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TETRAHEDRON: *ASYMMETRY*

Azasugar analogues: conformationally restricted vicinal diamine derived from (*S*)-(−)-pyroglutamic acid

Philip W. H. Chan,[a] Ian F. Cottrell [b] and Mark G. Moloney [a,*]

[a] *The Department of Chemistry, Dyson Perrins Laboratory, University of Oxford, South Parks Rd, Oxford, OX1 3QY, UK*
[b] *Department of Process Research, Merck Sharp and Dohme Research Laboratories, Hertford Rd, Hoddesdon, Herts, EN11 9BU, UK*

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Abstract

The preparation of a diamino substituted pyrrolidinone system in a diastereoselectively controlled manner is described. The procedure employed made use of electrophilic amination of a chiral bicyclic γ-lactam, which when subjected to sequential deprotection provided a simple route to a 3,4-diaminopyroglutaminol. The chemoselective deprotection of the amino functionality was also shown to be possible under mild hydrogenolytic conditions.

3-Amino- and 4-aminopyrrolidine moieties have been shown to exhibit an impressively broad spectrum of biological activity, either as entities in their own right, or as sub-structural units of larger molecules;[1–3] (−)-cucurbitine **1**, a possible compound for the treatment for bilharziasis, the neuroexcitatory amino acid APDC **2**,[4] emonapride **3**,[5] an antipsychotic agent, and lactam **4**,[6] a sub-unit of the cyclic hexapeptides microsclerodermins A and B, are examples. It was therefore surprising to us to find that natural products containing a 3,4-diaminopyrrolidinone functionality were virtually unknown, and perhaps as a consequence synthetic routes to this class of compounds have been little explored; on the other hand, 1,2-diaminoacids are relatively well described.[7–9] One compound of this class was reported by Eckstein et al.[10] in 1959, where the preparation of *trans*-3,4-diaminopyrrolid-2-one **5** was reported. We therefore report here the first synthesis of this class of compounds which makes use of electrophilic amination[11] of a chiral γ-lactam in the key step; such compounds might be expected to possess unusual biological activity, as shown by recent reports of the application of α- or β-aminopyrrolidinones as peptidomimetics.[12]

* Corresponding author. E-mail: mark.moloney@chem.ox.ac.uk

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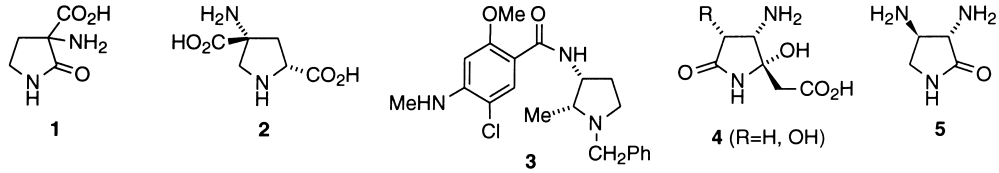
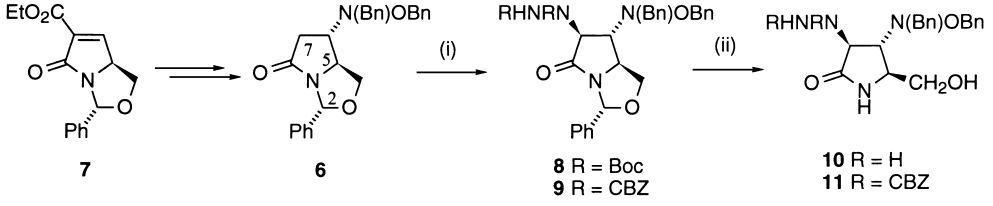


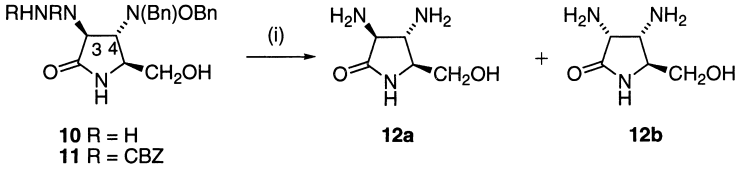
In order to extend the synthetic utility of amino substituted cyclic systems of type **6**, readily prepared from enone **7** using chemistry developed within our laboratory,[13,14] electrophilic amination at the C-7 position as a means of accessing a *trans*-3,4-diamino substituted pyrrolidine was undertaken. Deprotonation of bicyclic lactam **6** with LDA followed by quenching of the resultant enolate with either di-*tert*-butyl azodicarboxylate or dibenzyl azodicarboxylate afforded the corresponding diamino lactams **8** and **9** in excellent yields (70% and 85%, respectively), and as single diastereomers. Although the stereochemical outcome of these reactions could not be unequivocally determined by standard NOE spectroscopic techniques due to the presence of rotamers, the stereochemistry at C-6 and C-7 was, however, believed to be *trans*, since this was expected to give rise to the most thermodynamically stable product (Scheme 1) (vide infra).[15]



Scheme 1. (i) LDA, −78°C, then DBAD for **8** or CBZN=NCBZ for **9**, 8 h; (ii) TFA, DCM, rt

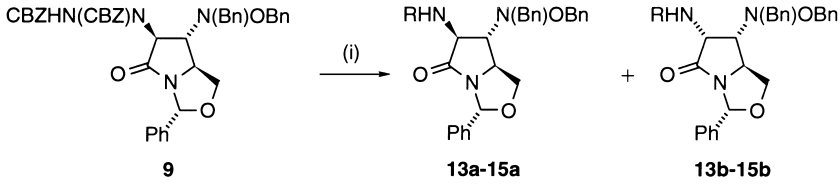
Acid-mediated deprotection of both adducts **8** and **9**, following standard procedures (TFA, DCM, rt), furnished the corresponding products **10** and **11** (the latter in 67% yield as a single isomer) but the former resisted all attempts at purification. Once again, the stereochemistry of both alcohols **10** and **11** could not be unequivocally determined by NOE techniques, although both the ^{1}H and ^{13}C NMR spectra of **11** indicated that it was a single diastereomer.

Hydrogenolysis of the hydrazine adduct **10** (10% Pd/C, AcOH, 4 bar) afforded 3,4-diaminopyroglutaminols **12a**,**b** in excellent yield (77%) but as an inseparable mixture of diastereomers in a ratio of **12a**:**12b**=6:1 after purification by ion exchange chromatography.[16] Similarly, the dibenzylcarbamate derivative **11** was converted to the same product **12** in excellent yield (75%) and also as a mixture of isomers in a ratio of **12a**:**12b**=5:1 (Scheme 2). Since we had earlier shown that the chiral integrity of C-3 is unaffected by these conditions,[13] we assumed that epimerisation occurred exclusively at C-4 under the acidic conditions of the reaction; this was later shown to be the case. The relative stereochemistry of the major adduct **12a** could not be unequivocally determined by NOE techniques, but was tentatively assigned as having the *trans*-configuration on the basis of a full NOE spectroscopic analysis of a derivative (vide infra). This epimerisation under the acidic conditions presumably becomes possible once the bulky *N*-protecting groups are removed.



Scheme 2. (i) H_2(g), Pd/C, glacial acetic acid, 4 bar, rt, 48 h

Because it was not possible to unequivocally determine the stereochemical outcome of the electrophilic amination of compound **6** from the analysis of the products **8**–**12**, the chemoselective deprotection of the diamino substrate **9** using milder conditions was examined. Hydrogenolysis of **9** (10% Pd/C, EtOAc, 4 bar) was found to give three different products depending on the reaction time. After 22 hours, the partially deprotected hydrazine adducts **13a**,**b** were obtained in good yield and as an inseparable mixture of diastereomers. Careful ^{1}H NMR examination using dry deuterio-DMSO showed that, of the two possible benzyloxycarbamate protecting groups, deprotection of the *N*-alkylated nitrogen centre was preferential; no evidence for the NH_2 group, which would have arisen from the removal of the benzyl carboxylate protecting group of the terminal nitrogen of the adduct, was observed. After two days, a mixture of the two products **14a**,**b** and **15a**,**b** was obtained, which could be separated by flash column chromatography to give **14a**,**b** in good yield and as the major adduct. After one week, a reversal in the yields of these products was observed; this time the fully deprotected amino derivative **15a**,**b** was obtained in good yield and as the major product (Scheme 3 and Table 1). NMR spectroscopy indicated the formation of the hydrazine and amine derivatives **14** and **15**, and this was confirmed by mass spectroscopic analysis which showed molecular ion peaks at 445 and 430, respectively.



Scheme 3. (i) H_2(g), Pd/C, EtOAc, 4 bar, rt, and Table 1

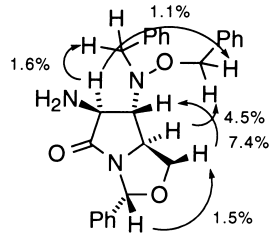
Spectroscopic analysis (NOE) of the amino analogue **15a** enabled the assignment of the *trans*-relative stereochemistry, the absolute stereochemistry being (6*R*,7*S*) (Fig. 1). The NOE triad from H-2→H-4_{endo}→H-6 indicated their spacial proximity on the *endo*-face; this was confirmed by a 4.5% NOE from H-5 (*endo*) to the *O*-methylene protons, consistent with *exo*-orientation of this bulky group as expected. An NOE from H-7 to the *N*-methylene protons indicated a *trans*-diamine orientation, i.e. *endo*-NH_2 at C-7. This therefore also further supported the major intermediate products **13a** and **14a** as having the *trans*-orientation, the absolute stereochemistry also being (6*R*,7*S*), and that this result could have only arisen from initial electrophilic amination of substrate **6** occurring exclusively from the *endo*-face of the bicyclic structure, i.e. *trans* to the bulky C-6 substituent, as expected.

The question arose as to the likely stage of the deprotection at which this epimerisation was occurring. No stereochemical lability of the starting material **9** has been noted, presumably due to the thermodynamically stable *trans*-arrangement of the bulky substituents, and the epimerisation observed in the products **12** appeared to be due to stepwise cleavage of the protecting groups in the hydrogenolysis deprotection.

Table 1
Yields and diastereomeric ratios of the hydrogenolysis products **13**–**15**

Reaction Time (h.)	Product	R	Yield (%)	Diastereomeric Ratio[a] 13a-15a:13b-15b
22	**13a,b**	NHCBZ	49	6:1
48	**14a,b**	NH_2	52	8:1
	15a,b	H	8	8:1
168	**14a,b**	NH_2	38	8.5:1
	15a,b	H	62	8:1

[a] Estimated from the ^{1}H NMR spectrum.



15a

Figure 1.

Since the partially deprotected adducts **14** and **15** were readily available, the configurational stability of both derivatives (1:1 C_6D_6/D_2O, 24 h, rt) was therefore examined. By careful ^1H NMR spectroscopic analysis, no change in the epimeric ratio of the amino product **15** was detected, but the ratio of the major product **14a** to that of the minor compound **14b** was found to have changed from 8:1 to 2:1, suggesting that epimerisation could indeed take place at an intermediate stage once cleavage of one of the benzylcarbamate protecting groups had occurred.

In summary, the development of a route to conformationally restricted diamino functionalised pyrrolidines, obtained in excellent yields and with a high degree of diastereocontrol, was shown to be possible through the electrophilic amination at C-7 of the β-amino chiral template **6**. Subsequent elaboration of these compounds provided an efficient route to the 3,4-diaminopyroglutaminol **12** in excellent yield, albeit with some loss of chiral integrity at C-4. Although the stereochemistry of some of the intermediates generated could not be directly determined by conventional analytical protocol, the chemoselective hydrogenolysis of compound **9** allowed the assignment of the absolute configuration of the major isomers obtained as well as revealing the source of the observed epimerisation.

Acknowledgements

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15. All new compounds gave satisfactory spectroscopic and/or high resolution mass spectrometric or analytical data.
16. Characterisation data for **12**: δ_H (500 MHz, D_2O) 2.98 and 3.07 (0.85H and 0.15H, respectively, each dd, *J* 7.9 and 7.9, 8.4 and 8.3, H-3), 3.28–3.38 (1.85H, m, H-2 and H-4(major)), 3.50–3.61 (1H, m, C**H**HOH), 3.70–3.75 (1H, m, CH**H**OH), 4.09 (0.15H, d, *J* 8.6, H-4(minor)); δ_C (125.8 MHz, D_2O, major stereoisomer only) 56.9 (C-3), 60.2 (C-2 and C-4), 61.1 (CH_2OH), 178.28 (CO). HRMS 146.0932 ($C_5H_{12}N_3O_2$ requires 146.0930).
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