COMMUNICATION

Synthesis and biological evaluation of phospholane and dihydrophosphole analogues of the glutamate receptor agonist AP4†

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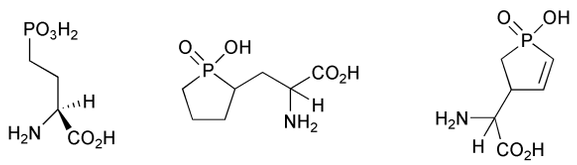
The syntheses and preliminary pharmacological characterisation of two novel cyclic phosphinic acid-containing amino acids designed as conformationally restricted analogues of the metabotropic glutamate receptor agonist AP4 (1) are reported.

Introduction

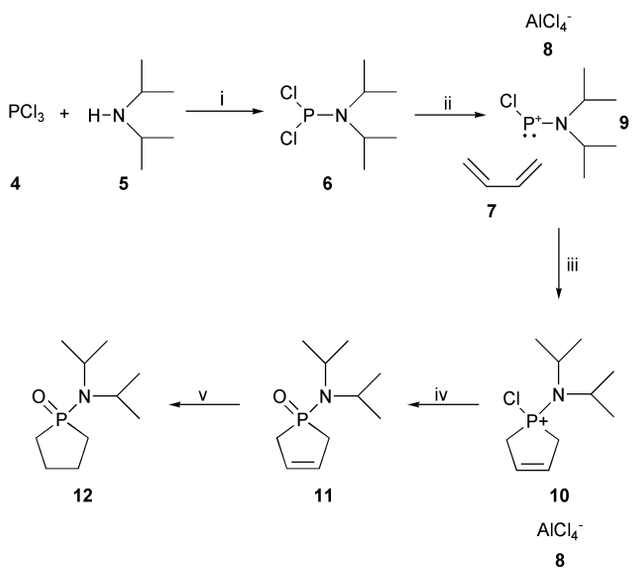
(*S*)-Glutamate is the principal excitatory neurotransmitter in the mammalian central nervous system. As such, it is involved with a wide range of processes in both normal and dysfunctional synaptic function.[1] (*S*)-2-Amino-4-phosphonobutanoic acid (AP4) (**1**) (Fig. 1) is one of the most potent and selective group III metabotropic glutamate (mGlu) receptor agonists reported. Although AP4 is selective for group III mGlu receptors over group I and group II, it is not selective for receptor subtypes within group III.[1] Conformationally restricted analogues of AP4 (**1**) were designed in an attempt to synthesise compounds with improved mGlu receptor subtype selectivity. This principle has been used in the design of many analogues of glutamic acid and AP4 (**1**).[1,2] The aim of this project was to synthesise analogues of AP4 (**1**) that were conformationally restricted in a novel way by constraining the terminal phosphonic acid group within a ring. A phospholane analogue (**2**) and a dihydrophosphole analogue (**3**) were designed (Fig. 1) with differing spacer units between the amino acid and the phosphinic acid and thus with a different degree of rigidity.



1 2 3

Fig. 1 AP4 (**1**), the phospholane analogue **2** and the dihydrophosphole analogue **3**, with differing spacer units between the amino acid moiety and the phosphinic acid and thus with a different degree of rigidity.

Retrosynthesis of **2** and **3** led us to believe that both could be synthesised from the common intermediate **11**. This could be obtained in two steps *via* a cheletropic cycloaddition between buta-1,3-diene and the phosphenium ion **9**, in a manner similar to that reported by Polniaszek.[3] The double bond could then be removed by hydrogenation to give **12** (Scheme 1) or epoxidised to afford **16** (Scheme 2). To synthesise **2**, the relative acidity of the methylene protons adjacent to the phosphoramide could be utilised allowing elaboration at this position by treatment with *n*-butyllithium and quenching with allyl bromide (Scheme 3). The ring-opening of epoxide **16** with diethyl acetamidomalonate followed by acid hydrolysis could furnish **3** (Scheme 2).



Scheme 1 *Reagents and conditions*: i) 2 equiv. **5**, Et_2O, 3 h, −10 °C, 79% yield; ii) $AlCl_3$, CH_2Cl_2, 1 h, RT; iii) buta-1,3-diene, CH_2Cl_2, 4 h, −10 °C; iv) 0.2 M EDTA–sat. $NaHCO_3$ 50 : 50, 4 h, −10 °C; steps ii–iv overall yield 44%; v) 5% Pd on carbon, H_2, MeOH, 99% yield.

Discussion

Synthesis of 1-(diisopropylamino)-1-oxo-2,5-dihydro-1-λ^5-phosphole (11)

Diisopropylphosphoramidous dichloride (**6**) (Scheme 1) was synthesised from phosphorus trichloride (**4**) and diisopropylamine (**5**).[4] The diisopropylphosphoramidous dichloride (**6**) was treated with aluminium chloride to form the phosphenium ion (**9**) (Scheme 1). A solution of buta-1,3-diene (**7**), at −10 °C, was cannulated on to the phosphenium ion-containing solution and this was stirred for 4 h at −10 °C. The cycloaddition formed the cyclic phosphoramidous monochloride derivative **10** (Scheme 1), which was then treated with aqueous sodium carbonate and EDTA. Purification afforded 1-(diisopropylamino)-1-oxo-2,5-dihydro-1-λ^5-phosphole (**11**) as a white

† Electronic supplementry information (ESI) available: mode of epoxide ring-opening and experimental data for **2** and **3**. See http://www.rsc.org/suppdata/p1/b2/b204891d/

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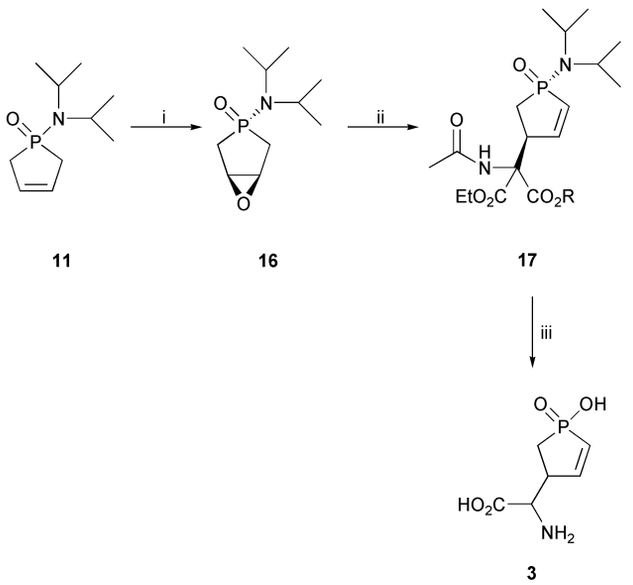
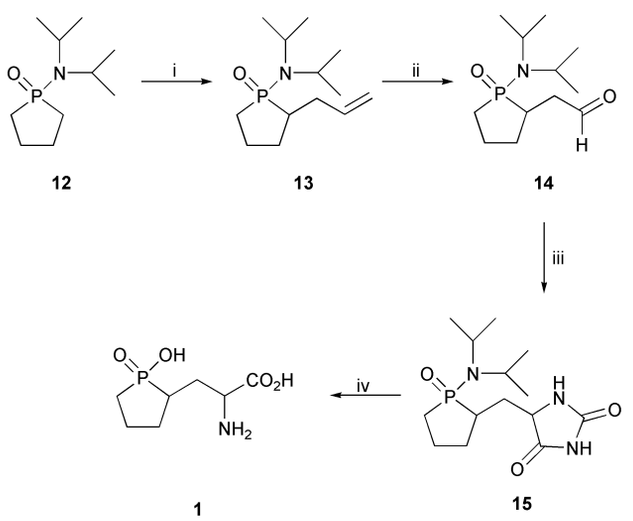


Scheme 2 *Reagents and conditions*: i) $Na_2CO_3 \cdot 1.5\ H_2O_2$, trifluoroacetic anhydride, CH_2Cl_2, 1.5 h, RT, 75% yield; ii) a, diethyl acetamidomalonate, NaH, DMF; b, add epoxide, 24 h, RT–80 °C; iii) 6 M HCl, sealed vessel, 24 h, 120 °C; 81% yield over ii and iii; all stereochemistry shown is relative; R = Et or H depending on the mechanism of epoxide opening.



Scheme 3 *Reagents and conditions*: i) a, *n*-BuLi, THF, 1 h, −78 °C, b, allyl bromide, THF, 1 h, −78 °C, 45% yield; ii) a, OsO_4, 1,4-dioxane : H_2O (75 : 25), 30 min, RT; b, $NaIO_4$, 5 h, RT; EtOAc, 30 min, overall crude yield 38%; iii) Bucherer–Bergs reaction: $(NH_4)_2CO_3$, KCN, 50% aqueous EtOH, sealed vessel, 80 °C; iv) 6 M HCl, sealed vessel, 24 h, 120 °C, 13% overall yield for ii–iv.

solid (44% yield from **6**) which was hydrogenated to give 1-(diisopropylamino)-1-oxo-1-λ^5-phospholane (**12**) as a white solid in 99% yield.

Synthesis of the phospholane analogue of AP4 (2)

Synthesis of 2-allyl-1-(diisopropylamino)-1-oxo-1-λ^5-phospholane (**13**) proceeded by reaction of 1-(diisopropylamino)-1-oxo-1-λ^5-phospholane (**12**) with *n*-butyllithium and allyl bromide in a manner similar to that used by Polniaszek [3] (Scheme 3). This was converted to aldehyde **14** using osmium tetraoxide to furnish an intermediate diol, which was subsequently oxidised using sodium periodate [5] (Scheme 3). The aldehyde (**14**) was not purified due to its high polarity making it unsuitable for silica gel column chromatography. However, it could be easily identified by ^{1}H NMR by the characteristic peak observed for the aldehyde proton at δ 9.90 ppm.

Hydantoin **15** was formed from aldehyde **14** using a modification of the Bucherer–Bergs reaction [6] (Scheme 3). Hydrolysis afforded 2-[(2-amino-2-carboxy)ethyl]-1-hydroxy-1-oxo-1-λ^5-phospholane (**1**) (13% yield from **13**) as a mixture of racemic diastereoisomers, which was purified using ion exchange resin chromatography.[7]

Synthesis of the dihydrophosphole analogue of AP4 (3)

Due to epoxide **16** being unsuitable for purification by silica gel column chromatography, a method of epoxidation was required in which all by-products could be removed by an aqueous work-up. A solution to this problem was the use of sodium percarbonate as a source of hydrogen peroxide. Sodium percarbonate has previously been used to generate trifluoroperoxyacetic acid for use in the Baeyer–Villiger reaction.[8] This methodology was used to generate trifluoroperoxyacetic acid, which was then used to effect the epoxidation of 1-(diisopropylamino)-1-oxo-2,5-dihydro-1-λ^5-phosphole (**11**).

The advantage of this method was that when the trifluoroperoxyacetic acid had reacted to form the epoxide and trifluoroacetic acid, the sodium carbonate reacted to form a salt that could be easily removed by washing with water. Recrystallisation of the crude product from chloroform furnished the pure epoxide (**16**) in 75% yield. The structure of **16** determined by X-ray crystallography§ (Fig. 2) shows that the

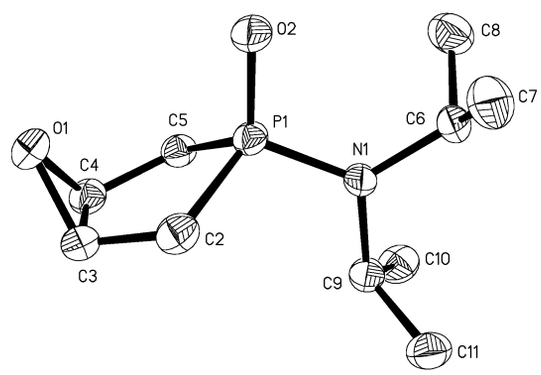


Fig. 2 Molecular unit in epoxide **16** showing displacement ellipsoids at 50% probability. H atoms are omitted for clarity. The *trans* relationship between the epoxide oxygen and the diisopropylamino group is clearly visible.

epoxide forms exclusively on the opposite face of the ring to that of the *N*-diisopropylamino moiety.

Diethyl acetamidomalonate was treated with sodium hydride to form the anion, which was then added to a solution of 1-(diisopropylamino)-3,4-epoxy-1-oxo-1-λ^5-phospholane (**16**) to give **17**.[7] Intermediate **17** was not isolated due to its high polarity making it unsuitable for silica gel column chromatography, but from the ^{1}H NMR spectrum of the crude product it was possible to see that a double bond was present, as there were two corresponding peaks at δ 5.7–6.6 ppm. Intermediate **17** was hydrolysed with 6 M aqueous hydrochloric acid in an acid digestion bomb (Parr Instruments, Illinois) for 24 h at 120 °C to yield crude (±)-4-(aminocarboxymethyl)-1-hydroxy-1-oxo-4,5-dihydro-1-λ^5-phosphole (**3**) as a mixture of racemic diastereoisomers. This was purified by ion exchange resin chromatography to yield pure **3** (81% yield).[7]

Pharmacological data

Preliminary evaluations of the biological activities of **2** and **3** were carried out using the neonatal rat spinal cord preparation.[1,7,9] Both **2** and **3** caused a depolarisation of motoneurones when applied to the hemisected neonatal rat spinal cord in the presence of tetrodotoxin (TTX). This activity is consistent with agonist action on ionotropic glutamate (iGlu) receptors or group I mGlu receptors rather than group III mGlu receptors. Using selective iGlu receptor antagonists, **2** and **3** were shown to act on AMPA receptors making it difficult to determine whether they have action on group III mGlu receptors using the neonatal rat spinal cord assay. Consequently **2** and **3** are being assessed for their biological

activity on cloned mGlu receptors, to determine what activity, if any, they possess.

As both **2** and **3** were tested as a mixture of racemic diastereomers it is possible that the AMPA receptor activity resides in one isomer and that another isomer has activity on group III mGlu receptors. Work is ongoing to synthesise the separate isomers of **2** and **3** in order to determine their activity on individual mGlu receptor subtypes.

Conclusion

Our aim was to synthesise analogues of AP4 where the terminal phosphono group was constrained as part of a ring. This objective was achieved, although the compounds that were synthesised display agonist activity on AMPA receptors making assessment of their activity on native group III mGlu receptors difficult. Work is ongoing to synthesise the individual stereoisomers in order to determine their biological activity.

We have developed a useful synthesis of amino acids that contain phosphorus heterocycles. This can now be exploited in the synthesis of analogues of **2** and **3**, which will help to develop a structure–activity profile for these compounds across a range of glutamate receptor subtypes.

Acknowledgements

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§ CCDC reference number 186273. See http://www.rsc.org/suppdata/p1/b2/b204891d/ for crystallographic files in .cif or other electronic format.

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