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Functionalised Pyrrolidinones Derived from *(S)*-Pyroglutamic Acid by Cycloaddition Reactions

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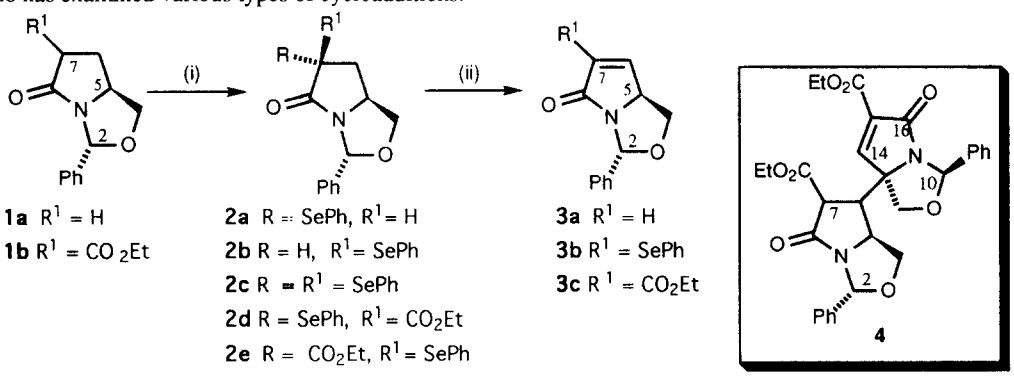
Abstract: The α,β-unsaturated bicyclic lactams **3a,c**, prepared from *(S)*-pyroglutamic acid, are useful substrates for cycloaddition reactions, giving excellent regio- and diastereocontrol; however, lactam **3c** has very superior reactivity with several dienes and dipoles under mild reaction conditions.

We have recently been interested in the development of methodology for the convenient synthesis of functionalised pyrrolidinones, since this class of compounds has potent and wide-ranging biological activity.[1,2] Our initial investigations have examined the hemiaminal ethers **1a,b** derived from pyroglutaminol[3,4] for alkylations at C-7 *via* the lactam enolate,[5,6] and similar work by other groups has been reported.[7-12] We report here the application of the enones **3a-c** to cycloaddition reactions, since this allows the simultaneous functionalisation at C-6 and C-7.[13] A related bicyclic system has been investigated exhaustively by Meyers,[14] who has examined various types of cycloadditions.[15-17]



(i) LDA for **1a** or NaH for **1b**, then PhSeCl; (ii) H_2O_2 or MCPBA, CH_2Cl_2

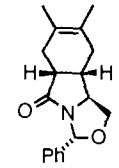
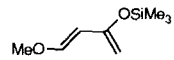
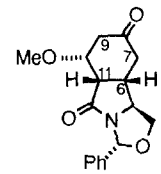
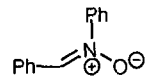
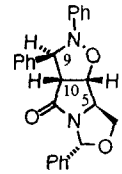
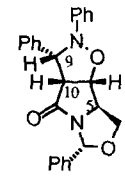
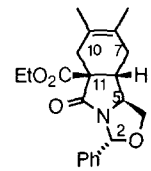
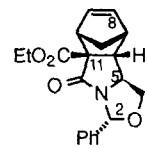
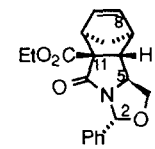
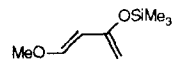
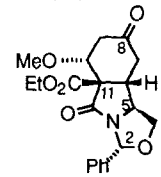
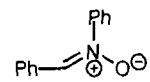
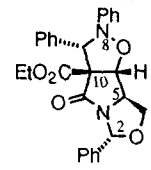
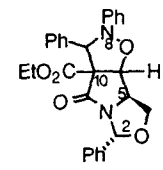
Scheme 1

Unsaturated lactams **3a-c** were readily available from the corresponding lactams **1a,b** by selenenation[6] to **2** followed by oxidation and elimination under standard conditions (H_2O_2 in dichloromethane (for **2a,b,d,e**) or MCPBA in dichloromethane (for **2c**)) (Scheme 1).[18] Although the enone **3a** was found to be very stable, enone **3c** was much less so, and could not be satisfactorily purified by column chromatography, returning

material contaminated with dimer **4**, which was a single diastereomer, but of unassigned stereochemistry. This self-condensation product arises by conjugate addition at C-6 by a second molecule through C-5; analogous conjugate additions of enone **3c** by a range of carbon nucleophiles has recently been reported.[19] The structure of **4** was established by careful ^{1}H, ^{13}C and COSY analysis, which showed the expected downfield vinylic chemical shifts (δ_H7.79 and δ_C133.5) of H-14 and C-14; H-14 was also clearly uncoupled. Similar dimerisation of other α,β-unsaturated lactams have been reported, with the same[20, 21] or different[22] regiochemistry. This same compound was formed when enone **3c** was stored for extended periods of time, and also when **3c** was treated with magnesium bromide etherate. However, by subjecting a carefully purified mixture of selenides **2d,e** to the elimination reaction, it was possible to obtain good quality enone **3c** which did not require further purification if used immediately.

The reactions of these compounds with a number of dienes and 1,3-dipoles were then investigated (Table 1). There have been some earlier reports of cycloadditions in related α,β-unsaturated lactams derived from pyroglutamic acid.[23-25] We found that the enone **3a** was in general relatively inert, and the reaction with 2,3-dimethyl-1,3-butadiene in refluxing toluene or xylene returned starting material only. However, under extremely forcing (high pressure) conditions, adduct **5** was obtained in excellent yield. The *exo*-stereochemistry of this product was later unequivocally established by correlation with an authentic sample (*vide infra*). 1-Methoxy-3-(trimethylsilyloxy)-1,3-butadiene[26-28] gave a low yield of the adduct **6**, and the use of a large excess of reagent (10 equiv.) and extended reaction times (48h) only marginally improved the yield to 31%. That addition to the enone **3a** occurred to the *exo*-face was evident from the 5.2% n.O.e. from H-4_{endo} to H-6, and the *cis*- relationship of H-6 and H-11 (J=9.9Hz) (Figure 1). The configuration of C-10 was established indirectly; a 3.8% n.O.e. from H-11 to H-9 allowed the assignment of the latter as H-9_{endo}, and a 6.6% n.O.e. from the C-10 methoxy substituent to H-9_{exo} confirmed their spatial proximity. No such n.O.e. was observed to H-9_{endo}. Thus, C-10 has the (*R*)-configuration, resulting from *endo*-diene addition. This is consistent with the known *endo*-diene selectivity of this compound,[26, 28] and similar diastereoselectivity which has been observed in a closely related system, where a similar chemical shift value is reported for H-10 (δ4.13) although coupling constant data was not obtained.[29] The dipole N-α-diphenylnitrone, upon reaction with enone **3a** in refluxing toluene for 24h gave the diastereomeric products **7a,b** in a ratio of 1:4.5. The regiochemistry of the addition was given by the downfield H-6 chemical shifts (δ4.96 and 5.03 respectively), indicating an oxygen substituent. This was confirmed from the COSY spectrum, which established the C-4/5/6/10/9 connectivity. The stereochemistry followed from n.O.e. results: the sequence of n.O.e. signals H-2—>H-4_{endo}—>H-6—>H-10 confirmed their all-*cis*- relationship for both diastereomers **7a,b** and therefore the *exo*-lactam stereochemistry shown (Figure 1). The C-9/C-10 relative stereochemistry was assigned as *trans*- for the minor diastereomer **7a** on the basis of a coupling constant of 9.0Hz, and *cis*- for **7b** (2.5Hz). This assignment is supported by the observation of similar coupling constants in a related system, which also gave a similar product distribution.[30] The reaction of 1,3-dipoles with the unactivated enone **3a** and other related compounds has recently been reported.[31, 32]

Table 1: Reaction of Lactams **3a,c** with Dienes and 1,3-Dipoles

Entry	Lactam	Diene/Dipole	Products (Yield%)	
1	**3a**			**5** (98)[a,b]
2	**3a**			**6** (31)[b]
3	**3a**		 **7a**	 **7b** (71)
4	**3c**			**8** (72)
5	**3c**		 **9a** (36)	 **9b** (18)
6	**3c**			**10** (53)
7	**3c**		 **11a** (64)	 **11b** (32)

[a] High pressure (19,000 atm, 24h); [b] Based on recovered starting material

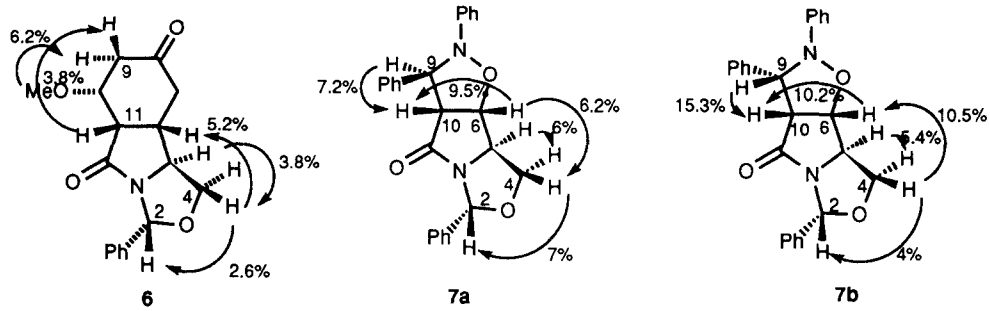


Figure 1

The vinyl selenide **3b** did not give clean addition with 1-methoxy-3-(trimethylsilyloxy)-1,3-butadiene, and this compound was not examined further. However, the activated enone **3c** was found to be extremely useful for cycloadditions, as might be expected due to the additional electron withdrawing ester substituent. Thus, treatment of enone **3c** with 5 equivalents of 2,3-dimethyl-1,3-butadiene in refluxing toluene for 72h gave only the product **8** in 72% yield. That the addition occurred to the *exo*- face of the bicyclic system was confirmed by the n.O.e. signals as shown in Figure 2. The identity of H-4$_{endo}$ was established by a 2% n.O.e. to H-2, and the observation of a 7.6% n.O.e. confirmed the *endo*-stereochemistry for H-6.

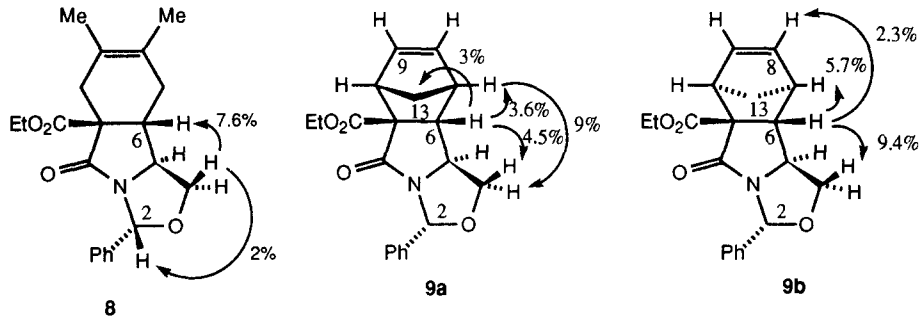


Figure 2

Reaction of enone **3c** with 5 equivalents of cyclopentadiene in refluxing toluene for 24h gave the diastereomeric products **9a** and **9b** in 36 and 18% yield respectively. That the major product **9a** derived from *endo*-diene addition was shown by the n.O.e. triad H-13—>H-6—>H-4$_{endo}$, and also H-7—>H-4$_{exo}$, confirming each of their respective *cis*- relationships (Figure 2). This also implies that addition of the diene has occurred to the *exo*-face (less hindered) of the lactam, as expected. The minor product **9b** gave the principal n.O.e. signals shown in Figure 2, indicating *exo*-(diene)/*exo*-(lactam) addition. This product distribution is in keeping with the known diastereoselectivity for Diels-Alder reactions.

The reaction of 1-methoxy-3-(trimethylsilyloxy)-1,3-butadiene[26-28] (6 equivalents) with enone **3c** in refluxing toluene for 48h, followed by treatment with TBAF gave the adduct **10** as a single diastereomer exclusively in 53% yield. The ^{1}H NMR spectrum showed no trimethylsilyl group, and the ^{13}C NMR spectrum contained a ketone carbonyl (δ_C=206ppm), indicating that desilylation had indeed been achieved. The regiochemistry was determined from the COSY spectrum, which indicated that H-5, H-6 and H-7 were

connected, but isolated from H-9 and H-10. A n.O.e. difference spectrum was used to assign the relative stereochemistry of the product (Figure 3). Irradiation of H-5, the known stereocentre, caused a 6.7% enhancement of one of the C-4 protons, identifying this as H-4_{exo}. Irradiation of H-4_{endo} caused a 6.5% enhancement of H-6, indicating that this proton also has the *endo*-configuration, and this stereochemistry is confirmed by the 4.8% enhancement of one of the H-7 protons obtained upon irradiation of H-5, indicating that addition of the diene component has occurred to the *exo*-face of the lactam **3c**. Unfortunately, no information could be obtained about the stereochemistry at the C-10 methoxy centre, but based on the assignment of the related compound **6**, and close literature precedent,[29] this is likely to be (*R*)-as shown.

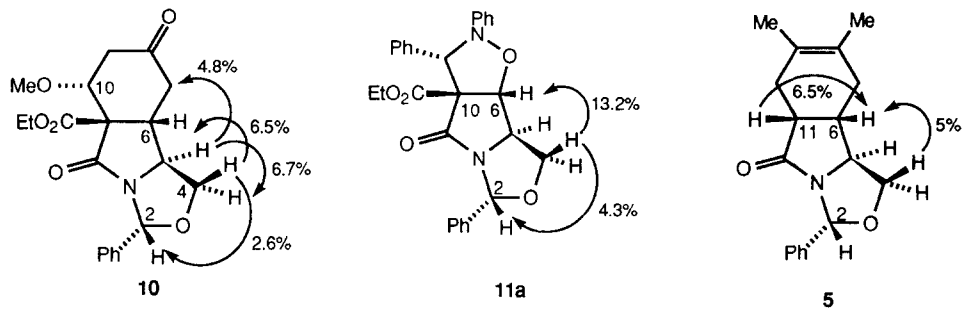
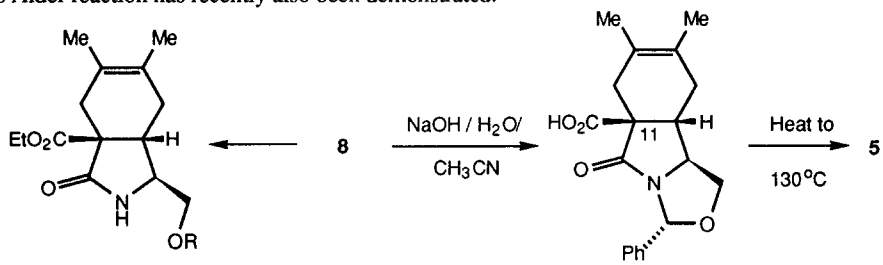


Figure 3

The addition of N-α-diphenyl nitrone gave predominantly *exo*- addition to the bicyclic lactam system. The reaction was performed by adding 2 equivalents of the nitrone to a solution of enone **3c** in toluene, and heating the mixture at reflux for 24h. Purification by silica chromatography (eluant 5:1 petrol/EtOAc) gave two diastereomeric cycloadducts **11a** and **11b** in 64% and 32% yields respectively. The overall yield was thus extremely high, confirming the substantial activating effect of the ethoxycarbonyl group. The regiochemistry of the cycloadducts was determined by a combination of ^{1}H NMR and COSY spectra. The COSY spectra indicated that, in both cases, the nitrone -NCH- proton was isolated, and not coupled to H-6, whilst the chemical shift of H-6 (δ5.25) indicated oxygen substitution. This regiochemistry is consistent with the work of Houk,[33, 34] who has shown that strongly electron withdrawing groups on the dipolarophile favour this regiochemical mode of addition. The stereochemistry of the two cycloadducts at the ring junctions (C-6 and C-10) was determined by n.O.e. difference spectroscopy. The important enhancements for the major product **11a** are shown in Figure 4, establishing that addition to the less hindered *exo*- face of the lactam occurred as expected, and a single crystal X-ray analysis[35] confirmed both this assignment and established the C-9 stereochemistry as (*S*)-, thus confirming that *endo*- addition of the dipole occurred. The stereochemical assignment for **11b** could not be made unequivocally from analysis of coupling constant or n.O.e. data. That the distribution of products **11a,b** was a thermodynamic mixture was shown by refluxing a pure sample of the nitrone cycloadduct **11b** in toluene for 8h, causing equilibration to a 5:4 mixture, favouring the *exo*- diastereomer **11a**.

Hydrolysis and decarboxylation of **8** gave **5** in 84% yield over the two steps (Scheme 2). The *cis*-relationship of H-6/H-11, and of their *endo*- orientation, was confirmed by n.O.e. studies (Figure 3). Noteworthy is the retention of the *cis*- ring junction upon decarboxylation at C-11; a similar reaction in a related system is reported to occur with isomerisation to the *trans*- ring junction.[36] However, this deprotection strategy could not be applied to the nitrone adducts **11a,b**, since decomposition resulted. Deprotection of lactam **8** gave the alcohol **13a** in 82% yield. Conversion of this compound to the MTPA[37] derivative indicated that **13a** was

of at least 88% e.e.; this result is important, since it demonstrates that, despite the acidity of H-5 of **3c**, as evidenced by its facile dimerisation to **4**, the chiral integrity of this position was not compromised. Similar observations in Michael reactions of a related compound have been reported.[21] The bicyclic system of **3** retains its stereochemical integrity for the reasons postulated in Seebach's principles of Self Regeneration of Stereocentres.[38] That complete chiral integrity *can* indeed be lost in a protected $\Delta^{3,4}$ pyroglutamate in the course of a Diels Alder reaction has recently also been demonstrated.[25]



13a R = H
13b R = MTPA

Scheme 2

Acknowledgements

We thank EPSRC and GlaxoWellcome for funding of a studentship to D.T.C., and we wish to gratefully acknowledge the use of the EPSRC Chemical Database Service at Daresbury[39] and the EPSRC National Mass Spectrometric Service Centre at Swansea. We thank Professor L.M. Harwood and Dr M. Bagley for conducting the high pressure experiment.

Experimental

The general procedures and the preparation of the required starting materials **1a,b** and **2a,b,d,e** have been previously reported.[6] Starting materials were obtained from Lancaster Synthesis.

(2R,5S)-1-Aza-3-oxa-8-oxo-2-phenyl-7,7-(bisphenylselenenyl)bicyclo[3.3.0]octane **2c.**

This compound was prepared (1.00g, 75%) by treating the lactam **1a** (530mg, 2.60mmol) with LiHMDS (1M in THF, 5.75ml), followed by quenching with phenylselenyl chloride (1.02g, 5.35mmol). Spectroscopic data was identical with that reported.[6]

(2R,5S)-1-Aza-3-oxa-8-oxo-2-phenyl-bicyclo[3.3.0]oct-6-ene **3a**

To a two necked flask fitted with a dropping funnel and a reflux condenser was added crude selenide mixture **2a,b** (250mg, 0.70mmol) in CH_2Cl_2 (20ml). This was rapidly stirred at room temperature and H_2O_2 (30wt.% solution in water, 0.20ml, 198mg) added dropwise over a 10 minute period. Care was taken to ensure that the reaction proceeded smoothly by occasional cooling in a bath of ice-cold water. After stirring at room temperature for a further 10 minutes the reaction mixture was warmed to reflux for 10 minutes to ensure complete reaction. Saturated $NaHCO_3$ solution (10ml) was added. The aqueous layer was re-extracted with CH_2Cl_2 (2x30ml), the combined organic fractions were dried ($MgSO_4$) and the solvent removed *in vacuo* to give the crude product as a pale orange solid which was purified by flash column chromatography (ethyl

acetate/petrol=1:1, R_f=0.30) or recrystallisation from chloroform/petrol to give the product **3a** as colourless needles (120mg, 86%). M.p. 91-92°C (Lit.[11] 83°C). $[\alpha]_D$ +234 (*c* 1.0, $CHCl_3$)(Lit.[11] +214 (*c* 0.275, $CHCl_3$).

(2R,5S)-1-Aza-3-oxa-8-oxo-2-phenyl-7-phenylselenylbicyclo[3.3.0]oct-6-ene **3b**

m-CPBA (50-60% (128mg, 0.40mmol)) was added portion wise to a stirred solution of selenoacetal **2c** (200mg, 0.38mmol) in CH_2Cl_2 (10ml) at 0°C. The reaction was stirred at this temperature for 30 minutes and the organic layer washed with saturated sodium bicarbonate (2x10ml), water (10ml) and brine (10ml). The solvent was removed *in vacuo* and the resultant residue purified by flash column chromatography (ethyl acetate/petrol=1:4). This yielded the product **3b** (105mg, 75%) as a colourless solid which was recrystallised from CH_2Cl_2/petrol. R_f=0.55(ethyl acetate/petrol=1:1). M.p. 159-160°C. $[\alpha]_D$ +215.4 (*c* 1.0, $CHCl_3$); ν_{max}($CHCl_3$) 1164, 1353, 1703(s)cm^{-1}; δ_H(200MHz, $CDCl_3$) 3.38(1H, dd, *J* 8.5Hz *J'* 8.0Hz, H-4*endo*), 4.18(1H, dd, *J* 6.5Hz *J'* 8.0Hz, H-4*exo*), 4.50(1H, m, H-5), 6.21(1H, s, H-2), 6.56(1H, d, *J* 2.0Hz, H-6), 7.30-7.70(10H, m, ArH); δ_C(50.3MHz, $CDCl_3$) 65.19(C-5), 68.65(C-4), 87.67(C-2), 125.76, 126.41, 128.67, 128.925, 129.325, 130.05, 135.99, 138.61, 140.07, 174.5; *m/z* [probe CI$^+$, NH_3] 375(MNH_4^+, 15), 358($M+H^+$, 100); Exact mass 358.0346; $C_{18}H_{16}NO_2Se$ requires 358.0346.

(2R, 5S)-7-Ethoxycarbonyl-8-oxo-2-phenyl-1-aza-3-oxa-bicyclo[3.3.0] oct-6-ene **3c**

To a solution of selenides **2d,e** (2.36g, 5.48mmol) in CH_2Cl_2 (30ml) at 30°C was added hydrogen peroxide (3.11g, 27.4mmol) and the mixture stirred vigorously for 30min. The reaction was quenched by pouring into $NaHCO_3$(aq)/CH_2Cl_2 (40ml, 1:1), and the organic layer was dried ($MgSO_4$) and evaporated *in vacuo* to give the desired product **3c** as a colourless oil (1.27g, 84%). R_f=0.1 (4:1 cyclohexane/EtOAc); $[\alpha]_D$ +177.2 (c 4.9, $CHCl_3$); δ_H (500MHz, $CDCl_3$) 1.37 (3H, t, *J* 7Hz, C<u>H</u>$_3$), 3.51 (1H, t, *J* 8Hz, H-4*endo*), 4.30-4.38 (3H, m, H-4*exo* & C<u>H</u>$_2$CH$_3$), 4.60-4.64 (1H, m, H-5), 6.26 (1H, s, H-2), 7.34-7.41 (3H, m, ArH), 7.52-7.54 (2H, m, ArH), 7.96 (1H, d, *J* 2Hz, H-6); δ_C (125.8MHz, $CDCl_3$) 13.79(<u>C</u>H$_3$), 61.08(<u>C</u>H$_2$CH$_3$), 62.01(C-5), 67.18(C-4), 87.52(C-2), 125.9, 128.2 & 128.4(Ar<u>C</u>H), 131.8(Ar<u>C</u>), 138.0(C-7), 154.3(C-6), 172.0(<u>C</u>O); *m/z* (Probe CI(NH_3)) 274 (MH^+, 58), 168 (100), 105 (49%).

Formation of Dimer **4**

A solution of enone **3c** (100mg, 0.37mmol) and magnesium bromide etherate[40] (190mg, 0.73mmol, 2.0ml of a 20% solution in diethylether) in THF (20ml) was stirred at room temperature for 2h. The mixture was partitioned between $NaHCO_3$/Et_2O (30ml, 1:1), the organic portion dried ($MgSO_4$) and the solvent removed *in vacuo* to give a pale yellow oil. Purification by silica chromatography (2:1 petrol/EtOAc) gave the dimer **4** (40mg, 40%). R_f=0.16 (2:1 petrol/EtOAc); δ_H (500MHz, $CDCl_3$) 1.25 (3H, t, *J* 7Hz, C<u>H</u>$_3$), 1.39 (3H, t, *J* 7Hz, C<u>H</u>$_3$), 3.24 (1H, dd, J_1 8.5Hz, J_2 5Hz, H-6), 3.42 (1H, d, *J* 8.5Hz, H-7), 3.65-3.69 (2H, m, H-4 & H-12), 3.73-3.77 (1H, m, H-5), 4.06-4.13 (3H, m, C<u>H</u>$_2$CH$_3$ & H-4), 4.24 (1H, d, *J* 9Hz, H-12), 4.36-4.38 (2H, m, C<u>H</u>$_2$CH$_3$), 6.17 & 6.20 (2H, 2xs, H-2 & H-10), 7.35-7.39 (8H, m, ArH), 7.52-7.53 (2H, m, ArH), 7.79(1H, s, H-14); δ_C (125.8MHz, $CDCl_3$) 13.9 & 14.1(2x<u>C</u>H$_3$), 29.6(C-6), 44.3(C-7), 53.7(C-5), 58.3(C-13), 62.0 & 62.1(2x<u>C</u>H$_2$CH$_3$), 70.8 & 71.1(C-4 & C-12), 87.5 & 89.2(C-2 & C-10), 125.7, 125.8 & 128.9(Ar<u>C</u>H), 133.5(C-15), 137.0 & 137.6(2xAr<u>C</u>), 154.9(C-14), 160.1, 168.1, 171.5 & 172.2(4x<u>C</u>O); *m/z* (DCI(NH_3)) 547 (MH^+, 12), 274 (100%).

(2R,5S,6S,11R)-8,9-Dimethyl-12-oxo-2-phenyl-1-aza-3-oxa-tricyclo[7.3.0^{1,5}.0^{6,11}] dodec-8-ene **5**

2,3-Dimethyl-1,3-butadiene (163mg, 0.225ml, 1.99mmol) and enone **3a** (100mg, 0.5mmol) in CH_2Cl_2 (2ml) was subjected to high pressure conditions (19000 atm, 25°C) for 24 hours. The crude reaction mixture was filtered through a plug of Celite® and the solvent removed under reduced pressure. The product was purified by flash column chromatography (ethyl acetate/petrol=1:3) (R_f=0.50 ethyl acetate/petrol=1:1) to give the product **5** as a colourless oil (110mg, 98% based on unreacted starting material). Unreacted starting material **3a** (20mg) was the second compound to be recovered. $[\alpha]_D$ +60 (*c* 1.0, $CHCl_3$). This material had identical spectroscopic properties with that prepared from intermediate **8** (*vide infra*).

(2R,5S,6S,10R,11S)-10-Methoxy-8, 12-dioxo-2-phenyl-1-aza-3-oxa-tricyclo[7.3.0^{1,5}.0^{6,11}]undecane **6**

1-Methoxy-3-(trimethylsilyloxy)-1,3-butadiene (2.0ml, 1.0g, excess) and enone **3a** (115mg, 1mmol) were refluxed in xylene for 48 hours. Water (10ml) was added and the product extracted into CH_2Cl_2. The organic fractions were combined, dried ($MgSO_4$) and the solvent removed under reduced pressure to give a complex mixture of products from which **6** was isolated by flash column chromatography (ethyl acetate: petrol=1:10 gradient to ethyl acetate). In addition to this starting material **3a** (70mg) was isolated. Yield (21mg, 31% based on recovered starting material). R_f=0.10 (ethyl acetate:petrol=1:1); M.p.117-119°C. ν_{max}($CHCl_3$) 1708(s) cm^{-1}. δ_H(500MHz, $CDCl_3$) 2.31(1H, dd *J* 2.5Hz *J'* 17.5Hz, H-9), 2.6-2.68(1H, m, H-7), 2.70-2.75(1H, m, H-7), 2.78-2.83(1H, m, H-6), 2.85-2.90(1H, dd, *J* 17.5, *J'* 3.3Hz, H-9), 3.07(1H, dd, *J* 3.8 *J'* 9.9Hz, H-11), 3.40(3H, m, O$\underline{C}H_3$), 3.50-3.55(1H, m, H-4$_{endo}$), 3.90-3.97(1H, m, H-5), 4.20-4.28(2H, m, H-4$_{exo}$ and H-10), 6.39(1H, s, H-2), 7.33-7.47(5H, m, ArH); δ_C($CDCl_3$) 35.3(C-11), 41.6 and 41.9(C-7 and C-9), 50.5(C-6), 57.7(O$\underline{C}H_3$), 65.6(C-5), 71.0(C-4), 76.1(C-10), 87.1(C-2), 125.9, 128.4, 128.6, 138.3 (ArC), 175.4(C-12), 207.2(C-8); *m/z* 302(MH$^+$, 100), 270(22), 195(8), 105(41), 91(22), 84(12), 77(9), 68(10), 58(9%); Exact mass 302.1392; $C_{17}H_{21}NO_4$ requires 302.1392.

(2R,5R,6S,9S,10S)-11-Oxo-2,8,9-triphenyl-1,8-diaza-3,7-dioxa-tricyclo[6.3.0^{1,5}.0^{6,10}]undecane **7a** *and (2R,5R,6S,9R,10S)-11-oxo-2,8,9-triphenyl-1,8-diaza-3,7-dioxa-tricyclo[6.3.0^{1,5}.0^{6,10}]undecane* **7b.**

Lactam **3a** (100mg, 0.50mmol) and N-α-diphenyl nitrone (150mg, 0.76mmol) were refluxed in dry toluene (10ml) under nitrogen for 24 hours. After cooling the organic layer was washed with water (10ml) and the aqueous layer extracted with ethyl acetate (2x10ml). The combined organic fractions were washed with brine (5ml), dried ($MgSO_4$) and the solvent removed *in vacuo*. The crude reaction mixture contained two products (approximate ratio= 4.5:1 from ^{1}H n.m.r. spectrum (200MHz, $CDCl_3$) of the crude reaction mixture) which were separated by flash column chromatography (ethyl acetate:petrol=1:5 gradient to ethyl acetate:petrol=1:1).

The first fraction (R_f=0.6 ethyl acetate: petrol=1:1) contained an inseparable mixture of the minor isomer of the cycloaddition product **7a** and starting nitrone (approximate ratio=2:3). COSY and n.O.e. experiments were carried out on this crude mixture. δ_H(500MHz, $CDCl_3$) 3.42(1H, dd *J* 9.0Hz *J'* 8.5Hz, H-4$_{endo}$), 3.79(1H, dd, *J* 9.0Hz *J'* 2.5Hz, H-10), 4.26(1H, m, H-5), 4.33(1H, dd, *J* 9.0Hz *J'* 8.5Hz, H-4$_{exo}$), 4.96(1H, d, *J* 9.0Hz, H-6), 5.25(1H, d, *J* 2.5Hz, H-9), 6.32(1H, s, H-2), 6.95-8.45(Ar); *m/z* [Probe CI, NH_3] 399(MH$^+$, 65), 198(80), 182(100%).

The second fraction contained the major isomer **7b** of the cycloaddition (R_f=0.4) which was obtained as a colourless solid (140mg, 71%). M.p. 147-149°C; Found: C, 75.26; H, 5.50; N, 7.03. $C_{25}H_{22}N_2O_3$ requires C, 75.26; H, 5.23; N, 6.93%; $[\alpha]_D$ +297.5(*c* 0.8, $CHCl_3$); ν_{max}($CHCl_3$) 1713(s) cm^{-1}; δ_H(500MHz, $CDCl_3$) 3.60(1H, dd *J* 8.0Hz *J'* 8.5Hz, H-4$_{endo}$), 3.94(1H, dd *J* 9.1Hz *J'* 8.5Hz, H-10), 4.25-4.29(1H, m, H-5), 4.36(1H, dd *J* 7.0Hz *J'* 8.0Hz, H-4$_{exo}$), 4.95(1H, d *J* 9.1Hz, H-9), 5.03-5.05(1H, dd *J* 2.2Hz *J'* 8.5Hz, H-6), 6.25(1H, s, H-2), 7.02-7.15(5H, m, ArH), 7.23-7.41(8H, m, ArH), 7.53-7.55(2H, m, ArH); δ_C(125.7MHz, $CDCl_3$) 61.20(C-5), 64.64, 69.37(C-6 and C-10), 71.52(C-4), 79.56(C-9), 86.75(C-2), 117.13, 123.74, 125.65, 127.71, 128.28, 128.44, 128.63, 128.88, 135.79, 148.71(ArC), 173.88(CO); *m/z*[Probe CI, NH_3] 399(MH^+, 90), 381(60), 182(60%).

(2R, 5S, 6S, 11S)-11-Ethoxycarbonyl-8,9-dimethyl-12-oxo-2-phenyl-1-aza-3-oxa-tricyclo [7.3.0^{1,5}.0^{6,11}] dodec-8-ene **8**

To a solution of enone **3c** (1.10g, 4.03mmol) in toluene (60ml) was added 2,3-dimethyl-1,3-butadiene (1.99g, 24.2mmol) and the mixture was heated at reflux for 72h until the starting material appeared to be consumed (t.l.c. analysis). The mixture was cooled and the solvent removed *in vacuo* to give a brown oil which was purified by silica chromatography (4:1 petrol/EtOAc) yielding the desired product **8** as a yellow oil (1.03g, 72%). R_f=0.35 (4:1 petrol/EtOAc); $[\alpha]_D$ +9.4 (*c* 1.15, $CHCl_3$); Found C, 71.06; H, 7.44; N, 4.04. $C_{21}H_{25}NO_4$ requires C, 70.96; H, 7.09; N, 3.94%; ν_{max} ($CHCl_3$) 3019(s), 1737(s), 1709(s), 1521(s) & 1424(s) cm^{-1}; δ_H (500MHz, $CDCl_3$) 1.30 (3H, t, *J* 7Hz, $CH_2C\underline{H}_3$), 1.68 (3H, s, $C\underline{H}_3$), 1.74 (3H, s, $C\underline{H}_3$), 1.95 (1H, d, *J* 17Hz, H-7), 2.29 (1H, dd, J_1 17Hz, J_2 6.5Hz, H-7), 2.42 (1H, d, *J* 16Hz, H-10), 2.82 (1H, d, *J* 16Hz, H-10), 2.97-3.00 (1H, m, H-6), 3.72 (1H, dd, J_1 13Hz, J_2 6Hz, H-5), 3.78-3.81 (1H, m, H-4$_{endo}$), 4.18-4.30 (3H, m, H-4$_{exo}$ & $C\underline{H}_2CH_3$), 6.35 (1H, s, H-2), 7.31-7.46 (5H, m, ArH); δ_C (125.8MHz, $CDCl_3$) 14.09($CH_2\underline{C}H_3$), 19.10 & 19.22(2x$\underline{C}H_3$), 32.35 & 33.85(C-7 & C-10), 42.23(C-6), 53.36(C-11), 59.77(C-5), 61.74($\underline{C}H_2CH_3$), 70.41 (C-4), 87.29(C-2), 124.2 & 125.6(C-8 & C-9), 125.9, 128.4 & 128.5(Ar$\underline{C}$H), 138.5(Ar$\underline{C}$), 171.1 & 173.2(2x$\underline{C}$O); *m/z* (Probe ($CI(NH_3)$) 356 (MH^+, 100), 106 (35%).

(2R, 5S, 6S, 7S, 10S, 11S)-11-Ethoxycarbonyl-12-oxo-2-phenyl-1-aza-3-oxa-tetracyclo [7.3.1^{7,10}.0^{1,5}.0^{6,11}] tridec-8-ene **9a** *& (2R, 5S, 6S, 7R, 10R, 11S)-11-ethoxycarbonyl-12-oxo-2-phenyl-1-aza-3-oxa-tetracyclo [7.3.1^{7,10}.0^{1,5}.0^{6,11}] tridec-8-ene* **9b**

To a solution of enone **3c** (180mg, 0.66mmol) in toluene (60ml) was added cyclopentadiene (261mg, 3.96 mmol), prepared in advance by thermal cracking (180°C) of the commercially available dimer, and the mixture was heated at reflux for 24h until the starting material appeared consumed (t.l.c. analysis). The mixture was cooled and the solvent removed *in vacuo* to give a yellow oil which was purified by silica chromatography (4:1 petrol/EtOAc) yielding the desired product as a mixture of diastereomers in 54% combined yield, and in ratio 2:1. Further purification by HPLC (cycloheptane/IPA, 9:1) provided the individual diastereomers as colourless solids.

Major diastereomer **9a**; Yield (80mg, 36%); R_f=0.20 (4:1 cyclohexane/EtOAc); m.p. 110-112°C; $[\alpha]_D$ +69.1 (*c* 3.3, EtOH); ν_{max} ($CHBr_3$) 1738(s), 1698(s) cm^{-1}; δ_H (250MHz, $CDCl_3$) 1.31 (3H, t, *J* 7Hz, $C\underline{H}_3$), 1.55 (1H, d, *J* 9Hz, H-13), 1.75 (1H, d, *J* 9Hz, H-13), 2.98-3.03 (1H, m, H-6), 3.07-3.12 (1H, m, H-10), 3.38-3.48 (1H, m, H-7), 3.62-3.72 (2H, m, H-4$_{endo}$ & H-5), 4.16-4.35 (3H, m, H-4$_{exo}$ & $C\underline{H}_2CH_3$), 6.23 (1H, s, H-2), 6.32-6.38 (2H, m, H-8 & H-9), 7.31-7.37 (5H, m, ArH); δ_C (125.8MHz, $CDCl_3$) 14.05($CH_2\underline{C}H_3$),

45.70, 47.26, 48.51 & 50.99(C-6, C-7, C-10 & C-13), 60.49(C-5), 61.89($\underline{C}H_2CH_3$), 68.94(C-11), 70.22 (C-4), 87.62(C-2), 125.7 & 128.4(Ar$\underline{C}$H), 136.2 & 136.5(C-8 & C-9), 139.0(Ar$\underline{C}$), 171.2 & 175.3(2x$\underline{C}$O); *m/z* (Thermospray) 340 (MH^+, 100), 274 (16%); Exact mass 340.1549. $C_{20}H_{22}NO_4$ (MH^+) requires 340.1549.

Minor diastereomer **9b**; Yield (40mg, 18%); R_f=0.25 (4:1 cyclohexane/EtOAc); m.p. 124-126°C; $[\alpha]_D$ +86.6 (*c* 0.82, EtOH); ν_{max} ($CHBr_3$) 1742(s) & 1699(s) cm^{-1}; δ_H (250MHz, $CDCl_3$) 1.28 (3H, t, *J* 7Hz, $C\underline{H}_3$), 1.61 (1H, dd, J_1 9.5Hz, J_2 2Hz, H-13), 1.81 (1H, d, br, *J* 9.5Hz, H-13), 2.59 (1H, s, br, H-7), 2.92 (1H, s, br, H-10), 3.43 (1H, s, br, H-6), 3.62-3.75 (2H, m, H-4_{endo} & H-5), 4.09-4.27 (2H, m, $C\underline{H}_2CH_3$), 4.27-4.33 (1H, m, H-4_{exo}), 6.17-6.23 (1H, m, H-8), 6.29-6.35 (2H, m, H-2 & H-9), 7.31-7.47 (5H, m, ArH); δ_C (125.8MHz, $CDCl_3$) 14.07($CH_2\underline{C}H_3$), 45.01, 47.26, 47.70 & 48.35(C-6, C-7, C-10 & C-13), 61.66 & 61.94 (C-5 & $\underline{C}H_2CH_3$), 70.29(C-11), 70.53(C-4), 87.98(C-2), 125.8, 128.4 & 128.5(Ar$\underline{C}$H), 137.3 & 137.7(C-8 & C-9), 139.0(Ar$\underline{C}$), 170.0 & 175.2(2x$\underline{C}$O); *m/z* (Thermospray) 340 (MH^+, 100%); Exact mass 340.1549. $C_{20}H_{22}NO_4$ (MH^+) requires 340.1549.

(2R,5S,6S,10R,11R)-11-Ethoxycarbonyl-10-methoxy-8,12-dioxo-2-phenyl-1-aza-3-oxa-tricyclo-[7.3.0^{1,5}.0^{6,11}]-dodecane **10**

To a solution of enone **3c** (86mg, 0.32mmol) in toluene (30ml) was added 1-methoxy-3-(trimethylsilyloxy)-1,3-butadiene (326mg, 1.92 mmol) and the mixture heated at reflux for 48h until the starting material appeared consumed (t.l.c. analysis). The mixture was cooled to 0°C, tetrabutylammonium fluoride (TBAF) (165mg, 0.64mmol) was added, and stirring was continued at 0°C for 15min and then at RT for 2h. The mixture was partitioned between EtOAc and water (40ml, 1:1), the organic layer dried ($MgSO_4$) and the solvent removed *in vacuo* to give a yellow oil. Purification by silica chromatography (2:1 CH_2Cl_2/EtOAc) yielded the desired product **10** as a yellow solid (64mg, 53%). R_f=0.2 (CH_2Cl_2); $[\alpha]_D$ +76.7 (c 1, $CHCl_3$); ν_{max} ($CHCl_3$) 1740(s), 1677(m), 1605(m) & 1589(m) cm^{-1}; δ_H (500MHz, $CDCl_3$) 1.34 (3H, t, *J* 7Hz, $CH_2C\underline{H}_3$), 2.52 (1H, dd, J_1 17, J_2 2.5Hz, H-9), 2.60-2.70 (2H, m, H-7), 2.82 (1H, dd, J_1 17Hz, J_2 3.5Hz, H-9), 3.29-3.36 (1H, m, H-6), 3.37 (3H, s, $OC\underline{H}_3$), 3.75 (1H, t, *J* 8Hz, H-4_{endo}), 3.94 (1H, m, H-5), 4.25 (1H, dd, J_1 8Hz, J_2 6Hz, H-4_{exo}), 4.31 (2H, q, *J* 7Hz, $C\underline{H}_2CH_3$), 4.54 (1H, t, *J* 3Hz, H-10), 6.36 (1H, s, H-2), 7.33-7.39 (3H, m, ArH), 7.44-7.46 (2H, m, ArH); δ_C (125.8MHz, DEPT, $CDCl_3$) 14.01($CH_2\underline{C}H_3$), 40.28(C-6), 40.94 & 41.26(C-7 & C-9), 58.14($O\underline{C}H_3$), 62.60($\underline{C}H_2CH_3$), 63.68(C-5), 63.90(C-11), 70.59(C-4), 78.49 (C-10), 87.46(C-2), 126.0, 128.5 & 128.7(Ar$\underline{C}$H), 138.1(Ar$\underline{C}$), 169.0 & 171.5(2x$\underline{C}$O), 206.3(C-8); *m/z* (Probe CI(NH_3)) 374 (MH^+, 100), 342 (43), 235 (18), 137 (52%); Exact mass 374.1604. $C_{20}H_{24}NO_6$ (MH^+) requires 374.1604.

(2R,5S,6S,9S,10S)-10-Ethoxycarbonyl-11-oxo-2,8,9-triphenyl-1,8-diaza-3,7-dioxa-tricyclo [6.3.0^{1,5}.0^{6,10}]-undecane **11a** *and (2R, 5S)-10-ethoxycarbonyl-11-oxo-2,8,9-triphenyl-1,8-diaza-3,7-dioxa-tricyclo [6.3.0^{1,5}.0^{6,10}]undecane* **11b**

To a solution of enone **3c** (457mg, 1.67mmol) in toluene (60ml) was added N-α-diphenylnitrone (660mg, 3.34 mmol), and the mixture was heated at reflux for 24h until the starting material appeared consumed (t.l.c. analysis). The mixture was cooled and the solvent removed *in vacuo* to give a colourless oil which was purified by silica chromatography (5:1 petrol/EtOAc) providing the individual diastereomers in 96%

combined yield, in a ratio of 2:1, as colourless solids. A small amount of the major diastereomer was recrystallised by vapour diffusion (EtOAc/petrol) to give rectangular crystals, on which a single crystal X-ray structural determination was performed.

Major isomer **11a**; Yield (503mg, 64%); R_f=0.21 (5:1 petrol/EtOAc); m.p. 148-149°C; $[\alpha]_D$ +72.5 (*c* 0.55, $CHCl_3$); Found C, 71.64; H, 5.72; N, 5.92. $C_{28}H_{26}N_2O_5$ requires C, 71.48; H, 5.57; N, 5.95%; δ_H (500MHz, $CDCl_3$) 1.28 (3H, t, *J* 7Hz, $C\underline{H}_3$), 3.75 (1H, t, *J* 8.5Hz, H-4$_{endo}$), 4.22-4.30 (2H, m, $C\underline{H}_2CH_3$), 4.31-4.35 (1H, m, H-5), 4.45 (1H, t, *J* 7.5Hz, H-4$_{exo}$), 5.26 (1H, d, *J* 2Hz, H-6), 5.36 (1H, s, H-9), 6.27 (1H, s, H-2), 7.01-7.05 (3H, m, ArH), 7.19-7.23 (4H, m, ArH), 7.31-7.37 (6H, m, ArH), 7.57-7.62 (2H, m, ArH); δ_C (125.8MHz, $CDCl_3$) 13.97($CH_2\underline{C}H_3$), 30.91(C-10), 62.82 & 63.53 (C-5 & $\underline{C}H_2CH_3$), 69.28 (C-6), 73.62(C-4), 82.36(C-9), 87.19(C-2), 118.2, 124.1, 125.7, 128.0, 128.3, 128.5 & 128.7(Ar$\underline{C}$H), 134.9, 138.0 & 147.9(Ar$\underline{C}$), 168.0 & 170.9(2x$\underline{C}$O); *m/z* (EI) 470 (M^+, 22), 274 (22), 197 (68), 181 (100), 168 (25), 149 (24), 105 (56), 91 (82), 77 (36%).

Minor isomer **11b**; Yield (252mg, 32%); R_f=0.16 (5:1 petrol/EtOAc); m.p. 170-171°C; $[\alpha]_D$ +152.0 (*c* 0.5, $CHCl_3$); Found C, 71.76; H, 5.18; N, 5.62. $C_{28}H_{26}N_2O_5$ requires C, 71.48; H, 5.57; N, 5.95%; δ_H (500MHz, $CDCl_3$) 0.82 (3H, t, *J* 7Hz, $C\underline{H}_3$), 3.81-3.84 (2H, m, $C\underline{H}_2CH_3$), 4.26-4.34 (2H, m, H-4), 4.48-4.52 (1H, m, H-5), 5.32 (1H, s, H-9), 5.48 (1H, d, *J* 5Hz, H-6), 6.33 (1H, s, H-2), 6.86-6.93 (3H, m, ArH), 7.14-7.18 (2H, m, ArH), 7.22-7.29 (3H, m, ArH), 7.35-7.40 (3H, m, ArH), 7.41-7.44 (2H, m, ArH), 7.46-7.49 (2H, m, ArH); δ_C (125.8MHz, $CDCl_3$) 13.19($CH_2\underline{C}H_3$), 41.50(C-10), 62.30(C-5), 65.10 ($\underline{C}H_2CH_3$), 72.98(C-6), 76.44(C-4), 87.86(C-2), 116.8, 122.9, 126.4, 128.4, 128.6, 128.8, 129.0, 129.1 & 129.3(Ar$\underline{C}$H), 135.4, 137.8(Ar$\underline{C}$), 171.6 & 180.3(2x$\underline{C}$O); *m/z* (EI) 470 (M^+, 43), 198 (100), 181 (81), 168 (21), 105 (48), 91 (41), 77 (31%).

Equilibration of Minor Nitrone Adduct **11b**

A solution of minor nitrone adduct **11b** (30mg, 0.06mmol) in toluene (30ml) was heated at reflux for 8h, then cooled and the solvent removed *in vacuo* to give a colourless oil. Analysis of the crude product by ^1H NMR indicated the presence of both major **11a** and minor **11b** nitrone adducts in ratio 5:4.

(2R, 5S, 6S, 11S)-11-Carboxyl-8,9-dimethyl-12-oxo-2-phenyl-1-aza-3-oza-tricyclo [7.3.0^{1,5}.0^{6,11}] dodec-8-ene **12**

A solution of adduct **8** (211mg, 0.59mmol), acetonitrile (5ml) and 1N NaOH (1ml) was stirred at RT for 17h, and then poured into H_2O/EtOAc (1:1, 40ml). The aqueous layer was acidified with 2M HCl to produce a white precipitate which was extracted with EtOAc (2x20ml). The organic solution was dried ($MgSO_4$), and the solvent was removed *in vacuo* to give **12** as a white powder (173mg, 89%). M.p. 143-144°C; $[\alpha]_D$ +36.0 (*c* 1.5, $CHCl_3$); Found C, 69.79; H, 6.76; N, 4.12. $C_{19}H_{21}NO_4$ requires C, 69.71; H, 6.46; N, 4.28%; ν_{max} ($CHCl_3$) 3300-2700(br), 1761(s), 1719(s), 1676(s) & 1392(s) cm^{-1}; δ_H (500MHz, $CDCl_3$) 1.70 (6H, s, 2x$C\underline{H}_3$), 1.96-1.99 (1H, m, H-10), 2.46-2.52 (2H, m, H-7), 2.61-2.64 (1H, m, H-10), 2.94-2.97 (1H, m, H-6), 3.72-3.77 (2H, m, H-4$_{endo}$ & H-5), 4.20-4.25 (1H, m, H-4$_{exo}$), 6.32 (1H, s, H-2), 7.33-7.39 (5H, m, ArH); δ_C (50.3MHz, $CDCl_3$) 19.04 & 19.43(2x$\underline{C}H_3$), 31.69 & 35.45(C-7 & C-10), 41.70(C-6), 57.66(C-11), 62.15(C-5), 70.58(C-4), 86.96(C-2), 123.8 & 124.6(C-8 & C-9), 125.9, 128.6 & 128.9(Ar$\underline{C}$H), 137.6 (Ar$\underline{C}$), 173.4 & 178.2 (2x$\underline{C}$O); *m/z* (DCI(NH_3)) 328 (MH^+, 15), 284 (100%).

(2R, 5S, 6S, 11R)-8,9-Dimethyl-12-oxo-2-phenyl-1-aza-3-oza-tricyclo [7.3.0^{1,5}.0^{6,11}] dodec-8-ene **5**

The above product **8** (126mg, 0.38mmol) was heated at 130°C under reduced pressure (0.5mmHg) for 1h. An oily residue was observed to condense near the top of the flask which, after cooling, was identified as the desired product **5**(103mg, 94%). R_f=0.25 (3:1 petrol/EtOAc); $[\alpha]_D$ +53.0 (c 2, $CHCl_3$); ν_{max} ($CHCl_3$) 2916(m), 1701(s), 1392(m) & 1358cm^{-1}(m); δ_H (500MHz, $CDCl_3$) 1.71 (3H, s, C<u>H</u>$_3$), 1.73 (3H, s, C<u>H</u>$_3$), 1.96-1.99 (1H, m, H-7), 2.26-2.35 (3H, m, H-10, H-10' & H-7), 2.53-2.58 (1H, m, H-6), 2.83-2.87 (1H, m, H-11), 3.58 (1H, t, *J* 8Hz, *J'* 7.5Hz, H-4), 3.72-3.76 (1H, m, H-5), 4.18 (1H, dd, J_1 8Hz, J_2 6.5Hz, H-4), 6.36 (1H, s, H-2), 7.32-7.43 (5H, m, ArH); δ_C (125.8MHz, $CDCl_3$) 19.20 & 19.47(2x<u>C</u>H$_3$), 30.83 & 32.91(C-7 & C-10), 36.91(C-11), 44.18(C-6), 64.18(C-5), 70.39 (C-4), 87.05(C-2), 124.5 & 125.9(C-8 & C-9), 128.4(Ar<u>C</u>H), 138.7(Ar<u>C</u>), 181.4 (<u>C</u>O); *m/z* (Probe CI(NH_3)) 284 (MH^+, 100%); Exact mass 283.1572. $C_{18}H_{21}NO_2$ (MH^+) requires 283.1572.

(2R, 3S, 8S)-8-Ethoxycarbonyl-2-hydroxymethyl-5,6-dimethyl-9-oxo-1-aza-bicyclo [4.3.0]non-5-ene ***13a***

To a solution of adduct **8** (230mg, 0.65mmol) in CH_2Cl_2 (10ml) was added trifluoroacetic acid (0.25ml) and the mixture stirred at RT for 4h. When the starting material appeared consumed (t.l.c. analysis) the solvent was removed *in vacuo* to give an oil, which was purified by silica chromatography (2:1 EtOAc/petrol) yielding the desired product **13a** as a yellow oil (142mg, 82%). R_f=0.11 (1:1 petrol/EtOAc); $[\alpha]_D$ -48.8 (c 0.8, $CHCl_3$); ν_{max} ($CHCl_3$) 3600-3180(br), 3050-2820(br), 1734(s) & 1703cm^{-1}(s); δ_H (500MHz, $CDCl_3$) 1.26 (3H, t, *J* 7Hz, CH_2C<u>H</u>$_3$), 1.69 (3H, s, C<u>H</u>$_3$), 1.70 (3H, s, C<u>H</u>$_3$), 1.92 (1H, dd, J_1 16Hz, J_2 2Hz, H-4), 2.21 (1H, dd, J_1 16Hz, J_2 6Hz, H-4), 2.33 (1H, d, *J* 16Hz, H-7), 2.58 (1H, d, *J* 16Hz, H-7), 2.66-2.69 (1H, m, H-3), 3.26-3.29 (1H, m, H-2), 3.56 (1H, dd, J_1 11.5Hz, J_2 7.5Hz, CH(<u>H</u>)O), 3.72 (1H, dd, J_1 11.5Hz, J_2 3Hz, C<u>H</u>(H)O), 4.15-4.22 (2H, m, C<u>H</u>$_2$CH$_3$), 7.22 (1H, s, N<u>H</u>); δ_C (125.8MHz, $CDCl_3$) 14.01 (CH_2<u>C</u>H$_3$), 19.07 & 19.44 (2x<u>C</u>H$_3$), 32.91 & 33.41 (C-4 & C-7), 40.24 (C-3), 56.44 (C-8), 60.70 (C-2), 61.77 (<u>C</u>H$_2$CH$_3$), 64.90 (<u>C</u>H$_2$O), 125.3 & 125.8 (C-5 & C-6), 172.2 & 176.5 (2x<u>C</u>O); m/z (Probe CI(NH_3)) 268 (MH^+, 100%). Exact mass 268.1549. $C_{14}H_{22}NO_4$ requires 268.1549.

Conversion to the MTPA derivative

To a solution of the alcohol **13a** (4 mg, 0.015 mmol) and pyridine (2.2 mg, 0.026 mmol) in $CHCl_3$ (0.3 ml) was added (S)-(-)-α-methoxy-α-trifluoromethylphenylacetyl chloride[37] (5.5 mg, 0.022 mmol) and the mixture was left in a vial at room temperature for 18 h. The solution was washed twice with water, then evaporated *in vacuo* to give the MTPA ester (6 mg, 83 %); R_f=0.31 (EtOAc:petrol, 2:1); δ_F (235 MHz, $CDCl_3$) -71.8549 (major), -72.2443 (minor) Intensity ratio 4.805:0.311; e.e. 87.8%; m/z (APCI) 484.2 ($M+H^+$, 9%), 268.2 (100%), 225.2 (17%), 222.1 (26%), 194.1 (10%).

As above, the alcohol **13a** (4 mg, 0.015 mmol) was reacted with pyridine (2.2 mg, 0.026 mmol) and (±)-α-methoxy-α-trifluoromethylphenylacetyl chloride (5.5 mg, 0.022 mmol) in $CHCl_3$ (0.3 ml) to give the MTPA ester (6 mg, 83%); R_f=0.30 (EtOAc:petrol, 2:1), δ_F (235 MHz, $CDCl_3$) -71.8583 (minor), -72.2464 (major).

References

1. Massiot, G.; Delaude, C. *The Alkaloids* **1986**, *27*, 300-321.
2. Wink, M. *The Alkaloids* **1993**, *43*, 1-118.

3. Thottathil, J. K.; Przbyla, C.; Malley, M.; Gougoutas, J. Z. *Tetrahedron Lett.* **1986**, *27*, 1533-1536.
4. Thottathil, J. K.; Moniot, J. M.; Mueller, R. H.; Wong, M. K. Y.; Kissick, T. P. *J. Org. Chem.* **1986**, *51*, 3140-3143.
5. Baldwin, J. E.; Moloney, M. G.; Shim, S. B. *Tetrahedron Lett.* **1991**, *32*, 1379-1380.
6. Beard, M. J.; Bailey, J. H.; Cherry, D. T.; Moloney, M. G.; Shim, S. B.; Statham, K.; Bamford, M.; Lamont, R. B. *Tetrahedron* **1996**, *52*, 3719-3740 and corrigenda 1997, **53**, 1177.
7. Hamada, Y.; Hara, O.; Kawai, A.; Ohno, Y.; Shiori, T. *Tetrahedron* **1991**, *47*, 8635-8652.
8. Hanessian, S.; Ratovelomanana, V. *Synlett.* **1991**, 222-224.
9. Armstrong, R. W.; DeMattei, J. A. *Tetrahedron Lett.* **1991**, *32*, 5749-5752.
10. Griffart-Brunet, D.; Langlois, N. *Tetrahedron Lett.* **1994**, *35*, 119-122.
11. Herdeis, C.; Hubmann, H. P.; Lotter, H. *Tetrahedron:Asymmetry* **1994**, *5*, 119-128.
12. Nagasaka, T.; Imai, T. *Chem. Pharm. Bull.* **1995**, *43*, 1081-1088.
13. For a preliminary account, see: Bamford, M.; Beard, M.; Cherry, D. T.; Moloney, M. G. *Tetrahedron: Asymmetry* **1995**, *6*, 337-340.
14. Meyers, A. I.; Brengel, G. P. *Chem. Commun.* **1997**, 1-8.
15. Busacca, C. A.; Meyers, A. I. *J. Chem. Soc., Perkin Trans. 1* **1991**, 2299-2316.
16. Fray, A. H.; Meyers, A. I. *Tetrahedron Lett.* **1992**, *33*, 3575-3578.
17. Fray, A. H.; Meyers, A. I. *J. Org. Chem.* **1996**, *61*, 3362-3374.
18. Reich, H. J.; Renga, J. M.; Reich, I. L. *J. Am. Chem. Soc.* **1975**, *97*, 5434-5437.
19. Dyer, J.; Keeling, S.; Moloney, M. G. *Tetrahedron Lett.* **1996**, *37*, 4573-4576.
20. Nagasaka, T.; Imai, T. *Heterocycles* **1995**, *41*, 1927-1930.
21. Nagasaka, T.; Imai, T. *Chem. Pharm. Bull.* **1997**, *45*, 36-42.
22. Grote, R.; Zeeck, A.; Stumpfel, J.; Zahner, H. *Liebigs Ann. Chem.* **1990**, 525-530.
23. Ohfune, Y.; Tomita, M. *J. Am. Chem. Soc.* **1982**, *104*, 3511-3513.
24. Ackarmann, J.; Matthes, M.; Tamm, C. *Helv. Chim. Acta* **1990**, *71*, 122-132 and references there-in.
25. Ezquerra, J.; Pedregal, C.; Collado, I.; Yruretagoyena, B.; Rubio, A. *Tetrahedron* **1995**, *51*, 10107-10114.
26. Danishevsky, S.; Hirama, M.; Gombatz, K.; Harayama, T.; Berman, E.; Schuda, P. F. *J. Am. Chem. Soc.* **1979**, 7022-7028.
27. Brownbridge, P. *Synthesis* **1983**, 85-104.
28. Danishevsky, S. *Acc. Chem. Res.* **1981**, *14*, 400.
29. Koot, W. J.; Hiemstra, H.; Speckamp, W. N. *J. Org. Chem.* **1992**, *57*, 1059-1061.
30. Rispens, M. T.; Keller, E.; deLange, B.; Zijlstra, R. W. J.; Feringa, B. L. *Tetrahedron:Asymmetry* **1994**, *5*, 607-624.
31. Wee, A. G. H. *J. Chem. Soc., Perkin Trans. 1* **1989**, 1363-1364.
32. Langlois, N.; Bac, N. V.; Dahuron, N.; Delcroix, J.-M.; Deyine, A.; Griffart-Brunet, D.; Chiaroni, A.; Riche, C. *Tetrahedron* **1995**, *51*, 3571-3586.
33. Houk, K. N.; Sims, J.; Duke, R. E.; Strozier, R. W.; George, J. K. *J. Am. Chem. Soc.* **1973**, *95*, 7287-7301.
34. Houk, K. N.; Sims, J.; Watts, C. R.; Luskus, L. J. *J. Am. Chem. Soc.* **1973**, *95*, 7301-7315.

35. Atomic Coordinates have been deposited with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from Cambridge Crystallographic Data Centre, 12 Union Rd, Cambridge. CB2 1EZ. U.K.
36. Vedejs, E.; Campbell, J. B.; Gadwood, R. C.; Rodgers, J. D.; Spear, K. L.; Watanabe, Y. *J. Org. Chem.* **1982**, *47*, 1534-1546.
37. Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543-2549.
38. Seebach, D.; Sting, A. R.; Hoffmann, M. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2708-2748.
39. Fletcher, D. A.; McMeeking, R. F.; Parkin, D. *J. Chem. Inf. Comput. Sci.* **1996**, *36*, 746-749.
40. Harwood, L. M.; Manage, A. C.; Robin, S.; Hopes, S. F. G.; Watkin, D.; Williams, C. E. *SynLett.* **1993**, *10*, 777-780.

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