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PAPER

Spirocyclic systems derived from pyroglutamic acid†

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The synthesis and likely conformational structure of rigid spirocyclic bislactams and lactam-lactones derived from pyroglutamic acid, and their suitability as lead structures for applications in drug development programmes using cheminformatic analysis, has been investgated.

The re-examination of the function and availability of natural products, and natural product inspired synthesis,[1–3] has proved to be a key impetus in recent drug development.[4,5] Spirocyclic lactams have become of considerable interest, as a result of their occurrence in structurally complex (*e.g.* the spiropyrrolidinyloxindole alkaloids[6,7]) or bioactive natural products[8] (*e.g.* alstonisine,[9] amathaspiramide,[10] azaspirene,[11] elacomine,[12] horsfiline,[13] pseurotin,[14] and spiroptryprostatin[15] (Fig. 1)). They are also of note due to their resemblance to natural products,[16] and novel spiropyrrolizidines as potent antimicrobial agents for human and plant pathogens,[17] spiroindolones as antimalarials[18] and spirocyclic lactams as inhibitors of p53:MDM2 have all been reported.[19] These systems have also come to prevalence for their use in templates, scaffolds and bioisosteres due to the orthogonal relationship between the two key planes of the intersecting heterocyclic rings[20] which offers interesting opportunities for conformational control and the design of well-defined molecular architecture, and spiro-bis-δ-lactams based on pyroglutamate[21] and proline[22] templates have been prepared for their potential as β-turn mimetics. However, the core spirocyclic system is of further interest since it obeys the 'Rule of Three' (M <300; Number of Hydrogen bond donors ≤3 and acceptors ≤3; cLogP = 3; Number of rotatable bonds ≤3; Polar Surface Area = 60 Å^2) which has been suggested to be optimal for the construction of fragment libraries,[23,24] and ring modification giving natural product analogues might easily be envisaged. Since the neglect of chiral centres has been recognized as a key deficiency of drug discovery methodology,[25] we have been interested in the development of novel chiral template systems suitable for library synthesis against diverse disease states[26,27] and have shown that conformationally controlled amino acid analogues may be readily accessed[28,29] by, for example, cycloadditions[30] and by electrophile-mediated ring closure.[26] We report here an extension of this concept, suitable for access to enantiopure spirocyclic lactam-lactam and lactam-lactone systems; some of this work has been reported in preliminary form[31] and very similar synthetic work has recently been published.[32] Various approaches for the rapid asymmetric synthesis of spiro-2-pyrrolidin-5-ones have recently been reported,[33–35] including by α-diazocarbonyl insertion chemistry,[36] Pd-catalyzed intramolecular amidations[37] and iodocarbocyclisations,[38] and lactone-lactam spirocyclic systems as mimics of lycoperdic acid have recently been reported.[39]

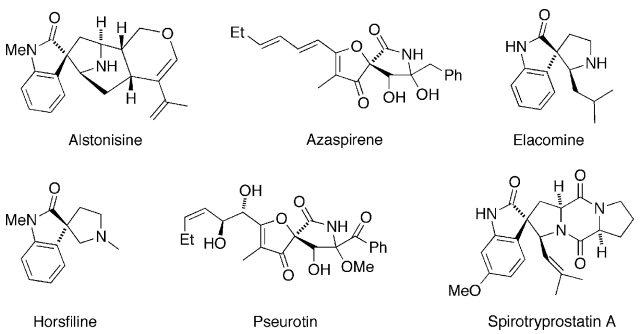

Fig. 1 Some Spirocyclic Natural Products.

We used as our starting point the bicyclic lactam system **2b**, readily prepared from ethyl pyroglutamate **1a** in three steps using literature methodology;[40] for the acylation of lactam **2a** to ethoxycarbonyl derivative **2b**, it was found that ethyl chloroformate gave a substantially better yield (90%) than the literature approach using diethyl carbonate.[40] Alkylation of ester **2b** with several bromonitriles/NaH in THF gave products **3a** and **4a**,**b** in good yields of 65, 68, and 42%, respectively (Scheme 1). Lactam **3a** was obtained as a 2:1 diastereomeric but inseparable mixture, for which the stereochemistry of the major isomer was assigned as 7*R*, arising by *exo*- attack of the electrophile; this assignment was made by comparison of the chemical shift difference of the C(6)H protons ($\Delta\delta$ 0.1) (bicyclic lactams formed *via exo*-alkylation reliably have a small chemical shift difference for the C(6)H protons of $\Delta\delta$ 0.2, but those from *endo*-alkylation show a larger difference of $\Delta\delta$ 0.8).[40,41] This structural assignment was confirmed by selective crystallisation and single crystal X-ray analysis for one of the diastereomers (Fig. 2).†[42] Lactam **4a** was similarly assigned the 7*R*

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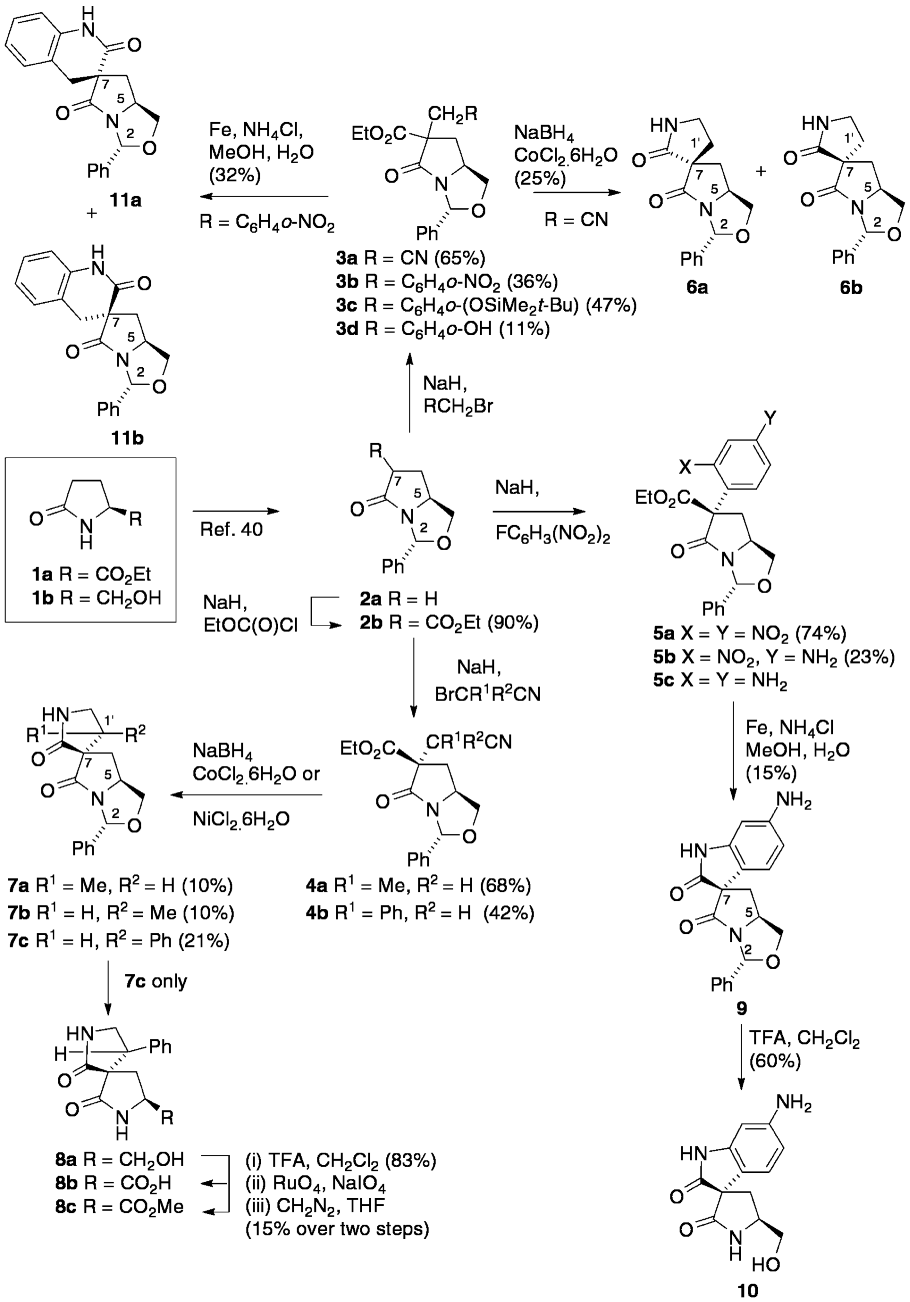

Scheme 1

stereochemistry ($\Delta\delta$ 0.35), but was epimeric at C-1′ as shown by the doubling of the signals of C(1′)Me in the ^{13}C NMR spectrum; this analysis was confirmed by NOE results (Fig. 3). Lactam **4b** was obtained as a single crystalline diastereomer, assigned as the *exo*- stereochemistry from the chemical shift difference of the C(6)H protons ($\Delta\delta$ 0.17), and this was confirmed by X-ray analysis allowing unequivocal assignment as (7*R*,1′*S*) (Fig. 2).†[42] The C(7)-alkylation reactions of the enolate derived from **2b** with substituted halonitriles therefore give high levels of *exo*- diastereoselectivity, and in the case of the phenyl substituted product **4b**, also excellent C(1′) diastereoselectivity.

Reduction of nitriles **3a**, **4a** and **4b** ($NaBH_4$, $CoCl_2{\cdot}H_2O$ or $NaBH_4$, $NiCl_2{\cdot}H_2O$)[29] followed by *in situ* cyclisation of the

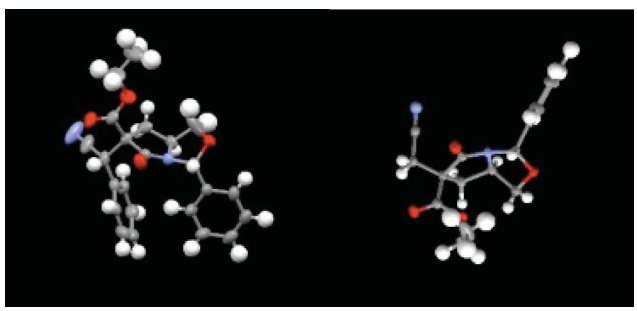

Fig. 2 X-ray structures for **3a** and **4b** (ellipsoids at 50% probability level).

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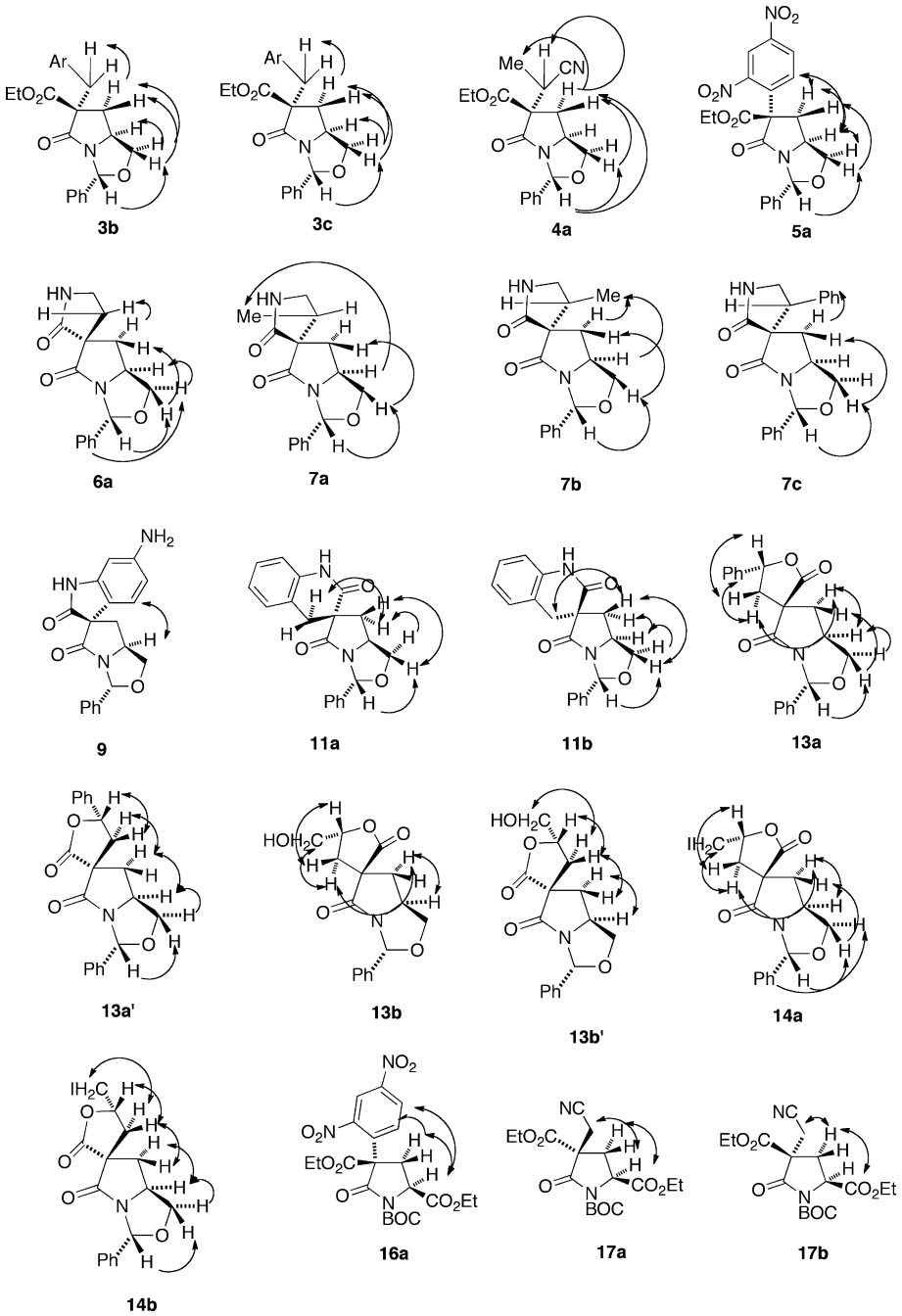

Fig. 3 NOE Data for Selected Compounds.

resulting amine gave the desired spirolactam systems **6a**,**b** (25% combined yield) and **7a–c** (10, 10 and 21%, respectively). The low yields are likely to be due to the formation of the strained spirobislactam system, and their very high polarity and water solubility (typically, a MeOH/EtOAc mixture is required for efficient elution in column chromatography) further complicated isolation; their polar nature was confirmed by estimation of their cLogP and PSA values using Marvin (Table 1).[43] Interestingly, despite their expected well-defined conformation, stereochemical assignment was unexpectedly difficult. Spirocyclisation was accompanied by large changes in the chemical shifts of the C(6)H protons relative to the starting lactams; for example, for **6a**, whose stereochemistry was established by NOE (Fig. 3), the C(6)H protons exhibited $\Delta\delta$ 0.9, but for **6b**, the value was $\Delta\delta$ 0.5. For lactams **7a**,**b**, the isomers were also obtained as a diastereomeric mixture (ratio **7a** : **7b** = 1 : 1) with C(6)H proton chemical shift difference values of $\Delta\delta$ 0.1 and $\Delta\delta$ 0.6, respectively; 2D-NOESY analysis convincingly indicated the proximal relationship of C(1′)Me, $C(6)H_{exo}$ and C(5)H of lactam **7b**, with the C(1)Me substituent located under the pyroglutaminyl ring. The stereochemistry of **7c** follows from the unequivocal assignment of precursor **4b**; the C(1′)*S* configuration in which the phenyl substituent is located under the pyroglutaminyl

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Table 1 Cheminformatic data for selected compounds

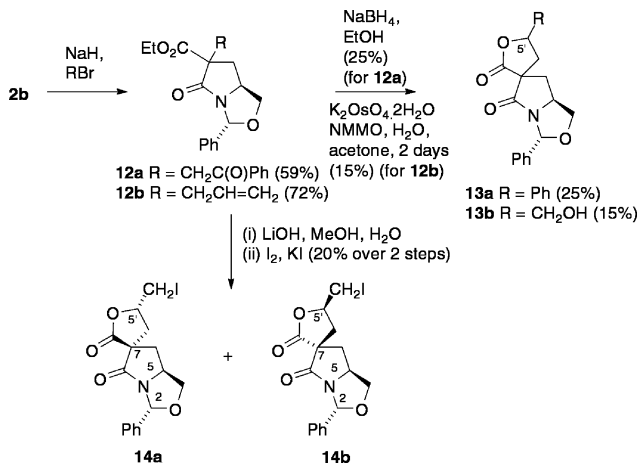
Compound	cLogP[a]	PSA[a]	MSA[a]	%PSA[a]
2b	1.77	55.8	402.3	13.9
6a	0.77	58.6	381.0	15.4
6b	0.77	58.6	381.0	15.4
7a	1.13	58.6	409.9	14.3
7b	1.13	58.6	409.9	14.3
7c	2.27	58.6	484.1	12.1
8c	–0.01	84.5	399.9	21.1
9	1.59	84.7	442.0	19.2
10	–1.15	104.5	325.5	32.1
11a	2.87	58.6	455.1	12.9
11b	2.87	58.6	455.1	12.9
15a	3.28	55.8	480.8	11.6
15b	0.87	76.1	415.9	18.3
16a	2.68	55.8	430.0	13.0
16b	2.68	55.8	430.0	13.0
19	0.51	102.1	501.1	20.4

[a] Partition coefficient (LogP), polar surface area (PSA), molecular surface area (Van der Waals MSA), %polar surface area (PSA/MSA × 100%) were all calculated using Marvin (www.chemaxon.org)[43]

ring was further confirmed by NOE analysis (Fig. 3) and by an anisotropic shielding effect from the nearby aromatic ring on C(6)H_{exo} (δ 1.9 as opposed to δ 2.8 in the unsubstituted lactam **6a**,**b**). Deprotection of **7c** efficiently yielded the pyroglutaminyl system **8a**; this compound is very polar (DMSO soluble only) and was not purified, but was readily converted to the corresponding ester **8c** in a two-step oxidation–esterification process in 15% overall yield.

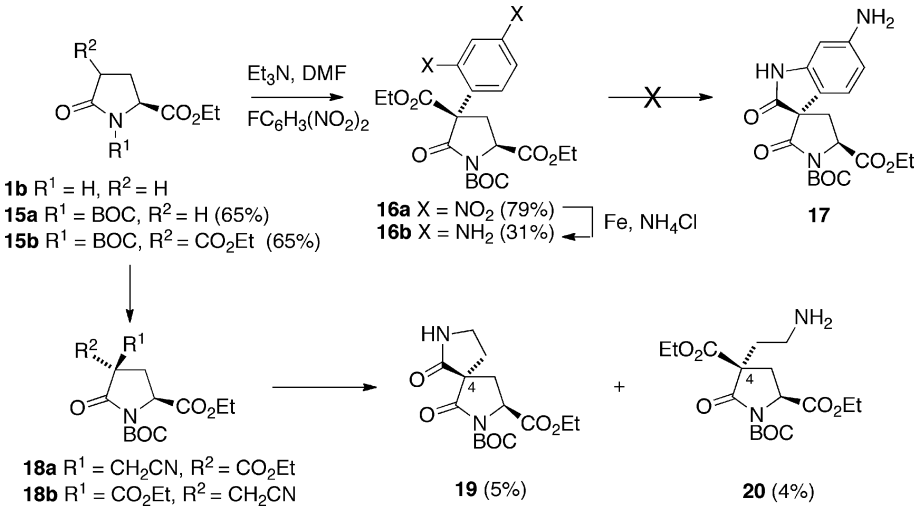
Examination of a C(7) aminoaryl substituted system was also of interest; although we have previously reported that related systems are readily available by an unusual ligand coupling using organolead triacetates.[41,44–49] In this case the required aminoaryl system **5a** was most readily accessible by nucleophilic aromatic substitution; similar arylation in related systems has been reported.[32,50,51] Thus, reaction of lactam **2b** with sodium hydride followed by 2,4-dinitro-1-fluorobenzene gave the *exo*-arylated product **5a** in 74% yield, whose stereochemistry was readily established by NOE analysis (Fig. 3); in this case, an observed $\Delta\delta$H(6) difference of 0.9 ppm was in contravention of the general trend described above, and we attribute this to an anisotropic effect from the adjacent aromatic ring. An attempted reduction of lactam **5a** using 10% Pd/C and ammonium formate gave only the partially reduced product **5b** in poor yield (23%), and longer reaction times or additional equivalents of ammonium formate gave complex reaction mixtures.[52] Application however of iron powder/ammonium chloride[53] reliably gave the required reduction, and this was followed by spontaneous lactamisation to give the desired product in 15% yield; the stereochemical outcome was again demonstrated by NOE analysis (Fig. 3), and in this case a small $\Delta\delta$H(6) difference of 0.17 ppm was also observed. Deprotection (TFA) gave alcohol **10** in 60% yield. A similar process has been recently reported by Sen, who developed this sequence for several bicyclic lactam series, and who identified better conditions for the reduction and achieved better overall yields by using the less bulky methyl ester system.[32]

Given the facility of the ring closures with appropriately positioned amine groups, it was of interest to examine whether hydroxyl-mediated ring closure, to give the corresponding spirolactone-lactam system, might also be feasible. Alkylation of lactam **2b** gave lactams **12a**,**b** (59 and 72% respectively), each as inseparable mixtures of diastereomers (Scheme 2). Reduction of lactam **12a** ($NaBH_4$) was followed by spontaneous cyclisation to give the lactone-lactam system **13a**, confirmed by the presence of carbonyl absorptions at 1752 and 1708 cm^{-1}, but in low yield (25%) and as a mixture of three stereoisomers. The major one was obtained in pure form without difficulty, but the two minor ones were more difficult to isolate; the stereochemistry of two of them was easily established by NOE analysis (Fig. 3) as being C(7)*R*, C(5′)*R* and C(7)*S*, C(5′)*S* and the third was assigned as possessing the C(7)*R*, C(5′)*S* stereochemistry, on the basis that it had a very similar ^{1}H NMR spectrum to the C(7)*R*, C(5′)*R* isomer but a large difference in the chemical shift value for the C(5′)H. Dihydroxylation of allyl derivative **12b** using potassium osmate/*N*-methylmorpholine oxide was also followed by spontaneous cyclisation, giving the lactone-lactam system **13b** in low yield (15%), for which careful chromatography allowed partial separation (Scheme 2); NOE analysis on these purified materials indicated the C(7)*R*, C(5′)*R* and C(7)*S*, C(5′)*S* stereochemistry (Fig. 3). Alternatively, ester hydrolysis (KOH, MeOH, H_2O) of lactam **12b** followed by immediate iodolactonisation (I_2, KI) gave the tricycles **14a** and **14b** in 20% yield, again as a partially separable mixture. Assignment of stereochemistry was achieved by NOE analysis (Fig. 3), and found to be C(7)*R*, C(5′)*R* and C(7)*S*, C(5′)*S*; it would appear therefore that the C(7) stereochemistry dictates the cyclisation outcome at the C(5′) centre. In all of this work, it was again observed that differences of the ^{1}H chemical shift of the H(6) proton allow assignment of the stereochemistry at C(7); thus, a small difference in the δH(6) proton (typically 0.1–0.4 ppm) occurs for C(7)*R*, thereby placing the lactone carbonyl on the *endo* face, and a large difference (typically 0.9 ppm) indicates the C(7)*S* stereochemistry.



Scheme 2

An attempt to develop this concept with appropriately functionalised benzyl systems met with varied success (Scheme 1); alkylation of lactam **2b** with NaH/2-nitrobenzyl bromide or 2-(*O*-TBDMS)benzyl bromide[54] gave the corresponding products **3b**,**c** in good yield (36 and 47% respectively). *Exo*-alkylation in both cases was confirmed by NOE analysis (Fig. 3), and by the fact that the chemical shift difference was small (0.2 ppm). Deprotection (TBAF) gave the expected alcohol **3d**, but without



Scheme 3

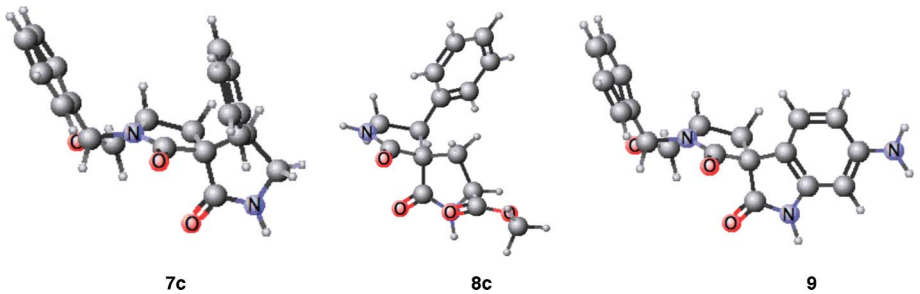


Fig. 4 Formation of Spirolactone-lactam systems.

any lactonisation being observed; conditions to promote this cyclisation could not be identified. On the other hand, reduction of **3b** (Fe, NH_4Cl, MeOH, H_2O, reflux) gave the expected spirocyclic bislactam product, but as a mixture of two diastereomers **11a**,**b** in 36% yield. The stereochemistry of each isomer was established by NOE analysis, and confirmed by the existence of a small difference of the ^1H chemical shift of the H(6) proton of the C(7)*R* isomer **11b** (0.44 ppm) but a larger difference in C(7)*S* isomer **11a** (0.94 ppm).

We further examined the application of this process to simple pyroglutamates; spontaneous lactamisation leading to spirocyclic products has been observed previously in simple lactam systems.[51] Ethyl pyroglutamate **1a** (Scheme 3) was BOC-protected to give lactam **15a** according to the literature precedent[55,56] and the C-4 ethoxycarbonyl residue introduced by treatment first with LiHMDS followed by ethyl chloroformate, giving the product **15b** in good yield (65%) as a mixture of two diastereomers. Arylation using a mixture of triethylamine/DMF with 2,4-dinitro-1-fluorobenzene gave the desired C-4 aryl product **16a** in excellent yield (79%) as a single diastereomer, whose stereochemistry was again established by NOE analysis (Fig. 3), arising by attack of the electrophile from the least hindered face.[57–61] Application of the iron–ammonium chloride conditions gave product **16b** in 31% yield, arising by reduction of both nitro groups, but cyclisation to give lactam **17** was neither spontaneous nor could be induced. An attempt to emulate the approach of Bella[50,51] by removal of the nitrogen protecting group prior to reduction and ring closure likewise did not lead to product formation; we assume that the slightly greater degree of freedom accessible in this system, compared to the bicyclic lactam series, renders ring closure reaction more difficult. In order to investigate this system further, we examined the reaction of the enolate of **15b** with bromoacetonitrile; this reaction gave two separable diastereomeric products **18a**,**b** as a 2 : 3 mixture in 92% yield, whose stereochemistry was again established by NOE analysis (Fig. 3). Treatment of the diastereomeric mixture of **18a**,**b** with $NaBH_4/CoCl_2$ gave the desired lactam **19**, but in very poor yield (5%), along with some uncyclised amine **20**. The C(4) stereochemistry of these compounds was not determined due to the low yield.

Modelling of representative structures was instructive using Marvin;[43] the near orthogonal relationship of the spirosystem carbonyl groups is illustrated for the energy minimised structures of **7c**, **8c** and **9** (Fig. 4) and also noteworthy is the parallel relationship of the aromatic rings in **7c** compared to their orthogonal relationship in **9**. More detailed molecular modelling of the elaborated forms of both the bicyclic and pyroglutaminyl templates was conducted in an effort to analyse their different conformational constraints. The preferred (lowest energy) conformations of these structures were calculated using the Hartree–Fock method (3-21G basis set)[62] after the initial starting conformation was obtained from a sequential conformational search using the GAMESS interface of the Chem3D Ultra v.10 software. After obtaining the lowest energy conformations of the compounds, the magnitude of

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the dihedral angle between the nitrogen substituent and the C2 (or C5) hydrogen was determined; the bicyclic template exhibits dihedral angles of 93.0° and 92.4° for **5c** and **9**, respectively, whilst the BOC pyroglutamate template gives 45.7°, 65.1°, 46.4°, and 47.6° dihedral angles for **16b**, **17**, **18b** and **19** respectively. This implies that systems derived from the bicyclic template **2a** exhibit *axial* hydrogen and *equatorial* alkyl at its C-5 position whilst those from the BOC template **15b** exhibit *equatorial* hydrogen and *axial* ester at the equivalent C-2 position (Fig. 5), consistent with minimisation of $A_{1,3}$ strain[63] in the conformationally more mobile pyroglutaminyl structure. The alternative conformer of the pyroglutamate system appears to suffer from destabilising 1,3-diaxial and/or dipole–dipole interactions between the C-2/C-4 substituents, and is therefore not preferred.

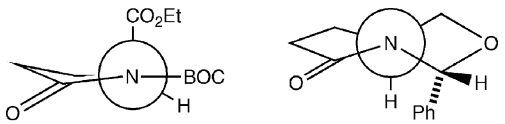

Fig. 5 Minimised Conformations for Selected Compounds.

Cheminformatic analysis of these compounds was of interest, and cLogP, PSA, and MSA values were calculated using Marvin (Table 1).[43] The polar surface area parameter (PSA), which correlates the presence of polar atoms with membrane permeability and therefore gives an indication of drug transport properties,[64] has been reported to have an optimal value of 70 < PSA < 120 Å^2 for a non-CNS orally absorbable drug.[65] Moreover, recently reported ADMET rules of thumb[66] indicate that neutral molecules with MW <400 and clogP <4 are likely to exhibit average values for a variety of indicators (including solubility, bioavailability, plasma protein binding, P-gp efflux and *in vivo* clearance), and therefore provide good library start points. It has also recently been established using a Random Forest statistical analysis that lipophilicity strongly correlates with adverse toxicity *in vivo*, with a significantly higher probability of an adverse indication if cLogP and PAS are less than 3 and 70 Å^2 respectively, than if they are greater than 3 and in the range 100–130 respectively.[67] For the spirocyclic systems reported here, it was found that cLogP values were typically in the range 0.7–2.9, but deprotection significantly reduced these values (compounds **8c** and **10**); this is to be expected after the removal of hydrophobic protecting group residues and is consistent with their observed low solubility in organic solvents. Polar Surface Area (PSA), with some exceptions, is generally less than 60 Å, and expressed as a percentage of the Molecular Surface Area (MSA), is typically in the range 12–18%. However, some compounds, notably the deprotected **8c**, **9**, **10** and Spiro-**19**, are noticeably higher both in PSA and %PSA, again as might be expected by the absence of hydrophobic residues. The spirocyclic compounds reported herein therefore generally fall within the rule-of-thumb criteria outlined above, and moreover their chemical functionality and well-defined three-dimensional conformation places them in unusual chemical space ideally suited for optimisation of drug-like properties.

Conclusion

We have demonstrated that spirocyclic lactams are readily available from pyroglutamate templates, and their cheminformatic parameters are within desired norms for lead-like structures. Their combination of chemical functionality, stereochemical conformation and cheminformatic parameters offers a unique system of potential value for the design of novel architectures suitable for application in the drug discovery process.

Experimental

(2*S*)-2-Ethoxycarbonyl-5-oxo-pyrrolidine **1a** was prepared from pyroglutamic acid, (2*S*)-2-hydroxymethyl-5-oxo-pyrrolidine **1b**, (2*R*,5*S*)-8-oxo-2-phenyl-1-aza-3-oxa-bicyclo[3.3.0] octane **2a** and (2*R*,5*S*,7*R,S*)-1-aza-7-allyl-7-(ethoxycarbonyl)-3-oxo-8-oxa-2-phenylbicyclo[3.3.0]-octane **12b** were all prepared using literature methodology.[30,40,41] Bromophenylacetonitrile was prepared according to Molina.[68] (2-(Bromomethyl)phenoxy)(*tert*-butyl)dimethylsilane was prepared from *tert*-butyldimethyl(*o*-tolyloxy)silane[69] using the method of Stern and Swenton.[70]

(2*R*,5*R*)-1-Aza-7-ethyloxycarbonyl-3-oxa-8-oxo-2-phenylbicyclo[3.3.0]octane 2b

To a stirred solution of lactam **2a** (4.00 g, 19.7 mmol) in THF (75 ml) was added sodium hydride ((oil dispersion 60%) 0.55 g, 13.7 mmol) at RT and the mixture was left to stir for 1 h. Ethyl chloroformate (2.7 ml, 27.9 mmol) was added and the mixture was refluxed for 16 h. The reaction was quenched with glacial acetic acid (6 ml), water (30 ml) was added to dissolve the gelatinous precipitate formed and the mixture was extracted with EtOAc (4 × 20 ml). The organics were shaken with brine, dried over $MgSO_4$ and concentrated under vacuum and the residue purified by flash column chromatography to give **2b** as a yellow oil, which slowly crystallised to give a yellow solid consisting of a 1 : 1 mixture of 7*S* and 7*R* diastereoisomers (4.86 g, 90%), with data as previously reported.[30,40]

(2*R*,5*S*,7*R*) and (2*R*,5*S*,7*S*)-1-Aza-7-(cyanomethyl)-7-(ethoxycarbonyl)-3-oxo-8-oxa-2-phenylbicyclo-[3.3.0]octane 3a

To a stirred suspension of pre-washed NaH (0.046 g, 1.9 mmol) in dry THF (5 ml) at 0 °C under nitrogen atmosphere was added a solution of lactam **2b** (0.315 g, 1.1 mmol) in THF (10 ml), and the mixture was stirred at RT for 20 min. A solution of bromoacetonitrile (0.19 g, 1.6 mmol) in THF (5 ml) was added and the mixture stirred at RT 16 h. The reaction was quenched by pouring the mixture into NH_4Cl (aq.)/EtOAc (25 ml, 1 : 1) and the aqueous portion was extracted with EtOAc (2 × 10 ml). The organic extracts were combined, washed with water (20 ml) and sat. brine (20 ml), dried over $MgSO_4$ and the solvent removed *in vacuo* to give an oil, which was purified by flash column chromatography [(40–60) Petrol/EtOAc, 7 : 3] to give the product **3a** (0.33 g, 65%) as a solid consisting of an inseparable 2 : 1 mixture of diastereomers. R_f = 0.16 [(40–60) Petrol/EtOAc, 7 : 3]; ν_{max}/cm^{-1} (thin film) 3089 (m), 3064 (m), 3027 (m), 2958 (s), 2940 (s), 2901 (s), 2249 (m), 1745 (s), 1704 (s), 1586 (m), 1546 (m); δ_H ($CDCl_3$, 200 MHz) 1.15–1.40 (6H, m, C<u>H</u>$_3$CH$_2$O, (A+B)), 2.05 (1H, dd, *J* 13.5 and 7.2, H(6)(B)), 2.45 (1H, dd, *J* 20.8 and

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14.5, H(6)(A)), 2.55 (1H, dd, *J* 14.3 and 4.3, H(6)(A)), 2.80–3.15 (5H, m, H(6)(B)+CH$_2$CN(A+B)), 3.55–3.75 (2H, m, H(4)(A+B)), 4.1–4.4 (8H, m, CH$_3$CH$_2$O(A+B)+H(5)(A+B)+H(4)(A+B)) 6.25 (2H, s, H(2)(A+B)), 7.20–7.50 (10H, m, ArH(A+B)); δ_C(CDCl$_3$, 100.6 MHz) 13.9 (CH$_3$CH$_2$O(A+B)), 22.8, 23.5 (CH$_2$CN(A+B)), 31.7 (C(6)(A)), 35.2 (C(6)(B)), 56.4, 56.6 (C(5)(A+B)), 63.0, 63.0 (CH$_3$CH$_2$O(A+B)), 71.4 (C(4)(A)), 71.9 (C(4)(B)), 87.0, 87.3 (C(2)(A+B)), 116.5, 116.7 (CN(A+B)), 125.9, 126.0, 128.3, 128.4, 128.5, 128.6, 128.8, 128.9 (ArCH(A+B)), 137.4, 137.7 (ArC(A+B)), 168.3, 168.8, 169.8, 172.4 (C=O(A+B)); ***m/z*** (ESI$^+$) 337 (M+Na$^+$,100%), 315 (M+H$^+$, 62%); **HRMS**: [M+H$^+$] Calculated for $C_{17}H_{19}O_4N_2$ 315.1346, Found: 315.1345.

(2*R*,5*S*,7*S*)-1-Aza-7-(2-nitrobenzyl)-7-(ethoxycarbonyl)-3-oxo-8-oxa-2-phenylbicyclo[3.3.0] octane 3b

To a stirred suspension of pre-washed NaH (0.12 g, 5.0 mmol) in dry THF (15 ml) at 0 °C under a nitrogen atmosphere was added a solution of lactam **2b** (0.43 g, 1.6 mmol) in THF (15 ml), and the mixture was stirred at RT for 20 min. A solution of 1-(bromomethyl)-2-nitrobenzene (0.50 g, 2.3 mmol) in THF (15 ml) was added and the mixture stirred at RT for 16 h. The reaction was quenched by pouring the mixture into NH$_4$Cl (aq.)/EtOAc (1 : 1) (100 ml) and the aqueous portion was extracted with EtOAc (2 × 50 ml). The organic extracts were combined, washed with water (50 ml) and sat. brine (50 ml), dried over MgSO$_4$ and the solvent removed *in vacuo* to give the product **3b** as a yellow solid (0.23 g, 36%). R_f = 0.17 [EtOAc/(40–60) Petrol, 1 : 4], $[\alpha]_D^{26}$ +46 (*c* = 3.9 in MeOH); **m.p.** 79–80 °C; ν_{max}/cm^{-1} (thin film) 3066 (m), 2983 (m), 2874 (m), 1743 (s), 1707 (bs), 1609 (m), 1577 (m), 1527 (s), 1353 (s); δ_H (CDCl$_3$, 200 MHz) 1.33 (3H, t, CH$_3$CH$_2$O), 2.35 (1H, dd, *J* 14.3 and 7.6, H(6)), 2.55 (1H, dd, *J* 14.3 and 5.0, H(6)), 3.43–3.63 (3H, m, H(4)+H(5)+CHHPh), 3.85 (1H, d, *J* 14.3, CHHPh), 4.10–4.40 (3H, m, H(4)+CH$_3$CH$_2$O), 6.27 (1H, s, H(2)), 7.20–7.45 (8H, m, ArH), 7.80–7.90 (1H, m, ArH); δ_C (CDCl$_3$, 100.6 MHz), 14.0 (CH$_3$CH$_2$O), 31.3 (C(6)), 34.5 (CH$_2$Ph), 56.2 (C(5)), 61.5 (C(7)), 62.4 (CH$_3$CH$_2$O), 71.8 (C(4)), 87.1 (C(2)), 124.6, 125.9, 126.0, 128.2, 128.4, 128.7, 132.6 (ArCH),133.1, 138.1 (ArC), 170.7, 174.0 (C=O); ***m/z*** (ESI$^+$) 469 (M+MeCN+NH$_4^+$, 100%); **HRMS** [M+H$^+$] Calculated for $C_{22}H_{23}N_2O_6$ 411.1556, Found: 411.1566.

(2*R*,5*S*,7*S*)-1-Aza-7-((2-*t*-butyldimethylsilyloxy)benzyl)-7-(ethoxycarbonyl)-3-oxo-8-oxa-2-phenylbicyclo[3.3.0] octane 3c

To a stirred suspension of pre-washed NaH (0.038 g, 1.6 mmol) in dry THF (5 ml) at 0 °C under a nitrogen atmosphere was added a solution of lactam **2b** (0.36 g, 1.3 mmol) in THF (10 ml), and the mixture was stirred at RT for 20 min. A solution of 2-(bromomethyl)phenoxy)(*tert*-butyl)dimethylsilane (0.70 g, 2.3 mmol) in THF (5 ml) was added and the mixture refluxed for 2 h and then stirred at RT for 16 h. The reaction was quenched by pouring into NH$_4$Cl (aq.)/EtOAc (60 ml, 1 : 1) and the aqueous portion extracted with EtOAc (2 × 60 ml). The organic extracts were combined, washed with water (60 ml) and sat. brine (60 ml), dried over MgSO$_4$ and the solvent removed *in vacuo*, and the resulting oil was purified by flash column chromatography [(40–60) Petrol/EtOAc, 85 : 15] to give the product **3c** as a single diastereomer (309 mg, 47%). R_f = 0.19 [EtOAc/(40–60) Petrol, 15 : 85]; $[\alpha]_D^{23}$ −38 (*c* = 3.6 in MeOH); ν_{max}/cm^{-1} (thin film) 3064 (m), 3034 (m), 2956 (m), 2932 (m), 2886 (m), 2859 (m), 1743 (s), 1709 (m), 1600 (w), 1581 (w), 1492 (s), 1256 (s); δ_H (400 MHz, CDCl$_3$) 0.20 (3H, s, MeSi), 0.25 (3H, s, MeSi), 1.00 (9H, s, ^{t}BuSi), 1.33 (3H, t, *J* 7.1, CH$_3$CH$_2$O), 2.37 (1H, dd, *J* 13.7 and 5.2, H(6)*endo*), 2.57 (1H, dd, *J* 13.7 and 8.0, H(6)*exo*), 3.20 (1H, d, *J* 13.8, CHHPh), 3.27–3.35 (1H, m, H(5)), 3.50–3.60 (2H, m, H(4)*endo*+CHHPh), 4.05 (1H, t, *J* 7.0, H(4)*exo*), 4.30 (2H, q, *J* 7.1, CH$_3$CH$_2$O), 6.27 (1H, s, H(2)), 6.73 (1H, t, *J* 7.5, ArH), 6.80 (1H, d, *J* 8.1, ArH), 7.05–7.13 (2H, m, ArH), 7.23–7.30 (2H, m, ArH), 7.30–7.35 (3H, m, ArH); δ_C (100.6 MHz, CDCl$_3$) –4.4, –3.9 (Me$_2$Si), 18.2 (SiC(CH$_3$)$_3$), 25.8 (SiC(CH$_3$)$_3$), 30.8 (C(6)), 32.8 (CH$_2$Ph), 56.4 (C(5)), 61.9 (CH$_3$CH$_2$O), 71.9 (C(4)), 87.0 (C(2)), 118.8, 121.4, 128.1, 128.5, 132.1 (ArCH), 126.1, 128.2 (ArCH), 126.7, 132.1, 154.1 (ArC), 171.5, 174.6 (C=O); **m/z** (ESI$^+$) 554 (M+NH$_4$+MeCN$^+$, 100%); **HRMS** [M+H$^+$] Calculated for $C_{28}H_{38}NO_5Si$ 496.2519, Found: 496.2520.

(2*R*,5*S*,7*S*)-1-Aza-7-(2-hydroxybenzyl)-7-(ethoxycarbonyl)-3-oxo-8-oxa-2-phenylbicyclo[3.3.0] octane 3d

The substrate **3c** (0.099 g, 0.20 mmol) was dissolved in THF (6 ml) and TBAF (0.6 ml of a 1 M solution in THF) was added and the solution was allowed to stir for 24 h under nitrogen. The reaction mixture was washed with sat. NH$_4$Cl (aq.) (3 ml), the organic layer separated extracted with ether (3 ml), the organic extracts combined and dried over MgSO$_4$ and the solvent removed *in vacuo*. Purification was by flash column chromatography with an eluent of [EtOAc/(40–60) Petrol, 1 : 3] to furnish the product **3d** as a white solid (8 mg, 11%). R_f = 0.16 [EtOAc/(40–60) Petrol, 1 : 3]; $[\alpha]_D^{23}$ +2.4 (*c* = 0.13 in DCM); **m.p.** 165–167 °C; ν_{max}/cm^{-1} (thin film) 3328 (bm), 2982 (w), 1739 (s), 1681 (s), 1595 (m), 1507 (w), 1456 (m), 1367 (m), 1261 (s), 1222 (s); δ_H (CDCl$_3$, 200 MHz) 1.33 (3H, t, *J* 7.1, CH$_3$CH$_2$O), 2.47 (1H, dd, *J* 13.7 and 5.7, H(6)*endo*), 2.55 (1H, dd, *J* 13.7 and 7.3, H(6)*exo*), 3.35 (2H, dd, *J* 21.9 and 4.3, CH$_2$Ph), 3.63 (1H, t, *J* 8.0, H(4)*endo*), 3.67–3.85 (1H, m, H(5)), 4.20 (1H, dd, *J* 7.5 and 5.9, H(4)*exo*), 4.27 (2H, q, CH$_3$CH$_2$O, *J* 7.1), 6.30 (1H, s, H(2)), 6.60 (1H, bs, OH), 6.73–6.85 (2H, m, ArH), 7.05–7.20 (2H, m, ArH), 7.23–7.43 (3H, m, ArH); δ_C (CDCl$_3$, 100.6 MHz) 14.0 (CH$_3$CH$_2$O), 32.0 (C(6)), 33.7 (CH$_2$Ph), 56.4 (C(5)), 61.9 (C(7)), 62.6 (CH$_3$CH$_2$O), 71.8 (C(4)), 87.0 (C(2)), 117.2, 120.6, 125.9, 128.4, 128.7, 128.8, 132.4 (ArCH), 122.3, 138.0, 154.8 (ArC), 172.2, 175.0 (C=O); ***m/z*** (ESI$^+$) 440 (M+NH$_4$+MeCN$^+$, 100%); **HRMS** [M+Na$^+$] Calculated for $C_{22}H_{23}NO_5Na$ 404.1475, Found: 404.1468.

Alkylations—general method

To a stirred suspension of pre-washed NaH (0.30 g, 1.7 equiv) in dry THF (10 ml) at 0 °C under a nitrogen atmosphere was added a solution of lactam **2b** (2.01 g, 7.30 mmol) in THF (15 ml), and the mixture was stirred at RT for 20 min. A solution of the electrophile (1.6 equiv.) in THF (10 ml) was added and the mixture stirred either at RT or reflux for 16 h. The reaction was quenched by pouring the mixture into NH$_4$Cl (aq.)/EtOAc (175 ml, 1 : 1) and the aqueous portion was extracted with EtOAc (2 × 70 ml). The organic extracts were combined, washed with water (50 ml) and sat. brine (50 ml), dried over MgSO$_4$ and the solvent removed *in vacuo* to give an oil, which was purified by flash column chromatography.

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(2*R*,5*S*,7*R*,1′*R*) and (2*R*,5*S*,7*R*,1′*S*)-1-Aza-7-(1′-cyano-1′-ethyl)-7-(ethoxycarbonyl)-3-oxo-8-oxa-2-phenyl-bicyclo[3.3.0]octane 4a

Solid; (1.63 g, 68% as inseparable diastereomers); R_f = 0.3 [(40–60) Petrol/EtOAc, 7 : 3]; ν_{max}/cm^{-1} (Nujol) 2921 (s), 2842 (s), 2237 (w), 1724 (m), 1697 (m), 1500 (w), 1454 (m), 1329 (m), 1296 (m); δ_H ($CDCl_3$, 200 MHz) 1.30 (3H, t, *J* 7.1, $C\underline{H}_3CH_2O$), 1.40 (3H, d, *J* 7.1, $\underline{Me}CHCN$), 2.45 (1H, dd, *J* 14.5 and 8.0, H(6)*exo*), 2.7 (1H, dd, *J* 14.4 and 3.5, H(6)*endo*), 3.50–3.80 (2H, m, H(4)*endo*+MeC$\underline{H}$CN), 4.10–4.40 (4H, m, $CH_3C\underline{H}_2O$+H(4)*exo*+H(5)), 6.3 (1H, s, H(2)), 7.20–7.50 (5H, m, ArH); δ_C ($CDCl_3$, 50.3 MHz) 14.4, 14.8 ($\underline{Me}CHCN$+$\underline{C}H_3CH_2O$), 28.8 (C(6)), 31.1 ($\underline{C}HCN$), 56.8 (C(5)), 62.6 (C(7)) 63.4 ($CH_3\underline{C}H_2O$), 71.6 (C(4)), 88.2 (C(2)), 120.9 (CN), 126.2, 129.0, 129.3 (ArCH), 138.1 (ArC), 168.4, 172.6 (C═O); ***m/z*** (ESI$^+$) 351 (M+Na$^+$, 100%); **HRMS** [M+H$^+$] Calculated for $C_{18}H_{21}O_4N_2$ 329.1501, Found 329.1491.

(2*R*,5*S*,7*R*,1′*S*)-1-Aza-7-(1′-cyano-1′-phenylmethyl)-7-(ethoxycarbonyl)-3-oxo-8-oxa-2-phenylbicyclo[3.3.0]octane 4b

Solid; (1.19 g, 42%); R_f = 0.2 [(40–60) Petrol/EtOAc, 3 : 1]; $[\alpha]_D^{23}$ –11.4 (*c* = 0.18 in $CHCl_3$); **m.p.** 125–126 °C; ν_{max}/cm^{-1} (thin film) 3064–2874 (bs), 2245 (m), 1959 (m), 1891 (m), 1811 (m), 1760 (s), 1708 (s), 1602 (m), 1586 (m), 1586 (m); δ_H ($CDCl_3$, 200 MHz) 1.37 (3H, t, *J* 7.2, $C\underline{H}_3CH_2O$), 2.63 (1H, dd, *J* 14.5 and 8.0, H(6)*exo*), 2.8 (1H,dd, *J* 14.6 and 5.3, H(6)*endo*), 3.1–3.3 (1H, m, H(5)), 3.53 (1H, t, *J* 8.4, H(4)*exo*), 4.17 (1H, t, *J* 7.8, H(4)*endo*), 4.37 (2H, q, *J* 7.2, $CH_3C\underline{H}_2$ O), 4.85 (1H, s, PhC$\underline{H}$CN), 6.1 (1H, s, H(2)), 6.8–7.7 (10H, m, ArH); δ_C ($CDCl_3$, 100.6 MHz) 14.0 ($\underline{C}H_3CH_2O$), 28.8 (C(6)), 40.9 ($\underline{C}HCN$), 56.2 (C(5)), 63.4 ($CH_3\underline{C}H_2O$), 65.4 (C(7)), 71.7 (C(4)), 86.8 (C(2)), 118.7 (CN), 125.7, 126.0, 126.1, 128.2, 128.5, 128.6, 128.7, 128.9, 129.1, 130.0 (ArCH) 137.2 (ArC), 168.6, 169.7 (C═O); ***m/z*** (ESI$^+$) 412 (M+Na$^+$,100%), 391 (M+H$^+$, 18%); **HRMS** [M+H$^+$] Calculated for $C_{23}H_{23}O_4N_2$ 391.1658, Found: 391.1650.

(2*R*,5*S*,7*R*)-1-Aza-7-(2,4-dinitrophenyl)-7-(ethoxycarbonyl)-3-oxo-8-oxa-2-phenylbicyclo-[3.3.0] octane 5a

To a stirred suspension of pre-washed NaH (0.032 g, 0.22 mmol) in dry THF (5 ml) at 0 °C under a nitrogen atmosphere was added a solution of lactam **2b** (0.18 g, 0.60 mmol) in THF (5 ml), and the mixture was stirred at RT for 20 min. A solution of 2,4-dinitro-1-fluorobenzene (0.1 ml, 0.8 mmol) in THF (5 ml) was added and the mixture stirred initially at RT for 1 h followed by gentle reflux for 24 h. The reaction was quenched by pouring the mixture into NH_4Cl (aq.)/EtOAc (1 : 1) (10 ml) and the aqueous portion extracted with EtOAc (3 × 10 ml). The organic extracts were combined, washed with water (10 ml) and brine (10 ml), dried over $MgSO_4$ and the solvent removed *in vacuo* to give an oil, which was purified by flash column chromatography [(40/60) Petrol/EtOAc, 17 : 1] to give the product **5a** as a yellow solid as a single diastereomer (1.0 g, 74%). R_f = 0.14 [EtOAc/(40–60) Petrol, 15 : 85]; $[\alpha]_D^{22}$ +7 (*c* = 0.13 in DCM); **m.p.** 208–210 °C; ν_{max}/cm^{-1} (thin film) 2945 (m), 2254 (w), 1740 (s), 1704 (s), 1609 (m), 1542 (m), 1350 (m); δ_H ($CDCl_3$, 200 MHz) 1.23 (3H, t, *J* 7.1, $C\underline{H}_3CH_2O$), 2.57 (1H, dd, *J* 14.7 and 7.9, H(6)*exo*), 3.47 (1H, dd, *J* 14.7 and 7.8, H(6)*endo*), 3.90 (1H, t, *J* 8.3, H(4)*endo*), 4.03–4.15 (1H, m, H(5)), 4.23 (2H, q, *J* 7.1, $CH_3C\underline{H}_2O$), 4.43 (1H, dd, *J* 7.7 and 5.8, H(4)*exo*), 6.43 (1H, s, H(2)), 7.37–7.60 (5H, m, ArH), 7.73 (1H, d, *J* 8.7, ArH), 8.45 (1H, dd, *J* 8.6 and 2.4, ArH), 8.97 (1H, d, *J* 2.4, ArH); δ_C ($CDCl_3$, 100.6 MHz) 13.8 ($\underline{C}H_3CH_2O$), 36.3 (C(6)), 56.1 (C(5)), 63.4 ($CH_3\underline{C}H_2O$), 66.6 (C(7)), 71.7 (C(4)), 87.9 (C(2)), 121.5, 125.9, 128.7 (ArCH), 128.1 (ArC), 129.2 (ArC), 131.4 (ArC), 137.9, 140.9, 147.3, 148.1 (ArC), 167.8, 172.1 ((C═O); **HRMS** [M+H$^+$] Calculated for $C_{21}H_{20}N_3O_8$ Found 442.1251, Calculated: 442.1250.

(2*R*,5*S*,7*R*)-1-Aza-7-(4-amino-2-nitrophenyl)-7-(ethoxycarbonyl)-3-oxo-8-oxa-2-phenylbicyclo[3.3.0]octane 5b

To a stirred suspension of **5a** (0.30 g, 0.68 mmol) and 10% Pd/C (0.03 g) in methanol (2 ml) was added ammonium formate (0.21 g, 3.4 mmol) in a single portion and the mixture was refluxed under nitrogen for 72 h. The mixture was filtered and the solvent removed *in vacuo*. The resulting oil was dissolved in DCM (10 ml) and washed with water (2 × 5 ml). The organics were washed with brine (2 × 5 ml), dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by flash chromatography [Petrol/EtOAc (2 : 1)] yielding compound **5b** (0.065 g, 23%). R_f 0.25 [EtOAc/(40/60) Petrol, 1 : 2]; $[\alpha]_D^{22}$ +134 (*c* = 0.25 in $CHCl_3$); ν_{max}/cm^{-1} (thin film) 3363 (bm), 1726 (m), 1635 (s), 1511 (s), 1339 (s), 1167 (s); δ_H (400 MHz, $CDCl_3$) 1.22 (3H, t, *J* 7.1, $C\underline{H}_3CH_2O$), 2.53 (1H, dd, *J* 14.3 and 7.7, H(6)*exo*), 3.38 (1H, dd, *J* 14.3 and 5.6, H(6)*endo*), 3.86 (1H, t, *J* 8.3, H(4)*endo*), 4.02–4.09 (1H, m, H(5)), 4.11 (2H, $N\underline{H}_2$), 4.18–4.23 (2H, m, $CH_3C\underline{H}_2O$), 4.33 (1H, dd, *J* 8.0 and 6.1, H(4)*exo*), 6.40 (1H, s, H(2)), 6.71 (1H, dd, *J* 8.5 and 2.7, ArH), 7.11 (1H, d, *J* 8.5, ArH), 7.36 (1H, d, *J* 2.7, ArH), 7.37–7.44 (3H, m, PhH), 7.49–7.53 (2H, m, PhH); δ_C (100 MHz, $CDCl_3$) 13.8 ($\underline{C}H_3CH_2O$), 37.3 (C6), 56.3 (C5), 62.6 ($CH_3\underline{C}H_2O$), 66.43 (C7), 71.7 (C4), 87.6 (C2), 111.7 (ArC), 119.4 (ArC), 123, 138.2, 147.3, 148.0 (ArC), 126.0, 128.6, 128.9 (ArC), 169.4, 173.6 (C═O); **HRMS**: [M+Na$^+$.] Calculated for $C_{21}H_{21}NNaO_6$, 434.1323, Found: 434.1313.

(2*R*,5*S*,7*R*) and (2*R*,5*S*,7*S*)-Spiro[1-aza-8-oxo-2-phenyl-3-oxa-bicyclo[3.3.0]octane]-7,3′-[pyrrolidin-2′-one] 6a and 6b

To a solution of the nitrile **3a** (1.21 g, 3.80 mmol) in ethanol (150 ml) was added $CoCl_2{\cdot}6H_2O$ (1.77 g, 7.40 mmol) and the mixture was stirred for 5 min. $NaBH_4$ (1.19 g, 31.5 mmol) was then added portion-wise to the purple solution which was accompanied by effervescence. After stirring for 16 h at RT, the ethanol was removed *in vacuo* and NH_4OH (aq.) (45 ml, 0.1 M) and EtOAc (150 ml) were added to the black residue with stirring. After 30 min, the black residue was removed by filtration through Celite®. The organic phase was washed with water (50 ml), and the aqueous phase was extracted with EtOAc (50 ml). The combined organic phase was dried over $MgSO_4$ and concentrated *in vacuo* to give the product as a dark oil. Purification by flash column chromatography [MeOH/EtOAc, 1 : 19] gave **6a** and **6b** (0.26 g, 25%) as a white solid as a mixture of partially separable diastereomers.

Data for 6a. R_f = 0.24 [MeOH/EtOAc (1 : 19)]; ν_{max}/cm^{-1} (thin film) 3300 (bm), 2944 (m), 2885 (m), 2247 (m), 1702 (s), 1694 (m), 1377 (m), 1355 (m); δ_H ($CDCl_3$, 200 MHz) 2.0–2.3 (2H, m, H(6)+H(4′)), 2.5–2.8 (2H, m, H(6)+H(4′)), 3.2–3.4 (1H, m, H(5′)), 3.5–3.65 (1H, m, H(5′)), 3.7–3.85 (1H, m, H(4)), 4.0–4.2 (1H, m, H(5)), 4.2–4.35 (1H, m, H(4)), 6.25 (1H, m, H(2)),

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6.9 (1H, bs, NH), 7.2–7.6 (5H, m, ArH); δ_C ($CDCl_3$, 100.6 MHz) 31.8 (C(4′)), 33.9 (C(6)), 39.9 (C(5′)), 56.4 (C(5)), 56.5 (C(7)) 71.6 (C(4)), 87.2 (C(2)), 125.9, 128.5, 128.6 (ArCH), 138.8 (ArC), 176.2, 177.0 (C═O); ***m/z*** (ESI$^+$) 331 (M+MeCN+NH_4^+, 100%); **HRMS** [M+MeCN+Na$^+$]: Calculated for $C_{17}H_{19}O_3N_3Na$ 336.1324, Found: 336.1332.

Data for 6b. R_f = 0.36 [MeOH/EtOAc, 1 : 19]; ν_{max}/cm^{-1} (thin film) 3279 (bm), 2895 (m), 1706 (s), 1493 (m), 1452 (m), 1356 (m), 1274 (m), 1222 (m); δ_H ($CDCl_3$, 200 MHz) 1.75–1.9 (1H, m, H(6)*endo*), 1.95–2.15 (1H, m, H(4′)), 2.6–2.9 (2H, m, H(6)*exo* +H(4′)), 3.2–3.4 (1H, m, H(5′)), 3.5 (1H, t, *J* 7.9, H(4)*endo*), 3.55–3.7 (1H, m, H(5′)), 4.15–4.25 (1H, m, H(4)*exo*), 4.3–4.55 (1H, m, H(5)), 6.3 (1H, s, H(2)), 6.5–6.9 (1H, bs, NH), 7.2–7.6 (5H, m, ArH); δ_C ($CDCl_3$, 100.6 MHz) 21.1 (C(4′)), 35.8 (C(6)), 40.0 (C(5′)), 56.4 (C(5)), 57.5 (C(7)), 72.0 (C(4)), 87.0 (C(2)), 126.0, 126.1, 128.5, 128.7, 129.1 (ArCH), 137.8 (ArC) 174.9, 176.1 (C═O); ***m/z*** (ESI$^+$) 297 (M+Na$^+$, 100%); **HRMS** [M+H$^+$]: Calculated for $C_{15}H_{17}O_3N_2$ 274.1317, Found: 274.1304.

Spirocyclisations: general method

To a solution of the nitriles **4a,b** (0.5 mmol, 1 equiv.) in ethanol (30 ml) was added $CoCl_2{\cdot}6H_2O$ or $NiCl_2{\cdot}6H_2O$ (1 mmol, 2.0 equiv.) and the mixture was stirred for was stirred for 5 min. $NaBH_4$ (4.8 mmol, 9.7 equiv.) was then added portion-wise to the purple solution which was accompanied by effervescence. After stirring for 16 h at RT, the ethanol was removed *in vacuo* and NH_4OH (aq.) (0.1 M, 10 ml) and EtOAc (20 ml) were added to the black residue with stirring. After 30 min of stirring, the black residue was removed by filtration through Celite®. The organic phase was washed with water (20 ml), and the aqueous phase extracted with EtOAc (3 × 10 ml). The combined organic phase was dried over $MgSO_4$ and concentrated *in vacuo* to give dark oil. After purification by flash column chromatography, all products were obtained as white solids.

(2*R*,5*S*,7*S*,4′*S*)-(4′-Methyl)-spiro[1-aza-8-oxo-2-phenyl-3-oxa-bicyclo[3.3.0]octane]-7,3′-[pyrrolidin-2′-one] 7a

A mixture of partially separable diastereomers was formed (ratio 1:1) (14.5 mg, 10%); R_f = 0.41 [EtOAc/MeOH, 19 : 1]; ν_{max}/cm^{-1} (thin film) 3283 (bm), 2926 (m), 1693 (s), 1452 (m), 1381 (m), 1355 (m), 1266 (m), 1156 (m); δ_H ($CDCl_3$, 200 MHz) 1.2 (3H, d, *J* 7.9, CHMe), 2.05 (1H, dd, *J* 7.9 and 4.4, H(6)*exo*), 2.30–2.60 (1H, m, H(4′)), 2.67 (1H, dd, *J* 13.8 and 4.4, H(6)*endo*) 3.35 (2H, d, *J* 9.1, 2xH(5′)), 3.55–3.75 (1H, m, H(4)*endo*), 4.00–4.15 (1H, m, H(5)), 4.20–4.35 (1H, m, H(4)*exo*), 5.85 (1H, bs, NH), 6.25 (1H, s, H(2)), 7.2–7.5 (5H, m, ArH); δ_C ($CDCl_3$, 100.6 MHz) 13.0 (MeCH), 30.6 (C(6)), 41.2 (C(4′)), 46.6 (C(5′)), 56.7 (C(5)), 61.8 (C(7)), 72.0 (C(4)), 87.1 (C(2)), 125.9, 128.4, 128.5 (ArCH), 138.8 (ArC), 174.7, 175.9 (C═O); ***m/z*** (ESI+) 287 (M+H$^+$, 100%), 304 (M+Na$^+$, 65%); **HRMS**: [M+MeCN+Na$^+$] Calculated for $C_{18}H_{21}O_3N_3Na$ 350.1481, Found: 350.1488.

(2*R*,5*S*,7*S*,4′*R*)-(4′-Methyl)-spiro[1-aza-8-oxo-2-phenyl-3-oxa-bicyclo[3.3.0]octane]-7,3′-[pyrrolidin-2′-one] 7b

(14.5 mg, 10%); R_f = 0.29 [EtOAc/MeOH, 19 : 1]; ν_{max}/cm^{-1} (thin film) 3380 (bw), 3035 (m), 2968 (s), 2249 (w), 1747 (m), 1716 (m), 1690 (m), 1496 (m); δ_H ($CDCl_3$, 400 MHz) 1.15 (3H, d, *J* 7.0, CHMe), 2.37 (2H, dd, *J* 7.7 and 4.9, 2xH(6)), 2.87 (1H, m, H(4′)), 2.97 (1H, m, H(5a′)), 3.83 (2H, m, H(5b′)+H(4*endo*)), 4.1 (1H, m, H(5)), 4.3 (1H, m, H(4*exo*)), 5.85 (1H, bs, NH), 6.3 (1H, s, H(2)), 7.25–7.5 (5H, m, ArH); δ_C ($CDCl_3$, 100.6 MHz) 15.3 (Me), 26.0 (C(6)), 37.2 (C(4′)), 47.5 (C(5′)), 56.5 (C(5)), 61.4 (C(7)), 71.8 (C(4)), 87.2 (C(2)), 128.6, 128.4, 125.9 (ArCH), 138.8 (ArC), 176.7, 176.2 (C═O); ***m/z*** (ESI$^+$) 345 (M+MeCN+NH_4^+, 100%); **HRMS**: [M+H$^+$] Calculated for $C_{16}H_{19}O_3N_2$ 287.1396, Found 287.1392.

(2*R*,5*S*,7*S*,4′*S*)-(4′-Phenyl)-spiro[1-aza-8-oxo-2-phenyl-3-oxa-bicyclo[3.3.0]octane]-7,3′-[pyrrolidin-2′-one] 7c

(37 mg, 21%); R_f = 0.25 [EtOAc]; $[\alpha]_D^{25}$ −63 (*c* = 0.24 in $CHCl_3$); **m.p.** 189–191 °C; ν_{max}/cm^{-1} (thin film) 3278 (bm), 3063 (m), 3032 (m), 2884 (m), 2248 (m), 1702 (bs), 1603 (m); δ_H ($CDCl_3$, 200 MHz) 1.9 (1H, dd, *J* 14 and 7.2, H(6)*exo*), 2.2 (1H, dd, *J* 13.9 and 4.5, H(6)*endo*), 3.50–3.80 (3H, m, H(4)*endo*+H(5)+H(5′)), 3.85–4.25 (3H, m, H(4)*exo*+H(5′)+H(4′)), 6.37 (1H, s, H(2)), 6.8 (1H, bs, NH), 7.1–7.5 (10H, m, ArH); δ_C ($CDCl_3$, 100.6 MHz) 27.6 (C(6)), 46.2 (C(5′)), 48.4 (C(4′)), 56.3 (C(5)), 62.5 (C(7)), 71.7 (C(4)), 87.3 (C(2)), 126.0, 127.7, 127.9, 128.4, 128.6, 129.1 (ArCH), 138.6, 139.1 (ArC) 175.4, 176.1 (C═O); ***m/z*** (ESI+) 371 (M+Na$^+$, 90%), 349 (M+H$^+$, 79%), 542 (100%); **HRMS**: [M+H$^+$]: Calculated for $C_{21}H_{21}O_3N_2$ 349.1552, Found 349.1559.

(3*R*,5*S*,9*S*)-3-Hydroxymethyl-9-phenyl-2,7-diaza-spiro[4.4]nonane-1,6-dione 8a

To a solution of the spirolactam **7c** (0.12 g, 0.34 mmol) in DCM (10 ml) at RT was added TFA (0.30 ml, 3.89 mmol) drop-wise with stirring. After 1 h of stirring at RT, the solvent was removed *in vacuo* to yield a white solid **8a** on purification by flash column chromatography on alumina [MeOH] (0.074 g, 83%). R_f = 0.44 [MeOH] (on silica); **m.p.** 132–134 °C; $[\alpha]_D^{22}$ −16 (*c* = 1.3 in MeOH); ν_{max}/cm^{-1} (thin film) 3425 (bs), 2095 (w), 1676 (bs), 1434 (m), 1266 (m), 1205 (m), 1139 (m); δ_H (DMSO, 200 MHz) 1.50–2.00 (2H, m, 2xH(4)), 2.95–3.15 (1H, m, H(3)), 3.25–4.10 (5H, m, 2xH(8)+H(9)+CH$_2$OH), 7.1–7.5 (5H m, ArH); δ_C (DMSO, 100.6 MHz) 29.3 (C(4)), 45.5 (C(9)), 47.8 (C(8)), 53.6 (C(3)), 58.3 (C(5)), 65.8 (CH_2OH), 128.0, 128.6, 129.2, 129.5 (ArCH), 140.4 (ArC), 175.9, 176.5 (C═O); ***m/z*** (ESI$^+$) 283 (M+Na$^+$, 100%), 261 (M+H$^+$, 48%); **HRMS** [M+H$^+$]: Calculated for $C_{14}H_{17}O_3N_2$ 261.1239, Found: 261.1243.

(3*R*,5*S*,9*S*)-3-Methyloxycarbonyl-9-phenyl-2,7-diaza-spiro[4.4]nonane-1,6-dione 8c

To a stirred solution of lactam **8a** (0.76 g, 2.9 mmol) in acetonitrile (35 ml) was added a solution of $NaIO_4$ (4.78 g, 22.0 mmol) in water (50 ml) and the reaction mixture was stirred at RT for 10 min. $RuCl_3.H_2O$ (0.09 g, 0.4 mmol) was added and the reaction mixture was allowed to stir for 16 h. The solvents were removed *in vacuo* and the residue was dissolved in THF (50 ml). A solution of diazomethane in ether was then added until in excess, and stirring continued for 1 h. Water (70 ml) was added to the mixture, the layers separated and the product extracted with EtOAc (3 × 70 ml). The organic phases were combined, dried over $MgSO_4$ and the solvent was removed *in vacuo*. Purification by flash column chromatography with EtOAc and then MeOH gave the product

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as a single diastereomer **8c** (0.126 g, 15%) as a pale oil. R_f = 0.03 [EtOAc]; ν_{max}/cm^{-1} (thin film) 3233 (s), 3011 (s), 1720 (bs), 1438 (s); δ_H ($CDCl_3$, 400 MHz) 1.97–2.10 (1H, m, H(4)*exo*), 2.43 (1H, dd, *J*13.7 and 4.1, H(4)*endo*), 3.53–3.60 (1H, m, H(9)), 3.73 (3H, s, OMe), 3.83–3.90 (1H, m, H(3)), 3.93–4.03 (2H, m, 2xH(8)), 7.15–7.40 (5H, m, ArH), 6.9–7.1 (2H, bs, NH); δ_C ($CDCl_3$, 100.6 MHz) 30.1 (C(4)), 46.4, 46.5 (C(8)+C(9)), 52.6 (MeO), 53.1 (C(3)), 127.8, 127.8, 129.1 (ArCH), 140.0 (ArC), 171.2, 171.5, 175.6, 175.7 (C=O); ***m/z*** (ESI+) 311 (M+Na$^+$, 72%), 289 (M+H$^+$, 29%), 599 (100%); **HRMS** [M+H$^+$]: Calculated for $C_{15}H_{17}N_2O_4$ 289.1188, Found 289.1187.

(2*R*,5*S*,7*S*)-Spiro[1-aza-8-oxo-2-phenyl-3-oxa-bicyclo[3.3.0]-octane-7,3′-[1′,3′-dihydro-2′-oxo-7′-aminoindolinone] 9

To a mixture of iron powder (340 mg, 0.0061 M) and ammonium chloride solution (aq.) (0.60 g, 0.012 M) in distilled water (10 ml) was added a methanolic solution of the substrate **5a** (0.45 g, 0.0011 M in 50 ml) over 10 min at RT. The resultant mixture was heated at gentle reflux for 2.5 h. Subsequent work up involved suction filtration through Celite®, washing with methanol (50 ml) and evaporation of the combined washings to dryness *in vacuo*. Purification by flash column chromatography with an eluent of [EtOAc/(40–60) Petrol, 3 : 7] gave the product **9** as a white solid (42 mg, 15%) as a single isomer. R_f = 0.36 [EtOAc]; $[\alpha]_D^{23}$ + 190 (*c* = 0.3 in DCM); **m.p.** 152–155 °C; ν_{max}/cm^{-1} (thin film) 3369 (bs), 1724 (s), 1692 (s), 1636 (s), 1512 (m), 1471 (m), 1340 (m), 1264 (m); δ_H (400 MHz, $CDCl_3$) 1.69 (2H, bs, N<u>H</u>$_2$), 2.53 (1H, dd, *J* 13.6 and 7.2, H(6)), 2.69 (1H, dd, *J* 13.7 and 5.1, H(6)) 3.85–3.95 (1H, m, H(4)), 4.33–4.45 (2H, m, H(4)+H(5)), 6.15–6.20 (1H, m, H(8′)), 6.28 (1H, dd, *J* 8.0 and 1.5 H(6′)), 6.37 (1H, s, H(2)), 6.99 (1H, d, *J* 8.1, H(5′)), 7.35–7.52 (5H, m, ArH), 8.27 (1H, bs, NH); δ_C ($CDCl_3$, 100.6 MHz) 33.6 (C(6)), 56.9 (C(5)), 71.9 (C(4)), 87.3 (C(2)), 97.9 (C8′), 109.0 (C(6)), 123.5 (C(5′)), 126.0, 128.5 (ArCH), 128.7 138.4, 142.2, 147.9 (ArC), 174.2, 176.70 (C=O); ***m/z*** (ESI+) 358 (100%, M+Na$^+$), 336 (57%, M+H$^+$); **HRMS** [M+Na$^+$] Calculated for $C_{19}H_{17}N_3O_4Na$ 358.1168, Found: 358.1162.

7′-Amino-3′-hydroxymethyl-1*H*-spiro[indole-3,3′-pyrrolidine]-1,2′-dione 10

To a stirred solution of spirolactam **9** (0.075 g, 0.20 mmol) in DCM (8 ml) at RT was added TFA (0.3 ml, 6.5 mmol). After 2 h at RT, the solvent was removed *in vacuo* to yield the product **10** as a viscous oil (33 mg, 60%) as a single isomer. δ_H (D_2O, 200 MHz) 2.37 (1H, dd, *J* 14.0 and 6.7, H(4)), 2.53 (1H, dd, *J* 13.9 and 7.7, H(4)), 3.60 (1H, dd, *J* 11.6 and 6.4, C<u>H</u>HOH), 3.73 (1H, dd, *J* 11.6 and 4.5, CH<u>H</u>OH), 4.07–4.20 (1H, m, H(3)), 6.95 (1H, d, *J* 1.8, ArH), 7.0 (1H, d, *J* 2.0, ArH), 7.05 (1H, d, *J* 2.1, ArH), 7.37 (1H, d, *J* 8.0, ArH); δ_C (D_2O, 125.75 MHz) 32.6 (C(4)), 54.2 (C_3), 64.0 (CH_2OH), 105.8, 124.3 (ArCH); **HRMS (Probe EI/FI)**: Calculated for $C_{12}H_{13}N_3O_3$ 247.0957, Found: 247.1657.

(2*R*,5*S*,7*S*/*R*)-Spiro-[1-aza-8-oxo-2-phenyl-3-oxa-bicyclo-[3.3.0]octane]-7,3′-[3′,4′-dihydro-2′-oxo-3′-quinoline] 11a,b

A methanolic solution of the substrate **3b** (0.18 g, 0.43 mmol) in water (2.3 ml) was added to a stirred slurry of iron powder (77.5 mg, 1.4 mmol) and ammonium chloride (0.12 g, 2.3 mmol) in distilled water (2.2 ml) over a duration of 10 min at RT. The resultant mixture was heated at a gentle reflux for 2.5 h. Subsequent workup involved hot filtration and a hot methanol wash (2 × 2 ml), and the solvent was removed from the combined washings *in vacuo*. Purification by flash column chromatography with an eluent of [EtOAc/(40–60) Petrol, 3 : 7] gave white solids (20 mg, 32%) in a ratio of 1 : 1.

Data for 11a. R_f = 0.05 [EtOAc/Petrol (40–60), 3 : 7]; $[\alpha]_D^{23}$ +10 (*c* = 0.12 in DCM); **m.p.** 246–248 °C; ν_{max}/cm^{-1} (thin film) 3265 (m), 2917 (m), 1700 (m), 1672 (m), 1595 (m), 1497 (m), 1374 (m); δ_H ($CDCl_3$, 200 MHz) 2.23 (1H, dd, *J* 13.8 and 7.6, H(6)*exo*), 2.67 (1H, dd, *J* 13.8 and 4.5, H(6)*endo*), 3.13 (1H, d, *J* 16.0, C<u>H</u>HPh), 3.47 (1H, d, *J* 16.0, CH<u>H</u>Ph), 3.75 (1H, t, *J* 8.1, H(4)*exo*), 4.10–4.25 (1H, m, H(5)), 4.30 (1H, dd, *J* 7.45 and 6.05, H(4)*endo*), 6.30 (1H, s, H(2)), 6.8 (1H, d, *J* 7.2, ArH), 6.95–7.57 (6H, m, ArH), 8.1 (1H, bs, NH); δ_c (125.75 MHz, $CDCl_3$) 32.3 (C(6)), 36.7 (<u>C</u>H$_2$Ph), 54.8 (C(7)), 55.8 (C(5)), 71.5 (C(4)), 87.5 (C(2)), 115.0, 123.5, 126.0, 128.1, 128.3, 128.4, 128.7 (ArCH), 120.8, 136.5, 138.7 (ArC), 169.4, 175.3 (C=O); ***m/z*** (ESI$^+$) 393 (M+NH$_4$+MeCN$^+$,100%); **HRMS** [M+Na$^+$] Calculated for $C_{20}H_{18}N_2O_3Na$ 357.1215, Found 357.1221.

Data for 11b. R_f = 0.13 [EtOAc/(40–60) Petrol, 3 : 7]; $[\alpha]_D^{23}$ +250 (*c* = 0.35 in DCM); **m.p.** 101–103 °C; ν_{max}/cm^{-1} (thin film) 2922 (s), 2851 (m), 1709 (s), 1675 (s), 1597 (m), 1461 (m), 1374 (m), 1322 (m), 1249 (m); δ_H ($CDCl_3$, 200 MHz) 1.83 (1H, dd, *J* 13.1 and 7.1, H(6)), 2.77 (1H, dd, *J* 13.1 and 6.7, H(6)), 2.95 (1H, d, *J* 16.2, C<u>H</u>HPh), 3.50–3.63 (2H, m, H(4)+CH<u>H</u>Ph), 4.20–4.30 (1H, m, H(5)), 4.37 (1H, t, *J* 6.9, H(4)), 6.37 (1H, s, H(2)), 6.70–6.78 (1H, m, ArH), 7.0–7.57 (7H, m, ArH), 8.60 (1H, bs, NH); δ_C ($CDCl_3$, 100.6 MHz) 35.2 (C(6)), 37.4 (<u>C</u>H$_2$Ph), 56.0 (C(7)), 56.4 (C(5)), 72.0 (C(4)), 87.0 (C(2)), 115.0, 123.7, 126.2, 127.8, 128.4, 128.5, 128.7 (ArCH), 121.6, 135.8, 137.6 (ArC), 169.3, 172.9 (C=O); **m/z** (ESI$^+$) 393 (M+NH$_4$+MeCN$^+$, 100%); **HRMS**: [M+H$^+$] Calculated for $C_{20}H_{19}N_2O_3$ 335.1396, Found: 335.1389.

(2*R*,5*S*,7*R*) and (2*R*,5*S*,7*S*)-1-Aza-7-(2-oxo-2-phenylethyl)-7-(ethoxycarbonyl)-3-oxo-8-oxa-2-phenyl-bicyclo[3.3.0] octane 12a

To a stirred suspension of pre-washed NaH (0.15 g, 6.0 mmol) in dry THF (40 ml) at 0 °C under nitrogen atmosphere was added a solution of lactam **2b** (0.88 g, 3.2 mmol) in THF (20 ml), and the mixture was stirred at RT for 20 min. A solution of α-bromoacetophenone (1.05 g, 2.70 mmol) in THF (20 ml) was added and the mixture was stirred at RT for 16 h. The reaction was quenched by pouring the mixture into NH_4Cl (aq.)/EtOAc (1 : 1) (100 ml) and the aqueous portion was extracted with EtOAc (2 × 50 ml). The organic extracts were combined, washed with water (50 ml) and sat. brine (50 ml), dried over $MgSO_4$ and the solvent removed *in vacuo*, which was purified by flash column chromatography [(40/60) Petrol/EtOAc, 40 : 1] to give **12a** (0.74 g, 59%) as a pale yellow oil and as an inseparable mixture of diastereomers A and B (ratio B : A 1 : 2). R_f = 0.20 [EtOAc/(40–60) Petrol, 1 : 4]; ν_{max}/cm^{-1} (thin film) 3064 (m), 2983 (m), 2253 (m), 1721 (s), 1707 (s), 1699 (s); δ_H ($CDCl_3$, 200 MHz) 1.23–1.37 (6H, m, C<u>H</u>$_3$CH$_2$O(A+B)) 1.93 (1H, dd, *J* 13.3 and 7.0, H(6)(B)), 2.40 (1H, dd, *J* 14.5 and 8.2, H(6)(A)), 3.03 (1H, dd, *J* 14.5 and 3.9, H(6)(A)), 3.25 (1H, dd, *J*13.3 and 7.3, H(6)(B)), 3.27–3.5 (2H, d, *J* 18.7, C<u>H</u>HCOPh(A+B)), 3.70 (1H, t, *J* 7.9, H(4)(B)), 3.80 (1H, t, *J* 8.3, H(4)(A)), 4.03–4.57 (10H, m, H(5) (A+B)+H(4)(A+B)+

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CHHCOPh (A+B)+$CH_3C\underline{H}_2O$(A+B)), 6.27 + 6.35 (2H, s, H(2)(A+B)), 7.05–7.67+ 7.67–8.10 (20H, m, ArH (A+B)); δ_C ($CDCl_3$, 100.6 MHz) 13.9 ($\underline{C}H_3CH_2O$(A+B)), 31.6 (C(6)(A)), 36.2 (C(6)(B)), 43.4 ($\underline{C}H_2COPh$(B)), 44.0 ($\underline{C}H_2COPh$(A)), 56.6 (C(5)(A)), 57.2 (C(5)(B)), 57.6 (C(7)(A)), 58.6 (C(7)(B)), 62.0, 62.1 ($CH_3\underline{C}H_2O$(A+B)), 71.4 (C(4)(A)), 72.3 (C(4)(B)) 87.2 (C(2)(B)), 87.6 (C(2)(A)), 126.0, 126.1, 128.0, 128.1, 128.3, 128.5, 128.70, 129.7, 133.6, 133.6 (ArCH(A+B)), 136.1, 136.2, 138.1, 138.6 (ArC(A+B)), 170.1, 172.7, 196.5, 196.8(C═O(A+B)); ***m/z*** (ESI$^+$) 452 (M+MeCN+NH_4^+,100%); **HRMS** [M+H$^+$] Calculated for $C_{23}H_{24}NO_5$ 394.1654, Found: 394.1646.

(2*R*,5*S*,7*R*,5′*R*), (2*R*,5*S*,7*S*,5′*S*) and (2*R*,5*S*,7*R*,5′*S*)-Spiro[1-oxa-8-oxo-2-phenyl-3-oxa-bicyclo[3.3.0]octane]-7,3′-[5′-phenyldihydrofuran-2′-one] 13a

The lactam **12a** (0.83 g, 2.1 mmol) were dissolved in EtOH (55 ml). At 0 °C, $NaBH_4$ (0.094 g, 2.5 mmol) was added portion-wise and the mixture was stirred for 2 h. The reaction mixture was acidified with glacial acetic acid until the solution was neutral in pH, filtered through a bed of Celite® and the solvent removed *in vacuo.* Purification by flash column chromatography [EtOAc/(40–60) Petrol, 1 : 5] gave the product isomers as white solids (0.18 g, 25%).

Data for 13a. R_f = 0.17 [EtOAc/(40–60) Petrol, 3.5 : 6.5]; $[\alpha]_D^{21}$ +155 (c = 0.2 in $CHCl_3$); **m.p.** 197–200 °C; ν_{max}/cm^{-1} (thin film) 1752 (m), 1708 (m), 1458 (m), 1387 (w), 1332 (w); δ_H ($CDCl_3$, 200 MHz) 2.45–2.95 (4H, m, 2xH(6)+2xH(4′)), 3.85 (1H, dd, *J* 8.6 and 7.8, H(4) *endo*), 4.10–4.25 (1H, m, H(5)), 4.35 (1H, dd, *J* 7.5 and 6.1, H(4)*exo*), 5.5 (1H, dd, *J* 9.6 and 6.8, H(5′)), 6.4 (1H, s, H(2)), 7.30–7.55 (10H, m, ArH); δ_C ($CDCl_3$, 100.6 MHz), 33.2 (C(6)), 42.7 (C(4′)), 56.5 (C(5)), 57.0 (C(7)), 71.1 (C(4)), 79.7 (C(5′)), 87.7 (C(2)), 125.9, 126.0, 128.5, 128.8, 128.9, 129.0 (ArCH), 137.9, 138.3 (ArC), 174.8 + 175.6 (C═O); ***m/z*** (ESI$^+$) 408 (M+MeCN+NH_4^+, 100%); **HRMS**: [M+H$^+$] Calculated for $C_{21}H_{20}NO_4$ 350.1392, Found: 350.1405.

Data for 13a′. R_f = 0.07 [EtOAc/(40–60) Petrol, 1 : 5], δ_H ($CDCl_3$, 200 MHz) 1.95 (1H, dd, *J* 13 and 7.3, H(6) *endo*), 2.15 (1H, dd, *J* 12.9 and 9.7, H(4b′)), 2.87 (1H, dd, *J* 12.9 and 6.8, H(6)*exo*), 3.20 (1H, dd, *J* 13, 6.3, H(4a′)), 3.60 (1H, dd, *J* 8.35 and 7.2, H(4)*endo*), 4.25 (1H, dd, *J* 8.3 and 6.5, H(4)*exo*), 4.50–4.67 (1H, m, H(5)), 5.90 (1H, dd, *J* 9.7 and 6.2, H(5′)), 6.37 (1H, s, H(2)), 7.30–7.63 (10H, m, ArH); δ_C ($CDCl_3$, 100.6 MHz), 36.0 (C(6)), 40.8 (C(4′)), 56.4 (C(5)), 58.4 (C(7)), 71.7 (C(4)), 79.9 (C(5′)), 87.1 (C(2)), 125.5, 126.0, 128.6, 128.7, 128.8, 129.0 (ArCH), 137.1, 138.6 (ArC), 172.2, 174.9 (C═O).

Data for 13a″. R_f = 0.04 [EtOAc/(40–60) Petrol, 1 : 5]; δ_H (200 MHz, $CDCl_3$) 2.20–2.40 (2H, m, H(6) *exo*+H(4a′)), 2.75 (1H, dd, *J* 14.0 and 4.4, H(6)*endo*), 3.13 (1H, dd, *J* 13.0 and 3.0, H(4b′)), 3.80 (1H, m, H(4)*exo*), 4.07–4.25 (1H, m, H(5)), 4.30–4.43 (1H, m, H(4)*endo*), 5.83–5.97 (1H, m, H(5′)), 6.30 (1H, s, H(2)), 7.20–7.60 (10H, m, ArH); δ_C ($CDCl_3$, 100.6 MHz), 31.9 (C(6)), 43.5 (C(4′)), 56.6 (C(5)), 58.1 (C(7)), 71.7 (C(4)), 79.2 (C(5′)), 87.5 (C(2)), 125.5, 126.0, 128.6, 128.8, 128.9, 128.9 (ArCH), 138.1, 138.2 (ArC), 174.6, 175.0 (C═O).

(2*R*,5*S*,7*R*,5′*R*) and (2*R*,5*S*,7*S*,5′*S*)-Spiro[1-oxa-8-oxo-2-phenyl-3-oxa-bicyclo[3.3.0]octane]-7,3′-[5′-hydroxymethyldihydrofuran-2′-one] 13b and 13b′

The lactam **12b** (0.25 g, 0.80 mmol) was dissolved in acetone (60 ml) and distilled water (7 ml). At −10 °C with stirring, $K_2OsO_4{\cdot}2H_2O$ (0.03 g, 0.08 mmol) was added and the reaction mixture was allowed to stir at RT for 2 days, after which the reaction had produced a black precipitate which was filtered under suction. The filtrate was diluted with Na_2SO_3 (aq.) (20 ml) and extracted with EtOAc (2 × 40 ml). The organic layers were combined, dried over Na_2SO_4 and the solvent removed *in vacuo.* Purification was by flash column chromatography with an eluent of [EtOAc/(40–60) Petrol, 3 : 1] to give a white solid as a partially separated mixture of diastereomers **13b** and **13b′** (35 mg, 15%).

Data for 13b. R_f = 0.31 [EtOAc/(40–60) Petrol, 3 : 1]; $[\alpha]_D^{23}$ +89 (c = 0.04 in $CHCl_3$); **m.p.** 156–158 °C; ν_{max}/cm^{-1} (thin film) 3490 (bm), 3030 (s), 1748 (s), 1691 (s), 1349 (m), 1158 (m), 1048 (m); δ_H ($CDCl_3$, 400 MHz) 2.27–2.47 (2H, m, H(6)+H(4′)), 2.60–2.80 (2H, m, H(4′)+H(6)), 3.60 (1H, bd, *J* 11.2, C$\underline{H}$HOH), 3.75 (1H, t, *J* 8.3, H(4)), 4.03 (1H, bd, *J* 12.3, CH$\underline{H}$OH), 4.15 (1H, bs, H(5)), 4.3 (1H, t, *J* 6.6, H(4)), 4.93 (1H, bs, H(5′)), 6.25 (1H, s, H(2)), 7.30–7.55 (5H, m, ArH); δ_C ($CDCl_3$, 100.6 MHz) 32.3, 35.4 (C(6)+C(4′)), 56.6 (C(5)), 57.7 (C(7)), 62.3 (CH_2OH), 71.6 (C(4)), 78.6 (C(5′)), 87.4 (C(2)), 125.9, 128.5, 128.9 (ArCH), 138.2 (ArC), 174.8, 175.5 (C═O); ***m/z*** (ESI-) 302 (M–H$^-$, 48%), 362 (100%); **HRMS** [M+H$^+$] Calculated for $C_{16}H_{18}NO_5$ 304.1185, Found: 304.1184.

Data for 13b′. R_f = 0.19 [EtOAc/(40–60) Petrol, 3 : 1], ν_{max}/cm^{-1} (thin film) 3427 (bs), 2931 (w), 1773 (m), 1697 (m), 1448 (m); δ_H ($CDCl_3$, 200 MHz) 1.97 (1H, dd, *J* 13.1 and 7.3, H(6)), 2.2 (1H, dd, *J* 12.9 and 8.7, H(4′)), 2.83 (1H, dd, *J* 12.9 and 6.9, H(4′)), 2.87 (1H, dd, *J* 13.1 and 6.9, H(6)) 3.57 (1H, t, *J* 7.9, H(4)), 3.63 (1H, d, *J* 12.5, C$\underline{H}$HOH), 4.03 (1H, d, *J* 12.6, CH$\underline{H}$OH) 4.23 (1H, dd, *J* 8.3 and 6.5, H(4)), 4.45–4.55 (1H, m, H(5)), 4.9–4.97 (1H, m, H(5′)), 6.3 (1H, s, H(2)), 7.3–7.5 (5H, m, ArH); δ_C ($CDCl_3$, 100.6 MHz) 32.6 (C(4′)), 36.4 (C(6)), 56.3 (C(5)), 58.2 (C(7)), 62.8 (CH_2OH), 71.7 (C(4)), 79.1 (C(5′)), 87.0 (C(2)), 126.0, 128.6, 128.9 (ArCH), 137.2 (ArC), 172.2, 175.2 (C═O); ***m/z*** (ESI$^+$) 362 (M+NH_4+MeCN$^+$, 100%); **HRMS** [M+MeCN+Na$^+$] Calculated for $C_{18}H_{20}N_2O_5Na$ 367.1270, Found: 367.1270.

(2*R*,5*S*,7*R*,5′*R*)- and (2*R*,5*S*,7*S*,5′*R*)-Spiro[1-oxa-8-oxo-2-phenyl-3-oxa-bicyclo[3.3.0]-octane]-7,3′-[5′-iodomethyldihydrofuran-2′-one] 14a,b

The lactam **12b** (0.17 g, 0.50 mmol) was dissolved in a mixture of MeOH/water (3 : 1) (11 ml) containing $LiOH{\cdot}H_2O$ (0.090 g, 2.1 mmol) and stirred at RT for 16 h. The resulting reaction mixture was then diluted with EtOAc (25 ml), washed with 1% HCl (aq.) (25 ml) and then extracted with EtOAc (2 × 25 ml). The organic layers were combined and washed with water (10 ml). The solvent was removed *in vacuo* to yield the acid (0.15 g, 100%) as a mixture diastereomers A and B (2 : 1 A : B). ν_{max}/cm^{-1} (thin film) 2982 (bs), 1708 (bs), 1378 (s), 1026 (s); δ_H ($CDCl_3$, 200 MHz) 1.93 (1H, dd, *J* 13.5 and 6.4, H(6)(B)), 2.47–2.95 (7H, m, 2xH(6)(A)+ H(6) (B)+ 2xH(8)(A+B))), 3.47–3.70 (2H, m, H(4)(A+B)), 4.03–4.20 (1H, m, H(5)(A)), 4.20–4.40 (3H, m, H(5)(B)+H(4)(A+B)),

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5.03–5.33 (4H, m, 2xH(10)(A+B)), 5.60–5.90 (2H, m, H(9)(A+B)), 6.33 (2H, s, H(2)(A+B)) 7.30–7.55 (10H, m, ArH(A+B)), 8.63 (2H, bs, CO_2H(A+B)); δ_C ($CDCl_3$, 100.6 MHz) 31.7 (C(6)(A)), 33.8 (C(6)(B)), 38.6 (C(8) (B)), 40.3 (C(8) (A)), 56.1 (C(5) (A)), 56.3 (C(5)(B)), 71.9 (C(4)(A)), 72.0 ((C(4)(B)), 87.0 (C(2)(B)), 87.1 (C(2)(A)) 120.0 (C(10) (B)), 120.7 (C(10)(A)), 125.9, 126.1, 128.5, 128.6, 128.8, 129.0(ArCH (A+B)), 137.6, 137.7 (ArC), 131.3, 132.4 (C(9)(A+B)), 172.8, 176.0 (C═O(A)), 173.4, 174.2 (C═O(B)); ***m/z*** (ESI^-) 242 ($M–CO_2–H^-$, 100%) 286 ($M–H^-$, 80%); **HRMS** [$M+H^+$]: Calculated for $C_{16}H_{18}NO_4$ 288.1236 Found: 288.1234.

The above acid (0.21 g, 0.70 mmol) was dissolved in $NaHCO_3$ (4 ml, 1 M) and a solution of I_2 (0.18 g, 0.70 mmol) and KI (0.36 g, 2.0 mmol) in water (13 ml) added drop-wise. The mixture was left to stir for 1 h at RT. The product was then extracted into ether (20 ml) and then washed with 5% $Na_2SO_3·5H_2O$ (aq.) (20 ml), sat. brine (20 ml) and then dried over $MgSO_4$. The organic layer was then filtered and concentrated *in vacuo* which was purified by flash column chromatography [(40–60) Petrol/EtOAc, 7 : 3] to give a mixture of **14a** and **14b** diastereomers as partially separable white solids (60 mg, 20%).

Data for 14a. R_f = 0.20 [EtOAc/(40–60) Petrol, 3 : 7]; $[\alpha]_D^{23}$ +150 (*c* = 0.69 in DCM), **m.p.** 179–180 °C; ν_{max}/cm^{-1} (thin film) 2916 (w), 1772 (s), 1699 (s), 1495 (m), 1453 (m), 1352 (m); δ_H ($CDCl_3$, 200 MHz) 2.05 (1H, dd, *J* 13.1 and 9.5, H(4b′)) 2.30 (1H, dd, *J* 14.1 and 7.8, H(6)*exo*), 2.73 (1H, dd, *J* 14.1 and 4.4, H(6)*endo*), 2.95 (1H, dd, *J* 13.1 and 6, H(4a′)), 3.35 (1H, dd, *J* 10.6 and 4.2, CHHI), 3.45 (1H, dd, *J* 10.5 and 7.3, CHHI), 3.75 (1H, t, *J* 8.1, H(4)*endo*), 4.07–4.27 (1H, m, H(5)), 4.83 (1H, dd, *J* 7.8 and 6.0, H(4)*exo*), 4.75–4.95 (1H, m, H(5′)), 6.33 (1H, s, H(2)), 7.27–7.60 (5H, m, ArH); δ_C ($CDCl_3$, 100.6 MHz) 6.5 (CH_2I), 31.8 (C(6)), 41.4 (C(4′)), 56.6 (C(5)), 58.1 (C(7)), 71.8 (C(4)), 76.1 (C(5′)), 87.5 (C(2)), 125.9, 128.6, 128.9 (ArCH), 138.1 (ArC), 174.4, 174.5 (C═O); ***m/z*** APCI (NH_3) 414 ($M+H^+$, 100%); **HRMS** [$M+H^+$] Calculated for $C_{16}H_{17}O_4IN$ 414.0202, Found: 414.0198.

Data for 14b. R_f = 0.11 [EtOAc/(40–60) Petrol, 3 : 7]; $[\alpha]_D^{21}$ +1.4 (*c* = 0.03 in DCM); **m.p.** 136–138 °C; δ_H ($CDCl_3$, 200 MHz) 2.0 (1H, dd, *J* 13.1 and 7.8, H(6)*endo*), 2.37 (1H, dd, *J* 13.9 and 8.1, H(4b′)), 2.75–2.95 (2H, m, H(6)*exo*+H(4a′)), 3.43–3.70 (3H, m, H(4)*endo*+CH_2I), 4.25 (1H, dd, *J* 8.45 and 6.4, H(4)*exo*), 4.45–4.55 (1H, m, H(5)), 4.55–4.85 (1H, m, H(5′)), 6.33 (1H, s, H(2)), 7.30–7.57 (5H, m, ArH); δ_C ($CDCl_3$, 100.6 MHz) 6.0 (CH_2I) 36.2 (C(6)), 37.7 (C(4′)), 56.3 (C(5)), 58.0 (C(7)), 71.7 (C(4)), 77.9 (C(5′)), 87.2 (C(2)), 125.9, 128.7, 129.0 (ArCH), 137.0 (ArC), 174.7, 175.6 (C═O).

(*S*)-1-*tert*-Butyl-2-ethyl-5-oxopyrrolidine-1,2-dicarboxylate 15a[55]

To a stirred mixture of **1a** (2.0 g, 12.7 mmol) in DCM (5 ml) was added triethylamine (2.7 ml 19 mmol) and DMAP (0.16 g, 1.2 mmol) and a further 15 ml of DCM added. Boc_2O (3.10 g, 13.7 mmol) dissolved in DCM (5 ml) was then added slowly. The reaction was left for 24 h at RT under a nitrogen atmosphere. The mixture was worked up by adding 30 ml of 0.1 M HCl and separating the aqueous and organic layers. The aqueous layer was washed with DCM (3 × 30 ml) and the combined organics were dried and concentrated *in vacuo*. The crude product was passed through a silica plug (20 ml) and eluted with EtOAc (3 × 40 ml). On solvent removal, a pale orange oil **15a** was obtained (2.12 g, 65%). R_f 0.54 [EtOAc]; δ_H (400 MHz, $CDCl_3$) 1.24 (3H, t, *J* 7.1, CH_3CH_2O), 1.43 (9H, s, $(CH_3)_3O$), 1.92–2.06 (1H, m, H(3)), 2.22–2.36 (1H, m, H(3)), 2.38–2.51 (1H, m, H(4)), 2.52–2.66 (1H, m, H(4)), 4.18 (2H, q, *J* 7.1, CH_3CH_2O), 4.55 (1H, dd, *J* 9.2, 3.0, H(4)); δ_C (100 MHz, $CDCl_3$) 14.0 (CH_3CH_2O), 21.4 (C(3)), 27.7 ($(CH_3)_3CO$), 31.0 (C(4)), 58.8 (C(2)), 61.5 (CH_3CH_2O), 83.4 ($(CH_3)_3CO$), 149.1, 171.2, 173.3 (C═O); ***m/z*** (ESI^+) 280 (100%, $M+Na^+$.).

(*S*)-1-(*tert*-Butoxycarbonyl)-4-(ethoxycarbonyl)pyroglutamate 15b[71]

To a stirred solution of **15a** (0.37 g, 1.44 mmol) in dry THF (5 ml) at −78 °C was added a 1 M solution of lithium hexamethyldisilazide (2.93 ml, 2.88 mmol) in THF (5 ml). After stirring for 1 h, ethyl chloroformate (0.16 ml, 1.73 mmol) was added and stirring continued for 16 h, allowing the reaction to warm to RT. The reaction mixture was quenched with saturated ammonium chloride solution (10 ml) and extracted with EtOAc (3 × 5 ml). The combined organics were dried over $MgSO_4$ and concentrated *in vacuo*. The resulting oil was purified by flash chromatography [40/60 Petrol : EtOAc (4 : 1)] yielding **15b** as an inseparable mixture of two diastereoisomers in the ratio of 2 : 1 (0.31 g, 65%). R_f 0.21 [EtOAc/(40/60) Petrol, 1 : 2]; $[\alpha]_D^{22}$ −10.6 (*c* = 2.6 in $CHCl_3$); ν_{max}/cm^{-1} (thin film) 2983 (bm), 1797 (s), 1736 (s), 1459 (s), 1371 (m), 1153 (m), 1028 (m); δ_H (500 MHz, C_6D_6) 0.86–0.94 (6H, t, *J* 7.1, CH_3CH_2O), 1.35 (9H, s, $(CH_3)_3CO$(A)), 1.39 (4.5H, s, $(CH_3)_3CO$(B)), 1.62–1.72 (1.5H, m, H(3)(A+B)), 2.29–2.41 (1.5H, m, H(3)(A+B)), 3.00 (0.5H, dd, *J* 9.8 and 4.9, H(4)(B)), 3.47 (1H, dd, *J* 10.7 and 9.0, H(4)(A)), 3.81–4.07 (8H, m, CH_3CH_2O(A+B)), 4.33 (0.5H, dd, *J* 9.5 and 4.1, H(2)(B)), 4.43 (1H, dd, *J* 9.6 and 2.1, H(2)(A)); δ_C (100 MHz, C_6D_6) 14.4 (CH_3CH_2O(A+B)), 24.9 (C(3)(A)), 25.7 (C(3)(B)), 28.2 ($(CH_3)_3CO$(A+B)), 49.3 (C(4)(A)), 49.5 (C(4)(B)), 57.6 (C(2)(A)), 58.0 (C(2)(B)), 61.8 (CH_3CH_2O(B)), 61.9 (CH_3CH_2O(A)), 62.1 (CH_3CH_2O(B)), 62.2 (CH_3CH_2O(A)), 83.6 ($(CH_3)_3CO$(B)), 83.8 ($(CH_3)_3CO$(A)), 150.6, 150.7, 166.8, 167.6, 168.1, 168.6, 170.9, 171.4 (C═O); **HRMS**: [$M+Na^+$.] Calculated for $C_{15}H_{23}NNaO_7$ 352.1367, Found: 352.1358.

(2*S*)-1-(*tert*-Butoxycarbonyl)-2,4-diethyl-4-(2,4-dinitrophenyl)-5-oxopyrrolidine-2,4-dicarboxylate 16a

To a stirred suspension of **15b** (1.58 g, 4.8 mmol) in dry DMF (35 ml) was added Et_3N (0.53 g, 5.3 mmol). The mixture was left stirring for 20 min and then 2,4-dinitro-1-fluorobenzene (1.07 g, 5.7 mmol) was added. The reaction was left to stir for 72 h. The reaction was worked up by the addition of saturated ammonium chloride (30 ml). The aqueous layer was separated and extracted with EtOAc (3 × 10 ml). The combined organics were then concentrated *in vacuo*. The crude oil was dissolved in EtOAc (10 ml) and washed with distilled water (2 × 5 ml), brine (5 ml) and dried over $MgSO_4$ and concentrated *in vacuo*. The solid was purified by flash chromatography [40/60 Petrol : EtOAc (3 : 1)] yielding **16a** (2.1 g, 79%). R_f 0.46 [EtOAc/(40/60) Petrol, 1 : 2]; $[\alpha]_D^{22}$ −38.4 (*c* = 1 in CH_2Cl_2); ν_{max}/cm^{-1} (thin film) 3734 (m), 2984, (s), 2361 (s), 2341 (s), 1735 (m), 1607 (s), 1540 (s), 1457 (m), 1353 (bm); δ_H (400 MHz, $CDCl_3$) 1.19 (3H, t, *J* 7.14, CH_3CH_2O), 1.35 (3H, t, *J* 7.14, CH_3CH_2O), 1.55 (9H, s, $(CH_3)_3CO$), 2.63 (1H, dd, *J* 14.3 and 10.2, H(3)), 3.53 (1H, dd, *J* 14.3 and 3.7, H(3)),

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4.09–4.24 (2H, m, $CH_3C\underline{H}_2O$), 4.32 (2H, q, *J* 7.0, $CH_3C\underline{H}_2O$), 4.69 (1H, dd, *J* 10.2 and 3.7, H(2)), 7.68 (1H, d, *J* 8.8, H(2′), 8.46 (1H, dd, *J* 8.8 and 2.5, H(3′), 8.88 (1H, d, *J* 2.5, H(5′); δ_C (100 MHz, $CDCl_3$) 13.64, 14.13 ($\underline{C}H_3CH_2O$), 27.8 (($\underline{C}H_3)_3CO$), 34.5 (C3), 56.4 (C2), 62.1 ($CH_3\underline{C}H_2O$), 62.6 (C4), 63.6 ($CH_3\underline{C}H_2O$), 85.0 (($CH_3)_3\underline{C}O$), 121.2 (C5′), 127.7 (C(3)′), 131.7 (C(2)′), 139.8 (ArC), 147.2, 148.6, 148.8 ($\underline{C}NO_2$+Boc C═O), 166.1, 167.8, 169.4 (C═O); **HRMS**: [M+Na$^+$.] Calculated for $C_{21}H_{25}N_3NaO_{11}$ 518.1381, Found: 518.1379.

(2*S*)-1-(*tert*-Butoxycarbonyl)-2,4-diethyl-4-(2,4-diaminophenyl)-5-oxopyrrolidine-2,4-dicarboxylate 16b

To a stirred mixture of iron powder (0.182 g, 3.25 mmol) and aqueous ammonium chloride (0.316 g, 5.96 mmol in 7 ml H_2O) was added **16a** (0.30 g, 0.54 mmol) in 35 ml of MeOH over the course of 10 minutes, and then refluxed for 2.5 h. The mixture was filtered through Celite® with MeOH (3 × 10 ml). An excess of EtOAc was then added and the organics were washed both with water (10 ml) and brine (10 ml), dried over $MgSO_4$ and concentrated *in vacuo.* Purification by flash chromatography [(40/60)Petrol : EtOAc, 1 : 2] yielded **16b** (0.08 g, 31%). R_f 0.41 [EtOAc]; δ_H (400 MHz, $CDCl_3$) 1.08–1.31 (6H, m, $C\underline{H}_3CH_2O$), 1.37 (9H, s, $(C\underline{H}_3)_3CO$), 2.5–3.0 (2H, m, H(3)), 4.03–4.19 (5H, m, H(2)+$CH_3C\underline{H}_2O$), 6.24 (1H, s, ArH), 6.32 (1H, d, *J* 7.5, ArH), 6.99 (1H, d, *J* 7.7, ArH); δ_C (100 MHz, $CDCl_3$) 13.9, 14.1 ($\underline{C}H_3CH_2O$), 28.3 (($\underline{C}H_3)_3CO$), 34.8 (C(3)), 50.4 (C(2)), 57.5 (C(2)), 61.5, 62.1 ($CH_3\underline{C}H_2O$), 79.7 (($CH_3)_3\underline{C}O$), 97.9, 109.1 (ArC), 116.0 (ArC), 124.6 (ArC), 142.7 ($\underline{C}NH_2$), 148.2, 154.9, 169.5, 172.3, 175.3 (C═O); **HRMS**: [M+Na$^+$.] Calculated for $C_{21}H_{29}N_3NaO_7$ 458.1903, Found: 458.1899.

(2*S*,4*R*) and (2*S*,4*S*)-1-*tert*-Butyl-2,4-diethyl-4-(cyanomethyl)-5-oxopyrrolidine-1,2,4-tricarboxylate 18a,b

To a stirred suspension of **15b** (0.50 g, 1.5 mmol) in dry THF (15 ml) was added NaH (0.044 g, 1.82 mmol) and the mixture stirred at RT for 30 min. A solution of bromoacetonitrile (0.274 g, 2.3 mmol) in THF (5 ml) was added and the mixture stirred at RT for 16 h. The reaction was quenched with ammonium chloride (10 ml) and the organic layer separated and the aqueous layer extracted with EtOAc (3 × 5 ml). The combined organics were washed with brine (10 ml), dried over $MgSO_4$ and concentrated *in vacuo.* Purification by flash chromatography [(40/60)petrol : EtOAc (3 : 1)] yielded a waxy white solid **18a**,**b** (0.52 g, 92%) as a mixture of two diastereoisomers (1 : 1.5), which were separated by further flash chromatography [(40/60)petrol : EtOAc (5 : 1)].

Data for 18a. R_f 0.26 [EtOAc/(40/60) Petrol, 1 : 2]; $[\alpha]_D^{22}$ −19.5 (*c* = 1 in CH_2Cl_2); ν_{max}/cm^{-1} (thin film) 2983 (bs), 2250 (m), 1796 (s), 1743 (s), 1371 (s) 1313 (s); δ_H (400 MHz, $CDCl_3$) 1.32 (6H, t, *J* 7.0, $C\underline{H}_3CH_2O$), 1.50 (9H, s, $(C\underline{H}_3)_3CO$), 2.12 (1H, dd, *J* 14.1 and 6.3, H(3)), 2.8 (1H, d, *J* 17.0, $C\underline{H}_2CN$), 3.03 (1H, dd, *J* 13.9 and 9.0, H(3)), 3.23 (1H, d, *J* 17.0, $C\underline{H}_2CN$), 4.22–4.34 (4H, m, $CH_3C\underline{H}_2O$), 4.73 (1H, dd, *J* 9.0 and 6.3, H(2)); δ_C (100 MHz, $CDCl_3$) 13.9, 14.0 ($\underline{C}H_3CH_2O$), 22.8 ($\underline{C}H_2CN$), 27.7 (($\underline{C}H_3)_3CO$), 30.5 (C3), 54.4 (C(4)), 56.8 (C(2)), 62.2, 63.5 ($CH_3\underline{C}H_2O$), 85.0 (($CH_3)_3\underline{C}O$), 116.1 ($CH_2\underline{C}N$), 148.5, 167.5, 167.7, 170.7 (C═O); **HRMS**: [M+Na$^+$.] Calculated for $C_{17}H_{24}N_2NaO_7$ 391.1476, Found: 391.1476.

Data for 18b. R_f 0.19 [EtOAc/(40/60) Petrol, 1 : 2]; $[\alpha]_D^{22}$ −12.7 (*c* = 1 in CH_2Cl_2); ν_{max}/cm^{-1} (thin film) 2982 (s), 2240 (m), 1775 (s), 1753 (s), 1753 (s), 1372 (s) 1342 (s), 1310 (s); δ_H (400 MHz, $CDCl_3$) 1.23–1.30 (6H, m, $C\underline{H}_3CH_2O$), 1.51 (9H, s, $(C\underline{H}_3)_3CO$), 2.52 (1H, dd, *J* 14.1 and 10.4, H(3)), 2.87 (1H, d, *J* 17.0, $C\underline{H}_2CN$), 2.93 (1H, dd, *J* 14.2 and 2.2, H(3)), 3.09 (1H, d, *J* 17.0, $C\underline{H}_2CN$), 4.15–4.35 (4H, m, $CH_3C\underline{H}_2O$), 4.73 (1H, dd, *J* 10.4 and 2.2, H(2)); δ_C (100 MHz, $CDCl_3$) 13.8, 14.1 ($\underline{C}H_3CH_2O$), 23.7 ($\underline{C}H_2CN$), 27.7 (($\underline{C}H_3)_3CO$), 30.4 (C(3)), 54.0 (C(4)), 56.2 (C(2)), 62.0, 63.4 ($CH_3\underline{C}H_2O$), 84.6 (($CH_3)_3\underline{C}O$), 115.8 ($\underline{C}N$), 148.5, 166.9, 167.4, 169.4 (C═O); **HRMS**: [M+Na$^+$.] Calculated for $C_{17}H_{24}N_2NaO_7$ 391.1476, Found: 391.1476.

(3*S*)-2-*tert*-Butyl-3-ethyl-1,6-dioxo-2,7-diazaspiro[4.4]nonane-2,3-dicarboxylate 19 and (2*S*)-1-(*tert*-butoxycarbonyl)-2,3-diethyl-4-(2-aminoethyl)-5-oxopyrrolidine-2,4-dicarboxylate 20

To a solution of **17a**,**b** (0.62 g, 1.69 mmol) in EtOH (75 ml) was added $CoCl_2 \cdot 6H_2O$ (0.80 g, 3.4 mmol) and the mixture was stirred for 5 min. $NaBH_4$ (0.51 g, 13.5 mmol) was then added portion-wise to the blue solution which was accompanied by effervescence and a colour change through green to black. After stirring for 16 h at RT, the ethanol was removed *in vacuo* and NH_4OH (24 ml, 0.1 M) and EtOAc (75 ml) were added with stirring. After 30 min, the green solution was filtered through Celite® and washed with EtOAc (40 ml). The organic phase was separated and washed with water (15 ml), brine (15 ml), dried over $MgSO_4$ and then concentrated *in vacuo* to give a pale yellow oil which was purified by flash chromatography [EtOAc] to yield **19** (0.025 g, 5%) and **20** (0.025 g, 4%).

Data for 19. R_f 0.40 [EtOAc]; $[\alpha]_D^{22}$ +8.0 (*c* = 0.5 in CH_2Cl_2); ν_{max}/cm^{-1} (thin film) 2981 (m), 1789 (s), 1705 (m), 1369 (s), 1309 9 (m); δ_H (400 MHz, $CDCl_3$) 1.3 (3H, t, *J* 7.1, $C\underline{H}_3CH_2O$), 1.5 (9H, s, $(C\underline{H}_3)_3CO$), 1.85 (1H, dd, *J* 13.5 and 4.4, H(3)), 2.02–2.16 (1H, m, H(1′)), 2.68–2.75 (1H, m, H(1′)), 2.94 (1H, dd, *J* 13.5 and 9.4, H(3)), 3.30–3.37 (1H, m, H(2′)), 3.62–3.70 (1H, m, H(2′)), 4.24 (2H, q, *J* 7.07, $CH_3C\underline{H}_2O$), 4.74 (1H, dd, *J* 9.4 and 4.4, H(2)), 6.48 (1H, bs, NH); δ_C (100 MHz, $CDCl_3$) 14.1 ($\underline{C}H_3CH_2O$), 27.8 (($\underline{C}H_3)_3CO$), 31.4 (C(3)), 32.8 (C(1′)), 39.6 (C(2′)), 53.8 (C(4)), 56.9 (C(2)), 61.8 ($CH_3\underline{C}H_2O$), 84.1 (($CH_3)_3\underline{C}O$), 149.0, 171.5, 172.1, 174.9 (C═O); **HRMS**: [M+Na$^+$.] Calculated for $C_{15}H_{22}N_2NaO_6$: 349.1370, Found: 349.1370.

Data for 20. R_f 0.53 [EtOAc]; $[\alpha]_D^{22}$ +5.6 (c = 0.5 in CH_2Cl_2); ν_{max}/cm^{-1} (thin film) 3355 (bm), 2980 (bm), 1710 (bm), 1513 (bm), 1368 (s); δ_H (400 MHz, $CDCl_3$) 1.19–1.33 (6H, m, $C\underline{H}_3CH_2O$), 1.41 (9H, s, $(C\underline{H}_3)_3CO$), 2.04–2.18, 2.52–2.68 (4H, m, H H(3) and $C\underline{H}_2CH_2NH_2$), 3.28–3.40, 3.44–3.58 (2H, m, $C\underline{H}_2NH_2$), 4.04–4.27 (4H, m, $CH_3C\underline{H}_2O$), 6.71, 6.59 (2H, bs, NH_2); δ_C (100 MHz, $CDCl_3$) 14.0 ($\underline{C}H_3CH_2O$), 28.2 (($\underline{C}H_3)_3CO$), 34.9 (C(3)), 36.0 ($\underline{C}H_2CH_2NH_2$), 40.0 ($\underline{C}H_2NH_2$), 50.7 (C(2)), 53.2 (C(4)), 61.5 ($CH_3\underline{C}H_2O$), 61.9 ($CH_3\underline{C}H_2O$), 80.0 (($CH_3)_3\underline{C}O$), 155.21, 160.0, 160.7, 172.1 (C═O); **HRMS**: [M+Na$^+$.] Calculated for $C_{17}H_{28}N_2NaO_7$ 395.1789, Found: 395.1785.

Single crystal X-ray diffraction data were collected at low temperature[72] for **3a** and **4b** on a Nonius Kappa CCD diffractometer.[73] Both structures were solved using SIR92[74] and refined using the CRYSTALS software suite[75] as per the ESI† (CIF file). The Flack *x* parameter[76] for **3a** refined to −0.6(16),

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however analysis of the Bijvoet pairs to gave a Hooft *y* parameter[77] of –0.4(5) giving a 97.6% probability that the structure is the correct hand (assuming enantiopurity).[78] Similarly, the Flack *x* parameter[76] for **4b** refined to 0.7(11), however analysis of the Bijvoet pairs to gave a Hooft *y* parameter of 0.0(5) giving a 91.3% probability that the structure is the correct hand (given enantiopurity).[77] In the absence of a strong anomalous signal, the Friedel pairs were merged for the final refinement for both structures. Crystallographic data (excluding structure factors) have been deposited with the Cambridge Crystallographic Data Centre (CCDC 814550 & 814551†) and copies of these data can be obtained free of charge *via* www.ccdc.cam.ac.uk/data_request/cif.

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