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Stereoselectivity in reactions of atropisomeric lactams and imides

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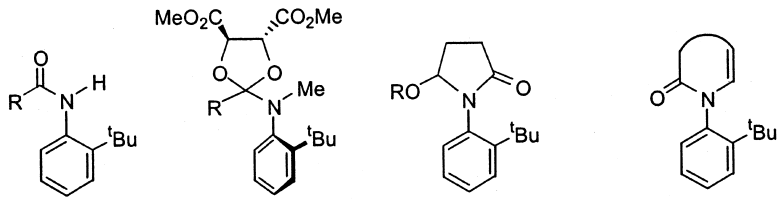
Abstract—A range of reactions of cyclic lactam systems is described in which an atropisomeric C–N axis controls the stereochemical outcome of ring substitution or addition. In the case of enantiopure menthol adducts, substitution via *N*-acyliminium intermediates occurred with essentially complete control. However, the range of nucleophiles that participate in the reaction is very limited and at present the removal of the *N*-aryl substituent is problematic. A six-membered enamide is of moderate configurational stability and the axis exerts synthetically useful levels of control over enolate alkylations of the system. A novel Lewis acid mediated enamide arylation process was identified.

1. Introduction

The seminal contribution by Curran and co-workers in 1994 showed that anilides having a bulky *ortho*-substituent showed significant promise in stereocontrolled reactions in which an atropisomeric C–N axis controls the formation of new stereogenic centre(s).[1] Since that time a number of groups, including our own, have further developed this chemistry with various amide, lactam and imide systems.[2–6] Although some of this work has focused on the atroposelective reactions of racemic systems, access to non-racemic derivatives of known absolute configuration has emerged as a key issue. Some non-racemic anilides have been obtained, either by the chiral pool approach, by asymmetric *N*-allylation of N–H amides such as **1**, or by selective crystallisation of tartrate anilides **2**.[7–10]

Our own studies have turned to the chemistry of cyclic systems bearing the *N-ortho-tert*-butylphenyl motif, and we previously described some aspects of the *N*-acyliminium chemistry of menthol-derived lactams of general structure **3**.[11] In attempting to progress this work, we also became interested in the atroposelective reactions of cyclic enamides represented by structure **4**, and have now explored the chemistry of the six-membered variant in some detail, including enolate alkylations, alkene reactivity and modification of the aromatic portion. The purpose of this paper is to describe these new results, in addition to providing full details of our earlier work.



1 **2** **3** R=menthyl **4**

2. Results and discussion

2.1. *N*-Acyliminium chemistry of a 5-membered lactam

Our initial explorations were focussed on the development of a chiral auxiliary approach for *N*-acyliminium chemistry

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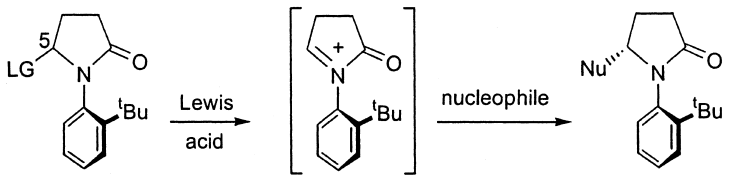


5 6 7

Scheme 1.

of lactams of general structure **5**, having a leaving group (LG) derived from a readily available chiral pool material, Scheme 1.

The idea was to generate a stereoisomerically pure lactam **5**, in which stereocentres in the auxiliary LG would fix the chiral C–N axis (and presumably the stereochemistry at C-5), allowing us to generate a chiral *N*-acyliminium intermediate **6**, the C–N axis in which would be responsible for the eventual stereochemical outcome, leading to **7**.[12]

Molecular modelling studies of the parent lactam (**5** LG=H) showed a relatively low energy barrier for rotation around the aryl C–N bond, which did not augur well for the configurational stability of the intermediate **6**.[13] Also, even if this intermediate was configurationally stable there was no guarantee that the C–N axis would exert a high level of control in the subsequent nucleophilic attack. Nevertheless, we considered this sequence potentially viable and we rapidly focussed on the idea of using readily available L-menthol as the leaving group.

Reduction of the readily available imide **8** with DIBAL gave the hydroxy lactam **9** in excellent yield. Condensation of this material with L-menthol under mildly acidic conditions then resulted in the formation of the two solid diastereomeric adducts **10** and **11**, Scheme 2.

Both of the isolated compounds were assigned as having the *ortho-tert*-butyl substituent on the opposite face of the lactam ring to the bulky menthyl substituent. The structure of the minor isomer **10** was readily secured by X-ray crystallography, as shown in Figure 1. The structure shown for **11** is based upon the fact that both **10** and **11** were shown to equilibrate with another isomer on brief warming in $CDCl_3$, but not with each other. In addition, isomers **10** and **11** gave enantiocomplementary results in substitution chemistry, vide infra. Both **10** and **11** proved to be reasonably stable as single atropisomers if stored as solids in the freezer.

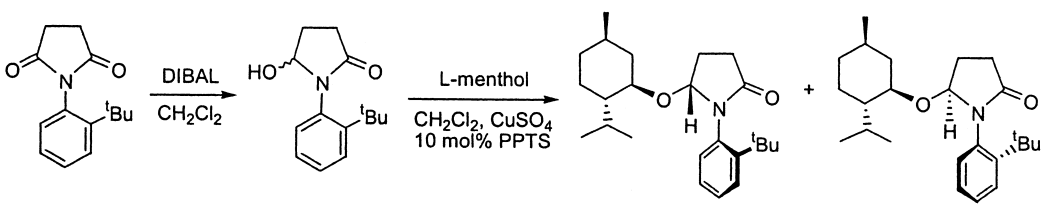
Initial attempts at *N*-acyliminium chemistry using Lewis acids such as $TiCl_4$ or $BF_3{-}OEt_2$ were not fruitful, and useful results were found only when we turned to the use of Me_3SiOTf. Under the influence of this catalyst, we were able to carry out efficient allylation or propargylation of **10** as shown in Scheme 3.

A temperature of about −40 °C was found to be important, since low temperatures (−78 °C) gave little or no reaction, whereas reaction at 0 °C was shown to give products of eroded ee. The products **12** and **13** were both found to be less stable with respect to the C–N axis than the menthol-containing precursors and they rapidly equilibrated to a diastereomeric mixture. As mentioned above, the use of the other available starting lactam **11** gave the enantiomeric product to **12** under the allylating conditions.

For ease of product analysis we chose to hydrogenate both the allyl and allenyl compounds to give the corresponding saturated propyl lactam **14**, Scheme 4.

Analysis of this compound by HPLC allowed separation of all four possible stereoisomers (one enantiomeric pair for each atropisomer), enabling us to determine that the substitution products **12** and **13** had been formed in essentially enantiomerically pure form (≥99% ee). We also needed to assign the configurations of the substitution products, and we chose to correlate allenyl adduct **13** (generated from **10**) with the known methoxymethyl lactam **15**, which had been described by Taguchi and co-workers, Scheme 5.[7e]

We assigned the stereochemistry shown on the basis of HPLC data, namely that the sequence shown gives the lactam with the longer elution time on analysis with a Chiralpak AD column, under conditions described by Taguchi. We have been unable to determine reliable specific rotation values for samples of this compound, and in fact the anomalously low $[\alpha]_D$ value that we reported initially prompted a re-examination of the sign of the value for **15**,



8 **9** 92% **10** less polar 25% **11** more polar 41%

Scheme 2.

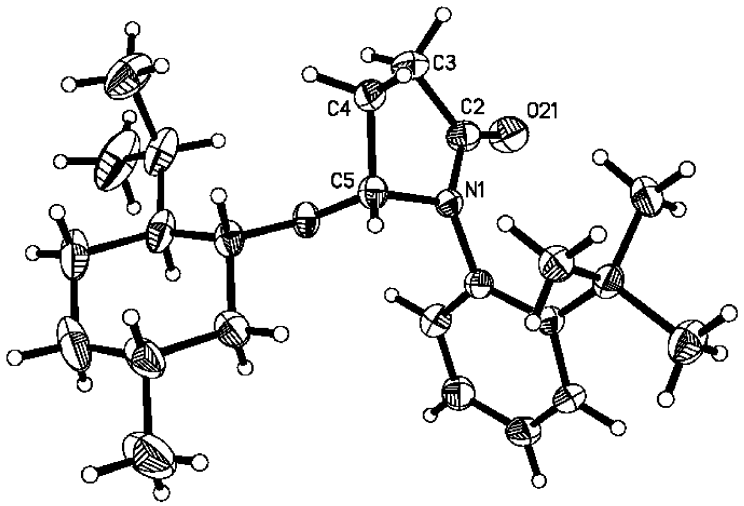
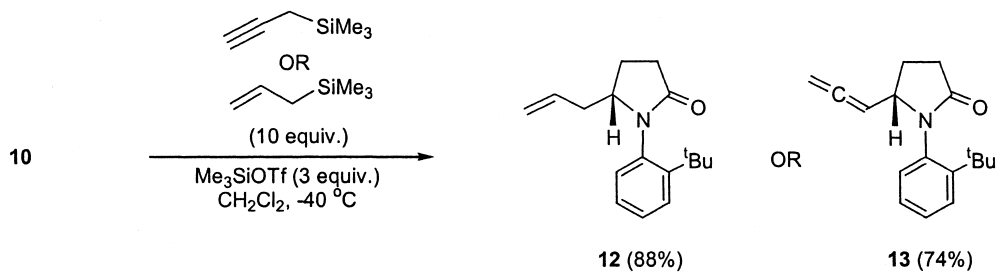
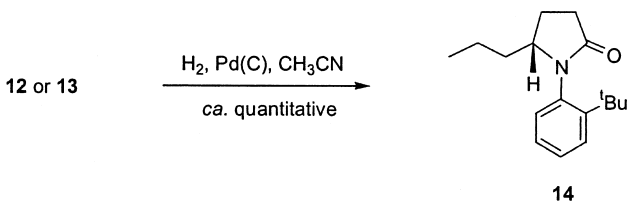


Figure 1. X-ray structure of lactam **10** (displacement elipsoids are drawn at the 50% probability level).



Scheme 3.



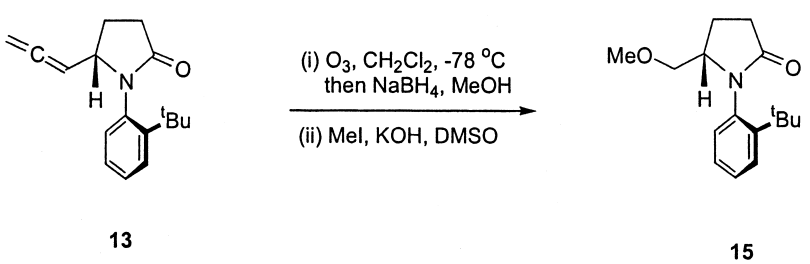
Scheme 4.

leading to a revision.[14] Fortunately none of the stereochemical assignments are affected.

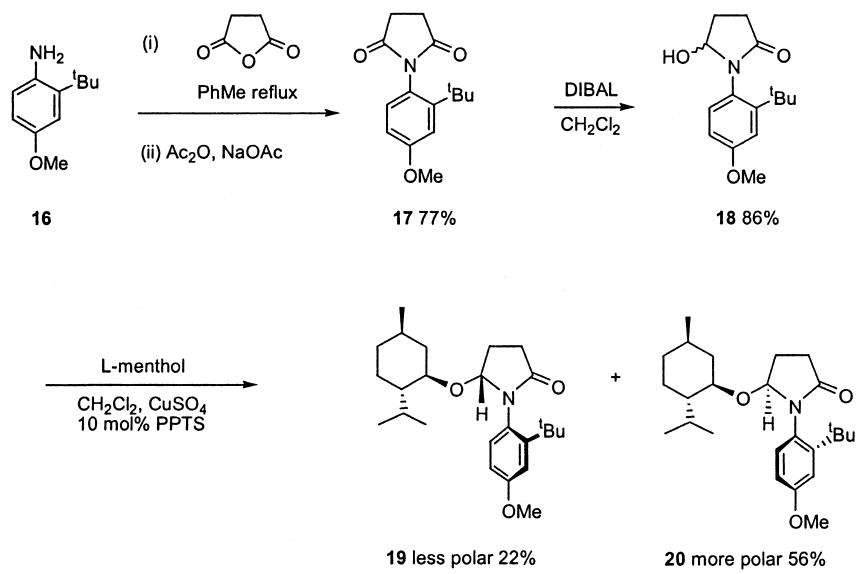
Overall, this work had established that substitution of the menthol adducts along the lines indicated in Scheme 1 was indeed possible, and we propose that this is due to stereochemical control exerted by the chiral C–N axis of the intermediate *N*-acyliminium ion. Unfortunately, we were unable to broaden the scope of the substitution process in that attempted reactions using Me_3SiCN or the enol silane from acetophenone as nucleophiles did not give the desired products.

In a final phase of this work, we also examined analogous transformations of lactams bearing an additional methoxy substituent on the *N*-aryl group. Imide **17** was prepared from the readily available aniline **16**, and subsequent DIBAL reduction and menthol condensation were carried out as described previously, Scheme 6.

This outcome of the menthol condensation was subject to an initial mis-assignment by us in the original communication.[11] Thus, we initially assigned the more polar isomer as **19**, based on erroneous specific rotation measurements of a subsequent product, vide infra. In retrospect, the analogy between Schemes 2 and 6 is very clear. Both systems produce mainly two isomers, each of which have a *trans* disposition of the menthol and *tert*-butyl groups, and in each case the less polar isomer is the minor one. That the less



Scheme 5.



Scheme 6.

polar one has structure **19** is very strongly suggested by the very close matching of the upfield region of the ^{1}H NMR spectrum for **19** with that of **10**, whilst the spectra for **11** and **20** also match well, but are very distinct to the other pair. Specific rotation data (all measured in $CHCl_3$ at the same concentration) also strongly suggest that **19** ($[\alpha]_D=-113$) is analogous to **10** ($[\alpha]_D=-101$), and that **20** ($[\alpha]_D=-18$) is analogous to **11** ($[\alpha]_D=-19$).

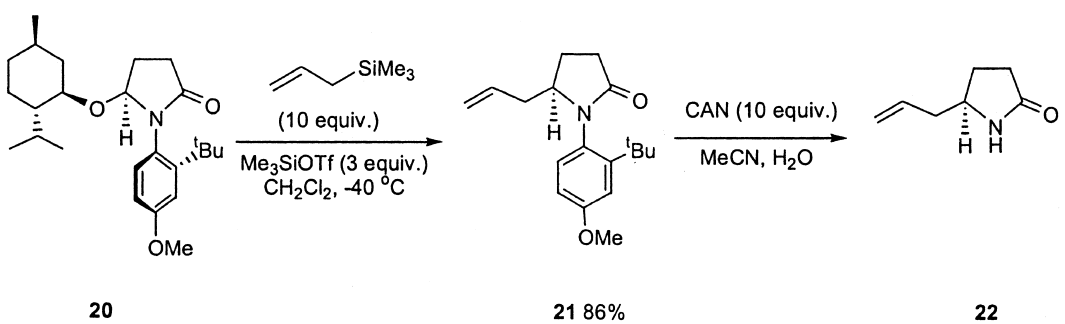
The more polar isomer **20** was allylated under our typical conditions to give product **21**, which was then subjected to reaction with excess of CAN, in an effort to remove the *N*-aryl substituent, Scheme 7.

Reaction of **20** with allylsilane gave **21**, the ee of which was shown by HPLC to be ca. 98% ee, which again demonstrates the high level of fidelity possible in this type of *N*-acyliminium ion reaction. Unfortunately, subsequent conversion into the known lactam **22** proved highly problematic, both in terms of chemical yields, which were mainly in the 30% region, and also that we obtained inconsistent measurements of the $[\alpha]_D$ value of the product.[15] The enantiomer of **22** shown in Scheme 7 is well established to be the (−)-isomer, but the enantiomerically pure compound has a low specific rotation of only $[\alpha]_D=4$ (*c* 0.65, CH_2Cl_2).[15d] Our product showed very low positive values of $[\alpha]_D$, leading us to believe that we had made the enantiomer of **22**, and leading to a mis-assignment of **20** and **21**. Although we are now confident of the assignment in Scheme 7 it rests solely on analogy with the earlier series, since we have been unable to convincingly correlate with lactam **22**.

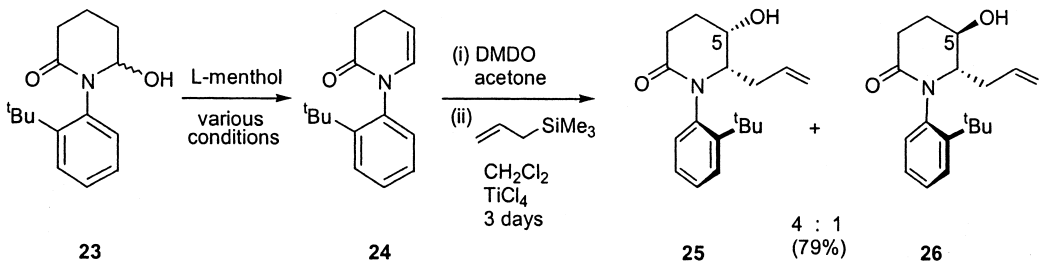
A natural extension of this work would have involved probing the homologous six-membered ring family of compounds. This did not prove possible since attempted formation of menthol adducts from hydroxylactam **23** always led to the enamide **24**, the product of elimination, Scheme 8.

It seemed to us that the double bond present in enamide **24** might enable useful substitution of the ring by sequential treatment with a powerful electrophile, followed by a nucleophile. To this end, we reacted enamide **24** with DMDO (osmylation conditions gave a similar result) and then exposed the crude product to reaction with allylsilane.[16] As shown, we obtained two products **25** and **26** in good overall yield, the stereochemistries of which were both determined by X-ray crystallography, Figures 2 and 3.

This allylation reaction is much more sluggish than those described with the five-membered menthol derived systems and the extended reaction time and relatively elevated temperature do not appear suitable for asymmetric synthesis using enantiomerically pure derivatives (racemisation by C–N rotation or reversible ring-opening of the intermediates would be expected). Also, the level of selectivity in the



Scheme 7.



Scheme 8.

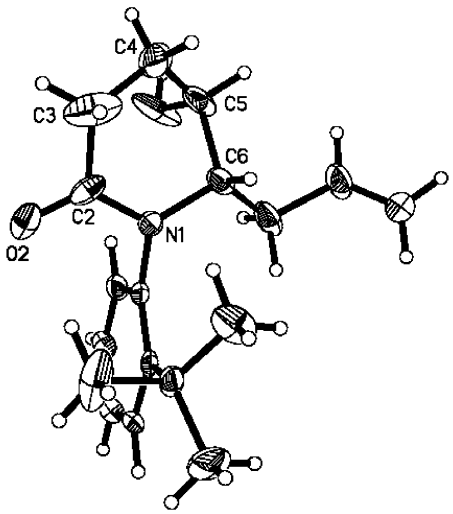


Figure 2. X-ray structure of lactam **25** (displacement elipsoids are drawn at the 30% probability level).

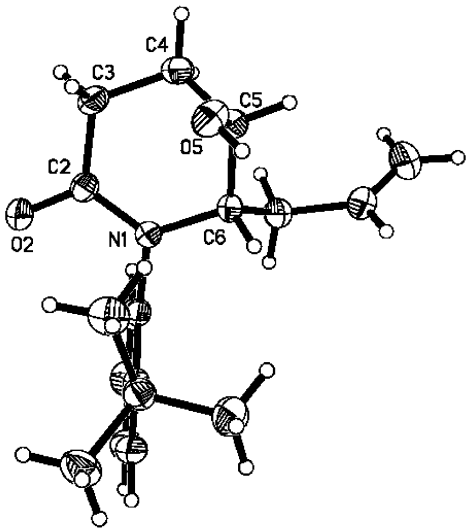


Figure 3. X-ray structure of lactam **26** (displacement elipsoids are drawn at the 50% probability level). Only one of two independent molecules is shown.

initial oxidation appears modest, judging by the ratio of C−5 epimers. Although in both product isomers the allyl group is arranged *anti* to the *ortho-tert*-butyl group, the relative ease of C−N rotation for most compounds with a saturated C−6 position means that this could be a thermodynamic effect (as in **15**). We also noted that these types of piperidinone, bearing stereodefined C-5 hydroxyl and C-6 allyl groups have recently been used as key intermediates in the synthesis of antimalarial alkaloids of the febrifugine group.[17]

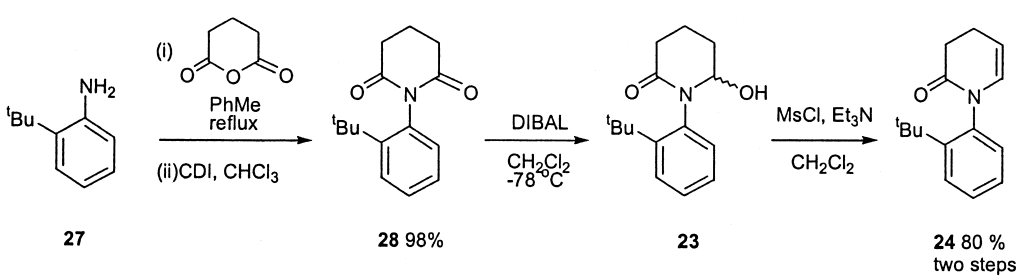
Although we did not pursue this line of investigation the ready availability of enamide **24** made it an interesting system for further study.

2.2. Synthesis and enolate chemistry of enamide 24

In order to conduct an extended study of the chemistry of enamide **24**, we optimised the supply of this material by means of the route shown in Scheme 9.

The synthesis of the imide **28** proved very straightforward and, following reduction to **23**, elimination was best done via mesylation, rather than simple acid catalysed dehydration. This simple sequence easily gave access to multigram quantities of the desired enamide **24**.

We had previously studied the levels of diastereocontol in enolate reactions of certain types of acyclic anilides having the *ortho-tert*-butyl motif.[3] Although we achieved some potentially useful levels of control the product analysis was hampered by the complicated conformational behaviour of these systems, and the products also proved recalcitrant to further transformation, especially hydrolysis. By contrast



Scheme 9.

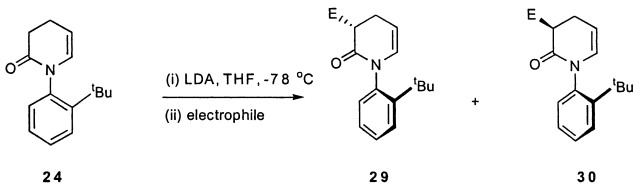


Table 1. Alkylation of enamide **24**

Entry	Electrophile	Product (%)	Ratio 29:30[a]
1	MeI	**29a** 81	6:1
2	$H_2C{=}CHCH_2Br$	**29b** 66	12:1
3	$PhCH_2Br$	**29c** 79	13:1
4	$HC{\equiv}CCH_2Br$	**29d** 62	12:1
5	$^nC_5H_{11}Br$	**29e** 88	7:1
6	EtI	**29f** 61	10:1
7	PhSSPh	**29 g** 81	12:1
8	$Me_3SiC{\equiv}CCH_2Br$	**29 h** 66	15:1

[a] Estimated from ^1H NMR spectra of crude reaction mixture.

enamide **24** is conformationally much simpler, and the presence of two potentially reactive functions in the ring might enable more facile removal of the aniline when desired.[18]

We started our investigation of the enolate chemistry of enamide **24** by carrying out a range of alkylations, under typical conditions, using LDA as the base, Table 1.

Enolate alkylation occurred cleanly at −78 °C to give the products in very good yields, and with good to excellent levels of selectivity. Atropisomer ratios were measured immediately after the alkylation, since we observed partial equilibration in samples stored at room temperature over a period of a few weeks. Although this gave us a rough idea of the conformational stability of these systems we did not quantify the energy barrier to rotation around the C–N axis for these products, and a more detailed study was reserved for the parent system, vide infra.

In all cases we assumed that the alkylation was controlled by the bulky *ortho-tert*-butyl substituent, leading to a predominance of the *anti* isomer **29** in the product, although we have no proof of this except in the case of sulfide **29g**, which proved amenable to X-ray crystallographic study, as shown in Figure 4.

We also tested the enolate reactions of enamide **24** with a range of aliphatic and aromatic aldehydes, but found that the aldol reactions are poorly controlled, giving rise to at least three major stereoisomeric products in each case. Therefore, we did not pursue this area further.

2.3. Kinetic resolution, absolute configuration and rotational energy barrier of enamide 24

In our previous work in this area we had used a chiral lithium amide base to achieve kinetic resolution of an acyclic atropisomeric amide, albeit with modest levels of selectivity,[3] and it was decided to conduct a related study with enamide **24** in order to obtain a sample of non-racemic compound. This would then enable us to establish a rotational energy barrier for the C–N axis through studying the rate of racemisation, and we might also be able to assign the absolute stereochemistry for this compound.

Partial alkylation of enamide **24** was, therefore, carried out, by initial deprotonation with a deficiency of the chiral base shown, followed by reaction with benzyl bromide, Scheme 10.

In reactions that were allowed to proceed to 53–74% conversion we were able to recover quantities of (−)-**24** (44–24%), along with the alkylated product **29c**. We analysed recovered enamide **24** from both a 74% and a 53% conversion reaction and found it to be of 74 and 62% ee, by HPLC, respectively. As in the related kinetic resolution reactions of acyclic amides the selectivity appears to be quite low, but the supply of small quantities of moderately enriched material was adequate for our purposes.

We next warmed a solution of **24** of 62% ee in $CHCl_3$ at 60 °C and monitored the ensuing racemisation by HPLC. A

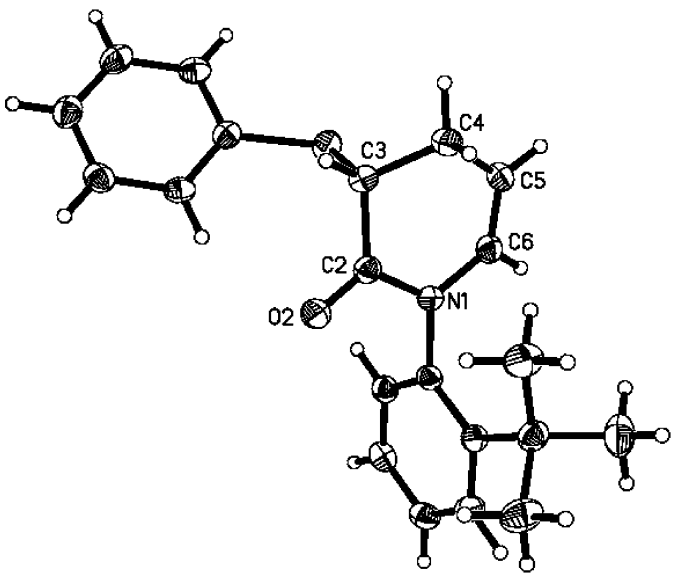
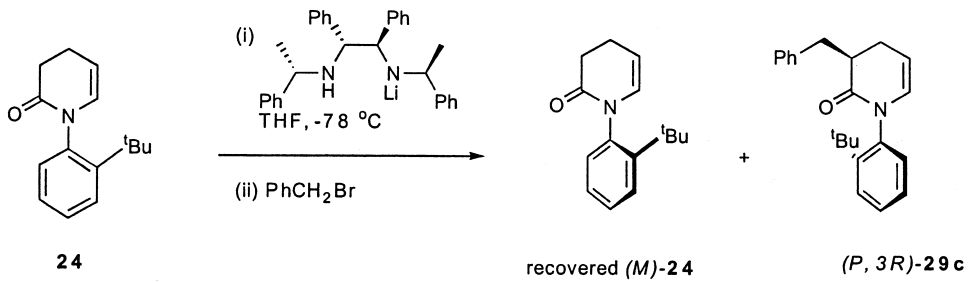


Figure 4. X-ray structure of enamide **29g** (displacement elipsoids are drawn at the 50% probability level).



24 recovered *(M)*-**24** *(P, 3R)*-**29c**

Scheme 10.

graph of the logarithm of the relative ee values of **24** as a function of time for the thermal racemisation indicates a very good linear relationship, Figure 5.[19]

The energy barrier to rotation around the C–N axis ($\Delta G^{\neq}$=+26.95 kcal mol^{-1}) was calculated using the slope of the graph ($-2k_{rot}$=-2.6×10^{-3} s^{-1}) and Eyring's equation, and the half-life for racemisation at 25 °C estimated to be 2.03×10^{6} s (ca 3 weeks). Therefore the enamide system is significantly less stable than most of the documented, 'Curran type', amide and imide systems incorporating this motif, but still rather more stable than the lactams having a saturated carbon at C-6 in the ring (like **25** and **26**).

The stereochemical assignment for **24** shown in Scheme 10 was determined by correlation with commercially available diacid **31**, as indicated in Scheme 11.

Thus, conversion of the diacid (*R*)-**31** into the known glutaric anhydride (+)-**32**, was followed by conversion into the isomeric mixture of imides **33**, which were easily separated.[20] An X-ray crystallographic structure determination of the minor product identified it as *syn*-**33** (or *P*,3*R*), as shown in Figure 6. We were then able to take the major product (which was clearly *anti*-**33**), which was at this stage of 72% ee, and subject it to our reduction–elimination sequence, to give a mixture of the new compound **34**,

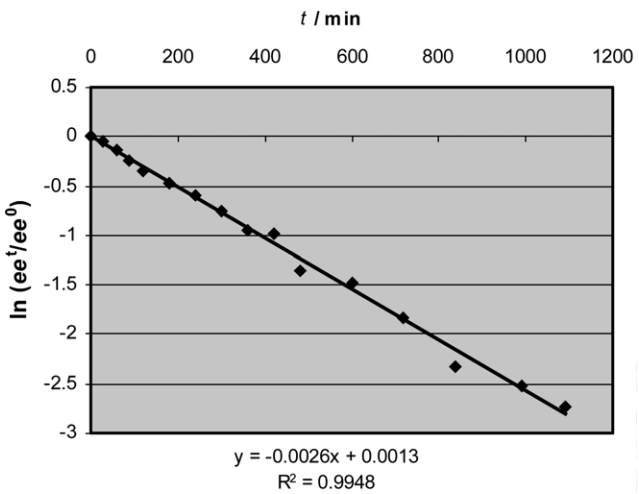


Figure 5. Plot of the logarithm of the relative ee value of **24** (ln ee^{t}/ee^{0}) vs time (t) for thermal racemisation of **24**. ee^{0}=the ee value obtained for recovered **24** from the kinetic resolution. ee^{t}=the ee value of **24** obtained after heating at 60 °C in $CHCl_3$ for the time indicated.

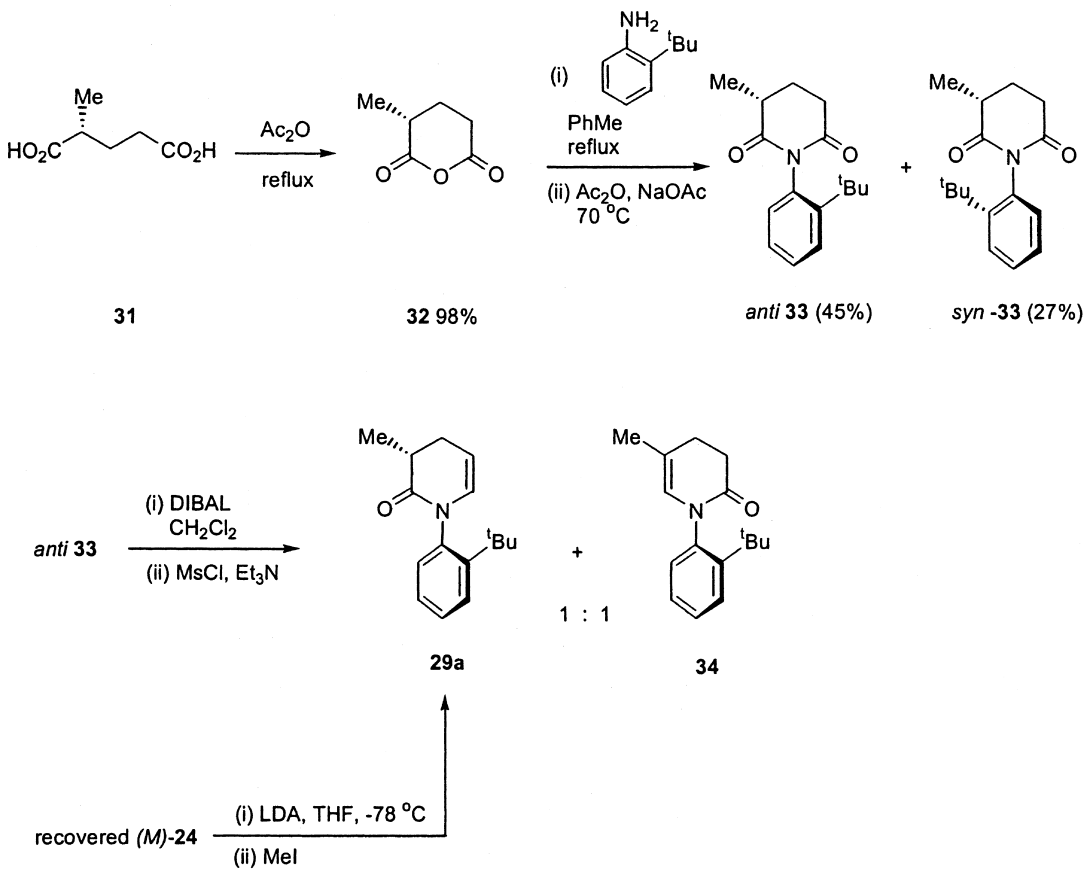
alongside enamide **29a**, which was a compound that we had prepared before in racemic form. To complete the correlation it remained for us to take enantiomerically enriched (73% ee) **24** from the kinetic resolution (recovered (*M*)-**24** in the Scheme) and methylate it to give **29a**. At this point both samples of **29a** showed substantial (+)-rotations but the sample from the enolate alkylation had a ca. 7:1 *anti*:*syn* ratio, whereas the sample from the reduction–elimination had a lower ratio (ca. 2:1). Therefore, in order to make a better comparison each sample of **29a** was equilibrated in refluxing $CDCl_3$ until each had the same, almost 1:1 ratio of rotamers. At this point both samples showed a specific rotation of $[\alpha]_D$=+55−56. That the values should match is a consequence of partial racemisation in the sequence leading to imide **33**, bringing it to a level (72% ee) almost matching our enamide recovered from the kinetic resolution.

At this point we had established the key aspects of the stereochemistry of enamide **24**, and decided to explore one final aspect of the reactivity of the system, namely reactions of the C=C bond.

2.4. Exploring the C=C reactivity of enamide 24

Initial studies showed that the C=C bond present in **24** was extremely reluctant to participate in a variety of C–C bond forming reactions, including [4+2] cycloaddition with either electron rich or poor diene partners, [2+2] type reactions with ketenes, or Heck reactions under a range of conditions. This was very disappointing since a number of common alkaloid systems might otherwise have been accessed via this approach.

However, during the course of an investigation into cleavage of the *tert*-butyl group from the *N*-aryl group of enamide **24**, we were surprised to discover some unexpected reactivity of the C=C bond. The $AlCl_3$ catalysed *trans-tert*-butylation of aromatics is well known, and has been used for the synthesis of substituted fluorenes.[21] Treatment of enamide **24** with $AlCl_3$ in benzene resulted in the anticipated loss of the *tert*-butyl group, but gave a product in which the enamide C=C was no longer present. Spectroscopic analysis revealed the product to be lactam **35a**, in which the enamide function has undergone a Friedel–Crafts alkylation reaction. Analogous reactions using toluene, bromobenzene or iodobenzene as reaction partners also gave arylated lactams **35b–d** in good yield, the products **35b** and **35c** being mixtures of *ortho*/*para* regioisomers, Scheme 12.



Scheme 11.

This type of enamide arylation appears novel in intermolecular mode, although we are aware of intramolecular varaints involving an activated, tethered aromatic ring, for example, Scheme 13.[22]

Attempts to employ anisole in this process led to none of the product lactam of structure **35**, and instead gave only recovered enamide and phenol. Since anisole appeared incompatible with $AlCl_3$ under these reaction conditions, we switched the Lewis acid to $TiCl_4$, and two novel lactam products **38** and **39** were obtained in which arylation occurred but the *tert*-butyl group remained intact, Scheme 14.

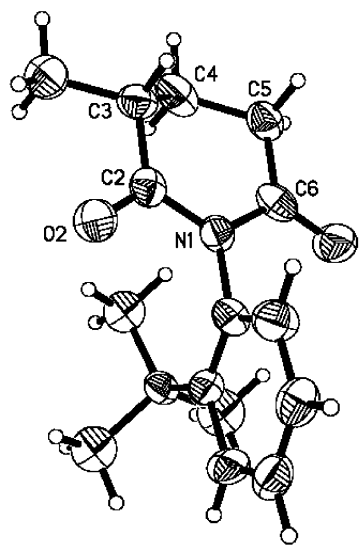
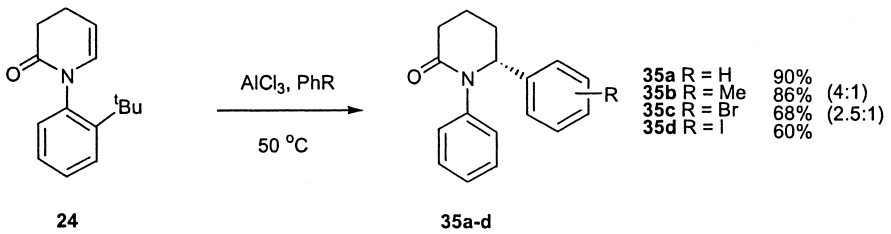


Figure 6. X-ray structure of imide *syn*-**33** (displacement elipsoids are drawn at the 50% probability level). One of the disordered *tert*-butyl components is omitted for clarity.

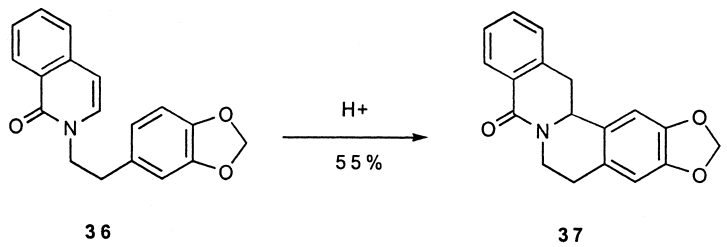
The NMR spectra for the major product **38** appeared broad and ill-resolved, presumbly due to conformational complications arising due to the highly congested nature of the system. Definitive proof of structure was obtained through an X-ray crystallographic structure determination, Figure 7.

This result seemed to indicate that addition to the enamide C=C is faster than the *trans-tert*-butylation, at least for anisole, which might enable the chiral axis to control the formation of the new stereogenic centre at C-6. In the interest of probing this possibility the reaction of enamide **24** of 63% ee with $AlCl_3$ in benzene was carried out and resulted in the recovery of the product **35a** of identical ee. The analogous reaction with bromobenzene did result in some erosion of ee, as the product **35c** from a reaction with enamide **24** of 73% ee had a lower ee value of 57%. This probably reflects a slower rate of alkylation for bromobenzene compared with benzene, allowing partial racemisation of **24** via C–N bond rotation, thus resulting in erosion of the product ee.

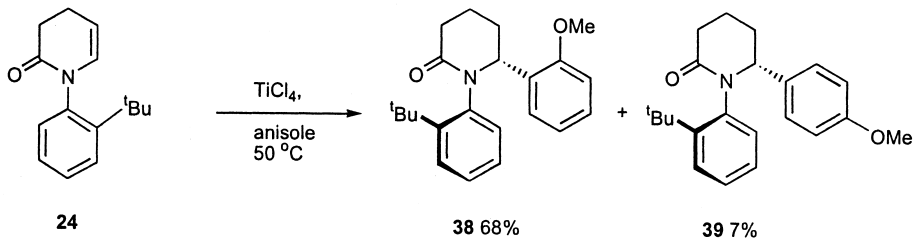
On the basis of the above results it appears that the Friedel–Crafts alkylation reaction occurs prior to cleavage of the



Scheme 12.



Scheme 13.



Scheme 14.

tert-butyl group and that the change from an sp^2 carbon in the C=C bond to an sp^3 carbon may be a requirement for the second step, cleavage of the *tert*-butyl group.

3. Summary and conclusion

We have described a range of reactions of cyclic lactam systems in which an atropisomeric C–N axis can control the stereochemical outcome of ring substitution or addition reactions. In the case of enantiopure menthol adducts **10**, **11** or **20**, substitution via *N*-acyliminium intermediates occurred with essentially complete control. However, the range of nucleophiles that participate in the reaction is very limited and at present the removal of the *N*-aryl substituent is problematic.

The six-membered enamide **24** is of moderate configurational stability and the axis exerts synthetically useful levels of control over the enolate alkylations of the system. A novel Lewis acid mediated enamide arylation process was also identified, which may have further applications in synthesis.

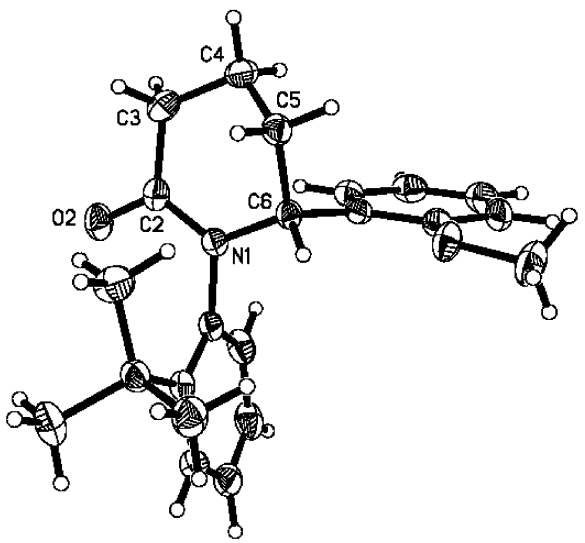


Figure 7. X-ray structure of lactam **38** (displacement elipsoids are drawn at the 50% probability level).

4. Experimental

4.1. General details

General experimental details can be found in our recent paper.[23]

In the present work, some high resolution mass spectra were also acquired on a PerSeptive Biosystems Mariner TOF instrument (TOF), with a resolution of 5000 ppm, calibrated using internal standards. In addition, where stated, purification was carried out using pre-packed Biotage 40 flash columns (KP-Sil, 60 Å, 32–63 μM).

The precursor chiral diamine base to the lithiated base shown in Scheme 10 was prepared from (*R*)-α-methylbenzylamine, according to a literature procedure.[24] Aniline **16** was prepared by methylation of the corresponding hydroxy aniline, which was in turn prepared according to the literature procedure.[25]

All ^{13}C NMR spectra of compounds in which atropisomers were observed are quoted for the major isomer only.

4.1.1. 1-(2-*tert*-Butylphenyl)-pyrrolidine-2,5-dione 8.[26] To solution of 2-*tert*-butylaniline (1.00 g, 6.70 mmol) in toluene (25 mL) was added succinic anhydride (0.81 g, 8.09 mmol) and the reaction mixture refluxed overnight, cooled, and filtered to give crude succinamic acid. A solution of this acid, sodium acetate (3.08 g, 37.5 mmol) in acetic anhydride (25 mL) was stirred at 70–80 °C overnight. The reaction mixture was poured onto H_2O (50 mL), extracted with $CHCl_3$ (3×50 mL), the combined organic extracts were washed with 2 N sodium hydroxide (3×50 mL), dried ($MgSO_4$) and evaporated under reduced pressure. The resulting white solid was recrystallised from EtOH to yield **8** as a crystalline white solid (1.43 g, 6.18 mmol, 92%), mp 139–141 °C, (lit.[26] 131–132 °C); ν_{max} ($CHCl_3$)/cm^{-1} 2969, 1714, 1382; δ_H (400 MHz; $CDCl_3$) 1.30 (9H, s, C(CH_3)$_3$), 2.88 (4H, s, 3-H), 6.85 (1H, dd, *J*=7.5, 1.6 Hz, Ar-*H*), 7.29 (1H, ddd, *J*=7.5, 7.3, 1.5 Hz, Ar-*H*), 7.40 (1H, ddd, *J*=8.1, 7.3, 1.6 Hz, Ar-*H*), 7.59 (1H, dd, *J*=8.1, 1.5 Hz, Ar-*H*); δ_C (67.5 MHz; $CDCl_3$) 28.6 (CH_2), 31.5 (CH_3), 34.4 (C), 127.3 (CH), 128.8 (CH), 129.7 (CH), 130.3 (C), 130.5 (CH), 147.8 (C), 177.3 (C=O); *m*/*z* (EI) 231 (M^+, 40%), 216 (100), 174 (26) (Found M^+, 231.1254. $C_{14}H_{17}NO_2$ requires *M*, 231.1259). Anal. Calcd for $C_{14}H_{17}NO_2$. C, 72.69; H, 7.41; N, 6.06%. Found: C, 72.56; H, 7.53; N, 6.11%

4.1.2. 1-(2-*tert*-Butylphenyl)-5-hydroxypyrrolidin-2-one 9. DIBAL (6.90 mL of a 1 M solution in CH_2Cl_2) was added dropwise to a stirred solution of imide **8** (0.80 g, 3.46 mmol) in CH_2Cl_2 (10 mL) at −78 °C. After 10 min stirring at −78 °C, H_2O (10 mL), and 2 N NaOH (2 mL) were cautiously added and the reaction mixture extracted with $CHCl_3$ (3×20 mL). The organic extracts were then washed with brine (20 mL), dried ($MgSO_4$) and evaporated under reduced pressure to yield a white solid. The crude mixture was then purified by flash column chromatography (100% EtOAc) to yield the title compound **9** (15:1 ratio of isomers) as white crystals (0.74 g, 0.32 mmol, 92%), mp 136–138 °C; ν_{max} ($CHCl_3$)/cm^{-1} 3590, 3367, 2949, 2868, 1714; δ_H (400 MHz, $CDCl_3$) 1.29 (9H major, s, C(CH_3)$_3$), 1.37 (9H minor, C(CH_3)$_3$), 1.97 (1H major+1H minor, m, 4-H_A), 2.25 (2H major+2H minor, m, 4-H_B+3-H_A), 2.58 (1H major+1H minor, m, 3-H_B), 4.24 (1H major+1H minor, d, *J*=5.5 Hz, O*H*), 5.18 (1H major+1H minor, t, *J*=5.3 Hz, 5-H), 7.03 (1H major+1H minor, dd, *J*=7.7, 1.6 Hz, Ar-*H*), 7.17 (1H major+1H minor, ddd, *J*=7.7, 7.4, 1.4 Hz, Ar-*H*), 7.27 (1H major+1H minor, ddd, *J*=8.0, 7.4, 1.6 Hz, Ar-*H*), 7.48 (1H major+1H minor, dd, *J*=8.0, 1.6 Hz, Ar-*H*); δ_C ($CDCl_3$, 68 MHz) 27.8 (CH_2), 28.3 (CH_2), 31.6 (CH_3), 35.4 (C), 86.2 (CH), 126.6 (CH), 128.0 (CH), 128.4 (CH), 132.8 (CH), 134.5 (C), 147.9 (C), 176.8 (C=O); *m*/*z* (EI) 233 (M^+, 52%), 216 (100), 174 (33) (Found M^+, 233.1409. $C_{14}H_{19}NO_2$ requires *M*, 233.1416). Anal. Calcd for $C_{14}H_{19}NO_2$. C, 72.06; H, 8.21; N, 5.80%. Found: C, 71.88; H, 8.26; N, 6.01%.

4.1.3. (*P*,5*R*)-1-(2-*tert*-Butylphenyl)-5-(2*S*-*iso*-propyl-5*R*-methylcyclohexyl-1*R*-oxy)-pyrrolidin-2-one (−)-10 and (*M*,5*S*)-1-(2-*tert*-butylphenyl)-5-(2*S*-*iso*-propyl-5*R*-methylcyclohexyl-1*R*-oxy)-pyrrolidin-2-one (−)-11. (−)-Menthol **8** (3.70 g, 23.7 mmol) and PPTS (0.56 g, 2.23 mmol) were added to a stirred solution of hydroxylactam **9** (5.25 g, 22.5 mmol) and anhydrous copper sulphate (10.0 g, 62.7 mmol) in CH_2Cl_2 (100 mL) and stirred at room temperature overnight. The reaction mixture was poured onto H_2O (100 mL) and extracted with $CHCl_3$ (3×100 mL), the combined organic extracts were then dried ($MgSO_4$) and evaporated under reduced pressure. The resultant solid was then purified by flash column chromatography (25–50% EtOAc7–petroleum ether) to give firstly the minor diastereoisomer (−)-**10** as white crystals (1.84 g, 4.95 mmol, 25%), $[\alpha]_D^{23}$=−101 (*c* 1.00, $CHCl_3$); mp 89–90 °C; ν_{max} ($CHCl_3$)/cm^{-1} 2956, 2921, 2871, 1698, 1061; δ_H (400 MHz; $CDCl_3$) 0.43 (1H, ddd, *J*=12.3, 12.3, 10.8 Hz, 6′-H_A), 0.69 (3H, d, *J*=6.6 Hz, 2″-Me_A), 0.73–0.79 (4H, m with d at 0.78, *J*=7.0 Hz, 5′-Me+3′-H_A), 0.86–0.93 (4H, m with d at 0.92, *J*=7.0 Hz, 2″-Me_B+4′-H_A), 1.17 (2H, m, 2′-H+5′-H), 1.34–1.38 (10H, m with s at 1.36, C(CH_3)$_3$+6′-H_B), 1.58 (2H, m, 3′-H_B+4′-H_B), 2.24 (3H, m, 4-H+1″-H), 2.44 (1H, ddd, *J*=17.0, 9.3, 1.6 Hz, 3-H_A), 2.73 (1H, ddd, *J*=17.0, 9.9, 8.8 Hz, 3-H_B), 3.03 (1H, dt, *J*=10.8, 10.3, 4.0 Hz, 1′-H), 5.07 (1H, d, *J*=4.8 Hz, 5-H), 7.19 (2H, m, Ar-*H*), 7.27 (1H, m, Ar-*H*), 7.48 (1H, m, Ar-*H*); δ_C (67.5 MHz; $CDCl_3$) 15.8 (CH_3), 21.0 (CH_3), 21.9 (CH_3), 22.8 (CH_2), 25.0 (CH), 26.2 (CH_2), 28.3 (CH_2), 31.0 (CH), 31.6 (CH_3), 34.0 (CH_2), 35.3 (C), 40.0 (CH_2), 47.8 (CH), 76.4 (CH), 90.4 (CH), 126.3 (CH), 127.3 (CH), 128.2 (CH), 133.6 (CH), 134.9 (C), 147.6 (C), 176.7 (C=O); *m*/*z* (EI) 371 (M^+, 2%), 216 (61), 176 (25) (Found M^+, 371.2824. $C_{24}H_{37}NO_2$ requires *M*, 371.2826), followed by the major diastereoisomer (−)-**11** as fine white needles (4.68 g, 12.6 mmol, 41%), $[\alpha]_D^{23}$=−19 (*c* 1.05, $CHCl_3$); mp 63–65 °C; ν_{max} ($CHCl_3$)/cm^{-1} 2955, 2925, 2870, 1698, 1065; δ_H (400 MHz; $CDCl_3$) 0.29 (3H, d, *J*=6.9 Hz, 2″-Me_A), 0.68 (3H, d, *J*=7.0 Hz, 2″-Me_B), 0.80 (2H, m, 3′-H_A+4′-H_A), 0.90 (3H, d, *J*=6.5 Hz, 5′-Me), 0.99 (1H, ddd, *J*=12.6, 12.1, 10.6 Hz, 6′-H_A), 1.13 (1H, m, 5′-H), 1.29–1.35 (10H, m with s at 1.35, C(CH_3)$_3$+2′-H), 1.55 (2H, m, 3′-H_B+4′-H_B), 1.75 (1H, m, 1″-H), 1.92 (1H, m, 6′-H_B), 2.12 (1H, m, 4-H_A), 2.39 (2H, m, 4-H_B+3-H_A), 2.72 (1H, m, 3-H_B), 3.00 (1H, ddd, *J*=10.6, 10.4, 4.3 Hz, 4′-H), 5.09 (1H, d, *J*=4.8 Hz, 5-H), 7.17 (2H, d, *J*=3.7 Hz, Ar-*H*), 7.26 (1H, m, Ar-*H*), 7.47 (1H, d, *J*=7.8 Hz, Ar-*H*); δ_C (67.5 MHz; $CDCl_3$) 15.3 (CH_3), 21.0 (CH_3), 22.2 (CH_3), 22.3 (CH_2), 24.1 (CH), 28.2 (CH_2), 28.4 (CH_2), 31.4 (CH), 31.7 (CH_3), 34.0 (CH_2), 35.5 (C), 42.8 (CH_2), 48.6 (CH), 78.3 (CH), 92.7 (CH), 126.4 (CH), 127.7 (CH), 128.2 (CH), 133.9 (CH), 134.5 (C), 147.3 (C), 176.4 (C=O); *m*/*z* (EI) 371 (M^+, 0.7%), 215 (68), 158 (74) (Found M^+, 371.2828. $C_{24}H_{37}NO_2$ requires *M*, 371.2826)

4.1.4. (*P*,5*S*)-5-Allyl-1-(2-*tert*-butylphenyl)-pyrrolidin-2-one (−)-12. To a stirred solution of pyrrolidin-2-one (−)-**10** (1.00 g, 2.69 mmol) and allyl trimethylsilane (4.20 mL, 26.8 mmol) in CH_2Cl_2 (10 mL) at −40 °C, was added dropwise trimethylsilyltrifluoromethanesulphonate (1.50 mL,

8.29 mmol). The reaction mixture was stirred at −40 °C for 8 h before H_2O (10 mL) was cautiously added. The reaction mixture was extracted with $CHCl_3$ (3×20 mL), the combined organic extracts were dried ($MgSO_4$) and evaporated under reduced pressure. The resulting yellow oil was purified by flash column chromatography (50% EtOAc–petroleum ether) to yield the title compound (−)-**12** (6:1 ratio of isomers) as a pale yellow oil (612 mg, 2.40 mmol, 88%), $[\alpha]_D^{23}=-35$ (*c* 1.00, $CHCl_3$); ν_{max} ($CHCl_3$)/cm^{-1} 2874, 1682; δ_H (400 MHz; $CDCl_3$) 1.39 (9H major, s, C(C*H*$_3$)$_3$), 1.41 (9H minor, C(C*H*$_3$)$_3$), 1.99 (1H major+1H minor, m, 4-H$_A$), 2.15 (1H major+1H minor, m, 4-H$_B$), 2.44 (4H major+4H minor, m, 3-H+1′-H), 3.93 (1H major+1H minor, m, 5-H), 5.07 (2H minor, m, 3′-H), 5.10 (2H major, m, 3′-H), 5.67 (1H major+1H minor, m, 2′-H), 6.97 (1H major, dd, *J*=7.7, 1.6 Hz, Ar-*H*), 6.98 (1H minor, dd, *J*=7.7, 1.6 Hz, Ar-*H*), 7.27 (2H major+2H minor, m, Ar-*H*), 7.56 (1H major+1H minor, m, Ar-*H*); δ_C (67.5 MHz; $CDCl_3$) 23.7 (CH_2), 29.7 (CH_2), 31.7 (CH_3), 35.7 (C), 37.8 (CH_2), 61.5 (CH), 118.5 (CH_2), 126.7 (CH), 128.4 (CH), 128.9 (CH), 132.8 (CH), 133.2 (CH), 134.6 (C), 148.2 (C), 175.5 (C=O); *m/z* (EI) 257 (M^+, 0.2%), 216 (100) (Found M^+, 257.1785. $C_{17}H_{23}NO$ requires *M*, 257.1780).

4.1.5. (*P*,5*S*)-1-(2-*tert*-Butylphenyl)-5-propa-1,2-dienylpyrrolidin-2-one (−)-13. To a stirred solution of pyrrolidin-2-one (−)-**10** (300 mg, 0.81 mmol) and propargyltrimethylsilane (1.20 mL, 8.05 mmol) in CH_2Cl_2 (5 mL) at −40 °C was added dropwise trimethylsilyltrifluoromethanesulphonate (0.43 mL, 2.38 mmol). The reaction mixture was stirred at −40 °C for 8 h before H_2O (5 mL) was cautiously added. The reaction mixture was extracted with $CHCl_3$ (3×10 mL), the combined organic extracts were then dried ($MgSO_4$) and evaporated under reduced pressure. The resulting yellow oil was purified by flash column chromatography (50% EtOAc–petroleum ether) to yield the title compound (−)-**13** (3:1 ratio of isomers) as a colourless oil (152 mg, 0.60 mmol, 74%), $[\alpha]_D^{23}=-61$ (*c* 1.10, $CHCl_3$); ν_{max} ($CHCl_3$)/cm^{-1} 2968, 1954, 1682; δ_H (400 MHz, $CDCl_3$) 1.28 (9H major, s, C(C*H*$_3$)$_3$), 1.29 (9H minor, C(C*H*$_3$)$_3$), 2.08 (1H major+1H minor, m, 4-H$_A$), 2.48 (3H major+3H minor, m, 4-H$_B$+3-H), 4.36 (1H major+1H minor, m, 5-H), 4.68 (2H major+2H minor, m, 3′-H), 5.01 (1H minor, 1′-H), 5.10 (1H major, dt, *J*=7.5, 6.6 Hz, m, 1′-H), 6.90 (1H major+1H minor, m, Ar-*H*), 7.19 (2H major+2H minor, m, Ar-*H*), 7.47 (1H major+1H minor, m, Ar-*H*); δ_C (67.5 MHz, $CDCl_3$) 25.9 (CH_2), 30.1 (CH_2), 32.0 (CH_3), 35.9 (C), 62.2 (CH), 77.4 (CH_2), 90.6 (CH), 126.9 (CH), 128.6 (CH), 128.8 (CH), 133.3 (CH), 135.2 (C), 148.6 (C), 175.7 (C=O), 208.6 (C=*C*=C); *m/z* (EI) 255 (M^+, 1%), 216 (100), 198 (66) (Found M^+, 255.1627. $C_{17}H_{21}NO$ requires *M*, 255.1623).

4.1.6. (5*R*)-1-(2-*tert*-Butylphenyl)-5-propylpyrrolidin-2-one (−)-14. A solution of pyrrolidin-2-one (−)-**12** (610 mg, 2.37 mmol) and 10% palladium on carbon (50.0 mg, 0.05 mmol) in MeCN (25 mL) was shaken under an atmosphere of hydrogen overnight. The reaction mixture was then filtered through celite and evaporated under reduced pressure to yield the title compound (−)-**14** (3:1 ratio of isomers) as a colourless oil (610 mg, 2.35 mmol, 99%), $[\alpha]_D^{23}=-22$ (*c* 1.00, $CHCl_3$); ν_{max} ($CHCl_3$)/cm^{-1} 2934, 2875, 1682; δ_H (400 MHz; $CDCl_3$) 0.84 (3H minor, 3′-H), 0.86 (3H major, t, *J*=7.2 Hz, 3′-H), 1.19 (2H major+2H minor, m, 2′-H), 1.30–1.41 (10H major+10H minor, m with major s at 1.38 and minor s at 1.41, C(C*H*$_3$)$_3$+1′-H$_A$), 1.49–1.56 (1H major+1H minor, m, 1′-H$_B$), 1.99 (1H major+1H minor, m, 4-H$_A$), 2.44 (3H major+3H minor, m, 4-H$_B$+3H), 3.89 (1H major+1H minor, m, 5-H), 6.92 (1H major, dd, *J*=7.7, 1.5 Hz, Ar-*H*), 6.96 (1H minor, dd, *J*=7.7, 1.5 Hz, Ar-*H*), 7.24 (2H major+2H minor, m, Ar-*H*), 7.55 (1H major+1H minor, m, Ar-*H*); δ_C (67.5 MHz; $CDCl_3$) 13.7 (CH_3), 18.4 (CH_2), 24.7 (CH_2), 30.0 (CH_2), 31.5 (CH_3), 35.4 (CH_2), 35.5 (C), 61.9 (CH), 126.4 (CH), 128.1 (CH), 128.6 (CH), 132.8 (CH), 134.6 (C), 148.0 (C), 175.3 (C=O); *m/z* (EI) 259 (M^+, 2%), 216 (58) 202 (100) (Found M^+, 259.1934. $C_{17}H_{25}NO$ requires *M*, 259.1936).

Similar reactions starting with allene **13** gave the same results.

All four isomers of **14** were separated by HPLC using a Chiralcel OD column [25 cm×0.46 cm i.d.; 2% *i*-PrOH in hexane; flow rate, 1.0 mL/min]. Samples of **14** originating with **10** gave two atropisomers eluting at 21.2 and 29.0 min, whereas samples originating with **11** gave two atropisomers eluting at 22.8 and 24.8 min. Each sample proved to be essentially enantiomerically pure (≥99% ee).

4.1.7. (*P*,5*S*)-1-(2-*tert*-Butylphenyl)-5-methoxymethylpyrrolidin-2-one 15.[7e,14] *Ozonolysis*. Ozone was bubbled through a solution of pyrrolidin-2-one (−)-**13** (150 mg, 0.59 mmol) in CH_2Cl_2 (5 mL) and MeOH (5 mL) at −78 °C, for 30 min, before sodium borohydride (75.0 mg, 1.98 mmol) was added and the reaction mixture stirred at room temperature overnight. The reaction mixture was then poured onto H_2O (10 mL) and extracted with $CHCl_3$ (3×10 mL), the combined organic extracts were then washed with brine (10 mL), dried ($MgSO_4$) and evaporated under reduced pressure to yield a yellow oil. The crude oil was then purified by flash column chromatography (100% EtOAc) to yield an intermediate hydroxymethyl compound as a white solid (94.0 mg, 0.38 mmol, 65%), $[\alpha]_D^{23}=-23$ (*c* 1.00, $CHCl_3$); mp 132–133 °C; ν_{max} ($CHCl_3$)/cm^{-1} 3652, 3400, 2958, 2878, 1682; δ_H (400 MHz; $CDCl_3$) 1.35 (9H, s, C(C*H*$_3$)$_3$), 2.25 (3H, m, 4-H+3-H$_A$), 2.64 (1H, dt, *J*=16.5, 9.3 Hz, 3-H$_B$), 3.43 (1H, dd, *J*=11.3, 1.8 Hz, 1′-H$_A$), 3.55 (1H, dd, *J*=11.3, 3.4 Hz, 1′-H$_B$), 3.74 (2H, m, 5-H+O*H*), 7.07 (1H, dd, *J*=7.7, 1.4 Hz, Ar-*H*), 7.18 (1H, ddd, *J*=7.7, 7.3, 1.5 Hz, Ar-*H*), 7.27 (1H, ddd, *J*=8.0, 7.3, 1.4 Hz, Ar-*H*), 7.50 (1H, dd, *J*=8.0, 1.5 Hz, Ar-*H*); δ_C (67.5 MHz; $CDCl_3$) 22.0 (CH_2), 30.6 (CH_2), 31.8 (CH_3), 35.7 (C), 62.0 (CH_2), 63.7 (CH), 127.0 (CH), 128.4 (CH), 128.6 (CH), 132.4 (CH), 134.8 (C), 148.1 (C), 177.3 (C=O); *m/z* (FAB) 248 (MH^+, 8%), 154 (100), 136 (66) (Found MH^+, 248.1651. $C_{15}H_{22}NO_2$ requires *M*, 248.1651).

Methylation. To a solution of the primary alcohol product (90.0 mg, 0.36 mmol) and KOH (82.0 mg, 1.46 mmol) in DMSO (2.5 mL) was added MeI (0.50 mL, 8.03 mmol) and the reaction mixture stirred at room temperature overnight. The reaction mixture was then poured onto H_2O (10 mL) and extracted with $CHCl_3$ (3×10 mL), the combined organic extracts were then washed with brine (10 mL), dried ($MgSO_4$) and evaporated under reduced pressure to yield

a yellow oil. The crude oil was then purified by column chromatography (60% EtOAc–petroleum ether) to yield the lactam **15** as a white solid (72 mg, 0.28 mmol, 76%), mp 94–95 °C (lit.[7e,14] 93–94.5 °C); ν_{max} ($CHCl_3$)/cm^{-1} 2958, 2881, 1682, 1121; δ_H (400 MHz; $CDCl_3$) 1.38 (9H, s, $C(CH_3)_3$), 2.16 (1H, m, 4-H_A), 2.37 (2H, m, 4-H_B +3-H_A), 2.66 (1H, m, 3-H_B), 3.31 (1H, dd, J=9.9, 2.3 Hz, 1′-H_A), 3.36 (3H, s, 1′-OMe), 3.44 (1H, dd, J=9.9, 3.5 Hz, 1′-H_B), 3.89 (1H, m, 5-H), 7.00 (1H, dd, J=7.7, 1.6 Hz, Ar-*H*), 7.27 (2H, m, Ar-*H*), 7.53 (1H, dd, J=8.0, 1.5 Hz, Ar-*H*); δ_C (67.5 MHz; $CDCl_3$) 22.7 (CH_2), 30.5 (CH_2), 31.8 (CH_3), 35.7 (C), 58.9 (CH_2), 62.0 (CH), 72.5 (CH_3), 127.0 (CH), 128.4 (CH), 128.7 (CH), 132.3 (CH), 135.1 (C), 148.4 (C), 176.9 (C); *m*/*z* (EI) 261 (M^+, 2%), 216 (100), 204 (24) (Found M^+, 261.1722. $C_{16}H_{23}NO_2$ requires *M*, 261.1729).

The enantiomers of **15** were separated by HPLC using a Chiralpak AD column [25 cm×0.46 cm i.d.; 10% *i*-PrOH in hexane; flow rate, 1.0 mL/min; t_R=7.3 min and 8.2 min]. Samples of **15** originating with **10** gave mainly the enantiomer with the longer retention time, allowing us to assign the stereochemistry as (*P*,5*S*).[7e]

4.1.8. 2-*tert*-Butyl-4-aminoanisole 16. To a stirred solution of 1-amino-2-*tert*-butylphenol (16.5 g, 100 mmol) in DMSO (250 mL) was added potassium *tert*-butoxide (12.2 g, 100 mmol) and the reaction mixture stirred for 2 h. Dimethyl sulphate (10.0 mL, 106 mmol) was added in one portion, the reaction mixture stirred for 5 min, poured onto H_2O (500 mL) and extracted with EtOAc (3×250 mL). The organic extracts were then washed with H_2O (3×250 mL), dried ($MgSO_4$) and evaporated under reduced pressure. The resultant black oil was then purified by distillation (165 °C/10 mmHg) followed by flash column chromatography (40% Et_2O–hexanes) to yield the title compound as a yellow oil (14.2 g, 80.1 mmol, 80%), ν_{max} ($CHCl_3$)/cm^{-1} 3471, 3390, 2954, 2911, 2834, 1622, 1054; δ_H (400 MHz, $CDCl_3$) 1.41 (9H, s, $C(CH_3)_3$), 3.54 (2H, br.s, NH_2), 3.74 (3H, s, OCH_3), 6.59 (2H, m, Ar-*H*) 6.86 (1H, d, J=2.5 Hz, Ar-*H*); δ_C (67.5 MHz, $CDCl_3$) 29.8 (CH_3), 34.7 (C), 55.8 (CH_3), 111.3 (CH), 114.0 (CH), 119.0 (CH), 136.1 (C), 138.6 (C), 152.9 (C); *m*/*z* (EI) 179 (M^+, 62%), 164 (100) (Found M^+, 179.1307. $C_{11}H_{17}NO$ requires *M*, 179.1310).

4.1.9. 1-(2-*tert*-Butyl-4-methoxyphenyl)-pyrrolidine-2,5-dione 17. Succinic anhydride (4.70 g, 47.0 mmol) was added to a solution of 3-*tert*butyl-4-aminoanisole **16** (7.00 g, 39.1 mmol) in toluene (50 mL) and heated to reflux overnight, cooled, and filtered to give a beige solid. This crude succinamic acid was added to solution of sodium acetate (1.60 g, 19.5 mmol) and acetic anhydride (50 mL) and was heated to 70 °C for 6 h. The reaction mixture was then poured onto H_2O, extracted with $CHCl_3$, washed with 2 N sodium hydroxide, dried over magnesium sulphate and evaporated under reduced pressure to yield a brown solid. The crude solid was purified by flash column chromatography (40% EtOAc–petroleum ether) to yield the title compound **17** as a white solid (7.81 g, 29.9 mmol, 77%), mp 130–131 °C; ν_{max} ($CHCl_3$)/cm^{-1} 3475, 2908, 2253, 1732; δ_H (400 MHz, $CDCl_3$) 1.27 (9H, s, $C(CH_3)_3$), 2.82 (4H, s, 3-H), 3.79 (3H, s, OMe), 6.79 (2H, m, Ar-*H*), 7.09 (1H, d, J=2.5 Hz, Ar-*H*); δ_C (67.5 MHz, $CDCl_3$) 28.8 (CH_2), 31.5 (CH_3), 35.7 (C), 55.7 (CH_3), 111.7 (CH), 115.3 (CH), 123.3 (C), 132.0 (CH), 149.6 (C), 160.2 (C), 177.9 (C=O); *m*/*z* (EI) 261 (M^+, 100%), 246 (88) (Found M^+, 261.1373. $C_{15}H_{19}NO_3$ requires *M*, 261.1365).

4.1.10. 1-(2-*tert*-Butyl-4-methoxyphenyl)-5-hydroxypyrrolidin-2-one 18. DIBAL (56.0 mL of a 1 M solution in CH_2Cl_2) was added dropwise to a stirred solution of imide **17** (7.30 g, 27.9 mmol) in CH_2Cl_2 (50 mL) at −78 °C. After 10 min stirring at −78 °C, H_2O (50 mL), and 2 N NaOH (10 mL) were cautiously added and the reaction mixture extracted with $CHCl_3$ (3×50 mL). The organic extracts were washed with brine (50 mL), dried ($MgSO_4$) and evaporated under reduced pressure to yield a white solid. The crude solid was then purified by flash column chromatography (100% EtOAc) to yield the title compound **18** (17:1 ratio of isomers) as a white solid (6.32 g, 24.0 mmol, 86%), mp 136–138 °C; ν_{max} ($CHCl_3$)/cm^{-1} 3597, 2960, 2837, 1694, 1052; δ_H (400 MHz, $CDCl_3$) 1.32 (9H major, s, $C(CH_3)_3$), 1.41 (9H minor, $C(CH_3)_3$), 2.09 (1H major+1H minor, m, 4-H_A), 2.37 (2H major+2H minor, m, 4-H_B+3-H_A), 2.66 (1H major+1H minor, m, 3-H_B), 3.53 (1H major+1H minor, d, J=4.6 Hz, O*H*), 3.81 (3H major+3H minor, s, OMe), 5.29 (1H major+1H minor, t, J=5.0 Hz, 5-H), 6.77 (1H major+1H minor, dd, J=5.8, 2.9 Hz, Ar-*H*), 7.04 (2H major+2H minor, m, Ar-*H*); δ_C (67.5 MHz, $CDCl_3$) 27.5 (CH_2), 28.4 (CH_2), 31.5 (CH_3), 35.6 (C), 55.3 (CH_3), 86.3 (CH), 110.8 (CH), 115.1 (CH), 127.3 (CH), 133.6 (CH), 149.7 (C), 159.2 (C), 176.9 (C=O); *m*/*z* (EI) 263 (M^+, 18%), 245 (50), 170 (36), 70 (100) (Found M^+, 263.1509. $C_{15}H_{21}NO_3$ requires *M*, 263.1521).

4.1.11. (*P*,5*R*)-1-(2-*tert*-Butylphenyl)-5-(2*S*-*iso*-propyl-5*R*-methylcyclohexyl-1*R*-oxy)-pyrrolidin-2-one (−)-19 and (*M*,5*S*)-1-(2-*tert*-butylphenyl)-5-(2*S*-*iso*-propyl-5*R*-methylcyclohexyl-1*R*-oxy)-pyrrolidin-2-one (−)-20. (−)-Menthol (3.70 g, 23.7 mmol) and PPTS (0.56 g, 2.23 mmol) were added to a stirred solution of pyrrolidin-2-one **18** (5.25 g, 22.5 mmol) and anhydrous copper sulphate (10.0 g, 62.7 mmol) in CH_2Cl_2 (100 mL) and stirred at room temperature overnight. The reaction mixture was poured onto H_2O (100 mL) and extracted with $CHCl_3$ (3×100 mL), the combined organic extracts were then dried ($MgSO_4$) and evaporated under reduced pressure. The resultant solid was then purified by flash column chromatography (25–50% EtOAc–petroleum ether) to give firstly the minor diastereoisomer (−)-**19** as a yellow oil (1.44 g, 3.59 mmol, 22%), $[\alpha]_D^{23}$=−113 (*c* 1.00, $CHCl_3$); ν_{max} ($CHCl_3$)/cm^{-1} 2956, 2926, 2870, 1697, 1052; δ_H (400 MHz; $CDCl_3$) 0.49 (1H, ddd, J=12.3, 12.3, 10.5 Hz, 6′-H_A), 0.73 (3H, d, J=6.6 Hz, 2″-Me_A), 0.78 (4H, m with d at 0.78, J=7.0 Hz, 5′-Me+3′-H_A), 0.92 (4H, m with d at 0.92, J=7.1 Hz, 2″-Me_B+4′-H_A), 1.22 (2H, m, 2′-H+5′H), 1.34 (9H, s, $C(CH_3)_3$), 1.45 (1H, m, 6′-H_B), 1.60 (2H, m, 3′-H_B+4′-H_B), 2.10 (1H, m, 1″-H), 2.21 (2H, m, 4-H), 2.43 (1H, dd, J=17.0, 9.3 Hz, 3-H_A), 2.68 (1H, ddd, J=17.0, 9.8, 9.4 Hz, 3-H_B), 3.05 (1H, dt, J=10.5, 4.0 Hz, 1′-H), 3.79 (3H, s, OMe), 5.05 (1H, d, J=4.5 Hz, 5-H), 6.74 (1H, dd, J=8.6, 2.9 Hz, Ar-*H*), 7.01 (1H, d, J=2.9 Hz, Ar-*H*), 7.12 (1H, d, J=8.6 Hz, Ar-*H*); δ_C (67.5 MHz; $CDCl_3$) 15.8 (CH_3), 21.1 (CH_3), 22.0 (CH_3), 22.9 (CH_2), 25.1 (CH), 26.1 (CH_2), 28.3 (CH_2), 30.4 (CH), 31.4 (CH_3), 33.9 (CH_2), 35.4

(C), 40.1 (CH_2), 48.0 (CH), 55.1 (CH_3), 76.1 (CH), 90.4 (CH), 110.4 (CH), 114.2 (CH), 127.8 (CH), 134.5 (CH), 149.1 (C), 158.9 (C), 177.1 (C=O); *m/z* (EI) 401 (M^+, 9%), 259 (16), 245 (100) (Found M^+, 401.2942. $C_{25}H_{39}NO_3$ requires *M*, 401.2930), followed by the major diastereoisomer (−)-**20** as a white solid (3.67 g, 9.14 mmol, 56%), $[\alpha]_D^{23}=-18$ (*c* 1.00, $CHCl_3$); mp 85–88 °C; ν_{max} ($CHCl_3$)/cm^{-1} 2955, 2925, 2870, 1698, 1065, 1051; δ_H (400 MHz; $CDCl_3$) 0.34 (3H, d, *J*=6.9 Hz, 2″-Me_A), 0.71 (3H, d, *J*=7.0 Hz, 2″-Me_B), 0.81 (2H, m, 3′-H_A+4′-H_A), 0.91 (3H, d, *J*=6.5 Hz, 5′-Me), 0.99 (1H, ddd, *J*=12.0, 11.8, 10.4 Hz, 6′-H_A), 1.14 (1H, m, 5′-H), 1.32–1.33 (10H, m with s at 1.33, C(CH_3)$_3$+2′-H), 1.53 (2H, m, 3′-H_B+4′-H_B), 1.80 (1H, m, 1″-H), 1.92 (1H, m, 6′-H_B), 2.12 (1H, m, 4-H_A), 2.37 (2H, m, 4-H_B+3-H_A), 2.70 (1H, m, 3-H_B), 3.02 (1H, ddd, *J*=10.5, 10.4, 4.1 Hz, 1′-H), 3.79 (3H, s, OMe), 5.05 (1H, d, *J*=4.4 Hz, 5-H), 6.71 (1H, dd, *J*=8.6, 1.5 Hz, Ar-*H*), 7.00 (1H, d, *J*=1.5 Hz, Ar-*H*), 7.11 (1H, d, *J*=8.6 Hz, Ar-*H*); δ_C (67.5 MHz; $CDCl_3$) 15.5 (CH_3), 21.2 (CH_3), 22.3 (CH_3), 22.5 (CH_2), 24.4 (CH), 28.3 (CH_2), 28.5 (CH_2), 31.6 (CH), 31.7 (CH_3), 34.2 (CH_2), 35.5 (C), 43.0 (CH_2), 48.9 (CH), 55.3 (CH_3), 78.4 (CH), 92.9 (CH), 110.6 (CH), 114.6 (CH), 128.4 (CH), 135.0 (CH), 149.1 (C), 158.7 (C), 177.6 (C=O); *m/z* (EI) 401 (M^+, 0.8%), 246 (19), 245 (100) (Found M^+, 401.2915. $C_{25}H_{39}NO_3$ requires *M*, 401.2930).

4.1.12. (*M*,5*R*)-5-Allyl-1-(2-*tert*-butyl-4-methoxyphenyl)-pyrrolidin-2-one (+)-21. To a stirred solution of pyrrolidin-2-one (−)-**20** (200 mg, 0.50 mmol) and allyltrimethylsilane (1.10 mL, 6.92 mmol) in CH_2Cl_2 (5 mL) at −40 °C, was added dropwise trimethylsilyltrifluoromethanesulphonate (0.35 mL, 1.94 mmol). The reaction mixture was stirred at −40 °C for 8 h before H_2O (5 mL) was cautiously added. The reaction mixture was extracted with $CHCl_3$ (3×10 mL), the combined organic extracts were then dried ($MgSO_4$) and evaporated under reduced pressure. The resulting yellow oil was purified by flash column chromatography (60% EtOAc–petroleum ether) to yield the title compound (+)-**21** (6:1 ratio of isomers) as a colourless oil (177 mg, 0.62 mmol, 90%), $[\alpha]_D^{23}=11$ (*c* 1.00, $CHCl_3$); ν_{max} ($CHCl_3$)/cm^{-1} 2959, 2838, 1682, 1051; δ_H (400 MHz, $CDCl_3$) 1.28 (9H major, s, C(CH_3)$_3$), 1.31 (9H minor, C(CH_3)$_3$), 1.88 (1H major+1H minor, m, 4-H_A), 2.05 (1H major+1H minor, m, 4-H_B), 2.36 (4H major+4H minor, m, 3-H+1′-H), 3.69 (3H minor, s, OMe), 3.70 (3H major, s, OMe), 3.82 (1H major+1H minor, m, 5-H), 4.95 (2H minor, m, 3′-H), 5.03 (2H major, m, 3′-H), 5.60 (1H major+1H minor, m, 2′-H), 6.68 (1H major+1H minor, dd, *J*=8.6, 2.9 Hz, Ar-*H*), 6.81 (1H major+1H minor, m, Ar-*H*), 6.99 (1H major+1H minor, d, *J*=2.8 Hz, Ar-*H*); δ_C (67.5 MHz, $CDCl_3$) 23.5 (CH_2), 29.3 (CH_2), 31.4 (CH_3), 35.6 (C), 37.7 (CH_2), 55.0 (CH_3), 61.4 (CH), 110.7 (CH), 115.2 (CH), 118.4 (CH), 127.2 (C), 133.3 (CH_2), 133.6 (CH), 158.9 (C), 149.5 (C), 175.9 (C=O); *m/z* (EI) 287 (M^+, 8%), 246 (100) (Found M^+, 287.1882. $C_{18}H_{25}NO_2$ requires *M*, 287.1885).

All four isomers of **21** were separated by HPLC using a Chiralcel OD column [25 cm×0.46 cm i.d.; 2% *i*-PrOH in hexane; flow rate, 1.0 mL/min]. Two atropisomers eluted at 32.9 and 48.2 min, and a further pair at 38.7 and 44.9 min. Samples of **21** originating with **20** gave the first pair of peaks as by far the major, allowing estimation of the ee as ca. 98%.

4.1.13. (*R*)-5-Allylpyrrolidin-2-one 22. To a solution of pyrrolidin-2-one (+)-**21** (175 mg, 0.61 mmol) in MeCN (12.5 mL), at 0 °C was added a solution of ceric ammonium nitrate (3.30 g, 6.02 mmol) in water (12.5 mL). The reaction mixture was then stirred at 0 °C for 5 h, before pouring onto H_2O (100 mL) and extracting with $CHCl_3$ (5×100 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated under reduced pressure to yield a yellow oil. The crude oil was then purified by flash column chromatography (100% EtOAc) to yield **22** as a yellow oil (21 mg, 0.17 mmol, 28%), ν_{max} ($CHCl_3$)/cm^{-1} 3432, 2927, 1693; δ_H (400 MHz, $CDCl_3$) 1.78 (2H, m, 4-H), 2.22 (4H, m, 3-H+1′-H), 3.71 (1H, app. quin, *J*=6.4 Hz, 5-H), 5.14 (2H, m, 3′-H), 5.75 (1H, m, 2′-H), 5.93 (1H, br. s, N*H*); δ_C (126 MHz, $CDCl_3$) 26.6 (CH_2), 29.9 (CH_2), 40.9 (CH_2), 53.3 (CH), 118.4 (CH_2), 133.5 (CH), 177.7 (C=O); *m/z* (EI) 125 (M^+, 0.2%), 84 (100) (Found M^+, 125.0834. $C_7H_{11}NO$ requires *M*, 125.0841).

4.1.14. 1-(2-*tert*-Butyl-phenyl)-piperidin-2,6-dione 28. *Amide bond formation*. To a solution of 2-*tert*-butylaniline **27** (77.6 mL, 48.6 mmol) in toluene (50 mL) was added glutaric anhydride (6.55 g, 57.4 mmol) and the reaction mixture was heated at reflux for 1 h, cooled, and filtered to give the crude butyric acid. The solid was washed with petroleum ether, to give the butyric acid (2:1 ratio of rotamers) as a white solid (12.5 g, 48.4 mmol, 98%), mp 120–123 °C (recrystallised from petroleum ether/EtOAc); ν_{max} ($CHCl_3$)/cm^{-1} 3516, 2969, 1710, 1578; δ_H (400 MHz, $CDCl_3$) 1.40 (9H major+9H minor, s, C(CH_3)$_3$), 1.95 (2H minor, 4-H), 2.12 (2H major, apparent quin, *J*=7.1 Hz, 4-H), 2.17 (2H minor, 5-H/3-H), 2.38 (2H minor, 3-H/5-H), 2.51 (4H major, apparent q, *J*=6.9 Hz, 5-H+3-H), 7.07 (1H minor, Ar-*H*), 7.15–7.30 (2H major+2H minor, m, Ar-*H*), 7.30 (1H major, d, *J*=7.0 Hz, Ar-*H*), 7.46 (1H minor, Ar-*H*); 7.51 (1H major, d, *J*=7.5 Hz, Ar-*H*); δ_C (100 MHz, $CDCl_3$) 20.6 (CH_2), 30.8 (CH_3), 33.1 (CH_2), 34.7 (C), 36.3 (CH_2), 126.7 (CH), 126.9 (CH), 127.2 (CH), 128.4 (CH), 134.9 (C), 143.0 (C), 170.9 (C=O), 178.2 (C=O); *m/z* (FAB) 264 (MH^+, 60%), 246 (10) 154 (100) (Found MH^+, 264.1603. $C_{15}H_{22}NO_3$ requires *M*, 264.1600). Anal. Calcd for $C_{15}H_{21}NO_3$. C, 68.44; H, 7.98; N, 5.32%. Found: C, 68.22; H, 7.95; N, 5.41%.

Imide formation. To a solution of the butyric acid (26.9 g, 0.10 mol) in $CHCl_3$ (500 mL) was added 1,1′-carbonyldiimidazole (17.8 g, 0.11 mol) and the reaction mixture heated at 70 °C overnight, and cooled. The reaction mixture was washed with H_2O (2×600 mL), and the aqueous re-extracted with $CHCl_3$ (2×200 mL). The combined organics were then washed with 2 N HCl (300 mL), then with water until washings were neutral, washed with brine (200 mL), dried ($MgSO_4$), and evaporated under reduced pressure to yield the title compound as a white solid (23.9 g, 0.10 mol, 98%), mp 116–118 °C (recrystallised from petroleum ether/EtOAc); ν_{max} ($CHCl_3$)/cm^{-1} 2966, 2908, 1734, 1682; δ_H (400 MHz, $CDCl_3$) 1.31 (9H, s, C(CH_3)$_3$), 2.10 (2H, apparent quin, *J*=6.6 Hz, 4-H), 2.81 (4H, apparent t, *J*=6.6 Hz, 3-H), 6.83 (1H, dd, *J*=7.7 Hz, 1.5, Ar-*H*), 7.28 (1H, ddd, *J*=7.7, 7.4, 1.5 Hz, Ar-*H*); 7.38 (1H, ddd, *J*=8.0,

7.4, 1.5 Hz, Ar-*H*), 7.58 (1H, dd, *J*=8.0, 1.5 Hz, Ar-*H*); δ_C (100 MHz, $CDCl_3$) 17.1 (CH_2), 31.7 (CH_3), 33.5 (CH_2), 35.9 (C), 127.3 (CH), 129.1 (CH), 131.0 (2×CH), 133.3 (C), 146.8 (C), 173.3 (C=O); *m/z* (EI) 245 (M^+, 0.8%), 188 (100) (Found M^+, 245.1410. $C_{15}H_{19}NO_2$ requires *M*, 245.1416). Anal. Calcd for $C_{15}H_{19}NO_2$. C, 73.47; H, 7.76; N, 5.71%. Found: C, 73.33; H, 7.78; N, 5.70%.

4.1.15. 1-(2-*tert*-Butyl-phenyl)-6-hydroxy-piperidin-2-one 23. DIBAL (166 mL of a 1 M solution in CH_2Cl_2) was added dropwise to a stirred solution of imide **28** (22.5 g, 91.7 mmol) in CH_2Cl_2 (300 mL) at −78 °C. After 15 min stirring at −78 °C, H_2O (160 mL), followed by 2 N NaOH (50 mL) were cautiously added and the reaction mixture poured into a saturated solution of Rochelles salt (1.20 L). The mixture was then extracted with CH_2Cl_2 (4×350 mL). The combined extracts were then washed with brine (350 mL), dried ($MgSO_4$), and evaporated under reduced pressure to yield a yellow oil. The crude mixture was then purified by flash column chromatography (50% EtOAc–petroleum ether) to give a yellow oil, which was triturated with petroleum ether/EtOAc to yield the title compound **23** (3:1 ratio of isomers) as a white solid (14.5 g, 58.8 mmol, 64%), mp 104–106 °C; ν_{max} ($CHCl_3$)/cm^{-1} 3667, 3592, 3405, 3124, 2961, 1722, 1698, 1650, 1573; δ_H (400 MHz, $CDCl_3$) 1.31 (9H major, s, $C(CH_3)_3$), 1.38 (9H minor, $C(CH_3)_3$), 1.77 (1H major+1H minor, m, 4-H_A), 1.96–2.04 (2H major+2H minor, m, 4-H_B+5-H_A), 2.22–2.39 (2H major+2H minor, m, 5-H_B+3-H_A), 2.50–2.55 (1H major+1H minor, m, 3-H_B), 3.69 (1H major+1H minor, br.s, O*H*), 4.96 (1H major, m, 6-H), 5.26 (1H minor, 6-H), 6.96 (1H minor, Ar-*H*), 7.10 (1H major, dd, *J*=7.6, 1.6 Hz, Ar-*H*), 7.18 (1H major+1H minor, ddd, *J*=7.6, 7.3, 1.6 Hz, Ar-*H*); 7.27 (1H major+1H minor, ddd, *J*=8.0, 7.3, 1.6 Hz, Ar-*H*), 7.51 (1H major, dd, *J*=8.0, 1.6 Hz, Ar-*H*) 7.56 (1H minor, Ar-*H*); δ_C (100 MHz, $CDCl_3$) 16.0 (CH_2), 29.4 (CH_2), 31.7 (CH_3), 33.1 (CH_2), 35.7 (C), 82.3 (CH), 126.8 (CH), 128.2 (CH), 128.9 (CH), 132.6 (CH), 139.0 (C), 146.6(C), 172.3 (C=O); *m/z* (TOF) 270 $(M+Na)^+$ (Found $M+Na^+$, 270.1476. $C_{15}H_{21}NO_2$+Na requires *M*, 270.1470). Anal. Calcd for $C_{15}H_{21}NO_2$. C, 72.87; H, 8.50; N, 5.67%. Found: C, 72.67; H, 8.53; N, 5.65%.

4.1.16. 1-(2-*tert*-Butyl-phenyl)-3,4-dihydro-1*H*-pyridin-2-one 24. To a solution of piperidine-2-one **23** (14.0 g, 56.8 mmol) in CH_2Cl_2 (500 mL) at 0 °C, was added Et_3N (24.0 mL, 172 mmol), then MsCl (6.66 mL, 86.1 mmol). The reaction mixture was stirred at room temperature for 2 h, then washed with H_2O (500 mL), a saturated solution of $NaHCO_3$ (500 mL), and brine (500 mL), dried ($MgSO_4$), and evaporated under reduced pressure. The resulting orange oil was purified by flash column chromatography (20% EtOAc–petroleum ether), to give the title compound as a white solid (10.6 g, 46.4 mmol, 81%), mp 91–93 °C (recrystallised from petroleum ether); ν_{max} ($CHCl_3$)/cm^{-1} 2960, 2775, 2577, 2465, 2263, 2144, 1723, 1698, 1672, 1573; δ_H (400 MHz, $CDCl_3$) 1.38 (9H, s, $C(CH_3)_3$), 2.44–2.49 (2H, m, 4-H), 2.66–2.70 (2H, m, 3-H), 5.24 (1H, dt, *J*=7.7, 4.4 Hz, 5-H), 6.07 (1H, dt, *J*=7.7, 1.6 Hz, 6-H), 7.01 (1H, dd, *J*=7.6, 1.7 Hz, Ar-*H*), 7.26 (1H, ddd, *J*=7.6, 7.3, 1.6 Hz, Ar-*H*), 7.32 (1H, ddd, *J*=8.0, 7.3, 1.7 Hz, Ar-*H*), 7.54 (1H, dd, *J*=8.0, 1.6 Hz, Ar-*H*); δ_C (100 MHz, $CDCl_3$) 20.5 (CH_2), 31.7 (CH_3), 32.2 (CH_2), 35.7 (C), 105.0 (CH), 127.6 (CH), 128.6 (CH), 128.7 (CH), 130.9 (CH), 132.9 (CH), 139.5 (C), 147.6 (C), 170.3 (C=O); *m/z* (TOF) 252 $(M+Na)^+$ (Found $M+Na^+$, 252.1364. $C_{15}H_{19}NO$+Na requires *M*, 252.1364). Anal. Calcd for $C_{15}H_{19}NO$. C, 78.60; H, 8.30; N, 6.11%. Found: C, 78.28; H, 8.36; N, 6.16%.

4.1.17. (5*S*,6*S*)-6-Allyl-1-(2-*tert*-butyl-phenyl)-5-hydroxy-piperidin-2-one 25 and (5*R*,6*S*)-6-allyl-1-(2-*tert*-butyl-phenyl)-5-hydroxy-piperidin-2-one 26. To a solution of **24** (1.20 g, 5.22 mmol) in dry acetone (30 mL) at 0 °C, was added DMDO (100 mL of an approx. 0.10 M solution). The reaction mixed was stirred at 0 °C for 1 h then concentrated and redissolved in CH_2Cl_2 (30 mL). To this solution, was added allyl trimethylsilane (4.14 mL, 26.1 mmol) and $TiCl_4$ (2.86 mL, 26.1 mmol) slowly. The reaction mixture was stirred at room temperature for 3 days, then diluted with CH_2Cl_2 (60 mL), washed with H_2O (50 mL), a saturated solution of $NaHCO_3$ (50 mL), and brine (50 mL), dried ($MgSO_4$), and evaporated under reduced pressure. The resulting crude mixture was purified by flash column chromatography (20% EtOAc–petroleum ether), to give: firstly the minor isomer **26** (R_f 0.4, 70:30 petroleum ether–EtOAc) as a white solid (170 mg, 0.60 mmol, 11%), δ_H (500 MHz, $CDCl_3$) 1.44 (9H, s, $C(CH_3)_3$), 1.94–2.05 (1H, m, 4-H_A), 2.09 (1H, m, 1′-H_A), 2.18 (1H, dddd, *J*=15.5, 9.9, 6.2, 4.0 Hz, 4-H_B), 2.51 (1H, ddd, *J*=17.6, 5.9, 4.0 Hz, 3-H_A), 2.65 (1H, dddd, *J*=16.1, 5.6, 3.8, 1.7 Hz, 1′-H_B), 2.74 (1H, ddd, *J*=17.6, 11.0, 6.2 Hz, 3-H_B), 3.78 (1H, ddd, *J*=9.9, 3.3, 3.2 Hz, 5-H), 4.23 (1H, m, 6-H), 5.09 (2H, m, 3′-H), 5.62 (1H, dddd, *J*=18.9, 10.5, 6.8, 5.6 Hz, 2′-H), 6.91 (1H, dd, *J*=7.7, 1.7 Hz, Ar-*H*), 7.20 (1H, ddd, *J*=7.7, 7.3, 1.5 Hz, Ar-*H*), 7.29 (1H, ddd, *J*=8.2, 7.3, 1.7 Hz, Ar-*H*), 7.58 (1H, dd, *J*=8.2, 1.5 Hz, Ar-*H*); δ_C (125 MHz, $CDCl_3$) 25.3 (CH_2), 28.2 (CH_2), 31.9 (CH_3), 36.1 (C), 37.8 (CH_2), 65.4 (CH), 66.9 (CH), 118.4 (CH_2), 126.3 (CH), 128.1 (CH), 129.8 (CH), 134.1 (2×CH), 138.2 (C), 147.0 (C), 171.2 (C=O); *m/z* (FAB) 288 (MH^+, 35%), 230 (12) (Found MH^+, 288.1962. $C_{18}H_{25}NO_2$ requires *M*, 288.1964); followed by the major isomer **25** (R_f 0.3, 70:30 petroleum ether–EtOAc) as a white solid (950 mg, 3.03 mmol, 63%), mp 140–142 °C (recrystallised from petroleum ether); ν_{max} ($CHCl_3$)/cm^{-1} 3622, 2960, 1643, 1597; δ_H (400 MHz, $CDCl_3$) 1.38 (9H, s, $C(CH_3)_3$), 1.93–2.00 (1H, m, 1′-H_A), 2.05–2.11 (2H, m, 4-H), 2.31 (1H, ddd, *J*=14.2, 10.5, 8.5 Hz, 1′-H_B), 2.50 (1H, ddd, *J*=17.7, 7.6, 5.7 Hz, 3-H_A), 2.71 (1H, dt, *J*=17.7, 8.0 Hz, 3-H_B), 3.76 (1H, ddd, *J*=10.7, 4.0, 2.9 Hz, 5-H), 4.48 (1H, m, 6-H), 5.07 (2H, m, 3′-H), 5.65 (1H, dddd, *J*=18.9, 10.5, 6.3, 5.7 Hz, 2′-H), 7.01 (1H, dd, *J*=7.8, 1.6 Hz, Ar-*H*), 7.19 (1H, ddd, *J*=7.8, 7.2, 1.7 Hz, Ar-*H*), 7.27 (1H, ddd, *J*=8.0, 7.2, 1.6 Hz, Ar-*H*), 7.53 (1H, dd, *J*=8.0, 1.7 Hz, Ar-*H*); δ_C (125 MHz, $CDCl_3$) 27.0 (CH_2), 28.4 (CH_2), 31.8 (CH_3), 34.6 (CH_2), 35.9 (C), 63.4 (CH), 64.2 (CH), 118.0 (CH_2), 126.4 (CH), 127.9 (CH), 129.0 (CH), 133.2 (CH), 134.5 (CH), 137.2 (C), 147.0 (C), 171.6 (C=O); *m/z* (FAB) 288 (MH^+, 100%), 230 (24) (Found MH^+, 288.1980. $C_{18}H_{25}NO_2$ requires *M*, 288.1964). Anal. Calcd for $C_{18}H_{25}NO_2$. C, 75.26; H, 8.71; N, 4.88%. Found: C, 75.53; H, 8.81; N, 4.94%.

4.1.18. 3-Alkyl-1-(2-*tert*-butyl-phenyl)-3,4-dihydro-1*H*-pyridin-2-one 29a–f. General procedure for alkylation of

24. To a stirred solution of di*iso*propylamine (0.14 mL, 1.00 mmol) in THF (5 mL) at −78 °C was added ^{n}BuLi (0.68 mL of a 1.60 M solution in hexanes), and the mixture then warmed to room temperature for 15 min before cooling to −78 °C. To the resulting solution of LDA, a solution of pyridin-2-one **24** (200 mg, 0.87 mmol) in THF (5 mL) was added. After 1.5 h the electrophile (8.70 mmol) was added and the reaction mixture stirred at −78 °C for 1 h. Saturated NH_4Cl solution (5 mL) was then added and the reaction mixture was allowed to warm to room temperature. The mixture was extracted with EtOAc (4×30 mL), the combined organic extracts were washed with brine (30 mL), dried ($MgSO_4$) and evaporated under reduced pressure. The resulting crude product was purified by flash column chromatography.

4.1.19. (3*R*)-1-(2-*tert*-Butyl-phenyl)-3-methyl-3,4-dihydro-1*H*-pyridin-2-one 29a. From **24** (200 mg, 0.87 mmol), the resulting yellow oil was purified by flash column chromatography (20% EtOAc–petroleum ether) to yield the title compound (6:1 ratio of isomers) as an oily solid (171 mg, 0.70 mmol, 81%), ν_{max} ($CHCl_3$)/cm^{-1} 2966, 2359, 1711, 1667; δ_H (400 MHz, $CDCl_3$) 1.30 (3H major, d, *J*=6.9 Hz, 3-Me), 1.33 (3H minor, 3-Me), 1.36 (9H major, s, C(CH_3)$_3$), 1.37 (9H minor, C(CH_3)$_3$), 2.24 (1H major+1H minor, dddd, *J*=16.9, 10.8, 4.0, 1.8 Hz, 4-H_A), 2.51 (1H major+1H minor, dddd, *J*=16.9, 14.1, 3.7, 1.2 Hz, 4-H_B), 2.72 (1H major+1H minor, ddq, *J*=14.1, 10.8, 6.9 Hz, 3-H), 5.17 (1H, ddd, *J*=7.7, 4.0, 3.7 Hz, 5-H), 5.25 (1H minor, 5-H), 6.04 (1H, ddd, *J*=7.7, 1.8, 1.2 Hz, 6-H), 6.07 (1H minor, 6-H), 6.98 (1H major+1H minor, dd, *J*=7.6, 1.6 Hz, Ar-*H*), 7.24 (1H major+1H minor, ddd, *J*=7.6, 7.3, 1.6 Hz, Ar-*H*), 7.31 (1H major+1H minor, ddd, *J*=8.0, 7.3, 1.6 Hz, Ar-*H*), 7.52 (1H major+1H minor, dd, *J*=8.0, 1.6 Hz, Ar-*H*); δ_C (100 MHz, $CDCl_3$) 15.7 (CH_3), 28.6 (CH_2), 31.7 (CH_3), 35.7 (C), 36.2 (CH), 104.0 (CH), 127.4 (CH), 128.5 (CH), 128.7 (CH), 131.1 (CH), 132.6 (CH), 139.6 (C), 147.4 (C), 173.1 (C=O); *m*/*z* (FAB) 244 (MH^+, 100%), 186 (92) (Found MH^+, 244.1716. $C_{16}H_{22}NO$ requires *M*, 244.1701).

4.1.20. (3*R*)-3-Allyl-1-(2-*tert*-butyl-phenyl)-3,4-dihydro-1*H*-pyridin-2-one 29b. From **24** (200 mg, 0.87 mmol), the resulting yellow oil was purified by flash column chromatography (10% EtOAc–petroleum ether) to yield the title compound (12:1 ratio of isomers) as a yellow oil (155 mg, 0.58 mmol, 66%), ν_{max} ($CHCl_3$)/cm^{-1} 2963, 1710, 1668; δ_H (400 MHz, $CDCl_3$) 1.37 (9H major+9H minor, s, C(CH_3)$_3$), 2.29–2.35 (2H major+2H minor, m, 4-H), 2.52 (1H major+1H minor, dddd, *J*=16.7, 6.0, 3.9, 1.2 Hz, 1′-H_A), 2.62–2.72 (2H major+2H minor, m, 1′-H_B+3-H), 5.08–5.19 (3H major+2H minor, m, 3′-H+5-H), 5.25 (1H minor, 5-H), 5.81–5.88 (1H major+1 H minor, m, 2′-H), 6.04 (1H major+1H minor, dt, *J*=7.8, 1.5 Hz, 6-H), 6.96 (1H major+1H minor, dd, *J*=7.6, 1.7 Hz, Ar-*H*), 7.25 (1H major+1H minor, ddd, *J*=7.6, 7.3, 1.6 Hz, Ar-*H*); 7.31 (1H major+1H minor, ddd, *J*=8.0, 7.3, 1.7 Hz, Ar-*H*), 7.53 (1H major+1H minor, dd, *J*=8.0, 1.6 Hz, Ar-*H*); δ_C (100 MHz, $CDCl_3$) 25.2 (CH_2), 31.7 (CH_3), 34.2 (CH_2), 35.7 (C), 40.8(CH), 103.9 (CH), 117.2 (CH_2), 127.5 (CH), 128.5 (CH), 128.7 (CH), 131.1 (CH), 132.5 (CH), 136.0 (CH), 139.5 (C), 147.5 (C), 172.0 (C=O); *m*/*z* (FAB) 270 (MH^+, 100%), 212 (80) (Found MH^+, 270.1851. $C_{18}H_{24}NO$ requires *M*, 270.1858).

4.1.21. (3*S*)-3-Benzyl-1-(2-*tert*-butyl-phenyl)-3,4-dihydro-1*H*-pyridin-2-one 29c. From **24** (200 mg, 0.87 mmol), the resulting yellow oil was purified by flash column chromatography (10% EtOAc–petroleum ether) to yield the title compound (13:1 ratio of isomers) as a yellow oil (218 mg, 0.68 mmol, 79%), ν_{max} ($CHCl_3$)/cm^{-1} 2959, 2358, 1668; δ_H (400 MHz, $CDCl_3$) 1.40 (9H major+9H minor, s, C(CH_3)$_3$), 2.19 (1H major+1H minor, dddd, *J*=17.1, 8.7, 4.3, 1.6 Hz, 4-H_A), 2.36 (1H major+1H minor, dddd, *J*=17.1, 6.6, 4.6, 1.6 Hz, 4-H_B), 2.78–2.88 (2H major+2H minor, m, 3-H+1′-H_A), 3.37 (1H major, dd, *J*=12.6, 3.2 Hz, 1′-H_B), 3.46 (1H minor, d, *J*=10.2 Hz, 1′H_B), 5.16 (1H major, dt, *J*=7.5, 4.5 Hz, 5-H), 5.21 (1H minor, 5-H), 6.09 (1H major+1H minor, dt, *J*=7.5, 1.6 Hz, 6-H), 7.00 (1H major+1H minor, dd, *J*=7.6, 1.6 Hz, Ar-*H*), 7.01 (1H minor, dd, *J*=7.4, 1.5 Hz, Ar-*H*), 7.24–7.30 (4H major+4H minor, m, Ar-*H*); 7.31–7.37 (3H major+3H minor, m, Ar-*H*), 7.56 (1H major+1H minor, dd, *J*=8.0, 1.6 Hz, Ar-*H*); δ_C (100 MHz, $CDCl_3$) 24.6 (CH_2), 31.8 (CH_3), 35.6 (CH_2), 35.8 (C), 43.0 (CH), 103.8 (CH), 126.4 (CH), 127.5 (CH), 128.5 (CH), 128.6 (CH), 128.8 (CH), 129.4 (CH), 131.1 (CH), 132.6 (CH), 139.4 (C), 139.5 (C), 147.5 (C), 172.1 (C=O); *m*/*z* (FAB) 320 (MH^+, 100%), 262 (77) (Found MH^+, 320.2039. $C_{22}H_{26}NO$ requires *M*, 320.2014).

4.1.22. (3*S*)-1-(2-*tert*-Butyl-phenyl)-3-prop-2-ynyl-3,4-dihydro-1*H*-pyridin-2-one 29d. From **29** (200 mg. 0.87 mmol), the resulting yellow oil was purified by flash column chromatography (10% EtOAc–petroleum ether) to yield the title compound (12:1 ratio of isomers) as a solid (144 mg, 0.22 mmol, 62%), mp 105–108 °C (recrystallised from petroleum ether); ν_{max} ($CHCl_3$)/cm^{-1} 3307, 2963, 2337, 1673, 1607; δ_H (400 MHz, $CDCl_3$) 1.35 (9H major, s, C(CH_3)$_3$), 1.37 (9H minor, s, C(CH_3)$_3$), 2.01 (1H minor, apparent t, *J*=2.7 Hz, 3′-H), 2.03 (1H major, apparent t, *J*=2.7 Hz, 3′-H), 2.42–2.51 (2H major+2H minor, m, 1′-H_A+4-H_A), 2.71–2.84 (2H major+2H minor, m, 4-H_B+3-H), 2.91 (1H major+1H minor, ddd, *J*=17.0, 3.9, 2.7 Hz, 1′-H_B), 5.24 (1H major, dt, *J*=6.6, 3.3 Hz, 5-H), 5.32 (1H minor, 5-H), 6.05 (1H major+1H minor, dt, *J*=6.6, 1.8, 6-H), 6.99 (1H major+1H minor, dd, *J*=7.7, 1.5 Hz, Ar-*H*), 7.24 (1H major+1H minor, ddd, *J*=7.7, 7.3, 1.6 Hz, Ar-*H*); 7.32 (1H major+1H minor, ddd, *J*=8.1, 7.3, 1.5 Hz, Ar-*H*), 7.53 (1H major+1H minor, dd, *J*=8.1, 1.6 Hz, Ar-*H*); δ_C (100 MHz, $CDCl_3$) 19.4 (CH_2), 25.6 (CH_2), 31.7 (CH_3), 35.7 (C), 40.4 (CH), 70.0 (CH), 82.0 (C), 104.2 (CH), 127.5 (CH), 128.7 (CH), 128.8 (CH), 131.1 (CH), 132.5 (CH), 139.1 (C), 147.2 (C), 170.4 (C=O); *m*/*z* (FAB) 268 (MH^+, 64%), 210 (48) (Found MH^+, 268.1718. $C_{18}H_{22}NO$ requires *M*, 268.1701).

4.1.23. (3*R*)-1-(2-*tert*-Butyl-phenyl)-3-pentyl-3,4-dihydro-1*H*-pyridin-2-one 29e. From **29** (200 mg, 0.87 mmol), the resulting yellow oil was purified by flash column chromatography (4% EtOAc–petroleum ether) to yield the title compound (7:1 ratio of isomers) as an oil (229 mg, 0.77 mmol, 88%), ν_{max} ($CHCl_3$)/cm^{-1} 2929, 2860, 1667, 1572; δ_H (400 MHz, $CDCl_3$) 0.91 (3H major+3H minor, t, *J*=7.0 Hz, 5′-H) 1.27–1.55 (16H major+16H minor, m, C(CH_3)$_3$ +1′-H_A+2′-H +3′H+4′-H), 1.90–1.93 (1H major+1H minor, m, 1′-H_B), 2.25 (1H major+1H minor, dddd, *J*=19.1, 10.6, 4.4, 1.5 Hz, 4-H_A), 2.52–2.58 (2H

major+2H minor, m, 3-H+4-H_B), 5.16 (1H major, dt, J=7.7, 4.4 Hz, 5-H), 5.23 (1H minor, 5-H), 6.03 (1H major+1H minor, dt, J=7.7, 1.5 Hz, 6-H), 6.95 (1H major+1H minor, dd, J=7.6, 1.7 Hz, Ar-*H*), 7.28 (1H major+1H minor, ddd, J=7.6, 7.3, 1.6 Hz, Ar-*H*), 7.34 (1H major+1H minor, ddd, J=8.0, 7.3, 1.7 Hz, Ar-*H*), 7.52 (1H major+1H minor, dd, J=8.0, 1.6 Hz, Ar-*H*); δ_C (100 MHz, $CDCl_3$) 14.1 (CH_3), 22.6 (CH_2), 25.7 (CH_2), 26.9 (CH_2), 29.7 (CH_2), 31.7 (CH_3), 31.9 (CH_2), 35.7 (C), 41.2 (CH), 103.8 (CH), 127.5 (CH), 128.4 (CH), 128.7 (CH), 131.1 (CH), 132.4 (CH), 139.7 (C), 147.6 (C), 172.8 (C=O); *m*/*z* (FAB) 300 (MH^+, 54%), 242 (64) (Found MH^+, 300.2339. $C_{20}H_{30}NO$ requires *M*, 300.2327).

4.1.24. (3*R*)-1-(2-*tert*-Butyl-phenyl)-3-ethyl-3,4-dihydro-1*H*-pyridin-2-one 29f. From **24** (200 mg, 0.87 mmol), the resulting yellow oil was purified by flash column chromatography (10% EtOAc–petroleum ether) to yield the title compound (10:1 ratio of isomers) as an oil (153 mg, 0.60 mmol, 61%), ν_{max} ($CHCl_3$)/cm^{-1} 2966, 2877, 1687; δ_H (400 MHz, $CDCl_3$) 1.03 (3H major+3H minor, t, J=7.5 Hz, 2′-H) 1.37 (9H major+9H minor, s, C(CH_3)$_3$), 1.55–1.64 (1H major+1H minor, m, 1′-H_A), 1.98 (1H major+1H minor, dqd, J=13.4, 7.5, 5.6 Hz, 1′-H_B), 2.28 (1H major+1 H minor, dddd, J=16.6, 8.2, 4.4, 1.3 Hz, 4-H_A), 2.45–2.58 (2H major+2H minor, m, 4-H_B+3-H), 5.17 (1H major, dt, J=7.8, 4.4 Hz, 5-H), 5.23 (1H minor, 5-H), 6.03 (1H major+1H minor, dt, J=7.8, 1.3 Hz, 6-H), 6.95 (1H major+1H minor, dd, J=7.6, 1.8 Hz, Ar-*H*), 7.22–7.51 (2H major+2H minor, m, Ar-*H*), 7.52 (1H major+1H minor, dd, J=8.0, 1.6 Hz, Ar-*H*), δ_C (100 MHz, $CDCl_3$) 11.7 (CH_3), 22.9 (CH_2), 25.3 (CH_2), 31.7 (CH_3), 35.7 (C), 42.7 (CH), 103.8 (CH), 127.6 (CH), 128.4 (CH), 128.7 (CH), 131.1 (CH), 132.4 (CH), 139.7 (C), 147.5 (C), 172.6 (C=O); *m*/*z* (TOF) 280 (M+Na)$^+$ (Found M+Na^+, 280.1682. $C_{17}H_{23}NO$+Na requires *M*, 280.1677).

4.1.25. (3*R*)-1-(2-*tert*-Butyl-phenyl)-3-phenylsulfanyl-3,4-dihydro-1*H*-pyridin-2-one *anti*-29g, (3*S*)-1-(2-*tert*-butyl-phenyl)-3-phenylsulfanyl-3,4-dihydro-1*H*-pyridin-2-one *syn*-29g. To a stirred solution of di*iso*propylamine (0.12 mL, 0.87 mmol) in THF (5 mL) at −78 °C was added ^{n}BuLi (0.56 mL of a 1.60 M solution in hexanes), followed by warming to room temperature for 15 min, then recooling to −78 °C. To the resulting LDA solution was added a solution of enamide **24** (200 mg, 0.87 mmol) in THF (5 mL). After 1 h at −78 °C, phenyl disulfide (1.90 g, 8.70 mmol) in a solution of THF (4 mL) was added and the reaction mixture stirred at −78 °C for 1 h. A solution of saturated NH_4Cl solution (5 mL) was then added and the reaction mixture was allowed to warm to room temperature. The reaction mixture was extracted with EtOAc (2×40 mL), the combined organic extracts were washed with brine (40 mL), dried ($MgSO_4$) and evaporated under reduced pressure. The resulting crude product was purified by biotage chromatography (2–20% EtOAc–petroleum ether) to give firstly the *anti*-adduct of **29g** (R_f 0.8, 70:30 petroleum ether–EtOAc) (10:1 ratio of *anti*:bis products) as a white solid (200 mg, 0.59 mmol, 68%), mp 85–90 °C; ν_{max} ($CHCl_3$/cm^{-1} 2962, 1672, 1488, 1467, 1440, 1396, 1356, 1299, 1145; δ_H (500 MHz, $CDCl_3$) 1.37 (9H, s, C(CH_3)$_3$), 2.69 (1H, ddd, J=17.4, 6.3, 3.4 Hz, 4-H_A), 2.96 (1H, dddd, J=17.4, 5.6, 2.9, 2.8 Hz, 4-H_B), 3.99 (1H, dd, J=5.6, 3.4 Hz, 3-H), 5.23 (1H, ddd, J=7.6, 6.3, 2.8 Hz, 5-H), 6.14 (1H, dd, J=7.6, 2.9 Hz, 6-H), 7.06 (1H, dd, J=7.6, 1.2 Hz, Ar-*H*), 7.25–7.34 (5H, m, Ar-*H*), 7.52 (1H, dd, J=7.8, 1.2 Hz, Ar-*H*), 7.61 (2H, d, J=7.6 Hz, Ar-*H*); δ_C (125 MHz, $CDCl_3$) 27.4 (CH_2), 31.8 (CH_3), 35.8 (C), 48.7 (CH), 102.2 (CH), 127.8 (2×CH), 128.6 (CH), 128.8 (CH), 129.0 (2×CH), 130.3 (CH), 132.8 (2×CH), 133.3 (CH), 136.7 (C), 139.4 (C), 147.8 (C), 168.0 (C=O); *m*/*z* (EI) (Found M^+, 337.1490. $C_{21}H_{23}NOS$ requires *M*, 337.1500); followed by the *syn*-adduct of **29g** (R_f 0.75, 30:70 petroleum ether–EtOAc) as an oil (30.0 mg, 0.09 mmol, 15%), ν_{max} ($CHCl_3$)/cm^{-1} 2962, 2873, 1672, 1587, 1485, 1440, 1398, 1358, 1303, 1146; δ_H (500 MHz, $CDCl_3$) 1.35 (9H, s, C(CH_3)$_3$), 2.63 (1H, ddd, J=17.8, 5.3, 5.2 Hz, 4-H_A), 2.97 (1H, ddd, J=17.8, 6.2, 3.4, 2.2 Hz, 4-H_B), 4.10 (1H, dd, J=6.3, 6.2 Hz, 3-H), 5.21 (1H, ddd, J=7.6, 5.2, 3.4 Hz, 5-H), 6.10 (1H, dd, J=7.6, 2.2 Hz, 6-H), 7.01 (1H, dd, J=7.6, 1.2 Hz, Ar-*H*), 7.21–7.33 (5H, m, Ar-*H*), 7.51 (1H, dd, J=7.9, 1.2 Hz, Ar-*H*), 7.57 (2H, dd, J=7.6, 1.3 Hz, Ar-*H*); δ_C (125 MHz, $CDCl_3$) 28.1 (CH_2), 31.6 (CH_3), 35.7 (C), 48.4 (CH), 103.4 (CH), 127.3 (CH), 127.5 (CH), 128.5 (CH), 128.8 (CH), 129.0 (2×CH), 131.3 (CH), 131.8 (2×CH), 133.0 (CH), 134.2 (C), 139.4 (C), 147.7 (C), 167.6 (C=O); *m*/*z* (EI) (Found M^+, 337.1486. $C_{21}H_{23}NOS$ requires *M*, 337.1500).

4.1.26. 1-(2-*tert*-Butyl-phenyl)-3-(3-trimethylsilanyl-prop-2-ynyl)-3,4-dihydro-1*H*-pyridin-2-one 29h. To a stirred solution of di*iso*propylamine (0.03 mL, 0.22 mmol) in THF (2 mL) at −78 °C was added ^{n}BuLi (0.14 mL of a 1.60 M solution in hexanes), followed by warming to room temperature for 15 min, then recooled to −78 °C. To the resulting LDA, a solution of pyridin-2-one **24** (50.0 mg, 0.22 mmol) in THF (2 mL) was added. After 1 h TMS-propargyl bromide (0.31 mL, 2.20 mmol) was added and the reaction mixture stirred at −78 °C for 1 h, saturated NH_4Cl solution (5 mL) was then added and the reaction mixture was allowed to warm to room temperature. The reaction mixture was extracted with EtOAc (2×20 mL), the combined organic extracts were washed with brine (20 mL), dried ($MgSO_4$) and evaporated under reduced pressure. The resulting crude product was purified by biotage chromatography (5% EtOAC–petroleum ether) to yield the title compound (15:1 ratio of isomers) as a yellow oil (50.0 mg, 0.15 mmol, 68%), ν_{max} ($CHCl_3$)/cm^{-1} 2961, 2908, 1673, 1488, 1440, 1399, 1364, 1286, 1151; δ_H (500 MHz, $CDCl_3$) 0.18 (9H major+9H minor, s, Si(CH_3)$_3$), 1.35 (9H+9H minor, s, C(CH_3)$_3$), 2.38–2.51 (2H major+2H minor, m with dd at 2.47, J=17.1, 10.2 Hz, 7-H and 4-H_A), 2.72–2.82 (2H major+2H minor, m, 4-H_B and 3-H), 2.96 (1H major+1H minor, dd, J=17.1, 3.7 Hz, 7-H_B), 5.24 (1H major, ddd, J=7.7, 5.0, 3.5 Hz, 5-H), 5.27 (1H minor, 5-H), 6.05 (1H major+1H minor, dd, J=7.7, 1.9 Hz, 6-H), 6.98 (1H major+1H minor, dd, J=7.7, 1.4 Hz, Ar-*H*), 7.24 (1H major+1H minor, ddd, J=7.7, 7.5, 1.2 Hz, Ar-*H*), 7.31 (1H major+1H minor, ddd, J=8.2, 7.5, 1.4 Hz, Ar-*H*), 7.52 (1H major+1H minor, dd, J=8.2, 1.2 Hz, Ar-*H*); δ_C (125 MHz, $CDCl_3$) 0.18 (CH_3), 20.9 (CH_2), 25.6 (CH_2), 31.7 (CH_3), 35.7 (C), 40.5 (CH), 86.4 (C), 104.3 (CH), 104.7 (C), 127.4 (CH), 128.6 (CH), 128.7 (CH), 131.1 (CH), 132.5 (CH), 139.2 (C), 147.2 (C), 170.5 (C=O); *m*/*z* (EI) (Found M^+, 339.2026. $C_{21}H_{29}NOSi$ requires *M*, 339.2018).

4.1.27. Kinetic resolution of 1-(2-*tert*-butyl-phenyl)-3,4-dihydro-1*H*-pyridin-2-one 24. To a stirred solution of chiral diamine[24] (273 mg, 0.65 mmol) in THF (5 mL) at −78 °C was added ^{n}BuLi (0.42 mL of a 1.60 M solution in hexanes), followed by warming to room temperature for 15 min, then recooled to −78 °C. To the resulting chiral base, a solution of pyridin-2-one **24** (200 mg, 0.87 mmol) in THF (5 mL) was added. After 1 h benzyl bromide (1.03 mL, 8.70 mmol) was added and the reaction mixture stirred at −78 °C for 1 h, saturated NH_4Cl solution (5 mL) was then added and the reaction mixture was allowed to warm to room temperature. The reaction mixture was extracted with EtOAc (2×40 mL), the combined organic extracts were washed with brine (20 mL), dried ($MgSO_4$) and evaporated under reduced pressure. The crude NMR indicated the reaction had proceeded to 74% conversion. The ee of the remaining starting material (73%) was determined by HPLC analysis using a Chirapak AD-H column [25 cm ×0.46 cm i.d.; 3% *i*-PrOH in hexane; flow rate, 0.4 mL/min; (−)-**24**; t_R=25.7 min, (+)-**24**; t_R=29.0 min].

The reaction was also carried using 0.25 equiv. of chiral base [chiral amine (92.0 mg, 0.22 mmol) and ^{n}BuLi (0.14 mL of a 1.60 M solution in hexanes)] to give enamide **24** of 15% ee; and 0.5 equiv. of chiral base [chiral amine (184 mg, 0.44 mmol) and ^{n}BuLi (0.27 mL of a 1.60 M solution in hexanes)] to give enamide **24** of 62% ee.

4.1.28. (3*R*)-(+)-Methylglutaric anhydride 32. A solution of (*R*)-(−)-2-methylglutaric acid **31** (2.00 g, 14.0 mmol) in Ac_2O (50 mL) was refluxed for 24 h. Removal of excess Ac_2O by azeotropic codistillation with dry toluene (27×40 mL) yielded a brown solid **32** (1.75 g, 13.7 mmol, 98%), which was used without further purification, mp 48–50 °C (lit.[20] 35–36 °C); $[\alpha]_D^{23}$=+38.9 (*c* 1.50, $CHCl_3$) (lit.[20] $[\alpha]_D$=+44.4 (neat); ν_{max} ($CHCl_3$)/cm^{-1} 2978, 2941, 2883, 1814, 1770, 1460, 1384, 1352, 1326; δ_H (400 MHz, $CDCl_3$) 1.38 (3H, d, *J*=6.9 Hz, 3-Me), 1.78 (1H, dddd, *J*=13.8, 12.1, 12.0, 5.1 Hz, 4-H_A), 2.07 (1H, dddd, *J*=12.0, 8.0, 5.3, 3.5 Hz, 4-H_B), 2.66 (1H, dqd, *J*=13.8, 6.9, 5.3 Hz, 3-H), 2.73 (1H, ddd, *J*, 18.2, 12.1, 5.9 Hz, 5-H_A), 2.93 (1H, ddd, *J*=18.2, 5.1, 3.5 Hz, 5-H_B); δ_C (125 MHz, $CDCl_3$) 15.8 (CH_3), 24.4 (CH_2), 30.2 (CH_2), 35.8 (CH), 166.9 (C═O), 169.7 (C═O); *m*/*z* (EI) (Found M$^+$, 128.0479. $C_6H_8O_3$ requires *M*, 128.0474).

The above procedure was also carried out using racemic 2-methylglutaric acid and yielded the racemic anhydride (1.80 g, 14.0 mmol, 100%).

4.1.29. (*M*,3*R*)-1-(2-*tert*-Butyl-phenyl)-3-methyl-piperidine-2,6-dione *anti*-33 and (*P*,3*R*)-1-(2-*tert*-butyl-phenyl)-3-methyl-piperidine-2,6-dione *syn*-33. A solution of 2-*tert*-butylaniline **27** (1.69 mL, 10.8 mmol) and (*R*)-(+)-2-methylglutaric anhydride **32** (1.67 g, 13.0 mmol) in toluene (50 mL) was refluxed for 15 h, evaporated and subsequently heated at 80 °C with NaOAc (5.32 g, 64.8 mmol) in Ac_2O (50 mL) for 15 h then poured into H_2O (150 mL), extracted with $CHCl_3$ (4×60 mL), washed with 2 N NaOH (60 mL), brine (60 mL), dried ($MgSO_4$) and concentrated to yield the crude product, which was purified by biotage chromatography (10–60% EtOAc–petroleum ether) to give firstly the least polar diastereoisomer *anti*-**33** (R_f 0.9, 1:1 petroleum ether–EtOAc) as an oil which slowly solidified (1.20 g, 4.60 mmol, 43%), mp 48–52 °C; $[\alpha]_D^{25}$=+20.6 (*c* 1.0, $CHCl_3$); ν_{max} ($CHCl_3$)/cm^{-1} 2962, 1732, 1682, 1488, 1460, 1355, 1311, 1284; δ_H (500 MHz, $CDCl_3$) 1.29 (9H, s, C(CH_3)$_3$), 1.39 (3H, d, *J*=6.9 Hz, 3-Me), 1.89 (1H, dddd, *J*=13.7, 11.8, 11.4, 4.6 Hz, 4-H_A), 2.17 (1H, dddd, *J*=13.7, 5.2, 5.0, 4.7 Hz, 4-H_B), 2.72 (1H, m, 3-H), 2.76 (1H, ddd, *J*=17.2, 11.9, 5.2 Hz, 5-H_A), 2.95 (1H, ddd, *J*=17.2, 4.7, 4.6 Hz, 5-H_B), 6.78 (1H, dd, *J*=7.7, 1.3 Hz, Ar-*H*), 7.25 (1H, ddd, *J*=7.7, 7.5 Hz, 1.4, Ar-*H*), 7.35 (1H, ddd, *J*=7.9, 7.5, 1.3 Hz, Ar-*H*), 7.57 (1H, dd, *J*=7.9, 1.4 Hz, Ar-*H*); δ_C (125 MHz, $CDCl_3$) 16.0 (CH_3), 25.5 (CH_2), 31.7 (CH_3), 33.0 (CH_2), 35.9 (C), 37.9 (CH), 127.2 (CH), 128.9 (CH), 129.1 (CH), 131.0 (CH), 133.5 (C), 146.7 (C), 173.5 (C═O), 176.1 (C═O); *m*/*z* (EI) (Found M$^+$, 259.1568. $C_{16}H_{21}NO_2$ requires *M*, 259.1572). The ee of *anti*-**33** (72% ee) was determined by HPLC analysis using a Chirapak AD-H column [25 cm×0.46 cm i.d.; 3% *i*-PrOH in hexane; flow rate, 0.4 mL/min; (−)-*anti*-**33**; t_R=34.2 min, (+)-*anti*-**33**; t_R=38.7 min]; followed by the most polar diastereoisomer *syn*-**33** (R_f 0.8, 1:1 petroleum ether–EtOAc) as a white solid (0.75 g, 3.00 mmol, 27%), mp 172–177 °C; $[\alpha]_D^{25}$=+19.0 (*c* 0.93, $CHCl_3$); ν_{max} ($CHCl_3$)/cm^{-1} 2970, 1732, 1682, 1602, 1460, 1356, 1310, 1171; δ_H (500 MHz, $CDCl_3$) 1.29 (9H, s, C(CH_3)$_3$), 1.40 (3H, d, *J*=7.0 Hz, 3-Me), 1.92 (1H, dddd, *J*=14.2, 12.3, 12.2, 4.7 Hz, 4-H_A), 2.14 (1H, dddd, *J*=14.2, 5.3, 4.5, 4.4 Hz, 4-H_B), 2.74 (1H, m, 3-H), 2.78 (1H, ddd, *J*=17.8, 12.3, 5.3 Hz, 5-H_A), 2.96 (1H, ddd, *J*=17.8, 4.7, 4.4 Hz, 5-H_B), 6.80 (1H, dd, *J*=7.6, 1.2 Hz, Ar-*H*), 7.27 (1H, ddd, *J*=7.6, 7.3, 1.2 Hz, Ar-*H*), 7.35 (1H, ddd, *J*=7.8, 7.3, 1.2 Hz, Ar-*H*), 7.56 (1H, dd, *J*=7.8, 1.2 Hz, Ar-*H*); δ_C (125 MHz, $CDCl_3$) 16.5 (CH_3), 24.8 (CH_2), 31.8 (CH_3), 32.9 (CH_2), 35.9 (C), 38.0 (CH), 127.3 (CH), 128.8 (CH), 128.9 (CH), 131.1 (CH), 134.0 (C), 146.7 (C), 173.2 (C═O), 175.8 (C═O); *m*/*z* (EI) (Found M$^+$, 259.1563. $C_{16}H_{21}NO_2$ requires *M*, 259.1572). The ee of *syn*-**33** (78% ee) was determined by HPLC analysis using a Chirapak AD-H column [25 cm×0.46 cm i.d.; 3% *i*-PrOH in hexane; flow rate, 0.4 mL/min; (+)-*syn*-**33**; t_R=42.4 min, (−)-*syn*-**33**; t_R=47.3 min].

The above procedure was also carried out using racemic 2-methylglutaric anhydride and yielded the racemic diastereoisomers *anti*-**33** (1.30 g, 5.00 mmol, 40%) and *syn*-**33** (0.42 g, 1.62 mmol, 14%).

4.1.30. (*M*,3*R*)-1-(2-*tert*-Butyl-phenyl)-3-methyl-3,4-dihydro-1*H*-pyridin-2-one 29a and (*P*)-1-(2-*tert*-butyl-phenyl)-5-methyl-3,4-dihydro-1*H*-pyridin-2-one 34. DIBAL (3.47 mL of a 1 M solution in CH_2Cl_2) was added dropwise to a stirred solution of imide *anti*-**33** (500 mg, 1.93 mmol) in CH_2Cl_2 (10 mL) at −78 °C. After 45 min stirring at −78 °C, H_2O (4 mL), followed by 2 N NaOH (2 mL) were added and the reaction mixture poured into a saturated solution of Rochelles salt (25 mL). The mixture was then extracted with CH_2Cl_2 (2×15 mL). The combined extracts were then washed with brine (20 mL), dried ($MgSO_4$), and evaporated under reduced pressure to give an oil which was dissolved in CH_2Cl_2 (15 mL). To this solution, at 0 °C, was added Et_3N (0.81 mL, 5.79 mmol), then MsCl (0.22 mL, 2.90 mmol). The reaction mixture was

stirred at room temperature for 1 h, then washed with H_2O (25 mL), a saturated solution of $NaHCO_3$ (25 mL), and brine (25 mL), dried ($MgSO_4$), and evaporated under reduced pressure. The resulting oil was purified by biotage chromatography (5–30% EtOAc–petroleum ether), to give firstly **29a** (2:1 ratio of isomers) (R_f 0.75, 1:1 petroleum ether–EtOAc) as an oily solid (110 mg, 0.45 mmol, 23%), $[\alpha]_D^{27}$=+46.6 (*c* 0.86, $CHCl_3$). All remaining data was in agreement with that previously reported for **29a**; followed by **34** (R_f 0.5, 1:1 petroleum ether–EtOAc) as an oily solid (110 mg, 0.45 mmol, 23%): $[\alpha]_D^{27}$=+10.3 (*c* 0.86, $CHCl_3$); ν_{max} ($CHCl_3$)/cm^{-1} 2967, 2936, 1666, 1488, 1393, 1364, 1285; δ_H (500 MHz, $CDCl_3$) 1.37 (9H, s, $C(CH_3)_3$), 1.77 (3H, s, 5-Me), 2.39 (2H, m, 4-H), 2.67 (2H, m, 3-H), 5.83 (1H, d, *J*=1.2 Hz, 6-H), 7.00 (1H, dd, *J*=7.5, 1.4 Hz, Ar-*H*), 7.25 (1H, ddd, *J*=7.7, 7.5, 1.5 Hz, Ar-*H*), 7.31 (1H, ddd, *J*=8.0, 7.7, 1.4 Hz, Ar-*H*), 7.52 (1H, dd, *J*=8.0, 1.5 Hz, Ar-*H*); δ_C (125 MHz, $CDCl_3$) 19.5 (CH_3), 26.1 (CH_2), 31.7 (CH_3), 31.9 (CH_2), 35.7 (C), 114.6 (C), 127.5 (CH), 127.6 (CH), 128.5 (CH), 128.7 (CH), 131.0 (CH), 139.7 (C), 147.5 (C), 169.6 (C=O); *m*/*z* (EI) (Found M^+, 243.1624. $C_{16}H_{21}NO$ requires *M*, 243.1623).

4.1.31. (*M*,3*R*)-1-(2-*tert*-Butyl-phenyl)-3-methyl-3,4-dihydro-1*H*-pyridin-2-one 29a. To a stirred solution of di*iso*propylamine (0.07 mL, 0.53 mmol) in THF (3 mL) at −78 °C was added ^{n}BuLi (0.33 mL of a 1.60 M solution in hexanes), followed by warming to room temperature for 15 min, then recooled to −78 °C. To the resulting LDA, a solution of *M*-pyridin-2-one **24** (73% ee) (100 mg, 0.44 mmol) in THF (3 mL) was added. After 1 h MeI (0.27 mL, 4.40 mmol) was added and the reaction mixture stirred at −78 °C for 1 h, saturated NH_4Cl solution (3 mL) was then added and the reaction mixture was allowed to warm to room temperature. The reaction mixture was extracted with EtOAc (2×20 mL), the combined organic extracts were washed with brine (20 mL), dried ($MgSO_4$) and evaporated under reduced pressure. The resulting crude product was purified by biotage chromatography (10% EtOAc–petroleum ether) to yield the title compound (7:1 ratio of isomers) as an oily solid (75 mg, 0.03 mmol, 70%), $[\alpha]_D^{27}$=+22.6 (*c* 0.69, $CHCl_3$). All remaining data was in agreement with that previously reported for **29a**.

For a direct comparison of the samples of (*M*,3*R*)-1-(2-*tert*-butyl-phenyl)-3-methyl-3,4-dihydro-1*H*-pyridin-2-one **29a**, synthesised from the chiral diacid precursor (R)-(−)-**31** and from the enantioenriched enamide *M*-**24**, both samples were thermally equilibrated to a ratio of 1.1:1 (from 2:1 and 7:1, respectively) and the resulting optical rotations measured as: $[\alpha]_D^{26}$=+54.8 (*c* 0.54, $CHCl_3$) and $[\alpha]_D^{27}$=+55.4 (*c* 0.24, $CHCl_3$), respectively.

4.1.32. 1,6-Diphenyl-piperidin-2-one 35a. A solution of enamide **24** (50.0 mg, 0.22 mmol) and $AlCl_3$ (294 mg, 2.20 mmol) in benzene (20 mL) was heated at 50 °C for 12 h. After cooling, the reaction mixture was poured into H_2O (20 mL) and extracted with $CHCl_3$ (3×20 mL). Combined extracts were washed with brine (20 mL), dried ($MgSO_4$), and evaporated under reduced pressure to give the crude product, which was purified by flash column chromatography (20–70% EtOAc–petroleum ether) to give the title compound as a pale orange solid (50.0 mg, 0.20 mmol, 90%), mp 125–127 °C; ν_{max} ($CHCl_3$)/cm^{-1} 2953, 1639, 1596, 1494, 1456, 1404, 1344, 1301; δ_H (400 MHz, $CDCl_3$) 1.83 (1H, m, 4-H_A), 1.93 (1H, m, 4-H_B), 2.03 (1H, m, 5-H_A), 2.36 (1H, dddd, *J*=13.5, 10.4, 5.3, 3.6 Hz, 5-H_B), 2.68 (1H, ddd, *J*=18.1, 8.3, 6.7 Hz, 3-H_A), 2.76 (1H, dt, *J*=18.1, 6.1 Hz, 3-H_B), 5.03 (1H, t, *J*=5.1 Hz, 6-H), 7.12–7.16 (3H, m, Ar-*H*), 7.22–7.26 (5H, m, Ar-*H*), 7.27–7.34 (2H, m, Ar-*H*); δ_C (125 MHz, $CDCl_3$) 17.5 (CH_2), 32.2 (CH_2), 32.5 (CH_2), 65.0 (CH), 126.6 (CH), 126.9 (2×CH), 127.2 (2×CH), 127.4 (CH), 128.4 (2×CH), 128.7 (2×CH), 141.3 (C), 142.3 (C), 170.7 (C=O); *m*/*z* (EI) (Found M^+, 251.1308. $C_{17}H_{17}NO$ requires *M*, 251.1310).

The above reaction was also carried out using enantioenriched (63% ee) enamide **24** (50.0 mg, 0.22 mmol) to yield the product **35a** described above (40.0 mg, 0.16 mmol, 72%, showing no erosion of ee (63% ee). The ee was determined by HPLC analysis using a Chirapak AD-H column [25 cm×0.46 cm i.d.; 5% *i*-PrOH in hexane; flow rate, 1.0 mL/min; (+)-**35a**; t_R=35.9 min, (−)-**35a**; t_R=30.9 min]; $[\alpha]_D^{25}$=+66.2 (*c* 0.52, $CHCl_3$).

4.1.33. 1-Phenyl-6-tolyl-piperidin-2-one 35b. A solution of enamide **24** (50.0 mg, 0.22 mmol) and $AlCl_3$ (294 mg, 2.20 mmol) in toluene (20 mL) was heated at 50 °C for 12 h. After cooling, the reaction mixture was poured into H_2O (20 mL) and extracted with $CHCl_3$ (3×20 mL). Combined extracts were washed with brine (20 mL), dried ($MgSO_4$), and evaporated under reduced pressure to give the crude product, which was purified by flash column chromatography (CH_2Cl_2, then 10–60% EtOAc–petroleum ether) to give the title compound (4:1 ratio of isomers) as pale brown solid (50.0 mg, 0.19 mmol, 86%), mp 112–115 °C; ν_{max} ($CHCl_3$)/cm^{-1} 2953, 1638, 1596, 1494, 1455, 1402, 1335, 1306; δ_H (500 MHz, $CDCl_3$) 1.75–1.82 (1H major+1H minor, m, 4-H_A), 1.87–2.00 (2H major+2H minor, m, 5-H_A+4-H_B), 2.20 (3H minor, Ar-Me), 2.26–2.34 (4H major, m with s at 2.29, 5-H_B +Ar-Me and 1H minor, 5-H_B), 2.64 (1H major+1H minor, ddd, *J*=18.1, 8.6, 6.8 Hz, 3-H_A), 2.73 (1H major+1H minor, dt, *J*=18.1, 6.0 Hz, 3-H_B), 4.98 (1H major, t, *J*=5.1 Hz, 6-H), 5.25 (1H minor, 6-H), 7.02–7.08 (3H minor, m, Ar-*H*), 7.09–7.15 (7H major, m, Ar-*H* and 2H minor, m, Ar-*H*), 7.20–7.26 (2H major, m, Ar-*H* and 3H minor, m, Ar-*H*), 7.39 (1H minor, d, *J*=7.5 Hz, Ar-*H*); δ_C (125 MHz, $CDCl_3$) 17.6 (CH_2), 21.1 (CH_3), 32.3 (CH_2), 32.6 (CH_2), 64.8 (CH), 126.5 (CH), 126.7 (2×CH), 127.2 (2×CH), 128.7 (2×CH), 129.0 (2×CH), 137.0 (C), 138.3 (C), 142.4 (C), 170.8 (C=O); *m*/*z* (EI) (Found M^+, 265.1469. $C_{18}H_{19}NO$ requires *M*, 265.1467).

4.1.34. 6-(4-Bromo-phenyl)-1-phenyl-piperidin-2-one 35c. A solution of enamide **24** (50.0 mg, 0.22 mmol) and $AlCl_3$ (294 mg, 2.20 mmol) in bromobenzene (15 mL) was heated at 50 °C for 12 h. After cooling, the reaction mixture was poured into H_2O (15 mL) and extracted with $CHCl_3$ (3×20 mL). Combined extracts were washed with brine (20 mL), dried ($MgSO_4$), and evaporated under reduced pressure to give the crude product, which was purified by flash column chromatography (CH_2Cl_2, then 10–70% EtOAc–petroleum ether) to give firstly the major isomer (R_f 0.3, 70:30 petroleum ether–EtOAc) as a pale brown

solid (35.0 mg, 0.11 mmol, 48%), mp 117–120 °C; ν_{max} ($CHCl_3$)/cm^{-1} 2954, 1642, 1596, 1494, 1465, 1406, 1340; δ_H (500 MHz, $CDCl_3$) 1.83–1.90 (2H, m, 4-H_A and 4-H_B), 2.07–2.18 (1H, m, 5-H_A), 2.29–2.36 (1H, m, 5-H_B), 2.68 (1H, dt, J=18.1, 7.9 Hz, 3-H_B), 2.77 (1H, dt, 18.1, 5.6, 3-H_A), 5.48 (1H, t, J=5.1 Hz, 6-H), 7.08–7.18 (4H, m, Ar-*H*), 7.24–7.28 (2H, m, Ar-*H*), 7.32 (1H, t, J=7.5 Hz, Ar-*H*), 7.44 (1H, d, J=7.6 Hz, Ar-*H*), 7.47 (1H, d, J=8.2 Hz, Ar-*H*); δ_C (125 MHz, $CDCl_3$) 17.5 (CH_2), 29.6 (CH_2), 32.7 (CH_2), 63.9 (CH), 122.5 (C), 126.8 (CH), 127.0 (2×CH), 127.3 (CH), 128.9 (3×CH), 129.1 (CH), 133.4 (CH), 139.7 (C), 142.0 (C), 171.0 (C=O); *m/z* (EI) (Found M^+, 329.0421 and 331.0346. $C_{17}H_{16}{}^{79}BrNO$ requires *M*, 329.0415 and $C_{17}H_{16}{}^{81}BrNO$ requires *M*, 331.0395); and secondly, a minor regioisomer (R_f 0.3, 70:30 petroleum ether–EtOAc) (8:1 mixture of atropisomers) as a brown oil (15.0 mg, 0.05 mmol, 20%), ν_{max} ($CHCl_3$)/cm^{-1} 2954, 1643, 1595, 1491, 1455, 1396, 1333, 1298; δ_H (500 MHz, $CDCl_3$) 1.81–2.00 (3H major+3H minor, m, 4-H_A and 4-H_B and 5-H_A), 2.31–2.37 (1H major+1H minor, m, 5-H_B), 2.66 (1H major+1H minor, ddd, J=17.9, 8.1, 7.0 Hz, 3-H_A), 2.73 (1H major+1H minor, dt, J=17.9, 6.3 Hz, 3-H_B), 4.99 (1H major, t, J=5.2 Hz, 6-H), 5.02 (1H minor, 6-H), 7.10–7.18 (4H major+4H minor, m with d at 7.11, J=8.1 Hz, Ar-*H*), 7.23–7.32 (4H major+4H minor, m, Ar-*H*), 7.43 (1H major+1H minor, d, J=8.3 Hz, Ar-*H*); δ_C (125 MHz, $CDCl_3$) 17.6 (CH_2), 32.3 (CH_2), 32.6 (CH_2), 64.6 (CH), 121.4 (C), 126.9 (CH), 127.3 (2×CH), 128.7 (2×CH), 129.0 (2×CH), 131.7 (2×CH), 140.6 (C), 142.1 (C), 170.7 (C=O); *m/z* (EI) (Found M^+, 329.0410. $C_{17}H_{16}^{79}BrNO$ requires *M*, 329.0415).

The above reaction was also carried out using enantioenriched (73% ee) enamide **24** (50.0 mg, 0.22 mmol) to yield the product **35c** described above (20.0 mg, 0.06 mmol, 28%, showing some erosion of ee (57% ee). The ee was determined by HPLC analysis using a Chirapak AD-H column [25 cm×0.46 cm i.d.; 5% *i*-PrOH in hexane; flow rate, 1.0 mL/min; (+)-**35c**; t_R=32.9 min, (−)-**35c**; t_R=29.5 min]; $[\alpha]_D^{25}$=+21.1 (*c* 0.36, $CHCl_3$).

4.1.35. 6-(4-Iodo-phenyl)-1-phenyl-piperidin-2-one 35d. A solution of enamide **24** (50.0 mg, 0.22 mmol) and $AlCl_3$ (294 mg, 2.20 mmol) in iodobenzene (15 mL) was heated at 50 °C for 12 h. After cooling, the reaction mixture was poured into H_2O (15 mL) and extracted with $CHCl_3$ (3×20 mL). Combined extracts were washed with brine (20 mL), dried ($MgSO_4$), and evaporated under reduced pressure to give the crude product, which was purified by flash column chromatography (CH_2Cl_2, then 20–70% EtOAc–petroleum ether) to give the title compound as a pale brown solid (50.0 mg, 0.13 mmol, 60%), mp 115–119 °C; ν_{max} ($CHCl_3$)/cm^{-1} 2954, 1640, 1596, 1494, 1456, 1405, 1344; δ_H (500 MHz, $CDCl_3$) 1.83 (1H, m, 4-H_A), 1.93 (1H, m, 4-H_B), 2.09 (1H, m, 5-H_A), 2.35 (1H, dddd, J=14.2, 9.9, 5.2, 3.7 Hz, 5-H_B), 2.67 (1H, ddd, J=18.1, 8.3, 7.0 Hz, 3-H_A), 2.74 (1H, dt, J=18.1, 6.0 Hz, 3-H_B), 5.01 (1H, t, J=5.1 Hz, 6-H), 7.12–7.14 (3H, m, Ar-*H*), 7.22–7.32 (6H, m, Ar-*H*); δ_C (125 MHz, $CDCl_3$) 17.6 (CH_2), 32.4 (CH_2), 32.7 (CH_2), 65.1 (CH), 126.8 (CH), 127.0 (2×CH), 127.3 (2×CH), 127.5 (C), 128.5 (2×CH), 128.9 (2×CH), 140.5 (C), 141.4 (C), 170.9 (C=O); *m/z* (EI) (Found M^+, 377.0268. $C_{17}H_{16}INO$ requires *M*, 377.0277).

4.1.36. 1-(2-*tert*-Butyl-phenyl)-6-(2-methoxy-phenyl)-piperidin-2-one 38 and 1-(2-*tert*-butyl-phenyl)-6-(4-methoxy-phenyl)-piperidin-2-one 39. A solution of enamide **24** (50.0 mg, 0.22 mmol) and $TiCl_4$ (0.24 mL, 2.20 mmol) in anisole (15 mL) was heated at 50 °C for 12 h. After cooling, the reaction mixture was poured into H_2O (20 mL) and extracted with $CHCl_3$ (3×20 mL). Combined extracts were washed with brine (20 mL), dried ($MgSO_4$), treated with decolourising charcoal, and evaporated under reduced pressure to give the crude product, which was purified by flash column chromatography (30–90% EtOAc–petroleum ether) to give firstly the major isomer **38** (R_f 0.20, 1:1 petroleum ether–EtOAc) as a white solid (50.0 mg, 0.15 mmol, 68%), mp 145–147 °C (recrystallised from petroleum ether/CH_2Cl_2); ν_{max} ($CHCl_3$)/cm^{-1} 2960, 1633, 1599, 1489, 1463, 1409, 1364, 1332, 1294, 1107, 1056; δ_H (500 MHz, $CDCl_3$, 50 °C) 1.49 (9H, s, $C(CH_3)_3$), 1.84 (1H, br m, 4-H_A), 1.96 (1H, br m, 5-H_A), 2.05 (1H, br m, 4-H_B), 2.40 (1H, dddd, J=12.8, 12.4, 5.7, 3.9 Hz, 5-H_B), 2.59 (1H, ddd, J=18.0, 10.2, 7.0 Hz, 3-H_A), 2.76 (1H, ddd, J=18.0, 5.5, 3.5 Hz, 3-H_B), 3.70 (3H, br.s, OMe), 5.29 (1H, br.s, 6-H), 6.76–6.89 (3H, m, Ar-*H*), 7.00 (1H, m, Ar-*H*), 7.11 (1H, dd, J=7.6, 7.2 Hz, Ar-*H*), 7.25 (2H, m, Ar-*H*), 7.48 (1H, d, J=8.0 Hz, Ar-*H*); δ_C (125 MHz, $CDCl_3$) 17.0 (CH_2), 28.2 (CH_2), 32.1 (CH_3), 32.7 (CH_2), 36.0 (C), 55.3 (CH_3), 58.6 (CH), 110.9 (CH), 119.7 (CH), 126.3 (CH), 127.6 (CH), 128.6 (CH), 128.9 (CH), 129.1 (CH), 131.5 (CH+C), 140.4 (C), 146.4 (C), 153.2 (C), 172.2 (C=O); *m/z* (FAB) (Found MH^+, 338.2120 $C_{22}H_{28}NO_2$ requires *M*, 338.2120). Anal. Calcd for $C_{22}H_{27}NO_2$. C, 78.34; H, 8.01; N, 4.15%. Found: C, 78.00; H, 7.93; N, 4.07%; followed by the minor isomer **39** (R_f 0.15, 1:1 petroleum ether–EtOAc) as an oil (15.0 mg, 0.04 mmol, 7%), ν_{max} ($CHCl_3$)/cm^{-1} 2958, 2838, 1729, 1633, 1612, 1510, 1487, 1463, 1406, 1364, 1295, 1167, 1136; δ_H (500 MHz, $CDCl_3$) 1.47 (9H, s, $C(CH_3)_3$), 1.82–1.88 (2H, m, 5-H_A and 4-H_A), 2.13–2.19 (1H, m, 4-H_B), 2.42–2.50 (1H, m, 5-H_B), 2.63 (1H, ddd, J=17.9, 10.9, 6.9 Hz, 3-H_A), 2.81 (1H, br dd, J=17.9, 5.0 Hz, 3-H_B), 3.80 (3H, s, OMe), 4.72 (1H, dd, J=4.8, 3.4 Hz, 6-H), 6.63 (1H, d, J=8.0 Hz, Ar-*H*), 6.86–6.89 (3H, m, Ar-*H*), 7.12–7.15 (3H, m, Ar-*H*), 7.49 (1H, d, J=8.1 Hz, Ar-*H*); δ_C (125 MHz, $CDCl_3$) 16.8 (CH_2), 30.5 (CH_2), 32.1 (CH_3), 32.6 (CH_2), 35.9 (C), 55.3 (CH_3), 65.6 (CH), 113.7 (2×CH), 126.3 (CH), 127.7 (CH), 128.9 (2×CH), 129.1 (CH), 131.9 (CH), 133.3 (C), 140.0 (C), 146.2 (C), 159.1 (C), 171.5 (C=O); *m/z* (EI) (Found M^+, 337.2039 $C_{22}H_{27}NO_2$ requires *M*, 337.2042).

4.2. X-ray crystallographic data

The structures of **10**, **25**, **26**, **29g**, **33** and **38** were determined by single-crystal X-ray diffraction studies. Crystal data and other details are given in Table 2. Data were collected on a Bruker SMART CCD area detector diffractometer in all cases except that of **10**, for which a Stoe Stadi-4 diffractometer was used, using Mo K_α X-radiation (λ= 0.71073 Å). In all cases the diffractometers were equipped with an Oxford Cryosystem open-flow nitrogen cryostat and data were collected at 150 K. The structures were solved by direct methods (SHELXS-97) and refined using full matrix least squares refinement against F^2, all non-H atoms were refined with anisotropic atomic displacement parameters (adps) and H atoms placed in geometrically calculated

Table 2. Crystallographic data and structure refinement details

Compound	**10**	**25**	**26**	**29g**	**33**	**38**
Chemical formula	$C_{24}H_{37}NO_2$	$C_{18}H_{25}NO_2$	$C_{18}H_{25}NO_2$	$C_{21}H_{23}NOS$	$C_{16}H_{21}NO_2$	$C_{22}H_{27}NO_2$
Mr	371.55	287.39	287.39	337.46	259.34	337.45
Crystal system	Monoclinic	Orthorhombic	Triclinic	Monoclinic	Orthorhombic	Triclinic
Space group	$P2_1$	$P2(1)2(1)2(1)$	P-1	$P2_1/c$	$P2_12_12_1$	P-1
a (Å)	10.787 (3)	9.226 (2)	10.1547 (8)	11.9803 (10)	8.510 (3)	8.2002 (8)
b (Å)	7.747 (3)	11.873 (3)	11.8289 (9)	11.8217 (10)	9.914 (3)	9.8021(10)
c (Å)	13.402 (5)	14.639 (4)	14.3724(11)	13.1329 (11	16.963 (5)	11.9046(12)
α (°)			83.764 (2)			103.989 (2)
β (°)	98.34 (3)		77.925 (2)	106.460 (2)		92.632 (2)
γ (°)			81.422 (2)			100.153 (2)
V (Å^3)	1108.1 (7)	1603.6 (12)	1664.0 (2)	1783.8 (4)	1431.1 (8)	910.0 (3)
Z	2	4	4	4	4	2
T (K)	150	150	150	150	150	150
Crystal form, colour	Block, colourless	Column, colourless	Block, colourless	Tablet, colourless	Column, colourless	Column, colourless
Crystal size (mm)	0.41×0.27×0.19	0.28×0.09×0.09	0.50×0.41×0.33	0.54×0.49×0.21	0.40×0.12×0.12	0.43×0.25×0.16
No. of measured reflections	2429	9977	19321	15736	6762	7994
Unique, obsd ($I>2\sigma(I)$) reflections	2110, 1722	1627, 1154	7432, 5943	4097, 3631	1478, 843	4091, 3420
R_{int}	0.023	0.040	0.022	0.029	0.121	0.030
$R[F^2>2\sigma(F^2)]$, $wR(F^2)$, S	0.048, 0.104, 1.18	0.079, 0.212, 1.06	0.041, 0.118, 1.07	0.038, 0.108, 1.06	0.056, 0.146, 0.95	0.042, 0.124, 1.07
No. of parameters	245	190	381	217	177	226
$\Delta\rho_{max}$, $\Delta\rho_{min}$ (eÅ^{-3})	0.18, −0.22	0.53, −0.53	0.31, −0.18	0.42, −0.19	0.16, −0.22	0.30, −0.18

positions and refined as part of a riding model, unless otherwise stated. The hydroxyl H-atom in **26** was located from a difference Fourier map and refined as a rigid rotor, as were the methyl H-atoms in **33**. There was also disorder present in the t-butyl group of **33**, which was modeled over 2 half occupied sites with isotropic adps.

Crystallographic data (excluding structure factors) for the structures in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 221091–221096. Copies of the data can be obtained free of charge, on application to CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK [fax: +44(0)-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk].

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