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TETRAHEDRON: *ASYMMETRY*

Preparation of L-N^{α}-Fmoc-4-[di-(*tert*-butyl)-phosphonomethyl]phenylalanine from L-tyrosine

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Abstract

The unnatural amino acid analogue, 4-(phosphonomethyl)phenylalanine (Pmp, **2**), has proven to be a valuable tool for studying protein-tyrosine kinase dependent signal transduction, where it is most often incorporated into peptides or peptide mimetics as a phosphatase-stable phosphotyrosyl mimetic. Although Pmp has been prepared previously bearing a number of protection strategies, the N^{α}-Fmoc 4-[di-(*tert*-butyl)phosphonomethyl] phenylalanine form [(N^{α}-Fmoc-L-Pmp($^{t}Bu_2$)-OH, **3**] is particularly attractive since it can be cleanly introduced into peptides using standard Fmoc protocols. Synthesis of **3** was first reported as its (D/L)-racemate, and subsequently as its L-**3** enantiomer, with the latter synthesis having relied on induction of chirality using a camphor sultam auxillary. Reported herein is an alternate enantioselective synthesis of L-**3** in high enantiomeric purity by procedures which derive the stereochemistry of the final product directly from the starting amino acid, without the need for chiral induction. A key feature of the route is the racemization-free nucleophilic substitution of lithium di-*tert*-butyl phosphite onto protected 4-bromomethylphenylalanine (**17**).

1. Introduction

The unique functional role of phosphotyrosyl residues (pTyr, **1**) in protein-tyrosine kinase (PTK) dependent signal transduction has made 'pTyr motifs' valuable thematic starting points for the development of signal transduction modulators.[1] However, a potential limitation of pTyr residues in vivo is hydrolytic lability of the phosphoryl-ester linkage in the presence of protein-tyrosine phosphatases (PTPs). In order to overcome such enzymatic lability, a number of pTyr mimetics have been reported, including L-(4-phosphonomethyl)phenylalanine (L-Pmp, **2**), which can exhibit biological properties similar to the parent pTyr residue, yet is stable to phosphatases.[2] For this reason, Pmp has proven to be a valuable analogue in a variety of signal transduction systems.[1] Recent reports of highly potent Pmp-containing Grb2 SH2

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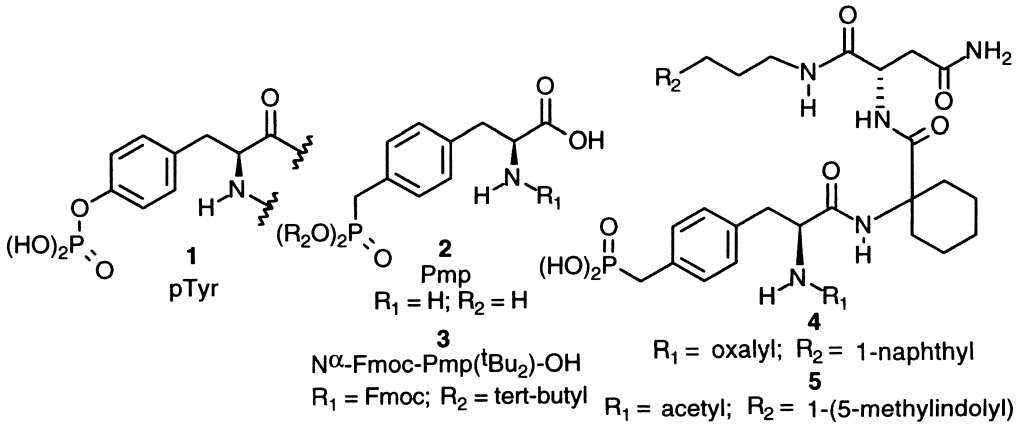
domain inhibitors such as **4**[3] and **5**[4] have renewed interest in the development of suitably protected analogues of Pmp for the preparation of inhibitors directed against this important signal transduction protein.

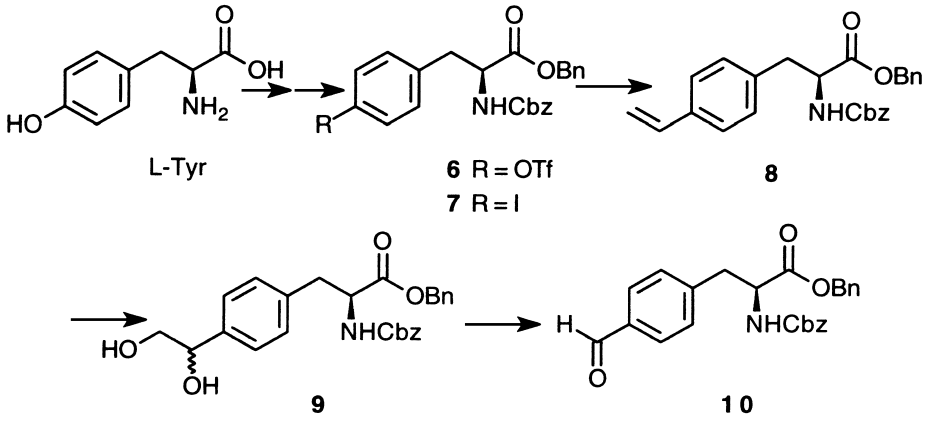


Since its original preparation in the racemic, free phosphonic acid form,[5] Pmp has been synthesized bearing a number of phosphonate protection strategies, most notably ethyl or methyl.[6–8] Alternatively, preparation of Pmp in its N^{α}-Fmoc 4-[di-(*tert*-butyl)phosphonomethyl]phenylalanine form [(N^{α}-Fmoc-Pmp($^{t}Bu_2$)-OH, **3**] is particularly attractive, since this possesses orthogonal protection compatible with standard Fmoc peptide synthesis protocols. Synthesis of **3** was first reported as its (D/L)-racemate,[9] and subsequently as its L-**3** enantiomer, with the latter synthesis having relied on induction of chirality using the camphor sultam auxillary.[10,11] In light of the above mentioned utility of N^{α}-Fmoc-L-Pmp($^{t}Bu_2$)-OH for the synthesis of extremely potent Grb2 SH2 domain inhibitors,[3] there is a renewed interest in the further development of new preparations of L-**3** from readily available starting materials. Accordingly, reported herein is an alternate enantioselective synthesis of L-**3** in which chirality is derived directly from readily available L-tyrosine without the need for chiral induction.

2. Synthesis

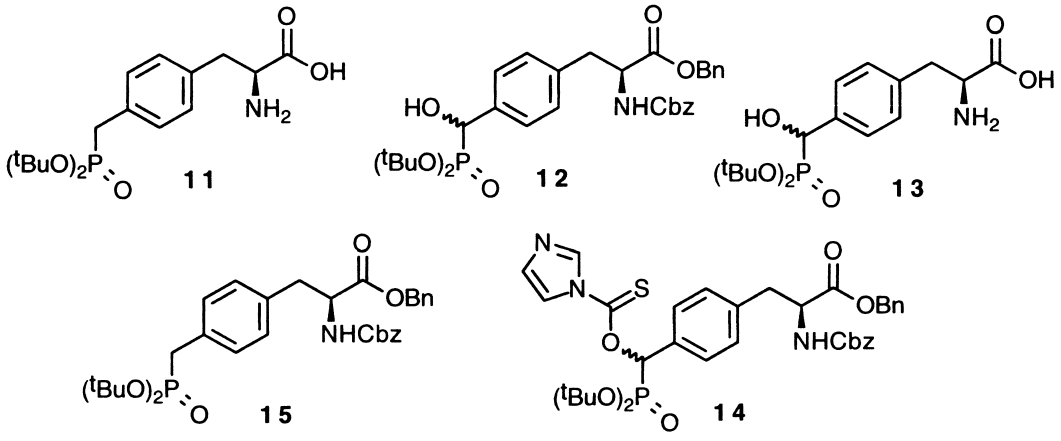
The 4-formylphenylalanine analogue **10** was envisioned to serve as a key intermediate for the introduction of di-*tert*-butyl phosphonic acid functionality via nucleophilic addition at the aldehyde site. Our initial approach toward **10** utilized palladium-catalyzed carbonylation[12] of either 4-iodophenylalanine analogue **7** or a tyrosine triflate analogue **6**. However, these reactions either failed to provide the desired product, or did so in extremely low yield. Alternatively, Yokomatsu et al. have shown that ozonolysis of a 4-vinylphenylalanine yields the corresponding 4-formyl derivative in high yield.[13] Accordingly, 4-vinyl-substituted **8** appeared to be an ideal precursor which could provide a clean, high yield route to desired **10** (Scheme 1). In practice, readily available tyrosine triflate analogue **6** proved to be superior over the more expensive 4-iodophenylalanine analogue **7**, because of the greater ease of removal of tin species by silica gel chromatography, although both **6** and **7** gave similar yields of **8**. In a departure from Yokomatsu et al.,[13] the vinyl group of **8** was oxidized to diol **9** by 4-methylmorpholine *N*-oxide in the presence of 1 mol% OsO_4 (85% yield), then oxidatively cleaved ($NaIO_4$ in ether:H_2O) to give a quantitative yield of key intermediate **10**. The entire sequence of steps was amenable to large scale up, and allowed the ready preparation of gram quantities of **10**.

With **10** in hand, two approaches toward L-Pmp($^{t}Bu_2$)-OH (**11**) were examined. In the first route,



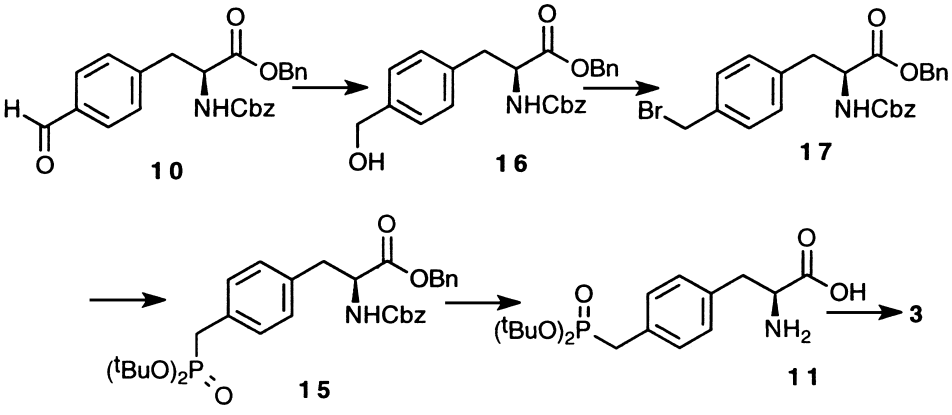
Scheme 1.

which appeared deceptively simple and direct, reaction of aldehyde **10** with the lithium salt of di-*tert*-butyl phosphite at −78°C in THF gave hydroxyphosphonate **12** (74% yield). Unfortunately, contrary to expectations, susequent hydrogenolysis cleaved the benzyl ester and CBz groups, but did not remove the phosphonate benzylic hydroxyl. Even under pressure in the presence of palladium black, reduction would not proceed beyond intermediate **13**, which was obtained in quantitative yield. Therefore, several alternate methods were examined in attempts to remove the benzylic hydroxyl of **12**. In one of these, it was found that thiocarbonyl diimidazole-mediated conversion to thio-ester **14** afforded deoxygenated **15** in 96% yield following reduction with tributyltin hydride and AIBN (2 steps).[14] However, the presence of residual sulfur species in **15** rendered the approach impractical due to resistance of benzyl protecting groups to subsequent catalytic hydrogenolysis.



Based on the reported ready displacement of benzylic bromides using di-*tert*-butyl phosphite,[15] a new strategy centred around 4-(bromomethyl)phenylalanine analogue **17** was developed (Scheme 2). Reduction of aldehyde **10** ($NaBH_4$) afforded intermediate benzyl alcohol **16** (quantitative yield), which upon treatment with CBr_4 and Ph_3P in acetonitrile, provided desired bromide **17** (79%). Reaction of **17** with one equivalent of the lithium or sodium salt of di-*tert*-butyl phosphite in THF:HMPA (−78°C to 0°C) gave the fully protected L-Pmp-derivative **15** (57%). When the reaction was repeated at room temperature overnight with 1.2 equivalents of di-*tert*-butyl phosphite lithium salt in an attempt to drive the reaction to completion, partial racemization (44% ee) was observed. Under even more rigorous conditions (reflux), total racemization occurred. Hydrogenolysis of **15** gave a quantitative yield of free

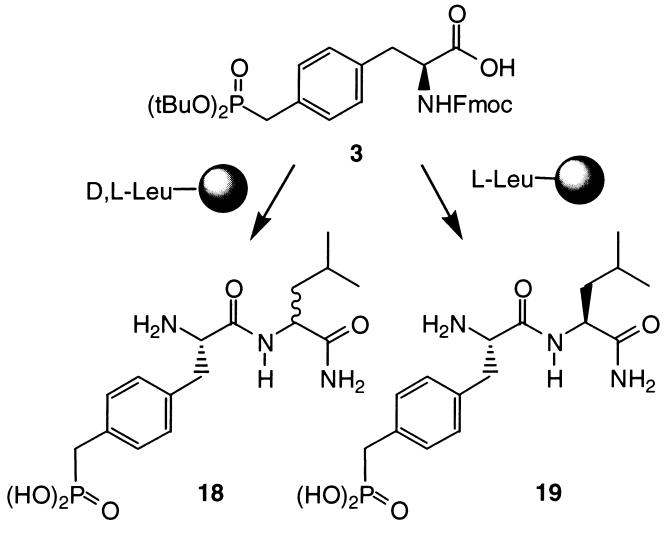
amino acid **11**, which was finally protected as the title Fmoc derivative **3** (71%) by standard procedures. The enantiomeric purity of **3** as measured by HPLC analysis of the Pmp-leucine dipeptide indicated >97% single enantiomer (see below).



Scheme 2.

3. Determination of enantiomeric purity

In order to determine the enantiomeric purity of final product **3**, leucine amide dipeptides were prepared by solid-phase techniques, with HPLC separation performed on resulting diastereomers (Scheme 3). Racemic D,L-leucine-containing dipeptides (**18**), having free terminal amino groups, first served as standards which showed good separation of diastereomers (diastereomeric retention time difference of 4.9 min). Next, dipeptide **19** was prepared using enantiomerically pure L-leucine, and shown to have less than 3% diastereomeric contamination resulting from D-Pmp.



Scheme 3.

4. Conclusions

Starting from readily available L-tyrosine, a practical synthesis of L-N^{α}-Fmoc-Pmp(^{t}Bu)-OH (**3**) in high enantiomeric purity is described. The route offers the conceptual advantage over the previously reported enantioselective synthesis[11] of deriving final stereochemistry from natural L-tyrosine itself without reliance on chiral induction, although this comes at a cost of increased length and lowered overall yield. The ready availability of **3** by this alternate route should facilitate biochemical studies in the signal transduction field. Exemplary of this is the recent utilization of **3** for the clean preparation of highly potent Grb2 SH2 domain inhibitor **4** on a large scale for animal studies in breast cancer model systems.[16]

5. Experimental

5.1. General

Melting points were determined on a MeI Temp II melting apparatus and are uncorrected. Elemental analysis were obtained from Atlantic Microlab Inc., Norcross, GA. Fast atom bombardment mass spectra (FABMS) were acquired with a VG Analytical 7070E mass spectrometer under the control of a VG 2035 data system using 4-nitrobenzyl alcohol (NBA) matrices. ^{1}H NMR data were obtained on a Bruker AC250 (250 MHz) instrument. Removal of solvents was performed by rotary evaporation under reduced pressure.

5.2. L-N$^{\alpha}$-*Benzyloxycarbonyl-4-[1-(2-ethenyl)]phenylalanine benzyl ester (**8**)*

To a solution of L-N^{α}-Cbz-4-(*O*-trifluoromethanesulfonate)tyrosine benzyl ester (**6**) (9.81 g, 18.26 mmol), $PdCl_2(PPh_3)_2$ (256 mg, 0.365 mmol) and LiCl (5.42 g, 128 mmol) in DMF (100 mL) was added tributylvinyltin (5.31 mL, 18.3 mmol) at room temperature under argon. The mixture was warmed to 90°C and stirred (24 h), then cooled and poured onto ice-water (250 mL) and extracted with EtOAc (2×100 mL). Combined organic extracts were washed with brine (2×100 mL), dried (Na_2SO_4), concentrated and purified by silica gel flash chromatography (EtOAc:hexanes, from 1:20 to 1:10) to provide **8** as a white solid (5.52 g, 73%): mp 77–79°C; $[\alpha]_D^{23}$ +4.2 ($CHCl_3$, c 0.12); ^{1}H NMR ($CDCl_3$) δ 7.34 (10H, m), 7.24 (2H, d, *J*=8.3 Hz), 6.97 (2H, d, *J*=8.1 Hz), 6.67 (1H, dd, *J*=10.7, 17.6 Hz), 5.71 (1H, dd, *J*=1.0, 17.6 Hz), 5.23 (1H, dd, *J*=0.8, 10.5 Hz), 5.20 (1H, m), 5.14 (2H, d, *J*=3.9 Hz), 5.10 (2H, s), 4.69 (1H, m), 3.10 (2H, d, *J*=5.6 Hz). FABMS (+VE, NBA) *m/z* 416 [MH^+]. Anal. calcd for $C_{26}H_{25}NO_4$: C, 75.2; H, 6.1; N, 3.4. Found: C, 75.0; H, 6.1; N, 3.3.

5.3. L-N$^{\alpha}$-*Benzyloxycarbonyl-4-(1,2-dihydroxyethyl)phenylalanine benzyl ester (**9**)*

To a solution of **8** (1.78 g, 4.29 mmol) in acetone:THF:H_2O (6:2:1; 27 mL) was added 4-methylmorpholine *N*-oxide (560 mg, 4.72 mmol) followed by 0.05 M OsO_4 in *tert*-butanol (0.9 mL, 0.045 mmol). The mixture was stirred at room temperature overnight, then treated with 10% Na_2SO_3 (10 mL) for 30 min, diluted with H_2O (50 mL) and extracted with EtOAc (3×50 mL). The combined organic extracts were washed with brine (50 mL), dried (Na_2SO_4), concentrated and purified by silica gel flash chromatography ($CHCl_3$:MeOH, from 40:1 to 20:1) to provide **9** as a white foam (1.81 g, 85%): ^{1}H NMR ($CDCl_3$) δ 7.30–7.41 (10H, m), 7.21 (2H, d, *J*=8.1 Hz), 6.99 (2H, d, *J*=7.6 Hz), 5.21 (1H, m), 5.15 (2H, d, *J*=4.1 Hz), 5.10 (2H, s), 4.77 (1H, dd, *J*=3.4 Hz, 7.8 Hz), 4.70 (1H, m), 3.73 (1H, dd, *J*=3.4

Hz, 11.0 Hz), 3.62 (1H, dd, *J*=8.0 Hz, 11.2 Hz), 3.11 (2H, d, *J*=5.6 Hz), 2.44 (1H, brs), 2.05 (1H, brs). FABMS (+VE, NBA) *m/z* 450 [MH^+].

5.4. L-N$^{\alpha}$-*Benzyloxycarbonyl-4-(formyl)phenylalanine benzyl ester (**10**)*

To a solution of diol **9** (1.70 g, 3.79 mmol) in ether (36 mL) was added a solution of $NaIO_4$ (890 mg, 4.14 mmol) in H_2O (7.2 mL) and the mixture was stirred at room temperature (3 h). The mixture was diluted with ether (50 mL) then washed with water (50 mL) and brine (2×50 mL), dried (Na_2SO_4) and concentrated under vacuum to provide **9** as a white solid sufficiently pure for further use (1.489 g, 94%): mp 65–67°C; $[\alpha]_D^{23}$ +4.9 ($CHCl_3$, c 0.32); ^{1}H NMR ($CDCl_3$) δ 9.95 (1H, s), 7.69 (2H, d, *J*=8.3 Hz), 7.35 (10H, m), 7.14 (2H, d, *J*=8.0 Hz), 5.05–5.29 (5H, m), 4.76 (1H, m), 3.15 (2H, m). FABMS (+VE, NBA) *m/z* 418 [MH^+]. Anal. calcd for $C_{25}H_{23}NO_5 \cdot 1/4H_2O$: C, 71.1; H, 5.6; N, 3.3. Found: C, 71.1; H, 5.6; N, 3.3.

5.5. L-N$^{\alpha}$-*Benzyloxycarbonyl-4-(hydroxymethyl)phenylalanine benzyl ester (**16**)*

To a solution of aldehyde **9** (2.47 g, 5.92 mmol) in THF (10 mL) with EtOH (50 mL) was added $NaBH_4$ (225 mg, 5.92 mmol) at 0°C, and the mixture was stirred (20 min) then diluted with H_2O (100 mL) and stirring continued. The mixture was extracted with EtOAc (2×50 mL) and dried (Na_2SO_4) then concentrated and purified by silica gel flash chromatography ($CHCl_3$:MeOH, from 100:1 to 50:1) to provide **16** as a white solid (2.47 g, 99%): mp 97–99°C; $[\alpha]_D^{23}$ +5.3 ($CHCl_3$, c 0.25); ^{1}H NMR (DMSO-d_6) δ 7.86 (1H, d, *J*=8.0 Hz), 7.17–7.40 (14H, m), 5.11 (2H, s), 4.98 (2H, dd, *J*=12.6, 15.9 Hz), 4.46 (2H, s), 4.27 (1H, m), 3.04 (1H, dd, *J*=5.4, 13.6 Hz), 2.87 (1H, dd, *J*=10.0, 13.7 Hz). FABMS (+VE, NH_3) *m/z* 437 [$(M+NH_4)^+$]. Anal. calcd for $C_{25}H_{25}NO_5$: C, 71.6; H, 6.0; N, 3.3. Found: C, 71.3; H, 6.0; N, 3.3.

5.6. L-N$^{\alpha}$-*Benzyloxycarbonyl-4-(bromomethyl)phenylalanine benzyl ester (**17**)*

To a solution of alcohol **16** (2.35 g, 5.60 mmol) in anhydrous MeCN (50 mL) was added CBr_4 (2.23 g, 6.72 mmol) followed by Ph_3P (1.91 g, 7.28 mmol) at 0°C under argon. After stirring at room temperature (30 min), additional CBr_4 (930 mg, 2.8 mmol) and Ph_3P (734 mg, 2.8 mmol) were added and stirring was continued (30 min). The mixture was concentrated and residue was purified by silica gel flash chromatography (hexane:EtOAc, from 7:1 to 4:1) to provide **17** as a white solid (2.12 g, 79%): mp 90–92°C; $[\alpha]_D^{23}$ +4.4 ($CHCl_3$, c 0.05); ^{1}H NMR ($CDCl_3$) δ 7.37 (10H, m), 7.23 (2H, d, *J*=8.3 Hz), 6.97 (2H, d, *J*=8.1 Hz), 5.22 (1H, d, *J*=8.8 Hz), 5.14 (2H, d, *J*=4.9 Hz), 5.10 (2H, s), 4.71 (1H, m), 4.45 (2H, s), 3.10 (2H, d, *J*=5.7 Hz) [Note: -OH did not show]. FABMS (+VE, NH_3) *m/z* 499 and 501 [$(M+NH_4)^+$]. Anal. calcd for $C_{25}H_{24}BrNO_4$: C, 62.2; H, 5.0; N, 2.9. Found: C, 62.5; H, 5.1; N, 2.9.

5.7. L-N$^{\alpha}$-*Benzyloxycarbonyl-4-[(di*-tert-*butyl)phosphonomethyl]phenylalanine benzyl ester [*L-N-*Cbz-Pmp(^{t}Bu$_2$)-OBn] (**15**)*

To a solution of di-*tert*-butyl phosphite (305 mg, 1.575 mmol) in THF (10 mL) was added 1.0 M lithium bis(trimethylsilyl)amide (LHMDS) in THF (1.6 mL, 1.6 mmol) at −78°C under argon. After 30 min, hexamethylphosphoramide (HMPA) (1.3 mL) was added and the mixture was stirred (30 min), then bromide **17** (760 mg, 1.575 mmol) in THF (3 mL) was added slowly and stirring was continued first at −78°C (2 h) then at 0°C (2 h). The reaction mixture was quenched by addition of aqueous NH_4Cl (20 mL), diluted with EtOAc (50 mL), and washed sequentially with H_2O (50 mL), aqueous NH_4Cl (50

mL) and brine (50 mL), then dried (Na_2SO_4) and concentrated. Crude product was purified by silica gel flash chromatography (hexane:EtOAc, from 3:1 to 2:1) to provide **15** as a clear oil which crystallized on standing (537 mg, 57%): mp 132–134°C; ^{1}H NMR ($CDCl_3$) δ 7.34 (10H, m), 7.12 (2H, dd, *J*=8.1, 2.2 Hz), 6.93 (2H, d, *J*=7.9 Hz), 5.05–5.26 (5H, m), 4.67 (1H, m), 3.09 (2H, m), 3.00 (2H, d, *J*=21.5 Hz), 1.40 (18H, s). FABMS (+VE, NH_3) *m/z* 613 [$(M+NH_4)^+$] and 596 [MH^+]. Anal. calcd for $C_{33}H_{42}NO_7P$: C, 66.5; H, 7.1; N, 2.4. Found: C, 66.6; H, 7.2; N, 2.3.

*5.8. L-4-((Di-tert-butyl)phosphonomethyl)phenylalanine [L-Pmp(^{t}Bu$_2$)-OH] (**11**)*

A solution of L-*N*-Cbz-Pmp(^{t}Bu$_2$)-OBn (**15**) (1.286 g, 2.16 mmol) in MeOH (20 mL) and THF (10 mL) was hydrogenolyzed (H_2-filled balloon) in the presence of palladium black (100 mg) at room temperature (overnight). Catalyst was removed by filtration and the filtrate was taken to dryness to provide **11** as a white foam (795 mg, 99%): ^{1}H NMR (DMSO-d_6) δ 7.17 (4H, m), 3.37 (1H, dd, *J*=3.4, 8.1 Hz), 3.30–3.70 (2H, brm), 3.10 (1H, dd, *J*=4.7, 14.2 Hz), 2.96 (2H, d, *J*=21.2 Hz), 2.82 (1H, dd, *J*=8.1 Hz, 14.6 Hz), 1.37 (18H, s) [Note: COOH did not show]. FABMS (+VE, NH_3) *m/z* 389 [$(M+NH_4)^+$]. Anal. calcd for $C_{18}H_{30}NO_5P\cdot 1/4H_2O$: C, 57.5; H, 8.2; N, 3.7. Found: C, 57.5; H, 8.2; N, 3.7.

*5.9. L-N$^\alpha$-(9-Fluorenylmethoxycarbonyl)-4-[(di-tert-butyl)phosphonomethyl]phenylalanine [L-N-Fmoc-Pmp(^{t}Bu$_2$)-OH] (**3**)*

A mixture of L-Pmp(^{t}Bu$_2$)-OH (**15**) (621 mg, 1.675 mmol), (9-fluorenylmethyloxy)succinimidyl carbonate Fmoc-OSu (572 mg, 1.7 mmol) and $NaHCO_3$ (422 mg, 5 mmol) in dioxane:water (1:1; 24 mL) was stirred at room temperature (overnight). The mixture was cooled to 0°C, acidified to pH 3 with 1N HCl, diluted with H_2O (50 mL), extracted with EtOAc (3×25 mL), and the combined organic phases were dried (Na_2SO_4) and concentrated. Crude product was purified by silica gel flash chromatography ($CHCl_3$:MeOH, 20:1) to provide **3** with ee≥94% (see below) as a white solid (710 mg, 71%): mp 78–80°C: $[\alpha]_D^{23}$ +22 ($CHCl_3$, c 0.20) [lit.[11] $[\alpha]_D^{23}$ +31 ($CHCl_3$, c 0.20)]; ^{1}H NMR (DMSO-d_6) δ 12.60 (1H, brs), 7.88 (2H, d, *J*=7.1 Hz), 7.68 (3H, m), 7.41 (2H, dd, *J*=6.8, 7.6 Hz), 7.33 (2H, m), 7.17 (4H, m), 4.18 (4H, m), 3.05 (1H, m), 2.94 (2H, d, *J*=21.2 Hz), 2.83 (1H, dd, *J*=10.8, 13.4 Hz), 1.32 (18H, s).

5.10. Determination of enantiomeric purity

Dipeptides **18** and **19** were prepared from L-*N*-Fmoc-Pmp(^{t}Bu$_2$)-OH (**3**) using Rink amide resin[17] (0.4 meq/g, purchased from Bachem Corp., Torrance, CA) with Fmoc-protocols similar to those described previously.[18] Fmoc-D,L-Leu and Fmoc-L-Leu-Rink amide resins were prepared by coupling the appropriate Fmoc-protected amino acids to Rink resin, with the resulting Fmoc-protected resins (12.5 mg) then being washed well with several 1 mL portions of *N*-methyl-2-pyrolidoinone (NMP). Fmoc amino protection was removed by treatment with 20% piperidine in NMP (0.5 mL, 1 min followed by 0.5 mL, 20 min). Resins were washed well with NMP (10×1 mL) then coupled overnight with a solution of active ester formed by reacting 12.5 μmol each of L-*N*-Fmoc-Pmp(^{t}Bu$_2$)-OH (**3**), 1-hydroxybenzotriazole (HOBt) and 1,3-diisopropylcarbodiimide (DIPCDI) in NMP (1.0 mL, 10 min). Resins were washed with NMP (10×1 mL), and *N*-terminal Fmoc-protection was removed by treatment with 20% piperidine in NMP (0.5 ml, 5 min). Deblocked resins were first washed with NMP (10×1 mL) and dichloromethane (10×2 mL), then dipeptides were cleaved from the resin using a mixture of trifluoroacetic acid (TFA, 1.85 mL), H_2O (100 μl) and triethylsilane (50 μl) (1 h), taken to dryness and analyzed by HPLC. Retention times of diastereomeric peaks, as determined using dipeptide **18** prepared from racemic D,L-

leucine, indicated diastereomers eluting at 18.8 min and 23.8 min. Enantiomeric contamination of L-*N*-Fmoc-Pmp(^{t}Bu$_2$)-OH (**3**) was then determined by similar analysis of dipeptide **19**, where diastereomeric contamination accounted for an area less than 3% of that observed for the major diastereomer. These results indicated greater than 94% enantiomeric purity.

Acknowledgements

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