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A Formal Synthesis of (-)-Cephalotaxine

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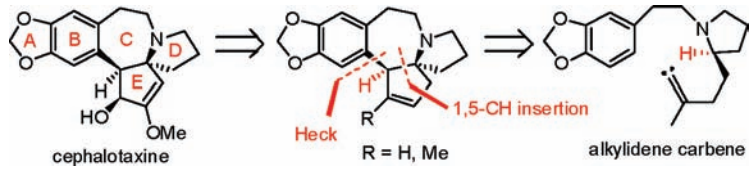
ABSTRACT



An enantioselective formal synthesis of the alkaloid (−)-cephalotaxine has been completed, using an alkylidene 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]

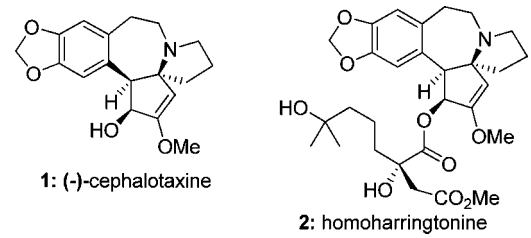


Figure 1. Structures of cephalotaxine (**1**) and homoharringtonine (**2**)

A number of racemic[2] and enantioselective[3] 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

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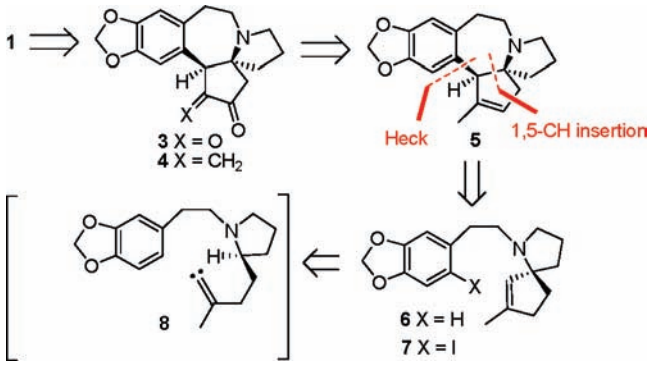
previous model study in this area showed that this spirocycle could be constructed using an alkylidene carbene 1,5-CH insertion reaction,[5] and we now wish to report the successful application of this novel strategy to an enantioselective formal total synthesis of **1**. Weinreb first showed that **1** can be synthesized from the related natural product demethylcephalotaxinone (**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).

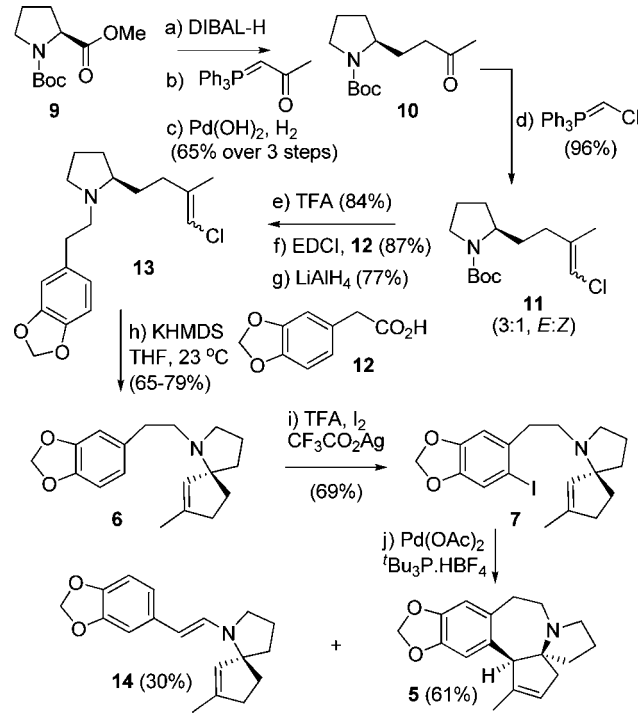
Scheme 1. Retrosynthetic Analysis of Cephalotaxine (**1**)



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** → **5**).[3e] 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 ($Pd(OH)_2/C$, 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 teatment 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, CF_3CO_2Ag) then gave the key Heck-cyclization precursor **7**.[3e] At this stage, an X-ray crystal structure of the iodide **7** was obtained (Figure 2).[7] In addition to demonstrating spirocycle 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** → **5**) proved to be much more difficult than we had expected and required extensive optimization (Scheme 2). Hermann and Beller's palladacycle catalyst[8] gave only low and capricious yields of **5**, while the use of more traditional conditions ($Pd(OAc)_2/Ph_3P/K_2CO_3$) gave the enamine **14** as the major product (84%)[9] with the desired pentacycle **5** representing only a minor

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(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.

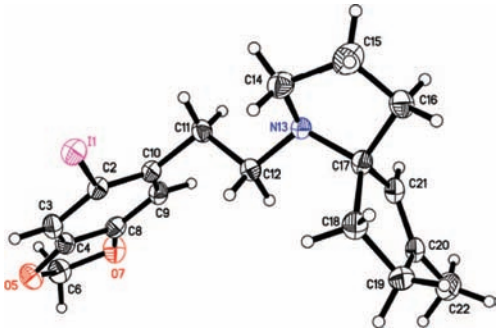
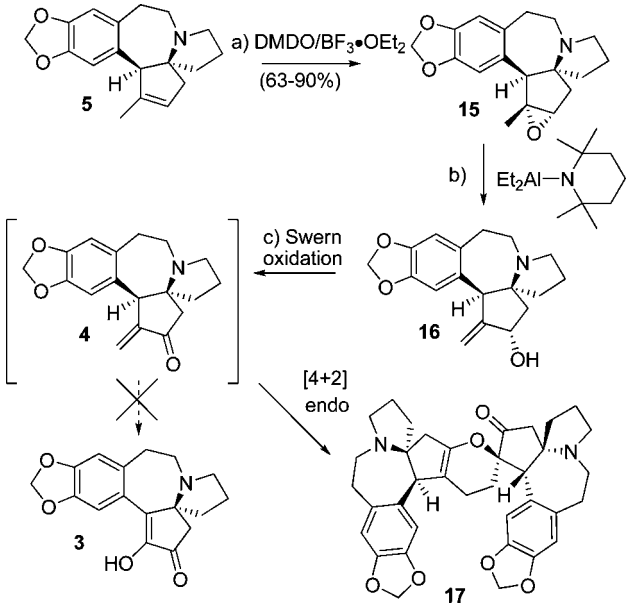


Figure 2. X-ray crystal structure of spirocycle **7**.

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 ($Pd(OAc)_2$, $BF_4H{\cdot}P^tBu_3$, 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 $Pd(OAc)_2$ as the palladium source in this reaction as the use of Pd(0) precatalysts (e.g., $Pd_2(dba)_3$) 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

Scheme 3. Elaboration of the E-Ring[a]



[a]Key: (a) $BF_3{\cdot}OEt_2$, Et_2O, −78 °C, then DMDO, CH_2Cl_2, 0 °C, 63−90%; (b) *n*-BuLi, TMP, $AlEt_2Cl$, toluene, 0 °C, quant; (c) $(COCl)_2$, 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/$BF_3{\cdot}OEt_2$ (63−90%)[11,12] or *m*-CPBA/TFA (60%), and the stereochemistry of the epoxide **15** was confirmed by X-ray crystallography (Figure 3).[7]

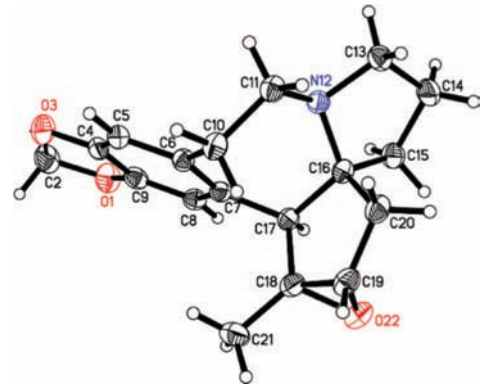
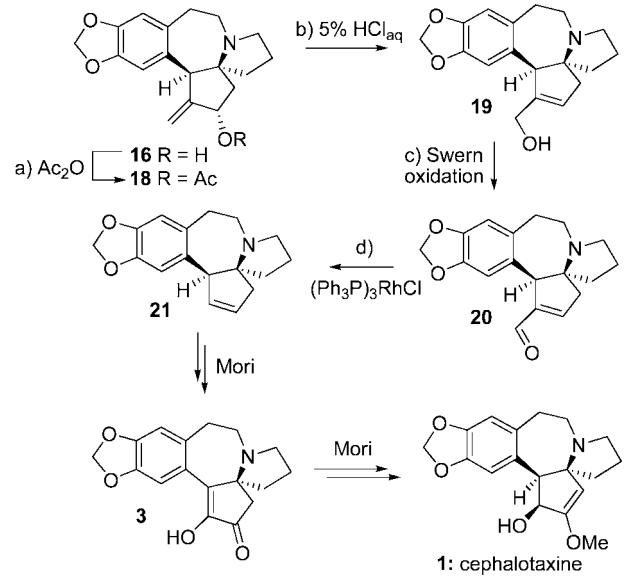


Figure 3. X-ray crystal structure of epoxide **15**.

Regioselective rearrangement of the epoxide **15** using Yamamoto's conditions[13]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 4. Completion of the Synthesis[a]



[a]Key: (a) Ac_2O, pyridine, 23 °C; (b) 5% aqueous HCl, reflux, 58% (three steps from **15**); (c) $(COCl)_2$, DMSO, NEt_3, DCM, −60 °C, 53%; (d) $Rh(PPh_3)_3Cl$, 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 decarbonylated 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 SiO_2 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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(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.

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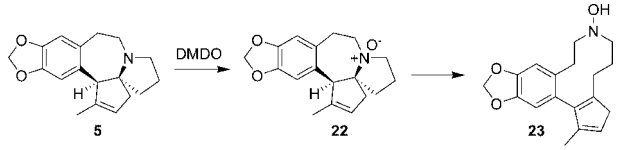
(12) The yield of **15** was dependent upon the success of forming the initial BF_3•amine adduct, and the main byproduct observed was the hydroxylamine **23**. We believe that **23** is formed by fragmentation of the *N*-oxide **22** and that **22** is formed by oxidation of the residual tertiary amine **5** that remains after incomplete BF_3•amine adduct formation of **5**.



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