A Short and Efficient Total Synthesis of (+)-Deoxoprosopinine via Diastereoselective Allylation of the Bicyclic *N*-Acyl Iminium Ion Formed in situ with a π-Nucleophile

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Received: 30.08.2012; Accepted after revision: 08.10.2012

Abstract: A short and efficient synthesis of (+)-deoxoprosopinine is reported involving Miyashita endoselective epoxide ring-opening reaction, diastereoselective allylation of the bicyclic *N*-acyl iminium ion formed in situ with a π-nucleophile, and olefin cross-metathesis as the key steps.

Key words: Miyashita epoxide opening, diastereoselectivity, allylation, cross-metathesis, piperidines

Piperidine alkaloids are very common chemical entities that are found abundantly in Nature and exhibit various biological activities.[1] Prosopis alkaloids are one class among the various naturally occurring biologically active piperidine alkaloids. Some of the prosopis alkaloids are: (+)-prosopinine (**2**), (+)-prosophylline (**4**), and their reduced analogues (+)-deoxoprosopinine (**1**), and (+)-deoxoprosophylline (**3**; Figure 1). These alkaloids were isolated from *Prosopis africana*[2] and exhibit antibiotic and anaesthetic properties. Structurally, these alkaloids contain a 2,6-disubstituted 3-piperidinol skeleton bearing an aliphatic alkyl side chain.

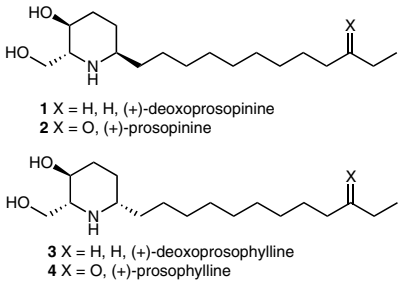
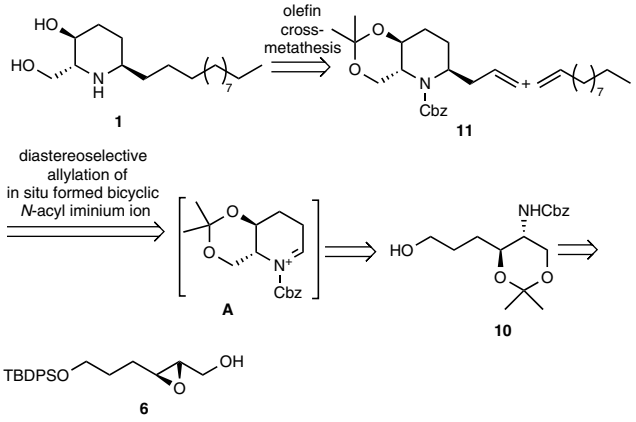


Figure 1 Prosopis alkaloids

Previously, we reported the synthesis of some piperidine-based alkaloids.[3] In continuation of our interest in the synthesis of piperidine alkaloids, we undertook the synthesis of **1** and the results are described herein. Although several syntheses have been reported for **1**,[4] we envisioned a strategically different route. Our strategy involves Miyashita endoselective epoxide ring opening and, more importantly, exploitation of the diastereoselective allylation of bicyclic *N*-acyl iminium ion formed in situ to construct 6-allyl piperidine derivative **11** and its subsequent transformation into the target molecule **1**. There are several reports concerning diastereoselective allylation of *N*-acyl iminium ions,[5] some of which account for the formation of *cis*-2,6-disubstituted piperidines[5a,b] and a few provide evidence for the formation of *trans*-2,6-disubstituted piperidines.[5d–f] We describe the total synthesis of **1** (Scheme 1) by utilizing a one-pot oxidation of **10** and diastereoselective allylation of the bicyclic *N*-acyl iminium ion[5c–e] (**A**) formed in situ, to furnish the allyl piperidine ring system **11** followed by its olefin cross-metathesis[6] with 1-undecene, the other olefinic partner, as the key steps en route to afford the target molecule. Amino alcohol **10**, in turn, could be derived from epoxy alcohol **6** by applying Miyashita's endoselective epoxide ring-opening reaction with azide nucleophile and subsequent conversion. Thus, it is evident that *trans*-2,6-disubstituted piperidine derivative **11** is the key building block in the synthesis of (+)-deoxoprosopinine **1**.



Scheme 1 Retrosynthetic analysis of (+)-deoxoprosopinine

We describe a short and efficient synthesis of **1** in eight steps from known chiral epoxy alcohol **6**[7] in 27% overall yield (Scheme 2). The chiral epoxy alcohol **6**, upon highly regioselective ring-opening reaction from the C-2 position by the azide nucleophile, afforded **7** (78%) as the major isomer (C2/C3, 9:1); the minor 1,2-diol, formed from C3 ring opening, was removed by $NaIO_4$-mediated oxida-

SYNLETT 2012, 23, 2814–2816
Advanced online publication: 09.11.2012
DOI: 10.1055/s-0032-1317514; Art ID: ST-2012-D0727-L
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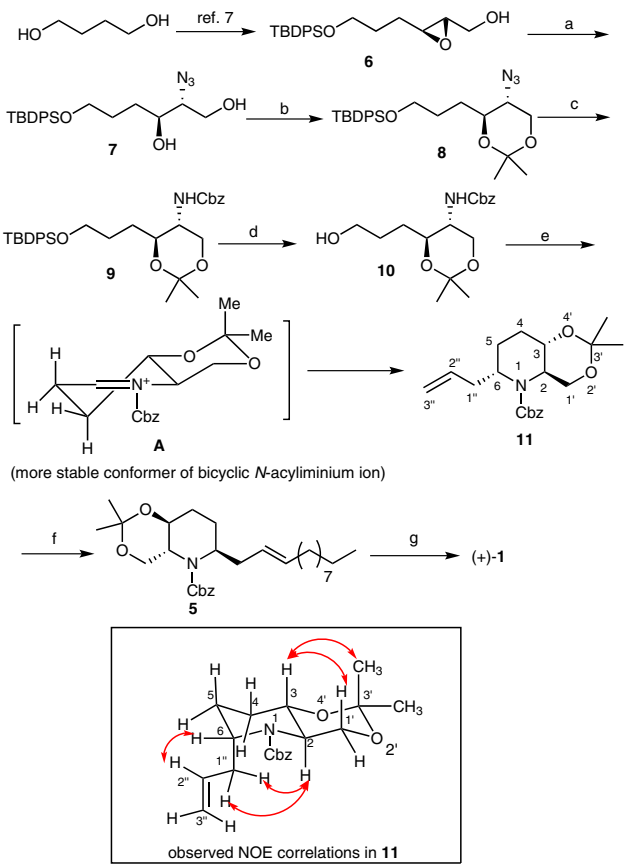
tive cleavage. The ring-opening reaction was carried out by utilizing the Miyashita[8] endoselective epoxide-opening protocol [NaN_3, $B(OMe)_3$, DMF, 60 °C, 3 h]. Diol **7**, thus obtained, was protected as its acetonide derivative **8** (92%) by using 2,2-dimethoxypropane and catalytic PTSA in anhydrous CH_2Cl_2. Subsequently, the azide functionality in **8** was converted into its benzyl carbamate by catalytic hydrogenation (H_2, Pd/C, EtOAc, r.t., 6 h), followed by treatment of the resulting amine with benzyl chloroformate and sodium bicarbonate in a EtOAc–H_2O (1:1) solvent system, which gave the corresponding carbamate **9** (83% over two steps). The TBDPS group was then deprotected (TBAF, anhydrous THF, 0 °C→r.t., 1 h) to afford the primary alcohol **10** (90%), which was oxidized under Dess–Martin conditions to afford an aldehyde that, without further purification, on exposure to trifluoroacetic acid (TFA) at –40 °C for 20 min, was converted into the bicyclic *N*-acyl iminium ion[5c–e] in situ. The iminium ion thus formed was diastereoselectively trapped by a π-type nucleophile (allyltrimethylsilane) to afford allyl piperidine **11** (70%) as an exclusive *trans* adduct.



Scheme 2 *Reagents and conditions*: (a) i. NaN_3, $B(OMe)_3$, DMF, 60 °C, 3 h, 78%; ii. $NaIO_4$, aq sat. $NaHCO_3$, THF–H_2O (4:1), 1 h; (b) 2,2-DMP, PTSA, anhydrous CH_2Cl_2, 0 °C→r.t., 2 h, 92%; (c) i. H_2, Pd/C, EtOAc, 6 h; ii. Cbz-Cl, $NaHCO_3$, EtOAc–H_2O (1:1), r.t., 2 h, 83%; (d) TBAF, anhydrous THF, 0 °C→r.t., 1 h, 90%; (e) i. Dess–Martin periodinane, anhydrous CH_2Cl_2, r.t., 1 h; ii. TFA, –40 °C, 20 min; iii. allyltrimethylsilane, –40 °C, 1.5 h, 70%; (f) G-II, 1-undecene, anhydrous CH_2Cl_2, reflux, 12 h, 90%; (g) i. H_2, Pd/C, EtOAc, 7 h, 90%; ii. cat. PTSA, MeOH, 0.5 h, 89%.

The structure and stereochemistry of allyl piperidine **11** were thoroughly characterized by extensive NMR experiments, including 2-D double quantum filtered correlation spectroscopy (DQF-COSY), nuclear Overhauser effect spectroscopy (NOESY) and HSQC. The strong NOE cross peaks observed between H2/H1″, H3/H1′, H3/CH_3 (acetonide methyl), and H6/H2″ protons are indicative of their relative spatial orientation, their relationship with one another, and their respective planar arrangement. Thus, the relative and absolute stereochemistry of C2 and C6 was unequivocally proved. Additionally, the coupling constant between H2 and H3 ($J_{H2–H3}$ = 10.2 Hz) confirms that these protons are *trans* to each other. Furthermore, the exclusive formation of the *trans*-isomer may be rationalized on the basis of stereoeletronically controlled addition of a π-type nucleophile (from allyltrimethylsilane) axially on the thermodynamically more stable conformation of bicyclic *N*-acyliminium ion,[5d,e] leading to **11**. The characteristic ^{1}H NMR signal of H2 appeared at δ = 3.21 ppm as a double-triplet (J = 6.1, 10.2 Hz) and the H6 proton appeared at δ = 4.52–4.40 ppm as a multiplet. Further support for the structure was provided by HRMS analysis (*m*/*z* $[M + Na]^+$ calcd for $C_{20}H_{27}NO_4Na$: 368.1837; found: 368.1834). The presence of terminal olefinic protons substantiated the assigned structure. Ally piperidine **11** constitutes the key building block in the synthesis of **1**.

The terminal olefin in **11** was utilized in olefin cross-metathesis, as a means of achieving C–C bond formation, with 1-undecene under standard conditions [G-II catalyst (10 mol%), anhydrous CH_2Cl_2, reflux, 12 h] to afford **5**. During this reaction, although no homodimerization of **11** was observed, 1-undecene did undergo dimerization. Consequently, to achieve complete conversion of **11** and obtain an optimum yield of the desired cross-product **5** (90%), it was found necessary to use 3.0 equivalents of 1-undecene. The ^{1}H NMR spectrum of **5** revealed the olefinic protons (δ = 5.58–5.42 and 5.32–5.21 ppm) as multiplets, in addition to other characteristic peaks pertaining to the aliphatic carbon chain.

With compound **5** having been obtained, its extrapolation to the target molecule **1** was all that remained. Accordingly, deprotection of the Cbz group and saturation of the double bond took place in one pot through catalytic hydrogenation of **5** (H_2, Pd/C, EtOAc, r.t., 7 h) to furnish acetonide-protected (+)-deoxoprosopinine, which was purified by column chromatography and characterized. Upon treatment of the latter with a catalytic amount of PTSA in methanol, (+)-**1** was obtained in 89% yield. The physical and spectroscopic data of synthetic **1** was consistent with the reported values.[4,9] The HRMS spectrum was also in agreement with the expected structure (*m*/*z* $[M + H]^+$ calcd for $C_{18}H_{38}NO_2$: 300.2902; found: 300.2911).

In conclusion, we report a short and efficient total synthesis of (+)-deoxoprosopinine through the Miyashita endoselective epoxide ring-opening reaction and diastereoselective allylation of the bicyclic *N*-acyl iminium ion formed in situ to furnish the allyl piperidine ring skeleton initially, which, on Grubbs olefin cross-metathesis reaction and deprotection, led to the final compound.

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This strategy could be adapted for the synthesis of related natural products.

Acknowledgment

Three of the authors (P.S., B.K.R., and K.V.M.R) thank the CSIR, New Delhi, for financial support in the form of fellowships.

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(9) **Compound 7:** Yellow oily liquid; $[\alpha]_D^{25}$ –13.1 (*c* 1.11, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$): δ = 7.68–7.58 (m, 4 H, Ar-H), 7.45–7.33 (m, 6 H, Ar-H), 3.85 (dd, *J* = 5.2, 1.3 Hz, 2 H, OCH_2), 3.76–3.72 (m, 1 H, OCH), 3.70 (t, *J* = 4.9 Hz, 2 H, OCH_2), 3.33 (q, *J* = 5.1 Hz, 1 H, -N_3CH), 1.92–1.78 (m, 1 H), 1.72 (quint, *J* = 6.4 Hz, 2 H), 1.65–1.53 (m, 1 H), 1.05 (s, 9 H, *t*-Bu). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 135.5, 132.9, 129.8, 127.7, 72.7, 66.5, 64.3, 63.1, 31.6, 28.6, 26.7, 19.0. HRMS: *m*/*z* $[M + Na]^+$ calcd for $C_{22}H_{31}N_3O_3NaSi$: 436.2032; found: 436.2052.
Compound 9: White solid; mp 71–72 °C; $[\alpha]_D^{25}$ –43.9 (*c* 0.90, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 7.66–7.60 (m, 4 H, Ar-H), 7.40–7.32 (m, 6 H, Ar-H), 7.31–7.26 (m, 5 H, Ar-H), 5.09–5.00 (m, 2 H, OCH_2), 4.49 (d, *J* = 8.7 Hz, 1 H, NH), 3.87 (td, *J* = 6.7, 3.8 Hz, 1 H, OCH), 3.66 (t, *J* = 4.8 Hz, 2 H, OCH_2), 3.57–3.49 (m, 1 H, NCH), 3.48–3.40 (m, 2 H, OCH_2), 1.84–1.64 (m, 2 H), 1.61–1.37 (m, 2 H), 1.32 (s, 6 H), 1.05 (s, 9 H, *t*-Bu). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 155.6, 136.1, 135.5, 133.9, 133.8, 129.5, 128.5, 128.1, 128.0, 127.5, 98.7, 72.0, 66.9, 63.4, 63.2, 50.1, 28.8, 28.0, 27.9, 26.9, 19.9, 19.2. HRMS: *m*/*z* $[M + Na]^+$ calcd for $C_{33}H_{43}NO_5NaSi$: 584.2808; found: 584.2805.
Compound 11: Syrupy liquid; $[\alpha]_D^{25}$ –33.1 (*c* 1.20, $CHCl_3$). ^1H NMR (600 MHz, $CDCl_3$): δ = 7.40–7.30 (m, 5 H, Ar-H), 5.70–5.63 (m, 1 H, olefinic), 5.11–4.99 (m, 4 H, 2 × olefinic, -OCH_2Ph), 4.52–4.40 (m, 3 H, OCH_2, NCH), 3.68 (dt, *J* = 10.2, 3.9 Hz, 1 H, OCH), 3.21 (dt, *J* = 10.2, 6.1 Hz, 1 H, NCH), 2.53–2.46 (m, 1 H, allylic), 2.34–2.26 (m, 1 H, allylic), 1.80–1.53 (m, 4 H), 1.49 (s, 3 H), 1.39 (s, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 155.2, 136.5, 134.6, 128.4, 128.0, 127.9, 117.4, 98.2, 70.9, 67.0, 62.7, 53.4, 52.3, 34.1, 25.9, 25.6, 19.0. HRMS: *m*/*z* $[M + Na]^+$ calcd for $C_{20}H_{27}NO_4Na$: 368.1837; found: 368.1834.
Compound 5: Oily liquid; $[\alpha]_D^{25}$ –35.4 (*c* 0.17, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 7.42–7.32 (m, 5 H, Ar-H), 5.58–5.42 (m, 1 H, olefinic), 5.32–5.21 (m, 1 H, olefinic), 5.10–5.04 (m, 2 H, OCH_2Ph), 4.53–4.34 (m, 3 H, OCH_2, OCH), 3.69 (dt, *J* = 8.3, 3.7 Hz, 1 H, NCH), 3.28–3.17 (m, 1 H, NCH), 2.52–2.16 (m, 4 H, allylic), 2.11–1.81 (m, 4 H), 1.52 (s, 3 H), 1.42 (s, 3 H), 1.37–1.18 (m, 14 H), 0.9 (t, *J* = 8.3 Hz, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 151.5, 133.8, 133.5, 128.4, 128.0, 127.8, 127.1, 125.6, 71.0, 67.0, 63.0, 62.6, 54.0, 53.5, 52.8, 33.0, 32.6, 32.0, 29.7, 29.5, 29.2, 29.0, 27.1, 26.6, 26.0, 25.5, 22.7, 19.1, 14.1. HRMS: *m*/*z* $[M + Na]^+$ calcd for $C_{29}H_{45}NO_4Na$: 494.3246; found: 494.3224.
Compound 1: Colorless solid; mp 89 °C; $[\alpha]_D^{25}$ +15.5 (*c* 0.43, $CHCl_3$) {Lit.[4b,c] $[\alpha]_D^{20}$ +14.6 (*c* 0.3, $CHCl_3$), Lit.[4d] $[\alpha]_D^{23}$ +12.2 (*c* 0.015, $CHCl_3$), Lit.[4e] $[\alpha]_D^{25}$ +15.3 (*c* 0.3, $CHCl_3$)}. ^1H NMR (300 MHz, $CDCl_3$): δ = 3.69–3.60 (m, 2 H, OCH_2), 3.58–3.49 (m, 1 H, OCH), 2.88 (q, *J* = 5.4 Hz, 1 H, NCH), 2.82–2.72 (m, 1 H, NCH), 2.33 (br s, 3 H), 1.79–1.44 (m, 4 H), 1.27 (s, 22 H), 0.88 (t, *J* = 6.7 Hz, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 67.9, 62.2, 58.0, 49.9, 33.7, 31.9, 29.6 (6C), 29.3, 28.5, 27.2, 26.3, 22.6, 14.1. HRMS: *m*/*z* $[M + H]^+$ calcd for $C_{18}H_{38}NO_2$: 300.2902; found: 300.2911.

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