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Asymmetric total synthesis of (2*S*,3*S*)-3-hydroxypipecolic acid

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ABSTRACT

A synthetic route to (2*S*,3*S*)-3-hydroxypipecolic acid was achieved from readily available nonchiral pool starting material *cis*-2-butene-1,4-diol and involved Claisen orthoester rearrangement, Sharpless asymmetric dihydroxylation and intramolecular lactamisation of azido lactone as the key steps.

Functionalized chiral piperidine core is an important constituent found in a large number of natural and synthetic compounds having medicinal significance.[1]

(2*S*,3*S*)-3-Hydroxypipecolic acid is a nonproteogenic cyclic β-hydroxy-α-amino acid; its enantiomer has been an important precursor in the synthesis of (−) swainsonine **2**,[2] a potent and specific inhibitor of α-D-mannosidase; its *cis* isomer forms a part of the structure of tetrazomine **5**,[3] an antitumor antibiotic, one carbon homologated analogue of **1** is also a constituent of (+)-febrifugine **4**,[4] a potentially powerful antimalarial agent and its reduced derivative (+)-prosophylline **3**[5] exhibits analgesic, anaesthetic and antibiotic activities (Fig. 1).

(2*S*,3*S*)-3-Hydroxypipecolic acid and its derivatives due to their attractive biological activities have motivated efforts of synthetic chemists towards its synthesis which resulted in many enantioselective syntheses of **1**.[6] However, most of the reported syntheses have drawbacks involving low enantioselectivity. To overcome these problems there still exists a need to develop a simple, practical, efficient and highly enantioselective synthesis of **1**.

Herein we wish to report a new and highly enantioselective synthesis of **1** employing hydroxy lactone **8** as a source of chirality, which can be readily accessed from commercially available cheap achiral starting material such as *cis*-2-butene-1,4-diol.

A retrosynthetic analysis of (2*S*,3*S*)-3-hydroxypipecolic acid is outlined in Scheme 1. The enantiomerically pure hydroxy lactone **8** was obtained in four steps from butene-1,4-diol **9** according to the sequence described by us earlier which involved a Claisen orthoester rearrangement[7] and Sharpless asymmetric dihydroxylation[8] to install the requisite chirality. We further surmised that piperidine core **6** could be constructed by intramolecular lactone ring opening of azidolactone **7**. Azidolactone **7** could be obtained from hydroxy lactone **8** (Scheme 1).

Accordingly, asymmetric synthesis of (2*S*,3*S*)-3-hydroxypipecolic acid **1** started from achiral starting material viz. *cis*-2-butene-1,4-diol (Scheme 2). The 1,4-diol **9** was rearranged to 1,2-diol **10** according to the procedure described in the literature.[9a] The primary alcohol of **10** was selectively benzylated to furnish the corresponding ether **11**. Claisen rearrangement of the allylic alcohol **11** with triethyl orthoacetate in the presence of catalytic propionic acid at 140 °C gave the, γ,δ-unsaturated ester **12**, which was converted into enantiomerically pure hydroxy lactone **8** via ene ester **12** according to the protocol described by us earlier.[9b,c,10] Hydroxy lactone **8** was converted into the corresponding mesylate **13** in 91% yield by using triethyl amine, mesyl chloride. The resultant mesylate **13** was subjected to S_N2 displacement with NaN_3 in DMF at 80 °C, to afford azidolatone **7** in 87% yield.

Reductive intramolecular cyclisation of azidolactone **7** using $Pd(OH)_2$ under H_2 atmosphere at 30 psi in methanol furnished

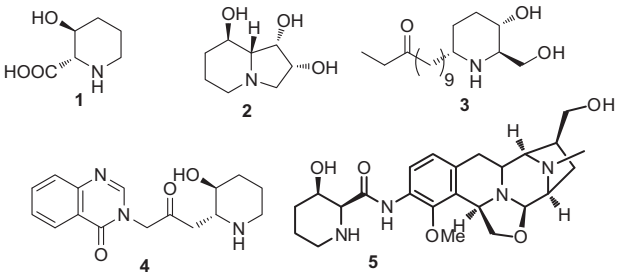
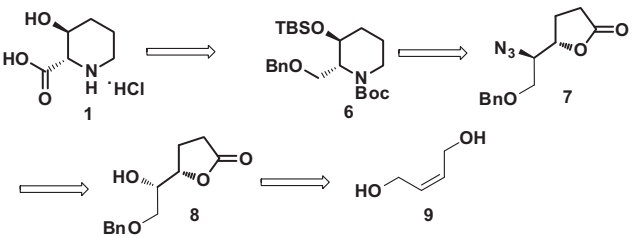


Figure 1. 3-Hydroxy pipecolic acid and its derivatives.



Scheme 1. Retrosynthetic analysis of (2*S*,3*S*)-3-hydroxypipecolic acid.

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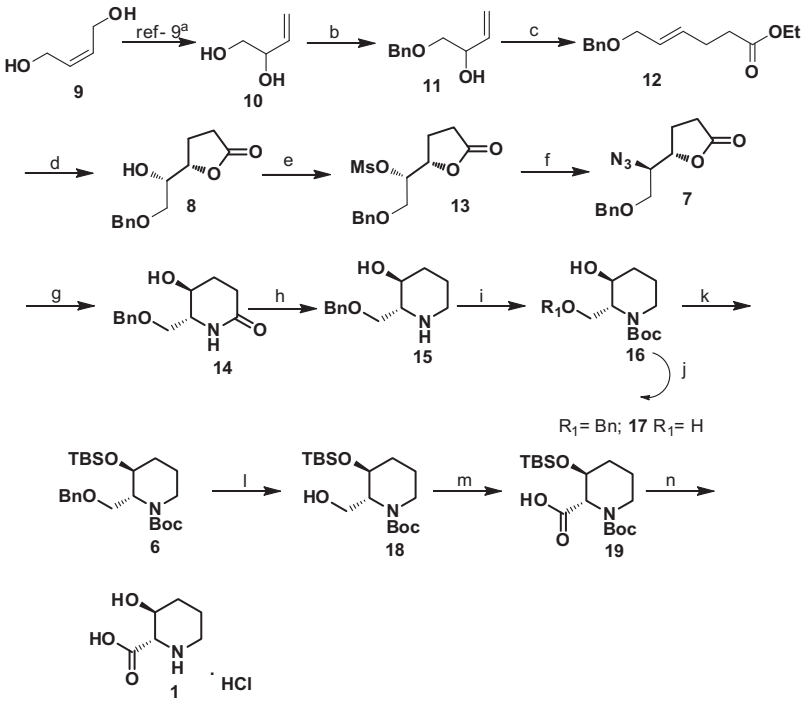

Scheme 2. Reagents and conditions: (a) $HgSO_4$, H_2SO_4 (cat), H_2O, 100 °C, 3 h, 65%; (b) KOH (1.1 equiv), BnCl (1.1 equiv), benzene, reflux, 8 h, 60%; (c) $CH_3C(OEt)_3$, propanoic acid (cat.), 140 °C, 3 h, 85%; (d) $K_3Fe(CN)_6$, K_2CO_3, $(DHQ)_2PHAL$, OsO_4, $MeSO_2NH_2$, 0 °C, 24 h, 94%; (e) MsCl, Et_3N, DMAP (cat.), DCM, 5 h, 91%; (f) NaN_3, DMF, 90 °C, 18 h, 87%; (g) $Pd/(OH)_2$, H_2, MeOH, 30 psi, rt, 3 h, 90%; (h) LAH, THF, 0 °C to rt, 3 h, 74%; (i) Boc anhydride, Et_3N, DMAP (cat.), dioxane/H_2O, 0 °C, 3 h, 90%; (j) Pd/C, H_2, MeOH, 70 psi, rt, 3 h, 93%; (k) TBSCl, imidazole, DMF, rt, 6 h, 90%; (l) Pd/C, H_2, 70 psi, rt, 3 h, 95%; (m) $RuCl_3$, $NaIO_4$, $CH_3CN/CCl_4/H_2O$ (1:1:3), rt, 30 min, 58%; (n) 6 N HCl, reflux, 2 h.

the desired six membered lactam **14**[12] in 90% yield. Lactam **14** was reduced using $LiAlH_4$ in anhydrous THF to afford the corresponding amine **15** in 74% yield. To avoid further functional group complication, amine group was protected as carbamate using Boc-anhydride, triethyl amine in dioxane/H_2O (1:1) to furnish urethane **16** in 90% yield. Compound **16** was subjected to hydrogenation using Pd/C in methanol at 70 psi to afford dihydroxy compound **17** in 93% yield (ee >99%).[13] Using the same strategy we prepared racemic intermediate of **17**[12] which was an important precursor of 3-hydroxy pipecolic acid.[6h,j] The hydroxy group of **16** was protected by using TBSCl, imidazole, DMAP cat. in anhydrous DMF which furnished TBS protected compound **6** in 90% yield. Compound **6** was subjected to hydrogenation by using Pd/C in methanol at 70 psi to furnish compound **18** into 95% yield. Oxidation of the primary hydroxyl group was achieved by using $RuCl_3$, $NaIO_4$ as an oxidant to afford acid **19**[11] in 58% yield. Finally, removal of both protecting groups under acidic condition using 6 N HCl completed the synthesis of (2*S*,3*S*)-3-hydroxypipecolic acid hydrochloride **1**. Spectral data of **1**[12] were in complete agreement with the ones reported in the literature.[6g]

In conclusion we have achieved the enantioselective total synthesis of (2*S*,3*S*)-3-hydroxypipecolic acid **1** based on Sharpless asymmetric dihydroxylation of olefinic ester **12**. Intramolecular lactone ring opening was employed as one of the key steps for the construction of piperidine core.

Acknowledgements

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12. All compounds were characterized by IR, ^{1}H NMR, ^{13}C NMR and mass spectral analysis: *compound* **14**: $[\alpha]_D^{25}$ = +30.34 (*c* 1.45, MeOH); IR ($CHCl_3$, cm^{-1}): 3435, 1672.97; ^{1}H NMR (200 MHz, $CDCl_3$ + CCl_4): δ 1.7–2.05 (m, 2H), 2.17–2.56 (m, 2H), 3.38–3.54 (m, 2H), 3.64–3.84 (m, 2H), 4.52 (s, 2H), 6.54 (s, 1H), 7.33 (s, 5H); ^{13}C (50 MHz, $CDCl_3$): δ 27.4, 28.0, 57.9, 65.3, 71.5, 73.2, 127.5, 127.7, 128.3, 137.2, 172.1; *Compound* **17**: mp = 133−135 °C; $[\alpha]_D^{25}$ = −27.58 (*c* 1.0, MeOH); ^{1}H 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 (125 MHz, C_2D_6SO + $CDCl_3$): δ 18.9, 26.6, 28.2, 39.8, 59.1, 59.9, 63.8, 79.1, 155.9; HRMS (CI+): calcd for $C_{11}H_{21}NO_4$: 231.1471; found: 231.1484; MS(CI): *m*/*z* = 231; XRD (single X-ray confirmed that the relative stereochemistry of both hydroxy and hydroxy methyl group are trans to each other). *Compound* **1**: $[\alpha]_D^{25}$ = +13.8 (*c* 1.0, H_2O); ^{1}H NMR (400 MHz, D_2O): δ 1.50–1.74 (m, 2H), 1.82–1.94 (m, 2H), 2.90–3.00 (m, 1H), 3.19–3.30 (m, 1H), 3.72 (d, *J* = 7.6 Hz, 1H), 3.94–4.03 (m, 1H).
13. For racemic dihydroxy compound (**17**) HPLC chiracel OD-H column (250 × 4.6 mm) isopropanol/*n*-hexane = 5:95 flow rate 0.5 ml/min, λ = 210 nm) retention time (min): Rt_1 = 15.52; Rt_2 = 17.34 (1:1) enantiomerically pure dihydroxy compound (**17**) HPLC chiracel OD-H column (250 × 4.6 mm) isopropanol/*n*-hexane = 5:95 flow rate 0.5 ml/min, λ = 210 nm) retention time (min): 17.34 (exclusive).