

Mark. D. Andrews,^a Andrew G. Brewster^b and Mark G. Moloney^{*a}

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

^b Zeneca Pharmaceuticals, Mereside, Alderley Park, Macclesfield, UK SK10 4TG

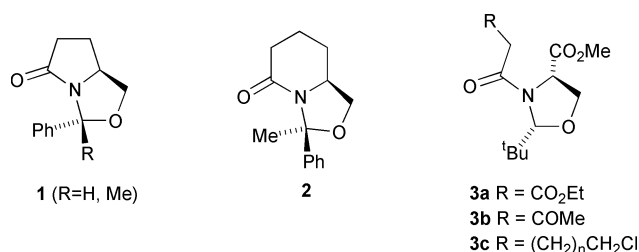
Received (in Cambridge, UK) 5th September 2001, Accepted 2nd November 2001

First published as an Advance Article on the web 5th December 2001

Highly diastereoselective reductions and organometallic additions in bicyclic lactams have been observed, which appear to result either from a stereoelectronic interaction of the pyramidalised nitrogen lone pair or from steric interactions in the bicyclic system. These products can be readily deprotected to give hydroxylated lactams.

Highly substituted lactam rings possess diverse biological activity, and much recent attention has focussed on excitatory amino acid chemistry, particularly as a result of the drive to better understand CNS function in mammalian systems.¹ It has recently also been shown that densely functionalised pyrrolidinones, such as lactacystin,² exhibit potent and selective activity in proteasome inactivation; there has therefore been considerable interest in the rapid construction of the pyrrolidinone framework,³ since such compounds may find application in the development of selective therapeutic agents for important parasitic infections.^{4,5}

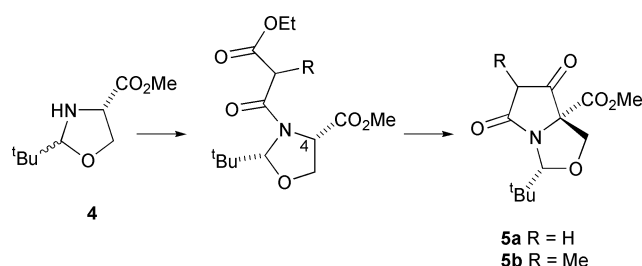
Our interest in this area has been concerned with the application of bicyclic lactams for the synthesis of diversely substituted lactam rings. Two lactam templates **1** and **2**, derived from pyroglutamic or pyroadipic acids respectively, have been used to access a variety of kainoid analogues as well as novel aminolactams, and make use of the inherent facial selectivity which comes from the bicyclic system.^{6–9} Another template **3**, derived from serine,¹⁰ has also been found to be applicable for the preparation of diversely functionalised lactams of well-defined stereochemistry. In this series, ring closure of **3a–c** by Dieckmann, Aldol or intramolecular cyclisation reactions respectively led to functionalised lactam systems which possess a quaternary α -amino centre with high diastereo- and enantio-control.^{11–14} We wished to further develop this chemistry to permit the introduction of hydroxy functionality around the ring periphery, and describe here that highly diastereocontrolled ring modifications using hydride or organometallic nucleophiles in bicyclic lactams are possible using steric, chelation or stereoelectronic control.



Results and discussion

Starting material synthesis

Lactams **5a,b** were prepared by our previously reported methodology (Scheme 1);^{11,12} oxazolidine **4**, itself readily obtained from serine and pivaldehyde in 90% yield, was acylated with the

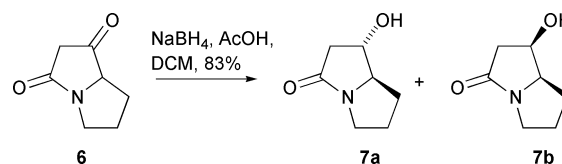


Scheme 1

required β -dicarbonyl unit and then cyclised to the tetramic acid by treatment with potassium *tert*-butoxide in *tert*-butyl alcohol.

Ketone reductions

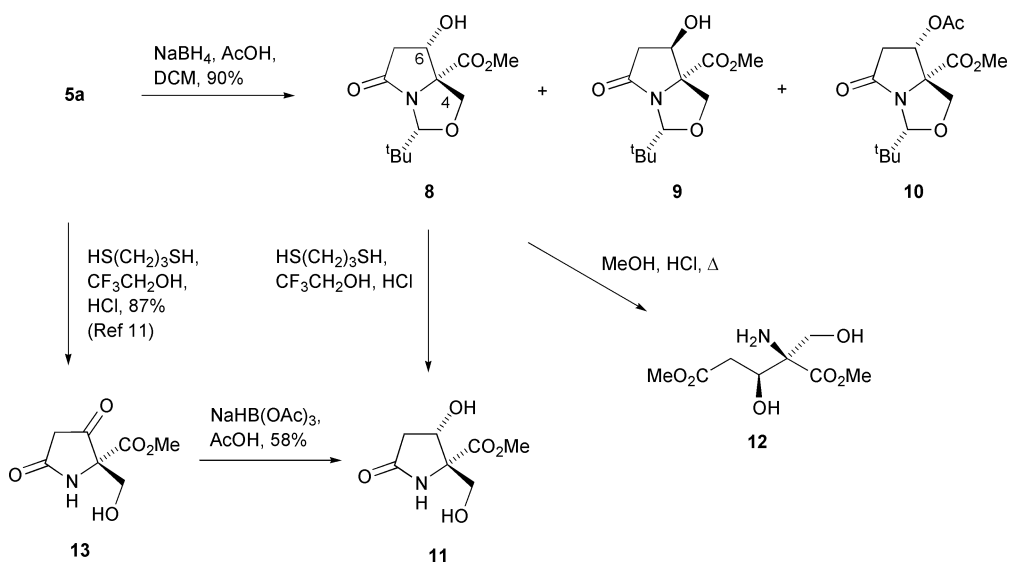
Our initial investigations were concerned with selective reductions in the bicyclic lactams **5a,b**; for this purpose, sodium triacetoxyborohydride appeared to be the reagent of choice, since Poncet and co-workers had earlier reported that reduction of the related bicyclic tetramic acid **6** with this reagent generated *in situ* from sodium borohydride and acetic acid in dichloromethane gave the alcohols **7a,b** in the ratio 95 : 5 (Scheme 2).¹⁵ This corresponds to preferential attack of the



Scheme 2

ketone carbonyl by borohydride from the sterically more hindered *endo*-face of the bicyclic system, *anti* to the nitrogen lone pair, and from a study of several substrates, the authors concluded that this was a general phenomenon.

Application of this method to the reduction of dicarbonyl compound **5a** gave a very similar result. Thus, reduction with sodium borohydride in a 1 : 9 mixture of acetic acid and dichloromethane gave a 63 : 1 mixture of the epimeric alcohols **8** and **9**, along with 0.1% of the acetate **10** (Scheme 3). That the major product was the alcohol **8**, with the indicated relative stereochemistry, was initially assumed on the basis of the results obtained by Poncet, but this was later confirmed by single crystal X-ray analysis of a derivative (*vide infra*). Recrystallisation from chloroform–petrol gave the major

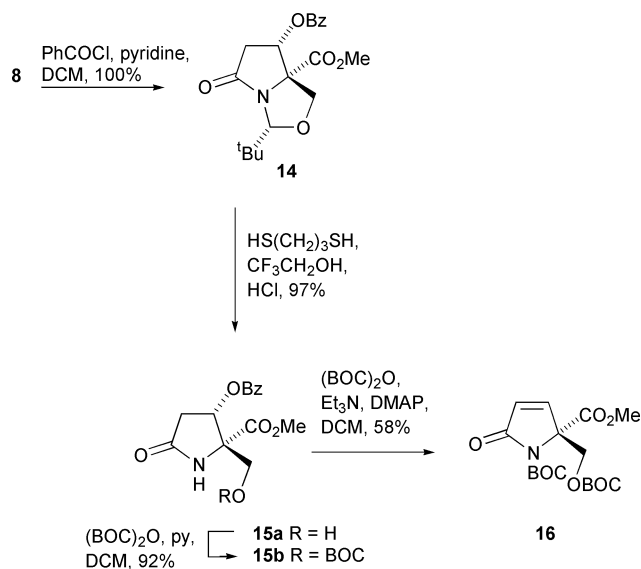


Scheme 3

epimer **8** in a yield of 81%. The relative stereochemistry of compound **10** was assumed to be the same as the major reduction product **8**, from which it was presumably formed under the reaction conditions.

Deprotection of lactam **8** to diol **11** was achieved in quantitative yield in a mixture of propane-1,3-dithiol and acidic trifluoroethanol.¹⁶ This synthesis of ester **11**, which was without recourse to column chromatography, was achieved in an excellent total yield of 42% from L-serine. Alternatively, both the oxazolidine and lactam rings of alcohol **8** could be cleaved by heating in methanolic HCl at reflux; after removal of solvent *in vacuo* and purification by column chromatography, the glutamate ester **12**, contaminated with 8% of the diol **11**, was obtained. Diol **11** could also be synthesised, in lower overall yield, by reversing the order of the last two steps in the synthesis above. Thus, deprotection of dicarbonyl **5a** as described above gave the unstable keto alcohol **13** in 87% yield.¹¹ Treatment of the crude product with sodium triacetoxyborohydride in acetic acid then led to the diol **11** in 58% yield.

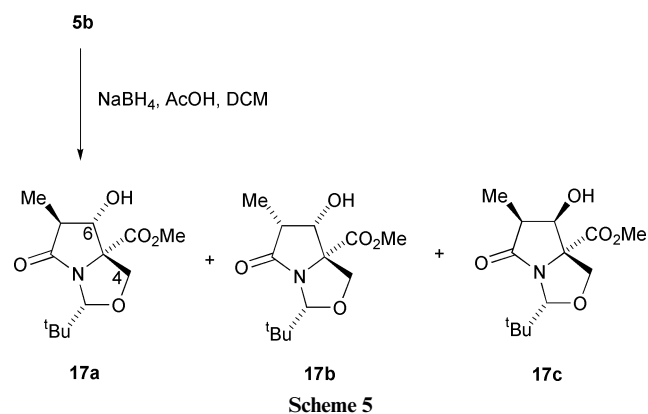
Confirmation of the stereochemical assignment above was possible by successful derivatisation to a crystalline compound. Alcohol **8** was protected in quantitative yield with benzoyl chloride and pyridine to give the benzoate ester **14** (Scheme 4) and deprotection with propane-1,3-dithiol in acidic trifluor-



Scheme 4

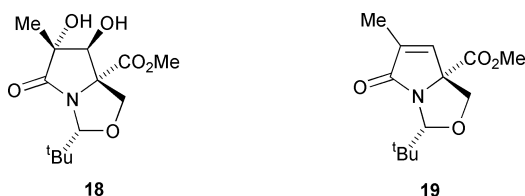
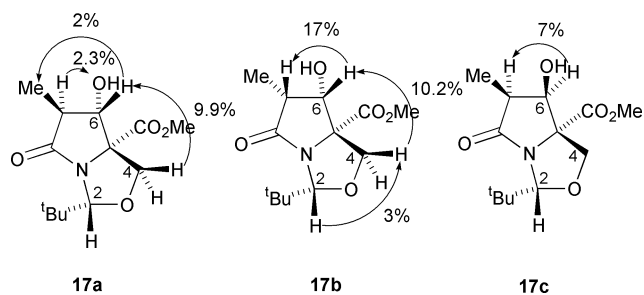
ethanol gave alcohol **15a** in 97% yield. Attempted *N*-Boc protection in fact gave the crystalline carbonate **15b** in 92% yield, whose relative stereochemistry was confirmed by single crystal X-ray structural analysis.¹⁷ This important result confirmed the earlier tentative stereochemical assignments of compounds **8**, **9** and **10**. *O,N*-Diprotection, using triethylamine as a base, with a catalytic amount of DMAP as a nucleophilic catalyst, in fact gave the elimination product **16** in 58% yield along with a 31% yield of the carbonate **15b**.

In view of the success of these reductions, it was of interest to examine the diastereocontrol of more elaborate systems of type **5b**. † Reduction of dicarbonyl **5b** with sodium borohydride in acetic acid and dichloromethane as described above gave, in addition to 29% of unreacted starting material, three diastereomeric alcohols **17a**, **17b** and **17c**, which were obtained, after careful purification, in yields of 32, 16 and 4% respectively (Scheme 5). Interestingly, it was found that this reduction



needed to be carried out in the absence of oxygen to prevent autoxidation, otherwise the diol product **18** was obtained in low yield.¹¹ The relative stereochemistries of these three alcohols were established by a series of NOE experiments (Fig. 1). For **17a** and **17b**, a sequence of irradiations easily gave the relative stereochemistry around the bicyclic ring system, but for the minor product **17c** only one enhancement gave any exact information and the overall stereochemistry was therefore assumed from the earlier assignments of isomers **17a,b**. Hydride addition, predominantly from the *endo*-face, which is *anti* to the nitrogen lone pair gives the major products **17a,b**.

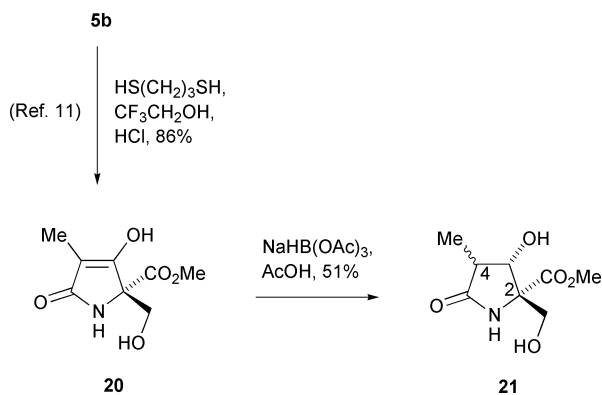
† This compound exists as the enol tautomer, but is drawn in the keto form for convenience.



The low overall yield for the reduction can probably be explained by steric hindrance from the C(7) methyl group.

In order to gain some information concerning the stability of these reduction products, epimerisation studies of the epimeric alcohols **17a** or **17b** were undertaken with sodium methoxide in methanol. For the former, no change was observed on stirring with base but lactam **17b** gave almost complete epimerisation to its C(7) epimer **17a** (de 94%), clearly indicating that alcohol **17a** is the thermodynamically more stable. Epimerisation at C(6) of the alcohols **17a** and **17b** was also attempted under the Mitsunobu conditions,¹⁸ but treatment with benzoic acid, triphenylphosphine and DEAD in THF gave none of the desired products, with the only compound isolated being the alkene **19**. Alcohol **17a** gave a 36% yield of this elimination product with 53% of starting material being recovered, while alcohol **17b** gave alkene **19** in 33% yield along with 38% recovered starting material.

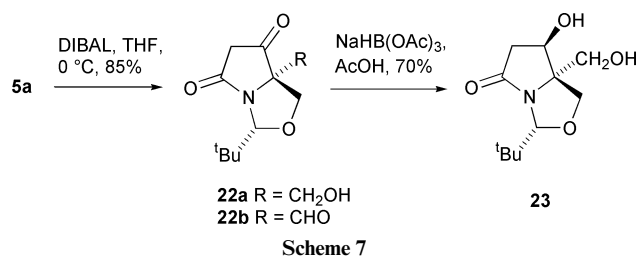
In an attempt to improve the reduction of dicarbonyl compound **5b**, it was decided to change the order of the steps in the synthesis by cleaving the oxazolidine ring before attempting the reduction of the ketone. Accordingly, dicarbonyl compound **5b** was converted to the unstable keto alcohol **20** as reported previously (Scheme 6).¹¹ Reaction with sodium triacetoxy-



Scheme 6

borohydride then gave diol **21** as an inseparable 3 : 2 mixture of two diastereomers in 51% yield. It was assumed that these diols were epimeric at C(4) rather than C(3) because of the excellent diastereocontrol exhibited previously in the sodium triacetoxyborohydride reduction of lactam **13**.

In view of the good to high levels of diastereoselectivity exhibited in ring carbonyl reductions, it was of interest to examine manipulation of the pyrrolidinone ring side-chains. Reduction of the C(5) ester function of **5a** proved to be possible



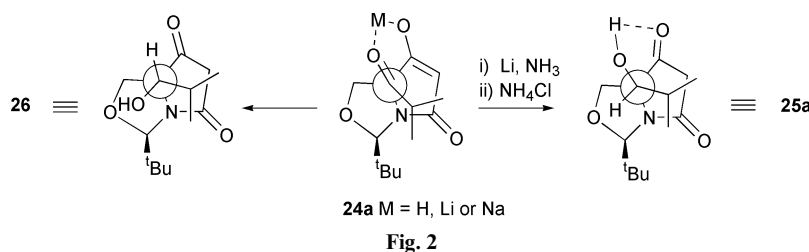
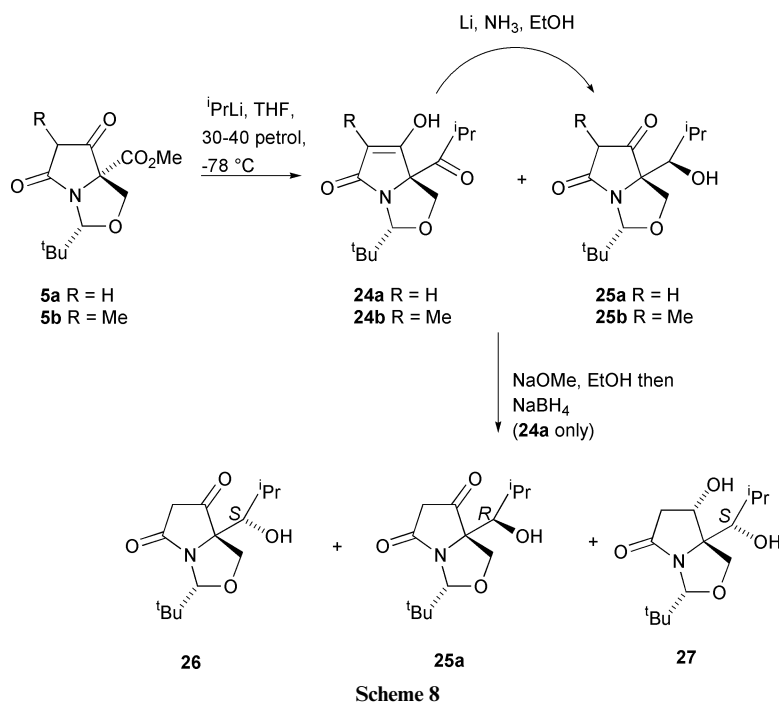
with 4 equivalents of a solution of DIBAL-H in hexane in THF at 0 °C, giving the crude alcohol **22a** in 85% yield (Scheme 7), although this compound was found to be unstable to chromatography. Attempts to oxidise this material to the aldehyde **22b** with TPAP or PCC were unsuccessful, and although evidence for successful Swern oxidation could be obtained by ¹H NMR analysis of the crude product, this material also proved to be unstable to isolation. Further reduction of **22a** with sodium triacetoxyborohydride in acetic acid gave diol **23** as a single diastereomer in 70% yield; the stereochemistry of this product was assumed to be as shown because of the presumed intramolecular chelated delivery of the hydride in the triacetoxyborohydride reduction, forcing hydride attack from the *Si* face of the ketone of **22a**.

In several of the above compounds, it was noted that consistent trends were observed in the ¹H NMR spectra which facilitated assignment of stereochemistry. Thus, for the C(6)*H*_{endo} compounds **8**, **10**, **17a** and **17b**, the difference in the C(4)*H*_{endo} and C(4)*H*_{exo} chemical shift values were typically 1.1–1.4 ppm, and were much larger than in the C(6)*H*_{exo} compounds **9**, **17c** and **23**, for which the difference was only 0.3 ppm. Conversely, the difference in C(7)*H*_{endo} and C(7)*H*_{exo} chemical shift values for the C(6)*H*_{endo} compounds **8** and **10** were typically only 0.4 ppm, significantly lower than the 0.9 ppm observed for the C(6)*H*_{exo} compounds **9**, **17c** and **23**. Similar trends in NMR data in functionalised pyrrolidinones have been ascribed to steric compression of the different proton nuclei around the periphery of the heterocyclic system.¹⁹

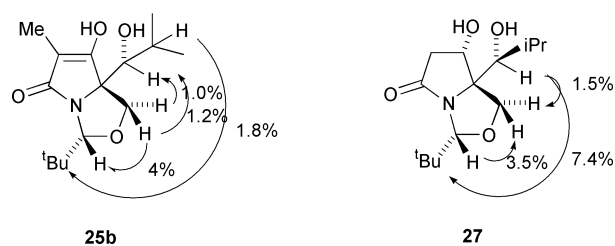
Organometallic additions

In view of the success of the diastereoselective reductions, it was also of interest to examine the possibility of introducing alcohol functionality using organometallic additions. Kikkawa and Yorifuji reported that, in the presence of triethylamine, aliphatic Grignard reagents react with esters to form the corresponding ketones in good yield.²⁰ Unfortunately, lactams **5a,b** were unreactive with isopropylmagnesium bromide, even on heating in THF at reflux, but with the more reactive alkyl-lithium species (5 equivalents in THF–petrol at –78 °C^{21,22}), ester **5a** gave an inseparable 3 : 1 mixture of ketone **24a** and the secondary alcohol **25a** in a total yield of 85% (Scheme 8). No tertiary alcohol due to reaction of ketone **24a** with another equivalent of isopropyllithium was observed in this reaction, presumably since this is a particularly hindered ketone. The ketone **24a**–alcohol **25a** product could be entirely converted to the alcohol product **25a** using lithium in ammonia–ethanol in 70% yield for the two steps from ester **5a**. Similarly, ester **5b** was reacted with excess isopropyllithium to give a partially separable 7 : 1 mixture of ketone **24b** and secondary alcohol **25b**. The formation of the secondary alcohols **25a,b** was due to reduction of the ketones **24a,b** by excess lithium metal in the reaction.²³

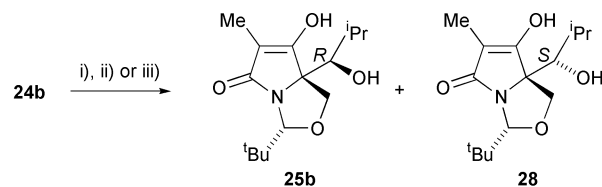
Reduction of the ketone **24a**–alcohol **25a** mixture with alkaline sodium borohydride in ethanol (in which the β-dicarbonyl enolate was formed, thereby protecting the ketone from reduction) gave 3 products: (*S*)-alcohol **26** was obtained in 36% yield, along with 19% of (*R*)-alcohol **25a**, present as a contaminant in the starting material, and a 20% yield of the over-reduction product, diol **27**. The yields of these products are quoted for the two steps from ester **5a**, and their stereochemistry was assigned



by a consideration of their IR spectral data. Thus, the product **25a**, also obtained by dissolving metal reduction (Li, NH₃, EtOH) of ketone **24a** as described above, exhibited a broad peak from 3600 to 2200 cm⁻¹ and peaks at 1680, 1650 and 1610 cm⁻¹, consistent with the presence of an intramolecular hydrogen bond. For the epimer **26**, the IR spectrum showed no evidence for such intramolecular hydrogen bonding, with the OH signal occurring at 3600–3100 cm⁻¹ and the carbonyl signal occurring at 1770 and 1710 cm⁻¹. These observations are consistent with reduction of the H-bonded ketone **24a** (or its metal chelated enolate, Fig. 2) which in the case of dissolving metal reduction, leads to the thermodynamically more stable H-bonded product **25a** in which steric interactions between the *i*Bu and *i*Pr groups are minimised. On the other hand, reduction of **24a** by NaBH₄ occurs by attack of hydride at the least hindered face, as indicated, to give the product **26** in which intramolecular hydrogen bonding is not possible, without causing unfavourable steric interactions between the *i*Bu and *i*Pr groups. That compounds **26** and **27** possessed the same side-chain stereochemistry (*S*) was established by the conversion of ketone **26** to alcohol **27** by catalytic hydrogenation with platinum oxide in ethyl acetate at 5 atm; under these conditions, the reaction was slow and gave only a low yield (25%) of product **27**, along with recovered starting material. The stereochemistry of **27** was in part determined by NOE (Fig. 3), which established the side-chain stereochemistry, and in part by use of the ¹H NMR patterns discussed above; thus, the Δδ of each of the H(4) signals, at 1.0 ppm, was consistent with the *exo* orientation of the C(6) hydroxy as indicated. Such a stereochemistry would have required hydrogen attack *anti* to the nitrogen lone pair, which, as noted above, appears to be the kinetically preferred mode of attack, and in any case the alternative *exo*-face reduction is clearly blocked by the bulky *i*Pr group.



Reduction of ketone **24b** was similarly achieved; treatment with sodium methoxide in ethanol followed by addition of sodium borohydride under nitrogen led to the (*S*)-alcohol **28** in 91% yield (Scheme 9). This reaction was performed under



Conditions	Yield %	Yield %
i) NaOMe, EtOH followed by NaBH ₄	0	91
ii) Na, THF, NH ₃ (l), NH ₄ Cl	48	9
iii) Li, THF, NH ₃ (l), NH ₄ Cl	89	0

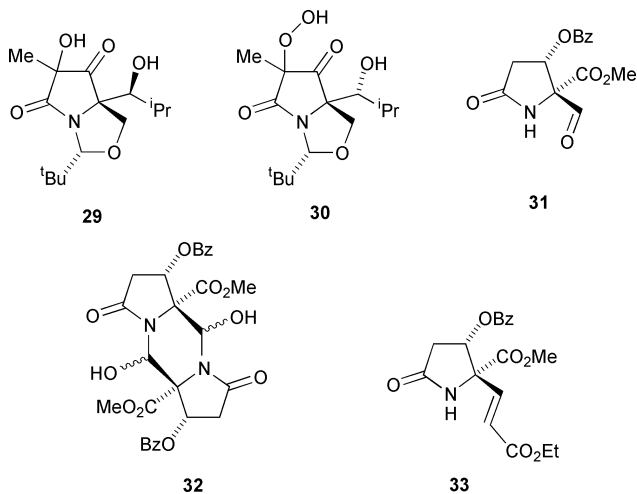
Scheme 9

nitrogen because both product alcohols **28** and **25b** were found to be extremely sensitive to autoxidation. On the other hand, dissolving metal reduction of ketone **24b** with lithium in liquid ammonia gave only the (*R*)-alcohol **25b** in 89% yield. Use of

sodium in liquid ammonia, however, led to a mixture of the (*R*)- and (*S*)-alcohols, the (*R*)-alcohol **25b** predominating, in a combined yield of 57%. The stereochemistries of the (*R*)- and (*S*)-alcohols **25b** and **28** were assigned by analogy with those of alcohols **25a** and **26**.

Again, useful patterns in the ^1H NMR spectra were observed: the appearance of the methine proton of the isopropyl side-chain in the ^1H NMR spectra of these compounds proved to be diagnostic of the alcohol stereochemistry. For those compounds assigned the (*S*)-stereochemistry, this methine proton appeared as an octet, with the coupling constants to the isopropyl methyl groups and the proton at the alcohol centre all being approximately 6.5 or 7.0 Hz. For those compounds assigned the (*R*)-stereochemistry, however, this methine proton appeared as a doublet of septets or a septet, the coupling constant to the proton at the alcohol centre being 2.0 Hz or less.

As noted above, alcohols **25b** and **28** were found to be unusually sensitive to aerial oxidation, and attempted recrystallisation of alcohol **28** from chloroform led to a decomposition owing to this instability. Purification of this decomposition mixture by column chromatography enabled the isolation of diol **29** in 7% yield. That the oxidation product was indeed the diol **29** was confirmed by mass spectrometry, both chemical ionisation and positive electrospray spectra showing peaks at 317 and 300 Da corresponding to $\text{M} + \text{NH}_4^+$ and $\text{M} + \text{H}^+$ ions respectively. Storage of alcohol **25b** in deuteriochloroform solution for 20 days led to relatively clean oxidation to give a single product as shown by ^1H NMR spectroscopy. Purification by column chromatography gave unchanged starting material in 50% recovery and a 30% yield of the peroxide **30**. That this compound was the peroxide and not the diol analogous to compound **29** was established from a positive starch iodide test. This was supported by mass spectrometry, and the positive electrospray spectrum of compound **30** clearly showed a peak at 316 Da indicating that the peroxide was indeed the product formed.



In view of the successful modification of the C(5) ester function of **5** by organometallic addition, it was of interest to investigate the reactions of the corresponding aldehyde. However, attempted oxidation of alcohol **15a** to the aldehyde **31** using Swern conditions gave not this product, but the corresponding dimer **32** in 42% yield; disappointingly, although this compound gave an acceptable yield (56%) of product **33** (along with 5% of the *Z*-isomer) by reaction with the stabilised Wittig reagent, non-stabilised ylides and Grignards, with or without Lewis acid activation, gave none of the desired products.

Conclusion

We have shown that hydroxylated pyrrolidinones are available by reduction or organometallic addition to protected tetramic

acid derivatives, which in the best cases proceed with excellent diastereocontrol. Deprotection permits rapid access to highly functionalised pyrrolidinones.

Experimental

Lactams **5a,b** were prepared by our previously reported methodology.¹¹

(2*R*,5*R*,6*S*)- and (2*R*,5*R*,6*R*)-2-*tert*-Butyl-6-hydroxy-5-methoxycarbonyl-8-oxo-3-oxa-1-azabicyclo[3.3.0]octane **8** and **9** and (2*R*,5*R*,6*S*)-6-acetoxy-2-*tert*-butyl-5-methoxycarbonyl-8-oxo-3-oxa-1-azabicyclo[3.3.0]octane **10**

To a solution of lactam **5a** (9.0 g, 35.3 mmol) in 10% AcOH in DCM (175 ml) at 0 °C was added, portionwise over 15 min, NaBH_4 (2.93 g, 77.6 mmol). The mixture was stirred at 0 °C for a further 15 min, at room temperature for 1.5 h and the solvent was then removed *in vacuo*. The residue was partitioned between EtOAc (250 ml) and sat. NaHCO_3 (aq) (250 ml) and the aqueous layer was re-extracted with EtOAc (2×100 ml). The aqueous layer was then acidified with 1M HCl and extracted with EtOAc (250 ml), the EtOAc layer being washed with brine (200 ml), dried (MgSO_4) and evaporated *in vacuo* to give recovered starting material **5a** (0.25 g, 2.8%). The neutral organic extracts were washed with brine (300 ml), dried (MgSO_4) and evaporated *in vacuo* to give a crude mixture of epimeric alcohols **8** and **9** (ratio 63 : 1). Recrystallisation from CHCl_3 -hexane gave alcohol **8** (7.36 g, 81%), contaminated with traces (<1.5%) of alcohol **9**, as a colourless crystalline solid; mp 129–130.5 °C; $R_f = 0.07$ (EtOAc–DCM, 1 : 3); $[\alpha]_D^{20} = +72.4$ ($c = 0.98$ in CHCl_3); found: C, 55.9; H, 7.3; N, 5.3; $\text{C}_{12}\text{H}_{19}\text{NO}_5$ requires: C, 56.0; H, 7.4; N, 5.5%; ν_{max} (Nujol) 3325 (br m), 1740 (s), 1690 (s) and 1680 (s) cm^{-1} ; δ_{H} (200 MHz, CDCl_3) 0.87 (9H, s, $\text{C}(\text{CH}_3)_3$), 2.83 (1H, dd, $J = 16.0$ Hz, $J' = 8.0$ Hz, $\text{CHH}'\text{CH}$), 3.05 (1H, br s, OH), 3.16 (1H, dd, $J = 16.0$ Hz, $J' = 10.5$ Hz, $\text{CHH}'\text{CH}$), 3.57 (1H, d, $J = 8.5$ Hz, $\text{C}(4)\text{HH}'$), 3.83 (3H, s, CO_2CH_3), 4.57 (1H, m, $\text{CHH}'\text{CH}$), 4.87 (1H, s, $^t\text{BuCH}$) and 4.89 (1H, d, $J = 8.5$ Hz, $\text{C}(4)\text{HH}'$); δ_{C} (50.3 MHz, CDCl_3) 24.7 ($\text{C}(\text{CH}_3)_3$), 36.0 ($\text{C}(\text{CH}_3)_3$), 43.0 ($\text{C}(7)\text{H}_2$), 52.6 (CO_2CH_3), 75.6 ($\text{C}(4)\text{H}_2$ and $\text{C}(6)\text{H}$), 77.5 ($\text{C}(5)$), 96.2 ($^t\text{BuCH}$) and 170.7 and 175.2 (carbonyls); m/z (CI) 258 ($\text{M} + \text{H}^+$, 100%) and 200 ($\text{M} + \text{H}^+ - ^t\text{BuH}$, 48).

Purification of the residue by careful column chromatography (EtOAc–petrol, 2 : 3) gave alcohols **8** (0.75 g, 8.3%) and **9** (0.04 g, 0.4%) as a crystalline solid; mp 104–105.5 °C; $R_f = 0.12$ (EtOAc–DCM, 1 : 3); $[\alpha]_D^{25} = +29.4$ ($c = 0.35$ in CHCl_3); found: C, 56.03; H, 7.68; N, 5.40; $\text{C}_{12}\text{H}_{19}\text{NO}_5$ requires: C, 56.02; H, 7.44; N, 5.45%; ν_{max} (CHCl_3) 3605 (w), 3500–3100 (br w), 2960 (m), 1740 (m), 1720 (s) and 1085 (s) cm^{-1} ; δ_{H} (200 MHz, CDCl_3) 0.89 (9H, s, $\text{C}(\text{CH}_3)_3$), 2.46 (1H, d, $J = 17.0$ Hz, $\text{CHH}'\text{CH}$), 3.38 (1H, dd, $J = 17.0$ Hz, $J' = 6.0$ Hz, $\text{CHH}'\text{CH}$), 3.81 (3H, s, CO_2CH_3), 4.24 (1H, d, $J = 9.0$ Hz, $\text{C}(4)\text{HH}'$), 4.41 (1H, t, $J = 6.0$ Hz, $\text{CHH}'\text{CH}$), 4.58 (1H, d, $J = 9.0$ Hz, $\text{C}(4)\text{HH}'$) and 4.92 (1H, s, $^t\text{BuCH}$); δ_{C} (125.7 MHz, CDCl_3) 24.88 ($\text{C}(\text{CH}_3)_3$), 36.21 ($\text{C}(\text{CH}_3)_3$), 44.65 ($\text{C}(7)\text{H}_2$), 52.92 (CO_2CH_3), 67.30 and 71.16 ($\text{C}(4)\text{H}_2$ and $\text{C}(6)\text{H}$), 77.89 ($\text{C}(5)$), 96.38 ($^t\text{BuCH}$) and 171.9 and 177.2 (CO); m/z (CI) 275 ($\text{M} + \text{NH}_4^+$, 9%), 258 ($\text{M} + \text{H}^+$, 100) and 200 (25), along with acetate **10** (5.11) (0.01 g, 0.1%) as a colourless oil, $R_f = 0.24$ (EtOAc–petrol, 3 : 7); ν_{max} (CHCl_3) 2960 (m), 1750 (s), 125 (s) and 1080 (m) cm^{-1} ; δ_{H} (200 MHz, CDCl_3) 0.86 (9H, s, $\text{C}(\text{CH}_3)_3$), 2.02 (3H, s, CH_3CO_2), 2.80 (1H, dd, $J = 15.5$ Hz, $J' = 8.0$ Hz, $\text{CHH}'\text{CH}$), 3.27 (1H, dd, $J = 15.5$ Hz, $J' = 11.0$ Hz, $\text{CHH}'\text{CH}$), 3.72 (1H, d, $J = 9.5$ Hz, $\text{C}(4)\text{HH}'$), 3.79 (3H, s, CO_2CH_3), 4.82 (1H, d, $J = 9.5$ Hz, $\text{C}(4)\text{HH}'$), 4.86 (1H, s, $^t\text{BuCH}$) and 5.22 (1H, dd, $J = 11.0$ Hz, $J' = 8.0$ Hz, $\text{CHH}'\text{CH}$); δ_{C} (125.7 MHz, CDCl_3) 20.41 (CH_3CO_2), 24.76 ($\text{C}(\text{CH}_3)_3$), 36.06 ($\text{C}(\text{CH}_3)_3$), 40.00 ($\text{C}(7)\text{H}_2$), 52.73 (CO_2CH_3), 73.39 and 73.91 ($\text{C}(4)\text{H}_2$, $\text{C}(5)$ and $\text{C}(6)\text{H}$), 95.99 ($^t\text{BuCH}$) and 169.5, 170.0 and 173.1 (CO); m/z (GCMS) 300 ($\text{M} + \text{H}^+$, 2%), 240 (100) and 182 (70).

(2R,3S)-3-Hydroxy-2-hydroxymethyl-2-methoxycarbonylpyrrolidin-5-one 11

To a solution of alcohol **8** (1.0 g, 3.89 mmol) in acidic 2,2,2-trifluoroethanol (2% w/v HCl) (15 ml) was added propane-1,3-dithiol (0.4 ml, 0.43 g, 4.0 mmol). The mixture was stirred at room temperature for 5 h and silica (5 ml) was added before the solvent was removed *in vacuo*. The silica loaded material was placed on top of a silica filled (50 ml) sinter funnel and eluted with EtOAc–hexane 1 : 1 (200 ml) followed by MeOH–EtOAc, 1 : 4 (200 ml) to give diol **11** (0.73 g, 99%) as an off-white, hygroscopic crystalline solid; mp 45–47 °C; $R_f = 0.09$ (MeOH–EtOAc, 1 : 9); $[a]_D^{25} = +16.9$ ($c = 1.13$ in MeOH); found: C, 44.1; H, 6.1; N, 7.4; $C_7H_{11}NO_5$ requires: C, 44.4; H, 5.9; N, 7.4%; ν_{max} (Nujol) 3340 (br s), 3290 (br s), 1735 (s) and 1685 (s) cm^{-1} ; δ_H (200 MHz, CD_3OD) 2.27 (1H, dd, $J = 17.0$ Hz, $J' = 3.5$ Hz, C(4)HH'), 2.73 (1H, dd, $J = 17.0$ Hz, $J' = 7.0$ Hz, C(4)HH'), 3.71 (1H, d, $J = 11.0$ Hz, CHH'OH), 3.76 (3H, s, CO_2CH_3), 3.91 (1H, d, $J = 11.0$ Hz, CHH'OH) and 4.36 (1H, dd, $J = 7.0$ Hz, $J' = 3.5$ Hz, C(3)HOH); δ_C (50.3 MHz, CD_3OD) 40.9 (C(4)H₂), 52.8 (CO_2CH_3), 65.6 (CH₂OH), 71.2 (C(3)H), 75.5 (C(2)) and 171.9 and 178.5 (CO); m/z (CI) 207 (M + NH₄⁺, 6%), 190 (M + H⁺, 100) and 130 (8).

(2R,3S)-3-Hydroxy-2-hydroxymethylglutamic acid dimethyl ester 12

A solution of alcohol **8** (200 mg, 0.78 mmol) in methanolic HCl (5% w/v HCl) (10 ml) was heated at reflux for 7.5 h. After cooling to room temperature the solvent was removed *in vacuo* and the residue was purified by column chromatography (MeOH–EtOAc, 1 : 9) giving glutamate **12** as a white foam contaminated with 8% of pyroglutamate **11** (170 mg); $R_f = 0.17$ (MeOH–EtOAc, 1 : 9); ν_{max} (Nujol) 3350 (br s), 1740 (s), 1440 (m) and 1250 (m) cm^{-1} ; δ_H (200 MHz, CD_3OD) 2.49 (1H, dd, $J = 16.0$ Hz, $J' = 10.0$ Hz, C(4)HH'), 2.71 (1H, dd, $J = 16.0$ Hz, $J' = 3.5$ Hz, C(4)HH'), 3.71 (3H, s, CO_2CH_3), 3.72 (1H, d, $J = 11.5$ Hz, CHH'OH), 3.85 (3H, s, CO_2CH_3), 3.96 (1H, d, $J = 11.5$ Hz, CHH'OH) and 4.52 (1H, dd, $J = 10.0$ Hz, $J' = 3.5$ Hz, C(3)H); δ_C (125.7 MHz, CD_3OD) 37.99 (CH₂CO₂Me), 52.46 and 53.93 (2 × CO_2CH_3), 62.18 (CH₂OH), 68.75 (CHOH), 70.21 (CNH₂) and 170.7 and 172.6 (ester CO); m/z (CI) 222 (M + H⁺, 100%) and 190 (17).

Alcohol 11 from lactam 13 by sodium triacetoxyborohydride reduction

To AcOH (3 ml) cooled in a water bath was added portionwise NaBH₄ (38 mg, 1 mmol) and the mixture was stirred until H₂ evolution ceased (about 10 min). A solution of keto alcohol **13** (90 mg, 0.48 mmol) in AcOH (2 ml) was then added dropwise and the mixture was stirred at room temperature for 5.5 h. Solvent was removed *in vacuo* and the residue was purified by column chromatography (EtOAc increasing polarity to MeOH–EtOAc, 1 : 4) to give diol **11** (52 mg, 58%) as a hygroscopic, off-white crystalline solid. Data as described above.

(2R,5R,6S)-6-Benzoyloxy-2-(tert-butyl)-5-methoxycarbonyl-8-oxo-3-oxa-1-azabicyclo[3.3.0]octane 14

To a solution of alcohol **8** (1.0 g, 3.89 mmol) and pyridine (1 ml, 0.72 g, 9.13 mmol) in DCM (25 ml) was added dropwise benzoyl chloride (1.0 ml, 1.22 g, 8.6 mmol). The mixture was heated at reflux for 24 h, allowed to cool to room temperature then partitioned between DCM (30 ml) and NH₄Cl (aq) (40 ml). The organic layer was washed with 5% aq NaHCO₃ (40 ml), water (40 ml) and brine (40 ml), dried (MgSO₄) and evaporated *in vacuo* to give a quantitative yield of the title compound **14** as colourless needles contaminated with benzoic acid. An analytical sample was prepared by column chromatography (EtOAc–petrol, 1 : 19 increasing polarity to EtOAc–petrol, 1 : 4) (93% recovery); mp 174.5–175.5 °C; $R_f = 0.56$

(EtOAc–petrol, 3 : 7); $[a]_D^{25} = +7.2$ ($c = 0.61$ in CHCl₃); found: C, 63.23; H, 5.97; N, 3.76; $C_{19}H_{23}NO_6$ requires: C, 63.14; H, 6.42; N, 3.88%; ν_{max} (CHCl₃) 2960 (m), 2870 (w), 1745 (m), 1725 (s) and 1600 (w) cm^{-1} ; δ_H (200 MHz, $CDCl_3$) 0.90 (9H, s, C(CH₃)₃), 2.99 (1H, dd, $J = 15.5$ Hz, $J' = 8.0$ Hz, C(7)HH'), 3.46 (1H, dd, $J = 15.5$ Hz, $J' = 11.0$ Hz, C(7)HH'), 3.69 (3H, s, CO_2CH_3), 3.85 (1H, d, $J = 9.0$ Hz, C(4)HH'), 4.94 (1H, s, BuCH), 4.95 (1H, d, $J = 9.0$ Hz, C(4)HH'), 5.50 (1H, dd, $J = 11.0$ Hz, $J' = 8.0$ Hz, C(6)H), 7.43–7.51 (2H, m, ArH), 7.58–7.66 (1H, m, ArH) and 7.98 (2H, d, $J = 7.0$ Hz, ArH); δ_C (50.3 MHz, $CDCl_3$) 24.6 (C(CH₃)₃), 35.8 (C(CH₃)₃), 40.1 (C(7)H₂), 52.7 (CO_2CH_3), 73.7, 73.8 and 75.7 (C(4)H₂, C(5) and C(6)H), 96.0 (BuCH), 128.5, 128.8, 129.7 and 133.9 (aromatic) and 165.7, 169.6 and 173.6 (CO); m/z (CI) 379 (M + NH₄⁺, 5%), 362 (M + H⁺, 100) and 304 (24).

(2R,3S)-3-Benzoyloxy-2-hydroxymethyl-2-methoxycarbonylpyrrolidin-5-one 15a

To a solution of crude bicycle **14** (400 mg, 1.11 mmol) in acidic trifluoroethanol (1.5% w/v HCl) (15 ml) was added propane-1,3-dithiol (0.12 ml, 129 mg, 1.20 mmol). The mixture was stirred at room temperature for 22 h and solvent was then removed *in vacuo* at room temperature. Purification by column chromatography (EtOAc increasing polarity to MeOH–EtOAc, 1 : 9) gave amido alcohol **15a** (315 mg, 97%) as a crystalline solid; mp 138–139.5 °C; $R_f = 0.29$ (EtOAc); $[a]_D^{25} = +61.9$ ($c = 1.11$ in CHCl₃); found: C, 57.21; H, 4.93; N, 4.57; $C_{14}H_{15}NO_6$ requires: C, 57.33; H, 5.16; N, 4.78%; ν_{max} (CHCl₃) 3420 (w), 3500–3150 (br w), 1725 (s), 1600 (w) and 1270 (s) cm^{-1} ; δ_H (200 MHz, $CDCl_3$) 2.53 (1H, dd, $J = 18.0$ Hz, $J' = 2.5$ Hz, C(4)HH'), 3.06 (1H, dd, $J = 18.0$ Hz, $J' = 7.0$ Hz, C(4)HH'), 3.65 (3H, s, CO_2CH_3), 3.94 (1H, d, $J = 11.5$ Hz, CHH'OH), 4.08 (1H, d, $J = 11.5$ Hz, CHH'OH), 4.72 (1H, br s, OH), 5.71 (1H, dd, $J = 7.0$ Hz, $J' = 2.5$ Hz, C(3)H), 7.39–7.46 (2H, m, ArH), 7.54–7.61 (1H, m, ArH) and 7.91–7.99 (3H, m, ArH and NH); δ_C (50.3 MHz, $CDCl_3$) 38.0 (C(4)H₂), 52.7 (CO_2CH_3), 65.2, 71.8 and 72.4 (CH₂OH, C(2) and C(3)H), 128.4, 128.8, 129.7 and 133.9 (ArC) and 164.8, 169.4 and 175.9 (CO); m/z (CI) 311 (M + NH₄⁺, 30%) and 294 (M + H⁺, 100).

(2R,3S)-3-Benzoyloxy-2-tert-butoxycarbonyloxymethyl-2-methoxycarbonylpyrrolidin-5-one 15b

To a solution of amido alcohol **15a** (50 mg, 0.17 mmol) and pyridine (28 μ l, 27 mg, 0.35 mmol) in DCM (3 ml) was added (BOC)₂O (75 mg, 0.34 mmol). The mixture was stirred at room temperature for 5 h and solvent was then removed *in vacuo*. Purification by column chromatography (EtOAc–petrol 2 : 3) gave carbonate **15b** (62 mg, 92%) as colourless needles; mp 144.5–146 °C; $R_f = 0.09$ (EtOAc–petrol, 3 : 7); $[a]_D^{25} = +63.9$ ($c = 1.08$ in CHCl₃); found: C, 58.28; H, 5.67; N, 3.30; $C_{19}H_{23}NO_8$ requires: C, 58.01; H, 5.89; N, 3.56%; ν_{max} (CHCl₃) 3430 (w), 1745 (s) and 1725 (s) cm^{-1} ; δ_H (200 MHz, $CDCl_3$) 1.47 (9H, s, C(CH₃)₃), 2.56 (1H, dd, $J = 17.5$ Hz, $J' = 3.5$ Hz, C(4)HH'), 2.99 (1H, dd, $J = 17.5$ Hz, $J' = 7.0$ Hz, C(4)HH'), 3.68 (3H, s, CO_2CH_3), 4.29 (1H, d, $J = 11.0$ Hz, CHH'OBoc), 4.61 (1H, d, $J = 11.0$ Hz, CHH'OBoc), 5.70 (1H, dd, $J = 7.0$ Hz, $J' = 3.5$ Hz, C(3)H), 6.70 (1H, br s, NH), 7.44 (2H, t, $J = 7.5$ Hz, ArH), 7.59 (1H, t, $J = 7.5$ Hz, ArH) and 7.94 (2H, d, $J = 7.5$ Hz, ArH); δ_C (50.3 MHz, $CDCl_3$) 27.6 (C(CH₃)₃), 37.1 (C(4)H₂), 53.1 (CO_2CH_3), 68.0, 69.1 and 71.6 (CH₂OBoc, C(2) and C(3)H), 83.4 (C(CH₃)₃), 128.6, 129.6 and 133.8 (ArC), 152.7 (carbonate CO) and 164.8, 168.4 and 173.7 (amide and ester CO); m/z (CI) 411 (M + NH₄⁺, 2%), 394 (M + H⁺, 2), 294 (100), 142 (50) and 105 (48).

(2S)-1-tert-Butoxycarbonyl-2-tert-butoxycarbonyloxymethyl-2-methoxycarbonyl-2,5-dihydro-1H-pyrrol-5-one 16

To a solution of amido alcohol **15a** (100 mg, 0.34 mmol), triethylamine (48 μ l, 35 mg, 0.34 mmol) and DMAP (42 mg,

0.34 mmol) in DCM (5 ml) was added (Boc)₂O (150 mg, 0.69 mmol). The mixture was stirred at room temperature for 5 h and solvent was then removed *in vacuo*. Purification by column chromatography (EtOAc–petrol, 1 : 3 increasing polarity to EtOAc–petrol 2 : 3) gave carbonate **15b** (41 mg, 31%) as colourless needles and alkene **16** (73 mg, 58%) as a colourless oil; $R_f = 0.34$ (EtOAc–petrol, 3 : 7); $[\alpha]_D^{25} = +34.7$ ($c = 2.39$ in CHCl_3); ν_{max} (CHCl_3) 2985 (m), 1790 (s), 1745 (s), 1370 (m) and 1330 (s) cm^{-1} ; δ_{H} (200 MHz, CDCl_3) 1.41 and 1.51 (18H, 2 \times s, 2 \times C(CH₃)₃), 3.74 (3H, s, CO₂CH₃), 4.76 (1H, d, $J = 12.0$ Hz, CHH'OBoc), 4.87 (1H, d, $J = 12.0$ Hz, CHH'OBoc), 6.22 (1H, d, $J = 6.5$ Hz, CH=CH') and 7.00 (1H, d, $J = 6.5$ Hz, CH=CH'); δ_{C} (50.3 MHz, CDCl_3) 27.3 and 27.7 (2 \times C(CH₃)₃), 53.1 (CO₂CH₃), 63.5 and 72.3 (CH₂OBoc and C(2)), 83.0 and 84.1 (2 \times C(CH₃)₃), 128.8 and 145.8 (vinylic), 148.2 and 153.1 (2 \times carbonate CO) and 167.2 and 168.6 (amide and ester CO); m/z (CI) 389 (M + NH₄⁺, 10), 372 (M + H⁺, 12), 216 (100) and 142 (100).

(2R,5R,6S,7S)-, (2R,5R,6S,7R)- and (2R,5R,6R,7S)-2-tert-Butyl-6-hydroxy-5-methoxycarbonyl-7-methyl-8-oxo-3-oxa-1-azabicyclo[3.3.0]octane 17a, 17b and 17c

To a deoxygenated solution of lactam **5b** (617 mg, 2.3 mmol) in 10% AcOH in DCM (20 ml) under N₂ was added, portionwise over 45 min, NaBH₄ (265 mg, 7 mmol). The mixture was stirred at room temperature for 20 h, the solvent was evaporated *in vacuo* and the residue was partitioned between EtOAc (40 ml) and 5% NaHCO₃ (aq) (40 ml). The aqueous layer was acidified with 2 M HCl and extracted with EtOAc (2 \times 20 ml). The EtOAc extracts were washed with brine (30 ml), dried (MgSO₄) and evaporated *in vacuo* to give unreacted starting material (**5b**) (181 mg, 29%). The organic layer was washed with brine (30 ml), dried (MgSO₄) and evaporated *in vacuo*. Purification by careful multiple column chromatography (DCM–EtOAc, 1 : 4 increasing polarity to DCM–EtOAc, 1 : 1) gave the alcohols **17c** (26 mg, 4%), **17a** (197 mg, 32%) and **17b** (100 mg, 16%) as colourless crystalline solids.

Data for 17a. Mp 104–105.5 °C; $R_f = 0.18$ (EtOAc–DCM, 1 : 9); $[\alpha]_D^{25} = +32.0$ ($c = 1.10$ in CHCl_3); found: C, 57.8; H, 7.7; N, 5.2; C₁₃H₁₂NO₅ requires: C, 57.6; H, 7.8; N, 5.2%; ν_{max} (CHCl_3) 3685 (w), 3605 (w), 2975 (m), 1720 (s), 1600 (w) and 1105 (m) cm^{-1} ; δ_{H} (200 MHz, CDCl_3) 0.88 (9H, s, C(CH₃)₃), 1.23 (3H, d, $J = 7.0$ Hz, CHCH₃), 2.60 (1H, br s, CHOH), 3.22 (1H, dq, $J_d = 10.5$ Hz, $J_q = 7.0$ Hz, CHCH₃), 3.52 (1H, d, $J = 9.0$ Hz, C(4)HH'), 3.83 (3H, s, CO₂CH₃), 4.04 (1H, dd, $J = 10.5$ Hz, $J' = 6.0$ Hz, CHOH), 4.89 (1H, s, ^tBuCH) and 4.92 (1H, d, $J = 9.0$ Hz, C(4)HH'); δ_{C} (50.3 MHz, CDCl_3) 11.9 (CHCH₃), 24.5 (C(CH₃)₃), 35.9 (C(CH₃)₃), 46.8 (CHCH₃), 52.6 (CO₂CH₃), 74.0 (C(4)H₂), 75.4 (C(5)), 81.2 (CHOH), 96.0 (^tBuCH) and 171.0 and 177.4 (carbonyls); m/z (CI) 289 (M + NH₄⁺, 4%), 272 (M + H⁺, 100) and 214 (M + H⁺ – ^tBuH, 30).

Data for 17b. Mp 112–115 °C; $R_f = 0.15$ (EtOAc–DCM, 1 : 9); $[\alpha]_D^{25} = +66.4$ ($c = 1.15$ in CHCl_3); ν_{max} (CHCl_3) 3685 (w), 3610 (w), 2960 (m), 1715 (s), 1600 (w) and 1090 (m) cm^{-1} ; δ_{H} (200 MHz, CDCl_3) 0.90 (9H, s, C(CH₃)₃), 1.42 (3H, d, $J = 7.5$ Hz, CHCH₃), 2.68 (1H, br d, $J = 7.0$ Hz, CHOH), 2.97 (1H, dq, $J_d = 9.0$ Hz, $J_q = 7.5$ Hz, CHCH₃), 3.45 (1H, d, $J = 8.5$ Hz, C(4)HH'), 3.82 (3H, s, CO₂CH₃), 4.54 (1H, dd, $J = 9.0$ Hz, $J' = 7.0$ Hz, CHOH), 4.87 (1H, s, ^tBuCH) and 4.93 (1H, d, $J = 8.5$ Hz, C(4)HH'); δ_{C} (125.7 MHz, CDCl_3) 11.97 (CHCH₃), 25.65 (C(CH₃)₃), 36.40 (C(CH₃)₃), 47.21 (CHCH₃), 53.34 (CO₂CH₃), 73.15, 75.14 and 78.55 (CHOH, C(4)H₂ and C(5)), 97.66 (^tBuCH) and 171.8 and 181.6 (CO); m/z (CI) 289 (M + NH₄⁺, 1%), 272 (M + H⁺, 100) and 214 (20).

Data for 17c. Mp 115–117 °C; $R_f = 0.23$ (EtOAc–DCM, 1 : 9); $[\alpha]_D^{25} = +28$ ($c = 0.1$ in CHCl_3); ν_{max} (CHCl_3) 3690 (w), 3610 (w),

3400–3200 (br), 1715 (s), 1600 (m) and 1130 (s) cm^{-1} ; δ_{H} (200 MHz, CDCl_3) 0.91 (9H, s, C(CH₃)₃), 1.18 (3H, d, $J = 7.5$ Hz, CHCH₃), 3.31 (1H, dq, $J_d = 5.0$ Hz, $J_q = 7.5$ Hz, CHCH₃), 3.82 (3H, s, CO₂CH₃), 4.23 (1H, d, $J = 9.0$ Hz, C(4)HH'), 4.40 (1H, d, $J = 5.0$ Hz, CHOH), 4.55 (1H, d, $J = 9.0$ Hz, C(4)HH') and 4.92 (1H, s, ^tBuCH); δ_{C} (125.7 MHz, CDCl_3) 7.77 (CHCH₃), 24.91 (C(CH₃)₃), 36.27 (C(CH₃)₃), 44.77 (CHCH₃), 52.88 (CO₂CH₃), 67.71 (CHOH), 74.40 (C(4)H₂), 75.75 (C(5)), 96.45 (^tBuCH) and 172.0 and 178.9 (CO); m/z (CI) 289 (M + NH₄⁺, 3%), 272 (M + H⁺, 100) and 214 (40).

Epimerisation of 17b with sodium methoxide

A solution of alcohol **17b** (20 mg, 0.07 mmol) and NaOMe (40 mg, 0.74 mmol) in MeOH (3 ml) was stirred at room temperature for 15.75 h and then partitioned between EtOAc (10 ml) and brine (5 ml), the organic layer being dried (MgSO₄) and evaporated *in vacuo* to give 20 mg of a 30 : 1 mixture of alcohol **17a**–alcohol **17b**.

Epimerisation of 17a with sodium methoxide

A solution of alcohol **17a** (15 mg, 0.06 mmol) and NaOMe (30 mg, 0.55 mmol) in MeOH (2.5 ml) was stirred at 0 °C for 5.25 h and then partitioned between EtOAc (10 ml) and brine (5 ml), the organic layer being dried (MgSO₄) and evaporated *in vacuo* to give 15 mg of alcohol **17a**, no other diastereomers being seen in the NMR spectrum.

(2R,5S)-2-tert-Butyl-5-methoxycarbonyl-7-methyl-8-oxo-3-oxa-1-azabicyclo[3.3.0]oct-6-ene 19

To a solution of triphenylphosphine (17 mg, 0.065 mmol), benzoic acid (8 mg, 0.066 mmol) and alcohol **17b** (16 mg, 0.059 mmol) in THF (2.5 ml) under N₂ was added dropwise a solution of diethyl azodicarboxylate (11 mg, 0.063 mmol) in THF (1.5 ml). The mixture was stirred at room temperature for 24 h and then partitioned between ether (5 ml) and 5% NaHCO₃ (aq) (5 ml). The ether layer was washed with brine (5 ml), dried (MgSO₄) and evaporated *in vacuo*. Purification by column chromatography (DCM increasing polarity to EtOAc–DCM, 1 : 3) gave starting material **17b** (6 mg, 38%) (after recrystallisation from CHCl_3 –hexane to remove triphenylphosphine oxide) and alkene **19** (5 mg, 33%) as a viscous oil; $R_f = 0.13$ (DCM); $[\alpha]_D^{25} = +210$ ($c = 0.22$ in CHCl_3); ν_{max} (CHCl_3) 2960 (m), 2870 (w), 1745 (s) and 1715 (s) cm^{-1} ; δ_{H} (200 MHz, CDCl_3) 0.97 (9H, s, C(CH₃)₃), 1.92 (3H, d, $J = 1.5$ Hz, CH=CCH₃), 3.26 (1H, d, $J = 8.5$ Hz, C(4)HH'), 3.76 (3H, s, CO₂CH₃), 4.69 (1H, s, ^tBuCH), 4.78 (1H, d, $J = 8.5$ Hz, C(4)HH') and 6.73 (1H, d, $J = 1.5$ Hz, CH=CCH₃); δ_{C} (125.7 MHz, CDCl_3) 11.04 (CH=CCH₃), 24.83 (C(CH₃)₃), 35.23 (C(CH₃)₃), 52.90 (CO₂CH₃), 71.11 (C(4)H₂), 75.60 (C(5)), 96.85 (^tBuCH), 138.6 and 139.3 (CH=CCH₃) and 169.9 and 178.3 (carbonyls); m/z (GCMS) 254 (M + H⁺, 100%) and 196 (15).

(2R,3S)-3-Hydroxy-2-hydroxymethyl-2-methoxycarbonyl-4-methylpyrrolidin-5-one 21

To AcOH (2 ml) cooled in a water bath was added portionwise NaBH₄ (30 mg, 0.79 mmol) and the mixture was stirred until H₂ evolution ceased (about 10 min). A solution of keto alcohol **20** (80 mg, 0.40 mmol) in AcOH (0.5 ml) was then added dropwise and the mixture was stirred at room temperature for 2.75 h. Solvent was removed *in vacuo* and the residue was purified by column chromatography (EtOAc increasing polarity to MeOH–EtOAc, 1 : 4) to give a 3 : 2 mixture of the epimers of diol **21** (41 mg, 51%) as a colourless glass; $R_f = 0.49$ and 0.41 (MeOH–EtOAc, 1 : 3); ν_{max} (KBr) 3700–2600 (br s), 1730 (s) and 1695 (s) cm^{-1} ; δ_{H} (200 MHz, D₂O) (major epimer) 1.00 (3H, d, $J = 7.5$ Hz, CHCH₃), 2.40 (1H, quin, $J = 7.5$ Hz, C(4)H), 3.56 (1H, d, $J = 12.0$ Hz, CHH'OH), 3.61 (3H, s, CO₂CH₃), 3.89 (1H, d, $J = 7.5$ Hz, C(3)HOH) and 3.93 (1H, d, $J = 12.0$ Hz,

CHH'OH); (minor epimer) 0.89 (3H, d, $J = 7.5$ Hz, CHCH₃), 2.67 (1H, quin, $J = 7.0$ Hz, C(4)H), 3.55 (1H, d, $J = 11.0$ Hz, CHH'OH), 3.61 (3H, s, CO₂CH₃), 3.85 (1H, d, $J = 11.0$ Hz, CHH'OH) and 4.18 (1H, d, $J = 6.0$ Hz, C(3)HOH); m/z (CI) 221 (M + NH₄⁺, 6%), 204 (M + H⁺, 100) and 144 (18).

(2R,5R)-2-tert-Butyl-5-hydroxymethyl-6,8-dioxo-3-oxa-1-azabicyclo[3.3.0]octane 22a

To a solution of ester **4a** (95 mg, 0.37 mmol) in THF (5 ml) at 0 °C was added a solution of DIBAL-H (0.94 M in hexane, 1.6 ml, 1.50 mmol). The reaction was stirred at 0 °C for 1 h, then quenched by the cautious addition of MeOH (1 ml) before partitioning between ether (20 ml) and 2 M HCl (20 ml). The aqueous layer was saturated with NaCl and re-extracted with EtOAc (20 ml), the combined organic extracts being washed with brine (30 ml), dried (MgSO₄) and evaporated *in vacuo* to give crude alcohol **22a** (72 mg, 85%) as a brown oil; δ_{H} (200 MHz, CDCl₃) 0.96 (9H, s, C(CH₃)₃), 3.05 (1H, d, $J = 21.5$ Hz, C(7)HH'), 3.53 (1H, d, $J = 21.5$ Hz, C(7)HH'), 3.56 (1H, d, $J = 9.0$ Hz, C(4)HH'), 3.78 (1H, d, $J = 9.0$ Hz, C(4)HH'), 3.82 (1H, d, $J = 11.0$ Hz, CHH'OH), 3.98 (1H, d, $J = 11.0$ Hz, CHH'OH) and 4.98 (1H, s, 'BuCH); δ_{C} (50.3 MHz, CDCl₃) 25.3 (C(CH₃)₃), 35.0 (C(CH₃)₃), 46.9 (C(7)H₂), 63.7 and 67.2 (CH₂OH and C(4)H₂), 79.7 (C(5)), 98.5 ('BuCH), 174.5 (amide CO) and 206.1 (ketone CO).

(2R,5R,6R)-2-tert-Butyl-6-hydroxy-5-hydroxymethyl-8-oxo-3-oxa-1-azabicyclo[3.3.0]octane 23

NaBH₄ (63 mg, 1.67 mmol) was added to AcOH (1.5 ml) and stirred at room temperature for 15 min. After H₂ evolution had ceased a solution of crude alcohol **22a** (38 mg, 0.17 mmol) in acetone (1.5 ml) was added and the mixture was stirred at room temperature for 2.5 h. Solvent was removed *in vacuo* and the residue was partitioned between EtOAc (10 ml) and 5% aq NaHCO₃ (5 ml). The aqueous layer was re-extracted with EtOAc (10 ml) and the combined organic layers were washed with brine (10 ml), dried (MgSO₄) and evaporated *in vacuo*. Purification by column chromatography (EtOAc–petrol, 3 : 1 increasing polarity to EtOAc) gave diol **23** (27 mg, 70%) as colourless crystals; mp 183–184.5 °C (decomp.); $R_{\text{f}} = 0.17$ (EtOAc); $[\alpha]_{\text{D}}^{21} = +77.3$ ($c = 0.33$ in MeOH); found: C, 57.3; H, 8.6; N, 5.8; C₁₁H₁₉NO₄ requires: C, 57.6; H, 8.4; N, 6.1%; ν_{max} (KBr) 3410 (m), 3365 (m), 2970 (m), 1695 (s) and 1080 (m) cm⁻¹; δ_{H} (200 MHz, CD₃OD) 0.93 (9H, s, C(CH₃)₃), 2.21 (1H, d, $J = 16.5$ Hz, C(7)HH'), 3.28 (1H, dd, $J = 16.5$ Hz, $J' = 5.5$ Hz, C(7)HH'), 3.60 (1H, d, $J = 11.0$ Hz, CHH'OH), 3.70 (1H, d, $J = 11.0$ Hz, CHH'OH), 3.78 (1H, d, $J = 9.0$ Hz, C(4)HH'), 4.03 (1H, d, $J = 9.0$ Hz, C(4)HH'), 4.41 (1H, d, $J = 5.5$ Hz, C(6)H) and 4.73 (1H, s, 'BuCH); δ_{C} (50.3 MHz, CD₃OD) 26.2 (C(CH₃)₃), 36.5 (C(CH₃)₃), 46.0 (C(7)H₂), 64.9, 67.9 and 70.6 (CH₂OH, C(4)H₂ and C(6)H), 77.2 (C(5)), 97.3 ('BuCH) and 180.5 (amide CO); m/z (CI) 230 (M + H⁺, 100%) and 172 (33).

(2R,5R)-2-tert-Butyl-6,8-dioxo-5-(2'-methylpropanoyl)-3-oxa-1-azabicyclo[3.3.0]octane 24a

To a suspension of Li (0.5% Na, 30% dispersion in mineral oil) (1.00 g, 43.2 mmol) in petrol (15 ml) was added isopropyl chloride (0.3 ml, 0.26 g, 3.3 mmol). The flask was placed in a sonicator for 5 minutes and isopropyl chloride (1.5 ml, 1.29 g, 16.4 mmol) was then added over 1 h so as to keep the mixture at a gentle reflux. After stirring for a further 1 h the reaction was cooled to -78 °C and a solution of ester **5a** (0.89 g, 3.49 mmol) in THF (15 ml) was added dropwise over 10 min. After 3 h at -78 °C the reaction was quenched by the cautious addition of water. After warming to room temperature the mixture was partitioned between ether (50 ml) and water (50 ml). The aqueous layer was acidified with 2 M HCl and extracted with ether (2 × 30 ml), the ether extract being washed with brine

(40 ml), dried (MgSO₄) and evaporated *in vacuo* to give an inseparable 3 : 1 mixture of ketone **24a** and alcohol **25a** (0.89 g) as a pale yellow crystalline solid; mp 191–192.5 °C; $R_{\text{f}} = 0.32$ (ketone), 0.36 (alcohol) (AcOH–EtOAc–DCM, 1 : 20 : 80); ν_{max} (KBr) 3600–3300 (br w), 3590 (w), 2980 (m), 2800–2100 (br w), 1730 (s), 1650 (s), 1575 (s), 1480 (s), 1315 (s) and 1295 (s) cm⁻¹; δ_{H} (500 MHz, CD₃OD) 0.87 (9H, s, C(CH₃)₃), 1.087 (3H, d, $J = 7.1$ Hz, CH(CH₃)(CH₃')), 1.09 (3H, d, $J = 6.5$ Hz, CH(CH₃)(CH₃')), 3.33 (1H, sept, $J = 6.8$ Hz, CH(CH₃)₂), 3.42 (1H, d, $J = 8.5$ Hz, C(4)HH'), 4.58 (1H, s, 'BuCH) and 4.84 (1H, d, $J = 8.5$ Hz, C(4)HH'); δ_{C} (125.7 MHz, CD₃OD) 19.47 and 21.78 (CH(CH₃)₂), 25.80 (C(CH₃)₃), 35.53 (CH(CH₃)₂), 35.85 (C(CH₃)₃), 68.95 (C(4)H₂), 76.68 (C(5)), 96.34 (CD=COH, $J_{\text{CD}} = 27$ Hz), 99.03 ('BuCH), 178.8 (amide CO), 183.8 (CD=COD) and 209.1 (ketone CO); m/z (CI) 285 (M + NH₄⁺, 3%), 268 (M + H⁺, 100), 210 (24) and 197 (26).

Data for **25a** are given below.

(2R,5R)-2-tert-Butyl-6-hydroxy-7-methyl-8-oxo-5-(2'-methylpropanoyl)-3-oxa-1-azabicyclo[3.3.0]oct-6-ene 24b

To a suspension of Li (0.5% Na, 30% dispersion in mineral oil) (230 mg, 9.94 mmol) in petrol (10 ml) was added isopropyl chloride (100 μ l, 86 mg, 1.1 mmol). The flask was placed in a sonicator for 5 minutes and isopropyl chloride (300 μ l, 238 mg, 3.3 mmol) was then added in 3 portions over 30 min. After stirring for a further 1.5 h the reaction was cooled to -78 °C and a solution of ester **5b** (237 mg, 0.88 mmol) in THF (10 ml) was added dropwise over 10 min. After 2 h at -78 °C the reaction was quenched by the cautious addition of water. After warming to room temperature the mixture was partitioned between ether (40 ml) and water (40 ml). The aqueous layer was acidified with 2 M HCl and extracted with ether (2 × 25 ml), the ether extract being washed with brine (40 ml), dried (MgSO₄) and evaporated *in vacuo*. Recrystallisation from EtOAc–CHCl₃–petrol gave ketone **24b** (62 mg, 25%) as colourless crystals. A second crop (82 mg, 33%) was obtained containing alcohol **25b** as a minor component (<4%). The residue was a 3 : 2 mixture of ketone **24b**–alcohol **25b** [65 mg, 16% ketone (**24b**), 10% alcohol (**25b**)]; mp 188–190.5 °C; $[\alpha]_{\text{D}}^{23} = +286$ ($c = 0.94$ in MeOH); ν_{max} (KBr) 3440 (br s), 2980 (s), 2680 (br m), 1730 (s), 1655 (s), 1605 (s), 1325 (s) and 1175 (s) cm⁻¹; δ_{H} (200 MHz, CD₃OD) 0.87 (9H, s, C(CH₃)₃), 1.04 (3H, d, $J = 7.0$ Hz, CH(CH₃)(CH₃')), 1.06 (3H, d, $J = 7.0$ Hz, CH(CH₃)(CH₃')), 1.69 (3H, s, CH₃C=COH), 3.24 (1H, sept, $J = 7.0$ Hz, CH(CH₃)₂), 3.33 (1H, d, $J = 8.5$ Hz, C(4)HH'), 4.83 (1H, s, 'BuCH) and 4.95 (1H, d, $J = 8.5$ Hz, C(4)HH'); δ_{C} (50.3 MHz, CDCl₃) 4.8 (CH₃C=COH), 18.0 and 20.2 (CH(CH₃)₂), 24.3 (C(CH₃)₃), 33.6 and 34.3 (CH(CH₃)₂ and C(CH₃)₃), 67.4 (C(4)H₂), 79.0 (C(5)), 97.4 ('BuCH), 103.8 (CH₃C=COH), 170.5 (amide CO), 183.1 (CH₃C=COH) and 208.9 (ketone CO); m/z (CI) 299 (M + NH₄⁺, 8%) and 282 (M + H⁺, 100).

(2R,5S,1'R)-2-tert-Butyl-6,8-dioxo-5-(1'-hydroxy-2'-methylpropyl)-3-oxa-1-azabicyclo[3.3.0]octane 25a

Ammonia (12 ml) was condensed in a flask fitted with a dry ice condenser at -78 °C and Li metal (0.35 g, 50.4 mmol) was then added. After 15 min at -78 °C a solution of ketone **24a** (contaminated with 25% alcohol **25a**) (100 mg, 0.37 mmol) in THF (4 ml) was added to the bronze solution and followed after a further 5 min by ethanol (1 ml). The mixture was allowed to warm to -33 °C over 10 min and further ethanol (1 ml) was added. After 30 min at -33 °C the reaction was quenched by the addition of excess ethanol (5 ml) and the mixture was allowed to warm to room temperature. The reaction mixture was partitioned between ether (15 ml) and water (15 ml), the ether layer being extracted with sat. NaHCO₃ (aq) (2 × 15 ml). The combined aqueous layers were acidified with conc. HCl and extracted with ether (2 × 20 ml), the ether layers being washed with brine (25 ml), dried (MgSO₄) and evaporated

in vacuo to give alcohol **25a** (74 mg, 70% from ester **5a**) as a pale pink crystalline solid; mp 168–170 °C; $R_f = 0.36$ (AcOH–EtOAc–DCM, 1 : 20 : 80); $[\alpha]_D^{25} = +98.2$ ($c = 1.14$ in CHCl_3); ν_{max} (KBr) 3600–2200 (br m), 2960 (s), 1680 (s), 1650 (s), 1610 (s) and 1290 (s) cm^{-1} ; δ_{H} (200 MHz, CDCl_3) 0.84 (3H, d, $J = 7.0$ Hz, $\text{CH}(\text{CH}_3)(\text{CH}_3')$), 0.99 (9H, s, $\text{C}(\text{CH}_3)_3$), 1.07 (3H, d, $J = 7.0$ Hz, $\text{CH}(\text{CH}_3)(\text{CH}_3')$), 2.14 (1H, d sept, $J_{\text{sept}} = 7.0$ Hz, $J_{\text{d}} = 1.5$ Hz, $\text{CH}(\text{CH}_3)_2$), 2.56 (1H, br s, OH), 3.22 (1H, d, $J = 22.0$ Hz, $\text{C}(7)\text{HH}'$), 3.46 (1H, d, $J = 9.0$ Hz, $\text{C}(4)\text{HH}'$), 3.54 (1H, d, $J = 22.0$ Hz, $\text{C}(7)\text{HH}'$), 3.77 (1H, br s, $\text{CHOH}(\text{Pr})$), 4.51 (1H, d, $J = 9.0$ Hz, $\text{C}(4)\text{HH}'$) and 4.97 ($^t\text{BuCH}$); δ_{C} (50.3 MHz, CDCl_3) 16.2 and 21.7 ($\text{CH}(\text{CH}_3)_2$), 25.6 ($\text{C}(\text{CH}_3)_3$), 27.9 ($\text{CH}(\text{CH}_3)_2$), 34.9 ($\text{C}(\text{CH}_3)_2$), 46.5 ($\text{C}(7)\text{H}_2$), 69.1, 77.0 and 79.3 ($\text{C}(4)\text{H}_2$, $\text{C}(5)$ and $\text{CHOH}(\text{Pr})$), 99.7 ($^t\text{BuCH}$), 174.2 (amide CO) and 208.0 (ketone CO); m/z (CI) 270 ($\text{M} + \text{H}^+$, 63%), 198 (59) and 140 (100).

(2R,5R,1'R)-2-tert-Butyl-6-hydroxy-7-methyl-8-oxo-5-(1'-hydroxy-2'-methylpropyl)-3-oxa-1-azabicyclo[3.3.0]octane 25b

Li reduction. Ammonia (5 ml) was condensed in a flask fitted with a dry ice condenser and Li metal (7 mg, 1.0 mmol) was then added. After 10 min at -33 °C a solution of ketone **24b** (20 mg, 0.07 mmol) in THF (3 ml) was added to the blue solution. After 10 min at -33 °C the reaction was quenched by the addition of excess solid NH_4Cl (0.5 g) and the mixture was allowed to warm to room temperature. The reaction mixture was partitioned between ether (15 ml) and water (15 ml), the water layer being re-extracted with ether (15 ml). The combined ether layers were washed with brine (25 ml), dried (MgSO_4) and evaporated *in vacuo* to give alcohol **25b** (18 mg, 89%) as a light brown foam; mp 135–138 °C; $R_f = 0.09$ (EtOAc–petrol, 3 : 7); $[\alpha]_D^{25} = +81.0$ ($c = 0.42$ in CHCl_3); ν_{max} (film) 3600–3100 (br m), 2960 (m), 2800–2600 (br w) and 1660 (s) cm^{-1} ; δ_{H} (200 MHz, CDCl_3) 0.91 (3H, d, $J = 7.0$ Hz, $\text{CH}(\text{CH}_3)(\text{CH}_3')$), 0.97 (9H, s, $\text{C}(\text{CH}_3)_3$), 1.00 (3H, d, $J = 7.0$ Hz, $\text{CH}(\text{CH}_3)(\text{CH}_3')$), 1.65 (3H, s, $\text{CH}_3\text{C}=\text{COH}$), 2.23 (1H, sept, $J = 7.0$ Hz, $\text{CH}(\text{CH}_3)_2$), 3.37 (1H, d, $J = 8.5$ Hz, $\text{C}(4)\text{HH}'$), 3.62 (1H, br s, CHOH), 4.06 (1H, br s, $\text{CHOH}(\text{Pr})$), 4.37 (1H, d, $J = 8.5$ Hz, $\text{C}(4)\text{HH}'$), 4.57 (1H, s, $^t\text{BuCH}$) and 8.32 (1H, br s, $\text{CH}_3\text{C}=\text{COH}$); δ_{C} (50.3 MHz, CDCl_3) 5.5 ($\text{CH}_3\text{C}=\text{COH}$), 15.1 and 21.4 ($\text{CH}(\text{CH}_3)_2$), 25.3 ($\text{C}(\text{CH}_3)_3$), 27.6 ($\text{CH}(\text{CH}_3)_2$), 34.6 ($\text{C}(\text{CH}_3)_3$), 71.0, 72.6 and 78.0 ($\text{C}(4)\text{H}_2$, $\text{C}(5)$ and $\text{CHOH}(\text{Pr})$), 97.7 ($^t\text{BuCH}$), 103.9 ($\text{CH}_3\text{C}=\text{COH}$), 172.7 (amide CO) and 182.2 ($\text{CH}_3\text{C}=\text{COH}$); m/z (CI) 317 ($\text{M} + \text{O} + \text{NH}_4^+$, 3%), 300 ($\text{M} + \text{O} + \text{H}^+$, 10), 284 ($\text{M} + \text{H}^+$, 100).

Na reduction. Ammonia (5 ml) was condensed in a flask at -78 °C, fitted with a dry ice condenser, containing NH_4Cl (105 mg, 1.96 mmol). A solution of ketone **24b** (33 mg, 0.12 mmol) in THF (3 ml) was added to the mixture. Na (40 mg, 1.74 mmol) was then added in four portions over 15 min and the mixture was allowed to warm to room temperature. The reaction mixture was partitioned between ether (15 ml) and 2 M HCl (15 ml), the aqueous layer being re-extracted with ether (15 ml). The combined ether layers were washed with brine (25 ml), dried (MgSO_4) and evaporated *in vacuo*. Purification by column chromatography (EtOAc–petrol, 1 : 3) gave alcohol **25b** (16 mg, 48%) and its epimer **28** (3 mg, 9%).

(2R,5S,1'S)-2-tert-Butyl-6,8-dioxo-5-(1'-hydroxy-2'-methylpropyl)-3-oxa-1-azabicyclo[3.3.0]octane 26

Method A. To a solution of crude ketone **24a** (contaminated with 25% alcohol **25a**) (154 mg) in EtOH (8 ml) was added NaOMe (43 mg, 0.80 mmol). After stirring at room temperature for 20 min, NaBH_4 (63 mg, 1.67 mmol) was added and the mixture was stirred for a further 12 h. After partitioning between ether (40 ml) and 2 M HCl (40 ml), the aqueous layer was washed with ether (30 ml), the combined organic extracts being washed with brine (50 ml), dried (MgSO_4) and

evaporated *in vacuo*. Purification by column chromatography (EtOAc–petrol, 1 : 4 increasing polarity to EtOAc) gave alcohol **26** (58 mg, 36% from ester (**5a**)), as a colourless oil, and a mixture of alcohol **25a** and diol **27**. The crude alcohol–diol mixture was partitioned between EtOAc (20 ml) and sat. NaHCO_3 (aq) (20 ml), the EtOAc layer being washed with brine (15 ml), dried (MgSO_4) and evaporated *in vacuo*. Precipitation from EtOAc–petrol gave diol **27** (32 mg, 20% from ester (**5a**)) as an amorphous solid. The aqueous layer was acidified with conc. HCl and extracted with EtOAc (2×10 ml), the organic extracts being washed with brine (15 ml), dried (MgSO_4) and evaporated *in vacuo* to give crude alcohol **25a** (31 mg, 19% from ester **5a**).

Method B. To a solution of crude ketone **24a** (32 mg) (contaminated with 25% alcohol (**25a**)) in EtOH (3 ml) was added NaOMe (7 mg, 0.13 mmol). After stirring at room temperature for 10 min NaBH_4 (7 mg, 0.19 mmol) was added and the mixture was stirred for a further 14 h. After partitioning between ether (20 ml) and 2 M HCl (20 ml) the aqueous layer was washed with ether (15 ml) and the combined organic extracts were washed with brine (25 ml), dried (MgSO_4) and evaporated *in vacuo*. Purification by column chromatography (EtOAc–petrol, 1 : 4 increasing polarity to EtOAc–petrol, 1 : 1) gave diol **27** (2 mg) and alcohol **26** (15 mg) as a colourless oil; $R_f = 0.23$ (EtOAc–petrol, 3 : 7); $[\alpha]_D^{25} = +97.4$ ($c = 1.48$ in CHCl_3); found: C, 62.40; H, 8.92; N, 5.05; $\text{C}_{14}\text{H}_{23}\text{NO}_4$ requires: C, 62.43; H, 8.61; N, 5.20%; ν_{max} (film) 3600–3100 (br m), 3585 (m), 2960 (m), 1770 (m) and 1710 (s) cm^{-1} ; δ_{H} (200 MHz, CDCl_3) 1.02 (9H, s, $\text{C}(\text{CH}_3)_3$), 1.04 (3H, d, $J = 7.0$ Hz, $\text{CH}(\text{CH}_3)(\text{CH}_3')$), 1.07 (3H, d, $J = 7.0$ Hz, $\text{CH}(\text{CH}_3)(\text{CH}_3')$), 1.87 (1H, oct, $J = 7.0$ Hz, $\text{CH}(\text{CH}_3)_2$), 2.53 (1H, br s, OH), 3.03 (1H, d, $J = 20.0$ Hz, $\text{C}(7)\text{HH}'$), 3.46 (1H, d, $J = 7.5$ Hz, CHOH), 3.68 (1H, d, $J = 9.5$ Hz, $\text{C}(4)\text{HH}'$), 3.68 (1H, dd, $J = 20.0$ Hz, $J' = 0.5$ Hz, $\text{C}(7)\text{HH}'$), 4.15 (1H, d, $J = 9.5$ Hz, $\text{C}(4)\text{HH}'$) and 4.97 (1H, s, $^t\text{BuCH}$); δ_{C} (50.3 MHz, CDCl_3) 19.8 and 20.9 ($\text{CH}(\text{CH}_3)_2$), 25.5 ($\text{C}(\text{CH}_3)_3$), 30.5 ($\text{CH}(\text{CH}_3)_2$), 35.2 ($\text{C}(\text{CH}_3)_3$), 48.9 ($\text{C}(7)\text{H}_2$), 68.4 ($\text{C}(4)\text{H}_2$), 77.3 (CHOH), 82.1 ($\text{C}(5)$), 97.7 ($^t\text{BuCH}$), 173.5 (amide CO) and 203.7 (ketone CO); m/z (CI) 287 ($\text{M} + \text{NH}_4^+$, 10%), 270 ($\text{M} + \text{H}^+$, 100) and 212 (15).

(2R,5S,6S,1'S)-2-tert-Butyl-6-hydroxy-8-oxo-5-(1'-hydroxy-2'-methylpropyl)-3-oxa-1-azabicyclo[3.3.0]octane 27

A solution of alcohol **26** (24 mg, 0.09 mmol) and PtO_2 (10 mg) in EtOAc (3 ml) was stirred at room temperature under 4–5 atm pressure of H_2 (Fischer bottle) for 16.5 h. The crude reaction mixture was then filtered through Celite[®] to remove PtO_2 and evaporated *in vacuo*. Purification by column chromatography (EtOAc–petrol, 3 : 7 increasing polarity to EtOAc–petrol, 1 : 1) gave unreacted starting material **26** (18 mg, 75%) and diol **27** (6 mg, 25%) as an amorphous solid; mp 144–146 °C (decomp.); $R_f = 0.18$ (EtOAc–petrol, 1 : 1); $[\alpha]_D^{25} = +95.3$ ($c = 0.30$ in CHCl_3); ν_{max} (CHCl_3) 3555 (m), 3315 (br m), 1670 (s) and 1350 (m) cm^{-1} ; δ_{H} (200 MHz, CDCl_3) 1.00 (9H, s, $\text{C}(\text{CH}_3)_3$), 1.07 (6H, d, $J = 6.5$ Hz, $\text{CH}(\text{CH}_3)_2$), 2.25 (1H, oct, $J = 6.5$ Hz, $\text{CH}(\text{CH}_3)_2$), 2.67 (1H, br d, $J = 5.0$ Hz, $\text{CHOH}(\text{Pr})$), 2.85 (1H, dd, $J = 16.5$ Hz, $J' = 8.5$ Hz, $\text{C}(7)\text{HH}'$), 3.04 (1H, dd, $J = 16.5$ Hz, $J' = 9.5$ Hz, $\text{C}(7)\text{HH}'$), 3.32 (1H, d, $J = 9.5$ Hz, $\text{C}(4)\text{HH}'$), 3.41 (1H, br d, $J = 10.5$ Hz, $\text{C}(6)\text{HOH}$), 3.85 (1H, dd, $J = 6.5$ Hz, $J' = 5.0$ Hz, $\text{CHOH}(\text{Pr})$), 4.38 (1H, d, $J = 9.5$ Hz, $\text{C}(4)\text{HH}'$), 4.41 (1H, q, $J = 9.0$ Hz, $\text{C}(6)\text{HOH}$) and 4.78 (1H, s, $^t\text{BuCH}$); δ_{C} (50.3 MHz, CDCl_3) 18.9 and 23.1 ($\text{CH}(\text{CH}_3)_2$), 26.0 ($\text{C}(\text{CH}_3)_3$), 30.2 ($\text{CH}(\text{CH}_3)_2$), 35.1 ($\text{C}(\text{CH}_3)_3$), 46.3 ($\text{C}(7)\text{H}_2$), 73.6, 74.4, 76.7 and 79.2 ($\text{C}(4)\text{H}_2$, $\text{C}(5)$, $\text{C}(6)\text{H}$ and $\text{CHOH}(\text{Pr})$), 97.0 ($^t\text{BuCH}$) and 177.4 (amide CO); m/z (CI) 272 ($\text{M} + \text{H}^+$, 100%) and 214 (15).

(2R,5R,1'S)-2-tert-Butyl-6-hydroxy-7-methyl-8-oxo-5-(1'-hydroxy-2'-methylpropyl)-3-oxa-1-azabicyclo[3.3.0]oct-6-ene 28

To a solution of ketone **24b** (50 mg, 0.18 mmol) in degassed EtOH (5 ml) under N_2 was added NaOMe (10 mg, 0.19 mmol).

After stirring at room temperature for 10 min NaBH₄ (14 mg, 0.37 mmol) was added and the mixture was stirred for a further 15 h. After partitioning between ether (20 ml) and 2 M HCl (20 ml) the aqueous layer was washed with ether (15 ml), the combined organic extracts being washed with brine (25 ml), dried (MgSO₄) and evaporated *in vacuo*. The crude material was triturated with cold ether, and the ether washings were concentrated *in vacuo* and purification of this material by column chromatography (EtOAc–petrol, 3 : 7) gave further alcohol **28** (2 mg, 4%) as a white powder; mp 173–174.5 °C; *R*_f = 0.19 (EtOAc–petrol, 3 : 7); [*a*]_D²⁵ = +94.0 (*c* = 0.72 in MeOH); *v*_{max} (KBr) 3565 (m), 3435 (br m), 2960 (s), 1655 (m) and 1610 (s) cm⁻¹; *δ*_H (200 MHz, CD₃OD) (enol tautomer) 1.00 (9H, s, C(CH₃)₃), 1.03 (6H, d, *J* = 6.5 Hz, CH(CH₃)₂), 1.62 (3H, s, CH₃C=COH), 2.12 (1H, oct, *J* = 6.5 Hz, CH(CH₃)₂), 3.44 (1H, d, *J* = 9.0 Hz, C(4)HH'), 3.62 (1H, d, *J* = 6.5 Hz, CHOH(Pr)), 4.27 (1H, d, *J* = 9.0 Hz, C(4)HH') and 4.45 (1H, s, BuCH); (keto tautomer) 0.95 (3H, d, *J* = 6.5 Hz, CH(CH₃)(CH₃')), 1.88 (1H, oct, *J* = 6.5 Hz, CH(CH₃)₂), 3.57 (1H, d, *J* = 6.5 Hz, CHOH(Pr)), 3.63 (1H, m, C(4)HH') and 4.14 (1H, d, *J* = 9.5 Hz, C(4)HH'); *δ*_C (50.3 MHz, CD₃OD) (enol tautomer) 6.5 (CH₃C=COH), 20.8 and 22.7 (CH(CH₃)₂), 26.6 (C(CH₃)₃), 31.7 (CH(CH₃)₂), 36.1 (C(CH₃)₃), 71.6, 76.9 and 77.5 (C(4)H₂, C(5) and CHOH(Pr)), 98.7 (BuCH), 104.5 (CH₃C=COH), 174.2 (amide CO) and 184.2 (CH₃C=COH); (keto tautomer) 7.1 (C(7)CH₃), 19.4 and 22.5 (CH(CH₃)₂), 26.3 (C(CH₃)₃), 32.0 (CH(CH₃)₂) and 69.8 and 78.0 (C(4)H₂ and CHOH(Pr)); *m/z* (CI) 284 (M + H⁺, 100%), 226 (M + H⁺ - BuH, 54) and 212 (46); exact mass 284.1859, C₁₅H₂₅NO₄ (MH⁺) requires 284.1862.

(2R,5S,1'S)-2-tert-Butyl-7-hydroxy-7-methyl-6,8-dioxo-5-(1'-hydroxy-2'-methylpropyl)-3-oxa-1-azabicyclo[3.3.0]octane 29

Attempted recrystallisation of crude alcohol **25b** (38 mg, 0.14 mmol), formed by the NaBH₄ reduction of ketone **24b**, from hot CHCl₃ gave decomposition. Purification of the residue by column chromatography (EtOAc–petrol, 1 : 4) gave, apart from starting material, the autoxidation product **29** (3 mg, 7%) as a colourless oil; *R*_f = 0.55 (EtOAc–petrol, 3 : 7); [*a*]_D²⁵ = +71 (*c* = 0.12 in CHCl₃); *v*_{max} (film) 3600–3100 (br m), 2960 (m), 1770 (m) and 1705 (s) cm⁻¹; *δ*_H (200 MHz, CDCl₃) 1.04 (3H, d, *J* = 7.0 Hz, CH(CH₃)(CH₃')), 1.05 (9H, s, C(CH₃)₃), 1.13 (3H, d, *J* = 7.0 Hz, CH(CH₃)(CH₃')), 1.36 (3H, s, C(7)CH₃), 1.94 (1H, oct, *J* = 7.0 Hz, CH(CH₃)₂), 2.96 (1H, br s, CHOH), 3.55 (1H, br d, *J* = 7.0 Hz, CHOH(Pr)), 3.60 (1H, d, *J* = 9.5 Hz, C(4)HH'), 4.22 (1H, d, *J* = 9.5 Hz, C(4)HH'), 4.95 (1H, s, BuCH) and 5.23 (1H, br s, OH); *δ*_C (125.7 MHz, CDCl₃) 16.61, 16.71 and 22.26 (CH(CH₃)₂ and C(7)CH₃), 25.87 (C(CH₃)₃), 28.04 (CH(CH₃)₂), 34.69 (C(CH₃)₃), 68.98, 76.58 and 86.94 (C(4)H₂, C(5), C(7) and CHOH), 100.9 (BuCH), 177.6 (amide CO) and 209.7 (ketone CO); *m/z* (CI) 317 (M + NH₄⁺, 18%), 300 (M + H⁺, 91), 245 (77) and 228 (100); *m/z* (electrospray) 317 (M + NH₄⁺, 6%) and 300 (M + H⁺, 100).

(2R,5S,1'R)-2-tert-Butyl-7-methyl-6,8-dioxo-7-peroxy-5-(1'-hydroxy-2'-methylpropyl)-3-oxa-1-azabicyclo[3.3.0]octane 30

A solution of alcohol **25b** (12 mg, 0.04 mmol) in CDCl₃ (0.5 ml) was left at room temperature for 20 days. Purification by column chromatography (EtOAc–petrol, 1 : 4) gave starting material (6 mg, 50%) and peroxide **30** (4 mg, 30%) as a yellow oil (positive peroxide test with starch/KI paper); *R*_f = 0.30 (EtOAc–petrol, 3 : 7); [*a*]_D²⁵ = +48 (*c* = 0.10 in CHCl₃); *v*_{max} (film) 3600–3100 (br m), 2965 (m), 1770 (m) and 1715 (s) cm⁻¹; *δ*_H (200 MHz, CDCl₃) 0.86 (3H, d, *J* = 7.0 Hz, CH(CH₃)(CH₃')), 1.02 (9H, s, C(CH₃)₃), 1.08 (3H, d, *J* = 7.0 Hz, CH(CH₃)(CH₃')), 1.47 (3H, s, C(7)CH₃), 1.93 (1H, d sept, *J*_{sept} = 7.0 Hz, *J*_d = 2.0 Hz, CH(CH₃)₂), 2.50 (1H, br s, CHOH), 3.60 (1H, d, *J* = 8.5 Hz, C(4)HH'), 3.75 (1H, br s, CHOH(Pr)), 4.60 (1H, d, *J* = 8.5 Hz, C(4)HH') and 5.02 (1H, s, BuCH); *δ*_C (125.7 MHz,

CDCl₃) 15.07, 19.06 and 21.20 (CH(CH₃)₂ and C(7)CH₃), 25.56 (C(CH₃)₃), 29.68 (CH(CH₃)₂), 35.32 (C(CH₃)₃), 69.08, 75.60, 77.40 and 78.91 (C(4)H₂, C(5), C(7) and CHOH), 97.65 (BuCH), 175.0 (amide CO) and 204.2 (ketone CO); *m/z* (CI) 317 (M + O + NH₄⁺, 9%), 300 (M + O + H⁺, 28), 298 (M + H⁺ - H₂O, 11) and 200 (100); *m/z* (electrospray) 316 (M + H⁺, 75%), 270 (72) and 200 (100).

(3S,4S,9S,10S)-4,10-Dibenzoyloxy-2,8-dihydroxy-3,9-dimethoxy-carbonyl-6,12-dioxo-1,7-diazatricyclo[7.3.0.0^{3,7}]dodecane 32

To a solution of (COCl)₂ (35 μl, 51 mg, 0.40 mmol) in DCM (3 ml) under N₂ at -78 °C was added DMSO (45 μl, 50 mg, 0.63 mmol). The mixture was stirred at -78 °C for 15 min and then a solution of alcohol **15a** (100 mg, 0.34 mmol) in DCM (1.5 ml) was added dropwise. After a further 15 min at -78 °C triethylamine (140 μl, 102 mg, 1.0 mmol) was added and the mixture was allowed to warm to room temperature over 10 min. After stirring at room temperature for 3 h the mixture was partitioned between DCM (10 ml) and H₂O (10 ml). The aqueous layer was re-extracted with DCM (10 ml) and the combined organic layers were dried (MgSO₄) and evaporated *in vacuo*. Purification by column chromatography (EtOAc–petrol, 1 : 1 increasing polarity to EtOAc–petrol, 3 : 1) gave dimer **32** (42 mg, 42%) as an off-white solid; mp 185.5–188 °C (decomp.); *R*_f = 0.20 (EtOAc–petrol, 1 : 1); [*a*]_D²⁵ = +50.3 (*c* = 1.49 in CHCl₃); *v*_{max} (CHCl₃) 3560 (w), 3440 (br w), 2960 (w), 1730 (s) and 1605 (w) cm⁻¹; *δ*_H (200 MHz, CDCl₃) 2.95 (4H, d, *J* = 9.5 Hz, 2 × CH₂CH), 3.54 (6H, s, 2 × CO₂CH₃), 5.55 (2H, d, exchangeable, *J* = 8.0 Hz, 2 × CHOH), 6.03 (2H, t, *J* = 9.5 Hz, 2 × CH₂CH), 6.36 (2H, d, *J* = 8.0 Hz, 2 × CHOH), 7.41–7.48 (4H, m, ArH), 7.57–7.64 (2H, m, ArH) and 7.94 (4H, d, *J* = 7.0 Hz, ArH); *δ*_C (50.3 MHz, CDCl₃) 35.4 (CH₂CH), 53.7 (CO₂CH₃), 70.6 and 73.2 (CH₂CH and CHOH), 72.3 (NCCO₂CH₃), 128.3 (ArC), 128.8, 129.7 and 134.1 (ArC) and 165.9, 168.6 and 172.7 (CO); *m/z* (CI) 583 (M + H⁺, <1%), 309 (M/2 + NH₄⁺, 100), 292 (M/2 + H⁺, 93), 142 (76) and 105 (85); exact mass 292.0828, C₁₄H₁₄NO₆ (M/2 + H⁺) requires 292.0821.

(2R,3S,E)-3-Benzoyloxy-2-methoxycarbonyl-2-(2'-ethoxycarbonylvinyl)pyrrolidin-5-one 33

To a solution of dimer **32** (72 mg, 0.12 mmol) in toluene (10 ml) was added ethoxycarbonylmethylenetriphenylphosphorane (90 mg, 0.26 mmol). The mixture was heated at reflux for 4 h, cooled to room temperature and partitioned between ether (25 ml) and NH₄Cl (aq) (25 ml). The organic layer was washed with brine (20 ml), dried (MgSO₄) and evaporated *in vacuo*. Purification by column chromatography gave a 2 : 9 mixture of (*Z*)-alkene–(*E*)-alkene **33** (22 mg, 26%) as a pale yellow oil and pure (*E*)-alkene **33** (28 mg, 33%) as a pale yellow glass; *R*_f = 0.42 (EtOAc–petrol, 1 : 1); [*a*]_D²⁵ = +54.7 (*c* = 1.35 in CHCl₃); *v*_{max} (CHCl₃) 3430 (w), 1725 (s) and 1270 (s) cm⁻¹; *δ*_H (200 MHz, CDCl₃) 1.30 (3H, t, *J* = 7.0 Hz, CO₂CH₂CH₃), 2.50 (1H, d, *J* = 17.5 Hz, C(4)HH'), 2.87 (1H, dd, *J* = 17.5 Hz, *J*' = 5.5 Hz, C(4)HH'), 3.68 (3H, s, CO₂CH₃), 4.22 (2H, q, *J* = 7.0 Hz, CO₂CH₂CH₃), 5.73 (1H, d, *J* = 5.5 Hz, C(3)H), 6.21 (1H, d, *J* = 15.5 Hz, CH=CH'), 7.26 (1H, d, *J* = 15.5 Hz, CH=CH'), 7.41–7.48 (3H, m, ArH and NH), 7.56–7.64 (1H, m, ArH) and 7.95 (2H, d, *J* = 7.0 Hz, ArH); *δ*_C (50.3 MHz, CDCl₃) 14.1 (CO₂CH₂CH₃), 36.3 (C(4)H₂), 53.4 (CO₂CH₃), 61.2 (CO₂-CH₂CH₃), 71.1 and 74.1 (C(2) and C(3)H), 123.8 and 142.5 (vinyl), 128.5, 128.6, 129.7 and 133.9 (ArC) and 164.7, 165.0, 167.8 and 174.3 (CO); *m/z* (CI) 379 (M + NH₄⁺, 100%), 362 (M + H⁺, 46), 257 (94), 240 (100), 208 (89) and 105 (70); exact mass 362.1234, C₁₈H₂₀NO₇ (MH⁺) requires 362.1240.

(*Z*)-isomer: *R*_f = 0.38 (EtOAc–petrol, 1 : 1); *δ*_H (200 MHz, CDCl₃) 1.28 (3H, t, *J* = 7.0 Hz, CO₂CH₂CH₃), 2.71 (1H, dd, *J* = 17.0 Hz, *J*' = 6.0 Hz, C(4)HH'), 2.95 (1H, dd, *J* = 17.0 Hz, *J*' = 7.5 Hz, C(4)HH'), 3.65 (3H, s, CO₂CH₃), 4.20 (2H, q,

$J = 7.0$ Hz, $\text{CO}_2\text{CH}_2\text{CH}_3$), 5.79 (1H, dd, $J = 7.5$ Hz, $J' = 6.0$ Hz, C(3H), 6.08 (1H, d, $J = 11.5$ Hz, $\text{CH}=\text{CH}'$), 6.68 (1H, d, $J = 11.5$ Hz, $\text{CH}=\text{CH}'$), 7.4–8.0 (6H, ArH and NH).

Acknowledgements

We thank EPSRC and AstraZeneca for funding of a studentship to MDA, and we wish to gratefully acknowledge the use of the EPSRC Chemical Database Service at Daresbury²⁴ and the EPSRC National Mass Spectrometry Service Centre at Swansea.

References

- 1 M. G. Moloney, *Nat. Prod. Rep.*, 1999, **16**, 485.
- 2 S. Omura, T. Fujimoto, K. Otaguro, K. Matsuzaki, R. Moriguchi, H. Tanaka and Y. Sasaki, *J. Antibiot.*, 1991, **44**, 113.
- 3 E. J. Corey, W. Li and T. Nagamitsu, *Angew. Chem., Int. Ed.*, 1998, **37**, 1676.
- 4 S. N. Crane and E. J. Corey, *Org. Lett.*, 2001, **3**, 1395.
- 5 E. J. Corey, W.-D. Z. Li, T. Nagamitsu and G. Fenteany, *Tetrahedron Lett.*, 1999, **55**, 3305.
- 6 J. H. Bailey, D. Cherry, J. Dyer, M. G. Moloney, M. J. Bamford, S. Keeling and R. B. Lamont, *J. Chem. Soc., Perkin Trans. 1*, 2000, 2783.
- 7 J. Dyer, S. Keeling, A. King and M. G. Moloney, *J. Chem. Soc., Perkin Trans. 1*, 2000, 2793.
- 8 J. H. Bailey, A. T. J. Byfield, P. J. Davis, A. C. Foster, M. Leech, M. G. Moloney, M. Muller and C. K. Prout, *J. Chem. Soc., Perkin Trans. 1*, 2000, 1977.
- 9 C. E. M. Davis, T. D. Heightman, S. A. Hermitage, M. G. Moloney and G. A. Woods, *Tetrahedron Lett.*, 1998, **39**, 1025.
- 10 D. Seebach and J. D. Aebi, *Tetrahedron Lett.*, 1984, **25**, 2545.
- 11 M. D. Andrews, A. G. Brewster, K. M. Crapnell, A. J. Ibbett, T. Jones, M. G. Moloney, C. K. Prout and D. Watkin, *J. Chem. Soc., Perkin Trans. 1*, 1998, 223.
- 12 M. D. Andrews, A. G. Brewster and M. G. Moloney, *Synlett*, 1996, 612.
- 13 M. D. Andrews, A. G. Brewster, J. Chuhan, A. J. Ibbett, M. G. Moloney, K. Prout and D. Watkin, *Synthesis*, 1997, 305.
- 14 M. D. Andrews, A. G. Brewster, M. G. Moloney and K. L. Owen, *J. Chem. Soc., Perkin Trans. 1*, 1996, 227.
- 15 N. Galeotti, J. Poncet, L. Chiche and P. Jouin, *J. Org. Chem.*, 1993, **58**, 5370.
- 16 E. J. Corey and G. A. Reichard, *J. Am. Chem. Soc.*, 1992, **114**, 10677.
- 17 M. D. Andrews, A. G. Brewster, J. Chuhan, M. G. Moloney and C. K. Prout, unpublished results.
- 18 D. L. Hughes, *Org. React. (N. Y.)*, 1992, **42**, 335.
- 19 R. W. Armstrong and J. A. DeMattei, *Tetrahedron Lett.*, 1991, **32**, 5749.
- 20 I. Kikkawa and T. Yorifuji, *Synthesis*, 1980, 877.
- 21 D. Bryce-Smith and E. E. Turner, *J. Chem. Soc.*, 1953, 861.
- 22 B. J. Wakefield, *Organolithium Methods*, Academic, London, 1988.
- 23 J. W. Huffman, in *Comprehensive Organic Synthesis*; Pergamon, Oxford, 1991, p. 107.
- 24 D. A. Fletcher, R. F. McMeeking and D. Parkin, *J. Chem. Inf. Comput. Sci.*, 1996, **36**, 746.