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Synthesis of (*E*)-Olefin Dipeptide Isosteres

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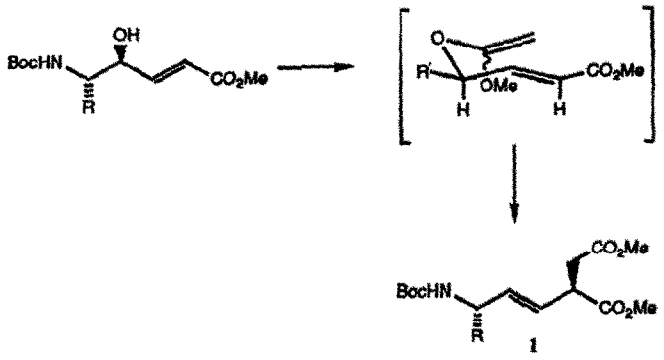
Abstract: A route to the synthesis of (*E*)-olefin dipeptide isosteres is reported. The key step involves an orthoester Claisen rearrangement of an allylic alcohol derived from commercially available amino acids. Chirality transfer from the alcohol center to the newly formed carbon-carbon bond provides a stereocontrolled introduction of the *C*-terminal aspartic acid "side chain" of the isosteres.

In the design of peptidomimetics, it is often desirable to evaluate the contribution of individual backbone peptide bonds in a particular interaction. One way of assessing the role of a specific amide bond is to substitute it with a replacement such as the (*E*)-olefin isostere[1] shown in figure 1.

Figure 1. (*E*)-olefin replacement for an amide bond in a peptide.

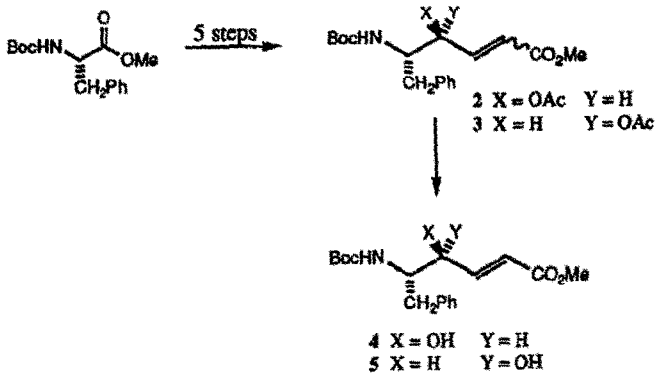
Numerous synthetic approaches to (*E*)-olefin dipeptide isosteres have appeared in the literature. The majority of examples, however, have not addressed the issue of stereocontrol.[1,2] For these cases, either the goal has been the construction of a glycine replacement, eliminating the need for a stereocontrolled synthesis, or the desired isostere has been synthesized as a mixture of stereoisomers. A few approaches to isosteres that have addressed the problem of stereocontrol, though, have appeared. One involves the S_N2' displacement of an optically pure mesylate[3]; chirality transfer from the mesylate to the newly formed C-C bond provides a stereocontrolled means of incorporating one of the isostere "side chains". Another approach utilizes a Julia olefin synthesis[4] in which each coupling partner has been prepared in optically pure form. A third approach employs sigmatropic rearrangements in the synthesis of isosteres with aliphatic "side chains".[5,6]

Our interest in the design of peptidomimetics prompted us to investigate the orthoester Claisen rearrangement[7] as a way to simultaneously introduce both an (*E*)-olefin amide replacement and the *C*-terminal amino acid side chain in a dipeptide isostere (Scheme 1).[5,6,8] The Claisen rearrangement remains a powerful tool for the synthetic chemist; the reaction is stereospecific with respect to the starting olefin, and the stereochemistry in acyclic systems can be predicted by a chairlike transition state. To test this strategy for the stereospecific synthesis of (*E*)-olefin dipeptide isosteres, the synthesis of the phenylalanineΨ[*E*-CH=CH]aspartic acid isostere 1 (R = CH_2Ph) was undertaken.



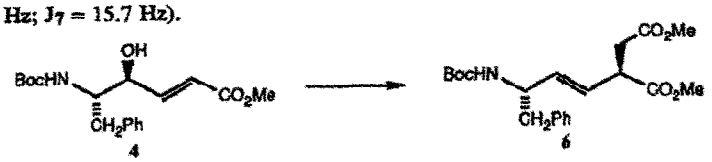
Scheme 1

Allylic acetates **2** and **3** were synthesized using a previously reported route in 5 steps from *N*-Boc-L-phenylalanine-methyl ester (Scheme 2).[3,9] This procedure produces an inseparable mixture of *cis*- and *trans*-olefins. The desired *trans*-olefins **4** and **5** were easily purified by flash chromatography after deprotection of the allylic acetate with sodium carbonate in methanol.

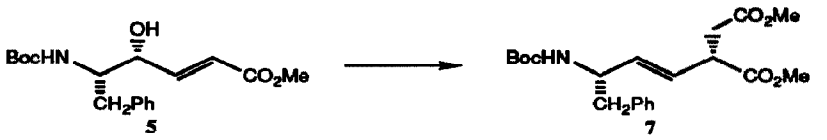


Scheme 2

The orthoester Claisen rearrangement of allylic alcohols **4** and **5** proceeded smoothly with trimethyl orthoacetate and catalytic benzoic acid in refluxing o-xylene to yield the desired (*E*)-olefin dipeptide isosteres **6** (49%) and **7** (90%) (eqs. 1 and 2).[10] ^{1}H NMR analysis of the coupling constants for the two olefinic protons of **6** and **7** established the trans geometry of the dipeptide isosteres (J_6 = 15.6 Hz; J_7 = 15.7 Hz).

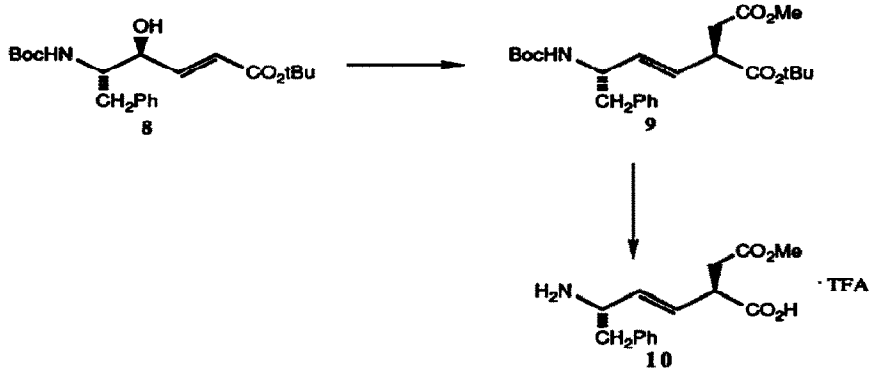


(eq. 1)



(eq. 2)

After the demonstrated conversion of **4** to **6** and **5** to **7**, the synthesis of a dipeptide isostere in which the *C*-terminal ester could be selectively deprotected in the presence of the "side chain" ester was attempted. A modification of the literature synthetic route to **2** and **3** provided the *C*-terminal *tert*-butyl ester **8**.[11] Treatment of **8** under the identical orthoester Claisen conditions used above provided the dipeptide isostere **9** in 55% yield (Scheme 3). Deprotection, using TFA, gave the (*E*)-olefin amino acid (>95%); this unit can be incorporated into a peptide backbone.



Scheme 3

The procedure outlined above provides a simple, efficient methodology for the stereocontrolled synthesis of (*E*)-olefin dipeptide isosteres. Specifically, the orthoester Claisen rearrangement is a direct route to isosteres in which the *C*-terminal amino acid replacement is for aspartic acid. Similarly, the treatment of **4** or **5** under Wittig-Still rearrangement conditions could provide access to the analogous serine isosteres.[6,8b,8c] Both the serine and aspartic acid "side chains" could also serve as handles to further functionalize these isosteres.

Typical Procedure for Orthoester Claisen Rearrangement:
Allylic acetate **4** (113 mg, 0.34 mmol), trimethyl orthoacetate (0.21 mL, 1.7 mmol), and benzoic acid (4 mg, 0.033 mmol) were dissolved in 5 mL o-xylene and refluxed for 4 h. A small amount of starting material was still present by TLC. Additional trimethyl orthoacetate (0.21 mL, 1.6 mmol) and benzoic acid (4 mg, 0.033 mmol) were added and the solution was refluxed an additional two hours. The solution was cooled to room temperature and the solvents removed. The residue was flash chromatographed on silica gel (5:1 hexanes: EtOAc) to provide the desired *trans*-olefin **6** (49%).

Acknowledgements. We acknowledge E. Reich for elemental analysis and the Department of Physical and Structural Chemistry for mass spectra.

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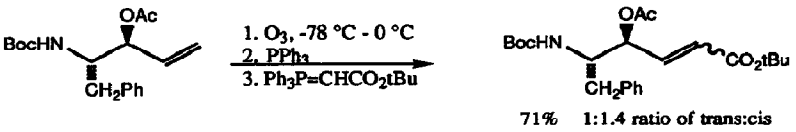
10. The diastereomeric excess for **6** and **7** is >95% by ^{1}H NMR (400MHz).
11. Compound **8** was synthesized in an analogous fashion to compound **4**,[3,9] except (*tert*-butoxycarbonylmethylene)triphenylphosphorane was used as the ylide in the Wittig reaction. In this example, the *cis*- and *trans*-olefins were separable by flash chromatography as the allylic acetates.



71% 1:1.4 ratio of trans:cis

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