ARTICLE

OBC
www.rsc.org/obc

Stereoselective synthesis of conformationally constrained ω-amino acid analogues from pyroglutamic acid

Emilie L. Bentz,[a] Rajesh Goswami,[a] Mark G. Moloney*[a] and Susan M. Westaway[b]

[a] *The Department of Chemistry, The University of Oxford, Chemistry Research Laboratory, Mansfield Road, Oxford, U.K OX1 3TA. E-mail: mark.moloney@chem.ox.ac.uk*

[b] *Department of Medicinal Chemistry, Neurology and GI CEDD, GlaxoSmithKline Research Ltd, New Frontiers Science Park, Third Ave, Harlow, Essex, U.K CM19 5AW*

Received 18th March 2005, Accepted 1st June 2005
First published as an Advance Article on the web 1st July 2005

Bicyclic lactams derived from pyroglutamic acid provide a useful scaffold for synthesis of conformationally restricted analogues of lysine, ornithine and glutamine, as well as an Ala–Ala dipeptide analogue. Amino alcohol and carboxylic acid derivatives are accessible from a common intermediate. In this strategy, the bicyclic lactam system not only controls, but also facilitates the determination of the stereochemistry of the synthetic intermediates.

The desire to mimic the effect of biologically active peptides and proteins for therapeutic purposes, but without the associated problems of oral bioavailability and rapid metabolism, has driven the development of peptide mimetics or peptidomimetics over the last decade.[1,2] Such mimics are designed to interact with a peptide active site or receptor binding site to exert agonistic or antagonistic effects.[3] The understanding of both the conformational behaviour of peptide mimetics[4,5] and their interaction with peptide receptors has dramatically advanced in recent years,[6,7] to the point where broad principles giving some predictive power have been established.[8] One requirement for the successful construction of effective peptidomimetics is the synthesis of conformationally constrained amino acids, a fact which has attracted considerable attention from synthetic chemists.[9–12] The conformational restriction in these compounds is most obviously achieved by incorporating one or more rings into the backbone of amino acid chimeras, and this strategy has been applied to a number of amino acids. Prominent among these has been the development of bicyclic dipeptide mimics.[13–15] However, these structures are also of interest in their own right, and such small molecules are of importance as ligands for a wide variety of biological receptors, including the mGluRs[16] and a novel class of *trans*-5,5-lactam antibiotics.[17]

Although the structurally restricted analogues of a number of amino acids have been described,[12,18–22] the ω-amino acids have, in general, only recently begun to attract attention. However, modified lysine chimeras derived from pyroglutamic acid[23] or proline,[21,24,25] and conformationally restricted lysine,[26] ornithine,[27,28] arginine[29–31] and glutamine,[32] have all recently been reported. The synthesis of cyano-[33] or indole-substituted[34] glutamate analogues, and of penmacric acid,[35] have also recently been described, although their biological activity has not been investigated.[36]

The well-defined conformation of pyroglutamic acid has previously been investigated in detail[37] and its suitability for application as a template for peptidomimetics has been proposed:[38] the pyrrolidinone ring simultaneously restricts τ_1, τ_2 and τ_3 to very limited range and defines the *cis*-amide bond (Fig. 1).[39] We have shown that the heterocyclic ring of pyroglutamic acid can be readily modified using a bicyclic lactam,[35,40–43] and that remote ring functionalisation leads to compounds which exhibit well-defined and tunable conformations.[43] The Hruby[44–51] and Madalengoitia[29–31,52] groups have recently exploited the conformationally restricted character of the heterocyclic ring of pyroglutamic acid to prepare a range of amino acid mimetics, and the value of C-3 substituted pyroglutamates as conformational controlling elements has been recognized.[53] We report here, as a further development of our work, that several conformationally restricted ω-amino analogues derived from a single pyroglutamate precursor are readily available. We planned to achieve this by modification of either the C-6 or C-7 position of bicyclic lactams **1a** and **1b** with α-haloesters, α-haloacetamides or α-halonitriles. Some of this work has been published in a preliminary form.[54]

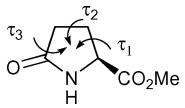
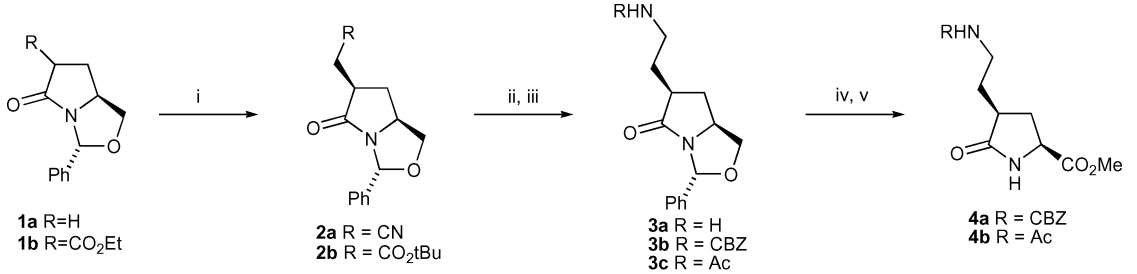


Fig. 1

We first examined the alkylation of lactam **1a** with bromoacetonitrile; this would generate a conformationally restricted lysine derivative (Scheme 1). Thus, the lactam enolate of lactam **1a** was treated with bromoacetonitrile to give, exclusively the *endo*-adduct (**2a**), in 55% yield. This was surprising, since our earlier



Scheme 1 (i) LDA, THF, −78 °C then $BrCH_2CN$ (55%) for **2a** or $BrCH_2CO_2t$-Bu (53%) for **2b**; (ii) $NaBH_4$, $CoCl_2$, EtOH (76%); (iii) CBZCl, Et_3N (64%) or AcCl, Et_3N, THF, 0 °C (75%); (iv) TFA, DCM, RT (80%); (v) RuO_2, $NaIO_4$ then CH_2N_2 (34%).

DOI: 10.1039/b503994k

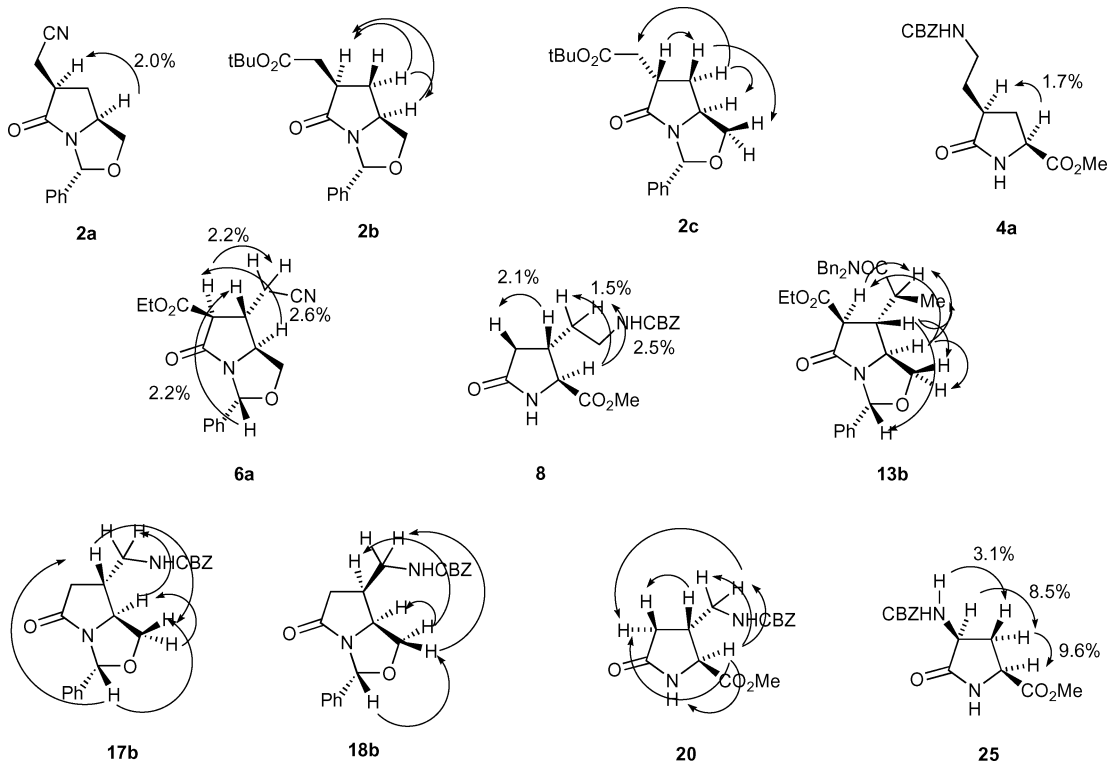
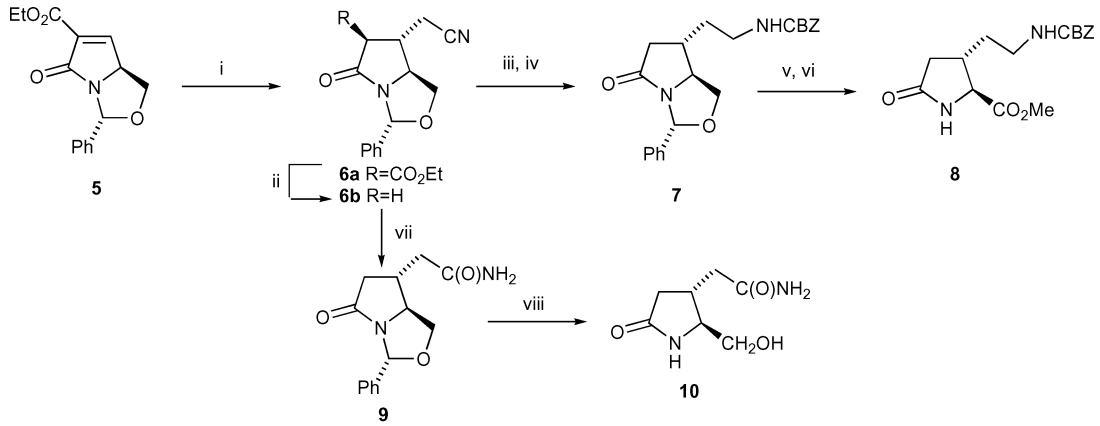


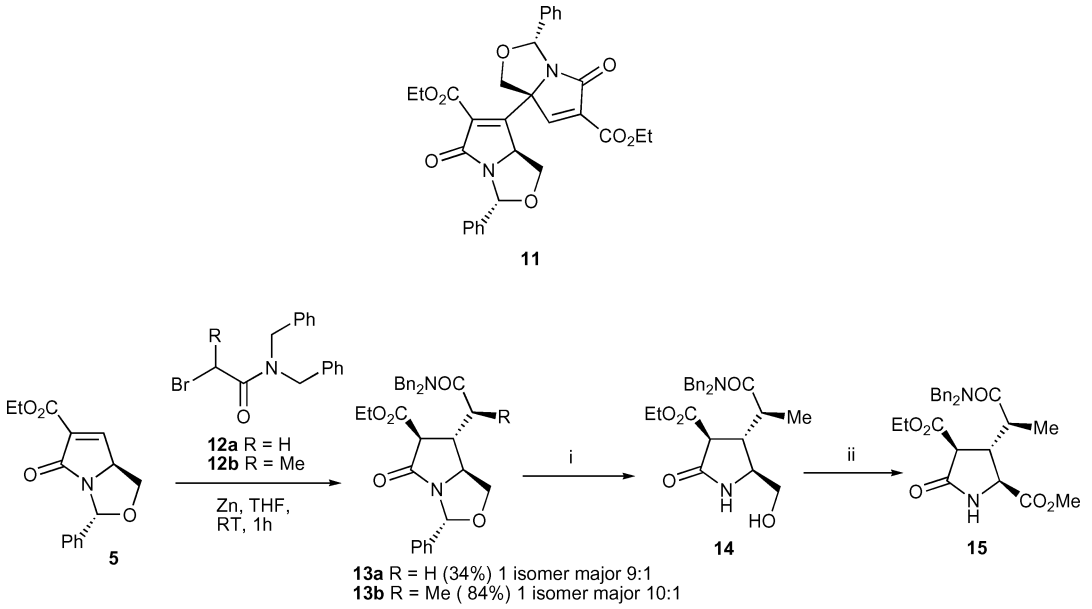
Fig. 2

work indicated that this type of alkylation normally proceeds under thermodynamic control to give the *exo*-product,[55] although reactive electrophiles do tend to give the kinetic *endo*-adduct. The *cis*-stereochemistry of **2a** was assigned on the basis of chemical shift data ($C(6)H_{exo}$ and $C(6)H_{endo}$ were found to be at 1.77–1.85 and 2.78–2.80, consistent with the earlier established rule of thumb that the C-7 *endo*-diastereomers possess higher R_f and optical rotation data, and a bigger difference in the chemical shift values of $C(6)H_{exo}$ and $C(6)H_{endo}$ than the C-7 *exo*-diastereomers)[56] and this assignment was confirmed by NOE data (Fig. 2): irradiation of C(5)H gave a 2.0% enhancement of the C(7)H proton, which in turn gave a 6.9% enhancement of $C(6)H_{exo}$. It was found that reaction with *t*-butyl α-bromoacetate also gave prominently the *endo*-adduct **2b** (53%), but in this case a small amount of the *exo*-isomer was additionally obtained (7%). The stereochemistry of each isomer was determined by NOE analysis, for which key enhancements were observed between C(5)H, $C(6)H_{exo}$ and C(7)H for *endo*-**2b**, and $C(4)H_{endo}$, $C(6)H_{endo}$ and C(7)H for *exo*-**2b** (Fig. 2). Reduction of the nitrile function of **2a** with sodium borohydride–cobalt(II)chloride gave the corresponding amine **3a** in 76% yield, and this intermediate was easily converted to the product **4a** in four steps and 16% overall yield. Thus, immediate protection of amine **3a** as the carbobenzyloxycarbonyl (CBZ) derivative **3b** was followed by acidic deprotection of the *O*,*N*-acetal, oxidation of the alcohol and *in situ*-esterification to give the methyl ester **4a**. The stereochemistry of **4a** was confirmed by further NOE analysis: irradiation of C(2)H gave a 1.7% enhancement of C(4)H and a 4.4% enhancement of the $C(3)H_{exo}$ (Fig. 2). Interestingly, although protection of amine **3a** as the *N*-acetyl derivative **3c** was efficient (75% yield), attempted elaboration to the corresponding derivative **4b** failed at the alcohol oxidation step.

We next examined the extension of this approach for the preparation of an ornithine derivative by conjugate addition using bromoacetonitrile to the known enone **5** (Scheme 2).[42] We had previously shown that addition of the Reformatsky reagents is effective for enone **5**; the relatively low basicity of these reagents is important to avoid unwanted dimerisation.[57] We found that Reformatsky-type reaction of bromoacetonitile with enone **5** proceeded efficiently at room temperature to



Scheme 2 (i) Zn, DMPU, $BrCH_2CN$ (69%), RT; (ii) $(Bu_3Sn)_2O$, toluene, δ, 16 h (68%); (iii) $NaBH_4$, $CoCl_2$, EtOH; (iv) CBZCl, Et_3N (44% over two steps); (v) TFA, DCM, RT (92%); (vi) PDC–DMF then CH_2N_2 (30%); (vii) H_2O_2, 1 M NaOH, EtOH, RT (75%); (viii) TFA, DCM, RT (70%).



Scheme 3 (i) TFA, DCM, RT (75%); (ii) PDC, DMF then CH_2N_2 (54%).

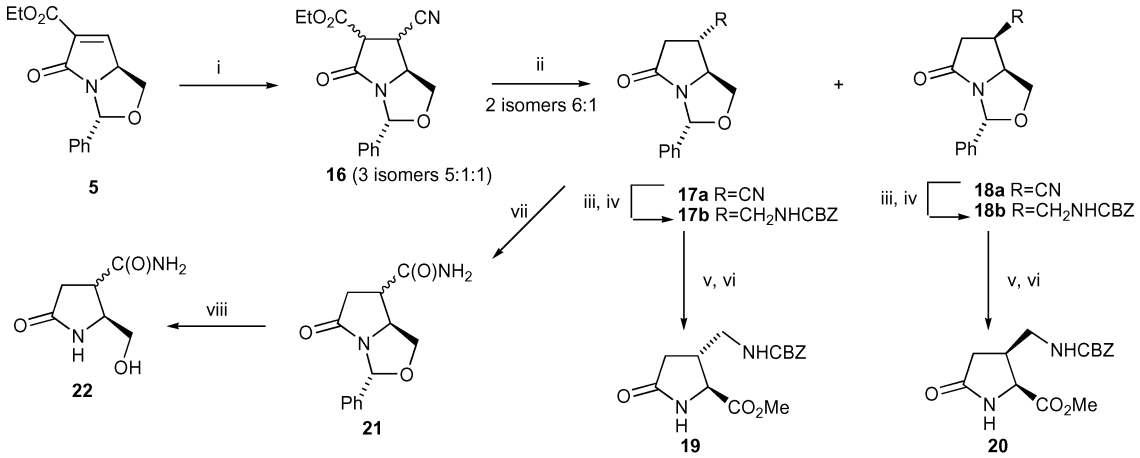
give the product **6a** in 69% yield as a single diastereomer (as shown by ^{13}C NMR spectroscopic analysis). The *exo*-stereochemistry of this adduct was assigned on the basis of NOE data (Fig. 2): mutual enhancement of C(7)H, CH_2CN and C(5)H indicated their co-location on the *exo*-face, while enhancements of C(6)H, C(4)H_{endo} and C(2)H confirmed their *endo*-location. Interestingly, although Reformatsky reagents have been known to participate in conjugate addition processes for some time,[58–64] they have rarely been used for this purpose until relatively recently.[43,57,65–67] Furthermore, organoindium[68–70] and organonickel[71] reagents have more recently found application in this regard. Hydrolysis and decarboxylation using bis(tri-*n*-butyltin) oxide in toluene at reflux[72] readily afforded the product **6b** in 68% yield. Reduction (excess $NaBH_4$ and $CoCl_2 \cdot 6H_2O$) and immediate *N*-protection gave derivative **7** in 44% yield over the 2 steps. This was elaborated as described above (deprotection, oxidation and *in situ* esterification) to give product **8** in 28% yield over the 2 steps. In this case, however, application of ruthenium tetroxide in the final oxidation step did not give the desired product, and this step was successfully performed only with PDC–DMF. The *trans*-relative stereochemistry of **8** was confirmed by NOE data (Fig. 2).

We expected to be able to access a glutamine analogue from intermediate **6b**; such compounds have been of recent interest.[32] Hydrolysis of **6b** with alkaline peroxide gave amide **9** in 75% yield, and hemiaminal ether deprotection under TFA conditions gave alcohol **10** in 70% yield, but all attempts at oxidation of this alcohol to the corresponding acid were unsuccessful (Scheme 2). We next examined the possibility of the direct addition of Reformatsky reagents derived from α-bromoacetamides using the above conditions. However, we found that addition of the Reformatsky reagents derived from α-bromoacetamide, α-bromopropionamide and *N*-benzyl α-bromopropionamide gave only dimer **11** as a single diastereomer. Suspecting that the acidic amide proton was the culprit, we examined the addition of *N*, *N*-dibenzyl α-bromoacetamide **12a**[73] and *N*, *N*-dibenzyl α-bromopropionamide **12b**[73] under the zinc-mediated conditions (Scheme 3). In the former case, addition occurred cleanly but only in moderate yield (34%) to give **13a**, but the propionamide was much more successful, giving a yield of 84% of amide **13b**, predominantly as one isomer. The stereochemistry of **13a** was established by NOE analysis, for which key enhancements were observed between C(4)H_{exo}, C(5)H, C(1′)H and C(7)H; and between C(1′)Me, C(4)H_{endo}, C(6)H_{endo} and C(2)H (Fig. 2). In the latter case, deprotection to alcohol **14**, followed by oxidation (PDC) and esterification, gave lactam **15** in high overall yield from **13b** (41%). However, *N*-benzyl deprotection was not attempted, since literature precedent indicated that this was accompanied by further hydrolysis to the carboxylic acid.[74]

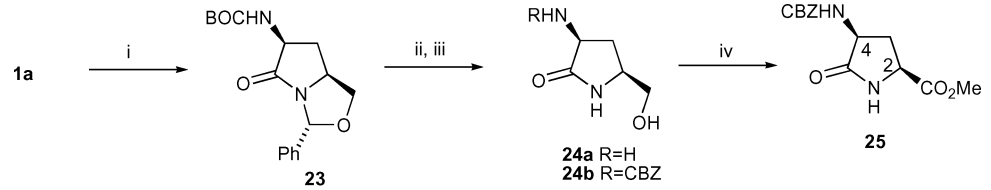
Given the success achieved with the addition of weakly basic Reformatsky reagents, it seemed likely that cyanide anion would be similarly effective.[75] This hypothesis proved to be correct, and the adduct **16** was easily obtained under mild conditions in high yield (Scheme 4), although as a mixture of 3 diastereomers (as indicated by ^{13}C NMR spectroscopy). Ester hydrolysis and decarboxylation gave the cyanides **17a** and **18a**. These were reduced and protected to give the readily separable lactams **17b** and **18b** (56 and 8%, respectively), the stereochemistry of each product established by NOE analysis (Fig. 2). These were easily deprotected (TFA), oxidized (PDC) and esterified (diazomethane) to give two conformationally restricted 2,4-diaminobutyric acid analogues, lactams **19** and **20**, in yields of 36 and 30%, respectively. Alternatively, nitrile hydrolysis to give amide **21**, followed by deprotection, provided access to alcohol **22** in an overall yield of 25%. This compound could not, however, be further oxidized.

The presence of an internal amide bond suggested that amination at the C-7 position of **1a** could be used to generate an unusual dipeptide mimetic, which incorporated a *cis*-peptide bond. Related aminopyrrolidinones, aminopiperidinones and larger ring heterocycles have recently attracted interest as enzyme inhibitors[76] and peptidomimetic structures.[44,77–81] Electrophilic amination of the enolate of lactam **1a** with diphenylphosphoryl azide,[82] followed by treatment with BOC_2O, gave exclusively the amino lactam **23** in 50% yield over the two steps (Scheme 5), the stereochemistry of the product established by NOE spectroscopy (Fig. 2). Critical to this assignment was the 2.3% enhancement observed between C(7)H and C(5)H. Acidic release of the protecting groups to give **24a**, and reprotection of the C-4 amino function as its CBZ derivative, gave the product **24b** in 51% yield over the two steps. Oxidation and esterification as described above then gave the product **25**, the *cis*-stereochemistry again confirmed by NOE spectroscopy (Fig. 2).

Molecular modelling of the *N*-acetyl analogue of compound **25**[83] demonstrated that two well-defined conformations existed, differing by 2.3 kcal mol^{-1} in energy, with the two substituents either pseudodiequatorial or diaxial, the latter being the more stable. Since a 2.7 kcal mol^{-1} energy difference corresponds to a 99 : 1 ratio of species at equilibrium,[84] the minor diequatorial



Scheme 4 (i) KCN, EtOH–H_2O, RT (78%); (ii) $(Bu_3Sn)_2O$, toluene, Δ, 16 h (58%) (**6a** : **6b** = 6 : 1); (iii) $NaBH_4$, $CoCl_2{\cdot}6H_2O$, EtOH; (iv) CBZCl, THF, Et_3N (64% over 2 steps, **17b** : **18b** = 7 : 1); (v) TFA, DCM, RT; (vi) PDC, DMF then CH_2N_2 (**19** (36%), **20** (20%)); (vii) H_2O_2, 1 M NaOH, EtOH, RT (56%); (viii) TFA, DCM, RT (45%).



Scheme 5 (i), LDA, THF, −78 °C then $(PhO)_2P(O)N_3$, then BOC_2O, −78 °C → 0 °C (46%) (ii) TFA, DCM, RT, 1 h (quantitative); (iii) CBZCl, DMF–THF, Et_3N, 0 °C, 3 h (51%); (iv) PDC–DMF, 40 °C, 12 h then CH_2N_2 (28%).

conformer would not be expected to be observable at room temperature by NMR analysis, and ^1H NMR VT analysis provided no evidence for the diequatorial conformer even at 223 K. The stability of the diaxial conformer could be attributed to the presence of A-strain[85] between the 2 substituents and the planar amide system. The importance of torsional strain in 5- and 6-membered ring heterocycles for the control of stereochemistry has been investigated in detail,[86] although its importance in lactams has only recently been appreciated.[87] Thus, adoption of the diaxial conformer (**26b**) minimises the interactions of the relatively bulky C(2) and C(4) substituents with the planar amide function (which would occur in the diequatorial conformer **26a**) by placing C(2)H and C(4)H in an eclipsing conformation with the lactam system (Fig. 3). Using the energy minimised structure for **26**, some calculated dihedral angles are given in Table 1; the diaxial conformer most closely resembles a Type VIa (*cis*) β-turn.[88] Thus, this compound could be considered to be a conformationally restricted L-Ala–L-Ala dipeptide analogue, with the central amide bond constrained in the *cis*-orientation, and the pyrrolidinone ring capable of providing a reverse turn in an attached peptide chain; as such it represents a potential low molecular weight non-hydrophobic turn inducer. A related aminopyrrolidinone has also been reported to induce Type II′ β-turn folding in a short peptide, and to exhibit hypoglycaemic activity.[89]

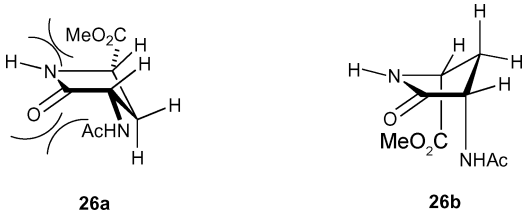
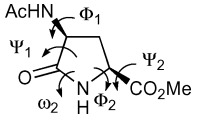


Fig. 3

In this paper, we have demonstrated the ease and synthetic value of hitherto overlooked conjugated addition reactions of Reformatsky reagents. Furthermore, the formation of conformationally restricted amino alcohols and amino acids illustrates the value of this synthetic strategy when applied to chiral bicyclic lactams derived from pyroglutamic acid: the scaffold exhibits diverse reactivity enabling functionalisation at different points around the heterocyclic ring, the bicyclic lactam system both controls but also facilitates the determination of the stereochemistry of synthetic intermediates, and the pyroglutaminyl ring makes for well-defined conformational behaviour in the amino acid derivatives.

Table 1 Dihedral angles for energy minimised[a] conformations of **26a,b**



	Ψ_1	Φ_2
Diequatorial	−139	+137
Diaxial	+94	−97

[a] Structures optimised with Chem 3D Pro 3.5 (MM2 Parameters), available from Cambridge Scientific.

Experimental

For detailed experimental procedures, see our earlier work.[55] The bicyclic lactam **1a** and its unsaturated analogue **5** were prepared using previously published methods.[57] Zinc was activated by shaking with a saturated solution of ammonium chloride for 5 min, then decanting the supernatant and washing with water, ethanol, diethyl ether, and then drying under high vacuum at RT for 3 h. *N*-Benzyl and *N*,*N*-dibenzylamides were prepared using the method of Hauser.[73]

(2*R*, 5*S*, 7*R*)-7-Cyanomethyl-8-oxo-2-phenyl-1-aza-3-oxa-bicyclo[3.3.0]octane (2a)

To *n*-BuLi (5.33 ml, 11.08 mmol) at 0 °C in THF (50 ml) was added diisopropylamine (1.77 ml, 12.56 mmol), the mixture stirred for 15 min and then cooled to −78 °C. A solution of lactam **1a** (1.5 g, 7.39 mmol) in THF (30 ml) was then added to the reaction mixture at −78 °C. After 30 min, bromoacetonitrile (0.99 ml, 14.78 mmol) in THF (20 ml) was added and the mixture stirred for 3 h at the same temperature. The reaction mixture was then quenched with aqueous saturated sodium bicarbonate solution (20 ml). After warming to RT water (30 ml) was added and the mixture extracted with ethyl acetate (30 ml). The aqueous layer was extracted with ethyl acetate (3 × 20 ml) and the combined organic extracts were washed with brine, dried over $MgSO_4$ and evaporated *in vacuo* to yield a yellow liquid. Purification using flash column chromatography (EtOAc–petrol(40/60), 1 : 1) gave a pale yellow solid (878 mg, 49%). R_f = 0.37 (EtOAc–petrol(40/60), 1 : 1); $[\alpha]_D^{22}$ = +218 (*c* 1.0 in $CHCl_3$), ν_{max}/cm^{-1} ($CHCl_3$) 2434, 2253, 1711, 1421; δ_H (400 MHz, $CDCl_3$) 1.77–1.85 (1H, m, C(6)H_{endo}), 2.64 (2H, m, CH_2CN), 2.78–2.80 (1H, m, C(6)H_{exo}), 3.19–3.28 (1H, m, C(7)H), 3.62 (1H, dd, *J* 8.2 and 7.4, C(4)H_{endo}), 4.13–4.20 (1H, m, C(5)H), 4.29 (1H, dd, *J* 8.3 and 6.3 C(4)H_{exo}), 6.32 (1H, s, C(2)H), 7.35–7.45 (5H, m, ArH); δ_C (90 MHz, $CDCl_3$) 18.59 (CH_2CN), 31.98 (C(6)), 42.10 (C(7)), 56.53 (C(5)), 72.10 (C(4)), 86.94 (C(2)), 117.65 (CN), 128.86 (ArCH), 137.86 (ArC), 174.24 (C(8)); *m/z* (CI^+) 243 (M + H^+, 100%), 216 (75), 204 (15); HRMS (M–H^+) 241.0977; $C_{14}H_{13}N_2O_2$ requires 241.0980.

(2*R*, 5*S*, 7*S*)-7/(2*R*, 5*S*, 7*R*)-7-(ᵗButyloxycarbonylmethyl)-8-oxo-2-phenyl-1-aza-3-oxa-bicyclo[3.3.0]octane (2b)

To *n*-BuLi (1.1 ml, 2.56 mmol) at 0 °C in THF (15 ml) was added diisopropylamine (0.41 ml, 2.9 mmol), the mixture stirred for 15 min and then cooled to −78 °C. A solution of lactam **1a** (350 mg, 1.71 mmol) in THF (7 ml) was then added to the reaction mixture. After 30 min, *t*-butyl bromoacetate (0.76 ml, 5.1 mmol) in THF (5 ml) was added, and the mixture stirred for 2 h at the same temperature. The reaction mixture was quenched with aqueous saturated sodium bicarbonate solution (10 ml). Water (10 ml) was added and the mixture extracted with EtOAc (20 ml). The aqueous layer was then extracted with EtOAc (3 × 10 ml) and the combined organic extracts were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo* to yield a yellow liquid. Purification using flash column chromatography (EtOAc–petrol(40/60), 3 : 7) gave *endo*-product **2b** (286 mg, 53%) as a pale yellow solid. R_f = 0.6 (EtOAc–petrol(40/60), 3 : 7); $[\alpha]_D^{22}$ = +170 (*c* 1.0, $CHCl_3$); ν_{max}/cm^{-1}($CHCl_3$) 2981, 1708, 1603, 1455, 1393, 1363, 1256, 1209, 1155; δ_H(400 MHz, $CDCl_3$) 1.45 (9H, s, C(CH_3)$_3$), 1.64–1.68 (1H, m, C(6)H_{endo}), 2.36–2.42 (1H, dd, *J* 13.6 and 7.2, CH_2CH), 2.62–2.67 (1H, m, C(6)H_{exo}), 2.76–2.81 (1H, dd, *J* 13.2 and 3.6, CH_2CH), 3.23–3.26 (1H, m, C(7)H), 3.55–3.58 (1H, t, *J* 6.0, C(4)H_{endo}), 4.08–4.12 (1H, m, C(5)H), 4.19–4.22 (1H, m, C(4)H_{exo}), 6.32 (1H, s, C(2)H), 7.23–7.45 (5H, m, PhH); δ_C(400 MHz, $CDCl_3$) 28.5 (C(CH_3)$_3$), 32.6 (C(6)), 36.6 (CH_2), 42.3 (C(7)), 57.1 (C(5)), 72.7 (C(4)), 81.3 ($CO_2C(CH_3)_3$), 87.2 (C(2)), 126.4, 128.8, 129.0, 129.4, 130.1, 134.9 (PhCH), 139.0 (PhC), 171.3 ($CO_2C(CH_3)_3$), 171.5 (C(8)); *m/z* (CI^+) 318 (M + H^+, 10%), 262 (100); HRMS (M + H^+) 318.1705; $C_{18}H_{24}NO_4$ requires 318.1701. The second product isolated was the *exo*-isomer as a colourless oil (36 mg, 7%). R_f = 0.39 [EtOAc–petrol(40/60), 3 : 7]; $[\alpha]_D^{22}$ = +68 (*c* 1.0, $CHCl_3$); ν_{max}/cm^{-1}($CHCl_3$) 3007, 2434, 2253, 1715, 1601, 1583, 1522, 1476, 1423, 1369, 1334, 1246, 1191; δ_H (400 MHz, $CDCl_3$) 1.37 (9H, s, C(CH_3)$_3$), 2.07–2.14 (1H, m, C(6)H_{endo}), 2.25–2.31 (1H, m, C(6)H_{exo}), 2.47–2.54 (1H, dd, *J* 16.2 and 10.0, CH_2CH), 2.77–2.81 (1H, dd, *J* 10.9 and 3.9, CH_2CH), 2.99–3.07 (1H, m, C(7)H), 3.40–3.45 (1H, t, *J* 8.6, C(4)H_{endo}), 4.03–4.10 (1H, m, C(5)H), 4.22–4.26 (1H, m, C(4)H_{exo}), 6.32 (1H, s, C(2)H), 7.28–7.48 (5H, m, PhH); δ_C (400 MHz, $CDCl_3$) 27.06 (C(6)), 28.01 (C(CH_3)$_3$), 37.58 (CH_2), 70.84 (C(7)), 56.96 (C(5)), 70.58 (C(4)), 81.20 ($C(CH_3)_3$), 87.59 (C(2)), 125.83, 128.38, 128.50, 129.72 (PhCH), 138.80 (PhC), 170.61 ($COOC(CH_3)_3$), 179.78 (C(8)); *m/z* (CI^+) 318 (M + H^+, 30%), 278, 262, 230, 174; HRMS (M + H^+) 318.1705; $C_{18}H_{24}NO_4$ requires 318.1702.

(2*R*, 5*S*, 7*S*)-7-(*N*-Benzyloxycarbonyl-2-aminoethyl)-8-oxo-2-phenyl-1-aza-3-oxa-bicyclo[3.3.0]octane (3b)

To a solution of nitrile **2a** (1.54 g, 6.37 mmol) in ethanol (125 ml) was added $CoCl_2.6H_2O$ (3.0 g, 12.75 mmol) and the mixture was stirred for 5 min. $NaBH_4$ (2.4 g, 63.76 mmol) was then added portionwise to the above blue solution, which was accompanied by effervescence. After 16 h stirring at room temperature, the ethanol was removed under a vacuum and ammonium hydroxide (3 ml) and ethyl acetate (70 ml) were added to the black residue with stirring. After 30 min, the black residue was removed by filtration through celite. The organic phase was washed with water (40 ml) and the aqueous phase extracted with EtOAc (3 × 15 ml). The combined organic phases were dried over $MgSO_4$ and evaporated *in vacuo* to give crude amine **3a** (1.2 g, 76% crude). To a chilled solution of this amine (1.08 g, 4.39 mmol) in THF (40 ml) was added freshly distilled benzylchloroformate (1.12 g, 6.58 mmol) and triethylamine (888 mg, 8.8 mmol) with vigorous stirring. After stirring the reaction mixture for 1.5 h, the THF was evaporated *in vacuo*, water (15 ml) and EtOAc (25 ml) were added and the aqueous phase was extracted with EtOAc (3 × 15 ml). The combined organic phases were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo* to give a colourless oil. Purification by flash colum chromatography (EtOAc–petrol(40/60), 3 : 2) gave the title compound **3b** (700 mg, 34% over two steps). R_f = 0.52 [EtOAc–petrol(40/60), 3 : 2]; $[\alpha]_D^{22}$ = +121 (*c* 1.0 in $CHCl_3$); ν_{max}/cm^{-1} ($CHCl_3$) 2400, 1706, 1603, 1587, 1518; δ_H (400 MHz, $CDCl_3$) 1.55–1.77 (2H, m, C(6)H_{endo}, CH_2CH), 1.98–2.1 (1H, m, CH_2CH), 2.57–2.64 (1H, m, C(6)H_{exo}), 2.89–2.97 (1H, m, C(7)H), 3.24–3.33 (1H, m, CH_2NH), 3.33–3.41 (1H, m, CH_2NH), 3.51 (1H, dd, *J* 15.7 and 7.8, C(4)H_{endo}), 4.06–4.15 (1H, m, C(5)H), 4.23 (1H, dd, *J* 7.8 and 6.5, C(4)H_{exo}), 5.09 (2H, s, CH_2Ph), 5.43 (1H, br, NH), 6.30 (1H, s, C(2)H), 7.30–7.44 (10H, m, ArH); δ_C (400MHz, $CDCl_3$) 30.71 (CH_2), 32.82, (C(6)), 39.16 (CH_2), 43.51 (C(7)), 56.83 (C(5)), 66.60 (CH_2Ph), 72.32 (C(4)), 86.77 (C(2)), 125.99, 128.08, 128.44, 128.47, 128.63 (ArC), 136.61 (ArC), 138.51 (ArC), 156.56 (NHCO), 178.35 (C(8)); *m/z* (CI^+) 403 (M + Na^+, 100%), 381 (M + H^+, 85), 337 (50), 273 (60); HRMS (M + H^+) 381.1804; $C_{22}H_{25}N_2O_4$ requires 381.1814.

(2*R*, 5*S*, 7*S*)-7-(*N*-Acetyl-2-aminoethyl)-8-oxo-2-phenyl-1-aza-3-oxa-bicyclo[3.3.0]octane (3c)

To a chilled solution at 0 °C of crude amine **3a** (354 mg, 1.44 mmol) in THF (25 ml) was added triethylamine (150 mg, 1.73 mmol), and the mixture stirred for 15 min. Freshly distilled acetic anhydride (176.3 mg, 1.73 mmol) was then added dropwise with vigorous stirring at 0 °C. After stirring the reaction mixture overnight at RT, the reaction mixture was concentrated *in vacuo*, and water (10 ml) and EtOAc (25 ml) were added. The aqueous phase was extracted with EtOAc (3 × 10 ml) and the combined organic phases were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo* to give a colourless oil. Purification by flash column chromatography (EtOAc–MeOH, 3 : 1) gave the title compound **3c** (248 mg, 60% over two steps). R_f = 0.52 (EtOAc–MeOH, 2 : 1); $[\alpha]_D^{22}$ = +157 (*c* 1.0 in $CHCl_3$); ν_{max}/cm^{-1} ($CHCl_3$) 1693, 1524, 1475, 1377, 1028, 929; δ_H (400 MHz, $CDCl_3$) 1.56–1.68 (2H, m, C(6)H_{endo}, CH_2CH), 1.92 (3H, s, CH_3CO), 1.95–2.12 (1H, m, CH_2CH), 2.56–2.63 (1H, m, C(6)H_{exo}), 2.87–2.95 (1H, m, C(7)H), 3.20–3.28 (1H, m, CH_2NH), 3.35–3.43 (1H, m, CH_2NH), 3.48–3.52 (1H, t, *J* 7.8, C(4)H_{endo}), 4.05–4.12 (1H, m, C(5)H), 4.18–4.22 (1H, dd, *J* 8.2 and 6.4, C(4)H_{exo}), 6.25 (1H, s, C(2)H), 6.98 (1H, br,

NHCO), 7.26–7.40 (5H, m, ArH); δ_C (400 MHz, $CDCl_3$) 23.14 (CH_3CO), 30.08 (CH_2), 33.02 (C(6)), 37.84 (CH_2), 44.18 (C(7)), 56.94 (C(5)), 72.31 (C(4)), 86.73 (C(2)), 125.96, 128.43, 128.70 (ArCH), 138.21 (ArC), 170.54 (NHCOMe), 178.39 (C(8)); *m/z* (CI^+) 289 ($M + H^+$, 100%).

(2*S*, 4*S*)-(*N*-Benzyloxycarbonyl-2-aminoethyl)-2-methyloxycarbonyl-5-oxo-pyrrolidine (4a)

To a solution of lactam **3b** (776 mg, 2.04 mmol) in DCM (39 ml) at RT was added TFA (1.57 ml, 20.4 mmol) with stirring. After 2 h, solvent was removed *in vacuo* and the residue purified by flash column chromatography (MeOH–EtOAc, 1 : 10) to give a pale yellow oil (511 mg, 85%). $R_f = 0.43$ (MeOH–EtOAc, 1 : 10); $[\alpha]_D^{22} = +32$ (*c* 1.0 in $CHCl_3$); ν_{max}/cm^{-1} ($CHCl_3$) 3432, 1789, 1702, 1224; δ_H (400 MHz, $CDCl_3$) 1.29–1.36 (1H, m, C(3)H), 1.48–1.53(1H, m, CH_2CH), 1.87–1.90 (1H, m, CH_2CH), 2.17–2.29 (1H, m, C(3)HH), 2.39–2.41 (1H, m, C(4)H), 3.20–3.29 (2H, m, CH_2CH), 3.30 (1H, d, *J* 6.36, C*H*OH), 3.61–3.63 (2H, m, C*H*OH and C(2)H), 5.04 (2H, s, CH_2Ph), 5.67–5.70 (1H, s, br, HNCO), 7.22–7.52 (5H, m, ArH); δ_C (400 MHz, $CDCl_3$) 29.28 (C(3)), 31.19 (CH_2), 39.03 (C(4) and (CH_2), 54.76 (C(2)), 65.31 (CH_2OH), 66.56 (CH_2Ph), 128.03, 128.45, 128.99 (ArCH), 136.58 (ArC), 156.79 (OC(O)N), 180.5 (C(8); *m/z* (CI^+) 293 ($M + H^+$, 15%), 249 (20), 185 (40), 159 (100); HRMS ($M + H^+$) 293.1501; $C_{15}H_{21}N_2O_4$ requires 293.1503.

To a stirred solution of the crude alcohol (343 mg, 1.17 mmol) in CH_3CN (10 ml) and CCl_4 (10 ml) was added a solution of $NaIO_4$ (754 mg, 3.52 mmol) in water (15 ml) and then RuO_2 (31.2 mg cat.). The mixture was stirred vigorously overnight. Solvents were removed *in vacuo* and the residue was dissolved in DMF, and then a solution of diazomethane in ether was added with stirring for 30 min. Water (30 ml) was added to the mixture and extracted with EtOAc (3 × 20 ml). The organic phases were combined, dried over $MgSO_4$ and concentrated *in vacuo* to give **4a** as a colourless oil (161 mg, 43% over two steps). $R_f = 0.47$ (MeOH–EtOAc, 1 : 20); $[\alpha]_D^{22} = +8.3$ (*c* 1.0 in $CHCl_3$); ν_{max}/cm^{-1} ($CHCl_3$) 1710, 1518, 1219; δ_H (400 MHz, $CDCl_3$) 1.63 (1H, ddd, *J* 20.2, 14 and 6.3, CH_2CH), 1.84 (1H, ddd, *J* 17.8, 12.9 and 8.9, C(3)H), 1.96 (1H, ddd, *J* 20.7, 13.8 and 6.9, CH_2CH), 2.45–2.51 (1H, m, C(4)H), 2.70 (1H, ddd, *J* 16.7, 12.8 and 8.5, C(3)H), 3.26–3.35 (2H, m, CH_2NH), 3.76 (3H, s, OCH_3), 4.17–4.22 (1H, m, C(2)H), 5.08 (2H, s, CH_2Ph), 5.42 (1H, br, NHCbz), 6.48 (1H, br, NH), 7.26–7.35 (5H, m, ArH); δ_C (400 MHz, $CDCl_3$) 31.15 (C(3)), 31.63 (CH_2), 38.96 (C(4)), 39.05 (CH_2), 52.63 (OCH_3), 53.66 (C(2)), 66.58 (CH_2Ph), 128.05 and 128.48 (ArCH), 136.57 (ArC), 156.56 (HNCOO), 172.01 (CO_2Me), 178.72 (CONH); *m/z* (CI^+) 343 ($M + Na^+$, 20%), 321, ($M + H^+$, 30), 187 (100); HRMS ($M + H^+$) 321.1450; $C_{16}H_{21}N_2O_5$ requires 321.1445.

(2*R*, 5*S*, 6*S*, 7*R*)-7-Ethyloxycarbonyl-6-cyanomethyl-8-oxo-2-phenyl-1-aza-3-oxa-bicyclo[3.3.0]octane (6a)

To activated Zn powder (3.2 g, 49 mmol) in THF (50 ml) under nitrogen atmosphere, iodine (290 mg, cat.) and bromoacetonitrile (0.93 ml, 13.7 mmol) were sonicated for 15 min at 35–40 °C. After cooling to 0 °C, DMPU (10 ml) was added followed by a solution of enone **5** (1.25 g, 4.57 mmol) in THF (40 ml). The mixture was quickly brought back to 40 °C using a heat gun and the solution was sonicated at that temperature for 15 min. After stirring for 1 h at room temperature, the reaction mixture was quenched with saturated aqueous NH_4Cl solution and EtOAc (50 ml) was added to the residue. The aqueous phase was extracted EtOAc (3 × 20 ml), and the combined organic phases were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash column chromatography (EtOAc–petrol(40/60), 1 : 2) gave the title compound **6a** (989 mg, 69%). $R_f =$ 0.7 (EtOAc–petrol(40/60), 1 : 1); $[\alpha]_D^{22} = +93$ (*c* 1.0 in $CHCl_3$); ν_{max}/cm^{-1} ($CHCl_3$) 1720; δ_H (400 MHz, $CDCl_3$) 1.35 (3H, t, *J* 7.2, CH_3CH_2), 2.59 (1H, dd, *J* 17.1 and 8.0, CHCN), 2.72 (1H, dd, *J* 9.1 and 2.2, CH′CN), 3.05–3.42 (1H, m, C(6)H), 3.72 (1H, d, *J* 11.1 and C(7)H), 3.86 (1H, dd, *J* 8.6 and 6.5, $C(4)H_{endo}$), 3.95 (1H, dd, *J* 13.6 and 6.5, C(5)H), 4.2–4.38 (3H, m, CH_3CH_2 and $C(4)H_{exo}$), 6.37 (1H, s, C(2)H), 7.33–7.44 (5H, m, ArH); δ_C (400 MHz, $CDCl_3$) 14.13 (CH_3), 20.01 (CH_2CN), 40.30 (C(6)), 56.22 (C(7)), 61.05 (C(5)), 62.45 (CH_3CH_2), 70.42 (C(4)), 87.45 (C(2)), 116.56, (CN), 125.80, 125.95, 126.02, 128.58, 128.79 (ArCH), 137.15 (ArCH)), 167.14 (CO_2Et), 169.67 (C(8)); *m/z* (CI^+) 337 ($M + Na^+$, 40%), 315 ($M + H^+$, 90), 232(65), 228(60); HRMS ($M–H^+$) 313.1188; $C_{17}H_{17}N_2O_2$ requires 313.1180.

(2*R*, 5*S*, 6*S*)-6-Cyanomethyl-8-oxo-2-phenyl-1-aza-3-oxa-bicyclo[3.3.0]octane (6b)

To the cyano ester **6a** (989 mg, 3.15 mmol) in toluene (125 ml) was added bis(tributyltin)oxide (3.47 ml, 6.30 mmol). After refluxing for 17 h, the reaction mixture was cooled, toluene was removed *in vacuo*, and water (30 ml) and ethyl acetate (40 ml) were added to the residue. The aqueous phase was extracted with EtOAc (3 × 20 ml), and the combined organic phases were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*, and the crude material purified using flash column chromatography [EtOAc–petrol(40/60), 1 : 1] to give the title compound **6b** (518 mg, 68%). $R_f = 0.27$ [EtOAc–petrol(40/60), 1 : 1]; $[\alpha]_D^{22} = +167$ (*c* 1.0 in $CHCl_3$); ν_{max}/cm^{-1} ($CHCl_3$) 2353, 1712, 1537, 1224; δ_H (400 MHz, $CDCl_3$) 2.51–2.80 (5H, m, C(6)H, $C(7)H_2$, CH_2CN), 3.70 (1H, t, *J* 7.7, $C(4)H_{endo}$), 3.92–3.97 (1H, m, C(5)H), 4.29 (1H, dd, *J* 8.6 and 6.4, $C(4)H_{exo}$), 6.37 (1H, s, C(2)H), 7.31–7.44 (5H, m, ArH), δ_C (400 MHz, $CDCl_3$) 21.51(CH_2CN), 36.32 (C(6)), 39.61 (C(7)), 63.43 (C(5)), 70.43 (C(4)), 87.37 (C(2)), 117.24 (CN), 125.83, 125.92, 128.54, 128.82 (ArCH), 137.69, (ArC), 175.26 (C(8)); *m/z* (CI^+) 243 ($M + H^+$, 100%), 149 (50); HRMS ($M–H^+$) 241.0977; $C_{14}H_{13}N_2O_2$ requires 241.0974.

(2*R*, 5*S*, 6*S*)-6-(*N*-Benzyloxycarbonyl-2-aminoethyl)-8-oxo-2-phenyl-1-aza-3-oxa-bicyclo[3.3.0]octane (7)

Using the method given for the reduction of nitrile **3b**, nitrile **6b** (447 mg, 1.85 mmol) was dissolved in ethanol (50 ml) and treated with $CoCl_2 \cdot 6H_2O$ (879 mg, 2.86 mmol) and $NaBH_4$ (702 mg, 14.34 mmol). Purification by flash colum chromatography (EtOAc–petrol(40/60), 7 : 3) gave the title compound **7** (309 mg, 44% over two steps). $R_f = 0.52$ (EtOAc–petrol(40/60), 7 : 3); $[\alpha]_D^{22} = +115$ (*c* 1.0 in $CHCl_3$); ν_{max}/cm^{-1} ($CHCl_3$) 1707, 1517; δ_H (400 MHz, $CDCl_3$) 1.73 (2H, ddd, *J* 18.9, 13.1 and 6.4, CH_2), 2.20–2.31 (1H, m, C(6)H), 2.51 (1H, dd, *J* 16.4 and 10.2, C(7)H), 2.68 (1H, dd, *J* 16.5 and 8.7, C(7)H), 3.17 (2H, ddd, *J* 18.1, 12.3 and 6.3, CH_2NH), 3.56 (1H, t, *J* 7.8, $C(4)H_{endo}$), 3.78–3.83 (1H, m, C(5)H), 4.22 (1H, *t*, *J* 7.4, $C(4)H_{exo}$), 5.01 (1H, br, NH), 5.09 (2H, s, CH_2Ph), 6.32 (1H, s, C(2)H), 7.30–7.45 (10H, m, ArH); δ_C (400 MHz, $CDCl_3$) 34.75, (CH_2), 37.32 (C(6)), 39.24 (CH_2), 40.64 (C(7)), 64.50 (C(5)), 66.82 (CH_2Ph), 71.34 (C(4), 86.85 (C(2)), 125.80, 125.95 (ArC), 128.14, 128.24, 128.44, 128.56, 128.61 (ArCH), 136.35 (ArC), 138.37 (ArC), 156.42 (HNCO), 176.53 (C(8)); *m/z* (CI^+) 403 ($M + Na^+$, 30%), 381 ($M + H^+$, 100); HRMS ($M + H^+$) 381.1814; $C_{22}H_{25}N_2O_2$ requires 381.1809.

(2*S*, 3*S*)-3-(*N*-Benzyloxycarbonyl-2-aminoethyl)-2-methyloxycarbonyl-5-oxo-pyrrolidine (8)

To a solution of lactam **7** (321 mg, 0.84 mmol) in DCM (8 ml) at RT was added TFA (0.65 ml, 8.4 mmol) while stirring. After 1 h at room temperature, the solvent was removed *in vacuo* and the residue purified by flash column chromatography (MeOH–EtOAc, 1 : 5) to give a pale yellow oil (511 mg, 92%). $R_f = 0.39$ (EtOAc–MeOH, 1 : 5); $[\alpha]_D^{22} = +23$ (*c* 1.0 in $CHCl_3$); ν_{max}/cm^{-1} ($CHCl_3$) 3620, 3418, 1780, 1710, 1220; δ_H (400 MHz, $CDCl_3$) 1.57–1.66 (1H, m, CHCH_2), 1.75–1.85 (1H, m, CHCH_2), 1.97–2.01 (1H, m, C(4)HH), 2.18–2.26 (1H, m, C(3)H), 2.51 (1H, dd, *J* 16.8 and 9.0, C(4)H), 3.21 (2H, dd, *J* 11.3 and 5.4, CH_2NH), 3.36–3.45 (1H, m, C(2)H), 3.46 (1H, dd, *J* 11.1 and 6.0, C*H*OH), 3.61 (1H, dd, *J* 11.4 and 4.1, C*H*OH), 5.06 (2H, s,

CH_2Ph), 6.49 (1H, br, NHC(O)), 7.32–7.41 (5H, m, ArH); δ_C (400 MHz, $CDCl_3$) 30.54 (C(3)), 35.70 (CH_2), 37.36 (C(4)), 39.50 (CH_2), 62.56 (C(2)), 65.17 (CH_2OH), 66.37 (CH_2Ph), 128.56, 129.13 (ArCH), 138.39 (ArC), 157.27 (HNCOO), 178.0 (C(5)); *m/z* (CI$^+$) 293 (M + H$^+$, 100%); HRMS (M + H$^+$) 293.1501; $C_{15}H_{21}N_2O_2$ requires 293.1503.

A solution of this alcohol (82 mg, 0.28 mmol) and pyridinium dichromate (489 mg, 1.40 mmol) in DMF was stirred at 40 °C for 16 h under N_2. After cooling to RT a solution of diazomethane (3 equiv.) in ether was added. The excess diazomethane was removed by purging nitrogen gas through the solution and then the mixture was poured into a saturated aqueous solution of $NaHCO_3$. The mixture was extracted with EtOAc (4 × 10 ml) and the combined organic phases were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash column chromatography (MeOH–EtOAc, 1 : 10) gave the title compound **8** as a colourless oil (28 mg, 30% over two steps). $R_f = 0.51$ (EtOAc–MeOH, 9 : 1); $[a]_D^{22} = +23$ (*c* 1.0 in $CHCl_3$); ν_{max}/cm^{-1} ($CHCl_3$) 1710, 1602, 1518; δ_H (400 MHz, $CDCl_3$) 1.70–1.77 (1H, m, CHCH_2), 1.90–1.97 (1H, m, CHCH_2), 2.06 (1H, dd, *J* 16.7 and 5.7, C(4)H), 2.53–2.63 (2H, m, C(3)H and C(4)H), 3.20–3.33 (2H, m, CH_2NH), 3.76 (3H, s, OCH_3), 3.91 (1H, d, *J* 5.0, C(2)H), 5.06 (1H, s, HNCbz), 5.1 (2H, s, CH_2Ph), 6.45 (1H, s, NHC(O)), 7.31 (5H, m, ArH); δ_C (400 MHz, $CDCl_3$) 35.2 (CH_2), 35.85 (C(4)), 36.10 (C(3)), 38.83 (CH_2), 52.63 (OCH_3), 60.55 (C(2)), 66.76 (CH_2Ph), 128.14, 128.19, 128.53 (ArCH), 136.34 (ArC), 156.35 (HN-COO), 171.97 (CO_2Me), 176.57 (C(8)); *m/z* (CI$^+$) 321 (M + H$^+$, 100%); HRMS (M + H$^+$) 321.1450; $C_{16}H_{21}N_2O_5$ requires 321.1445.

(2*R*, 5*S*, 6*S*)-6-(Carbamoylmethyl)-8-oxo-2-phenyl-1-aza-3-oxa-bicyclo[3.3.0]octane (9)

To a solution of lactam **6b** (208 mg, 0.83 mmol) in EtOH (15 ml) at room temperature were added H_2O_2 (35% aq, 960 µl, 10.8 mmol) and NaOH (1 M, 1.1 ml, 1.1 mmol). The mixture was stirred for 1 h at RT and then hydrolysed with water (2 ml). DCM (10 ml) was added and the aqueous layer was extracted with DCM (3 × 20 ml). The organic layer was dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude material was purified by flash column chromatography (EtOAc–MeOH, 9 : 1) afforded the amide **9** as a colourless oil (157 mg, 75%). $R_f = 0.28$ (EtOAc–MeOH, 9 : 1); ν_{max}/cm^{-1} ($CHCl_3$ film) 3408, 2909, 1682, 1413, 1224, 1047, 736; δ_H (400 MHz, $CDCl_3$) 2.30–2.65 (5H, m, C(6)H, C(7)H_2, CH_2CONH$_2$), 3.66 (1H, t, *J* 7.7, C(4)H$_{endo}$), 3.84 (1H, m, C(5)H), 4.28 (1H, t, *J* 7.2, C(4)H$_{exo}$), 6.10 (1H, s, NH*H*), 6.11 (1H, s, NH*H*), 6.24 (1H, s, C(2)H), 7.28–7.40 (5H, m, ArH); δ_H (500 MHz, $CDCl_3$–C_6H_6 1 : 1) 1.84 (1H, dd, *J* 15.8 and 9.8, C(7)*H*H), 1.97 (1H, dd, *J* 15.3 and 5.2, C(7)H*H*), 2.22 (1H, dd, *J* 15.8 and 9.7, C*H*HCONH$_2$), 2.41 (1H, m, C(6)H), 2.48 (1H, dd, *J* 15.9 and 8.9, CH*H*CONH$_2$), 3.54 (1H, t, *J* 8.2, C(4)H$_{endo}$), 3.61 (1H, m, C(5)H), 4.22 (1H, t, *J* 8.3, C(4)H$_{exo}$), 4.83 (1H, s, NH*H*), 5.23 (1H, s, NH*H*), 6.31 (1H, s, C(2)H), 7.19–7.44 (5H, m, ArH), δ_C (400 MHz, $CDCl_3$) 35.9 (C(6)), 39.1 (*C*H$_2$CONH$_2$), 40.4 (C(7)), 64.9 (C(5)), 72.1 (C(4)), 86.1 (C(2)), 126.0, 128.5, 128.7 (ArCH), 138.5 (ArC), 173.3, 176.1 (C(8) and CONH$_2$); *m/z* (ESI+) 283 (M + Na$^+$, 100%); HMRS (M + H$^+$) 261.1239; $C_{14}H_{17}N_2O_3$ requires 261.1244.

(2*R*, 4*S*)-(2-Hydroxymethyl-5-oxopyrrolidin-3-yl)acetamide (10)

Lactam **9** (189 mg, 0.73 mmol) was treated with TFA (560 µl, 7.3 mmol) in DCM (7.5 ml). Flash column chromatography (EtOAC–MeOH, 7 : 3) afforded the alcohol **10** as a colourless oil (88 mg, 70%). $R_f = 0.15$ (EtOAc–MeOH, 7 : 3); ν_{max}/cm^{-1} ($CHCl_3$ film) 3219, 2929, 1681, 1422, 1321, 1011; δ_H (400 MHz, D_2O) 2.05, 2.28–2.60 (5H, m, C(4)H_2, CH_2CONH$_2$, C(3)H), 3.40–3.48 (2H, m, C*H*HOH, C(2)H), 3.56 (1H, m, CH*H*OH); δ_C (400 MHz, D_2O) 33.1 (C(3)), 36.3, 39.5 (C(4), *C*H$_2$CONH$_2$), 61.7 (C(2)), 63.3 (CH_2OH), 177.4, 180.4 (CONH$_2$ and C(5)); *m/z* (ESI+) 236 (M + Na + CH_3CN^+, 100), 195 (M + Na$^+$, 50), 173 (MH$^+$, 30); HMRS (M + Na + CH_3CN^+) 236.1006; $C_9H_{15}N_3O_3Na$ requires 236.1011.

(2*R*, 5*S*, 6*S*, 7*R*, 1′*R*)-7-Ethyloxycarbonyl-6-((*N*,*N*-dibenzylcarbamoyl)methyl)-8-oxo-2-phenyl-1-aza-3-oxa-bicyclo[3.3.0]octane (13a)

To a suspension of activated zinc (333 mg, 5.3 mmol) in THF (11 ml) was added iodine (27 mg, 0.2 mmol), followed by *N*,*N*-dibenzyl-2-bromopropionamide **12a** (1.07 g, 3.2 mmol). The mixture was sonicated at 30–35 °C for 15 min. With stirring at 0 °C, DMPU (1.4 ml) followed by the enone **5** (292 mg, 1.1 mmol) were added and the mixture quickly warmed to 40 °C with a heat gun and then sonicated at 30–35 °C for 15 min. After 1 h at RT, the mixture was quenched with a solution of saturated ammonium chloride (5 ml) and ethyl acetate (5 ml), and the organic layer was separated, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude material was purified by flash column chromatography (petrol(40/60)–EtOAc 3 : 2) to afford **13a** as a yellow oil (185 mg, 34%). $R_f = 0.31$ (petrol(40/60)–EtOAc, 3 : 2); $[a]_D^{23} = +33.3$ (*c* 1.0 in $CHCl_3$); ν_{max}/cm^{-1} ($CHCl_3$ film) 3064, 3031, 2982, 1709, 1647, 1451, 1365, 1220, 1028, 911, 734, 700; δ_H (400 MHz, $CDCl_3$) 1.31 (3H, t, *J* 7.2 Hz, OCH_2CH_3), 2.60 (1H, m, C(6)C*H*H), 2.84 (1H, m, C(6)CH*H*), 3.20–3.29 (1H, m, C(6)H), 3.60 (1H, m, C(7)H), 3.85–3.91 (1H, m, C(5)H), 3.98 (1H, m, C(4)H$_{endo}$), 4.20–4.31 (2H, m, CH_3CH_2), 4.39–4.50 (3H, m, C*H*HPh and CH_2Ph), 4.60 (1H, m, C(4)H$_{exo}$), 4.75 (1H, d, *J* 14.7, CH*H*Ph), 6.12 (1H, s, C(2)H), 7.10–7.50 (15H, m, ArH); δ_C (400 MHz, $CDCl_3$) 14.2 (CH_3), 33.1 (C(6)*C*H$_2$), 40.0 (C(6)), 48.4 and 49.8 (CH_2Ph), 57.4 (C(7)), 61.9 (CH_3CH_2), 63.4 (C(5)), 73.2 (C(4)), 86.8 (C(2)), 125.8, 126.0, 126.2, 127.5, 127.9, 128.1, 128.2, 128.3, 128.5, 128.7, 129.1, 129.2 (ArCH), 135.9, 136.8, 138.5 (ArC)), 168.3, 170.1, 170.7 (C=O); *m/z* (ESI+) 535 (M + Na$^+$, 80%), 512 (M + H$^+$, 100%).

(2*R*, 5*S*, 6*S*, 7*R*, 1′*R*)-7-Ethyloxycarbonyl-6-(1-(*N*,*N*-dibenzyl-carbamoyl)ethyl)-8-oxo-2-phenyl-1-aza-3-oxa-bicyclo[3.3.0]-octane (13b)

To a suspension of activated zinc (334 mg, 5.4 mmol) in THF (11 ml) was added iodine (27 mg, 0.2 mmol), followed by *N*,*N*-dibenzyl-2-bromopropionamide **12b** (1.07 g, 3.2 mmol). The mixture was sonicated at 30–35 °C for 15 min. With stirring, DMPU (1.4 ml) followed by the enone **5** (292 mg, 1.1 mmol) were added and the mixture was sonicated at 30–35 °C for 15 min. After 1 h at RT, the mixture was quenched with a solution of saturated ammonium chloride (5 ml) and ethyl acetate (5 ml) and the organic layer was separated, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude material was purified by flash column chromatography (petrol(40/60)–EtOAc, 7 : 3) to afford **13b** as a yellow oil (471 mg, 84%). $R_f = 0.39$ (petrol(40/60)–EtOAc, 3 : 2); ν_{max}/cm^{-1} ($CHCl_3$ film) 3385, 1709, 1642, 1453, 735, 700; δ_H (400 MHz, $CDCl_3$) 1.21 (3H, t, *J* 7.0 , Me), 1.32 (3H, t, *J* 7.2 , OCH_2CH_3), 2.83–2.90 (1H, m, C(H)Me), 3.10–3.18 (1H, m, C(6)H), 3.65–3.7 (2H, m, C(4)H$_{endo}$ and C(7)H), 4.01–4.09 (1H, m, C(5)H), 4.19–4.35 (3H, m, CH_3CH_2 and C(4)H$_{exo}$), 4.45 (1H, d, *J* 14.7, C*H*HPh), 4.50 (2H, s, CH_2Ph), 4.73 (1H, d, *J* 14.7, CH*H*Ph), 6.31 (1H, s, C(2)H), 7.15–7.47 (15H, m, ArH); δ_C (400 MHz, $CDCl_3$) 14.1 (CH_3), 14.3 (CH_3), 37.2 (C(H)Me), 46.07 (C(6)), 48.6 and 49.8 (CH_2Ph), 53.4 (C(7)), 56.1 (C(5)), 59.0 (CH_3CH_2), 72.6 (C(4)), 86.8 (C(2)), 126.0, 126.1, 127.7, 127.9, 128.1, 128.2, 128.4, 128.5, 128.7, 129.0, 129.2 (ArCH), 136.3, 137.0, 138.2 (ArC)), 168.7, 170.5, 174.7 (C=O); *m/z* (ESI+) 549 (M + Na$^+$, 90%), 527 (M + H$^+$, 100%).

(2*S*, 3*S*, 4*S*, 1′*S*)-3-(1-(Dibenzylcarbamoyl)ethyl)-2-hydroxy-methyl-5-oxo-pyrrolidine-4-carboxylic acid ethyl ester (14)

Lactam **13b** (258 mg, 0.49 mmol) was treated with TFA (378 µL, 4.9 mmol) in DCM (5 ml). Flash column chromatography

(EtOAc–MeOH, 9 : 1) afforded the alcohol **14** as a colourless oil (161 mg, 75%). R_f = 0.40 (EtOAc–MeOH, 9 : 1); ν_{max}/cm^{-1} ($CHCl_3$ film) 3382, 2360, 1695, 1453, 1205, 1080, 700; δ_H (400 MHz, $CDCl_3$) 1.18–1.25 (6H, m, CH_3, CH_2CH_3), 2.88–2.95 (2H, m, C(3)H, C*H*Me), 3.46 (1H, m, C*H*HOH), 3.54 (1H, m, C(4)H), 3.63–3.68 (2H, m, CH*H*OH, C(2)H), 4.17 (2H, m, $CO_2CH_2CH_3$), 4.36–4.52, 4.79 (4H, m, CH_2Ph), 6.92 (1H, s, NH), 7.10–7.40 (10H, m, ArH); δ_C (400 MHz, $CDCl_3$) 13.8 (CH_3), 15.0 (OCH_2CH_3), 38.8, 42.4 (C(3), CHMe), 48.5, 49.8 (CH_2Ph), 52.8 (C(4)), 58.1 (C(2)), 62.2 (OCH_2CH_3), 64.6 (CH_2OH), 126.2, 127.6, 127.9, 128.1, 128.7, 129.1, 129.8 (ArCH), 136.1, 136.8 (ArC), 170.67, 173.4, 175.4 (CO_2Et, $CONH_2$ and C(5)); *m/z* (ESI+) 461(M + Na^+ 100), 439 (M + H^+, 40%); HMRS (M + H^+) 439.2232; $C_{25}H_{31}N_2O_5$ requires 439.2233.

(2*S*, 3*S*, 4*S*, 1′*S*)-3-(1-Dibenzylcarbamoyl-ethyl)-5-oxo-pyrrolidine-2,4-dicarboxylic acid 4-ethyl ester 2-methyl ester (15)

Lactam **14** (40 mg, 0.09 mmol) was treated with PDC (159 mg, 0.46 mmol) in DMF (2 ml), and then diazomethane in Et_2O. Flash column chromatography (EtOAc–MeOH, 98 : 2) afforded **15** as a colourless oil (23 mg, 54%). R_f = 0.55 (EtOAc–MeOH, 98 : 2); $[\alpha]_D^{23}$ −4.0 (*c* 1.3 in $CHCl_3$); ν_{max}/cm^{-1} ($CHCl_3$ film) 2980, 2360, 1714, 1639, 1437, 1209, 1029, 700; δ_H (400MHz, $CDCl_3$) 1.23 (3H, d, *J* 7.1, CH_3), 1.30 (3H, t, *J* 7.1, CH_2CH_3), 3.13 (1H, q, *J* 6.8, CHMe), 3.29 (1H, d, *J* 6.6, 5.7, C(3)H), 3.73 (3H, s, CO_2CH_3), 3.82 (1H, d, *J* 6.6, C(4)H), 4.10 (1H, d, *J* 5.7, C(2)H), 4.24 (2H, m, $CO_2CH_2CH_3$), 4.50–4.54, 4.70–4.74 (4H, m, CH_2Ph), 6.54 (1H, m, NH), 7.14–7.40 (10H, m, ArH); δ_C (400 MHz, $CDCl_3$) 14.1 (OCH_2CH_3), 15.8 (CH_3), 37.4 (*C*HMe), 45.1 (C(3)), 48.4, 49.8 (CH_2Ph), 51.5 (C(4)), 52.7 (CO_2CH_3), 56.8 (C(2)), 61.9 (OCH_2CH_3), 126.3, 127.6, 128.2, 128.7, 129.1 (ArCH), 136.2, 137.1 (ArC), 169.4, 171.3, 171.5, 174.7 (CO_2Me, CO_2Et, $CONH_2$ and C(5)); *m/z* (ESI+) 489(M + Na^+ 100); HMRS (M + H^+) 467.2185; $C_{26}H_{31}N_2O_6$ requires 467.2182.

7-Ethyloxycarbonyl-6-cyano-8-oxo-2-phenyl-1-aza-3-oxa-bicyclo[3.3.0]octane (16)

To a solution of **5** (618 mg, 2.25 mmol) in EtOH (7 ml) at RT was added KCN (176 mg, 2.7 mmol) dissolved in the minimal amount of water. After stirring 1 h at RT, the mixture was quenched with a solution of saturated ammonium chloride (5 ml) and extracted with EtOAc (2 × 7 ml). The organic layer was separated, dried over $MgSO_4$, filtered and concentrated *in vacuo* to give a purple oil. The crude material was purified by flash column chromatography (petrol(40/60)–EtOAc, 3 : 2) to afford **16** as a pale yellow oil and as a mixture of diastereomers (528 mg, 78%). R_f = 0.45 (petrol(40/60)–EtOAc, 3 : 2); ν_{max}/cm^{-1} ($CHCl_3$ film) 2985, 2254, 1725, 1450, 1330, 1214, 1179, 908, 732; δ_H (400 MHz, $CDCl_3$) major compound: 1.33 (3H, t, *J* 7.2 Hz, OCH_2CH_3), 3.73 (1H, m, C(6)H), 3.82 (1H, m, C(4)H_{endo}), 4.15 (1H, d, *J* 10.2Hz, C(7)H), 4.23–4.40 (4H, m, CH_3CH_2, C(5)H and C(4)H_{exo}), 6.30 (1H, s, C(2)H), 7.30–7.41 (5H, m, ArH); δ_C (400 MHz, $CDCl_3$) major compound: 14.1 (CH_3), 31.9 (C(6)), 55.2 (C(7)), 59.4 (C(5)), 62.9 (CH_3CH_2), 70.0 (C(4)), 87.9 (C(2)), 117.3 (CN), 125.9, 126.0, 128.6, 129.2 (ArCH), 136.7 (ArC)), 166.0 (CO_2Et), 168.3 (C(8)); minor compound: 14.0 (CH_3), 29.5, 33.4 (C(6)), 55.1, 55.6 (C(7)), 57.3, 61.2 (C(5)), 63.0, 63.2 (CH_3CH_2), 68.2–69.4 (C(4)), 87.8, 88.7 (C(2)), 116.0, 116.5 (CN), 125.9, 126.0, 126.6, 126.8, 128.4, 128.7, 129.0, 129.1 (ArCH), 136.3, 137.0 (ArC)), 165.8, 165.9 (CO_2Et), 168.5, 169.1 (C(8)); *m/z* (CI+) 301 (M + H^+, 100%); HMRS (M + H^+) 301.1183; $C_{16}H_{17}N_2O_4$ requires 301.1188.

(2*R*, 5*S*, 6*RS*)-6-Cyano-8-oxo-2-phenyl-1-aza-3-oxa-bicyclo[3.3.0]octane (17a, 18a)

A solution of nitrile **16** (223 mg, 0.74 mmol) and $(Bu_3Sn)_2O$ (756 μL, 1.48 mmol) in toluene (30 ml) was treated by analogy with the synthesis of **3b**. Flash column chromatography (DCM–MeOH, 98 : 2) afforded the mixture **17a** and **18a** as a pale yellow solid (95 mg, 58%). R_f = 0.45 (DCM–MeOH, 98 : 2); δ_H (400 MHz, $CDCl_3$) major compound 2.91 (1H, m, C(7)H), 3.09–3.20 (2H, m, C(6)H, C(7)H), 3.52 (1H, m, C(4)H_{endo}), 4.25 (1H, m, C(4)H_{exo}), 4.32 (1H, m, C(5)H), 6.35 (1H, s, C(2)H), 7.30–7.45 (5H, m, ArH), δ_C (400 MHz, $CDCl_3$) major compound: 28.6 (C(6)), 38.1 (C(7)), 61.6 (C(5)), 69.9 (C(4)), 87.8 (C(2)), 118.5 (CN), 125.9, 128.6, 129.1 (ArCH), 137.0, (ArC), 173.4 (C(8)); minor compound: 25.6 (C(6)), 37.0 (C(7)), 58.7 (C(5)), 68.0 (C(4)), 88.3 (C(2)), 117.6 (CN), 125.9, 128.6, 129.0 (ArCH), 137.6, (ArC), 174.2 (C(8)).

(2*R*, 5*S*, 6*S*)-6-(*N*-Benzyloxycarbonyl-2-aminomethyl)-8-oxo-2-phenyl-1-aza-3-oxa-bicyclo[3.3.0]octane (17b) and (2*R*, 5*S*, 6*R*)-6-(*N*-benzyloxycarbonyl-2-aminomethyl)-8-oxo-2-phenyl-1-aza-3-oxa-bicyclo[3.3.0]octane (18b)

By analogy with the synthesis of **7**, the mixture of nitriles **17a** and **18a** (85 mg, 0.37 mmol), $CoCl_2.H_2O$ (176 mg, 0.74 mmol) and $NaBH_4$ (140 mg, 3.7 mmol) in EtOH (10 ml) gave an amine which as used in the next step without further purification. The crude amine, benzoyloxycarbonyl chloride (79 μl, 0.55 mmol) and Et_3N (103 μl, 0.74 mmol) in THF (6.5 ml), followed by flash column chromatography (petrol(40/60)–EtOAc, 30 : 70) afforded **17b** as a pale yellow solid (76 mg, 56% over two steps) and **18b** as a pale yellow solid (10 mg, 8% over two steps); ν_{max}/cm^{-1} ($CHCl_3$ film) 3451, 3019,1710, 1514, 1215, 755; **17b**: R_f = 0.27 (petrol(40/60)–EtOAc, 30 : 70); δ_H (400 MHz, $CDCl_3$) 1.91–2.02 (1H, m, C(6)H), 2.16 (1H, dd, *J* 16.6 and 9.3, C(7)H_{exo}), 2.27 (1H, dd, *J* 16.6 and 7.6, C(7)H_{endo}), 2.80–2.87 (2H, m, CH_2NH), 3.16 (1H, t, *J* 7.8, C(4)H_{endo}), 3.49–3.57 (1H, m, C(5)H), 3.83 (1H, *t*, *J* 7.8, C(4)H_{exo}), 5.02 (1H, br, NH), 5.12 (2H, s, CH_2Ph), 6.58 (1H, s, C(2)H), 7.13–7.33 (8H, m, ArH), 7.53 (2H, m, ArH); δ_C (400 MHz, $CDCl_3$) 37.9 (C(7)), 39.7 (C(6)), 44.1 (CH_2), 62.5 (C(5)), 67.0 (CH_2Ph), 71.1 (C(4), 87.6 (C(2)), 126.7,128.8,128.8, 128.9 (ArCH), 137.4 (ArC), 139.9 (ArC), 156.8 (HNCO), 176.8 (C(8)); **18b**; R_f = 0.36 (petrol(40/60)–EtOAc, 30 : 70); δ_H (400 MHz, $CDCl_3$) 1.88 (1H, dd, *J* 17.2 and 6.6, C(7)H_{endo}), 2.07–2.17 (1H, m, C(6)H), 2.25 (1H, dd, *J* 17.2 and 9.2, C(7)H_{exo}), 2.54 (2H, m, C*H*HNH), 2.88 (2H, m, CH*H*NH), 3.18 (1H, m, C(4)H_{endo}), 3.40 (1H, m, C(5)H), 3.59 (1H, m, C(4)H_{exo}), 4.30 (1H, br, NH), 5.15 (2H, s, CH_2Ph), 6.60 (1H, s, C(2)H), 7.13–7.29 (6H, m, ArH), 7.38 (2H, m, ArH), 7.51 (2H, m, ArH).

(2*S*, 3*S*)-3-(*N*-Benzyloxycarbonyl-2-aminomethyl)-2-methyloxycarbonyl-5-oxo-pyrrolidine (19)

By analogy with the synthesis of **8**, lactam **17b** (170 mg, 0.46 mmol) and TFA (358 μl, 4.6 mmol) in DCM (4 ml), followed by flash column chromatography (EtOAc–MeOH, 5 : 1) afforded the alcohol as a pale yellow oil (56 mg, 44%). R_f = 0.31 (EtOAc–MeOH, 4 : 1); $[\alpha]_D^{22}$ = +32 (*c* 0.58 in $CHCl_3$); ν_{max}/cm^{-1} ($CHCl_3$ film) 3330, 3019, 1691, 1215, 756; δ_H (400 MHz, $CDCl_3$) 1.93–2.01 (1H, m, C(3)H), 2.16–2.31 (1H, m, C(4)*H*H), 2.32–2.49 (1H, m, C(4)H*H*), 3.02–3.20 (1H, m, C(2)H), 3.29–3.42 (2H, m, CH_2NH), 3.57 (1H, br, CH_2NH), 4.41 (2H, m, CH_2OH), 5.00 (2H, s, CH_2Ph), 6.09 (1H, br, NHC(O)), 7.09–7.35 (5H, m, ArH); δ_C (400 MHz, $CDCl_3$) 36.4 (C(3)), 43.9 (C(4)), 59.6 (C(2)), 60.4 (CH_2), 64.4 (CH_2OH), 66.7 (CH_2Ph), 127.9, 128.1, 128.5 (ArCH), 136.4 (ArC), 157.2 (HNCOO), 178.8 (C(5)); *m/z* (CI) 294 (MH^+, 100%), 311(40); HMRS 294.0978; (MH^+, $C_{14}H_{16}NO_6$ requires 294.0978).

This alcohol (50 mg, 0.18 mmol) was treated with PDC (313 mg, 0.90 mmol) in DMF (3.5 ml), immediately followed by diazomethane in Et_2O. Flash column chromatography (EtOAc–MeOH, 9 : 1) afforded **19** as a colourless oil (20 mg, 36%). R_f = 0.37 (EtOAc–MeOH, 9 : 1); ν_{max}/cm^{-1} ($CHCl_3$ film) 3435, 3018, 1708, 1215, 756; δ_H (400 MHz, $CDCl_3$) 2.16 (1H, dd,

J 17.3 and 5.4, C(4)H), 2.52 (1H, dd, *J* 17.3 and 9.2, C(4)H), 2.68–2.76 (1H, m, C(3)H), 3.31–3.41 (2H, m, CH_2NH), 3.73 (3H, s, OCH_3), 4.01 (1H, d, *J* 4.2, C(2)H), 5.10 (2H, s, CH_2Ph), 5.51 (1H, br, HNCbz), 6.77 (1H, br, NHC(O)), 7.20–7.39 (5H, m, ArH); δ_C (400 MHz, $CDCl_3$) 33.3 (C(4)), 38.7 (C(3)), 44.1 (CH_2), 52.8 (OCH_3), 58.6 (C(2)), 67.0 (CH_2Ph), 128.2, 128.3, 128.6 (ArCH), 136.2 (ArC), 156.8 (HN–COO), 172.0 (CO_2Me), 176.9 (C(8)); HMRS 307.1288; ($M + H^+$, $C_{15}H_{19}N_2O_5$ requires 307.1294).

(2*S*, 3*R*)-3-(*N*-Benzyloxycarbonyl-2-aminomethyl)-2-methyloxycarbonyl-5-oxo-pyrrolidine (20)

Lactam **18b** (90 mg, 0.24 mmol) was treated with TFA (189 µl, 2.4 mmol) in DCM (2.5 ml). Flash column chromatography (EtOAc–MeOH, 4 : 1) afforded the alcohol as a pale yellow oil (35 mg, 51%). $R_f = 0.25$ (EtOAc–MeOH, 4 : 1). This alcohol (35 mg, 0.13 mmol) was immediately treated with PDC (219 mg, 0.63 mmol) in DMF (2.5 ml), followed by diazomethane in Et_2O. Flash column chromatography (EtOAc–MeOH, 9 : 1) afforded **20** as a colourless oil (8 mg, 20%). $R_f = 0.33$ (EtOAc–MeOH, 9 : 1); δ_H (400 MHz, $CDCl_3$) 2.10–2.19 (1H, dd, *J* 17.3 and 6.2, C(4)*H*H), 2.49–2.59 (1H, dd, *J* 17.3 and 9.2, C(4)H*H*), 2.71–2.82 (1H, m, C(3)H), 2.29–2.47 (2H, m, CH_2NH), 3.79 (3H, s, OCH_3), 4.06 (1H, d, *J* 4.2, C(2)H), 5.10 (2H, s, CH_2Ph), 5.15 (1H, br, HNCbz), 5.99 (1H, br, NHC(O)), 7.30–7.40 (5H, m, ArH); δ_C (400 MHz, $CDCl_3$) 33.3 (C(4)), 38.7 (C(3)), 44.1 (CH_2), 52.7 (OCH_3), 58.5 (C(2)), 66.9 (CH_2Ph), 128.0, 128.2, 128.5 (ArCH); HMRS ($M + H^+$), 307.1288; $C_{15}H_{19}N_2O_5$ requires 307.1294.

(2*R*, 5*S*, 6*S*)-6-Carbamoyl-8-oxo-2-phenyl-1-aza-3-oxa-bicyclo[3.3.0]octane (21)

To a solution of diastereomers **17a** and **18a** (102 mg, 0.45 mmol) in EtOH (8 ml) at RT were added H_2O_2 (35% aq, 514 µl, 5.8 mmol) and NaOH (1 M, 0.58 ml, 0.58 mmol). The mixture was stirred for 1 h at RT and then hydrolysed with water (2 ml). DCM (10 ml) was added and the aqeous layer was extracted with DCM (3 × 20 ml). The organic layer was dried over $MgSO_4$, filtered and concentrated under vacuum. The crude material was purified by flash column chromatography (EtOAc–MeOH, 9 : 1) to afford the amide **21** as a pale yellow oil (39 mg, 35%). $R_f = 0.30$ (EtOAc–MeOH, 9 : 1); δ_H (400 MHz, $CDCl_3$) major compound: 2.70 (1H, m, C(7)H), 2.99–3.16 (2H, m, C(6)H, C(7)H), 3.65 (1H, m, C(4)H_{endo}), 4.20 (1H, m, C(4)H_{exo}), 4.37 (1H, m, C(5)H), 6.18 (1H, s, N*H*H), 6.31 (1H, s, C(2)H), 6.48 (1H, s, NH*H*), 7.28–7.43 (5H, m, ArH), δ_C (400 MHz, $CDCl_3$) major compound: 35.4 (C(7)), 44.7 (C(6)), 61.4 (C(5)), 70.7 (C(4)), 87.3 (C(2)), 126.0, 128.6, 128.9 (ArCH), 137.64, (ArC), 173.4, 176.0 (C(8) and $CONH_2$); *m/z* (ESI+) 247 ($M + H^+$, 100%); HMRS ($M + H^+$) 247.1084; $C_{13}H_{15}N_2O_3$ requires 247.1083.

(2*S*, 3*S*)-2-(Hydroxymethyl)-5-oxopyrrolidine-3-carboxamide (22)

To a solution of **21** (104 mg, 0.42 mmol) in DCM (4 ml) at room temperature was added TFA (326 µl, 4.2 mmol). After 1 h stirring at RT with exposure to air, the solvent was removed *in vacuo* to give a yellow sticky oil. The crude material was purified by flash column chromatography (EtOAc–MeOH, 7 : 3) to afford the alcohol **22** as a pale yellow oil (30 mg, 45%). $R_f = 0.30$ (EtOAc–MeOH, 7 : 3); δ_H (400 MHz, D_2O) 2.46 (1H, dd, *J* 17.7 and 6.2, C(4)*H*H), 2.65 (1H, dd, *J* 17.7 and 9.8, C(4)H*H*), 3.01–3.10 (1H, m, C(3)H), 3.48–3.65 (2H, m, CH_2OH), 3.80 (1H, m, C(2)H); δ_C (400 MHz, D_2O) 34.4 (C(4)), 41.5 (C(3)), 59.6 (C(2)), 63.4 (CH_2OH), 178.3, 179.4 ($CONH_2$ and C(5)); *m/z* (ESI+) 181($M + Na^+$ 100), 159 ($M + H^+$, 5%); HMRS ($M + Na^+$) 181.0591; $C_6H_{10}N_2O_3Na$ requires 181.0589.

(2*R*,5*S*,7*S*)-7-(*N*-*tert*-Butyloxycarbonylamino)-8-oxo-2-phenyl-1-aza-3-oxa-bicyclo[3.3.0]octane (23)

To *n*-BuLi (0.54 ml, 1.18 mmol) at 0 °C in THF (2 ml) was added diisopropylamine (0.17 ml, 1.18 mmol) and the mixture stirred for 15 min, and then cooled to −78 °C. A solution of lactam **1a** (200 mg, 0.98 mmol) in THF (3 ml) was then added to the reaction mixture at −78 °C. After 30 min, diphenylphosphorylazide (0.42 ml, 1.97 mmol) was added and the mixture stirred for 5 min, di-*tert*-butyl-dicarbonate (430 mg, 1.97 mmol) was then added and the reaction mixture stirred overnight. Solvent concentration *in vacuo* and flash column chromatography (EtOAc–petrol(40/60), 1 : 3) gave compound **23** as a pale yellow solid (144 mg, 46%). $R_f = 0.28$ (EtOAc–petrol(40/60), 3 : 7); $[a]_D^{22} = +201$ (*c* 1.0 in $CHCl_3$), ν_{max}/cm^{-1} ($CHCl_3$) 2320, 1710, 1700; δ_H (400 MHz, $CDCl_3$) 1.46 (9H, s, 3xCH_3), 1.73–1.81 (1H, m, C(6)H_{endo}), 2.93–3.03 (1H, m, C(6)H_{exo}), 3.63 (1H, dd, *J* 8.2 and 7.3, C(4)H_{endo}), 4.03–4.10 (1H, m, C(5)H), 4.24–4.27 (1H, dd, *J* 8.2 and 6.4, C(4)H_{exo}), 4.63–4.64 (1H, m, C(7)H), 5.25 (1H, br, NH), 6.35 (1H, s, C(2)H), 7.18–7.44 (5H, m, ArH); δ_C (400 MHz, $CDCl_3$) 28.29 (C(CH_3)$_3$), 35.83 (C(6)), 55.05 (C(5)), 55.17 (C(7)), 72.07 (C(4)), 86.95 (C(2)), 126.08, 128.49, 128.79, 129.75 (ArCH), 137.783 (ArC), 155.52 (NHC(O)), 174.02 (C(8)); *m/z* (CI^+) 341 ($M + Na^+$, 20%), 263 (100); HRMS ($M + H^+$) 319.1657; $C_{17}H_{23}N_2O_4$ requires 319.1658.

(2*S*, 4*S*)-(*N*-Benzyloxycarbonylamino)-2-methyloxycarbonyl-5-oxo-pyrrolidine (25)

To a stirred solution of carbamate **23** (124 mg, 0.39 mmol) in DCM (10 ml) at RT was added TFA (0.3 ml, 3.9 mmol). After 1 h, the solvent was removed *in vacuo* to give a pale yellow gum which was purified by ion exchange chromatography to give alcohol **24a** as a colourless oil (50 mg, 98%). ν_{max}/cm^{-1} ($CHCl_3$) 3420, 1690, 1220; δ_H (400 MHz, DMSO-d_6) 1.43–1.49 (1H, m, C(3)H), 2.42–2.48 (1H, m, C(3)H), 3.39–3.43 (1H, m, CHOH), 3.55–3.61 (2H, m, CHOH and C(2)H), 3.65–3.69 (1H, m, C(4)H); δ_C (400 MHz, DMSO-d_6) 31.14 (C(3)), 51.81 (C(2)), 52.82 (C(4)), 63.28 (*C*HHOH), 180.31 (CO); *m/z* (CI^+) 131 ($M + H^+$, 70%).

To a solution of this amino alcohol (31 mg, 0.24 mmol) in THF (5 ml) was added freshly distilled benzyl chloroformate (0.04 ml, 0.26 mmol) and triethylamine (0.07 ml, 0.47 mmol) with vigorous stirring. After stirring the reaction mixture for 2 h, THF was removed *in vacuo*, and water (5 ml) and EtOAc (10 ml) were added. The aqueous phase was extracted with EtOAc (3 × 5 ml), and the combined organic phases were washed with brine and dried over $MgSO_4$ and concentrated *in vacuo* to give carbamate **24b** as a colourless oil. To this crude material (28 mg) was added pyridinium dichromate (204.4 mg, 0.58 mmol) in DMF (3.0 ml) and the resultant mixture was stirred overnight at 40 °C under N_2. After cooling to RT, a solution of diazomethane (2 equivalents) in ether was added. The excess diazomethane was removed by purging nitrogen gas through the solution, and the mixture was poured into a saturated aqueous solution of $NaHCO_3$ which was then extracted with EtOAc (4 × 5 ml). The combined organic phases were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo* to give a colourless oil. Purification by flash column chromatography (EtOAc 100%) gave the title compound **25** (8 mg, 26% over two steps). $R_f = 0.37$ (100% EtOAc); $[\alpha]_D^{22} = +12$ (*c* 1.0 in $CHCl_3$), ν_{max}/cm^{-1} ($CHCl_3$) 3435, 2360, 2340, 1720, 1510; δ_H (400 MHz, $CDCl_3$) 2.02–2.10 (1H, m, C(3)H_{endo}), 3.07–3.12 (1H, m, C(3)H_{exo}), 3.83 (3H, s, OCH_3), 4.25–4.29 (1H, m, C(2)H), 4.40–4.45 (1H, m, C(4)H), 5.12 (1H, d, J 12.1, CHPh), 5.17 (1H, d, J 12.1, CHPh), 5.63 (1H, br, NHCbz), 6.70 (1H, br, NHC(O)), 7.35–7.42 (10H, m, ArH); δ_C (400 MHz, $CDCl_3$) 33.74 (C(3)), 51.75 (C(4)), 52.12 (C(2)), 52.79 (OCH_3), 67.08 (CH_2Ph), 128.06, 128.17, 128.51 (ArCH), 136.15 (ArC), 156.35 (HN*C*OO), 171.39 (*C*O_2Me), 173.81 (C(5)); *m/z* (CI^+) 315 ($M + Na^+$, 60%), 293 ($M + H^+$, 50), 249 (100); HRMS ($M + H^+$) 293.1132; $C_{14}H_{17}N_2O_5$ requires 293.1137.

Acknowledgements

We thank the Felix Foundation for funding of a studentship to RG GSK and EPSRC for funding (ELB) and we wish to gratefully acknowledge the use of the EPSRC Chemical Database Service at Daresbury[90] and the EPSRC National Mass Spectrometry Service Centre at Swansea.

References

1 G. L. Olson, D. R. Bolin, M. P. Bonner, M. Bos, C. M. Cook, D. C. Fry, B. J. Graves, M. Hatada, D. E. Hill, M. Kahn, V. S. Madison, V. K. Rusiecki, R. Sarabu, J. Sepinwall, G. P. Vincent and M. E. Voss, *J. Med. Chem.*, 1993, **36**, 3039.
2 M. D. Fletcher and M. M. Campbell, *Chem. Rev.*, 1998, **98**, 763.
3 J. Gante, *Angew. Chem., Int. Ed. Engl.*, 1994, **33**, 1699.
4 J. S. Nowick, *Acc. Chem. Res.*, 1999, **32**, 287.
5 S. H. Gellman, *Acc. Chem. Res.*, 1998, **31**, 173.
6 R. P. Cheng, S. H. Gellman and W. F. Degrado, *Chem. Rev.*, 2001, **101**, 3219.
7 M. W. Peczuh and A. D. Hamilton, *Chem. Rev.*, 2000, **100**, 2479.
8 J. Venkatraman, S. C. Shankaramma and P. Balaram, *Chem. Rev.*, 2001, **101**, 3131.
9 A. J. Souers and J. A. Ellman, *Tetrahedron*, 2001, **57**, 7431.
10 S. E. Gibson, N. Guillo and M. J. Tozer, *Tetrahedron*, 1999, **55**, 585.
11 A. Dutta, in *Amino Acids, Proteins and Peptides*, ed. J. S. Davies, Royal Society of Chemistry, Cambridge, 1998, vol. 29.
12 S. Hanessian, G. McNaughton-Smith, H.-G. Lombart and W. D. Lubell, *Tetrahedron*, 1997, **53**, 12789.
13 S. A. Habay and C. E. Schafmeister, *Org. Lett.*, 2004, **6**, 3369.
14 L. Belvisi, L. Colombo, L. Manzoni, D. Potenza and C. Scolastico, *SYNLETT*, 2004, 1449.
15 D. E. Davies, P. M. Doyle, R. D. Hill and D. W. Young, *Tetrahedron*, 2004, **61**, 301.
16 M. G. Moloney, *Nat. Prod. Rep.*, 2002, **19**, 597.
17 P. W. Smith, A. R. Whittington, K. N. Cobley, A. Jaxa-Chamiec and H. Finch, *J. Chem. Soc., Perkin Trans. 1*, 2001, 21.
18 S. Hanessian, R. Margarita, A. Hall and X. Luo, *Tetrahedron Lett.*, 1998, **39**, 5883.
19 S. Hanessian, N. Bernstein, R.-Y. Yang and R. Maguire, *Bioorg. Med. Chem. Lett.*, 1999, **9**, 1437.
20 S. Hanessian and R. Margarita, *Tetrahedron Lett.*, 1998, **39**, 5887.
21 Q. Wang, N. A. Sasaki and P. Potier, *Tetrahedron*, 1998, **54**, 15759.
22 R. Sharma and W. D. Lubell, *J. Org. Chem.*, 1996, **61**, 202.
23 P. J. Murray, *Tetrahedron Lett.*, 1998, **39**, 6721.
24 N. Pellegrini, M. Schmitt and J.-J. Bourguignon, *Tetrahedron Lett.*, 2003, **44**, 6779.
25 J. Quancard, A. Labonne, Y. Jacquot, G. Chassaing, S. Lavielle and P. Karoyan, *J. Org. Chem.*, 2004, **69**, 7940.
26 S. Cappelletti, M. Pegna, A. Zaliani and M. Pinori, *Lett. Pept. Sci.*, 1995, **2**, 161.
27 J. Eustache, A. Grob, C. Lam, O. Sellier and G. Schulz, *Bioorg. Med. Chem. Lett.*, 1998, **8**, 2961.
28 T. E. Renau, R. Leger, L. Filonova, E. M. Flamme, M. Wang, R. Yen, D. Madsen, D. Griffith, S. Chamberland, M. N. Dudley, V. J. Lee, O. Lomovskaya, W. J. Watkins, T. Ohta, K. Nakayama and Y. Ishida, *Bioorg. Med. Chem. Lett.*, 2003, **13**, 2755.
29 R. Zhang and J. S. Madalengoitia, *J. Org. Chem.*, 1999, **64**, 330.
30 R. Zhang, A. Mamai and J. S. Madalengoitia, *J. Org. Chem.*, 1999, **64**, 547.
31 R. Zhang, F. Brownewell and J. S. Madalengoitia, *Tetrahedron Lett.*, 1999, **40**, 2707.
32 J. S. Sabol, G. A. Flynn, D. Friedrich and E. W. Huber, *Tetrahedron Lett.*, 1997, **38**, 3687.
33 C. Dugave, J. Cluzeau, A. Menez, M. Gaudry and A. Marquet, *Tetrahedron Lett.*, 1998, **39**, 5775.
34 M. F. Brana, M. Garranzo and J. Perez-Castells, *Tetrahedron Lett.*, 1998, **39**, 6569.
35 M. Anwar, J. H. Bailey, L. Dickinson, H. Edwards, R. Goswami and M. G. Moloney, *Org. Biomol. Chem.*, 2003, **1**, 2364.
36 J. H. Grimes, Y. M. Angell and W. D. Kohn, *Tetrahedron Lett.*, 2003, **44**, 3835.
37 P. K. C. Paul, D. J. Osguthorpe and M. M. Campbell, *J. Chem. Soc., Perkin Trans. 1*, 1990, 3363.
38 P. K. C. Paul, P. A. Burney, M. M. Campbell and D. J. Osguthorpe, *Bioorg. Med. Chem. Lett.*, 1992, **2**, 141.
39 J. A. Monn, M. J. Valli, R. A. True, D. D. Schoepp, J. D. Leander and D. Lodge, *Bioorg. Med. Chem. Lett.*, 1993, **3**, 95.
40 P. W. H. Chan, I. F. Cottrell and M. G. Moloney, *J. Chem. Soc., Perkin Trans. 1*, 2001, 2997.
41 P. W. H. Chan, I. F. Cottrell and M. G. Moloney, *J. Chem. Soc., Perkin Trans. 1*, 2001, 3007.
42 J. H. Bailey, D. Cherry, J. Dyer, M. G. Moloney, M. J. Bamford, S. Keeling and R. B. Lamont, *J. Chem. Soc., Perkin Trans. 1*, 2000, 2783.
43 J. Dyer, S. Keeling, A. King and M. G. Moloney, *J. Chem. Soc., Perkin Trans. 1*, 2000, 2793.
44 W. Wang, J. Yang, J. Ying, C. Xiong, J. Zhang, C. Cai and V. J. Hruby, *J. Org. Chem*, 2002, **67**, 6353.
45 C. Z. Cai, V. A. Soloshonok and V. J. Hruby, *J. Org. Chem.*, 2001, **66**, 1339.
46 V. A. Soloshonok, C. Z. Cai, V. J. Hruby, L. Van Meervelt and T. Yamazaki, *J. Org. Chem.*, 2000, **65**, 6688.
47 C. Z. Cai, V. J. Hruby and V. A. Soloshonok, *Abstr. Pap. Am. Chem. Soc.*, 2000, **219**, 225.
48 V. A. Soloshonok, C. Z. Cai and V. J. Hruby, *Angew. Chem., Int. Ed.*, 2000, **39**, 2172.
49 V. A. Soloshonok, C. Z. Cai and V. J. Hruby, *Tetrahedron Lett.*, 2000, **41**, 135.
50 V. A. Soloshonok, C. Z. Cai and V. J. Hruby, *Tetrahedron: Asymmetry*, 1999, **10**, 4265.
51 V. A. Soloshonok, C. Z. Cai, V. J. Hruby, L. Van Meervelt and N. Mischenko, *Tetrahedron*, 1999, **55**, 12031.
52 R. Zhang, F. Brownewell and J. S. Madalengoitia, *J. Am. Chem. Soc.*, 1998, **120**, 3894.
53 C. Cai, T. Yamada, R. Tiwari, V. J. Hruby and V. A. Soloshonok, *Tetrahedron Lett.*, 2004, **45**, 6855.
54 R. Goswami and M. G. Moloney, *Chem. Commun.*, 1999, 2333.
55 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.
56 J. H. Bailey, A. T. J. Byfield, P. J. Davis, A. C. Foster, M. Leech, M. G. Moloney, M. Muller and C. K. Prout, *J. Chem. Soc., Perkin Trans. 1*, 2000, 1977.
57 J. Dyer, S. Keeling and M. G. Moloney, *Tetrahedron Lett.*, 1996, **37**, 4573.
58 J. C. Dubois, J. P. Guette and H. B. Kagan, *Bull. Soc. Chim. Fr.*, 1966, 3008.
59 M. Gaudemar and J. Cure, *Bull. Soc. Chim. Fr.*, 1969, 2471.
60 J. L. Moreau, Y. Frangin and M. Gaudemar, *Bull. Soc. Chim. Fr.*, 1970, 4511.
61 G. Daviaud, M. Massy and P. Migniac, *Tetrahedron Lett.*, 1970, **11**, 5169–5170.
62 C. Gandolfi, G. Doria, M. Amendola and E. Dradi, *Tetrahedron Lett.*, 1970, **11**, 3923.
63 N. Goasdoue and M. Gaudemar, *J. Organomet. Chem.*, 1972, **39**, 17.
64 R. Gopalchari and R. N. Iyer, *Indian J. Chem., Sect. B*, 1976, **14**, 700.
65 B. S. Bronk, S. J. Lippard and R. L. Danheiser, *Organometallics*, 1993, **12**, 3340.
66 R. Menicagli and S. Samaritani, *Tetrahedron*, 1996, **52**, 1425.
67 A. G. Brewster, S. Broady, M. Hughes, M. G. Moloney and G. A. Woods, *Org. Biomol. Chem.*, 2004, **2**, 1800.
68 S. Araki, T. Shimizu, S. J. Jin and Y. Butsugan, *J. Chem. Soc., Chem. Commun.*, 1991, 824.
69 K. Lee, H. Kim, T. Miura, K. Kiyota, H. Kusama, S. Kim, N. Iwasawa and P. H. Lee, *J. Am. Chem. Soc.*, 2003, **125**, 9682.
70 P. H. Lee, H. Kim, K. Lee, D. Seomoon, S. Kim, H. Kim, H. Kim, M. Lee, E. Shim, S. Lee, M. Kim, M. Han, K. Noh and M. Sridhar, *Bull. Korean Chem. Soc.*, 2004, **25**, 1687.
71 I. Perez, J. P. Sestelo, M. A. Maestro, A. Mourino and L. A. Sarandeses, *J. Org. Chem.*, 1998, **63**, 10074.
72 C. J. Salomon, E. G. Mata and O. A. Mascarotti, *J. Org. Chem.*, 1994, **59**, 7259.
73 C. R. Hauser, B. E. Hudson, B. Abramovitch and J. C. Shivers, *Org. Synth.*, 1955, **3**, 142.
74 Y. Aoyagi, R. Asakura, N. Koudah, R. Yamamoto, T. Kuromatsu, A. Shimura and A. Ohta, *Synthesis*, 1996, 970.
75 J. Ciller, C. Seoane and J. L. Sato, *Liebigs Ann. Chem.*, 1985, **1**, 51.
76 R. Shankar and A. I. Scott, *Heterocycles*, 1996, **42**, 145.
77 K. Tanaka and H. Sawanishi, *Tetrahedron: Asymmetry*, 2000, **11**, 3837.
78 T. Lehmann, D. Michel, M. Glanzel, R. Waibel and P. Gmeiner, *Heterocycles*, 1999, **51**, 1389.
79 A. Nouvet, M. Binard, F. Lamaty, J. Martinez and R. Lazaro, *Tetrahedron*, 1999, **55**, 4685.
80 P. Benovsky, G. A. Stephenson and J. R. Stille, *J. Am. Chem. Soc.*, 1998, **120**, 2493.

81 S. Derrer, N. Feeder, S. J. Teat, J. E. Davies and A. B. Holmes, *Tetrahedron Lett.*, 1998, **39**, 9309.
82 J. M. Vilalgorodo, A. Linden and H. Heimgartner, *Helv. Chim. Acta*, 1996, **79**, 213.
83 Structures optimised with Chem 3D Pro 3 (MM2 parameters), available from Cambridge Scientific.
84 N. Isaacs, *Physical Organic Chemistry*, Longman, London, 1995, p. 98.
85 R. W. Hoffmann, *Chem. Rev.*, 1989, 1841.
86 D. Seebach, B. Lamatsch, R. Amstutz, A. K. Beck, M. Dobler, M. Egli, R. Fitzi, M. Gautschi, B. Herradon, P. C. Hidber, J. J. Irwin, R. Locher, M. Maestro, T. Maetzke, A. Mourino, E. Pfammatter, D. A. Plattner, C. Schlickli, W. B. Schweizer, P. Seiler, G. Stucky, W. Petter, J. Escalante, E. Juaristi, D. Quintana, C. Miravitlles and E. Molins, *Helv. Chim. Acta*, 1992, **75**, 913.
87 K. Ando, N. S. Green, Y. Li and K. N. Houk, *J. Am. Chem. Soc.*, 1999, **121**, 5334.
88 G. D. Rose, L. M. Gierasch and J. A. Smith, *Adv. Protein Chem.*, 1985, **37**, 1.
89 N. J. Ede, I. D. Rae and M. T. W. Hearn, *Tetrahedron Lett.*, 1990, **31**, 6071.
90 D. A. Fletcher, R. F. McMeeking and D. Parkin, *J. Chem. Inf. Comput. Sci.*, 1996, **36**, 746.