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The enantiospecific synthesis of novel lysine analogues incorporating a pyrrolidine containing side chain

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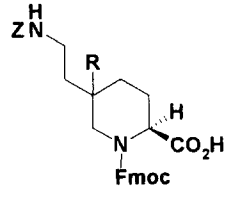
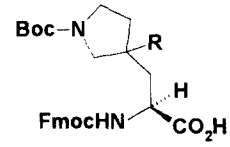
Abstract: Two novel analogues of lysine have been prepared in high enantiomeric and diastereomeric purity. These unnatural α-amino acids possess modified aminoalkyl side chains incorporating a pyrrolidine nucleus as a cyclic constraint.

Key Words: amino acids and derivatives; ring transformations; x-ray crystal structure; protecting groups

As part of an ongoing medicinal chemistry programme we recently reported [1] the homochiral synthesis of functionalised pipecolic acids **1**, as constrained analogues of lysine. We are using these novel amino acids to provide valuable information on the bioactive conformation of pharmacologically active peptides and β-turn mimetics. *N*-Substituted α-amino acids such as proline and pipecolic acid share the ability to exert a significant influence on the local, secondary structure of polypeptides containing them [2]. For this reason we considered that the pyrrolidines **2**, in which the additional constraint is confined entirely to the side chain, would represent a new and complementary class of lysine analogues.



1a; R = β-H
1b; R = α-H



2a; R = β-H
2b; R = α-H

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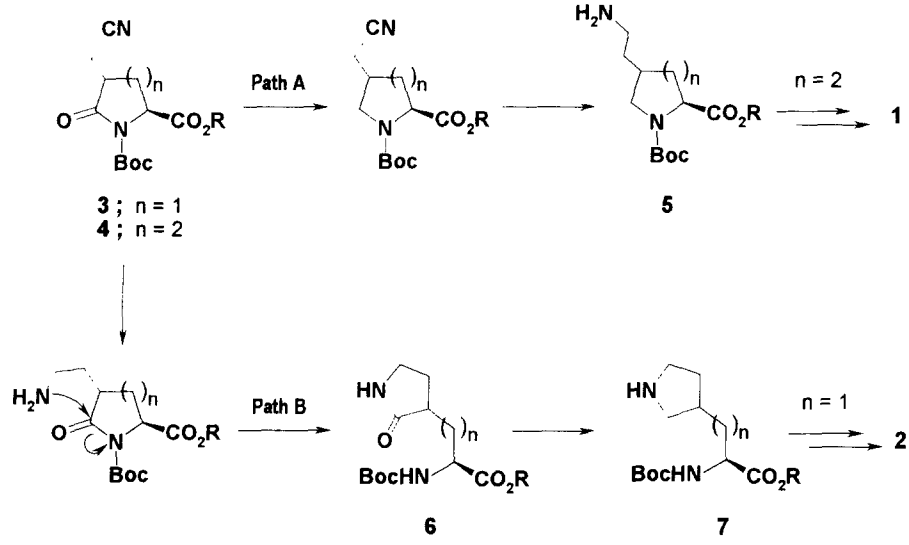
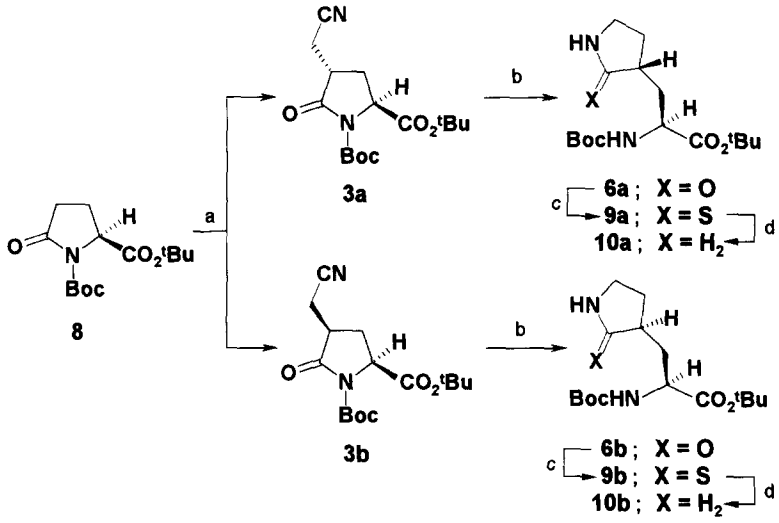
A notable feature of the proposed synthetic strategy (Scheme 1) is the concept of using the homologous, lactams **3** and **4** to prepare examples of both generic structures **5** and **7**. We have already demonstrated that chemoselective reduction of the amidic carbonyl group in the *N*-Boc piperidone **4**, followed by catalytic hydrogenation, provides an efficient route, *via* path A, to the pipecolic acids **1**. However, studies conducted by Young *et al.* [3] suggested that prior reduction of the nitrile function in the corresponding *N*-Boc pyrrolidone **3**, would invoke a spontaneous 'ring switching' reaction, *via* path B, to furnish the rearranged lactam **6** (n = 1). The realisation of this latter process is reported herein.

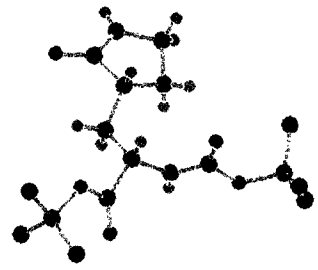


Scheme 1

The lactam ester **8** (Scheme 2), conveniently prepared from (*S*)-pyroglutamic acid by reported procedures [4], was alkylated as previously described by Ezquerra *et al.* [5], to give a 2:1 mixture of diastereomeric nitriles **3a** and **3b** in a combined yield of 65%. Following separation by a combination of chromatography and crystallisation each diastereomer was independently subjected to catalytic reduction. Initially this proved disappointing, since hydrogenation under neutral or basic conditions gave complex reaction mixtures from which, in the case of **3a,** it was possible to isolate the corresponding pyrrolidone **6a,** but only in low yield. In contrast, reduction of the nitriles **3** under acidic conditions gave cleanly, in both cases, a more polar product (by TLC) presumably corresponding to the amine hydrochlorides, which are stable under these conditions. On buffering the reaction mixtures to pH 8 with sodium bicarbonate, these initially formed intermediates were replaced with a less polar product (by TLC) and the desired epimeric lactams **6a** and **6b** were obtained in high yield. The structure of **6a**, derived from the *trans*

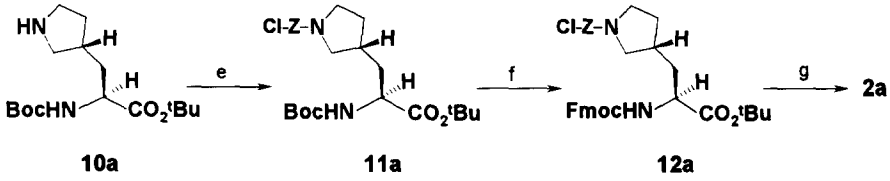
substituted pyroglutamate **3a**, and its stereochemical assignment as 2*S*, 4*R*, was confirmed at this stage by a single crystal, X-ray diffraction analysis.





X-Ray Crystal Structure of Pyrrolidine **6a**

(For the 2*S*, 4*R* stereoisomer)



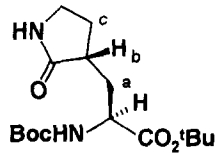
Scheme 2

Reagents and Conditions: a) LiHMDS, ICH_2CN, THF, 65%; b) i. H_2, PtO_2, EtOH, 1% HCl, ii. $NaHCO_3$, H_2O, 85%; c) Lawesson's reagent, PhMe, reflux, 75-85%; d) i. CH_2=$CHCH_2Br$, CH_2Cl_2, Et_3N, ii. $Na(CN)BH_3$, MeOH, AcOH; e) 2-Cl-ZONSu, Et_3N, CH_2Cl_2, 55-65 %; f) i. TFA, CH_2Cl_2, ii. FmocONSu, $NaHCO_3$, H_2O, dioxane, 70-75%; g) HBr, AcOH, ii. Boc_2O, $NaHCO_3$, H_2O, dioxane, 80-85%.

Attempts to reduce the secondary amide in **6a** directly, with a variety of borane reagents gave a mixture of products and therefore a more chemoselective method was sought. In a modification of the Sundberg procedure [6], the thioamides **9** were treated with allyl bromide and the resulting thioiminoethers reduced, *in situ*, with sodium cyanoborohydride. In order to provide a protective group pattern in line with the requirements of solid phase peptide synthesis, each of the secondary amines **10** were converted into the 2-chlorobenzyl carbamates **11**; the *N*-Boc groups removed selectively with TFA, and the amines reprotected as the Fmoc derivatives, delivering the orthogonally protected diamine esters **12.** For each isomer, the *tert*-butyl ester and the benzyl

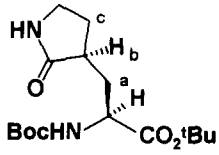
carbamate groups were removed with HBr in acetic acid and the pyrrolidine nitrogen then reprotected as the *N*-Boc derivative to furnish the desired amino acids **2a** and **2b** in high yield. The incorporation of these novel lysine mimics into biologically active peptides will be reported in due course.

Selected Physical and Spectroscopic Data for Pyrrolidones 6a and 6b:



6a

m.p. 126-128°C (EtOAc); R_f [Ethyl acetate] 0.47 ($KMnO_4$); δ_H (400 MHz; $CDCl_3$) 1.42 (9H, s, $CO_2{}^tBu$), 1.45 (9H, s, $CO_2{}^tBu$), 1.75 (1H, m, 1H-a), 1.90 (1H, m, 1H-c), 2.25 (1H, m, 1H-a), 2.34 (1H, m, 1H-c), 2.48 (1H, m, H-b), 3.31 (2H, dd, *J* 9, 6, CH_2NH), 4.23 (1H, dd, *J* 15, 7, $CHCO_2{}^tBu$), 5.65 (1H, d, *J* 8, NH), 6.02 (1H, br s, NHBoc); δ_C (100 MHz; $CDCl_3$) 28.0 (q + t), 28.4 (q), 33.6 (t), 38.6 (d), 40.4 (t), 53.0 (d), 79.6 (s), 82.0 (s), 155.5 (s), 171.5 (s), 179.6 (s).



6b

m.p. 148-150°C; R_f [Ethyl acetate] 0.47 ($KMnO_4$); δ_H (400 MHz; $CDCl_3$) 1.42 (9H, s, $CO_2{}^tBu$), 1.44 (9H, s, $CO_2{}^tBu$), 1.78 (1H, m, 1H-a), 1.84 (1H, m, 1H-c), 2.09 (1H, m, 1H-a), 2.39-2.51 (2H, m, 1H-c, H-b), 3.33 (2H, m, CH_2NH), 4.17 (1H, m $CHCO_2{}^tBu$), 5.27 (1H, d, *J* 8, NH), 5.80 (1H, br s, NHBoc); δ_C (100 MHz; $CDCl_3$) 27.9 (q), 28.2 (t), 28.3 (q), 34.6 (t), 37.9 (d), 40.2 (t), 52.7 (d), 79.7 (s), 82.0 (s), 155.7 (s), 171.5 (s), 179.6 (s).

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