Concise Enantioselective Syntheses of (+)-L-733,060 and (2*S*,3*S*)-3-Hydroxypipecolic Acid by Cobalt(III)(salen)-Catalyzed Two-Stereocenter Hydrolytic Kinetic Resolution of Racemic Azido Epoxides

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Received: 21.08.2013; Accepted after revision: 01.10.2013

Abstract: An efficient synthesis of the 2,3-disubstituted piperidines (+)-L-733,060 and (2*S*,3*S*)-3-hydroxypipecolic acid (≥99% ee) in high optical purity from commercially available starting materials is described. The strategy involves a cobalt-catalyzed hydrolytic kinetic resolution of a racemic azido epoxide with two stereocenters and an intramolecular reductive cyclization as key reactions.

Key words: azides, epoxides, stereoselective synthesis, Wittig reactions, cyclizations, piperidines

Chiral 2,3-disubstituted piperidine moieties with a β-hydroxy functional groups are found in numerous natural products and are common subunits in drugs and drug candidates.[1] Selected examples include (+)-L-733,060 (**1**)[2] and (+)-CP-99,994 (**2**),[3] both potent and selective neurokinin-1 substance P receptor antagonists; febrifugine (**4**),[4] an antimalarial agent; (-)-swainsonine (**5**),[5] an inhibitor of lysosomal α-mannosidase and a potent anticancer drug; and (2*S*,3*S*)-3-hydroxypipecolic acid [**3**; (2*S*,3*S*)-3-hydroxypiperidine-2-carboxylic acid],[6] a key precursor in the syntheses of **4** and **5** (Figure 1).

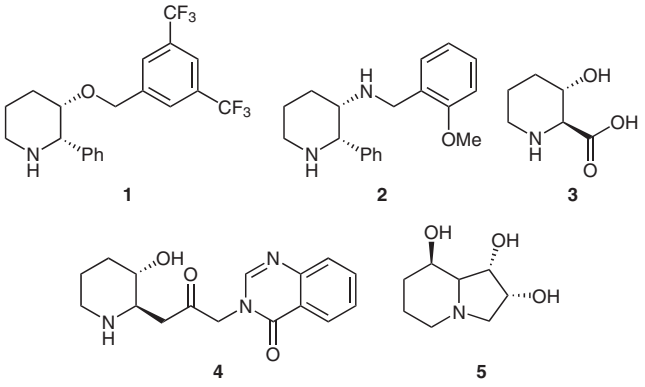
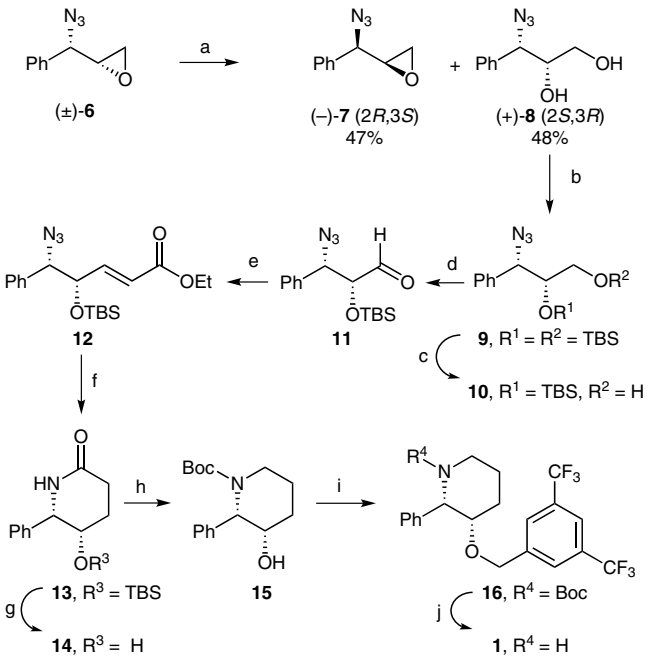


Figure 1 Biologically active 2,3-disubstituted piperidines

Because of the biomedical importance of the products, the synthesis of these β-hydroxy piperidines has attracted much attention in recent years; however, many of the synthetic approaches employ starting materials from the chiral pool and involve enzymatic resolution as a key reaction.[7,8]

We recently reported a flexible method that involves a cobalt-catalyzed hydrolytic kinetic resolution (HKR) of racemic azido epoxides with two contiguous stereocenters to generate the corresponding diols and epoxides in high optical purities (97–99% ee) in a single step.[9a] Here, we report a short enantioselective synthesis of two important bioactive molecules, (+)-L-733,060 (**1**) and (2*S*,3*S*)-3-hydroxypipecolic acid (**3**), based on a two-stereocenter HKR of racemic azido epoxides.

The synthesis of (+)-L-733,060 (**1**; Scheme 1) commenced with the racemic azido epoxide **6**, prepared from



Scheme 1 *Reagents and conditions*: (a) (*S*,*S*)-(salen)Co(III)OAc (0.5 mol%), H_2O (0.49 equiv), 0 °C, 14 h; (b) TBSCl (2 equiv), imidazole, CH_2Cl_2, 25 °C, 12 h; yield 98%. (c) CSA, MeOH, 0 °C, 6 h, yield 95%; (d) Dess–Martin periodinane, CH_2Cl_2, 25 °C, 1 h, yield 98%; (e) $(EtO)_2POCH_2CO_2Et$, NaH, THF, 0 to 25 °C, 3 h, yield 94%; (f) 10% Pd/C, H_2 (1 atm), MeOH, 25 °C, 12 h, then EtOH, reflux, 1 h, yield 85%; (g) TBAF, THF, 0–25 °C, 2 h, yield 96%; (h) (i) $BH_3{\cdot}SMe_2$, THF, reflux, 10 h; (ii) $(Boc)_2O$, Et_3N, DMAP (cat.), CH_2Cl_2, 0 to 25 °C, 12 h, yield 76% (two steps); (i) 3,5-bis(trifluoromethyl)benzyl bromide, NaH, DMF, 80 °C, 12 h, yield 85%; (j) TFA, CH_2Cl_2, 0 to 25 °C, 18 h, yield 89%.

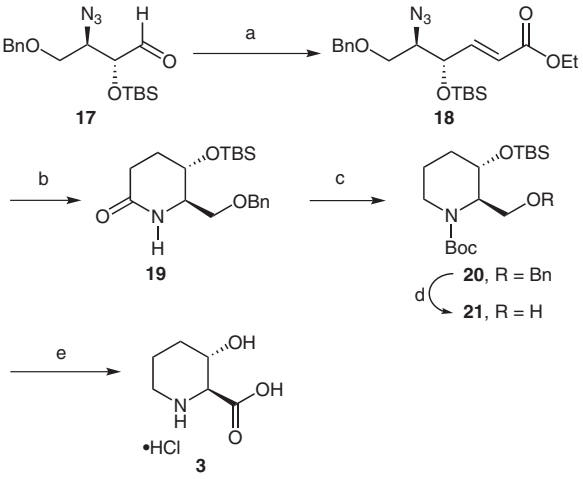
SYNLETT 2014, 25, 0102–0104
Advanced online publication: 12.11.2013
DOI: 10.1055/s-0033-1340074; Art ID: ST-2013-B0807-L

commercially available cinnamyl alcohol by our previously reported procedure.[9a] The racemic azido epoxide **6** was subjected to HKR with (*S*,*S*)-salen–cobalt(III) acetate complex[9b] (0.5 mol%) and water (0.49 equiv), which gave the corresponding diol **8** (48%, 98% ee) and chiral epoxide **7** (47%) in high optical purity. The diol **8** was readily separated from epoxide **7** by simple flash column chromatography on silica gel.

Both free hydroxy groups in diol **8** were protected to give the disilyl ether derivative **9**, which was then selectively deprotected to give the monosilyl ether **10** in 95% yield. Dess–Martin oxidation of **10** gave the crude aldehyde **11** in 98% yield; this underwent a Wittig–Horner reaction to give the corresponding (*E*)-azido ester **12** in 94% yield. Intramolecular reductive cyclization of **12** by hydrogenation over 10% palladium/carbon gave the *cis*-2,3-disubstituted piperidinone **13** in 85% yield. Deprotection of the silyl group in **13** with tetrabutylammonium fluoride gave the lactam **14**. Reduction of lactam **14** with borane–dimethyl sulfide in tetrahydrofuran, followed by protection of the secondary amine gave the *syn*-amino alcohol **15** in 76% yield for the two steps. Having constructed the piperidine core with the desired *syn* stereochemistry, we O-alkylated amino alcohol **15** with 3,5-bis(trifluoromethyl)benzyl bromide in the presence of sodium hydride to give the protected amine **16**. Finally, deprotection under acidic conditions gave L-733,060 (**1**) in 89% yield (overall yield 19% from **6** in ten steps).

The synthesis of (2*S*,3*S*)-3-hydroxypipecolic acid (**3**; Scheme 2) commenced from (2*Z*)-but-2-ene-1,4-diol, which was converted into the azido aldehyde **17** by HKR, as we previously reported.[9c] The key intermediate **20** (Scheme 2) was readily synthesized from **17**, essentially by following a similar sequence of reactions to that shown in Scheme 1. Wittig olefination and intramolecular reductive cyclization gave the *trans*-2,3-disubstituted piperidinone core **19** in 90% yield with an intact benzyloxy group. Reduction of piperidinones **19** with borane–dimethyl sulfide followed by protection in situ gave *trans*-piperidine derivative **20** in 80% yield. Hydrogenation of **20** over palladium/carbon in methanol at 70 psi gave the corresponding alcohol **21** in 96% yield. Finally, oxidation of alcohol **21** with ruthenium(II) chloride and sodium periodate,[8f,10] followed by removal of both protecting groups under acidic condition (6 M aq HCl), completed the synthesis of (2*S*,3*S*)-3-hydroxypipecolic acid (**3**; overall yield 43% from **17** in six steps). The ^{1}H and ^{13}C NMR and other spectra of (+)-L-733,060 (**1**) and (2*S*,3*S*)-3-hydroxypipecolic acid (**3**) were in complete agreement with the values reported in the literature.[7d,7e,8f,o]

In summary, we have developed short and practical enantioselective syntheses of (+)-L-733,060 (**1**) and (2*S*,3*S*)-3-hydroxypipecolic acid (**3**) with good overall yields and high optical purities (ee ≤99%). The key reaction in each case was a cobalt-catalyzed HKR of a racemic azido epoxide with two stereocenters. The other operationally simple reaction sequences included a Wittig reaction and an intramolecular reductive cyclization. The synthetic strategy has significant potential for further extension to other stereoisomers and related analogues of multifunctional piperidine alkaloids, owing to the flexibility available in syntheses of racemic azido epoxides with various stereochemical combinations and various substituents.



Scheme 2 *Reagents and conditions*: (a) $(EtO)_2POCH_2CO_2Et$, NaH, THF, 0–25 °C, 1 h, yield 93%; (b) 10% Pd/C, H_2 (1 atm), MeOH, 25 °C, 24 h, yield 90%; (c) $BH_3{\cdot}SMe_2$, THF, reflux, 6 h, then Na_2CO_3, $(Boc)_2O$, CH_2Cl_2/H_2O (1:1), 25 °C, 12 h, yield 80%; (d) 10% Pd/C, H_2 (70 psi), MeOH, 25 °C, 24 h, yield 96%; (e) (i) $RuCl_3$ (2 mol%), $NaIO_4$ (4 equiv), $MeCN/CCl_4/H_2O$ (1:1:3), 25 °C, 30 min; (ii) 6 M aq HCl, reflux, 2 h, yield 68% (two steps).

Acknowledgment

D.A.D. and P.V.C. thank CSIR, New Delhi for the award of research fellowships. The authors are also grateful to Dr. V. V. Ranade, chair of the Chemical Engineering and Process Development Division, for his constant encouragement and support.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett. Included are experimental procedures and spectral data for compounds **7**–**21**.

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(11) **Hydrolytic Kinetic Resolution of Azido Epoxide 6**
AcOH (0.014 g, 0.24 mmol) was added to a solution of (*S*,*S*)-(salen)Co(II) complex (0.024 mmol, 0.5 mol%) in toluene (1 mL), and the mixture was stirred at 25 °C in open air for 30 min. During this time the color changed from orange–red to a dark brown. The solution was then concentrated under reduced pressure to give the Co(III)–salen complex as a brown solid. To this were added the racemic azido epoxide **6** (0.84 g, 4.85 mmol) and H_2O (0.043 g, 2.42 mmol) at 0 °C, and the resulting mixture was stirred at 0 °C for 14 h. When the reaction was complete (TLC), the crude product was purified by column chromatography [silica gel, PE–EtOAc] to give chiral azido epoxide **7** (9:1 PE–EtOAc) and the chiral azido diol **8** (1:1 PE–EtOAc) in pure form.

(2*R*,3*S*)-3-Azido-3-phenylpropane-1,2-diol (8)
Yellow liquid; yield: 450 mg (48%, 98% ee); $[\alpha]_D^{25}$ +188 (*c* 1, $CHCl_3$) (lit.[9a] –188 for the antipode). IR ($CHCl_3$): 1602, 2099, 2932, 3052, 3392 (br) cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 3.30 (dd, *J* = 11.5, 6.0 Hz, 1 H), 3.44 (d, *J* = 11.5 Hz, 1 H), 3.80 (br s, 1 H), 3.62–3.94 (m, 1 H), 4.52 (d, *J* = 8.1, 1 H), 7.28–7.35 (m, 5 H). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 2.8, 68.1, 75.0, 127.5, 128.7, 128.9, 136.2. Anal. Calcd for $C_9H_{11}N_3O_2$: C, 55.95; H, 5.74; N, 21.75. Found: C, 56.10; H, 5.65; N, 21.60; HPLC: Chiral OD-H column, hexane–*i*-PrOH (90:10, 0.5 mL/min), 254 nm; $t_{R(major)}$ = 14.84 min, $t_{R(minor)}$ = 15.57 min.

(2*S*)-2-[(*R*)-Azido(phenyl)methyl]oxirane (7)
Yellow liquid; yield: 400 mg (47%); $[\alpha]_D^{25}$ –120 (*c* 1, $CHCl_3$) (lit.[9a] +120 for the antipode). IR ($CHCl_3$): 2105, 2932, 3025 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 2.73–2.84 (m, 2 H), 3.23–3.29 (m, 1 H), 4.25 (d, *J* = 6.1, 1 H), 7.35–7.47 (m, 5 H). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 44.6, 54.6, 66.8, 127.2, 128.8, 128.9, 135.7. Anal. Calcd for $C_9H_9N_3O$: C, 61.70; H, 5.18; N, 23.99. Found: C, 61.79; H, 5.14; N, 23.90.

(12) **(2*S*,3*S*)-3-{[3,5-Bis(trifluoromethyl)benzyl]oxy}-2-phenylpiperidine [1; (+)-L-733,060]**
Colorless oil; yield: 110 mg (89%), $[\alpha]_D^{25}$ +35.2 (*c* 0.66, $CHCl_3$) {lit.[7j] +34.29 (*c* 1.32, $CHCl_3$)}. IR (neat): 1277, 1370, 2950 cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz): δ = 1.40–2.04 (m, 3 H), 2.22 (br d, *J* = 13 Hz, 1 H), 2.60 (s, 1 H), 2.76–2.81 (m, 1 H), 3.23–3.38 (m, 1 H), 3.66 (s, 1 H), 3.84 (s, 1 H), 4.12 (d, *J* = 12.0 Hz, 1 H), 4.54 (d, *J* = 12.2 Hz, 1 H), 7.20–7.50 (m, 7 H), 7.78 (s, 1 H). ^{13}C NMR ($CDCl_3$, 50 MHz): 20.6, 27.5, 47.1, 64.0, 70.5, 77.2, 120.9, 124.1, 127.7, 128.5, 128.7, 128.9, 131.2, 141.6, 142.3. Anal. Calcd for $C_{20}H_{19}F_6NO$: C, 59.55; H, 4.75; N, 3.47. Found: C, 59.52; H, 4.81; N, 3.56.

(2*S*,3*S*)-3-Hydroxypiperidine-2-carboxylic Acid [3; (2*S*,3*S*)-3-Hydroxypipecolic Acid]
Colorless solid; yield: 20 mg (68%); mp 232 °C; $[\alpha]_D^{25}$ +14.2 (*c* 1, H_2O) {lit.[8f] $[\alpha]_D^{23}$ +14.5 (*c* 0.4, H_2O)}. IR (neat): 1685, 3420 cm^{-1}. ^1H NMR (200 MHz, D_2O): δ = 1.62–1.80 (m, 2 H), 2.00–2.08 (m, 2 H), 3.10 (s, 1 H), 3.32–3.39 (m, 1 H), 3.80 (d, *J* = 7.6 Hz, 1 H), 4.10–4.17 (m, 1 H). ^{13}C NMR (50 MHz, D_2O): δ = 20.0, 30.1, 43.9, 62.5, 65.9, 171.3. Anal. Calcd for $C_6H_{11}NO_3$: C, 49.65; H, 7.64; N, 9.65. Found: C, 49.60; H, 7.69; N, 9.70.

