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Experimental

Procedures for the preparation of D,L-**6** and conversion to L-**6** were adapted from the literature and are referenced. Detailed experimental descriptions will be provided on request. Reference and compound numbers refer to those in the main text.

^1H and ^{13}C NMR spectra were recorded on a Bruker ACP-300 spectrometer and chemical shifts are reported in δ (ppm) relative to 3-(trimethylsilyl)propionic-2,2,3,3-d_4 acid, sodium salt. Infrared spectra were measured on a Nicolet 510 FT-IR spectrometer. Optical rotations were obtained at ambient temperature using a Perkin-Elmer 141 polarimerer and were measured at the sodium D line. All chemicals were obtained from Aldrich or Sigma unless otherwise noted. Porcine kidney D-Amino acid oxidase was from Sigma. Solvents were purified according to Perrin et al.[25] Chiral HPLC analyses were conducted on a Beckman System Gold (two model 125 pumps, model 166 UV detector, Rheodyne model 7725 injector) using a chiral mobile phase containing L-aspartame (Asp-Phe-OMe) and Cu(II).[26] Separation was on a Waters Novapak C_{18} reverse phase column (3.9 x 150 mm) along with an Upchurch C_{18} guard column (4.3 x 10 mm) at a flow rate 1.5 mL/min and UV detection was at 234 nm.

The preparation of D,L-**6** and conversion to L-**6** is shown below in Scheme 3. 4,5-Dehydro-D,L-pipecolic acid (D,L-**6**) was prepared according to the procedure of Burgstahler and Aiman as later modified by these authors.[19] Diethylacetamidomalonate was condensed with *cis*-1,4-dichloro-2-butene to give diethyl N-acetyl-1,2,3,6-tetrahydropyridine-2,2-dicarboxylate which was saponified and decarboxylated without isolation. Purification by crystallization from aqueous ethanol gave D,L-**6** in 50 - 60% yield.

Conversion of D,L-**6** to L-**6** was accomplished by repeatedly oxidizing D-**6** to the corresponding imine through the stereospecific action of D-amino acid oxidase, followed by borohydride reduction of the imine to D,L-**6**.[20] After four cycles the product was isolated by cation exchange chromatography (AG-50) and purified by recrystallization from methanol/acetone. NMR spectra of purified **6** are shown in Figure 4. Enantiomeric excess was greater than 95% as determined by optical rotation and chiral HPLC (Figure 5). **4,5-Dehydro-L-pipecolic acid (L-6)**: mp 264-265 °C (lit.[27] 273-274 °C); ^1H-NMR (300 MHz, ^2H_2O) δ 2.52 (m, 1H, H-3a), 2.73 (m, 1H, H-3b), 3.79 (bs, 2H, H-6), 4.17 (dd, J = 10.7, 5.5 Hz, H-2), 5.80 (m, 1H, H-5), 6.00 (m, 1H, H-4); ^{13}C-NMR (75 MHz, ^2H_2O) 27.7 (C-3), 44.7 (C-6), 56.4 (C-2), 122.6, 127.3 (C-4 and C-5), 174.7 (C-1); IR (KBr) 3200-3600, 1745, 1570 cm^{-1}; $[\alpha]_D$ -181.9° (H_2O) (lit.[27] -201°); HREIMS 127.0633 (127.0633 calcd. for $C_6H_9NO_2$).

SCHEME 3

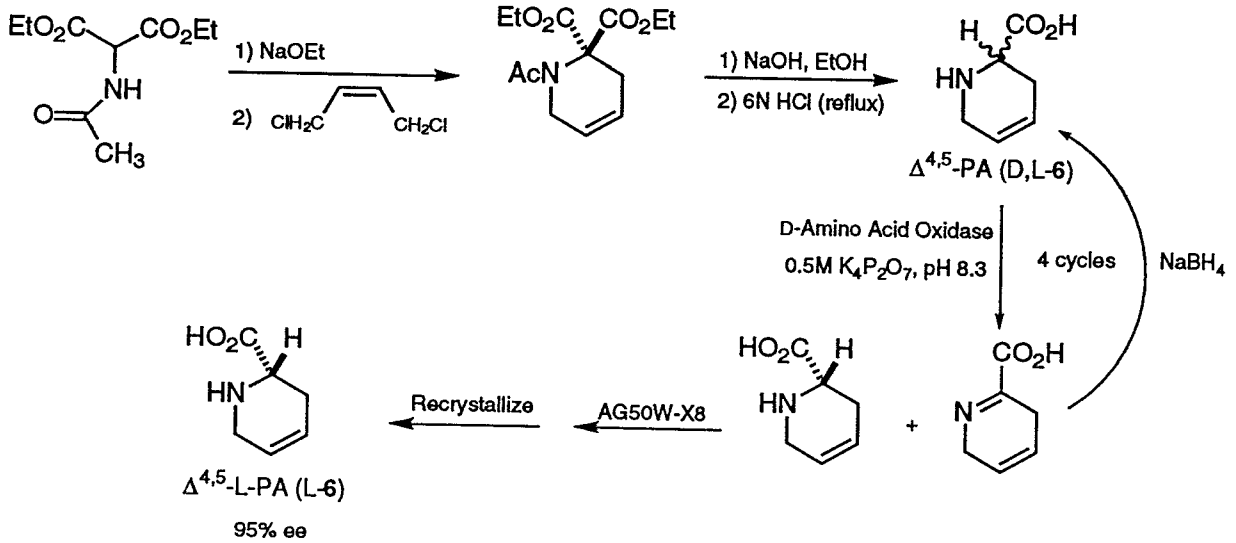

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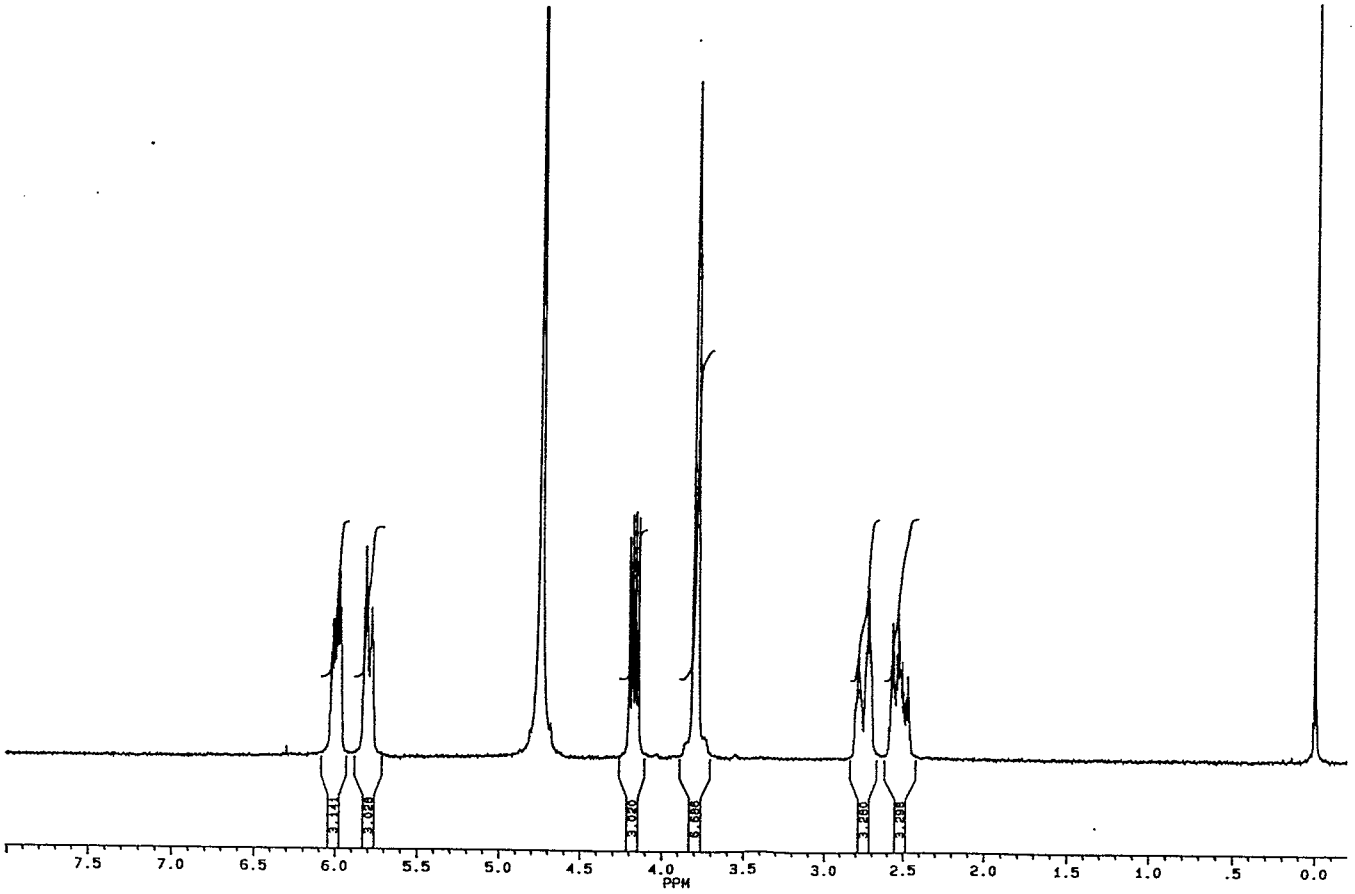
Figure 4. ^{1}H and ^{13}C NMR spectra of **L-6**



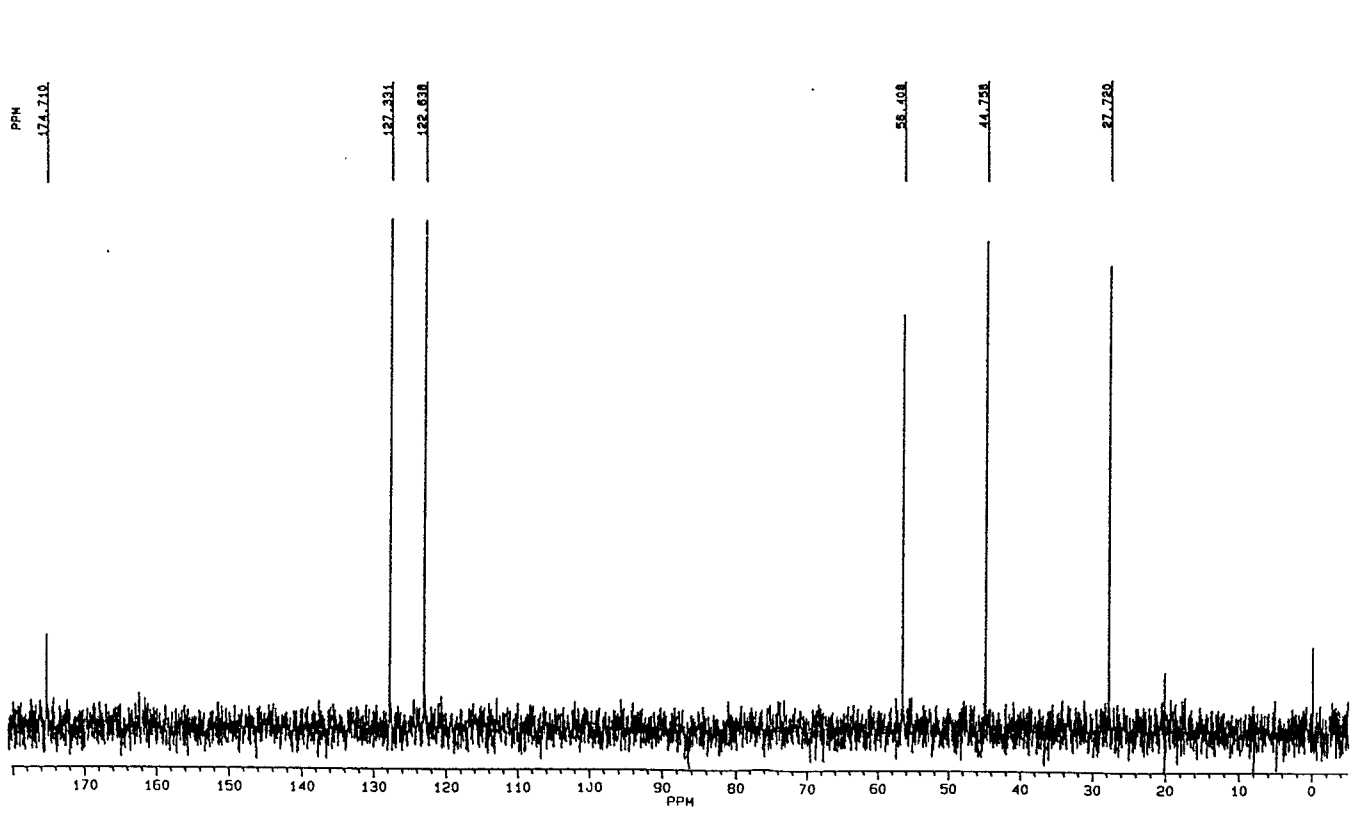


Figure 5. HPLC analyses of D,L-**6** and L-**6**