Solid Phase Synthesis of Olefin and Hydroxyethylene Peptidomimetics

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The development of enzyme inhibitors often makes use of peptide bond replacements to mimic the transition state for amide hydrolysis and/or to increase the metabolic stability of the compound. Previous reports of the preparation of enzyme inhibitor libraries have focused on elaboration of a specific moiety such as an hydroxyethylene,[1a] diol,[1b] or a phosphonic ester.[2] This communication outlines a flexible and potentially more general approach to peptidomimetics[3] using a resin-bound amino acid aldehyde **1** (Figure 1) which is frequently employed in solution for this purpose.[4] This is the first published report of the preparation and chemistry of such *N-linked* α-amino aldehydes; others have described *carbonyl-bound* versions and employed them in solid phase synthesis.[5]

The synthesis of **1** begins with acyl imidazole-modified Wang resin **2**, first reported by Hauske and Dorff[6] (Scheme 1). Reaction of **2** with an amino alcohol (5 equiv) in refluxing THF for 18−36 h[7] leads to resin-bound amino alcohols. Estimation of the efficiency of this reaction was carried out by cleaving the molecule from the resin using trifluoroacetic acid, followed by NMR analysis of the crude amino alcohol. By this measure, the yield of the reaction ranged from 75% (phenylalaninol) to 90% (alaninol). Oxidation with pyridine−sulfur trioxide complex[8] delivers amino aldehydes **1a**−**c**, whose FTIR spectra show a strong absorption at 1732 cm^{-1} for the aldehyde carbonyl and a corresponding decrease in the absorption centered at 3420 cm^{-1}. A second exposure of this material to the oxidation conditions did not result in a further decrease in signal intensity in the OH region of the IR spectrum. Using this approach, it also proved possible to attach dipeptide alcohol H-Leu-Phe-CH_2OH and convert it to the corresponding aldehyde in the same manner. Wittig olefination of **1a**−**c** using NaHMDS and methylene triphenylphosphonium bromide (5 equiv) in THF at room temperature leads to allylic amines **3a**−**c**. The aldehyde absorption was completely absent in the FTIR spectra of these products, suggestive of complete reaction. In order to confirm the success of this transformation, the leucine and phenylalanine derivatives were cleaved (TFA/CH_2Cl_2) and converted to known

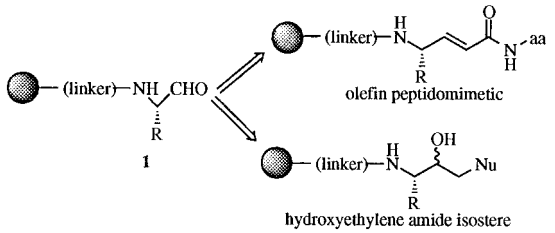
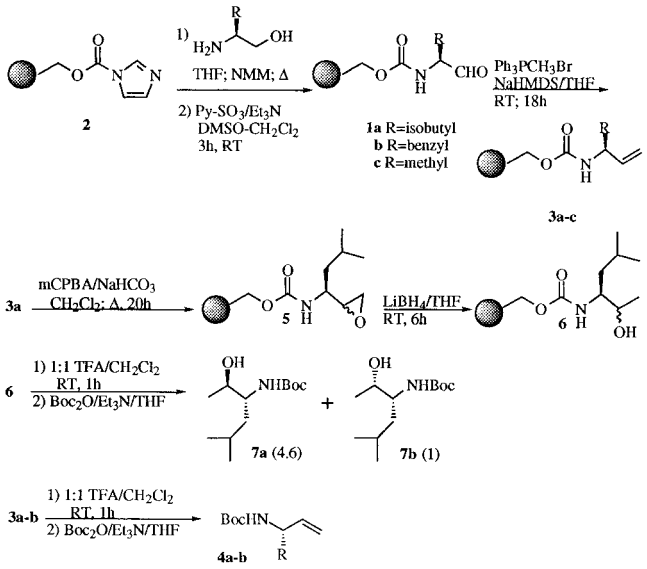


Figure 1.

Scheme 1



N-Boc compounds **4a**,**b**,[9] which were isolated in 21% yield (based on loading of the starting Wang resin). The 300 MHz NMR spectra of these samples were identical to those originally reported. Epoxidation of **3a** with purified mCPBA in buffered methylene chloride at reflux furnished oxirane **5**, a useful intermediate for the synthesis of hydroxyethylene peptidomimetics using nitrogen[10] and sulfur[11] nucleophiles.[12] To evaluate the stereoselectivity of the epoxidation reaction and to compare this solid phase sequence with its solution counterpart (15:1 *threo:erythro*[9]), **5** was reduced with $LiBH_4$ in THF (1 mol equiv) at room temperature to secondary alcohol **6**. Cleavage and carbamate formation as with **3** (*vide supra*) led to alcohols **7a,b**[13] as a 4.6:1 *threo:erythro* mixture in 65% net yield from allylic amine **3**.

The preparation of olefinic peptidomimetics is exemplified using the phenylalanine and alanine (**1b** and **1c**, respectively) resin-bound aldehydes, as shown in Scheme 2. Using phosphorane **9a**, Wittig reaction requires prolonged reflux in THF (3−4 days) to deliver the corresponding allyl esters **8b**,**c**. A similar period of time is necessary for complete conversion of **3a** to ester **8a** (X = Me) using **9b**. The commercially available Horner−Emmons reagent **9c**[14] (5 equiv) reacts with **3b,c** under milder conditions to furnish α,β-unsaturated acids **10b,c** after

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(4) For examples see: (a) Baker, W. R.; Pratt, J. K. *Tetrahedron* **1993**, *49*, 8739−8756. (b) Gennari, C.; Pain, G.; Moresca, D. *J. Org. Chem.* **1995**, *60*, 6248−6249.

(5) (a) Fehrentz, J. A.; Paris, M.; Heitz, A.; Velek, J.; Liu, C. F.; Winternitz, F.; Martinez, J. *Tetrahedron Lett.* **1995**, *36*, 7871−7874. (b) Murphy, A. M.; Dagnino, R., Jr.; Vallar, P. L.; Trippe, A. J.; Sherman, S. L.; Lumpkin, R. H.; Tamura, S. Y.; Webb, T. R. *J. Am. Chem. Soc.* **1992**, *114*, 3156−3157.

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(13) Reetz, M. T.; Rolfing, K.; Griebenow, N. *Tetrahedron Lett.***1994**, *35*, 1969−1972. $[\alpha]_D$ values and NMR spectra for these alcohols are not reported in this work. Ocain and Rich (*J. Med. Chem.* **1988**, *31*, 2193−2199) also disclose this structure but give no physical characterization.

(14) Aldrich, Catalog # 27021-0.

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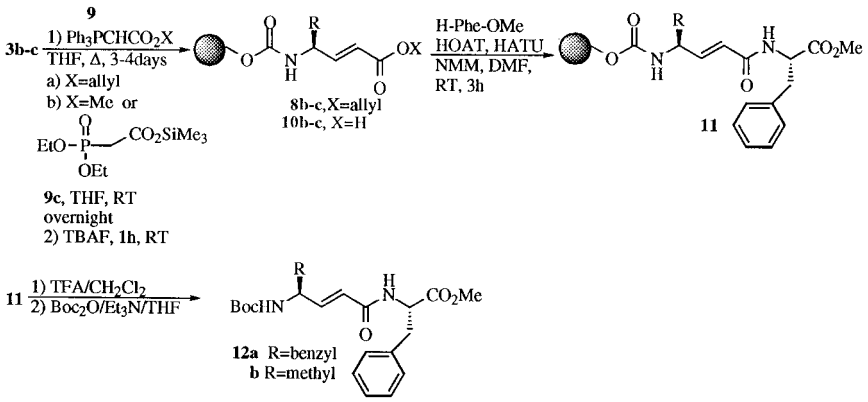
Scheme 2



brief (1 h) treatment of the resin with tetrabutylammonium fluoride to ensure complete cleavage of the labile trimethylsilyl ester. The carbonyl region of the FTIR spectra of the products **10** again shows complete disappearance of the aldehyde absorption and is not resolved into individual peaks for the acid and urethane. The presence of a carboxylic acid was suggested by broad absorbance in the region between 3400 and 3000 cm^{-1}.

Coupling of these acids with phenylalanine methyl ester using HATU and HOAT in the presence of *N*-methylmorpholine in DMF gives dipeptides **11**. FTIR of the product shows disappearance of the broad OH signal; only signals attributable to the NH protons are observed in the region around 3400 cm^{-1}. In addition, new peaks at 1682 and 1734 cm^{-1}, indicative of amide and ester moieties, respectively, are also present. Cleavage and N-terminal derivatization furnished **12a** and **12b** as white solids in 21 and 25% yield, respectively, following flash chromatography. NMR analysis of the crude reaction mixture indicated in each case that only the *E* isomer was produced in the Horner−Emmons reaction.

In both of these sequences, NMR spectra of the crude products obtained *following derivatization* with Boc anhydride indicate that, in addition to product, the most significant contaminant (ca. 10%) is excess di-*tert*-butyl dicarbonate. This "off resin" step, used herein as a means to facilitate purification, represents an additional site for structural diversity in the products. Resin-derived aromatic byproducts (based on NMR absorption in the 6.8−7.5 ppm region, <10%) can be detected in the products prior to this reaction. The modest isolated yields of products resulting from these sequences are most likely associated with the instability of the urethane linker to the basic conditions of the Wittig reactions as well as the acidic medium of the mCPBA epoxidation.[15] Mass spectral analysis of cleaved products, e.g. **4**, **7**, and **11**, did not detect ions associated with starting materials for these reactions, confirming the FTIR observations noted above. Second-generation versions of this chemistry will explore other linker strategies, as well as modified reaction conditions and/or reagents to effect these transformations.

In summary, the preparation of amino acid and dipeptide aldehydes bound to a solid support *via* the N-terminus has been demonstrated for the first time. The synthesis of olefinic peptidomimetics and amino acid-derived epoxides, themselves central intermediates in hydroxyethylene peptide isostere synthesis,[3b,c,9−12] by reaction sequences similar to those employed in solution has been demonstrated. Modest stereoselectivity (*threo* > *erythro*) was obtained in the epoxidation of resin-bound allylic amine **3a**. This can be rationalized in part to be due to the elevated temperature employed. Exclusive formation of the *E* isomer in the Horner−Emmons reaction of aldehydes **3b**,**c** with phosphonate **9c** was observed. These results establish the utility of supported amino aldehydes in solid phase approaches to peptide isosteres and further expand the spectrum of chemistry that can be applied for the preparation of libraries which are useful for enzyme inhibitor development.

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Supporting Information Available: Listing of experimental procedures for the syntheses of **1**−**12** along with physical data for **7a** and **12a**,**b** and FTIR spectra for all of the intermediates (18 pages). See any current masthead page for ordering and Internet access instructions.

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(15) Examination of the resin by FTIR following cleavage indicates that all of the material has been cleaved in both sequences. The benzyl urethane linker appears to be somewhat unstable to *m*-chlorobenzoic acid generated as a result of olefin epoxidation of a structurally unrelated series of molecules being studied in these laboratories, based on FTIR analysis of the resin following the reaction and mass recovery following TFA cleavage.