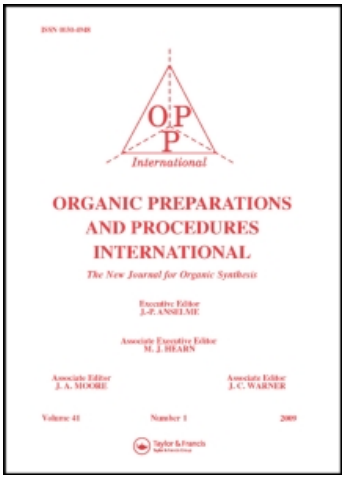

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AN EFFICIENT LARGE SCALE PREPARATION OF D,L-2-AMINO-5-PHOSPHONOPENTANOIC ACID (D,L-AP5)

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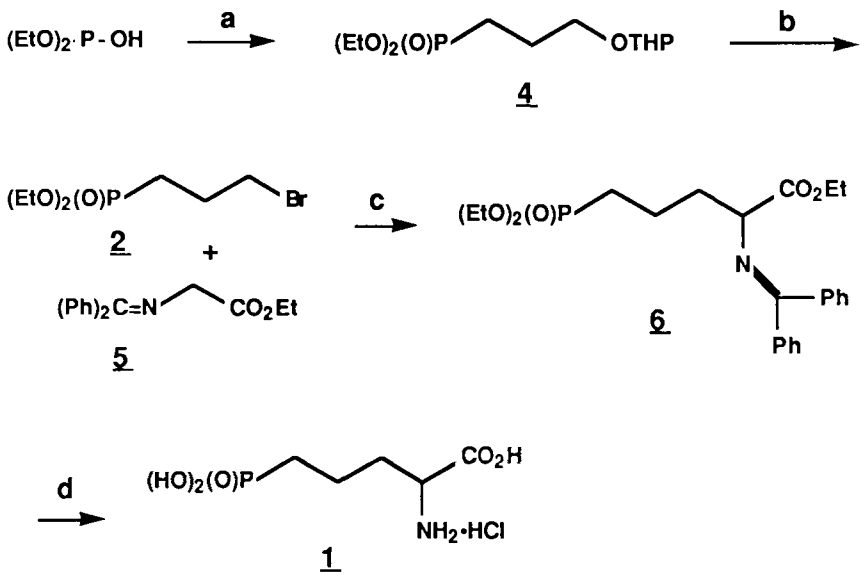
As a part of our program in excitatory amino acids,[1] large quantities of the N-methyl-D-aspartic acid receptor antagonist, D,L-2-amino-5-phosphonopentanoic acid (1)[2] were required. However, the literature synthesis[3] of 1 involved chemistry that was difficult to duplicate and not amenable to the synthesis of large quantities (ca. 50 g). The reported synthesis[3] of 1 involves alkylation of sodium diethyl acetamidomalonate with diethyl 3-bromopropylphosphonate (2), which in turn is prepared by Michaelis-Arbuzov reaction of 1,3-dibromopropane with triethyl phosphite. In our hands, however, the Arbuzov reaction gave variable yields of multiple product mixtures which netted only low yields of the desired alkylating agent 2. The reported overall yield for this synthesis, to prepare 0.32 g of D,L-1[3], was only 8%. In light of our initial failures and projected difficulties in scaling-up this process, we have developed an expeditious large scale (50 g) synthesis that provides D,L-1 (as the hydrochloride salt) in 5 steps and in 46% overall yield.

Alkylation of an excess (1.4 eq.) of sodium diethyl phosphite (NaH, THF, diethyl phosphite, RT) with the THP-ether of 3-bromopropanol (3) afforded the desired phosphonate 4. Because of difficulties encountered in the direct transformation of 4 to the bromide 2, it was more expedient to first remove the THP-ether by treatment at room temperature with methanol containing a trace of d-camphorsulfonic acid. After evaporation of methanol and 2-methoxy-

tetrahydropyran *in vacuo*, the resulting alcohol in dichloromethane and pyridine was added to a 0° suspension of freshly prepared triphenylphosphine dibromide[4] in dichloromethane. This sequence (3 steps) produced a 54% yield of the desired bromide 2, contaminated with a trace of triphenylphosphine oxide[5].



a) 1. NaH, THF, RT. 2. $THPO(CH_2)_3Br$ (3). b) 1. MeOH, d-camphorsulfonic acid, RT. 2. Ph_3PBr_2, CH_2Cl_2, pyridine. c) 1. $NaN(SiMe_3)_2$, THF, -78°C. 2. 2, -78 to 0°C. d) 6N HCl, reflux.

The benzophenone ketimine 5 proved to be a useful glycine enolate synthon for the preparation of amino acids *via* alkylation.[6] Treatment of 5 with LDA in THF in the presence of DMPU[7] followed by alkylation with 2 afforded, after chromatography, a 38% yield of the desired adduct 6. More efficient alkylation was achieved by formation of the enolate of 5 (1.4 eq.) with sodium bis(trimethylsilyl)amide (1.4 eq.) in THF at -78° followed by addition of 2 and warming to 0° for 4-5 hrs. We obtained an 87% yield of adduct 6 after Prep 500 HPLC. Use of an excess of the sodium enolate was essential to ensure complete consumption of 2, as separation of 2 and 6 was difficult. Finally, heating 6 to reflux in 6N HCl hydrolyzed the imine and esters and removal of water and HCl *in vacuo*

afforded D,L-1•HCl as a hard white foam (97%). The overall yield for the five steps (the first three with only one purificaton) was 46%. Material was homogenous by ^{1}H and ^{13}C NMR and elemental analysis. Results of *in vivo* testing with 1 are reported elsewhere.[8]

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EXPERIMENTAL SECTION

All experiments were run under a positive pressure of dry nitrogen. Tetrahydrofuran (THF) was distilled from sodium/benzophenone ketyl prior to use. All other solvents and reagents were used as obtained. ^{1}H and ^{13}C NMR spectra were obtained on a GE QE-300 spectrometer at 300.15 MHz and 75.48 MHz, respectively, with tetramethylsilane as an internal standard. Coupling constants reported for ^{13}C NMR refer to ^{13}C-^{31}P couplings. Exact mass spectra were determined on a Varian-Mat 731 spectrometer.

Diethyl 3-Bromopropylphosphonate (2).-To a 2L round bottom flask, equipped with a magnetic stirrer, 250 mL pressure-equalizing addition funnel and nitrogen inlet, was added sodium hydride (25 g of a 60% suspension in oil, 0.63 mol). Oil was removed by the addition of hexane (ca. 80 mL) followed by stirring, allowing the sodium hydride to settle and decantation of the hexane. After repeating the procedure two more times, sodium hydride was suspended in 800 mL of THF and the addition funnel charged with diethyl phosphite (84 mL, 90 g, 0.65 mol), which was added at RT at a rate to maintain vigorous hydrogen evolution (ca. 1.5 hr). After addition, the mixture was heated to reflux for 2 hrs, then cooled to RT and 3-tetrahydropyranyloxy-1-bromopropane (100 g, 0.45 mol) was added via the addition funnel in 50 mL of THF. After addition, the mixture was stirred overnight at RT, heated to reflux for 2 hr, cooled to RT, filtered to remove sodium bromide, and concentrated *in vacuo* to one-half of the original volume. Then 500 mL of ether was added and the organic layer was washed with 500 mL of 10% aqueous sodium bisulfate, then the aqueous layer extracted twice with 250 mL each of ether. The combined organic extracts were washed with 500 mL of 2N aqueous sodium hydroxide (to remove excess diethyl phosphite), then dried (magnesium sulfate), filtered and concentrated *in vacuo* to afford 125 g (100%) of the THP-ether-phosphonate (4) as a clear, colorless oil.

The crude THP-ether (4) was dissolved in 500 mL of methanol and treated with 0.1 g of d-camphorsulfonic acid, stirred overnight at RT, then concentrated *in vacuo* to afford 87 g (99%) of the corresponding alcohol.

Then, to a 2L round bottom flask, equipped with a magnetic stirrer, nitrogen inlet and 125 mL pressure-equalizing addition funnel, was added triphenylphosphine (148 g, 0.57 mol) and 600 mL of dichloromethane. After cooling to 0°, the addition funnel was charged with bromine (29 mL, 90 g, 0.57 mol), which was added dropwise over 30 min. Enough extra bromine was added dropwise *via* pipet (<1mL) until the yellow color just persisted, and then triphenylphosphine was added until the yellow color just disappeared. The 125 mL addition funnel was replaced with a 500 mL pressure-equalizing addition funnel and charged with the above alcohol in 100 mL each of dichloromethane and pyridine, and the solution added dropwise over 30 min at 0°. After 1 hr warming to RT, 50 mL of ethanol was added and the mixture concentrated *in vacuo*. Dichloromethane (300 mL) was added and the precipitated pyridinium hydrobromide removed by filtration; the filtrate was washed three times with 500 mL each of 10% aqueous sodium bisulfate. The combined aqueous washes were extracted once with 100 mL of dichloromethane and the combined organic extracts were dried (sodium sulfate), filtered and concentrated *in vacuo*. The resultant solid was stirred 10 min with 1L of ether (to precipitate triphenylphosphine oxide), filtered and concentrated *in vacuo* (residue A). The precipitate was stirred 10 min with 1L of 50/50 ether/hexane, filtered, and the filtrate combined with residue A and concentrated *in vacuo* (residue B). The precipitate was stirred 10 min with 1L of hexane, filtered, and the filtrate combined with residue B and concentrated *in vacuo* to afford a yellow oily residue. Prep 500 HPLC (gradient elution with 50/50 toluene/ethyl acetate to 100% ethyl acetate) afforded 62.9 g (54%, three steps) of the desired 2 as a yellow, clear oil, >95% pure by ^{1}H NMR (<5% triphenylphosphine oxide by ^{1}H NMR integration). IR ($CHCl_3$) cm^{-1}: 2941, 2932, 2908,1393. ^{1}H NMR ($CDCl_3$): δ 4.12 (m, 4H), 3.49 (t, J = 6 Hz, 2H), 2.16 (m, 2H), 1.91, (m, 2H), 1.35 (t, J = 7 Hz, 6H). ^{13}C NMR ($CDCl_3$): δ 61.7 (d, J = 6.8 Hz), 33.6 (d, J = 18.9 Hz), 26.0 (d, J = 3.8 Hz), 24.5 (d, J = 142.7 Hz), 16.5 (d, J = 6.0 Hz). MS: Calcd for $C_7H_{16}BrO_3P$: 258.0012; found: 258.0028.

Triethyl 5-Phosphono-2-(N-diphenylketimino)pentanoate (6).-To a 2L 3-neck round bottom flask, equipped with a magnetic stirrer, a thermometer, a 250 mL pressure equalizing addition funnel and a nitrogen inlet, was added sodium bis(trimethylsilyl)amide (350 mL of a 1.0 M solution in THF, 0.35 mol) along with 250 mL of additional THF. After cooling to -72° (internal temperature) the addition funnel was charged with ethyl N-diphenylketiminoglycinate (97 g, 0.37 mol) in 200 mL of THF and this solution was added dropwise while the internal temperature was maintained below -65°; the addition took about 30 min. To the solution which

had been stirred for an additional 30 min at -78° (external temperature) was then rapidly added at -78° 2 (62.9 g, 0.24 mol) in 150 mL of THF; the cooling bath was removed immediately and the mixture allowed to warm up to 0° for 4 hrs. The reaction mixture was partitioned between 500 mL of ether and 500 mL of 10% aqueous sodium bisulfate. The organic layer was separated from the aqueous layer and extracted twice with 500 mL each of 10% aqueous sodium bisulfate then dried (magnesium sulfate), filtered and concentrated *in vacuo*. Prep 500 HPLC of the residue (gradient elution with 50/50 toluene/ethyl acetate to 100% ethyl acetate) afforded 93 g (87%) of the desired compound 6 as a clear, light yellow oil.

IR ($CHCl_3$) cm^{-1}: 3000, 1735. ^1H NMR ($CDCl_3$): δ 7.1-7.7 (m, 10H), 4.17 (m, 2H), 4.06 (m, 4H), 2.02, (m, 2H), 1.45-1.75 (m, 4H), 1.31 (t, J = 6 Hz, 6H), 1.25 (t, J = 7.5 Hz, 3H). ^{13}C NMR ($CDCl_3$): δ 172.0, 139.5, 136.4, 130.4, 128.8, 128.7, 128.6, 128.1, 127.9, 64.9, 61.5 (d, J = 6.8 Hz), 60.9, 34.4 (d, J = 17.4 Hz), 25.6 (d, J = 141.1 Hz), 19.2 (d, J = 5.3 Hz), 16.5 (d, J = 5.3 Hz), 14.2. Anal. Calcd for $C_{24}H_{32}NO_5P$: C, 64.71; H, 7.24; N, 3.14. Found: C, 64.76; H, 7.09; N, 3.35.

D,L-2-Amino-5-phophonopentanoic acid (1).-To a 1L round bottom flask, equipped with a reflux condenser and magnetic stirrer, was added 6 (92.8 g, 0.21 mol) and 250 mL of 6N aqueous hydrochloric acid, and the mixture was heated at reflux overnight. After cooling to RT, the aqueous material was extracted twice with 200 mL each of ether, once with 200 mL of dichloromethane, once again with 200 mL of ether, then concentrated *in vacuo*. The resultant hard foam was broken up with a spatula under ether, filtered, washed with ether and dried *in vacuo* at 60° overnight to afford 42.7 g of D,L-1•HCl. The residue left in the flask was dissolved in water, transferred to a 250 mL round bottom flask and concentrated *in vacuo*. An additional 5 g of material was obtained after grinding the foam and removal with ether, then drying the solid *in vacuo* at 60° overnight; the total yield was 47.7 g (97%) of D,L-1•HCl.

IR (KBr) cm^{-1}: 2250-3600, 1740. ^1H NMR (D_2O): δ 4.07 (t, J =6 Hz, 1H), 1.5-2.2 (m, 6H). ^{13}C NMR (D_2O): δ 172.8, 53.5, 31.4 (d, J = 17.4 Hz), 26.8 (d, J = 135.9 Hz), 19.2 (d, J = 3.8 Hz). Anal. Calcd for $C_5H_{13}ClNO_5P$: C, 25.71; H, 5.61; N, 6.00. Found: C, 26.01; H, 5.91; N, 5.84.

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