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A Short Enantioselective Synthesis of Pipecolic Acid.

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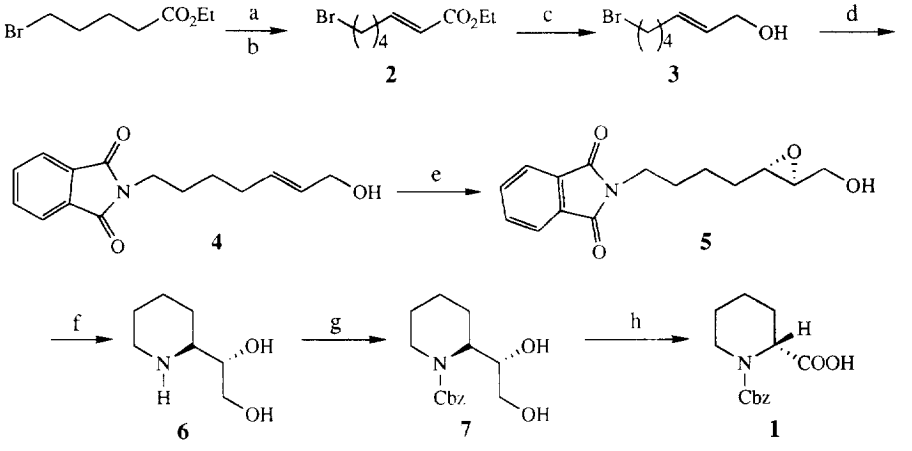
Abstract: A simple enantioselective route to pipecolic acid is described. The key step involves the Sharpless asymmetric epoxidation of an N-protected aminoheptenol which spontaneously cyclises to a piperidine derivative on deprotection.

Although regioselective ring-opening of chiral epoxy alcohols by nucleophiles,[1] specifically ammonia and amines,[2] has been used in the synthesis of chiral acyclic amino acids,[3] as far as we are aware the intramolecular version of this process leading to chiral heterocyclic amino acids has not been explored. Enantiopure cyclic amino acids are compounds of considerable biochemical and pharmaceutical interest. We disclose in this communication the asymmetric synthesis of pipecolic acid[4] **1** as an illustration of this simple intramolecular route from epoxy alcohols to cyclic amino acids which should be capable of extension to a wide range of natural and unnatural amino acids.

The starting material in the synthesis was the readily available and inexpensive ethyl 5-bromovalerate (Scheme 1). Reduction with DIBAL-H at -78°C followed by a Wittig olefination yielded α,β-unsaturated ester **2** in very good overall yield.



Scheme 1. a: DIBAL-H, $PhCH_3$, -78°C, 1h, 90%. b: $Ph_3P{=}CHCO_2Et$, CH_2Cl_2, rt, 12h, 82%. c: DIBAL-H, $PhCH_3$, 0°C, 2h, 86%. d: PhthNK, DMF, Δ, 1.5h, 82%. e: $Ti(OiPr)_4$, (+)-DIPT, tBuOOH, CH_2Cl_2, -40°C, 78%. f: NH_2NH_2, EtOH, rt, 3 days, quant. g: BnOCOCl, K_2CO_3, THF, H_2O, 12h, 85%.h: $RuCl_3$, $NaIO_4$, H_2O/ CH_3CN/ CCL_4, rt, 2h, 52%.

Reduction of **2** to the allylic alcohol **3** was achieved with DIBAL-H at 20°C in 86% yield. The necessary nitrogen atom was introduced by nucleophilic substitution of the bromide in **3** with potassium phthalimide in DMF to furnish **4** in 82% yield.

Sharpless epoxidation[5] of **4** at -40°C produced the (-)-epoxy alcohol **5**[6] in high yield (78%) and enantiomeric excess (>95%)[7] using (+)-DIPT as the chiral auxiliary. When **5** was treated with hydrazine in ethanol (0.2M) at 20°C for 3 days to bring about deprotection of the amine function, intramolecular nucleophilic opening of the epoxide occurred spontaneously and amino diol **6**[8] was formed in quantitative yield. To complete the synthesis, **6** was N-protected with benzyl chloroformate to afford (+)-**7**[10] and oxidative cleavage[9] of the diol with $RuCl_3$/ $NaIO_4$ in CH_3CN:CCL_4:H_2O at 20°C afforded (R)-N-Cbz-pipecolic acid **1**[11] in 52% yield and >95% ee and identical with a sample prepared from authentic (R)-pipecolic acid.

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6.- **5**: white solid, m.p. 71-72°C; ^{1}H NMR ($CDCl_3$, 300 MHz): 7.85 (2H, m), 7.72 (2H, m), 3.90 (1H, dd, J= 12.4; 2.1 Hz), 3.71 (2H, dd, J= 7.2; 7.0 Hz), 3.64 (1H, dd, J= 12.4, 4.0 Hz), 2.95 (2H, m), 1.75 (2H, m), 1.64 (2H, m), 1.53 (2H,m); ^{13}C NMR ($CDCl_3$, 75 MHz): 168.4, 133.9, 131.9, 123.2, 123.1, 61.6, 58.3, 55.5, 37.6, 37.5, 31.0, 28.2, 23.2; $[\alpha]_D$ = -18.0 (c= 1, CH_2Cl_2).
7.- The optical purity was checked by ^{1}H NMR shift study using europium (III) tris[3-(heptafluoro-propylhydroxymethylene) (+)-camphorate] ($Eu(hfc)_3$) of the corresponding acetate.
8.- **6**: oil; ^{1}H NMR ($CDCl_3$, 300MHz): 3.82-3.58 (5H, m), 3.10 (1H, m), 2.79 (1H, m), 2.54 (1H, m), 1.84 (1H, m), 1.61 (2H, m), 1.36 (3H, m); m/z: 145 (M^+, 6), 131 (3), 126 (5), 114 (7), 84 (100), 56 (25), 41 (10).
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10.- **7**: white solid, m.p.= 72-74°C; ^{1}H NMR ($CDCl_3$, 300 MHz): 7.36 (5H, m), 5.13 (2H, m), 4.10 (2H, m), 3.79 (1H, m), 3.53 (3H, m), 2.70 (1H, ddd, J= 13.5; 12.6; 2.5 Hz), 2.54 (1H, m), 2.19 (1H, m), 1.60 (5H, m); IR (KBr): 3405, 2937, 2867, 1668, 1429, 1354, 1263 cm^{-1}; m/z: 279 (M^+, 3), 248 (10), 231 (8), 218 (35), 174 (50), 108 (11), 91 (100), 79 (12), 65 (10), 55 (7), 41 (7); $[\alpha]_D$ = + 41.8 (c= 0.5, CH_2Cl_2).
11.- **1**: white solid, m.p.= 84°C; ^{1}H NMR ($CDCl_3$, 300 MHz): 7.32 (5H, m), 5.15 (2H, m), 5.00, 4.90 (1H,br d, J= 4.8 Hz), 4.14-4.04 (1H, m), 3.07-2.99 (1H, m), 2.25 (1H, dd, J= 13.6; 12.7 Hz), 1.73- 1.63 (3H, m), 1.47- 1.31 (2H, m); $[\alpha]_D$ = + 77.6 (c= 0.2, CH_2Cl_2).
12.- The optical purity was checked by ^{1}H NMR shift study using $Eu(hfc)_3$ of the corresponding methyl ester of **1**, ee > 95%.

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