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Readily available amino acid building blocks for the synthesis of phosphole-containing peptides

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Abstract—Nucleophilic substitution of a phospholide anion onto protected 3-iodoalanine leads to the formation of an amino acid with an appended phosphole in excellent yield. Manipulation of the protecting groups, leads to building blocks suitable for the synthesis of phosphole-containing polypeptides.

Phospholes, unsaturated phosphorus-containing five-membered heterocycles, exhibit a wide range of chemistry, making them attractive building blocks for a wide variety of purposes including ligands in catalysis, precursors for other phosphorus heterocycles and new materials.[1–3] In particular, complexes of phospholes with late transition metals, such as palladium and rhodium, have been used successfully in various important catalytic transformations.[4–6] In order to develop novel biocompatible transition metal catalysts, we set out to synthesise amino acids with a phosphole in the side chain. When suitably protected, these may serve as building blocks to be integrated into polypeptides, thus forming the basis for biocompatible transition metal catalysts quite different to native enzymes.

To the best of our knowledge, no phosphole-containing amino acids have been previously described, although phospholes with appended carboxylic acids,[7] esters[8] and amines[9,10] have been reported. Typically, the relative low stability of poorly substituted phospholes limits the scope of available reagents and transformations that can be carried out successfully, thus complicating the synthesis of a molecule containing a phosphole linked to other functional groups. On the other hand, several phosphine amino acids have been reported. An amino acid with an appended phospholane was synthesised as a racemic mixture.[11] Although these compounds appear to be promising glutamate receptor agonists, racemic mixtures are of limited interest as ligands for asymmetric catalysis. The easiest way to obtain enantiopure nonnatural amino acids is by using a natural amino acid as the starting material. Such an approach was adopted by Gilbertson and co-workers in a general synthesis of phosphine-containing amino acids derived from serine.[12] By coupling aryl and alkyl phosphine chlorides to an amino acid zinc/copper reagent, the desired phosphine-containing amino acids were obtained in moderate to good yields. Unfortunately, when applying this methodology to phospholes, the zinc/copper reagent reduces the electrophilic halogenophosphole to the corresponding bis-phosphole and no phosphole amino acid is formed. Furthermore, this approach is limited by the fact that only a few 1-halogenophospholes are available.[13,14]

Based on these initial results, we decided to investigate the substitution of nucleophilic phospholide species on an electrophilic amino acid derivative. The synthesis is depicted in Scheme 1. Starting with *N*-Boc protected serine **1**, the acid was protected selectively using MeI. Subsequently, using Ph_3P and I_2 in the presence of imidazole, the fully protected 3-iodioalanine methyl ester **2** was formed.[15] This compound was found to be relatively unreactive towards lithium 2,5-diphenylphospholide,[13] even in the presence of $Pd(dba)_2$ as catalyst. This failure probably results from the extensive delocalisation of the negative charge within the ring and the concomitant decrease of the nucleophilicity of the phosphorus atom. More satisfying results were obtained with the 3,4-dimethyl derivative which displays much higher nucleophilicity. Reaction of 1 equiv of lithium 3,4-

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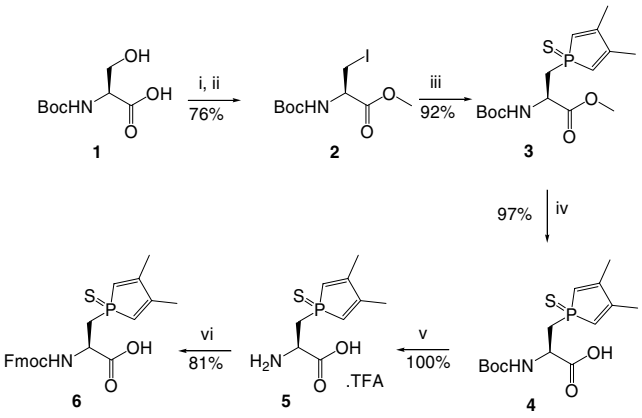

Scheme 1. Synthesis of phosphole amino acid **6**. Reagents and conditions: (i) MeI, $KHCO_3$ in DMF; (ii) PPh_3, I_2, imidazole in CH_2Cl_2 for 3.5 h at 0 °C; (iii) Li-3,4-dimethylphosphole, then S_8 in THF; (iv) 1 M NaOH, overnight; (v) 50% TFA in DCM for 3 h; (vi) FmocOSu, $KHCO_3$ in H_2O/dioxane.

dimethylphospholide salt[16] with **2** at 0 °C in THF gave a new compound which exhibited a signal at −13 ppm in ^{31}P NMR spectroscopy.

This compound could be isolated, but was highly prone to oxidation, as expected for a 1-alkyl-3,4-dimethylphosphole derivative. We therefore chose to protect the phosphorus lone pair with sulfur. Addition of 1.1 equiv of S_8 smoothly protected the phosphole within 1 h at room temperature. A colour change from yellow to deep red was observed and the ^{31}P NMR confirmed the total conversion to the *S*-protected phosphole product **3** with a chemical shift at 46.7 ppm.[17] The sulfur not only protected the compound against oxidation, but also greatly enhanced its acid and base stability, two properties which are essential for further use of this compound as a building block in peptide synthesis. The sulfur could be removed cleanly by reaction with $P(CH_2CH_2CN)_3$ at 70 °C in 4 h,[18] but this must be done only after the amino acid analogue is integrated into the desired polypeptide. Although **3** is relatively stable, it could not be purified by flash chromatography without considerable product degradation, probably due to rearrangement reactions that occur on the silica gel.[19,20] The phosphole amino acid was therefore purified through precipitation from a toluene solution with petroleum ether, and obtained in 92% yield. The purity was confirmed by NMR analysis. When performing the substitution reaction at −78 °C instead of 0 °C, the yield was reduced to approximately 50%. Apparently, at low temperature, the phospholide anion also reacts as a base to deprotonate the α-proton of **2**. The *N*-Boc amidoacrylic acid formed in this side reaction, can be recovered from the petroleum ether fraction.

The phosphole sulfide moiety proved to be remarkably stable during the manipulation of the amino acid protection groups. The desired Fmoc protected amino acid was thus obtained in near quantitative yield with respect to phosphole **3**. Overnight treatment of phosphole **3** with aqueous NaOH yielded the Boc protected phosphole amino acid **4**.[21] Further deprotection using TFA cleanly resulted in phosphole amino acid **5**.[22] To take full advantage of the extensively developed Fmoc-based peptide chemistry,[23] **5** was subsequently treated with FmocOSu to give the desired Fmoc protected phosphole amino acid **6**.[24] We are currently investigating the application of this building block in the formation of phosphole-containing polypeptides.

Acknowledgements

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15. Trost, B. M.; Rudd, M. T. *Org. Lett.* **2003**, *5*, 4599–4602; To a solution of triphenylphosphine (3.28 g, 12.5 mmol) and imidazole (850 mg, 12.5 mmol) in CH_2Cl_2 (30 mL) was added I_2 (3.17 g, 12.5 mmol) at 0 °C. On complete dissolution of the I_2 the temperature was raised to room temperature and after 10 min, re-cooled to 0 °C. *N*-(*tert*-Butoxycarbonyl)-L-serine methyl ester (2.19 g, 10 mmol) was added and the mixture was stirred for 3.5 h at 0 °C. The reaction was quenched with aqueous sodium thiosulfate, extracted using EtOAc, washed with brine, dried ($MgSO_4$) and evaporated to dryness. The crude product was purified on silica gel (10–30% EtOAc in petroleum ether) to yield **2** in 76% yield. ^1H NMR (300 MHz, $CDCl_3$): $\delta = 1.27$ (s, 9H, CCH_3), 3.40 (m, 2H, CH_2I), 3.62 (s, 3H, OCH_3), 4.36 (m, 1H, αCH), 5.49 (d, $J = 8$ Hz, 1H, NH). ^{13}C NMR (75.5 MHz, $CDCl_3$): $\delta = 169.8$ (COOMe), 154.7 (COO-*t*-Bu), 80.0 (*t*-Bu), 53.8 (Me), 52.9 (αC), 29 (*t*-Bu), 7.79 (βC).

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17. To a stirred solution of 3,4-dimethyl-1-phenylphosphole (1.43 mL, 7.60 mmol) in dry THF (15 mL) was added Li wire (4 cm, ~26 mmol). When the reaction was complete as indicated by ^{31}P NMR, the excess Li was removed and $AlCl_3$ (169 mg, 1.27 mmol) was added. After 30 min, **2** (2.50 g, 7.60 mmol) in THF (15 mL) was added at 0 °C. When the addition was complete, the cold bath was removed. After 10 min, S_8 (269 mg, 8.40 mmol) was added and the solution was stirred for another 30 min. The reaction was quenched with sodium thiosulfate, extracted with EtOAc, washed with brine, dried ($MgSO_4$) and evaporated to dryness. The crude compound was then redissolved in toluene and precipitated with petroleum ether to yield **3** in 92% yield. ^1H NMR (300 MHz $CDCl_3$): $\delta = 1.45$ (s, 9H, CCH_3), 2.05 (s, 6H, $2CH_3$), 2.65 (m, 2H, CH_2P), 3.78 (s, 3H, OCH_3), 4.60 (m, 1H, αCH), 5.61 (d, $J = 7.8$ Hz, 1H, NH), 6.00 (d, $J = 30$ Hz, 2H, PCH). ^{13}C NMR (75.5 MHz, $CDCl_3$): $\delta = 171.4$ (COOMe), 154.9 (COO-*t*-Bu), 153.5 (d, $J = 18.0$ Hz, C-3 phosphole), 123.6 (d, $J = 80.3$ Hz, C-2 phosphole), 80.4 (*t*-Bu), 52.8 (Me), 49.9 (αC), 32.8 (d, $J = 53.2$ Hz, βC), 28.3 (*t*-Bu), 17.5 (d, $J = 17.7$ Hz) and 17.42 (d, $J = 17.6$ Hz, Me-phosphole). ^{31}P NMR (121.5 MHz, $CDCl_3$): 46.9 ppm. HRMS EI^+: 345.0358 (calcd 345.1164, $C_{15}H_{24}NO_4PS$). Mp: >250 °C.
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21. To a solution of **3** (2.1 g, 6.08 mmol) in THF (12 mL) was added 1 M NaOH (12 mL) and the solution was stirred overnight. The reaction was acidified with dilute HCl, extracted with CH_2Cl_2, washed with brine, dried ($MgSO_4$) and evaporated to dryness to yield **4** as a yellow crystalline solid in 97% yield. ^1H NMR (300 MHz, $CDCl_3$): $\delta = 1.43$ (s, 9H, CCH_3), 2.03 (s, 6H, $2CH_3$), 2.63 (m, 2H, CH_2P), 4.60 (m, 1H, αCH), 5.70 (d, $J = 7.4$ Hz, 1H, NH), 6.02 (d, $J = 31.3$ Hz, 2H, PCH). ^{13}C NMR (75.5 MHz, $CDCl_3$): $\delta = 174.9$ (COOH), 155.2 (COO-*t*-Bu), 153.8 (d, $J = 18.4$ Hz) and 153.6 (d, $J = 18.5$ Hz, C-3 phosphole), 124.0 (d, $J = 80.4$ Hz) and 123.4 (d, $J = 80.8$ Hz, C-2 phosphole), 80.6 (*t*-Bu), 49.8 (αC), 33.0 (d, $J = 51.6$ Hz, βC), 28.3 (*t*-Bu), 17.4 (d, $J = 17.8$ Hz) and 17.3 (d, $J = 17.7$ Hz, Me-phosphole). ^{31}P NMR (121.5 MHz, $CDCl_3$): 46.7 ppm. HRMS EI^+: 331.0867 (calcd 331.1007, $C_{14}H_{22}NO_4PS$). Mp: >250 °C.
22. To a solution of **4** (1.95 g, 5.90 mmol) in CH_2Cl_2 (10 mL) was added TFA (9 mL) and water (1 mL). The mixture was stirred for 3 h, diluted with toluene and dried under reduced pressure to yield **5** as a yellow solid in quantitative yield. ^1H NMR (300 MHz, MeOD): $\delta = 2.13$ (s, 6H, $2CH_3$), 2.54 (m, 2H, CH_2P), 4.50 (m, 1H, αCH), 6.16 (m, 2H, PCH). ^{13}C NMR (75.5 MHz, MeOD): $\delta = 170.6$ (CO), 156.3 (d, $J = 19.0$ Hz) and 155.8 (d, $J = 19.0$ Hz, C-3 phosphole), 124.9 (d, $J = 22.6$ Hz) and 123.8 (d, $J = 23.0$ Hz, C-2 phosphole), 50.2 (αC), 31.9 (d, $J = 50.0$ Hz, βC), 17.4 (d, $J = 18.2$ Hz) and 17.3 (d, $J = 18.2$ Hz, Me-phosphole). ^{31}P NMR (121.5 MHz, MeOD): 47.3 ppm. ^{19}F NMR (282.4 MHz, MeOD): 78.7 ppm. Mp: 120–121 °C.
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24. To a solution of FmocOSu (1.99 g, 5.90 mmol) in dioxane (25 mL) was added **5** (1.94, 5.90 mmol) and $KHCO_3$ (1.48 g, 14.75 mmol) in water (25 mL) at 0 °C. After 30 min, the cold bath was removed and the solution was stirred for another 4 h. The reaction mixture was diluted with EtOAc and extracted with $NaHCO_3$. The organic layer was washed with brine, dried ($MgSO_4$) and evaporated to dryness. The crude product was redissolved in hot toluene and precipitated with petroleum ether to give **6** as a light yellow crystalline solid in 81% yield. ^1H NMR (300 MHz, $CDCl_3$): $\delta = 1.93$ (s, 6H, $2CH_3$), 2.65 (m, 2H, CH_2P), 4.06 (m, 1H, $CHCH_2$), 4.35 (m, 2H, CH_2O), 4.73 (m, 1H, αCH), 5.97 (d, $J = 31.6$ Hz) and 5.94 (d, $J = 31.6$ Hz, 2H, PCH), 6.22 (d, $J = 6.7$ Hz, 1H, NH), 7.31–7.77 (m, 8H, aromatic Fmoc), 8.43 (br s, 1H, OH). ^{13}C NMR (75.5 MHz, $CDCl_3$): $\delta = 174.6$ (COOH), 156.0 (NCO), 154.1 (d, $J = 18.0$ Hz) and 154.0 (d, $J = 17.8$ Hz, C-3 phosphole), 143.7, 143.5, 141.2, 127.8, 127.1, 124.8, 120.1 (aromatic Fmoc), 123.1 (d, $J = 80.3$ Hz, C-2 phosphole), 67.5 (CH_2O), 53.6 (αC), 46.9 ($CHCH_2$), 33.0 (d, $J = 51.6$ Hz, βC), 17.3 (d, $J = 17.4$ Hz, Me-phosphole). ^{31}P NMR (121.5 MHz, $CDCl_3$): 46.6 ppm. HRMS EI^+: 453.0475 (calcd 353.1164, $C_{24}H_{24}NO_4PS$). Mp: 134–135 °C.