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An efficient stereoselective synthesis of (+)-deoxoprosophylline

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Abstract—An efficient stereoselective synthesis of (+)-deoxoprosophylline from readily available *p*-anisaldehyde is described. Key steps in the synthesis include the stereoselective amination of *anti*-1,2-dibenzyl ether using chlorosulfonyl isocyanate, intermolecular olefination, and Pd-catalyzed intramolecular cyclization.

A large number of polyhydroxylated piperidine alkaloids have been found in nature, and have been reported to have valuable biological and pharmacological properties.[1] Among these, 2,6-disubstituted piperidine-3-ols, such as, *Prosopis* alkaloids **1**–**4** and *Cassia* alkaloids **5** and **6** have received much recent attention as potential medical agents, due to their varied pharmacological properties, which include anesthetic, analgesic, and antibiotic activities (Fig. 1).[2]

In particular, (+)-deoxoprosophylline **1**, the reduced adduct of (+)-prosophylline **2** isolated from the leaves of *Prosopis africana* Taub,[3] has attracted considerable interest as an important synthetic target molecule because of its potent biological activities and interesting structural features involving a polar head group and a hydrophobic aliphatic tail. The polar piperidine ring core of these alkaloids is known to be essentially required for the inhibition of various glycosidases, and to have therapeutic potential for the treatment of diseases such as diabetes, viral infections, and cancer.[4] On the other hand, the lipophilic aliphatic tail serves to facilitate transfer across lipid membranes.[5] However, although many studies have been conducted on glycosidase inhibitors, their structural and inhibitory activity relationships are not well understood.

Several methods for synthesizing (+)- and (−)-deoxoprosophyllines have been reported,[6–8] and the majority of these methods have relied upon the chiral starting materials, like sugars[6] and amino acids;[7] however, methods of asymmetric syntheses are rather scarce.[8] As a

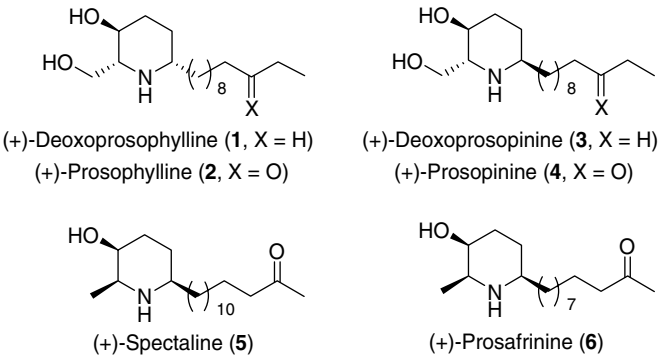

Figure 1. Structure of *Prosopis* alkaloids and *Cassia* alkaloids.

Keywords: Deoxoprosophylline; Intermolecular olefination; Intramolecular cyclization; Chlorosulfonyl isocyanate.
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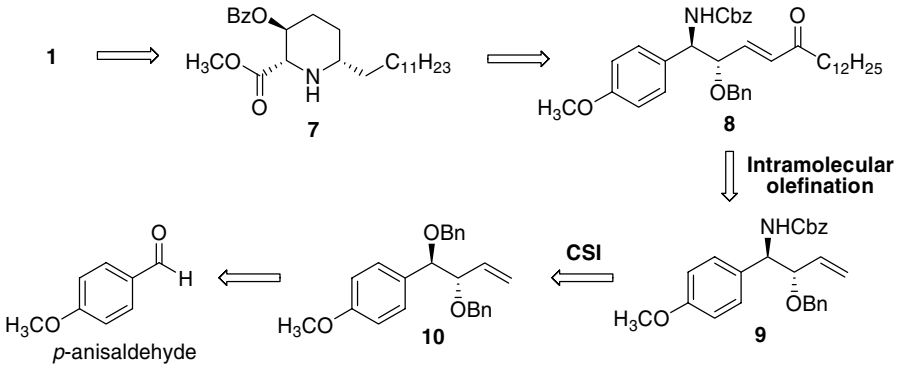
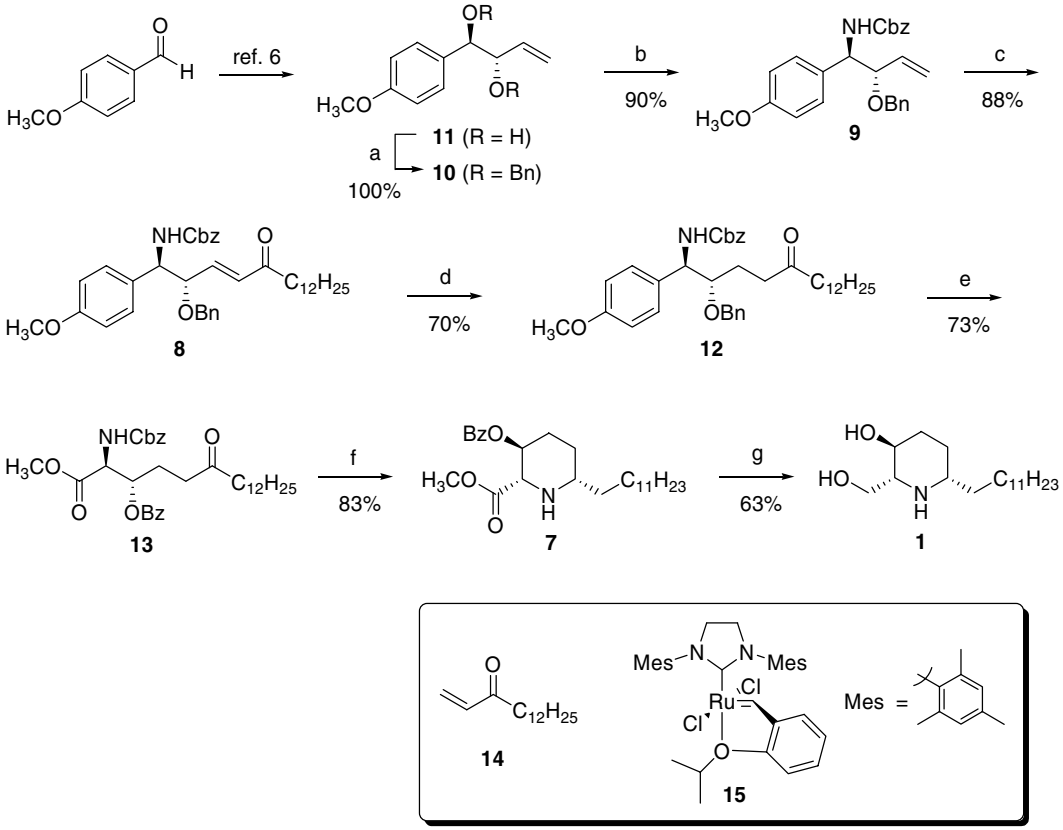
result of our previous studies on the stereoselective amination of various allylic ethers using chlorosulfonyl isocyanate (CSI),[9] and on the application of this method to the total synthesis of polyhydroxylated alkaloids,[10] we became interested in developing an efficient synthetic route to (+)-deoxoprosophylline. Herein, we describe the novel total synthesis of **1** via the stereoselective amination of *anti*-1,2-dibenzyl ether using CSI, intermolecular olefination, and Pd-catalyzed intramolecular cyclization.

The retrosynthetic analysis of **1** is outlined in Scheme 1. Piperidine **7** was prepared from *anti*-1,2-amino alcohol **9** by intermolecular olefination using Hoveyda 2nd Grubbs catalyst followed by the oxidation of the *p*-methoxyphenyl moiety and Pd-catalyzed intramolecular cyclization. The *anti*-amino alcohol **9** was synthesized via the regioselective and diastereoselective introduction of the NHCbz group into *anti*-1,2-dibenzyl ether **10** using CSI.

The total synthesis of **1** began with the commercially available *p*-anisaldehyde, which was converted into *anti*-1,2-diol **11** with high enantioselectivity (95% ee) according to the literature (Scheme 2).[10c,d] Treatment of the diol **11** with benzyl bromide and sodium hydride in the presence of DMF and THF gave *anti*-1,2-dibenzyl ether **10** in quantitative yield. The regioselective and diastereoselective CSI reaction of **10** was carried out in



Scheme 1. Retrosynthetic analysis.



Scheme 2. Reagents and conditions: (a) NaH, BnBr, THF/DMF (1:1), 11 h; (b) (i) CSI, Na_2CO_3, toluene, −78 °C, 24 h; (ii) 25% Na_2SO_3, 24 h; (c) **14**, **15**, toluene, 80 °C, 48 h; (d) PtO_2, H_2, EtOAc, 2 h; (e) (i) cat. $RuCl_3$, $NaIO_4$, H_2O/CH_3CN/EtOAc (2:1:1), 4 h; (ii) CH_2N_2, Et_2O, 0 °C, 1 h; (f) 10% Pd/C, H_2, MeOH, 24 h; (g) (i) LAH, THF, 12 h; (ii) 8 N KOH, MeOH, reflux, 10 h.

toluene solution at −78 °C for 24 h, followed by desulfonylation with aqueous 25% sodium sulfite solution to give the desired *anti*-1,2-amino alcohol **9** with high diastereoselectivity (*anti*:*syn* = 49:1, 98% ds) in 90% yield. The diastereoselectivity of **9** can be explained by the neighboring group effect, whereby the NHCbz group orientation retains its original configuration in benzyl ether via a double inversion of the configuration.[10c,d] Cross-metathesis of **9** with pentadec-1-en-3-one (**14**)[11] using Hoveyda 2nd Grubbs catalyst **15** in toluene at 80 °C provided (*E*)-α,β-unsaturated ketone **8**,[12] which was then hydrogenated using PtO_2 for 2 h to afford **12** in 70% yield.

Oxidation of **12** with $RuCl_3$ (0.15 equiv) and $NaIO_4$ (17 equiv) in $H_2O/CH_3CN/EtOAc$ (2:1:1)[13] gave the intermediate carboxylic acid, in which the benzyl group had been oxidized to benzoate.[14] Treatment of the crude carboxylic acid with diazomethane gave the desired methyl ester **13**. Removal of the Cbz group by palladium-catalyzed hydrogenolysis and simultaneous intramolecular cyclization afforded piperidine **7** in 83% yield. From observations of vicinal coupling constants and NOE correlations, the cyclization of **13** provided **7** as a sole product due to an unfavorable 1,3-diaxial interaction between the ring side chain (COOMe) and the incoming nucleophile (H) in chair-like transition states of the cyclic iminium intermediate.[7d,15] Finally, reduction of ester **7** with $LiAlH_4$ in THF and removal of the benzoate group using 8 N KOH in MeOH furnished (+)-deoxoprosophylline **1** with specific rotation and spectral data (^1H and ^{13}C NMR) identical to those reported in the literature.[16]

In conclusion, we describe the stereoselective total synthesis of (+)-deoxoprosophylline via the stereoselective amination of *anti*-1,2-dibenzyl ether using CSI, intermolecular olefination, and Pd-catalyzed intramolecular cyclization as key transformations. It is evident that this synthetic route can be applied to the preparation of various polyhydroxylated piperidine alkaloids or other natural products containing a nitrogen atom in the ring.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2007.07.034.

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16. *Selected physical and spectroscopic data for* **1**: mp 85–87 °C [lit.[8a] 85–86 °C]; $[\alpha]_D^{25}$ +13.1 (*c* 1.0, $CHCl_3$) [lit.[8a] $[\alpha]_D^{24}$ +13.5 (*c* 0.3, $CHCl_3$)]; ^1H NMR (300 MHz, $CDCl_3$) δ 0.91 (t, 3H, $J = 7.5$ Hz), 1.04–1.45 (m, 22H), 1.76–1.82 (m, 1H), 2.06–2.11 (m, 1H), 2.22–2.62 (br m, 5H), 3.50 (br, 1H), 3.75 (dd, 1H, $J = 11.1$, 4.8 Hz), 3.87 (dd, 1H, $J = 11.1$, 3.9 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.33, 22.91, 26.43, 29.57, 29.83, 29.87, 30.02, 31.34, 32.15, 34.16, 36.78, 56.29, 63.50, 64.83, 70.77; HRMS (FAB) Calcd for $C_{18}H_{38}NO_2$ $[M+H^+]$ 300.2903, found 300.2901.