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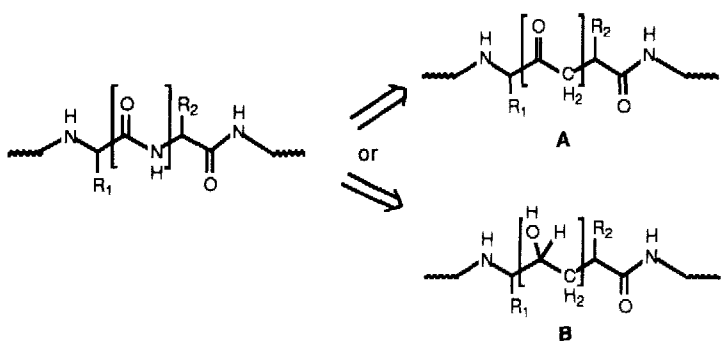
A SIMPLE SYNTHETIC APPROACH TO Cbz-Phe-Ψ-(CH2)Gly-Pro-OMe AND RELATED PEPTIDE ISOSTERES

Robert V Hoffman* and Hwa-Ok Kim
Department of Chemistry
New Mexico State University
Las Cruces, NM 88003-0001

Summary. *A new approach to ketomethylene and hydroxymethylene peptide isosteres has been developed which is simple, direct, and highly convergent A key feature is construction of the central bond of a γ-keto ester by alkylation of a t-butyl β-keto ester with an α-bromo ester.*

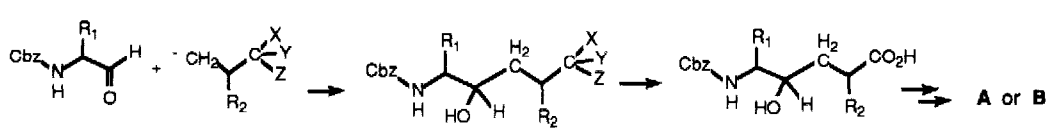
There has been a great deal of recent interest in the synthesis of peptide isosteres in which an amide bond of a peptide is replaced by an electronically and sterically similar grouping of elements that is not hydrolytically labile.[1] The peptide isostere binds to a proteolytic enzyme in a fashion similar to the natural substrate but is unreactive, thus inhibiting the normal protease activity of the enzyme Since protease activity is a crucial component in the progression of several diseases, peptide isosteres which specifically inhibit proteolytic enzymes associated with these diseases are potentially valuable therapeutic agents for their mediation While a variety of functional groups have been examined as amide replacements in peptide isosteres, two of the most popular are the ketomethylene **A** and the hydroxymethylene **B** groups[2] (Scheme 1)

Scheme 1



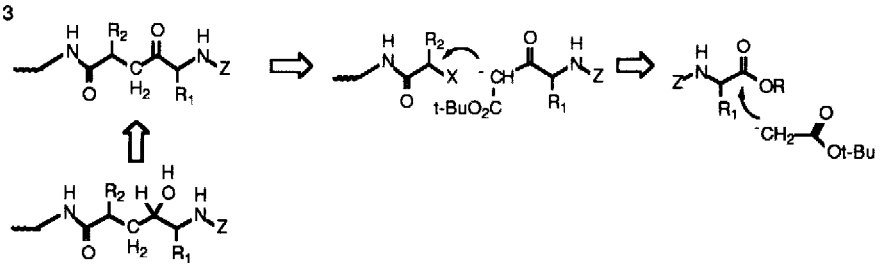
The most common route to these γ-oxidized acid derivatives is reaction of a three carbon nucleophile with an electrophile derived from a protected amino acid- usually an aminoaldehyde. Subsequent manipulation gives a γ-oxidized acid in the appropriate oxidation state (C=O or CH-OH) Coupling the acid group with an amino acid continues the peptide chain (Scheme 2) [2]

Scheme 2

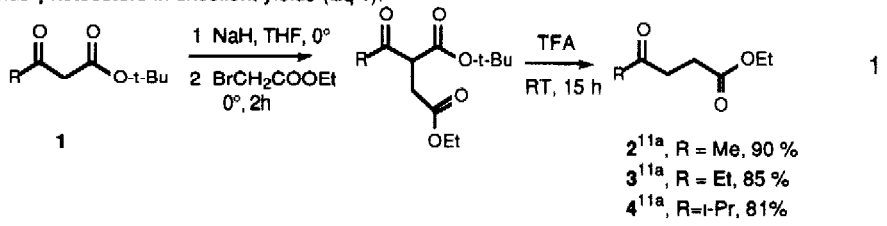


It occurred to us that another strategy of great promise for the assembly of peptide isosteres is to construct the central bond of a γ-ketoacid derivative which could then be elaborated directly to a ketomethylene peptide isostere, or which could be reduced to the γ-hydroxyacid and then elaborated into the hydroxymethylene peptide isostere. The key bond would be formed by reaction of a t-butyl β-ketoester enolate with an α-substituted ester This strategy is depicted in Scheme 3. Reaction of the enolate of diethyl malonate with α-bromoketones to yield a γ-keto ester has been used to make peptide isosteres, however the alkylation occurs only in poor yields.[3] The present approach uses α-substituted acid derivatives as alkylating agents. This reversed polarity, in which the carboxyl end of the isostere is added as an *electrophile* results in much improved efficiency , convergency, and employs more readily available starting materials.

Scheme 3



In order to demonstrate the utility of this approach, it was necessary to validate several of the component reactions in the sequence. A key step is the alkylation of a *t*-butyl β-ketoester with an α-substituted ester Acid catalyzed decarboxylation would yield the γ-keto ester This reaction was first described by Triebs[4] for the synthesis of ethyl levulinate, but has largely been ignored since that first example We find that with slight modification, it is a very simple and direct method for the preparation of γ-ketoacid derivatives, which are themselves very useful intermediates.[5] Alkylation of the sodium enolate of **1** (readily prepared from*t*-butyl acetate[6]) with ethyl bromoacetate in THF followed by treatment with TFA yields γ-ketoesters in excellent yields (Eq 1).

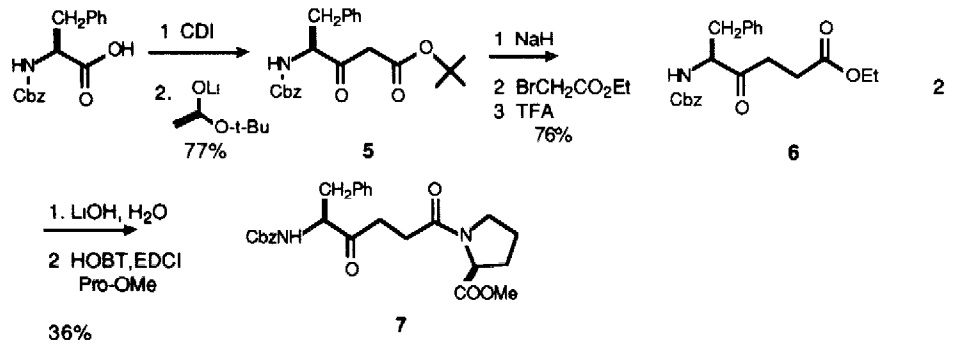


1

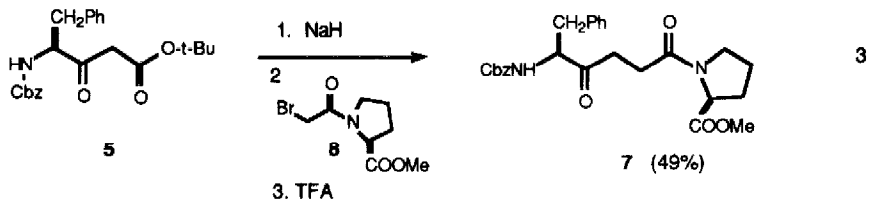
2[11a], R = Me, 90 %
3[11a], R = Et, 85 %
4[11a], R=i-Pr, 81%

Extension of this strategy to the synthesis of peptide isosteres was achieved by acylation of t-butyl acetate with a protected amino acid using carbonyldiimidazole as an activating agent.[7] The aminoacylated β-ketoester **5**[11b] was obtained in good yield and was converted uneventfully to the γ-ketoester **6**[11b], also in good yield (Eq. 2). Hydrolysis (LiOH) and coupling (HOBT, EDCI) with proline methyl ester gave a moderate yield of the ketomethylene peptide isostere Cbz-Phe-Ψ-(CH_2)Gly-Pro-OMe (**7**).[8, 11a] Isostere **7** is a potent inhibitor of angiotensin converting enzyme and thus is of interest for the treatment of hypertension.[8]

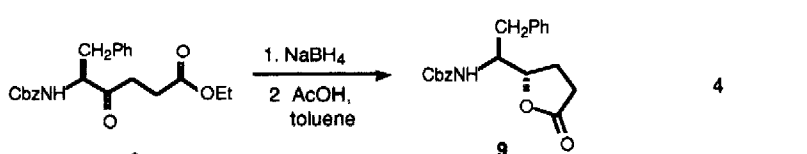
A more convergent approach to **7** was tested as shown in Equation 3. In this strategy, a bromoacetamide derivative of an amino acid **8**[9] is used to alkylate the β-ketoester **5**, thus producing the ketomethylene isostere **7** directly. This route constitutes a very simple and direct way to produce ketomethylene isosteres in good overall yields. Only one



diastereomer was detected which confirms that the assembly of the product occurrs without epimerization of either amino acid subunit.



In order to produce hydroxymethylene peptide isosteres, the stereochemistry of the reduction of the γ-ketoester **6** was examined under conditions ($NaBH_4$, MeOH, 0°C) that had shown good stereoselectivity in the reduction of statone, a lower homolog of ketomethylene peptide isosteres.[7a,c,10] The resulting hydroxy ester was cyclized to lactone **9**[11b] and analyzed by nmr spectroscopy (Eq 4) Two diastereomers (88%) in a 1.8 1 ratio were evident in the nmr spectrum, however, assignment of the 4S and 4R isomers was not possible Thus ketoester **6** was converted to the Boc-protected analog and reduced with $NaBH_4$. Comparison of the major and minor diastereomers of the Boc analog of lactone **9** with the known 4S derivative[2d] by ^{13}C nmr spectroscopy showed that the 4R isomer was the major stereoisomer. The relative abundances permitted the ^1H nmr spectrum to be assigned for both the Boc-protected compound as well as the Cbz protected example **9**. The diastereomer ratios were also determined using hplc and were identical to those determined by ^{13}C nmr. Reduction of **6** using $NaBH_4$ in ethanol at -78°C[10a] gave 67% of a mixture of 4R and 4S isomers, again in 1 8 :1 ratio. Use of $Me_4NB(OAc)_3H$ at 0° C gave 54% of a 2 1 mixture of the same isomers These diastereomers are separable by radial chromatography Methods for conversion of **9** to hydroxymethylene peptide isosteres have been reported previously [2b,2e]



0° C, MeOH 1.8.1 (4R : 4S), 88%
-78° C,EtOH 1 8 1 (4R · 4S), 67%
0° C, $Me_4NB(OAc)_3H$, 2:1, (4R . 4S), 54%

In summary a new approach to ketomethylene and hydroxymethylene peptide isosteres has been developed which is simple, direct, and highly convergent Two aspects of the process which need further attention are the alkylation of *t*-butyl β-ketoesters with α-substituted acid derivatives other than bromoacetate, and the improvement of stereoselectivity in the reduction of the ketomethylene peptide isosteres

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11 a Spectral data matched literature values b New compound characterized by spectral data and satisfactory elemental analysis.

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