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Application of the chiral base desymmetrisation of imides to the synthesis of the alkaloid jamtine and the antidepressant paroxetine

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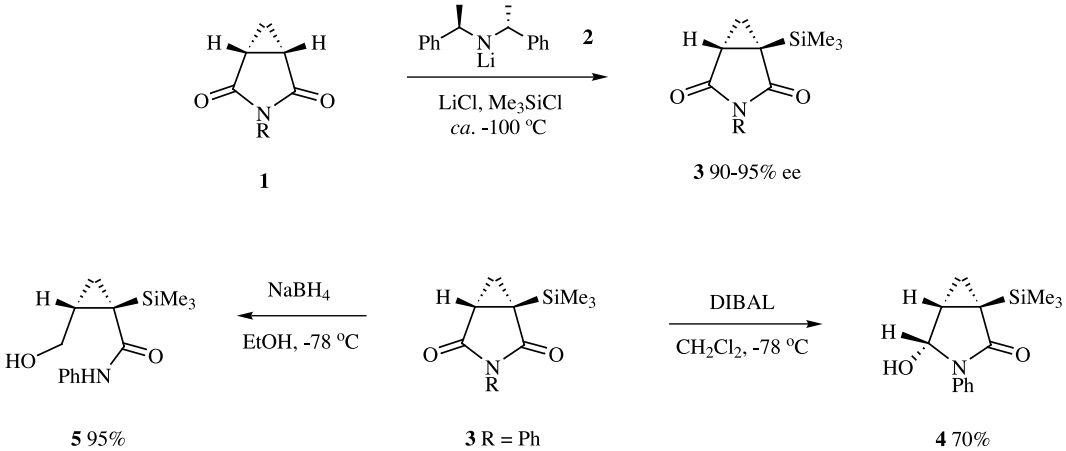
Abstract—The synthesis of the alkaloid jamtine and the antidepressant paroxetine have been addressed by a strategy involving asymmetric desymmetrisation of prochiral imides by a chiral lithium amide base. A short reaction sequence, starting with a cyclohexane fused succinimide, led to the structures originally reported for the alkaloid jamtine and its derived *N*-oxide. The structures synthesised are shown not to correspond with those originally reported. A second sequence involves desymmetrisation of a 4-arylglutarimide, and provides a short enantioselective synthesis of the drug substance paroxetine.

1. Introduction

In previous studies we have demonstrated that the concept of desymmetrisation by enolisation with a chiral lithium amide base can be applied to certain types of cyclic imide.[1] For example, reaction of cyclopropane fused imide **1** with chiral base **2** and chlorotrimethylsilane under in situ quench conditions gave products **3** (with various groups R) in good yield and high levels of enantioselectivity, Scheme 1.

We also showed that subsequent imide manipulation could be controlled by the trimethylsilyl substituent, for example the highly regiocontrolled reduction of **3** (R=Ph) to give either hydroxylactam **4** or hydroxyamide **5**. We have subsequently applied this type of concept to the asymmetric synthesis of specific target molecules, namely the drug substance (−)-paroxetine **6**,[2] and the unusual alkaloid jamtine **7**,[3] and its *N*-oxide **8** that was reported as a natural product.

These synthetic objectives required us to develop new aspects of both the initial imide desymmetrisation reaction and the subsequent regiocontrolled imide manipulation. In



Scheme 1.

Keywords: asymmetric synthesis; enantioselective enolisation; chiral lithium amide base; imides; paroxetine; jamtine.
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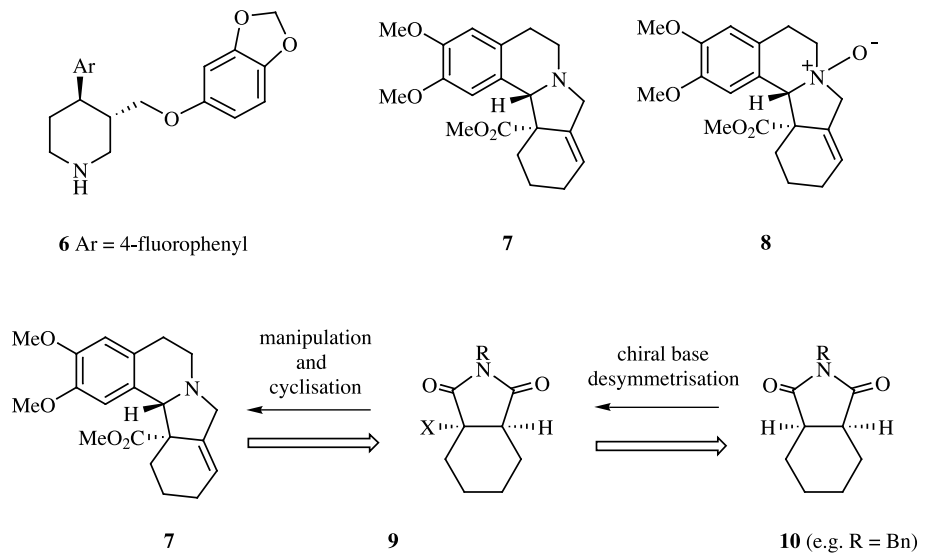


6 Ar = 4-fluorophenyl **7** **8**

7 **9** **10** (e.g. R = Bn)

Scheme 2.

this paper, we describe this work in full detail, including the new enantioselective route to **6**, which utilises a simple glutarimide starting material, and the first asymmetric syntheses of **7** and **8**, which has established that these structures do not correspond to the reported natural products.

2. Results and discussion

2.1. Chiral base reactions of cyclohexane fused imides: a synthesis of jamtine

In seeking to apply our chiral base chemistry to interesting alkaloid targets we were attracted to a report from the group of Padwa,[4] describing the first synthesis of an unusual alkaloid called jamtine **7**. This compound was originally reported by Rahman and co-workers, in the form of an *N*-oxide **8**, as one of a small group of isoquinoline alkaloids isolated from the climbing shrub *Cocculus hirsutus*.[5] This plant is commonly found in parts of Pakistan and its various parts are reputed to have therapeutic properties according to local folk medicine.[6]

We were interested in the asymmetric synthesis of jamtine, along the lines shown in Scheme 2, starting from a chiral imide **9**, in which the substituent X would be introduced by the initial chiral base desymmetrisation of a simple cyclohexane fused imide **10**, and would ultimately become the carbomethoxy substituent present in the natural product.

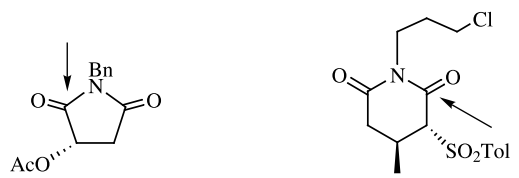
This idea presented two specific issues to be overcome. First, in our previous work, succinimides having a fused cyclohexane ring proved to be the sole substrates that did not give good results on reaction with chiral base **2**. Secondly, the elaboration of **9** towards jamtine would require regioselective reaction at the imide carbonyl proximal to the installed group X. This complementary mode of reaction, compared to that seen in reduction of **3** to give **4** has limited precedent, but appeared viable through electronic or chelation modes of activation.[7]

We first established that effective asymmetric substitution of imides of general structure **9** could be accomplished by switching to mono-lithium amide base **11**. The use of this base enabled conversion of imide **10** into alkylated derivatives **12** or **13** in reasonable yields and with excellent levels of enantioselectivity in the latter case (we did not determine the ee of **12**), Scheme 3.[8]

It was also of interest to examine the regiochemistry of subsequent reductions of these products to see if they conformed to the trends identified previously. Reduction of benzyl derivative **12** was poorly controlled, giving mixtures of regioisomeric products **14** and **15** with either $NaBH_4$ in EtOH or DIBAL-H in CH_2Cl_2, Scheme 4.

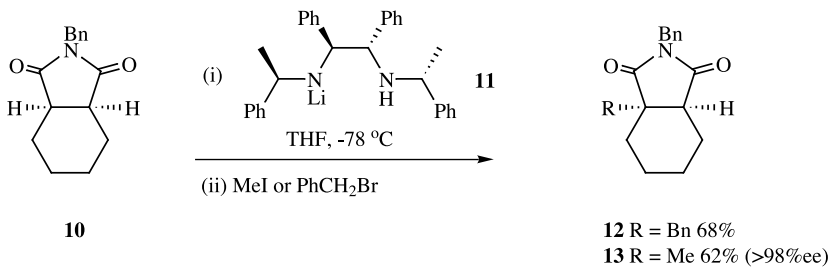
Although the ratios are not useful, they are in line with previous observations that these two types of reduction tend to give regiocomplementary results, with $NaBH_4$ reducing the apparently more hindered carbonyl function preferentially.[7a] Somewhat surprisingly, reduction of methyl derivative **13** with either type of reagent led to the formation of only the single regioisomeric product **16** in good yield.

Although the product ratios seen in these preliminary reactions were not encouraging, we were much more interested in the reductions of imides bearing an α-substituent that incorporated functionality appropriate for our total synthesis of jamtine. In the literature, the highly regioselective reduction of imides derived from malic acid, e.g. **17**, is very well known to occur at the more electrophilic carbonyl (arrowed) using $NaBH_4$,[9] and recently the reduction of sulfonyl imide **18** was reported to follow the same trend.[10]

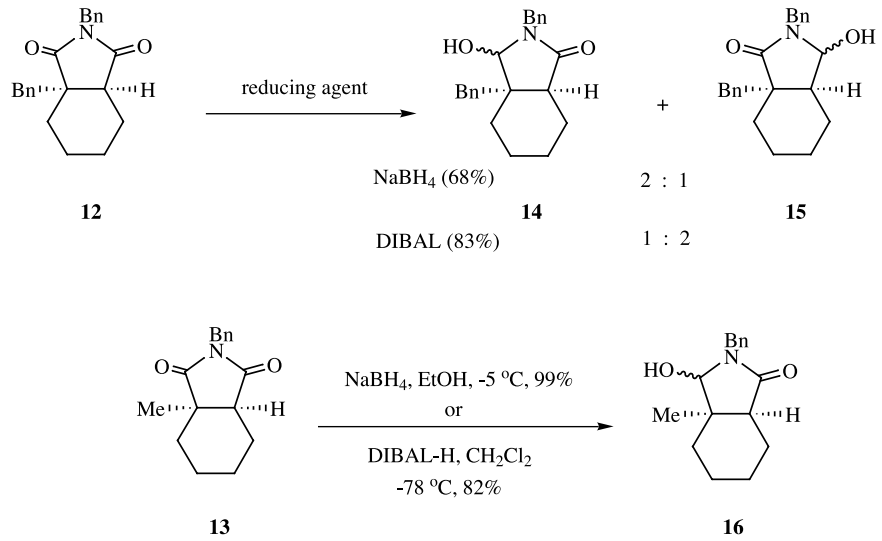


17 **18**

Based on this precedent we felt confident that the use of a



Scheme 3.



Scheme 4.

carboxylic ester as the group X, in Scheme 2, would prove viable, and would enable the most direct access to the target alkaloids. This proved to be the case, with the synthesis of jamtine and its *N*-oxide following exactly our planned route, as summarised below.

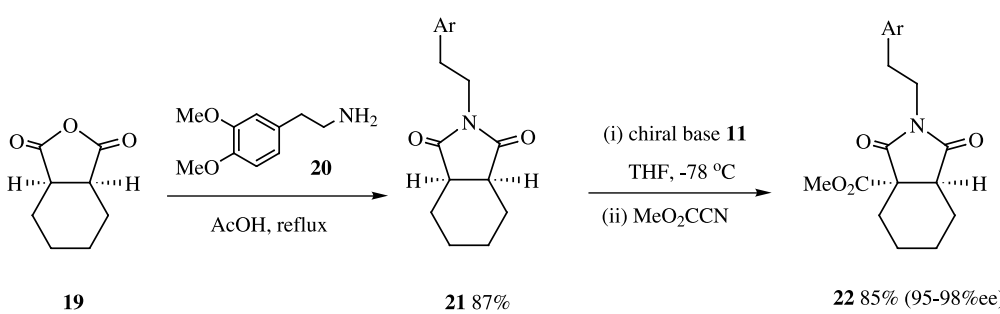
Thus, efficient and highly enantioselective introduction of the required methoxycarbonyl function to imide **21**, itself easily available from commercial materials **19** and **20**, was effected using chiral base **11**, by employing Mander's reagent as the electrophilic quench, Scheme 5.

At present, our assignment of absolute stereochemistry of these products (and those in Schemes 3 and 4) is based on analogy with earlier examples.[1] We anticipated further clarification on completing the total synthesis, but this was not forthcoming for reasons that will become clear (vide infra).

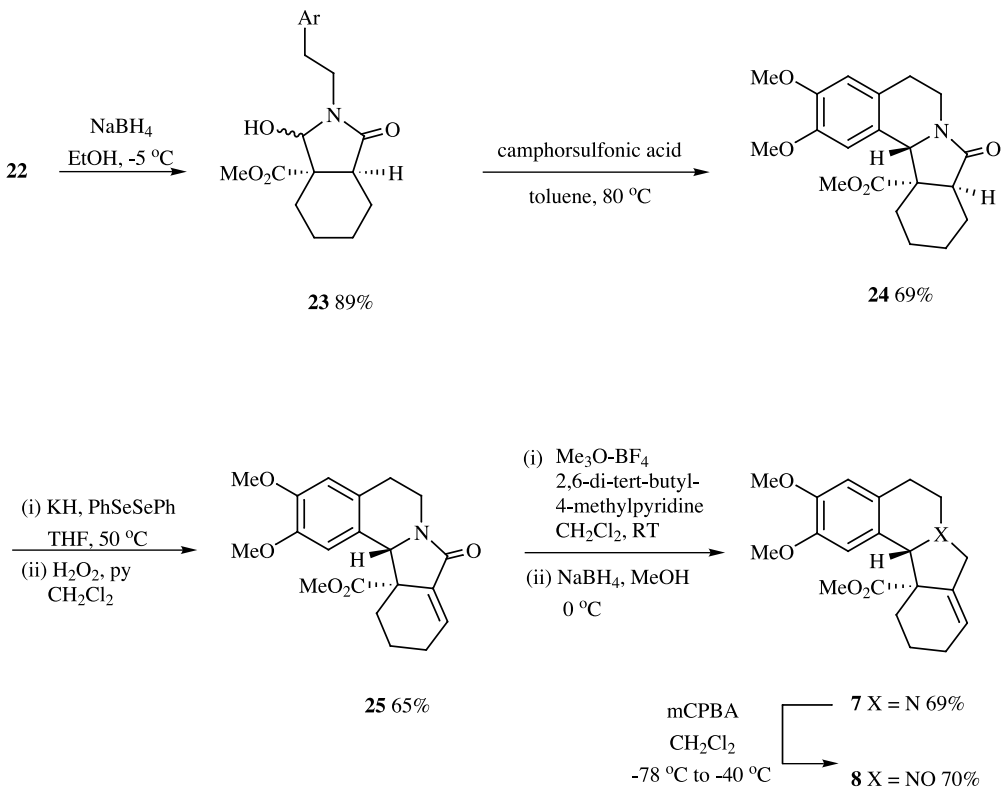
With more than adequate supplies of essentially enantiomerically pure imide **22** available, we were gratified to find that subsequent reduction was entirely regioselective to give hydroxylactam **23**, which then underwent stereoselective cyclisation under typical *N*-acyliminium ion conditions to give the complete alkaloid skeleton in the form of lactam (+)-**24**, Scheme 6.

Dehydrogenation using a selenoxide *syn*-elimination gave **25**, which is an intermediate in the Padwa synthesis of jamtine.[4] Finally, we used a method for selective lactam reduction reported by Martin and co-workers to transform unsaturated lactam **25** into jamtine **7**.[11] On exposure to *m*CPBA in CH_2Cl_2 at low temperature **7** was converted into the corresponding *N*-oxide **8**.

At this stage, it became clear that there were substantial differences between the NMR spectroscopic data for



Scheme 5.



Scheme 6.

synthetic **8** and those reported for the natural product 'jamtine oxide'. That our synthesis had delivered the structures **7** and **8** as shown became clear following our communication with Professor Padwa, who had completed the syntheses of these alkaloids by a different approach. Our NMR spectroscopic data for these compounds, and for the earlier intermediate **25**, were practically identical to those of Padwa and co-workers, and furthermore, this group had secured the structure of **25** by X-ray crystallographic analysis.[12] The contrast between the data from the two independent syntheses of jamtine *N*-oxide and those reported by Rahman and co-workers is perhaps best highlighted by the ^{13}C NMR data, Table 1.

At present we have no explanation for the differences in the data. That the natural product 'jamtine oxide' could be the opposite *N*-oxide diastereomer to the one that we have prepared appears a remote possibility. A more likely explanation is that the original structural assignment requires reassessment.

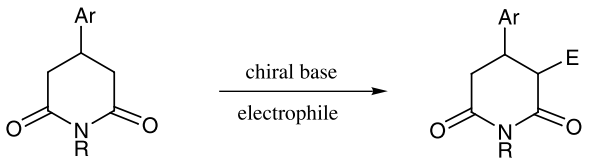
Despite the remaining questions over the real identity of the natural product from the *C. hirsutus* shrub we have demonstrated the utility of the chiral base desymmetrisation of imides in the synthesis of alkaloids having the distinctive 'jamtine' skeleton **7**, and have also established the potential of a methoxycarbonyl function to control the regiochemistry of imide reduction. Our completely stereocontrolled route delivers the tetracyclic isoquinoline structure **7** in six steps from commercial materials and in an overall yield of around 20%. The approach has potential applications in the synthesis of a number of other types of alkaloid system, including erythrina and yohimbane types.

2.2. Chiral base reactions of glutarimides: a synthesis of paroxetine

In all of the chiral base desymmetrisation reactions of imides demonstrated to this point, a ring-fused imide was chosen so as to avoid issues of diastereoselectivity in either the deprotonation or electrophilic quenching steps. However, this places limitations on the use of this desymmetrisation approach, and we considered the more challenging chiral base metallations of other types of imide an attractive goal. Foremost amongst these was the transformation of

Table 1. Comparison of ^{13}C NMR data for *N*-oxide **8** with literature

Isolation (Rahman)	Synthetic (Padwa)	Synthetic (this work)
172.6	172.1	171.9
158.8	148.7	148.6
158.8	148.0	147.8
135.2	131.1	130.8
134.6	127.7	127.1
134.4	125.1	124.9
131.1	121.9	121.7
124.4	111.6	110.6
112.4	110.2	109.4
80.7	90.3	90.0
73.9	76.5	75.9
62.2	64.1	63.8
56.4	58.0	57.7
56.3	56.3	56.1
55.9	56.2	55.8
52.3	52.2	52.0
31.2	33.0	32.8
27.1	25.8	25.6
25.3	24.3	24.1
22.4	19.5	19.3



Scheme 7.

prochiral glutarimides, such as **26** into chiral products **27**, Scheme 7.

Such a transformation would significantly expand the range of target alkaloids potentially available by this approach, and the synthesis of varied piperidines is especially attractive because of their diverse biological activities. Of the simpler systems that we considered, we identified the commercial drug substance (−)-paroxetine **6** as a potential candidate for asymmetric synthesis.[13]

The literature concerning the reactions of metal enolates derived from glutarimides is sparse.[14] In our hands enolate alkylation reactions of glutarimides **26**, with various Ar and R substituents, were low yielding when using LDA as the base, and some doubly substituted products were also obtained. Mono-lithiated chiral bases, such as base **2** and base **11** also gave rather disappointing yields, and we were prompted to use the diamine system in the form of its bis-lithium amide **29**, which gave the results shown in Table 2.

The use of **29** in its bis-lithiated form enabled the formation of the desired products **30** in good yields, with good to excellent levels of ee, and as single diastereoisomers. The use of a strongly dibasic system may seem to invite over-alkylation to give compounds **31**, but in reality the use of bis-lithiated base proved essential for reasonable yields of **30**. The *trans* arrangement of the newly installed substituent, relative to the fluorophenyl group was evident from the J values of associated ring protons ($J_{H3}-J_{H4}$ typically=11–13 Hz). The absolute configurations shown follow from the conversion of one adduct **30i** into paroxetine, as shown below.

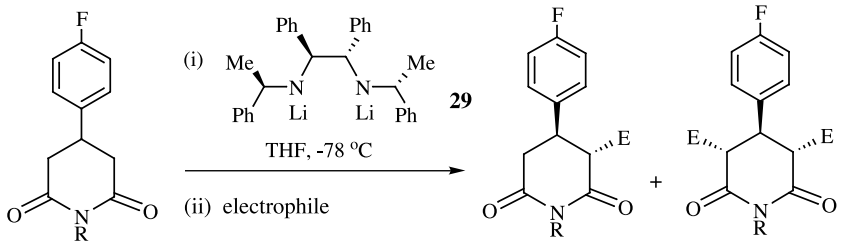
The somewhat variable nature of the levels of ee attracted our attention. Overall, the NBn series of compounds appeared to give better levels of induction than the NMe series, but in both cases the results were found to be variable. We noticed a broad correlation between reactions that gave significant amounts of bis-substituted by-product **31** and those that gave the highest levels of asymmetric induction. For example, in the reaction leading to **30i**, high levels of ee were found if the desired product was accompanied by 10–20% of **31**, whereas in reactions that produced very little of **31** the ee could drop as low as 80%.

These findings suggested that the observed ee for the products **30** was the result of an initial asymmetric enolisation of the starting imide **28**, followed by an ee enhancing kinetic resolution of **30**, Scheme 8.

This type of effect has been reported previously in diverse types of transformation, including *meso*-diol esterification,[15] diester hydrolysis,[16] catalytic asymmetric desymmetrisation processes involving coupling of prochiral bis triflates or dihalides,[17,18] and a chiral glycine synthesis involving H to D exchange.[19]

In order to further verify this effect in our system we exposed racemic **30a** to an excess of bis-lithiated base **29**

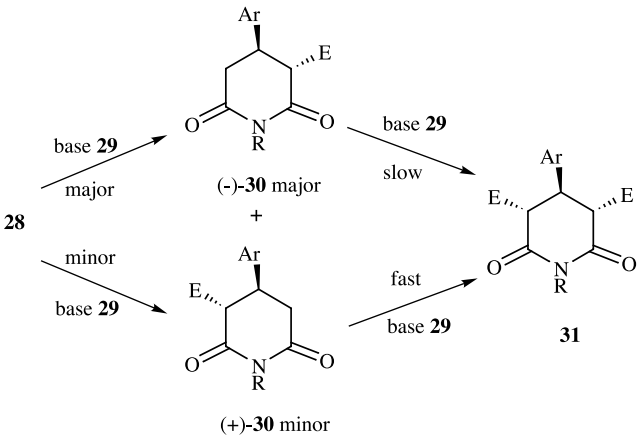
Table 2. Enantioselective substitution of glutarimides **28**



28 R = Me, Bn **30** **31**

Entry	R	Electrophile	Product **30** (%)	ee of **30**	**30/31**[a]
1	Me	MeI	**30a** (73)	86	3.5:1
2	Me	BnBr	**30b** (58)	74	2.5:1 (7)
3	Me	$ArCH_2Br$[b]	**30c** (63)	77	3:1 (9)
4	Me	MeO_2CCN	**30d** (87)	75	20:1
5	Bn	MeI	**30e** (65)	97	3:1 (14)
6	Bn	allylBr	**30f** (52)	90	(7)[c]
7	Bn	BnBr	**30g** (61)	97	2:1 (22)
8	Bn	PhCHO[d]	**30h** (75)	97	(0)[e]
9	Bn	MeO_2CCN	**30i** (71)	97	6.5:1

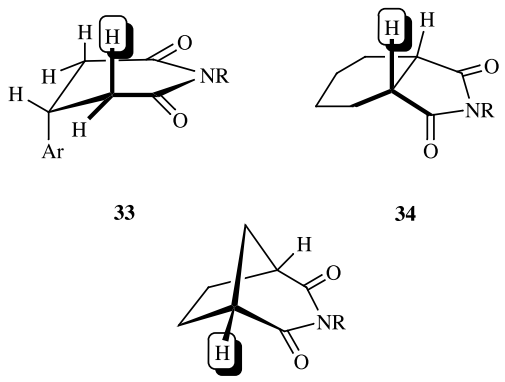
[a] Ratios estimated from ^{1}H NMR spectra of crude reaction mixture. Figures in brackets are isolated yields of **31**.
[b] Ar=4-bromophenyl.
[c] Ratio not determined.
[d] Isolated as a ca. 1:1 mixture of diastereomers.
[e] No doubly substituted product was detected.



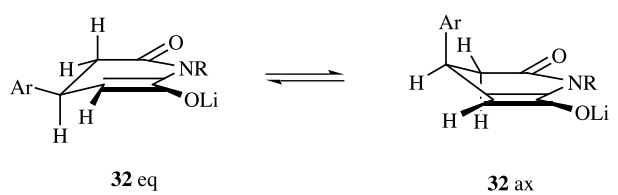
Scheme 8.

and then alkylated with MeI to generate **31a**. When a 46% conversion into **31a** was achieved the remaining **30a** showed an ee of 13%. Although this level of enrichment is rather low, representing a selectivity factor *S* below 2, our findings broadly parallel the observations of Gotov and Schmalz.[18] We also found that carboxymethyl derivative **30i** could be enriched from ca. 44% ee to 81% ee by further metallation with base **29** and reaction with MeO_2CCN.

These results support the picture of 'constructive kinetic



resolution' superimposed upon the initial asymmetric enolisation, illustrated in Scheme 8. We assume that this type of process may be operative in all of the asymmetric substitutions described here, although the extent of kinetic resolution may be dependent upon the nature of the substituent introduced as well as the extent to which 'over-alkylation' is allowed to proceed. Therefore, we did not consider it worthwhile to attempt to quantify the effect further.



Scheme 9.

The sense of enantioselectivity seen here, and also the high level of diastereocontrol observed in all of the alkylations deserves some further comment. In addressing the latter issue we examined molecular models of the intermediate enolate having the aromatic substituent in either a pseudoequatorial or pseudoaxial orientation, i.e. **32** eq. and **32** ax., as shown below (Scheme 9).

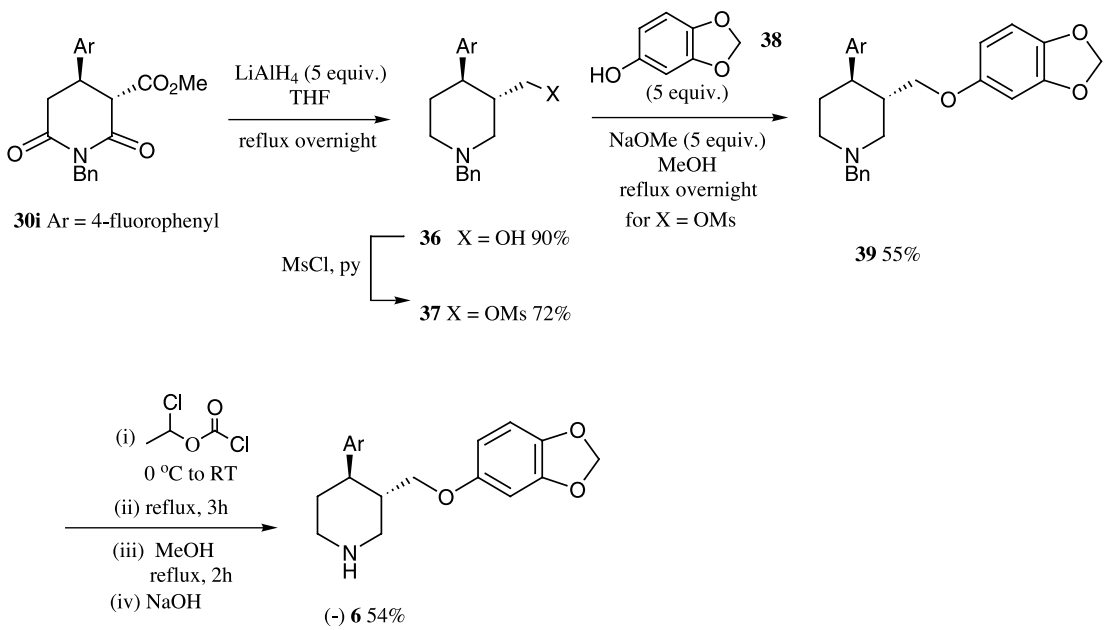
We could see little reason to invoke conformational anchoring of the system, for example with the 4-phenyl substituent pseudoequatorial (**32** eq.), since the flatness of the imide portion of the ring means that the alternative **32** ax. suffers no destabilising 1,3-diaxial interactions. A certain degree of conformational mobility for phenyl substituted cyclohexenes and related systems has been noted in the past, further supporting the plausibility of conformation **32** ax.[20] In the equatorial conformer **32** eq. there is no obvious facial bias to the system that would predict the high diastereoselectivities that we observe, and in fact an axial mode of alkylation would result in the unobserved *cis*-isomer. Alkylation via **32** ax. appears attractive in that a stereoelectronically preferred axial mode of alkylation can occur on a very exposed face of the enolate (from below as drawn), whereas the other (top) face is clearly hindered by the aromatic substituent.

If this explanation has some validity, and it is accepted that the imide ring in **28** is also probably conformationally mobile, then a model for deprotonation involving an imide with an axially disposed aromatic substituent also appears reasonable. In this model the base **29** would remove a pseudoaxial hydrogen from the exposed face of the imide, avoiding any interaction with the aromatic substituent—i.e. the circled hydrogen in **33** is removed.

This idea gains some further credibility if the sense of deprotonation in this compound is compared to that assigned earlier in the deprotonation of imide **21** using base **11** (the mono and bis-lithiated bases **11** and **29** have always displayed the same sense of selectivity), illustrated as **34**. An obvious similarity can be seen if in both cases the base approaches from above (the most accessible face) and removes the circled hydrogen, which is in an analogous orientation in both structures (i.e. on the left hand side when viewed from above). Even a stereoelectronically dissimilar bridgehead deprotonation of imide **35**, carried out using base **29**, appears to follow the same trend.[21]

The availability of highly enantioenriched glutarimides in synthetically useful quantities via this method should be useful for the preparation of a range of targets, including biologically potent piperidines. To illustrate this point, and to establish the sense of asymmetric induction in the chiral base reactions shown in Table 2, we carried out the conversion of imide **30i** into the aforementioned drug substance (−)-paroxetine, as shown in Scheme 10.

Reduction of imide **30i** (97% ee) gave piperidine alcohol **36**, to which the appropriate sesamol side-chain **38** was introduced by conventional means, via the intermediate mesylate **37**.[22] Deprotection of the piperidine nitrogen then

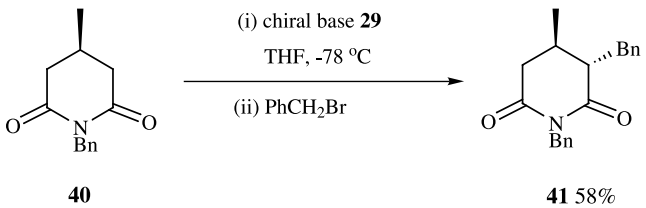


Scheme 10.

gave the desired drug substance (−)-**6** as the free amine after base treatment.[23]

The synthetic paroxetine prepared this way had $[\alpha]_D^{20}=-84$ (c=0.77, MeOH), which is comparable with reported values, allowing us to assign the absolute stereochemistry of intermediates as shown in Scheme 10 and Table 2.

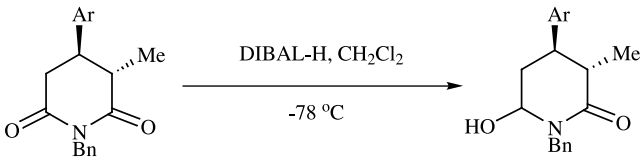
Finally, two further aspects of the glutarimide chemistry were briefly explored. First, we were interested to see if similar levels of diastereo- and enantioselectivity could be achieved in chiral base reactions of a 4-alkyl (rather than aryl) substituted glutarimide. Methyl substituted glutarimide **40** was therefore subjected to our typical deprotonation conditions and alkylated with benzyl bromide, to give **41**, Scheme 11.



Scheme 11.

The product was obtained as a single diastereomer with an enantiomeric excess of 67%. The absolute configuration shown for **41** is tentative at present and is assigned only by analogy with reactions of imides **28**. Although the selectivity appears somewhat reduced from the levels achieved in Table 2, we have not examined this process in detail and consider this a promising indication that workable levels of induction can indeed be achieved in the 4-alkyl series.

Secondly, we were interested in the regioselectivity of imide reduction in the chiral glutarimides, and therefore imide **30e** was subjected to standard reduction with DIBAL-H at low temperature. As shown in Scheme 12, this reaction proved very high yielding and entirely regioselective, giving hydroxylactam **42**.



Scheme 12.

Based on the scant evidence available in the literature,[24] regioselective reduction at the less substituted carbonyl function is to be anticipated. Although we have not been able to examine the generality of this result, the selectivity observed in this example augurs well for synthetic applications that require controlled reduction (e.g. lactam synthesis) or substitution adjacent to the ring nitrogen.

3. Summary and conclusion

The imide desymmetrisation reactions described above further expand the applications of chiral lithium amide bases in organic synthesis. The initial asymmetric enolisation process can be usefully combined with a subsequent regioselective imide transformation, as demonstrated in our synthesis of jamtine, although simple removal of both imide carbonyl functions can also be useful, as shown by our new route to paroxetine. This type of stereo- and regiocontrolled imide transformation appears to be a very powerful approach to a wide range of alkaloid systems, and we hope to further exemplify this strategy in the near future.

The synthesis of the proposed structures of jamtine, and its corresponding oxide has demonstrated that the data for these

compounds does not correspond to that for the originally isolated natural products. Further study is required to establish the true identities of these compounds.

4. Experimental

4.1. General details

General experimental details can be found in our recent paper.[1a] Starting imides **10** and **28** were prepared by condensation of the readily available anhydrides,[13d] with the appropriate amine, according to the method of Garratt and co-workers.[8b] Note that all *meso* products **31** that we isolated have the 3,4-*anti*, 4,5-*anti* configuration and we have not included stereochemical descriptors for the pseudoasymmetric C-4 position.

4.2. Typical procedure for chiral base reactions of ring fused imides using external quench

4.2.1. (3a*S*,7a*R*)-2,3a-Dibenzyl-hexahydro-isoindole-1,3-dione 12. A solution of mono-lithiated base **11** was prepared by addition of a solution of *n*-BuLi (0.44 mL, 2.5 mol dm^{-3} solution in hexanes, 1.10 mmol) to a stirred solution of the appropriate chiral diamine (462 mg, 1.10 mmol) in dry THF (5 mL) at −78°C under N_2. The resulting dark pink solution was allowed to warm to room temperature and stirred for 30 min, then cooled to −78°C and added, dropwise over 30 min, to a stirred solution of imide **10** (243 g, 1.00 mmol) in dry THF (10 mL) under N_2 at −78°C. Following completion of addition the resulting orange solution was stirred at −78°C for 1 h and then benzyl bromide (0.60 mL, 5.05 mmol) was added in one portion. The yellow solution obtained was stirred at −78°C for 3 h then quenched with saturated aqueous NH_4Cl solution and extracted with CH_2Cl_2 (3×50 mL). The organic phases were combined, dried ($MgSO_4$) and concentrated in vacuo to give an oily solid. Purification by flash silica chromatography (9:1 petroleum ether/EtOAc) gave the title compound **12** as a white solid (225 mg, 68%); mp 70–72°C; $[\alpha]_D^{23}$=+30 (*c* 1.0 in $CHCl_3$); ν_{max} ($CHCl_3$/cm^{-1}) 2941, 2860 (CH), 1770, 1698 (C=O), 1395, 1345, 1138, 1077, 959; δ_H (500 MHz, $CDCl_3$) 1.17–1.24 (1H, m), 1.43–1.64 (5H, m), 1.80–1.84 (1H, m), 2.10–2.14 (1H, m), 2.58 (1H, dd, *J*=2.7, 6.1 Hz, C*H*CON), 2.79 (1H, d, *J*=13.8 Hz, CCH_2Ph), 3.34 (1H, d, *J*=13.8 Hz, CCH_2Ph), 4.56 (1H, d, *J*=14.3 Hz, NCH_2Ph), 4.60 (1H, d, *J*=14.3 Hz, NCH_2Ph), 7.10–7.12 (2H, m, Ar*H*), 7.20–7.30 (8H, m, Ar*H*); δ_C (125 MHz, $CDCl_3$) 20.2 (CH_2), 20.7 (CH_2), 21.4 (CH_2), 32.9 (CH_2), 39.2 (CH_2), 41.8 (CH, *C*HCON), 42.0 (CH_2), 48.4 (C, *C*CH_2Ph), 127.0 (CH, Ar*C*H), 127.6 (CH, Ar*C*H), 128.2 (CH, Ar*C*H), 128.5 (CH, Ar*C*H), 128.6 (CH, Ar*C*H), 130.0 (CH, Ar*C*H), 135.9 (C, Ar*C*), 136.6 (C, Ar*C*), 178.3 (C=O), 181.7 (C=O); MS (EI) *m*/*z* 333 (M^+, 86%), 242 (12%), 91 (C_7H_7, 100%) (HRMS: found M^+ 333.1742. $C_{22}H_{23}NO_2$ requires M, 333.1729).

4.2.2. (3a*S*,7a*R*)-2-Benzyl-3a-methyl-hexahydro-isoindole-1,3-dione 13. The above typical procedure was followed using starting imide **10** (243 mg, 1.00 mmol) and methyl iodide (0.31 mL, 5.0 mmol) and the resulting oily solid purified by flash silica chromatography (14:1 petroleum ether 40/60–EtOAc) to give the title compound **13** as a colourless oil (160 mg, 62%); $[\alpha]_D^{23}$=−59 (*c* 1.0 in $CHCl_3$); ν_{max} ($CHCl_3$/cm^{-1}) 2941, 2862 (CH), 1772, 1704 (C=O), 1396, 1345, 1079; δ_H (500 MHz, $CDCl_3$) 1.15–1.26 (1H, m), 1.33 (3H, s, *Me*), 1.38–1.43 (2H, m), 1.45–1.50 (1H, m), 1.51–1.71 (3H, m), 2.08 (1H, ddd, *J*=4.4, 8.3, 14.2 Hz), 2.54 (1H, dd, *J*=3.8, 6.4 Hz, C*H*CON), 4.63 (1H, d, *J*=14.3 Hz, NCH_2Ph), 4.67 (1H, d, *J*=14.3 Hz, NCH_2Ph), 7.26–7.34 (3H, m, Ar*H*), 7.36–7.40 (2H, m, Ar*H*); δ_C (125 MHz, $CDCl_3$) 20.1 (CH_2), 21.3 (CH_2), 21.4 (CH_2), 21.5 (CH_3), 32.7 (CH_2), 42.1 (CH_2), 43.1 (C, *C*CH_3), 46.9 (CH, *C*HCON), 127.8 (CH, Ar*C*H), 128.5 (CH, Ar*C*H), 128.6 (CH, Ar*C*H), 136.1 (C, Ar*C*), 178.2 (C=O), 182.5 (C=O); MS (EI) *m*/*z* 257 (M^+, 100%), 214 (11%), 106 (30%), 96 (46%) (HRMS: found M^+ 257.1421. $C_{16}H_{19}NO_2$ requires M, 257.1416). The ee was determined as >98% by HPLC (OD Column, 2% EtOH in hexane, 0.6 mL/min), the retention times were 20 min (minor) and 22 min (major).

4.3. Imide reductions using $NaBH_4$ or DIBAL-H (Scheme 4)[1,9]

4.3.1. (3a*S*,7a*R*)-2,3a-Dibenzyl-3-hydroxy-octahydro-isoindol-1-one 14 and (3a*S*,7a*R*)-2,7a-dibenzyl-3-hydroxy-octahydro-isoindol-1-one 15. To a stirred solution of mono-benzylated imide **12** (30 mg, 0.09 mmol) in CH_2Cl_2 (2 mL) at −78°C was added DIBAL-H (0.18 mL, 1.0 mol dm^{-3} solution in CH_2Cl_2, 0.18 mmol). The reaction mixture was then stirred at −78°C for 20 min before quenching with water. The solution was filtered to remove the aluminium salts then diluted with CH_2Cl_2 (25 mL) and washed with water (25 mL). The organic phase was dried ($MgSO_4$), filtered and concentrated in vacuo to give a yellow solid which consisted of a 1:2 mixture of the title compounds **14** and **15**, with **15** being a mixture of two diastereomers. Purification by flash silica chromatography (petroleum ether 40/60–Et_2O 2:1) allowed almost complete separation of this mixture (combined yield 25 mg, 83%).

*Data for (3a*S*,7a*R*)-2,3a-dibenzyl-3-hydroxy-octahydro-isoindol-1-one* **14**. ν_{max} ($CHCl_3$/cm^{-1}) 3586 (OH), 2931, 2859 (CH), 1688 (C=O), 1454, 1077; δ_H (500 MHz, $CDCl_3$) 1.29–1.54 (3H, m), 1.58–1.72 (3H, m), 2.11–2.17 (2H, m), 2.21–2.24 (1H, m, C*H*CON), 2.78 (1H, d, *J*=13.8 Hz, CCH_2Ph), 2.85 (1H, d, *J*=13.8 Hz, CCH_2Ph), 4.27 (1H, d, *J*=14.5 Hz, NCH_2Ph), 4.61 (1H, d, *J*=14.5 Hz, NCH_2Ph), 4.93 (1H, d, *J*=8.4 Hz, simplifies to s on D_2O shake, C*H*OH), 7.00–7.10 (2H, m, Ar*H*), 7.18–7.31 (8H, m, Ar*H*); δ_C (125 MHz, $CDCl_3$) 21.1 (CH_2), 21.5 (CH_2), 23.0 (CH_2), 29.8 (CH_2), 39.0 (CH_2), 43.4 (CH_2), 44.2 (C, *C*CH_2Ph), 45.3 (CH, *C*HCON), 86.2 (CH, *C*HOH), 126.7 (CH, Ar*C*H), 127.4 (CH, Ar*C*H), 128.2 (CH, Ar*C*H), 128.5 (CH, Ar*C*H), 128.7 (CH, Ar*C*H), 130.4 (CH, Ar*C*H), 137.3 (C, Ar*C*), 174.1 (C=O); MS (EI) *m*/*z* 335 (M^+, 4%), 317 (M−H_2O, 25%), 226 (33%). 91 (C_7H_7, 49%), 51 (100%) (HRMS: found M^+ 335.1894. $C_{22}H_{25}NO_2$ requires M, 335.1885).

*Data for (3a*S*,7a*R*)-2,7a-dibenzyl-3-hydroxy-octahydro-isoindol-1-one* **15**. Less polar diastereoisomer. ν_{max} ($CHCl_3$/cm^{-1}) 3569 (OH), 2932, 2859 (CH), 1723, 1688 (C=O), 1453, 1094, 972; δ_H (500 MHz, $CDCl_3$) 1.09–1.16 (1H, m), 1.19 (1H, d, *J*=10.5 Hz, disappears on D_2O shake,

CHO*H*), 1.36–1.41 (1H, m), 1.47–1.68 (5H, m), 1.66–1.70 (2H, m), 2.72 (1H, d, *J*=13.5 Hz, CCH_2Ph), 3.34 (1H, d, *J*=13.5 Hz, CCH_2Ph), 4.08 (1H, d, *J*=14.5 Hz, NCH_2Ph), 4.55 (1H, dd, *J*=5.6, 10.4 Hz, simplifies to d, *J*=5.6 Hz, on D_2O shake, C*H*OH), 4.80 (1H, d, *J*=14.5 Hz, NCH_2Ph), 7.21–7.35 (10H, m, Ar*H*); δ_C (125 MHz, $CDCl_3$) 20.3 (CH_2), 20.9 (CH_2), 21.9 (CH_2), 31.5 (CH_2), 39.6 (CH_2), 43.4 (CH_2), 43.5 (CH, *C*HCHOH), 48.2 (C, *C*CH_2Ph), 83.5 (CH, *C*HOH), 126.8 (CH, Ar*C*H), 127.6 (CH, Ar*C*H), 128.6 (CH, Ar*C*H), 128.7 (CH, Ar*C*H), 130.5 (CH, Ar*C*H), 136.7 (C, Ar*C*), 138.1 (C, Ar*C*), 177.2 (C=O); MS (EI) *m/z* 335 (M^+, 1%), 317 (M−H_2O, 14%), 227 (23%), 226 (88%), 91 (C_7H_7, 100%), 51 (18%) (HRMS: found M^+ 335.1895. $C_{22}H_{25}NO_2$ requires M, 335.1885).

Data for (3aS,7aR)-2,7a-dibenzyl-3-hydroxy-octahydro-isoindol-1-one **15**. More polar diastereoisomer. ν_{max} ($CHCl_3$/cm^{-1}) 3616 (OH), 2932, 2862 (CH), 1724, 1692 (C=O), 1452, 1097, 969; δ_H (500 MHz, $CDCl_3$) 1.50–1.75 (6H, m), 1.82–1.87 (1H, m), 1.88–1.92 (1H, m), 2.10 (1H, d, *J*=6.3 Hz), 2.83 (1H, d, *J*=13.8 Hz, CCH_2Ph), 3.16 (1H, d, *J*=13.8 Hz, CCH_2Ph), 4.09 (1H, d, *J*=15.3 Hz, NCH_2Ph), 4.55 (1H, app. dt, *J*=6.3 Hz, C*H*OH), 4.80 (1H, d, *J*=14.5 Hz, NCH_2Ph), 6.92–7.01 (2H, m, Ar*H*), 7.16–7.31 (8H, m, Ar*H*); δ_C (125 MHz, $CDCl_3$) 21.2 (CH_2), 21.5 (CH_2), 23.0 (CH_2), 33.3 (CH_2), 36.3 (CH, *C*HCHOH), 39.1 (CH_2), 43.4 (CH_2), 46.8 (C, *C*CH_2Ph), 83.4 (CH, *C*HOH), 126.5 (CH, Ar*C*H), 127.3 (CH, Ar*C*H), 127.7 (CH, Ar*C*H), 128.3 (CH, Ar*C*H), 128.6 (CH, Ar*C*H), 130.5 (CH, Ar*C*H), 136.8 (C, Ar*C*), 138.2 (C, Ar*C*), 179.3 (C=O).

Reduction of imide ***12*** *using* $NaBH_4$. To a stirred solution of imide **12** (35 mg, 0.11 mmol) in EtOH (3 mL) at −5°C under N_2, was added, portionwise over 5 min, $NaBH_4$ (20 mg, 0.53 mmol). The reaction mixture was then stirred at room temperature for 15 h and then carefully quenched with 1% aq. HCl until a pH of 5/6 had been reached and then extracted with CH_2Cl_2 (3×50 mL). The organic phases were combined then washed with saturated aqueous $NaHCO_3$ solution (10 mL), dried ($MgSO_4$), filtered and concentrated in vacuo to give a sticky solid that consisted of a 2:1 mixture of products **14** and **15**. Purification by flash silica chromatography (petroleum ether 40/60–Et_2O 2:1) allowed almost complete separation of this mixture (combined yield 24 mg, 68%) with data described as above.

4.3.2. (3a*S*,7a*S*)-2-Benzyl-3-hydroxy-3a-methyl-octahydro-isoindole-1,3-dione 16. DIBAL-H reduction of methylated imide **13** (45 mg, 0.18 mmol), as described above for **12**, gave the title compound **16** as a single isomer as a white solid (37 mg, 82%); mp 150–152°C; $[\alpha]_D^{23}$=+54 (*c* 1.0 in $CHCl_3$); ν_{max} ($CHCl_3$/cm^{-1}) 3585 (OH), 2935, 2861 (CH), 1688 (C=O), 1455, 1357, 1074; δ_H (500 MHz, $CDCl_3$) 1.12 (3H, s, *Me*), 1.15–1.57 (6H, m), 1.59–1.66 (1H, m), 2.04–2.12 (2H, m), 3.30 (1H, d, *J*=8.3 Hz, disappears on D_2O shake, CHO*H*), 4.22 (1H, d, *J*=14.5 Hz, NCH_2Ph), 4.64 (1H, d, *J*=8.3 Hz, simplifies to s on D_2O shake, C*H*OH), 4.79 (1H, d, *J*=14.5 Hz, NCH_2Ph), 7.24–7.33 (5H, m, Ar*H*); δ_C (125 MHz, $CDCl_3$) 21.2 (CH_2), 21.4 (CH_2), 21.9 (CH_3), 23.1 (CH_2), 28.2 (CH_2), 40.3 (C, *C*CH_3), 43.0 (CH_2), 47.9 (CH, *C*HCON), 89.0 (CH, *C*HOH), 127.4 (CH, Ar*C*H), 128.4 (CH, Ar*C*H), 128.6 (CH, Ar*C*H), 137.1 (C, Ar*C*), 174.6 (C=O); MS (EI) *m/z* 257 (M^+, 64%), 241 (M−H_2O, 21%), 210 (23%), 136 (63%), 91 (C_7H_7, 100%) (HRMS: found M^+ 259.1575. $C_{16}H_{21}NO_2$ requires M, 259.1572).

Reduction of imide ***13*** *using* $NaBH_4$. The same procedure as described above for reduction of **12** was followed using methylated imide (100 mg, 0.39 mmol) **13** with a reaction time of 5 h, to give the title compound **16** as a single isomer as a white solid (100 mg, 99%) with data as described above.

4.4. Synthesis of jamtine and jamtine *N*-oxide (Schemes 5 and 6)

4.4.1. (3a*S*,7a*R*)-2-[2-(3,4-Dimethoxyphenyl)-ethyl]-hexahydro-isoindole-1,3-dione 21. To a stirred solution of 1,2 cyclohexane carboxylic acid anhydride (6.16 g, 40 mmol) in glacial AcOH (80 mL) at room temperature was added 2-(3,4-dimethoxyphenyl)-ethylamine (6.74 mL, 40 mmol) and the resulting mixture then heated at reflux for 18 h. Following cooling to room temperature water (80 mL) and CH_2Cl_2 (80 mL) were added. The organic phase was separated and washed with 2 mol dm^{-3} HCl (80 mL), saturated aqueous $NaHCO_3$ solution (80 mL) and water (80 mL), then dried ($MgSO_4$), filtered and concentrated in vacuo to give a pale orange solid. Purification by flash silica chromatography (3:1 petroleum ether 40/60–EtOAc) gave the title compound **21** as a white solid (11.04 g, 87%); mp 87.5–89.5°C; ν_{max} ($CHCl_3$/cm^{-1}) 3034, 2942, 2860 (CH), 1701 (C=O), 1516, 1399, 1263, 1156, 1025, 797; δ_H (400 MHz, $CDCl_3$) 1.29 (2H, br. s), 1.38 (2H, br. s), 1.56 (2H, br. s), 1.76 (2H, br. s), 2.74 (2H, br. s), 2.85 (2H, app. t, *J*=7.4 Hz), 3.71 (2H, app. t, *J*=7.4 Hz), 3.82 (3H, s, O*Me*), 3.85 (3H, s, O*Me*), 6.73–6.66 (3H, m, Ar*H*); δ_C (100 MHz) 21.6 (CH_2), 23.6 (CH_2), 32.9 (CH_2), 39.2 (CH_2), 39.6 (CH, *C*HCON), 55.8 (CH_3, O*Me*), 111.2 (CH, Ar*C*H), 112.0 (CH, Ar*C*H), 121.0 (CH, Ar*C*H), 130.3 (C, Ar*C*), 147.7 (C, Ar*C*), 148.8 (C, Ar*C*), 179.7 (C=O); MS (EI) *m/z* 317 (M^+, 28%), 164 ($C_{10}H_{12}O_2$, 100%), 151 ($C_9H_{11}O_2$, 28%) (HRMS: found M^+ 317.1634. $C_{18}H_{23}NO_4$ requires M, 317.1627).

4.4.2. (3a*S*,7a*S*)-2-[2-(3,4-Dimethoxyphenyl)-ethyl]-1,3-dioxo-octahydro-isoindole-3a-carboxylic acid methyl ester 22. The typical procedure for imide alkylation using base **11** was followed using starting imide **21** (1.42 g, 4.48 mmol) and Mander's reagent (0.71 mL, 8.96 mmol) and the resulting oily solid purified by flash silica chromatography (9:1 petroleum ether 40/60–EtOAc then 4:1) to give the title compound **22** as a colourless oil (1.45 g, 86%); $[\alpha]_D^{20}$=−61 (*c* 1.0 in $CHCl_3$); ν_{max} ($CHCl_3$/cm^{-1}) 2936 (CH), 1743 (C=O), 1707 (C=O), 1516, 1351, 1029, 801; δ_H (500 MHz, $CDCl_3$) 1.06–1.08 (1H, m), 1.31–1.41 (3H, m), 1.50–1.65 (3H, m), 2.00 (1H, ddd, *J*=4.7, 8.8, 13.9 Hz), 2.28–2.32 (1H, m), 2.90 (2H, app. dt, *J*=2.8, 7.4 Hz), 3.22 (1H, dd, 3.7, 6.6, C*H*CON), 3.76 (3H, CO_2*Me*), 3.77–3.81 (1H, m), 3.84 (3H, s, O*Me*), 3.87 (3H, s, O*Me*). 6.73–6.78 (3H, m, Ar*H*); δ_C (125 MHz, $CDCl_3$) 20.0 (CH_2), 20.3 (CH_2), 21.0 (CH_2), 28.0 (CH_2), 32.2 (CH_2), 39.3 (CH_2), 43.3 (CH, *C*HCON), 52.8 (CH_3, CO_2*Me*), 53.6 (C, *C*CO_2Me), 55.4 (CH_3, O*Me*), 55.5 (CH_3, O*Me*), 110.9 (CH, Ar*C*H), 111.6 (CH, Ar*C*H), 120.7 (CH, Ar*C*H), 129.5 (C, Ar*C*), 147.5 (C, Ar*C*), 148.5 (C, Ar*C*), 169.8 (C=O), 175.6 (C=O), 177.1 (C=O); MS (EI) *m/z*

375 (M^+, 50%), 164 ($C_{10}H_{12}O_2$, 100%), 151 ($C_9H_{11}O_2$, 45%) (HRMS: found M^+ 375.1676. $C_{20}H_{25}NO_6$ requires M, 375.16818). The ee was determined as 97% by HPLC (OD Column, 3% EtOH in hexane, 0.6 mL/min), the retention times were 50 min (major) and 70 min (minor).

4.4.3. (3a*S*,7a*S*)-2-[2-(3,4-Dimethoxyphenyl)-ethyl]-3-hydroxy-1-oxo-octahydro-isoindole-3a-carboxylic acid methyl ester 23. To a stirred solution of carbomethoxy imide **22** (1.00 g, 2.67 mmol) in EtOH (25 mL) at −5°C under N_2, was added, portionwise over 5 min, $NaBH_4$ (0.20 g, 5.28 mmol). The reaction mixture was stirred at −5°C for 45 min, then carefully quenched with 1% aq. HCl until a pH of 5/6 had been reached and then extracted with CH_2Cl_2 (3×50 mL). The organic phases were combined then washed with saturated aqueous $NaHCO_3$ solution (100 mL), dried ($MgSO_4$), filtered and concentrated in vacuo to give the title compound **23** as a sticky solid (0.90 g, 90%); ν_{max} ($CHCl_3$/cm^{-1}) 3607 (OH), 3030, 2929 (CH), 1697 (C═O), 1515, 1201, 797; δ_H (500 MHz, $CDCl_3$/DMSO-d_6) 1.01–1.13 (1H, m), 1.14–1.25 (1H, m), 1.28–1.36 (1H, app. dt, *J*=3.6, 13.4 Hz), 1.36–1.50 (2H, m), 1.52–1.60 (1H, m), 1.54–1.57 (1H, m), 1.95 (1H, br. d, *J*=14.3 Hz), 2.05 (1H, br. d, *J*=14.3 Hz), 2.68–2.81 (3H, m), 3.33 (1H, ddd, *J*=5.5, 9.0, 14.1 Hz), 3.66 (3H, O*Me*), 3.76 (3H, O*Me*), 3.78 (3H, O*Me*), 5.09 (1H, d, *J*=6.4 Hz, disappears on D_2O shake, CHO*H*), 5.24 (1H, d, *J*=6.4 Hz, simplifies to s on D_2O shake, C*H*OH), 6.65–6.70 (3H, m, Ar*H*); δ_C (125 MHz, $CDCl_3$) 21.6 (CH_2), 21.7 (CH_2), 22.3 (CH_2), 24.8 (CH_2), 33.1 (CH_2), 40.7 (CH_2), 44.1 (CH, *C*HCON), 52.0 (C, *C*CO_2Me), 52.4 (CH_3, CO_2*Me*), 55.8 (CH_3, O*Me*), 84.8 (CH, *C*HOH), 110.9 (CH, Ar*C*H), 111.8 (CH, Ar*C*H), 120.7 (CH, Ar*C*H), 131.6 (C, Ar*C*), 147.2 (C, Ar*C*), 148.5 (C, Ar*C*), 172.6 (C═O), 174.6 (C═O); MS (EI) *m*/*z* 377 (M^+, 10%), 359 (M−H_2O, 69%), 344 (48%), 191 (53%), 164 ($C_{10}H_{12}O_2$, 100%) (HRMS: found M^+ 377.1830. $C_{20}H_{27}NO_6$ requires M 375.1838).

4.4.4. (8a*S*,12a*S*,12b*R*)-8-Oxo-5,8,8a,9,11,12,12b-octahydro-6*H*-isoindolo[1,2-*a*]isoquinoline-12a-carboxylic acid methyl ester 24. To a stirred solution of hydroxylactam **23** (0.90 g, 2.39 mmol) in toluene (25 mL) at 80°C under N_2 was added camphor-sulfonic acid (0.90 g, 3.60 mmol), portionwise over 5 min. The reaction mixture was stirred at 80°C for 90 min then allowed to cool to room temperature then quenched with saturated aqueous $NaHCO_3$ solution (50 mL) and extracted with CH_2Cl_2 (3×50 mL). The organic phases were combined, dried ($MgSO_4$), filtered and concentrated in vacuo to give a pale brown oil. Purification by flash silica chromatography (petroleum ether 40/60–EtOAc 1:2) gave the title compound **24** as a white solid (0.75 g, 88%); mp 139.5–141.5°C; $[\alpha]_D^{20}$=+125 (*c* 1.0 in $CHCl_3$). (Found: C, 67.04; H, 7.02; N, 3.84. $C_{20}H_{25}NO_5$ requires C, 66.83; H, 7.01; N, 3.90%); ν_{max} ($CHCl_3$/cm^{-1}) 3017, 2929 (CH), 1729, 1684 (C═O), 1229, 1196, 791; δ_H (500 MHz, $CDCl_3$) 1.34–1.42 (1H, m), 1.61 (1H, ddd, *J*=3.9. 11.3, 25.4 Hz), 1.65–1.72 (1H, m), 1.79–1.85 (2H, m), 2.15–2.24 (2H, m), 2.33 (1H, app. dt, *J*=4.5, 14.6 Hz), 2.61 (1H, br. d, *J*=13.0 Hz), 2.69 (1H, dd, *J*=6.1, 11.3 Hz, C*H*CON), 2.87–2.95 (2H, m), 3.32 (3H, s, CO_2*Me*), 3.92 (3H, s, O*Me*), 3.94 (3H, s, O*Me*), 4.45–4.47 (1H, m), 4.98 (1H, s, C*H*N), 6.65 (1H, s, Ar*H*), 6.72 (1H, s, Ar*H*); δ_C (125 MHz, $CDCl_3$) 21.1 (CH_2), 22.1 (CH_2), 25.5 (CH_2), 28.1 (CH_2), 28.5 (CH_2), 37.3 (CH_2), 46.3 (CH, *C*HCON), 51.3 (CH_3, CO_2*Me*), 52.7 (C, *C*CO_2Me), 55.6 (CH_3, O*Me*), 55.9 (CH_3, O*Me*), 60.1 (CH, *C*HN), 108.9 (CH, Ar*C*H), 111.6 (CH, Ar*C*H), 124.2 (C, Ar*C*), 127.7 (C, Ar*C*), 147.3 (C, Ar*C*), 147.8 (C, Ar*C*), 173.6 (C═O), 175.8 (C═O); MS (EI) *m*/*z* 359 (M^+, 97%), 344 (M−CH_3, 79%), 191 (100%), 176 (31%) (HRMS: found M^+ 359.1749. $C_{20}H_{25}NO_5$ requires M, 359.1733).

4.4.5. (12a*S*,12b*R*)-8-Oxo-5,8,11,12,12b-hexahydro-6*H*-isoindolo[1,2-*a*]isoquinoline-12a-carboxylic acid methyl ester 25. To a stirred solution of lactam **24** (0.62 g, 1.73 mmol) and PhSeSePh (1.62 g, 5.18 mmol) in dry THF (25 mL) under N_2 at room temperature was added KH (0.35 g, 8.75 mmol), portionwise over 5 min. After initial effervescence had subsided the reaction mixture was heated to 50°C and stirred for 2 h. The mixture was then allowed to cool to room temperature and quenched with saturated aqueous NH_4Cl solution (2 mL), followed by dilution with CH_2Cl_2 (25 mL) and the addition of pyridine (1 mL) and 30% aqueous H_2O_2 (10 mL). The resulting mixture was stirred at room temperature for 15 h then carefully quenched with saturated aqueous Na_2SO_3 solution (20 mL). The aqueous phase was further extracted with CH_2Cl_2 (2×50 mL). The organic phases were then combined, washed with brine (50 mL), dried ($MgSO_4$), filtered and concentrated in vacuo to give a brown oil. Purification by flash silica chromatography gave the title compound **25** as a white solid (0.40 g, 65%); mp 153.9–155.8°C (lit.[4,12] mp 155–157°C); $[\alpha]_D^{20}$=+78 (*c* 1.0 in $CHCl_3$); ν_{max} ($CHCl_3$/cm^{-1}) 3011, 2940 (CH), 1731, 1681 (C═O), 1609 (C═C), 1234, 1200, 788; δ_H (500 MHz, $CDCl_3$) 1.59–1.71 (2H, m), 1.94–1.96 (1H, m), 2.23–2.25 (1H, m), 2.29–2.35 (1H, m), 2.63 (1H, br. d, *J*=15.3 Hz), 2.82 (1H, app. dt, *J*=5.0, 13.6 Hz), 2.91–2.95 (2H, m), 3.20 (3H, s, CO_2*Me*), 3.86 (3H, s, O*Me*), 3.89 (3H, s, O*Me*), 4.50 (1H, dd, *J*=5.0, 12.6 Hz), 4.65 (1H, s, C*H*N), 6.59 (1H, s, Ar*H*), 6.62 (1H, s, Ar*H*) 6.67 (1H, app. t, *J*=3.5 Hz, C═C*H*); δ_C (125 MHz, $CDCl_3$) 19.4 (CH_2), 24.3 (CH_2), 28.3 (CH_2), 30.1 (CH_2), 37.2 (CH_2), 51.5 (CH_3, CO_2*Me*), 53.9 (C, *C*CO_2Me), 55.9 (CH_3, O*Me*), 56.1 (CH_3, O*Me*), 65.1 (CH, *C*HN), 109.3 (CH, Ar*C*H), 111.5 (CH, Ar*C*H), 123.6 (C, Ar*C*), 127.4 (C, Ar*C*), 130.4 (CH, C═*C*H), 134.5 (C, *C*═CH), 147.7 (C, Ar*C*), 148.3 (C, Ar*C*), 166.9 (C═O), 171.1 (C═O); MS (EI) *m*/*z* 357 (M^+, 58%), 192 (56%), 166 (100%) (HRMS: found M^+ 357.1565. $C_{20}H_{23}NO_5$ requires M, 357.1576).

4.4.6. Jamtine 7. To a stirred solution of enamide **25** (75 mg, 0.21 mmol) in dry CH_2Cl_2 (2 mL) at room temperature under N_2 was added Me_3OBF_4 (78 mg, 0.53 mmol) followed by 2,6-di-*tert*-butyl 4-methyl pyridine (150 mg, 0.73 mmol). The resulting dark yellow solution was stirred at room temperature for 22 h then cooled to 0°C and diluted with MeOH (2 mL) followed by the addition of $NaBH_4$ (48 mg, 1.27 mmol). The pale yellow solution obtained was stirred at 0°C for 10 min then quenched with saturated aqueous $NaHCO_3$ solution (5 mL) and extracted with CH_2Cl_2 (3×5 mL). The organic phases were combined, dried ($MgSO_4$) and concentrated in vacuo to give a dark yellow oil. Purification by flash silica chromatography (CH_2Cl_2 then 5% MeOH, then 10%) gave jamtine **7** as a pale yellow solid (50 mg, 69%); $[\alpha]_D^{20}$=+30 (*c* 1.0 in

$CHCl_3$); ν_{max} ($CHCl_3$/cm^{-1}) 2937, 2836 (CH), 1720 (C=O), 1612 (C=C), 1463, 1357, 1133, 864; δ_H (500 MHz, $CDCl_3$) 1.52–1.56 (2H, m), 1.83–1.91 (1H, m), 2.12 (2H, br. s), 2.53 (1H, app. dt, *J*=3.6, 15.3 Hz), 2.75 (1H, ddd, *J*=3.6, 10.2, 11.8 Hz), 2.83 (1H, dd, *J*=3.8, 9.0 Hz), 2.91 (1H, ddd, *J*=4.9, 10.2, 15.3 Hz), 3.12 (1H, ddd, *J*=3.6, 4.9, 11.8 Hz), 3.30 (3H, s, CO_2Me), 3.42 (1H, ddd, *J*=1.7, 3.0, 12.0 Hz), 3.85 (4H, s, O*Me* and C*H*N), 3.89 (3H, s, O*Me*), 3.99 (1H, ddd, *J*=3.0, 5.2, 12.0 Hz), 5.72 (1H, br. s, C=C*H*), 6.58 (1H, s, Ar*H*), 6.63 (1H, s, Ar*H*); δ_C (125 MHz, $CDCl_3$) 19.9 (CH_2), 24.4 (CH_2), 27.3 (CH_2), 32.0 (CH_2), 47.9 (CH_2), 51.5 (CH_3, CO_2Me), 55.8 (CH_3, O*Me*), 56.1 (CH_3, O*Me*), 56.9 (C, *C*CO_2Me), 57.1 (CH_2, *C*H_2N), 71.4 (CH, *C*HN), 110.1 (CH, Ar*C*H), 111.1 (CH, Ar*C*H), 121.1 (CH, C=*C*H), 127.1 (C, *C*=CH or Ar*C*), 128.5 (C, *C*=CH or Ar*C*), 138.0 (C, *C*=CH or Ar*C*), 146.6 (C, Ar*C*), 147.4 (C, Ar*C*), 173.4 (C=O); MS (ES) *m/z* 344 ([M+H]$^+$, 100%), 340 (56%) (HRMS: found [M+H]$^+$ 344.1874. $C_{20}H_{25}NO_4$ requires [M+H], 344.1862).

4.4.7. Jamtine *N*-oxide 8. To a stirred solution of jamtine **7** (30 mg, 0.09 mmol) in dry CH_2Cl_2 under N_2 at −78°C was added *m*CPBA (70–75%, 35 mg, 0.14 mmol) in one portion. The resulting solution was stirred at −78 to −40°C for 2 h, and then solid Na_2CO_3 (50 mg) was added. The reaction mixture was filtered, then concentrated in vacuo to give a yellow oil. Purification by flash silica column chromatography (CH_2Cl_2–MeOH 95:5 then 9:1 then 1:1) gave jamtine *N*-oxide **8** as a colourless oil (22 mg, 70%); $[\alpha]_D^{27}$=+12 (*c* 0.15 in $CHCl_3$); ν_{max} ($CHCl_3$/cm^{-1}) 2937 (CH), 1720 (C=O), 1602 (C=C), 1464, 1360, 1121, 1011, 864; δ_H (500 MHz, $CDCl_3$) 1.46–1.59 (1H, m), 1.83 (1H, app. t, *J*=13.3 Hz), 1.88–1.94 (1H, m), 2.12–2.34 (2H, m), 2.75–2.91 (2H, m), 3.23–3.28 (1H, m), 3.29 (3H, s, CO_2Me), 3.74–3.84 (2H, m), 3.85 (3H, s, O*Me*), 3.86 (3H, s, O*Me*), 4.40 (1H, d, *J*=13.2 Hz), 4.81 (1H, s, C*H*N), 4.92 (1H, d, *J*=13.2 Hz), 6.02 (1H, s, C=C*H*), 6.60 (1H, s, Ar*H*), 6.64 (1H, s, Ar*H*); δ_C (125 MHz, $CDCl_3$) 19.3 (CH_2), 24.1 (CH_2), 25.6 (CH_2), 32.8 (CH_2), 52.0 (CH_3, CO_2Me), 55.8 (CH_3, O*Me*), 56.1 (CH_3, O*Me*), 57.7 (C, *C*CO_2Me), 63.8 (CH_2, *C*H_2N), 75.9 (CH_2, *C*H_2N), 90.0 (CH, *C*HN), 109.4 (CH, Ar*C*H), 110.6 (CH, Ar*C*H), 121.7 (C, *C*=CH or Ar*C*), 124.9 (C, *C*=CH or Ar*C*), 127.1 (CH, C=C*H*), 130.8 (C, *C*=CH or Ar*C*), 147.8 (C, Ar*C*), 148.6 (C, Ar*C*), 171.9 (C=O); MS (ES) *m/z* 360 ([M+H$^+$], 100%) (HRMS: found [M+H]$^+$ 360.1806. $C_{20}H_{25}NO_5$ requires [M+H], 360.1811).

4.5. Typical procedure for chiral base reaction of glutarimides 28 (Table 2)

4.5.1. (3*S*,4*R*)-1,3-Dimethyl-4-(4-fluorophenyl)piperidine-2,6-dione (−) 30a and (3*R*,5*S*)-4-(4-fluorophenyl)-1,3,5-trimethylpiperidine-2,6-dione 31a. A solution of bis-lithium amide base **29** was prepared by treatment of the corresponding chiral amine (342 mg, 0.81 mmol) in THF (4.0 mL) with *n*-BuLi (1.02 mL of a 1.6 M solution in hexanes, 1.63 mmol) at −78°C under N_2. The resulting solution was allowed to warm to room temperature, stirred for 30 min, and then cooled to −78°C before dropwise addition, via cannula over 5 min, to a stirred solution of the imide **28** (R=Me) (150 mg, 0.68 mmol) in THF (10 mL), maintaining a temperature of −78°C±1. The reaction mixture was then stirred for 45 min after which the mixture was diluted with further THF (14 mL) before addition of methyl iodide (0.43 mL, 6.8 mmol). The reaction mixture was then warmed to −40°C±1 and stirred at this temperature for a further 4 h before quenching with saturated aqueous NH_4Cl solution (10 mL) and extraction into Et_2O (40 mL). The aqueous phase was separated and re-extracted with Et_2O (2×20 mL). The organic extracts were combined, washed with 2 M HCl (3×80 mL), followed by saturated aqueous $NaHCO_3$ (80 mL) then brine (80 mL), dried ($MgSO_4$), filtered and concentrated in vacuo to give a 3.5:1 mixture of mono-methylated glutarimide **30a** and bis-methylated glutarimide **31a**. The products were purified via flash column chromatography on silica gel (40% Et_2O/petroleum ether) to yield mono-methylated glutarimide **30a** as a pale yellow solid (117 mg, 73%). The minor component was not isolated from this particular reaction, but the presence of bis-methylated glutarimide **31a** was verified by comparison of the ^{1}H NMR spectrum of the crude reaction mixture with data from a pure sample of bis-methylated glutarimide from other reactions.

*Data for mono-methylated glutarimide **30a**.* Mp 121–123°C; $[\alpha]_D^{24}$=−32 (*c* 1.08 in $CHCl_3$): ν_{max} ($CHCl_3$)/cm^{-1} 2961 and 2908 (C–H), 1725 and 1668 (C=O), 1607, and 1510 (Ar); δ_H (400 MHz) 1.13 (3H, d, *J*=6.8 Hz, CHCH_3), 2.72 (1H, dq, *J*=11.4, 6.8 Hz, C*H*CH_3), 2.78 (1H, dd, *J*=17.7, 13.3 Hz, C$H_{ax}H_{eq}$CHAr), 2.95 (1H, dd, *J*=17.7, 4.1 Hz, $CH_{ax}H_{eq}$CHAr), 2.98 (1H, m, C*H*Ar), 3.21 (3H, s, NCH_3), 7.07 (2H, m, Ar*H*), 7.15 (2H, m, Ar*H*); δ_C (100.6 MHz) 14.3 (CH*C*H_3), 27.0 (N*C*H_3), 40.7 (*C*H_2CHAr), 42.0 (*C*HAr), 43.3 (*C*HCH$_3$), 116.1 (J_{C-F}= 22 Hz, Ar*C*H), 128.6 (J_{C-F}=8 Hz, Ar*C*H), 136.4 (J_{C-F}= 3 Hz, Ar*C*), 162.1 (J_{C-F}=246 Hz, Ar*C*), 171.3 (*C*=O), 174.8 (*C*=O); MS (EI) *m/z* 235 (M$^+$, 100%), 220 (M−CH_3, 5), 149 (45), 136 (79), 122 (44), 113 (18), 109 (38), 86 (12) (HRMS: found M$^+$, 235.1008. $C_{13}H_{14}NO_2F$ requires M, 235.1009). The ee was determined as 86% by HPLC (OD column, 3% EtOH in hexane, 0.8 mL/min), the retention times were 35.2 min (minor) and 38.1 min (major).

*Data for bis-methylated glutarimide **31a**.* ν_{max} ($CHCl_3$)/cm^{-1} 2978, 2938 and 2883 (C–H), 1723 and 1666 (C=O), 1606, and 1508 (Ar); δ_H (400 MHz) 1.05 (6H, d, *J*=6.7 Hz, 2×CHCH_3), 2.60 (1H, dd, *J*=12.1, 12.1 Hz, C*H*Ar), 2.74 (2H, dq, *J*=12.1, 6.7 Hz, 2×C*H*CH_3), 3.21 (3H, s, NCH_3), 7.04–7.15 (4H, m, Ar*H*); δ_C (100.6 MHz) 14.5 (CH*C*H_3), 27.5 (N*C*H_3), 43.4 (*C*HCH$_3$), 49.5 (*C*HAr), 116.1 (J_{C-F}= 21 Hz, Ar*C*H), 129.1 (J_{C-F}=8 Hz, Ar*C*H), 136.0 (Ar*C*), 162.0 (J_{C-F}=246 Hz, Ar*C*), 174.5 (*C*=O); MS (EI) *m/z* 250 ([M+H]$^+$, 14%), 249 (M$^+$, 58), 234 (M−CH_3, 5), 206 (8), 195 (6), 163, (29), 149 (8), 137 (20), 136 (100), 135 (28), 121 (10), 113 (38), 109 (23), 96 (13), 85 (14), 58 (20), 51 (18) (HRMS found M$^+$, 249.1161. $C_{14}H_{16}NO_2F$ requires M, 249.1165).

4.6. Typical procedure for synthesis of racemic glutarimides using LDA–LiCl

4.6.1. *trans*-1,3-Dimethyl-4-(4-fluorophenyl)piperidine-2,6-dione (±) 30a. LDA was prepared by addition of *n*-BuLi (1.08 mL of a 1.5 M solution in hexanes, 1.62 mmol) to a solution of ^{i}Pr$_2$NH–HCl (112 mg, 0.80 mmol) in THF (4 mL) at −78°C, followed by warming to room

temperature over 15 min. The resulting solution of LDA and LiCl was then cooled to −78°C, before being added dropwise via cannula over 5 min to a stirred solution of the imide **28** (R=Me) (150 mg, 0.68 mmol) in THF (10 mL), maintaining a temperature of −78°C±1. The reaction mixture was stirred for 45 min after which it was diluted with further THF (14 mL) before addition of methyl iodide (0.42 mL, 6.78 mmol). The reaction mixture was then warmed to −40°C±1 and stirred for 4 h before quenching with saturated aqueous NH_4Cl solution (20 mL) and extraction into Et_2O (40 mL). The aqueous phase was separated and re-extracted with Et_2O (2×20 mL). The organic extracts were combined washed with brine (80 mL), dried ($MgSO_4$), filtered and concentrated in vacuo. The product was purified via flash column chromatography on silica gel (40% EtOAc/petroleum ether) to yield mono-methylated glutarimide **30a** as a pale yellow solid (48 mg, 30%). Spectroscopic data matched that of corresponding chiral base reaction (HRMS [EI] found M^+, 235.1006. $C_{13}H_{14}NO_2F$ requires M, 235.1009).

4.6.2. (3*S*,4*R*)-3-Benzyl-4-(4-fluorophenyl)-1-methylpiperidine-2,6-dione (−) 30b and (3*R*,5*S*)-3,5-dibenzyl-4-(4-fluorophenyl)-1-methylpiperidine-2,6-dione 31b. A chiral base reaction, using the typical procedure described above, employing imide **28** (R=Me) (147 mg, 0.67 mmol) and benzyl bromide (0.79 mL, 6.67 mmol) gave a 2.5:1 mixture of mono-benzylated glutarimide **30b** and bis-benzylated glutarimide **31b**. The products were purified via flash column chromatography on silica gel (40% Et_2O/petroleum ether) to yield mono-benzylated glutarimide **30b** as an oil (120 mg, 58%) and bis-benzylated glutarimide **31b** as an oil (19.9 mg, 7%).

*Data for mono-benzylated glutarimide **30b**.* $[\alpha]_D^{20}=-4.2$ (*c* 1.05 in $CHCl_3$): ν_{max} ($CHCl_3$)/cm^{-1} 2935 and 2858 (C–H), 1727 and 1682 (C=O), 1607 and 1494 (Ar); δ_H (400 MHz) 2.73 (1H, dd, *J*=17.2, 10.7 Hz, CH_{ax}H$_{eq}$CHAr), 2.92 (1H, dd, *J*=17.2, 4.5 Hz, CH$_{ax}H_{eq}$CHAr), 2.92 (1H, m, CHCH_AH$_B$Ph), 3.04 (1H, ddd, *J*=10.7, 10.0, 4.5 Hz, C*H*Ar), 3.13–3.22 (2H, m, C*H*CH$_2$Ph and CHCH$_A$$H_B$Ph), 3.21 (3H, s, NC$H_3$), 7.00–7.12 (5H, m, Ar*H*), 7.20–7.29 (4H, m, Ar*H*); δ_C (125.8 MHz) 27.0 (N*C*H$_3$), 34.4 (CH*C*H$_2$Ph), 37.8 (*C*HAr), 39.8 (*C*H$_2$CHAr), 49.4 (*C*HCH$_2$Ph), 116.1 (J_{C-F}=22 Hz, Ar*C*H), 126.7 (Ar*C*H), 128.5 (Ar*C*H), 128.8 (J_{C-F}=7 Hz, Ar*C*H), 129.4 (Ar*C*H), 136.4 (Ar*C*), 138.2 (Ar*C*), 162.1 (J_{C-F}=246 Hz, Ar*C*), 171.0 (*C*=O), 174.0 (*C*=O); MS (FAB) *m/z* 312 ([M+H]$^+$, 8%), 176 (18), 154 (26), 136 (20), 123 (10), 109 (21), 95 (41), 81 (47) 69 (76), 57 (100) (HRMS found [M+H]$^+$, 312.1406. $C_{19}H_{18}NO_2$ requires [M+H], 312.1399). The ee was determined as 74% by HPLC (OD column, 2% IPA in hexane, 0.8 mL/min), the retention times were 56.4 min (minor) and 65.1 min (major).

*Data for bis-benzylated glutarimide **31b**.* ν_{max} ($CHCl_3$)/cm^{-1} 2956, 2931 and 2871 (C–H), 1722 and 1667 (C=O), 1605 and 1495 (Ar); δ_H (400 MHz) 2.79 (2H, dd, *J*=14.2, 6.4 Hz, 2×CHCH_AH$_B$Ph), 2.86 (1H, dd, *J*=12.1, 12.1 Hz, C*H*Ar), 2.98 (2H, dd, *J*=14.2, 3.2 Hz, 2×CHCH$_A$$H_B$Ph), 3.06 (2H, ddd, *J*=12.1, 6.4, 3.2 Hz, 2×C*H*CH$_2$Ph), 3.23 (3H, s, NCH_3), 6.89–7.32 (14H, m, Ar*H*); δ_C (125.8 MHz) 27.8 (N*C*H$_3$), 33.9 (CH*C*H$_2$Ph), 43.6 (*C*HAr), 50.8 (*C*HCH$_2$Ph), 116.1 (J_{C-F}=22 Hz, Ar*C*H), 126.4 (Ar*C*H), 128.3 (Ar*C*H), 128.8 (Ar*C*H), 129.3 (Ar*C*H), 135.0 (Ar*C*), 139.1 (Ar*C*), 162.2 (J_{C-F}=247 Hz, Ar*C*), 173.8 (*C*=O); MS (EI) *m/z* 401 (M^+, 19%), 310 (M−C_7H_7, 14), 210 (91), 131 (23), 106 (97), 105 (100), 91 (C_7H_7, 64), 79 (13), 77 (C_6H_5, 18), 51 (14) (HRMS: found M^+, 401.1802. $C_{26}H_{24}NO_2F$ requires M, 401.1791).

Glutarimide **30b** was prepared in racemic form (24%) by use of LDA–LiCl as base, according to the typical procedure given above.

4.6.3. (3*S*,4*R*)-3-(4-Bromobenzyl)-4-(4-fluorophenyl)-1-methylpiperidine-2,6-dione (−) 30c and (3*R*,5*S*)-3,5-bis(4-bromobenzyl)-4-(4-fluorophenyl)-1-methylpiperidine-2,6-dione 31c. A chiral base reaction, using the typical procedure described above, employing imide **28** (R=Me) (150 mg, 0.68 mmol) and 4-bromobenzyl bromide (1.70 g, 6.78 mmol) gave a 3.0:1 mixture of mono-bromobenzylated glutarimide **30c** and bis-bromobenzylated glutarimide **31c**. The products were purified via flash column chromatography on silica gel (30% EtOAc/petroleum ether) to yield mono-bromobenzylated glutarimide **30c** as an oil (115 mg, 63%) and bis-bromobenzylated glutarimide **31c** as an oil (33.3 mg, 9%).

*Data for mono-bromobenzylated glutarimide **30c**.* $[\alpha]_D^{20}=-25$ (*c* 1.62 in $CHCl_3$): ν_{max} ($CHCl_3$)/cm^{-1} 2960 (C–H), 1726 and 1681 (C=O), 1606 and 1512 (Ar); δ_H (400 MHz) 2.70 (1H, dd, *J*=17.2, 11.5 Hz, CH_{ax}H$_{eq}$CHAr), 2.83 (1H, m, CHCH_AH$_B$Ar), 2.91 (1H, dd, *J*=17.2, 4.4 Hz, CH$_{ax}H_{eq}$CHAr), 2.99 (1H, ddd, *J*=11.5, 11.0, 4.4 Hz, C*H*Ar), 3.13 (2H, m, C*H*CH$_2$Ar and CHCH$_A$$H_B$Ar), 3.19 (3H, s, NC$H_3$), 6.86 (2H, m, Ar*H*), 7.08 (4H, m, Ar*H*), 7.33 (2H, m, Ar*H*); δ_C (125.8 MHz) 27.2 (N*C*H$_3$), 33.5 (CH*C*H$_2$Ar), 38.3 (*C*HAr), 40.5 (*C*H$_2$CHAr), 49.6 (*C*HCH$_2$Ar), 116.3 (J_{C-F}=22 Hz, Ar*C*H), 120.7 (Ar*C*), 128.9 (J_{C-F}=8 Hz, Ar*C*H), 131.3 (Ar*C*H), 131.6 (Ar*C*H), 136.1 (Ar*C*), 137.3 (Ar*C*), 162.2 (J_{C-F}=247 Hz, Ar*C*), 170.8 (*C*=O), 174.1 (*C*=O); MS (EI) *m/z* 392 (($C_{19}H_{17}NO_2F^{81}Br$+H)$^+$, 30), 391 (($C_{19}H_{17}NO_2F^{81}Br$)$^+$, 97), 390 (($C_{19}H_{17}NO_2F^{79}Br$+H)$^+$, 30), 389 (($C_{19}H_{17}NO_2F^{79}Br$)$^+$, 100), 235 (18), 221 (21), 220 (91), 210 (56), 181 (31), 149 (64), 136 (19), 135 (19), 133 (21), 122 (59), 121 (21), 109 (36), 106 (40), 105 (70), 101 (19), 91 (31), 90 (24), 89 (22), 77 (22) (HRMS: found M^+, 389.0431. $C_{19}H_{17}NO_2F^{79}Br$ requires M, 389.0427). The ee was determined as 77% by HPLC (OJ column, 2% IPA and 1% MeCN in hexane, 0.8 mL/min), the retention times were 75.5 min (minor) and 90.9 min (major).

*Data for bis-bromobenzylated glutarimide **31c**.* ν_{max} ($CHCl_3$)/cm^{-1} 2937 (C–H), 1723 and 1672 (C=O), 1606 and 1488 (Ar); δ_H (400 MHz) 2.75 (2H, dd, *J*=14.2, 6.4 Hz, 2×CHCH_AH$_B$Ar), 2.79 (1H, dd, *J*=12.2, 12.2 Hz, C*H*Ar), 2.91 (2H, dd, *J*=14.2, 3.1 Hz, 2×CHCH$_A$$H_B$Ar), 3.00 (2H, ddd, *J*=12.2, 6.4, 3.1 Hz, 2×C*H*CH$_2$Ar), 3.21 (3H, s, NCH_3), 6.76 (4H, m, Ar*H*), 7.08 (4H, m, Ar*H*), 7.29 (4H, m, Ar*H*); δ_C (125.8 MHz) 27.8 (N*C*H$_3$), 33.3 (CH*C*H$_2$Ar), 43.8 (*C*HAr), 50.7 (*C*HCH$_2$Ar), 116.3 (J_{C-F}=22 Hz, Ar*C*H), 120.3 (Ar*C*), 130.0 (J_{C-F}=8 Hz, Ar*C*H), 131.0 (Ar*C*H), 131.4 (Ar*C*H), 134.8 (Ar*C*), 138.0 (Ar*C*), 162.2 (J_{C-F}=248 Hz, Ar*C*), 173.3 (*C*=O); MS (EI) *m/z* 561 (($C_{26}H_{22}NO_2F^{81}Br_2$)$^+$, 28%), 560 (($C_{26}H_{22}NO_2F^{79}Br^{81}Br$+H)$^+$, 17), 559 (($C_{26}H_{22}NO_2F^{79}Br^{81}Br$)$^+$, 55), 558

(($C_{26}H_{22}NO_2F^{79}Br_2$+H)$^+$, 9), 557 (($C_{26}H_{22}NO_2F^{79}Br_2$)$^+$, 36), 450 (9), 391 (12), 390 (58), 389 (10), 388 (58), 267 (19), 242 (18), 240 (36), 237 (18), 212 (9), 211 (40), 210 (97), 209 (46), 171 ($C_7H_6^{81}Br$, 23), 170 ($C_7H_6^{79}Br$+H, 10), 169 ($C_7H_6^{79}Br$, 92), 148 (100), 109 (17), 106 (64), 105 (89), 91 (19), 90 (28), 51 (38) (HRMS: found M$^+$, 557.0022. $C_{26}H_{22}NO_2F^{79}Br_2$ requires M, 557.0001).

Glutarimide **30c** was prepared in racemic form (12%) by use of LDA–LiCl as base, according to the typical procedure given above.

4.6.4. (3*S*,4*R*)-4-(4-Fluorophenyl)-1-methyl-2,6-dioxopiperidine-3-carboxylic acid methyl ester (−) 30d and dimethyl (3*R*,5*S*)-4-(4-fluorophenyl)-1-methyl-2,6-dioxo-3,5-piperidinedicarboxylate 31d. A chiral base reaction, using the typical procedure described above (but with reaction time of only 30 min at −78°C after adding MeO_2CCN), employing imide **28** (R=Me) (150 mg, 0.68 mmol) and methyl cyanoformate (0.08 mL, 1.02 mmol) gave a 20:1 mixture of mono-methyl ester glutarimide **30d** and bis-methyl ester glutarimide **31d**. The crude product was purified via flash column chromatography on silica gel (80% Et_2O/petroleum ether) to yield mono-methyl ester glutarimide **30d** as a white solid (165 mg, 87%). The minor component was not isolated from this particular reaction, but the presence of bis-methyl ester glutarimide **30d** was verified by comparison of the ^{1}H NMR spectrum of the crude reaction mixture with data from a pure sample of bis-methyl ester glutarimide from other reactions.

*Data for mono-methyl ester glutarimide **30d***. Mp 80–83°C; $[\alpha]_D^{24}$=−30 (*c* 1.81 in $CHCl_3$): ν_{max} ($CHCl_3$)/cm^{-1} 2956 (C–H), 1749, 1730 and 1681 (C=O), 1608 and 1512 (Ar); δ_H (400 MHz) 2.85 (1H, dd, *J*=17.4, 11.9 Hz, C*H*$_{ax}$H$_{eq}$-CHAr), 2.99 (1H, dd, *J*=17.4, 4.5 Hz, CH$_{ax}$*H*$_{eq}$CHAr), 3.20 (3H, s, NC*H*$_3$), 3.64 (3H, s, OC*H*$_3$), 3.69 (1H, ddd, *J*=11.9, 11.5, 4.5 Hz, C*H*Ar), 3.82 (1H, d, *J*=11.5 Hz, C*H*CO$_2$CH$_3$), 7.04 (2H, m, Ar*H*), 7.19 (2H, m, Ar*H*); δ_C (125.8 MHz) 27.1 (N*C*H$_3$), 37.7 (*C*H$_2$CHAr), 38.9 (*C*HAr), 52.9 (*C*HCO$_2$CH$_3$), 56.4 (O*C*H$_3$), 116.3 (*J*$_{C-F}$=22 Hz, Ar*C*H), 128.5 (*J*$_{C-F}$= 8 Hz, Ar*C*H), 134.5 (Ar*C*), 162.3 (*J*$_{C-F}$=247 Hz, Ar*C*), 168.2 (*C*=O), 168.6 (*C*=O), 170.4 (*C*=O); MS (EI) *m*/*z* 279 (M$^+$, 8%), 221 (16), 220 (M−CO$_2$CH$_3$, 100), 149 (17), 135 (9), 121 (7) (HRMS: found M$^+$, 279.0909. $C_{14}H_{14}NO_4F$ requires M, 279.0907). The ee was determined as 75% by HPLC (OD column, 3% EtOH in hexane, 0.8 mL/min), the retention times were 83.4 min (minor) and 91.9 min (major).

*Data for bis-methyl ester glutarimide **31d***. ν_{max} ($CHCl_3$)/cm^{-1} 2956 (C–H), 1749, 1730 and 1682 (C=O), 1607 and 1512 (Ar); δ_H (500 MHz) 3.25 (3H, s, NC*H*$_3$), 3.62 (6H, s, 2×OC*H*$_3$), 3.83 (2H, d, *J*=12.9 Hz, 2×C*H*CO$_2$CH$_3$), 4.04 (1H, dd, *J*=12.9, 12.9 Hz, C*H*Ar), 7.04 (2H, m, Ar*H*), 7.19 (2H, m, Ar*H*); δ_C (125.8 MHz) 27.6 (N*C*H$_3$), 40.8 (*C*HAr), 52.9 (O*C*H$_3$), 55.8 (*C*HCO$_2$CH$_3$), 116.3 (*J*$_{C-F}$=22 Hz, Ar*C*H), 129.1 (*J*$_{C-F}$=8 Hz, Ar*C*H), 131.9 (Ar*C*), 162.6 (Ar*C*), 167.5 (*C*=O), 170.4 (*C*=O); MS (EI) *m*/*z* 337 (M$^+$, 13%), 279 (40), 278 (M−CO$_2$CH$_3$, 100), 277 (19), 247 (15), 246 (53), 234 (31), 221 (42), 220 (45), 219 (14), 189 (19), 181 (32), 133 (46), 121 (27), 101 (23), 59 (CO$_2$CH$_3$, 23) (HRMS found M$^+$, 337.0966. $C_{16}H_{16}NO_6F$ requires M, 337.0962).

Glutarimide **30d** was prepared in racemic form (38%) by use of LDA–LiCl as base, according to the typical procedure given above.

4.6.5. (3*S*,4*R*)-1-Benzyl-4-(4-fluorophenyl)-3-methylpiperidine-2,6-dione (−) 30e and (3*R*,5*S*)-1-benzyl-4-(4-fluorophenyl)-3,5-dimethylpiperidine-2,6-dione 31e. A chiral base reaction, using the typical procedure described above, employing imide **28** (R=Bn) (202 mg, 0.68 mmol) and methyl iodide (3.0 mL, 48.2 mmol) gave a 3:1 mixture of mono-methylated glutarimide **30e** and bis-methylated glutarimide **31e**. The products were purified via flash column chromatography on silica gel (40% Et_2O/petroleum ether) to yield mono-methylated glutarimide **30e** as a white solid (137 mg, 65%) and bis-methylated glutarimide **31e** as a white solid (32 mg, 14%).

*Data for mono-methylated glutarimide **30e***. Mp 115–118°C; $[\alpha]_D^{22}$=−21 (*c* 1.02 in $CHCl_3$); ν_{max} ($CHCl_3$)/cm^{-1} 3090–2881 (C–H), 1726 and 1681 (C=O), 1606 and 1512 (Ar); δ_H (400 MHz) 1.11 (3H, d, *J*=6.8 Hz, CHC*H*$_3$), 2.72 (1H, dq, *J*=11.2, 6.8 Hz, C*H*CH$_3$), 2.78 (1H, dd, *J*=17.7, 13.2 Hz, C*H*$_{ax}$H$_{eq}$CHAr), 2.94 (1H, m, C*H*Ar), 2.94 (1H, dd, *J*=17.7, 4.2 Hz, CH$_{ax}$*H*$_{eq}$CHAr), 4.97 (1H, d, *J*= 13.8 Hz, NC*H*$_A$H$_B$Ph), 5.02 (1H, d, *J*=13.8 Hz, NCH$_A$*H*$_B$Ph), 7.02 (2H, m, Ar*H*), 7.11 (2H, m, Ar*H*), 7.29 (3H, m, Ar*H*), 7.38 (2H, m, Ar*H*); δ_C (100.6 MHz) 14.4 (CH*C*H$_3$), 40.8 (*C*H$_2$CHAr), 41.9 (*C*HAr), 43.4 (N*C*H$_2$Ph), 43.5 (*C*HCH$_3$), 116.1 (*J*$_{C-F}$=21 Hz, Ar*C*H), 127.6 (Ar*C*H), 128.5 (Ar*C*H), 128.6 (Ar*C*H), 128.9 (Ar*C*H), 136.3 (Ar*C*), 137.3 (Ar*C*), 162.1 (*J*$_{C-F}$=246 Hz, Ar*C*), 171.0 (*C*=O), 174.5 (*C*=O); MS (EI) *m*/*z* 311 (M$^+$, 100%), 283 (M−CO, 14), 268 (10), 161 (25), 146 (48), 136 (25), 109 (25), 106 (36), 104 (39), 91 (C_7H_7, 43), 77 (C_6H_5, 11) (HRMS: found M$^+$, 311.1334. $C_{19}H_{18}NO_2F$ requires M, 311.1322). The ee was determined as 97% by HPLC (OD column 5% IPA in hexane, 0.8 mL/min), the retention times were 49.8 min (minor) and 59.5 min (major).

*Data for bis-methylated glutarimide **31e***. Mp 124–126°C; ν_{max} ($CHCl_3$)/cm^{-1} 3089–2881 (C–H), 1722 and 1682 (C=O), 1605 and 1512 (Ar); δ_H (500 MHz) 1.04 (6H, d, *J*= 6.8 Hz, 2×CHC*H*$_3$), 2.60 (1H, dd, *J*=12.2, 12.2 Hz, C*H*Ar), 2.74 (2H, dq, *J*=12.2, 6.8 Hz, 2×C*H*CH$_3$), 5.01 (2H, s, NC*H*$_2$Ph) 7.04–7.12 (3H, m, Ar*H*), 7.26 (2H, m, Ar*H*), 7.29–7.32 (2H, m, Ar*H*), 7.41 (2H, m, Ar*H*); δ_C (125.8 MHz) 14.4 (CH*C*H$_3$), 43.9 (N*C*H$_2$Ph), 44.0 (*C*HCH$_3$), 49.3 (*C*HAr), 116.1 (*J*$_{C-F}$=21 Hz, Ar*C*H), 127.5 (Ar*C*H), 128.5 (Ar*C*H), 129.0 (Ar*C*H), 135.9 (Ar*C*H), 137.5 (Ar*C*), 162.0 (*J*$_{C-F}$=247 Hz, Ar*C*), 174.2 (*C*=O); MS (EI) *m*/*z* 325 (M$^+$, 100%), 282 (11), 161 (53), 136 (39), 133 (20), 106 (42), 91 (C_7H_7, 29), 77 (C_6H_5, 4) (HRMS found M$^+$, 325.1486. $C_{20}H_{20}NO_2F$ requires M, 325.1478).

Glutarimide **30e** was prepared in racemic form (34%) by use of LDA–LiCl as base, according to the typical procedure given above.

4.6.6. (3*S*,4*R*)-3-Allyl-1-benzyl-4-(4-fluorophenyl)piperidine-2,6-dione (−) 30f and (3*R*,5*S*)-1-benzyl-3,5-diallyl-4-(4-fluorophenyl)piperidine-2,6-dione 31f. A chiral base reaction, using the typical procedure described above, employing imide **28** (R=Bn) (201 mg, 0.68 mmol) and

allyl bromide (2.0 mL, 23.1 mmol) gave a mixture of mono-allylated glutarimide **30f** and bis-allylated glutarimide **31f** (the ratio could not readily be determined from the ^{1}H NMR spectrum of the crude material). The products were purified via flash column chromatography on silica gel (40% Et_2O/petroleum ether) to yield mono-allylated glutarimide **30f** as an oil (118 mg, 52%) and bis-allylated glutarimide **31f** as an oil (19 mg, 7%).

*Data for mono-allylated glutarimide **30f**.* $[\alpha]_D^{27}$=+17 (*c* 1.27 in $CHCl_3$): ν_{max} ($CHCl_3$)/cm^{-1} 2961, 2927 and 2855 (C–H), 1725 and 1680 (C=O), 1605 and 1510 (Ar); δ_H (400 MHz) 2.14 (1H, ddd, *J*=14.2, 8.2, 5.0 Hz, C*H*$_A$H$_B$-CH=CH$_2$), 2.71 (1H, dddd, *J*=14.2, 6.0, 5.0, 1.7 Hz, CH$_A$*H*$_B$CH=CH$_2$), 2.77 (1H, dd, *J*=17.2, 11.6 Hz, C*H*$_{ax}$-H$_{eq}$CHAr), 2.88 (1H, dt, *J*=10.9, 5.0 Hz, C*H*CH$_2$CH=CH$_2$), 2.94 (1H, dd, *J*=17.2, 4.4 Hz, CH$_{ax}$*H*$_{eq}$CHAr), 3.19, (1H, td, *J*=11.6, 4.4 Hz, C*H*Ar), 4.91 (1H, ddd, *J*=17.1, 3.0, 1.7 Hz, CH$_A$=CH$_B$*H*$_C$), 4.98 (1H, d, *J*=13.8 Hz, NC*H*$_A$H$_B$Ph), 5.04 (1H, d, *J*=13.8 Hz, NCH$_A$*H*$_B$Ph), 5.04 (1H, m, CH$_A$=C*H*$_B$H$_C$), 5.64 (1H, dddd, *J*=17.1, 10.2, 8.2, 6.0 Hz, C*H*$_A$=CH$_B$H$_C$), 7.04 (2H, m, Ar*H*), 7.11 (2H, m, Ar*H*), 7.25–7.33 (3H, m, Ar*H*), 7.38 (2H, m, Ar*H*); δ_C (125.8 MHz) 32.5 (*C*H$_2$CH=CH$_2$), 37.8 (*C*HAr), 40.2 (*C*H$_2$CHAr), 43.3 (NCH$_2$Ph), 47.8 (*C*HCH$_2$CH=CH$_2$), 116.0 (*J*$_{C-F}$=21 Hz, Ar*C*H), 118.7 (CH=*C*H$_2$), 127.6 (Ar*C*H), 128.5 (Ar*C*H), 128.8 (*J*$_{C-F}$=8 Hz, Ar*C*H), 128.9 (Ar*C*H), 133.6 (*C*H=CH$_2$), 136.1 (Ar*C*), 137.1 (Ar*C*), 162.0 (*J*$_{C-F}$=247 Hz, Ar*C*), 170.8 (*C*=O), 173.3 (*C*=O); MS (EI) *m*/*z* 338 ([M+H]$^+$, 21%), 337 (M$^+$, 100), 162 (23), 146 (20), 106 (18), 91 (C$_7$H$_7$, 31), 77 (C$_6$H$_5$, 3), 50 (26) (HRMS: found M$^+$, 337.1482. $C_{21}H_{20}NO_2F$ requires M, 337.1478). The ee was determined as 90% by HPLC (OD column, 5% IPA in hexane, 0.8 mL/min), the retention times were 34.7 min (minor) and 38.4 min (major).

*Data for bis-allylated glutarimide **31f**.* ν_{max} ($CHCl_3$)/cm^{-1} 2925 and 2863 (C–H), 1723 and 1672 (C=O), 1606 and 1496 (Ar); δ_H (400 MHz) 1.94 (2H, ddd, *J*=14.2, 8.7, 4.6 Hz, 2×C*H*$_A$H$_B$CH=CH$_2$), 2.70 (2H, dm, *J*=14.2 Hz, 2×CH$_A$*H*$_B$CH=CH$_2$), 2.84 (2H, dt, *J*=12.4, 4.6 Hz, 2×C*H*CH$_2$CH=CH$_2$), 3.04, (1H, dd, *J*=12.4, 12.4 Hz, C*H*Ar), 4.85 (2H, ddm, *J*=17.0, 1.0 Hz, CH$_A$=CH$_B$*H*$_C$), 5.01 (2H, dm, *J*=10.2 Hz, CH$_A$=C*H*$_B$H$_C$), 5.04 (2H, s, NC*H*$_2$Ph), 5.59 (2H, dddd, *J*=17.0, 10.2, 8.7, 5.5 Hz, C*H*$_A$=CH$_B$H$_C$), 7.05–7.15 (4H, m, Ar*H*), 7.27–7.34 (3H, m, Ar*H*), 7.40 (2H, m, Ar*H*); δ_C (125.8 MHz) 31.9 (*C*H$_2$CH=CH$_2$), 41.6 (*C*HAr), 43.8 (NCH$_2$Ph), 48.2 (*C*HCH$_2$CH=CH$_2$), 116.0 (*J*$_{C-F}$=21 Hz, Ar*C*H), 118.6 (HC=*C*H$_2$), 127.5 (Ar*C*H), 128.4 (Ar*C*H), 128.8 (Ar*C*H), 129.6 (*J*$_{C-F}$=7 Hz, Ar*C*H), 133.7 (H*C*=CH$_2$), 134.9 (Ar*C*), 137.3 (Ar*C*), 162.0 (*J*$_{C-F}$=162.0 Hz, Ar*C*), 172.7 (*C*=O); MS (EI) *m*/*z* 378 ([M+H]$^+$, 37%), 377 (M$^+$, 100), 336 (M−C$_3$H$_5$, 20), 296 (12), 188 (45), 187 (20), 186 (35), 147 (21), 146 (16), 133 (13), 132 (14), 109 (20), 106 (24), 91 (C$_7$H$_7$, 85), 77 (C$_6$H$_5$, 4) (HRMS: found M$^+$, 377.1795. $C_{24}H_{24}NO_2F$ requires M, 377.1791).

Glutarimide **30f** was prepared in racemic form (28%) by use of LDA–LiCl as base, according to the typical procedure given above.

4.6.7. (3*S*,4*R*)-1,3-Dibenzyl-4-(4-fluorophenyl)piperidine-2,6-dione (+) -30g and (3*R*,5*S*)-4-(4-fluorophenyl)-1,3,5-tribenzylpiperidine-2,6-dione 31g. A chiral base reaction, using the typical procedure described above, employing imide **28** (R=Bn) (201 mg, 0.68 mmol) and benzyl bromide (2.0 mL, 16.7 mmol) gave a 2:1 mixture of mono-benzylated glutarimide **30g** and bis-benzylated glutarimide **31g**, respectively. The products were purified via flash column chromatography on silica gel (40% Et_2O/petroleum ether) to yield mono-benzylated glutarimide **30g** as an oil (160 mg, 61%) and bis-benzylated glutarimide **31g** as an oil (72 mg, 22%).

*Data for mono-benzylated glutarimide **30g**.* $[\alpha]_D^{27}$=+11 (*c* 1.15 in $CHCl_3$): ν_{max} ($CHCl_3$)/cm^{-1} 2931 and 2858 (C–H), 1725 and 1681 (C=O), 1606, 1585, 1495 and 1454 (Ar); δ_H (500 MHz) 2.64 (1H, dd, *J*=17.2, 10.7 Hz, C*H*$_{ax}$H$_{eq}$CHAr), 2.77 (1H, dd, *J*=14.1, 5.3 Hz, CHC*H*$_A$H$_B$Ph), 2.81 (1H, dd, *J*=17.2, 4.6 Hz, CH$_{ax}$*H*$_{eq}$CHAr), 2.91 (1H, ddd, *J*=10.7, 10.2, 4.6 Hz, C*H*Ar), 3.07 (1H, dt, *J*=10.2, 5.3 Hz, C*H*CH$_2$Ph), 3.17, (1H, dd, *J*=14.1, 5.3 Hz, CHCH$_A$*H*$_B$Ph), 4.93 (2H, s, NC*H*$_2$Ph), 6.83 (2H, m, Ar*H*), 6.91 (4H, m, Ar*H*), 7.06 (3H, m, Ar*H*), 7.15–7.26 (5H, m, Ar*H*); δ_C (125.8 MHz) 34.4 (CH*C*H$_2$Ph), 37.3 (*C*HAr), 39.8 (*C*H$_2$-CHAr), 43.4 (N*C*H$_2$Ph), 49.3 (*C*HCH$_2$Ph), 116.1 (*J*$_{C-F}$=21 Hz, Ar*C*H), 126.7 (Ar*C*H), 127.6 (Ar*C*H), 128.5 (Ar*C*H), 128.8 (*J*$_{C-F}$=8 Hz, Ar*C*H), 129.0 (Ar*C*H), 129.5 (Ar*C*H), 136.3 (Ar*C*), 137.0 (Ar*C*), 137.7 (Ar*C*), 162.0 (*J*$_{C-F}$=247 Hz, Ar*C*), 170.8 (*C*=O), 173.7 (*C*=O); MS (EI) *m*/*z* 388 ([M+H]$^+$, 36%), 387 (M$^+$, 100), 296 (M−C$_7$H$_7$, 12), 268 (15), 256 (44), 169 (14), 147 (14), 106 (23), 91 (C$_7$H$_7$, 72), 77 (C$_6$H$_5$, 6) (HRMS: found M$^+$, 387.1645. $C_{25}H_{22}NO_2F$ requires M, 387.1635). The ee was determined as 97% by HPLC (OD column, 4% IPA and 1% MeCN in hexane, 0.8 mL/min), the retention times were 23.5 min (major) and 45.1 min (minor).

*Data for bis-benzylated glutarimide **31g**.* ν_{max} ($CHCl_3$)/cm^{-1} 3052, 2961, 2933 and 2857 (C–H), 1724 and 1678 (C=O), 1604 and 1512 (Ar); δ_H (400 MHz) 2.75 (2H, dd, *J*=14.2, 6.2 Hz, 2×CHC*H*$_A$H$_B$Ph), 2.82 (1H, dd, *J*=12.1, 12.1 Hz, C*H*Ar), 3.03 (2H, dd, *J*=14.2, 3.3 Hz, 2×CHCH$_A$-*H*$_B$Ph), 3.07, (2H, ddd, *J*=12.1, 6.2, 3.3 Hz, 2×C*H*CH$_2$Ph), 5.05 (2H, s, NC*H*$_2$Ph), 6.79 (4H, m, Ar*H*), 6.99–7.17 (10H, m, Ar*H*), 7.30–7.36 (5H, m, Ar*H*); δ_C (125.8 MHz) 33.7 (CH*C*H$_2$Ph), 43.0 (*C*HAr), 44.3 (N*C*H$_2$Ph), 50.6 (*C*HCH$_2$Ph), 116.0 (*J*$_{C-F}$=21 Hz, Ar*C*H), 126.3 (Ar*C*H), 127.5 (Ar*C*H), 128.3 (Ar*C*H), 128.5 (Ar*C*H), 129.0 (Ar*C*H), 129.3 (Ar*C*H), 130.1 (*J*$_{C-F}$=8 Hz, Ar*C*H), 135.1 (Ar*C*), 137.1 (Ar*C*), 138.8 (Ar*C*), 162.2 (*J*$_{C-F}$=246 Hz, Ar*C*), 173.3 (*C*=O); MS (EI) *m*/*z* 478 ([M+H]$^+$, 21%), 477 (M$^+$, 53), 386 (M−C$_7$H$_7$, 29), 265 (22), 238 (21), 212 (17), 149 (31), 131 (56), 106 (15), 91 (C$_7$H$_7$, 100), 83 (23), 77 (C$_6$H$_5$, 6), 74 (22), 59 (31), 51 (42) (HRMS: found M$^+$, 477.2120. $C_{32}H_{28}NO_2F$ requires M, 477.2104).

Glutarimide **30g** was prepared in racemic form (31%) by use of LDA–LiCl as base, according to the typical procedure given above.

4.6.8. (3*S*,4*R*)-1-Benzyl-4-(4-fluorophenyl)-3-(1-hydroxy-1-phenylmethyl)piperidine-2,6-dione (+) 30h. A chiral base reaction, using the typical procedure described above, employing imide **28** (R=Bn) (201 mg, 0.68 mmol)

and benzaldehyde (0.14 mL, 1.35 mmol) gave a crude product **30h** as a ca. 1:1 mixture of diastereomers. Purification by flash column chromatography on silica gel (40% Et_2O/petroleum ether) gave firstly the less polar diastereomer of **30h** as a pale yellow solid (110 mg, 40%): $[\alpha]_D^{19}$=+11 (*c* 1.22 in $CHCl_3$): ν_{max} ($CHCl_3$)/cm^{-1} 3606 (OH), 3478 (br, OH), 3066, 3034, 2927 and 2890 (C–H), 1729 and 1681 (C=O), 1606, and 1514 (Ar); δ_H (500 MHz) 2.69 (1H, dd, *J*=18.4, 9.1 Hz, C$H_{ax}H_{eq}$CHAr), 3.07 (2H, m, $CH_{ax}H_{eq}$CHAr and C*H*Ar), 3.29 (1H, dd, *J*=7.0, 4.1 Hz, C*H*CH(OH)Ph), 4.07 (1H, d, *J*=7.2 Hz, O*H*), 4.98 (1H, d, *J*=14.3 Hz, NCH_AH_BPh), 5.01 (1H, d, *J*=14.3 Hz, NCH_AH_BPh), 5.08 (1H, dd, *J*=7.2, 4.1 Hz, C*H*(OH)Ph), 6.84–6.90 (4H, m, Ar*H*), 7.05–7.14 (2H, m, Ar*H*), 7.19–7.27 (8H, m, Ar*H*); δ_C (125.8 MHz) 34.8 (*C*HAr), 39.0 (*C*H_2CHAr), 43.2 (N*C*H_2Ph), 54.0 (*C*HCH(OH)Ph), 74.3 (*C*H(OH)Ph), 116.0 (J_{C-F}=21 Hz, Ar*C*H), 126.3 (Ar*C*H), 127.6 (Ar*C*H), 128.0 (Ar*C*H), 128.4 (Ar*C*H), 128.6 (Ar*C*H), 128.7 (Ar*C*H), 136.7 (Ar*C*), 140.5 (Ar*C*), 161.8 (J_{C-F}=247 Hz, Ar*C*), 171.1 (*C*=O), 174.1 (*C*=O); MS (FAB) *m/z* 404 ([M+H]$^+$, 11%), 386 (M−OH, 12), 211 (23), 176 (10), 154 (19), 136 (81), 123 (15), 109 (30), 95 (50), 91 (C_7H_7, 40), 81 (53), 77 (C_6H_5, 17), 69 (80), 57 (89), 55 (100) (HRMS: found [M+H]$^+$ 404.1634. $C_{25}H_{22}NO_3F$ requires [M+H], 404.1662).

The ee was determined as 97% by HPLC (OD column, 2% IPA and 1% MeCN in hexane, 0.8 mL/min), the retention times were 109.8 min (minor) and 121.5 min (major).

Further elution then gave the more polar diastereomer of **30h** as a colourless oil (95 mg, 35%): $[\alpha]_D^{24}$=+10 (*c* 1.51 in $CHCl_3$); ν_{max} ($CHCl_3$)/cm^{-1} 3601 (OH), 3543 (br, OH), 3090 and 2923 (C–H), 1725 and 1681 (C=O), 1607, and 1494 (Ar); δ_H (500 MHz) 2.79 (1H, dd, *J*=17.6, 7.4 Hz, C$H_{ax}H_{eq}$CHAr), 2.87 (1H, dd, *J*=17.6, 5.4 Hz, $CH_{ax}H_{eq}$CHAr), 3.01 (1H, d, *J*=6.0 Hz, O*H*), 3.26 (1H, m, C*H*Ar), 3.31 (1H, dd, *J*=7.0, 4.9 Hz, C*H*CH(OH)Ph), 4.97 (1H, dd, *J*=6.0, 4.9 Hz, C*H*(OH)Ph), 4.97 (1H, m, NCH_AH_BPh), 5.02 (1H, d, *J*=13.8 Hz, NCH_AH_BPh), 6.93–7.01 (4H, m, Ar*H*), 7.24–7.35 (10H, m, Ar*H*); δ_C (125.8 MHz) 36.2 (*C*HAr), 37.8 (*C*H_2CHAr), 43.3 (N*C*H_2Ph), 55.5 (*C*HCH(OH)Ph), 73.4 (*C*H(OH)Ph), 116.1 (J_{C-F}=21 Hz, Ar*C*H), 125.8 (Ar*C*H), 127.7 (Ar*C*H), 128.2 (Ar*C*H), 128.5 (Ar*C*H), 128.6 (J_{C-F}=8 Hz, Ar*C*H), 128.8 (Ar*C*H), 129.0 (Ar*C*H), 136.7 (Ar*C*), 136.8 (Ar*C*), 141.4 (Ar*C*), 161.9 (J_{C-F}=246 Hz, Ar*C*), 170.8 (*C*=O), 172.6 (*C*=O); MS (FAB) *m/z* 404 ([M+H]$^+$, 4%), 386 (M−OH, 3), 307 (24), 289 (12), 176 (12), 155 (28), 154 (100), 139 (14), 138 (35), 137 (64), 136 (71), 120 (12), 107 (26), 105 (11), 95 (11), 91 (C_7H_7, 21), 90 (14), 89 (20), 77 (C_6H_5, 22), 69 (20), 57 (31), 55 (27) (HRMS found [M+H]$^+$ 404.1646. $C_{25}H_{22}NO_3F$+H requires [M+H], 404.1662).

Glutarimide **30h** was prepared in racemic form as a ca. 1:1 ratio of diastereomers (50% yield) by use of LDA–LiCl as base, according to the typical procedure given above.

4.6.9. (3*S*,4*R*)-1-Benzyl-4-(4-fluorophenyl)-2,6-dioxo-piperidine-3-carboxylic acid methyl ester (−) 30i and dimethyl (3*R*,5*S*)-1-benzyl-4-(4-fluorophenyl)-2,6-dioxo-3,5-piperidinedicarboxylate 31i. A chiral base reaction, using the typical procedure described above (but with reaction time of only 30 min at −78°C after adding MeO_2CCN), employing imide **28** (R=Bn) (199 mg, 0.67 mmol) and methyl cyanoformate (0.11 mL, 1.34 mmol) gave a 6.5:1 mixture of mono-methyl ester glutarimide **30i** and bis-methyl ester glutarimide **31i**. The products were purified via flash column chromatography on silica gel (30% EtOAc/petroleum ether followed by dichloromethane) to yield mono-methyl ester glutarimide **30i** as a white solid (168 mg, 71%) and bis-methyl ester glutarimide **31i** contaminated with **30i**.

*Data for mono-methyl ester glutarimide **30i**.* Mp 135–137°C; $[\alpha]_D^{28}$=−31 (*c* 0.74 in $CHCl_3$): ν_{max} ($CHCl_3$)/cm^{-1} 2955 and 2902 (C–H), 1748, 1730 and 1680 (C=O), 1608, and 1512 (Ar); δ_H (400 MHz) 2.82 (1H, dd, *J*=17.5, 11.2 Hz, C$H_{ax}H_{eq}$CHAr), 3.02 (1H, dd, *J*=17.5, 4.6 Hz, $CH_{ax}H_{eq}$CHAr), 3.65 (3H, s, OCH_3), 3.68 (1H, ddd, *J*=11.2, 10.9, 4.6 Hz, C*H*Ar), 3.81 (1H, d, *J*=10.9 Hz, C*H*CO_2CH_3), 4.96 (1H, d, *J*=13.8 Hz, NCH_AH_BPh), 5.03 (1H, d, *J*=13.8 Hz, NCH_AH_BPh), 7.01 (2H, m, Ar*H*), 7.13 (2H, m, Ar*H*), 7.29 (3H, m, Ar*H*), 7.37 (2H, m, Ar*H*); δ_C (100.6 MHz) 37.5 (*C*HAr), 38.8 (*C*H_2CHAr), 43.5 (N*C*H_2Ph), 52.9 (O*C*H_3), 56.4 (*C*HCO_2CH_3), 116.2 (J_{C-F}=21 Hz, Ar*C*H), 127.8 (Ar*C*H), 128.4 (Ar*C*H), 128.6 (Ar*C*H), 129.1 (Ar*C*H), 134.4 (Ar*C*), 136.5 (Ar*C*), 162.3 (J_{C-F}=247 Hz, Ar*C*), 168.1 (*C*=O), 168.3 (*C*=O), 170.8 (*C*=O); MS (FAB) *m/z* 356 ([M+H]$^+$, 22%), 307 (32), 289 (15), 176 (13), 154 (100), 136 (73), 120 (13), 107 (22), 91 (C_7H_7, 25), 77 (C_6H_5, 20) (HRMS: found [M+H]$^+$, 356.1299. $C_{20}H_{18}NO_4F$ requires [M+H], 356.1298). The ee was determined as 97% by HPLC (OD column, 3% EtOH in hexane, 0.8 mL/min), the retention times were 75.8 min (minor) and 88.5 min (major).

*Data for bis-methyl ester glutarimide **31i**.* ν_{max} ($CHCl_3$)/cm^{-1} 3038, and 2956 (C–H), 1750, 1730 and 1682 (C=O), 1606, and 1513 (Ar);δ_H (400 MHz) 3.62 (6H, s, 2×OCH_3), 3.83 (2H, d, *J*=12.0 Hz, 2×C*H*CO_2CH_3), 4.06 (1H, dd, *J*=12.0, 12.0 Hz, C*H*Ar), 5.01 (2H, s, NCH_2Ph), 7.02 (2H, m, Ar*H*), 7.12–7.20 (2H, m, Ar*H*), 7.29–7.35 (3H, m, Ar*H*), 7.38–7.42 (2H, m, Ar*H*); δ_C (125.8 MHz) 40.7 (*C*HAr), 44.2 (N*C*H_2Ph), 53.0 (O*C*H_3), 55.8 (*C*HCO_2CH_3), 116.3 (J_{C-F}=22 Hz, Ar*C*H), 128.1 (Ar*C*H), 128.5 (Ar*C*H), 128.7 (Ar*C*H), 129.3 (Ar*C*H), 132.0 (Ar*C*), 136.0 (Ar*C*), 162.6 (J_{C-F}=248 Hz, Ar*C*), 167.4 (*C*=O), 170.8 (*C*=O); MS (FAB) *m/z* 414 ([M+H]$^+$, 3%), 319 (2), 369 (2), 329 (4), 307 (26), 289 (12), 176 (10), 154 (100), 136 (68), 120 (11), 107 (21), 91 (C_7H_7, 16), 77 (C_6H_5, 16), 69 (20), 57 (22) (HRMS: found [M+H]$^+$, 414.1359. $C_{22}H_{20}NO_6F$ requires [M+H], 414.1353).

Glutarimide **30i** was prepared in racemic form (25%) by use of LDA–LiCl as base, according to the typical procedure given above.

4.6.10. Kinetic resolution of racemic *trans*-1,3-dimethyl-4-(4-fluorophenyl)piperidine-2,6-dione 30a. Chiral lithium amide base **29** was prepared from the corresponding chiral amine (304 mg, 0.72 mmol) in THF (4.0 mL) at −78°C under an atmosphere of nitrogen, by addition of *n*-BuLi (0.90 mL of a 1.6 M solution in hexanes, 1.44 mmol), followed by warming to room temperature over 15 min. The resulting solution of the chiral base **29** was then cooled to

−78°C, before being added dropwise via cannula over 5 min to a stirred solution of racemic mono-methylated glutarimide **30a** (102 mg, 0.43 mmol) in THF (5 mL), maintaining a temperature of −78°C±1. The reaction mixture was then stirred for 45 min before dilution with further THF (8 mL) followed by addition of methyl iodide (0.27 mL, 4.35 mmol). The reaction mixture was then warmed to −40°C±1 and stirred at this temperature for a further 4 h before quenching with saturated aqueous NH_4Cl solution (20 mL) and extraction into EtOAc (2×15 mL). The organic extracts were combined, washed with 2 M HCl (3×30 mL), followed by saturated aqueous $NaHCO_3$ (30 mL) then brine (30 mL), dried ($MgSO_4$), filtered and concentrated in vacuo to give a 1.2:1 mixture of mono-methylated glutarimide **30a** and bis-methylated glutarimide **31a**, respectively. Chiral HPLC analysis of the crude mixture established that 46% conversion of racemic mono-methylated glutarimide **30a** into bis-methylated glutarimide **31a** had occurred, and that the ee of recovered mono-methylated glutarimide **30a** had increased to 13%.

4.6.11. Enantiomeric enrichment of (3*S*,4*R*)-1-benzyl-4-(4-fluorophenyl)-2,6-dioxopiperidine-3-carboxylic acid methyl ester (−) 30i by kinetic resolution. Chiral lithium amide base **29** was prepared from the corresponding chiral amine (118 mg, 0.28 mmol) in THF (1.5 mL) at −78°C under an atmosphere of nitrogen, by addition of *n*-BuLi (0.35 mL of a 1.6 M solution in hexanes, 0.56 mmol), followed by warming to room temperature over 15 min. The resulting solution of the chiral base **29** was then cooled to −78°C, before being added dropwise via cannula over 5 min to a stirred solution of mono-methyl ester glutarimide **30i** (58 mg, 0.16 mmol, 44% ee) in THF (1 mL), maintaining a temperature of −78°C±1. The reaction mixture was then stirred for 45 min after which THF (1 mL) followed by methyl cyanoformate (0.03 mL, 3.29 mmol) were added. The reaction mixture was then stirred at −78°C±1 for a further 1 h before quenching with saturated aqueous NH_4Cl solution (20 mL) and extraction into Et_2O (2×30 mL). The organic extracts were combined, washed with 2 M HCl (3×60 mL), followed by saturated aqueous $NaHCO_3$ (60 mL) then brine (60 mL), dried ($MgSO_4$), filtered and concentrated in vacuo to give a 1.4:1 mixture of recovered mono-methyl ester glutarimide **30i** and bis-methyl ester glutarimide **31i**. Purification via flash column chromatography on silica gel (DCM) yielded a mixture of bis-methyl ester glutarimide **31i** and mono-methyl ester glutarimide **30i** (18 mg) as a colourless oil and recovered mono-methyl ester glutarimide **30i** (8 mg, 15%) as a white solid. Chiral HPLC analysis of the recovered mono-methyl ester glutarimide **30i** established that the ee had increased from 44% to 81%.

4.7. Total synthesis of paroxetine (−)-6 (Scheme 10)

4.7.1. (3*S*,4*R*)-1-Benzyl-4-(4-fluorophenyl)-3-piperidine-methanol 36. Imide **30i** (97% ee) (204 mg, 0.57 mmol) dissolved in THF (2.1 mL) was added dropwise to a stirred solution of $LiAlH_4$ (2.9 mL of a 1 M solution in THF, 2.9 mmol) whilst being cooled by an ice bath. The reaction mixture was then warmed to room temperature and then heated at reflux overnight. After this time the flask was cooled to room temperature, water (1.0 mL) was added dropwise and the mixture was stirred for 10 min. 2 M NaOH (3.0 mL) was then added and the reaction mixture was left to stir for a further 10 min. The mixture was then poured into saturated Rochelle's salt solution (30 mL) and extracted with EtOAc (4×20 mL). The organic extracts were combined, washed with brine (3×20 mL), dried ($MgSO_4$), filtered and concentrated in vacuo to yield piperidine alcohol **36** as a colourless oil (155 mg, 90%), which was used without further purification: ν_{max} ($CHCl_3$)/cm^{-1} 3626 (OH), 3085–2763 (C–H), 1604 and 1511 (Ar); δ_H (400 MHz) 1.70–1.95 (2H, m, 5-CH_2), 2.05 (3H, m, 2-CH_AH$_B$, 3-C*H* and 6-CH_AH$_B$), 2.35 (1H, ddd, *J*=11.5, 11.5, 4.1 Hz, 4-C*H*), 3.00 (1H, dm, *J*=11.5 Hz, 6-CH$_A$$H_B$), 3.23 (1H, dd, *J*=10.9, 6.2 Hz, CH_AH$_B$OH), 3.23 (1H, m, 2-CH$_A$$H_B$), 3.38 (1H, dd, *J*=10.9, 2.6 Hz, CH$_A$$H_B$OH), 3.58 (1H, d, *J*=13.0 Hz, NCH_AH$_B$Ph), 3.65 (1H, d, *J*=13.0 Hz, NCH$_A$$H_B$Ph), 6.95–7.01 (2H, m, Ar*H*), 7.14–7.37 (7H, m, Ar*H*); δ_C (125.8 MHz) 34.5 (5-*C*H$_2$), 44.2 (4-*C*H), 44.3 (3-*C*H), 54.0 (6-*C*H$_2$), 57.4 (2-*C*H$_2$), 63.6 (N*C*H$_2$Ph), 64.0 (*C*H$_2$OH), 115.4 (J_{C-F}=21 Hz, Ar*C*H), 127.1 (Ar*C*H), 128.3 (Ar*C*H), 128.9 (J_{C-F}=8 Hz, Ar*C*H), 129.4 (Ar*C*H), 138.1 (Ar*C*), 140.2 (Ar*C*), 161.5 (J_{C-F}=244 Hz, Ar*C*); MS (EI) *m*/*z* 299 (M$^+$, 35%), 208 (M−C$_7$H$_7$, 15), 176 (20), 146 (15), 134 (11), 120 (46), 109 (12), 91 (C$_7$H$_7$, 100), 65 (12), 57 (17), 51 (27) (HRMS: found M$^+$, 299.1682. $C_{19}H_{22}NOF$ requires M, 299.1686).

4.7.2. (3*S*,4*R*)-1-Benzyl-4-(4-fluorophenyl)-3-methyl-sulfonatepiperidine 37. Mesyl Chloride (0.05 mL, 0.57 mmol) was added to a solution of piperidine alcohol **36** (155 mg, 0.52 mmol) in pyridine (1.6 mL) at 10°C. The reaction mixture was left to stir for 1 h after which the reaction mixture was poured into a 10% solution of $NaHCO_3$ (10 mL) and extracted with Et_2O (3×20 mL). The organic extracts were combined, dried ($MgSO_4$), filtered and concentrated in vacuo to give mesylate **37** as an oil (141 mg, 72%), which was used without further purification: ν_{max} ($CHCl_3$)/cm^{-1} 2924 and 2767 (C–H), 1606, 1509 and 1404 (Ar), 1350 (OSO_2CH_3); δ_H (400 MHz) 1.73 (2H, m, 5-CH_2), 1.97 (2H, m, 2-CH_AH$_B$ and 3-C*H*), 2.16 (1H, m, 6-CH_AH$_B$), 2.31 (1H, m, 4-C*H*), 2.74 (3H, s, OSO_2CH_3), 2.90 (1H, dm, *J*=11.8 Hz, 6-CH$_A$$H_B$), 3.08 (1H, dd, *J*=9.3, 3.4 Hz, 2-CH$_A$$H_B$), 3.47 (1H, d, *J*=13.1 Hz, NCH_AH$_B$Ph), 3.55 (1H, d, *J*=13.1 Hz, NCH$_A$$H_B$Ph), 3.72 (1H, dd, *J*=9.9, 6.8 Hz, CH_AH$_B$OSO$_2$CH$_3$), 3.84 (1H, dd, *J*=9.9, 3.0 Hz, CH$_A$$H_BOSO_2CH_3$), 6.93 (2H, m, ArH), 7.10 (2H, m, Ar*H*), 7.17–7.27 (5H, m, Ar*H*); δ_C (125.8 MHz) 34.4 (5-*C*H$_2$), 36.9 (OSO$_2$*C*H$_3$), 41.5 (4-*C*H), 43.8 (3-*C*H), 53.6 (6-*C*H$_2$), 56.6 (2-*C*H$_2$), 63.3 (N*C*H$_2$Ph), 70.8 (*C*H$_2$-OSO$_2$CH$_3$), 115.7 (J_{C-F}=21 Hz, Ar*C*H), 127.3 (Ar*C*H), 128.4 (Ar*C*H), 128.9 (Ar*C*H), 129.3 (Ar*C*H), 137.8 (Ar*C*), 138.7 (Ar*C*), 161.7 (J_{C-F}=245 Hz, Ar*C*); MS (EI) *m*/*z* 378 ([M+H]$^+$, 16%), 337 (M$^+$, 58), 300 ((M−C$_6$H$_5$)$^+$, 14), 298 (21), 282 (50), 267 (48), 146 (21), 134 (53), 120 (24), 109 (16), 91 (C$_7$H$_7$, 100), 77 (C$_6$H$_5$, 5), 65 (17), 57 (22), 50 (27) (HRMS: found M$^+$, 377.1452. $C_{20}H_{24}NO_3SF$ requires M, 377.1461).

4.7.3. (3*S*,4*R*)-1-Benzyl-4-(4-fluorophenyl)-3-[3,4-(methylenedioxy)-phenoxymethyl] piperidine 39. Sesamol **38** (245 mg, 1.77 mmol) was added to a suspension of NaOMe (97 mg, 1.80 mmol) in MeOH (2 mL) at room temperature and left to stir for 30 min. Mesylate **37** (134 mg) was then added and the reaction mixture was

heated at reflux overnight. The reaction mixture was cooled to room temperature and the solvent removed in vacuo. The residue was diluted with EtOAc (60 mL), washed with 2 M NaOH (3×60 mL), dried ($MgSO_4$), filtered and concentrated in vacuo. The product was purified via flash column chromatography using silica gel (40% EtOAc/petroleum ether) to give piperidine **39** as an oil (81 mg, 55%): ν_{max} ($CHCl_3$)/cm^{-1} 3085–2766 (C–H), 1605 and 1511 (Ar); δ_H (400 MHz) 1.75–1.92 (2H, m, 5-CH_2), 2.00–2.14 (2H, m, 2-CH_AH_B and 3-CH), 2.23 (1H, m, 6-CH_AH_B), 2.50 (1H, ddd, J=11.5, 11.5, 4.5 Hz, 4-CH), 3.00 (1H, dm, J=11.5 Hz, 6-CH$_A$$H_B$), 3.26 (1H, dd, J=11.1, 1.6 Hz, 2-CH$_A$$H_B$), 3.45 (1H, dd, J=9.3, 6.8 Hz, CH_AH_BOAr), 3.56 (1H, d, J=13.1 Hz, NCH_AH_BPh), 3.56 (1H, m, CH$_A$$H_B$-OAr), 3.66 (1H, d, J=13.1 Hz, NCH$_A$$H_B$Ph), 5.89 (2H, s, OC$H_2$O), 6.12 (1H, dd, J=8.5, 2.5 Hz, 6′-ArCH), 6.34 (1H, d, J=2.5 Hz, 2′-ArCH), 6.63 (1H, d, J=8.5 Hz, 5′-ArCH), 6.96–7.05 (2H, m, ArH), 7.14–7.19 (2H, m, ArH), 7.21–7.39 (5H, m, ArCH); δ_C (100.6 MHz) 34.4 (5-CH_2), 42.2 (4-CH), 44.2 (3-CH), 53.9 (6-CH_2), 57.7 (2-CH_2), 63.5 (NCH_2Ph), 69.7 (CH_2OAr), 98.1 (2′-ArCH), 101.1 (OCH_2O), 105.3 (6′-ArCH), 107.9, (5′-ArCH), 115.4 (J_{C-F}=21 Hz, ArCH), 127.1 (ArCH), 128.3 (ArCH), 128.9 (J_{C-F}=8 Hz, ArCH), 129.3 (ArCH), 138.2 (ArC), 139.9 (ArC), 141.6 (3′-ArC), 148.2 (4′-ArC), 154.5 (1′-ArC), 161.5 (J_{C-F}=244 Hz, ArC); MS (EI) m/z 419 (M^+, 21%), 282 ((M−$C_7H_5O_3$)$^+$, 48), 267 (58), 134 (36), 91 (C_7H_7, 100) (HRMS: found M^+, 419.1898. $C_{26}H_{26}NO_3F$ requires M, 419.1897).

4.7.4. (3*S*,4*R*)-4-(4-Fluorophenyl)-3-[(3,4-(methylene-dioxy)-phenoxymethyl]piperidine (paroxetine) (−)-6. 1-Chloroethyl chloroformate (0.03 mL, 0.27 mmol) was added to a solution of piperidine **39** (73 mg, 0.17 mmol) dissolved in dichloroethane (1.5 mL) at 0°C. The reaction mixture was then allowed to warm to room temperature and was then heated at reflux for 3 h. After this time the reaction mixture was allowed to cool to room temperature and the solvent evaporated in vacuo. The residue was then dissolved in MeOH (1 mL) and the solution heated at reflux for a further 2 h. The reaction mixture was then allowed to cool to room temperature, before the solvent was evaporated and the product triturated with Et_2O. The product was then washed with 2 M NaOH solution and extracted into EtOAc, dried ($MgSO_4$), filtered and concentrated in vacuo. The product was purified via flash column chromatography using silica gel (7% MeOH/dichloromethane) to yield the free amine (−)-**6** as a white solid (31 mg, 54%): $[\alpha]_D^{21}$=−84 (c 0.77 in MeOH) (lit. $[\alpha]_D^{21}$=−75.5 (c 1.2, MeOH) for >97:3 er,[13c] and $[\alpha]_D^{21}$=−80.8 (c 1.25, MeOH) via enantiopure intermediates[13e]); ν_{max} ($CHCl_3$)/cm^{-1} 2923 and 2884 (C–H), 1631, 1606 and 1510 (Ar); δ_H (400 MHz) 1.75 (1H, ddm, J=12.4, 3.8 Hz, 5-CH_2), 1.81 (1H, m, 5-CH$_A$$H_B$), 2.09 (1H, m, 3-C$H$), 2.60 (1H, ddd, J=11.6, 11.6, 3.8 Hz, 4-CH), 2.70 (1H, dd, J=11.7, 11.4 Hz, 2-CH_AH_B), 2.76 (1H, ddd, J=12.1, 11.8, 2.4 Hz, 6-CH_AH_B), 3.20 (1H, dm, J=12.0 Hz, 6-CH$_A$$H_B$), 3.44 (2H, m, 2-CH$_A$$H_B$ and CH_AH_BOAr), 3.57 (1H, dd, J=9.3, 2.7 Hz, CH$_A$$H_B$OAr), 5.88 (2H, s, OC$H_2$O), 6.13 (1H, dd, J=8.4, 2.3 Hz, 6′-ArCH), 6.34 (1H, d, J=2.3 Hz, 2′-ArCH), 6.62 (1H, d, J=8.4 Hz, 5′-ArCH), 6.98 (2H, t, J=8.6 Hz, ArH), 7.17 (2H, dd, J=8.3, 5.6 Hz, ArH); δ_C (125.8 MHz) 35.0 (5-CH_2), 42.7 (4-CH), 44.4 (3-CH), 46.8 (6-CH_2), 50.1 (2-CH_2), 69.4 (CH_2OAr), 98.0 (2′-ArCH), 101.1 (OCH_2O), 105.6 (6′-ArCH), 107.9, (5′-ArCH), 115.5 (J_{C-F}=21 Hz, ArCH), 128.9 (J_{C-F}=8 Hz, ArCH), 139.8 (ArC), 141.6 (3′-ArC), 148.2 (4′-ArC), 154.4 (1′-ArC), 161.6 (J_{C-F}=244 Hz, ArC); MS (EI) m/z 330 ([M+H]$^+$, 18%), 329 (M^+, 78), 192 ((M−$C_7H_5O_3$), 100), 138 (60), 135 (18), 109 (24), 70 (53) (HRMS: found M^+, 329.1430. $C_{19}H_{20}NO_3F$ requires M, 329.1427).

4.7.5. Asymmetric benzylation of 40 to give (3*R*,4*S*)-1,3-dibenzyl-4-methylpiperidine-2,6-dione (+) 41. A chiral base reaction, using the typical procedure described above for glutarimide alkylation, employing imide **40** (201 mg, 0.92 mmol) and benzyl bromide (1.1 mL, 9.24 mmol) gave a crude product that was purified via flash column chromatography on silica gel (gradient elution, petroleum ether to 40% Et_2O/petroleum ether) to yield mono-benzylated glutarimide **41** as an oil (164 mg, 58%): $[\alpha]_D^{21}$=+34 (c 1.25 in $CHCl_3$); ν_{max} ($CHCl_3$)/cm^{-1} 2961, 2932 and 2875 (C–H), 1723 and 1681 (C=O), 1604 and 1495 (Ar); δ_H (400 MHz) 1.12 (3H, d, J=6.7 Hz, CHCH_3), 1.99 (1H, m, CHCH$_3$), 2.43 (1H, dd, J=17.2, 8.3 Hz, CH_{ax}H$_{eq}$CHCH$_3$), 2.70 (1H, dd, J=12.8, 6.6 Hz, CHCH$_2$-Ph), 2.83 (1H, dd, J=17.2, 4.7 Hz, CH$_{ax}$$H_{eq}$CHCH$_3$), 3.12 (1H, dd, J=14.1, 5.4 Hz, CH_AH_BPh), 3.29 (1H, dd, J=14.1, 6.6 Hz, CH$_A$$H_B$Ph), 5.03 (1H, d, J=14.4 Hz, NCH_AH_BPh), 5.06 (1H, d, J=14.4 Hz, NCH$_A$$H_B$Ph), 7.17 (2H, m, Ar$H$), 7.23–7.39 (8H, m, Ar$H$); δ_C (125.8 MHz) 19.8 (CHCH$_3$), 26.1 (CHCH$_3$), 34.9 (CHCH$_2$Ph), 38.3 (CH$_2$CHCH$_3$), 43.0 (NCH_2Ph), 50.5 (CHCH$_2$Ph), 126.7 (ArCH), 127.3 (ArCH), 128.4 (ArCH), 128.6 (ArCH), 128.7 (ArCH), 129.2 (ArCH), 137.3 (ArC), 137.9 (ArC), 171.4 (C=O), 174.2 (C=O); MS (EI) m/z 307 (M^+, 75%), 265 (13), 231 (13), 216 (M−C_7H_7,17), 189 (17), 188 (70), 160 (11), 146 (40), 131 (42), 106 (56), 105 (28), 104 (35), 91 (C_7H_7, 100), 77 (C_6H_5, 16), 65 (22), 57 (19) (HRMS: found M^+, 307.1572. $C_{20}H_{21}NO_2$ requires M, 307.1572). The ee was determined as 67% by HPLC (OJ column, 3% EtOH in hexane, 1.0 mL/min), the retention times were 43.6 min (major) and 51.6 min (minor).

Glutarimide **41** was prepared in racemic form (21%) by use of LDA–LiCl as base, according to the typical procedure given above.

4.7.6. 1-Benzyl-4-(4-fluorophenyl)-6-hydroxy-3-methyl-piperidine-2-one 42. To a solution of imide **30e** (39 mg, 0.12 mmol) in dichloromethane (1 mL) at −78°C was added DIBAL-H (0.25 mL of a 1.0 M solution in dichloromethane, 0.25 mmol). The reaction mixture was then stirred at this temperature for 3 h before water (1 mL) was added and the resulting mixture allowed to warm to room temperature. The product was extracted with dichloromethane (3×10 mL), the organic extracts combined, dried ($MgSO_4$), filtered and concentrated in vacuo to give hydroxy lactam **42** as a colourless oil (37 mg, 94%): ν_{max} ($CHCl_3$)/cm^{-1} 3579 (OH), 2929 (C–H), 1644 (C=O), 1606 and 1510 (Ar); δ_H (400 MHz) 1.01 (3H, d, J=6.5 Hz, CHCH_3), 1.92 (1H, ddd, J=13.6, 11.7, 7.8 Hz, CH_AH_BCHAr), 2.31 (1H, ddd, J=13.6, 5.6, 3.3 Hz, CH$_A$$H_B$CHAr), 2.52 (2H, m, C$H$Ar and C$HCH_3$), 2.85 (1H, br s, O$H$), 4.47 (1H, d, J=14.6 Hz, NCH_AH_BPh), 4.86 (1H, dd, J=7.8, 5.6 Hz, CHOH), 5.01 (1H, d, J=14.6 Hz, NCH$_A$$H_B$Ph), 6.96 (2H, t, J=8.7 Hz,

ArH), 7.07 (2H, dd, J=8.7, 5.3 Hz, ArH), 7.20–7.30 (5H, m, ArH); δ_C (100.6 MHz) 15.3 ($CH\underline{C}H_3$), 40.2 ($\underline{C}H_2$), 42.7 ($\underline{C}$HAr), 43.1 ($\underline{C}HCH_3$), 46.0 (CH_2), 79.4 (C$\underline{H}$OH), 115.8 (J_{C-F}=21 Hz, Ar$\underline{C}$H), 127.5 (Ar$\underline{C}$H), 128.3 (Ar$\underline{C}$H), 128.7 (J_{C-F}=8 Hz, Ar$\underline{C}$H), 128.8 (Ar$\underline{C}$H), 137.8 (Ar$\underline{C}$), 138.6 (Ar$\underline{C}$), 162.0 (J_{C-F}=247 Hz, Ar$\underline{C}$), 173.3 ($\underline{C}$=O); MS (EI) m/z 313 (M^+, 7%), 295 ($M-H_2O$, 72), 283 (54), 238 (41), 227 (19), 186 (60), 163 (23), 147 (22), 133 (26), 109 (24), 91 (C_7H_7, 100), 65 (34) (HRMS: found M^+, 313.1478. $C_{19}H_{20}NO_2F$ requires M, 313.1463).

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