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A concise and stereoselective synthesis of (+)- and (−)-deoxoprosophylline

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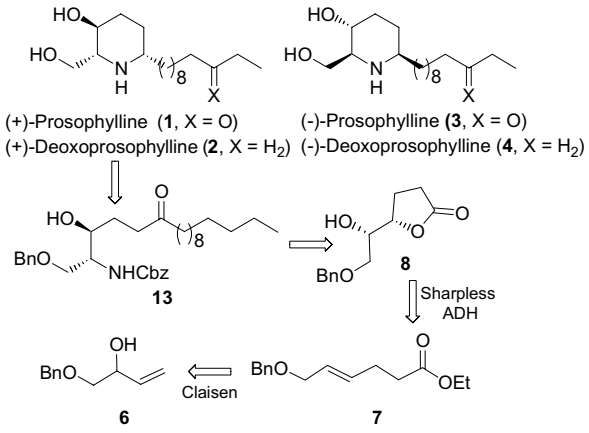
Abstract—An efficient synthesis of (+)- and (−)-deoxoprosophylline was accomplished from the readily available *cis*-2-butene-1,4-diol in which the Sharpless asymmetric dihydroxylation was used as the key step.

Multifunctionalized piperidine alkaloids possessing the 2,6-disubstituted piperidin-3-ol skeleton have been found abundantly in nature.[1] Prosopis alkaloids, one of the subgroups of these piperidine alkaloids, were isolated from *Prosopis africana* Taub.[2] Structurally, these compounds possessing a polar head group and a hydrophobic aliphatic tail can be considered as cyclic analogues of the membrane lipid sphingosine.[3] Besides their interesting structural features, these polysubstituted piperidine alkaloids exhibit a variety of pharmacological properties, such as anaesthetic, analgesic, and antibiotic activities.[4]

Although many elegant synthesis of (+)- and (−)-deoxoprosophylline have been documented in the literature,[5] most of the syntheses use chiral pool starting materials such as sugars, amino acids and involve many steps. Due to their interesting structural features and the biological significance of this class of compounds, we were encouraged to design a short and effective synthesis of (+)- and (−)-deoxoprosophylline, using Sharpless asymmetric dihydroxylation as the source of chirality. Scheme 1 shows our retrosynthetic analysis for deoxoprosophylline. As illustrated in Scheme 1, the retrosynthetic strategy envisions the use of hydroxy lactone **8** as the key intermediate for the proposed synthesis, which would be formed from the allylic alcohol **6** by a Claisen orthoester rearrangement and Sharpless asymmetric dihydroxylation.



Scheme 1. Retrosynthetic analysis for **2**.

As outlined in Scheme 2, the desired monoprotected allylic alcohol **6** was prepared in two steps from the inexpensive and readily available *cis*-2-butene-1,4-diol **5** according to the literature procedure.[6] Claisen rearrangement of the allylic alcohol **6** with triethyl orthoacetate in the presence of catalytic propionic acid at 140 °C gave the, γ,δ-unsaturated ester **7**.[7] Sharpless asymmetric dihydroxylation[8] employing AD-mix-α and in situ cyclization of the, γ,δ-unsaturated ester **7** furnished the hydroxy lactone **8**. Mesylation of the hydroxy lactone **8** and displacement of the mesylate with NaN_3 in DMF at 90 °C gave the azido lactone **10**. The azide was

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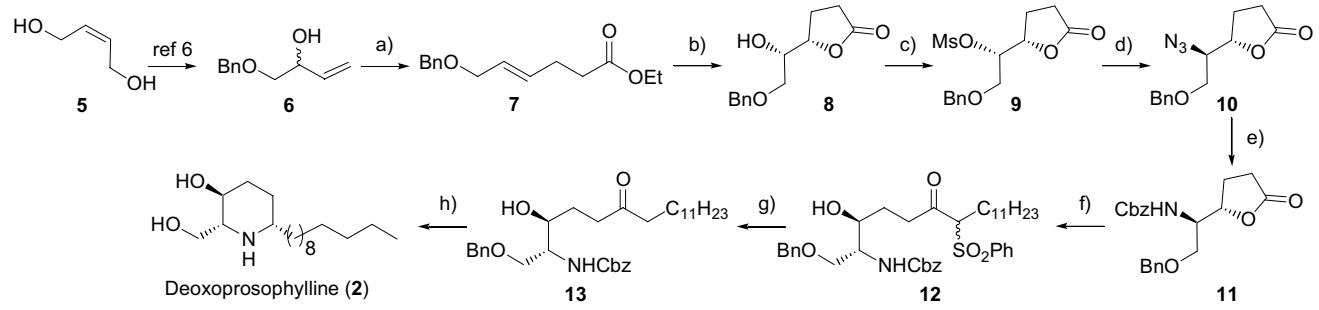

Scheme 2. Reagents and conditions: (a) $CH_3C(OEt)_3$, cat. propionic acid, 140 °C, 2 h, 94%; (b) AD-mix-α, $CH_3SO_2NH_2$, *t*-BuOH:H_2O (1:1), 24 h, 0 °C, 95%, 93% ee; (c) CH_3SO_2Cl, Et_3N, DCM, 92%; (d) NaN_3, DMF, 90 °C, 89%; (e) i. TPP, H_2O, C_6H_6, 8 h, ii. CbzCl, Et_3N, cat. DMAP, DCM, 75% for two steps; (f) $C_{12}H_{25}SO_2Ph$, *n*-BuLi, THF, −78 °C, 2 h, 94%; (g) 6% Na–Hg, Na_2HPO_4, CH_3OH, −10 °C, 95%; (h) 20% $Pd(OH)_2$/C, H_2, CH_3OH, rt, 24 h, 76%.

reduced to the amine by using triphenylphosphine and water and the resulting amine was protected as its Cbz derivative by using CbzCl, TEA in the presence of a catalytic amount of DMAP.

Opening of the lactone of **11** was achieved using $C_{12}H_{25}SO_2Ph$ and *n*-BuLi.[9,10] Desulfonylation of **12** using 6% Na–Hg and Na_2HPO_4 at −10 °C gave the ketone **13**.[11] Removal of the protecting groups and cyclization of the ketone **13** using catalytic $Pd(OH)_2$ and H_2 in a one pot reaction, afforded (+)-deoxoprosophylline **2** in 76% yield. Having accomplished the synthesis of natural **2**, we turned our attention towards the synthesis of its enantiomer. Accordingly, γ,δ-unsaturated ester **7** was transformed in a similar fashion to afford (−)-deoxoprosophylline **4** following a similar sequence however, using AD-mix-β. The physical and spectroscopic data of our synthetic materials **2**[12] and **4** were in good agreement with those described in the literature.[5d,e]

In summary, (+)- and (−)-deoxoprosophylline were synthesized in efficient yields from readily available *cis*-2-butene-1,4-diol. The present synthesis of (+)- and (−)-deoxoprosophylline having an overall yield of 37% in eight steps starting from the known allyl alcohol **6** is better than earlier reported syntheses. By using Sharpless asymmetric dihydroxylation as the key step, we have demonstrated that both enantiomers of deoxoprosophylline can be readily accessed.

Acknowledgements

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12. Selected physical and spectroscopic data for **2**: mp 85–86 °C, $[\alpha]_D^{24}$ +13.5 (*c* 0.3, $CHCl_3$). ^1H NMR (200 MHz, $CDCl_3$) δ, ppm: 0.88 (3H, t, $J = 6.5$ Hz), 1.26 (24H, m), 1.72–1.79

(1H, m), 2.02–2.06 (1H, m), 2.54–2.58 (2H, m), 2.98 (3H, br), 3.47 (1H, dt, $J = 10.1, 4.3$ Hz), 3.71 (1H, dd, $J = 10.9$, 5.1 Hz), 3.83 (1H, dd, $J = 10.9$, 4.3 Hz). ^{13}C NMR (50 MHz) δ: 14.18, 22.75, 26.27, 29.37, 29.7, 29.8, 30.83, 31.97, 33.77, 36.35, 56.23, 63.4, 63.88, 69.8 ppm.