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Asymmetric Diels-Alder Reactions Employing Modified Camphor-Derived Oxazolidin-2-one Chiral Auxiliaries

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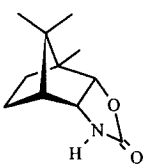
Abstract: Transposition of the dormant methyl group from C-1 in chiral oxazolidin-2-one **2** to C-7 in a six step synthetic sequence from (1*R*)-camphor **5** creates a novel transfigomer **4** with sufficient π-topological bias to induce excellent levels of asymmetric induction in Lewis-acid catalysed Diels-Alder reactions of its α, β-unsaturated carboximide derivatives with cyclopentadiene. Further modification of **4** by replacement of the C-7 methyl group with an ethyl substituent raises the level of diastereoselectivity for the acrylate derivative **11a** from 81 to >95% *d.e.*.

Introduction

The pioneering work of Evans[1] on the utilisation of optically-pure oxazolidin-2-ones derived from α-amino acids as chiral auxiliaries for use in asymmetric synthesis has inspired development of more efficient variants derived from other natural sources such as terpenes[2] and carbohydrates.[3] As part of on-going studies in this area, we have synthesised the *endo*- and *exo*-variants **1**[4] and **2**[5] respectively, both of which are sterically constrained by the rigid bornyl system, and demonstrated their usefulness as chiral reagents in a variety of asymmetric transformations. In particular, these auxiliaries have proved to be effective in achieving high levels



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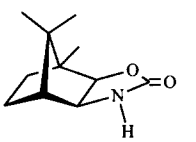
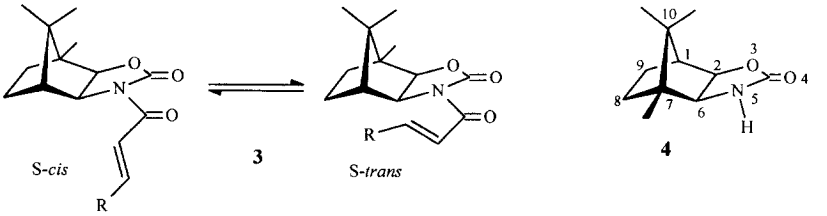


2

of asymmetric induction in alkylation, acylation and aldol reactions, but Diels-Alder cycloadditions were much less successful due to the lack of sufficient π-topological bias imparted by the auxiliary when bearing *N*-acryloyl substituents, *e.g.* **3**. The origin of the poor stereoselection arises from the free rotation of the carbonyl-C_α bond in the *N*-acryloyl moiety of the dienophile. This allows attack by the diene on both enantiofaces, *i.e.* the dienophile can react in either the S-*trans* or S-*cis* conformation despite the adjacent enantiopure bornyl substituent and the presence of a Lewis-acid catalyst [Et_2AlCl or $TiCl_2(OPr^i_2)$], which brings about bidentate chelation and freezes the *N*-carbonyl rotor. In order to render the faces diastereotopic and bring about

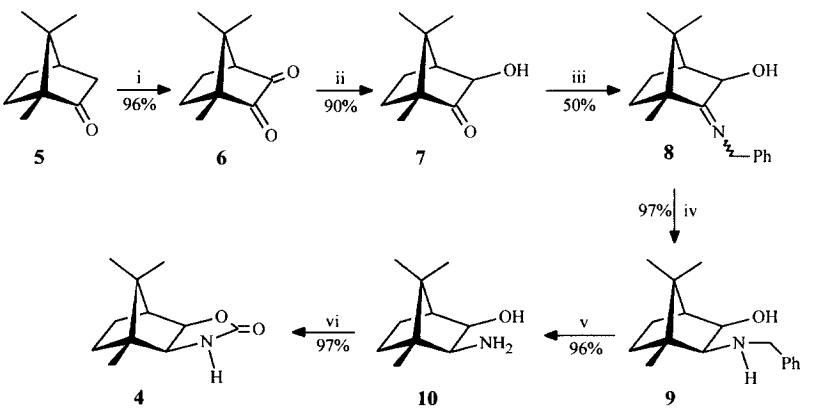
asymmetric induction, it is clearly necessary to modify the chiral framework in systems such as **2** (and **1**) . This steric bias can, in principle, be effected by transposition of the passive methyl group from the rear of the bornane ring to the front, *i.e.* proximal to the active site of the auxiliary, and hence create the positional isomer **4**. We surmised that with chelation control this transposition of steric bias should lead to an increase in steric repulsion between the *N*-acryloyl moiety and the bornane ring in the S-*trans* conformer, and thus lead to better stereoselection *via* the S-*cis* conformer during Diels-Alder reactions. Palomo and co-workers have recently reported the synthesis of **4** in a communication,[6] but hitherto they have only described the Diels-Alder reaction on the crotonyl derivative **11b**.



Results and Discussion

1. Synthesis of (1*S*, 2*R*, 6*S*, 7*R*, *exo*)-3-oxa-5-aza-7,10,10-trimethyltricyclo[5.2.1.0]decan-4-one 4

The synthesis of isomer **4** in an optically pure state was achieved in a six-step process in 39% overall yield starting from (1*R*)-camphor **5** (Scheme 1). Thus, following the previous work carried out by Langlois and co-workers,[7] oxidation of **5** to camphorquinone **6** using selenium dioxide in acetic anhydride[8] was followed by



Scheme 1. *Reagents and conditions*: (i), SeO_2, Ac_2O, reflux, 24h; (ii), L-selectride®, THF, -78°C, 4h; (iii), $PhCH_2NH_2$, 4A molecular sieves, THF, r.t., 72h; (iv), $NaBH_4$, MeOH, r.t., 5.5h; (v), 10% Pd-C, H_2, EtOH; (vi), triphosgene, DME/DCM/H_2O, NaOH.

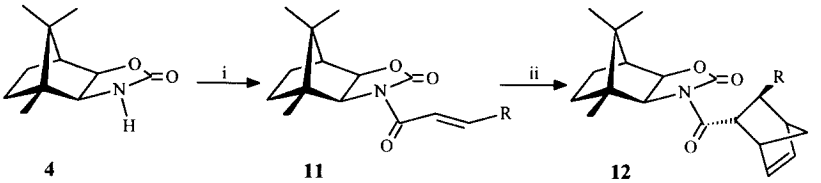
stereoselective reduction with L-Selectride® in tetrahydrofuran (THF) to afford the desired *exo*-α-hydroxyketone **7** exclusively. We sought to avoid the disposal problems associated with the first step, and the expense of the second, by direct conversion of **5** into **7** *via* its silylenol ether[9] and subsequent oxidation with *m*-chloroperoxybenzoic acid, but this approach led to an inseparable 2:1 mixture of *endo*- and *exo*-isomers. In the next step, **7** was transformed into the corresponding *N*-benzylimine **8** by treatment with benzylamine in THF in the presence of 4Å molecular sieves, albeit in only 50% yield. Attempts to improve the yield by varying the reaction temperature and the nature of the dehydrating agent failed, but reduction of imine **8** with sodium borohydride in methanol proceeded smoothly to yield the desired *exo,exo*-hydroxy-*N*-benzylamine **9**, which was deprotected by catalytic hydrogenation with 10% palladium on charcoal to afford *exo,exo*-hydroxyamine **10**. Finally, treatment of **10** with triphosgene and excess sodium hydroxide[10] led to the virtually quantitative formation of the desired oxazolidin-2-one **4**, which after recrystallisation from cyclohexane:ethyl acetate yielded colourless crystals (m.p. = 196.3-197.3°C). Unfortunately, the crystals formed were unsuitable for an X-ray crystal structure but the absolute stereochemistry of the novel auxiliary **4** was proven conclusively by obtaining an X-ray structure for the crotonate Diels-Alder adduct **12b** (*vide infra*).

2. Utility of chiral auxiliary 4 in Diels-Alder cycloaddition reactions

A significant advance in asymmetric Diels-Alder reactions in recent times has been the increased use of Lewis-acid catalysts to control rotameric preference.[1] When compared to non-catalysed Diels-Alder reactions, catalysed versions proceed at greatly enhanced rates as well as with dramatically increased levels of regio- and stereo-selectivity.

The required unsaturated carboximides **11** are easily prepared in excellent yield (89 - 99%) by treatment of the oxazolidin-2-one auxiliary **4** with freshly prepared ethylmagnesium bromide at 0°C in THF followed by the appropriate acid chloride at -78°C (Scheme 2). The Diels-Alder reactions were carried out by addition of diethylaluminium chloride (1.6 equiv.) to a cooled stirred solution of the appropriate dienophile **11** (1 equiv.) and freshly cracked cyclopentadiene (10 equiv.) in dichloromethane. The addition of catalyst to the reaction mixture was accompanied by a yellow colouration which faded on completion of the reaction. The reactions of the acrylate **11a** and crotonate **11b** were carried out at -78°C, whilst the less reactive cinnamate **11c** needed to be warmed to -20°C before reaction would occur.

In each case, reaction occurred in almost quantitative yield and the diastereomeric product ratios were determined by high-field NMR spectroscopic (250 MHz) analysis of the crude product after filtration through silica gel to remove excess cyclopentadiene. The resonances of interest were the two doublet of doublets between δ 5.5 and 6.5 due to the olefinic protons in the cycloadducts **12**. Integration of these signals allowed the *endo*/*exo* selectivities and the diastereomeric excesses (*d.e.*) to be measured.



4 **11** **12**

Scheme 2. *Reagents and conditions*: (i), EtMgBr, THF, 0°C, RCH=CHCOCl, -78°C, **11a**, R = H (88%), **11b**, R = Me (90%), **11c**, R = Ph (99%); (ii), Et_2AlCl, cyclopentadiene, DCM, -78°C (-20°C for **11c**), **12a**, R = H (100%), **12b**, R = Me (92%), **12c**, R = Ph (100%).

The results are summarised in Table 1 and clearly demonstrate the efficiency of **10** as a chiral control element in Lewis-acid mediated Diels-Alder reactions. In each case *endo*-diastereoselection is exceptionally good and well in excess of levels previously attained with chiral oxazolidin-2-one **1**,[4] although the relatively poor level of diastereoselection (81% *d.e.*) obtained with acrylate **11a** presumably reflects the lack of sufficient steric repulsion between the acrylate moiety and the methyl group on the front face of the auxiliary to bring about overwhelming population differences between the chelated S-*cis* and S-*trans* conformers. Nonetheless, the benefit of introducing a methyl group onto the front face of the auxiliary **10** is underlined when the results of the corresponding Diels-Alder reaction of **2** are considered. In this case, *endo*:*exo* selectivities of only *ca.* 4:1 are observed with corresponding low levels of diastereoselection in the range of 48-68%.[11]

Table 1. Diethylaluminium chloride-promoted asymmetric Diels-Alder reactions of unsaturated carboximides derived from auxiliaries **4** and **21** with cyclopentadiene[a]

Dienophile	Temp/°C	Yield (%)	*endo*:*exo*	*d.e.*(%) (corresponding *d.e.* for **1**)
11a	-78	100	100:0	81 (60)
11b	-78	92	100:0	>99 (60)
11c	-20	100	100:0	>99 (99)
22a	-78	92	100:0	>95
22b	-78	91	100:0	>99

[a] Methylene chloride was used as solvent with Et_2AlCl (1.6equiv.) as catalyst.

The absolute stereochemical outcome of the products was determined by obtaining an X-ray crystal structure for the crotonyl-derived adduct **12b** (Fig. 1), which showed that attack of the diene occurred on the C_α-*si* face of the chelated dienophile, *i.e.* opposite to that obtained with the *endo*-variant **1**.[4]

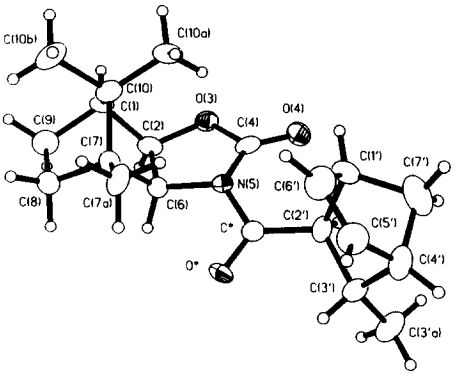


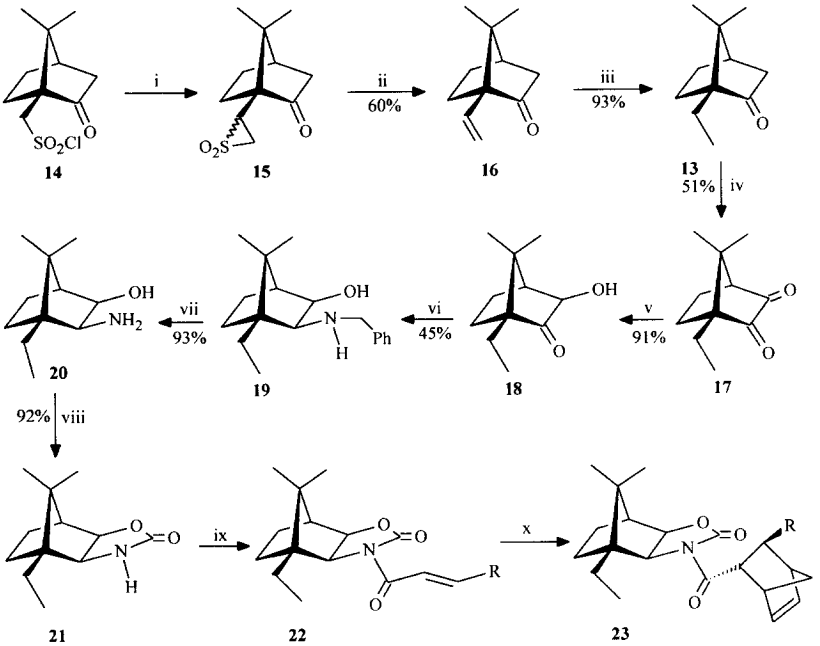
Figure 1. View of the X-ray Structure of Diels-Alder Adduct 12b.

3. Synthesis of (1*S*, 2*R*, 6*S*, 7*R*)-3-oxa-5-aza-7-ethyl-10,10-dimethyl-tricyclo[5.2.1.$0^{2,6}$]decan-4-one 21

In order to improve on the selectivity provided by the auxiliary **4** in Lewis-acid mediated Diels-Alder reactions involving the acrylate derivative **11a**, it was decided to increase the steric bulk at the front face of the auxiliary by replacing the methyl group at C-7 with an ethyl group to create the homologue **21** with the required topological bias to control the rotameric preference. To this end, a synthetic route similar to that adopted for **4** was followed as outlined in Scheme 3, starting from 10-methylcamphor **13**, which can be prepared in a three-step sequence from commercially available 10-camphorsulfonyl chloride **14**. Thus, treatment of **14** with diazomethane followed by neat thermolysis of the crude episulphone **15** produced methylenecamphor **16** as a waxy solid in 60% yield after Kügelrohr distillation. Catalytic hydrogenation of the latter using 10% palladium on charcoal in ethanol gave rise to the desired 10-methylcamphor **13** in excellent yield (93%), but subsequent treatment with selenium dioxide in acetic anhydride under reflux afforded 10-methylcamphorquinone **17** in only 51% yield. Variation of both reaction time and stoichiometry failed to improve the yield, but fortunately unreacted starting material could be recovered and recycled. Stereoselective reduction of **17** proceeded smoothly with L-Selectride® to yield hydroxy ketone **18** in 91% yield. Attempts to prepare the *N*-benzylimine derivative of **18** (*cf.* Scheme 1) failed; variation of temperature and dehydration agent led only to complex mixtures, but the problem was circumvented by direct synthesis of **19** in 45% yield by reductive amination of **18** using titanium(IV)isopropoxide and sodium cyanoborohydride.[12] The *exo, exo*-stereochemistry of **19** was verified by comparison of its ^{1}H NMR spectrum with that of the methyl analogue **9**. In essence, three doublets appeared at δ 3.64, 2.85 and 1.79 ppm due to the protons attached to C-3, C-2 and C-4, respectively with corresponding coupling constants of 7.2, 7.2 and 4.7 Hz, which are almost identical to those displayed by **9**.

The final steps in the synthesis were achieved in a straight-forward manner by catalytic hydrogenation of **19** followed by treatment of the resulting α,β-amino alcohol **20** with triphosgene to afford the desired oxazolidin-2-one **21** as pale-yellow fluffy crystals (m.p. = 138-140°C from xylene/cyclohexane). The overall

yield of **21** for the eight-step synthetic sequence from 10-camphorsulfonyl chloride was only 9%, but sufficient material was obtained to evaluate its synthetic utility in Lewis-acid mediated Diels-Alder reactions.



Scheme 3. *Reagents and conditions*: (i), CH_2N_2, Et_2O, 0°C, 3h; (ii), 95°C; (iii), 10% Pd-C, H_2, EtOH; (iv), SeO_2, Ac_2O; (v), L-Selectride®, THF, -78°C; (vi), Ti(IV)O^{i}Pr, $PhCH_2NH_2$, EtOH, $NaBH_3CN$; (vii), 10% Pd-C, H_2, EtOH; (viii),triphosgene, DME/DCM/H_2O, NaOH; (ix), Et_2Zn, RCH=CHCOCl, 25°C, **22a,** R = H (31%), **b**, R = Me (33%); (x), Et_2AlCl, cyclopentadiene, DCM, -78°C, **23a**, R = H (92%), **b**, R= Me (91%).

4. Lewis-acid mediated Diels-Alder reactions utilising auxiliary 21

Our initial attempts to prepare *N*-acryloyl derivatives of **21** using freshly prepared ethylmagnesium bromide as described previously failed, and only starting material was recovered even after boiling under reflux for *ca.* 24 hours. This obstacle was overcome by utilising an alternative procedure developed by us,[13] whereby the auxiliary was treated with diethylzinc at room temperature followed by cooling to -78°C and subsequent reaction with the appropriate acid chloride (Scheme 3). Even so, acrylate **22a** and crotonate **22b** were obtained in only 31% and 38% yields respectively, along with significant amounts of unreacted **21**. This difficulty in bringing about the functionalisation of **21** is presumably a consequence of the increased steric hindrance arising from the incorporation of an ethyl group at C-7.

The degree of stereoselectivity (*d.e.*%) for the Diels-Alder reaction of dienophiles **22** with cyclopentadiene was determined as before by integration of the signals arising from the olefinic protons in the high field ^{1}H NMR spectra of the cycloadducts **23**. Table 1 shows that the *endo*:*exo* selectivity is excellent in

both cases, and in particular that the *d.e.* for the acrylate **22a** is increased to >95% from 81% for its homologue **11a**.

In conclusion, these experiments show that the reason for the poor diastereoselection in Diels-Alder reactions of cyclopentadiene with **1** and **2** as the chiral control elements is clearly steric in origin and that transposition of the dormant methyl group from C-1 into the vicinity of the reaction site at C-7 is sufficient to improve π-face discrimination to acceptable levels. These can be raised to even higher levels by the introduction of an ethyl group instead of a methyl, although synthesis of the required auxiliary **21** requires eight steps starting from commercially available 10-camphorsulphonyl chloride **14**.

Experimental

Melting points are uncorrected. ^{1}H and ^{13}C NMR spectra were obtained on a Brucker AC-250 operating at 250 MHz or 62.9 MHz or on a Brucker WH-360 operating at 360 MHz or 90.6 MHz respectively. IR spectra were recorded on a Biorad FTS-7 spectrometer and accurate mass measurements determined on a Kratos MS 50TC mass spectrometer. Elemental analyses were determined on a Perkin Elmer 2400 CHN elemental analyser. Tetrahydrofuran and ether were distilled prior to use from sodium/benzophenone ketyl and methylene chloride was distilled from finely divided (Fisons) calcium hydride. Thin layer chromatography was carried out on silica gel 60 F_{254} plates and visualised by UV irradiation and/or dipping the plate into a solution of concentrated sulphuric acid in ethanol (5:95) followed by gentle flaming. Flash chromatography was conducted using silica gel 60 (220-240 mesh). All reagents were used as supplied by commercial sources unless otherwise stated. For all X-ray stuctures reported, atomic coordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre.

***(1R, 3R, exo)-3-Hydroxy-1,7,7-trimethylbicyclo[2.2.1]-heptan-2-one* (7).** A modification of Langlois *et al*'s method[7] was used. To a solution of camphorquinone **6**[8] (4.40g, 26.5mmol) in dry THF (50ml) at -78°C under argon, was added a solution of L-Selectride® (28ml of a 1.0M solution, 28mmol, 1.1eq). The reaction mixture was then stirred at -78°C for 4 hours then quenched by the addition of a solution of hydrochloric acid in methanol (3.0M, 18ml) at the same temperature, and stirred for 10 minutes. The THF was then evaporated *in vacuo* and the aqueous residue extracted into methylene chloride (3x50ml). The organic layers were then dried over magnesium sulphate, filtered and evaporated *in vacuo* to give a yellow oil. The oil was purified by flash chromatography (silica, hexane:ether (95:5)) to give **7** as a colourless oil (3.99g, 90%); ^{13}C NMR (50.32MHz, $CDCl_3$) δ 220.39(C=O), 77.17(CH), 69.36(C), 49.15(CH), 46.61(C), 28.45(CH_2), 20.84(CH_3), 19.89(CH_3), 8.85(CH_3) ppm; FT IR ν_{max} (thin film) 3440(OH), 1748(C=O) cm^{-1}.

***(1R, 3R, exo)-N-Benzyl-3-imino-3-hydroxy-1,7,7-trimethylbicyclo[2.2.1]heptane* (8).** Again a modification of the Langlois method[7] was employed. To a solution of the keto alcohol **7** (2.06g, 12.3mmol) in dry THF (50ml) under argon was added benzylamine (2.89g, 27mmol), and 4Å molecular sieves (3.12g, dried under vacuum at 90°C for 1 hour). The reaction mixture was then stirred at room temperature for 3 days. The mixture was then

filtered through a pad of celite and washed with ether. The solvent was removed *in vacuo* to give a yellow oil. The oil was then purified by flash chromatography (silica, hexane:ether (9:1-4:1)) to give **8** as a colourless solid (3.17g, 50%); ^{13}C NMR (50.32MHz, $CDCl_3$) δ 181.56(C=N), 140.58(Ar C), 128.05(2Ar CH), 127.29(2Ar CH), 126.18(Ar CH), 69.81(CH), 54.31(CH_2), 51.95(C), 49.99(CH), 44.15(C), 32.31(CH_2), 19.14(CH_3), 19.03(CH_3), 18.29(CH_2), 11.66(CH_3) ppm; FT IR ν_{max} (nujol) 3145(OH), 1674(C=N) cm^{-1}.

***(1R, 2S, 3R, exo)-N-Benzyl-2-amino-3-hydroxy-1,7,7-trimethylbicyclo[2.2.1]heptane* (9).**[7] Sodium borohydride (10.50g, 276.3mmol, 10eq) was added in small portions to a stirred solution of the imine **8** (7.10g, 27.6mmol) in methanol (150ml). The reaction mixture was then allowed to stir at room temperature for 5.5 hours. Saturated sodium chloride solution (75ml) was then added and the mixture stirred for 10 minutes, then extracted into methylene chloride (3x100ml). The organic layers were then combined, dried over magnesium sulphate, filtered and evaporated *in vacuo* to give **9** as a clear colourless oil (6.90g, 97%); ^{1}H NMR (250.13MHz, $CDCl_3$) δ 7.35-7.25(5H, cm, Ph), 3.77(2H, s, $PhC\underline{H}_2$), 3.63(1H, d, J = 7.3 Hz, C<u>H</u>OH), 2.70(1H, d, J = 7.3 Hz, C<u>H</u>NH), 1.80(1H, d, J = 4.5 Hz, bridgehead), 1.66-1.51(2H, cm), 1.09-0.83(2H, cm), 1.01(3H, s, CH_3), 0.87(3H, s, CH_3), 0.77(3H, s, CH_3) ppm; ^{13}C NMR (62.90MHz, $CDCl_3$) δ 139.52(Ar C), 128.31(2Ar CH), 127.99(2Ar CH), 127.07(Ar CH), 74.35(CH), 69.66(CH), 55.20(CH_2), 50.94(CH), 48.13(C), 46.41(C), 36.21(CH_2), 23.61(CH_2), 21.58(CH_3), 21.01(CH_3), 11.63(CH_3) ppm; FT IR ν_{max} (thin film) 3357(bs, HN and OH) cm^{-1}.

***(1R, 2S, 3R, exo)-2-Amino-3-hydroxy-1,7,7-trimethylbicyclo[2.2.1]heptane* (10).**[9] A solution of the amino alcohol **9** (2.34g, 9.03mmol) in methanol (60ml) was stirred with 10% Pd/C (0.30g, *ca.* 0.1eq) under a hydrogen atmosphere for 48 hours. The reaction mixture was then filtered through a pad of celite and evaporated *in vacuo* to give **10** as a colourless solid (1.47g, 96%); ^{1}H NMR (200.13MHz, $CDCl_3$) δ 3.62(1H, d, J = 7.4 Hz, C<u>H</u>OH), 3.02(3H, bs, NH_2 and OH), 2.84(1H, d, J = 7.4 Hz, C<u>H</u>NH_2), 1.74(1H, d, J = 4.5 Hz, bridgehead), 1.64-1.42(2H, cm), 1.20-0.80(2H, cm), 1.00(3H, s, CH_3), 0.85(3H, s, CH_3), 0.73(3H, s, CH_3) ppm; ^{13}C NMR (50.32MHz, $CDCl_3$) δ 75.02(CH), 62.43(CH), 50.86(CH), 47.79(C), 46.53(C), 35.74(CH_2), 23.79(CH_2), 21.73(CH_3), 20.73(CH_3), 11.86(CH_3) ppm; FT IR ν_{max} (nujol) 3391(NH_2), 3297(NH_2), 3155(OH) cm^{-1}.

***(1S, 2R, 6S, 7R exo)-3-Oxa-5-aza-7,10,10-trimethyltricyclo[5.2.1.0^{2,6}]decan-4-one* (4).** A solution of 6M NaOH (2ml) was added to the amino alcohol **10** (0.50g, 2.96mmol) in DME (20ml). The reaction mixture was then cooled to -5°C (ice/salt) and treated with a solution of triphosgene (0.38g,1.28mmol) in anhydrous methylene chloride (10ml).The mixture was then stirred at this temperature for 1 hour, then warmed to room temperature and stirred for a further 2.5 hours. The reaction mixture was then extracted into methylene chloride (3x10ml). The combined organic layers were then dried over magnesium sulphate, and subsequent filtration and evaporation *in vacuo* gave **4** as a colourless solid (0.57g,98%); m.p. = 196.3-197.3°C (cyclohexane:ethyl acetate) (Lit.[6] = 202-204°C); $[\alpha]_D^{21}$ = +1.2° (c=1.02, CH_2Cl_2); ^{1}H NMR (250MHz,$CDCl_3$)

δ 7.25(1H, bs, NH), 4.56(1H, dd, *J* = 8.6, 0.5 Hz, CHO), 3.57(1H, dd, *J* = 8.1, 1.3 Hz, CHN), 2.08(1H, d, *J* = 5.1 Hz, bridgehead), 1.76-1.68(1H, cm), 1.51-1.39(2H, cm), 1.05(3H, s, CH_3), 0.96-0.93(1H, cm),0.89(3H, s, CH_3), 0.86(3H, s, CH_3) ppm; ^{13}C NMR (50.32MHz,$CDCl_3$) δ 160.91(C=O), 83.99(CH), 65.43(CH), 47.94(CH), 47.36(C), 46.08(C), 32.64(CH_2), 22.94(CH_3), 22.76(CH_2), 18.97(CH_3), 10.46(CH_3) ppm; FT IR ν_{max} (nujol) 3286(NH),1756(C=O) cm^{-1}; (Found: *m/z*, 196.13312 (MH^+), $C_{11}H_{18}NO_2$ requires 196.13375); (Found: C, 67.2; H, 9.2; N, 7.1. $C_{11}H_{17}NO_2$ requires C, 67.6; H 8.8, N 7.2%.)

(1S, 2R, 6S, 7R, exo)-N-Acryloyl-3-oxa-5-aza-7,10,10-trimethyltricyclo[5.2.1.$0^{2,6}$]decan-4-one **(11a).** Ethyl bromide (0.21g, 1.93mmol) was added to magnesium turnings (0.04g, 1.67mmol) in dry THF (6ml) under argon. When the magnesium had dissolved dry THF (15ml) was added and the mixture cooled to 0°C and treated with a solution of auxiliary **4** (0.20g, 1.03mmol) and quinol (10mg) in dry THF (10ml). After 15minutes the reaction mixture was cooled to -78°C and freshly distilled acryloyl chloride (0.17g, 2.09mmol) added. The mixture was then stirred for 15 minutes, and the temperature then raised to 0°C for 40 minutes, then allowed to warm to room temperature. After 90 minutes the reaction was quenched with saturated ammonium chloride solution and the mixture concentrated *in vacuo*. The aqueous residue was then extracted into methylene chloride (3x20ml). The combined organic layers were dried over magnesium sulphate, and subsequent filtation and evaporation *in vacuo* yielded a yellow oil. The oil was subjected to flash chromatography (silica, hexane:ether (4:1)) to give **11a** as a colourless solid (0.22g,88%); m.p. = 93.4-94.7°C (hexane); $[\alpha]_D^{21}$ = +82.7° (c=1.00,CH_2Cl_2); ^1H NMR (250.13MHz, $CDCl_3$) δ 7.46(1H, dd, *J* = 17.0, 10.4 Hz, proton of $=CH_2$ trans to proton on adjacent carbon), 6.48(1H, dd, *J* = 17.0, 1.8 Hz, proton of $=CH_2$ cis to proton on adjacent carbon), 5.84(1H, dd, *J* = 10.4, 1.8 Hz, C<u>H</u>=CH_2) 4.50(1H, dd, *J* = 8.0, 0.63 Hz, CHO), 4.45(1H, d, *J* = 8.0 Hz, CHN), 2.14(1H, d, *J* = 5.1 Hz, bridgehead), 1.87-1.71(1H, cm), 1.60-1.48(1H, cm), 1.29-1.15(1H, cm), 1.08-0.94(1H, cm), 0.99(3H, s, CH_3), 0.91(3H, s, CH_3), 0.87(3H, s, CH_3) ppm; ^{13}C NMR (62.90MHz, $CDCl_3$) δ 165.47(C=0), 154.78(C=O), 131.71(CH_2), 127.69(CH), 81.30(CH), 69.66(CH), 50.01(C), 47.45(CH), 46.33(C), 33.10(CH_2), 22.62(CH_3 and CH_2), 19.50(CH_3), 11.90(CH_3) ppm; FT IR ν_{max} (nujol) 1787, 1758(C=O), 1695(C=O), 1616(C=C)cm^{-1}; (Found: *m/z*, 250.14451 (MH^+), $C_{14}H_{20}NO_3$ requires 250.14432).

(1S, 2R, ,6S, 7R, exo)-N-Crotonoyl-3-oxa-5-aza-7,10,10-trimethyltricyclo[5,2,1,$0^{2,6}$]decan-4-one **(11b).** Prepared by the same general procedure as above giving **11b** as a colourless solid (0.28g, 90%); m.p. = 141.4-143.4°C (cyclohexane); $[\alpha]_D^{21}$ = +46.0° (c= 0.50, CH_2Cl_2); ^1H NMR (250.13MHz, $CDCl_3$) δ 7.25-7.03(2H, cm, CH=CH), 4.49-4.41(2H, cm, CHO and CHN), 1.92(3H, dd, *J* = 6.5, 1.2 Hz, CH=C<u>H</u>$_3$), 1.89-1.80(1H, cm), 1.52(1H, ddd, *J* = 11.8, 11.8, 4.5 Hz, CH_2), 1.22(1H, dt, *J* = 9.2, 4.0 Hz, CH_2), 1.06-1.00(1H, cm), 0.98(3H, s, CH_3), 0.89(3H, s, CH_3), 0.86(3H, s, CH_3) ppm; ^{13}C NMR (62.90MHz, $CDCl_3$) 165.49(C=O), 154.86(C=O), 146.16(CH), 122.10(CH), 81.06(CH), 65.58(CH), 49.89(C), 47.45(CH), 46.28(C), 33.07(CH_2),

22.61(CH_2+CH_3), 19.44(CH_3), 18.32(CH_3), 11.85(CH_3) ppm; FT IR ν_{max} (nujol) 1758(C=O), 1682(C=O), 1632(C=C) cm^{-1}; (Found: *m/z*, 264.16015 (MH^+), $C_{15}H_{22}NO_3$ requires 264.15997).

***(1S, 2R, 6S, 7R, exo)-N-Cinnamoyl-3-oxa-5-aza-7,10,10-trimethyltricyclo[5.2.1.0^{2,6}]decan-4-one* (11c).** Prepared by the general procedure as above to give **11c** a colourless solid (0.71g, 100%); m.p. = 141.5-142.5°C (cyclohexane); $[\alpha]_D^{21}$ = +149.6° (c=1.03,CH_2Cl_2); ^{1}H NMR (250.13MHz, $CDCl_3$) δ 7.91(1H, d, *J* = 15.7 Hz, COC<u>H</u>=CH), 7.80(1H, d, *J* = 15.8 Hz, C=C<u>H</u>Ph), 7.61-7.57(2H, cm, Ph), 7.39-7.34(3H, cm, Ph), 4.51(2H, s, CHO and CHN), 2.16(1H, d, *J* = 5.1 Hz, bridgehead), 1.81-1.75(1H, cm), 1.56(1H, dt, 12.4, 4.6 Hz, CH_2), 1.31-1.21(1H, cm), 1.05-1.03(1H, cm), 1.03(3H, s, CH_3), 0.95(3H, s, CH_3), 0.88(3H, s, CH_3) ppm; ^{13}C NMR (62.90MHz, $CDCl_3$) δ 165.69(C=0), 154.95(C=O), 145.74(CH), 134.44(Ar C), 130.36(Ar CH), 128.65(2 Ar CH), 128.39(2 Ar CH), 117.32(CH), 81.15(CH), 65.75(CH), 50.10(C), 47.45(CH), 46.32(C), 33.09(CH_2), 22.61(CH_2 and CH_3), 19.50(CH_3), 11.93(CH_3) ppm; FT IR ν_{max} (nujol) 1764(C=O), 1678(C=O), 1618(C=C) cm^{-1}; (Found: *m/z*, 326.17662 (MH^+), $C_{20}H_{24}NO_3$ requires 326.17526).

***(1S, 2R, 6S, 7R, exo)-N-((3'R, 4'S, 5'S, 6'R)-5'-Methylbicyclo[2.2.1]heptene-4'-carbonyl)-3-oxa-5-aza-7,10,10-trimethyltricyclo[5.2.1.0^{2,6}]decan-4-one* (12b).** To a solution of the crotonate **11b** (0.21g, 0.78mmol) in dry methylene chloride (20ml) at -78°C under argon was added freshly cracked cyclopentadiene (0.52g, 7.83mmol, 10eq.). Diethylaluminium chloride (0.7ml of a 1.8M solution, 1.26mmol, 1.6eq.) was then added and the reaction mixture stirred at -78°C for 20minutes, then quenched with saturated ammonium chloride solution. The mixture was then extracted into methylene chloride (3x20ml) and the combined organic layers dried over magnesium sulphate. Subsequent filtration and evaporation *in vacuo* gave a pale yellow solid. The solid was subjected to flash chromatography (silica, hexane:ether (4:1)) to yield **12b** as a colourless solid (0.24g,92%); m.p. = 174.3-175.3°C (cyclohexane); $[\alpha]_D^{21}$ = +178° (c= 1.00, CH_2Cl_2); ^{1}H NMR (360.13MHz, $CDCl_3$) δ 6.35(1H, dd, *J* = 5.6, 3.2 Hz, C=CH), 5.78(1H, dd, *J* = 5.7, 2.7 Hz, CH=C), 4.44(1H, d, *J* = 8.1 Hz, CHO), 4.35(1H, d, *J* = 8.1 Hz, CHN), 3.55(1H, dd, *J* = 4.4, 3.4 Hz, cycloadduct bridgehead CH), 3.28(1H,s, CH), 2.47(1H, d, *J* = 1.4 Hz, cycloadduct bridgehead CH), 2.12(1H, d, *J* = 5.1 Hz, auxiliary bridgehead), 2.12-2.06(1H, cm), 1.81-1.72(1H, cm), 1.44(1H, d, *J* = 1.7 Hz, CH), 1.54-1.41(2H, cm), 1.22-1.13(1H, cm), 1.06(3H, d, *J* = 7.1 Hz, CHC<u>H</u>$_3$), 1.02(3H, s, CH_3), 1.00-0.89(1H, cm), 0.86(3H, s, CH_3), 0.81(3H, s, CH_3) ppm; ^{13}C NMR (50.32MHz, $CDCl_3$) δ 174.22(C=O), 154.74(C=O), 139.74(CH), 130.75(CH), 80.97(CH), 65.70(CH), 51.70(CH), 49.65(C), 49.01(CH), 47.51(CH and CH_3), 47.10(CH_2), 46.20(C), 35.08(CH), 33.19(CH_2), 22.59(CH and CH_2), 20.24(CH_3), 19.23(CH_3), 11.92(CH_3) ppm; FT IR ν_{max} (nujol) 1757(C=0), 1705(C=O) cm^{-1}; (Found: *m/z*, 330.20691(MH^+), $C_{20}H_{28}NO_3$ requires 330.20691); (Found: C, 72.6; H, 8.1; N, 4.6. $C_{20}H_{27}NO_3$ requires C, 72.9; H, 8.3; N, 4.3%).

***(1S, 2R, 6S, 7R, exo)-N-((3'R, 4'S, 5'S, 6'R)-5'-Phenylbicyclo[2.2.1]heptene-4'-carbonyl)-3-oxa-5-aza-7,10,10-trimethyltricyclo[5.2.1.0^{2,6}]decan-4-one* (12c).** Reaction protocol as that described above except reaction temperature was -20°C gave **12c** as a colourless solid(0.23g, 99%); m.p. = 176.5-178°C; $[\alpha]_D^{21}$ =

+169.3 (c=1.05, CH_2Cl_2); ^{1}H NMR (250.13MHz, $CDCl_3$) δ 7.27-7.16(5H, cm, Ph), 6.54(1H, dd, *J* = 5.6, 3.2 Hz, HC=C<u>H</u>), 5.96(1H, dd, *J* = 5.6, 2.8 Hz, C<u>H</u>=CH), 4.44(1H, d, *J* = 8.2 Hz, CHO), 4.37(1H, d, *J* = 8.1 Hz, CHN), 4.22(1H, dd, 5.3, 3.4 Hz, CHCO), 3.51(1H, bs), 3.37(1H, dd, *J* = 5.3, 1.8 Hz, CHPh), 2.99(1H, bs), 2.15(1H, d, *J* = 5.1 Hz, cycloadduct bridgehead CH), 1.97(1H, d, *J* = 8.7 Hz, auxiliary bridgehead), 1.79-1.52(3H, cm), 1.30-1.10(1H, cm), 1.07(3H, s, CH_3), 1.06-0.73(1H, cm), 0.90(3H, s, CH_3), 0.88(3H, s, CH_3) ppm; ^{13}C NMR (62.90MHz, $CDCl_3$) δ 173.82(C=O), 154.64(C=O), 143.76(Ar C), 40.25(CH), 132.06(CH), 128.27(2 Ar CH), 127.40(2 Ar CH), 125.87(Ar CH), 81.09(CH), 65.78(CH), 50.99(CH), 49.72(C), 49.12(CH), 48.13(CH_2), 47.53(CH), 47.42(CH), 46.26(C), 45.61(CH), 33.20(CH_2), 22.60(CH_2 and CH_3), 19.29(CH_3), 11.98(CH_3) ppm; FT IR ν_{max} (nujol) 1760(C=O), 1703(C=O) cm^{-1}; (Found: *m/z*, 392.22334 (MH^+) $C_{25}H_{30}NO_3$ requires 392.22257).

(1R, 2R, 6S, 7R, exo)-N-((3'R, 4'S, 6'R)-5'-Bicyclo[2.2.1]heptene-4'-carbonyl)-3-oxa-5-aza-7,10,10-trimethyltricyclo[5.2.1.0^{2,6}]decan-4-one **(12a).** Procedure as described previously for **12b** yielded **12a** as a colourless solid (0.22g, 99%).; ^{1}H NMR (250.13MHz, $CDCl_3$) δ (major isomer) 6.26(1H, dd, *J* = 5.6, 3.1 Hz, C<u>H</u>=CH), 5.85(1H, dd, *J* = 5.6, 2.8 Hz, CH=C<u>H</u>), 4.45(1H, d, *J* = 8.0 Hz, CHO), 4.34(1H, d, *J* = 8.1 Hz, CHN), 4.06(1H, dt, *J* = 8.3, 4.2 Hz, COC<u>H</u>CH_2), 3.36(1H, bs), 2.92(1H, bs), 2.14(1H, d, *J* = 5.0 Hz, auxiliary bridgehead), 1.83-0.92(8H, cm), 1.04(3H, s, CH_3), 0.88(3H, s, CH_3), 0.84(3H, s, CH_3) ppm; ^{13}C NMR (62.90MHz, $CDCl_3$) δ 174.61(C=O), 154.78(C=O), 138.37(CH), 130.77(CH), 81.07(CH), 65.87(CH), 50.45(CH_2), 49.76 (C), 47.59(CH), 46.82(CH), 46.27(C), 42.97 (CH), 42.69(CH), 33.29(CH_2), 28.06(CH_2), 22.65(CH_2 and CH_3), 19.31(CH_3), 12.02(CH_3) ppm; FT IR ν_{max} (nujol) 1769(C=O), 1711(C=O) cm^{-1}; (Found: *m/z*, 316.19215 (MH^+), $C_{19}H_{26}NO_3$ requires 316.19127).

(1S, 2R, 6S, 7R, exo)-N-((3'R, 4'S, 5'S, 6'R)-5'-Methylbicyclo[2.2.1]hept-1'-ene-4'-carbonyl)-3-oxa-5-aza-7-ethyl-10,10-dimethyltricyclo[5.2.1.0^{2,6}]decan-4-one **(23b).** Same procedure as above gave **23b** as a pale yellow gum (which partially solidified on standing) (0.09g, 91%); $[\alpha]_D^{21}$ = +88.0° (c=2.00, $CHCl_3$); ^{1}H NMR (250.13MHz, $CDCl_3$) δ 6.36(1H, dd, *J* = 5.7, 3.2 Hz, C<u>H</u>=CH), 5.78(1H, dd, *J* = 5.7, 2.8 Hz, CH=C<u>H</u>), 4.45(2H, s, CHO and CHN), 3.64(1H, dd, *J* = 4.6, 3.4 Hz, COC<u>H</u>$CH(CH_3)$), 3.27(1H, bs, cycloadduct bridgehead), 2.48(1H, bs, cycladduct bridgehead), 2.13-2.06(2H, cm, including auxiliary bridgehead), 1.83-1.41(4H, cm), 1.27-0.80(4H, cm), 1.08(3H, d, *J* = 7.1 Hz, CH_3CH), 1.02(3H, s, CH_3), 0.89(6H, t and s, *J* = 7.5 Hz, CH_2CH_3 and CH_3) ppm; ^{13}C NMR (62.90MHz, $CDCl_3$) δ 174.41(C=O), 155.05(C=O), 139.79(<u>C</u>H=CH), 130.74(CH=<u>C</u>H), 81.04(CH), 63.98(CH), 53.00(C), 51.90(CH), 49.09(CH), 47.97(CH), 47.67(CH), 47.18(CH_2), 46.80(C), 35.32(CH), 29.17(CH_2), 23.54(CH_3), 22.34(CH_2), 20.26(CH_3), 19.25(CH_3), 18.08(CH_2), 9.64(CH_3) ppm; FT IR ν_{max} (thin film) 1771(C=O), 1703(C=O), 1657(C=C) cm^{-1}; (Found: *m/z*, 344.22271 (MH^+), $C_{21}H_{30}NO_3$ requires 344.22257).

(1S, 2R, 6S, 7R, exo)-N-((3'R, 4'S, 6'R)-Bicyclo[2.2.1]hept-1'-ene-4'-carbonyl)-3-oxa-5-aza-7-ethy-10,10-dimethyltricyclo[5.2.1.0^{2,6}]decan-4-one **(23a).** Reaction conditions as before gave **23a** as a colourless solid

(0.16g, 92%); m.p. = 97.0-99.0°C (hexane); $[\alpha]_D^{21}$ = +100.0° (c=1.75, $CHCl_3$); ^{1}H NMR (250.13MHz, $CDCl_3$) δ 6.27(1H, dd, *J* = 5.6, 3.0 Hz, C<u>H</u>=CH), 5.81(1H, dd, *J* = 5.7, 2.8 Hz, CH=C<u>H</u>), 4.45(2H, s, CHO and CHN), 4.16(1H, dt, *J* = 8.0, 3.6 Hz, COC<u>H</u>CH_2), 3.34(1H, bs, cycloadduct bridgehead), 2.93(1H, bs, cycloadduct bridgehead), 2.12(1H, d, *J* = 5.0 Hz, auxiliary bridgehead), 1.84-1.70(2H, cm), 1.62-1.51(2H, cm), 1.46-1.41(2H, cm), 1.30-1.10(3H, cm), 1.04(3H, s, CH_3), 1.00-0.84(1H, cm), 0.91(3H, t, *J* = 7.4 Hz, $CH_2C\underline{H}_3$), 0.90(3H, s, CH_3) ppm; ^{13}C NMR (62.90MHz, $CDCl_3$) δ 174.68(C=O), 155.09(C=O), 138.43(<u>C</u>H=CH), 130.65(CH=<u>C</u>H), 81.10(CH), 64.13(CH), 53.07(C), 50.52(CH_2), 48.00(CH), 47.03(CH), 46.82(C), 43.01(CH), 42.75(CH), 29.21(CH_2), 28.08(CH_2), 23.57(CH_3), 22.34(CH_2), 19.30(CH_3), 18.16(CH_2), 9.67(CH_3) ppm; FT IR ν_{max} (nujol) 1759(C=O), 1707(C=O) cm^{-1}; (Found: *m/z*, 330.20714 (MH^+), $C_{20}H_{28}NO_3$ requires 330.20692).

***(1R)-1-Vinyl-7,7-dimethylbicyclo[2.2.1]hepan-2-one* (16).**[14] A solution of (1*S*)-(+)-10-camphorsulphonyl chloride **14** (6.02g, 23.98mmol) in ether (100ml) was added dropwise over 1 hour to an ethereal solution of diazomethane (30mmol). The mixture was stirred at 0°C for 2 hours and then concentrated *in vacuo*, filtered and evaporated *in vacuo* to give an orange oil which was recrystallised from methanol at -20°C to give colourless crystals of episulphone **15**. Owing to its instability the crude episulphone **15** (1.12g, 4.91mmol) was heated to 95°C (with a condenser fitted) for 30 minutes, during which time gas was seen to be evolved. The resulting crude yellow liquid was distilled on a Kugelrohr (3mmHg, 120°C) to give **16** as a colourless waxy solid (0.57g, 60% based on camphorsulphonyl chloride); m.p. = 62-64°C (Lit[14] = 64-65°C); $[\alpha]_D^{21}$ = +16.4° (c=2.15, MeOH); ^{1}H NMR (250.13MHz, $CDCl_3$) δ 5.76(1H, dd, *J* = 17.6, 11.1 Hz, C<u>H</u>=CH_2), 5.33(1H, dd, *J* = 11.1, 1.7 Hz, proton of =CH_2 cis to H), 5.16(1H, dd, *J* = 17.6, 1.7 Hz, proton of =CH_2 trans to H), 2.40(1H, ddd, *J* = 18.3, 4.6, 2.2 Hz, CH<u>H</u>CO), 2.11-1.81(4H, cm, including bridgehead), 1.48-1.32(2H, cm), 0.88(3H, s, CH_3) 0.87(3H, s, CH_3) ppm; ^{13}C NMR (62.90MHz, $CDCl_3$) δ 217.11(C=O), 131.98(<u>C</u>H=CH_2), 118.76(CH=<u>C</u>H_2), 63.90(C), 48.29(C), 43.41(CH_2), 43.15(CH), 26.71(CH_2), 25.67(CH_2), 19.90(CH_3), 19.13(CH_3) ppm; FT IR ν_{max} (nujol) 1747(C=O), 1640(C=C) cm^{-1}.

***(1R)-1-Ethyl-7,7-dimethylbicyclo[2.2.1]heptan-2-one* (13).** 10% Pd/C (0.70g, 0.1eq) was added to a solution of vinylcamphor **16** (6.25g, 38.1mmol) in ethanol (80ml). The reaction mixture was then stirred under an atmosphere of hydrogen for 16 hours. The mixture was then filtered through a pad of celite and the filtrate evaporated *in vacuo* to give **13** as a clear colourless liquid (5.81g, 93%); $[\alpha]_D^{21}$ = +24.8° (c=2.85, EtOH); ^{1}H NMR (250.13MHz, $CDCl_3$) δ 2.30(1H, ddd, *J* = 18.1, 4.8, 3.3 Hz, C<u>H</u>HO), 2.02-1.93(1H, cm, bridgehead), 1.92-1.15(7H, cm), 0.98(3H, t, *J* = 7.6 Hz, $CH_2C\underline{H}_3$), 0.94(3H, s, CH_3), 0.85(3H, s, CH_3) ppm; ^{13}C NMR (62.90MHz, $CDCl_3$) δ 219.74(C=O), 60.17(C), 47.17(C), 43.36(CH and CH_2), 26.72(CH_2), 26.31(CH_2), 20.22(CH_3), 19.71(CH_3), 18.18(CH_2), 9.43(CH_3) ppm; FT IR ν_{max} (thin film) 1741(C=O) cm^{-1}.

***(1R)-1-Ethyl-7,7-dimethylbicyclo[2.2.1]heptan-2,3-dione* (17).** Selenium dioxide (11.10g, 100mmol, 3eq) was added to a solution of 10-methyl-camphor **13** (5.95g, 35.8mmol) in acetic anhydride (30ml), and the

mixture then heated under reflux for 48 hours. A further portion of selenium dioxide (11.01g, 99mmol, 3eq) was added and reflux continued for another 24 hours. The mixture was allowed to cool and neutralised with 30% sodium hydroxide solution, then taken to pH 8, and filtered through a pad of celite. The solid residue was washed with ether until the ether ran colourless (*ca.* 1.5 litres). The filtrate was separated and the organic layer dried over magnesium sulphate, filtered and evaporated *in vacuo* to give a yellow oil. The oil was subjected to flash chromatography (silica, hexane:ether (95:5)) to give **17** as a yellow solid (3.26g, 51%); m.p. = 56.0-56.7°C (methanol/water); $[\alpha]_D^{21}$ = -157° (c=1.00, CH_2Cl_2); ^{1}H NMR (250.13MHz, $CDCl_3$) δ 2.51(1H, d, *J* = 4.9 Hz, bridgehead), 2.17-2.04(1H, cm), 1.97-1.86(1H, cm), 1.76-1.51(3H, cm), 1.46-1.32(1H, cm), 1.02(3H, t, *J* = 7.6 Hz, $CH_2C\underline{H}_3$), 1.00(3H, s, CH_3), 0.89(3H, s, CH_3) ppm; ^{13}C NMR (62.90MHz, $CDCl_3$) δ 204.69(C=O), 202.78(C=O), 61.27(C), 58.11(CH), 42.76(C), 26.44(CH_2), 21.75(CH_2), 21.28(CH_3), 17.82(CH_2), 17.65(CH_3), 9.19(CH_3) ppm; FT IR ν_{max} (nujol) 1756(bs, 2C=O) cm^{-1}; (Found: *m/z*, 181.12301 (MH^+), $C_{11}H_{17}O_2$ requires 181.12285).

***(1R, 3R, exo)-3-Hydroxy-1-ethyl-7,7-dimethylbicyclo[2.2.1]heptan-2-one* (18).** L-Selectride® (25ml of a 1.0M solution, 25mmol, 1.1eq) was added to a solution of 10-methyl-camphorquinone **17** (4.00g, 22.2mmol) in dry THF (80ml) at -78°C under argon. The reaction mixture was allowed to stir at -78°C for 1.5 hours, then quenched by the addition of a 3M solution of hydrochloric acid in methanol (40ml total volume) and stirred at -78°C for 20 minutes. The THF was then removed *in vacuo* and the aqueous residue extracted into methylene chloride (3x100ml). Subsequent drying over magnesium sulphate, filtration and evaporation *in vacuo* of the combined organic layers gave an unpleasant smelling yellow liquid. The liquid was purified by flash chromatography silica, hexane:ether (9:1 - 3:1)) to give **18** as a clear colourless oil (3.64g, 91%); $[\alpha]_D^{21}$ = +77.3° (c=1.5, CH_2Cl_2); ^{1}H NMR (250.13MHz, $CDCl_3$) δ 3.65(1H, s, C<u>H</u>OH), 3.25(1H, bs, CHO<u>H</u>), 2.00-1.87(2H, cm, includes bridgehead), 1.71-1.28(3H, cm), 1.22-1.04(1H, cm), 0.97-0.79(10H, cm, including $3CH_3$) ppm; ^{13}C NMR (62.90MHz, $CDCl_3$) δ 220.42(C=O), 77.15(CH), 59.89(C), 49.35(CH), 47.00(C), 24.78($2CH_2$), 21.00(CH_3), 20.54(CH_3), 17.65(CH_2), 9.16(CH_3) ppm; FT IR ν_{max}(thin film) 3459(OH), 1749(C=O)cm^{-1}; (Found: *m/z*, 183.13843 (MH^+), $C_{11}H_{19}O_2$ requires 183.13851).

***(1R, 2S, 3R, exo)-N-Benzyl-2-amino-3-hydroxy-1-ethyl-7,7-dimethyl-bicyclo[2.2.1]heptane* (19).** The general procedure outlined by Mattson *et al*[12] was used. A mixture of **18** (1.05g, 5.77mmol), benzylamine (0.64g, 5.98mmol, 1.0eq) and titanium(IV)isopropoxide (2.07g, 7.92mmol, 1.4eq) were stirred together at room temperature under a drying tube for 1 hour, FT IR then showed the absence of any ketone band. Ethanol (7ml) was then added followed by the addition of sodium cyanoborohydride (0.25g, 3.97mmol, 0.7eq), and the reaction mixture stirred at room temperature for 22 hours. Water (2ml) was added and the mixture filtered and concentrated *in vacuo*. The residue was dissolved in ethyl acetate and again filtered and evaporated *in vacuo* to yield a cloudy creamy coloured oil. The oil was purified by flash chromatography (silica, hexane:ether (95:5 - 4:1)) to give **19** as a clear colourless oil (0.70g, 45%); $[\alpha]_D^{21}$ = -44.0° (c=1.50, CH_2Cl_2); ^{1}H NMR

(250.13MHz, $CDCl_3$) δ 7.35-7.25(5H, cm, Ph), 3.75(2H, s, $PhC\underline{H}_2$), 3.64(1H, d, *J* = 7.2 Hz, C<u>H</u>OH), 2.85(1H, d, *J* = 7.2 Hz, C<u>H</u>NH), 1.79(1H, d, *J* = 4.7 Hz, bridgehead), 1.78-1.57(1H, cm), 1.50-1.16(4H, cm), 1.11-0.82(1H, cm), 0.99(3H, s, CH_3), 0.90(3H, t, *J* = 7.5Hz, $CH_2C\underline{H}_3$), 0.75(3H, s, CH_3) ppm; ^{13}C NMR (62.90MHz, $CDCl_3$) δ 139.33(Ar C), 128.39(2Ar CH), 128.08(2Ar CH), 127.21(Ar CH), 74.02(CH), 67.12(CH), 55.64(CH_2), 52.06(C), 51.45(CH), 46.74(C), 32.70(CH_2), 23.29(CH_2), 21.98(CH_3), 21.21(CH_3), 19.22(CH_2), 9.38(CH_3) ppm; FT IR ν_{max} (thin film) 3357(OH), 3330(NH) cm^{-1}; (Found: *m/z*, 274.21663 (MH^+), $C_{18}H_{28}NO$ requires 274.21709).

***(1R, 2S, 3R, exo)-2-Amino-3-hydroxy-1-ethyl-7,7-dimethylbicyclo[2.2.1]heptane* (20).** 10% Pd/C (0.16g, 0.3eq) was added to a solution of the amino-alcohol **19** (0.66g, 2.42mmol) in methanol (15ml) and the reaction mixture stirred under an atmosphere of hydrogen for 48 hours. The mixture was then filtered through a pad of celite, then evaporated *in vacuo* to give a very pale yellow oil. The oil was purified by dry flash chromatography (silica, ether:methanol (100:0 - 0:100)) to give **20** as a colourless waxy solid (0.41g, 93%); m.p. = >270°C decomposes; $[\alpha]_D^{21}$ = -44.2° (c=1.00, CH_2Cl_2); ^{1}H NMR (250.13MHz, $CDCl_3$) δ 3.55(1H, d, *J* = 7.5 Hz, C<u>H</u>OH), 2.99(1H, d, *J* = 7.5 Hz, C<u>H</u>NH_2), 2.48(3H, bs, OH and NH_2), 1.78(1H, d, *J* = 4.7 Hz, bridgehead), 1.64-1.51(1H, cm), 1.46-1.34(2H, cm), 1.24-0.74(3H, cm), 0.97(3H, s, CH_3), 0.88(3H, t, *J* = 7.4 Hz, $CH_2C\underline{H}_3$), 0.72(3H, s, CH_3) ppm; ^{13}C NMR (62.90MHz, $CDCl_3$) δ 74.75(CH), 58.82(CH), 51.31(C), 51.11(CH), 46.83(C), 32.22(CH_2), 23.51(CH_2), 22.07(CH_3), 20.63(CH_3), 19.10(CH_2), 9.18(CH_3) ppm; FT IR ν_{max} (nujol) 3453 and 3328(NH_2) cm^{-1} both superimposed on a bs(OH); (Found: *m/z*, 184.17109 (MH^+), $C_{11}H_{22}NO$ requires 184.17014).

***(1S, 2R, 6S, 7R, exo)-3-Oxa-5-aza-7-ethyl-10,10-dimethyltricyclo[5.2.1.0^{2,6}]decan-4-one* (21).** The primary amino alcohol **20** (0.38g, 2.08mmol) in DME (10ml) was treated with a solution of sodium hydroxide (2ml of a 6M solution, 12mmol, 6eq), then cooled to -5°C (ice/salt). Triphosgene (0.28g, 0.94mmol, 0.4eq) in methylene chloride (8ml) was then added and the mixture stirred for 1 hour at -5°C, then at room temperature for a further 1.5 hours. TLC (silica, cyclohexane:ethyl acetate (2:1)) indicated reaction was complete, so water (20ml) was added and the mixture extracted into methylene chloride (3x50ml). The combined organic layers were dried over magnesium sulphate, filtered and evaporated *in vacuo* to give a pale brown solid. The crude product was subjected to dry flash chromatography (silica, hexane:ether (100:0 - 0:100)) to give **21** as a very pale yellow crystalline solid (0.40g, 92%); m.p. = 138.0-140.0°C (xylene/cyclohexane); $[\alpha]_D^{21}$ = -10.0° (c=1.25, CH_2Cl_2); ^{1}H NMR (250.13MHz, $CDCl_3$) δ 7.21(1H, bs, NH), 4.54(1H, d, *J* = 8.1 Hz, CHO), 3.72(1H, dd, *J* = 8.1, 0.9 Hz, CHN), 2.06(1H, d, *J* = 5.1 Hz, bridgehead), 1.78-1.65(1H, cm), 1.53-1.16(3H, cm), 1.10-0.78(2H, cm), 1.03(3H, s, CH_3), 0.84(3H, t, *J* = 7.5 Hz, $CH_2C\underline{H}_3$), 0.83(3H, s, CH_3) ppm; ^{13}C NMR (62.90MHz, $CDCl_3$) δ 161.03(C=O), 83.84(CH), 62.40(CH), 51.18(C), 48.14(CH), 46.51(C), 29.27(CH_2), 23.26(CH_3), 22.59(CH_2), 19.02(CH_3), 18.15(CH_2), 9.28(CH_3) ppm; FT IR ν_{max} (nujol) 3253(NH), 3141(NH),

1733(C=O), 1713(C=O) cm^{-1}; (Found: *m/z*, 210.14970 (MH^+), $C_{12}H_{20}NO_2$ requires 210.14940); (Found: C, 68.7; H, 9.1; N, 6.5. $C_{12}H_{19}NO_2$ requires C, 68.9; H, 9.1; N, 6.7%)

***(1S, 2R, 6S, 7R, exo)-N-Crotonoyl-3-oxa-5-aza-7-ethyl-10,10-dimethyltricyclo[5.2.1.$0^{2,6}$]decan-4-one* (22b).** Diethylzinc (1.0ml of a 1.0M solution, 1.00mmol, 1.1eq) was added to a solution of the auxiliary **21** (0.18g, 0.86mmol) in dry ether (12ml) under argon, and the mixture stirred at room temperature for 1 hour. The reaction mixture was then cooled to -78°C and treated with crotonyl chloride (0.30g, 2.87mmol, 3eq), then allowed to warm to room temperature and stirred for 1.5 hours. The mixture was warmed to 25°C and stirred for 4 hours, then left to stir at room temperature overnight. The reaction was quenched by the careful addition of saturated sodium bicarbonate solution, then treated with a 1:1 mixture of 1M hydrochloric acid and saturated ammonium chloride solution until two distinct layers were observed. The layers were then separated and the aqueous further extracted into ether (3x50ml). The combined organic layers were dried over magnesium sulphate, filtered and evaporated *in vacuo* to give a yellow oil. The oil was purified by flash chromatography (silica, hexane:ether (95:5 - 8:1)) to give unreacted auxiliary **21** (0.06g, 33%) and **22b** as a colourless solid (0.90g, 38%); m.p. = 134-136°C; $[\alpha]_D^{21}$ = +48.7° (c=0.75, CH_2Cl_2); ^{1}H NMR (250.13MHz, $CDCl_3$) δ 7.25-7.03(2H, cm, C<u>H</u>=C<u>H</u>), 4.54-4.45(2H, cm, CHO and CHN), 2.11(1H, d, *J* = 5.0 Hz, bridgehead), 1.92(3H, d, *J* = 5.2 Hz, C=CHC<u>H</u>$_3$), 1.82-1.70(2H, cm), 1.63-1.51(1H, cm), 1.30-1.12(3H, cm), 0.98(3H, s, CH_3), 0.95(3H, t, *J* = 7.4 Hz, CH_2C<u>H</u>$_3$), 0.89(3H, s, CH_3) ppm; ^{13}C NMR (62.90MHz, $CDCl_3$) δ 165.66(C=O), 155.13(C=O), 145.90(<u>C</u>H=C), 122.60(C=<u>C</u>H), 81.11(CH), 63.91(CH), 53.13(C), 47.93(CH), 46.80(C), 29.26(CH_2), 23.53(CH_3), 22.31(CH_2), 19.42(CH_3), 18.34(CH_2 and CH_3), 9.72(CH_3) ppm; FT IR ν_{max} (nujol) 1759(C=O), 1690(C=O), 1634(C=C) cm^{-1}; (Found: *m/z*, 278.17594 (MH^+), $C_{16}H_{24}NO_3$ requires 278.17562).

***(1S, 2R, 6S, 7R, exo)-N-Acryloyl-3-oxa-5-aza-7-ethyl-10,10-dimethyltricyclo[5.2.1.$0^{2,6}$]decan-4-one* (22a).** Procedure as above yielded unreacted auxiliary **21** (0.13g, 50%) and **22a** as a colourless solid (0.10g, 31%); m.p. = 84.0-86.0°C (hexane); $[\alpha]_D^{21}$ = +66.8° (c=0.75, $CHCl_3$); ^{1}H NMR (250.13MHz, $CDCl_3$) δ 7.42(1H, dd, *J* = 17.0, 10.3 Hz, C<u>H</u>=CH_2), 6.48(1H, dd, *J* = 17.0, 1.7 Hz, proton of CH=C<u>H</u>$_2$ trans to H), 5.85(1H, dd, *J* = 10.5, 1.7 Hz, proton of CH=C<u>H</u>$_2$ cis to H), 4.54(1H, distorted d, *J* = 8.0 Hz, CHO), 4.50(1H, distorted d, *J* = 8.2 Hz, CHN), 2.14(1H, d, *J* = 5.0 Hz, bridgehead), 1.86-1.73(1H, cm), 1.66-1.54(1H, cm), 1.33-1.15(3H, cm), 1.07-0.96(1H, cm), 1.00(3H, s, CH_3), 0.98(3H, t, *J* = 7.3 Hz, CH_2C<u>H</u>$_3$), 0.91(3H, s, CH_3) ppm; ^{13}C NMR (62.90MHz, $CDCl_3$) δ 165.69(C=O), 155.07(C=O), 130.94(<u>C</u>H=CH_2), 128.19(CH=<u>C</u>H$_2$), 81.36(CH), 64.00(CH), 53.27(C), 47.95(CH), 46.88(C), 29.31(CH_2), 23.54(CH_3), 22.34(CH_2), 19.48(CH_3), 18.39(CH_2), 9.74(CH_3) ppm; FT IR ν_{max} (nujol) 1759(C=O), 1698(C=O), 1616(C=C) cm^{-1}; (Found: *m/z*, 264.15964 (MH^+), $C_{15}H_{22}NO_3$ requires 264.15997).

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