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Synthesis of (−)-Deoxoprosophylline, (+)-2-*epi*-Deoxoprosopinine, and (2*R*,3*R*)- and (2*R*,3*S*)-3-Hydroxypipecolic Acids from D-Glycals

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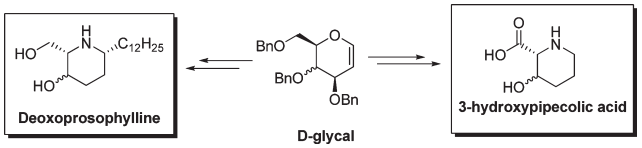

New syntheses of (−)-deoxoprosophylline, (+)-2-*epi*-deoxoprosopinine, and (2*R*,3*R*)- and (2*R*,3*S*)-3-hydroxypipecolic acids are reported. Utilization of the chiral functionalities of Perlin aldehydes, derived from 3,4,6-tri-*O*-benzyl glycals, has been done along with chemoselective saturation of olefins and reductive aminations as key steps.

A number of naturally occurring piperidine alkaloids and their derivatives exhibit important biological properties. In addition, a number of other N-heterocyclic compounds have also been found to be useful as pharmaceuticals and agrochemicals.[1] In particular, hydroxylated pyrrolidine, piperidine, pyrrolizidine, and indolizidine alkaloids and their derivatives have received extensive attention due to their well-established action as glycosidase inhibitors.[2] Among piperidine alkaloids, *Prosopis africana* alkaloids[3] such as

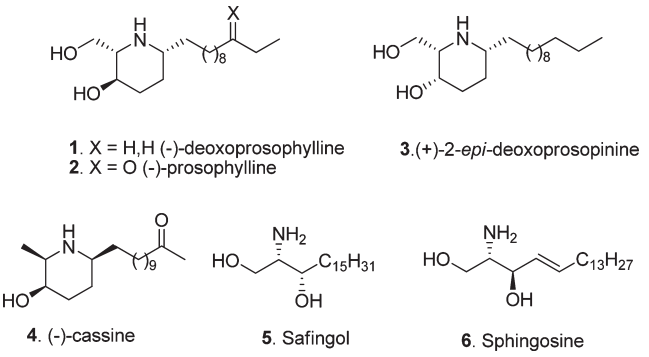

FIGURE 1. Structures of prosophyllines and related molecules.

1−**3** and *Cassia*[4] alkaloid **4** (Figure 1) are medicinally important as they possess anesthetic, analgesic, and antibiotic activities.[5] (−)-Deoxoprosophylline (**1**), (−)-prosophylline, and (+)-2-*epi*-deoxoprosopinine (**3**), having interesting structural features of 2,6-cis-disubstituted piperidin-3-ol, were isolated from the leaves of *Prosopis africana* Taub.[3] These contain a hydrophobic aliphatic tail and a hydrophilic headgroup and thus could be assumed to resemble the cyclic structure of safingol (**6**) and sphingosine (**7**).[6] While the polar headgroup is essential for glycosidase inhibition,[7] the aliphatic long chain facilitates lipid membrane penetration. These distinctive properties enhance the therapeutic potential of these compounds for the treatment of diseases such as diabetes, viral infection, and cancer. Due to these promising biological activities and structural features, many newer approaches toward the synthesis of these molecules have been developed. There are several reports in literature for the synthesis of these molecules starting from chiral building blocks such as amino acids,[8] carbohydrates,[9] vitamin C,[10] and malic acid.[11] However, either some of these building blocks are expensive or the syntheses may require many steps. Thus, for example, synthesis of (+)-deoxoprosophylline from D-glycals was achieved in 15−16 steps.[9a−c] Further, only one report is available for the synthesis of the target

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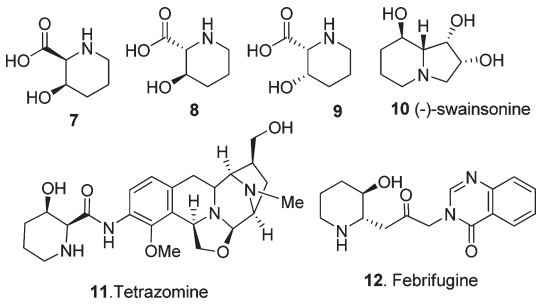


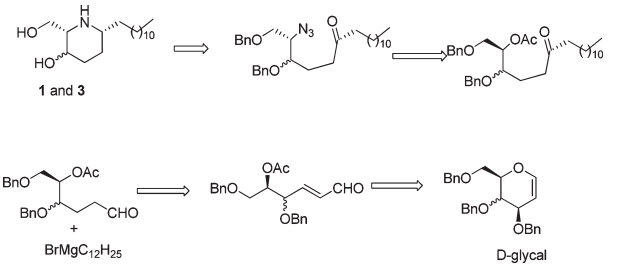
FIGURE 2. Structures of pipecolic acids and related molecules.

molecule **1** from D-glucose and that requires 24 steps.[9e] An improved asymmetric synthesis of (+)-2-*epi*-dexoprosopinine (**3**) was reported by Enders et al. in 11 steps by using SAMP hydrazone as a chiral auxiliary.[12a] More recently, Huang et al.[12b] reported the synthesis of **3** using SmI_2-mediated coupling of (*S*)-3-silyloxyglutarimide.[12b]

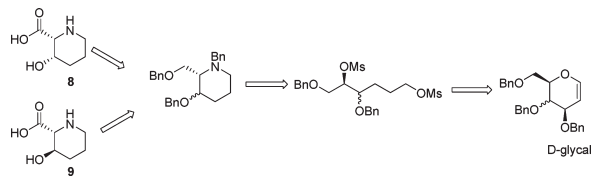
The 3-hydroxypipecolic acid motif is present in a wide variety of natural and unnatural products.[13] These molecules are considered as homologated forms of the hydroxyproline moiety or constrained analogues of serine. In general, 3-hydroxypipecolic acid **7** (Figure 2) and its stereoisomers **8** and **9** are useful chiral building blocks for the synthesis of a variety of pharmaceutically important molecules. Thus, the structural features of the *cis* isomer **7** are present in the naturally occurring antitumor antibiotic tetrazomine[14] **11**. On the other hand, the *trans* isomer **8** is a precursor for potent α-mannosidase inhibitor (−)-swainsonine[15] and is also found to be an integral part of the potent antimalarial agent febrifugine (**12**).[16]

Due to the medicinal importance of 3-hydroxypipecolic acids, synthetic efforts toward such molecules have gained much attention.[17] The usual pathways can be classified as (i) an asymmetric synthesis approach,[18] (ii) a chiron approach,[19,20] and (iii) enzymatic resolution.[21] While asymmetric synthesis approaches involve either dihydroxylation or epoxidation followed by nucleophilic attack with nitrogen, chiron approaches utilize chiral pool starting materials such as chiral amino acids and carbohydrates.[20]

SCHEME 1. Retrosynthetic Analysis of (−)-Dexoprosophylline and (+)-2-*epi*-Deoxoprosopinine



SCHEME 2. Retrosynthetic Analysis of 3-Hydroxypipecolic Acids



In continuation of our recent work on functionalization of D-glycals toward bioactive natural products,[22] we have reported[6] the synthesis of safingol and its stereoisomer from Perlin aldehydes[23] derived from D-glycals. In this paper, we report the synthesis of (−)-dexoprosophylline **1**, (+)-2-*epi*-dexoprosopinine **3**, and 3-hydroxypipecolic acids from Perlin aldehydes. Our retrosynthetic analysis toward the synthesis of (−)-dexoprosophylline (**1**) and (+)-2-*epi*-dexoprosopinine (**3**) is shown in Scheme 1. The target molecules can be prepared from azido ketones by reductive cyclization, which in turn, can be prepared from the corresponding aldehydes by Grignard reaction followed by oxidation. These aldehydes can be easily prepared from Perlin aldehydes which can be obtained from D-glycals upon acid hydrolysis.[23]

The hydroxy pipecolic acids can be prepared (Scheme 2) from the benzyl-protected piperidines, which can be obtained from the dimesylates derived from Perlin aldehydes.

The synthetic approaches toward **1** and **3** are outlined in Scheme 3. Thus, 3,4,6-tri-*O*-benzylated glycals **13** and **14** were subjected to Perlin hydrolysis[23] followed by acetylation to afford the respective *trans*-enals **15** and **16** in 92% and 52% yields, respectively. Chemoselective saturation of double bond in **15** and **16** was carried out under H_2/Pd−C conditions to give **17** and **18** in good yields. The so-obtained aldehydes

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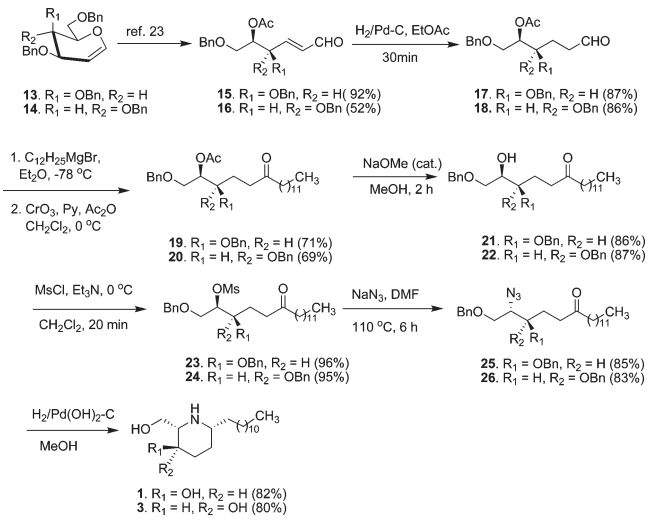
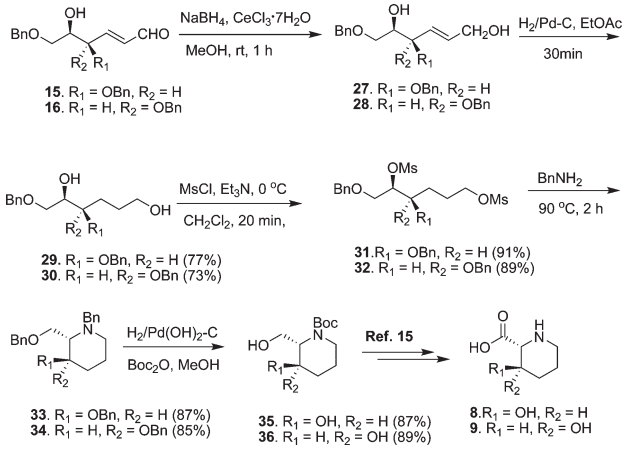
SCHEME 3. Synthesis (−)-Deoxoprosophylline and (+)-2-*epi*-Deoxoprosopinine



were subjected to Grignard reaction using dodecylmagnesium bromide at −78 °C in Et_2O to give a diastereomeric mixture of alcohol at the C-6 center. The free hydroxyl was consecutively oxidized using the CrO_3, Ac_2O, pyridine system[24] to give ketones **19** and **20** in 71% and 69% yields, respectively. Methanolysis of acetates **19** and **20** with NaOMe/MeOH gave the hydroxyl ketones **21** and **22**, respectively, in good yields. Conversion of the C-2 hydroxyl group as mesylate followed by an S_N2 displacement with sodium azide gave the products **25** and **26** with complete inversion of configuration in excellent yields. These azido ketones underwent reduction and reductive ring closure followed by debenzylation in one step when they were treated with H_2/20% $Pd(OH)_2$-C on **25** and **26** to give single isomers of (−)-deoxoprosophylline (**1**) and (+)-2-*epi*-dexoprosopinine (**3**) in a good overall yield of 33% and 17%, respectively. The spectral data of the synthesized compounds **1** and **3** were in absolute agreement with the reported data of the respective molecules.[8f,12]

Finally, syntheses of 3-hydroxypipecolic acids are shown in Scheme 4. Synthesis again starts with Perlin hydrolysis derived aldehydes. Thus, reduction of *trans* enals **15** and **16** with $NaBH_4$−$CeCl_3 \cdot 7H_2O$ under Luche conditiosn[25] gave the diols **27** and **28** in good yields. Chemoselective saturation of the double bonds of **27** and **28** was carried out under H_2/Pd−C conditions to give **29** and **30** in 77% and 73% yields respectively. Mesylation of the free hydroxyl group of **29** and **30** using mesyl chloride and Et_3N gave the mesylates **31** and **32**, respectively, in excellent yields, and the products were characterized by the presence of mesyl peaks as a singlet at δ 2.99 in their ^{1}H NMR spectra. The so-formed dimesylate derivatives were then subjected to cyclization with neat benzylamine at 90 °C to give the cyclized derivatives **33** and **34** by intermolecular followed by intramolecular nucleophilic substitution reactions. Debenzylation and in situ Boc protection gave the piperidines **35** and **36** in 87% and 89% yields, respectively. The spectral data of synthesized

SCHEME 4. Synthesis of 3-Hydroxypipecolic Acids



molecules were in absolute match with the reported data.[20b,26] Conversion of compounds **35** and **36** into the target molecules was performed using literature method.[15]

In conclusion, we have developed new synthetic routes to the synthesis of (−)-deoxoprosophylline, (+)-2-*epi*-deoxoprosopinine, and 3-hydroxypipecolic acids by utilizing the sugar-derived chiral starting materials.

Experimental Section

(−)-Deoxoprosophylline (1). To a solution of azido ketone **25** in EtOH (5 mL) and concd HCl (0.25 mL) was added $Pd(OH)_2$/C (100 mg), and the resulting mixture was stirred under 1 atm hydrogen for 36 h. After completion of the reaction, catalyst was removed by filtration over Celite and washed with ethyl acetate (10 mL). The combined organic layer was concentrated in vacuo. The residue was dissolved in water (5 mL) and extracted once with ether (5 mL). The aqueous layer was made alkaline with 1 N NaOH and extracted thoroughly with $CHCl_3$ (3 × 5 mL). The combined organic layer was dried over Na_2SO_4 and concentrated in vacuo. The white solid was recrystallized from acetone to give (−)-deoxoprosophylline (**1**) (46 mg, 80%): mp 89−90 °C (from acetone); $[\alpha]^{28}_D = -10.7$ (*c* 0.2, $CHCl_3$) [lit.[8b] mp 91−91.5 °C; $[\alpha]^{28}_D = -10.3$ (*c* 0.1 $CHCl_3$)]; IR (neat film) 3443, 3250, 2922, 2850, 1090, 1020 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.86 (t, J = 6.9 Hz, 3H), 1.29 (br s, 22H), 1.33−1.49 (m, 2H), 1.63−1.67 (m, 1H), 1.91 (s, 3H), 2.08−2.12 (m, 1H), 2.64−2.66 (m, 1H), 2.76−2.78 (m, 1H), 3.76 (dt, J = 4.6 Hz, J = 10.7 Hz, 1H), 3.80 (dd, J = 2.2 Hz, J = 12.6 Hz, 1H), 4.0 (dd, J = 2.3 Hz, J = 12.6 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.1, 22.6, 24.2, 25.8, 28.3, 29.3, 29.4 (2C), 29.5, 29.6, 29.7, 31.8, 32.2, 33.4, 57.3, 59.1, 63.8, 65.2; HRMS calcd for $C_{18}H_{38}NO_2$ $[M + H]^+$ 300.2903, found 300.2902.

(+)-2-*epi*-Deoxoprosopinine (3). The same procedure as used for (−)-deoxoprosophylline was adopted for the synthesis of (+)-2-*epi*-deoxoprosopinine: yield 47 mg, 82%; colorless solid; mp 57−58 °C (from acetone); $[\alpha]^{28}_D = +3.3$ (*c* 0.6, MeOH) [lit.[26] mp 59 °C; $[\alpha]^{28}_D = +3.0$ (*c* 0.6 MeOH)]; IR (neat film) 3340, 3259, 2922, 2853, 1092, 1018 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.88 (t, J = 6.6 Hz, 3H), 1.25 (br s, 22H), 1.53−1.57 (m, 2H), 1.75−1.80 (m, 2H), 1.96 − 2.05 (m, 3H), 2.83−2.85 (m, 1H), 2.96 (br s, 1H), 3.89−3.99 (m, 2H), 4.07−4.09 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.2, 22.7, 24.7, 25.6, 29.2−30.2 (7C), 31.1, 32.0, 37.1, 57.4, 61.0, 63.4, 65.9; HRMS calcd for $C_{18}H_{38}NO_2$ $[M + H]^+$ 300.2903, found 300.2906.

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(2*S*,3*R*)-*tert*-Butyl-3-hydroxy-2-(hydroxymethyl)piperidine-1-carboxylate (35). To a solution of piperidine **33** (150 mg, 0.374 mmol) and Boc_2O (163 mg, 0.748 mmol) in dry methanol was added 10% $Pd(OH)_2/C$ (150 mg) in one portion. The resulting mixture was stirred under 1 atm of hydrogen for 48 h. After completion of reaction, the catalyst was removed by filtration over Celite and washed with ethyl acetate (10 mL). The combined organic layer was concentrated in vacuo. The residue was purified by column chromatography (EtOAc/MeOH = 9:1) to yield **35** (75 mg, 87%): colorless oil; $[\alpha]^{28}{}_D = +15.0$ (*c* 0.4, CH_2Cl_2); IR (neat film) 3391, 2929, 2858, 1664, 1251, 1172, 147, 996 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.44 (m, 10H), 1.66−1.73 (m, 2H), 1.79−1.85 (m, 1H), 2.88−2.97 (m, 1H), 3.10 (br s, 1H), 3.13 (br s, 1H), 3.64−3.70 (m, 2H), 3.81−3.83 (m, 1H), 3.93−3.94 (m, 1H), 4.08−4.12 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 19.4, 27.0, 28.3, 40.6, 59.9, 60.4, 64.9, 80.2, 156.6; HRMS calcd for $C_{11}H_{21}NNaO_4$ $[M + Na]^+$ 254.1368, found 254.1369.

(2*S*,3*S*)-*tert*-Butyl-3-hydroxy-2-(hydroxymethyl)piperidine-1-carboxylate (36). The same procedure as used to obtain **35** was utilized for the synthesis of **36**: yield 47 mg, 84%, as an oil; $[\alpha]^{28}{}_D = +13$ (*c* 0.45, MeOH); IR (neat film) 3372, 2932, 1666, 1178, 1072, 996 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.45 (s, 10H), 1.55−1.63 (m, 1H), 1.67−1.70 (m, 1H), 1.83 (dd, J = 3.8 Hz, J = 12.6 Hz, 1H), 2.77 (br s, 1H), 3.55 (br s, 1H), 3.67−3.91 (m, 4H), 4.09 (dd, J = 6.85 Hz, J = 11.4 Hz 1H), 4.44 (dd, J = 6.4 Hz, J = 12.3 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 23.7, 28.2, 28.3, 39.5, 55.9, 59.2, 69.3, 80.3, 155.6; HRMS calcd for $C_{11}H_{21}NNaO_4$ $[M + Na]^+$ 254.1368, found 254.1369.

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Supporting Information Available: General experimental methods and ^1H and ^{13}C NMR spectra for compounds **1**, **3**, **17**−**26**, and **29**−**36**. This material is available free of charge via the Internet at http://pubs.acs.org.