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Total synthesis of (−)-centrolobine

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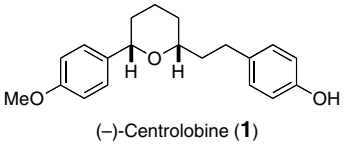
ABSTRACT

Stereoselective synthesis of (−)-centrolobine, an anti-*Leishmania* agent, was accomplished via an intramolecular Barbier-type reaction of iodo-ester with *n*- or *t*-butyllithium followed by Lewis acid-promoted Et_3SiH reduction of the resulting hemiacetal.

(−)-Centrolobine (**1**) is a natural product isolated from the heartwood of *Centrolobium robustum*[1] and from the stem of *Brosinum potabile*[2] in the Amazon forest (Fig. 1). It exhibits activity against *Leishmania amazonensis promastigotes*, a parasite associated with leishmaniasis, which is a major health problem in Brazil.[1c,3] Its structure, which contains 2,6-*syn*-tetrahydropyran, was elucidated by the synthesis of racemic **1**[1a,1b] and the absolute structure was determined in 2002 by the first enantioselective total synthesis of (−)-**1**.[4] Since then, a number of groups have reported the total synthesis of **1** in both racemic[5] and optically active forms.[6]

We have recently reported that treatment of an acyclic iodo-ester with *n*- or *t*-butyllithium effected intramolecular cyclization to give the hemiacetal, which was reduced with Et_3SiH in the presence of $BF_3{\cdot}Et_2O$ to give 2,6-*syn*-tetrahydropyran.[7] As an application of this method to the synthesis of natural products, we focused our attention on the synthesis of (−)-centrolobine (**1**). Retrosynthetic analysis revealed two possible synthetic routes, A and B, using iodo-esters **2** and **3**, respectively (Fig. 2). We now report our results using both synthetic routes A and B.



(−)-Centrolobine (**1**)

Figure 1. Structure of (−)-centrolobine (**1**).

First, we examined route A using the iodo-ester **2** (Scheme 1). Addition of Grignard reagent **5** to acid chloride **4** in the presence of CuBr and LiBr in THF[8] afforded ketone **6**[5d] in 98% yield. Asymmetric reduction of **5** with $BH_3{\cdot}THF$ in the presence of (*R*)-(+)-2-methyl-CBS-oxazaborolidine **7**[9] gave (*S*)-alcohol **8**[5d] in 96% yield. Reduction of the ester **8** with $LiAlH_4$ followed by TBS protection afforded TBS ether **9** (99% ee)[10] in 97% yield. Coupling of the alcohol **9** and carboxylic acid **10**[11] was carried out by Shiina's method[12] using 2-methyl-6-nitrobenzoic anhydride (MNBA) to give ester **11** in 98% yield. Removal of the TBS group followed by iodination with I_2 and Ph_3P[13] gave the required iodo-ester **2** in 87% yield. Upon treatment of **2** with *n*- or *t*-butyllithium in THF at −78 °C, an intramolecular Barbier-type reaction[14] took place to give an equilibrium

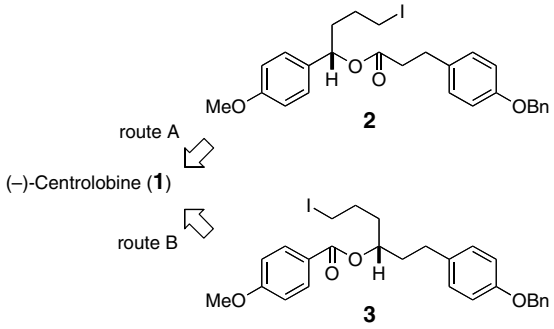


Figure 2. Synthetic routes A and B.

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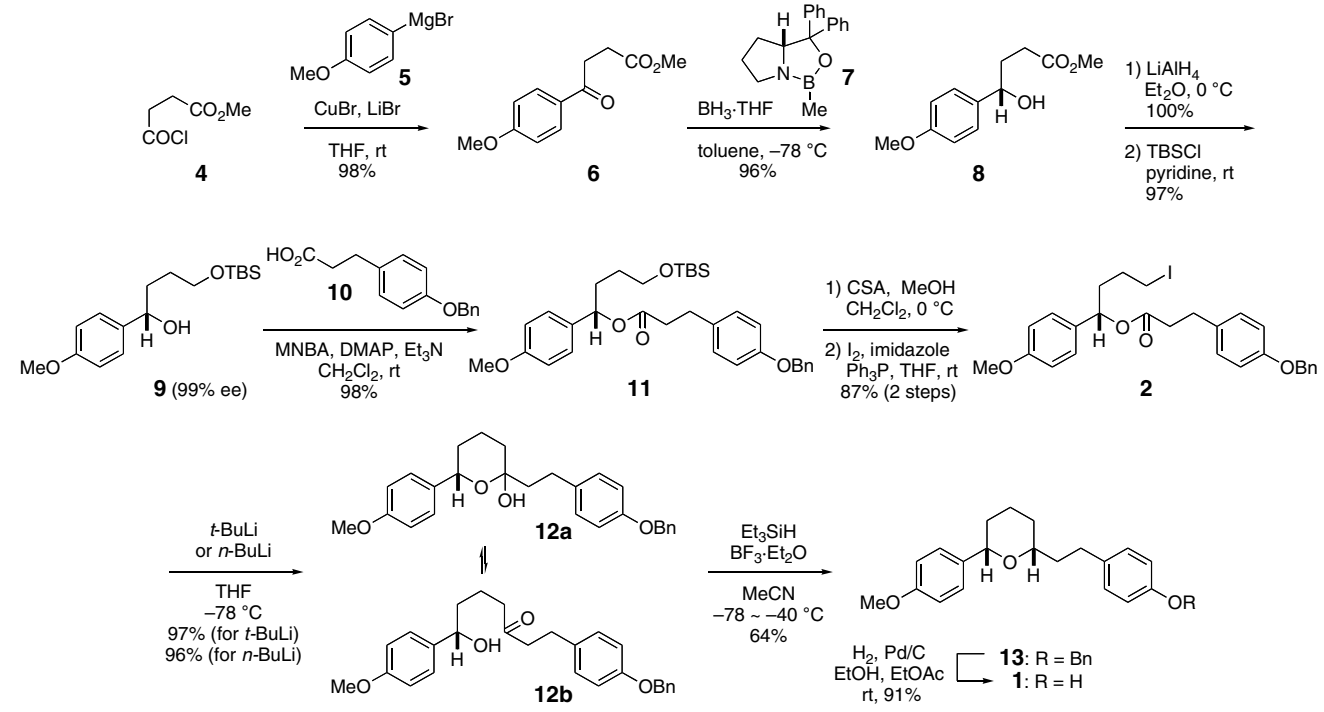


Scheme 1.

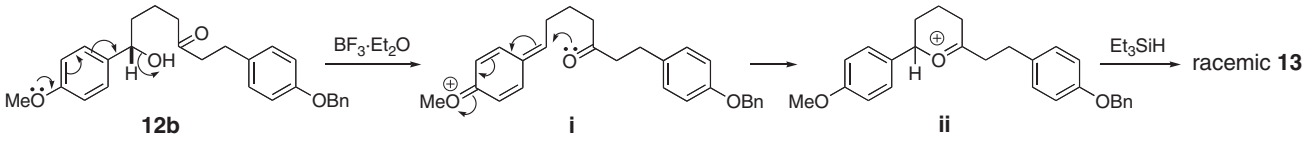
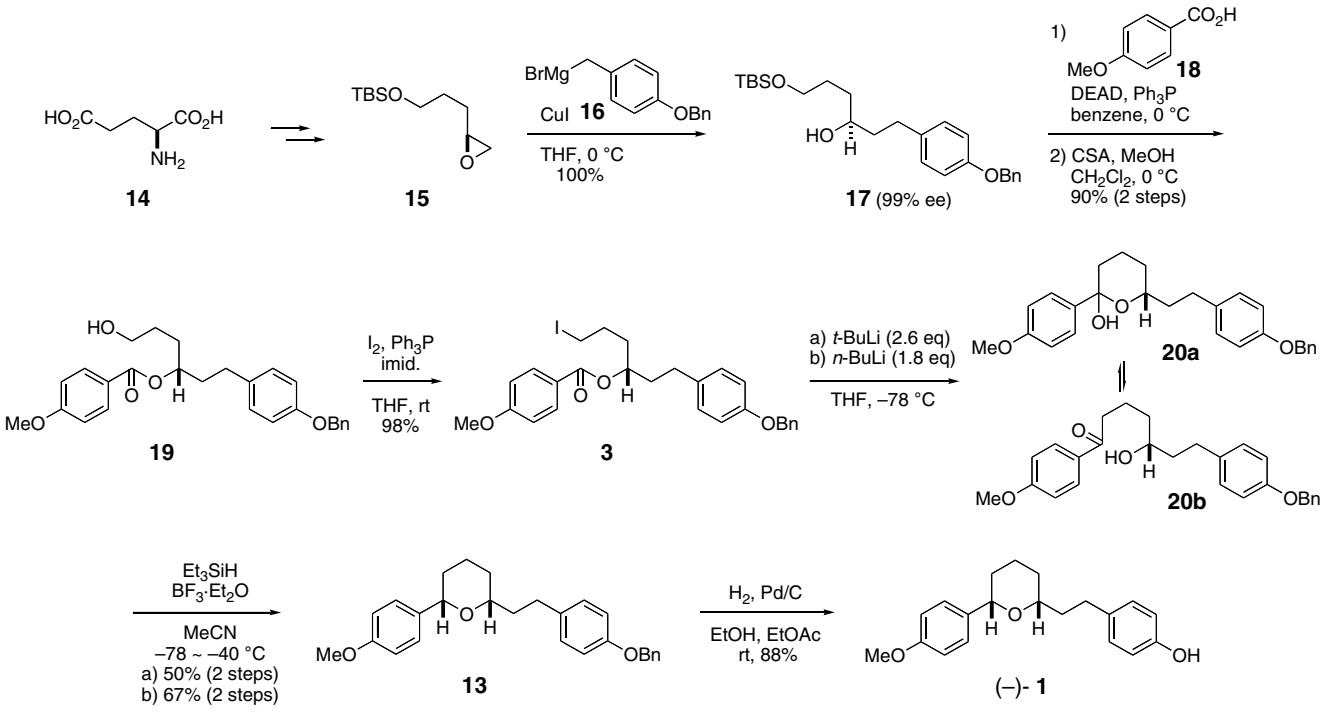


Figure 3. Mechanism for reaction of **12** with Et_3SiH and $BF_3{\cdot}Et_2O$.



Scheme 2.

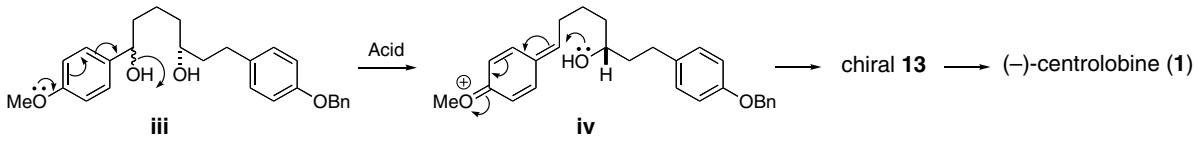
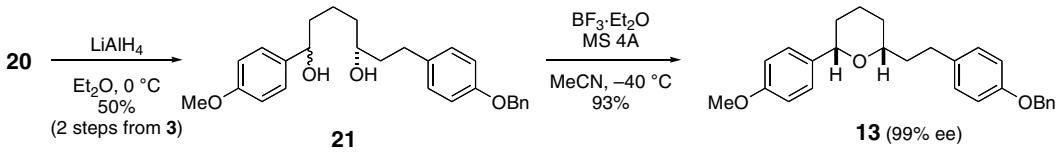


Figure 4. Synthetic plan for (−)-**1** via cyclization of diol **iii**.



Scheme 3.

mixture of hemiacetal **12a** and ketone **12b** (ca. 1:1.8 ratio in $CDCl_3$) in 96% or 97% yield, respectively. Treatment of **12** with Et_3SiH in the presence of $BF_3{\cdot}Et_2O$[15] effected reductive etherification to give 2,6-*syn*-tetrahydropyran **13** in 64% yield. However, the $[\alpha]_D$ value of **13** was 0; that is, the product **13** is unfortunately *racemic*. Thus, hydrogenolysis of the benzyl ether **5** gave racemic centrolobine (**1**). This racemization presumably takes place as follows (Fig. 3). Removal of the hydroxyl group of **12b** with $BF_3{\cdot}Et_2O$ would easily proceed owing to the effect of the electron-donating MeO group;[16] thus, the chirality of **12** would be lost at this stage. Then, the carbonyl oxygen would attack the diene-oxonium ion **i** to give tetrahydropyran oxonium ion **ii**. Subsequent reduction of the oxonium ion **ii** with Et_3SiH would provide racemic **13**.

Next, we examined the other route B, in which no epimerization was expected (Scheme 2). The synthesis commenced with the known chiral epoxide **15**,[17] which was prepared starting from L-glutamic acid (**14**). Coupling of the epoxide **15** and Grignard reagent **16** in the presence of CuI in THF afforded (*R*)-alcohol **17** (99% ee),[10] quantitatively.[18] The Mitsunobu reaction[19] of **17** with *p*-methoxybenzoic acid (**18**) in the presence of DEAD and Ph_3P effected esterification accompanied with inversion of the hydroxyl group to give an ester, which was treated with CSA in MeOH to give alcohol **19** in 90% yield (2 steps). After iodination of **19** (98% yield), treatment of the resulting **3** with *n*-BuLi or *t*-BuLi afforded an equilibrium mixture of hemiacetal **20a** and ketone **20b** (ca. 1:1.1 ratio in $CDCl_3$), which was subjected to $BF_3{\cdot}Et_2O$-mediated Et_3SiH reduction to give optically active 2,6-*syn*-tetrahydropyran **13** in 67% or 50% yield (2 steps), respectively. Finally, hydrogenolysis of **13** on Pd/C in EtOH-EtOAc afforded (−)-centrolobine (**1**) (98% ee)[20] in 88% yield. The spectral data of synthetic (−)-**1**[21] were identical with those of natural centrolobine (**1**).

Treatment of **12b** with $BF_3{\cdot}Et_2O$ promoted removal of the hydroxyl group as shown in Figure 3. Thus, when diol **iii**, which should be formed by reduction of **20**, is treated with acid, removal of the hydroxyl group and intramolecular addition of the hydroxyl group in **iv** should proceed successively to give optically active 2,6-*syn*-tetrahydropyran **13**, from which (−)-centrolobine (**1**) can be obtained (Fig. 4). Therefore, this synthetic route was examined (Scheme 3). $LiAlH_4$ reduction of the mixture **20**, prepared from **3** by *n*-BuLi treatment, afforded diol **21** in 50% yield (2 steps). After several attempts at cyclization, it was found that treatment of diol **21** with $BF_3{\cdot}Et_2O$ in the presence of MS 4A in MeCN at −40 °C afforded optically active tetrahydropyran **13** (99% ee)[22] in 93% yield.[23]

In summary, total synthesis of (−)-cetrolobine (**1**) was accomplished via an intramolecular Barbier-type cyclization of iodo-ester **3** with *n*- or *t*-BuLi, followed by $BF_3{\cdot}Et_2O$-mediated Et_3SiH reduction of the resulting hemiacetal.

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20. The enantiomeric excess (ee) was determined by HPLC analysis (Daicel Chiralpak AD-H, 2-propanol/*n*-hexane = 1:15).

21. Recrystallization of synthetic (−)-**1** from *n*-hexane–EtOAc gave colorless needles. mp 85.5–86.5 °C (100% ee)[20] (lit.[1] mp 84–86 °C); $[\alpha]_D^{24}$ −91.7 (*c* 0.77, $CHCl_3$) [lit.[1] $[\alpha]_D^{20}$ −92.1 (*c* 1, $CHCl_3$)]; IR (KBr) 3387, 2925, 1610, 1511, 1451, 1300, 1244, 1088, 1036, 805, 568 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.32–7.29 (m, 2H), 7.06–7.02 (m, 2H), 6.89–6.86 (m, 2H), 6.73–6.70 (m, 2H), 4.29 (dd, *J* = 11.2, 2.0 Hz, 1H), 3.80 (s, 3H), 3.47–3.40 (m, 1H), 2.74–2.61 (m, 2H), 1.95–1.80 (m, 3H), 1.76–1.67 (m, 1H), 1.66–1.57 (m, 2H), 1.55–1.45 (m, 1H), 1.38–1.26 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.7, 153.5, 135.9, 134.7, 129.5 (2C), 127.1 (2C), 115.1 (2C), 113.6 (2C), 79.1, 77.2, 55.3, 38.3, 33.3, 31.3, 30.7, 24.1; HRMS (ESI) calcd for $C_{20}H_{24}O_3Na$ ($M+Na^+$) 335.1618, found 335.1618.
22. The enantiomeric excess (ee) was determined by HPLC analysis (Daicel Chiralcel OD-H, 2-propanol/*n*-hexane = 1:99).
23. In the first total synthesis of (±)-centrolobine,[1b] a similar cyclization was carried out by treatment with $ZnCl_2$.