Bioorganic & Medicinal Chemistry Letters, Vol.1, No.9, pp. 441-444, 1991
Printed in Great Britain

0960-894X/91 $3.00 + .00

SYNTHESIS OF 3(S)-PHOSPHONOACETYL-2(R)-PIPERIDINECARBOXYLIC ACID, A CONFORMATIONALLY-RESTRICTED GLUTAMATE ANTAGONIST

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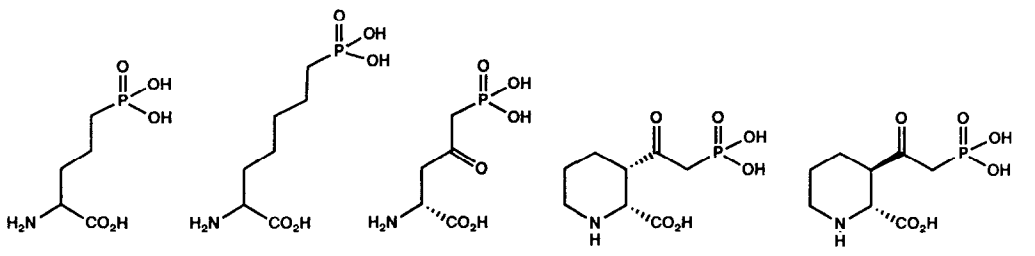
(*Received* 10 *June* 1991)

Abstract: *The synthesis of the conformationally-restricted β-ketophosphonic acid, 3(S)-phosphonoacetyl-2(R)-piperidinecarboxylic acid (4) is described. This compound is a competitive, glutamate antagonist (IC_{50} = 40 nM vs [^{3}H]CPP) of the NMDA receptor complex.*

Modulation of the excitatory amino acid receptors may have important therapeutic potential for central nervous system disorders such as epilepsy, anxiety, migraine, and neurodegeneration associated with stroke, trauma, and Huntington's chorea[1]. These receptor complexes are activated by glutamic and aspartic acids and are pharmacologically characterized by their affinities for N-methyl-D-aspartic acid (NMDA), kainic acid, α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA) and trans-1-aminocyclopentyl-1,3-dicarboxylic acid (ACPD)[2,3]. The NMDA receptor has been the most extensively studied and found to have multiple regulatory sites; one of these, the glutamic acid binding site, is potently inhibited in vitro by phosphono substituted R-amino acids (e.g., AP5 (1) and AP7 (2)). We have found that addition of a β-keto group, such as found in (R)-4-oxo-5-phosphononorvaline (3), not only increased receptor binding affinity, but also led to good in vivo activity in a number of animal disease models[4].



1 2 3 4 5

To further explore the utility of β-ketophosphonates as competitive NMDA antagonists, we have designed a number of conformationally restricted β-ketophosphonates using a heuristic computer-aided molecular modeling approach. Using a pharmacophore[5] which was developed by searching for common, low energy conformations of compounds such as 1, 2, and 3, it became apparent that conformationally-restricted piperidine analogues of 3 were desirable synthetic targets. While both the six-membered ring isomers 4 (cis) and 5 (trans) fit the pharmacophore in gross terms, the cis isomer (4) could be aligned in order to correctly orientate the phosphonic acid relative to the carbon backbone of the molecule (Fig.).

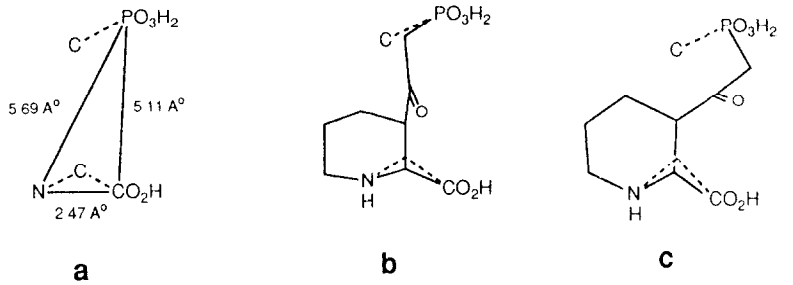
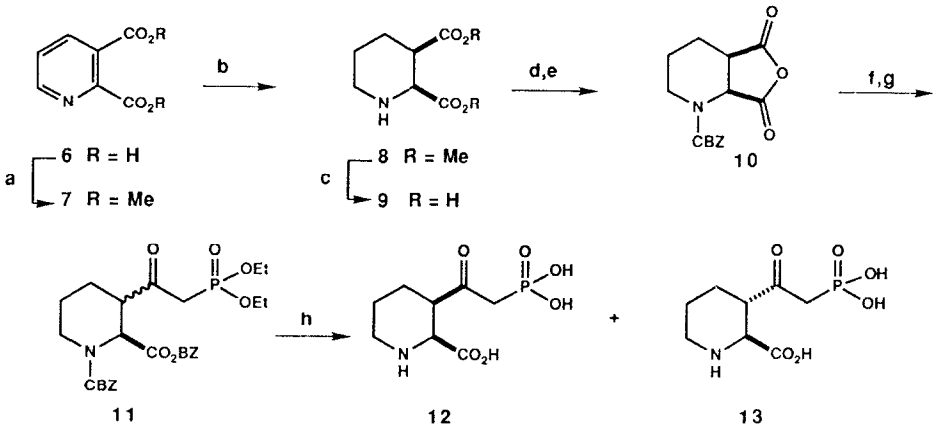


Figure. (a) Pharmacophore for competitive, phosphonoamino acid NMDA antagonists[5]. (b) Superimposition of the *cis* conformationly-restricted analogue **4**. (c) Superimposition of the *trans* analogue **5**.

Two syntheses of 4 have been developed. In the first synthesis (Scheme 1), the stereochemical centers were fixed in the cis form by proceeding via the cyclic anhydride 10. Thus, pyridine-2,3-dicarboxylic

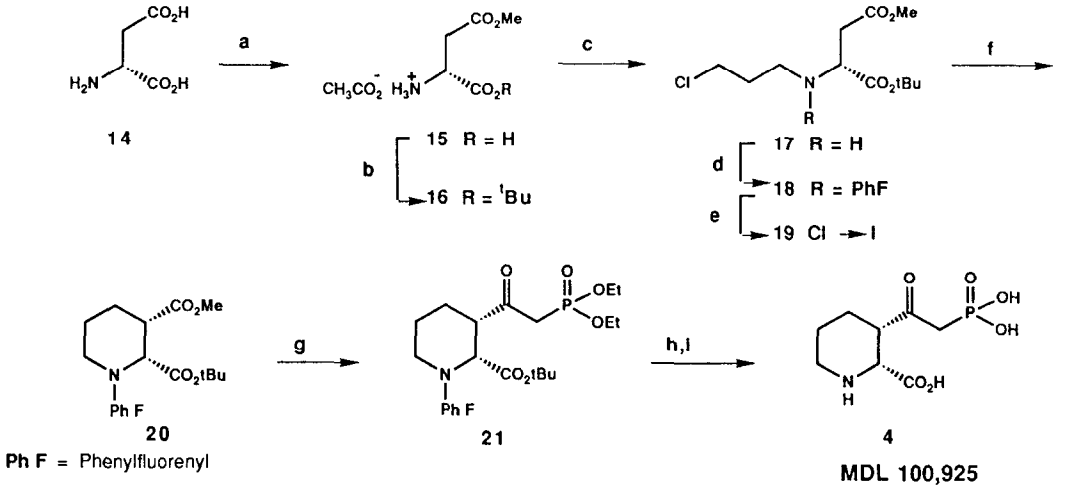


Scheme 1. a) MeOH, HCl, 83% b) $Pd(OH)_2$, H_2, 96%. c) 1M HCl, 52% d) CBZCl, 98% e) $(CH_3CO)_2O$, 100% f) $LiCH_2PO(OEt)_2$ g) $C_6H_5CH_2Br$, $HN(C_6H_{11})_2$, 17% from 10 h) 6M HCl, 91%.

acid (6) was esterified to the dimethyl ester (7), then catalytically reduced (H_2, 50 psi, $Pd(OH)_2$, MeOH) to give predominantly the cis diester (8)[7] in 96% yield. Mild acid hydrolysis with 1 M aq. hydrochloric acid, protection of the amine (CBZ) followed by treatment with acetic anhydride formed the critical intermediate (10). Treatment of the anhydride (10) with lithium methyl diethylphosphonate[8] at -78°C gave the β-ketophosphonate (11)[8], isolated as the benzyl ester. Analysis of 11 by TLC (silica, EtOH, hexane, diethyl ether [1:7:32]), however, showed that epimerization

had occurred yielding approximately a 2:1 mixture of the cis to trans isomers. Deprotection of 11 was accomplished by refluxing 6 M aq. hydrochloric acid for 24 h and yielded approximately a 1:1 ratio of the cis (12) and trans (13) isomers. Prolonged vigorous acid or base treatment resulted in an equilibrium ratio of 1:10, respectively. Separation of isomers (12) and (13) was achieved by high performance ion exchange chromatography on a 10 μm SAX analytical column.

When these racemic compounds were assayed for binding affinity at the NMDA site (using [^{3}H]-CPP as the radioligand)[10], the cis isomer (12, IC_{50} = 68+7 nM) was found to be more potent then the trans (13, IC_{50} = 533+38 nM) in accord with the modeling predictions. In order to circumvent the epimerization problem in the synthesis of 4, and to afford the pure 2R isomer, a conceptually different approach was developed using R-aspartic acid (14) as a chiral template according to chemistry developed by Rapoport[11] in his synthesis of vindoline. This approach (Scheme 2) offered the dual advantages that the R stereochemistry was set at the beginning of the synthesis from a readily available starting



Scheme2. a) MeOH, $SOCl_2$, 62%. b) $CH_3CO_2C(CH_3)_3$, $HClO_4$, 76%. c) $Br(CH_2)_3Cl$, $NaHCO_3$; 55%. d) PhFBr, $Pb(NO_3)_2$, $NEt(iPr)_2$, 85%. e) NaI; 100%. f) LDA, 2,6-diisopropylphenol, 65 % g) $LiCH_2PO(OCH_2CH_3)_2$, 66% h) TFA, TMSI, 52% i) propylene oxide, MeOH.

material and that use of the phenylfluorenyl[12] protecting group should minimize racemization problems.

The α- and β-carboxylic acid groups of (R)-aspartic acid (14) were selectively functionalized by a two step procedure involving methylation of the distal group by treatment with thionyl chloride in methanol (15) at -5°C followed by transesterification with tert-butyl acetate and perchloric acid (16). N-Alkylation with chlorobromopropane afforded (17, ca. 55% yield). Protection of (17) was best accomplished by dropwise addition of diisopropylethylamine to a mixture of 17, phenylfluorenyl bromide and lead nitrate in acetonitrile/chloroform to provide 18 in 85% yield. This compound was converted in quantitative yield to the crystalline iodide 19 employing Finkelstein conditions. Cyclization of 19 to

the piperidine 20 (62%) required warming of the enolate of 19, formed at -78°C with LDA, to -35°C for several hours. Careful conditions were needed to quench the resulting piperidinyl enolate in order to avoid significant amounts of the trans isomer as well as the desired cis. For example, addition of acetic acid led to a large amount of the trans isomer. However, when bulky 2,6-diisopropylphenol was chosen as the proton source and added to the enolate (cooled to -75°C), the cis isomer (20) was obtained exclusively in 65% yield.

Treatment of 20 with 3.2 equivalents of lithium methyl diethylphosphonate[8] at -78°C chemoselectively, and with no apparent epimerization, afforded the fully-protected chiral β-ketophosphonate (21) in 66% yield as an oil. Deprotection was readily accomplished in two steps by treatment with aqueous trifluoroacetic acid to remove the phenylfluorenyl group followed by trimethylsilyliodide in dichloromethane/acetonitrile. The resulting amino acid 4 (MDL 100,925), obtained in 52% yield, was purified by propylene oxide precipitation of the hydrochloride salt from methanol and recovered as a colorless powder[13].

This pure enantiomer (4) proved to be a potent NMDA glutamate site antagonist with an IC_{50} = 40±4 nM. Further studies which more fully explore the structure-activity relationships of these β-ketophosphonates will be reported in due course.

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