

Journal of
Medicinal Chemistry

J. Med. Chem., 1996, 39(16), 3046-3048, DOI: [10.1021/jm960331f](https://doi.org/10.1021/jm960331f)

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Experimental

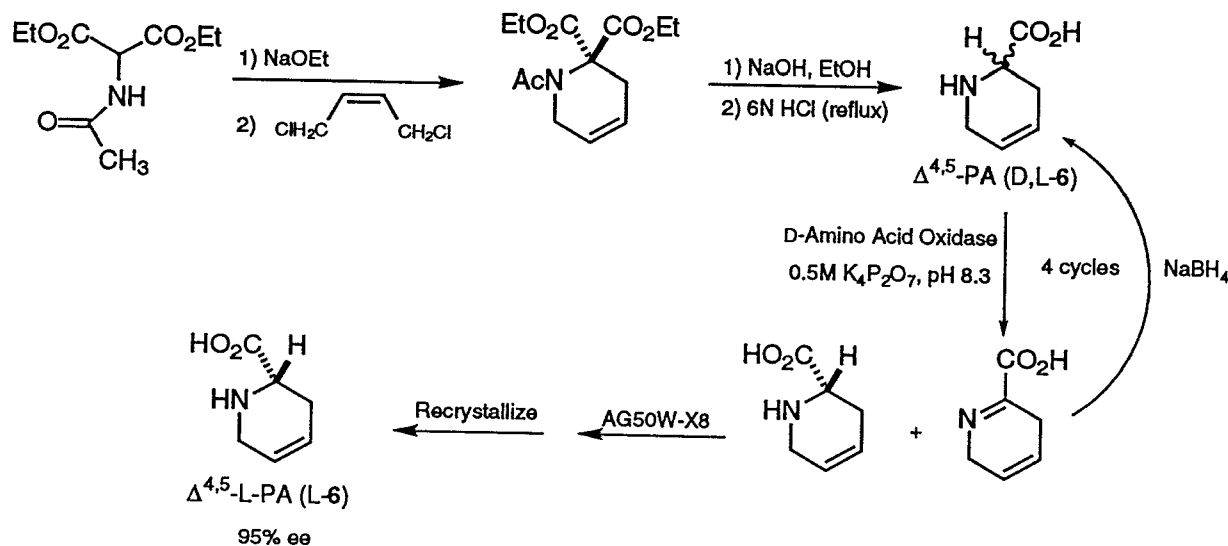
Procedures for the preparation of D,L-**6** and conversion to L-**6** were adapted from the literature and are referenced. Detailed experimental descriptions will be provided on request. Reference and compound numbers refer to those in the main text.

^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 polarimeter 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, $^2\text{H}_2\text{O}$) 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, $^2\text{H}_2\text{O}$) 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} ; $[\alpha]_{\text{D}} -181.9^\circ$ (H_2O) (lit.²⁷ -201°); HREIMS 127.0633 (127.0633 calcd. for $\text{C}_6\text{H}_9\text{NO}_2$).

SCHEME 3



References

- (19) Burgstahler, A. W.; Aiman, C. E. A Direct Synthesis of D,L-Baikiain. *J. Org. Chem.* **1960**, *25*, 489-492 and 2263.
- (20) Huh, J. W.; Yokoigawa, K.; Esaki, N.; Soda, K. Total Conversion of Racemic Pipecolic Acid into the L-Enantiomer by a Combination of Enantiospecific Oxidation with D-Amino Acid Oxidase and Reduction with Sodium Borohydride. *Biosci. Biotech. Biochem.* **1992**, *56*, 2081-2082.
- (25) Perrin, D.D.; Armarego, W.L.F.; Perrin, D.R. *Purification of Laboratory Chemicals*; 2nd Ed., Pergamon Press: New York, 1980.
- (26) Lam, S.; Azumaya, H.; Karmen, A. High-Performance Liquid Chromatography of Amino Acids in Urine and Cerebrospinal Fluid. *J. Chromatogr.* **1984**, *302*, 21-29.
- (27) King, F.E.; King, T.J.; Warwick, A.J. The Chemistry of Extractives from Hardwoods. Part III. Baikiain, an Amino Acid Present in *Baikiaea plurijuga*. *J. Chem. Soc.* **1950**. 3590-3597.

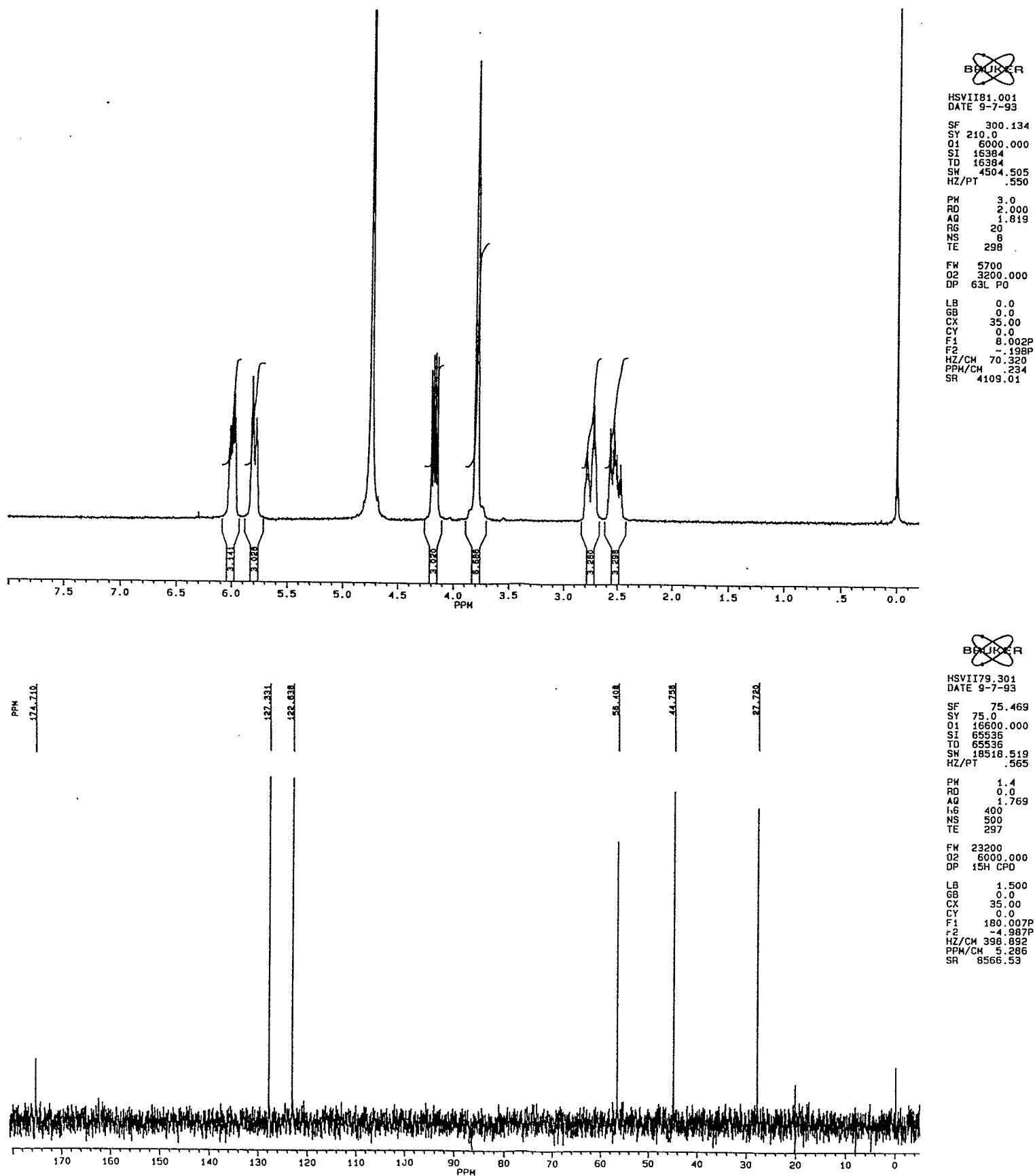
Figure 4. ^1H and ^{13}C NMR spectra of L-6

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

