A new and versatile procedure for the incorporation of α,β-diamino acids into peptides

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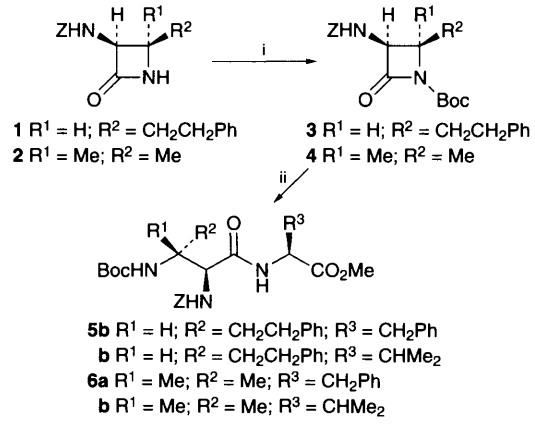
A new route to peptide segments incorporating α,β-diamino acids either at the α- or β-positions is provided by enzymeimimetic ring opening of 3-amino β-lactams with α-amino acid esters promoted by sodium azide or potassium cyanide.

The concept of structural modification of peptide fragments to confer on them specific properties is of current interest in the study and design of new bioactive targets.[1] Whilst the majority of the investigations on this topic have dealt with the synthesis and use of α-amino acids, relatively less work has been done with α,β-diamino acids.[2] Moreover, most of these studies have been conducted on β-amino alanine derivatives and, therefore, little is known about the synthesis and properties of β-substituted α,β-diamino acid-derived peptides.[3] On the other hand, the preparations of α,β-diamino acids with different and selectively removable protecting groups, allowing the incorporation into peptide chains either by the α- or the β-amino function still remain limited.[4] A synthesis of nonproteinogenic α,β-diamino acids directly combined with a peptide coupling reaction would constitute a tactically new approach to short peptide segments. Towards this goal, we have recently developed a new route to enzyme inhibitors based on an enzyme-mimetic ring opening of 3-alkoxy β-lactams with α-amino acid esters.[5] Here we report our observations on the utility of this approach for the synthesis of short peptide fragments containing α,β-diamino acids as key elements. Additional attractive attributes of this approach include an easy convergent access to the required β-lactams as the cyclisized forms of α,β-diamino acids, *i.e.* from imines *via* cycloaddition and/or *via* ester enolate condensation,[6] and an expanded scope of the β-lactam chemistry.[7]

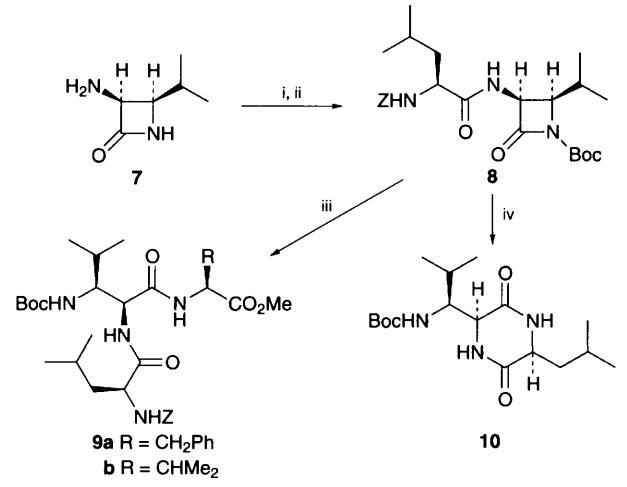
As shown in Scheme 1, the approach was guided by the observation that the introduction of the Boc group at the N-1 position in both **1** and **2** proceeded chemoselectively to give the differentially protected β-lactams **3** and **4** respectively.†



Scheme 1 *Reagents and conditions*: i, $(Boc)_2O$ (1.2 equiv.), MeCN, DMAP (10%), room temp., 24 h, 70–82%; ii, (*S*)-$H_2NCH(R^3)CO_2Me$ (1.1 equiv.), DMF, NaN_3 (1 equiv.), room temp., 14 h, 70–89%

Further, the presence of an electron withdrawing group at the N-1 position also anticipated the expected enzyme-mimetic ring opening with α-amino acid esters.[8] However, whilst the β-lactam **3** [syrup, $[\alpha]_D^{25}$ − 11.5 (*c* 1.1, CH_2Cl_2)] coupled efficiently with both (*S*)-phenylalanine methyl ester and (*S*)-valine methyl ester in *N,N*-dimethylformamide in the presence of sodium azide promoter,‡ the β-lactam **4** [mp 111–112 °C, $[\alpha]_D^{25}$ +13.1 (*c* 1.0, CH_2Cl_2)] with a C-4 quaternary carbon atom did not react with these α-amino acid esters, even when a twofold excess of NaN_3 was added. We found that the coupling of **4** with (*S*)-phenylalanine methyl ester could be achieved efficiently by changing the additive NaN_3 to KCN.[9] Under these conditions the dipeptide product **6a** [mp 151–152 °C, $[\alpha]_D^{25}$ +20.9 (*c* 1.0, CH_2Cl_2)] was obtained within about 10 h in 89% isolated yield. Similarly, the more hindered (*S*)-valine methyl ester could be acylated with **4** in the presence of KCN within about 20 h to give **6b** [mp 159–161 °C, $[\alpha]_D^{25}$ +4.5 (*c* 1.0, CH_2Cl_2)] in 85% yield. In both cases, no epimerization occurred during coupling reactions, thus proving the utility of this approach to short peptide segments incorporating constrained α,β-diamino acid residues.§

A further example which defines the scope of this novel procedure for the incorporation of β-substituted β-aminoalanines into peptides is shown in Scheme 2. We thought that using a β-lactam already incorporating an α-amino acid side chain at C-3 position, a variety of tripeptide units with different *C*-terminal amino acids should be obtained from a common starting material. To ascertain this, the β-lactam **7** was first acylated with (*S*)-*Z*-LeuF and *N*-methylmorpholine (NMM) according to Carpino's[10] procedure and the resulting compound treated with $(Boc)_2O$ and DMAP. The introduction of the Boc group also proceeded chemoselectively to give **8** [mp 152–



Scheme 2 *Reagents and conditions*: i, ZLeuCOF (1.1 equiv.), NMM (1.5 equiv.), CH_2Cl_2, 1 h, 80%, ii, $(Boc)_2O$ (1.5 equiv.), MeCN, DMAP (10%), room temp., 12 h, 90%; iii, (*S*)-$H_2NCH(R)CO_2Me$ (1.2 equiv.), DMF, NaN_3 (1 equiv.) room temp., 14 h, 75–80%; iv, H_2, Pd/C, EtOH, room temp., 14 h, 90%

154 °C, $[\alpha]_D^{25}$ +185 (*c* 1.0, CH_2Cl_2)] in 72% overall yield. We were gratified to observe that this β-lactam dipeptide also coupled efficiently under the influence of either NaN_3 or KCN with both (*S*)-phenylalanine methyl ester and (*S*)-valine methyl ester to give **9a** [mp 191–193 °C, $[\alpha]_D^{25}$ −8.3 (*c* 1.0, CH_2Cl_2)] and **9b** [mp 196–198 °C, $[\alpha]_D^{25}$ −27.6 (*c* 1.0, CH_2Cl_2)] in 80 and 75% yields respectively. Finally, another example illustrating the versatility of this approach is the formation in 90% yield of the piperazinedione **10** [mp 244–246 °C, $[\alpha]_D^{25}$ +12.8 (*c* 0.9, MeOH)], a compound that might be subsequently employed for the study and design of new peptidomimetic therapeutics.[1,¶]

In summary, the present study sets the basis for a *de novo* design of α,β-diamino acid-derived peptides without the necessity to previously prepare each differentially *N*-protected individual nonproteinogenic amino acid. As a consequence, the approach should be readily extended to the synthesis of cyclic peptides, peptidomimetics and biologically active substances incorporating α,β-diamino acids as key elements.[11]

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Footnotes

† A small amount of chemoselectivity was lost when the amount of $(Boc)_2O$ was increased from 1.2 to 2 equiv. For conditions, see Scheme 1.

‡ Under these conditions **5a** [mp 188–190 °C, $[\alpha]_D^{25}$ +26.5 (*c* 1.0, CH_2Cl_2)] and **5b** [mp 173–175 °C, $[\alpha]_D^{25}$ +12.3 (*c* 1.0, CH_2Cl_2)] were obtained in 73 and 77% yields respectively. In the absence of NaN_3 no reaction was observed.

§ The absence of epimerization was checked by HPLC of the corresponding dipeptide products using a Si-60 Licrosorb column (EtOAc eluent). The epimerization of the α-amino acid esters was not observed when they were exposed to KCN in DMF at room temperature overnight.

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