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Synthesis of the Pro-Gly Dipeptide Alkene Isostere Using Olefin Cross-Metathesis

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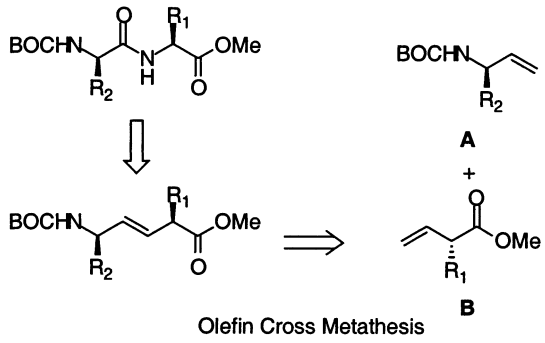
Abstract: An approach to the synthesis of dipeptide olefin isosteres using intermolecular olefin cross-metathesis is presented. In particular, a synthesis of the Pro-Gly isostere (**1**) is reported. Conversion of *N*-BOC-proline into the corresponding vinyl-substituted carbamate provides the N-terminal cross-metathesis partner (**2**). Methyl 3-butenoate (**3**) is employed as the C-terminal component. Treatment of the two partners in an optimized molar ratio affords the cross product **1** (83% yield). Three other examples are demonstrated to evaluate the potential of the approach.

Isosteric surrogates for the amide bond have been a focus of intense research for some years. In particular, the field of peptidomimetics has stimulated this field, since isosteric replacement of amides in bioactive peptides is often proposed to lead to elevated bioavailability.[1,2] More recently, isosteres have been used as probes in mechanistic studies targeted at dissecting the role of individual amides in peptide-based asymmetric catalysts. In this context, we recently required a derivative of the Pro-Gly (**1**) dipeptide isostere for one such investigation.[3] For synthesis, we adapted the protocol of Sammes, which was based on a multistep route that relies on Wittig olefination chemistry.[4] As an alternative, we have now investigated olefin cross-metathesis as a potentially more straightforward route.[5]

In principle, olefin metathesis provides a convergent appproach to the synthesis of the target molecules (Scheme 1). Replacement of the internal amide of the dipeptide with a *trans*-alkene yields an unsaturated β,γ-unsaturated-δ-amino acid. Retrosynthetic disconnection of the internal alkene yields an allylic amine for the N-terminal partner (**A**);[6] the C-terminal partner arises as a 3-butenoate ester (**B**). Since these two synthons could be accessed by known methods, their coupling by olefin metathesis would yield the desired product.

SCHEME 1



Since our recent studies of peptide-based asymmetric catalysis required the synthesis of **1**, our studies required vinyl-substituted pyrrolidine **2** (eq 1). BOC-protected proline methyl ester was reduced to the corresponding aldehyde in the presence of DIBAL in accordance with literature precedent.[4] Standard Wittig olefination (CH_3PPh_3Br, *n*BuLi, THF, −78 °C, 41%) delivered vinyl-substituted pyrrolidine (**2**). The issue of potential racemization was addressed at a later point, through direct analysis of the optical purity of **1**. We were able to confirm that the entire synthesis occurs with <10% racemization, as compound **1** was obtained in 80% ee.[7] It is significant to note that the minor enantiomer of the desired peptidomimetic is effectively removed during subsequent peptide synthesis since peptide-derived diastereomers are often readily separable by conventional chromatography. This is indeed our experience with peptides containing isostere **1**. The critical olefin cross-metathesis reaction was then demonstrated to proceed in 83% yield (based on **3**) following carefully optimized conditions (CH_2Cl_2, 0.19 M, 40 °C). In particular, methyl 3-butenoate (**3**, 1 equiv) was combined with pyrrolidine **2** (5 equiv) and the Grubbs catalyst (**4**)[8] to afford **1** in 83% yield. Presumably, the need for a molar ratio ≠ 1:1 is due to the differential reactivity of the two olefin coupling partners. In the case of the Pro-Gly alkene isostere, it is unfortunate that the

(1) For several examples of the synthesis of *trans*-alkene dipeptide isosteres, see: (a) Spaltenstein, A.; Carpino, P. A.; Miyake, F.; Hopkins, P. B. *J. Org. Chem.* **1987**, *52*, 3759. (b) Ibuka, T.; Habashita, H.; Otaka, A.; Fujii, N.; Oguchi, Y.; Uyehara, T.; Yamamoto, Y. *J. Org. Chem.* **1991**, *56*, 4370. (c) Tourwe, D.; Couder, J.; Ceusters, M.; Meert, D.; Burks, T. F.; Kramer, T. H.; Davis, P.; Knapp, R.; Yamamura, H. I.; Leysen, J. E.; Van Binst, G. *Int. J. Pept. Protein Res.* **1992**, *39*, 131. (d) Wipf, P.; Fritch, P. C. *J. Org. Chem.* **1994**, *59*, 4875. (e) Gardner, R. R.; Liang, G.-B.; Gellman, S. H. *J. Am. Chem. Soc.* **1995**, *117*, 3280. (f) Masse, C. E.; Knight, B. S.; Stavropoulos, P.; Panek, J. S. *J. Am. Chem. Soc.* **1997**, *119*, 6040. (g) Wipf, P.; Henninger, T. C.; Geib, S. J. *J. Org. Chem.* **1998**, *63*, 6088. (h) Tamamura, H.; Yamashita, M.; Nakajima, Y.; Sakano, K.; Otaka, A.; Ohno, H.; Ibuka, T.; Fujii, N. *J. Chem. Soc., Perkin Trans. 1* **1999**, 2983.

(2) For a general review of peptidomimetics, see: (a) Gante, J. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 1699. (b) Bursavich, M. G.; Rich, D. H. *J. Med. Chem.* **2002**, *45*, 541.

(3) Vasbinder, M. M.; Jarvo, E. R.; Miller, S. J. *Angew. Chem., Int. Ed.* **2001**, *40*, 2824.

(4) Miles, N. J.; Sammes, P. G.; Kennewell, P. D.; Westwood, R. *J. Chem. Soc., Perkin Trans. 1* **1985**, 2299.

(5) For several recent examples of olefin cross-metathesis, see: (a) Chatterjee, A. K.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 1751. (b) Blackwell, H. E.; O'Leary, D. J.; Chatterjee, A. K.; Washenfelder, R. A.; Bussmann, D. A.; Grubbs, R. H. *J. Am. Chem. Soc.* **2000**, *122*, 58. (c) Choi, T.; Chatterjee, A. K.; Grubbs, R. H. *Angew. Chem., Int. Ed.* **2001**, *40*, 1277.

(6) All studies were performed on BOC-protected amines to prevent amine binding to the catalyst.

(7) The optical purity of **1** was rigorously determined using ^{19}F NMR spectroscopy to analyze the (*S*)-(+)-Mosher amide derived from compound **1**. Prior to formation of the amide, isostere **1** was subjected to standard TFA deprotection of the BOC-group. For (*S*)-(+)-Mosher amide of (±)-**1**: ^{19}F NMR ($CFCl_3$, 500 MHz, 50 °C) δ −70.59 (s, 3F), −71.08 (s, 3F). For (*S*)-(+)-Mosher amide of optically enriched compound **1**: ^{19}F NMR ($CFCl_3$, 500 MHz, 50 °C) major isomer peak δ −71.14 (s, 3F), minor isomer peak δ −69.91 (s, 3F). ^{19}F NMR integration shows <10% racemization of compound **1** (i.e., compound **1** exhibits 80% ee). Optical rotation of compound **1** was compared to the literature,[4] $[\alpha]_D^{20}$ −21.4; compound **1** prepared through the method described in (eq 1), $[\alpha]_D^{20}$ −23.7 (*c* 1.0, MeOH; 80% ee).

(8) (a) Schwab, P.; Grubbs, R. H.; Ziller, J. W. *J. Am. Chem. Soc.* **1996**, *118*, 100. (b) Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 953.

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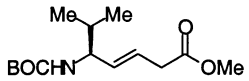
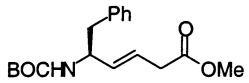
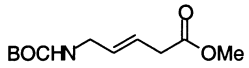
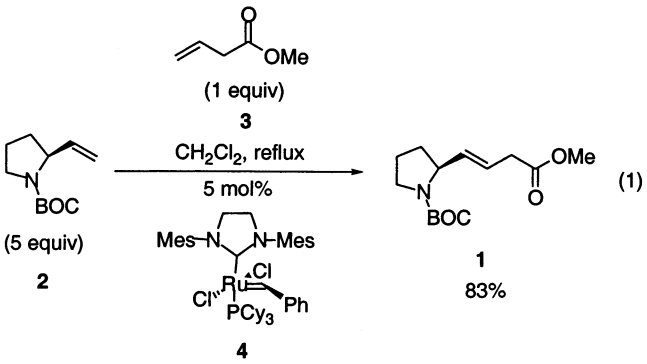
TABLE 1. Dipeptide Isosteres Prepared by Cross-Metathesis[a]

Entry	Product	Amine equiv	Yield (%) (E/Z)
1		3.0	60 (>10:1)
2		3.0	67 (>10:1)
3		2.0	31 (>10:1)

[a] All reactions were conducted with the ester monomer as the limiting agent and with the amine monomer in excess. Reactions in Table 1 were conducted on racemic material. See Experimental Section for details.

"more expensive" piece is used in excess.[9] Nevertheless, the overall synthesis of Pro-Gly isostere (**1**) proceeds in good overall yield and is operationally straightforward in comparison to preexisting routes.



While we have not carried out a comprehensive study of all possible combinations of amino acids for derivatization and coupling to the corresponding dipeptide isosteres, we have examined several examples to demonstrate that the approach may have general potential. As shown in Table 1, cross products can be obtained in reasonable yields when allylic amines based on valine or phenylalanine are crossed with methyl 3-butenoate (entries 1 and 2, 60 and 67% yields, respectively).[10,11] Likewise, the Gly-Gly dipeptide isostere can be prepared in 31% yield using the standard procedure (entry 3). In each case, the *E*/*Z* ratio was found to be 10:1 or greater (^{1}H NMR analysis). Although the yield is low in this last case, the ready availability of each starting material for this particular cross-metathesis makes the method attractive. In all cases, the competing byproducts are those derived from homodimerization of the individual cross partners.

In summary, we have developed an efficient synthesis of the Pro-Gly dipeptide alkene isostere that takes advantage of metal-catalyzed olefin cross-metathesis. The procedure relies on straightforward derivatization of proline and coupling to a commercially available butenoate ester. In addition, three other examples have been carried out to demonstrate that the approach may have more general utility in its application to other dipeptide alkene isosteric peptidomimetics.

Experimental Section

General. Proton NMR spectra (400 MHz) are reported in parts per million (δ) relative to internal tetramethylsilane (TMS, δ 0.0) or with the solvent reference relative to TMS employed as the internal standard ($CDCl_3$, δ 7.26 ppm). Data are reported as follows: chemical shift (multiplicity [singlet (s), doublet (d), triplet (t), quartet (q), and multiplet (m)], coupling constants [Hz], integration). Carbon NMR spectra (100 MHz) were recorded with complete proton decoupling. Carbon chemical shifts are reported in parts per million (δ) relative to TMS with the respective solvent resonance as the internal standard ($CDCl_3$, δ 77.0). Fluorine NMR spectra are reported in parts per million (δ) relative to internal fluorotrichloromethane (δ 0.0 ppm) as the internal standard. NMR data were collected at 25 °C, unless otherwise indicated. Analytical thin-layer chromatography (TLC) was performed using Silica Gel 60 F254 precoated plates (0.25 mm thickness). TLC R_f values are reported. Visualization was accomplished by irradiation with a UV lamp and/or staining with $KMnO_4$ solution. Flash column chromatography was performed using Silica Gel 60A (32−63 μm). Optical rotations were at the sodium D line (path length 50 mm). Elemental analyses were performed by Robertson Microlit (Madison, NJ). High-resolution mass spectra were obtained at the Mass Spectrometry Facilities at Boston College (Chestnut Hill, MA). The method of ionization is given in parentheses.

All reactions were carried out under a nitrogen atmosphere employing oven- and flame-dried glassware. All solvents were distilled from appropriate drying agents prior to use. Methyl 3-butenoate was used as received.

Pro-Gly Isostere (1). To a solution of Grubbs catalyst **4** (10.6 mg, 0.0125 mmol) in 1.3 mL CH_2Cl_2 were added simultaneously via syringe pyrrolidine **2** (247 mg, 1.25 mmol) and methyl 3-butenoate (26.7 μL, 0.250 mmol). The flask was fitted with a reflux condensor, and the resulting maroon solution was refluxed (40 °C) under nitrogen for 24 h. The black reaction mixture was then concentrated under reduced pressure and purified directly by silica gel chromatography (3%−20% ethyl acetate/hexanes). The desired hetereodimer was isolated as a clear viscous oil (83% yield based on ester). Recovery of any unreacted pyrrolidine **2** could be achieved and resubmitted to the above reaction conditions. Isolation of homodimerization byproduct resulting from methyl 3-butenoate accounts for the remaining mass balance. Characterization of compound **1** has been previously reported.[4]

The remaining isosteres (entries 1−3) were synthesized as described above with stoichiometry as indicated in Table 1. The reaction of entry 3 was allowed to reflux (40 °C) under nitrogen for 12 h. Longer reaction times (greater than 12 h) or increased reaction temperatures resulted in formation of the isomerized, conjugated olefin as an inseparable mixture of isomers.[12]

Val-Gly Isostere (Entry 1). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.72−5.64 (m, 1H), 5.50 (dd, J = 5.1, 15.4 Hz, 1H), 4.54 (broad s, 1H), 3.98 (broad s, 1H), 3.68 (s, 3H), 3.08 (d, J = 7.0 Hz, 2H), 1.77 (broad s, 1H), 1.44 (s, 9H), 0.89 (m, 6H); ^{13}C NMR ($CDCl_3$,

(9) Unreacted pyrrolidine **2** can be recovered upon flash chromatography (0.8−1.6 equiv in three separate experiments) and resubmitted to olefin cross-metathesis.

(10) For alternative syntheses of the Phe-Gly (*E*)-alkene dipeptide isostere, see: (a) Cox, M. T.; Heaton, D. W.; Horbury, J. *J. Chem. Soc., Chem. Commun.* **1980**, 799. (b) Jenmalm, A.; Berts, W.; Li, Y.-L.; Luthman, K.; Csoregh, I.; Hacksell, U. *J. Org. Chem.* **1994**, *59*, 1139. (c) Kranz, M.; Kessler, H. *Tetrahedron Lett.* **1996**, *37*, 5359.

(11) For the synthesis of the requisite allylic amines based on valine and phenylalanine, see: (a) Liu, G.; Cogan, D. A.; Ellman, J. A. *J. Am. Chem. Soc.* **1997**, *119*, 9913. (b) Cogan, D. A.; Liu, G.; Ellman, J. A. *Tetrahedron* **1999**, *55*, 8883.

(12) For representative observations of olefin isomerization during olefin metathesis reactions, see: (a) Joe, D.; Overman, L. E. *Tetrahedron Lett.* **1997**, *38*, 8635. (b) Cadot, C.; Dalko, P. I.; Cossy, J. *Tetrahedron Lett.* **2002**, *43*, 1839.

100 MHz) δ 171.9, 155.5, 133.3, 122.8, 79.3, 57.3, 51.9, 37.8, 32.7, 28.6, 18.9, 18.4; IR (0.005 M/CH_2Cl_2, cm^{-1}) 3370, 2961, 2936, 2873, 1741, 1699; TLC R_f 0.52 (30% ethyl acetate/hexanes). Anal. Calcd for $C_{14}H_{25}NO_4$: C, 61.97; H, 9.29; N, 5.16. Found: C, 62.21; H, 9.44; N, 5.13. Exact mass calcd for $[C_{14}H_{25}N_1O_4Na]+$ *m*/*z* 294.1681, found 294.1677 (ESI).

Phe-Gly Isostere (Entry 2). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.30−7.16 (broad m, 5H), 5.68−5.60 (m, 1H), 5.56 (dd, J = 5.1, 15.7 Hz, 1H), 4.50 (broad s, 1H), 4.41 (broad s, 1H), 3.67 (s, 3H), 3.04 (d, J = 6.6 Hz, 2H), 2.83 (d, J = 6.2 Hz, 2H), 1.40 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 171.6, 154.8, 137.1, 133.7, 129.4, 128.1, 126.2, 122.3, 79.3, 52.7, 51.8, 41.6, 37.5, 28.4; IR (0.005 M/CH_2Cl_2, cm^{-1}) 3370, 2974, 2930, 1740, 1712; TLC R_f 0.25 (30% ethyl acetate/hexanes). Anal. Calcd for $C_{18}H_{25}NO_4$: C, 67.69; H, 7.89; N, 4.39. Found: C, 67.51; H, 7.85; N, 4.36. Exact mass calcd for $[C_{18}H_{25}N_1O_4Na]+$ *m*/*z* 342.1681, found 342.1695 (ESI).

Gly-Gly Isostere (Entry 3). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.75−5.67 (m, 1H), 5.64−5.57 (m, 1H), 4.64 (broad s, 1H), 3.74 (broad m, 2H), 3.69 (s, 3H), 3.08(d, J = 6.9 Hz, 2H), 1.44 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 171.9, 155.6, 130.8, 123.6, 79.5, 52.1, 42.3, 37.6, 28.6; IR (0.005 M/CH_2Cl_2, cm^{-1}) 3357, 2977, 2954, 2931, 1740, 1714; TLC R_f 0.34 (30% ethyl acetate/hexanes). Anal. Calcd for $C_{11}H_{19}NO_4$: C, 57.62; H, 8.35; N, 6.11. Found: C, 57.63; H, 8.49; N, 6.27. Exact mass calcd for $[C_{11}H_{19}N_1O_4$-Na]+ *m*/*z* 252.1212, found 252.1200 (ESI). The isomerized olefin accounts for on average 5−10% of the mass balance; the two olefins are inseparable on silica gel.

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