Natural Product Synthesis

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Total Synthesis of Hirsutellone B**

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Hirsutellones,[1] pyrrospirones,[2] and pyrrocidines[3] belong to a growing class of fungal secondary metabolites whose biological properties include antifungal and antibiotic activities. Particularly impressive are the activities of hirsutellones A and B (**1a** and **1b**, Figure 1)[1] against *Mycobacterium*

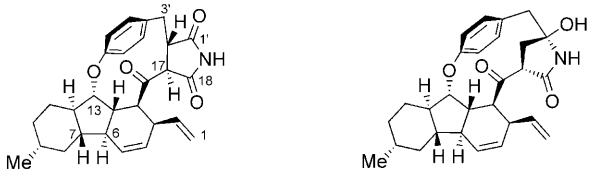
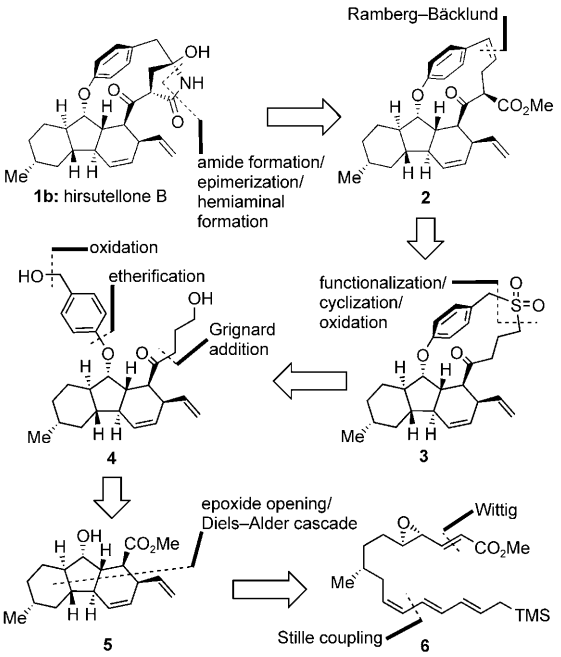


Figure 1. Molecular structures of hirsutellones A (**1a**) and B (**1b**).

tuberculosis [MIC = 0.78 μg mL^{-1} (MIC = minimum inhibitory concentration)], the causative pathogen of tuberculosis.[4] Isolated from the insect pathogenic fungus *Hirsutella nivea* BCC 2594, the hirsutellones share a number of unique structural features, including a 6,5,6-fused tricyclic core, a γ-lactam- or succinimide-containing moiety, a 12- or 13-membered *p*-cyclophane structural motif which encompasses an aryl ether linkage, and ten stereogenic centers. In view of their promising biological properties as lead compounds for new antituberculosis drugs and because of their challenging molecular architectures, the hirsutellones are deemed important synthetic targets.[5] Herein we report the total synthesis of hirsutellone B (**1b**) in its enantiomerically pure form through a strategy that features a number of novel cascade sequences and chemoselective reactions.

From the five rings within the hirsutellone B molecule (**1b**), the most synthetically challenging is the 13-membered *p*-cyclophane, whose strain is exacerbated by the presence of the other structural motifs associated with it. Its forging was therefore designed to proceed through a sequence involving formation of a larger ring and subsequent ring contraction. For the equally intriguing fused tricyclic core of the target molecule, we intended a cascade sequence from an acyclic carbon chain precursor containing an epoxide moiety as an initiating site and a trimethylsilyl group as a terminator. Scheme 1 presents, in retrosynthetic format, the devised



Scheme 1. Retrosynthetic analysis of hirsutellone B (**1b**). TMS = trimethylsilyl.

synthetic strategy for the total synthesis of hirsutellone B (**1b**) as it finally evolved. Thus, the hydroxy γ-lactam moiety was expected to be formed spontaneously from the corresponding keto amide, whose origin was traced back to the styrene-containing *p*-cyclophane **2**. The latter compound was then retrosynthetically expanded to the less strained 14-membered sulfone ring **3** through a Ramberg–Bäcklund reaction. Disassembly of cyclic sulfone **3** with excision of the sulfur atom led to diol **4**, whose further disconnection, as shown in Scheme 1, generated tricyclic core **5** as its possible precursor. Finally, rupture of the three indicated carbon–carbon bonds within **5**, through a [4+2] cycloaddition/ring forming epoxide opening, revealed the TMS-epoxy tetraene **6** as a likely precursor. The latter compound was expected to undergo the designed sequential ring closures upon activation with a suitable Lewis acid to afford stereoselectively the desired [6,5,6]-tricyclic core **5**.

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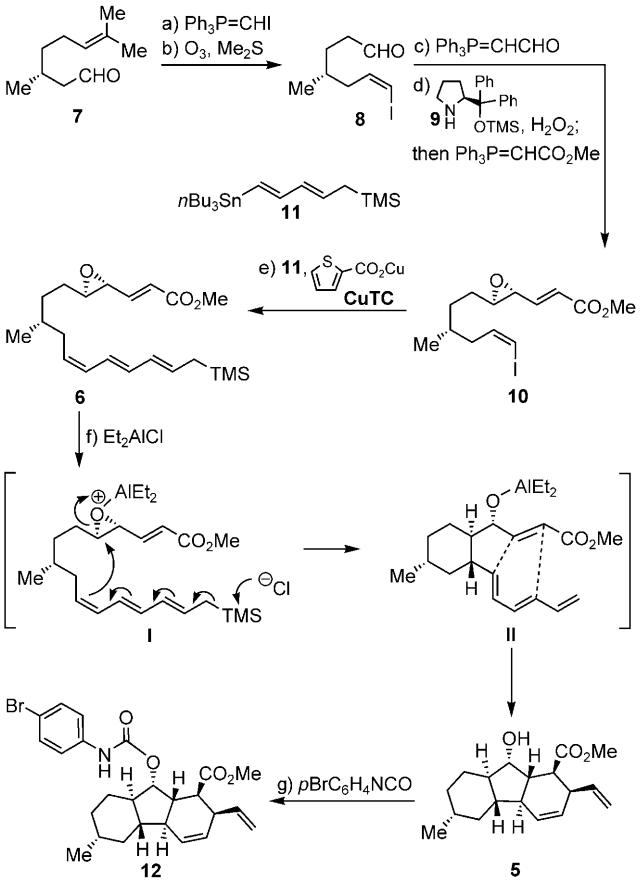
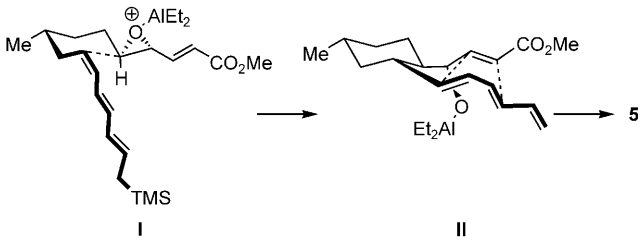
The enantioselective construction of the hirsutellone tricyclic core **5** commenced with (*R*)-(+)-citronellal (**7**) and proceeded as summarized in Scheme 2. Thus, Stork–Zhao olefination of **7** with phosphorane $Ph_3P{=}CHI$ (generated from



Scheme 2. Enantioselective construction of hirsutellone core **5** and carbamate **12**. Reagents and conditions: a) $Ph_3PCH_2I_2$ (1.1 equiv), KHMDS (1.1 equiv), THF, −78→25 °C, 1 h; b) O_3, CH_2Cl_2; then Me_2S (10.0 equiv), −78→25 °C, 10 h, 80% for two steps; c) $Ph_3P{=}CHCHO$ (1.1 equiv), $CHCl_3$, 70 °C, 24 h; d) cat. **9** (10 mol%), H_2O_2 (aq., 35% w/w, 1.3 equiv), 0→25 °C, 8 h, CH_2Cl_2; then $Ph_3P{=}CHCO_2Me$ (1.2 equiv), 25 °C, 1 h, 58% overall yield from **8**; e) **11** (2.0 equiv), CuTC (3.0 equiv), NMP, 25 °C, 6 h, 70%; f) Et_2AlCl (5.0 equiv), CH_2Cl_2, −78→25 °C, 12 h, 50%; g) p-BrC_6H_4NCO (3.0 equiv), 4-DMAP (3.1 equiv), CH_2Cl_2, 0→25 °C, 10 h, quant. KHMDS = potassium hexamethyldisilazide, CuTC = copper(I) thiophene-2-carboxylate, NMP = *N*-methyl-2-pyrrolidinone, 4-DMAP = 4-dimethylaminopyridine.

$Ph_3PCH_2I_2$ and KHMDS)[6] furnished the corresponding *Z*-olefinic iodide, which was subjected to selective ozonolysis to afford iodo aldehyde **8** in 80% overall yield. Reaction of the latter with the stabilized phosphorane $Ph_3P{=}CHCHO$, and subsequent Jørgensen asymmetric epoxidation[7] of the resulting α,β-unsaturated aldehyde, with H_2O_2 in the presence of proline-derived catalyst **9**,[7b] resulted in the formation of the expected epoxy aldehyde, whose condensation with $Ph_3P{=}CHCO_2Me$ furnished epoxy ester iodide **10** (58% overall yield). Coupling of olefinic iodide **10** with the stannane TMS derivative **11**[8] in the presence of CuTC[9] led to cyclization precursor **6** in 70% yield. The much anticipated intramolecular epoxide opening/Diels–Alder reaction was induced by Et_2AlCl (CH_2Cl_2, −78→25 °C) to afford the targeted tricyclic core **5** in 50% yield as a single diastereoisomer. It is assumed that this highly productive reaction proceeds through species **I** (Lewis acid activation), leading to intermediate **II** [of which the protonated form (**6a**, not shown) was isolated and fully characterized], which then undergoes reaction (under the Lewis acid conditions) to give the final product (**5**).

The stereochemical outcome of the first ring closure involved in this cascade is a consequence of the preferred transition-state conformation **I** (shown in Scheme 3), whereas



Scheme 3. Postulated preferred transition-state conformations of **I** and **II** leading to tricyclic core product **5**.

endo transition-state **II** (Scheme 3) explains the stereoselectivity of the incipient [4+2] cycloaddition reaction to afford product **5** exclusively. The structure of **5** was determined by NMR spectroscopic means and was confirmed unambiguously through X-ray crystallographic analysis of its carbamate derivative **12**[10] [prepared from **5** by reaction with p-BrC_6H_4NCO and 4-DMAP, quant.; m.p. 215 °C (hexanes/CH_2Cl_2), see ORTEP drawing, Figure 2].[10]

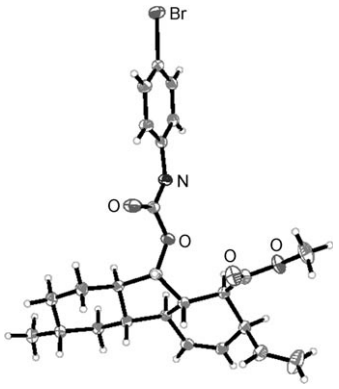
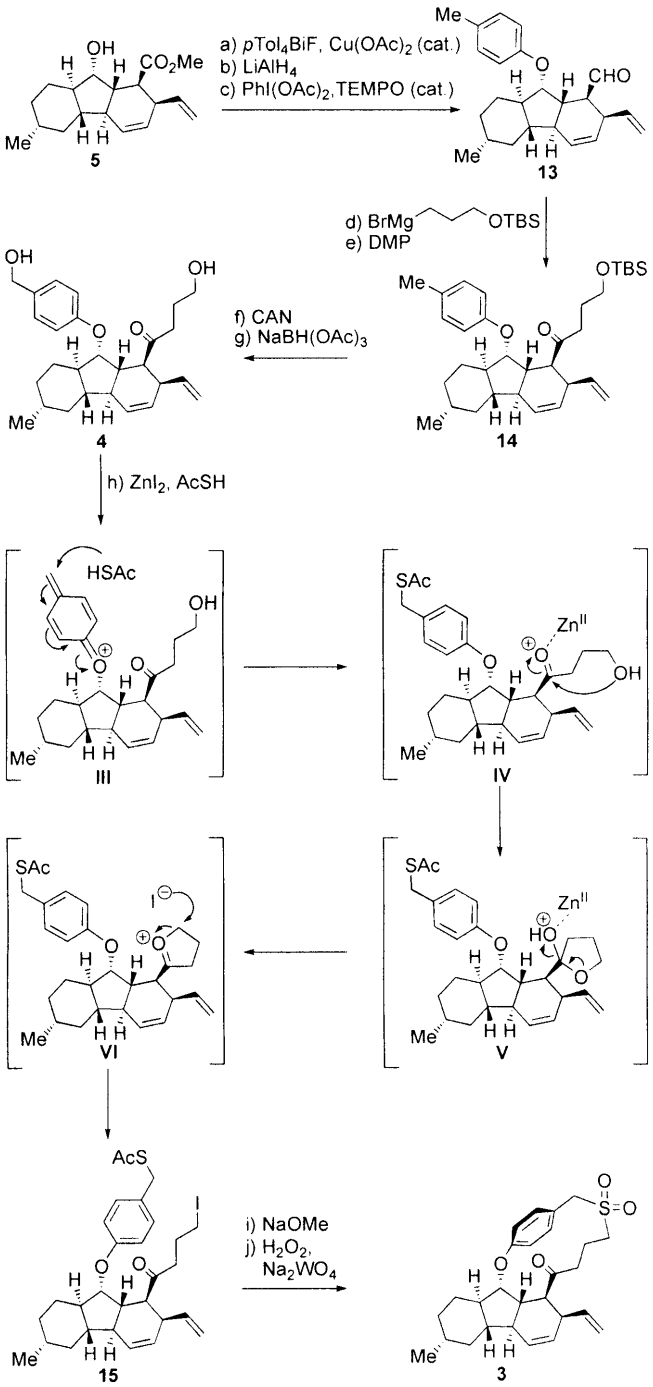


Figure 2. X-ray derived ORTEP drawing of carbamate **12** (thermal ellipsoids at 30% probability).

Having reached the tricyclic core **5** of the hirsutellone molecule, its elaboration into the macrocyclic sulfone **3** became our next objective. Scheme 4 details the conversion of **5** into **3** through a sequence that involved a Barton etherification,[11] a cascade-based selective functionalization of a diol, and a macrocyclization. Thus, hydroxy methyl ester **5** was reacted with p-Tol_4BiF in the presence of Cy_2NEt and

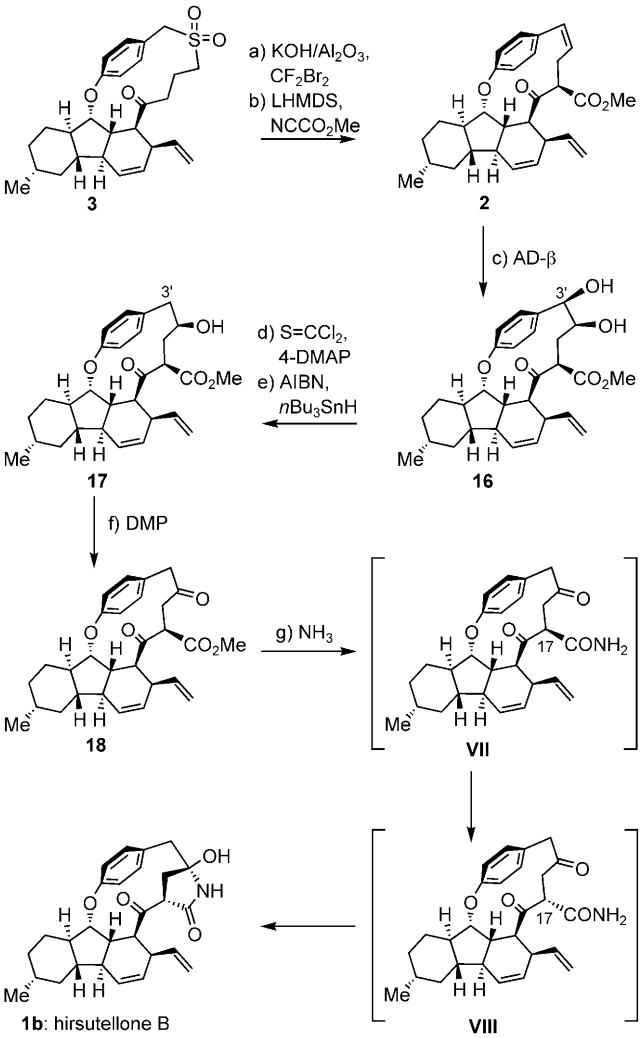


Scheme 4. Construction of sulfone **3**. Reagents and conditions: a) pTol$_4$BiF (2.5 equiv), Cy_2NMe (2.5 equiv), $Cu(OAc)_2$ (20 mol%), PhMe, 25 °C, 12 h; b) $LiAlH_4$ (3.0 equiv), Et_2O, 0→25 °C, 2.5 h; c) TEMPO (0.2 equiv), $PhI(OAc)_2$ (1.5 equiv), CH_2Cl_2, 25 °C, 12 h, 78% for three steps; d) $BrMg(CH_2)_3OTBS$ (3.0 equiv), THF, 0→25 °C, 5 h; e) DMP (1.3 equiv), CH_2Cl_2, 0→25 °C, 2 h, 91% for two steps; f) CAN (5.0 equiv), MeCN/H_2O (20:1), 25 °C, 2.5 h; g) $NaBH(OAc)_3$ (5.0 equiv), PhH, 25 °C, 12 h, 81% for two steps; h) ZnI_2 (5.0 equiv), AcSH (2.0 equiv), CH_2Cl_2, 25 °C, 6 h, 68%; i) NaOMe (1.4 equiv), MeOH/THF (1:1, 1.0 mM), 25 °C, 36 h; j) H_2O_2 (aq., 35% w/w, 15 equiv), Na_2WO_4 (1.0 equiv), THF/MeOH (1:1), 0→25 °C, 2 h, 79% for two steps. Cy = cyclohexyl, Ac = acetyl, TEMPO = 2,2,6,6-tetramethylpiperidine-1-oxyl, TBS = *tert*-butyldimethylsilyl, DMP = Dess–Martin periodinane, CAN = cerium(IV) ammonium nitrate, THF = tetrahydrofuran.

catalytic amounts of $Cu(OAc)_2$ according to the improved etherification protocol of Mukaiyama et al.,[12] and the resulting aryl ether methyl ester was reduced with $LiAlH_4$ to afford, after oxidation with $PhI(OAc)_2$-TEMPO, aldehyde **13** (78% overall yield for three steps). Extension of the carbonyl side chain of **13** was accomplished by addition of $TBSOCH_2CH_2CH_2MgBr$ and subsequent oxidation of the resulting secondary alcohol with DMP to give ketone **14** in 91% overall yield. Functionalization of the aryl methyl group in **14** to give the desired dihydroxy compound **4** was then carried out with CAN in aqueous MeCN (oxidation/desilylation) and subsequent reduction of the resulting aldehyde with $NaBH(OAc)_3$ (81% overall yield for the two steps). Diol **4** was then exposed to the action of ZnI_2 and AcSH in CH_2Cl_2 at ambient temperature,[13] conditions that facilitated its chemoselective conversion into iodo thioacetate **15** (68% yield), presumably through the cascade involving reactive species **III**–**VI**, as shown in Scheme 4. Treatment of the iodo thioacetate **15** with NaOMe in THF/MeOH (1:1) at ambient temperature and then oxidation of the resulting macrocyclic sulfide with H_2O_2 and Na_2WO_4 furnished targeted macrocyclic sulfone **3** in 79% overall yield for the two steps (deacetylation/cyclization, oxidation).

With the 14-membered macrocyclic sulfone **3** in hand, its contraction to a 13-membered macrocyclic olefin and additional functionalization to give hirsutellone B (**1b**) became possible as demonstrated in Scheme 5. Thus, treatment of sulfone **3** with alumina-impregnated KOH (KOH/Al_2O_3) in the presence of CF_2Br_2 in CH_2Cl_2/tBuOH (1:1) at 0→25 °C led to the corresponding olefin (exclusively Z and in high yield) through a Ramberg–Bäcklund reaction.[14] Diastereoselective carboxymethylation of this product (LHMDS, $NCCO_2Me$) then furnished keto ester **2** (61% overall yield for two steps).[15] From the three olefinic bonds of tetracycle **2**, the one residing within the strained 13-membered p-cyclophane ring proved the most reactive towards AD-mix-β ($MeSO_2NH_2$, tBuOH/H_2O (1:1), ambient temperature),[16] allowing efficient generation of diol **16**, which was formed as a single crystalline diastereoisomer in 90% yield (m.p. 191–192 °C; hexane/EtOAc). Its structure was unambiguously proven by X-ray crystallographic analysis (see ORTEP drawing, Figure 3).[17]

The benzylic nature of the C3′ hydroxy group of **16** facilitated its selective removal through Barton deoxygenation (nBu$_3$SnH, AIBN) of its thionocarbonate (prepared by exposure to Cl_2C=S and 4-DMAP), leading to hydroxy ester **17** (65% overall yield for two steps). Oxidation of alcohol **17** with DMP proceeded smoothly to afford keto ester **18** in 92% yield. Finally, heating of **18** with NH_3 in MeOH/H_2O (1:1) at 120 °C for 1 h led to hirsutellone B (**1b**) in 50% yield [18] through a cascade sequence involving amidation, epimerization (at C17) and cyclization (through transient intermediates **VII** and **VIII**, Scheme 5).[18] The physical properties (^{1}H and ^{13}C NMR, MS data) of synthetic hirsutellone B matched those reported for the natural material.[1a] Its optical rotation {$[\alpha]_D^{27} = +250$ ($c = 0.14$, MeOH)} was essentially identical to that of the natural substance {$[\alpha]_D^{25} = +256$ ($c = 0.20$, MeOH)},[1a] proving the absolute configuration of hirsutellone B as that shown in structure **1b**.



Scheme 5. Completion of the total synthesis of hirsutellone B (**1b**). Reagents and conditions: a) CF_2Br_2 (5.0 equiv), KOH/Al_2O_3 (15% w/w, 2 g per mmol), CH_2Cl_2/*t*BuOH (1:1), 0→25 °C, 2 h; b) LHMDS (3.3 equiv), $NCCO_2Me$ (8.3 equiv), THF, −78→−50 °C, 0.5 h, 61% for two steps; c) AD-mix-β (1.0 equiv), $MeSO_2NH_2$ (1.7 equiv), *t*BuOH/H_2O (1:1), 25 °C, 18 h, 90%; d) $S{=}CCl_2$ (1.5 equiv), 4-DMAP (3.0 equiv), CH_2Cl_2, 0→25 °C, 1 h; e) AIBN (2.0 equiv), nBu_3SnH (10 equiv), PhMe, 100 °C, 2 h, 65% for two steps; f) DMP (2.0 equiv), CH_2Cl_2, 25 °C, 2 h, 92%; g) NH_3, MeOH/H_2O (4:1), 120 °C, 1 h, 50%. LHMDS = lithium hexamethyldisilazide.

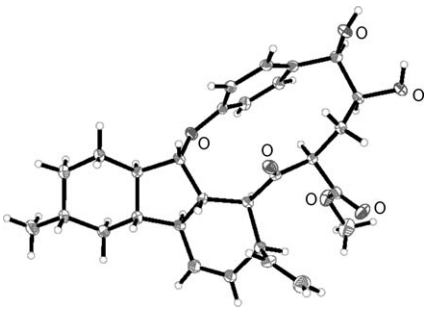


Figure 3. X-ray derived ORTEP drawing of diol **16** (thermal ellipsoids at 30% probability).

The described chemistry renders hirsutellone B (**1b**) readily available through chemical synthesis, and opens the way for the total synthesis of its naturally occurring siblings and designed analogues for chemical biology and medicinal chemistry studies directed toward the development of new antituberculosis drugs.[4] Furthermore, the employed synthetic strategy features a number of novel cascade reactions[19] that may find further applications in complex molecule construction.

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[18] The corresponding decarboxymethylation compound (1,4-diketone **18a**, not shown) was also observed as a side product in this reaction. The likely formation of imine moieties at the two carbonyl sites of substrate **18** is reversible under the reaction conditions (i.e. H_2O), thus allowing the eventual generation of the product (i.e. **1b**). An alternative mechanism may involve initial attack of NH_3 at the C2′ carbonyl group and subsequent ring closure.

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