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Total synthesis of (−)-physovenine from (−)-3a-hydroxyfuroindoline

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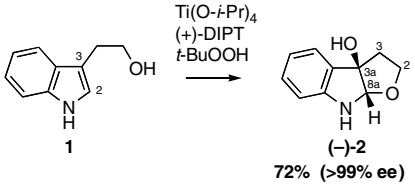
Abstract—Total synthesis of calabar bean alkaloid (−)-physovenine (−)-**3** has been achieved in a concise manner starting from optically active (−)-3a-hydroxyfuroindoline (−)-**2**, synthesized via modified Sharpless epoxidation of tryptophol **1**. Our strategy involved a stereospecific radical substitution reaction and regioselective oxidation at the C5 position.

Herein, we describe a highly efficient route to synthesize (−)-physovenine (−)-**3** using (−)-3a-hydroxyfuroindoline (−)-**2**. Previously, a synthetic strategy for madindoline A was developed, involving an asymmetric oxidative ring-closure reaction of tryptophol **1** to give (−)-**2** by modified Sharpless epoxidation [Ti(O-*i*Pr)$_4$, (+)-DIPT, *t*BuOOH, CH_2Cl_2, −20 °C] (Scheme 1).[1,2] This reaction proceeded with high enantioselectivity in good yield. Interest in the synthetic utility of this oxidative ring-closure reaction led us to apply this method to the synthesis of other indole alkaloids with furoindoline skeletons.

Calabar bean isolate (−)-physostigmine (−)-**4** is an acetylcholinesterase inhibitor with a pyrroindoline moiety.[3] (−)-Physovenine (−)-**3** with a furoindoline moiety is known as a minor component of the calabar bean extract (Fig. 1).[3] Furthermore, the pharmacological activity of (−)-**3** is approximately equal to that of (−)-**4**. Although the syntheses of (−)-**3** and (−)-**4** have been carried out by Ogasawara and co-workers[4,5] and Overman and co-workers,[6,7] construction of the pyrroindoline and furoindoline skeletons remains as attractive synthetic targets.

In an attempt to synthesize the pyrroindoline and furoindoline moieties, (−)-**3** was selected as the initial target. Synthesis of intermediate (−)-**11** by a stereospecific substitution reaction of 3a-hydroxyfuroindoline and selective oxidation at C-5 were the key steps.

In an effort to synthesize (−)-physovenine, the hydroxyl group at **2** was substituted with a methyl group. All efforts to substitute 3a-*O*-acetate directly with a methyl



Scheme 1. The enantioselective synthesis of (−)-**2**.

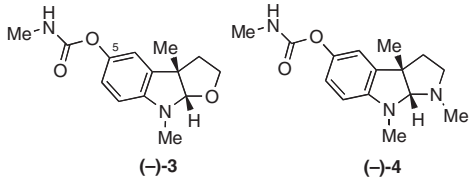


Figure 1. Structures of (−)-physovenine (−)-**3** and (−)-physostigmine (−)-**4**.

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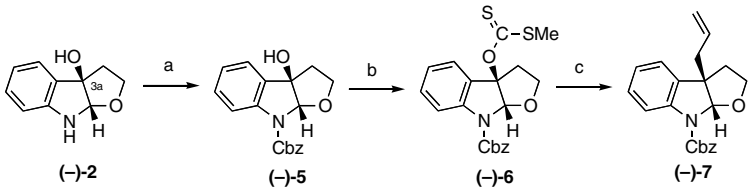
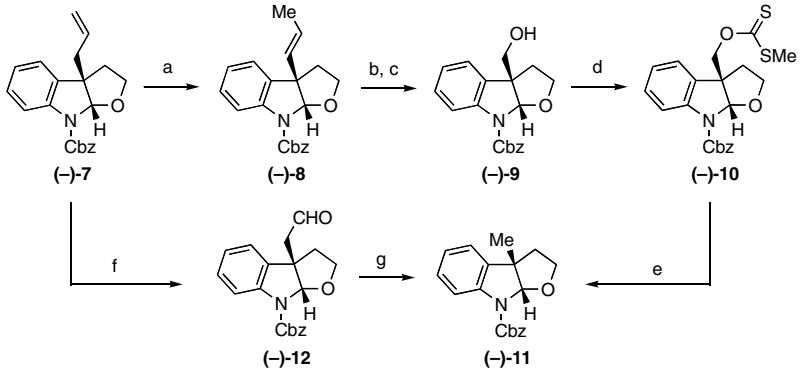


Scheme 2. Reagents and conditions: (a) CbzCl, Py, CH_2Cl_2, 0 °C, 98%. (b) NaH, CS_2, MeI, THF, 0 °C to rt, 97%. (c) Allyltributyltin, *hv*, benzene, 87%.

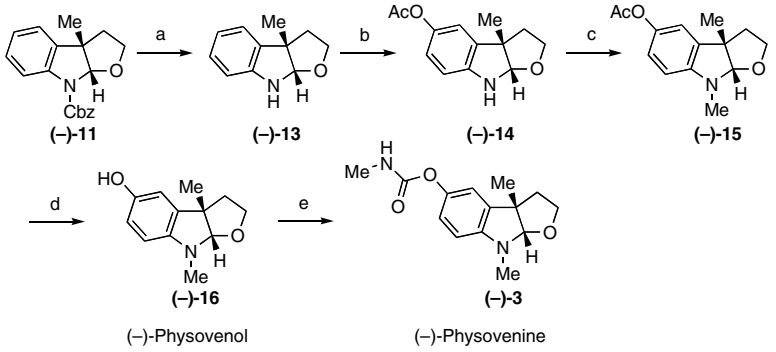
group were unsuccessful, therefore, a stepwise method using radical allylation was employed.[8] Protection of the aromatic amine in (−)-**2** with CbzCl followed by treatment of (−)-**5** with NaH, CS_2 and MeI afforded xantate (−)-**6**. Subsequent radical substitution of (−)-**6** with allyltributylstannane gave allyl compound (−)-**7** in 87% yield. The 3a-8a *cis* configuration in (−)-**7** was determined by NOE proton correlations, indicating that the reaction proceeded with retention of configuration (Scheme 2). All intermediates were achieved with the correct enantioselectivity (>99% ee).

In order to convert the allyl group into a methyl group, two different pathways were investigated (Scheme 3); olefin migration of the allyl group to a methylvinyl group, and direct oxidation of the allyl group without olefin migration. The former procedure yielded an undesirable result due to low yield in the radical hydrogenation of the primary carbon in the last step. The latter process involved oxidative cleavage of the allyl group with O_3, followed by reduction of the ozonide to give an aldehyde, and subsequent deformylation using $RhCl(PPh_3)_3$ to yield (−)-**11**.[9] This process resulted in moderate overall yield in a few steps.

The (−)-3a-methylfuroindoline (−)-**11** was subsequently oxygenated at the C5-position and *N*-methylation of indoline was carried out (Scheme 4). After removal of the Cbz group, oxidation at the C5-position of (−)-**13** with $Pb(OAc)_4$ gave the desired compound (−)-**14** in 43% (73%; based on recovered) yield.[10] Deprotection of Cbz prior to oxidation was crucial to this reaction. Oxidation of (−)-**11** did not proceed, presumably due to the reduced electron density on the aromatic moiety.



Scheme 3. Reagents and conditions: (a) $PdCl_2(PhCN)_2$, CH_2Cl_2, rt, 94%. (b) O_3, CH_2Cl_2, then Me_2S, −78 °C to rt. (c) $NaBH_4$, rt, 83% (two steps). (d) NaH, CS_2, MeI, THF, 0 °C to rt, 98%. (e) Bu_3SnH, AIBN, toluene, 80 °C, 29%. (f) O_3, CH_2Cl_2, then Me_2S, −78 °C to rt, 86%. (g) $RhCl(PPh_3)_3$, toluene, 45 °C, 69%.



Scheme 4. Reagents and conditions: (a) H_2, Pd/C, AcOEt, rt, 98%. (b) $Pb(OAc)_4$, CH_2Cl_2, then Zn, 0 °C, 42% (73%)*. (c) HCHO aq, AcOEt, rt, 2 h, then H_2, Pd/C, 93%. (d) Sulfonic acid resin MP, MeOH, rt, 98%. (e) MeNCO, cat. Na, Et_2O, rt, 84%. *Based on recovered.

Reductive *N*-alkylation to (−)-**15** was carried out via *N*-formylation of (−)-**14** followed by hydrogenation in a good yield. In this step, the mixture of (−)-**14** and formaldehyde was stirred well in order to ensure complete *N*-formylation prior to hydrogenation. In cases in which *N*-formylation did not complete, the furoindoline moiety was reduced preferentially. Acidic conditions[11] were preferred in the deacetylation of (−)-**15**, in order to obtain (−)-physovenol (−)-**16** in high yield. Finally, (−)-**16** was converted to (−)-physovenine (−)-**3**, mp 123–124.5 °C, $[\alpha]_D^{25}$ − 92 (*c* 0.71, EtOH); [natural:[12] mp 124–125 °C, $[\alpha]_D^{22.5}$ − 92 (EtOH)] by carbamoylation of the phenolic hydroxy group with methylisocyanate.[13]

Asymmetric total synthesis of (−)-physovenine (−)-**3** in 19.4% overall yield (>99% ee) was achieved in 11 steps. While some steps in this synthetic scheme may require further improvements, the overall process proceeded enantioselectively with the least number of steps and gave the highest yield reported thus far for the total synthesis of (−)-physovenine (−)-**3**.

Acknowledgements

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