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Pyrrolidinones derived from (*S*)-pyroglutamic acid: penmacric acid and analogues †

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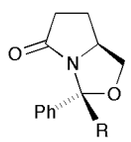
Received 10th April 2003, Accepted 13th May 2003
First published as an Advance Article on the web 5th June 2003

Alkylation reactions using α-halolactams or lactam enolates derived from bicyclic lactam templates can proceed with high *endo*- or *exo*- diastereoselectivity respectively. In the latter case, stereochemical correction by means of enolate generation and hindered phenol quench is possible with moderate efficiency. This protocol has been applied to the synthesis of protected penmacric acid and its analogues.

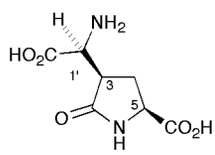
Introduction

Functionalised pyrrolidinones have emerged as an important class of architecturally well-defined and synthetically readily available templates which are now finding extensive application as conformationally controlling peptidomimetics[1–6] or as pharmacologically active agents,[7,8] especially in the area of neuroexcitatory chemistry.[9,10] Natural products containing a pyrrolidine core are well-known, and exhibit diverse biological activity; recently identified unusual examples include kaitocephalin,[11] lemonomycin[12] and aeruginosin.[13] Over the last decade, significant advances in general synthetic methods, providing access to this class of compounds with excellent stereocontrol, have been made. Two general strategies have been developed: the elaboration of chiral templates, exemplified by the elegant work of Meyers and co-workers, which uses chiral *O*,*N*-acetal bicyclic lactams,[14,15] and the preparation of functionalised pyrrolidinones using ring closure reactions, exemplified by the recent work by Soloshonok *et al.*[16] and of Alvarez-Ibarra *et al.*.[17] Our own work in this area has made use of the hemiaminal ethers‡ **1a** and **1b** derived from pyroglutamic acid as a chiral template.[18,19] These compounds are of value since they can be readily prepared in enantiopure form; the hydroxyl and amide functionalities are simultaneously protected by a single benzylidene protecting group, making for economy in molecular mass; and the protecting group provides a bicyclic template which might be expected to exert good diastereocontrol. We[20–26] and others,[18,19,25,27–49] have demonstrated that the introduction of functionality α-, β- and γ- to the lactam carbonyl of **1** is readily possible in a stereocontrolled sense. The robustness of this protocol has been demonstrated by its recent application for the synthesis of multi-kilo quantities of 3,5-disubstituted-2-pyrrolidinones for evaluation as collagen-induced thrombocyte aggregation inhibitors by Yee *et al.* at Boehringer Ingelheim.[50] The stereocontrol in reactions of lactam templates has been of some interest[32,43,51–53] and we have shown that unusual stereocontrol is possible for bicyclic lactam **1b** by the application of remote steric effects around the ring periphery.[54] We have demonstrated that this approach provides access to novel kainoid analogues[22,24] and conformationally well-defined amino acid analogues,[55] and report here its application to the synthesis of analogues of penmacric acid.

Penmacric acid **2** was first isolated in 1975 independently in British[56] and Belgian[57] laboratories from the seeds of the leguminous tree *Pentaclethra macrophylla*, commonly known as "owala seeds" or "pauco nuts", in less than 0.5% w/w of the dry bean endosperm; these legumes are indigenous to the humid lowlands of West Africa, the seeds of which are both a staple food in the local diet, and also find application for their medicinal value.[58,59] These seeds also contain proline, pipecolic acid, 5-hydroxypipecolic acid and betaine. The absolute configuration of penmacric acid was initially assigned from ^{1}H NMR studies in association with CD measurements and this was later supported by a single crystal X-ray structure.[60] Detailed ^{1}H NMR studies indicate the solution C_s envelope conformation of the acid is very close to that observed in the solid state, in which C(3)–C(2)–N(1)–C(5) are co-planar (torsion angle −3.3°) with C-4 out of this plane (the angle between this plane and that of C(3)–C(4)–C(5) is 32.3°).[61,62] A number of chemical studies were carried out on penmacric acid by the Belgian workers who originally reported its isolation;[63] thus, the lactam of penmacric acid is hydrolysed under a variety of acidic conditions to the substituted adipic acid **3** which recloses in dilute acid solution to give either of two possible substituted pipecolic acids **4** and **5** (Scheme 1). Despite detailed chemical studies nothing is known about the biological origin or role of penmacric acid.



1a R = H
1b R = Me



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The possibility of a synthetic strategy to access penmacric acid from bicyclic lactam **1a** by either of two key disconnections, *via* an α-halolactam and a suitable glycine enolate equivalent (Fig. 1a) or a lactam enolate and a glycinyl cation equivalent (Fig. 1b) is readily apparent, and our work in that regard is discussed herein. The expected inversion of stereochemistry in the alkylation step of route *a* would give the desired 3(*R*) stereochemistry of penmacric acid, but introduction of the required stereochemistry at the 1′ position was less certain in the same step. That route *b* was likely to be a realistic prospect had been demonstrated earlier by Young and co-workers,[64,65] who showed that related additions using pyroglutamic acid and *N*-tosyl imines proceeded in a highly stereocontrolled fashion, and more recently that similar control in analogous aldehyde additions was also possible.[66]

† Part V. For parts I–IV see refs. 20–22, 24
‡ This nomenclature conforms to IUPAC recommendations 1995, see ref. 76.

DOI: 10.1039/b303924b

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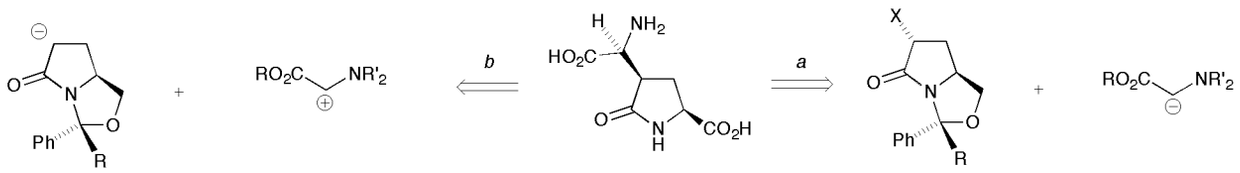
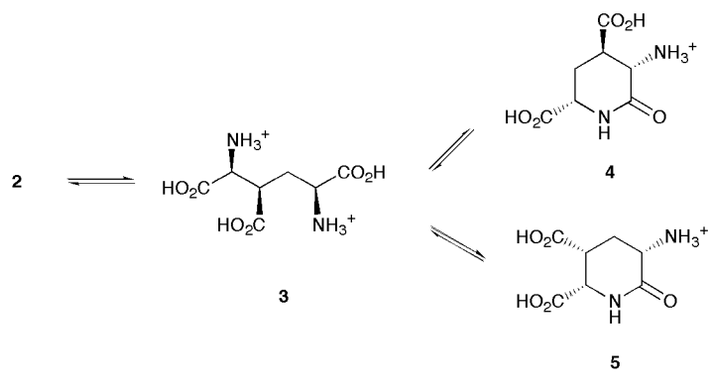
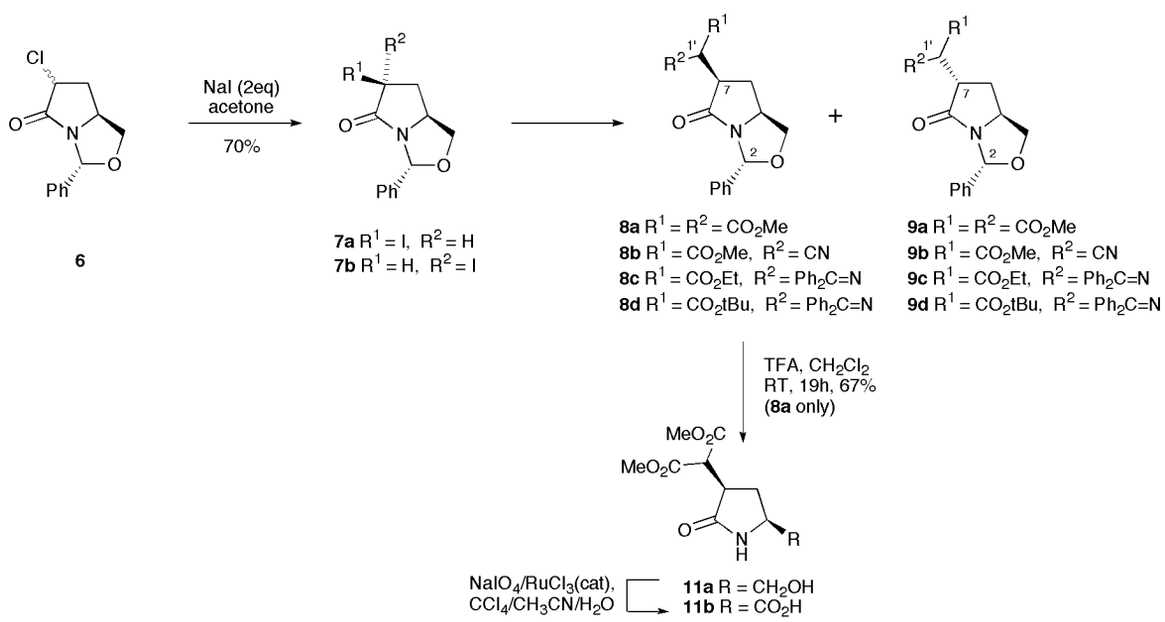


Fig. 1



Scheme 1



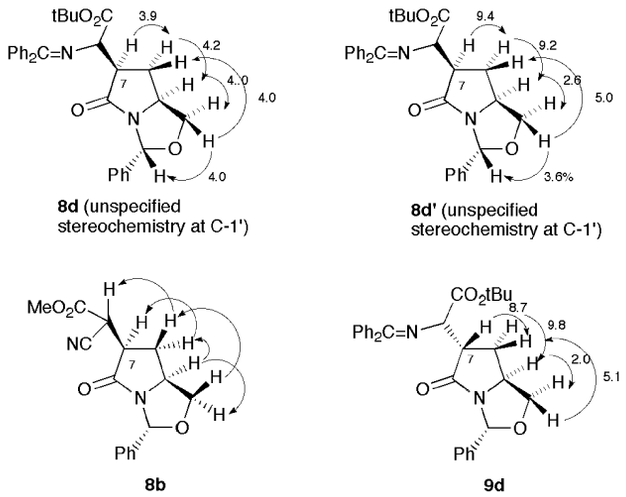
Scheme 2

Results and discussion

Reactions with glycine enolates

Our initial investigation was based on the observation that α-chlorolactams **6** could be readily prepared by treating the lactam enolate derived from **1a** with *p*-toluenesulfonyl chloride (Scheme 2); reaction of lactam **6** under Finkelstein conditions (NaI–acetone) gave good yields (70%) of the *endo*- and *exo*- iodides **7a**,**b**, in a ratio of up to 6 : 1; the *exo*-iodide **7b** predominated regardless of the *endo* : *exo* ratio of the starting material. Direct synthesis of these iodides by trapping of the enolate of lactam **1a** with either I_2 or NIS, as reported by Meyers and co-workers,[67] proved to be unsatisfactory, giving low yields and product mixtures which were difficult to purify.

Iodides **7a**,**b** proved to be useful alkylating agents; reaction of *exo*-iodide **7b** with the sodium enolate of dimethyl malonate (generated using sodium hydride in THF) gave two products in a combined yield of 80%, which were identified as the *endo*-**8a** and *exo*-**9a** malonates in a ratio of 2.1 : 1. Their stereochemistry could not be established directly by NOE analysis due to overlapping signals in the ^{1}H NMR spectrum, but was made indirectly by comparison of ^{1}H NMR spectra, $[\alpha]_D$ and R_f values using a previously established protocol;[26,38,43,54] thus, the *endo*- diastereomer **8a** possessed higher R_f and optical rotation data, and a bigger difference in the chemical shift values for $C(6)H_{exo}$ and $C(6)H_{endo}$, than the *exo*- diastereomer **9a**, for which $C(6)H_{exo}$ and $C(6)H_{endo}$ were overlapping. Reaction of *endo*- iodide **7a** under these conditions gave an *exo* : *endo* product **9a** : **8a** in a ratio of 1.7 : 1. Reaction of *exo*- iodide **7b** with the sodium enolate of methyl cyanoacetate gave *endo*- and *exo*-lactams **8b** and **9b** in excellent 84% overall yield and a 5.4 : 1 ratio (each as a mixture of diastereomers at C-1′); the stereochemistry of **8b** was established by NOESY analysis (Fig. 2), and that of **9b** by observation of overlapping signals for $C(6)H_{exo}$ and $C(6)H_{endo}$, which is characteristic of the $C\text{-}7_{exo}$ stereochemistry as demonstrated from the rules noted above. We assume that the diastereochemical attrition in these reactions is a result of the epimerisation of starting **7a** and **7b** catalysed by the release of iodide in the course of the displacement reaction.



8d (unspecified stereochemistry at C-1′)

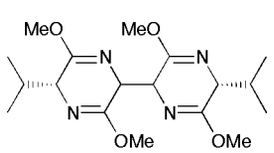
8d′ (unspecified stereochemistry at C-1′)

8b

9d

Fig. 2

The use of the glycinate anion derived from *N*-(diphenylmethylene)glycine ethyl ester (formed by treatment with LDA in THF at 0 °C) in this reaction with *exo*-iodide **7b** gave a diastereomeric mixture of products **8c** and **8c′** (epimeric at C-1′) and **9c** (single diastereomer, but unassigned stereochemistry at C-1′) in yields of 20, 6 and 63% respectively, whose stereochemistry could not be unequivocally established by NOE spectroscopy, but was made by comparison with compounds **8d**, **8d′** and **9d** (Scheme 2); the empirical rules mentioned above failed in this case.[26,38,43,54] Repetition of this reaction with *endo*-iodide **7a** gave the most polar isomer *exo*-**9c** in good yield (63%) as the major product. This selectivity could not be improved using the anion of *N*-(diphenylmethylene)-glycine *tert*-butyl ester, which similarly gave three isomers of the products **8d** and **8d′** (epimeric at C-1′) and **9d** in yields of 17, 14 and 39% respectively. In this case, however, the stereochemistry of C(7)H could be assigned on the basis of NOE data (Fig. 2) and these assignments are further supported by consistency with the rules of thumb cited above. However, no information about the stereochemistry at C(1′) was forthcoming, and the configuration of this stereocentre remains unassigned for all three products; for compounds **8c**,**d** and **9c**,**d**, $J_{1'\text{-}7}$ values of between 2.5 and 4.0 Hz were consistent with a C(1′)H–C(7)H *gauche* conformation. It was observed that whereas the *exo*-isomer **9d** was indefinitely stable when stored at 4 °C, the *endo*- isomers **8d** and **8d′** decomposed within a few weeks. The clear predominance of the *exo*- isomer product in all reactions of these glycine imines contrasted with the workable *endo*- selectivity in the formation of **8a**, and this was undesirable for the synthesis of penmacric acid. Surprisingly, reaction of *exo*- iodide **7b** with the lithium anion of the Schöllkopf bislactim ether[68] gave not the expected product of substitution, but instead lactam **1a** and dimer **10** in good yield (66%). Reaction of iodides **7a**,**b** with the anions of 2-phenyl-5-oxazolone, diethylacetamidomalonate and methyl nitroacetate gave no products of substitution, but instead returned starting materials, often with epimerisation at C(7)H.



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The *endo*-malonate **8a** could be readily deprotected to give the corresponding alcohol **11a** in 67% yield, but oxidation of this product to the carboxylic acid **11b** under Sharpless conditions[69] proceeded in low yield (10%); this has proved to be a recurring problem in this reaction (*vide infra*). Although application of acidic conditions (TFA or *p*-TsOH) for deprotection of lactams **8c**,**d** and **9c**,**d** gave mixtures of inseparable, unidentifiable products, it was found that the neutral conditions of Fasth and co-workers (NH_2OH, EtOH, H_2O)[70] gave completely selective deprotection of the *endo*- imines **8c** and **8c′** to give amines **12a** and **13a** in yields of 87 and 46% respectively, and each of these was reprotected to give the *N*-acetyl derivative **12b** and **13b** (Ac_2O, Et_3N, $CHCl_3$,) in yields of 62 and 58% (Scheme 3). A similar sequence for the *exo*- imine **9c** gave the corresponding *N*-acetyl derivative **14**. Careful NOE analysis of **12b** and **13b** indicated a large enhancement of the C(7)H signal occurs on irradiation of $C(6)H_{exo}$ but not on irradiation of $C(6)H_{endo}$, confirming the $C(7)H_{exo}$ assignment made earlier for the imines **8c** and **8c′**. Assignment of C(1′)H as (*R*) and (*S*) respectively for these compounds is more tentative, and assumes that intramolecular H-bonding stabilises the conformation indicated; this is consistent with the observation that for the amides **12b** and **13b**, in the IR spectrum, the NH frequency is observed at 3310 and 3326 cm^{-1} and the lactam carbonyls at 1690 and 1680 cm^{-1} respectively (these are lower than those displayed in compounds for which hydrogen bonding is not possible[71]). In this arrangement, C(1′)H for lactam **12b** exhibits NOE enhancements with both $C(6)H_{exo}$ and $C(6)H_{endo}$, as expected, but C(1′)H for lactam **13b** shows a NOE only with $C(6)H_{endo}$ (Scheme 3). Such a conformation is consistent with the observed $J_{\text{H-7/H1}'}$ values of 3.5 and 3.0 Hz for **12a** and **12b** respectively.

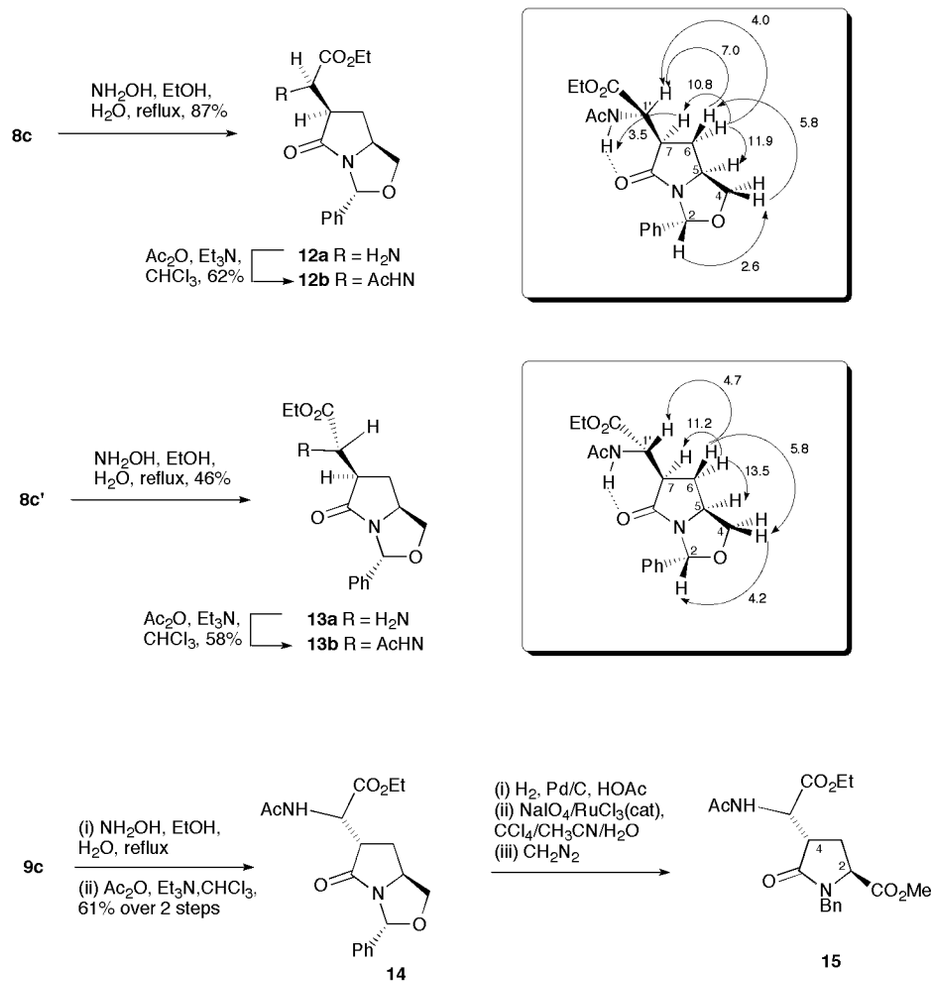
However, *O*,*N*-deprotection under acidic conditions (TFA, CH_2Cl_2) for all of **8d**, **8d′** and **9d** led to consumption of starting material and very poor mass recovery of a product which possessed the correct molecular weight for the desired product; suspecting that the problematic step was the strong acidic acetal deprotection, application of an alternative three step deprotection sequence (hydrogenation, oxidation and esterification) for lactam **14** was attempted, and this gave lactam **15** (23% over the three steps), which is a diastereomer of penmacric acid in protected form.

Although this route provided access to epimers of penmacric acid, because of the poor diastereoselectivity in the alkylation step leading to imines **8d**, **8d′** and **9d**, and difficulties with deprotection, an alternative route was investigated.

Reaction with imines

The alternative disconnection, indicated in Fig. 1b, based on reaction of a lactam enolate with a glycine cation equivalent was of interest. The addition of pyroglutamate enolates to aldehydes and imines has been studied in some detail[64–66] and similar processes have been briefly examined in the case of bicyclic lactam **1a**.[26] These reactions have been found to proceed with some diastereocontrol; for example, reaction of the lactam enolate of **1a** with benzaldehyde gave a product mixture consisting of **16a** and **17a** in a ratio of *exo*- : *endo*- = 2 : 1 (Scheme 4). Reaction of this same lactam enolate with chloral gave adducts **16b** and **17b** with high *endo*- selectivity (1 : 2.7) and excellent overall yield (86%, Scheme 4); their stereochemistry was assigned on the basis of C(6)H chemical shift values as discussed above. Intending to apply the Corey–Link procedure for amino acid synthesis,[72] *endo*-**17b** was converted in one pot to azido ester **18** in 41% yield, but this compound appeared by NMR spectroscopic analysis to be a mixture of diastereomers and all attempts to manipulate either the azide or *O*,*N*-acetal function failed.

With this precedent, we anticipated that the required stereochemistry for penmacric acid would be available from the reaction of lactam **1a** with an activated imine. However, these additions proved not to be so stereoselective as the aldehyde additions indicated above. Thus, the *N*-tosyl imine derived from

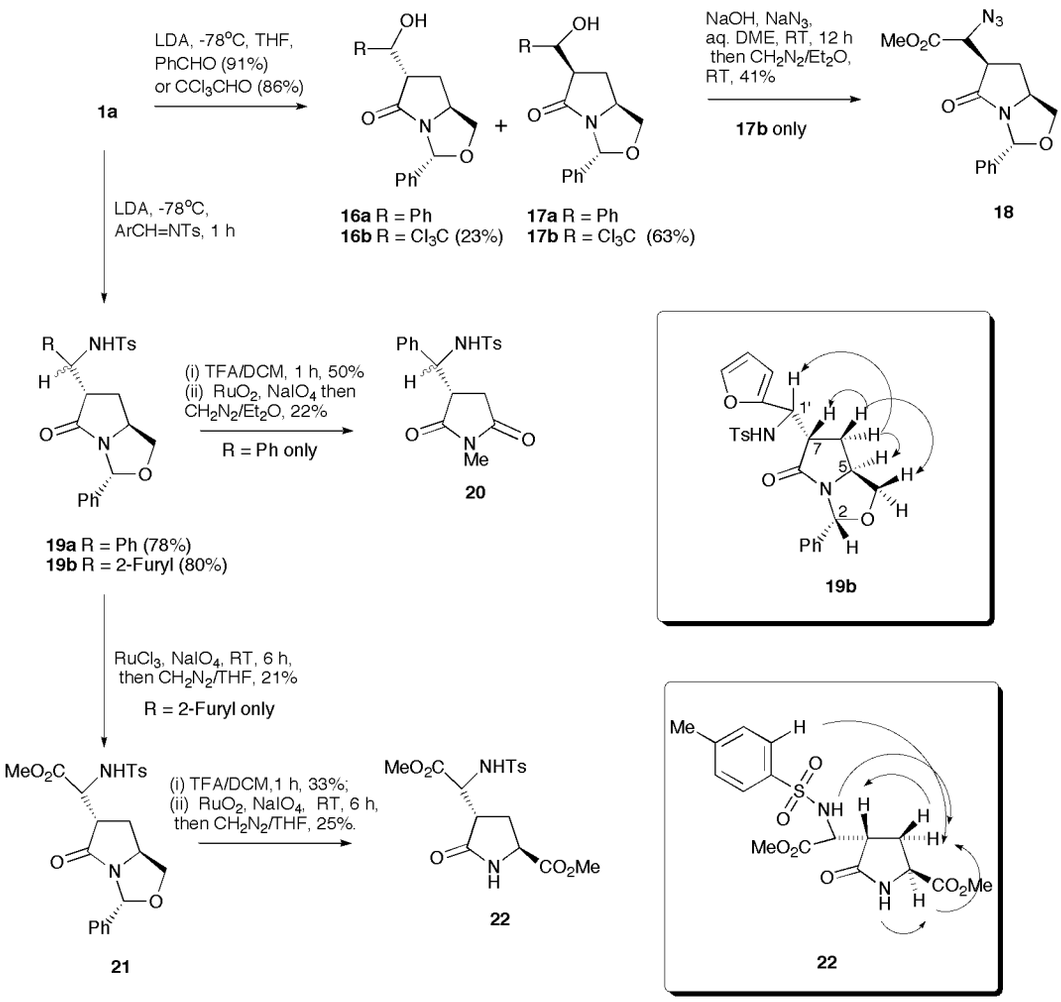


Scheme 3

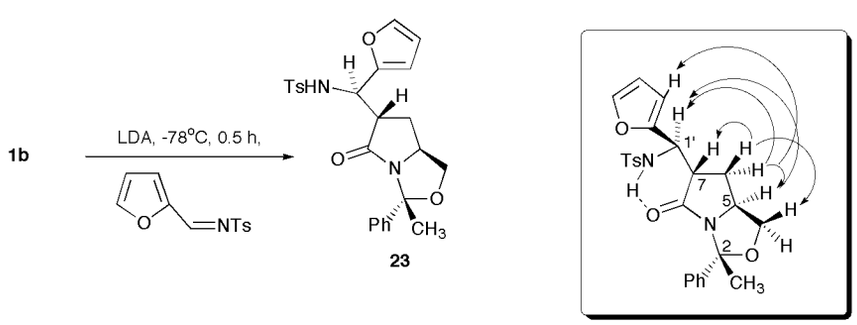
benzaldehyde was reacted with the enolate of **1a**, and this was found to give a high yield of *exo*-adduct **19a** only, but as a mixture of diastereomers at the C-1′ position. Careful crystallization of this mixture enabled isolation of the (2*R*,5*S*,7*S*,1′*R*) diastereomer suitable for single-crystal X-ray analysis, and this confirmed the earlier stereochemical assignment.[73] This structure also confirmed the shallow concave structure of the bicyclic ring system, which probably accounts for the low diastereoselectivity in reactions at C-7, and also indicated the presence of intermolecular hydrogen bonding between NHTs and lactam carbonyl components. Deprotection (TFA, DCM), oxidation using the Sharpless conditions[69] and immediate treatment with diazomethane gave succinimide **20** in low yield, with no phenyl group cleavage as intended; we have previously observed such decarboxylations and further oxidations in these systems. Application of the *N*-tosyl imine derived from furfuraldehyde to this sequence similarly gave the *exo*- adduct **19b** in excellent yield, as a 2 : 1 mixture of diastereomers at the C-1′ position, and whose stereochemistry was established by NOESY analysis and by consideration of C(6)H chemical shift data, but this time oxidative cleavage of the furyl ring and immediate protection (diazomethane) successfully gave ester **21** as a single diastereomer, albeit in low yield (21%). The indicated $C(7)_{exo}$ stereochemistry was established again by the similar chemical shift values for C(6)H (δ 2.1 and 2.3). *O*,*N*-Acetal ring cleavage, further oxidation and esterification gave the C-7 *exo*-epimer of penmacric acid **22**, as a 5 : 1 mixture of diastereomers at the C-1′ position, whose stereochemistry (apart from C-1′) was established by NOESY analysis (Scheme 4).

The high *exo*-stereoselectivity of these reactions had been surprising, since all our earlier work had indicated that C-7 epimeric mixtures favouring the *endo*-isomer were more likely. However, a recent finding has been that switching from *O*,*N*-acetal **1a** to analogue **1b** led to a marked increase in *endo*-selectivity for alkylation reactions, and this we attributed to increased planarity of the intermediate enolate structure with consequent enhancement of stereoelectronic control for the reaction.[23] This phenomenon appears to be general in pyrrolidinone systems, and has attracted some attention.[74] Of interest, therefore, was the outcome of reactions of lactam **1b** with an *N*-tosyl imine (Scheme 5). Once again, however, exclusive *exo*-aminoalkylation at C-7 occurred with the *N*-tosyl imine derived from furfuraldehyde, to give **23** in excellent yield (76%), mostly as a single diastereomer, as established from the similar C(6)H values (δ 1.9 and 2.2) and from NOESY analysis. The (*R*)- stereochemistry at C-1′ was tentatively assigned by NOESY analysis, and assumes H-bonding between NH and the lactam carbonyl (as indicated by the IR spectrum, in which the NH frequency was at 3350 and 3250, and the lactam carbonyl at 1689 cm^{-1}).

In an attempt to correct this undesirable stereochemical outcome, epimerisation of the C-7 position of *exo*- lactam adduct **19b** to convert it to the *endo*- isomer **24a** was performed using NaH (2.2 eq.) in refluxing THF for 5 hours, followed by quenching of the reaction mixture with di-*tert*-butylphenol (Scheme 6). The *endo*- adduct **24a** (indicated by the wide separation of the C(6)H signals at δ 1.3 and 2.3, and from NOESY analysis (Fig. 3)) was formed in 27% yield, but 45% of the starting material was also recovered, although these were readily separable by chromatography. Epimerisation of lactam **23** under these conditions gave 26% of the desired product **24b**, but also 45% of recovered starting material and 22% of the elimination product **25**; facile eliminations of β-amino lactams



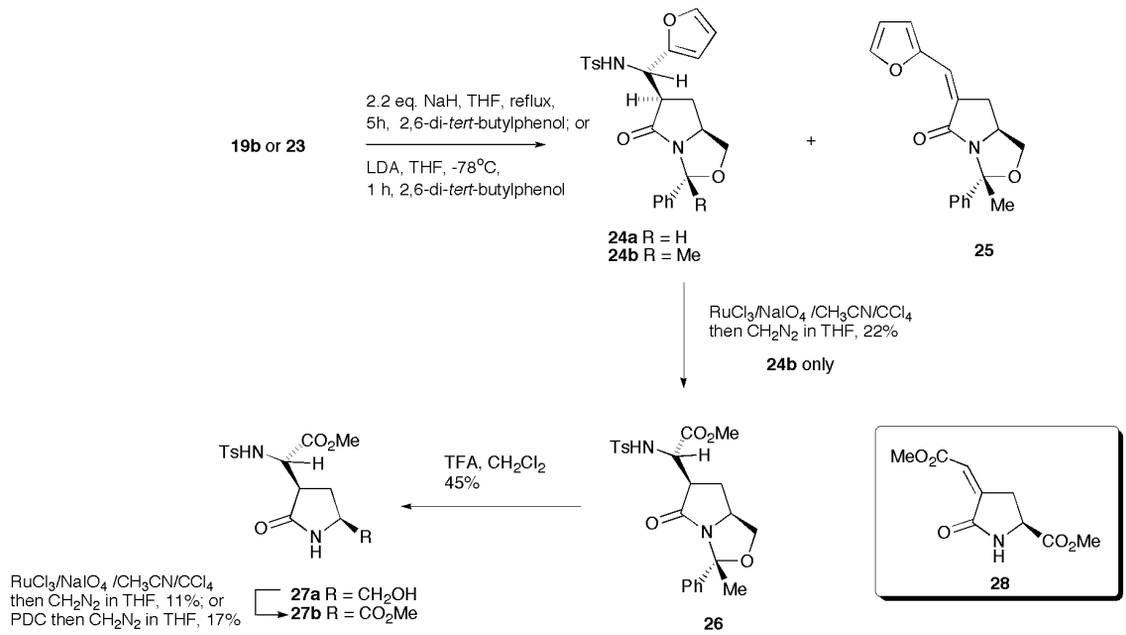
Scheme 4



Scheme 5

have been previously reported.[64] The C(7) *endo*- stereochemistry was initially postulated on the basis of the widely separated chemical shift values for C(6)H (δ 1.3 and 2.22) and confirmed by NOE analysis (Fig. 3), and the (*S*)-stereochemistry at C-1′ was again tentatively assigned by NOESY analysis, assuming H-bonding between NH and the lactam carbonyl (as indicated by the IR spectrum, in which the NH resonated at 3350 and 3250, and the lactam carbonyl resonated at 1687 cm^{-1}). The conformation indicated in Fig. 3 is consistent with the observed $J_{H\text{-}7/H1'}$ values of 5.2 and 5.0 Hz for compounds **24a**,**b** respectively. When 2.5 equivalents of LDA were used followed by quenching with di-*tert*-butylphenol, 22% of the *endo*-adduct **24a** was obtained, but application of this reaction to lactam **23** gave only 18% of the epimerised *endo*-adduct **24b** still as a mixture of diastereomers at C-1′. Compound **24b** was converted to ester **26** in low yield (Scheme 6), whose stereochemistry was again assigned by C(6)H chemical shift values (δ 1.9 and 2.4) and confirmed by NOESY (Fig. 3) and a $J_{H\text{-}7/H1'}$ value of 4.3 Hz. Deprotection (TFA, 45%) was followed by the usual oxidation-protection sequence, and gave lactam **27b** in 8% yield over the three steps, a compound with the correct relative configuration for penmacric acid. This compound also proved to be prone to elimination to give compound **28**.

In conclusion, we have demonstrated that alkylation reactions using α-halolactams or lactam enolates derived from bicyclic lactam templates can proceed with high *endo*- or *exo*- diastereoselectivity respectively. In the latter case, stereochemical correction by means of enolate generation and hindered phenol quench is possible with moderate efficiency. This protocol has been applied to the synthesis of protected penmacric acid and its analogues.



Scheme 6

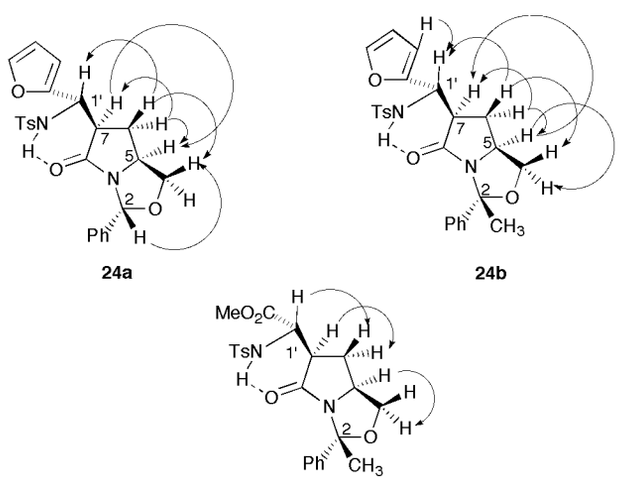


Fig. 3

Experimental

For detailed experimental procedures, see our earlier work.[26] NMR signals for different C-1′ diastereomers where relevant are labeled as A and B whenever they could be resolved; otherwise, both signals are superimposed.

(2*R*,5*S*,7*S*)- and (2*R*,5*S*,7*R*)-1-Aza-3-oxa-8-oxo-2-phenyl-7-iodobicyclo[3.3.0]octane 7a and 7b

A crude mixture of chlorides **6** (4.50 g, 18.9 mmol)[26] and sodium iodide (5.68 g, 37.9 mmol) was refluxed in acetone (200 ml) for 10 hours. The solvent was removed *in vacuo* to give a solid residue that was partitioned between water (40 ml) and DCM (50 ml). The aqueous layer was extracted with ethyl acetate or DCM (2 × 50 ml) and the combined organic layers were washed with brine (50 ml) and dried ($MgSO_4$). The solvent was removed under reduced pressure giving a dark oil that contained two products which were separated by flash column chromatography (ethyl acetate–petrol = 1 : 4 gradient to ethyl acetate–petrol = 1 : 1). The first isolated product (R_f = 0.5, ethyl acetate–petrol = 1 : 1) was the *endo* iodide **7a** which was recrystallised from diethyl ether–petrol or chloroform–petrol to give the product as colourless needles (1.0 g, 16%). Mp 125–7 °C. (Found: C, 43.92; H, 3.48; N4.28. $C_{12}H_{12}NO_2I$ requires C, 43.79; H, 3.67; N,4.26%); $[\alpha]_D$ +244 (*c* 1.0 $CHCl_3$); $\nu_{max}(CHCl_3)$/ cm^{-1} 1718(s); δ_H(200 MHz, $CDCl_3$) 2.38–2.52(1H, m, C(6)H_{endo}), 3.05–3.20(1H, m, C(6)H_{exo}), 3.79(1H, dd, *J* 10.0, 9.5 Hz, C(4)H_{endo}), 4.12–4.35(2H, m, C(5)H and C(4)H_{exo}), 5.05(1H, dd, *J* 10.0, 7.5 Hz, C(7)H), 6.35(1H, s, C(2)H), 7.32–7.53(5H, m, ArH); δ_C(50.3 MHz, $CDCl_3$) 18.3(C(6)), 37.0(C(7)), 58.1(C(5)), 71.2(C(4)), 87.98(C(2)), 126.2, 128.7, 129.0, 136.3, 173.4; *m*/*e*[Probe CI^+, (NH3)] 330(100%, MH^+), 202(70). The second product (R_f = 0.3) was the *exo* iodide **7b** which was recrystallised from diethyl ether–petrol to give colourless needles (3.4 g, 54%). Mp 85–87 °C. (Found: C, 43.84; H, 3.37; N, 4.11. $C_{12}H_{12}NO_2I$ requires C, 43.79; H, 3.67; N, 4.26%); $[\alpha]_D$ +105.3 (*c* 1.0 $CHCl_3$); $\nu_{max}(CHCl_3)$/cm^{-1} 1718(s); δ_H(200 MHz, $CDCl_3$) 2.36–2.64(2H, m, C(6)H), 3.66(1H, m, C(4)H), 4.22–4.40(2H, m, C(5)H and C(4)H), 4.61(1H, dd, *J* 6.5, 5.5 Hz, C(7)H), 6.31(1H, s, C(2)H), 7.30–7.50(5H, m, ArH); δ_C(50.3 MHz, $CDCl_3$) 19.05(C(6)), 38.52(C(7)), 57.90(C(5)), 70.73(C(4)), 86.96(C(2)), 126.2, 128.9, 129.1, 137.9, 175.4(C(8)); *m*/*e* [Probe CI, NH_3] 330(MH^+, 95%), 202(100).

(2*R*,5*S*,7*R*) and (2*R*,5*S*,7*S*)-1-Aza-3-oxa-8-oxo-2-phenyl-7-(di(methoxycarbonyl)methyl) bicyclo[3.3.0]octane 8a and 9a

Dimethyl malonate (187 mg, 1.41 mmol) was added to a rapidly stirred suspension of sodium hydride (60% in mineral oil (40 mg, 1.0 mmol)) in dry THF (20 ml) at 0 °C. When evolution of bubbles had ceased the reaction was stirred for a further 15 minutes. A solution of *exo* iodide **7b** (310 mg, 0.95 mmol) in THF (5 ml) was added and the reaction stirred at 0 °C for 30 minutes. Water (10 ml) was added and the aqueous layer extracted with DCM (2 × 30 ml). The combined organic fractions were dried ($MgSO_4$) and the solvent removed under reduced pressure to yield the product as a mixture of 2 diastereomers **8a** : **9a** (ratio approximately 2 : 1) which were separated by flash column chromatography (ethyl acetate–petrol = 1 : 9 gradient to ethyl acetate–petrol = 1 : 1). The first isomer (R_f = 0.6, ethyl acetate–petrol = 1 : 1) was *endo* malonate **8a** which was a colourless oil (170 mg, 53%). $[\alpha]_D$ +139 (*c* 3.0 $CHCl_3$); $\nu_{max}(CHCl_3)$/ cm^{-1} 1736(s), 1704(s), 1438, 1357, 1270; δ_H(200 MHz, $CDCl_3$) 2.01–2.13(1H, m, C(6)H_{endo}), 2.51–2.66(1H, m, C(6)H_{exo}), 3.52–3.73(2H, m, C(4)H_{endo} and C(7)H), 3.78(3H, s, OCH_3), 3.80(3H, s, OCH_3), 3.92(1H, d, *J* 6.5 Hz, C(1′)H), 4.13–4.32(2H, m, C(4)H_{exo} and C(5)H), 6.29(1H, s,

C(2)H), 7.29–7.45(5H, m, ArH); δ_C(50.3 MHz, $CDCl_3$) 28.48(C(6)), 44.93(C(7)), 51.14, 52.74, 52.80, 56.84, 72.18(C(6)), 87.18(C(2)), 126.0, 128.4, 128.6, 138.4, 168.1, 168.6, 175.4; *m/e*[probe CI^+, NH_3] 334(MH^+,100%). The second isomer, a pale oil, (R_f = 0.5) was *exo* malonate **9a** (85 mg, 27%). $[\alpha]_D$ +134 (*c* 1.05 $CHCl_3$); ν_{max}($CHCl_3$)/cm^{-1} 1704, 1736; δ_H(200 MHz, $CDCl_3$) 2.05–2.38(2H, m, C(6)H), 3.27–3.47(2H, m, C(4)H_{endo} and C(7)H), 3.70(3H, s, OCH_3), 3.79(3H, s, OCH_3), 3.96(1H, d, *J* 5.5 Hz, C(1′)H), 4.04–4.28(2H, m, C(4)H_{exo} and C(5)H), 6.31(1H, s, C(2)H), 7.34–7.43(5H, m, ArH); δ_C(50.3 MHz, $CDCl_3$) 24.39(C(6)), 43.73(C(7)), 51.88, 52.71, 52.83, 57.05, 70.60(C(4)), 87.46(C(2)), 125.8, 128.4, 128.5, 138.7, 167.9, 168.2, 177.2; *m/e*[probe CI^+, NH_3] 334(MH^+,100%); HRMS 334.1291; MH^+ requires 334.1291.

(2*R*,5*S*,7*R*) and (2*R*,5*S*,7*S*)-1-Aza-3-oxa-8-oxo-2-phenyl-7-(methyloxycarbonylcyanomethyl) bicyclo[3.3.0]octane 8b and 9b

To NaH (39.0 mg, 1.0 mmol) in THF (5 ml) at 0 °C was added methyl cyanoacetate (123 mg, 1.2 mmol) and the solution stirred for 30 minutes under nitrogen. A solution of *exo*-iodide **7b** (273 mg, 0.83 mmol) in THF (15 ml) was added to the reaction mixture at 0 °C. After 1 hour the reaction mixture was quenched with aqueous saturated ammonium chloride. Ethyl acetate (20 ml) and cold water (15 ml) were added to the reaction mixture and the aqueous layer was extracted with EtOAc (3 × 10 ml). The organic layers were washed with brine (20 ml), then dried ($MgSO_4$). Solvent removed *in vacuo* yielded a brown oil which was purified by flash column chromatography on silica [EtOAc–petrol(40/60), 1 : 2] to give *endo*-**8b** (176 mg, 71%) as a pale yellow oil and a mixture of diastereomers. R_f = 0.37 [EtOAc–petrol(40/60), 2 : 3]; ν_{max}/cm^{-1} ($CHCl_3$) 3027, 2341, 2254, 1753, 1712, 1603, 1403, 1265, 1209; δ_H(400 MHz, $CDCl_3$) 1.98–2.10(1H, m, C(6)H_{endo}(A + B)), 2.65–2.75(1H, m, C(6)H_{exo}(A + B)), 3.57–3.63(1H, m, C(7)H(A + B)), 3.64–3.74(1H, m, C(4)H_{endo}(A + B)), 3.85(3H, s, CO_2CH_3(A)), 3.87(3H, s, CO_2CH_3(B)), 4.01–4.04(1H, m, C(1′)H(A), 4.19–4.29(2H, m, C(5)H(A + B) and C(1′)H(B)), 4.23–4.39(1H, m, C(4)H_{exo}(A + B)), 6.29(1H, s, C(2)H(A)), 6.32(1H, s, C(2)H(B)), 7.41–7.49(5H, m, ArH(A + B)); δ_C(400 MHz, $CDCl_3$) 27.80, 28.8(C(6)(A + B)), 36.90, 38.10(C(1′)(A + B)), 45.5, 45.7(C(7)(A + B)), 53.6, 53.9(CO_2CH_3(A + B)), 56.6, 57.8(C(5)(A + B)), 70.6, 72.1(C(4)(A + B)), 87.3(C(2)(A + B)), 89.9, 114.4, 115.0(CN(A + B)), 125.9, 126.0, 128.5, 128.6, 128.8, 128.9(Ph*C*H(A + B)), 135.5, 137.8, 138.1(Ph*C*(A + B)), 164.5, 165.2(*C*O_2Me(A + B)), 172.8, 173(C(8)(A + B)); *m/e* (CI^+) 301 (MH^+, 45%), 274 (10), 246 (30), 213 (20), 204 (40); HRMS 301.1185, MH^+ requires 301.1188.

The second product was the *exo*-substituted product **9b** (32 mg, 12.9%) as a yellow oil. R_f = 0.22 [EtOAc–petrol(40/60), 2 : 3]; ν_{max}($CHCl_3$)/cm^{-1} 3684, 3010, 2433, 2253, 1754, 1713, 1601, 1580, 1521, 1476, 1423, 1283, 1190; δ_H(400 MHz, $CDCl_3$) 2.29–2.43(2H, m, C(6)H(A + B)), 3.30–3.40(1H, m, C(7)H(A + B)), 3.40–3.50(1H, m, C(4)H_{endo}(A + B)), 3.80(3H, s, $COOCH_3$(A)), 3.90(3H, s, $COOCH_3$(B)), 4.03–4.32(3H, m, C(5)H, C(4)H_{exo}, C(1′)H(A + B)), 6.31(1H, s, C(2)H(A)), 6.34(1H, s, C(2)H(B)), 7.40(5H, m, ArH(A + B)); δ_C(400 MHz, $CDCl_3$) 24.3(C(6)(A + B)), 38.2, 39.2(C(1′)(A + B)), 44.5, 44.6(C(7)(A + B)), 53.4, 54.1(CO_2CH_3), 56.9, 57.2(C(5)(A + B)), 70.6(C(4)(A + B)), 87.6(C(2)(A + B)), 114.1, 114.8(CN(A + B)), 125.8, 126.0, 128.5, 128.7, 128.8(Ph*C*H(A + B)), 137.8, 138.1(Ph*C*(A + B)), 164.4, 165.0(*C*O_2Me(A + B)), 174.6, 175.1(C(8)(A + B)); *m/e* (CI^+) 301.0 (MH^+, 100%); HRMS 301.1193, MH^+ requires 301.1188.

(2*R*,5*S*,7*R*) and (2*R*,5*S*,7*S*)-1-Aza-3-oxa-8-oxo-2-phenyl-7-[ethyloxycarbonyl(benzhydrylideneamino)methyl]bicyclo[3.3.0]-octane 8c, 8c′ and 9c

A solution of *N*-(diphenylmethylene)glycine ethyl ester (85 mg, 0.32 mmol) in THF (5 ml) was added dropwise to a solution of LDA (0.30 mmol) under nitrogen in THF (10 ml) precooled to −78 °C. After stirring for 15 minutes a solution of *endo*-iodide **7a** (100 mg, 0.30 mmol) in THF (5 ml) was added. The reaction was stirred at −78 °C for 1 hour, warmed to room temperature and quenched with water (10 ml). The aqueous layer was extracted with DCM (3 × 20 ml), the combined organic extracts were dried ($MgSO_4$) and the solvent removed *in vacuo*. The product was obtained as a mixture of diastereomers which were separated by flash column chromatography (ethyl acetate–petrol = 1 : 20 gradient to 1 : 1). The *endo*- product **8c** (R_f = 0.55 ethyl acetate–petrol = 1 : 1) was a pale yellow oil that decomposed upon standing at room temperature (29 mg, 20%). δ_H(500 MHz, $CDCl_3$) 1.24(3H, t, *J* 7.0 Hz, C$H_3$$CH_2$), 2.53–2.59(1H, m, C(6)$H_{endo}$), 2.63–2.69(1H, m, C(6)$H_{exo}$), 3.67–3.71(1H, m, C(7)H), 3.77(1H, dd, *J* 8.0, 8.0 Hz, C(4)H_{endo}), 4.10–4.21(3H, m, H5 and OCH2), 4.33(1H, dd, *J* 6.0, 8.0 Hz, C(4)H_{exo}), 4.71(1H, d, *J* 3.0 Hz, H-1′), 6.24(1H, s, C(2)H), 7.29–7.65(15H, m, ArH); δ_C(125 MHz, $CDCl_3$) 14.15(CH_3), 24.79(C(6)), 48.81(C(7)), 56.82(C(5)), 61.22, 63.80, 72.21(C(4)), 86.77(C(2)), 125.9, 127.9, 128.1, 128.3, 128.4, 128.5, 128.6, 128.8, 130.5, 136.5, 138.9, 139.5, 170.6, 172.9, 176.2; *m/e*[probe CI^+, NH_3] 469(MH^+, 100%); HRMS 469.2127, MH^+ requires 469.21273.

The second isomer **8c′** was a minor component which was crystallised from ether as translucent needles (8 mg, 5.6%). Mp 166–7 °C; $[\alpha]_D$ +32(*c* 0.85 $CHCl_3$); (Found: C, 74.18; H, 5.35; N, 5.52. $C_{29}H_{28}N_2O_4$ requires C, 74.34; H, 6.02; N, 5.98%); ν_{max}($CHCl_3$)/cm^{-1} 1730(s), 1709(s); δ_H(500 MHz, $CDCl_3$) 1.28(3H, t, *J* 7.0 Hz, CH_3), 2.06–2.12(1H, m, C(6)H_{endo}), 2.53–2.59(1H, m, C(6)H_{exo}), 3.39–3.45(1H, m, C(7)H), 3.67(1H, dd, *J* 8.0, 8.0 Hz, C(4)H_{endo}), 4.10–4.28(4H, m, C(5)H and OCH_2, and C(4)H_{exo}), 4.50(1H, d, *J* 4.0 Hz, H-1′), 6.39(1H, s, C(2)H), 7.21–7.68(15H, m, ArH); δ_C(125 MHz, $CDCl_3$) 14.08(CH_3), 26.56(C(6)), 48.25(C(7)), 56.72(C(5)), 61.33, 64.84, 72.37(C(4)), 87.10(C(2)), 126.0, 127.5, 128.1, 128.3, 128.4, 128.7, 128.9, 130.6, 135.9, 139.0, 170.2, 172.1, 176.2; *m/e* [probe CI^+, NH_3] 469(MH^+, 100%), 182(90%).

The third isomer to be recovered from the column (R_f = 0.25) was product **9c** (90 mg, 63%), a colourless solid which was recrystallised from diethyl ether or chloroform–petrol. Mp 138–40 °C. (Found: C, 74.17; H, 5.82; N, 5.98. $C_{29}H_{28}N_2O_4$ requires C, 74.34; H,6.02; N, 5.98%); $[\alpha]_D$ −106 (*c* 1.0 $CHCl_3$); ν_{max}-($CHCl_3$)/cm^{-1} 1731, 1698; δ_H(500 MHz, $CDCl_3$) 1.26(3H, t, *J* 7.0 Hz, CH_3), 2.17–2.24(1H, m, C(6)H_{endo}), 2.86–2.91(1H, m, C(6)H_{exo}), 3.43–3.50(2H, m, C(7)H and C(4)H_{endo}), 4.13–4.28(3H, m, OCH_2 and C(4)H_{exo}), 4.36–4.41(1H, m, C(5)H), 4.66(1H, d, *J* 2.5 Hz, H-1′), 6.26(1H, s, C(2)H), 7.00–7.62(15H, m, ArH); δ_C(125 MHz, $CDCl_3$) 14.14(CH_3), 25.59(C(6)), 48.98(C(7)), 59.02(C(5)), 61.35, 65.29, 72.16(C(4)), 86.60(C(2)), 125.8, 127.8, 128.1, 128.2, 128.4, 128.7, 128.9, 130.6, 135.7, 138.2, 139.1, 170.3, 172.9, 176.1; *m/e* [probe CI^+, NH_3] 469(100%, MH^+), 362(30).

(2*R*,5*S*,7*R*) and (2*R*,5*S*,7*S*)-1-Aza-3-oxa-8-oxo-2-phenyl-7-[*tert*-butyloxycarbonyl(benzhydrylideneamino)methyl]bicyclo-[3.3.0]octane 8d, 8d′ and 9d

N-(Diphenylmethylene)glycine *tert*-butyl ester (0.480 g, 1.63 mmol) in THF (20 ml) was added to a solution of LDA (1.52 mmol) in THF (15 ml) at −78 °C and under nitrogen. The resulting bright yellow solution was stirred at −78 °C for 15 minutes, *exo* iodide **7b** (0.500 g, 1.52 mmol) in THF (20 ml) was added and the reaction mixture was stirred at −78 °C for 1 hour and then at room temperature for a further 16 hours, during which time it decolourised. The solvent was removed under reduced pressure and ethyl acetate (50 ml) added. The resulting organic phase was washed with distilled water (4 × 20 ml), dried over magnesium sulfate and evaporated to dryness, yielding a yellow oil which was purified by flash

column chromatography on silica (10 : 1 petroleum ether : ethyl acetate). The *endo*- product **8d** was a yellow solid (0.144 g, 17%): Mp 42–46 °C; R_f 0.40 (3 : 1 petroleum ether: ethyl acetate); (Found: C, 75.20; H, 6.38; N, 5.47. $C_{31}H_{32}N_2O_4$ requires C, 74.98; H, 6.49; N, 5.64%); $[\alpha]_D^{23}$ +218 (*c* 0.05, $CHCl_3$); $\nu_{max}(CHCl_3)/cm^{-1}$ 1727 (CO); δ_H(500 MHz, $CDCl_3$) 1.43(9H, s, $C(CH_3)3$), 2.52–2.58(1H, m, $C(6)H_{exo}$), 2.68–2.73(1H, m, $C(6)H_{endo}$), 3.66(1H, ddd, *J* 9.5, 9.5, 3.0 Hz, C(7)H), 3.81(1H, dd, *J* 8.0, 8.0 Hz, $C(4)H_{endo}$), 4.15–4.19(1H, m, C(5)H), 4.34(1H, dd, *J* 8.0, 6.0 Hz, $C(4)H_{exo}$), 4.62(1H, d, *J* 3.0 Hz, C(1′)H), 6.26(1H, s, C(2)H), 7.30–7.66(15H, m, ArH); δ_C(50.3 MHz, $CDCl_3$) 24.31(C(6)), 27.89($C(CH_3)_3$), 48.93(C(7)), 56.89(C(5)), 64.43(C(1′)), 72.24(C(4)), 81.65($OC(CH_3)_3$), 86.88(C(2)), 126.2, 127.8, 128.1, 128.3, 128.5, 128.6, 128.8, 129.0, 129.3, 130.3, 130.6(ArC), 137.0, 139.3, 139.9(4° ArC), 170.2, 172.8 and 176.9(Ph_2C=N, C(8) and $CO_2{}^tBu$); *m*/*e* (probe CI; NH_3) 497 (MH^+, 20%), 397 (73), 182 (100).

The second isomer **8d′** was a white solid, which was recrystallised from petroleum ether–ethyl acetate (0.116 g, 14%): mp 125–127 °C; R_f 0.32 (3 : 1 petroleum ether: ethyl acetate); $[\alpha]_D^{23}$ + 59 (*c* 0.14, $CHCl_3$); ν_{max} $(CHCl_3)/cm^{-1}$ 1712 (CO); δ_H(500 MHz, $CDCl_3$) 1.54(9H, s, $C(CH_3)_3$), 2.02–2.08(1H, m, $C(6)H_{endo}$), 2.58–2.65(1H, m, $C(6)H_{exo}$), 3.51(1H, ddd, *J* 10.0, 10.0, 4.0 Hz, $C(7)H_{exo}$), 3.71(1H, dd, *J* 8.0, 8.0 Hz, $C(4)H_{endo}$), 4.13–4.19(1H, m, C(5)H), 4.29(1H, dd, *J* 8.0, 8.0 Hz, $C(4)H_{exo}$), 4.41(1H, d, *J* 4.0 Hz, C(1′)H), 6.48(1H, s, C(2)H), 7.27–7.88(15H, m, ArH); δ_H(50.3 MHz, $CDCl_3$) 26.83(C(6)), 27.94($C(CH_3)_3$), 48.23(C(7)), 56.64(C(5)), 65.66(C(1′)), 72.36(C(4)), 81.77($OC(CH_3)_3$), 87.14(C(2)), 126.1, 126.3, 127.8, 128.3, 128.6, 128.8, 129.1, 130.7(ArC), 136.4, 139.4(4°ArC), 169.4, 172.0 and 176.7(Ph_2C=N, C(8) and $CO_2{}^tBu$); *m*/*e* (probe CI, NH_3) 497 (MH^+, 100%), 397 (22), 395 (11); HRMS (CI) 497.2460, MH^+ requires 497.2440.

The third diastereomer (0.297g, 39%) was a transparent glass **9d** which solidified very slowly. Mp 94–96 °C; R_f 0.19 (3 : 1 petroleum ether: ethyl acetate); $[\alpha]_D^{23}$ −49.6 (*c* 1.8, $CHCl_3$); ν_{max}-(thin film)/cm^{-1} 1730(sh) (ester CO), 1704 (lactam CO); δ_H(500 MHz, $CDCl_3$) 1.44 (9H, s, $C(CH_3)_3$), 2.16–2.21(1H, m, $C(6)H_{endo}$), 2.89–2.94(1H, m, $C(6)H_{exo}$), 3.40–3.43(1H, m, C(7)H), 3.48(1H, dd, *J* 8.5, 8.0 Hz, $C(4)H_{endo}$), 4.25(1H, dd, *J* 8.0, 6.0 Hz, $C(4)H_{exo}$), 4.39–4.42(1H, m, C(5)H), 4.56(1H, d, *J* 2.5 Hz, C(1′)H), 6.27(1H, s, C(2)H), 7.01–7.83(15H, m, ArH); δ_C(50.3 MHz, $CDCl_3$) 25.49(C(6)), 27.89($C(CH_3)_3$), 50.19(C(7)), 59.13(C(5)), 65.92(C(1′), 72.28(C(4)), 81.86($C(CH_3)_3$), 86.65(C(2)), 126.1, 128.0, 128.3, 128.5, 128.6, 128.9, 129.1, 130.3, 130.7(ArC), 136.1, 138.5, 139.5(4° ArC), 169.8, 172.8 and 176.7(Ph_2C = N, C(8) and $CO_2{}^tBu$); *m*/*e*(probe CI, NH_3) 497(MH^+, 100%), 395 (10), 390 (12), 289 (10); HRMS (CI) 497.2463, MH^+ requires 497.2440.

Reaction of iodides 7b with Schöllkopf reagent

n-Butyllithium (2.5 M solution in hexanes (0.238 ml, 0.60 mmol)) was added dropwise to a solution of (2*R*)-2,5-dihydro-2-isopropyl-3,6-dimethoxypyrazine[68] (0.55 mmol, 102 mg) in THF (10 ml) at −78 °C. The reaction was stirred for 15 minutes and a solution of *exo*-iodide **7b** (250 mg, 0.750 mmol) in THF (5 ml) added. The reaction was warmed to room temperature and stirred for a further 15 minutes. Water (10 ml) was added and then aqueous layer extracted with DCM (3 × 30 ml). The combined organic fractions were dried ($MgSO_4$) and the solvent removed *in vacuo* to give a pale oil which was purified by flash column chromatography (ethyl acetate–petrol = 3 : 7 gradient to ethyl acetate–petrol = 3 : 2) to give dimer **10** which was a pale yellow low melting solid (68 mg, 66%); $\nu_{max}(CHCl_3)/cm^{-1}$ 1240, 1437, 1462, 1700; $\delta_H(CDCl_3)$ 0.64 (6H, d, *J* 7.0 Hz, 2 × CH_3), 1.02(6H, d, *J* 7.0 Hz, 2 × CH_3), 2.25(2H, m, 2 × $CH(Me)_2$), 3.52(6H, s, OMe), 3.65(2H, m, 2 × $CHMe_2$), 3.75(6H, s, OMe), 3.88(1H, d, *J* 4.0 Hz, CHN), 4.52(1H, d, *J* 4.0 Hz, CHN). δ_C(50.3 MHz, $CDCl_3$) 16.39, 19.06, 31.47, 52.28, 52.49, 57.76, 60.25, 60.58, 161.3, 164.8; *m*/*e* [probeCI$^+$, NH_3] 367(100%, MH^+).

(2*S*,4*R*)-4-[Di(methoxycarbonyl)methyl]-2-hydroxymethyl-5-oxopyrrolidine 11a

endo-Malonate **8a** (0.100 g, 0.3 mmol) and trifluoroacetic acid (0.72 ml, 9.38 mmol) in dichloromethane (10 ml) were stirred at room temperature for 3 hours, and the reaction mixture was left to stand for 16 hours. The dichloromethane solvent was removed under reduced pressure. The resulting oil was purified by flash column chromatography on silica (15 : 1 ethyl acetate–MeOH gradient to 9 : 1), to give the product **11a** as a glassy yellow oil (0.049 g, 67%): R_f 0.59 (3 : 1 ethyl acetate–MeOH); (Found: C, 46.52; H, 5.84; N, 4.31. $C_{10}H_{15}NO_6$ requires C, 48.98; H, 6.16; N, 5.71%); $[\alpha]_D^{21}$ +24 (*c* 1.2, $CHCl_3$); ν_{max}(thin film)/cm^{-1} 3355(br), 1735, 1688; δ_H(200 MHz, $CDCl_3$) 1.66–1.82(1H, br m, C(3)H), 2.27–2.41(1H, br m, C(3)H), 3.13–3.25(1H, br m, C(4)H), 3.39–3.48(1H, br m, CHHOH), 3.73–3.88(9H, m, 2 × OCH_3, C(2)H, CHHOH, C(1′)H), 4.47 and 7.57(2 × br s, 2H, NH and OH); δ_C(125.8 MHz, $CDCl_3$) 26.43(C(3)), 41.47(C(4)), 51.27 and 54.51(C(2) and C(1′)), 52.69 and 52.73(2 × OCH_3), 64.83(CH_2OH), 168.4 and 168.9 (2 × CO_2Me), 177.13(C(5)); MS(APCI$^+$) *m*/*e* 246 (MH^+, 20%), 214(45), 186(3), 182(100).

(2*S*,4*R*)-2-Carboxy-4-[di(methoxycarbonyl)methyl]-5-oxopyrrolidine 11b

Sodium periodate (0.208 g, 0.97 mmol) and ruthenium(III) chloride (0.010 g) were added to a solution of lactam **11a** (0.056 g, 0.23 mmol) in tetrachloromethane (7 ml), acetonitrile (7 ml) and water (10 ml) and the mixture was stirred vigorously at room temperature for 4 hours. Methanol (2 ml) was added to the resulting orange/brown mixture to destroy excess oxidant and the mixture was stirred for a further 20 minutes. Water (15 ml) and ethyl acetate (15 ml) were added and the layers were separated. Brine (10 ml) was added to the aqueous layer, which was then extracted with ethyl acetate (3 × 15 ml). The combined organic layers were washed with brine, dried ($MgSO_4$) and evaporated under reduced pressure to give a red/brown oil, which was subjected to flash column chromatography on silica (ethyl acetate). The product (5.6 mg, 10%) was obtained as a brown oil after chromatography (3 : 1 ethyl acetate–MeOH): ν_{max} (thin film)/cm^{-1} 3334(br) (NH and OH), 1735(s), 1704(sh), 1437; δ_H(500 MHz, $CDCl_3$) 2.06–2.10(1H, br m, C(3)H), 2.68(1H, br m, C(3)H), 3.16–3.17(1H, br m, C(4)H), 3.71(3H, s, OCH_3), 3.76(3H, s, OCH_3), 3.81–3.89(1H, br m, C(1′)H)), 4.23(1H, br m, C(2)H), 4.65 and 7.59(2H, 2 × br s, OH and NH); *m*/*e* (APCI$^-$) 258 (M – H+, 38%), 226 (62), 200 (26), 182 (100).

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

A 0.5 M solution of hydroxylamine hydrochloride in 80% v/v EtOH in water (2.0 ml) was added to a solution of imine **8c** (0.228 g, 0.49 mmol) in dichloromethane (25 ml) and the solution was heated under reflux for 16 hours. Dichloromethane (15 ml) was then added and the organic phase was washed with 5% sodium hydrogen carbonate solution (2 × 10 ml) and dried over magnesium sulfate and the solvent was removed *in vacuo*. The resulting yellow oil was purified by flash column chromatography on silica (ethyl acetate eluent) to give the product as a pale yellow oil (0.129 g, 87%): R_f 0.53 (3 : 1 ethyl acetate–MeOH); $[\alpha]_D^{21}$ +186 (*c* 1.04, $CHCl_3$); ν_{max}(thin film)/cm^{-1} 3397(w), 1732, 1704; δ_H(200 MHz, $CDCl_3$) 1.28(3H, t, *J* 7.0 Hz, OCH_2CH_3), 1.95–2.10(1H, m, C(6)H), 2.21–2.36(1H, m, C(6)H), 3.45(1H, ddd, *J* 10.0, 10.0, 3.0 Hz, C(7)H), 3.64(1H, dd, *J* 8.0, 8.0 Hz, C(4)H), 4.03–4.27(5H, m, OCH_2CH_3, C(5), C(4)H and C(1′)H), 6.30(1H, s, C(2)H), 7.31–7.47(m, 5H,

ArH); δ_C(50.3 MHz, $CDCl_3$) 14.08(CH_3), 24.02(C(6)), 49.2 and 52.64(C(1′) and C(7)), 56.54(C(5)), 61.36(OCH_2CH_3), 71.96(C(4)), 86.77(C(2)), 126.2, 128.6, 128.8(ArC), 139.0(4° ArC), 173.9 and 176.8(C(8) and CO_2Et); *m/e* (electrospray) 305(MH^+, 100%), 288(86), 257(6); HRMS(CI) 304.1423, MH^+ requires 304.1433.

(2*R*,5*S*,7*R*,1′*S*)-1-Aza-3-oxa-8-oxo-2-phenyl-7-[amino(ethoxycarbonyl)methyl]bicyclo[3.3.0]octane 13a

This compound was prepared from imine **8c**′ on a 0.110 g scale by the above method, except that the number of equivalents and the molarity of the hydroxylamine hydrochloride solution were doubled and the time of reflux was 2 hours. Flash column chromatography on silica afforded the product as an orange oil (0.033 g, 46%): R_f 0.41 (3 : 1 ethyl acetate–MeOH); (Found: C, 62.92; H, 7.33; N, 8.16. $C_{16}H_{20}N_2O_4$ requires C, 63.14; H, 6.62; N, 9.20%); $[\alpha]_D^{21}$ +141 (*c* 1.25, $CHCl_3$); ν_{max}(film)/cm^{-1} 3386(w), 1735, 1701; δ_H(200 MHz, $CDCl_3$) 1.31(3H, t, *J* 7.0 Hz, OCH_2CH_3), 2.02–2.17(1H, m, C(6)H), 2.45–2.59(1H, m, C(6)H), 3.53–3.68(3H, m, C(7)H, C(4)H and C(5)H), 4.06–4.30(4H, m, C(4)H, C(1′)H and OCH_2CH_3), 6.31(1H, s, C(2)H), 7.32–7.45(5H, m, ArH); δ_C(125 MHz, $CDCl_3$) 14.11(OCH_2CH_3), 28.05(C(6)), 48.94 and 54.69(C(7) and C(1′)), 56.62(C(5)), 61.36(OCH_2CH_3), 72.10(C(4)), 86.72(C(2)), 126.0, 128.4, 128.6(ArC), 138.5(4° ArC), 173.5 and 175.9(C(8) and CO_2Et); *m/e* ($APCI^+$) 305(MH^+, 97%), 288(100), 242(14), 231(19), 204(94).

(2*R*,5*S*,7*R*,1′*R*)-1-Aza-3-oxa-8-oxo-2-phenyl-7-[*N*-acetylamino-(ethoxycarbonyl)methyl]bicyclo[3.3.0]octane 12b

At −5 °C, acetic anhydride (0.042 g, 0.41 mmol) was added to a solution of amine **12a** (0.10 g, 0.33 mmol) and triethylamine (0.067 g, 0.66 mmol) in chloroform (9 ml). The mixture was stirred at −5 °C for 10 minutes and then at 0 °C for a further 4 hours. Following washing with citric acid solution (10% in H_2O; 3 × 8 ml) and drying over magnesium sulfate, the solvent was evaporated. The resulting yellow oil was purified by flash column chromatography on silica (1 : 1 petroleum ether–ethyl acetate gradient to 1 : 3) to give the product, a pale yellow oil (0.071 g, 62%): R_f 0.14 (1 : 3 petroleum ether–ethyl acetate); (Found: C, 62.26; H, 6.84; N, 7.68. $C_{18}H_{22}N_2O_5$ requires C, 62.42; H, 6.40; N, 8.09%); $[\alpha]_D^{25}$ +120 (*c* 0.20, $CHCl_3$); ν_{max} (film)/cm^{-1} 3313, 1739, 1703, 1690; δ_H(500 MHz, $CDCl_3$) 1.28(3H, t, *J* 7.0 Hz, OCH_2CH_3), 2.01(3H, s, $CH_3C(O)$), 2.14–2.20(1H, m, $C(6)H_{endo}$), 2.54–2.60(1H, m, $C(6)H_{exo}$), 3.27(1H, ddd, *J* 10.5, 10.5, 3.5 Hz, $C(7)H_{exo}$), 3.66(1H, dd, *J* 8.0, 8.0 Hz, $C(4)H_{endo}$), 4.07–4.16(1H, m, C(5)H), 4.17–4.27(3H, m, $C(4)H_{exo}$ and OCH_2CH_3), 4.84(1H, dd, *J* 8.5, 3.5 Hz, C(1′)H), 6.23(1H, s, C(2)H), 7.11(1H, br d, *J* 8.5 Hz, NH), 7.29–7.42(5H, m, ArH); δ_C(50.3 MHz, $CDCl_3$) 13.98(OCH_2CH_3), 22.94($H_3CC(O)$), 28.22(C(6)), 48.19 and 51.51(C(7) and C(1′)), 57.07(C(5)), 61.82(OCH_2CH_3), 72.26(C(4)), 86.89(C(2)), 126.2, 128.7, 129.0(ArC), 138.6(4° ArC), 169.9, 170.7 and 176.9($CH_3C(O)N$, C(8) and CO_2Et); *m/e* (probe CI, NH_3) 347(MH^+, 100%), 303(4), 288(4), 273(7), 231(14), 211(8), 202(26).

(2*R*,5*S*,7*R*,1′*S*)-1-Aza-3-oxa-8-oxo-2-phenyl-7-[*N*-acetylamino-(ethoxycarbonyl)methyl]bicyclo[3.3.0]octane 13b

This compound was prepared from amine **13a** on a 0.067 g scale by the same method as above and was obtained as a pale oil (0.045 g, 58%). R_f 0.15 (1 : 3 petroleum ether–ethyl acetate); (Found: C, 62.72; H, 6.58; N, 7.09. $C_{18}H_{22}N_2O_5$ requires C, 62.42; H, 6.40; N, 8.09%) $[\alpha]_D^{25}$ +200 (*c* 0.46, $CHCl_3$); ν_{max} (thin film)/cm^{-1} 3326m(br), 1742(s), 1704(s), 1680(s); δ_H(200 MHz, $CDCl_3$) 1.30(3H, t, *J* 7.0 Hz, OCH_2CH_3), 1.75–1.91(1H, m $C(6)H_{endo}$), 2.10(3H, s, $CH_3C(O)$), 2.52–2.67(1H, m, $C(6)H_{exo}$), 3.49(1H, dd, *J* 7.5, 7.5 Hz, $C(4)H_{endo}$), 3.79–3.91(1H, m, $C(7)H_{exo}$), 4.14(1H, m, C(5)H), 4.19–4.32(3H, m, $C(4)H_{exo}$ and OCH_2CH_3), 4.88(1H, dd, *J* 9.0, 3.0 Hz, C(1′)), 6.30(1H, s, C(2)H), 6.41(1H, br d, *J* 9.0 Hz, NH), 7.34–7.40(5H, m, ArH); δ_C(50.3 MHz, $CDCl_3$) 13.90(OCH_2CH_3), 23.08($CH_3C(O)N$), 28.88(C(6)), 48.38 and 50.81(C(7) and C(1′)), 56.74(C(5)), 62.02(OCH_2CH_3), 72.14(C(4)), 86.63(C(2)), 126.1, 128.6, 128.9(ArC), 138.1(ArC), 170.4, 171.5 and 175.6($CH_3C(O)N$, C(8) and CO_2Et); *m/e* (probe CI, NH_3) 347(MH^+, 100%), 288(4), 273(4), 231(10), 211(5), 202(28).

(2*R*, 5*S*, 7*S*)-1-Aza-3-oxa-8-oxo-2-phenyl-7-[*N*-acetylamino-(ethoxycarbonyl)methyl]bicyclo[3.3.0]octane 14

A 1 M solution of hydroxylamine hydrochloride in 80% v/v EtOH in water (0.51 ml) was added to a solution of *exo* imine **9c** (60 mg, 0.13 mmol) in dichloromethane (25 ml) and the mixture heated under reflux for 16 hours. Dichloromethane (15 ml) was added and the organic phase was washed with 5% sodium hydrogen carbonate solution (2 × 10 ml). The aqueous layers were combined and extracted with ethyl acetate (2 × 15 ml). The combined organic layers were dried ($MgSO_4$) and the solvent removed *in vacuo* to yield the crude amine as a brown oil. This was immediately treated with acetic anhydride (39 mg, 0.38 mmol) and triethylamine (38 mg, 0.38 mmol) in chloroform (10 ml). The mixture was stirred at −5 °C for 10 minutes then at 0 °C for a further 4 hours. It was washed with citric acid solution (10% in H_2O; 3 × 10 ml) and dried($MgSO_4$). The solvent was removed *in vacuo* and the crude oil was purified by flash column chromatography (ethyl acetate) to give the product **14** as a colourless oil (40 mg, 61% over 2 steps): R_f 0.12 (1 : 6 petrol–ethyl acetate); ν_{max} (thin film)/cm^{-1} 2924(br m), 1737(s), 1700(s), 1667(s); δ_H(200 MHz, $CDCl_3$) 1.14(3H, t, *J* 7.0 Hz, OCH_2CH_3), 2.03(3H, s, $CH_3C(O)$), 2.12–2.24(1H, m, $C(6)H_{endo}$), 2.38–2.51(1H, m, $C(6)H_{exo}$), 3.01–3.10(1H, m, C(7)H), 3.42(1H, dd, *J* 8.5, 8.5 Hz, $C(4)H_{endo}$), 4.00–4.28(4H, m, C(5)H, $C(4)H_{exo}$ and OCH_2CH_3), 4.90(1H, dd, *J* 5.0, 8.5 Hz, C(1′)H), 6.28(1H, s, C(2)H), 6.81(1H, br d, *J* 8.5 Hz, NH), 7.37–7.39(5H, m, ArH); δ_C(50.3 MHz, $CDCl_3$) 13.85(OCH_2CH_3), 23.04($H_3CC(O)$), 25.48(C(6)), 47.73 and 53.08(C(7) and C(1′)), 57.37(C(5)), 61.93(OCH_2CH_3), 71.49(C(4)), 86.90(C(2)), 125.7, 128.4 and 128.6(ArC), 138.4(4 °C), 169.9(2 × CO), 176.3(CO); *m/e*($APCI^+$) 347(MH^+, 100%), HRMS(CI^+) 347.1607, MH^+ requires 347.1606.

(2*S*,4*S*)-*N*-Benzyl-2-methoxycarbonyl-4-[*N*-acetylamino-(ethoxycarbonyl)methyl]-5-oxopyrrolidine 15

Lactam **14** (50 mg, 0.14 mmol) was hydrogenated to yield the crude alcohol product (40 mg): ν_{max} (film)/cm^{-1} 3286(br m, OH, NH), 1738(s, ester CO), 1672(s, lactam CO); *m/e* ($APCI^+$) 349 (MH^+, 100%). This was immediately oxidized according to the Sharpless protocol[69] to give a white solid (12 mg) LRMS ($APCI^+$) *m/e* 363 (MH^+, 100%), which was in turn immediately treated with diazomethane in ether. The solvent was removed *in vacuo* to give a pale yellow oil which was purified by flash column chromatography on silica (ethyl acetate). The product was obtained as a mixture of C-1′ diastereomers in a ratio of 1 : 2 (12 mg, 23% over 3 steps): R_f 0.31, 0.24 (EtOAc); ν_{max} (film)/cm^{-1} 3320(br m), 1742(s), 1695(s); δ_H(500 MHz, $CDCl_3$) (major diastereomer) 1.21(3H, t, *J* 7.0 Hz, OCH_2CH_3), 2.06(3H, s, $CH_3C(O)$), 2.27–2.33(1H, m, C(3)H), 2.46–2.51(1H, m, C(3)H), 2.98–3.03(1H, m, C(4)H), 3.68(3H, s, OCH_3), 3.98–4.01(2H, m, NCHPh and C(2)H), 4.08–4.20(2H, m, OCH_2CH_3), 4.88(1H, dd, *J* 3.5, 9.0 Hz, C(1′)H), 4.99(d, *J* 15.0 Hz, 1H, NCHPh), 7.17–7.39(5H, m, ArH), 7.23(1H, d, *J* 8.5 Hz, NH); δ_H(500 MHz, $CDCl_3$)(minor diastereomer) 1.32(3H, t, *J* 7.0 Hz, OCH_2CH_3), 2.02(s, 3H, $CH_3C(O)$), 2.27–2.33(1H, m, C(3)H), 2.67–2.71(1H, m, C(3)H), 3.47–3.52(1H, m, C(4)H), 3.69(3H, s, OCH_3), 3.91(1H, dd, *J* 1.5, 9.5 Hz, C(2)H), 3.98–4.01(1H, m, NCHPh), 4.21–4.32(m, 2H, OCH_2CH_3), 4.80(1H, dd, *J* 3.5, 8.5 Hz, C(1′)H), 4.97(1H, d, *J* 14.5 Hz, NCHPh), 6.35(1H, d, *J* 8.0 Hz, NH), 7.17–7.39(5H, m, ArH); *m/e* (probe CI, NH_3) 377 (MH^+, 100%).

(2*R*,5*S*,7*S*,1′*RS*)-7-(Phenyl-*N*-tosylaminomethyl)-8-oxo-2-phenyl-1-aza-3-oxabicyclo[3.3.0]octane 19a

To ″BuLi (0.65 ml, 1.3 mmol) at 0 °C in THF (6 ml) under nitrogen was added diisopropylamine (0.2 ml, 1.2 mmol) and the mixture stirred for 15 minutes at −78 °C. A solution of the lactam **1a** (220 mg, 1.1 mmol) in THF (5 ml) was added, and after 30 minutes, *N*-benzylidene-4-methyl-benzenesulfonamide (365 mg, 1.4 mmol) in THF (4 ml) was added to the mixture and stirring continued for 1 hour. The reaction mixture was then quenched with aqueous saturated sodium bicarbonate solution (5 ml), and the mixture extracted with ethyl acetate (30 ml). The combined organic extracts were washed with brine, dried ($MgSO_4$) and concentrated *in vacuo* to yield a yellow oil. Purification using flash column chromatography [EtOAc–petrol (40/60), 1 : 1] gave a white crystalline solid **19a** as a mixture of inseparable diastereomers at C-1′ (397 mg, 79%). R_f = 0.34 [EtOAc–Petrol(40/60), 1 : 2]; $\nu_{max}(CHCl_3)/cm^{-1}$ 1692, 1599, 1495, 1356; δ_H(400 MHz, $CDCl_3$) 1.78–1.85(1H, m, C(6)H_{endo}-(A)), 2.00–2.07(3H, m, C(6)H_{exo}(A), C(6)H_{endo} and C(6)H_{exo}(B)), 2.31 and 2.34(3H, s, CH_3(A + B)), 3.01–3.07(1H, m, C(7)H(A)), 3.17–3.20(2H, m, C(7)H(B) and C(5)H(A or B)), 3.30–3.34(1H, t, *J* 9.0 Hz, C(4)H_{endo}(A + B)), 3.76–3.83(1H, m, C(5)H(B or A)), 3.99–4.04 and 4.05–4.16(1H, m, C(4)H_{exo}-(A + B)), 4.39–4.48 and 4.65–4.75(1H, m, C(1′)H(A + B)), 6.17 and 6.25(1H, s, C(2)H(A + B)), 6.41 and 6.61(1H, 2 × d, *J* 3.2 and 8.7 Hz, NH(A + B)), 7.01–7.17 and 7.20–7.37 and 7.43–7.52(14H, m, ArH); δ_C(400 MHz, $CDCl_3$) 21.4 and 21.5(CH_3(A + B)), 25.1 and 25.6(C(6)(A + B)), 50.0 and 50.2(C(7)(A + B)), 56.8 and 57.2(C(5)(A + B)), 58.6 and 59.6(C(1′)(A + B)), 71.1 and 71.3(C(4)(A + B)), 86.8 and 87.1(C(2)(A + B)), 125.8, 125.9, 126.8, 127.2, 127.5, 127.6, 127.9, 128.1, 128.3, 128.4, 128.5, 128.6, 129.1, 129.3(Ph*C*(A + B)), 136.3, 136.8, 137.7, 137.9, 138.0(Ph*C*(A + B)), 142.7 and 143.1(*C*SO_2N, *C*CH_3 (A + B)), 176.5 and 177.2(C(8)(A + B)); *m*/*e* (CI^+) 463(MH^+, 55%), 292, 203, 166; HRMS 463.1691, MH^+ requires 463.1690.

(3*S*, 1′*RS*)-*N*-Methyl-3-(phenyl-*N*-tosylaminomethyl)-succinimide 20

To a solution of lactam **19a** (168 mg, 0.36 mmol) in DCM (5 ml) at room temperature was added TFA (0.3 ml, 3.6 mmol). After 1 hour solvent was removed *in vacuo* and the product purified by flash colum chromatography (6% MeOH in EtOAc) to give a pale yellow oil (72 mg, 53%). R_f = 0.28 (100% EtOAc) or 0.48 (EtOAc–MeOH, 1 : 16); ν_{max}/cm^{-1} 3684, 3436, 3037, 2401, 1682, 1521; δ_H(400 MHz, CD_3OD) 1.83–1.88(1H, m, C(3)H(A + B)), 1.95–2.03(1H, m, C(3)H(A)), 2.10–2.14(1H, m, C(3)H(B)), 2.32 and 2.36(3H, s, CH_3(A + B)), 2.86–2.94(1H, m, C(4)H(A + B)), 3.09–3.13(1H, m, C(2)H(A)), 3.30–3.36(1H, m, C(2)H(B)), 3.38–3.48(2H, m, CH_2OH(A + B)), 4.63–4.64(1H, d, *J* 6.7 Hz, C(6)H(A)), 4.84–4.88(1H, d, *J* 4.2 Hz, C(6)H(B)), 7.08–7.57(9H, m, ArH and FurylH(A + B)); δ_C(400 MHz, CD_3OD) 21.76 and 21.80(CH_3(A + B)), 26.26 and 26.54(C(3)(A + B)), 48.85 and 49.04(C(4)(A + B)), 55.80 and 56.01(C(2)(A + B)), 59.42 and 60.16(C(6)(A + B)), 66.01 and 66.16(CH_2OH(A + B)), 128.5, 128.6, 128.6, 129.0, 129.2, 129.3, 129.5, 129.7, 130.6, 130.8,(ArC), 139.5, 139.9 and 144.9(PhC(A + B)), 179.4(*C*(5)(A + B)); *m*/*e* 375(MH^+, 100%); HRMS 375.1378, MH^+ requires 375.1383.

To a stirred solution of the above pyrrolidinone (133 mg, 0.35 mmol) in CH_3CN (3 ml) and CCl_4 (3 ml) was added a solution of $NaIO_4$ (760 mg, 3.5 mmol) in water (4.5 ml) and then $RuCl_3.H_2O$ (7.4 mg cat.). The mixture was stirred vigorously overnight. The solvents were removed *in vacuo* and the residue was dissolved in THF (4 ml) and then a solution of diazomethane in ether was added with stirring. Water (20 ml) was added and the mixture extracted with EtOAc (3 × 20 ml). The organic phases were combined, dried over $MgSO_4$ and concentrated *in vacuo* to give succinimide **20** as a yellow oil (32 mg, 22% over two steps). R_f = 0.47 [EtOAc–Petrol (40/60), 1 : 1], $\nu_{max}(CHCl_3)/cm^{-1}$ 3053, 2983, 1700, 1600, 1422, 1265, 1220; δ_H(400 MHz, $CDCl_3$) 2.32 and 2.36(3H, s, CH_3(A + B)), 2.40–2.50(1H, m, C(4)H(A + B)), 2.51–2.60(1H, m, C(4)H(A)), 2.70–2.80(1H, m, C(4)H(B)), 2.82 and 2.86(3H, m, NCH_3-(A + B)), 3.22–3.44(1H, m, C(3)H(A + B)), 4.48–4.52(1H, m, C(1′)H(A)), 4.70–4.79(1H, m, C(1′)H(B)), 6.20(1H, d, *J* 3.6 Hz, NH), 6.53(1H, d, *J* 8.9 Hz, NH), 6.90–7.55(9H, m, ArH and FurylH(A + B)); δ_C(400 MHz, $CDCl_3$) 21.41 and 21.47 (CH_3(A)), 24.74–24.82(CH_3(B)), 30.96 and 31.36(C(4)-(A + B)), 44.63 and 44.89(C(3)(A + B)), 57.54 and 58.64(C(1′)(A + B)), 126.9, 127.2, 127.2, 127.4, 128.5, 128.5, 126.7, 128.8, 129.3, 129.4(ArC and FurylC(A + B)), 136.3, 136.5, 137.2, 143.5(ArC), 161.7 and 177.4(C(2) and C(5)-(A + B)); *m*/*e*(CI^+) 373(MH^+, 20%), 260, 250, 208, 202, 155; HRMS 373.1222, MH^+ requires 373.1224; 390.1488, M+NH_4+ requires 390.1487.

(2*R*,5*S*,7*S*,1′*RS*)-7-(*N*-Tosylamino-furan-2-yl-methyl)-8-oxo-2-phenyl-1-aza-3-oxa-bicyclo[3.3.0]octane 19b

To ″BuLi (0.7 ml, 1.7 mmol) at 0 °C in THF (10 ml) was added diisopropylamine (0.26 ml, 1.9 mmol) and the mixture cooled to −78 °C. A solution of lactam **1a** (289 mg, 1.42 mmol) in THF (5 ml) was then added to the reaction mixture at −78 °C. After 30 minutes, *N*-furan-2-ylmethylene-4-methyl-benzenesulfonamide (461 mg, 1.85 mmol) in THF (5 ml) was added to the mixture and then after stirring for 1 hour at the same temperature, the reaction mixture was quenched with aqueous saturated sodium bicarbonate solution (20 ml). Water (30 ml) was added and the mixture extracted with ethyl acetate (30 ml). The aqueous layer was extracted with ethyl acetate (3 × 20 ml) and the combined organic extracts were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo* to yield the crude product as a mixture of diastereomers. Purification by chromatography [EtOAc–Petrol (40/60), 1 : 1] gave a pale yellow solid (530 mg, 82%). R_f = 0.54 [EtOAc–Petrol (40/60), 7 : 3]; $\nu_{max}(CHCl_3)/cm^{-1}$ 3355, 3270, 1697, 1599, 1495, 1452; δ_H(400 MHz, $CDCl_3$) 1.96–2.06(1H, m, C(6)H_{endo}(A)), 2.08–2.13(2H, m, C(6)H_{endo}, C(6)H_{exo}(B)), 2.21–2.30(1H, C(6)H_{exo}(A)), 2.35 and 2.36(3H, s, CH_3(A + B)), 3.13–3.20(1H, m, C(7)H(B)), 3.22–3.30(1H, m, C(7)H(A)), 3.32–3.37(1H, m, C(4)H_{endo}(A + B)), 3.60–3.62(1H, m, C(5)H(B)), 3.79–3.88(1H, m, C(5)H(A)), 4.06–4.17(1H, m, C(4)H_{exo}(A + B)), 4.73(1H, t, *J* 6.5 Hz, C(1′)H(A)), 4.78–4.85(1H, m, C(1′)H(B)), 6.02–6.17(2H, m, FurylH(A + B) and 1H, m, SO_2NH(A)), 6.22 and 6.23(1H, s, C(2)H(A + B)), 6.43–6.45(1H, d, *J* 8.45 Hz, SO_2NH(B)), 7.12–7.20(3H, m, ArH and FurylH), 7.25–7.36(5H, m, ArH), 7.57–7.69(2H, m, ArH); δ_C(400 MHz, $CDCl_3$) 21.43 and 21.47(CH_3(A + B)), 24.76 and 25.13(C(6)(A + B)), 48.69 and 49.24(C(7)(A + B)), 52.45 and 52.75(C(1′)(A + B)), 57.02 and 57.16(C(5)(A + B)), 71.23(C(4)(A + B)), 86.84 and 87.05(C(2)), 108.73, 108.83, 110.17, 110.29, 125.8, 126.4, 126.8, 127.1, 128.3, 128.4, 128.6, 129.3, 129.4, 129.6, 136.8, 137.5, 138.2, 138.3, 142.4, 142.4, 143.0, 143.3(ArC and FurylC), 176.4 and 176.7; *m*/*e* (CI^+) 453(MH^+, 90%), 282(100), 204(15), 157(30); HRMS 453.1484, MH^+ requires 453.1485.

(2*R*, 5*S*, 7*S*, 1′*RS*)-7-(Methyloxycarbonyl-*N*-tosylamino-methyl)-8-oxo-2-phenyl-1-aza-3-oxabicyclo[3.3.0]octane 21

To a stirred solution of lactam **19b** (435 mg, 0.96 mmol) in CH_3CN (5 ml) and CCl_4 (5 ml) was added a solution of $NaIO_4$ (2.1 g, 9.62 mmol) in water (7.5 ml) and $RuCl_3{\cdot}H_2O$ (20 mg cat.). The mixture was stirred vigorously for 4 hours. The solvents were removed *in vacuo* and the residue was dissolved in THF. A solution of diazomethane in ether was then added with stirring which was continued for 30 minutes. Water (20 ml) was added to the mixture and the aqueous layer extracted with ethyl acetate (3 × 20 ml). The organic phases were combined, dried over $MgSO_4$ and concentrated *in vacuo* to give lactam **21** as a

colourless oil and mixture of diastereomers which was purified by flash column chromatography on silica [EtOAc–Petrol (40/60), 3 : 2] (90 mg, 21% over two steps). R_f = 0.35 [EtOAc–Petrol (40/60), 7 : 3]; $[\alpha]_D^{22}$ +98 (*c* 1, $CHCl_3$); $\nu_{max}(CHCl_3)/cm^{-1}$ 3332, 3020, 1744, 1708, 1598, 1482, 1354, 1264, 1210, 1165; δ_H(400 MHz, $CDCl_3$) 2.05–2.12(1H, m, C(6)H_{endo}), 2.26–2.33(1H, m, C(6)H_{exo}), 2.38(3H, s, $ArCH_3$), 3.02–3.09(1H, m, C(7)H), 3.35–3.45(4H, m, C(4)H_{endo} and CO_2CH_3), 4.01–4.08(1H, m, C(5)H), 4.16–4.22(1H, m, C(4)H_{exo}), 4.26–4.30(1H, dd, *J* 5.6 and 9.9 Hz, C(1′)H), 6.01–6.03(1H, d, *J* 9.9 Hz, SO_2NH), 6.24(1H, s, C(2)H), 7.20–7.45(7H, m, ArH), 7.69–7.81(2H, m, ArH); δ_C(400 MHz, $CDCl_3$) 21.04(CH_3), 24.48(C(6)), 48.08(C(7)), 52.94(CO_2CH_3), 56.44(C(1′)), 57.23(C(5)), 71.24(C(4)), 87.09(C(2)), 125.9, 125.9, 127.3, 128.4, 128.5, 128.6, 128.7, 129.1, 129.6, 129.7, 135.9 and 136.4, 138.3, 138.4 and 143.8(ArC), 170.2(CO_2Me), 175.48(C(8)); *m*/*e*(CI^+) 445(MH^+, 100%), 289, 274, 242; HRMS 445.1433, MH^+ requires 445.1435.

(2*S*,4*S*,1′*RS*)-2-Methyloxycarbonyl-4-(methyloxycarbonyl-*N*-tosylaminomethyl)-5-oxopyrrolidine 22

To a solution of lactam **21** (557 mg, 1.25 mmol) in DCM (10 ml) at room temperature was added TFA (0.96 ml, 12.53 mmol) while stirring. After 1 hour, the solvent was removed *in vacuo* and the product purified by flash column chromatography (15% MeOH in EtOAc) to give a pale yellow oil (146 mg, 33%). R_f = 0.35 (MeOH–EtOAc, 1 : 9); $\nu_{max}(CHCl_3)/cm^{-1}$ 3368, 1743, 1691, 1598, 1438, 1342, 1210, 1163; δ_H(400 MHz, $CDCl_3$) 1.89–1.96(1H, m, C(3)H), 2.04–2.11(1H, m, C(3)H), 2.36–2.44(3H, s, CH_3), 3.05–3.11(1H, m, C(4)H), 3.38(3H, s, CO_2CH_3), 3.44–3.48(1H, m, C*H*HOH), 3.68–3.71(1H, m, CH*H*OH), 3.75–3.83(1H, m, C(2)H), 4.11–4.23(1H, br, OH), 4.33–4.36(1H, dd, *J* 4.0 and 9.9 Hz, C(1′)H), 6.70–6.72(1H, d, *J* 9.9 Hz, NHTs), 7.24–7.29(2H, m, ArH), 7.63(1H, br, NH), 7.67–7.78(2H, m, ArH); δ_C(400 MHz, $CDCl_3$) 21.50(CH_3), 24.52(C(3)), 44.19(C(4)),52.55(CO_2CH_3),54.75(C(2)),56.01(C(1′)),65.15(CH_2-OH), 127.2, 127.4, 129.4, 129.6, 136.2, 143.4 and 143.8(ArC), 170.4(*C*O_2Me), 177.0(CO); *m*/*e*(CI^+) 357(MH^+, 100%), 297, 186, 154; HRMS 357.1120, MH^+ requires 357.1117.

To a stirred solution of the above alcohol (100 mg, 0.28 mmol) in CH_3CN (2 ml) and CCl_4 (2 ml) was added a solution of $NaIO_4$ (600 mg, 2.81 mmol) in water (3 ml) and the mixture stirred at room temperature for 10 minutes. Then $RuCl_3.H_2O$ (6.50 mg cat.) was added and the mixture stirred vigorously overnight. The solvents were removed *in vacuo* and the residue was dissolved in THF. A solution of diazomethane in ether was then added with stirring which was continued for 30 minutes. Water (10 ml) was added to the mixture and extracted with ethyl acetate (3 × 10 ml). The organic phases were combined, dried ($MgSO_4$) and concentrated *in vacuo* to give ester **22** a yellow oil (37 mg, 25% over two steps). R_f = 0.52 (100% EtOAc); $\nu_{max}(CHCl_3)/cm^{-1}$ 3025, 2326, 1743, 1410, 1320, 1224, 1163; δ_H(400 MHz, $CDCl_3$) 2.28–2.35(1H, m, C(3)H), 2.37–2.48(4H, m, CH_3 and C(3)H), 2.85–2.94(1H, m, C(4)H), 3.48(3H, s, CO_2CH_3), 3.78(3H, s, CO_2CH_3), 4.20(1H, m, C(2)H), 4.25–4.35(1H, dd, *J* 9.6 and 4.3 Hz, C(1′)H), 6.19(1H, d, *J* 8.8 Hz, SO_2NH), 6.48(1H, br, NH), 7.27–7.31(2H, m, ArH), 7.69–7.76(2H, m, ArH); δ_C(400 MHz, $CDCl_3$) 21.52(CH_3), 26.36(C(3)), 42.36(C(4)), 52.71(CO_2CH_3) 55.25 and 55.37(C(1′) and C(2)), 127.3, 127.3, 129.56, 136.7 and 143.7(ArC), 170.3, 172.1(*C*O_2CH_3), 175.4 and 175.7(CO); *m*/*e*(CI^+) 385(MH^+, 100%), 325, 182, 155; HRMS 385.1069, MH^+ requires 385.1068.

(2*R*, 5*S*, 7*S*, 1′*R*)-7-(*N*-Tosylaminofuran-2-yl-methyl)-8-oxo-2-phenyl-2-methyl-1-aza-3-oxabicyclo[3.3.0]octane 23

To *n*BuLi (0.26 ml, 0.57 mmol, 2.35 M in hexane) at 0 °C in THF (3 ml) was added diisopropylamine (0.1 ml, 0.62 mmol) and the mixture stirred for 15 minutes at −78 °C. A solution of lactam **1b** (103 mg, 0.47 mmol) in THF (2 ml) was added and the mixture stirred for 30 minutes. *N*-Furan-2-ylmethylene-4-methyl-benzenesulfonamide (154 mg, 0.62 mmol) in THF (2 ml) was added to the reaction mixture. The reaction mixture was quenched after stirring for 1 hour, with aqueous saturated ammonium chloride solution (1 ml). Water (20 ml) was added and the mixture extracted with ethyl acetate (10 ml). The aqueous layer was then extracted with ethyl acetate (3 × 15 ml) and the combined organic extracts were washed with brine, dried ($MgSO_4$) and concentrated *in vacuo* to yield a brown liquid. Purification of this yellow liquid using flash column chromatography [EtOAc–Petrol (40/60), 3 : 2] gave a pale yellow solid (168 mg, 76%). R_f = 0.29 [EtOAc–Petrol (40/60), 2 : 3]; $[\alpha]_D^{22}$ +72 (*c* 1, $CHCl_3$); $\nu_{max}(CHCl_3)/cm^{-1}$ 3350, 3250, 3026, 1689, 1406, 1265, 1222, 1210, 1162; δ_H(400 MHz, $CDCl_3$) 1.85–2.02(3H, s, C(2)CH_3(A + B) and 1H, m, C(6)H(A) and 2H, m, C(6)H(B)), 2.11–2.22(1H, m, C(6)H(A)), 2.37 and 2.38(3H, s, CH_3(A + B)), 3.17–3.28(1H, m, C(5)H(B) and 1H, m, C(7)H(B)), 3.31–3.37(1H, m, C(7)H(A)), 3.45–3.52(1H, m, C(4)H_{endo}(A + B)), 3.56–3.63(1H, m, C(5)H(A)), 3.89–4.00(1H, m, C(4)H_{exo}(A + B)), 4.71–4.79(1H, m, C(1′)H(A + B)), 6.01–6.12(2H, m, FurylH(A + B)), 6.64–6.67(1H, d, *J* 9.1 Hz, SO_2NH(A + B)), 6.84–6.85 and 7.05–7.16(1H, m, FurylH(A + B)), 7.15–7.20(2H, m, ArH(A + B)), 7.26–7.41(5H, m, ArH(A + B)), 7.59–7.66(2H, m, ArH(A + B)); δ_C(400 MHz, $CDCl_3$) 21.45 and 21.51(CH_3(A + B)), 25.51 and 26.69(C(6)(A + B)), 25.62(CH_3(A + B)), 50.56 and 52.22(C(7)(A + B)), 52.33 and 52.49(C(1′)(A + B)), 58.94 and 59.05(C(5)(A + B)), 70.14(C(4)(A + B)), 94.00 and 94.23(C(2)(A + B)), 108.76, 110.1, 110.3, 124.9, 125.0, 126.8, 127.1, 127.9, 128.1, 128.2, 129.3, 129.5,136.8, 137.7, 142.38, 142.5, 142.6, 143.3, 150.0(ArC and FurylC(A + B)), 171.5 and 171.9(C(8)(A + B)); *m*/*e*(CI^+) 467 (MH^+, 100%); HRMS 467.1640, MH^+ requires 467.1639.

(2*R*, 5*S*, 7*R*, 1′*S*)-7-(*N*-Tosylaminofuran-2-ylmethyl)-8-oxo-2-phenyl-1-aza-3-oxa-bicyclo[3.3.0]octane 24a

To *n*BuLi (0.54 ml, 1.14 mmol, 2.12 M in hexane) at 0 °C in THF (6 ml) was added diisopropylamine (0.17 ml, 1.23 mmol) and the mixture stirred for 15 minutes. The mixture was cooled down to −78 °C in an acetone–dry ice bath. A solution of lactam **19b** (207 mg, 0.45 mmol) in THF (5 ml) was added to the mixture. After 30 minutes, 2,6-di-*tert*-butylphenol (264 mg, 1.28 mmol) in THF (5 ml) was added. Water (20 ml) was then added and the mixture extracted with ethyl acetate (10 ml). The aqueous layer was then extracted with ethyl acetate (3 × 15 ml) and the combined organic extracts were washed with brine, dried ($MgSO_4$) and concentrated *in vacuo* to yield the product, which was purified by flash column chromatography to give lactam **24a** as a pale yellow solid (37 mg, 19%). R_f = 0.37 [EtOAc–Petrol(40/60), 2 : 3]; $[\alpha]_D^{22}$ +114 (*c* 1, $CHCl_3$); ν_{max}(film)/cm^{-1} 3040, 2400, 1695, 1601, 1522, 1476, 1428, 1238; δ_H(400 MHz, $CDCl_3$) 1.45–1.53(1H, m, C(6)H_{endo}), 2.35(3H, s, CH_3), 2.39–2.49(1H, m, C(6)H_{exo}), 2.68–2.72(1H, t, *J* 8.1 Hz, C(4)H_{endo}), 3.40–3.47(1H, m, C(7)H), 3.98–4.02(1H, m, C(5)H), 4.03–4.10(1H, m, C(4)H_{exo}), 4.73–4.77(1H, dd, *J* 5.2, 9.6 Hz, C(1′)H), 4.90(1H, br s, OH), 5.98–6.17(2H, m, FurylH), 6.19(1H, s, C(2)H), 7.05–7.07(1H, d, *J* 9.6 Hz, NH), 7.13–7.83(10H, m, ArH and FurylH); δ_C(400 MHz, $CDCl_3$) 21.44(CH_3), 25.84(C(6)), 47.85(C(7)), 52.18(C(1′)), 56.61(C(5)), 72.01(C(4)), 86.76(C(2)), 109.6, 110.5(FurylC), 125.9 126.4, 126.7, 128.5, 128.8, 129.3, 129.7, 137.7, 138.2, 142.1, 142.8 and 143.6(ArC), 176.6(C(8)); *m*/*e*(CI^+) 453(MH^+, 20%), 282(100%); HRMS 453.1484, MH^+ requires 453.1493.

(2*R*, 5*S*, 7*R*, 1′*S*)-7-(*N*-Tosylaminofuran-2-ylmethyl)-8-oxo-2-phenyl-2-methyl-1-aza-3-oxabicyclo[3.3.0]octane 24b

To lactam **23** (73 mg, 0.15 mmol) in dry THF (5 ml) under nitrogen was added NaH (18.8 mg, 0.47 mmol, 60% dispersed in mineral oil) at 0 °C and the mixture heated to reflux for

5 hours. The mixture was then quenched with 2, 6-di-*tert*-butylphenol (160 mg, 0.78 mmol) in THF (2 ml) at 0 °C. Water (10 ml) was added and the mixture extracted with ethyl acetate (10 ml). The aqueous layer was extracted with EtOAc (3 × 15 ml) and the combined organic extracts were washed with brine, dried ($MgSO_4$) and concentrated *in vacuo* to yield a brown liquid. Purification of this yellow liquid using flash column chromatography gave lactam **24b** as a pale yellow oil (20 mg, 27%) and a side product **25** (13 mg, 20%). R_f = 0.32 [EtOAc–Petrol(40/60), 3 : 7]; $[\alpha]_D^{22}$ +20 (*c* 1, $CHCl_3$); $\nu_{max}(CHCl_3)/cm^{-1}$ 3350, 3250, 3026, 1686, 1349, 1289, 1163; δ_H(400 MHz, $CDCl_3$) 1.31–1.41(1H, m, C(6)H_{endo}), 1.80(3H, s, C(2)CH_3), 2.22–2.31(1H, m, C(6)H_{exo}), 2.30(3H, s, CH_3), 3.10–3.15(1H, t, *J* 7.6 Hz, C(4)H_{endo}), 3.31–3.36(1H, m, C(7)H), 3.84–3.94(2H, m, C(5)H and C(4)H_{exo}), 4.68–4.72(1H, dd *J* 9.7, 5.0 Hz, C(1′)H), 4.93(1H, br, SO_2NH), 5.97–6.08(2H, m, FurylH), 7.06–7.76(10H, m, ArH and FurylH); δ_C(400 MHz, $CDCl_3$) 20.02(*C*H_3), 26.15(C(2)CH_3), 27.73(C(6)), 50.14(C(7)), 52.63(C(1′)), 58.79(C(5)), 70.61(C(4)), 94.69(C(2)), 106.1, 110.0(FurylC), 125.5, 127.0, 127.3, 127.8, 128.7, 128.9, 129.8, 130.0, 130.3, 130.5, 130.7(ArC), 138.4 and 139.6(ArC), 142.5(FurylC), 143.2, 143.3, 144.1(*C*SO_2N, *C*CH'_3), 173.0(C(8)); *m*/*e*(CI$^+$) 467(MH$^+$, 30%); HRMS 467.1640, MH$^+$ requires 467.1641.

6-Furan-2-ylmethylene-3-methyl-3-phenyltetrahydropyrrolo-[1,2-*c*]oxazol-5-one 25

Oil, R_f = 0.64 (EtOAc–Petrol, 3 : 7); $[\alpha]_D^{22}$ +39 (*c* 1, $CHCl_3$), $\nu_{max}(CHCl_3)/cm^{-1}$ 1674, 1475, 1256, δ_H(400 MHz, $CDCl_3$) 2.02(3H, s, C(2) CH_3), 2.86(1H, m, C(6)H), 3.32(1H, m, C(6)H), 3.63(1H, m, C(4)H), 4.12(1H, m, C(5)H), 4.24(1H, m, C(4)H) 6.51(1H, m, FurylH), 6.58(1H, d, *J* 3.4 Hz, C(1′)H), 7.19–7.56(6H, m, FurylH and C_6H_5), δ_C(400 MHz, $CDCl_3$), 25.52(C(2)CH_3), 25.87(C(6)), 70.49(C(4)), 94.96(C(2)), 112.1(FurylC), 114.0(FurylC), 125.1, 127.9, 128.3(PhCH), 143.7(Ar*C*), 144.2(*C*H^e), 151.9(*C*(1′)), 167.93(C(8)); *m*/*e*(CI$^+$) 296 (MH$^+$, 100%); HRMS 296.1130, MH$^+$ requires 296.1287.

(2*R*, 5*S*, 7*R*, 1′*S*)-7-(Methoxycarbonyl-*N*-tosylmethyl)-8-oxo-2-phenyl-2-methyl-1-aza-3-oxabicyclo[3.3.0]octane 26

To a stirred solution of lactam **24b** (200 mg, 0.43 mmol) in CH_3CN (3 ml) and CCl_4 (3 ml) was added a solution of $NaIO_4$ (0.96g, 4.5 mmol) in water (5 ml) and $RuCl_3.H_2O$ (10 mg cat.). The mixture was stirred vigorously for 4 hours. Dichloromethane (10 ml) was added and the aqueous layer extracted with dichloromethane (2 × 15 ml). The solvent was evaporated and the residue was dissolved in THF. A solution of diazomethane in ether was then added with stirring which continued for 30 minutes. Water (20 ml) was added and the aqueous layer extracted with ethyl acetate (3 × 15 ml). The organic phases were combined, dried ($MgSO_4$) and concentrated *in vacuo* to give a light orange oil which was purified by flash column chromatography on silica [EtOAc–Petrol (40/60), 2 : 3] to give ester **26**, a colourless oil (43 mg, 22% over two steps). R_f = 0.26 (EtOAc–Petrol, 2 : 3); $[\alpha]_D^{22}$ +129 (*c* 1, $CHCl_3$), $\nu_{max}(CHCl_3)/cm^{-1}$ 3020(m), 1741(m), 1680(s), 1216(s); δ_H(400 MHz, $CDCl_3$) 1.90–2.02(1H, m, C(6)H_{endo}), 1.94(3H, s, C(2)CH_3), 2.32–2.38(1H, m, C(6)H_{exo}), 2.48(3H, s, CH_3), 3.30–3.36(1H, m, C(7)H), 3.59(3H, s, CO_2CH_3), 3.68–3.72(1H, t, *J* 15.7 Hz, C(4)H_{endo}), 4.02–4.07(1H, m, C(5)H), 4.12–4.16(1H, m, C(4)H_{exo}), 4.34–4.40(1H, dd, *J* 4.3, 9.2 Hz, *C*(1′)H), 6.08(1H, d, *J* 9.3 Hz, NH), 7.27–7.52(7H, m, ArH), 7.78(2H, d, *J* 8.8 Hz, ArH); δ_C(400 MHz, $CDCl_3$), 21.52(CH_3Ph), 25.56(C(2)CH_3), 26.75(C(6)), 49.30(C(7)), 52.61(CO_2CH_3), 54.48(C(1′)), 58.60(C(5)), 69.89(C(4)), 94.39(C(2)), 124.9, 126.4, 127.4. 127.7, 128.0, 128.5, 129.5, 129.9(ArC), 143.3 and 143.6(*C*SO_2N and *C*CH_3), 170.1(C(8) and 171.1 and CO); *m*/*e*(CI$^+$) 458 (MH$^+$, 100%), 339(55); HRMS 459.1584, MH$^+$ requires 459.1590.

(2*S*, 4*R*, 1′*S*)-2-Hydroxymethyl-4-(methyloxycarbonyl-*N*-tosylaminomethyl)-5-oxopyrrolidine 27a

To a solution of ester **26** (60 mg, 0.13 mmol) in DCM (5 ml) at room temperature was added trifluoroacetic acid (0.09 ml, 1.3 mmol) and the solution stirred for 1 h. The solvent was removed *in vacuo* to give a pale orange gum which was purified by flash column chromatography (10% MeOH in EtOAc) to give alcohol **27a** as a pale yellow oil (21 mg, 45%). R_f = 0.39 (EtOAc–MeOH), 5 : 1); $[\alpha]_D^{20}$ +203 (*c* 1, $CHCl_3$), $\nu_{max}(CHCl_3)/cm^{-1}$ 3344, 3020, 1741, 1698, 1494, 1290, 1164; δ_H(400 MHz, CD_3OD) 1.72–1.78(1H, m, C(3)H), 2.18–2.26(1H, m, C(3)H), 2.43(3H, s, CH_3Ph), 2.92–3.02(1H, m, C(4)H), 3.32(3H, s, CO_2CH_3), 3.44–3.70(3H, m, CH_2OH and C(2)H)), 4.26(1H, d, *J* 5.6 Hz, C(1′)H), 7.37(2H, d, *J* 8.2 Hz, ArH), 7.32(2H, d, *J* 8.4 Hz, ArH); δ_C(400 MHz, $CDCl_3$), 21.89(*C*H_3Ph), 26.26(*C*(3)), 46.03(*C*(4), 50.29(CO_2CH_3), 53.11(C(2)), 73.77(*C*HOH), 128.7, 130.9, 131.0, 131.3(ArCH), 139.5(*C*SO_2), 145.3(Ph*C*CH_3), 172.7(CO_2Me), 177.7(C(5)); *m*/*e*(TOF ES+) 357 (MH$^+$, 100%); HRMS 357.1131, MH$^+$ requires 357.1120.

(2*S*, 4*R*, 1′*S*)-2-Methyloxycarbonyl-4-(methyloxycarbonyl-*N*-tosylaminomethyl)-5-oxopyrrolidine 27b

To a stirred solution of lactam **27a** (45 mg, 0.13 mmol) in CH_3CN (2 ml) and CCl_4 (2 ml) was added a solution of $NaIO_4$ (0.248 g, 1.24 mmol) in water (3 ml) and the mixture stirred at room temperature for 10 minutes. $RuCl_3{\cdot}H_2O$ (6.50 mg) was added, and the mixture was stirred vigorously overnight. Dichloromethane (10 ml) was added and the aqueous layer was extracted with dichloromethane (2 × 15 ml). The solvent was evaporated and residue was dissolved in THF. A solution of diazomethane in ether was then added with stirring which continued for 30 minutes. Water (20 ml) was added and the aqueous layer extracted with ethyl acetate (3 × 15 ml). The organic phases were combined, dried ($MgSO_4$) and concentrated *in vacuo* to give a colourless oil which was purified by flash column chromatography on silica [EtOAc–Petrol (40/60), 2 : 3] giving the product **27b** as a yellow oil (8 mg, 17%). R_f = 0.41 (EtOAc–Petrol, 2 : 3); $\nu_{max}(CHCl_3)/cm^{-1}$ 3042, 1703, 1412, 1259, 1210, 1134; δ_H(400 MHz, $CDCl_3$) 1.81–1.87(1H, m, C(3)H), 1.96–2.24(1H, m, C(3)H), 2.43(3H, s, $PhCH_3$), 2.96–3.04 (1H, m, C(4)), 3.45(3H, s, CO_2CH_3), 3.52(3H, s, CO_2CH_3), 3.50(1H, br, NH) 3.74–3.82(1H, m, C(2)H), 4.5(1H, m, C(1′)H), 7.01(1H, br, NH), 7.28(2H, d, *J* 8.6 Hz, ArH), 7.74(2H, d, *J* 8.3 Hz, ArH); δ_C(400 MHz, $CDCl_3$), 21.4(CH_3Ph), 23.0(C(3)), 43.6(C(4)), 52.3(CO_2CH_3), 53.7(CO_2CH_3), 55.4(C(1′)), 64.4(C(2)), 126.3, 127.1, 129.3, 129.6,(ArC), 136.9(*C*SO_2N), 143.4(*C*CH_3), 170.6(*C*O_2CH_3), 175.9(C(5); *m*/*e*(APCI$^+$) 385 (MH$^+$, 100%); HRMS 385.1072, MH$^+$ requires 385.1069.

Acknowledgements

We wish to gratefully acknowledge the use of the EPSRC Chemical Database Service at Daresbury[75] and the EPSRC National Mass Spectrometry Service Centre at Swansea. R.G. gratefully acknowledges support from the Felix Foundation and M. A. from the Pakistani Ministry of Science and Technology.

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