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# Short Synthesis of (−)-Cephalotaxine Using a Radical Cascade

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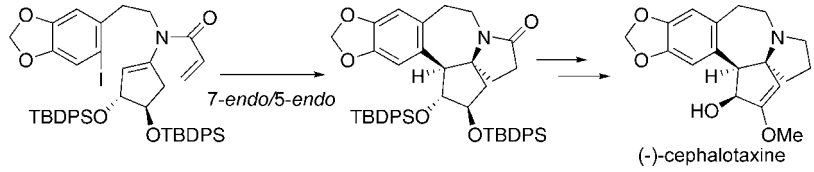
## ABSTRACT




**The short total synthesis of (−)-cephalotaxine is described. The concise construction of the pentacyclic core of this alkaloid was achieved by a radical cascade involving 7-*endo* and 5-*endo* cyclizations.**

Cephalotaxus alkaloids are a class of cytotoxic natural products first isolated from Asian plum yews *Cephalotaxus drupacea* and *Cephalotaxus fortunei*.[1,2] Cephalotaxine (**1**) has attracted much attention from many chemists due to a combination of its fascinating pentacyclic structure (ABCDE ring system in Figure 1) and the antileukemic activity of its ester derivatives such as harringtonine (**2**)[3] and homoharringtonine (**3**).[3] Since the first total synthesis of (±)-cephalotaxine by Weinreb[4] and Semmelhack,[5] a number of approaches to the synthesis of this compound have been reported, and several efforts have culminated in a total synthesis of a racemic mixture[6] of optically active[7] cephalotaxines. One of the most frequently used strategies is $C_4-C_{13}$ bond formation, i.e., formation of the C-ring of the cephalotaxine structure.

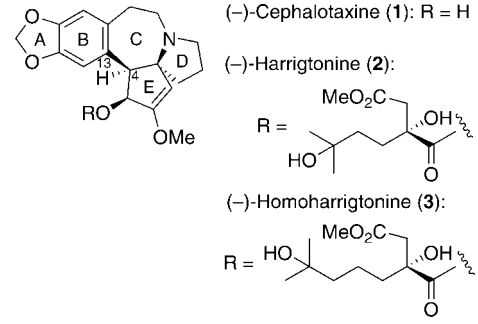



**Figure 1.** Cephalotaxine and its ester derivatives.

In a previous paper, we reported the concise construction of a cephalotaxine skeleton **6** using a radical cascade[8,9] that involved $Bu_3SnH$-mediated 7-*endo*-selective aryl radical cyclization of enamide **4** followed by a 5-*endo-trig* cyclization of the resultant α-amidoyl radical intermediate **5** (Scheme 1).[10] A characteristic feature of the reaction is simultaneous construction of the C and D rings of the caphalotaxine skeleton. Herein, we report an application of this method to a short synthesis of (−)-cephalotaxine.

(1) Paudler, W. W.; Kerley, G. I.; McKay, J. *J. Org. Chem.* **1963**, *28*, 2194.

(2) For reviews on the Cephalotaxus alkaloids, see: (a) Weinreb, S. M.; Semmelhack, M. F. *Acc. Chem. Res.* **1975**, *8*, 158–164. (b) Huang, L.; Xue, Z. *The Alkaloids*; Academic Press: New York, 1984; Vol. 23, pp 157−226. (c) Jalil Miah, M. A.; Hudlicky, T.; Reed, J. W. *The Alkaloids*; Academic Press: San Diego, 1998; Vol. 51, pp 199−269.

(3) (a) Powell, R. G.; Weisleder, D.; Smith, C. R., Jr. *J. Pharm. Sci.* **1972**, *61*, 1227. (b) Corbett, T. H.; Griswold, D. P., Jr.; Roberts, B. J.; Peckham, J. C.; Schabel, F. M. *Cancer* **1977**, *40*, 2660. (c) Smith, C. R., Jr.; Mikolajczak, K. l.; Powell, R. G. *Anticancer Agents Based on Natural Product Models*; Cassady, J. M., Douros, J. D., Eds.; Academic Press: New York, 1980; Chapter 11. (d) Hudlicky, T.; Kwart, L. D.; Reed, J. W. *Alkaloids, Chemical and Biological Perspectives*; Pelletire, S. W. J., Ed.; Wiley: New York, 1987; Vol. 5, Chapter 5. (e) Kantarjian, H. M.; Talpaz, M.; Santini, V.; Murgo, A.; Cheson, B.; O'Brien, S. M. *Cancer* **2001**, *92*, 1591. See also ref 2b and 2c.

(4) Auerbach, J.; Weinreb, S. M. *J. Am. Chem. Soc.* **1972**, *94*, 7172.

(5) Semmelhack, M. F.; Chong, B. P.; Jones, I. D. *J. Am. Chem. Soc.* **1972**, *94*, 8629.

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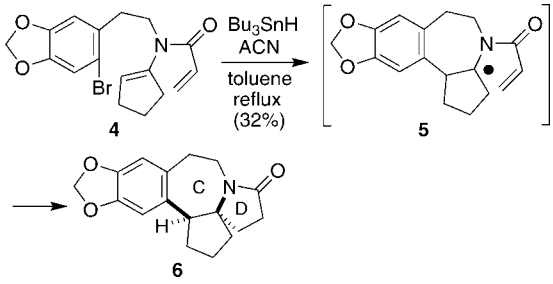
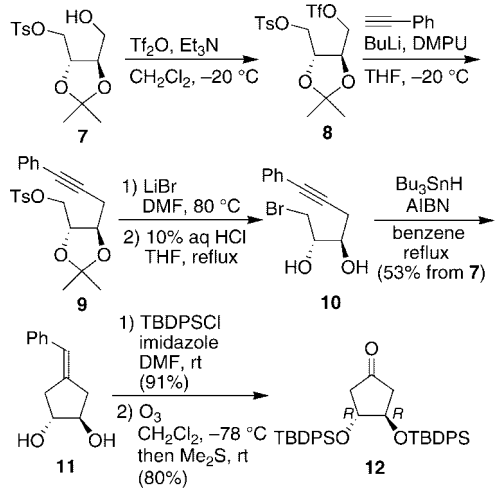
**Scheme 1**




Scheme 2 shows the preparation of the key, optically active cyclopentanone **12**. Diethyl D-(−)-tartrate was converted into

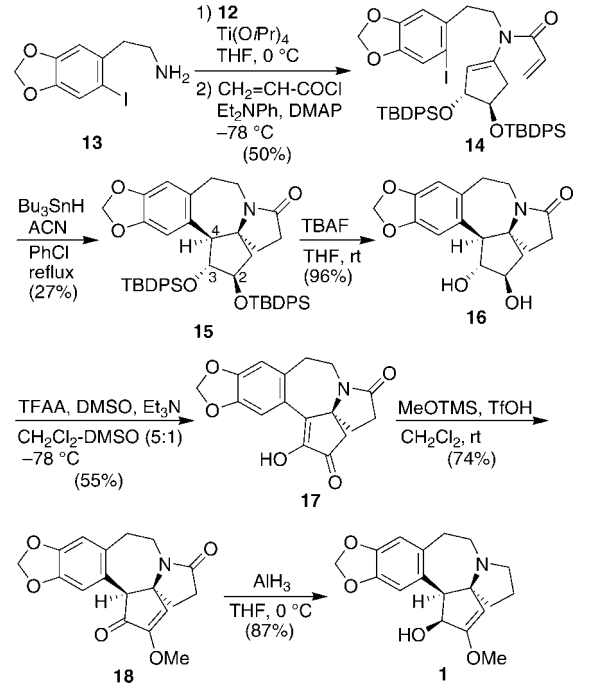
**Scheme 2**




trifrate **8**[11] via tosylate **7**,[12] and the reaction of **8** with lithium phenylacetylide afforded compound **9**. Bromination of tosylate **9** with lithium bromide followed by removal of the acetonide group afforded compound **10**. Compound **10** was then subjected to $Bu_3SnH$-mediated radical cyclization to give five-membered product **11** in 53% yield from **7**. Protection of two hydroxyl groups of compound **11** with TBDPSCl followed by ozonolysis afforded the desired cyclopentanone **12**.[13]

Condensation of amine **13**[15] with cyclopentanone **12** in the presence of $Ti(OiPr)_4$ afforded an imine, which was acylated with acryloyl chloride to give enamide **14**in 50% yield (Scheme 3). When enamide **14** was treated with

**Scheme 3**




$Bu_3SnH$ in the presence of 1,1′-azobiscyclohexanecarbonitrile (ACN) in boiling chlorobenzene, a radical cascade reaction occurred to give desired pentacyclic compound **15** in 27% yield. The $^1H$ NMR spectrum of **15** [$\delta$ 2.81 (1H, d, $J$ = 9.8

(6) For recent examples of the synthesis of (±)-cephalotaxine, see: (a) Burkholder, T. P.; Fuchs, P. L. *J. Am. Chem. Soc.* **1990**, *112*, 9601. (b) Ishibashi, H.; Okano, M.; Tamaki, H.; Maruyama, K.; Yakura, T.; Ikeda, M. *J. Chem. Soc., Chem. Commun.* **1990**, 1436. (c) Ikeda, M.; Okano, M.; Kosaka, K.; Kido, M.; Ishibashi, H. *Chem. Pharm. Bull.* **1993**, *41*, 276. (d) Lin, X.; Kavash, R. W.; Mariano, P. S. *J. Am. Chem. Soc.* **1994**, *116*, 9791. (e) Lin, X.; Kavash, R. W.; Mariano, P. S. *J. Org. Chem.* **1996**, *61*, 7335. (f) Tietze, L. F.; Schirok, H. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1124. (g) Koseki, Y.; Sato, H.; Watanabe, Y.; Nagasaka, T. *Org. Lett.* **2002**, *4*, 885. (h) Li, W.-D. Z.; Wang, Y.-Q. *Org. Lett.* **2003**, *5*, 2931. (i) Li, W.-D. Z.; Ma, B.-C. *J. Org. Chem.* **2005**, *70*, 3277. (j) Ma, B.-C.; Wang, Y.-Q.; Li, W.-D. Z. *J. Org. Chem.* **2005**, *70*, 4528. (k) Li, W.-D. Z.; Wang, X.-W. *Org. Lett.* **2007**, *9*, 1211.

(7) For synthesis of (−)-cephalotaxine, see: (a) Isono, N.; Mori, M. *J. Org. Chem.* **1995**, *60*, 115. (b) Nagasaka, T.; Sato, H.; Saeki, S. *Tetrahedron: Asymmetry* **1997**, *8*, 191. (c) Ikeda, M.; El Bialy, S. A. A.; Hirose, K.; Kotake, M.; Sato, T.; Bayomi, S. M. M.; Shehata, I. A.; Abdelal, A. M.; Gad, L. M.; Yakura, T. *Chem. Pharm. Bull.* **1999**, *47*, 983. (d) Tietze, L. F.; Schirok, H. *J. Am. Chem. Soc.* **1999**, *121*, 10264. (e) Planas, L.; Perard-Viret, J.; Royer, J. *J. Org. Chem.* **2004**, *69*, 3087. (f) Eckelbarger, J. D.; Wilmot, J. T.; Gin, D. Y. *J. Am. Chem. Soc.* **2006**, *128*, 10370. (g) Zhao, Z.; Mariano, P. S. *Tetrahedron* **2006**, *62*, 7266. (h) Liu, Q.; Ferreira, E. M.; Stoltz, B. M. *J. Org. Chem.* **2007**, *72*, 7352. (i) Esmieu, W. R.; Worden, S. W.; Catterick, D.; Wilson, C.; Hayes, C. J. *Org. Lett.* **2008**, *10*, 3045.

(8) For reviews on radical cascades, see: (a) McCarroll, A. J.; Walton, J. C. *Angew. Chem., Int. Ed.* **2001**, *40*, 2224. (b) McCarroll, A. J.; Walton, J. C. *J. Chem. Soc., Perkin Trans. 1* **2001**, 3215.

(9) For reviews on the synthesis of heterocyclic compounds and natural products using radical cyclization, see: (a) Jasperse, C. P.; Curran, D. P.; Fevis, T. L. *Chem. Rev.* **1991**, *91*, 1237. (b) Li, J. J. *Alkaloids: Chemical Perspectives*; Pelletire, S. W., Ed.; Wiley: New York, 2001; *Vol. 5*, Chapter 4. (c) Renaud, P.; Sibi, M. P. *Radical in Organic Synthesis*; Wiley-VCH: Weinheim, 2001. (d) Majumdar, K. C.; Mukhopadhyay, P. P.; Basu, P. K. *Heterocycles* **2004**, *63*, 1903.

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(11) Kotsuki, H.; Kadota, I.; Ochi, M. *J. Org. Chem.* **1990**, *55*, 4417.

(12) Tosylate **7** was prepared by reaction of the corresponding diol, which, in turn, was readily prepared from diethyl D-tartrate, with *p*-toluenesulfonyl chloride. Diol is now commercially available.

(13) (3*S*,4*S*)-3,4-Dihydroxycyclopentane, whose protection with TBDPSCl would give the enantiomer of **12**, was reported to be prepared from diethyl L-tartrate using FAMSO,[14] but, in our hand, only a very low yield of (3*R*,4*R*)-congener was obtained from diethyl D-tartrate.

(14) Khanapure, S. P.; Najafi, N.; Manna, S.; Yang, J.-J.; Rokach, J. *J. Org. Chem.* **1995**, *60*, 7548.

(15) Tietze, L. F.; Schirok, H. *J. Am. Chem. Soc.* **1999**, *121*, 10264.

Hz, H-4), 4.41 (1H, td, $J = 11.6$, 7.3 Hz, H-2), and 4.56 (1H, dd, $J = 9.8$, 7.3 Hz, H-3)] showed it to be a single isomer having the stereochemistry depicted in Scheme 3. Removal of the two TBDPS groups of **15** with TBAF gave diol **16** in 96% yield. A successive oxidation of **16** with TFAA, DMSO, and triethylamine afforded compound **17**[7e] in 55% yield. At this stage, a formal total synthesis of (−)-cephalotaxine (**1**) from compound **17** was accomplished, whereas, since a specific rotation of **17** was not indicated in the literature, ketone **17** was treated with methoxytrimethylsilane to give methoxy ketone **18** by using the known procedure.[7e] Finally, two carbonyl groups of **18** were reduced with alane to give (−)-cephalotaxine (**1**), $[\alpha]_D$ −185 ($c$ = 0.175, $CHCl_3$) [lit.[3a] $[\alpha]_D$ −188 ($c = 0.5$, $CHCl_3$), lit.[7e] $[\alpha]_D$ −182 ($c = 0.21$, $CHCl_3$)]. The other spectral data were in accord with the literature values.

In summary, we achieved a rapid total synthesis of (−)-cephalotaxine (**1**) using a radical cascade as the key step. The use of a radical cascade involving two *endo*-selective cyclizations allowed us to create the pentacyclic skeleton of **1** in one step. Further studies directed toward improvement of the yield of the radical cascade product and toward the synthesis of other cephalotaxus alkaloids using this strategy are now in progress in our laboratory.

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

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