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Total Synthesis of (±)-Cephalosol

Yuanzhen Xie,[†] Ning Wang,[‡] Bin Cheng,[‡] and Hongbin Zhai*[,†,‡]

Department of Chemistry, University of Science and Technology of China, Hefei 230026, China, and State Key Laboratory of Applied Organic Chemistry, Lanzhou University, Lanzhou 730000, China

zhaih@lzu.edu.cn

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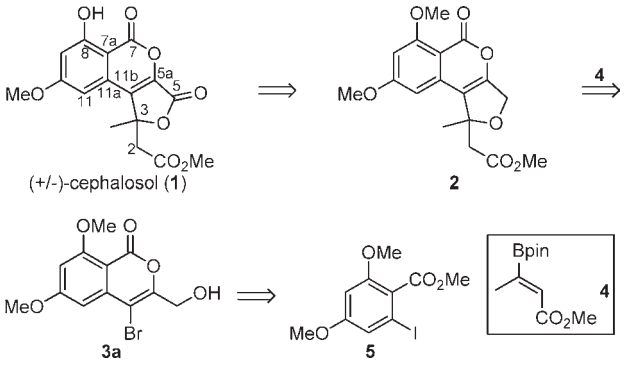
ABSTRACT

A concise and efficient total synthesis of (±)-cephalosol has been completed (5 steps from known ester 5, 39% overall yield), featuring a Cu(II)-promoted haloisocoumarin formation and sequential Suzuki cross-coupling/intramolecular oxo-Michael addition.

(−)-Cephalosol was isolated as a potent antimicrobial metabolite by Tan and co-workers from *Cephalosporium acremonium* IFB-E007, an endophytic fungal strain.[1] The host plant, *Trachelospermun jasminoides* (Lindl.) Lem. (Apocynaceae), has long been used in traditional Chinese medicine (TCM) to treat arthritis and other inflammatory diseases.[1] The natural product possesses a novel tricyclic backbone featuring a conjugated unsaturated γ-lactone fused to an isocoumarin at C-5a and C-11b. Attached to the sole quaternary center [C-3, of (*S*) configuration] are methyl and methoxycarbonylmethyl groups. Moreover, this metabolite showed prominent antimicrobial bioactivities as confirmed with human pathogenic microbes including *Escherichia coli*, *Pseudomonas fluorescens*, *Trichophyton rubrum*, and *Candida albicans*; the MIC values ranged from 1.95 to 7.8 μg/mL. As a result, this molecule should be a superb target for the synthetic communities. Indeed, the first total synthesis of (±)-cephalosol (**1**, Scheme 1) has already been reported by Arlt and Koert.[2]

Herein, we wish to disclose our studies in developing a new convergent total synthesis. We envisioned that **1** could be constructed from **2** by allylic oxidation followed by a selective ether cleavage. Tricycle **2** should be accessible via Suzuki coupling of bromoisocoumarin **3a** with boronate **4** followed by an intramolecular oxo-Michael addition. Bromoisocoumarin **3a** in turn could be generated from the known ester **5**[3] by Sonogashira coupling and Cu(II)-promoted haloisocoumarin formation.

Scheme 1. Retrosynthetic Analysis of (±)-Cephalosol (**1**)



[†] University of Science and Technology of China.
[‡] Lanzhou University.

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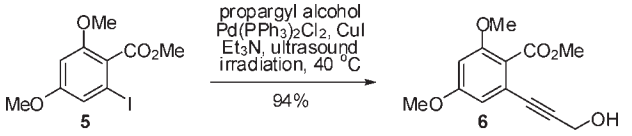
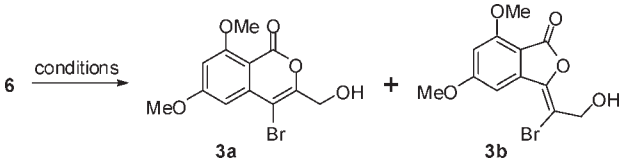
Scheme 2. Synthesis of Alkyne **6** via Sonogashira Coupling



Our synthesis commenced from ester **5**[3] (Scheme 2), which was smoothly converted into alkyne **6** by Sonogashira coupling with propargyl alcohol.[4] The synthesis of 4-haloisocoumarins have been extensively investigated during the past decade.[5] For instance, $Cy_2NH \cdot HX$[5e] could enhance $CuCl_2$- or $CuBr_2$-promoted cyclization of *o*-(1-alkynyl)benzoates for the synthesis of 4-haloisocoumarins. However, reaction of **6** by employing this protocol[5e] led to the formation of **3a** (6-*endo*, 13%) as the minor product compared to **3b** (5-*exo*, 70%, major), as shown in entry 1, Table 1. The cyclization conditions were optimized by scrutinizing the effects of different bases and temperatures (entries 2–6). To our delight, treatment of **6** with $CuBr_2$ and pyridine in 1,2-dichloroethane at reflux produced **3a** and **3b** in 71% and 13% yields, respectively (entry 5).

Table 1. Optimization of $CuBr_2$-Promoted Cyclization of **6**[a]

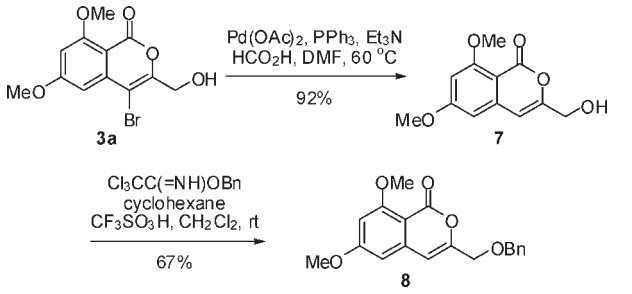


entry	conditions	yield[c] (**3a**/**3b**%)
1	$CuBr_2$, $Cy_2NH \cdot HBr$, 80 °C	13/70[b]
2	$CuBr_2$, reflux	28/38
3	$CuBr_2$, K_2CO_3, reflux	36/30
4	$CuBr_2$, Cs_2CO_3, reflux	42/28
5	**$CuBr_2$, py, reflux**	**71/13**
6	$CuBr_2$, DBU, reflux	10/6

[a] Reaction conditions: **6** (1.0 equiv), $CuBr_2$ (2.1 equiv), base (1.5 equiv) in $(ClCH_2)_2$ for 2 h. [b] $Cy_2NH \cdot HBr$ (0.1 equiv). [c] Isolated yield.

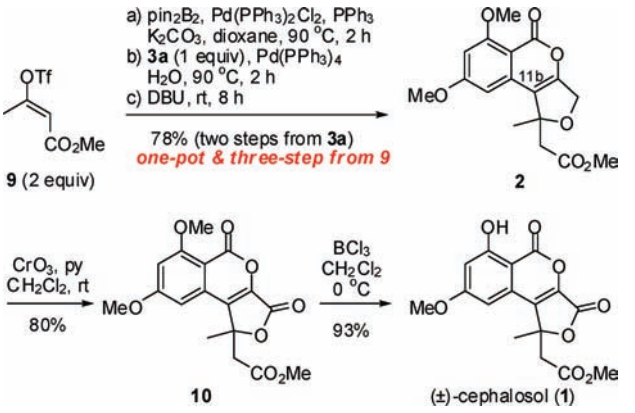
Since it was difficult to clearly distinguish the structures of **3a** and **3b** by ^1H and ^{13}C NMR analyses only, the presumed **3a** was transformed into the known compound **7**[6] via palladium-catalyzed debromination[7] with triethylammonium formate (Scheme 3). Unfortunately, our ^1H NMR data failed to match those documented for **7** in the literature.[6] Nevertheless, the data of the corresponding

Scheme 3. Confirmation of the Structure of **3a**



benzyl ether **8**[8] (obtained by benzylation[9] of **7** with benzyl 2,2,2-trichloroacetimidate) were identical to those reported, which indicated that the NMR data for **7** in the literature[6] might not be accurate.

Scheme 4. Completion of the Synthesis of (±)-Cephalosol (**1**)



With **3a** in hand, a four-carbon side chain had to be appended to C-11b[10] of **3a** in order to construct the lactone moiety (C ring) in **1**. Due to its susceptibility to protodeboronation,[11] boronate **4** must be generated in situ, for example, from enol triflate **9**[12] by Suzuki coupling with pin_2B_2 (Scheme 4).[13] Without any purification, the freshly prepared boronate **4** was immediately exposed to **3a** in the presence of 10 mol % of $Pd(PPh_3)_4$ in dioxane/H_2O (7:1) at 90 °C for 2 h. The reaction mixture was then directly treated with DBU to trigger the desired intramolecular oxo-Michael addition, and tricycle **2** was thus afforded in 78% yield. Finally, oxidation of **2** with the

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Collins reagent provided **10** (80%), which underwent selective ether cleavage at C-8 to give (±)-cephalosol (**1**) in 93% yield.[2]

In summary, we have accomplished a five-step total synthesis of (±)-cephalosol from ester **5** in 39% overall yield. Cu(II)-promoted haloisocoumarin formation and sequential Suzuki coupling/intramolecular oxo-Michael addition are worth noting for the current strategy.

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