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A novel, concise and efficient protocol for non-natural piperidine compounds†

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Formal synthesis of L-*altro*-1-deoxynojirimycin, *cis*-3-hydroxy-pipecolic acid along with synthesis of (*R*)-piperidinol and a conceptually different advanced intermediate for non-natural piperidine alkaloids is reported from *cis*-butene-1,4-diol. The key reactions involved are Johnson–Claisen rearrangement, Sharpless asymmetric dihydroxylation, reductive lactamization and novel regioselective elimination.

Naturally and non-naturally occurring polyhydroxy compounds containing a piperidine core have shown promising biological activity, specifically as glycosidase inhibitors, anticancer agents and antiviral agents.[1] D-Fagomine (Fig. 1) has inhibitory activity towards mammalian α-glucosidase and β-galactosidase enzymes.[2] Most of the synthetic efforts have been devoted towards the synthesis of D-fagomine **1** (Fig. 1) and its isomers which possess D configuration. Relatively there has been less attention paid towards the synthesis L- configured fagomine **2** (Fig. 1) and its isomers. Recently, there is report on synthesis of L-fagomine (ref. 3 and 4) and its isomers. In literature,[5] there are various protocols used for synthesis of fagomine **1** (Fig. 1) and its isomers. (*S*)-Pipecolic acid **3** (ref. 6) (Fig. 1) is a natural product and forms an important structural core for many alkaloids[7] and bicyclic alkaloids.[8]

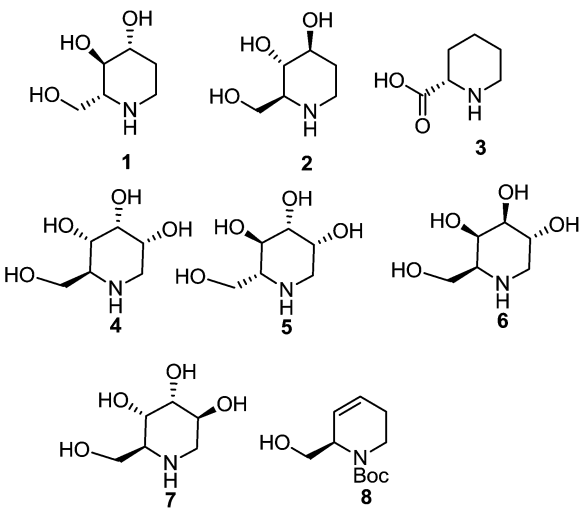
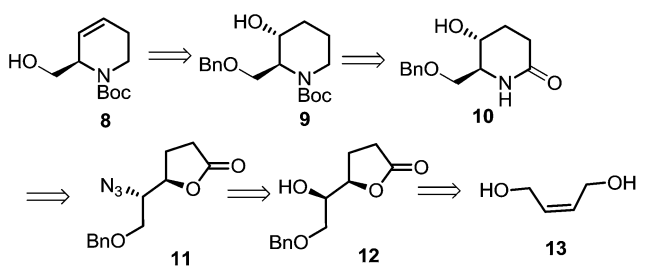


Fig. 1 Piperidine alkaloids.

Literature survey revealed that L-isomer of deoxynojirimycin (DNJ) also possesses inhibitory activity against various glycosidases.[9a] L-1-Deoxyallonojirimycin (L-*allo*-1-DNJ) **4** has been reported to have more inhibitor activity against α-mannosidase than the D-*manno*-DNJ **5** (Fig. 1). Based on the protocol reported by our group towards the asymmetric synthesis of piperidine alkaloids[15a] we wish to report the utility of key synthon **16** for the synthesis of polyhydroxypiperidine alkaloids *viz.* L-fagomine **2**, its isomers, L-*allo*-1-DNJ **4**,[9] L-*galacto*-1-deoxynojirimycin (L-*galacto*-1-DNJ) **6** (ref. 10) and L-*altro*-1-deoxynojirimycin (L-*altro*-1-DNJ) **7**.[11,19]

A retrosynthetic analysis of **8** is outlined in Scheme 1. Unsaturated piperidine framework **8** can be obtained from hydroxy compound **9** which in turn could be prepared from the



Scheme 1 Retrosynthetic analysis of (*R*)-*tert*-butyl-2-hydroxymethyl)-5,6-dihydropyridine-1(2*H*)-carboxylate.

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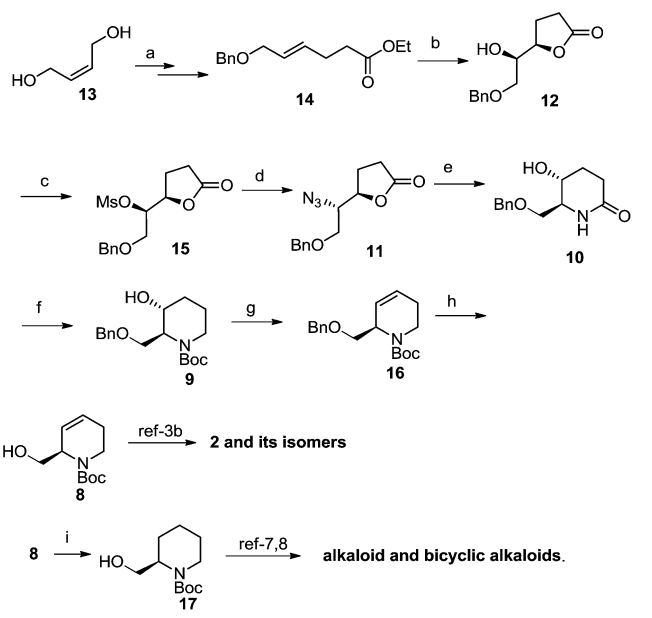
lactam **10**. Lactam **10** could be easily generated from azidolactone **11** *via* reductive lactamisation. Azidolactone **11** could be obtained from hydroxy lactone **12**. Hydroxy lactone **12** in turn can be accessed from *cis*-butene-1,4-diol **13**.

Accordingly, asymmetric synthesis of piperidine core **8** started from achiral cheap starting material *viz.* *cis*-2-butene-1,4-diol (Scheme 2). *cis*-Butene-1,4-diol was rearranged to unsaturated ester **14** according to the procedure described in the literature.[12,13] Unsaturated ester **14** was subjected to Sharpless asymmetric dihydroxylation reaction[14] to furnish enantiomerically enriched[15b] hydroxy lactone **12**. Hydroxy lactone **12** was converted into corresponding mesylate **15** by using TEA and methanesulphonyl chloride in 91% yield. The resultant mesylate **15** was subjected to S_N2 displacement with sodium azide in DMF at 80 °C to furnish azidolactone **11** in 87% yield. Reductive lactamisation on **11** was carried out by using $Pd(OH)_2$ under H_2 atmosphere at 30 psi to afford lactam **10**. Lactam **10**, without purification, was reduced using LAH in THF to give amine which without purification was treated with $(Boc)_2O$ to provide carbamate **9** in 63% yield (over two steps).

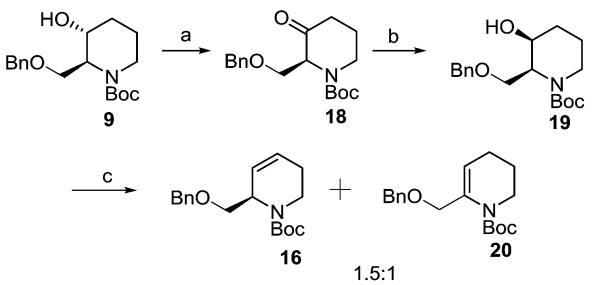
Earlier we have reported the synthesis of other enantiomer of compound **9**.[15a] Conversion of alcohol **9** into the corresponding iodide was attempted using triphenyl phosphine and iodine in the presence of imidazole as the base but surprisingly, it furnished olefin **16** (ref. 21) as the only product in excellent yield (Scheme 2). We did not observe its regioisomer.

In order to study the effect of stereochemistry of hydroxyl group on the outcome of the reaction, we synthesized *cis* isomer[16] **19** by oxidation of **9** to afford **18** (Scheme 3), followed by reduction with sodium borohydride. Alcohol **19** was subjected to the treatment with triphenyl phosphine, imidazole and iodine to provide two regioisomeric olefins **16** and **20** (1.5 : 1) in 60% yield. This clearly demonstrated that the stereochemistry of hydroxyl group has a profound effect on the outcome of product formation. The high distereoselectivity in the reduction of carbonyl **18** to *cis* alcohol **19** can be predicted according to Felkin's torsional strain model which favours the axial attack of hydride. This is in good agreement with the observation made by Zhu and coworkers where they observed similar results.[16] In alcohol **19** hydroxyl group is in axial position and there are two protons present anti to hydroxyl group at C_1 and C_3 in piperidine ring (Scheme 4). This stereochemistry allows elimination from both the sides, where as In case of compound **9** only C_3 proton is anti to the hydroxyl group and this allows elimination from this side only (Scheme 5). Hence, single elimination product **16** is observed.

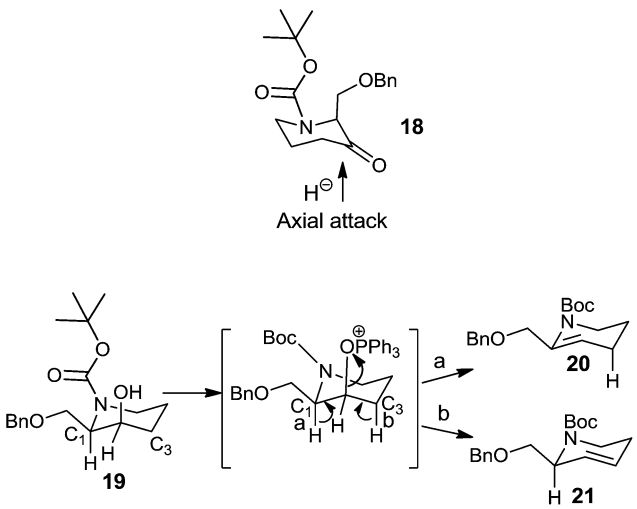
O-Debenzylation of **16** was carried out by using sodium metal in anhydrous THF in liquid ammonia to afford homoallylic alcohol **8** in 88% yield. It is pertinent to mention that homoallylic alcohol[3b] **8** is an important precursor for the total synthesis of L-fagomine **2** and its congeners. The olefin **8** was



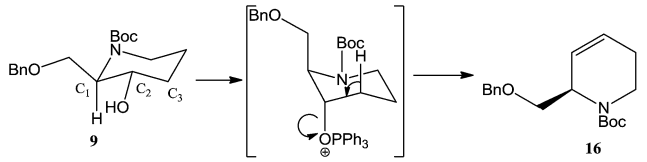
Scheme 2 Reagents and conditions: (a) ref. 12 and 13; (b) $K_3Fe(CN)_6$, K_2CO_3, $(DHQD)_2PHAL$, OsO_4, $MeSO_2NH_2$, *t*-BuOH : H_2O (1 : 1), 0 °C, 24 h, 94%; (c) MsCl, Et_3N, DMAP (cat.), DCM, 5 h, 91%; (d) NaN_3, DMF, 80 °C, 18 h, 87%; (e) $Pd(OH)_2$, H_2, MeOH, 30 psi, rt, 3 h, 93%; (f) (i) LAH, THF, 0 °C to rt, 3 h; (ii) $(Boc)_2O$, TEA, DMAP (cat.), THF rt, overnight, 63% (over two steps); (g) PPh_3, imidazole, I_2, toluene, 120 °C, 30 min, 85%; (h) Na (metal), THF, ammonia, −78 °C, 10 min, 88% and (i) Pd/C, H_2, MeOH, 50 psi, 92%.



Scheme 3 Reagents and conditions: (a) IBX, EtOAc, reflux, 3 h, 95%; (b) $NaBH_4$, MeOH, 0 °C, 30 min, 88% and (c) PPh_3, imidazole, I_2, toluene, reflux, 30 min, 60%.



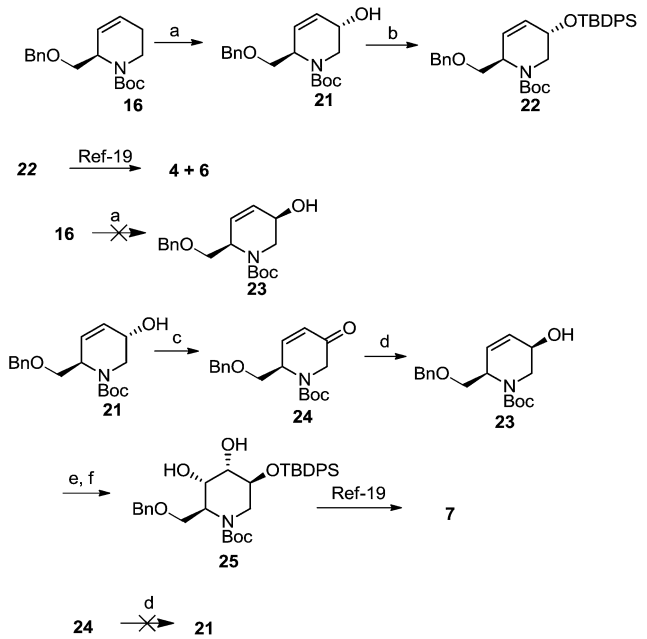
Scheme 4 Formation of compounds **19**–**21**.



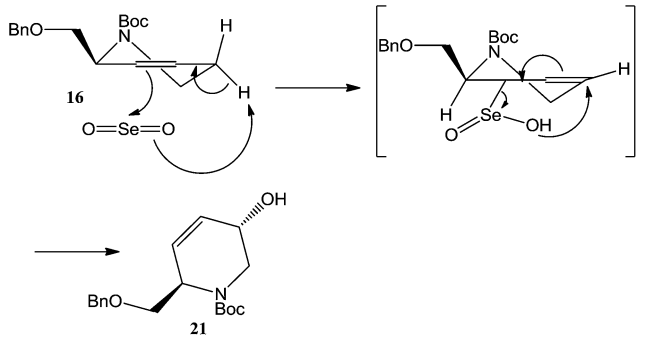
Scheme 5 Exclusively formation of compound **16**.

reduced by using Pd/C as the catalyst in methanol under H_2 atmosphere at 50 psi to afford hydroxymethyl piperidine core **17** which is an important precursor for the construction of bicyclic, substituted piperidine alkaloids[7,8] and (*R*)-pipecolic acid. Following the same reaction sequence, racemic compound **17** was synthesized. There was no epimerization either during elimination or reduction of the olefin which was confirmed by chiral HPLC (ee > 97%),[17] and specific rotation (Scheme 6).

To extend application of advanced intermediate **16**, olefin compound **16** was subjected to allylic oxidation[18] by using selenium dioxide in 1,4-dioxane under reflux condition to provide alcohol **21** in 35% yield (Scheme 4). Interestingly, this oxidation took place in regiospecific and stereoselective manner. We did not observe the formation of other diastereomer **23**. This may be attributed to the distorted chair conformation of compound **16**. The oxidation by SeO_2 is favoured from less hindered side as depicted, which leads to the formation of alcohol **21** as the only observable product. (Scheme 7). Alcohol **21** was protected as its silyl ether by using imidazole, TBDPSCl in DCM at room temperature to furnish compound **22**. Since the intermediate *ent*-**22** (ref. 19) was earlier



Scheme 6 Reagents and conditions: (a) SeO_2, 1,4-dioxane, reflux, 3 h, 35%; (b) TBDPSCl, imidazole, DMAP (cat.), DCM, 15 h; (c) IBX, EtOAc, reflux, 3 h, 90%; (d) $NaBH_4$, $CeCl_3$ $7H_2O$, MeOH, 0 °C, 80%; (e) TBDPSCl, imidazole, DMAP (cat.), DCM, 15 h and (f) $RuCl_3$, $NaIO_4$, CH_3CN : EtOAc : H_2O, 0 °C, 54% (over two steps).



Scheme 7 Stereospecific formation of allyl alcohol **21**.

converted to D-*allo*-1-DNJ **4** and D-*galacto*-1-DNJ **6**, hence the present work constitutes formal syntheses of L-*allo*-1-DNJ **4** and L-*galacto*-1-DNJ **6**. Oxidation of allylic alcohol **21** was performed by using IBX in ethyl acetate under reflux conditions to give enone **24** in 90% yield. Enone **24** was reduced under Luche's reaction condition by using sodium borohydride in presence of $CeCl_3$ $7H_2O$ in methanol at 0 °C to provide β-allylic alcohol **23** in 80% yield. Alcohol **23** was protected as its TBDPS ether and was subjected to flash dihydroxylation[20] to furnish **25** in 54% yield (over two steps) as a single diastereomer. Since, compound **25** has been elaborated to L-*altro*-1-DNJ, this constitutes a formal synthesis of L-*altro*-1-DNJ.[19] It is pertinent to note that synthesis of compound **19** also constitutes formal synthesis of *cis*-3-hydroxypipecolic acid.[21] Spectral data of the compounds **25** and **19** were in good agreement with those reported in literature.[19,22]

Conclusion

We have accomplished the syntheses of various compounds containing piperidine core from a common precursor by employing Sharpless asymmetric dihydroxylation, reductive lactamization, novel regioselective elimination, regiospecific, stereospecific allylic oxidation, stereoselective reduction and stereoselective dihydroxylation as the key steps.

Since our method is flexible, one can access the corresponding enantiomers by switching the chiral ligands during asymmetric dihydroxylation.

Acknowledgements

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17 For racemic compound **17**, HPLC Kromasil 5-Amycoat column (250 × 4.6 mm) isopropanol–pet. ether = 4 : 96 flow rate 0.5 ml min^{-1}, (λ = 200 nm) retention time (min): Rt_1 = 22.8; Rt_2 = 24.8 (1 : 1) for enantiomerically pure hydroxymethyl piperidine core **17** HPLC Kromasil 5-Amycoat column (250 × 4.6 mm) isopropanol– pet. ether = 4 : 96 flow rate 0.5 ml min^{-1}, λ = 200 nm) retention time (min): 22.8 (ee > 97%) (major).

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21 Preparation of compound **16**: a mixture of alcohol **9** (0.5 g, 1.55 mmol), PPh_3 (1.34 g, 5.11 mmol), imidazole (0.33 g, 4.96 mmol) and I_2 (0.86 g, 3.41 mmol) was stirred under nitrogen atmosphere in anhydrous toluene (10 ml) at 110 °C for 30 minutes. After completion of the reaction (TLC), the reaction mixture was cooled at room temperature and was diluted with saturated solution of $Na_2S_2O_3$ and extracted with ethyl acetate (3 × 60 ml).The organic layer was dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure. The residue was purified on silica gel by eluting with light pet. ether : EtOAc (9 : 1) to afford **16** as a colorless syrup. The

syrup was treated with pet. ether and filtered through a cotton bed to remove the solid impurities and this was repeated 3–4 times to afford **16** as a colorless syrup (0.40 g, 85% yield). Compound **16**: ESIMS (*m*/*z*): 326.28(Na+); HRMS calculated for [$C_{18}H_{25}NO_3$ + Na] + 326.1727; found: 326.1734; ^{1}H NMR (200 MHz, $CDCl_3$ + CC_4): 1.45 (s, 9H), 1.88–2.04 (m, ^{1}H), 2.13–2.30 (m, 1H), 2.94 (bs, 1H), 3.47–3.61 (m, 2H), 4.15 (bs, 1H), 4.49–4.66 (m, 3H), 5.70–5.79 (m, 1H), 5.90–5.98 (m, 1H), 7.23–7.35 (m, 5H); ^{13}C (50 MHz, $CDCl_3$ + CCl_4): 24.9, 28.5, 71.3, 73.0, 79.5, 126.7, 127.4, 128.3, 138.3, 154.5; please see spectroscopic properties (^{1}H NMR data and ^{13}C NMR spectra) of other relevent compounds in ESI.†

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