Pyrrolidinones derived from (*S*)-pyroglutamic acid. Part 1. Conformationally constrained glutamate

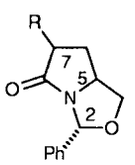
Jonathan H. Bailey,[a] David T. Cherry,[a] James Dyer,[a] Mark G. Moloney,*[a] Mark J. Bamford,[b] Steve Keeling[b] and R. Brian Lamont[b]

[a] *The Department of Chemistry, Dyson Perrins Laboratory, The University of Oxford, South Parks Road, Oxford, UK OX1 3QY. E-mail: mark.moloney@chem.ox.ac.uk*
[b] *GlaxoWellcome, Medicines Research Centre, Gunnels Wood Road, Stevenage, Hertfordshire, UK SG1 2NY*

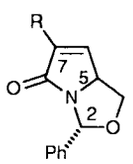
Received (in Cambridge, UK) 13th March 2000, Accepted 2nd June 2000
Published on the Web 24th July 2000

Novel conformationally constrained pyroglutaminols and pyroglutamates are readily available using an α,β-unsaturated bicyclic lactam as a template for diastereocontrolled enolate additions in the key step; zinc enolates are particularly effective in this regard. The bicyclic ring system both controls and permits the determination of ring stereochemistry. The utility of this methodology is demonstrated by a formal total synthesis of the NMDA receptor agonist, CPAA **11**.

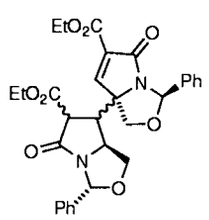
Much recent attention has focused on the use of highly functionalised pyrrolidinones as excitatory amino acid analogues[1] and as conformationally controlling peptidomimetics.[2–5] We have recently been interested in the development of methodology for the convenient synthesis of such functionalised pyrrolidinones, since this class of compounds has potent and wide-ranging biological activity. Our initial investigations have examined the hemiaminal ethers **1a**,**b**† derived from pyroglutaminol[6,7] for alkylations at C-7 *via* the lactam enolate,[8,9] and similar work by other groups has been reported in recent years.[6,9–22] We were attracted to this template since it could be readily prepared in enantiopure form, and the hydroxy and amide functionalities were simultaneously protected by a single benzylidene protecting group; this protecting group also provided a bicyclic template which might be expected to exert good diastereocontrol and additionally provided a linking group suitable for anchoring to an inert support. In the event, diastereoselection in alkylations of the lactam enolate were disappointing, although recent work suggests that high levels of *exo*-[23] or *endo*-[24–26] alkylation may be possible using carefully controlled reaction conditions or modified substrates.



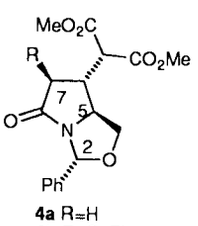
1a R=H
1b R=CO_2Et



2a R=H
2b R=SePh
2c R=CO_2Et



3



4a R=H
4b R=SePh
4c R=CO_2Et
4d R=CH_2Ph

The application of the enones **2a**,**c** to cycloaddition reactions has also attracted considerable attention, because of the possibility of simultaneous functionalisation and control of stereochemistry at two ring positions,[27–30] and **2a** has recently found application in the synthesis of peptidomimetics[31,32] and stereodefined glutamates[33,34] and pyroglutamates.[35] Although conjugate additions to simple α,β-unsaturated lactams have been reported to be difficult,[36] activated pyrrolidinones[14,37–49] and bicyclic lactams[9,19,20,50–54] have been successfully functionalised in this manner. The activated systems **2b**,**c** were of considerable interest to us because of their expected higher reactivity to conjugate addition, and we report here in detail the synthesis of functionalised pyrrolidinones which uses such a strategy in the key step; this methodology has previously been reported in preliminary form.[55] Noteworthy is that, despite the acidity of H-5 of **2c**, as evidenced by its facile dimerisation to **3**, the chiral integrity of this position is maintained;[27,56] that complete chiral integrity *can* indeed be lost in a protected simple $\Delta^{3,4}$-pyroglutamate has been demonstrated in the course of a Diels–Alder reaction.[57] For the reasons postulated in Seebach's Principles of Self Regeneration of Stereocentres, the bicyclic system ensures that deprotonation of H-5 of **2c** always regenerates the original (most stable) ring stereochemistry upon reprotonation.[58] The high acidity of related compounds[59,60] and similar dimerisations are already known,[12,31] and a natural product of similar structure has been reported.[61] A related bicyclic system has been investigated exhaustively by Meyers and co-workers, who have examined various types of ring manipulations to access a diversity of functionalised products.[62–64]

Conjugate addition reactions

We initially investigated conjugate additions to the enone **2a**, prepared by our previously reported method.[27] Although the addition of the enolate of dimethyl malonate to enone **2a** under kinetic conditions (LDA at −78 °C) returned unreacted starting material, the Stefanofsky conditions[65,66] (1 equivalent $NaNH_2$

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

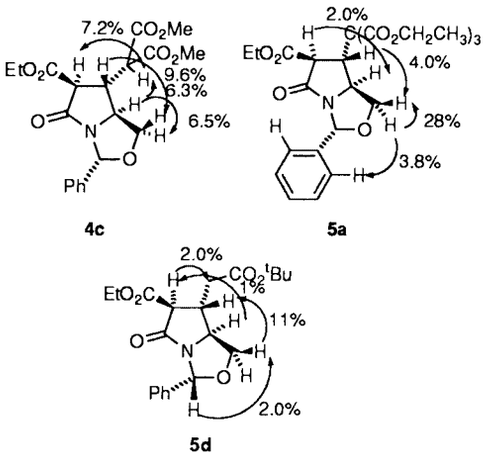


Fig. 1 NOE data for selected compounds.

in refluxing THF–HMPA) gave the desired product **4a** in 57% yield. Application of the same conditions but with substitution of DMPU for HMPA gave a 55% yield of the same product. However, an attempt to extend this reaction to other nucleophiles (Meldrum's acid, methyl thiophenylacetate,[54] methyl phenylacetate and *tert*-butyl acetate) was unsuccessful. Subsequent elaboration of **4a** by generation of the dienolate (3 equivalents of LDA) followed by quenching with benzyl bromide at −78 °C, gave the all-*trans* product **4d** in 37% yield, whose stereochemistry at C-6 and C-7 was confirmed by single crystal X-ray spectroscopic analysis.[67]

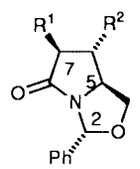
In an effort to gain improved generality for this conjugate addition, we examined the vinyl selenide **2b** and the acylated lactam **2c**, prepared as previously described,[27] since both were expected to be more reactive than **2a**. Conjugate addition of dimethyl malonate to **2b** using the $NaNH_2$ (1 equivalent)–DMPU–THF conditions gave the product **4b** in 45% yield as a single diastereomer, whose stereochemistry was assumed on the basis of the assignment discussed above. However, enone **2c** proved to be substantially more reactive, and application of the same reaction conditions gave a 30% isolated yield of the desired adduct **4c**, the stereochemistry of which was assigned by NOE difference spectroscopy (Fig. 1). Irradiation of H-5, the known stereocentre, caused a 6.5% enhancement of H-4_{exo} and a 6.3% enhancement of the malonate side-chain proton, indicating that the malonate group is on the *exo*-face of the molecule and therefore that H-6 has the *endo*-configuration. This assignment was confirmed by irradiation of H-6_{endo} and of the malonate side-chain proton which caused enhancements of H-4_{endo} (9.6%) and H-7 (7.2%) respectively, indicative of the all-*trans* arrangement of ring substituents, which would be expected to be thermodynamically preferred. Repetition of this reaction with a catalytic quantity of $NaNH_2$ (13 mol%) gave a greatly improved isolated yield of 70% of **4c**, again as the same diastereomer.

Interestingly, addition reactions to **2c** proved to be much more general than those to **2a**, and the enolates of several dicarbonyl derivatives gave the expected adducts **5a**–**c** in moderate to very good yield (Table 1). Conjugate addition of triethyl methanetricarboxylate under phase transfer conditions[68] (Bu_4NHSO_4, K_2CO_3, anhydrous toluene at 60 °C) gave the expected adduct **5a** as a single diastereomer in 60% yield, whose relative stereochemistry was assigned by NOE analysis (Fig. 1). The *cis* arrangement of H-5 and H-7 and of H-4_{endo} and H-6_{endo} was confirmed by 2 and 4% enhancements respectively; the C-6/7 substituents thus adopt the expected thermodynamically more stable *trans* arrangement. Since trialkyl methanetricarboxylates can be easily converted to malonic esters,[69] this route would readily provide access to compounds of type **4c**. The reactions of methyl cyanoacetate and ethyl acetoacetate each gave an inseparable mixture of diastereomers

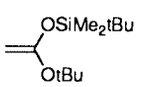
Table 1 Conjugate additions to **2c**

Product	Conditions[a]	Diastereomer ratio[d]	Yield (%)
4c	A	1[b]	30
4c	B	1[b]	70
5a	C	1[b]	60
5b	A	1:1	54
5c	D	1:1:4.5:4.5	72
5d	E	1:5.5:43.5	77
5e	F	[c]	27
5f	G	1:5:9:35	56
5g	H	1:17:17:74	53

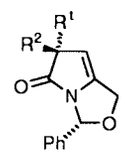
[a] A = $NaNH_2$ (1 eq.), DMPU, THF; B = $NaNH_2$ (13 mol%), DMPU, THF; C = K_2CO_3, Bu_4NHSO_4; D = $Ba(OH)_2$ (10 mol%), EtOH; E = Zn, ultrasound, THF, DMPU (9% v/v), 30–35 °C; F = Zn, ultrasound, dioxane, 35 °C; G = Zn, ultrasound, THF, −5 °C; H = Zn, ultrasound, THF, −10 °C. [b] Only (6*S*,7*S*) diastereomer obtained. [c] Not determined. [d] After purification.



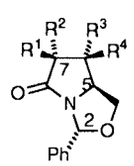
5a R^1=CO_2Et; R^2=$C(CO_2Et)_3$
5b R^1=CO_2Et; R^2=$CH(CN)CO_2Me$
5c R^1=CO_2Et; R^2=$CH(C(O)Me)CO_2Et$
5d R^1=CO_2Et; R^2=CH_2CO_2tBu
5e R^1=CO_2Et; R^2=CH_2CO_2Et
5f R^1=CO_2Et; R^2=$CH(Me)CO_2Me$
5g R^1=CO_2Et; R^2=$CH(Ph)CO_2Me$
5h R^1=CO_2H; R^2=CH_2CO_2tBu
5i R^1=H; R^2=CH_2CO_2tBu



7



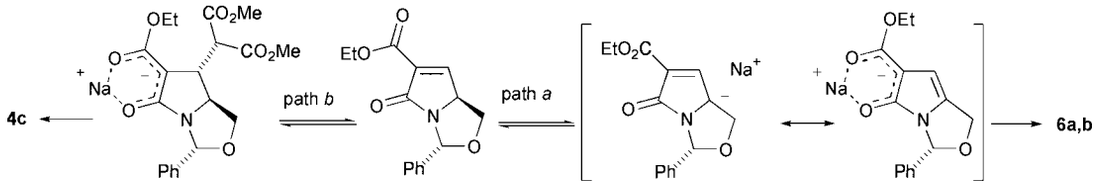
6a R^1=CH_2Ph, R^2=CO_2Et
6b R^1=CO_2Et, R^2=CH_2Ph



8a R^1=H; R^2=CO_2Et; R^3=CH_2CO_2tBu; R^4=H
8b R^1=H; R^2=CO_2Et; R^3=H; R^4=CH_2CO_2tBu

5b,**c** in 54 and 72% yields respectively; in the latter case, no intramolecular trapping of the C-7 enolate by the acetyl carbonyl group was observed, contrary to a literature observation for additions with (*E*)-chalcone.[70] However, again Meldrum's acid, methyl thiophenylacetate and *tert*-butyl acetate gave complex mixtures of unidentifiable products under the above conditions.

Of interest was the possibility of trapping the intermediate enolate of the Michael addition of malonate with an alkylating agent, prior to quenching, in order to generate *trans*-6,7-disubstituted products directly; thus, enone **2c** was treated with dimethyl malonate under the conditions described above, followed by benzyl bromide, and the mixture stirred at room temperature for 3 h. Careful purification by silica chromatography (eluant 3:1 petrol–EtOAc) allowed isolation of three products; the major product was the simple Michael adduct **4c** (37%), with no addition of benzyl bromide. The remaining two proved to be a diastereomeric mixture of the alkylated lactams **6a**,**b** obtained in 41% combined yield respectively. The former product **6a** displayed allylic coupling (*J* 2 Hz) between H-4 and H-6, and mass spectrometry indicated the required molecular mass, but attempted determination of the stereochemistry at C-7 by NOE difference spectroscopy was not successful. The minor product **6b** could not be isolated in pure form, but its ^1H NMR spectrum displayed similarities to the major product **6a**. In particular there was the same allylic coupling pattern between H-4 and H-6, and the aromatic region indicated the



Scheme 1

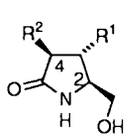
presence of two phenyl rings. The proposed mechanism for formation of compounds **4c** and **6** is shown in Scheme 1. Deprotonation of the starting enone **2c** (path *a*), operating in competition with the conjugate addition reaction (path *b*), would generate an enolate capable of alkylating at either the α- or γ-positions. Reaction, however, clearly proceeds *via* the more stabilised β-dicarbonyl enolate to give the product **6** as a diastereomeric mixture; the major diastereomer is likely to be the *exo*-benzyl one **6a** on the basis of our earlier work.[8] A similar deconjugative dialkylation in a monocyclic pyrrolidinone has recently been reported.[71] Attempts to alkylate lactam **4c** by deprotonation with NaH or KHMDS followed by reaction with benzyl bromide were not successful.

Attention was therefore turned to other enolates and their equivalents for the conjugate addition reaction. Silyl ketene acetals were of interest, since reports exist of the 1,4-conjugate additions without any competing 1,2-additions using Lewis acid catalysis.[72] These additions have been reported in dry acetonitrile,[73] and we expected that the competing dimerisation reaction to give **3** would be minimised under such anhydrous conditions. Silyl ketene acetal **7** and enone **2c** were therefore stirred in dry acetonitrile, and the expected adduct **5d** was obtained in 47% yield as an 8:1 mixture in favour of the all-*trans* diastereomer shown. Although this proved to be a simple procedure, high yielding and convenient alternatives to effect conjugate addition were still needed, and Reformatsky reagents offered considerable promise in this regard, but surprisingly few applications for conjugate additions, especially for diastereoselective additions,[74,75] have been reported.[76–78] We were pleased to find that the Reformatsky reagents which were derived from several bromoesters, generated in THF using ultrasonic irradiation,[79,80] when treated with enone **2c** gave the products **5d–g** (Table 1); these were generally obtained as predominantly one diastereomer, with minor amounts of the other diastereomers. The yields of the reaction were found to be highly solvent dependent, and for the reaction of the Reformatsky reagent derived from *tert*-butyl bromoacetate, THF and diglyme gave better yields of **5d** than dioxane and toluene (50, 52, 18 and 39% respectively); the best yield, of 77%, was obtained in a DMPU and THF solvent mixture. However, the competing dimerisation reaction described above, leading to adduct **3**, was observed when formation of the Reformatsky reagent was attempted *in situ* in the presence of the enone **2c**; pre-formation of the Reformatsky reagent was therefore essential. Further investigations showed that no reaction occurred at 0 °C, and warming to about 20 °C only gave a sluggish rate, with the optimum temperature range for the addition reaction being 30–35 °C. Ethyl bromoacetate gave only a low yield (27%) of the corresponding adduct using the unoptimised conditions. In the case of methyl 2-bromopropionate and α-bromophenylpropionate, the Reformatsky reagents needed to be generated at −6 °C, with the subsequent addition at not greater than 0 °C. Under these conditions, the products **5f,g** were obtained in yields of 56 and 53% respectively as a mixture of several diastereomers (Table 1).

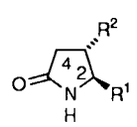
In the one case amenable to ^{1}H NOE analysis (the major diastereomer of compound **5d**, Fig. 1), for which the requisite NOE results were obtained by using a mixed $CDCl_3$–C_6D_6 (1:1.7) solvent in which H-4$_{endo}$, H-5, H-6 and H-7 were resolved, irradiation of H-5 gave a 1% enhancement of H-7 which in turn gave a 2.0% enhancement of one of the methylene protons α to the *tert*-butyl ester, thus indicating the *exo*-orientations of H-7 and the C-6 substituent. More significantly, irradiation of H-4$_{endo}$ gave a 10.8% enhancement of H-6 confirming the assignment of stereochemistry at C-6, this being consistent with the expected stereochemistry derived from *exo* (less hindered) conjugate addition of the Reformatsky reagent. The major diastereomer was therefore assigned the relative stereochemistry arising from *exo*-attack by the organometallic reagent at C-6 followed by *exo*-protonation, giving the *trans*-C-6/7 relative stereochemistry as expected on steric grounds, that is (6*S*,7*S*)-**5d** (Fig. 1). The assignment of the stereochemistry of the other diastereomers came from equilibration studies. Attempted equilibration of the mixture of isomers **5d** obtained from the reaction with *tert*-butyl bromoacetate did not lead to a significant change in the diastereoisomer ratio, consistent with the fact that the product formation is operating under thermodynamic control: thus, a 15:1 ratio of diastereomers of **5d** (in favour of the 6*S*,7*S* adduct) was, after standing for 3 days in $CDCl_3$, found to have an almost unchanged ratio (11:1). Conversely, a sample enriched in the original minor diastereomer by careful HPLC purification (containing only 17% of the 6*S*,7*S* diastereomer **5d**) was found to equilibrate when dissolved in $CDCl_3$ to a ratio of 1:1 after 8 days; thus, this diastereomer was assigned to be epimeric at C-7, that is, was the (6*S*,7*R*)-**8a**. Further treatment of this mixture with NaH for 2 h at rt followed by an aqueous methanol quench gave a product in which the 6*S*,7*S* diastereomer **5d** had increased to 86:14; thus the diastereomeric ratio was completely reversed. The least abundant diastereomer (0.2% of the total product) was expected to have 6*R*,7*R* absolute stereochemistry **8b**. The diastereoselectivity of the other cases leading to **5e–g** is expected to be similar.

Elaboration to pyroglutamates

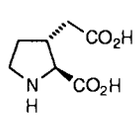
The convenient entry to these lactams would be of value only if selective deprotection was possible, thereby allowing access to functionalised pyrrolidinones. Treatment of lactam **5a** with TFA gave a rapid reaction in which the deprotected pyroglutaminol **9a** was obtained in excellent yield. However, the



9a R^1=C(CO_2Et)$_3$, R^2=CO_2Et
9b R^1=CH_2CO_2tBu, R^2=CO_2Et



10a R^1=CH_2OH, R^2=CH_2CO_2tBu
10b R^1=CH_2OH, R^2=CH_2CO_2H
10c R^1=CO_2Me, R^2=CH_2CO_2Me



11

same conditions, when applied to the Reformatsky adduct **5d** gave only a 45% yield of the required product **9b**. Since the *O*,*N*-hemiaminal ether cleavage was faster than that of the

tert-butyl ester, application of shorter reaction times (15 min) for **5d** was found to give a high yielding (79%) formation of the desired pyrrolidinone **9b**.

Selective hydrolysis of the ethyl ester over the *tert*-butyl ester of **5d** was readily achieved using an aqueous solution of sodium hydroxide in ethanol; however, the yield of carboxylic acid **5h** was dependent on reaction time and temperature, and the best conditions were either 3.75 h at room temperature, or 1 h at rt followed by 1 h at 40 °C, giving high product yields in the range 88–98%; longer periods of time at room temperature gave lower yields. The starting diastereomeric ratio of 1:6 favouring the *trans*-C-6/7 isomer of adduct **5d** changed to give a diastereomeric ratio of 1:16 in the carboxylic acid product **5h**, presumably also in favour of the *trans*-C-6/7 isomer, although this was not determined. Decarboxylation was readily effected by heating at low pressure to give compound **5i** in high crude yield (~94%). However, this compound proved to be considerably more acid sensitive than similarly hemiaminal ether protected analogues; deprotection occurred even in deuterochloroform over a 12 h period, reaching completion after several days. An alternative route to access compound **5i** directly was Krapcho dealkoxycarbonylation.[81] Compound **5d** was heated for 4 h at 150 °C in wet DMSO with LiCl, and although complete ethyl ester cleavage was achieved, partial *N*,*O*-acetal deprotection also occurred. This could be taken to completion by treating the crude material with TFA in dichloromethane, and chromatography then gave the expected alcohol product **10a** in 81% yield.

Hemiaminal ether deprotection of compound **5i** was easily achieved by treatment with TFA in DCM for 40 min to give the alcohol **10a** in a yield of 55%. This compound has been reported as an intermediate[82] in the synthesis of (−)-(2*S*,3*R*)-2-carboxypyrrolidine-3-acetic acid (CPAA) **11**,[54] an NMDA receptor agonist,[83] and the synthesis of **10a** by the bicyclic lactam route therefore constitutes a formal total synthesis of **11**. Removal of the *tert*-butyl ester of **10a** by further treatment with TFA and subsequent oxidation of the resulting hydroxy acid using ruthenium tetraoxide with direct methyl esterification (diazomethane) of the diacid gave the dimethyl ester **10c** in 53% yield over the three steps from alcohol **10a**. This compound is a conformationally restricted form of glutamic acid.

^{1}H NMR spectroscopy

Earlier studies[8,17] on simple derivatives of bicyclic lactam **1a** have highlighted consistent correlations between certain signals in the ^{1}H NMR spectra.‡ Thus, it has been observed that the H-2 signal always occurs as a singlet in the chemical shift range of 6.3–6.5 ppm, and this is a useful peak for the indication of diastereomeric purity. The signal corresponding to H-4$_{endo}$ occurs at a significantly lower chemical shift than that of H-4$_{exo}$ and since the observed coupling constants for H-4$_{endo}$ are consistently almost identical at ~8 Hz, this resonance often appears as a triplet or poorly resolved doublet of doublets. In contrast, the H-4$_{exo}$ exhibits a large geminal coupling (~8 Hz) to H-4$_{endo}$ and a smaller coupling (~6 Hz) to H-5, and therefore often appears as a well resolved doublet of doublets. The signals arising from the two C-6 hydrogens were dependent on the structure, with a small difference between H-6$_{exo}$ and H-6$_{endo}$ being observed for *exo*-products and a large difference for *endo*-products **1a** (R′ ≠ H). This has been explained using a steric argument.[17] Similiar consistencies in the ^{1}H NMR spectra of all the compounds **4** and **5** prepared in the current study were noted. For example, all these compounds exhibited a similar splitting pattern and chemical shift separation ($\Delta\delta$) for H-4$_{exo}$ and H-4$_{endo}$. The H-4$_{endo}$ signal was often observed as a triplet or just resolved doublet of doublets typically in the range δ 3.7–3.9, but the H-4$_{exo}$ signal often occurred as a well resolved doublet of doublets at lower field (δ 4.2–4.5). The chemical shift value for H-6 was typically in the range of δ 3.0–3.6, except for those compounds with a C-7 aromatic substituent, which gave higher field resonances centred about δ 2.6. These trends appear to be quite general and are valuable in the establishment of structural assignments. Therefore, in addition to controlling the stereochemistry of ring manipulations, the bicyclic system also facilitates the determination of ring stereochemistry by a consideration of chemical shift, coupling constant and NOE data.

Evidence for association phenomena of **10a** in solution came from the observation that the ^{1}H NMR spectra recorded in $CDCl_3$ were dependent on concentration; changes in the shift of the N*H* and O*H* signals, and in the splitting of the O*H* and of the adjacent methylene signals were evident. At greater concentration (30 mg ml^{-1}) these methylene signals were displayed as a doublet of doublets as a result of a large geminal coupling and a smaller vicinal coupling to H-2. There was no coupling to the exchanging O*H*, which was displayed as a broad singlet. At low concentration (*ca.* 1 mg ml^{-1}), the O*H* exhibited coupling to the adjacent methylene protons and appeared as a broad triplet, and the methylene signals were observed to be multiplets.

‡ Similar correlations have been observed in pyroglutamate systems.[84]

Conclusion

Highly functionalised pyrrolidinones are available in a short sequence from pyroglutamic acid, in which a bicyclic ring system both controls and permits the determination of ring stereochemistry; the method is novel and simple but potentially generalisable. The utility of this methodology is demonstrated by a formal total synthesis of the NMDA receptor agonist, CPAA.

Experimental

For general experimental procedures and the preparation of lactams **2a**–**2c**, see our earlier reports.[8,27]

(+)-(2*R*,5*S*,6*R*)-6-[Bis(methoxycarbonyl)methyl]-8-oxo-2-phenyl-3-oxa-1-azabicyclo[3.3.0]octane 4a

A mixture of enone **2a** (0.10 g, 0.50 mmol), dimethyl malonate (0.10 g, 0.75 mmol), sodium amide (0.020 g, 0.52 mmol), DMPU (1 cm^3), and THF (10 cm^3) was refluxed for 3 h under nitrogen. The mixture was quenched with cold water, extracted with ethyl acetate, and the organic phase washed with cold water. The organic layer was dried over $MgSO_4$, concentrated *in vacuo* and the crude product purified by flash column chromatography (EtOAc–petrol 1:1, R_f 0.2) (0.075 g, 45%) (Found: C, 61.3; H, 5.9; N, 4.4. $C_{17}H_{19}NO_6$ requires C, 61.3; H, 5.7; N, 4.2%); $[a]_D$ +134.3 (*c* 1.05 in $CHCl_3$); λ_{max}($CHCl_3$)/nm 259 (log ε 1.5); ν_{max}($CHCl_3$)/cm^{-1} 1757 (s), 1736 (s), 1708 (s); δ_H (200 MHz, $CDCl_3$) 2.68–2.75 (2H, m, H-7$_{endo}$ and C*H*(CO$_2$Me)$_2$), 2.85–3.05 (1H, m, H-6$_{endo}$), 3.56 (1H, d, *J* 10.0, H-7$_{exo}$), 3.70–3.80 (7H, m, 2 × OCH$_3$ and H-4$_{endo}$), 4.00 (1H, m, H-5), 4.34 (1H, dd, *J* 8.5, *J′* 6.5, H-4$_{exo}$), 6.35 (1H, s, H-2), 7.30–7.50 (5H, m, ArH); δ_C (50.3 MHz, $CDCl_3$) 38.70 (C-6), 52.94 (C-7), 54.90 (O*C*H$_3$), 62.86 (C-5), 72.43 (C-4), 86.88 (C-2), 126.14, 128.66, 128.86 and 138.61 (ArC), 168.28, 168.48, 175.10 (3 × CO); *m*/*z* (CI) 334 (M + H$^+$, 100%), 228 (5), 201 (7), 172 (12), 144 (7), 105 (9).

(2*R*,5*S*,6*R*,7*S*)-6-[Bis(methoxycarbonyl)methyl]-8-oxo-2-phenyl-7-phenylselenyl-3-oxa-1-azabicyclo[3.3.0]octane 4b

A mixture of vinyl selenide **2b** (0.050 g, 0.14 mmol), dimethyl malonate (28 mg, 0.21 mmol), sodium amide (6 mg, 0.14 mmol) and DMPU (1 cm^3) in THF (10 cm^3) was refluxed for 5 h under

nitrogen. The mixture was quenched with cold water (10 cm^3), extracted with EtOAc, and the organic phase washed with brine (10 cm^3). The organic fractions were dried ($MgSO_4$) and concentrated *in vacuo* to afford the crude product as a pale yellow oil; initial purification by bulb-to-bulb distillation (100 °C, 1 mmHg) gave a thick, dark oil. The product was isolated by flash column chromatography (EtOAc–petrol 3:7, R_f 0.4) to give the major product **4b** as a colourless solid (0.025 g, 45%). Mp 140–142 °C (Found: C, 56.7; H, 4.55. $C_{23}H_{22}NO_6Se$ requires C, 57.6; H, 4.68%); $\nu_{max}(CHCl_3)/cm^{-1}$ 1189, 1438, 1708, 1735, 1755; δ_H (500 MHz, $CDCl_3$) 2.68–2.73 (1H, m, H-6), 2.99 (1H, dd, *J* 8.5, *J′* 8.5, H-4$_{endo}$), 3.73 (3H, s, OCH_3), 3.76 (1H, d, *J* 7.5, C*H*(CO_2Me)$_2$), 3.80 (3H, s, OCH_3), 3.96 (1H, m, H-5), 4.15 (1H, d, *J* 10.0, H-7), 4.23 (1H, dd, *J* 8.5, *J′* 8.5, H-4$_{exo}$), 6.18 (1H, s, H-2), 7.30–7.43 (8H, m, ArH), 7.68 (2H, m, ArH); δ_C (125.7 MHz, $CDCl_3$) 43.97, 48.51 (C-6), 52.91, 52.98 (C-7), 60.29 (C-5), 72.63 (C-4), 87.20 (C-2), 125.94, 126.19, 128.43, 128.70, 129.27, 129.38, 136.56 and 138.20 (ArC), 167.96, 172.20 (2 × CO); *m*/*z* 490 ($M + H^+$, 70%), 334 (90), 202 (100).

(+)-(2*R*,5*S*,6*R*,7*S*)-6-[Bis(methoxycarbonyl)methyl]-7-ethoxycarbonyl-8-oxo-2-phenyl-3-oxa-1-azabicyclo[3.3.0]octane 4c

Dimethyl malonate (0.31 mg, 2.3 mmol) was added to a suspension of sodium amide (47 mg, 1.2 mmol) in dry THF (30 cm^3) and DMPU (2 cm^3) and the mixture stirred at rt for 5 min. Alkene **2c** (0.32 g, 1.2 mmol) in THF (5 cm^3) was added and the mixture heated at reflux for 3 h. The reaction was quenched by pouring the mixture into NH_4Cl(aq)–MeOH (100 cm^3, 1:1) and the aqueous portion extracted with EtOAc (2 × 20 cm^3). Organic extracts were combined, washed with water and brine, dried ($MgSO_4$) and the solvent removed *in vacuo* to give an oil which was purified by silica chromatography (petrol–EtOAc 3:1) to give the desired product **4c** (0.14 g, 30%). R_f 0.1 (petrol–EtOAc 2:1); $[\alpha]_D$ +79.6 (*c* 1.5 in $CHCl_3$); $\nu_{max}(CHCl_3)/cm^{-1}$ 1737 (s), 1714 (s), 1602 (m); δ_H (500 MHz, $CDCl_3$) 1.35 (3H, t, *J* 7, CH_2CH_3), 3.37–3.42 (1H, m, H-6$_{endo}$), 3.61 (1H, d, *J* 8.5, C*H*(CO_2Me)$_2$), 3.73 (3H, s, OCH_3), 3.77 (3H, s, OCH_3), 3.81–3.89 (1H, m, H-4$_{endo}$), 3.87 (1H, t, *J* 9.5, H-7), 3.96–4.00 (1H, m, H-5), 4.20–4.35 (2H, m, CH_2CH$_3$), 4.42 (1H, dd, *J* 8.5 and 6, H-4$_{exo}$), 6.33 (1H, s, H-2), 7.31–7.38 (3H, m, Ar*H*), 7.42–7.46 (2H, m, Ar*H*); δ_C (50.3 MHz, $CDCl_3$) 14.02 (CH_2CH_3), 41.24 (C-6), 52.93 and 55.98 (C-7 and C-9), 53.66 (CO_2CH_3), 61.04 (C-5), 62.10 (CH_2CH_3), 72.66 (C-4), 87.07 (C-2), 126.1, 128.7 and 129.0 (Ar*C*H), 138.3 (Ar*C*), 168.0, 168.2, 168.4 and 170.3 (4 × *C*O); *m*/*z* (CI(NH_3)) 406 (MH^+, 100%), 274 (31), 150 (43), 133 (14); HRMS 406.1502. $C_{20}H_{24}NO_8$ (MH^+) requires 406.1502.

(+)-(2*R*,5*S*,6*S*,7*S*)-7-Benzyl-6-[bis(methoxycarbonyl)methyl]-8-oxo-2-phenyl-3-oxa-1-azabicyclo[3.3.0]octane 4d

Lactam **4a** (0.15 g, 0.5 mmol) in THF (5 cm^3) was added dropwise to a pre-cooled LDA (0.9 cm^3, 1.6 mmol ml^{-1}, 1.4 mmol) in THF (5 cm^3) at −78 °C and stirred for 1 h. To this mixture was added a solution of benzyl bromide (0.077 g, 0.5 mmol) in THF (3 cm^3) and the mixture was stirred for 2 h at −78 °C. The mixture was quenched with cold water, diluted with EtOAc (30 cm^3) and washed with water (2 × 25 cm^3). The crude product was purified by flash column chromatography (EtOAc–hexane 1:1) to give the title compound **4d** (0.071 g, 37%). Mp 108–109 °C; R_f 0.8 (Found: C, 67.8; H, 5.8; N, 3.3. $C_{24}H_{25}NO_6$ requires C, 68; H, 6.0; N, 3.3%); $[\alpha]_D$ (*c* 0.06 in $CHCl_3$) +126.7; $\nu_{max}(CHCl_3)/cm^{-1}$ 2980 (m), 1750 (m), 1734 (s), 1707 (s), 1225 (s); $\lambda_{max}(CHCl_3)$/nm 265 (log ε 1.9); δ_H (200 MHz, $CDCl_3$) 2.6 (1H, m, H-6), 3.0 (1H, m, H-4$_{endo}$), 3.05 (2H, m, CH_2Ph), 3.2 (1H, m, H-7), 3.35 (1H, d, *J* 8.8, CH(CO_2Me)$_2$), 3.75 (6H, s, 2 × CH_3), 4.0 (1H, m, H-4$_{exo}$), 4.2 (1H, m, H-5), 6.3 (1H, s, H-2), 7.2–7.5 (10H, m, ArH); δ_C (50 MHz, $CDCl_3$) 35.4 (PhCH_2), 41.3 (C-6), 49.5 (C-7), 53.2 (*C*H(CO_2Me)$_2$), 52.7 and 52.8 (2 × *C*H_3), 60.2 (C-5), 72.4 (C-4), 86.9 (C-2), 126.1, 126.1, 128.6, 128.7, 128.9, 129.7, 138.1, 138.7 (ArC), 168.3, 168.7 and 176.7 (3 × CO); *m*/*z* (CI(NH_3)) 424 ($M + H^+$, 100%), 291 (10), 262 (12), 105 (12), 91(28).

Attempted tandem Michael-trapping reaction of enone 2c

Dimethyl malonate (522 mg, 3.94 mmol) was added to a suspension of sodium amide (81 mg, 1.97 mmol) in dry THF (30 cm^3) and DMPU (2 cm^3) and the mixture was stirred at rt for 5 min. Enone **2c** (539 mg, 1.97 mmol) in THF (5 cm^3) was added *via* syringe and the mixture heated at reflux for 3 h. The mixture was cooled, benzyl bromide (338 mg, 1.97 mmol) was added and stirring was continued at rt for 2.5 h. The reaction was quenched by pouring the mixture into NH_4Cl(aq)–MeOH (100 cm^3, 1:1) and the aqueous portion extracted with EtOAc (2 × 20 cm^3). Organic extracts were combined, washed with water and brine, dried ($MgSO_4$) and the solvent removed *in vacuo* to give a yellow oil. Analysis by ^1H NMR spectroscopy indicated the presence of three products in a ratio of 8:5:1, and these were isolated by silica chromatography (petrol–EtOAc 3:1) as malonate adduct **4c** (0.29 g, 37%), and the benzyl derivatives **6a**,**b**.

Data for **6a**: 0.25 g, 34%; R_f 0.3 (petrol–EtOAc 2:1); $\nu_{max}(CHCl_3)/cm^{-1}$ 1719 (s), 1704 (s), 1222 (s); δ_H (500 MHz, $CDCl_3$) 1.27 (3H, t, *J* 7, CH_3), 3.38–3.39 (2H, m, CH_2Ph), 4.18–4.26 (2H, m, CH_2CH$_3$), 4.33 (1H, dd, *J* 13.5 and 2, H-4), 4.54 (1H, dd, *J* 13.5 and 2, H-4), 5.03 (1H, t, *J* 2, H-6), 5.89 (1H, s, H-2), 7.19–7.30 (6H, m, ArH), 7.37–7.44 (4H, m, ArH); *m*/*z* (CI(NH_3)) 364 (MH^+, 100%).

Data for **6b**: 0.051 g, 7%; R_f 0.2 (petrol–EtOAc 2:1); δ_H (200 MHz, $CDCl_3$) 1.32 (3H, t, *J* 7, CH_3), 3.34–3.38 (2H, m, CH_2Ph), 4.15–4.33 (2H, m, CH_2CH$_3$), 4.37–4.66 (2H, m, H-4), 5.11–5.15 (1H, m, H-6), 6.78–6.85 (2H, m, ArH), 7.09–7.43 (8H, m, ArH).

(+)-(2*R*,5*S*,6*R*,7*S*)-7-Ethoxycarbonyl-6-[tris(ethoxycarbonyl)-methyl]-8-oxo-2-phenyl-3-oxa-1-azabicyclo[3.3.0]octane 5a

To enone **2c** (0.19 g, 0.71 mmol) under N_2(g) was added triethyl methanetricarboxylate (0.20 g, 0.85 mmol), tetrabutylammonium hydrogen sulfate (12 mg, 0.035 mmol), toluene (3 cm^3) and anhydrous potassium carbonate (29 mg, 0.21 mmol). The mixture was stirred at rt for 40 min and then at 60 °C for 4 h. After cooling to rt, water (5 cm^3) was added and this mixture was extracted with diethyl ether (2 × 10 cm^3). The combined organic phases were washed with brine (10 cm^3), dried ($MgSO_4$) and evaporated *in vacuo* to give an orange oil. Purification using flash column chromatography (EtOAc–light petroleum 1:3) yielded **5a** as a colourless oil as a single diastereomer (0.22 g, 61%). R_f 0.24; $[\alpha]_D^{25}$ +57.12 (*c* 0.55 in $CHCl_3$) (Found: C, 59.44; H, 6.46; N, 2.68. $C_{25}H_{31}NO_{10}$ requires C, 59.40; H, 6.18; N, 2.77%); ν_{max}(film)/cm^{-1} 1737 (s), 1714 (s); δ_H (200 MHz, $CDCl_3$) 1.23 (9H, t, *J* 7.0, 3 × CH_3), 1.34 (3H, t, *J* 7.0, CH_3CH$_2$), 3.63 (1H, dd, *J* 7.5 and 4.5, H-6), 3.75 (1H, t, *J* 8.5, H-4$_{endo}$), 4.00–4.10 (2H, m, H-5 and H-7), 4.19–4.37 (8H, m, 4 × OCH_2), 4.43 (1H, dd, *J* 8.0 and 6.0, H-4$_{exo}$), 6.32 (1H, s, H-2), 7.30–7.45 (5H, m, Ar*H*); δ_H (500 MHz, C_6D_6) 0.79 (9H, t, *J* 7.0, 3 × CH_3), 1.05 (3H, t, *J* 7.0, CH_3CH$_2$), 3.86 (6H, q, *J* 7.0, 3 × OCH_2CH$_3$), 3.89 (1H, t, *J* 8.0, H-4$_{endo}$), 4.00 (1H, dd, *J* 7.5 and 4.0, H-6), 4.05–4.19 (2H, 2 × dq, *J* 11.0 and 7.0, CH_3CH_2), 4.26–4.29 (1H, m, H-5), 4.46 (1H, d, *J* 7.5, H-7), 4.52 (1H, dd, *J* 8.0 and 6.0, H-4$_{exo}$), 6.55 (1H, s, H-2), 6.99–7.08 (3H, m, Ar*H*), 7.51–7.53 (2H, dd, *J* 8.5 and 1.5, ArC*H ortho*- to C(9)); δ_C (50.3 MHz, $CDCl_3$) 13.6 (3 × *C*H_3), 14.0 (*C*H_3CH$_2$), 42.4 (C-6), 55.9 (C-7), 61.1 (C-5), 62.1 (CH_3CH_2), 63.0 (C(CO_2-*C*H_2CH$_3$)$_3$), 67.8 (*C*(CO_2Et)$_3$), 72.5 (C-4), 87.4 (C-2), 126.0, 128.6 and 128.9 (Ar*C*H), 138.6 (C-9), 166.1, 169.6 and 171.7 (3 × *C*O); *m*/*z* (CI(NH_3)) 506 ($M + H^+$, 100%), 274 (77), 250 (76), 233 (63).

(2*R*,5*S*,6*R*,7*S*)-7-Ethoxycarbonyl-6-[cyano(methoxycarbonyl)-methyl]-8-oxo-2-phenyl-3-oxa-1-azabicyclo[3.3.0]octane 5b

To a stirred suspension of $NaNH_2$ (80–90%, 34 mg, 0.74 mmol) in THF (5 cm^3) and DMPU (2 cm^3) was added methyl cyanoacetate (0.146 g, 1.47 mmol). After 5 min at rt, enone **2c** (0.201 g, 0.735 mmol) in THF (17 cm^3) was added. After 10 min the mixture was heated at reflux for 20 min and then cooled to rt. Water (30 cm^3) was added and, following extraction of the solution with EtOAc (3 × 50 cm^3), the organics were dried ($MgSO_4$) and evaporated *in vacuo*. Purification using flash column chromatography (EtOAc–light petroleum, 1 : 2) gave the product **5b** as a pale yellow, viscous gum (0.15 g, 54%) consisting of four diastereomers in a ratio of 48 : 41 : 9 : 2. Only NMR spectroscopic data for the major diastereomer (A) and the next major diastereomer (B) are quoted. R_f 0.24 (EtOAc–light petroleum 1 : 2) (Found: C, 61.50; H, 5.65; N, 7.36. $C_{19}H_{20}N_2O_6$ requires C, 61.28; H, 5.41; N, 7.52%); $\nu_{max}(CHCl_3)/cm^{-1}$ 2254 (w), 1753 (s), 1722 (s); δ_H (500 MHz, C_6D_6) 1.03–1.09 (6H, m, CH_3CH_2, (A and B)), 2.68 (1H, d, *J* 8.5, H-7 (B) or H-10 (B)), 2.82 (1H, d, *J* 8.0, H-7 (A), or H-10 (A)), 3.06 (3H, s, CO_2CH_3 (B)), 3.10 (3H, s, CO_2CH_3 (A)), 3.20–3.29 (2H, m, H-6 (A and B)), 3.31–3.38 (3H, m, H-4_{endo} (A), H-4_{endo} (B) and H-5 (B)), 3.51 (1H, dd, *J* 13.5 and 7.0, H-5 (A)), 3.58 (1H, d, *J* 10.8, H-7 (A) or H-10 (A)), 3.65 (1H, d, *J* 10.0, H-7 (B) or H-10 (B)), 3.96–4.17 (6H, m, H-4_{exo} (A and B) and CH_3CH_2 (A and B)), 6.26 (1H, s, H-2 (A)), 6.34 (1H, s, H-2 (B)), 7.06–7.14 (6H, m, Ar*H*, (A and B)), 7.44–7.48 (4H, m, *o*-Ar*H*, (A and B)); δ_C (50.3 MHz, $CDCl_3$) 13.9 and 14.0 (CH_3CH_2), 39.2 (C-6), 42.3 (C-7), 54.1 (CO_2CH_3), 55.2 and 55.5 (C-5), 59.83 and 60.8 (C-10), 62.5 (CH_3CH_2), 71.3 and 71.6 (C-4), 87.3 and 87.5 (C-2), 114.3 (*C*N), 126.2, 128.8 and 129.2 (Ar*C*H), 137.5 (C-9), 164.9, 167.5, 167.8, 168.9 and 169.8 (*C*O); *m*/*z* (CI(NH_3)) 390 (M + NH_4^+, 12%), 373 (M + H^+, 53), 291 (23), 274 (100).

(2*R*,5*S*,6*R*,7*S*)-7-Ethoxycarbonyl-6-[ethoxycarbonyl(acetyl)-methyl]-8-oxo-2-phenyl-3-oxa-1-azabicyclo[3.3.0]octane 5c

To a stirred solution of enone **2c** (0.16 g, 0.59 mmol) and ethyl acetoacetate (0.077 g, 0.59 mmol) in ethanol (5 cm^3) at rt was added activated barium hydroxide (*ca*. 10 mol%, 11 mg, activated by heating barium hydroxide octahydrate at 200 °C for 3.5 h). After 24 h, hydrochloric acid (1 M, aq.) was added to bring the acidity of the mixture to pH 4. Water (30 cm^3) was added and the mixture was then extracted with EtOAc (3 × 20 cm^3) and the organics washed with brine, dried ($MgSO_4$), and evaporated *in vacuo* to give a yellow oil. Purification using flash column chromatography (EtOAc–light petroleum 1 : 3) gave the product **5c** as a colourless oil (0.17 g, 72%), consisting of four diastereomers in an approximate ratio of 1 : 1 : 4.5 : 4.5. Only the NMR spectroscopic data for the two major diastereomers (A and B) are quoted. R_f 0.30 (EtOAc–light petroleum 1 : 3) (Found: C, 62.74; H, 6.38; N, 3.39. $C_{21}H_{25}NO_7$ requires C, 62.52; H, 6.25; N, 3.47%); $\nu_{max}(CHCl_3)/cm^{-1}$ 1718 (s), 1740 (s), 700 (m); δ_H (500 MHz, $CDCl_3$) 1.29–1.32 (12H, m, 2 × CH_3CH_2 (A and B)), 2.27 (6H, s, CH_3CO (A and B)), 3.33–3.41 (2H, m, H-6 (A and B)), 3.69 (2H, d, *J* 9.0, H-7 or C(10)*H* (A and B)), 3.74–3.77 (2H, m, H-5 (A) and H-7 (A) or H-10 (A)), 3.79 (1H, d, *J* 9.6, H-7 (A) or H-10 (A)), 3.84–3.89 (2H, m, H-4 (A and B)), 3.96–4.00 (1H, m, H-5 (B)), 4.16–4.34 (8H, m, 2 × CH_3CH_2 (A and B)), 4.44 (2H, dd, *J* 8.5 and 6.0, H-4 (A and B)), 6.31 (1H, s, H-2 (B)), 6.32 (1H, s, H-2 (A)), 7.31–7.45 (10H, m, Ar*H* (A and B)); δ_C (50.3 MHz, $CDCl_3$) 13.8, 13.9 and 14.1 (CH_3CH_2), 29.5 and 29.6 (CH_3CO), 10.3 and 10.5 (C-6), 56.1 and 56.2 (C-10), 60.9, 61.5, 61.9, 62.0, 62.1, 62.4 and 62.5 (C-5, C-7 and CH_3CH_2), 72.9 (C-4), 87.0 (C-2), 126.1, 128.7 and 129.0 (ArCH), 138.5 and 138.6 (C-9), 167.7, 168.1, 168.7, 170.4 and 170.8 (*C*O), 201.5 (CH_3CO); *m*/*z* (CI(NH_3)) 404 (M + H^+, 100%), 274 (10).

General method of Reformatsky reagent conjugate addition

Activated zinc powder and iodine (20 mol% of the enone) were placed in a round-bottom flask under an inert atmosphere. The specified solvent (usually THF) and then the bromoester were added and the contents subjected to sonication (decolouration of brown I_2 occurred). A solution of enone **2c** in the specified solvent was then added *via* cannula, keeping the contents at the specified temperature. Sonication may have then been continued at the specified temperature for a further 15 min. The reaction was quenched by adding a mixture of water and ice and stirring for 5 min or until the ice had melted. Ammonium chloride solution (sat. aq.) was then added to dissolve the precipitate, if formed, and the mixture then extracted with ethyl acetate or DCM. Drying ($MgSO_4$) and evaporation *in vacuo* gave the crude product as a liquid or oil which was purified by flash column chromatography to yield the product as a mixture of diastereomers.

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

Method 1. A solution of enone **2c** (0.16 g, 0.59 mmol) and ketene silyl acetal **7** (0.20 g, 0.88 mmol) in CH_3CN (5 cm^3) was stirred at 55 °C for 1 h. Another aliquot of acetal (74 mg) was then added, and after 30 min the solvent was evaporated *in vacuo*. Purification by flash column chromatography (EtOAc–petrol (40–60) 1 : 4) gave the title compound **5d** as a colourless oil (0.11 g, 47%) having a diastereomeric composition of **8a** : **8b**, 8 : 1.

Method 2. Following the general procedure, *tert*-butyl bromoacetate (5.4 g, 28 mmol), zinc (3.0 g, 46 mmol) and iodine (0.23 g, 1.8 mmol) were sonicated at 35–40 °C in THF (75 cm^3) for 15 min. After stirring for 30 min at rt, DMPU (12 cm^3) was added, followed by a solution of enone **2c** (2.5 g, 9.2 mmol) in THF (20 cm^3) at 0 °C. The mixture was quickly brought to 35–40 °C by careful heating and was then sonicated for 15 min at this temperature. After stirring at rt for 30 min the reaction was worked-up and extracted with EtOAc to give an orange liquid. Dry flash chromatography (EtOAc–petrol (40–60) 1 : 3) partially removed the DMPU to give an orange liquid. Further purification using flash column chromatography (EtOAc–petrol (40–60) 2 : 7) gave the title compound as a colourless oil consisting of two diastereomers (**5d** : **8a**, 6 : 1) (2.8 g, 77%), with a de ⩾98% at position C-6. R_f 0.13 (EtOAc–light petroleum 1 : 5) (Found: C, 65.55; H, 7.03; N, 3.39. $C_{21}H_{27}NO_6$ requires C, 64.77; H, 6.99; N, 3.60%); $\nu_{max}(CHCl_3)/cm^{-1}$ 1718 (s), 1370 (s), 1154 (s); δ_H (500 MHz, C_6D_6) (major diastereomer, **5d**) 1.03 (3H, t, *J* 7.0, CH_3CH_2), 1.25 (9H, s, $C(CH_3)_3$), 1.81 (1H, dd, *J* 16.5 and 9.5, $CHHCO_2{}^tBu$), 2.12 (1H, dd, *J* 16.5 and 5.5, $CHHCO_2{}^tBu$), 3.01–3.06 (1H, m, H-6), 3.27 (1H, d, *J* 10.5, H-7), 3.26–3.31 (1H, m, H-5), 3.56 (1H, t, *J* 8.5, H-4_{endo}), 3.99–4.13 (2H, 2 × dq, *J* 11.0 and 7.0, CH_2CH_3), 4.16 (1H, dd, *J* 8.5 and 6.0, H-4_{exo}), 6.37 (1H, s, H-2), 7.05–7.16 (3H, m, ArH), 7.53–7.55 (2H, m, ArH); δ_H (500 MHz, $CDCl_3$) 1.34 (3H, t, *J* 7.0, CH_3CH_2), 1.44 (9H, s, $C(CH_3)_3$), 2.45 (1H, dd, *J* 16.5 and 10.0, $CHHCO_2{}^tBu$), 2.61 (1H, dd, *J* 16.5 and 4.5, $CHHCO_2{}^tBu$), 3.04–3.10 (1H, m, H-6), 3.61 (1H, d, *J* 11.0, H-7), 3.84–3.88 (2H, m, H-4_{endo} and H-5), 4.22–4.35 (2H, 2 × dq, *J* 11.0 and 7.0, CH_3CH_2), 4.39–4.43 (1H, m, H-4_{exo}), 6.32 (1H, s, H-2), 7.31–7.38 (3H, m, ArH), 7.44–7.46 (2H, m, ArH); δ_C (50.3 MHz, $CDCl_3$) (major diastereomer, **5d**) 14.0 (CH_2CH_3), 27.9 ($CH_3)_3C$), 38.3 ($CH_2CO_2{}^tBu$), 39.4 (C-6), 57.3 (C-7), 61.9 (CH_2CH_3), 62.7 (C-5), 72.4 (C-4), 81.6 ($C(CH_3)_3$), 86.9 (C-2), 126.2, 128.6 and 128.9 (Ar*C*H), 138.4 (C-9), 168.6 and 170 (3 × *C*O); δ_H (250 MHz, $CDCl_3$) (minor diastereomer, **8a**) 1.31 (3H, t, *J* 7.0, CH_3CH_2), 1.44 (9H, s, $C(CH_3)_3$), 2.48 (1H, dd, *J* 16.5 and 10.0, $CHHCO_2{}^tBu$), 2.62 (1H, dd, *J* 16.5 and 6.0, $CHHCO_2{}^tBu$), 2.81–2.93 (1H, m, H-6), 3.72 (1H, d, *J* 8.5, H-7), 3.79 (1H, dd, *J* 8.0 and 6.5, H-4), 4.14 (1H, q, *J* 7.0, H-5), 4.20–4.28 (3H, m,

CH_3CH_2 and H-4), 6.34 (1H, s, H-2), 7.32–7.47 (5H, m, ArH); *m/z* (CI(NH_3)) 390 (M + H^+, 100%), 334 (46).

A minor amount (8 mg) of **8b** was isolated. R_f 0.17 (EtOAc–petrol (40–60) 1:4); ν_{max}(film)/cm^{-1} 1724 (s), 1368 (m), 1259 (m), 1224 (m), 1154 (s), 700 (w); δ_H (500 MHz, $CDCl_3$) 1.33 (3H, t, *J* 7.0, CH_3CH_2), 1.46 (9H, s, $C(CH_3)_3$), 2.45 (1H, dd, *J* 16.5 and 9.0, $CHHCO_2{}^tBu$), 2.52 (1H, dd, *J* 16.5 and 7.0, $CHHCO_2{}^tBu$), 3.32 (1H, d, *J* 6.5, H-7), 3.39–3.44 (1H, m, H-6), 3.56 (1H, t, *J* 8.5, H-4), 4.08 (1H, dd, *J* 8.5 and 6.5, H-4), 4.27 (2H, q, *J* 7.0, CH_3CH_2), 4.34–4.38 (1H, m, H-5), 6.34 (1H, s, H-2), 7.33–7.39 (3H, m, ArH), 7.43–7.46 (2H, m, Ar*H*); δ_C (125.8 MHz, $CDCl_3$) 14.09 (CH_3CH_2), 27.97 ($C(CH_3)_3$), 33.77 and 35.99 (C-4 and $CH_2CO_2{}^tBu$), 56.13, 59.94, 61.85 and 62.09 (C-4, C-5, C-7 and CH_3CH_2), 81.71 ($C(CH_3)_3$), 87.78 (C-2), 125.89, 128.44 and 128.69 (Ar*C*H), 138.05 (C-9), 168.21, 170.04 and 172.54 (3 × *C*O); *m/z* (APCI$^+$) 390 (M + H^+, 19%), 334 (100); HRMS (CI$^+$) 390.1917. $C_{21}H_{28}NO_6$ requires 390.1917.

Epimerisation experiments on the adduct 5d

Preparative HPLC {33 × 4.6 mm 5 Micron ABZ+PLUS, mobile phase A [H_2O + 0.1% (v/v) formic acid], mobile phase B [95:5 (v/v) MeCN–H_2O + 0.07% formic acid], gradient (0 to 100% B in 3.5 min holding for 1.0 min then returned to 0% B over 0.2 min), 3.0 ml min^{-1}} was used to partially separate the two diastereomers **5d** and **8a**. A sample enriched in the minor diastereomer (**5d**:**8a**, 1:5) was found after 8 days to have a ratio of **5d**:**8a**, 1:1, and on treatment with NaH (excess) in THF for 2 h at rt, quenching with water–MeOH, 1:1 at rt, and extraction with EtOAc, drying ($MgSO_4$) and evaporation *in vacuo*, a ratio of **5d**:**8a**, 6:1 was obtained. A sample of **5d**:**8a**, 15:1 was shown to have a ratio of **5d**:**8a**, 11:1 after standing in $CDCl_3$ for 3 days.

(2*R*,5*S*,6*S*,7*S*)-7-Ethoxycarbonyl-6-ethoxycarbonylmethyl-8-oxo-2-phenyl-3-oxa-1-azabicyclo[3.3.0]octane 5e

Following the general Reformatsky addition procedure, ethyl bromoacetate (0.14 g, 0.85 mmol), zinc (84 mg, 1.2 mmol) and iodine (18 mg, 0.14 mmol) were sonicated at 35 °C in dioxane (5 cm^3) for 5 min. A solution of enone **2c** (0.19 g, 0.71 mmol) in dioxane (5 cm^3) was then added and sonication was continued for 10 min. After standing for 18.5 h the mixture was worked-up and extracted with DCM to give a dark yellow oil. Purification using flash column chromatography (EtOAc–light petroleum 2:5) gave a colourless oil consisting of mostly one diastereomer. R_f 0.33 (EtOAc–light petroleum 2:5) (Found: C, 62.89; H, 6.34; N, 3.73. $C_{19}H_{23}NO_6$ requires C, 63.15; H, 6.42; N, 3.88%); ν_{max}($CHCl_3$)/cm^{-1} 1729 (s), 700 (m); δ_H (500 MHz, $CDCl_3$) 1.26 (3H, t, *J* 7.0, OCH_2CH_3), 1.33 (3H, t, *J* 7.0, OCH_2CH_3), 2.53 (1H, dd, *J* 17.0 and 10.0, $CHHCO_2Et$), 2.68 (1H, dd, *J* 17.0 and 5.0, $CHHCO_2Et$), 3.07–3.13 (1H, m, H-6), 3.64 (1H, d, *J* 11.0, H-7), 3.84–3.89 (2H, m, H-4_{endo} and H-5), 4.12–4.17 (2H, m, OCH_2CH_3), 4.23–4.34 (2H, m, $CO_2CH_2CH_3$), 4.38–4.43 (1H, m, H-4_{exo}), 6.32 (1H, s, H-2), 7.31–7.45 (5H, m, ArH); δ_C (50.3 MHz, $CDCl_3$) 14.1 (2 × CH_2CH_3), 37.1 (CH_2CO_2Et), 39.5 (C-6), 47.3 (C-7), 61.1 and 62.0 (2 × OCH_2CH_3), 62.7 (C-5), 72.3 (C-4), 86.8 (C-2), 126.0, 128.5 and 128.8 (Ar*C*H), 138.1 (C-9), 168.1, 170.1 and 171.0 (3 × *C*O); *m/z* (CI(NH_3)) 379 (M + NH_4^+, 3%), 362 (100).

(2*R*,5*S*,6*R*,7*S*)-7-Ethoxycarbonyl-6-[1-(methoxycarbonyl)-ethyl]-8-oxo-2-phenyl-3-oxa-1-azabicyclo[3.3.0]octane 5f

Following the general procedure, methyl (±)-2-bromopropionate (0.26 g, 1.6 mmol), zinc (0.17 mg, 2.6 mmol) and iodine (13 mg, 0.10 mmol) were sonicated at 0–5 °C in THF (6 cm^3) for 7 min. A solution of the enone **2c** in THF (2 cm^3) was then added over 10 min, washing out the flask with THF (2 cm^3). The mixture was then sonicated for 15 min at 0–5 °C, and then worked-up, and extracted with DCM to give a grey transparent oil. Purification using flash column chromatography (EtOAc–petrol (40–60) 1:3) gave incompletely separated diastereomers.

Diastereomer A. ν_{max}(film)/cm^{-1} 2982 (m), 1739 (s), 1712 (s), 1456 (m), 1369 (m), 1267 (s), 1181 (s), 702 (m); δ_H (500 MHz, $CDCl_3$) 1.22 (3H, d, *J* 7.0, CH_3CH), 1.34 (3H, t, *J* 7.0, CH_3CH_2), 2.63–2.68 (1H, m, H-10), 3.00–3.05 (1H, m, H-6), 3.66 (3H, s, CO_2CH_3), 3.76 (1H, t, *J* 8.0, H-4_{endo}), 3.80 (1H, d, *J* 10.5, H-7), 3.87–3.92 (1H, m, H-5), 4.21–4.35 (3H, m, CH_3CH_2 and H-4_{exo}), 6.32 (1H, s, H-2), 7.33–7.38 (3H, m, ArH), 7.44–7.45 (2H, m, ArH); δ_C (50.3 MHz, $CDCl_3$) 14.1 and 14.4 (CH_3CH_2 and CH_3CH), 41.3 (C-6), 45.4 (C-10), 51.9 (CO_2CH_3), 56.2 (C-7), 60.3 (C-5), 61.9 (CH_3CH_2), 72.1 (C-4), 86.9 (C-2), 125.90, 128.4 and 128.7 (Ar*C*H), 138.9 (C-9), 168.5, 170.8 and 174.1 (3 × *C*O); *m/z* (CI(NH_3)) 362 (M + H^+, 100%); HRMS 362.1604, $C_{19}H_{21}NO_6$ requires 362.1604.

Diastereomer B. ν_{max}(film)/cm^{-1} 2982 (m), 1735 (s), 1713 (s), 1456 (m), 1372 (m), 1264 (s), 1205 (s), 1177 (s), 702 (m); δ_H (500 MHz, $CDCl_3$) 1.20 (3H, d, *J* 7.0, CH_3CH), 1.35 (3H, t, *J* 7.0, CH_3CH_2), 2.63–2.69 (1H, m, H-10), 3.02–3.07 (1H, m, H-6), 3.69 (1H, d, *J* 10.5, H-7), 3.71 (3H, s, CO_2CH_3), 3.80 (1H, t, *J* 8.0, H-4_{endo}), 3.85–3.89 (1H, m, H-5), 4.24–4.36 (3H, m, CH_3CH_2 and H-4_{exo}), 6.32 (1H, s, H-2), 7.33–7.38 (3H, m, ArH), 7.44–7.45 (2H, m, ArH); δ_C (125.8 MHz, $CDCl_3$) 14.10 and 15.58 (CH_3CH_2 and CH_3CH), 42.92 (C-6), 45.56 (C-10), 52.05 (CO_2CH_3), 56.69 (C-7), 61.68 (C-5), 61.97 (CH_3CH_2), 72.42 (C-4), 86.85 (C-2), 125.90, 128.42 and 128.71 (Ar*C*H), 138.08 (C-9), 168.81, 170.50 and 174.50 (3 × *C*O); *m/z* (CI(NH_3)) 362 (M + H^+, 100%); HRMS 362.1609, $C_{19}H_{21}NO_6$ requires 362.1604.

(2*R*,5*S*,6*R*,7*S*)-7-Ethoxycarbonyl-6-[(methoxycarbonyl)(phenyl)]methyl-8-oxo-2-phenyl-3-oxa-1-azabicyclo[3.3.0]octane 5g

Following the general procedure, methyl (±)-α-bromophenylacetate (0.37 g, 1.62 mmol), zinc (0.18 mg, 2.71 mmol) and iodine (14 mg, 0.11 mmol) were sonicated at −6 °C (ice–brine bath) in THF (6 cm^3) for 4 min. A solution of the enone **2c** in THF (2 cm^3) was then added over 10 min at −10 °C, washing out the flask with THF (2 cm^3). Stirring was continued at −10 to −6 °C for 30 min and then at rt for 2 min. The reaction was worked-up, using DCM for extraction, to give a grey gelatinous solid. Purification using flash column chromatography (EtOAc–petrol (40–60) 1:3) gave incompletely separated diastereomers (20 mg, 9%) and (100 mg, 44%).

Diastereomer A. ν_{max}(film)/cm^{-1} 1734 (s), 1708 (s), 753 (m), 701 (m); δ_H (500 MHz, C_6D_6) 0.74 (3H, t, *J* 7.0, CH_3CH_2), 3.07 (3H, s, CO_2CH_3), 3.09 (1H, d, *J* 11.5, H-7), 3.25 (1H, d, *J* 10.5, H-11), 3.46–3.50 (1H, m, H-5), 3.56–3.72 (3H, m, H-6, overlap with 2 × dq, *J* 11.0 and 7.0, CH_3CH_2), 3.80 (1H, t, *J* 8.5, H-4_{endo}), 4.36 (1H, dd, *J* 8.5 and 6.0, H-4_{exo}), 6.41 (1H, s, H-2), 6.92–7.18 (8H, m, ArH), 7.61–7.62 (2H, m, Ar*H*); δ_C (125.8 MHz, $CDCl_3$) 13.85 (CH_3CH_2), 45.85 (C-6), 52.50 (OCH_3), 55.73 (C-7), 57.00 (C-11), 61.55 (CH_3CH_2), 62.33 (C-5), 72.68 (C-4), 86.87 (C-2), 125.94, 126.57, 128.30, 128.37, 128.45, 128.74 and 129.02 (Ar*C*H), 135.24 (C-10), 138.27 (Ar*C*), 168.15, 170.45 and 172.58 (3 × *C*O); *m/z* (CI(NH_3)) 424 (M + H^+, 100%), 352 (3), 244 (13); HRMS 424.1759, $C_{24}H_{26}NO_6$ requires 424.1760.

Diastereomer B. ν_{max}(film)/cm^{-1} 1738 (s), 1711 (s), 702 (m), 666 (m); δ_H (500 MHz, C_6D_6) 1.12 (3H, t, *J* 7.0, CH_3CH_2), 3.09 (1H, t, *J* 7.5, H-4), 3.14 (1H, d, *J* 11.0, H-7), 3.18 (3H, s, CO_2CH_3), 3.21–3.25 (2H, m, H-4 and H-5), 3.50–3.55 (1H, m, H-6), 3.58 (1H, d, *J* 10.0, H-11), 4.13–4.23 (2H, 2 × dq, *J* 11.0 and 7.0, CH_3CH_2), 6.35 (1H, s, H-2), 6.93–7.12 (8H, m, ArH), 7.50 (2H, dd, *J* 8.5 and 1.5, ArH); δ_C (50.3 MHz, $CDCl_3$)

14.1 (CH_3CH_2), 46.5 (C-6), 52.3 (CH_3CO_2), 54.7 (C-7), 57.7 (C-11), 61.0 (C-5), 61.9 (CH_3CH_2), 71.9 (C-4), 86.9 (C-2), 126.1, 128.6, 129.0 and 129.5 (ArCH), 135.8 (C-10), 138.2 (C-9), 169.0, 170.7 and 172 (3 × CO); *m/z* (CI(NH_3)) 424 (M + H^+, 100%), 325 (3), 244 (8); HRMS 424.1760, $C_{24}H_{26}NO_6$ requires 424.1760.

General method of *N*,*O*-acetal deprotection

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

(−)-(2*S*,3*R*,4*S*)-4-Ethoxycarbonyl-2-hydroxymethyl-5-oxo-3-[tris(ethoxycarbonyl)methyl]pyrrolidine 9a

Following the general method, the adduct **5a** (0.19 g, 0.37 mmol) was reacted with TFA (0.5 cm^3) in DCM (20 cm^3) for 40 min. The solvent was removed *in vacuo* and the resultant orange liquid was purified using flash column chromatography (EtOAc–light petroleum 2:1, then EtOAc–light petroleum–MeOH 20:10:1) to give the title compound **9a** as a colourless oil (0.14 g, 93%). Recrystallisation from hot EtOAc–light petroleum gave **9c** as fine white crystals (0.097 g, 68%) as a single diastereomer. R_f 0.22 (EtOAc–light petroleum 4:1); $[a]_D^{22}$ −10.8 (*c* 1.0 in CH_3OH) (Found: C, 51.82; H, 6.53; N, 3.41. $C_{18}H_{27}NO_{10}$ requires C, 51.80; H, 6.52; N, 3.36%); mp 101 °C; ν_{max}($CHCl_3$)/cm^{-1} 3428 (w), 3440 (m), 1737 (s), 1303 (s), 1138 (s); δ_H (200 MHz, CD_3OD) 1.28 (9H, t, *J* 7.0, 3 × CH_3), 1.30 (3H, t, *J* 7.0, CH_3CH_2), 3.22 (1H, dd, *J* 4.0 and 3.0, H-3), 3.36 (1H, d, *J* 4.5, H-4), 3.57 (1H, dd, *J* 10.0 and 8.0, CHHOH), 3.67–3.73 (1H, m, H-2), 3.82–3.88 (1H, dd, *J* 10.0 and 3.0, CHHOH), 4.21 (2H, q, *J* 7.0, OCH_2), 4.26 (6H, q, *J* 7.0, 3 × OCH_2CH_3); δ_C (50.3 MHz, CD_3OD) 12.6 (3 × OCH_2CH_3), 12.9 (CH_3CH_2), 41.6 (C-3), 53.2 (C-4), 58.4 (C-2), 61.7 (OCH_2), 62.6 (3 × OCH_2), 65.4 (CH_2OH), 68.8 ($C(CO_2Et)_3$), 166.1 (4 × CO_2Et), 172.3 (CONH); *m/z* (CI(NH_3)) 418 (M + H^+, 100%), 187 (15).

(2*R*,3*S*,4*S*)-3-*tert*-Butoxycarbonylmethyl-4-ethoxycarbonyl-2-hydroxymethyl-5-oxopyrrolidine 9b

Following the general method, the Reformatsky adduct **5d** (6:1 diastereomer ratio) (44 mg, 0.11 mmol) was reacted with TFA (0.5 cm^3) in DCM (7 cm^3) for 15 min. Purification using flash column chromatography (EtOAc–light petroleum 1:2, then EtOAc–light petroleum–MeOH 20:15:2) gave the title compound **9b** as a colourless oil consisting of a 1:5 mixture of diastereomers (27 mg, 79%). R_f 0.23; ν_{max}(film)/cm^{-1} 3266 (m), 2982 (m), 1728 (s), 1367 (m), 1258 (m), 1154 (s); δ_H (300 MHz, $CDCl_3$) (major diastereomer) 1.30 (3H, t, *J* 7.0, CH_3CH_2), 1.44 (9H, s, $C(CH_3)_3$), 2.47 (1H, dd, *J* 16.0 and 7.5, CHHCO$_2$^{t}Bu), 2.50 (1H, dd, *J* 16.0 and 6.5, CHHCO$_2$^{t}Bu), 2.81–2.90 (2H, m, H-3 and OH), 3.26 (1H, d, *J* 7.0, H-4), 3.45–3.50 (1H, m, H-2), 3.63 (1H, dd, *J* 11.5 and 6.5, CHHOH), 3.77 (1H, dd, *J* 11.5 and 3.5, CHHOH), 4.24 (2H, q, *J* 7.0, CH_3CH_2), 7.16 (1H, br s, NH); δ_C (50.3 MHz, $CDCl_3$) (major diastereomer) 14.0 (CH_3CH_2), 28.0 ($C(CH_3)_3$), 36.6 (C-3), 39.0 (CH_2CO_2^{t}Bu), 54.1 (C-4), 60.1 (C-2), 61.9 (CH_3CH_2), 64.5 (CH_2OH), 81.5 ($C(CH_3)_3$), 169.8, 170.4 and 172.2 (3 × CO); *m/z* (APCI$^+$) 302 (M + H^+, 47%), 246 (100); HRMS 302.1604, $C_{14}H_{25}NO_6$ requires 302.1604.

(2*R*,5*S*,6*S*,7*S*)-6-*tert*-Butoxycarbonylmethyl-7-carboxy-8-oxo-2-phenyl-3-oxa-1-azabicyclo[3.3.0]octane 5h

To a solution of a 1:6 mixture of the Reformatsky adducts **5d**:**8a** (0.23 g, 0.60 mmol) in EtOH (15 cm^3) was added NaOH solution (1 M, 3 cm^3) at rt. The mixture was stirred at rt for 1 h and then at 40 °C for 1 h. Water (50 cm^3) was then added and the solution extracted with EtOAc (10 cm^3). Acidification of the aqueous with HCl (2 M) followed by extraction with EtOAc (4 × 20 cm^3) gave, after drying ($MgSO_4$) and evaporation *in vacuo*, **5h** as a colourless foam (0.21 g, 95%) as a mixture of two diastereomers (*ca.* 1:16); ν_{max}(film)/cm^{-1} 2940 (m), 1722 (s), 1368 (m), 1221 (m), 1154 (s), 700 (m); δ_H (300 MHz, $CDCl_3$) (major diastereomer) 1.45 (9H, s, $C(CH_3)_3$), 2.49 (1H, dd, *J* 17.5 and 11.0, CHHCO$_2$^{t}Bu), 2.89–3.01 (2H, m, CHHCO$_2$^{t}Bu and H-6), 3.61 (1H, d, *J* 11.0, H-7), 3.82–3.97 (2H, m, H-4$_{endo}$ and H-5), 4.48 (1H, dd, *J* 8.5 and 6.0, H-4$_{exo}$), 6.30 (1H, s, H-2), 7.35–7.49 (5H, m, ArH), 8.64 (1H, br s, COOH); δ_C (50.3 MHz, $CDCl_3$) (major diastereomer) 28.0 ($C(CH_3)_3$), 38.4 (CH_2CO_2^{t}Bu), 39.6 (C-6), 54.5 (C-7), 62.9 (C-5), 72.6 (C-4), 81.7 ($C(CH_3)_3$), 86.7 (C-2), 126.0, 128.6 and 129.1 (ArCH), 137.3 (C-9), 169.4, 170.5 and 171.6 (3 × CO); *m/z* (APCI$^-$) 360 ((M − H)$^-$, 100%), 260 (94); HRMS 362.1600, $C_{19}H_{24}NO_6$ requires 362.1603.

(2*R*,5*S*,6*R*)-6-*tert*-Butoxycarbonylmethyl-8-oxo-2-phenyl-3-oxa-1-azabicyclo[3.3.0]octane 5i

The acid **5h** (0.21 g, 0.57 mmol) was heated at 135 °C at 0.7 mbar for 35 min to give a pale yellow oil which was purified using flash column chromatography (EtOAc–light petroleum 1:2) to give the title compound as a colourless oil (0.11 g, 63%). R_f 0.30 (EtOAc–petrol (40–60) 1:2); $[a]_D^{23}$ +118.7 (*c* 1 in $CHCl_3$); ν_{max}(film)/cm^{-1} 2925 (m), 1722 (s), 1368 (m), 1251 (w), 1218 (w), 1151 (w), 700 (m); δ_H (300 MHz, $CDCl_3$) 1.45 (9H, s, $C(CH_3)_3$), 2.41–2.74 (5H, m, H-6, H-7 and CH_2CO_2^{t}Bu), 3.70–3.75 (1H, t *J* 8.5, H-4$_{endo}$), 3.84–3.89 (1H, m, H-5), 4.34 (1H, dd, *J* 8.5 and 6.5, H-4$_{exo}$), 6.34 (1H, s, H-2), 7.33–7.46 (5H, m, ArH); δ_C (50.3 MHz, $CDCl_3$) 28.0 ($C(CH_3)_3$), 35.8 (C-6), 39.6 and 40.3 (C-7 and CH_2CO_2^{t}Bu), 64.7 (C-5), 76.5 (C-4), 81.3 ($C(CH_3)_3$), 86.7 (C-2), 125.9, 128.4 and 128.6 (ArCH), 138.4 (C-9), 170.7 and 176.0 (2 × CO); *m/z* (APCI$^+$) 318 (M + H^+, 100%), 262 (37); HRMS (CI$^+$) 318.1705, $C_{18}H_{24}NO_4$ (M + H^+) requires 318.1705.

(2*S*,3*R*)-3-*tert*-Butoxycarbonylmethyl-2-hydroxymethyl-5-oxopyrrolidine 10a

Lactam **5i** (0.11 g, 0.42 mmol) was reacted with TFA (1.5 cm^3) in DCM (10 cm^3) for 40 min. Work-up and extraction of the aqueous phase with DCM gave a colourless crystalline solid (35 mg) which was purified using flash column chromatography (EtOAc–petrol 1:1 and then EtOAc–petrol–MeOH 40:10:3) to give the title compound **10a** as a colourless crystalline solid (45 mg, 55%). R_f 0.28 (EtOAc–petrol–MeOH 40:10:3); mp 99–102 °C; $[a]_D^{23}$ +20.0 (*c* 0.11 in $CHCl_3$); ν_{max}($CHCl_3$)/cm^{-1} 3432 (m), 3366 (m, br), 1720 (s), 1697 (s), 1370 (m), 1151 (s), 1094 (s); δ_H (500 MHz, $CDCl_3$, *c* 30 mg ml^{-1}) 1.45 (9H, s, $C(CH_3)_3$), 2.08 (1H, dd, *J* 5.5 and 17.0, CHHCO$_2$^{t}Bu), 2.36 (1H, dd, *J* 7.5 and 16.0, H-4), 2.47 (1H, dd, *J* 7.0 and 16.0, H-4), 2.50–2.57 (1H, m, H-3), 2.65 (1H, dd, *J* 9.0 and 17.0 (CHHCO$_2$^{t}Bu), 3.44–3.47 (1H, m, H-2), 3.52 (1H, dd, *J* 6.5 and 11.5, CHHOH), 3.73 (1H, dd, *J* 3.0 and 11.5, CHHOH), 3.92 (1H, br s, OH), 7.35 (1H, br s, NH); δ_H (500 MHz, $CDCl_3$, *c* 3 mg ml^{-1}) 1.45 (9H, s, $C(CH_3)_3$), 2.08 (1H, dd, *J* 5.5 and 17.0, CHHCO$_2$^{t}Bu), 2.36 (1H, dd, *J* 7.0 and 16.0, H-4), 2.47 (1H, dd, *J* 7.5 and 16.0, H-4), 2.50–2.57 (1H, m, H-3), 2.65 (1H, dd, *J* 9.0 and 17.0, CHHCO$_2$^{t}Bu), 2.74 (1H, br t (unresolved), OH), 3.44–3.47 (1H, m, H-2), 3.53–3.58 (1H, m, CHHOH), 3.74–3.76 (1H, m, CHHOH), 6.66 (1H, br s, NH); δ_C (50.3 MHz, $CDCl_3$) 28.0 ($C(CH_3)_3$), 32.5 (C-3), 36.6 and 40.0 (C-4 and CH_2CO_2^{t}Bu) 61.8 (C-2), 64.5 (CH_2OH), 81.1 ($C(CH_3)_3$), 171.0 and 178.4 (2 × CO); *m/z* (APCI$^+$) 459 (2M + H^+, 23%), 230 (M + H^+, 71), 174 (100).

(2*S*,3*R*)-3-Carboxymethyl-2-hydroxymethyl-5-oxopyrrolidine 10b

To a solution of compound **10a** (16 mg, 0.07 mmol) in DCM (1.5 cm^3) was added TFA (0.6 cm^3) dropwise at rt. The flask was swirled and left to stand at rt for 1 h. The solvent was then removed *in vacuo*, and then under high vacuum (2 mbar) for several days to give the crude title compound **10b** as a colourless gum (33 mg). ν_{max} (film)/cm^{-1} 3316 (s, br), 2934 (m, br), 1674 (s), 1394 (m), 1318 (m), 1277 (m), 1225 (m), 1202 (m), 1087 (w), 1054 (w); δ_H (500 MHz, CD_3OD) 2.11 (1H, dd, *J* 16.5 and 4.5, C*H*HCO_2H), 2.48 (1H, dd, *J* 18.0 and 9.5, H-4H), 2.58–2.69 (3H, m, H-4, H-3 and CH*H*CO_2H), 3.45 (1H, dd, *J* 9.0 and 4.0, H-2), 3.56 (1H, dd, *J* 11.5 and 5.5, C*H*HOH), 3.66 (1H, dd, *J* 11.5 and 4.0, CH*H*OH); δ_C (125.8 MHz, CD_3OD) 34.06 (C-3), 37.68 and 39.49 (C-4 and CH_2CO_2H), 63.01 (C-2), 65.05 (CH_2OH), 175.42 and 179.81 (2 × *C*O); *m*/*z* ($APCI^+$) 174 ($M + H^+$, 100%).

(2*S*,3*R*)-3-Methoxycarbonylmethyl-2-methoxycarbonyl-5-oxopyrrolidine 10c

To a solution of crude **10b** (18 mg) in CH_3CN (1 cm^3) and CCl_4 (2 cm^3) was added a solution of $NaIO_4$ (60 mg, 0.28 mmol) in water (1.5 cm^3) and then ruthenium(IV) oxide hydrate (2 mg). The mixture was stirred vigorously for 4.5 h and then diazomethane in diethyl ether was added with stirring at 0 °C. The excess diazomethane was then quenched with acetic acid (2 drops). After evaporating half the volume of diethyl ether, the mixture was extracted with EtOAc (2 × 10 cm^3). Drying ($MgSO_4$) and evaporation *in vacuo* gave a yellow oil which was purified using flash column chromatography (EtOAc–petrol (40–60) 4:1) to give the title compound **10c** as a colourless oil (8 mg, 53% from compound **10a**). R_f 0.21 (EtOAc–petrol (40–60) 4:1); $[a]_D^{23}$ +32.9 (*c* 0.34 in $CHCl_3$); ν_{max}(film)/cm^{-1} 3351 (w, br), 3244 (w, br), 1736 (s), 1702 (s), 1438 (m), 1380 (m), 1214 (s), 1181 (m), 996 (m); δ_H (500 MHz, $CDCl_3$) 2.15 (1H, dd, *J* 17.0 and 7.0, C*H*HCO_2Me), 2.57 (1H, dd, *J* 16.0 and 8.0, H-4H), 2.68 (1H, dd, *J* 17.0 and 9.0, CH*H*CO_2Me), 2.78 (1H, dd, *J* 16.0 and 6.0, H-4*H*), 2.91–1.98 (1H, m, H-3), 3.72 (3H, s, CO_2CH_3), 3.79 (3H, s, CO_2CH_3), 4.03 (1H, d, *J* 5.5, H-2), 6.27 (1H, br s, N*H*); δ_C (125.8 MHz, $CDCl_3$) 35.07 (C-3), 35.73 and 38.11 (CH_2CO_2Me and C-4), 51.93 and 52.75 (CO_2CH_3), 59.82 (C-2), 166.96, 171.49 and 176.08 (3 × *C*O); *m*/*z* ($APCI^+$) 216 ($M + H^+$, 100%), 431 (33); HRMS (CI^+) 216.0872, $C_9H_{13}NO_5$ requires 216.0872.

Acknowledgements

We thank EPSRC and GlaxoWellcome for funding of studentships to DTC and JD, and we wish to gratefully acknowledge the use of the EPSRC Chemical Database Service at Daresbury[85] and the EPSRC National Mass Spectrometry Service Centre at Swansea.

References

1 M. G. Moloney, *Nat. Prod. Rep.*, 1999, **16**, 485.
2 M. D. Fletcher and M. M. Campbell, *Chem. Rev.*, 1998, **98**, 763.
3 A. Dutta, in *Specialist Periodical Reports "Amino acids, Peptides and Proteins"*, ed. J. S. Davies, Royal Society of Chemistry, Cambridge, 1998.
4 S. Hanessian, G. McNaughton-Smith, H.-G. Lombart and W. D. Lubell, *Tetrahedron*, 1997, **53**, 12789.
5 J. Gante, *Angew. Chem., Int. Ed. Engl.*, 1994, **33**, 1699.
6 J. K. Thottathil, C. Przybyla, M. Malley and J. Z. Gougoutas, *Tetrahedron Lett.*, 1986, **27**, 1533.
7 J. K. Thottathil, J. M. Moniot, R. H. Mueller, M. K. Y. Wong and T. P. Kissick, *J. Org. Chem.*, 1986, **51**, 3140.
8 M. J. Beard, J. H. Bailey, D. T. Cherry, M. G. Moloney, S. B. Shim, K. Statham, M. Bamford and R. B. Lamont, *Tetrahedron*, 1996, **52**, 3719.
9 J. E. Baldwin, M. G. Moloney and S. B. Shim, *Tetrahedron Lett.*, 1991, **32**, 1379.
10 C. Herdeis, A. Aschenbrenner, A. Kirfel and F. Schwabenlander, *Tetrahedron: Asymmetry*, 1997, **8**, 2421.
11 N. Langlois, O. Calvez and M.-O. Radom, *Tetrahedron Lett.*, 1997, **38**, 8037.
12 T. Nagasaka and T. Imai, *Chem. Pharm. Bull.*, 1997, **45**, 36.
13 T. Nagasaka and T. Imai, *Heterocycles*, 1995, **41**, 1927.
14 C. Herdeis, H. P. Hubmann and H. Lotter, *Tetrahedron: Asymmetry*, 1994, **5**, 119.
15 D. Griffart-Brunet and N. Langlois, *Tetrahedron Lett.*, 1994, **35**, 119.
16 D. Griffart-Brunet and N. Langlois, *Tetrahedron Lett.*, 1994, **35**, 2889.
17 R. W. Armstrong and J. A. DeMattei, *Tetrahedron Lett.*, 1991, **32**, 5749.
18 Y. Hamada, O. Hara, A. Kawai, Y. Ohno and T. Shiori, *Tetrahedron*, 1991, **47**, 8635.
19 S. Hanessian and V. Ratovelomanana, *Synlett*, 1991, 222.
20 S. Hanessian and V. Ratovelomanana, *Synlett*, 1990, 501.
21 N. E. Allen, *Tetrahedron*, 1989, **30**, 1905.
22 Y. Hamada, A. Kawai, Y. Kohno, O. Hara and T. Shioiri, *J. Am. Chem. Soc.*, 1989, **111**, 1524.
23 R. Zhang, F. Brownewell and J. S. Madalengoitia, *Tetrahedron Lett.*, 1999, **40**, 2707.
24 M. Fujita, O. Kitagawa, Y. Yamada, H. Izawa, H. Hasegawa and T. Taguchi, *J. Org. Chem.*, 2000, **65**, 1108.
25 O. Hara, J. Takizawa, T. Yamatake, K. Makino and Y. Hamada, *Tetrahedron Lett.*, 1999, **40**, 7787.
26 J. H. Bailey, A. T. J. Byfield, P. J. Davis, A. C. Foster, M. Leech, M. G. Moloney, M. Müller and C. K. Prout, *J. Chem. Soc., Perkin Trans. 1*, 2000, 1977.
27 J. H. Bailey, D. T. Cherry, K. M. Crapnell, M. G. Moloney, S. B. Shim, M. Bamford and R. B. Lamont, *Tetrahedron*, 1997, **53**, 11731.
28 M. Bamford, M. Beard, D. T. Cherry and M. G. Moloney, *Tetrahedron: Asymmetry*, 1995, **6**, 337.
29 N. Langlois, N. V. Bac, N. Dahuron, J.-M. Delcroix, A. Deyine, D. Griffart-Brunet, A. Chiaroni and C. Riche, *Tetrahedron*, 1995, **51**, 3571.
30 K. Shimamoto and Y. Ohfune, *Tetrahedron Lett.*, 1989, **30**, 3803.
31 R. Zhang, A. Mamai and J. S. Madalengoitia, *J. Org. Chem.*, 1999, **64**, 547.
32 R. Zhang and J. S. Madalengoitia, *J. Org. Chem.*, 1999, **64**, 330.
33 J. Ezquerra, C. Pedregal, I. Merino, J. Florez, J. Barluenga, S. Garcia-Granda and M.-A. LLorca, *J. Org. Chem.*, 1999, **64**, 6554.
34 N. Langlois, *Tetrahedron Lett.*, 1999, **40**, 8801.
35 V. Soloshonok, C. Cai, V. J. Hruby, L. V. Meervelt and N. Mischenko, *Tetrahedron*, 1999, **55**, 12031.
36 L. E. Overman and A. J. Robichaud, *J. Am. Chem. Soc.*, 1989, **111**, 300.
37 A. G. M. Barratt, J. Head, M. L. Smith, N. S. Stock, A. J. P. White and D. J. Williams, *J. Org. Chem.*, 1999, **64**, 6005.
38 G. Guillena, B. Mancheno, C. Najera, J. Ezquerra and C. Pedregal, *Tetrahedron*, 1998, **54**, 9447.
39 J. Cossy, M. Cases and D. G. Pardo, *Synlett*, 1998, 507.
40 H. Nakamura, Y. Oba and A. Murai, *Tetrahedron Lett.*, 1993, **24**, 2779.
41 M. P. Cook and C. M. Pollock, *J. Org. Chem.*, 1993, **58**, 7474.
42 C. Herdeis and H. P. Hubmann, *Tetrahedron: Asymmetry*, 1992, **3**, 1213.
43 H. Nagashima, H. Wakamatsu, N. Ozaki, T. Ishii, M. Watanabe, T. Tajima and K. Itoh, *J. Org. Chem.*, 1992, **57**, 1682.
44 W. J. Koot, H. Hiemstra and W. N. Speckamp, *Tetrahedron Lett.*, 1992, **33**, 7969.
45 K. C. Woo and K. Jones, *Tetrahedron Lett.*, 1991, **32**, 6949.
46 P. Somfai, M. H. Hua and D. Tanner, *Tetrahedron Lett.*, 1991, **32**, 283.
47 T. J. Hagen, *Synlett*, 1990, 63.
48 M. Yanagida, K. Hashimoto, M. Ishida, H. Shinozaki and H. Shirahama, *Tetrahedron Lett.*, 1989, **30**, 3799.
49 H. Nagashima, N. Ozaki, M. Washiyama and K. Itoh, *Tetrahedron Lett.*, 1985, **26**, 657.
50 S. Hanessian and S. Ninkovic, *J. Org. Chem.*, 1996, **61**, 5418.
51 S. Hanessian, S. Ninkovic and U. Reinhold, *Tetrahedron Lett.*, 1996, **37**, 8971.
52 H. Yoda, H. Kitayama, T. Katagiri and K. Takabe, *Tetrahedron*, 1992, **48**, 3313.
53 A. I. Meyers and L. Snyder, *J. Org. Chem.*, 1992, **57**, 3814.
54 N. Langlois and R. Z. Andriamialisoa, *Tetrahedron Lett.*, 1991, **32**, 3057.
55 J. Dyer, S. Keeling and M. G. Moloney, *Chem. Commun.*, 1998, 461.
56 J. Dyer, S. Keeling and M. G. Moloney, *Tetrahedron Lett.*, 1996, **37**, 4573.

57 J. Ezquerra, C. Pedregal, I. Collado, B. Yruretagoyena and A. Rubio, *Tetrahedron*, 1995, **51**, 10107.
58 D. Seebach, A. R. Sting and M. Hoffmann, *Angew. Chem.*, *Int. Ed. Engl.*, 1996, **35**, 2708.
59 F. Zanardi, L. Battistini, G. Rassu, M. Cornia and G. Casiraghi, *J. Chem. Soc.*, *Perkin Trans. 1*, 1995, 2471.
60 F. Zanardi, L. Battistini, M. Nespi, G. Rassu, P. Spanu, M. Cornia and G. Casiraghi, *Tetrahedron: Asymmetry*, 1996, **7**, 1167.
61 R. Grote, A. Zeeck, J. Stumpfel and H. Zahner, *Liebigs Ann. Chem.*, 1990, 525.
62 A. H. Fray and A. I. Meyers, *J. Org. Chem.*, 1996, **61**, 3362.
63 A. H. Fray and A. I. Meyers, *Tetrahedron Lett.*, 1992, **33**, 3575.
64 C. A. Busacca and A. I. Meyers, *J. Chem. Soc.*, *Perkin Trans. 1*, 1991, 2299.
65 Y. N. Stefanovsky and L. Z. Viteva, *Monatsh. Chem.*, 1981, **112**, 125.
66 Y. N. Stefanovsky and L. Z. Viteva, *Monatsh. Chem.*, 1980, **111**, 1287.
67 Atomic coordinates have been deposited with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from Cambridge Crystallographic Data Centre, 12 Union Rd, Cambridge, UK CB2 1EZ, CCDC reference number 207/446. The structures were solved and refined with full matrix least squares analysis using SHELXTL (G. M. Sheldrick, Nicolet Instrument Corporation, SHELXTL PLUS V3.4, 1988). Crystal data and data collection parameters for compound **4d**: $C_{24}H_{25}NO_6$; $M = 423.47$; orthorhombic; space group $P2_12_12_1$; μ(Cu-Kα) = 0.72 mm^{-1}; $R = 0.049$; unit cell dimensions $a = 8.143(6)$, $b = 9.410(8)$, $c = 28.78(2)$ Å; $V = 2205(5)$ $Å^3$; temperature = 295 K; $Z = 4$; measured reflections 3218; $D_c = 1.28$ g cm^{-3}.
68 J. Skarzewski, *Synthesis*, 1990, 1125.
69 H. P. Pagett, I. G. Csendes and H. Rapoport, *J. Org. Chem.*, 1979, **44**, 3492.
70 A. Garcia-Raso, J. Garcia-Roso, J. V. Sinisterra and R. Mestres, *J. Chem. Educ.*, 1986, **63**, 443.
71 I. Baussanne, A. Chiaroni, H. P. Housson, C. Riche and J. Royer, *Tetrahedron Lett.*, 1994, **35**, 3931.
72 P. Perlmutter, *Conjugate Additions in Organic Synthesis*, Pergamon, Oxford, 1992.
73 Y. Kita, J. Segawa, J.-i. Haruta, H. Yasuda and Y. Tamura, *J. Chem. Soc.*, *Perkin Trans. 1*, 1982, 1099.
74 J. Leonard, E. Diez-Barra and S. Merino, *Eur. J. Org. Chem.*, 1998, 2051.
75 J. Leonard, *Contemp. Org. Synth.*, 1994, **1**, 387.
76 M. W. Rathke and P. Weipert, in *Comprehensive Organic Synthesis*, Pergamon, Oxford, 1991, vol. 2.
77 J. Boersma, in *Comprehensive Organometallic Chemistry*, ed. G. Wilkinson, Pergamon, Oxford, 1982, vol. 2.
78 N. Goasdoue and M. Gaudemar, *J. Organomet. Chem.*, 1972, **39**, 17.
79 B.-H. Han and P. Boudjouk, *J. Org. Chem.*, 1982, **47**, 5030.
80 F. A. J. Kerdesky, R. J. Ardecky, M. V. Lakshmikantham and M. P. Cava, *J. Am. Chem. Soc.*, 1981, **103**, 1992.
81 A. P. Krapcho, *Synthesis*, 1982, 805.
82 T. Sato, K. Matsubayashi, K. Yamamoto, H. Ishikawa, H. Ishibashi and M. Ikeda, *Heterocycles*, 1995, **40**, 261.
83 C. Tsai, J. A. Schnider and J. Lehmann, *Neurosci. Lett.*, 1988, **92**, 298.
84 J. Ezquerra, C. Pedregal, A. Rubio, B. Yruretagoyena, A. Escribano and F. Sanchez-Ferrando, *Tetrahedron*, 1993, **49**, 8665.
85 D. A. Fletcher, R. F. McMeeking and D. Parkin, *J. Chem. Inf. Comput. Sci.*, 1996, **36**, 746.