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Bioinspired Synthesis of Hirsutellones A, B and C

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Abstract

The total synthesis of hirsutellones A (1), B (2) and C (3) has been achieved through a bioinspired late-stage sequence starting from advanced intermediate 6. The sequence proceeded via labile intermediate 17,1'-dehydrohirsutellone B (5) and delivered, in addition to the natural products (1–3), hirsutellone analogue 1',2',17-*epi*-hirsutellone C (1',2',17-*epi*-3).

Heterodimeric hirsutellone F (4) and 17,1'-dehydrohirsutellone B (5),² the putative biosynthetic precursor to hirsutellones 1–4 (Scheme 1), were recently added to the growing class of hirsutellones [A (1), B (2) and C (3),¹ Scheme 1]. Isolated from the seed fungus *Trichoderma* sp. BCC 7579 incubated in a bioreactor (as opposed to incubation in an Erlenmeyer flask) by Isaka and coworkers, hirsutellone F (4) was shown to decompose to its apparent components, 17,1'-dehydrohirsutellone B (5) and hirsutellone A (1), upon exposure to basic conditions as shown in Scheme 1.² When the decomposition of 4 was carried out in the presence of NaBH₄, hirsutellone B (2) was obtained in addition to hirsutellone A (1). Furthermore, it was determined that when the basic decomposition of 4 was performed in the presence of H₂O₂-NaOH, hirsutellone C (3) was generated together with hirsutellone A (1). Apparently, in the latter reactions, the fleeting intermediate 5 was intercepted (17,1'-reduction or epoxidation) to a significant extent prior to its conversion to hirsutellone A (1) through base-induced bond migration accompanied by ring expansion. These observations prompted the isolation chemists to propose a late-stage biosynthetic hypothesis involving labile intermediate 5 as the biogenetic precursor of all hirsutellones shown in Scheme 1.³ In this communication, we report the *in situ* generation of this 17,1'-dehydrohirsutellone B (5) and its conversion to hirsutellones A (1), B (2) and C (3), thereby confirming the Isaka hypothesis and achieving the first total synthesis of hirsutellones A (1) and C (3) and a second generation total synthesis of hirsutellone B (2).^{4,5} These natural products are notable not only for their novel molecular architectures, but also for their promising antituberculosis properties (active against *Mycobacterium tuberculosis*, MIC = 0.78 µg/mL for 1–3).¹

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Supporting Information Available: Schemes with respective reagents and conditions, experimental procedures, characterization data for all compounds reported and cif file (pdf). This material is available free of charge via the Internet at <http://pubs.acs.org>.

Our initial attempts to obtain the desired 17,1'-dehydrohirsutellone B (**5**) through the obvious route involving site-selective oxidation of hirsutellone B (**2**) failed, presumably due to steric hindrance at C-17 and the arrangement of the β -ketoamide moiety carbonyl groups of the substrate (**2**) (most likely locked in an eclipsed conformation). Finding ourselves in this predicament, we decided to explore the development of a synthetic strategy to the targeted biosynthetic precursor (**5**) from the previously synthesized intermediate **6**⁴ (Scheme 2). Thus, diol **6** was successfully converted to hydroxy lactone **7** through the action of *p*-TsOH (87% yield), and then deoxygenated through a two-step sequence involving thiocarbonate formation [PhOC=SCl] and reduction (*n*-Bu₃SnH, AIBN)⁶ to afford the expected β -keto lactone in 78% overall yield. NMR spectroscopic analysis of the latter compound revealed its exclusive existence in CDCl₃ solution as its enol form **8** (Scheme 2). An X-ray crystallographic analysis of a single crystal of this compound obtained from CH₂Cl₂/hexanes (m.p. 163–166 °C, dec.) confirmed its enolic structure in the solid state and proved the *E*-geometry of its enol system (see ORTEP, Scheme 2). Exposure of enol **8** to DDQ and K₂CO₃ led to the corresponding α -hydroxy ketone, whose dehydration with Martin's sulfurane⁷ gave keto furanone **9** in 73% overall yield.

With the procurement of keto furanone **9**, only amidation, oxidation, and ring closure remained in order to reach the targeted molecule (**5**). The direct amidation of **9** proved difficult, yielding only 17% of the desired hydroxy amide (**12**) after 48 h of heating in neat NH₃ (85% based on recovered **9**) as shown in Scheme 3. In contrast, epoxidation of **9** with H₂O₂ under basic conditions (aq. NaOH) at 0 °C led to epoxy lactone **10** in 90% yield within 30 min (single diastereoisomer, α -stereochemistry assigned by NOE studies, see Scheme 3). Pleasantly, ammonolysis of the lactone moiety of epoxy lactone **10** proceeded smoothly to afford epoxy hydroxy amide **11** in excellent yield (91%), requiring only bubbling of NH₃ gas through a solution of the substrate in MeOH:THF:H₂O (4:4:1) at 0 °C for 1 h. The latter compound was then deoxygenated through the action of SmI₂, leading to the desired unsaturated hydroxy amide **12** in 67% yield.⁸ In this reaction the initially formed 1,2-diol suffers stereoselective dehydration to afford the desired geometrical isomer of the unsaturated hydroxy amide as confirmed later in the sequence (see ring closure **14**→**5**+2'-*epi*-**5**, Scheme 4).

Exposure of **12** to DMP then produced keto amide **14** which spontaneously cyclized, furnishing a mixture of 17,1'-dehydrohirsutellone B (**5**, major) and 2'-*epi*-17,1'-dehydrohirsutellone B (2'-*epi*-**5**, minor), two labile intermediates (not detectable by TLC) whose structures were inferred from their successful conversion to the naturally occurring hirsutellones A (**1**), B (**2**) and C (**3**), and 1',2',17-*epi*-hirsutellone C (1',2',17-*epi*-**3**), respectively, as shown in Scheme 4. Synthetic hirsutellones A, B and C exhibited identical physical properties to those reported for the natural products.¹ Exhibiting spectroscopic and spectrometric data consistent with its structure, compound 1',2',17-*epi*-**3** has not been reported as a natural product as yet. However, it should not be a surprise if it is found in nature in the future, given the ease by which it is formed from 2'-*epi*-**5** (17,1'-dehydro-2'-*epi*-hirsutellone B). 1',2',17-*epi*-Hirsutellone C (1',2',17-*epi*-**3**) was also obtained from epoxy hydroxy amide **11** by DMP oxidation as shown in Scheme 5 (85% yield).

The described chemistry provides support for the Isaka biosynthetic hypothesis for hirsutellones A–C (**1–3**), constitutes the first total synthesis of hirsutellones A (**1**), C (**3**) and 1',2',17-*epi*-hirsutellone C (1',2',17-*epi*-**3**), as well as a second synthesis of hirsutellone B (**2**).

Supplementary Material

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Scheme 1.

Molecular Structures of Hirsutellones A (**1**), B (**2**), C (**3**) and F (**4**), Their Postulated Biogenetic Precursor 17,1'-Dehydrohirsutellone B (**5**) and Isaka's Confirmed Late-stage Biosynthetic Hypothesis for Hirsutellones **1–3**²

Scheme 2.
Synthesis of Keto Furanone **9**

Scheme 3.
Preparation of Hydroxyamide **12**

Scheme 4.

Biomimetic Synthesis of Hirsutellones A (**1**), B (**2**) and C (**3**) and 1',2',17-*epi*-Hirsutellone C (1',2',17-*epi*-**3**)

Scheme 5.

Conversion of Epoxy Amide **11** to 1',2',17-*epi*-Hirsutellone C (1',2',17-*epi*-3)