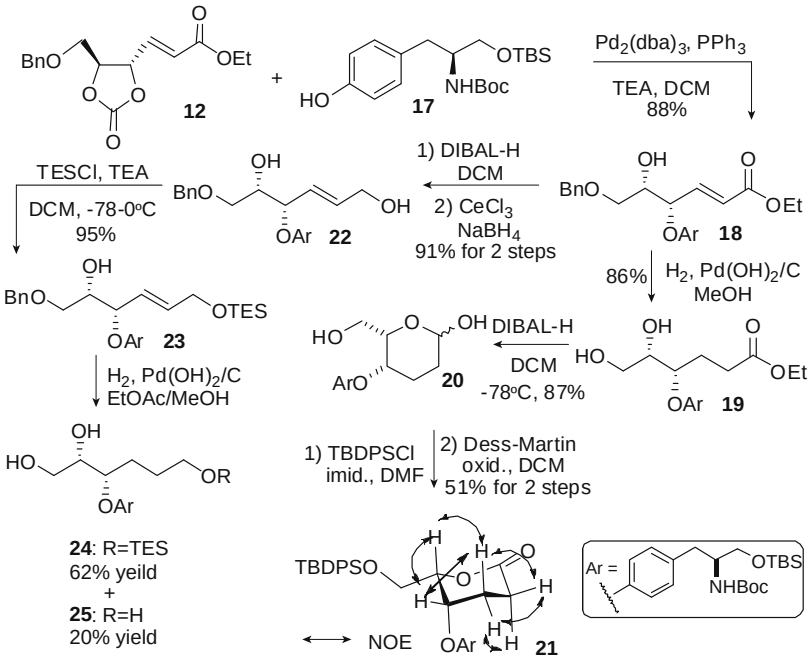


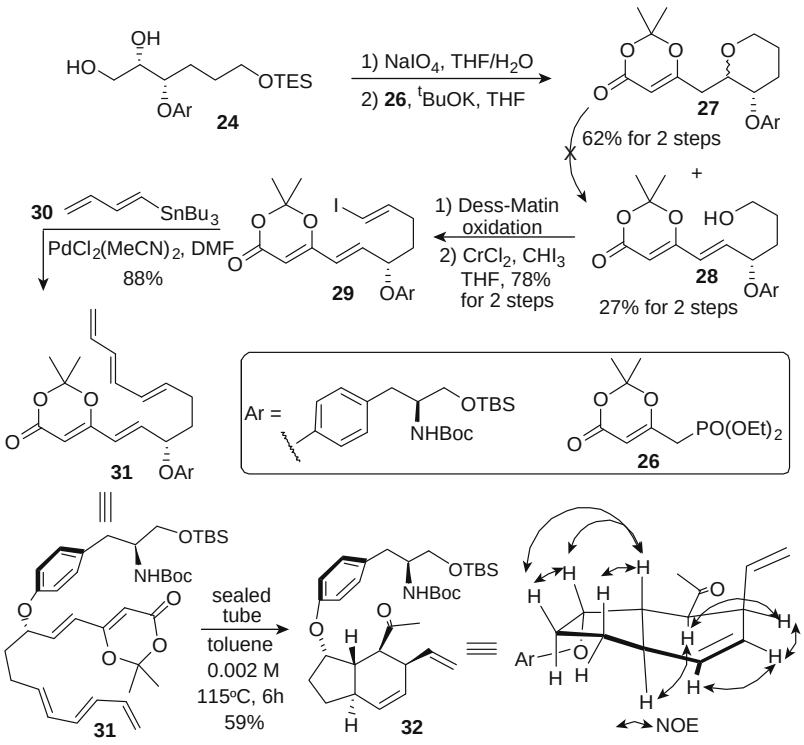
Figure 1. Molecular structures of hirsutellone, GKK1032, pyrrocidine, and pyrrospirone families.



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



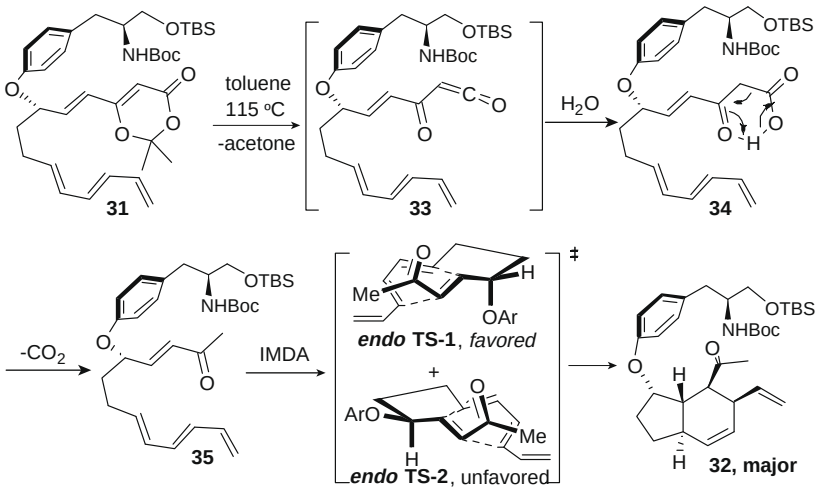
Scheme 2.



Scheme 3.

A tentative pathway from **31** to **32** was proposed as shown in Scheme 4. In our opinion, the weak nucleophilicity of carbamate and the steric hindrance around the amino group in **31** might hamper the preferred *intramolecular* capture of ketene, but instead benefit *intermolecular* reaction of ketene with some adventitious water in the system to form an unstable β-keto acid, leading to a methyl ketone **35** by releasing one molecule of carbon dioxide. Then **32** was formed through an IMDA reaction via a favored *endo*-type transition-state (**TS-1**). However, though this stereochemical preference is in agreement with other reported examples,[8,23] a reasonable explanation is still required.[24]

The synthetic route described above completed the construction of AB ring moiety of the hirsutellones with the proper stereochemistry, and acted as a guide for tuning the reactivity of intramolecular ketene trapping. We are currently endeavored to promote the lactam formation and optimize the synthesis sequence as well to improve the total yield of **31**.



Scheme 4.

Acknowledgments

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Supplementary data

Supplementary data (characterization data and NMR spectra of selected new compounds were provided) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.03.158.

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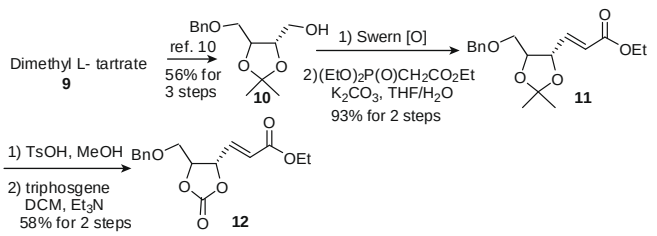
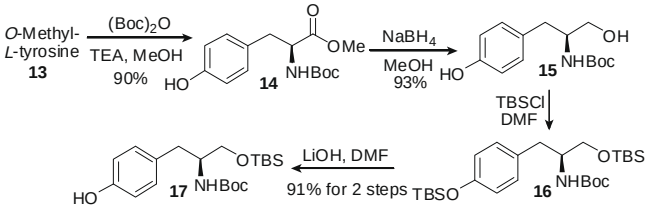
11. A seven-step sequence was followed to prepare **12**:



12. A routine synthetic sequence was followed to afford **17**:



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22. Compound **32**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.05 (br d, J = 8.0, 2H), 6.67 (br d, J = 8.0, 2H), 5.96 (d, J = 9.6, 1H), 5.54–5.60 (m, 1H), 5.46 (dt, J = 9.6, 3.2, 1H), 5.03 (m, 2H), 4.89 (t, J = 4.8, 1H), 4.71 (br d, J = 7.2, 1H), 3,77 (br s, 1H), 3.50 (dd, J = 9.6, 3.6, A of AB, 1H), 3.47 (dd, J = 9.6, 3.2, B of AB, 1H), 3.33 (m, 1H), 2.73 (br d, J = 6.8, 2H), 2.52 (m, 1H), 2.20–2.25 (m, 1H), 2.04 (s, 3H), 1.90–1.97 (m, 1H), 1.71–1.80 (m, 2H), 1.41 (s, 9H), 1.20–1.30 (m, 2H), 0.07 (s, 6H); HRMS (ESI) calculated for $[C_{33}H_{51}NO_5Si+Na]^+$ 592.3434, found 592.3445.
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