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COMMUNICATION

Syntheses of (−)-pelletierine and (−)-homopipecolic acid†

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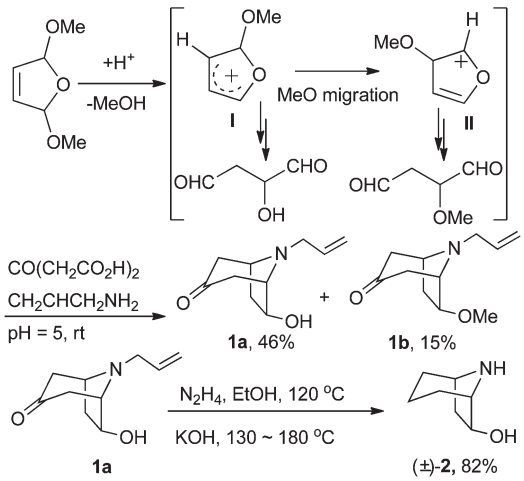
Enantiomeric syntheses of (−)-homopipecolic acid and (−)-pelletierine have been achieved by chiral resolution of tropanol followed by Baeyer–Villiger oxidation. The methodology provides a practical route for the synthesis of optically pure piperidines.

Substituted piperidine systems are often found in many natural alkaloids and medicinal compounds with potent biological activities.[1] Enantiopure functionalized piperidines have attracted much attention from synthetic chemists, resulting in abundant approaches to their synthesis.[2] In recent years, various strategies for introduction of chirality in piperidines have been developed, briefly described as follows: (1) Enzymatic resolutions.[3] (2) Organocatalyst-mediated reactions such as aza-1,4-addition,[4] aza-Henry reaction,[5] aminooxylation,[6] addition with lithiopiperidine[7] or lithiated *N*-BOC allylamine derivatives.[8] (3) Readily available chiral amines as nitrogen sources, including phenylethylamine,[9] Betti base,[10] phenylglycinol,[11] sulfinamide,[12] naphthyl-ethylamine,[13] SAMP/RAMP hydrazones,[14] and ROPHy/SOPHy oxime ethers.[15] (4) Chiral auxiliaries as templates, including Evans' oxazolidinone for asymmetric azidation[16] and Brown's IPC-borane for asymmetric allylation.[17] (5) Asymmetric transition-metal catalyzed reactions, *e.g.* Sharpless epoxidation,[18] ring-opening olefin metathesis,[19] Ti-mediated allylation,[20] intramolecular hydroamination,[21] hydrogenation of aromatics,[22] aza-Diels–Alder reaction,[23] cycloisomerization of homopropargylic amines.[24] (6) Chiral pool derived routes.[25] Here, we report enantiomeric syntheses of (*R*)-homopipecolic acid and (*R*)-pelletierine, from optically active 6-tropanol, easily prepared by Robinson annulation followed by resolution with (L)-tartaric acid.

Our synthesis commenced with the preparation of tropanone derivative **1a**, readily available by a modified Robinson tropanone synthesis.[19] Acidic hydrolysis of commercially available 2,5-dimethoxydihydrofuran in a hydrochloric acid solution at room temperature gave 2-hydroxybutanedial. The resulting aldehyde solution was combined with allylamine, acetone dicarboxylic acid in an acetate buffer solution at pH 5.0 overnight to afford alcohol **1a** in 46% yield accompanied by a side product in 15% yield, identified as methyl ether **1b**. The formation of methyl ether **1b** could be attributed to the occurrence of methoxy migration during the hydrolysis. Protonation of 2,5-dimethoxydihydrofuran followed by loss of a methanol produced a cation species **I** as an intermediate for annulation to form alcohol **1a**. However, the methoxy group migration brought the formation of cation **II** which was the precursor for the further reaction to yield methyl ether **1b** (Scheme 1). Treatment of tropanone derivative **1a**, with hydrazine and KOH at an elevated temperature reduced the ketone group to a methylene group and removed the allyl group simultaneously, affording 6-tropanol (**2**) in 82% yield.



Scheme 1 Synthesis of tropanol **2**.

Enantiomerically pure 6-tropanol (**2**) was achieved by chiral resolution using (+)-tartaric acid as a resolving agent. Mixing of racemic 6-tropanol (**2**) with equal molar amount of (+)-tartaric acid produced tartrate salts which could be recrystallized in methanol to afford chirally pure salts as single crystals. The crystal structure has been elucidated clearly by X-ray crystallographic analysis as (1*R*,5*S*,6*R*)-tropanol with (+)-tartaric acid (Fig. 1).

After removal of tartaric acid with a basic solution, optically pure tropanol (+)-**2** was reacted with CbzCl in the presence K_2CO_3 in THF to give carbamate (+)-**3** in 99% yield with 98.4%

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†Electronic supplementary information (ESI) available: Experimental procedure, all ^{1}H, ^{13}C NMR spectra and assignment for all compounds, and HPLC chromatograms of (+)-**3**, (+)-**6** and (+)-**9**, and crystallographic data of (+)-**2**-tartrate salt in CIF format. CCDC 855622. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c2ob06984a

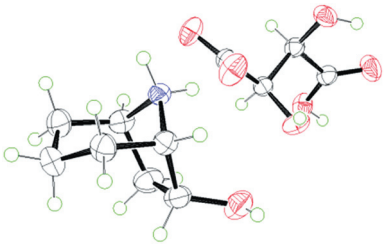
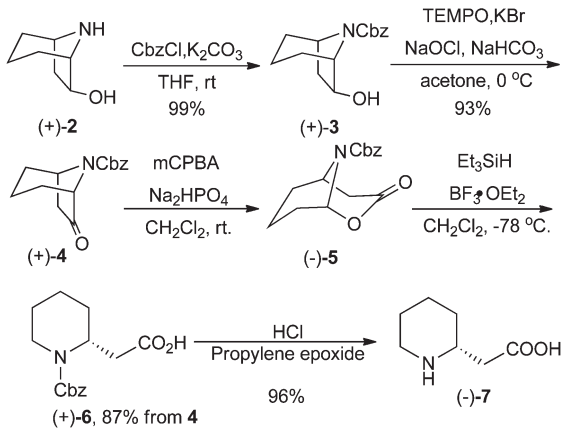
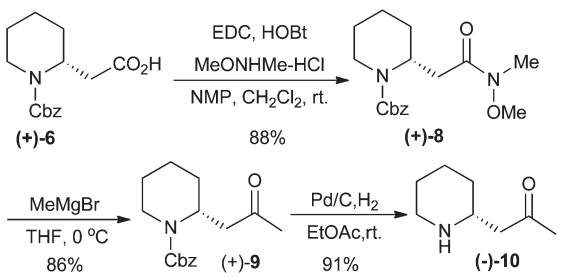


Fig. 1 ORTEP drawing of (*R*,*R*)-tartrate salt of tropanol (+)-**2**.



Scheme 2 Synthesis of (*R*)-homopipecolic acid (−)-**7**.



Scheme 3 Synthesis of (*R*)-pelletierine (−)-**10**.

ee confirmed by chiral HPLC analysis ((+)-**3** t_R 5.6 min; (−)-**3** t_R 7.1 min). With enantiopure tropanol derivative (+)-**3** in hand, subsequent TEMPO-catalyzed bleach oxidation furnished ketone (+)-**4** in 93% yield. Reaction of ketone (+)-**4** with one equivalent of mCPBA in the presence of Na_2HPO_4 in CH_2Cl_2 resulted in a selective Bayer–Villiger oxidation to provide lactone (−)-**5**.[26] The amount of mCPBA was crucial in the reaction in that excess of mCPBA brought about a yield decrease in this reaction.[27] Lactone (−)-**5** was a quite unstable substance in either acidic or oxidative conditions. Silica gel purification of lactone (−)-**5** resulted in the formation of 5,6-didehydropipecolic acid and reduced the yield of the desired lactone. Thus, reduction of crude lactone (−)-**5** with triethylsilane–boron trifluoride in CH_2Cl_2 at −78 °C afforded a 87% yield of *N*-Cbz homopipecolic acid (+)-**6** over two steps, as white solids: mp 72–74 °C, $[\alpha]_D^{25}$ + 2.8° (c: 1.9, $CHCl_3$) (93% ee, (+)-**6** t_R 19.4 min; (−)-**6** t_R 22.5 min).[28] Chiral HPLC analysis of acid (+)-**6** confirmed the chiral integrity arrived intact during the processes mentioned above. Thus, reflux in a 6 N HCl solution was carried out to remove the Cbz protecting group, followed by treatment with propylene oxide to remove excess hydrogen chloride, giving (*R*)-homopipecolic acid (**7**) in 93% yield. The specific rotation value of (−)-**7**, $[\alpha]_D^{25}$ −24.0° (c: 0.4, H_2O) was consistent with the reported value,[9a] $[\alpha]_D^{25}$ −23.4° (c: 0.4, H_2O) (Scheme 2).

Subsequent transformations to (*R*)-pelletierine were straightforward (Scheme 3): acid (+)-**6** was coupled with methoxymethylamine using EDC–HOBt activation protocol, yielding Weinreb amide (+)-**8** in 88% yield. Addition of 3.5 equivalents of MeMgBr in THF at 0 °C yielded Cbz-protected pelletierine (+)-**9** in 86% yield as a colorless oil: $[\alpha]_D^{25}$ + 12.0° (c: 2.5, $CHCl_3$) (96.1% ee, (+)-**9** t_R 10.5 min; (−)-**9** t_R 11.7 min), (lit.[28] $[\alpha]_D^{25}$ + 10.2° (c: 2.5, $CHCl_3$). Exposure of *N*-protected pelletierine (+)-**9** in a hydrogen atmosphere to palladium on carbon in ethyl acetate produced free pelletierine (−)-**10** in 91% yield. The specific rotation value of (−)-**10**, $[\alpha]_D^{25}$ −19.6° (c: 0.7, EtOH) was also consistent with the reported value, $[\alpha]_D^{25}$ −22.1° (c: 4.1, EtOH).[29]

In conclusion, enantiomeric syntheses of (*R*)-homopipecolic acids and (*R*)-pelletierine have been achieved from (+)-6-tropanol, available from Robinson annulation and followed by resolution with (+)-tartaric acid. Baeyer–Villiger oxidation of 6-tropanone (+)-**4** provided lactone (−)-**5** as a key intermediate. The enantiomeric excess values of *N*-Cbz homopipecolic acid (+)-**6** and *N*-Cbz pelletierine (+)-**9** have been confirmed by chiral HPLC analysis, as well as their specific rotation values. Subsequent extension of this methodology towards other natural products of interest is currently underway.

Acknowledgements

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