ORGANIC LETTERS

2005
Vol. 7, No. 1
103−106

Convergent Approach to (*E*)-Alkene and Cyclopropane Peptide Isosteres

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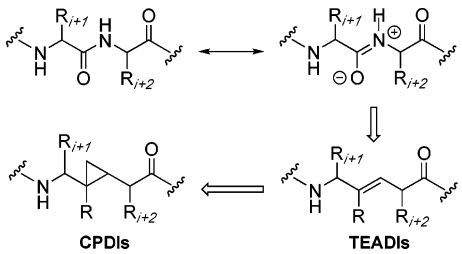
Received November 2, 2004

ABSTRACT



Trisubstituted (*E*)-alkene isosteres (TEADIs) and novel cyclopropane amide bond isosteres (CPDIs) were synthesized by aldimine addition and three-component aldimine addition–cyclopropanation methodologies, respectively. These new peptide mimetics can serve as *β*-turn promoters.

Peptide bond isosteres can assist in the investigation of receptor−ligand and enzyme−substrate interactions.[1] In particular, the replacement of the scissile peptide bond with nonhydrolyzable isosteric functions is an important design motif in medicinal chemistry.[2−7] In recent years, many nonhydrolyzable mimetics have been developed, including (*E*)-alkene (ψ[(*E*)-C(R)═CH]) **2**,[2] ketomethylene (ψ[$COCH_2$]) **3**,[3] hydroxyethylene (ψ[$CH(OH)CH_2$]) **4**,[1a,4] dihydroxyethylene (ψ[CH(OH)CHOH]) **5**,[5] hydroxyethylamine (ψ[$CH(OH)CH_2NH$]) **6**,[6] and methyleneamine (ψ[CH_2NH])-**7**[7] moieties (Figure 1).

The relatively rigid trisubstituted (*E*)-alkenes **2** (ψ[(*E*)-C(R)═CH], TEADIs) represent useful, conformationally preorganized structural mimetics[2c−e] and have been used as surrogates of hydrolytically labile amide bonds in a number of enzyme inhibitors.[2a,8] The primary objective of this strategy is the accurate mimicry of the geometry of the

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10.1021/ol0477529 CCC: $30.25
Published on Web 12/08/2004

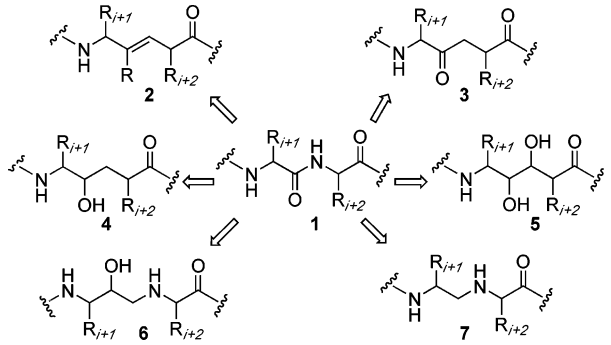


Figure 1. Peptide bond linkage and isosteric replacements.

peptide bond; however, trisubstituted (*E*)-alkenes like many other amide bond substitutes lack effective hydrogen bond donor and acceptor functions and do not provide for the large dipole moment of the resonance-stabilized amide group. In addition, alkenes can suffer from potential isomerization, oxidation, and general chemical lability. On the basis of the latter considerations, we have designed trisubstituted cyclopropane dipeptide isosteres (ψ[RCp], CPDIs) that we expect to display increased stability compared with the corresponding trisubstituted (*E*)-alkene dipeptide isosteres (Figure 2).

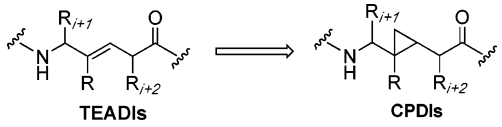
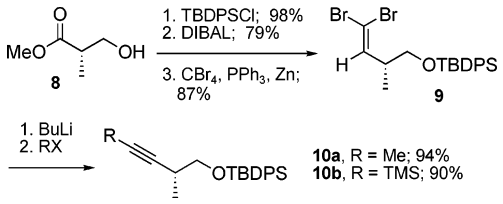


Figure 2. Evolution of CPDIs from TEADIs.

Martin and co-workers have developed related side-chain-rigidifying cyclopropyl peptidomimetics COCpCO and NHCpNH.[9] These moieties also replace the scissile amide bond in the backbone of peptide sequences. However, our design of cyclopropane mimetics (CPDIs) represents the first use of the cyclopropane ring as an exact isosteric replacement of the labile dipeptide bond linkage.

The preparation of TEADIs and CPDIs was faciliated by a new Zr/Zn-mediated methodology for the synthesis of allylic and *C*-cyclopropylalkylamines.[10] For the preparation of the precursor alkynes, commercially available enantiomerically pure hydroxy ester **8** was protected with *tert*-butylchlorodiphenylsilane (Scheme 1). DIBAL reduction and Corey−Fuchs reaction gave dibromoolefin **9**,[11] which was treated with *n*-BuLi and quenched with methyl iodide and

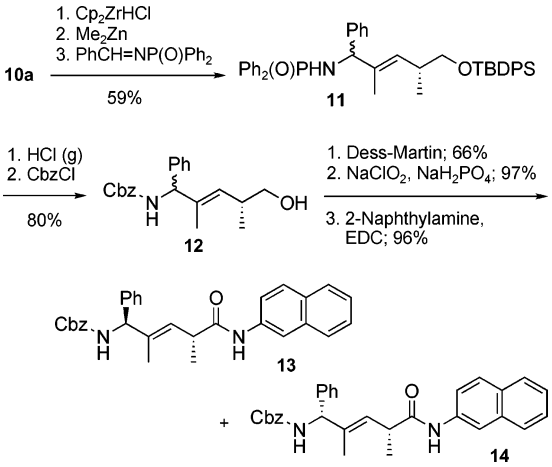
Scheme 1. Synthesis of Methyl- and TMS-Substituted Alkynes



trimethylchlorosilane to afford alkynes **10a** and **10b** in high yield.

Hydrozirconation[12] of **10a** with Cp_2ZrHCl followed by transmetalation to Me_2Zn and addition of *N*-diphenylphosphinoylimine provided the allylic amide **11** in 59% yield as a 1:1 mixture of diastereomers. Deprotection of **11**, N-acylation with CbzCl, oxidation of alcohol **12** with Dess−Martin periodinane[13] and sodium chlorite,[14] and coupling with 2-naphthylamine led to the methyl-substituted TEADIs **13** and **14**, which were easily separated by chromatography on SiO_2 (Scheme 2).[15]

Scheme 2. Synthesis of Methyl-Substituted (*E*)-Alkene Dipeptide Isosteres



TMS-substituted alkene dipeptide isosteres **19** and **20** were prepared analogously. The diastereomeric products were separated by chromatography on SiO_2 (Scheme 3). The configuration of **19** and **20** was assigned by X-ray structural analysis of syn isomer **20** (Figure 3).

The three-component aldimine addition−cyclopropanation methodology allowed efficient access to the cyclopropyl

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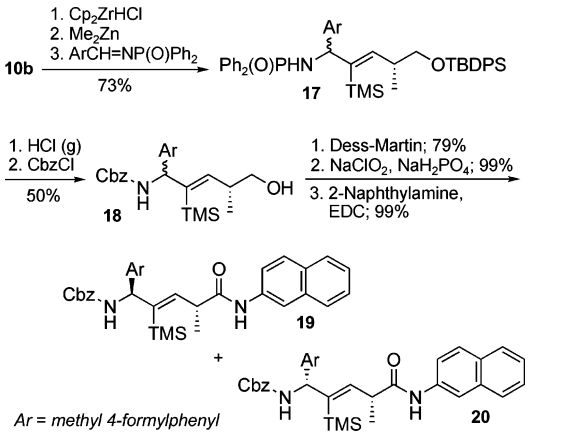
Scheme 3. Synthesis of TMS-Substituted Alkene Dipeptide Isosteres



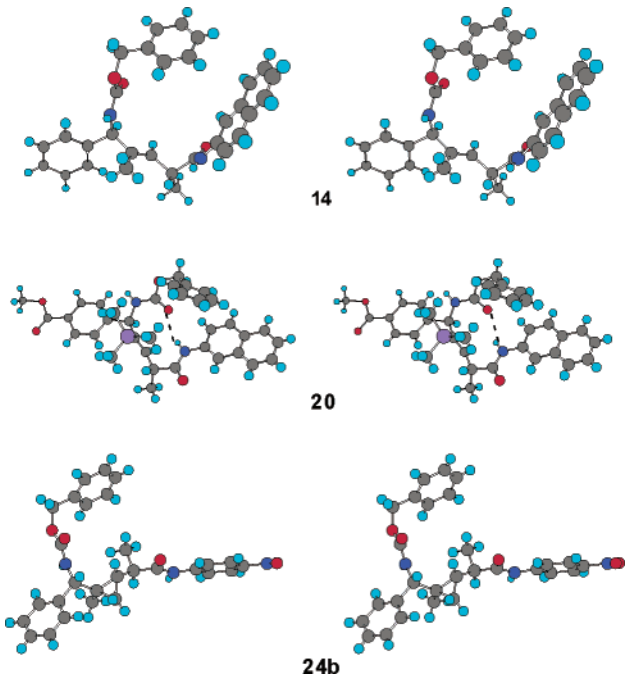
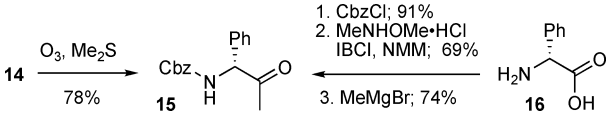


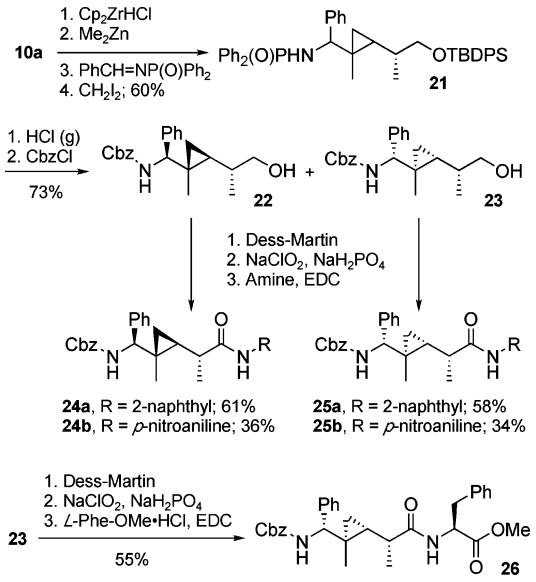
Figure 3. Stereoviews of X-ray structures of **14**, **20**, and **24b**.

analogues from the same starting materials (Scheme 4). An inseparable mixture of *N*-phosphinoylamino cyclopropanes **21** was obtained in 60% yield with a diastereoselectivity of 3:2 (syn,syn:syn,anti). Global deprotection and N-protection with CbzCl afforded a separable mixture of alcohols **22** and

(15) Structural assignment of **13** and **14** was based initially on the ozonolysis product **15**, which was compared to the product obtained from D-phenylglycine. Later, a single-crystal X-ray analysis of **14** confirmed this assignment (Figure 3). (a) Son, Y.; Park, C.; Koh, J. S.; Choy, N.; Lee, C. S.; Choi, H.; Kim, S. C.; Yoon, H. *Tetrahedron Lett.* **1994**, *35*, 3745. (b) Nahm, S.; Weinreb, S. M. *Tetrahedron Lett.* **1981**, *22*, 3815.



Scheme 4. Synthesis of Cyclopropane Dipeptide Isosteres (CPDIs)



23, which were individually converted to cyclopropane dipeptide isosteres (ψ[MeCp], CPDIs) **24** and **25**. The assembly of pseudotripeptide **26** was easily achieved directly from alcohol **23**.

Relevant information about the differences in the conformational properties of TEADIs and CPDIs could be obtained by X-ray structural analysis of **14**, **20**, and **24b** (Figure 3). By comparison to the dihedral angles of typical β-turns,[16] we found that TEADI **20** closely mimicked a type II′ β-turn conformation (ideal dihedral angles are $\phi_2 = 60°$, $\psi_2 = -120°$, $\phi_3 = -80°$, $\psi_3 = 0°$), including the ten-membered hydrogen bonding interaction (N−H·O hydrogen bond distance = 2.52 Å, a typical β-turn hydrogen bond is ∼2.3 Å). This conformation minimized $A^{1,3}$ allylic strain, which is particularly severe for compound **20** due to the steric bulk of the TMS substituent. The type II′ β-turn has been found in earlier analyses of trisubstituted alkene peptide isosteres.[2c] It was interesting to note, however, that the conformation of the other isosteres differed considerably. TEADI **14** can be classified as a type V′ β-turn, which is a less common relative of the type II′ β-turn. The major difference between types II′ and V′ lies in the ψ-angles, in particular ψ_3. Quite likely, the larger steric bulk of the TMS vs the methyl group forces a decrease in the value of the ψ_3 dihedral angle, which destabilizes the more open V′-type conformation and facilitates the formation of the intramolecular hydrogen bond. In proteins, type V′ β-turns occur much less frequently than type II′, and they are often not hydrogen-bonded. However, for both types, the $D_{i+1}L_{i+2}$-configuration at the amino acid α-carbons is preferred, which is the configuration present in both **14** and **20**. In contrast, the $L_{i+1}L_{i+2}$-configuration present in **24b** would be expected to stabilize turn types I and III; however, possibly due to the greater flexibility of

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Table 1. Solid-State Dihedral Angles of Dipeptide Isosteres **14**, **20**, and **24b**

isostere	distance between C_{i+1} and α-C_{i+2}	distance between α-C_{i+1} and α-C_{i+2}	ϕ_2	ψ_2	ϕ_3	ψ_3	turn classification	H-bond
14	2.546 Å	3.904 Å	114.4°	−117.1°	−112.6°	100.1°	V′	−
20	2.642 Å	4.034 Å	65.8°	−121.1°	−101.5°	−4.2°	II′	+
24b	2.653 Å	3.894 Å	−122.3°	76.0°	−148.3°	153.0°	IV	−

substituents attached to the cyclopropane group, two angles (ψ_2 and ψ_3) differ by >40° from type I, and therefore this reverse turn should be classified as a type IV β-turn (Table 1). Not unexpectedly, the introduction of the cyclopropane group slightly increases the conformational freedom of the peptide backbone vs the corresponding alkene peptide bond isosteres. This is illustrated by an increase in the distance of the methyl group-bearing $C_{(i+1)}$ and the allylic α-$C_{(i+2)}$, responsible for the $A^{1,3}$-interaction, from 2.546 to 2.653 Å in **14** and **24b**.

The distances between α-$C_{(i+1)}$ and α-$C_{(i+2)}$ were found to be very similar to the parent amide bond (3.8 Å[17]) for both TEADIs (**14**, 3.904 Å; **20**, 4.034 Å) and the corresponding CPDI (**24b**, 3.894 Å). Accordingly, all isosteres represent sterically relevant replacements for the amide linkage in peptides (Table 1).

In conclusion, we have developed a general protocol for the efficient synthesis of trisubstituted (*E*)-alkene dipeptide isosteres (ψ[(*E*)-C(R)═CH], TEADIs) and the novel cyclopropane-based dipeptide isosteres (ψ[MeCp], CPDIs) using our new one-pot aldimine addition methodology. Three representative X-ray studies provide insight into the potential of these peptide mimetics to act as β-turn promoters. Compared to TEADIs, which have a strong preference for type II turns, CPDIs have a more flexible backbone disposition but still prefer a reverse turn conformation. We expect that CPDIs will show greater resistance to oxidative, CYP450-mediated biological metabolism,[18] thus extending and improving upon the peptidase resistance of TEADIs. Both dipeptide isostere classes can serve as scaffolds for structure−activity studies of biologically active peptide sequences.

Acknowledgment. This work has been supported by the NIH P50-GM067082 program. J.X. gratefully acknowledges an Andrew W. Mellon Predoctoral Fellowship. We thank Dr. Steven J. Geib (University of Pittsburgh) for X-ray crystallographic analyses of **14**, **20**, and **24b**.

Supporting Information Available: Experimental procedures and spectral data for all new compounds, including copies of ^{1}H and ^{13}C NMR spectra for **10a**,**b**, **13**, **14**, **19**, **20**, **24a**,**b**, **25a**,**b**, and **26**, and crystal information files (CIF) for compounds **14**, **20**, and **24b**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL0477529

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