Tetrahedron Vol. 48, No. 37, pp. 7979-8006, 1992
Printed in Great Britain

0040-4020/92 $5.00+.00

Enantiospecific Preparation of [(2R, 6S)-*endo*]-5-Aza-1,10,10-trimethyl-3-oxatricyclo[5.2.1.$0^{2,6}$]decan-4-one by a Nitrene-mediated Route from [(1S)-*endo*]-(-)-Borneol and its Utility as a Chiral Auxiliary in Some Asymmetric Transformations

Malcolm R. Banks[a], Alexander J. Blake[a], J. I. G. Cadogan[b], Ian M. Dawson[a], Ian Gosney[a], Keith J. Grant[a], Suneel Gaur[a], Philip K. G. Hodgson[b], Kevin S. Knight[b], Glen W. Smith[b], and Dian E. Stevenson (nee Thomson)[a].

[a] Department of Chemistry, University of Edinburgh, West Mains Road, Edinburgh,EH9 3JJ, Scotland

[b]B.P. International Ltd., Sunbury Research Centre, Chertsey Road, Sunbury-on-Thames, Middlesex, TW16 7LN, England

(*Received in USA* 3 *August* 1992)

Abstract: Attempted chiral aziridination of styrene by addition of optically-active alkoxycarbonylnitrene **5** derived from [(1S)-*endo*]-(-)-bornyl *p*-nitrobenzenesulphonoxycarbonate **4** is reported. No measurable asymmetric induction is observed under the various conditions employed, but in the absence of alkene, a tricyclic oxazolidin-2-one **8** is formed to which preparatively simpler access can be gained by thermal decomposition of azidoformate **7**, either in 1,1,2,2-tetrachloroethane (50%) or by spray pyrolysis (58%). The oxazolidin-2-one **8** is demonstrated to be a successful chiral auxiliary by contemporary standards in a variety of asymmetric transformations, including alkylation, acylation, and aldol reactions for which high levels of asymmetric induction are observed. Diethylaluminium chloride-catalysed Diels-Alder reactions exhibit poorer selectivity except for the cinnamoyl derivative **23** which is stereospecific.

Introduction

Compared to the chiral epoxidation of alkenes[1] the corresponding process for aziridination has received scant attention, although Nozaki *et al*[2] have succeeded, albeit with resolution, by using a chiral modification of Hassner's classical method *via* β-iodocarbamates[3]. More recently, Atkinson and co-workers[4] have achieved modest-to-exclusive stereoselectivities by the oxidation of an *N*-aminobenzimidazole and *N*-aminoquinazolones in the presence of prochiral alkenes. Recent evidence[5] indicates that such aziridinations involve electrophilic addition of intermediate *N*-acetoxyaminoquinazolone and not a free nitrene or nitrenium ion. Chiral aziridination by addition of optically-active nitrenes to prochiral alkenes has, to the best of our knowledge, not been used. We now report the generation of the optically-active alkoxycarbonyl nitrene **5**, and the outcome of its potentially enantioselective addition to styrene. Furthermore, we wish to relate the serendipitous discovery of a new chiral

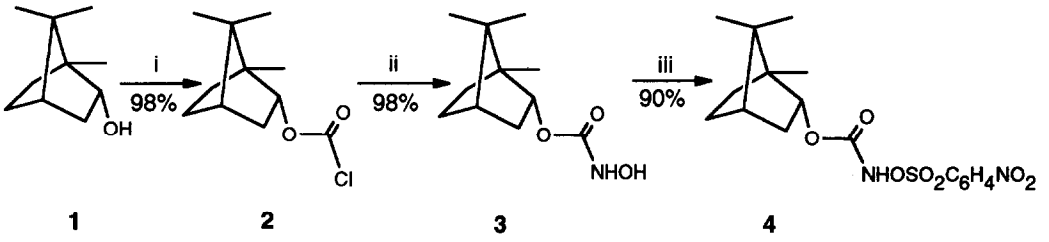
---

We dedicate this paper to Professor Charles Rees, FRS not only for his outstanding contribution to chemistry and encouragement of others, but for his perspicacious wit and friendship.

oxazolidin-2-one **8**, which was found amongst the minor products during these initial studies, and subsequently isolated in bulk quantities, to further bolster the existing armoury of chiral auxiliaries based on this nucleus and used in a range of asymmetric manipulations.

1. Attempted chiral nitrene-mediated aziridination

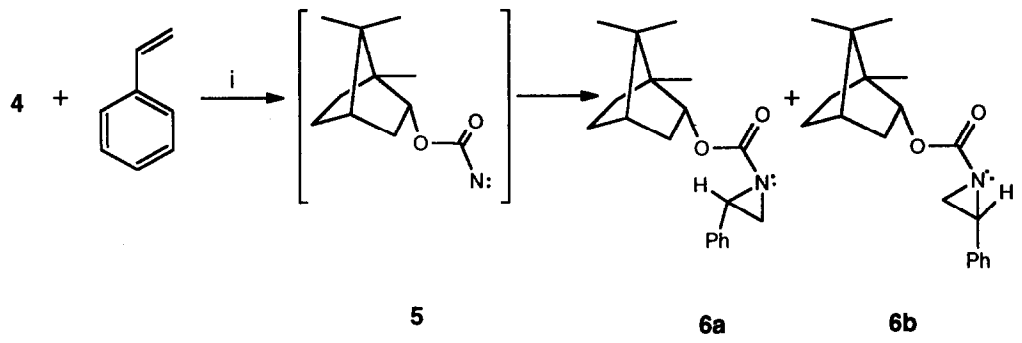
Our choice of precursor for nitrene **5** was [(1S)-*endo*]-1,7,7-trimethylbicyclo[2.2.1]heptan-2-*p*-nitrobenzenesulphonoxycarbamate **4** hereafter called [(1S)-*endo*]-(-)-bornyl *p*-nitrobenzenesulphonoxycarbamate, which is easily prepared as shown in Scheme 1 by a similar route to that originally used for Lwowski's reagent[6].Thus, chloroformylation of optically pure [(1S)-*endo*]-(-)-borneol **1** with phosgene followed by *N*-hydroxycarbamation with hydroxylamine and subsequent esterification with *p*-nitrobenzenesulphonyl chloride gave the desired reagent **4** in 85% overall yield.



Scheme 1. *Reagents and conditions:* (i), phosgene, triethylamine, toluene-ether, 0°C, 4h; (ii), hydroxylamine hydrochloride, sodium hydrogen carbonate, ether, 25°C, 12h; (iii), *p*-nitrobenzenesulphonyl chloride, triethylamine, ether, 25°C.

The optically-active nitrene **5** was generated from **4** as depicted in Scheme 2 in a two-phase system[7] and trapped with the prochiral alkene styrene to give 1-([(1S)-*endo*]-(-)-bornoxycarbonyl)-2-phenylaziridine **6** as its *trans*-invertomer (21%). The enantioselectivity of the reaction was determined by proton-decoupled ^{13}C NMR. spectroscopy since the ^{1}H chemical shifts of the aziridine ring protons in the two diastereomeric products **6a** and **6b** were unresolvable even at high field (360 MHz). No difference in the relative proportions of the two diastereomers could be detected. Indeed, the ^{13}C NMR spectrum of the crude reaction mixture was identical to that for an authentic 1:1 mixture of both diastereomers prepared from the reaction of racemic 2-phenylaziridine with [(1S)-*endo*]-(-)-bornylchloroformate **2**. In particular, two pairs of resonances of equal intensity were observed for the aziridine carbons at δ39.11 and δ38.87, and δ34.37 and δ33.94 in both cases. Attempts to promote some selectivity by lowering the temperature were equally frustrated by the failure of the reagent **4**, to react with the generating base (triethylamine) at temperatures below -5°C. Use of *n*-butyl lithium as base gave decomposition products.

From these results it is evident that the use of the [(1S)-*endo*]-(-)-bornyl moiety as the chiral auxiliary in an alkoxycarbonylnitrene does not lead to any discernable enantiomeric excess in aziridine formation under the conditions employed. Apparently, the bornyl moiety is



5 6a 6b

Scheme 2. *Reagents and conditions:* (i), benzyltriethylammonium chloride, sodium hydrogen carbonate, dichloromethane-water, 25°C.

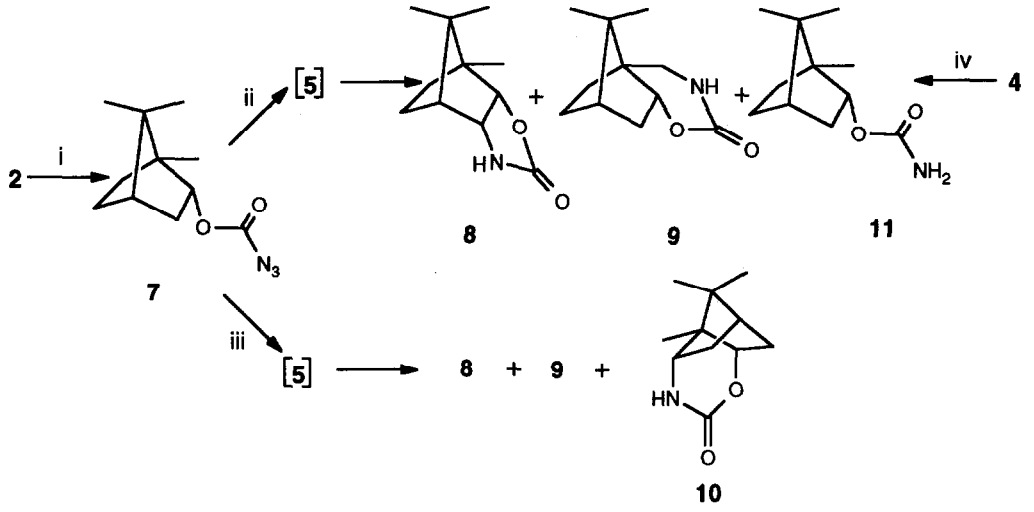
too remote from the bond-making centre to allow for any discrimination in the activation energies of the different transition states leading to the two possible diastereomers **6a** and **6b**. Further to these experiments, it is worth noting that no measurable asymmetric induction took place during aziridine formation between styrene or 1-methylcyclohexene and carboethoxynitrene (EtO_2C-N:) when the latter was generated in a two-phase system[8] using (-)-*N*-benzylcinchonidinium chloride as a chiral phase-transfer catalyst, or in a homogenous system[6] by the action of (S,S)-(+)-2,3-dimethoxy-1,4-bis(dimethylamino)butane as a chiral base.

In spite of the futility of our efforts to induce chirality in the foregoing aziridination reactions, we had occasion to examine in detail the outcome of the benzyltriethylammonium chloride-catalysed reaction in the absence of styrene (Scheme 3). In this scenario, analysis of the crude reaction mixture revealed the presence of three products which were shown to be derived directly from nitrene **5**. These were isolated by flash chromatography and identified as the tricyclic oxazolidin-2-one **8** (43%), the six-membered tetrahydro-1,3-oxazin-2-one **9** (36%) and carbamate **11** (14%). Mindful of the seminal work by Evans in the development of chiral oxazolidin-2-ones similar to **8** as effective chiral auxiliaries for the elaboration of stereogenic centres *via* acyl derivatives[9], we sought to suppress the formation of co-products **9** and **11** and improve the synthetic yield of **8** in enantiomerically pure form by exploring alternative methods of generating the precursor nitrene **5**. Herein we describe the optimum conditions for the synthesis of **8** and its utilisation as a chiral auxiliary in an array of asymmetric reactions.

2. Preparation of [(1s)-*endo*]-(-)-borneol-derived oxazolidin-2-one 8

Current methodology for access to preparatively useful chiral oxazolidin-2-ones, whether as reagents for stereoregulated aldol condensations[10] or resolution of racemic amines[11], employ direct cyclocarbamation of relatively expensive optically pure β-amino alcohols, or resort to the more tedious separation of similarly prepared racemic analogues[12]. For the improved preparation of the new chiral reagent **8** in an optically pure state we undertook a *de novo*

study of both thermolytic and photolytic methods of generating nitrene intermediate **5** from the azidoformate **7** by loss of nitrogen (Scheme 3). We envisaged the use of the device of intramolecular nitrene delivery[13], coupled with the conformational rigidity offered by the bornyl moiety, would ensure transfer of chirality from the existing chiral centre at C(2) to the nascent centre at C(3), by preferential insertion of **5** into the secondary *endo*-C-H bond. Various conditions were employed including neat thermolysis (8,48%), solution thermolysis in either boiling chlorobenzene (47%) or 1,1,2,2-tetrachloroethane (50%), flash vacuum pyrolysis (fvp) at 300°C (46%), and photolysis in CH_2Cl_2 (39%). Spray vacuum pyrolysis[14] using a modified apparatus and a vertical furnace was found to be the optimal method producing **8** in 58% yield (Scheme 3).



Scheme 3. *Reagents and conditions:* (i), sodium azide, tetrabutylammonium bromide, dichloromethane-water, 25°C, 4h; (ii), photolysis, 400W, dichloromethane, 30°C, 160m; (iii), spray pyrolysis, 300°C, 0.1-0.5 mmHg, or fvp, 300°C, 0.01-0.005 mmHg, or solution thermolysis in 1,1,2,2-tetrachloroethane, 147°C; (iv), benzyltriethylammonium chloride, sodium hydrogen carbonate, dichloromethane-water, 25°C.

Pyrolytic methods yielded the tricyclic oxazolidin-2-one **8** admixed with easily separated (by flash chromatography on silica using cyclohexane:ethyl acetate as eluent) six-membered tetrahydro-1,3-oxazin-2-one **9** and isomeric **10**, whose structure was determined by X-ray crystallography (Fig. 1a), in the ratio of *ca.* 2:1:1. Non-pyrolytic methods such as photolysis or Lwowski-type reactions did not produce compound **10**, but instead gave rise to carbamate **11** from hydrogen abstraction by the nitrene **5**. The preferred formation of **8** over **9** and **10** presumably reflects the bias towards 5- *vs.* 6-membered ring formation, coupled with the propensity by the nitrenoformate intermediate **5** for secondary H-insertion relative to primary in a cyclic system. Further crystallisation from di-*iso*-propyl ether or ethyl acetate: n-

hexane furnished well-formed crystals of the chiral oxazolidin-2-one **8** (m.p. 163-163.5°C; $[\alpha]^{21.5}$ -73.4°, c=5.1, ethanol); its structure was confirmed by microanalysis, mass spectral (including parent molecular ion by electron impact),and NMR data. X-Ray diffraction analysis confirmed the stereochemical integrity of **8** and has shown that the absolute configuration of the chiral centres at C(2) and C(6) is (2R, 6S), (Fig. 1b).

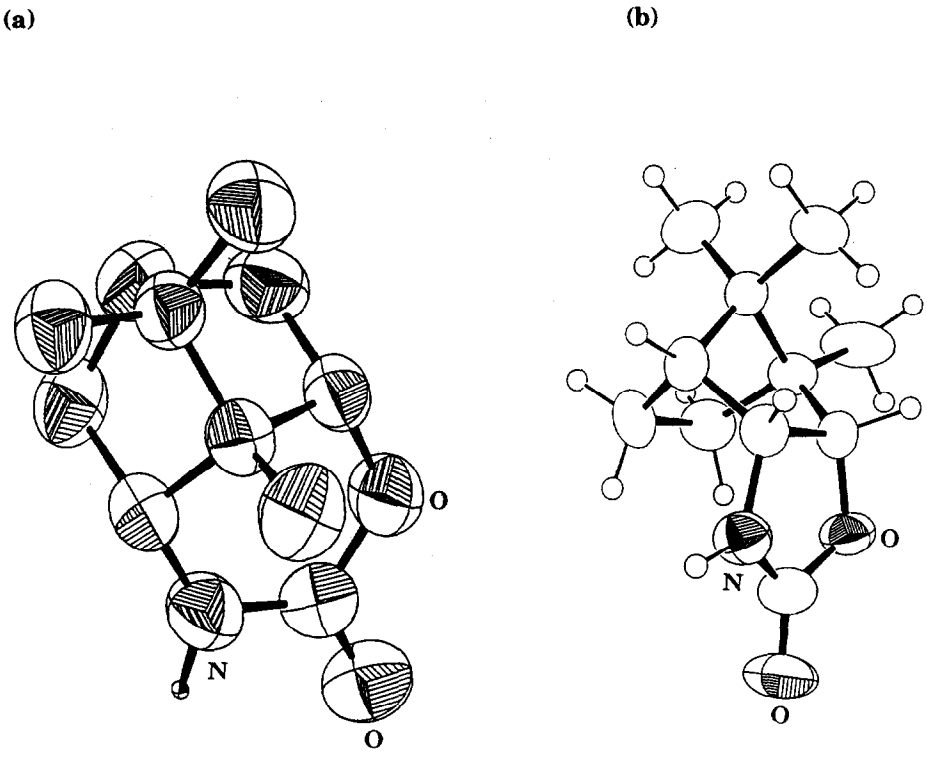


Figure 1. (a) Molecular structure of 1,3-oxazin-2-one **10**, and (b) of oxazolidin-2-one **8**.

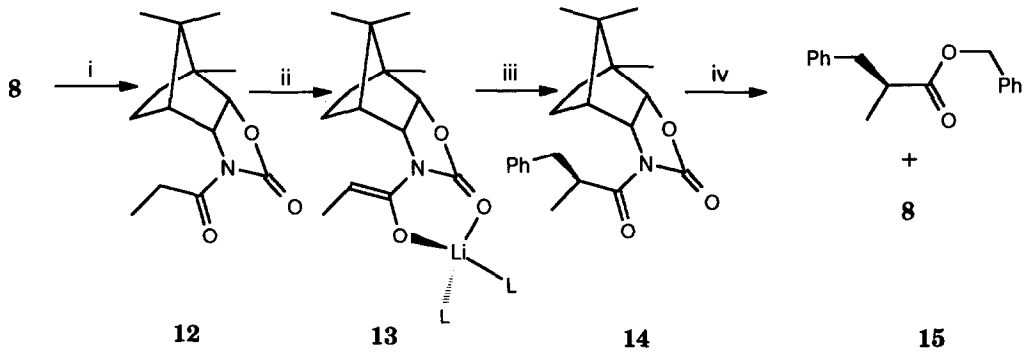
3. Utility of chiral auxiliary 8 in asymmetric transformations

Chiral oxazolidin-2-ones have been used extensively for substrate-controlled asymmetric synthesis, especially in the context of their *N*-acyl derivatives as precursors to chiral imide enolate synthons in carbon-carbon bond-forming reactions. In this connection, the bornyl-based oxazolidinone **8** was felt to be a promising candidate as a chiral auxiliary for the following reasons: (i) optically pure **8** can be readily prepared in multi-gram quantities in three simple steps from inexpensive *endo*-(-)-borneol; (ii) the highly crystalline nature of **8** imparts good crystallinity to derivatives, and consequently aids its synthetic utility in preparing optically pure products; (iii) the rigidity of the bornyl moiety attached to the oxazolidinone should dictate excellent π-topological bias as enjoyed by other camphor-based

auxiliaries[15,16,17]; (iv) the expected ease of non-destructive removal of the chiral auxiliary from the desired chiral synthon without racemization, and its propitious recyclability. On these grounds, we now report our observations on the stereochemical control imparted by **8** in diastereoselective alkylation, acylation and aldol processes with the respective enolate derived from the *N*-propionyl analogue **12**, and the level of chiral induction attainable with **8** bearing acryloyl substituents in Diels-Alder reactions.

(i) Alkylation and acylation reactions

Acylation of oxazolidinone **8** with *N*-propionyl chloride in the presence of sodium hydride or *n*-butyl lithium led to an almost quantitative yield of the *N*-propionyl imide **12** (Scheme 4). For the alkylation studies reported in Table 1, the lithium enolate **13** was generated by treatment of **12** with lithium di-*iso*-propylamide in tetrahydrofuran at -78°C. At this temperature the imide enolate **13** failed to alkylate, even with the more reactive benzyl bromide, but reaction did ensue at a convenient rate upon raising the temperature to -10°C. At temperatures >0°C the lithium enolate **13** decomposed, apparently *via* a ketene pathway[18].



Scheme 4. *Reagents and conditions:* (i), sodium hydride, toluene, 110°C, 1h then propionyl chloride, 25°C, 1h; or *n*-butyl lithium, tetrahydrofuran, -78°C, 30m, then propionyl chloride, 1h, 25°C; (ii), lithium di-*iso*-propylamide, tetrahydrofuran, -78°C, 30m; (iii). benzyl bromide, sodium iodide, tetrahydrofuran, -8°C, 18h; (iv). benzyl alcohol, *n*-butyl lithium, tetrahydrofuran, -78°C, 45m.

The diastereomeric composition of the crude alkylated product was determined by 400 MHz ^{1}H NMR spectral analysis and the results in Table 1 reflect the superb diastereofacial selection dictated by **8** for all alkylations, even with the less sterically demanding ethyl iodide (entry c), although this result was marred by the very poor yield. Attempts to improve the latter by replacing ethyl iodide with ethyl tosylate proved futile. On the other hand, an improvement in the yield with benzyl bromide from 62 to 80% was achieved by the judicious addition of sodium iodide to the reaction (entry d).

The absolute stereochemical configuration for the benzylated product **14** was determined by X-ray crystallography (Fig. 2), and also by adoption of Evan's transesterification method for racemisation-free removal of the oxazolidinone auxiliary with lithium benzyloxide[18]. As shown in Scheme 4, this procedure transformed **14** into the (*S*)-benzyl ester **15** in 96% yield ([α] +24.6°) in good agreement with the rotation (-26.9°) for the (R)-enantiomer[18]. The sense of diastereofacial bias is readily rationalised in terms of attack by the alkylating agent at the C_α-*re* face of the lithium-chelated (**Z**)-enolate **13**.

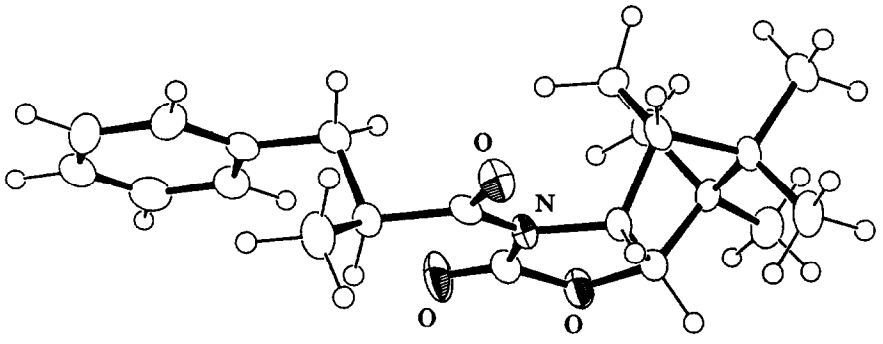


Figure 2. Molecular structure of benzylated derivative 14.

These results demonstrate the viability of **8** as a chiral auxiliary for the asymmetric alkylation of acyl derivatives, although it is recognised that enolate formation with lithium di-*iso*-propylamide can lead to severely reduced yields, albeit with good selectivity. This limitation has been recognised by others in the development of effective auxiliary-mediated asymmetric enolate alkylation[16,18,19] and for this reason, further studies are under way to probe the effect of counterion (Na *vs.* Li) and reaction conditions, particularly temperature, on yields without adversely affecting the selectivity. In contrast to the foregoing alkylation processes, acylation reagents reacted rapidly with the chelated (**Z**)-enolate **13** even at -78°C to afford the desired β-keto imides (entries e-h, Table 1). In order to preserve the integrity of the newly created chiral centre under the highly basic conditions employed, the reactions had to be quenched almost immediately with a saturated solution of aqueous ammonium chloride. In all but one case (entry g), the kinetic diastereoselection was found to be very good-to-excellent, although both acetylation (entry e) and propionylation (entry f) were marred by the formation of small amounts of *O*-acylated products. This problem was avoided in the former

case by employing Mander's reagent (entry h),which yielded only *C*-substitution[20]. Despite immediate quenching, the β-dicarbonyl adduct obtained from benzoylation (entry g) underwent rapid epimerization *via* enol formation as evidenced by the appearance of strong hydroxy absorptions in both IR and NMR spectra. This outcome contrasts strikingly with the low kinetic acidity exhibited by the corresponding β-keto imide derived from Evan's valinol-based oxazolidin-2-one[21] for which propitious steric effects negate the influence of the exocyclic imide carbonyl toward acidification of the acyclic methine hydrogen.

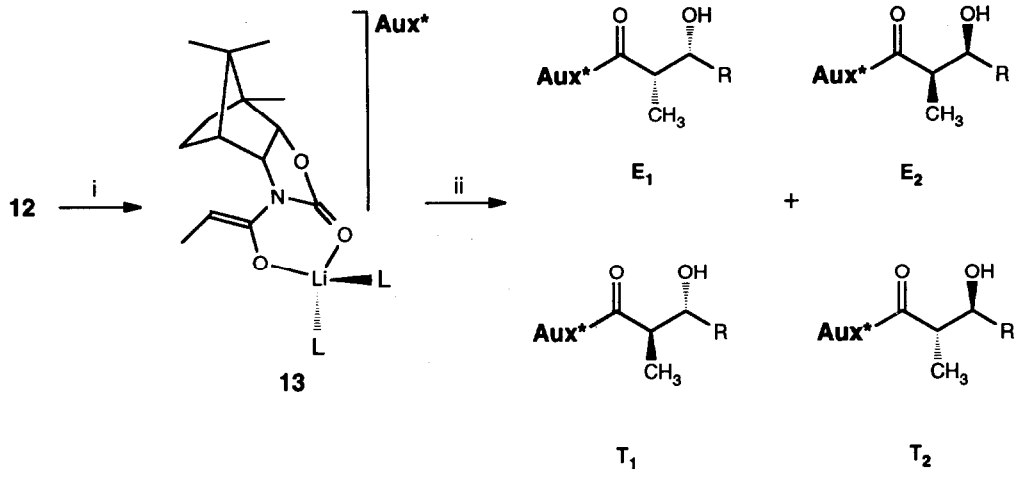
Table 1. Stereoselectivity of alkylation and acylation reactions of the lithium enolate **13** derived from *N*-propionyl imide **12** (Scheme 4)

entry	electrophilic reagent	reaction time	C *vs.* O selection (%)	isolated yield (%)	de (%)
a	benzyl bromide	18h	-	62	>99
b	allyl bromide	18h	-	70	>99
c	ethyl iodide	4h	-	6	>99
d	benzyl bromide/sodium iodide	18h	-	80	>99
e	acetyl chloride	45s	85:15	88	82
f	propionyl chloride	60s	85:15	89	>99
g	benzoyl chloride	120s	100:0	95	a
h	methyl cyanoformate	90s	100:0	99	82

a. enolisation occurred to cause racemisation.

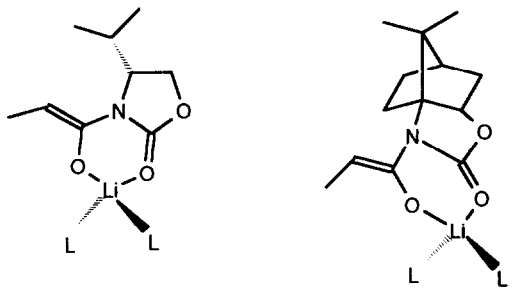
(ii) Aldol diastereoselection *via* chiral enolates derived from *N*-propionyl imide 12

The demand for enantiomerically pure β-hydroxycarbonyl-containing compounds has led to a rapidly growing interest in chiral metal-mediated enolates which can achieve exceptionally high diastereoselectivity[22]. Of these, use of optically pure oxazolidin-2-ones as recyclable chiral auxiliaries has emerged as an attractive option for aldol condensations[23]. With access to the aforementioned *N*-propionyloxazolidinone **12** in hand, our investigation commenced with the lithium-chelated (*Z*)-enolate **13**, generated under kinetic conditions (*vide supra*) and reacted with freshly distilled benzaldehyde (R=Ph). After 30s, the reaction was quenched with saturated ammonium chloride solution to afford all four possible diastereomeric adducts (E_1, E_2, T_1, T_2) (Scheme 5) in the ratio 55.4:28.7:10.3:5.7 by consideration of the carbinol resonances in the 360 MHz ^{1}H NMR spectrum. An equally low level of stereoregulation was found for the lithium-enolate condensation of **13** with isobutyraldehyde (R=Me_2CH), for which HPLC analysis gave a product distribution for the four aldol stereoisomers of 64.7:22.5:7.9:4.9. This poor quality of aldol diastereoselection is akin to that reported with Evan's (S)-valinol-based oxazolidin-2-one for which the analogous condensation of the corresponding lithium enolate **16**, the observed diastereomer ratios were 10.6:11.0:71.4:7.0[10]. Likewise, the diastereoselectivity of the corresponding aldol reactions with the (+)-camphor-based imide lithium enolate **17** is equally moderate[16].



Scheme 5. *Reagents and conditions:* (i),lithium di-*iso*-propylamide, tetrahydrofuran, -78°C; (ii), RCHO.

Much greater diastereoselectivity is achieved in both these cases by use of boron-chelated enolates. Indeed, aldol condensations from the boron enolate analogous to **16** exhibited complete *erythro*-stereoselection and absolute stereochemical control, and in the case of that corresponding to **17**[16], the combined *threo*-adduct contaminants never exceeded 0.9%. The same behaviour gratifyingly occurred with the boron enolate generated from **12**. Subsequent condensation with both benzaldehyde and isobutyraldehyde furnished single diastereomerically pure *erythro*-adducts whose assignment was confirmed from low *J*-values for the carbinol resonances (J=<6 Hz), and in the case of benzaldehyde adduct **18**, by X-ray crystallography.



16 **17**

The ORTEP diagram shown in Fig. 3 confirms the absolute stereochemistry of the two newly formed chiral centres to be *erythro* (**E_2**). This sense of diastereofacial selectivity is opposite to that reported above for the boron enolate corresponding to **16**, but is the same as that

obtained from the oxazolidin-2-one prepared from (1S,2R)-norephredrine[10], and the (+)-camphor-based boron enolate corresponding to **17** (*vide supra*)[16].

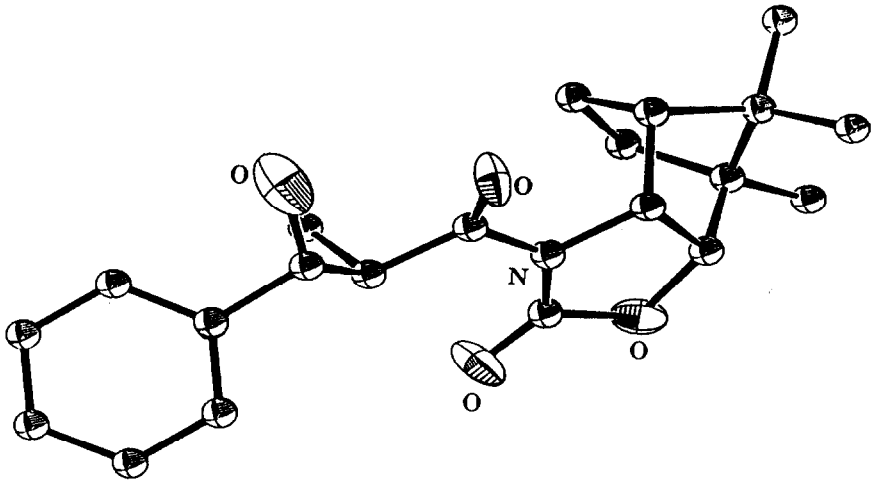
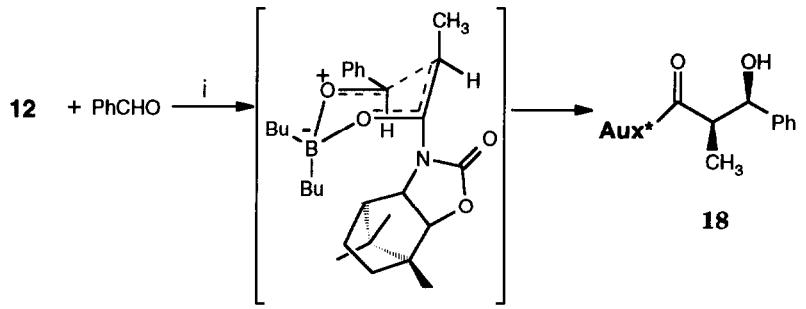


Figure 3. View of the X-ray structure of aldol-adduct 18.

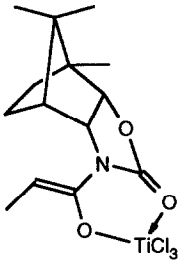
The origin of the remarkable stereospecificity in these boron enolate-mediated reactions and the *erythro*-stereochemistry of the adducts can be rationalised in terms of the preferred chair-like transition state shown in Scheme 6, given the reasonable postulate that the aldol condensation proceeds *via* a pericyclic process [10] , and that chelation with the carbonyl group in the auxiliary is absent (*cf.* corresponding lithium enolate **13**).



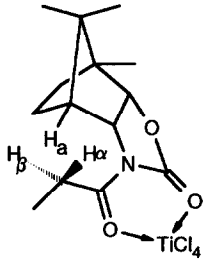
Scheme 6. *Reagents and conditions:*(i), di-*n*-butylboron triflate, di-*iso*-propylethylamine, tetrahydrofuran, 0°C, 10m, then -78°C, 30m; (ii), benzaldehyde.

Despite these successes neither the lithium- or boron-enolates derived from **12** condensed with acetaldehyde readily. In the former case, total consumption required approx. 1.5h and led to dehydration products as well as cleavage of the auxiliary. A similar reluctance to react was also observed for the corresponding titanium enolate **19**, even with benzaldehyde. In initial studies, attempts to form the latter, by treatment with titanium tetrachloride, failed

despite the advent of a deep purple coloration. Instead, high-field NMR spectroscopy revealed the presence of the bidentate complex **20** as evidenced by the observation of the distinctive pair of quartets for each of the diastereotopic protons H_α and H_β arising from the immobilisation of the *N*-acyl function. Moreover, irradiation of the bridgehead proton H_a enhanced H_β by 3%, but caused no change to H_α thereby confirming the 'locked' structure as depicted in **20**.



19



20

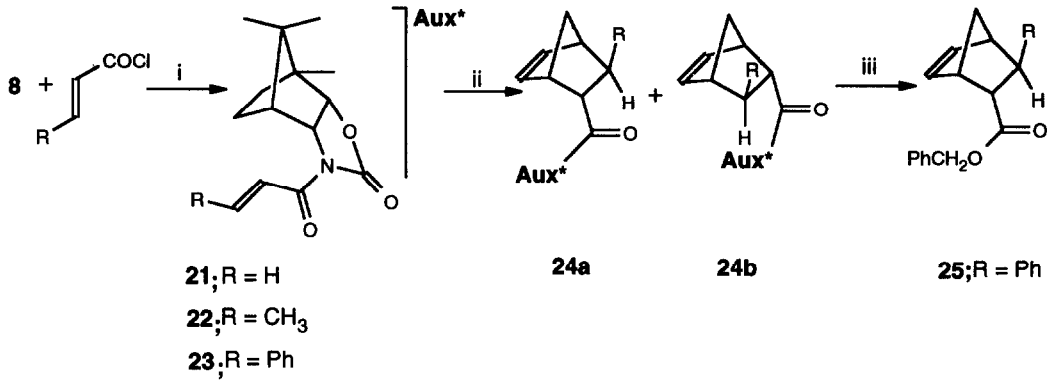
It was found that reaction did occur, albeit to 40% completion, by changing the base to triethylamine, and only after a prolonged reaction period (48h) at room temperature. Despite its sluggishness, this condensation is notable in the antithetical formation of only the *threo*-adducts (T_1, R=Ph) and (T_2, R=Ph), the stereochemical assignments being made from carbinol proton coupling constants (J=9 and 11 Hz), in the ratio of 13:1. At this stage it is not proven which is the major diastereomer, but irrespective of this fact, the sole formation of '*anti*' adducts is noteworthy, especially when compared to the stereochemical control of the titanium(IV) enolate derived from the *exo*-analogue of **12**[17] which affords predominant amounts of the *erythro*-diastereomer (E_1), the product predicted from chelation control. This dichotomy is under further investigation, coupled with attempts to force the reaction to completion.

(iii) Diels-Alder cycloadditions

Our initial attempts to prepare chiral acrylate derivatives as dienophiles in Diels-Alder cycloaddition reactions as a route to optically-active cyclohexenes involved the reaction of an ethereal solution of the sodium salt of **8** with the appropriate α,β-unsaturated acid chloride. However, in the case of acryloyl chloride the procedure was frustrated by polymerisation, which is believed to be anionic in nature. The problem was circumvented by use of Evan's elegant method[24] whereby the oxazolidinone **8** was successively treated with methylmagnesium bromide and the acid chloride under carefully defined conditions to afford the desired dienophile **21** in 75% isolated yield. The same procedure also yielded the crotonoyl- and cinnamoyl dienophiles **22** (85%) and **23** (81%) respectively in a pure and crystalline state without the problem of polymerisation (Scheme 7).

It is well established in Diels-Alder cycloaddition reactions with chiral unsaturated carboximides such as **21-23**, that the rotameric preference must be controlled in order to

observe high diastereoselectivity. In the absence of Lewis acid promoters four planar conformers, *e.g.* **A-D** are possible (Fig. 4), although a combination of dipole-dipole interactions and steric destabilization favours only the S-*cis* conformer **C**[25].Chelation alters this



Scheme 7. Diels-Alder cycloadditions. *Reagents and conditions:* (i), methylmagnesium bromide, tetrahydrofuran, 0°C, then cooled to -78°C, acryloyl chloride, (ii), cyclopentadiene, catalyst, (iii) benzyl alcohol, *n*-butyl lithium, tetrahydrofuran, -78°C for 30m then 25°C, 3h.

conformer preference and in Lewis acid promoted reactions, rotameric preference is directed towards S-*cis* conformer **A** rather than S-*trans* **B** due to steric constraints in the latter (see Fig. 4).The bias depends on the temperature used and also the nature of the Lewis acid catalyst, but in essence, bidentate chelation by the promoter to both carbonyl groups freezes the *N-C* rotor and allows π-face discrimination, although the direction of attack depends upon the topological bias provided by the auxiliary.

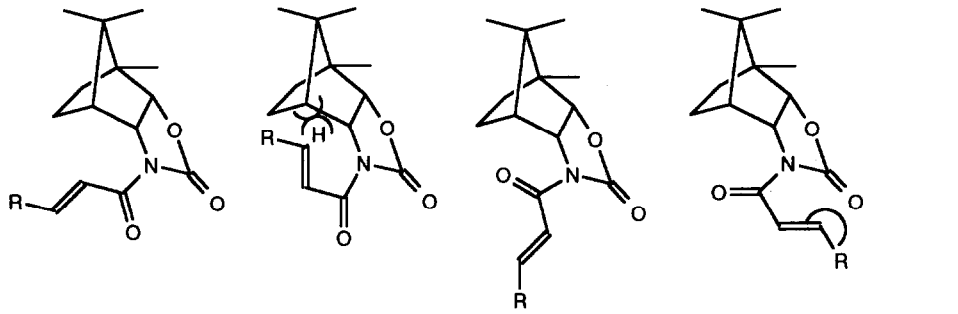


Figure 4. Conformations adopted by *N*-substituted acryloyl derivatives of **8**.

Our results with auxiliary **8** proved disappointing. The cycloaddition of acryloyl imide **21** with excess cyclopentadiene employing $TiCl_2(OPr^i)_2$ (4 equiv.) in dichloromethane at -78°C afforded only *endo*-adducts **24a** and **24b** , albeit in the ratio of 2:1, and derived respectively from conformers **A** (R=H) and **B** (R=H). Use of an excess of Et_2AlCl (1.4 equiv.) as the promoter under identical conditions led to a modest improvement of the ratio to 4:1. The results are summarised in Table 2, together with *endo*-diastereoselectivities obtained for crotonoyl imide **22** and cinnamoyl imide **23** in the same reaction. A surprising feature is the loss of selectivity on going from the acryloyl imide **21** (entry b) to the crotonoyl dienophile **22** (entry g) which also gives rise to small amounts of otherwise unobserved *exo*-adducts; use of Et_2AlCl as catalyst failed to enhance the diastereoselection. The level of reactivity for the uncatalysed crotonoyl reaction is also diminished (entry f) when compared to the acryloyl dienophile **21** (entry a), and after 24h it is recovered virtually unchanged. Dienophile reactivity is markedly improved in the presence of Et_2AlCl (entry h), but the diastereoselectivity remains unchanged compared to the corresponding acryloyl reaction (entry c). The cinnamoyl dienophile **23** is the least reactive yet thus far the most diastereoselective, and even after three days and the addition of more cyclopentadiene, led to only a 22% yield of a single adduct (entry i). Change of Lewis acid promoter from $TiCl_2(OPr^i)_2$ to Et_2AlCl improved reactivity considerably (entry j), and even at -20°C afforded within 1m an excellent yield of distereomerically pure cycloadduct **24a** (R=Ph) (92%). The sense of asymmetric induction in the latter reaction was established by removal of the chiral auxiliary from the adduct by treatment with lithium benzyloxide in tetrahydrofuran (0°C, 3h). Comparison of the literature value for the optical rotation of the isolated benzyl ester **25** ($[\alpha] = -121.1^0$) confirmed its optical purity and opposite sense to that obtained by Evans *et al*[24] with their (S)-valinol-derived oxazolidinone (antipode $[\alpha] = +121.0^0$).

Table 2. Lewis acid promoted reactions of dienophiles **21-23** with cyclopentadiene (and isoprene)

entry	R	catalyst/temp(°C)	diene	isolated yield (%)	ratio	de (%)
a	H	none,0°C	cyclopentadiene	69	1.1:1	
b	H	$TiCl_2(OPr^i)_2$, -78°C	cyclopentadiene	83	2:1	33
c	H	Et_2AlCl, -78°C	cyclopentadiene	98	4:1	60
d	H	$TiCl_2(OPr^i)_2$, -78°C	isoprene	80	2:1	33
e	H	Et_2AlCl, -78°C	isoprene	94	5:1	69
f	CH_3	none,0°C	cyclopentadiene	10	a	a
g	CH_3	$TiCl_2(OPr^i)_2$, -78°C	cyclopentadiene	92	3:2	20
h	CH_3	Et_2AlCl, -78°C	cyclopentadiene	96	4:1	60
i	Ph	$TiCl_2(OPr^i)_2$, -78°C	cyclopentadiene	22	a	a
j	Ph	Et_2AlCl, -20°C	cyclopentadiene	92	>99:1	99

a. reaction is very slow and only a small amount of product was formed after 24h.

As expected on the basis of the foregoing results, only the acryloyl dienophile **21** underwent cycloaddition with the much less reactive acyclic diene isoprene. Once again, Et_2AlCl-catalysed reaction produced a significantly better level of diastereoselection (5:1) (entry e) than the corresponding reaction (entry d) with $TiCl_2(OPr^i)_2$ (2:1). In both cases, the ratios could only be determined by ^1H 360 Mz NMR with the aid of a europium chiral shift reagent.

From these results it is evident that auxiliary **8** induces consistently low levels of diastereofacial differentiation in Lewis acid mediated asymmetric Diels-Alder reactions of cyclopentadiene (and isoprene), apart from with the cinnamoyl imide **23**. Although in all cases investigated, *endo/exo* ratios are extremely high, *endo*-diastereoface selectivity never exceeds 67%, except for the cycloaddition with the relatively less reactive cinnamoyl dienophile (entry j) which is stereospecific. The reason for the poor diastereoselection is probably steric in origin and reflects the inability of **8** to provide the necessary topological bias in Diels-Alder reactions and establish significant population differences between the chelated S-*cis* and S-*trans* conformers **A** and **B**, respectively (Fig. 3). We are currently investigating other likewise terpenoid-based oxazolidinones with the necessary control element to improve π-face discrimination.

Acknowledgements

We are grateful to Dr T. C. Gallagher and Tim Donohoe for their helpful contributions during a British Petroleum Vacation Scholarship (T. D.).

EXPERIMENTAL

Melting points are uncorrected. ^1H and ^{13}C NMR spectra were obtained on a Brucker-270 operating at 270 MHz or 50.3 MHz respectively, or a Brucker-270 operating at 270 MHz or 67.9 MHz, or a Brucker WH-360 operating at 360 MHz or 90.56 MHz, or a Brucker 400 operating at 400 MHz or 100.57 MHz. IR spectra were recorded on a Perkin-Elmer 781 spectrometer and accurate mass measurements determined on a Kratos MS 50TC mass spectrometer. Elemental analyses were determined on a Carlo-Erba 1106 analyser and polarimetry measurements were carried out on an Optical Activity Ltd. instrument using sodium light. UV spectra were obtained on a SP 800A spectrophotometer. Tetrahydrofuran and ether were distilled prior to use from sodium/benzophenone ketyl and dichloromethane 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). For all X-ray structures reported, atomic coordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre.

[(1S)-*endo*]-1,7,7-Trimethylbicyclo[2.2.1]heptan-2-chloroformate (2). A solution of [(1S)-*endo*]-(-)-borneol (9.0g, 58 mmol) and dry pyridine (4.61g, 58 mmol) in anhydrous ether (200 ml) was added dropwise to a rapidly stirred solution of phosgene (20% w/v in toluene, 86

ml, 174 mmol) under argon at 0°C. After the addition was complete the reaction mixture was stirred at room temperature for 4h and filtered. The precipitate was washed well with anhydrous ether. The ether fractions were combined and evaporated *in vacuo* to yield **2** as a pale yellow oil (12.1g, 97%); $bp_{0.7}$ 85°C (Kugelrohr); $[\alpha]^{21.5}$ = -36.5°, c = 5.1 (ethanol); M^+ 216.0917 $C_{11}H_{17}ClO_2$ requires 216.0917; ν_{max} (thin film) 1780 (s, C=O) cm^{-1};^1H NMR (200 MHz, $CDCl_3$) δ 0.8-0.9 (3s, 9H, 3xCH_3), 1.0-2.5 (m, 7H), 5.0 (ddd, 1H, C*H*O).

[(1S)-*endo*]-1,7,7-Trimethylbicyclo[2.2.1]heptan-2-*N*-hydroxycarbamate (3). Chloroformate **2** (7.0g, 35 mmol) in ether (10 ml) was added dropwise to a stirred mixture of finely ground hydroxylamine hydrochloride (2.5g, 35 mmol) and potassium carbonate (4.4g, 32 mmol)in ether containing water (0.5 ml) at 0°C. The mixture was stirred at room temperature for 12h, filtered and evaporated *in vacuo* to give **3** as a colourless crystalline solid (6.74g, 98%); mp 85°C; M^+ 213.1366 $C_{11}H_{19}NO_3$ requires 213.1365; ν_{max} (mull) 3280 (br. s -OH), 1690 (s, C=O) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 0.82 (s, 3H, CH_3), 0.84 (s, 3H, CH_3), 0.87(s, 3H, CH_3), 0.7-2.5 (m, 7H), 4.0 (br. s, 1H), 4.85 (m, 1H,C*H*O), 7.0 (br. s, 1H).

[(1S)-*endo*]-1,7,7-Trimethylbicyclo[2.2.1]heptan-2-*p*-nitrobenzenesulphonoxycarbamate (4). p-Nitrobenzenesulphonyl chloride (4.65g, 21 mmol) was added gradually to an ice-cold stirred solution of *N*-hydroxycarbamate in ether (150 ml). Concurrently triethylamine (1.81g, 18 mmol) in ether (25 ml) was added dropwise, ensuring that the reaction mixture was acidic at all times. The mixture was stirred at room temperature for 48h, filtered and the filtrate evaporated *in vacuo* to give **4** as a yellow solid (7.63g, 90%) which was recrystallised from chloroform/*n*-hexane to give fine cream needles; mp 138-139°C; $[\alpha]^{22}$ = -16.3°, c = 5.0 (ethanol); (Found: C, 51.5; H 5.63; N 7.04%. $C_{17}H_{22}N_2O_7S$ requires C, 51.3; H, 5.6; N, 7.0%); M^+ 398 $C_{17}H_{22}N_2O_7S$ requires 398; ν_{max} (mull) 3240, 3200, 1750 (s, C=O), 1535, 1195 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 0.6-2.4 (m, 16H), 4.75 (m, 1H, C*H*O), 8.27 (m, 4H), 9.6 (br. s 1H); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 155.85, 157.17, 139.15, 130.71, 123.98, 83.75, 48.79, 47.74, 44.47, 35.94, 27.65, 26.64, 19.37, 18.47, 12.97.

Addition of [(1S)-*endo*]-1,7,7-trimethylbicyclo[2.2.1]heptan-2-oxycarbonylnitrene (5) to styrene. Benzyltriethylammonium chloride (0.07g, 0.3 mmol) was added to a stirred mixture of **4** (0.5g, 1.25 mmol) and styrene (0.5g, 4.3 mmol) in aquous sodium hydrogen carbonate solution (1M, 10 ml) and dichloromethane (6 ml). The mixture was stirred vigorously for 5h at ambient temperature following which dichloromethane (50 ml) was added and the two fractions separated. The organic fraction was washed with water (3x50 ml), dried (magnesium sulphate), and the solvent removed *in vacuo* to give a yellow oil. Residual styrene was removed under high vacuum at room temperature to give a viscous yellow oil containing equal amounts of the diastereomers of 1-([(1S)-*endo*]-1,7,7-trimethylbicyclo[2.2.1]heptan-2-oxycarbonyl)-2-phenylaziridine **6a** and **6b** (20%, as determined by ^1H NMR integral) as shown by spectral comparison with an authentic sample (*vide infra*).

1-([(1S)-*endo*]-1,7,7-trimethylbicyclo[2.2.1]heptan-2-oxycarbonyl)-2-(R,S)-phenylaziridine (6a and 6b). [(1S)-*endo*]-1,7,7-Trimethylbicyclo[2.2.1]heptan-2-chloroformate **2** (0.36g, 1.66 mmol) in anhydrous ether (4 ml) was added dropwise to an ice

cold stirred solution of 2-phenylaziridine[3] (0.198g, 1.66 mmol) and triethylamine (0.336g, 3.33 mmol) in anhydrous ether (10 ml). The mixture was stirred at room temperature for 1h, filtered, and the solvent removed *in vacuo* to yield **6a** and **6b** as a colourless oil (0.49g, 96%); $[\alpha]^{24}$ = -23.3°, c = 4.0 (ethanol); M^+ 299.1880 $C_{19}H_{25}NO_2$ requires 299.18852; ν_{max} (thin film) 1720 (s, C=O) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 0.8-2.0 (m, 16H), 2.33 (m, 1H, H-1_b), 2.67 (dd, 1H, J=1.0, 6.0 Hz, H-1_a), 3.56 (m, 1H, H-3), 4.85 (br. d, 1H, C*H*O), 7.31 (s, 5H); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 163.0, 136.65, 136.48, 128.07, 127.43, 125.99, 81.59, 48.43, 47.43, 44.37, 39.11, 38.87, 36.28, 36.09, 34.37, 33.94, 27.60, 26.53, 19.28, 18.40, 13.14.

Reaction of [(1S)-*endo*]-1,7,7-trimethylbicyclo[2.2.1]heptan-2-*p*-nitrobenzenesulphonoxycarbamate (4) with benzyltriethylammonium chloride. Benzyltriethylammonium chloride (0.1g, 4.39 mmol) was added to a stirred mixture of **4** (3.5g, 8.79 mmol) in aqueous sodium hydrogen carbonate solution (1M, 50 ml) and dichloromethane (180 ml). The reaction mixture was stirred vigorously overnight at room temperature, following which dichloromethane (100 ml) was added and the mixture washed with water (3x50 ml). The organic phase was dried (magnesium sulphate), evaporated *in vacuo*, and the product subjected to flash chromatography (silica, gradient elution 10/90 v/v-100/0 v/v ethyl acetate-*n*-hexane). Three fractions were collected in the following order:-

[(1S)-*endo*]-1,7,7-trimethylbicyclo[2.2.1]heptan-2-carbamate (11) (0.234g, 14%); mp 124-126°C; $[\alpha]^{22}$= -34.4°, c = 4.96 (ethanol); M^+ 197.1425 $C_{11}H_{19}NO_2$ requires 197.1421; ν_{max} (KBr) 3480, 3340 (br. d, NH_2),1700, 1605 (s, $CO.NH_2$) cm^{-1}; ^1H NMR (200 MHz,$CDCl_3$) δ 0.83 (s, 3H, CH_3), 0.84 (s, 3H, CH_3), 0.88 (s, 3H, CH_3), 0.97 (dd, 1H, J=13.7, 3.4 Hz), 1.19 (m, 2H), 1.61 (m, 2H), 1.84 (m, 1H), 2.24 (m, 1H), 4.74 (ddd, 1H, J=9.9, 3.3, 2 Hz, C*H*O), 5.11 (br. s, 2H, NH_2); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 157.5, 80.4, 48.6, 47.7, 44.7, 36.5, 27.8, 26.7, 19.5, 18.6, 13.3;

[(2R, 6S)-*endo*]-5-aza-1,10,10-trimethyl-3-oxatricyclo[5.2.1.$0^{2,6}$]decan-4-one (8) (0.74g,43%); mp 163-163.5°C; $[\alpha]^{21.5}$= -73.4°, c = 5.1 (ethanol); (Found: C, 67.6; H, 9.0; N, 7.2%. $C_{11}H_{17}NO_2$ requires C, 67.7; H, 8.8; N, 7.2%); ν_{max} (KBr) 3300 (br. s, NH), 1755 (s, C=O), 1715 (s, NH) cm^{-1}; ^1H NMR (200 MHz,$CDCl_3$) δ 0.90 (s, 3H, CH_3), 0.94 (s, 6H, 2xCH_3), 1.30 (m, 2H, CH_2), 1.65 (m, 2H, CH_2), 1.87 (m, 1H, CH), 4.16 (dd, 1H, J=9.82, 4.68 Hz, C*H*N), 4.60 (dd, 1H, J=9.94, 1.68 Hz, C*H*O), 5.56 (br. s, 1H, NH); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 160.5, 85.71, 54.66, 49.04, 48.44, 29.51, 26.34, 19.97, 19.71, 17.82, 14.00;

[(6S)-*endo*)]-3-aza-11,11-dimethyl-5-oxatricyclo[6.2.1.$0^{1,6}$]undecan-4-one (9)(0.62g, 36%); mp 170-171°C; $[\alpha]^{23}$= +72.1°, c = 5.1 (ethanol); (Found: C, 67.5; H, 8.8; N, 7.1%. $C_{11}H_{17}NO_2$ requires C, 67.7; H, 8.8; N, 7.2%); ν_{max} (KBr) 3345 (br. s, NH), 1713 (s, C=O), 1668 (s, NH) cm^{-1}; ^1H NMR (200 MHz,$CDCl_3$) δ 0.94 (s, 3H, CH_3), 0.95 (s, 3H, CH_3), 1.37 (m, 3H), 1.80 (m, 2H, CH_2), 2.95 (dd, 1H, J=10.7, 3.9 Hz, CH_bN), 3.3 (d, 1H, J=10.7 Hz, CH_aN), 4.51 (ddd, 1H, J=10.1, 4.4, 2.0 Hz, C*H*O), 6.25 (br. s, NH); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 155.92, 80.24, 46.16, 45.86, 44.48, 43.50, 32.75, 27.36, 24.50, 19.72, 18.42.

[(1S)-*endo*]-1,7,7-Trimethylbicyclo[2.2.1]heptan-2-azidoformate (7). Chloroformate **2** (10g, 46 mmol) in dichloromethane (50 ml) was added over 10 m to a rapidly stirred solution of sodium azide (6.0g, 92 mmol) and tetrabutylammonium bromide (0.2g) in water (50 ml). The reaction mixture was stirred for 4h, separated and the aqueous fraction was extracted

with dichloromethane (2x20 ml). The organic fractions were combined, washed with water (x1), dried (magnesium sulphate), and evaporated *in vacuo* to yield **7** as a slightly yellow oil (10.1g, 98%);$bp_{0.15}$ 85°C; $[\alpha]^{22.5}$ = -42°, c = 4.9 (ethanol); M^+ 223.13207 $C_{11}H_{17}N_3O_2$ requires 223.1321; ν_{max} (thin film) 2150, 2115 (s, N_3), 1720 (s, C=O) cm^{-1}; ^1H NMR (200 MHz,$CDCl_3$) δ 0.86 (s, 3H, CH_3), 0.87 (s, 3H, CH_3), 0.89 (s, 3H, CH_3), 1.08 (dd, 1H, J=13.96, 3.42 Hz, CH), 1.28 (m, 2H, CH_2), 1.78 (m, 3H), 2.39 (m, 1H, CH), 4.89 (m, 1H, C*H*O); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 157.42, 84.58, 48.83, 47.77, 44.53, 63.10, 27.65, 26.56, 19.39, 18.53, 13.14.

Pyrolysis of azidoformate 7. The azidoformate **7** (20g, 89.6 mmol) was passed through a vertical spray pyrolysis apparatus at 300°C with a vacuum of 0.1-0.5 mmHg. The products were collected in a vessel cooled with dry-ice (16.08g, 92%) and purified by flash chromatography (silica, gradient elution 10/90 v/v-100/0 v/v ethyl acetate-*n*-hexane). Three products were eluted in the following order:- **[(2R, 6S)-*endo*]-5-aza-1,10,10-trimethyl-3-oxatricyclo[5.2.1.$0^{2,6}$]decan-4-one (8)** (9.96g, 57%); and a mixture of **[(6S)-*endo*)]-3-aza-11,11-dimethyl-5-oxatricyclo[6.2.1.$0^{1,6}$]undecan-4-one (9)** (2.97g, 17%) and **[(4R,8S)-*endo*]-6-aza-1,10,10-trimethyl-3-oxa-tricyclo[6.1.1.1]decan-4-one (10)** (4.37g, 25%); mp 170°C; (Found: C, 67.4; H, 9.0; N, 7.2%. $C_{11}H_{17}NO_2$ requires C, 67.7; H, 8.8; N, 7.2%); ^1H NMR (200 MHz,$CDCl_3$) δ 3.45 (m, 1H, C*H*N), 4.5 (m, 1H, C*H*O), 7.1 (br. NH); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 152.31, 82.69, 54.24, 48.58, 46.10, 41.28, 39.22, 36.63, 19.24, 18.64, 11.07. In addition azidoformate **7** was pyrolysed in a FVP apparatus at 300°C to give **8** (46%), **9** (23%), and **10** (23%).

Solution pyrolysis of 7. A solution of **7** (25g, 112 mmol) in 1,1,2,2-tetrachloroethane (TCE) (20ml) was added over 90m *(via* a syringe pump) to TCE (250 ml) at reflux under an argon atmosphere. The solvent was removed *in vacuo* and the brown oil obtained (21.8g, 99%) was subjected to flash chromatography (silica, eluted with ether) to yield **8** (8.00g, 37%). ^1H NMR (200 MHz) of crude reaction mixture prior to chromatography showed a product distribution of **8** (50%), **9** (39%), **10** (11%). Trace amounts of unreacted **7** and **11** were recovered during chromatography, the order of elution being **7**, **11**, and **8**, **9** and **10** were eluted together.

Photolysis of 7. A solution of **7** (5.28g, 23.6 mmol) in anhydrous dichloromethane (700 ml) was irradiated with uv light (400 W) for 160m and evaporated *in vacuo* to yield a brown oil (4.61 g, 100%).^1H NMR (200 MHz) analysis of the crude oil showed a product distribution of **8** (39%), **9** (25%), and **11** (35%). The oil was purified by flash chromatography (silica, *n*-hexane:ethyl acetate) which gave **11** (1.6g, 34%), **8** (1.7g, 36%), and **9** (1.1g, 25%).

[(2R, 6S)-*endo*]-*N*-Propionyl-5-aza-1,10,10-trimethyl-3-oxatricyclo[5.2.1.$0^{2,6}$]decan-4-one (12). A solution of **8** (2g, 10.2 mmol) in anhydrous toluene (100 ml) was added to a stirred suspension of oil-free sodium hydride (0.27g, 11.2 mmol) in toluene (30 ml) under argon. The reaction mixture was heated under reflux for 1h, cooled to room temperature and treated dropwise with propionyl chloride (1.0g, 10.8 mmol) in toluene (3 ml). The mixture was stirred for a further 1h, poured into saturated sodium hydrogen carbonate solution and the two fractions were separated. The organic fraction was washed with water, dried (magnesium sulphate) and evaporated *in vacuo* to give a colourless oil (2.62g) which was purified by

Kugelrohr distillation (2.42g, 95%); $bp_{0.25}$ 165°C; $[\alpha]^{26}$ = -150.6°, c = 5.0 (ethanol); M^+ 251.1524 $C_{14}H_{21}NO_3$ requires 251.1521; ν_{max} (thin film) 1780 (s, C=O), 1700 (s, C=O) cm^{-1}; ^1H NMR (200 MHz,$CDCl_3$) δ 0.90 (s, 3H, CH_3), 0.91 (s, 3H, CH_3), 0.93 (s, 3H, CH_3), 1.09 (t, 3H,CH_3, J=7.34 Hz), 1.1-1.7 (m, 4H), 2.24 (t, 1H, CH, J=4.0 Hz), 2.90 (dq, 2H, CH_2, J=7.73, 7.29 Hz), 4.45-4.6 (m, 2H); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 174.0, 154.2, 82.4, 57.5, 49.2, 48.3, 47.6, 28.8, 26.1, 19.7, 17.8, 13.6, 8.1.

Preparation of 12 using *n*-butyl lithium. A solution of **8** (3.99g, 20 mmol) in anhydrous tetrahydrofuran (40 ml) at -78°C under argon was treated with *n*-butyl lithium (1.6M, 15.53 ml, 1.2 eq) and stirred for 30m, treated with freshly distilled propionyl chloride (2.74g, 30 mmol, 1.49 eq.), stirred for another 60m then allowed to come to ambient temperature. The reaction mixture was quenched with sodium carbonate solution, concentrated *in vacuo* and extracted with dichloromethane (4x40 ml). The combined organic extracts were washed successively with water (20 ml) and brine, dried (magnesium sulphate), filtered and evaporated to yield a pale yellow oil which was purified by flash chromatography (silica, ether:*n*-hexane, 2:1) or by distillation ($bp_{0.25}$ 165°C) gave **12** as a colourless oil (4.42g, 90%).

ASYMMETRIC TRANSFORMATIONS

Lithium enolate 13. A solution of lithium diisopropylamide (2.18 mmol, 1.1 eq.) was prepared by the dropwise addition of 1.6M butyl lithium (1.36 ml) to a solution of anhydrous diisopropylamine (0.221g, 2.18 mmol, 1.1 eq.) in dry tetrahydrofuran (30 ml) at 0°C under argon. The solution was stirred at 0°C for 30m, cooled to -78°C and treated with a solution of **12** (0.498g, 1.98 mmol, 1 eq.) in tetrahydrofuran (5 ml). The reaction mixture was stirred at this temperature for a further 30m before being treated with a range of substrates.

(i) Alkyl halides- General procedure:

(a) Benzyl bromide in the presence of sodium iodide. To a freshly prepared solution of LDA (0.11g, 8.94 mmol) *vide supra* in dry tetrahydrofuran (5 ml) at -78°C under argon, was added dropwise a solution of **12** (0.20g, 0.79 mmol) in dry tetrahydrofuran (8 ml). The reaction mixture was stirred at -78°C for 1h and treated with freshly distilled benzyl bromide (0.513g, 4.06 mmol, 5 eq.) followed by sodium iodide (pre-dried in a vacuum oven, 0.146g, 0.97 mmol, 1.2 eq.). The reaction mixture was warmed to -8°C (KCl, ice) and stirred overnight, quenched with ammonium chloride solution and concentrated *in vacuo*. The oil so obtained was treated with water (30 ml) and extracted with dichloromethane (4x60 ml). The combined organic extracts were washed successively with saturated sodium hydrogen carbonate, brine and dried (magnesium sulphate). Filtration and evaporation *in vacuo* gave an oil which was subjected to flash chromatography (silica, gradient elution *n*-hexane:ether 100:0 - 0:100) to give a colourless solid **[(2R,6S)]-*N*-((2'S)-benzylpropionyl)-5-aza-1,10,10-trimethyl-3-oxatricyclo[5.2.1.$0^{2,6}$]decan-4-one 14** which was recrystallised from methanol (0.218g, 80%); mp 100.5-101.5°C; $[\alpha]^{21}$ = -63.4°, c = 2.12 (dichloromethane); (Found: C, 74.0; H, 8.16; N, 4.12%. $C_{21}H_{27}NO_3$ requires C, 73.87; H, 7.97; N,4.10%); ν_{max} (thin film) 1760 (s, C=O), 1680 (s, C=O) cm^{-1}; ^1H NMR (200 MHz,$CDCl_3$) δ 0.91-0.93 (2xs, 9H, 3xCH_3), 1.11-1.52 (d, J=6.76 Hz, 3H, CH_3 superimposed on cm, 4H, 2xCH_2), 2.17 (t, 1H, CH,

J=4.18 Hz), 2.57 (dd, 1H, CH_2, J=13.19, 7.76 Hz), 3.12 (dd, 1H, CH_2, J=13.18, 7.23 Hz), 4.14 (m, 1H), 4.38 (dd, 1H,C*H*O J=9.64, 1.0 Hz), 4.55 (ddd, 1H, C*H*N, J=9.85, 4.27, 1.0 Hz), 7.12-7.30 (cm, 5H, aromatic H); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 176.38, 153.76, 139.10, 129.04, 128.06, 126.04, 82.16, 57.75, 49.16, 48.23, 47.47, 39.53, 39.41, 26.05, 19.69, 19.01, 17.83, 16.47, 13.64. This was the only isomer detected.

(b) Ethyl iodide. This reaction was carried out as described for benzyl bromide *vide supra* to give **[(2R,6S)]-*N*-((2'S)-methylbutanoyl)-5-aza-1,10,10-trimethyl-3-oxatricyclo[5.2.1.$0^{2,6}$]decan-4-one** as a colourless solid (17 mg,6%) ; M^+ 279.182, $C_{16}H_{25}NO_3$ requires 279.183; ^1H NMR (200 MHz,$CDCl_3$) δ 0.93 (t, 3H, CH_3, J=7 Hz), 0.95 (s, 3H, CH_3), 0.96 (s, 3H, CH_3), 0.97 (s, 3H, CH_3), 1.15 (d, 3H, J=7Hz), 1.20-1.85 (m. 6H), 2.3 (t, 1H, J=4 Hz), 3.69 (sextet, 1H, J=7 Hz), 4.45-4.63 (m, 2H, C*H*O, C*H*N).

(c) Allyl bromide. This reaction was carried out as described above but with the exclusion of sodium iodide and quenched after 4h. The product was purified by flash chromatography and yielded **[(2R,6S)]-*N*-(2'S)-methylbut-3-enoyl)-5-aza-1,10,10-trimethyl-3-oxatricyclo[5.2.1.$0^{2,6}$]decan-4-one** as a colourless solid which was crystallised from aqueous methanol (70%); mp 79-80°C; (Found: C, 69.7; H, 8.71; N, 4.73%. $C_{17}H_{25}NO_3$ requires C, 70.07; H, 8.65; N,4.81%); ^1H NMR (200 MHz,$CDCl_3$) δ 0.96 (s, 3H, CH_3), 0.97 (s, 3H, CH_3), 0.98 (s, 3H, CH_3), 1.15 (d, 3H, J=6Hz), 1.20 (m, 1H), 1.39 (m, 1H), 1.55-1.70 (m, 2H), 2.15 (m, 1H), 2.27 (m, 1H), 2.51 (m 1H), 3.88 (m, 1H), 4.49-4.60 (m, 2H), 4.96-5.12 (m, 2H), 5.79 (m, 1H).

(d) Cleavage of benzyl adduct (14) with lithium benzyloxide. A stirred solution of benzyl alcohol (0.07g, 0.69 mmol) in anhydrous tetrahydrofuran (4 ml) at 0°C under argon was treated dropwise with *n*-butyl lithium (1.6M, 0.33 ml, 1.5 eq.). The mixture was stirred at 0°C for 15m then cooled to -78°C and treated dropwise with a solution of **14** (0.119g, 0.349 mmol) in anhydrous tetrahydrofuran (6 ml). The reaction mixture was stirred at -78°C for 15m, warmed to room temperature and stirred for a further 30m, quenched with saturated ammonium chloride solution (5 ml) and concentrated *in vacuo*. Water (15 ml) was added and the reaction products were extracted into dichloromethane (3x20 ml). The combined organic extracts were washed with saturated sodium hydrogen carbonate solution, brine, dried (magnesium sulphate), filtered and evaporated *in vacuo* to yield an oily solid (0.17g) which was purified by flash chromatography (silica, gradient elution *n*-hexane:ether 100:0 - 0:100) to yield **(2S)-phenylmethylbenzyl propionate** as a colourless waxy solid (0.085g, 96%), further elution gave the cleaved auxiliary **8** (0.057g, 84%). The ester had the following physical properties:- $[\alpha]^{21}$ = +24.59°, c = 4.25 (dichloromethane) cf. lit. value of antipode -26° c = 6.12 (dichloromethane)[18]; ^1H NMR (200 MHz,$CDCl_3$) δ 1.16-1.19 (d, 3H, CH_3, J=6.67 Hz), 2.64-2.89 (cm, 2H, CH_2), 2.99-3.08 (cm, 1H, CH), 5.07 (s, 2H, O-CH_2), 7.12-7.34 (cm, 10H, aromatic H); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 175.77, 139.14, 135.92, 128.89, 128.39, 128.27, 127.98, 126.22, 66.02, 41.41, 39.64, 29.62, 16.73.

(ii) Acyl halides- General procedure:

(a) Acetyl chloride. A stirred solution of the enolate of **12** (0.2g,0.791 mmol) in anhydrous tetrahydrofuran (12 ml) at -78°C under argon was treated rapidly with freshly distilled acetyl chloride (0.1g, 1.27 mmol, 1.6 eq.) in anhydrous tetrahydrofuran (2 ml). The reaction

mixture was stirred for 45s, quenched with ammonium chloride solution, concentrated *in vacuo* and the residue was extracted with dichloromethane (4x25 ml). The organic fractions were combined, washed with brine, dried (magnesium sulphate), filtered and evaporated *in vacuo* to yield **[(2R,6S)]-*N*-((2'S)-methyl-3-oxobutanoyl)-5-aza-1,10,10-trimethyl-3-oxatricyclo[5.2.1.0^{2,6}]decan-4-one** as an oil (0.204, 88%). Crystallisation from methanol gave a colourless solid (major product) (76 mg, 33%); mp 139-140.5°C; $[\alpha]^{23}$ =-51.1°, c = 3 (dichloromethane); M^+ (EI) 293.1617 $C_{16}H_{23}NO_4$ requires 293.1627; ν_{max} (mull) 2915, 1780 (s,C=O), 1722 (s,C=O), 1701 (s,C=O), 1362, 1292, 1225 cm^{-1}; ^{1}H NMR (200 MHz,$CDCl_3$) δ 0.90 (s, 3H, CH_3), 0.92 (s, 3H, CH_3), 0.93 (s, 3H, CH_3), 1.30-1.33 (d, 3H, CH_3, J=7.33 Hz), 1.30-1.58 (cm, 4H, 2xCH_2), 2.28 (s, 3H, CH_3CO), 4.49-4.51 (cm, 2H,C*H*O, C*H*N, superimposed on q, 1H, J=7.5 Hz); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 205.46, 169.75, 154.42, 83.10, 57.74, 53.05, 49.28, 48.44, 47.81, 28.19, 26.12, 19.69, 18.84, 17.89, 13.67, 12.20.

The reaction was repeated with the following substrates:-

(b)Propionyl chloride. The reaction was carried out as described above but was quenched after 1m to yield **[(2R,6S)-*N*-((2'S)-methyl-3-oxopentanoyl)-5-Aza-1,10,10-trimethyl-3-oxatricyclo[5.2.1.0^{2,6}]decan-4-one** as an oil (89%). Crystallisation from methanol gave the major product as a colourless solid (62 mg, 26%);; mp 120-121°C; $[\alpha]^{22}$ =-53.3°, c = 3 (dichloromethane);M^+ (EI) 307.1785 $C_{17}H_{25}NO_4$ requires 307.17835; ν_{max} (mull) 2922, 1765 (s,C=O), 1718 (s, C=O), 1705 (s, C=O), 1360, 1223, 1215 cm^{-1};^{1}H NMR (200 MHz,$CDCl_3$) δ 0.89 (s, 3H, CH_3), 0.91 (s, 3H, CH_3), 0.92 (s, 3H, CH_3), 0.99-1.06 (t, 3H, CH_3,J=7.24Hz), 1.28-1.32 (d, 3H, CH_3, J=7.28Hz, superimposed 1.16-1.62 cm, 4H, 2xCH_2), 2.11-2.29 (bs, 1H,), 2.46-2.80 (2xdq, 2H,CH_2, J=18.13, 7.33 Hz), 4.50-4.80 (cm, 2H, C*H*O, C*H*N, superimposed on q, 1H, J=7.29 Hz, CH); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 208.09, 170.00, 154.36, 83.05, 57.79, 52.46, 49.25, 48.42, 47.82, 33.68, 26.15, 19.69, 18.89, 17.88, 13.65, 12.58, 7.39.

(c)Benzoyl bromide. The reaction was quenched after after 2m and crystallisation from methanol gave **[(2R,6S)]-*N*-((2'S)-benzoylpropionyl)-5-aza-1,10,10-trimethyl-3-oxatricyclo[5.2.1.0^{2,6}]decan-4-one** as a colourless solid (126 mg, 48%); mp 133°C; $[\alpha]^{21}$ =+1.75°; c = 0.8 (dichloromethane); M^+ (EI) 355.1776 $C_{21}H_{25}NO_4$ requires 355.17835; ν_{max} (mull) 3365 (br. s, enol O-H), 2965, 1770 (s, C=O), 1705 (s, C=O), 1680 (s, C=O), 1600 (enol, C=C), 1215, 975 cm^{-1};^{1}H NMR (200 MHz,$CDCl_3$) δ 0.94 (2xs, 6H, 2xCH_3), 0.97 (s, 3H, CH_3), 1.44-1.44 (d, 3H, CH_3, J=7.26 Hz), superimposed on 1.16-1.71 (cm, 4H, 2xCH_2), 2.36-2.39 (t, 1H, J=4.21 Hz), 4.49-4.54 (d, 1H,C*H*O, J=10.23 Hz), 4.57-4.64 (dd, 1H, C*H*N, J=9.81, 4.24 Hz), 5.31-5.42 (q, 1H, J=7.27 Hz), 7.38-7.60 (cm, 3H, aromatic H), 7.78-7.99 (dd, 2H, aromatic H, J=6.82, 1.67 Hz); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 170.29, 169.39, 154.29, 134.94, 132.94, 131.57, 129.61, 128.43, 128.23, 127.50, 127.15, 83.07, 57.73, 49.22, 48.46, 48.39, 47.78, 26.07, 19.64, 18.82, 17.83, 13.60, 13.42.

(d)Methyl cyanoformate (Manders reagent)[20]. The reaction was quenched after 1.5m to yield **[(2R,6S)]-*N*-((2'S)-methylformylpropionyl)-5-aza-1,10,10-trimethyl-3-oxatricyclo[5.2.1.0^{2,6}]decan-4-one** as a colourless solid (81mg, 99%); mp 103-104.5°C; $[\alpha]^{21}$ = -96.99°, c = 4.05 (dichloromethane); M^+ (EI) 309.1575 $C_{16}H_{23}NO_5$ requires 309.15761; ν_{max} (mull) 2923, 1770 (s, C=O), 1740 (s, C=O), 1698 (s, C=O),1358, 1223, 1213 766 cm^{-1}; ^{1}H NMR (200 MHz,$CDCl_3$) δ 0.89 (s, 3H, CH_3), 0.91 (2xs, 6H, 2xCH_3), 1.33-1.37

(d, 3H, CH_3, J=7.29 Hz), 1.11-1.58 (cm, 4H, 2xCH_2), 2.27 (bs, 1H), 3.64 (s, 3H, OCH_3), 4.44-4.50 (cm, 2H, C*H*O, C*H*N), superimposed on 4.35-4.45 (q, 1H, J=7.29 Hz, CH); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 170.78, 169.18, 154.02, 82.85, 57.79, 52.08, 49.19, 48.34, 47.69, 45.32, 26.04, 19.60, 18.76, 17.79, 13.57, 12.91.

(iii) Aldehydes (the aldol reaction)- General procedure using metal-enolates of 12:

(a) Benzaldehyde. Neat freshly distilled benzaldehyde (0.21g, 1.98 mmol, 1eq.) was added rapidly to a freshly prepared solution of lithium enolate of **12** *vide supra* (1.98 mmol, 1 eq.) at -78°C and the reaction mixture was quenched after 30s with saturated ammonium chloride solution (5 ml). Water (50 ml) was added and the reaction products were extracted into ether (3x20 ml). The organic fractions were combined, dried (magnesium sulphate), filtered and evaporated to dryness *in vacuo* to give a colourless crystalline mass of the aldol products (0.69g, 97%); ^1H NMR (360 MHz, $CDCl_3$) showed that all four possible diastereomeric aldol products were present in a ratio of 55.4:28.7:10.3:5.7.

(b) *iso*-Butyraldehyde. The reaction was carried out using freshly distilled *iso*-butyraldehyde (0.122g, 1.69 mmol, 2.1 eq.) and lithium enolate of **12** (0.79 mmol). The reaction was quenched after 2m and the products isolated (*vide supra*) (0.225, 88%) as an oil which solidified on standing. HPLC analysis (silica, spherisorb 5μ, *n*-hexane:ether, 5:1) gave a product distribution of 64.7:22.5:7.9:4.9 cf. EVANS 71.4:11.0:10.6:7.0.[10].

(c) Acetaldehyde. The reaction was conducted for 90s and 180s before quenching but starting material was still present. The reaction was then conducted for 1.75h. To freshly prepared lithium enolate **13** (0.598 mmol) in anhydrous tetrahydrofuran (10 ml) at -78°C under argon, freshly distilled acetaldehyde (1 ml, 0.78g, 17.8 mmol, 30 eq.) in anhydrous tetrahydrofuran (5 ml) was added and stirred for 1.75h, quenched with saturated ammonium chloride solution and extracted with dichloromethane (3x40 ml). The combined organic extracts were washed with saturated sodium hydrogen carbonate solution, brine, dried (magnesium sulphate), filtered and evaporated *in vacuo* to yield a brown oil (0.18g, 100%) which was analysed by ^1H NMR. FAB-MS (thioglycerol) showed not only aldol products but dehydrated products as well as cleaved auxiliary **8** to be present.

(d)Using the boron enolate 18 of 12. To a solution of **12** (0.3g, 1.2 mmol) in anhydrous dichloromethane (5 ml) at 0°C under argon was added di-*n*-butylboron triflate (1M in dichloromethane, 1.31 ml, 1.31 mmol, 1.1 eq.) followed by di-*iso*-propylethylamine (0.18g,1.43 mmol,1.2 eq.). The mixture was stirred for 30m then cooled to -78°C and treated with a variety of substrates.

(e) Aldehydes- General procedure:

A solution of aldehyde (1.31 mmol) in tetrahydrofuran (1 ml) was added dropwise to the boron enolate solution *vide supra* at -78°C and stirred for 30m, the temperature was allowed to rise to 20°C and the mixture stirred for a further 1.5h, quenched with a pH7 phosphate buffer (50 ml) and the organic phase separated. The aqueous phase was extracted with dichloromethane (3x30 ml). The organic fractions were combined and evaporated *in vacuo*. The resultant oil was treated with 30% w/v hydrogen peroxide solution (2 ml) at 0°C for 1h and then thoroughly extracted with ether. The ether extracts were combined, dried (sodium

sulphate) and evaporated. The products were isolated following purification by flash chromatography.

(f) *iso*-Butyraldehyde. The protocol just described was followed and a single product **[(2R,6S)]-*N*-((3'R)-hydroxy-(2'R)-methyl-4'-methylpentanoyl)-5-aza-1,10,10-trimethyl-3-oxatricyclo[5.2.1.0^{2,6}]decan-4-one** was isolated as a colourless solid which was recrystallised from ethyl acetate-petroleum ether (86%); mp 161-162°C; (Found: C, 66.8; H, 9.32; N, 4.44%. $C_{18}H_{29}NO_4$ requires C,66.84; H,9.04; N,4.33%); ν_{max} (mull) 1770, 1660 cm^{-1}; m/z (CI) 324 (M^++1, 20%), 306 (100%), 252 (95%), 196 (80%); ^{1}H NMR (200 MHz,$CDCl_3$) δ 0.90 (d, 3H, J=7Hz), 0.97 (s, 3H, CH_3), 0.98 (s, 3H, CH_3), 0.99 (s, 3H, CH_3), 1.02 (d, 3H, J=7 Hz, CH_3), 1.15 (m, 1H), 1.23 (d, 3H, J=8Hz), 1.40 (m, 1H), 1.58-1.75 (m, 3H), 2.30 (t, 1H, J=4Hz), 2.87 (br, 1H, OH), 3.52 (dd, 1H, J=8.0, 2.5 Hz), 4.02 (qd, 1H, J=6.0, 2.5 Hz), 4.4-4.64 (cm, 2H).

(g)Benzaldehyde. [(2R,6S)]-*N*-((3'R)-hydroxy-(2'R)methyl-3'-phenylpropionyl)-5-aza-1,10,10-trimethyl-3-oxatricyclo[5.2.1.0^{2,6}]decan-4-one 18 was isolated as a single product by following the method described above and was recrystallised from ethyl acetate-petroleum ether (52%); mp 136-137°C; ν_{max} (mull) 1770, 1658cm^{-1} ; ^{1}H NMR (200 MHz,$CDCl_3$) δ 0.95 (s, 3H, CH_3), 0.98 (br. s, 6H, 2xCH_3),1.17 (d, 3H, J=7Hz), 1.05-1.44 (m, 2H), 1.55-1.73 (m, 2H), 2.30 (t, 1H, J=4Hz), 3.00 (br, 1H, OH), 4.14 (qd, 1H, J=7.0, 3.5 Hz), 4.45-4.58 (m, 2H), 5.12 (d, 1H, J=3.5 Hz), 7.21-7.45 (m, 5H, aromatic H).

(h) Procedure for the generation of titanium(IV)enolate 19 and subsequent aldol reaction with benzaldehyde: To a stirred solution of **12** (0.200g, 7.97 mmol) in anhydrous dichloromethane (4 ml) at -78°C under argon was added titanium tetrachloride (0.51 ml, 8.8 mmol, 1.1 eq.). The resulting solution was stirred for 10m and treated dropwise with triethylamine (0.1g, 9.88 mmol, 1.2 eq.) in dichloromethane (2 ml). Stirring was continued at -78°C for a further 90m before freshly distilled benzaldehyde (0.108g,1.02 mmol, 1.2 eq.) in dichloromethane (4 ml) was added dropwise. The reaction mixture was stirred for 48h at room temperature, quenched with saturated ammonium chloride solution and extracted with dichloromethane (3x40 ml). The combined organic extracts were washed with saturated sodium hydrogen carbonate solution, brine, dried (magnesium sulphate), filtered and evaporated *in vacuo* to yield a yellow oil (0.312g, 109%) which was analysed by ^{1}H (200 MHz)NMR. The analysis revealed that as well as contamination with benzaldehyde and benzoic acid there was only two isomers present. The main features in the spectrum were two carbinol resonances at δ 5.09-5.14 (d, 1H, J=10.94 Hz, PhC.OH.*H*) (major isomer) and δ 5.15-5.5.19 (d, 1H, J=9.0 Hz, PhC.OH.*H*) (minor isomer), and an α-methine resonance at δ 4.68-4.80 (dq, 1H, J=10.92,6.92 Hz, PhC.OH.H-C*H*.CH_3.CO.) (major isomer).

(v) Diels-Alder reactions:

(a) Preparation of [(2R, 6S)-*endo*]-*N*-Acryloyl-5-aza-1,10,10-trimethyl-3-oxatricyclo[5.2.1.0^{2,6}]decan-4-one (21). To a solution of oxazolidinone **8** (0.5g, 2.56 mmol) in anhydrous tetrahydrofuran (40 ml) under argon at 0°C methyl magnesium bromide (3.0 M in ether, 0.9 ml,2.7 mmol, 1.05 eq.) was added and stirred for 10m. The temperature was lowered to -78°C and the reaction mixture was treated with freshly distilled acryloyl chloride (0.3g, 3.3 mmol, 1.3 eq.), stirred for 10m, and the temperature was raised to 0°C. The mixture

was stirred for 75m quenched with aqueous ammonium chloride and extracted into ether (3x75 ml). The combined organic extracts were washed with saturated sodium hydrogen carbonate solution, brine, dried (magnesium sulphate), filtered and evaporated *in vacuo* to yield a colourless solid which was subjected to flash chromatography (silica, *n*-hexane:ethyl acetate 7:1) (0.48g, 75%); mp 47-50°C; $[\alpha]^{21.5}$ = -156.9°, c = 2.58 (dichloromethane); M^+ 249.1371 $C_{14}H_{19}NO_3$ requires 249.136475; ν_{max} (mull) 2930, 1770 (s, C=O), 1690 (s, C=O), 1620, 1460, 1415, 1380 cm^{-1}; ^1H NMR (200 MHz,$CDCl_3$) δ 0.95 (s, 3H, CH_3), 0.96 (s, 3H, CH_3), 0.97 (s, 3H, CH_3), 1.09-1.7 (m, 4H, 2x CH_2), 2.31 (t, 1H, J=4.2Hz), 4.49-4.66 (cm, 2H, C*H*O, C*H*N), 5.85 (dd, 1H, J=10.45, 1.86Hz), 6.50 (dd, 1H, J=17, 1.92Hz), 7.55 (dd, 1H, J=17, 10.48 Hz); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 164.96, 154.04, 131.39, 127.19, 82.63, 57.82, 49.33, 48.44, 47.68, 26.18, 19.76, 19.66, 17.92, 13.67.

(b) Preparation of [(2R, 6S)-*endo*]-*N*-Crotonoyl-5-aza-1,10,10-trimethyl-3-oxatricyclo[5.2.1.$0^{2,6}$]decan-4-one (22). A solution of oxazolidinone **8** (1.0g, 5.13 mmol) in anhydrous tetrahydrofuran (30 ml) was added to a freshly prepared solution of methyl magnesium bromide (0.73g, 6.15 mmol, 1.2 eq.) in anhydrous ether (30 ml) at 0°C under argon and stirred for 20m before the temperature was lowered to -78°C. Freshly distilled crotonoyl chloride (0.65g, 6.22 mmol, 1.2 eq.) was added and the mixture stirred for 20m and the temperature raised to 0°C. The reaction mixture was stirred at this temperature for 1h then at ambient temperature overnight. Thin layer chromatography on silica (*n*-hexane:ethyl acetate) revealed a trace of starting material. The reaction mixture was quenched with ammonium chloride solution and extracted with ether (3x50 ml). The combined organic extracts were washed with saturated sodium hydrogen carbonate solution, brine, dried (magnesium sulphate), filtered and evaporated *in vacuo* to yield a pale yellow solid which was subjected to flash chromatography (silica, *n*-hexane:ethyl acetate 7:1) (1.15g, 85%); mp 117-121°C; $[\alpha]^{21.5}$ = -173.9°, c = 4.94 (dichloromethane); M^+ 263.1521 $C_{15}H_{21}NO_3$ requires 263.152125; ν_{max} (mull) 2920, 1763(s, C=O), 1682 (s, C=O), 1635, 1375, 1208, 1050 cm^{-1}; ^1H NMR (200 MHz,$CDCl_3$) δ 0.90-0.91 (2xs, 9H, 3xCH_3), 1.08-1.61 (cm, 4H,2xCH_2), 1.88 (dd,3H, CH_3, J=6.69, 1.44 Hz), 2.24 (t, 1H, CH, J=4.2 Hz), 4.45 (ddd, 1H, C*H*O, J=9.78, 2.2, 0.6 Hz), 4.56 (ddd, 1H, C*H*N, J=9.8, 4.3, 1.22 Hz), 7.05 (dq, 1H, CH_3CH=CH, J=15.26, 6.56 Hz), 7.27 (dq, 1H, CH=C*H*CO), J=15.25, 1.50 Hz); ^{13}C NMR (90.56 MHz, $CDCl_3$) δ 164.95, 154.05, 146.17, 121.65, 82.34, 57.76, 49.25, 48.30, 47.78, 26.17, 19.71, 19.59, 18.19, 17.85, 13.60.

(c) Preparation of [(2R, 6S)-*endo*]-*N*-Cinnamoyl-5-aza-1,10,10-trimethyl-3-oxatricyclo[5.2.1.$0^{2,6}$]decan-4-one (23). A solution of oxazolidinone **8** (0.624g, 3.2 mmol) in anhydrous tetrahydrofuran (40 ml) was added to a freshly prepared solution of methyl magnesium bromide (0.73g, 6.15 mmol, 1.2 eq.) in anhydrous ether (30 ml) at 0°C under argon and stirred for 10m before the temperature was lowered to -78°C. Freshly distilled cinnamoyl chloride (0.64g, 3.84 mmol, 1.2 eq.) in anhydrous tetrahydrofuran (5 ml) was added and the mixture stirred for 20m and then warmed to room temperature and stirred overnight. The reaction mixture was quenched with ammonium chloride solution concentrated *in vacuo* taken up in water (20 ml) and extracted with dichloromethane (3x60 ml). The combined organic extracts were washed with saturated sodium hydrogen carbonate solution, brine, dried (magnesium sulphate), filtered and evaporated *in vacuo* to yield a solid

which was subjected to flash chromatography (silica, *n*-hexane:ethyl acetate 7:1) (0.84g, 81%); mp 169.5-170.5°C (*n*-hexane:di-*iso*-propylether); $[\alpha]^{23.5}$ = -133.0°, c = 4.22 (dichloromethane); M+325.1674 $C_{20}H_{23}NO_3$ requires 325.167775; ν_{max} (mull) 2920, 1760 (s, C=O), 1680 (s, C=O), 1615 (C=C), 1378, 1368, 1210, 1048 cm^{-1}; ^1H NMR (200 MHz,$CDCl_3$) δ 0.97-0.98 (2xs, 9H, 3xCH_3), 1.09-1.67 (cm, 4H,2xCH_2), 2.35 (t, 1H,CH, J=8.41 Hz), 4.53 (dd, 1H, C*H*O, J=11.1, 1.42 Hz), 4.64 (ddd, 1H, C*H*N, J=11.1, 4.50, 1.33 Hz), 7.34-7.39 (cm, 3H, aromatic H), 7.58-7.63 (cm, 2H, aromatic H), 7.81 (d, 1H, PhC*H*=CH-, J=15.74Hz), 8.00 (d, 1H,CH=C*H*CO, J=15.73 Hz); ^{13}C NMR (90.56 MHz, $CDCl_3$) δ 165.16, 154.15, 145.80, 134.46, 130.33, 128.63, 128.37, 116.90, 82.43, 57.94, 49.29, 48.35, 47.82, 26.20, 19.73, 19.66, 17.88, 13.62.

(d) Diels-Alder reaction between acryloyl compound (21) and cyclopentadiene at -78°C.

Without the use of a catalyst. Freshly cracked cyclopentadiene (1.50g, 22.7 mmol, 12 eq.) was added to a solution of **21** (0.48g, 1.93 mmol) in anhydrous dichloromethane (50 ml) at 0°C under argon. The reaction mixture was stirred at 0°C for 23h evaporated *in vacuo* and subjected to flash chromatography to yield a colourless solid (0.42g, 69%). High-field ^1H NMR (360 MHz) analysis showed the presence of two isomers in the ratio of 1.1:1.

Using $TiCl_2(OPr^i)_2$ as a catalyst[15]. A solution of **21** (0.162g, 0.651 mmol) in anhydrous dichloromethane (3 ml) at -78°C under argon was treated with titanium(IV) chloride (0.52g, 2.74 mmol 4eq.) followed by titanium(IV) *iso*-propoxide (0.74g, 2.60 mmol, 4 eq.). Freshly cracked cyclopentadiene (0.43g, 7.17 mmol, 11 eq.) was added and the reaction mixture was stirred for 22h, poured onto crushed ice and extracted with dichloromethane (3x20 ml). The combined organic fractions were washed with saturated sodium hydrogen carbonate solution, brine, dried (magnesium sulphate), filtered and evaporated *in vacuo* to yield a solid which was subjected to flash chromatography (silica, gradient elution *n*-hexane:ether 100:0-50:50) to give a colourless solid (0.17g, 83%). The solid consisted of a mixture of two *endo*-isomers in a ratio of 2:1, which were separated by column chromatography (TLC silica (70g), *n*-hexane:ether 40:1). **[(2R,6S)]-*N*-((3'R,4'R,6'R)-Bicyclo[2.2.1]heptene-4'-carbonyl)-5-aza-1,10,10-trimethyl-3-oxatricyclo[5.2.1.$0^{2,6}$]decan-4-one** (*minor isomer*):-mp 143-145.5°C (*n*-hexane:di-*iso*-propylether); $[\alpha]^{23}$ =-25.1°, c = 1.95 (dichloromethane); M+315.1839 $C_{19}H_{25}NO_3$ requires 315.183425; ν_{max} (mull) 2924, 1770 (s, C=O), 1755 (s, C=O), 1695 (C=C), 1280, 1220, 1040 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 0.92 (s, 3H, CH_3), 0.94 (s, 3H, CH_3), 0.96 (s, 3H, CH_3), 1.06-1.68 (cm, 7H), 1.97 (ddd, 1H, J=12.77, 9.09, 3.74 Hz), 2.15-2.27 (cm, 1H), 2.91 (bs, 1H, CH), 3.28 (bs, 1H), 4.00-4.05 (ddd, 1H,J=9.11, 4.42, 3.47Hz), 4.48-4.49 (cm, 2H, C*H*N, C*H*N), 5.85 (dd, 1H, =C*H*, J=5.64, 2.85 Hz), 6.20 (dd, 1H, =C*H*, J=5.64, 3.08 Hz);^{13}C NMR (50.3 MHz, $CDCl_3$) δ 174.51, 153.93, 137.65, 131.50, 82.26, 58.07, 49.93, 49.23, 48.18, 47.76, 46.12, 43.09, 42.68, 29.42, 26.16, 19.55, 19.30, 17.83, 13.65. **[(2R,6S)]-*N*-((3'S,4'S,6'S)-Bicyclo[2.2.1]heptene-4'-carbonyl)-5-aza-1,10,10-trimethyl-3-oxatricyclo[5.2.1.$0^{2,6}$]decan-4-one** (major isomer):- mp 155-157.5°C ; $[\alpha]^{22}$ = -287.5°, c = 3.08 (dichloromethane); (Found: C, 72.3; H, 8.0; N, 4.4%. $C_{19}H_{25}NO_3$ requires C,72.5; H,8.05; N,4.72%); M+315.1823 $C_{19}H_{25}NO_3$ requires 315.183425; ν_{max} (mull) 2920, 1790 (s, C=O), 1775 (s, C=O), 1640 (C=C), 1460, 1380 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 0.90 (s, 3H,

CH_3), 0.93 (s, 3H, CH_3), 0.95 (s, 3H, CH_3), 1.08-1.70 (cm, 7H), 1.86 (ddd, 1H, J=12.6, 9.0, 4.7 Hz), 2.19 (t, 1H, J=4.0Hz), 2.90 (bs, 1H), 3.36 (bs, 1H), 4.03 (ddd, 1H, J=9.0, 4.4, 3.4Hz), 4.45 (dd, 1H, J=9.3, 1.3 Hz), 4.51 (ddd, 1H, J=9.9,4.2, 1.2 Hz), 5.77 (dd, 1H, =C*H*, J=5.6, 2.8 Hz), 6.20 (dd, 1H, =C*H*,J=5.6, 3.0 Hz); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 174.31, 153.89, 137.88, 130.95, 82.17, 57.62, 50.00, 49.18, 48.19, 47.53, 46.26, 42.79, 42.63, 28.80, 26.14, 19.60, 19.35, 17.73, 13.55.

Using Et_2AlCl as a catalyst. To a rapidly stirred solution of **21** (0.102g, 0.41 mmol) in anhydrous dichloromethane (2 ml) under argon at -78°C was added freshly cracked cyclopentadiene (0.27g, 4.1 mmol, 10 eq.) followed by diethylaluminium chloride (1.8M in toluene, 0.3 ml, 0.54 mmol, 1.4 eq.). After 3m the reaction was quenched with hydrochloric acid (2M, 5ml) and stirred for 5m. The two fractions were separated and the aqueous fraction was extracted with dichloromethane (3x10 ml). The combined organic fractions were washed with saturated sodium hydrogen carbonate solution, brine, dried (magnesium sulphate), filtered and evaporated *in vacuo* to yield a solid which was subjected to flash chromatography (silica, gradient elution *n*-hexane:ether 100:0-50:50) to give a colourless solid (0.124g, 98%). The solid consisted of a mixture of the same two *endo*-isomers (*vide supra*) but in a ratio of 4:1.

(f)Diels-Alder reaction between acryloyl compound (21) and isoprene at -78°C.

Using $TiCl_2(OPr^i)_2$ as a catalyst. The same protocol as for cyclopentadiene (*vide supra*) the reaction was conducted for 46h before quenching. Work-up provided a colourless oil (0.08g, 80%) which crystallised on standing. ^1H NMR (360 MHz) using a europium chiral shift reagent (tris[3-(heptafluoropropylhydroxymethylene)-d-camphorato]europium(III)) revealed that the two *endo*-isomers were present in a ratio of 2:1.

Using Et_2AlCl as a catalyst. Adopting the same procedure as above work-up yielded a colourless solid (0.24g, 94%) which contained the *endo*-isomers in a ratio of 5:1.

(g)Diels-Alder reaction between crotonoyl compound (22) and cyclopentadiene at -78°C.

Using $TiCl_2(OPr^i)_2$ as a catalyst. To a stirred solution of titanium(IV) chloride (0.29g, 1.53 mmol, 4 eq.) and titanium(IV) *iso*-propoxide (0.43g, 1.51 mmol, 4 eq.) in anhydrous dichloromethane (2 ml) at -78°C under argon was added a solution of **22** (0.1g, 0.38 mmol) in anhydrous dichloromethane (3 ml). Freshly cracked cyclopentadiene (0.25g, 3.79 mmol) was added and the mixture stirred for 20h, poured onto crushed ice and extracted with dichloromethane (3x20 ml). The combined organic fractions were washed with saturated sodium hydrogen carbonate solution, brine, dried (magnesium sulphate), filtered and evaporated *in vacuo* to yield the product which was subjected to flash chromatography(silica, gradient elution *n*-hexane:ether 100:0-50:50) to give a colourless solid (0.115g, 92%). The product was analysed by ^1H NMR (360 MHz) and was shown to contain four isomers in the ratio of 51:34:11:4. Major isomers were not characterised due to difficulty in separation of these compounds.

Using Et_2AlCl as a catalyst. To a stirred solution of **22** (0.1g, 3.8 mmol) in anhydrous dichloromethane (2 ml) at -78°C under argon was added diethylaluminium chloride (1.8M in toluene, 0.3 ml, 0.539 mmol, 1.4 eq.) which produced a bright yellow complex. This complex

was treated rapidly *via* a canula with pre-cooled freshly cracked cyclopentadiene (1.0g, 15 mmol, 40 eq.). After 5m the colour had faded and the reaction mixture was diluted with dichloromethane (50 ml) and quenched with dilute hydrochloric acid (2M, 10 ml). The organic layer was separated and the aqueous fraction extracted with ether (3x30 ml). The combined organic fractions were washed with saturated sodium hydrogen carbonate solution, brine, dried (magnesium sulphate), filtered and evaporated *in vacuo* to yield the product which was subjected to flash chromatography (silica, gradient elution *n*-hexane:ether 100:0-50:50) to give a colourless solid (0.12g, 96%). Analysis of the product revealed the same four isomers in the ratio 67:15:3:15.

(h) Diels-Alder reaction between cinnamoyl compound (23) and cyclopentadiene at -78°C.

Using Et_2AlCl as a catalyst. To a stirred solution of **23** (0.101g, 0.311 mmol) in anhydrous dichloromethane (2 ml) at -78°C under argon was added diethylaluminium chloride (1.8M in toluene, 1.0 ml, 0.568 mmol, 1.8 eq.) which produced a deep yellow/orange complex. This complex was treated rapidly *via* a canula with pre-cooled freshly cracked cyclopentadiene (1.0g, 15 mmol, 48 eq.). The reaction mixture was warmed to -20°C and within 1m the colour had faded to pale yellow/green, it was diluted with dichloromethane (50 ml) and quenched with dilute hydrochloric acid (2M, 10 ml). The organic layer was separated and the aqueous fraction extracted with dichloromethane (3x30 ml). The combined organic fractions were washed with saturated sodium hydrogen carbonate solution, brine, dried (magnesium sulphate), filtered and evaporated *in vacuo* to yield the product which was subjected to flash chromatography (silica, gradient elution *n*-hexane:ether 100:0-0:100) to give **[(2R,6S)]-*N*-((3'S,4'R,5'R,6'S)-5'-phenylbicyclo[2.2.1] heptene-4'-carbonyl)-5-aza-1,10,10-trimethyl-3-oxatricyclo[5.2.1.$0^{2,6}$]decan-4-one 24** as a colourless solid (0.11g, 92%). Analysis of the product by ^1H NMR (360 MHz) revealed only one isomer; mp 131-134°C (*n*-hexane:di-*iso*-propylether); $[\alpha]^{21}$ = -263.6°, c = 2.54 (dichloromethane); M^+391.2149 $C_{25}H_{29}NO_3$ requires 391.214725; ν_{max} (mull) 2930, 1778 (s, 2xC=O), 1700 (C=C), 1338, 1225, 1212, 1060 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 0.94 (s, 3H, CH_3), 0.97 (s, 3H, CH_3), 0.98 (s, 3H, CH_3), 1.14-1.25 (cm, 1H), 1.39-1.45 (m, 1H), 1.58-1.73 (dd, 1H, J=8.69, 1.69 Hz, superimposed on cm, 2H), 1.98 (bd, 1H, J=8.72 Hz),2.25 (t, 1H, CH, J=4.22 Hz), 2.99-3.01 (cm, 1H, CH), 3.34 (dd, 1H, CH, J=5.26, 1.68 Hz), 3.56 (bs, 1H, CH), 4.22 (dd, 1H, CH, J=5.27, 3.35 Hz), 4.48 (dd, 1H, C*H*O, J=9.78, 1.59 Hz), 4.57 (ddd, 1H, C*H*N, J=9.89, 4.47, 1.18 Hz), 5.87 (dd, 1H, =CH, J=5.63, 2.75Hz), 6.52 (dd, 1H, =CH, J=5.63, 3.19 Hz),7.14-7.29 (cm, 5H, aromatic H); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 173.54, 153.91, 143.63, 140.08,131.86, 128.24, 127.34, 125.85, 82.24, 57.66, 50.33, 49.24, 48.31, 48.09, 47.51, 47.31, 46.12, 26.18, 19.71, 19.43, 17.83, 13.64.

(i)Cleavage of the cycloadduct 24 formed in the reaction between 17 and cyclopentadiene : chiral ester formation. *n*-Butyl lithium (1.6M, 1 ml, 1.6 mmol, 1.2 eq.) was added to a solution of benzyl alcohol (0.272g, 2.52 mmol, 2 eq.) in anhydrous tetrahydrofuran (5 ml) at -78°C under argon and the mixture was stirred for 30m, then treated with cinnamate adduct **24** (0.5g, 1.28 mmol) in anhydrous tetrahydrofuran (5 ml). The mixture was warmed to 0°C and stirred for 75m and then at ambient temperature for 3h, quenched with ammonium chloride solution and concentrated *in vacuo*. Water (40 ml) was

added and the reaction products were extracted into dichloromethane (4x60 ml). The combined organic fractions were washed with saturated sodium hydrogen carbonate solution, brine, dried (magnesium sulphate), filtered and evaporated *in vacuo* to yield an oil which was subjected to flash chromatography (silica, gradient elution *n*-hexane:ether 19:1-7:3) to give chirally pure **benzyl(3S,4S,5R,6R)-5-phenylbicyclo[2.2.1] heptene-4-carboxylate 25** (0.333g, 86%). Further elution (*n*-hexane:ether 1:4) yielded the recovered chiral auxiliary **8** (0.142g, 57%). Physical data for the ester: $[\alpha]^{21}$ = -121.1° ,cf. lit value of antipode +121.0°, c = 1.36 (dichloromethane)[24]; M^+391.2149 $C_{25}H_{29}NO_3$ requires 391.214725; ν_{max} (thin film) 2980, 1735 (s, C=O), 1502, 1458, 1335, 1260, 11701338, 1220 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.64-1.70 (dd, 1H, CH_2, J=8.67, 1.76 Hz), 1.88 (bd, 1H, CH_2, J=8.33 Hz), 3.12-3.14 (cm, 2H), 3.15 (bd, 1H,CH_2, J=3.63Hz), 3.34 (bs, 1H, CH), 5.17 (d, 1H, CH_2, J=12.42 Hz), 5.26 (d, 1H, CH_2, J=12.40 Hz), 6.17 (dd, 1H, =CH, J=5.65, 2.75 Hz), 6.51 (dd, 1H, =CH, J= 5.65, 3.21 Hz), 7.25-7.47 (cm, 10H, 2x aromatic H); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 173.76, 143.93, 138.89, 135.98, 134.17, 128.23, 127.83, 127.76, 127.20, 125.79, 65.95, 51.99, 48.02, 47.18, 46.95, 46.11.

References

1. Sharpless, K. B.; Behrens, C. H.; Katsuki, T.; Lee, A.. W. M.; Martin, V. S.; Takatini, M.; Viti, S. M., Walker, F. J.; Woodward, S. S. *Pure Appl. Chem.*, **1983**, *55*, 589.
2. Fujita, S.; Imamura, K.; Nozaki, H. *Bull. Chem. Soc. Jpn.*, **1971**, *44*, 1975.
3. Hassner, A.; Lorber, M. E.; Heathcock, C. *J. Org. Chem*,**1967**, *32*, 540.
4. Atkinson, R. S.; Fawcett, J.; Russell, D. R.; Tughan, G. *J. Chem. Soc., Chem. Commun.*, **1986**, 832,834.
5. Atkinson, R. S.; Kelly, B. J. *J. Chem. Soc., Chem. Commun.*, **1987**, 1362.
6. Lwowski, W.; Maricich, T. J. *J. Am. Chem. Soc.*, **1965**, *87, 3630.*
7. Seno, M.; Namba, T.; Kise, H. *Bull. Chem. Soc. Jpn.*, **1979**, *52*, 2975; *J. Org. Chem*, **1978**, *43*, 3345.
8. Aitkin, R. A.; Gosney, I.; Farries, H.; Palmer M. H.; Simpson I.; Cadogan J. I. G.; Tinley E. J. *Tetrahedron*, **1984**, *40*, 2487.
9. Evans, D. A.. *Aldrichimica Acta,* **1982**, *15*, 318.
10. Evans, D. A..; Bartoli, J.; Shih, T. L. *J. Am. Chem. Soc.*, **1981**, *103,* 2127; Evans, D. A..; Nelson, J. V.; Evans, D. A..;Vogel, E.; Taber, T. R. *J. Am. Chem. Soc.*, **1981**, *103,* 3099.
11. Pirkle, W. H.; Finn, J. in *Asymmetric Synthesis;* Morrison, J. D., Ed., N.Y., Academic Press, **1983**, *1*, 87.
12. Pirkle, W. H.; Simmonds, K. A. *J. Org. Chem*, **1983**, *48*, 2520.
13. Meth-Cohn, O. *Acc. Chem. Res.*, **1987**, *20*, 18; Lwowski, W., Ed.; *Nitrenes*, Wiley Interscience New York, **1970**.
14. Clancy, M.; Hawkins, D. G.; Hesabi, M. M.; Meth-Cohn, O.; Rhouati, S. *J. Chem. Res. (S)*, **1982**, 78.
15. Oppolzer W.; Chapius, C.; Bernardinelli, G. *Tetrahedron Lett.*, **1984**, *25*, 5885; Oppolzer W.; Kelly, H. J.; Bernardinelli, G. *Tetrahedron Lett.*, **1984**, *25*, 5889; Oppolzer W.; Chapius, C.; Bernardinelli, G. *Helv. Chim. Acta,* **1984**, *67*, 1397.

16. Yan, T-H.; Chu, V-V.; Lin, T-C.; Wu, C-H.; Liu, L-H. *Tetrahedron Lett.*, **1991**, *32*, 4959; Yan, T-H.; Chu, V-V.; Lin, T-C.; Tseng, W-H.; Cheng, T-W. *Tetrahedron Lett.*, **1991**, *32*, 5563.
17. During the course of this work a paper appeared by Bonner, M. P.; Thornton, E. R. *J. Am. Chem. Soc.*, **1991**, *113*,1299, describing the synthesis of the *exo*-analogue of **8** from (1R)-(-)-camphorquinone by conversion into the corresponding *exo, exo*-aminoalcohol followed by cyclocarbamation. We prepared this compound from *exo*-borneol [prepared by LS-Selectride reduction of (1R)-camphor] using our protocol and will report our results elsewhere.
18. Evans, D. A.; Ennis, M. D.; Mathre, D. J. *J. Am. Chem. Soc.*, **1982**, *104*, 1737.
19. Chu, K. S.; Negrete, G. R.; Konopelski, J. P.; Lakner, F. J.; Woo, N-T.; Olmstead, M.M. *J. Am. Chem. Soc.*, **1992**, *114*,1800.
20. Mander, L. N.; Sethi, P. *Tetrahedron Lett.*, **1983**, *24*, 5425; see also *Aldrichimica Acta*, **1987**, *20*, 53.
21. Evans, D. A..; Ennis, M. D.; Le T. *J. Am. Chem. Soc.*, **1984**, *106*, 1154.
22. Evans D. A.. in *Asymmetric Synthesis;* Morrison, J. D., Ed., N.Y., Academic Press, **1984**, *3*, 1; Oppolzer, W., *Tetrahedron*, **1987**, *43*, 1969.
23. Evans,D. A.; Clark, J. S.; Metternich, R.; Novack, V. J.; Sheppard, G. S. *J. Am. Chem. Soc.*, **1990**, *112*, 866.
24. Evans, D. A..; Chapman, K. T.; Bisaha, J. *J. Am. Chem. Soc.*, **1988**, *110*, 1238.
25. Curran, D. P.; Kim, B. H.; Dougherty, J.; Heffner, T. A. *Tetrahedron Lett.*, **1988**, *29*, 3555.