A Route to Dipeptides containing β-Amino-α-hydroxy Acid Fragments by Coupling of *N*-Boc-β-Lactams with α-Amino Esters. Application to the Synthesis of (−)-Bestatin

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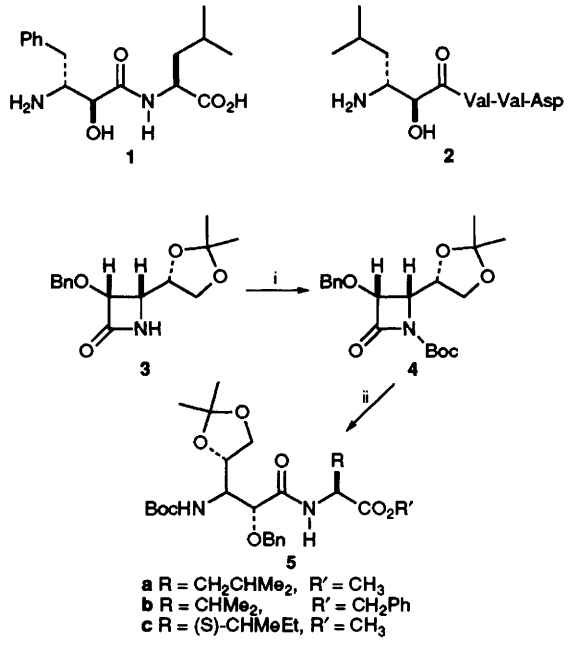
α-Amino esters are smoothly acylated by *N*-Boc-3-alkoxy-4-alkyl-β-lactams in DMF under the influence of sodium azide, giving a novel dipeptide coupling reaction.

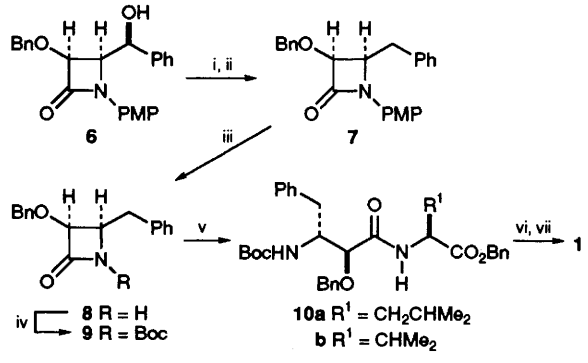
In recent years, the development of new approaches to the stereocontrolled synthesis of β-amino-α-hydroxy acids,[1] for their incorporation into peptides, has acquired central interest within the context of new enzyme inhibitors.[2] Important members of this class of compounds are bestatin **1** and amastatin **2**, two low molecular weight peptidic immunomodifiers,[3] with antitumor and antimicrobial activity.[4] The synthesis of these compounds requires the coupling of two structural units, the corresponding N-terminal β-amino-α-hydroxy acid and the C-terminal amino acid leucine or the C-terminal tripeptide Val-Val-Asp respectively. In this context, we[5] and others[6] have suggested the N_1–C_2 β-lactam scission of 3-alkoxy-β-lactams as a method of choice for the production of β-amino-α-hydroxy acids, which in turn could be subsequently coupled, through established techniques,[7] with the corresponding α-amino acid to give the desired dipeptide. However, the direct coupling of a β-lactam framework with α-amino esters, which should be of interest in terms of synthetic strategy, has been the subject of very few investigations,[8] and most notably with very little merit.[9]

To examine the approach, the readily available β-lactam **3**[10] [mp 87–89 °C (hexane–Et_2O); $[\alpha]^{25}_D$ = +64.4 (*c* 1.0, CH_2Cl_2)] was selected for development. First, the *N*-unsubstituted-β-lactam **3** was *N*-Boc protected under usual conditions[11] and the resulting *N*-Boc-β-lactam **4** [mp 104–105 °C (hexane–Et_2O); $[\alpha]^{25}_D$ = +72.8 (*c* 1.0, CH_2Cl_2)] treated with some representative α-amino esters. For instance, when this β-lactam compound was subjected to treatment with twofold excess of (*S*)-leucine methyl ester at room temperature in methylene chloride as solvent the dipeptide product **5a** was, indeed, smoothly formed, but a long reaction time was required to achieve a reasonable yield of the desired **5a** [mp 114–115 °C (hexane–Et_2O); $[\alpha]^{25}_D$ = +1.8 (*c* 1.0, CH_2Cl_2)]. Under these conditions, β-branched α-amino esters such as (*S*)-valine benzyl ester and (*S*)-isoleucine methyl ester gave only very poor yields of the expected dipeptide products. After attempts to solve this important limitation, we found that sodium azide in DMF as solvent was very effective in promoting the coupling reaction, even when a slight excess of the corresponding α-amino ester was used. By that means compounds **5b** [mp 98–99 °C (hexane–Et_2O); $[\alpha]^{25}_D$ = +4.9° (*c* 1.0, CH_2Cl_2)] and **5c** [mp 80–81 °C (hexane–Et_2O); $[\alpha]^{25}_D$ = +10.5° (*c* 1.0, CH_2Cl_2)] were obtained in 80% and 75% yields respectively.† The choice of sodium azide was primarily guided by its nucleophilic ability as compared with other nitrogen based nucleophiles[12] and by the fact that the acyl azide method for peptide coupling reactions has been shown to be virtually racemization free.[13]

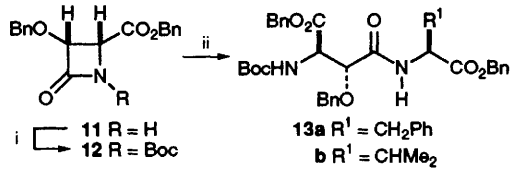
At this stage we focused on the application of this methodology for the synthesis of (−)-bestatin **1**. As illustrated in Scheme 2 the requisite β-lactam **9** was prepared from the readily available β-lactam **6**.[6a,c,14] Namely, deoxygenation of **6** under modified Barton's conditions[15] led to the β-lactam **7** [mp 85–86 °C (Et_2O); $[\alpha]^{25}_D$ = −65.1 (*c* = 0.83, CH_2Cl_2)] in 60% yield.‡ *N*-Dearylation[16] of **7** and further exposure of the resulting crude compound **8** to *N*-Boc protection as above furnished the β-lactam **9** in 73% overall yield [mp 112–113 °C (Et_2O); $[\alpha]^{25}_D$ = −96.7 (*c* 1.0, CH_2Cl_2)]. The coupling reaction of **9** with (*S*)-leucine benzyl ester and NaN_3 proceeded as expected to afford the dipeptide product **10a** in 88% yield.§ Treatment of **10a** with trifluoroacetic acid followed by exposure of the resulting crude free amino dipeptide to H_2 (1 atm) over 10% Pd/C gave (−)-bestatin **1** in 98% overall yield which was identical, in all respects, to that previously reported *via* conventional peptide coupling reactions.¶ Another example that illustrates the effectiveness of NaN_3 for these coupling reactions is further shown by the high yield of **10b** under conditions which in the absence of NaN_3 provided only a trace of the dipeptide product.‖



Scheme 1 *Reagents and conditions*: i $(Boc)_2O$, DMAP, CH_3CN, room temp. 24 h; ii, (*S*)-$H_2NCH(R)CO_2R'$ (1.3 equiv.), DMF, room temp. NaN_3 (0.1 equiv.), 20–24 h



Scheme 2 *Reagents and conditions*: i, NaH, CS_2, THF, 0 °C, then, MeI (3 equiv.), room temp., 30 min; ii, n-Bu_3SnH, Et_3B, benzene, room temp; iii, $(NH_4)_2Ce(NO_3)_6$, CH_3CN-H_2O, 0 °C; iv, $(Boc)_2O$, DMAP CH_3CN, room temp., 24 h; v, (*S*)-H_2N-CH(R)CO_2Bn (1.3 equiv.), DMF, room temp., NaN_3 (1.0 equiv), 20–24 h; vi, F_3CCO_2H, CH_2Cl_2, 0 °C, 1 h; vii, H_2, Pd/C (1 atm), EtOH, room temp., 48 h



Scheme 3 *Reagents and conditions*: i, $(Boc)_2O$, DMAP, CH_3CN, room temp., 24 h; ii, (*S*)-$H_2NCH(R^1)CO_2Bn$, DMF, room temp., NaN_3 (0.1 equiv.), 20–24 h

To extend the scope of the present method the reaction of the *N*-Boc-β-lactam **12**, obtainable from **11**,[17] with benzyl esters of (*S*)-phenylalanine and (*S*)-valine was also examined. In particular, we thought that the present coupling reaction should also be of interest for the synthesis of dipeptide units containing the β-hydroxyaspartic acid moiety.[17,18] Actually, when each α-amino ester was allowed to react with **12** in the presence of NaN_3, the reaction proceeded selectively at the imide function to give products **13a** and **13b** in 80 yield and 75% yield respectively. In the absence of NaN_3 only a 50% of conversion was observed in the reaction of **12** with (*S*)-valine benzyl ester, thus confirming the effectiveness of sodium azide in promoting these coupling reactions.

In conclusion, the examples described serve to demonstrate that 3-alkoxy-*N*-Boc-β-lactams can indeed act as acylating agents for stepwise peptide synthesis under mild reaction conditions.[19]

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Footnotes

† Reaction of **4** with both (*S*)-leucine methyl ester and (*S*)-valine benzyl ester at room temperature for 17 h in DMF led to a mixture of **5a** and **b** along with the starting **4** in a ratio 90:10 and 50:50 respectively.

‡ We first examined deoxygenation of **6** under usual Barton's conditions, but in all attempts the yields were low, typically 20–30%. The best result was obtained using triethylborane and performing the reaction at room temperature on a 2 mmol scale.

§ The coupling reaction could also be performed in methylene chloride in a 1:4 ratio, β-lactam:α-amino acid, to give **10** in quantitative yield.

¶ mp 234–235 °C (THF); $[\alpha]_D^{20}$ −15.7 (*c* 0.54, 1 mol dm^{-3} HCl). Lit *3a* mp 233–236 °C, $[\alpha]_D^{20}$ −15.5 (*c* 1.0, 1 mol dm^{-3} HCl).

‖ For instance, the reaction of **9** with (*S*)-valine benzyl ester in a 1:2 ratio in DMF as solvent produced **10b** in 22% yield. When the amount of the α-amino ester was decreased to 1.3, only traces of **10b** were detected by ^1H NMR. Under these conditions and in the presence of NaN_3, a 80% yield of the desired peptide product was obtained. We also noted the formation of benzyl alcohol, proceeding probably from the starting α-amino acid benzyl ester, when the coupling reaction was slow.

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