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

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Abstract: An efficient synthesis of the 2,3-disubstituted piperidines (+)-L-733,060 and (2S,3S)-3-hydroxy-pipeolic 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 neronkin-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 (2S,3S)-3-hydroxy-pipeolic acid [6; (2S,3S)-3-hydroxy-piperidine-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.9 Here, we report a short enantioselective synthesis of two important biochemical molecules, (+)-L-733,060 (1) and (2S,3S)-3-hydroxy-pipeolic 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%), H2O (0.49 equiv), 0 °C, 14 h; (b) TBSCI (2 equiv), imidazole, CH2Cl2, 25 °C, 12 h; yield 98%; (c) CSA, MeOH, 0 °C, 6 h, yield 95%; (d) Dess–Martin periodinane, CH2Cl2, 25 °C, 1 h, yield 98%; (e) (i) (EtO)2POCH2CO2Et, NaH, THF, 0 to 25 °C, 3 h, yield 96%; (f) 10% Pd/C, H2 (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) BH3·SMes2, THF, reflux, 10 h; (ii) (Boc)2O, Et,N, DMAP (cat.), CH2Cl2, 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, CH2Cl2, 0 to 25 °C, 18 h, yield 89%.

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commercially available cinnamyl alcohol by our previously reported procedure. The racemic azido epoxide 6 was subjected to HKR with (S,S)-salen–cobalt(III) acetate complex (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-amine 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 (2S,3S)-3-hydroxyippecolic acid (3; Scheme 2) commenced from (2Z)-but-2-ene-1,4-diol, which was converted into the azido aldehyde 17 by HKR, as we previously reported. 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 benzylxoy group. Reduction of piperidinones 19 with borane–dimethyl sulfide followed by protection in situ gave trans-piperidinone 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,8e,10 followed by removal of both protecting groups under acidic condition (6 M aq HCl), completed the synthesis of (2S,3S)-3-hydroxyippecolic acid (3; overall yield 43% from 17 in six steps). The 1H and 13C NMR and other experimental procedures and spectral data for compounds 7–21.

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.

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**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.

**References**