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Functionalised Pyrrolidinones derived from *(S)*-Pyroglutamic Acid

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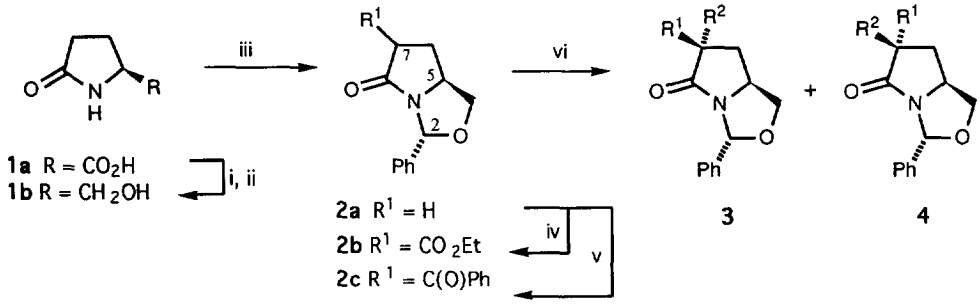
Abstract: The generation of the lactam enolate derived from bicyclic lactams **2a-c**, prepared from *(S)*-pyroglutamic acid **1a**, and subsequent reaction with a range of electrophiles, is reported. *Exo*-diastereoselectivity is generally favoured. The deprotection of some of these adducts to give functionalised hydroxymethylpyrrolidinones is readily achieved by simple hemiaminal ether cleavage under acidic conditions.

Highly functionalised pyrrolidines are compounds of considerable importance, since they are a source of useful synthetic intermediates,[1] chiral auxiliaries,[2] and ligands.[3] They also occur in a variety of natural products and pharmaceutically active compounds, either as isolated ring systems or embedded in more complex structures, which often possess wide ranging biological activity. There has been considerable recent interest in the development of methodology for accessing these compounds in enantiomerically pure form, and the use of *(S)*-pyroglutamic acid **1a** has been notable in this regard, having now been investigated in considerable detail by Ezquerra and Pedregal.[4] However, the related hydroxymethylpyrrolidinone **1b**, after suitable protection, has also been shown to provide a useful source of synthetic intermediates for pyrrolidine synthesis. In particular, the bicyclic lactam **2a**, the synthesis and reactions of which were reported some years ago,[5, 6] in which the hydroxyl and amide functionalities are simultaneously protected as an oxazolidine,[7] has particular appeal as a starting material: lactam **2a** is of relatively low molecular weight, is fully protected, does not suffer competitive deprotonation at the C-5 position, and in addition might be expected to give good stereocontrol in any alkylations at C-7 as a result of its bicyclic ring structure. We report here in detail the results of work designed to demonstrate the synthetic potential of this lactam **2a** by functionalisation α- to the lactam carbonyl.[8, 9] Recently the use of this compound or closely related ones has attracted interest from a number of research groups,[10-15] and the chemistry of an isomeric bicyclic lactam has been extensively investigated by Meyers.[16]

When lactam **2a**, prepared from (*S*)-ethyl pyroglutamate by reduction to alcohol **1b**,[17] followed by cyclisation with benzaldehyde according to the literature procedure,[5, 6] was treated with LDA at -78°C, and the resulting lactam enolate quenched with a range of electrophiles, the products **3-6** were obtained, in medium to good chemical yield (Scheme 1 and Table 1).

A variety of alkyl halides (allyl bromide, benzyl bromide, *p*-nitrobenzyl bromide, cyclohexenyl bromide and methyl iodide) and other electrophiles (iodine, *N*-bromosuccinimide, phenylselenenyl chloride, *p*-tosyl chloride, and benzaldehyde) gave moderate to good overall yields of the *exo*- and *endo*- products **3a-i** and **4a-i**

respectively, with a diastereoselectivity of between 1.3:1 to 8.5:1, generally in favour of the *exo*- isomer. The highest diastereoselectivities were obtained with more sterically demanding electrophiles. The exception to this trend was methyl iodide, which as has been previously reported by Armstrong,[12] gave predominantly the *endo*-diastereomer **4i**. Preference for the formation of the *endo*- chloride **4h** was also observed when the lactam enolate was quenched with *p*-tosyl chloride. Selenenation gave, in addition to the desired products **3f,4f**, a small amount (12%) of the diselenide **3** (R^1=R^2=SePh). The relative configurations of compounds **3** and/or **4** were determined by n.O.e. NMR experiments, and in some cases confirmed by single crystal X-ray analysis.[18] In keeping with observations reported by Armstrong[12] and Nagasaka[15], the *endo*- isomers were generally less polar and had higher optical rotations than the corresponding *exo*- isomers; similarly, the H-4_{exo} and H-6_{exo} protons resonated downfield of the corresponding *endo*- protons. The predominance of the *exo*-diastereoisomers **3** is consistent with approach of the electrophile from the least hindered (convex) face of the lactam enolate, although the modest diastereoselectivity which is observed is probably due to the fact that the observed stereocontrol is derived largely from the steric bulk at C-5 and that the phenyl substituent at the hemiaminal ether* carbon (C-2) is sufficiently far removed that it has little direct stereochemical influence at the reacting centre (C-7). In fact, the infra-red stretching frequency (1705cm^{-1}) and carbon chemical shift (170p.p.m.) are indicative of an amide-type carbonyl at C-8, rather than a ketone carbonyl, thereby enforcing a more planar geometry of the four atoms C-7, C-8, N-1 and C-2. Both single crystal X-ray analysis and molecular modelling studies show that the bicyclic system is very open, with some pyramidalisation of the amide nitrogen, which accounts for the small and variable stereochemical bias which is observed.[18]



(i) EtOH/H^+, 81%; (ii) $NaBH_4$, EtOH, 83%; (iii) PhCHO, TsOH, toluene, reflux, 77%; (iv) NaH, $(EtO)_2CO$, toluene, reflux, 70%; (v) NaH, $PhCO_2Me$, toluene, reflux, 83%; (vi) Base followed by electrophile (see Table).

Scheme 1

The reaction of the enolate of lactam **2a** with benzaldehyde gave the corresponding adduct as a separable mixture of the three diastereomers **5a,b,c** in the ratio 1.3:1:1 respectively in 91% overall yield; the relative configurations were determined by ^1H NMR spectroscopic analysis and confirmed by single crystal X-ray crystallography.[18] Reaction of the enolate of **2a** with *p*-nitrobenzaldehyde gave the corresponding adducts as an inseparable mixture of diastereomers in low yield. This lack of diastereoselectivity contrasted with the aldol reactions of protected pyroglutamates with benzaldehydes which have been reported to proceed with high

* This nomenclature conforms to IUPAC Recommendations 1995 (*Pure. Appl. Chem.*, 1995, **67**, 1309-1375)

diastereocontrol,[19] and highlights again the open structure of the bicyclic lactam enolate derived from **2a**. Thus *exo*- addition of benzaldehyde gives virtually no facial selectivity at the aldehyde carbon, further demonstrating the lack of influence that the C-2 phenyl substituent has on diastereoselectivity; it is only in the case of *endo*- addition that *Si*- face attack at the aldehyde leading to **5a** becomes preferred, presumably because this places the benzaldehyde phenyl substituent away from the bicyclic ring system in the transition state leading to the product (Figure 1). When dimethyl oxalate was used as the electrophile, a 25% yield of the corresponding monoacyl derivative **2a** (R^1=$COCO_2Me$) was obtained, as a 2.6:1 mixture of diastereomers, although benzylchloroformate gave the diacyl product **3** (R^1=R^2=CO_2CH_2Ph). An attempt to react the lactam enolate with acetyl chloride gave the diacyl product **3** (R^1=R^2=COMe) in only 15% yield, along with compound **6**, arising by condensation of the initially formed product with another equivalent of lactam enolate.

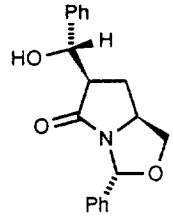
Table 1: Yields of Products **3** and **4** from lactam **2** according to Scheme 1.

Substrate	Method[a]	Product	Products **3**, **4**		Yield(%)	Ratio **3**:**4**
			R^1	R^2		
2a	A	**3a, 4a**	CH_2=$CHCH_2$-	H-	74	1.3:1.0
2a	A	**3b, 4b**	$PhCH_2$-	H-	60	2.1:1.0
2a	A	**3c,4c**	I-	H-	44	2.7:1.0
2a	A	**3d, 4d**	$pNO_2C_6H_4CH_2$-	H-	62	3.6:1.0
2a	A	**3e, 4e**	Br	H-	42	3.8:1.0
2a	A	**3f, 4f**	PhSe-	H-	38	3.8:1.0
2a	A	**3g, 4g**	3-Cyclohexenyl-	H-	41	8.6:1.0
2a	A	**3h, 4h**	Cl-	H-	77	1.0:2.5
2a	A	**3i, 4i**	Me-	H-	76	1.0:2.9
2b	B	**3j, 4j**	PhSe-	EtO_2C-	73	1.5:1.0
2b	B	**3k, 4k**	Me-	EtO_2C-	67	1.7:1.0
2b	B	**3l, 4l**	CH_2=$CHCH_2$-	EtO_2C-	68	4.7:1.0
2b	B	**3m, 4m**	$PhCH_2$-	EtO_2C-	75	7.5:1.0
2b	B	**3n, 4n**	$pNO_2C_6H_4CH_2$-	EtO_2C-	94	10.0:1.0
2b	B	**3o**	$CH_3C(O)$-	EtO_2C-	85	b
2b	B	**3p**	CH_2=$CMeCH_2$-	EtO_2C-	33[d]	b
2b	B	**3q, 4q**	3-Cyclohexenyl-	EtO_2C-	72[d]	c
2c	B	**3r, 4r**	$PhCH_2$-	PhC(O)-	63	5.0:1.0
2c	B	**3s, 4s**	Me-	PhC(O)-	47	2.0:1.0

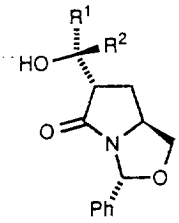
[a] Method A: LDA, THF, -78°C then electrophile; Method B: NaH, THF, 0°C then electrophile and reflux;
[b] Only *exo*- product isolated; [c] Not determined; [d] Alkylation conducted with co-solvents DMPU and TMEDA

The acylated derivatives **2b,c** were readily prepared by refluxing lactam **2a** with a mixture of sodium hydride and diethyl carbonate[20] or methyl benzoate[21] to give lactams **2b,c** in 70 and 83% yield respectively. Although the ethoxycarbonyl derivative **2b** was obtained as a 1:1 inseparable mixture of epimers at the C-7 position, the phenacyl derivative **2c** was obtained after chromatography followed by crystallisation as exclusively the *endo*- isomer. This was established by a ^{1}H NMR n.O.e. experiment conducted on a freshly prepared sample, and confirmed by single crystal X-ray analysis.[18] However, rapid equilibration of the pure

endo- isomer occurred in chloroform solution, to give a mixture of the *endo*-, *exo*- and enolic tautomers in the ratio 2:4:1. Deuterium exchange with H-7 was observed when a solution of lactam **2c** in $CDCl_3$ was shaken with D_2O/K_2CO_3, further confirming that such an equilibrium was in operation.



5a



5b R^1 = Ph, R^2 = H
5c R^1 = H, R^2 = Ph

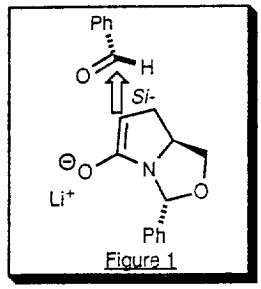
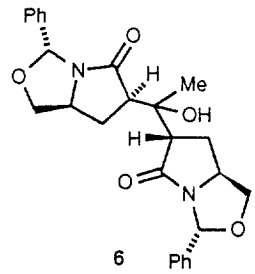


Figure 1



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The compound **2b** was readily alkylated and acylated using sodium hydride in THF, to give the corresponding products **3j-q** and **4j-q** generally in better yield and diastereoselectivity than for lactam **2a** (Table 1). Similarly to the products from lactam **2a**, the *endo*- isomeric products were generally less polar and had higher optical rotations than the corresponding *exo*- isomers, although the differences in this case were less marked; the H-6_{endo} protons resonated downfield of the corresponding H-6_{exo} protons. The relative stereochemistry of the adducts was assigned by n.O.e. experiments, and in the case of product **3n**, by single crystal X-ray analysis (Figure 2a)[22]. As would be expected, the larger the difference in bulk of the electrophile and the C-7 ethoxycarbonyl substituent, the greater the preference for *exo*- attack leading to diastereomer **3** in which the least bulky substituent is placed on the more crowded *endo*- face; this is maximised for electrophiles such as the benzyl bromides, but least significant for phenylselenenyl chloride. Similar diastereoselectivity has been observed in the reactions of pyroglutamic acid derivatives.[1]

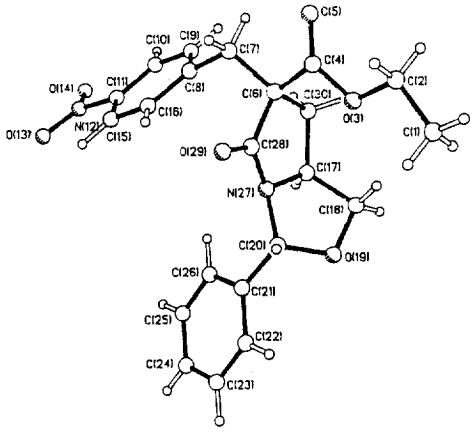


Figure 2a

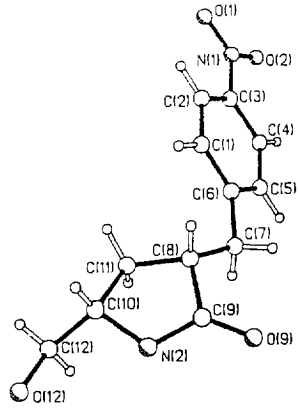
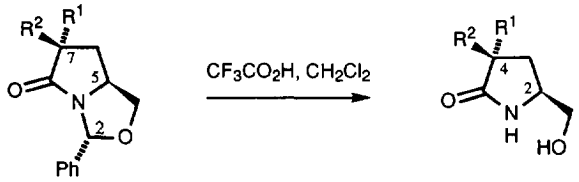


Figure 2b

However, when phenacyl derivative **2c** was treated with NaH/THF followed by benzyl bromide, the products **3b,4b** (1:1 ratio) were unexpectedly obtained. Since this could have been due to debenzoylation during aqueous work-up, the reaction was repeated but without work-up. Direct chromatographic purification of the crude reaction mixture gave the expected product **3r,4r** in 63% yield as a 5:1 mixture of diastereomers. Analogous methylation of **2c** gave the corresponding products **3s,4s** in 47% yield as an inseparable 2 : 1 mixture.

Deprotection of some of these intermediates to give functionalised hydroxymethyl pyrrolidinones (Table 2) was readily achieved by treatment of the lactams **3, 4** with trifluoroacetic acid in dichloromethane at room temperature. The structure of the alcohol **7b** was confirmed by single crystal X-ray analysis (Figure 2b).

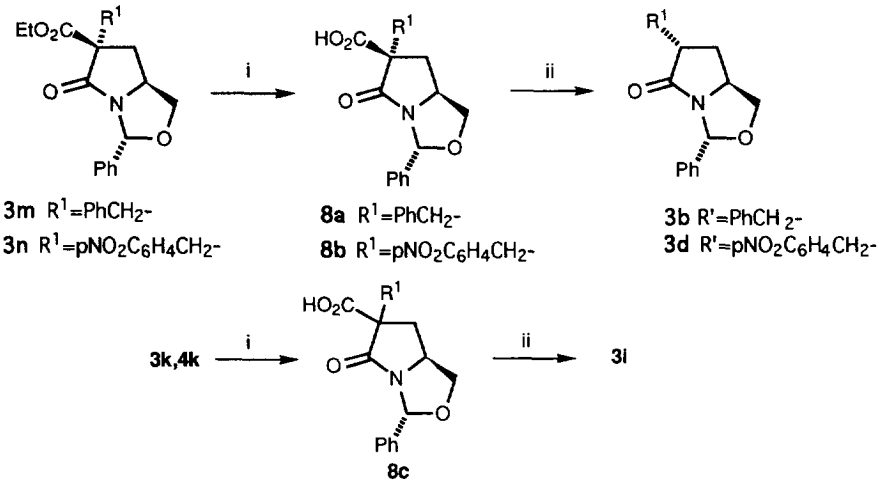


3, 4 **7**

Scheme 2

Table 2: Deprotection of Bicyclic Lactams **3,4** to Hydroxymethylpyrrolidinones **7**

Substrate	R^1	R^2	Product	Yield(%)
3b	$PhCH_2$-	H-	**7a**	86
4d	H-	$pNO_2C_6H_4CH_2$-	**7b**	78
3m	$PhCH_2$-	EtO_2C-	**7c**	76
3n	EtO_2C-	$PhCH_2$-	**7d**	61
3p	CH_2=$CMeCH_2$-	EtO_2C-	**7e**	25
3,4q	3-Cyclohexenyl-	EtO_2C-	**7f**	36



(i) 1N NaOH, CH_3CN, r.t., 24h; (ii)130°C, vac.

Scheme 3

The lactams **3m,n** were readily hydrolysed to acids **8a,b** under basic conditions in 96 and 71% yields respectively (Scheme 3). Decarboxylation of **8a** proceeded smoothly to give a 70% yield of lactam **3b**, and **8b** under the same conditions gave a separable 9:1 mixture of lactams **3d,4d** in 58% yield. A mixture of **3k,4k** (1:3.5) was hydrolysed in 95% yield to give acids **8c** as a mixture of diastereomers at C-7 in the same ratio, and decarboxylation gave exclusively lactam **3i** in 81% yield. Thus, decarboxylation of C-7 substituted ethoxycarbonyl lactams **2b** gives dominant or exclusive formation of the *exo-* isomer, and this presumably reflects the greater thermodynamic stability of this epimer at the elevated reaction conditions.

Thus, bicyclic lactam **2** is a readily prepared template suitable for further manipulation to a variety of functionalised pyrrolidinones. Work to improve diastereoselectivity and apply this methodology to natural product syntheis and their analogues is under active investigation in our laboratories.

Experimental

Proton and carbon nuclear magnetic resonance spectra were recorded on Varian Gemini 200 and Bruker AM-200, Bruker AM-250 and Bruker AM-500 spectrometers. Infra-red spectra were recorded using Perkin-Elmer 1750 FT-IR or Nicolet 5SXC FT-IR spectrometers. Low resolution mass spectra were recorded on VG Micromass ZAB 1F and VG Masslab 20-250 spectrometers using ammonia desorption chemical ionisation, chemical ionisation, electron impact or positive argon fast atom bombardment techniques. Gas Chromatography Mass Spectra were recorded on a VG-Trio-1 spectrometer. Accurate mass measurements were recorded on a VG ZAB-E instrument by manual peak matching, and were conducted by Dr. J.A. Ballantine at University College, Swansea. Optical rotations were recorded on a Perkin-Elmer 241 polarimeter, at a temperature of 25°C, using a path length of 1dm. Preparative high performance liquid chromatography was performed using Chiralcel OD or Chiralpak AD columns (internal dimensions 25cmx2cm), and using cycloheptane/IPA (9:1) as the eluant. All solvents were redistilled before use. Tetrahydrofuran was distilled over sodium/benzophenone and stored over molecular sieves under argon. (+)-(*2R, 5S*)-1-aza-3-oxa-2-phenylbicyclo[3.3.0]octan-8-one **2a** was prepared according to the literature procedure $[\alpha]_D$ +268.9 (*c* 1, $CHCl_3$)(lit.[6] +269.6 (*c* 1, $CHCl_3$)).

General Method for the Reaction of Lactam 2a with Electrophiles.

To a solution of LDA (1.1-1.4eq, prepared from butyllithium and diisopropylamine in THF at 0°C, then cooled to -78°C), was added lactam **2a** in THF, and the solution stirred for 0.5h. To this reaction mixture, a solution of the electrophile (1.1eq) in THF was added and stirred for 1h at -78°C. The reaction mixture was quenched with cold water (40 ml), and brine (20 ml) was added to saturate the aqueous phase. The organic layer was separated and the aqueous layer was extracted with EtOAc or dichloromethane (2 x 30 ml). The combined organic phases were washed with water (1 x 50 ml) and brine (1 x 50 ml), dried over $MgSO_4$, concentrated, and purified by flash chromatography to give the products.

The following compounds were prepared using the above general procedure:

(+)-(2R,5S,7R) and (+)-(2R,5S,7S)-1-aza-3-oxa-2-phenyl-7-allylbicyclo[3.3.0]octan-8-one **3a,4a**

These products were obtained using allyl bromide on a 5.0mmol scale of the lactam **2a**.

3a Obtained as an oil (500mg, 41.8%); R_f=0.30(EtOAc/light petroleum = 2:3); Found: C, 73.9; H, 7.08; N, 5.76. $C_{15}H_{17}NO_2$ requires C, 74.1; H, 7.04, N, 5.76 %; $[\alpha]_D$ +150 (*c* 1.05, $CHCl_3$); $\upsilon_{max}(CHCl_3)$ 1698 cm^{-1}; δ_H (500 MHz,$CDCl_3$) 2.06-2.15(2H, m, H-6_{exo} and H-6_{endo}), 2.35-2.41 (1H, m, C<u>H</u>CH=CH_2),

2.57-2.62 (1H, m, CH'CH=CH_2), 2.76-2.82 (1H, m, H-7$_{endo}$), 3.41-3.44 (1H, dd, *J* 8.0, 8.0Hz, H-4$_{endo}$), 4.03-4.08 (1H, m, H-5), 4.21-4.25 (1H, dd, *J* 8.0, 6.5Hz, H-4$_{exo}$), 5.10-5.17 (2H, m, CH=CH_2), 5.77-5.85 (1H, m, CH=CH_2), 6.34 (1H, s, H-2), 7.31-7.46 (5H, m, ArH); δ_C (50 MHz, $CDCl_3$) 27.12 (CH_2), 36.29 (C-6), 44.26 (C-7), 57.21 (C-5), 71.22 (C-4), 87.25 (C-2), 117.6 (CH_2=C), 125.9, 128.36, 128.44, 134.7, 138.9 (ArC), 180.1 (C-8); *m/z* [CI, NH_3] 244 ($M+H^+$, 100%).

4a Obtained as an oil (380mg, 31.7%); R_f=0.40(EtOAc/light petroleum = 2:3); Found: C, 73.9; H, 7.08; N, 5.76. $C_{15}H_{17}NO_2$ requires C, 74.1; H, 7.04, N, 5.76 %; $[\alpha]_D$ +176 (*c* 1.20, $CHCl_3$); υ_{max}($CHCl_3$) 1702 cm^{-1}; δ_H (500 MHz,$CDCl_3$) 1.61-1.66 (1H, m, H-6$_{endo}$), 2.19-2.26 (1H, m, CHC=C), 2.51-2.56 (1H, m, H-6$_{exo}$), 2.62-2.68 (1H, m, CHC=C), 2.96-3.03 (1H, m, H-7$_{exo}$), 3.50-3.52 (1H, dd, *J* 8.0, 8.0Hz, H-4$_{endo}$), 4.06-4.12 (1H, m, H-5), 4.23-4.26 (1H, dd, *J* 8.0, 6.5Hz, H-4$_{exo}$), 5.08-5.14 (2H, dd, *J* 15.8, 7.9Hz,CH=CH_2), 5.77-5.85 (1H, m, CH_2=CH), 6.34 (1H, s, H-2), 7.30-7.47 (5H, m, ArH); δ_C (50 MHz, $CDCl_3$) 31.27 (CH_2C=), 34.77 (C-6), 44.55 (C-7), 56.61 (C-5), 72.40 (C-4), 86.81 (C-2), 117.4 (CH_2=), 126.2, 128.6, 128.8, 135.5 (CH=), 138.9, 178.1 (C-8); *m/z* [CI, NH_3] 244 ($M+H^+$, 100%).

(+)-(2R,5S,7R) and (+)-(2R,5S,7S)-1-aza-3-oxa-2-phenyl-7-(phenylmethyl)bicyclo[3.3.0]octan-8-one **3b, 4b**

These products were obtained using benzyl bromide on a 4.9mmol scale of the lactam **2a**.

3b. Obtained as a colourless solid (580 mg, 40.3%); R_f = 0.3 (light petroleum/EtOAc = 1:1); Found: C, 77.9; H, 6.68; N, 4.74. $C_{19}H_{19}NO_2$ requires C, 77.8; H, 6.5; N, 4.8 %; $[\alpha]_D$ +66.2 (*c* 1.0, $CHCl_3$); υ_{max}($CDCl_3$) 1705(s) cm^{-1}; λ_{max} ($CHCl_3$) 242 nm (log ε = 2.9); δ_H (200 MHz, $CDCl_3$) 1.98-2.05 (1H, m, H-6$_{endo}$), 2.15-2.20 (1H, m, H-6$_{exo}$), 2.90-2.95 (1H, m, PhCH), 3.00-3.10 (1H, m, H-7$_{endo}$), 3.18-3.22 (1H, m, PhCH'), 3.40-3.42 (1H, dd, *J* 8.5, 8.1Hz, H-4$_{endo}$), 3.74-3.88 (1H, m, H-5), 4.11-4.18 (1H, dd, *J* 7.8, 8.1Hz, H-4$_{exo}$), 6.34 (1H, s, H-2), 7.20 - 7.40 (10H, m, ArH); δ_C (50 MHz, $CDCl_3$) 27.25 (C-6), 37.72 (PhCH_2), 46.59 (C-7), 57.13 (C-5), 71.27 (C-4), 87.21 (C-2), 126.1, 126.8, 128.5, 128.7, 129.3, 138.5, 139.0 (ArC), 178.0 (C-8); *m/z* [CI, NH_3] 311 ($M+NH_4^+$, 2%), 294 ($M+H^+$, 100). n.O.e. irradiation at δ2.1 gave enhancements to (2.0, 11.6%; 3.8, 8.7%); 2.0 (2.1, 21% ; 3.0, 7.7% ; 3.4, 4%); 3.8 (4.15, 8.2% ;2.15, 6.6%).

4b. Obtained as a crystalline solid (280 mg, 19.4%); R_f = 0.6(light petroleum/EtOAc = 1:1); M.p. 63-65°C; $[\alpha]_D$ +220 (*c* 1.0, $CHCl_3$); δ_H (200 MHz, $CDCl_3$) 1.60-1.70 (1H, m, H-6$_{endo}$), 2.40-2.50 (1H, m, H-6$_{exo}$), 2.70-2.80 (1H, m, PhCH), 3.15-3.40 (3H, m, H-7$_{exo}$, PhCH and H-4$_{endo}$), 4.00-4.10 (1H, m, H-5), 4.15-4.20 (1H, m, H-4$_{exo}$), 6.37 (1H, s, H-2), 7.20-7.50 (10H, m, ArH); δ_C (50 MHz, $CDCl_3$) 31.54 (C-6), 36.44 (PhCH_2), 46.82 (C-7), 56.53 (C-5), 72.17 (C-4), 86.81 (C-2), 126.1, 126.6, 128.6, 128.7, 129.1 (ArC); *m/z* [CI, NH_3]; 311 ($M+NH_4^+$, 2%), 294 ($M+H^+$, 100), 106 (15); n.O.e. irradiation at δ4.05 (2.4, 8.9% ; 3.2, 2.0%).

(+)-(2R,5S,7R) and (+)-(2R,5S,7S)-1-aza-3-oxa-2-phenyl-7-iodobicyclo[3.3.0]octan-8-one **3c,4c**

These products were obtained using iodine on a 4.9 mmol scale of the lactam **2a**.

3c: R_f=0.3(light petroleum/EtOAc = 1:1) was recrystallised from diethyl ether/light petroleum to give the product as colourless needles (520mg, 32%); M.p. 85-87°C; Found C, 43.84; H, 3.37; N, 4.11. $C_{12}H_{12}NO_2I$ requires C, 43.79; H, 3.37; N, 4.11%; $[\alpha]_D$ +105.3 (*c* 1.0, $CHCl_3$); υ_{max}($CHCl_3$) 1718(s) cm^{-1}; δ_H(200MHz, $CDCl_3$) 2.36-2.64 (2H, m, H-6), 3.66 (1H, m, H-4), 4.22-4.40 (2H, m, H-5 and H-4), 4.61

(1H, dd, *J* 6.5, 5.5Hz, H-7), 6.31(1H, s, H-2), 7.30-7.50(5H, m, ArH); δ_C(50.3MHz, $CDCl_3$) 19.05, 38.52, 57.90, 70.73, 86.96, 126.24, 128.86, 129.14, 137.91, 175.37; *m/z* [CI, NH_3] 330($M+H^+$, 95%), 202(100).

4c: R_f=0.5(EtOAc/light petroleum=1:1) was recrystallised from diethyl ether/light petroleum or chloroform/light petroleum to give the product as colourless needles (200mg, 12%); M.p. 125-127°C; Found: C, 43.92; H, 3.48; N, 4.28. $C_{12}H_{12}NO_2I$ Requires C, 43.79; H, 3.68; N, 4.28%. $[\alpha]_D$ +243.6 (*c* 1.0, $CHCl_3$); υ_{max}($CHCl_3$) 1718(s) cm^{-1}; δ_H(200MHz, $CDCl_3$) 2.38-2.52 (1H, m, H-6_{endo}), 3.05-3.20 (1H, m, H-6_{exo}), 3.79 (1H, dd, *J* 10.0, 9.5Hz, H-4_{endo}), 4.12-4.35 (2H, m, H-5 and H-4_{exo}), 5.05 (1H, dd, *J* 10.0, 7.5Hz, H-7), 6.35 (1H, s, H-2), 7.32-7.53 (5H, m, ArH); δ_C(125.MHz, $CDCl_3$) 18.32, 37.02, 58.10, 71.17, 87.98, 126.16, 128.74, 129.04, 136.28, 173.43; *m/z* [CI, NH_3] 330($M+H^+$, 100%), 202(70).

(+)-(2R,5S,7R) and (+)-(2R,5S,7S)-1-aza-3-oxa-2-phenyl-7-(4'-nitrophenylmethyl)bicyclo[3.3.0]octan-8-one **3d,4d**

These products were obtained using p-nitrobenzyl bromide on a 1.0mmol scale of the lactam **2a**.

3d. R_f = 0.1(light petroleum/EtOAc = 2:1)(156mg, 48%); Found: C, 67.2; H, 5.33; N, 8.05. $C_{19}H_{18}N_2O_4$ requires C, 67.4; H, 5.40, N, 8.30%; $[\alpha]_D$ +50.7 (*c* 1.1, $CHCl_3$); υ_{max}($CHCl_3$); 1705(s), 1515(s), 1340(s) cm^{-1}; δ_H (200 MHz,$CDCl_3$) 2.04-2.12 (2H, m, H-6_{exo} and H-6_{endo}), 3.00-3.26 (3H, m, $ArCH_2$ and H-7_{endo}), 3.35-3.45 (1H, dd, *J* 8.0, 8.5Hz, H-4_{endo}), 3.75-3.85 (1H, m, H-5), 4.18 (1H, dd, *J* 8.0, 6.5Hz, H-4_{exo}), 6.30 (1H, s, H-2), 7.30-7.50 (7H, m, ArH), 8.10-8.20 (2H, m, ArH); δ_C (50 MHz, $CDCl_3$) 27.00 (C-6), 37.49 (Ar$\underline{C}H_2$), 45.99 (C-7), 56.96 (C-5), 71.14 (C-4), 87.18 (C-2), 123.8, 125.9, 128.6, 128.8, 130.1, 138.7, 147.1, 146.3 (ArC), 178.9 (C-8); *m/z* [CI, NH_3] 356 ($M+NH_4^+$, 5%), 339 (M+H, 100), 309(25), 106(22).

4d.R_f = 0.3(light petroleum/EtOAc = 2:1) (45.0mg, 13.5%); Found: C, 67.1; H, 5.70; N, 7.94. $C_{19}H_{18}N_2O_4$ requires C, 67.4; H, 5.40, N, 8.30%; $[\alpha]_D$ +184 (*c* 0.4, $CHCl_3$); υ_{max}($CHCl_3$) 1705(s), 1605(m), 1595(m), 1515(s), 1345(s) cm^{-1}; λ_{max} ($CHCl_3$) 274 nm (log ε = 4.2); δ_H (200 MHz,$CDCl_3$) 1.60-1.70 (1H, m, H-6_{endo}), 2.40-2.50 (1H, m, H-6_{exo}), 2.82-2.90 (1H, m, ArC$\underline{H}$), 3.20- 3.30 (1H, m, H-7_{exo}), 3.35-3.50 (2H, m, ArCH and H-4_{endo}), 4.05-4.12 (1H, m, H-5), 4.20-4.25 (1H, m, H-4_{exo}), 6.35 (1H, s, H-2), 7.30- 7.50 (7H, m, Ar$\underline{H}$), 8.2 (2H, d, *J* 8.6Hz, Ar$\underline{H}$ *o*- to NO_2); δ_C (50 MHz, $CDCl_3$) 29.90 (C-6), 36.19 (Ar$\underline{C}H_2$), 46.45 (C-7), 56.49 (C-5), 72.14 (C-4), 86.88 (C-2), 123.9, 126.1, 128.6, 128.8, 129.8, 130.0, 138.9, 147.0, 148.3 (ArC); *m/z* [CI, NH_3] 356($M+NH_4^+$, 8%), 339(M+H, 100), 309(60), 106(45); n.O.e. irradiation at δ4.1 (3.25, 2.0% ; 2.45, 8.0%); 2.45 (1.6, 23% ; 3.0, 8.4% ; 4.1, 12.4%); 1.65 (2.45, 23.5% ; 3.5, 9.3%) .

(2R,5S,7R) and (+)-(2R,5S,7S)-1-aza-3-oxa-2-phenyl-7-bromobicyclo[3.3.0]octan-8-one **3e,4e**

These products were obtained using N-bromosuccinimide on a 2.5mmol scale of the lactam **2a**.

3e: R_f=0.4 (EtOAc/light petroleum 1:1) (230mg, 33%), a colourless oil which discoloured rapidly upon standing at RT. υ_{max}($CHCl_3$) 1718(s) cm^{-1}; δ_H(200MHz, $CDCl_3$) 2.40-2.70 (2H, m, H-6), 3.60 (1H, dd *J* 7.5, 7.5Hz, H-4_{endo}), 4.21-4.53 (3H, m, H-4_{exo}, H-5 and H-7), 6.31 (1H, s, H-2), 7.31-7.45 (5H, m, ArH); δ_C(50.3MHz, $CDCl_3$) 36.89, 45.84, 57.62, 71.11, 86.87, 126.22, 128.82, 129.13, 137.77, 173.11; *m/z* [CI, NH_3] 301($M+NH_4^+$ ^{81}Br, 5%), 299($M+NH_4^+$ ^{79}Br, 5), 294(20), 284(25), 282(25), 204(100); Exact mass 282.0130, $C_{12}H_{13}NO_2Br$ requires 282.01297.

4e: Rf=0.55(EtOAc/light petroleum 1:1) (60mg, 8.6%) which was recrystallised from diethyl ether/light petroleum as colourless needles. M.p. 137-138°C; $[\alpha]_D$ +258.4 (*c* 1.0, $CHCl_3$); υ_{max}($CHCl_3$) 1719(s) cm^{-1}; δ_H(200MHz, $CDCl_3$) 2.26-2.41 (1H, m, H-6), 3.03-3.19 (1H, m, H-6), 3.70 (1H, dd, *J* 7.0, 8.5Hz, H-4), 4.03-4.19 (1H, m, H-5), 4.28-4.36 (1H, dd, *J* 6.5, 8.5Hz, H-4), 4.87 (1H, dd, *J* 8.5, 8.5Hz, H-7), 6.38 (1H, s, H-2), 7.31-7.45 (5H, m, Ar-H); δ_C(50.3MHz, $CDCl_3$) 36.36, 44.75, 56.53, 71.72, 87.81, 125.93, 128.51, 128.85, 137.88, 171.41; *m/z* [CI, NH_3] 301($M+NH_4^+$ ^{81}Br, 10%), 299($M+NH_4^+$ ^{79}Br, 10), 284($M+H^+$ ^{81}Br, 40), 282($M+H^+$ ^{79}Br, 40), 204(100), 106(40); Exact mass 282.0130, $C_{12}H_{13}NO_2Br$ requires 282.01297.

(+)-(2R,5S,7R) and (+)-(2R,5S,7S)-1-aza-3-oxa-2-phenyl-7-(phenylselenenyl)bicyclo[3.3.0]octan-8-one **3f,4f**

These products were obtained using phenylselenenyl bromide or chloride on a 1mmol scale of the lactam **2a**.

3f. R_f = 0.4(hexane/EtOAc = 2:1)(530mg, 30.1%); Found: C, 60.3; H, 5.10; N, 3.74. $C_{18}H_{17}NO_2Se$ requires C, 60.3; H, 4.80; N, 3.90%; $[\alpha]_D$ +44.8 (*c* 0.4, $CHCl_3$); υ_{max}($CHCl_3$) 1700(s) cm^{-1}; δ_H (200 MHz, $CDCl_3$) 2.50 (2H, dd, *J* 5.5, 6.7Hz, H-6_{endo} andH-6_{exo}), 3.40 (1H, dd, *J* 8.0, 8.0Hz, H-4_{endo}), 3.54-3.65 (1H, m, H-5), 3.98 (1H, dd, *J* 5.5, 6.5Hz, H-7_{endo}), 4.16 (1H, dd, *J* 8.0, 6.0Hz, H-4_{exo}), 6.27 (1H, s, H-2), 7.10-7.40 and 7.60-7.70 (10H, m, ArH); δ_C (50 MHz, $CDCl_3$) 33.30 (C-6), 42.74 (C-7), 57.39 (C-5), 71.87 (C-4), 89.94 (C-2), 126.1, 128.5, 128.7, 129.16, 129.28, 136.7 (ArC), 178.0 (C-8); *m/z* [CI, NH_3] 360 ($M+2^+$, 100%), 358 (M^+, 50), 204 (75), 105 (15).

4f. R_f = 0.7(hexane/EtOAc = 2:1)(140mg, 8.0%); Found: C, 60.5; H, 4.56; N, 3.92. $C_{18}H_{17}NO_2Se$ requires C, 60.3; H, 4.80; N, 3.90%; $[\alpha]_D$ +248 (*c* 1.0, $CHCl_3$); υ_{max} ($CHCl_3$) 1700cm^{-1}; λ_{max} ($CHCl_3$) 242 nm (log ε = 3.5); δ_H (200MHz, $CDCl_3$) 1.80-2.10 (1H, m, H-6_{endo}), 2.75-2.95 (1H, m, H-6_{exo}), 3.10 (1H, dd, *J* 7.5, 7.5Hz, H-4_{endo}), 4.00-4.18 (2H, m, H-4_{exo} and H-5), 4.40 (1H, dd, *J* 9.5, 9.5Hz, H-7_{exo}), 6.30 (1H, s, H-2), 7.20- 7.75 (10H, m, ArH); n.O.e. irradiation at δ4.05 (4.40, 1.8% ;4.1, 2.0% ; 2.8, 6.2%); δ_C (50 MHz, $CDCl_3$) 31.70 (C-6), 43.72 (C-7), 56.61 (C-5), 71.74 (C-4), 87.39 (C-2), 126.1, 127.1, 128.6, 128.8, 129.4, 135.8 (ArC), 175.0 (C-8); *m/z* [CI, NH_3] 360 (M+2, 20%), 358 (M^+, 13), 204 (100), 202(50), 106 (12), 78 (20).

(+)-(2R,5S)-1-aza-3-oxa-2-phenyl-7,7'-(diphenylselenenyl)bicyclo[3.3.0]octan-8-one. (310mg, 12%) R_f=0.55 (EtOAc/light petroleum = 1:2); Found: C, 56.0, H, 4.06, N, 2.74. $C_{18}H_{16}NO_2Se_2$ requires C, 56.2; H, 4.12; N, 2.73%; $[\alpha]_D$ +154 (*c* 1.1, $CHCl_3$); υ_{max} ($CHCl_3$) 1725cm^{-1}; δ_H (200MHz, $CDCl_3$) 2.44-2.69 (2H, m, H-6_{endo} and H-6_{exo}), 2.96-3.04 (1H, dd, *J* 8.0, 8.0Hz, H-4_{endo}), 3.28-3.43 (1H, m, *J* 8.0Hz, H-5), 3.92-4.00 (1H, dd, *J* 6.5, 8.0Hz, H-4_{exo}), 6.18 (1H, s, H-2), 7.12-7.48 and 7.62-7.66 and 7.70-7.81 (15H, m, ArH); δ_C (50 MHz, $CDCl_3$) 40.50 (C-6), 55.80 (C-5), 71.90 (C-4), 87.10 (C-2), 125.9, 126.0, 128.3, 128.4, 128.6, 129.0, 129.2, 129.5, 129.7, 137.1, 137.4, 138.0 (ArC), 174.0 (C-8); *m/z* [CI, NH_3] 516 ($M+2^+$, 80%), 512 (50), 360 (100), 358(90).

(2R,5S,7S, 1'RS) and (2R,5S,7R, 1'RS)-1-aza-3-oxa-2-phenyl-7-(cyclohex-2-enyl)bicyclo[3.3.0]octan-8-one **3g,4g**[6]

These products were obtained using cyclohex-2-enyl bromide on a 5.0mmol scale of the lactam **2a**.

3g Obtained as an oil (510mg, 36.8%); R_f=0.45(EtOAc/light petroleum = 1:1); υ_{max}($CHCl_3$) 1697 cm^{-1}; δ_H (200 MHz,$CDCl_3$) 1.23-2.20 (8H, m, ring H and H-6), 2.70-2.87 (2H, m), 3.35-3.45 (1H, m, H-4_{endo}), 3.97-4.21 (2H, m, H-4_{exo} and H-5), 5.51-5.56 (1H, m, C<u>H</u>=C), 5.79-5.86 (1H, m, C<u>H</u>=C), 6.34 (1H, s, H-2), 7.30-7.47 (5H, m, ArH); *m/z* [CI, NH_3] 284 ($M+H^+$, 100%).

4g Obtained as a waxy solid(60mg, 4.3%); R_f= 0.50(EtOAc/light petroleum = 1:1); δ_H (200 MHz,$CDCl_3$) 1.2-2.10 (7H, m, ring H, H-6_{endo} and H-6_{exo}), 2.25-2.45 (1H, m, ring H), 2.60-3.10 (2H, m, ring H and H-7), 3.40-3.60 (1H, m, H-4_{endo}), 4.0-4.3 (2H, m, H-5 and H-4_{exo}), 5.3-5.9 (2H, m, C<u>H</u>=C<u>H</u>), 6.35 and 6.37 (1H, 2 x s, H-2), 7.30-7.50 (5H, m); *m/z* [CI, NH_3] 284 ($M+H^+$, 100%).

(+)-(2R,5S,7R) and (+)-(2R,5S,7S)-1-aza-3-oxa-2-phenyl-7-chlorobicyclo[3.3.0]octan-8-one **3h, 4h**

These products were obtained using *p*-tosyl chloride on a 24.6 mmol scale of the lactam **2a**.

3h: Colourless solid that was recrystallised from CH_2Cl_2/light petroleum (1.28g, 22%); R_f= 0.10(EtOAc/light petroleum = 1:5). M.p. 122-124°C; Found: C, 60.30, H, 5.09, N, 5.84. $C_{12}H_{12}NO_2Cl$ requires C, 60.64, H, 5.09, N, 5.89%. $[\alpha]_D$ +197.6(*c* 1.0, $CHCl_3$); υ_{max}($CHCl_3$) 1718(s) cm^{-1}; δ_H(200MHz, $CDCl_3$) 2.33-2.60(2H, m, H-6_{endo} and H-6_{exo}), 3.58(1H, dd *J* 8.0, 8.0Hz, H-4_{endo}), 4.24-4.53(3H, m, H-4_{exo}, H-5 and H-7), 6.31(1H, s, H-2), 7.34-7.45(5H, m, ArH); δ_C(50.3MHz, $CDCl_3$) 36.27, 57.33, 57.69, 71.27, 86.92, 126.19, 128.82, 129.14, 137.67, 172.48; *m/z* [CI, NH_3] 255($M+NH_4^+$ ^{35}Cl, 10%), 240($M+H^+$ ^{37}Cl, 40), 238($M+H^+$ ^{35}Cl, 100).

4h: Obtained as a colourless solid after purification by recrystallisation from either diethyl ether/light petroleum or chloroform/light petroleum (3.21g, 55%); (R_f=0.3 EtOAc:light petroleum=1:5); M.p. 123-125°C; Found: C, 60.75, H, 4.95, N, 5.82. $C_{12}H_{12}NO_2Cl$ Requires C, 60.64, H, 5.09, N, 5.89%. $[\alpha]_D$ +140.9 (*c* 2.2, $CHCl_3$). υ_{max}($CHCl_3$) 1723(s) cm^{-1}; δ_H(200MHz, $CDCl_3$) 2.15(1H, m, H-6), 3.03(1H, m, H-6), 3.66(1H, dd, *J* 8.0, 8.5Hz, H-4), 4.03-4.09(1H, m, H-5), 4.31(1H, dd, *J* 6.0, 8.5Hz, H-4), 4.81(1H, dd, *J* 8.5, 7.0Hz, H-7), 6.39(1H, s, H-2), 7.31-7.46(5H, m, ArH); δ_C(125.MHz, $CDCl_3$) 36.76, 55.39, 56.57, 72.06, 87.61, 125.95, 128.51, 128.87, 137.72, 171.02; *m/z* [CI, NH_3] 240($M+H^+$ ^{37}Cl, 30%), 238($M+H^+$ ^{35}Cl, 100).

(+)-(2R,5S,7R) and (+)-(2R,5S,7S)-1-aza-3-oxa-2-phenyl-7-methylbicyclo[3.3.0]octan-8-one **3i,4i**

These products were obtained using methyl iodide on a 1.5mmol scale of the lactam **2a**.

3i Obtained as a white solid after recrystallisation from EtOAc/light petroleum (62.0mg, 19.4%)(R_f=0.1 EtOAc:light petroleum=1:4); Found: C, 71.53, H, 6.93, N, 6.04. $C_{13}H_{15}NO_2$ requires C, 71.87, H, 6.95, N, 6.45%; $[\alpha]_D$ +126 (*c* 0.20, $CHCl_3$); υ_{max}($CHCl_3$) 1702 cm^{-1}; δ_H (500 MHz,$CDCl_3$) 1.36-1.37 (3H, d, *J* 7.5Hz, CH_3), 1.97-2.05 (1H, m, H-6_{exo}), 2.17-2.13 (1H, m, H-6_{endo}), 2.70-2.78 (1H, m, H-7_{endo}), 3.41-3.45 (1H, m, H-4_{endo}), 4.07-4.12 (1H, m, H-5), 4.24 (1H, dd, *J* 8.0, 6.3Hz, H-4_{exo}), 6.33 (1H, s, H-2), 7.32-7.47 (5H, m, ArH); δ_C (125 MHz, $CDCl_3$) 17.76 (CH_3), 30.16 (C-6), 39.43 (C-7), 57.00 (C-5), 71.03 (C-4), 87.46 (C-2), 125.9, 128.4, 128.4, 139.1(ArC), 181.7 (C-8); *m/z* [CI, NH_3] 218 ($M+H^+$, 100%). n.O.e. irradiation at δ2.0 (4.1, 7.6% ; 2.7, 2.2% ; 2.2, 12.8%); 2.2 (4.1, 3.1% ; 3.4, 4.2% ; 2.75, 6.0% ; 2.0, 10.8%); 2.75 (2.2, 2.0% ; 1.35, 3.0%); 4.1 (2.0, 5.9% ;4.25, 2.7%).

4i Obtained as an oil (182mg, 56.9%); R_f = 0.15(light petroleum/EtOAc = 4:1); $[\alpha]_D$ +180 (*c* 1.0, $CHCl_3$); υ_{max}($CHCl_3$) 1702 cm^{-1}; δ_H (500 MHz,$CDCl_3$) 1.24-1.26 (3H, d, *J* 7.0Hz, CH_3), 1.52-1.58 (1H, m, H-6_{endo}), 2.60-2.66 (1H, m, H-6_{exo}), 2.94-3.00 (1H, m, H-7_{exo}), 3.52-3.55 (1H, dd, *J* 7.5, 8.5Hz, H-

4_{endo}), 4.08-4.12(1H, m, H-5), 4.22-4.25 (1H, dd, *J* 6.5, 8.5Hz, H-4_{exo}), 6.35 (1H, s, H-2), 7.32-7.38 and 7.45-7.46 (5H, m, ArH); δ_C (50 MHz, $CDCl_3$) 15.44 (CH_3), 34.79 (C-6), 40.01 (C-7), 56.57 (C-5), 72.48 (C-4), 86.90 (C-2), 126.2, 128.6, 128.7, 137.0 (ArC), 176.0 (C-8); *m/z* [CI, NH_3] 218 ($M+H^+$, 100%). n.O.e. irradiation at δ1.55 (3.5, 4.1%; 2.95, 2.0%; 2.6, 15.8%); 2.6 (4.1, 7.1%; 2.95, 4.0%; 1.55, 17.0%); 2.95 (2.6, 2.3%; 1.2, 4.0%); 4.1 (2.6, 5.5%; 2.95, 1.3%; 4.23, 3.1%). Exact mass 218.1181, $C_{13}H_{15}NO_2$ requires 218.11810.

(+)-(2R,5S,7R,1'R), (+)-(2R,5S,7S,1'R) and (+)-(2R,5S,7S,1'S) 1-aza-3-oxa-2-phenyl-7-(phenyl(hydroxy)-methyl)bicyclo[3.3.0]octan-8-one **5a, 5b and 5c**

These products were obtained using benzaldehyde (575mg, 5.0 mmol) as the electrophile on a 4.9mmol scale of the lactam **2a** (1.0g).

5a: R_f= 0.50 (Ethyl acetate:light petroleum=1:1) (551mg, 36%) was recrystallised from chloroform/light petroleum. M.p. 148-150°C; Found: C, 74.05; H, 5.91; N, 4.39. $C_{19}H_{19}NO_3$ requires C, 73.76; H, 6.19; N, 4.53%; $[\alpha]_D$ +127.2 (*c* 1.0, $CHCl_3$); υ_{max}($CHCl_3$) 3685(m), 1689(s)cm^{-1}; δ_H(200MHz, $CDCl_3$) 1.55-1.61(1H, m, H-6_{endo}), 1.98-2.13(1H, m, H-6_{exo}), 3.15-3.29(1H, m, H-7_{exo}), 3.50(1H, dd, *J* 8.0, 7.5Hz, H-4_{endo}), 3.99-4.13(1H, m, H-5), 4.23(1H, dd, *J* 8.0, 6.5Hz, H-4_{exo}), 4.83(1H, d, *J* 9.5Hz, C<u>H</u>(OH)Ph), 6.40(1H, s, H2), 7.30-7.50(10H, m, Ar<u>H</u>). δ_C(50.3MHz, $CDCl_3$) 29.4, 51.7, 56.8, 72.2 75.9, 86.1, 126.1, 126.9, 127.1, 128.4, 128.6, 128.7, 129.0, 138.1, 140.8, 178.5; *m/z* [CI, NH_3] 310 ($M+H^+$, 100%), 292 (50), 204 (90); n.O.e. irradiation at δ1.6 (2.0, 22%; 3.5, 7.2%; 4.8, 6.3%); 2.1 (1.5, 20.1%; 3.2, 7.7%; 4.0, 11.8%); 3.3 (2.0, 5.2%; 4.0, 2.3%; 5.2, 4%; 7.4, 7.2%); 3.5 (1.5, 6.7%; 4.2, 22.7%); 4.1 (2.0, 8.1%; 3.2, 2%; 4.2, 4.6%); 4.3 (3.5, 23.1%; 4.0, 4.5%); 4.8 (5.2, 9.4%).

5b: R_f= 0.35 (EtOAc:light petroleum=1:1) was a colourless solid (445mg, 29.1%) which was recrystallised from chloroform/light petroleum. M.p. 180-182°C; Found: C, 73.58; H, 6.48; N, 4.47. $C_{19}H_{19}NO_3$ requires C, 73.76; H, 6.19; N, 4.53%; $[\alpha]_D$ +70.2 (*c* 1, $CHCl_3$); υ_{max}($CHCl_3$) 3684(m), 1694(s), 1520(s), 1423(s) cm^{-1}; δ_H(500MHz, $CDCl_3$) 1.74-1.81(1H, m, H-6_{endo}), 2.36-2.42(1H, m, H-6_{exo}), 2.82(1H, d, *J* 4.0Hz, exch D_2O, O<u>H</u>), 3.08-3.14(1H, m, H-7_{endo}), 3.35(1H, m, H-4_{endo}), 3.93-4.00(1H, m, H-5), 4.17(1H, dd, *J* 6.0, 8.0Hz, H-4_{exo}), 5.35(1H, t, *J* 4.0Hz, C<u>H</u>(OH)Ph), 6.33(1H, s, H-2), 7.26-7.45(10H, m, Ar<u>H</u>); δ_C(50.3MHz, $CDCl_3$) 21.9, 51.0, 58.1, 71.6, 72.2, 87.4, 125.8, 126.0, 127.8, 128.5, 128.6, 138.8, 142.1, 178.6; *m/z* [CI, NH_3] 310($M+H^+$, 40%), 292(20), 204(100); n.O.e. irradiation at 1.7 (2.4, 20.4%; 3.1, 9.8%; 3.3, 6.4%); 2.4 (1.7, 19.6%; 3.1, 4%; 4.0, 13.9%; 5.4, 2.2%); 3.05 (1.7, 6%; 5.4, 8%); 3.3 (4.2, 23.5%); 4.0 (2.4, 7.7%; 4.2, 6.3%); 4.15 (3.4, 25.7%; 4.0, 6%); 5.3 (1.7, 4%; 2.7, 6%; 3.1, 7%; 7.4, 6.7%).

5c: R_f=0.15 (EtOAc:light petroleum=1:1) was recrystallised from chloroform/light petroleum. M.p. 132-140°C; Found: C, 74.10; H, 6.15; N, 4.53. $C_{19}H_{19}NO_3$ requires C, 73.76; H, 6.19; N, 4.53%; $[\alpha]_D$ +124.8(*c* 1.0, $CHCl_3$); υ_{max}($CHCl_3$) 3685(m), 1691(s)cm^{-1}; δ_H(200MHz, $CDCl_3$) 1.76-1.90(1H, m, H-6_{endo}), 2.01-2.16(1H, m, H-6_{exo}), 3.02-3.14(1H, m, H-7_{exo}), 3.35(1H, dd, *J* 8.0, 9.0Hz, H-4_{endo}), 3.73-3.87(1H, m, H-5), 4.01(1H, s, exch D_2O, OH), 4.15(1H, dd, *J* 7.5, 6.0Hz, H-4_{exo}), 4.93(1H, d, *J* 8.0Hz, C<u>H</u>(OH)Ph), 6.31(1H, s, H-2), 7.3-7.45(10H, m, Ar<u>H</u>); δ_C(50.3MHz, $CDCl_3$) 24.1, 51.4, 57.0, 70.8 74.9, 86.5, 126.5, 127.0, 128.8, 128.9 129.0, 138.7, 140.2, 178.5; *m/z* [CI, NH_3] 310($M+H^+$, 20%), 246(50), 204(100), 105(50); n.O.e. irradiation at δ1.8 (2.1, 19.7%; 3.1, 10%; 3.35, 5.1%; 3.8, 3.4%); 2.1 (1.8, 18.7%; 3.1, 3.9%; 3.8, 13.5%; 4.9, 3.6%); 3.1 (1.8, 6.1%; 3.35, 2%; 3.95, 2.6%; 4.9, 3.1%; 7.4, 6%); 3.35

(1.8, 5%; 3.1, 1.8%; 4.2, 22.5%; 6.2, 2%); 3.8 (1.8, 2%; 2.1, 6.6%; 4.1, 6%); 4.15 (3.35, 24.6%; 3.8, 5.7%); 4.9 (2.1, 2%; 3.1, 2.4%; 3.9, 3.8%).

(2R,5S)-1-Aza-3-oxa-2-phenyl-7,7-diacetylbicyclo[3.3.0]octan-8-one **3** (R^1=R^2=COMe)*and compound* **6**

These compounds were synthesised with acetyl chloride (0.368ml, 5.17mmol) or acetic anhydride (0.464ml, 5.0mmol) as the acylating agent on a 4.9mmol scale of lactam **2a** (1.0g).

3 (R^1=R^2=COMe): (210mg, 15%); δ_H(200MHz, $CDCl_3$) 2.18(3H, s, -COMe), 2.40(3H, s, -COMe), 2.43-2.6(1H, m, H-6_{endo}), 2.80-2.95(1H, m, H-6_{exo}), 3.35(1H, m, H-4), 3.89-4.01(1H, m, H-5), 4.23(1H, dd, *J* 9.0, 6.0Hz, H-4), 6.34(1H, s, H-2), 7.25-7.50(5H, m, ArH); *m/z* [CI^+, GCMS] 288(100% $M+H^+$).

6: was obtained as a colourless solid (529mg, 48%) which was recrystallised from EtOAc/light petroleum. M.p. 180-182°C; Found: C, 69.53%, H, 6.02, N, 5.99 $C_{26}H_{28}N_2O_4$ requires C, 69.62; H, 6.30; N, 6.25%; $[\alpha]_D$ +271.4 (*c* 1.0, $CHCl_3$); υ_{max}($CHCl_3$) 3440(br), 1720(s), 1700 cm^{-1}; δ_H(500MHz, $CDCl_3$) 1.44(3H, s, Me), 1.97-2.03(1H, m, H-6'$_{endo}$), 2.08-2.14(1H, m, H-6_{endo}), 2.17-2.24(1H, m, H-6_{exo}), 2.54-2.59(1H, m, H-6'$_{exo}$), 3.05(1H, dd, *J* 5.0, 10.0Hz, H-7'$_{exo}$), 3.17(1H, dd, *J* 10.0, 7.5Hz, H-7$_{endo}$), 3.39-4.46(2H, m, H-4$_{endo}$ and H-4'$_{endo}$), 3.99(1H, s, exch D_2O, -OH), 4.01-4.06(1H, m, H-5), 4.15-4.20(1H, m, H-5'), 4.20-4.33(2H, m, H-4$_{exo}$ and H-4'$_{exo}$), 6.33(1H, s, H-2), 6.34(1H, s, H-2), 7.30-7.46(10H, m, ArH); δ_C(50.3MHz DEPT, $CDCl_3$) 21.52(q), 23.07(t), 24.62(t), 50.92(d), 52.15(d), 56.72(d), 57.52(d), 70.58(t), 71.63(t), 74.19(s), 87.49(d), 87.87(d), 126.05(d), 126.20(d), 128.54(d), 128.69(d), 128.88(d), 138.85(s), 177.73(s), 180.46(s); *m/z* [CI, NH_3] 448(10%, $M+H^+$), 246(90), 204(100).

(2R,5S)-1-aza-3-oxa-2-phenyl-7-(4'nitrophenyl(hydroxy)methyl)bicyclo[3.3.0]octan-8-one

The product was obtained using *p*-nitrobenzaldehyde (83mg, 0.6mmol) as the electrophile after chromatography(hexane/EtOAc=2:1) as an inseparable mixture of diastereoisomers (47 mg, 27%). Found: C, 65.0; H, 5.34; N, 7.60%. $C_{19}H_{18}N_2O_5$ requires C, 64.4; H, 5.10; N, 7.90%; υ_{max}($CHCl_3$) 1685(s), 1605(m), 1520(m) cm^{-1}; δ_H (200 MHz, $CDCl_3$) 3.1-3.3(2H, m, H-6_{exo} and H-6_{endo}), 3.4(1H, m, H-7), 3.6(1H, m, H-4), 4.1(1H, m, H-5), 4.3(1H, m, H-4), 4.9(1H, d, *J* 9.4Hz, C<u>H</u>(OH)Ar), 5.4 and 5.55 (1H, 2xs), 6.37 and 6.4(1H, 2 x s, 2 x H-2), 7.3 - 8.3(9H, m, ArH); *m/z* [CI, NH_3] 355($M+H^+$, 2%), 307 (8), 204 (75), 122 (100).

(+)-(2R,5S)-1-aza-3-oxa-7,7-dicarbobenzyloxy-2-phenylbicyclo[3.3.0]octan-8-one **3**(R^1=R^2=CO_2CH_2Ph)

The product was obtained, using benzyl chloroformate (94mg, 0.6mmol) as the electrophile, after column chromatography (hexane/EtOAc = 2:1, R_f 0.4) (88mg, 37.4%); Found: C, 71.2; H, 5.53; N, 3.13. $C_{28}H_{25}NO_6$ requires C, 71.4; H, 5.30; N, 2.97 %; $[\alpha]_D$ +98.8 (*c* 0.09, $CHCl_3$); λ_{max} ($CHCl_3$) 256 nm (log ε = 3.0); δ_H (200 MHz, $CDCl_3$) 2.60-2.75 (1H, m, H-6_{endo}), 2.95-3.05 (1H, m, H-6_{exo}), 3.65 (1H, m, H-4_{endo}), 4.00-4.30 (2H, m, H-4_{exo} and H-5), 5.15 and 5.35 (4H, m, 2 x PhC<u>H_2</u>), 6.40 (1H, s, H-2), 7.20-7.45 (15H, m, ArH); δ_C (50 MHz, $CDCl_3$) 33.96 (C-6), 55.87 (C-5), 67.80(C-7), 68.14(CH_2), 68.24(CH_2), 71.50 (C-4), 87.20 (C-2), 126.1, 128.1, 128.3, 128.5, 128.7, 128.9, 135.0, 137.7 (ArC), 166.5, 166.8, 168.4(C=O); *m/z* [CI, NH_3] 489 ($M+NH_4^+$, 15%), 472 ($M+H^+$, 75), 338 (40), 246 (14), 228 (30), 108 (25), 91 (100).

(2R,5S,7RS)-1-aza-7-methoxyoxalyl-3-oxa-2-phenylbicyclo[3.3.0]octan-8-one **2a** (R^1=$COCO_2Me$)

The product was obtained using dimethyl oxalate (65mg, 0.55 mmol) as the electrophile, after column chromatography (EtOAc/hexane = 4:1, R_f = 0.6) as an inseparable mixture of diastereoisomers at C-7 (36mg, 25%, *exo-: endo-* = 2.6:1). Found: C, 62.2; H, 5.20; N, 4.74. $C_{15}H_{15}NO_5$ requires C, 62.3; H, 5.20; N, 4.8 % ; υ_{max}($CHCl_3$) 1735(s), 1665(s) cm^{-1}; δ_H ($CDCl_3$, 200MHz) 2.90-3.50 (4H, m, H-6_{exo}, H-6_{endo}, H-7, and H-4_{endo}), 3.85 and 3.90 (total of 3H, 2 x s, 2 x $OC\underline{H}_3$), 4.05-4.20 (1H, m, H-5), 4.25-4.40 (1H, m, H-4_{exo}), 6.30 and 6.35 (1H, 2 x s, H-2), 7.30-7.50 (5H, m, ArH); δ_C ($CDCl_3$, 50 MHz) 25.85 (C-6), 52.67($O\underline{C}H_3$), 56.89 (C-5), 70.98 (C-4), 87.58 (C-2), 112.1 (C-7), 126.9, 127.1, 128.7, 128.8, 129.0, 138.5 (ArC), 150.0 and 163.2 ($\underline{C}(O)\underline{C}(O)CH_3$) and 177.0 (C-8); *m/z* [CI, NH_3] 307 ($M+NH_4^+$, 4%), 290 ($M+H^+$, 100), 230 (15).

(2R, 5S, 7RS)-7-Ethoxycarbonyl 2-phenyl-1-aza-3-oxa-bicyclo[3.3.0]octan-8-one **2b**

A pre-dried solution of lactam **2a** (4.3g, 21.2mmol) and diethylcarbonate (10.0g, 84.8mmol) in toluene (80ml) was prepared by heating the mixture at reflux for 5h in a vessel fitted with a Dean-Stark trap allowing azeotropic removal of water. Pre-washed NaH (1.69g, 42.4mmol) was carefully added to the solution at 0°C, and the mixture was brought back to reflux. After 16h the mixture was cooled to 0°C and quenched with glacial acetic acid (2.2g) to give a thick brown suspension. Filtration and solvent removal *in vacuo* gave a yellow-orange oil which was purified by silica chromatography (3:1 light petroleum/EtOAc) to give the product as a yellow solid (4.1g, 70%), as a 1:1 mixture of diastereomers.

R_f 0.3 (1:1 light petroleum/EtOAc); M.p. 85-87°C; $[\alpha]_D$ +178.3 (c 1, $CHCl_3$); Found: C, 65.63; H, 6.08; N, 5.06. $C_{15}H_{17}NO_4$ requires C, 65.44; H, 6.24; N, 5.09%; υ_{max}($CHCl_3$) 1737(s), 1713(s) cm^{-1}; δ_H (500MHz, $CDCl_3$) (**7*R* diastereomer**) 1.32 (3H, t, *J* 7Hz, $C\underline{H}_3$), 2.16 (1H, ddd, *J* 13.5, 9.5, 6Hz, H-6), 2.76 (1H, ddd, *J* 13.5, 7.5, 3Hz, H-6), 3.53 (1H, t, *J* 8Hz, H-4), 3.65 (1H, dd, *J* 9.5, 3Hz, H-7), 4.21-4.35 (4H, m, $C\underline{H}_2CH_3$, H-4 , H-5), 6.33 (1H, s, H-2), 7.31-7.47 (5H, m, Ar$\underline{H}$); δ_H (500MHz, $CDCl_3$) (**7*S* diastereomer**) 1.34 (3H, t, *J* 7Hz, $C\underline{H}_3$), 2.42 (1H, ddd, *J* 13.5, 9.5, 6Hz, H-6), 2.58 (1H, ddd, *J* 13.5, 9.5, 7Hz, H-6), 3.69 (1H, t, *J* 8Hz, H-4), 3.88 (1H, t, *J* 9.5Hz, H-7), 4.10-4.16 (1H, m, H-5), 4.21-4.35 (3H, m, $C\underline{H}_2CH_3$, H-4), 6.34 (1H, s, H-2), 7.31-7.47 (5H, m, Ar$\underline{H}$); δ_C (50.3MHz, $CDCl_3$) 14.02 ($\underline{C}H_3$), 27.38, 27.71 (2xC-6), 51.52, 52.25 (2xC-7), 56.90, 57.95 (2xC-5), 61.87, 62.02 ($2x\underline{C}H_2CH_3$), 71.64, 71.86 (2xC-4), 87.12, 87.32 (2xC-2), 126.1, 128.7, 128.9 (ArCH), 138.5 (ArC), 169.4 and 172.5 (2 x CO); n.O.e. (500MHz, $CDCl_3$) (**7*S* diastereomer**) Irradiation at 2.42 (2.58, 14%; 3.69, 5.2%; 3.88, 2.5%; 4.10, 2.7%); 2.58 (2.42; 17%; 3.88, 7.7%; 4.10, 10.2%); 3.88 (2.58, 4.8%; 4.10, 1%); 4.10 (2.58, 6.1%; 4.3, 3.6%); *m/z* [CI, NH_3] 276 ($M+H^+$, 100%), 204 (22), 105 (8).

General method for Reaction of Lactam **2b** *with Electrophiles*

To a stirred suspension of pre-washed NaH (1.1equiv.) in dry THF (30ml) at 0°C under a nitrogen atmosphere was added a solution of lactam **2b** (1 equiv.) in THF (5ml) *via* syringe, and the mixture was stirred at RT for 20min. A solution of electrophile (1.1equiv.) in THF (5ml) was added *via* syringe and the mixture stirred either at RT or at reflux for between 1h and 16h. The reaction was quenched by pouring the mixture into NH_4Cl(aq)/EtOAc (50ml, 1:1) and the aqueous portion was extracted with EtOAc (2x20ml). Organic extracts were combined, washed with water and brine, dried ($MgSO_4$) and the solvent removed *in vacuo* to give an oil which was purified by silica chromatography (3:1 light petroleum/EtOAc) to give the two possible diastereomeric products, frequently as an inseparable mixture. Further careful silica chromatography or HPLC separation gave the individual diastereomers in homogeneous form.

(+)-(2R, 5S, 7R) and (+)-(2R, 5S, 7S)-7-ethoxycarbonyl-2-phenyl-7-phenylselenyl-1-aza-3-oxa-bicyclo-[3.3.0]octan-8-one **3j,4j**

These products were obtained using phenylselenyl chloride on a 11 mmol scale of lactam **2b.**

3j: (1.95g, 44%); R_f 0.15 (4:1 cyclohexane/EtOAc); $[\alpha]_D$ +11.4 (c 2, $CHCl_3$); Found: C, 58.30; H, 5.15; N, 3.51. $C_{21}H_{21}NO_4Se$ requires C, 58.61; H, 4.92; N, 3.25%; $\upsilon_{max}(CHCl_3)$ 1709(s) cm^{-1}; δ_H (500MHz, $CDCl_3$) 1.36 (3H, t, *J* 7Hz, CH_3), 2.60 (1H, dd, *J* 14.5, 7Hz, H-6), 2.94 (1H, dd, *J* 14.5, 6Hz, H-6), 3.14-3.20 (1H, m, H-5), 3.48 (1H, t, *J* 8Hz, H-4), 4.11-4.14 (1H, m, H-4), 4.33 (2H, dq, *J* 7, 2Hz, CH_2CH_3), 6.25 (1H, s, H-2), 7.10 (3H, t, *J* 7.5Hz, *m*-SeArH, *p*-SeArH), 7.29-7.39 (5H, m, Ar), 7.61 (2H, m, *o*-SeArH); δ_C (50.3MHz, $CDCl_3$) 13.91 (CH_3), 36.31 (C-6), 55.57 (C-5), 57.81 (C-7), 63.01 (CH_2CH_3), 72.11 (C-4), 86.98 (C-2), 126.3, 127.0, 128.2, 130.1, 138.4 (ArCH), 126.0, 138.2 (ArC), 169.1, 172.2 (2xCO); *m/z* [CI, NH_3] 432 ($M+H^+$, 2), 293 (15), 276 (100), 106 (12%).

4j: (1.28g, 29%); R_f 0.25 (4:1 cyclohexane/EtOAc); $[\alpha]_D$ +209.3 (*c* 2, $CHCl_3$); Found: C, 58.36; H, 4.92; N, 3.22. $C_{21}H_{21}NO_4Se$ requires C, 58.61; H, 4.92; N, 3.25%; $\upsilon_{max}(CHCl_3)$ 1717(s) cm^{-1}; δ_H (500MHz, $CDCl_3$) 1.26 (3H, t, *J* 7Hz, CH_3), 2.14 (1H, dd, *J* 14, 6Hz, H-6), 3.06 (1H, dd, *J* 14, 7Hz, H-6), 3.12-3.15 (1H, m, H-4), 4.06-4.11 (2H, m, H-4, H-5), 4.22 (2H, q, *J* 7Hz, CH_2CH_3), 6.27 (1H, s, H-2), 7.29-7.45 (8H, m, ArH), 7.70-7.72 (2H, m, *o*-SeArH); δ_C (50.3MHz, $CDCl_3$) 13.91 (CH_3), 36.49 (C-6), 56.22 (C-5), 58.90 (C-7), 62.70 (CH_2CH_3), 71.56 (C-4), 87.46 (C-2), 126.0, 128.4, 128.7, 129.2, 129.8, 137.6 (ArCH), 126.5, 137.9 (ArC), 169.1, 171.0 (2xCO); *m/z* [CI, NH_3] 449 ($M+NH_4^+$, 15%), 432 ($M+H^+$, 48), 325 (15), 293 (22), 276 (100), 106 (20).

(+)-(2R, 5S, 7S) and (+)-(2R, 5S, 7R)-7-ethoxycarbonyl-7-methyl-2-phenyl-1-aza-3-oxa-bicyclo[3.3.0]octan-8-one **3k, 4k**

These products were obtained using methyl iodide on a 0.73 mmol scale of lactam **2b.** Usual work-up, followed by HPLC separation (9:1 cycloheptane/IPA) yielded the individual diastereomers as colourless oils in 67% overall yield, and in a ratio of 1.7:1.

3k: (89mg,42%); R_f 0.35 (1:1 light petroleum/EtOAc); $[\alpha]_D$ +159.6 (*c* 3.3, EtOH); $\upsilon_{max}(CHCl_3)$ 1741(s), 1708(s) cm^{-1}; δ_H (500MHz, $CDCl_3$) 1.32 (3H, t, *J* 7Hz, CH_2CH_3), 1.60 (3H, s, CH_3), 2.23 (1H, dd, *J* 13.5, 7.5Hz, H-6_{exo}), 2.59 (1H, dd, *J* 13.5, 5Hz, H-6_{endo}), 3.71 (1H, t, *J* 7.5Hz, H-4_{endo}), 4.12-4.17 (1H, m, H-5), 4.22-4.31 (3H, m, H-4_{exo} and CH_2CH_3), 6.33 (1H, s, H-2), 7.32-7.39 (3H, m, ArH), 7.46-7.48 (2H, m, ArH); δ_C (50.3MHz, $CDCl_3$) 13.92 (CH_2CH_3), 21.52 (CH_3), 35.07 (C-6), 55.86 (C-7), 56.06 (C-5), 61.87 (CH_2CH_3), 71.63 (C-4), 87.39 (C-2), 126.1, 128.7, 128.9 (ArCH), 138.8 (ArC), 172.0, 177.0 (2xCO); n.O.e. experiment (500MHz, $CDCl_3$) Irradiation at 2.23 (2.59, 23.2%; 4.15, 10.7%); 2.59 (2.23, 18.7%; 3.71, 5.2%; 4.15, 2.9%); 3.71 (2.59, 5.4%; 4.15, 2.4%; 4.25, 20.6%); 4.15 (2.23, 6.5%; 4.25, 4%); *m/z* [CI, NH_3] 290 ($M+H^+$, 100%); Exact mass 290.1392. $C_{16}H_{20}NO_4$ ($M+H^+$) requires 290.1392; G.C. purity 99.8%.

4k: (53mg, 25%); R_f 0.3 (1:1 light petroleum/EtOAc); $[\alpha]_D$ +168.1 (*c* 1.9, EtOH); $\upsilon_{max}(CHCl_3)$ 1712(s) cm^{-1}; δ_H (250MHz, $CDCl_3$) 1.27 (3H, t, *J* 7Hz, CH_2CH_3), 1.51 (3H, s, CH_3), 1.78 (1H, dd, *J* 13, 7Hz, H-6), 2.93 (1H, dd, *J* 13, 6Hz, H-6), 3.51-3.60 (1H, m, H-4), 4.16-4.29 (4H, m, H-4, H-5, CH_2CH_3), 6.34 (1H, s, H-2), 7.31-7.46 (5H, m, ArH); δ_C (50.3MHz, $CDCl_3$) 13.91 (CH_2CH_3), 20.64 (CH_3), 38.62 (C-6), 56.16 (C-5), 56.65 (C-7), 61.88 (CH_2CH_3), 72.08 (C-4), 86.93 (C-2), 126.1, 126.2,

128.7, 128.9 (ArCH), 138.2 (ArC), 172.0, 174.3 (2xCO); m/z (Thermospray) 290 ($M+H^+$, 100%); Exact mass 290.1392. $C_{16}H_{20}NO_4$ ($M+H^+$) requires 290.1392; G.C. purity 91.0%.

(2R, 5S, 7S) and (2R, 5S, 7R)-7-allyl-7-ethoxycarbonyl-2-phenyl-1-aza-3-oxa-bicyclo[3.3.0]octan-8-one **31,41**

These products were obtained using allyl bromide on a 0.73 mmol scale of lactam **2b.** Usual work-up, followed by HPLC separation (9:1 cycloheptane/IPA) yielded individual diastereomers as colourless oils in 68% overall yield, and in a ratio of 4.7:1.

3l: (129mg, 56%); R_f 0.4 (4:1 cyclohexane/EtOAc); $\upsilon_{max}(CHBr_3)$ 1739(s), 1706(s) cm^{-1}; δ_H (250MHz, $CDCl_3$) 1.31 (3H, t, *J* 7Hz, CH_3), 2.36 (1H, dd, *J* 13.5, 7.5Hz, H-6_{exo}), 2.52 (1H, dd, *J* 13.5, 5Hz, H-6_{endo}), 2.63-2.84 (2H, m, $CH_2CH=CH_2$), 3.67 (1H, t, *J* 8Hz, H-4), 3.97-4.10 (1H, m, H-5), 4.20-4.32 (3H, m, H-4, CH_2CH_3), 5.14-5.25 (2H, m, $CH_2CH=CH_2$), 5.68-5.86 (1H, m, $CH_2CH=CH_2$), 6.32 (1H, s, H-2), 7.32-7.48 (5H, m, ArH); δ_C (50.3MHz, $CDCl_3$) 14.03 (CH_3), 31.01 (C-6), 39.03 ($CH_2CH=CH_2$), 56.21 (C-5), 59.21 (C-7), 61.94 (CH_2CH_3), 71.66 (C-4), 87.42 (C-2), 119.8 ($CH_2CH=CH_2$), 125.9, 128.4, 128.6 (ArCH), 132.5 ($CH_2CH=CH_2$), 138.6 (ArC), 170.8, 175.2 (2xCO); n.O.e. experiment (500MHz, $CDCl_3$) Irradiation at 2.36 (2.52, 4.0, 5.75); 2.52 (2.36, 3.67, 4.0); 2.68 (2.36, 2.75, 5.2, 5.75); 2.75 (2.36, 2.68, 5.2, 5.75); 4.0 (2.36, 5.75); *m/z* (Thermospray) 316 ($M+H^+$, 100%); Exact mass 316.1549. $C_{18}H_{22}NO_4$ ($M+H^+$) requires 316.1549; G.C. purity (100%).

4l: (28mg, 12%); R_f 0.4 (4:1 cyclohexane/EtOAc); Found: C, 63.34; H, 6.91; N, 4.22. $C_{18}H_{21}NO_4$ requires C, 68.55; H, 6.71; N, 4.44%; $\upsilon_{max}(CHBr_3)$ 1709(s) cm^{-1}; δ_H (250MHz, $CDCl_3$) 1.27 (3H, t, *J* 7Hz, CH_3), 1.87 (1H, dd, *J* 13.5, 7Hz, H-6), 2.57 (1H, dd, *J* 13.5, 7Hz, H-6), 2.78-2.90 (2H, m, $CH_2CH=CH_2$), 3.48-3.58 (1H, m, H-4), 4.16-4.32 (4H, m, H-4, H-5, CH_2CH_3), 5.11-5.21 (2H, m, $CH_2CH=CH_2$), 5.62-5.80 (1H, m, $CH_2CH=CH_2$), 6.32 (1H, s, H-2), 7.31-7.45 (5H, m, ArH); δ_C (50.3MHz, $CDCl_3$) 14.08 (CH_3), 34.65 (C-6), 38.58 ($CH_2CH=CH_2$), 56.30 (C-5), 60.54 (C-7), 61.95 (CH_2CH_3), 72.08 (C-4), 86.91 (C-2), 119.5 ($CH_2CH=CH_2$), 126.0, 128.5, 128.7 (ArCH), 132.7 ($CH_2CH=CH_2$), 138.1 (ArC), 170.5, 172.8 (2xCO); *m/z* (Thermospray) 316 ($M+H^+$, 100%).

(+)-(2R, 5S, 7S) and (+)-(2R, 5S, 7R)-7-phenylmethyl-7-ethoxycarbonyl-2-phenyl-1-aza-3-oxa-bicyclo[3.3.0]octan-8-one **3m,4m**

These products were obtained using benzyl bromide on a 0.73 mmol scale of lactam **2b.** Usual work-up, followed by HPLC separation (9:1 cycloheptane/IPA) yielded individual diastereomers as colourless solids in 75% overall yield, and in a ratio of 7.5:1.

3m: (175mg, 66%); R_f 0.20 (4:1 cyclohexane/EtOAc); $[\alpha]_D$ +8.36 (*c* 6.7, EtOH); Found: C, 72.32; H, 6.23; N, 3.71. $C_{22}H_{23}NO_4$ requires C, 72.31; H, 6.34; N, 3.83%; $\upsilon_{max}(CHBr_3)$ 2980(w), 1737(s), 1703(s) cm^{-1}; δ_H (250MHz, $CDCl_3$) 1.34 (3H, t, *J* 7.5Hz, CH_3), 2.38 (1H, dd, *J* 13.5, 7.5Hz, H-6_{exo}), 2.51 (1H, dd, *J* 13.5, 6Hz, H-6_{endo}), 3.15 (1H, d, *J* 14Hz, CHHPh), 3.21-3.34 (1H, m, H-5), 3.45 (1H, d, *J* 14Hz, CHHPh), 3.54 (1H, t, *J* 8Hz, H-4), 4.04-4.12 (1H, m, H-4), 4.22-4.36 (2H, m, CH_2CH_3), 6.25 (1H, s, H-2), 7.16-7.23 (7H, m, ArH), 7.29-7.35 (3H, m, ArH); δ_C (50.3MHz, $CDCl_3$) 13.95 (CH_3), 31.35 (C-6), 39.79 (CH_2Ph), 56.08 (C-5), 61.69 (C-7), 62.08 (CH_2CH_3), 71.88 (C-4), 87.02 (C-2), 126.2, 127.3, 128.5, 128.6, 128.8, 130.4 (ArCH), 135.9, 138.3 (ArC), 171.6, 174.4 (2xCO); n.O.e. experiment (500MHz,

$CDCl_3$) Irradiation at 2.38 (2.51, 21%; 3.15, 4%; 3.30, 14%; 2.51 (2.38, 9.5%); 3.15 (3.45, 29%); 3.45 (3.15, 26%); *m/z* (Thermospray) 366 ($M+H^+$, 100%).

4m: (24mg, 9%); R_f 0.27 (4:1 cyclohexane/EtOAc); $[\alpha]_D$ +189.7 (*c* 0.68, EtOH); $\upsilon_{max}(CHBr_3)$ 2979(w), 2926(w), 1708(s) cm^{-1}; δ_H (250MHz, $CDCl_3$) 1.28 (3H, t, *J* 7.0Hz, $C\underline{H}_3$), 1.88 (1H, dd, *J* 13, 6.5Hz, H-6), 2.77 (1H, dd, *J* 13, 6.5Hz, H-6), 2.96 (1H, t, *J* 7.5Hz, H-4), 3.25-3.38 (2H, m, $C\underline{H}_2Ph$), 4.02-4.18 (2H, m, H-4, H-5), 4.24 (2H, dq, *J* 7.0, 2Hz, $C\underline{H}_2CH_3$), 6.26 (1H, s, H-2), 7.17-7.43 (10H, m, Ar$\underline{H}$); *m/z* (Thermospray) 366 (MH^+, 100%); Exact mass 366.1705. $C_{22}H_{24}NO_4$ ($M+H^+$) requires 366.1705; G.C. purity 97.3%.

(+)-(2R, 5S, 7S) and (+)-(2R, 5S, 7R)-7-ethoxycarbonyl-7-p-nitrophenylmethyl-2-phenyl-1-aza-3-oxa-bicyclo[3.3.0]octan-8-one **3n,4n**

These products were obtained using *p*-nitrobenzyl bromide on a 0.73 mmol scale of lactam **2b.** Usual work-up, followed by silica chromatography (4:1 cyclohexane/EtOAc) yielded individual diastereomers as colourless solids in 94% overall yield, and in a ratio of 10:1.

3n: (254mg, 85%); R_f 0.15 (4:1 cyclohexane/EtOAc); $[\alpha]_D$ +22.5 (*c* 1, $CHCl_3$); Found: C, 64.62; H, 5.33; N, 6.78. $C_{22}H_{22}N_2O_6$ requires C, 64.38; H, 5.40; N, 6.83%; $\upsilon_{max}(CHBr_3)$ 2980(m), 1738(s), 1703(s), 1605(s), 1522(m), 1450(m), 1397(m), 1349(m) cm^{-1}; δ_H (250MHz, $CDCl_3$) 1.34 (3H, t, *J* 7Hz, $C\underline{H}_3$), 2.31 (1H, dd, *J* 14, 8Hz, H-6_{exo}), 2.57 (1H, dd, *J* 14, 5.5Hz, H-6_{endo}), 3.22 (1H, d, *J* 13Hz, $C\underline{H}HC_6H_4NO_2$), 3.26-3.36 (1H, m, H-5), 3.53 (1H, d, *J* 13Hz, $CH\underline{H}C_6H_4NO_2$), 3.55 (1H, t, *J* 8Hz, H-4_{endo}), 4.15 (1H, dd, *J* 8, 5.5Hz, H-4_{exo}), 4.24-4.36 (2H, m, $C\underline{H}_2CH_3$), 6.24 (1H, s, H-2), 7.15-7.21 (2H, m, *m*-$NO_2Ar\underline{H}$), 7.29-7.37 (5H, m, Ar$\underline{H}$), 7.94-8.00 (2H, m, *o*-$NO_2Ar\underline{H}$); δ_C (50.3MHz, $CDCl_3$) 13.91 ($\underline{C}H_3$), 31.30 (C-6), 39.49 ($\underline{C}H_2Ar$), 55.84 (C-5), 61.45 (C-7), 62.39 ($\underline{C}H_2CH_3$), 71.87 (C-4), 86.78 (C-2), 123.6, 125.9, 128.6, 129.1, 131.2 (Ar$\underline{C}$H), 138.2, 143.8, 147.3 (Ar$\underline{C}$), 170.9, 173.3 (2x$\underline{C}$O); n.O.e. experiment (500MHz, $CDCl_3$) 2.31 (2.57, 28%; 3.22, 2.7%; 3.35, 12.7%); 2.57 (2.31, 21.6%; 3.35, 3%; 3.55, 6.3%); 3.22 (3.53, 25.3%); 3.35 (2.31, 5.7%; 4.15, 7.2%; 6.24, 2%; 7.15, 3%); 3.55 (2.57, 2%; 3.22, 17.7%; 4.15, 14.2%; 6.24, 2%); *m/z* (Thermospray) 411 ($M+H^+$, 100%).

4n: (27mg, 9%); R_f 0.22 (4:1 cyclohexane/EtOAc); M.p. 131-132°C; $[\alpha]_D$ +159.4 (*c* 0.34, EtOH); Found: C, 63.98; H, 5.34; N, 6.70. $C_{22}H_{22}N_2O_6$ requires C, 64.38; H, 5.40; N, 6.83%; $\upsilon_{max}(CHBr_3)$ 2924(m), 1710(s), 1605(w), 1521(s), 1346(s) cm^{-1}; δ_H (250MHz, $CDCl_3$) 1.27 (3H, t, *J* 7.5Hz, $C\underline{H}_3$), 1.81 (1H, dd, *J* 13, 7.5Hz, H-6), 2.81 (1H, dd, *J* 13, 6.5Hz, H-6), 3.21 (1H, t, *J* 7.5, H-4), 3.32 (1H, d, *J* 14Hz, $C\underline{H}HC_6H_4NO_2$), 3.50 (1H, d, *J* 14Hz, $CH\underline{H}C_6H_4NO_2$), 4.09-4.29 (4H, m, H-4, H-5, $C\underline{H}_2CH_3$), 6.29 (1H, s, H-2), 7.32-7.50 (7H, m, *m*-$NO_2Ar\underline{H}$, Ar$\underline{H}$), 8.08-8.29 (2H, m, *o*-$NO_2Ar\underline{H}$); δ_C (50.3MHz, $CDCl_3$) 14.05 ($\underline{C}H_3$), 34.84 (C-6), 39.04 ($\underline{C}H_2Ar$), 56.29 (C-5), 61.82 (C-7), 62.37 ($\underline{C}H_2CH_3$), 71.80 (C-4), 87.00 (C-2), 123.7, 131.0, 126.0, 128.5, 128.8 (Ar$\underline{C}$H), 137.7 (Ar$\underline{C}$), 144.2, 147.3 ($NO_2Ar\underline{C}$), 169.8, 172.2 (2x$\underline{C}$O); *m/z* (Thermospray) 411 ($M+H^+$, 100%).

(+)-(2R, 5S, 7R)-7-Acetyl-7-ethoxycarbonyl-2-phenyl-1-aza-3-oxa-bicyclo[3.3.0] octane **3o**

Following the general procedure, lactam **2b** (250mg, 0.91mmol), NaH (44mg, 1.09mmol) and acetyl chloride (85mg, 1.09mmol) were reacted together and heated at reflux for 4h. Usual work-up, followed by silica chromatography (10:1 CH_2Cl_2/EtOAc) yielded the product as a colourless oil (245mg, 85%) as a single diastereomer. R_f 0.3 (3:1 CH_2Cl_2/EtOAc); $[\alpha]_D$ +160.4 (*c* 2.25, $CHCl_3$); $\upsilon_{max}(CHCl_3)$ 1739(s), 1714(s) cm^{-1}

; δ_H (500MHz, $CDCl_3$) 1.34 (3H, t, *J* 7Hz, $CH_2\underline{CH_3}$), 2.36 (1H, dd, *J* 13.5, 6Hz, H-6), 2.47 (3H, s, $\underline{CH_3}$), 3.22 (1H, dd, *J* 13.5, 7.5Hz, H-6), 3.67 (1H, t, *J* 8Hz, H-4), 4.04-4.09 (1H, m, H-5), 4.24-4.37 (3H, m, H-4, $\underline{CH_2}CH_3$), 6.34 (1H, s, H-2), 7.33-7.45 (5H, m, Ar$\underline{H}$); δ_C (50.3MHz, $CDCl_3$) 13.95 ($CH_2\underline{CH_3}$), 27.24 (C-6), 30.85 ($\underline{CH_3}$), 56.14 ($\underline{CH_2}CH_3$), 62.67 (C-5), 71.89 (C-4), 73.69 (C-7), 87.52 (C-2), 125.9, 128.6, 128.9 (Ar$\underline{C}$H), 137.8 (Ar$\underline{C}$), 167.5, 169.9 (2x$\underline{C}$O), 197.8 ($\underline{C}$OMe); *m/z* [CI, NH_3] 318 ($M+H^+$, 22), 276 (100%).

(+)-(2R, 5S, 7S)-7-(2-methylprop-3-enyl)-7-ethoxycarbonyl-2-phenyl-1-aza-3-oxa-bicyclo[3.3.0]octan-8-one **3p**

Prepared from lactam **2b** and 3-chloro-2-methyl propene on a 0.36mmol scale using the co-solvents DMPU/TMEDA. (39mg, 33%); R_f 0.40 (4:1 light petroleum/EtOAc); M.p. 38-40°C; $[\alpha]_D$ +74.6 (*c* 1.9, $CHCl_3$); Found: C, 69.40; H, 6.85; N, 4.33%. $C_{19}H_{23}NO_4$ requires C, 69.28; H, 7.04; N, 4.25%; $\upsilon_{max}(CHCl_3)$ 1743(s), 1708(s) cm^{-1}; δ_H (200MHz, $CDCl_3$) 1.33 (3H, t, *J* 7.1Hz, $CH_2\underline{CH_3}$), 1.71 (3H, s, $\underline{CH_3}C{=}CH_2$), 2.47 (1H, dd, *J* 13.8, 8.0Hz, H-6), 2.62 (1H, dd, *J* 13.9, 4.6Hz, H-6), 2.67 (1H, d, *J* 14.6Hz, =CC$\underline{H}$H), 2.91 (1H, d, *J* 14.6Hz, =CCH$\underline{H}$), 3.67-3.63 (1H, m, H-4), 4.02-4.08 (1H, m, H-5), 4.24-4.30 (3H, m, $\underline{CH_2}CH_3$ and H-4), 4.76 (1H, s, =C$\underline{H}$H) 4.92 (1H, s, =CH$\underline{H}$), 6.32 (1H, s, H-2), 7.33-7.49 (3H, m, Ar$\underline{H}$), 7.45-7.47 (2H, m, Ar$\underline{H}$); δ_C (125.7MHz, $CDCl_3$) 14.0 ($\underline{CH_3}$), 23.2 ($\underline{CH_3}C{=}CH_2$), 30.3, 42.2 (C-6 and =$\underline{C}CH_2$), 56.1 (C-5), 59.2 (C-7), 62.0 ($\underline{CH_2}CH_3$), 71.5 (C-4), 87.4 (C-2), 115.0 (=CH_2), 125.8, 128.4, 128.6 (Ar$\underline{C}$H), 138.5 (Ar$\underline{C}$), 141.1 ($CH_3\underline{C}$=), 171.0 ,175.6 (2xCO); *m/z* (GCMS) 330 ($M+H^+$, 100%), 106 (75%).

(2R, 5S, 7R)-7-(3-cyclohexenyl)-7-ethoxycarbonyl-2-phenyl-1-aza-3-oxa-bicyclo[3.3.0] octan-8-one **3q,4q**

Prepared from lactam **2b** and 3-bromocyclohexene on a 0.36mmol scale using the co-solvents DMPU/TMEDA as an inseparable mixture of diasteromers. (94mg, 72%); R_f 0.44 (3:1 light petroleum/EtOAc); $\upsilon_{max}(CHCl_3)$ 3360(br, w), 1744(s), 1708(s), 1451(w), 1391(w), 1358(w) cm^{-1}; δ_H (500MHz, $CDCl_3$) 1.15-1.22 (2H, m, ring H), 1.32, 1.33 (6H, 2xt, *J* 7.1Hz, $\underline{CH_3}$), 1.54-1.63 (2H, m, ring H), 1.79-1.86 (4H, m, ring H), 1.96-2.00 (4H, m, ring H), 2.21-2.24 (2H, m, H-6), 2.52 (1H, dd, *J* 14.1, 3.0Hz, H-6), 2.59 (1H, dd, *J* 14.4, 3.6Hz, H-6), 3.22-3.24 (1H, m, ring H), 3.29-3.32 (1H, m, ring H), 3.61-3.67 (2H, m, H-4), 3.90-4.00 (2H, m, H-5), 4.22-4.29 (6H, m, 2x$\underline{CH_2}CH_3$ and H-4), 5.37-5.39 (1H, m, CH=C$\underline{H}$), 5.43-5.46 (1H, m, CH=C$\underline{H}$), 5.85-5.90 (2H, m, C$\underline{H}$=CH) 6.30, 6.31 (2H, 2xs, H-2), 7.32-7.43 (10H, m, Ar$\underline{H}$); δ_C (50.3MHz, $CDCl_3$) 14.1 (2x$\underline{CH_3}$), 21.7, 21.8, 24.7, 24.9, 25.1, 25.9, 26.8, 39.7, 40.4, 56.1(C-5), 56.7 (C-5), 62.1 (C-7), 63.5, 63.7 (2x$\underline{CH_2}CH_3$), 71.0, 71.7 (2xC-4), 87.4, 87.8 (2xC-2), 125.8, 125.9, 127.1, 128.4, 128.5 (Ar$\underline{C}$, $\underline{C}$H=CH), 131.1, 131.6 (CH=$\underline{C}$H), 170.3, 171.0 (2xCO), 175.1, 175.4 (2xCO); *m/z* [CI, NH_3] 356 ($M+H^+$, 100%).

(+)-(2R,5S,7R)-8-Oxo-2-phenyl-7-phenylacetyl-1-aza-3-oxa-bicyclo[3.3.0]octane **2c**

A solution of lactam **2a** (500mg, 2.83mmol) and methylbenzoate (460mg, 3.40mmol) in dry THF (5ml) was added slowly to sodium hydride (312mg of a 60% dispersion in mineral oil, 7.20mmol) in refluxing dry THF (20ml). After 4hr, the mixture was cooled, carefully diluted with saturated ammonium chloride and extracted with diethyl ether (3x25ml). The organic residue was dried over $MgSO_4$ and concentrated *in vacuo* to afford the crude product, an amber oil. This was purified by flash chromatography (9:1, light petroleum:EtOAc,

R_f=0.65(*endo*), 0.23(*exo*))to give a pale yellow oil containing a mixture of *endo, exo* and tautomeric isomers. One isomer was isolated as a pale yellow solid which was recrystallised from light petroleum/EtOAc to give white crystals. X-ray crystallography showed this to be the *endo* isomer: (0.72g, 83%); Mp 127-129°C; $[\alpha]_D$ +66.3° (*c* 1.1, $CHCl_3$); Found: C, 74.24; H, 5.46; N, 4.51. $C_{19}H_{17}NO_3$ requires; C, 74.25; H, 5.58; N, 4.56%; $\upsilon_{max}(CHCl_3)$ 1680(s), 1710(s) cm^{-1}; δ_H (500MHz, $CDCl_3$); 2.48-2.54 (1H, m, H-6), 2.77-2.82 (1H, m, H-6), 3.73 (1H, dd, *J* 8.0, 8.1, H-4), 4.21-4.25 (1H, m, H-5), 4.36-4.37 (1H, dd, *J* 6.1, 8.1, H-4), 4.94 (1H, dd, *J* 8.9, 8.9, H-7), 6.27 (1H, s, H-2), 7.28-7.35 (8H, m, ArH), 8.08 (2H, m, ArH); δ_C (50.3MHz, $CDCl_3$); 25.3 (C-6), 53.0 (C-7), 56.9 (C-5), 87.4 (C-2), 126.2-128.9 and 133.9 (ArC), 173.3 (CO), 195.1 (CO); *m/z* [CI, NH_3]; 308 ($M+H^+$, 98%), 325 ($M+NH_4^+$, 2%); n.O.e (500MHz, $CDCl_3$); irradiation at 2.5 (2.80, 23.1%; 4.20, 9%; 4.95, 7.5%); 2.80 (2.50, 14%; 3.85, 5.7%; 4.20, 3.7%); 3.85 (4.40, 24.4%); 4.20 (2.50, 8.5%; 4.40, 5.3%); 4.40 (3.85, 26%; 4.20, 2%); 4.95 (2.50, 6.3%); 6.30 gave no enhancement.

Exo: δ_H (500MHz, $CDCl_3$); 2.15-2.20 (1H, m, H-6), 2.96-3.01 (1H, m, H-6), 3.62 (1H, dd, H-4, *J* 8.0, 8.0), 4.30 (1H, dd, H-4, *J* 6.4, 8.3), 4.44-4.49 (1H, m, H-5), 4.73 (1H, dd, H-7, *J* 9.0, 2.3), 6.35 (1H, s, H-2), 7.28-7.75 (8H, m, ArH), 8.22 (2H, t, *o*-ArH); δ_C (50.3MHz, $CDCl_3$); 28.4 (C-6), 56.0 (C-7), 58.3 (C-5), 87.5 (C-2), 127.8-130.8 and 134.1 (ArC), 172.6 (CO), 194.2 (CO).

Enol: δ_H (500MHz, $CDCl_3$); 2.75-2.85 (1H, m, H-6), 3.28-3.38 (2H, m, H-6 and H-4), 4.19-4.20 (1H, m, H-4), 4.21-4.25 (1H, m, H-5), 6.41 (1H, s, H-2).

(-)-(2R, 5S, 7R)-7-Benzyl-7-benzoyl-8-oxo-2-phenyl-1-aza-3-oxa-bicyclo[3.3.0]octane **3r**

To a stirred suspension of pre-washed sodium hydride (13mg, 0.33mmol) in dry THF (10ml) at 0°C under N_2, was added a solution of **2c** (85mg, 0.28mmol) in dry THF (5ml). After stirring at RT for 30min, benzyl bromide (37µl, 0.31mmol) was added. The reaction mixture was brought to reflux, and after 20h was concentrated *in vacuo* to give the crude product as a mixture of diastereomers in the ratio 5:1. Purification by column chromatography (6:1 light petroleum/ EtOAc) gave two diastereomers (69mg, 63%), but only the major isomer **3r** could be isolated as a single diastereomer (39mg, 35%); R_f 0.17 (6:1 light petroleum/EtOAc); $[\alpha]_D$ -9.8 (*c* 1.5, $CHCl_3$); $\upsilon_{max}(CHCl_3)$ 1704(s), 1680(s) cm^{-1}; δ_H (200MHz, $CDCl_3$) 2.46 (1H, dd, *J* 14.0, 8.0Hz, H-6_{exo}-), 2.64 (1H, dd, *J* 14.0, 6.5Hz, H-6_{endo}-), 3.13-3.23 (1H, m, H-5), 3.29 (1H, d, *J* 13.7Hz, CHHPh), 3.48-3.58 (2H, m, CHHPh, H-4_{endo}-), 3.95-4.04 (1H, m, H-4_{exo}-), 6.44 (1H, s, H-2), 7.11-7.53 (13H, m, ArH), 7.93 (2H, m, *o*-ArH); δ_C (50.3MHz, $CDCl_3$) 34.3 (C-6), 40.9 (CH_2Ph), 56.2 (C-5), 66.3 (C-7), 71.6 (C-4), 87.3 (C-2), 126.1-137.3 (ArC), 175.2, 198.2 (2xCO); n.O.e experiment (500MHz, $CDCl_3$) 2.46 (2.64, 27%; 3.20, 13%; 7.21, 8.2%); 2.64 (2.46, 23%; 3.53, 5.6%; 7.93, 5.6%); 4.0 (3.20, 9.2%; 3.53, 23.6%); 6.44 (7.20, 2.9%; 7.93, 3.2%); *m/z* [CI, NH_3]; 398 ($M+H^+$, 100%); Exact mass 398.1755. $C_{26}H_{24}NO_3$ ($M+H^+$) requires 398.1756.

(2R, 5S,7R)-7-Methyl-7-benzoyl-8-oxo-2-phenyl-1-aza-3-oxa-bicyclo[3.3.0]octane **3s,4s**

To a stirred suspension of pre-washed sodium hydride (13mg, 0.33mmol) in dry THF (10ml) at 0°C under N_2 was added a solution of lactam **2c** (85mg, 0.28mmol) in dry THF (5ml). After stirring at RT for 30min, methyl iodide (19µl, 0.31mmol) was added. The reaction mixture was brought to reflux, and after 15h was concentrated *in vacuo* to give the crude product as a brown oil. Purification by column chromatography (4:1 light petroleum/ EtOAc) gave an inseparable mixture of diastereomers (42mg, 47%) in the ratio 2:1

(colourless oil). R_f 0.35 (4:1 light petroleum/EtOAc); υ_{max}($CHCl_3$) 1707(s), 1676(s) cm^{-1}; δ_H (200MHz, $CDCl_3$) 1.68 (3H, s, C<u>H</u>$_3$), 1.74 (3H, s, C<u>H</u>$_3$), 1.77-1.79 (1H, m, H-6), 2.25 (1H, dd, *J* 13.3, 7.2Hz, H-6), 2.80 (1H, dd, *J* 13.4, 5.8Hz, H-6), 3.32 (1H, dd, *J* 12.4, 5.8Hz, H-6), 3.63-3.66, 3.72-3.76, 4.19-4.32 (6H, 2xH-4, 2xH-5), 6.40 (1H, s, H-2), 6.49 (1H, s, H-2) 7.29-7.53 (16H, m, Ar<u>H</u>), 8.19-8.20 (2H, m, *o*-Ar<u>H</u>), 8.21-8.22 (2H, m, *o*-Ar<u>H</u>); δ_C (125.7MHz, $CDCl_3$) 22.4, 22.9, 37.4, 40.5 (2xC-6, 2x<u>C</u>H$_3$), 56.1, 56.3 (2xC-5), 60.8, 63.0 (2xC-7), 71.7, 71.8 (2xC-4), 87.1, 87.4 (2xC-2), 125.9-132.4 (Ar<u>C</u>H), 135.2, 135.6, 137.5, 137.9 (Ar<u>C</u>), 175.8, 177.5 (2x<u>C</u>O), 197.1, 198.6 (2x<u>C</u>O); *m/z* [CI, NH_3] 339 ($M+NH_4^+$, 15%), 322 ($M+H^+$, 100%).

(-)-(2S, 4R)-4-Benzyl-2-hydroxymethyl-5-oxo-pyrrolidine **7a**

To a stirred solution of lactam **3b** (161mg, 0.55mmol) in CH_2Cl_2 (30ml), was added trifluoroacetic acid (0.46ml). After stirring at RT for 10h, solvent was removed *in vacuo* to give the crude product which was purified by column chromatography (EtOAc) to yield the product as a pale yellow oil (97mg, 86%).
R_f 0.3 (10:1 EtOAc/MeOH); $[\alpha]_D$ -4.5 (*c* 0.8, $CHCl_3$); υ_{max}($CHCl_3$) 3431(s), 3500-3100(br), 2933(m), 1695(s) cm^{-1}; δ_H (500MHz, $CDCl_3$) 1.85-2.00 (2H, m, H-3), 2.68 (1H, dd, *J* 13.5, 9.5Hz, PhC<u>H</u>(H)), 2.79-2.85 (1H, m, H-4), 3.12 (1H, s, br, O<u>H</u>), 3.19 (1H, dd, *J* 13.5, 4Hz, PhCH(<u>H</u>)), 3.44-3.47 (1H, m, C<u>H</u>(H)O), 3.57-3.65 (2H, m, H-2 & CH(<u>H</u>)O), 6.78 (1H, s, br, N<u>H</u>), 7.21-7.35 (5H, m, Ar<u>H</u>); δ_C (125.8MHz, $CDCl_3$) 28.53 (C-3), 37.08 (Ph<u>C</u>H$_2$), 42.38 (C-4), 54.06 (C-2), 65.09 (<u>C</u>H$_2$O), 126.4, 128.5 & 129.0 (Ar<u>C</u>H), 139.0 (Ar<u>C</u>), 179.0 (CO); *m/z* [CI, NH_3] 223 ($M+NH_4^+$, 2), 206 ($M+H^+$, 100%); Exact mass 206.1177. $C_{12}H_{16}NO_2$ ($M+H^+$) requires 206.1181.

(+)-(2S,4S)-2-Hydroxymethyl-4 (p-nitrophenylmethyl)-5-oxo-pyrrolidine **7b**

Lactam **4d** (138mg, 0.400mmol) in a mixed solvent (MeOH:H_2O:TFA = 10ml:10ml:5ml) was stirred for 3h at r.t. and then for 2h at 50°C. The mixture was concentrated *in vacuo*, ether (30 ml) added, stored at -4°C overnight, and the product filtered by washing with cold ether (2 x 10 ml) to give the compound **7b** as a colourless solid (80mg, 78%). M.p. = 176-177 °C; Found: C, 55.8; H, 5.29; N, 10.6. $C_{12}H_{14}N_2O_4$ requires C, 57.6; H, 5.60; N, 11.2; $[\alpha]_D$+168.6 (*c* 0.07, $CHCl_3$); υ_{max}(KBr) 3365(s), 2915(m), 1688(s), 1650(s), 1605(m), 1510(s), 1343(s) cm^{-1}; λ_{max} ($CHCl_3$) 250 nm (log ε = 3.3); δ_H (200 MHz, CD_3OD) 1.4-1.6 (1H, m, H-3), 2.0 (1H, m, H-3'), 2.7 - 2.9 (2H, m, C<u>H</u>$_2$Ar), 3.2 - 3.7 (4H, m, HOC<u>H</u>$_2$, H-2 and H-4), 7.48(2H, d, ArH *m*- to NO_2), 8.15 (2H, d, ArH *o*- to NO_2); δ_C (50 MHz, D_2O) 31.5 (C-3), 36.7 (Ph<u>C</u>H$_2$), 43.2 (C-4), 57.0 (C-2), 130.9, 124.6 (Ar<u>C</u>); *m/z* [CI, NH_3] 251 (M+ H^+, 60 %), 221 (100), 106 (35).

(-)-(2S, 4S)-4-Benzyl-4-ethoxycarbonyl-2-hydroxymethyl-5-oxo-pyrrolidine **7c**

To a stirred solution of lactam **3m** (61mg, 0.17mmol) in CH_2Cl_2 (20ml), was added trifluoroacetic acid (0.14ml). After stirring at RT for 6h, solvent was removed *in vacuo* to give the crude product as a yellow oil. Purification by flash column chromatography (1:4 light petroleum/EtOAc) and recrystallisation, gave the product as a white crystalline solid (35mg, 76%). R_f 0.13 (4:1 EtOAc/light petroleum); M.p. 128-131°C; $[\alpha]_D$ -30.3 (*c* 0.30, $CHCl_3$); Found: C, 64.88; H, 6.88; N, 4.82%. $C_{15}H_{19}NO_4$ requires C, 64.95; H, 6.92; N, 5.05%; υ_{max}($CHCl_3$) 3427(m), 3300(br, m), 1740(s), 1698(s), 1455(m), 1260(m), 1095(m), 1032(m) cm^{-1}; δ_H (500MHz, $CDCl_3$) 1.28 (3H, t, *J* 7.1Hz, CH_2C<u>H</u>$_3$), 2.24-2.28 (2H, m, C(3)-<u>H</u>$_2$), 3.01-3.06 (1H, m, H-2), 3.15 (1H, d, *J* 14.0Hz, C<u>H</u>HPh), 3.29 (1H, d, *J* 14.0Hz, CH<u>H</u>Ph), 3.41 (1H, dd, *J* 11.0, 7.0Hz,

CHHOH), 3.54 (1H, dd, *J* 11.0, 3.1Hz, CHHOH), 4.22 (2H, q, *J* 7.1Hz, CH_2CH_3), 7.21-7.28 (6H, m, ArH, NH); δ_C (125.7MHz, $CDCl_3$) 13.9 (CH_3), 30.8 (C-3), 39.5 (CH_2Ph), 53.5, 56.8 (C-4), (C-2), 61.9 (CH_2CH_3), 65.5 (CH_2OH), 127.0, 128.4, 130.1, 135.8 (ArC), 171.9, 175.7 (2xCO); *m/z* [CI, NH_3] 295 ($M+NH_4^+$, 5%), 278 ($M+H^+$, 100%); Exact mass 278.1388. $C_{15}H_{20}NO_4$ ($M+H^+$) requires 278.1392.

(+)-(2S, 4R)-4-phenylmethyl-4-ethoxycarbonyl-2-hydroxymethyl-5-oxo-pyrrolidine **7d**

To a stirred solution of lactam **4m** (52mg, 0.14mmol) in CH_2Cl_2 (15ml), was added trifluoroacetic acid (0.12ml). After stirring at RT for 12h, solvent was removed *in vacuo* to give the crude product as a yellow oil. Purification by column chromatography (EtOAc) yielded the product as a pale yellow oil (24mg, 61%). R_f 0.25 (EtOAc); $[\alpha]_D$ +78.7 (*c* 0.6, $CHCl_3$); υ_{max}($CHCl_3$) 3428(w), 3300(br, w), 2930(m), 1735(s), 1708(s) cm^{-1}; δ_H (500MHz, $CDCl_3$) 1.28 (3H, t, *J* 7.1Hz, CH_3), 1.73 (1H, dd, *J* 13.3, 8.0Hz, C(3)-H), 2.46 (1H, dd, *J* 13.3, 7.3Hz, C(3)-H) 2.99 (1H, dd, *J* 11.3, 7.7Hz, CHHOH), 3.20 (1H, d, *J* 14.0Hz, CHHPh), 3.26 (1H, d, *J* 14.0 Hz, CHHPh), 3.50 (1H, dd, *J* 11.3, 3.2Hz, CHHOH), 3.83 (1H, m, H-2), 4.21 (2H, q, *J* 7.1Hz, CH_2CH_3), 7.12 (1H, s, NH), 7.17-7.28 (5H, m, ArH); δ_C (125.7MHz, $CDCl_3$) 14.0 (CH_3), 31.0 (C-3), 38.9, 53.9, 57.2 (CH_2Ph, C(4), C(2)), 61.9 (CH_2CH_3), 65.6 (CH_2OH), 126.9, 128.4, 130.1, 136.4 (ArC), 171.0, 174.8 (2xCO); *m/z* [CI, NH_3] 295 ($M+NH_4^+$, 10%), 278 ($M+H^+$, 100%).

(+)-(2S, 4R)-4-(2-methylprop-3-enyl)-4-ethoxycarbonyl-2-hydroxymethyl-5-oxo-pyrrolidine **7e**

To a stirred solution of lactam **3p** (35mg, 0.10mmol) in CH_2Cl_2 (10ml), was added trifluoroacetic acid (0.1ml). After stirring at RT for 8h, solvent was removed *in vacuo* to give the crude product which was purified by column chromatography (EtOAc) to give the product as a yellow oil (6mg, 25%). R_f 0.13 (EtOAc); $[\alpha]_D$ +8.3 (*c* 0.7, $CHCl_3$); υ_{max}($CHCl_3$) 3427(m), 3300(m, br), 1740(s), 1703(s), 1448(w), 1420(w) cm^{-1}; δ_H (500MHz, $CDCl_3$) 1.28 (3H, t, *J* 7.1Hz, CH_3), 1.71 (3H, s, CH_3C=), 2.31 (1H, dd, *J* 13.8, 8.5Hz, C(3)-H), 2.42 (1H, dd, *J* 13.7, 4.7Hz, C(3)-H), 2.51 (1H, d, *J* 14.6Hz, =CCHH), 2.85 (1H, d, *J* 14.6Hz, =CCHH), 2.89-3.06 (1H, br, s, CH_2OH), 3.58 (1H, dd, *J* 10, 7.2Hz, CHHOH), 3.67-3.73 (2H, m, CHHOH and H-2), 4.19 (2H, q, *J* 7.1Hz, CH_2CH_3), 4.73 (1H, s, =CHH), 4.89 (1H, s, =CHH), 7.27 (1H, s, NH); δ_C (125.7MHz, $CDCl_3$) 13.9 (CH_3), 23.2 (CH_3C=), 29.7, 30.7 (C-3 and =CCH_2), 42.3 (C-2), 53.5 (C-4), 62.1 (CH_2CH_3), 65.8 (CH_2OH), 115.0 (=CH_2), 141.0 (CH_3C=), 172.0, 175.8 (2xCO); *m/z* [CI, NH_3] 242 ($M+H^+$, 100%); Exact mass 242.1396. $C_{12}H_{20}NO_4$ ($M+H^+$) requires 242.1392.

(2S, 4R)-4-(Cyclohex-3-enyl)-4-ethoxycarbonyl-2-hydroxymethyl-5-oxo-pyrrolidine **7f**

To a stirred solution of lactam **3,4q** (95mg, 0.27mmol) in CH_2Cl_2 (10ml), was added trifluoroacetic acid (0.24ml). After stirring at RT for 10h, solvent was removed in vacuo to give the crude product. Purification by column chromatography (1:1 light petroleum/EtOAc) gave the product as a mixture of diastereomers (26mg, 36%). R_f 0.19 (EtOAc); υ_{max}($CHCl_3$) 3424(m), 3300(br, m), 1739(s), 1703(s), 1447(w), 1419(w) cm^{-1}; δ_H (200MHz, $CDCl_3$) 1.09-1.18 (2H, m, ring H), 1.23-1.31 (6H, m, 2xCH_3), 1.54-1.63 (2H, m, ring H), 1.71-1.82 (4H, m, ring H), 1.95-2.05 (4H, m, ring H), 2.13-2.41 (4H, m, 2xH-3), 3.12-3.28 (2H, m, ring H), 3.53-3.81 (6H, m, 2xH-2, 2xCH_2OH), 4.16-4.24 (4H, m, 2xCH_2CH_3), 4.93 (2H, br, s, OH), 5.28-5.35 (2H, m, CH=CH), 5.80-5.89 (2H, m, CH=CH); δ_C (125.7MHz, $CDCl_3$) 14.0 (2xCH_3), 21.7, 24.2, 24.9, 25.0, 27.1, 27.7, 29.6 (2xC-3 and ring C), 39.9, 40.3 (ring C), 53.6, 54.1, 59.4 (2xC-4, 2xC-2, 62.1 (2xCH_2CH_3), 63.5, 63.7 (CH_2OH), 125.9, 126.1 (CH=CH) 131.1, 131.5 (CH=CH), 171.1 (2xCO), 171.6,

175.1 (2xCO); *m/z* [CI, NH_3] 268 ($M+H^+$, 100%); Exact mass 268.1556. $C_{14}H_{22}NO_4$ ($M+H^+$) requires 268.1549.

(2R, 5S, 7S)-7-Phenylmethyl-7-carboxyl-2-phenyl-1-aza-3-oxa-bicyclo[3.3.0]octan-8-one **8a**

A solution of lactam **3m** (135mg, 0.37mmol) in acetonitrile (5ml) and 1N NaOH (1ml) was stirred at RT for 16h, and then poured into H_2O/EtOAc (20ml, 1:1). The aqueous layer was acidified with 2M HCl to produce a white precipitate which was extracted with EtOAc (2x20ml). The organic solution was dried ($MgSO_4$), and the solvent was removed *in vacuo* to give a white solid (120mg, 96%). $[\alpha]_D$ + 35.9 (*c* 1.5, $CHCl_3$); υ_{max}($CHCl_3$ sol) 3300-2600(br), 1762(s), 1712(s), 1672(s), 1456(s) and 1397(s) cm^{-1}; δ_H (200MHz, $CDCl_3$) 2.45-2.65 (2H, m, H-6), 3.15-3.30 (2H, m, CH_2Ph), 3.30-3.55 (2H, m, H-4 and H-5), 4.10-4.20 (1H, m, H-4), 6.22 (1H, s, H-2), 7.15-7.45 (10H, m, ArH), 8.50-9.00 (1H, s, br, CO_2H); δ_C (125.8MHz, $CDCl_3$) 30.90 (C-7), 32.47 (C-6), 42.87 (CH_2Ph), 55.70 (C-5), 72.09 (C-4), 86.66 (C-2), 126.1, 127.7, 128.4, 128.5, 129.0 and 129.9 (ArCH), 134.3 and 137.0 (ArC), 175.5 (CO); *m/z* [CI, NH_3] 394 ($(M+H-CO_2)^+$, 100%).

(2R, 5S, 7S)-7-Carboxyl-7-p-nitrophenylmethyl-2-phenyl-1-aza-3-oxa-bicyclo[3.3.0] octan-8-one **8b**

A solution of lactam **3n,** acetonitrile (3ml) and 1N NaOH (1ml) was stirred at RT for 16h, and then poured into H_2O/EtOAc (20ml, 1:1). The aqueous layer was acidified with 2M HCl to produce a white precipitate which was extracted with EtOAc (2x20ml). The organic solution was dried ($MgSO_4$), and the solvent was removed *in vacuo* to give a white powdery solid (55mg, 71%). $[\alpha]_D$ +70.1 (*c* 1.1, $CHCl_3$); υ_{max}($CHCl_3$) 3200-2600(br), 1764(s), 1708(s), 1674(s), 1520(s) and 1349(s) cm^{-1}; δ_H (200MHz, $CDCl_3$) 2.40-2.65 (2H, m, H-6), 3.15-3.60 (4H, m, H-4, H-5 and $CH_2C_6H_4NO_2$), 4.15-4.25 (1H, m, H-4), 6.22 (1H, s, H-2), 7.15-7.40 (7H, m, ArH), 7.96 (2H, d, *J* 7Hz, *o*-NO_2ArH), 8.90-9.10 (1H, s, br, CO_2H); δ_C (125.8MHz, $CDCl_3$) 29.50 (C-7), 32.14 (C-6), 41.88 ($CH_2C_6H_4NO_2$), 55.52 (C-5), 71.99 (C-4), 86.51 (C-2), 123.6, 125.7, 128.6, 129.4 and 130.8 (ArCH), 137.0 and 147.4 (ArC), 172.3 (CO); *m/z* [CI, NH_3] 339 ($(M+H-CO_2)^+$, 100%), 106 (29).

(2R, 5S, 7R)-1-aza-3-oxa-2-phenyl-7-(phenyl methyl)bicyclo[3.3.0]octan-8-one **3b**

A sample of solid lactam **8a** (73mg, 0.22mmol) was heated at 150°C under reduced pressure (0.5mmHg) for 2h. The desired product **3b** sublimed from the reaction mixture (44mg, 70%) to give material with identical spectroscopic characteristics as those reported above.

(2R,5S,7R)-1-aza-3-oxa-2-phenyl-7-(4-nitrophenylmethyl)bicyclo[3.3.0]octan-8-one **3d**

A sample of lactam **8b** (62mg, 0.16mmol) was heated at 150°C under reduced pressure (0.5mmHg) for 2h. The desired product **3d,4d** sublimed from the reaction mixture (32mg, 58%) to give material with identical spectroscopic characteristics as those reported above.

(2R, 5S, 7RS)-7-Carboxyl-7-methyl-2-phenyl-1-aza-3-oxa-bicyclo[3.3.0] octan-8-one **8c**

A mixture of lactams **3k,4k** (ratio 1:3.5) (44mg, 0.15mmol), acetonitrile (5ml) and 1N NaOH (1ml) was stirred at RT for 16h, and then poured into H_2O/EtOAc (20ml, 1:1). The aqueous layer was acidified with 2M HCl to produce a white precipitate which was extracted with EtOAc (2x20ml). The organic solution was dried ($MgSO_4$), and the solvent was removed *in vacuo* to give a white solid (40mg, 95%), which was shown by ^1H NMR to be a mixture of product diastereomers **8c** (ratio 1:3.5). $[\alpha]_D$ +35.9 (*c* 1.5, $CHCl_3$); υ_{max}($CHCl_3$) 3300-2600(br), 1708(br) cm^{-1}; δ_H (200MHz, $CDCl_3$) 1.55 (3H, s, CH_3, major), 1.65 (3H, s, CH_3, minor),

1.77-1.88 (1H, m, H-6, major), 2.28-2.40 (1H, m, H-6, minor), 2.50-2.62 (1H, m, H-6, minor), 2.90-3.00 (1H, m, H-6, major), 3.50-3.75 (2H, m, H-4), 4.15-4.35 (4H, m, H-4 and H-5), 6.32 (1H, s, H-2, minor), 6.36 (1H, s, H-2, major), 7.30-7.50 (10H, m, 2xArH); δ_C (50.3MHz, $CDCl_3$) 20.60 (CH_3), 38.12 (C-6), 55.84 (C-7), 56.21 (C-5), 72.07 (C-4), 87.14 (C-2), 126.1, 126.3, 128.7 and 129.0 (ArCH), 138.9 (ArC), 174.3 (CO); *m/z* [CI, NH_3] 279 ($M+NH_4^+$, 2%), 262 ($M+H^+$, 4), 218 (100).

(+)-(2R,5S,7R)-1-aza-3-oxa-2-phenyl-7-methylbicyclo[3.3.0]octan-8-one **3i**

A mixture of diastereomers of lactam **8c** (ratio 1:3.5) (40mg, 0.15mmol) was heated at 150°C under reduced pressure (0.5mmHg) for 1h. The desired product **3i** sublimed from the reaction mixture (27mg, 81%) to give material with identical spectroscopic characteristics as those reported above.

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22. Although the X-ray structural analysis confirmed the relative stereochemistry assigned by NMR spectroscopy, it also indicated that **3n** was racemic, an entirely unexpected result given the non-zero optical rotation of the bulk sample. HPLC analysis indeed confirmed the racemic nature of the crystalline sample of **3n**, but HPLC examination of the mother liquor demonstrated >99% optical purity. It was therefore concluded that the racemic crystals were formed by preferential crystallisation of the major enantiomer with the small amount of opposite enantiomer present, which arose from the starting (S)-pyroglutamic acid which was of 97% e.e.

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