Pyrrolidinones derived from (*S*)-pyroglutamic acid. Part 3. β-Aminopyrrolidinones

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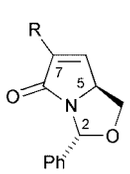
Received (in Cambridge, UK) 26th July 2001, Accepted 19th September 2001
First published as an Advance Article on the web 25th October 2001

The conjugate addition of activated nitrogen nucleophiles, such as hydroxylamine and hydrazine derivatives, to α,β-unsaturated bicyclic lactam **1a** gave the corresponding β-amino products **9a**–**g** in good yield and excellent diastereoselectivity. These products can be manipulated to afford enantiopure β-aminopyrrolidinones of potential application as conformationally-constrained, substituted glutamate templates of well-defined stereochemistry.

Much attention has focused on the use of asymmetric β-amino acids as α-amino acid surrogates,[1] and more recently these compounds have found application in stereochemically well-defined bicyclic templates as mechanism-based protease inhibitors[2] and artificial receptors.[3] Such compounds can now be accessed by a diversity of synthetic methodology.[4–6] A particularly valuable approach to this class of compound is by diastereocontrolled or enantiocontrolled conjugate addition of nitrogen nucleophiles to an α,β-unsaturated system.[7] We have recently reported the application of the unsaturated bicyclic lactam **1a** derived from pyroglutamic acid for the synthesis of highly functionalised pyrrolidinones[8,9] as excitatory amino acid analogues.[10] A key step in this synthesis used a conjugate addition of a zinc enolate, and the efficiency of this process suggested that an obvious extension would be to heteroatom nucleophiles. Although the conjugate addition of amines,[11–14] azides,[15] amine equivalents,[16–22] and more recently chiral amines[23,24] is relatively well known for acyclic systems[25,26] and for unsaturated lactones,[27] these reactions are less common in pyrrolidinone substrates.[28] However, Langlois and Calvez[29] and we[30,31] recently disclosed that conjugate addition of nitrogen nucleophiles to unsaturated bicyclic lactams was viable. A related bicyclic lactam, extensively investigated by Meyers, has been shown to undergo conjugate addition with a variety of carbon and heteroatom nucleophiles under mild conditions,[32,33] and the value of aminopyrrolidinones as novel ligand systems is evident from some work of Rapoport and Williams.[34] We report here that the α,β-unsaturated lactam **1a** is a useful template for conjugate additions of nitrogen nucleophiles, giving the corresponding β-amino products **9a**–**g** in good yield with high diastereocontrol, providing a direct route to conformationally well-defined β-amino-γ-lactams.

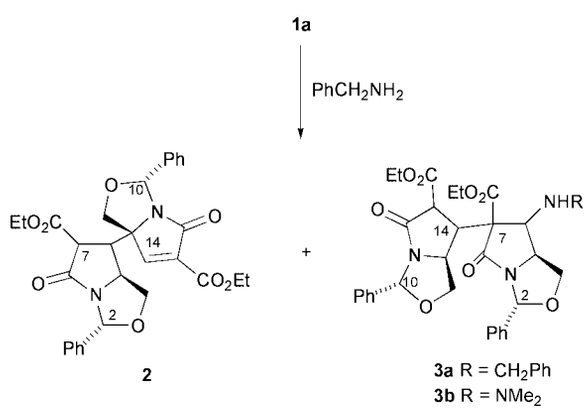


1a R = CO_2Et
1b R = H

Results and discussion

Conjugate addition reactions

We found that the enone **1b** was unreactive with benzylamine and *O*-benzylhydroxylamine under the reported reaction conditions for closely related substrates,[35,36] although conditions for the successful conduct of this transformation have been recently reported.[29,37,38] However, the activated lactam **1a** was found to be highly reactive with benzylamine in DCM containing 2–10 equivalents of water as a proton source (Scheme 1),

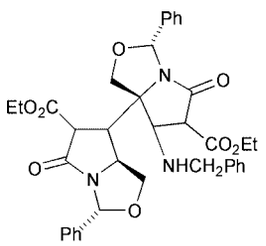


Scheme 1

and the observed products were the dimer **2**[39] (arising by the direct condensation of 2 molecules of **1a**) and adduct **3a** (arising by initial conjugate addition of benzylamine followed by trapping of the resulting enolate with enone **1a**), in yields of 60 and 30% respectively, both as single diastereomers but whose relative stereochemistry could not be assigned due to overlapping signals in their ^{1}H NMR spectra. For this reason also, the structure of **3a** could not be unequivocally confirmed, and another possibility was adduct **4**. That product **3a** in fact possessed the structure shown, and not the alternative **4**, which would have arisen by initial dimerisation of **1b** to **2** followed by conjugate addition of benzylamine and might have been expected to possess a similar NMR spectrum to **3a**, was shown by treating dimer **2** with benzylamine; dimer **2** was recovered

DOI: 10.1039/b106782f

almost quantitatively. Similar dimerisations have been reported in the conjugate additions of thiols to unsaturated lactones[40] and also in a related enone system.[41] The acidity of the γ-hydrogen of lactam **1a**, crucial to this dimerisation process, has been used to synthetic advantage in a related system.[42] Alteration of the number of equivalents of water, the reaction time, the solvent (DCM or THF), the proton source (by using nitrophenol or dinitrophenol in place of water) or the amine (by using aniline or sodium phthalimide in place of benzylamine) did not prevent the formation of these dimeric products, nor could simple conjugate addition be obtained. However, the fact that the product **3a** was obtained at all indicated that conjugate addition was indeed possible, although clearly quenching of the intermediate enolate formed in this process was problematic.



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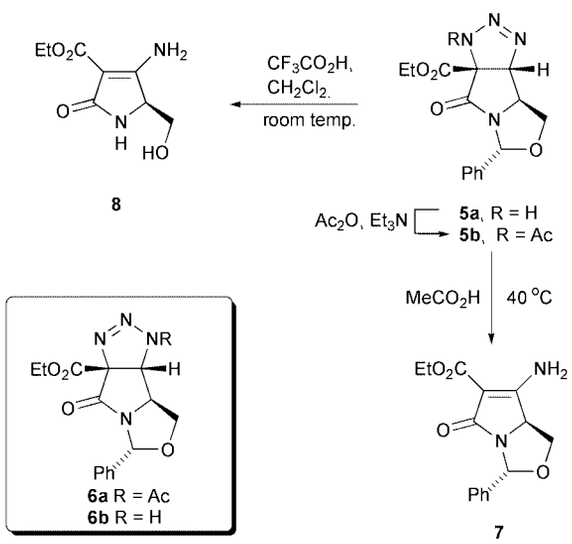
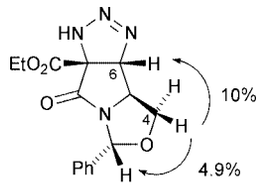
Since the unfavourable basicity of benzylamine was clearly the cause of the dimerisation process, examination of less basic azide was made. However, sodium azide addition to **1a** in acetic acid–THF solvent in fact gave pyrazoline **5a** as a single diastereomer in excellent yield (80%) (Scheme 2); *p*-nitro-



Scheme 2

benzenesulfonyl azide and mesyl azide were unreactive under these conditions. Although crystalline, no suitable X-ray crystallographic data for compound **5a** could be obtained and regiochemical and stereochemical analysis was performed indirectly. Thus, NOE difference spectroscopy indicated a *cis*-arrangement of C(2)H, C(4)H_{endo} and C(6)H, confirming that the cycloaddition occurred to the less hindered *exo*-face of lactam **1a** (Fig. 1). Further structural characterisation of compound **5a** (R = H) was achieved by conversion (Ac_2O, Et_3N, −5 °C) to the *N*-acetyl derivative **5b** in 67% yield, along with 6% of its isomer **6a**. The structure of **5b** was confirmed by ^{1}H NMR long range coupling experiments [pulsed field gradient HQMC (5 : 3 : 4)], which showed that the newly introduced carbonyl function was only three bonds removed from the C-7 ester carbonyl function. The conjugate addition of azides to give similar adducts in related systems has been previously reported.[43,44] Treatment of pyrazoline **5a** with acetic acid

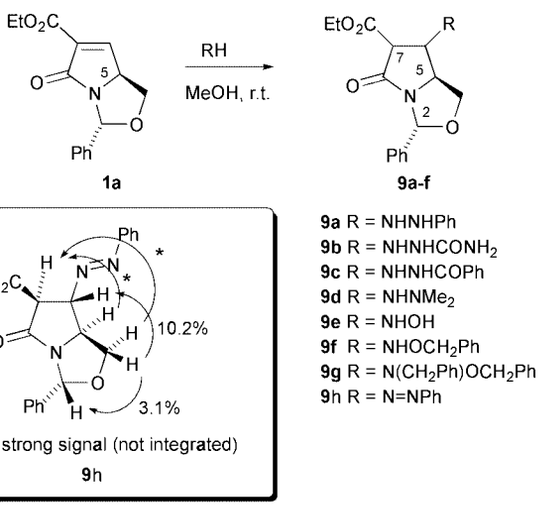


5a

Fig. 1

surprisingly gave the enamine **7**, albeit in low yield (18%); alternatively, treatment with TFA–CH_2Cl_2 gave the pyroglutaminol **8** directly in 40% yield. These reactions most likely proceed by protonation of the tautomer **6b** followed by elimination across the C-6–C-7 bond with concomitant loss of nitrogen.

In keeping with the above results, the activated enone **1a** was found to give a very rapid reaction with a variety of other α-nucleophiles,[45] including substituted hydroxylamines and hydrazines, to give the corresponding adducts **9a–g** in almost quantitative yield (Scheme 3 and Table 1); in all cases, one



Scheme 3

diastereomer was obtained predominantly, although up to four diastereomers could be detected by ^{13}C NMR spectroscopy for **9a**, **b**, **e** and **f**. A significant improvement in the diastereoselectivity for **9g** was obtained by using the more bulky nucleophile, *O*-benzyl-*N*-benzylhydroxylamine, and in this case the adduct was stable enough to permit chromatographic purification. In the case of the phenylhydrazine adduct **9a**, the regioselectivity of addition was established by careful ^{1}H NMR spectroscopic analysis in dry d_6-DMSO, which did not indicate the presence of an NH_2 group, consistent with the addition of the terminal amine function as expected.

These reactions proved to be easily reproducible except in the case of dimethylhydrazine, which gave variable amounts of the expected product **9d** along with some of the dimeric product **3b**, as indicated by spectroscopic analysis of the crude reaction mixture. The stereochemistry of the major adducts **9a**, **c**, **f**, and **g** was shown to be (2*R*,5*S*,6*S*,7*R*) by a series of NOE experiments (Table 1), corresponding to the expected *exo*- (less hindered) approach of the amine nucleophile followed by *exo*-protonation to give the C-6–C-7 *trans*-product; the major adducts for **9b**, **d**, and **e** are also expected to possess this stereochemistry, but this could not be confirmed due to their instability. Therefore, not only does the bicyclic ring system of **1** *control* the stereochemistry of the addition process, but it also facilitates the *assignment* of stereochemistry by NOE analysis, since the C(2)H⟶C(4)H_{endo}⟶C(6)H_{endo} and C(5)H⟶C(7)H_{exo} enhancement sequence is easily detected.

The hydrazine derivatives **9a–d** were found to be unstable to silica and aqueous conditions, undergoing facile β-elimination,

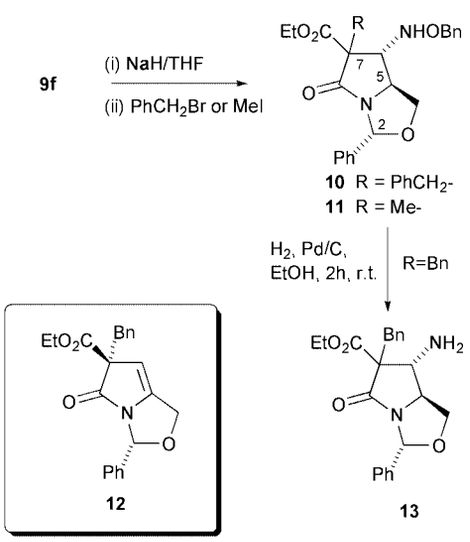
Table 1 Reaction of enone **1a** with nitrogen nucleophiles, and NOE spectroscopic data for the major diastereomers of the products **9a**, **c**, **f** and **g**

Nucleophile RH	Product	Yield (%)	Diastereomer ratio[a]	NOE Enhancement (%)		
				H-2–H-4$_{endo}$	H-4$_{endo}$–H-6	H-5–H-7
$PhNHNH_2$	**9a**	93	12 : 1 : 1 : 1	3.2	8.8	√[b]
$NH_2CONHNH_2$	**9b**	92	12 : 2 : 2 : 1	—	—	—
$PhCONHNH_2$	**9c**	92	10 : 1 : 1	2.2	3	√[b]
Me_2NNH_2	**9d**	92[d]	—[c]	—	—	—
$HONH_2$	**9e**	93	16 : 7 : 4 : 1	—	—	—
$PhCH_2ONH_2$	**9f**	96	20 : 2 : 2 : 1	1.8	26	2
$PhCH_2ONH_2(CH_2Ph)$	**9g**	99	9 : 1	1.9	7.4	5

[a] Estimated from the ^{1}H NMR spectrum. [b] NOE Enhancement not integrated although enhancement was detected. [c] Not determined. [d] Crude yield, which contains some of the dimeric product **3b**.

and the phenylhydrazine adduct **9a** was also found to be prone to aerial oxidation, and readily converted to the orange azo derivative **9h** (λ_{max} = 273 nm) on standing over 18 hours. This compound was sufficiently stable to allow chromatographic purification, and stereochemical assignment was possible using standard NOE techniques, confirming the earlier assignment for the starting material (Scheme 3). Due to their evident instability, deprotection of these compounds was not attempted. Even though the hydroxylamine adducts **9e**–**g** were more robust, attempted N–O reductive cleavage nonetheless led to decomposition.

Since the instability of some of these adducts was due to a facile β-elimination process under acidic conditions, alkylations at C-7 were examined in order to block the elimination reaction. Good yields of the alkylated adducts **10** and **11** (Scheme 4)



Scheme 4

could be achieved by treating **9f** (mixture of diastereomers) with NaH and then benzyl bromide or methyl iodide (61 and 58% respectively) but with poorer diastereoselectivity than in the simple conjugate additions (43 : 24 : 4 : 1 and 8 : 8 : 1 : 1 respectively); in contrast to their precursor **9f**, the products **10** and **11** were indeed stable to silica as expected. However, the adduct **9g** was found to be unreactive to alkylation, probably due to the steric bulk of the C-6 substituent. Using the same alkylation conditions, the hydroxylamine adduct **9e** gave unsaturated bicyclic lactam **12** in low yield and as a single diastereomer whose stereochemistry could not be assigned by NOE analysis; we have previously observed similar products which arise from an elimination–alkylation sequence under the conditions of this reaction.[8] Careful purification of the diastereomeric mixture **10** allowed the isolation of the major diastereomer (7*R*)-**10′** as a gum whose stereochemistry was assigned by a series of NOE experiments (Fig. 2); the *cis*-

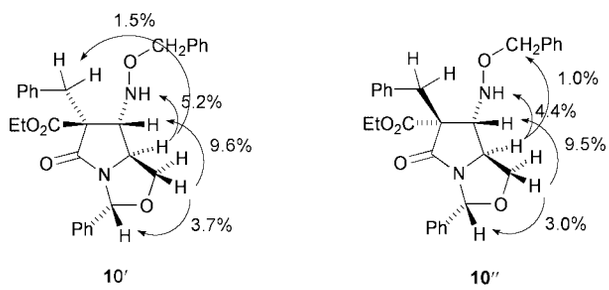


Fig. 2

relationship of C(2)H, C(4)H$_{endo}$ and C(6)H was evident from their respective mutual enhancements. Irradiation of the C(5)*H* signal was found to give a 1.5% enhancement of the newly introduced benzylic methylene protons, indicating that alkylation proceeded from the *exo*-face of the bicyclic ring and the absolute stereochemistry of the adduct was therefore (6*S*,7*R*). The next major isomer (7*S*)-**10″** was also isolated in partially purified form, and its stereochemistry at C-6 shown to be the same as isomer **10′** by NOE, implying that the C-7 stereochemistry must be epimeric with **10′**. The remaining minor diastereomers of **10** must therefore be epimeric at C-6 relative to **10′** and **10″**, *i.e.* of (6*R*) stereochemistry, but this mode of conjugate addition is not favoured due to the sterically encumbered addition pathway. Separation of the methyl derivatives **10b** was not possible, precluding stereochemical analysis.

The C(6)H$_{endo}$ stereochemistry of **10** and **11** confirms the preferred stereochemistry for the amine conjugate addition, but there is clearly poor diastereoselectivity of the alkylation step at C-7. Similar poor diastereoselectivity of alkylation reactions has also been observed in related systems.[8,9] This stereochemical outcome appears to be due to competing steric directing effects from both the C-6 amine substituent, which favours *endo*-alkylation at C-7, and the inherent stereochemical bias of the bicyclic lactam system, which favours *exo*-alkylation at C-7.[46] However, it is possible that a further *endo*-directing effect at C-7 is due to a favourable electronic interaction of the enolate π-system with the nitrogen lone pair of the lactam ring.[47]

Deprotection reactions

Having demonstrated that adducts **9** were readily available, in some cases with high stereochemical control, it was of interest to examine their suitability for further elaboration. *O*-Benzyl deprotection of partially purified **10** (**10′**–**10″** = 93 : 7) was not possible with Zn–HOAc or Zn–HCl, from which unreacted starting material was recovered, but deprotection could be readily achieved under catalytic hydrogenation conditions with ethanol solvent to give the product **13** as an inseparable diastereomeric mixture (Scheme 4) in good yield (53%) in a ratio of 14 : 1; that N–O bond cleavage occurred was evident from the molecular ion signal in the mass spectrum at 381 Da.

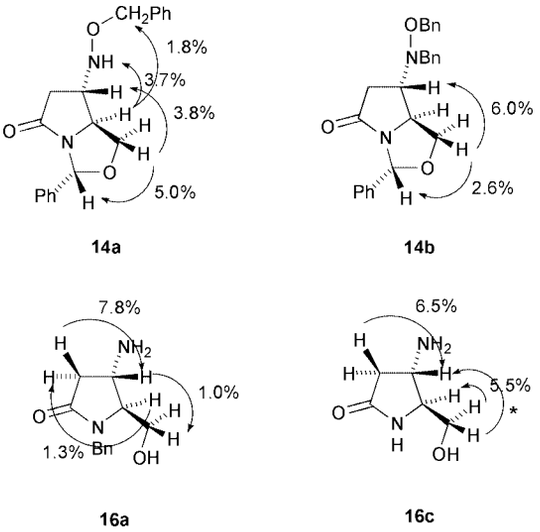


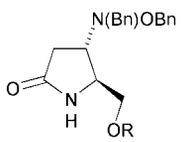
Fig. 3

Alternatively, ester hydrolysis was examined; although standard alkaline hydrolysis conditions returned unreacted starting material, the use of bis(tributyltin) oxide in refluxing toluene[48] gave concomitant hydrolysis and decarboxylation of **9f** and **g** affording the lactams **14a** and **15a** (as an inseparable 6.5 : 1 mixture) and **14b** (single diastereomer only) in yields of 62 and 70% respectively (Scheme 5). This method however did not yield the corresponding product from the semicarbazide adduct **9b**, instead giving only decomposition. Confirmation of the stereochemistry again came from an NOE analysis similar to that discussed above (Fig. 3).

Hydrogenolysis of **14b** using HOAc (4 bar, 2 days)[49] as solvent gave the *N*-benzyl lactam **16a** in diastereomerically pure form, in 44% yield after ion exchange (Dowex 50W-X8); the use of ethanol as solvent gave no reaction. Similarly, the benzyloxyamino mixture **14a**–**15a** under the same conditions gave the acetate salt of compound **16a** in excellent yield (97%), although as a mixture of diastereomers.

Initial acidic deprotection of **14b** gave *trans*-alcohol **16b** in 81% yield, and subsequent hydrogenolysis followed by ion-exchange gave the *trans*-aminolactam **16c** in 75% yield. Except for intermediate **16b**, for which dynamic effects in the NMR spectrum precluded NOE analysis, stereochemistry was again confirmed by NOE (Fig. 3). Noteworthy was that in the ^{1}H NMR spectrum, the resonance of C(4)*H* (*pro-R*) was found to appear at a higher field than its geminal C(4)*H* (*pro-S*) signal for both compounds **16a** and **16b**; this was presumably due to the adjacent amino substituent.

The enantiopurity of alcohol **16b** was established by conversion to the corresponding α-methoxy-α-(trifluoromethyl)-phenylacetic acid (MTPA) derivatives with (−)- and (±)-MTPA chloride and pyridine in DCM at room temperature (yields 91 and 85% respectively).[50,51] The ^{19}F NMR spectrum of the former compound gave only one resonance as expected at −71.87 ppm whilst two peaks were observed at −71.87 and −71.89 ppm in the spectrum of the latter compound. This established that alcohol **16b** was enantiopure, at least within the detection limits of NMR spectroscopy, a significant result since this demonstrated that substrate **1a** is not epimerised at C-5 under the basic reaction conditions required for the conjugate addition (Scheme 3). This confirms earlier results which indicate that enone **1a** is stereochemically robust: thus, Diels–Alder[39] and conjugate addition reactions using Reformatsky reagents[8] have previously been shown to proceed without loss of stereochemistry at C-5. This is despite the acidity of this position, as evidenced by the facile dimerisation described above (Scheme 1). The design of the bicyclic lactam system, which exploits the elegant work of Seebach as espoused in his Principles of Self-Regeneration of Stereocentres,[52] ensures that, even if deprotonation at C-5 had occurred, the original stereochemistry would be returned upon reprotonation; in this sense, the bicyclic system acts as a stereochemical "protecting group".



17a R = (*S*)-MTPA
17b R = (±)-MTPA

^{1}H NMR spectroscopy

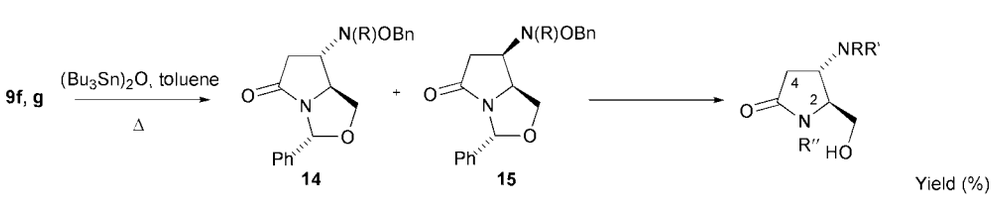
In earlier studies, it has been noted that consistent patterns in the NMR spectra of variously substituted bicyclic lactams are observed, and these patterns have been maintained in the compounds prepared in the present work.[8,9] Unsurprisingly, the C(2)H resonance is similar but non-identical across all diastereomers, and serves as a useful marker for diastereomeric purity. The signal arising from C(4)H$_{endo}$ was found to be consistently more upfield typically by 0.2–0.5 ppm from its geminal partner, C(4)H$_{exo}$ (Table 2). Furthermore, C(4)H$_{endo}$ usually appeared as a triplet or poorly resolved doublet of doublets with a coupling constant of about 8 Hz (this has also been observed in alkyl substituted systems[8,9]) and C(4)H$_{exo}$ appeared as a multiplet or doublet of doublets. The signal due to C(7)H appeared at 3.78–4.50 ppm and as a doublet (J = 9–10 Hz).

Conclusion

We have shown that although conjugate addition of simple amines to an α,β-unsaturated pyrrolidinone is problematic, the addition of activated nitrogen nucleophiles gives excellent yields of the expected adducts with high diastereoselectivity. These can be selectively deprotected under standard conditions to give good yields of enantiopure β-aminopyrrolidinones, further demonstrating the synthetic value of bicyclic lactam systems derived from pyroglutamic acid.

Experimental

For general experimental procedures and the preparation of lactams **1a** and **b**, see our earlier reports.[39,46]



14,15	Yield (%)	Ratio 14 :15
a R = H	62	6.5 :1
b R = Bn	70	**14b** only

	Yield (%)
16a R = H, R′ = H, R′′ = Bn	62
16b R = Bn, R′ = OBn, R′′ = H	81
16c R = H, R′ = H, R′′ = H	75

Scheme 5

Table 2 ^{1}H NMR data for the products **5** and **9a**–**h**

Compound	δH-2	δH-4$_{endo}$	δH-4$_{exo}$	δH-7
5	6.35	3.80 (t, *J* 9.2)	4.51 (dd, *J* 8.1, 6.4)	—
9a	6.35	3.86 (dd, *J* 8.6, 6.5)	4.23 (dd, *J* 8.6, 6.5)	3.93 (d, *J* 10.3)
9b	6.30	3.80 (dd, *J* 8.7, 6.5)	4.01 (dd, *J* 10.0, 6.3)	3.87 (d, *J* 9.9)
9c	6.42	3.61 (dd, *J* 8.5, 6.6)	3.93–4.05 (m)	3.93–4.05 (m)
9e	6.31	3.75 (t, *J* 8.2)	4.05–4.25 (m)	4.03 (d, *J* 7.8)
9f	6.44	3.46–3.49 (m)	3.87 (dd, *J* 12.1, 6.0)	3.78 (d, *J* 9.6)
9g	6.49	3.39 (t, *J* 8.0)	3.84 (br t, *J* 7.2)	4.29–4.39 (m)
9h	6.47	4.02–4.07 (m)	4.41–4.47 (m)	4.48 (d, *J* 9.0)

General method A: conjugate addition

To a stirred solution of the nitrogen nucleophile in DCM, MeOH or THF containing 1–10 equivalents of water, was added slowly dropwise enone **1a** or **b** dissolved in the same solvent and the solution allowed to stir for 1–20 h at RT. Brine (20 ml) was added to the reaction mixture and extracted with EtOAc (3 × 20 ml). The combined organic layers were then washed with water (2 × 20 ml), dried over $MgSO_4$ and filtered. Concentration *in vacuo* gave the title compound as a mixture of diastereomers. The reactions using hydrazine nucleophiles were not subjected to aqueous work-up.

Dimer 2[46]

Reaction of enone **1a** (0.8 mmol) with benzylamine (2 equiv.) in DCM (2.5 ml) and water (2 equiv.) for 45 min according to general method A gave dimer **2** as a bright yellow gum; R_f 0.26 (2 : 1 petrol–EtOAc); δ_H (500 MHz, $CDCl_3$) 1.24 (3H, t, *J* 7.2, CH_3), 1.39 (3H, t, *J* 7.2, CH_3), 3.24 (1H, dd, *J* 8.5 and 5.3, C(6)H), 3.42 (3H, d, *J* 8.4, C(7)H), 3.62–3.69 (2H, m, C(4)H and C(12)H), 3.73–3.77 (1H, m, C(5)H), 4.05–4.14 (3H, m, CH_2CH_3 and C(4)H), 4.24 (1H, d, *J* 8.9, C(12)H), 4.33–4.39 (2H, m, CH_2CH_3), 6.17 and 6.26 (2H, 2 × s, C(2)H and C(10)H), 7.30–7.41 (8H, m, ArCH), 7.51–7.53 (2H, m, ArCH), 7.80 (1H, s, C(14)H); *m*/*z* (APCI$^+$) 547 (M + H$^+$, 100%).

Adduct 3a

Reaction of enone **1a** (0.8 mmol) with benzylamine (1 equiv.) in DCM (2.5 ml) and water (1 mmol) for 45 min according to general method A gave dimer **3a** as a bright yellow gum and as a mixture of diastereomers in a ratio of 7 : 2 : 1; R_f 0.11 (2 : 1 petrol–EtOAc); ν_{max}(film)/cm^{-1} 3310 (w), 2982 (m), 1740 (s), 1708 (s); δ_H (500 MHz, $CDCl_3$) 1.17 and 1.34 (6H, m, 2 × CH_3), 3.38–4.71 (15H, m, 2 × CH_2CH_3, $NHCH_2Ph$, 2 × C(4)H, 2 × C(12)H, C(5)H, C(13)H, C(6)H, C(14)H, C(7)H), 6.24 and 6.37, 6.28 and 6.42, 6.30 and 6.35 (2H, 2 × s, C(2)H and C(10)H for each diastereomer), 7.21–7.51 (15H, m, ArCH); δ_C (125.8 MHz, $CDCl_3$) 13.75, 13.85 and 14.01 (2 × CH_3), 40.64 and 44.66 (C-15), 52.27, 52.42 and 52.77 ($NHCH_2Ph$), 54.58, 54.68, 55.02, 57.44, 59.41, 59.84, 60.99, 65.55, 65.68 (C-5, C-13, C-6, and C-14), 62.02, 62.47 and 62.59 (2 × CH_3CH_2), 70.29, 72.40 and 73.43 (C-4 and C-12), 87.18, 87.29, 87.55 and 88.45 (C-2 and C-10), 125.63, 125.85, 126.10, 127.49, 127.82, 127.91, 128.05, 128.38, 128.53, 128.60, 128.78 and 128.96 (ArCH), 136.77, 138.31 and 138.39 (ArC), 168.33, 169.82, 170.98, 171.17, 171.42 and 174.28 (4 × CO); *m*/*z* (APCI$^+$) 654 (M + H$^+$, 100%); HRMS 653.2736, $C_{37}H_{39}N_3O_8$ (M$^+$) requires 653.2737.

(+)-(1*R*,3a*S*,3b*R*,6a*S*)-7-Oxo-1-phenyl-2,3,3a,3b,6,6a,7,7a-octahydro-1*H*-2-oxa-4,5,6,7a-tetraazacyclopenta[*a*]pentalene-6a-carboxylic acid ethyl ester 5a

Glacial acetic acid (26 mg, 0.44 mmol) was added to a solution of sodium azide (57 mg, 0.88 mmol) dissolved in water (2.5 ml) whilst stirring at RT. The enone **1a** (120 mg, 0.44 mmol) dissolved in THF (7.5 ml) was then added slowly dropwise and the reaction mixture was allowed to stir for 30 min. Water (15 ml) was added and the solution was extracted with DCM (3 × 15 ml). The combined organic layers were then washed with saturated sodium bicarbonate (2 × 15 ml), dried over $MgSO_4$, filtered and concentrated *in vacuo* to give a bright yellow gum which was then purified by recrystallisation (1 : 1 petrol–EtOAc) to give the product **5a** as a white solid (111 mg, 80%); R_f 0.28 (1 : 1 petrol–EtOAc); $[\alpha]_D^{25}$ +74.1 (*c* 1.3, $CHCl_3$); mp 130.0–132.5 °C; found C 57.03; H 4.58; N 18.15; calculated C 56.96; H 5.10; N 17.71%; ν_{max}(film)/cm^{-1} 3304 (m), 2983 (w), 1718 (s), 1454 (w); δ_H (500 MHz, $CDCl_3$) 1.34 (3H, t, *J* 7.1, CH_3), 3.80 (1H, t, *J* 9.2, C(4)H$_{endo}$), 4.12 (1H, ddd, *J* 8.8, 6.4 and 2.0, C(5)H), 4.33 (2H, q, *J* 7.1, CH_3CH_2), 4.51 (1H, dd, *J* 8.1 and 6.4, C(4)H$_{exo}$), 5.35 (1H, d, *J* 2.1, C(6)H), 6.35 (1H, s, C(6)H), 7.33–7.44 (5H, m, ArCH), 9.02 (1H, s, NH); δ_C (125.8 MHz, $CDCl_3$) 13.94 (CH_3), 61.85 (C-5), 63.53 (CH_3CH_2), 69.28 (C-4), 72.73 (C-10), 83.47 (C-6), 87.89 (C-6), 125.79, 128.58 and 129.03 (ArCH), 137.35 (ArC), 166.94 and 171.34 (2 × CO) (NMR assignments follow the numbering shown in Fig. 1); *m*/*z* (electrospray) 317 (M + H$^+$, 100%), 289 (35), 275 (15).

(1*R*,3a*S*,3b*R*,6a*S*)-6-Acetyl-7-oxo-1-phenyl-2,3,3a,3b,6,6a,7,7a-octahydro-1*H*-2-oxa-4,5,6,7a-tetraazacyclopenta[*a*]pentalene-6a-carboxylic acid ethyl ester 5b and (1*R*,3a*S*,3b*R*,6a*S*)-4-acetyl-7-oxo-1-phenyl-2,3,3a,3b,4,6a,7,7a-octahydro-1*H*-2-oxa-4,5,6,7a-tetraazacyclopenta[*a*]pentalene-6a-carboxylic acid ethyl ester 6a

Triethylamine (106 mg, 1.05 mmol) was added to a solution of the triazoline **5a** (166 mg, 0.53 mmol) dissolved in $CHCl_3$ (5 ml) whilst stirring at −5 °C. Acetic anhydride (54 mg, 0.53 mmol) was then added and the reaction mixture was allowed to stir for 4 h. Citric acid (10% in water, 25 ml) was added and the organic layer was partitioned, dried over $MgSO_4$, filtered and evacuated *in vacuo*. Purification of the crude product was carried out using flash column chromatography (2 : 1 petrol–EtOAc as eluent). Evaporation *in vacuo* gave the product as a pale white gum (138 mg, 73%) in a ratio of **5b**–**6a** = 11 : 1; R_f 0.25 (2 : 1 petrol–EtOAc); ν_{max}(film)/cm^{-1} 2985 (w), 1762 (s), 1726 (s), 1707 (s); *m*/*z* (electrospray) 359 (M + H$^+$, 55%), 331 (100).

Data for **5b**: δ_H (200 MHz, $CDCl_3$) 1.42 (3H, t, *J* 7.2, CH_3CH_2), 2.58 (3H, s, $COCH_3$), 3.69–3.81 (1H, m, C(4)H$_{endo}$), 3.97 (1H, dd, *J* 9.6 and 6.3, C(5)H), 4.31–4.58 (3H, m, C(4)H$_{exo}$ and CH_3CH_2), 4.90 (1H, s, C(6)H), 6.37 (1H, s, C(6)H), 7.30–7.48 (5H, m, ArCH); δ_C (50.3 MHz, $CDCl_3$) 13.88 (CH_3), 22.11 (CH_3), 54.43 (C-5), 63.25 (C-6), 63.93 (CH_3CH_2), 68.47 (C-4), 88.42 (C-6), 98.62 (C-10), 125.96, 126.20, 128.79 and 129.31 (ArCH), 137.19 (ArC), 164.39, 167.50 and 168.96 (3 × CO) (NMR assignments follow the numbering for **5a** shown in Fig. 1); data for **6a**: δ_H (200 MHz, $CDCl_3$) 1.42 (3H, t, *J* 7.2, CH_3CH_2), 2.63 (3H, s, $COCH_3$), 3.29 (1H, t, *J* 8.9, C(4)H), 4.15 (1H, q, *J* 7.1, C(5)H), 4.31–4.58 (3H, m, C(4)H and CH_3CH_2), 4.86 (1H, s, C(6)H), 6.33 (1H, s, C(6)H), 7.30–7.48 (5H, m, ArCH); δ_C (50.3 MHz, $CDCl_3$) 13.88 (CH_3), 22.11 (CH_3), 53.03 (C-5), 60.64 (C-6), 64.17 (CH_3CH_2), 67.33 (C-4), 87.44 (C-6), 98.62 (C-10), 125.96, 126.20, 128.79 and 129.31 (ArCH), 137.59

(ArC), 164.39, 167.50 and 168.96 (3 × CO) (NMR assignments follow the numbering for **5a** shown in Fig. 1).

7-Ethoxycarbonyl-8-oxo-2-phenyl-6-amino-3-oxa-1-azabicyclo-[3.3.0]oct-6-ene 7

Triazoline **5a** (100 mg, 0.35 mmol) was treated with glacial acetic acid (1 equiv.) in dichloromethane, the solvent removed and the product isolated by chromatography (3 : 1 light petroleum–ethyl acetate) to give the product **7** as a yellow oil (16 mg, 18%); R_f 0.24; ν_{max}(film)/cm^{-1} 3583 (w), 3332 (m), 1730 (s), 1692 (s), 1647 (s); δ_H (500 MHz, $CDCl_3$) 1.33 (3H, t, *J* 7.2, CH_3CH$_2$), 3.36 (1H, t, *J* 8.9, C(4)H$_{endo}$), 4.26 (2H, q, *J* 7.1, CH$_3$CH$_2$), 4.45 (1H, dd, *J* 6.0 and 8.1, C(5)H), 4.71 (1H, dd, *J* 6.2 and 8.8, C(4)H$_{exo}$), 5.68 (2H, br s, NH$_2$), 6.17 (1H, s, C(2)H), 7.30–7.49 (3H, m, ArCH), 7.50–7.60 (2H, m, ArCH); δ_C (125.8 MHz, $CDCl_3$) 14.44 (CH_3), 59.86 (C-5), 60.20 (CH$_3$CH_2), 70.82 (C-4), 86.95 (C-2), 103.5 (C-6), 126.19, 128.52 and 128.86 (ArCH), 138.16 (ArC), 146.68, 164.99 and 169.80 (2 × CO); *m*/*z* (electrospray) 289 (M + H$^+$, 100%); HRMS 289.1188, $C_{15}H_{17}N_2O_4$ (M + H$^+$) requires 289.1188.

4-Amino-5-hydroxymethyl-2-oxo-2,5-dihydro-1*H*-pyrrole-3-carboxylic acid ethyl ester 8

To a solution of triazoline **5a** (160 mg, 0.051 mmol) in dichloromethane was added trifluoroacetic acid, and the mixture stirred for 15 min. The solvent was removed, and the product **8** isolated by chromatography (EtOAc then 10 : 1 EtOAc–MeOH) as a yellow gum (40 mg, 40%); R_f 0.19 (EtOAc); ν_{max}(film)/cm^{-1} 3333 (s), 1702 (s), 1689 (s), 1657 (s), 1652(s); δ_H (500 MHz, $CDCl_3$) 1.30 (3H, t, *J* 7.1, CH_3CH$_2$), 3.50 (1H, dd, *J* 10.5 and 6.8, C*H*OH), 4.01 (1H, br s, OH), 4.08 (1H, br d, *J* 9.9, C(2)H), 4.16–4.29 (2H, m, CH$_3$CH$_2$), 4.31 (1H, br s, CHOH), 5.99 (2H, br s, NH$_2$), 8.23 (1H, br s, NH); δ_C (125.8 MHz, $CDCl_3$) 14.32 (CH_3), 57.41 (C-2), 60.15 (CH$_3$CH_2), 63.56 (CH$_2$OH), 100.9 (C-4), 147.13 (C-3), 165.28 and 168.23 (2 × CO); *m*/*z* (electrospray) 201 (M + H$^+$, 100%); HRMS 201.0875, $C_8H_{12}N_2O_4$ (M + H$^+$) requires 201.0879.

7-Ethoxycarbonyl-8-oxo-2-phenyl-6-(2-phenylhydrazino)-3-oxa-1-azabicyclo[3.3.0]octane 9a

Using general method A, phenylhydrazine (36 mg, 0.33 mmol) was reacted with the enone **1a** (90 mg, 0.33 mmol) in MeOH (10 ml) for 1 h to give the title compound **9a** as a bright yellow gum (116 mg, 93%) in a diastereomeric ratio of 12 : 1 : 1 : 1.

Data for the major isomer (2*R*,5*S*,6*S*,7*R*): R_f 0.45 (1 : 1 petrol–EtOAc); ν_{max}(film)/cm^{-1} 3312 (w), 2982 (w), 1740 (s), 1708 (s), 1603 (m), 1496 (m); δ_H (500 MHz, $CDCl_3$) 1.34 (3H, t, *J* 7.1, CH_3CH$_2$), 3.86 (1H, dd, *J* 8.6 and 6.5, C(4)H$_{endo}$), 3.93 (1H, d, *J* 10.3, C(7)H), 4.01 (1H, q, *J* 6.5, C(5)H), 4.16 (1H, dd, *J* 10.3 and 6.5, C(6)H), 4.23 (1H, dd, *J* 8.6 and 6.5, C(4)H$_{exo}$), 4.25–4.36 (2H, m, CH$_3$CH_2), 5.31 (1H, br s, NH), 6.35 (1H, s, C(2)H), 6.82–6.91 (3H, m, ArCH), 7.20–7.45 (7H, m, ArCH); δ_C (125.8 MHz, $CDCl_3$) 14.13 (CH_3), 55.78 (C-7), 61.50 (C-5), 62.05 (CH$_3$CH_2), 64.73 (C-6), 70.58 (C-4), 87.10 (C-2), 112.16, 112.72, 112.93, 119.48, 120.17, 126.00, 128.46, 128.74 and 129.24 (ArCH), 137.67 and 148.69 (2 × ArC), 168.10 and 169.64 (2 × CO); *m*/*z* 382 (M + H$^+$, 60%), 380 (100).

6-[2-(Aminocarbonyl)hydrazino]-7-ethoxycarbonyl-8-oxo-2-methyl-2-phenyl-3-oxa-1-azabicyclo[3.3.0]octane 9b

Using general method A, semicarbazide hydrochloride (33 mg, 0.30 mmol) was reacted with sodium acetate (24 mg, 0.30 mmol) and the enone **1a** (74 mg, 0.27 mmol) in MeOH (5 ml) for 1 h to give the product **9b** as a bright yellow gum (189 mg, 92%) and as an inseparable diastereomeric mixture in a ratio of 12 : 2 : 1 : 1.

Data for the major isomer (2*R*,5*S*,6*S*,7*R*): ν_{max}(film)/cm^{-1} 3589 (m), 3464 (m), 2983 (w), 1735 (s), 1707 (s), 1690 (s), 1579 (m); δ_H (500 MHz, $CDCl_3$) 1.30 (3H, t, *J* 7.1, CH_3CH$_2$), 3.80 (1H, dd, *J* 8.7 and 6.6, C(4)H$_{endo}$), 3.87 (1H, d, *J* 9.9, C(7)H), 3.95 (1H, dd, *J* 12.1 and 6.4, C(5)H), 4.01 (1H, dd, *J* 10.0 and 6.3, C(4)H$_{exo}$), 4.18–4.31 (3H, m, CH$_3$CH_2 and C(6)H), 4.62 (1H, br s, N*H*NHCO), 5.81 (2H, br s, NH_2), 6.30 (1H, s, C(2)H), 7.30–7.48 (5H, m, ArCH), 7.73 (1H, br s, NHN*H*CO); δ_C (125.8 MHz, $CDCl_3$) 14.09 (CH_3), 55.64 (C-7), 60.89 (C-5), 62.23 (CH$_3$CH_2), 64.21 (C-6), 70.30 (C-4), 87.27 (C-2), 126.04, 126.88, 128.53 and 128.68 (ArCH), 137.11 and 137.56 (2 × ArC), 161.72, 167.96, 169.66 and 175.47 (4 × CO); *m*/*z* (electrospray) 349 (M + H$^+$, 100%).

6-[2-Benzoylhydrazino]-7-ethoxycarbonyl-8-oxo-2-phenyl-3-oxa-1-azabicyclo[3.3.0]octane 9c

Using general method A, benzoylhydrazine (59 mg, 0.44 mmol) was reacted with enone **1a** (119 mg, 0.44 mmol) in MeOH (5 ml) to give the product **9c** as a yellow gum (165 mg, 92%) and as an inseparable diastereomeric mixture in a ratio of 10 : 1 : 1.

Data for the major isomer (2*R*,5*S*,6*S*,7*R*): ν_{max}(film)/cm^{-1} 3280 (m), 3064 (w), 1736 (s), 1709 (s), 1654 (s); δ_H (500 MHz, C_6D_6) 0.92 (3H, t, *J* 7.1, CH_3CH$_2$), 3.61 (1H, dd, *J* 8.5 and 6.6, C(4)H$_{endo}$), 3.85 (1H, q, *J* 6.5, C(5)H), 3.93–4.05 (4H, m, C(4)H$_{exo}$, C(7)H and CH$_3$CH_2), 4.33 (1H, dd, *J* 10.2 and 6.6, C(6)H), 6.42 (1H, s, C(2)H), 7.01–7.15 (5H, m, ArCH), 7.44–7.46 (2H, m, ArCH), 7.71–7.76 (3H, m, ArCH), 8.45 (1H, br s, NH); δ_C (125.8 MHz, C_6D_6) 14.01 (CH_3), 57.46 (C-7), 61.54 (C-5), 61.90 (CH$_3$CH_2), 65.75 (C-6), 70.46 (C-4), 87.61 (C-2), 126.52, 127.40, 127.54, 127.81, 128.01, 128.20, 128.62, 131.65 and 132.01 (Ar*C*H), 132.58, 133.07 and 138.68 (3 × ArC), 168.91 and 170.62 (2 × CO); *m*/*z* (electrospray) 448 (M + K$^+$, 10%), 432 (M + Na$^+$, 20), 427 (M + NH$_4^+$, 45), 410 (M + H$^+$, 100).

7-Ethoxycarbonyl-6-hydroxyamino-8-oxo-2-phenyl-3-oxa-1-azabicyclo[3.3.0]octane 9e

Using general method A, hydroxylamine hydrochloride (27 mg, 0.39 mmol) was reacted with sodium acetate (32 mg, 0.39 mmol) and the enone **1a** (107 mg, 0.39 mmol) in MeOH (5 ml) for 1 h to give the product **9e** as a yellow gum (112 mg, 93%) in an inseparable diastereomeric mixture in a ratio of 16 : 7 : 4 : 1. Data for the major isomer (2*R*,5*S*,6*S*,7*R*): ν_{max}(film)/cm^{-1} 3374 (br s), 1737 (s), 1715 (s); δ_H (300 MHz, $CDCl_3$) 1.34 (3H, t, *J* 7.1, CH_3CH$_2$), 3.75 (1H, t, *J* 8.2, C(4)H), 3.80–3.91 (1H, m, C(5)H), 4.03 (1H, d, *J* 7.8, C(7)H), 4.05–4.25 (1H, m, C(4)H), 4.26–4.42 (4H, m, CH_2CH$_3$ and C(6)H), 5.73 (1H, br s, NH), 6.31 (1H, s, C(2)H), 7.31–7.60 (5H, m, ArCH); δ_C (50.3 MHz, $CDCl_3$) 14.06 (CH_3), 54.90 (C(7)H), 60.40 (C(5)H), 62.43 (CH$_3$CH_2), 66.81 (C-6), 70.46 (C-4), 87.34 (C-2), 125.93, 128.53 and 128.92 (ArCH), 137.72 (ArC), 168.31 and 170.42 (2 × CO); *m*/*z* (electrospray) 307 (M + H$^+$, 35%), 274 (100).

7-Ethoxycarbonyl-6-benzyloxyamino-8-oxo-2-phenyl-3-oxa-1-azabicyclo[3.3.0]octane 9f

Using general method A, *O*-benzylhydroxylamine hydrochloride (86 mg, 0.54 mmol) was reacted with sodium acetate (44 mg, 0.54 mmol) and enone **1a** (134 mg, 0.49 mmol) in MeOH (5 ml). Concentration *in vacuo* gave the product **9f** as a yellow gum (187 mg, 96%) as an inseparable diastereomeric mixture in a ratio of 20 : 2 : 2 : 1.

Data for the major isomer (2*R*,5*S*,6*S*,7*R*): R_f 0.55 (1 : 1 petrol–EtOAc); found C 66.14; H 6.02; N 7.25; calculated C 66.65; H 6.10; N 7.07%; ν_{max}(film)/cm^{-1} 3240 (w), 1745 (s), 1712 (s); δ_H (500 MHz, C_6D_6) 1.06 (3H, t, *J* 7.1, CH_3), 3.46–3.49 (1H, m, C(4)H$_{endo}$), 3.51–3.55 (1H, m, C(5)H), 3.78 (1H, d, *J* 9.6, C(7)H), 3.87 (1H, dd, *J* 12.1 and 6.0, C(4)H$_{exo}$), 4.02–4.08 (1H, m, CH$_3$C*H*H), 4.11–4.18 (2H, m, CH$_3$CH*H* and C(6)H), 4.51 (2H, s, NHOCH_2), 5.30 (1H, br s, N*H*), 6.44 (1H, s, C(2)H), 7.07–7.40 (7H, m, ArCH), 7.48–7.58 (2H, m, ArCH); δ_C (125.8

MHz, $CDCl_3$) 13.97 (CH_3), 54.52 (C-7), 60.55 (C-5), 61.80 (CH_3CH_2), 64.14 (C-6), 70.27 (C-4), 76.55 (OCH_2), 86.96 (C-2), 125.40, 128.08, 128.31, 128.52 and 128.59 (ArCH), 136.77 and 137.61 (2 × ArC), 167.73 and 169.90 (2 × CO); *m*/*z* (electrospray) 397 ($M + H^+$,75%), 122 (100).

6-*O*,*N*-Dibenzylhydroxyamino-7-ethoxycarbonyl-8-oxo-2-phenyl-3-oxa-1-azabicyclo[3.3.0]octane 9g

Using general method A, *N*-benzyl-*O*-benzylhydroxylamine[53] (154 mg, 0.72 mmol) dissolved in MeOH (10 ml) reacted with the enone **1a** (197 mg, 0.72 mmol) in MeOH (5 ml). Concentration *in vacuo* of the mixture gave the product **9g** as a yellow gum (348 mg, 99%) in a diastereomeric ratio of 9 : 1.

Found C 71.42; H 6.08; N 6.06; calculated C 71.59; H 6.21; N 5.76%; ν_{max}(film)/cm^{-1} 3064 (w), 3032 (w), 2981 (w), 2876 (w), 1742 (s), 1715 (s); *m*/*z* (APCI$^+$) 487 ($M + H^+$, 100%).

Data for the major isomer (2*R*,5*S*,6*S*,7*R*): δ_H (500 MHz, C_6D_6) 1.05 (3H, t, *J* 7.1, CH_3CH_2), 3.39 (1H, t, *J* 8.0, C(4)H_{endo}), 3.64 (1H, d, *J* 12.9, NC*H*HPh), 3.70 (1H, d, *J* 12.9, NCH*H*Ph), 3.84 (1H, br t, *J* 7.2, C(4)H_{exo}), 3.98 (1H, br s, C(5)H), 4.02–4.08 (1H, m, CH_3CHH), 4.14–4.21 (2H, m, CH_3CH*H* and C(6)H), 4.29–4.39 (3H, m, C(7)H and $NOCH_2Ph$), 6.49 (1H, s, C(2)H), 7.04–7.58 (15H, m, ArCH); δ_C (50.3 MHz, $CDCl_3$) 14.19 (CH_3), 55.28 (C-7), 59.62 (C-5), 61.40 (CH_3CH_2), 61.86 (C-4), 69.95 (C-6), 70.99 (NCH_2Ph), 76.95 (OCH_2Ph), 87.61 (C-2), 126.59, 128.40, 128.83, 129.32, 130.13, and 130.71 (ArCH), 136.85 and 139.15 (3 × ArC), 169.02 and 170.65 (2 × CO).

Data for the minor isomer (2*R*,5*S*,6*S*,7*S*): δ_H (500 MHz, C_6D_6) 1.05 (3H, t, *J* 7.1, CH_3CH_2), 3.09 (1H, t, *J* 8.0, C(4)H), 3.64 (1H, d, *J* 12.9, NC*H*HPh), 3.70 (1H, d, *J* 12.9, NCH*H*Ph), 3.76 (1H, br t, *J* 7.2, C(4)H), 3.98 (1H, br s, C(5)H), 4.02–4.08 (1H, m, CH_3CHH), 4.14–4.21 (2H, m, CH_3CH*H* and C(6)H), 4.29–4.39 (1H, m, C(7)H), 4.50–4.55 (2H, m, $NOCH_2Ph$), 6.61 (1H, s, C(2)H), 7.04–7.58 (15H, m, ArCH).

7-Ethoxycarbonyl-8-oxo-2-phenyl-6-(2-phenylazo)-3-oxa-1-azabicyclo[3.3.0]octane 9h

Adduct **9a** (90 mg, 0.33 mmol) was dissolved in DCM (5 ml) and stirred at RT for 18 h, and the reaction mixture concentrated *in vacuo* to give a dark orange gum. Purification by flash column chromatography (2 : 1 petrol–EtOAc as eluent) and evaporation *in vacuo* gave the title compound **9h** (20 mg, 35%) and as an inseparable diastereomeric mixture in a ratio of 17 : 2 : 1.

Data for the major isomer (2*R*,5*S*,6*S*,7*R*): R_f 0.62 (1 : 1 petrol–EtOAc); ν_{max}(film)/cm^{-1} 1718 (s), 1624 (w), 1496 (w); λ_{max} 273 nm (log ε 4.04); δ_H (500 MHz, $CDCl_3$) 1.35 (3H, t, *J* 7.1, CH_3CH_2), 4.02–4.07 (1H, m, C(4)H_{endo}), 4.26–4.38 (2H, m, CH_3CH_2), 4.41–4.47 (2H, m, C(4)H_{exo} and C(5)H), 4.48 (1H, d, *J* 9.0, C(7)H), 5.02–5.05 (1H, m, C(6)H), 6.47 (1H, s, C(2)H), 7.31–7.67 (10H, m, ArCH); δ_C (125.8 MHz, $CDCl_3$) 14.14 (CH_3), 55.36 (C-7), 60.29 (C-5), 62.12 (CH_3CH_2), 70.18 (C-4), 77.66 (C-6), 87.52 (C-2), 113.41, 121.95, 122.70, 126.00, 126.20, 127.16, 128.51, 128.51, 128.82, 128.98, 129.11, 129.50, 129.72, 131.74 and 134.43 (ArCH), 137.75 and 151.15 (2 × ArC), 167.60 and 170.58 (2 × CO); *m*/*z* (electrospray) 380 ($M + H^+$, 100%).

General method B: alkylation

To a stirred solution of pre-washed sodium hydride in THF under an N_2 atmosphere at 0 °C was added adduct dissolved in THF. On warming to RT, the solution was allowed to stir for 20 min. The alkyl halide was then added and the reaction mixture was brought up to reflux for 1–18 h. On cooling to RT, the reaction mixture was quenched with saturated NH_4Cl(aq.) (25 ml), extracted with EtOAc (3 × 20 ml), washed with water (2 × 25 ml) and dried over $MgSO_4$. Filtration and concentration *in vacuo* gave the crude product.

7-Benzyl-6-benzyloxyamino-7-ethoxycarbonyl-8-oxo-2-phenyl-3-oxa-1-azabicyclo[3.3.0]octane 10

Using general method B, the adduct **9f** (289 mg, 0.7 mmol) was reacted with pre-washed sodium hydride (58 mg, 60%, 14.6 mmol) and benzyl bromide (174 µl, 14.6 mmol) in THF (10 ml) and refluxed for 18 h. Purification by flash column chromatography (5 : 1, 4 : 1 and then 1 : 1 petrol–EtOAc as eluent) gave three diastereomers of the title compound **10** (217 mg, 61% overall yield), from which only the (2*R*,5*S*,6*S*,7*S*) isomer **10′** could be obtained in pure form.

Data for (+)-(2*R*,5*S*,6*S*,7*R*)-isomer **10′**: concentration *in vacuo* of one of the fractions gave the product as a bright yellow gum (46 mg, 13%); R_f 0.46 (2 : 1 petrol–EtOAc); $[\alpha]_D^{25}$ +120.3 (*c* 1.2, $CHCl_3$); ν_{max}(film)/cm^{-1} 3205 (w), 1744 (s), 1442 (m), 1028 (m); δ_H (500 MHz, $CDCl_3$) 1.29 (3H, t, *J* 7.1, CH_3CH_2), 3.09 (1H, t, *J* 7.8, C(4)H_{endo}), 3.22 (1H, d, *J* 14.1, C*H*HPh), 3.60 (1H, dd, *J* 9.2 and 6.6, C(6)H), 3.61 (1H, d, *J* 14.0, CH*H*Ph), 3.98 (1H, dd, *J* 13.5 and 6.7, C(5)H), 4.08 (1H, dd, *J* 8.3 and 6.5, C(4)H_{exo}), 4.23–4.29 (2H, m, CH_3CH_2), 4.62 (1H, d, *J* 11.6, OC*H*HPh), 4.65 (1H, d, *J* 11.6, OCH*H*Ph), 6.08 (1H, d, *J* 9.3, N*H*), 6.20 (1H, s, C(2)H), 7.27–7.43 (15H, m, ArCH); δ_C (128.5 MHz, $CDCl_3$) 13.94 (CH_3), 36.68 (CH_2Ph), 61.81 (C-5), 62.10 (CH_3CH_2), 64.57 (C-6), 70.87 (C-4), 76.34 (OCH_2Ph), 86.42 (C-2), 125.99, 127.14, 128.11, 128.42, 128.50, 128.55, 128.70 and 130.82 (ArCH), 136.06, 137.09 and 137.77 (3 × ArC), 168.90 and 170.74 (2 × CO); *m*/*z* (APCI$^+$) 487 ($M + H^+$, 100%); HRMS 487.2238, $C_{29}H_{31}N_2O_5$ ($M + H^+$) requires 487.2233.

7-Ethoxycarbonyl-6-benzyloxyamino-7-methyl-8-oxo-2-phenyl-3-oxa-1-azabicyclo[3.3.0]octane 11

Using general method B, the adduct **9f** (120 mg, 0.30 mmol) was reacted with pre-washed sodium hydride (24 mg, 60%, 0.61 mmol) and methyl iodide (38 µl, 0.61 mmol) in THF (10 ml) at reflux for 1 h. Purification by flash column chromatography (3 : 1 and then 1 : 1 petrol–EtOAc as eluent) gave the product **11** (72 mg, 58%), as an inseparable mixture of diastereomers in a ratio of 10 : 10 : 1 : 1; R_f 0.5 (1 : 1 petrol–EtOAc); ν_{max}(film)/cm^{-1} 3068 (w), 2990 (w), 2952 (m), 2852 (w), 1790 (s), 1496 (m), 1451 (s); δ_H (500 MHz, $CDCl_3$) 1.27, 1.28 and 1.30 (3H, t, *J* 7.1, CH_3CH_2), 1.50, 1.53, 1.55 and 1.62 (3H, s, CH_3), 3.41 (t, *J* 7.6), 3.71–3.77 (m), and 3.87 (1H, dd, *J* 8.6 and 6.6, C(4)H_{endo} and C(6)H), 4.03 (q, *J* 6.7) and 4.16–4.29 (4H, m, CH_3CH_2, C(4)H_{exo} and C(5)H), 4.67 and 4.68 (2H, s, OCH_2Ph), 5.68 (br s) and 6.14 (1H, d, *J* 8.5, N*H*), 6.27 and 6.35 (1H, s, C(2)H), 7.31–7.44 (10H, m, ArCH); δ_C (128.5 MHz, $CDCl_3$) 13.95, 14.02 and 14.38 (CH_3CH_2), 19.06 (CH_3), 59.10 and 59.21 (C-7), 60.11 and 61.58 (C-5), 61.85 and 61.90 (CH_3CH_2), 67.13 and 71.87 (C-6), 70.73 (C-4), 76.38 and 76.56 (OCH_2Ph), 86.31, 86.69 and 86.87 (C-2), 125.97, 126.04, 126.43, 128.20, 128.41, 128.45, 128.63, 128.72 and 128.78 (ArCH), 136.91, 137.01, 137.48 and 137.72 (2 × ArC), 169.24 and 170.45, 172.08 and 174.45 (2 × CO); *m*/*z* (APCI$^+$) 411 ($M + H^+$, 100%); HRMS 411.1919, $C_{23}H_{27}N_2O_5$ ($M + H^+$) requires 411.1912.

Attempted alkylation of the hydroxylamine adduct 9e: formation of (+)-(2*R*,7*R*)-7-ethoxycarbonyl-7-benzyl-8-oxo-2-phenyl-3-oxa-1-azabicyclo[3.3.0]oct-5-ene 12

Using general method B, the hydroxylamine adduct **9e** (100 mg, 0.33 mmol) was reacted with pre-washed sodium hydride (26 mg, 60%, 0.65 mmol) and benzyl bromide (112 mg, 0.65 mmol) in THF (10 ml) and refluxed for 18 h. Purification by flash column chromatography (5 : 1 and then 4 : 1 petrol–EtOAc as eluent) and concentration *in vacuo* gave compound **12** as a single diastereomer (30 mg, 25%). R_f 0.58 (1 : 1 petrol–EtOAc); $[\alpha]_D^{25}$ +201.5 (*c* 0.8, $CHCl_3$); found C 72.64; H 5.93; N 4.31; calculated C 72.71; H 5.82; N 3.85%; δ_H (500 MHz, $CDCl_3$) 1.29 (3H, t, *J* 7.1, CH_3CH_2), 3.39 (1H, d, *J* 13.5,

C*H*HPh), 3.42 (1H, d, *J* 13.5, CH*H*Ph), 4.19–4.28 (2H, m, CH_3CH_2), 4.35 (1H, dd, *J* 13.4 and 1.7, C(4)H_{endo}), 4.56 (1H, dd, *J* 13.4 and 1.9, C(4)H_{exo}), 5.05 (1H, t, *J* 1.8, C(6)H), 5.91 (1H, s, C(2)H), 7.21–7.30 (5H, m, ArCH), 7.38–7.48 (5H, m, ArCH); δ_C (125.8 MHz, $CDCl_3$) 13.94 (CH_3), 39.06 (CH_2Ph), 61.97 (CH_3CH_2), 62.90 (C-4), 70.03 (C-7), 86.23 (C-2), 96.89 (C-6), 126.48, 126.95, 127.92, 128.58, 129.52, 129.59 and 130.15 (ArCH), 135.26 and 136.06 (ArC), 145.45 (C-5), 168.85 and 169.63 (2 × CO); *m*/*z* (APCI$^+$) 386 (M + Na^+, 5%), 364 (M + H^+, 100).

General method C: hydrogenolysis

To a vigorously stirred solution of the starting material dissolved in absolute ethanol, EtOAc or glacial acetic acid in a Fischer–Porter apparatus was added palladium supported on carbon (Pd/C). The heterogeneous solution was then evacuated and flushed with H_2 six times at RT. The reaction mixture was subjected to H_2 at the given pressure and time. The mixture was filtered through Celite and the resultant filtrate was concentrated *in vacuo*. Purification of the crude product was carried out by either flash column chromatography or ion-exchange chromatography.

(2*R*,5*S*,6*S*,7*S*)-6-Amino-7-benzyl-7-ethoxycarbonyl-8-oxo-2-phenyl-3-oxa-1-azabicyclo[3.3.0]octane 13

Using general method C, a diastereomeric mixture of the adduct **10** (70 mg, 0.14 mmol) was reacted with palladium (80 mg, 10% on carbon) in absolute ethanol (15 ml) and H_2 (2 bar) for 18 h. Purification by flash column chromatography (1 : 3 petrol–EtOAc and then EtOAc as eluent) gave the product **13** as a pale yellow gum (29 mg, 53%) as an inseparable diastereomeric mixture in a ratio of 14 : 1.

Data for (2*R*,5*S*,6*S*,7*S*)-isomer: R_f 0.29 (1 : 5 petrol–EtOAc); ν_{max}(film)/cm^{-1} 3409 (w), 3341 (w), 1732 (s), 1704 (s), 1454 (w), 1026 (m); δ_H (500 MHz, $CDCl_3$) 1.33 (3H, t, *J* 7.1, CH_3CH_2), 3.14 (1H, dt, *J* 7.9 and 6.1, C(5)H), 3.24 (1H, d, *J* 14.2, C*H*HPh), 3.50 (1H, d, *J* 14.2, CH*H*Ph), 3.78 (1H, dd, *J* 8.6 and 5.8, C(4)H_{endo}), 4.03 (1H, d, *J* 8.0, C(6)H), 4.07 (1H, dd, *J* 8.6 and 6.5, C(4)H_{exo}), 4.26–4.33 (2H, m, CH_3CH_2), 6.35 (1H, s, C(2)H), 7.14–7. 34 (10H, m, ArC*H*); δ_C (50.3 MHz, $CDCl_3$) 14.16 (CH_3), 34.55 (CH_2Ph), 62.04 (CH_3CH_2), 62.10 (C-5), 63.15 (C-6), 65.94 (C-7), 70.36 (C-4), 87.10 (C-2), 126.23, 127.07, 128.31, 128.42, 128.67, 130.49, and 131.39 (ArCH), 135.76 and 137.36 (2 × ArC), 170.75 and 172.66 (2 × CO); *m*/*z* (APCI$^+$) 381 (M + H^+, 100%); HRMS 381.1818, $C_{22}H_{25}N_2O_4$ (M + H^+) requires 381.1811.

(2*R*,5*S*,6*S*)-6-Benzyloxyamino-8-oxo-2-phenyl-3-oxa-1-azabicyclo[3.3.0]octane 14a and (2*R*,5*S*,6*R*)-6-benzyloxyamino-8-oxo-2-phenyl-3-oxa-1-azabicyclo[3.3.0]octane 15a

Bis(tributyltin) oxide (0.52 ml, 10.20 mmol) was added to lactam **9f** (202 mg, 5.10 mmol) dissolved in toluene (10 ml) with stirring and was then brought to reflux for 18 h. On cooling to RT, a mixture of EtOAc (20 ml) and saturated sodium bicarbonate (20 ml) was added and the organic layer was separated. The aqueous layer was further extracted using EtOAc (2 × 20 ml) and the combined organic layers were washed with water (50 ml), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification of the crude product was carried out using flash column chromatography (2 : 1 followed by 1 : 1 and then 1 : 2 petrol–EtOAc as eluent) which gave the product **14a**–**15a** as a yellow gum (102 mg, 62%) and as an inseparable diastereomeric mixture in a ratio of 6.5 : 1; R_f 0.27 (1 : 1 petrol–EtOAc); ν_{max}(film)/cm^{-1} 3246 (w), 3031 (w), 2917 (w), 1708 (s), 1495 (w), 1454 (w), 1355 (m); *m*/*z* (APCI$^+$) 325 (M + H^+, 100%); HRMS 325.1552, $C_{19}H_{21}N_2O_3$ (M + H^+) requires 325.1552.

Data for **14a**: δ_H (300 MHz, $CDCl_3$) 2.67 (2H, dd, *J* 8.8 and 4.7, C(7)H), 3.52 (1H, dd, *J* 9.2 and 8.3, C(4)H_{endo}), 3.72 (1H, dd, *J* 8.7 and 5.0, C(6)H), 3.97 (1H, m, C(5)H), 4.22 (1H, dd, *J* 8.3 and 6.7, C(4)H_{exo}), 4.71 (2H, s, NOCH_2Ph), 5.61 (1H, br s, NH), 6.28 (1H, s, C(2)H), 7.29–7.45 (10H, m, ArCH); δ_C (50.3 MHz, $CDCl_3$) 37.71 (C-7), 59.35 (C-5), 63.97 (C-6), 66.71 (C-4), 78.79 (OCH_2Ph), 87.72 (C-2), 125.80, 126.00, 128.23, 128.45, 128.52, 128.59, 129.03 and 129.18 (ArCH), 137.16 and 138.28 (2 × ArC), 175.27 (CO).

Data for **15a**: δ_H (300 MHz, $CDCl_3$) 2.67 (2H, dd, *J* 8.8 and 4.7, C(7)H), 3.64 (1H, m, C(4)H_{endo}), 3.72 (1H, td, *J* 8.7 and 5.0, C(6)H), 3.97 (1H, m, C(5)H), 4.22 (1H, dd, *J* 8.3 and 6.7, C(4)H_{exo}), 4.71 (2H, s, NOCH_2Ph), 5.61 (1H, br s, N*H*), 6.33 (1H, s, C(2)H), 7.29–7.45 (10H, m, ArCH); δ_C (50.3 MHz, $CDCl_3$) 37.71 (C-7), 60.39 (C-5), 63.97 (C-6), 70.42 (C-4), 76.42 (OCH_2Ph), 87.07 (C-2), 125.80, 126.00, 128.23, 128.45, 128.52, 128.59, 129.03 and 129.18 (ArCH), 137.16 and 138.28 (ArC), 175.27 (CO).

(+)-(2*R*,5*S*,6*S*)-6-*O*,*N*-Dibenzylhydroxyamino-8-oxo-2-phenyl-3-oxa-1-azabicyclo[3.3.0]octane 14b

Bis(tributyltin) oxide (5.41 ml, 10.60 mmol) was added to the bicyclic lactam **9g** (2.58 g, 5.31 mmol) dissolved in toluene (75 ml) and then refluxed for 18 h. On cooling to RT, a mixture of EtOAc (50 ml) and saturated sodium bicarbonate (50 ml) was added and the organic layer was separated. The aqueous layer was further extracted using EtOAc (2 × 50 ml) and the combined organic layers were washed with water (100 ml), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification of the crude product was carried out using flash column chromatography (3 : 1 and then 2 : 1 petrol–EtOAc as eluent) which gave the product **14b** as a white solid (1.54 g, 70%). R_f 0.17 (3 : 1 petrol–EtOAc); mp 72–74 °C; $[\alpha]_D^{25}$ +92 (*c* 1.2, $CHCl_3$); found C 75.25; H 6.40; N 7.28; calculated C 75.30; H 6.30; N 6.80%; ν_{max}(film)/cm^{-1} 3031 (w), 2877 (w), 1711 (s), 1496 (w), 1454 (w), 1349 (m); δ_H (500 MHz, $CDCl_3$) 2.63 (1H, dd, *J* 16.1 and 8.2, C(7)H), 3.02 (1H, m, C(7)H), 3.51 (1H, ddd, *J* 10.0, 8.3 and 5.7, C(6)H), 3.68 (1H, br t, *J* 6.9, C(4)H_{endo}), 3.82 (1H, d, *J* 13.0, NC*H*HPh), 3.98 (1H, d, *J* 13.0, NCH*H*Ph), 4.13–4.19 (2H, m, C(4)H_{exo} and C(5)H), 4.35 (1H, br d, *J* 10.0, NOC*H*HPh), 4.45 (1H, d, *J* 10.4, NOCH*H*Ph), 6.34 (1H, s, C(2)H), 7.11–7.14 (2H, m, ArCH), 7.30–7.45 (13H, m, ArCH); δ_C (125.8 MHz, $CDCl_3$) 38.05 (C-7), 61.42 (NCH_2Ph), 62.35 (C-5), 67.20 (C-6), 70.91 (C-4), 76.46 (NOCH_2Ph), 86.87 (C-2), 125.74, 125.99, 127.92, 128.26, 128.39, 128.42, 128.46, 128.60, 129.01 and 129.89 (ArCH), 136.05, 136.13 and 138.11 (ArC), 174.61 (CO); *m*/*z* (APCI$^+$) 415 (M + H^+, 100%).

(+)-(2*S*,3*S*)-3-Amino-1-benzyl-2-hydroxymethyl-5-oxopyrrolidine 16a

Using general method C, lactam **14a** (112 mg, 0.27 mmol) was reacted with Pd/C (336 mg, 10%) in glacial acetic acid (20 ml) and H_2 (4 bar) for 48 h. Purification by ion-exchange chromatography (water and then 2 M ammonia in water as eluent) and concentration *in vacuo* gave the product **16a** as an orange gum (22 mg, 44%); $[\alpha]_D^{25}$ +157 (*c* 0.6, H_2O); ν_{max}(film)/cm^{-1} 3289 (m), 2926 (w), 1666 (s), 1451 (m); δ_H (500 MHz, D_2O) 2.08 (1H, dd, *J* 17.7 and 3.3, C(4)H), 2.75 (1H, dd, *J* 17.7 and 7.8, C(4)H), 3.16 (1H, d, *J* 2.9, C(2)H), 3.32–3.41 (1H, m, C(3)H), 3.51 (1H, dd, *J* 12.6 and 2.6, C*H*HOH), 3.65 (1H, dd, *J* 12.6 and 3.6, CH*H*OH), 4.05 (1H, d, *J* 15.4, NC*H*HPh), 4.70 (1H, d, *J* 15.2, NCH*H*Ph), 7.17–7.29 (5H, m, ArCH); δ_C (125.8 MHz, D_2O) 40.01 (C-4), 44.70 (NCH_2), 47.09 (C-2), 59.49 (CH_2OH), 68.41 (C-3), 127.94, 128.23 and 129.23 (ArCH), 135.93 (ArC), 176.98 (CO); *m*/*z* (APCI$^+$) 221 (M + H^+, 100%), HRMS 221.1290, $C_{12}H_{17}N_2O_2$ (M + H^+) requires 221.1290.

General method D: deprotection

Trifluoroacetic acid was added to a stirred solution of the starting material dissolved in either DCM or $CHCl_3$ at RT for

the indicated time. Brine (20 ml) was then added to the reaction mixture and extracted with EtOAc (3 × 20 ml). The combined organic layers were then washed with water (2 × 20 ml), dried over $MgSO_4$ and filtered. Concentration *in vacuo* and purification by flash column chromatography gave the title compound.

(+)-(2*S*,3*S*)-3-*O*,*N*-Dibenzylhydroxyamino-2-hydroxymethyl-5-oxopyrrolidine 16b

Using general method D, the starting material **14a** (20 mg, 0.05 mmol) dissolved in $CHCl_3$ (3 ml) was reacted with trifluoroacetic acid (0.5 ml) for 1 h. Purification by flash column chromatography (10 : 1 EtOAc–MeOH as eluent) and evaporation *in vacuo* gave the title compound **16b** as a yellow gum (13 mg, 81%); R_f 0.36 (8 : 1 EtOAc–MeOH); $[\alpha]_D^{25}$ +54 (*c* 0.8, $CHCl_3$); ν_{max}(film)/cm^{-1} 3307 (m), 1685 (s), 1496 (w), 1207 (m); δ_H (500 MHz, $CDCl_3$) 2.45 (1H, br dd, *J* 16.6 and 8.6, C(4)H), 2.64 (1H, br s, C(4)H), 3.37–3.45 (2H, m, C(3)H and C*H*HOH), 3.67–3.70 (1H, m, CH*H*OH), 3.76 (1H, d, *J* 12.9, NC*H*HPh), 3.81 (1H, br s, C(2)H), 3.93 (1H, d, *J* 12.9, NCH*H*Ph), 4.36–4.42 (2H, m, NOCH_2Ph), 6.93 (1H, br s, N*H*), 7.11–7.38 (10H, m, ArCH); δ_C (125.8 MHz, $CDCl_3$) 59.05 (C-2), 60.35 (C-3), 62.63 (N*C*H$_2$Ph), 64.42 (*C*H$_2$OH), 76.43 (NO*C*H$_2$Ph), 127.72, 128.11, 128.31, 128.41, 129.01 and 129.75 (Ar*C*H), 136.41 and 136.61 (2 × ArC), 177.08 (CO); *m*/*z* (APCI$^+$) 327 (M + H$^+$, 100%); HRMS 327.1709, $C_{19}H_{23}N_2O_3$ (M + H$^+$) requires 327.1709.

(+)-(2*S*,3*S*)-3-Amino-2-hydroxymethyl-5-oxopyrrolidine 16c

Using general method D, Pd/C (220 mg, 10%) was reacted with adduct **16b** (110 mg, 0.34 mmol) dissolved in glacial acetic acid (15 ml) and H_2 (4 bar) for 48 h. Purification by ion-exchange chromatography (water and then 2 M ammonia in water as eluent) gave the title compound **16c** as an orange gum (33 mg, 75%); $[\alpha]_D$ +34 (*c* 1.6, H_2O); ν_{max}(film)/cm^{-1} 3340 (m), 1684 (s), 1388 (w), 1314 (w); δ_H (500 MHz, D_2O) 2.13 (1H, dd, *J* 17.7 and 3.7, C-4), 2.74 (1H, dd, *J* 17.7 and 7.8, C-4), 3.48–3.50 (1H, m, C(2)H), 3.50–3.53 (1H, m, C(3)H), 3.57 (1H, dd, *J* 11.9 and 4.9, C*H*HOH), 3.65 (1H, dd, *J* 11.9 and 3.8, CH*H*OH); δ_C (125.8 MHz, D_2O) 38.84 (C-4), 48.54 (C-3), 62.15 (*C*H$_2$OH), 64.22 (C-2), 179.23 (CO); *m*/*z* (APCI$^+$) 131 (M + H$^+$, 100%), 114 (M − NH$_2$, 20); HRMS 131.0821, $C_5H_{11}N_2O_2$ requires 131.0821.

MTPA derivative 17a

To a solution of the alcohol **16b** (14 mg, 0.04 mmol) and pyridine (3 drops) in DCM (2 ml) was added (*S*)-α-methoxy-α-trifluoromethylphenylacetyl chloride[50,51] (16 mg, 0.06 mmol). The reaction mixture was then stirred at RT for 20 h and partitioned between hydrochloric acid (2 M, 15 ml) and diethyl ether (15 ml). The ether layer was washed with water (15 ml) and brine (15 ml), dried over $MgSO_4$ and evaporated *in vacuo*. Initial ^{1}H and ^{19}F NMR analysis indicated a diastereomeric excess of at least 95%. Purification by flash column chromatography (1 : 2 petrol–EtOAc as eluent) gave the product **17a** as a yellow gum (21 mg, 91%); R_f 0.39 (1 : 3 petrol–EtOAc); ν_{max}(film)/cm^{-1} 3226 (w), 3032 (w), 2950 (w), 1753 (s), 1702 (s), 1453 (m), 1253 (s), 1170 (s); δ_H (500 MHz, $CDCl_3$) 2.31 (1H, dd, *J* 16.3 and 8.6, C(4)H), 2.61 (1H, br s, C(4)H), 3.27 (1H, ddd, *J* 8.7, 6.4 and 5.6, C(3)H), 3.47 (3H, s, OCH_3), 3.74 (1H, d, *J* 12.9, NC*H*Ph), 3.86 (1H, br s, C(5)H), 3.97–4.03 (2H, m, NC*H*Ph and C*H*HO), 4.38–4.48 (3H, m, NOCH_2Ph and CH*H*O), 5.46 (1H, s, N*H*), 7.15–7.17 (2H, m, ArCH), 7.28–7.45 (13H, m, ArCH); δ_C (125.8 MHz, $CDCl_3$) 55.45 (O*C*H$_3$), 60.37 (C-2 and C-3), 62.33 (N*C*H$_2$Ph), 67.50 (*C*H$_2$O), 76.25 (NO*C*H$_2$Ph), 127.12, 127.95, 128.33, 128.40, 128.57, 128.65, 129.11, 129.64 and 129.89 (Ar*C*H), 131.72, 136.09 and 136.11 (3 × ArC), 166.36 (ester CO), 174.93 (amide CO); δ_F (235.2 MHz, $CDCl_3$) −71.87 (CF_3); *m*/*z* (APCI$^+$) 543 (M + H$^+$, 65%), 423 (100).

The corresponding derivative from (±)-MTPA-Cl was prepared using a similar method: initial ^{1}H and ^{19}F NMR analysis indicated the presence of two diastereomers **17b** in a ratio of 1 : 1; R_f 0.39 (1 : 3 petrol–EtOAc); δ_F (235.2 MHz, $CDCl_3$) −71.87 and −71.89 (2 × CF_3).

Acknowledgements

We thank EPSRC and Merck Sharp and Dohme for funding of a studentship to PWHC, and we wish to gratefully acknowledge the use of the EPSRC Chemical Database Service at Daresbury[54] and the EPSRC National Mass Spectrometry Service Centre at Swansea.

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