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A formal asymmetric synthesis of (2*S*,4*R*)-4-hydroxypipecolic acid via Co(III)(salen)-catalyzed two stereocentered HKR of racemic azido epoxide

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ABSTRACT

An efficient formal synthesis of (2*S*,4*R*)-4-hydroxypipecolic acid has been achieved in high optical purity (99% ee) from readily available benzaldehyde. The strategy employs an iodine-induced intramolecular cyclization of a carbonate and Co-catalyzed Hydrolytic Kinetic Resolution (HKR) of two stereocentered racemic azido epoxide as the key reactions to construct chiral 1,3-amino alcohol functionality.

The synthesis of chiral functionalized pipecolic acids is of considerable interest since this structural unit is widely found in biologically active natural products and synthetic pharmaceuticals.[1] In particular, (2*S*,4*R*)-4-hydroxypipecolic acid **1** (Fig. 1) is a naturally occurring non proteinogenic amino acid, isolated from the leaves of *Calliandra pittieri* and *Strophantus scandeus*.[2] It is a constituent of cyclodepsipeptide antibiotics such as virginiamycin S_2.[3] It is also a key precursor in the syntheses of NMDA receptor antagonists[4] and HIV-protease inhibitor such as palinavir **2**.[5] In addition, 4-hydroxypipecolic acid derivatives have been used in protein design to study its conformational effect in peptidomimetics.[6] Due to its potential biomedical importance, considerable effort has been directed toward the enantioselective synthesis of **1**.[7,8] However several of them suffer from certain limitations such as the use of chiral building blocks,[7] inefficient separation of diastereoisomers,[7c] expensive reagents[7m] and a lengthy number of steps,[7f,8e] etc.

Jacobsen's Hydrolytic Kinetic Resolution (HKR) with chiral cobalt catalysts has been comprehensively studied to afford chiral epoxides and diols of high ee's in excellent yields.[9] Recently, a two-stereocentered HKR is also known for terminal epoxides bearing adjacent C–O, C–N and C–C binding substituents to furnish enantiopure *syn* or *anti* alkoxy and azido epoxides and the corresponding 1,2-diols in high optical purity.[10] As part of our research program aimed at developing enantioselective synthesis of biologically active molecules,[11] here we report a short enantioselective synthesis of (2*S*,4*R*)-4-hydroxypipecolic acid, for the first time by employing two stereocentered HKR of racemic 1,3-azido epoxide (Schemes 1 and 2).

Our synthesis of (2*S*,4*R*)-4-hydroxypipecolic commenced with commercially available benzaldehyde **3**, which on treatment with zinc allylbromide gave phenylbutenol **4** in 82% yield (Scheme 1). The phenylbutenol **4** was then readily transformed into racemic *syn*-1,3-epoxy alcohol **7** in three steps:[12] (i) homoallylic alcohol **4** was protected as its *tert*-butyl carbonate **5** in 92% yield (di-*tert*-butyldicarbonate, DMAP and CH_3CN); (ii) diastereoselective iodine-induced carbonate cyclization of **5** furnished iodocarbonate derivative **6** in 80% yield (NIS, CH_3CN, −40 °C to 0 °C, 12 h); and (iii) methanolysis of **6** under basic conditions gave racemic *syn*-epoxy alcohol **7**. The *syn*-epoxy alcohol **7** was further subjected to mesylation reaction followed by treatment with NaN_3 in DMF at 50 °C. This produced the required racemic *anti*-1,3-azido epoxide **8** in 83% yield with complete inversion at benzylic position as confirmed by ^{13}C NMR. Compound **8** was then subjected to HKR with (*R*,*R*)-salen $Co^{III}(OAc)$[9] complex (0.5 mol %) and H_2O (0.49 equiv), which produced the corresponding chiral azido diol **9**[13] (48% and 99% ee) and the chiral azido epoxide **10** (49% and 98% ee) in high optical purity. Compounds **9** and **10** were readily separated by a simple flash column chromatographic purification.

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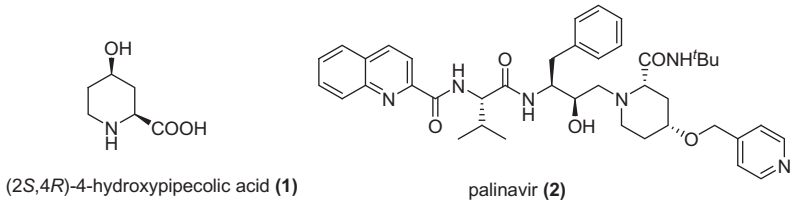
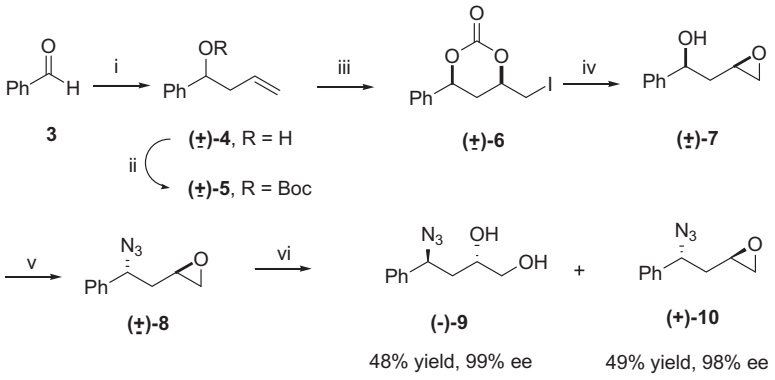
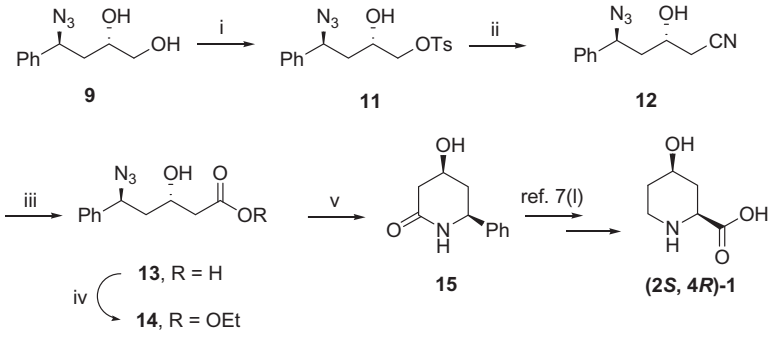


Figure 1. Structures of (2*S*,4*R*)-4-hydroxypipecolic acid **1** and palinavir **2**.



Scheme 1. Reaction conditions: (i) 3-bromoprop-1-ene, Zn, NH_4Cl, THF/H_2O, 25 °C, 2 h, 82%; (ii) $(Boc)_2O$, DMAP, CH_3CN, 25 °C, 5 h, 92%; (iii) NIS, CH_3CN, −40 °C to 0 °C, 12 h, 80%; (iv) K_2CO_3, MeOH, 0 °C to 25 °C, 4 h, 95%; (v) (a) MsCl, NEt_3, CH_2Cl_2, 0 °C, 45 min.; (b) NaN_3, DMF, 50 °C, 4 h, 83% over two step; (vi) (*R*,*R*)-Co^{III}(salen) (0.5 mol %), H_2O (0.49 equiv), 0–25 °C, 12 h.



Scheme 2. Reaction conditions: (i) TsCl, NEt_3, Bu_2SnO, DMAP, 0 °C, 2 h, 98%; (ii) NaCN, EtOH/H_2O (4:1), 25 °C, 24 h, 80%; (iii) 3 M NaOH, aq H_2O_2, 12 h, 50 °C, 93%; (iv) cat. H_2SO_4, EtOH, reflux, 4 h, 84%; (v) 10% Pd/C, MeOH, 25 °C, 12 h, 87%.

Azido diol **9** was further used for the synthesis of (2*S*,4*R*)-4-hydroxy pipecolic acid (Scheme 2). Selective monotosylation of primary hydroxyl group of azido diol **9** afforded compound **11** (TsCl, NEt_3, Bu_2SnO, DMAP, 0 °C). It was then subjected to nucleophilic displacement with NaCN to give nitrile **12** in 80% yield. The structure of **12** was confirmed by its characteristic IR frequencies (2100 and 2253 cm^{-1}) due to azide and nitrile functions, respectively. Hydrogen peroxide catalyzed hydrolysis of the nitrile **12** in aqueous NaOH produced acid **13**, which was converted to the ethyl ester **14** in 84% yield via acid catalyzed esterification (cat. H_2SO_4, EtOH, reflux). Finally, the ethyl ester **14** was subjected to intramolecular reductive cyclization over Pd/C, H_2 (1 atm) to provide the known key intermediate *cis*-2,4-disubstituted piperidinone **15** (overall yield 12%). The spectral data and optical rotation of the synthesized key intermediate *cis*-2,4-disubstituted piperidinone **15** are in good agreement with reported values.[7l,14] Hence this Letter constitutes a formal synthesis of (2*S*,4*R*)-4-hydroxy pipecolic acid **1**.

In conclusion, a formal asymmetric synthesis of 4-hydroxy pipecolic acid (**1**) is described with good overall yield and high optical purity, that are achieved using two-stereocentered Co-catalyzed HKR of racemic *anti*-1,3-azido epoxide. This synthetic strategy has significant potential for the synthesis of a variety of other biologically important molecules containing 1,3-amino alcohol functionality.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2015.01.113.

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13. *Physical and spectral data for (2S,4S)-4-azido-4-phenylbutane-1,2-diol* (**9**) Yield: 48%, yellow colored liquid, $[\alpha]_D^{25}$ −98.29 (*c* 1, $CHCl_3$); IR: ($CHCl_3$, cm^{-1}) 3455, 2094; ^1H NMR (200 MHz, $CDCl_3$): δ 1.75–1.90 (m, 2H), 2.44 (br s, 1H), 2.88 (br s, 1H), 3.45–3.54 (m, 1H), 3.72–3.77(m, 1H), 3.97–4.10 (m, 1H), 4.76–4.83 (dd, *J* = 5.2, 9.5 Hz, 1H), 7.26–7.40 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 40.0, 62.7, 66.7, 68.9, 126.7, 128.4, 128.9, 139.8; HRMS (*m*/*z*): calculated $[M+Na]^+$ for $C_{10}H_{13}O_2N_3Na^+$: 230.0900 found: 230.0897; Optical purity: 99% ee determined by HPLC analysis (Chiral OD-H column, *n*-hexane/2-propanol (85:15), 0.5 mL/min, 254 nm). Retention time: t_{minor} = 21.50 and t_{major} = 25.69 min.
14. *Physical and spectral data for (4S,6S)-4-hydroxy-6-phenylpiperidin-2-one* (**15**) Yield: 87%; colorless solid, mp 215 °C {lit.[71] mp 211–213 °C}; $[\alpha]_D^{25}$ −51.80 (*c* 1, MeOH) {lit.[71] $[\alpha]_D^{20}$ −51.9 (*c* 0.56, MeOH)}; IR: (neat, cm^{-1}): 3355, 3030, 1651; ^1H NMR (200 MHz, MeOH-d^4): δ 1.52–1.70 (q, *J* = 12.6 Hz, 1H), 2.21–2.37 (m, 2H), 2.64–2.74 (m, 1H), 4.03–4.17 (m, 1H), 4.47–4.54 (dd, *J* = 4.3, 11.3 Hz, 1H), 4.75 (br s, 1H), 7.29–7.37 (m, 5H); ^{13}C NMR (50 MHz, MeOH-d^4): δ 41.5, 42.8, 56.3, 65.7, 127.5, 129.1, 130.0, 143.6, 174.2; HRMS (*m*/*z*): calculated $[M+Na]^+$ for $C_{11}H_{13}O_2NNa^+$: 214.0838 found: 214.0834.