Pergamon

Tetrahedron Letters 43 (2002) 4973–4976

TETRAHEDRON LETTERS

A useful synthesis of the Phe-Arg phosphinic acid dipeptide isostere

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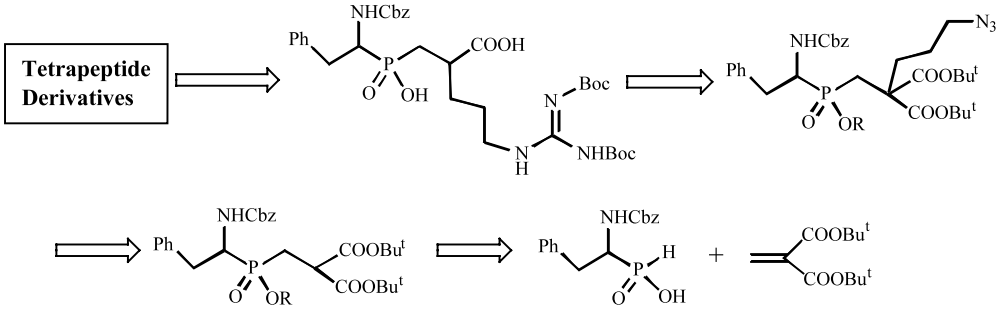
Received 27 March 2002; accepted 14 May 2002

Abstract—A modular method for construction of polypeptides containing the Phe-Arg phosphinic acid isostere is described.

Peptidomimetic analogs have found wide application as bioavailable and potent mimetics of naturally occurring biologically active peptides.[1] Work continues in the field to develop diverse non-peptidic scaffolds and amide isosteres to increase metabolic stability, to restrict the conformational properties of short peptides and to provide three-dimensional mimics of peptide motifs such as β-turns and α-helices.[2,3]

During our design and screening of peptidomimetic receptor agonists, we became interested in synthesizing isosteres of Phe-Arg. Arginine bears a basic guanidino group which is positively charged at neutral pH and is involved in many important physiological and pathophysiological processes. Many enzymes and receptors display a preference for the arginine residue that is found in natural substrates and in synthetic inhibitors.[4,5] Previously, we reported a practical synthesis of Phe-Arg carba analog Boc-D-Phe-Ψ[CH_2CH_2]-L-Arg(NO_2]-OH.[6] Rich et al.[7] reported the protected hydroxyethylene dipeptide isostere of Phe-Arg and tripeptide derivatives as components of potential peptidase inhibitors. Recently, we also reported a novel asymmetric synthesis of Ψ[Phe^P-Phe] analogs.[8]

We now report the successful extension of this work to the ready preparation of phosphinic acid dipeptide isosteric Phe^P-Arg analogs, since unnatural Ψ[P(O)OHCH_2] peptide analogs also provide the peptidomimetic chemist additional metabolically stable isosteres/scaffolds. We expect these and related analogs will allow further opportunities to scan the conformational requirements within receptor ligand pharmacophores. For example, several of the analogs reported herein include potential simplified pharmacophoric mimics of the melanocortin receptor agonist tetra-



Scheme 1.

Keywords: phosphinic acid dipeptide; PheP-Arg isostere; methylenemalonate ester; phosphinate conjugate addition.
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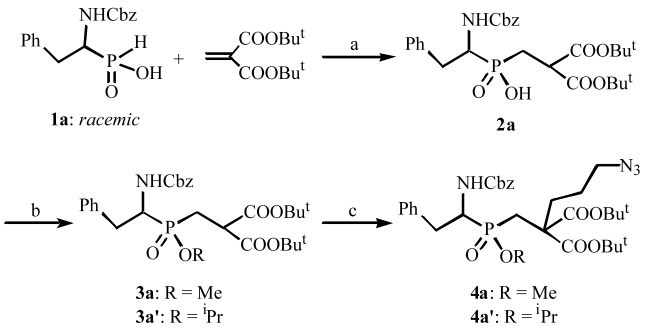
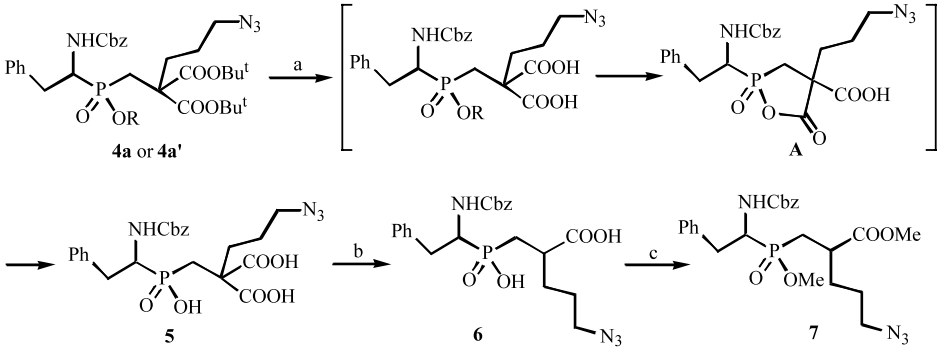
0040-4039/02/$ - see front matter
PII: S0040-4039(02)00957-7



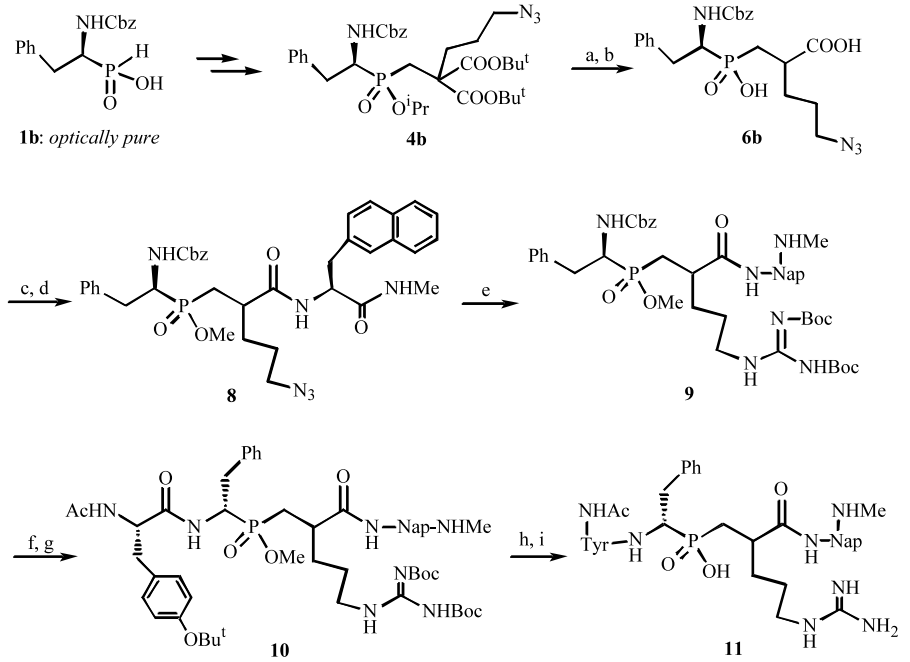
Scheme 2. *Reagents and conditions*: (a) $^{i}Pr_2NEt$, TMS–Cl, CH_2Cl_2; (b) CH_2N_2 for **3a** (68% from **1a**), EDCI, $^{i}PrOH$, CH_2Cl_2 for **3a′** (72% from **1a**); (c) *t*-BuOK, $I(CH_2)_3N_3$, DME, (44% for **4a**, 88% for **4a′**).

peptide recognition sequence His-Phe-Arg-Trp, based on related attempts by Hruby, Benoit, Bednarek, Wikberg and others cited by them.[9,10]

Phosphinic acid dipeptides have been synthesized by conjugate addition of a mono-substituted phosphinate to certain α-substituted acrylates in which the α-substituent comprises the C-terminus side chain, however this route may fail depending on the nature of the side chain.[11] We now describe an alternative modular strategy in which di-*tert*-butyl methylenemalonate serves as the Michael acceptor,[12] permitting subsequent alkylation next to the C-terminus from a common phosphinylmethylenemalonate intermediate to introduce side chain substituents at will. Scheme 1 illustrates this strategy for the construction of dipeptides containing the Phe-Arg phosphinic acid core.



Scheme 3. *Reagents and conditions*: (a) TFA, CH_2Cl_2; (b) toluene, reflux; (c) CH_2N_2, 61% (from **4a**).



Scheme 4. *Reagents and conditions*: (a) TFA, CH_2Cl_2; (b) toluene, reflux; (c) 1,1′-carbonyldiimidazole (CDI), 2-Nap-NHMe, THF; (d) CH_2N_2, 46% (from **4b**); (e) Lindlar catalyst, H_2, *N*,*N*′-bis(*tert*-butoxycarbonyl)-1*H*-pyrazole-1-carboxamidine, EtOH, 63%; (f) 10% Pd–C, HCO_2NH_4, MeOH; (g) AcNH-Tyr(*t*-Bu)-OH, HOBT, EDCI, *N*-methylmorpholine, THF, 79% (from **9**); (h) TMS–Br, CH_2Cl_2; (i) TFA, CH_2Cl_2, 100%.

In the specific example of Scheme 2, the racemic phosphinic acid **1a**[13] was activated by silylation,[14] then reacted with di-*tert*-butyl methylene malonate followed by esterification with diazomethane to afford adduct **3a** in 68% yield. Alkylation of **3a** with 1-azido-3-iodopropane[15] using potassium *tert*-butoxide resulted in partial demethylation to give azide **4a** in only 44% yield. However, when **2a** was converted to the bulkier isopropyl ester **3a′**, subsequent alkylation gave azide **4a′** in 88% yield.

As shown in Scheme 3, treatment of **4a** or **4a′** with TFA–CH_2Cl_2 (1:1, v/v) converted either ester to triacid **5**, presumably through intermediate **A**.[16] When **5** was refluxed in toluene for 4 h, the desired diacid **6** was obtained, which was characterized through the corresponding dimethyl ester **7** (mixture of diastereomers).[17]

To illustrate the convenience of this approach to a tetrapeptide containing the Phe^P-Arg core, we conducted the same initial sequence starting with the known optically pure phosphinic acid **1b**.[13b] The diastereomeric diacids **6b** were coupled with optically pure (*S*)-2-naphthylalanine-*N*-methylamide[18] to give **8** in 46% overall yield from **4b**. Conversion of the azide to guanidine was most conveniently carried out by a one-pot sequence of chemoselective Lindlar reduction[19] and in-situ guanidination with *N*,*N′*-bis(*tert*-butoxycarbonyl)-1*H*-pyrazole-1-carboxamidine, as summarized in Scheme 4.

Debenzylation of **9** at the N-terminus using ammonium formate and 10% Pd–C, followed by coupling with AcNH-Tyr(*t*-Bu)-OH,[20] afforded tetrapeptides **10** in 79% yield. Compounds **8**, **9**, and **10** are all mixtures of four diastereomers, clearly reflected in their H-decoupled ^{31}P NMR spectra, showing four singlet peaks.[21] Demethylation of **10** with bromotrimethylsilane,[22] followed by treatment with trifluoroacetic acid, produced free tetrapeptides **11** which could be separated by HPLC to give approximately equal amounts of both stereochemically pure tetrapeptides **11a** and **11b**,[23] in which phosphorus is no longer a stereogenic center due to prototropic equilibration.

The scope of this strategy toward diverse Phe^P-Arg polypeptides is under investigation. Unfortunately, the series exemplified above did not exhibit biological activity similar to cyclic peptide mimics of the His-Phe-Arg-Trp pharmacophore, suggesting this isosteric approach did not provide conformations necessary for the melanocortin receptors.

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17. Compound **7** is a mixture of eight isomers (i.e. four pairs of enantiomers): ^1H NMR ($CDCl_3$, 400 MHz): δ 1.51–1.72 (m, 5H), 2.27 (m, 1H), 2.84 (m, 2H), 3.24–3.30 (m, 3H), 3.65–3.76 (m, 6H, 2×Me), 4.36 (m, 1H), 4.92–5.14 (m, 3H, NH+Cbz), 7.21–7.35 (m, 10H) ppm; ^{31}P NMR ($CDCl_3$, 162 MHz): δ 52.9, 53.0, 53.1, 54.2 ppm; IR (CH_2Cl_2): 3227 (NH), 3031, 2952, 2098 (N_3), 1716 (C=O), 1260, 1209, 1040 cm^{-1}; MS (APCI, Pos.): 503 (M+H).
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21. Analytical and spectral data for selected compounds: Compound **3b**: a white solid, mp: 85–86°C, ^1H NMR ($CDCl_3$, 400 MHz): δ 1.30 (d, $J = 6.1$ Hz, 3H), 1.38 (d,

$J=6.1$ Hz, 3H), 1.48 (s, 18H), 2.37 (m, 2H), 2.85 (m, 1H), 3.26 (m, 1H), 3.61 (dt, $J=11.6$ Hz, 6.9 Hz, 1H), 4.37 (m, 1H), 4.78 (m, 1H), 4.94, 5.02 (AB, $J_{AB}=12.4$ Hz, 2H), 5.31 (br d, $J=10.3$ Hz, NH), 7.18–7.32 (m, 10H) ppm; ^{31}P NMR ($CDCl_3$, 162 MHz): δ 50.2 ppm; IR (CH_2Cl_2): 3222 (NH), 2979, 1728 (C=O), 1258, 1137 cm^{-1}; MS (APCI, Pos.): 590 (M+H). Anal. calcd for $C_{31}H_{44}NO_8P$: C, 63.14; H, 7.52; N, 2.38; found: C, 63.12; H, 7.70; N, 2.38%. Compound **4b**: a white gum, ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.28 (d, $J=6.1$ Hz, 3H), 1.39 (d, $J=6.1$ Hz, 3H), 1.47 (s, 9H), 1.48 (s, 9H), 1.45–1.53 (m, 2H), 2.17 (m, 2H), 2.38 (m, 2H), 2.79 (m, 1H), 3.23–3.34 (m, 3H), 4.31 (m, 1H), 4.79 (m, 1H), 4.93–5.00 (m, 3H, NH+Cbz), 7.17–7.37 (m, 10H) ppm; ^{31}P NMR ($CDCl_3$, 162 MHz): δ 49.8 ppm; IR (CH_2Cl_2): 3225 (NH), 2978, 2934, 2097 (N_3), 1728 (C=O), 1258, 1141 cm^{-1}. Anal. calcd for $C_{34}H_{49}N_4O_8P$: C, 60.70; H, 7.34; N, 8.33; Found: C, 60.44; H, 7.52; N, 8.09%. Compound **8**: a white solid, ^{1}H NMR (CD_3OD, 400 MHz): δ 1.10–1.40 (m, 3H), 1.70–1.95 (m, 1H), 2.18–2.24 (m, 2H), 2.70, 2.71, 2.77, 2.78 (4×s, 3H, N-Me), 2.40–2.80 (m, 2H), 2.88–3.00 (m, 2H), 3.10–3.50 (m, 3H), 3.51, 3.64, 3.70, 3.79 (4×d, $J=10.4$ Hz, 3H, O-Me), 4.20 (m, 1H), 4.63–4.90 (m, 1H), 4.94–5.03 (m, 2H, Cbz), 7.18–7.31 (m, 10H), 7.40–7.50 (m, 3H), 7.70–7.85 (m, 4H) ppm; ^{31}P NMR (CD_3OD, 162 MHz): δ 55.1, 55.7, 56.7, 56.8 ppm; MS (API-ES, Pos.): 699 (M+H), 721 (M+Na); HRMS (M+H): calcd 699.3060, found: 699.3081. Compound **9**: a white solid, ^{1}H NMR (CD_3OD, 400 MHz): δ 1.08–1.31 (m, 3H), 1.48, 1.49, 1.50, 1.53, 1.54, 1.55, 1.57 (s, 18H, 2×Boc), 1.75 (m, 1H), 2.25 (m, 1H), 2.50 (m, 1H), 2.68, 2.69, 2.76, 2.78 (4×s, 3H, N-Me), 2.65–3.50 (m, 7H), 3.53, 3.66, 3.70, 3.77 (4×d, $J=10.4$ Hz, 3H, OMe), 4.21 (m, 1H), 4.60 (m, 1H), 4.92–5.00 (m, 2H, Cbz), 7.17–7.29 (m, 10H), 7.40–7.45 (m, 3H), 7.74–7.82 (m, 4H) ppm; ^{31}P NMR (CD_3OD, 162 MHz): δ 55.2, 55.9, 56.80, 56.84 ppm; IR (CH_2Cl_2): 3284 (NH), 2977, 1721 (C=O), 1644 (C=O), 1538, 1134, 1048 cm^{-1}; MS (API-ES, Pos.): 915 (M+H), 937 (M+Na); HRMS (M+H): calcd 915.4422, found: 915.4429. Anal. calcd for $C_{48}H_{63}N_6O_{10}P$: C, 63.01; H, 6.94; N, 9.18; found: C, 62.96; H, 7.01; N, 8.92%. Compound **10**: a white solid, ^{1}H NMR (CD_3OD, 400 MHz): δ 1.30, 1.31 (s, 9H, *t*-Bu), 1.48, 1.49, 1.50, 1.55, 1.56 (s, 18H, 2×Boc), 1.14–1.50 (m, 2H), 1.82–1.88 (m, 5H), 2.25 (m, 1H), 2.35–2.55 (m, 3H), 2.55–2.80 (m, 5H), 2.80–3.30 (m, 3H), 3.49–3.78 (m, 5H), 4.42–4.75 (m, 3H), 6.85–7.10 (m, 4H), 7.15–7.35 (m, 5H), 7.35–7.50 (m, 3H), 7.70–7.85 (m, 4H) ppm; ^{31}P NMR (CD_3OD, 162 MHz): δ 53.9, 55.0, 56.3, 56.8 ppm; IR (CH_2Cl_2): 3280 (NH), 2977, 1721 (C=O), 1651 (C=O), 1644 (C=O), 1161, 1134, 1048 cm^{-1}; MS (API-ES, Pos.): 1042 (M+H), 1064 (M+Na); HRMS (M+H): calcd 1042.5419, found: 1042.5400. Anal. calcd for $C_{55}H_{76}N_7O_{11}P$: C, 63.38; H, 7.35; N, 9.41; found: C, 63.29; H, 7.25; N, 9.15%.

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23. Preparative HPLC separation was performed on a Polaris C18-A 10 μ column (50 mm×25 cm), operated at room temperature and eluted at 60 mL/min flow rate, using a linear gradient of water containing 0.1% TFA (from 95 to 0%) and acetonitrile (from 5 to 100%) over 60 min, with UV detection at 214 nm. Compound **11a** (with retention time = 8.61 min): ^{1}H NMR (CD_3OD, 300 MHz): δ 1.30, 1.51 (m, 2H), 1.82–1.88 (m, 5H), 2.25 (m, 1H), 2.37–2.55 (m, 3H), 2.55–2.76 (m, 5H), 2.80–3.30 (m, 3H), 3.49–3.78 (m, 5H), 4.20–4.40 (m, 3H), 6.24 (m, 4H), 6.80–6.65 (m, 5H), 6.91–7.00 (m, 3H), 7.20–7.31 (m, 4H) ppm; ^{13}C NMR (CD_3OD, 75 MHz): δ 174.6, 171.5, 171.4, 170.4, 155.7, 154.5, 136.6, 136.5, 134.2, 132.2, 131.1, 128.4, 127.6, 126.8, 126.5, 126.4, 126.0, 125.9, 125.6, 125.0, 124.6, 124.1, 113.5, 53.8, 52.1 49.7, 48.4, 39.1, 38.5, 36.0, 34.9, 31.6, 29.8, 29.6, 28.4, 24.1, 23.9, 19.8; ^{31}P NMR (CD_3OD, 121 MHz): δ 47.4; MS (ESI): m/z 772.6 (M+1). Compound **11b** (with retention time = 8.96 min): ^{1}H NMR (CD_3OD, 300 MHz): ^{1}H NMR (CD_3OD, 300 MHz): δ 1.32, 1.52 (m, 2H), 1.83–1.87 (m, 5H), 2.26 (m, 1H), 2.37–2.55 (m, 3H), 2.55–2.78 (m, 5H), 2.80–3.31 (m, 3H), 3.49–3.78 (m, 5H), 4.20–4.40 (m, 3H), 6.24 (m, 4H), 6.80–6.45 (m, 5H), 6.85–7.00 (m, 3H), 7.22–7.34 (m, 4H) ppm; ^{13}C NMR (CD_3OD, 75 MHz): δ 174.4, 171.6, 170.8, 170.4, 155.2, 154.5, 136.2, 136.1, 134.2, 132.1, 131.0, 128.5, 127.8, 126.8, 126.4, 126.0, 125.9, 125.6, 125.0, 124.6, 124.1, 113.5, 53.8, 52.1 49.7, 48.4, 39.1, 38.5, 36.4, 34.9, 31.6, 29.3, 29.6, 28.4, 24.2, 23.8, 19.8; ^{31}P NMR (CD_3OD, 121 MHz): δ 49.0; MS (ESI): m/z 772.6 (M+1). Because we have been unable to obtain an X-ray crystal of either **11a** or **11b**, their stereochemical assignments are undetermined.