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Novel peptidomimetic structures: enantioselective synthesis of conformationally constrained lysine, ornithine and alanine analogues from pyroglutamic acid

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Conformationally constrained lysine and ornithine analogues, and an L-Ala-L-Ala dipeptide analogue, are available from pyroglutamic acid.

The synthesis of conformationally constrained amino acids is of considerable current interest;[1–4] in addition to their intrinsic interest as ligands for a wide variety of biological receptors, incorporation of these structural elements into peptide chains can be used to generate novel structures of relevance to biological or materials application.[5] Although structurally restricted analogues of a number of amino acids have been described,[6–10] the ω-amino acids have generally only recently begun to attract attention. However, modified lysine chimeras, derived from pyroglutamic acid,[11] and from proline,[9] and a peptidomimetic which includes a conformationally restricted lysine analogue[12] have all recently been reported, as have ornithine[13] and arginine analogues.[14] The synthesis of cyano[15] or indole[16] substituted glutamate analogues has also recently been described.

We have used the readily available lactam **1a** as a template for manipulation to a variety of functionalised pyrrolidinones[17–20] and recently shown its application to the synthesis of conformationally restricted glutamates[21] and aminopyrrolidones.[22] We report here the extension of this versatile approach to the synthesis of several other conformationally restricted amino acids. The well-defined conformation of pyroglutamic acid has been investigated in detail[23] and its application as a template for peptidomimetics previously proposed;[24] the pyrrolidone ring simultaneously restricts τ_1, τ_2 and τ_3 to very limited ranges (from a simple molecular modeling energy minimised structure,[25] these are −144, +23 and −17° respectively) and defines the *cis*-amide bond (Fig. 1).[26]

The lysine chimera was obtained as follows: the enolate of lactam **1a** was treated with $BrCH_2CN$ (Scheme 1), unusually to give exclusively the *endo* adduct **2** in 55% yield;[27] similar alkylations generally proceed under thermodynamic control to give the *exo* product.[19] The *cis* stereochemistry of **2** and **4** was assigned on the basis of NOE data. Reduction of the nitrile function with $NaBH_4$–$CoCl_2$ gave the corresponding amine **3** in 76% yield, and this intermediate was easily converted to the product **4** in a four step (protection, deprotection, oxidation and *in situ* esterification) sequence in 16% overall yield.

The ornithine chimera was obtained from lactam **1b**. Selenenation and elimination to the known enone **5** followed by conjugate addition of the Reformatsky reagent derived from $BrCH_2CN$ gave adduct **6a** in 69% yield as a single diastereomer, as shown by ^{13}C NMR spectroscopic analysis. This strategy has proved to be very successful for manipulation of this position of a pyrrolidone ring.[21] Hydrolysis and decarboxylation using $(Bu_3Sn)_2O$[28] readily afforded the product **6b** in 68% yield, and

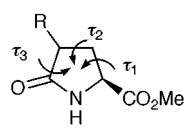
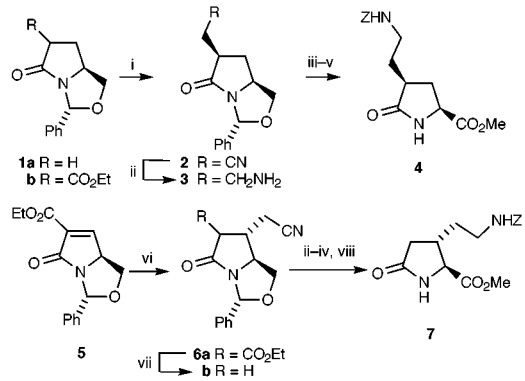


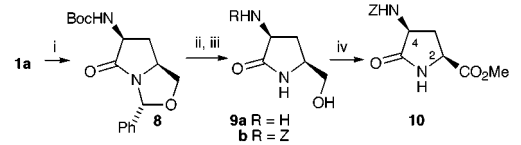
Fig. 1



Scheme 1 *Reagents and conditions*: i, LDA, THF, −78 °C then $BrCH_2CN$ (55%); ii, $NaBH_4$, $CoCl_2$, EtOH; iii, ZCl, Et_3N; iv, TFA; v, RuO_2, $NaIO_4$ then CH_2N_2 (34%); vi, Zn, DMPU, $BrCH_2CN$ (69%), room temp.; vii, $(Bu_3Sn)_2O$, toluene, Δ, 16 h (68%); viii, PDC, DMF, then CH_2N_2 (35%).

a similar sequence to that described above gave the product **7** in 14% yield over the four steps. In this case, however, application of RuO_4 in the final oxidation step did not give the desired product, and this step was successful only with PDC/DMF. The *trans* relative stereochemistry of **6a** and **7** was again shown by NOE data.

The presence of an internal amide bond suggested that amination at the C-7 position of **1a** could be used to generate an unusual dipeptide mimetic. Related aminopyrrolidones, aminopiperidones and larger ring heterocycles have recently attracted interest as enzyme inhibitors[29] and peptidomimetic structures.[30–33] Amination of the enolate of lactam **1a** with $(PhO)_2P(O)N_3$ followed by treatment with Boc_2O gave the amino lactam **8** in 50% yield (Scheme 2); surprisingly, the *endo* product, whose stereochemistry was subsequently established, was obtained exclusively. Acidic release of the protecting groups, and reprotection of the C-4 amino function as its benzyloxycarbonyl (Z) derivative, gave the product **9b** in 51% yield over the two steps. Oxidation and esterification in the usual way then gave the product **10**, which was a single stereoisomer at room temperature by NMR analysis, and whose *cis* stereochemistry was shown by NOE spectroscopy. Molecular modeling of the *N*-acetyl analogue **11** of compound **10**[25] demonstrated that two well defined conformations existed, differing by 2.3 kcal mol^{-1} in energy, with the two substituents either pseudodiequatorial or diaxial, and the latter being the more stable; since a 2.7 kcal mol^{-1} energy difference corresponds to a 99:1 ratio of species at equilibrium,[34] the



Scheme 2 *Reagents and conditions*: i, LDA, THF, −78 °C, then $(PhO)_2P(O)N_3$, then Boc_2O, −78→O °C (50%) ii, TFA, CH_2Cl_2, room temp., 1 h (quant.); iii, ZCl, DMF–THF, Et_3N, 0 °C, 3 h (51%); iv, PDC, DMF, 40 °C, 12 h, then CH_2N_2 (28%).

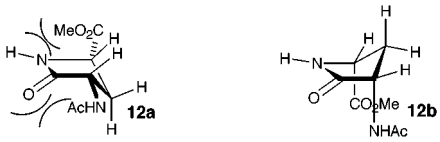
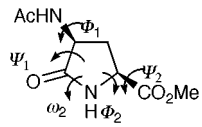


Fig. 2 Conformations of **12a** and **12b**.

minor diequatorial conformer would not be expected to be observable at room temperature by NMR analysis, and ^{1}H NMR VT analysis provided no evidence for the diequatorial conformer even at 223 K. The stability of the diaxial conformer could be attributed to the presence of A-strain[35] between the two substituents and the planar amide system; the importance of torsional strain in five- and six-membered ring heterocycles for the control of stereochemistry has been investigated in detail,[36] although its importance in lactams has only recently been appreciated.[37] Thus, the diaxial conformer minimises the interations of the relatively bulky C(2) and C(4) substituents with the planar amide function (which would occur in the diequatorial conformer **12a**) by placing C(2)-H and C(4)-H in an eclipsing conformation with the lactam system **12b** (Fig. 2). Using the energy minimised structure for **11**, some calculated dihedral angles are given in Table 1; the diaxial conformer most closely resembles a Type VIa (*cis*) β-turn.[38] Thus, this compound could be considered to be a conformationally restricted L-Ala-L-Ala dipeptide analogue, with the central amide bond constrained in the *cis* orientation, and the pyrrolidone ring capable of providing a reverse turn in an attached peptide chain; as such it represents a potential low molecular weight non-hydrophobic turn inducer. A related aminopyrrolidone has also been reported to induce Type II′ β-turn folding in a short peptide, and to exhibit hypoglycaemic activity.[39]

Table 1 Dihedral angles for energy minimised[a] conformations of **11**



Conformation	Ψ_1 (°)	Φ_2 (°)
Diequatorial	−139	+137
Diaxial	+94	−97

[a] Structures optimised with Chem3D Pro 3.5, available from Cambridge Scientific (MM2 parameters).

In view of the increasing interest in the use of variously modified proline derivatives for subtle conformational control in short peptide sequences,[40–44] the ready synthetic accessibility of enantiopure functionalised pyrrolidones may enable their application as amino acid surrogates particularly where well-defined conformational restriction is required.

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