PERKIN 1

Pyrrolidinones derived from (*S*)-pyroglutamic acid. Part 4. α, β-Diaminopyrrolidinones

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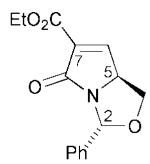
The electrophilic amination of a β-aminolactam, itself derived from the conjugate addition of *O*,*N*-dibenzylhydroxylamine to a highly activated α,β-unsaturated bicyclic lactam, provides direct access to conformationally constrained diamines. Sequential deprotection allows the synthesis of 3,4-diaminopyroglutaminols.

There has been substantial recent interest in the use of highly functionalised pyrrolidinones as excitatory amino acid analogues[1] and as conformationally controlling peptidomimetics,[2–5] and we have reported that the bicyclic lactam **1**, readily obtained from pyroglutamic acid,[6,7] provides a useful template for the preparation of conformationally restricted substituted pyrrolidinones.[8,9] Our recent work has also shown that suitable modification of the hemiaminal ether moiety of this bicyclic template can be used to control the diastereoselectivity of enolate alkylations by using competing steric and stereoelectronic effects to advantage.[10] Of particular interest was extension of this approach to allow the synthesis of conformationally constrained diamines from lactam **1**, since similar diamines[11,12] have found application as ligands[13,14] and chiral auxiliaries.[15] In general, amino functionalised pyrrolidines are not especially well known, although examples of natural products include (−)-cucurbitine **2**,[16] 3-aminoproline **3**,[17] and viomycidine **4**.[18] However, aminopyrrolidines have become increasingly important for their biological and pharmacological properties, and examples include the neuroexcitatory compound (2*R*,4*R*)-4-aminopyrrolidine-2,4-dicarboxylic acid (APDC) **5**,[19] aminoprolinol **6**[20] and 4-aminoproline **7**.[21] Surprisingly, there appear to be no natural products containing a 3,4-diaminopyrrolidinone functionality, and perhaps for this reason there has been little interest in developing synthetic routes to this class of compounds, although Eckstein *et al.*[22] reported the isolation of *trans*-3,4-diaminopyrrolidin-2-one **8** as a reaction by-product. However, since such compounds could be of considerable interest for diverse applications, we decided to examine the conversion of enone **1** to enantiopure diamino products, a sequence which was expected to be rapid and direct.



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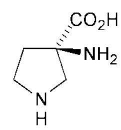

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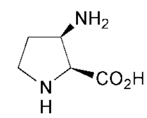

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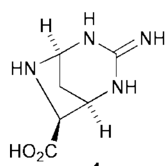

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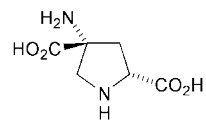

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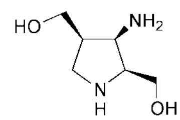

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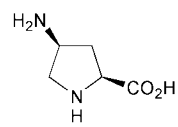

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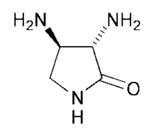

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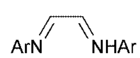
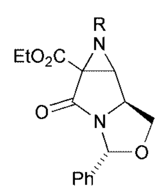


9, Ar = C_6H_4OMe

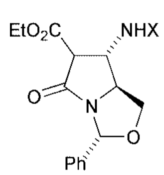


10a R = Ts
10b R = H

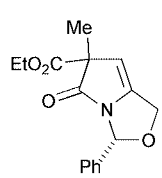
Results and discussion

Initial investigations

On the basis of favourable literature precedent for the Diels–Alder reaction of maleic anhydride with *N*,*N′*-bis(*p*-methoxyphenyl)ethylenediimine **9**,[23] and of our own work indicating that lactam **1** exhibited good reactivity in cycloaddition reactions,[24] we attempted reaction of the enone **1** in toluene with diimine **9**, but none of the desired product could be observed by either ^{1}H NMR or mass spectroscopy after 18 hours at reflux (Scheme 1). Extension of the reaction time to 36 hours or changing the solvent to xylene gave no improvement.



11a X = NMe_2
11b X = OBn



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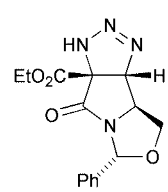

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In an alternative approach, the formation of the aziridine **10a** from enone **1** was examined: ring opening of this compound with amine nucleophiles was expected to provide access to a variety of 3,4-diamino functionalised pyrrolidinones.[25] However, reaction of α,β-unsaturated lactam **1** with toluene-*p*-sulfonamide–(diacetyloxyiodo)benzene, recently shown to be applicable to aziridination of electron rich[26] and electron poor[27] double bonds, was unsuccessful. Furthermore, intramolecular cyclisation of *N*,*N*-dimethylhydrazino derivative **11a**[28] as a route to the aziridine **10b** was also examined; quaternisation (MeI) of the amine function of **11a** and base treatment (NaH) was expected to give the aziridine directly. However, the only product obtained from this process was the unsaturated lactam **12** as an inseparable mixture of two diastereomers in a ratio of 1 : 1; this compound has previously been isolated from attempted alkylation reactions of lactam **1**.[28] Intramolecular cyclisation of hydroxylamine **11b** to the corresponding aziridine using the conditions of Cardillo *et al.*,[29] as well as collapse of the triazoline ring of **13** under photolytic conditions, a well known process,[30–33] was also unsuccessful.

Amination reactions

In view of the above difficulties, our attention turned to electrophilic amination[34] as a means of effecting carbon–nitrogen bond formation, although noteworthy was that such a process has not previously been used in lactam systems. Lactam **14** was chosen for this purpose, since this substrate was readily prepared as a single diastereomer[28] and the bulky *exo*-substituent at C-6 was expected to promote addition of the electrophile from the *endo*-face of the bicyclic system, thereby allowing diastereocontrolled access to a vicinal diamine product.

We were unable to achieve direct electrophilic amination of **14** with lithium *tert*-butyl-*N*-tosyloxycarbamate as recently reported by Armstrong and co-workers,[35] but deprotonation with LDA gave the corresponding enolate, which, when quenched with either di-*tert*-butyl azodicarboxylate or dibenzyl azodicarboxylate, afforded the corresponding diaminolactams **15a** and **15b** in excellent yields (70 and 85% respectively) and as single diastereomers after purification by flash column chromatography. However, as both products **15a** and **15b** were obtained as gums, single crystal X-ray crystallography was not possible and neither was NOE analysis, since the NMR spectra were complicated by rotameric equilibria. The stereochemistry at C-6 and C-7 was assumed to be *trans* since this would give the most thermodynamically stable product (Scheme 1).

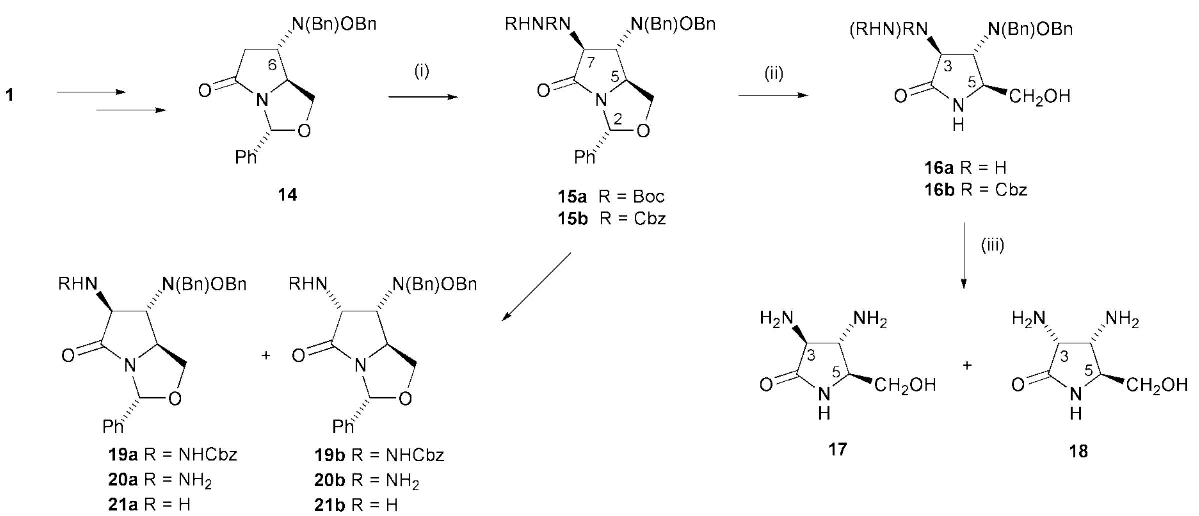
Acid-mediated deprotection of both adducts **15a** and **15b** furnished the corresponding lactams **16a** and **16b** in excellent yields (quantitative and 67% respectively, Scheme 1). However, whilst the isolation of the dibenzylcarbamate derivative **16b** could be readily achieved by flash column chromatography, this was not the case for hydrazine **16a**. Once again, the stereochemistry of both alcohols **16a** and **16b** could not be determined by NOE analysis. However, as shown by ^{1}H and ^{13}C NMR spectroscopy, both of these products were single diastereomers, and it is assumed that both compounds were obtained with C-3–C-4 *trans*-stereochemistry.

Hydrogenolysis of the hydrazine **16a** with 10% Pd/C in glacial acetic acid under a 4 bar pressure of hydrogen furnished the expected 3,4-diaminopyroglutaminol in excellent yield (77%), but with some epimerisation (ratio of products **17** : **18** = 6 : 1, Scheme 1). Similarly, the dibenzylcarbamate derivative **16b** was converted to the same products in excellent yield (75%), as a mixture of isomers in a ratio of **17** : **18** = 5 : 1. Once again, X-ray crystal structure analysis or NOE spectroscopic analysis was not possible to rigorously assign stereochemistry, but some of our earlier work[9] had shown that lactams with the *trans*-configuration at C-3 and C-4 possessed larger coupling constants than their *cis*-counterparts. The relative stereochemistry of the major adduct **17** was therefore assigned as *trans*, since the coupling constant of the C(3)H signal (8.8 Hz) was found to be larger than that for the minor product **18** (7.9 Hz).

Epimerisation studies

The epimerisation observed during the final hydrogenolytic deprotection step of **16a**, **b** (Scheme 1) was surprising, and warranted further investigation. The most likely explanation was that one of the intermediates generated during the reaction underwent epimerisation at C-3 in the acidic deprotection conditions;[28] this was later shown to be the case as follows.

Chemoselective deprotection of the carefully purified 3,4-diamine **15b** (*i.e.* as a single diastereoisomer) using milder hydrogenolysis conditions was examined, by changing the reaction solvent from glacial acetic acid to ethyl acetate. Under these conditions, the hemiaminal ether protecting group was expected to be unaffected, leaving the bicyclic ring system intact, which was then expected to allow either X-ray crystal structure or NOE analysis to be performed. Under these conditions, hydrogenolysis of lactam **15b** was found to give three different products depending on the reaction time, corresponding to successive deprotection of each of the hydrazine protecting groups, followed by N–N bond cleavage. Thus, if the reaction was allowed to proceed for 22 hours, then the partially deprotected hydrazine **19a** was obtained in good yield along

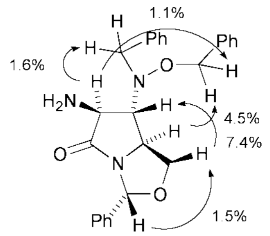


Scheme 1 *Reagents and conditions*: (i) LDA, then BocN=NBoc for **15a**, or CbzN=NCbz for **15b**; (ii) TFA, DCM, RT; (iii) H_2, Pd/C, HOAc, 4 bar, RT.

Table 1 Yields and diastereomeric ratios of hydrogenolysis products **19**–**21**

Product	R	Reaction time/h	Yield (%)	Diastereomeric ratio [a] **a** : **b**
19a, **b**	NHCBZ	22	49	6 : 1
20a, **b**	NH_2	48	52	8 : 1
21a, **b**	H	48	8	8 : 1
20a, **b**	NH_2	168	38	8.5 : 1
21a, **b**	H	168	62	8 : 1

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



21a

Fig. 1

with a minor amount of **19b** (Scheme 1 and Table 1). Careful ^1H NMR examination of **19a**, **b** using deutero-DMSO under a nitrogen atmosphere showed that the terminal hydrazine nitrogen carried the Cbz protecting group; no evidence for an NH_2 group, which would have arisen from the removal of the benzyl carboxylate protecting group, of the terminal nitrogen was observed. Furthermore, we found that if the reaction time was extended to two days then an inseparable mixture of two products, consisting predominantly of hydrazinolactam **20a**, **b**, but with a minor amount of aminolactam **21a**, **b**, was obtained. If the reaction was allowed to proceed for one week, a reverse in the ratios of these analogues was observed; this time the fully deprotected aminolactam **21a**, **b** was obtained in good yield as the major product, again as a mixture of inseparable isomers.

As all three products **19**–**21** were obtained as gums, X-ray crystallography to determine their structure could not be performed. Furthermore, NOE analysis of the adducts **19** and **20** was not possible since the signals corresponding to the protons of interest overlapped with each other in their respective ^1H NMR spectra. However, NOE analysis of the amino analogue **21a** was possible (Fig. 1); the *cis*-relationship of the H-2⟶H-4$_{endo}$⟶H-6 triad was evident from their mutual enhancement upon irradiation, and similarly the *cis*-relationship of H-5, the C-6 hydroxylamine substituent and H-7 was established. The stereochemistry of amino compound **21a** was therefore deduced to be the (*R*,*S*,*S*,*S*)-configuration, indicating that the initial electrophilic amination of substrate **14** most likely occurred exclusively from the *endo*-face of the bicyclic structure, giving the *trans*-6,7-diamino stereochemistry of lactam **15** as shown.

Epimerisation at C-7 of **15b** during deprotection might have been due to stepwise cleavage of protecting groups in the hydrogenolysis deprotection. Since the partially deprotected adducts **20** and **21** were readily available, the epimerisation of these derivatives was therefore examined. Thus, both compounds were dissolved in a 1 : 1 mixture of deuterobenzene and D_2O and allowed to stand for 24 hours at room temperature. Using ^1H NMR spectroscopic analysis, it was found that whilst no change in the isomeric ratio of the amino analogue **21** could be detected, a significant change in the diastereomeric ratio of the hydrazine adduct **20** was indeed observed; the ratio of the major product **20a** to that of the minor compound **20b** decreased from 8 : 1 to 2 : 1. These results indicated that facile epimerisation during the course of the deprotection occurred at the stage in which the α-hydrazine function of **19** and/or **20** was generated.

Conclusion

In summary, the development of a route to a conformationally restricted pyrrolidinone was shown to be possible through the electrophilic amination at C-7 of lactam **14**. Subsequent elaboration of compounds **15a** and **15b** was then shown to provide a route to the 3,4-diaminopyroglutaminol **17**–**18** in excellent yield, although the diastereoselectivity was compromised by about 14% epimerisation in the deprotection step, due to the unexpected lability of hydrazine **20**. These 3,4-diaminopyroglutaminols are conformationally constrained diamines, and may find application as organometallic ligands or as azasugar analogues.

Experimental

For general experimental procedures and the preparation of lactam **1**, see our earlier reports.[24]

(+)-(2*R*,5*S*,6*R*,7*S*)-7-[1,2-Bis(*tert*-butoxycarbonyl)hydrazino]-6-*O*,*N*-dibenzylhydroxyamino-8-oxo-2-phenyl-3-oxa-1-aza-bicyclo[3.3.0]octane 15a

To a stirred solution of *n*-butyllithium (0.53 ml, 2.00 M, 1.06 mmol) in THF (5 ml) under an inert N_2 atmosphere at 0 °C was added diisopropylamine (0.16 ml, 1.17 mmol) and the mixture was allowed to stir for 15 min. The freshly prepared solution of LDA was then cooled to −78 °C and the bicyclic lactam **14** (220 mg, 0.53 mmol) dissolved in THF (5 ml) was added slowly *via* cannula and the reaction mixture was allowed to stir for 30 min. Di-*tert*-butyl azodicarboxylate (244 mg, 1.06 mmol) dissolved in THF (5 ml) was then added slowly *via* cannula to the reaction mixture and allowed to stir at −78 °C for 8 h. The reaction mixture was then quenched at −78 °C with saturated sodium bicarbonate (10 ml) and allowed to slowly warm up to RT. Filtration through Celite and removal of solvent *in vacuo* gave the crude product. Purification by flash column chromatography and evaporation *in vacuo* of the combined fractions furnished the title compound **15a** as a colourless gum (240 mg, 70%); R_f 0.34 (3 : 1 petrol–EtOAc); $[a]_D^{25}$ +39.2 (*c* 0.6, $CHCl_3$); ν_{max}(film)/cm^{-1} 3282 (w), 2979 (m), 1722 (s), 1368 (s), 1153 (s); δ_H (400 MHz, $CDCl_3$) 1.42, 1.43, 1.44, 1.46, 1.48, 1.52 and 1.55 (18H, 7 × s, rotameric 6 × CH_3), 3.56–3.77 (2H, br m, C(4)H$_{endo}$ and C(5)H), 3.98–4.19, 4.20–4.30, 4.31–4.43 (9H, 4 × br m, CH_2Ph, OCH_2Ph, C(4)H$_{exo}$, C(6)H and C(7)H), 5.53, 5.70, 6.43 and 6.51 (1H, 4 × br s, rotameric NH), 6.33 (1H, br s, C(2)H), 6.93–7.07 (2H, m, ArCH), 7.20–7.26 (3H, m, ArCH), 7.29–7.42 (8H, m, ArCH), 7.46–7.53 (2H, m, ArCH); δ_C (100.7 MHz, $CDCl_3$) 27.62, 28.03 and 28.18 (6 × CH_3), 58.70 and 59.10 (C-5), 61.85 and 62.10 (NCH_2Ph), 69.99 (C-6), 71.62 (C-4), 76.69 ($NOCH_2Ph$), 86.96 (C-2), 125.99, 127.43, 127.58, 128.20, 128.33, 128.51, 128.81, 129.11 and 130.09 and 130.36 (ArCH), 136.20, 137.50 and 137.82 (3 × ArC), 154.7, 155.12 and 170.60 (3 × CO); *m*/*z* (electrospray) 645 (M + H^+, 100%), 667 (M + Na^+, 42); HRMS 645.3288, $C_{36}H_{45}N_4O_7$ (M + H^+) requires 645.3288.

(+)-(2*R*,5*S*,6*R*,7*S*)-7-[1,2-Bis(benzyloxycarbonyl)hydrazino]-6-*O*,*N*-dibenzylhydroxyamino-8-oxo-2-phenyl-3-oxa-1-azabicyclo-[3.3.0]octane 15b

To a stirred solution of *n*-butyllithium (0.97 ml, 2.5 M, 2.42 mmol) in THF (10 ml) under an inert N_2 atmosphere at 0 °C was added diisopropylamine (0.37 ml, 2.66 mmol) and allowed to stir for 15 min. The freshly prepared solution of LDA was then cooled to −78 °C and the bicyclic lactam **14** (500 mg, 1.21 mmol) dissolved in THF (15 ml) was added slowly *via* cannula and the reaction mixture was allowed to stir for 30 min. Dibenzyl azodicarboxylate (800 mg, 2.42 mmol) dissolved in THF (15 ml) was then added slowly *via* cannula to the reaction mixture which was allowed to stir at −78 °C for 8 h. The reaction mixture was then quenched at −78 °C with saturated sodium bicarbonate (10 ml) and allowed to slowly warm up to RT. Filtration through Celite and removal of the solvent *in vacuo* gave the crude product. A mixture of EtOAc (50 ml) and water (50 ml) was then added to the gum and the organic layer was separated. The aqueous layer was further extracted using EtOAc (50 ml) and the combined organic layers were washed with water (100 ml), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash column chromatography and evaporation *in vacuo* of the combined fractions furnished the title compound **15b** as a colourless gum (728 mg, 85%); R_f 0.19 (3 : 1 petrol–EtOAc); $[\alpha]_D^{25}$ +44.6 (*c* 0.5, $CHCl_3$); ν_{max}(film)/cm^{-1} 3500 (m), 3270 (m), 3032 (m), 2958 (m), 2879 (m), 1724 (s), 1219 (s); δ_H (400 MHz, $CDCl_3$) 3.45–3.67 (1H, br m, C(4)H_{endo}), 3.67–3.81 (1H, br m, C(5)H), 4.01–4.23 (5H, br m, C(4)H_{exo}, C(6)H, NCH_2Ph and NOCHHPh), 4.44 (1H, br d, *J* 9.5, NOCHHPh), 5.01–5.31 (5H, br m, C(7)H and 2 × OCH_2Ph), 5.61 and 5.79 (1H, 2 × br s, rotameric NH), 6.33 (1H, br s, C(2)H), 6.81–7.57 (25H, m, ArCH); δ_C (50.3 MHz, $CDCl_3$) 58.05 (C-5), 61.83 (NCH_2Ph), 67.96 (OCH_2Ph), 68.79 (OCH_2Ph), 69.82 (C-6), 71.52 (C-4), 77.03 ($NOCH_2Ph$), 86.99 (C-2), 126.01, 127.59, 128.13, 128.30, 128.51, 128.59, 128.87, 129.05 and 130.20 (ArCH), 135.35, 136.26 and 137.02 (ArC), 156.06 (acyclic CO), 174.61 (cyclic CO); *m*/*z* (APCI$^+$) 713 (M + H$^+$, 100%), 735 (M + Na$^+$, 5); HRMS 713.2975, $C_{42}H_{40}N_4O_7$ (M + H$^+$) requires 713.2975.

(3*S*,4*R*,5*S*)-4-*O*,*N*-Dibenzylhydroxyamino-3-hydrazino-5-hydroxymethyl-2-oxopyrrolidine 16a

Trifluoroacetic acid (0.5 ml) was added to adduct **15a** (240 mg, 0.37 mmol) dissolved in DCM (10 ml) at RT and allowed to stir for 1 h. Concentration *in vacuo* gave the crude product as a dark orange gum (188 mg, 100%). However, purification of the crude product by standard techniques was found to be unsuccessful; *m*/*z* (APCI$^+$) 106 (100%), 357 (M + H$^+$, 14).

(−)-(3*S*,4*R*,5*S*)-3-(1,2-Bis[benzyloxycarbonyl]hydrazino)-4-*O*,*N*-dibenzylhydroxyamino-5-hydroxymethyl-2-oxopyrrolidine 16b

Trifluoroacetic acid (0.5 ml) was added to adduct **15b** (400 mg, 0.56 mmol) dissolved in DCM (30 ml) at RT and allowed to stir for 2.5 h. Concentration *in vacuo* and subsequent purification by flash column chromatography (1 : 2 petrol–EtOAc as eluent) and concentration *in vacuo* gave the product **16b** as a pale pink foam (236 mg, 67%); R_f 0.25 (1 : 2 petrol–EtOAc); $[\alpha]_D^{23.5}$ −44.8 (*c* 2.9, $CHCl_3$); ν_{max}(film)/cm^{-1} 3260 (br), 2946 (w), 1720 (s), 1220 (s), 1054 (m); δ_H (200 MHz, $CDCl_3$) 2.60 (1H, br s, NH), 3.15–3.80 (5H, br m, NCH_2Ph, NOCHHPh, CHO*H* and C(5)H), 3.95–4.35 (3H, br m, NOCHHPh, C*H*OH and C(4)H), 4.95–5.25 (4H, br m, 2 × NCO_2CH_2Ph), 5.30–5.55 (1H, br m, C(3)H), 6.80–7.55 (20H, m, ArCH); δ_C (50.3 MHz, $CDCl_3$) 56.29 (C-5), 61.58 (N*C*H_2Ph), 63.99 (NCO_2), 66.40 (C-3), 67.78 (NCO_2), 68.40 (*C*H_2), 77.70 ($NOCH_2Ph$), 127.38, 127.98, 128.10, 128.23, 128.53 and 130.09 (ArCH), 135.57, 136.43 and 137.83 (ArC), 155.73 and 156.75 (acyclic CO), 171.89 (cyclic CO); *m*/*z* (APCI$^+$) 625 (M + H$^+$, 100%); HRMS 625.2659, $C_{35}H_{37}N_4O_7$ (M + H$^+$) requires 625.2662.

General hydrogenolysis method

To a vigorously stirred solution of the starting material dissolved in absolute ethanol, EtOAc or glacial acetic acid in a Fischer–Porter apparatus was added palladium supported on carbon (Pd/C). The heterogeneous solution was then evacuated and flushed with H_2 six times at RT. The reaction mixture was subjected to H_2 at the given pressure and time. The mixture was filtered through Celite and the resultant filtrate was concentrated *in vacuo*. Purification of the crude product was carried out by either flash column chromatography or ion-exchange chromatography.

(3*S*,4*S*,5*S*)-3,4-Diamino-5-hydroxymethyl-2-oxopyrrolidine 17 and (3*R*,4*S*,5*S*)-3,4-diamino-5-hydroxymethyl-2-oxopyrrolidine 18

Using the above general method, lactam **16a** (192 mg, 0.54 mmol) was dissolved in glacial acetic acid (15 ml) and reacted with palladium supported on carbon (Pd/C) (384 mg, 10%) under a hydrogen atmosphere (4 bar) for 72 h. Standard work-up and purification of the crude product by ion-exchange chromatography (water and then 2 M ammonia in water as eluent) gave the gummy product (60 mg, 77%) as an inseparable diastereomeric mixture of **17**–**18** (6 : 1); ν_{max}(film)/cm^{-1} 3348 (br), 1693 (s), 1379 (w); data for major isomer only δ_H (500 MHz, D_2O) 3.06 (1H, t, *J* 8.2, C(4)H), 3.36 (1H, d, *J* 8.8, C(5)H), 3.38–3.42 (1H, m, C(3)H), 3.61 (1H, dd, *J* 12.2 and 5.1, CHHOH), 3.72 (1H, dd, *J* 12.2 and 2.6, CHHOH); δ_C (125.8 MHz, D_2O) 56.96 (C(4)H), 60.16 (C(5)H and C(3)H), 61.08 (CH_2OH), 178.28 (CO); *m*/*z* (APCI$^+$) 146 (M + H$^+$, 100%); HRMS 146.0932, $C_5H_{12}N_3O_2$ (M + H$^+$) requires 146.0930.

Using the same general method, the lactam **16b** (450 mg, 0.72 mmol) was dissolved in glacial acetic acid (40 ml) and reacted with Pd/C (450 mg, 10%) and H_2 (4.5 bar) for 72 h. Purification by ion-exchange chromatography (water and then 2 M ammonia in water as eluent) gave the gummy product (78 mg, 75%) as an inseparable diastereomeric mixture of **17**–**18** (5 : 1) with identical data to those above.

(2*R*,5*S*,6*S*,7*S*)-7-[2-(Benzyloxycarbonyl)hydrazino]-6-*O*,*N*-dibenzylhydroxyamino-8-oxo-2-phenyl-3-oxa-1-azabicyclo-[3.3.0]octane 19a and (2*R*,5*S*,6*S*,7*R*)-7-[2-(benzyloxycarbonyl)-hydrazino]-6-*O*,*N*-dibenzylhydroxyamino-8-oxo-2-phenyl-3-oxa-1-azabicyclo[3.3.0]octane 19b

Using the general hydrogenolysis method, Pd/C (400 mg, 10%) was reacted with compound **15b** (400 mg, 0.56 mmol) dissolved in EtOAc (40ml) and H_2 (4 bar) for 22 h. Purification by flash column chromatography (1 : 2 petrol–EtOAc as eluent) gave the partially deprotected compound **19** as a yellow gum (160 mg, 49%) as an inseparable mixture of diastereomers in a ratio of **19a** : **19b** = 6 : 1, along with the starting material **15b** (88 mg); R_f 0.22 (2 : 1 petrol–EtOAc); ν_{max}(film)/cm^{-1} 3304 (br), 2958 (m), 2880 (m), 1716 (s); *m*/*z* (APCI$^+$) 579 (M + H$^+$, 100%); HRMS 579.2617, $C_{34}H_{35}N_4O_5$ (M + H$^+$) requires 579.2607.

Data for **19a**: δ_H (400 MHz, $CDCl_3$) 3.44 (1H, dd, *J* 9.5 and 6.1, C(6)H), 3.59 (1H, t, *J* 7.5, C(4)H_{endo}), 3.80–4.40 (6H, m, NCH_2Ph, NOC*H*HPh, C(4)H_{exo}, C(5)H, and C(7)H), 4.50 (1H, br d, *J* 10.1, OCHHPh), 4.59 (1H, br s, NHNH), 5.18 (2H, s, NCO_2CH_2Ph), 6.31 (1H, s, C(2)H), 6.88 (1H, br s, NHNH), 7.06–7.52 (20H, m, ArCH); δ_C (100.7 MHz, $CDCl_3$) 57.44 (C-5), 61.60 (NCH_2Ph), 65.56 (C-7), 67.20 (NCO_2), 70.53 (C-6), 71.49 (C-4), 76.58 ($NOCH_2Ph$), 86.62 (C-2), 126.07, 127.73, 128.22, 128.29, 128.39, 128.42, 128.49, 128.53, 128.56, 128.87, 128.96, 129.16, 129.28, 129.54 and 129.91 (ArCH), 136.01, 136.32, 136.84 and 137.69 (4 × ArC), 156.85 (acyclic CO), 172.97 (cyclic CO).

Data for **19b**: δ_H (400 MHz, $CDCl_3$) 3.44 (1H, dd, *J* 9.5 and 6.1, C(6)H), 3.62–3.73 (1H, m, C(4)H_{endo}), 3.80–4.40 (6H, m, NCH_2Ph, NOC*H*HPh, C(4)H_{exo}, C(5)H, and C(7)H), 4.50 (1H, br d, *J* 10.1, OC*H*HPh), 4.59 (1H, br s, NHNH), 5.18 (2H, s, NCO_2CH_2Ph), 6.34 (1H, s, C(2)H), 7.02 (1H, br d, *J* 5.0, NHNH), 7.06–7.52 (20H, m, ArCH); δ_C (100.7 MHz, $CDCl_3$) 56.84 (C-5), 61.60 (NCH_2Ph), 65.56 (C-7), 67.20 (NCO_2), 70.53 (C-6), 71.49 (C-4), 76.56 ($NOCH_2Ph$), 86.96 (C-2), 126.07, 127.73, 128.22, 128.29, 128.39, 128.42, 128.49, 128.53, 128.56, 128.87, 128.96, 129.16, 129.28, 129.54 and 129.91 (ArCH), 136.01, 136.32, 136.84 and 137.69 (4 × ArC), 156.85 (acyclic CO), 172.97 (cyclic CO).

(2*R*,5*S*,6*S*,7*S*)-6-*O*,*N*-Dibenzylhydroxyamino-7-hydrazino-8-oxo-2-phenyl-3-oxa-1-azabicyclo[3.3.0]octane 20a, (2*R*,5*S*,6*S*,7*R*)-6-*O*,*N*-dibenzylhydroxyamino-7-hydrazino-8-oxo-2-phenyl-3-oxa-1-azabicyclo[3.3.0]octane 20b, and (2*R*,5*S*,6*S*,7*S*)-7-amino-6-*O*,*N*-dibenzylhydroxyamino-8-oxo-2-phenyl-3-oxa-1-azabicyclo[3.3.0]octane 21a and (2*R*,5*S*,6*S*,7*R*)-7-amino-6-*O*,*N*-dibenzylhydroxyamino-8-oxo-2-phenyl-3-oxa-1-azabicyclo-[3.3.0]octane 21b

Reaction 1: following the general method for hydrogenolysis, Pd/C (632 mg, 10%) was reacted with compound **15b** (632 mg, 0.89 mmol) dissolved in EtOAc (30 ml) and H_2 (4 bar) for 48 h. Purification by flash column chromatography (1 : 1 petrol–EtOAc and then EtOAc as eluent) gave the two products **20** and **21**. Compound **21** was obtained as a yellow gum (29 mg, 8%) and as a mixture of inseparable diastereomers in a ratio of **21a** : **21b** = 8 : 1, along with compound **20** as a yellow gum (205 mg, 52%) and as a mixture of inseparable diastereomers in a ratio of **20a** : **20b** = 8 : 1.

Reaction 2: following the same general method, Pd/C (132 mg, 10%) was reacted with compound **15b** (132 mg, 0.19 mmol), dissolved in EtOAc (15 ml), and H_2 (4 bar) for 7 days. Purification by flash column chromatography (1 : 1 petrol–EtOAc and then EtOAc as eluent) gave the two isolated products **20** and **21**. Compound **20** was obtained as a yellow gum (30 mg, 38%) and as a mixture of inseparable diastereomers in a ratio of **20a** : **20b** = 8.5 : 1, with compound **21** as a yellow gum (51 mg, 62%) and as a mixture of inseparable diastereomers in a ratio of **21a** : **21b** = 8 : 1.

Data for **20**: R_f 0.23 (1 : 2 petrol–EtOAc); ν_{max}(film)/cm^{-1} 3356 (w), 3283 (w), 3031 (m), 2925 (m), 2878 (m), 1707 (s), 1359 (m); *m*/*z* (APCI) 445 (M + H$^+$, 100%); HRMS 445.2236, $C_{26}H_{29}N_4O_3$ (M + H$^+$) requires 445.2240.

Data for **20a**: δ_H (500 MHz, C_6D_6) 3.24 (2H, br s, NH_2), 3.52 (1H, t, *J* 7.5, C(4)H_{endo}), 3.75 (1H, dd, *J* 8.7 and 5.6, C(6)H), 3.80–4.07 (4H, m, NC*H*HPh, C(7)H, C(5)H, C(4)H_{exo}), 4.20–4.26 (2H, m, NCH*H*Ph and OCH*H*Ph), 4.30 (1H, d, *J* 10.7, OC*H*HPh), 6.50 (1H, s, C(2)H), 6.88–7.28 (11H, m, ArCH), 7.30–7.43 (2H, m, ArCH), 7.47–7.71 (2H, m, ArCH); δ_C (100.7 MHz, C_6D_6) 59.25 (C-5), 61.87 (NCH_2Ph), 62.56 (C-7), 68.90 (C-6), 71.77 (C-4), 77.04 (OCH_2Ph), 87.47 (C-2), 126.79, 126.84, 127.96, 128.19, 128.29, 128.44, 128.53, 128.75, 128.80, 128.91, 128.96, 129.46, 130.49 and 130.63 (ArCH), 137.25, 137.54 and 138.33 (3 × ArC), 174.70 (CO).

Data for **20b**: δ_H (500 MHz, C_6D_6) 2.25 (1H, dd, *J* 15.9 and 8.1, C(7)H), 2.59–2.77 (1H, br m, NH), 2.93 (1H, ddd, *J* 14.1, 8.2 and 5.9, C(6)H), 3.24 (2H, br s, NH_2), 3.31 (1H, d, *J* 13.0, NCHHPh), 3.44 (1H, d, *J* 13.0, NCH*H*Ph), 3.52 (1H, t, *J* 7.5, C(4)H_{endo}), 3.89–3.97 (1H, m, C(4)H_{exo}), 3.89–4.07 (1H, m, C(5)H), 4.10 (1H, d, *J* 10.5, OC*H*HPh), 4.15 (1H, d, *J* 10.4, OCH*H*Ph), 6.55 (1H, s, C(2)H), 6.88–7.28 (11H, m, ArCH), 7.30–7.7.43 (2H, m, ArCH), 7.47–7.71 (2H, m, ArCH); δ_C (100.7 MHz, C_6D_6) 59.25 (C-5), 61.66 (NCH_2Ph), 62.56 (C-7), 67.80 (C-6), 71.10 (C-4), 76.85 (OCH_2Ph), 87.71 (C-2), 126.79, 126.84, 127.96, 128.19, 128.29, 128.44, 128.53, 128.75, 128.80, 128.91, 128.96, 129.46, 130.49 and 130.63 (ArCH), 137.20, 137.54 and 139.78 (3 × ArC), 174.70 (CO).

Data for **21**: R_f 0.31 (1 : 2 petrol–EtOAc); ν_{max}(film)/cm^{-1} 3380 (w), 3031 (w), 2878 (m), 1714 (s), 1356 (br), 1218 (w); *m*/*z* (APCI$^+$) 122 (100%), 430 (M + H$^+$, 90); HRMS 430.2123, $C_{26}H_{28}N_3O_3$ (M + H$^+$) requires 430.2131.

Data for **21a**: δ_H (500 MHz, C_6D_6) 1.19 (2H, br s, NH_2), 2.86 (1H, dd, *J* 9.7 and 6.6, C(6)H), 3.30 (1H, t, *J* 7.4, C(4)H_{endo}), 3.69 (1H, d, *J* 13.4, NCHHPh), 3.76 (1H, d, *J* 8.8, C(7)H), 3.84 (1H, dd, *J* 13.1 and 6.5, C(5)H), 3.89–3.92 (1H, m, C(4)H_{exo}), 4.06 (1H, d, *J* 13.3, NCHHPh), 4.15 (1H, d, *J* 10.6, OCHHPh), 4.20 (1H, d, *J* 10.6, OCHHPh), 6.47 (1H, s, C(2)H), 6.93–7.19 (11H, m, ArCH), 7.33 (2H, d, *J* 7.1, ArCH), 7.55 (2H, d, *J* 7.4, ArCH).

Data for **21b**: δ_H (500 MHz, C_6D_6) 1.19 (2H, br s, NH_2), 2.86 (1H, dd, *J* 9.7 and 6.6, C(6)H), 3.30 (1H, t, *J* 7.4, C(4)H_{endo}), 3.69 (1H, d, *J* 13.4, NC*H*HPh), 3.76 (1H, d, *J* 8.8, C(7)H), 3.84 (1H, dd, *J* 13.1 and 6.5, C(5)H), 3.89–3.92 (1H, m, C(4)H_{exo}), 4.06 (1H, d, *J* 13.3, NCH*H*Ph), 4.15 (1H, d, *J* 10.6, OC*H*HPh), 4.20 (1H, d, *J* 10.6, OCH*H*Ph), 6.60 (1H, s, C(2)H), 6.93–7.19 (11H, m, ArCH), 7.33 (2H, d, *J* 7.1, ArCH), 7.67 (2H, d, *J* 7.4, ArCH); δ_C (100.7 MHz, C_6D_6) 58.49 (C-5), 58.85 (C-7), 62.17 (NCH_2Ph), 71.96 (C-4), 77.02 (OCH_2Ph), 77.11 (C-6), 87.69 (C-2), 126.83, 128.18, 128.29, 128.53, 128.75, 128.78, 128.93, 128.99, 129.57 and 130.51 (ArCH), 137.31, 138.02 and 139.57 (3 × ArC), 176.00 (CO).

Epimerisation of lactam 20a, b. To a solution of adduct **20a**, **b** (30 mg, 0.07 mmol) dissolved in C_6D_6 (0.5 ml) was added D_2O (0.5 ml). The mixture was vigorously shaken for 30 s and allowed to stand for 24 h. On completion, the organic layer was decanted. ^{1}H NMR analysis showed a change in the diastereomeric ratio of compound **20** from **20a** : **20b** = 8 : 1 to **20a** : **20b** = 2 : 1.

Attempted epimerisation of lactam 21a, b. To a solution of adduct **21a**, **b** (25 mg, 0.06 mmol) dissolved in C_6D_6 (0.5 ml) was added D_2O (0.5 ml). The mixture was vigorously shaken for 30 s and allowed to stand for 24 h. On completion, the organic layer was decanted. ^{1}H NMR analysis showed that there was no change observed in the diastereomeric ratio of compound **21a**, **b** (**21a** : **21b** = 8 : 1).

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