^{13}C NMR ppm 14.55 (CH_3), 21.45 (CH_3CO), 61.92 (C-4), 71.80 (CH_2N^+), 78.94, 81.72, and 83.90 (C-1, C-2, and C-3), 170.44 and 172.95 (C=O). Anal. Calcd for $C_{35}H_{58}BrNO_5$: C, 64.40; H, 8.96; N, 2.15. Found: C, 64.55; H, 9.01; N, 2.10.

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Registry No. 1, 73068-66-3; 2, 14233-62-6; 2 (R = Ac), 138858-67-0; 3, 138858-50-1; 4, 138858-51-2; 5, 138858-52-3; 6, 138858-53-4; 7, 138858-54-5; 8, 138858-55-6; 9, 138858-56-7; 10, 138858-57-8; 11, 138858-58-9; 12, 138858-59-0; 13, 138858-60-3; 14, 138858-61-4; 15, 138858-62-5; 16, 138858-63-6; 17, 138858-64-7; 18, 138858-65-8; 19, 138858-66-9; $Ph_3P{=}CH(CH_2)_{14}CH_3$, 103411-90-1; $Br(CH_2)_5COOCH_2CF_3$, 128691-25-8; $Br(CH_2)_5COCl$, 22809-37-6.

Synthesis of (*R*)- and (*S*)-4,5-Diaminovaleric Acids

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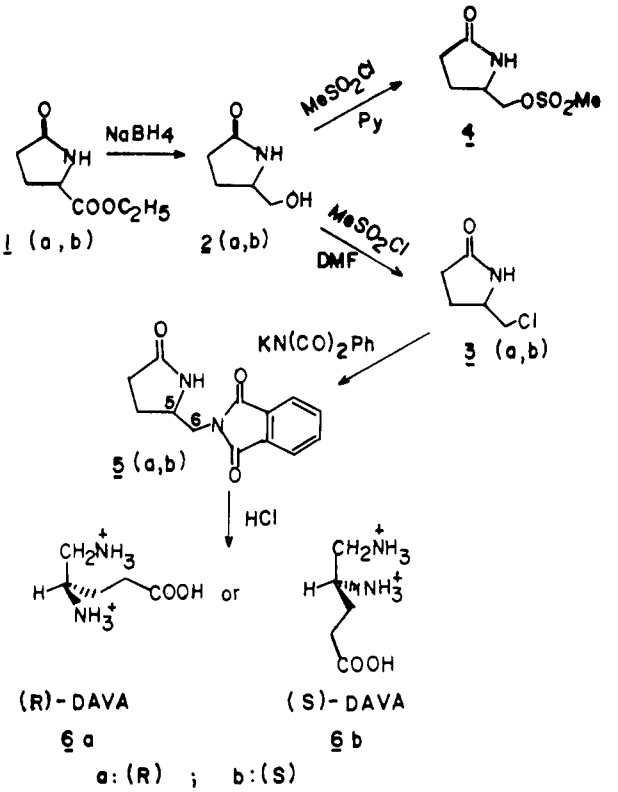
Two completely different pathways exist for the biosynthesis of 5-aminolevulinic acid (ALA), the precursor of all biological tetrapyrroles.[1] In the one pathway the pyridoxal-dependent ALA synthase (EC 2.3.1.37) catalyzes the condensation of glycine and succinyl-CoA; the resulting 2-amino-3-ketoadipic acid is spontaneously decarboxylated to ALA (Shemin pathway).[2] This pathway is found in nonphotosynthetic eukaryotes and in some bacteria. In the other pathway the C_5 chain of L-glutamic acid is converted to that of ALA by a complex reaction sequence involving three enzymes and $tRNA^{Glu}$ (C_5 pathway).[1,3] The C_5 pathway is found in plants and in many very different kinds of bacteria such as cyanobacteria, green sulfur and purple sulfur bacteria,[1c,3c] in the archaebacterium *Methanobacterium thermoautotrophicum*,[4] and even in organisms such as *Escherichia coli*,[5] *Bacillus subtilis*,[6] and *Clostridium thermoaceticum*.[7] In the last step of the C_5 pathway, catalyzed by glutamate-1-semialdehyde (GSA) aminotransferase (EC 5.4.3.8),[8] an intermolecular transamination occurs between two molecules of GSA.[9] This aminotransferase is unusual since no amino donor or acceptor in addition to GSA is required, a circumstance related to the fact that GSA carries an oxo and an amino group on adjacent carbons. It is likely that in the course of the conversion of GSA to ALA an intermolecular amino group transfer occurs, resulting in the formation of 4,5-diaminovaleric acid (DAVA).[10] The role of this putative intermediate has not been investigated. A synthesis of DAVA has been described thus far, via a Bamberger ring cleavage of 3-imidazole-4(5)-ylpropanoate, obtained from urocanic acid by catalytic reduction.[11] This synthesis necessarily yields the DAVA racemate. An attempt of ammonolysis on 4,5-dibromovaleric acid only afforded amorphous material.[12] We report a novel DAVA synthesis that permits the preparation of the required (*R*)-DAVA and (*S*)-DAVA, using commercially available precursors.

Scheme I



The starting materials were the *R* and *S* isomers of 5-carbethoxy-2-pyrrolidone (ethyl pyroglutamate) (1) (Scheme I). The reduction of the carbethoxy residue to give the 5-(hydroxymethyl)-2-pyrrolidone (2) has been achieved in the past using hydrogen at 200–300 atm/220 °C over copper–chromium oxide,[13] hydrogen over Ni Raney at 1000 psi,[14] and lithium borohydride.[15] More recently, the latter reductant was used to reduce the S enantiomer

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1b to the *S* alcohol **2b**.[16] We found that sodium borohydride is a very efficient reducing agent of both enantiomers of **1** and converted them into **2** in 80% yields. To ascertain that no base-catalyzed racemization took place during the reduction, each of the 5-hydroxymethyl lactams **2** was heated with sodium methoxide in methanol during 2–3 h. No changes in the $[\alpha]_D$ values were detected. The 5-hydroxymethyl lactams **2a** and **2b** were transformed into the chloromethyl derivatives **3a** and **3b** by reaction with mesyl chloride in dimethylformamide at 65 °C. To control that no acid-catalyzed racemization took place, each of the chloromethyl lactams **3** was kept in a hydrogen chloride–dimethylformamide solution for 48 h at 25 °C. No changes in the $[\alpha]_D$ values were detected. When the reaction was carried out in pyridine, only the methanesulfonyl derivative **4** was obtained. The latter reacted only very slowly with nucleophilic reagents; therefore, the synthesis was pursued using the chloromethyl derivatives **3**. By reaction of **3a** and **3b** with potassium phthalimide the corresponding phthalimido derivatives **5a** and **5b** were obtained in good yields. Their mass spectra were revealing: the fragmentation pattern included fragments of m/z 84 (cleavage at the C_5–C_6 bond), as well as of m/z 98 (cleavage at the C_6–N bond). Acid hydrolysis of **5** with concentrated hydrochloric acid afforded in good yields both enantiomers of 4,5-diaminovaleric acid **6** as their hydrochlorides. The ^{13}C NMR and ^1H NMR spectra of **6** confirmed their structure. No changes in the $[\alpha]_D$ values of the enantiomers were detected when each of them was heated in concentrated hydrochloric acid for 6 h.

This synthetic approach allows not only the synthesis of both enantiomers of **6**, but also opens the possibility of selectively introducing ^{15}N labels at each of its two nitrogens, a feature which will be helpful to clarify the mechanistic details of the events which underlay the conversion of glutamate 1-semialdehyde to 4,5-diaminovaleric acid.

Experimental Section

General Procedures. Melting points were determined on a Kofler melting point apparatus and are uncorrected. ^1H NMR and ^{13}C NMR spectra were routinely recorded in $CDCl_3$ on a Varian FT-80A spectrometer. Mass spectra were obtained on a QPGS-MS 1000 Shimadzu spectrometer. The silica gel used in column chromathography was TLC Kieselgel (Riedel-de Haën). TLC was performed on precoated silica gel F-254 plates (Merck, 0.25-mm-layer thickness), or on precoated cellulose plates (Merck, 0.1-mm-layer thickness). The lactams were spotted using iodine vapor, and the amino acids by spraying with a ninhydrin solution (0.5% ninhydrin, 0.4% acetic acid, 5% 2,6-lutidine in acetone). Optical activities were measured with a Perkin Elmer Model 10141 automatic polarimeter.

(*R*)-(−)-5-(Hydroxymethyl)-2-pyrrolidone (2a). Small portions of $NaBH_4$ (1.5 g) were added over 30 min to a stirred solution of 3 g of **1a** (Aldrich) in a mixture of 30 mL of anhydrous methanol and 30 mL of dry tetrahydrofuran. The mixture was kept at 5 °C, and complete reduction was achieved after 1 h. It was monitored by TLC using 10% methanol in chloroform as developing solvent. The solution was then evaporated to dryness, the residue was dissolved in a small volume of distilled water, the aqueous solution was adjusted to pH 6 with acetic acid and was applied to a Dowex 50 (H^+) column (2.5 × 24 cm). The resin was washed with water (150 mL), and the eluate was evaporated to dryness in vacuo. The residue was dissolved in a small volume of 10% methanol in chloroform, the solution was applied to a TLC silica gel column (2 × 30 cm) packed and prewashed with the same solvent, and the alcohol **2a** was eluted using the same eluant under a slight pressure of nitrogen. The eluates were monitored using silica gel TLC. The fractions which contained **2a** were pooled and evaporated to dryness in vacuo. The oily residue was finally distilled (151 °C (0.1 mm)); the colorless distillate solidified upon cooling: mp ca. 30 °C 1.8 g (80%); ^{13}C NMR (Cl_3CD) δ 179.20 (CO), 65.20 (CH), 56.30 (CH_2OH), 30.00 (CH_2-3), 25.50 (CH_2-4); ^1H NMR (Cl_3CD) δ 7.50 (br, 1 H, NH), 4.80 (m, 1 H, OH), 3.50 (m, 3 H, CH_2-6, H-5), 2.00 (m, 4 H, CH_2); ^1H NMR (CH_3OD) δ 3.80 (m, 3 H, CH_2-6, H-5), 2.25 (m, 4 H, CH_2); mass spectrum, m/z (relative intensity) 115 (13, M^+), 84 (100); $[\alpha]^{20}_D$ −24° (*c* 2.5, methanol).

Anal. Calcd for $C_5H_9NO_2$: C, 52.2; H, 7.8; N, 12.2. Found: C, 52.1; H, 7.7; N, 12.1.

(*S*)-(+)-5-(Hydroxymethyl)-2-pyrrolidone (2b) was obtained following the procedure described for **2a**. From the 6.0 g of **1b** (Aldrich), 3.5 g (80%) of **2b** (bp 152 °C (0.1 mm)) was obtained: $[\alpha]^{20}_D$ +24° (*c* 3.0, methanol) (lit.[16] $[\alpha]^{20}_D$ +29° (ethanol)).

Anal. Calcd for $C_5H_9NO_2$: C, 52.2; H, 7.8; N, 12.2. Found: C, 52.2; H, 7.9; N, 12.3.

(*R*)-(+)-5-(Chloromethyl)-2-pyrrolidone (3a). To a solution of (*R*)-(−)-5-hydroxymethyl lactam **2a** (1.6 g) in 30 mL of dimethylformamide was added 3.2 mL (3 equiv) of mesyl chloride, and the solution was kept at 65 °C during 16 h. It was then evaporated to dryness in vacuo, and the residue was dissolved in a small volume of 3% methanol in chloroform and was applied to a TLC silica gel column (2 × 30 cm) packed, prewashed, and eluted with the same solvent. The eluates which contained the chloromethyl derivative **3a** were pooled and evaporated to dryness in vacuo. The oily residue was distilled (bp 128 °C (0.1 mm)), and the distillate solidified on cooling: mp ca. 35 °C; 1.2 g (65%); ^{13}C NMR (Cl_3CD) δ 178.00 (CO), 54.90 (CH), 47.60 (CH_2Cl), 29.50 (CH_2-3), 24.50 (CH_2-4); ^1H NMR (Cl_3CD) δ 7.40 (br, 1 H, NH), 3.80 (m, 1 H, H-5), 3.50 (m, 2 H, CH_2Cl), 2.10 (m, 4 H, CH_2); mass spectrum, m/z (relative intensity) 133 (4, M^+), 84 ($M^+ - CH_2Cl$, 100); $[\alpha]^{20}_D$ +1.6° (*c* 2.5, ethanol).

Anal. Calcd for C_5H_8ClNO: C, 44.9; H, 6.0; N, 10.5. Found: C, 45.1; H, 6.2; N, 10.4.

(*S*)-(−)-5-(Chloromethyl)-2-pyrrolidone (3b) was obtained from **2b** following the procedure described for **3a**. From 2.0 g of **2b** was obtained 1.2 g (58%) of the chloromethyl derivative **3b** (bp 126 °C (0.1 mm)) as a colorless oil which solidified at room temperature: mp ca. 32 °C; $[\alpha]^{20}_D$ −1.6° (*c* 2.5, methanol) (lit.[16] $[\alpha]^{20}_D$ −18° (*c* 2.5, ethanol)).

Anal. Calcd for C_5H_8ClNO: C, 44.9; H, 6.0; N, 10.5. Found: C, 45.0; H, 6.1; N, 10.6.

(*R*)-(−)-5-(Phthalimidomethyl)-2-pyrrolidone (5a). The (R)-(+)-chloromethyl derivative **3a** (1.2 g) was dissolved in 70 mL of anhydrous dimethylformamide, 3.4 g (2 equiv) of potassium phthalimide was added, and the mixture was heated at 150 °C during 16 h with constant stirring. The solution was evaporated to dryness in vacuo, the residue was dissolved in water (20 mL), and the aqueous solution was extracted with ethyl acetate (3 × 15 mL). The pooled extracts were dried (Na_2SO_4) and evaporated to dryness, the residue was dissolved in a small volume of 3% methanol in chloroform, and the solution was applied to a TLC silica gel column (2 × 20 cm). The phthalimido derivative **5a** was eluted using the same solvent, the eluate was evaporated to dryness, and the residue was crystallized from chloroform–hexane: 1.3 g (60%); mp 185–186 °C; ^{13}C NMR (Cl_3CD) δ 177.10 (CONH), 168.40 (CO), 133.10, 131.00, 123.00 (Ph), 53.40 (CH), 42.10 (CH_2N), 29.33 (CH_2-3), 24.40 (CH-4); ^1H NMR (Cl_3CD) δ 7.75 (m, 4 H, Ph), 6.55 (b, 1 H, NH), 4.00 (m, 1 H, H-5), 3.80 (m, (m, 2 H, CH_2-6), 2.10 (m, 4 H, CH_2); mass spectrum, m/z (relative intensity) 244 (1, M^+), 160 (6, phthalimido), 84 (100, pyrrolidone); $[\alpha]^{20}_D$ −27° (*c* 1.5, methanol).

Anal. Calcd for $C_{13}H_{12}N_2O_3$: C, 63.9; H, 4.9; N, 11.5. Found: C, 63.8; H, 4.8; N, 11.4.

(*S*)-(+)-5-(Phthalimidomethyl)-2-pyrrolidone (5b) was obtained from **3b** following the procedure described for **5a**. From 1.2 g of **3b** was obtained 1.4 g (64%) of **5b**: mp 185–186 °C (chloroform–hexane); $[\alpha]^{20}_D$ +27° (*c* 1.5, methanol).

Anal. Calcd for $C_{13}H_{12}H_2O_3$: C, 63.9; H, 4.9; N, 11.5. Found: C, 63.8; H, 4.8; N, 11.6.

(*R*)-(+)-4,5-Diaminovaleric Acid Dihydrochloride (6a). The phthalimido derivative **5a** (1 g) was suspended in 30 mL of concentrated hydrochloric acid, and the mixture was heated under reflux for 16 h. The solution was then cooled at 5 °C, the phthalic acid was filtered, the filtrate was evaporated to dryness in vacuo, and the white residue was crystallized from methanol–ethyl

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acetate: 0.6 g (70%); mp 176–177 °C (lit.[11] mp 174–175 °C for the racemate); ^{13}C NMR (D_2O) δ 177.00 (CO), 49.94 (CH), 41.76 (CH_2N), 30.23 (CH_2-2) 27.89 (CH_2-3); ^1H NMR (D_2O) δ 3.70 (m, 1 H, CH-4), 3.35 (m, 2 H, CH_2-5), 2.60 (m, 2 H, CH_2-2), 2.10 (m, 2 H, CH_2-3); mass spectrum, m/z (relative intensity) 114 (16, M^+ – 18, 5-(aminomethyl)-2-pyrrolidone), 98 (22, 5-methylene-2-pyrrolidone), 84 (40, 2-pyrrolidone); $[\alpha]^{20}_D$ +4.6° (c 2.5, water). On cellulose TLC it had R_f 0.18 (2-propanol/hydrochloric acid/water, 5/1/1).

Anal. Calcd for $C_5H_{14}Cl_2N_2O_2$: C, 29.3; H, 6.9; N, 13.7. Found: C, 29.2; H, 6.8; N, 13.6.

(*S*)-(–)-4,5-Diaminovaleric acid dihydrochloride (6b) was obtained following the procedure described for its enantiomer **6a**. From 1 g of **5b** was obtained 0.7 g (85%) of **6b**: mp 180–181 °C (methanol–ethyl acetate); $[\alpha]^{20}_D$ –4.6° (c 1.5, water). On cellulose TLC it had R_f 0.15 (solvent as for **6a**).

Anal. Calcd for $C_5H_{14}C_{12}N_2O_2$: C, 29.3; H, 6.9; N, 13.7. Found: C, 29.3; H, 6.8; N, 13.8.

(*R*)-5-(((Methylsulfonyl)oxy)methyl)-2-pyrrolidone (4). Mesyl chloride (2.5 mL) was added to a stirred solution of 0.4 g of **2a** in 5 mL of anhydrous pyridine kept at 5 °C. The mixture was stirred at 25 °C during 90 min, and it was then evaporated to dryness in vacuo. The residue was dissolved in a small volume of 10% methanol in chloroform, and the solution was applied to a TLC silica gel column (2 × 20 cm) packed and prewashed with the same solvent. The mesylate was eluted with the same eluant, the eluate was evaporated to dryness, and the residue was recrystallized from chloroform–hexane: 0.3 g (60%); mp 75–76 °C; ^{13}C NMR (D_2O) δ 178.00 (CO), 71.10 (CH), 52.30 (CH_2O), 36.81 (CH_3), 29.10 (CH_2-3), 22.10 (CH_2-4); ^1H NMR (Cl_3CD) δ 7.10 (s, 1 H, NH), 4.10 (m, 3 H, CH_2O, H-5), 3.10 (s, 3 H, CH_3), 2.10 (m, 4 H, CH_2).

Anal. Calcd for $C_6H_{11}NO_4S$: C, 37.3; H, 5.7; N, 7.2. Found: C, 37.2; H, 5.8; N, 7.1.

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Registry No. **1a**, 68766-96-1; **1b**, 7149-65-7; **2a**, 66673-40-3; **2b**, 17342-08-4; **3a**, 138541-53-4; **3b**, 72479-04-0; **4**, 138541-54-5; **5a**, 138541-55-6; **5b**, 138541-56-7; **6a**, 138661-27-5; **6b**, 130338-27-1; potassium phthalimide, 1074-82-4.

Chemoselective Synthesis of Functionalized Conjugated Nitroalkenes

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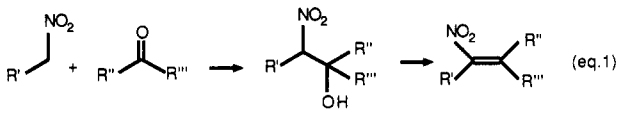
Unsaturated nitro compounds have proved to be valuable precursors to a wide variety of target molecules. Historically, the nitroalkenes were of importance because of their biological activity such as insecticides,[1,2] fungicides,[1,3–5] and pharmacologically active substances.[6–9]

The utility of nitroalkenes in organic synthesis is largely due to their easy conversion into a variety of functionalities.[10] Alternatively they are powerful dienophiles in Diels–Alder reactions or readily undergo addition reactions with many different nucleophiles.

The classical preparation of nitroalkenes involves the Henry condensation reaction of aldehyde or ketone with a nitroalkane followed by dehydratation of the resultant β-nitro alcohol[11] (eq 1).



(eq.1)

Several methods, using reagents such as methanesulfonyl chloride,[12] phthalic anhydride,[13,14] dicyclohexylcarbodiimide (DCC),[15] and pivaloyl chloride[16,17] have been used for the dehydration step. However some of these are indirect methods or require high temperature and, moreover, they seem of little utility in the dehydration of functionalized β-nitro alcohols. The importance of functionalized nitroalkenes prompted us to search for a chemoselective and more convenient dehydrating agent for functionalized β-nitro alcohols.

In a previous paper we reported[18] a mild, simple heterogeneous method for synthesis of 2-nitroalkanols from nitroalkanes and aldehydes on an alumina surface at room temperature and in the absence of a solvent. Later we noted[19] that this solvent-free nitro-aldol reaction between functionalized nitroalkanes and aryl aldehydes such as 2-furaldehyde gave 1-(2-furyl)-2-nitroalk-1-enes in high yields.

Based on these previous results we have found that basic alumina is a far superior catalyst for the chemoselective dehydration of the functionalized β-nitro alcohols.

Our method is carried out at 40 °C by simply dissolving the appropriate nitroalkanol in dichloromethane, with basic alumina (activity I according to Brockmann). After stirring at 40 °C for the right time (see Table I), the product is isolated, as the *E* isomer,[20] in good yields (60–85%) by filtration, evaporation, and purification by distillation or chromatography. In this procedure the formation of conjugated nitroalkenes is preferred even if the other isomer is expected by Saytzeff orientation (23

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