Total Synthesis

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Total Synthesis of (−)-Cephalotaxine and (−)-Homoharringtonine via Furan Oxidation–Transannular Mannich Cyclization

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Dedicated to Professor Larry E. Overman

Abstract: *Homoharringtonine and its congener cephalotaxine were synthesized. Oxidative ring-opening of a furan unveils an amine-tethered dicarbonyl, which undergoes spontaneous transannular Mannich cyclization. The cascade builds the full cephalotaxine substructure in a single operation in 60% yield. A Noyori reduction enabled synthesis of the title compounds with excellent enantioselectivity ($k_{rel}=278$).*

The polycyclic alkaloid (−)-homoharringtonine (HHT, Figure 1) is produced by the plum yew *Cephalotaxus harringtonii*.[1] HHT binds to the peptidyl transferase center of the human ribosome and inhibits protein translation.[2] (−)-HHT shows nanomolar cytotoxity against leukemia cells, and after a long evaluation as a chemotherapeutic, it was approved for use in the US in 2012 for the treatment of chronic myeloid leukemia.[3]

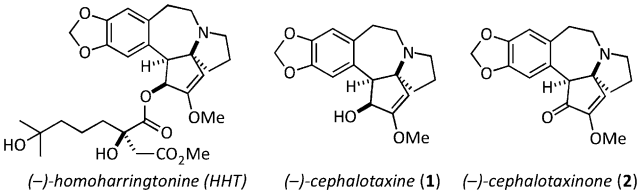


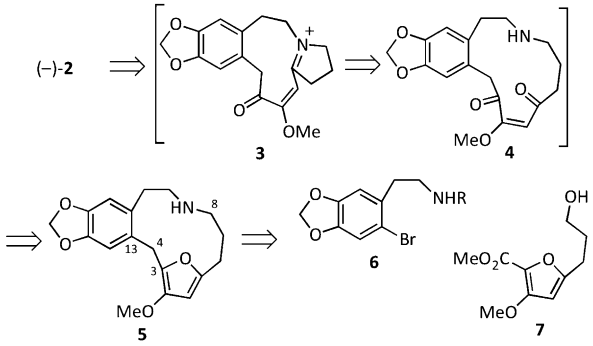
Figure 1. Cephalotaxus alkaloids.

Total syntheses of HHT have been reported;[4] however, HHT is prepared commercially through esterification of (−)-cephalotaxine (**1**),[5] a related alkaloid also found in *C. harringtonii*. Cephalotaxine is more abundant in the plant (ca. 50% of the alkaloid content), but it lacks the ester sidechain of HHT and is biologically inactive. Cephalotaxine was first prepared by Weinreb in 1972,[6] and it has been prepared dozens of times during the past decades.[7,8] Despite such efforts, commercial HHT is still prepared from plant-derived cephalotaxine.

Many side-chain analogues of HHT are known and have been evaluated,[9] a fact that is perhaps unsurprising considering the semi-synthetic providence of commercial HHT, and the dependence of biological activity on the ester side chain. Some HHT ester congeners have exciting biological activities.

Crystallographic studies suggest that the amine-substituted benzodioxole portion of HHT (i.e., the "cephalotaxine portion") is implicated in binding to the ribosome.[2a] However, relatively few congeners of HHT are known that vary the polycyclic cephalotaxine substructure.[10] We decided to develop an efficient synthesis of these natural cephalotaxus alkaloids and synthetic congeners.

Cephalotaxine (**1**) has been prepared by borohydride reduction of cephalotaxinone (**2**). The β-aminoketone functional group in **2** suggested preparation through a Mannich cyclization of intermediate **3** (Scheme 1). Retrosynthetic



Scheme 1. Synthetic plan for cephalotaxinone.

simplification of the iminium ion leads to 1,4-diketone **4**. Unsaturated diketone **4** could be made by oxidative opening of the corresponding macrocyclic furan **5**.[11] Strategically, use of the furan was appealing because its aromaticity would mask the reactive carbon atoms of the unsaturated 1,4-diketone prior to the key Mannich cyclization event.

Intermediate **5** is a 12-membered macrocycle, and synthesis of such medium-sized rings is not trivial. However, we hypothesized that the same factors complicating medium-ring synthesis, namely ring strain and transannular interactions, would increase the propensity of the substrate to undergo a dearomatization and subsequent transannular Mannich reaction.

We envisioned formation of the C8–N bond (cephalotaxine numbering) arising from a phenethylamine and an oxygenated carbon; either through a substitution reaction or through a reductive amination. However, an optimal method to construct the diarylmethylene group was less obvious. We considered preparing **5** through construction of either the C3–

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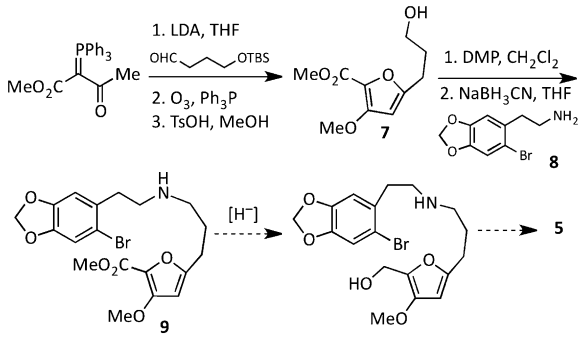
C4 or C4–C13 bond. Initially, we decided on pursuing formation of the C4–C13 bond because structures **6** are well-known, and coupling partner **7** resembles molecules Wasserman and co-workers reported in a single-operation furan synthesis.[12]

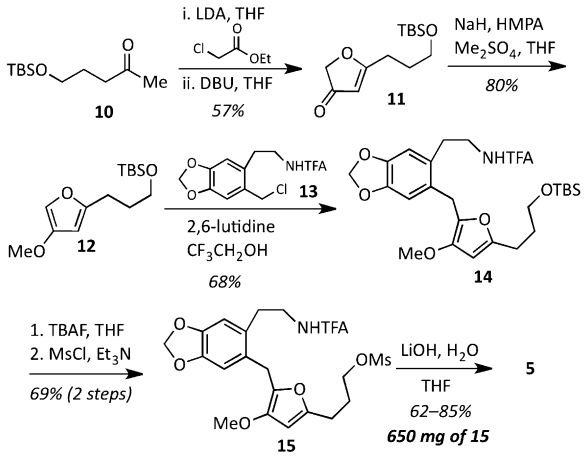
Wasserman's strategy was extended to compound **7**, which contains a primary alcohol (Scheme 2). Alcohol **7** could be coupled with known amine **8** through reductive amination to



Scheme 2. Wasserman-based furan synthesis. LDA = lithium diisopropyl amide, THF = tetrahydrofuran, Ts = toluene sulfonyl, DMP = Dess—Martin periodinane.

form **9**. However, conditions to give macrocycle **5** could not be identified. Interestingly, the ester functionality in **9** was surprisingly resistant to any type of hydride reduction or nucleophilic additions. Similarly, the ester in **7** (or alcohol protected congeners) was resistant to reduction or intermolecular addition of nucleophilic reagents derived from **8**. Potentially, the lack of electrophilicity of **7** and **9** arises from the lone pairs on the methoxy group and the furanyl oxygen, which can donate to the ester carbonyl, thereby decreasing reactivity.

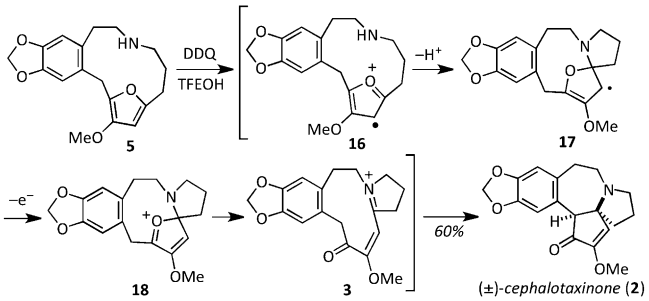
We next decided to take an alternative approach, involving formation of the C4–C3 bond by way of a Friedel–Crafts alkylation[13] of a furan (Scheme 3). Beginning with TBS-protected hydroxypentanone **10**,[14] Claisen-type condensation and cyclization gave furanone **11**.[15] Methylation gave



Scheme 3. Synthesis of the macrocycle. DDQ = 2,3-dichloro-5,6-dicyano-p-benzoquinone, TFA = trifluoroacetyl.

methoxyfuran **12**. Subjection of furan **12** to known benzyl chloride **13**[16] (prepared from homopiperonylamine) gave smooth bond formation yielding **14**. The protected alcohol was activated as the corresponding mesylate (**15**). Treatment of **15** with aqueous base led to cyclization with concomitant removal of the TFA group to give macrocycle **5**.[17,18] This final cyclization was quite robust; no dimer or oligomers were detected during the formation of the 12-membered ring. Moreover, the reaction was conducted on scales as large as 650 mg with good isolated yields of **5**.

Key intermediate **5** was first subjected to DDQ in *tert*-butanol as reported by Sayama (Scheme 4).[11] Gratifyingly, the reaction gave cephalotaxinone, albeit in low yield (ca.



Scheme 4. Racemic synthesis of cephalotaxine.

10%). Oxidative furan openings are responsive to the reaction solvent, and the oxidations often result in incorporation of the alcoholic solvent to the furan. Sayama found that sterically hindered (i.e., non-nucleophilic) solvents tend to give less solvolysis products. We suspected that polar non-nucleophilic solvents would stabilize the charged reactive intermediates without solvolytic trapping, and could increase the reaction yield. In the event, we discovered that trifluoroethanol markedly increased the reaction yield to 60%.

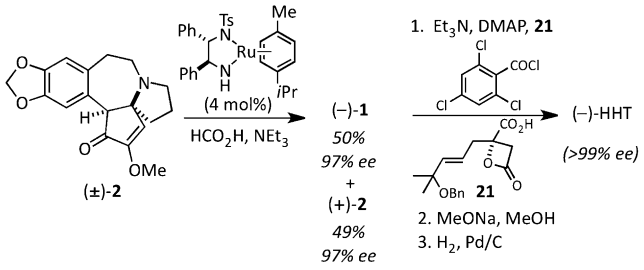
Mechanistically, single-electron oxidation of **5** gives a radical cation **16**. Transannular trapping of the radical oxocarbenium ion by the tethered amine results in **17**. Oxidation of **17** gives oxocarbenium ion **18**. Fragmentation of **18** releases iminium ion **3**, which can undergo Mannich cyclization to give (±)-cephalotaxinone (**2**) as a single diastereomer.

Synthesis of non-racemic cephalotaxinone could, at least in principle, be accomplished by rendering the key transformation (**5**→**2**) enantioselective; however, it was unclear which step of the mechanism would need to be controlled. Considering the plausible mechanism shown, the enantiodetermining step may be the final Mannich reaction. Alternatively, if hypothetical intermediate **3** has a conformation that is stable on the timescale of the Mannich step, then there would be a possibility of conformational chirality of the undecatrienone ring. In such a scenario, the initial transannular addition to the furanyl radical cation **16** could be enantiodetermining. Finally, such a scenario would require good transfer of point-to-conformational chirality, and non-reversibility of the mechanistic steps.

In these scenarios, the enantiodeterming step is an addition to a cationic species. The counteranion is a dichlor-

odicyanohydroquinone anion. Efforts to control this process by introducing a chiral counteranion were unsuccessful, despite adding several chiral protic acids in multiple solvents. No measureable enantioenrichment of cephalotaxinone was ever observed.

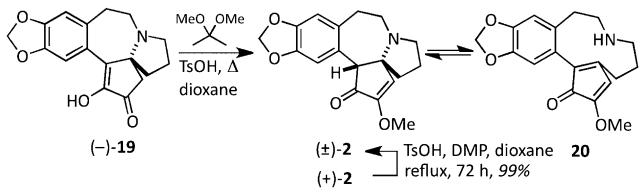
We next pursued a resolution-based strategy for the synthesis of enantioenriched cephalotaxine. No enantioselective reduction of **2** has been reported. Gratifyingly, Noyori's conditions[19] gave excellent results, producing (−)-cephalotaxine (**1**) with very high enantioselectivity (97% *ee*) at 50% conversion (Scheme 5, $k_{rel} = 278$). Spectroscopic data and



Scheme 5. Kinetic resolution of cephalotaxine. DMAP = 4-dimethylaminopyridine.

optical rotation for (−)-cephalotaxine matched those previously reported.[4–7] The major enantiomer of **1** is predicted by Noyori's model and was verified by comparison to previously reported optical rotation data. (−)-Cephalotaxine was then advanced to (−)-HHT following the procedure of Gin and coworkers.[4] Spectral data and optical rotation for (−)-HHT also matched those from previous reports.[4,5]

With the undesired (+)-**2** in hand, attempts were made to racemize this material. Previously, Mori[20] and Stoltz[21,22] observed racemization during the methylation of (−)-**19** to give (±)-**2** (Scheme 6). They attributed the racemization to



Scheme 6. Racemization of cephalotaxinone.

formation of intermediate achiral cyclopentadienone **20**. This suggested racemization of (+)-**2** should be possible, and it would allow recycling of the unwanted cephalotaxinone enantiomer. Gratifyingly, subjection of (+)-**2** to Mori/Stoltz conditions resulted in racemization, giving (±)-**2**. This allows simple recycling of the unwanted enantiomer of cephalotaxinone.[23]

In summary, we have completed a total synthesis of (−)-cephalotaxine and (−)-homoharringtonine. Our key transformation involved an oxidative furan opening with spontaneous transannular Mannnich reaction. A Noyori reduction converts (±)-cephalotaxinone to (−)-cephalotaxine with excellent enantioselectivity. The unwanted enantiomer of cephalotaxinone can be recycled through racemization in high yield. Overall, our synthesis of (−)-cephalotaxine is 9 steps and occurs in more than 5% chemical yield, which compares well with previous syntheses.

Acknowledgements

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Conflict of interest

The authors declare no conflict of interest.

Keywords: alkaloids · cephalotaxine · homoharringtonine · Mannich reactions · total synthesis

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Communications

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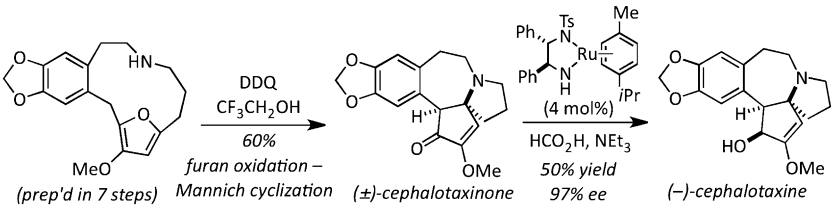
Total Synthesis of (−)-Cephalotaxine and (−)-Homoharringtonine via Furan Oxidation–Transannular Mannich Cyclization



Change of ring size: Oxidative ring-opening of a furan unveils an amine-tethered dicarbonyl, which undergoes spontaneous transannular Mannich cyclization. The cascade builds the full cephalotaxine substructure in a single operation in 60% yield. A Noyori reduction enabled synthesis of the title compounds with excellent enantioselectivity (k_{rel} = 278).