# A Rapid, Asymmetric Synthesis of the Decahydrofluorene Core of the Hirsutellones

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#### ABSTRACT



A tandem ketene-trapping/Diels—Alder cyclization sequence was the pivotal transformation in an efficient, asymmetric synthesis of a decahydrofluorene tricyclic structure possessing eight stereogenic centers and key features of the hirsutellone class of antitubercular natural products. The hirsutellone-like  $\beta$ -keto ester that was fashioned by this sequence (13 steps; 6% overall yield) demonstrated significant inhibitory activity against *Mycobacterium tuberculosis*. The mechanism of action of this antitubercular compound is not yet known.

Tuberculosis is an infectious pulmonary disease caused by the pathogenic species Mycobacterium tuberculosis. Approximately one-third of the world's population is infected with the tuberculosis bacterium, resulting in over 1.5 million deaths each year.<sup>1</sup> Given the global impact of this devastating illness, there has been a renewed interest in finding new antitubercular agents to combat the significant issues of drug resistance and mycobacterial persistence.<sup>2</sup> In their search for new antibacterial metabolites, Isaka et al. reported the isolation of six bioactive polyketides from the fungus Hirsutella nivea BCC 2594 in 2005.<sup>3</sup> The hirsutellone family of natural products exhibits antimicrobial activity against M. tuberculosis, with minimum inhibitory concentration (MIC) values in the range 0.78–3.125  $\mu$ g/mL.<sup>3</sup> The intriguing polycyclic architecture of the hirsutellones features an unusual 13-membered p-cyclophane ether, a succinimide or  $\gamma$ -lactam ring, and a decahydrofluorene ring system containing eight stereocenters, of which seven are contiguous. The degree of structural complexity exhibited by these natural products combined with their strong antitubercular properties make the hirsutellones compelling objectives for chemical synthesis.

We reasoned that a thermal, retro-Diels—Alder fragmentation of the 2,2-dimethyl-1,3-dioxinone heterocycle of a compound of type **1** (Figure 1) would cause the formation of a transient acyl ketene.<sup>4</sup> This reactive species might then be capable of triggering both a lactam ring formation and an intramolecular Diels—Alder cycloaddition (see arrows in **2**) to give pentacycle **3**, a compound possessing key elements of the structure of hirsutellone B (**4**). While the ordering of the proposed lactamization and Diels—Alder events implied in intermediate **2** seemed unclear, this plan for rapidly forming the hirsutellone molecular architecture is supported by several published examples of nucleophilic trappings of

<sup>(1)</sup> World Health Organization, Fact Sheet 104, March 2007.

<sup>(2)</sup> Sacchettini, J. C.; Rubin, E. J.; Freundlich, J. S. *Nat. Rev. Microbiol.* **2008**, *6*, 41.

<sup>(3)</sup> Isaka, M.; Rugseree, N.; Maithip, P.; Kongsaeree, P.; Prabpai, S.; Thebtaranonth, Y. *Tetrahedron* **2005**, *61*, 5577.

<sup>(4) (</sup>a) Jäger, G.; Wenzelburger, J. *Liebigs Ann. Chem.* **1976**, 1689. (b) Sato, M.; Ogasawara, H.; Yoshizumi, E.; Kato, T. *Chem. Pharm. Bull.* **1983**, *31*, 1902. (c) Hyatt, J. A.; Feldman, P. L.; Clemens, R. J. J. Org. Chem. **1984**, *49*, 5105.



**Figure 1.** Proposed cascade for rapid construction of the polycyclic core of hirsutellone B.

transient acyl ketenes.<sup>4</sup> To the best of our knowledge, there is no published example of a tandem intramolecular ketenecapture/Diels—Alder cyclization; however, the laboratories of Roush and Boeckman have described impressive examples of tandem intermolecular acyl ketene-trapping/intramolecular Diels—Alder reactions in complex natural product synthesis.<sup>5</sup> In the course of pursuing a synthesis of hirsutellone B (4), we achieved a solvolytic capture of an acyl ketene intermediate and a fully stereocontrolled synthesis of the decahydrofluorene core architecture of the hirsutellone class of natural products. This compound possesses promising inhibitory activity against the *M. tuberculosis* strain mc<sup>2</sup>7000. Our synthesis of this tricyclic  $\beta$ -keto ester is described in this report.

The construction of the hirsutellone decahydrofluorene tricycle began with a stereoface-selective Diels–Alder reaction (Scheme 1). Use of Seebach's DIOZ chiral auxiliary<sup>6</sup> (derived from D-valine) gave complete diasteroselectivity in the reaction of **5** with excess isoprene, which was complete within 20 min at -40 °C. This observation stood in marked contrast to reactions using other oxazolidinone auxiliaries which provided much lower diastereomeric ratios and required longer reaction times.<sup>7</sup> After several unsuccessful attempts to excise the DIOZ auxiliary by direct reduction, we retreated to an efficient two-step procedure involving the conversion of imide **6** to benzyl ester **7**,<sup>6</sup> followed by a complete reduction of the ester moiety to alcohol **8** with diisobutylaluminum hydride (DIBAL-H). By this sequence, alcohol **8** was available in >99% ee.<sup>8</sup>

It was our intent to establish the methyl-bearing stereogenic center of the goal structure by a face-selective

(6) Hintermann, T.; Seebach, D. *Helv. Chim. Acta* **1998**, *81*, 2093.

(8) See the Supporting Information for details.



hydrogenation of the alkene formed in the initial Diels–Alder construction. Thus, we were pleased to discover that a hydroxyl-directed hydrogenation of **8** using Crabtree's catalyst<sup>9</sup> at 0 °C afforded compound **9** as a single diastereomer. To set the stage for a needed one carbon homologation, alcohol **9** was oxidized to the corresponding aldehyde by the Swern method.<sup>10</sup> A subsequent Wittig reaction<sup>11</sup> with the phosphorane derived from phosphonium salt **10** produced a 1:6 mixture of geometrically isomeric vinyl ethers in 84% yield from **9**; for clarity, only the major, *trans*-vinyl ether isomer **11** is shown.

As shown in Scheme 2, when the mixture of isomeric vinyl ethers was dihydroxylated by the Upjohn method (OsO<sub>4</sub>/NMO),<sup>12</sup> an electrophilic  $\alpha$ -hydroxy aldehyde **12** was generated and subsequently intercepted with the known phosphorane **13**,<sup>13</sup> resulting in the exclusive formation of *trans*-alkene **14** in 50% yield and as a 4:1 mixture of separable alcohol epimers. In order to establish the identity of the major diastereomer, a short sequence was carried out to generate a rigid structure from which the stereochemistry could be determined by nuclear Overhauser effect (NOE) correlations (Scheme 2). First, removal of the silyl protecting group with acetic acid in aqueous THF afforded the desired diol. Treatment of this compound with triphosgene in the presence of pyridine and 4Å molecular sieves afforded the cyclic carbonate **15** in 85% yield over the two steps. NMR

<sup>(5) (</sup>a) Roush, W. R.; Brown, B. B. *J. Org. Chem.* **1993**, 58, 2162. (b) Boeckman, R. K., Jr.; Shao, P.; Wrobleski, S. T.; Boehmler, D. J.; Heintzelman, G. R.; Barbosa, A. J. *J. Am. Chem. Soc.* **2006**, *128*, 10572.

<sup>(7)</sup> Reactions utilizing the chiral auxiliary (*R*)-4-benzyl-2-oxazolidinone gave 3:1 dr and required 12 h at -30 °C.

<sup>(9)</sup> Crabtree, R. H.; Davis, M. W. J. Org. Chem. 1986, 51, 2655.

<sup>(10)</sup> Omura, K.; Swern, D. Tetrahedron 1978, 34, 1651.

<sup>(11)</sup> Maryanoff, B. E.; Reitz, A. B. Chem. Rev. 1989, 89, 863.

<sup>(12)</sup> VanRheenen, V.; Kelly, R. C.; Cha, D. Y. Tetrahedron Lett. 1976, 17, 1973.

<sup>(13)</sup> Bodurow, C.; Carr, M. A.; Moore, L. L. Org. Prep. Proc. Int. 1990, 22, 109.

Scheme 2



analysis of 15 allowed for an unambiguous assignment of the (R)-configuration at the hydroxyl-bearing stereogenic center in compound 14 (Scheme 2).

From alcohol **14**, the substrate for the pivotal ketenetrapping/intramolecular Diels—Alder sequence could be fashioned in four steps (Scheme 3). Thus, protection of the secondary hydroxyl group of **14** was accomplished by deprotonation with *n*-butyllithium followed by addition of methyl chloroformate to give methyl carbonate **16**. Acidinduced cleavage of the silyl protecting group then afforded a primary alcohol, which was subsequently oxidized to aldehyde **17** by the action of the Dess—Martin periodinane (DMP)<sup>14</sup> in 74% yield over the two steps. The required triene chain was then introduced by a Wittig reaction between aldehyde **17** and the phosphorane derived from phosphonium salt **18**.<sup>15</sup> We found that biphasic reaction conditions (Scheme 3)<sup>16</sup> were uniquely successful for carrying out this Wittig reaction, which produced triene **19** in 66% yield.

We were pleased to observe that heating of triene **19** to 110 °C in an 8:1 mixture of toluene/methanol<sup>17</sup> gave rise to the desired tricycle **20** in 85% yield. NOE correlation data was used to assign the relative stereochemistry of **20** (Scheme 3); the stereochemical relationships in compound **20** correspond to those found in the decahydrofluorene core structure of the hirsutellone natural products. Our interest in the design and synthesis of new compounds with activity against tuberculosis prompted us to submit samples of compound **20** to the Sacchetini laboratory at Texas A&M University for a study of its performance in assays for antitubercular activity. While its mode of action is not yet known, compound **20** demonstrated an MIC of 1.21  $\mu$ g/mL



versus *M. tuberculosis*  $mc^{2}7000$ .<sup>18</sup> Efforts to elucidate the origin of biological activity of the hirsutellone-like tricycle **20** are currently underway.

The design for synthesis described herein guided the development of an expedient construction of the tricyclic core of the hirsutellone class of natural products in 6% overall yield over 13 steps from  $\alpha$ , $\beta$ -unsaturated imide **5**. The high yield and diastereoselectivity of the tandem ketene-trapping/Diels-Alder sequence lends credence to the possibility of generating even more complexity in a single step through an intramolecular capture of a putative acyl ketene intermediate. Efforts to realize this more ambitious chemical objective are currently underway.

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**Supporting Information Available:** Experimental procedures and full characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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