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Enantiopure bicyclic piperidinones: stereocontrolled conjugate additions leading to substituted piperidinones

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The conjugate additions of Reformatsky reagents, organocuprate reagents, and hydroxylamines to a [4.3.0]-bicyclic enelactam derived from 6-oxopipecolic acid have been investigated, and found to be efficient, proceeding with excellent *exo*-stereocontrol, with the exception of *N*-benzyl-*O*-benzylhydroxylamine, which gives predominantly the product of *endo*-addition. These adducts can be readily converted to substituted piperidinones.

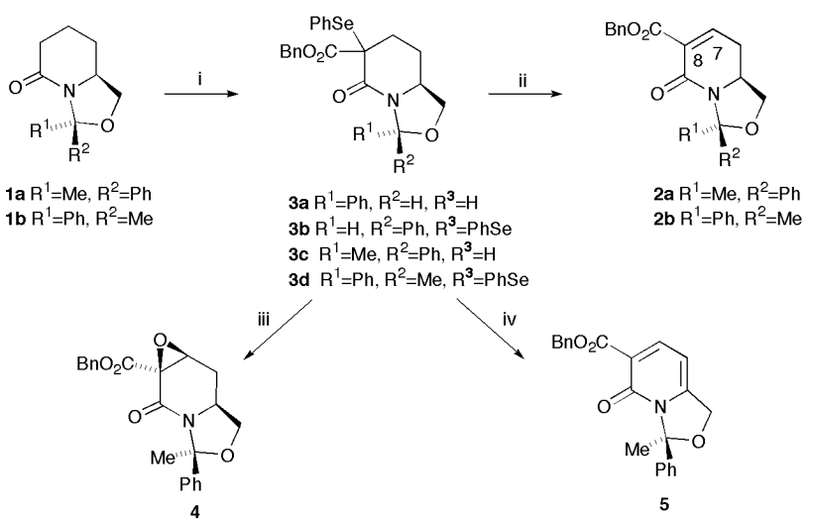
In the previous paper,[1] we described a direct route for the synthesis of enantiopure bicyclic piperidinones **1a**,**b** and an investigation of the alkylation of their derived enolates. Of potentially greater interest, however, are the corresponding unsaturated derivatives **2a**,**b** which would permit manipulation of C(7) and C(8) either separately or simultaneously, to give the corresponding highly functionalised piperidinones. However, a likely requirement for activation in such reactions is evident from an earlier report by Overman that unsaturated δ-lactams are not particularly susceptible to conjugate addition reactions.[2] Activation of these systems has been achieved in one of three ways: an electron-withdrawing group may be attached to nitrogen,[3] the carbonyl group may be converted to a thiolactam,[4,5] or an electron-withdrawing group may be attached to the α-carbon.[6] The latter strategy has proved to be effective in the analogous [3.3.0] bicyclic system, which has permitted highly diastereocontrolled modifications using carbon, oxygen and nitrogen nucleophiles.[7–11] A similar strategy has been extensively developed for piperidinones by Amat and Bosch,[12,13] who have achieved highly diastereoselective conjugate additions[14,15] in an enantiopure bicyclic oxazolopiperidinone template.[16] Significantly, in both of these [3.3.0] and [4.3.0] bicyclic systems, *exo*-additions (*i.e.* sterically least encumbered additions to the convex face of the template) are favoured, although this preference can be overridden, at least in unactivated [4.3.0] systems, by local substituent bulk effects, in which case *endo*-additions have been observed.[14] Conjugate additions to α,β-unsaturated monocyclic γ-lactams of organocuprates,[15,17–19] nitroalkanes,[20] stabilized enolates,[15] and even of phenylboronic acids under Rh(I) catalysis[21] have since been reported. The issue of stereocontrol in these additions has been the subject of some investigation,[22] and steric and A-strain phenomena have been invoked to explain observed diastereoselectivities.[17,18,20] Alternative methodologies leading to similar piperidinones from these conjugate addition reactions, but instead using ring closure reactions,[23,24] and zip-type processes[25] have been reported. The significance of substituted piperidines as conformational controlling elements is becoming increasingly apparent, and methodology to access these systems correspondingly more important.[17,20,24,26]

In this paper, we describe our work in the context of conjugate additions to unsaturated piperidinone systems, and the application of these intermediates by further ring modifications to highly functionalised heterocyclic systems.

Results and discussion

Synthesis of enone

We expected that the required enones **2a** and **2b** would be readily available from selenides **3b** and **3d** (Scheme 1). Although these compounds have been prepared by sequential conversion



Scheme 1 *Reagents and conditions*: (i) LiHMDS/THF/−78 °C then $PhCH_2OC(O)Cl$ then PhSeBr; (ii) $NaIO_4$, $NaHCO_3$, MeOH, H_2O or H_2O_2, py, CH_2Cl_2; (iii) 5 equiv. H_2O_2, CH_2Cl_2; (iv) $NaIO_4$, H_2O.

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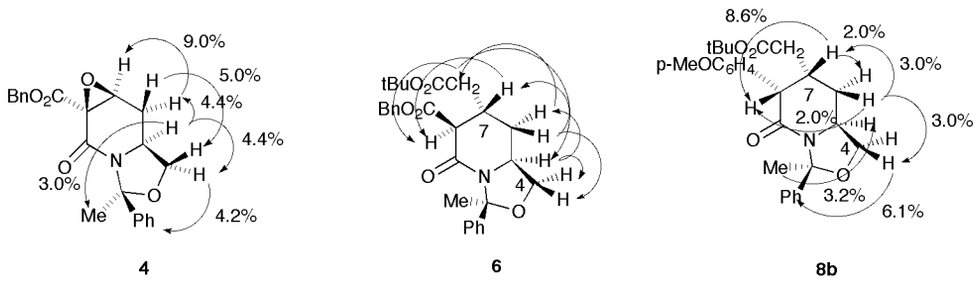
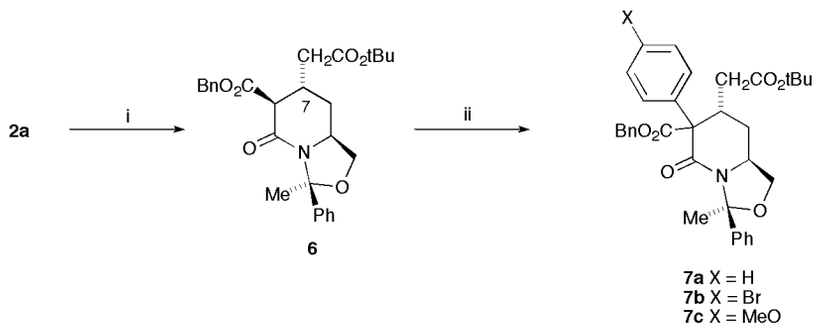


Fig. 1 NOE results for compounds **4**, **6** and **8b**.



Scheme 2 *Reagents and conditions*: (i) $BrZnCH_2CO_2tBu$, THF, DMPU (76%); (ii) *p*-X-$C_6H_4Pb(OAc)_3$, py.

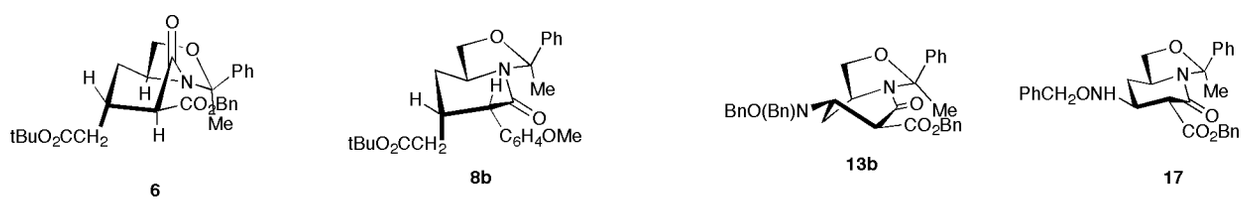


Fig. 2 Preferred conformations for **6**, **8b**, **13b** and **17**.

of bicyclic lactams **1a**,**b** to ester derivatives **3a**,**c** and thence to selenides **3b**,**d** as described in our previous paper,[1] we found that a one-pot synthesis, based on successful similar conversions which had been reported in the literature,[27] was very effective. Thus, treatment of lactam **1a** with 2.2 equiv. LiHMDS, followed successively by one equivalent each of benzyl chloroformate and phenylselenenyl bromide, gave the desired product **3b** in 78% yield as approximately a 1 : 1 ratio of diastereomers. Interestingly, application of this route to hemiaminal ether **1b** gave consistently lower yields of the corresponding selenide **3d** (9% at best over the two steps). Surprisingly, oxidative elimination of lactam **3b** to its α,β-unsaturated derivative was highly reagent-dependent: use of hydrogen peroxide–DCM gave only epoxide **4** (stereochemistry established by NOE analysis (Fig. 1)), but effective conversion of selenide **3b** to enone **2a** could be achieved either by reaction with a mixture of $NaIO_4$, $NaHCO_3$, MeOH, H_2O (70% yield) or with H_2O_2 in a solution of DCM and pyridine (88% yield). If the base was omitted from these reactions, the unstable pyridone **5** was formed in low yield (10%). Interestingly, application of the former conditions to selenide **3d** gave only a 45% yield of enone **2b**.

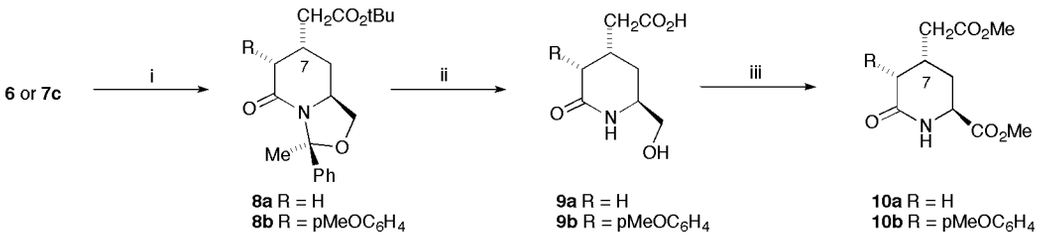
Reformatsky conjugate additions

Because of our earlier success with the conjugate addition of Reformatsky reagents,[11,28] we examined similar reactions with enone **2a** and found that the adduct **6** was formed in 76% yield as a single diastereomer as assigned by NOESY analysis (Scheme 2 and Fig. 1). Addition of the Reformatsky reagent occurred to the least hindered *exo*-face, as expected, but the C(7)H/C(8)H relationship was more difficult to assign: a mutual NOE enhancement upon irradiation of $C(7)CH_2$ with both C(8)H, C(6)H and C(5)H is consistent with their *cis*-disposition and therefore the *endo*-location of the C(8) substituent; this, along with a C(7)H/C(8)H coupling constant of 7.5 Hz, suggests a boat-like piperidinone ring conformation as indicated in Fig. 2. Similar *trans*-diastereoselectivity in conjugate addition reactions has been observed in the analogous reactions of the [3.3.0] systems.[10] This single step transformation is noteworthy, introducing as it does a two-carbon unit terminating in an ester, given that related conversions in the literature using for example, ethyl 1,3-dithiolane-2-carboxylate[14] or allylcuprate,[29] require two or more steps to achieve the same outcome.

Table 1 Reaction of adduct **2** with lead complexes (Scheme 2)

Product	Aryllead triacetate	Yield (%)	Diastereomeric ratio
7a	$PhPb(OAc)_3$	69	3 : 1
7b	$BrC_6H_4Pb(OAc)_3$	93	5 : 1
7c	$MeOC_6H_4Pb(OAc)_3$	59	2 : 1

The value of these adducts as useful synthetic intermediates was demonstrated as follows: it is well known that aryllead(IV) tricarboxylate complexes may be used to generate quaternary carbon centres at β-dicarbonyl positions,[30,31] although more recently the application of palladium-based methodology has also been reported.[32] Reformatsky adduct **6** would be a suitable substrate for such reactions, as it contains a highly activated site at C-8. The expected products would be particularly interesting as they could be considered to be homologues of kainic acid, and of potential interest as glutamate agonists and/or antagonists.[33] Reaction of adduct **6** with preformed aryllead triacetates (from the corresponding arylboronic acid and lead tetraacetate/mercury(II) acetate[34]) in refluxing chloroform–pyridine gave the corresponding α-arylated products **7a**–**c** in good to excellent yield, and as a mixture of diastereomers (Table 1). Hydrogenolysis and decarboxylation (H_2 at 4 bar, 10% palladium on carbon, ethyl acetate, and a reaction time of 72 hours, followed by heating of the crude product) of adducts **6** and **7c** gave



Scheme 3 *Reagents and conditions*: (i) H_2, 4 bar, Pd/C then Δ; (ii) TFA, CH_2Cl_2; (iii) RuO_2, $NaIO_4$, CCl_4, MeCN, H_2O then CH_2N_2.

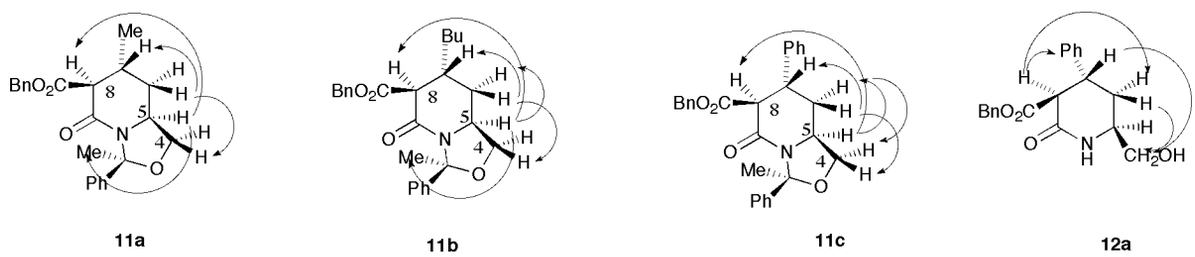


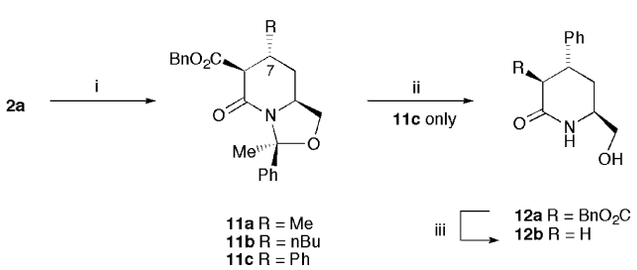
Fig. 3 NOE results for compounds **11a**, **11b**, **11c** and **12a**.

excellent yields of the decarboxylated products **8a** and **8b** (84 and 67% respectively, Scheme 3). The C(7)CH_2 *exo*-stereochemistry was again confirmed by a NOE with C(5)H of lactam **8b** and the C(8)H_{endo} stereochemistry was suggested by enhancements along the sequence of C(8)H, C(7)H, C(6)H_{endo}, C(4)H_{endo} and C(2)Ph which indicated their common *endo*-configuration; interestingly the enhancement at C(6)H_{exo} (2.0%) upon irradiation of C(7)H suggested a half-chair conformation with the C-7 substituent pseudoaxial and the C-8 one pseudo-equatorial (Figs. 1 and 2). Also suggestive of the C(8)*exo* substituent stereochemistry is the fact that **8b** exhibited a large negative $[\alpha]_D$ value, seen earlier in products of C(8) *exo*-alkylation,[1] and $^3J_{7,8}$ was 5.5 Hz.

Deprotection of lactams **8a**,**b**, using conditions established earlier (TFA/DCM)[1] gave simultaneous removal of the t-butyl ester and oxazolidine protecting groups, to give the products **9a**,**b** in excellent yield (98% and 100% respectively) which were not purified, but used immediately (Scheme 3). Two-step conversion (oxidation followed by immediate esterification of these products using conditions reported earlier[10]) gave diesters **10a**,**b** in low (but unoptimised) yield (16 and 27%); their stereochemistry is assumed from the structural assignments of their precursors. Lactam **10b** is the first example of a homokainoid thus far reported.

Cuprate conjugate additions

The success of Reformatsky reagents described above and of literature precedent,[22] suggested that organocuprates would prove to be productive for conjugate additions to enone **2a**. Treatment of enone **2a** with several diorganocopperlithium reagents (Scheme 4 and Table 2) gave the corresponding C(7)H_{exo}/C(8)H_{endo} adducts **11a**–**c** in modest yields (compound **11a** was obtained with 7% of the C(7) epimer, but **11b**,**c** were diastereomerically pure). Their stereochemistry was evident



Scheme 4 *Reagents and conditions*: (i) R_2CuLi, ether; (ii) 15% TFA, $CHCl_3$ (52%); (iii) $(Bu_3Sn)_2O$, toluene, reflux (62%).

Table 2 Reactions of organocuprates with enone **2a** (Scheme 4)

Product	R	Yield (%)
11a	Me	19
11b	Bu	36
11c	Ph	42

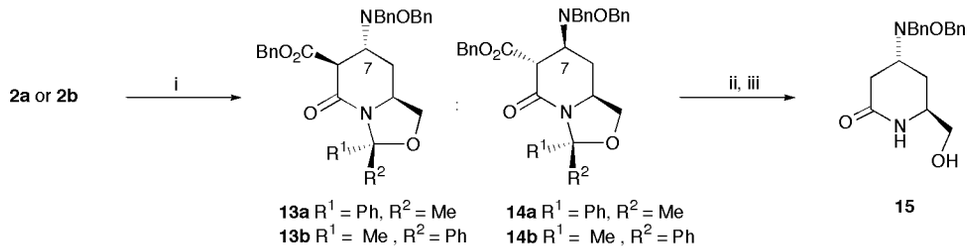
Table 3 Reaction of lactams **2a** and **2b** with *N*,*O*-dibenzylhydroxylamine (Scheme 5)

Reactant	Conditions	Product	Ratio **13 : 14**	Yield (%)
2b	MeOH, r.t.	**13a**,**14a**	9 : 1	30
2b	MeOH, reflux	**13a**,**14a**	—	—
2b	$CHCl_3$, reflux	**13a**,**14a**	9 : 1	63
2a	$CHCl_3$, reflux	**13b**,**14b**	8–10 : 1	45

from NOESY analysis (Fig. 3), in which key enhancements were C(7)H_{endo}/C(6)H_{endo}/C(4)H_{endo} and C(2)Me/C(5)H/C(8)H, and a similar boat piperidinone ring conformation to adduct **2** was suggested by $^3J_{7,8}$ values of 7.0, 6.5 and 9.0 for **11a**,**b**,**c** respectively. This was a significantly higher level of diastereocontrol than that obtained in the monocyclic systems of Mann,[22] and is in accord with the diastereoselectivity observed in the Reformatsky additions to the bicyclic system described above. By way of demonstrating the value of these intermediates, deprotection of lactam **11c** (TFA, $CHCl_3$) to give **12a** and then removal of the C-8 ester ($(Bu_3Sn)_2O$, toluene, reflux) gave lactam **12b** in 32% yield over the two steps.

Amine conjugate additions

Of further interest was examination of the addition of nitrogen nucleophiles, to generate the corresponding β-aminoester derivatives, a reaction which proved to be highly facile in the [3.3.0] series.[8,9] However, addition of *N*,*O*-dibenzylhydroxylamine to both C-2 epimeric lactams **2a** and **2b** proved to be sluggish although highly diastereoselective (Scheme 5 and Table 3), giving best reaction in refluxing chloroform, and favouring additions to the *exo*-face of both bicyclic systems. Stereochemical assignment was by NOE analysis in the usual way (Fig. 4) and a diequatorial conformation for each of **13a**, **13b** and **14b** was indicated by $^3J_{7,8}$ values of 8.0, 10.0 and 7.5 Hz respectively. Key enhancements in lactam **13a** were C(6)H_{exo} and C(8)H ⟶ NOCH_2Ph, for **13b** were C(2)Ph ⟶ C(4)H_{endo} ⟶ C(6)H_{endo} ⟶ C(7)H_{endo}, and C(8)H ⟶ NOCH_2Ph, and for **14b** were C(6)H_{endo} ⟶ C(4)H_{endo} and C(2)Ph and C(8)H, and C(4)H_{exo} ⟶ C(5)H ⟶ C(6)H_{exo} ⟶ C(7)H. The required *trans*-



Scheme 5 *Reagents and conditions*: (i) $PhCH_2ONHCH_2Ph$; (ii) $(Bu_3Sn)_2O$, toluene, reflux (38%); (iii) 15% TFA, $CHCl_3$ (63%).

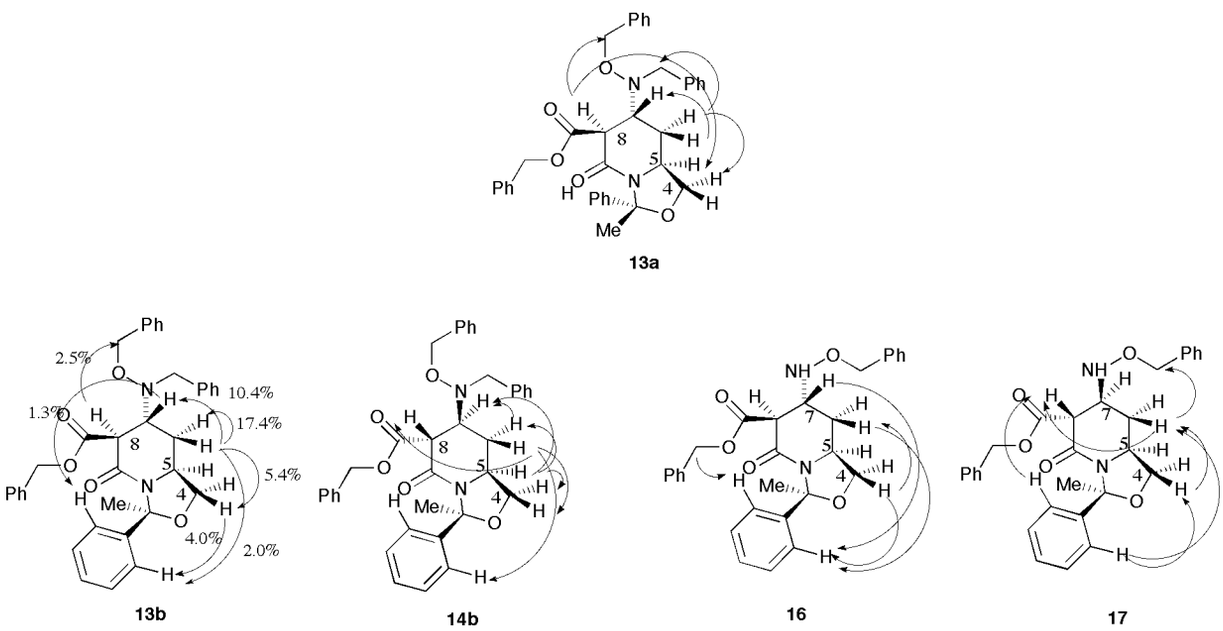


Fig. 4 NOE results for compounds **13a**, **13b**, **14b**, **16** and **17**.

stereochemical arrangement of **13a** and **13b** could be supported in a *trans*-diequatorial chair-like piperidinone ring, as indicated in Fig. 2. Single step hydrogenolytic deprotection of lactam **13b** was not successful, but sequential removal of ester ($(Bu_3Sn)_2O$, toluene) and then oxazolidine (TFA) protecting groups gave alcohol **15** in modest yield (25%) over the two steps (Scheme 5).

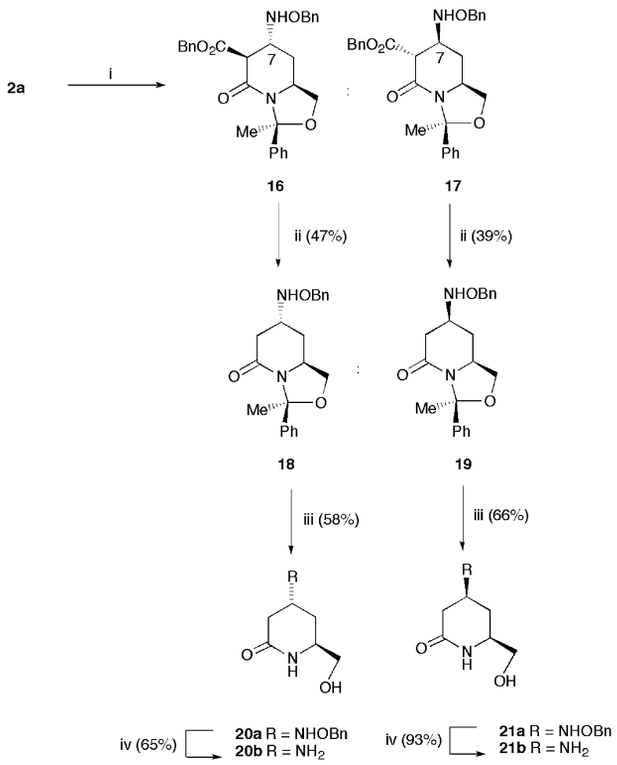
Suspecting that this lack of reactivity may be a direct result of steric hindrance of the bulky amine nucleophile, the reaction of *O*-benzylhydroxylamine with lactam **2a** was examined. In this case, we were delighted to find that the reaction proceeded in 91% yield within 3 hours. The most striking result from this reaction, however, was the diastereomeric ratio. In direct contrast to the *N*,*O*-dibenzylhydroxylamine reaction, the C(7)H_{exo} **17** and not the C(7)H_{endo} diastereomer **16** dominated by a ratio of 2 : 1. The stereochemistry and *trans*-substitution pattern of both the *exo*-**16** and *endo*-**17** products were again confirmed by ^{1}H NMR NOESY analysis (Fig. 4). Thus, the indicated assignment for the minor isomer **16** was supported by the enhancement sequence C(2)Ph ⟶ C(4)H_{endo} ⟶ C(6)H_{endo} and C(7)H ⟶ C(2)Ph; the C-8 stereochemistry was supported by an enhancement between C(8)CH_2Ph and C(2)Ph, and a coupling constant for $J_{7,8}$ of 6.0 Hz for **16** was observed. Similarly, for the major isomer **17**, key enhancements were C(2)Ph ⟶ C(4)H_{endo} ⟶ C(6)H_{endo} ⟶ C(7)NHOCH_2Ph ⟶ C(8)H, further supported by a crosspeak between C(2)Ph and C(8)H. Furthermore, coupling constant data ($J_{6endo,5}$ = 10.5 Hz, $J_{6endo,7}$ = 12.0 Hz, $J_{8,7}$ = 8.0 Hz) suggested the diequatorial conformation for **17**, in which the piperidinone ring existed in a chair conformation as indicated in Fig. 2.

To provide a direct comparison of reactivity with the *N*,*O*-dibenzylhydroxylamine addition reactions examined earlier (Scheme 5), the addition of *O*-benzylhydroxylamine was carried out in refluxing chloroform. ^{1}H-NMR spectroscopic analysis of the crude reaction mixture showed the reaction had gone to completion, and that the *endo*- : *exo*- ratio was again 2 : 1. Furthermore, refluxing either the pure *exo*-**16** or pure *endo*-adduct **17** in chloroform for 15 hours led to an *endo*- : *exo*- ratio of 2 : 1 in both cases. It would therefore appear that the *endo*-diastereomer **17**, with the smaller C-7 substituent when compared to **14b**, is the thermodynamic product in this case, favoured by the chair conformation of the piperidinone ring which allows the bulky C(7) and C(8) substituents to adopt diequatorial positions, and the *exo*-diastereomer **16** is the kinetic one.

Although the diastereoselectivity for *O*-benzylhydroxylamine addition was poorer than for *N*,*O*-dibenzylhydroxylamine, the vastly superior yield for the former allowed full deprotection for each of the *exo*-**16** and *endo*-**17** diastereomers (Scheme 6). Thus, benzyl ester cleavage ($(Bu_3Sn)_2O$) gave lactams **18** and **19**, oxazolidine ring opening (TFA) gave alcohols **20a** and **21a**, and hydrogenolysis (H_2, 5 bar, 10% Pd/C) gave the amines **20b** and **21b**, in reactions which proceeded in good to excellent yield.

Stereochemical considerations

The stereochemistry of conjugate addition to unsaturated piperidinones has attracted some recent attention. For monocyclic systems using organometallic nucleophiles, the A^{1,3} strain of the ring system and the size of the nucleophile appear to be controlling factors,[20,22] but more recent work suggests that chelation control can become dominant in suitable substrates.[17] In the case of [4.3.0] bicyclic systems, it would appear that enone systems activated with ester substituents give *exo*-addition in all cases,[15] presumably since addition to the convex face is favoured on steric grounds, but that unactivated enones possessing an allylic substituent can proceed with *endo*-



Scheme 6 *Reagents and conditions*: (i) $PhCH_2ONH_2$·HCl, NaOAc, MeOH, r.t. (91%); (ii) $(Bu_3Sn)_2O$, toluene, reflux; (iii) 15% TFA, $CHCl_3$; (iv) 10% Pd–C/H_2, glacial HOAc.

addition.[14] In the latter case, the global preference for convex face addition appears to be overridden by a local preference for reaction giving a (pseudo)diequatorial outcome.

In the case of the [4.3.0] systems derived from oxopipecolic acid as considered in this work, the same preference for *exo*-face addition exists for bulky organometallic and amine nucleophiles, since this permits approach from the less hindered convex face of the bicyclic system; however, although this generates a product with (pseudo)diequatorial substituents, the piperidinone ring would appear to be in a boat-like or half chair conformation (*e.g.* compounds **6** and **13b** in Fig. 2). In the case of smaller nucleophiles, proceeding by a reversible addition, such as hydroperoxide or *O*-benzylhydroxylamine, *endo*-face addition becomes feasible, and this mode is favoured by a product in which the same (pseudo)diequatorial disposition of substituents leaves the piperidinone ring in a chair conformation, leading to a global energy minimum; favourable chelation control might also assist in this facial selectivity.

Conclusion

We have shown that highly stereoselective conjugate addition reactions to bicyclic [4.3.0] lactams derived from 6-oxopiperidine carboxylic acid are possible, using organometallic and amine nucleophiles, and that these adducts can be readily elaborated to substituted enantiopure piperidinones.

Experimental

One-pot method for the preparation of selenides 3b and 3d. A solution of lithium bis(trimethylsilyl)amide in hexanes (1.0 M, 2.2–4.0 equiv.) was added dropwise *via* cannula to a solution of the lactam **1a** or **1b**[1] (1 equiv.) in THF (40 ml) at −78 °C and under an inert atmosphere. After stirring for 20 minutes a solution of benzyl chloroformate (1.1 equiv.) in THF (15 ml) was added dropwise *via* cannula. After stirring for 20 minutes at −78 °C, a solution of phenylselenenyl bromide (1.4 equiv.) in THF (15 ml) was added dropwise *via* cannula and the reaction mixture stirred for 1 hour. The reaction was then quenched with 5% NH_4Cl(aq) (20 ml) and the aqueous layer was washed with EtOAc (3 × 20 ml). The organic layers were combined, dried ($MgSO_4$) and the solvent removed *in vacuo.* Purification by flash column chromatography (20% EtOAc : petroleum ether (bp 60–80 °C)) on silica gel gave monobenzoylated material (approx. 1%) along with the desired product **3b** (78%) or **3d** (9%) as a mixture of diastereomers in a ratio of 1.3–1.6 : 1. Data for both compounds are as reported in our previous paper.[1]

(−)-(2*S*,5*S*,7*S*,8*S*)-1-Aza-8-benzyloxycarbonyl-7,8-epoxy-2-methyl-3-oxa-9-oxo-2-phenylbicyclo[4.3.0]nonane 4. To a solution of a mixture of the selenides **3b**[1] (64 mg, 0.12 mmol) in DCM (12.5 ml) was added hydrogen peroxide (70 mg, 0.61 mmol). The mixture was then stirred vigorously for one hour at 30 °C. The reaction was quenched with sat. aq. $NaHCO_3$ (5 ml), extracted with DCM (3 × 10 ml), and solvent was removed *in vacuo*. The residue was purified using flash column chromatography, eluting with 40% EtOAc : Petrol to yield the product **4** as a colourless oil (46 mg, 99%); R_f 0.28 (40% EtOAc : Petrol); $[a]_D^{25}$ −77.5 (*c* 0.31, $CHCl_3$); ν_{max}(film)/cm^{-1} 1753s, 1669s; δ_H (500 MHz; $CDCl_3$) 1.91 (1H, dd, *J* 11.0 and 14.5, C(6)H_{endo}), 2.09 (3H, s, C(2)Me), 2.60 (1H, ddd, *J* 3.5, 4.0 and 11.0, C(6)H_{exo}), 3.43 (1H, t, *J* 8.5, C(4)H_{endo}), 3.86 (1H, d, *J* 3.5, C(7)H), 3.97–4.04 (1H, m, C(5)H), 4.18 (1H, dd, *J* 6.0 and 8.5, C(4)H_{exo}), 5.36 (2H, s, CO_2CH_2), 7.32–7.54 (10H, m, ArH); δ_C (125.8 MHz; $CDCl_3$) 26.0 (C(2)Me), 26.6 (C(6)), 51.7 (C(5)), 58.1 (C(8)), 58.6 (C(7)), 68.2 (C(4)), 68.8 (CO_2CH_2), 98.0 (C(2)), 126.1, 126.2, 128.7, 128.8, 128.9, 129.1 (ArCH), 135.5 (ArC), 141.4 (ArC), 160.9 (C=O), 165.7 (C=O); *m*/*z* (APCI$^+$) 380.2 (MH^+, 100%); HRMS: 380.1499 (MH^+, ES$^+$). $C_{22}H_{21}NO_5$ requires 380.1498.

(−)-(2*S*,5*S*)-1-Aza-8-benzyloxycarbonyl-2-methyl-3-oxa-9-oxo-2-phenylbicyclo[4.3.0]non-7-ene 2a. To a solution of selenides **3b**[1] (0.95 g, 1.8 mmol) in methanol (50 ml) was added a solution of sodium periodate (0.78 g, 3.6 mmol) and sodium bicarbonate (0.15 g, 1.8 mmol) in water (30 ml). The mixture was stirred for 1 hour, when t.l.c. analysis suggested that reaction was complete. A 1 : 1 mixture of sat. aq. NH_4Cl and EtOAc (30 ml) was added, and the organic layer separated. The aqueous layer was extracted with EtOAc (3 × 25 ml), the organic layers combined and dried with brine (25 ml) and over $MgSO_4$, and solvent was removed *in vacuo*. The residue was separated by column chromatography eluting with 40% EtOAc : Petrol to give the product **2a** as a colourless oil (0.51 g, 82%); R_f 0.24 (40% EtOAc : Petrol); $[a]_D^{25}$ −69.9 (*c* 1.09, $CHCl_3$); ν_{max}(film)/cm^{-1} 1735s, 1666s, 1246s; δ_H (500 MHz; $CDCl_3$) 2.10 (3H, s, C(2)Me), 2.27–2.33 (1H, m, C(6)H_{endo}), 2.50–2.56 (1H, m, C(6)H_{exo}), 3.46 (1H, t, *J* 9.0, C(4)H_{endo}), 4.06–4.13 (1H, m, C(5)H), 4.16 (1H, dd, *J* 6.0 and 9.0, C(4)H_{exo}), 5.25–5.32 (2H, m, CO_2CH_2), 7.26–7.57 (11H, m, C(7)H and ArH); δ_C (125.8 MHz; $CDCl_3$) 26.1 (C(2)Me), 27.2 (C(6)), 55.4 (C(5)), 66.8 (C(4)), 68.4 (CO_2CH_2), 96.5 (C(2)), 125.6, 127.9, 128.0, 128.1, 128.2, 128.4 (ArCH), 131.1 (C(8)), 135.5 (ArC), 142.0 (ArC), 145.7 (C(7)), 158.4 (C=O), 163.5 (C=O); *m*/*z* (APCI$^+$) 364 (MH^+, 100%), 362 (19); HRMS: 364.1552 (MH^+, ES$^+$). $C_{22}H_{21}NO_4$ requires 364.1549.

The same compound could be obtained by the following alternative procedure: Pyridine (0.18 ml, 2.24 mmol) was added to a solution of a mixture of selenides **3b** (583 mg, 1.12 mmol) in DCM (10 ml) and cooled to 0 °C. 30% H_2O_2(aq) (0.34 ml, 2.99 mmol) was then added dropwise with rapid stirring. After 20 minutes, the reaction mixture was warmed to room temperature and stirred for 20 min, before quenching with 1 : 1 DCM : 10% aq. $NaHCO_3$ (20 ml). The aqueous layer was washed with DCM (10 ml) and the organic layers combined, washed with 10% aq. HCl (2 ml), brine (4 ml), dried ($MgSO_4$)

and the solvent removed *in vacuo*. Purification by flash column chromatography on silica gel (30% EtOAc : Petrol) gave only the desired product **2a** as a colourless oil (70 mg, 88%).

(−)-(2*S*)-1-Aza-8-benzyloxycarbonyl-2-methyl-3-oxa-9-oxo-2-phenylbicyclo[4.3.0]nona-5,7-diene 5. To a solution of selenides **3b**[1] (1.42 g, 2.7 mmol) in methanol (50 ml) was added a solution of sodium periodate (1.17 g, 5.5 mmol) in water (30 ml). The mixture was stirred at room temperature for 3 hours, and then worked up with the addition of 50 ml of a 1 : 1 mixture of EtOAc and sat. aq. NH_4Cl. The aqueous layer was extracted with EtOAc (3 × 25 ml), dried with brine (20 ml) and over $MgSO_4$. Solvent was removed *in vacuo* and the residue separated by flash column chromatography (40% EtOAc : Petrol) to give the product **5** as a colourless oil (98 mg, 10%) that decomposed on standing to a brown gum. R_f 0.16 (40% EtOAc : Petrol); $[a]_D^{22}$ −212.0 (*c* 1.13, $CHCl_3$); ν_{max}(film)/cm^{-1} 1734s, 1698m, 1667s, 1605m, 1554s, 666m; δ_H (400 MHz; $CDCl_3$) 2.30 (3H, s, C(2)Me), 4.94 (1H, dd, *J* 1.0 and 14.5, C(4)H), 5.07 (1H, dd, *J* 1.0 and 14.5, C(4)H), 5.28–5.38 (2H, m, CO_2CH_2), 6.12 (1H, dt, *J* 7.5 and 1.0, C(6)H), 7.18–7.54 (10H, m, ArH), 8.22 (1H, d, *J* 7.5, C(7)H); δ_C (100.6 MHz; $CDCl_3$) 25.1 (C(2)Me), 66.6 (C(4)), 68.3 (CO_2CH_2), 96.8 (C(6)), 103.3 (C(2)), 119.6 (C(5)), 125.8, 127.8, 128.2, 128.4, 128.6, 129.0 (ArCH), 136.1 (ArC), 139.2 (ArC), 146.2 (C(7)), 150.5 (C(8)), 157.4 (C=O), 164.2 (C=O); *m*/*z* 384 (M+Na$^+$, 33%), 362 (MH$^+$, 100), 254 (20); HRMS: 384.1210 (M+Na$^+$, ES$^+$). $C_{22}H_{19}NO_4$ requires 384.1212.

(−)-(2*R*,5*S*)-1-Aza-8-benzyloxycarbonyl-2-methyl-3-oxa-9-oxo-2-phenylbicyclo[4.3.0]non-7-ene 2b. The selenide **3d**[1] (95 mg, 0.2 mmol) was reacted with sodium periodate (78 mg, 0.4 mmol) and sodium bicarbonate (15 mg, 0.2 mmol) in water. The mixture was stirred for 1 hour at room temperature before quenching. The residue was separated by flash column chromatography on silica gel, eluting with 40% EtOAc : Petrol, to give the product **2b** as an oil (30 mg, 45%); R_f 0.43 (50% EtOAc : Petrol); $[a]_D^{23}$ +38.7 (*c* 0.8, $CHCl_3$); ν_{max}(film)/cm^{-1} 1736s, 1663s, 1422s; δ_H (500 MHz; $CDCl_3$) 2.07 (3H, s, Me), 2.44–2.51 (1H, m, C(6)H$_{endo}$), 2.54–2.60 (1H, m, C(6)H$_{exo}$), 3.84–3.87 (1H, m, C(4)H$_{endo}$), 4.04–4.10 (1H, m, C(5)H), 4.14–4.17 (1H, m, C(4)H$_{exo}$), 5.24 (1H, d, *J* 12.5, PhC*H*HO), 5.29 (1H, d, *J* 12.5, PhCH*H*O), 7.27–7.58 (9 H, m, C(7)H and ArCH), 7.38–7.42 (2H, m, ArH); δ_C (125.7 MHz; $CDCl_3$) 25.7 (Me), 29.0 (C(6)), 55.3 (C(5)), 66.8 (CH_2Ph), 69.9 (C(4)), 96.9 (C(2)), 125.8, 128.2, 128.2, 128.5 (ArCH), 130.8 (C(7)), 135.6, 141.6 (ArC), 144.8 (C(8)), 157.7 (CON), 163.6 (PhCH$_2$O*C*O); *m*/*z* (APCI$^+$) 364 (MH$^+$, 100%); HRMS: 364.1549 (MH$^+$, CI). $C_{22}H_{22}NO_4$ requires 364.1554.

(−)-(2*S*,5*S*,7*R*,8*S*)-1-Aza-8-benzyloxycarbonyl-7-(*tert*-butyloxycarbonylmethyl)-2-methyl-3-oxa-9-oxo-2-phenylbicyclo[4.3.0]nonane 6. To a solution of α-bromo *tert*-butyl acetate (0.25 g, 1.3 mmol) and iodine (0.022 g, 0.09 mmol) in THF (11 ml) was added zinc (0.14 g, 2.1 mmol). This mixture was heated to 35 °C in an ultrasound bath for 15 minutes. The suspension was then cooled to 0 °C in an ice bath, and DMPU (1 ml) was added. A solution of the enone **2a** (0.16 g, 0.43 mmol) in THF (2.5 ml) was then added by syringe. The reaction mixture was then returned to the ultrasound bath for a further 15 minutes. The reaction was then quenched with ice/water (2 ml), and sufficient sat. aq. NH_4Cl was added to ensure that the precipitate dissolved. The mixture was extracted with DCM (3 × 15 ml), the organic fractions were recombined, and solvent removed *in vacuo*. The residue was purified by flash column chromatography eluting initially with 20% EtOAc : Petrol and increasing the polarity gradually to 30% EtOAc : Petrol, to give the product **6** as a colourless oil (0.16 g, 76%); R_f 0.48 (40% EtOAc : Petrol); $[a]_D^{22}$ −70.5 (*c* 0.85, $CHCl_3$); ν_{max}(film)/cm^{-1} 1728s, 1666s, 1440w, 1153s; δ_H (400 MHz; $CDCl_3$) 1.43 (9 H, s, tBu), 1.84–1.89 (1H, m, C(6)H$_{exo}$), 1.94–2.02 (1H, m, C(6)H$_{endo}$), 2.03 (3H, s, C(2)Me), 2.33 (1H, dd, *J* 8.0 and 15.5, C(7)C*H*), 2.44 (1H, dd, *J* 5.5 and 15.5, C(7)C*H*), 2.93–2.97 (1H, m, C(7)H), 3.42 (1H, t, *J* 9.0, C(4)H$_{endo}$), 3.47 (1H, d, *J* 7.5, C(8)H), 3.95–4.07 (1H, m, C(5)H), 4.14 (1H, dd, *J* 5.5 and 9.0, C(4)H$_{exo}$), 5.23 (1H, d, *J* 12.5, PhC*H*), 5.28 (1H, d, *J* 12.5, PhC*H*), 7.26–7.50 (10H, m, ArH); δ_C (100.6 MHz; $CDCl_3$) 25.8 (Me), 28.0 (C*Me*$_3$), 28.6 (C(6)), 32.0 (C(7)), 39.8 (C(7)*C*H$_2$), 54.1 (C(5)), 54.3 (C(8)), 67.2 (C(4)), 69.1 (Ph*C*H$_2$), 81.4 (*C*Me$_3$), 96.6 (C(2)), 125.5, 125.7, 128.1, 128.2, 128.3, 128.6 (ArCH), 135.5 (Ar*C*), 141.4 (Ar*C*), 163.9 (C=O), 169.7 (C=O), 170.4 (C=O); *m*/*z* (APCI$^+$) 480 (MH$^+$, 100%), 424 (73); HRMS: 480.2381 (MH$^+$, CI). $C_{28}H_{33}NO_6$ requires 480.2386.

(2*S*,5*S*,7*R*)-1-Aza-8-benzyloxycarbonyl-7-(*tert*-butyloxycarbonylmethyl)-2,8-diphenyl-2-methyl-3-oxa-9-oxobicyclo[4.3.0]nonane 7a. To a solution of the Reformatsky adduct **6** (61 mg, 0.1 mmol) in $CHCl_3$ (10 ml) was added phenyllead triacetate (0.117 g, 0.3 mmol) and pyridine (0.050 g, 0.6 mmol). The mixture was heated to reflux for 72 hours, and then filtered through Celite®, washed with 10% H_2SO_4 (5 ml), extracted with $CHCl_3$ (3 × 15 ml) and dried with brine (10 ml) and over $MgSO_4$. Solvent was removed *in vacuo*, and the residue purified by flash column chromatography, eluting with 30% EtOAc : Petrol to give the product **7a** as a colourless oil as an inseparable mixture of two diastereomers in a 3 : 1 ratio (0.049 g, 69%); R_f 0.26 (40% EtOAc : Petrol); $[a]_D^{22}$ −23.5 (*c* 1.6, $CHCl_3$); ν_{max}(film)/cm^{-1} 1729s, 1681s, 1369m, 1152s; δ_H (400 MHz; $CDCl_3$) 1.37 (9H, s, CMe$_3$ major), 1.41 (9H, s, CMe$_3$ minor), 1.74–1.87 (1H, m, C(6)H$_{endo}$), 1.88 (3H, s, C(2)Me major), 1.99 (3H, s, C(2)Me minor), 2.02–2.17 (2H, m, C(6)H$_{exo}$ and C(7)C*H*), 2.85 (1H, dd, *J* 11.0 and 16.5, C(7)C*H*), 2.93–2.98 (1H, m, C(7)H), 3.40 (1H, t, *J* 8.5, C(4)H$_{endo}$ major), 3.52–3.60 (1H, m, C(5)H major), 3.77 (1H, t, *J* 8.0, C(4)H$_{endo}$ minor), 3.82–3.90 (1H, m, C(5)H minor), 3.99 (1H, dd, *J* 5.5 and 8.5, C(4)H$_{exo}$ major), 4.07 (1H, dd, *J* 6.5 and 8.0, C(4)H$_{exo}$ minor), 5.18 (1H, d, *J* 11.5, PhC*H*$_2$ major), 5.23–5.31 (2H, m, PhC*H*$_2$ minor), 5.55 (1H, d, *J* 11.5, PhC*H*$_2$ major), 7.12–7.67 (15H, m, ArH); δ_C (100.6 MHz; $CDCl_3$) 24.8 (C(2)Me minor), 25.1 (C(2)Me major), 27.8 (CMe$_3$ minor), 28.0 (CMe$_3$ major), 28.4 (C(6) major), 29.7 (C(6) minor), 37.8 (C(7)*C*H$_2$ major), 37.9 (C(7)*C*H$_2$ minor), 38.9 (C(7) major), 40.1 (C(7) minor), 52.1 (C(5) minor), 53.1 (C(5) major), 65.7 (C(8) major), 66.0 (C(8) minor), 67.6 (CO_2CH_2), 70.1 (C(4) major), 70.5 (C(4) minor), 80.6 (*C*Me$_3$ major), 81.1 (*C*Me$_3$ minor), 96.5 (C(2)), 125.3, 125.4, 125.5, 126.4, 127.6, 127.9, 128.0, 128.1, 128.2, 128.3, 128.5, 128.6, 128.8, 129.2 (ArCH), 134.7 (ArC), 136.0 (ArC), 136.1 (ArC), 141.8 (ArC), 142.2 (ArC), 166.5 (C=O), 169.7 (C=O major), 170.2 (C=O minor), 172.0 (C=O); *m*/*z* (APCI$^+$) 556 (MH$^+$, 87%), 500 (100), 114 (43); HRMS: 556.2694 (MH$^+$, ES). $C_{34}H_{37}NO_6$ MH$^+$ requires 556.2699.

(2*S*,5*S*,7*R*)-1-Aza-8-benzyloxycarbonyl-8-(*p*-bromophenyl)-7-(*tert*-butyloxycarbonylmethyl)-2-methyl-3-oxa-9-oxo-2-phenylbicyclo[4.3.0]nonane 7b. To a solution of adduct **6** (27 mg, 0.05 mmol) in $CHCl_3$ (10 ml) was added bromophenyllead triacetate (61 mg, 0.1 mmol) and pyridine (22 mg, 0.28 mmol). The mixture was heated to reflux for 72 hours, and then filtered through Celite®, washed with 10% H_2SO_4 (5 ml), extracted with $CHCl_3$ (3 × 15 ml) and dried with brine (10 ml) and over $MgSO_4$. Solvent was removed *in vacuo*, and the residue purified by flash column chromatography, eluting with 30% EtOAc : Petrol to give the product **7b** as a colourless oil as an inseparable mixture of two diastereomers in a 5 : 1 ratio (0.033 g, 93%); R_f 0.30 (40% EtOAc : Petrol); $[a]_D^{22}$ −12.9 (*c* 0.41, $CHCl_3$); ν_{max}(film)/cm^{-1} 1732s, 1684s; δ_H (400 MHz; $CDCl_3$) 1.37 (9H, s, CMe$_3$ major), 1.40 (9 H, s, CMe$_3$ minor), 1.75–1.82 (1H, m, C(6)H$_{endo}$), 1.87 (3H, s, C(2)Me major), 2.05 (3H, s, C(2)Me minor), 2.07–2.14 (2H, m, C(6)H$_{exo}$ and C(7)C*H*), 2.81 (1H, dd, *J* 11.0 and 16.5, C(7)C*H*), 2.86–2.91 (1H, m, C(7)H), 3.43 (1H, t, *J* 9.0,

C(4)H_{endo} major), 3.54–3.60 (1H, m, C(5)H), 3.73 (1H, dd, *J* 8.0 and 11.0, C(4)H_{endo} minor), 4.00 (1H, dd, *J* 5.5 and 9.0, C(4)H_{exo} major), 4.28 (1H, dd, *J* 6.0 and 8.0, C(4)H_{exo} minor), 5.18 (1H, d, *J* 12.0, PhC*H* major), 5.14–5.26 (2H, m, $PhCH_2$ minor), 5.50 (1H, d, *J* 12.0, PhC*H* major), 6.95–7.64 (14H, m, ArH); δ_C (100.6 MHz; $CDCl_3$) 25.0 (C(2)Me), 27.5 (CMe_3), 28.4 and 29.7 (C(6)), 37.3 (C(7)CH_2), 38.7 (C(7)), 53.1 (C(5) major), 56.1 (C(5) minor), 60.4 (C(8) minor), 65.2 (C(8) major), 67.8 (CO_2CH_2), 70.2 (C(4)), 80.8 (CMe_3 major), 81.2 (CMe_3 minor), 96.5 (C(2) major), 97.3 (C(2) minor), 121.8, 125.3, 128.0, 128.1, 128.2, 128.3, 128.4, 128.5, 128.7, 128.9, 129.2, 130.1, 131.4, 132.3 (ArCH), 134.5 (ArC), 135.3 (ArC), 137.1 (ArC), 142.0 (ArC), 166.0 (C=O), 169.3 (CH_2C=O), 171.8 (C=O); *m*/*z* ($APCI^+$) 637 (MH^+, ^{79}Br, 88%), 636 (MH^+, ^{81}Br, 88%), 580 (80), 578 (100); HRMS: 634.1808 (MH^+, ES). $C_{34}H_{36}NO_6Br$ requires 634.1804.

(2*S*,5*S*,7*R*)-1-Aza-8-benzyloxycarbonyl-7-(*tert*-butyloxycarbonylmethyl)-8-(*p*-methoxyphenyl)-2-methyl-3-oxa-9-oxo-2-phenylbicyclo[4.3.0]nonane 7c. To a solution of the Reformatsky adduct **6** (0.35 g, 0.7 mmol) in $CHCl_3$ (40 ml) was added *p*-methoxyphenyllead triacetate (0.72 g, 1.5 mmol) and pyridine (0.29 g, 3.7 mmol). The mixture was heated to reflux for 72 hours, and then filtered through Celite®, washed with 10% H_2SO_4 (10 ml), extracted with $CHCl_3$ (3 × 25 ml) and dried with brine (20 ml) and over $MgSO_4$. Solvent was removed *in vacuo*, and the residue purified by flash column chromatography, eluting with 30% EtOAc : Petrol to give the product **7c** as a colourless oil as an inseparable mixture of two diastereomers in a 2 : 1 ratio (0.25 g, 59%); R_f 0.10 (20% EtOAc : Petrol); $[a]_D^{24}$ −59.7 (*c* 1.2, $CHCl_3$); ν_{max}(film)/cm^{-1} 1732s, 1682s; δ_H (400 MHz; $CDCl_3$) 1.36 (9 H, s, CMe_3 major), 1.40 (9 H, s, CMe_3 minor), 1.74–1.81 (1H, m, C(6)H_{endo}), 1.87 (3H, s, C(2)Me major), 2.03–2.10 (2H, m, C(6)H_{exo} and C(7)C*H*), 2.12 (3H, s, C(2)Me minor), 2.79–2.93 (2H, m, C(7)C*H*, and C(7)H), 3.41 (1H, t, *J* 8.5, C(4)H_{endo} major), 3.46–3.56 (1H, m, C(5)H and 1H, m, C(4)H_{endo} minor), 3.80 (3H, s, OMe major), 3.82 (3H, s, OMe minor), 3.98 (1H, dd, *J* 6.0 and 8.5, C(4)H_{exo} major), 4.06 (1H, dd, *J* 6.0 and 8.0, C(4)H_{exo} minor), 5.16 (1H, d, *J* 12.0, PhC*H*), 5.52 (1H, d, *J* 12.0, PhC*H*), 6.86 (2H, d, *J* 9.0, ArH *m* to OMe major), 6.88 (2H, d, *J* 9.0, ArH *m* to OMe minor), 7.03 (2H, d, *J* 9.0, ArH *o* to OMe major), 7.18 (2H, d, *J* 9.0, ArH *o* to OMe minor), 7.21–7.51 (10H, m, ArH); δ_C (100.6 MHz; $CDCl_3$) 25.1 (C(2)Me), 28.0 (CMe_3), 28.4 (C(6)), 37.7 (C(7)CH_2), 38.8 (C(7)), 53.1 (C(5)), 55.2 (OMe), 65.0 (C(8)), 67.5 (CO_2CH_2), 70.1 (C(4)), 80.6 (CMe_3), 96.5 (C(2)), 113.8 (ArC), 125.4 (ArC), 128.0, 128.2, 128.3, 128.6, 128.8, 129.2, 129.4, 130.0 (ArCH), 134.7 (ArC), 142.2 (Ar*C*), 158.7 (ArC), 166.7 (C=O), 169.8 (C=O), 172.1 (C=O); *m*/*z* ($APCI^+$) 587 (MH^+, 100%), 531 (23), 114.0 (35); HRMS: 586.2795 (MH^+, ES). $C_{35}H_{39}NO_7$ MH^+ requires 586.2805.

(−)-(2*S*,5*S*,7*R*)-1-Aza-7-(*tert*-butyloxycarbonylmethyl)-2-methyl-3-oxa-9-oxo-2-phenylbicyclo[4.3.0]nonane 8a. To a solution of adduct **6** (0.65 g, 1.3 mmol) in EtOAc (30 ml) was added 10% Pd–C (0.65 g). The mixture was degassed carefully, and then placed under a hydrogen atmosphere (4 bar). The reaction was stirred for 72 hours, and then evacuated to remove excess hydrogen. The suspension was then filtered through Celite® to remove the catalyst, and solvent was removed *in vacuo*. The residue was purified by flash column chromatography (40% EtOAc : Petrol) to give the product **8a** as a colourless oil (0.40 g, 84%); R_f 0.26 (40% EtOAc : Petrol); $[a]_D^{24}$ −44.6 (*c* 1.25, $CHCl_3$); ν_{max}(film)/cm^{-1} 1726s, 1654s, 1151s; δ_H (400 MHz; $CDCl_3$) 1.45 (9 H, s, CMe_3), 1.73–1.79 (1H, m, C(6)H_{endo}), 1.80–1.85 (1H, m, C(6)H_{exo}), 2.05 (3H, s, C(2)Me), 2.27 (1H, dd, *J* 7.5 and 16.0, C(7)C*H*), 2.33 (1H, dd, *J* 7.5 and 15.5, C(8)H), 2.39 (1H, dd, *J* 7.0 and 15.5, C(8)H), 2.58 (1H, dd, *J* 6.0 and 16.0, C(7)C*H*), 2.63–2.66 (1H, m, C(7)H), 3.41 (1H, dd, *J* 8.5 and 9.5, C(4)H_{endo}), 3.95–3.99 (1H, m, C(5)H), 4.13 (1H, dd, *J* 6.0 and 8.5, C(4)H_{exo}), 7.26–7.45 (5H, m, ArH); δ_C (100.6 MHz; $CDCl_3$) 25.8 (C(7)), 28.1 (CMe_3), 28.5 (C(2)Me), 30.1 (C(6)), 38.8 (C(7)CH_2), 41.1 (C(8)), 54.2 (C(5)), 69.2 (C(4)), 81.0 (CMe_3), 96.0 (C(2)), 125.5, 128.0, 128.1 (ArCH), 141.9 (ArC), 167.9 (C=O), 170.9 (C=O); *m*/*z*($APCI^+$) 346 (MH^+, 100%); HRMS: 346.2012 (MH^+, CI). $C_{20}H_{27}NO_4$ requires 346.2018.

(−)-(2*S*,5*S*,7*R*,8*S*)-1-Aza-7-(*tert*-butyloxycarbonylmethyl)-8-(*p*-methoxyphenyl)-2-methyl-3-oxa-9-oxo-2-phenylbicyclo[4.3.0]nonane 8b. To a solution of lactam **7c** (0.24 g, 0.4 mmol) in EtOAc (30 ml) was added 10% Pd–C (0.24 g). The mixture was degassed carefully, and then placed under a hydrogen atmosphere (4 bar). The reaction was stirred for 72 hours, and then evacuated to remove excess hydrogen. The suspension was filtered through Celite®, and solvent was removed *in vacuo*. Crude NMR analysis revealed that decarboxylation was not complete, so the residue was heated under vacuum (200 °C, 1 mm) for two hours. The residue was purified by flash column chromatography (40% EtOAc : Petrol) to give the product **8b** as a colourless oil (0.12 g, 67%); R_f 0.33 (40% EtOAc : Petrol); $[a]_D^{25}$ −75.0 (*c* 1.18, $CHCl_3$); ν_{max}(film)/cm^{-1} 1724s, 1654s, 1514s; δ_H (400 MHz; $CDCl_3$) 1.41 (9 H, s, CMe_3), 1.92–2.00 (1H, m, C(6)H_{endo}), 2.03–2.08 (1H, m, C(6)H_{exo}), 2.10 (3H, s, C(2)Me), 2.12–2.24 (2H, m, C(7)CH_2), 2.80–2.86 (1H, m, C(7)H), 3.66 (1H, dd, *J* 8.0 and 10.0, C(4)H_{endo}), 3.78 (3H, s, OMe), 3.91 (1H, d, *J* 5.5, C(8)H), 4.09–4.26 (2H, m, C(4)H_{exo} and C(5)H), 6.84–7.58 (9 H, m, ArH); δ_C (100.6 MHz; $CDCl_3$) 25.0 (C(2)Me), 27.7 (C(6)), 28.0 (CMe_3), 35.0 (C(7)), 36.5 (C(7)CH_2), 52.7 (C(8)), 53.1 (C(5)), 55.2 (OMe), 70.0 (C(4)), 80.9 (CMe_3), 95.7 (C(2)), 113.9, 125.6, 128.1 (ArCH), 128.4 (ArC), 130.6 (ArCH), 141.6 (ArC), 158.5 (ArC), 167.9 (C=O), 171.3 (C=O); *m*/*z* ($APCI^+$) 452 (MH^+, 100%); HRMS: 452.2442 (MH^+, ES). $C_{27}H_{33}NO_5$ requires 452.2437.

(+)-(2*S*,4*R*)-(2-Hydroxymethyl-6-oxopiperidin-4-yl)acetic acid 9a. To a solution of lactam **8a** (0.061 g, 0.2 mmol) in DCM (20 ml) was added TFA (0.5 ml). The reaction mixture was stirred for 4 hours at room temperature, at which point t.l.c. analysis indicated that no starting material was present. Solvent was removed *in vacuo*, and the residue purified by flash column chromatography eluting with 10% MeOH : EtOAc, to give the product **9a** as a brown oil (14 mg, 33%); R_f 0.25 (10% MeOH : EtOAc); $[a]_D^{22}$ +1.71 (*c* 0.35, $CHCl_3$); ν_{max}(film)/cm^{-1} 3362br, 1686s, 1639s; δ_H (500 MHz; d_4-MeOH) 1.45 (9 H, s, CMe_3), 1.60–1.66 (1H, m, C(3)H), 1.84–1.87 (1H, m, C(3)H), 2.04–2.11 (1H, m, C(5)H), 2.26–2.28 (1H, m, C(5)H), 2.29–2.50 (3H, m, C(4)H and C(4)CH_2), 3.31 (1H, br, N*H*), 3.48–3.60 (3H, m, C(2)CH_2, C(2)H); δ_C (125.8 MHz; d_4-MeOH) 27.5 (C(4)), 28.3 (CMe_3), 29.4 (C(5)), 41.4 (C(4)CH_2), 52.9 (C(2)), 54.8 (C(5)), 65.7 (C(2)CH_2), 82.0 (CMe_3), 173.0 (C=O), 174.3 (C=O); *m*/*z* ($APCI^+$) 244 (MH^+, 100%), 230 (55), 216 (20), 189 (70), 158 (60); HRMS: 244.1552 (MH^+, ES). $C_{12}H_{21}NO_4$ requires 244.1549.

(2*S*,4*S*,5*S*)-(2-Hydroxymethyl-5-(4-methoxyphenyl)-6-oxopiperidin-4-yl)acetic acid 9b. To a solution of the product **8b** (0.121 g, 0.3 mmol) in DCM (10 ml) was added TFA (0.5 ml). The reaction mixture was stirred with regular monitoring by t.l.c. and mass spectrometry. After five minutes there was evidence that the t-butyl group had been removed. The reaction mixture was stirred for a further hour to ensure completion of the reaction. Solvent was removed *in vacuo* to give the crude product **9b**, which was used immediately in the oxidation reaction.

(+)-(2*S*,4*R*)-2-Methoxycarbonyl-4-(methoxycarbonylmethyl)-6-piperidinone 10a. To a solution of the alcohol **9a** (57 mg, 0.3 mmol) in acetonitrile (1 ml) and carbon tetrachloride (2 ml) was added a solution of sodium periodate (0.26 g, 1.2 mmol) and ruthenium dioxide (2 mg) in water (1.5 ml). The reaction

mixture was stirred for 72 hours, and then ethereal diazomethane solution (distilled from the dropwise addition of a solution of Diazald®(2 g) in Et_2O (19 ml) to a solution of KOH (0.59 g) in water (0.98 ml), Et_2O (2 ml) and EtOH (4 ml) heated to 70 °C) was added until excess diazomethane was present, as shown by the persistent yellow colour of the organic phase. Acetic acid (2 drops) was then added to quench excess diazomethane. The reaction mixture was extracted with EtOAc (2 × 15 ml), and solvent removed *in vacuo*. The residue was purified by flash column chromatography eluting with EtOAc to give the product **10a** as a colourless oil (11 mg, 16%); R_f 0.54 (10% MeOH : EtOAc); $[a]_D^{24}$ +30.5 (*c* 0.55, $CHCl_3$); ν_{max}(film)/cm^{-1} 1737s, 1659s; δ_H (400 MHz; $CDCl_3$) 1.81–1.90 (1H, m, C(3)H$_{exo}$), 2.11 (1H, dd, *J* 9.0 and 17.5, C(4)CH_2), 2.22–2.26 (1H, m, C(3)H$_{endo}$), 2.34–2.44 (3H, m, C(4)H and 2 × C(5)H), 2.57 (1H, ddd, *J* 1.5, 5.0 and 17.5, C(4)C*H*), 3.70 (3H, s, Me), 3.79 (3H, s, Me), 4.12–4.19 (1H, m, C(2)H), 6.26 (1H, br, N*H*); δ_C (100.6 MHz; $CDCl_3$) 26.9 (C(4)), 29.9 (C(3)), 37.0 (C(4)*C*H$_2$), 39.1 (C(5)), 51.8 (CH$_2$CO$_2$*Me*), 52.8 (2-CO$_2$*Me*), 53.1 (C(2)), 170.6 (C=O), 171.6, 171.7 (2 × C=O); *m*/*z* (APCI$^+$) 230 (MH$^+$, 100%), 202 (47), 138 (38); HRMS: 230.1024 (MH$^+$, ES). $C_{10}H_{15}NO_5$ requires 230.1028.

(2*S*,4*S*,5*S*)-2-Methyloxycarbonyl-4-(methyloxycarbonylmethyl)-5-(*p*-methoxyphenyl)-6-piperidinone 10b. To a solution of crude alcohol **9b** in acetonitrile (2 ml) and ethyl acetate (2 ml) was added $RuCl_3$ (2 mg) and sodium periodate (0.24 g, 1.1 mmol) in water (3 ml). The reaction mixture was stirred for 2 hours, and then quenched with diazomethane as before. The reaction mixture was extracted with EtOAc (2 × 10 ml) and solvent was removed *in vacuo*. The residue was purified by two flash columns (eluting with 10% MeOH : EtOAc) to give the product **10b** as a colourless oil (2 mg, 22%); R_f 0.23 (10% MeOH : EtOAc); ν_{max}(film)/cm^{-1} 1737s, 1659s, 1212m; δ_H (400 MHz; $CDCl_3$) 1.87 (1H, dd, *J* 8.5 and 16.0, C(4)CH_2), 2.07 (1H, dd, *J* 6.5 and 16.0, C(4)CH_2), 2.11–2.23 (1H, m, C(3)H), 2.25–2.51 (1H, m, C(3)H), 2.53–2.75 (1H, m, C(4)H), 3.64 (1H, d, *J* 11.0, C(5)H), 3.79 (1H, s, OMe), 3.81 (1H, s, CO$_2$*Me*), 3.82 (1H, s, CO$_2$*Me*), 4.29–4.38 (1H, m, C(2)H), 6.62 (1H, br, N*H*), 6.86 (2H, d, *J* 8.5, ArH *m* to OMe), 7.08 (2H, d, *J* 8.5, ArH *o* to OMe); δ_C (100.6 MHz; $CDCl_3$) 25.9 (C(3)), 32.0 (C(4)), 37.3 (C(4)*C*H$_2$), 50.3 (CO$_2$*Me*), 52.9 (C(5)), 53.2 (C(2)), 55.2 (OMe), 80.8 (CH$_2$CO$_2$*Me*), 114.0 (ArC), 126.4 (C(5)), 129.4 (ArC), 136.1 (ArC), 158.8 (C=O), 170.9 (C=O), 171.7 (C=O); *m*/*z* (APCI$^+$) 336 (MH$^+$, 28%), 322 (75), 308 (33), 294 (100); HRMS: 336.1451 (MH$^+$, ES). $C_{17}H_{21}NO_6$ requires 336.1447.

Organocuprate general addition procedure

The required organolithium reagent (4.0 equiv.) was added dropwise to a suspension of CuI (2.0 equiv.) in dry Et_2O (8 ml) at −78 °C and under an inert atmosphere. The temperature was raised to −15 °C for 10 minutes and then lowered to −78 °C. A solution of the lactam **2a** (1.0 equiv.) in dry Et_2O (5 ml) was then added dropwise *via* cannula and the reaction mixture warmed to −15 °C. After 2 h the reaction was quenched with 1 M aq. HCl (10 ml). The resulting precipitate was filtered off and the organic layer washed with saturated aq. NH_4Cl (2 × 5 ml), dried ($MgSO_4$) and the solvent removed *in vacuo*.

(2*S*,5*S*,7*R*,8*S*)-1-Aza-8-benzyloxycarbonyl-2,7-dimethyl-3-oxa-9-oxo-2-phenylbicyclo[4.3.0]nonane 11a. Using the general organocuprate addition procedure, a solution of lactam **2a** (102 mg, 0.28 mmol) in Et_2O was reacted with MeLi in Et_2O (1.6 M, 0.70 ml, 1.12 mmol) and CuI (107 mg, 0.56 mmol) in Et_2O. Purification by flash column chromatography on silica gel eluting with 15% EtOAc : Petrol yielded the product as a yellow oil consisting mainly of lactam **11a**, along with some of the C-7 epimer in a ratio of 14 : 1 (23 mg, 19%). R_f 0.15, 0.20 (20% EtOAc : Petrol); ν_{max}(film)/cm^{-1} 1740s, 1661s; δ_H (400 MHz; $CDCl_3$) 1.15 (3H, d, *J* 7.0, CH_3CH), 1.68 (1H, dt, *J* 4.0, 13.5, C(6)H$_{exo}$), 1.91–1.99 (1H, m, C(6)H$_{endo}$), 2.03 (3H, s, Me), 2.63–2.69 (1H, m, C(7)H), 3.24 (1H, d, *J* 7.0, C(8)H), 3.43 (1H, dd, *J* 9.0, 9.5, C(4)H$_{endo}$), 3.97–4.03 (1H, m, C(5)H), 4.13 (1H, dd, *J* 6.0, 8.5, C(4)H$_{exo}$), 5.21 (2H, d, *J* 12.5, PhC*H*HO), 5.27 (2H, d, *J* 12.5, PhCH*H*O), 7.25–7.51 (20 H, m, ArCH); δ_C (100.6 MHz, $CDCl_3$) 20.9 (*C*H$_3$CH), 25.7 (2-Me), 30.0 (C(7)), 30.2 (C(6)), 54.0 (C(5)), 56.6 (C(8)), 67.1 (Ph*C*H$_2$), 69.9 (C(4)), 96.4 (C(2)), 125.5, 128.0, 128.2, 128.3, 128.4, 128.5 (ArCH), 135.6, 141.5 (ArC), 164.4 (CON), 170.1 (PhCH$_2$O*C*O); *m*/*z* (APCI$^+$) 403 (MNa$^+$, 70%), 380 (MH$^+$, 15); HRMS: 380.1865 (MH$^+$, CI). $C_{26}H_{32}O_4N$ requires 380.1863.

(−)-(2*S*,5*S*,7*R*,8*S*)-1-Aza-8-benzyloxycarbonyl-7-*n*-butyl-2-methyl-3-oxa-9-oxo-2-phenylbicyclo[4.3.0]nonane 11b. Using the general organocuprate addition procedure, a solution of lactam **2a** (102 mg, 0.28 mmol) in Et_2O was reacted with *n*-BuLi in cyclohexanes (2.5 M, 0.54 ml, 1.12 mmol) and CuI (107 mg, 0.56 mmol) in Et_2O. Purification by flash column chromatography on silica gel eluting with 15% EtOAc : Petrol yielded the product **11b** as a yellow oil and as a single diastereomer (42 mg, 36%); R_f 0.28 (15% EtOAc : Petrol); $[a]_D^{23}$ −99.2 (*c* 1.0, $CHCl_3$); ν_{max}(film)/cm^{-1} 2931s, 1741s, 1664s; δ_H (400 MHz; $CDCl_3$) 0.89 (3H, t, *J* 6.2, CH_3CH$_2$), 1.28–1.32 (4 H, m, br, CH$_3$CH_2-CH_2CH$_2$), 1.42–1.51 (2H, m, CH$_3$CH$_2$CH$_2$CH_2),1.76–1.82 (1H, m, C(6)H$_{exo}$), 1.85–1.93 (1H, m, C(6)H$_{endo}$), 2.03 (3H, s, Me), 2.45–2.53 (1H, m, C(7)H), 3.31 (1H, d, *J* 6.5, C(8)H), 3.42–3.45 (1H, m, C(4)H$_{endo}$), 3.90–3.97 (1H, m, C(5)H), 4.09–4.15 (1H, m, C(4)H$_{exo}$), 5.21 (1H, d, *J* 12.5, PhC*H*HO), 5.27 (1H, d, *J* 12.5, PhCH*H*O), 7.25–7.53 (10H, m, ArCH); δ_C (100.6 MHz, $CDCl_3$) 13.9 (*C*H$_3$CH$_2$), 22.6 (CH$_3$*C*H$_2$), 25.7 (Me), 28.5 (C(6)), 28.8 (CH$_3$CH$_2$*C*H$_2$), 35.3 (CH$_2$*C*H$_2$CH), 35.5 (C(7)), 54.2 (C(5)), 55.2 (C(8)), 67.1 (Ph*C*H$_2$), 69.1 (C(4)), 96.5 (C(2)), 125.5, 125.6, 128.0, 128.2, 128.2, 128.4, 128.5 (ArCH), 135.6, 141.4 (ArC), 164.3 (CON), 170.3 (PhCH$_2$O*C*O); *m*/*z* (APCI$^+$) 445 (MNa$^+$, 100%), 422 (MH$^+$, 30); HRMS: 422.2328 (MH$^+$, CI). $C_{26}H_{32}O_4N$ requires 442.2331.

(−)-(2*S*,5*S*,7*R*,8*S*)-1-Aza-8-benzyloxycarbonyl-2,7-diphenyl-2-methyl-3-oxa-9-oxobicyclo[4.3.0]nonane 11c. Using the general organocuprate addition procedure, a solution of lactam **2a** (100 mg, 0.28 mmol) in Et_2O was reacted with 1.6 M PhLi in cyclohexane–Et_2O (0.69 ml, 1.10 mmol) and CuI (105 mg, 0.55 mmol) in Et_2O. Purification by flash column chromatography (silica gel) eluting with 15% EtOAc : Petrol yielded the product **11c** as a yellow oil and as a single diastereomer (52 mg, 42%); R_f 0.23 (15% EtOAc : Petrol); $[a]_D^{23}$ −83.8 (*c* 0.8, $CHCl_3$); ν_{max}(film)/cm^{-1} 1743s, 1665s; δ_H (400 MHz; C_6D_6) 1.27 (1H, dt, *J* 4.5, 13.5, C(6)H$_{exo}$), 1.59–1.67 (1H, m, C(6)H$_{endo}$), 2.17 (3H, s, Me), 3.10 (1H, t, *J* 8.5, C(4)H$_{endo}$), 3.34–3.45 (2H, m, C(5)H, C(4)H$_{exo}$), 3.61–3.67 (1H, m, C(7)H), 3.75 (1H, d, *J* 9.0, C(8)H), 4.99 (1H, d, *J* 12.5, PhC*H*HO), 5.03 (1H, d, *J* 12.5, PhCH*H*O), 7.00–7.78 (15H, m, ArCH); δ_C (100.6 MHz, C_6D_6) 27.0 (Me), 32.6 (C(6)), 41.4 (C(7)), 55.2 (C(5)), 56.2 (C(8)), 67.2 (Ph*C*H$_2$), 69.3 (C(4)), 97.2 (C(2)), 126.5, 127.3, 127.4, 127.7, 128.1, 128.2, 128.3, 128.5, 128.8, 129.3 (ArCH), 136.7, 143.4, 144.1 (ArC), 164.8 (CON), 169.7 (PhCH$_2$O*C*O); *m*/*z* (APCI$^+$) 442 (MH$^+$, 100%); HRMS: 442.2024 (MH$^+$, CI). $C_{28}H_{28}O_4N$ requires 442.2018.

(−)-(2*S*,4*R*,5*S*)-2-Hydroxymethyl-4-phenyl-5-benzyloxycarbonyl-6-piperidinone 12a. Trifluoroacetic acid (1 ml) was added dropwise to a solution of adduct **11c** (65 mg, 0.2 mmol) in $CHCl_3$ (10 ml) and the mixture stirred for 2 hours at room temperature. Removal of the solvent *in vacuo* and purification by flash column chromatography on silica gel eluting with 80% EtOAc : Petrol yielded the product **12a** as a white solid (26 mg, 52%); mp 145 °C; R_f 0.14 (15% EtOAc : Petrol); $[a]_D^{23}$ −23.5 (*c* 0.6, $CHCl_3$); ν_{max}(film)/cm^{-1} 3393br, 1736m, 1665s, 1222s, 1160s; δ_H (400 MHz; MeOD) 2.06–2.11 (1H, m, C(3)H$_{endo}$),

2.15–2.20 (1H, m, C(3)H_{exo}), 3.52–3.56 (2H, m, C(2)H and C(4)H), 3.65 (2H, d, *J* 6.5, CH_2OH), 3.71 (1H, d, *J* 11.0, C(5)H), 4.98 (1H, d, *J* 12.5, PhC*H*HO), 5.07 (1H, d, *J* 12.5, PhCH*H*O), 7.06–7.32 (10H, m, ArCH); δ_C (100.6 MHz, MeOD), 31.0 (C(3)), 40.2 (C(4)), 53.8 (C(2)), 57.2 (C(5)), 65.7 (CH_2OH), 68.1 (Ph*C*H_2), 128.7, 128.9, 129.3, 129.4, 129.7, 129.8, 130.0, 130.3 (ArCH), 137.4, 143.2 (ArC), 170.0 (CON), 171.7 (PhCH_2O*C*O); *m*/*z* (APCI$^+$) 363 (MNa$^+$, 90%), 340 (MH$^+$, 25); HRMS: 340.1554 (MH$^+$, CI). $C_{20}H_{22}O_4N$ (MH$^+$) requires 340.1549.

(−)-(2*S*,4*R*)-2-Hydroxymethyl-4-phenyl-6-piperidinone 12b. Bis(tributyltin) oxide (0.10 ml, 0.19 mmol) was added dropwise to a solution of alcohol **12a** (32 mg, 0.1 mmol) in toluene (5 ml) and the mixture heated under reflux for 18 hours. The solvent was removed *in vacuo* to furnish the crude product as a brown oil. Purification by flash column chromatography on silica gel, eluting with 2% MeOH : EtOAc, yielded the product **12b** as a clear oil (12 mg, 62%); R_f 0.25 (10% MeOH : EtOAc); $[\alpha]_D^{23}$ −8.2 (*c* 0.5, $CHCl_3$); ν_{max}(film)/cm^{-1} 3289s, 1640s; δ_H (400 MHz; MeOD) 2.03–2.07 (2H, m, C(3)H), 2.52 (1H, dd, *J* 8.5, 17.5, C(5)H_{exo}), 2.62 (1H, dd, *J* 5.5, 17.5, C(5)H_{endo}), 3.30–3.37 (1H, m, C(4)H), 3.41–3.47 (1H, m, C(2)H), 3.59 (2H, t, *J* 6.5, CH_2OH), 7.19–7.36 (5H, m, ArCH); δ_C (100.6 MHz, MeOD) 32.0 (C(3)), 36.1 (C(4)), 38.9 (C(5)), 53.5 (C(2)), 66.0 (CH_2OH), 128.2, 128.2, 130.1 (ArCH), 145.3 (ArC), 175.3 (CON); *m*/*z* (APCI$^+$) 206 (MH$^+$, 80%); HRMS: 206.1181(MH$^+$, CI). $C_{12}H_{16}O_2N$ requires 206.1183.

N,*O*-Dibenzylhydroxylamine general addition procedure

N,*O*-Dibenzylhydroxylamine (2 equiv.) was added dropwise to a solution of unsaturated lactam (1 equiv.) in either chloroform or MeOH and the mixture stirred for 24 hours. The solvent was then removed *in vacuo*, and the residue purified by flash column chromatography on silica, eluting with 20% EtOAc : Petrol.

(2*R*,5*S*,7*R*,8*S*)-1-Aza-8-benzyloxycarbonyl-7-(benzyl(benzyloxy)amino)-2-methyl-3-oxa-9-oxo-2-phenylbicyclo[4.3.0]nonane 13a and (2*R*,5*S*,7*S*,8*R*)-1-aza-8-benzyloxycarbonyl-7-(benzyl(benzyloxy)amino)-2-methyl-3-oxa-9-oxo-2-phenylbicyclo[4.3.0]nonane 14a. Using the general procedure, *N*,*O*-dibenzylhydroxylamine (400 mg, 1.88 mmol) was added dropwise to a solution of lactam **2b** (340 mg, 0.94 mmol) in methanol (30 ml) and the mixture stirred at room temperature for 24 hours. The solvent was removed *in vacuo*, and the residue purified by flash column chromatography on silica, eluting with 20% EtOAc : Petrol, to yield the product as a colourless oil and an inseparable mixture of diastereomers in a **13a : 14a** ratio of 10 : 1 (162 mg, 30%). Data for the major diastereomer **13a**: R_f 0.22, 0.28 (20% EtOAc : Petrol); ν_{max}($CHCl_3$)/cm^{-1} 1740s, 1671s, 1496s, 1455s; δ_H (500 MHz; C_7D_8, 70 °C) 1.45–1.51 (1H, m, C(6)H_{endo}), 1.97–2.02 (1H, m, C(6)H_{exo}), 2.03 (3H, s, Me), 3.30–3.33 (1H, m, C(4)H_{endo}), 3.55–3.60 (5H, m, C(5)H, C(4)), 3.62 (1H, d, *J* 13.0, PhC*H*HN), 3.73–3.79 (1H, m, C(7)H), 3.80 (1H, d, *J* 13.0, PhCH*H*N), 3.93 (1H, d, *J* 8.0, H″), 4.32 (1H, d, *J* 10.0, PhC*H*HON), 4.40 (1H, d, *J* 10.0, PhCH*H*ON), 5.05 (1H, d, *J* 12.5, PhC*H*HOCO), 5.22 (1H, d, *J* 12.5, PhCH*H*OCO), 7.01–7.62 (20 H, m, ArCH); δ_C (125.7 MHz, C_7D_8, 70 °C) 26.3 (Me), 28.2 (C(6)), 54.3 (C(8)), 54.9 (C(5)), 60.5 (PhCH_2N), 61.2 (C(7)), 67.1 (Ph*C*H_2OCO), 69.6 (C(4)), 77.3 (Ph*C*H_2ON), 97.7 (C(2)), 125.0, 125.2, 125.4, 127.9, 128.0, 128.2, 128.2, 128.5, 128.6, 128.6, 128.8, 128.9, 129.1, 129.3 (ArCH), 137.0, 137.6, 143.8 (ArC), 164.2 (CON), 169.3 (PhCH_2O*C*O); *m*/*z* (APCI$^+$) 577 (MH$^+$, 100%), 365 (20); HRMS: 577.2704 (MH$^+$, CI). $C_{36}H_{36}O_5N_2$ requires 577.2702.

(−)-(2*S*,5*S*,7*R*,8*S*)-1-Aza-8-benzyloxycarbonyl-7-(benzyl(benzyloxy)amino)-2-methyl-3-oxa-9-oxo-2-phenylbicyclo[4.3.0]nonane 13b, (−)-(2*S*,5*S*,7*S*,8*R*)-1-aza-8-benzyloxycarbonyl-7-(benzyl(benzyloxy)amino)-2-methyl-3-oxa-9-oxo-2-phenylbicyclo[4.3.0]nonane 14b. Using the general procedure, *N*,*O*-dibenzylhydroxylamine (250 mg, 1.17 mmol) was added dropwise to a solution of the lactam **2a** (213 mg, 0.59 mmol) in chloroform (15 ml) and the mixture heated under reflux for 48 hours. The solvent was removed *in vacuo* and purification by flash column chromatography on silica gel, eluting with 20% EtOAc : Petrol, yielded the product as a colourless oil and as a separable mixture of two diastereomers in a **13b** : **14b** ratio of 8–10 : 1.

Major diastereomer **13b**: (137 mg, 41%); R_f 0.31 (20% EtOAc : Petrol); $[\alpha]_D^{25}$ −96.7 (*c* 1.3, $CHCl_3$); ν_{max}(film)/cm^{-1} 1744m, 1672s, 1532m, 1210s; δ_H (400 MHz; C_7D_8) 1.00–1.10 (1H, m, br, C(6)H_{endo}), 1.96–2.00 (1H, m, br, C(6)H_{exo}), 2.07 (3H, s, Me), 3.00 (1H, t, *J* 9.0, C(4)H_{endo}), 3.50 (1H, d, *J* 13.0, PhC*H*HN), 3.55 (1H, dd, *J* 6.5, 2.5, C(4)H_{exo}), 3.70–3.75 (1H, m, C(5)H), 3.74 (1H, d, *J* 13.0, PhCH*H*N), 3.90–3.96 (1H, m, C(7)H), 4.09 (1H, d, *J* 10.0, C(8)H), 4.26 (1H, d, *J* 10.0, PhC*H*HON), 4.54 (1H, d, *J* 10.0, PhCH*H*ON), 5.17 (1H, d, *J* 12.3, PhC*H*HOCO), 5.37 (1H, d, *J* 12.3, PhCH*H*OCO), 7.01–7.36 (18H, m, ArH), 7.66–7.68 (2H, m, ArH); δ_C (50.3 MHz, $CDCl_3$) 25.7 (C(6)), 26.4 (Me), 54.4 (C(8)), 56.2 (C(5)), 60.2 (Ph*C*H_2N), 61.3 (C(7)), 67.2 (Ph*C*H_2OCO), 69.2 (C(4)), 77.0 (PhCH_2ON), 97.1 (C(2)), 125.6, 127.7, 128.0, 128.2, 128.2, 128.3, 128.4, 128.5, 128.5, 128.9, 129.0, 129.6 (ArCH), 135.9, 136.4, 136.5, 142.1 (ArC), 164.2 (CON), 169.3 (PhCH_2O*C*O); *m*/*z* (APCI$^+$) 577 (MH$^+$, 100%), 364 (70); HRMS: 577.2703 (MH$^+$, CI). $C_{36}H_{36}O_5N_2$ (MH$^+$) requires 577.2702.

Minor diastereomer **14b**: (15 mg, 4%); R_f 0.25 (20% EtOAc : Petrol); $[\alpha]_D^{25}$ −48.0 (*c* 0.8, $CDCl_3$); ν_{max}($CDCl_3$)/cm^{-1} 1737s, 1663s; δ_H (400 MHz; C_7D_8) 1.41–1.44 (1H, m, br, C(6)H_{endo}), 1.64–1.69 (1H, m, br, C(6)H_{exo}), 2.12 (3H, s, Me), 3.02–3.07 (1H, m, C(4)H_{endo}), 3.30–3.38 (1H, m, C(5)H), 3.50–3.53 (1H, m, C(4)H_{exo}), 3.59 (1H, d, *J* 13.0, PhC*H*HN), 3.76 (1H, d, *J* 13.5, PhCH*H*N), 3.79–3.84 (1H, m, C(7)H), 4.05 (1H, d, *J* 7.5, C(8)H), 4.42 (1H, d, *J* 10.5, PhC*H*HON), 4.54 (1H, s, br, PhCH*H*ON), 5.05 (1H, d, *J* 12.5, PhC*H*HOCO), 5.12 (1H, d, *J* 12.5, PhCH*H*OCO), 7.01–7.30 (18H, m, ArH), 7.56–7.61 (2H, m, ArH); δ_C (100.6 MHz, $CDCl_3$) 25.1 (Me) 25.6 (C(6)), 54.3 (C(8)), 55.4 (C(5)), 59.0 (Ph*C*H_2N), 62.7 (C(7)), 67.3 (Ph*C*H_2OCO), 69.0 (C(4)), 77.0 (Ph*C*H_2ON), 96.4 (C(2)), 125.6, 125.8, 127.7, 128.0, 128.1, 128.3, 128.3, 128.4, 128.5, 128.5, 128.9, 129.0, 129.5 (ArCH), 135.5, 136.5, 136.7, 141.0 (ArC), 162.9 (CON), 170.0 (PhCH_2O*C*O); HRMS: 577.2703 (MH$^+$, CI). $C_{36}H_{36}O_5N_2$ (MH$^+$) requires 577.2702.

(+)-(2*S*,4*R*)-2-Hydroxymethyl-4-(benzyl(benzyloxy)amino)-6-piperidinone 15. Bis(tributyltin) oxide (0.10 ml, 0.19 mmol) was added dropwise to a solution of adduct **13b** (55 mg, 0.1 mmol) in toluene (5 ml) and the mixture heated under reflux for 18 hours. The solvent was removed *in vacuo* and purification by flash column chromatography on silica gel, eluting with 30% EtOAc : Petrol, yielded a colourless oil (15 mg, 38%); R_f 0.25 (30% EtOAc : Petrol); $[\alpha]_D^{24}$ −75.1 (*c* 1.3, $CHCl_3$); ν_{max}(film)/cm^{-1} 1655s, 1469s, 1381s; δ_H (400 MHz; $CDCl_3$) 1.55–1.67 (1H, m, C(6)H_{endo}), 2.01 (3H, s, Me), 2.26–2.30 (1H, m, br, C(6)H_{exo}), 2.71 (1H, dd, *J* 6.0, 15.5, C(8)H_{endo}), 2.87 (1H, dd, br, *J* 8.0, 15.0, C(8)H_{exo}), 3.36 (1H, t, *J* 9.0, C(4)H_{endo}), 3.42–3.48 (1H, m, C(7)H), 3.93 (1H, d, *J* 13.0, PhC*H*HN), 4.01 (1H, d, *J* 13.0, PhCH*H*N), 4.08–4.19 (2H, m, C(5)H, C(4)H_{exo}), 4.45 (2H, s, br, PhCH_2O), 7.18–7.48 (15H, m, ArCH); δ_C (100.63 MHz, $CDCl_3$) 25.9 (Me), 27.1 (C(6)), 37.1 (C(8)), 55.1 (C(5)), 58.2 (C(7)), 59.8 (Ph*C*H_2N), 69.3 (C(4)), 78.2 (Ph*C*H_2ON), 96.1 (C(2)), 125.6, 127.6, 127.7 128.2, 128.4, 128.4, 128.5, 129.0, 129.5 (ArCH), 136.5, 136.9, 142.1 (ArC), 167.6 (CON); *m*/*z* (APCI$^+$) 443 (MH$^+$, 100%), 109.8(25); HRMS: 443.2337 (MH$^+$, ES). $C_{28}H_{30}O_3N_2$ requires 443.2335.

Trifluoroacetic acid (0.75 ml) was added dropwise to the above compound (40 mg, 0.1 mmol) in chloroform (10 ml) and the reaction mixture stirred for 2 hours. The solvent was

removed *in vacuo* and purification by flash column chromatography on silica gel, eluting with 10% MeOH : EtOAc, yielded the product **15** as a colourless oil (19 mg, 63%); R_f 0.35 (10% MeOH : EtOAc); $[\alpha]_D^{24}$ +20.2 (*c* 0.9, $CHCl_3$); ν_{max}(film)/cm^{-1} 3312m, 1651s; δ_H (400 MHz; $CDCl_3$) 1.77–1.83 (1H, m, C(3)H_{endo}), 2.00–2.07 (1H, m, C(3)H_{exo}), 2.53 (1H, dd, *J* 5.0, 17.5, C(5)H_{endo}), 2.74 (1H, d, br, *J* 14.0, C(5)H_{exo}), 3.22 (1H, s, br, C(4)H), 3.46 (1H, dd, *J* 8.0, 11.0, C*H*HOH), 3.63 (1H, dd, *J* 4.0, 11.0, CH*H*OH), 3.76 (1H, s, br, C(2)H), 3.87 (1H, d, *J* 13.0, PhC*H*HN), 3.98 (1H, d, *J* 13.0, PhCH*H*N), 4.26 (1H, d, br, *J* 8.0, PhC*H*HO), 4.35 (1H, d, *J* 10.0, PhCH*H*O), 7.01–7.42 (10H, m, ArCH); δ_C (100.6 MHz, $CDCl_3$) 26.9 (C(3)), 34.7 (C(5)), 51.1 (C(2)), 57.1 (C(4)), 59.9 (PhCH_2N), 66.2 (CH_2OH), 77.3 (PhCH_2O), 127.6 128.0, 128.3, 128.3, 129.0, 130.0 (ArCH), 136.3, 137.0, 142.1 (ArC), 172.0 (CON); *m*/*z* (APCI$^+$) 341 (MH$^+$, 100%), 272 (20), 128 (50); HRMS: 341.1869 (MH$^+$, ES). $C_{20}H_{25}O_3N_2$ requires 341.1865.

(−)-(2*S*,5*S*,7*R*,8*S*)-1-Aza-8-benzyloxycarbonyl-7-(benzyloxyamino)-2-methyl-3-oxa-9-oxo-2-phenylbicyclo[4.3.0]nonane 16, (−)-(2*S*,5*S*,7*S*,8*R*)-1-aza-8-benzyloxycarbonyl-7-(benzyloxyamino)-2-methyl-3-oxa-9-oxo-2-phenylbicyclo[4.3.0]nonane 17. To a solution of *O*-benzylhydroxylamine.HCl (62 mg, 0.4 mmol) in methanol (4 ml) at room temperature was added NaOAc (32 mg, 0.4 mmol) with stirring. A solution of lactam **2a** (128 mg, 0.4 mmol) in methanol (4 ml) was then added dropwise and the reaction mixture stirred at room temperature for 3 hours. The reaction was quenched with brine (20 ml) and the aqueous layer extracted with EtOAc (3 × 20 ml). The organic fractions were combined, washed with water (10 ml), dried ($MgSO_4$) and the solvent removed *in vacuo*. Purification by flash column chromatography on silica gel, eluting with 20% EtOAc : Petrol, yielded the product as a colourless oil and as a separable mixture of two diastereomers **16 : 17** ratio of 1 : 2.

Major diastereomer **17**: (111 mg, 65%); R_f 0.14 (30% EtOAc : Petrol); $[\alpha]_D^{22}$ −38.0 (*c* 1.7, $CHCl_3$); ν_{max}(film)/cm^{-1} 1738s, 1661s; δ_H (400 MHz; $CDCl_3$) 1.55 (1H, ddd, *J* 10.5, 12.0, 12.5, C(6)H_{endo}), 2.03 (3H, s, Me), 2.23–2.28 (1H, ddd, *J* 3.0, 5.0, 13.0, C(6)H_{exo}), 3.43 (1H, dd, *J* 9.0, 10.0, C(4)H_{endo}), 3.74 (1H, d, *J* 8.0, C(8)H), 3.86–3.96 (2H, m, C(7)H, C(5)H), 4.08 (1H, dd, *J* 6.0, 8.5, C(4)H_{exo}), 4.67 (2H, s, PhCH_2ONH), 5.20 (1H, d, *J* 12.5, PhC*H*HOCO), 5.24 (1H, d, *J* 12.5, PhCH*H*OCO), 7.27–7.40 (13H, m, ArH), 7.44–7.47 (2H, m, ArH); δ_C (50.3 MHz, $CDCl_3$) 25.2 (Me), 29.0 (C(6)), 54.7 (C(8)), 55.1 (C(5)), 58.7 (C(7)), 67.3 (Ph*C*H_2OCO), 69.0 (C(4)), 77.8 (Ph*C*H_2ON), 96.6 (C(2)), 125.9, 126.0, 128.1, 128.3, 128.4, 128.9 (ArCH), 135.8, 137.5, 141.4 (ArC), 162.9 (CON), 169.4 (PhCH_2O*C*O); *m*/*z* (APCI$^+$) 487 (MH$^+$, 30%), 364 (100); HRMS: 487.2225 (MH$^+$, ES). $C_{29}H_{31}O_5N_2$ requires 487.2233.

Minor diastereomer **16**: (44 mg, 26%); R_f 0.23 (30% EtOAc : Petrol); $[\alpha]_D^{22}$ −82.6 (*c* 0.7, $CHCl_3$); ν_{max}(film)/cm^{-1} 1732s, 1651s, 1372s, 1323s, 1240s; δ_H (400 MHz; $CDCl_3$) 1.77–1.85 (1H, ddd, *J* 7.0, 11.0, 14.0, C(6)H_{endo}), 1.95–2.00 (1H, ddd, *J* 4.5, 8.0, 11.5, C(6)H_{exo}), 2.01 (3H, s, Me), 3.36 (1H, dd, *J* 8.5, 9.0, C(4)H_{endo}), 3.64 (1H, d, *J* 6.0, C(8)H), 3.95–4.04 (2H, m, C(7)H, C(5)H), 4.06 (1H, dd, *J* 6.0, 8.0, C(4)H_{exo}), 4.66 (2H, d, *J* 3.0, PhCH_2ONH), 5.21 (1H, d, *J* 12.5, PhC*H*HOCO), 5.28 (1H, d, *J* 12.5, PhCH*H*OCO), 7.25–7.43 (13H, m, ArH), 7.46–7.50 (2H, m, ArH); δ_C (100.6 MHz, $CDCl_3$) 25.8 (Me), 28.6 (C(6)), 53.5(C(8)), 54.6 (C(5)), 56.8 (C(7)), 67.2 (Ph*C*H_2OCO), 68.7 (C(4)), 76.8 (Ph*C*H_2ON), 96.8 (C(2)), 125.6, 127.7, 128.0, 128.1, 128.2, 128.3, 128.4, 128.4, 128.5, 128.5, 128.9 (ArCH), 135.3, 137.1, 141.5 (ArC), 163.2 (CON), 169.3 (PhCH_2O*C*O); *m*/*z* (APCI$^+$) 487 (MH$^+$, 30%), 364 (100); HRMS: 487.2224 (MH$^+$, ES). $C_{29}H_{31}O_5N_2$ requires 487.2233.

(−)-(2*S*,5*S*,7*R*)-1-Aza-7-(benzyloxyamino)-2-methyl-3-oxa-9-oxo-2-phenylbicyclo[4.3.0]nonane 18 and (−)-(2*S*,5*S*,7*S*)-1-aza-7-(benzyloxyamino)-2-methyl-3-oxa-9-oxo-2-phenylbicyclo-[4.3.0]nonane 19. Bis(tributyltin) oxide (0.32 ml, 0.62 mmol) was added dropwise to a solution of adduct **16** and **17** (ratio of 1 : 2) (154 mg, 0.32 mmol) in toluene (10 ml) and the mixture heated under reflux for 24 hours. The reaction was then quenched with 1 : 1 saturated aqueous $NaHCO_3$: EtOAc (10 ml). The aqueous layer was washed with EtOAc (3 × 5 ml) and the organic fractions combined, washed with water (10 ml), dried ($MgSO_4$) and the solvent removed *in vacuo*. Purification by flash column chromatography on silica gel, eluting with 60% EtOAc : Petrol, yielded the separable diastereomers **18** and **19** as a colourless oil.

Lactam **19**: (43 mg, 39%); R_f 0.22 (80% EtOAc : Petrol); $[\alpha]_D^{23}$ −37.9 (*c* 0.8, $CHCl_3$); ν_{max}(film)/cm^{-1} 1651s, 1028s; δ_H (400 MHz; $CDCl_3$) 1.37–1.45 (1H, ddd, *J* 10.0, 10.0, 12.0, C(6)H_{endo}), 2.05 (3H, s, Me), 2.29–2.34 (1H, ddd, *J* 4.0, 5.0, 13.0, C(6)H_{exo}), 2.49 (1H, dd, *J* 8.0, 17.0, C(8)H_{endo}), 2.64 (1H, dd, *J* 6.5, 17.0, C(8)H_{exo}), 3.43 (1H, dd, *J* 9.0, 10.0, C(4)H_{endo}), 3.60 (1H, m, C(7)H), 3.89 (1H, m, C(5)H), 4.10 (1H, dd, *J* 6.0, 9.0, C(4)H_{exo}), 4.76 (2H, s, PhCH_2O), 5.49 (1H, s, br, NH), 7.27–7.43 (8 H, m, ArH), 7.44–7.48 (2H, m, ArH); δ_C (100.6 MHz, $CDCl_3$) 25.5 (Me), 29.9 (C(6)), 36.9 (C(8)), 55.2 (C(7)), 55.7 (C(5)), 68.8 (C(4)), 77.1 (Ph*C*H_2ON), 96.0 (C(2)), 125.8, 128.0, 128.1, 128.5, 128.5 (ArCH), 137.4, 141.3 (ArC), 166.3 (CON); *m*/*z* (APCI$^+$) 353 (MH$^+$, 30%), 233 (100), 178 (15), 125 (40); HRMS: 353.1862 (MH$^+$, ES). $C_{21}H_{25}O_3N_2$ requires 353.1865.

Lactam **18**: (24 mg, 47%); R_f 0.35 (80% EtOAc : Petrol); $[\alpha]_D^{23}$ −63.8 (*c* 0.4, $CHCl_3$); ν_{max}(film)/cm^{-1} 1651s, 1028s; δ_H (400 MHz; $CDCl_3$) 1.54–1.60 (1H, ddd, *J* 5.0, 8.0, 13.5, C(6)H_{endo}), 2.03 (3H, s, Me), 2.12–2.16 (1H, m, C(6)H_{exo}), 2.31 (1H, dd, *J* 4.0, 17.5, C(8)H_{exo}), 2.69 (1H, dd, *J* 6.5, 17.5, C(8)H_{endo}), 3.39–3.44 (1H, m, C(4)H_{endo}), 3.69–3.73 (1H, m, C(7)H), 4.01 (2H, m, C(5)H, C(4)H_{exo}), 4.72 (1H, d, *J* 12.0, PhC*H*HO), 4.76 (1H, d, *J* 12.0, PhCH*H*O), 7.25–7.46 (10H m, ArH); δ_C (100.6 MHz, $CDCl_3$) 25.8 (Me), 29.0 (C(6)), 36.7 (C(8)), 53.4 (C(5)), 53.8 (C(7)), 69.5 (C(4)), 77.6 (Ph*C*H_2ON), 96.4 (C(2)), 126.1, 128.4, 128.6, 128.9, 129.3 (ArCH), 137.8, 142.1 (ArC), 166.6 (CON); *m*/*z* (APCI$^+$) 353 (MH$^+$, 100%), 245 (20), 233 (30), 125 (40); HRMS: 353.1865 (MH$^+$, ES). $C_{21}H_{25}O_3N_2$ requires 353.1865.

(+)-(2*S*,4*R*)-2-Hydroxymethyl-4-(benzyloxyamino)-6-piperidinone 20a. Trifluoroacetic acid (0.5 ml) was added to a solution of lactam **18** (36 mg, 0.1 mmol) in chloroform (3 ml). After stirring for 2 hours, the solvent was removed *in vacuo*. Purification by flash column chromatography on silica gel, eluting initially with 4% MeOH : EtOAc and increasing the polarity gradually to 8% MeOH : EtOAc, yielded the product **20a** as a colourless oil (15 mg, 58%); R_f 0.24 (10% MeOH : EtOAc); $[\alpha]_D^{22}$ +4.4 (*c* 0.8, $CHCl_3$); ν_{max}(film)/cm^{-1} 3245m, 1651s; δ_H (400 MHz; acetone-d_6) 1.68–1.75 (1H, ddd, *J* 3.0, 8.5, 13.5, C(3)H_{endo}), 1.92–2.03 (1H, m, C(3)H_{exo}), 2.22 (1H, ddd, *J* 1.5, 4.5, 17.5, C(5)H_{exo}), 2.43 (1H, dd, *J* 5.0, 17.5, C(5)H_{endo}), 3.45 (1H, dd, *J* 7.0, 11.0, C*H*HOH), 3.49–3.55 (1H, m, C(4)H), 3.58 (1H, dd, *J* 5.0, 11.0, CH*H*OH), 3.61–3.69 (1H, m, C(2)H), 4.71 (2H, s, PhCH_2O), 7.28–7.40 (5H, m, ArCH); δ_C (100.6 MHz, $CDCl_3$) 27.1 (C(3)), 34.7 (C(5)), 50.9 (C(2)), 52.2 (C(4)), 66.2 (CH_2OH), 77.4 (PhCH_2O), 128.4, 128.9, 129.0, 130.2 (ArCH), 137.9 (ArC), 172.2 (CON); *m*/*z* (APCI$^+$) 251 (MH$^+$, 65%), 192 (50), 128 (100); HRMS: 251.1394 (MH$^+$, ES). $C_{13}H_{19}O_3N_2$ requires 251.1395.

(+)-(2*S*,4*S*)-2-Hydroxymethyl-4-(benzyloxyamino)-6-piperidinone 21a. Trifluoroacetic acid (0.5 ml) was added to a solution of adduct **19** (56 mg, 0.2 mmol) in chloroform (3 ml). After stirring for 2 hours the solvent was removed *in vacuo* to yield a yellow gum. Purification by flash column chromatography on silica gel, eluting initially with 4% MeOH : EtOAc and increasing the polarity gradually to 8% MeOH : EtOAc, yielded the product **21a** as a colourless oil (26 mg, 66%); R_f 0.23 (10% MeOH : EtOAc); $[\alpha]_D^{22}$ +14.6 (*c* 0.5, $CHCl_3$); ν_{max}(film)/cm^{-1} 3248m, 1651s; δ_H (400 MHz; $CDCl_3$) 1.23–1.31 (1H, q, *J* 12.0, C(3)H_{endo}), 2.01–2.05 (1H, d, br, *J* 12.0, C(3)H_{exo}), 2.17 (1H, dd,

J 11.5, 17.0, C(5)H_{endo}), 2.58 (1H, dd, *J* 4.5, 17.0, C(5)H_{exo}), 3.32–3.37 (1H, m, C(4)H), 3.40 (1H, dd, *J* 3.0, 8.0, C*H*HOH), 3.49–3.53 (1H, m, C(2)H), 3.68 (1H, dd, *J* 3.0, 11.0, CH*H*OH), 4.69 (2H, s, PhCH_2O), 7.27–7.53 (5H, m, ArCH); δ_C (100.6 MHz, $CDCl_3$) 28.9 (C(3)), 35.1 (C(5)), 52.8 (C(2)), 53.7 (C(4)), 65.6 (CH_2OH), 76.7 ($PhCH_2O$), 128.0, 128.4 (ArCH), 137.3 (ArC), 172.2 (CON); *m*/*z* ($APCI^+$) 251 (MH^+, 100%); HRMS: 251.1398 (MH^+, ES). $C_{13}H_{19}O_3N_2$ requires 251.1395.

General hydrogenolysis procedure

To a vigorously stirred solution of the starting material dissolved in either EtOAc, TFA or glacial acetic acid contained within Fischer–Porter apparatus, was added 10% palladium on activated charcoal. The suspension was then evacuated and flushed with H_2(g) four times at room temperature. The reaction was then subjected to H_2(g) at the given pressure and stated time. On completion, the mixture was filtered through Celite® and the solvent removed *in vacuo*.

(+)-(2*S*,4*R*)-2-Hydroxymethyl-4-amino-6-piperidinone 20b. Using the general hydrogenolysis procedure, adduct **20a** (120 mg, 0.48 mmol) was dissolved in glacial acetic acid (10 ml) and then 10% Pd–C (120 mg) was added with vigorous stirring. The mixture was degassed and then placed under an atmosphere of hydrogen (5 bar) for 48 hours. Purification using ion exchange chromatography (using water and then 2 M ammonia in water as eluent) yielded the product **20b** as a brown oil (45 mg, 65%); $[\alpha]_D^{22}$ +25.8 (*c* 0.6, H_2O); ν_{max}(film)/cm^{-1} 3420s, 1636s; δ_H (400 MHz; MeOD) 1.76–1.81 (1H, m, C(3)H_{endo}), 1.89–1.93 (1H, m, C(3)H_{exo}), 2.20 (1H, dd, *J* 7.0, 17.5, C(5)$_{exo}$), 2.58 (1H, dd, *J* 5.0, 17.5, C(5)H_{endo}), 3.45–3.48 (1H, m, C(4)H), 3.51 (1H, dd, *J* 6.0, 11.0, C*H*HOH), 3.58 (1H, dd, *J* 5.5, 11.0, CH*H*OH), 3.61–3.67 (1H, m, C(2)H); δ_C (100.6 MHz, $CDCl_3$) 29.7 (C(3)), 38.5 (C(5)), 42.1 (C(4)), 50.5 (C(2)), 64.4 (CH_2OH), 174.6 (CON); *m*/*z* ($APCI^+$) 145 (MH^+, 100%), 128 (30); HRMS: 145.0978 (MH^+, ES). $C_6H_{13}O_2N_2$ (MH^+) requires 145.0977.

(+)-(2*S*,4*S*)-2-Hydroxymethyl-4-amino-6-piperidinone 21b. Using the general hydrogenolysis procedure, adduct **21a** (0.2 mmol) was dissolved in glacial acetic acid (10 ml) and then 10% Pd–C (52 mg) was added with vigorous stirring. The mixture was degassed and then placed under an atmosphere of hydrogen (5 bar) for 48 hours. Purification using ion exchange chromatography (using water and then 2 M ammonia in water as eluent) yielded the product **21b** as a green oil (26 mg, 93%); $[\alpha]_D^{22}$ −25.8 (*c* 0.6, H_2O); ν_{max}(film)/cm^{-1} 3436s, 1646s; δ_H (400 MHz; D_2O) 1.31 (1H, dd, *J* 12.0, 24.0, C(3)H_{endo}), 1.96 (1H, dd, *J* 2.5, 23.0, C(3)H_{exo}), 2.06 (1H, dd, *J* 11.0, 17.5, C(5)H_{endo}), 2.47–2.54 (1H, m, C(5)H_{exo}), 3.17–3.25 (1H, m, C(4)H), 3.42 (1H, dd, *J* 5.5, 11.0, C*H*HOH), 3.46–3.52 (1H, m, C(2)H), 3.58 (1H, dd, *J* 4.0, 11.0, CH*H*OH); δ_C (100.6 MHz, D_2O) 32.1 (C(3)), 38.4 (C(5)), 44.1 (C(4)), 52.7 (C(2)), 64.0 (CH_2OH), 174.7 (CON); *m*/*z* ($APCI^+$) 145 (MH^+, 100%), 128 (50); HRMS: 145.0977 (MH^+, ES). $C_6H_{13}O_2N_2$ requires 145.0977.

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