Regioselective Dieckmann cyclisations leading to enantiopure highly functionalised tetramic acid derivatives

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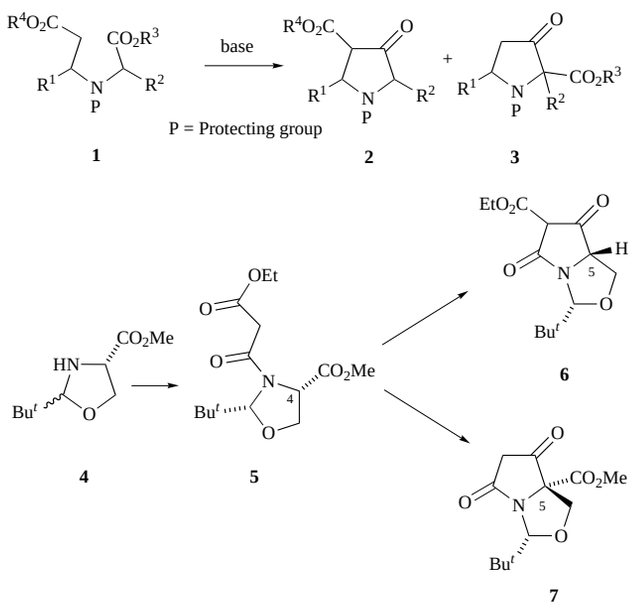
Regioselective Dieckmann cyclisations using an *N*-acyloxazolidine derived from L-serine give substituted tetramic acids in high yield and enantioselectivity. The products are easily deprotected under mild conditions to give hydroxymethyltetramic acids.

Introduction

Nitrogen heterocycles occur widely in nature, in isolation and as structural subunits in many families of alkaloids, and possess wide ranging biological and pharmaceutical activities. Tetramic acids are a particularly important sub-group, and are well known for their potent antibiotic, antiviral, and antifungal as well as cytotoxic activity.[1] Older methodology for the construction of these types of compounds has been limited in scope and stereocontrol,[2,3] although more recent work has addressed these difficulties.[4–8] The construction of tetramic acids by means of a Dieckmann cyclisation of a suitable precursor has been known for some time, and offers a particularly straightforward approach: the earliest reactions studied were those of closures of *N*-functionalised glycine derivatives **1**, which were shown to give high yields of cyclised product **2** for a range of substituents (R^1 and R^2), and for a variety of *N*-protecting groups (P).[9–11] Later closer examination of these reactions indicated that the regiocontrol of ring closure was not total, and that both products **2** and **3** were obtained.[12–14] Early studies to extend this approach to amino acid derivatives **1** ($R^2 = CO_2R$) derived from chiral amino acids indicated initially that only racemic products **2** ($R^2 = CO_2R$) were obtained, due to the strongly alkaline conditions required for the ring closure, and the enhanced acidity of the α-proton in the products,[15] as was seen in the synthesis of the antibiotic holomycin.[16] Recent more careful examination however has indicated that reaction conditions can be found in which racemisation can be minimised[17–19] or avoided completely[20–22] by judicious choice of reagents and conditions.

An alternative to these reagent-controlling approaches would be to modify the substrate in such a way that chirality could not be lost, and the usefulness of such a substrate-controlling approach has been amply demonstrated by Seebach's 'Self Regeneration of Stereocentres'.[23,24] In order to avoid possible problems with racemisation in the formation of chiral tetramic acids, we decided to apply Seebach's elegant idea to the construction of cyclic compounds. Our strategy is shown in Scheme 1; acylation of the well known serine-derived oxazolidine **4**[23] with a malonyl residue would give *N*-acyl derivative **5**. Cyclisation under standard Dieckmann conditions was expected to give the pyroglutamate **6** *via* the more stable side chain enolate in a manner analogous to the formation of adduct **2**. The chirality of the acidic C(5) position of the product pyroglutamate **6** under the strongly basic cyclisation conditions was expected to be maintained by Seebach's principle, in which the oxazolidine ring acts as a chiral protecting group. An alternative pathway, leading to tetramic acid **7** *via* generation of the less stable enolate at C(4) of oxazolidine **5** was not expected to be observed. Interestingly, this approach had not been applied to ring closure reactions (Dieckmann, aldol or alkylations) which used the Seebach-type chiral enolates when we began our work, although reports of stereocontrolled ring closures using similar ideas have appeared recently.[25–29] This approach was of considerable interest to us as it was expected to permit a simple, short, efficient and versatile route to functionalised heterocycles, which would allow control of both relative and absolute stereochemistry. Some of our work in this area has been published[30–32] and we describe here in full details of our work on the Dieckmann cyclisation route to tetramic acids.



Scheme 1

Synthesis of *N*-acyl oxazolidines

According to the method developed by Seebach and co-

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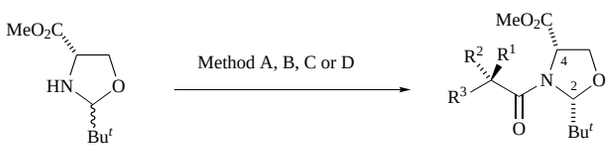
Table 1 Preparation of *N*-acyl oxazolidines **8a**–**k**

Compound	R^1	R^2	R^3	Method[a]	Yield (%)
8a	H	H	EtO_2C	A	88
8b[b]	H	Me	EtO_2C	B	94
8c[c]	Ph	H	EtO_2C	A	75[d,e]
8d	H	H	NC	A	82
8e	H	H	Ph	B	90
8f	Ph	H	Ph	B	60[d]
8g	H	H	$EtO_2C(CH_2)_2$	B	48
8h	H	—	EtO_2CCH=	B	79
8i	H	H	$(EtO_2C)_2CH$	B	45
8j	MeO_2CCH_2	H	EtO_2C	C	60
8k	MeO_2CCH_2	H	Bu^tO_2C	D	50

[a] Method A: DCCI, DMAP, $R^1R^2R^3CCO_2H$; method B: $R^1R^2R^3$-CCOCl, py, DCM; method C: $KOBu^t$, **8a**, $BrCH_2CO_2Me$, THF; method D: $KOBu^t$, **8** ($R^1 = Bu^tO_2C$, $R^2 = R^3 = H$), $BrCH_2CO_2Me$, THF. [b] Mixture of **8b**,**9a**, ratio 2.6 : 1. [c] Mixture of **8c**,**9b**, ratio 9 : 1. [d] Structure confirmed by single crystal X-ray analysis. [e] See ref. 38.



4 8a–k

Scheme 2 Method A: $R^1R^2R^3CCO_2H$, DCCI, DMAP, DCM; method B: $R^1R^2R^3CCOCl$, pyridine, DCM; method C: $KOBu^t$, **8a**, $BrCH_2CO_2Me$, THF; method D: $KOBu^t$, **8** ($R^1 = R^2 = H$, $R^3 = Bu^tO_2C$), $BrCH_2CO_2MeTHF$

workers,[33,34] L-serine methyl ester hydrochloride was condensed with pivaldehyde in the presence of triethylamine to generate oxazolidine **4**. After simple filtration and removal of the solvent *in vacuo*, crude oxazolidine **4** was obtained as a 1 : 1 mixture of *cis*- and *trans*-isomers in 82–93% yield on up to 20 g scale.

The acylation of this oxazolidine could be achieved using either carboxylic acids by dicyclohexylcarbodiimide (DCCI)–dimethylaminopyridine (DMAP) coupling (Method A) for **8a**,**c**,**d**, or with acid chlorides with pyridine as catalyst (Method B) for **8b**,**e**–**i** (Scheme 2 and Table 1). Acylation was readily achieved with malonates, but higher homologues were much more difficult to obtain in good yield and high purity. Once *N*-acylated, the oxazolidine ring was found to be very stable, in contrast to the parent oxazolidine **4**. In the case of **8i**, the required acid chloride (as a keto–enol tautomeric mixture) was obtained by alkylation of diethyl malonate with *tert*-butyl bromoacetate, followed by selective ester hydrolysis and treatment of thionyl chloride, using the literature procedure.[35,36] Oxazolidine **8j** was obtained by alklyation of **8a** with methyl bromoacetate using potassium *tert*-butoxide in THF in 60% yield. The synthesis adopted for oxazolidine **8k** was analogous to the route to compound **8j**. Thus, oxazolidine **4** was coupled to *tert*-butyl hydrogen malonate under standard conditions to form the *N*-acylated oxazolidine, which was then alkylated with methyl bromoacetate to give cyclisation precursor **8k** in 50% yield.

In keeping with earlier observations in related *N*-acyl oxazolidines,[37] oxazolidines **8** possessed the C(2),C(4) *cis*-relative stereochemistry, as determined from nOe experiments for **8b** and single crystal X-ray analysis for **8c**[38] and **8f**[39] (Fig. 1), although the parent heterocycle was obtained as a 1 : 1 mixture of diastereomers; presumably ring-chain tautomerism permits equilibration to the more stable product in which both substituents are pseudoequatorial.[40,41] On the basis of the C(2)H chemical shifts, all of the oxazolidines **8** possess the same relative stereochemistry. The substituents on the nitrogen atom are not planar, and the nitrogen is clearly partially pyramidalised, as has been observed in the X-ray structures of other similar *N*-acyl oxazolidines.[37] This pyramidalisation places the *N*-acyl substituent *trans*- to the C(2) and C(4) substituents of the

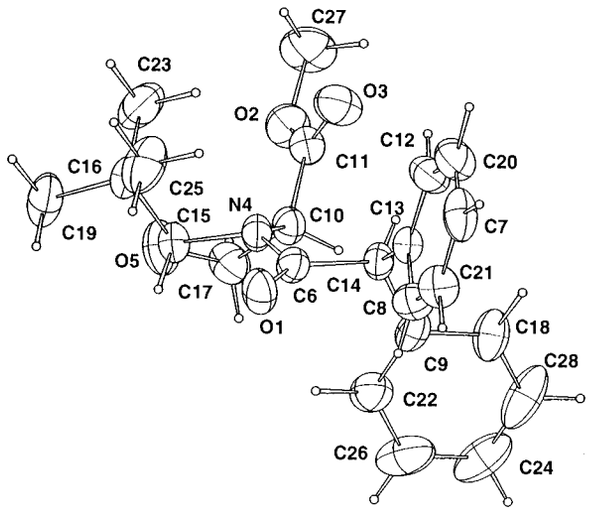
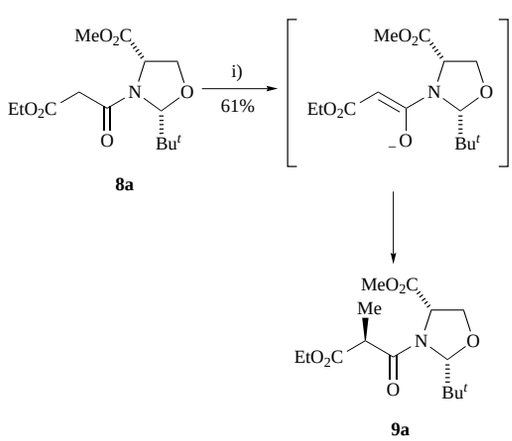


Fig. 1 X-Ray crystallographic structure for compound **8f**, with ellipsoids at 50% probability level

oxazolidine ring. The amide carbonyl is still orientated so as to allow some overlap with the nitrogen lone pair, the carbonyl oxygen being directed towards the bulky *tert*-butyl group, placing the *N*-acyl substituent towards the sterically less demanding methyl ester attached to C(4) of the oxazolidine ring.

Treatment of oxazolidine **4** with pyridine and ethyl α-methylmalonyl chloride led to a separable mixture of the epimeric *cis*-oxazolidines **8b** and **9a** in a ratio of 2.6 : 1; however, unequivocal assignment of the side chain stereochemistry by spectroscopic means was not possible. The above assignment was tentatively arrived at as follows: the addition of potassium *tert*-butoxide to a solution of methyl iodide and oxazolidine **8a** in THF at −65 °C followed by warming to room temperature led to a 61% yield of oxazolidine **9a** with no sign of the side chain epimer **8b** (Scheme 3). Assuming that a planar enolate was formed then it



Scheme 3 *Reagents and conditions*: i) MeI, THF, $KOBu^t$

would have been most likely to adopt the conformation shown with the carbonyl oxygen towards the bulky *tert*-butyl group. The (*Z*)-enolate shown would have been favoured over the alternative (*E*)-enolate as this places the ethyl ester away from the methyl ester attached to the oxazolidine ring. Alkylation occurring from the upper face, as drawn (*Si* face) would then have generated the oxazolidine **9a**. That compound **9a** is the thermodynamically more stable compound was indicated by the complete interconversion of **8b** to **9a** after storage at room temperature for 8 months; this is consistent with the phenyl derivative **8c**, for which the same side-chain stereochemistry corresponds to the more thermodynamically stable isomer. The *cis*-nature of the C(2) and C(4) substituents of oxazolidine **9a** was consistent with the results of an nOe experiment (Fig. 2). It

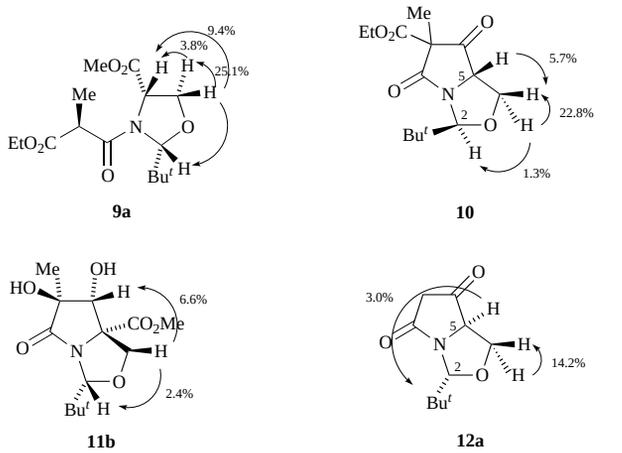
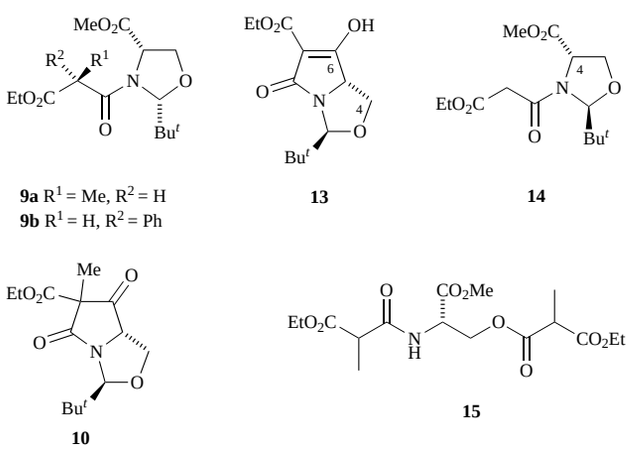


Fig. 2 ^{1}H nOe Spectroscopic data

should be noted, however, that this side-chain stereochemistry was not retained upon subsequent cyclisation (see below).

In the preparation of phenylmalonate **8c**, the side chain epimer **9b** was also obtained in 10% yield, which was found to be readily epimerised to the major epimer **8c** upon column chromatography. That **8c** was indeed the thermodynamically stable epimer was confirmed by equilibration experiments under the basic conditions of the acylation reaction (DMAP).

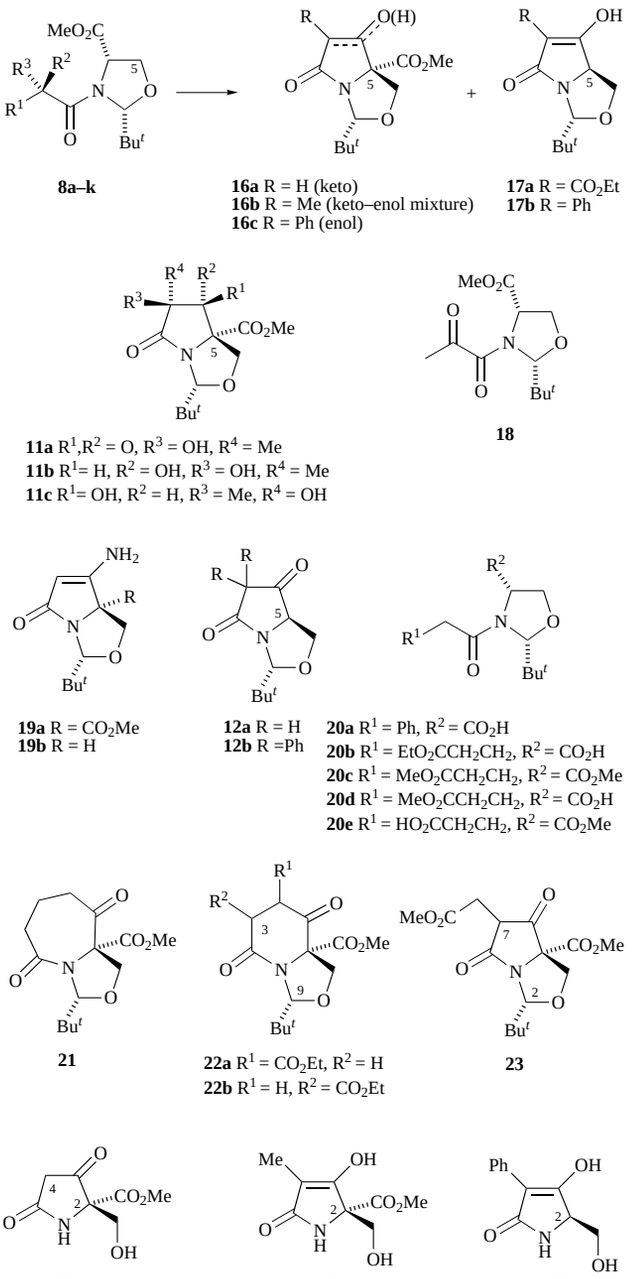
In some cases, evidence for the formation of the *trans*-oxazolidine isomer of oxazolidine **8**, at least as a minor by-product, was obtained. Thus, compound **13**, arising by initial C(4) epimerisation of *trans*-oxazolidine **14** to the more stable *ent*-**8a** followed by Dieckmann cyclisation, was observed as a side product in 3.5% yield in the formation of oxazolidine **8a**. Confirmation of the structure of **13** came by comparison with



its enantiomer **17a** which was synthesised independently (see below). The isolated yield of **13** is consistent with the observation that **8a** was in fact formed as a 7.8 : 1 mixture of diastereomers (**8a** : **14**) as shown in the ^{1}H NMR spectrum, although these were not separable. A similar product **10** was observed in 0.7% yield after the acylation of oxazolidine **4** with ethyl-α-methyl malonic acid and DCCI when the reaction was carried out at elevated temperature; the diacylated serine derivative **15** was also isolated as a minor byproduct from this reaction. The assignment of the relative stereochemistry of bicyclic compound **10** was supported by the results of an nOe experiment (Fig. 2). Irradiation of the C(5) proton gave enhancement of one of the C(4) protons while irradiation of the other C(4) proton gave enhancement of the C(2) proton. This indicated that the C(2) and C(5) protons were on opposite sides of the oxazolidine ring. However, the low yields of these *trans*-oxazolidine-derived products is indicative of the high level of stereocontrol exerted across the oxazolidine ring by the bulky *tert*-butyl substituent.

Cyclisation reactions

In an initial investigation[30] of the Dieckmann cyclisation of **8a** with lithium diisopropylamide (LDA) at −78 °C, the tetramic acid **16a**, in the keto form, was unexpectedly found to be the major product, along with variable amounts of the alternative tetramic acid **17a**. More reliable conditions for the cyclisation



used potassium *tert*-butoxide in 2-methylpropan-2-ol at reflux, which gave a 3 : 1 ratio of **16a** : **17a** in the crude product. These could be separated by partitioning between ethyl acetate and sodium dihydrogen phosphate; tetramic acid **16a** was obtained from the organic layer in 73% yield after column chromatography and tetramic acid **17a** was isolated in 12% yield from the aqueous layer by acidification and extraction with ethyl acetate, although could not be further purified due to its instability on silica or alumina. Significantly, compound **17a** was found to be the enantiomer of compound **13**. Thus, the expected mode of ring closure, leading to products of type **6** (Scheme 1) did not appear to be preferred.

Cyclisation of either of the epimeric oxazolidines **8b** or **9a** under the KOBu^t–Bu^{t}OH conditions gave the tetramic acid product **16b**, as a mixture of keto [epimeric at C(7)] and enol

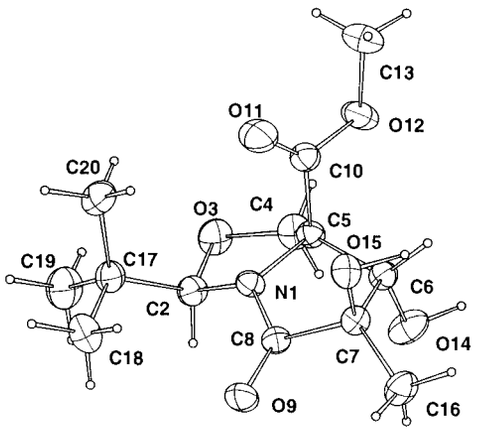


Fig. 3 X-Ray crystallographic structure for compound **16c**, with ellipsoids at 50% probability level

tautomers, in near quantitative yield (96%). Interestingly, this product was found to be particularly prone to autooxidation on prolonged storage, to give both the hydroxy substituted product **11a** and the keto amide compound **18**. The stereochemistry of this compound was assigned indirectly. Reduction of **11a** with sodium borohydride or by catalytic hydrogenation (PtO_2–H_2–EtOAc) gave the *trans*- diol **11b** in 93 and 99% yield respectively, whose relative stereochemistry was partly established by nOe experiments. (Fig. 2). The *trans*- dihydroxy stereochemistry was assumed on the basis of a chelation controlled intramolecular borohydride reduction.[42] This same compound was a by-product in the reduction of enol **16b** with sodium borohydride–acetic acid,[43] along with the alternative *trans*- diol **11c**, in which rigorous exclusion of atmospheric oxygen had not been made. The structure of **11c** was unequivocally assigned by single crystal X-ray analysis (Fig. 3).[39] Hydroxy ketone **11a** and keto amide **18** could be prepared directly from **16b** by deprotonation (NaH) followed by reaction with the hydroxylating reagent MoOPD (MoO_5·py·DMPU‡)[44] in 31 and 14% yield respectively. The phenyl oxazolidine derivatives (either epimer **8c** or **9b**) gave the tetramic acid product **16c** exclusively in the enolic form as has been reported previously.[38] This compound could be easily hydrolysed and decarboxylated (NaOH at reflux followed by heating *in vacuo*) with retention of stereochemistry at C(5), to give the tetramic acid **17b** {$[\alpha]_D^{20}$ +75.5 (*c* 0.43 in DMF)}, which possessed the same relative stereochemistry at C(5) as **17a** (see below). A similar mode of ring closure was also obtained for the cyano derivative **8d** with sodium methoxide in methanol, giving the enamine **19a** in 82% yield. However, with KOBu′–Bu′OH at reflux, the decarboxylated product **19b** was obtained in 71% yield, along with enamine **19a** (7%) and tetramic acid **12a** (trace). For this reaction to occur, the Bu′OH needed to be slightly wet, presumably to allow the initial hydrolysis of **19a** prior to decarboxylation.

However, not all cyclisations were found to be so facile. The phenylacetyl derivative **8e**, in which only one mode of cyclisation was possible, that being from the *N*-acyl side chain to the methyl ester of the oxazolidine ring, gave a very poor yield (22%) of the product **17b** upon treatment with NaOMe–MeOH, along with 10% of the hydrolysed starting material **20a** and 27% of unreacted starting material **8e**. However, with KOBu′–Bu′OH at reflux, the exclusive product was **20a** (80% yield) obtained from hydrolysis. It is noteworthy that compound **17b** produced in this way was identical to material produced from oxazolidine **8c** followed by decarboxylation, but with a lower optical rotation {$[\alpha]_D^{20}$ +63.7 (*c* 0.48 in DMF)} and later HPLC investigation showed this compound to have an ee of only 88%. Clearly, this cyclisation had occurred with initial C(4) epimerisation of the substrate oxazolidine **8e**. The diphenyl derivative **8f** gave no reaction upon treatment with base. Reaction of **8g** with potassium *tert*-butoxide in 2-methylpropan-2-ol at reflux gave starting material and acid **20b** in 37% yield, while reaction with sodium methoxide in methanol gave a mixture of the transesterified diester **20c** and the acids **20b**,**d**. The hydrolysed materials were presumably due to traces of water present in the alcohol solvents. No material due to a Dieckmann cyclisation was observed in any reaction. Attempts to form a six-membered ring by Dieckmann cyclisation of diester **8h** were completely unsuccessful, giving intractable mixtures of products, and no traces of any products due to intramolecular cyclisation were observed.

Since a possible reason for the lack of cyclisation of **8g** was that the expected product **21** is an α,α-disubstituted β-dicarbonyl and as such cannot form a stable product anion, which provides the usual driving force for the Dieckmann cyclisation, the cyclisation of the substrates **8i**–**k** was examined. The cyclisation of oxazolidine **8i** to the 5,6-bicyclic compound **22a** proceeded in much lower yield than expected (18%), and in the case of **8j**, Dieckmann cyclisation gave the two products **23** and **22b** as an inseparable mixture and in a ratio of 8:3 and 40% overall yield. Cyclisation of **8k** gave a mixture of unreacted starting material and **23**, which could not be purified.

Determination of enantiomeric excess

Although retention of stereochemistry using Seebach's protocol, in which an acetal or oxazolidine function essentially acts as a chiral protecting group, has been demonstrated in a wide range of systems, the optical purity of several representative Dieckmann cyclisation adducts was investigated. Racemic samples of tetramic acids **16a**, **16b** and **17b** were synthesised, using identical procedures to those described earlier, from (±)-serine methyl ester hydrochloride. Comparison of these samples with those prepared in the enantiopure series (from L-serine, ee 97–99%) by chiral HPLC (Chiralcel OD, in 98% hexane, 2% ethanol, 0.1% TFA) allowed determination of the ee values, which were > 90, > 98, and 88% for **16a**,**b** and **17b** respectively. For dicarbonyl **16a** the value quoted is a minimum value, spiking experiments showing that the minor enantiomer could not be detected below levels of 5%. These results indicate that this route to α-substituted pyroglutamates generates products of excellent enantiomeric purity. The smaller ee of tetramic acid **17b** is notable as it is the only product formed by cyclisation from the *N*-acyl side chain onto the C(4) methyl ester of oxazolidine **8**; it is believed that a lower ee is obtained in this case due to the presence of a small amount of the *trans*-oxazolidine, which upon cyclisation leads to the enantiomer of **17b**.

The tetramic acids **12a** and *ent*-**12a** were prepared by hydrolysis of enamine **19b** ($NaHCO_3$, Pr^iOH) and hydrolysis and decarboxylation of tetramic acid **13** respectively; these compounds gave identical spectroscopic properties, but had equal and opposite optical rotations; the *cis*- C(5)H and C(2)Bu′ relative stereochemistry was shown by ^1H nOe analysis (Fig. 2). Chemical correlation of tetramic acid **17b** with dicarbonyl **12a** was achieved by conversion of both compounds to the diarylated derivative **12b**. According to the procedure of Pinhey,[45,46] a solution of lead tetraacetate (LTA), phenylboronic acid and a catalytic amount of mercury(II) acetate in chloroform was heated at 40 °C for 1 h, then stirred at room temperature in order to form the aryllead species. A solution of the compound to be arylated and pyridine in chloroform was then added and the mixture heated at 40 °C for another hour. After work-up and purification by column chromatography, the diarylated compound **12b** was obtained in 56% yield from dicarbonyl **12a** and 83% yield from tetramic acid **17b**. The material obtained from the two routes had identical physical and spectroscopic properties and the $[\alpha]_D$ values were also in excellent agreement. This confirmed that the products **17b** and **12a**,**b** were of identical absolute configuration at C(5)

‡ DMPU is 1,3-dimethyl-3,4,5,6-tetrahydro-1*H*-pyrimidin-2-one.

Table 2 Deprotection of Dieckmann adducts

Starting material	Product	Reaction time *t*/h	Yield (%)
16a	**24**	17	87
16b	**25**	4.25	86
17b	**26**	5	50

and that this in fact was *inverted* relative to the oxazolidine precursor **8**.

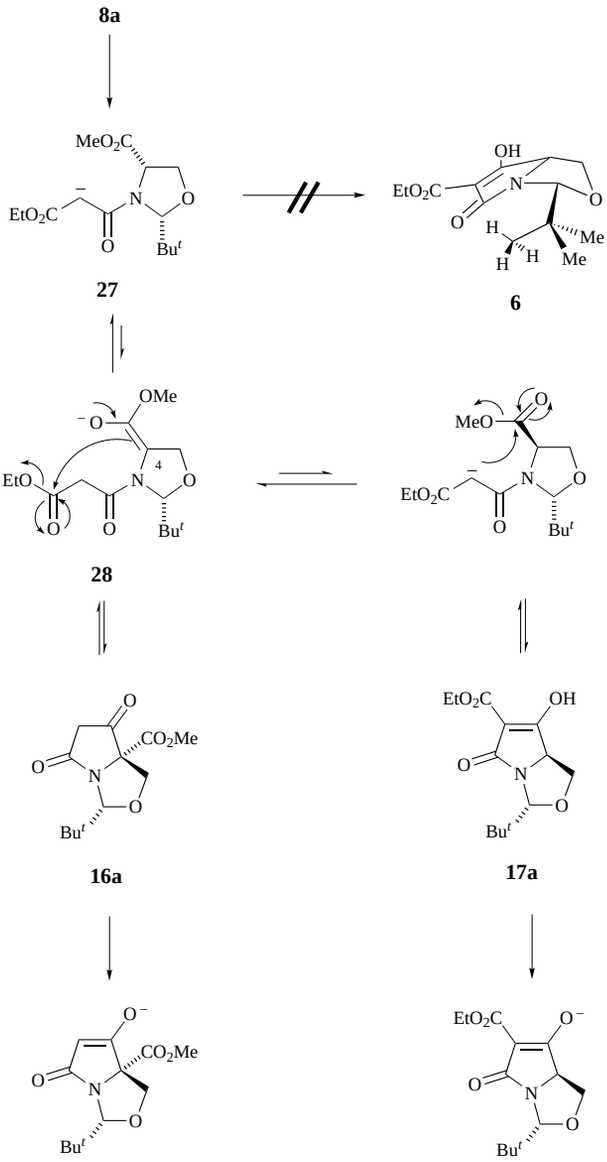
Deprotection

The Corey protocol[47] for oxazolidine deprotection was applied to tetramic acids **16a**, **16b** and **17b**. Thus, propane-1,3-dithiol was added to a solution of the dicarbonyl in acidic trifluoroethanol and the mixture was stirred at room temperature for 4–17 h depending on the substrate (Table 2). Purification was achieved simply by partitioning the reaction mixture between ethyl acetate and water, evaporation of the aqueous layer giving the free lactam alcohols **24**–**26**. Although compounds **25** and **26** were obtained exclusively as the enolic tautomer, compound **24** was found to be a mixture of the keto and enol forms. Unlike compound **26**, the two amido alcohols **24** and **25** were found to be quite unstable, possibly due to a facile retro-aldol reaction.

Discussion

The results of the above investigation of Dieckmann cyclisations of *N*-acyl oxazolidines indicated that the favoured route of cyclisation was for an anion at C(4) of the oxazolidine ring of substrates **8** to attack an electrophilic site attached to the *N*-acyl side chain, rather than the expected alternative mode of closure from the *N*-acyl side chain enolate to the C(4) ester. Furthermore, if cyclisation did occur from the *N*-acyl side chain onto the ester attached to C(4) of the oxazolidine ring, then it was with inversion of stereochemistry at C(4).

A proposed explanation for this behaviour is given in Scheme 4 for the cyclisation of oxazolidine **8a**, as this reaction generated both possible cyclisation products. Treatment of oxazolidine **8a** with base presumably first generates the enolate anion **27** by deprotonation at the most acidic side chain β-dicarbonyl site. This anion cannot cyclise directly onto the methyl ester as this would generate the tetramic acid **6** with the bulky *tert*-butyl group on the *endo*- face of the bicyclic system. It is proposed that this compound is too sterically hindered to form; there is some precedent for this, since Nagasaka and Imai have reported that highly functionalised bicyclic lactam systems with *endo*-substituents are much less stable than those with the corresponding *exo*- substituents.[48–50] Therefore, an equilibrium is established with enolate **28**, which has three main fates. It can cyclise to generate the major product **16a**, which under the reaction conditions will be deprotonated to form a stable anion, or it can reprotonate at C(4) to generate either a *cis*- or *trans*-oxazolidine. Given the favouring of the *cis*- over the *trans*-relative stereochemistry in this kind of system, reprotonation will normally regenerate starting material. However, if the *trans*-oxazolidine is formed then cyclisation can occur to generate the observed minor product **17a** which will also be deprotonated under the reaction conditions to generate a stable anion. This stability of the product would appear to be crucial, as ring closures to the 5,6- and 5,7-bicyclic oxazolidine products **21** and **22** were not successful, although attempts to enforce such larger ring closures by introducing a stabilising substituent in order to drive the reaction to completion did not substantially assist this pathway. Molecular modelling studies[51] suggest that the 5,6-bicyclic ring system of the expected products may be particularly unstable, with the 6-membered ring existing in a twist-boat conformation, and therefore does not provide for a sufficiently large driving force for the reaction.



Scheme 4

Conclusion

N-Acyl oxazolidines can undergo highly regioselective and diastereoselective Dieckmann cyclisation reactions under standard ring closure conditions, in a reaction which is controlled by the bulk of the *tert*-butyl substituent in a five membered ring. These compounds are useful templates for further manipulation to highly functionalised pyrrolidinones in enantiopure form; of particular note is the formation of the new stereogenic quaternary centre at C(5).

Experimental

General procedures

NMR spectra were recorded on Varian Gemini 200, Bruker AC 200 and Bruker AM-500 spectrometers. Carbon assignments were routinely made with the assistance of the results from a DEPT sequence. Two dimensional COSY spectra and nuclear Overhauser effect (nOe) enhancements were recorded on a Bruker AM-500 (500 MHz) spectrometer. Infrared spectra were recorded as thin films, as Nujol mulls, in $CHCl_3$ solution or by means of a KBr disc using a Perkin-Elmer 1750 FT-IR spectrometer. Mass spectra (*m*/*z*) were recorded on a VG Micromass ZAB 1F and VG Masslab 20-250 spectrometers using ammonia desorption chemical ionisation (DCI), chemical ionisation (CI) or Fast Atom Bombardment (FAB) techniques. Gas Chrom-

atography Mass Spectra (GC–MS) were recorded on a VG Trio-1 spectrometer. Positive electrospray mass spectra were recorded on a VG Bio-Q spectrometer. Optical rotations were recorded on a Perkin-Elmer 241 polarimeter, at the temperature quoted. Microanalyses were performed by the microanalytical services of the Dyson Perrins Laboratory and Zeneca Pharmaceuticals, Alderley Edge, Cheshire. Melting points were recorded on a Stuart Scientific SMP1 melting point device and are uncorrected. Thin layer chromatography (TLC) was performed using Merck aluminium foil backed sheets precoated with Kieselgel 60 F_{254}. Plates were visualised using UV light (254 nm) or a solution of 5% w/v dodeca-molybdophosphoric acid in EtOH followed by heat. Flash column chromatography was carried out using Sorbsil™ C_{60}H(40–60 μm) silica gel. Petrol refers to light petroleum of bp 30–40 °C unless otherwise stated.

THF was distilled from sodium–benzophenone ketyl under N_2 prior to use. *n*-Butyllithium was used as a solution in hexanes and was standardised with diphenylacetic acid prior to use.[52] All other reagents were used as obtained from commercial sources.

Racemic samples of compounds **4**, **8a**, **8b**, **8e**, **16a**, **16b** and **17b** were prepared as for the enantiopure materials. Details for the synthesis of **8c**, **9b** and **16c** have been published.[38]

(4*S*)-2-*tert*-Butyl-4-methoxycarbonyl-1,3-oxazolidine 4[33,34]

To finely powdered L-serine methyl ester hydrochloride, prepared by standard procedures,[53] (5.0–15.0 g) in petrol (100 ml 5 g^{-1}) was added NEt_3 (1.2 equiv.) and trimethylacetaldehyde (1.5 equiv.). The mixture was heated at reflux, with continuous removal of water, for 16 h, filtered and the residue washed with diethyl ether (3 × 100 ml). The combined filtrates were evaporated *in vacuo* to give a crude 1:1 mixture of the *cis*- and *trans*-isomers of oxazolidine **4** (82–93%) as a pale yellow oil; R_f 0.54 [EtOAc–dichloromethane (DCM), 6:1]; ν_{max}(film)/cm^{-1} 3315 (w), 2955 (s), 2870 (s), 1740 (s), 1205 (s), 1115 (s) and 1140 (s); δ_H(200 MHz, $CDCl_3$) 0.91 and 0.98 [9H, s, C(CH_3)$_3$], 2.45 (1H, br s, N*H*), 3.6–4.1 [6H, m, CO_2CH_3, C(4)H and C(5)HH′] and 4.26 [1H, s, C(2)H]; *m*/*z* (GC–MS) 188 (M + H^+, 15%), 130 (100) and 102 (25).

Acylations: General method A

To a stirred solution of 2-*tert*-butyl-4-methoxycarbonyl-1,3-oxazolidine, dicyclohexylcarbodiimide (DCCI) or ethyl dimethylaminopropylcarbodiimide hydrochloride salt, and DMAP in DCM (7/10 of total volume) at 0 °C was added, dropwise, a solution of the appropriate acid in DCM or CH_3CN (3/10 of total volume). The mixture was stirred at 0 °C for 15 min then at room temperature for 3–5 h. The reaction mixture was filtered to remove dicyclohexyl urea, the residue being washed with DCM (3 × 15 ml), and the combined filtrates were evaporated *in vacuo*.

Acylations: General method B

To a stirred solution of 2-*tert*-butyl-4-methoxycarbonyl-1,3-oxazolidine and pyridine in DCM (7/10 of total volume) at 0 °C was added, dropwise, a solution of the appropriate acid chloride in DCM (3/10 of total volume). The mixture was stirred at 0 °C for 15 min then at room temperature for 3–5 h. The volume was made up to 50 ml with DCM, the reaction mixture was washed with NH_4Cl (aq) (40 ml), 10% $NaHCO_3$ (aq) (40 ml) and brine (40 ml), dried ($MgSO_4$) and evaporated *in vacuo*.

(2*R*,4*S*)-2-*tert*-Butyl-3-ethoxycarbonylacetyl-4-methoxycarbonyl-1,3-oxazolidine 8a

According to general method A oxazolidine **4** (2.50 g, 13.4 mmol), 4-dimethylaminopyridine (DMAP) (0.10 g, 0.82 mmol) and DCCI (2.89 g, 14.0 mmol) in DCM (15 ml) were reacted with ethyl hydrogen malonate (1.85 g, 14.0 mmol) in DCM (10 ml). The crude reaction mixture, after filtration, in DCM (100 ml) was washed with 1M aqueous KH_2PO_4 (3 × 50 ml), dried ($MgSO_4$) and evaporated *in vacuo*. A solution of the crude reaction mixture in EtOAc–petrol, (3:7, 10 ml) was loaded onto a silica filled (100 ml) sinter funnel and washed with EtOAc–petrol, (1:19, 200 ml). Product was removed by eluting with EtOAc–petrol, 1:1 (300 ml), removal of solvent *in vacuo* giving the *title compound* **8a** (3.45 g, 88%) as a colourless viscous oil; R_f 0.35 (EtOAc–DCM, 1:9); $[\alpha]_D^{20}$ −59.4 (*c* 3.06 in $CHCl_3$) (Found: C, 55.39; H, 7.71; N, 4.56. $C_{14}H_{23}NO_6$ requires C, 55.80; H, 7.69; N, 4.65%); ν_{max}(film)/cm^{-1} 2980 (m), 2960 (m), 1745 (s), 1675 (s), 1390 (s), 1370 (s) and 1220 (s); δ_H(500 MHz, $CDCl_3$) (7.8:1 mixture of diastereomers) (major diastereomer **8a**) 0.91 [9H, s, C(CH_3)$_3$], 1.30 (3H, t, *J* 7.2, $CO_2CH_2CH_3$), 3.51 (1H, d, *J* 15.4, COC*H*H′CO), 3.69 (1H, br d, *J* 15.4, COCH*H*′CO), 3.80 (3H, s, CO_2CH_3), 4.01 [1H, m, C(5)H], 4.22 (2H, q, *J* 7.2, $CO_2CH_2CH_3$), 4.56 [1H, m, C(5)H′], 4.72 [1H, m, C(4)H] and 5.33 [1H, s, C(2)H]; (minor diastereomer **14**) 1.00 [9H, s, C(CH_3)$_3$], 1.29 (3H, t, *J* 7.2, $CO_2CH_2CH_3$), 3.51 (1H, d, *J* 15.4, COC*H*H′CO), 3.69 (1H, br d, *J* 15.4, COCH*H*′CO), 3.80 (3H, s, CO_2CH_3), 4.01 (1H, m), 4.48 (1H, m) and 4.60 (1H, m) [C(4)H and C(5)H$_2$] and 5.49 [1H, br s, C(2)H]; δ_C(50.3 MHz, $CDCl_3$) 13.8 ($CO_2CH_2CH_3$), 25.3 [C(CH_3)$_3$], 37.1 [*C*(CH_3)$_3$], 42.9 ($COCH_2CO$), 52.6 (CO_2CH_3), 59.3 [C(4)], 61.6 ($CO_2CH_2CH_3$), 67.6 [C(5)], 96.6 [C(2)], 167.7 and 170.1 (carbonyls); *m*/*z* (CI), 319 (M + NH_4^+, 1%), 302 (M + H^+, 28), 244 (9), 216 (100) and 130 (58); ^{1}H–^{13}C correlation (200–50.3 MHz, $CDCl_3$) 0.91–25.3, 1.30–13.8, 3.80–52.6, 4.01–67.6, 4.22–61.6, 4.72–59.3 and 5.33–96.6; nOe experiment (500 MHz, $CDCl_3$) irradiation at δ_H 4.01 gave enhancements at δ 4.56 (11.4%), 4.72 (6.1) and 5.33 (2); irradiation at δ_H 4.56 gave enhancements at δ 3.51 (4.1%), 3.69 (4.7) and 4.01 (6); irradiation at δ_H 4.72 gave an enhancement at δ 4.01 (11.2%).

The aqueous layer (from above) was acidified with 2 M aqueous HCl and extracted with EtOAc (3 × 50 ml), the EtOAc extracts being washed with brine (100 ml), dried ($MgSO_4$) and evaporated *in vacuo* to give (−)-(2*S*,5*S*)-2-*tert*-butyl-7-ethoxycarbonyl-6-hydroxy-8-oxo-1-aza-3-oxabicyclo[3.3.0]oct-6-ene **13** (126 mg, 3.5%) as an amorphous white solid, mp 138.5–140.5 °C (decomp.); $[\alpha]_D^{20}$ −90.3 (*c* 1.05 in $CHCl_3$); with identical spectroscopic data for compound **17**.

(2*R*,4*S*,2′*S*)-2-*tert*-Butyl-4-methoxycarbonyl-3-(2-ethoxycarbonyl)propanoyl-1,3-oxazolidine 9a and (2*R*,4*S*,2′*R*)-2-*tert*-butyl-4-methoxycarbonyl-3-(2-ethoxycarbonyl)propanoyl-1,3-oxazolidine 8b

According to general method B oxazolidine **4** (4.20 g, 22.4 mmol) was reacted with pyridine (3.8 ml, 3.72 g, 47.0 mmol) and ethyl α-methylmalonyl chloride (7.39 g, 44.9 mmol) (prepared by the treatment of ethyl hydrogen α-methylmalonate[54] with thionyl chloride) in DCM (75 ml). Purification by column chromatography (EtOAc–petrol, 1:4 increasing polarity to EtOAc–petrol, 2:3) gave oxazolidine **9a** (1.74 g, 25%) as a colourless crystalline solid, a 1:9 mixture of oxazolidine **9a**:oxazolidine **8b** (0.45 g, 6%) and oxazolidine **8b** (4.43 g, 63%) (giving an overall ratio of **9a**:**8b** = 1:2.6) as a viscous oil.

Oxazolidine **9a** mp 44–45.5 °C; R_f 0.51 (EtOAc–DCM, 1:9); $[\alpha]_D^{21}$ −63.3 (*c* 2.18 in $CHCl_3$) (Found: C, 56.96; H, 8.08; N, 4.38. $C_{15}H_{25}NO_6$ requires C, 57.13; H, 7.99; N, 4.44%); ν_{max}($CHCl_3$)/cm^{-1} 2980 (m), 2960 (m), 2875 (w), 1745 (s), 1675 (s) and 1390 (m); δ_H(200 MHz, $CDCl_3$) 0.87 [9H, s, C(CH_3)$_3$], 1.24 (3H, t, *J* 7.0, $CO_2CH_2CH_3$), 1.46 (3H, d, *J* 6.5, $CHCH_3$), 3.76 (1H, q, *J* 6.5, $CHCH_3$), 3.79 (3H, s, CO_2CH_3), 3.95 [1H, m, C(5)H], 4.16 (2H, q, *J* 7.0, $CO_2CH_2CH_3$), 4.56 [1H, dd, *J* 2.0, *J*′ 8.5, C(5)H′], 4.91 [1H, dd, *J* 2.0, *J*′ 7.0, C(4)H] and 5.33 [1H, s, C(2)H]; δ_C(50.3 MHz, $CDCl_3$) 13.8 and 14.2 ($CHCH_3$ and $CO_2CH_2CH_3$), 25.4 [C(CH_3)$_3$], 37.0 [*C*(CH_3)$_3$], 45.5 ($CHCH_3$), 52.7 (CO_2CH_3), 59.3 [C(4)], 61.5 ($CO_2CH_2CH_3$), 67.5 [C(5)], 96.4 [C(2)], 170.3, 170.4 and 172.0 (carbonyls); *m*/*z* (CI) 333 (M + NH_4^+, 10%), 316 (M + H^+, 83), 230 (100) and 130 (38); nOe experiment (500 MHz, $CDCl_3$) irradiation at δ_H 3.95 gave

enhancements at δ 4.56 (25.1%), 4.91 (9.4) and 5.33 (3.4); irradiation at δ_H 4.56 gave enhancements at δ 3.95 (20.0%) and 4.91 (3.8); irradiation at δ_H 4.91 gave enhancements at δ 3.76 (14.0%) and 3.95 (5.7); irradiation at δ_H 5.33 gave an enhancement at δ 0.87 (8.2%). Oxazolidine **8b**, R_f 0.29 (EtOAc–petrol, 3:7); $[\alpha]_D^{22}$ −23.7 (*c* 1.50 in $CHCl_3$); ν_{max}(film)/cm^{-1} 2960 (m), 1740 (s), 1670 (m), 1210 (m) and 1175 (m); δ_H(200 MHz, $CDCl_3$) 0.91 [9H, s, $C(CH_3)_3$], 1.25 (3H, t, *J* 7.0, $CO_2CH_2CH_3$), 1.40 (3H, d, *J* 7.0, $CHCH_3$), 3.68 (1H, q, *J* 7.0, $CHCH_3$), 3.76 (3H, s, CO_2CH_3), 3.90–4.07 [1H, m, C(5)H], 4.42–4.60 [2H, m, C(4)HC(5)H′], 4.18 (2H, q, *J* 7.0, $CO_2CH_2CH_3$) and 5.33 [1H, s, C(2)H]; δ_C(50.3 MHz, $CDCl_3$) 13.2 and 13.6 ($CHCH_3$ and $CO_2CH_2CH_3$), 25.1 [$C(CH_3)_3$], 37.1 [$C(CH_3)_3$], 45.4 ($CHCH_3$), 52.3 (CO_2CH_3), 59.0 [C(4)], 61.0 ($CO_2CH_2CH_3$), 67.7 [C(5)], 96.3 [C(2)] and 164.7, 170.4 and 171.6 (carbonyls); *m*/*z* (CI) 333 ($M + NH_4^+$, 5%), 316 ($M + H^+$, 77), 230 (100) and 130 (62) (HRMS: found MH^+, 316.1757. $C_{15}H_{26}NO_6$ requires MH^+, 316.1760).

(2*R*,4*S*)-2-*tert*-Butyl-3-cyanoacetyl-4-methoxycarbonyl-1,3-oxazolidine 8d

According to general method A oxazolidine **4** (0.81 g, 4.3 mmol), DMAP (0.053 g, 0.43 mmol) and DCCI (0.89 g, 4.3 mmol) in DCM (10 ml) were reacted with cyanoacetic acid (0.37 g, 4.3 mmol) in CH_3CN (5 ml). Purification by column chromatography (EtOAc–DCM, 1:19) gave oxazolidine **8d** (0.90 g, 82%) as a colourless crystalline solid; mp 99–104 °C; R_f 0.20 (EtOAc–DCM, 1:9); $[\alpha]_D^{21}$ −35.8 (*c* 1.11 in $CHCl_3$) (Found: C, 56.51; H, 7.19; N, 10.77. $C_{12}H_{18}N_2O_4$ requires C, 56.68; H, 7.14; N, 11.02%); ν_{max}($CHCl_3$)/cm^{-1} 2960 (m), 2260 (w), 1750 (s), 1690 (s) and 1390 (s); δ_H(200 MHz, $CDCl_3$) 0.90 [9H, s, $C(CH_3)_3$], 3.66 (1H, d, *J* 18, $CHH'CN$), 3.76 (1H, d, *J* 18, $CHH'CN$), 3.83 (3H, s, CO_2CH_3), 4.08–4.16 [1H, m, C(5)H], 4.48–4.56 [2H, m, C(4)HC(5)H′] and 5.31 [1H, s, C(2)H]; δ_C(50.3 MHz, $CDCl_3$), 25.3 [$C(CH_3)_3$], 26.8 (CH_2CN), 37.4 [$C(CH_3)_3$], 52.9 (CO_2CH_3), 59.0 [C(4)], 67.8 [C(5)], 97.3 [C(2)], 114.2 (CH_2CN) and 163.6 and 169.6 (carbonyls); *m*/*z* (GC–MS) 272 ($M + NH_4^+$, 100%), 255 ($M + H^+$, 12), 186 (35) and 169 (74).

(2*R*,4*S*)-2-*tert*-Butyl-3-phenylacetyl-4-methoxycarbonyl-1,3-oxazolidine 8e

According to general method B oxazolidine **4** (1.87 g, 10.0 mmol) was reacted with pyridine (1.19 g, 15.0 mmol) and phenylacetyl chloride (1.86 g, 12.0 mmol) in DCM (30 ml). Purification by dry flash chromatography (petrol, increasing polarity to DCM) followed by recrystallisation from hexane gave oxazolidine **8e** (2.74 g, 90%) as a colourless crystalline solid, mp 59.5–61.5 °C; R_f 0.29 (DCM); $[\alpha]_D^{21}$ −2.3 (*c* 1.93 in $CHCl_3$) (Found: C, 66.76; H, 7.66; N, 4.39. $C_{17}H_{23}NO_4$ requires C, 66.86; H, 7.59; N, 4.59%); ν_{max}($CHCl_3$)/cm^{-1} 2960 (s), 2875 (m), 1750 (s), 1670 (s), 1385 (s) and 1365 (s); δ_H(200 MHz, $CDCl_3$) 0.92 [9H, s, $C(CH_3)_3$], 3.80 (6H, m) and 4.44 (1H, m) and 4.60 (1H, m) [CO_2CH_3, C(4)HC(5)H_2 and $PhCH_2$], 5.34 [1H, s, C(2)H] and 7.30 (5H, m, ArH); δ_C(50.3 MHz, $CDCl_3$), 25.5 [$C(CH_3)_3$], 37.3 [$C(CH_3)_3$], 42.2 ($PhCH_2$), 52.6 (CO_2CH_3), 58.8 [C(4)], 67.8 [C(5)], 96.8 [C(2)], 127.1, 128.8 and 128.9 (ArCH), 134.2 (ArC) and 170.4 and 172.3 (carbonyls); *m*/*z* (GC–MS) 306 ($M + H^+$, 88%), 248 (15), 220 (61) and 130 (100).

(2*R*,4*S*)-2-*tert*-Butyl-3-diphenylacetyl-4-methoxycarbonyl-1,3-oxazolidine 8f

According to general method B oxazolidine **4** (200 mg, 1.07 mmol) was reacted with pyridine (0.12 ml, 117 mg, 1.48 mmol) and diphenylacetyl chloride[55] (295 mg, 1.28 mmol) in DCM (10 ml). Purification by column chromatography (EtOAc–petrol, 1:9) gave oxazolidine **8f** (243 mg, 60%) as a crystalline solid, mp 106–107 °C; R_f 0.40 (EtOAc–petrol, 3:17); $[\alpha]_D^{20}$ +178.3 (*c* 2.00 in $CHCl_3$) (Found: C, 72.05; H, 7.10; N, 3.52. $C_{23}H_{27}NO_4$ requires C, 72.42; H, 7.13; N, 3.67%); ν_{max}($CHCl_3$)/cm^{-1} 2960 (m), 1800 (w), 1740 (s), 1675 (s), 1385 (s), 1370 (s) and 1180 (s); δ_H(200 MHz, $CDCl_3$) 0.93 [9H, s, $C(CH_3)_3$], 3.70 [1H, m, C(5)H], 3.87 (3H, s, CO_2CH_3), 4.46 [1H, m, C(5)H′], 4.58 [1H, m, C(4)H], 5.41 (1H, s, Ph_2CH), 5.44 [1H, s, C(2)H] and 7.3 (10H, m, ArH); δ_C(50.3 MHz, $CDCl_3$) 25.5 [$C(CH_3)_3$], 37.2 [$C(CH_3)_3$], 52.7 (CO_2CH_3), 56.7 (Ph_2CH), 58.9 [C(4)], 67.6 [C(5)], 96.8 [C(2)], 127.1, 127.8, 128.4, 128.7, 129.0, 129.4 (ArCH), 137.2, 140.4 (ArC), 170.5 and 173.4 (carbonyls); *m*/*z* (DCI) 399 ($M + NH_4^+$, 1%), 382 ($M + H^+$, 89), 324 (18), 296 (17), 167 (98) and 130 (100); ^1H–^{13}C correlation (200–50.3 MHz, $CDCl_3$) 0.93–25.5, 3.87–52.7, 4.46–67.6, 4.58–58.9, 5.41–56.7 and 5.44–96.8; nOe experiment (500 MHz, $CDCl_3$) irradiation at δ_H 3.70 gave enhancements at δ 4.46 (26.7%), 4.58 (9.8) and 5.44 (2); irradiation at δ_H 4.46 gave an enhancement at δ 3.70 (22.7%); irradiation at δ_H 4.58 gave enhancements at δ 3.7 (8.6%) and 5.41 (16); irradiation at δ_H 5.41 gave enhancements at δ 0.93 (2.6%) and 4.58 (14); irradiation at δ_H 5.44 gave enhancements at δ 0.93 (10%), 3.70 (3) and 4.58 (4.5).

(2*R*,4*S*)-3-(4-Ethoxycarbonyl)butanoyl-2-*tert*-butyl-4-methoxycarbonyl-1,3-oxazolidine 8g

According to general method B oxazolidine **4** (0.50 g, 2.67 mmol) was reacted with pyridine (0.26 g, 3.34 mmol) and ethyl glutaryl chloride[56,57] (0.52 g, 2.94 mmol) in DCM (10 ml). Purification by column chromatography (EtOAc–DCM, 1:9) gave oxazolidine **8g** (0.42 g, 48%); R_f 0.27 (EtOAc–DCM, 1:9); $[\alpha]_D^{21}$ −31.8 (*c* 1.85 in $CHCl_3$) (Found: C, 58.40; H, 8.32; N, 3.95. $C_{16}H_{27}NO_6$ requires C, 58.34; H, 8.26; N, 4.25%); ν_{max}($CHCl_3$)/cm^{-1} 2960 (m), 1730 (s), 1670 (s) and 1400 (s); δ_H(200 MHz, $CDCl_3$) 0.91 [9H, s, $C(CH_3)_3$], 1.26 (3H, t, *J* 7.0, $CO_2CH_2CH_3$), 1.93–2.07 (2H, m, $CH_2CH_2CH_2$), 2.27–2.62 (4H, m, $CH_2CH_2CH_2CH_2$), 3.79 (3H, s, CO_2CH_3), 4.03–4.18 (3H, m), 4.48 (1H, m) and 4.62 [1H, m, $CO_2CH_2CH_3$ and C(4)HC(5)H_2] and 5.33 [1H, s, C(2)H]; δ_C(50.3 MHz, $CDCl_3$), 13.8 ($CO_2CH_2CH_3$), 19.7 ($CH_2CH_2CH_2$), 25.4 [$C(CH_3)_3$], 32.8 and 33.6 ($CH_2CH_2CH_2CH_2$), 37.2 [$C(CH_3)_3$], 52.3 (CO_2CH_3), 58.8 [C(4)], 60.0 ($CO_2CH_2CH_3$), 67.8 [C(5)], 96.5 [C(2)], 170.4, 173.3 and 173.7 (carbonyls); *m*/*z* (CI) 330 ($M + H^+$, 100%), 272 (28) and 244 (82).

(2*R*,4*S*)-2-*tert*-Butyl-3-(3-ethoxycarbonylpropenoyl)-4-methoxycarbonyl-1,3-oxazolidine 8h

According to general method B oxazolidine **4** (0.50 g, 2.67 mmol) was reacted with pyridine (0.3 ml, 0.29 g, 3.71 mmol) and ethyl maleoyl chloride[58] (0.56 g, 3.45 mmol) in DCM (25 ml). Purification by column chromatography (EtOAc–petrol, 1:4) gave oxazolidine **8h** (0.66 g, 79%); R_f 0.47 (EtOAc–petrol, 3:7); $[\alpha]_D^{25}$ −87.9 (*c* 1.00 in $CHCl_3$) (Found: C, 57.33; H, 7.43; H, 4.75. $C_{15}H_{23}NO_6$ requires C, 57.49; H, 7.40; N, 4.47%); ν_{max}(film)/cm^{-1} 2960 (m), 2905 (w), 1750 (s), 1725 (s), 1670 (s), 1305 (s) and 1175 (s); δ_H(200 MHz, $CDCl_3$) 0.89 [9H, s, $C(CH_3)_3$], 1.28 (3H, t, *J* 7.0, $CO_2CH_2CH_3$), 3.79 (3H, s, CO_2CH_3), 3.96 [1H, m, C(5)H], 4.55 [2H, m, C(4)HC(5)H′], 4.22 (2H, q, *J* 7.0, $CO_2CH_2CH_3$), 5.33 [1H, s, C(2)H], 6.84 (1H, d, *J* 15.5, $CH=CH'$) and 7.29 (1H, d, *J* 15.5, $CH=CH'$); δ_C(50.3 MHz, $CDCl_3$) 14.1 ($CO_2CH_2CH_3$), 25.5 [$C(CH_3)_3$], 37.4 [$C(CH_3)_3$], 52.9 (CO_2CH_3), 59.3 [C(4)], 61.2 ($CO_2CH_2CH_3$), 67.8 [C(5)], 96.7 [C(2)], 132.6 and 134.9 ($CH=CH$) and 165.3 and 169.6 (carbonyls); *m*/*z* (CI) 314 ($M + H^+$, 60%), 256 and 228.

(2*R*4*S*)-2-*tert*-Butyl-4-methoxycarbonyl-3-[3,3-bis(ethoxycarbonyl)propanoyl]-1,3-oxazolidine 8i

To a stirred solution of NaOH (1.9 g, 50 mmol) and Bu_4NCl (6.9 g, 25 mmol) in H_2O (30 ml) was added a solution of diethyl malonate (4.0 g, 25 mmol) and *tert*-butyl bromoacetate (4.8 g, 25 mmol) in DCM (20 ml), and the mixture was stirred at room temperature for 24 h. The organic layer was washed with water (2 × 25 ml), dried ($MgSO_4$) and evaporated *in vacuo*. Purification by column chromatography (petrol–EtOAc, 9:1) gave *tert*-butyl 3,3-bis(ethoxycarbonyl)propionate[36] (4.8 g, 70%) as a

1:1 mixture of keto:enol tautomers as a pale yellow oil; R_f 0.69 (petrol–EtOAc, 2:1); δ_H(200 MHz, $CDCl_3$) 1.23 (6H, 2 × t, *J* 7.0, CH_3CH_2), 1.40 [9H, s, $C(CH_3)_3$], 2.82 (2H, d, *J* 7.5, $CH_2CO_2Bu^t$, keto), 3.02 (2H, s, $CH_2CO_2Bu^t$, enol), 3.73 [1H, t, *J* 7.5, $CH(CO_2Et)_2$, keto] and 4.16 (4H, 2 × q, *J* 7.0, CH_3CH_2); δ_C(50.3 MHz, $CDCl_3$) 13.8 (CH_3CH_2), 27.8 [$CH_3)_3C$], 34.1 and 38.4 ($CH_2CO_2Bu^t$, keto and enol), 47.9 [$CH(CO_2Et)_2$, keto], 61.4 (CH_3CH_2), 81.0 [$C(CH_3)_3$], 168.3, 169.0 and 169.4 (carbonyls); *m*/*z* (GC–MS) 292 ($M + NH_4^+$, 9%), 275 ($M + H^+$, 7), 236 (100) and 219 (44).

To the above triester (4.8 g, 17 mmol) in DCM (50 ml) was slowly added TFA (20 ml). The mixture was stirred at room temperature for 4 h then evaporated *in vacuo*. The residue was washed with DCM (2 × 20 ml) and removal of solvent *in vacuo* gave 3,3-bis(ethoxycarbonyl)propionic acid[35,59] (3.6 g, 95%) as a 1:1 mixture of keto:enol tautomers as a brown oil; R_f 0.27 (EtOAc–DCM, 6:1); $\nu_{max}(CHCl_3)/cm^{-1}$ 2986 (br s), 2584 (m), 2360 (m), 1789 (s), 1744 (s), 1559 (w), 1230 (s); δ_H(200 MHz, $CDCl_3$), 1.28 (6H, 2 × t, *J* 7.0, CH_3CH_2), 3.04 (2H, d, *J* 7.5, CH_2CO_2H, keto), 3.27 (2H, s, CH_2CO_2H, enol), 3.83 [1H, t, *J* 7.5, $CH(CO_2Et)_2$, keto], 4.22 (4H, q, *J* 7.0, CH_3CH_2) and 8.68 (1H, br s, CO_2H); δ_C(50.3 MHz, $CDCl_3$) 13.4 and 13.6 (CH_3CH_2, keto and enol), 32.7 and 37.1 (CH_2CO_2H, keto and enol), 47.6 [$CH(CO_2Et)_2$, keto], 53.2 [C=C(OH)OEt, enol], 62.5 and 62.9 (CH_3CH_2, keto and enol), 169.0, 169.5, 176.8 and 177.3 (carbonyls).

The above acid (3.6 g, 17 mmol) and $SOCl_2$ (20 ml) was refluxed for 20 h. Excess $SOCl_2$ was removed *in vacuo* giving the corresponding acid chloride (3.7 g, 95%) in the enolic form as a brown oil; $\nu_{max}(CHCl_3)/cm^{-1}$ 3032 (w), 2987 (w), 1822 (w), 1786 (s), 1736 (s), 1642 (w); δ_H(200 MHz, $CDCl_3$), 1.29 and 1.40 (6H, 2 × t, *J* 7.0, CH_3CH_2), 3.19 (2H, s, CH_2COCl), 4.30 and 4.42 (4H, 2 × q, *J* 7.0, CH_3CH_2).

According to general method B, oxazolidine **4** (1.7 g, 9 mmol), pyridine (0.9 g, 12 mmol) and DMAP (0.1 g, 0.8 mmol) in DCM (45 ml) were reacted with the above acid chloride (2.4 g, 10 mmol) in DCM (20 ml). Purification by column chromatography (EtOAc–DCM, 6:1) gave oxazolidine **8i** (1.6 g, 45%) as a mixture of keto and enol tautomers as a brown oil; R_f 0.69 (EtOAc–DCM, 6:1); $\nu_{max}(CHCl_3)/cm^{-1}$ 3029 (w), 2984 (w), 2361 (w), 1734 (s), 1668 (m), 1259 (m), 1227 (m) and 1215 (s); $[\alpha]_D^{20}$ −36.0 (*c* 1.0 in $CHCl_3$); δ_H(500 MHz, $CDCl_3$) 0.86 and 0.91 [9H, 2 × s, $C(CH_3)_3$], 1.28 and 1.31 (6H, 2 × t, *J* 7.2, CH_3CH_2), 3.64 (2H, s, CH_2CON), 3.77 (3H, s, CO_2CH_3), 3.97 [1H, m, C(5)H], 4.26 and 4.28 (4H, 2 × q, *J* 7.2, CH_3CH_2), 4.54 [2H, m, C(4)H and C(5)H′], 5.27 and 5.29 [1H, 2 × s, C(2)H]; δ_C(125.8 MHz, $CDCl_3$), 13.8 (CH_3CH_2), 25.3 [$CH_3)_3C$], 37.1 [$C(CH_3)_3$], 52.8 (CO_2CH_3), 59.8 [C(4)], 61.9 and 62.1 (CH_3CH_2 and CH_2CON), 67.6 [C(5)], 96.4 [C(2)], 162.6, 164.1, 166.2, 169.5 (carbonyls); *m*/*z* (GC–MS) 388 ($M + H^+$, 15%), 386 (31), 300 (41), 186 (100), 161 (59), 158 (35), 130 (48), 102 (35) and 86 (88).

(2*R*,4*S*)-2-*tert*-Butyl-4-methoxycarbonyl-3-(2-ethoxycarbonyl-3-methoxycarbonyl)propanoyl-1,3-oxazolidine 8j

To a stirred solution of oxazolidine **8a** (1.0 g, 3.3 mmol) and methyl bromoacetate (0.8 g, 5.0 mmol) in THF (30 ml) at −78 °C was added portionwise $KOBu^t$ (0.4 g, 3.5 mmol). The mixture was stirred under nitrogen and allowed to warm at room temperature over 2 h, then poured into water (50 ml). The water–THF mixture was extracted with diethyl ether (2 × 40 ml), and the organic extracts were washed with brine (50 ml), dried ($MgSO_4$) and evaporated *in vacuo*. Purification by column chromatography (petrol–EtOAc, 2:1) gave oxazolidine **8j** (0.74 g, 60%) as a yellow oil; R_f 0.51 (petrol–EtOAc, 2:1); $[\alpha]_D^{23}$ −60.9 (*c* 1.0 in $CHCl_3$); $\nu_{max}(CHCl_3)/cm^{-1}$ 3029 (m), 2958 (s), 2909 (m), 2876 (m), 1740 (s), 1674 (s), 1482 (m), 1438 (s), 1368 (s), 1265 (s), 1228 (s) and 1174 (s); δ_H(200 MHz, $CDCl_3$) 0.76 and 0.78 [9H, 2 × s, $C(CH_3)_3$], 1.14 and 1.17 (3H, 2 × t, *J* 7.0, CH_3CH_2), 2.86 (2H, m, CH_2CO_2Me), 3.44 (1H, m, $CHCO_2Et$), 3.58 and 3.69 (6H, 2 × s, 2 × CO_2CH_3), 3.85 [1H, m, C(5)H], 4.07 and 4.10 (2H, 2 × q, *J* 7.0, CH_3CH_2), 4.46 [1H, m, C(5)H′], 4.94 [1H, m, C(4)H] and 5.20 [1H, s, C(2)H]; δ_C(50.3 MHz, $CDCl_3$) 13.9 (CH_3CH_2), 25.5 [$CH_3)_3C$], 33.8 ($CH_2CO_2CH_3$), 37.3 [$C(CH_3)_3$], 47.5 ($CHCO_2Et$), 51.9 and 52.8 (2 × CO_2CH_3), 59.2 [C(4)H], 62.1 (CH_3CH_2), 67.6 [C(5)], 96.6 [C(2)], 168.4, 169.9 and 171.4 (carbonyls); *m*/*z* (CI) 374 ($M + H^+$, 12%), 330 (7), 225 (8) and 188 (100).

(2*R*,4*S*)-2-*tert*-Butyl-4-methoxycarbonyl-3-(2-*tert*-butoxycarbonyl-3-methoxycarbonyl)propanoyl-1,3-oxazolidine 8k

To a stirred solution of oxazolidine **4** (250 mg, 1.34 mmol), DMAP (10 mg, 0.08 mmol) and DCCI (287 mg, 1.47 mmol) in DCM (3 ml) at 0 °C was added dropwise a solution of *tert*-butyl hydrogen malonate (236 mg, 1.47 mmol) in DCM (2 ml). The reaction mixture was stirred at 0 °C for 15 min, then at room temperature for 19 h. The mixture was filtered to remove dicyclohexyl urea, then made up to 10 ml with DCM and washed with 1 M aqueous KH_2PO_4 (3 × 5 ml), dried ($MgSO_4$) and evaporated *in vacuo*. A solution of the crude reaction mixture in EtOAc–petrol, 3:7 (5 ml) was loaded onto a silica filled sinter funnel and washed with EtOAc–petrol, 1:19 (100 ml). The product was removed by elution with EtOAc–petrol, 1:1 (150 ml), removal of solvent *in vacuo* giving the product (357 mg, 81%) as a white oil; R_f 0.40 (petrol–EtOAc, 2:1); $[\alpha]_D^{23}$ −58.5 (*c* 1.0 in $CHCl_3$); $\nu_{max}(CHCl_3)/cm^{-1}$ 3037 (w), 3011 (w), 2981 (m), 2959 (m), 2877 (w), 1740 (s), 1674 (s), 1370 (s) and 1224 (s); δ_H(200 MHz, $CDCl_3$) (mixture of conformers) 0.89 and 0.98 [9H, 2 × s, $(CH_3)_3C$], 1.46 [9H, s, $(CH_3)_3CO_2$], 3.43 (2H, m, $COCH_2CO$), 3.79 (3H, s, CO_2CH_3), 3.99 and 4.53 [2H, 2 × m, C(5)H_2], 4.71 [1H, m, C(4)H] and 5.31 [1H, s, C(2)H]; δ_C(50.3 MHz, $CDCl_3$), 25.6 [$(CH_3)_3C$], 27.9 [$(CH_3)_3CO_2$], 37.1 [$(CH_3)_3C$], 43.9 ($COCH_2CO$), 52.8 (CO_2CH_3), 59.1 [C(4)], 67.7 [C(5)], 82.4 [$(CH_3)_3CO_2C$], 96.6 [C(2)], 167.5 and 170.1 (carbonyls); *m*/*z* (CI) 330 ($M + H^+$, 11%), 226 (14), 225 (100) and 168 (17).

To the above oxazolidine (357 mg, 1.08 mmol) and methyl bromoacetate (248 mg, 1.62 mmol) in THF (10 ml) at −78 °C was added portionwise $KOBu^t$ (127 mg, 1.13 mmol). The mixture was stirred under nitrogen and allowed to warm to room temperature over 2 h, then poured into water (20 ml). The water–THF mixture was extracted with diethyl ether (2 × 15 ml), and the organic extracts were washed with brine (20 ml), dried ($MgSO_4$) and evaporated *in vacuo*. Purification by column chromatography (petrol–EtOAc, 4:1) gave oxazolidine **8k** (217 mg, 50%) as a pale yellow oil; R_f 0.44 (petrol–EtOAc, 2:1); $[\alpha]_D^{22}$ −44.0 (*c* 1.0 in $CHCl_3$); $\nu_{max}(CHCl_3)/cm^{-1}$ 3028 (m), 3011 (m), 2982 (m), 2957 (m), 2908 (m), 2877 (m), 1736 (m), 1672 (s), 1370 (s) and 1224 (s); δ_H(200 MHz, $CDCl_3$), 0.88 and 0.97 [9H, 2 × s, $(CH_3)_3C$], 1.45 [9H, s, $(CH_3)_3CO_2$], 2.7–3.2 (2H, m, $CH_2CO_2CH_3$), 3.42 (1H, m, $CHCO_2Bu^t$), 3.64–3.79 (6H, m, 2 × CO_2CH_3), 3.95 and 4.12 [2H, 2 × m, C(5)H_2], 4.56 [1H, m, C(4)H] and 5.30 [1H, 2 × s, C(2)H]; δ_C(50.3 MHz, $CDCl_3$), 25.5 [$(CH_3)_3C$], 27.9 [$CH_3)_3CO$], 33.9 ($CH_2CO_2CH_3$), 37.3 [$(CH_3)_3C$], 47.7 ($CHCO_2Bu^t$), 52.4 and 52.6 (2 × CO_2CH_3), 59.2 [C(4)], 67.5 [C(5)], 82.5 (Me_3CO) and 96.5 [C(2)]; *m*/*z* (CI) 402 ($M + H^+$, 33%), 346 (22), 316 (20), 240 (31), 188 (100) and 158 (17).

(2*S*,5*S*)-2-*tert*-Butyl-7-ethoxycarbonyl-7-methyl-6,8-dioxo-1-aza-3-oxabicyclo[3.3.0]octane 12 and *N*,*O*-bis(2-ethoxycarbonylpropanoyl)-L-serine methyl ester 15

To a solution of oxazolidine **4** (10.0 g, 53 mmol), DMAP (0.5 g, 4.1 mmol) and DCCI (11.0 g, 53 mmol) in DCM (80 ml) at reflux was added a solution of ethyl hydrogen α-methylmalonate (7.80 g, 53 mmol) in DCM (20 ml). The mixture was stirred at room temperature for 2 h, filtered, the residue being washed with DCM (2 × 75 ml), and the combined filtrates were evaporated *in vacuo*. Purification by column chromatography (DCM increasing polarity to EtOAc–DCM, 1:4) gave β-keto ester **10** (99 mg, 0.7%) as a viscous oil, oxazolidine **9a** (1.68 g, 10%) as a crystalline solid, diacylated serine **15** (0.36 g, 1.8%) as

a pale yellow oil and a 3:1 mixture of oxazolidine **9a** and diacylated serine **15** (8.44 g).

Lactam **10** R_f 0.20 (DCM); $[\alpha]_D^{25}$ −150 (*c* 0.55 in $CHCl_3$); ν_{max}(film)/cm^{-1} 2970 (m), 1785 (m), 1720 (s), 1230 (s) and 1185 (s); δ_H(200 MHz, $CDCl_3$), 0.97 [9H, s, $C(CH_3)_3$], 1.27 (3H, t, *J* 7.0, $CO_2CH_2CH_3$), 1.47 (3H, s, CCH_3), 3.50 [1H, m, C(4)H], 4.10–4.37 [3H, m, C(4)H′ and $CO_2CH_2CH_3$], 4.61 [1H, m, C(5)H] and 5.14 [1H, s, C(2)H]; δ_C(125.7 MHz, $CDCl_3$) 13.8 and 13.9 (CCH_3 and $CO_2CH_2CH_3$), 24.6 [$C(CH_3)_3$], 36.5 (CMe_3), 62.9 [C(5)], 63.8 (C(7)], 66.7 and 67.1 [C(4) and $CO_2CH_2CH_3$], 95.7 [C(2)], 164.7 and 171.1 (ester and amide CO) and 201.4 (ketone CO); *m*/*z* (GC–MS) 301 ($M + NH_4^+$, 100%), 284 ($M + H^+$, 57) and 226 (11); nOe experiment (500 MHz, $CDCl_3$) irradiation at δ_H 3.50 gave enhancements at δ 4.30 (22.8%) and 5.14 (1.3); irradiation at δ_H 4.61 gave enhancement at δ 4.30 (5.7%); irradiation at δ_H 5.14 gave no enhancements.

Amide **15** R_f 0.47 (EtOAc–petrol, 3:7); $[\alpha]_D^{25}$ +28.3 (*c* 1.02 in $CHCl_3$); ν_{max}(film)/cm^{-1} 3600 (w), 3360 (m), 2985 (m), 1735 (s), 1685 (s) and 1215 (s); δ_H(200 MHz, $CDCl_3$) 1.24 (6H, t, *J* 7.0, 2 × $CO_2CH_2CH_3$), 1.38 (6H, t, *J* 7.5, 2 × $CHCH_3$), 3.27–3.46 (2H, m, 2 × $CHCH_3$), 3.74 (3H, s, CO_2CH_3), 4.10–4.22 (4H, m, 2 × $CO_2CH_2CH_3$), 4.37–4.62 (2H, m, $CHCH_2O$), 4.78–4.83 (1H, m, $CHCH_2O$) and 7.28 (1H, br s, NH); δ_C(50.3 MHz, $CDCl_3$) 13.4, 13.9 and 14.5 (2 × $CO_2CH_2CH_3$ and 2 × $CHCH_3$), 45.8, 46.4 and 51.7 (2 × $CHCH_3$ and $CHCH_2O$), 52.7 (CO_2CH_3), 61.5, 64.0 and 64.2 (2 × $CO_2CH_2CH_3$ and $CHCH_2O$) and 168.9, 169.4 and 171.3 (carbonyls); *m*/*z* (GC–MS) 376 ($M + H^+$, 75%) and 230 (100).

(2*R*,5*R*)-2-*tert*-Butyl-5-methoxycarbonyl-6,8-dioxo-1-aza-3-oxabicyclo[3.3.0]octane 14a, and (2*R*,5*R*)-2-*tert*-butyl-7-ethoxycarbonyl-6-hydroxy-8-oxo-1-aza-3-oxabicyclo[3.3.0]oct-6-ene 17a

A solution of oxazolidine **8a** (3.54 g, 11.7 mmol) and KOBu′ (1.38 g, 12.3 mmol) in Bu′OH (60 ml) was heated at reflux for 3 h then cooled to room temperature and partitioned between diethyl ether (60 ml) and water (2 × 50 ml). The aqueous layer was acidified with 2 M HCl and extracted with EtOAc (2 × 50 ml). The organic extracts were washed with 1 M aqueous NaH_2PO_4 (3 × 25 ml) and brine (75 ml), dried ($MgSO_4$) and filtered through a silica plug (100 ml), washing through with EtOAc (350 ml). Removal of solvent *in vacuo* gave dicarbonyl **16a** (2.19 g, 73%) as an orange crystalline solid, mp 115–120 °C; R_f 0.21 (EtOAc–MeOH, 3:1); $[\alpha]_D^{20}$ +100.3 (*c* 2.02 in $CHCl_3$) (Found: C, 56.68; H, 6.57; N, 5.46. $C_{12}H_{17}NO_5$ requires: C, 56.46; H, 6.71; N, 5.49%); ν_{max}($CHCl_3$)/cm^{-1} 2960 (m), 2880 (m), 1785 (m), 1750 (s), 1725 (s) and 1290 (s); δ_H(200 MHz, $CDCl_3$) 0.91 [9H, s, $C(CH_3)_3$], 3.17 [1H, d, *J* 21.0, C(7)H], 3.63 [1H, d, *J* 9.0, C(4)H], 3.74 [1H, d, *J* 21.0, C(7)H′], 3.83 (3H, s, CO_2CH_3), 4.81 [1H, d, *J* 9.0, C(4)H′] and 5.09 [1H, s, C(2)H]; δ_C(50.3 MHz, $CDCl_3$) 24.4 [$C(CH_3)_3$], 35.3 (CMe_3), 44.6 [C(7)], 53.5 (CO_2CH_3), 67.7 [C(4)], 80.4 [C(5)], 98.2 [C(2)], 167.0, 172.6 and 198.6 (carbonyls); *m*/*z* (CI) 273 ($M + NH_4^+$, 12%), 256 ($M + H^+$, 100), 198 (78) and 170 (6).

The NaH_2PO_4 extracts, from above, were acidified with conc. HCl and extracted into EtOAc (2 × 50 ml), the organic extracts being washed with brine (70 ml), dried ($MgSO_4$) and evaporated *in vacuo* to give ester **17a** (380 mg, 12%) as an amorphous white solid, mp 138.5–140.5 °C (decomp.); $[\alpha]_D^{20}$ +39.6 (*c* 1.10 in $CHCl_3$); ν_{max}($CHCl_3$)/cm^{-1} 2965 (m), 1715 (s), 1660 (m) and 1625 (m); δ_H(500 MHz, [$^2H_6$]benzene) 1.04 [9H, s, $C(CH_3)_3$], 1.11 (3H, t, *J* 7.1, $CO_2CH_2CH_3$), 2.87 [1H, m, C(4)H], 3.65 [1H, m, C(4)H′], 3.80 [1H, dd, *J* 6.8, *J′* 9.2, C(5)H], 4.12 (2H, m, $CO_2CH_2CH_3$) and 4.97 [1H, s, C(2)H]; δ_C(50.3 MHz, $CDCl_3$) 13.8 ($CO_2CH_2CH_3$), 24.3 [$C(CH_3)_3$], 35.5 (CMe_3), 61.5, 61.8 and 67.2 [C(4), C(5)H and $CO_2CH_2CH_3$], 95.0 [C(2) and *C*=COH], 167.2 (ester and amide CO) and 186.3 (C=*C*OH); *m*/*z* (FAB) 314 ($M + Na^+$, 46%), 292 ($M + Na^+$, 100) and 270 ($M + H^+$, 24) (HRMS: found MH^+, 270.1329. $C_{13}H_{20}NO_5$ requires MH^+, 270.1341); nOe experiment (500 MHz, [$^2H_6$]benzene) irradiation at δ_H 2.87 gave enhancements at δ 3.65 (17.0%) and 4.97 (2.0); irradiation at δ_H 3.65 gave enhancement at δ 2.87 (19.3%); irradiation at δ_H 3.80 gave no enhancements; irradiation at δ_H 5.00 gave enhancements at δ 1.04 (10.0%) and 2.87 (1.0).

(2*R*,5*R*)-2-*tert*-Butyl-5-methoxycarbonyl-7-methyl-6,8-dioxo-1-aza-3-oxabicyclo[3.3.0]octane 16b

To a solution of oxazolidine **8b** (0.40 g, 1.27 mmol) in Bu′OH (15 ml) was added KOBu′ (0.156 g, 1.39 mmol). The mixture was heated at reflux, with a drying tube fitted, for 3 h, cooled and poured into water (40 ml). The aqueous layer was washed with diethyl ether (2 × 25 ml), acidified with 2 M HCl and extracted with diethyl ether (2 × 30 ml). The ethereal extracts were washed with brine (40 ml), dried ($MgSO_4$) and evaporated *in vacuo* to yield β-keto amide **16b** as a white foam (mixture of tautomers, the ratio of major keto epimer:minor keto epimer was 8.5:1) (0.33 g, 96%). An analytical sample was prepared by column chromatography (EtOAc–petrol, 1:4 increasing polarity to EtOAc), mp 94–100 °C; R_f 0.14 (EtOAc); $[\alpha]_D^{25}$ +76.8 (*c* 0.98 in $CHCl_3$) (Found: C, 58.10; H, 7.20; N, 5.06. $C_{13}H_{19}NO_5$ requires C, 57.98; H, 7.11; N, 5.20%); ν_{max}($CHCl_3$)/cm^{-1} 3680 (w), 3560 (br w), 3400 (br w), 2960 (m), 1785 (m), 1725 (s) and 1295 (m); δ_H(500 MHz, $CDCl_3$) (enol tautomer) 0.93 [9H, s, $C(CH_3)_3$], 1.71 (3H, s, $C=CCH_3$), 3.43 [1H, d, *J* 8.5, C(4)HH′], 3.80 (3H, s, CO_2CH_3), 4.67 [1H, s, C(2)H] and 4.78 [1H, d, *J* 8.5, C(4)HH′]; (major keto tautomer) 0.92 [9H, s, $C(CH_3)_3$], 1.29 (3H, d, *J* 7.5, $CHCH_3$), 3.55 [1H, d, *J* 9.0, C(4)HH′], 3.70 (1H, q, *J* 7.5, $CHCH_3$), 3.83 (3H, s, CO_2CH_3), 4.82 [1H, d, *J* 9.0, C(4)HH′] and 5.07 [1H, s, C(2)H]; (minor keto tautomer) 0.92 [9H, s, $C(CH_3)_3$], 1.58 (3H, d, *J* 8.0, $CHCH_3$), 3.05 (1H, q, *J* 8.0, $CHCH_3$), 3.56 [1H, d, *J* 9.0, C(4)HH′], 3.82 (3H, s, CO_2CH_3), 4.83 [1H, d, *J* 9.0, C(4)HH′] and 5.07 [1H, s, C(2)H]; δ_C(50.3 MHz, $CDCl_3$) (enol tautomer) 6.0 ($C=CCH_3$), 24.5 [$C(CH_3)_3$], 34.9 (CMe_3), 53.0 (CO_2CH_3), 69.7 [C(4)], 74.3 [C(5)], 96.5 [C(2)], 103.6 [C(7)], 169.1 and 169.1 (amide and ester CO) and 182.4 [C(6)]; (major keto tautomer) 7.3 ($CHCH_3$), 24.5 [$C(CH_3)_3$], 35.4 (CMe_3), 49.3 [C(7)], 53.6 (CO_2CH_3), 68.2 [C(4)], 79.1 [C(5)], 98.0 [C(2)], 167.0 and 175.8 (amide and ester CO) and 201.2 [C(6)]; *m*/*z* (DCI) 287 ($M + NH_4^+$, 4%), 270 ($M + H^+$, 100); nOe experiment (500 MHz, $CDCl_3$) irradiation at δ_H 3.55 gave enhancements at δ 4.82 (26.8%) and 5.07 (1.6); irradiation at δ_H 3.70 gave an enhancement at δ 1.29 (5.5%); irradiation at δ_H 4.82 gave enhancements at δ 3.43 (3.3%) and 3.55 (25); irradiation at δ_H 5.07 gave enhancements at δ 0.92 (10.3%) and 3.55 (2.6).

(2*R*,5*R*)-2-*tert*-Butyl-6-hydroxy-8-oxo-7-phenyl-1-aza-3-oxabicyclo[3.3.0]oct-6-ene 17

A solution of ester **16c** (1.00 g, 3.0 mmol) in 1 M aqueous NaOH (25 ml) was heated at reflux for 2 h. After cooling to room temperature the solution was washed with diethyl ether (20 ml), then acidified with conc. HCl to give a white precipitate which was extracted into diethyl ether (2 × 20 ml). The ethereal extracts were washed with brine (30 ml), dried ($MgSO_4$) and evaporated *in vacuo* to an intermediate as a white foam which was heated at 100 °C *in vacuo* for 1 h. Purification by column chromatography (EtOAc–hexane, 1:1) gave the *title compound* **17b** (0.60 g, 73%) as a white powder, mp >210 °C (decomp.); R_f 0.13 (EtOAc–hexane, 1:1); $[\alpha]_D^{20}$ +75.5 (*c* 0.43 in DMF); ν_{max}(KBr)/cm^{-1} 3300–2800 (bm), 2960 (m), 2875 (m), 2800–2300 (m), 1615 (s), 1595 (s), 1400 (s), 1370 (s), 1350 (s) and 1340 (s); δ_H(200 MHz, [$^2H_6$]acetone) 0.95 [9H, s, $C(CH_3)_3$], 3.41 [1H, m, C(4)H], 4.32 [1H, m, C(4)H′], 4.48 [1H, m, C(5)H], 4.77 [1H, s, C(2)H], 7.2 (1H, m, ArH), 7.33 (2H, m, ArH) and 8.0 (2H, m, ArH); *m*/*z* (CI) 291 ($M + NH_4^+$, 2%), 274 ($M + H^+$, 68) and 216 (100).

(2*R*,5*R*)-2-*tert*-Butyl-6-hydroxy-8-oxo-7-phenyl-1-aza-3-oxabicyclo[3.3.0]oct-6-ene 17b

A solution of oxazolidine **8e** (1.50 g, 4.91 mmol) and NaOMe (290 mg, 5.40 mmol) in MeOH (25 ml) was heated at reflux for 17 h. After cooling to room temperature the reaction mixture was partitioned between DCM (50 ml) and water (50 ml). The DCM layer was dried ($MgSO_4$) and evaporated *in vacuo*. Purification by column chromatography (DCM) gave unreacted starting material (412 mg, 27%). The aqueous layer was acidified with 2 M HCl and extracted with diethyl ether (2 × 25 ml), the ether extracts being washed with brine (30 ml), dried ($MgSO_4$) and evaporated *in vacuo*. Purification by column chromatography (DCM increasing polarity to EtOAc–DCM, 1:9) gave tetramic acid **17b** (295 mg, 22%) as a white powder with identical spectroscopic properties to those described above. $[a]_D^{20}$ +63.7 (*c* 0.48 in DMF).

(2*R*,5*R*,7*S*)-2-*tert*-Butyl-7-hydroxy-5-methoxycarbonyl-7-methyl-6,8-dioxo-1-aza-3-oxabicyclo[3.3.0]octane 11a and (2*R*,4*S*)-2-*tert*-butyl-4-methoxycarbonyl-3-(2-oxopropanoyl)-1,3-oxazolidine 18

To a solution of lactam **16b** (68 mg, 0.25 mmol) in THF (3 ml) was added NaH (60% dispersion in mineral oil) (12 mg, 0.30 ml). The mixture was cooled to −60 °C and MoO_5·pyridine·DMPU (145 mg, 0.38 mmol) was added. The reaction was allowed to warm to room temperature over 2 h and then stirred for a further 23 h. The mixture was partitioned between diethyl ether (20 ml) and 2 M HCl (20 ml), the ether layer being washed with sat. $NaHCO_3$ (aq) (20 ml). The aqueous layers were extracted with diethyl ether (2 × 15 ml), the combined organic extracts being washed with brine (40 ml), dried ($MgSO_4$) and evaporated *in vacuo*. Recrystallisation from $CHCl_3$–petrol gave hydroxy lactam **11a** (17 mg, 24%) as colourless needles, mp 188–191 °C; R_f 0.09 (EtOAc–DCM, 1:9); $[a]_D^{22}$ +77.8 (*c* 1.08 in $CHCl_3$) (Found: C, 54.90; H, 6.97; N, 4.68. $C_{13}H_{19}NO_6$ requires: C, 54.73; H, 6.71; N, 4.91%); $\nu_{max}(CHCl_3)/cm^{-1}$ 3560 (w), 1790 (m), 1750 (s) and 1730 (s); δ_H(200 MHz, $CDCl_3$) 0.94 [9H, s, $C(CH_3)_3$], 1.75 [3H, s, $C(OH)CH_3$], 3.61 (1H, br s, O*H*), 3.63 [1H, d, *J* 9.0, C(4)H], 3.86 (3H, s, CO_2CH_3), 4.87 [1H, d, *J* 9.0, C(4)H′] and 5.09 [1H, s, C(2)H]; δ_C(50.3 MHz, $CDCl_3$), 23.7 and 24.7 [$C(OH)CH_3$ and $C(CH_3)_3$], 35.2 (CMe_3), 53.8 (CO_2CH_3), 69.5 [C(4)], 77.2 and 77.6 [C(5) and C(7)], 98.9 [C(2)], 166.4 and 177.9 (ester and amide CO) and 201.0 (ketone CO); *m*/*z* (CI) 303 ($M + NH_4^+$, 100%), 286 ($M + H^+$, 62) and 200 (41).

Purification of the mother liquor, from above, by column chromatography (EtOAc–petrol, 1:9 increasing polarity to EtOAc–petrol, 1:1) gave hydroxy lactam **11a** (5 mg, 7%) and α-dicarbonyl **18** (9 mg, 14%) as a colourless oil; R_f 0.50 (EtOAc–petrol, 3:7); $[a]_D^{25}$ −7.4 (*c* 0.43 in $CHCl_3$); $\nu_{max}(CHCl_3)/cm^{-1}$ 2960 (m), 1750 (s), 1725 (m) and 1660 (s); δ_H(200 MHz, $CDCl_3$) 0.99 [9H, s, $C(CH_3)_3$], 2.51 (3H, s, $COCH_3$), 3.80 (3H, s, CO_2CH_3), 4.25 (1H, m) and 4.41 (1H, m) and 5.22 (1H, dd, *J* 5.0, *J*′ 8.5) [C(4)H and C(5)H_2] and 5.40 [1H, s, C(2)H]; δ_C(125.7 MHz, $CDCl_3$) 26.04 and 27.32 [$C(CH_3)_3$ and $COCH_3$], 38.30 (CMe_3), 52.73 (CO_2CH_3), 58.13 [C(4)], 68.78 [C(5)], 97.53 [C(2)], 163.8 and 170.0 (ester and amide CO) and 197.9 (ketone CO); *m*/*z* (GC–MS) 258 ($M + H^+$, 23%), 200 (20) and 172 (100).

(2*R*,5*R*,6*R*,7*S*)-2-*tert*-Butyl-6,7-dihydroxy-5-methoxycarbonyl-7-methyl-8-oxo-1-aza-3-oxabicyclo[3.3.0]octane 11b

Method A. To a solution of ketone **11a** (60 mg, 0.21 mmol) in 10% AcOH in DCM (3 ml) was added $NaBH_4$ (16 mg, 0.42 mmol). The mixture was stirred for 2.25 h and the solvent was removed *in vacuo.* The residue was partitioned between EtOAc (10 ml) and 10% $NaHCO_3$ (aq) (10 ml), the organic layer was washed with brine (5 ml), dried ($MgSO_4$) and evaporated *in vacuo*. Recrystallisation from $CHCl_3$–petrol gave diol **11b** (56 mg, 93%) as colourless crystals.

Method B. To a solution of ketone **11a** (48 mg, 0.17 mmol) in EtOAc (3 ml) was added PtO_2 (5 mg, 0.02 mmol). The mixture was degassed and then placed under H_2. After stirring under H_2 for 26 h the catalyst was removed by filtering through Celite and solvent was removed *in vacuo* to give diol **11b** (48 mg, 99%) as colourless crystals, mp 64–67 °C; R_f 0.39 (EtOAc); $[a]_D^{22}$ +20.5 (*c* 0.95 in $CHCl_3$) (Found: C, 54.43; H, 7.45; N, 4.98. $C_{13}H_{21}NO_6$ requires: C, 54.34; H, 7.37; N, 4.88%); $\nu_{max}(CHCl_3)/cm^{-1}$ 3700–3000 (br w), 3600 (w), 1750 (m) and 1725 (s); δ_H(200 MHz, $CDCl_3$) 0.90 [9H, s, $C(CH_3)_3$], 1.59 [3H, s, $C(OH)CH_3$], 3.51 [1H, d, *J* 8.5, C(4)*H*H′], 3.82 (3H, s, CO_2CH_3), 3.98 (1H, br d, *J* 5.0, CHO*H*), 4.21 [1H, br s, C(O*H*)CH_3], 4.40 (1H, d, *J* 5.0, C*H*OH), 4.86 [1H, s, C(2)H] and 4.99 [1H, d, *J* 8.5, C(4)HH′]; δ_C(50.3 MHz, $CDCl_3$) 20.1 [$C(OH)CH_3$], 24.8 [$C(CH_3)_3$], 35.5 [$C(CH_3)_3$], 52.6 (CO_2CH_3), 73.6 and 75.1 [$C(4)H_2$ and *C*(5)], 79.7 and 81.4 [*C*HOH and $C(OH)CH_3$], 96.7 [Bu′*C*H) and 169.8 and 179.7 (carbonyls); *m*/*z* (CI) 288 ($M + H^+$, 100%) and 202 (32); nOe experiment (500 MHz, $CDCl_3$) irradiation at δ_H 3.50 gave enhancements at δ 4.40 (6.6%), 4.86 (2.4) and 4.99 (17.2); irradiation at δ_H 4.40 gave enhancements at δ 3.51 (5.7%); irradiation at δ_H 4.86 gave an enhancement at δ 0.90 (7.5%); irradiation at δ_H 5.00 gave an enhancement at δ 3.51 (15.6%).

(2*R*,5*R*,6*S*,7*R*)-2-*tert*-Butyl-6,7-dihydroxy-5-methoxycarbonyl-7-methyl-8-oxo-1-aza-3-oxabicyclo[3.3.0]octane 11c

To a solution of enol **16b** (100 mg, 0.37 mmol) in 10% AcOH in DCM (2.5 ml) was added, portionwise over 30 min, $NaBH_4$ (28 mg, 0.74 mmol). The mixture was stirred at room temperature for 1 h, the solvent was evaporated *in vacuo* and the residue was partitioned between EtOAc (25 ml) and 5% aq. $NaHCO_3$ (2 × 15 ml). The organic layer was washed with brine (15 ml), dried ($MgSO_4$) and evaporated *in vacuo*. Purification by column chromatography (DCM increasing polarity to DCM–EtOAc, 1:1) gave diol **11b** (20 mg, 19%) and diol **11c** (24 mg). Recrystallisation from $CDCl_3$ gave pure diol **11c** (5 mg, 5%) as colourless needles; R_f 0.45 (EtOAc); δ_H(200 MHz, CD_3OD) 0.94 [9H, s, $C(CH_3)_3$], 1.26 [3H, s, $C(OH)CH_3$], 3.77 (3H, s, CO_2CH_3), 4.14 (1H, s, C*H*OH), 4.15 [1H, d, *J* 9.0, C(4)HH′], 4.26 [1H, d, *J* 9.0, C(4)HH′] and 4.76 [1H, s, C(2)H]; δ_C(126.7 MHz, CD_3OD) 18.7 [$C(OH)CH_3$], 25.9 [$C(CH_3)_3$], 37.0 (CMe_3), 53.1 (CO_2CH_3), 70.4 [C(4)H], 76.4 [C(5)], 80.3 (*C*HOH), 82.0 [*C*(OH)CH_3], 99.2 [C(2)] and 174.7 and 181.1 (carbonyls); *m*/*z* (DCI) 288 ($M + H^+$, 100%), 202 (15) and 157 (50).

(2*R*,5*S*)-6-Amino-2-*tert*-butyl-5-methoxycarbonyl-8-oxo-1-aza-3-oxabicyclo[3.3.0]oct-6-ene 19a

To a solution of nitrile **8d** (105 mg, 0.41 mmol) in MeOH (5 ml) was added NaOMe (24 mg, 0.44 mmol). The mixture was stirred at room temperature for 16 h then partitioned between diethyl ether (20 ml) and H_2O (20 ml). The aqueous layer was acidified with 2 M HCl and extracted with diethyl ether (20 ml), the ether extract being washed with 0.5 M Na_2HPO_4 (10 ml). The combined organic extracts were washed with brine (10 ml), dried ($MgSO_4$), and evaporated *in vacuo* to give enamine **19a** (86 mg, 82%) as a pale yellow crystalline solid, mp 129–131 °C; R_f 0.39 (EtOAc); $[a]_D^{21}$ +241 (*c* 0.99 in $CHCl_3$) (Found: C, 56.51; H, 7.20; N, 10.71. $C_{12}H_{18}N_2O_4$ requires: C, 56.68; H, 7.14; N, 11.02%); $\nu_{max}(CHCl_3)/cm^{-1}$ 3510 (w), 3405 (w), 2865 (w), 1735 (m), 1695 (m) and 1645 (s); δ_H(200 MHz, $CDCl_3$) 0.87 [9H, s, $C(CH_3)_3$], 3.43 [1H, d, *J* 8.5, C(4)H], 3.77 (3H, s, CO_2CH_3), 4.59 and 4.70 [2H, 2 × s, C(2)H and C(7)H], 4.68 [1H, d, *J* 8.5, C(4)H′] and 5.43 (2H, br s, N*H*$_2$); δ_C(50.3 MHz, $CDCl_3$) 24.8 [$C(CH_3)_3$], 35.1 (CMe_3), 53.3 (CO_2CH_3), 70.7 [C(4)], 75.5 [C(5)], 90.2 [C(7)], 97.2 [C(2)] and 163.2, 170.3 and 181.1 [carbonyls and C(6)]; *m*/*z* (CI) 255 ($M + H^+$, 100%) 197 (33).

(2*R*,5*S*)-6-Amino-2-*tert*-butyl-8-oxo-1-aza-3-oxabicyclo[3.3.0]-oct-6-ene 19b

To a solution of oxazolidine **8d** (0.656 g, 2.58 mmol) in 1%

water in Bu′OH (15 ml) was added KOBu′ (0.318 g, 2.84 mmol). The mixture was heated at reflux for 1.5 h, cooled, and poured into water (40 ml). The aqueous layer was extracted with diethyl ether (2 × 20 ml), the ether extracts being washed with brine (25 ml), dried ($MgSO_4$) and evaporated *in vacuo*. Purification by column chromatography (EtOAc–petrol, 1:1) gave enamine **19a** (45 mg, 7%). The aqueous layer was acidified with 2 M HCl and extracted with diethyl ether (2 × 25 ml). The ether extracts were washed with brine (40 ml), dried ($MgSO_4$) and evaporated *in vacuo* to give crude enamine **19b** (0.41 g, 71%) as a yellow foam. A sample was recrystallised from $CHCl_3$ to give pale yellow crystals, mp 173–185 °C (decomp.); R_f 0.15 (EtOAc); $[\alpha]_D^{21}$ +106 (*c* 0.54 in MeOH); $\nu_{max}(CHCl_3)/cm^{-1}$ 3520 (w), 3415 (m), 2970 (m), 1685 (m), 1640 (s) and 1600 (m); δ_H(200 MHz, $CDCl_3$) 0.95 [9H, s, $C(CH_3)_3$], 3.35 [1H, t, *J* 8.0, C(4)H], 4.17–4.34 [2H, m, C(4)H′ and C(5)H], 4.74 and 4.76 [2H, 2 × s, C(7)H and C(2)H] and 4.92 (2H, br s, NH_2); δ_C(50.3 MHz, $CDCl_3$) 24.5 [$C(CH_3)_3$], 35.7 (CMe_3), 63.8 [C(5)H], 68.7 [C(4)], 90.5 [C(7)], 94.8 [C(2)], 165.2 (amide CO) and 181.1 [C(6)]; *m*/*z* (CI) 197 ($M + H^+$, 100%) and 139 ($M + H^+ - Bu'H$, 45) (HRMS: found MH^+, 197.1290. $C_{10}H_{17}N_2O_2$ requires MH^+, 197.1290); nOe experiment (500 MHz, $CDCl_3$) irradiation at δ_H 3.35 gave enhancements at δ 4.21 (16.4%), 4.30 (2.8) and 4.78 (1.4); Irradiation at δ_H 4.21 gave an enhancement at δ 3.35 (20.6%); irradiation at δ_H 4.30 gave no enhancements; irradiation at δ_H 4.78 gave enhancements at δ 0.95 (4.0%) and 3.35 (1.0).

(2*R*,5*R*)-2-*tert*-Butyl-6,8-dioxo-1-aza-3-oxabicyclo[3.3.0]octane 12 from enamine 19a

A solution of enamine **19a** (37 mg, 0.19 mmol) in Pr^iOH (1 ml) and 2 M aqueous NaOH (1 ml) was heated at reflux for 16.25 h, cooled to room temperature and then partitioned between 2 M aqueous HCl (5 ml) and EtOAc (5 ml). The aqueous layer was extracted with EtOAc (5 ml) and the combined organic extracts were washed with brine (7 ml), dried ($MgSO_4$) and evaporated *in vacuo*. Purification by column chromatography (EtOAc–petrol, 1:1 increasing polarity to EtOAc) gave dicarbonyl **12a** (7 mg, 19%) as off-white crystals, mp 148–152 °C (decomp.); R_f 0.13 (EtOAc–DCM, 1:1); $[\alpha]_D^{22}$ +126 (*c* 0.48 in MeOH); $\nu_{max}(CHCl_3)/cm^{-1}$ 2965 (m), 1775 (m), 1720 (s), 1370 (m), 1360 (m) and 1305 (m); δ_H(500 MHz, $CDCl_3$) 0.97 [9H, s, $C(CH_3)_3$], 3.14 [1H, dd, *J* 22.0, *J*′ 1.5, C(7)H], 3.45 [1H, d, *J* 22.0, C(7)H′], 3.56 [1H, dd, *J* 8.5, *J*′ 9.5, C(4)H], 4.26 [1H, dd, *J* 7.5, *J*′ 8.5, C(4)H′], 4.36 [1H, m, C(5)H] and 5.18 [1H, s, C(2)H]; δ_C(125.7 MHz, $CDCl_3$) 24.7 [$C(CH_3)_3$], 36.2 (CMe_3) 44.5 [C(7)], 66.5 [C(5)], 68.7 [C(4)], 96.4 [C(2)], 172.5 (amide CO) and 202.6 (ketone CO); *m*/*z* (CI) 215 ($M + NH_4^+$, 2%), 198 ($M + H^+$, 35) and 140 ($M + H^+ - Bu'H$, 100) (HRMS: found MH^+, 198.1130. $C_{10}H_{16}NO_3$ requires MH^+, 198.1130); nOe experiment (500 MHz, $CDCl_3$) irradiation at δ_H 3.56 gave enhancements at δ 4.26 (14.2%) and 5.18 (2.0); irradiation at δ_H 4.26 gave an enhancement at δ 3.56 (14.9%); irradiation at δ_H 4.36 gave an enhancement at δ 0.97 (3.0%); irradiation at δ_H 5.18 gave enhancements at δ 0.97 (5.2%) and 3.56 (2.0).

(2*S*,5*S*)-2-*tert*-Butyl-6,8-dioxo-1-aza-3-oxabicyclo[3.3.0]octane *ent* 12a

A solution of ester **13** (100 mg, 0.37 mmol) in wet CH_3CN (10 ml) was heated at reflux for 20.5 h, cooled to room temperature and partitioned between EtOAc (20 ml) and 2 M aqueous HCl (25 ml). The aqueous layer was extracted with EtOAc (20 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, 1:1 increasing polarity to EtOAc) gave dicarbonyl *ent*-**12a** (52 mg, 71%) as off-white crystals, mp 148–152 °C (decomp.); R_f 0.13 (EtOAc–DCM, 1:1) whose spectroscopic data was identical to **12a**; $[\alpha]_D^{21}$ −101 (*c* 0.74 in MeOH).

(6*R*,9*R*)-9-*tert*-Butyl-4-ethoxycarbonyl-6-methoxycarbonyl-2,5-dioxo-1-aza-8-oxabicyclo[4.3.0]nonane 22a

A solution of oxazolidine **8i** (200 mg, 0.52 mmol) and NaOMe (30 mg, 0.55 mmol) in MeOH (8 ml) was heated at reflux with a drying tube fitted for 6 h, then cooled to room temperature and poured into water (20 ml). The solution was washed with diethyl ether (2 × 10 ml), acidified with 2 M aqueous HCl and extracted with diethyl ether (2 × 15 ml). The organic extracts were washed with brine (20 ml), dried ($MgSO_4$) and evaporated *in vacuo* to give crude bicyclic compound **22a** (32 mg, 18%) as an orange oil; R_f 0.39 petrol–EtOAc, 2:1); δ_H(200 MHz, $CDCl_3$) 0.88 and 0.90 [9H, 2 × s, $C(CH_3)_3$], 1.28 (3H, m, CH_3CH_2), 3.3–4.4 [9H, m, C(3)H, C(4)H, CO_2CH_3, CH_3CH_2, C(7)H], 4.95 [1H, m, C(7)H′] and 5.31 [1H, s, C(9)H]; *m*/*z* (CI) 342 ($M + H^+$, 11%), 286 (14), 225 (22) and 213 (20).

(2*R*,5*R*)-2-*tert*-Butyl-5-methoxycarbonyl-7-methoxycarbonylmethyl-6,8-dioxo-1-aza-3-oxabicyclo[3.3.0]octane 23 and (6*R*,9*R*)-9-*tert*-butyl-3-ethoxycarbonyl-6-methoxycarbonyl-2,5-dioxo-1-aza-8-oxabicyclo[4.3.0]nonane 22b

A solution of oxazolidine **8j** (200 mg, 0.54 mmol) and NaOMe (31 mg, 0.57 mmol) in MeOH (8 ml) was heated at reflux with a drying tube fitted for 4 h, then cooled to room temperature and poured into water (20 ml). The solution was washed with diethyl ether (2 × 10 ml), acidified with 2 M aqueous HCl and extracted with diethyl ether (2 × 15 ml). The organic extracts were washed with brine (20 ml), dried ($MgSO_4$) and evaporated *in vacuo*. Purification by column chromatography (petrol–EtOAc, 2:1) gave an 8:3 mixture of compounds **23** and **22b** (70 mg, 40%) as an orange oil.

Lactam **23**, R_f 0.23 (petrol–EtOAc, 2:1); δ_H(500 MHz, $CDCl_3$) 0.93 [9H, s, $C(CH_3)_3$], 3.04 (2H, 2 × dd, *J* 18.2, *J*′ 3.8, CH_2CO_2Me), 3.54 [1H, t, *J* 3.8, C(7)H], 3.67 (3H, s, CO_2CH_3), 3.83 (3H, s, CO_2CH_3), 4.03 [1H, d, *J* 8.4, C(4)H], 4.81 [1H, d, *J* 8.4, C(4)H′] and 5.08 [1H, s, C(2)H]; δ_C(125.8 MHz, $CDCl_3$) 24.7 [$C(CH_3)_3$], 29.9 (CH_2CO_2Me), 35.5 (CMe_3), 49.9 [C(7)], 52.6 (CO_2CH_3), 53.6 (CO_2CH_3), 68.3 [C(4)], 79.7 [C(5)], 98.4 [C(2)], 167.3, 171.4 and 174.6 (carbonyls); *m*/*z* (GC–MS) 328 ($M + H^+$, 100%), 270 (19) and 86 (28).

Lactam **22b** R_f 0.57 (petrol–EtOAc, 2:1); δ_H(500 MHz, $CDCl_3$) 0.92 [9H, s, $C(CH_3)_3$], 1.26 (3H, m, CH_3CH_2), 3.46 [2H, d, *J* 8.6, C(4)H_2], 3.81 (3H, s, CO_2CH_3), 3.8–3.9 [3H, m, CH_3CH_2 and C(3)H], 4.08 [1H, d, *J* 8.5, C(7)H], 4.86 [1H, d, *J* 8.5, C(7)H′] and 5.05 [1H, s, C(9)H]; δ_C(125.8 MHz, $CDCl_3$) 25.6 [$C(CH_3)_3$], 30.2 [C(4)], 35.1 (CMe_3), 52.5 [C(3)], 53.2 (CO_2CH_3), 59.2 (CH_3CH_2), 69.9 [C(7)], 78.1 [C(6)], 96.9 [C(9)], 168.6, 168.9, 176.0 and 178.4 (carbonyls); *m*/*z* (GC–MS) 342 ($M + H^+$, 100%), 284 (28) and 86 (36).

Attempted cyclisation of oxazolidine 8k

A solution of oxazolidine **8k** (100 mg, 0.25 mmol) and NaOMe (14 mg, 0.26 mmol) in MeOH (5 ml) was heated at reflux with a drying tube fitted for 4 h, then cooled to room temperature and poured into water (10 ml). The solution was washed with diethyl ether (2 × 10 ml), acidified with 2 M aqueous HCl and extracted with diethyl ether (2 × 15 ml). The organic extracts were washed with brine (20 ml), dried ($MgSO_4$) and evaporated *in vacuo* to give a crude 1:1 mixture of compounds **8k** and **23** (27 mg, 33%).

(2*R*,4*S*)-2-*tert*-Butyl-3-phenylacetyl-4-carboxy-1,3-oxazolidine 20a

To a solution of oxazolidine **8e** (150 mg, 0.49 mmol) in undried Bu′OH (5 ml) was added KOBu′ (58 mg, 0.52 mmol). The mixture was heated at reflux for 3 h, cooled to room temperature and partitioned between diethyl ether (15 ml) and water (15 ml). The aqueous layer was acidified with 2 M HCl and extracted with diethyl ether (2 × 15 ml). The ether extracts were washed with brine (15 ml), dried ($MgSO_4$) and evaporated *in vacuo*. Recrystallisation from ethyl acetate–hexane gave acid **20a**

(115 mg, 80%) as colourless crystals, mp 153–155 °C; R_f 0.10 (MeOH–EtOAc, 1:9); $[a]_D^{25}$ +9.4 (*c* 0.51 in MeOH) (Found: C, 66.16; H, 6.86; N, 4.76; $C_{16}H_{21}NO_4$ requires C, 65.96; H, 7.27; N, 4.81%); ν_{max}(KBr)/cm^{-1} 3400–2400 (m), 2970 (m), 1755 (m), 1740 (m), 1720 (m), 1665 (s) and 1655 (s); δ_H(200 MHz, CD_3COCD_3) 0.90 [9H, s, $C(CH_3)_3$], 3.83 (1H, d, *J* 15.5, PhC*H*H′), 3.92 (1H, d, *J* 15.5, PhCH*H*′), 4.04 (1H, m) and 4.44 (1H, dd, *J* 3.0, *J*′ 8.5) and 5.00 (1H, dd, *J* 3.0, *J*′ 7.5) [C(4)HC(5)H_2], 5.29 [1H, s, C(2)H] and 7.27 (5H, m, ArH); δ_C(50.3 MHz, CD_3COCD_3) 25.3 [C(*C*H_3)$_3$], 37.2 (*C*Me$_3$), 41.4 (Ph*C*H_2), 58.9 [C(4)], 68.0 [C(5)], 96.4 [C(2)], 126.7, 128.4 and 129.7 (ArCH), 136.0 (ArC) and 171.3 and 172.6 (carbonyls); *m*/*z* (DCI) 292 (M + H^+, 100%), 234 (20), 206 (48) and 116 (52).

(2*R*,4*S*)-3-[3-(ethoxycarbonyl)propanoyl]-2-*tert*-butyl-4-carboxy-1,3-oxazolidine 20b

To a solution of oxazolidine **8g** (0.15 g, 0.46 mmol) in Bu′OH (5 ml) was added KOBu′ (0.054 g, 0.48 mmol). The mixture was heated at reflux, with a drying tube fitted, for 4.5 h, cooled and poured into water (25 ml). The aqueous layer was washed with diethyl ether (2 × 10 ml), acidified with 2 M HCl and extracted with diethyl ether (2 × 15 ml). The ether extracts were washed with brine (20 ml), dried ($MgSO_4$) and evaporated *in vacuo*. Purification by column chromatography (EtOAc–DCM, 1:3 increasing polarity to EtOAc) gave acid **20b** (53 mg, 37%) as a crystalline solid, mp 93.5–97 °C; R_f 0.10 (EtOAc); $[a]_D^{21}$ −93.1 (*c* 2.04 in $CHCl_3$); ν_{max}($CHCl_3$)/cm^{-1} 3670 (w), 3500 (w), 3400–2400 (br), 2970 (m), 1730 (s), 1670 (m), 1595 (m), 1480 (m) and 1420 (m); δ_H(200 MHz, $CDCl_3$) 0.93 [9H, s, C(CH_3)$_3$], 1.25 (3H, t, *J* 7.0, $CO_2CH_2CH_3$), 1.92–2.06 (2H, m, $CH_2CH_2CH_2$), 2.36–2.54 (4H, m, $CH_2CH_2CH_2$), 4.07–4.25 and 4.45–4.95 and 5.20–5.40 [6H, m, $CO_2CH_2CH_3$, C(4)HC(5)H_2 and C(2)H] and 9.40–9.60 (1H, br, CO_2H); δ_C(50.3 MHz, $CDCl_3$) 14.0 ($CO_2CH_2CH_3$), 20.0 ($CH_2CH_2CH_2$), 25.8 [C(*C*H_3)$_3$], 33.0 and 33.8 (CH_2CH_2-CH_2), 37.6 (*C*Me$_3$), 59.0 [*C*(4)], 60.6 ($CO_2CH_2CH_3$), 68.1 [C(5)], 97.0 [C(2)] and 174.0 and 174.6 (carbonyls); *m*/*z* (DCI) 316 (M + H^+, 78%), 270 (14), 258 (20), 230 (100) and 143 (81).

Acids 20c–e

To a solution of oxazolidine **8g** (0.10 g, 0.30 mmol) in MeOH (5 ml) was added NaOMe (0.017 g, 0.32 mmol). The mixture was heated at reflux, with a drying tube fitted, for 6 h, cooled and poured into water (25 ml). The aqueous mixture was extracted with diethyl ether (2 × 10 ml), the ether extracts being washed with brine (10 ml), dried ($MgSO_4$) and evaporated *in vacuo* to give oxazolidine **20c** (43 mg, 45%) as a viscous oil; R_f 0.16 (EtOAc–petrol, 3:7); $[a]_D^{21}$ −28.1 (*c* 2.06 in $CHCl_3$); ν_{max}($CHCl_3$)/cm^{-1} 2955 (m), 1735 (s), 1670 (s), 1440 (m) and 1400 (m); δ_H(200 MHz, $CDCl_3$) 0.88 [9H, s, C(CH_3)$_3$], 1.90–2.04 (2H, m, $CH_2CH_2CH_2$), 2.28–2.60 (4H, m, $CH_2CH_2CH_2$), 3.65 (3H, s, CO_2CH_3), 3.77 (3H, s, CO_2CH_3), 4.05 and 4.44 and 4.58 [3H, m, C(4)HC(5)H_2] and 5.30 [1H, s, C(2)H]; *m*/*z* (GC–MS) 316 (M + H^+, 95%), 258 (12), 230 (100) and 130 (30).

The aqueous layer was acidified with 2 M aqueous HCl and extracted with diethyl ether (2 × 15 ml). The ether extracts were washed with brine (20 ml), dried ($MgSO_4$) and evaporated *in vacuo* to give an equimolar mixture of the acids **20d**,**e** (31 mg, 34%) as a viscous oil; R_f 0.17 (EtOAc); ν_{max}($CHCl_3$)/cm^{-1} 3400–2400 (br), 2960 (m), 1730 (s), 1670 (m), 1440 (m), 1415 (m) and 1400 (m); δ_H(200 MHz, $CDCl_3$) 0.88 and 0.92 [9H, 2 × s, C(CH_3)$_3$], 1.85–2.06 (2H, m, $CH_2CH_2CH_2$), 2.27–2.60 (4H, m, $CH_2CH_2CH_2$), 3.65 and 3.78 (3H, 2 × s, CO_2CH_3), 4.02–4.30 and 4.42–4.71 and 5.15–5.37 [4H, m, C(4)HC(5)H_2 and C(2)H] and 7.54 (1H, br s, CO_2H); *m*/*z* (DCI) 302 (M + H^+, 100%), 244 (31), 216 (93) and 130 (67).

(2*R*,5*R*)-2-*tert*-Butyl-6,8-dioxo-7,7-diphenyl-1-aza-3-oxa-bicyclo[3.3.0]octane 12b

To $Pb(OAc)_4$ (87 mg, 0.20 mmol), phenylboronic acid (25 mg, 0.21 mmol) and $Hg(OAc)_2$ (6 mg, 0.02 mmol) was added $CHCl_3$ (5 ml). The mixture was stirred at 40 °C for 1 h and then at room temperature for 3.5 h. A solution of pyridine (0.1 ml, 98 mg, 1.24 mmol) and tetramic acid **17b** (50 mg, 0.18 mmol) was then added and the reaction was stirred at 40 °C for 80 min followed by 20 h at room temperature. The mixture was filtered through a Celite plug and partitioned between $CHCl_3$ (10 ml) and 3 M H_2SO_4 (10 ml). The aqueous layer was washed with $CHCl_3$ (10 ml) and the combined organic layers were dried ($MgSO_4$) and evaporated *in vacuo*. Purification by column chromatography (EtOAc–petrol, 1:9) gave diarylated compound **12b** (53 mg, 83%) as a colourless crystalline solid, mp 70–73 °C; R_f 0.56 (EtOAc–petrol, 3:17); $[a]_D^{23}$ +33 (*c* 0.19 in $CHCl_3$); ν_{max}(film)/cm^{-1} 2960 (m), 2870 (w) and 1715 (s); δ_H(200 MHz, $CDCl_3$) 1.00 [9H, s, C(CH_3)$_3$], 3.74 (1H, quintet, *J* 7.0) and 4.42 (2H, quintet, *J* 7.0) [C(4)H_2C(5)H], 5.31 [1H, s, C(2)H], 6.97–7.02 (2H, m, ArH), 7.27–7.33 (3H, m, ArH) and 7.43 (5H, s, ArH); δ_C(50.3 MHz, $CDCl_3$) 24.8 [C(*C*H_3)$_3$], 36.5 [*C*(CH_3)$_3$], 66.1 [C(5)], 66.9 [C(4)], 70.3 [C(7)], 96.5 [C(2)], 128.0, 128.2, 128.5, 128.6, 129.1 and 129.3 (ArH), 136.0 and 137.2 (ArC), 175.2 (amide CO) and 204.7 (ketone CO); *m*/*z* (GC–MS) 367 (M + NH_4^+, 15%), 350 (M + H^+, 100) and 86 (38) (HRMS: found MH^+, 350.1761. $C_{22}H_{24}NO_3$ requires *M*H^+, 350.1756).

(2*R*)-2-Hydroxymethyl-2-methoxycarbonylpyrrolidine-3,5-dione 24

To a solution of lactam **16a** (260 mg, 1.02 mmol) in acidic 2,2,2-trifluoroethanol (2% w/v HCl) (5 ml) was added propane-1,3-dithiol (110 μl, 119 mg, 1.10 mmol). The mixture was stirred at room temperature for 17 h then partitioned between EtOAc (25 ml) and water (25 ml). The organic layer was washed with water (15 ml) and the combined aqueous layers were evaporated *in vacuo* to give alcohol **24** (166 mg, 87%); R_f 0.29 (MeOH–EtOAc, 1:3); ν_{max}(film)/cm^{-1} 3345 (br s), 2960 (m), 1780 (m), 1735 (s), 1700 (s) and 1250 (s); δ_H(200 MHz, D_2O) 3.06 [0.3H, s, C(4), enol], 3.52 (3H, s, CO_2CH_3), 3.54 [0.7H, s, C(4), keto], 3.61 (0.3H, d, *J* 12.0, C*H*H′OH, enol), 3.64 (0.7H, d, *J* 12.0, C*H*H′OH, keto), 3.77 (0.3H, d, *J* 12.0, CH*H*′OH, enol) and 3.86 (0.7H, d, *J* 12.0, CH*H*′OH, keto); δ_C(50.3 MHz, D_2O) 54.1 (CO_2CH_3, keto), 54.9 (CO_2CH_3, enol), 64.9 (*C*H_2OH, keto), 65.0 (*C*H_2OH, enol), 76.7 [C(2), enol], 78.1 [C(2), keto], 168.1 and 175.2 (amide and ester CO) and 204.1 (ketone CO); *m*/*z* (CI) 205 (M + NH_4^+, 83%) and 188 (M + H^+, 100).

(2*R*)-3-Hydroxy-2-hydroxymethyl-2-methoxycarbonyl-4-methyl-2,5-dihydro-1*H*-pyrrol-5-one 25

To a solution of dicarbonyl **16b** (125 mg, 0.46 mmol) in acidic 2,2,2–trifluoroethanol (1.5% w/v HCl) (5 ml) was added propane-1,3-dithiol (50 μl, 54 mg, 0.50 mmol). The mixture was stirred at room temperature for 4.25 h then partitioned between EtOAc (25 ml) and water (25 ml). The organic layer was washed with water (15 ml) and the combined aqueous layers were evaporated *in vacuo* to give alcohol **25** (80 mg, 86%) as a yellow foam; R_f 0.11 (MeOH–EtOAc, 1:3); δ_H(200 MHz, D_2O) 1.57 (3H, s, C=CCH_3), 3.69 (3H, s, CO_2CH_3), 3.86 (1H, d, *J* 12.0, C*H*H′OH) and 4.00 (1H, d, *J* 12.0, CH*H*′OH); δ_C(50.3 MHz, D_2O) 4.8 (C=C*C*H_3), 53.3 (CO_2CH_3), 62.1 (*C*H_2OH), 69.0 [C(2)], 103.1 (C=*C*CH_3) and 164.5, 169.6 and 178.4 (carbonyls and C=COH); *m*/*z* (CI) 219 (M + NH_4^+, 50%), 202 (M + H^+, 42), 189 (100) and 172 (65).

(2*R*)-3-Hydroxy-2-hydroxymethyl-4-phenyl-2,5-dihydro-1*H*-pyrrol-5-one 26

To a solution of β-keto amide **16c** (100 mg, 0.35 mmol) in 1.5% w/v HCl in CF_3CH_2OH (5 ml) was added propane-1,3-dithiol (40 μl, 43 mg, 0.40 mmol). The mixture was stirred at room temperature for 5 h then partitioned between water (10 ml) and EtOAc (10 ml). The aqueous layer was evaporated *in vacuo* to give alcohol **26** (38 mg, 50%) as an off white solid, mp 122–127 °C (decomp.); R_f 0.35 (MeOH–EtOAc, 1:3); $[a]_D^{22}$ +40.7

(c 0.28 in MeOH); ν_{max}(KBr)/cm^{-1} 3700–2200 (br s), 1665 (s), 1500 (m), 1390 (s), 775 (m) and 695 (m); δ_H(200 MHz, CD_3OD) 3.86 (1H, dd, J 11.5, J' 5.0), 4.01 (1H, dd, J 11.5, J' 3.0) and 4.35 (1H, m) [C(2)H and CH_2OH], 7.21–7.39 (3H, m, aromatic) and 7.65–7.69 (2H, m, aromatic); δ_C(50.3 MHz, CD_3OD) 60.5 [C(2) and CH_2OH], 105.4 (PhC=COH), 127.0, 128.0 and 128.3 (aromatic CH), 129.6 (aromatic C) and 172.9 and 176.3 (amide CO and C=COH); m/z (CI) 223 (M + NH_4^+, 35%) and 206 (M + H^+, 100) (HRMS: found MH^+, 206.0813. $C_{11}H_{11}NO_3$ requires MH^+ 206.0817).

X-Ray data for compounds 8f and 16c

Crystal data and data collection parameters for compound 8f. $C_{23}H_{27}NO_4$, M = 381.471, orthorhombic, a = 7.7872(5), b = 13.758(2), c = 19.885(3), V = 2130.5 Å^3, space group $P2_12_12_1$, Z = 4, D_c = 1.19 g cm^{-3}, crystal dimensions 0.10 × 0.20 × 0.45 mm, λ(Cu-K$_\alpha$) = 1.5418 Å, μ = 6.18 cm^{-1}, $\omega/2\theta$ scan ($0 \leqslant 2\theta \leqslant 144°$; $-1 \leqslant h \leqslant 9$; $-1 \leqslant k \leqslant 16$; $-1 \leqslant l \leqslant 24$), F(000) = 816, T = 295(2) K, R = 0.0340 for 1102 unique reflections $I > 3\sigma(I)$, R_{int} = 0.034.

Crystal data and data collection parameters for compound 16c. $C_{13}H_{21}NO_6$, M = 287.3, monoclinic, a = 5.953(2), b = 9.951(2), c = 12.188(2), β = 90.99(2)°, V = 722 Å^3, space group $P2_1$, Z = 2, D_x = 1.322 g cm^{-3}, crystal dimensions 0.20 × 0.30 × 0.40 mm; λ(Cu-K$_\alpha$) = 1.5418 Å, μ = 8.40 cm^{-1}, $\omega/2\theta$ scan ($0 \leqslant 2\theta \leqslant 72°$; $-7 \leqslant h \leqslant 7$; $-1 \leqslant k \leqslant 12$; $-1 \leqslant l \leqslant 15$; F(000) = 308, T = 296 K, R = 0.039 for 2770 unique reflections $I > 3\sigma(I)$, R_{int} = 0.022.

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