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Constrained phenylalanyl peptides *via* a [2+2+2]-cycloaddition strategy

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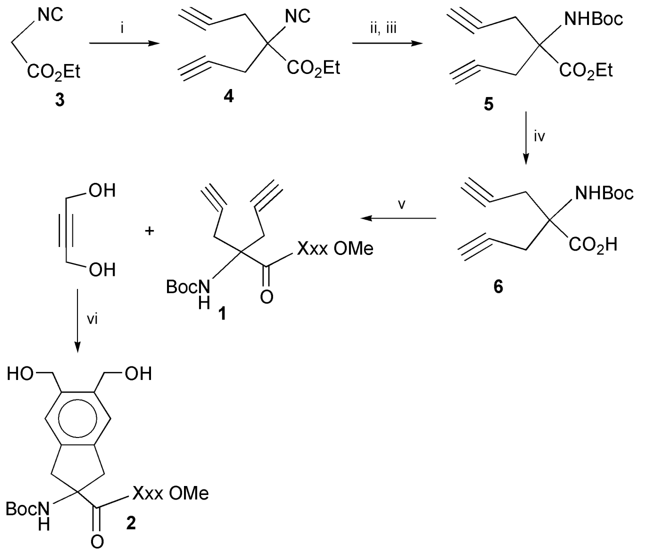
Peptide modification potentially valuable for peptidomimetic and combinatorial chemistry applications is described involving a [2+2+2]-cycloaddition reaction leading to conformationally constrained phenylalanyl peptides.

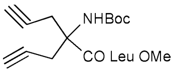
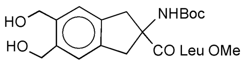
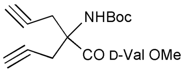
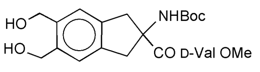
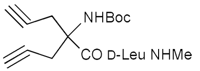
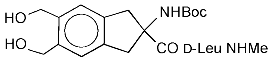
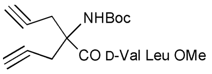
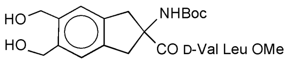
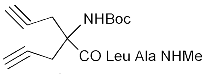
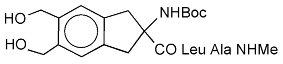
Aromatic amino acids like phenylalanine and tyrosine are often important elements of peptide pharmacophores. Novel methods to generate conformationally restrained analogs from suitable precursor peptides evoke interest,[1–3] particularly for combinatorial chemistry applications. A variety of benzenoid molecules are accessible through [2+2+2] or [4+2]-cycloaddition reactions.[4] Applied to suitable peptide precursors, the reaction may provide an approach to conformationally constrained aryl amino acid residues *in situ*. Artificial amino acids with olefin, diene, allene or acetylene groups in the side chain have been described[5] and could be useful synthons for conformationally constrained aryl amino acid residues approachable in a [2+2+2]-type cycloaddition reaction. Conversion of a suitable diacetylenic dipeptide precursor **1** into a constrained phenylalanyl peptide **2** in a [2+2+2]-cycloaddition reaction catalyzed by Wilkinson's catalyst[6] is illustrated in Scheme 1.† The reaction conditions are mild enough to be compatible with the acid and base labile protecting groups that are normally required for peptide synthesis.

The precursor peptide **1** could be easily made in a standard peptide synthesis protocol starting from the dipropargyl glycine **6** as the specific building block amino acid. The Boc-protected form of **6** was easily made from ethyl isocyanoacetate **3** serving as the glycine synthon.[7] Dipropargylation in refluxing acetonitrile–K$_2$CO$_3$ in the presence of tetrabutylammonium hydrogen sulfate as the phase transfer catalyst furnished the isonitrile derivative **4** in good yield (69%). Acid catalysed hydrolysis, followed by Boc-protection gave **5**. Saponification of **5** furnished the Boc protected amino acid **6**.



Scheme 1 *Reagents*: (i) K$_2$CO$_3$, propargyl bromide, ^{n}Bu$_4$NHSO$_4$; (ii) HCl, EtOH; (iii) CHCl$_3$, (Boc)$_2$O; (iv) aq NaOH, MeOH; (v) HCl H$_2$N Xxx CO$_2$Me, HOBt, THF, NMM; (vi) (Ph$_3$P)$_3$RhCl, EtOH, reflux.

Table 1 Representative constrained phenylalanyl peptides

Starting peptide	[2+2+2]-Cycloaddition product	Yield (%)[a]
 **1a**	 **2a**	66
 **1b**	 **2b**	54
 **1c**	 **2c**	75
 **1d**	 **2d**	70
 **1e**	 **2e**	65

[a] Yields refers to [2+2+2]-cycloaddition product

Condensation of the Boc-protected building block amino acid **6** with various amino acid ester derivatives in a standard DCC-mediated peptide procedure[8] furnished the dipeptide (*e.g.*) **1a** or longer peptides Boc-Dprg-Xxx-OMe (with Xxx = L-Leu, D-Val, D-Leu, D-Val-L-Leu, L-Leu-L-Ala, L-Leu-D-Val-L-Leu). Treatment with five-fold excess of but-2-yn-1,4-diol, a model monoyne so chosen as to avoid the formation of diastereomers, furnished representative constrained phenylalanyl peptides shown in Table 1.

The additional methylene bridge connecting the α-carbon with the aromatic ring not only restrains the phenylalanyl moiety but also the backbone, restricting its conformational freedom, and this has potential to influence the pharmacological profile[9] of the parent Phe or Tyr peptide variant. Additional structural variations are feasible and can add to the versatility of the combinatorial chemistry approaches. For instance, the diol functionality in the product peptides here is a useful site for possible further molecular manipulations.

In summary, a peptide modification capable of generating constrained phenylalanyl peptide variants in a [2+2+2]-cycloaddition reaction is reported and could be potentially useful for both peptidomimetic and combinatorial chemistry applications.

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Notes and references

† Dprg = dipropargyl glycine. Boc = *tert*-butoxycarbonyl. The peptides were purified by silica gel column chromatography or by HPLC. The purity of the peptides was judged by TLC and high field (300 MHz) NMR spectroscopy.

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(**1a**) ^{1}H NMR 300 MHz, CDCl$_3$) δ 7.02 (broad, 1H), 5.38 (broad s, 1H), 4.60–4.67 (td, J = 8.6, 5.1 Hz, 1H), 3.72 (s, 3H), 2.86–3.05 (m, 4H), 2.09–2.14 (m, 2H), 1.58–1.67 (m, 3H), 1.46 (s, 9H), 0.93 (t, J = 6.9 Hz, 6H). $[\alpha]_D$ −38.89° (*c*. 1). Mass: 378 (M + H).

(**1b**) ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.13 (broad, 1H), 5.35 (broad s, 1H), 4.56 (dd, J = 8.6, 4.5 Hz, 1H), 3.73 (s, 3H), 2.87–3.06 (m, 4H), 2.16–2.22 (m, 1H), 2.10–2.13 (m, 2H), 1.46 (s, 9H), 0.96 (d, J = 6.7 Hz, 3H), 0.91 (d, J = 6.9 Hz, 3H). $[\alpha]_D$ +11.71° (*c*. 1). Mass: 364 (M + H).

(**1c**) ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.00 (broad s, 1H), 6.54 (d, J = 8.0 Hz, 1H), 5.34 (s, 1H), 4.45–4.52 (m, 1H), 2.80–3.20 (m, 4H), 2.74 (d, J = 4.7 Hz, 3H), 2.17 (t, J = 2.7 Hz, 1H), 2.12 (t, J = 2.5 Hz, 1H), 1.68–1.95 (m, 3H), 1.47 (s, 9H), 0.93 (d, J = 2.7 Hz, 3H), 0.90 (d, J = 2.5 Hz, 3H). $[\alpha]_D$ −11.87° (*c*. 1). Mass: 377 (M + H).

(**1d**) ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.24 (broad, 1H), 6.68 (d, J = 8.0 Hz, 1H), 5.29 (s, 1H), 4.52–4.56 (m, 1H), 4.30 (dd, J = 7.8, 3.6 Hz, 1H), 3.67 (s, 3H), 2.84–3.20 (m, 4H), 2.19 (t, J = 2.9 Hz, 1H), 2.13 (t, J = 2.5 Hz, 1H), 1.91–1.96 (m, 1H) 1.67–1.73 (m, 3H), 1.47 (s, 9H), 0.90–0.93 (t, 12H). $[\alpha]_D$ + 10.55° (*c*. 1). Mass: 378 (M + H). $[\alpha]_D$ + 0.011° (*c*. 1). Mass: 477 (M + H).

(**1e**) ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.41 (d, J = 8.0 Hz, 1H), 6.81 (d, J = 4.0 Hz, 1H), 6.71 (d, J = 4.7 Hz, 1H), 5.43 (s, 1H), 4.47–4.53 (m, 1H), 4.21–4.27 (m, 1H), 2.81–3.15 (overlapped two ABq, 4H), 2.77 (d, J = 4.67 Hz, 3H), 2.22 (t, J = 3.0 Hz, 1H), 2.13 (t, J = 2.7 Hz, 1H), 1.71–1.85 (m, 2H), 1.46 (s, 9H), 1.42 (d, J = 7.2 Hz, 3H), 0.98 (d, J = 6.2 Hz, 3H), 0.94 (d, J = 6.0 Hz, 3H). $[\alpha]_D$ + 10.55° (*c*. 1). Mass: 448 (M + H).

(**1f**) ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.10 (broad, 1H), 6.78 (d, 1H), 6.69 (d, 1H), 5.26 (s, 1H), 4.48–4.56 (m, 1H), 4.35–4.42 (m, 1H), 4.18–4.25 (m, 1H), 3.69 (s, 3H), 2.77–3.10 (m, 4H), 2.12–2.30 (m, 3H), 1.60–1.85 (m, 3H), 1.46 (s, 9H), 0.91–0.98 (m, 18H). $[\alpha]_D$ − 24.52° (*c*. 1). Mass: 590 (M + H).

(**2a**) ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.20 (s, 1H), 7.17 (s, 1H), 6.91 (broad, 1H), 5.20 (s, 1H), 4.71 (q, J = 11.0 Hz, 4H), 4.59–4.65 (m, 1H), 3.70 (s, 3H), 3.72 (1/2 ABq, J = 16.8 Hz, 1H), 3.54 (1/2 ABq, J = 16.4 Hz, 1H), 3.15–3.25 (m, 2H), 1.51–1.61 (m, 3H), 1.42 (s, 9H), 0.92 (t, J = 5.8 Hz, 6H). $[\alpha]_D$ +15.14° (*c*. 1). Mass: 464 (M + H).

(**2b**) ^{1}H NMR (300 MHz, CHCl$_3$) δ 7.17 (s, 1H), 7.15 (s, 1H), 7.11 (d, J = 7.6 Hz, 1H), 5.36 (s, 1H), 4.65 (q, J = 12.0 Hz, 4H), 4.52–4.56 (m, 1H), 3.72 (s, 3H), 3.69 (1/2 ABq, J = 16.4 Hz, 1H), 3.51 (1/2 ABq, J = 16.5 Hz, 1H), 3.18 (dd, J = 26.8, 17.5 Hz, 2H), 2.17–2.19 (m, 1H), 1.42 (s, 9H), 0.95 (d, J = 6.9 Hz, 3H), 0.87 (d, J = 6.9 Hz, 3H). $[\alpha]_D$ −4.36° (*c*. 1). Mass: 450 (M + H).

(**2c**) ^{1}H NMR (300 MHz, CD$_3$OD) δ 8.01 (d, J = 8.0 Hz, 1H), 7.84 (broad, 1H), 7.24 (s, 3H), 4.62 (s, 4H), 4.36–4.41 (m, 1H), 3.71 (1/2 ABq, J = 16.4 Hz, 1H), 3.43 (1/2 ABq, 16.4 Hz, 1H), 3.10 (dd, J = 16.3, 6.9 Hz, 2H), 2.73 (d, J = 4.39 Hz, 3H), 1.65 (m, 3H), 1.44 (s, 9H), 0.94 (d, J = 5.85 Hz, 3H), 0.89 (d, J = 5.49 Hz, 3H). $[\alpha]_D$ + 13.11° (*c*. 1). Mass: 463 (M + H).

(**2d**) ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.27 (broad, 1H), 7.22 (s, 1H), 7.18 (s, 1H), 6.75 (d, J = 5.4 Hz, 1H), 5.36 (s, 1H), 4.62–4.80 (m, 4H), 4.48–4.55 (m, 1H), 4.29 (dd, J = 7.8, 4.3 Hz, 1H), 3.86 (1/2 ABq, J = 17.2 Hz, 1H), 3.68 (s, 3H), 3.52 (1/2 ABq, J = 16.4 Hz, 1H), 3.0 (dd, J = 40.0, 16.8 Hz, 2H), 2.44 (m, 1H), 1.66 (m, 3H), 1.42 (s, 9H), 0.91–0.97 (t, 12H). $[\alpha]_D$ −13.31° (*c*. 1). Mass: 563 (M + H).

(**2e**) ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.54 (d, J = 7.6 Hz, 1H), 7.22 (s, 1H), 7.19 (s, 1H), 6.91 (d, J = 3.6 Hz, 1H), 6.77 (d, 5.4 Hz, 1H), 5.81 (s, 1H), 4.61–4.78 (m, 4H), 4.46–4.51 (m, 1H), 4.23–4.29 (m, 1H), 3.95 (1/2 ABq, J = 16.8 Hz, 1H), 3.41 (1/2 ABq, J = 16.8 Hz, 1H), 3.04 (d, J = 16.8 Hz, 2H), 2.71 (d, J = 4.3 Hz, 3H), 1.70 (broad, 3H), 1.42 (s, 12H), 0.98 (d, J = 6.2 Hz, 3H), 0.94 (d, J = 6.3 Hz, 3H). $[\alpha]_D$ −7.89° (*c*. 1). Mass: 534 (M + H).

(**2f**) ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.43 (d, 2H), 6.24 (d, 2H), 5.32–5.38 (m, 2H), 4.58–4.65 (m, 3H), 4.18–4.23 (m, 4H), 3.72 (s, 3H), 2.78–2.81 (m, 2H), 2.32–2.37 (m, 2H), 2.21 (m, 1H), 1.63 (m, 6H), 1.25 (s, 9H), 0.93–0.98 (m, 18H). $[\alpha]_D$ + 4.96° (*c*. 1). Mass: 713 (M + HCl).

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