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Enantioselective synthesis of (2*S*)-2-(4-phosphonophenylmethyl)-3-aminopropanoic acid suitably protected for peptide synthesis

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Abstract—Protected D-β-2-(4-phosphono) phenylalanine was prepared by a multistep synthesis, involving the diastereoselective alkylation of a chiral enolate. This new compound can be further incorporated into peptidic backbone by means of solid-phase peptide synthesis in order to synthesize short peptides adopting β-turn or α-helix conformations.

Oligomers of β-amino acids have emerged recently as a new class of peptidomimetics. These β-peptides are able to fold into helices, β-turns or β-sheet structures,[1] thus receiving increasing attention in view of their better resistance to in vivo degradation, and modified pharmacological properties.

The asymmetric synthesis of β-amino acids substituted only on the carbon adjacent to the acid group is much less documented in the literature than that of α-amino acids. However, interesting syntheses were developed recently. Seebach[2] and Juaristi[3] have published a methodology in which a chiral perhydropyrimidone is alkylated at the α-carbon. Lavielle's group[4,5] also recently showed that alkylation of Oppolzer's sultam could be extended to homoglycine enolates. More classical but versatile and efficient is the synthesis described by Wyatt et al.[6] giving several examples of 2-substituted chiral 3-aminopropanoic acids. Using their method, we focused on the preparation of the title compound **6c**, in which the stereochemistry of the chiral center is controlled by means of diastereoselective alkylation of an enolate bearing the Evans[7] oxazolidinone chiral auxiliary. In the course of our structure–activity relationship studies, molecular modeling showed that we needed a β-2 amino acid analogous to a phosphorylated tyrosine, having the unnatural (2*S*) configuration and being resistant to phosphatases. Indeed, although the 4-phosphonophenyl group is not structurally a true mimetic of the *O*-phosphorylated tyrosine, this moiety was chosen for two reasons. On the one hand, it has a higher acidity[8,9] than the phosphonomethyl group, the pK_a of the aryl phosphonic acid being comparable to that of the naturally-occurring phosphate. On the other hand, as far as the interactions with the phosphonic acid are concerned, due to the higher flexibility exhibited by the β-2 amino acid, we can expect that a β-2 4-phosphonophenylalanine would interact in a similar way to a phosphotyrosine. Several mimetics of phosphotyrosine already exist, some of them being commercially available. However, no compound corresponding to the required β-2 analogue being described, we decided to prepare it.

To obtain an efficient multigram scale synthesis for the precursor **2**, we elected to make use of the classical malonate synthesis. As depicted in Scheme 1, the preparation of 3-(4-diethylphosphonobenzyl)-propanoic acid started with the alkylation of di-*tert*-butyl malonate by 4-bromobenzyl bromide. Di-*tert*-butyl malonate (5 g) was deprotonated by sodium hydride or KO*t*-Bu and the resulting anion alkylated with 4-bromobenzyl bromide, leading to **1a**. The aromatic bromide was subsequently displaced by a diethylphosphoryl group, the precursor of the phosphonic acid, a non-hydrolyzable phosphate analogue. This reaction was achieved by reaction of diethyl phosphite, catalyzed by $Pd^{(0)}$, leading to di-terbutyl (4-diethylphosphono-benzyl)malonate (**1b**). Subsequent TFA cleavage of the *tert*-butyl ester groups, followed by concomittant decarboxylation by

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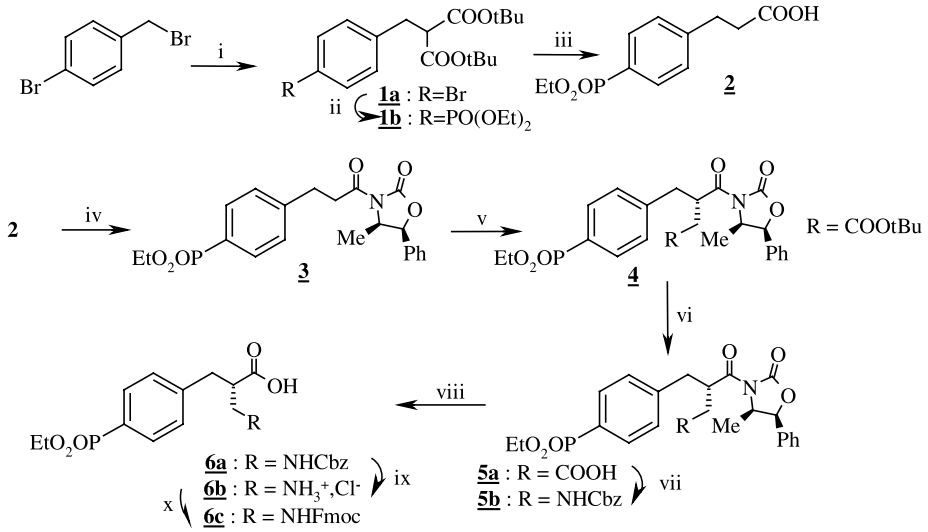

Scheme 1. (i) $CH_2(COOt\text{-}Bu)_2$, NaH or KO*t*-Bu, THF; (ii) $HPO(OEt)_2$, $Pd(PPh_3)_4$; (iii) TFA, CH_2Cl_2 then toluene, reflux; (iv) *i*-BuOCOCl, *N*-methylmorpholine, THF then (4*R*,5*S*)-4-methyl-5-phenyl-2-oxazolidinone, lithiated with *n*-BuLi; (v) NaHMDS, THF −78°C then $BrCH_2COOt$-Bu, −78°C, 2 h; (vi) TFA, CH_2Cl_2; (vii) Ph_2PON_3, Et_3N, toluene rt then 1 h reflux; (viii) LiOH, H_2O_2, THF–water then aqueous Na_2SO_3; (ix) H_2, Pd/C, EtOH; (x) Fmoc-Cl, $NaHCO_3$, dioxane–water.

refluxing for several hours in toluene, led to the expected 3-(4-diethylphosphono)-propanoic acid (**2**).

Having this precursor in hand, we performed the *N*-acylation of the lithiated Evans chiral oxazolidinone (4*R*,5*S*)-4-methyl-5-phenyl-1,3-oxazolidin-2-one with the 'mixed anhydride' from our substituted propanoic acid **2**, via activation with isobutyl chloroformate. The use of the 'mixed anhydride' was preferred to the chloride, the acylation with the chloride giving very low yields. The resulting compound **3** bearing the chiral auxiliary required for diastereoselective alkylation was obtained with a 53% yield only, presumably due to a partial decomposition of the mixed anhydride. Taking into account the preliminary observations of Wyatt and coworkers,[6] we incorporated an acid moiety as the precursor of the β-amino group. This was achieved through diastereoselective alkylation of the sodium enolate (NaHMDS) of **3** with *tert*-butyl bromoacetate at −78°C, giving **4** with a diastereomeric excess of 80%, the minor diastereomer being readily separated by means of flash chromatography. The absolute configuration of the chiral center was postulated by analogy with the numerous examples of alkylation of such chiral enolates. Deprotection of the acid (TFA–CH_2Cl_2) was readily achieved but a slight racemization of **5a** was observed by ^1H NMR, the undesired diastereomer being separated by flash chromatography in the following step. The straight transformation of the acid into a Cbz-protected amino group was obtained by a variant of the Curtius rearrangement. First, treatment at room temperature with diphenylphosphoryl azide afforded the acyl azide, the latter being subsequently decomposed by refluxing in toluene, giving the isocyanide which was trapped in situ by benzyl alcohol in the presence of triethylamine.

The *N*-acyl oxazolidinone **5b** underwent a smooth saponification with lithium hydroperoxide in THF–water, giving the free acid which was easily purified by flash chromatography, eluting with EtOAc–cyclohexane in the presence of 1% formic acid. The acid **6a** and recovered chiral oxazolidinone were obtained in 75 and 94% yields, respectively. Replacement of the Cbz protecting group by Fmoc, suitable for solid-phase peptide synthesis, was achieved by hydrogenolysis under atmospheric pressure and subsequent reprotection with Fmoc-Cl in dioxane–water affording 0.97 mmol of the final amino acid **6c**. Yields: **1a** 63%, **1b** 81%, **2** 84%, **3** 53%, **4** 63%, **5a** quant, **5b** 67%, **6a** 75%, **6b** quant, **6c** 67%. The optical rotatory power for **6c** was measured in chloroform and methanol, giving two different values: $[\alpha]_D$ (20°C) = −8 (c = 0.5, $CHCl_3$); $[\alpha]_D$ (20°C) = −3 (c = 0.5, MeOH).

In conclusion, (D)-4-phosphono-β-2-phenylalanine suitably protected for further incorporation into peptides, was prepared in ten steps from inexpensive materials. Using the widely used Evans oxazolidinone, the synthesis proved to be efficient, providing this novel compound with a good enantioselectivity. It is worth noting that, as both enantiomers of *cis*-4-methyl-5-phenyl-1,3-oxazolidin-2-one are commercially available, either of the two enantiomers of the β-amino acid can be prepared following this synthetic procedure. This compound is a good candidate for α-helices and β-turn-containing short peptides, bearing a 4-phosphono group to mimic the phosphorylated tyrosine residue.

Structural data of compounds **1a**–**6a**: **1a** δ_H (DMSO) 1.28 (18H, s), 2.87 (2H, d, J = 8.2 Hz), 3.52 (1H, t, J = 8.2 Hz), 7.16 (2H, d, J = 7.8 Hz), 7.42 (2H, d, J = 8.2

Hz); **1b** δ_H (DMSO) 1.16 (6H, t, $J=7.2$ Hz), 1.26 (18H, s), 2.99 (2H, d, $J=8.0$ Hz), 3.57 (1H, t, $J=8.0$ Hz), 3.86–4.01 (4H, m), 7.36 (2H, dd, $J=7.8$, 4.1 Hz), 7.42 (2H, dd, $J=13.1$, 8.2 Hz); **2** δ_H (DMSO) 1.17 (6H, t, $J=7.2$ Hz), 2.53 (2H, t, $J=7.5$ Hz), 2.84 (2H, t, $J=7.5$ Hz), 3.86–4.03 (4H, m), 7.36 (2H, dd, $J=7.8$, 4.1 Hz), 7.57 (2H, dd, $J=13.1$, 7.8 Hz); **3** δ_H ($CDCl_3$) 0.82 (3H, d, $J=6.6$ Hz), 1.26 (6H, t, $J=7.2$ Hz), 2.99 (2H, t, $J=7.4$ Hz), 3.12-3.27 (2H, m), 3.95–4.12 (4H, m), 4.68 (1H, quint, $J=6.7$ Hz), 5.58 (1H, d, $J=7.2$ Hz), 7.20–7.38 (7H, m), 7.67 (2H, dd, $J=13.1$, 8.0 Hz)); **4** δ_H ($CDCl_3$) 0.81 (3H, d, $J=6.6$ Hz), 1.16–1.25 (6H, m), 1.31 (9H, s), 2.26 (1H, dd, $J=16.9$, 4.3 Hz), 2.65 (1H, dd, $J=12.1$, 10.5 Hz), 2.74 (1H, dd, $J=16.9$, 10.5 Hz), 3.00 (1H, dd, $J=12.1$, 5.8 Hz), 3.96–4.08 (4H, m), 4.42–4.48 (1H, m), 4.54–4.62 (1H, m), 5.30 (1H, d, $J=7.2$ Hz), 7.19–7.36 (7H, m), 7.69 (2H, dd, $J=13.1$, 8.0 Hz); **5a** δ_H ($CDCl_3$) 0.76 (3H, d, $J=6.6$ Hz), 1.17–1.25 (6H, m), 2.35 (1H, dd, $J=17.5$, 4.5 Hz), 2.64 (1H, dd, $J=17.4$, 9 Hz), 2.84 (1H, dd, $J=17.4$, 10.4 Hz), 3.03 (1H, dd, $J=17.5$, 7.1 Hz), 3.64–4.09 (4H, m), 4.42–4.61 (1H, m), 4.58 (1H, quint, $J=7.2$ Hz), 5.35 (1H, d, $J=7.2$ Hz), 7.18–7.70 (9H, m); **5b** δ_H ($CDCl_3$) 0.76 (3H, d, $J=6.6$ Hz), 1.17–1.26 (6H, m), 2.76–3.10 (2H, m), 3.48 (2H, t, $J=6.8$ Hz), 3.95–4.08 (4H, m), 4.26–4.32 (1H, m), 4.49 (1H, quint, $J=7.0$ Hz), 5.02 (2H, s), 5.28 (1H, d, $J=7.2$ Hz), 7.18–7.36 (7H, m) 7.66 (2H, dd, $J=13.2$, 7.8 Hz); **6a** δ_H ($CDCl_3$) 1.19 (6H, t, $J=7.1$ Hz), 2.85–3.49 (5H, m), 3.92–4.14 (4H, m), 5.02 (2H, s), 5.30 (1H, br s), 7.20–7.34 (7H, m), 7.62 (2H, dd, $J=13.2$, 7.9 Hz); **6b** δ_H (D_2O) 1.29 (6H, t, $J=7.3$ Hz), 3.03–3.29 (5H, m), 4.07–4.18 (4H, m), 7.46 (2H, dd, $J=7.8$, 4.1 Hz), 7.46 (2H, dd, $J=13.2$, 7.8 Hz), δ_C (D_2O) 43.3, 58.3, 61.6, 65.0, 80, 125.6 (d, $J=214$ Hz), 129.8 (d, $J=18$ Hz), 131.5 (d, $J=12$ Hz), 140.2, 164.7; **6c** δ_H ($CDCl_3$) 1.22 (3H, t, $J=6.8$ Hz), 1.23 (3H, t, $J=6.8$ Hz), 2.60-3.48 (5H, m), 3.88–4.07 (4H, m), 4.14 (1H, t, $J=6.9$ Hz), 4.30 (2H, d, $J=6.9$ Hz), 5.34 (1H, br t), 7.20–7.70 (12H, m).

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References

1. Seebach, D.; Ciceri, P. E.; Overhand, M.; Jaun, B.; Rigo, D. *Helv. Chim. Acta* **1996**, *79*, 2043–2066.
2. Seebach, D.; Boog, A.; Schweizer, W. B. *Eur. J. Org. Chem.* **1999**, 335–360.
3. Juaristi, E.; Quintana, D.; Balderas, M.; Garcia-Perez, E. *Tetrahedron: Asymmetry* **1996**, *7*, 2233–2246.
4. Ponsinet, R.; Chassaing, G.; Lavielle, S. *Tetrahedron: Asymmetry* **1998**, *9*, 865–871.
5. Ponsinet, R.; Chassaing, G.; Vaissermann, J.; Lavielle, S. *Eur. J. Org. Chem.* **2000**, 83–90.
6. Arvanitis, E.; Ernst, H.; Ludwig, A. A.; Robinson, A. J.; Wyatt, P. B. *J. Chem. Soc., Perkin Trans. 1* **1998**, 521–528.
7. Evans, D. A.; Ennis, M. D.; Mathre, D. J. *J. Am. Chem. Soc.* **1982**, *104*, 1737–1739.
8. Domchek, S. M.; Auger, K. R.; Chetterjee, S.; Burke, T. R., Jr.; Shoelson, S. E. *Biochemistry* **1992**, *31*, 9865–9870.
9. Liu, W.-Q.; Roques, B. P.; Garbay, C. *Tetrahedron Lett.* **1997**, *38*, 1389–1392.