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Stereoselective Synthesis of (−)-Centrolobine†

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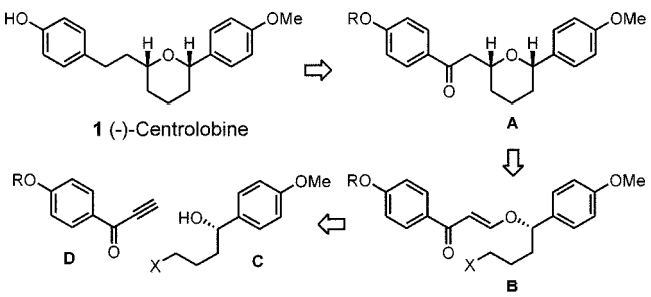
(−)-Centrolobine (**1**) was isolated from the heartwood of *Centrolobium robustum* and from the stem of *Brosimum potabile* in the amazon forest.[1,2] It features a *cis*-2,6-disubstituted tetrahydropyran core structure. It is now well established that *cis*-2,5-disubstituted tetrahydrofurans and *cis*-2,6-disubstituted tetrahydropyrans are obtained stereoselectively *via* radical cyclization of β-alkoxyacrylates,[3] and we intended to use radical cyclization reaction of β-alkoxyvinyl ketones in the synthesis of this compound.

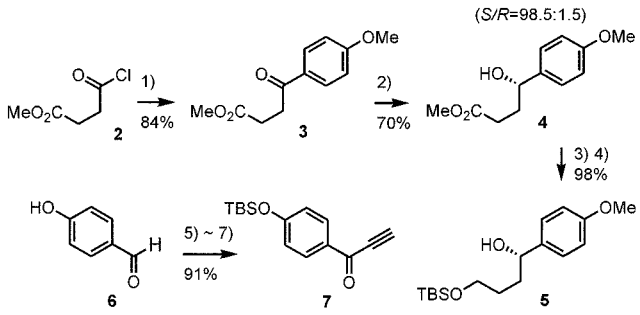
In the retrosynthetic analysis, radical cyclization reaction of the β-alkoxyvinyl ketone **B** is expected to give the tetrahydropyran **A**, which may be transformed into **1** *via* carbonyl reduction. The intermediate **B** may be prepared *via* combination of the secondary alcohol **C** and the arylpropynone **D** (Scheme 1). Reaction of the acid chloride **2** with arylcopper reagent[4] provided the ketone **3**, which was converted into the secondary alcohol **4** *via* asymmetric reduction by (−)-*B*-chlorodiisopinocampheylborane.[5] LAH reduction of **4** and selective TBS protection led to the intermediate **5**. The complementary fragment arylpropynone **7** was synthesized from 4-hydroxybenzaldehyde (**6**) in a 3-step sequence (Scheme 2).

The β-alkoxyvinyl ketone **8** was prepared *via* reaction of **5** and **7** in the presence of *N*-methylmorpholine,[6] which was then converted into the bromide **9** *via* TBS deprotection and bromide substitution. In the presence of tris(trimethylsilyl)-silane and AIBN in benzene under reflux, the bromide **9** was converted into the tetrahydropyran **10** in good yield. The final conversion from **10** to **1** required use of sodium cyanoborohydride and boron trifluoride (Scheme 3).[7,8]

In this synthesis, the *cis*-2,6-disubstituted tetrahydropyran core of (−)-centrolobine was successfully introduced *via* radical cyclization of a β-alkoxyvinyl ketone intermediate.



Scheme 1



Scheme 2. 1) 1.2 eq. 4-MeOPhMgBr, 1.2 eq. CuBr, 2.4 eq. LiBr, THF, r.t. 30 min; 2) 1.1 eq. (−)-Ipc$_2$BCl, THF, −25 °C, 36 h; 3) 1.5 eq. LAH, ether, 0 °C ~ r.t. 1 h; 4) 1.05 eq. TBSCl, 2.5 eq. imidazole, DCM, 0 °C ~ r.t. 1 h; 5) 2.0 eq. NaH, 1.5 eq. TBSCl, THF, 0 °C ~ r.t. 1 h; 6) 1.5 eq. CHCMgBr, THF, 0 °C ~ r.t. 1 h; 7) 2.0 eq. $BaMnO_4$, DCM, r.t. 24 h.

†Dedicated to Prof. Yong Hae Kim in commemoration of his distinguished academic career.

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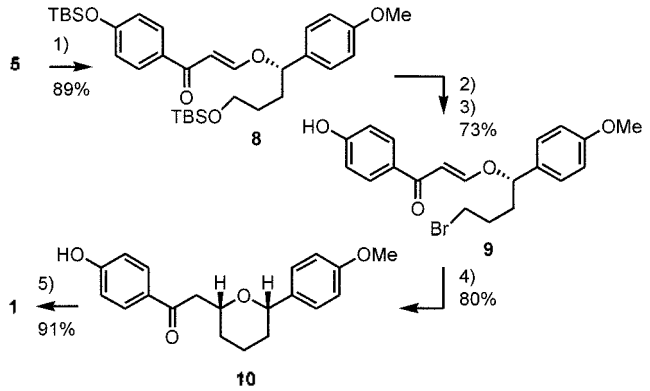

Scheme 3. 1) 1.5 eq. **7**, 0.5 eq. NMM, DCM, r.t. 24 h; 2) 2.5 eq. TBAF, THF, r.t. 1 h; 3) 1.5 eq. CBr_4, 1.2 eq. PPh_3, 3.0 eq. TEA, DCM, r.t. 1 h; 4) 1.2 eq. $(Me_3Si)_3SiH$, 0.2 eq. AIBN, PhH, reflux, 3 h; 5) 5.0 eq. $BF_3{\cdot}OEt_2$, 4.0 eq. $NaBH_3CN$, THF, r.t. 72 h.

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