Synthesis of optically pure threonine-containing dipeptides by regio- and stereo-controlled ring expansion of aziridine-2-imide derivatives

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The regio- and stereo-selective ring expansion of chiral *N*-(α-amino acyl)aziridine-2-imides to oxazolines and subsequent ring opening to optically pure threonine-containing dipeptides with the desired stereochemistry is described.

β-Hydroxy α-amino acids are structural units present in a large number of naturally occurring biologically active compounds.[1] For instance, hexadepsipeptide antibiotic azinothricin,[2] depsipeptides variapeptin and citropeptin,[3] and the macrocyclic lactone antiobiotic lysobactin[4] contain in their sequence several β-hydroxy-α-amino acids linked together.

The importance of these amino acids has stimulated the development of numerous methods for their stereoselective synthesis.[5] Nevertheless a conceptually new strategy for the preparation of non-proteogenic α-amino acid derivatives starting from suitable heterocyclic compounds has been recently investigated for direct use in peptide coupling reactions. Ring-opening coupling reactions of enantiomerically pure 3-hydroxy β-lactams with various (*S*)-amino acid esters to give the corresponding dipeptides have been described by Ojima *et al*.,[6] while access to non-proteogenic peptide fragments of lysobactin from chiral azetidin-2-ones has been recently reported by Palomo *et al*.[7]

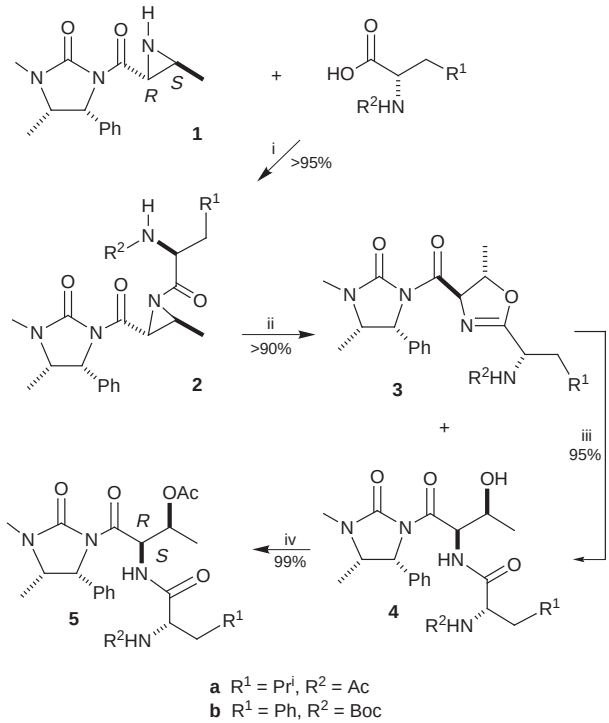
We describe here a new and efficient strategy for the synthesis of threonine-containing dipeptides starting from enantiomerically pure aziridine-2-imides *via* a ring expansion to oxazolines[8] that occurs in a regio- and stereo-controlled manner.[9]

Thus the enantiopure aziridine (2′*R*, 3′*S*)-**1**[10] was treated with *N*-acetylleucine and DCC in CH_2Cl_2–MeCN giving compound **2a** in 95% yield, which spontaneously converted into oxazoline-4-imide **3a** (Scheme 1), obtained in quantitative yield and purified by flash chromatography. Hydrolysis of **3a** performed with TsOH in MeOH–H_2O gave dipeptide **4a** in almost quantitative yield. The *trans* configuration of aziridine **2a** was retained in **3a** as shown by the oxazoline coupling constant value of H4 and H5 ($J_{H4–H5}$ = 4.7 Hz; lit.,[11] J_{trans} = 4–7 Hz). The regiochemistry of the aziridine ring expansion was easily established by ^{1}H NMR analysis of **3a** and confirmed by ^{1}H NMR decoupling experiments on **4a**.

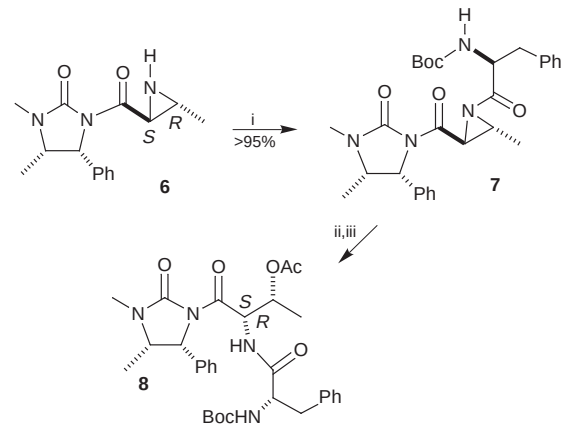
In a similar way, **2b** was obtained by treatment of **1** with *N*-Boc-phenylalanine and DCC. The ring expansion of **2b** was promoted by $BF_3{\cdot}Et_2O$ in the presence of trace water and afforded at once the (*S*)-Phe-(2′*R*, 3′*S*)-Thr derivative **4b**, which is immediately treated with Ac_2O to give **5**.[12] Under these acidic conditions, fast ring opening of oxazoline **3b** to **4b** was observed, **3b** being detected in only trace amounts in the ^{1}H NMR spectrum of the crude reaction mixture.

These results show that (2*R*, 3*S*)-threonine can be easily introduced in a polypeptide sequence. The design and synthesis of modified peptides offers opportunities for drug preparation. Among the modifications designed to obtain higher biological activity and greater resistance to enzymatic hydrolysis, the substitution of non-proteinogenic amino acids in a polypeptide sequence is of current interest.

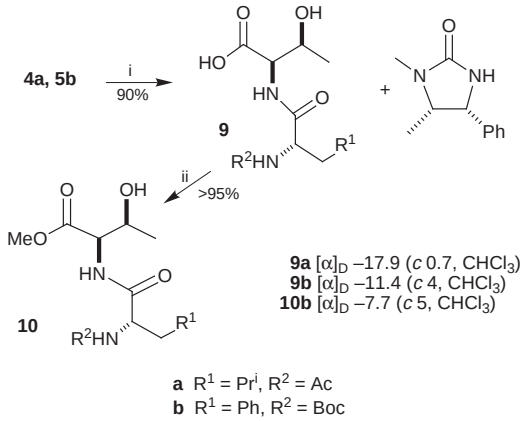
In order to prepare the (2*S*, 3*R*)-threonine-containing dipeptide, the *trans* aziridine **6**[10] was treated with *N*-Boc-phenylalanine and DCC to give **7**. The ring expansion was performed under the conditions reported for **2b** and compound **8** was finally isolated in good yield after acetylation. The ^{1}H NMR and ^{13}C NMR spectra confirmed the structure (Scheme 2).



Scheme 1 *Reagents and conditions*: i, DCC (1.1 equiv.), CH_2Cl_2–MeCN, 12 h, room temp.; ii, $BF_3{\cdot}Et_2O$ (1 equiv.), CH_2Cl_2, room temp.; iii, TsOH (1.1 equiv.), MeOH–H_2O, room temp.; iv, Ac_2O (1.2 equiv.), pyridine (1.2 equiv.), CH_2Cl_2, 2 h, room temp.



Scheme 2 *Reagents and conditions*: i, DCC (1.1 equiv.), CH_2Cl_2–MeCN, 12 h, room temp.; ii, $BF_3{\cdot}Et_2O$ (1 equiv.), CH_2Cl_2, room temp.; iii, Ac_2O (1.2 equiv.), pyridine (1.2 equiv.), CH_2Cl_2, 2 h, room temp.

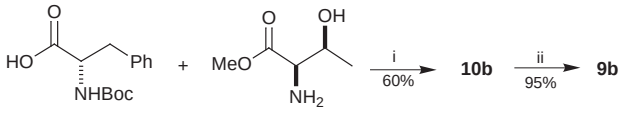


Scheme 3 *Reagents and conditions*: i, LiOH (3 equiv.), H_2O_2 (4 equiv.), THF–H_2O, 2 h, 0 °C; ii, CH_2N_2.

Finally, to obtain the free dipeptide, **4a** was submitted to non-destructive removal of the chiral auxiliary under Evans' conditions,[13] by means of LiOOH in THF–H_2O (Scheme 3). After 2 h the *N*-acetyl-(*S*)-Leu-(2*R*, 3*S*)-Thr dipeptide **9a** was recovered in good yield. Longer reaction times should be avoided; indeed, after 6 h the reaction mixture contained 10% of epimerized product.

On the basis of these results, **5b** was hydrolysed over 2 h giving without any epimerization the *N*-Boc-(*S*)-Phe-(2*R*, 3*S*)-Thr dipeptide **9b**,[14] which was essentially pure after work-up according to analysis of the crude reaction mixture. Compound **9b** was converted by means of CH_2N_2 into the corresponding methyl ester **10b**.[15]

In order to confirm the stereochemistry of the aziridine ring expansion *via* an S_Ni mechanism for **2** and **7**, an authentic sample of dipeptide **8b** was prepared from commercially available (2*R*, 3*S*)-threonine and (*S*)-phenylalanine (Scheme 4).



Scheme 4 *Reagents and conditions*: i, DCC (1.1 equiv.), CH_2Cl_2–MeCN, 12 h, room temp.; ii, LiOH (2 equiv.), H_2O_2 (3 equiv.), THF–H_2O, 1 h, 0 °C.

The (2*R*, 3*S*)-threonine methyl ester and *N*-Boc-(*S*)-phenylalanine were coupled with DCC in CH_2Cl_2–MeCN and the desired dipeptide derivative was obtained in satisfactory yield. This compound was treated with LiOOH in THF–H_2O[13] and afforded the corresponding carboxylic acid. Both **9b** and **10b** showed ^{1}H NMR and ^{13}C NMR spectra which were identical, and optical rotation values which were comparable, with the authentic samples.

In conclusion, we have reported a new method that permits the synthesis of β-hydroxy α-amino acids coupled with other α-amino acids, starting from aziridine derivatives. Furthermore, due to the observed retention of configuration in the ring expansion of the starting aziridine, the stereochemistry of the final dipeptide can be fixed by using the appropriate starting material.

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Notes and references

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12 *Selected data* for **5**: δ_H($CDCl_3$) 0.80 (d, *J* 6.7, 3H, CH_3CHCHPh), 1.20 (d, *J* 6.5, 3H, CH_3CHOAc), 1.32 (s, 9H, But), 1.95 (s, 3H, COCH_3), 2.88 (s, 3H, NCH_3), 2.95–3.18 (m, 2H, CH_2Ph), 4.00 (dq, *J* 6.7, 8.4, 1H, CH_3C*H*CHPh), 4.34–4.50 (m, 1H, C*H*CH_2Ph), 4.88 (d, *J* 6.0, 1H, *H*NBoc), 5.05 (d, *J* 8.4, 1H, CH_3CHC*H*Ph), 5.50 (dq, *J* 1.3, 6.5, C*H*OAc), 6.08 (dd, *J* 1.3, 9.5, 1H, C*H*CHOAc), 6.65 (d, *J* 9.5, 1H, *H*NCHCH), 7.02–7.46 (m, 10H, ArH); δ_C($CDCl_3$) 14.7, 20.8, 24.9, 25.6, 28.2, 33.9, 49.1, 54.3, 55.5, 59.9, 70.4, 77.8, 126.9, 128.2, 128.6, 129.2, 136.2, 136.3, 155.0, 155.4, 168.5, 170.5, 171.2.

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14 *Selected data* for **9b**: ν_{max}/cm^{-1} 3300 br, 3050, 1720, 1700, 1660; δ_H($CDCl_3$) 0.93 (d, *J* 6.0, CH_3), 1.35 (s, 9H, But), 2.85–3.20 (m, 2H, CH_2Ph), 4.20–4.40 (m, 1H, C*H*OH), 4.40–4.67 (m, 2H, C*H*CHOH + C*H*CH_2Ph), 5.40 (d, *J* 6.0, 1H, *H*NBoc), 6.00–6.40 (m, 3H, OH + *H*NCHCH + CO_2H), 7.10–7.40 (m, 5H, ArH); δ_C($CDCl_3$) 19.3, 28.2, 38.9, 55.7, 57.4, 67.6, 80.1, 127.0, 128.6, 129.3, 136.4, 156.3, 172.2, 173.4; [α]D −11.4 (*c* 4, $CHCl_3$).

15 *Selected data* for **10b**: ν_{max}/cm^{-1} 3350, 3050, 1750, 1694, 1659, 1525; δ_H($CDCl_3$) 1.00 (d, *J* 6.1, 3H, CH_3), 1.32 (s, 9H, But), 2.95 (dd, *J* 6.7, 13.9, 1H, CH_2Ph), 3.11 (dd, *J* 6.2, 13.9, 1H, CH_2Ph), 3.67 (s, 3H, CO_2CH_3), 4.20–4.32 (m, 1H, C*H*OH), 4.40–4.60 (m, 2H, C*H*CHOH + C*H*CH_2Ph), 5.40–5.58 (br s, 1H, *H*NBoc), 7.10–7.33 (m, 6H, ArH + *H*NCHCH); δ_C($CDCl_3$) 19.5, 28.0, 33.6, 38.3, 52.2, 57.5, 67.2, 79.8, 126.5, 128.2, 129.1, 136.5 155.2, 171.2, 172.2; [α]D −7.7 (*c* 5, $CHCl_3$).

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