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Bioinspired Synthesis of Hirsutellones A, B, and C

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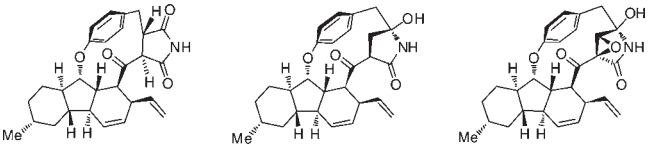
ABSTRACT



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 co-workers, 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 $NaBH_4$, 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 H_2O_2−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 based-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]

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**)

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(2) Isaka, M.; Prathumpai, W.; Wongsa, P.; Tanticharoen, M. *Org. Lett.* **2006**, *8*, 2815–2817.

(1) Isaka, M.; Rugseree, N.; Maithip, P.; Kongsaeree, P.; Prabpai, S.; Thebtaranonth, Y. *Tetrahedron* **2005**, *61*, 5577–5583.

(3) A similar late-stage biosynthetic hypothesis has been reported previously in a series of GKK1032 derivatives; see: Oikawa, H. *J. Org. Chem.* **2003**, *68*, 3552–3557.

(4) Nicolaou, K. C.; Sarlah, D.; Wu, T. R.; Zhan, W. *Angew. Chem., Int. Ed.* **2009**, *48*, 6870–6874.

(5) For previous synthetic studies toward hirsutellones, see: (a) Tilley, S. D.; Reber, K. P.; Sorensen, E. J. *Org. Lett.* **2009**, *11*, 701–703. (b) Huang, M.; Huang, C.; Liu, B. *Tetrahedron Lett.* **2009**, *50*, 2797–2800. (c) Huang, M.; Song, L.; Liu, B. *Org. Lett.* **2010**, *12*, 2504–2507. (d) Halvorsena, G. T.; Roush, W. R. *Tetrahedron Lett.* **2011**, *52*, 2072–2075.

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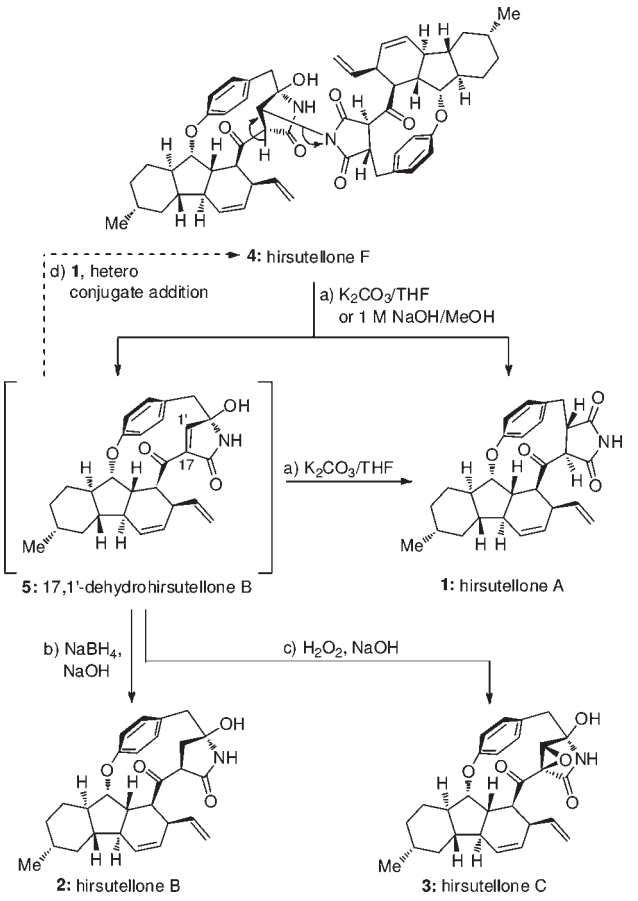
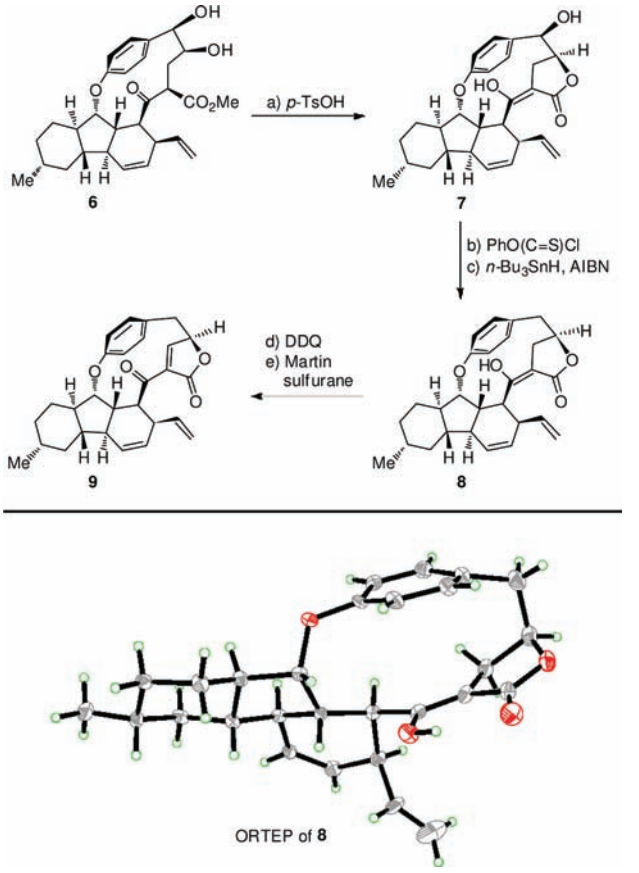
Scheme 1. Molecular Structures of Hirsutellones A (**1**), B (**2**), C (**3**), and F (**4**), Their Postulated Biogenetic Precursor 17,1′-Dehydrohirsutellone B (**5**), and Isaka's Confirmed Late-Stage Biosynthetic Hypothesis for Hirsutellones **1**–**3**[2]



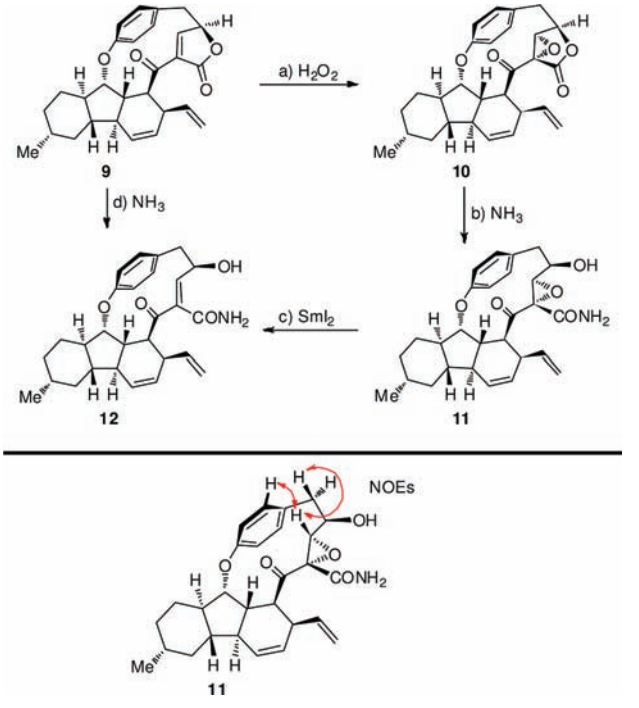
(most likely locked in an eclipsed conformation). Finding ourselves in this predicament, we decided to explore the development of a synthetic strategy to the targeted biosynthetic precursor (**5**) from the previously synthesized intermediate **6**[4] (Scheme 2). Thus, diol **6** was successfully converted 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*-Bu_3SnH, 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 $CDCl_3$ solution as its enol form **8** (Scheme 2). An X-ray crystallographic analysis of a single crystal of this compound obtained from CH_2Cl_2/hexanes (mp 163–166 °C, dec.) confirmed its enolic structure in the solid state and proved the *Z*-geometry of its enol system (see ORTEP, Scheme 2). Exposure of enol **8** to DDQ and K_2CO_3 led to the corresponding α-hydroxy ketone, whose dehydration with Martin's sulfurane[7] gave keto furanone **9** in 73% overall yield.

(6) Barton, D. H. R.; McCombie, S. W. *J. Chem. Soc., Perkin Trans.* **1975**, 1574–1585.
(7) Martin, J. C.; Arhart, R. J. *J. Am. Chem. Soc.* **1971**, *93*, 4327–4329.

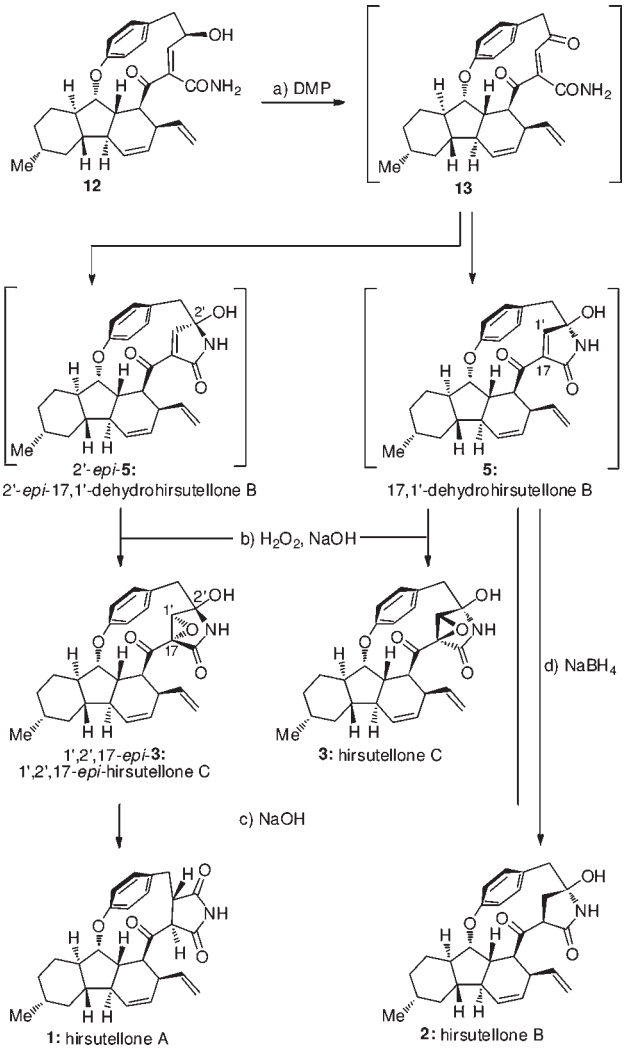
Scheme 2. Synthesis of Keto Furanone **9**



Scheme 3. Preparation of Hydroxyamide **12**



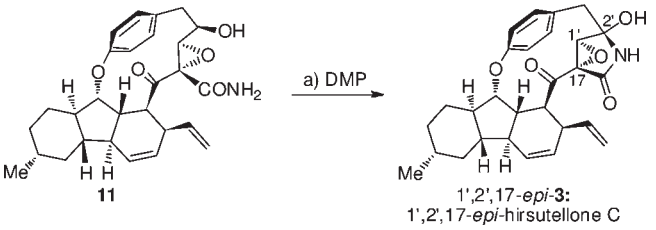
Scheme 4. Biomimetic Synthesis of Hirsutellones A (**1**), B (**2**), and C (**3**) and 1′,2′,17-*epi*-Hirsutellone C (1′,2′,17-*epi*-**3**)



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 NH_3 (85% based on recovered **9**) as shown in Scheme 3. In contrast, epoxidation of **9** with H_2O_2 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 NH_3 gas through a solution of the substrate in MeOH/THF/H_2O (4:4:1) at 0 °C for 1 h. The latter compound was then deoxygenated through the action of SmI_2, 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

(8) Molander, G. A.; Hahn, G. *J. Org. Chem.* **1986**, *51*, 2596–2599.

Scheme 5. Conversion of Epoxy Amide **11** to 1′,2′,17-*epi*-Hirsutellone C (1′,2′,17-*epi*-**3**)



isomer of the unsaturated hydroxy amide as confirmed later in the sequence (see ring closure **13** → **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**) and 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**).

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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.