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Novel Peptide Surrogates : The Retroreduced Isostere[1]

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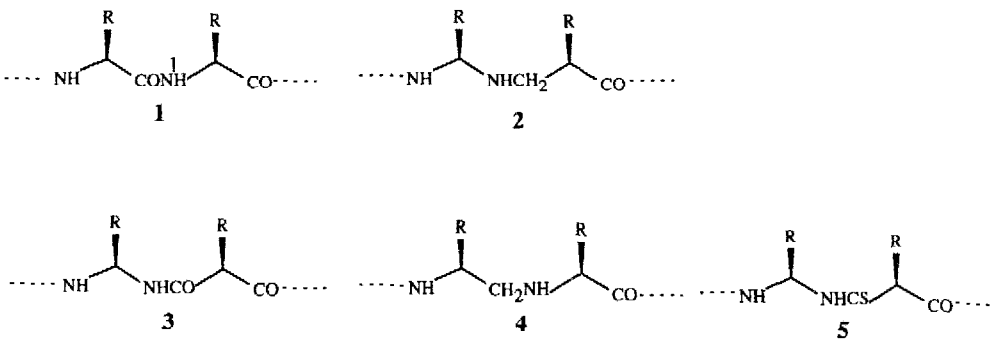
Summary: New peptide mimetics incorporating eneamine units are described. Tripeptides containing a retroamide and a reduced retroamide have been prepared.

In our continuing search for novel surrogates for amides (**1**) which could confer useful properties to biologically interesting peptides[2], we have targeted the *'retro-reduced'* isostere (**2**) by molecular graphics analysis of protease enzyme active sites. Replacement of the scissile bond of enzyme substrates with such an isostere could provide potential enzyme inhibitors. This is a structural variant of the important retroinverso (**3**) and reduced (**4**) isosteres introduced by Goodman[3] and Szelke[4] respectively.

Figure 1



1 **2** **3** **4** **5**

Our initial attempts to prepare these compounds by Raney nickel reduction of retroinverso endothiono peptides(**5**)[1], were unsuccessful and so we turned our attention to *alternative routes.*

Curtius rearrangement of the acyl azide of N-acetyl phenyl alanine, at room temperature in dilute HCl[5], provides the monoacyl gem-diamine hydrochloride **7**, in up to 65% yield. We have found that condensation of **7** with α-aldehydo esters (prepared by the Meyers dihydro-1,3-oxazine route[6]) affords the eneamines **8** (R = Me, ^{i}Pr, Bz; R' = Me, Et) as

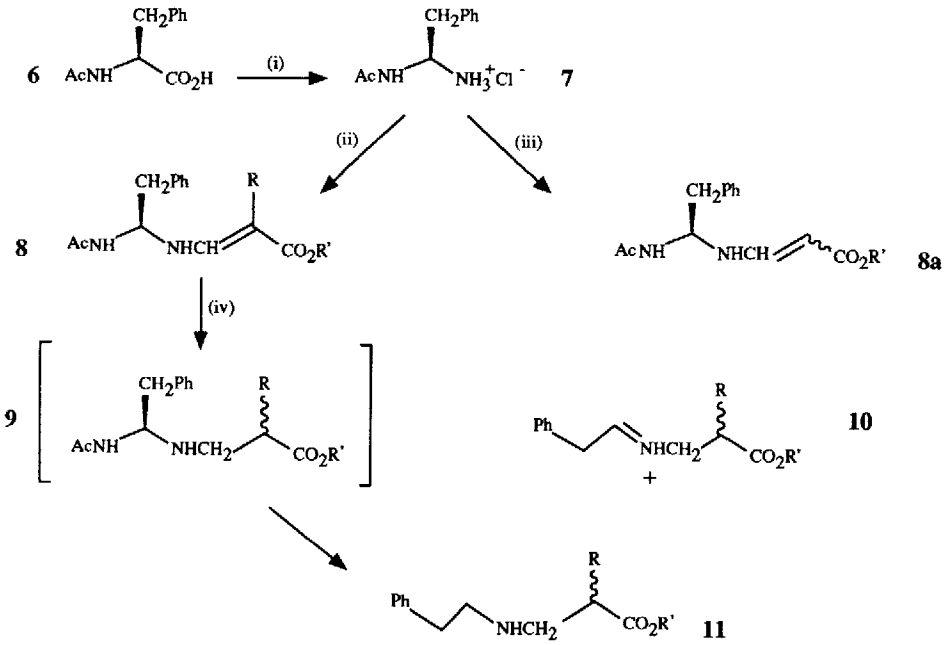
colourless solids or oils in good yield, and as a single geometrical isomer, except where R=Me, R'=Et, when a 4:1 mixture of E and Z isomers was obtained.

Michael addition of **7** to methyl propiolate provided the unsubstituted eneamine ester **8a** as an oil in 30% yield, thus giving access to the Phe-Gly-like pseudodipeptides.

This series of compounds (**8** & **8a**) represents a new family of highly conformationally restricted pseudodipeptides. Barriers exists to rotation about the eneamine N-C bond and in both the ϕ and φ torsional modes of the second 'residue', due to delocalisation of π bonding through the conjugated eneamine-ester unit.

Atmospheric pressure hydrogenation of **8** over 10% Pd on charcoal in the presence of one equivalent of acetic acid yielded not the retroreduced pseudodipeptide, **9**, as anticipated but the β amino ester **11** and acetamide as the only products. Hydrogenation in the absence of acid proceeded slowly even at elevated pressure. After 20h at 120 psi, nmr of the crude reaction mixture indicated about 50% reaction. One of the observed product species was thought to be the retroreduced pseudodipeptide **9**. On completion of the reaction the only isolable products were again acetamide and amino ester **11**.

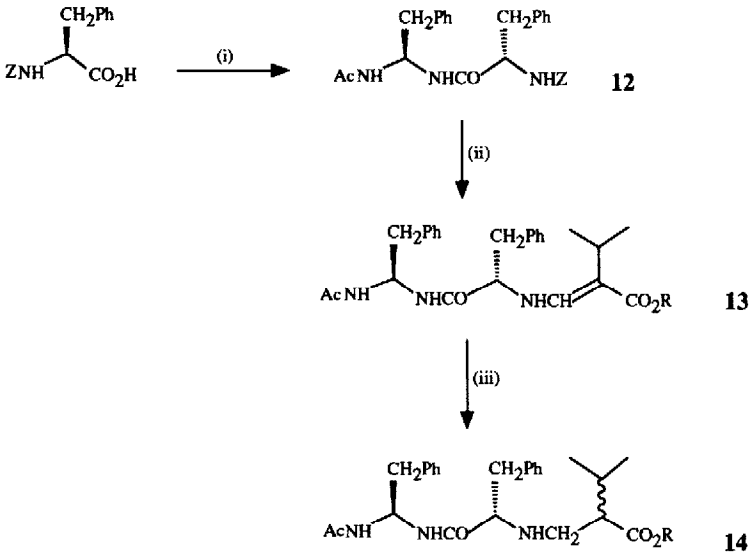
Figure 2



REAGENTS (i) a) EtOCOCl, Bu_3N b) NaN_3 c) 0.2M HCl (ii) Et_3N, OHCCH(R)CO_2R', THF reflux (iii) Methyl propiolate, Et_3N, THF reflux (iv) H_2/Pd, AcOH

From these observations we believe that hydrogenation of **8** gives the desired pseudodipeptide **9**, which is unstable and eliminates acetamide, the process being accelerated by acid. The resultant iminium species **10**, is then further reduced to the observed amino-ester **11**. These conclusions are in accord with Loudon's study of the hydrolysis of monoacyl gem diamines under acidic and basic conditions[5].

Figure 3



REAGENTS (i) a) EtOCOCl, Bu_3N b) **7** (ii) a) H_2/Pd, AcOH b)Et_3N, OHCCH(^{i}Pr)CO_2R, THF reflux (iii) H_2/Pd, AcOH

In an attempt to overcome this instability we decided to prepare a pseudotripeptide series with an amide replacement prior to the retroreduced isostere in the backbone, which would preclude decomposition due to the amide leaving group as observed in **9**.

The synthesis of this series is shown in Figure 3 (R= Me,Et). Coupling of L-Z-phenyl alanine with **7** using the mixed anhydride method afforded **12** as a single diastereomer in 55% yield. Hydrogenation of **12** and condensation of the resultant amine with the α-aldehydo ester prepared previously, provided the retroinverso-eneamine compound **13**, in 65% yield for the two steps. 'Tripeptide' **13**, represents a new structural type, in which both retroinverso and extended conformation features have been incorporated. Hydrogenation yielded the target retroinverso-retroreduced pseudotripeptide **14**, as a pair

of diastereomers, which was isolated in high yield as its hydrochloride salt.

Thus we have demonstrated that retroreduced pseudodipeptides are intrinsically unstable but the isostere can be used in combination with a second amide replacement to confer stability. Biological evaluation of the compounds described is in progress and will be reported at a later date. Conformational analysis of these new structural types, using molecular dynamics, will aso be reported.

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REFERENCES AND NOTES

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