Tetrahedron Letters Vol.30,No.39,pp 5193-5196,1989 0040-4039/89 $3.00 + .00
Printed in Great Britain Pergamon Press plc

NEW PREPARATIONS OF THE N-METHYL-D-ASPARTATE RECEPTOR ANTAGONIST, 4-(3-PHOSPHONOPROPYL)-2-PIPERAZINECARBOXYLIC ACID (CPP)

Christopher F. Bigge,* Sheryl J. Hays, Perry M. Novak, James T. Drummond,
Graham Johnson, and Thomas P. Bobovski
Parke-Davis Pharmaceutical Research Division, Warner-Lambert Company
2800 Plymouth Road, Ann Arbor, Michigan 48105

Abstract. Two new methods to ensure selective alkylation of the N^4 of 2-piperazinecarboxylic acid to give 4-(3-phosphonopropyl)-2-piperazinecarboxylic acid (**CPP, 1**) are reported. CPP can be conveniently prepared using a copper chelate to selectively protect the N^1 position during alkylation. A second procedure uses methyl-4-BOC-1-CBZ-2-piperazinecarboxylate **5** as a versatile intermediate, which was further elaborated to CPP.

4-(3-Phosphonopropyl)-2-piperazinecarboxylic acid (CPP) is a high affinity competitive antagonist of the N-methyl-D-aspartate (NMDA) subtype of glutamate receptor.[1,2] [^{3}H]-CPP has become the ligand of choice to evaluate NMDA receptors in vitro,[3,4] and has been utilized to quantify the distribution of NMDA receptors in the rat brain.[5] CPP also has been shown to reduce ischemia-induced hippocampal brain damage in a gerbil ischemia model.[6]

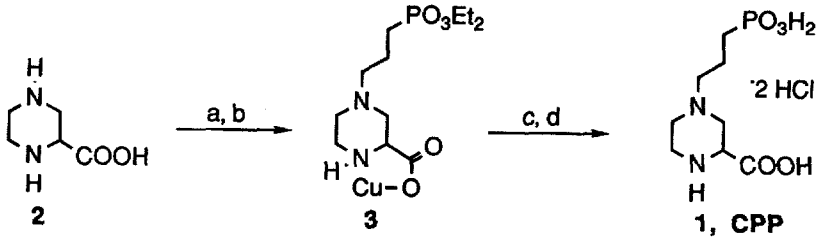
The original synthesis of CPP involved, as the key step, a heterogenous addition-elimination coupling between 2-piperazinecarboxylic acid and diethyl 3-bromoprop-2-enyl-1-phosphonate in aqueous sodium hydroxide solution.[7] In our hands this procedure was ineffective, and we set out to develop a useful synthesis whereby we could ensure selective alkylation of N^4 of the piperazine ring. Herein we report two methods which successfully give CPP.

First, we chose copper chelation chemistry to selectively protect the α-amino acid functionality and free N^4 for selective alkylation. Later, to allow greater versatility, we intended to prepare an intermediate that could be manipulated in organic solvents, be available to unambiguous alkylation at either or both nitrogen atoms, and permit convenient scale-up. Synthesis of methyl 4-BOC-1-CBZ-2-piperazinecarboxylate **5** provided a versatile intermediate for the synthesis of CPP. Intermediate **5** and its partially deprotected derivatives, may also find broad utility in the synthesis of novel peptides.

Copper chelation was chosen to protect the α-amino acid moiety and allow the selective alkylation of N^4 of the piperazine ring system, Scheme 1. In a typical experiment, a solution of 2-piperazinecarboxylic acid[8] **2** in water was treated with excess $CuCO_3 \cdot Cu(OH)_2$ and heated to reflux for 1 hour. The undissolved copper salts were removed by filtration after cooling, and the aqueous blue solution was mixed with the diethyl 3-iodopropylphosphonate[11] (1.8 eq) and heated to 70°C for 18 hours. The solution was cooled, extracted with methylene chloride, and hydrogen sulfide was bubbled through the water layer. The precipitated copper sulfide was filtered off, and the water was concentrated and applied to

a Dowex 50W ion exchange column. Inorganic salts were eluted off the column with 0.5 N HCl. The purified diethyl phosphonate adduct was eluted from the column with 0.8 N HCl as a yellow oil. The ester was hydrolyzed in refluxing 6 N HCl for 24 h to give CPP **1** in a 22% overall yield from **2**. Purification was accomplished on a Dowex 50W ion exchange column by elution with 1 N HCl containing 10% ethanol.

Scheme 1.



a. $CuCO_3 \cdot Cu(OH)_2$; b. $ICH_2CH_2CH_2PO_3Et_2$; c. H_2S; d. 6 N HCl, reflux.

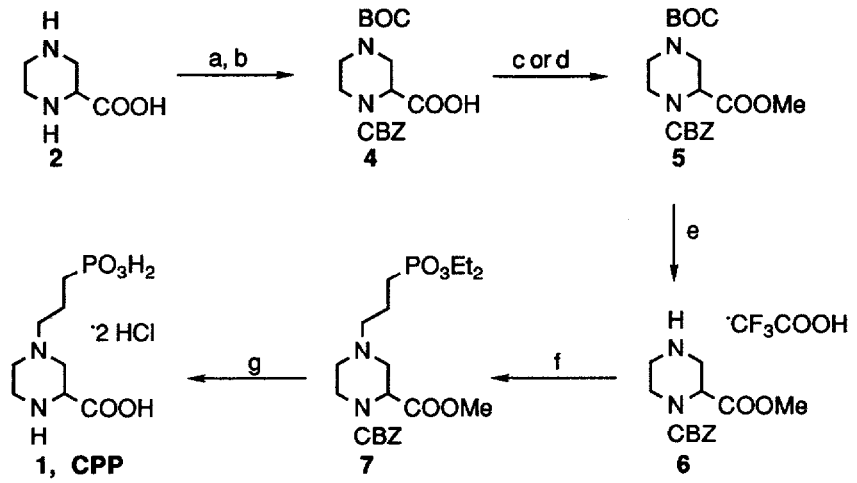
An alternative approach was taken to allow the synthesis of **1** in organic solvents. The fully protected **5** was prepared from 2-piperazinecarboxylic acid as shown in Scheme 2. Using a sequential one-pot protection procedure similar to that used to protect lysine,[10] a solution of 2-piperazinecarboxylic acid (24.1 g, 0.185 mol) in 1:1 dioxane-water (1.2 L) was maintained at pH 11 with 50% aqueous sodium hydroxide during the addition of a solution of 2-(±-butyloxycarbonyloxyimino)-2-phenylacetonitrile (BOC-ON,[11] 51 g, 0.21 mol) in dioxane (0.3 L). After 3 h, the reaction mixture was cooled in an ice bath and the pH was adjusted to pH 9.5 with 6 N HCl. Benzylchloroformate was added dropwise to the cold solution while maintaining the pH with 50% aqueous sodium hydroxide. The reaction was warmed to room temperature and stirred for 24 h. The solution was washed with diethyl ether (4 x 250 mL), the aqueous layer was acidified to pH 2 and extracted with ethyl acetate (4 x 250 mL).[12] The organic layer was dried over magnesium sulfate, filtered and evaporated to give a pale yellow oil.[13]

The methyl ester **5** was obtained by treatment of a tetrahydrofuran solution of the crude acid with excess diazomethane. Alternatively, the methyl ester could be obtained on large scale by treatment of a saturated sodium bicarbonate solution of the intermediate carboxylic acid **4** with a methylene chloride solution of methyl iodide and Adogen 464,[11,14] or preferably by refluxing an acetone solution of the carboxylic acid, dimethylsulfate and potassium carbonate.[15] The N^4-BOC group was removed quantitatively by treatment of a methylene chloride solution of **5** with trifluoroacetic acid to give the trifluoroacetate salt **6**, in a 53% yield from **2**. The N^4 deprotected intermediate **6** (10 g, 25.5 mmol) in ethanol (60 mL) was alkylated with diethyl 3-bromopropylphosphonate (7.9 g, 30.6 mmol). After workup, the CPP precursor **7** was purified on silica gel (ethyl acetate as eluant) to give a colorless oil (10.53 g). Hydrolysis of **7** in refluxing 6 N HCl (250 mL) followed by

evaporation of the water in vacuo afforded a white solid. In order to remove excess HCl, the solid was triturated with acetone and evaporated, then water was added and evaporated two more times, and dried in vacuo to give analytical CPP•2 HCl **1** in 81% yield from **6**.

Using the versatile synthon **5**, we have routinely synthesized CPP and other related NMDA antagonists on a multigram scale. Since **5** can be selectively deprotected at any of its reactive functional groups, it represents an attractive intermediate for the synthesis of novel CPP related compounds and allows the elaboration of structure activity relationships in this developing field.

Scheme 2.



a. BOC-ON,[12] pH 11, 1:1 dioxane-H_2O; b. CBZCl, pH 9.5; c. CH_2N_2, THF; d. CH_3I, $NaHCO_3$, Adogen 464[12], CH_2Cl_2; or $(CH_3O)_2SO_2$, K_2CO_3, acetone, reflux; e. CF_3COOH, CH_2Cl_2; f. $BrCH_2CH_2CH_2PO_3Et_2$, Na_2CO_3, EtOH, 12 h, reflux; g. 6 N HCl, reflux.

References and Footnotes

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8. 2-Pyrazinecarboxylic acid was reduced quantitatively in aqueous sodium hydroxide solution (1 eq) with 20% Pd/C as catalyst under a hydrogen atmosphere (50 psi). After reduction to sodium 2-piperazinecarboxylate, the filtered solution may be used directly in the protection sequence to **5**, or can be isolated by conversion to the dihydrochloride salt and crystallized from water.
9. Diethyl 3-iodopropylphosphonate is the Finkelstein product of diethyl 3-bromopropylphosphonate. The synthesis of diethyl 3-bromopropylphosphonate is described in T. Kamiya, M. Hashimoto, K. Hemmi, H. Takeno U.S. Pat. 4,206,156.
10. E. P. Heimer, C.-T. Wang, T. J. Lambros Org. Prep. and Proc. Int. 1983, 15, 379-85.
11. BOC-ON and Adogen 464 are registered trademarks of the Aldrich Chemical Company, Inc.
12. Extraction with toluene instead of ethyl acetate provided a purer intermediate **4**, at the expense of slightly lower overall yield.
13. The intermediate **4** was deprotected with trifluoroacetic acid, alkylated with diethyl 3-bromophosphonate, and hydrolyzed to give CPP. However, the alkylation produced a lower yield than the methyl ester derivative **5**.
14. V. Bocchi, G. Casnati, A. Dossena, R. Marchelli Synthesis 1979, 957-61; A solution of **4** (3 g) in saturated sodium bicarbonate solution was treated with a methylene chloride solution (15 mL) of Adogen 464 and methyl iodide. After stirring for 24 h, the reaction mixture was extracted with methylene chloride and the organic layer was washed with water. After drying ($MgSO_4$), 1.8 g of **5** was obtained by filtration of crystals from the methylene chloride solution.
15. J. Grundy Tetrahedron Letters 1972, 9, 757-60; A solution of **4** (251 g, 0.69 mol) in acetone (1 L) was treated with potassium carbonate (124 g, 0.89 mol) and dimethylsulfate (78 mL, 0.83 mol) and was refluxed for 6 h. The reaction mixture was filtered, concentrated and the residue dissolved in diethyl ether. The ether solution was washed with saturated sodium bicarbonate solution and water. After drying, 221 g of **5** was obtained (85%).
16. Selected physical data for intermediates and CPP.

1 4-(3-Phosphonopropyl)-2-piperazinecarboxylic acid dihydrochloride. mp dec. > 195°C.

4 1,2,4-Piperazinetricarboxylic acid, 4-(1,1-dimethylethyl) 1-(phenylmethyl) ester. ^{1}H-NMR ($CDCl_3$) - 1H, s, 9.15 ppm; 5 H, s, 7.25; 2H, s, 5.10; 9 H, s, 1.40.

5 4-(1,1-Dimethylethyl) 2-methyl 1-phenylmethyl 1,2,4-piperazinetricarboxylate. ^{1}H-NMR ($CDCl_3$) - 5H, s, 7.35 ppm; 2H, s, 5.17; 3H, d, 3.73; 9H, s, 1.49; mp 85-86°C.

6 2-Methyl 1-phenylmethyl 1,2-piperazinedicarboxylate, trifluoroacetate (1:1)(salt). ^{1}H-NMR ($CDCl_3$) - 5H, s, 7.47 ppm; 2H, s, 5.27; 3H, s, 3.83; mp 129-130°C.

7 2-Methyl 1-phenylmethyl 4-[3-(diethoxyphosphinyl)propyl]-1,2-piperazine dicarboxylate. ^{1}H-NMR ($CDCl_3$) - 5H, s, 7.25 ppm; 2H, s, 5.05; 3H, s, 3.65; 6H, t, 1.25.

(Received in USA 22 March 1989)