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Two successive one-pot reactions leading to the expeditious synthesis of (−)-centrolobine

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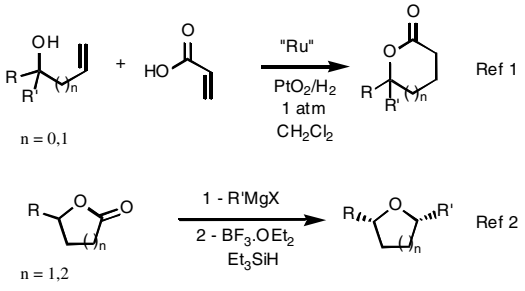
Abstract—A very short and efficient synthesis of (−)-centrolobine has been achieved by using two successive one-pot reactions. The first sequence involves a cross-metathesis reaction/hydrogenation/lactonization and the second sequence is a Grignard addition/reduction.

The most straightforward synthesis of functionalized organic compounds would 'ideally' require the development of one-pot or successive one-pot reactions from commercially available and inexpensive starting materials. The use of catalysts able to mediate multiple processes at different rates or under varied conditions would further simplify these assembly protocols. Recently, we have shown that a one-pot tandem cross-metathesis/hydrogenation procedure could be achieved at room temperature under atmospheric pressure of hydrogen in the presence of the Hoveyda ruthenium catalyst **II** and PtO_2 to produce substituted lactones from homoallylic alcohols.[1] Furthermore, we have shown that 2,5-disubstituted tetrahydrofurans were obtained with good diastereoselectivity from lactones by addition of Grignard reagents, followed by $BF_3{\cdot}OEt_2$–Et_3SiH reduction, in a one-pot procedure.[2] (Scheme 1).



Scheme 1.

Here, we report a straightforward synthesis of optically pure (−)-centrolobine that highlights the utility of these two successive one-pot reactions. (−)-Centrolobine is an antiprotozoal natural product from the Amazon forest isolated from the heartwood of *Centrolobium robustum* and from the stem of *Brosinium potabile*.[3] (Fig. 1).

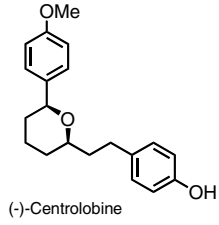


Figure 1.

Although the basic structure of (−)-centrolobine was elucidated in 1964,[3a] its absolute configuration was only established in 2002 by an enantioselective total synthesis.[4] Since then, two enantioselective syntheses of (−)-centrolobine have been achieved, one uses a Prins cyclization,[5] and the other a reductive etherification of δ-trialkylsilyloxy substituted ketones.[6]

Keywords: Centrolobine; One-pot reaction; Cross-metathesis; Allyltitanation.
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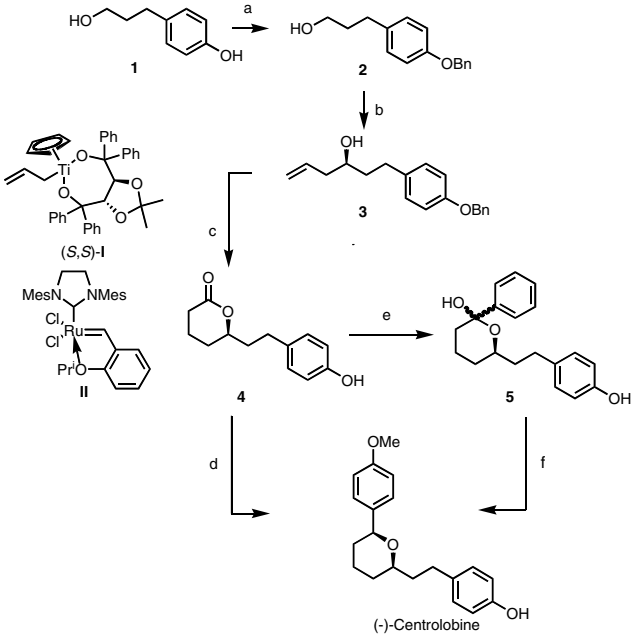
Our total synthesis of (−)-centrolobine involves the initial selective protection of 3-(4-hydroxyphenyl)-1-propanol **1** to the corresponding monobenzyl ether **2** (90% yield) by using benzylbromide (0.95 equiv) [NaH (0.95 equiv), DMF, 50 °C, 12 h]. Two steps were necessary to transform **2** into the optically active homoallylic alcohol **3**, a precursor of the tetrahydropyran ring of (−)-centrolobine. After oxidation of **2** with PCC (CH_2Cl_2, rt, quantitative), the resulting aldehyde was treated with the highly face-selective enantioselective allyltitanium complex (*S*,*S*)-**I**[7] (Scheme 2). In this manner, the homoallylic alcohol **3** was obtained in 61% yield with an enantiomeric excess superior to 95%.[8]



Scheme 2. Synthesis of (−)-centrolobine. (a) NaH, BnBr, DMF, reflux 90%; (b) i. PCC, CH_2Cl_2, rt, quantitative; ii. (*S*,*S*)-**I**, ether, −78 °C, 61%; (c) acrylic acid (4.2 equiv), **II** (3.7 mol%), CH_2Cl_2, two days then Pd/C (2.2 mol%), H_2, four days, 56%; (d) i. 4-methoxyphenylmagnesium bromide (4 equiv) THF, −78 °C, 1 h; ii. TMSOTf (4 equiv) and Et_3SiH (4 equiv), −78 °C then rt, 1 h, 23%; (e) 4-methoxyphenylmagnesium bromide (3 equiv) THF, −78 °C, 1 h; (f) $BF_3{\cdot}Et_2O$ (3 equiv) and Et_3SiH (4 equiv), CH_2Cl_2, −78 °C then rt, 1 h, 40% from **4**.

The transformation of homoallylic alcohol **3** into lactone **4** was achieved according to the one-pot procedure that we have previously devised[1] with the modification of using the more commonly used Pd/C instead of PtO_2 in the hydrogenation step. After treating the homoallylic alcohol **3** with acrylic acid (4.2 equiv) in the presence of the Hoveyda's catalyst **II** (3.7 mol%) in CH_2Cl_2 for two days at rt, Pd/C (2.2 mol%) was added and the reaction mixture was placed under one atmosphere of hydrogen for four days. Lactone **4** was produced in 56% yield from homoallylic alcohol **3**.[9] This transformation implies four one-pot reactions, a cross-metathesis (CM), a hydrogenation, a lactonization and a debenzylation. The use of Pd/C instead of PtO_2 allowed us to improve the in situ debenzylation of the phenol function. Lactone **4** was then transformed into (−)-centrolobine in two steps. After treatment of **4** in THF at −78 °C for 1 h with 4-methoxyphenylmagnesium bromide (3.0 equiv), lactol **5** was obtained in equilibrium with the 5-hydroxyketone. The addition of Et_3SiH (4.0 equiv), in the presence of $BF_3{\cdot}Et_2O$ (3.0 equiv) (CH_2Cl_2, −78 °C then rt, 1 h), to the crude lactol **5** afforded (−)-centrolobine with a nonoptimized 40% overall yield from lactone **4**. (−)-Centrolobine was thus obtained in a 12% overall yield from 3-(4-hydroxyphenyl)-1-propanol **1**. The analytical and spectroscopic data of (−)-centrolobine thus obtained including IR, ^1H NMR and ^{13}C NMR as well as the optical rotation $[\alpha]_D^{20}$ –94.0 (*c* 0.33, $CHCl_3$) were in perfect agreement with those previously reported in the literature ($[\alpha]_D^{20}$ –92.2 (*c* 1.0, $CHCl_3$)).[3d]

It is worth noting that a one-pot transformation of **4** into (−)-centrolobine, implying two successive one-pot reactions, was also tested. Lactone **4** was transformed into (−)-centrolobine by addition of 4-methoxyphenylmagnesium bromide (1 M solution in THF, 4.0 equiv, CH_2Cl_2, −78 °C), followed by the addition at −78 °C of TMSOTf (4.0 equiv) and Et_3SiH (4.0 equiv). After this successive one-pot reaction (−)-centrolobine was isolated in 23% yield (Scheme 2).

The two reported synthetic approaches to (−)-centrolobine are very short and efficient. By performing two successive one-pot reactions, purification of the intermediates was avoided and this is very attractive for large scale preparations. As the reactions used are quite versatile, an expeditious preparation of a small library of analogues should be achieved in a straightforward manner. This work is ongoing in our laboratories as well as the structure–activity relationship of the libraries.

Acknowledgements

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References and notes

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8. The enantiomeric excess was determined by HPLC. Column: OD-H, eluent: hexane/*i*-PrOH: 95/5; 1.0 mL/min, retention time: 15.4 min.
9. Spectroscopic data: lactone **4**: $[\alpha]_D^{20}$ − 54.4 (*c* 1.0, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ (ppm) 7.00 (d, J = 8.5 Hz, 2H); 6.70 (d, J = 8.5 Hz, 2H); 5.40 (br s, OH); 4.30 (m, 1H); 2.80–2.30 (m, 4H); 2.00–1.65 (m, 5H); 1.50 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 172.4 (s); 154.0 (s); 132.7 (s); 129.4 (2d); 115.3 (2d); 79.5 (d); 37.5 (t); 30.0 (t); 29.3 (t); 27.7 (t); 18.3 (t); IR (NaCl): ν (cm^{-1}) 3350, 1730, 1520, 1440, 1420, 1260, 1050, 900, 740, 710; MS (EI, 70 eV): *m*/*z* 220 (M, 50%); 160 (11%); 133 (85%); 120 (18%); 107 (100%).