Total Synthesis of (+)-Cephalosporolide E and (–)-Cephalosporolide F en route to Bassianolone

Rodney A. Fernandes,* Arun B. Ingle

Department of Chemistry, Indian Institute of Technology Bombay, Powai 400076 Mumbai, Maharashtra, India
Fax +91(22)25767152; E-mail: rfernand@chem.iitb.ac.in

Received 22 September 2009

Abstract: A stereoselective synthesis of (+)-cephalosporolide E and (–)-cephalosporolide F en route to bassianolone is described. The key steps involve cross metathesis to get the desired β,γ-unsaturated ester, asymmetric dihydroxylation to install the β-hydroxy-γ-lactone moiety and spiroketalization. Although attempts to get free bassianolone failed, the first total synthesis of natural cephalosporolides E and F has been achieved in nine steps and 6.3% and 3.5% overall yields, respectively.

Key words: bassianolone, cephalosporolides, cross metathesis, asymmetric dihydroxylation, spiroketalization

In 2005, Oltra and co-workers[1] isolated (+)-bassianolone (**1**), a rare antimicrobial precursor of cephalosporolides E (**2**) and F (**3**) from the entomoparasitic fungus *Beauveria bassiana* (Figure 1). The chemical structure of **1** was established by NMR study of its bisacetate derivative, and the relative and absolute configuration was ascertained by chemical correlation with **2** and **3**.[1] It was also converted into cephalosporolides E and F by passing through a pad of silica gel where it undergoes spiroketalization. This confirmed the relative (3*S**,4*S**,9*R**) configurations.[1] Cephalosporolides E and F were isolated by Hanson and co-workers[2] from the fungus *Cephalosporium aphidicola* and later by Rukachaisirikul and co-workers[3] from the entomopathogenic fungus *Cordyceps militaris* BCC 2816. These are believed to be simple artifacts formed during the isolation process. However, the presence of spirotricyclic core in several other isolated natural products[4] augments that these could be of natural origin. We planned to synthesize (+)-bassianolone (**1**) and found that, under normal laboratory conditions, it was indeed difficult to suppress its spiroketalization, giving **2** and **3**. Hence in this paper we discuss the first total synthesis of natural cephalosporolides E and F en route to bassianolone. There is only one synthesis reported in the literature on unnatural (–)-cephalosporolide E and (+)-cephalosporolide F.[5]

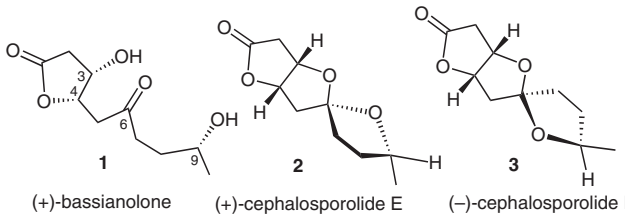
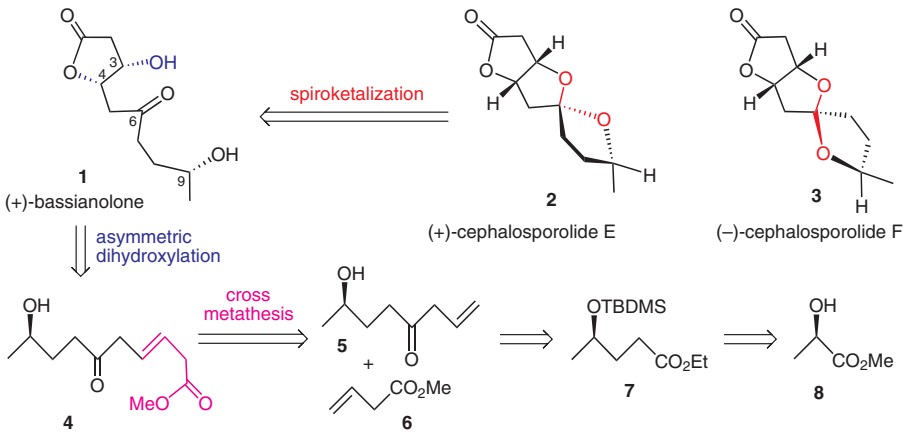


Figure 1 (+)-Bassianolone and cephalosporolides E and F

Our synthesis is based on the separation of cephalosporolides E and F formed after spiroketalization of bassianolone (**1**) as shown in our retrosynthetic analysis (Scheme 1). Bassianolone (**1**) can be visualized to be obtained by asymmetric dihydroxylation of the β,γ-unsaturated ester **4** with concomitant lactonization. Compound **4** can be assembled by a cross metathesis of olefin fragments **5** and **6**. The compound **5** can be derived from **7**

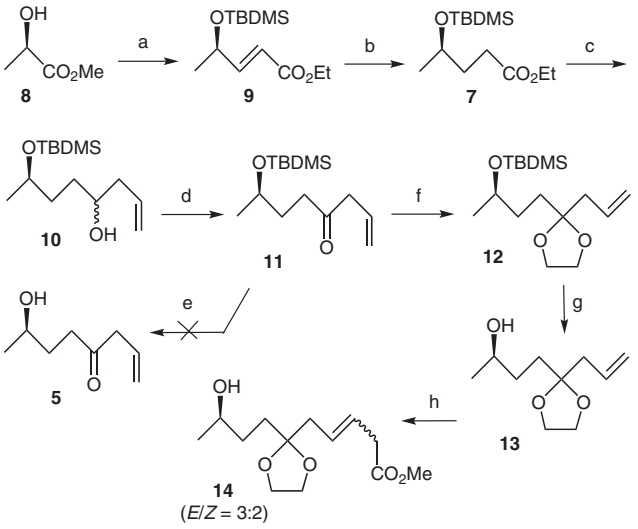


Scheme 1 Retrosynthetic analysis of bassianolone and cephalosporolides E and F

SYNLETT 2010, No. 1, pp 0158–0160
Advanced online publication: 01.12.2009
DOI: 10.1055/s-0029-1218538; Art ID: G30709ST

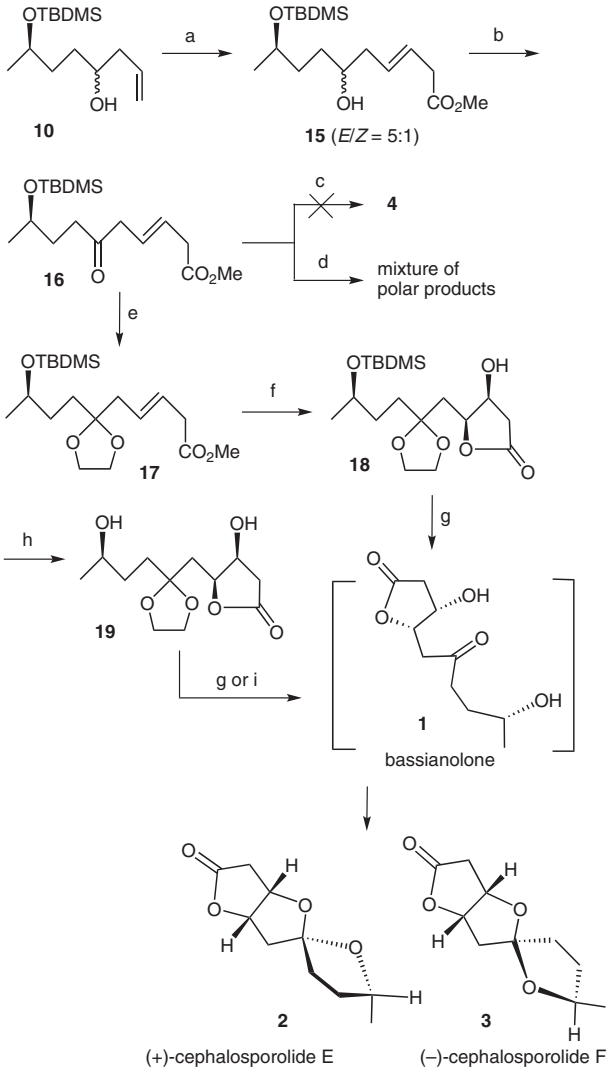
through allyl addition, and the latter can be readily elaborated from commercially available (*R*)-methyl lactate (**8**), which fixes the desired (9*R*) configuration.

We first attempted the synthesis of olefin fragment **5** as shown in Scheme 2. Protection of the hydroxyl group in (*R*)-methyl lactate (**8**) as *tert*-butyldimethylsilyl ether followed by reduction of the ester, and Wittig olefination of the resulting aldehyde provided ester **9**[6] in 82% overall yield. Double-bond reduction by catalytic hydrogenation gave the ester **7** in excellent yields (98%). Sequential reduction of the ester group in **7** to the aldehyde, subsequent allyl Grignard addition to give the alcohol **10** (92% over two steps), and further PCC oxidation gave the desired ketone **11**. All attempts to remove the TBDMS group either using TBAF–THF or 2 M HCl–MeOH or PTSA–MeOH to get **5** gave a complex mixture. Closer analysis of this mixture indicated products formed by partial isomerization of the double bond to the α,β-position and acetal formation due to the γ-hydroxyl group. To overcome this, the ketone functionality was protected as ketal **12** in 77% yield. Subsequent deprotection of the TBDMS ether afforded the alcohol **13**. A cross-metathesis[7] reaction of **13** with **6** using Grubbs second-generation catalyst gave the β,γ-unsaturated ester **14** (76%), however, with poor *E*/*Z* (3:2) selectivity.



Scheme 2 Attempted synthesis of **5** and cross metathesis. *Reagents and conditions*: (a) (i) imidazole (1.2 equiv), TBDMSCl (1.1 equiv), CH_2Cl_2, r.t., 12 h; (ii) DIBAL-H (1.0 equiv), CH_2Cl_2, –78 °C, 1.5 h; (iii) $Ph_3P{=}CHCO_2Et$ (1.2 equiv), THF, r.t., 12 h, 82% overall; (b) H_2/Pd-C, EtOH, r.t., 12 h, 98%; (c) (i) DIBAL-H (1.05 equiv), CH_2Cl_2, –78 °C, 1.5 h; (ii) allylMgCl (1.2 equiv), THF, 0 °C, 1 h, r.t., 1 h, 92%; (d) PCC (2.0 equiv), NaOAc (2.0 equiv), CH_2Cl_2, 0 °C to r.t., 4 h, 83%; (e) Bu_4NF (2.0 equiv), THF, r.t., 2 h; or 2 N HCl, MeOH, r.t., 4 h; or PTSA (cat), MeOH, r.t., 4 h; (f) $(CH_2OH)_2$ (30.0 equiv), PTSA (cat), C_6H_6, reflux, 14 h, 77%; (g) Bu_4NF (2.0 equiv), THF, r.t., 2 h, 75%; (h) Grubbs II, **6** (5.0 equiv), CH_2Cl_2, reflux, 12 h, 76%.

We then moved our attention to the cross metathesis of olefin fragments **10** and **6** (Scheme 3). Overwhelmingly, compound **15** was obtained with improved *E*/*Z* selectivity of calculated 5:1 (82%). IBX oxidation of alcohol **15** afforded the ketone **16** in good yields (89%). Further the removal of TBDMS group failed to deliver compound **4**. Hence we attempted asymmetric dihydroxylation[8] of olefin **16**. This afforded an inseparable mixture of polar products. These could arise from initial dihydroxylation, concomitant lactonization, and subsequent acetalization of the C-3 hydroxy group with the ketone functionality. However, the products formed at various stages of this sequence could not be separated for analysis. We then moved our attention to protect the ketone functionality. Thus ketalization of **16** with ethylene glycol provided **17** (77%). Subsequent asymmetric dihydroxylation of **17** cleanly afforded the lactone **18** as a single diastereomer in



Scheme 3 Synthesis of cephalosporolides E and F en route to bassianolone. *Reagents and conditions*: (a) Grubbs II, **6** (5.0 equiv), CH_2Cl_2, reflux, 12 h, 82%; (b) IBX (1.6 equiv), EtOAc, reflux, 6 h, 89%; (c) Bu_4NF (2.0 equiv), THF, r.t., 2 h; (d) $K_3Fe(CN)_6$, K_2CO_3, $MeSO_4NH_2$, $(DHQ)_2PHAL$, $K_2OsO_4{\cdot}2H_2O$, *t*-BuOH–H_2O (1:1), 0 °C, 24 h; (e) $(CH_2OH)_2$ (30.0 equiv), PTSA (cat.), C_6H_6, reflux, 14 h, 77%; (f) $K_3Fe(CN)_6$, K_2CO_3, $MeSO_4NH_2$, $(DHQ)_2PHAL$, $K_2OsO_4{\cdot}2H_2O$, *t*-BuOH–H_2O (1:1), 0 °C, 24 h, 70%; (g) 2 N HCl, MeOH, r.t., 8 h or PTSA (cat.), MeOH, r.t., 8 h; (h) Bu_4NF (1.5 equiv), THF, r.t., 2 h, 70%; (i) CAN (2.5 equiv), MeCN–H_2O (1:1), 70 °C, 5 min, **2** (59%), **3** (33%).

good yield (70%).[9] The acid-catalyzed deprotection of TBDMS ether and the ketal group failed to deliver free bassianolone (**1**) in a single step. A stepwise removal of TBDMS group first, followed by the ketal group, was executed. The compound **18** when treated with excess of TBAF, deprotection of the ketal group was also observed giving the mixture of **2** and **3**, and no free bassianolone was obtained. When compound **18** was treated with 1.5 equivalents of TBAF, the deprotection of only TBDMS ether was observed to give **19** (70%).[10] All attempts under varied acid-catalyzed conditions to deprotect the ketal functionality proved futile to obtain free bassianolone. In all cases the mixture of **2** and **3** was obtained in variable yields. In one of the attempts with CAN-mediated[11] deprotection of the ketal functionality a cleaner deprotection–spiroketalization occurred affording **2** and **3** in higher yields. The crude mixture of **2** and **3** was easily separated by flash column chromatography providing **2** (59%) and **3** (33%). The spectral and analytical data of (+)-cephalosporolide E (**2**) along with its optical rotation $[\alpha]_D^{25}$ +49.2 (*c* 0.25, $CHCl_3$) were in excellent agreement with that reported {lit.[2] $[\alpha]_D^{30}$ +51.3 (*c* 0.42, $CHCl_3$)}.[2] Similarly, (–)-cephalosporolide F (**3**) had $[\alpha]_D^{25}$ –69.1 (*c* 0.15, $CHCl_3$) {lit.[1] $[\alpha]_D^{25}$ –33.3 (*c* 0.79, $CHCl_3$) and lit.[5] $[\alpha]_D^{25}$ +95.2 (*c* 0.9, $CHCl_3$) for its enantiomer}. The spectral data for (–)-cephalosporolide F (**3**) matched well with that reported.[2]

In summary, the first total synthesis of natural (+)-cephalosporolide E and (–)-cephalosporolide F has been achieved starting from (*R*)-methyl lactate and employing cross metathesis, asymmetric dihydroxylation, and spiroketalization as the key steps. The synthesis is completed in nine steps and overall yields of 6.3% and 3.5% for **2** and **3**, respectively.

Acknowledgment

Financial support by IRCC, Indian Institute of Technology Bombay is gratefully acknowledged. A.B.I. thanks CSIR New Delhi for a research fellowship.

References and Notes

(1) Oller-López, J. L.; Iranzo, M.; Mormeneo, S.; Oliver, E.; Cuerva, J. M.; Oltra, J. E. *Org. Biomol. Chem.* **2005**, *3*, 1172.
(2) Ackland, M. J.; Hanson, J. R.; Hitchcock, P. B.; Ratcliffe, A. H. *J. Chem. Soc., Perkin Trans. 1* **1985**, 843.
(3) Rukachaisirikul, V.; Pramjit, S.; Pakawatchai, C.; Isaka, M.; Supothina, S. *J. Nat. Prod.* **2004**, *67*, 1953.
(4) (a) Seibert, S. F.; Krick, A.; Eguereva, E.; Kehraus, S.; Kónig, G. M. *Org. Lett.* **2007**, *9*, 239. (b) Li, X.; Yao, Y.; Zheng, Y.; Sattler, I.; Lin, W. *Arch. Pharm. Res.* **2007**, *30*, 812. (c) Li, X.; Sattler, I.; Lin, W. *J. Antibiot.* **2007**, *60*, 191.
(5) Ramana, C. V.; Suryawanshi, S. B.; Gonnade, R. G. *J. Org. Chem.* **2009**, *74*, 2842.
(6) (a) Massad, S. K.; Hawkins, L. D.; Baker, D. C. *J. Org. Chem.* **1983**, *48*, 5180. (b) Kim, D.; Lee, J.; Shim, P. J.; Lim, J. I.; Doi, T.; Kim, S. *J. Org. Chem.* **2002**, *67*, 772. (c) Stivala, C. E.; Zakarian, A. *Org. Lett.* **2009**, *11*, 839.
(7) For olefin cross metathesis, see: (a) Connon, S. J.; Blechert, S. *Angew. Chem. Int. Ed.* **2003**, *42*, 1900. (b) Chatterjee, A. K.; Choi, T.-L.; Sanders, D. P.; Grubbs, R. H. *J. Am. Chem. Soc.* **2003**, *125*, 11360. (c) Lipshutz, B. H.; Aguinaldo, G. T.; Ghorai, S.; Voigtritter, K. *Org. Lett.* **2008**, *10*, 1325; and references cited therein.
(8) Reviews: (a) Zaitsev, A. B.; Adolfsson, H. *Synthesis* **2006**, 1725. (b) Bolm, C.; Hildebrand, J. P.; Muniz, K. In *Catalytic Asymmetric Synthesis*, 2nd ed.; Ojima, I., Ed.; Wiley-VCH: Weinheim, **2000**, 399. (c) Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483. (d) Johnson, R. A.; Sharpless, K. B. *Asymmetric Catalysis in Organic Synthesis*; Ojima, I., Ed.; VCH: New York, **1993**, 227.
(9) ^{1}H NMR and ^{13}C NMR studies of purified product indicated single diastereomer.
Data for 18
Colourless oil; $[\alpha]_D^{25}$ +10.2 (*c* 0.2, $CHCl_3$). IR ($CHCl_3$): ν = 3463, 3022, 2973, 1772, 1646, 1528, 1421, 1347, 1216, 1045, 927, 669 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$/TMS): δ = 0.02 (s, 3 H), 0.03 (s, 3 H), 0.86 (s, 9 H), 1.11 (d, *J* = 6.1 Hz, 3 H), 1.43–1.49 (m, 2 H), 1.50–1.58 (m, 1 H), 1.72–1.80 (m, 1 H), 2.24–2.37 (m, 2 H), 2.54 (d, *J* = 17.7 Hz, 1 H), 2.72 (dd, *J* = 17.7, 5.8 Hz, 1 H), 3.44 (br s, OH), 3.75–3.80 (m, 1 H), 3.93–4.02 (m, 4 H), 4.36–4.38 (m, 1 H), 4.55–4.60 (m, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = –4.83, –4.39, 18.0, 23.6, 25.7 (3 C), 32.7, 33.7, 34.1, 37.7, 64.1, 64.5, 67.9, 68.3, 80.9, 110.1, 175.3. HRMS (ESI-TOF): *m/z* calcd for $C_{18}H_{34}O_6Si$ + Na: 397.2022; found: 397.2028.
(10) **Data for 19**
Colourless oil; $[\alpha]_D^{25}$ –20.4 (*c* 0.1, $CHCl_3$). IR ($CHCl_3$): ν = 3440, 3018, 2965, 2931, 1773, 1636, 1458, 1407, 1378, 1216, 1160, 1062, 949, 668 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$/TMS): δ = 1.21 (d, *J* = 6.4 Hz, 3 H), 1.47–1.57 (m, 2 H), 1.79–1.87 (m, 2 H), 2.33–2.36 (m, 2 H), 2.56 (d, *J* = 17.7 Hz, 1 H), 2.76 (dd, *J* = 17.8, 5.9 Hz, 1 H), 3.36–3.45 (br s, OH), 3.78–3.82 (m, 1 H), 3.98–4.06 (m, 4 H), 4.39–4.41 (m, 1 H), 4.56–4.61 (m, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 23.6, 33.3 (2 C), 34.3, 37.9, 64.3, 64.7, 67.6, 68.5, 81.1, 110.1, 175.5. HRMS (ESI-TOF): *m/z* calcd for $C_{12}H_{20}O_6$ + H: 261.1338; found: 261.1341.
(11) Ates, A.; Gautier, A.; Leroy, B.; Plancher, J.-M.; Quesnel, Y.; Vanherck, J.-C.; Markó, I. E. *Tetrahedron* **2003**, *59*, 8989.