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Formal syntheses of (2*R*,3*R*)-3-hydroxy pipecolic acid and (2*R*,3*S*)-3-hydroxy pipecolic acid from L-ascorbic acid

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ABSTRACT

Formal syntheses of both *cis* and *trans* 3-hydroxy pipecolic acids is achieved from L-ascorbic acid. Present synthesis describes use of chiral pool approach in which epimerization, Staudinger reaction and Cyclization reactions were employed as key steps.

Chiral piperidine framework of alkaloid compounds has gained great deal attention due to their promising biological activity and structural features. Piperidine alkaloids from monohydroxyl piperidine to polyhydroxy piperidine framework compounds are involved in various biological processes. Recently it has been reported that non-natural piperidine core compounds are also involved in various carbohydrate biological processes. Functionalized piperidine framework is an important constituent of many natural and synthetic compounds having medicinal significance.[1] *cis*-3-Hydroxy pipecolic acid **1** forms an important core for tetrazomine **3**[2] which possesses antitumor antibiotic activity. *trans*-3-Hydroxy pipecolic acid **2** is an important constituent for swainsonine **4**,[3] (+)-prosopinine **5** and (+)-febrifugine **6**[4] which are biologically active molecules. The remarkable biological activities and structural features of derivatives of compounds **1** and **2** have motivated many organic chemists towards their syntheses. The synthetic challenge is the construction of piperidine framework and installation of hydroxy functionality in a stereoselective manner. In literature,[5] various protocols have been reported. In continuation of our work towards synthesis of piperidine alkaloids,[6] herein, we wish to report syntheses of both *cis* and *trans*-pipecolic acid precursors **1a** and **2a** (Scheme 1) from a common precursor by employing simple reaction conditions and commercially available starting materials like L-ascorbic acid **10** as the chiral template (Fig. 1).

According to retrosynthetic plan (Scheme 1), it was envisioned that diols **1a** and **2a** could be easily generated from azide **7** via reductive intramolecular N-alkylation. Azide **7** can be easily accessed from ester **8**. Ester **8** could be derived from alcohol **9** which can be readily generated from L-ascorbic acid **10**.

Synthesis of 3-hdroxypipecolic acid began from a commercially available chiral material viz. ascorbic acid **10**. Ascorbic acid was transformed to alcohol **9** by the known literature protocol.[7] Alcohol **9** was oxidized to corresponding aldehyde **11** which without purification was subjected to two carbon Wittig homologation to provide α,β-unsaturated ester **12** (*E*/*Z* 9:1) (in Scheme 2). *trans* olefin **13** was obtained exclusively after performing Wittig Horner reaction conditions.[8] Double bond of α,β-unsaturated ester **12** was reduced using $Pd/(OH)_2$ as catalyst and $HCOONH_4$ as hydrogen source[9] in methanol under reflux condition to furnish ester **8** in 92% yield (in Scheme 3). Interestingly, epimerization of the allylic centre was observed to furnish product **8**, as a mixture of diastereomers, which was confirmed by NMR spectroscopy. Several attempts to avoid epimerization met with failure. So, it was decided to carry forward inseparable diastereomeric mixture **8** for further steps and separate them at the later stage. Thus, inseparable diastereomeric mixture of ester **8** was subjected to reduction. The ester functionality of compound **8** was reduced by using LiBr and $NaBH_4$ to furnish alcohol **14** in 88% yield.[10] Alcohol **14** was converted into its mesylate derivative followed by the treatment with NaN_3 in DMF at 80 °C to furnish azide **15** in 70% yield (over two steps).[11] Terminal acetonide moiety of compound **15** was deprotected using $AcOH/H_2O$ (8:2) at room temperature to obtain diol **16** in 85% yield. Our initial attempt was conversion of diol **16** to its mono TBS derivative **17**. However, conversion of diol **16** to mono TBS derivative **17** by using TBSCl, imidazole in

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0040-4039/

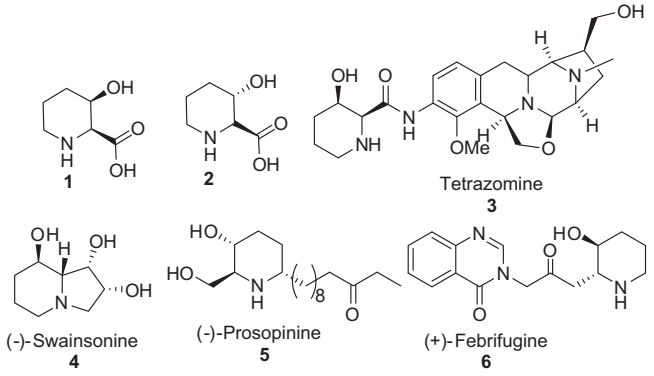
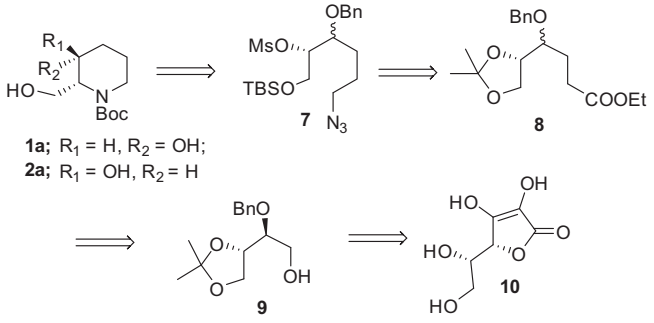
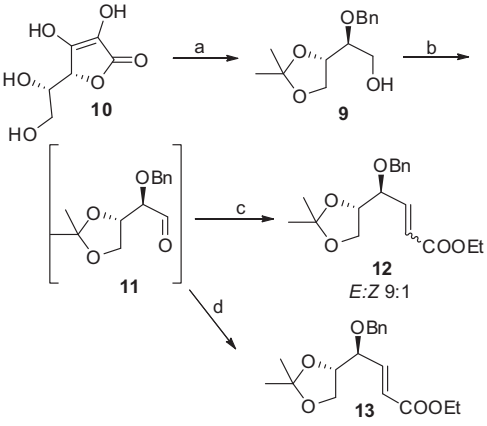


Figure 1. Alkaloids with 3-hydroxy pipecolic acid fragment.

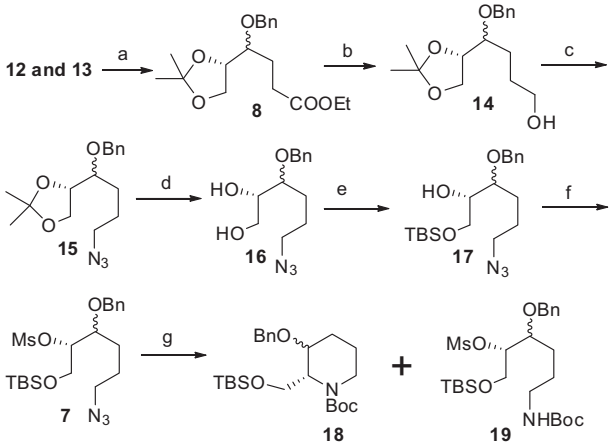


Scheme 1. Retrosynthetic analysis.

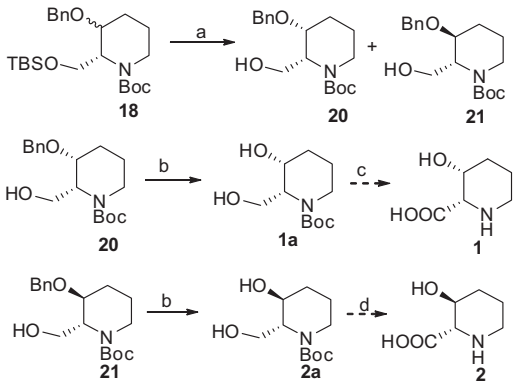


Scheme 2. Reagents and conditions: (a) Ref. 7; (b) Swern oxidation or IBX, EA, reflux, 3 h; (c) $PPh_3CHCOOEt$, DCM, 0 °C to rt, overnight, 80% (over two steps); (d) $(EtO)_2P(O)CH_2COOEt$, NaH, benzene, 80% (over two steps).

DMF or DCM as the solvent was found to be less productive. This issue was solved by selective protection by using TBSOTf, TEA in DCM at 0 °C to provide *O*-TBS derivative **17** in 90% yield.[6c] Secondary hydroxy group of compound **17** was converted to its mesyl derivatives using MsCl, TEA in DCM at 0 °C to afford *O*-mesylate compound **7** in 92% yield. Our next concern was cyclization which was achieved by employing Staudinger reaction conditions[12] using PPh_3 in benzene/H_2O followed by treatment with $(Boc)_2O$ to furnish cyclic carbamate **18** in 50% yield along with uncyclized carbamate **19** in 10% yield. The *O*-TBS deprotection of compound **18** was achieved using TBAF in THF solvent to furnish the column separable hydroxy methyl compounds **20** and **21** in 80% (*dr* 6:4) yield (in Scheme 4).



Scheme 3. Reagents and conditions: (a) $Pd(OH)_2/C$, $HCOONH_4$, MeOH, reflux, 2 h, 92%; (b) LiBr, $NaBH_4$, MeOH/H_2O, 3 h, 88%; (c) (i) MsCl, TEA, DCM, 0 °C, 30 min, (ii) NaN_3, DMF, 90 °C, 6 h, 70% (over two steps); (d) AcOH/H_2O (8:2), rt, 85%; (e) TBSOTf, TEA, DCM, 0 °C, 30 min, 90%; (f) MsCl, TEA, DCM, 0 °C, 30 min, 92%; (g) (i) PPh_3, benzene/H_2O (9:1), reflux, (ii) $(Boc)_2O$, TEA, DMAP (Cat.), THF, rt, 50% (over two steps).



Scheme 4. Reagents and conditions: (a) TBAF, THF, 0 °C to rt, 80%; (b) $Pd(OH)_2$, H_2, MeOH, rt, 85%; (c) Ref. 5a; (d) Ref. 6a.

The column separated benzyl ether compounds **20** and **21** were separately subjected to hydrogenation to provide diol **1a** and **2a**, respectively, in 85% yields. The spectroscopic properties and rotation values of compounds *ent*-**1a** and **2a** were in good agreement with the reported one. The chiral purity of *trans*-diol **2a** was established by chiral HPLC analysis. Diols **1a**[13] and **2a**[14] were further elaborated to the *cis* and *trans*-pipecolic acids (**1** and **2**) by the known literature protocol.[5a,6a]

In conclusion, we have achieved the formal syntheses of (2*R*,3*R*)-3-hydroxy pipecolic acid **1** and (2*R*,3*S*)-3-hydroxy pipecolic acid **2** by utilizing epimerization and reductive cyclization as the key step from the common precursor.

Acknowledgements

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Supplementary data

Supplementary data (supplementary material includes experimental details ^1H, ^{13}C NMR spectra and HRMS for new compounds) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2014.12.103.

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13. *Spectral data for* ***1a****:* mp: 115–117 °C, lit.[5a] 114–116 °C; yield: 85%; $[\alpha]_D^{25}$ −24 (*c* 0.7, MeOH); lit.[5a] for *ent*-**1a** $[\alpha]_D^{20}$ +23.1 (*c* 1.03, MeOH); IR ($CHCl_3$, cm^{-1}): 3448, 2934, 1686; ^1H NMR (400 MHz, $CDCl_3$): δ 1.48 (s, 9H), 1.59–1.82 (m, 4H), 2.89 (br s, 1H), 3.68–3.80 (m, 2H), 3.92–4.01 (m, 1H), 4.11 (dd, *J* = 6.0 & 11.0 Hz, 1H), 4.25–4.34 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 23.7, 28.2, 28.3, 39.5, 55.9, 59.2, 69.3, 80.3, 155.6; ESIMS (*m*/*z*): 232.3 $(M+H)^+$; HRMS (Na+) calcd for $C_{11}H_{21}NO_4$: 231.1470. Found: 231.1484.
14. *Spectral data for* ***2a****:* mp: 133–135 °C; $[\alpha]_D^{25}$ −27.58 (*c* 1.0, MeOH); IR ($CHCl_3$, cm^{-1}): 3435, 1666; ^1H NMR (200 MHz, CD_3OD): δ 1.15–1.29 (m, 1H), 1.39 (s, 9H), 1.61–1.82 (m, 3H), 2.69–2.82 (m, 1H), 3.45–3.61 (m, 2H), 3.89–3.92 (m, 2H), 4.08–4.16 (m, 1H); ^{13}C NMR (125 MHz, $C_2D_6SO + CDCl_3 + CCl_4$): δ 18.95, 26.57, 28.15, 39.79, 59.13, 59.91, 63.83, 79.12, 155.92; HRMS (Na^+): calcd for $C_{11}H_{21}NO_4$: 231.1484. Found: 231.1470; GCMS (*m*/*z*): 231.