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# Enantiopure bicyclic piperidinones: stereoselectivity in lactam enolate alkylations

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The synthesis and alkylation of [4.3.0]-bicyclic lactams, derived from 6-oxopipecolic acid, have been investigated. Alkylation can proceed with predominantly *exo*-diastereoselectivity, but the efficiency of this process depends on the substitution at the hemiaminal ether system. These products can be readily deprotected to give substituted hydroxymethyl lactams in good yield.

The synthesis of substituted piperidines, piperidinones and indolizidines[1–5] is of importance because of their widespread occurrence in nature, their wide-ranging biological activity, and more recently for their conformational controlling properties.[6–14] Although a number of routes to these compounds have been reported, involving, for example, the elaboration of amino acids[15–19] or other chiral starting materials,[20–26] and chiral auxiliary mediated,[27–30] catalytic[31,32] or desymmetrisation processes,[33–35] the most general strategies for piperidine synthesis appear to be the CN(R,S) method developed by Husson and Royer,[36] the 2,3-dihydro-4-pyridone strategy extensively developed by Comins,[37,38] the bicyclic lactam methodology developed by Meyers,[39–41] and the chiral deprotonation mediated approach of Beak.[42] Of interest to us are such general approaches, enabling the preparation of piperidines, substituted at any or all of the ring carbons, in a diastereoselective and enantioselective manner, which are applicable to combinatorial or parallel synthetic technologies. We have recently described that racemic or enantiopure 6-oxo-2-hydroxymethylpiperidine **1** is readily available in 5 steps from lysine and in 60% overall yield.[43] Herein we describe the synthesis of bicyclic lactams **2a**–**e** derived from this alcohol, and report on their diastereoselective functionalisation *via* the lactam enolate; some of this work has been previously published in preliminary form.[44,45] A similar strategy, applied to the analogous [3.3.0] bicyclic system, has proved to be very successful, permitting ring manipulations in a highly diastereocontrolled sense,[46–52] and providing access to analogues of natural products[48,50,53] and conformationally restricted systems.[54] That such a protocol is robust has been demonstrated by its recent application by Boehringer-Ingelheim Pharmaceuticals for the synthesis of multi-kilo quantities of 3,5-disubstituted-2-pyrrolidinones for evaluation as collagen-induced thrombocyte aggregation inhibitors.[55] We expected all of these advantages to be directly transferable to the [4.3.0] series, and that ready functionalisation of the piperidine ring would be possible; a similar strategy has recently been extensively developed by Amat and Bosch,[56,57] who have achieved diastereoselective alkylations[58] and conjugate additions[58–60] in an enantiopure bicyclic oxazolopiperidinone template.[61]

## Results and discussion

Reaction of racemic lactam **1**[43] with benzaldehyde or 2-methoxypropene in toluene at reflux and catalytic *p*-toluenesulfonic acid gave the corresponding racemic hemiaminal ethers **2a**, **b** (as a separable mixture of diastereomers) or **2c** in 22% and 54% yield respectively. The diastereomers **2a** and **2b** were assigned as *exo*- and *endo*- respectively by a series of NOE experiments (Fig. 1); the $C(2)H_{endo}$ stereochemistry of **2a** was evident from the enhancement series $C(6)H_{endo} \rightarrow C(4)H_{endo} \rightarrow C(2)H$ and the $C(2)H_{exo}$ stereochemistry of **2b** from the enhancement series $C(5)H \rightarrow C(4)H_{exo} \rightarrow C(2)H$. Noteworthy is that similar cyclisations in the related [3.3.0] pyrrolidinone series are reported to give only the *exo*-diastereomer.[62] Of significance in the $^1H$ NMR COSY spectrum of **2a** was a strong long range W-coupling between $C(6)H_{exo}$ and $C(8)H_{exo}$ and this is consistent with a preferred half chair conformation established by MM analysis (Chem 3D with PM3 parameters) (Fig. 2). When we began this work, these systems were not well-known, but since then a related bicyclic piperidine has been reported[63] and similar bicyclic piperidinones, in which the methylene and oxygen of the oxazolidine ring are transposed relative to **2**, have been investigated for their synthetic utility.[61] Surprisingly, however, the ratio of **2a : 2b** was found to depend upon the purity of the starting lactam **1**.[44] This was traced to the catalytic activity of boric acid, present as an impurity from the sodium borohydride reduction step leading to the formation of alcohol **1**, which mediated a reaction in which the kinetic product **2b** equilibrates to **2a**, the thermodynamic product; therefore, all further cyclisation reactions were conducted in the presence of catalytic boric acid/*p*-toluenesulfonic acid; the equilibration of related epimeric oxazolidines by ring chain tautomerism has been reported.[64] Conversion of enantiopure lactam **1**[43] to the bicyclic derivative (*S*,*S*)-**2a** was accomplished in better yield (82%) than in the racemic series as described above using benzaldehyde dimethyl acetal (Scheme 1).[45]

Reaction of enantiopure lactam **1**[43] with acetophenone dimethyl acetal[65] gave the corresponding hemiaminal ether (*S*,*S*)-**2d**, but with variable amounts of its C(2) epimer **2e**, and in variable (30–64%) yield. The stereochemistry of this compound was established by NOE analysis (Fig. 1), in which an enhancement from C(5)H to C(2)Me indicated the stereochemistry at C(2); simple molecular modeling (Chem 3D with PM3 parameters) indicated a distorted boat conformation for the piperidinone ring (Fig. 2) with the phenyl ring orientated in such a way that steric effects were minimized on the *endo*-face of the bicyclic system.

However, we rapidly found lack of reproducibility in this reaction, obtaining low yields and highly variable ratios of **2d** and **2e**; this forced a detailed examination of the formation of these compounds. From our previous work in this area,[44] we

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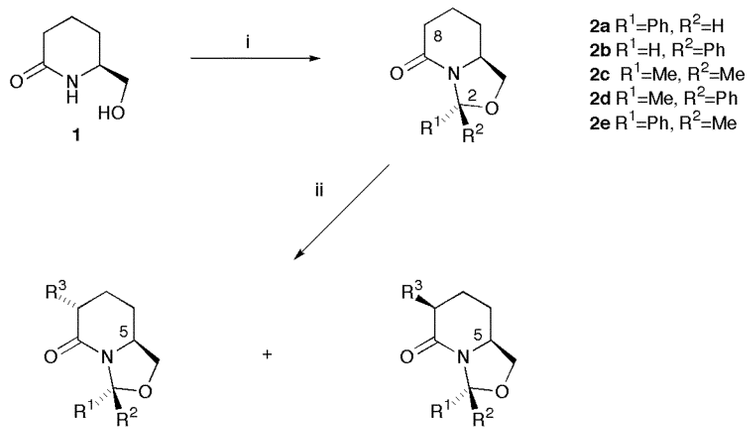
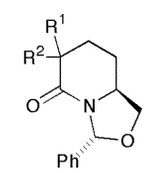



**Scheme 1** *Reagents and conditions*: (i) PhCHO or $PhCH(OMe)_2$, cat. *p*-TsOH, toluene, reflux (for **2a**–**2b**), or $MeC(OMe)=CH_2$, cat. *p*-TsOH, toluene, reflux (for **2c**), or $PhCH(OMe)_2$, cat. *p*-TsOH, $B(OH)_3$ (1 equiv.), reflux (for (*S*,*S*)-**2d**/(*R*,*S*)-**2e**); (ii) LDA/THF/−78 °C then $R^3X$.



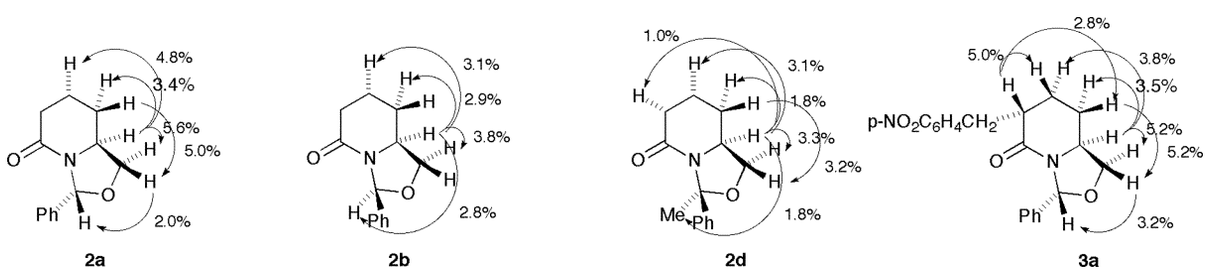




**Fig. 1**

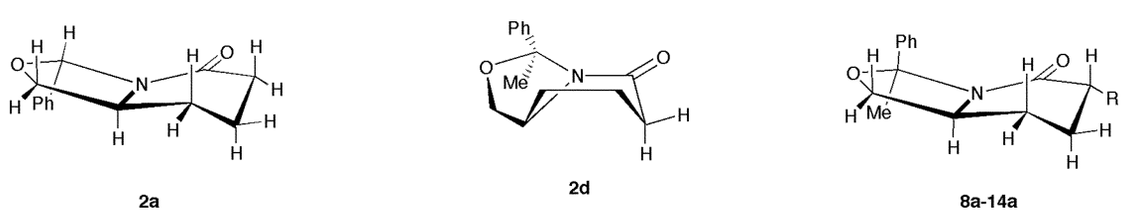



**Fig. 2**

were aware that a *p*-TsOH/$B(OH)_3$ catalytic system gave most efficient conversion of alcohol **1** to hemiaminal ether **2a**, and so a detailed examination of the reaction leading to (2*S*)-**2d** : (2*R*)-**2e** was undertaken by GC. When alcohol **1** and acetophenone dimethyl acetal was heated at reflux with the same catalyst mixture in toluene at 110 °C, the (2*S*) **2d** : (2*R*) **2e** product ratio was 1.5 : 1 after 30 minutes, and this slowly reversed over 27 h to 1 : 2; a similar outcome was observed in the absence of boric acid. Significantly, however, reduction of temperature of this reaction to 80 °C gave an entirely different outcome: after 2 h at this temperature, the (2*S*) : (2*R*) product ratio was 4.8 : 1 and this was virtually unaltered after 22 h (4.4 : 1). These results indicated that the (2*S*) kinetic product **2d** could be converted to the (2*R*) **2e** thermodynamic product under appropriate conditions, although this product distribution of **2d**,**e** was critically dependent on very small changes to the reaction parameters. Pyridinium *p*-toluenesulfonate (PPTS) was found to be particularly effective as the acid catalyst, and the results of a study using three different solvents (toluene, chloroform, and dichloromethane) and reaction times are given in Table 1. When toluene at reflux was used as the solvent, a mixture of diastereomers was obtained, and although the diastereoselectivity was highest in dichloromethane, chloroform gave the best combination of yield and stereochemical outcome. By way of confirmation of previous results, and since we now had pure (2*S*)-**2d** lactam in hand, this material was subjected to more vigorous conditions (acetophenone dimethyl acetal, PPTS, toluene, reflux), and interconversion of this isomer to a (2*S*) **2d** : (2*R*) **2e** product mixture (1 : 2) was observed after 24 hours. Although the (2*S*) **2d** isomer is clearly the kinetic product, the energy

**Table 1** GC analysis for formation of lactams **2d**,**e** from alcohol **1** with PPTS, $PhMeC(OMe)_2$ in various solvents and temperatures

| Entry | Solvent | Temperature | Reaction time | Ratio (2*S*) **2d** : (2*R*) **2e** | Yield **2d** |
|---|---|---|---|---|---|
| 1 | Toluene | 110 °C | 45 min | 23.4 : 1.0 | Not determined |
| | | | 3 hours | 9.5 : 1.0 | Not determined |
| | | | 20 hours | 1.0 : 1.6 | Not determined |
| | | | 40 hours | 1.0 : 2.2 | Not determined |
| 2 | Chloroform | 70 °C | 20 min | (2*S*) only | |
| | | | 2 hours | (2*S*) only | |
| | | | 18 hours | 70.0 : 1 | 78% |
| 3 | DCM | 40 °C | 20 min | No product observed | |
| | | | 2 hours | (2*S*) only | |
| | | | 18 hours | 150.0 : 1 | 50% |

difference is very small; molecular modeling calculations (Chem 3D, MOPAC PM3 parameters) suggest only a 0.1 kJ $mol^{-1}$ difference in energy, and this compares with a 1.6 kJ $mol^{-1}$ difference for **2a**,**b**, for which the former is clearly the more stable. Thus, the most reliable procedure, giving **2d** exclusively, proved to be alcohol **1** and acetophenone dimethyl acetal in chloroform and PPTS at reflux.

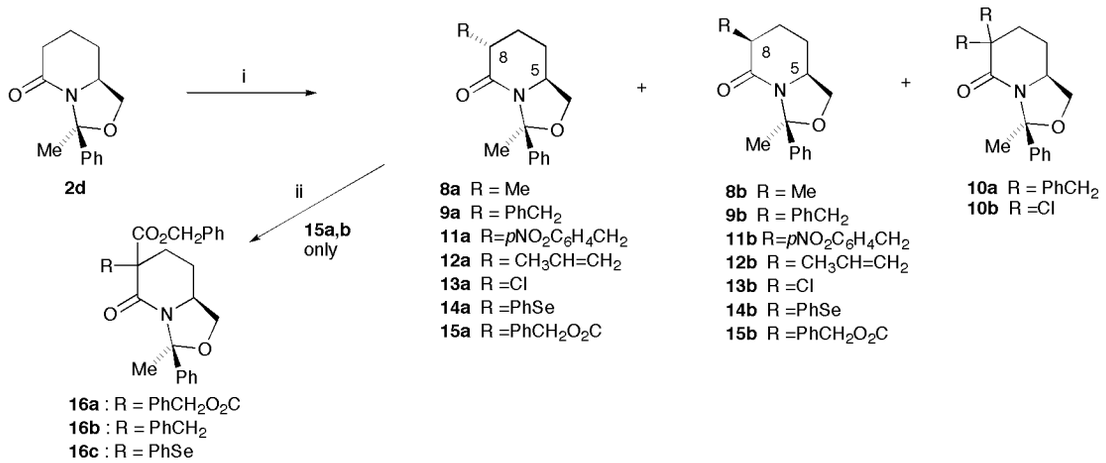
That hemiaminal ethers **2a**–**e** were useful synthetic intermediates was demonstrated by their elaboration to substituted bicyclic piperidinone derivatives by generation of the lactam enolate.[66–70] At the time we began this work, lactam enolate formation in piperidinones was not well precedented, although it has since been developed in oxopipecolic acids,[71,72] and more recently stereocontrolled enolate generation has become possible using chiral lithium amides.[73] Thus, treatment of the major diastereomer (±)-**2a** with LDA in THF at −78 °C, followed by the addition of *p*-nitrobenzyl bromide, gave the corresponding alkylated product as a mixture of two diastereomers **3a** and **3b** at the new chiral carbon (C(8)), in a ratio of 5 : 1 (assignments made by NOE analysis, with crucial mutual enhancements for **3a** of C(8)H ⟶ C(7)$H_{endo}$ and C(6)$H_{endo}$ ⟶ C(4)$H_{endo}$ ⟶ C(2)H, and C(7)$H_{exo}$ ⟶ C(5)$H_{exo}$ ⟶ C(4)$H_{exo}$ (see Fig. 1)), with a total yield of 43%. The predominance of product **3a** is presumably due to steric factors, with the electrophile approaching from the *exo*-face of the bicyclic ring system, as the phenyl substituent at C(2) would appear to be too far removed to directly influence the stereochemistry of alkylation at C(8). When methyl iodide was used as the electrophile in the above sequence, a better yield of 60% of the methylated products **4a** and **4b** was obtained, but in a poorer (2 : 1) diastereomeric ratio, demonstrating that the diastereoselectivity was dependent on the bulk of the incoming electrophile. When the dimethyl derivative (±)-**2c** was treated with LDA and either *p*-nitrobenzyl bromide or methyl iodide, derivatives **5a**,**b** and **6a**,**b** were obtained in modest yields of 28% and 43% respectively but with no diastereocontrol. Related bicyclo[4.3.0] heterocycles have been shown to exhibit significant conformational fluxionality,[74] and this may account for the lack of diastereoselectivity observed in the alkylations of **2c**: for this compound, the presence of two methyl substituents at C(2) means that no steric advantage is achieved in a conformational equilibrium, unlike **2a**, where the C(2)Ph is presumably in a (pseudo)equatorial position. That disubstitution was feasible was evident by the initial introduction of an ester function (NaH, diethyl carbonate) to give **7a** in 81% yield followed by selenenylation (NaH, PhSeCl, 70%) leading to **7b**, but without diastereocontrol, or by direct double selenenylation (LiHMDS, PhSeCl, 50%) leading to **7c**. However, unlike the successful deprotonation and subsequent alkylations of *exo*-**2a** and **2c**, neither starting material nor product could be recovered from a similar reaction involving (±)-*endo*-**2b**; for this reason, as well as the generally low yields and diastereoselectivity in the reactions of **2a**, we examined the reactions of hemiaminal ether **2d** in some detail.

Initial investigations of enantiopure (*S*,*S*)-**2d** established that formation of the enolate and subsequent alkylation, contrary to lactams **2a** and **2c**, was not straightforward. Husson and co-workers have reported similar difficulties in the alkylation of a closely related bicyclic system, which they were unable to alkylate after deprotonation with either LDA or s-BuLi[75] (later work by Amat[58] was able to achieve the alkylation of this system readily with LDA and either methyl iodide or benzyl bromide, in moderate yield (40%) but with excellent diastereoselectivity, while Young has also reported acylation in simple piperidinone derivatives,[72] and Puschl[76] has achieved hydroxylations using LiHMDS for the deprotonation step). The lack of reactivity of lactam **2d** may be due to developing A-strain[77] in its enolate. However, reaction of this lactam with s-BuLi in THF at −78 °C, followed by warming to −30 °C, gave the distinctive red colour of the enolate, and this could be readily reacted with electrophiles to give a mixture of *exo*-isomers **8a**–**15a** and *endo*-isomers **8b**–**15b** (Table 2); separation, however, of these diastereomeric products was not always straightforward due to their similar polarity, and the presence of unreacted starting material, but their ratio was readily established by NMR spectroscopic analysis (C(2)Me) of the crude reaction products. Benzylation gave, in addition to **9a**,**b**, significant amounts (18%) of dibenzyl adduct **10a**. In the case of tosyl chloride and benzyl chloroformate, it was found that reverse addition, namely addition of the enolate to a solution of the alkylating agent, gave improved yields of **13a**,**b** and **15a**,**b** respectively, since this minimized the formation of disubstituted products **10b** and **16a** respectively. Unfortunately, none of these products were crystalline, and stereochemical assignment relied upon NOE difference and NOESY spectra (Fig. 3), although their stereochemistry could also be deduced from characteristic chemical shift patterns observed in $^1$H NMR spectra. Thus, for example, mutual enhancements of C(8)H, C(7)$H_{endo}$, C(6)$H_{endo}$, C(4)$H_{endo}$ and of C(7)$H_{exo}$, C(6)$H_{exo}$, C(5)H, C(4)$H_{exo}$ for compounds **9a**, **11a**, and **12a** indicated the *exo*-stereochemistry of the C(8) substituent, and the enhancements between C(8)H and C(6)$H_{endo}$ and of C(7)$H_{exo}$ with C(5)H suggested that the conformation of the piperidinone ring was such that the C(8) substituent was in a pseudoequatorial position (Fig. 2) as might be expected. For all of compounds **8**–**13** and **15**, the *endo*-isomer has a more positive value of $[\alpha]_D$ and the major (*exo*-) isomer was more polar. Furthermore, it was observed that the *endo*-isomers consistently exhibited larger values for *J*(C(5)H/C(4)$H_{exo}$) than for

**Table 2** Reaction of bicyclic lactam (*S*,*S*)-**2d** with electrophiles according to Scheme 2

| Electrophile | Product | Yield (%) | Ratio *exo* : *endo* |
|---|---|---|---|
| Methyl iodide | **8a**,**b** | 80 | 1 : 1 |
| Benzyl bromide | **9a**,**b** | 69 | 10 : 1 |
| *para*-Nitrobenzyl bromide | **11a**,**b** | 28 | 3 : 2 |
| Allyl bromide | **12a**,**b** | 95 | 2 : 1 |
| Tosyl chloride | **13a**,**b** | 44 | 5 : 3 |
| Tosyl chloride[a] | **13a**,**b** | 51 | 5 : 3 |
| Phenyl selenenyl chloride | **14a**,**b** | 52 | 7 : 4 |
| Benzyl chloroformate | **15a**,**b** | 28 | 1 : 1 |
| Benzyl chloroformate[a] | **15a**,**b** | 72 | 1 : 1 |

[a] Reverse addition: see main text.




**Scheme 2** *Reagents and conditions*: (i) s-BuLi/THF/−78 °C then RX (Table 1); (ii) NaH then $PhCH_2Br$ for **16b**, or PhSeBr for **16c**.

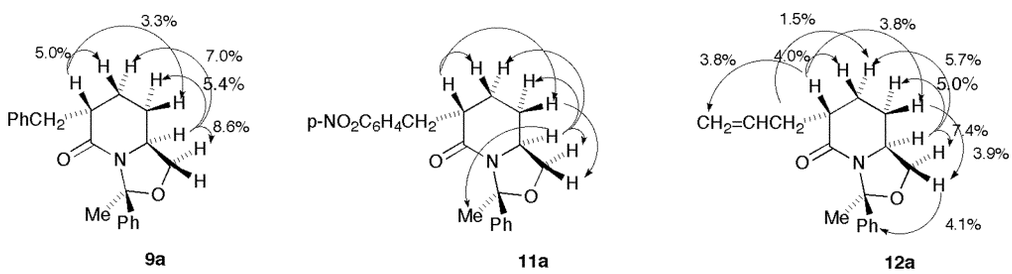
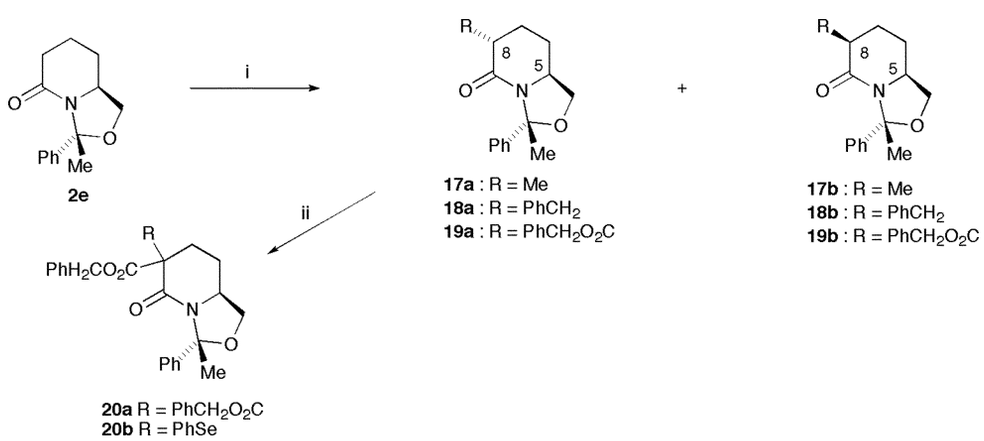



**Fig. 3**




**Scheme 3** *Reagents and conditions*: (i) s-BuLi/THF/−78 °C then RX; (ii) NaH the PhSeCl (**20b** only).

the *exo*-isomers, and this probably reflects the fact that the *endo*-substituted systems are less concave, by virtue of intramolecular steric interactions. The diastereoselectivity of these reactions is clearly dependent on the size of the incoming electrophile, with the small methyl iodide showing the least selectivity, and the large benzyl bromide the greatest. Interestingly, similar alkylations performed on the related Amat–Bosch [4.3.0] template are reported to give the *exo*- diastereomer as the sole product.[58]

Since significant quantities of the 2*R* bicyclic lactam **2e** had been synthesised in the course of investigations of the 2*S* bicyclic lactam **2d**, investigation of differences in reactivity of their respective enolates was made. Two alkylation reactions were therefore performed on bicyclic lactam (*R*,*S*)-**2e** using the same conditions as shown in Scheme 2; in this case, the yields of the products **17b** and **18a**,**b** were significantly lower than in the case of lactam **2d** (Scheme 3 and Table 3), and more surprisingly, gave only the *endo*-product **17b** for methylation, and a much lower preference for the *exo*-isomer **18a** in the benzylation. The *endo*-stereochemistry followed from NOESY analysis, in which key significant enhancements were observed between $C(7)H_{endo}$, $C(6)H_{endo}$, $C(4)H_{endo}$ and of C(8)H, $C(7)H_{exo}$, $C(6)H_{exo}$, C(5)H, and $C(4)H_{exo}$for compounds **17b**, **18a** and **18b** (Fig. 4). Lactam **2e**, with the more bulky methyl substituent at the C(2) position on the *endo*- face, therefore leads to a much higher proportion of the *endo*-isomer compared to the lactam **2d** in a contra-steric alkylation process. We have observed similar selectivity in the [3.3.0] series, and ascribed this to a stronger stereoelectronic directing effect from the nitrogen atom when the bicyclic system is forced into a more planar conformation by a bulky substituent on the concave face[49] and a similar explanation seems likely for the [4.3.0] system. Interestingly, application of the reverse addition protocol, so successfully applied for **2d** for the synthesis of benzyloxycarbonyl deriv-

**Table 3** Reaction of bicyclic lactam (*R*,*S*)-**2e** with electrophiles according to Scheme 3

| Electrophile | Product | Yield(%) | *exo* : *endo* ratio |
|---|---|---|---|
| Methyl iodide | **17a**,**b** | 46 | 0 : 1 |
| Benzyl bromide | **18a**,**b** | 25 | 2 : 1 |
| Benzyl chloroformate[a] | **19a**,**b** | 50 | 1 : 1 |

[a] Reverse addition: see main text.

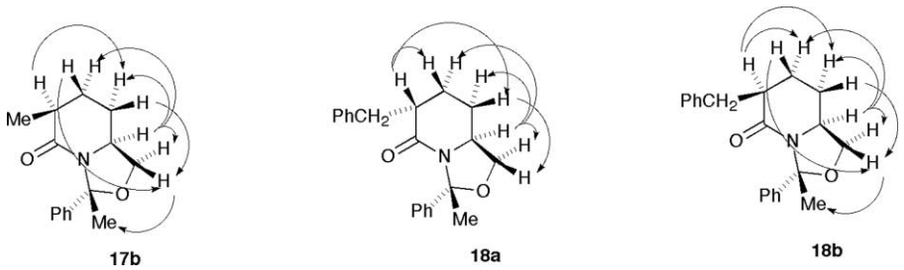


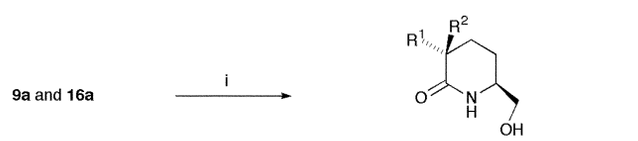

**Fig. 4**

atives **15a**,**b**, proved to be less effective, giving the product **19a**,**b** as a diastereomeric mixture in low and variable (6–14%) yield, along with 25–46% yield of the diacylated product **20a**.

Lactams **15a**,**b** could be further alkylated or selenylated after deprotonation with sodium hydride; the products **16b**,**c** were obtained in yields of 55 and 70% and diastereoselectivities of 4 : 1 and 1 : 1 respectively, although the diastereomers were not separable. Interestingly, a similar procedure applied to lactam **19a**,**b** gave the expected product **20b** as a mixture of diastereomers, but in highly variable yield (37–66%).

## Deprotection

In order to demonstrate the synthetic utility of these compounds, representative deprotections were undertaken. Thus, treatment of lactams **9a** and **16a** with 20% trifluoroacetic acid in dichloromethane gave 73 and 74% yield of the corresponding alcohols **21a**,**b** (Scheme 4).




**Scheme 4** *Reagents and conditions*: (i) TFA, $CH_2Cl_2$, rt.

## Conclusion

The convenient synthesis and elaboration of hemiaminal ethers derived from 6-oxopipecolic acid opens up their potential application to the synthesis of a wide range of substituted piperidines and piperidinones, and successes in this direction will be reported in subsequent papers.

## Experimental

$^1$H NMR spectra were recorded on Varian Gemini 200 (200 MHz) and Bruker AM-500 (500 MHz) spectrometers. $^{13}$C NMR spectra were recorded on the same spectrometers at 50.3 MHz and at 125.8 MHz respectively. Chemical shifts (d) are reported in parts per million (ppm) and were referenced to the residual solvent peak. Multiplicities are reported as broad (br), singlet (s), doublet (d), triplet (t), quartet (q) and multiplet (m). Coupling constants (*J*) are reported in Hertz (Hz) to the nearest 1 Hz when obtained from 200 MHz spectra, and to the nearest 0.1 Hz when obtained from 500 MHz spectra. Infra-red spectra were recorded as thin films, in $CHCl_3$ solution or as a Nujol® mull, using a Perkin-Elmer 1750 FT-IR spectrometer. Only selected peaks are reported, and absorption maxima (in $cm^{-1}$) are described as strong (s), medium (m), weak (w) or broad (br). Mass spectra (*m*/*z*) were recorded on VG Micromass ZAB 1F and VG Masslab 20–250 spectrometers using ammonia desorption chemical ionisation (DCI), chemical ionisation (CI) or fast atom bombardment (FAB) techniques. Gas chromatography mass spectra (GCMS) were recorded on a VG Trio-1 spectrometer. Major peaks are listed with intensities quoted as percentages of the base peak. Microanalyses were performed by the microanalytical service of the Dyson Perrins Laboratory. Melting points were recorded on a Stuart Scientific SMP1 melting point device and are uncorrected. Thin layer chromatography (TLC) was performed using Merck aluminium foil backed sheets precoated with Kieselgel 60 $F_{254}$. Plates were visualised using UV light (254 nm) or a solution of 5% w/v *dodeca*-molybdophosphoric acid in EtOH followed by heat. Flash column chromatography was carried out using Sorbsil™ $C_{60}$ H(40–60 mm) silica gel. THF was distilled from sodium/benzophenone under $N_2$ prior to use. Toluene, hexane, DCM and EtOAc were purified by distillation before use. Light petroleum refers to that fraction of light petroleum ether boiling at 30–40 °C, and this was purified by distillation before use. n-Butyllithium was used as a solution in hexanes and was standardised with diphenylacetic acid prior to use. All other reagents were used as obtained from commercial sources. NMR signals for the major diastereomer of a given product are labeled as A and the minor as B whenever they could be resolved; otherwise, both signals are superimposed.

### (±)-(2*R**,5*S**) and (2*R**,5*R**)-1-Aza-3-oxa-9-oxo-2-phenylbicyclo[4.3.0]nonane 2a and 2b

To a solution of lactam **1** (0.38 g, 2.94 mmol) in toluene (30 ml) were added benzaldehyde (0.70 g, 5.4 mmol) and *p*-toluenesulfonic acid (0.01 g, 0.05 mmol), and the mixture heated at reflux for 72 h using a Dean–Stark condenser. The solvent was removed *in vacuo* to afford a crude mixture of two diastereomeric products **2a** and **2b** in approx. 5 : 1 ratio. This residue was purified by flash column chromatography in 50% light petroleum/50% EtOAc, which afforded pure *O*,*N*-hemiaminal ether **2a** (0.100 g, 16%), and **2b** (0.036 g, 6%), although the latter compound could not be obtained free from **2a**.

Lactam **2a**: $R_f$ (EtOAc) 0.40; Found: C, 72.1; H, 6.97; N, 6.31. Calc. for $C_{13}H_{15}NO_2$: C, 71.9; H, 6.96; N, 6.45%. $\nu_{max}$ ($CHCl_3$)/$cm^{-1}$ 1640s; $\delta_H$ (500 MHz, $CDCl_3$) 1.29–1.37 (1H, m, C(6)$H_{endo}$), 1.69–1.80 (1H, m, C(7)$H_{exo}$), 1.94–2.00 (1H, m, C(7)$H_{endo}$), 2.10–2.17 (1H, m, C(6)$H_{exo}$), 2.28–2.37 (1H, m, C(8)$H_{exo}$), 2.45–2.51 (1H, m, C(8)$H_{endo}$), 3.55 (1H, m, C(4)$H_{endo}$), 3.82 (1H, m, C(5)H), 4.37 (1H, m, C(4)$H_{exo}$), 6.42 (1H, s, C(2)H), 7.32–7.43 (3H, m, Ar*H*), 7.46–7.57 (2H, m, Ar*H*); $\delta_C$(50.3 MHz, $CDCl_3$) 20.1 (C(7)), 25.4 (C(6)), 31.4 (C(8)), 56.2 (C(5)), 72.9 (C(4)), 88.5 (C(2)), 126.5, 128.2, 128.5 (Ar*C*), 139.1 (4° Ar*C*), 168.0 (C(9)); *m*/*z* (DCI GCMS) 218 (M + $H^+$, 100%). Material prepared from enantiopure lactam **1** gave identical spectroscopic data, with $[\alpha]^{22}$ +129 (*c* 1, $CHCl_3$).

Lactam **2b**: $R_f$ (EtOAc) 0.31; $\nu_{max}$ ($CHCl_3$)/$cm^{-1}$ 1657s; $\delta_H$ (500 MHz, $CDCl_3$) 1.50–1.70 (1H, m, C(6)$H_{endo}$), 1.75–2.0 (1H, m, C(7)$H_{exo}$), 2.05–2.25 (2H, m, C(7)$H_{endo}$ and C(6)$H_{exo}$), 2.35–2.55 (2H, m, C(8)$H_{exo}$ and C(8)$H_{endo}$), 3.65–3.75 (1H, m, C(4)$H_{endo}$), 3.75–3.95 (1H, m, C(5)H), 4.15–4.25 (1H, m, C(4)$H_{exo}$), 6.22 (1H, m, C(2)H), 7.32–7.39 (5H, m, Ar*H*); $\delta_C$(50.3 MHz, $CDCl_3$) 21.0 (C(7)), 24.9 (C(6)), 31.2 (C(8)), 57.8 (C(5)), 70.2 (C(4)), 89.8 (C(2)), 126.6, 128.7, 128.9 (Ar*C*), 138.8 (4° Ar*C*), 168.2 (C(9)); *m*/*z* (DCI GCMS) 218 (M + $H^+$, 100%); HRMS: 218.1811 ($MH^+$). $C_{13}H_{16}NO_2$ requires 218.1181.

Material prepared from enantiopure lactam **1** gave identical spectroscopic data, with $[\alpha]^{22}$ −39 (c 1, $CHCl_3$).

### (±)-1-Aza-2,2-dimethyl-3-oxa-9-oxobicyclo[4.3.0]nonane 2c

2-Methoxypropene (2.50 g, 34.7 mmol) was added to a suspension of lactam **1** (0.49 g, 3.8 mmol) in dry toluene, to which *p*-toluenesulfonic acid (0.01 g, 0.05 mmol) was added. The mixture was heated at 100 °C for 18 h, and after cooling, the toluene was removed *in vacuo* and the residue partitioned between EtOAc and water. The organic layer was separated and dried over $MgSO_4$. Filtration and removal of the solvent under vacuum afforded the crude product, which was purified by flash column chromatography using 20% EtOAc/80% light petroleum as the eluent, to afford the product **2c** (0.35 g, 54%); $R_f$ (EtOAc) 0.40; $\nu_{max}$ ($CHCl_3$/cm$^{-1}$) 1630s; $\delta_H$ (200 MHz, $CDCl_3$) 1.20–1.40 (1H, m, C(6)$H_{endo}$), 1.55 (6H, 2 × s, C$H_3$), 1.6–1.8 (1H, m, C$H_2$), 1.88–2.04 (2H, m, C$H_2$), 2.25–2.37 (2H, m, C(8)H), 3.42 (1H, m, C(4)$H_{endo}$), 3.5–3.7 (1H, m, C(5)H), 4.16 (1H, m, C(4)$H_{exo}$); $\delta_C$ (50.3 MHz, $CDCl_3$) 20.9 (C(7)), 24.0 (*C*$H_3$), 25.5 (C(6)), 25.6 (*C*$H_3$), 31.9 (C(8)), 57.5 (C(5)), 69.4 (C(4)), 94.6 (C(2)), 167.3 (C(9)); *m*/*z* (DCI GCMS) 170 (M + $H^+$, 100%), 154 (22); HRMS: 170.1181 ($MH^+$); $C_9H_{16}NO_2$ requires 170.1181.

### (−)-(2*S*,5*S*)-1-Aza-2-methyl-3-oxa-9-oxo-2-phenylbicyclo[4.3.0]nonane 2d and (−)-(2*R*,5*S*)-1-aza-2-methyl-3-oxa-9-oxo-2-phenylbicyclo[4.3.0]nonane 2e

To a suspension of the lactam **1** (3.52 g, 27.3 mmol) in toluene (125 ml) was added *p*-toluenesulfonic acid (1.3 g, 6.8 mmol) and pre-dried boric acid (0.42 g, 6.8 mmol), and the mixture heated to reflux with continuous removal of water using a Dean–Stark apparatus. After 5 hours the mixture was cooled to room temperature and the Dean–Stark apparatus was removed. Acetophenone dimethyl acetal (10 ml, excess) was then added, and the mixture was again brought to reflux for a further 19 hours. The mixture was then allowed to cool to room temperature and partitioned between EtOAc : water. The aqueous layer was then extracted with ethyl acetate (3 × 30 ml). The combined organic extracts were then washed with sat. aq. $NaHCO_3$ (30 ml), water (30 ml) and dried with brine (40 ml) and over $MgSO_4$ and the solvent was removed *in vacuo*. Acetophenone dimethyl acetal was then removed by Kugelrohr distillation, and the residue purified by flash column chromatography on silica gel, eluting progressively with 20% EtOAc : petrol, 40% EtOAc : petrol, 60% EtOAc : petrol and EtOAc to yield two products, lactam **2e** as a yellow oil (1.50 g, 24%) and lactam **2d** as a white solid (1.97 g, 31%).

Lactam **2d**: mp 116–117 °C; $R_f$ 0.32 (EtOAc); $[\alpha]_D^{26}$ −6.86 (*c* 0.51, $CHCl_3$); Found: C, 73.2; H 7.9; N, 5.6. $C_{14}H_{17}NO_2$ requires C, 72.7; H, 7.4; N, 6.1%; $\nu_{max}$ (film)/cm$^{-1}$ 1651s; $\delta_H$(200 MHz; $CDCl_3$) 1.47–1.53 (1 H, m, C(6)$H_{endo}$), 1.80–1.90 (1 H, m, C(7)$H_{exo}$), 2.01–2.15 (5 H, m, C(6)$H_{exo}$, C(7)$H_{endo}$ and C$H_3$), 2.38–2.51 (2 H, m, C(8)$H_{endo}$ and C(8)$H_{exo}$), 3.47 (1 H, dd, *J* 8.0 and 10.0, C(4)$H_{endo}$), 3.79–3.89 (1 H, m, C(5)H), 4.11 (1 H, dd, *J* 5.0 and 8.0, C(4)$H_{exo}$), 7.31–7.46 (3 H, m, ArH), 7.57–7.62 (2 H, m, ArH); $\delta_C$ (200 MHz, $CDCl_3$) 20.9 (C(6)), 24.8 (C(7)), 25.2 (*C*$H_3$), 32.1 (C(8)), 57.7 (C(5)), 69.1 (C(4)), 95.9 (C(2)), 125.8, 126.0, 128.1, 128.3 (Aryl *C*H), 141.9 (Aryl *C*), 168.0 (C-9); *m*/*z* (GCMS) 232 ($MH^+$, 100%).

Lactam **2e**: $R_f$ 0.36 (EtOAc); $[\alpha]_D^{24}$ +161.1 (*c* 1.0, $CHCl_3$); $\nu_{max}$ (film)/cm$^{-1}$ 3503m, 1649s, 1408m, 1325w; $\delta_H$ (400 MHz; $CDCl_3$) 1.27–1.49 (1 H, m, C(6)$H_{endo}$), 1.69–1.81 (1 H, m, C(7)$H_{exo}$), 1.96–2.04 (1 H, m, C(7)$H_{endo}$), 2.05 (1 H, s, Me), 2.06–2.18 (1 H, m, C(6)$H_{exo}$), 2.34–2.49 (2 H, m, C(8)H), 3.38–3.78 (2 H, m, C(5)H and C(4)$H_{endo}$), 4.24 (1 H, dd, *J* 5.5 and 7.5, C(4)$H_{exo}$), 7.28–7.49 (3 H, m, Ph), 7.56–7.59 (2H, m, Ph); $\delta_C$(100.6 MHz; $CDCl_3$) 20.8 (C(6)), 24.9 (Me), 26.3 (C(7)), 32.3 (C(8)), 57.5 (C(5)), 70.2 (C(4)), 96.1 (C(2)), 123.1, 125.7 and 128.0 (Ar*C*H), 142.5 (Ar*C*), 167.3 (C(9)); *m*/*z* (APCI$^+$) 232 ($MH^+$, 56%), 232 (77), 216 (100); HRMS: 232.1334 ($MH^+$, ES$^+$). $C_{14}H_{17}NO_2$ requires 232.1338.

An improved method gave lactam **2d** exclusively: to a solution of alcohol **1** (4.37 g, 34.0 mmol) in chloroform (200 ml) was added pyridinium *p*-toluenesulfonate (0.85 g, 3.40 mmol) and acetophenone dimethyl acetal (7.26 ml, 44.0 mmol). The suspension was heated at 70 °C for 18 hours, and then allowed to cool to room temperature before the solvent was removed *in vacuo*. The residue was then purified by flash column chromatography on silica gel, eluting with EtOAc, to give exclusively the diastereomer **2d** as a white solid (6.13 g, 78%).

### (±)-(2*R**,5*S**,8*S**)-1-Aza-8-(*p*-nitrobenzyl)-3-oxa-9-oxo-2-phenylbicyclo[4.3.0]nonane 3a

To a solution of LDA (0.13 g, 1.2 mmol) in THF (10 ml) under nitrogen at −78 °C was added lactam **2a** (0.18 g, 0.83 mmol), and the solution stirred for 30 min. *p*-Nitrobenzyl bromide (0.22 g, 1.0 mmol) was added in a 2 ml portion of THF, and the reaction mixture stirred for a further 2 h. After allowing the solution to warm to room temperature, the reaction was quenched by adding saturated ammonium chloride in methanol (5 ml). The resulting liquor was partitioned between EtOAc and water, the organic layer separated and the solvent removed *in vacuo*. Purification by flash column chromatography, using 10% EtOAc/90% light petroleum, increasing the EtOAc proportion slowly to 100%, gave **3a** as the major product (0.10 g, 34%). $R_f$ (EtOAc) 0.55; $\nu_{max}$ ($CHCl_3$)/cm$^{-1}$ 1640s; $\delta_H$ (500 MHz, $CDCl_3$) 1.32–1.40 (1H, m, C(6)$H_{endo}$), 1.44–1.52 (1H, m, C(7)$H_{exo}$), 1.87–1.92 (1H, m, C(7)$H_{endo}$), 2.08–2.12 (1H, m, C(6)$H_{exo}$), 2.67–2.73 (1H, m, C(8)$H_{endo}$), 3.10–3.18 (2H, m, ArC$H_2$), 3.51–3.54 (1H, m, C(4)$H_{endo}$), 3.67–3.73 (1H, m, C(5)H), 4.32–4.35 (1H, m, C(4)$H_{exo}$), 6.38 (1H, s, C(2)H), 7.21–7.27 (2H, d, *J* 8.7, *p*-$NO_2C_6H_4$), 7.36–7.41 (5H, m, Ar*H*), 7.98–8.00 (2H, d, *J* 8.7, *p*-$NO_2C_6H_4$); $\delta_C$ (500 MHz, $CDCl_3$) 25.0 and 25.4 (C(6), C(7)), 37.5 (Ar*C*$H_2$), 43.0 (C(8)), 56.8 (C(5)), 72.9 (C(4)), 88.9 (C(2)), 123.4, 123.4, 126.6, 128.3, 128.8, 130.3 (Ar*C*), 138.8 (4° Ar*C*), 146.7 and 146.8 (4° Ar*C*), 169.0 (C(9)); *m*/*z* (DCI) 370 (M + $NH_4^+$, 5%), 353 (M + $H^+$, 100). HRMS: 353.1501 ($MH^+$). $C_{20}H_{21}N_2O_4$ requires 353.1501.

### (±)-(2*R**,5*S**,8*R**)-1-Aza-8-methyl-3-oxa-9-oxo-2-phenylbicyclo[4.3.0]nonane 4a

Lactam **2a** (0.14 g, 0.63 mmol) was added to a solution of LDA (0.094 g, 0.88 mmol) in THF (10 ml) at −78 °C under nitrogen, and the solution stirred for 30 min. MeI (0.200 g) was added, and the new solution stirred for a further 1 h. The solution was quenched by adding saturated ammonium chloride in MeOH (5 ml). Organic products were extracted into EtOAc and the two layers separated. The organic layer was washed with water, separated and dried over $MgSO_4$. Filtration and removal of the solvent afforded a mixture of products and starting materials. The product was obtained as a mixture of diastereomers of approx. ratio 2 : 1, from which lactam **4a** was isolated by flash column chromatography (0.069 g, 47%). Diastereomer **4b** was not recovered in pure form. Data for **4a**: $R_f$ (EtOAc) 0.60; Found: C, 72.4; H, 7.3; N, 6.0. Calc. for $C_{14}H_{17}NO_2$: C, 72.7; H, 7.4; N, 6.1%; $\nu_{max}$ ($CHCl_3$)/cm$^{-1}$ 1635s; $\delta_H$ (200 MHz, $CDCl_3$) 1.26 (3H, d, C$H_3$), 1.38–1.61 (2H, m, C$H_2$), 2.03–2.20 (2H, m, C$H_2$), 2.30–2.49 (1H, m, C(8)H), 3.57 (1H, m, C(4)$H_{endo}$), 3.81–3.96 (1H, m, C(5)H), 4.38 (1H, m, C(4)$H_{exo}$), 6.41 (1H, s, C(2)H), 7.33–7.56 (5H, m, ArH); $\delta_C$ (500 MHz, $CDCl_3$) 17.8 (*C*$H_3$), 25.3 (C(7)), 29.0 (C(6)), 37.1 (C(8)), 56.9 (C(5)), 73.2 (C(4)), 88.7 (C(2)), 126.7, 128.5 and 128.8 (ArC), 139.5 (ArC) and 171.9 (C(9)); *m*/*z* (DCI) 232 (M + $H^+$, 100%).

### (±)-(5*S**,8*S**) and (5*S**,8*R**)-1-Aza-2,2-dimethyl-8-(*p*-nitrobenzyl)-3-oxa-9-oxobicyclo[4.3.0]nonane 5a,b

To a solution of LDA (0.23 g, 2.1 mmol) in THF (10 ml) under nitrogen at −78 °C was added lactam **2c** (0.26 g, 1.5 mmol), and

the solution stirred for 30 min. *p*-Nitrobenzyl bromide (0.39 g, 1.8 mmol) was added in a 2 ml portion of THF, and the reaction mixture stirred for a further 2 h. After allowing the solution to warm up slowly to room temperature the reaction was quenched by adding saturated ammonium chloride in methanol (5 ml). The resulting liquor was partitioned between EtOAc and water, the organic layer separated and the solvent removed *in vacuo*. Purification using flash column chromatography with 10 : 90 EtOAc/light petroleum, increasing the EtOAc proportion slowly to 100%, gave **5a**,**b** (mixture of diastereomers in a ratio of approx. 3 : 2) as a yellow oil (0.130 g, 28%). $R_f$ (EtOAc) 0.69 and 0.90; $\nu_{max}$ ($CHCl_3$)/cm$^{-1}$ 1635s, 1520s; $\delta_H$ (200 MHz, $CDCl_3$) 1.21–1.47 (2H, m, C(7)H), 1.61 and 1.63 (6H, 2s, $C(CH_3)_2$), 1.67–1.98 (2H, m, C(6)H), 2.92–3.04 (2H, m, C(4)H$_{endo}$and C(8)H), 3.28–3.56 (3H, m, C(5)H and Ar$CH_2$), 4.02–4.14 (1H, m, C(4)H$_{exo}$), 7.37 (2H, m, ArH), 8.14 (2H, m, ArH); $\delta_C$ (50.3 MHz, $CDCl_3$) 23.9 ($CH_3$), 25.1 and 26.6 (C(7)), 25.7 ($CH_3$), 26.6 (C(6)), 37.4 and 37.7 (Ar$CH_2$), 42.0 and 43.4 (C(8)), 56.6 and 57.8 (C(5)), 69.3 and 69.5 (C(4)), 94.78 and 94.9 (C(2)), 123.7 (ArC), 130.0 (ArC), 146.8 and 148.1 (ArC), 168.0 and 169.1 (C(9)); *m*/*z* (DCI GCMS) 305 (M + H$^+$, 100%), 275 (50); HRMS: 305.1501 (MH$^+$), $C_{16}H_{21}N_2O_4$ requires 305.1501.

**(±)-(5*S**,8*R**) and (5*S**,8*S**)-1-Aza-2,2,8-trimethyl-3-oxa-9-oxobicyclo[4.3.0]nonane 6a**,**b**

Lactam **2c** (0.13 g, 0.77 mmol) was added to a solution of LDA (0.12 g, 1.1 mmol) in THF (10 ml) at −78 °C under nitrogen, and the solution stirred for 30 min. MeI (0.20 g, 1.4 mmol) was added, and the new solution stirred for a further 1 h. The solution was quenched by adding saturated ammonium chloride in MeOH (5 ml), the solution extracted with EtOAc and the layers separated. The organic layer was washed with water, separated and dried over $MgSO_4$. Filtration and removal of the solvent, purification (flash column chromatography) afforded the product as a mixture of diastereomers **6a** and **6b** of approx. ratio 5 : 4 by $^{13}$C NMR spectroscopic analysis (0.060 g, 43%). $R_f$ (EtOAc) 0.66; $\nu_{max}$ ($CHCl_3$)/cm$^{-1}$ 1645; $\delta_H$ (200 MHz, $CDCl_3$) 1.22–1.27 (3H, m, $CH_3$), 1.36–1.52 (2H, m, C(7)H), 1.52–1.60 (6H, 2s, $(CH_3)_2$), 1.84–2.07 (2H, m, C(6)H), 2.25–2.45 (1H, m, C(8)H), 3.40–3.52 (1H, m, C(4)H$_{endo}$), 3.61–3.76 (1H, m, C(5)H), 4.00–4.13 (1H, m, C(4)H$_{exo}$); $\delta_C$ (50.3 MHz, $CDCl_3$) 17.3 and 18.8 (8-$CH_3$), 22.7 and 25.4 (C(7)), 23.9, 24.1, 25.5 and 25.8 (2 × ($CH_3$)$_2$), 27.9 and 30.1 (C(6)), 35.6 and 37.1 (C(8)), 56.9 and 58.0 (C(5)), 69.4 and 69.6 (C(4)), 94.4 and 94.6 (C(2)), 170.4 and 171.4 (C(9)); *m*/*z* (DCI GCMS) 184 (M + H$^+$, 100%); HRMS: 184.1338 (MH$^+$). $C_{10}H_{18}NO_2$ requires 184.1338.

**(2*R*,5*S*)-8-Ethoxycarbonyl-9-oxo-2-phenyl-1-aza-3-oxa-bicyclo[4.3.0]nonane 7a**

A solution of lactam **2a** (1.00 g, 4.62 mmol) and diethyl carbonate (2.86 ml, 5 eq) in toluene (20 ml) was heated at reflux for 5 hours using a Dean–Stark trap. Prewashed sodium hydride (0.407 g, 2.2 eq, 60% dispersion) was carefully added at 0 °C and the solution brought back to reflux for a further 16 hours. The mixture was cooled to 0 °C, quenched with glacial acetic acid (0.48 ml) and the suspension filtered. The solvent was removed *in vacuo* and the resulting yellow oil purified by flash column chromatography, eluting with 3 : 1 petrol/EtOAc and gradually increasing polarity to 2 : 1 petrol/EtOAc. This gave the product **7a** as an inseparable diastereoisomeric mixture (1.08 g, 81%) in the ratio 11 : 14. $R_f$ 0.26, 0.39 (1 : 1 petrol/EtOAc); $\nu_{max}$ ($CHCl_3$/cm$^{-1}$) 1734s, 1651s, 1175; $\delta_H$ (500 MHz, $CDCl_3$) 1.24–1.27 and 1.29–1.31 (3H, 2 × t, *J* 7.1, $CH_3CH_2$), 1.40–1.47 and 1.76–1.83 (1H, m, C(6)H), 1.97–2.30 (3H, m, C(7)H$_2$ and C(6)H), 3.42–3.45 (1H, 2 × t, *J* 6.9, C(8)H), 3.57–3.65 (1H, 2 × dd, C(4)H, *J* 8.2, 9.6), 3.82–3.95 (1H, m, C(5)H), 4.18–4.28 (2H, 2 × q, $CH_3CH_2O$), 4.34–4.37 and 4.40–4.43 (1H, 2 × dd, *J* 6.0, 8.2 and *J* 5.7, 8.1, C(4)H), 6.43 (1H, s, C(2)H), 7.30–7.37 (3H, m, ArH), 7.45–7.50 (1H, m, ArH), 7.50–7.52 (1H, m, ArH); $\delta_C$ (200 MHz, $CDCl_3$) 13.88, 13.97 ($CH_3CH_2$) 22.2 (C(6)), 24.0, 24.6 (C(7)), 47.0, 49.29 (C(8)), 56.2, 56.3 (C(5)), 61.5 ($CH_3CH_2$), 72.8 (C(4)), 88.8, 89.0 (C(2)), 126.5, 127.0, 128.5, 128.6, 128.9, 129.0, 129.2 (Ar*C*H), 138.6, 139.0 (Aryl*C*), 164.4 (C-9), 170.9, 171.3 (C=O); *m*/*z* (CI($NH_3$)) 290 (MH$^+$, 100%).

**(2*R*,5*S*)-8-Ethoxycarbonyl-9-oxo-2-phenyl-8-phenylselenenyl-1-aza-3-oxabicyclo[4.3.0]nonane 7b**

To a stirred suspension of NaH (0.074 g, 1.2 eq, 60% dispersion) in dry THF (5 ml) under a $N_2$ atmosphere was added, *via* a syringe at 0 °C, a solution of the lactam **7a** (0.448 g, 1.55 mmol) in dry THF (5 ml). After 10 min, a solution of phenylselenyl chloride (0.341 g, 1.15 eq) in dry THF (5 ml) was added, *via* syringe, at room temperature. The solution was heated to reflux for 15 hours. This solution was carefully poured into saturated $NH_4Cl$ (15 ml)/EtOAc (15 ml) and the organic layer washed with water (15 ml) and brine (15 ml). After drying over $MgSO_4$, the solvent was removed *in vacuo* to give an orange oil. Purification by flash column chromatography, eluting with 4 : 1 petrol/EtOAc gave lactam **7b** as two separable diastereoisomers as yellow oils (0.48 g, 70%) in a ratio of 0.4 : 0.6.

Minor diastereoisomer: $R_f$ 0.58 (1 : 1 petrol/EtOAc); $[a]_D^{25}$ +13.8 (*c* 0.99, $CHCl_3$); $\nu_{max}$ ($CHCl_3$/cm$^{-1}$) 1724s, 1651s; $\delta_H$ (500 MHz, $CDCl_3$) 1.21–1.24 (3H, t, *J* 7.1, $CH_3CH_2$), 1.70–1.77 (1H, m, C(6)H), 1.91–1.97 (1H, m, C(6)H), 2.09–2.14 (1H, m, C(7)H), 2.28–2.33 (1H, m, C(7)H), 3.50–3.53 (1H, dd, *J* 8.4, C(4)H), 3.78–3.84 (1H, m, C(5)H), 4.18–4.22 (2H, q, *J* 7.1, $CH_3CH_2$), 4.24–4.27 (1H, dd, *J* 6.0, 8.1, C(4)H), 6.45 (1H, s, C(2)H), 7.30–7.37, 7.40–7.41, 7.42–7.48, 7.73–7.74 (10H, m, ArH); *m*/*z* (CI($NH_3$)) 446 (MH$^+$, 80%), 290 (100%).

Major diastereoisomer: $R_f$ 0.51 (1 : 1 petrol/EtOAc); $[a]_D^{25}$ −2.97 (*c* 0.16, $CHCl_3$); $\nu_{max}$ ($CHCl_3$/cm$^{-1}$) 1727s, 1651s; $\delta_H$ (500 MHz, $CDCl_3$) 1.31–1.34 (3H, t, *J* 7.1, $CH_3CH_2$), 1.57–1.66 (1H, m, C(6)H), 1.89–1.94 (1H, m, C(6)H), 2.03–2.09 (1H, m, C(7)H), 2.42–2.46 (1H, m, C(7)H), 3.42–3.47 (1H, m, C(5)H), 3.51–3.54 (1H, dd, *J* 8.1, 9.6, C(4)H), 4.23–4.37 (3H, m, C(4)H and $CH_3CH_2$), 6.42 (1H, s, C(2)H), 7.03–7.06, 7.27–7.31, 7.34–7.41, 7.49–7.51 (10H, m, ArH); $\delta_C$ DEPT (200 MHz, $CDCl_3$) 14.1 ($CH_3$), 23.8 (C-6), 32.8 (C-7), 56.3 (C-5), 62.7 ($CH_2$), 72.9 (C-4), 89.4 (C-2), 126.5, 127.3, 128.3, 128.9, 129.3, 138.0 (ArC), 126.2 (C-8), 138.3 (ArC), 165.1 (C-9), 170.5 (C=O); *m*/*z* (CI($NH_3$)) 446 (MH$^+$, 80%), 290 (100).

**(+)-(2*R*,5*S*)-1-Aza-3-oxa-9-oxo-2-phenyl-8,8-bis(phenylselenenyl)bicyclo[4.3.0]nonane 7c**

To a solution of lactam **2a** (0.38 g, 1.7 mmol) in THF (15 ml) under nitrogen at −78 °C was added LiHMDS (3.6 ml × 1 M in THF) dropwise, and the solution stirred for 15 minutes. Phenyl selenenyl chloride (0.696 g, 3.63 mmol) was added in THF (10 ml) under nitrogen and the solution allowed to stir for 30 minutes at −78 °C. The solution was allowed to warm to room temperature over 1 hour, then quenched with water (20 ml). The product was extracted with $CH_2Cl_2$ (3 × 20 ml), washed with brine (25 ml) then dried over $Na_2SO_4$. The solvent was removed *in vacuo* to afford a crude product which was recrystallised from EtOAc/petrol giving the title compound **7c** as a white crystalline solid (0.458 g, 50%). $R_f$ 0.66 (50 : 50 EtOAc : petrol); Found C, 57.03; H, 4.49; N, 2.22; required for $C_{25}H_{23}NO_2Se_2$ C, 56.71; H, 4.38; N, 2.65%; $[a]_D^{25}$ +109.4 (*c* 1.0, $CHCl_3$); $\nu_{max}$ ($CHCl_3$)/cm$^{-1}$ 1641(s); $\delta_H$ (500 MHz, $CDCl_3$) 1.64–1.71 (2H, m, C(6)H), 1.95–2.05 (2H, m, C(7)H), 3.47–3.54 (2H, m, C(4)H and C(5)H), 4.28–4.30 (1H, m, C(4)H), 6.38 (1H, s, C(2)H), 6.96–7.81 (15H, m, ArH); $\delta_C$ (50.3 MHz, $CDCl_3$) 22.8 (C(6)), 33.0 (C(7)), 56.9 (C(5)), 72.9 (C(4)), 89.7 (C(2)), 126.9, 127.5, 128.0, 128.5, 128.8, 129.0, 129.1, 129.4, 129.9, 130.0, 135.5, 136.9, 138.2 (ArC), 138.6 (C-8), 168.09 (C(9)); *m*/*z* (DCI, $NH_3$) 530 (MH$^+$, 10%), 374 (65), 218 (100).

**(2*S*,5*S*,8*R*) and (2*S*,5*S*,8*S*)-1-Aza-2-methyl-8-methyl-3-oxa-9-oxo-2-phenylbicyclo[4.3.0]nonane 8a,b**

To a stirred flask of THF (20 ml) under $N_2$ at −78 °C was added s-BuLi (0.68 ml, 0.66 mmol). A solution of the lactam **2d** (0.10 g, 0.44 mmol) in THF (10 ml) was then added slowly. After five minutes a dark brown colour was observed. Methyl iodide (0.04 ml, 0.66 mmol) was then added by syringe, and the reaction mixture was seen to turn pink. The reaction mixture was allowed to warm to room temperature over 30 minutes, when TLC indicated that reaction was complete. The reaction was then quenched with sat. aq. $NH_4Cl$ (20 ml), extracted with EtOAc (4 × 25 ml) and dried over $MgSO_4$. Solvent was removed *in vacuo*, and the residue purified by flash column chromatography on silica eluting with 40% EtOAc : petrol to yield an inseparable mixture of **8a**,**b** as a colourless oil (0.089 g, 82%); $R_f$ 0.26 and 0.13 (40% EtOAc : petrol); $\nu_{max}$(film)/cm$^{-1}$ 3583m, 1649s, 1420m, 1325m, 1240m, 1028m, 764m, 697m and 666s; $\delta_H$(500 MHz; $CDCl_3$) 1.26 (3H, d, *J* 3.5, C(8)Me (B)), 1.27 (3H, d, *J* 3.5, C(8)Me (A)), 1.51–1.73, 1.94–1.99, 2.05–2.12 and 2.17–2.21 (4H, m, C(6)H and C(7)H (A) and (B)), 2.03 (3H, s, C(2)Me (B)), 2.04 (3H, s, C(2)Me (A)), 2.43–2.53 (1H, m, C(8)H), 3.39 (1H, dd, *J* 8.5 and 10.0, C(4)H$_{endo}$ (B)), 3.52 (1H, dd, *J* 8.5 and 10.5, C(4)H$_{endo}$ (A)), 3.87–3.97 (1H, m, C(5)H), 4.08 (1H, dd, *J* 5.5 and 8.5, C(4)H$_{exo}$ (A)), 4.13 (1H, dd, *J* 6.0 and 8.5, C(4)H$_{exo}$ (B)), 7.26–7.57 (5H, m, ArH); $\delta_C$(125.8 MHz; $CDCl_3$) 16.9 (C(8)Me (B)), 17.0 (C(8)Me (A)), 23.3 (C(7) (B)), 24.9 (C(2)Me (A)), 25.3 (C(7) (A)), 25.8 (C(2)Me (B)), 28.1 (C(6) (B)), 30.5 (C(6) (A)), 36.3 (C(8) (B)), 37.3 (C(8) (A)), 56.8 (C(5) (B)), 58.2 (C(5) (A)), 69.3 (C(4)), 95.5 (C(2) (B)), 96.0 (C(2) (A)), 125.5, 125.6, 125.7, 127.8, 128.1, 128.1 (Ar*C*H), 141.7 (ArH (B)), 142.3 (ArH (A)), 170.2 (C(9) (A)), 171.7 (C(9) (B)); *m*/*z* (APCI$^+$) 268 (M + $NH_4^+$, 26%), 246 ($MH^+$, 100); HRMS: 246.1492 ($MH^+$, CI). $C_{15}H_{20}NO_2$ requires 246.1494.

**(+)-(2*S*,5*S*)-1-Aza-8-dibenzyl-2-methyl-3-oxa-9-oxo-2-phenyl-bicyclo[4.3.0]nonane 10a, (2*S*,5*S*,8*R*)-1-Aza-8-benzyl-2-methyl-3-oxa-9-oxo-2-phenyl-bicyclo[4.3.0]nonane 9b and (−)-(2*S*,5*S*,8*S*)-1-Aza-8-benzyl-2-methyl-3-oxa-9-oxo-2-phenyl-bicyclo[4.3.0]nonane 9a**

To stirred THF (30 ml) cooled to −78 °C under $N_2$ was added s-BuLi (0.75 ml, 0.98 mmol). Lactam **2d** (0.15 g, 0.65 mmol) in dry THF (5 ml) was then added slowly and the reaction was allowed to warm to −30 °C. Benzyl bromide (0.670 g, 3.92 mmol) in dry THF (5 ml) was then added slowly. After 15 min, the reaction mixture was quenched with distilled water (25 ml), extracted with EtOAc (3 × 25 ml) and dried with brine (25 ml) and over $MgSO_4$. Solvent was removed *in vacuo* and the residue separated by column chromatography eluting with 20% EtOAc : petrol to yield three products.

Major diastereomer (*exo*) **9a**: Yield 0.132 g (63%); $R_f$ 0.13 (20% EtOAc : petrol); $[\alpha]_D^{25}$ −25.8 (*c* 1.03, $CHCl_3$); $\nu_{max}$(film)/cm$^{-1}$ 1648s, 1495w, 1445w, 1424m; $\delta_H$(500 MHz; $CDCl_3$) 1.50–1.60 (1H, m, C6(H)$_{endo}$), 1.55–1.62 (1H, m, C(7)H$_{exo}$), 1.94–1.99 (1H, m, C(7)H$_{endo}$), 2.00–2.06 (1H, m, C(6)H$_{exo}$), 2.07 (3 H, s, C(2)Me), 2.65–2.71 (1H, m, C(8)H), 2.84 (1H, dd, *J* 9.0 and 13.5, PhC*H*), 3.35 (1H, dd, *J* 4.0 and 13.5, PhC*H*), 3.50 (1H, dd, *J* 8.5 and 10.5, C(4)H$_{endo}$), 3.70–3.76 (1H, m, C(5)H), 4.04 (1H, dd, *J* 5.5 and 8.5, C(4)H$_{exo}$), 7.21–7.50 (10H, m, ArH); $\delta_C$(125.8 MHz; $CDCl_3$) 24.9 (C(2)*C*H$_3$), 25.1 and 26.9 (C(6) and C(7)), 37.4 (*C*H$_2$Ph), 43.8 (C(8)), 57.9 (C(5)), 69.2 (C(4)), 95.8 (C(2)), 125.6, 126.2, 127.9, 128.1, 128.3, 129.4 (Ar*C*H), 139.7, 141.6 (Ar*C*), 168.7 (C(9)); *m*/*z* (APCI$^+$) 322 ($MH^+$, 100%), 202 (94); HRMS: 322.1807 ($MH^+$,CI). $C_{21}H_{23}NO_2$ requires 322.1807.

Minor diastereomer (*endo*) **9b**: Yield 0.013 g (6%); $R_f$ 0.26 (20% EtOAc : petrol); $\nu_{max}$(film)/cm$^{-1}$ 1644s, 1422m; $\delta_H$(500 MHz; $CDCl_3$) 1.39–1.48 (1H, m, C(6)H$_{endo}$), 1.65–1.71 (1H, m, C(7)H$_{exo}$), 1.75–1.81 (1H, m, C(7)H$_{endo}$), 1.82–1.89 (1H, m, C(6)H$_{exo}$), 2.07 (3 H, s, C(2)Me), 2.59–2.65 (1H, m, C(8)H), 2.73 (1H, dd *J* 10.0 and 13.5, PhC*H*), 3.33 (1H, dd *J* 4.0 and 13.5, PhC*H*), 3.67 (1H, dd *J* 8.0 and 8.0, C(4)H$_{endo}$), 3.72–3.78 (1H, m, C(5)H), 4.16 (1H, dd *J* 6.0 and 8.0, C(4)H$_{exo}$), 7.00–7.61 (10H, m, ArH); *m*/*z* (APCI$^+$) 322 ($MH^+$, 100%); HRMS: 322.1807 ($MH^+$, CI). $C_{21}H_{23}NO_2$ requires 322.1807.

Dialkylated lactam **10a**: Yield 0.047 g (18%); $R_f$ 0.38 (20% EtOAc : petrol); $[\alpha]_D^{25}$ +2.41 (*c* 0.79, $CHCl_3$); $\nu_{max}$(film)/cm$^{-1}$ 1636s, 1419m; $\delta_H$(500 MHz; $CDCl_3$) 0.77–0.86 (1H, m, C(6)H$_{endo}$), 0.88–0.95 (1H, m, C(7)H$_{exo}$), 1.56–1.60 (1H, m, C(7)H$_{endo}$), 1.87–1.95 (1H, m, C(6)H$_{exo}$), 1.94 (3H, s, C(2)Me), 2.39 (1H, d, *J* 13.0, PhC*H*), 2.67 (1H, d, *J* 13.0, PhC*H*), 3.02–3.09 (1H, m, C(5)H), 3.34 (1H, dd, *J* 8.5 and 10.5, C(4)H$_{endo}$), 3.38 (1H, d, *J* 13.0, PhC*H*), 3.48 (1H, d, *J* 13.0, PhC*H*), 3.86 (1H, dd, *J* 6.0 and 8.5, C(4)H$_{exo}$), 7.00–7.48 (15H, m, ArH); $\delta_C$(125.8 MHz; $CDCl_3$) 23.29 and 24.31 (C(6) and C(7)), 28.4 (C(2)Me), 45.7 (PHCH), 47.1 (PHCH), 48.7 (C(8)), 57.3 (C(5)), 69.9 (C(4)), 95.9 (C(2)), 126.3, 126.5, 126.6, 127.8, 127.9, 128.1, 128.1, 130.7, 132.0 (Ar*C*H), 137.7 (ArC), 141.8 (ArC), 170.5 (C(9)); *m*/*z* (APCI$^+$) 412 ($MH^+$, 100%), 292 (31); HRMS: 412.2277 ($MH^+$, CI). $C_{28}H_{29}NO_2$ requires 412.2277.

**(−)-(2*S*,5*S*,8*R*)-1-Aza-2-methyl-8-(*p*-nitrobenzyl)-3-oxa-9-oxo-2-phenylbicyclo[4.3.0]nonane 11b and (−)-(2*S*,5*S*,8*S*)-1-aza-2-methyl-8-(*p*-nitrobenzyl)-3-oxa-9-oxo-2-phenylbicyclo[4.3.0]-nonane 11a**

To a solution of the lactam **2d** (0.59 g, 2.5 mmol) in THF (50 ml) cooled to −78 °C under nitrogen was added s-BuLi (3.1 ml, 2.5 mmol), and the reaction mixture was allowed to warm to −30 °C over fifteen minutes. The enolate solution was then added to a solution of freshly recrystallised *p*-nitrobenzyl bromide (0.66 g, 3.1 mmol) in THF (10 ml) at −78 °C by cannula. After 45 minutes the reaction was quenched by the addition of sat. aq. $NH_4Cl$ (25 ml), and extracted with EtOAc (3 × 25 ml), dried with brine (25 ml) and over $MgSO_4$. Solvent was then removed *in vacuo*. The residue was separated on silica gel eluting with 40% EtOAc : petrol to yield the products as yellow oils.

Major diastereomer (*exo*) **11a**: Yield 0.16 g (18%); $R_f$ 0.14 (40% EtOAc : petrol); $[\alpha]_D^{25}$ −65.5 (*c* 1.0, $CHCl_3$); $\nu_{max}$(film)/cm$^{-1}$ 1647s, 1603w, 1518s, 1494w, 1427m, 1370w, 1346s, 1323m, 1244m; $\delta_H$(400 MHz; $CDCl_3$) 1.46–1.59 (2H, m, C(6)H$_{exo}$ and C(7)H$_{endo}$), 1.91–2.00 (1H, m, C(6)H$_{endo}$), 2.02–2.09 (1H, m, C(7)H$_{exo}$), 2.04 (3H, s, C(2)Me), 2.66–2.79 (1H, m, C(8)H), 2.98 (1H, dd, *J* 9.0 and 14.0, PhC*H*), 3.40 (1H, dd, *J* 4.0 and 14.0, PhC*H*), 3.50 (1H, dd, *J* 8.5 and 10.5, C(4)H$_{endo}$), 3.71–3.78 (1H, m, C(5)H), 4.04 (1H, dd, *J* 5.5 and 8.5, C(4)H$_{exo}$), 7.27–8.15 (9H, m, ArH); $\delta_C$(100.6 MHz; $CDCl_3$) 24.8 (C(2)Me), 24.9 (C(7)), 26.9 (C(6)), 37.1 (C(2)*C*H$_2$), 43.4 (C(8)), 56.4 (C(5)), 69.1 (C(4)), 95.7 (C(2)), 123.6, 125.5, 128.0, 128.2, 128.5, 130.2 (Ar*C*H), 141.3 (ArC), 136.6 (ArC), 147.8 (Ar*C*NO$_2$), 167.8 (C(9)); *m*/*z* (APCI$^+$) 367.2 ($MH^+$, 100%), 337 (23), 247 (98); HRMS: 367.1653 ($MH^+$, ES$^+$). $C_{21}H_{22}N_2O_4$ requires 367.1658.

Minor diastereomer (*endo*) **11b**: Yield 0.10 g (11%); $R_f$ 0.07 (40% EtOAc : petrol); $[\alpha]_D^{25}$ −52.1 (*c* 1.04, $CHCl_3$); $\nu_{max}$(film)/cm$^{-1}$ 1648s, 1559w, 1519w, 1494w, 1426m, 1370m, 1345m, 1324m, 1243m, 1182m; $\delta_H$(400 MHz; $CDCl_3$) 1.50–1.62 (1H, m, C(6)H$_{endo}$), 1.81–1.85 (1H, m, C(7)H$_{exo}$), 1.97–2.00 (1H, m, C(7)H$_{endo}$), and 2.34–2.49 (1H, m, C(6)H$_{exo}$), 2.05 (3H, s, C(2)Me), 2.85–3.00 (1H, m, C(8)H), 3.35 (1H, t, *J* 10.0, PhC*H*), 3.45 (1H, dd, *J* 8.0 and 10.0, PhC*H*), 3.56 (1H, dd, *J* 8.5 and 10.5, C(4)H$_{endo}$), 3.90–3.98 (1H, m, C(5)H), 4.16 (1H, dd, *J* 6.0 and 8.5, C(4)H$_{exo}$), 7.26–7.53 (9H, m, ArH); $\delta_C$(100.6 MHz; $CDCl_3$) 20.6 (C(6)), 24.9 (C(2)Me), 25.8 (C(7)), 32.1 (Ph*C*H), 44.0 (C(8)), 58.0 (C(5)), 69.5 (C(4)), 96.4 (*C(2)*), 123.6, 125.4, 125.5, 125.6, 125.7, 127.9, 128.2, 130.2 (Ar*C*H), 140.8 (ArC), 142.4 (ArC), 163.3 (C(9)), 170.3 (Ar*C*NO$_2$); *m*/*z* (APCI$^+$) 367 ($MH^+$, 100%), 337 (19), 247 (99); HRMS: 367.1661 ($MH^+$, ES$^+$). $C_{21}H_{22}N_2O_4$ requires 367.1658.

**(2*S*,5*S*,8*S*)-8-Allyl-1-aza-2-methyl-3-oxa-9-oxo-2-phenylbicyclo[4.3.0]nonane 12b and (−)-(2*S*,5*S*,8*R*)-8-allyl-1-aza-2-methyl-3-oxa-9-oxo-2-phenylbicyclo[4.3.0]nonane 12a**

To a stirred flask of THF (20 ml) cooled to −78 °C under nitrogen was added sBuLi (1.08 ml, 0.98 mmol). The lactam **2d** (0.15 g, 0.65 mmol) was then dissolved in THF (10 ml) and added slowly to the mixture using a syringe. The reaction was allowed to warm slightly to −30 °C. Freshly distilled allyl bromide (0.12 g, 0.98 mmol) dissolved in THF (5 ml) was then added and the dark red colour of the anion disappeared. After 30 minutes the reaction was quenched with sat. aq. $NH_4Cl$ (30 ml). The aqueous layer was separated and extracted with EtOAc (3 × 30 ml). The organic extracts were then combined and dried with brine (25 ml) and over $MgSO_4$. Solvent was removed *in vacuo*. The residue was then separated by column chromatography on silica gel, eluting with 20% EtOAc : petrol to give two colourless oils.

Major diastereomer (*exo*) **12a**: Yield 0.11 g (64%); $R_f$ 0.28 (20% petrol : EtOAc); $[a]_D^{25}$ −60.0 (*c* 0.09, $CHCl_3$); $\nu_{max}$(film)/$cm^{-1}$ 1660s, 1559m, 1540m, 1522m, 1506m, 1457m, 1420m; $\delta_H$(500 MHz; $CDCl_3$) 1.58–1.69 (2H, m, C(6)$H_{endo}$ and C(7)$H_{exo}$), 2.06 (3H, s, C(2)Me), 2.09–2.17 (2H, m, C(6)$H_{exo}$ and C(7)$H_{endo}$), 2.35–2.41 (1 H, m, $CH_2$=CHC*H*), 2.46–2.52 (1H, m, C(8)H), 2.66–2.71 (1H, m, $CH_2$=CHC*H*), 3.52 (1H, dd, *J* 8.5 and 10.5, C(4)$H_{endo}$), 3.83–3.89 (1H, m, C(5)H), 4.08 (1H, dd, *J* 5.5 and 8.5, C(4)$H_{exo}$), 5.08–5.14 (2H, m, CH=C$H_2$), 5.75–5.83 (1H, m, C*H*=$CH_2$), 7.28–7.47 (5H, m, ArH); $\delta_C$(125.8 MHz; $CDCl_3$) 24.8 (C(2)Me), 25.0 (C(7)), 26.9 (C(6)), 35.7 ($CH_2$=CHC$H_2$), 41.4 (C(8)), 57.8 (C(5)), 69.1 (C(4)), 95.5 (C(2)), 117.0 (CH=C$H_2$), 125.5, 127.7, 127.9 (ArCH), 135.7 (CH=$CH_2$), 141.5 (ArC), 168.7 (C(9); *m*/*z* (APCI$^+$) 272 ($MH^+$, 100%), 152 (81); HRMS: 272.1651 ($MH^+$, CI). $C_{17}H_{21}NO_2$ requires 272.1650.

Minor diastereomer (*endo*) **12b**: Yield 0.054 g (30%); $R_f$ 0.32 (20% EtOAc : petrol); $\nu_{max}$(film)/$cm^{-1}$ 1654s. 1419m, 764m; $\delta_H$(500 MHz; $CDCl_3$) 1.48–1.57 (1H, m, C(6)$H_{endo}$), 1.72–1.80 (1H, m, C(7)$H_{exo}$), 1.92–2.02 (1H, m, C(7)$H_{endo}$), 2.21–2.27 (1H, m, C(6)$H_{exo}$), 2.63–2.72 (3H, m, C(8)H and $CH_2$=CHC*H*), 2.02 (3H, s, C(2)Me), 3.39 (1H, dd, *J* 9.0 and 10.0, C(4)$H_{endo}$), 3.89–3.93 (1H, m, C(5)H), 4.11 (1H, dd, *J* 6.0 and 9.0, C(4)$H_{exo}$), 5.05–5.12 (2H, m, CH=C$H_2$), 5.82–5.89 (1H, m, C*H*=$CH_2$), 7.25–7.44 (5 H, m, ArH); $\delta_C$(125.8 MHz; $CDCl_3$) 23.2 (C(7)), 24.7 (C(6)), 25.6 (C(2)Me), 35.7 ($CH_2$=CH*C*$H_2$), 40.9 (C(8)), 56.7 (C(5)), 69.2 (C(4)), 96.0 (C(2)), 116.8 ($CH_2$CH=*C*$H_2$), 125.5, 127.8, 128.1 (ArCH), 136.5 ($CH_2$*C*H=$CH_2$), 142.1 (ArC), 170.4 (C(9)); *m*/*z* (APCI$^+$) 272 ($MH^+$, 100%); HRMS: 272.1644 ($MH^+$, CI). $C_{17}H_{21}NO_2$ requires 272.1650.

**(−)-(2*S*,5*S*)-1-Aza-8-dichloro-2-methyl-3-oxa-9-oxo-2-phenylbicyclo[4.3.0]nonane 10b, (+)-(2*S*,5*S*,8*S*)-1-aza-8-chloro-2-methyl-3-oxa-9-oxo-2-phenylbicyclo[4.3.0]nonane 13b and (−)-(2*S*,5*S*,8*R*)-1-aza-8-chloro-2-methyl-3-oxa-9-oxo-2-phenylbicyclo[4.3.0]nonane 13a**

To a solution of lactam **2d** (0.332 g, 1.4 mmol) in THF (20 ml) cooled to −78 °C under nitrogen was added s-BuLi (1.69 ml, 1.7 mmol). The solution was stirred for 15 minutes and allowed to warm slightly to −30 °C. The enolate was then transferred by syringe to a solution of tosyl chloride (0.410 g, 2.2 mmol) in THF (20 ml) cooled to −78 °C. After 1.5 h the reaction was quenched using sat. aq. $NH_4Cl$ (25 ml), and the mixture extracted with EtOAc (3 × 25 ml). The organic extracts were then dried with brine (25 ml) and over $MgSO_4$. Solvent was removed *in vacuo* and the residue separated by column chromatography on silica gel (40% EtOAc : petrol) to give two colourless oils **13b** (74 mg, 19%) and **13a** (123 mg, 32%).

Dichlorolactam **10b**: $R_f$ 0.32 (40% EtOAc : petrol); $[a]_D^{25}$ −75.5 (*c* 0.65, $CHCl_3$); $\nu_{max}$(film)/$cm^{-1}$ 1686s, 1495w, 1447m, 1422m, 1378m, 1325m, 1226m; $\delta_H$(500 MHz; $CDCl_3$) 2.08 (3H, s, C(2)Me), 2.09–2.18 (2H, m, C(6)H), 2.81–2.87 (1H, m, C(7)H), 3.06 (1H, dt, *J* 4.0 and 15.0, C(7)H), 3.59 (1H, dd, *J* 8.5 and 10.0, C(4)$H_{endo}$), 4.03–4.09 (1H, m, C(5)H), 4.12 (1H, dd, *J* 5.5 and 8.5, C(4)$H_{exo}$), 7.30–7.49 (5H, m, ArH); $\delta_C$(125.8 MHz; $CDCl_3$) 22.7 (C(6)), 25.0 (C(2)Me), 44.1 (C(7)), 58.2 (C(5)), 68.9 (C(4)), 83.3 (C(8)), 96.4 (C(2)), 125.4, 128.3 and 128.4 (ArCH), 140.5 (ArC), 160.2 (C(9)); *m*/*z* (APCI$^+$) 300.1 ($MH^+$, 100%), 301.9 ($MH^+$ $^{35}Cl$ $^{37}Cl$, 50%), 304 ($MH^+$ $^{37}Cl$ $^{37}Cl$), 266 (32), 232 (44), 180 (38), 146 (38), 122 (52); HRMS: 300.0559 ($MH^+$,CI). $C_{14}H_{15}NO_2Cl_2$ requires 300.0558.

Major diastereomer (*exo*) **13a**: $R_f$ 0.19 (40% EtOAc : petrol); $[a]_D^{25}$ −30.4 (*c* 0.58, $CHCl_3$); $\nu_{max}$(film)/$cm^{-1}$ 1666s, 1494w, 1446m, 1427m, 1371m, 1244m, 1222m; $\delta_H$(500 MHz; $CDCl_3$) 1.92–2.04 (2H, m, C(6)H and C(7)H), 2.05 (3H, s, C(2)Me), 2.30–2.41 (2H, m, C(6)H and C(7)H), 3.51 (1H, dd, *J* 8.5 and 10.5, C(4)$H_{endo}$), 3.84–3.90 (1H, m, C(5)H), 4.09 (1H, dd, *J* 5.5 and 8.5, C(4)$H_{exo}$), 4.45 (1H, dd, *J* 3.5 and 4.5, C(8)H), 7.27–7.59 (5H, m, ArH); $\delta_C$(125.8 MHz; $CDCl_3$) 20.3 (C(6)), 24.9 (C(2)Me), 31.4 (C(7)), 55.2 (C(5)), 57.9 (C(8)), 68.8 (C(4)), 95.6 (C(2)), 125.3, 128.1, 128.2 (ArCH), 140.8 (ArC), 163.1 (C(9)); *m*/*z* (APCI$^+$) 266 ($MH^+$, 11%), 268 ($MH^+$ $^{37}Cl$, 3), 232 (100); HRMS: 266.0948 ($MH^+$, CI). $C_{14}H_{16}NO_2Cl$ requires 266.0948.

Minor diastereomer (*endo*) **13b**: $R_f$ 0.28 (40% EtOAc : petrol); $[a]_D^{25}$ +47.2 (*c* 0.11, $CHCl_3$); $\nu_{max}$(film)/$cm^{-1}$ 1664s, 1494w, 1446m, 1426m, 1370m, 1325m, 1270m, 1211m, 1180m; $\delta_H$(500 MHz; $CDCl_3$) 1.59–1.68 (1H, m, C(6)H), 2.03 (3H, s, C(2)Me), 2.11–2.21 (2H, m, C(6)H and C(7)H), 2.45–2.52 (1H, m, C(7)H), 3.71 (1H, t, *J* 8.5, C(4)$H_{endo}$), 3.96–4.02 (1H, m, C(5)H), 4.18 (1H, dd, *J* 6.5 and 8.5, C(4)$H_{exo}$), 4.48 (1H, dd, *J* 6.0 and 8.0, C(8)H), 7.26–7.79 (5H, m, ArH); $\delta_C$(125.8 MHz; $CDCl_3$) 25.0 (C(6) and C(2)Me), 30.8 (C(7)), 55.7 and 55.9 (C(5) and C(8)), 69.9 (C(4)), 96.7 (C(2)), 125.5, 128.2, 128.2 (ArCH), 141.6 (ArC), 163.4 (C(9)); *m*/*z*(APCI$^+$) 266 ($MH^+$, 21%), 268 ($MH^+$, $^{37}Cl$, 7), 232 (100), 146 (94); HRMS: 266.0948 ($MH^+$,CI). $C_{14}H_{16}NO_2Cl$ requires 266.0948.

**(−)-(2*S*,5*S*,8*S*)-1-Aza-2-methyl-3-oxa-9-oxo-2-phenyl-8-phenylselenylbicyclo[4.3.0]nonane 14b and (−)-(2*S*,5*S*,8*R*)-1-aza-2-methyl-3-oxa-9-oxo-2-phenyl-8-phenylselenylbicyclo-[4.3.0]nonane 14a**

To a stirred flask of THF (20 ml) cooled to −78 °C under nitrogen was added s-BuLi (0.94 ml, 0.84 mmol). The lactam **2d** (0.13 g, 0.56 mmol) was then dissolved in THF (10 ml) and added slowly to the mixture using a syringe. The reaction was allowed to warm slightly to −30 °C. Phenylselenenyl chloride (0.16 g, 0.84 mmol) dissolved in THF (10 ml) was then added and the dark red colour of the anion disappeared. After 30 minutes the reaction was quenched with sat. aq. $NH_4Cl$ (25 ml). The aqueous layer was separated and extracted with EtOAc (3 × 25 ml). The organic extracts were then combined and dried with brine (25 ml) and over $MgSO_4$, and the solvent removed *in vacuo*. The residue was then separated by column chromatography on silica gel, eluting initially with 20% EtOAc : petrol and increasing the polarity to 40% EtOAc : petrol to give the products as two yellow oils.

Major diastereomer (*exo*) **14a**: Yield 71 mg (33%); $R_f$ 0.06 (20% EtOAc : petrol); $[a]_D^{25}$ −26.8 (*c* 0.37, $CHCl_3$); $\nu_{max}$(film)/$cm^{-1}$ 1652s, 1578w, 1494w, 1477w, 1447m, 1438m, 1423m, 1375m, 1322m; $\delta_H$(500 MHz; $CDCl_3$) 1.88–1.96 (1H, m, C(6)$H_{endo}$), 2.01–2.06 (1H, m, C(7)$H_{exo}$), 2.11 (3H, s, C(2)Me), 2.30–2.38 (2H, m, C(6)$H_{exo}$ and C(7)$H_{endo}$), 3.59 (1H, dd, *J* 8.5 and 10.5, C(4)$H_{endo}$), 3.93–3.99 (1H, m, C(5)H), 4.09 (1H, t, *J* 5.0, C(8)H), 4.15 (1H, dd, *J* 5.5 and 8.5, C(4)$H_{exo}$), 7.30–7.70 (10H, m, ArH); $\delta_C$(125.8 MHz; $CDCl_3$) 22.2 (C(6)), 25.0 (C(2)Me), 28.9 (C(7)), 43.5 (C(8)), 58.0 (C(5)), 69.2 (C(4)), 95.5 (C(2)), 125.6, 128.0, 128.2, 129.1 and 129.2 (ArCH), 131.57 (ArC), 141.4 (ArC), 166.6 (C(9)); *m*/*z* (APCI$^+$) 388 ($MH^+$, 100%), 386 (50); HRMS: 388.0820 ($MH^+$, CI). $C_{20}H_{21}NO_2Se$ requires 388.0815.

Minor diastereomer (*endo*) **14b**: Yield 41 mg (19%); $R_f$ 0.11 (20% EtOAc : petrol); $[\alpha]_D^{25}$ −120.5 (*c* 0.39, $CHCl_3$); $\nu_{max}$(film)/$cm^{-1}$ 1650s, 1416m, 1370m, 1322m, 1241m; $\delta_H$(500 MHz; $CDCl_3$) 1.53–1.60 (1H, m, C(6)$H_{endo}$), 2.00–2.14 (2H, m, C(6)$H_{exo}$ and C(7)$H_{exo}$), 2.02 (3H, s, C(2)Me), 2.41–2.46 (1H, m, C(7)$H_{endo}$), 3.44 (1H, dd, *J* 9.0 and 10.0, C(4)$H_{endo}$), 3.82–3.87 (1H, m, C(5)H), 4.03 (1H, t, *J* 7.5, C(8)H), 4.09 (1H, dd, *J* 6.0 and 9.0, C(4)$H_{exo}$), 7.28–7.71 (10H, m, ArH); $\delta_C$(125.8 MHz; $CDCl_3$) 25.1 (C(7) and C(2)Me), 29.0 (C(6)), 41.8 (C(8)), 56.6 (C(5)), 69.0 (C(4)), 96.5 (C(2)), 125.7, 127.9, 128.1, 128.4, 129.0 and 135.8 (Ar*C*H), 131.5 (ArC), 141.4 (ArC), 166.4 (C(9)); *m*/*z* ($APCI^+$) 388 ($MH^+$, 100%), 386 (51); HRMS: 388.0819 ($MH^+$, CI). $C_{20}H_{21}NO_2Se$ requires 388.0816.

### (+)-(2*S*,5*S*)-1-Aza-8,8-dibenzyloxycarbonyl-2-methyl-3-oxa-9-oxo-2-phenylbicyclo[4.3.0]nonane 16a, (2*S*,5*S*,8*S*) and (2*S*,5*S*,8*R*)-1-aza-8-benzyloxycarbonyl-2-methyl-3-oxa-9-oxo-2-phenylbicyclo[4.3.0]nonane 15a and 15b

To a solution of the lactam **2d** (1.59 g, 6.9 mmol) in THF (50 ml) at −78 °C under nitrogen was added s-BuLi (8.2 ml, 8.2 mmol). The mixture was stirred for 15 minutes and allowed to warm to −30 °C. The enolate solution was then transferred by cannula into a solution of benzyl chloroformate (2.34 g, 13.7 mmol) in THF (10 ml) at −78 °C. The reaction was stirred for three hours, and then quenched with sat. aq. $NH_4Cl$ (25 ml), extracted with EtOAc (3 × 30 ml), dried with brine (30 ml) and over $MgSO_4$, and solvent was removed *in vacuo*. Separation of the residue by flash column chromatography (20% EtOAc : petrol) on silica gel gave 0.335 g (10%) of the diacylated product and 1.128 g (45%) of a mixture of diastereomers of the monoacylated product. An improved purification method, whereby the residue was separated on an alumina column gave 9.17 g (72%) of a mixture of the diastereomers **15a**,**b**.

Diastereomeric mixture **15a**,**b**: $R_f$ 0.32 and 0.22 (40% EtOAc : petrol); $\nu_{max}$(film)/$cm^{-1}$ 1736s, 1655s, 1497w, 1430m, 1372m; $\delta_H$(500 MHz; $CDCl_3$) 1.51–1.59, 1.80–1.88, 1.96–2.01, 2.07–2.17, 2.20–2.34 (4H, m, C(6)H and C(7)H), 2.03 and 2.05 (3H, 2 × s, C(2)Me), 3.44 (1H, dd, *J* 8.5 and 10.0, C(4)$H_{endo}$ (B)), 3.46 (1H, dd, *J* 8.5 and 10.0, C(4)$H_{endo}$ (A)), 3.55 (1H, dd, *J* 2.0 and 9.5, C(8)H (B)), 3.56 (1H, dd, *J* 4.0 and 11.0, C(8)H (A)), 3.81–3.91 (1H, m, C(5)H), 4.08 (1H, dd, *J* 5.5 and 8.5, C(4)$H_{exo}$ (A)), 4.10 (1H, dd, *J* 6.0 and 8.5, C(4)$H_{exo}$ (B)), 5.16–5.26 (2H, m, $CO_2CH_2$), 7.24–7.51 (10H, m, ArH); $\delta_C$(125.8 MHz; $CDCl_3$) 22.5 (C(7) (A)), 24.3 (C(7) (B)), 25.0 (C(6) (B)), 25.1 (C(6) (A)), 25.1 (C(2)Me (A)), 25.2 (C(2)Me (B)), 48.1 (C(5) (A)), 50.0 (C(5) (B)), 57.1 (C(8) (A)), 57.7 (C(8) (B)), 66.8 (C(4) (B)), 67.1 (C(4) (A)), 68.7 ($CO_2CH_2$ (A)), 69.1 ($CO_2CH_2$ (B)), 96.2 (C(2) (A)), 96.3 (C(2) (B)), 125.6, 127.9, 128.0, 128.1, 128.2, 128.5, 128.5 (Ar*C*H), 135.5 (ArC), 140.9 ($CH_2CO_2C$ (A)), 141.3 ($CH_2CO_2C$ (B)), 163.3 (C(9)), 170.6 (*C*=O, (B)), 170.9 (*C*=O (A)); *m*/*z* ($APCI^+$) 366 ($MH^+$, 100%), 246 (27), 156 (27); HRMS: 366.1711 ($MH^+$,CI). $C_{22}H_{23}NO_4$ requires 366.1705.

Diacylated lactam **16a**: $R_f$ 0.53 (40% EtOAc : petrol); $[\alpha]_D^{25}$ +46.0 (*c* 2.1, $CHCl_3$); $\nu_{max}$(film)/$cm^{-1}$ 1732s, 1673s, 1221s; $\delta_H$(500 MHz; $CDCl_3$) 1.55–1.63 (1H, m, C(6)$H_{endo}$), 1.93–2.00 (1H, m, C(6)$H_{exo}$), 1.98 (3H, s, C(2)Me), 2.60–2.70 (2H, m, C(7)H), 3.38 (1H, dd, *J* 8.5 and 10.0, C(4)$H_{endo}$), 3.58–3.67 (1H, m, C(5)H), 4.04 (1H, dd, *J* 5.5 and 8.5, C(4)$H_{exo}$), 5.15–5.32 (4H, m, 2 × $CO_2CH_2$), 7.24–7.52 (15H, m, ArH); $\delta_C$(125.8 MHz; $CDCl_3$) 22.1 (C(6)), 25.3 (C(2)Me), 28.3 (C(7)), 56.3 (C(5)), 64.6 (C(8)), 67.9 and 68.1 (2 × $CH_2$Ph), 69.4 (C(4)), 96.7 (C(2)), 125.6, 127.9, 128.1, 128.2, 128.4, 128.5 (Ar*C*H), 134.9 and 135.1 (2 × ArC), 162.3 (C(9)), 167.5, 167.6 (C=O); *m*/*z* ($APCI^+$) 500 ($MH^+$, 100%); HRMS: 500.2070 ($MH^+$,CI). $C_{30}H_{29}NO_6$ requires 500.2073.

### (+)-(2*R*,5*S*,8*S*)-1-Aza-2-methyl-8-methyl-3-oxa-9-oxo-2-phenylbicyclo[4.3.0]nonane 17b

To a solution of the lactam **2e** (0.21 g, 0.90 mmol) in THF (10 ml) cooled to −78 °C under nitrogen was added sBuLi (1.1 ml, 0.99 mmol). The reaction mixture was stirred for 30 minutes, and then methyl iodide (0.07 ml, 1.1 mmol) was added by syringe. The reaction mixture was stirred for 30 minutes, and then allowed to return to room temperature, and quenched with sat. aq. $NH_4Cl$ (25 ml). The biphasic system was then 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 on silica gel, eluting with 40% EtOAc : petrol to yield the title compound **17b** as a colourless oil (0.102 g, 46%). $R_f$ 0.33 (40% EtOAc : petrol); $[\alpha]_D^{25}$ +126.1 (*c* 0.53, $CHCl_3$); $\nu_{max}$(film)/$cm^{-1}$ 2937m, 1648s, 1420m, 1324m, 1237m, 1028m; $\delta_H$(400 MHz; $CDCl_3$) 1.26 (3H, d, *J* 7.0, C(8)Me), 1.58–1.67 (2H, m, C(6)H and C(7)H), 1.94–2.11 (2H, m, C(6)H and C(7)H), 2.03 (3H, s, C(2)Me), 2.44–2.48 (1H, m, C(8)H), 3.71–3.80 (2H, m, C(5)H and C(4)$H_{endo}$), 4.15 (1H, dd, *J* 5.5 and 7.5, C(4)$H_{exo}$), 7.28–7.57 (5H, m, ArH); $\delta_C$(100.6 MHz; $CDCl_3$) 17.5 (C(8)Me), 24.4 (C(6)), 25.6 (C(8)Me), 27.5 (C(7)), 35.9 (C(8)), 56.5 (C(5)), 69.8 (C(4)), 96.3 (C(2)), 125.6, 128.0 and 128.1 (Ar*C*H), 142.6 (Ar*C*), 171.4 (C(9)); *m*/*z* ($APCI^+$) 246 ($MH^+$); HRMS: 246.1490 ($MH^+$, CI). $C_{15}H_{19}NO_2$ requires 246.1494.

### (+)-(2*R*,5*S*,8*R*)-1-Aza-8-benzyl-2-methyl-3-oxa-9-oxo-2-phenylbicyclo[4.3.0]nonane 18b and (+)-(2*R*,5*S*,8*S*)-1-aza-8-benzyl-2-methyl-3-oxa-9-oxo-2-phenylbicyclo[4.3.0]nonane 18a

To a solution of the lactam **2e** (0.21 g, 0.90 mmol) in THF (10 ml) cooled to −78 °C under nitrogen was added s-BuLi (1.1 ml, 0.99 mmol). The reaction mixture was stirred for 30 minutes, and then a solution of benzyl bromide (0.18 g, 1.08 mmol) in THF (20 ml) was added by syringe. The reaction mixture was stirred for 30 minutes, and then allowed to return to room temperature, and quenched with sat. aq. $NH_4Cl$ (25 ml). The biphasic system was then 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 on silica gel, eluting initially with 20% EtOAc : petrol and increasing the polarity to 40% EtOAc : petrol to yield the title compounds as two colourless oils.

Major diastereomer (*exo*) **18a**: Yield 48 mg (16%); $R_f$ 0.48 (40% EtOAc : petrol); $[\alpha]_D^{25}$ +25.0 (*c* 1.4, $CHCl_3$); $\nu_{max}$(film)/$cm^{-1}$ 3503w, 1645s, 1495w, 1446w, 1421m, 1377w, 1319w, 1230w, 1077w; $\delta_H$(400 MHz; $CDCl_3$) 1.36–1.57 (2H, m, C(6)$H_{endo}$ and C(7)$H_{exo}$), 1.86–1.92 (1H, m, C(7)$H_{endo}$), 1.97–2.02 (1H, m, C(6)$H_{exo}$), 2.10 (3H, s, C(2)Me), 2.62–2.70 (1H, m, C(8)H), 2.90 (1H, dd, *J* 8.5 and 13.5, PhC*H*), 3.23 (1H, dd, *J* 4.0 and 13.5, PhC*H*), 3.62–3.69 (2H, m, C(5)H and C(4)$H_{endo}$), 4.18 (1H, m, C(4)$H_{exo}$), 7.10–7.55 (10H, m, ArH); $\delta_C$(100.6 MHz; $CDCl_3$) 24.4 (C(2)Me), 26.0 (C(7)), 26.3 (C(6)), 37.4 (Ph*C*H), 43.9 (C(8)), 58.1 (C(5)), 70.2 (C(4)), 96.2 (C(2)), 126.2, 126.3, 128.1, 128.3 and 129.5 (Ar*C*H), 139.5 (ArC), 142.2 (ArC), 168.8 (C(9)); *m*/*z* ($APCI^+$) 344 (M + $NH_4^+$, 100%); HRMS: 322.1815 ($MH^+$, $ES^+$). $C_{21}H_{23}NO_2$ requires 322.1807.

Minor diastereomer (*endo*) **18b**: Yield 27 mg (9%); $R_f$ 0.58 (40% EtOAc : petrol); $[\alpha]_D^{25}$ +134.6 (*c* 1.2, $CHCl_3$); $\nu_{max}$(film)/$cm^{-1}$ 1647s, 1496w, 1420m, 1370m, 1320w, 1238m; $\delta_H$(400 MHz; $CDCl_3$) 1.38–1.48 (1H, m, C(6)$H_{endo}$), 1.64–1.71 (1H, m, C(7)$H_{endo}$), 1.73–1.81 (1H, m, C(7)$H_{exo}$), 1.82–1.89 (1H, m, C(6)$H_{exo}$), 2.07 (3H, s, C(2)Me), 2.58–2.65 (1H, m, C(8)H), 2.73 (1H, dd, *J* 10.0 and 13.5, PhC*H*), 3.32 (1H, dd, *J* 4.0 and 13.5, PhC*H*), 3.67 (1H, t, *J* 8.0, C(4)$H_{endo}$), 3.72–3.79 (1H, m, C(5)H), 4.16 (1H, dd, *J* 6.0 and 8.0, C(4)$H_{exo}$), 7.19–7.61 (10H, m, ArH); $\delta_C$(100.6 MHz; $CDCl_3$) 23.7 (C(7)), 23.9 (C(6)), 25.2 (C(2)Me), 37.7 (Ar*C*$H_2$), 56.7 (C(5)), 69.9 (C(4)), 96.3 (C(2)), 125.8, 126.3, 128.1, 128.4 and 129.2 (ArCH), 139.9 ($CH_2$*C*Ar),

142.4 (ArC), 170.2 (C(9)); *m/z* (APCI$^+$) 344 (M + $NH_4^+$, 100%), 229 (23), 202 (18); HRMS: 322.1811 ($MH^+$, ES$^+$). $C_{21}H_{23}NO_2$ requires 322.1807.

**(2*S*,5*S*,8*RS*)-1-Aza-8-benzyl-8-benzyloxycarbonyl-2-methyl-3-oxa-9-oxo-2-phenylbicyclo[4.3.0]nonane 16b**

Prewashed sodium hydride (8 mg, 0.34 mmol) was suspended in THF (10 ml) and cooled to 0 °C under nitrogen. A solution of lactams **15a**,**b** (0.11 g, 0.31 mmol) in THF (5 ml) was then added, and the mixture stirred for 45 minutes. Benzyl bromide (58 mg, 0.34 mmol) was then added, and the reaction stirred for four hours, until TLC indicated that no starting material was present. The reaction was then quenched with 50 ml 1 : 1 EtOAc : sat. aq. $NH_4Cl$, extracted with EtOAc (3 × 30 ml), dried with brine (25 ml) and over $MgSO_4$, and the solvent removed *in vacuo*. The residue was separated by flash column chromatography on silica gel, eluting with 20% EtOAc : petrol to give **16b** as an inseparable mixture of diastereomers (77 mg, 55%); $R_f$ 0.23 and 0.18 (20% EtOAc : petrol); $\nu_{max}$(film)/cm$^{-1}$ 1740s, 1653s, 1496w, 1423m, 1370m, 1323w, 1223m; $\delta_H$(500 MHz; $CDCl_3$) 0.93–1.01(1 H, m, C(6)$H_{endo}$), 1.78–1.84(1 H, m, C(7)$H_{exo}$), 1.97–2.06 (1 H, m, C(7)$H_{endo}$) and 2.26–2.33 (1 H, m, C(7)$H_{exo}$), 2.96 (1H, d, *J* 13.5, PhC*H* (B)), 3.24 (1H, d, *J* 13.5, PhC*H* (A)), 3.31 (1H, dd, *J* 8.5 and 9.5, C(4)$H_{endo}$ (A)), 3.37 (1H, t, *J* 8.5, C(4)$H_{endo}$ (B)), 3.47 (1H, d, *J* 13.5, PhC*H* (A)), 3.62–3.69 (1H, m, C(5)H), 3.79 (1H, d, *J* 13.5, PhC*H* (B)), 3.82 (1H, dd, *J* 6.5 and 8.5, C(4)$H_{exo}$ (B)), 4.00 (1H, dd, *J* 6.0 and 8.5, C(4)$H_{exo}$ (A)), 5.10 (1H, d, *J* 12.5, $CO_2CH_2$ (B)), 5.19 (1H, d, *J* 12.0, $CO_2CH_2$ (A)), 5.23 (1H, d, *J* 12.0, $CO_2CH_2$ (A)), 5.34 (1H, d, *J* 12.5, $CO_2CH_2$ (B)), 7.06–7.51 (15H, m, ArH); $\delta_C$(125.8 MHz; $CDCl_3$) 22.9 (C(7) (B)), 23.2 (C(7) (A)), 24.5 (C(2)Me), 29.3 (C(6) (A)), 29.8 (C(6) (B)), 40.5 (Ph*C*H (B)), 41.0 (Ph*C*H (A)), 55.8 (C(5) (A)), 55.9 (C(5) (B)), 67.3 ($CO_2CH_2$(A)), 68.2 ($CO_2CH_2$ (B)), 69.8 (C(4)), 96.2 (C(2)), 125.6, 125.9, 126.8, 127.0, 127.9, 128.1, 128.3, 128.4, 128.5, 128.6, 130.3, 130.5, 131.1 (Ar*C*H), 135.3 (ArC), 136.5 (ArC), 141.6 (ArC), 166.1 (C(9)), 172.0 (*C*=O); *m/z* (APCI$^+$) 456 ($MH^+$, 100%); HRMS: 456.2178 ($MH^+$, APCI$^+$). $C_{29}H_{29}NO_4$ requires 456.2175.

**(2*S*,5*S*,8*RS*)-1-Aza-8-benzyloxycarbonyl-2-methyl-3-oxa-9-oxo-2-phenyl-8-phenylselenylbicyclo[4.3.0]nonane 16c**

Prewashed sodium hydride (29 mg, 1.2 mmol) was suspended in THF (10 ml) and cooled to 0 °C under nitrogen. The lactam **15a**,**b** (0.29 g, 0.80 mmol) was dissolved in THF (5 ml) and added to the reaction mixture. This mixture was then stirred for 1 hour, after which phenylselenenyl chloride (0.17 g, 0.88 mmol) in THF (5 ml) was added. The reaction was monitored by TLC and quenched after 5 hours by the addition of 50 ml 1 : 1 EtOAc : sat. aq. $NH_4Cl$. The mixture was then extracted with EtOAc (3 × 25 ml), dried with brine (25 ml) and over $MgSO_4$, and solvent was removed *in vacuo*. The residue was then separated on silica gel eluting with 20% EtOAc : petrol to give the products **16c** in an inseparable diastereomeric mixture (0.29 g, 70%); $R_f$ 0.23 and 0.18 (20% EtOAc : petrol); $\nu_{max}$(film)/cm$^{-1}$ 1736s, 1655, 1438m, 1246m; $\delta_H$(500 MHz; $CDCl_3$) 1.47–1.56 (1H, m, C(6)$H_{endo}$), 1.81–1.88 (1H, m, C(7)$H_{exo}$), 2.13–2.33 (1H, m, C(7)$H_{endo}$), 2.25–2.53 (1 H, m, C(6)$H_{exo}$), 1.96 (3H, s, C(2)Me (A)), 1.99 (3H, s, C(2)Me (B)), 3.31 (1H, t, *J* 8.5, C(4)$H_{endo}$ (A)), 3.37 (1H, dd, *J* 4.5 and 7.0, C(4)$H_{endo}$ (B)), 3.42–3.50 (1H, m, C(5)H), 3.93 (1H, dd, *J* 4.0 and 7.0, C(4)$H_{exo}$ (B)), 3.98 (1H, dd, *J* 6.0 and 8.5, C(4)$H_{exo}$ (A)), 5.15 (1H, d, *J* 12.0, $CO_2CH_2$ (A)), 5.23 (2H, s, $CO_2CH_2$), 5.33 (1H, d, *J* 12.0, $CO_2CH_2$), 7.12–7.68 (15H, m, ArH); $\delta_C$(125.8 MHz; $CDCl_3$) 23.2 (C(6) (A)), 24.0 (C(6) (B)), 24.8 (C(2)Me (B)), 25.7 (C(2)Me (A)), 30.5 (C(7) (A)), 24.8 (C(7) (B)), 55.4 (C(5) (A)), 56.9 (C(8) (A)), 57.9 (C(5) (B)), 60.4 (C(8) (B)), 67.7 ($CO_2CH_2$ (A)), 67.9 ($CO_2CH_2$ (B)), 68.7 (C(4) (B)), 69.5 (C(4) (A)), 96.6 (C(2) (B)), 96.9 (C(2) (A)), 125.5, 125.8, 126.1, 126.5, 126.6, 127.9, 128.1, 128.3, 128.5, 128.5, 128.6, 128.7, 128.8, 128.9, 129.2, 129.6, 129.7 (Ar*C*H), 135.2, 138.3, 138.4, 140.9, 141.9 (ArC), 163.3 (C(9) (B), 164.7 ((C(9) (A)), 169.4 (*C*=O (A)), 170.7 (*C*=O (B)); *m/z* (APCI$^+$) 522 ($MH^+$, 100%), 520 (62), 366 (57); HRMS: 522.1181 ($MH^+$, APCI$^+$). $C_{28}H_{27}NO_4{}^{80}Se$ requires 522.1184.

**(2*R*,5*S*,8*R*)- and (2*R*,5*S*,8*S*)-1-Aza-8-benzyloxycarbonyl-2-methyl-3-oxa-9-oxo-2-phenylbicyclo[4.3.0]nonane 19a,b and (+)-(2*R*,5*S*)-1-aza-8-dibenzyloxycarbonyl-2-methyl-3-oxa-9-oxo-2-phenylbicyclo[4.3.0]nonane 20a**

To a solution of the lactam **2e** (1 eq) in THF (50 ml) at −78 °C under an inert atmosphere was added *sec*-BuLi (1.15 eq). The mixture was stirred for 15 minutes and allowed to warm to −30 °C. The enolate solution was then transferred by cannula into a solution of the benzyl chloroformate (1.2 eq) in THF (10 ml) at −78 °C. The reaction was stirred for 3 hours, and then quenched with saturated $NH_4Cl$ (aq) (25 ml). The aqueous layer was extracted with EtOAc (3 × 30 ml), washed with brine (30 ml), dried ($MgSO_4$), and the solvent removed *in vacuo*. Purification by flash column chromatography (20% EtOAc : petrol) on silica gel gave the diacylated product **20a** as a brown oil (25–46%) and the monoacylated product as an inseparable mixture of two diastereomers **19a**,**b** in a 1 : 1 ratio and 6–14% yield (estimated from $^1$H-NMR spectrum) along with 25–46% of unreacted starting material. The yield of the monoacyl adduct could be improved to 36–50% by using benzyl cyanoformate.

Monoacylated diastereomers **19a**,**b**; $R_f$ 0.23 (40% EtOAc : petrol); $\nu_{max}$(film)/cm$^{-1}$ 1738s, 1659s, 1265s; $\delta_H$(500 MHz; $C_6D_6$) 0.47–0.54 (1 H, m, C(6)$H_{endo}$ (A)), 0.83–0.87 (1 H, m, C(6)$H_{exo}$, (B)), 0.92–0.99 (1 H, m, C(6)$H_{exo}$ (A)), 1.12–1.20 (2 H, m, C(6)$H_{endo}$, C(7)$H_{exo}$ (B)), 1.41–1.48 (1 H, m, C(7)$H_{endo}$ (A)), 1.64–1.72 (2 H, m, C(7)$H_{exo}$(A), C(7)$H_{endo}$ (B)), 1.93, 1.95 (3 H, 2 × s, Me), 2.78 (1 H, dd, *J* 8.5, 10.0, C(4)$H_{endo}$ (A)), 2.84 (1 H, dd, *J* 8.0, 10.0, C(4)$H_{endo}$ (B)), 2.88–2.91 (1 H, m, C(5)H (B)), 3.08–3.10 (1 H, m, C(5)H (A)), 3.12 (1 H, dd, *J* 4.0, 7.0, C(8)H (B)), 3.15 (1 H, dd, *J* 7.5, 10.0, C(8)H (A)), 3.24–3.30 (2H, m, C(4)$H_{exo}$), 4.78–4.90 (4H, m, PhC$H_2$O), 6.82–7.51 (20H, m, ArCH); $\delta_C$(100.6 MHz $C_6D_6$) 21.2 (C(6) (B)), 22.8 (C(6) (A)), 23.6 (C(7) (A)), 24.1 (C(7) (B)), 24.5, 24.5, (2 × Me), 47.2 (C(8) (B)), 49.0 (C(8) (A)), 55.9 (C(5) (A)), 56.2 (C(5) (B)), 65.6, 65.6 (2 × Ph*C*$H_2$O), 67.3, 67.6 (2 × C(4), 94.7, 95.1 (2 × C(2)), 124.8, 125.0, 125.1, 126.5, 126.7, 126.7, 126.9, 126.9, 127.0, 127.0, 127.1, 127.1, 127.1, 127.2, 127.3, 127.3 (ArCH), 134.5, 135.0, 141.1, 141.2 (ArC), 161.9, 162.1 (2 × CON), 169.5, 169.7 (2 × PhC$H_2$O*C*O); *m/z* (APCI$^+$) 366 ($MH^+$ 100%), 232 (15), 112 (50); HRMS: 366.1710 ($MH^+$). $C_{22}H_{24}NO_4$ requires 366.1705.

Lactam **20a**: $R_f$ 0.53 (40% EtOAc : petrol); $[\alpha]_D^{23}$ +86.9 (*c* 1.0, $CHCl_3$); $\nu_{max}$(film)/cm$^{-1}$ 1735s, 1670s, 1455s; $\delta_H$(400 MHz; $CDCl_3$) 1.47–1.56 (1 H, m, C(6)$H_{endo}$), 1.93–2.01 (1 H, m, C(6)$H_{exo}$), 2.02 (3 H, s, Me), 2.50–2.58 (1 H, m, C(7)$H_{exo}$), 2.60–2.68 (1 H, m, C(7)$H_{endo}$), 3.57–3.64 (2 H, m, C(4)$H_{endo}$ and C(5)H), 4.01–4.06 (1 H, m, C(4)$H_{exo}$), 5.15–5.34 (4 H, m, 2 × PhC$H_2$O), 7.24–7.54 (15 H, m, ArCH); $\delta_C$(100.6 MHz; $CDCl_3$) 22.3 (C(6)), 25.4 (Me), 28.4 (C(7)), 56.3 (C(5)), 64.3 (C(8)), 67.9, 68.1 (2 × *C*$H_2$Ph), 69.9 (C(4)), 97.2 (C(2)), 125.6, 127.9, 128.1, 128.3, 128.4, 128.5, 128.6 (ArCH), 134.9, 135.2, 141.9 (ArC), 161.7 (CON), 167.7, 167.8 (2 × PhC$H_2$O*C*O); *m/z* (APCI$^+$) 500 ($MH^+$ 20%); HRMS: 500.2078 ($MH^+$). $C_{30}H_{30}NO_6$ requires 500.2073.

**(2*R*,5*S*,8*R*) and (2*R*,5*S*,8*S*)-1-Aza-8-benzyloxycarbonyl-2-methyl-3-oxa-9-oxo-2-phenyl-8-phenylselenylbicyclo[4.3.0]-nonane 20b**

Prewashed sodium hydride (1.5 eq.) was suspended in THF (5 ml) and cooled to 0 °C under an inert atmosphere. A solution of lactam **19a** (160 mg, 0.44 mmol) in THF (5 ml) was then added. After stirring for 1 hour at 0 °C, phenylselenyl chloride (92 mg, 0.48 mmol) in THF (5 ml) was added dropwise *via* cannula. The reaction was then stirred for 5 hours at 25 °C

before it was quenched with 1 : 1 saturated $NH_4Cl$ (aq) : EtOAc (20 ml) The aqueous layer was washed with EtOAc (3 × 10 ml) and the organic fractions were combined, washed with brine (10 ml), dried ($MgSO_4$) and solvent removed *in vacuo*. The residue was then purified by flash column chromatography on silica gel, eluting with 20% EtOAc : petrol. Purification by flash column chromatography yielded the product **20b** as a 1.6 : 1.0 ratio of diastereomers in 66% overall yield.

Major diastereomer: $R_f$ 0.25 (20% EtOAc : petrol); $[a]_D^{23}$ −12.7 (*c* 0.7, $CHCl_3$); $\nu_{max}$(film)/$cm^{-1}$ 1724s, 1656s, 1421s, 1256s, 1236s; $\delta_H$(500 MHz; $CDCl_3$) 1.42–1.50 (1 H, m, C(6)$H_{endo}$), 1.84–1.88 (1 H, m, C(6)$H_{exo}$), 2.02 (3 H, s, Me), 2.04–2.13 (1 H, m, C(7)$H_{endo}$), 2.34–2.38 (1 H, m, C(7)$H_{exo}$), 3.49–3.58 (1 H, m, C(4)$H_{endo}$ and C(5)H), 4.16–4.20 (1 H, m, C(4)$H_{exo}$), 5.26 (1 H, d, *J* 12.0, PhC*H*), 5.37 (1 H, d, *J* 12.0, PhC*H*), 7.17–7.66 (15 H, m, ArC*H*); $\delta_C$(125.7 MHz; $CDCl_3$) 24.2 (Me), 24.6 (C(6)), 33.6 (C(7)), 55.3 (C(8)), 57.4 (C(5)), 67.9 (*C*$H_2$Ph), 70.0 (C(4)), 96.6 (C(2)), 126.0, 126.6, 128.1, 128.2, 128.4, 128.5, 128.8, 129.3 (ArCH), 135.3, 138.1, 141.9 (ArC), 163.4 (CO), 170.8 (PhC$H_2$O*C*); *m*/*z*(APCI$^+$) 524 ($MH^+$, 30%), 524 ($MH^+$, 20), 522 ($MH^+$, 50), 522 ($MH^+$, 100), 520 ($MH^+$, 60), 518 ($MH^+$, 30), 232 (30); HRMS: 522.1177 ($MH^+$, CI). $C_{28}H_{28}N^{80}SeO_4$ requires 522.1184.

Minor diastereomer: mp 110 °C; $R_f$ 0.31 (20% EtOAc : petrol); $[a]_D^{23}$ +79.4 (*c* 1.1, $CHCl_3$); Found: C, 64.5; H, 5.3; N, 2.5. $C_{28}H_{27}N^{80}SeO_4$ requires C, 64.5; H, 5.3; N, 2.5%; $\nu_{max}$(film)/$cm^{-1}$ 1724s, 1661s, 1417s, 1374s, 1261s; $\delta_H$(500 MHz; $CDCl_3$) 1.72–1.78 (1 H, m, C(6)$H_{endo}$), 1.88–1.98 (1 H, m, C(6)$H_{exo}$), 2.08 (3 H, s, Me), 2.10–2.18 (1 H, m, C(7)$H_{endo}$), 2.35–2.41 (1 H, m, C(7)$H_{exo}$), 3.35–3.40 (1 H, m, C(5)H), 3.70–3.73 (1 H, m, C(4)$H_{endo}$), 3.92–3.95 (1 H, m, C(4)$H_{exo}$), 5.20 (1 H, d, *J* 12.0, PhC*H*), 5.24 (1 H, d, *J* 12.0, PhC*H*), 7.24–7.67 (15 H, m, ArCH); $\delta_C$(125.7 MHz; $CDCl_3$) 25.2 (C(6)), 26.4 (Me), 29.9 (C(7)), 54.5 (C(5)), 56.8 (C(8)), 67.9 (*C*$H_2$Ph), 69.4 (C(4)), 97.5 (C(2)), 125.5, 126.6, 128.1, 128.2, 128.4, 128.5, 128.8, 129.6 (ArCH), 135.0, 138.3, 141.8 (ArC), 164.4 (CO), 169.7 (PhC$H_2$O*C*); *m*/*z* (APCI$^+$) 524.3 ($MH^+$, 20%), 524 ($MH^+$, 30), 522 ($MH^+$, 40), 522 ($MH^+$, 100), 520 ($MH^+$, 60), 518 ($MH^+$, 20), 232 (30); HRMS: 522.1173 ($MH^+$, CI). $C_{28}H_{28}N^{80}SeO_4$ requires 522.1184.

### (−)-(2*S*, 5*S*)-5-Benzyl-2-hydroxymethyl-6-piperidinone 21a

To a solution of lactam **9a** (0.016 g, 0.05 mmol) in DCM (10 ml) was added TFA (0.5 ml). The reaction mixture was stirred for 30 minutes, at which point TLC analysis indicated that no starting material was present. Solvent was removed *in vacuo*, and the residue separated by flash column chromatography (10% MeOH : EtOAc) to give the product **21a** as a colourless oil (8 mg, 73%); $R_f$ 0.37 (10% MeOH : EtOAc); $[a]_D^{25}$ −6.96 (*c* 0.23, $CHCl_3$); $\nu_{max}$(film)/$cm^{-1}$ 3554br, 1641s, 1454m; $\delta_H$(500 MHz; $CDCl_3$) 1.27–1.35 (1H, m, C(3)H), 1.41–1.54 (1H, m, C(3)H), 1.78–1.82 (2H, m, C(4)H), 2.47–2.53 (1H, m, C(5)H), 2.60 (1H, br, O*H*), 2.69 (1H, dd, *J* 10.0 and 13.5, PhC$H_2$), 3.42–3.56 (3H, m, C(2)H, PhC$H_2$, CHOH), 3.69 (1H, dd, *J* 3.0 and 11.0, CHOH), 7.12 (1H, br, N*H*), 7.20–7.33 (5H, m, ArH); $\delta_C$(125.8 MHz; $CDCl_3$) 24.3 (C(3)), 25.1 (C(4)), 37.2 (Ph*C*$H_2$), 42.8 (C(5)), 55.1 (C(2)), 66.3 (C(2)*C*$H_2$), 126.2, 128.4, 129.2 (Ar*C*H), 139.6 (ArC), 174.7 (C(6)); *m*/*z* (APCI$^+$) 220 ($MH^+$,100%); HRMS: 220.1338 (CI). $C_{13}H_{17}NO_2$ requires 220.1338.

### (+)-(2*S*)-5,5-Di(benzyloxycarbonyl)-2-hydroxymethyl-6-piperidinone 21b

To a solution of lactam **16a** (0.08 g, 0.16 mmol) in DCM (20 ml) was added TFA (2 ml). The reaction mixture was stirred for five hours at room temperature, solvent was removed *in vacuo*, and the residue separated by flash column chromatography, eluting with EtOAc to give the product **19b** as a colourless oil (47 mg, 74%); $R_f$ 0.32 (EtOAc); $[a]_D^{25}$ +7.52 (*c* 0.63 in $CHCl_3$); $\nu_{max}$(film)/$cm^{-1}$ 3348br, 1732s, 1673s, 1498w, 1456m, 1379w, 1647w, 1322w, 1271m, 1222m 1186m, 1090m; $\delta_H$(500 MHz; $CDCl_3$) 1.26–1.35 (1 H, m, C(3)H), 1.71–1.77 (1H, m, C(3)H), 2.39 (1H, dt, *J* 3.5 and 13.5, C(4)H), 2.53 (1H, ddd, *J* 3.5, 5.5 and 13.5, C(4)H), 2.92 (1H, br, O*H*), 3.29 (1H, dd, *J* 8.0 and 12.0, $OCH_2$), 3.50–3.55 (2H, m, $OCH_2$and C(2)H), 5.22 (4H, s, 2 × $CO_2CH_2$), 7.28–7.37 (10H, m, ArH), 7.45 (1H, br, N*H*); $\delta_C$(125.8 MHz; $CDCl_3$) 20.5 (C(3)), 27.4 (C(4)), 54.5 (C(2)), 63.2 (C(5)), 65.3 (O*C*$H_2$), 67.9, 68.0 (2 × $CO_2CH_2$), 128.0, 128.2, 128.3, 128.4, 128.5 (Ar*C*H), 135.0, 135.1 (ArC), 166.3 (C(6)) 167.4, 167.8 (2 × *C*=O); *m*/*z* (APCI$^+$) 398 ($MH^+$, 100%), 156 (41); HRMS: 398.1613 ($MH^+$,$CI^+$). $C_{23}H_{23}NO_6$ requires 398.1604.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