

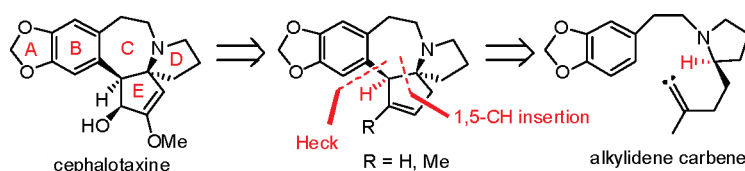
A Formal Synthesis of (-)-Cephalotaxine

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ABSTRACT



An enantioselective formal synthesis of the alkaloid (–)-cephalotaxine has been completed, using an alkyldiene carbene 1,5-CH insertion reaction as a key step to construct the spiro[4.4]azanonane core D/E-ring system. A Heck-type cyclization was used to close the tetrahydroazepine C-ring and a selective epoxidation–rearrangement sequence was used to elaborate the E-ring.

Since its isolation in 1963,¹ the polycyclic alkaloid (–)-cephalotaxine (**1**) has become an enduring target for total chemical synthesis (Figure 1).^{2,3} The continued interest in this molecule is due to a combination of its fascinating chemical structure and it being the parent of a larger family of related alkaloid esters that show clinically useful anticancer activity. Homoharringtonine (**2**), for example, is undergoing clinical trials for use as an antileukemia drug.⁴

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(1) (a) Isolation: Paudler, W. W.; Kerley, G. I.; McKay, J. *J. Org. Chem.* **1963**, 28, 2194. (b) Structure elucidation: Abraham, D. J.; Rosenstein, R. D.; McGandy, E. L. *Tetrahedron Lett.* **1969**, 4085. (c) Arora, S. K.; Bates, R. B.; Grady, R. A.; Powell, R. G. *J. Org. Chem.* **1974**, 39, 1269.

(2) (a) Racemic syntheses: Auerbach, J.; Weinreb, S. M. *J. Am. Chem. Soc.* **1972**, 94, 7172. (b) Semmelhack, M. F.; Chong, B. P.; Jones, L. D. *J. Am. Chem. Soc.* **1972**, 94, 8629. (c) Semmelhack, M. F.; Chong, B. P.; Stauffer, R. D.; Rogerson, T. D.; Chong, A.; Jones, L. D. *J. Am. Chem. Soc.* **1975**, 97, 2507. (d) Weinreb, S. M.; Auerbach, J. *J. Am. Chem. Soc.* **1975**, 97, 2503. (e) Burkholder, T. P.; Fuchs, P. L. *J. Am. Chem. Soc.* **1988**, 110, 2341. (f) Kuehne, M. E.; Bornmann, W. G.; Parsons, W. H.; Spitzer, T. D.; Blount, J. F.; Zubieta, J. *J. Org. Chem.* **1988**, 53, 3439. (g) Burkholder, T. P.; Fuchs, P. L. *J. Am. Chem. Soc.* **1990**, 112, 9601. (h) Ishibashi, H.; Okano, M.; Tamaki, H.; Maruyama, K.; Yakura, T.; Ikeda, M. *J. Chem. Soc., Chem. Commun.* **1990**, 1436. (i) Ikeda, M.; Okano, M.; Kosaka, K.; Kido, M.; Ishibashi, H. *Chem. Pharm. Bull.* **1993**, 41, 276. (j) Lin, X.; Kavash, R. W.; Mariano, P. S. *J. Am. Chem. Soc.* **1994**, 116, 9791. (k) Lin, X.; Kavash, R. W.; Mariano, P. S. *J. Org. Chem.* **1996**, 61, 7335. (l) Tietze, L. F.; Schirok, H. *Angew. Chem., Int. Ed. Engl.* **1997**, 36, 1124. (m) Koseki, Y.; Sato, H.; Watanabe, Y.; Nagasaka, T. *Org. Lett.* **2002**, 4, 885. (n) Li, W.-D. Z.; Wang, Y.-Q. *Org. Lett.* **2003**, 5, 2931. (o) Li, W.-D. Z.; Ma, B.-C. *J. Org. Chem.* **2005**, 70, 3277. (p) Ma, B.-C.; Wang, Y.-Q.; Li, W.-D. Z. *J. Org. Chem.* **2005**, 70, 4528. (q) Li, W.-D. Z.; Wang, X.-W. *Org. Lett.* **2007**, 9, 1211.

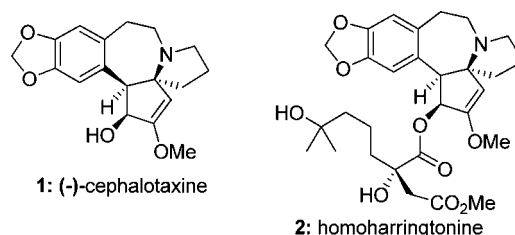


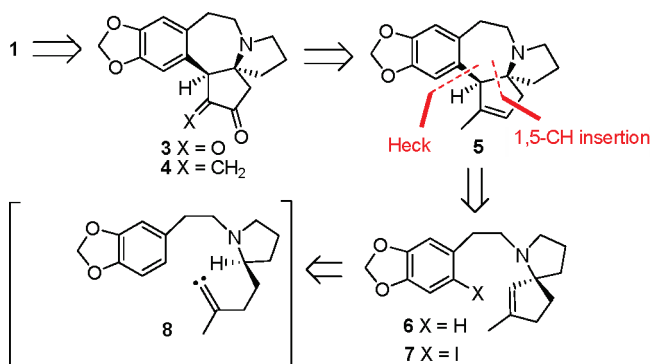
Figure 1. Structures of cephalotaxine (**1**) and homoharringtonine (**2**)

A number of racemic² and enantioselective³ syntheses of cephalotaxine have been published to date, and the efficient asymmetric construction of the embedded spiro[4.4]azanonane ring system has proven to be a significant challenge. Our

(3) (a) Enantioselective syntheses: Zhong, S.; Liu, W.; Ling, Y.; Li, R. *Zhongguo Yaowu Huaxue Zazhi* **1994**, 4, 84. (b) Isono, N.; Mori, M. *J. Org. Chem.* **1995**, 60, 115. (c) Nagasaka, T.; Sato, H.; Saeki, S.-I. *Tetrahedron: Asymmetry* **1997**, 8, 191. (d) Ikeda, M.; El Bialy, S. A. A.; Hirose, K.-I.; 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. (e) Tietze, L. F.; Schirok, H. *J. Am. Chem. Soc.* **1999**, 121, 10264. (f) El Bialy, S. A. A.; Ismail, M. A.; Gad, L. M.; Abdelal, A. M. M. *Med. Chem. Res.* **2002**, 11, 293. (g) Planas, L.; Perard-Viret, J.; Royer, J. *J. Org. Chem.* **2004**, 69, 3087. (h) Eckelbarger, J. D.; Wilmot, J. T.; Gin, D. Y. *J. Am. Chem. Soc.* **2006**, 128, 10370. (i) Zhao, Z.; Mariano, P. S. *Tetrahedron* **2006**, 62, 7266. (j) Liu, Q.; Ferreira, E. M.; Stoltz, B. M. *J. Org. Chem.* **2007**, 72, 7352.

previous model study in this area showed that this spirocycle could be constructed using an alkylidene carbene 1,5-CH insertion reaction,⁵ and we now wish to report the successful application of this novel strategy to an enantioselective formal total synthesis of **1**. Weinreb first showed that **1** can be synthesized from the related natural product demethyl-cephalotaxinone (**3**) in two steps,^{2a} and this dione therefore became our interim target. We were aware of previous synthetic work that had shown that β -amino ketones such as **3** have to be handled with care as they can undergo racemization of the nitrogen-bearing quaternary stereocenter via sequential elimination–Michael addition reactions.^{2k,3b} In order to minimize our exposure to this racemization problem, we decided to attempt installation of the α -dicarbonyls at a late stage in our synthesis from the cyclopentene **5** via oxidation to the enone **4** and subsequent oxidative cleavage to provide **3** (Scheme 1).

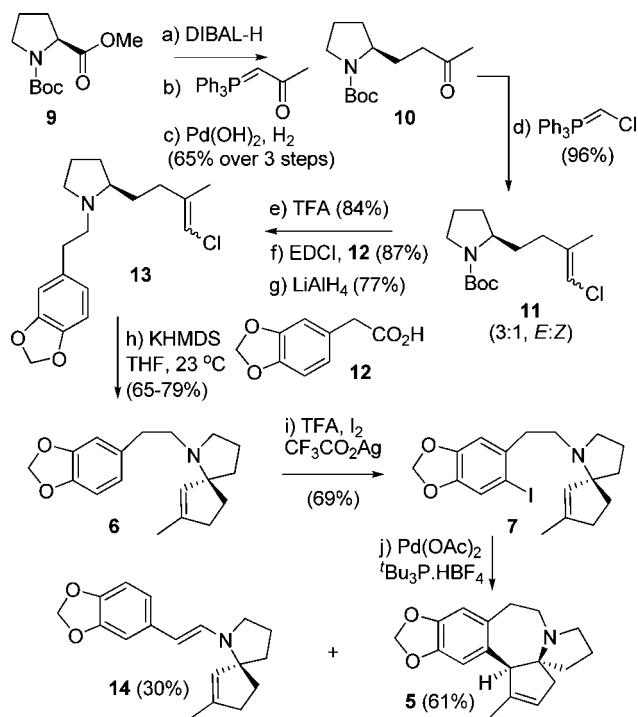
Scheme 1. Retrosynthetic Analysis of Cephalotaxine (**1**)



Disconnection of **5** revealed the spiro[4.4]azanonane **7** as an advanced precursor, with the tetrahydroazepine ring being formed in the synthetic direction via a Heck-type cyclization similar to that used by Tietze et al. (i.e., **7** $\rightarrow$ **5**).^{3c} We envisaged that the aromatic iodide **7** could be accessed from **6**, which itself could be constructed via a 1,5-CH insertion reaction of the pyrrolidine-substituted alkylidene carbene **8**. Our first synthetic task, therefore, was to prepare a suitable precursor to the alkylidene carbene **8**.

Our chosen carbene precursor was the vinyl chloride **13**, and this was easily prepared in seven steps from *N*-Boc-proline methyl ester (**9**) (Scheme 2). Reduction of **9** with Dibal-H gave

Scheme 2. Synthesis of Pentacycle **5**



the corresponding aldehyde, and this was homologated with 1-triphenylphosphoranylidene-2-propanone to give the *E*-enone. Catalytic hydrogenation ($\text{Pd}(\text{OH})_2/\text{C}$, H_2) then gave **10**, and a second Wittig reaction then afforded the vinyl chloride **11** (3:1, *E:Z*) in good overall yield. Deprotection (TFA, CH_2Cl_2), amide formation with the carboxylic acid **12** (EDCI, HOBT), and reduction of the resulting amide (LiAlH_4) then afforded the desired alkylidene carbene precursor **13**. The pivotal alkylidene carbene 1,5-CH insertion reaction was then effected by treatment of **13** with KHMDS (2 equiv)⁶ at room temperature to afford the desired spiro[4.4]azanonane **6** in good yield (65–79%). Regioselective iodination of the aromatic ring (TFA, I_2 , $\text{CF}_3\text{CO}_2\text{Ag}$) then gave the key Heck-cyclization precursor **7**.^{3c} At this stage, an X-ray crystal structure of the iodide **7** was obtained (Figure 2).⁷ In addition to demonstrating spiro-cycle formation, the presence of the iodine atom allowed us to confirm the molecule's absolute stereochemistry, thus demonstrating that the 1,5-CH insertion reaction had proceeded with retention of configuration as expected.

The Heck cyclization (**7** $\rightarrow$ **5**) proved to be much more difficult than we had expected and required extensive optimization (Scheme 2). Hermann and Beller's palladacycle catalyst⁸ gave only low and capricious yields of **5**, while the use of more traditional conditions ($\text{Pd}(\text{OAc})_2/\text{Ph}_3\text{P}/\text{K}_2\text{CO}_3$) gave the enamine **14** as the major product (84%)⁹ with the desired pentacycle **5** representing only a minor

(4) (a) Levy, V.; Zohar, S.; Bardin, C.; Vekhoff, A.; Chaoui, D.; Rio, B.; Legrand, O.; Sentenac, S.; Rousselot, P.; Raffoux, E.; Chast, F.; Chevret, S.; Marie, J. P. *Br. J. Cancer* **2006**, *95*, 253. (b) Kantarjian, H. M.; Talpaz, M.; Santini, V.; Murgo, A.; Cheson, B.; O'Brien, S. M. *Cancer* **2001**, *92*, 1591.

(5) Worden, S. M.; Mapitise, R.; Hayes, C. J. *Tetrahedron Lett.* **2002**, *43*, 6011.

(6) (a) Taber, D. F.; Christos, T. E.; Neubert, T. D.; Batra, D. J. *Org. Chem.* **1999**, *64*, 9673. (b) Taber, D. F.; Neubert, T. D. *J. Org. Chem.* **2001**, *66*, 143. (c) Taber, D. F.; Neubert, T. D.; Rheingold, A. L. *J. Am. Chem. Soc.* **2002**, *124*, 12416. (d) Auty, J. M. A.; Churcher, I.; Hayes, C. J. *Synlett* **2004**, 1443. (e) Hayes, C. J.; Sherlock, A. E.; Selby, M. D. *Org. Biol. Chem.* **2006**, *4*, 193. (f) Bradley, D. M.; Mapitise, R.; Thomson, N. M.; Hayes, C. J. *J. Org. Chem.* **2002**, *67*, 7613. (g) Green, M. P.; Prodger, J. C.; Sherlock, A. E.; Hayes, C. J. *Org. Lett.* **2001**, *3*, 3377.

(7) The crystallographic data have been deposited with the Cambridge Crystallographic Data Centre. CCDC 682009 contains the supplementary crystallographic data for **7**, and CCDC 682010 contains the supplementary crystallographic data for **15**. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

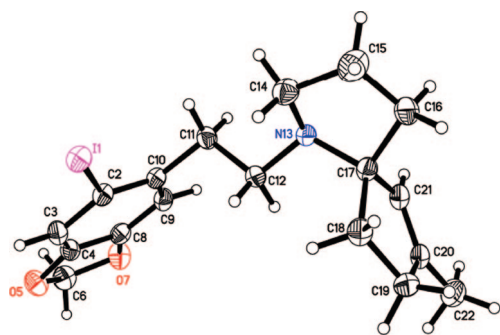


Figure 2. X-ray crystal structure of spirocycle 7.

component (14%). In contrast to these somewhat disappointing results, the desired cyclization could be effected in acceptable yield (61%) by using a slightly modified version of Fu's conditions ($\text{Pd}(\text{OAc})_2$, $\text{BF}_4\text{H}\cdot\text{P}^t\text{Bu}_3$, Cs_2CO_3 , dioxane reflux).¹⁰ Under these conditions, the enamine **14** was still formed (30%), but it was easily separated from **5** via SiO_2 column chromatography. It was essential to use $\text{Pd}(\text{OAc})_2$ as the palladium source in this reaction as the use of $\text{Pd}(0)$ precatalysts (e.g., $\text{Pd}_2(\text{dba})_3$) gave inferior results with the reduced compound **6** (12%) being produced in addition to the enamine **14** (23%) and the desired compound **5** (41%).

Having closed the C-ring of cephalotaxine, our next challenge was elaboration of the E-ring (Scheme 3). Under

$\text{BF}_3\cdot\text{OEt}_2$ (63–90%)^{11,12} or $m\text{-CPBA/TFA}$ (60%), and the stereochemistry of the epoxide **15** was confirmed by X-ray crystallography (Figure 3).⁷

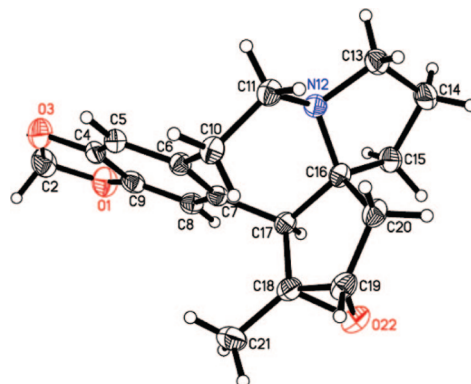
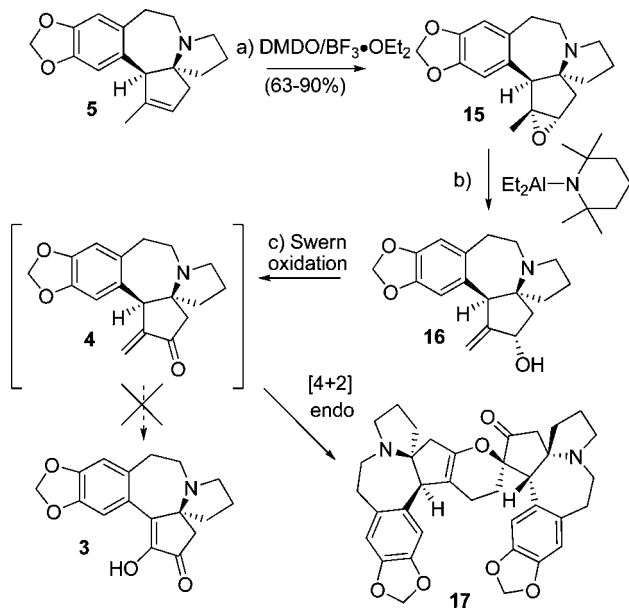


Figure 3. X-ray crystal structure of epoxide **15**.

Regioselective rearrangement of the epoxide **15** using Yamamoto's conditions¹³ then produced the allylic alcohol **16** in quantitative yield, and oxidation of **16** under Swern conditions finally afforded the desired enone **4**. Unfortunately, we were not able to effect the desired oxidative cleavage reaction of **4** to produce demethylcephalotaxinone (**3**) as the enone **4** proved to be quite unstable and spontaneously dimerized in solution to afford the endo hetero-Diels–Alder adduct **17** in a regio- and stereoselective manner (Scheme 3).¹⁴ As oxidative cleavage of **4** was not possible, a modified strategy for the completion of the synthesis was developed (Scheme 4).

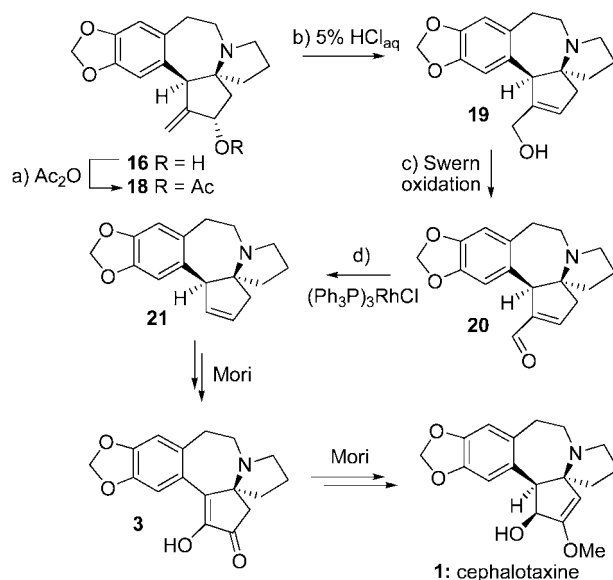
Scheme 3. Elaboration of the E-Ring^a



^aKey: (a) $\text{BF}_3\cdot\text{OEt}_2$, Et_2O , -78°C , then DMDO, CH_2Cl_2 , 0°C , 63–90%; (b) $n\text{-BuLi}$, TMP, AlEt_2Cl , toluene, 0°C , quant; (c) $(\text{COCl})_2$, DMSO, NEt_3 , DCM, -60°C , quant (to **4**).

carefully optimized conditions the alkene was epoxidized in the presence of the tertiary amine using either DMDO/

Scheme 4. Completion of the Synthesis^a



^aKey: (a) Ac_2O , pyridine, 23°C ; (b) 5% aqueous HCl, reflux, 58% (three steps from **15**); (c) $(\text{COCl})_2$, DMSO, NEt_3 , DCM, -60°C , 53%; (d) $\text{Rh}(\text{PPh}_3)_3\text{Cl}$, toluene, reflux, 20–40%.

First, the secondary alcohol **16** was converted to the acetate **18**, which was then exposed to 5% HCl_(aq) to afford the primary alcohol **19** (Scheme 4). Swern oxidation of **19** then afforded aldehyde **20**, which was then treated with Wilkinson's catalyst in toluene at reflux.¹⁵ Pleasingly, the decar-

bonylated product **21** was recovered cleanly from this reaction (100% mass recovery), although a significant amount of material was lost during the final chromatographic purification on SiO₂ gel. Since Mori^{3b} has shown previously that **21** can be converted into **1**, via demethylcephalotaxinone (**3**), we have successfully completed a novel formal synthesis of (–)-cephalotaxine (**1**) using an alkylidene carbene 1,5-CH insertion as a key step.

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Supporting Information Available: Detailed experimental procedures, spectroscopic data, and copies of ¹H NMR spectra for all new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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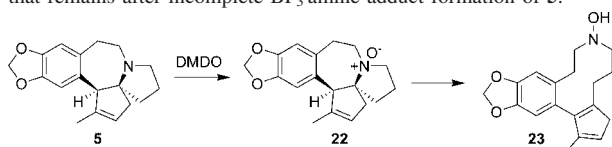
(8) Herrmann, W. A.; Brossmer, C.; Reisinger, C.-P.; Riermeier, T. H.; Oefele, K.; Beller, M. *Chem. Eur. J.* **1997**, *3*, 1357.

(9) An enamine similar to **14** was observed in our previous model study, and a mechanistic rationalization was proposed. See ref 5 for full details.

(10) Littke, A. F.; Fu, G. C. *J. Am. Chem. Soc.* **2001**, *123*, 6989.

(11) Ferrer, M.; Sanchez-Baeza, F.; Messeguer, A.; Diez, A.; Rubiralta, M. *J. Chem. Soc., Chem. Commun.* **1995**, 293.

(12) The yield of **15** was dependent upon the success of forming the initial BF₃amine adduct, and the main byproduct observed was the hydroxylamine **23**. We believe that **23** is formed by fragmentation of the *N*-oxide **22** and that **22** is formed by oxidation of the residual tertiary amine **5** that remains after incomplete BF₃amine adduct formation of **5**.



(13) Yasuda, A.; Tanaka, S.; Oshima, K.; Yamamoto, H.; Nozaki, H. *J. Am. Chem. Soc.* **1974**, *96*, 6513.

(14) Chrobok, A.; Goessinger, E.; Kalb, R.; Orglmeister, E.; Schwaiger, J. *Tetrahedron* **2007**, *63*, 8326.

(15) Ohno, K.; Tsuji, J. *J. Am. Chem. Soc.* **1968**, *90*, 99.