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# COMPETITIVE NMDA ANTAGONISTS THAT BASE THEIR ACTIVITY ON A UNIQUE CONFORMATIONAL EFFECT

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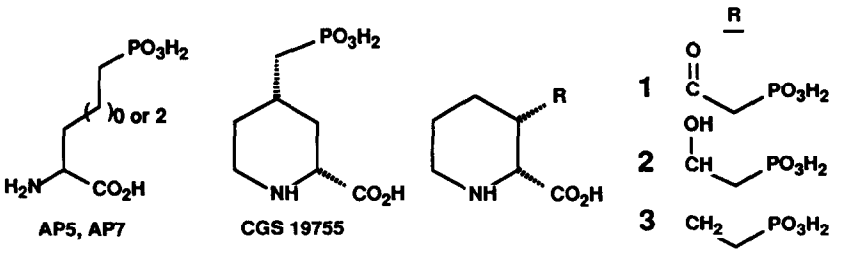
**Abstract**: The synthesis of two NMDA antagonists, *cis* -3-(1-oxi-2-phosphonoethyl)-2-piperidinecarboxylic acid and *cis* -3-(1-hydroxy-2-phosphonoethyl)-2-piperidinecarboxylic acid (**1** and **2**), is reported. The enantiomers of **1** were also prepared. NMR analysis showed that **1** prefers a $3_{ax}$, $2_{eq}$ chair conformation due to internal hydrogen bonding.

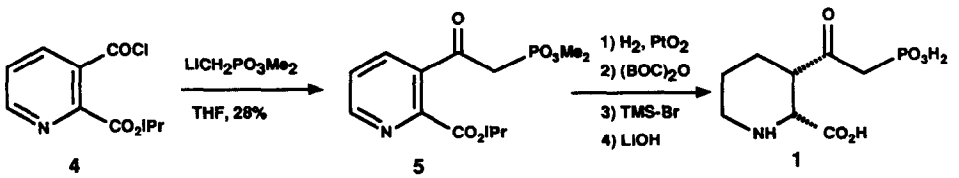
The most potent competitive antagonists at the NMDA subtype of excitatory amino acid receptors belong to the ω-phosphono substituted α-amino acid type. With a starting point in the prototypical AP5 and AP7,[1] whose R-forms are more active, the receptor affinity has been improved at least a twenty fold with compounds like CGS 19755.[2] The pharmacological activity of this class of compounds is of interest in potential therapy of epilepsy, neurodegeneration associated with stroke, and in pain treatment.[3]




While exploring the effects of structural modifications of antagonists based on the piperidine nucleus we discovered, and report here, that the 3-substituted compounds **1** and **2** are among the better antagonists found so far. We have also found that the receptor affinity most likely stems from a unique conformational effect caused by an internal hydrogen bond, that differentiates **1** and **2** from their less active[4] non-oxygenated congener **3**.

The synthesis of **1**, Scheme 1, started with a reaction of the known[4] acid chloride **4** with lithiated dimethyl methanephosphonate which produced moderate yields of the β-ketophosphonate **5**. Hydrogenation over Pt and BOC protection gave an intermediate that could be chromatographically purified. However, after facile removal of the phosphonate esters and the BOC group with bromotrimethylsilane the subsequent basic hydrolysis always caused some *cis-trans* isomerization. By careful ion-exchange chromatography on a $H^+$ -saturated

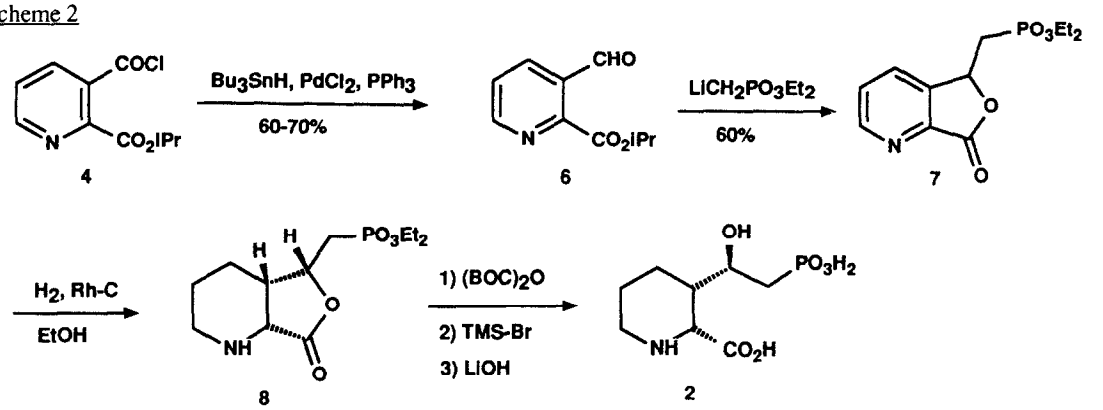
Scheme 1



column it was possible to separate the isomers (*trans* isomer eluting first) and to obtain **1** in a 96 % pure form. Subsequent to completion of our work the asymmetric synthesis of **1** was published by Whitten et al.[5]

Alcohol **2** was obtained via the sequence shown in Scheme 2. Pd-catalyzed tin hydride reduction[13] of acid chloride **4** gave the crystalline aldehyde **6** in 60-70 % yields. Addition of diethyl lithium methanephosphonate to a THF solution of this aldehyde at -70°C and lactonization during 2 h resulted in moderate to good yields of

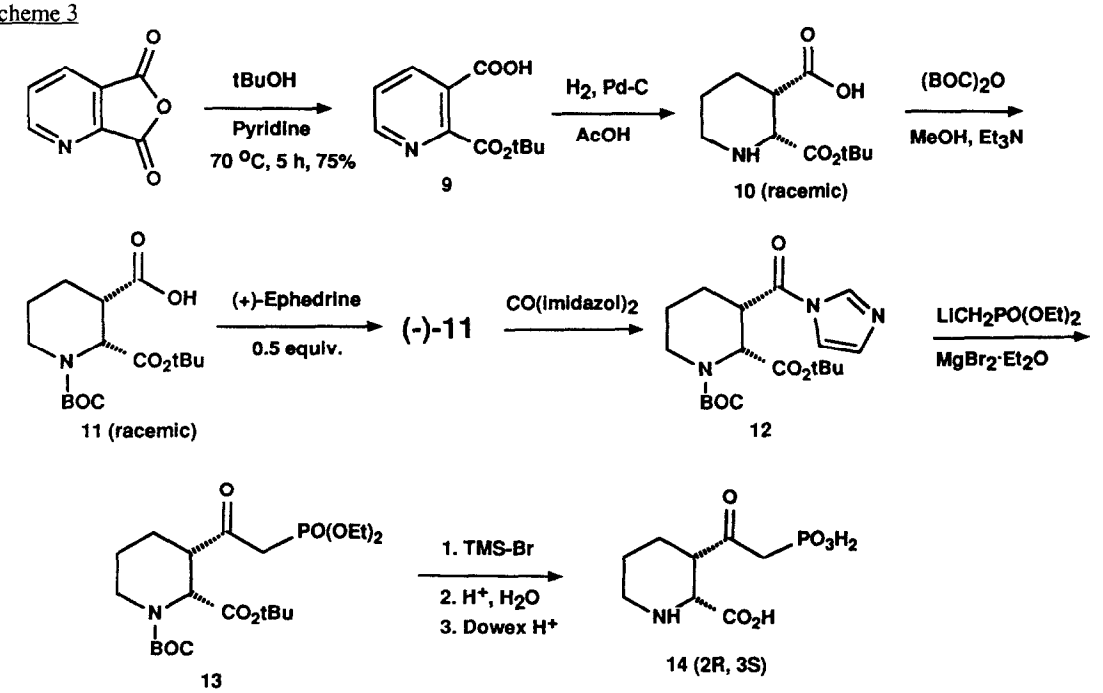
Scheme 2




the crystalline lactone **7** which was taken through the remaining few steps to give **2** (45% from **7**). That compound **2** has the relative stereochemistry shown appears likely by considering the most accessible approach of hydrogen to the pyridine-lactone **7**. This was proved by $^1$H-NMR analysis of the intermediate lactone **8**. Measured coupling constants match closely and only the calculated values of the $2_{ax}$, $3_{eq}$ *endo* isomer of **8**.[6]

The racemic NMDA antagonists **1** and **2** exhibited $K_i$ values of 69 and 106 nM, respectively, in inhibition of $^3$H-CGS 19755 binding in a rat cortex preparation.[7] In the same assay CGS 19755 had a $K_i$ of 40 nM.

Scheme 3

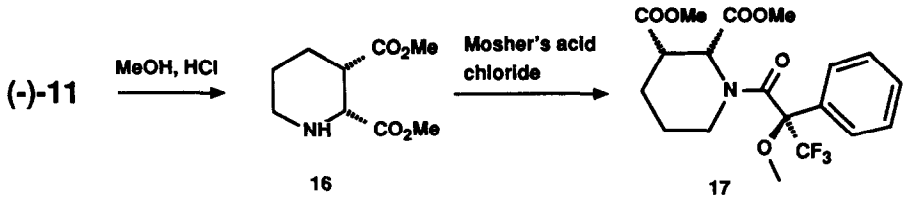


Since the antagonist **1** was of interest for development as a potential new drug various ways of synthesizing the enantiomers were considered. An asymmetric synthesis involving the chemistry described above was not judged feasible. Instead we developed the following synthesis (Scheme 3) in which classical resolution of an intermediate carboxylic acid was applied.

The t-butyl ester **9** was prepared from quinolinic acid anhydride by heating with t-butyl alcohol in a pyridine solution. Hydrogenation over palladium gave the amino acid **10** in almost quantitative yield. A few attempts to resolve **10** by using camphorsulfonic acids were unsuccessful and efforts were concentrated on the BOC-ylated derivative **11**. This could be resolved by forming diastereomeric salts with 0.5 equivalents of ephedrine and recrystallize from ethyl acetate. A single recrystallization gave an enantiomer of **11** that had 95 % ee as evidenced by conversion to the dimethyl ester **16** (Scheme 4) and its Mosher derivative **17** that was analyzed by $^1$H-NMR and capillary GLC.

Later on it was found that the amino acid **10** could be resolved via diastereomeric salts with the phosphate diester of 2,2'-dihydroxy-1,1'-binaphtyl.

Scheme 4

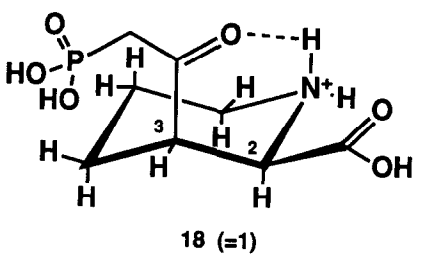



The (-) and (+) enantiomers of **11** were tentatively assigned the 2*R* and 2*S* configurations, respectively, by reference to hydrolysis to the known enantiomers of *cis*-2,3-piperidinedicarboxylic acid which have been assigned tentative configurations based on biological activity.[8]

Separate conversions of the enantiomers to the final products went via formation of the isolated imidazole derivatives **12** and reactions with a lithium methanephosphonate in the presence of a magnesium salt to prevent epimerization. This coupling did not proceed well and never reached above 30 % yield. Deprotection with TMS-Br and aqeous acid, to remove the t-butyl ester, gave the enantiomers **14** and **15** (assumed D and L isomers of **1**).

The enantiomer **14**, that was tentatively assigned the 2*R* configuration, proved to be the better NMDA antagonist compared to **15**, $K_i$ values 64 nM and > 1 µM, respectively. This represents a lower limit of difference in activity since the enantiomeric purities of **14** and **15** could not be determined. The result is in agreement with that of Whitten et al., who prepared **14** from D-aspartic acid,[5] and also proves our assignments of absolute configurations.

The higher activity of 4-keto-AP5 compared to AP5 has been explained through a keto-enol tautomerization of the ß-ketophosphonate.[9] However, a less far-fetched explanation, that also applies to




18 (=1)

| Coupled hydrogens | Coupling constant (Hz) | Calculated dihedral angle (CAGPLUS) | Dihedral angle in MMX model |
|---|---|---|---|
| 2ax - 3eq | 3.8 | 52 | 54 |
| 3eq - 4eq | 2.8 | 61 | 65 |
| 3eq - 4ax | 5.8 | -42 | -51 |
| 4eq - 5eq | 3.2 | -59 | -62 |
| 4eq - 5ax | 3.8 | 56 | 55 |
| 4ax - 5eq | 3.8 | 56 | 54 |
| 4ax - 5ax | 14.2 | 180 | 171 |
| 5eq - 6eq | 3.4 | 55 | 62 |
| 5eq - 6ax | 3.2 | -57 | -54 |
| 5ax - 6eq | 3.8 | -58 | -54 |
| 5ax - 6ax | 13.0 | 182 | 171 |

compounds **1** and **2** on the one hand and the deoxy compound **3** on the other, is the possibility for **1** and **2** of a conformer-stabilizing internal hydrogen bond as shown in structure **18**. The predominance of the $3_{ax}$, $2_{eq}$ conformation of **1** (=**18**) in a water solution was corroborated by measurements of all vicinal coupling constants and comparison of derived dihedral angels (CAGPLUS)[10], with the angles of a fully molecular mechanics minimized structure (MMX force field)[11]. As can be seen from the Table the agreement is quite good.

The global minimum of the alcohol **2** is also the one which implies an internal hydrogen bond.

The present conformation studies readily explain the different activities of compounds **1-3**. They also fit nicely into the findings of Krogsgaard-Larsen and coworkers regarding the conformational behaviour of *trans*-2,3-piperidine-dicarboxylic acid.[12] This compound actually prefers a diaxial conformation because of a very favourable carboxylate-ammonium interaction that overrides the steric resistance.

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6) Measured coupling constants of **8**: $J_{H\text{-}2,\,H\text{-}3} = 6.3$Hz; $J_{H\text{-}3,\,H\text{-}3'} = 4.1$Hz. The calculated coupling constants from a MMX minimized model having a chair ($2_{ax}$, $3_{eq}$) conformation were 6.0 and 4.1Hz, respectively.

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