Methyl- and (Trifluoromethyl)alkene Peptide Isosteres: Synthesis and Evaluation of Their Potential as β-Turn Promoters and Peptide Mimetics

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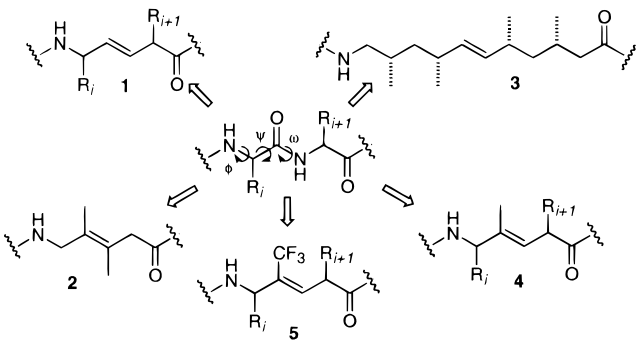
Despite the promise of amide bond isosteres for improving the resistance toward degradation by exoproteases by several orders of magnitude, the use of nonhydrolyzable substitutes for the amide group has often led to disappointing decreases in biological activity.[1] The frequent lack of success with ground-state amide bond mimetics stands in contrast to the very promising use of hydroxyethylene protease inhibitors as mimics of the tetrahedral intermediate in amide bond hydrolysis.[2] Nonetheless, the development of effective amide bond isosteres holds considerable promise as a stepping stone toward the rational design of small molecule analogues of bioactive oligo- and polypeptides. Analogues such as thiomethylene and aminomethylene isosteres, however, exchange the conformationally restricted amide function with highly flexible single bonds. Disubstituted (*E*)-alkene isosteres **1** provide a better fit for the C_i-(α)−C_{i+1}(α) distance (3.8 Å) but are inadequate mimetics of the electrostatic potential surface as well as the backbone *φ*,*ψ*-dihedral angles. Gellman and co-workers designed the tetrasubstituted (*E*)-alkene Gly-Gly dipeptide mimetic **2** to induce conformational rigidification and promote *β*-hairpin formation.[3] More recently, Hoffman and co-workers reported the use of gauche pentane interactions for the design of *β*-hairpin analogue **3**.[4] We were interested in exploring the use of trisubstituted (*E*)-alkene isosteres such as **4** as *β*-turn mimetics. A combination of $A^{1,3}$- and $A^{1,2}$-strain leads to considerable restrictions in *φ*,*ψ*-dihedral angles in these substrates, and the Ramachandran plot of the methylalkene isostere of alanine is closely related to the parent amino acid.[5] In contrast, the disubstituted (*E*)-alkene analogue is conformationally much more flexible. Even greater steric restrictions are observed for a trifluoromethylated derivative **5** where only ca. 15% of the Ramachandran plot area remains within 15 kJ/mol of the energy minimum. Methylalkene moieties are abundant in terpenes and polypropionate natural products and have indeed been shown to serve as surrogates of backbone amide functions in enzyme−inhibitor complexes.[6]



The mimicry of the electronic properties of the amide bond represents perhaps the most challenging parameter for effective isostere design. Electrostatically, the (trifluoromethyl)alkene represents a better match of the amide bond than any other common alkene isostere (Figure 1).

Efficient synthetic approaches toward diastereomerically and enantiomerically pure alkene peptide isosteres are under intense investigation.[8] A particularly promising convergent pathway utilizes the S_N2'-addition of cuprate reagents to alkenyl aziridines and allylic mesylates.[9] The former approach has also been applied to solid-phase synthesis.[10] We have now extended these methods toward a general synthesis of methyl- and (trifluoromethyl)alkene isosteres and, for the first time, systematically compared the solid state conformations of these peptide mimetics.

Swern oxidation of the epoxy alcohol **6**, obtained in 92% ee by Sharpless epoxidation,[11] followed by Wittig chain extension and epoxide−aziridine conversion,[12] provided alkenyl aziridine **7** in 13% overall yield (Scheme 1). N-Acylation, copper(I)-catalyzed S_N2'-addition,[9] and aminolysis[13] gave the D-Ala-L-Ala isostere **9** in 28% yield.

A modified strategy was necessary for the preparation of (trifluoromethyl)alkene **14** (Scheme 2). Carboxylation[14] of trifluorotrichloroethane **10**, esterification with benzyl alcohol, and Reformatzky addition−elimination[15] with acetaldehyde yielded the trifluoroalkene **11** as a 2:3 mixture of (*E*)- and (*Z*)-isomers. The (*Z*)-isomer was isolated by column chromatography on SiO_2 and subjected to a Sharpless asymmetric dihydroxylation.[16] The resulting diol was obtained in 73% ee and converted to the epoxide under Mitsunobu conditions. Reduction to the aldehyde and Wittig chain extension provided alkenyl oxirane **12**. After sodium azide opening, the resulting azido alcohol could not be

(1) See, for example: (a) Fincham, C. I.; Higginbottom, M.; Hill, D. R.; Horwell, D. C.; O'Toole, J. C.; Ratcliffe, G. S.; Rees, D. C.; Roberts, E. *J. Med. Chem.* **1992**, *35*, 1472. (b) Kaltenbronn, J. S.; Hudspeth, J. P.; Lunney, E. A.; Michniewicz, B. M.; Nicolaides, E. D.; Repine, J. T.; Roark, W. H.; Stier, M. A.; Tinney, F. J.; Woo, P. K. W.; Essenburg, A. D. *J. Med. Chem.* **1990**, *33*, 838. (c) Wai, J. S.; Bamberger, D. L.; Fisher, T. E.; Graham, S. L.; Smith, R. L.; Gibbs, J. B.; Mosser, S. D.; Oliff, A. I.; Pompliano, D. L.; Rands, E.; Kohl, N. E. *Bioorg. Med. Chem.* **1994**, *2*, 939.

(2) Vacca, J. P.; Condra, J. H. *Drug Discov.* **1997**, *2*, 261.

(3) Gardner, R. R.; Liang, G.-B.; Gellman, S. H. *J. Am. Chem. Soc.* **1995**, *117*, 3280.

(4) Schopfer, U.; Stahl, M.; Brandl, T.; Hoffmann, R. W. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1745.

(5) Ramachandran plots were obtained with Macromodel 5.5 using the MM2 force field. See the Supporting Information.

(6) See, for example: Ikeda, Y.; Schultz, L. W.; Clardy, J.; Schreiber, S. L. *J. Am. Chem. Soc.* **1994**, *116*, 4143.

(7) Calculated dipole moments were obtained with Spartan 5.0.1 (Wavefunction, Inc.) and AM1 semiempirical parametrization.

(8) For some recent examples, see: (a) Kranz, M.; Kessler, H. *Tetrahedron Lett.* **1996**, *37*, 5359. (b) Devadder, S.; Verheyden, P.; Jaspers, H. C. M.; Van Binst, G.; Tourwé, D. *Tetrahedron Lett.* **1996**, *37*, 703. (c) Welch, J. T.; Lin, J. *Tetrahedron* **1996**, *52*, 291. (d) Ibuka, T.; Akaji, M.; Mimura, N.; Habashita, H.; Nakai, K.; Tamamura, H.; Fujii, N.; Yamamoto, Y. *Tetrahedron Lett.* **1996**, *37*, 2849. (e) Daly, M. J.; Ward, R. A.; Thompson, D. F.; Procter, G. *Tetrahedron Lett.* **1995**, *36*, 7545. (f) Wai, J. S.; Fisher, T. E.; Embrey, M. W. *Tetrahedron Lett.* **1995**, *36*, 3461. (g) Bartlett, P. A.; Otake, A. *J. Org. Chem.* **1995**, *60*, 3107.

(9) (a) Wipf, P.; Fritch, P. C. *J. Org. Chem.* **1994**, *59*, 4875. (b) Ibuka, T.; Nakai, K.; Habashita, H.; Hotta, Y.; Fujii, N.; Mimura, N.; Miwa, Y.; Taga, T.; Yamamoto, Y. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 652. (c) Ibuka, T.; Habashita, H.; Funakoshi, S.; Fuji, N.; Oguchi, Y.; Uyehara, T.; Yamamoto, Y. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 801.

(10) Wipf, P.; Henninger, T. *J. Org. Chem.* **1997**, *62*, 1586.

(11) Gao, Y.; Hanson, R. M.; Klunder, J. M.; Ko, S. Y.; Masamune, H.; Sharpless, K. B. *J. Am. Chem. Soc.* **1987**, *109*, 5765.

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(14) A modification of the procedure used by Fujita and Kiyama (Fujita, M.; Hiyama, T. *Bull. Chem. Soc. Jpn.* **1987**, *60*, 4377) was used. The yield was improved from 18% to 50%.

(15) Allmendinger, T.; Lang, R. W. *Tetrahedron Lett.* **1991**, *32*, 339.

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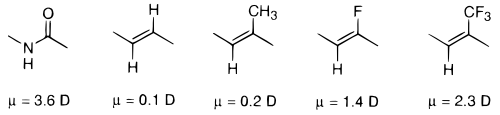
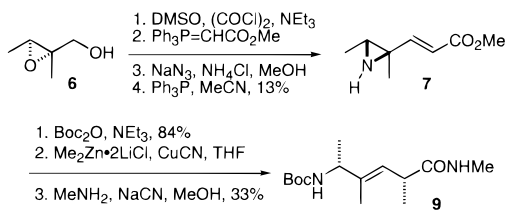
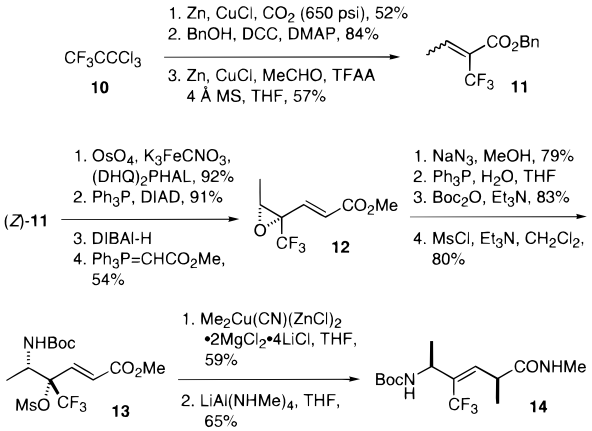


Figure 1. AM1-calculated dipole moments of the amide bond and selected alkene isosteres.[7]

Scheme 1



Scheme 2



converted to the aziridine by treatment with triphenylphosphine due to the resistance toward S_N2-displacement at the carbon α to the powerful electron-withdrawing CF_3 substituent. Instead, Staudinger reduction of the azide led to the amino alcohol which was converted to the carbamate and mesylated to give **13**. In contrast to the lack of success of effecting an S_N2 reaction α to the CF_3 group, allylic S_N2' displacement of the mesylate occurred readily and, after transamidation of the methyl ester,[17] provided the desired trifluoromethyl L-Ala-D-Ala alkene isostere **14** in 9% overall yield from (*Z*)-**11**.

For direct experimental comparison with **9** and **14**, the disubstituted alkene isostere **18** was prepared by conversion of diol **15**[18] to the cyclic sulfate,[19] selective azide displacement at the α-carbon, aziridine formation, and S_N2'-cuprate opening of N-nosylated amide **17** (Scheme 3).[10] After conversion of the nosyl group to the Boc-carbamate, L-Ala-D-Ala mimic **18** was isolated in 3% overall yield.

X-ray structural analyses of isosteres **9**, **14**, and **18** revealed an ideal type-II (or -II′) β-turn structure[20] for the trisubstituted alkenes, whereas the disubstituted alkene **18** assumed a much more opened bend (Figure 2). Only **9** and **14** were intramolecularly hydrogen bonded with O−HN distances of 2.11 and 2.19 Å, respectively. In agreement with the modeling data, these solid-state structures demonstrate that the $A^{1,3}$ strain across the double bond is primarily responsible for the restriction in ϕ_2 and ψ_2 dihedral angles.

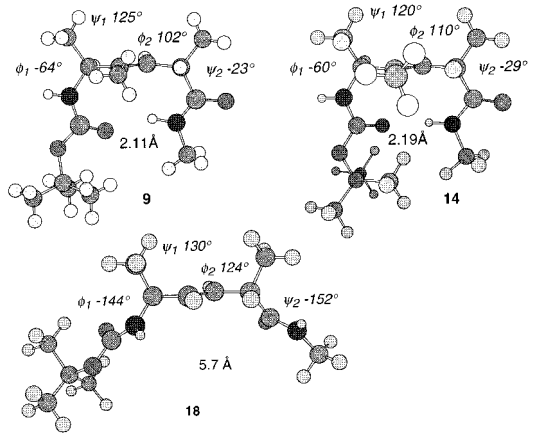
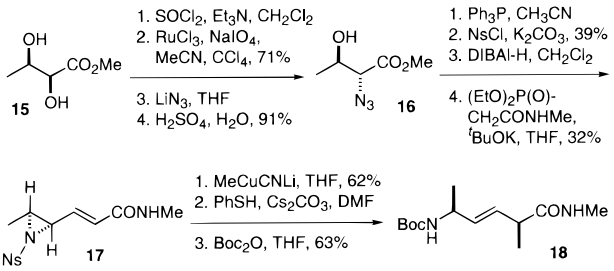


Figure 2. X-ray structures of alkene peptide isosteres **9**,[22] **14**, and **18**.[23]

Scheme 3



In conclusion, we have been able to devise enantioselective synthetic approaches for L-Ala-D-Ala (or enantiomeric) dipeptide alkene isostere sequences that, for the first time, included the preparation of a (trifluoromethyl)alkene isostere. Our X-ray study has established that methyl- and trifluoromethyl-substituted alkenes provide conformationally considerably more highly preorganized backbone-rigidified peptide mimetics than the parent disubstituted alkenes. The D−L methyl-(*E*)-alkene isostere sequence **9** prefers an intramolecularly hydrogen bonded type-II′ β-turn in the solid state. The corresponding trifluoromethyl analogue **14** representing an L−D sequence shows a preference for a type-II β-turn and folds almost perfectly pseudoenantiomeric to **9**. The conformational properties of **9** and **14** follow closely those of regular peptides, since a type II β-turn is generally preferred by an L-Ala-D-Ala sequence and a type-II′ by the corresponding D−L dipeptide.[21] Glycine often replaces the nonproteinogenic D-amino acid in these turns. Our current investigations are directed toward comparing the solution conformations and the biological profiles of methyl- and (trifluoromethyl)alkene peptide isosteres as well as toward the synthesis and conformational analysis of L−L (and D−D) dipeptide analogues.

Acknowledgment. This work was supported by the National Institutes of Health and Merck Research Laboratories.

Supporting Information Available: Ramachandran plots, experimental procedures, and compound characterization data (33 pages).

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(17) Solladie-Cavallo, A.; Bencheqroun, M. *J. Org. Chem.* **1992**, *57*, 5831.
(18) Derived from L-threonine: Servi, S. *J. Org. Chem.* **1985**, *50*, 5865.
(19) Gao, Y.; Sharpless, K. B. *J. Am. Chem. Soc.* **1988**, *110*, 7538.
(20) Bend types are classified according to the dihedral angles of the two central residues. An ideal type II β-turn has backbone dihedral angles of −60° (ϕ_1) and 120° (ψ_1), and 80° (ϕ_2) and 0° (ψ_2): Chou, P. Y.; Fasman, G. D. *J. Mol. Biol.* **1977**, *115*, 135. Type II′ is enantiomeric to type II. Due to its D-Ala-L-Ala-derived chirality, **9** actually has dihedral angles typical for a type II′ β-turn, the mirror image of the L-Ala-D-Ala−derived **14**.
(21) Smith, J. A.; Pease, L. G. *CRC Crit. Rev. Biochem.* **1980**, *8*, 315.
(22) To simplify comparisons across the series, the mirror image of **9** is used in this figure.
(23) The atomic coordinates for this work are available on request from the Director of the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, U.K. Any request should be accompanied by the full literature citation for this paper.