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Formal Total Synthesis of (±)-Cephalotaxine and Congeners via Aryne Insertion Reaction

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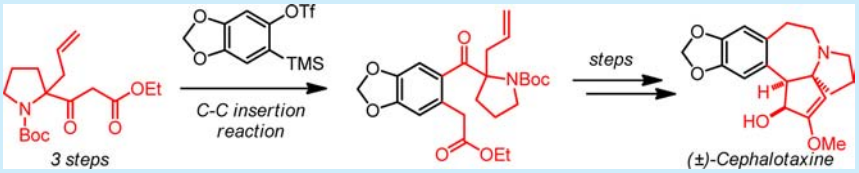
Supporting Information



ABSTRACT: The formal total synthesis of pentacyclic core alkaloid, (±)-cephalotaxine is achieved in nine steps from known 2-allylpyrrolidine-2-carboxaldehyde using aryne insertion reaction as a key step in 10% overall yield. The developed novel strategy enabled easy access to cephalotaxine congeners.

Cephalotaxine (**1**) is a pentacyclic alkaloid with benzazepine nucleus isolated from Chinese traditional medicine, *Cephalotaxus harringtonii* by Paudlar and co-workers.[1] The structures of natural products were well characterized by the research group of Powell using X-ray analysis in 1974 (Figure 1).[2] One of the esters of cephalotaxine namely homoharringtonine (**2**) was approved by Food and Drug Administration (FDA) for treatment of orphan leukemia in 2012 (syn. omacetaxine mepesuccinate, OmaproTM).[3]

The early syntheses of cephalotaxine (**1**) were reported independently by Weinreb et al.,[4] and Semmelhack et al.,[5] in 1972. Since then, several research groups have engaged in total synthesis of the pentacyclic core and related natural products.[1b,6,7] A recent review by Abdelkafi and Nay provides an excellent overview in this field.[8] The research group of Hong has recently reported the total synthesis of (±)-cephalotaxine (**1**) involving diastereoselective *N*-iminium ion cyclization as the key step.[9]

The clinical approval of Omacetaxine mepesuccinate as an orphan drug, and the biological significance and structural complexity of 1-azabicyclo[5.3.0]decane skeleton prompted us to take up the research program toward the synthesis of cephalotaxine (**1**).

A retrosynthetic analysis revealed that **4a** would be an ideal building block which can be transformed to **3**, popularly called

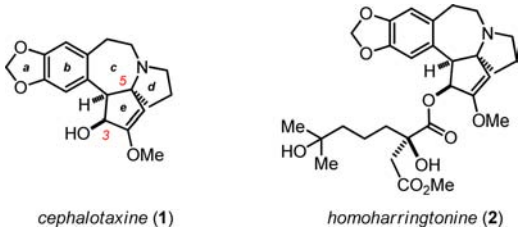
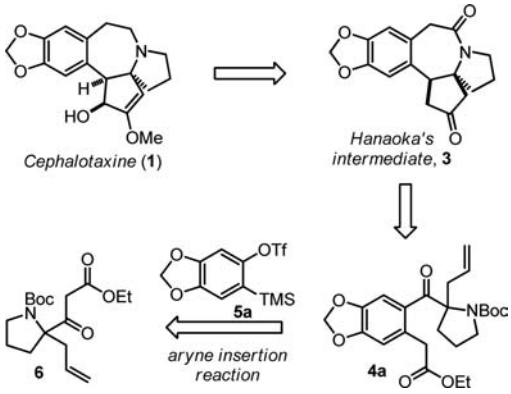


Figure 1. Structures of cephalotaxine and homoharringtonine.

Scheme 1. Retrosynthetic Analysis of Cephalotaxine



Hanaoka's intermediate (Scheme 1). This pentacyclic frame has already been converted to cephalotaxine (**1**) by Hanaoka.[10] We believed that an efficient approach to **4a** would not only constitute formal total synthesis of target alkaloid **1**, but would also enable synthesis of structural analogues. A close look at **4a** provided a clue that a simple aryne insertion reaction of β-ketoester **6** and benzyne precursor **5a** would be the ideal reaction to achieve **4a** and other variants for analogue synthesis. This aryne insertion reaction has hitherto been less explored in construction of complex alkaloids.[11] Recently, Stoltz and co-workers efficiently utilized the acyl alkylation of arynes in total synthesis of (+)-amurensinine and (−)-curvularin.[12] This C−C bond insertion is an interesting reaction to explore the synthesis of complex natural products as a key step.

Starting from the known pyrrolidine-2-carbaldehyde derivative, **7**[13] (easily synthesized from commercially inexpensive *L*-proline on multigram scale), was subjected to Roskamp

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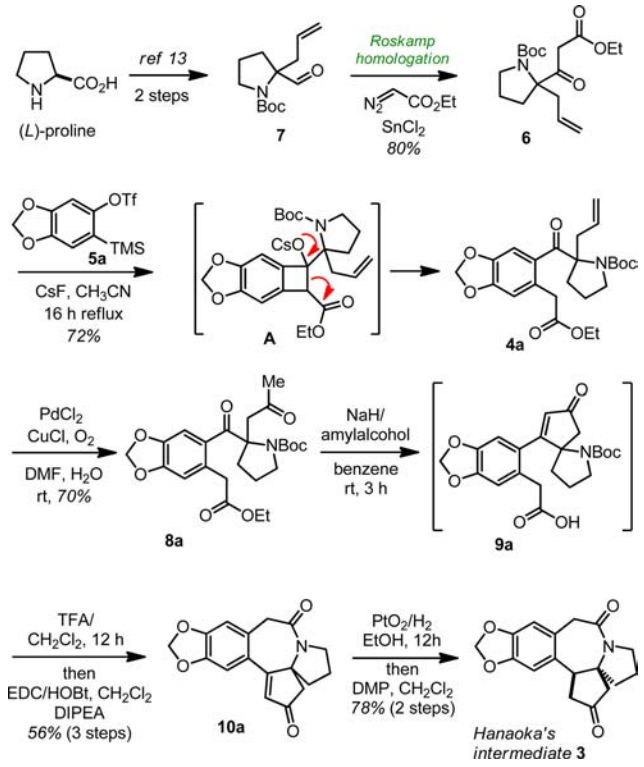
Scheme 2. Synthesis of Hanaoka's Intermediate 3



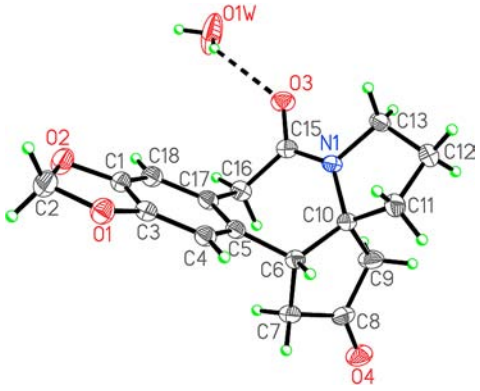
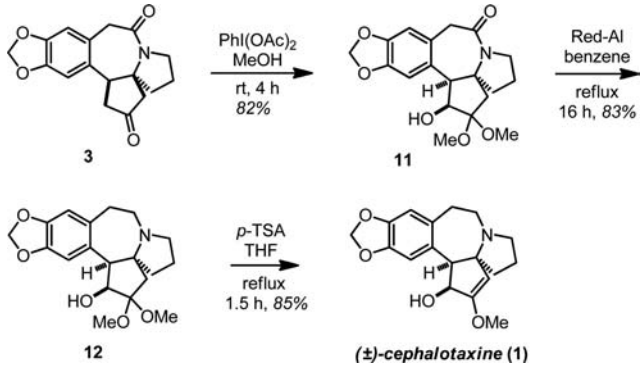


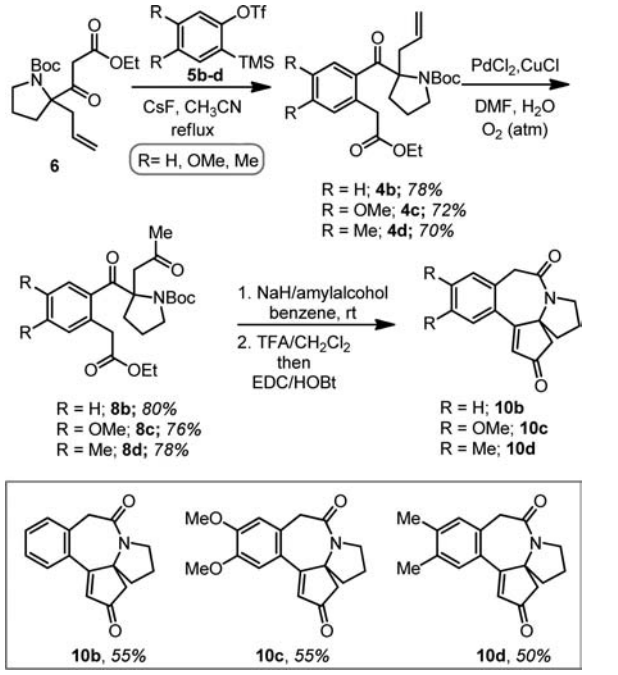
Figure 2. ORTEP diagram of Hanaoka's intermediate **3** hemihydrate.

Scheme 3. Total Synthesis of Cephalotaxine



homologation[14] with diazo ester and catalytic $SnCl_2$ to synthesize the β-keto ester **6** in 80% yield (Scheme 2). The "benzyne" generated from methylenedioxy aryne precursor **5a** under

Scheme 4. Synthesis of Analogues of Cephalotaxine Core



flouride-induced 1,2-elimination[15] allowed a smooth [2 + 2]-cycloaddition to furnish unstable benzocyclobutene intermediate **A**. This strained ring underwent C−C bond cleavage of the cyclobutene ring and installed two substitutions on the aryl ring. The product **4a** has an all carbon framework required to build the rings C and E. The Wacker oxidation[16] of **4a** with catalytic $PdCl_2$ and CuCl in the presence of oxygen atmosphere gave the requisite methyl ketone **8a** in 70% yield. A facile intramolecular aldol reaction triggered by NaH in the amyl alcohol/benzene solvent mixture and subsequent hydrolysis of the ester group were executed in one-pot to yield the spiro pyrrolidine **9a**.[17] The crude intermediate **9a** was subjected to TFA in CH_2Cl_2 to remove the Boc-protection at room temperature. Sequential addition of excess DIPEA and EDC/HOBt in the same pot provided pentacyclic frame **10a** in 56% isolated yield. The synthesis of pentacyclic enone **10a** from **8a** involving four synthetic transformations (aldol reaction, ester hydrolysis, Boc deprotection, and amidation) was accomplished with a single chromatographic purification. Reduction of **10a** using Adam's catalyst (PtO_2)[18] under hydrogen atmosphere provided ketolactam **3** along with a slight amount of over reduced alcohol at the C-3 position as an inseparable mixture. This crude mixture on oxidation with Dess-Martin periodinane allowed us to isolate Hanaoka's intermediate **3** as a single diastereomer in 78% yield for two steps. The highly diastereoselective fused pentacyclic ring system of compound **3** was confirmed by single crystal X-ray diffraction studies (Figure 2).[19]

Next Hanaoka's intermediate **3** was converted to (±)-cephalotaxine (**1**) following a known procedure in three steps (Scheme 3).[10] Thus, we have achieved the total synthesis of (±)-cephalotaxine (**1**) in nine steps from known pyrrolidine-2-carbaldehyde **7** using over the shelf chemicals in 10% overall yield.

The easy access to multiple grams of compound **6** prompted us to attempt insertion reaction on various arynes, namely, benzyne, dimethoxybenzyne, and dimethylbenzyne.[20] Following the synthetic route as used for the synthesis of cephalotaxine in

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Scheme 2, various aryne precursors **5b−d** were subjected to smooth aryne insertion reaction with compound **6** afforded **4b−d** followed by Wacker oxidation to give **8b−d** in excellent yields. Subsequent NaH mediated aldol reaction resulted in analogues of cephalotaxine **10b−d** in good yields (Scheme 4).

In summary, the pentacyclic alkaloid natural product cephalotaxine and its analogues are synthesized using an aryne insertion reaction which demonstrates the power of C−C bond insertion in complex natural product synthesis. This strategy permits a scalable synthesis of (±)-cephalotaxine and its congeners, wherein diverse aryl groups are introduced smoothly.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b00659.

Experimental procedures, characterization details and ^{1}H and ^{13}C NMR spectra of new compounds (PDF)
Single crystal X-ray data for compound **3** (CIF)

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Notes

The authors declare no competing financial interest.

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(19) CCDC-1445554 (**3**) contains the supplementary crystallographic data for this paper. This data can be obtained free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html or from the Cambridge Crystallographic Data Centre (CCDC), 12 Union Road, Cambridge CB2 1EZ, UK. Fax: + 44(0) 1223 336 033. E-mail: deposit@ccdc.cam.ac.uk.

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