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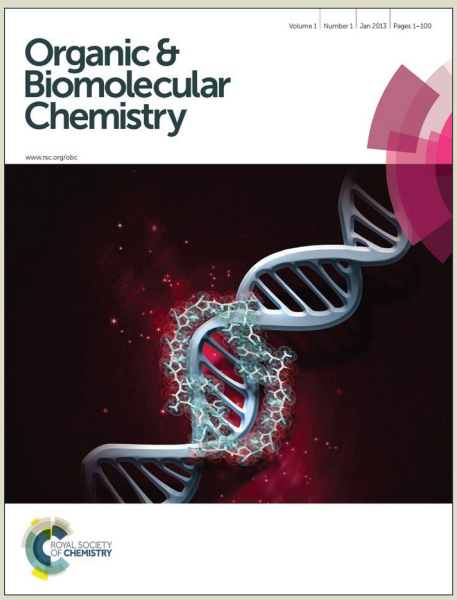

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Uncatalysed diaryldiazo cyclopropanations on bicyclic lactams: access to annulated prolines

Lawrence Harris, Martin Gilpin, Amber L. Thompson, Andrew R. Cowley and Mark G. Moloney*

The Department of Chemistry, Chemistry Research Laboratory, The University of Oxford, 12 Mansfield Road, Oxford. OX1 3TA.

GlaxoSmithKline Research & Development Ltd, New Frontiers Science Park, Third Avenue, Harlow, Essex, CM19 5AW.

Abstract: The uncatalysed cycloaddition of substituted diaryldiazo compounds onto bicyclic unsaturated lactams derived from pyroglutamic acid efficiently leads to highly functionalised azatricyclononanes. The products are readily elaborated to deprotected pyroglutamate derivatives, providing rapid access to conformationally constrained amino acids and their analogues. Preliminary assessment of antibacterial activity against one Gram positive and one Gram negative organism indicated high levels of efficacy in some cases.

Conformationally constrained amino acid analogues (CCAAs) have attracted considerable interest over recent years for their applications in pharmacologically active compounds,[1-3] and especially for peptidomimetics[4-7] and neurotransmitters.[3, 8-10] Key reasons are that their well-defined conformation is likely to suffer a lower entropic cost upon binding to the target receptor, and this is often coupled with a greater degree of selectivity/potency[1] and metabolic stability.[3, 10] Moreover, different conformationally constrained analogues of the same parent ligand may show selectivity to different receptors or receptor subtypes,[9, 11] and as a result, spirocyclic systems for example have become very important.[12] Cyclopropanes are popular conformationally restricted spirocyclic motifs, and for this reason the development of novel methodology for cyclopropanation processes has been of significant recent interest.[13] Cyclopropanation of electron deficient alkenes under catalysed[14-19] or uncatalysed conditions[20-24] leading to the synthesis of contiguous chiral centres[25] and hindered systems[26] has become widely available. We have shown that bicyclic lactams derived from pyroglutamic acid provide useful scaffolds for modification of the ring periphery by cycloaddition reactions,[27] as well as nucleophilic additions of organometallics[28, 29] and amines,[30] and of interest was whether this approach could be extended to include cyclopropyl-

annulated structures, especially since such systems have become of significance as GluR agonists/antagonists.[29] Recent work by Madalengoitia has accessed such systems using sulfur ylid additions,[31-35] but we report here that azabicyclo[3.1.0]hexanes may also be formed by direct stereoselective cyclopropanation of bicyclic lactams **1a,b** (Scheme 1) using substituted diaryldiazomethanes **2a-d** and 9-diazo-9*H*-fluorenes **3a-f** (Figure 1) under thermal conditions; some of this work has appeared earlier in preliminary form.[36]

The required diaryldiazo compounds **2a-d** and **3a-f** were easily generated either by conversion of the corresponding ketone to the hydrazone followed by yellow mercuric oxide oxidation, or to the tosylhydrazone followed by basic elimination.[37] They are highly coloured crystalline solids or viscous oils, readily storable at 0 ^{o}C, which only decompose at elevated temperature.[38] These compounds were reacted with unsaturated lactams **1a,b**, prepared as previously reported (Scheme 1 and Table 1);[27, 29] earlier work has shown that **1b** is significantly more reactive than **1a** as a result of the presence of the additional electron withdrawing group.[39] In an initial investigation, reaction of enone **1a** with diphenyldiazomethane **2c** in acetone solvent at reflux gave cyclopropane **4a** in 23% yield, along with the olefin product **6a**, in 26% yield; however, the reaction was sluggish, and did not go to completion even after 1 week (Table 1, entry 1). Pyrazoline **5** was also obtained in 26% yield, which although indefinitely stable at room temperature, upon heating at reflux in toluene quantitatively yielded cyclopropane **4a**; the alternative regiosisomeric pyrazoline was not isolated. Pyrazoline formation, but not cyclopropanation, has been reported using a similar approach in related systems,[40, 41] and DABCO-promoted synthesis of pyrazoles directly from tosylhydrazones and nitroalkenes is known.[42] By contrast, similar reaction of diazofluorene **3a** was much more efficient, giving cyclopropyl adduct **7a** in good yield (66%) as the only isolable product, although the analogous dibromo derivative **3b** gave only a very low return of the expected product **7b** (Table 1, entries 2 and 3). The *exo*-stereochemistry of the isolated cyclopropane products **156/4a** and **159/7a** was confirmed by single crystal X-ray analysis (Figure 2)[43] but similar confirmation of the structure of **5** was not possible, since satisfactory crystals could not be obtained. Similar carbene additions to fullerenes[44] and of heteroaryl carbenes[38] are known.

However, this process was found to be much more efficient when applied to activated enone **1b** (Scheme 1 and Table 1, entries 4-13), giving the expected cyclopropanation product**s 4b-e** and **8a-f** as single diastereomers in good yield, even though the starting compound is very prone to dimerisation to give adduct **10**.[27] Of interest is that the increase in electron density of the diazo series **2a→2d** gives significantly increased yields of

cyclopropane adducts (Table 1, entries 4-7), and that in some cases these were obtained along with products of type **6**, although the corresponding fluorenyl derivatives **9** were not observed. In this case, the use of room temperature or refluxing acetone conditions was dictated by the stability of the diazo compound partner. These reactions were found to be significantly faster than for lactam **1a**, and no pyrazoline adducts analogous to **5** were isolated. In contrast to the series of substituted diphenyldiazomethanes, reaction of **1b** with a range of substituted diazofluorenes furnished the product cyclopropanes exclusively (Scheme 1 and Table 1, entries 8-13). Significantly, with unsymmetrical diazo compounds **3b,c,e**, two diastereomeric *exo*-cyclopropanes were obtained in unequal amounts (Table 2, entries 9, 10, 12) although their separation required lengthy chromatography. The best yields were obtained with relatively electro-neutral diazo compounds **3a,b** and **3e**, while a slight decrease is observed for the 2- and 2,7-substituted bromo-derivatives **3c,d** and the most electron deficient diazo compound, **3f**, produced the lowest yield. In the literature, diazo **3f** is reported to be unstable,[45] but after two days exposure to the reaction conditions, it was possible to isolate a portion of the unreacted diazo compound after column chromatography of the reaction mixture. The *exo*-stereochemistry of the structures **8c**, **8d** and **8e'** was assigned in several cases using NOE analysis (Figure 3). The two non-crystalline diastereomers **8b,b'** were separable but were distinguishable by ^{1}H NMR spectroscopy only with difficulty. Assignment of stereochemistry in this case required a series of NOE and TOCSY experiments (Figure 3), utilizing firstly, the existence of the key NOE enhancement observed *via* irradiation of the δ3.5 singlet for H-6 to identify the proximal aromatic hydrogen, secondly NOE from the aromatic CH_2OH to flanking *o*-hydrogens, and finally a TOCSY spectrum to identify which of the three possible aromatic rings on which these hydrogens were located. Moreover, of interest was that in the ^{1}H NMR spectra, the signal at *ca.* δ3.5, diagnostic of cyclopropyl H-6, always occurs as a singlet as a result of its orthogonality to *H*-5; a similar feature has been previously reported by Hendrata *et al.*[46] This stereochemical assignment was confirmed for products **4c-e**, **8a**, **8d** and **8e'**[24] by single crystal X-ray analysis (Figure 2),[43] and would appear to be a sterically preferred outcome, since the concave nature of the original template **1b** clearly hinders that face. This analysis also clearly shows the proximity between H-6 of the lactam bicycle and the aromatic protons of the substituted cyclopropanes **4a** and **4c-e**, as was often detected by nOe analysis.

In contrast to the reactivities of diaryldiazomethanes and fluorenyldiazomethanes towards **1b**, ethyl diazoacetate **11a** furnished the 2-pyrazoline **12**, which is presumably the

most stable tautomer, and whose regiochemistry was established on the basis of careful analysis of ^{13}C shift data (Scheme 1). This is a similar outcome to the cycloaddition reaction with 4-naphthoxybutenolide.[25] However, diazomalonates **11b** and **11c** gave no such reaction, even when used as the solvent, and only dimer **10** was formed.

Table 1: Products and yields from the reaction according to Scheme 1.

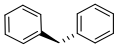
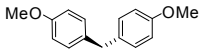
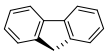
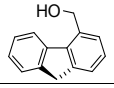
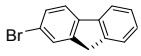
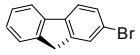
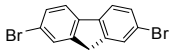
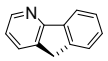
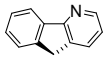
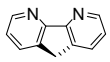
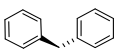
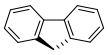
Entry	Substrate	Diazo compound	Conditions[a]	Substituents	Product(s) (Yield,%)
1	**1a**	**2c**	A	X = H	**4a** (23); **5**(26); **6**a(26)
2	**1a**	**3a**	A	A = D = H, B = C = CH	**7a** (66)
3	**1a**	**3c**	A	A = D = Br, B = C = CH	**7b** (<5)
4	**1b**	**2a**	A	X = NO_2	**4b** (0)[b]
5	**1b**	**2b**	A	X = I	**4c** (19)[b]
6	**1b**	**2c**	A	X = H	**4d** (29); **6d** (46)
7	**1b**	**2d**	B	X = OMe	**4e** (64); **6e** (16)
8	**1b**	**3a**	A	A = D = H, B = C = CH	**8a** (95)
9	**1b**	**3b**	A	A = D = H, B = C(CH_2OH), C = CH	**8b** (36)
				A = D = H, B = CH, C = C(CH_2OH)	**8b'** (36)
10	**1b**	**3c**	A	A = Br, B = C = CH, D = H	**8c** (45)
				A = H, B = C = CH, D = Br	**8c'** (24)
11	**1b**	**3d**	A	A = Br, B = C = CH, D = Br	**8d** (64)
12	**1b**	**3e**	A	A = D = H, B = N, C =CH	**8e** (58)
				A = D = H, B = CH, C = N	**8e'** (39)
13	**1b**	**3f**	A	A = D = H, B = C = N	**8f** (41)
14	**1b**	**11a**	A	A = H, B = CO_2Et	**12** (74)
15	**1b**	**11b**	A	A = B = CO_2Me	-[b]
16	**1b**	**11c**	A	A = Ph, B = CO_2Et	-[b]

[a] Conditions: A, refluxing acetone; B, acetone at room temperature; [b]Dimer **10** isolated

The oxazolidine ring of these cyclopropanes could be deprotected in high yields (Table 2), using TFA (10 equiv.) with an equivolumetric amount of water and DCM as solvent, although reactions were often slow and needed vigorous conditions and/or longer reaction times to allow complete consumption of starting material. All products (**13a-l**) maintained the characteristic singlet H-3 in the range δ 3.10-3.66 ppm in their ^1H NMR spectra derived from H-6 of their parent cyclopropanes, clearly indicating that the *exo*-cyclopropane survived the deprotection procedure. Noteworthy was that all deprotected compounds **13a-l** were only sparingly soluble in DCM and $CHCl_3$, in contrast to their parent

cyclopropanes, which were all highly soluble. Several were crystalline solids and single X-ray crystallographic analysis of **13a** and **13c** confirmed the expected *exo*- stereochemistry (Figure 4),[43] which also showed that the aryl ring systems of phenyl analogue **13a** are orthogonal to the coplanar arrangement enforced in fluorene analogue **13c.**

Table 2: Yields of Deprotected Products (Scheme 2) and ^{1}H NMR Shift of *H*3

Lactam	R	Ar^1 Ar^2	Product	Yield/%	δ(*H*3)/ppm
4d	EtO_2C		**13a**	78	3.38
4e	EtO_2C		**13b**	80	3.10
8a	EtO_2C		**13c**	92	3.14
8b'	EtO_2C		**13d**	32	3.34
8c	EtO_2C		**13e**	72	3.14
8c'	EtO_2C		**13f**	58	3.15
8d	EtO_2C		**13g**	0 (**13e**, 59%)	-
8e	EtO_2C		**13h**	76	3.51
8e'	EtO_2C		**13i**	67	3.49
8f	EtO_2C		**13j**	96	3.66
4a	H		**13k**	73	d 2.54
7a	H		**13l**	93	d 2.75

However, the deprotection of some cyclopropanes gave different behaviour. For example, the basicity of the aza-fluorene moiety clearly had an effect on the ease of the *N*,*O*-acetal hydrolysis, since aza-fluorene compounds **13h,i** and bipyridine **13j** all required a greater number of equivalents (20-30 equiv.) of TFA for their efficient production from starting material. Additionally, purification of azafluorenes **13h-j** by washing out impurities with

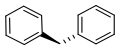
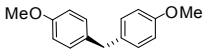
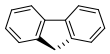
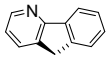
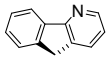
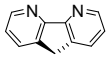
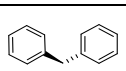
EtOAc, rather than column chromatography, was more effective. Of particular interest was that 2',7'-dibromo-fluorenyl cyclopropane **8d** did not give the expected product **13g**, but instead gave mono-debrominated diastereoisomer **13e** as the major product in 59% yield, in which the departing bromine atom was the one at ArC(7') (structure established by mass spectrometry, ^{1}H and ^{13}C NMR analysis, and the stereochemistry was elucidated by NOE analysis (Table 2 and Scheme 2)). Of interest is that in Suzuki chemistry, the bromine substituents of dibromofluorenes are notoriously labile,[47] and it is possible that a trace impurity of metal in the deprotection of the the di-bromo substituted cyclopropane **8d** effected the unwanted debromination. By comparison, deprotection of the two mono-bromo diastereomers **18c** and **18c'** gave the corresponding deprotected products **13e** and **13f** in good yield.

Conversion of these derivatives to the pyroglutamate products was investigated; both **13c** and **13l** were subjected to PDC oxidations and direct esterification (Scheme 2) to furnish the desired products **14a** and **14b** but in poor yields of 37 and 28% respectively, and attempted optimization with other oxidants (ruthenium tetroxide, chromic oxide) gave no improvement. When these conditions were applied to diphenyl **13a**, surprisingly fluorenyl derivative **14a** was obtained in 29% yield, and none of the expected product diphenyl product was obtained. Similar oxidative cyclodehydrogenation reactions has been reported in electron rich polyaromatic systems in the presence of $FeCl_3$.[47-49] and more recently such transformations have been shown to have synthetic value.[50-52] Swern oxidation was attempted in order to avoid this, but instead of giving the aldehyde directly, dimer **15** was obtained in 66% yield; single crystal X-ray analysis of **16** allowed determination of the stereochemistry (Figure 4) and indicated that the central six-membered diketopiperazine ring adopts the boat conformation.[43] Although this type of dimerisation had been previously reported,[39] the stereochemistry of the observed product was unknown. Ester hydrolysis of the pyroglutaminols was also investigated following a literature procedure;[53] diaryl-cyclopropane **13b,** fluorenyl-cyclopropane **13c**, azafluorenyl **13i** and diazafluroenyl **13j** derivatives all furnished **16** and **17a-c** in excellent yield (Scheme 2). The glutamic acid and proline analogues **18a** and **18b** were also readily obtained by similar hydrolysis of the respective di- and mono-esters **14a** and **14b** (Scheme 2). In the case of the deprotection of hydroxymethyl **8b'**, the desired product **13d** was isolated in only poor yield (38%) and this was very unsatisfactory given the difficulty of separating **8b** and **8b'**. Alcohol **8b** was therefore subjected to a TEMPO-catalysed oxidation,[54] followed by methylation *via* diazomethane, and found to yield methyl ester **19a** quantitatively and cleanly (Scheme 3). Applying these

conditions to the mixture of diastereomers **8b** and **8b'** gave easily separable diastereomers **19a,b** in quantitative yield, and these in turn could be easily deprotected under acidic conditions in excellent yields to give products **20a** and **20b** respectively (Scheme 3).

In order to access pyrrolidine systems, reduction of bicyclic lactam **8a** with lithium aluminium hydride gave diol **21a** in 73% yield after column chromatography (Scheme 4) although this product was found to decompose on standing; immediate double Swern oxidation furnished the di-aldehyde **21b** in 88% yield after column chromatography. The two proton signals at 9.65-9.85 ppm corresponding to each of aldehydes at C(2) and C(4) and the corresponding aldehydic carbon signals could also be clearly seen in the ^{13}C NMR spectra. However, a pure sample of dialdehyde **21b** was even less stable than the parent diol precursor (**21a**), and degraded within a matter of hours in air at room temperature. Selective simultaneous oxidation of both aldehyde groups with $NaClO_2$ did not produce diester **22** as the major product of this reaction but instead gave lactam **23** in low yield (12%).

Table 3: Yields of BOC Protected Alcohols (Scheme 5)

Substrate		**Product**		**By-product**
R = EtO_2C		**R = CH_2OH**	**Yield(/%)**	
13a		**24a**	64	**25a** Trace
13b		**24b**	39	**25b** Trace
13c		**24c**	48	**25c** Yes (50%)
13h		**24d**	41	**25d** Yes(impure)
13i		**24e**	22	**25e** Yes (22%)
13j		**24f**	0	-
Substrate		**Product**		**Starting material observed**
R = H		**R = H**	**Yield(/%)**	
13k		**24g**	82	-

An alternative approach was therefore sought, and although reaction of pyroglutaminol **13c** with $LiAlH_4$ followed by BOC protection gave the product aminodiol **24c** in poor (12%) yield, a better approach was found to be diborane reduction followed by BOC-derivatisation, which for **13a-c,h-j** successfully gave the fully reduced diols **24a-f** (Scheme 5 and Table 3), often along with under-reduced lactams **25a-f**. However, lactam **13j** yielded no product after workup from its reduction, possibly due to its polarity. In contrast to the mediocre yields of **13**, reduction of the diphenyl-substituted **13k** proceeded relatively cleanly to give **24g** in an 82% yield and no starting material was observed or recovered after 2 days under the reaction conditions. In all cases, rotameric equilibration in the NMR spectra was evident, and to confirm this, both ^{1}H and ^{13}C NMR spectra of diol **24c** were obtained at 383 K in *d*-6 toluene as a solvent; separated rotameric peaks were seen to have partially coalesced in the ^{1}H NMR spectrum while no rotameric doubling was observed in the ^{13}C NMR spectrum at this temperature.

TEMPO-catalysed oxidation of diol **24c** (Scheme 5), followed by direct column chromatography eluting with DCM/MeOH/AcOH (90:5:4), gave diacid **26a** after chromatography. However, for ease of purification and characterisation, diacid **26**a was immediately converted to the dimethyl-ester **26b** with diazomethane, which was easily obtained from column chromatography in yields varying from 34-65%, and re-converted to pure diacid **26a** by near-quantitative alkaline hydrolysis (96%). Exposure of diacid **26a** to dry TFA in DCM for 3 hours gave clean deprotection to give diacid **27** in 59% yield. However, application of these TEMPO conditions to diaryls **24a** and **24b** gave complete consumption of starting material but no concomitant formation of the expected products, while **24d** led to mostly recovered starting material (79%), although use of excess quantities of oxidising reagents gave not only the desired product **28a** in only 4% yield, but also C(2)-*mono*-oxidised **28b** in a 30% yield after column chromatography, and a trace quantity (<2%) of C(4)-*mono*-oxidised **28c** (Scheme 6). This product distribution implies that oxidation of the C(4)-primary alcohol of diol **24d** is slower than oxidation of the C(2)-primary alcohol. Similar oxidation of diastereoisomer **24e** yielded an analogous result, although only the C(2) *mono*-oxidised product **28e** was isolated with a significant yield (7 %). On the premise that slower oxidation of $C(4)CH_2OH$ was likely, it was expected that the attempted single oxidation of the C(2)-primary alcohol of proline-analogue precursor **24g** would give a cleaner result (Scheme 7); in fact, ester **29a** was obtained in 68% yield after column chromatography. Near quantitative hydrolysis, furnishing acid **29b** and subsequent BOC-deprotection (*via* HCl in dry ether) yielded the final proline templated **29c**.

Bioassay Studies

Many of the pyroglutaminols **13**, and their derivatives, showed significant activity in hole-plate assay against *S. aureus* and *E. coli* (Table 4, ESI), in which assessment is made by measuring the diameter of the zone of inhibition after overnight incubation, using cephalosporin c as a positive control.[55] Although not providing full Minimum Inhibitory Concentration data, this method provides a useful preliminary assessment of antibacterial activity. Both fluorenyl containing alcohols **13c** and **13l** and diacid **18a** (entries 1, 2 and 5 respectively) were very active against *S. aureus*, while mono acid **18b** and mono-bromo **13e** (entries 6 and 8 respectively) were very active against *E. coli*. Remarkably, the alternative mono-bromo diastereoisomer **13f** (entry 7) was inactive, as were all of the phenyl analogues (entries 13-16). Of interest is the relative activity of the fluorenyl systems compared to the inactivity of the phenyl analogues (entries 13-16). A possible structural reason for these activities is the planar aromatic ring systems for the fluorenyl analogues, whereas the gem-diphenyl system is non-planar (as observed in the crystal structures, Figures 2 and 3).

Reaction Mechanism

Mechanistically, the cyclopropanation reaction may proceed via carbene (singlet or triplet) insertion or cycloaddition processes (pyrazoline formation) followed by extrusion of nitrogen (Scheme 8, Paths A and B). The former seems unlikely since the majority of reactions are conducted with excess diazo compound in refluxing acetone, well below the decomposition temperature for diazofluorene and diphenylmethyldiazo compounds (decomposition is reported at >120^{o}C, and some are stable even to >165^{o}C[37]), and for the more stable diazo compounds **3c** and **3e**, the reaction could even be conducted at room temperature. For lactam **1b**, there is also the possibility of dimerisation (Path C). The diazo compound **2** and **3** are also prone to conversion to the azine (Path D), and Huisgen *et al.* [56] gives the half life ($t_{1/2}$) of self-decomposition (Path E) of diphenyldiazomethane (**2c**) (one of the least stable diazo compounds used in solution) in a DMF solution of 72 days at 25 ^{o}C and 10 days at 40 ^{o}C. The rate of formation of carbenes derived from the more stable diazofluorenes (*via* Path E) at room temperature (20 ^{o}C) would therefore seem to be negligible, and in the cases of **3a-d** and **3e-f**, unreacted diazo compound could even be isolated pure from the reaction mixture after column chromatography. Therefore, diazofluorenes would most likely yield cyclopropanes by initial pyrazoline formation from 1,3-dipolar cycloaddition with enones **1a** and **1b** (Path A)

followed by extrusion of N_2 (Path F). Furthermore, the rate of reaction of enone **1b** is greater than **1a**, consistent with a concerted pathway giving the pyrazoline products **30** and **31** which immediately collapse leading to the formation of the observed products **33** and **34** (Path F). In the case of **1a**, both pyrazolines are formed, only one of which immediately collapses to the products **33** and **34**, and the other (**30**), which can easily be isolated, only does so at elevated temperature. The collapse of pyrazolines to cyclopropanes has been investigated in detail,[57-59] and the formation of both pyrazoline and cyclopropyl products have been observed in the reactions of diazo compounds with unsaturated maleimide systems.[60] The rates of such 1,3-dipolar cycloadditions for a series of diaryldiazo compounds were found to be largely governed by the HOMO(diazomethane)-LUMO(dipolarophile) interaction.[56, 61] Diphenyldiazomethane is a nucleophilic 1,3-dipole[61-63] which reacts preferentially with electrophilic C=C bonds, and the rate of reaction increases when the dipolarophile becomes more electron deficient. This is reflected in relative reaction rates, and for example, in the reaction of diazofluorene (**3a**), 2-bromodiazofluorene (**3c**) and 2,7-dibromodiazofluorene (**3d**) with both **1a** and **1b**, yields and rates are typically: **8a** (95%, 1-2 days), **8c** and **8c'** (69%, 2 days), **8d** (64%, 3 days), **7a** (66%, 1 week), and **7b** (<5%, 3 weeks). Increased steric hindrance in the transition state might also account for the observed selectivity of 45 : 24 (*approx*. 2 : 1) for **8c** : **8c'**. The collapse of 1-pyrazolines to give cyclopropane and alkene products has been the subject of a number of investigations, and the product distributions are a combination of steric and electronic effects.[57-59] Amongst the mechanisms for thermal collapse of pyrazoline adducts, the formation of a (90,90) trimethylene intermediate[64-67] has been proposed and is used to explain the general retention of stereochemistry of the initial pyrazoline. The stepwise or concerted formation of similar diradical species has also been investigated,[68] and Nakano *et al.*[64] found that the thermal stability of a series of pentasubstituted 1-pyrazolines increased with variation of the diazo substitution in the order fluorenyl < diphenyl < phenylmethyl < dimethyl. The abnormal stability of certain pyrazolines has been attributed to the inhibition of conformations which are favourable for decomposition.[69] Thus, it seems that fluorenyl-spiro-cyclopropanes **8a-8f** are likely to form *via* (90,90) trimethylene intermediates, from rapid collapse of their respective pyrazoline adducts (Path F), which must all be unstable at or above room temperature.

Conclusion

We have demonstrated that direct cyclopropanation of electronically activated unsaturated pyrrolidinones using diaryl diazo compounds allows stereoselective access to

conformationally well-defined tri- and tetracycloannulated cyclopropyl systems in high yield, some of which exhibit high levels of antibacterial activity. Given the renaissance of interest in the use of pyroglutamates as structurally well-defined building blocks and in drug discovery,[70-72] this approach demonstrates that escape from flatland is readily achieved using modular chemistry for the generation of 3D templates and scaffolds[73] for rapid library construction.[74, 75]

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Experimental

For general experimental procedures, see our earlier report.[76] (2*R*,5*S*)-1-Aza-3-oxa-8-oxo-2-phenyl-bicyclo-[3.3.0]oct-6-ene **1a** and (2*R*,5*S*)-1-aza-7-ethyloxycarbonyl-3-oxa-8-oxo-2-phenyl-bicyclo-[3.3.0]oct-6-ene **1b w**ere prepared using literature methods.[27]

(2*R*,5*S*,6*S*,7*S*)-1-Aza-2,9,9-triphenyl-8-oxo-3-oxa-tricyclo[4.3.0^{1,5}.0^{6,7}]-nonane 4a, (3a*S*,6*R*,8a*R*,8b*S)*-3,3,6-triphenyl-7-oxa-3,3a,6,7,8,8a-hexahydropyrazolo[3,4-a] pyrrolizin-4(8bH)-one 5 and (2*R*,5*S*)-1-aza-6-benzhydryl-8-oxo-2-phenyl-3-oxa-bicyclo[3.3.0]oct-6-ene 6a

A mixture of **2c** (282 mg, 1.45 mmol) and **1a** (288 mg, 1.43 mmol) in acetone (15 mL) was purged with N_2 before being heated to reflux and left for 3 d. The mixture was concentrated *in vacuo* to give a viscous red oil which was purified by column chromatography over silica eluting with EtOAc/Petrol (1 : 7 → 1 : 5) to give (in order of elution) **6a** as a yellow oil (138 mg, 26%), **4a** as a white powder (120 mg, 23%) and **5** as a white solid (146 mg, 26%).

6a; R_f = 0.36 (EtOAc/Petrol, 1 : 3); $[\alpha]_D^{21}$ +69.6 (c = 1.0, $CHCl_3$); υ_{max}/cm^{-1} (film) 3017, 1702 (C=O), 1495, 1452, 1334, 1217, 1030, 756, 702, 667; δ_H(400.2 MHz; $CDCl_3$) 3.28 (1H, t, *J* 8.3, C(4)*H*H), 3.71 (1H, dd, *J* 6.9, 8.2, C(4)H*H*), 4.49-4.54 (1H, m, C(5)*H*), 5.01 (1H, s, C*H*Ph_2), 5.73 (1H, t, *J* 1.3, C(7)*H*), 6.16 (1H, s, C(2)*H*), 7.18-7.25 (4H, m, Ar*H*), 7.27-7.40 (9H, m, Ar*H*), 7.48-7.52 (2H, m, Ar*H*); δ_C(100.6 MHz; $CDCl_3$) 52.7 (*C*HPh_2), 66.1 (*C*(5)),

68.3 (*C*(4)), 87.2 (*C*(2)), 125.4 (*C*(7)), 126.1 (Ar*C*H), 127.6 (*p*-Ar*C*H), 127.6 (*p*-Ar'*C*H), 128.4 (Ar*C*H), 128.5 (*p*-Ar*C*H), 128.6, 128.7, 128.9, 129.0 (all Ar*C*H), 138.8, 139.4, 139.5 (all Ar*C*), 166.8 and 177.0 (*C*(6) and (*C*=O)); *m/z* (ESI+) 426 ($[M+MeCN+NH_4]^+$, 100%);

4a; R_f = 0.25 (EtOAc/Petrol, 1 : 3); m.p. 180 °C (dec.); $[\alpha]_D^{18}$ +78.3 (c = 1.0, $CHCl_3$); υ_{max}/cm^{-1} (film) 1704 (C=O); δ_H(400.2 MHz; $CDCl_3$) 2.80 (1H, ddd, *J* 1.1, 2.4, 6.1, C(6)*H*), 2.86 (1H, dd, *J* 2.2, 6.2, C(7)*H*), 3.59 (1H, ddd, *J* 2.5, 7.6, 9.8, C(4)*H*H), 3.75-3.83 (1H, m, C(5)*H*), 4.14-4.19 (1H, m, C(4)H*H*), 6.21 (1H, s, C(2)*H*), 6.46 (2H, d, *J* 7.5, Ar*H*), 7.05-7.09 (2H, m, Ar*H*), 7.12-7.45 (9H, m, Ar*H*), 7.51-7.53 (2H, m, Ar*H*); δ_C(100.6 MHz; $CDCl_3$) 31.9 (*C*(7)), 36.6 (*C*(6)), 43.2 (*C*(9')), 58.5 (*C*(5)), 68.5 (*C*(4)), 86.7 (*C*(2)), 125.4, 127.0, 127.1, 127.4, 128.0, 128.0, 128.7, 129.1, 129.9 (all Ar*C*H), 136.9, 138.4, 143.0 (all Ar*C*), 176.3 (*C*=O); HRMS 368.1643 ($[M+H]^+$, $C_{25}H_{22}NO_2$ requires 368.1645); Found C, 82.31; H, 5.37; N, 3.89 % ($C_{25}H_{21}NO_2$ requires C, 81.72; H, 5.76; N, 3.81 %);

5; R_f = 0.19 (EtOAc/Petrol, 1 : 3); m.p. 180 °C (dec.); $[\alpha]_D^{21}$ +565.5 (c = 1.0, $CHCl_3$); υ_{max}/cm^{-1} (film) 1716 (C=O); δ_H(400.2 MHz; $CDCl_3$) 3.66 (1H, t, *J* 8.7, C(4)*H*H), 3.87 (1H, d, *J* 8.8, C(7)*H*), 4.21 (1H, ddd, *J* 2.4, 6.7, 8.9, C(5)*H*), 4.48 (1H, dd, *J* 6.7, 8.0, C(4)H*H*), 5.53 (1H, dd, *J* 8.8, C(6)*H*), 6.22 (1H, s, C(2)*H*), 6.96-7.00 (4H, m, Ar*H*), 7.25-7.31 (6H, m, Ar*H*), 7.36-7.41 (1H, m, Ar*H*), 7.43-7.44 (2H, m, Ar*H*), 7.70-7.74 (2H, m, Ar*H*); δ_C(100.6 MHz; $CDCl_3$) 52.0 (*C*(7)), 59.2 (*C*(5)), 69.7 (*C*(4)), 86.8 (*C*(2)), 90.9 (*C*(6)), 105.1 *C*Ph_2), 125.4, 127.2, 127.5 (all Ar*C*H), 128.1 (*p*-Ar*C*H), 128.2, 128.2 (both Ar*C*H), 128.3 (*p'*-Ar*C*H), 128.4 (*p''*-Ar*C*H), 128.9 (Ar*C*H), 137.7, 139.0, 140.3 (all Ar*C*), 174.9 (*C*=O); HRMS 396.1707 ($[M+H]^+$, $C_{25}H_{22}N_3O_2$ requires 396.1707).

(2*R*,5*S*,6*S*,7*S*)-Spiro[1-aza-3-oxa-8-oxo-2-phenyl-tricyclo[4.3.0^{1,5}.0^{6,7}]nonane-9,9'-fluorene] 7a

A mixture of **3a** (771 mg, 4.01 mmol) and **1a** (251 mg, 1.25 mmol) in acetone (25 mL) was purged with N_2 before being heated to reflux and left for 16 h. The mixture was concentrated *in vacuo* to give a red solid. The red solid obtained was passed through a plug of silica, eluting with DCM/Petrol (2 : 3) to remove the excess of diazo **3a** and give a light brown solid which was purified by column chromatography over silica eluting with EtOAc/Petrol (1 : 5) to yield **7a** (302 mg, 65%) as a white solid; R_f = 0.20 (EtOAc/Petrol, 1 : 3); m.p. 153 ^oC; $[\alpha]_D^{21}$ +257.3 (c = 6.2, $CHCl_3$); υ_{max}/cm^{-1} (film) 3061, 1709 (C=O), 1449, 1343, 1221, 1159, 1027, 774, 749, 732, 716, 699; δ_H(400.2 MHz; $CDCl_3$) 2.98 (1H, d, *J* 6.1, C(7)*H*), 3.03 (1H, d, *J* 6.1, C(6)*H*), 3.83 (1H, t, *J* 8.6, C(4)*H*H), 4.22 (1H, dd, *J* 9.0, 6.4, C(5)*H*), 4.41 (1H, t, *J* 7.0, C(4)H*H*), 6.52 (1H, s, C(2)*H*), 6.91 (1H, d, *J* 7.7, Ar*H*), 6.98-7.04 (1H, m, Ar*H*), 7.26-7.51 (7H, m, Ar*H*), 7.57-7.61 (2H, m, Ar*H*), 7.78 (1H, d, *J* 7.5, Ar*H*), 7.81-7.85 (1H, m, Ar*H*); δ_C(100.6 MHz; $CDCl_3$) 35.5 (*C*(7)), 37.5 (*C*(6)), 39.2 (*C*(9)), 57.9 (*C*(5), 69.7 (*C*(4)), 88.6 (*C*(2)), 118.6, 119.8, 120.4, 123.7, 126.0, 126.0, 127.2, 127.5, 127.6, 128.6, 128.7 (all Ar*C*H), 138.5, 138.8, 140.3, 142.2, 145.5 (all Ar*C*), 174.8 (*C*=O); *m/z* (ESI+) 424 ($[M+MeCN+NH_4]^+$, 34%); HRMS 388.1308 ($[M+Na]^+$, $C_{25}H_{19}NNaO_2$ requires 388.1308).

(2*R*,5*S*,6*S*,7*S*)-2',7'-Dibromospiro[1-aza-3-oxa-8-oxo-2-phenyl-tricyclo[4.3.0^{1,5}.0^{6,7}] nonane-9,9'-fluorene] 7b

A mixture of diazo **3b** (320 mg, 0.91 mmol) and **1a** (123 mg, 0.61 mmol) in acetone (10 mL) was heated at reflux for 3 weeks (under an N_2 atmosphere) before being concentrated *in vacuo*. Column chromatography over silica gel eluting with EtOAc/Petrol (1 : 3) yielded a residue containing cyclopropane **161/7b** and other unidentified products (30 mg) after concentration. This residue was dissolved in EtOAc and the solution was allowed to evaporate slowly leaving crystalline **161/7b** (3 mg, 1%); R_f = 0.35 (DCM); υ_{max}/cm^{-1} (film) 1709 (C=O), 1451, 812; δ_H(500.3 MHz; $CDCl_3$) 3.04 (2H, s, C(6)*H* and C(7)*H*), 3.84 (1H, dd, *J* 8.0, 9.0,

C(4)*H*H), 4.24 (1H, dd, *J* 6.4, 9.0, C(5)*H*), 4.45 (1H, dd, *J* 6.4, 8.0, C(4)H*H*), 6.51 (1H, s, C(2)*H*), 7.06 (1H, d, *J* 1.6, ArC(1')*H*), 7.37-7.41 (1H, m, Ar*H*), 7.44-7.53 (4H, m, Ar*H*), 7.56-7.59 (2H, m, Ar*H*), 7.60 (1H, d, *J* 8.1, Ar*H*), 7.64 (1H, d, *J* 8.1, Ar*H*), 7.74 (1H, d, *J* 1.6, ArC(8')*H*); δ_C(125.8 MHz; $CDCl_3$; Me_4Si) 36.0, 37.6 (*C*(6) and *C*(7)), 38.8 (*C*(9')), 57.8 (*C*(5)), 69.5 (*C*(4)), 89.1 (*C*(2)), 121.2, 121.6 (both Ar*C*H), 121.6 (Ar*C*Br), 121.8 (Ar*C*Br), 122.2 (Ar*C*H), 125.9 (*p*-Ph*C*H), 126.9, 128.8, 129.0, 130.8, 131.0 (all Ar*C*H), 136.6, 138.3, 140.1, 142.0, 147.2 (all Ar*C*), 174.3 (*C*=O); *m/z* (ESI-) 522 ($[M-H]^-$, 78%); HRMS 521.9536 ($[M-H]^-$, $C_{25}H_{16}BrNO_2$ requires 521.9534).

(2*R*,5*S*,6*S*,7*R*)-1-Aza-9,9-di(*p*-iodophenyl)-7-ethoxycarbonyl-8-oxo-3-oxa-2-phenyl-tricyclo[4.1.0^{1,5}.0^{6,7}]nonane 4c

A solution of **2b** (370 mg, 0.83 mmol) and freshly prepared **1a** (223 mg, 0.82 mmol) in acetone (10 mL) was purged with N_2 before being heated to reflux and left for 16 h. The mixture was concentrated *in vacuo* to give a red oil which was purified by column chromatography over silica eluting with EtOAc/Petrol (1 : 5) to yield **4c** (106 mg, 19%) as a white crystalline solid; R_f = 0.23 (EtOAc/Petrol, 1 : 3); m.p. 200 ^oC (dec.); $[\alpha]_D^{21}$ -30.2 (c = 6.3, $CHCl_3$); υ_{max}/cm^{-1} (film) 1741 (C=O); δ_H(400.2 MHz; $CDCl_3$) 1.04 (3H, t, *J* 7.2, C*H*$_3$CH$_2$O), 3.44 (1H, s, C(6)*H*), 3.56-3.66 (2H, m, C(4)*H*H, C(5)*H*), 4.04 (2H, q, *J* 7.2, CH$_3$C*H*$_2$O), 4.21 (1H, dd, *J* 6.4, 5.1, C(4)H*H*), 6.23 (1H, s, C(2)*H*), 6.45-6.49 (2H, m, Ar*H*), 7.07-7.12 (2H, m, Ar*H*), 7.16-7.27 (5H, m, Ar*H*), 7.59-7.64 (2H, m, Ar*H*), 7.72 (2H, d, *J* 8.46, Ar*H*); δ_C(100.6 MHz; $CDCl_3$) 13.9 (C*H*$_3$CH$_2$O), 32.6 (*C*(6)), 46.2, 48.9 (*C*(4) and *C*(9')), 56.2 (*C*(5)), 62.0 (CH$_3$*C*H$_2$O), 68.4 (*C*(4)), 87.2 (*C*(2)), 93.4 (Ar*C*I), 93.8 (Ar*C*I), 125.3, 128.3, 128.4, 130.1, 130.9, 136.6, 137.8, 137.8, 137.9, 138.5, 164.4 and 171.2 (both (*C*=O)); *m/z* (ESI+) 750 ($[M+MeCN+NH_4]^+$, 100%); HRMS 713.9595 ($[M+Na]^+$, $C_{28}H_{23}NNaO_4$ requires 713.9609).

(2*R*,5*S*,6*S*,7*R*)-1-Aza-9,9-diphenyl-7-ethoxycarbonyl-3-oxa-8-oxo-2-phenyl-tricyclo [4.1.0^{1,5}.0^{6,7}]nonane 4d, and (*2R,5S*)-1-Aza-6-benzhydryl-7-ethoxycarbonyl-3-oxa-8-oxo-2-phenyl-bicyclo-[3.3.0]oct-6-ene 6d

A solution of **2c** (0.71 g, 3.7 mmol) and freshly prepared **1a** (0.98 g, 3.6 mmol) in acetone (25 mL) was purged with N_2 before being heated to reflux and left for 3 d. The mixture was concentrated *in vacuo* to give a yellow oil which was purified by column chromatography over silica eluting with EtOAc/Petrol (1 : 5) to yield **4d** (0.46 g, 29%) as a white powder and **6d** (0.60 g, 46%) as a pale yellow, viscous oil. Also obtained from the reaction was the azine of diphenyl diazomethane.

4d; R_f = 0.16 (EtOAc/Petrol 1 : 3); m.p. 177-179 ^oC; $[\alpha]_D^{21}$ +235.6 (c = 3.0, $CHCl_3$); υ_{max}/cm^{-1} (film) 1743 (C=O); δ_H(400.2 MHz; C_6D_6) 0.76 (3H, m, *J* 7.07, C*H*$_3$CH$_2$O), 3.11 (1H, s, C(6)*H*), 3.23-3.31 (2H, m, C(4)*H*H, C(5)*H*), 3.71 (1H, dd, *J* 6.19, 4.93, C(4)H*H*), 3.85 (2H, q, *J* 7.07, CH$_3$C*H*$_2$O), 6.49 (1H, s, C(2)*H*), 6.59-6.64 (2H, m, Ar*H*), 6.89-7.05 (9H, m, Ar*H*), 7.23-7.27 (2H, m, Ar*H*), 7.41 (2H, br s, Ar*H*); δ_C(100.6 MHz; $CDCl_3$) 13.7 (*C*H$_3$CH$_2$O), 33.0 (*C*(6)), 46.3 and 50.2 ((*C*(7) and (*C*(9)), 56.2 (*C*(5)), 61.5 (CH$_3$C*H*$_2$O), 68.4 (*C*(4)), 87.0 (*C*(2)), 125.3, 127.3, 127.6, 127.9, 128.0, 128.2, 128.5, 128.9, 129.1 (all Ar*C*H), 137.4, 138.1, 138.7 (Ar*C*), 164.7 and 171.8 (both *C*=O); *m/z* (ESI+) 901 ([2M+Na]$^+$, 100%), 499 ([M+MeCN+NH$_4$]$^+$, 52%); HRMS 462.1667 ([M+Na]$^+$, $C_{28}H_{25}NNaO_4$ requires 462.1676);

6d; R_f = 0.35 (EtOAc/Petrol, 1 : 3); $[\alpha]_D^{21}$ +195.3 (c = 1.0, $CHCl_3$); υ_{max}/cm^{-1} (film) 3020, 1745 and 1718 (C=O), 754, 702, 669; δ_H(400.2 MHz; C_6D_6; Me_4Si) 1.00 (3H, t, *J* 7.1, C*H*$_3$CH$_2$O), 2.62 (1H, t, *J* 8.5, C(4)*H*H), 2.88 (1H, dd, *J* 6.8, 8.5, C(4)H*H*), 4.01 (2H, m, CH$_3$C*H*$_2$O), 4.34 (1H, dd, *J* 6.8, 8.5, C(5)*H*), 6.15 (1H, s, C*H*Ph$_2$), 6.42 (1H, s, C(2)*H*), 6.90-6.94 (2H, m, Ar*H*), 7.01-7.29 (11H, m, Ar*H*), 7.74 (2H, d, *J* 7.4, Ar*H*); δ_C(100.6 MHz; C_6D_6) 13.9 (*C*H$_3$CH$_2$O), 50.4 (*C*HPh$_2$), 61.2 (CH$_3$*C*H$_2$O), 65.1 (*C*(5)), 68.4 (*C*(4)), 87.6 (*C*(2)),

126.5, 127.3, 127.9, 128.2 (all Ar*C*H), 128.5 (*C*(7)), 128.6, 128.6, 128.7, 129.0, 129.6 (all Ar*C*H), 139.7, 139.9, 140.4 (all Ar*C*), 162.2, 168.8, 172.3 (*C*(6) and 2 x (*C*=O)); *m/z* (ESI+) 498 ($[M+MeCN+NH_4]^+$, 100%); HRMS 440.1856 ($[M+H]^+$, $C_{28}H_{26}NO_4$ requires 440.1856).

(2*R*,5*S*,6*S*,7*R*)-1-Aza-9,9-di(*p*-methoxyphenyl)-7-ethoxycarbonyl-3-oxa-8-oxo-2-phenyl-tricyclo[4.1.0^{1,5}.0^{6,7}]nonane 4e and (*2R,5S*)-1-Aza-6-(*p,p'*-dimethoxy)benzhydryl-7-ethoxycarbonyl-3-oxa-8-oxo-2-phenyl-bicyclo-[3.3.0]oct-6-ene 6e

A solution of diazo **2d** (247 mg, 0.97 mmol) and **1b** (143 mg, 0.52 mmol) in acetone (5 mL) was degassed and stirred in an atmosphere of N_2 for 16 h at r.t. Then, EtOH (3 mL) was added and the mixture was heated at reflux for 4 h until the solution had turned yellow. Concentration *in vacuo* resulted in a yellow solid containing cyclopropane **4e** and olefin **6e**. Purification by column chromatography over silica gel eluting with EtOAc/Petrol (1:4→1:1) yielded cyclopropane **4e** (168 mg, 64%) as a crystalline white solid and olefin **6e** (41 mg, 16 %) as a yellow oil.

4e; R_f = 0.06 (EtOAc/Petrol, 1 : 4); m.p. 149 ^oC; $[\alpha]_D^{18}$ -69.7 (c = 1, $CHCl_3$); υ_{max}/cm^{-1} (film) 2957, 1738 (C=O), 1435, 1368, 1252, 1169, 1072, 1024, 880, 823, 781; δ_H(500.3 MHz; $CDCl_3$) 1.02 (3H, t, *J* 7.1, C*H*$_3$CH$_2$O), 3.44 (1H, s, C(6)*H*), 3.60-3.66 (2H, m, C(4)*H*H, C(5)*H*), 3.74 (3H, s, C'*H*$_3$O), 3.80 (3H, s, C*H*$_3$O), 3.94-4.05 (2H, m, CH$_3$C*H*$_2$O), 4.19 (1H, dd, *J* 11.3, 12.9, C(4)H*H*), 6.22 (1H, s, C(2)*H*), 6.49 (2H, d, *J* 7.7, *o*-Ph*H*), 6.76-6.79 (2H, m, Ar*H* (*o*- to OC'H$_3$)), 6.89 (2H, d, *J* 8.9, Ar*H* (*o*- to OCH$_3$)), 7.05-7.09 (2H, m, *m*-Ph*H*), 7.14-7.19 (1H, m, *p*-Ph*H*), 7.26-7.29 (2H, m, Ar*H* (*m*- to OC'H$_3$)), 7.39 (2H, d, *J* 7.7, Ar*H* (*m*- to OCH$_3$)); δ_C(125.8 MHz; $CDCl_3$) 13.9 (*C*H$_3$CH$_2$O), 33.1 (*C*(6)), 47.0 and 49.1 (*C*(7) and *C*(9')), 55.2 and 55.3 (OC'H$_3$ and OCH$_3$), 56.4 (*C*(5)), 61.6 (CH$_3$*C*H$_2$O), 68.6 (*C*(4)), 87.0 (*C*(2)), 113.8 (Ar*C*H (*o*- to OC'H$_3$)), 114.5 (Ar*C*H (*o*- to OCH$_3$)), 125.5 (*o*-Ph*C*H), 128.0 (*m*-Ph*C*H), 128.1 (*p*-Ph*C*H), 129.3 (Ar*C*H (*m*- to OC'H$_3$)), 129.9 (Ar*C* (*p*- to OC'H$_3$)), 130.0

(Ar*C*H (*m*- to OCH_3)), 131.1 (Ar*C* (*p*- to OCH_3)), 138.3 (Ph*C*), 158.8 and 159.1 (Ar'*C*OCH_3 and Ar*C*OCH_3), 164.9, 171.8 (both *C*=O); *m/z* (ESI+) 500 ($[M+H]^+$, 87%); HRMS 522.1883 ($[M+Na]^+$, $C_{30}H_{29}NNaO_6$ requires 522.1887);

6e; R_f = 0.13 (EtOAc/Petrol, 1:4); $[\alpha]_D^{18}$ +31.7 (c = 2.2, $CHCl_3$); υ_{max}/cm^{-1} (film) 2936, 2838, 2251, 1742 (C=O), 1718 (C=O), 1609, 1583, 1511, 1462, 1420, 1371, 1341, 1303, 1252, 1178, 1113, 1071, 952, 836, 812, 734, 700; δ_H(400.2 MHz; $CDCl_3$) 1.23 (3H, t, *J* 7.1, C*H*$_3$CH$_2$O), 2.92 (1H, t, *J* 8.5, C(4)*H*H), 3.08 (1H, dd, *J* 6.8, 8.5, C(4)H*H*), 3.79 (3H, s, C'*H*$_3$O), 3.80 (3H, s, C*H*$_3$O), 4.20 (2H, q, *J* 7.1 CH$_3$C*H*$_2$O), 4.51 (1H, dd, *J* 6.8, 8.5, C(5)*H*), 6.02 (1H, s, C*H*(Ar)$_2$), 6.14 (1H, s, C(2)*H*), 6.83-6.88 (4H, m, *o*- to OC'H$_3$ and OCH_3), 7.02-7.08 (4H, m, *m*- to OC'H$_3$ and OCH_3), 7.31-7.39 (3H, m, *m*-Ph*H*, *p*-Ph*H*), 7.60-7.64 (2H, m, *o*-Ph*H*); δ_C(100.6 MHz; $CDCl_3$) 14.0 (*C*H$_3$CH$_2$O), 48.6 (*C*H(Ar)$_2$), 55.2 and 55.3 (O*C*'H$_3$ and O*C*H$_3$), 61.3 (CH$_3$*C*H$_2$O), 64.8 (*C*(5)), 68.5 (*C*(4)), 87.1 (*C*(2)), 114.1 and 114.3 (Ar*C*H (*o*- to OC'H$_3$ and OCH_3)), 126.0 (*o*-Ph*C*H), 128.4 (*m*-Ph*C*H), 128.6 (*p*-Ph*C*H), 128.8 (*C*(7)), 129.3, 129.3 (both Ar*C*H (*m*- to O*C*'H$_3$ and O*C*H$_3$)), 131.7 and 132.2 (Ar*C* (*p*- to O*C*'H$_3$ and O*C*H$_3$)), 138.5 (Ph*C*), 158.6 and 159.2 (Ar'*C*OCH_3 and Ar*C*OCH_3), 161.8, 172.5, 171.1 (*C*(6) and 2 x (*C*=O)); *m/z* (ESI+) 499 ($[M-H]^-$, 100%); HRMS 522.1886 ($[M+Na]^+$, $C_{30}H_{29}NNaO_6$ requires 522.1887).

(2*R*,5*S*,6*S*,7*R*)-Spiro[1-aza-7-ethoxycarbonyl-8-oxo-3-oxa-2-phenyl-tricyclo [4.3.0^{1,5}.0^{6,7}]nonane-9,9'-fluorene] 8a

A mixture of **3a** (1.35 g, 7.00 mmol) and freshly prepared **1b** (0.91g, 3.34 mmol) in acetone (50 mL) was purged with N_2 before being heated to reflux and left for 19 h. The mixture was concentrated *in vacuo* to give a red solid which was purified by column chromatography over silica eluting with DCM/Petrol (1 : 1) to remove the excess of diazo **3a** and a close running impurity, then EtOAc/Petrol (1 : 4) to yield **8a** as a white solid (1.39 g, 95%); R_f = 0.20

(EtOAc/Petrol, 1 : 3); m.p. 193-195 ^{o}C; $[\alpha]_D^{18}$ +145.5 (c = 2.4, $CHCl_3$); υ_{max}/cm^{-1} (film) 2988, 1713 (C=O), 1451, 1372, 1275, 1159, 1133, 1024, 948, 749, 701; δ_H(400.2 MHz; $CDCl_3$) 1.03 (3H, t, *J* 7.1, C*H*$_3$CH$_2$O), 3.44 (1H, s, C(6)*H*), 3.93 (1H, dd *J* 8.0, 9.5, C(4)*H*H), 4.10-4.16 (2H, m, CH$_3$C*H*$_2$O), 4.19 (1H, dd, *J* 6.1, 9.5, C(5)*H*), 4.49 (1H, dd, *J* 6.1, 8.0, C(4)H*H*), 6.52 (1H, s, C(2)*H*), 6.94-6.99 (1H, m, Ar*H*), 7.01 (1H, d, *J* 7.8, Ar*H*), 7.23-7.28 (1H, m, Ar*H*), 7.31-7.52 (6H, m, Ar*H*), 7.57-7.61 (2H, m, Ar*H*), 7.77 (1H, d, *J* 7.6, Ar*H*) 7.81 (1H, d, *J* 7.6, Ar*H*); δ_C(100.6 MHz; $CDCl_3$) 13.9 (*C*H$_3$CH$_2$O), 37.7 (*C*(6)), 43.3 and 49.4 (*C*(7) and *C*(9')), 56.4 (*C*(5)), 62.2 (CH$_3$*C*H$_2$O), 69.7 (*C*(4)), 88.8 (*C*(2)), 119.8, 120.3, 120.4, 123.8, 125.9, 127.2, 127.4, 127.9, 128.1, 128.5, 128.8 (all Ar*C*H), 138.4, 138.9, 139.2, 142.0, 142.4 (all Ar*C*), 164.5 and 170.8 (both (*C*=O)); *m/z* (ESI+) 496 ($[M+MeCN+NH_4]^+$, 100%), 460 ($[M+Na]^+$, 12%), 438 ($[M+H]^+$, 4%), 898 ($[2M+Na]^+$, 5%); HRMS 460.1529 ($[M+Na]^+$, $C_{28}H_{23}NNaO_4$ requires 460.1525); Found C, 76.92; H, 5.44; N, 3.28 %; $C_{28}H_{23}NO_4$ requires C, 76.87; H, 5.30; N, 3.20 %.

(2*R*,5*S*,6*S*,7*R*,9*S*)-4'-Hydroxymethylspiro[1-aza-7-ethoxycarbonyl-3-oxa-8-oxo-2-phenyl-tricyclo[4.3.0^{1,5}.0^{6,7}]nonane-9,9'-fluorene] 8b and (2*R*,5*S*,6*S*,7*R*,9*R*)-5'-Hydroxymethylspiro[1-aza-7-ethoxycarbonyl-8-oxo-3-oxa-2-phenyl-tricyclo [4.3.0^{1,5}.0^{6,7}]nonane-9,9'-fluorene] 8b'

A mixture of diazo **3b** (200 mg, 0.89 mmol) and **1b** (200 mg, 0.73 mmol) in acetone (10 mL) was purged with N_2 before being heated to reflux and left for 2 d. After concentration *in vacuo* the crude mixture was purified by column chromatography over silica gel eluting with EtOAc/Petrol (1 : 3) to give **8b** (122 g, 32%) and **8b'** (122 g, 32%) as clear gums.

8b; R_f = 0.25 (EtOAc/Petrol, 2:3); $[\alpha]_D^{19}$ +131.0 (c = 1.0, $CHCl_3$); υ_{max}/cm^{-1} (film) 3487 br (OH), 2983, 1714 (C=O), 1440, 1374, 1275, 1135, 1023, 733, 700; δ_H(400.2 MHz; $CDCl_3$) 1.04 (3H, t, *J* 7.1, C*H*$_3$CH$_2$O), 1.98 (1H, br s, CH$_2$O*H*), 3.45 (1H, s, C(6)*H*), 3.93 (1H, dd, *J*

8.0, 9.4, C(4)*H*H), 4.06-4.17 (2H, m, CH_3CH_2O), 4.20 (1H, dd, *J* 6.0, 9.4, C(5)*H*), 4.50 (1H, dd, *J* 6.0, 8.0, C(4)H*H*), 5.10 (2H, s, CH_2OH), 6.49 (1H, s, C(2)*H*), 6.94-7.01 (2H, m, ArC(1')*H*, ArC(7')*H*), 7.23-7.28 (1H, m, ArC(2')*H*), 7.35-7.49 (5H, m, ArC(3')*H*, ArC(6')*H*, *m*-Ph, *p*-Ph), 7.55-7.60 (3H, m, ArC(8')*H*, *o*-Ph), 7.98 (1H, d, *J* 7.8, ArC(5')*H*); δ_C(100.6 MHz; $CDCl_3$) 13.9 (CH_3CH_2O), 38.2 (*C*(6)), 43.0, 49.9 (*C*(7) and *C*(9')), 56.4 (*C*(5)), 62.2 (CH_3CH_2O), 63.7 (CH_2OH), 69.8 (*C*(4)), 88.9 (*C*(2)), 119.7 (Ar*C*(1')H), 123.4 (Ar*C*(8')H), 124.3 (Ar*C*(5')H), 125.9 (*o*-Ph*C*H), 127.0 (Ar*C*(2')H), 127.1 (Ar*C*(7')H), 127.7, 128.4, 128.6 and 128.8 (Ar*C*(3')H, Ar*C*(6')H, *o*-Ph*C*H and *m*-Ph*C*H), 135.4, 136.9, 138.3, 139.4, 142.1, 143.1 (all Ar*C*), 164.6, 170.8 (both (*C*=O)); *m/z* (ESI+) 468 ($[M+H]^+$, 100%); HRMS 490.1626 ($[M+Na]^+$, $C_{29}H_{25}NNaO_5$ requires 490.1625);

8b'; R_f = 0.28 (EtOAc/Petrol, 2:3); $[\alpha]_D^{22}$ +133 (c = 1.0, $CHCl_3$); υ_{max}/cm^{-1} (film) 3484 (br, OH), 2983, 1712 (C=O), 1374, 1275, 1135, 1020, 742, 700; δ_H(400.2 MHz; $CDCl_3$) 1.02 (3H, t, *J* 7.1, CH_3CH_2O), 2.10 (1H, t, *J* 5.5, CH_2OH), 3.43 (1H, s, C(6)*H*), 3.91 (1H, dd, *J* 8.0, 9.4, C(4)*H*H), 4.06-4.17 (2H, m, CH_3CH_2O), 4.17 (1H, dd, *J* 6.1, 9.4, C(5)*H*), 4.47 (1H, dd, *J* 6.1, 8.0, C(4)H*H*), 5.01-5.11 (2H, m, CH_2OH), 6.48 (1H, s, C(2)*H*), 6.95 (1H, t, *J* 7.8, Ar*H*), 7.00 (1H, d, *J* 7.8, Ar*H*), 7.26 (1H, td, *J* 0.6, 7.6, Ar*H*), 7.35-7.47 (5H, m, Ar*H*), 7.51 (1H, d, *J* 7.5, Ar*H*), 7.54-7.59 (2H, m, Ar*H*), 7.95 (1H, d, *J* 7.8, Ar*H*); δ_C(100.6 MHz; $CDCl_3$) 13.9 (CH_3CH_2O), 38.2 (*C*(6)), 43.1 and 49.9) (*C*(7) and *C*(9')), 56.3 (*C*(5)), 62.2 (CH_3CH_2O), 63.7 (CH_2OH), 69.7 (*C*(4)), 88.9 (*C*(2)), 120.0, 122.8, 123.9 (all Ar*C*H), 125.9 (Ph*C*H), 126.9, 127.1, 128.1, 128.2 (all Ar*C*H), 128.6 (Ph*C*H), 128.8 (Ar*C*H), 135.9, 138.3, 138.7, 139.9, 140.2, 142.5, (all Ar*C*), 164.5, 170.8 (both (*C*=O)); *m/z* (ESI+) 468 ($[M+H]^+$, 100%); HRMS 490.1625 ($[M+Na]^+$, $C_{29}H_{25}NNaO_5$ requires 490.1625).

(2*R*,5*S*,6*S*,7*R*,9*S*)-2'-Bromospiro[1-aza-7-ethoxycarbonyl-8-oxo-3-oxa-2-phenyl-tricyclo [4.3.0^{1,5}.0^{6,7}]nonane-9,9'-fluorene] 8c and (2*R*,5*S*,6*S*,7*R*,9*R*)-7'-Bromospiro[1-aza-7-ethoxycarbonyl-3-oxa-8-oxo-2-phenyl-tricyclo[4.3.0^{1,5}.0^{6,7}] nonane-9,9'-fluorene] 8c'

Diazo **3c** (1.26 g, 4.61 mmol) and **1b** (0.66 g, 2.42 mmol) were stirred in DCM (20 mL) at r.t. for 2 d in an atmosphere of N_2. After concentration the crude mixture was purified by column chromatography over silica gel eluting with EtOAc/Petrol (1 : 3) to afford **8c** (0.56 g, 45%) and **8c'** (0.30 g, 24%) as white solids;

8c; R_f = 0.52 (EtOAc/Petrol, 1 : 3); m.p. 148-149 ^oC; $[\alpha]_D^{25}$ +156.9 (c = 0.84, $CHCl_3$); υ_{max}/cm^{-1} (film) 2981, 1714 (C=O), 1447, 1373, 1272, 1133, 1023, 827, 773, 728, 701; δ_H(400.2 MHz; $CDCl_3$) 1.10 (3H, t, *J* 7.1, C*H*$_3$CH$_2$O), 3.44 (1H, s, C(6)*H*), 3.91 (1H, dd, *J* 8.1, 9.4, C(4)*H*H), 4.09-4.25 (3H, m, CH$_3$C*H*$_2$O, C(5)*H*), 4.49 (1H, dd, *J* 6.1, 7.9, C(4)H*H*), 6.50 (1H, s, C(2)*H*), 6.97 (1H, t, *J* 7.7, ArC(6')*H*), 7.15 (1H, d, *J* 1.5, ArC(1')*H*), 7.34 (1H, t, *J* 7.3, ArC(7')*H*), 7.38-7.52 (5H, m, Ar*H*), 7.55-7.62 (3H, m, Ar*H*), 7.75 (1H, d, *J* 7.5, ArC(8')*H*); δ_C(100.6 MHz; $CDCl_3$; Me_4Si) 14.0 (*C*H$_3$CH$_2$O), 37.8 (*C*(6)), 42.9 and 49.4 (*C*(7) and *C*(9')), 56.3 (*C*(5)), 62.5 (CH$_3$*C*H$_2$O), 69.6 (*C*(4)), 88.9 (*C*(2)), 120.5 (Ar*C*H), 120.9 (Ar*C*Br), 121.1, 123.8, 123.8 (all Ar*C*H), 125.8 (Ph*C*H), 127.8, 128.3 (both Ar*C*H), 128.6 (Ph*C*H), 128.8, 131.0 (*p*-Ph*C*H), 138.2 (Ph*C*), 138.2, 138.7, 141.3, 144.0 (all Ar*C*), 164.1 (*C*=O), 170.3 (*C*=O); HRMS 538.0651 ([M+Na]$^+$, $C_{28}H_{22}NNaO_4$ requires 538.0624);

8c'; R_f = 0.35 (EtOAc/Petrol, 1 : 3); m.p. 194 ^oC; $[\alpha]_D^{25}$ +42.2 (c = 1, $CHCl_3$); υ_{max}/cm^{-1} (film) 2982, 1715 (C=O), 1443, 1371, 1287, 1163, 1131, 1024, 829, 734, 700; δ_H(400.2 MHz; $CDCl_3$) 1.02 (3H, t, *J* 7.1, C*H*$_3$CH$_2$O), 3.42 (1H, s, C(6)*H*), 3.90 (1H, t, *J* 8.7, C(4)*H*H), 4.06-4.18 (3H, m, CH$_3$C*H*$_2$O, C(5)*H*), 4.44 (1H, dd, *J* 6.2, 7.9, C(4)H*H*), 6.51 (1H, s, C(2)*H*), 6.97 (1H, t, *J* 7.7, ArC(1')*H*), 7.26 (1H, t, *J* 7.6, ArC(2')*H*), 7.35-7.51 (5H, m, Ar*H*), 7.54-7.61 (3H, m, Ar*H*), 7.69 (1H, d, *J* 7.6, ArC*H*), 7.74 (1H, d, *J* 1.6, ArC(8')*H*); δ_C(100.6 MHz; $CDCl_3$) 13.8 (*C*H$_3$CH$_2$O), 38.0 (*C*(6)), 43.0 and 49.4 (*C*(7) and *C*(9')), 56.3 (*C*(5)), 62.2

(CH_3CH_2O), 69.5 (*C*(4)), 88.2 (*C*(2)), 119.8, 120.3 (Ar*C*H), 121.3 (Ar*C*Br), 121.4 (Ar*C*H), 125.7 (Ph*C*H), 126.7, 127.5, 128.1, 128.7 (all Ar*C*H), 128.9 (Ph*C*H), 131.2 (*p*-Ph*C*H), 138.0 (Ph*C*), 138.1, 140.8, 141.2, 141.6 (all Ar*C*), 164.1 (*C*=O), 171.0 (*C*=O); HRMS 538.0636 ($[M+Na]^+$, $C_{28}H_{22}NNaO_4$ requires 538.0624).

(2*R*,5*S*,6*S*,7*R*)-2',7'-Dibromospiro[1-aza-7-ethoxycarbonyl-3-oxa-8-oxo-2-phenyl-tricyclo [4.3.0^{1,5}.0^{6,7}]nonane-9,9'-fluorene] 8d

A mixture of diazo **3d** (302 mg, 0.86 mmol) and **1b** (180 mg, 0.66 mmol) in acetone (10 mL) was purged with N_2 before being heated to reflux and left for 24 h. After concentration *in vacuo* the crude material was purified by column chromatography over silica gel eluting with EtOAc/Petrol (1 : 3) to afford product **8d** (251 mg, 64%) as a white solid; R_f = 0.29 (EtOAc/Petrol, 1 : 3); m.p. 185-187 ^oC; $[\alpha]_D^{18}$ +69.1 (c = 0.75, $CHCl_3$); υ_{max}/cm^{-1} (film) 1716 (C=O); δ_H(400.2 MHz; $CDCl_3$) 1.10 (3H, t, *J* 7.1, C*H*$_3$CH$_2$O), 3.44 (1H, s, C(6)*H*), 3.91 (1H, dd, *J* 8.1, 9.2, C(4)*H*H), 4.12-4.26 (3H, m, CH$_3$C*H*$_2$O, C(5)*H*), 4.48 (1H, dd, *J* 6.2, 8.0, C(4)H*H*), 6.51 (1H, s, C(2)*H*), 7.13 (1H, d, *J* 1.5, ArC(1')*H*), 7.43-7.60 (9H, m, Ar*H*), 7.73 (1H, d, *J* 1.6, ArC(8')*H*); δ_C(100.6 MHz; $CDCl_3$) 14.0 (*C*H$_3$CH$_2$O), 38.2 (*C*(6)), 42.6 and 49.5 (*C*(7) and *C*(9')), 56.3 (*C*(5)), 62.6 (CH$_3$*C*H$_2$O), 69.5 (*C*(4)), 89.4 (*C*(2)), 121.2 (Ar*C*H), 121.3 (Ar*C*), 121.5 (Ar*C*H), 121.9 (Ar*C*), 123.8 (Ar*C*H), 125.8 (Ph*C*H), 126.9 (Ar*C*H), 128.9 (Ar*C*H), 129.0 (Ph*C*H), 131.2, 131.5 (both Ar*C*H), 137.2, 137.9, 140.2, 140.6, 143.7 (Ar*C*), 163.8, 170.6 (both (*C*=O)); *m/z* (ESI+) 654 ($[M+MeCN+NH_4]^+$, 48%); HRMS 617.9709 ($[M+Na]^+$, $C_{28}H_{21}Br_2NNaO_4$ requires 617.9711).

(2*R*,5*S*,6*S*,7*R*,9*S*)-1,4'-Diazaspiro[7-ethoxycarbonyl-3-oxa-8-oxo-2-phenyl-tricyclo [4.3.0^{1,5}.0^{6,7}]nonane-9,9'-fluorene] 8e and (2*R*,5*S*,6*S*,7*R*,9*R*)-1,5'-Diazaspiro[7-ethoxycarbonyl-3-oxa-8-oxo-2-phenyl-tricyclo[4.3.0^{1,5}.0^{6,7}]nonane-9,9'-fluorene] 8e'

Diazo **3e** (1.56 g, 8.07 mmol) and **1b** (1.34 g, 4.90 mmol) were stirred in DCM (25 mL) at r.t. for 2 d in an atmosphere of N_2. After concentration the crude mixture was purified by column chromatography over silica gel eluting with EtOAc/Petrol (1 : 3 → 1 : 1) to afford **8e** (0.83 g, 39%) as a yellow foam and **8e'** (1.90 g, 58%) as a white solid.

8e; R_f = 0.42 (EtOAc/Petrol, 1:1); m.p. 174-176 ^oC (EtOAc/Petrol); $[\alpha]_D^{20}$ +96.4 (c = 1, $CHCl_3$); υ_{max}/cm^{-1} (film) 2983, 1715 (C=O), 1449, 1420, 1373, 1258, 1178, 1023, 738, 700; δ_H(500.3 MHz; $CDCl_3$) 1.06 (3H, t, *J* 7.1, C*H*$_3$CH$_2$O), 3.49 (1H, s, C(6)*H*), 3.92 (1H, dd, *J* 8.0, 9.5, C(4)*H*H), 4.08-4.18 (2H, m, CH$_3$C*H*$_2$O), 4.22 (1H, dd, *J* 6.1, 9.5, C(5)*H*), 4.52 (1H, dd, *J* 6.1, 8.0, C(4)H*H*), 6.51 (1H, s, C(2)*H*), 7.07 (1H, m, ArC(7')*H*), 7.14 (1H, dd, *J* 4.9, 7.9, ArC(2')*H*), 7.35 (1H, dd, *J* 1.4, 7.9, ArC(1')*H*), 7.39-7.49 (4H, m, ArC(6')*H*, *m*-Ph*H*, *p*-Ph*H*), 7.53 (1H, d, *J* 8.0, ArC(8')*H*), 7.56-7.59 (2H, m, *o*-Ph*H*), 8.14 (1H, d, *J* 7.2 ArC(5')*H*), 8.60 (1H, dd, *J* 1.4, 4.9 ArC(3')*H*); δ_C(125.8 MHz; $CDCl_3$) 14.0 (*C*H$_3$CH$_2$O), 37.2 (*C*(6)), 41.7 and 48.9 (*C*(7) and *C*(9')), 56.2 (*C*(5)), 62.5 (CH$_3$*C*H$_2$O), 69.7 (*C*(4)), 88.9 (*C*(2)), 121.2 (Ar*C*(2')H), 120.2 (Ar*C*(8')H), 121.5 (Ar*C*(5')H), 125.8 (*o*-Ph*C*H), 128.1 (Ar*C*(1')H), 128.6, 128.7 and 128.9 (*p*-Ph*C*H, ArC(6')H and *m*-Ph*C*H), 129.5 (ArC(7')H), 135.9, 138.2, 139.5, 141.7 (all Ar*C*), 149.3 (Ar*C*(3')H), 158.2 (Ar*C*), 164.3, 170.1 (both (*C*=O)); *m/z* (ESI+) 439 ($[M+H]^+$, 100%), 877 ($[M+H]^+$, 91%), 461 ($[M+Na]^+$, 100%); HRMS 461.1472 $[M+Na]^+$, $C_{27}H_{22}N_2NaO_4$ requires 461.1476);

8e' R_f = 0.67 (EtOAc/Petrol, 1:1); m.p. 85 ^oC; $[\alpha]_D^{25}$ +111 (c = 1, $CHCl_3$); υ_{max}/cm^{-1} (film) 2980, 1716 (C=O), 1280, 737; δ_H(700.1 MHz; $CDCl_3$) 1.02 (3H, t, *J* 7.1, C*H*$_3$CH$_2$O), 3.52 (1H, s, C(6)*H*), 3.92 (1H, t, *J* 8.7, C(4)*H*H), 4.09-4.18 (3H, m, C(5)*H*, CH$_3$C*H*$_2$O), 4.53 (1H, t, *J* 6.9, C(4)H*H*), 6.49 (1H, s, C(2)*H*), 6.83 (1H, dd, *J* 4.9, 7.9, ArC(7')*H*), 7.07 (1H, d, *J* 7.8, ArC(1')*H*), 7.37 (1H, t, *J* 7.5, ArC(2')*H*), 7.40-7.50 (4H, m, ArC(3')*H*, *m*-Ph*H*, *p*-Ph*H*), 7.56 (2H, d, *J* 7.4, *o*-Ph*H*), 7.67 (1H, d, *J* 7.9, ArC(8')*H*), 8.09 (1H, d, *J* 7.5, ArC(4')*H*), 8.53 (1H, d, *J* 4.7, ArC(6')*H*); δ_C(125.8 MHz; $CDCl_3$) 13.9 (*C*H$_3$CH$_2$O), 37.4 (*C*(6)), 41.6 and 48.4

(*C*(7) and *C*(9')), 56.6 (*C*(5)), 62.4 (CH_3CH_2O), 69.7 (*C*(4)), 88.9 (*C*(2)), 120.3 (Ar*C*(1')H), 121.1 (Ar*C*(4')H), 121.3 (Ar*C*(7')H), 125.8 (*o*-Ph*C*H), 128.6 (*m*-Ph*C*H), 128.5, 129.0 and 129.2 (m-Ph*C*H, Ar*C*(3')H and Ar*C*(2')H), 131.2 (Ar*C*(8')H), 133.4, 138.2, 138.8, 142.5 (all Ar*C*), 149.0 (Ar*C*(6')H), 160.8 (Ar*C*), 164.1, 170.6 (both (*C*=O)); *m/z* (ESI+) 877 ($[2M+H]^+$, 100%); 439 ($[M+H]^+$, 58%); HRMS 439.1649 ($[M+H]^+$, $C_{27}H_{23}N_2O_4$ requires 439.1652).

(2*R*,5*S*,6*S*,7*R*)-1,4',5'-Triazaspiro[7-ethoxycarbonyl-3-oxa-8-oxo-2-phenyl-tricyclo [4.3.0^{1,5}.0^{6,7}]nonane-9,9'-fluorene] 8f

A mixture of diazo **3f** (340 mg, 1.75 mmol) and **1b** (170 mg, 0.63 mmol) in acetone (10 mL) was heated to 40 ^oC for 3 d (under an N_2 atmosphere) before being concentrated *in vacuo*. Column chromatography over silica gel eluting with Et_2O/DCM (1 : 4) yielded **8f** as a grey solid (114 mg, 41%); R_f = 0.17 (Et_2O/DCM, 1 : 4); m.p. dec. 113 ^oC; $[\alpha]_D^{18}$ +77.9 (c = 1.65, $CHCl_3$); υ_{max}/cm^{-1} (film) 2984, 1716 (C=O), 1565, 1402, 1259, 1175, 1021, 745, 701; δ_H(400.2 MHz; $CDCl_3$) 1.04 (3H, t, *J* 7.1, CH_3CH$_2$O), 3.55 (1H, s, C(6)*H*), 3.91 (1H, dd, *J* 8.2, 9.1, C(4)*H*H), 4.05-4.21 (3H, m, CH$_3$CH_2O, C(5)*H*), 4.55 (1H, dd, *J* 6.1, 8.2, C(4)H*H*), 6.49 (1H, s, C(2)*H*), 6.92 (1H, dd, *J* 4.8, 8.1 ArC(7')*H*), 7.22-7.27 (1H, m, ArC(2')*H*), 7.39-7.49 (4H, m, *m*-Ph*H*, *p*-Ph*H*, ArC(1')*H*), 7.53-7.57 (2H, m, *o*-Ph*H*), 7.70-7.74 (1H, m, ArC(8')*H*), 8.65 (1H, d, *J* 4.7, ArC(6')*H*), 8.74 (1H, d, *J* 4.7, ArC(3')*H*); δ_C(125.8 MHz; $CDCl_3$) 13.9 (*C*H$_3$CH$_2$O), 36.8 (*C*(6)), 48.2 (*C*(7)), 56.3 (*C*(5)), 62.6 (CH$_3$*C*H$_2$O), 69.6 (*C*(4)), 77.2 (*C*(9')), 88.9 (*C*(2)), 122.7, 122.8 (Ar*C*(2')H and Ar*C*(7')H), 125.7 (*o*-Ph*C*H), 128.5 (Ar*C*(1')H), 128.5 (*m*-Ph*C*H), 129.0 (*p*-Ph*C*H), 131.4 (Ar*C*(8')H), 134.3, 136.6 (both Ar*C*), 138.0 (Ph*C*), 150.1, 150.4 (Ar*C*(6')H and Ar*C*(3')H), 156.8, 159.2 (both Ar*C*), 163.8, 169.9 (both (*C*=O)); *m/z* (ESI+) 440 ($[M+H]^+$, 77%), 879 ($[2M + H]^+$, 100%); HRMS 462.1422 ($[M+Na]^+$, $C_{26}H_{21}N_3NaO_4$ requires 462.1424).

Dimethyldiazomalonate 11b[77]

A mixture of dimethyl malonate (1.73 mL, 15.1 mmol), *p*-ABSA (3.71 g, 15.4 mmol), Et_3N (6.33 mL, 45.4 mmol) in MeCN (50 mL) was stirred for 14 h. The mix was washed with Et_2O/Petrol (1 : 1) and the solid precipitate allowed to settle before the liquid was decanted away. This process was repeated several times before the combined organic washes were concentrated *in vacuo* to leave a yellow oil which was purified by column chromatography over silica eluting with Et_2O/Petrol (1 : 4) to give **11b** as a clear yellow oil (2.02 g, 84%); υ_{max}/cm^{-1} (neat) 2959, 2139 (CN_2), 1763 (C=O), 1696, 1439, 1334, 1276, 1192, 1100, 761; δ_H(400.2 MHz; $CDCl_3$; Me_4Si) 3.75 (6H, s, C*H*$_3$); δ_C(100.6 MHz; $CDCl_3$; Me_4Si) 52.2 (*C*H_3), 161.1 (*C*=O).

6',7'-Diaza-5a,8-diethyloxycarbonyl-2-oxa-3-phenyl-1,2,3,5a,6,8b-hexahydrocyclo penta[a]pyrrolizin-5(8aH)-one 12

A solution of ethyldiazoacetate **11a** (0.32 mL, 3 mmol) and **1b** (0.27 g, 1 mmol) in acetone (15 mL) was heated at reflux for 16 h. The mixture was concentrated and the resulting oil was purified by column chromatography over silica gel eluting with EtOAc/Petrol (1 : 2) to give **12** as yellow-orange oil (74%); R_f = 0.46 (EtOAc/Petrol, 2:1); $[\alpha]_D^{18}$ -52.2 (c = 4.63, $CHCl_3$); υ_{max}/cm^{-1} (film) 3331 (NH), 2984, 1723 (C=O), 1565, 1380, 1221, 1133, 748, 701; δ_H(400.2 MHz; C_6D_6) 0.84 and 0.97 (2 x 3H, t, *J* 7.1, 2 x C*H*$_3$CH$_2$O), 3.55 (1H, dd, *J* 8.0, 8.9, C(4)*H*H), 3.83-4.05 (5H, m, 2 x CH$_3$C*H*$_2$O, C(5)*H*), 4.06 (1H, d, *J* 2.3, C(6)*H*), 4.11 (1H, dd, *J* 6.2, 8.0, C(4)H*H*), 6.43 (1H, s, C(2)*H*), 6.99-7.09 (3H, m, Ph*H*), 7.41-7.45 (2H, m, Ph*H*), 7.95 (1H, s, N*H*); δ_C(100.6 MHz; $CDCl_3$) 14.0 and 14.2 (2 x *C*H$_3$CH$_2$O), 51.3 (*C*(6), 61.8, 61.8 (*C*(5) and CH$_3$*C*H$_2$O), 63.5 (CH$_3$*C*'H$_2$O), 70.3 (*C*(4)), 80.3 (*C*(7)), 87.8 (*C*(2), 125.8, 128.5 (*o*-Ph*C*H and *m*-Ph*C*H), 128.9 (*p*-Ph*C*H), 137.6 and 140.7 (EtO$_2$C*C*=N and Ph*C*),

161.3, 167.5, 171.7 (3 x (*C*=O)); HRMS 410.1324 ($[M+H]^+$, $C_{19}H_{21}N_3NaO_6$ requires 410.1323).

General Procedure for TFA Mediated Deprotection of Cyclopropane Adducts To a solution of cyclopropane (1 mmol) in DCM (10-20 mL) at r.t. was added a solution of TFA (0.77 mL, 10 mmol) in water (0.77 mL). The mixture was stirred for 5 h before being concentrated *in vacuo*. Toluene (8 mL) was added followed by 1 drop of water and the mixture was re-concentrated *in vacuo*. The addition of toluene and water followed by re-concentration was repeated (x 2) to give a brown viscous oil which was purified by column chromatography over silica gel yielding deprotected alcohol.

General Procedure for Hydrolysis of Esters

To a solution of ester (0.1 mmol) in MeOH (2.25 mL) and water (0.75 mL) was added lithium hydroxide (21 mg, 0.5 mmol (per mol of ester)). After stirring at r.t. for 2 d, MeOH was removed *in vacuo*. EtOAc (5 mL) and water (3 mL) were added and the organic layer was separated and concentrated to give the unwanted organic extracts. EtOAc (5 mL) was added and conc. HCl was added dropwise until pH 1 was achieved. The organic layer was separated and the aqueous was extracted with EtOAc (4 x 5 mL) before the combined organic extracts were dried over Na_2SO_4 and concentrated to give product acid which required no further purification.

(2*S*,3*R*,4*R*)-1-Aza-6,6-diphenyl -4-ethoxycarbonyl-2-hydroxymethyl-5-oxo -bicyclo [3.1.0]hexane 13a

Following general procedure, after column chromatography eluting with EtOAc/Petrol(60/80) (2 : 1), cyclopropane **4d** (304 mg, 0.69 mmol) yielded alcohol **13a** as a white solid (110 mg, 45%); R_f = 0.15 (EtOAc/Petrol, 2 : 1); m.p. 109 ^oC; $[\alpha]_D^{21}$ -152.7 (c = 6.6, $CHCl_3$); υ_{max}/cm^{-1} (film) 3400 (br, NH, OH), 2981, 1733 (C=O), 1495, 1448, 1311, 1112, 1043, 750, 708;

δ_H(400.2 MHz; C_6D_6) 0.79 (3H, t, *J* 7.1, C*H*$_3$CH$_2$O), 3.38 (1H, s, C(3)*H*), 3.51 (1H, t, *J* 4.6, C(2)*H*), 3.81-3.93 (4H, m, C*H*$_2$OH, CH$_3$C*H*$_2$O), 4.92 (1H, br s, CH$_2$O*H*), 6.71 (1H, s, N*H*), 6.98-7.03 (1H, m, *p*-Ph*H*), 7.05-7.14 (3H, m, *m*-Ph*H*, *p*-Ph'*H*), 7.20 (2H, t, *J* 7.8, *m*-Ph'*H*), 7.44 (2H, d, *J* 7.3, *o*-Ph*H*), 7.59 (2H, d, *J* 7.2, *o*-Ph'*H*); δ_C(100.6 MHz; C_6D_6) 13.8 (*C*H$_3$CH$_2$O), 33.0 (*C*(3)), 44.9 and 47.1 (*C*(6) and *C*(4)), 54.0 (*C*(2)), 61.1 and 65.4 (*C*H$_2$OH and CH$_3$*C*H$_2$O), 127.3, 127.5, 128.3, 128.5, 129.1, 129.4 (all Ph*C*H), 138.1 and 140.5 (Ph*C*) and (Ph'*C*), 166.0 and 171.3 (2 x (*C*=O)); *m/z* (ESI+) 410 ([M+MeCN+NH$_4$]$^+$, 100%); HRMS 374.1359 ([M+Na]$^+$, $C_{21}H_{21}NNaO_4$ requires 374.1363).

(2*S*,3*R*,4*R*)-1-Aza-di(*p*-methoxyphenyl)-4-ethoxycarbonyl-2-hydroxymethyl-5-oxo-6,6-bicyclo[3.1.0]hexane 13b

Following the general procedure, after column chromatography eluting with EtOAc, cyclopropane **4e** (113 mg, 0.23 mmol) yielded alcohol **13b** as a white solid (75 mg, 80%); R_f = 0.20 (EtOAc); $[\alpha]_D^{17}$ -147 (c = 1.3, $CHCl_3$); υ_{max}/cm^{-1} (film) 3346, 2957, 2838, 1732 (C=O), 1696 (C=O), 1608, 1580, 1512, 1418, 1404, 1295, 1248, 1178, 1113, 1033, 830, 735, 687; δ_H(400.2 MHz; $CDCl_3$) 0.90 (3H, t, *J* 7.1, C*H*$_3$CH$_2$O), 3.10 (1H, s, C(3)*H*), 3.42 (1H, t, *J* 5.0, C(2)*H*), 3.60-3.80 (8H, m, C*H*'$_3$O, C*H*$_3$O, C*H*$_2$OH), 3.82-3.96 (2H, m, CH$_3$C*H*$_2$O), 5.98 (1H, s, NH), 6.72 (2H, d, *J* 8.8, Ar'*H* (*o*- to OMe)), 7.72 (2H, d, *J* 8.8, Ar*H* (*o*- to OMe)), 7.21 (2H, d, *J* 8.8, Ar'*H* (*m*- to OMe)), 7.32 (2H, d, *J* 8.8, Ar*H* (*m*- to OMe)); δ_C(100.6 MHz; $CDCl_3$) 13.7 (*C*H$_3$CH$_2$O), 32.6 (*C*(3)), 44.2 and 46.1 (*C*(4) and *C*(6)), 53.2 (*C*(2)), 55.2, 55.2 (*C*H$_3$O and *C*'H$_3$O), 61.3 (CH$_3$*C*H$_2$O), 65.3 (*C*H$_2$OH), 113.7 and 114.3 (ArC'*H* (*o*- to OMe), -ArC*H* (*o*- to OMe)), 129.4 (Ar'C*H* (*m*- to OMe)), 129.5 (Ar'*C* (*p*- to OMe)), 129.6 (ArC*H* (*m*- to OMe)), 131.8 (Ar*C* (*p*- to OMe)), 158.6 and 158.7 (Ar*C*'OMe and Ar*C*OMe), 165.9 and 171.0 (both *C*=O); *m/z* (ESI+) 412 ([M+H]$^+$, 87%), 434 ([M+Na]$^+$, 73%), 845 ([M+Na]$^+$, 100%); HRMS 434.1580 ([M+Na]$^+$, $C_{23}H_{25}NNaO_6$ requires 434.1574).

(2*S*,3*S*,4*R*)-1-Aza-4-ethoxycarbonyl-2-hydroxymethyl-5-oxo-spiro[bicyclo[3.1.0] hexane-6,9'-fluorene] 13c

Following the general procedure, after column chromatography eluting with EtOAc/Petrol(60/80) (2 : 1), cyclopropane **8a** (177 mg, 0.40 mmol) yielded alcohol **13c** as a white solid (130 mg, 92%); R_f = 0.30 (EtOAc); m.p. 176-177 ^oC; $[\alpha]_D^{21}$ +74.0 (c = 3.1, $CHCl_3$); υ_{max}/cm^{-1} (film) 3318, 1697, 1450, 1262, 1199, 1109, 731; δ_H(500.3 MHz; $CDCl_3$) 1.02 (3H, t, *J* 7.1, C*H*$_3$CH$_2$O), 2.23 (1H, br s, O*H*), 3.14 (1H, s, C(3)*H*), 3.88-3.95 (2H, m, C*H*$_2$OH), 4.06 (1H, t, *J* 5.4, C(2)*H*), 4.07-4.23 (2H, m, CH$_3$C*H*$_2$O), 6.56 (1H, s, N*H*), 7.02 (1H, d, *J* 7.8, Ar*H*), 7.23-7.27 (2H, m, Ar*H*), 7.38 (1H, t, *J* 7.5, Ar*H*), 7.43 (1H, t, *J* 7.5, Ar*H*), 7.51 (1H, d, *J* 7.9 Ar*H*), 7.78 (1H, d, *J* 7.6, Ar*H*), 7.85 (1H, d, *J* 7.6 Ar*H*); δ_C(125.8 MHz; $CDCl_3$) 13.9 (*C*H$_3$CH$_2$O), 36.9 (*C*(3)), 40.4 and 46.7 (*C*(4) and *C*(6)), 53.4 (*C*(2)), 62.2 (CH$_3$*C*H$_2$O), 65.4 (*C*H$_2$OH), 119.8, 120.5, 120.6, 122.7, 127.2, 127.7, 127.7, 128.1, (all Ar*C*H), 138.8, 139.3, 142.2, 142.5, (all Ar*C*), 164.9, 169.0 (both (*C*=O)); *m/z* (ESI+) 408 ([M+MeCN+NH$_4$]$^+$, 100%); HRMS 372.1201 ([M+Na]$^+$, $C_{21}H_{19}NNaO_4$ requires 372.1206).

(2*S*,3*S*,4*R*,6*R*)-1-Aza-2,5'-dihydroxymethyl-4-ethoxycarbonyl-5-oxo-spiro[bicyclo [3.1.0]hexane-6,9'-fluorene] 13d

Following the general procedure, after column chromatography eluting with EtOAc, cyclopropane **8b'** (251 mg, 0.54 mmol) yielded alcohol **13d** as a white solid (65 mg, 32 %); R_f = 0.24 (EtOAc); m.p. dec. 170 ^oC (EtOAc); $[\alpha]_D^{18}$ +54.7 (c = 1.65, MeOH); υ_{max}/cm^{-1} (film) 3357 (br, OH), 1694 (C=O), 1429; δ_H(400.2 MHz; *d*4-MeOD) 1.01 (3H, t, *J* 7.1, C*H*$_3$CH$_2$O), 3.34 (1H, s, C(3)*H*), 3.72-3.83 (2H, m, C(2)C*H*$_2$OH), 3.95 (1H, t, *J* 5.7, C(2)*H*), 3.98-4.12 (2H, m, CH$_3$C*H*$_2$O), 5.03 (2H, s, ArC*H*$_2$OH), 7.03 (1H, d, *J* 7.7, Ar*H*), 7.24-7.31 (2H, m, Ar*H*), 7.40 (1H, td, *J* 1.0, 7.6, Ar*H*), 7.46 (1H, d, *J* 7.9, Ar*H*), 7.51 (1H, d, *J* 7.5,

Ar*H*), 7.95 (1H, d, *J* 7.8, Ar*H*); δ_C(100.6 MHz; *d*4-MeOD) 14.3 (*C*H_3CH_2O), 38.9 (*C*(3)), 41.2 and 49.2 (*C*(4) and *C*(9')), 55.2 ((*C*(2)), 62.9 (CH$_3$*C*H$_2$O), 63.7 (Ar*C*H$_2$OH), 65.5 (C(2)*C*H$_2$OH), 121.4, 122.6, 125.1, 127.8, 127.8, 128.2, 128.8 (Ar*C*H), 138.1, 140.2, 141.1, 141.1, 144.4 (Ar*C*), 166.5 and 171.3 (*C*=O); *m/z* (ESI+) 380 ([M+H]$^+$, 100%), 402 ([M+Na]$^+$, 97%); HRMS 402.1305 ([M+Na]$^+$, $C_{22}H_{21}NNaO_5$ requires 402.1312).

(2*S*,3*S*,4*R*,6*S*)-1-Aza-2'-bromo-4-ethoxycarbonyl-2-hydroxymethyl-5-oxo-spiro [bicyclo[3.1.0]hexane-6,9'-fluorene] 13e

By Deprotection of Dibromo **8d**

Following the general procedure, after column chromatography eluting with EtOAc/Petrol (2 : 1), dibromocyclopropane **8d** (268 mg, 0.45 mmol) yielded alcohol **13e** as a white solid (134 mg, 59 %).

By Deprotection of Mono-Bromo **8c**

Following the general procedure, after column chromatography eluting with EtOAc/Petrol (2 : 1), mono-bromocyclopropane **8c** (250 mg, 0.48 mmol) yielded alcohol **13e** as a white solid (149 mg, 72%); R_f = 0.38 (EtOAc); m.p. dec. > 195 ^{o}C; $[\alpha]_D^{25}$ +101 (c = 1, MeOH); υ_{max}/cm^{-1} (film) 3356 (br OH), 1717 (C=O); δ_H(500.3 MHz; $CDCl_3$) 1.11 (3H, t, *J* 7.1, C*H*$_3$CH$_2$O), 3.14 (1H, s, C(3)*H*), 3.88-3.96 (2H, m, C*H*$_2$OH), 4.05 (1H, t, *J* 5.5, C(2)*H*), 4.10-4.18 (1H, m, CH$_3$C*H*HO), 4.23-4.32 (1H, m, CH$_3$CH*H*O), 6.61 (1H, s, NH), 7.18 (1H, d, *J* 1.7, ArC(1')*H*), 7.25-7.29 (1H, m, ArC(6')*H*), 7.44 (1H, t, *J* 7.5, ArC(7')*H*), 7.49 (1H, d, *J* 8.4, ArC(5')*H*), 7.51 (1H, dd, *J* 1.7, 8.1, ArC(3')*H*), 7.64 (1H, d, *J* 8.1 ArC(4')*H*), 7.82 (1H, d, *J* 7.5, ArC(8')*H*); δ_C(125.8 MHz; $CDCl_3$) 14.1 (*C*H$_3$CH$_2$O), 37.1 (*C*(3)), 40.1 and 46.8, (*C*(4) and *C*(9')), 53.4 (*C*(2)), 62.5 (CH$_3$*C*H$_2$O), 65.3 (*C*H$_2$OH), 120.7 (Ar*C*(8')H), 120.9 (Ar*C*(2')), 121.1 (Ar*C*(4')H), 122.8 (Ar*C*(5')H), 124.0 (Ar*C*(1')H), 128.1 (Ar*C*(6')H), 128.4 (Ar*C*(7')H), 138.8 (Ar*C*(3')H), 138.3, 138.6, 141.5, 144.3 (all Ar*C*), 164.5, 168.7 (both

(*C*=O)); *m/z* (ESI-) 428 ([M-H]$^-$, 100%), 426 ([M-H]$^-$, 97%); HRMS 450.0314 ([M+Na]$^+$, $C_{21}H_{18}BrNNaO_4$ requires 450.0311).

(2*S*,3*S*,4*R*,6*R*)-1-Aza-7'-bromo-4-ethoxycarbonyl-2-hydroxymethyl-5-oxo-spiro [bicyclo[3.1.0]hexane-6,9'-fluorene] 13f

Following the general procedure, after column chromatography eluting with EtOAc, cyclopropane **8c'** (88 mg, 0.17 mmol) yielded alcohol **13f** as a white solid (42 mg, 58 %); R_f = 0.61 (EtOAc); m.p. dec. 204-206 ^oC; $[\alpha]_D^{25}$ -1.2 (c = 0.52, MeOH); υ_{max}/cm^{-1} (film) 1745 (C=O), 1684; δ_H(500.3 MHz; $CDCl_3$) 1.02 (3H, t, *J* 7.1, C*H*$_3$CH$_2$O), 2.12 (1H, t, *J* 5.3, CH$_2$O*H*), 3.15 (1H, d, *J* 1.2, C(3)*H*), 3.89-3.98 (2H, m,C*H*$_2$OH), 4.03-4.07 (1H, m, C(2)*H*), 4.07-4.21 (2H, m, CH$_3$C*H*$_2$O), 6.21 (1H, s, N*H*), 7.01 (1H, d, *J* 7.8, ArC(1')*H*), 7.27 (1H, td, *J* 0.9, 7.8, ArC(2')*H*), 7.39 (1H, td, *J* 0.9, 7.7, ArC(3')*H*), 7.56 (1H, dd, *J* 1.7, 8.1, ArC(6')*H*), 7.62 (1H, d, *J* 1.7, ArC(8')*H*), 7.70 (1H, d, *J* 8.1, ArC(5')*H*), 7.70 (1H, d, *J* 8.1, ArC(4')*H*); δ_C(125.8 MHz; $CDCl_3$) 13.9 (*C*H$_3$CH$_2$O), 37.1 (*C*(3)), 40.1 and 46.8 (*C*(4) and *C*(9')), 53.4 (*C*(2)), 62.3 (CH$_3$*C*H$_2$O), 65.4 (*C*H$_2$OH), 119.9 (Ar*C*(4')H), 120.5 (Ar*C*(1')H), 121.5 (Ar*C*(7')), 121.7 (Ar*C*(5')H), 125.9 (Ar*C*(8')H), 127.6 (Ar*C*(2')H), 128.0 (Ar*C*(3')H), 131.3 (Ar*C*(6')H), 138.2, 140.9, 141.6, 142.0, (all Ar*C*), 164.5 and 169.2, (both (*C*=O)); *m/z* (ESI-) 426 ([M-H]$^-$, 99%), 428 ([M-H]$^-$, 100%); HRMS 426.0346 ([M-H]$^-$, $C_{21}H_{17}BrNO_4$ requires 426.0346).

(2*S*,3*S*,4*R*,6*S*)-1,4'-Diaza-4-ethoxycarbonyl-2-hydroxymethyl-5-oxo-spiro [bicyclo[3.1.0]hexane-6,9'-fluorene] 13h

To a solution of cyclopropane **8e** (156 mg, 0.36 mmol) in DCM (4 mL) at r.t. was added a mixture containing TFA (0.55 mL, 7.12 mmol) and water (0.55 mL). Purification by column chromatography over silica gel eluting with (EtOAc) yielded deprotected alcohol **13h** (95 mg,

76 %) as a white solid; R_f = 0.06 (EtOAc); m.p. dec. > 176 ^oC; $[\alpha]_D^{24}$ +29.9 (c = 1.25, MeOH); υ_{max}/cm^{-1} (film) 3252 (br, OH), 1700 (C=O), 1591, 1421, 1284, 1253, 1180, 1103, 1045, 755, 737; δ_H(400.2 MHz; *d*4-MeOD) 1.07 (3H, t, *J* 7.1, C*H*$_3$CH$_2$O), 3.51 (1H, s, C(3)*H*), 3.78 (1H, dd, *J* 5.9, 11.2, C*H*HOH), 3.83 (1H, dd, *J* 5.3, 11.2, CH*H*OH), 3.97 (1H, t, *J* 5.5, C(2)*H*), 4.04-4.18 (2H, m, CH$_3$C*H*$_2$O), 7.32 (1H, dd, *J* 5.1, 7.9, ArC(2')*H*), 7.44-7.49 (1H, m, ArC(6')*H*), 7.52-7.57 (2H, m, ArC(1')*H*, ArC(7')*H*), 7.61 (1H, d, *J* 7.9, ArC(5')*H*), 8.16 (1H, d, *J* 7.6, ArC(8')*H*), 8.53 (1H, dd, *J* 1.2, 5.1, ArC(3')*H*); δ_C(100.6 MHz; *d*4-MeOD) 14.4 (*C*H$_3$CH$_2$O), 38.4 (*C*(3)), 39.8 and 54.9 (*C*(4) and *C*(9')), 55.3 (*C*(2)), 63.2 (CH$_3$*C*H$_2$O), 65.4 (*C*H$_2$OH), 122.7 (Ar*C*(8')H), 123.0 (Ar*C*(2')H), 124.1 (Ar*C*(2')H), 129.8 (Ar*C*(6')H), 131.2, 133.4 (Ar*C*(1')H and Ar*C*(7')H), 138.7, 141.5, 141.8 (all Ar*C*), 148.7 (Ar*C*(3')H), 158.3 (Ar*C*), 166.0, 170.6 (both (*C*=O)); *m/z* (ESI+) 351 ([M+H]$^+$, 89%), 373([M+Na]$^+$, 35%), 701 ([2M+H]$^+$, 94%), 723 ([2M+Na]$^+$, 100%); HRMS 351.1332 ([M+H]$^+$, $C_{20}H_{19}N_2O_4$ requires 351.1339).

(2*S*,3*S*,4*R*,6*R*)-1,5'-Diaza-4-ethoxycarbonyl-2-hydroxymethyl-5-oxo-spiro [bicyclo[3.1.0]hexane-6,9'-fluorene] 13i

To a solution of cyclopropane **8e'** (128 mg, 0.29 mmol) in DCM (4 mL) at r.t. was added a mixture containing TFA (0.45 mL, 5.84 mmol) and water (0.45 mL). Purification by column chromatography over silica gel eluting with (EtOAc) yielded deprotected alcohol **13i** (68 mg, 67 %) as a white solid. R_f = 0.07 (EtOAc); m.p. dec. 150-151 ^oC; $[\alpha]_D^{25}$ +51.7 (c = 0.92, MeOH); υ_{max}/cm^{-1} (film) 3265 (br, OH), 1701 (C=O), 1585, 1457, 1401, 1256, 1187, 1108; δ_H(400.2 MHz; *d*4-MeOD) 1.03 (3H, t, *J* 7.1, C*H*$_3$CH$_2$O), 3.49 (1H, s, C(3)*H*), 3.78 (1H, dd, *J* 5.9, 11.2, C*H*HOH), 3.83 (1H, dd, *J* 5.2, 11.2, CH*H*OH), 3.95 (1H, t, *J* 5.6, C(2)*H*), 4.02-4.16 (2H, m, CH$_3$C*H*$_2$O), 7.14 (1H, d, *J* 7.3, ArC(1')*H*), 7.37 (1H, dd, *J* 5.1, 8.0, ArC(7')*H*), 7.43-7.53 (2H, m, ArC(3')*H*, ArC(2')*H*), 7.96 (1H, dd, *J* 1.3, 8.0, ArC(8')*H*), 8.07-8.11 (1H, m,

ArC(4')*H*), 8.55 (1H, dd, 1.2, 5.1, ArC(6')*H*); δ_C(100.6 MHz; *d*4-MeOD) 14.3 (*C*H_3CH_2O), 38.6 (*C*(3)), 39.6, 49.9 (*C*(4), and *C*(9')), 55.6 (*C*(2)), 63.2 (CH_3*C*H_2O), 65.4 (*C*H_2OH), 122.2 (Ar*C*(1')H), 122.3 (Ar*C*(4')H), 123.4 (Ar*C*(7')H), 129.4 (Ar*C*(3')H), 131.3 (Ar*C*(2')H), 133.6 (Ar*C*(8')H), 136.2, 137.9, 145.0 (all Ar*C*), 147.9 (Ar*C*(6')H), 160.7 (Ar*C*), 165.7, 170.5 (both (*C*=O)); *m/z* (ESI+) 351 ($[M+H]^+$, 74%), 701 ($[2M+H]^+$, 100%), 723 ($[2M+Na]^+$, 43%); HRMS 351.1339 ($[M+H]^+$, $C_{20}H_{19}N_2O_4$ requires 351.1339).

(2*S*,3*S*,4*R*)-1,4',5'-Triaza-4-ethoxycarbonyl-2-hydroxymethyl-5-oxo-spiro[bicyclo [3.1.0]hexane-6,9'-fluorene] 13j

To a solution of cyclopropane **8f** (59 mg, 0.13 mmol) in DCM (4 mL) at r.t. was added a mixture containing TFA (0.26 mL, 3.36 mmol) and water (0.10 mL). The mixture was stirred for 5 h before being concentrated *in vacuo*. Toluene (2 mL) was added followed by 1 drop of water and the mixture was re-concentrated *in vacuo*. The addition of toluene and water followed by re-concentration was repeated (x 2) to give a brown viscous oil which was dissolved in the minimum amount of MeOH and heated to 60 ^oC. EtOAc was added dropwise to the solution until a white solid began to precipitate. After cooling to r.t. the brown liquid was removed before the white precipitate was washed with EtOAc (2 x 1 mL) and dried *in vacuo* to leave alcohol **13j** as a white solid (45 mg, 96%); m.p. dec. > 110 ^oC; $[\alpha]_D^{25}$ +44 (c = 0.18, MeOH); υ_{max}/cm^{-1} (film) 3217 (br, OH), 1733 (br, C=O), 1358, 1257, 1183, 1122; δ_H(400.2 MHz; *d*4-MeOD) 1.10 (3H, t, *J* 7.1, C*H*$_3$CH$_2$O), 3.66 (1H, s, C(3)*H*), 3.77-3.87 (2H, m, C*H*$_2$OH), 4.00 (1H, t, *J* 5.4, C(2)*H*), 4.07-4.21 (2H, m, CH$_3$C*H*$_2$O), 7.53 (2H, br s, ArC(2')*H*, ArC(7')*H*), 7.74 (1H, d, *J* 7.7, ArC(8')*H*), 8.07 (1H, d, *J* 7.9, ArC(1')*H*), 8.74 (2H, br s, ArC(3')*H*, ArC(6')*H*); δ_C(125.8 MHz; *d*4-MeOD) 14.3 (*C*H_3CH$_2$O), 38.1 (*C*(4)), 38.6 (*C*(3)), 48.3 (*C*(9')), 55.6 (*C*(2)), 63.4 (*C*H_2OH), 65.2 (CH$_3$*C*H_2O), 125.1, 125.3 (Ar*C*(2')H and Ar*C*(7')H), 132.2, 133.4 (Ar*C*(1')H and Ar*C*(8')H), 137.1, 140.1 (both Ar*C*), 149.7,

149.9 (Ar*C*(3')H and Ar*C*(6')H), 155.7, 158.5 (both Ar*C*), 165.6, 170.2 (both *C*=O); *m/z* (ESI+) 352 ([M+H]$^+$, 100%); HRMS 374.1106 ([M+Na]$^+$, $C_{19}H_{17}N_3NaO_4$ requires 374.1111).

(2*S*,3*R*,4*S*)-1-Aza-6,6-diphenyl-2-hydroxymethyl-5-oxo-bicyclo[3.1.0]hexane 13k

Following the general procedure, after column chromatography eluting with EtOAc, cyclopropane **4a** (110 mg, 0.30 mmol) yielded alcohol **13k** as a white solid (62 mg, 74%); R_f = 0.31 (MeOH/EtOAc, 1 : 9); m.p. 159-160 ^{o}C; $[\alpha]_D^{22}$ -33.2 (c = 1.1, $CHCl_3$); υ_{max}/cm^{-1} (film) 3406, 3350 (NH), 3055, 1687, 1496, 1447, 1266, 737, 706; δ_H(400.2 MHz; $CDCl_3$) 2.49 (1H, d, *J* 6.2, C(4)*H*), 2.54 (1H, d, *J* 6.2, C(3)*H*), 2.67 (1H, br s, CH_2OH), 3.53 (1H, t, *J* 4.5, C(2)*H*), 3.66 (1H, dd, *J* 6.3, 11.2, C*H*HOH), 3.74 (1H, dd, *J* 11.2, CH*H*OH), 5.58 (1H, s, N*H*), 7.11-7.32 (8H, m, Ph*H*), 7.42 (2H, d, *J* 7.92, Ph*H*); δ_C(100.6 MHz; $CDCl_3$) 30.9 (*C*(4)), 35.1 (*C*(3)), 39.5 (*C*(6)), 55.4 (*C*(2)), 65.6 (*C*H_2OH), 126.7 (*p*-Ph*C*H), 127.0 (Ph*C*H), 127.5 (*p*-Ph'*C*H), 128.5, 128.9, 129.8 (all Ph*C*H), 136.5, 143.4 (Ph*C* and Ph*C'*), 175.5 (*C*=O); *m/z* (ESI-) 278 ([M-H]$^-$, 100%); HRMS 302.1151 ([M+Na]$^+$, $C_{18}H_{17}NaNO_2$ requires 302.1151).

(2*S*,3*S*,4*S*)-1-Aza-2-hydroxymethyl-5-oxo-spiro[bicyclo[3.1.0]hexane-6,9'-fluorene] 13l

Following the general procedure, after column chromatography eluting with EtOAc, cyclopropane **7a** (194 mg, 0.53 mmol) yielded alcohol **13l** as a white solid (136 mg, 93%); R_f = 0.16 (EtOAc); m.p. 176-178 ^{o}C; $[\alpha]_D^{21}$ +235.5 (c = 2.6, $CHCl_3$); υ_{max}/cm^{-1} (film) 3286, 1682, 1448, 1204, 1138, 731; δ_H(400.2 MHz; $CDCl_3$) 2.42 (1H, d, *J* 5.1, (C(4)*H*)), 2.75 (1H, d, *J* 5.1, (C(3)*H*)), 3.37-3.61 (2H, m, CH_2OH), 3.76 (1H, br s, (C(2)*H*)), 4.57 (1H, br s, CH_2OH), 6.69 (1H, d, *J* 7.3, ArC*H*), 7.03 (1H, t, *J* 7.4, ArC*H*), 7.09-7.22 (2H, m, ArC*H*), 7.22-7.32 (2H, m, ArC*H*), 7.63 (2H, t, *J* 7.1, ArC*H*), 7.80 (1H, s, N*H*); δ_C(100.6 MHz; $CDCl_3$) 34.2 (*C*(4)), 35.7 (*C*(9')), 35.8 (*C*(3)), 55.7 (*C*(2)), 64.7 (*C*H_2OH), 118.9, 119.5, 120.3, 122.3, 127.0, 127.4, 127.4, 127.4 (all Ar*C*H), 138.2, 140.1, 142.0, 145.5 (all Ar*C*),

174.7 (*C*=O); *m/z* (ESI+) 336 ([M+MeCN+NH_4]$^+$, 100%); HRMS 300.0993 ([M+Na]$^+$, $C_{18}H_{15}NNaO_2$ requires 300.0995).

(2*S*,3*S*,4*R*)-1-Aza-4-ethoxycarbonyl-2-methoxycarbonyl-5-oxo-spiro[bicyclo[3.1.0] hexane-6,9'-fluorene] 14a

A solution of **13c** (149 mg, 0.43 mmol) and PDC (825 mg, 2.34 mmol) in DMF (10 mL) was stirred under N_2 for 2 d at 40 ^oC. After cooling to 0 ^oC, a solution of diazomethane in Et_2O was distilled into the reaction mixture. After standing for 30 mins, the mixture was purged with N_2 to remove excess diazomethane. Sat. aq. $NaHCO_3$ (20 mL) and EtOAc (20 mL) were added and the layers were separated. The aqueous layer was extracted with EtOAc (3 x 20 mL) before the combined organic extracts were dried over $MgSO_4$ and the solvent removed *in vacuo* to leave a brown oil which was purified by column chromatography over silica eluting with EtOAc/Petrol (1 : 2) to give **14a** (59 mg, 37%) as a white wax; R_f = 0.35 (EtOAc/Petrol, 2 : 1); $[\alpha]_D^{18}$ -17.8 (c = 5.1, $CHCl_3$); υ_{max}/cm^{-1} (film) 3286 (br, NH), 1723, 1450, 1266, 1110, 1018, 744; δ_H(400.2 MHz; $CDCl_3$) 1.06 (3H, t, *J* 7.1, C*H*$_3$CH$_2$O), 3.62 (1H, s, C(3)*H*), 3.88 (3H, s, CO$_2$C*H*$_3$), 4.08-4.28 (2H, m, CH$_3$C*H*$_2$O), 4.52 (1H, s, C(2)*H*), 7.09 (1H, d, *J* 7.7, Ar*H*), 7.15-7.21 (1H, m, Ar*H*), 7.25-7.30 (1H, m, Ar*H*), 7.38-7.49 (3H, m, Ar*H*), 7.66 (1H, s, N*H*), 7.80 (1H, d, *J* 7.6, Ar*H*), 7.87 (1H, d, *J* 7.6, Ar*H*); δ_C(100.6 MHz; $CDCl_3$) 14.0 (*C*H$_3$CH$_2$O), 36.9 (*C*(3)), 41.0 and 46.1 (*C*(4) and *C*(6)), 53.2 (CO$_2$*C*H$_3$), 54.0 (*C*(2)), 62.2 (CH$_3$*C*H$_2$O), 119.9, 120.6, 120.7, 122.3, 127.2, 127.9, 128.0, 128.3 (all Ar*C*H), 138.1, 139.3, 141.7, 142.5 (all Ar*C*), 164.0, 169.1, 169.9 (all (*C*=O)); *m/z* (ESI+) 436 ([M+MeCN+NH_4]$^+$, 100%), 813 ([2M+MeCN+NH_4]$^+$, 30%), 777 ([2M+Na]$^+$, 13%), 1154 ([3M+Na]$^+$, 5%), 400 ([M+Na]$^+$, 3%); HRMS 400.1153 ([M+Na]$^+$, $C_{22}H_{19}NNaO_5$ requires 400.1155).

(2*S*,3*S*,4*S*)-1-Aza-2-methoxycarbonyl-5-oxo-spiro[bicyclo[3.1.0]hexane-6,9'-fluorene] 14b

A solution of **13l** (61 mg, 0.22 mmol) and PDC (385 mg, 1.11 mmol) in DMF (4.5 mL) was stirred under N_2 for 2 d at 40 ^oC. After cooling to 0 ^oC, a solution of diazomethane in Et_2O was distilled directly into the reaction mixture. After standing for 30 min, the mixture was purged with N_2 to remove excess diazomethane. The mixture was concentrated *in vacuo* to give a dark brown solid. Sat. aq. $NaHCO_3$ (10 mL) and EtOAc (10mL) were added and the layers were separated. The aqueous layer was extracted with EtOAc (3 x 10 mL) before the combined organic extracts were washed with brine, dried over $MgSO_4$ and the solvent removed *in vacuo* to leave a pale green oil which was purified by column chromatography over silica eluting with EtOAc/Petrol (1 : 1) to give **14b** (19 mg, 29%) as a clear gum; R_f = 0.24 (EtOAc/Petrol, 2 : 1); $[\alpha]_D^{21}$ +112.0 (c = 1.0, $CHCl_3$); υ_{max}/cm^{-1} (film) 3225, 3063, 2954, 1749 and 1704 (2 x C=O), 1449, 1216, 773; δ_H(400.2 MHz; $CDCl_3$); 2.99 (1H, d, *J* 6.3, C(3)*H*), 3.17 (1H, d, *J* 6.25, C(4)*H*), 3.85 (3H, s, CO_2CH_3), 4.56 (1H, s, C(2)*H*), 6.96 (1H, d, *J* 7.6, Ar*H*), 7.01 (1H, s, N*H*), 7.19 (1H, dt, *J* 1.1, 7.6, Ar*H*), 7.33 (1H, dt, *J* 1.1, 7.6, Ar*H*), 7.38-7.46 (3H, m, Ar*H*), 7.81 (1H, d, *J* 7.6, Ar*H*), 7.89 (1H, d, *J* 7.6, Ar*H*); δ_C(100.6 MHz; $CDCl_3$) 34.5, 34.5 (*C*(3) and *C*(4)), 36.6 (*C*(6)), 53.1 (CO_2CH_3), 55.4 (*C*(2)), 118.9, 119.8, 120.7, 122.1, 127.4, 127.6, 127.7, 127.8 (all Ar*C*H), 138.5, 139.6, 142.4, 145.4 (Ar*C*), 170.7, 172.7 (both (*C*=O)); *m/z* (ESI+) 364 ($[M+MeCN+NH_4]^+$, 100%), 669 ($[2M+MeCN+NH_4]^+$, 23%); HRMS 328.0944 ($[M+Na]^+$, $C_{19}H_{15}NNaO_3$ requires 328.0944).

Attempted synthesis of (2*S*,3*R*,4*R*)-1-aza-6,6-diphenyl-4-ethoxycarbonyl-2-methoxy carbonyl-5-oxo-bicyclo[3.1.0]-hexane 14a

A solution of **13a** (114 mg, 0.32 mmol) and PDC (565 mg, 1.62 mmol) in DMF (6 mL) was stirred under N_2 for 2 d at 40 ^oC. After cooling to 0 ^oC, a solution of diazomethane in Et_2O was distilled directly into the reaction mixture. After standing for 1 h, AcOH was added to quench any excess diazomethane. The mixture was concentrated *in vacuo* to give a dark

brown solid. Sat. aq. $NaHCO_3$ (10 mL) and EtOAc (10mL) were added and the layers were separated. The aqueous layer was extracted with EtOAc (3 x 10 mL) before the combined organic extracts were washed with brine, dried over $MgSO_4$ and the solvent removed *in vacuo* to leave a pale green oil which was purified by column chromatography over silica eluting with EtOAc/Petrol (1 : 3) to give **14a** (35 mg, 29%) as a white wax whose spectroscopic properties were identical to those reported above.

Attempted synthesis of (2*S*,3*R*,4*R*)-4-ethoxycarbonyl-5-oxo-6,6-diphenyl-1-aza bicyclo[3.1.0]hexane-2-aldehyde[78]

To a solution of oxalyl chloride (20 μL, 0.23 mmol) in dry DCM (1 mL) at -78 ^oC was added DMSO (50 μL). After 15 mins a solution of **13a** (70 mg, 0.19 mmol) in DCM (0.33 mL) was added dropwise. The mixture was then left to stir at -78 ^oC for 35 min before triethylamine (0.32 mL) was added (all in one go) and the left to stir for 45 min before taking to -42 ^oC. After 10 min, water (1 mL) was added (all in one go) and the mixture was allowed to warm to r.t. before DCM (5 mL) and water (5 mL) were added. The organic layer was removed and the aqueous layer washed with DCM (2 x 10 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated *in vacuo*. The crude was purified by column chromatography over silica eluting with EtOAc/Petrol (1 : 5) to give **15** (46 mg, 66%) as a white solid; m.p. 176-177 ^oC, Rf = 0.73 (EtOAc); $[\alpha]_D^{18}$ -84.8 (c = 1.4, $CHCl_3$); υ_{max}/cm^{-1} (film) 3428 (OH), 3060, 2981, 1732 (C=O), 1496, 1409, 1264, 1138, 1085, 1022; δ_H(400.2 MHz; $CDCl_3$) 0.89 (6H, t, *J* 7.1, C*H*$_3$CH$_2$O), 2.30-3.20 (2H, br s, O*H*), 3.33 (2H, d, *J* 8.0, C(2)*H*), 3.37 (2H, s, C(3)*H*), 3.90 (4H, q, *J* 7.1, CH$_3$C*H*$_2$O), 5.16 (2H, d, *J* 8.0, C(*H*)(N)(OH)), 7.14-7.26 (6H, m, Ph*H*), 7.26-7.40 (10H, m, Ph*H*), 7.48 (4H, d, *J* 7.6, Ph*H*); δ_C(100.6 MHz; $CDCl_3$) 13.6 (*C*H$_3$CH$_2$O), 31.7 (*C*(3)), 44.0 and 48.9 (*C*(4) and *C*(6)), 52.9 (*C*(2)), 61.5 (CH$_3$*C*H$_2$O), 74.5 (R*C*(H)(N)(OH)), 127.6, 127.8, 128.2, 128.6, 128.7, 129.0 (all Ph*C*H), 136.0, 129.0 (both

Ph*C*), 164.5 and 168.4 (both (*C*=O)); *m/z* (ESI+) 757 ([M+NH_4+MeCN]$^+$, 100%), 721 (([M+Na]$^+$, 25%).

(2*S*,3*R*,4*R*)-1-Aza-6,6-di(*p*-methoxyphenyl)-2-hydroxymethyl-5-oxo-bicyclo[3.1.0] hexane-4-carboxylic acid 16

Following general procedure, a solution of **13b** (12 mg, 29 μmol), MeOH (0.9 mL), water (0.3 mL) and lithium hydroxide (6 mg, 143 μmol) was stirred at r.t. for 2 d. The work-up procedure yielded **16** as a white solid (11 mg, 100%) which required no further purification; m.p. dec. > 134 ^oC; $[\alpha]_D^{22}$ -105 (c = 0.55, MeOH); υ_{max}/cm^{-1} (film) 3315 (br OH), 2936, 2838, 1731 (C=O), 1671 (C=O), 1609, 1581, 1512, 1441, 1292, 1248, 1178, 1114, 1032, 841, 735; δ_H(500.3 MHz; *d*4-MeOD) 3.25 (1H, s, C(3)*H*), 3.45 (1H, t, *J* 5.1, C(2)*H*), 3.55-3.69 (2H, m, CH_2OH), 3.71 (3H, s, OCH_3), 3.73 (3H, s, OC'H_3), 6.77 (2H, d, *J* 8.4, Ar'*H* (*o*- to OMe)), 6.85 (2H, d, *J* 8.3, Ar*H* (*o*- to OMe)), 7.31 (2H, d, *J* 8.4, Ar'*H* (*m*- to OMe)), 7.39 (2H, d, *J* 8.4, Ar*H* (*m*- to OMe)); δ_C(125.8 MHz; *d*4-MeOD) 35.0 (*C*(3)), 45.5 (*C*(9')), 54.9 (*C*(4)), 55.0 (*C*(2)), 55.7 (*C*H_3O), 55.7 (*C*'H_3O), 65.3 (*C*H_2OH), 114.8 (Ar'*C*H (*o*- to OMe)), 115.3 (Ar*C*H (*o*- to OMe)), 130.8 (Ar'*C*H (*m*- to OMe)), 130.9 (Ar*C*H (*m*- to OMe)), 131.5 and 133.7 (Ar'*C* (*p*- to OMe) and Ar*C* (*p*- to OMe)), 160.2 and 160.4, (Ar'*C*OCH_3 and Ar*C*OCH_3), 161.4 and 174.3 (both (*C*=O)); *m/z* (ESI-) 382 ([M-H]$^-$, 100%); HRMS 406.1257 ([M+Na]$^+$, $C_{21}H_{21}NNaO_6$ requires 406.1261).

(2*S*,3*S*,4*R*)-1-Aza-2-hydroxymethyl-5-oxo-spiro[bicyclo[3.1.0]hexane-6,9'-fluorene]-4-carboxylic acid 17a

Following the general procedure, a solution of **13c** (90 mg, 0.26 mmol), MeOH (6 mL), water (2 mL) and lithium hydroxide (57 mg, 1.36 mmol) was stirred at r.t. for 2 d. The work-up procedure yielded **17a** as a white powder (80 mg, 97%) which required no further

purification; m.p. 196°C (dec.); $[\alpha]_D^{20}$ +70.5 (c = 1.65, EtOH); δ_H(400.2 MHz; MeOD, D_2O) 3.30 (1H, s, C(3)*H*), 3.77-3.87 (2H, m, CH_2OH), 3.97 (1H, t, *J* 5.4, C(2)*H*), 7.17 (1H, d, *J* 7.7, Ar*H*), 7.28-7.36 (2H, m, Ar*H*), 7.41 (1H, t, *J* 7.5, Ar*H*), 7.44-7.52 (2H, m, Ar*H*), 7.84 (1H, d, *J* 7.58, Ar*H*), 7.91 (1H, d, *J* 7.5, Ar*H*); δ_C(100.6 MHz; MeOD, D_2O) 37.5 (*C*(3)), 40.7 (*C*(9')), 54.3 (*C*(2)), 64.3 (*C*H_2OH), 120.0 (Ar*C*H), 120.7, 121.2, 122.9, 127.6, 127.8, 128.1, 128.5, 139.2 (Ar*C*), 139.5 (Ar*C*), 142.6 (Ar*C*), 142.7 (Ar*C*), 167.3 and 170.9 (both (*C*=O)); *m/z* (ESI-) 962 ([3M-H]$^-$, 100%), 641 ([2M-H]$^-$, 94%); HRMS 320.0923 ([M-H]$^-$, $C_{19}H_{14}NO_4$ requires 320.0917).

(2*S*,3*S*,4*R*,6*R*)-1,5'-Diaza-2-hydroxymethyl-5-oxo-spiro[bicyclo[3.1.0]hexane-6,9'-fluorene]-4-carboxylic acid 17b

To a solution of **13i** (11 mg, 33 μmol) in MeOH/H_2O (3 : 1) (1.2 mL) was added LiOH (7 mg, 167 μmol). The mix was stirred vigorously for 2 d and concentrated *in vacuo*. D_2O (1 mL) was added and the solution was concentrated, to leave **17b** as a mixture containing excess LiOD; δ_H(500.3 MHz; D_2O) 2.97 (1H, s, C(3)*H*), 3.65-3.74 (3H, m, CH_2OH, C(2)*H*), 6.95 (1H, m, ArC(4')*H*), 7.09 (1H, dd, *J* 5.0, 8.2, ArC(7')*H*), 7.23-7.29 (2H, m, ArC(2')*H*, ArC(3')*H*), 7.52 (1H, dd, *J* 1.3, 8.2, ArC(8')*H*), 7.67-7.71 (1H, m, ArC(1')*H*), 8.22 (1H, dd, *J* 1.3, 5.0, ArC(6')*H*); δ_C(125.8 MHz; D_2O) 37.6 (*C*(4)), 38.0 (*C*(3)), 51.0 (*C*(9')), 55.0 (*C*(2)), 64.1 (*C*H_2OH), 120.2 (Ar*C*(1')H), 120.7 (Ar*C*(4')H), 121.9 (Ar*C*(7')H), 127.5 and 129.5 (Ar*C*(2')H and Ar*C*(3')H), 130.8 (Ar*C*(8')H), 134.5, 136.7, 144.1 (all Ar*C*), 147.0 (Ar*C*(6')H), 159.2 (Ar*C*), 170.0 and 173.1 (both (*C*=O)); *m/z* (ESI-) 321 ([M-H]$^-$, 100%); HRMS 321.0874 ([M-H]$^-$, $C_{18}H_{13}N_2O_4$ requires 321.0881).

(2*S*,3*S*,4*R*)-1,4',5'-Triaza-2-hydroxymethyl-5-oxo-spiro[bicyclo[3.1.0]hexane-6,9'-fluorene]-4-carboxylic acid 17c

To a solution of **13j** (16 mg, 46 μmol) in MeOH/H_2O (3 : 1) (1.8 mL) was added LiOH (10 mg, 228 μmol). The mix was stirred vigorously for 2 d and concentrated *in vacuo*. D_2O (1 mL) was added and the solution was concentrated, to leave **17c** as a mixture containing excess LiOD; δ_H(500.3 MHz; D_2O) 3.16-3.20 (1H, br s, C(3)*H*), 3.68-3.78 (2H, m, CH_2OH), 3.81-3.87 (1H, m, C(2)*H*), 7.23-7.31 (2H, m, ArC(2')*H*, ArC(7')*H*), 7.44-7.49 and 7.73-7.78 (2H, m, ArC(1')*H*, ArC(8')*H*), 8.42-8.48 (2H, m, ArC(3')*H*, ArC(6')*H*); δ_C(125.8 MHz; D_2O) 35.9 (*C*(4)), 38.6 (*C*(3)), 51.2 (*C*(9')), 56.1 (*C*(2)), 64.3 (*C*H_2OH), 123.7 and 123.7 (Ar*C*(2')H and Ar*C*(7')H), 129.9 and 131.3 (Ar*C*(1')H and Ar*C*(8')H), 136.1, 139.5 (both Ar*C*), 148.3 and 148.4 (Ar*C*(3')H and Ar*C*(6')H), 154.3, 157.3 (both Ar*C*), 168.3, 173.0 (both (*C*=O)); *m/z* (ESI-) 322 ([M-H]$^-$, 100%); HRMS 328.0918 ([M-H]$^-$, $C_{17}H_{11}LiN_3O_4$ requires 328.0915).

(2*S*,3*S*,4*R*)-1-Aza-5-oxo-spiro[bicyclo[3.1.0]hexane-6,9'-fluorene]-2,4-biscarboxylic acid 18a

Following the general procedure, a solution of **14a** (25 mg, 66 μmol), MeOH (2.1 mL), water (0.7 mL) and lithium hydroxide (40 mg, 953 μmol) was stirred at r.t. for 3 d. The work-up procedure yielded **18a** as a white solid (22 mg, 100%) which required no further purification; m.p. dec. > 171 ^oC; $[\alpha]_D^{18}$ +20.3 (c = 0.6, MeOH); υ_{max}/cm^{-1} (film) 3584, 3386 (br COO-H), 1680 (C=O), 1447, 1214; δ_H(500.3 MHz; *d*4-MeOD) 3.54 (1H, s, C(3)*H*), 4.51 (1H, s, C(2)*H*), 7.21 (1H, d, *J* 7.8, Ar*H*), 7.27-7.34 (2H, m, Ar*H*), 7.42 (1H, t, *J* 7.5, Ar*H*), 7.47 (1H, t, *J* 7.5, Ar*H*), 7.53 (1H, d, *J* 7.9, Ar*H*), 7.87 (1H, d, *J* 7.6, Ar*H*), 7.94 (1H, d, *J* 7.6, Ar*H*); δ_C(125.8 MHz; *d*4-MeOD) 38.7 (*C*(3)), 42.1 (*C*(9')), 54.9 (*C*(2)), 55.3 (*C*(4)), 120.9, 121.7, 122.2, 123.6, 128.5, 128.6, 129.0, 129.4 (all Ar*C*H), 139.9, 140.6, 143.6, 144.0 (all Ar*C*), 167.2, 171.2, 173.2 (all (*C*=O)); *m/z* (ESI-) 334 ([M-H]$^-$, 100%); HRMS 334.0739 ([M-H]$^-$, $C_{19}H_{13}NO_5$ requires 334.0721).

(2*S*,3*S*,4*S*)-1-Azaspiro-5-oxo[bicyclo[3.1.0]hexane-6,9'-fluorene]-2-carboxylic acid 18b

Following the general procedure, a solution of **14b** (10 mg, 33 μmol), MeOH (1.5 mL), water (0.5 mL) and lithium hydroxide (20 mg, 477 μmol) was stirred at r.t. for 2 d. The work-up procedure yielded **18b** as a glassy solid (9 mg, 100%) which required no further purification; m.p. dec. > 171 ^{o}C; $[\alpha]_D^{18}$ +101.7 (c = 0.35, MeOH); υ_{max}/cm^{-1} (film) 3240 (br COOH), 3070, 1750 (sh C=O), 1700 (C=O), 1449, 1218, 733; δ_H(500.3 MHz; *d*4-MeOD) 2.98 (1H, d, *J* 6.3, C(3)*H*), 3.18 (1H, d, *J* 6.3, C(4)*H*), 4.55 (1H, s, C(2)*H*), 7.09 (1H, d, *J* 7.6, Ar*H*), 7.30-7.49 (5H, m, Ar*H*), 7.85 (1H, d, *J* 7.5, Ar*H*), 7.95 (1H, d, *J* 7.6, Ar*H*); δ_C(125.8 MHz; *d*4-MeOD) 35.6 (*C*(4)), 36.2 (*C*(3)), 37.5 (*C*(9')), 57.0 (*C*(2)), 120.3, 120.7, 121.7, 123.2, 128.4, 128.4, 128.9, 128.9 (all Ar*C*H), 139.6, 141.0, 143.8, 146.9 (all Ar*C*), 173.6 and 175.3 (both (*C*=O)); *m/z* (ESI-) 290 ([M-H]$^-$, 94%); HRMS 314.0787 ([M+Na]$^+$, $C_{18}H_{13}NNaO_3$ requires 314.0788).

(2*R*,5*S*,6*S*,7*R*,9*S*)-4'-Methoxycarbonylspiro[1-aza-7-ethoxycarbonyl-3-oxa-8-oxo-2-phenyl-tricyclo[4.3.0^{1,5}.0^{6,7}]nonane-9,9'-fluorene] 19a

To a mixture of **8b** (213 mg, 0.46 mmol), TEMPO (11 mg, 0.07 mmol), NaH_2PO_4 (3.1 mL, 0.67 M) and MeCN (3.6 mL) at 37 ^{o}C was added $NaClO_2$ (120 mg, 1.32 mmol) followed by 5 drops of 8% aq. NaOCl. The mixture was stirred vigorously for 5 h before allowing to cool to r.t. and then poured over an ice-cold solution of sodium sulfite (1.0 g in 1.0 mL water and 2.0 g of ice). EtOAc (5 mL) was added and the organic layer was separated. The aqueous layer was extracted with EtOAc (4 x 5 mL), before the combined organics were dried over Na_2SO_4 and concentrated *in vacuo* to yield the crude acid a white solid which was used without further purification; HRMS 482.1598 ([M+H]$^+$, $C_{29}H_{24}NO_6$ requires 482.1599); The residue was dissolved in EtOAc (10 mL) and diazomethane (approx. 3 mmol) was distilled directly into the solution. After 0.5 h, the excess diazomethane was quenched with AcOH and the solvents were removed *in vacuo* to leave **19a** as a white foam (210 mg, 93%) which required

no further purification. $[\alpha]_D^{25}$ +114 (c = 1.0, $CHCl_3$); υ_{max}/cm^{-1} (film) 2983, 1716 (C=O), 1435, 1272, 1135, 1027, 731; δ_H(400.2 MHz; $CDCl_3$) 1.02 (3H, t, *J* 7.1, C*H*$_3$CH$_2$O), 3.46 (1H, s, C(6)*H*), 3.93 (1H, dd, *J* 8.0, 9.4, C(4)*H*H), 4.03 (3H, s, CO$_2$C*H*$_3$), 4.04-4.16 (2H, m, CH$_3$C*H*$_2$O), 4.19 (1H, dd, *J* 6.1, 9.4, C(5)*H*), 4.50 (1H, dd, *J* 6.1, 7.8, C(4)H*H*), 6.50 (1H, s, C(2)*H*), 6.98-7.03 (1H, m, Ar*H*), 7.11 (1H, dd, *J* 0.9, 7.8, Ar*H*), 7.27 (1H, t, *J* 7.8, Ar*H*), 7.32-7.60 (7H, m, Ar*H*), 7.72 (1H, dd, *J* 1.0, 7.7, Ar*H*), 8.26 (1H, d, *J* 7.9, Ar*H*); δ_C(100.6 MHz; $CDCl_3$) 13.8 (*C*H$_3$CH$_2$O), 37.8 (*C*(6)), 42.4 and 49.7 (*C*(7) and *C*(9')), 52.4 (CO$_2$*C*H$_3$), 56.1 (*C*(5)), 62.2 (CH$_3$*C*H$_2$O), 69.6 (*C*(4)), 88.8 (*C*(2)), 123.0, 123.0, 124.8, 125.8, 126.2 (Ar*C*H), 126.7 (Ar*C*CO$_2$CH$_3$), 127.9, 128.0, 128.5, 128.8, 129.2 (Ar*C*H), 137.6 (Ph*C*), 138.2, 139.6, 140.6, 143.6 (Ar*C*), 164.4, 168.5, 170.4 (*C*=O); HRMS 496.1754 ($[M+H]^+$, $C_{30}H_{26}NO_6$ requires 496.1755).

(2*R*,5*S*,6*S*,7*R*,9*R*)-5'-Methoxycarbonylspiro[1-aza-7-ethoxycarbonyl-3-oxa-8-oxo-2-phenyl-tricyclo[4.3.0^{1,5}.0^{6,7}]nonane-9,9'-fluorene] 19b

A (1 : 1) mixture of diastereoisomers **8b and 8b'** (291 mg) was oxidised by an identical procedure to that described for the preparation of **19a** above, with quantitative conversion. Column chromatography over silica gel eluting with EtOAc/Petrol (1 : 3) furnished **19b**. $[\alpha]_D^{25}$ +84 (c = 1.2, $CHCl_3$); υ_{max}/cm^{-1} (film) 2983, 1721 (C=O), 1433, 1372, 1276, 1134, 1049, 734; δ_H(400.2 MHz; $CDCl_3$) 1.02 (3H, t, *J* 7.1, C*H*$_3$CH$_2$O), 3.47 (1H, s, C(6)*H*), 3.92 (1H, dd, *J* 8.0, 9.4, C(4)*H*H), 4.01 (3H, s, CO$_2$C*H*$_3$), 4.06-4.15 (2H, m, CH$_3$C*H*$_2$O), 4.18 (1H, dd, *J* 6.1, 9.4, C(5)*H*), 4.51 (1H, dd, *J* 6.1, 8.0, C(4)H*H*), 6.49 (1H, s, C(2)*H*), 6.95-6.71 (2H, m, Ar*H*), 7.28 (1H, t, *J* 7.6, Ar*H*), 7.34-7.48 (4H, m, *o*-Ph*H*, *p*-Ph*H*, Ar*H*), 7.55-7.57 (2H, m, *m*-Ph*H*), 7.65-7.70 (2H, m, Ar*H*), 8.16 (1H, d, *J* 7.9, Ar*H*); δ_C(50.3 MHz; $CDCl_3$) 13.8 (*C*H$_3$CH$_2$O), 38.4 (*C*(6)), 42.6 and 50.0 (*C*(7) and *C*(9')), 52.5 (CO$_2$*C*H$_3$), 56.3 (*C*(5)), 62.3 (CH$_3$*C*H$_2$O), 69.8 (*C*(4)), 88.9 (*C*(2)), 119.9, 124.4 (both Ar*C*H), 125.7 (*p*-Ph*C*H), 126.2,

126.6 (both Ar*C*H), 127.4 (Ar*C*CO_2Me), 127.9 (*p*-Ph*C*H), 127.9 (Ar*C*H), 128.6 (*m*-Ph*C*H), 128.9, 129.4 (both Ar*C*H), 137.4, 138.3, 140.7 (all Ar*C*), 140.9 (Ph*C*), 142.8 (Ar*C*), 164.4, 168.7, 171.1 (all (*C*=O)); HRMS 518.1575 ($[M+Na]^+$, $C_{30}H_{25}NNaO_6$ requires 518.1574).

(2*S*,3*S*,4*R*,6*S*)-1-Aza-4-ethoxycarbonyl-2-hydroxymethyl-4'-methoxycarbonyl-5-oxo-spiro[bicyclo[3.1.0]hexane-6,9'-fluorene] 20a

To a solution of cyclopropane **19a** (100 mg, 0.20 mmol) in DCM (4 mL) at r.t. was added a mixture containing TFA (0.16 mL, 2.0 mmol) and water (0.16 mL). After removal of solvents the resultant oil was dissolved in EtOAc (1 mL). Petrol was added dropwise until a white precipitate had formed and the filtrate was revoved *via* pipette leaving **20a** as a white solid (74 mg, 90%) which required no further purification; m.p. dec. > 140 ^oC; $[\alpha]_D^{25}$ +79.9 (c = 0.76, $CHCl_3$); υ_{max}/cm^{-1} (film) 3333 br (OH), 2383, 2358, 1723 (C=O), 1442, 1279; δ_H(500.3 MHz; $CDCl_3$) 0.98 (3H, t, *J* 7.1, CH_3CH_2O), 3.27 (1H, s, C(3)*H*), 3.36 (1H, br s, O*H*), 3.69-3.76 (1H, m, C*H*HOH), 3.80-3.86 (1H, m, CH*H*OH) 3.90-3.95 (1H, m, C(2)*H*), 3.96-4.14 (2H, m, CH_3CH_2O), 4.03 (3H, s, $ArCO_2CH_3$), 7.13 (1H, d, *J* 7.6, ArC(1')*H*), 7.20 (1H, t, *J* 7.6, ArC(6')*H*), 7.26 (1H, t, *J* 7.7, ArC(2')*H*), 7.39 (1H, t, *J* 7.6, ArC(7')*H*), 7.50 (1H, d, *J* 7.9, ArC(5')*H*), 7.57 (1H, s, N*H*), 7.71 (1H, d, *J* 7.6, ArC(3')*H*), 8.29 (1H, d, *J* 7.9, ArC(8')*H*); δ_C(125.8 MHz; $CDCl_3$) 13.9 (CH_3CH_2O), 37.4 (*C*(3)), 39.7 and 47.6 (*C*(4) and *C*(9')), 52.5 ($ArCO_2CH_3$), 53.7 (*C*(2)), 62.2 (CH_3CH_2O), 64.5 (CH_2OH), 122.2 (Ar*C*(5')), 123.3 (Ar*C*(1')H), 125.0 (Ar*C*(8')H), 126.3 (Ar*C*(2')H), 126.8 (Ar*C*(4')CO_2CH_3), 128.1 (Ar*C*(7')H), 128.7 (Ar*C*(6')H), 129.2 (Ar*C*(3')H), 137.8, 139.6, 140.6, 144.0 (all Ar*C*), 165.2, 168.8, 169.7 (all (*C*=O)); HRMS 430.1259 ($[M+Na]^+$, $C_{23}H_{21}NNaO_6$ requires 430.1261).

(2*S*,3*S*,4*R*,6*R*)-1-Aza-4-ethoxycarbonyl-2-hydroxymethyl-5'-methyloxycarbonyl-5-oxo-spiro[bicyclo[3.1.0]hexane-6,9'-fluorene] 20b

To a solution of cyclopropane **19b** (94 mg, 0.19 mmol) in DCM (4 mL) at r.t. was added a mixture containing TFA (0.15 mL, 2.0 mmol) and water (0.15 mL). After removal of solvents the resultant oil was dissolved in EtOAc (1 mL). Petrol was added dropwise until a white precipitate had formed and the filtrate was revoved *via* pipette leaving **20b** as a white solid (57 mg, 74%) which required no further purification; $[\alpha]_D^{25}$ +33.7 (c = 0.51, $CHCl_3$); υ_{max}/cm^{-1} (film) 3345 (br, OH), 1724 (C=O), 1704 (C=O), 1434, 1138, 1117; δ_H(500.3 MHz; $CDCl_3$) 1.00 (3H, t, *J* 7.1, C*H*$_3$CH$_2$O), 2.71 (1H, br s, O*H*), 3.21 (1H, s, C(3)*H*), 3.79-3.90 (2H, m, CH$_2$OH), 3.96 (1H, br s, C(2)*H*), 4.01-4.18 (2H, m, CH$_3$CH$_2$O), 4.03 (3H, s, ArCO$_2$CH$_3$), 7.00 (1H, d, *J* 7.6, ArC(1')*H*), 7.18 (1H, t, *J* 7.7, ArC(7')*H*), 7.27-7.31 (1H, m, ArC(2')*H*), 7.37 (1H, t, *J* 7.3, ArC(3')*H*), 7.60 (1H, br s, N*H*), 7.63 (1H, d, *J* 7.9 ArC(6' or 8')*H*), 7.67 (1H, d, *J* 7.9 ArC(6' or 8')*H*), 8.18 (1H, d, *J* 7.6 ArC(4')*H*); δ_C(125.8 MHz; $CDCl_3$) 13.9 (*C*H$_3$CH$_2$O), 37.9 (*C*(3)), 39.7 and 39.8 (*C*(4) and *C*(9')), 52.5 (ArCO$_2$*C*H$_3$), 53.9 (*C*(2)), 62.3 (CH$_3$*C*H$_2$O), 68.5 (*C*H$_2$OH), 120.0 (Ar*C*(1')H), 124.3 (Ar*C*(4')H), 125.4 (Ar*C*(6' or 8')H), 127.0 (Ar*C*(7')H), 127.4 (Ar*C*(5')CO$_2$CH$_3$), 127.7 (Ar*C*(3')H), 127.8 (Ar*C*(2')H), 129.2 (Ar*C*(6' or 8')H), 137.4, 140.6, 140.8, 143.1 (all Ar*C*), 165.0, 168.8, 168.9 (all (*C*=O)); HRMS 430.1258 ($[M+Na]^+$, $C_{23}H_{21}NNaO_6$ requires 430.1261).

(2*S*,3*S*,4*R*)-1-Aza-1-benzyl-spiro[bicyclo[3.1.0]hexane-6,9'-fluorene]-2,4-bismethanol 21a[79]

To a suspension of $LiAlH_4$ (100 mg, 2.64 mmol) in THF (3 mL) at r.t. under an atmosphere of N_2 was added a solution of cyclopropane **8a** (250 mg, 0.57 mmol) in THF (6 mL). After stirring for 1 h, the mixture was heated to reflux for 14 h before being allowed to cool to r.t. Sat. aq. $NaHCO_3$ was added dropwise to the mixture until gas evolution ceased and the reaction mixture was poured into sat. aq. $NaHCO_3$ (15 mL) before EtOAc (25 mL) was added. The mixture was shaken vigorously and allowed to settle before the organic layer was removed *via* pipette. The aqueous was extracted with EtOAc (3 x 20 mL) (*via* pipette) and the

combined organics were dried over $MgSO_4$ before being concentrated *in vacuo*. Column chromatography over silica gel eluting with EtOAc/Petrol (1 : 1 → 3.5 : 1) yielded diol **21a** as a viscous oil (160 mg, 73%); R_f = 0.20 (EtOAc/Petrol, 1 : 1); $[\alpha]_D^{30}$ -5.95 (c = 1, $CHCl_3$); υ_{max}/cm^{-1} (film) 3356 (OH), 3061, 2872, 1449, 1176, 1028, 920, 796, 740, 701; δ_H(400.2 MHz; $CDCl_3$) 2.78 (1H, s, C(3)*H*), 3.00-3.50 (2H, br s, O*H*), 3.46 (1H, d, *J* 10.1, C(4)C*H*HOH), 3.70-3.76 (3H, m, C(4)CH*H*OH, C(2)*H*, C(2)C*H*HOH), 3.92-4.00 (2H, m, C(2)H*H*OH, C(5)*H*H), 4.07 (1H, d, *J* 12.0, C(5)H*H*), 4.11 (2H, s, PhCH_2N), 7.21 (1H, d, *J* 7.5, Ar*H*), 7.29-7.50 (9H, m, Ar*H*), 7.77 (1H, d, *J* 7.7, Ar*H*), 7.85 (1H, d, *J* 7.5, Ar*H*), 7.91 (1H, d, *J* 7.8, Ar*H*); δ_C(100.6 MHz; $CDCl_3$) 40.7 (*C*(3)), 44.3 and 44.7 (*C*(4) and *C*(9')), 54.2 (Ph*C*H_2N), 57.7 (C(4)*C*H_2OH), 61.3 (*C*(5)), 63.3 (*C*(2)), 63.3 (C(2)*C*H_2OH), 119.8, 120.1, 122.3, 125.5, 126.2, 126.3, 126.3, 126.4, 127.2, 127.2 (all Ar*C*H and *p*-Ph*C*H), 128.5 and 128.6 (*o*-Ph*C*H and *m*-Ph*C*H), 139.0, 139.5, 141.7, 142.4, 144.6 (Ph*C* and 4 x Ar*C*); *m/z* (ESI+) 384 ($[M+H]^+$, 100%), 406 ($[M+Na]^+$, 39%); HRMS 384.1960 ($[M+H]^+$, $C_{26}H_{26}NO_2$ requires 384.1958).

(2*S*,3*S*,4*R*)-1-Aza-1-benzyl-spiro[bicyclo[3.1.0]hexane-6,9'-fluorene]-2,4-bisaldehyde 21b[34]

To a solution of oxalyl chloride (0.05 mL, 0.55 mmol) in DCM (2.7 mL) at -78 °C was added dry DMSO (0.08 mL, 1.13 mmol), dropwise. After 15 min a solution of diol **21a** (103 mg, 0.27 mmol) in DCM (1 mL) was added dropwise. Then, Et_3N (0.45 mL, 3.23 mmol) was added and the mixture was allowed to warm to -30 °C over 40 min. Water (5 mL) was added to quench the reaction mixture. The organic layer was separated and the aqueous was extracted with DCM (3 x 5 mL), before the combined organics were dried over Na_2SO_4 and concentrated *in vacuo* to leave a brown oil which was purified over a plug of silica gel eluting with DCM/Petrol (1 : 1) to give bis-aldehyde **21b** as a viscous oil (90 mg, 88%); δ_H(400.2 MHz; $CDCl_3$) 3.28 (1H, d, *J* 10.9, C(5)*H*H), 3.54 (1H, s, C(3)*H*), 4.06 (1H, d, *J* 3.0, C(2)*H*),

4.17 (2H, s, PhC*H*$_2$N), 4.20 (1H, d, *J* 10.9, C(5)H*H*), 7.26-7.50 (11H, m, Ar*H*), 7.84 (1H, d, *J* 7.5, Ar*H*), 7.90 (1H, d, *J* 7.6, Ar*H*), 9.70 (1H, d, *J* 3.0, C(2)C*H*O), 9.80 (1H, s, C(4)C*H*O); δ_C(125.8 MHz; $CDCl_3$) 40.2 (*C*(3)), 48.2 (*C*(9')), 50.6 (*C*(5)), 51.2 (*C*(4)), 54.7 (Ph*C*H$_2$N), 69.4 (*C*(2)), 120.4, 120.6, 122.9, 125.4, 126.6, 126.8, 127.6, 127.7, 127.8 (all Ar*C*H and *p*-Ph*C*H), 128.7, 129.0 (*o*-Ph*C*H and *m*-Ph*C*H), 137.7, 139.2, 140.0, 141.0, 142.0 (Ph*C* and 4 x Ar*C*), 196.1 and 200.4 (both(*C*=O)); *m/z* (ESI+) 379 ($[M+H]^+$, 71%).

(3*S*,4*R*)-1-Aza-1-benzyl-4-methoxycarbonyl-2-oxo-spiro[bicyclo[3.1.0]hexane-6,9'-fluorene] 23[80, 81]

To a solution of freshly prepared bisaldehyde **21b** (100 mg, 0.26 mmol) and 2-methyl-2-butene (5 mL) in MeCN (5 mL) and 2-methyl-2-propanol (8.5 mL) at 0 ^oC was slowly added a solution of $NaClO_2$ (1.33 g, 14.71 mmol) and NaH_2PO_4 (1.33 g, 11.1 mmol) in water (2.8 mL). The mixture was stirred at r.t. for 1.5 h before being quenched by dropwise addition of sat. aq. $Na_2S_2O_3$ (6 mL). Then, EtOAc (10 mL) and water (10 mL) were added. The organic layer was separated and the aqueous layer was extracted with EtOAc (3 x 10 mL) before the combined organics were washed with brine, dried over Na_2SO_4 and concentrated *in vacuo* to leave a yellow oil. The resultant oil was dissolved in EtOAc (3 mL) and diazomethane (approx. 3 mmol) was distilled directly into the solution. After 0.5 h, the excess diazomethane was quenched with AcOH and the solvents were removed *in vacuo*. The resultant oil was purified by column chromatography over silica gel eluting with EtOAc/Petrol (1 : 3) to furnish pyrrolidinone **23** as a viscous oil (12 mg, 12% over two steps); R_f = 0.19 (EtOAc/Petrol, 1 : 3); $[\alpha]_D^{17}$ -176 (c = 0.82, $CHCl_3$); υ_{max}/cm^{-1} (film) 1736 (C=O), 1698 (C=O), 1480, 1438, 1250, 1122, 911, 734, 703; δ_H(400.2 MHz; $CDCl_3$) 3.53 (3H, s, C*H*$_3$O), 3.60 (1H, d, *J* 1.6, C(3)*H*), 3.78 (1H, dd, *J* 1.6, 12.4, NC*H*HPh), 3.88 (1H, d, *J* 12.4, NCH*H*Ph), 4.18 (1H, d, *J* 14.4, C(5)*H*H), 5.02 (1H, d, *J* 14.4, C(5)H*H*), 6.73 (1H, d, *J* 7.6,

Ar*H*), 7.12 (1H, td, *J* 1.2, 7.6, Ar*H*), 7.23-7.28 (2H, m, Ar*H*), 7.34-7.46 (7H, m, Ar*H*), 7.75 (1H, d, *J* 7.2, Ar*H*), 7.84 (1H, d, *J* 7.2, Ar*H*); δ_C(100.6 MHz; $CDCl_3$) 38.6 (*C*(3)), 40.7 and 42.1 (*C*(4) and *C*(9)), 46.7 (N*C*H_2Ph), 48.5 (*C*(5)), 52.5 (*C*H_3O), 119.7, 120.6, 122.1, 122.6, 127.1, 127.3, 127.7, 128.0, 128.2 (Ar*C*H and *p*-Ph*C*H), 129.0 and 129.1 (o-Ph*C*H and *p*-Ph*C*H), 134.8 (Ph*C*), 139.0, 139.6, 141.2, 142.3 (all Ar*C*), 167.4 and 168.3 (both (*C*=O)); *m/z* (ESI+) 396 ($[M+H]^+$, 36%); HRMS 418.1417 ($[M+Na]^+$, $C_{26}H_{21}NNaO_3$ requires 418.1414).

(2*S*,3*R*,4*R*)-1-Aza-1-*tert*-butyloxycarbonyl-6,6-diphenyl-bicyclo[3.1.0]hexane-2,4-bismethanol 24a

BH_3 (1 M in THF, 2.5 mL) was added to a solution of lactam **13a** (87 mg, 0.25 mmol) in THF (1 mL) under an atmosphere of N_2. The mixture was then heated at reflux for 2 d before cooling to r.t. NaOH (1 M, 4 mL) was added dropwise and the mixture was stirred for 10 min before the THF was removed *in vacuo*. EtOAc (5 mL) was added and the organic layer was separated. The aqueous layer was extracted with EtOAc (4 x 10 mL) before the combined organics were washed with brine, dried over Na_2SO_4 and concentrated *in vacuo* to give a white residue. The residue was dissolved in DCM (3 mL) and di-*tert*-butyl dicarbonate (87 mg, 0.40 mmol) was added. The solution was stirred for 12 h before being concentrated *in vacuo* to give a white residue which was purified by column chromatography over silica gel eluting with EtOAc/Petrol (2 : 1) to furnish **24a** as a white foam (63 mg, 64 %); R_f = 0.22 (EtOAc/Petrol, 2 : 1); $[\alpha]_D^{25}$ -146.9 (c = 0.5, $CHCl_3$); υ_{max}/cm^{-1} (film) 3397 (OH), 2976, 1669 (C=O), 1418, 1171, 1125, 710; δ_H(500.3 MHz; $CDCl_3$) Approximate rotamer ratio (A:B) = (6:4), 1.13 (9H^B, s, (C*H*$^B{}_3$)$_3$CO), 1.14 (9H^A, s, (C*H*$^A{}_3$)$_3$CO), 2.01-2.06 (1H^A, m, C(4)CH_2O*H*^{A}), 2.13 (1H^A, s, C(3)*H*^{A}), 2.16-2.22 (1H^B, m, C(4)CH_2O*H*^{B}), 2.23 (1H^B, s, C(3)*H*^{B}), 2.79-2.83 (1H^A, m, C(2)CH_2O*H*^{A}), 3.40 (1H^B, dd, *J* 3.2, 11.5, C(4)C*H*^{B}HOH), 3.51 (1H^A, dd, *J* 3.6, 11.5, C(4)C*H*^{A}HOH), 3.68-4.03 (5H^A and 6H^B, m, C(2)*H*^{B}, C(2)C$H_2{}^{A+B}$OH,

C(5)CH_2^{A+B}, C(4)HH^{A+B}OH), 4.20 (1H^A, dd, *J* 3.1, 5.2, C(2)H^A), 7.10-7.16 (2H, m, *p*-Ph*H*, *p*-Ph*H*'), 7.20-7.39 (8H, m, Ar*H*); δ_C(125.8 MHz; $CDCl_3$) 28.1 and 28.2 ((CH_3)$_3$CO), 32.3 and 32.9 (*C*(3)), 39.2 and 39.8, 42.7 and 42.8 (*C*(4) and (*C*(9')), 48.6 and 49.0 (*C*(5)), 59.3 (*C*(2)), 63.4 and 63.6 (C(4)CH_2OH), 65.9 and 66.2 (C(2)CH_2OH), 79.3 and 79.5 ((CH$_3$)$_3$*C*O), 126.6 and 126.7 (*p*-Ph*C*H), 126.8 (*p*-Ph'*C*H), 128.0 and 128.1, 128.6, 128.7 and 128.8), 129.0 and 129.1 (*o*-Ph*C*H, *o*-Ph'*C*H, *m*-Ph*C*H and *m*-Ph'*C*H), 138.1 and 138.3 and 141.9 (Ph*C* and Ph'*C*), 152.4 and 153.8 (*C*=O); *m/z* (ESI+) 813 ([M+Na]$^+$, 100%), 396 ([M+H]$^+$, 43%); HRMS 418.1984 ([M+Na]$^+$, $C_{24}H_{29}NNaO_4$ requires 418.1989).

(2*S*,3*R*,4*R*)-1-Aza-1-*tert*-butyloxycarbonyl-6,6-di(*p*-methoxyphenyl)-bicyclo [3.1.0]hexane-2,4-bismethanol 24b

BH_3 (1 M in THF, 5.0 mL) was added dropwise to a solution of **13b** (285 mg, 0.69 mmol) in THF (7 mL) under an atmosphere of N_2. The mixture was then heated at reflux for 2 d before cooling to r.t. NaOH (1 M, 15 mL) was added dropwise and the mixture was stirred for 10 min before the THF was removed *in vacuo*. EtOAc (15 mL) was added and the organic layer was separated. The aqueous layer was extracted with EtOAc (4 x 10 mL) before the combined organics were washed with brine, dried over Na_2SO_4 and concentrated *in vacuo* to give a white residue. The residue was dissolved in DCM (5 mL) and di-*tert*-butyl dicarbonate (227 mg, 1.04 mmol) was added. The solution was stirred for 12 h before being concentrated *in vacuo* to give an oil which was purified by column chromatography over silica gel eluting with EtOAc/Petrol (2 : 1) to furnish diol **24b** as a colourless viscous oil (123 mg, 39%); R_f = 0.11 (EtOAc/Petrol, 2 : 1); $[\alpha]_D^{20}$ -101.2 (c = 0.75, $CHCl_3$); υ_{max}/cm^{-1} (film) 3406 (OH), 2935, 1669 (C=O), 1608, 1511, 1413, 1367, 1289, 1246, 1176, 1124, 1036, 911, 835, 733; δ_H(500.3 MHz; $CDCl_3$) Approximate rotamer ratio (A:B) = (3:2); 1.14 (9H^B, s, (CH$^B_3$)$_3$CO), 1.15 (9H^A, s, (CH$^A_3$)$_3$CO), 2.06 (1H^A, s, C(3)H^A), 2.15 (1H^B, s, C(3)H^B), 2.37 (1H^A, br s, OH'^{A}), 2.71

(1H^{B}, br s, OH'^{B}), 2.85 (1H^{A}, br s, OH^{A}), 3.17 (1H^{B}, br s, OH^{B}), 3.38 (1H^{B}, d, *J* 11.5, C(2)C*H*^{B}HOH), 3.50 (1H^{A}, d, *J* 11.4, C(2)C*H*^{A}HOH), 3.65 (11H^{A} + 12H^{B}, m, C(2)*H*^{B}, C(2)H*H*$^{(A+B)}$OH, C*H'*$_3$O, C*H*$_3$O, C(5)*H*$_2$, C(4)C*H*$_2$OH), 4.17 (1H^{A}, dd, *J* 3.4, 4.8, C(2)*H*^{A}), 6.73-6.83 (4H, m, Ar*H*$^{(A+B)}$ (*o*- to OMe)), 7.17-7.27 (4H, m, Ar*H*$^{(A+B)}$ (*m*- to OMe)); δ_C(125.8 MHz; $CDCl_3$) 28.0 and 28.1 ((*C*H$_3$)$_3$CO), 32.5 and 33.0 (*C*(3)), 39.4 and 39.9 (*C*(4)), 41.2 and 41.2 (*C*(9')), 48.7 and 49.0 (C(4)*C*H$_2$OH), 55.0 (*C'*H$_3$O), 55.2 (*C*H$_3$O), 59.3 and 59.5 (*C*(2)), 63.2 and 63.5 (C(2)*C*H$_2$OH), 65.7 and 66.0 (*C*(5)), 79.3 and 79.4 ((CH$_3$)$_3$*C*O), 114.1 (Ar'*C*H (*o*- to OMe)), 114.1 (Ar*C*H (*o*- to OMe)), 128.8 and 128.9 (Ar'*C*H (*m*- to OMe)), 129.8 and 129.9 (Ar*C*H (*m*- to OMe)), 130.7 and 130.9 (Ar'*C* (*p*- to OMe)), 134.4 (Ar*C* (*p*- to OMe)), 152.6 and 153.8 (*C*=O), 158.0 and 158.1 (Ar*C'*OMe), 158.1 and 158.2 (Ar*C*OMe); *m/z* (ESI+) 456 ([M+H]$^+$, 92%), 912 ([2M+H]$^+$, 100%); HRMS 472.2188 ([M+Na]$^+$, $C_{26}H_{33}NNaO_6$ requires 472.2200).

(2*S*,3*S*,4*R*)-1-Aza-1-*tert*-butyloxycarbonyl-spiro[bicyclo[3.1.0]hexane-6,9'-fluorene]-2,4-bismethanol 24c and (2*S*,3*S*,4*R*)-1-Aza-5-oxo-spiro[bicyclo[3.1.0]hexane-6,9'-fluorene]-2,4-bismethanol 25c

Method 1: A mixture of lactam **13c** (211 mg, 0.60 mmol) and $LiAlH_4$ (110 mg, 2.90 mmol) in THF (10 mL) was heated at reflux under an atmosphere of N_2 for 16 h. After cooling to r.t. the mixture was added dropwise to water (50 mL) under a constant flow of N_2 and then concentrated to remove THF. EtOAc (20 mL) was added and the precipitate was filtered and washed with EtOAc (2 x 15 mL). The organic layer was separated and the aqueous extracted with EtOAc (3 x 15 mL) before the combined organics were washed with brine, dried over Na_2SO_4 and concentrated *in vacuo* leaving an off white solid. The residual solid was dissolved in EtOAc (5 mL) and di-*tert*-butyl dicarbonate (127 mg, 0.58 mmol) was added. This mixture was stirred at r.t. for 14 h before the solvent was removed *in vacuo*. Purification

by column chromatography over silica gel eluting with EtOAc/Petrol (2 : 1 → 1 : 1) gave **24c** as a white foam (32 mg, 13 %) and **25c** as a crystalline solid (100 mg, 54%).

Method 2: BH_3 (1M in THF, 17 mL) was added to a solution of lactam **13c** (882 mg, 2.52 mmol) in THF (5 mL) under an atmosphere of N_2. The mixture was then heated at reflux for 2 d before cooling to r.t. NaOH (1 M, 25 mL) was added dropwise and the mixture was stirred for 10 min before THF was removed *in vacuo*. EtOAc (20 mL) was added and the organic layer was separated. The aqueous layer was extracted with EtOAc (4 x 15 mL) before the combined organics were washed with brine, dried over Na_2SO_4 and concentrated *in vacuo* to give a white residue. The residue was dissolved in DCM (20 mL) and di-*tert*-butyl dicarbonate (881 mg, 4.03 mmol) was added. The solution was stirred for 12 h before being concentrated *in vacuo* to give a white residue which was purified by column chromatography over silica gel eluting with EtOAc/Petrol (2 : 1 → 1 : 1) to furnish **24c** as a white foam (472 mg, 48 %) and **25c** as a crystalline solid (398 mg, 51%);

24c; R_f = 0.44 (EtOAc/Petrol, 2 : 1); $[\alpha]_D^{22}$ -21.4 (c = 1, $CHCl_3$); υ_{max}/cm^{-1} (film) 3385 (OH), 2361, 1669 (C=O), 1393, 1170, 1125, 739; δ_H(400.2 MHz; $CDCl_3$) Approximate rotamer ratio (A:B) = (6:4), 1.56 ($9H^B$, s, $(CH^B_3)_3CO$), 1.57 ($9H^A$, s, $(CH^A_3)_3CO$), 2.70 ($1H^A$, s, C(3)H^A), 2.72 ($1H^B$, s, C(3)H^B), 2.98 ($1H^A$, br s, OH'^A), 3.49-4.40 ($1H^B$, m, OH'^B and 9H, m, O*H*, C(2)*H*, C(2)CH_2OH, C(5)*HH*, C(4)CH_2OH), 6.98 (1H, d, *J* 7.9, Ar*H*), 7.12-7.44 (5H, m, Ar*H*), 7.83 (1H, d, *J* 7.5, Ar*H*), 7.89 (1H, d, *J* 7.5, Ar*H*); δ_C(100.6 MHz; $CDCl_3$) 28.5 ((*C*H_3)$_3$CO), 38.2 and 39.2 (*C*(3)), 42.9, 43.2 and 43.2, 43.3 (*C*(4) and (*C*(9')), 52.4 and 52.5 (C(4)*C*H_2OH), 60.3 and 60.5 (*C*(2)), 60.6 and 60.8 (C(2)*C*H_2OH), 65.0 (*C*(5)), 80.6 and 80.7 ((CH$_3$)$_3$*C*O), 119.8 and 119.9, 120.4 and 120.4, 122.1 and 122.2, 123.3 and 123.4 (4 x Ar*C*H), 126.5, 126.6, 126.6, 126.7, 126.7, 126.8, 127.0, 127.2 (4 x Ar*C*H), 139.5 and 139.6, (141.0 and 141.1, 141.8 and 141.9, 143.8 and 144.1 (4 x Ar*C*), 154.2 (*C*=O); *m/z* (ESI+) 416

([M+Na]$^+$, 100%), 394 ([M+H]$^+$, 57%); HRMS 416.1831 ([M+Na]$^+$, $C_{24}H_{27}NNaO_4$ requires 416.1832);

25c; R_f = 0.20 (EtOAc); m.p. dec. >250 ^oC (EtOAc); $[\alpha]_D^{19}$ +134 (c = 0.69, MeOH); δ_H(500.3 MHz; *d*4-MeOD) 3.13 (1H, s, C(3)*H*), 3.77 (1H, dd, *J* 6.2, 11.1, C(2)C*H*HOH), 3.82 (1H, dd, *J* 5.8, 11.1, C(2)CH*H*OH), 3.89 (1H, d, *J* 12.6, C(4)C*H*HOH), 4.00 (1H, t, *J* 5.8, C(2)*H*), 4.27 (1H, d, *J* 12.6, C(4)CH*H*OH), 7.25 (1H, d, *J* 7.6, Ar*H*), 7.29 (1H, t, *J* 7.6, Ar*H*), 7.37 (1H, t, *J* 7.4, Ar*H*), 7.40-7.45 (2H, m, Ar*H*), 7.49 (1H, d, *J* 7.9, Ar*H*), 7.87 (1H, d, *J* 7.5, Ar*H*), 7.90 (1H, d, *J* 7.6, Ar*H*); δ_C(125.8 MHz; $CDCl_3$) 38.0 (*C*(3)), 41.7 and 47.0 (*C*(4) and *C*(9')), 55.4 (*C*(2)), 57.3 (C(4)*C*H_2OH), 65.7 (C(2)*C*H_2OH), 121.0, 121.4, 123.5, 123.7, 128.0, 128.4, 128.6, 128.7 (all Ar*C*H), 140.7, 141.5, 143.1, 143.8 (all Ar*C*), 176.7 (*C*=O); *m/z* (ESI-) 306 ([M-H]$^-$, 100%); HRMS 330.1099 ([M+Na]$^+$, $C_{19}H_{17}NNaO_3$ requires 330.1101).

(2*S*,3*S*,4*R*,6*S*)-1,4'-Diaza-1-*tert*-butyloxycarbonyl-spiro[bicyclo[3.1.0]hexane-6,9'-fluorene]-2,4-bismethanol 24d

BH_3 (1 M in THF, 6.6 mL) was added dropwise to a solution of **13h** (330 mg, 0.94 mmol) in THF (4 mL) under an atmosphere of N_2. The mixture was then heated at reflux for 2 d before cooling to r.t. NaOH (1 M, 15 mL) was added dropwise and the mixture was stirred for 10 min before the THF was removed *in vacuo*. EtOAc (15 mL) was added and the organic layer was separated. The aqueous layer was extracted with EtOAc (4 x 10 mL) before the combined organics were washed with brine, dried over Na_2SO_4 and concentrated *in vacuo* to give a white residue. The residue was dissolved in EtOAc (5 mL) and di-*tert*-butyl dicarbonate (308 mg, 1.41 mmol) was added. The solution was stirred for 12 h before being concentrated *in vacuo* to give an oil which was purified by column chromatography over silica gel eluting with EtOAc/Petrol (2 : 1) to furnish diol **24d** as a white solid (152 mg, 41%); R_f = 0.32 (EtOAc); m.p. softens at 100 ^oC; $[\alpha]_D^{25}$ -69.1 (c = 1.0, MeOH); δ_H(500.3 MHz; *d*4-MeOD)

1.58 (4.5H, s, (C*H*$_3$)$_3$CO), 1.60 (4.5H, s, (C*H*$_3$)$_3$CO), 2.92 (0.5H, s, C(3)*H*), 2.94 (0.5H, s, C(3)*H*), 3.70-4.35 (7H, m, C(2)*H*, C(2)C*H*$_2$OH, C(4)C*H*$_2$OH, C(5)*H*$_2$), 7.01 (1H, dd, *J* 9.6, 8.3, ArC(5')*H*), 7.33 (1H, dd, *J* 7.8, 5.1, ArC(2')*H*), 7.36-7.40 (1H, m, ArC(6')*H*), 7.49 (1H, d, *J* 7.3, ArC(7')*H*), 7.73 (1H, d, *J* 7.7, ArC(1')*H*), 8.18 (1H, d, *J* 7.8, ArC(8')*H*), 8.48 (1H, d, *J* 5.1, ArC(3')*H*); δ_C(125.8 MHz; *d*4-MeOD) 29.0 (*C*H$_3$)$_3$CO), 39.7 and 40.7 (*C*(3)), 42.4 and 42.5 (*C*(4) and *C*(9')), 53.6 and 53.9 (C(4)*C*H$_2$OH), 59.1 and 60.4 (C(2)*C*H$_2$OH), 62.2 and 62.3 (*C*(2)), 63.5 and 64.3 (*C*(5)), 82.0 ((CH$_3$)$_3$*C*O), 122.3 (Ar*C*(2')H), 122.7 (Ar*C*(8')H), 124.4 (Ar*C*(5')H), 128.4 (Ar*C*(7')H), 130.3 and 130. (Ar*C*(6')H), 132.0 (Ar*C*(1')H), 140.6 and 140.7, 142.0, 143.9 and 144.0 (all Ar*C*), 148.0 (Ar*C*(3')H), 155.3 and 155.4 (Ar*C*), 159.2 and 159.3 (*C*=O); *m/z* (ESI+) 395 ([M+H]$^+$, 100%); HRMS 395.1961 ([M+H]$^+$, $C_{23}H_{27}N_2O_4$ requires 395.1965).

(2*S*,3*S*,4*R*,6*R*)-1,5'-Diaza-1-*tert*-butyloxycarbonyl-spiro[bicyclo[3.1.0]hexane-6,9'-fluorene]-2,4-bismethanol 24e and (2*S*,3*S*,4*R*,6*R*)-1,5'-Diaza-5-oxo-spiro[bicyclo[3.1.0]hexane-6,9'-fluorene]-2,4-bismethanol 25e

BH_3 (1 M in THF, 6 mL) was added dropwise to a solution of **13i** (308 mg, 0.88 mmol) in THF (5 mL) under an atmosphere of N_2. The mixture was then heated at reflux for 2 d before cooling to r.t. NaOH (1 M, 15 mL) was added dropwise and the mixture was stirred for 10 min before the THF was removed *in vacuo*. EtOAc (15 mL) was added and the organic layer was separated. The aqueous layer was extracted with EtOAc (4 x 10 mL) before the combined organics were washed with brine, dried over Na_2SO_4 and concentrated *in vacuo* to give a white residue. The residue was dissolved in a small quantity of MeOH (0.5 mL) and EtOAc (3 mL) was added. The MeOH was removed slowly *in vacuo* at 40 ^oC, leaving a precipitate in the EtOAc solution. The precipitate was allowed to settle and the EtOAc was removed *via* pipette, before being washed with more EtOAc (2 x 3 mL) and dried *in vacuo* to leave **25e** (60

mg, 22%) as a white powder. The combined EtOAc washes were concentrated *in vacuo*, leaving an oil, to which, EtOAc (4 mL) and di-*tert*-butyl dicarbonate (164 mg, 0.56 mmol) were added. The solution was stirred for 12 h before being concentrated *in vacuo* to give an oil which was purified by column chromatography over silica gel eluting with EtOAc/Petrol (2 : 1) to furnish diol **24e** as a wax (77 mg, 22%);

24e; R_f = 0.51 (EtOAc); $[\alpha]_D^{25}$ -12.1 (c = 0.65, $CHCl_3$); υ_{max}/cm^{-1} (film) 3375 (br OH), 1691 (C=O), 1393, 1163, 1122, 746; δ_H(500.3 MHz; $CDCl_3$) 1.54 (3/7 x 9H, s, $(CH^B_3)_3CO$), 1.57(4/7 x 9H, s, $(CH^A_3)_3CO$), 2.73 (4/7 x 1H, s, C(3)H^A), 2.76 (3/7 x 1H, s, C(3)H^B), 3.87-4.37 (7H, m, C(2)*H*, C(2)CH_2OH, C(4)CH_2OH, C(5)H_2), 7.07-7.12 (1H, m, Ar*C*(7')H), 7.19-7.26 (2H, m, Ar*C*(2')H, Ar*C*(8')H), 7.39-7.45 (2H, m, Ar*C*(1')H, Ar*C*(3')H), 8.07-8.11 (1H, m, Ar*C*(4')H), 8.50-8.54 (1H, m, Ar*C*(6')H); δ_C(125.8 MHz; *d*4-MeOD) 28.5 ($CH_3)_3CO$), 38.3 and 39.3 (*C*(3)), 41.3 and 41.4 and 43.7 (*C*(4) and *C*(9')), 52.7, and 52.8 (C(4)CH_2OH), 60.4, 60.6 (*C*(2) and C(2)CH_2OH), 64.8 and 64.9 (*C*(5)), 80.9 ($(CH_3)_3CO$), 121.0, 121.2) (Ar*C*(4')H and Ar*C*(7')H), 122.0 and 122.1 (Ar*C*(8' or 2')H), 127.2 and 127.3 and 128.6 (Ar*C*(1')H and Ar*C*(3')H), 130.7 and 130.9 (Ar*C*(8' or 2')H), 135.4 and 135.5, 138.8 and 138.9, 144.5, 144.7 (All Ar*C*), 147.4 (Ar*C*(6')H), (153.4, 154.0) (Ar*C*), (160.2, 160.2) (*C*=O); *m/z* (ESI+) 395 ($[M+H]^+$, 100%); HRMS 395.1962 ($[M+H]^+$, $C_{23}H_{27}N_2O_4$ requires 395.1965);

25e; m.p. dec. > 200 °C; $[\alpha]_D^{25}$ +74 (c = 1, MeOH); δ_H(500.3 MHz; *d*4-MeOD) 3.22 (1H, s, C(3)*H*), 3.75 (1H, dd, *J* 6.2, 10.9, C(2)*H*HOH), 3.80 (1H, dd, *J* 5.7, 10.9, C(2)H*H*OH), 3.88 (1H, d, *J* 12.6, C(4)*H*HOH), 3.95 (1H, t, *J* 5.9, C(2)*H*), 4.30 (1H, d, *J* 12.6 C(4)H*H*OH), 7.30 (1H, dd, *J* 5.0, 8.0, ArC(2')*H*), 7.35-7.39 (1H, m, ArC(8')*H*), 7.49-7.54 (2H, m, ArC(6')*H* and ArC(7')*H*), 7.91 (1H, dd, *J* 1.3, 8.0, ArC(1')*H*), 8.10-8.14 (1H, m, ArC(5')*H*), 8.52 (1H, dd, *J* 1.3, 5.0, ArC(3')*H*); δ_C(125.8 MHz; *d*4-MeOD) 38.3 (*C*(3)), 40.0 and 47.1 (*C*(4) and *C*(9')), 55.8 (*C*(2)), 57.1 (C(4)CH_2OH), 65.8 (C(2)CH_2OH), 122.1 (Ar*C*(5')*H*), 122.9 (Ar*C*(2')*H*), 124.0 (Ar*C*(8')*H*), 128.8 and 130.3 (Ar*C*(6')*H* and Ar*C*(7')*H*), 132.2 (Ar*C*(1')*H*), 136.9,

139.4, 145.1 (all Ar*C*), 148.7 (Ar*C*(3')*H*), 161.1 (Ar*C*), 176.0 (*C*=O); *m/z* (ESI-) 307 ($[M-H]^-$, 100%); HRMS 309.1234 ($[M+H]^+$, $C_{18}H_{17}N_2O_3$ requires 309.1234).

(2*S*,3*R*,4*R*)-1-Aza-1-*tert*-butyloxycarbonyl-6,6-diphenyl-bicyclo[3.1.0]hexane-2-methanol 24g

BH_3 (1 M in THF, 2 mL) was added dropwise to a solution of **13k** (79 mg, 0.28 mmol) in THF (2 mL) under an atmosphere of N_2. The mixture was then heated at reflux for 2 d before cooling to r.t. NaOH (1 M, 10 mL) was added dropwise and the mixture was stirred for 10 min before the THF was removed *in vacuo*. EtOAc (10 mL) and water (5 mL) were added and the organic layer was separated. The aqueous layer was extracted with EtOAc (4 x 12 mL) before the combined organics were washed with brine, dried over Na_2SO_4 and concentrated *in vacuo* to give crude secondary amine as a white residue; *m/z* (ESI+) 267 ($[M+H]^+$, 100%); HRMS 266.1539 ($[M+H]^+$, $C_{18}H_{20}NO$ requires 266.1539); The residue was dissolved in DCM (3 mL) and di-*tert*-butyl dicarbonate (93 mg, 0.43 mmol) was added. The solution was stirred for 12 h before being concentrated *in vacuo* to give an oil which was purified by column chromatography over silica gel eluting with EtOAc/Petrol (1 : 3) to furnish **24g** as a colourless gum (85 mg, 82%); R_f = 0.15 (EtOAc/Petrol, 1:3); $[\alpha]_D^{25}$ -25 (c = 0.5, $CHCl_3$); δ_H(400.2 MHz; $CDCl_3$) 1.14 (5.4H, s, $(CH_3)_3CO$), 1.15 (3.6H, s, $(CH_3)_3CO$), 1.59-2.36 (3H, m, C(3)*H*, C(4)*H*, O*H*), 3.52-3.58 (1H, m, C(5)*H*H), 3.69-3.77 (1.4H, m, CH_2OH), 3.69-3.77 (0.6H, m, C(5)H*H*), 3.79-3.86 (0.6H, m, CH_2OH), 3.90 (0.4H, d, *J* 11.7, C(5)H*H*), 3.99 (0.4H, t, *J* 5.2, C(2)*H*), 4.24 (0.6H, dd, *J* 4.0, 7.7, C(2)*H*), 7.05-7.14 (3H, m, Ph*H*), 7.17-7.26 (3H, m, Ph*H*), 7.31-7.39 (4H, m, Ph*H*); δ_C(100.6 MHz; $CDCl_3$) 28.0 and 28.1) ($(CH_3)_3CO$), 30.3 and 30.4 (*C*(4)), 33.2 and 33.7 (*C*(3)), 35.7 and 35.8 (*C*(6)), 46.1 and 46.2 (*C*(5)), 59.6 and 59.7 (*C*(2)), 65.1 and 66.2 (CH_2OH), 79.5 and 79.7 ($(CH_3)_3CO$), 125.9, 126.7, 127.0, 128.3, 128.6, 129.1, 129.2 (all Ph*C*H), 136.0 and 136.3 (Ph'*C*), 145.2 and 145.4 (Ph*C*), 152.6 and 154.7

(*C*(O)(NR_2)(OR)); *m/z* (ESI+) 388 ($[M+Na]^+$, 82%), 366 ($[M+H]^+$, 71%); HRMS 388.1877 ($[M+Na]^+$, $C_{23}H_{27}NNaO_3$ requires 388.1883).

(2*S*,3*S*,4*R*)-1-Aza-1-*tert*-butyloxycarbonyl-spiro[bicyclo[3.1.0]hexane-6,9'-fluorene]-2,4-biscarboxylic acid 26a[53]

To a solution of ester **26b** (40 mg, 0.09 mmol) in MeOH (3 mL) and water (1 mL) was added lithium hydroxide (37 mg, 0.89 mmol). After stirring at r.t. for 2 d, MeOH was removed *in vacuo*. EtOAc (5 mL) was added and the organic layer was separated and concentrated to give unwanted organic material. Then, EtOAc (5 mL) and HCl (0.25 M, 10 mL) were added sequentially to the aqueous mixture. The organic layer was separated and the aqueous was extracted with EtOAc (3 x 5 mL) before the combined organic extracts were dried over Na_2SO_4 and concentrated to give diacid **26a** as a white foam (36 mg, 96 %) which required no further purification; $[\alpha]_D^{19}$ +489 (c = 2, $CHCl_3$); υ_{max}/cm^{-1} (film) 2980 (COO-H), 1708 (C=O), 1396, 1259, 1180, 1146, 738; δ_H(500.3 MHz; $CDCl_3$) 1.48 (4.5H, s, (C*H*$_3$)$_3$CO), 1.53 (4.5H, s, (C*H*$_3$)$_3$CO), 3.06 (0.5H, s, C(3)*H*), 3.28 (0.5H, s, C(3)*H*), 4.01 (0.5H, d, *J* 12.8, C(5)*H*H), 4.17 (0.5H, d, *J* 12.6, C(5)*H*H), 4.25 (0.5H, d, *J* 12.8, C(5)H*H*), 4.28 (0.5H, d, *J* 12.6, C(5)H*H*), 4.51 (0.5H, s, C(2)*H*), 4.69 (0.5H, s, C(2)*H*), 7.02 (0.5H, d, *J* 7.7, Ar*H'*), 7.10 (0.5H, d, *J* 7.7, Ar*H'*), 7.12-7.44 (5H, m, Ar*H*), 7.72 (0.5H, d, *J* 7.7, Ar*H''*), 7.75 (0.5H, d, *J* 7.2, Ar*H''*), 7.84 (1H, d, *J* 7.3, Ar*H'''*), 9.0 (2H, br, 2 x CO_2*H*); δ_C(125.8 MHz; $CDCl_3$) 28.2 and 28.4 (*C*H$_3$)$_3$CO), 37.9 and 39.1 (*C*(3)), 43.4, 44.0, 44.2, 44.3 (*C*(4) and *C*(9')), 49.8 and 49.9 (*C*(5)), 60.5 and 60.9 (*C*(2)), 82.0 ((CH$_3$)$_3$*C*O), 119.4 and 119.6 (Ar*C*H''), 120.7 (Ar*C*H'''), 121.9 and 122.2 (Ar*C*H), 123.5 and 123.8 (Ar*C*H'), 127.2 and 127.3, 127.5 and 127.7, 127.6 (4 x Ar*C*H), 138.5 and 138.6, 139.2 and 139.3, 142.5 and 142.8 (4 x Ar*C*), 153.3 and 154.0 (*C*(O)(NR_2)(OR)), 171.6 and 171.8 (*C*O_2H), 174.0 and 174.8 (*C'*O_2H); *m/z* (ESI-) 420 ($[M-H]^-$, 100%); HRMS 420.1455 ($[M-H]^-$, $C_{24}H_{22}NO_6$ requires 420.1453).

(2*S*,3*S*,4*R*)-1-Aza-1-*tert*-butyloxycarbonyl-spiro[bicyclo[3.1.0]hexane-6,9'-fluorene]-2,4-bismethyl-ester 26b

A mixture of alcohol **24c** (300 mg, 0.76 mmol), TEMPO (36 mg, 0.23 mmol), CH_3CN (7.6 mL), and NaH_2PO_4 (7.6 mL, 0.67 M) was warmed to 45 ^oC and allowed to cool to 37 ^oC. Then, $NaClO_2$ (414 mg, 4.57 mmol) was added followed by 3 drops of 10-13% aq. NaOCl. The solution was maintained at 37 ^oC for 20 h and then poured over an ice-cold saturated solution of sodium thiosulfate (10 mL). The resulting mixture was extracted with EtOAc (4 x 10 mL) and the combined layers were dried over Na_2SO_4 and concentrated to yield the crude diacid **26a**. A portion of the crude diacid **26a** (39 mg, 93 μmol) was dissolved in EtOAc (3 mL) and diazomethane (approx. 3 mmol) was distilled directly into the solution. After 0.5 h, the excess diazomethane was quenched with AcOH and the solvents were removed *in vacuo*. The resultant oil was purified by column chromatography over silica gel eluting with DCM/Petrol (1 : 1) to furnish ester **26b** as a white wax (41 mg, 34 % over two steps); R_f = 0.14 (DCM/Petrol, 1:1); $[\alpha]_D^{21}$ -68.4 (c = 0.8, $CHCl_3$); υ_{max}/cm^{-1} (film) 1740 (2 x (C=O)), 1704 (C=O); 1449, 1386, 1268, 1205, 1121, 737; δ_H(400.2 MHz; $CDCl_3$) Approximate rotamer ratio (A:B) = (11:10); 1.50 (9H^A, s, (C*H*^{A} $_3$)$_3$CO), 1.57 (9H^B, s, (C*H*^{B} $_3$)$_3$CO),), 3.15 (1H^A, s, C(3)*H*^{A}), 3.18 (1H^B, s, C(3)*H*^{B}), 3.58 (3H^B, s, C(4)$CO_2CH_3^B$), 3.58 (3H^A, s, C(4)$CO_2CH_3^A$), 3.86 (3H^A, s, C(2)$CO_2CH_3^A$), 3.87 (3H^B, s, C(4)$CO_2CH_3^B$), 4.04 (1H^B, d, *J* 12.1, C(5)*H*^{B}H), 4.11 (1H^A, d, *J* 12.2, C(5)*H*^{A}H), 4.25 (1H^B, d, *J* 12.1, C(5)H^B*H*), 4.30 (1H^A, d, *J* 12.2, C(5)H^A*H*), 4.58 (1H^A, s, C(2)*H*^{A}), 4.70 (1H^B, s, C(2)*H*^{B}), 7.11 (1H^B, d, *J* 7.9, Ar*H*^{B}), 7.14 (1H^A, d, *J* 7.9, Ar*H*^{A}), 7.23-7.48 (5H, m, Ar*H*), 7.79 (1H, d, *J* 7.5, Ar*H*), 7.90 (1H, d, *J* 7.3, Ar*H*); δ_C(100.6 MHz; $CDCl_3$) 28.2 and 28.4 ((*C*H$_3$)$_3$CO), 37.9 and 38.8 (*C*(3)), 43.4, 43.5, 43.7, 44.5 (*C*(4) and *C*(9')), 49.5 and 49.6 (*C*(5)), 52.4, 52.5, 52.6, 52.8 (C(2)CO_2CH_3, C(4)CO_2CH_3), 60.2 and 60.6 (*C*(2)), 81.2 ((CH$_3$)$_3$*C*O), 119.6 and 119.6, 120.7,

121.7 and 121.8, 123.7 and 123.7, 127.1 and 127.1, 127.3 and 127.5, 127.4, 127.7 (all Ar*C*H), 138.3 and 138.4, 139.4, 142.2 and 142.3, 142.6 and 142.6 (all Ar*C*), 152.6 and 153.1 (*C*(O)(NR_2)(OR), 167.5 and 167.5 (C(4)*C*O_2CH_3), 171.0 and 171.3 (C(2)*C*O_2CH_3); *m/z* (ESI+) 450 ($[M+H]^+$, 77%); HRMS 472.1722 ($[M+Na]^+$, $C_{26}H_{27}NNaO_6$ requires 472.1731).

(2*S*,3*S*,4*R*)-1-Aza-spiro[bicyclo[3.1.0]hexane-6,9'-fluorene]-2,4-biscarboxylic acid 27

A solution of diacid **26a** in TFA (2 mL) was stirred at room temperature for 3 h before being concentrated *in vacuo* to give a viscous brown oil. The oil was washed with EtOAc (2 mL) and allowed to stand until a white precipitate had settled. The organic solution was removed *via* pipette to give amino acid analogue **27** as a white solid (9 mg, 59%); m.p. dec. > 235 ^oC; δ_H(500.3 MHz; $CDCl_3$/*d*-TFA (6 : 1)) 3.82 (1H, d, *J* 2.5, C(3)*H*), 4.40 (1H, d, *J* 13.9, C(5)*H*H), 4.68 (1H, d, *J* 13.9, C(5)H*H*), 5.28 (1H, s, C(2)*H*), 7.12 (1H, d, *J* 7.9, Ar*H*), 7.34-7.38 (1H, m, Ar*H*), 7.39-7.43 (2H, m, Ar*H*), 7.48-7.52 (1H, m, Ar*H*), 7.60-7.64 (1H, m, Ar*H*), 7.86 (1H, d, *J* 7.6, Ar*H*), 8.01 (1H, d, *J* 7.6, Ar*H*); δ_C(125.8 MHz; $CDCl_3$/*d*-TFA (6 : 1)) 38.7 (*C*(3)), 44.6 and 48.5 (*C*(4) and *C*(9')), 49.9 (*C*(5)), 60.8 (*C*(2)), 120.5, 122.2, 122.9, 123.1, 127.4, 127.9, 129.3, 129.8 (All Ar*C*H), 136.4, 138.8, 140.0, 143.3 (All Ar*C*), 171.9 (*C*=O) (one (*C*=O) missing - obscured by *d*-TFA); *m/z* (ESI-) 320 ($[M-H]^-$, 100%); HRMS 320.0930 ($[M-H]^-$, $C_{19}H_{14}NO_4$ requires 320.0928).

(2*S*,3*S*,4*R*,6*S*)-1,4'-Diaza-1-*tert*-butyloxycarbonyl-spiro[bicyclo[3.1.0]hexane-6,9'-fluorene]-2,4-bismethyl-ester 28a and (2*S*,3*S*,4*R*,6*S*)-1,4'-diaza-1-*tert*-butyloxycarbonyl-4-hydroxymethyl-spiro[bicyclo [3.1.0]hexane-6,9'-fluorene]-2-methyl-ester 28b

A mixture of alcohol **24a** (62 mg, 0.16 mmol), TEMPO (13 mg, 0.08 mmol), CH_3CN (3.1 mL), and NaH_2PO_4 (2.7 mL, 0.67 M) was warmed to 45 ^oC and allowed to cool to 37 ^oC. Then, $NaClO_2$ (110 mg, 1.22 mmol) was added followed by 6 drops of 8% aq. NaOCl. The solution was maintained at 37 ^oC for 16 h and then poured over an ice-cold solution of

Na_2SO_3 (1.6 g) in water (1.6 mL) and ice (3.4 g). The resulting mixture was extracted with EtOAc (4 x 5 mL) and the combined layers were dried over Na_2SO_4 and concentrated *in vacuo*, before being dissolved in EtOAc (3 mL). Diazomethane (approx. 3 mmol) was distilled directly into the solution. After 0.5 h, the excess diazomethane was quenched with AcOH and the solvents were removed *in vacuo*. THF (3 mL) was added to the aqueous layer which was then stirred vigorously before diazomethane (approx. 3 mmol) was distilled directly into the mixture. After addition was complete, the THF was removed *in vacuo* before the aqueous was extracted with EtOAc (3 x 5 mL). The combined organics were dried over Na_2SO_4 and concentrated *in vacuo*. Both fractions were combined and purified by column chromatography over silica gel eluting with EtOAc/Petrol (1 : 1) to give diester **28a** as a white wax (3 mg, 4%), and **28b** as a clear viscous oil (20 mg, 30 %);

28a; R_f = 0.64 (EtOAc/Petrol, 2:1); υ_{max}/cm^{-1} (film) 2962, 2360, 2341, 1739 (C=O), 1705 (C=O), 1438, 1387, 1260, 1209, 1175, 1019, 740; δ_H(400.2 MHz; $CDCl_3$) 1.49 (4.5 H, s, $(CH^A{}_3)_3CO$), 1.56 (4.5 H, s, $(CH^B{}_3)_3CO$),), 3.21 (0.5 H, s, C(3)H^A), 3.24 (0.5 H, s, C(3)H^B), 3.59 (1.5 H, s, C(4)$CO_2CH_3^A$), 3.60 (1.5 H, s, C(4)$CO_2CH_3^B$), 3.86 (1.5 H, s, C(2)$CO_2CH_3^B$), 3.87 (1.5 H, s, C(2)$CO_2CH_3^A$), 4.01 (0.5 H, d, *J* 12.3, C(5)H^AH), 4.09 (0.5 H, d, *J* 12.4, C(5)H^BH), 4.28 (0.5 H, d, *J* 12.3, C(5)HH^A), 4.34 (0.5 H, d, *J* 12.4, C(5)HH^B), 4.59 (0.5 H, s, C(2)H^A), 4.71 (0.5 H, s, C(2)H^B), 7.15-7.25 (2H, m, ArC(2')*H*, ArC(5')*H*), 7.39-7.49 (1H, m, ArC(6')*H*), 7.54-7.60 (1H, m, ArC(7')*H*), 7.75 (1H, br s, ArC(1')*H*), 8.39 (1H, br s, ArC(8')*H*), 8.58 (1H, d, *J* 4.9, ArC(3')*H*); δ_C(125.8 MHz; $CDCl_3$) 28.2 and 28.4 ($(CH_3)_3CO$), 37.9 and 38.8 (*C*(3)), 42.2, 42.4, 43.9 and 44.5 (*C*(4) and *C*(9')), 49.1 (*C*(5)), 52.8, 52.9) (C(2)CO_2CH_3 and C(4)CO_2CH_3), 60.0 and 60.4 (*C*(2)), 81.6 ($(CH_3)_3CO$), 121.4 and 123.8, 123.9 (Ar*C*(2')H and Ar*C*(5')H), 128.7 (Ar*C*(7')H)), 152.5 and 153.0 (*C*(O)(NR_2)(OR), 167.3 and 167.4 (C(4)CO_2CH_3), 170.7 and 171.0 (C(2)CO_2CH_3); *m/z* (ESI+) 451 ($[M+H]^+$, 100%); HRMS 451.1879 ($[M+H]^+$, $C_{25}H_{27}N_2O_6$ requires 451.1864).

28b; R_f = 0.12 (EtOAc/Petrol, 2:1); $[\alpha]_D^{25}$ -33 (c = 1.0, $CHCl_3$); υ_{max}/cm^{-1} (film) 3200 (OH), 3000, 1750, 1699, 1406, 1175, 1126, 739; δ_H(500.3 MHz; $CDCl_3$) 1.49 (4.5H, s, $(CH_3)_3CO$), 1.59 (4.5H, s, $(CH_3)_3CO$), 2.71 (0.5H, s, C(3)*H*), 2.72 (0.5H, s, C(3)*H*), 3.64 (1H, br s, O*H*), 3.83 (1.5H, s, CO_2CH_3), 3.83 (1.5H, s, CO_2CH_3), 4.07-4.21 (3H, m, C(4)CH_2OH, C(5)*H*H), 4.34 (0.5H, d, *J* 12.1 C(5)H*H*), 4.37 (0.5H, d, *J* 12.1 C(5)H*H*), 4.59 (0.5H, s, C(2)*H*), 4.69 (0.5H, s, C(2)*H*), 7.05 (0.5H, d, *J* 4.9, ArC(2')*H*), 7.07 (0.5H, d, *J* 4.9, ArC(2')*H*), 7.07 (1H, m, Ar(5')*H*), 7.24-7.31 (2H, m, ArC(6')*H*, ArC(7')*H*), 7.35-7.38 (1H, m, ArC(1')*H*), 7.91-7.95 (1H, m, ArC(8')*H*), 8.28 (1H, dd, *J* 1.1, 4.9, ArC(3')*H*); δ_C(125.8 MHz; $CDCl_3$) 28.3 and 28.5 ($CH_3)_3CO$), 37.9 and 38.3 (*C*(3)), 41.0, 43.8, 44.5 (*C*(4) and *C*(9')), 60.7 and 61.1 (*C*(2)), 61.1 and 61.2 (*C*(5)), 77.2 (CO_2CH_3), 81.1 and 81.2 ($(CH_3)_3CO$), 120.2 and 120.3 (Ar*C*(2')H), 121.6 (Ar*C*(8')H), 123.1 (Ar*C*(5')H), 127.5 (Ar*C*(7')H), 129.2, 129.3 (Ar*C*(1')H), 129.3 129.5 (Ar*C*(6')H), 137.6, 140.6, 140.7 and 140.8 (all Ar*C*), 147.3 (Ar*C*(3')H), 152.7 and 153.4 (*C*(O)(NR_2)(OR)), 158.3 (Ar*C*), 172.1 and 172.2 (CO_2CH_3); *m/z* (ESI+) 423 ($[M+H]^+$, 100%); HRMS 423.1909 ($[M+H]^+$, $C_{24}H_{27}N_2O_5$ requires 423.1914).

Attempted Synthesis of (2*S*,3*S*,4*R*,6*R*)-1,5'-diaza-1-*tert*-butyloxycarbonyl-spiro [bicyclo[3.1.0]hexane-6,9'-fluorene]-2,4-bismethyl-ester 28d and (2*S*,3*S*,4*R*,6*R*)-1,5'-diaza-1-*tert*-butyloxycarbonyl-4-hydroxymethyl-spiro[bicyclo [3.1.0]hexane-6,9'-fluorene]-2-methyl-ester 28e.

A mixture of alcohol **24b** (53 mg, 0.13 mmol), TEMPO (12 mg, 0.08 mmol), CH_3CN (2.6 mL), and NaH_2PO_4 (2.3 mL, 0.67 M) was warmed to 45 ^oC and allowed to cool to 37 ^oC. $NaClO_2$ (97 mg, 1.07 mmol) was added followed by 9 drops of 8% aq. NaOCl. The solution was maintained at 37 ^oC for 16 h and then poured over an ice-cold solution of Na_2SO_3 (1.4 g) in water (1.4 mL) and ice (2.9 g). The resulting mixture was extracted with EtOAc (4 x 5 mL) and the combined layers were dried over Na_2SO_4 and concentrated *in vacuo*, before being

dissolved in EtOAc (3 mL). Diazomethane (approx. 3 mmol) was distilled directly into the solution. After 0.5 h, the excess diazomethane was quenched with AcOH and the solvents were removed *in vacuo*. THF (3 mL) was added to the aqueous layer which was then stirred vigorously before diazomethane (approx. 3 mmol) was distilled direcly into the mixture. After addition was complete, the THF was removed *in vacuo* before the aqueous was extracted with EtOAc (3 x 5 mL). The combined organics were dried over Na_2SO_4 and concentrated *in vacuo*. Both fractions were combined and purified by column chromatography over silica gel eluting with EtOAc/Petrol (1 : 2) to give ester **28e** as a clear viscous oil (4 mg, 7%); υ_{max}/cm^{-1} (film) 3385 (br OH), 2977, 1750 (C=O), 1700 (C=O), 1393, 1207, 1369, 800; δ_H(400.2 MHz; $CDCl_3$) 1.49 (4.5H, s, $(CH_3)_3CO$), 1.57 (4.5H, s, $(CH_3)_3CO$), 2.80 (0.5H, s, C(3)*H*), 2.82 (0.5H, s, C(3)*H*), 3.85 (1.5H, s, CO_2CH_3), 3.85 (1.5H, s, CO_2CH_3), 3.96 (0.5H, d, *J* 12.0, C(5)*H*H), 4.03 (0.5H, d, *J* 12.2, C(5)*H*H), 4.08-4.23 (2H, m, C(4)CH_2OH), 4.30 (0.5H, d, *J* 12.0, C(5)H*H*), 4.34 (0.5H, d, *J* 12.2, C(5)H*H*), 4.56 (0.5H, s, C(2)*H*), 4.67 (0.5H, s, C(2)*H*), 7.12-7.20 (2H, m, Ar*H*), 7.40-7.47 (3H, m, Ar*H*), 8.08-8.18 (1H, m, Ar*H*), 8.55 (0.5H, dd, *J* 1.6, 5.3, ArC(8')*H*), 8.57 (0.5H, dd, *J* 1.6, 5.3, ArC(6')*H*); δ_H(500.3 MHz; $CDCl_3$) 28.3 and 28.4 (($CH_3)_3CO$), 38.8 and 39.6 (*C*(3)), 41.1 and 41.2, 43.5 and 44.2 (*C*(4) and *C*(9')), 52.3 and 52.4 (*C*(5)), 52.7 and 52.8 (CO_2CH_3), 60.4 and 60.6 (C(4)CH_2OH), 61.0 and 61.3 (C(*2*)), 81.4 (($CH_3)_3CO$), 121.3, 121.5, 121.7, 121.9, 121.9, 127,7, 129.0 (all Ar*C*H), 131.5, 144.0, 147.0, 159.8 (all Ar*C*), 152.9 and 153.4 (*C*(O)(NR_2)(OR)), 171.9 and 172.0 (C(2)CO_2CH_3); *m/z* (ESI+) 867 ($[2M+Na]^+$, 100%), 423 ($[M+H]^+$, 63%); HRMS 445.1740 ($[M+H]^+$, $C_{24}H_{26}N_2NaO_5$ requires 445.1734).

(2*S*,3*R*,4*R*)-1-Aza-1-*tert*-butyloxycarbonyl-6,6-diphenyl-bicyclo[3.1.0]hexane-2-methyl-ester 29a[54]

A mixture of alcohol **24g** (85 mg, 0.23 mmol), TEMPO (6 mg, 0.04 mmol), CH_3CN (1.8 mL), and NaH_2PO_4 (1.6 mL, 0.67 M) was warmed to 37 ^oC. Then, $NaClO_2$ (63 mg, 0.70 mmol) was added followed by 3 drops of 8% aq. NaOCl. The solution was maintained at 37 ^oC for 5 h and then poured over an ice-cold solution of Na_2SO_3 (0.25 g in 0.5 mL water and 1 g of ice). The resulting mixture was extracted with EtOAc (4 x 5 mL) and the combined layers were dried over Na_2SO_4 and concentrated. The residue was dissolved in EtOAc (10 mL) and diazomethane (approx. 3 mmol) was distilled directly into the solution. After 0.5 h, the excess diazomethane was quenched with AcOH and the solvents were removed *in vacuo*. The resultant oil was purified by column chromatography over silica gel eluting with DCM to furnish ester **29a** as a white wax (62 mg, 68%). R_f = 0.14 (DCM); $[\alpha]_D^{20}$ -8.39 (c = 1.55, $CHCl_3$); υ_{max}/cm^{-1} (film) 2976, 1752, 1702, 1405, 1174, 1113, 760, 709; δ_H(400.2 MHz; $CDCl_3$) Approximate rotamer ratio (A:B) = (5:4), 1.14 ($9H^A$, s, $(CH^A_3)_3CO$), 1.15 ($9H^B$, s, $(CH^B_3)_3CO$), 2.20-2.29 (1H, m, C(4)*H*), 2.31 ($1H^B$, d, *J* 7.3, C(3)H^B), 2.37 ($1H^A$, d, *J* 7.3, C(3)H^A), 3.66-3.74 ($1H^A$ and $2H^B$, m, C(5)*H*H, C(5)HH^B), 3.76 ($3H^A$, s, $(CO_2CH^A_3)$), 3.77 ($3H^B$, s, $(CO_2CH^B_3)$), 3.87 ($1H^A$, d, *J* 11.3, C(5)HH^A), 4.39 ($1H^A$, s, C(2)H^A), 4.58 ($1H^B$, s, C(2)H^B), 7.07-7.15 (3H, m, Ar*H*), 7.18-7.25 (3H, m, Ar*H*), 7.30-7.37 (4H, m, Ar*H*); δ_C(100.6 MHz; $CDCl_3$) 28.0 ($(CH_3)_3CO$), 30.1 and 30.3 (*C*(4)), 34.0 and 34.2 (*C*(3)), 36.4 (*C*(6)), 46.1 and 46.4 (*C*(5)), 52.3 (CO_2CH_3), 59.5 and 60.0 (*C*(2)), 79.4 and 79.5 ($O(C(CH_3)_3)$, 126.2, 126.9, 127.1, 128.4, 128.8) (all Ph*C*H), 135.7 and 135.8 (PhAr*C*), 144.7 and 144.8 (Ph'Ar*C*), 152.2 and 152.6 ((*C*O)(NR_2)(OR)), 173.6 and 176.6 (CO_2CH_3); *m/z* (ESI+) 394.2 ($[M+H]^+$, 48%); HRMS 416.1837 ($[M+Na]^+$, $C_{24}H_{27}NNaO_4$ requires 416.1832).

(2*S*,3*R*,4*R*)-1-Aza-1-*tert*-butyloxycarbonyl-6,6-diphenyl-bicyclo[3.1.0]hexane-2-carboxylic acid 29b[53]

To a solution of **29a** (60 mg, 0.15 mmol) in MeOH (5.1 mL) and water (1.7 mL) was added lithium hydroxide (32 mg, 0.76 mmol). After stirring at r.t. for 2 d, MeOH was removed *in vacuo*. EtOAc (5 mL) was added and the organic layer was separated and concentrated to give unwanted organic material. Then, EtOAc (5 mL) and HCl (0.25 M, 10 mL) were added sequentially to the aqueous mixture. The organic layer was separated and the aqueous was extracted with EtOAc (4 x 5 mL) before the combined organic extracts were dried over Na_2SO_4 and concentrated to give acid **29b** as a white solid (56 mg, 97%) which required no further purification; m.p. dec.190°C; $[\alpha]_D^{25}$ -40 (c = 1.25, $CHCl_3$); $[\alpha]_D^{22}$ -51.2 (c = 0.5, $CHCl_3$); υ_{max}/cm^{-1} (film) 2978, 1700 (C=O), 1495, 1426, 1368, 1172, 1139, 760, 709; δ_H(500.3 MHz; $CDCl_3$) Approximate rotamer ratio (A:B) = (2:1), 1.15 (9H^A, s, (C*H*$^A_3$)$_3$CO), 1.18 (9H^B, s, (C*H*$^B_3$)$_3$CO), 2.26 (1H^B, dd, *J* 4.5, 7.2, C(4)*H*^{B}), 2.30 (1H^A, dd, *J* 4.5, 7.2, C(4)*H*^{A}), 2.47 (1H^B, d, *J* 7.2, C(3)*H*^{B}), 2.66 (1H^A, d, *J* 7.4, C(3)*H*^{A}), 3.62 (1H^A, dd, *J* 4.7, 11.5, C(5)*H*^{A}H), 3.70 (1H^B, dd, *J* 4.6, 11.4, C(5)*H*^{B}H), 3.76 (1H^A, d, *J* 11.5, C(5)H*H*^{A}), 3.90 (1H^B, d, *J* 11.4, C(5)H*H*^{B}), 4.42 (1H^B, s, C(2)*H*^{B}), 4.53 (1H^A, s, C(2)*H*^{A}), 7.08-7.16 (3H, m, Ar*H*), 7.19-7.27 (3H, m, Ar*H*), 7.30-7.40 (4H, m, Ar*H*); δ_C(125.8 MHz; $CDCl_3$) 28.0 ((*C*H$_3$)$_3$CO), 30.1 and 30.6 (*C*(4)), 32.3 and 34.0 (*C*(3)), 36.1 and 36.5 (*C*(6)), 46.2 and 46.6 (*C*(5)), 59.8 and 59.9 (*C*(2)), 79.9 and 81.3 (O(*C*(CH$_3$)$_3$)), 126.3, 126.8, 126.9, 127.2, 127.3, 128.4, 128.4, 128.8, 128.9, 128.9, 129.1 (6 x Ph*C*H), 135.6 and 135.7 (Ph*C*), 144.4 and 144.6 (Ph'*C*), 152.2 and 154.9 (*C*(O)(NR$_2$)(OR), 173.6 and 176.6 (*C*O$_2$H); *m/z* (ESI-) 378 ([M-H]$^-$, 100%); HRMS 402.1676 ([M+Na]$^+$, $C_{23}H_{25}NNaO_4$ requires 402.1676).

(2*S*,3*R*,4*R*)-1-Aza-6,6-diphenyl-bicyclo[3.1.0]hexane-2-carboxylic acid 29c

A solution of acid **29b** (20 mg, 53 μmol) in DCM (1 mL) and dry HCl (2 M in Et_2O, 3 mL) was stirred vigorously for 3 h. The mixture was concentrated before EtOAc (1 mL) was added followed by dropwise addition of petrol. After the precipitate had settled removal of the

solvent (*via* pipette) and concentration *in vacuo* left **29c** as a white foam (15 mg**,** 100%); $[\alpha]_D^{19}$ -24.8 (c = 0.85, MeOH); υ_{max}/cm^{-1} (film) 3406 (br), 3059, 3027, 1730 (sh), 1677 (C=O), 1495, 1447, 1198, 1136, 711, 698; δ_H(500.3 MHz; *d*4-MeOD) 2.71 (1H, t, *J* 5.9, C(4)*H*), 2.86 (1H, d, *J* 7.4, C(3)*H*), 3.58 (1H, d, *J* 12.5, C(5)*H*H), 3.88 (1H, dd, *J* 5.3, 12.3, C(5)H*H*), 4.45 (1H, s, C(2)*H*), 7.13-7.18 (1H, m, *p*-Ph'*H*), 7.21-7.29 (4H, m, *o*- and *m*-Ph'*H*), 7.36-7.42 (1H, m, *p*-Ph*H*), 7.47-7.54 (4H, m, *o*- and *m*-Ph*H*); δ_C(125.8 MHz; *d*4-MeOD) 32.0 (*C*(4)), 36.1 (*C*(3)), 41.2 (*C*(6)), 48.0 (*C*(5)), 62.7 (*C*(2)), 128.0 (*o*-Ph'*C*H), 128.4 (Ph'*C*H), 129.6 (*o*-Ph*C*H), 129.8 (Ph'*C*H), 131.3, 131.7 (both Ph*C*H), 136.2 and 145.6 (Ph*C* and Ph'*C*), 170.9 (CO_2H); *m/z* (ESI+) 280 ($[M+H]^+$, 100%); HRMS 280.1330 ($[M+H]^+$, $C_{18}H_{18}NO_2$ requires 280.1332).

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55. Bioassay of products:[82] Microbiological assays were performed by the hole- plate method with the test organism *Staphylococcus aureus* N.C.T.C. 6571 or *E. coli* X580. Solutions (100 □l) of the compounds to be tested (4 mg/ml) were loaded into wells in bioassay plates, and incubated overnight at 37 ^{o}C. The diameters of the resultant inhibition zones were measured (±1mm), and relative potency estimated by reference to standards prepared with Cephalosporin C.
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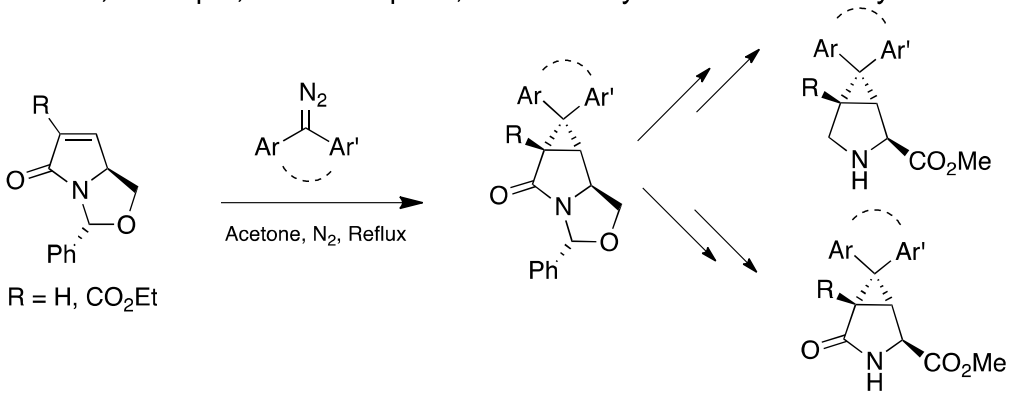
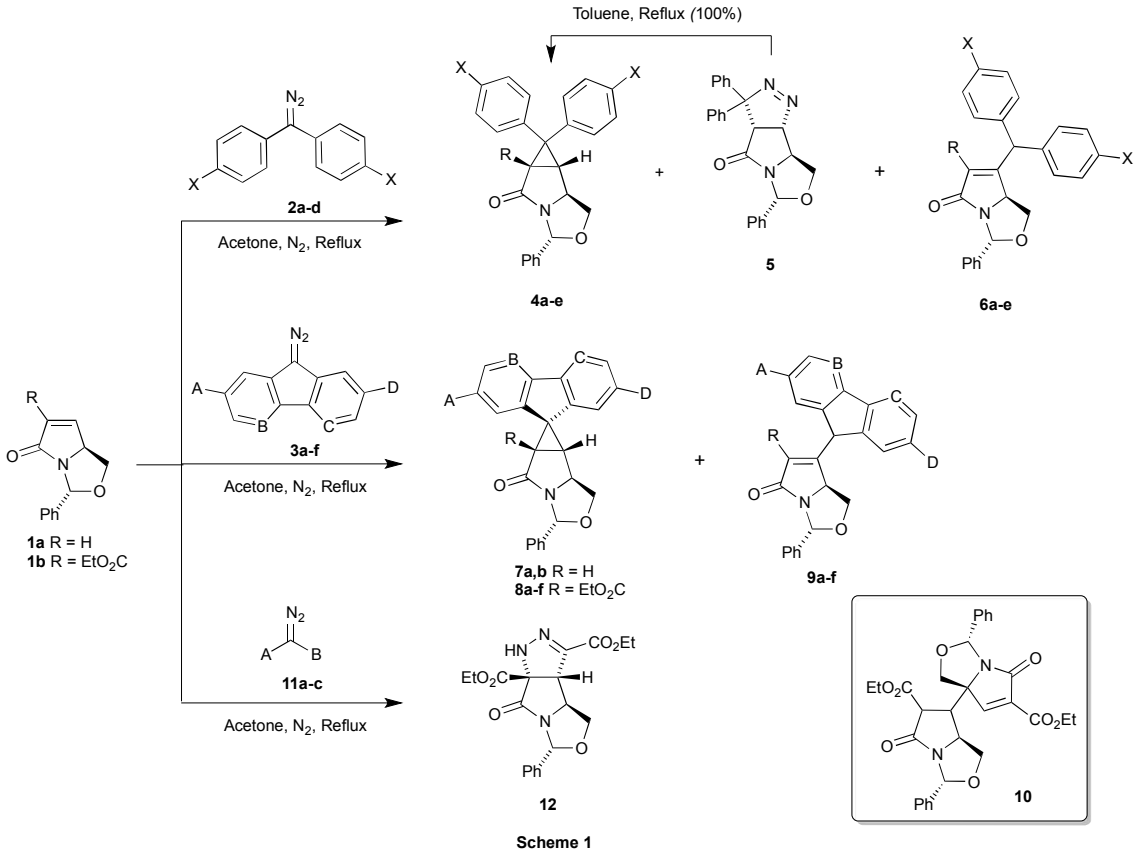
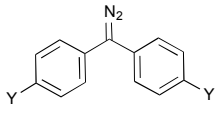
Uncatalysed diaryldiazo cyclopropanations on bicyclic lactams: access to conformationally constrained amino acids

L. Harris, M. Gilpin, A.L. Thompson, A.R. Cowley and M.G. Moloney

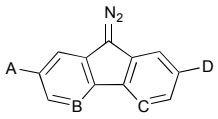




Scheme 1



2a Y = NO_2
2b Y = I
2c Y = H
2d Y = OMe



	A	B	C	D
3a	H	CH	CH	H
3b	H	$C(CH_2OH)$	CH	H
3c	Br	CH	CH	H
3d	Br	CH	CH	Br
3e	H	N	CH	H
3f	H	N	N	H

Figure 1

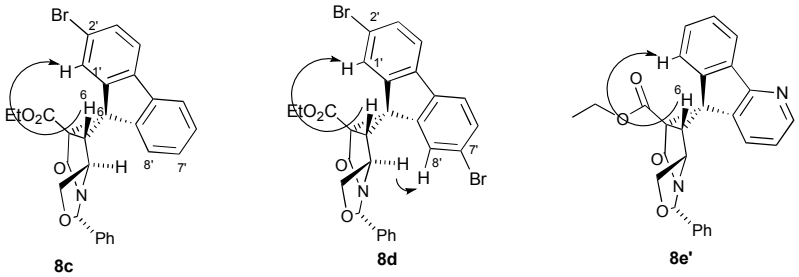
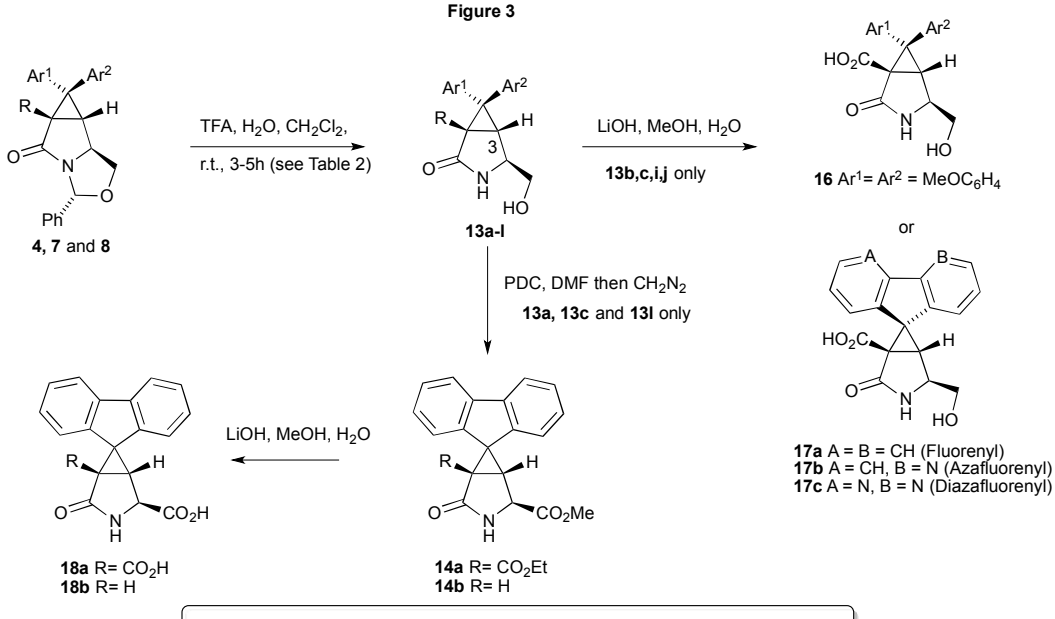
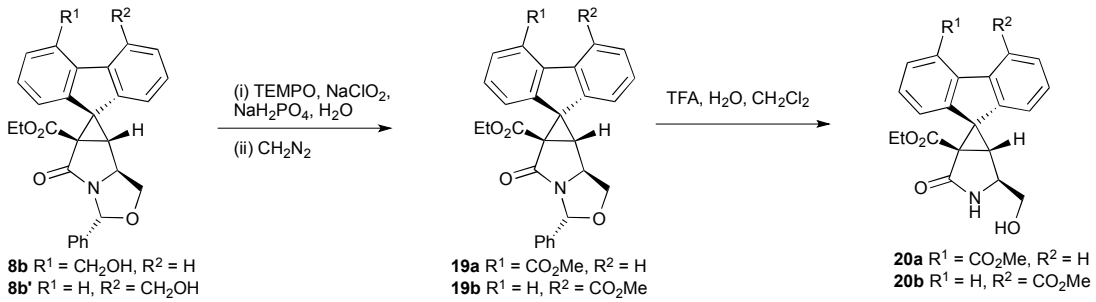


Figure 3



Scheme 2



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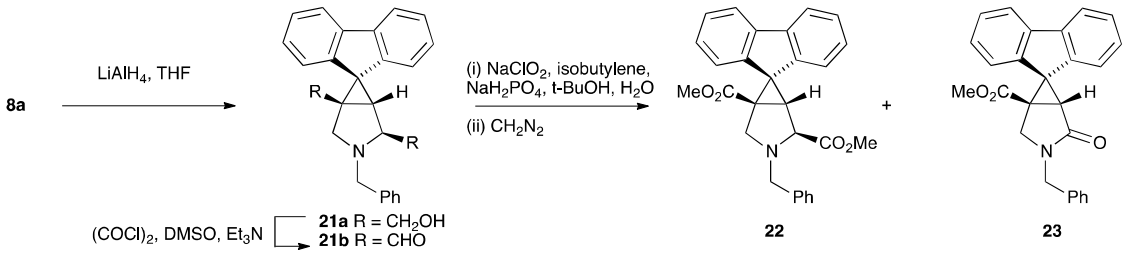
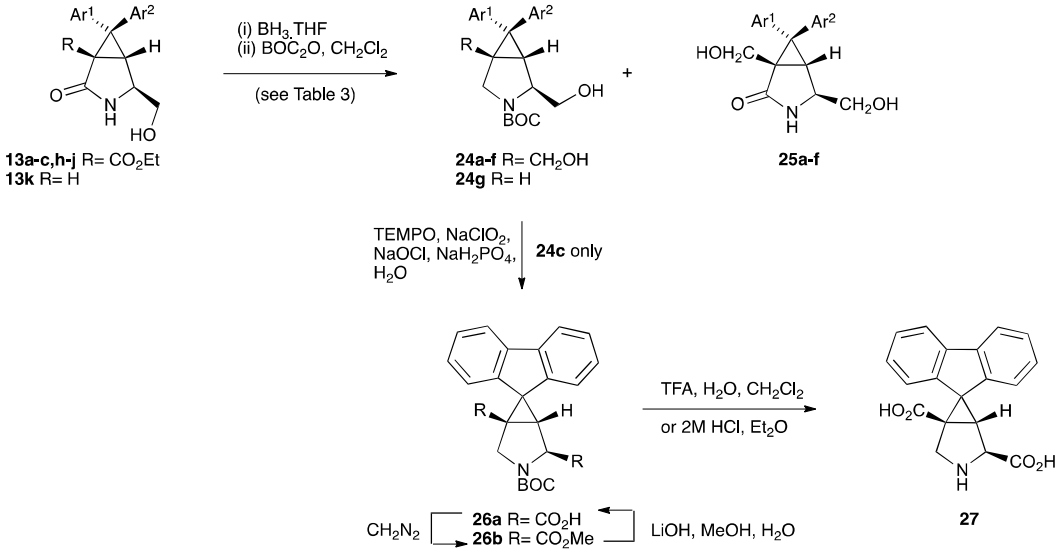


Scheme 4



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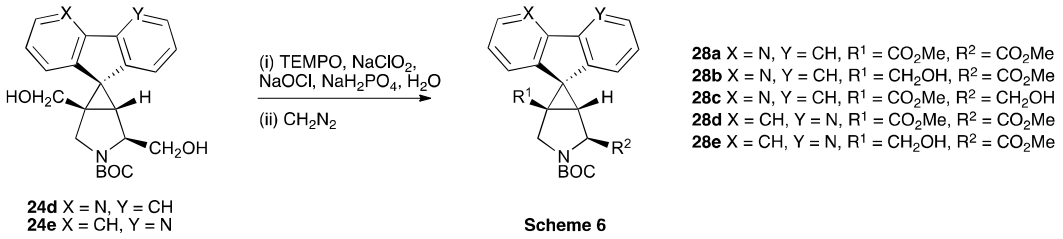

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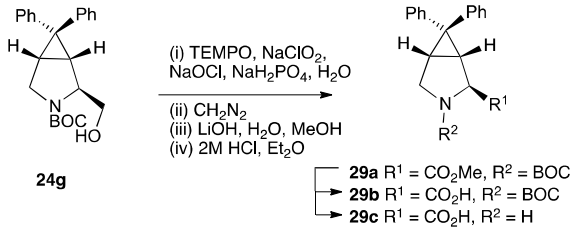
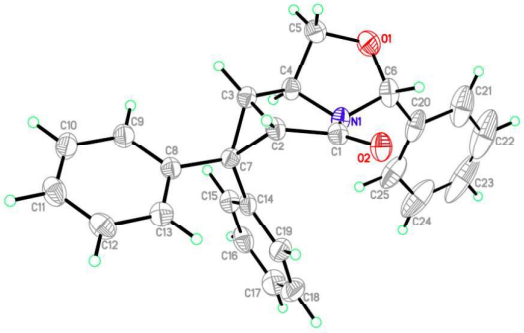


Scheme 7



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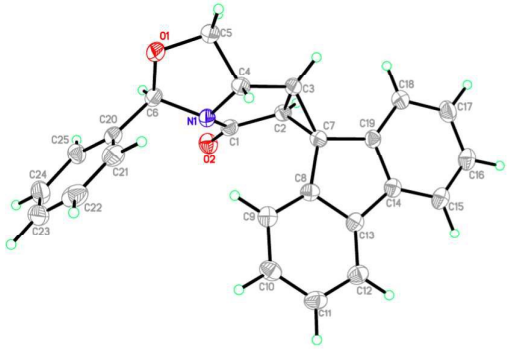

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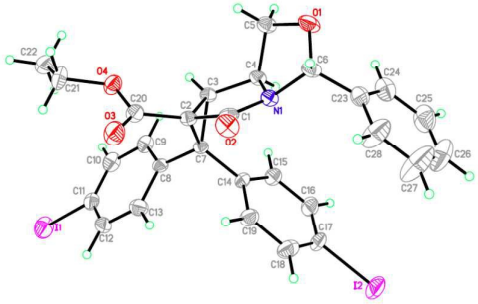

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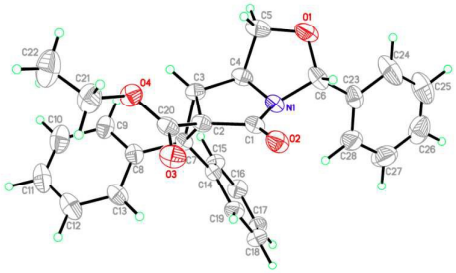

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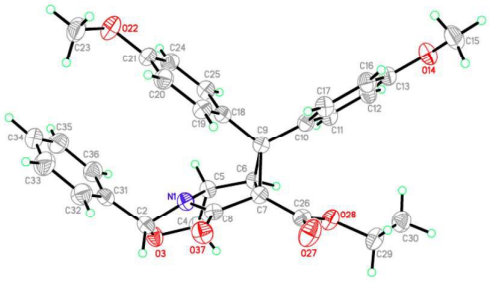

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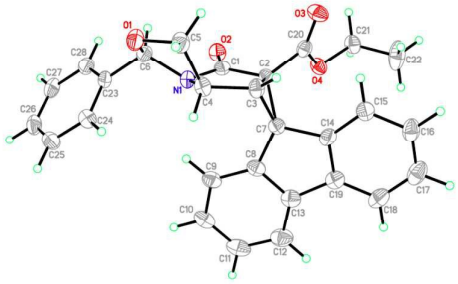

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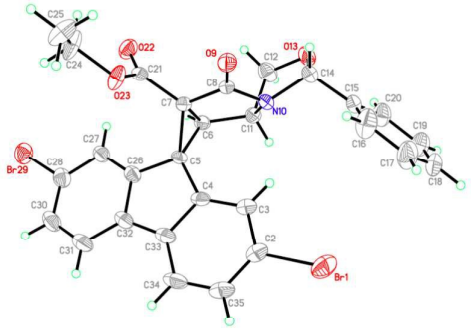

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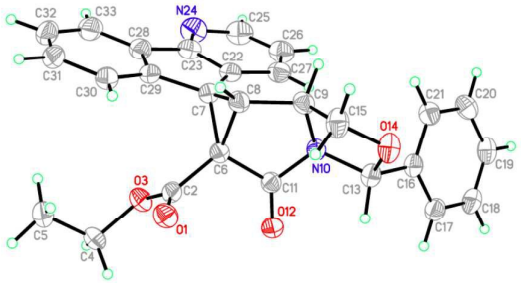
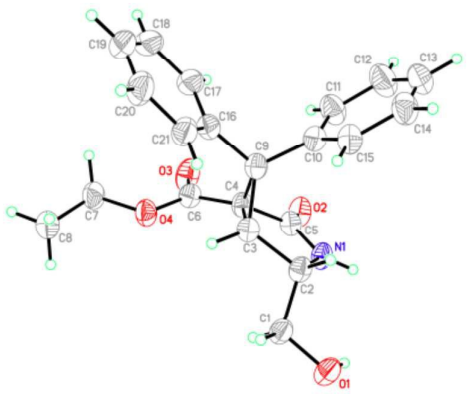


8e'

Figure 2



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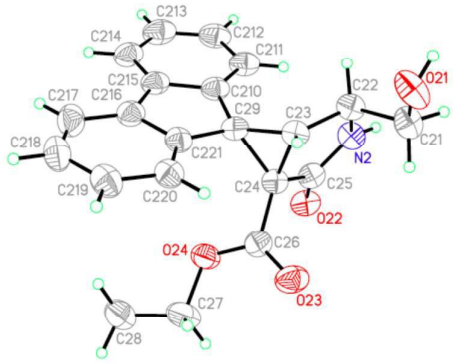

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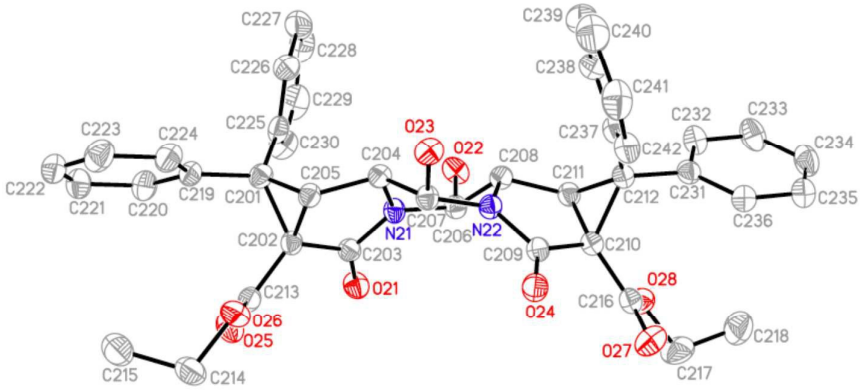

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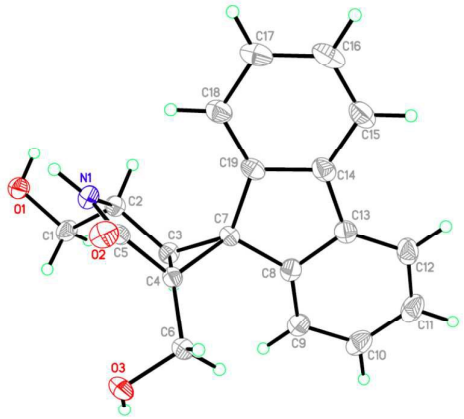
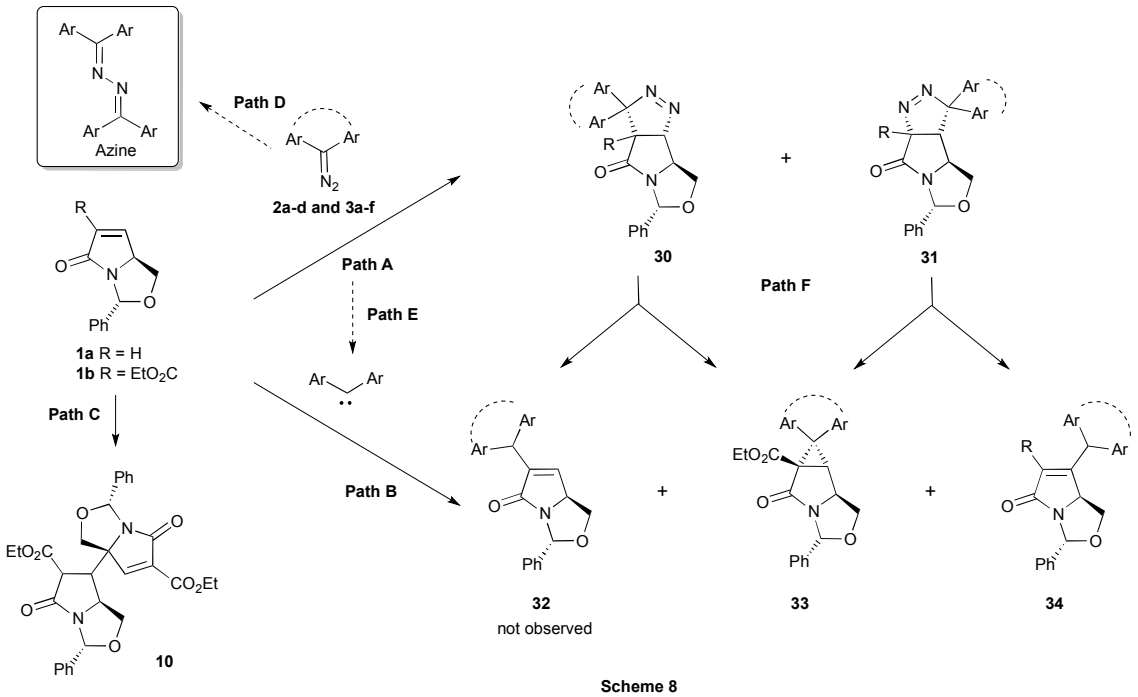


25c

Figure 4



Scheme 8