# A Concise Synthesis of (–)-Deoxoprosopinine

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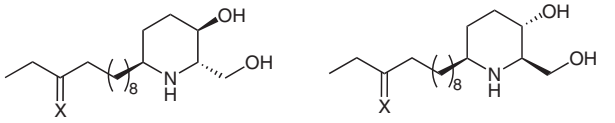
**Abstract:** A simple and highly efficient approach to (–)-deoxoprosopinine from racemic epoxide as a starting material is described employing a Jacobsen's hydrolytic kinetic resolution (HKR) and Sharpless asymmetric dihydroxylation (AD) as key steps.

**Key words:** Jacobsen's HKR, Sharpless AD, hydroboration–oxidation, piperidine alkaloids, total synthesis

Naturally occurring alkaloids containing multifunctionalized piperidine rings are found abundantly in nature and many of them exhibit biological activity of medicinal interest.[1] Prosopis alkaloids, one of the subgroup of these piperidine alkaloids, were isolated from the leaves of *Prosopis afrikana* Tab, contains 2,6-disubstituted piperidin-3-ol piperidine framework such as prosopinine (**1**), prosophylline (**2**), and their deoxo analogues deoxoprosopinine (**3**), deoxoprosophylline (**4**), respectively (Figure 1).[2] These alkaloids exhibit antibiotic, anaesthetic, analgesic, and CNS stimulating properties and therefore have attracted considerable interest as synthetic targets.

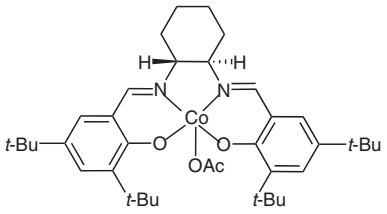



(–)-prosopinine (**1**, X = O) (+)-prosophylline (**2**, X = O)
(–)-deoxoprosopinine (**3**, X = $H_2$) (+)-deoxoprosophylline (**4**, X = $H_2$)

**Figure 1**

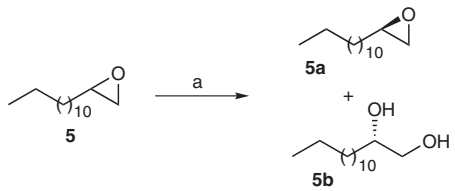
Various syntheses of this class of compounds have been reported. Majority of the syntheses of deoxoprosopinine employ chiral pool starting materials such as sugars and amino acids and involve many steps.[3] As part of our ongoing program towards asymmetric synthesis of biologically active natural products,[4] we became interested in developing a simple and flexible route to (–)-deoxoprosopinine. Herein, we report a new and short synthesis of (–)-deoxoprosopinine employing a Jacobsen's HKR and a Sharpless AD as the source of chirality.

The synthesis of (–)-deoxoprosopinine started from commercially available racemic 1,2-epoxytetradecane (**5**) which was subjected to Jacobsen's HKR using (*R*,*R*)-Co(III)(salen)·OAc catalyst (Figure 2) to give (*R*)-1,2-epoxytetradecane (**5a**) as a single enantiomer (>99% ee),[5] which was easily isolated from the more polar diol **5b** by distillation (Scheme 1).




(*R*,*R*)-Co(III)(salen)·OAc

**Figure 2**




**Scheme 1** *Reagents and conditions*: (a) (*R*,*R*)-Co(III)(salen)·OAc (0.5 mol%), distilled $H_2O$ (0.55 equiv), 0 °C, 24 h, (41% for **5a**, 43% for **5b**).

With enantiomerically pure (*R*)-1,2-epoxytetradecane (**5a**) in hand, we then subjected it to copper-catalyzed (CuI) regioselective opening with vinylmagnesium bromide to give the homoallylic alcohol **6** in excellent yield. The free hydroxyl group of **6** was converted into *O*-mesylate, which on nucleophilic displacement with sodium azide in anhydrous DMF afforded compound **7** in 93% yield. The azide **7** was subjected to Staudinger reaction[6] and converted into amine, which on Cbz protection with benzyl chloroformate led to **8** in 90% yield (two steps, one pot). The compound **8** was then subjected to hydroboration–oxidation reaction to afford the alcohol **9** in 87% yield. With substantial amount of **9** in hand, our next aim was to carry out the two-carbon homologation by means of Wittig reaction in order to generate the *trans*-olefin required for AD reaction. To this end, compound **9** was oxidized to the aldehyde under Swern conditions,[7] followed by treatment with (ethoxycarbonylmethylene)triphenylphosphorane in anhydrous THF at room temperature to furnish the *trans*-Wittig product **10** in excellent yield (Scheme 2).

The dihydroxylation of olefin **10** with osmium tetroxide and potassium ferricyanide as co-oxidant in the presence of $(DHQD)_2PHAL$ under the Sharpless asymmetric conditions[8] gave the diol **11** in 97% yield as a single

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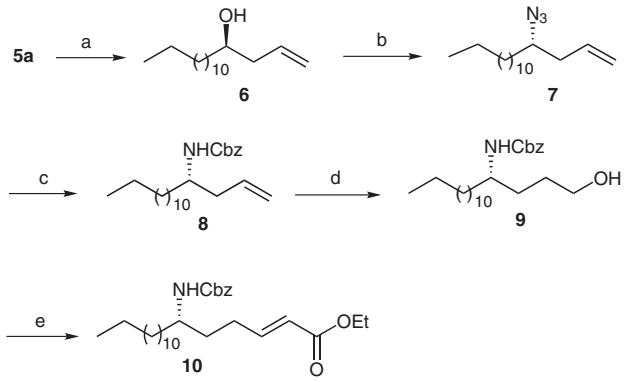
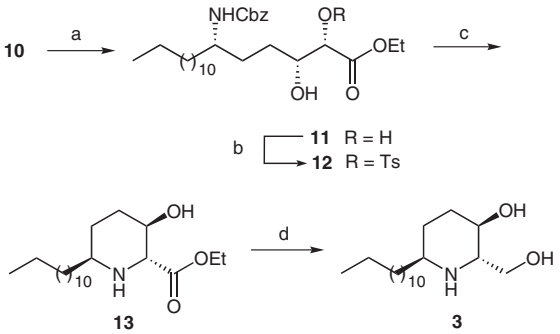



**Scheme 2** *Reagents and conditions*: (a) vinylmagnesium bromide, CuI, THF, –78 °C, 12 h, 94%; (b) i) MsCl, $Et_3N$, anhyd $CH_2Cl_2$, 2 h; ii) $NaN_3$, anhyd DMF, 45 °C, 93%; (c) i) $PPh_3$, THF–$H_2O$ (6:1), r.t., 12 h; ii) benzyl chloroformate, $Na_2CO_3$, 1,4-dioxane–$H_2O$ (1:1), 0 °C to r.t., 90% (two-step, one-pot); (d) i) $BH_3{\cdot}SMe_2$, THF, 0 °C to r.t., 3 h; ii) 2 equiv NaOH, $H_2O_2$, 0 °C to r.t., 6 h, 87%; (e) i) $(COCl)_2$, DMSO, $CH_2Cl_2$, –78 °C, 30 min, $Et_3N$, –60 °C, 30 min; (ii) $Ph_3P{=}CHCO_2Et$, THF, r.t., 24 h, 96%.

diastereoisomer (>98% de).[9] Regioselective monotosylation[10] of this diol with tosyl chloride (TsCl) resulted in the α-tosylate **12** in excellent yield. Concomitant deprotection of Cbz and nucleophilic displacement of α-tosylate on hydrogenation with $Pd(OH)_2$ led to the cyclized product **13**[11] in 97% yield. Finally, reduction of **13** with $LiAlH_4$ produced (–)-deoxoprosopinine (**3**) in 86% yield; mp 90 °C (ref. 3a: 89.5–90 °C); $[\alpha]_D^{25}$ –15. 81 (*c* 0.30, $CHCl_3$) {ref. 3a: $[\alpha]_D^{25}$ –14.7 (*c* 0.30, $CHCl_3$)} (Scheme 3). The physical and spectroscopic data were in full agreement with the literature.[3a]




**Scheme 3** *Reagents and conditions*: (a) $(DHQD)_2PHAL$, $OsO_4$ (0.4 mol%), $K_2CO_3$, $K_3Fe(CN)_6$, $MeSO_2NH_2$, *t*-BuOH–$H_2O$ (1:1), 0 °C, 24 h, 97%; (b) TsCl, $Et_3N$, $CH_2Cl_2$, 5 °C, 72 h, 88%; (c) 20% $Pd(OH)_2$/C, $H_2$, EtOAc, r.t., 12 h, 97%; (d) $LiAlH_4$, THF, 0 °C to r.t., 2 h, 86%.

In conclusion, a simple, flexible and highly efficient route to (–)-deoxoprosopinine has been developed employing Jacobsen's HKR and Sharpless asymmetric dihydroxylation as the key steps. The merits of this synthesis are high enantio- and diastereoselectivity with high yielding reaction steps. The synthetic strategy described has significant potential for stereochemical variations at C-2, C-3, and C-6 positions and further extension to other stereoisomers, and analogues such as *epi*-deoxoprosopinine and deoxoprosophylline. Currently, studies are in progress in this direction.

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(9) The diastereoselectivity was determined from $^{1}$H NMR and $^{13}$C NMR spectral data. Spectral data of compound **11**: mp 137 °C; $[\alpha]_D^{25}$ +6.90 (*c* 1.00, $CHCl_3$). IR ($CHCl_3$): ν = 3434, 3018, 2927, 1719, 1508, 1216 cm$^{-1}$. $^{1}$H NMR (200 MHz, $CDCl_3$): δ = 0.89 (t, *J* = 5.95 Hz, 3 H), 1.26–1.70 (m, 29 H), 2.27 (br s, 2 H), 3.62–3.71 (m, 1 H), 3.91 (d, *J* = 6.45 Hz, 1 H), 4.06 (d, *J* = 1.61 Hz, 1 H), 4.29 (q, *J* = 6.72, 13.70 Hz, 2 H), 4.55 (d, *J* = 8.87 Hz, 1 H), 5.10 (s, 2 H), 7.32–7.38 (m, 5 H) ppm. $^{13}$C NMR (50 MHz, $CDCl_3$): δ = 14.0, 22.6, 25.8, 29.2, 29.6, 29.8, 31.4, 31.8, 35.5, 51.1, 61.8, 66.4, 72.3, 73.4, 127.9, 128.4, 136.5, 156.2, 173.4 ppm. ESI-MS: *m/z* = 516 $[M + Na]^+$. Anal. Calcd (%) for $C_{28}H_{47}NO_6$: C, 68.12; H, 9.60; N, 2.84. Found: C, 68.17; H, 9.58; N, 2.82.

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(11) Spectral data of compound **13**: mp 96 °C; $[\alpha]_D^{25}$ +5.65 (*c* 0.60, $CHCl_3$). IR ($CHCl_3$): ν = 3583, 3436, 3019, 2928, 1725, 1519, 1455, 1215 cm$^{-1}$. $^{1}$H NMR (200 MHz, $CDCl_3$): δ = 0.88 (t, *J* = 6.07 Hz, 3 H), 1.26–1.79 (m, 30 H), 2.11 (br s, 1 H), 2.65–2.74 (m, 1 H), 3.58 (d, *J* = 4.06 Hz, 1 H), 4.11–4.17 (m, 1 H) 4.21 (q, *J* = 7.12, 13.86 Hz, 2 H) ppm. $^{13}$C NMR (50 MHz, $CDCl_3$): δ = 14.0, 14.2, 22.6, 26.1, 28.0, 29.3, 29.5, 29.6, 31.8, 35.8, 51.6, 60.8, 61.5, 65.5, 172.2 ppm. ESI-MS: *m/z* = 342 $[M + H]^+$. Anal. Calcd (%) for $C_{20}H_{39}NO_3$: C, 70.33; H, 11.51; N, 4.10. Found: C, 70.35; H, 11.48; N, 4.12.