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AMIDE BOND SURROGATES: A GENERAL SYNTHETIC ROUTE TO TRANS CARBON-CARBON DOUBLE BOND ISOSTERES.+

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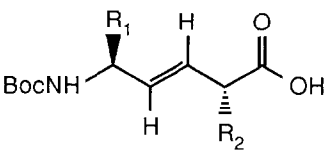
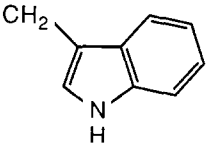
Summary: A practical synthesis toward trans double bond replacements of amide bond pseudopeptides has been accomplished. This methodology provides a general route to a wide range of modified peptide analogs which may have biological significance.

The concept of replacing amide bonds in peptides with suitable isosteric units has been drawing a great deal of attention in recent years. Such modified peptide analogs have the potential for circumventing some of the therapeutic limitations of peptides, i.e., poor enzymatic stability, poor oral absorption, and marginal ability to cross the blood-brain barrier. Several amide bond replacements have been reported previously. Among these amide bond mimics, the trans carbon-carbon double bond appears to be the most suitable in terms of mimicking the rigidity, bond angle and bond length of the amide bond.[1,2]

In designing syntheses of double bond isosteric pseudodipeptides having the general structure **1**, reaction schemes must be employed that are compatible with sensitive functionalities present in certain natural amino acids (e.g., Trp, Asp, Ser, etc.). In addition, it is highly desirable to control the stereochemistry at both alpha-centers and at the double bond. So far, existing methodologies have provided double bond replacement analogs with limited substitution patterns (e.g. Gly-Gly[3c], Leu-Gly[3e], Tyr-Gly[2a], Pro-Gly[3a], Phe-Phe[3b,3d], Tyr-Ala[3d], Pro-Phe[3a], Ala-Ala[3a], Pro-Leu[3a]).



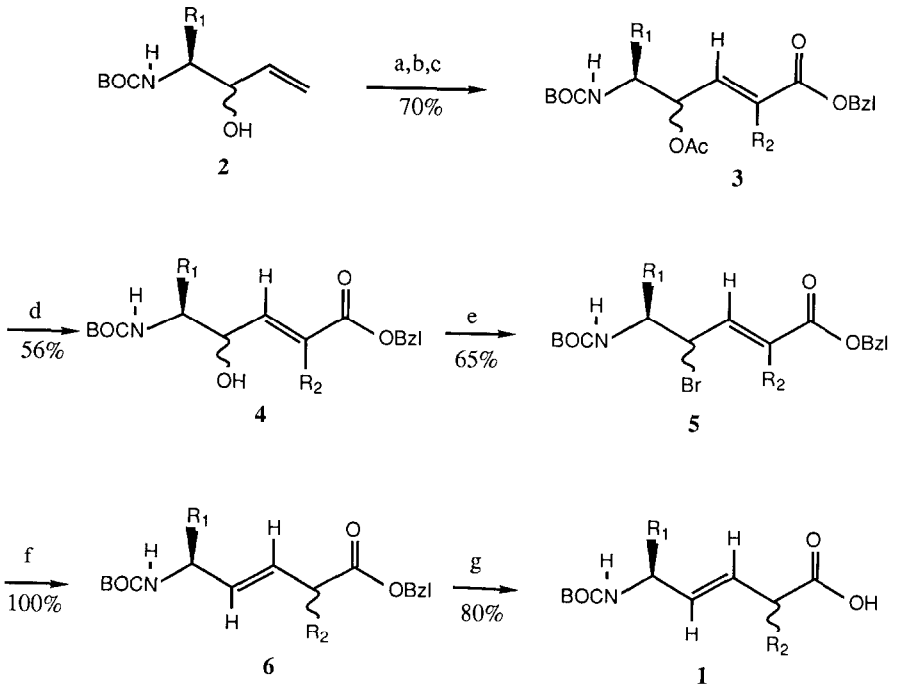
1

	R_1	R_2
a.	$CH_2CO_2C(CH_3)_3$	$CH_2C_6H_5$
b.	$CH_2CH(CH_3)_2$	$CH_2CO_2C(CH_3)_3$
c.	H	

+This paper is dedicated to Professor George Büchi on the occasion of his 65th birthday.

Herein, we report a general, efficient route to the synthesis of trans carbon-carbon double bond replacement isosteres using natural amino acids as starting materials. Three pseudodipeptides Aspψ[E-CH=CH]Phe (**1a**), Leuψ[E-CH=CH]Asp (**1b**) and Glyψ[E-CH=CH]Trp (**1c**) were prepared. The synthesis of Asp ψ [E-CH=CH]Phe (**1a**) will be described to represent the procedure. The diastereomeric alcohol **2a**[4] was derived from the reaction of vinyl magnesium bromide and optically pure Boc-beta-tert-butyl aspartic acid-alpha-carboxaldehyde.[5] Compound **2a** was converted to the appropriate protected pseudodipeptide **3a** via a three step sequence. Careful methanolysis of the acetyl protecting group of **3a** yields the corresponding alcohol **4a** in 56% yield accompanied by lactonized products **8**, **9** and starting material **3a**, which were readily removed via flash silica gel chromatography. The reaction conditions for this hydrolysis are crucial. With longer reaction times (> 1 hr.), the newly formed allylic alcohol **4a** will convert further to lactones **8** and **9** plus other by-products, i.e., Michael addition and transesterification of the alpha, beta-unsaturated benzyl ester will occur. Mild bromination of **4a** gave the desired allylic bromide, **5a**, which was treated with zinc metal in acetic acid medium[7] to provide appropriately protected **6a** in quantitative yield. The newly created alpha-center at the Phe residue was racemic at this point and attempts to separate the diastereomeric pseudodipeptides at either the ester **6a** or acid **1a** stage failed. Pseudodipeptides **6b**[6] and **6c** were prepared in identical fashion. The coupling constants between pairs of olefinic protons in **6a**, **6b** and **6c** were 15.5, 16 and 15 Hz respectively, thus, establishing the trans stereochemistry for newly formed double bonds in each. This was consistent with literature precedent.[7]

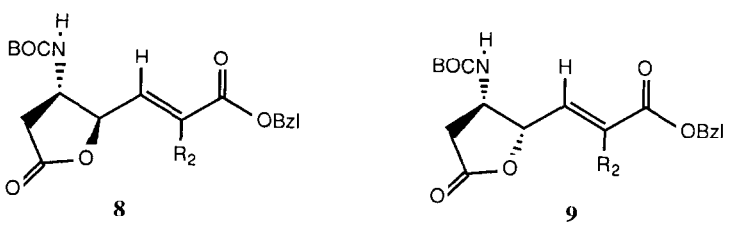
We are currently utilizing the above methodology to incorporate trans carbon-carbon double bond isosteres into biologically important peptides. We also are in the process of extending these studies to synthesize other amide bond surrogates such as ketomethylene and hydroxyethylene replacements. Full experimental details and biological results will be reported elsewhere.



a. Ac_2O/Pyr., b. NMO/$NaIO_4$/OsO_4(cat), c $Ph_3P{=}CR_2CO_2Bzl$,

d. Na_2CO_3/CH_3OH/rt./45min., e. Ph_3P/CBr_4/THF, f Zn/HOAc,

g. 1,4-Cyclohexadiene/Pd/C/CH_3OH



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References and Notes

1. For a comprehensive review on peptide backbone modifications, see A.F. Spatola "Chemistry and Biochemistry of Amino Acids, Peptides and Proteins"; B. Weinstein, Ed.; Marcel Dekker, New York, **1983**, Vol. 7, Chapter 5.

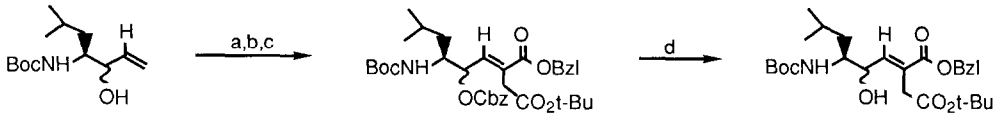
2. (a) M.M. Hann, P.G. Sammes, J. Chem. Soc., Perkin I, **1982**, 307; (b) M.M. Hann, P.G. Sammes, J. Chem. Soc., Chem. Comm. **1980**, 234.

3. (a) N.J. Miles, P.G. Sammes, P.D. Kennewell, R. Westwood, J. Chem. Soc., Perkin I, **1985**, 2299; (b) M.T. Cox, D.W. Heaton, J. Horbury, J. Chem. Soc., Chem. Comm. **1980**, 799; (c) M.T. Cox, J. J. Gormley, C.F. Hayward, N.N. Petter, J. Chem. Soc., Chem. Comm. **1980**, 800; (d) A. Spaltenstein, P.A. Carpino, F. Miyake, P.B. Hopkins, Tetrahedron Lett. **1986**, 2095; (e) R.L. Johnson, J. Med. Chem. **1984**, 27, 1351.

4. The allylic alcohol **2a** was carried through the reaction sequence as a mixture of diastereomers because, for practical purposes, separation of diastereomers at this stage is not necessary.

5. The aldehyde was prepared by reduction of the 3,5-dimethyl pyrazolide ester of Boc-beta-t-butyl-L-aspartic acid with lithium aluminum hydride in tetrahydrofuran at -78°C; R. Nishizawa, T. Saino, J. Med. Chem. **1977**, 20, 510.

6. In the Leuψ[E-CH=CH]Asp series, methanolysis of the acetyl group of **3b** gave the corresponding **4b** in only 30% yield accompanied with many by-products. Alternatively, the allylic alcohol **4b** was synthesized in good yield via catalytic transfer hydrogenation of the benzyloxycarbonyl precursor **10**. The rational for the facile removal of the benzyloxycarbonate protecting group in the presence of the benzyl ester in compound **10** is unclear.



2b **10** **4b**

a. Cbz-OSu/DMAP., (90%). b. NMO/$NaIO_4$/OsO_4(cat). c. $Ph_3P{=}CR_2CO_2Bzl$, (66%).
d. 1,4-Cyclohexadiene/Pd/C/MeOH/rt /1hr , (80%)

7. C.E. Moppett, J.K. Sutherland, J. Chem. Soc. (C), **1968**, 3040, and references cited therein.

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