Chiron approach to formal synthesis of both antipodes of *cis* 3-hydroxypipecolic acid

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ABSTRACT

The efficient and practical formal syntheses of both enantiomers of *cis* 3-hydroxypipecolic acid were accomplished from *cis* aziridine-2-carboxylate as the common synthetic precursor. The key steps involved are stereo and regioselective aziridine ring opening, reductive cyclization and selective N-debenzylation over O-debenzylation reactions.

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The 3-hydroxypiperidine, one of the most privileged scaffolds, is present in a variety of natural products.[1] Among the family of 3-hydroxypiperidines, 3-hydroxy derivatives of pipecolic acid (Fig. 1) are a constituent of many compounds having potent biological activities[2] and are used in the preparation of conformationally restricted peptides and ligand binding studies.[3] The *cis*-isomer **1** is a structural unit of the antitumor antibiotic tetrazomine **3**,[4] while reduced analogue of *ent*-**1** viz. *ent*-**2** is component of isofebrifugine, an antimalarial agent.[5] Non-peptidic NK-1 receptor antagonists viz. 5[6] and 6[7] have a *cis*-relationship between the phenyl and ether groups on the piperidine ring (Fig. 1). *trans* (2R,3R)-3-Hydroxypipecolic acid has been used as a precursor in the synthesis of (−)-swainsonine,[8] a potent anti-cancer drug and specific inhibitor of α-D-mannosidase.[9] Enantiomer *trans* (2S,3S)-3-hydroxypipecolic acid is found in (+)-febrifugine, a potent antimalarial agent,[10] and its reduced derivatives have been the components of (+)-prosopinine and (+)-prosophylline which exhibit analgesic, anaesthetic and antibiotic activities.[11]

As a consequence of its biological significance, stereoisomeric 3-hydroxypipecolic acid has become an important target for many synthetic organic chemists and several synthetic strategies have been reported in the literature.[12,13] Synthetically, *cis* derivatives

are relatively less explored compared to their *trans* counterparts. However, among the chiral pool approaches towards the synthesis of *cis* 3-hydroxypipecolic acid, most of the reported syntheses have
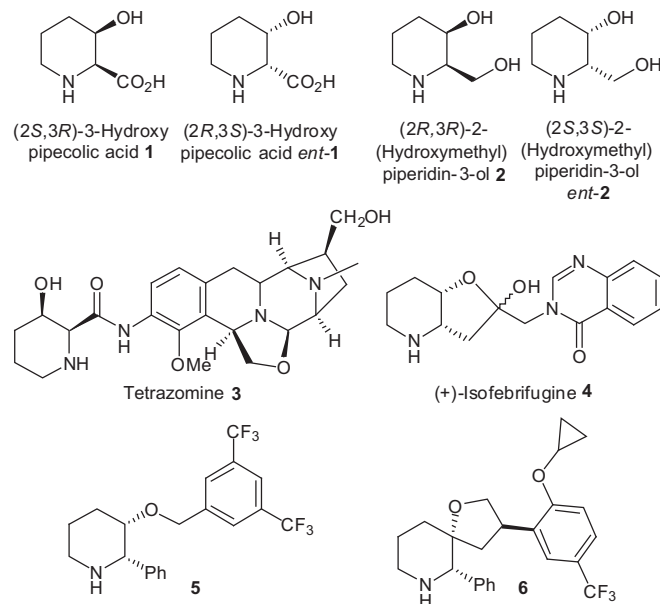

Figure 1. 3-Hydroxypipecolic acid and its derivatives.

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utilized serine derivatives as the precursor.[13a–f] The two approaches had incorporated D-glucose[13g,h] while L-proline[13i] and D-glycal[13j] were utilized to incorporate chirality. To the best of our knowledge, based on literature survey, only one synthesis has been reported to access *cis* 3-hydroxypipecolic acid enantiomers from the common starting material.[13f]

The potential application of 3-hydroxypipecolic acids coupled with our continued interest towards the development of efficient and practical approaches towards piperidine alkaloids,[13k,14] led us to explore a new method towards their synthesis. We herein report the stereoselective syntheses of both the antipodes of *cis* 3-hydroxypipecolic acid starting from *cis* aziridine-2-carboxylate as the common synthetic precursor which could be easily derived from D-mannitol diacetonide.

Aziridine-2-carboxylates have been considered as prominent precursors towards the synthesis of α and β-amino acid building blocks because of their inherent ability towards nucleophilic ring opening reactions.[15] In spite of that, aziridines are relatively less explored compared to their oxygenated three-membered ring partner and even termed as 'ugly cousins' of oxiranes[15c] because of their less reactivity and selectivity towards ring opening by nucleophiles. However, proper manipulations of functionalities attached to the aziridine ring can greatly enhance their reactivity and improve their applicability as important synthons towards the preparation of various amino building blocks. The desymmetrization of *cis* aziridine-2-carboxylate 7 (having latent plane of symmetry element) by nucleophilic ring opening at either side of aziridine ring would generate enantiomeric amines. In an attempt to exploit this aspect of aziridine 7 as shown in retrosynthetic analysis (Scheme 1), it was envisioned that desired *syn* 1,2-amino-alcohol stereochemistry of piperidine skeleton of *cis*-3-hydroxypipecolic acid viz. 1 and *ent*-1 can be achieved from respective amino-alcohols 9 and 11 having requisite chirality. The amino-alcohols 9 and 11 in turn can be accessed by regio and stereoselective aziridine ring opening reaction of appropriate α,β-unsaturated aziridine esters 8 and 10 by the hydroxyl group as the nucleophile. The required aziridines 8 and 10 can be easily prepared by regioselective functionalization on either side of *cis* aziridine-2-carboxylate 7. Ester and acetonide functionalities of aziridine 7 can serve as a handle for desymmetrization.

Actual synthesis began with *cis*-aziridine-2-carboxylate 7 which was prepared from D-mannitol diacetonide using known literature procedure.[16] We recently exploited *cis* aziridine 7 towards the total
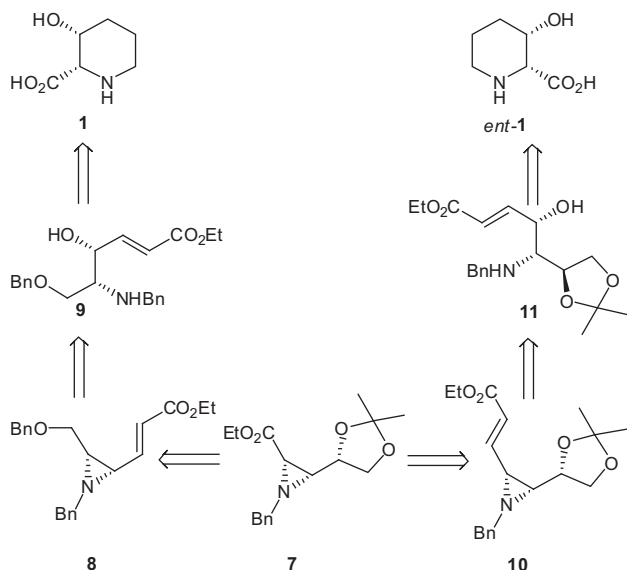
syntheses of (*R*) and (*S*)-pipecolic acid.[14e] In continuation of our work, *cis*-aziridine-2-carboxylate 7 was reduced using LAH/THF to give alcohol 12 in 90% yield. The hydroxyl group of compound 12 was protected as its benzyl ether using benzyl bromide and NaH in DMF to furnish benzyl ether 13 in 95% yield. Compound 13 was subjected to acetonide deprotection using PTSA/MeOH to afford diol 14 in 85% yield. Diol 14 on oxidative cleavage using sodium metaperiodate in acetone/water provided aldehyde which was used as such for Wittig olefination with PPh3CHCO2Et and catalyst benzoic acid in refluxing toluene (a method used for the formation of *E* as major isomer)[17] to furnish compound 8 in 85% yield over two steps. The resultant α,β-unsaturated ester aziridine 8 was subjected to regio and stereoselective aziridine ring opening reaction in acidic conditions[18] (TFA, 2 equiv) by water as nucleophile to form vicinal amino alcohol 9. Once the stereocentres at amine and hydroxyl functionality of amino-alcohol 9 were fixed with the desired stereochemistry, the hydroxyl group of amino-alcohol 9 was selectively protected as its TBS ether derivative 15 using TBSCl, imidazole and catalyst DMAP under reflux condition in dichloromethane with 90% yield. Compound 15 on hydrogenation using 10% Pd(OH)2 in ethanol[19] underwent concomitant double bond reduction, selective N-debenzylation and cyclization to furnish desired stereoisomer lactam 16 in 88% yield with requisite piperidine skeleton. Further, lactam 16 was reduced to amine using BH3·DMS to furnish crude amine, which without purification was protected as its *N*-Boc derivative using Boc-anhydride and triethylamine as the base to give intermediate 17 in 80% yield. Intermediate 17 is well reported in the literature and can be converted into (2*S*,3*R*)-3-hydroxypipecolic acid 1 in three steps in 73% yield.[20] Spectral and analytical data of compound 17 thus obtained are in good agreement with reported one.[24] Thus, this constitutes the formal synthesis of (2*S*,3*R*)-3-hydroxypipecolic acid 1 (Scheme 2).

The formal synthesis of enantiomeric (2*R*,3*S*)-3-hydroxypipecolic acid *ent*-1 (Scheme 3) started with common synthetic precursor viz. *cis*-aziridine-2-ester 7 which on propagation from ester side using DIBAL-H reduction to crude aldehyde followed by Wittig homologation gave α,β-unsaturated aziridine-ester 10. Aziridine

Scheme 1. Retrosynthetic analysis for *cis*-3-hydroxypipecolic acid.
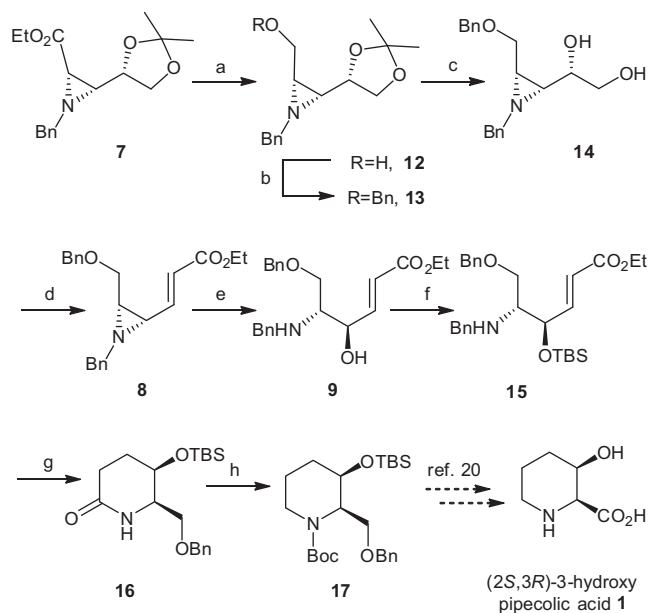
Scheme 2. Reagents and conditions: (a) LAH, THF, 0 °C, 1 h, 90%; (b) BnBr, NaH, cat. TBAI, DMF, 95%; (c) PTSA, CH3OH, 85%; (d) (1) NaIO4, (CH3)2CO/H2O (2:1), (2) Ph3PCHCO2Et, cat. PhCO2H, PhMe, reflux, 85% (over two steps); (e) TFA, CH3CN/H2O (9:1), 85%; (f) TBSCl, Imd. cat. DMAP, CH2Cl2, reflux, 90%; (g) H2, 10% Pd(OH)2/C, EtOH, 88%; (h) (1) BH3·DMS, THF, (2) (Boc)2O, CH2Cl2, Et3N, 80% (over two steps).
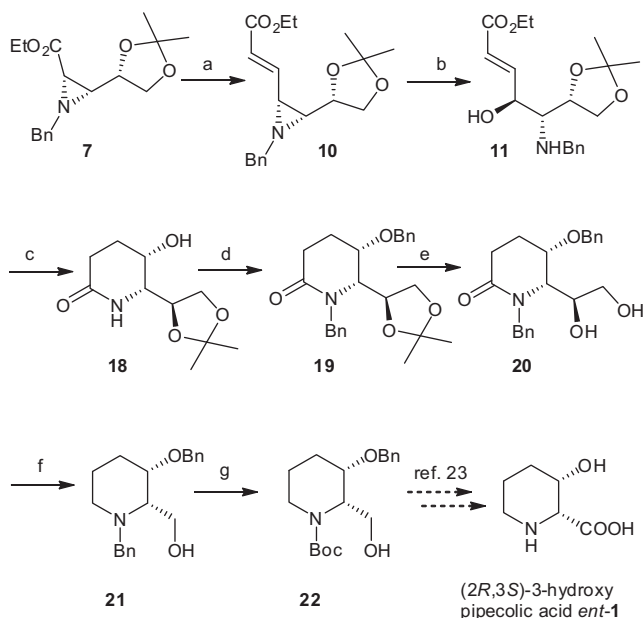
**Scheme 3.** Reagents and conditions: (a) (1) DIBAL-H, CH$_2$Cl$_2$, −78 °C, (2) Ph$_3$PCHCO$_2$Et, cat. PhCO$_2$H, PhMe, reflux, 82%, (over two steps); (b) TFA, CH$_3$CN/H$_2$O, (9:1), 75%; (c) 10% Pd/C, HCO$_2$NH$_4$, MeOH, 60 °C, 90%; (d) BnBr, NaH, cat. TBAI, DMF, 85%; (e) 80% aq AcOH; (f) (1) NaIO$_4$, (CH$_3$)$_2$CO/H$_2$O, (2:1), (2) BH$_3$·DMS, THF, 65%, over 3 steps; (g) (1) H$_2$, 10% Pd(OH)$_2$/C, EtOH, (2) (Boc)$_2$O, Et$_3$N, CH$_2$Cl$_2$, 80% over 2 steps.

ester **10** on treatment with trifluoroacetic acid in CH$_3$CN–H$_2$O[18] underwent regio and stereoselective aziridine ring opening reaction to furnish δ-hydroxy, γ-amino, α,β-unsaturated ester **11** with requisite stereocentres. Compound **11** was subjected to transfer hydrogenation condition[21] using the catalyst Pd/C (10%) and ammonium formate in refluxing methanol, which underwent concomitant double bond reduction, N-debenzylation and cyclization to afford 3-hydroxy substituted δ-lactam **18** with excellent yield (90%). Absolute stereochemistry of lactam **18** was confirmed by a single crystal XRD spectroscopy which clearly showed the *cis* relationship between hydroxy and acetonide (with one fixed stereocentre) functionalities of lactam **18** (Fig. 2).[22]

Protection of lactam **18** as its N- and O-benzyl derivative was carried out using BnBr, NaH and cat. TBAI in DMF to furnish dibenzylated compound **19** in 85% yield. Acetonide group deprotection of lactam **19** in 80% aq acetic acid at 80 °C afforded diol **20**. Crude diol **20** was subjected as such to oxidative cleavage to give crude
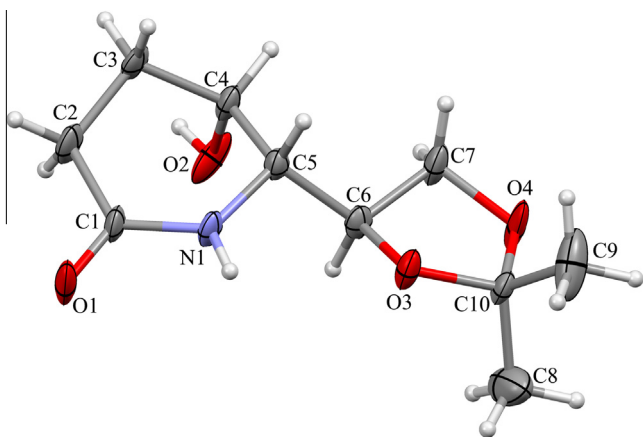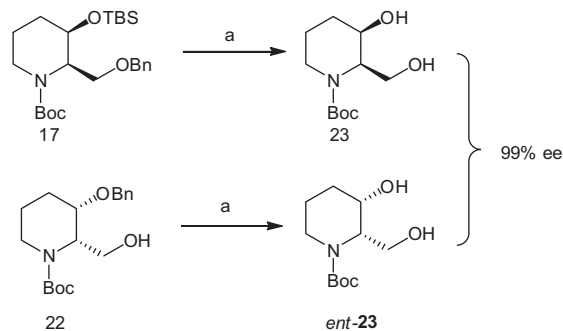
Scheme 4. Reagents and conditions: (a) H$_2$, 10% Pd/C, MeOH, 95%.

aldehyde which, without purification was subjected to concomitant aldehyde and amide reduction using BH$_3$·DMS in THF to afford N-benzyl alcohol **21** in 65% yield over three steps. Further, N-benzyl group of compound **21** was selectively deprotected over O-benzyl group[18] using 10% Pd(OH)$_2$/C in ethanol followed by protection of resultant amine as N-Boc derivative using Boc-anhydride to furnish compound **22** which is well reported in the literature and can be exploited for the synthesis of (2R,3S)-3-hydroxypipecolic acid *ent*-**1** over four steps.[23] Spectral and analytical data of compound **22** are in accordance with the reported values.[24]

In order to establish the enantiomeric purity of *cis* 3-hydroxypipecolic acid enantiomers, compounds **17** and **22** were converted to their respective dihydroxy compounds **23** and *ent*-**23**. Chiral HPLC analysis of both diol showed 99% enantiomeric excess (Scheme 4).[25]

In conclusion, efficient and practical formal syntheses of *cis* 3-hydroxypipecolic acid enantiomers were accomplished from *cis* aziridine-2-carboxylate as a common chiral synthetic precursor. Syntheses involved stereoselective and regioselective aziridine ring opening, reductive cyclization and selective N-debenzylation over O-debenzylation as the key reactions. Synthesis of (2S,3R)-3-hydroxypipecolic acid has been accomplished in 8 purification steps with 24% overall yield while (2R,3S)-3-hydroxypipecolic acid was achieved in 9 purification steps with 12% overall yield starting from *cis* aziridine-2-carboxylate.

Acknowledgments

Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2014.09.118.

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Figure 2. ORTEP diagram of compound **18**.

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24. *Data for selected compounds*: compound **17**: R_f: 0.5 (pet. ether–ethyl acetate, 7:3); yield: 80% (over two steps); $[\alpha]_D^{25}$ +5.2 (c 1.2, CHCl$_3$), lit.[20] $[\alpha]_D^{23}$ +5.3 (c 0.66, CHCl$_3$); IR (CHCl$_3$, cm^{-1}): ν_{max} 2930, 1691, 1630, 1450, 1289; ^{1}H NMR (400 MHz, CDCl$_3$+CCl$_4$): δ 0.06 (s, 3H), 0.07 (s, 3H), 0.87 (s, 9H), 1.46 (s, 9H), 1.40–1.54 (m, 2H), 1.63–1.66 (m, 2H), 2.72–2.76 (m, 1H), 3.70–3.97 (m, 4H), 4.40–4.62 (m, 3H), 7.27–7.30 (m, 5H); ^{13}C NMR (100 MHz, CDCl$_3$+CCl$_4$): δ −4.8, 18.1, 24.0, 25.8, 28.4, 29.7, 37.3, 56.1, 64.4, 69.4, 72.6, 79.3, 127.3, 128.2, 138.7, 155.0.MS (ESI): m/z: 458.23 (M+Na)⁺; HRMS: calculated for C$_{24}$H$_{42}$O$_4$NSi-436.2878, found-436.2886. Compound **22**: R_f: 0.5 (pet. ether–ethyl acetate, 7:3); IR (CHCl$_3$, cm^{-1}): ν_{max} 3448, 2986, 1655, 1454, 1371, 1262; $[\alpha]_D^{25}$ +16.3 (c 0.3, CHCl$_3$), lit.[23] {$[\alpha]_D^{25}$ +16.7 (c 1.31, CHCl$_3$)}; ^{1}H NMR (400 MHz, CDCl$_3$+CCl$_4$): δ 1.42–1.44 (m, 1H), 1.47 (s, 9H), 1.55–1.68 (m, 1H), 1.63–1.74 (m, 1H), 1.97–2.22 (m, 1H), 2.75 (br s, 2H), 3.61–3.64 (m, 1H), 3.74 (br s, 1H), 3.87 (br s, 1H), 4.02 (dd, J = 6.0 & 12.0 Hz, 1H), 4.61–4.72 (m, 3H), 7.25–7.35 (m, 5H); ^{13}C NMR (100 MHz, CDCl$_3$+CCl$_4$): δ 23.9, 25.8, 28.4, 39.2, 53.5, 59.1, 70.9, 76.5, 80.1, 127.5, 127.8, 128.5, 137.9; MS (ESI): m/z: 344.16 [M+Na]⁺; HRMS: calculated for C$_{18}$H$_{28}$O$_4$N-322.2013, found-322.2008.
25. HPLC: for racemic compound **23**: chiralcel OJ-H column (250 × 4.6 mm), isopropanol: pet. ether = 01:99, flow rate 0.5 ml/min, λ = 210 nm, retention time (min): rt1 = 73.24, rt2 = 81.33 (1:1); HPLC: for enantiomerically pure compound (2R,3R)-**23**: rt1 = 73.34 (major); for (2S,3S)-*ent*-23: rt2 = 81.01 (major).