An Efficient Synthesis of (±)-3-Amino-2-(4-chlorophenyl)-propylphosphonic Acid (PHACLOFEN)

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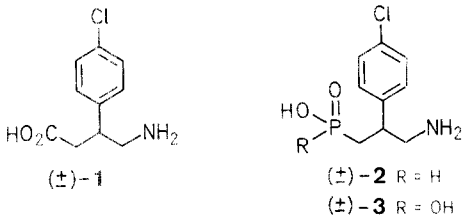
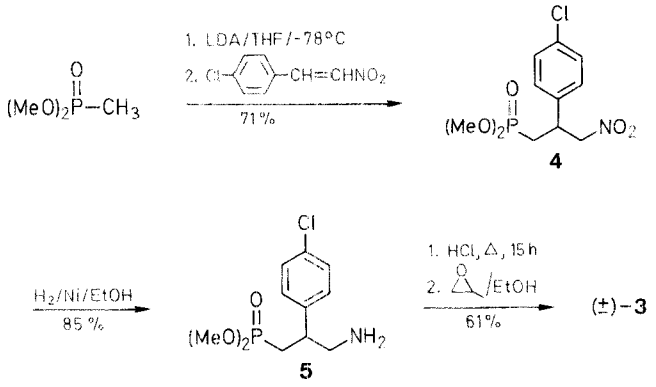
A three step, highly efficient synthesis of the GABA-B antagonist, Phaclofen, is described, which features a Michael addition of a phosphonate to a β-nitrostyrene.

The bioisosteric replacement of a carboxylic acid by phosphorus remains an interesting approach in the search for novel, biologically active compounds.[1] In recent years, we have developed methods for the synthesis of α,β- and γ-aminophosphonous acids,[2,3] as analogues of the corresponding carboxylic acids and found a significant number to exhibit biological activity.

In our studies on γ-aminophosphonous acids,[3] we synthesized, amongst others the phosphonous analogue **2** of the market product Lioresal (**1**) and found the two compounds to have similar biological profiles. The corresponding phosphonic acid analogue **3** was likewise synthesised.



In view of more recent interest in this analogue Phaclofen (**3**) as a GABA-B antagonist,[4,5] we are prompted to report our synthesis of **3** as the published procedure[6] involves a seven stage process with a low overall yield. The first step involves a Michael addition of the phosphonate carbanion from dimethyl methylphosphonate to 4-chloro-β-nitrostyrene. Normal addition of the olefin to the preformed carbanion results in an instantaneous deep-red colouration and moderate yields (≈ 35%). However, by inverse addition of the anion to 1.5 equivalents of the nitro olefin, this yield is improved (> 70%).



Catalytic reduction of the nitro group in **4** occurs readily without loss of the aromatic chlorine; the resulting amine **5** is hydrolysed without purification to **3**, initially as the hydrochloride salt. Treatment with propylene oxide in ethanol then gives racemic Phaclofen as a white powder.

This simple three step process, using readily available starting materials, provides **3** in an overall yield of 37%.

Melting points were determined on a Büchi melting-point apparatus and are uncorrected. ^{1}H-NMR spectra were obtained on a Jeol FX 90 spectrometer operating at 89.55 MHz. Chemical shifts are relative to either TMS or 3-(trimethylsilyl)propionic acid sodium salt references. ^{31}P-NMR spectra were obtained on a Jeol FX 90 spectrometer operating at 36.2 MHz with 85% H_3PO_4 as external reference. Column chromatography was performed on Merck Silica Kieselgel 60 on 70–230 mesh. THF was dried by distillation, distilled from sodium/benzophenone. BuLi was obtained from Fluka AG.

Dimethyl 2-(4-Chlorophenyl)-3-nitropropylphosphonate (4):
A solution of LDA is prepared at 0 °C from BuLi (30 mL, 48.3 mmol) and diisopropylamine (4.9 g, 48.3 mmol) in THF (100 mL). This solution is cooled to −78 °C and dimethyl methylphosphonate (5.0 g, 40.3 mmol) in THF (50 mL) is added via syringe under Argon. This mixture is stirred for 1 h at −78 °C before being added to a solution of 4-chloro-β-nitrostyrene (11.1 g, 60.4 mmol) in THF (100 mL) at −78 °C over a period of 20 min. The mixture is allowed to warm to room temperature, aq. NH_4Cl (50 mL) added and the whole extracted with ether (3 × 100 mL). Drying ($MgSO_4$) and removal of solvent give a residue which is chromatographed on silica using EtOAc as eluent to give **4** as an oil; yield: 8.74 g (71%).

$C_{11}H_{15}ClNO_5P$	calc.	C 42.94	H 4.91	N 4.55	P 10.07
(307.7)	found	43.11	4.99	4.19	9.83

^{31}P-NMR ($CDCl_3$): δ = +29.3.

^{1}H-NMR ($CDCl_3$): δ = 2.2 (2H, dd, J = 1.8, 7.2 Hz); 3.7 (6H, dd, J = 10.8 Hz); 3.9 (m, 1H); 4.8 (m, 2H); 7.3 (m, 4H).

Dimethyl 3-Amino-2-(4-chlorophenyl)propylphosphonate (5):
Phosphonate **4** (3.6 g, 11.7 mmol) is dissolved in a solution of 8% ammonia in EtOH (28.6 g). To this is added Raney Nickel (3 mL) in EtOH (15 mL), and the resulting mixture is hydrogenated to a pressure of 1 bar until hydrogen uptake ceases. ^{31}P-NMR analysis of the reaction mixture indicates no starting material, but a signal for **5** at δ = +32.9 (EtOH). The mixture is filtered and the solvent removed to give **5**; yield: 2.8 g (85%). Attempted purification by distillation results in decomposition. The crude product is used directly in the next stage.

(±)-3-Amino-2-(4-chlorophenyl)propylphosphonic Acid ±-(3):
A mixture of **5** (5.4 g, 18.6 mmol) in 36% aq. HCl (50 mL) is refluxed for a period of 15 h. The mixture allowed to cool, and co-evaporated several times with water. The crude residue is dissolved in water (25 mL), washed with ether (25 mL) and the aqueous extract evaporated to give a sticky solid. This is dissolved in EtOH (50 mL), propylene oxide (~ 2 mL) added and the mixture stirred at room temperature. After a short time a precipitate forms. Stirring is continued until the solid is free of halogen, whereupon the solid is filtered and dried to give **3**; yield: 2.8 g (61%); mp 275–280 °C.

$C_9H_{13}ClNO_3P$	calc.	C 43.30	H 5.52	N 5.61	P 12.41
(249.7)	found	42.97	5.16	5.48	12.04

^{31}P-NMR (D_2O): δ = +20.9.

^{1}H-NMR (D_2O): δ = 2.5 (2H, dd, J = 18, 6.5 Hz); 3.8 (m, 3H); 7.8 (m, 4H).

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