PERKIN 1

Pyrrolidinones derived from (*S*)-pyroglutamic acid. Part 2.[1] Conformationally constrained kainoid analogues

James Dyer,[a] Amanda King,[a] Steve Keeling[b] and Mark G. Moloney *[a]

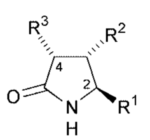
[a] *The Department of Chemistry, Dyson Perrins Laboratory, The University of Oxford, South Parks Road, Oxford, UK OX1 3QY. E-mail: mark.moloney@chem.ox.ac.uk*

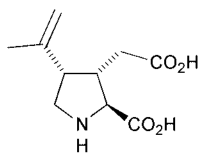
[b] *GlaxoWellcome, Medicines Research Centre, Gunnels Wood Road, Stevenage, Hertfordshire, UK SG1 2NY*

Received (in Cambridge, UK) 13th March 2000, Accepted 2nd June 2000
Published on the Web 24th July 2000

Novel conformationally constrained glutamate analogues are readily available from (*S*)-pyroglutamic acid using a bicyclic lactam as a synthetic template; diastereocontrolled modification of the pyrrolidine ring using a sequential conjugate addition–substitution strategy permits access to several kainoid analogues in a versatile strategy. The pyrrolidinone ring conformation appears to be controllable by the nature of remote substituents on the heterocyclic ring.

In the preceding paper,[1] we detailed our methodology using a bicyclic template derived from (*S*)-pyroglutamic acid for the diastereocontrolled synthesis of C-3 substituted pyroglutaminols and pyroglutamates **1a**–**c**. In this paper, we describe the further elaboration of these templates, leading ultimately to the 4-aryl-5-oxo and 4-arylmethyl-5-oxo analogues **1d** of kainic





1a R^1=CH_2OH, R^2=$C(CO_2Et)_3$, R^3=CO_2Et
1b R^1=CH_2OH, R^2=CH_2CO_2tBu, R^3=CO_2Et
1c R^1=CO_2Me, R^2=CH_2CO_2Me, R^3=H
1d R^1=CO_2Me, R^2=CH_2CO_2Me, R^3=CH_2Ph or Ar

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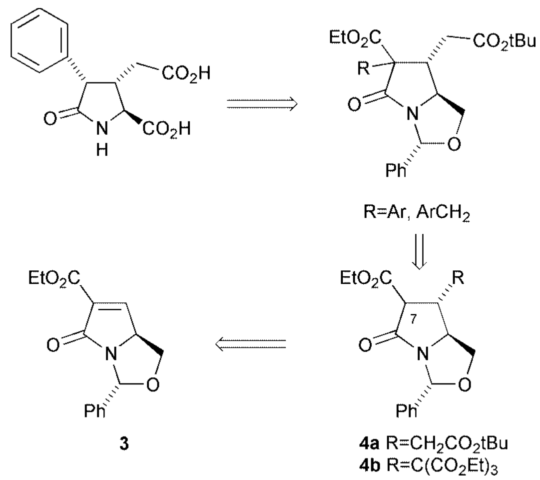
acid† **2**;[2] this strategy allows for the sequential modification of C-3 and C-4 substituents of the kainoids, thereby permitting access to a diverse range of compounds. There has been considerable recent interest in the development of novel methodology to provide access to kainoids and their analogues,[3,4] including organometallic[5–7] and radical approaches.[8,9] These analogues may be considered to be conformationally restricted forms of glutamate; such compounds are of importance as excitatory amino acid analogues[3] and as conformationally controlling peptidomimetics.[10–13]

We expected to develop an efficient and versatile route to analogues of the kainoid group of amino acids from enone **3** (Scheme 1) using the bicyclic system to control diastereoselectivity. As described in the preceding paper,[1] the C-7 ethoxycarbonyl activating group of **3** is of crucial importance for efficient conjugate addition, but it also offered considerable potential for further manipulation at C-7 *after* the conjugate addition step since the β-dicarbonyl system thus generated can be easily alkylated.[14] Furthermore, we expected to be able to use the β-dicarbonyl moiety of **4** for α-arylation reactions using aryllead(IV) triacetates, a strategy which has been developed in detail in recent years.[15,16] The required lead(IV) reagents are readily available by direct plumbation of an aromatic ring or by lead/boron exchange of an arylboronic acid. Elaboration to the desired C-4 aryl functionalised pyroglutamates would then require only a short sequence of steps.



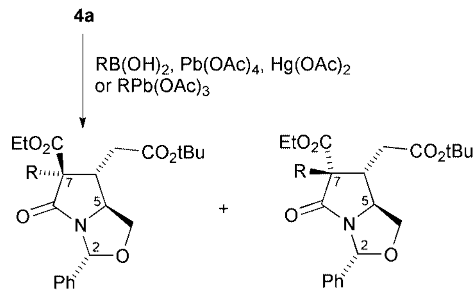
Scheme 1

Ring functionalisation by arylation and alkylation

Although the tricarboxylate conjugate adduct **4b** (Scheme 1) was found not to react when subjected to phenyllead triacetate, presumably due to the substantial steric hindrance from the bulky C-6 substituent, the *tert*-butyloxycarbonylmethyl compound **4a** proved to be suitable for the introduction of a variety of aryl groups to give moderate to excellent combined yields of the diastereomeric products **5** and **6** (Scheme 2 and Table 1); aryllead reagents with either electron withdrawing or electron donating groups on the aromatic ring were applicable. However, the diastereomeric products **5** and **6** could be separated only with difficulty. In the case of phenyllead triacetate (generated *in situ* from lead(IV) tetraacetate and phenylboronic acid), the reaction proved to be sluggish, and the product was obtained in only 20% yield even after a 3 day reaction at room temperature. Optimisation of this reaction, by using an increased number of equivalents of aryllead reagent and heating the reaction at reflux for 3 days gave a greatly improved yield of 86% of the

† IUPAC name for kainic acid is (2-carboxy-4-isopropenylpyrrolidin-3-yl)acetic acid.

DOI: 10.1039/b002001j



5a R = Ph
5b R = *o*-MeOC$_6$H$_4$
5c R = *m*-MeOC$_6$H$_4$
5d R = *p*-MeC$_6$H$_4$
5e R = *p*-CF$_3$C$_6$H$_4$
5f R = *p*-BrC$_6$H$_4$
5g R = *p*-MeOC$_6$H$_4$
5h R = PhCH$_2$

6a R = Ph
6b R = *o*-MeOC$_6$H$_4$
6c R = *m*-MeOC$_6$H$_4$
6d R = *p*-MeC$_6$H$_4$
6e R = *p*-CF$_3$C$_6$H$_4$
6f R = *p*-BrC$_6$H$_4$
6g R = *p*-MeOC$_6$H$_4$
6h R = PhCH$_2$

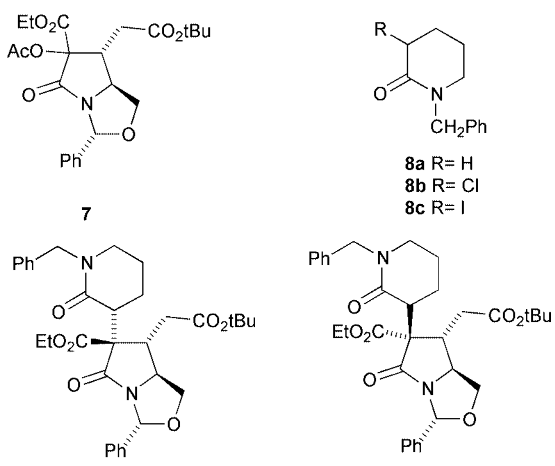
Scheme 2

Table 1 Arylations and alkylations of lactam **4a** giving products **5**, **6**

Compound	R	Yield (%) 5	Yield (%) 6
a	Ph	61	25
b	*o*-MeOC$_6$H$_4$	45	27
c	*m*-MeOC$_6$H$_4$	67	17
d	*p*-MeC$_6$H$_4$	42	18
e	*p*-CF$_3$C$_6$H$_4$	50	22
f	*p*-BrC$_6$H$_4$	52	22
g	*p*-MeOC$_6$H$_4$	26	12
h	PhCH$_2$	34	41

diastereomeric products **5a** and **6a** in a ratio of 2.4:1, and the stereochemistry of **5a** was established by NOE studies (Fig. 1). The *exo* orientation of the C-7 phenyl group was determined from a set of enhancements observed between the *ortho* protons of this group, H-4$_{exo}$ and the *ortho* protons of the C-2 phenyl ring. The *exo* orientation of the C-6 substituent was also confirmed by the observation of enhancements between the spatially proximal hydrogens H-2, H-4$_{endo}$, and H-6.

The reaction of **4a** with *o*-methoxyphenyllead triacetate (generated *in situ* from lead(IV) tetraacetate and *o*-methoxyphenylboronic acid[16]) under the above conditions for 2 days gave, after careful chromatography, a mixture of unreacted starting material **4a** (27%), the desired diastereomeric products **5b** and **6b** in 40% overall yield, and the acetate **7**; α-acetoxylation is a well documented side-reaction for lead(IV) carboxylates.[17] This latter product may arise due to the greater steric



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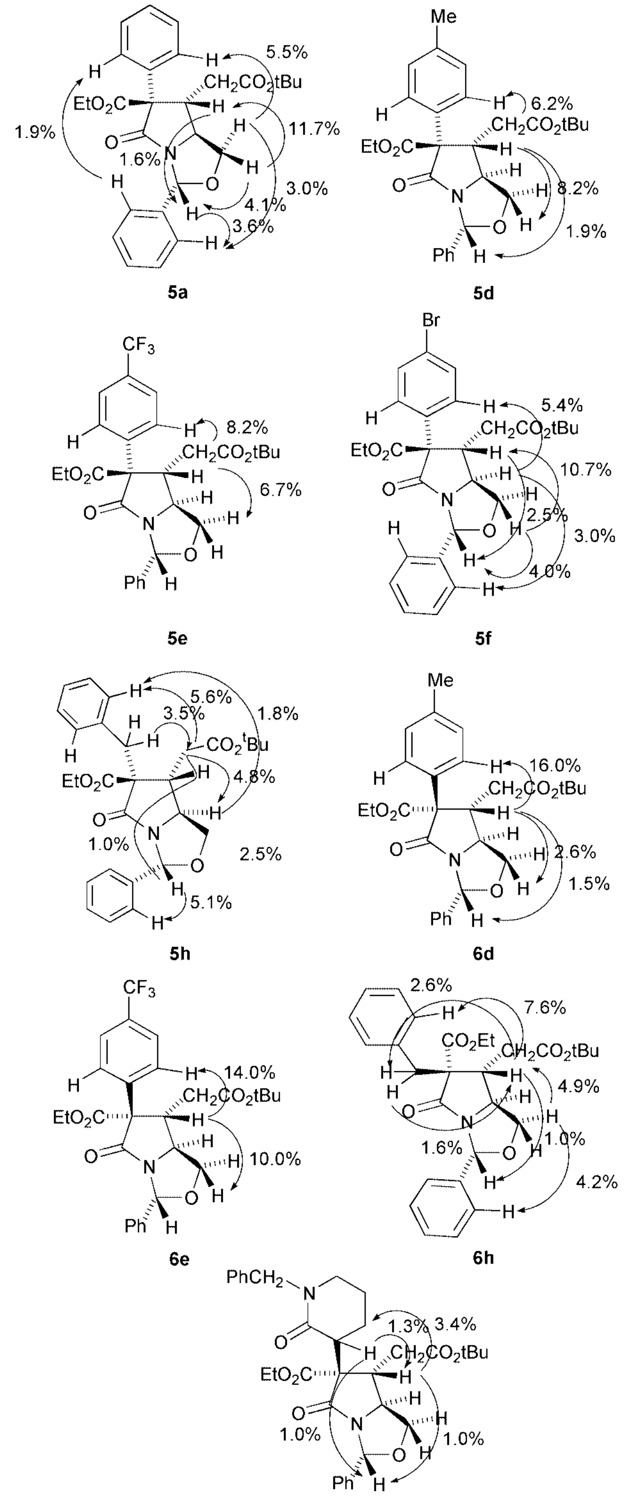
8a R= H
8b R= Cl
8c R= I

9a

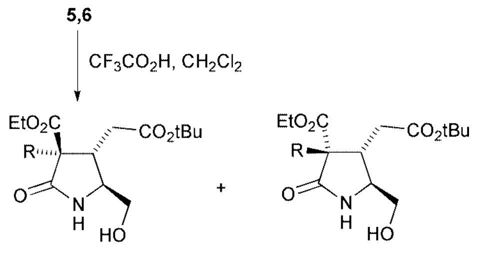
9b



5a **5d** **5e** **5f** **5h** **6d** **6e** **6h** **9b**

Fig. 1 NOE data for selected compounds.

bulk of the *o*-methoxyphenyl group, thus allowing the competing acetoxylation process to occur. A cleaner and higher yielding arylation reaction was achieved with *o*-methoxyphenyllead(IV) triacetate (prepared according to the literature method[16]), giving a 72% yield of **5b** and **6b** in a ratio of 1.7:1. The *m*-methoxyphenyl derivatives **5c**:**6c** were obtained in 84% yield and a ratio of 4:1. The *p*-methylphenyl, *p*-trifluoromethylphenyl and *p*-bromophenyl derivatives **5d–f** and **6d–f** were obtained in combined yields of 60, 72 and 74% respectively as 2.3:1 ratio of diastereomers. The stereochemical assignment of these stereoisomers was possible by the presence of NOE spectroscopic enhancements from either the methylene of the C-6 substituent or H-5 to the *o*-aromatic protons of the C-7 sub-



10a R = Ph
10b R = *p*-MeOC$_6$H$_4$
10c R = PhCH$_2$

11a R = Ph
11b R = *p*-MeOC$_6$H$_4$
11c R = PhCH$_2$

Scheme 3

Table 2 Deprotections of lactams **5**, **6** giving products **10**, **11**

Compound	Ratio	Product	R_f	Yield (%)
5a, **6a**	2.1 : 1	**10a**, **11a**	0.24, 0.32	81
5g, **6g**	2.3 : 1	**10b**, **11b**	0.22, 0.27	38
5h	—	**10c**	0.20	86
6h	—	**11c**	0.27	77

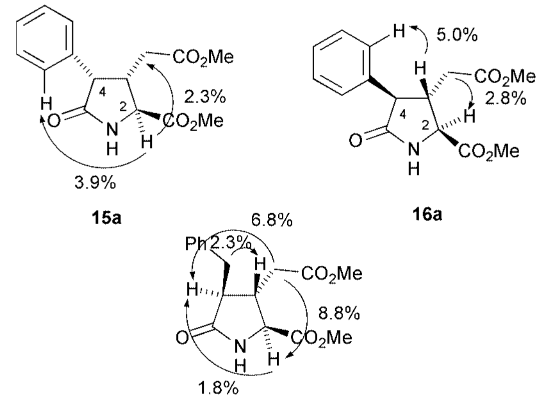
stituent for the diastereomers **5**, or from H-6 to the same aromatic protons for diastereomer **6** (Fig. 1). However, unlike the cases outlined above, reaction with *p*-methoxyphenyllead(IV) triacetate proved to be very problematic; the best result was obtained when lactam **4a** was converted to the corresponding enolate (NaH–THF) followed by treatment with *p*-methoxyphenyllead(IV) triacetate and pyridine at rt for 5 days. Purification by column chromatography gave the products **5g** and **6g** in a yield of 38% as a 2.3 : 1 ratio.

The alkylation at C-7 of bicyclic lactam **4a** was also investigated. Conversion of lactam **4a** to the corresponding enolate (NaH–THF) followed by addition of benzyl bromide gave the products **5h** and **6h** in a yield of 75% as a 1 : 1.2 ratio. Stereochemical assignment using a series of NOE experiments as before was possible for both diastereomers of **5h** and **6h** (Fig. 1). Alternatively, alkylation of **4a** with α-iodovalerolactam **8c** (readily obtained from *N*-benzylvalerolactam **8a** in three steps *via* the chloride **8b**) gave the diastereomeric products **9a**, **b** in 36% yield (ratio 1 : 1), and the stereochemistry of **9b** was assigned by NOE analysis (Fig. 1).

Conversion to pyroglutamate derivatives

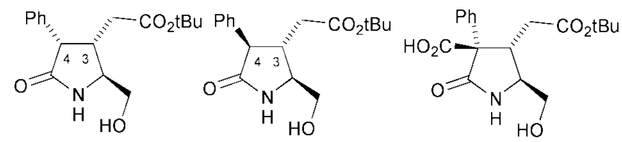
Deprotection of lactams **5a**, **g**, **h** and **6a**, **g**, **h**, by exposure to TFA in dichloromethane for 15 minutes gave the expected alcohols **10a**–**c** and **11a**–**c** in moderate to excellent yield (Scheme 3 and Table 2); unlike the arylated bicyclic starting materials which were separable only with difficulty by chromatography, each of the diastereomerically pure alcohols **10** and **11** could be easily obtained. As with the starting lactams **5** and **6**, the *endo* aryl compounds **11** had greater R_f values than their C-4 epimers **10**.

In order to realise our goal of developing a short synthesis of the kainoid group of amino acids using this strategy, removal of the C-7 ethoxycarbonyl substituent of intermediates **5**, **6** was required; the C-7 *exo* stereochemistry was desired for the most commonly occurring and most biologically active kainoids.[4] Hydrolysis and decarboxylation of **10a** with sodium hydroxide in ethanol at room temperature followed by heating under vacuum gave the product diastereomers **12** and **13**, along with the acid **14**. Further heating of this mixture effected complete decarboxylation, giving an overall yield of the products **12**, **13** of 82% in a ratio of 1 : 1.4; noteworthy is the high proportion of the product **12** possessing the desired kainic acid configuration. The diastereomers were identified from examination of the ^{1}H NMR spectrum which showed a similar distinctive splitting pattern for each diastereomer as observed for the arylated bicyclic compounds **5**, **6**. Thus, the signals from the methylene protons α to the *tert*-butyl ester were coincident for the *trans*-C-3/4 compound **13**, and separated by 2.7 ppm for the *cis*-C-3/4 compound **12**. The alcohols **12**, **13** (1 : 1) were treated with TFA to remove the *tert*-butyl group, and then oxidised using ruthenium(IV) oxide/sodium periodate and methylated with diazomethane; the expected diastereomers **15a** and **16a** were each obtained in 33% yield. The stereochemical assignment of **15a** and **16a** as shown was confirmed from NOE experiments performed on each diastereomer, the results of which are shown in Fig. 2. The diastereomer **16a** showed enhancements between the H-2 and the C-6 methylene substituent, and between the H-3 and the C-4 *ortho*-phenyl signals, which were indicative of the all-*trans* disposition of H-2, -3 and -4. The diastereomer **15a** displayed enhancements between the C-4 *ortho*-phenyl signal and that of H-2, and the *cis* disposition of H-2 and the C-3 substituent was indicated from the enhancement of the methylene signal on irradiation of H-2. In addition to the NOE data, the ^{1}H NMR spectra of these compounds displayed the previously discussed features for these diastereomeric arylated compounds; thus, the methylene signal was coincident for the *trans*-C-3/4 compound **16a** and split for the *cis*-C-3/4 compound **15a**, which could be attributed to the shielding environment imposed upon the methylene hydrogens when positioned *cis* to the anisotropic phenyl ring.

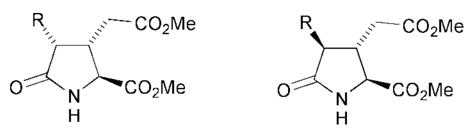


15a **16a** **16b**

Fig. 2

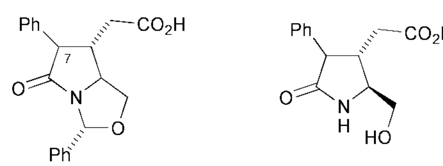


12 **13** **14**

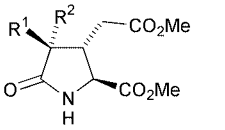


15a R = Ph
15b R = PhCH$_2$

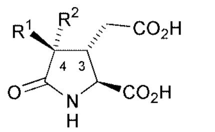
16a R = Ph
16b R = PhCH$_2$



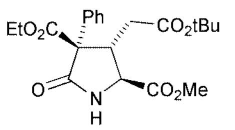
17 **18**



19a $R^1 = EtO_2C$, $R^2 = Ph$
19b $R^1 = Ph$, $R^2 = EtO_2C$



20a $R^1 = H$, $R^2 = Ph$
20b $R^1 = Ph$, $R^2 = H$



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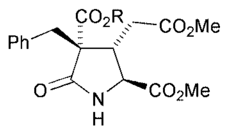


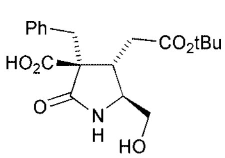
22a R = Et
22b R = Me

Although it was anticipated that better diastereocontrol would be obtained if the decarboxylation step was performed on the bicyclic lactams **5** and **6**, in practice the initial ester hydrolysis step proved to be unreliable. Thus, hydrolysis with alcoholic sodium hydroxide of the phenyl adduct **5a**, **6a** (2:1) gave slow ethyl ester hydrolysis and decarboxylation, along with some *tert*-butyl ester hydrolysis. Complete *tert*-butyl ester hydrolysis resulted upon repetition of this reaction at 50 °C for 5–8 h to give acid **17** as a mixture of diastereomers at C-7. Hemiaminal ether deprotection was then easily achieved by treatment with TFA in dichloromethane for 4.5 h at room temperature to give **18**, and alcohol oxidation was effected using ruthenium(IV) oxide–sodium periodate. The crude dicarboxylic acid product was immediately converted to the dimethyl ester (MeOH, H_2SO_4, reflux) to give the expected product as the two diastereomers **15a** and **16a**. However, the two minor products **19a**, **19b** were also isolated in low yield from this sequence, arising from incomplete hydrolysis in the initial step. Hydrolysis of the dimethyl ester **16a** by treatment with sodium hydroxide in aqueous tetrahydrofuran gave the diacids **20a**, **b** in high yield (83%) in a ratio of 1:3.8, that is, favouring the *trans*-C-3/4 arrangement. This was confirmed by re-esterification with methanol–conc. H_2SO_4 which gave a 1:5 diastereomeric mixture of the dimethyl ester product **15a** and **16a**.

The C-4 disubstituted derivative **21** was readily obtained using the above oxidation–esterification sequence on pyrrolidinone **10a** in good yield (41%), but under the same conditions the alcohol **11a** gave no product.

Attempted hydrolysis and decarboxylation of the benzyl compound **6h** proved to be problematic. Because of the easier hydrolysis which had been observed for lactams **10a** and **11a**, attention was turned towards the hydrolysis of the readily separable benzyl compounds **10c** and **11c**. Selective ethyl ester hydrolysis of **11c** with NaOH (1 M), treatment with TFA then with RuO_2–$NaIO_4$ and finally with diazomethane, gave the dimethyl monoethyl ester and trimethyl ester products **22a** and **22b** in yields of 23% and 25% respectively. This result shows that some ethyl ester hydrolysis had occurred, but highlights the sterically hindered nature of the C-4 esters in substrates of this type.

A similar sequence was used for compound **10c**; hydrolysis with NaOH gave the carboxylic acid **23** in a yield of 99%.



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Decarboxylation (heating at 135 °C at 0.5 mbar), deprotection (TFA), oxidation and esterification (diazomethane) gave the completely separated product diastereomers **15b** and **16b** in overall yields of 7 and 31% respectively from the alcohol **10c**. The ^{1}H NMR spectrum of the *trans*-C-3/4 compound **16b** was amenable to NOE analysis for stereochemical determination, and the significant enhancements are shown in Fig. 2. Enhancements between H-4, the methylene protons of the C-3 substituent, and H-2 indicated their *cis* relationship; this stereochemistry would be expected for the major diastereomer on consideration of steric interactions.

Table 3 Coupling constants and dihedral angles

Compound	Coupling constant/ Hz[a]	C(2)H–C(3)H Dihedral angle/°
15a (R = H)	6.0 (6.5)	118
15a	5.5 (5.5)	117
16a	6.5 (6.5)	121
15b	8.0 (8.0)	153
16b	2.5 (2.5)	125

[a] In $CDCl_3$ (C_6D_6).

Table 4 Selected ^{1}H NMR spectroscopic data for compounds **5**, **6**

Compound	δ H-2	H-4$_{endo}$	H-4$_{exo}$	CH_2CO^{t}Bu	R_f
5a	6.43	3.97	4.43	1.64, 2.42	0.19
6a	6.37	3.90	4.35	2.70–2.78	0.21
5b	6.38	3.98	4.42	1.71, 2.70	0.11
6b	6.41	3.90	4.20–4.33	2.63, 2.93	0.30
5c	6.43	3.73	4.46	1.66, 2.45	0.36
6c	6.37	3.90	4.36	2.74–2.76	0.36
5d	6.42	3.70	4.43	1.66, 2.43	0.38
6d	6.36	3.88	4.27	2.72	0.38
5e	6.42	3.70	4.44	1.64, 2.39	0.39
6e	6.48	3.85	4.29	2.69–2.81	0.49
5f	6.41	3.97	4.43	1.67, 2.38	0.29
6f	6.35	3.89	4.21–4.38	2.63–2.73	0.40
5h	6.29	3.78	4.23	2.58–2.70	0.19
6h	6.17	3.12	4.16	2.26–2.42	0.29

Conformational studies

This synthetic route represents a novel and simple, but potentially generalisable approach to highly functionalised pyrrolidinones, and is complementary to existing literature protocols. In particular, it provides access to novel pyroglutamate analogues of the kainoid group of amino acids possessing substituents with π-electron density at C-4; the synthesis of conformationally constrained pyroglutamates has attracted recent attention.[18] It was apparent from examination of the ^{1}H NMR spectra of the final dimethyl ester pyroglutamates **15a**, **b** and **16a**, **b**, as well as the unsubstituted derivative **15** (R = H),[1] that the coupling constants between the H-2 and H-3 varied between diastereomers and with the type of C-4 substituent (Table 3); molecular modelling studies of each of these compounds[19] confirmed these experimental findings, since the H-2–H-3 dihedral angle was found to vary depending on the nature of the C-4 substituent, and appears to be greatest for the more sterically congested C-4 (aryl) series of compounds **6a**, **b**. Thus, it would appear that analogues of well defined glutamate conformers could be available by variation in the C-4 substituent of compounds of type **15** and **16**.

NMR spectroscopy

In common with the simpler systems discussed in the preceding paper, a consistent pattern was observed with regard to chemical shifts and coupling constant values in the NMR spectra (Table 4). Thus, for the aryl adducts **5a**–**e** and **6a**–**e**, H-4$_{endo}$ has a lower chemical shift than H-4$_{exo}$ with Δδ of about 0.4; however, **6h** is exceptional, and this difference is more than double, a result which can be attributed to the anisotropy of the adjacent benzyl substituent. Similar anisotropy is responsible for the well separated resonances of the C-6 methylene substituent protons of the *exo* aryl diastereomers **5**, but coincident resonance in *endo* aryl **6**.

Experimental

For general experimental procedures, see our earlier reports.[14,20]

General arylation methods

Method 1. To a mixture of lead(IV) tetraacetate, arylboronic acid and mercury(II) acetate in an inert atmosphere was added ethanol-free chloroform and the mixture was then stirred at 40 °C for 2 h. A solution of the lactam **4a** in chloroform was then added and the mixture heated at reflux for 72 h. After cooling to rt the mixture was filtered through Celite®, washed with chloroform, and the organic layer washed with sulfuric acid (10% aq.). The aqueous phase was washed twice with chloroform and the combined organic phases were dried ($MgSO_4$), filtered and evaporated *in vacuo* prior to purification.

Method 2. To a solution of the lactam **4a** in ethanol-free chloroform was added pyridine and the aryllead(IV) complex. The mixture was then heated at reflux under an argon atmosphere for the specified period. After cooling, the mixture was worked-up as above.

Method 3. To a stirred solution of the lactam **4a** in THF at rt was added sodium hydride (1.1 eq.). After 1 h this solution was transferred to a solution of the aryllead(IV) complex (1.5 eq.) in pyridine (2 ml), using THF (1 ml) to rinse the flask out. The mixture was then stirred at room temperature. After 3 days another aliquot of pyridine (2 ml) and aryllead(IV) complex (1.2 eq.) was added. The mixture was then worked-up after a further 2 days as above.

Method 4. A solution of lactam **4a** and the required aryllead compound[15,21] (1.05 eq.) was heated under reflux in chloroform (10 ml) with pyridine (3 eq.) for 72 h. The reaction mixture was cooled to rt, diluted with chloroform (10 ml), washed with 2 M HCl (10 ml) and water (15 ml), dried ($MgSO_4$) and the solvent removed *in vacuo*.

(2*R*,5*S*,6*S*,7*R*)- and (2*R*,5*S*,6*S*,7*S*)-6-*tert*-Butoxycarbonylmethyl-7-ethoxycarbonyl-3-oxa-8-oxo-2,7-diphenyl-1-azabicyclo[3.3.0]octanes 5a and 6a

According to Method 1, lactam **4a** (0.30 g, 0.77 mmol) was reacted with phenylboronic acid (0.19 g, 1.5 mmol), lead(IV) tetraacetate (0.72 g, 1.5 mmol), mercury(II) acetate (49 mg, 0.15 mmol), and pyridine (0.37 g, 4.62 mmol) in $CHCl_3$ (30 ml) at reflux for 3 days to give after work-up and purification using flash column chromatography (Et_2O–cyclohexane, 1:3) the product as a colourless glass of diastereomeric ratio **5a**:**6a** of 2.4:1 (0.31 g, 86%).

Data for 5a. R_f 0.19; ν_{max}(film)/cm^{-1} 2980 (s), 1368 (m), 1245 (s), 1154 (s), 1050 (m), 1028 (m), 701 (m), 665 (m); δ_H (500 MHz, $CDCl_3$) 1.31 (3H, t, *J* 7.0, CH_3CH_2), 1.41 (9H, s, $C(CH_3)_3$), 1.64 (1H, dd, *J* 16.5 and 11.5, $CHHCO_2{}^tBu$), 2.42 (1H, dd, *J* 16.5 and 4.0, $CHHCO_2{}^tBu$), 3.58–3.62 (1H, m, H-6), 3.69–3.74 (1H, m, H-5), 3.97 (1H, dd, *J* 9.0 and 7.5, H-4$_{endo}$), 4.35 (2H, q, *J* 7.0, CH_3CH_2), 4.43 (1H, dd, *J* 9.0 and 6.0, H-4$_{exo}$), 6.43 (1H, s, H-2), 7.11–7.13 (2H, m, Ar*H*), 7.30–7.45 (6H, m, Ar*H*), 7.57–7.59 (2H, m, Ar*H*); δ_C (125.8 MHz, $CDCl_3$) 14.01 (CH_3CH_2), 28.00 ($C(CH_3)_3$), 35.99 ($CH_2CO_2{}^tBu$), 44.49 (C-6), 61.32 (C-5), 62.40 (CH_3CH_2), 69.72 (C-7) and 72.68 (C-4), 81.28 ($C(CH_3)_3$), 86.99 (C-2), 126.11, 127.95, 128.03, 128.46, 128.60 and 128.81 (Ar*C*H), 134.10 (ArC), 138.37 (ArC), 169.90, 170.68 and 170.88 (3 × *C*O).

Data for 6a. R_f 0.21; ν_{max}(film)/cm^{-1} 2980 (s), 1368 (m), 1245 (s), 1154 (s), 1050 (m), 1028 (m), 701 (m), 665 (m); δ_H (500 MHz, $CDCl_3$) 1.25 (3H, t, *J* 7.0, CH_3CH_2), 1.44 (9H, s, $C(CH_3)_3$), 2.70–2.78 (2H, m, $CH_2CO_2{}^tBu$), 3.08–3.12 (1H, m, H-6), 3.90 (1H, dd, *J* 9.0 and 7.5, H-4$_{endo}$), 4.12 (1H, dd, *J* 14.0 and 7.5, H-5), 4.21–4.33 (2H, m, CH_3CH_2), 4.35 (1H, dd, *J* 9.0 and 6.0, H-4$_{exo}$), 6.37 (1H, s, H-2), 7.33–7.44 (8H, m, Ar*H*), 7.48–7.50 (2H, m, Ar*H*); δ_C (125.8 MHz, $CDCl_3$) 14.00 (CH_3CH_2), 28.03 ($C(CH_3)_3$), 34.48 ($CH_2CO_2{}^tBu$), 47.38 (C-6), 62.00 and 62.16 (CH_3CH_2 and C-5), 68.41 (C-7) and 72.48 (C-4), 81.54 ($C(CH_3)_3$), 86.53 (C-2), 126.12, 128.00, 128.46 and 128.74 (Ar*C*H), 135.41 (ArC), 137.98 (ArC), 169.42, 170.28 and 171.09 (3 × *C*O); *m*/*z* (CI(NH_3)) 466 (M + H$^+$, 100%); HRMS 466.2230, $C_{27}H_{32}NO_6$ requires 466.2231.

(2*R*,5*S*,6*S*,7*R*)- and (2*R*,5*S*,6*S*,7*S*)-6-*tert*-Butoxycarbonylmethyl-7-ethoxycarbonyl-7-*o*-methoxyphenyl-3-oxa-8-oxo-2-phenyl-1-azabicyclo[3.3.0]octanes 5b and 6b

According to Method 1, lactam **4a** (73 mg, 0.19 mmol) was reacted with 2-methoxyphenylboronic acid (59 mg, 0.38 mmol), lead(IV) tetraacetate (0.18 g, 0.38 mmol), mercury(II) acetate (12 mg, 0.04 mmol), and pyridine (89 mg, 1.1 mmol) in $CHCl_3$ (10 ml) at reflux for 2 days. Work-up and purification by flash column chromatography (EtOAc–DCM, 50:1) gave several products, including lactam **4a** (20 mg, 27%), the aryl product **5b** and the acetate product **7** (4 mg, 5%).

According to Method 2, *o*-methoxyphenyllead(IV) triacetate (0.22 g, 0.44 mmol) and the lactam **4a** (86 mg, 0.22 mmol) were reacted in pyridine (87 mg, 1.1 mmol) and $CHCl_3$ (6 ml) at reflux for 3 days. Work-up gave the crude mixture as a yellow glass which was shown to be a mixture of product diastereomers **5b**, **6b** (1.7:1), along with some starting lactam **4a**, which was purified by flash column chromatography (DCM–MeOH–Et_3N, 200:1:1) to give the product as incompletely separable diastereoisomers (79 mg, 72%).

Data for 5b. R_f 0.11 (Et_2O–Petrol (30–40), 1:2); ν_{max}(film)/cm^{-1} 1718 (s), 1493 (m), 1459 (m), 1367 (m), 1308 (m), 1248 (s), 1154 (s), 1026 (m), 755 (m), 700 (m); δ_H (500 MHz, $CDCl_3$) 1.24 (3H, t, *J* 7.0, CH_3CH_2), 1.40 (9H, s, $C(CH_3)_3$), 1.71 (1H, dd, *J* 16.5 and 12.0, $CHHCO_2{}^tBu$), 2.70 (1H, dd, *J* 16.5 and 3.5, $CHHCO_2{}^tBu$), 3.69–3.73 (1H, m, H-5), 3.76–3.82 (4H, m, H-6 and OCH_3), 3.98 (1H, t, *J* 8.5, H-4$_{endo}$), 4.23–4.30 (2H, m, CH_3CH_2), 4.42 (1H, dd, *J* 8.5 and 6.0, H-4$_{exo}$), 6.38 (1H, s, H-2), 6.89–6.94 (2H, m, Ar*H*), 7.12–7.14 (1H, m, Ar*H*), 7.29–7.32 (1H, m, Ar*H*), 7.35–7.43 (3H, m, Ar*H*), 7.56–7.58 (2H, m, Ar*H*); δ_C (125.8 MHz, $CDCl_3$) 14.05 (CH_3CH_2), 28.00 ($C(CH_3)_3$), 34.76 ($CH_2CO_2{}^tBu$), 43.12 (C-6), 55.07 (OCH_3), 61.76 (C-5), 61.92 (CH_3CH_2), 67.31 (C-7), 72.69 (C-4), 80.98 ($C(CH_3)_3$), 87.02 (C-2), 111.24 (Ar*C*H), 121.53 (Ar*C*H), 123.81 (Ar*C*H), 126.07 (Ar*C*H), 128.34 (Ar*C*H), 128.50 (Ar*C*H), 128.72 (Ar*C*H), 129.50 (C-16), 138.54 (ArC), 156.90 (Ar*C*), 170.02 ($CO_2CH_2CH_3$), 171.47 (*C*(O)N) + $CO_2{}^tBu$); *m*/*z* (APCI$^+$) 496 (M + H$^+$, 21%), 440 (100).

Data for 6b. R_f 0.30 (DCM–EtOAc, 50:1); $[\alpha]_D^{26}$ +148.4 (*c* 0.31 in $CHCl_3$); ν_{max}(film)/cm^{-1} 1720 (s), 1494 (m), 1461 (m), 1368 (m), 1309 (m), 1252 (s), 1224 (s), 1154 (s), 1026 (m), 755 (m), 699 (m); δ_H (500 MHz, $CDCl_3$) 1.25 (3H, t, *J* 7.0, CH_3CH_2), 1.41 (9H, s, $C(CH_3)_3$), 2.63 (1H, dd, *J* 17.0 and 3.0, $CHHCO_2{}^tBu$), 2.93 (1H, dd, *J* 17.0 and 11.5, $CHHCO_2{}^tBu$), 3.02–3.06 (1H, m, H-6), 3.84 (3H, s, OCH_3), 3.90 (1H, dd, *J* 8.5 and 7.0, H-4$_{endo}$), 4.11–4.15 (1H, m, H-5), 4.20–4.33 (3H, m, CH_3CH_2 and H-4$_{exo}$), 6.41 (1H, s, H-2), 6.97 (1H, d, *J* 8.0, Ar*H*), 7.00–7.03 (1H, m, Ar*H*), 7.32–7.39 (5H, m, Ar*H*), 7.46–7.48 (2H, m, Ar*H*); δ_C (125.8 MHz, $CDCl_3$) 14.33 (CH_3CH_2), 28.02 ($C(CH_3)_3$), 34.32 ($CH_2CO_2{}^tBu$), 47.54 (C-6), 55.71

(OCH_3), 61.62 (CH_3CH_2), 61.85 (C-5), 66.67 (C-7), 72.52 (C-4), 81.06 ($C(CH_3)_3$), 86.76 (C-2), 112.26 (Ar*C*H), 121.09 (Ar*C*H), 125.57 (Ar*C*H), 126.16 (Ar*C*H), 128.39 (Ar*C*H), 128.58 (Ar*C*H), 128.77 (Ar*C*H), 129.35 (Ar*C*H), 138.25 (ArC), 157.28 (ArC), 169.09 (*C*(O)N), 170.87 ($CO_2CH_3CH_2$), 171.69 ($CO_2{}^tBu$); *m*/*z* (APCI$^+$) 496 (M + H$^+$, 33%), 440 (100), 262 (57); HRMS (CI$^+$) 496.2335, $C_{28}H_{33}NO_7$ (M + H$^+$) requires 496.2335.

Data for acetate 7. R_f 0.30 (EtOAc–petrol (40–60), 1:2); ν_{max}(film)/cm^{-1} 1728 (s), 1370 (m), 1231 (m), 1155 (m); δ_H (500 MHz, $CDCl_3$) 1.31 (3H, t, *J* 7.0, CH_3CH_2), 1.45 (9H, s, $C(CH_3)_3$), 2.23 (3H, s, $COCH_3$), 2.51 (1H, dd, *J* 17.0 and 11.0, $CHHCO_2{}^tBu$), 2.86 (1H, dd, *J* 17.0 and 3.5, $CHHCO_2{}^tBu$), 3.12–3.16 (1H, m, H-6), 3.88–3.93 (2H, m, H-4H and H-5), 4.27–4.37 (2H, m, CH_3CH_2), 4.37–4.42 (1H, m, H-4*H*), 6.33 (1H, s, H-2), 7.33–7.39 (3H, m, Ar*H*), 7.44–7.46 (2H, m, Ar*H*); δ_C (125.8 MHz, $CDCl_3$) 13.98 (CH_3CH_2), 21.07 ($COCH_3$), 28.02 ($C(CH_3)_3$), 34.71 ($CH_2CO_2{}^tBu$), 44.68 (C-6), 61.27 (C-5), 62.63 (CH_3CH_2), 72.58 (C-4), 81.69 ($C(CH_3)_3$), 87.16 (C-2), 88.07 (C-7), 126.14, 128.49 and 128.86 (Ar*C*H), 137.69 (ArC), 165.19, 166.63, 169.37 and 170.57 (4 × *C*O); *m*/*z* (CI(NH_3)) 448 (M + H$^+$, 92%), 392 (69); HRMS (CI$^+$) 448.1971, $C_{23}H_{30}NO_8$ (M + H$^+$) requires 448.1971.

(2*R*,5*S*,6*S*,7*R*)- and (2*R*,5*S*,6*S*,7*S*)-6-*tert*-Butoxycarbonylmethyl-7-ethoxycarbonyl-7-*m*-methoxyphenyl-3-oxa-8-oxo-2-phenyl-1-azabicyclo[3.3.0]octanes 5c and 6c

According to Method 4, lactam **4a** (118 mg, 0.30 mmol) and *m*-methoxyphenyllead triacetate[21] (161 mg, 0.42 mmol) were reacted together to give a pale yellow oil (126 mg, 84%). The two diastereomers **5c** and **6c** were present in the ratio 4:1 but were not separable by flash column chromatography.

Data for 5c. 101 mg, 67%; R_f 0.36 (petrol–EtOAc, 3:1); ν_{max}($CHCl_3$)/cm^{-1} 2982 (m), 1720 (br, s), 1515 (m); δ_H (400 MHz, $CDCl_3$) 1.32 (3H, t, *J* 7.1, CH_2CH_3), 1.41 (9H, s, $C(CH_3)_3$), 1.66 (1H, dd, *J* 16.5 and 11.5, $CHCO_2{}^tBu$), 2.45 (1H, dd, *J* 16.5 and 3.7, $CHCO_2{}^tBu$), 3.54–3.58 (1H, m, H-6), 3.60 (3H, s, OCH_3), 3.73 (1H, dd, *J* 13.8 and 7.7, H-4_{endo}), 3.85–3.95 (1H, m, H-5), 4.35 (2H, q, *J* 7.1, CH_2CH_3), 4.44–4.48 (1H, m, H-4_{exo}), 6.43 (1H, s, H-2), 6.64–7.61 (9H, m, Ar*H*); δ_C (50.3 MHz, $CDCl_3$) 13.91 (CH_2CH_3), 27.91 ($C(CH_3)_3$), 35.74 ($CH_2CO_2{}^tBu$), 44.29 (C-6), 54.96 ($ArOCH_3$), 61.11 (C-5), 62.40 (CH_2CH_3), 69.70 (C-7), 72.89 (C-4), 81.32 ($C(CH_3)_3$), 86.67 (C-2), 113.02, 114.15, 120.60, 126.23, 128.78 and 129.03 (Ar*C*H), 135.6, 138.75 and 160.12 (Ar*C*), 170.0, 170.2 and 171.29 (*C*O); *m*/*z* (CI, NH_3) 440 (52%); HRMS 496.2335. $C_{28}H_{33}NO_6$ (M + H$^+$) requires 496.5485.

Data for 6c. 25 mg, 17%; R_f 0.36 (petrol–EtOAc, 3:1); ν_{max}/cm^{-1} ($CHCl_3$) 2982 (m), 1720 (s), 1515 (m); δ_H (400 MHz, $CDCl_3$) 1.25 (3H, t, *J* 7.1, CH_2CH_3), 1.44 (9H, s, $C(CH_3)_3$), 2.74–2.76 (2H, m, $CH_2CO_2{}^tBu$), 3.08–3.11 (1H, m, H-6), 3.82 (3H, s, OCH_3), 3.90 (1H, dd, *J* 8.9 and 7.3, H-4_{endo}), 4.12 (1H, dt, *J* 7.2 and 7.2, H-5), 4.28 (2H, q, *J* 7.1, CH_2CH_3), 4.32–4.38 (1H, m, H-4_{exo}), 6.37 (1H, s, H-2), 6.88–7.60 (9H, m, Ar*H*); δ_C (50.3 MHz, $CDCl_3$) 13.91 (CH_2CH_3), 27.91 ($C(CH_3)_3$), 34.5 ($CH_2CO_2{}^tBu$), 47.9 (C-6), 55.2 ($ArOCH_3$), 61.9 (C-5), 62.05 (CH_2CH_3), 68.2 (C-7), 72.2 (C-4), 81.5 ($C(CH_3)_3$), 86.6 (C-2), 113.1, 114.2, 120.2, 128.7, 129.0 and 129.8 (Ar*C*H), 137.0, 138.1 and 159.9 (Ar*C*), 169.7, 170.2 and 171.3 (*C*O); *m*/*z* (CI, NH_3) 440 (52%); HRMS 496.2335. $C_{28}H_{33}NO_6$ (M + H$^+$) requires 496.5485.

(2*R*,5*S*,6*S*,7*R*)- and (2*R*,5*S*,6*S*,7*S*)-7-Ethoxycarbonyl-6-*tert*-butoxycarbonylmethyl-7-*p*-methylphenyl-3-oxa-8-oxo-2-phenyl-1-azabicyclo[3.3.0]octanes 5d and 6d

According to Method 4, lactam **4a** (156 mg, 0.40 mmol) was reacted with *p*-methylphenyllead triacetate[21] (200 mg, 0.55 mmol) to yield the title compound as two separate diastereomers **5d** and **6d** in a ratio of 2.3:1 as yellow oils (115 mg, 60%).

Data for 5d. 81 mg, 42%; R_f 0.38 (petrol–EtOAc, 3:1); ν_{max}(film)/cm^{-1} 2980 (m), 2933 (m), 1724 (br, s), 1515 (w); δ_H (400 MHz, $CDCl_3$) 1.30 (3H, t, *J* 7.1, CH_2CH_3), 1.44 (9H, s, $C(CH_3)_3$), 1.66 (1H, dd, *J* 16.4 and 11.2, $CHCO_2{}^tBu$), 2.33 (3H, s, $ArCH_3$), 2.43, (1H, dd, *J* 16.4 and 3.8, $CHCO_2{}^tBu$), 3.53–3.62 (1H, m, H-6), 3.70 (1H, dd, *J* 13.7 and 7.5, H-4_{endo}), 3.86–4.00 (1H, m, H-5), 4.33 (2H, q, *J* 7.0, CH_2CH_3), 4.42–4.45 (1H, m, H-4_{exo}), 6.42 (1H, s, H-2), 7.00 (2H, d, *J* 8.2, Ar*H*), 7.14 (2H, d, *J* 8.2, Ar*H*), 7.34–7.60 (5H, m, Ar*H*), δ_C (100.7 MHz, $CDCl_3$) 14.05 (CH_2CH_3), 20.85 ($ArCH_3$), 26.78 ($C(CH_3)_3$), 34.36 ($CH_2CO_2{}^tBu$), 47.23 (C-6), 61.95 (CH_2CH_3), 62.16 (C-5), 68.04 (C-7), 72.57 (C-4), 81.30 ($C(CH_3)_3$), 86.38 (C-2), 126.01, 127.74, 128.67, 129.03 and 132.34 (Ar*C*H), 137.67 and 137.96 (Ar*C*), 169.45, 170.34 and 170.71 (*C*O); *m*/*z* (CI, NH_3) 480 (MH$^+$, 30%), 424 (100); HRMS 480.2385. $C_{28}H_{33}NO_6$ (M + H$^+$) requires 480.2386.

Data for 6d. 34 mg, 18%; R_f 0.38 (petrol–EtOAc, 3:1); ν_{max}(film)/cm^{-1} 2980 (m), 2933 (m), 1724 (br, s), 1515 (w); δ_H (400 MHz, $CDCl_3$) 1.30 (3H, t, *J* 7.1, CH_2CH_3), 1.41 (9H, s, $C(CH_3)_3$), 2.36 (3H, s, $ArCH_3$), 2.72, (2H, d, *J* 7.6, $CH_2CO_2{}^tBu$), 3.08–3.12 (1H, m, H-6), 3.86–3.90 (1H, m, H-4_{endo}), 4.01–4.15 (1H, m, H-5), 4.24–4.29 (1H, m, H-4_{exo}), 4.34 (2H, q, *J* 7.1, CH_2CH_3), 6.36 (1H, s, H-2), 7.20–7.60 (9H, m, Ar*H*); δ_C (100.7 MHz, $CDCl_3$) 13.66 (CH_2CH_3), 20.27 ($ArCH_3$), 27.43 ($C(CH_3)_3$), 35.45 ($CH_2CO_2{}^tBu$), 44.17 (C-6), 61.00 (C-5), 61.62 (CH_2CH_3), 69.02 (C-7), 72.10 (C-4), 80.45 ($C(CH_3)_3$), 86.59 (C-2), 125.79, 127.61, 127.96, 128.11, 128.32 and 128.97 (Ar*C*H), 137.23 and 138.36 (Ar*C*), 169.52, 170.53 and 170.23 (*C*O); *m*/*z* (CI, NH_3) 480 (MH$^+$, 30%), 424 (100); HRMS 480.2385. $C_{28}H_{33}NO_6$ (MH$^+$) requires 480.2386.

(2*R*,5*S*,6*S*,7*R*)- and (2*R*,5*S*,6*S*,7*S*)-6-*tert*-Butoxycarbonylmethyl-7-ethoxycarbonyl-3-oxa-8-oxo-2-phenyl-7-*p*-trifluoromethylphenyl-1-azabicyclo[3.3.0]octanes 5e and 6e

According to Method 4, lactam **4a** (106 mg, 0.27 mmol) was reacted with *p*-trifluoromethylphenyllead triacetate[21] (151 mg, 0.36 mmol) to yield two separate diastereomers **5e**, **6e** in a 2.3:1 ratio (104 mg, 72%).

Data for 5e. Yellow oil; 72 mg, 50%; R_f 0.39 (petrol–EtOAc, 3:1); ν_{max}(film)/cm^{-1} 3019 (br, m), 2930 (m), 1721 (br, s), 1515 (w); δ_H (400 MHz, $CDCl_3$) 1.31 (3H, t, *J* 7.1, CH_2CH_3), 1.41 (9H, s, $C(CH_3)_3$), 1.64 (1H, dd, J_1 16.4, J_2 10.7, $CHCO_2{}^tBu$), 2.39 (1H, dd, J_1 16.4, J_2 4.0, $CHCO_2{}^tBu$), 3.63–3.74 (2H, m, H-4_{endo} and H-6), 3.97–4.01 (1H, m, H-5), 4.35 (2H, q, *J* 7.1, CH_2CH_3), 4.42–4.46 (1H, m, H-4_{exo}), 6.42 (1H, s, H-2), 7.26 (2H, d, *J* 7.2, Ar*H*), 7.38–7.47 (3H, m, Ar*H*), 7.56 (2H, m, Ar*H*), 7.61 (2H, d, *J* 7.2, Ar*H*); δ_C (100.7 MHz, $CDCl_3$) 13.98 (CH_2CH_3), 27.96 ($C(CH_3)_3$), 35.80 ($CH_2CO_2{}^tBu$), 44.32 (C-6), 61.35 (C-5), 62.72 (CH_2CH_3), 69.66 (C-7), 72.56 (C-4), 81.58 ($C(CH_3)_3$), 87.03 (C-2), 125.72, 125.75, 126.02, 128.51, 128.64, 128.67 and 128.99 (Ar*C*H), 138.09 and 138.10 (Ar*C*), 169.21, 170.12 and 170.43 (*C*O); *m*/*z* (CI, NH_3) 534 (MH$^+$, 12%), 478 (100); HRMS 534.2097. $C_{28}H_{33}NO_6$ (M + H$^+$) requires 534.2103.

Data for 6e. Colourless oil; 22%; R_f 0.49 (petrol–EtOAc, 3:1); ν_{max}(film)/cm^{-1} 3019 (br), 2930 (m), 1721 (br, s), 1515 (w); δ_H (400 MHz, C_6D_6) 0.69 (3H, t, *J* 7.1, CH_2CH_2), 1.24 (9H, s, $C(CH_3)_3$), 2.69–2.81, (2H, m, $CH_2CO_2{}^tBu$), 2.98–3.02 (1H, m, H-6), 3.73 (2H, q, *J* 7.1, CH_2CH_3), 3.83–3.86 (1H, m, H-4_{endo}), 3.89–3.93 (1H, m, H-5), 4.28–4.31 (1H, m, H-4_{exo}), 6.48 (1H, s, H-2), 7.14–7.18 (3H, m, Ar*H*), 7.29 (2H, d, *J* 8.4, Ar*H*), 7.40 (2H, d, *J* 7.2, Ar*H*), 7.61 (2H, d, *J* 7.4, Ar*H*); δ_C (101 MHz, $CDCl_3$) 14.0 (CH_2CH_3), 28.1 ($C(CH_3)_3$), 34.8 ($CH_2CO_2{}^tBu$), 47.2 (C-6), 62.0 (CH_2CH_3), 62.6 (C-5), 68.3 (C-7), 72.3 (C-4), 81.8 (*C*(CH_3)$_3$), 86.2 (C-2), 125.0, 125.9, 126.0, 128.3 and 128.9 (Ar*C*H), 136.1, 137.8 and 139.1 (Ar*C*), 168.6, 169.7 and 170.3 (*C*O); *m*/*z* (CI, NH_3) 534 (MH^+, 12%), 478 (100); HRMS 534.2097. $C_{28}H_{33}NO_6$ (M + H^+) requires 534.2103.

(2*R*,5*S*,6*S*,7*R*)- and (2*R*,5*S*,6*S*,7*S*)-7-*p*-Bromophenyl-6-*tert*-butoxycarbonylmethyl-7-ethoxycarbonyl-3-oxa-8-oxo-2-phenyl-1-azabicyclo[3.3.0]octanes 5f and 6f

According to Method 2, lactam **4a** (33 mg, 0.08 mmol) was reacted with *p*-bromophenyllead(IV) triacetate (92 mg, 0.17 mmol) in pyridine (34 mg, 0.42 mmol) and $CHCl_3$ (2 ml) at reflux for 41 h giving, after work-up, a yellow oil containing solid material. The crude product ratio **5f**:**6f** was 2.3:1. Purification by column chromatography (Et_2O–petrol (40–60), 1:2) gave the inseparable products **5f**:**6f** (34 mg, 74%).

Data for 5f. R_f 0.29; ν_{max}(film)/cm^{-1} 2979 (w), 1721 (s), 1492 (w), 1368 (m), 1243 (m), 1153 (m), 1079 (w), 1028 (w), 1012 (w), 757 (w), 741 (w), 699 (w); δ_H (300 MHz, $CDCl_3$) 1.31 (3H, t, *J* 7.0, C*H*$_3$CH$_2$), 1.41 (9H, s, C(C*H*$_3$)$_3$), 1.67 (1H, dd, *J* 16.5 and 11.0, C*H*HCO$_2$^{t}Bu), 2.38 (1H, dd, 16.5 and 4.0, CH*H*CO$_2$^{t}Bu), 3.56–3.72 (2H, m, H-5 and H-6), 3.97 (1H, dd, *J* 9.0 and 7.5, H-4$_{endo}$), 4.34 (2H, q, *J* 7.0, CH$_3$C*H*$_2$), 4.43 (1H, dd, *J* 9.0 and 6.0, H-4$_{exo}$), 6.41 (1H, s, H-2), 6.98–7.02 (2H, m, Ar*H*), 7.36–7.50 (5H, m, Ar*H*), 7.54–7.57 (2H, m, Ar*H*); δ_C (50.3 MHz, $CDCl_3$) 14.0 (*C*H$_3$CH$_2$), 28.0 (C(*C*H$_3$)$_3$, 35.8 (*C*H$_2$CO$_2$^{t}Bu), 44.3 (C-6), 61.3 (C-5), 62.5 (CH$_3$*C*H$_2$), 69.3 (C-7), 72.5 (C-4), 81.4 (*C*(CH$_3$)$_3$), 87.0 (C-2), 122.2 (Ar*C*), 126.0, 128.6, 128.9, 129.8, 131.9 (Ar*C*H), 133.1 (Ar*C*), 138 (Ar*C*), 169.4, 170.3 and 170.5 (3 × *C*O); *m*/*z* (APCI$^+$) 546 (M(^{81}Br) + H^+, 12%), 544 (M(^{79}Br) + H^+, 8), 490 (100); HRMS (CI$^+$) 544.1335, $C_{27}H_{31}{}^{79}BrNO_6$ requires 544.1335.

Data for 6f. R_f 0.40; δ_H (300 MHz, $CDCl_3$) 1.25 (3H, t, *J* 7.0, C*H*$_3$CH$_2$), 1.45 (9H, s, C(C*H*$_3$)$_3$), 2.63–2.73 (2H, m, C*H*$_2$CO$_2$-^{t}Bu), 3.02–3.09 (1H, m, H-6), 3.89 (1H, dd, *J* 9.0 and 7.0 H-4$_{endo}$), 4.08–4.15 (1H, m, H-5), 4.21–4.38 (3H, m, H-4$_{exo}$ and CH$_3$C*H*$_2$), 6.35 (1H, s, H-2), 7.28–7.57 (9H, m, Ar*H*); other data as for **5f** above.

(2*R*,5*S*,6*S*,7*R*)- and (2*R*,5*S*,6*S*,7*S*)-6-*tert*-Butoxycarbonylmethyl-7-ethoxycarbonyl-7-*p*-methoxyphenyl-3-oxa-8-oxo-2-phenyl-1-azabicyclo[3.3.0]octanes 5g and 6g

According to Method 3, lactam **4a** (57 mg, 0.15 mmol) was reacted with *p*-methoxyphenyllead(IV) triacetate (0.20 g, 0.40 mmol) to give a yellow/brown oil (73 mg) which was purified using flash column chromatography (Et_2O–cyclohexane, 1:2) to give the inseparable products **5g**:**6g** in the ratio 2.3:1 as a colourless glass (45 mg, 38%); R_f 0.18 (Et_2O–petrol (40–60).

Data for 5g. δ_H (300 MHz, $CDCl_3$) 1.41 (9H, s, C(C*H*$_3$)$_3$), 1.68 (1H, dd, *J* 16.5 and 11.0, C*H*HCO$_2$^{t}Bu), 2.41 (1H, dd, *J* 16.5 and 4.0, CH*H*CO$_2$^{t}Bu), 3.79 (3H, s, OC*H*$_3$), 6.41 (1H, s, H-2), 6.84–6.87 (2H, m, Ar*H*), 7.02–7.05 (2H, m, Ar*H*); *m*/*z* (APCI$^+$) 496 (M + H^+, 79%) 440 (100).

Data for 6g. δ_H (300 MHz, $CDCl_3$) 1.41 (9H, s, C(C*H*$_3$)$_3$), 2.68–2.71 (2H, m, C*H*$_2$CO$_2$^{t}Bu), 3.82 (3H, s, OC*H*$_3$), 6.41 (1H, s, H-2), 7.02–7.05 (2H, m, Ar*H*), 6.93–6.96 (2H, m, Ar*H*); *m*/*z* data as above for **5g**.

(2*R*,5*S*,6*S*,7*S*)- and (2*R*,5*S*,6*S*,7*R*)-7-Benzyl-6-*tert*-butoxycarbonylmethyl-7-ethoxycarbonyl-3-oxa-8-oxo-2-phenyl-1-azabicyclo[3.3.0]octanes 5h and 6h

To a stirred suspension of pre-washed NaH (32 mg, 1.4 mmol) in THF in a nitrogen atmosphere (3 ml) was added a solution of the lactam **4a** (0.50 g, 1.3 mmol) in THF (6 ml) at 0 °C. Benzyl bromide (0.24 g, 1.4 mmol) was then added to the solution which was then heated at reflux for 14 h; the reaction was quenched by adding NH_4Cl (sat. aq.) (2 ml) and then water (5 ml) to dissolve the white precipitate. The mixture was extracted with DCM (3 × 10 ml), dried ($MgSO_4$) and evaporated *in vacuo* to give a colourless oil which was purified using flash column chromatography (EtOAc–cyclohexane, 5:1) to give the products as single diastereomers as colourless oils in a total yield of 75%.

Data for 5h. 0.21 g, 34%; R_f 0.19 (EtOAc–cyclohexane, 5:1); $[\alpha]_D^{23}$ +66.6 (*c* 0.35 in $CHCl_3$); ν_{max}(film)/cm^{-1} 2980 (w), 1727 (s), 1368 (m), 1221 (m), 1156 (m), 700 (m); δ_H (300 MHz, $CDCl_3$) 1.34 (3H, t, *J* 7.0, C*H*$_3$CH$_2$), 1.47 (1H, s, C(C*H*$_3$)$_3$), 2.58–2.70 (2H, m, C*H*$_2$CO$_2$^{t}Bu), 2.98 (1H, d, *J* 14.0, C*H*HPh), 3.19–3.27 (1H, m, H-6), 3.32–3.39 (1H, m, H-5), 3.49 (1H, d, *J* 14.0, CH*H*Ph), 3.78 (1H, dd, *J* 9.0 and 7.5, H-4$_{endo}$), 4.23 (1H, dd, *J* 9.0 and 6.0, H-4$_{exo}$), 4.25–4.34 (2H, m, CH$_3$C*H*$_2$), 6.29 (1H, s, H-2), 7.05–7.36 (10H, m, Ar*H*); δ_C (50.3 MHz, $CDCl_3$) 14.1 (*C*H$_3$CH$_2$), 28.0 (C(*C*H$_3$)$_3$), 33.8 and 35.7 (*C*H$_2$CO$_2$^{t}Bu and *C*H$_2$Ph), 45.4 (C-6), 61.8 (C-5), 62.1 (*C*H$_2$CH$_3$), 64.8 (C-7), 72.5 (C-4), 81.6 (*C*(CH$_3$)$_3$), 86.5 (C-2), 126.3, 127.0, 128.2, 128.3, 128.7 and 130.5 (Ar*C*H), 135.5 (ArC), 137.8 (ArC), 170.6, 171.9 (3 × *C*O); *m*/*z* (APCI$^+$) 480 (M + H^+, 58%); HRMS (CI$^+$) 480.2386, $C_{28}H_{34}NO_6$ (M + H^+) requires 480.2386.

Data for 6h. 0.25 g, 41%; R_f 0.29 (EtOAc–cyclohexane, 5:1); $[\alpha]_D^{26}$ +146.3 (*c* 0.23 in $CHCl_3$); ν_{max}(film)/cm^{-1} 2980 (w), 1728 (s), 1710 (s), 1368 (m), 1226 (m), 1155 (m), 701 (m); δ_H (300 MHz, $CDCl_3$) 1.30 (3H, t, *J* 7.0, C*H*$_3$CH$_2$), 1.41 (9H, s, C(C*H*$_3$)$_3$), 2.26–2.42 (2H, m, C*H*$_2$CO$_2$^{t}Bu), 2.55–2.62 (1H, m, H-6), 3.12 (1H, t, *J* 8.5, H-4$_{endo}$), 3.20 (1H, d, *J* 14.0, C*H*HPh), 3.47 (1H, d, *J* 14.0, CH*H*Ph), 3.90–3.97 (1H, m, H-5), 4.16 (1H, dd, *J* 8.5 and 6.0, H-4$_{exo}$), 4.21–4.31 (2H, m, CH$_3$C*H*$_2$), 6.17 (1H, s, H-2), 7.26–7.45 (10H, m, Ar*H*); δ_C (50.3 MHz, $CDCl_3$) 14.1 (*C*H$_3$CH$_2$), 28.0 (C(*C*H$_3$)$_3$), 35.13 and 36.47 (*C*H$_2$CO$_2$^{t}Bu and *C*H$_2$Ph), 41.2 (C-6), 62.0 (CH$_3$*C*H$_2$), 62.8 (C-5), 65.4 (C-7), 72.4 (C-4), 81.4 (C–CH$_3$)$_3$), 86.2 (C-2), 126.00, 127.2, 128.4, 128.6, 128.7 and 130.8 (Ar*C*H), 136.0 (ArC), 138.1 (ArC), 169.7, 170.6 and 171.0 (3 × *C*O); *m*/*z* (APCI$^+$) 480 (M + H^+, 16%), 424 (100); HRMS (CI$^+$) 480.2386, $C_{28}H_{34}NO_6$ (M + H^+) requires 480.2386.

N-Benzylvalerolactam 8a [22,23]

To a stirred solution of δ-valerolactam (1.95 g, 20 mmol) in dry THF (27 ml) at 0 °C was added pre-washed sodium hydride (0.57 g, 24 mmol). After stirring for 30 mins, benzyl bromide (3.7 g, 22 mmol) was added and stirring was continued at rt for 2 h and then heated under reflux for 19 h. After cooling to rt, the reaction was quenched with sat. NH_4Cl (10 ml) and the aqueous phase washed with EtOAc (3 × 15 ml). The organic layers were combined, washed with water (15 ml), dried ($MgSO_4$) and the solvent removed *in vacuo* to yield a yellow oil. The oil was purified by flash column chromatography (petrol–EtOAc, 2:1) to give the title compound (1.6 g, 85%). R_f 0.11 (petrol–EtOAc, 2:1); ν_{max} (film)/cm^{-1} 3028 (w), 2945 (m), 2965 (m), 1650 (s); δ_H (200 MHz, $CDCl_3$) 1.78–1.81 (4H, m, 2 × H-4 and 2 × H-5), 2.48 (2H, t, *J* 6.5, 2 × H-3), 3.20 (2H, t, *J* 6.0, 2 × H-6), 4.61 (2H, s, C*H*$_2$Ph), 7.25–7.35 (5H, m, Ar*H*); *m*/*z* (CI, NH_3) 190 (MH^+, 100%).

N-Benzyl-3-chlorovalerolactam 8b and *N*-benzyl-3,3-dichlorovalerolactam

To a stirred solution of lactam **8b** (1.3 g, 7.0 mmol) in dry THF (10 ml) at −78 °C under an inert atmosphere, was added *sec*-butyllithium (0.91 M in hexanes, 8.5 ml, 7.7 mmol) and the reaction mixture was stirred for 30 mins. Toluene-*p*-sulfonyl chloride (2.0 g, 11 mmol) in dry THF (5 ml) was added and the reaction mixture slowly warmed to rt. After 16 h the resulting suspension was quenched with sat. NH_4Cl (20 ml) and the aqueous layer was washed with EtOAc (3 × 10 ml). The organic layers were combined, washed with water (15 ml), dried ($MgSO_4$), and the solvent removed *in vacuo* to yield a yellow oil. Purification by flash column chromatography (petrol–EtOAc, 3 : 2) afforded both the mono-substituted product **8b** as a yellow solid (1.11 g, 71%) and the dichloro product as an orange solid (0.075 g, 4%).

Data for 8b. R_f 0.28 (petrol–EtOAc, 2 : 1); mp 72–73 °C; ν_{max}($CHCl_3$)/cm^{-1} 3012 (m), 2963 (m), 1649 (s), 1494 (m); δ_H (500 MHz, $CDCl_3$) 1.79 (1H, m, H-5), 2.22 (3H, m, 2 × H-4 and H-5), 3.25 (2H, m, 2 × H-6), 4.46 (1H, d, *J* 14.6, C*H*HPh), 4.52 (1H, t, *J* 4.5, C*H*Cl), 4.73 (1H, d, *J* 14.6, CH*H*Ph), 7.25–7.36 (5H, m, Ar*H*); δ_C (125.8 MHz, $CDCl_3$) 18.41 (C-5), 30.95 (C-4), 46.89 (C-6), 50.46 (CH_2Ph), 54.97 (C-3), 127.55, 127.97 and 128.62 (Ar*C*H), 136.38, (Ar*C*), 166.02 (C-2); *m*/*z* (CI, NH_3) 226 (MH^+, ^{37}Cl, 12%), 224 (MH^+, ^{35}Cl, 39), 190 (100); HRMS 224.0842. $C_{12}H_{15}NOCl$ (M + H^+) requires 224.0842.

Dichlorovalerolactam. R_f 0.47 (petrol–EtOAc, 2 : 1); mp 70–73 °C; ν_{max} ($CHCl_3$)/cm^{-1} 2969 (m), 1678 (s); δ_H (500 MHz, $CDCl_3$) 2.01–2.07 (2H, m, 2 × H-5), 2.77–2.80 (2H, m, 2 × H-4), 3.30 (2H, t, *J* 6.2, 2 × H-6), 4.60 (2H, s, CH_2Ph), 7.25–7.36 (5H, m, Ar*H*); δ_C (125.8 MHz, $CDCl_3$) 19.93 (C-5), 43.56 (C-4), 47.13 (C-6), 51.30 (CH_2Ph), 82.92 (C-3), 127.73, 127.93 and 128.71 (Ar*C*H), 135.84 (Ar*C*), 163.68 (C-2); *m*/*z* (CI, NH_3) 262 (M + H^+, 12%), 260 (69), 258 (100), 224 (35), 190 (100).

N-Benzyl-3-iodovalerolactam 8c

A solution of lactam **8b** (388 mg, 1.2 mmol) and sodium iodide (32 mg, 2.2 mmol) in acetone (10 ml) were heated under reflux for 17 h. After cooling to rt, the resulting precipitate was removed by filtration and the filtrate concentrated *in vacuo*. The concentrate was dissolved in EtOAc (10 ml), washed with water (10 ml), dried ($MgSO_4$) and the solvent removed *in vacuo*. Purification by flash column chromatography (petrol–EtOAc, 1 : 1) afforded the title compound **8c** as a yellow oil (510 mg, 90%). R_f 0.40 (petrol–EtOAc, 1 : 1); ν_{max}($CHCl_3$)/cm^{-1} 3007 (m), 1636 (s); δ_H (200 MHz, $CDCl_3$) 1.78–1.85 (1H, m, H-5), 2.01–2.10 (1H, m, H-5), 2.18–2.29 (2H, m, 2 × H-4), 3.35–3.42 (2H, m, 2 × H-6), 4.42 (1H, d, *J* 14.5, C*H*HPh), 4.82, (1H, d, *J* 14.5, CH*H*Ph), 4.92–4.95 (1H, m, C*H*Cl), 7.26–7.37 (5H, m, Ar*H*); δ_C (125.8 MHz, $CDCl_3$) 20.53 (C-5), 23.17 (C(3)), 32.49 (C-4), 46.85 (C-6), 50.52 (CH_2Ph), 127.52, 128.00 and 128.66 (Ar*C*H), 136.65 (Ar*C*), 167.84 (C-2); *m*/*z* (CI, NH_3) 316 (MH^+, 42%), 190 (100); HRMS 316.0198, $C_{12}H_{15}NOI$ (M + H^+) requires 316.1476.

(2*R*,5*S*,6*S*,7*R*)- and (2*R*,5*S*,6*S*,7*S*)-7-(*N*-Benzyl-2-oxopiperidin-3-yl)-6-*tert*-butoxycarbonylmethyl-7-ethoxycarbonyl-3-oxa-8-oxo-2-phenyl-1-azabicyclo[3.3.0]octanes 9a and 9b

Lactam **4a** (195 mg, 0.50 mmol) in dry THF (2 ml) was reacted with sodium hydride (17 mg, 0.70 mmol) and subsequently with a solution of iodolactam **8c** (150 mg, 0.48 mmol) in dry THF (2 ml). Purification by flash column chromatography (petrol–EtOAc, 3 : 2), gave the two separable diastereomers **9a** and **9b** in a 1.1 : 1 ratio and as pale yellow oils (102 mg, 36%).

Data for 9a. 54 mg, 19%; R_f 0.64 (petrol–EtOAc, 1 : 1); ν_{max}($CHCl_3$)/cm^{-1} 3020 (m), 1718 (s), 1637 (s); δ_H (400 MHz, $CDCl_3$) 1.27 (3H, t, *J* 7.2, CH_2CH_2), 1.44 (9H, s, C(CH_3)$_3$), 1.69–1.96, (4H, m, 2 × CH_2), 2.06–2.09 (1H, m, ring proton), 2.88–2.92 (1H, m, ring proton), 3.18–3.27 (3H, m, H-6 and CH_2), 3.44–3.48 (1H, m, ring proton), 3.86–3.92 (1H, m, H-4_{endo}), 4.06–4.15 (1H, m, H-5), 4.21–4.31 (3H, m, H-4_{exo} and CH_2CH_3), 4.53 (1H, d, *J* 14.8, C*H*HPh), 4.58 (1H, d, *J* 14.8, CH*H*Ph), 6.27 (1H, s, H-2), 7.16–7.47 (10H, m, Ar*H*); δ_C (100.7 MHz, $CDCl_3$) 13.96 (CH_2CH_3), 22.69 (CH_2), 22.99 (CH_2), 28.09 (C(CH_3)$_3$), 35.11 (CH_2), 42.00 (C-6), 45.02 (CH_2), 48.82 (CH_2), 50.29 (CH_2Ph), 61.47 (CH_2CH_3), 62.81 (C-5), 65.60 (C-7), 72.47 (C-4), 80.77 (*C*(CH_3)$_3$), 86.68 (C-2), 126.11, 127.30, 127.40, 127.85, 128.14, 128.40 and 128.50 (Ar*C*H), 136.87, 137.01 and 138.06 (Ar*C*), 168.99, 170.03, 171.72 and 172.17 (*C*O); *m*/*z* (CI, NH_3) 577 (MH^+, 100%), 521 (8); HRMS 577.2907. $C_{33}H_{41}N_2O_7$ (MH^+) requires 577.2914.

Data for 9b. 48 mg, 17%; R_f 0.54 (petrol–EtOAc, 1 : 1); ν_{max}($CHCl_3$)/cm^{-1} 3020 (m), 1718 (s), 1637 (s); δ_H (400 MHz, $CDCl_3$) 1.32 (3H, t, *J* 7.1, CH_2CH_3), 1.46 (9H, s, C(CH_3)$_3$), 1.50–1.56, (1H, m, ring proton), 1.82–1.96 (2H, m, CH_2), 2.21–2.29 (1H, m, ring proton), 2.53 (2H, d, *J* 5.4, CH_2), 2.84–2.89 (1H, m, H-6), 3.16–3.22 (2H, m, CH_2), 3.36 (1H, dd, *J* 12.8 and 5.1, ring proton), 3.89–3.91 (2H, m, H-4_{endo} and H-5), 4.26–4.37 (3H, m, H-4_{exo} and CH_2CH_3), 4.60 (1H, d, *J* 14.8, C*H*HPh), 4.63 (1H, d, *J* 14.8, CH*H*Ph), 6.37 (1H, s, H-2), 7.25–7.50 (10H, m, Ar*H*); δ_C (100.7 MHz, $CDCl_3$) 14.12 (CH_2CH_3), 22.63 (CH_2), 23.41 (CH_2), 28.02 (C(CH_3)$_3$), 36.44 (CH_2), 41.77 (C-6), 44.83 (CH_2), 46.06 (CH_2), 50.52 (CH_2Ph), 61.74 (CH_2CH_3), 63.14 (C-5), 65.56 (C-7), 71.78 (C-4), 81.44 (*C*(CH_3)$_3$), 87.08 (C-2), 126.02, 126.26, 127.18, 127.51, 128.00, 128.04, 128.31 and 128.65 (Ar*C*H), 137.15 and 138.36 (Ar*C*), 167.85, 169.78, 171.01 and 171.78 (*C*O); *m*/*z* (CI, NH_3) 577 (MH^+, 100%), 521 (8); HRMS 577.2907, $C_{33}H_{41}N_2O_7$ (MH^+) requires 577.2914.

General method for deprotection

To a solution of the *N*,*O*-acetal in DCM at rt was added TFA. After the specified time period, the acid was neutralised by careful addition of saturated aqueous sodium hydrogen carbonate solution or an aqueous solution of sodium hydroxide with stirring in an ice bath. After separation of the two layers, and extraction of the aqueous with DCM, the organics were dried ($MgSO_4$) and evaporated *in vacuo* to give the crude product which was purified using flash column chromatography.

(2*S*,3*S*,4*R*)- and (2*S*,3*S*,4*S*)-3-*tert*-Butoxycarbonylmethyl-4-ethoxycarbonyl-2-hydroxymethyl-5-oxo-4-phenylpyrrolidines 10a and 11a

Following the general method, the lactam **5a**, **6a** (2.1 : 1) (0.17 g, 0.35 mmol), was reacted with TFA (1.5 ml) in DCM (10 ml) for 45 min. Purification using flash column chromatography (EtOAc–petrol (40–60), 1 : 1 and then EtOAc–petrol (40–60)–MeOH, 200 : 200 : 15) gave the title compound as two diastereomers in a combined yield of 81%.

Data for 10a. White crystalline solid (70 mg, 53%); R_f 0.24 (EtOAc–petrol (40–60)–MeOH, 20 : 15 : 2); $[\alpha]_D^{22}$ −42.0 (*c* 0.35, $CHCl_3$); mp 138–142 °C; ν_{max}($CHCl_3$)/cm^{-1} 3424 (m), 3248 (m, br), 1720 (s), 1369 (m), 1228 (s), 1154 (s), 1095 (m), 1055 (m), 1037 (m), 946 (w), 701 (m); δ_H (300 MHz, $CDCl_3$, *c* 34.6 mg ml^{-1}) 1.30 (3H, t, *J* 7.0, CH_3CH_2), 1.40 (9H, s, C(CH_3)$_3$), 1.86 (2H, d, *J* 7.5, $CH_2CO_2{}^tBu$), 3.24–3.29 (1H, m, H-3), 3.55 (1H, br s, O*H*), 3.53–3.61 (3H, m, H-2 and C*H*HOH), 3.76 (1H, dd, *J* 11.5 and 3.0, CH*H*OH), 4.24–4.41 (2H, m, CH_3CH_2), 7.19–7.38 (5H, m, Ar*H*), 7.56 (1H, br s, N*H*); δ_C (125.8 MHz, $CDCl_3$) 13.96 (CH_3CH_2), 27.95 (C(CH_3)$_3$), 36.01 ($CH_2CO_2{}^tBu$), 41.07 (C-3), 59.01 (C-2), 62.42 (CH_3CH_2), 63.63 (CH_2OH), 64.85 (C-4), 81.22 (*C*(CH_3)$_3$), 127.83, 128.45 and 128.61 (Ar*C*H), 134.13 (C-6), 170.47, 171.31 and 173.87 (3 × *C*O); *m*/*z* ($APCI^+$) 378 (M + H^+, 14%), 322 (100), 250 (9); HRMS 378.1917, $C_{20}H_{28}NO_6$ requires 378.1917.

Data for 11a. Colourless oil (38 mg, 28%); R_f 0.32 (EtOAc–petrol (40–60)–MeOH, 20 : 15 : 2); $[\alpha]_D^{23}$ −14.1 (*c* 0.425 in $CHCl_3$); ν_{max}(film)/cm^{-1} 3336 (m, br), 2979 (m), 1724 (s), 1368 (m), 1300 (m), 1232 (m), 1153 (s), 1063 (m), 847 (w), 699 (m); δ_H (300 MHz, $CDCl_3$, *c* 9 mg ml^{-1}) 1.28 (3H, t, *J* 7.0, CH_3CH_2), 1.44 (9H, s, C(CH_3)$_3$), 2.53 (1H, dd, *J* 17.0 and 10.0, C*H*H$CO_2{}^tBu$), 2.72 (2H, dd, *J* 17.0 and 2.5, CH*H*$CO_2{}^tBu$ and O*H*), 3.18–3.25 (1H, m, H-3), 3.52 (1H, dd, *J* 12.0 and 5.5, C*H*HOH), 3.67–

3.71 (1H, m, H-2), 3.80 (1H, dd, *J* 12.0 and 3.0, CH*H*OH), 4.22–4.32 (2H, m, CH_3CH_2), 6.41 (1H, br s, N*H*), 7.29–7.41 (3H, m, Ar*H*), 7.44–7.48 (2H, m, Ar*H* *ortho*- to C-6); δ_C (50.3 MHz, $CDCl_3$) 14.1 (CH_3CH_2), 27.9 (C(CH_3)$_3$), 34.6 ($CH_2CO_2{}^tBu$), 42.4 (C-3), 59.9 (C-2), 62.0 (CH_3CH_2), 62.8 (CH_2OH), 63.8 (C-4), 81.8 (*C*(CH_3)$_3$), 127.7, 128.0 and 128.3 (Ar*C*H), 136.3 (C-6), 169.6, 171.8 and 173.1 (3 × *C*O); *m*/*z* (APCI$^+$) 378 (M + H$^+$, 8%), 322 (100).

(2*S*,3*S*,4*R*)- and (2*S*,3*S*,4*S*)-3-*tert*-Butoxycarbonylmethyl-4-ethoxycarbonyl-2-hydroxymethyl-4-*p*-methoxyphenyl-5-oxopyrrolidines 10b and 11b

Following the general method, lactam **5g**, **6g** (31 mg), was reacted with TFA (0.3 ml) in DCM (2 ml) for 45 min. Purification by recrystallisation from EtOAc–petrol (40–60) gave the major diastereomer **10b** as a white solid (4 mg, 25%). Purification of the mother liquor by chromatography (EtOAc–petrol (40–60)–MeOH, 20 : 20 : 2) gave the minor diastereomer **11b** as a colourless oil (2 mg, 13%).

Data for 10b. White crystalline solid; R_f 0.22 (EtOAc–petrol (40–60)–MeOH, 20 : 20 : 2); mp 156–159 °C; $[\alpha]_D^{25}$ −153.3 (*c* 0.015 in $CHCl_3$); ν_{max}($CDCl_3$, *c* 7.5 mg ml^{-1})/cm^{-1} 3425 (m), 3330 (m, br), 2983 (w), 1718 (s), 1613 (w), 1514 (m), 1477 (m), 1370 (m), 1253 (s), 1154 (s); δ_H (300 MHz, $CDCl_3$, *c* 7.3 mg ml^{-1}) 1.30 (3H, t, *J* 7.0, CH_3CH_2), 1.41 (9H, s, C(CH_3)$_3$), 1.85 (2H, dd, *J* 17.0 and 9.0, C*H*H$CO_2{}^tBu$), 1.96 (2H, dd, *J* 17.0 and 6.0, CH*H*$CO_2{}^tBu$), 2.74 (1H, br t, *J* 6.0, O*H*), 3.27–3.33 (1H, m, H-3), 3.51–3.65 (2H, m, H-2 and C*H*HOH), 3.78–3.88 (4H, m, CH*H*OH and OCH_3), 4.26–4.38 (2H, m, CH_3CH_2), 6.83 (1H, br s, N*H*), 6.86–6.91 (2H, m, Ar*H*), 7.12–7.17 (2H, m, Ar*H*); δ_C (125.8 MHz, $CDCl_3$, *c* 7.5 mg ml^{-1}) 13.98 (CH_3CH_2), 27.98 (C(CH_3)$_3$), 36.27 ($CH_2CO_2{}^tBu$), 41.11 (C-3), 55.29 (OCH_3), 58.72 (C-2), 62.42 (CH_3CH_2), 63.89 (C-4), 64.00 (CH_2OH), 81.35 (*C*(CH_3)$_3$), 114.04 (Ar*C*), 126.22 (C-6), 129.57 (Ar*C*), 158.99 (MeO-*C*), 170.63, 171.50 and 173.39 (3 × *C*O); *m*/*z* (APCI$^+$) 408 (M + H$^+$, 25%), 352 (100), 280 (23).

Data for 11b. R_f 0.27 (EtOAc–petrol (40–60)–MeOH, 20 : 20 : 2); $[\alpha]_D^{26}$ −18.0 (*c* 0.05 in $CHCl_3$); ν_{max}(film)/cm^{-1} 3351 (m), 1725 (s), 1712 (s), 1515 (m), 1298 (m), 1254 (s), 1183 (m), 1155 (s), 1068 (m), 1037 (m); δ_H (500 MHz, $CDCl_3$, *c* 2 mg ml^{-1}) 1.29 (3H, t, *J* 7.0, CH_3CH_2), 1.45 (9H, s, C(CH_3)$_3$), 2.52 (1H, dd, *J* 17.0 and 10.0, C*H*H$CO_2{}^tBu$), 2.71 (1H, dd, *J* 17.0 and 2.5, CH*H*$CO_2{}^tBu$), 3.17–3.21 (1H, m, H-3), 3.55 (1H, dd, *J* 12.0 and 5.5, C*H*HOH), 3.66–3.70 (1H, m, H-2), 3.80–3.83 (4H, m, CH*H*OH and OCH_3), 4.23–4.29 (2H, m, CH_3CH_2), 6.06 (1H, br s, N*H*), 6.90–6.93 (2H, m, Ar*H*), 7.38–7.41 (2H, m, Ar*H*); δ_C (125.8 MHz, $CDCl_3$, *c* 2 mg ml^{-1}) 14.15 (CH_3CH_2), 27.98 (C(CH_3)$_3$), 34.47 ($CH_2CO_2{}^tBu$), 42.46 (C-3), 55.26 (OCH_3), 59.57 (C-2), 62.03 (CH_3CH_2), 62.93 (C-4 and CH_2OH), 81.98 (C(CH_3)$_3$), 113.80 (Ar*C* *meta*- to C-6), 128.26 (C-6), 129.13 (Ar*C*), 159.06 (MeO*C*), 169.86, 172.21 and 172.87 (3 × *C*O); *m*/*z* (APCI$^+$) 408 (M + H$^+$, 23%), 352 (100).

(2*S*,3*S*,4*S*)-4-Benzyl-3-*tert*-butoxycarbonylmethyl-4-ethoxycarbonyl-2-hydroxymethyl-5-oxopyrrolidine 10c

Following the general method, the lactam **5h** (85 mg, 0.22 mmol), was reacted with TFA (0.5 ml) in DCM (10 ml) for 1 h. Purification using flash column chromatography (EtOAc–petrol (40–60), 1 : 1 then EtOAc–petrol (40–60)–MeOH, 20 : 15 : 1) gave the title compound as a colourless oil, as a single diastereomer (60 mg, 86%); R_f 0.20 (EtOAc–petrol (40–60)–MeOH, 20 : 15 : 1); $[\alpha]_D^{23}$ +13.91 (*c* 0.115 in $CHCl_3$); ν_{max}($CDCl_3$, *c* 9 mg ml^{-1})/cm^{-1} 3424 (m), 3245 (m, br), 1719 (s), 1370 (m), 1251 (m), 1155 (s), 1098 (s), 1040 (m); δ_H (300 MHz, $CDCl_3$, *c* 9 mg ml^{-1}) 1.29 (3H, t, *J* 7.0, CH_3CH_2), 1.48 (9H, s, C(CH_3)$_3$), 2.42 (1H, dd, *J* 16.5 and 7.5, C*H*H$CO_2{}^tBu$), 2.59 (1H, br t, O*H*), 2.70–2.76 (1H, m, H-3), 2.76 (1H, dd, *J* 16.5 and 7.0, CH*H*$CO_2{}^tBu$), 3.06 (1H, d, *J* 14.5, C*H*HPh), 3.24 (1H, dd, *J* 16.0 and 7.5, H-2), 3.40–3.47 (1H, m, C*H*HOH), 3.45 (1H, d, *J* 14.5, CH*H*Ph), 3.60–3.69 (1H, m, CH*H*OH), 4.20–4.31 (2H, m, CH_3CH_2), 6.43 (1H, s, N*H*), 7.23–7.34 (5H, m, Ar*H*); δ_C (50.3 MHz, $CDCl_3$, *c* 64 mg ml^{-1}) 13.9 (CH_3CH_2), 28.0 (C(CH_3)$_3$), 33.4 and 35.2 ($CH_2CO_2{}^tBu$ and CH_2Ph), 41.3 (C-3), 59.3 (C-2), 59.8 (C-4), 61.9 (CH_3CH_2), 63.1 (CH_2OH), 81.5 (*C*(CH_3)$_3$), 127.0, 128.3 and 130.2 (Ar*C*H), 135.9 (C-7), 170.9, 171.6 and 175.3 (3 × *C*O); *m*/*z* (APCI$^+$) 392 (M + H$^+$, 6%), 336 (100); HRMS 392.2073, $C_{21}H_{30}NO_6$ requires 392.2073.

(2*S*,3*S*,4*R*)-4-Benzyl-3-*tert*-butoxycarbonylmethyl-4-ethoxycarbonyl-2-hydroxymethyl-5-oxopyrrolidine 11c

Following the general method, the lactam **6h** (0.11 g, 0.23 mmol), was reacted with TFA (0.65 ml) in DCM (13 ml) for 1 h. Purification using flash column chromatography (EtOAc–petrol (40–60)–MeOH, 20 : 15 : 1) gave the title compound as a colourless crystalline solid, as a single diastereomer (70 mg, 77%); R_f 0.27 (EtOAc–petrol (40–60)–MeOH, 20 : 15 : 1); mp 110–111 °C; $[\alpha]_D^{24}$ +58.3 (*c* 0.12 in $CHCl_3$); ν_{max}($CDCl_3$, *c* 10 mg ml^{-1})/cm^{-1} 3424 (m), 3333 (m, br), 1710 (s), 1369 (m), 1300 (m), 1198 (m), 1153 (s); δ_H (300 MHz, $CDCl_3$, *c* 10 mg ml^{-1}) 1.33 (3H, t, *J* 7.0, CH_3CH_2), 1.46 (9H, s, C(CH_3)$_3$), 2.11 (1H, t, *J* 6.0, O*H*), 2.29 (1H, dd, *J* 16.5 and 8.5, C*H*H$CO_2{}^tBu$), 2.38 (1H, dd, *J* 16.5 and 5.0, CH*H*$CO_2{}^tBu$), 2.60–2.67 (1H, m, H-3), 2.98–3.06 (1H, m, H-2), 3.15 (1H, d, *J* 14.0, C*H*HPh), 3.40 (1H, d, *J* 14.0, CH*H*Ph), 3.47–3.54 (2H, m, CH_2OH), 4.18–4.36 (2H, m, CH_3CH_2), 6.20 (1H, br s, N*H*), 7.21–7.31 (5H, m, ArC*H*); δ_C (50.3 MHz, $CDCl_3$, *c* 98 mg ml^{-1}) 14.2 (CH_3CH_2), 27.9 (C(CH_3)$_3$), 35.5 and 36.5 ($CH_2CO_2{}^tBu$ and CH_2Ph), 37.3 (C-3), 60.2 (C-2), 60.7 (C-4), 61.8 (CH_3CH_2), 63.9 (CH_2OH), 81.5 (*C*(CH_3)$_3$), 126.9, 128.3 and 130.9 (Ar*C*H), 135.9 (C-7), 170.1, 170.0 and 174.3 (3 × *C*O); *m*/*z* (APCI$^+$) 392 (M + H$^+$, 21%), 336 (100); HRMS 392.2073, $C_{21}H_{30}NO_6$ (M + H$^+$) requires 392.2073.

(2*S*,3*S*,4*R*)- and (2*S*,3*S*,4*S*)-3-*tert*-Butoxycarbonylmethyl-2-hydroxymethyl-5-oxo-4-phenylpyrrolidines 12 and 13

To a solution of **10a** (69 mg, 0.18 mmol) in EtOH (5 ml) at rt was added NaOH (1M, aq., 1.1 ml, 1.1 mmol) with stirring. After 5 h, water (15 ml) was added and the solution extracted with EtOAc (5 × 15 ml). Drying ($MgSO_4$) and evaporation *in vacuo* gave the title compound as a white solid (17 mg, 30%). Acidification of the aqueous layer with HCl (1 M, aq.) then extraction with EtOAc, drying ($MgSO_4$) and evaporation *in vacuo* gave a colourless gum (42 mg), which was a mixture of the title compounds and the acid **14**. The combined material was heated *in vacuo* (0.8 mbar) at 135 °C for 30 min to give the title compounds as a white solid consisting of a 1 : 1 mixture of **12** and **13** (46 mg, 82%). R_f 0.28 (EtOAc–petrol (40–60)–MeOH, 20 : 15 : 2); ν_{max}($CHCl_3$)/cm^{-1} 3424 (m), 3312 (m, br), 1698 (s), 1369 (m), 1152 (s), 1090 (m);

Data for 12. δ_H (500 MHz, $CDCl_3$, *c* 2 mg ml^{-1}) 1.38 (9H, s, C(CH_3)$_3$), 1.87 (1H, dd, *J* 17.0 and 7.5, C*H*H$CO_2{}^tBu$), 1.96 (1H, br s, O*H*), 2.10 (1H, dd, *J* 17.0 and 8.0, CH*H*$CO_2{}^tBu$), 2.84–2.90 (1H, m, H-3), 3.50–3.53 (1H, m, H-2), 3.55–3.61 (1H, m, C*H*HOH), 3.79 (1H, dd, *J* 11.0 and 3.5, CH*H*OH), 3.98 (1H, d, *J* 9.5, H-4), 6.68 (1H, s, N*H*), 7.13–7.15 (2H, m, Ar*H*), 7.24–7.38 (3H, m, Ar*H*); δ_C (125.8 MHz, $CDCl_3$, *c* 30 mg ml^{-1}) 27.85 (C(CH_3)$_3$), 35.27 ($CH_2CO_2{}^tBu$), 37.47 (C-3), 51.60 (C-4), 60.29 (C-2), 64.07 (CH_2OH), 80.80 (*C*(CH_3)$_3$), 127.41, 128.71, 128.78 and 129.26 (Ar*C*H), 135.22 (C-6), 171.16 and 178.74 (2 × *C*O); other data as below for **13**.

Data for 13. δ_H (500 MHz, $CDCl_3$, *c* 2 mg ml^{-1}) 1.38 (9H, s, C(CH_3)$_3$), 1.96 (1H, br s, O*H*), 2.44–2.53 (2H, m, $CH_2CO_2{}^tBu$), 2.58–2.65 (1H, m, H-3), 3.46 (1H, d, *J* 10.0, H-4), 3.55–3.61 (2H, m, C*H*HOH and H-2), 3.82–3.86 (1H, m, CH*H*OH), 6.48

(1H, s, N*H*), 7.24–7.38 (5H, m, Ar*H*); δ_C (125.8 MHz, $CDCl_3$, *c* 30 mg ml^{-1}) 27.91 (C(CH_3)$_3$), 37.81 ($CH_2CO_2{}^tBu$), 42.01 (C-3), 54.47 (C-4), 59.90 (C-2), 63.72 (CH_2OH), 81.27 (*C*(CH_3)$_3$), 127.41, 128.71, 128.78 and 129.26 (Ar*C*H), 137.84 (C-6), 170.82 and 177.45 (2 × *C*O); *m*/*z* (APCI$^+$) 250 (100%), 306 (M + H$^+$, 10); HRMS 306.1705, $C_{17}H_{24}NO_4$ requires 306.1705.

(2*S*,3*S*,4*R*)- and (2*S*,3*S*,4*S*)-2-Methoxycarbonyl-3-methoxycarbonylmethyl-5-oxo-4-phenylpyrrolidines 15a and 16a

Method 1. To a solution of the phenylated adduct **5a**, **6a** (2:1) (0.874 g, 1.9 mmol) in THF–water–EtOH (3:2:1, 30 ml) was added NaOH (0.45 g, 11 mmol). The biphasic mixture was then stirred at rt for 37.5 h. The mixture was acidified with HCl (2 M, aq.) and then evaporated directly *in vacuo* to give a yellow gum and white solid. This residue was dissolved in TFA–water (7 ml–2 ml) and stirred at 30 °C for 2 h. Solvent evaporation *in vacuo* gave a cloudy pink oil which was dissolved in NaOH (2 M, aq., 16 ml) and extracted with DCM (2 × 10 ml). The aqueous layer was then acidifed with HCl (2 M, aq., 16 ml) and extracted with EtOAc (3 × 20 ml). Drying ($MgSO_4$) and evaporation *in vacuo* gave a yellow gum. Ths material (0.256 g) was stirred vigorously with ruthenium(IV) oxide hydrate (27 mg, *ca.* 20 mol%) and $NaIO_4$ (0.880 g, 4.1 mmol, *ca.* 4 eq.) in a mixture of CH_3CN–CCl_4–water, 2:2:3 (35 ml) for 14 h. Acidification with HCl (1 M, aq.) and extraction with EtOAc (4 × 15 ml) gave a pale yellow foam. Treatment of this foam with MeOH (10 ml), and H_2SO_4 (conc., 6 drops) under reflux for 16 h gave, after extraction with EtOAc, drying ($MgSO_4$), and evaporation *in vacuo*, a colourless oil which was purified using flash column chromatography (EtOAc–cyclohexane, 2:1) to give the title compounds **15a** and **16a** as two single diastereomers as colourless crystalline solids.

Method 2. To compounds **12** and **13** (1:1 ratio) (29 mg, 0.10 mmol) in DCM (3 ml) was added TFA (1.5 ml) with swirling. The homogeneous solution was left to stand at rt for 1 h and then the solvent was removed *in vacuo* at 40 °C to give a colourless glass. To this material (24 mg, 0.1 mmol) in CCl_4 (2 ml) and CH_3CN (2 ml) was added a solution of $NaIO_4$ (81 mg, 0.38 mmol) in water (3 ml) and then ruthenium(IV) oxide hydrate (2.5 mg). The mixture was stirred vigorously for 3 h, then HCl (2 M, aq., 6 drops) and water (10 ml) were added. Extraction with EtOAc (3 × 15 ml), drying ($MgSO_4$) and evaporation *in vacuo* gave a grey–green glass (42 mg), which was dissolved in MeOH (2 ml) and then H_2SO_4 (conc., 2 drops) added. After heating at reflux for 4.75 h the mixture was cooled to rt, water (5 ml) was added and then the solution was extracted with EtOAc (2 × 15 ml). Drying ($MgSO_4$) and evaporation *in vacuo* gave a yellow oil which was purified using flash column chromatography (EtOAc–petrol (40–60), 2:1) to give the two single title diastereomers **15a** and **16a** as colourless crystalline solids (2 × 9 mg, 65%).

Method 3. To a solution of the diacid **20a**, **b** (4:1 ratio) (32 mg) in MeOH (2 ml) was added H_2SO_4 (conc., 2 drops) and the solution heated at reflux for 48 h. After cooling to rt, water was added and the solution extracted with EtOAc. Drying ($MgSO_4$) and evaporation *in vacuo* gave a pale yellow oil which was purified using flash column chromatography (EtOAc–petrol (40–60), 2:1) to give the product as two diastereomers **15a** (4 mg, 11%), **16a** (25 mg, 70%).

Data for 15a. R_f 0.27 (EtOAc–petrol (40–60), 2:1); $[\alpha]_D^{23}$ +72.6 (*c* 0.135 in $CHCl_3$); mp 147–148 °C; ν_{max}($CHCl_3$)/cm^{-1} 3429 (m), 3235 (m, br), 1718 (s), 1438 (m), 1171 (s), 701 (m); δ_H (500 MHz, $CDCl_3$) 2.07 (1H, dd, *J* 17.0 and 8.5, C*H*HCO_2CH_3), 2.53 (1H, dd, *J* 17.0 and 7.0, CH*H*CO_2CH_3), 3.28–3.34 (1H, m, H-3), 3.60 (3H, s, CO_2CH_3), 3.84 (3H, s, CO_2CH_3), 4.03 (1H, d, *J* 8.9, H-4), 4.10 (1H, d, *J* 6.5, H-2), 6.41 (1H, br s, N*H*), 7.14 (2H, m, Ar*H*), 7.29–7.37 (3H, m, Ar*H*); δ_C (125.8 MHz, $CDCl_3$) 34.07 (CH_2CO_2Me), 40.18 (C-3), 50.45 (C-4), 51.75 and 52.87 (2 × CO_2CH_3), 58.59 (C-2), 127.82, 128.91 and 129.19 (Ar*C*H), 134.19 (C-6), 171.31, 171.76 and 176.65 (3 × *C*O); *m*/*z* 292 (M + H$^+$, 100%); HRMS 292.1193, $C_{15}H_{17}NO_5$ requires 292.1185. HPLC purity: de = 94% (40% EtOH–*n*-heptane, 1 ml min^{-1}, λ = 215 nm, Chiralpak AD column).

Data for 16a. R_f 0.22 (EtOAc–petrol (40–60), 2:1); $[\alpha]_D^{23}$ +4.7 (*c* 0.3 in $CHCl_3$); mp 97–98 °C; ν_{max}($CHCl_3$)/cm^{-1} 3430 (m), 3248 (m, br), 1719 (s), 1438 (m), 1148 (s), 700 (m); δ_H (500 MHz, $CDCl_3$) 2.67–2.76 (2H, m, CH_2CO_2Me), 2.87–2.93 (1H, m, H-3), 3.55 (4H, s and d, *J* 10.0, CO_2CH_3 and H-4), 3.78 (3H, s, CO_2CH_3), 4.21 (1H, d, *J* 8.0, H-2), 6.74 (1H, br s, N*H*), 7.21–7.23 (2H, m, Ar*H ortho*- to C-6), 7.29–7.30 (1H, m, Ar*H*), 7.34–7.37 (2H, m, Ar*H*); δ_C (62.9 MHz, $CDCl_3$) 35.7 (CH_2CO_2Me), 44.9 (C-3), 51.7 (C-4), 52.7 and 53.3 (CO_2CH_3), 58.0 (C-2), 127.7, 128.7 and 128.9 (Ar*C*H), 136.7 (C-6), 171.2 and 175.9 (2 × *C*O); *m*/*z* 292 (M + H$^+$, 100%); HRMS (electrospray) 292.1179, $C_{15}H_{17}NO_5$ requires 292.1185. HPLC purity: de = 100% (40% EtOH–*n*-heptane, 1 ml min^{-1}, λ = 215 nm, Chiralpak AD column).

(2*S*,3*S*,4*R*)- and (2*S*,3*S*,4*S*)-4-Ethoxycarbonyl-3-methoxycarbonylmethyl-2-methoxycarbonyl-5-oxo-4-phenylpyrrolidines 19a, b

Data for 19a. ν_{max}(film)/cm^{-1} 3312 (m), 1732 (s), 1438 (m), 1381 (m), 1219 (s), 1109 (m); δ_H (500 MHz, $CDCl_3$) 1.28 (3H, t, *J* 7.0, CH_3CH_2), 2.48 (1H, dd, *J* 16.0 and 6.5, C*H*HCO_2Me), 2.97 (1H, dd, *J*, 16.0 and 7.0, CH*H*CO_2Me), 3.15–3.19 (1H, m, H-3), 3.31 (3H, s, CO_2CH_3), 3.38 (3H, s, CO_2CH_3), 3.62 (1H, d, *J* 11.0, H-2), 7.03 (1H, br s, N*H*), 7.20–7.22 (2H, m, Ar*H*), 7.28–7.36 (3H, m, Ar*H*); *m*/*z* 364 (M + H$^+$, 100%); HRMS (electrospray) 364.1405, $C_{18}H_{22}NO_7$ requires 364.1396.

Data for 19b. ν_{max}(film)/cm^{-1} 3312 (m, br), 1732 (s), 1438 (m), 1381 (m), 1219 (s), 1109 (m); δ_H (500 MHz, $CDCl_3$) 1.28 (3H, t, *J* 7.0, CH_3CH_2), 2.81–2.89 (2H, m, CH_2CO_2Me), 3.50–3.57 (1H, m, H-3), 3.65 (3H, s, CO_2CH_3), 3.72 (3H, s, CO_2CH_3), 4.25–4.29 (3H, d, *J* 10.0 and q, *J* 7.0, H-2 and CH_3CH_2), 6.26 (1H, br s, N*H*), 7.32–7.40 (3H, m, Ar*H*), 7.44–7.46 (2H, m, Ar*H*); δ_C (50.3 MHz, $CDCl_3$) 14.0 (CH_3CH_2), 33.3 (CH_2CO_2Me), 45.8 (C-3), 52.0 and 52.6 (2 × CO_2CH_3), 59.0 (C-2), 62.3 (CH_3CH_2), 63.5 (C-4), 127.9, 128.1 and 128.3 (Ar*C*H), 135.6 (C-6) 168.9, 170.7, 171.5 and 172.7 (4 × *C*O).

(2*S*,3*S*,4*R*)- and (2*S*,3*S*,4*S*)-2-Carboxy-3-carboxymethyl-5-oxo-4-phenylpyrrolidines 20a, b

To a stirred solution of **16a** (52 mg, 0.18 mmol) in THF–water–MeOH, (3:2:1, 2 ml) was added NaOH (29 mg, 0.72 mmol) at rt. After 16 h water was added and the solution extracted with EtOAc (1 × 15 ml). The aqueous phase was acidified with HCl (1 M, aq.) which gave a white precipitate. Extraction with EtOAc (4 × 15 ml), drying ($MgSO_4$) and evaporation *in vacuo* gave the title compound as a colourless glass (39 mg, 83%) consisting of two diastereomers **20a**, **b** (1:4); ν_{max} (KBr)/cm^{-1} 3255 (m, br), 3035 (m, br), 2928 (m, br), 1713 (s), 1660 (s), 1407 (m), 1236 (s), 760 (m), 702 (s).

Data for 20a. δ_H (500 MHz, CD_3OD) 1.94 (1H, dd, *J* 17.5 and 9.5, C*H*HCO_2H), 2.54 (1H, dd, *J* 17.5 and 5.5, CH*H*CO_2H), 3.44–3.47 (1H, m, H-3), 3.96 (1H, d, *J* 9.0, H-4), 4.09 (1H, d, *J* 7.5, H-2), 7.14–7.16 (2H, Ar*H ortho*- to C-6), 7.23–7.36 (3H, m, Ar*H*); *m*/*z* (APCI$^+$) 264 (M + H$^+$, 94%); HRMS (FAB$^+$) 264.0875, $C_{13}H_{14}NO_5$ requires 264.0872.

Data for 20b. δ_H (500 MHz, CD_3OD) 2.65–2.74 (2H, m, CH_2CO_2H), 2.78–2.83 (1H, m, H-3), 3.62 (1H, d, *J* 9.0, H-4), 4.19 (1H, d, *J* 7.5, H-2), 7.23–7.36 (5H, m, Ar*H*); δ_C (125.8

MHz, CD_3OD) 37.41 (CH_2CO_2H), 46.69 (C-3), 55.02 (C-4), 60.25 (C-2), 128.58, 129.79 and 130.01 (Ar*C*H), 139.06 (C-6), 173.17, 173.33 and 178.78 (3 × *C*O).

(2*S*,3*S*,4*R*)-3-*tert*-Butoxycarbonylmethyl-4-ethoxycarbonyl-2-methoxycarbonyl-5-oxo-4-phenylpyrrolidine 21

To a solution of compound **10a** in CH_3CN (0.5 ml) and CCl_4 (0.5 ml) was added a solution of $NaIO_4$ (20 mg, 0.10 mmol) in water (0.75 ml) and then ruthenium(IV) oxide hydrate (0.6 mg). The mixture was stirred vigorously at rt for 2 h and then a solution of diazomethane in diethyl ether was added with stirring which was continued for 5 min. Water (5 ml) was then added to the mixture which was then extracted with EtOAc (3 × 10 ml). Drying ($MgSO_4$) and evaporation *in vacuo* gave a black oil which was purified using column chromatography (EtOAc–petrol (40–60), 1 : 1) to give the title compound **21** as a colourless oil (4 mg, 41%); R_f 0.27 (EtOAc–petrol (40/60), 1 : 1); $[\alpha]_D^{23}$ −26.3 (*c* 0.175 in $CHCl_3$); ν_{max}(film)/cm^{-1} 3202 (m, br), 2979 (m), 2927 (m), 1725 (s), 1448 (m), 1368 (m), 1219 (s), 1154 (s), 1029 (m), 736 (m), 703 (m); δ_H (500 MHz, $CDCl_3$) 1.26 (3H, t, *J* 7.0, CH_3CH_2), 1.42 (9H, s, $C(CH_3)_3$), 1.81–1.85 (1H, m, C*H*HCO$_2{}^t$Bu), 2.05–2.14 (1H, m, CH*H*CO$_2{}^t$Bu), 3.82 (3H, s, CO_2CH_3), 3.93–3.98 (2H, m, H-2 and H-3), 4.27 (2H, q, *J* 7.0, CH_3CH_2), 6.31 (1H, s, N*H*), 7.27–7.38 (5H, m, Ar*H*); δ_C (125.8 MHz, $CDCl_3$) 13.84 (CH_3CH_2), 27.97 ($C(CH_3)_3$), 36.82 ($CH_2CO_2{}^t$Bu), 44.04 (C-3), 52.77 (CO_2CH_3), 57.35 (C-2), 62.63 (CH_3CH_2), 63.64 (C-4), 81.26 ($C(CH_3)_3$), 127.98, 128.43 and 128.74 (Ar*C*H), 133.77 (C-6), 169.31, 170.41, 171.07 and 172.35 (4 × *C*O); *m*/*z* (APCI$^+$) 406 (M + H$^+$, 5%), 350 (100); HRMS 406.1866, $C_{21}H_{28}NO_7$ requires 406.1866.

(2*S*,3*S*,4*R*)-4-Benzyl-4-ethoxycarbonyl-2-methoxycarbonyl-3-methoxycarbonylmethyl-5-oxopyrrolidine 22a and (2*S*,3*S*,4*R*)-4-benzyl-2,4-bis(methoxycarbonyl)-3-methoxycarbonylmethyl-5-oxopyrrolidine 22b

To a solution of alcohol **11c** (47 mg, 0.12 mmol) in EtOH (3 ml) was added NaOH (1 M, aq., 0.72 ml, 0.72 mmol) and the mixture stirred at rt for 20.5 h. Water (15 ml) was then added and the solution extracted with EtOAc (1 × 10 ml). Acidification with HCl (2 M, aq., 2 ml), extraction with EtOAc (3 × 15 ml), drying ($MgSO_4$) and evaporation *in vacuo* gave a colourless foam (33 mg). This foam was then dissolved in DCM (2 ml) and TFA (0.25 ml) was added with swirling at rt. After 1 h the solvent was removed *in vacuo* and then more rigorously removed under high vacuum (2 mbar) to give an opaque pale brown gum.

To a solution of this gum in CH_3CN (1 ml) and CCl_4 (1 ml) was added a solution of $NaIO_4$ (71 mg, 0.33 mmol) in water (1.5 ml) and then ruthenium(IV) oxide hydrate (2 mg). The mixture was stirred vigorously at rt for 5 h and then a solution of diazomethane in diethyl ether added at 0 °C with stirring until the effervescence ceased and the upper ether layer remained yellow. The excess diazomethane was allowed to evaporate at rt for several hours and then the mixture was extracted with EtOAc (3 × 10 ml), dried ($MgSO_4$) and evaporated *in vacuo* to give a colourless oil (29 mg). Purification using column chromatography (EtOAc–petrol (40–60), 6 : 5) gave **22a** (10 mg, 23%) as a single diastereomer as a colourless oil and **22b** as a colourless oil.

Data for 22a. R_f 0.27 (EtOAc–petrol (40–60), 6 : 5); $[\alpha]_D^{23}$ +69.0 (*c* 0.335 in $CHCl_3$); ν_{max}(film)/cm^{-1} 3318 (w, br), 3234 (w, br), 1738 (s), 1709 (s), 1438 (m), 1378 (m), 1219 (s), 1065 (m), 1009 (m), 770 (m), 705 (m); δ_H (300 MHz, $CDCl_3$) 1.33 (3H, t, *J* 7.0, CH_3CH_2), 2.48 (1H, dd, *J* 16.5 and 6.5, C*H*HCO$_2$Me), 2.69 (1H, dd, *J* 16.5 and 7.5, CH*H*CO$_2$Me), 3.00–3.08 (1H, m, H-3), 3.18 (1H, d, *J* 14.0, C*H*HPh), 3.43 (1H, d, *J* 14.0, CH*H*Ph), 3.58 (3H, s, CO_2CH_3), 3.70 (3H, s, CO_2CH_3), 4.02 (1H, d, *J* 8.5, H-2), 4.19–4.36 (2H, m, CH_3CH_2), 6.34 (1H, br s, N*H*), 7.21–7.34 (5H, m, Ar*H*); δ_C (125.8 MHz, $CDCl_3$) 14.15 (CH_3CH_2), 34.31 (CH_2CO_2Me), 36.40 (CH_2Ph), 39.55 (C-3), 51.92 and 52.56 (2 × CO_2CH_3), 58.84 (C-2), 60.16 (C-4), 62.09 (CH_3CH_2), 127.02, 128.38 and 130.91 (Ar*C*H), 135.28 (C-7), 169.55, 170.38, 171.13 and 173.34 (4 × *C*O); *m*/*z* (APCI$^+$) 400 (M + Na$^+$, 52%), 378 (M + H$^+$, 100); HRMS (CI$^+$) 378.1553, $C_{19}H_{24}NO_7$ requires 378.1553.

Data for 22b. R_f 0.21 (EtOAc–petrol (40–60), 6 : 5); ν_{max}(film)/cm^{-1} 3316 (w, br), 3233 (w, br), 1739 (s), 1711 (s), 1437 (m), 1379 (m), 1222 (s), 1066 (m), 990 (m), 770 (m), 706 (m); δ_H (300 MHz, $CDCl_3$) 2.46 (1H, dd, *J* 16.5 and 6.5, C*H*HCO$_2$Me), 2.68 (1H, dd, *J* 16.5 and 7.0, CH*H*CO$_2$Me), 3.00–3.08 (1H, m, H-3), 3.19 (1H, d, *J* 14.0, C*H*HPh), 3.44 (1H, d, *J* 14.0, CH*H*Ph), 3.58 (3H, s, CO_2CH_3), 3.70 (3H, s, CO_2CH_3), 3.81 (3H, s, CO_2CH_3), 4.02 (1H, d, *J* 8.5, H-2), 6.39 (1H, br s, N*H*), 7.23–7.32 (5H, m, Ar*H*); δ_C (128.5 MHz, $CDCl_3$) 34.37 (CH_2CO_2Me), 36.52 (CH_2Ph), 39.56 (C-3), 51.94, 52.57 and 52.76 (3 × CO_2CH_3), 58.68 (C-2), 60.18 (C-4), 127.06, 128.40 and 130.88 (Ar*C*H), 135.17 (C-7), 170.06, 170.32, 171.10 and 173.21 (4 × *C*O); *m*/*z* (APCI$^+$) 386 (M + Na$^+$, 40%), 364 (M + H$^+$, 100); HRMS (CI$^+$) 364.1396, $C_{18}H_{22}NO_7$ (M + H$^+$) requires 364.1396.

(2*S*,3*S*,4*S*)-4-Benzyl-3-*tert*-butoxycarbonylmethyl-4-carboxy-2-hydroxymethyl-5-oxopyrrolidine 23

To a solution of the alcohol **10c** (60 mg, 0.15 mmol) in EtOH (5 ml) was added NaOH (1 M, aq., 0.92 ml, 0.92 mmol). The mixture was stirred at rt for 5 h and then water (20 ml) was added and the mixture extracted with EtOAc (1 × 10 ml). Acidification of the aqueous layer with HCl (2 M, 1.5 ml), extraction with EtOAc (4 × 20 ml), drying ($MgSO_4$) and evaporation *in vacuo* gave the title compound as a colourless foam (55 mg, 99%); ν_{max} ($CDCl_3$)/cm^{-1} 3417 (w), 3300 (br, s), 1724 (br, s), 1456 (m), 1394 (s), 1370 (s), 1155 (s), 843 (m); δ_H (300 MHz, $CDCl_3$) 1.47 (9H, s, $C(CH_3)_3$), 2.48 (1H, dd, *J* 16.5 and 8.0, C*H*H-CO$_2{}^t$Bu), 2.93–3.10 (3H, m), 3.10–3.23 (1H, br s), 3.24–3.36 (1H, d, *J* 14.0), 3.36–3.52 (1H, br s) (C*H*$_2$Ph, H-2, CH*H*-CO$_2{}^t$Bu, H-3 and C*H*HOH), 3.56–3.79 (2H, br s, CH*H*OH and OH), 7.16–7.29 (5H, m, Ar*H*), 7.52 (2H, br s, N*H* and CO$_2$*H*); δ_C (50.3 MHz, $CDCl_3$) 28.0 ($C(CH_3)_3$), 33.6 ($CH_2CO_2{}^t$Bu), 36.5 (CH_2Ph), 40.4 (C-3), 58.5 (C-4), 59.4 (C-2), 61.7 (CH_2OH), 82.0 ($C(CH_3)_3$), 127.3, 128.4 and 130.2 (Ar*C*H), 135 (C-7), 171.6, 173.3 and 176.9 (3 × *C*O); *m*/*z* (APCI$^+$) 386 (M + Na$^+$, 2%), 320 (21), 264 (100); *m*/*z* (APCI$^-$) 362 ((M− H)$^-$, 7%), 318 (35), 262 (100); HRMS (FAB$^+$) 364.1780, $C_{19}H_{26}NO_6$ requires 364.1760.

(2*S*,3*S*,4*R*)- and (2*S*,3*S*,4*S*)-4-Benzyl-2-methoxycarbonyl-3-methoxycarbonylmethyl-5-oxopyrrolidines 15b and 16b

The acid **23** was heated at 135 °C/0.7 mbar for 2 h, and then at 150 °C for 1 h to give a colourless glass; to this material in DCM (4 ml) was added TFA (0.75 ml) with swirling at rt. After standing for 1 h the solvent was removed *in vacuo* and more rigorously removed by heating at 30 °C at 0.7 mbar for 12 h to give a pale yellow glass. To a solution of this glass in CH_3CN (2 ml) and CCl_4 (2 ml) was added a solution of $NaIO_4$ (120 mg, 0.56 mmol) in water (3 ml) followed by ruthenium(IV) oxide hydrate (4 mg). After stirring the mixture vigorously for 3 h, a solution of diazomethane in diethyl ether was added with stirring at 0 °C until the upper ether layer remained yellow. After allowing the excess diazomethane to evaporate at rt the mixture was extracted with EtOAc (3 × 10 ml), and then dried ($MgSO_4$) and evaporated *in vacuo* to give a dark grey oil which was purified using flash column chromatography (EtOAc–petrol (40–60), 2 : 1) to give **15b** (3 mg, 7%) as a colourless oil which slowly crystallised, and **16b** (14 mg, 31%) as a colourless oil, both as single diastereomers.

Data for 15b. R_f 0.21 (EtOAc–petrol (40–60), 2:1); $[a]_D^{23}$ +5.6 (*c* 0.13 in $CHCl_3$); mp 108–111 °C; ν_{max}(film)/cm^{-1} 3233 (w, br), 1735 (s), 1707 (s), 1437 (m), 1380 (m), 1260 (m), 1213 (s), 1178 (m), 1015 (m), 699 (m); δ_H (500 MHz, $CDCl_3$) 2.50 (1H, dd, *J* 16.5 and 9.5, C*H*HCO_2Me), 2.63 (1H, dd, *J* 16.5 and 5.0, CH*H*CO_2Me), 3.04–3.13 (2H, m, H-4 and C*H*HPh), 3.26 (1H, dd, *J* 15.0 and 4.0, CH*H*Ph), 3.65 (3H, s, CO_2CH_3), 3.78 (3H, s, CO_2CH_3), 4.01 (1H, d, *J* 2.5, H-2), 5.98 (1H, br s, N*H*), 7.22–7.24 (3H, m, Ar*H*), 7.30–7.33 (2H, m, Ar*H*); δ_C (125.8 MHz, $CDCl_3$) 31.16 and 32.95 (*C*H_2CO_2Me and *C*H_2Ph), 38.42 (C-3), 43.48 (C-4), 51.94 and 52.80 (2 × CO_2CH_3), 58.14 (C-2), 126.58, 128.39 and 128.72 (Ar*C*H), 138.36 (C-7), 171.56, 171.88 and 177.43 (3 × *C*O); *m/z* ($APCI^+$) 306 (M + H^+, 100%), 246 (79); HRMS (CI^+) 306.1341, $C_{16}H_{19}NO_5$ requires 306.1341.

Data for 16b. R_f 0.17 (EtOAc–petrol (40–60), 2:1); $[a]_D^{23}$ +67.9 (*c* 0.66 in $CHCl_3$); ν_{max}(film)/cm^{-1} 3231 (w), 1735 (s), 1703 (s), 1437 (m), 1377 (m), 1327 (m), 1213 (s), 1180 (m), 992 (m), 703 (m); δ_H (500 MHz, $CDCl_3$) 2.35 (1H, dd, *J* 16.0 and 6.5, C*H*HCO_2Me), 2.45 (1H, dd, *J* 16.0 and 5.0, CH*H*CO_2Me), 2.82 (1H, dd, *J* 14.0 and 8.5, C*H*HPh), 3.26 (1H, dd, 14.0 and 3.5, CH*H*Ph), 3.65 (3H, s, CO_2CH_3), 3.76 (3H, s, CO_2CH_3), 4.08 (1H, d, *J* 6.0, H-2), 6.53 (1H, br s, N*H*), 7.24–7.37 (5H, m, Ar*H*); δ_H (500 MHz, C_6D_6) 2.00 (1H, dd, *J* 16.0 and 7.0, C*H*HCO_2Me), 2.06 (1H, dd, *J* 16.0 and 5.5, CH*H*CO_2Me), 2.40–2.44 (1H, m, H-4), 2.60–2.65 (1H, m, H-3), 2.80 (1H, dd, *J* 14.0 and 8.5, C*H*HPh), 3.18 (3H, s, CO_2CH_3), 3.21 (4H, s and dd, *J* 14.0 and 4.5, CO_2CH_3 and CH*H*Ph), 3.62 (1H, d, *J* 6.5, H-2), 6.98 (1H, t, *J* 7.5, Ar*H*), 7.05–7.15 (5H, m, Ar*H* and N*H*); δ_C (125.8 MHz, $CDCl_3$) 36.14 (*C*H_2Ph), 36.93 (*C*H_2CO_2Me), 39.53 (C-3), 47.62 (C-4), 51.70 and 52.62 (2 × CO_2CH_3) 58.29 (C-2), 126.63, 128.59 and 129.15 (Ar*C*H), 138.10 (C-7), 171.38, 171.58 and 177.16 (3 × *C*O); *m/z* ($APCI^+$) 306 (M + H^+, 100%), 246 (60); HRMS (CI^+) 306.1341, $C_{16}H_{19}NO_5$ requires 306.1341.

Acknowledgements

We thank EPSRC and GlaxoWellcome for funding of studentships to J. D., and we wish to gratefully acknowledge the use of the EPSRC Chemical Database Service at Daresbury[24] and the EPSRC National Mass Spectrometry Service Centre at Swansea.

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