Published in final edited form as:

Angew Chem Int Ed Engl. 2009 ; 48(37): 6870–6874. doi:10.1002/anie.200903382.

Total Synthesis of Hirsutellone B**

K. C. Nicolaou*, David Sarlah, T. Robert Wu, and Weiqiang Zhan

Department of Chemistry and The Skaggs Institute for Chemical Biology The Scripps Research Institute, 10550 North Torrey Pines Road, La Jolla, CA 92037 (USA)

Keywords

antituberculosis; cascade; reactions; natural; product; total; synthesis

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 tuberculosis* (MIC = 0.78 µg/mL), 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 that 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 followed by 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. Figure 2 presents, in retrosynthetic format, the devised synthetic strategy for the total synthesis of hirsutellone B (**1b**) as it finally evolved. Thus, the hydroxyl 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 Figure 2, 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 TMS epoxy tetraene **6** as a likely precursor. The latter compound was expected to undergo the designed

**We gratefully acknowledge financial support from the National Institutes of Health (USA), National Science Foundation (CHE-0603217), Natural Sciences and Engineering Research Council, Canada (postdoctoral fellowship to T.R.W.) and Skaggs Institute for Research. We thank Dr. M. Isaka and Prof. Y. Thebtaranonth for NMR spectra of natural hirsutellone B.

* Department of Chemistry and Biochemistry, University of California, San Diego, 9500 Gilman Drive, La Jolla, CA 92093 (USA), Fax: (+1) (858) 784-2469, kcn@scripps.edu.

Supporting information for this article is available on the WWW under <http://www.angewandte.org> or from authors.

sequential ring closures upon activation with a suitable Lewis acid to afford stereoselectively the desired [6,5,6]-tricyclic core **5**.

The enantioselective construction of the hirsutellone tricyclic core **5** commenced with (*R*)-(+)-citronellal (**7**) and proceeded as summarized in Scheme 1. Thus, Stork-Zhao olefination of **7** with phosphorane $\text{Ph}_3\text{P}=\text{CHI}$ (generated from $\text{Ph}_3\text{PCH}_2\text{I}_2$ 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 $\text{Ph}_3\text{P}=\text{CHCHO}$, followed by 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 $\text{Ph}_3\text{P}=\text{CHCO}_2\text{Me}$ furnished epoxy ester iodide **10** (58 % overall yield). Coupling of olefinic iodide **10** with 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 , $-78 \rightarrow 25^\circ\text{C}$) 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 undergoes further reaction (under the Lewis acid conditions) to 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 Figure 3), whereas endo transition state **II** (Figure 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 $p\text{BrC}_6\text{H}_4\text{NCO}$ and 4-DMAP, quant.; m.p. 215°C (hexanes/ CH_2Cl_2), see ORTEP drawing, Figure 4].^[10]

Having reached the tricyclic core **5** of the hirsutellone molecule, its further elaboration to macrocyclic sulfone **3** became our next objective. Scheme 2 details the conversion of **5** to **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 $p\text{Tol}_4\text{BiF}$ in the presence of Cy_2NEt and catalytic amounts of $\text{Cu}(\text{OAc})_2$ 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 $\text{PhI}(\text{OAc})_2\text{--TEMPO}$, aldehyde **13** (80 % overall yield for three steps). Extension of the carbonyl side chain of **13** was accomplished by addition of $\text{TBSOCH}_2\text{CH}_2\text{CH}_2\text{MgBr}$, followed by 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 the desired bis-diol **4** was then carried out with CAN in aq. MeCN (oxidation/desilylation) followed by subsequent reduction of the resulting aldehyde with $\text{NaBH}(\text{OAc})_3$ (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 to iodo thioacetate **15** (68 % yield), presumably through the cascade involving reactive species **III–VI**, as shown in Scheme 2. Treatment of iodo thioacetate **15** with NaOMe in $\text{THF}:\text{MeOH}$ at ambient temperature, followed by oxidation of the resulting macrocyclic sulfide with $\text{H}_2\text{O}_2\text{--Na}_2\text{WO}_4$, furnished targeted macrocyclic sulfone **3** in 79 % overall yield for the two steps (deacetylation/cyclization, oxidation).

With 14-membered macrocyclic sulfone **3** in hand, its contraction to a 13-membered macrocyclic olefin and further functionalization to hirsutellone B (**1b**) became possible as demonstrated in Scheme 3. Thus, treatment of sulfone **3** with alumina-impregnated KOH ($\text{KOH}/\text{Al}_2\text{O}_3$) in the presence of CF_2Br_2 in $\text{CH}_2\text{Cl}_2:\text{tBuOH}$ at $0 \rightarrow 25^\circ\text{C}$ 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 (MeSO₂NH₂, *t*BuOH:H₂O, 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 5). [17]

The benzylic nature of the C–3' hydroxy group of **16** facilitated its selective removal through Barton deoxygenation (*n*Bu₃SnH, AIBN) of its thionocarbonate (prepared by exposure to Cl₂C=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 NH₃ in MeOH:H₂O at 120 °C for 1 h led to hirsutellone B (**1b**) in 50 % yield,[18] through a cascade sequence involving amidation, epimerization (at C–17), and cyclization (through transient intermediates **VII** and **VIII**, Scheme 3).[18] The physical properties (¹H and ¹³C NMR, mass spec) of synthetic hirsutellone B matched those reported for the natural material.[1a] Its optical rotation {[α]_D²⁵ = +250 (*c* = 0.14, MeOH)} was essentially identical to that of the natural substance {[α]_D²⁵ = +256 (*c* = 0.20, MeOH)},[1a] proving the absolute configuration of hirsutellone B as that shown in structure **1b**.

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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

References

1. a) Isaka M, Rugseree N, Maithip P, Kongsaree P, Prabpai S, Thebtaranonth Y. Tetrahedron 2005;61:5577–5583. b) Isaka M, Prathumpai W, Wongsap P, Tanticharoen M. Org Lett 2006;8:2815–2817. [PubMed: 16774264]
2. Shiono Y, Shimanuki K, Hiramatsu F, Koseki T, Tetsuya M, Fujisawa N, Kimura K. Bioorg Med Chem Lett 2008;18:6050–6053. [PubMed: 18952424]
3. He H, Yang HY, Bigelis R, Solum EH, Greenstein M, Carter GT. Tetrahedron Lett 2002;43:1633–1636.
4. For selected reviews on this topic, see: a) Sacchettini JC, Rubin EJ, Freundlich JS. Nat Rev Microbiol 2008;6:41–52. [PubMed: 18079742] b) Cohn DL, Bustreo F, Raviglione MC. Clin Infect Dis 1997;24:S121–S130. [PubMed: 8994791] c) Tripathi RP, Tewari N, Dwivedi N, Tiwari VK. Med Res Rev 2005;25:93–131. [PubMed: 15389729]
5. For previous studies toward the total synthesis of hirsutellones, see: a) Tilley SD, Reber KP, Sorensen EJ. Org Lett 2009;11:701–703. [PubMed: 19119873] b) Huang M, Huang C, Liu B. Tetrahedron Lett 2009;50:2797–2800.
6. Stork G, Zhao K. Tetrahedron Lett 1989;30:2173–2174.
7. a) Marigo M, Franzén J, Poulsen TB, Zhuang W, Jørgensen KA. J Am Chem Soc 2005;127:6964–6965. [PubMed: 15884935] b) Hayashi Y, Gotoh H, Hayashi T, Shoji M. Angew Chem 2005;117:4282–4287. Angew Chem Int Ed 2005;44:4212–4215.
8. Stannane **11** was prepared by Negishi coupling of (*E*)-*n*Bu₃SnCH=CHZnCl and (*E*)-ICH=CHCH₂TMS using Pd(PPh₃)₄ as a catalyst.
9. Allred GD, Liebeskind LS. J Am Chem Soc 1996;118:2748–2749.

10. CCDC 736469 (*p*-bromophenyl carbamate **12**) contains the supplementary crystallographic data for this compound. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
11. Abramovitch RA, Barton DHR, Finet KP. *Tetrahedron* 1988;44:3039–3071. and references therein.
12. Mukaiyama T, Sakurai N, Ikegai K. *Chem Lett* 2006;35:1140–1141.
13. Gauthier JY, Bourdon F, Young RN. *Tetrahedron Lett* 1986;27:15–18.
14. Chan TL, Fong S, Li Y, Man TO, Poon CD. *J Chem Soc, Chem Commun* 1994:1771–1772.
15. The isomeric *O*-carboxymethylated compound was also isolated as a minor product (20 % yield) in this reaction.
16. Jacobsen EN, Marko I, Mungall WS, Schröder G, Sharpless KB. *J Am Chem Soc* 1988;110:1968–1970.
17. CCDC 736468 (diol **16**) contains the supplementary crystallographic data for this compound. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
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. H₂O), thus allowing the eventual generation of the product (i.e. **1b**). An alternative mechanism may involve initial attack of NH₃ at the C–2' carbonyl group followed by ring closure.
19. For selected reviews, see: a) Nicolaou KC, Montagnon T, Snyder SA. *Chem Commun* 2003:551–564. b) Tietze, LF.; Brasche, G.; Gericke, K. *Domino Reactions in Organic Synthesis*. Wiley-VCH; Weinheim: 2006. p. 672 c) Nicolaou KC, Edmonds DJ, Bulger PG. *Angew Chem* 2006;118:7292–7344. *Angew Chem Int Ed* 2006;45:7134–7186.

1a: hirsutellone A

1b: hirsutellone B

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

Figure 2.
Retrosynthetic analysis of hirsutellone B (**1b**).

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

Figure 4.
X-ray derived ORTEP drawing of carbamate **12** (thermal ellipsoids at 30 % probability); gray C, green H, blue N, red O.

Figure 5.
X-ray derived ORTEP drawing of diol **16** (thermal ellipsoids at 30 % probability); gray C, green H, blue N, red O.

Scheme 1.

Enantioselective construction of hirsutellone core **5** and carbamate **12**. Reagents and conditions: a) $\text{Ph}_3\text{PCH}_2\text{I}_2$ (1.1 equiv), KHMDS (1.1 equiv), THF , $-78 \rightarrow 25^\circ\text{C}$, 1 h; b) O_3 , CH_2Cl_2 ; then Me_2S (10.0 equiv), $-78 \rightarrow 25^\circ\text{C}$, 10 h, 80 % for two steps; c) $\text{Ph}_3\text{P}=\text{CHCHO}$ (1.1 equiv), CHCl_3 , 70°C , 24 h; d) cat. **9** (10 mol %), H_2O_2 (aq., 35 % w/w, 1.3 equiv), $0 \rightarrow 25^\circ\text{C}$, 8 h, CH_2Cl_2 ; then $\text{Ph}_3\text{P}=\text{CHCO}_2\text{Me}$ (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 , $-78 \rightarrow 25^\circ\text{C}$, 12 h, 50 %; g) $p\text{BrC}_6\text{H}_4\text{NCO}$ (3.0 equiv), 4-DMAP (3.1 equiv), CH_2Cl_2 , $0 \rightarrow 25^\circ\text{C}$, 10 h, quant. KHMDS = potassium hexamethyldisilazide, CuTC = copper(I) thiophene-2-carboxylate, NMP = *N*-methyl-2-pyrrolidinone.

Scheme 2.

Construction of sulfone **3**. Reagents and conditions: a) $p\text{Tol}_4\text{BiF}$ (2.5 equiv), Cy_2NMe (2.5 equiv), $\text{Cu}(\text{OAc})_2$ (20 mol %), PhMe , 25°C , 12 h; b) LiAlH_4 (3.0 equiv), Et_2O , $0 \rightarrow 25^\circ\text{C}$, 2.5 h; c) TEMPO (0.2 equiv), $\text{PhI}(\text{OAc})_2$ (1.5 equiv), CH_2Cl_2 , 25°C , 12 h, 78 % for three steps; d) $\text{BrMg}(\text{CH}_2)_3\text{OTBS}$ (3.0 equiv), THF , $0 \rightarrow 25^\circ\text{C}$, 5 h; e) DMP (1.3 equiv), CH_2Cl_2 , $0 \rightarrow 25^\circ\text{C}$, 2 h, 91 % for two steps; f) CAN (5.0 equiv), $\text{MeCN}:\text{H}_2\text{O}$ (20:1), 25°C , 2.5 h; g) $\text{NaBH}(\text{OAc})_3$ (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), $\text{MeOH}:\text{THF}$ (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), $\text{THF}:\text{MeOH}$ (1:1), $0 \rightarrow 25^\circ\text{C}$, 2 h, 79 % for two steps. Ac = acetyl, TEMPO = 2,2,6,6-tetramethylpiperidine-1-oxyl, TBS =

tert-butyldimethylsilyl, DMP = Dess–Martin periodinane, CAN = cerium(IV) ammonium nitrate, THF = tetrahydrofuran.

Scheme 3.

Completion of the total synthesis of hirsutellone B (**1b**). Reagents and conditions: a) CF₂Br₂ (5.0 equiv), KOH/Al₂O₃ (15 % w/w, 2 g per mmol), CH₂Cl₂/*t*BuOH (1:1), 0→25 °C, 2 h; b) LHMDS (3.3 equiv), NCCO₂Me (8.3 equiv), THF, -78→-50 °C, 0.5 h, 61 % for two steps; c) AD-mix-β (1.0 equiv), MeSO₂NH₂ (1.7 equiv), *t*BuOH/H₂O (1:1), 25 °C, 18 h, 90 %; d) S=CCl₂ (1.5 equiv), 4-DMAP (3.0 equiv), CH₂Cl₂, 0→25 °C, 1 h; e) AIBN (2.0 equiv), *n*Bu₃SnH (10 equiv), PhMe, 100 °C, 2 h, 65 % for two steps; f) DMP (2.0 equiv), CH₂Cl₂, 25 °C, 2 h, 92 %; g) NH₃, MeOH/H₂O (4:1), 120 °C, 1 h, 50 %. LHMDS = lithium hexamethyldisilazide, 4-DMAP = 4-dimethylaminopyridine.