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An asymmetric dihydroxylation route to (2*S*,3*S*)-3-hydroxypipecolic acid

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Abstract—A concise enantioselective synthesis of (2*S*,3*S*)-3-hydroxypipecolic acid **1** starting from 1,4-butanediol using Sharpless asymmetric dihydroxylation and the regioselective nucleophilic opening of a cyclic sulfate as the key steps is described.

Chiral, non-racemic piperidines are common structural units found in many biologically and medicinally important natural and non-natural products. It is thus not surprising that many new asymmetric synthetic methods have been developed for their syntheses.[1] 3-Hydroxypipecolic acids **1**–**3** (Fig. 1), six-membered cyclic α-amino-β-hydroxy acids, constitute non-natural variants of a structural motif often encountered in a variety of molecules and may be regarded as expanded hydroxylated proline or conformationally restricted serine derivatives.[2] The piperidine unit of 3-hydroxypipecolic acid is found in a number of biologically important products. For example, the *cis*-isomer **2** forms a part of the structure of tetrazomine,[3] an anti-tumor antibiotic, while the *trans*-isomer **1** is a precursor of (−)-swainsonine, which has shown potent and specific α-D-mannosidase inhibitory activity.[4] It is also found in the structure of febrifugine, a potent anti-malarial agent.[5] From a synthetic point of view, only a few enantioselective syntheses of **1** or its isomers have been reported. While the majority of these syntheses utilize either chiral pool starting materials[3–6] or enzymatic resolution,[7] reports in which all the stereogenic centers are constructed by asymmetric synthesis are rather scarce.[8] As a part of our research program aimed at developing enantioselective syntheses of naturally occurring amino alcohols,[9] we became interested in developing a simple and feasible route to 3-hydroxypipecolic acid. Herein we report a new and enantioselective synthesis of **1** employing the Sharpless asymmetric dihydroxylation as the source of chirality. The synthesis of the target compound **1** (Scheme 1) commenced from 1,4-butanediol **4**, a commercially available starting material.

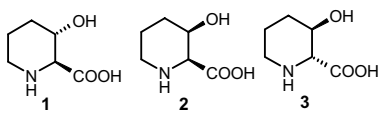

Figure 1.

Mono hydroxyl protection of **4** with *p*-methoxybenzyl bromide in the presence of NaH gave **5** in 80% yield. Compound **5** was oxidized to the aldehyde and subsequently treated with (ethoxycarbonylmethylene)-triphenylphosphorane in benzene under reflux to furnish the Wittig product **6** in 80% yield. Dihydroxylation of olefin **6** under the Sharpless asymmetric dihydroxylation conditions[10] using $(DHQ)_2PHAL$ ligand gave the diol **7**[11] in 85% yield and 97% ee.[12]

Our initial attempt to convert the α-hydroxyl group of **7** to an azide through its tosylate took a longer time to complete the reaction affording the product **9** in only moderate yield. Accordingly, the diol **7** was first converted into its cyclic sulfite derivative in 92% yield by treatment with $SOCl_2$ and Et_3N, which was further oxidized using $NaIO_4$ and a catalytic amount of $RuCl_3{\cdot}H_2O$ to furnish the corresponding cyclic sulfate **8** in excellent yield. The essential feature of our synthetic strategy shown in Scheme 1 was based on the presumption that the nucleophilic opening of the cyclic sulfate **8** would occur in a regiospecific manner at the α-carbon atom. Indeed the cyclic sulfate **8** reacted with NaN_3 with apparent complete selectivity for attack at C-2, the α-position, to furnish the azido alcohol **9** in 94% yield. The carbonyl

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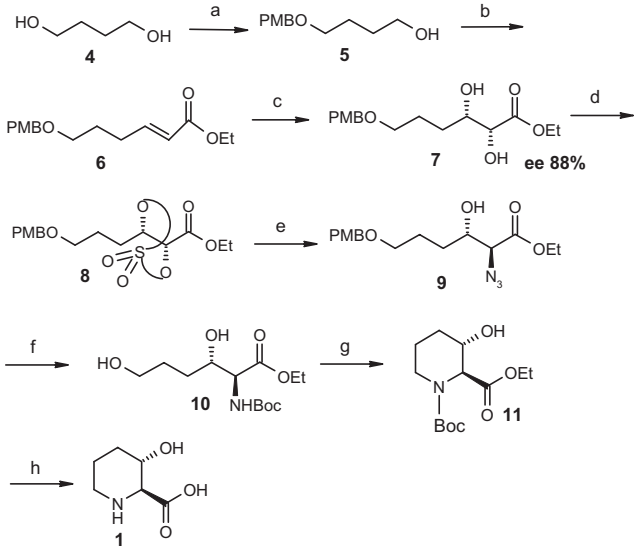

Scheme 1. Reagents and conditions: (a) DMF, NaH, *p*-$MeOC_6H_4CH_2Br$, 80%. (b) (i) PCC, NaOAc, Celite, CH_2Cl_2, 0 °C; (ii) $Ph_3P{=}CHCO_2Et$, benzene, reflux 4 h, 80%. (c) K_2CO_3, K_3FeCN_6, $CH_3SO_2NH_2$, $(DHQ)_2PHAL$ (1 mol%), 0.1 M OsO_4 (0.4 mol%), *t*-BuOH/H_2O (1:1), 85%. (d) (i) $SOCl_2$, Et_3N, CH_2Cl_2, 0 °C, 20 min; (ii) $RuCl_3{\cdot}H_2O$, $NaIO_4$, $CCl_4/CH_3CN/H_2O$ (1:1:1.5), 0 °C, 2 h, 92%. (e) NaN_3, DMF, 80 °C, 94%. (f) (i) DDQ, CH_2Cl_2, H_2O; (ii) H_2/Pd–C, Boc_2O, EtOAc, 70%. (g) MsCl, Et_3N, CH_2Cl_2, −78 °C, 95%. (h) (i) $LiOH{\cdot}H_2O$, THF, MeOH, H_2O, 6 h; (ii) TFA/CH_2Cl_2 (1:1), 1.5 h; then Dowex 50, 90%.

group must be responsible for the increased reactivity of the α-position.[13]

Deprotection of the *p*-methoxybenzyl group with DDQ followed by reduction of the azide **9** under hydrogenation conditions in the presence of Boc_2O gave the amino diol **10**.[14] Compound **10** was subjected to cyclization using methanesulfonyl chloride and triethylamine at −78 °C to afford **11** in 95% yield. The subsequent ester hydrolysis with lithium hydroxide in THF/H_2O followed by deprotection of the Boc group with trifluoroacetic acid furnished (2*S*,3*S*)-3-hydroxypipecolic acid **1** as a white solid [mp −232–236 °C (lit.[5] 230–238 °C)] {$[\alpha]_D^{20}$ +13.5 (*c* 0.2, 10% aq. HCl) [lit.[5] $[\alpha]_D^{20}$ +12.90 (*c* 0.23, 10% aq. HCl)]} in 90% yield. The physical and spectroscopic data of **1** are in full agreement with the literature data.[6a]

In conclusion, a practical and enantioselective synthesis of 3-hydroxypipecolic acid **1** has been achieved using Sharpless asymmetric dihydroxylation with regioselective opening of a cyclic sulfate. To the best of our knowledge, this is the first asymmetric synthesis of 3-hydroxypipecolic acid using Sharpless asymmetric dihydroxylation as the source of chirality. The synthetic strategy described has significant potential for further extension to other isomers and related analogues. Currently studies are in progress in this direction.

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11. The spectral data for **7**: $[\alpha]_D^{20}$ +2.87 (*c* 1.08, $CHCl_3$) IR ($CHCl_3$, cm^{-1}): ν_{max} 1032, 1130, 1248, 1513, 1612, 1736, 2864, 2938, 3440; ^1H NMR (500 MHz, $CDCl_3$): δ 1.30 (t, 3H, *J* = 6 Hz), 1.73 (m, 4H), 2.82 (br s, 2H), 3.49 (t, 2H, *J* = 6 Hz), 3.80 (s, 3H), 3.91 (d, 1H, *J* = 5 Hz), 4.06 (m, 1H), 4.26 (q, 2H, *J* = 5 Hz), 4.44 (s, 2H), 6.87 (d, 2H, *J* = 10 Hz), 7.25 (d, 2H, *J* = 10 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 13.77, 25.69, 30.03, 42.58, 54.83, 61.21, 69.51, 72.12, 73.41, 113.48, 128.97, 130.14, 158.87, 173.21; Mass (ESI): 312 (M^+); Anal. Calcd for $C_{16}H_{24}O_6$: C, 61.52; H, 7.74. Found: C, 61.66; H, 7.70.
12. For the measurement of the enantiomeric excess, the diol **7** was converted into its dibenzoate. The enantiomeric purity of the dibenzoate was estimated to be 97% by chiral HPLC analysis using Lichocart 250-4 (4 mm ID × 25 cm) HPLC-Cartridge (R.R.-Whelk-01), 10% *i*-PrOH in hexane, 0.8 mL/min.

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14. The spectral data for **10**: $[\alpha]_D^{20}$ −10.74 (*c* 1.00, $CHCl_3$): IR ($CHCl_3$, cm^{-1}): ν_{max} 1711, 1736, 2935, 3431; ^1H NMR (200 MHz, $CDCl_3$): δ 1.27 (t, 3H, $J = 6$ Hz), 1.42 (s, 9H), 1.69 (m, 4H), 3.66–3.75 (m, 3H), 3.94 (br s, 2H), 4.16–4.26 (m, 3H), 5.58 (br s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 14.08, 28.27, 29.97, 30.33, 58.67, 61.43, 62.16, 72.56, 80.17, 155.93, 170.80; Mass (ESI): 291 (M^+), 203, 147; Anal. Calcd for $C_{13}H_{25}NO_6$: C, 53.59; H, 8.65; N, 4.81. Found: C, 53.52; H, 8.55; N, 4.95.