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Enantiodiscrimination of racemic electrophiles by diketopiperazine enolates: asymmetric synthesis of methyl 2-amino-3-aryl-butanoates and 3-methyl-aspartates

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Abstract—Enolates of (*S*)-*N*,*N*′-bis-(*p*-methoxybenzyl)-3-*iso*-propylpiperazine-2,5-dione exhibit high levels of enantiodiscrimination in alkylations with (*RS*)-1-aryl-1-bromoethanes and (*RS*)-2-bromoesters, affording substituted diketopiperazines containing two new stereogenic centres in high de. Deprotection and hydrolysis of the resultant substituted diketopiperazines provides a route to the asymmetric synthesis of homochiral methyl 2-amino-3-aryl-butanoates and 3-methyl-aspartates in high de and ee.

1. Introduction

The design and synthesis of novel peptides incorporating conformationally constrained amino acid residues are currently an area of much scientific attention.[1] β-Alkyl-α-amino acids are one class of conformationally constrained amino acids that have been shown to modulate peptide secondary structure and produce beneficial changes in the action of biologically active peptides.[2] These compounds are also non-proteinogenic α-amino acid components of a number of natural products[3] and the asymmetric synthesis of this class of α-amino acid, requiring the stereoselective formation of two contiguous stereogenic centres, is a growing field of research.[4] Although the application of chiral auxiliary strategies for the selective generation of a single stereogenic centre is well established, the application of chiral auxiliaries to discriminate between the enantiomers of racemic electrophiles to afford selectively products containing two contiguous stereogenic centres are less common.[5]

Previous investigations from this laboratory have introduced a diketopiperazine derived chiral auxiliary (*S*)-*N*,*N*′-bis-(*p*-methoxybenzyl)-3-*iso*-propylpiperazine-2,5-dione **1** for the asymmetric synthesis of homochiral α-amino acids. Alkylations of the lithium enolate of **1** proceed with high levels of trans-selectivity, affording (*R*)-α-amino acids in homochiral form after *N*-deprotection and hydrolysis.[6] In an extension of this methodology, we report herein our studies directed toward the selective alkylation of the lithium and potassium enolates **2** and **3** of parent diketopiperazine **1**

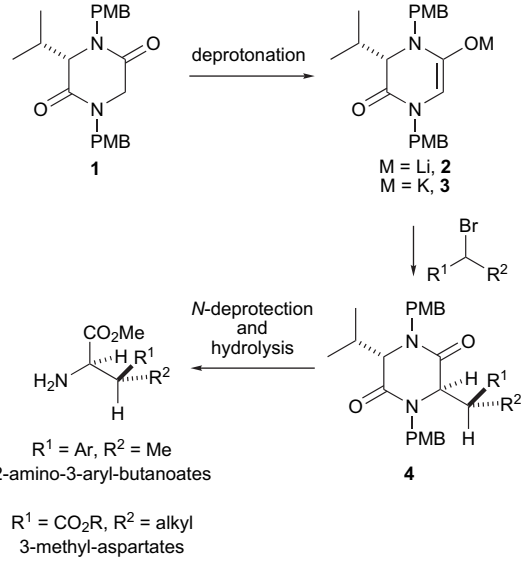

Figure 1. Proposed enantiodiscrimination strategy for the asymmetric synthesis of 2-amino-3-aryl-butanoates and 3-methyl-aspartates.

Keywords: Enantiodiscrimination; Diketopiperazine; 3-Methyl-aspartate.
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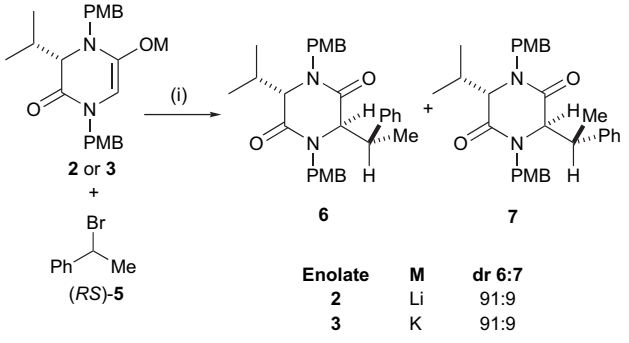
with one enantiomer of (*RS*)-1-aryl-1-bromoethanes and (*RS*)-2-bromoesters. This strategy would allow the formation of two stereogenic centres in a single reaction step, one by asymmetric synthesis and the other by enantiodiscrimination, and facilitate the asymmetric synthesis of methyl 2-amino-3-aryl-butanoates and 3-methyl-aspartates after *N*-deprotection and hydrolysis of intermediates **4** (Fig. 1). Part of this work has been communicated previously.[7]

2. Results and discussion

2.1. Enantiodiscrimination of (*RS*)-1-aryl-1-bromoethanes for the asymmetric synthesis of 2-amino-3-aryl-butanoates

Initial investigations focused upon the reaction of (*RS*)-1-aryl-1-bromoethanes with the lithium enolate **2** of (*S*)-*N*,*N*′-bis-(*p*-methoxybenzyl)-3-*iso*-propylpiperazine-2,5-dione **1**. Treatment of lithium enolate **2**[8] with 10 equiv of (*RS*)-1-phenyl-1-bromoethane **5** gave a 91:9 mixture of two diastereoisomers **6** and **7** (82% de). Fractional crystallisation of the crude reaction mixture furnished the major diastereoisomer **6** in 60% yield and >98% de. When lithium enolate **2** was allowed to react with 1 equiv of (*RS*)-**5** for 3 h the reaction proceeded to 56% conversion, and unreacted **5** was recovered in 43% yield. The specific rotation of the recovered **5** {$[\alpha]_D^{21}$ −25.9 (*c* 4.8 in $CHCl_3$); lit.[9] $[\alpha]_D^{23}$ −90.8 (*c* 2.8 in $CHCl_3$) for 81% ee} indicated that it was enriched in the (*S*)-enantiomer (24% ee), consistent with the preferential reaction of enolate **2** with (*R*)-**5** and partial racemisation of the residual electrophile by bromide ion.[10] The diastereoselectivity of this reaction proved to be insensitive to the nature of the enolate metal counterion since treatment of the potassium enolate **3**[11] with 2.2 equiv of (*RS*)-**5** afforded a 91:9 mixture of **6** and **7**, from which the major diastereoisomer **6** was isolated in 57% yield (>98% de) by recrystallisation (Scheme 1).



Scheme 1. Reagents and conditions: (i) (*RS*)-PhCH(Br)Me (2.2 equiv), THF, −78 °C, 12 h.

The C(3) and C(6) trans-relative configuration within both diastereoisomers **6** and **7** was initially assigned by analysis of ^{1}H NMR spectroscopic data, with both diastereoisomers **6** and **7** exhibiting *iso*-propyl group chemical shifts diagnostic for the trans-relative configuration.[12] The (1′*S*)-configuration within the major diastereoisomer **6** was then assigned by consideration of the configuration of the recovered (*S*)-electrophile, assuming the major reaction pathway follows an S_N2 displacement. This assignment was unequivocally confirmed by single crystal X-ray diffraction of the major diastereoisomer **6**, with the absolute (3*S*,6*S*,1′*S*) configuration following from the known configuration of the (*S*)-valine derived stereogenic centre (Fig. 2).

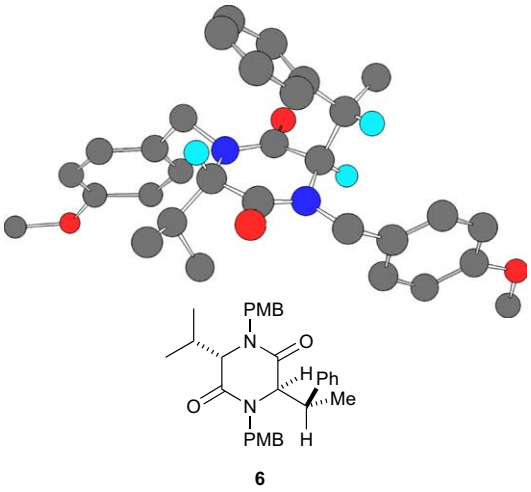
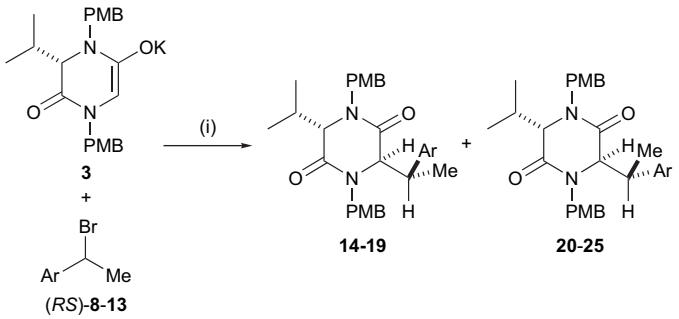


Figure 2. Chem 3D representation of the X-ray crystal structure of **6** (some H atoms omitted for clarity).

The ability of the enolate of **1** to discriminate between the enantiomers of a range of (*RS*)-1-aryl-1-bromoethanes **8**–**13** was next examined. Preliminary studies using lithium enolate **2** afforded low levels of conversion; however, treatment of potassium enolate **3** with 2.2 equiv of racemic electrophiles **8**–**13** afforded diketopiperazines **14**–**25** in 70% de to >95% de, as assessed by ^{1}H NMR spectroscopic analysis of the crude reaction product (Scheme 2). Purification of the crude reaction product in each case by chromatography and/or recrystallisation afforded diketopiperazines **14**–**19** in 45–75% yield, and in >98% de in each case. These results indicate that this enantiodiscrimination protocol is tolerant of both *ortho*- and *para*-substituted aryl groups and for both electron poor and electron rich aryl groups within the 1-aryl-1-bromoethane structure. Notable results within this series indicate that the potassium enolate **3** reacts with lower stereoselectivity with electronically activated (*RS*)-1-(*p*-methoxyphenyl)-1-bromoethane **10** than the parent (*RS*)-1-phenyl-1-bromoethane system, affording **16** in 70% de. However, the potassium enolate **3** reacts with the electronically deactivated (*RS*)-1-(2′-pyridyl)-1-bromoethane **11** to give **17** in 92% de. Furthermore, potassium enolate **3** showed superior levels of enantiodiscrimination in the reactions with the bulky *o*-tolyl-(*RS*)-**9**, 1-naphthyl-(*RS*)-**12** and 2-naphthyl-(*RS*)-**13** electrophiles, affording **15**, **18** and **19** in >95, 91 and 90% de, respectively (Scheme 2).

The (3*R*,6*S*,1′*S*) configuration of the major diastereoisomers **14**–**19** isolated from this protocol was assigned initially by analogy with that determined unambiguously for the alkylation reaction with (*RS*)-1-phenyl-1-bromoethane **5**. In support of this assignment, the relative configuration of 2′-pyridyl-**17** was established by X-ray crystallographic analysis, with the absolute (3*R*,6*S*,1′*S*) configuration following from the (*S*)-valine derived stereogenic centre (Fig. 3).

Having demonstrated the ability of the potassium enolate **3** to discriminate readily between the antipodes of



Electrophile	Ar	Conversion %	dr %[a]	Product	Yield (de) %[b]
5	Ph	85	91:9	**6**	57 (>98)
8	*p*-tolyl	100	91:9	**14**	61 (>98)
9	*o*-tolyl	100	>97.5:<2.5	**15**	69 (>98)
10	*p*-OMeC$_6$H$_4$	100	85:15	**16**	64 (>98)
11	2-pyridyl	100	96:4	**17**	85 (>98)
12	1-naphthyl	55	95.5:4.5	**18**	47 (>98)
13	2-naphthyl	83	95:5	**19**	68 (>98)

Scheme 2. Reagents and conditions: (i) (*RS*)-ArCH(Br)Me (2.2 equiv), THF, −78 °C, 12 h. [[a]As indicated by ^{1}H NMR analysis of the crude reaction product; [b]Purified yield of major diastereoisomer.]

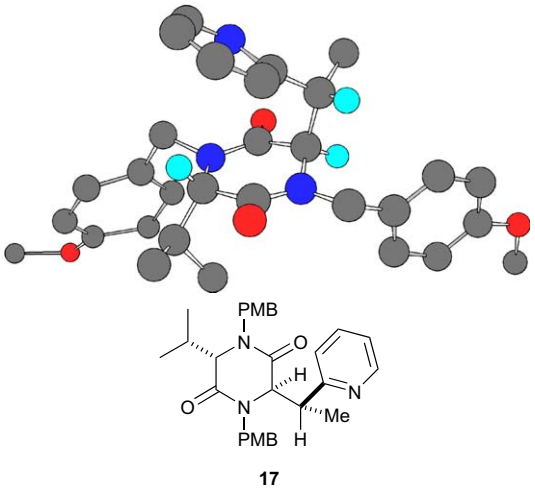
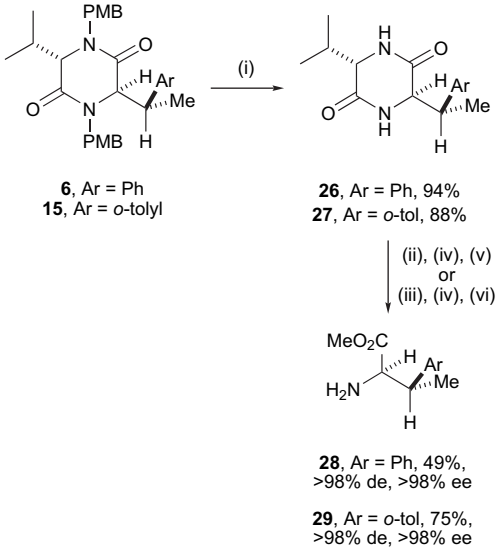


Figure 3. Chem 3D representation of the X-ray crystal structure of **17** (some H atoms omitted for clarity).

(*RS*)-1-aryl-1-bromoethanes **5** and **8**–**13**, the deprotection and hydrolysis of a representative set of substrates to the corresponding 2-amino-3-aryl-butanoates was investigated. *N*-Deprotection of **6** (>98% de) with ceric ammonium nitrate (CAN) afforded diketopiperazine **26** in 94% isolated yield and >98% de, which was hydrolysed by prolonged treatment with 5 M HCl at 100 °C. The resultant mixture of α-amino acid hydrochloride salts was converted to the corresponding methyl esters, with chromatographic purification giving methyl (2*R*,3*R*)-2-amino-3-phenyl-butanoate **28** in 45% overall yield and >98% de (Scheme 3). Following the same protocol, *N*-deprotection of *o*-tolyl-**15** (>98% de) with CAN afforded diketopiperazine **27** in 88% yield and >98% de. Although the hydrolysis of diketopiperazine **27** with hydrochloric acid proved prohibitively slow, treatment with concentrated hydroiodic acid at reflux led to clean hydrolysis within 24 h. Conversion of the resultant crude product mixture of α-amino acid hydroiodide salts to the corresponding methyl esters afforded **29** in 75% yield and >98% de after the volatile (*S*)-valine methyl ester was evaporated (Scheme 3). The enantiomeric excess of **28** was determined as >98% ee by examination of the ^{19}F NMR spectrum of the Mosher's amide derivative and comparison with authentic racemic samples, and the ee of **29** was assigned by analogy.

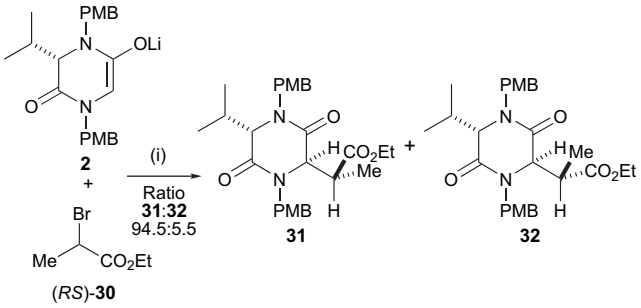


Scheme 3. Reagents and conditions: (i) CAN, MeCN/H_2O (v/v 2:1); (ii) HCl (5 M, aq), reflux, four days; (iii) HI, reflux, 24 h; (iv) MeOH, $SOCl_2$; (v) $NaHCO_3$, then chromatography; (vi) evaporation.

2.2. Enantiodiscrimination of (*RS*)-2-bromoesters for the asymmetric synthesis of 3-methyl-aspartates

Having established that lithium and potassium enolates **2** and **3** effectively discriminate between the enantiomers of (*RS*)-1-aryl-1-bromoethanes, allowing the asymmetric synthesis of methyl 2-amino-3-aryl-butanoates, subsequent investigations focused upon the reaction of lithium enolate **2** with (*RS*)-2-bromoesters. Treatment of lithium enolate **2** with (*RS*)-ethyl 2-bromopropanoate **30** (10 equiv or 2.2 equiv) gave a 94.5:5.5 mixture of **31** and **32**, from which

31 and **32** were isolated in 93 and 3% yield, respectively, as single diastereoisomers after chromatography (Scheme 4). The relative trans-configuration of the C(3) and C(6) diketopiperazine ring substituents within **31** and **32** was supported by the diagnostic *iso*-propyl group chemical shifts that indicate this relative configuration.[12] The configuration of the (2′*R*)-stereogenic centre within major diastereoisomer **31** was preliminarily assigned from analysis of the unreacted electrophile, as ethyl 2-bromopropanoate **30** recovered from reaction of enolate **2** with (*RS*)-**30** (2.2 equiv) was enantiomerically enriched in the (*S*)-enantiomer (16% yield, 34% ee) {$[\alpha]_D^{23}$ −11.1 (*c* 1.1 in $CHCl_3$), lit.[13] for enantiomer $[\alpha]_D^{23}$ +37.0 (*c* 1.0 in $CHCl_3$)}. Assuming an S_N2 process in this reaction, this specific rotation indicates that enolate **2** reacts preferentially with (*R*)-**30**, affording the major diastereoisomer **31** with (2′*R*)-configuration. The 34% ee obtained for the recovered electrophile is lower than the calculated value of 74% ee that is expected given the 94.5:5.5 ratio of alkylation products **31**:**32**; this discrepancy presumably reflects the known capacity of bromide ions to racemise ethyl 2-bromo-propanoate **30**.[14]

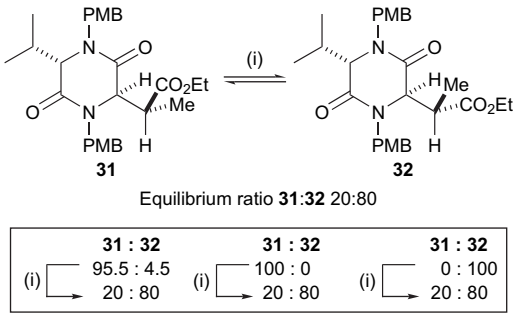


Scheme 4. Reagents and conditions: (i) (*RS*)-**30** (2.2 equiv or 10 equiv), THF, −78 °C, 12 h.

Although the observed major product **31** in this reaction is expected to arise from a stereospecific and enantioselective S_N2 alkylation of the electrophile, it may potentially derive from thermodynamic equilibration of the 2′-stereogenic centre α to the ester functionality of the kinetic product under the basic reaction conditions. In order to establish that the predominant isomer **31** did not derive from equilibration of the kinetic product, the epimerisation of the 2′-stereogenic centre was examined. Treatment of the 94.5:5.5 mixture of **31**:**32** with lithium ethoxide in dry ethanol, in the presence of methyl iodide as an electrophilic scavenger, afforded a 20:80 mixture of **31**:**32**. The highly crystalline **32** was readily isolated via recrystallisation of the crude reaction mixture in 66% yield. The 20:80 ratio of **31**:**32** represents the thermodynamic equilibrium position, since similar treatment of a homochiral sample of either **31** or **32** gave identical 20:80 mixtures of **31**:**32** (Scheme 5).

The relative configuration of **32** was unequivocally confirmed by single crystal X-ray analysis, with the absolute (3*R*,6*S*,2′*S*) configuration determined from the (*S*)-valine derived stereogenic centre (Fig. 4).

The generality of this enantiodiscrimination process was then explored. Variation of the alkyl ester group within the (*RS*)-2-bromopropanoate structure did not markedly affect the level of enantiodiscrimination: alkylation of enolate **2**



Scheme 5. Reagents and conditions: (i) LiHMDS, MeI, anhydrous EtOH.

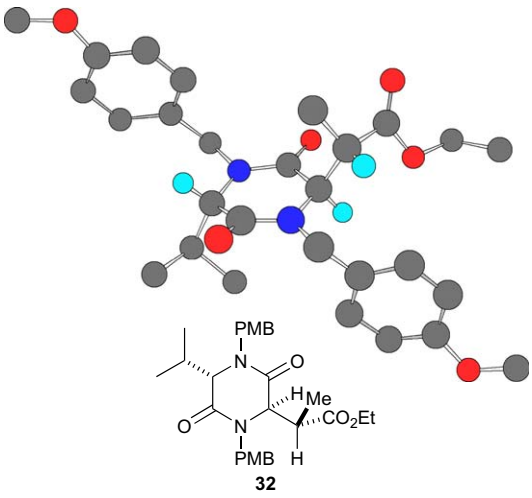
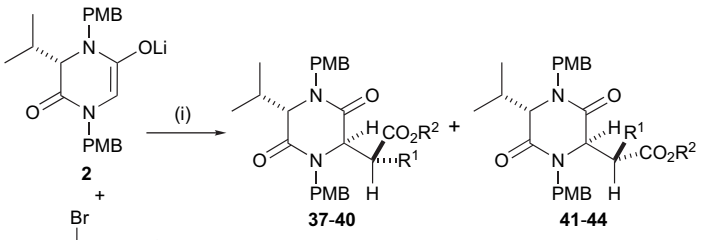


Figure 4. Chem 3D representation of the X-ray crystal structure of **32** (some H atoms omitted for clarity).

with (*RS*)-methyl 2-bromopropanoate **33** gave diketopiperazine **37** in 92% de, and in 87% yield and >98% de after chromatography, while alkylation of **2** with (*RS*)-*tert*-butyl 2-bromopropanoate **34** gave diketopiperazine **38** in 92% de, and in 83% yield and >98% de after chromatography. Enolate **2** was also found to discriminate efficiently between the enantiomers of (*RS*)-ethyl 2-bromobutyrate **35** and (*RS*)-ethyl 2-bromoheptanoate **36** to afford *trans*-alkylated diketopiperazines **39** and **40**, respectively, in 84 and 88% de, which after chromatographic purification gave **39** and **40** in 82 and 86% yield, respectively, and in >98% de in each case. ^{1}H NMR data for the major diastereoisomeric reaction products **37**–**40** were similar in each case to that of **31** derived from alkylation of enolate **2** with (*RS*)-ethyl 2-bromopropanoate **30**, with the absolute (3*R*,6*S*,2′*R*) configuration of these products assigned by analogy to that unambiguously assigned in the related (*RS*)-ethyl 2-bromopropanoate system (Scheme 6).

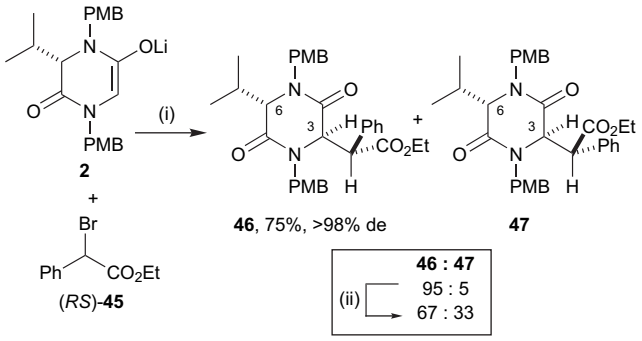
Having observed effective enantiodiscrimination of (*RS*)-2-bromoalkylacetates **5** and **8**–**13** and (*RS*)-1-aryl-1-bromoethanes **30** and **33**–**36** with enolates **2** and **3**, the reaction of enolate **2** with (*RS*)-ethyl 2-bromophenylacetate **45** was undertaken. Treatment of lithium enolate **2** with (*RS*)-**45** gave a 95:5 mixture of **46**:**47** (90% de) from which **46** was isolated in 75% yield and >98% de (Scheme 7). The relative configuration within **46** was established by single crystal X-ray diffraction, while the absolute (3*R*,6*S*,2′*S*) configuration derives from the known (*S*)-valine derived stereocentre



Electrophile	R^1	R^2	dr %[a]	Product	Yield (de) %[b]
30	Me	Et	94.5:5.5	**31**	93 (>98)
33	Me	Me	96:4	**37**	87 (>98)
34	Me	^{t}Bu	96:4	**38**	83 (>98)
35	Et	Et	92:8	**39**	82 (>98)
36	C_5H_{11}	Et	94:6	**40**	86 (>98)

Scheme 6. Reagents and conditions: (i) (*RS*)-$R^1CH(Br)CO_2R^2$ (2.2 equiv), THF, −78 °C. [[a]As indicated by ^{1}H NMR analysis of the crude reaction product; [b]Purified yield of major diastereoisomer.]

(Fig. 5). The major diastereoisomer **46** does not derive from equilibration of the kinetic product since treatment of **46** (>98% de) with lithium ethoxide catalysed regioselective *C*(2′) epimerisation to afford a 67:33 mixture of **46**:**47**. Attempts to establish the thermodynamic equilibrium position in this reaction via prolonged epimerisation were hampered by decomposition of the materials. The identification of **46** as the major diastereoisomer in this reaction is consistent with enolate **2** preferentially reacting with the (*S*)-enantiomer of (*RS*)-ethyl 2-bromophenylacetate **45** in an S_N2 process.



Scheme 7. Reagents and conditions: (i) (*RS*)-**45** (2.2 equiv), THF, −78 °C; (ii) LiHMDS, anhydrous EtOH.

The deprotection and hydrolysis of **31** and **32** to the corresponding 3-methyl-aspartates was then investigated. Attempted *N*-deprotection by treatment of **31** with CAN in $MeCN/H_2O$ afforded diketopiperazine **48** in low yield, possibly due to ester hydrolysis under the acidic reaction conditions. However, *N*-deprotection of **31** was readily achieved by treatment with refluxing TFA, affording diketopiperazine **48** in 60% yield and >98% de. Initial attempts to hydrolyse **48** under strongly acidic conditions led to partial epimerisation at the 2′-stereogenic centre and, in order to circumvent this problem, conversion of **48** to bis-lactim ether **49** was investigated in the expectation that hydrolysis would then proceed readily under mild acid conditions.[15] Treatment of **48** with trimethyloxonium tetrafluoroborate (Me_3OBF_4) in DCM over a period of four days gave a 60:20:20 mixture of the desired bis-lactim ether **49**, and two more polar components, tentatively assigned as the corresponding

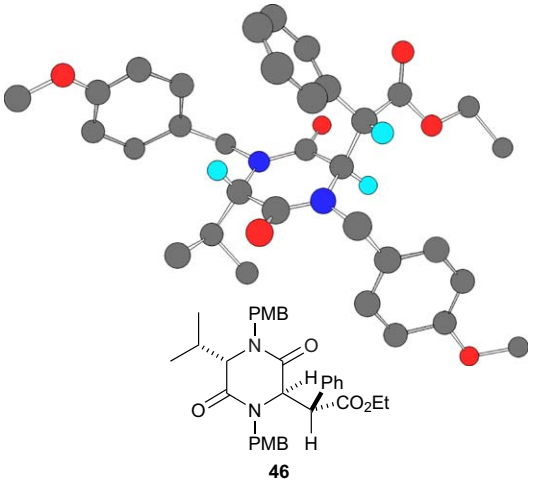
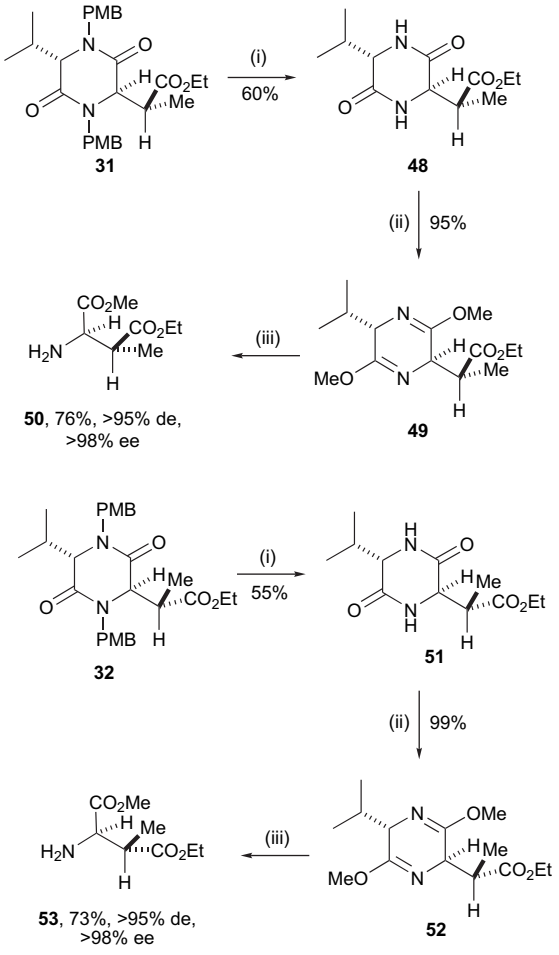


Figure 5. Chem 3D representation of the X-ray crystal structure of **46** (some H atoms omitted for clarity).

mono-lactim ethers of **48**. Attempted chromatographic purification of bis-lactim ether **49** proved difficult, resulting in significant mass loss and low isolated yield (~50%). In order to drive this methylation to completion, treatment of **48** with Me_3OBF_4 in the ionic liquid solvent *N*-butyl-*N*′-methylimidazolium tetrafluoroborate ($Bmim\cdot BF_4$)[16] was followed, affording bis-lactim ether **49** as the sole reaction product in 95% yield. The ionic liquid solvent system presumably serves to stabilise the intermediate hydrotetrafluoroborate salts of the lactim ethers and facilitates the reaction by solvation of both Me_3OBF_4 and charged intermediates that are poorly soluble in organic solvents. Subsequent hydrolysis of bis-lactim ether **49** with 0.5 M aq TFA at rt afforded a mixture of **50** and (*S*)-valine methyl ester as the trifluoroacetate salts, which were converted to free amines and separated by distillation giving **50** in 76% yield, >95% de and >98% ee[17] (Scheme 8). Following the success of this protocol, the deprotection and hydrolysis of **32** by a similar protocol was then investigated. *N*-Deprotection of **32** by treatment with refluxing TFA afforded diketopiperazine **51** in 55% yield and >98% de, with subsequent treatment of **51** with Me_3OBF_4 in $Bmim\cdot BF_4$ affording bis-lactim ether **52** in 99% yield. Hydrolysis of bis-lactim ether **52** afforded **53** and (*S*)-valine methyl ester as the trifluoroacetate salts,

which after conversion to the corresponding free amines and distillation gave **53** in 73% yield, >95% de and >98% ee (Scheme 8).



Scheme 8. Reagents and conditions: (i) TFA, reflux; (ii) Me_3OBF_4 (4 equiv), Bmim·BF_4, four days; (iii) 0.5 M aq TFA, then $NaHCO_3$.

2.3. Models for enantiorecognition

For the reaction of the potassium enolate **3** with (*RS*)-1-aryl-1-bromoethanes **5** and **8**–**13**, the observed enantiodiscrimination must be controlled by steric interactions between the enolate and electrophile in the alkylation transition state. The (3*R*,6*S*,1′*S*) configuration of the major diastereoisomer in each case and the observed specific rotation of the recovered electrophiles from these alkylations indicate that the reaction preferentially proceeds via approach of the (*R*)-electrophile to enolate **3** *anti* to the C(3) *iso*-propyl group. Assuming that this reaction takes place in an S_N2 process and that the substituents of the electrophile are staggered relative to the carbon framework of the enolate, the bromide leaving group will be electronically activated when orientated perpendicular to the adjacent π-system of the aromatic ring.[18] Analysis of the X-ray crystal structures indicates that *trans*-substituted *N*-alkylated diketopiperazines **6**, **17**, **32** and **46** all have a conformational preference in which the small C(1′)*H* substituent occupies the most sterically crowded position adjacent to the *N*(4)-*p*-methoxybenzyl substituent, minimising *syn*-pentane interactions. Assuming

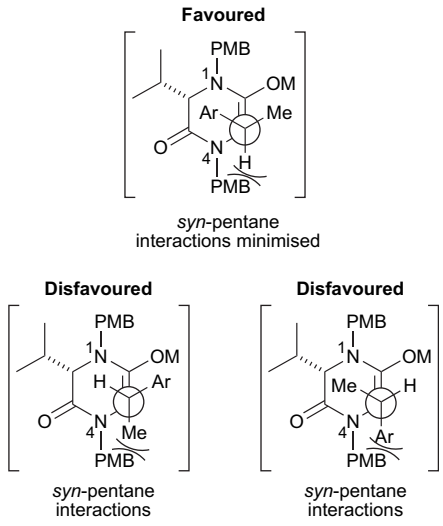


Figure 6. Generic model for enantiodiscrimination.

that the reaction of enolate **3** with (*RS*)-1-aryl-1-bromoethanes **5** and **8**–**13** occurs via a late, product-like transition state, and using this crystal structure analysis of the products as a basis for the transition state, a simple model may be used to predict the more reactive enantiomer of the electrophile. In the transition state, the overriding assumption of this model is that the C(1)*H* of the (*RS*)-1-aryl-1-bromoethane electrophile occupies the sector above the *N*(4)-*p*-methoxybenzyl substituent, minimising *syn*-pentane interactions (Fig. 6).

Following this rationale, in considering the reaction of the two enantiomers of (*RS*)-1-aryl-1-bromoethanes **5** and **8**–**13** with the enolate of **1**, (*R*)-1-aryl-1-bromoethanes approach with the planar aryl group over the diketopiperazine ring with the sp^3 hybridised methyl group oriented away from the diketopiperazine ring; a similar approach of the (*S*)-1-aryl-1-bromoethanes places the sp^3 methyl group in a sterically encumbered position where it suffers steric interactions with the diketopiperazine ring framework, disfavouring reaction of this enantiomer (Fig. 7).

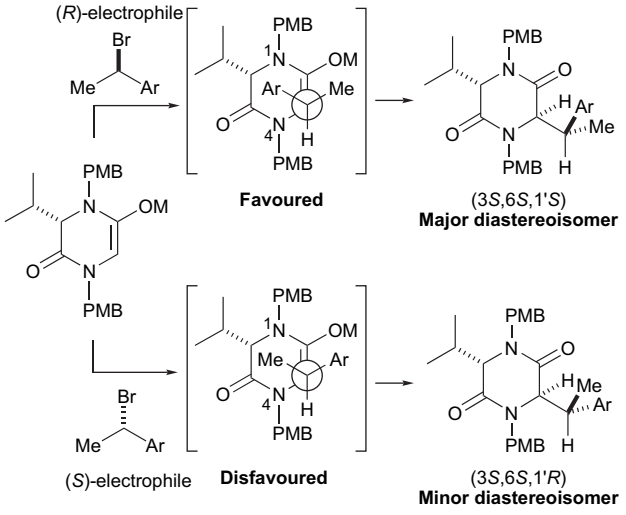


Figure 7. Model for the preferential reaction of enolate **3** with (*R*)-ArCH(Br)Me.

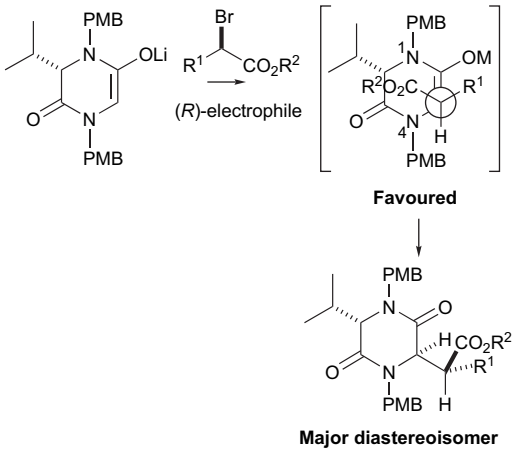


Figure 8. Model for the preferential reaction of enolate **2** with (*R*)-$R^1CH(Br)CO_2R^2$.

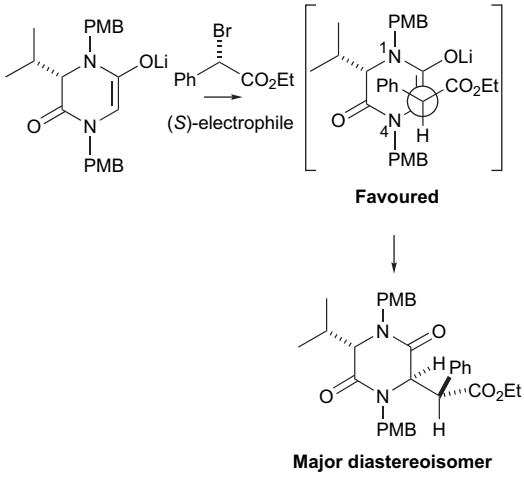


Figure 9. Model for preferential reaction of enolate **2** with (*S*)-$PhCH(Br)CO_2Et$.

For the reactions of lithium enolate **2** with (*RS*)-2-bromoesters **30**, **33**–**36** and **45** the enantiodiscrimination may be controlled either by chelation between the ester group and the enolate counterion or by steric factors similar to those above. Again assuming the overall requirement for the C(2)*H* of the (*RS*)-2-bromoester to occupy the sector above the *N*(4)-*p*-methoxybenzyl substituent, the discrimination reactions involving **30** and **33**–**36** are consistent with the reaction proceeding under steric control[19] with preferential reaction of the (*R*)-electrophile (Fig. 8: planar ester group over ring, sp^3 alkyl group away from ring) while the reaction involving **45** proceeds under chelation control (Fig. 9: planar aryl group over ring, planar ester chelating to enolate counterion).

3. Conclusion

In conclusion, enolates derived from (*S*)-*N*,*N*′-bis-(*p*-methoxybenzyl)-3-*iso*-propylpiperazine-2,5-dione **1** exhibit a high degree of enantiodiscrimination in alkylations with a range of (*RS*)-1-aryl-1-bromoethanes **5** and **8**–**13**, and (*RS*)-2-bromoesters **30**, **33**–**36** and **45** to afford trans-alkylated products in high de. The deprotection and hydrolysis of representative recognition products within each series has established the efficacy of this process for the asymmetric synthesis of methyl 2-amino-3-aryl-butanoates and 3-methyl-aspartates and in high de and ee.

4. Experimental

4.1. General

All reactions involving organometallic or other moisture-sensitive reagents were carried out under a nitrogen or argon atmosphere using standard vacuum line techniques and glassware that was flame dried and cooled under nitrogen before use. Solvents were dried according to the procedure outlined by Grubbs and co-workers.[20] Water was purified by an Elix® UV-10 system. All other solvents were used as supplied (analytical or HPLC grade) without prior purification. Organic layers were dried over $MgSO_4$. Thin layer chromatography was performed on aluminium plates coated with 60 F_{254} silica. Plates were visualised using UV light (254 nm), iodine, 1% aq $KMnO_4$, or 10% ethanolic phosphomolybdic acid. Flash column chromatography was performed on Kieselgel 60 silica.

Elemental analyses were recorded by the microanalysis service of the Inorganic Chemistry Laboratory, University of Oxford, UK. Melting points were recorded on a Gallenkamp Hot Stage apparatus and are uncorrected. Optical rotations were recorded on a Perkin–Elmer 241 polarimeter with a water-jacketed 10 cm cell. Specific rotations are reported in 10^{-1} deg cm^2 g^{-1} and concentrations in gram per 100 mL. IR spectra were recorded on Bruker Tensor 27 FTIR spectrometer as either a thin film on NaCl plates (film) or a KBr disc (KBr), as stated. Selected characteristic peaks are reported in cm^{-1}. NMR spectra were recorded on Bruker Avance spectrometer in the deuterated solvent stated. The field was locked by external referencing to the relevant deuteron resonance. Low-resolution mass spectra were recorded on either a VG MassLab 20-250 or a Micromass Platform 1 spectrometer. Accurate mass measurements were run on either a Bruker MicroTOF and were internally calibrated with polyanaline in positive and negative modes, or a Micromass GCT instrument fitted with a Scientific Glass Instruments BPX5 column (15 m×0.25 mm) using amyl acetate as a lock mass.

4.1.1. General procedure 1: alkylation of 1. To a stirred solution of **1** (1.0 equiv) in degassed THF (50 mL g^{-1}) at −78 °C was added a solution of LiHMDS (1.0 M in THF, 1.1 equiv) or KHMDS (0.5 M in PhMe, 0.9 equiv). The resultant solution was allowed to stir at −78 °C for 1 h prior to the addition of the electrophile. The mixture was stirred at −78 °C for 12 h then allowed to warm to rt before NH_4Cl (satd aq) was added. The mixture was partitioned between EtOAc and H_2O. The aqueous phase was extracted twice with EtOAc and the combined organic layers were dried and concentrated in vacuo to yield the crude product.

4.1.1.1. (3*S*,6*S*,1′*S*)-*N*,*N*′-Bis-(*p*-methoxybenzyl)-6-*iso*-propyl-3-(1′-phenylethyl)piperazine-2,5-dione 6. Compound **1** (200 mg, 0.50 mmol) in THF (10 mL), LiHMDS (1.0 M in THF, 0.55 mL, 0.55 mmol) and (*RS*)-**5** (944 mg, 5.0 mmol) were reacted according to Section 4.1.1 to afford

a crude solid. Recrystallisation from EtOAc gave **6** as colourless blocks (151 mg, 60%); mp 214–216 °C; $[\alpha]_D^{23}$ +43.5 (*c* 1.1 in $CHCl_3$); ν_{max} (KBr) 1655 (C=O); δ_H (400 MHz, $CDCl_3$) 0.64 (3H, d, *J* 6.8, CH_3CHCH_3), 0.98 (3H, d, *J* 6.8, CH_3CHCH_3), 1.50 (3H, d, *J* 7.3, ArCHCH_3), 2.08 (1H, m, C*H*$(CH_3)_2$), 3.03 (1H, d, *J* 2.5, $(CH_3)_2CHCH$), 3.60 (1H, m, PhC*H*CH_3), 3.79 (3H, s, OCH_3), 3.82 (3H, s, OCH_3), 3.91 (1H, d, *J* 14.5, NCH_2ArOMe), 4.04 (1H, d, *J* 15.0, NCH_2ArOMe), 4.10 (1H, d, *J* 1.9, C(3)*H*), 4.54 (1H, d, *J* 15.0, NCH_2ArOMe), 5.49 (1H, d, *J* 14.5, NCH_2ArOMe), 6.70–7.40 (13H, m, Ar); δ_C (100 MHz, $CDCl_3$) 15.3, 16.5, 19.2, 30.5, 41.0, 46.2, 47.3, 55.2, 55.3, 62.8, 63.2, 113.8, 114.2, 127.2, 128.3, 128.6, 129.6, 130.4, 140.3, 158.9, 159.4, 165.5, 165.7; *m/z* (CI^+) 501 ($[M+H]^+$, 8%), 121 (100); HRMS (ESI^+) $C_{31}H_{36}N_2NaO_4^+$ ($[M+Na]^+$) requires 523.2567, found 523.2553.

4.1.1.2. X-ray crystal structure determination for 6. Data were collected using an Enraf–Nonius κ-CCD diffractometer with graphite monochromated Mo Kα radiation using standard procedures at 124 K. The structure was solved by direct methods (SIR97). All non-hydrogen atoms were refined with anisotropic thermal parameters. Hydrogen atoms were added at idealised positions. The structure was refined using CRYSTALS.[21]

Crystal data for **6** $[C_{31}H_{36}N_2O_4]$: M=500.64; monoclinic; space group $P1\,21\,1$, a=7.5802(2) Å, b=28.1447(6) Å, c=12.4766(4) Å; β=94.4890(11)°; V=2653.62 Å^3; Z=4; μ=0.073 mm^{-1}; colourless plate; crystal dimensions= 0.04×0.04×0.26 mm^3. A total of 5600 unique reflections were measured for $3<\theta<27$ and 5598 reflections were used in the refinement. The final parameters were wR_2= 0.1290 and R_1=0.0955 (all data).

Crystallographic data (excluding structure factors) have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC280792. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK [fax: +44 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk].

4.1.1.3. Alkylation of potassium enolate 3 with (*RS*)-5. Compound **1** (2.0 g, 5.0 mmol) in THF (100 mL), KHMDS (0.5 M in PhMe, 9.1 mL, 4.5 mmol) and (*RS*)-**5** (2.03 g, 11.0 mmol) were reacted according to Section 4.1.1, to yield a suspension of colourless solid in a brown oil. Analysis of the high field ^{1}H NMR spectrum of the crude product indicated that the diastereoisomers **6** and **7** were formed in a de of 82%, 85% of the starting **1** being converted to alkylated products. Fractional recrystallisation from EtOAc/hexane led to the isolation of **6** (1.41 g, 57%).

4.1.1.4. Recovery of α-methylbenzyl bromide (*S*)-5. To **1** (500 mg, 1.26 mmol) in degassed THF (20 mL) at −78 °C was added a solution of LiHMDS (1.39 mL, 1 M in THF, 1.39 mmol). The resultant solution was allowed to stir at −78 °C for 1 h prior to the addition of (*RS*)-**5** (233 mg, 1.26 mmol). The mixture was stirred at −78 °C for 3 h, NH_4Cl (satd aq) was added, and the mixture was allowed to warm to rt. The mixture was partitioned between EtOAc and H_2O. The aqueous phase was extracted with EtOAc and the combined organic layers were dried and concentrated in vacuo to yield the crude product. Chromatography (alumina, eluent 30–40° petrol/Et_2O 9:1) gave (*S*)-**5** as a colourless oil (100 mg, 43%); $[\alpha]_D^{23}$ −25.9 (*c* 4.8 in $CHCl_3$); {lit.[9] $[\alpha]_D^{23}$ −90.8 (*c* 2.8 in $CHCl_3$) for 81% ee sample}.

4.1.2. General procedure 2: preparation of (*RS*)-1-aryl-1-bromo-ethanes 8–10. Concentrated HBr (48% in H_2O, 10 mL) was added to alcohol in PhMe (6 mL per 7 mmol) and the resulting mixture was rapidly stirred for 12 h then partitioned between Et_2O and H_2O. The organic phase was washed sequentially with H_2O and $NaHCO_3$ (satd aq), dried and concentrated in vacuo.

4.1.2.1. (*RS*)-1-(1′-Bromoethyl)-4-methyl-benzene (*RS*)-8. 1-(4-Methylphenyl)ethanol (5.0 g, 37 mmol) was treated as described in Section 4.1.2 to give (*RS*)-**8** as a yellow oil (5.7 g, 78%) which was used without further purification; ν_{max} (film) 1514, 1441, 817, 719; δ_H (500 MHz, $CDCl_3$) 2.11 (3H, d, *J* 6.9, ArCHBrCH_3), 2.4 (3H, s, ArCH_3), 5.29 (1H, q, *J* 6.9, ArC*H*$BrCH_3$), 7.22–7.42 (4H, m, Ar); δ_C (125 MHz, $CDCl_3$) 21.2, 26.8, 49.8, 126.7, 129.3, 138.2, 140.3; *m/z* ($APCI^+$) 119 ($[C_9H_{11}]^+$, 100%).

4.1.2.2. (*RS*)-1-(1′-Bromoethyl)-2-methyl-benzene (*RS*)-9. 1-(2-Methylphenyl)ethanol (5.0 g, 37 mmol) was treated as described in Section 4.1.2 to give (*RS*)-**9** as a yellow oil (6.4 g, 87%), which was used without further purification; ν_{max} (film) 1491, 1463, 761, 723; δ_H (400 MHz, $CDCl_3$) 2.10 (3H, d, *J* 6.9, ArCHBrCH_3), 2.43 (3H, s, ArCH_3), 5.45 (1H, q, *J* 6.9, ArC*H*$BrCH_3$), 7.16–7.58 (4H, m, Ar); δ_C (100 MHz, $CDCl_3$) 19.0, 25.6, 46.1, 125.8, 126.6, 128.2, 130.7, 135.4, 140.8; *m/z* ($APCI^+$) 119 ($[C_9H_{11}]^+$, 100%).

4.1.2.3. (*RS*)-1-(1′-Bromoethyl)-4-methoxy-benzene (*RS*)-10. 1-(4-Methoxyphenyl)ethanol (5.0 g, 33 mmol) was treated as described in Section 4.1.2 to give (*RS*)-**10** as a colourless oil (6.0 g, 84%), which was used without further purification; ν_{max} (film) 1610, 1513, 1252, 831; δ_H (500 MHz, $CDCl_3$) 2.07 (3H, d, *J* 6.9, ArCHBrCH_3), 3.83 (3H, s, OCH_3), 5.27 (1H, q, *J* 6.9, ArC*H*$BrCH_3$), 6.89–7.41 (4H, m, Ar); δ_C (125 MHz, $CDCl_3$) 22.4, 50.0, 55.2, 114.0, 128.0, 135.4, 159.4; *m/z* ($APCI^+$) 135 ($[C_9H_{11}O]^+$, 100%).

4.1.3. General procedure 3: preparation of (*RS*)-1-aryl-1-bromo-ethanes 11–13. The alkyl aromatic substrate (1.0 equiv), NBS (1.1 equiv) and benzoylperoxide (0.01 equiv) were dissolved in CCl_4 (8.0 mL per mmol of aromatic substrate) and then refluxed at 70 °C for 3 h. The solution was filtered, and the filtrate concentrated in vacuo.

4.1.3.1. (*RS*)-2-(1′-Bromoethyl)pyridine (*RS*)-11. 2-Ethylpyridine (10.0 g, 93 mmol), NBS (16.5 g, 102 mmol), benzoylperoxide (200 mg, 0.93 mmol) and CCl_4 (744 mL) were reacted according to Section 4.1.3 to yield a yellow oil, containing a 2:1 mixture of (*RS*)-**11** and 2-(1′,1′-dibromoethyl)pyridine. Chromatography (silica, eluent Et_2O/hexane 1:1) gave (*RS*)-**11** as an oil (7.4 g, 43%) and 2-(1′,1′-dibromoethyl)pyridine as an oil (5.6 g, 23%).

Data for (*RS*)-**11**: ν_{max} (film) 1590, 1571, 787; δ_H (400 MHz, $CDCl_3$) 2.07 (3H, d, *J* 6.9, CHBrCH_3), 5.25 (1H, q, *J* 6.9, C*H*$BrCH_3$), 7.19–8.60 (4H, m, Ar); δ_C (100 MHz, $CDCl_3$)

25.0, 49.2, 121.6, 123.1, 137.2, 149.1, 169.2; *m/z* (CI$^+$) 188 ([M+H]$^+$, ^{81}Br, 42%), 186 (41).

Data for 2-(1′,1′-dibromoethyl)pyridine: ν_{max} (film) 1754, 1787, 1586; δ_H (400 MHz, $CDCl_3$) 3.01 (3H, s, CH_3CBr$_2$), 6.95–8.53 (4H, m, Ar); δ_C (100 MHz, $CDCl_3$) 39.3, 62.4, 122.5, 123.5, 137.1, 147.5, 162.0; *m/z* (CI$^+$) 268 ([M+H]$^+$, ^{81}Br^{81}Br, 49%), 266 (100), 264 (50), 186 (28), 184 (22), 105 (10).

4.1.3.2. (*RS*)-1-(1′-Bromoethyl)naphthalene (*RS*)-12. 1-Ethylnaphthalene (5.0 g, 32 mmol), NBS (6.3 g, 35 mmol), benzoylperoxide (70 mg, 0.29 mmol) and CCl_4 (256 mL) were reacted according to Section 4.1.3. Trituration with hot pentane and concentration of the supernatant in vacuo gave (*RS*)-**12** as a brown oil (7.0 g, 94%); ν_{max} (film) 1691, 1598, 1511, 775; δ_H (400 MHz, $CDCl_3$) 2.32 (3H, d, *J* 6.9, ArCHBrCH_3), 6.06 (1H, q, *J* 6.9, ArC*H*BrCH$_3$), 7.50–8.31 (7H, m, *Ar*CHBrCH$_3$); δ_C (100 MHz, $CDCl_3$) 25.5, 45.1, 123.6, 123.8, 125.5, 126.0, 126.9, 128.6, 128.7, 130.4, 133.6, 138.0; *m/z* (EI$^+$) 236 ([M]$^+$, ^{81}Br, 10%), 234 (12), 155 (100), 127 (12); HRMS (EI$^+$) $C_{12}H_{10}^{81}Br^+$ ([M+H]$^+$, ^{81}Br) requires 234.9945, found 234.9941; $C_{12}H_{10}^{79}Br^+$ ([M+H]$^+$, ^{79}Br) requires 232.9966, found 232.9961.

4.1.3.3. (*RS*)-2-(1′-Bromoethyl)naphthalene (*RS*)-13. 2-Ethylnaphthalene (5.0 g, 32 mmol), NBS (6.3 g, 35 mmol), benzoylperoxide (70 mg, 33 mmol) and CCl_4 (256 mL) were reacted according to Section 4.1.3. Trituration with hot pentane and concentration of the supernatant in vacuo gave (*RS*)-**13** as a brown solid (7.2 g, 97%); mp 50–53 °C; ν_{max} (KBr) 1691, 1599, 1597, 751; δ_H (400 MHz, $CDCl_3$) 2.17 (3H, d, *J* 6.9, ArCHBrCH_3), 5.43 (1H, q, *J* 6.9, ArC*H*BrCH$_3$), 7.27–8.18 (7H, m, Ar); δ_C (100 MHz, $CDCl_3$) 26.7, 50.1, 125.1, 126.5, 127.9, 128.1, 128.5, 128.7, 131.0, 133.0, 133.1, 140.4; *m/z* (EI$^+$) 235 ([M+H]$^+$, ^{81}Br, 53%), 233 (55), 155 (100), 127 (32).

4.1.3.4. (3*R*,6*S*,1′*S*)-*N*,*N*′-Bis-(*p*-methoxybenzyl)-6-*iso*-propyl-3-(1′-(4-methylphenyl)ethyl)piperazine-2,5-dione 14. Compound **1** (200 mg, 0.5 mmol) in THF (10 mL), KHMDS (0.5 M in PhMe, 1.24 mL, 0.6 mmol) and (*RS*)-**8** (0.17 mL, 1.1 mmol) were reacted according to Section 4.1.1 to afford a brown oil. Chromatography (silica gel, eluent 30–40° petrol/Et_2O 4:1) gave **14** as a colourless solid (160 mg, 61%); mp 133–135 °C; $[\alpha]_D^{21}$ +46.5 (*c* 1.3 in $CHCl_3$); ν_{max} (KBr) 1653, 1515, 1441; δ_H (500 MHz, $CDCl_3$) 0.65 (3H, d, *J* 6.9, CH_3CHCH$_3$), 0.96 (3H, d, *J* 6.9, CH$_3$CHCH_3), 1.49 (3H, d, *J* 7.3, ArCHCH_3), 2.08 (1H, m, (CH$_3$)$_2$C*H*), 2.40 (3H, s, ArCH_3), 3.04 (1H, d, *J* 2.4, (CH_3)$_2$CHC*H*), 3.56 (1H, m, ArC*H*CH$_3$), 3.79 (3H, s, OCH_3), 3.82 (3H, s, OCH_3), 3.93 (1H, d, *J* 14.5, NCH_2ArOMe), 4.00 (1H, d, *J* 15.0, NCH_2ArOMe), 4.07 (1H, d, *J* 1.9, C*H*CH(CH$_3$)Ar), 4.61 (1H, d, *J* 15.0, NCH_2ArOMe), 5.49 (1H, d, *J* 14.5, NCH_2ArOMe), 6.72–6.76 (4H, m, Ar), 6.86–6.88 (2H, m, Ar), 7.08–7.14 (6H, m, Ar); δ_C (125 MHz, $CDCl_3$) 15.2, 16.7, 19.8, 21.0, 30.3, 40.3, 46.0, 47.0, 55.2, 55.1, 62.4, 63.1, 113.7, 114.1, 127.0, 127.1, 128.1, 129.1, 129.6, 130.4, 136.7, 136.9, 158.8, 159.3, 165.4, 165.5; *m/z* (APCI$^+$) 515 ([M+H]$^+$, 100%), 121 (45); HRMS (CI$^+$) $C_{32}H_{39}N_2O_4^+$ ([M+H]$^+$) requires 515.2909, found 515.2921.

4.1.3.5. (3*R*,6*S*,1′*S*)-*N*,*N*′-Bis-(*p*-methoxybenzyl)-6-*iso*-propyl-3-(1′-(2-methylphenyl)ethyl)piperazine-2,5-dione 15. Compound **1** (200 mg, 0.5 mmol) in THF (10 mL), KHMDS (0.5 M in PhMe, 1.24 mL, 0.6 mmol) and (*RS*)-**9** (0.17 mL, 1.1 mmol) were reacted according to Section 4.1.1 to afford a brown oil. Chromatography (silica gel, eluent cyclohexane/EtOAc 1:1) gave **15** as a colourless solid (179 mg, 69%); mp 120–122 °C; $[\alpha]_D^{21}$ +80.8 (*c* 1.0 in $CHCl_3$); ν_{max} (KBr) 1652, 1514; δ_H (400 MHz, $CDCl_3$) 0.64 (3H, d, *J* 6.9, CH_3CHCH$_3$), 1.04 (3H, d, *J* 6.9, CH$_3$CHCH_3), 1.40 (3H, d, *J* 7.2, ArCHCH_3), 2.22 (1H, m, (CH$_3$)$_2$C*H*), 2.38 (3H, s, ArCH_3), 3.26 (1H, d, *J* 2.3, (CH$_3$)$_2$CHC*H*), 3.52 (1H, d, *J* 14.5, NCH_2ArOMe), 3.77 (3H, s, OCH_3), 3.79 (3H, s, OCH_3), 3.87 (1H, m, ArC*H*CH$_3$), 4.23 (1H, d, *J* 14.9, NCH_2ArOMe), 4.24 (1H, d, *J* 1.4, C*H*CH(CH$_3$)Ar), 4.72 (1H, d, *J* 14.9, NCH_2ArOMe), 5.36 (1H, d, *J* 14.5, NCH_2ArOMe), 6.74–6.81 (4H, m, Ar), 6.83–6.85 (2H, m, Ar), 7.04–7.06 (2H, m, Ar), 7.17–7.32 (4H, m, Ar); δ_C (100 MHz, $CDCl_3$) 15.3, 15.8, 19.7, 20.2, 30.5, 39.7, 46.4, 47.6, 55.2, 61.7, 62.9, 113.9, 113.9, 126.1, 127.2, 127.3, 127.5, 127.8, 129.6, 130.1, 131.0, 137.3, 139.8, 159.0, 159.2, 165.8, 167.0; *m/z* (APCI$^+$) 515 ([M+H]$^+$, 30%), 121 (100); HRMS (CI$^+$) $C_{32}H_{39}N_2O_4^+$ ([M+H]$^+$) requires 515.2909, found 515.2904.

4.1.3.6. (3*R*,6S,1′*S*)-*N*,*N*′-Bis-(*p*-methoxybenzyl)-6-*iso*-propyl-3-(1′-(4-methoxyphenyl)ethyl)piperazine-2,5-dione 16. Compound **1** (200 mg, 0.5 mmol) in THF (10 mL), KHMDS (0.5 M in PhMe, 1.24 mL, 0.6 mmol) and (*RS*)-**10** (0.17 mL, 1.1 mmol) were reacted according to Section 4.1.1 to afford a brown oil. Chromatography (silica gel, eluent cyclohexane/Et_2O 4:1) gave **16** as a colourless solid (169 mg, 64%); mp 151–153 °C; $[\alpha]_D^{23}$ +34.0 (*c* 1.5 in $CHCl_3$); ν_{max} (KBr) 1650, 1513, 1440, 1247; δ_H (400 MHz, $CDCl_3$) 0.64 (3H, d, *J* 6.9, CH_3CHCH$_3$), 0.97 (3H, d, *J* 6.9, CH$_3$CHCH_3), 1.49 (3H, d, *J* 7.3, ArCHCH_3), 2.08 (1H, m, (CH$_3$)$_2$C*H*), 3.04 (1H, d, *J* 2.4, (CH$_3$)2CHCH), 3.53 (1H, m, NCHC*H*(Ar)CH$_3$), 3.78 (3H, s, OCH_3), 3.82 (3H, s, OCH_3), 3.83 (3H, s, OCH_3), 3.95 (1H, d, *J* 14.5, NCH_2ArOMe), 4.00 (1H, d, *J* 15.0, NCH_2ArOMe), 4.04 (1H, d, *J* 1.5, C*H*CH(CH$_3$)Ar), 4.60 (1H, d, *J* 15.0, NCH_2ArOMe), 5.50 (1H, d, *J* 14.5, NCH_2ArOMe), 6.70–6.76 (4H, m, Ar), 6.83–8.89 (4H, m, Ar), 7.08–7.16 (4H, m, Ar); δ_C (100 MHz, $CDCl_3$) 15.3, 17.6, 19.9, 30.3, 39.9, 46.2, 47.0, 55.2, 55.3, 62.6, 63.2, 113.8, 113.8, 114.2, 127.0, 127.1, 128.9, 129.3, 129.6, 130.5, 131.8, 158.9, 158.9, 159.4, 165.5, 165.5; *m/z* (APCI$^+$) 531 ([M+H]$^+$, 45%), 121 (100); HRMS (CI$^+$) $C_{32}H_{39}N_2O_5^+$ ([M+H]$^+$) requires 531.2858, found 531.2867.

4.1.3.7. (3*R*,6*S*,1′*S*)-*N*,*N*′-Bis-(*p*-methoxybenzyl)-6-*iso*-propyl-3-(1′-(2-pyridyl)ethyl)piperazine-2,5-dione 17. Compound **1** (200 mg, 0.5 mmol) in THF (10 mL), KHMDS (0.5 M in PhMe, 1.24 mL, 0.6 mmol) and (*RS*)-**11** (0.17 mL, 1.1 mmol) were reacted according to Section 4.1.1 to afford a brown oil. Chromatography (silica gel, eluent cyclohexane/Et_2O 4:1) gave **17** as a yellow solid (216 mg, 85%); mp 109–112 °C; $[\alpha]_D^{19}$ +22.8 (*c* 1.3 in $CHCl_3$); ν_{max} (film) 1656, 1513, 1439; δ_H (400 MHz, $CDCl_3$) 0.72 (3H, d, *J* 6.9, CH_3CHCH$_3$), 1.04 (3H, d, *J* 6.9, CH$_3$CHCH_3), 1.41 (3H, d, *J* 6.0, ArCHCH_3), 2.25 (1H, m, (CH$_3$)$_2$C*H*), 3.43 (1H, d, *J* 2.7, (CH$_3$)$_2$CHC*H*), 3.70 (1H, d, *J* 14.8, NCH_2ArOMe), 3.78 (3H, s, OCH_3), 3.80 (3H, s, OCH_3),

3.95 (1H, d, *J* 14.8, CH_2ArOMe), 4.46 (1H, d, *J* 1.8, C*H*CH(CH_3)Ar), 5.06 (1H, d, *J* 14.8, NCH_2ArOMe), 5.31 (1H, d, *J* 14.8, NCH_2ArOMe), 6.76–6.82 (4H, m, Ar), 6.91–6.95 (2H, m, Ar), 7.01–7.05 (2H, m, Ar), 7.17–7.22 (2H, m, py), 7.60 (1H, m, py), 8.53 (1H, m, C_6H–py); δ_C (100 MHz, $CDCl_3$) 15.1, 16.2, 20.4, 31.7, 44.2, 46.4, 47.3, 55.7, 55.7, 62.8, 63.2, 114.4, 114.4, 122.3, 122.5, 127.9, 128.0, 130.3, 130.5, 137.0, 149.6, 159.5, 162.0, 165.8, 166.8; *m/z* (APCI$^+$) 502 ([M+H]$^+$, 100%), 121 (75); HRMS (CI$^+$) $C_{30}H_{36}N_3O_4^+$ ([M+H]$^+$) requires 502.2706, found 502.2713.

4.1.3.8. X-ray crystal structure determination for 17. Data were collected using a Enraf–Nonius κ-CCD diffractometer with graphite monochromated Mo Kα radiation using standard procedures at 190 K. The structure was solved by direct methods (SIR97). All non-hydrogen atoms were refined with anisotropic thermal parameters. Hydrogen atoms were added at idealised positions. The structure was refined using CRYSTALS.[21]

Crystal data for **17** [$C_{30}H_{35}N_3O_4$]: M=501.62; monoclinic; space group $P1\,21\,1$; a=7.5984(1) Å, b=28.2598(5) Å, c=12.3274(2) Å; β=94.2499(9)°; V=2639.8 Å^3; Z=4; μ=0.084 mm^{-1}; colourless plate; crystal dimensions 0.1×0.3×0.6 mm^3. A total of 6119 unique reflections were measured for $1<\theta<27$ and 5622 reflections were used in the refinement. The final parameters were wR_2=0.033 and R_1=0.038 (all data).

Crystallographic data (excluding structure factors) have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC280651. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK [fax: +44 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk].

4.1.3.9. (3*R*,6*S*,1′*S*)-*N*,*N*′-Bis(*p*-methoxybenzyl)-6-*iso*-propyl-3-(1′-(1-naphthyl)ethyl)piperazine-2,5-dione 18. Following Section 4.1.1 using **1** (200 mg, 0.5 mmol), KHMDS (0.5 M in toluene, 1.24 mL, 0.6 mmol), THF (10 mL) and (*RS*)-**12** (0.12 mL, 1.1 mmol) afforded a crude solid containing 55:45 mixture of **18** and **1**. Chromatography (silica gel, eluent 30–40° petrol/Et_2O 9:1) gave **18** as a colourless oil (130 mg, 47%); $[\alpha]_D^{22}$ +60.6 (*c* 1.2 in $CHCl_3$); ν_{max} (film) 1642, 1513, 1454; δ_H (400 MHz, $CDCl_3$) 0.67 (3H, d, *J* 7.0, CH_3CHCH$_3$), 1.11 (3H, d, *J* 7.0, (CH$_3$)CHCH_3), 1.43 (3H, d, *J* 7.1, ArCHCH_3), 2.36 (1H, m, (CH$_3$)$_2$C*H*), 3.18 (1H, d, *J* 14.3, NCH_2ArOMe), 3.62 (3H, s, OCH_3), 3.70 (1H, d, *J* 3.0, (CH$_3$)$_2$CHC*H*), 3.80 (3H, s, OCH_3), 4.03 (1H, d, *J* 14.7, NCH_2ArOMe), 4.61 (1H, m, CH$_3$C*H*Ar), 4.67 (1H, s, C*H*CH(CH$_3$)Ar), 5.14 (1H, d, *J* 14.3, NCH_2ArOMe), 5.31 (1H, d, *J* 14.7, NCH_2ArOMe), 6.15–6.17 (2H, m, Ar), 6.37–6.39 (2H, m, Ar), 6.87–6.90 (2H, m, Ar), 7.19–7.21 (2H, m, Ar), 7.45–8.54 (7H, m, naphthyl); δ_C (100 MHz, $CDCl_3$) 13.4, 15.5, 20.1, 30.7, 41.0, 46.6, 46.7, 55.1, 55.3, 61.8, 62.3, 113.3, 114.2, 123.6, 124.6, 125.2, 125.9, 126.8, 127.0, 127.4, 128.1, 128.7, 130.0, 130.7, 131.9, 134.0, 138.8, 158.7, 159.3, 165.9, 167.6; *m/z* (APCI$^+$) 551 ([M+H]$^+$, 100%), 121 (78); HRMS (CI$^+$) $C_{35}H_{39}N_2O_4^+$ ([M+H]$^+$) requires 551.2909, found 551.2908.

4.1.3.10. (3*R*,6*S*,1′*S*)-*N*,*N*′-Bis(*p*-methoxybenzyl)-6-*iso*-propyl-3-(1′-(2-naphthyl)ethyl)piperazine-2,5-dione 19. Following Section 4.1.1 using **1** (200 mg, 0.5 mmol), THF (8 mL), KHMDS (0.5 M in toluene, 1.24 mL, 0.6 mmol) and (*RS*)-**13** (259 mg in 2 mL of THF, 1.1 mmol) afforded a brown solid containing 83:17 mixture of **19** and **1**. Chromatography (silica gel, eluent cyclohexane/EtOAc 9:1) gave **19** as a colourless solid (180 mg, 68%); mp 188–191 °C; $[\alpha]_D^{21}$ −48.6 (*c* 1.5 in $CHCl_3$); ν_{max} (KBr) 1654, 1514; δ_H (400 MHz, $CDCl_3$) 0.67 (3H, d, *J* 7.0, CH_3CHCH$_3$), 0.9 (3H, d, *J* 7.0, CH$_3$CHCH_3), 1.64 (3H, d, *J* 7.3, ArCHCH_3), 2.06 (1H, m, (CH$_3$)$_2$C*H*), 3.01 (1H, d, *J* 2.5, (CH$_3$)$_2$CHC*H*), 3.68 (3H, s, OCH_3), 3.80 (1H, m, C*H*(CH$_3$)Ar), 3.79 (1H, d, *J* 14.9, NCH_2ArOMe), 3.82 (3H, s, OCH_3), 4.05 (1H, d, *J* 14.5, NCH_2ArOMe), 4.19 (1H, d, *J* 1.4, C*H*CH(CH$_3$)Ar), 4.71 (1H, d, *J* 14.9, NCH_2ArOMe), 5.56 (1H, d, *J* 14.5, NCH_2ArOMe), 6.27–6.34 (4H, m, Ar), 6.84–6.89 (2H, m, Ar), 7.14–7.16 (2H, m, Ar), 7.32–7.90 (7H, m, naphthyl); δ_C (100 MHz, $CDCl_3$) 15.4, 17.0, 19.7, 30.2, 40.6, 45.7, 45.8, 55.1, 55.3, 61.9, 63.2, 113.6, 114.2, 125.9, 126.3, 126.3, 126.6, 126.9, 126.9, 127.6, 128.1, 128.1, 129.4, 130.6, 132.6, 133.5, 137.6, 158.7, 159.4, 165.3; *m/z* (APCI$^+$) 551 ([M+H]$^+$, 80%), 121 (100); HRMS (CI$^+$) $C_{35}H_{39}N_2O_4^+$ ([M+H]$^+$) requires 551.2909, found 551.2923.

4.1.3.11. (3*R*,6*S*,1′*S*)-6-*iso*-Propyl-3-(1′-phenylethyl)-piperazine-2,5-dione 26. Compound **6** (450 mg, 0.9 mmol) and CAN (1.7 g, 5.4 mmol) in acetonitrile (10 mL) and water (5 mL) were stirred at rt for 12 h. After the addition of satd aq K_2CO_3 (20 mL) the mixture was extracted with dichloromethane and the organic fractions combined, dried and concentrated in vacuo. Trituration of the resultant solid with hexane gave **26** as a colourless solid (218 mg, 94%); mp 253–255 °C; $[\alpha]_D^{21}$ +74.8 (*c* 1.0 in $CHCl_3$); ν_{max} (KBr) 3189, 3056, 1668; δ_H (400 MHz, $CDCl_3$) 0.89 (3H, d *J* 7.0, CH_3CHCH$_3$), 1.02 (3H, d, *J* 7.0, CH$_3$CHCH_3), 1.35 (3H, d, *J* 7.1, PhCHCH_3), 2.41 (1H, m, C*H*(CH$_3$)$_2$), 3.70–3.72 (1H, m, PhC*H*CH$_3$), 3.76 (1H, d, *J* 1.6, (CH$_3$)$_2$CHC*H*), 4.17 (1H, d, *J* 1.5, C*H*CH(CH$_3$)Ph), 5.64 (1H, s, N*H*), 6.16 (1H, s, N*H*), 7.27–7.42 (5H, m, Ar); δ_C (100 MHz, $CDCl_3$) 11.9, 15.7, 18.5, 32.1, 41.9, 56.0, 60.2, 127.6, 127.7, 129.2, 140.3, 167.2, 167.5; *m/z* (APCI$^+$) 261 ([M+H]$^+$, 100%); HRMS (CI$^+$) $C_{15}H_{21}N_2O_2^+$ ([M+H]$^+$) requires 261.1603, found 261.1604.

4.1.3.12. (3*R*,6*S*,1′*S*)-6-*iso*-Propyl-3-(1′-(2-methylphenyl)ethyl)piperazine-2,5-dione 27. Compound **15** (300 mg, 0.6 mmol) and CAN (3.6 mmol) in acetonitrile (3 mL) and water (3 mL) were stirred for 1 h at rt. The organic solvent was evaporated, ether was added (20 mL) and the resultant solid filtered and washed with ether to give **27** as a colourless solid (145 mg, 88%); mp 166–168 °C; $[\alpha]_D^{25}$ +64.0 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 1683; δ_H (400 MHz, $CDCl_3$) 0.89 (3H, d, *J* 6.8, (CH_3)$_2$CH), 1.03 (3H, d, *J* 6.8, (CH_3)$_2$CH), 1.31 (1H, d, *J* 7.0, CH_3CH), 2.40–2.47 (1H, m, (CH$_3$)$_2$C*H*), 2.43 (3H, s, CH_3Ph), 3.87 (1H, br s, (CH$_3$)$_2$CHC*H*), 3.97–4.04 (1H, m, C*H*CH$_3$), 4.04 (1H, br s, C*H*CHCH$_3$), 5.62 (1H, s, N*H*), 6.14 (1H, s, N*H*), 7.19–7.29 (4H, m, Ar); δ_C (100 MHz, $CDCl_3$) 12.3, 15.8, 18.5, 19.3, 32.2, 37.8, 57.6, 60.0, 126.4, 126.7, 127.4, 131.4, 136.1, 138.5, 167.5; HRMS (CI$^+$) $C_{12}H_{18}NO_2^+$ ([M+H]$^+$) requires 275.1760, found 275.1761.

4.1.3.13. (2*R*,3*S*)-Methyl 2-amino-3-phenyl-butanoate 28. Compound **26** (380 mg, 1.32 mmol) was heated in HCl (5 M aq, 50 mL) at 100 °C for 24 h. After this the volatile material was removed in vacuo and the resulting mixture was subjected to these conditions twice more. The resulting mixture of amino acids was then dissolved in MeOH (20 mL) and $SOCl_2$ (5 mL) added (CARE!) and the mixture then refluxed for 2 h, cooled to rt and the volatile material removed in vacuo. The residue was partitioned between satd aq $NaHCO_3$ (30 mL) and DCM (30 mL), the organic layer washed with satd brine (30 mL), dried and the solvent removed in vacuo. Chromatography (silica, ether/dimethylethylamine 20:1) afforded a mixture of (*S*)-valine methyl ester and **28**. (*S*)-Valine methyl ester was removed in vacuo to give **28** as a colourless oil (126 mg, 49%); $[\alpha]_D^{23}$ −49.9 (*c* 1.5 in $CHCl_3$); ν_{max} (film) 3386, 3311, 3029, 2952, 1740, 1602; δ_H (400 MHz, $CDCl_3$) 1.31 (3H, d, *J* 7.1, CHC*H*$_3$), 1.43 (2H, br s, N*H*$_2$), 3.20 (1H, m, C*H*Ph), 3.62 (3H, s, OC*H*$_3$), 3.64 (1H, d, *J* 5.4, C*H*NH$_2$), 7.20–7.33 (5H, m, Ph); δ_C (100 MHz, $CDCl_3$) 15.2, 43.8, 52.2, 61.0, 127.2, 128.1, 128.8, 143.4, 175.5; *m*/*z* (APCI$^+$) 194 ([M+H]$^+$, 58%), 133 (100); HRMS (ESI$^+$) $C_{11}H_{16}NO_2^+$ ([M+H]$^+$) requires 194.1181, found 194.1176.

4.1.3.14. (2*R*,3*S*)-2-Amino-3-(2-methylphenyl)-butyric acid methyl ester 29. Compound **27** (100 mg, 0.4 mmol) in hydroiodic acid (57% in water, 15 mL) was refluxed for 24 h then the solvent was evaporated in vacuo to afford a mixture of amino acids, which were dissolved in MeOH (20 mL) and cooled to 0 °C and thionyl chloride (1.0 mL) added. The mixture was subject to reflux overnight then concentrated in vacuo. The mixture of the methyl ester amino hydrochlorides was partitioned between DCM and aq $NaHCO_3$, the organic phase dried and concentrated in vacuo. Removal of (*S*)-valine methyl ester under vacuum gave **29** as a colourless oil (62 mg, 75%); $[\alpha]_D^{25}$ −18.1 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 1738; δ_H (400 MHz, $CDCl_3$) 1.29 (3H, d, *J* 7.1, C*H*$_3$CH), 2.38 (3H, s, C*H*$_3$Ph), 2.69 (2H, br s, N*H*$_2$), 3.51–3.57 (1H, m, C*H*CH$_3$), 3.66 (3H, s, OC*H*$_3$), 3.71 (1H, d, *J* 5.3, C*H*NH$_2$), 7.12–7.27 (4H, m, Ar); δ_C (100 MHz, $CDCl_3$) 14.7, 19.4, 37.9, 52.0, 58.3, 126.1, 126.6, 126.7, 130.6, 135.6, 140.7, 174.3; *m*/*z* (ES$^+$) 208 ([M+H]$^+$, 100%,); HRMS (CI$^+$) $C_{12}H_{18}NO_2^+$ ([M+H]$^+$) requires 208.1338, found 208.1345.

4.1.3.15. (3*R*,6*S*,2′*R*)- and (3*R*,6*S*,2′*S*)-*N*,*N*′-Bis(*p*-methoxybenzyl)-3-*iso*-propyl-6-(2′-ethylpropanoate)piperazine-2,5-dione 31 and 32. Compound **1** (200 mg, 0.5 mmol) in THF (10 mL), LiHMDS (0.55 mL, 1 M in THF, 0.55 mmol) and (*RS*)-**30** (0.64 mL, 5.0 mmol) were reacted according to Section 4.1.1 to give a crude oil from which excess of (*RS*)-**30** was removed under vacuum (1 mmHg, ambient temperature). Chromatography (silica, ether/hexane 1:1) gave **31** as a colourless solid (first to elute, 230 mg, 93%) and **32** as a colourless solid (second to elute, 15 mg, 3%).

Data for **31**: mp 112–114 °C (ether); $[\alpha]_D^{23}$ −13.3 (*c* 1.0 in $CHCl_3$); ν_{max} (KBr) 1730, 1646; δ_H (400 MHz, $CDCl_3$) 0.77 (3H, d, *J* 6.9, C*H*$_3$CHCH$_3$), 1.13 (3H, d, *J* 6.9, CH$_3$CHC*H*$_3$), 1.14 (3H, d, *J* 7.2, (EtO$_2$C)CHC*H*$_3$), 1.15 (3H, t, *J* 7.2, OCH$_2$C*H*$_3$), 2.30 (1H, m, CH$_3$C*H*CH$_3$), 3.48 (1H, dq, *J* 1.6, 7.2, (EtO$_2$C)C*H*CH$_3$), 3.69 (1H, d, *J* 15.2, NC*H*$_2$ArOMe), 3.79 (4H, m, OC*H*$_3$ and 6-*H*), 3.80 (3H, s, OC*H*$_3$), 3.89 (1H, d, *J* 14.7, NC*H*$_2$ArOMe), 3.95 (1H, m, OC*H*$_2$CH$_3$), 4.14 (1H, m, OC*H*$_2$CH$_3$), 4.57 (1H, s, 3-*H*), 5.28 (1H, d, *J* 15.2, NC*H*$_2$ArOMe), 5.34 (1H, d, *J* 14.7, NC*H*$_2$ArOMe), 6.84 (4H, m, Ar*H*), 7.18 (4H, m, Ar*H*); δ_C (100 MHz, $CDCl_3$) 11.8, 14.0, 16.4, 19.8, 31.3, 42.4, 46.0, 47.1, 55.2, 61.2, 113.9, 114.2, 127.4, 127.7, 129.4, 129.9, 159.1, 159.3, 165.7, 165.8, 173.7; *m*/*z* (APCI$^+$) 497 ([M+H]$^+$, 50%), 121 (100); HRMS (CI$^+$) $C_{28}H_{37}N_2O_6^+$ ([M+H]$^+$) requires 497.2645, found 497.2652.

Data for **32**: $C_{28}H_{36}N_2O_6$ requires C, 67.7; H, 7.3; N, 5.6%. Found C, 67.7; H, 7.3; N, 5.6%; mp 136 °C (ethyl acetate/hexane); $[\alpha]_D^{23}$ +62.4 (*c* 1.0 in $CHCl_3$); ν_{max} (KBr) 2984, 2933, 1739, 1640; δ_H (400 MHz, $CDCl_3$) 0.83 (3H, d, *J* 6.9, C*H*$_3$CHCH$_3$), 0.98 (3H, d, *J* 6.9, CH$_3$CHC*H*$_3$), 1.10 (3H, d, *J* 7.0, (EtO$_2$C)CHC*H*$_3$), 1.26 (3H, t, *J* 7.1, OCH$_2$C*H*$_3$), 2.30 (1H, m, CH$_3$C*H*CH$_3$), 3.10 (1H, dq, *J* 1.6, 6.9, (EtO$_2$C)C*H*CH$_3$), 3.778 (1H, d, *J* 3.1, 6-*H*), 3.782 (1H, d, *J* 14.7, NC*H*$_2$ArOMe), 3.81 (6H, s, 2×OC*H*$_3$), 3.99 (1H, d, *J* 14.9, NC*H*$_2$ArOMe), 4.14–4.38 (2H, m, OC*H*$_2$CH$_3$), 4.70 (1H, d, *J* 3.2, 3-*H*), 5.27 (1H, d, *J* 14.9, NC*H*$_2$ArOMe), 5.43 (1H, d, *J* 14.7, NC*H*$_2$ArOMe), 6.86–6.88 (4H, m, Ar), 7.14–7.27 (4H, m, Ar); δ_C (100 MHz, $CDCl_3$) 8.6, 11.8, 14.1, 31.7, 40.0, 46.1 46.2, 55.23, 55.26, 60.0, 60.8, 62.2, 114.0, 114.2, 126.9, 127.3, 130.0, 130.2, 159.3, 159.4, 164.4, 165.8, 172.0; *m*/*z* (APCI$^+$) 497 ([M+H]$^+$, 10%), 121 (100).

4.1.3.16. X-ray crystal structure determination for 32. Data were collected using an Enraf–Nonius Mach 3 diffractometer with graphite monochromated Cu radiation using standard procedures at 193 K. The structure was solved by direct methods (SIR97). All non-hydrogen atoms were refined with anisotropic thermal parameters. Hydrogen atoms were added at idealised positions. The structure was refined using CRYSTALS.[21]

Crystal data for **32** [$C_{28}H_{36}N_2O_6$]: *M*=496.6, monoclinic; space group *P*1 21 1; *a*=9.220(2) Å, *b*=12.304(2) Å, *c*=12.354(3) Å; *β*=105.376(18)°; *V*=1351.3 Å^3; *Z*=2; *μ*=0.697 mm^{-1}; colourless plate; crystal dimensions 0.02×0.6×0.6 mm^3. A total of 2892 unique reflections were measured for $19<\theta<23$ and 2789 reflections were used in the refinement. The final parameters were wR_2=0.061 and R_1=0.046 (all data).

Crystallographic data (excluding structure factors) have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC280790. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk].

4.1.3.17. Recovery of ethyl 2-bromopropanoate 30. To **1** (200 mg, 0.5 mmol) in degassed anhydrous THF (10 mL) at −78 °C was added a solution of LiHMDS (1.0 M in THF, 0.55 mL, 0.55 mmol). The resultant solution was allowed to stir at −78 °C for 1 h prior to the addition of (*RS*)-**30** (140 mg, 0.77 mmol). The mixture was stirred at −78 °C for 12 h then allowed to warm to rt when solid NH_4Cl (250 mg) was added. The solvent was removed in vacuo and the residue distilled (1 mmHg, ambient temperature)

to afford (*S*)-**30** (23 mg, 16%); $[\alpha]_D^{23}$ −11.1 (*c* 1.1 in $CHCl_3$); {lit.[13] for enantiomer $[\alpha]_D^{23}$ +37.0 (*c* 1.0 in $CHCl_3$)}.

4.1.3.18. Epimerisation of 31 and 32. LiHMDS (1.6 mL, 1 M in THF, 1.60 mmol) was added to a 94.5:5.5 mixture of **31**:**32** (787 mg, 1.60 mmol) and methyl iodide (100 μL, 1.60 mmol) in anhydrous ethanol (50 mL), and the mixture stirred for 12 h at rt. NH_4Cl (satd aq) was then added and the mixture was partitioned between EtOAc and H_2O. The aqueous phase was extracted with EtOAc and the combined organic layers were dried and concentrated in vacuo to yield a crude solid 20:80 mixture of **31**:**32**. Crystallisation from EtOAc/hexane gave **32** (522 mg, 66%).

4.1.3.19. (3*R*,6*S*,2′*R*)-*N*,*N*′-Bis(*p*-methoxybenzyl)-3-*iso*-propyl-6-(2′-methylpropanoate)piperazine-2,5-dione 37. Compound **1** (200 mg, 0.5 mmol) in THF (10 mL), LiHMDS (0.55 mL, 1 M in THF, 0.55 mmol) and (*RS*)-**33** (835 mg, 5.0 mmol) were reacted together according to Section 4.1.1 to give a crude oil from which excess of (*RS*)-**33** was removed under vacuum (1 mmHg, ambient temperature). Chromatography (silica, ether/hexane 1:1) gave **37** as a colourless solid (212 mg, 87%); $[\alpha]_D^{23}$ −10.4 (*c* 1.0 in $CHCl_3$); ν_{max} (KBr) 2958, 1730, 1644; δ_H (400 MHz, $CDCl_3$) 0.79 (3H, d, *J* 7.0, C*H*$_3$CHCH$_3$), 1.08 (3H, d, *J* 7.0, CH$_3$CHC*H*$_3$), 1.15 (3H, d, *J* 7.2, (EtO$_2$C)CHC*H*$_3$), 2.31 (1H, m, CH$_3$C*H*CH$_3$), 3.49 (1H, dq, *J* 1.6, 7.2, (EtO$_2$C)C*H*CH$_3$), 3.59 (3H, s, CO$_2$C*H*$_3$), 3.68 (1H, d, *J* 15.2, NCH$_2$ArOMe), 3.77 (1H, d, *J* 3.4, 6-*H*), 3.79 (3H, s, OC*H*$_3$), 3.80 (3H, s, OC*H*$_3$), 3.88 (1H, d, *J* 14.7, NCH$_2$ArOMe), 4.52 (1H, d, *J* 1.6, 3-*H*), 5.31 (1H, d, *J* 15.2, NC*H*$_2$ArOMe), 5.36 (1H, d, *J* 14.7, NC*H*$_2$ArOMe), 6.82–6.87 (4H, m, Ar), 7.13–7.21 (4H, m, Ar); δ_C (100 MHz, $CDCl_3$) 12.0, 16.4, 19.8, 26.9, 31.3, 42.1, 45.9, 47.1, 52.1, 55.2, 55.3, 60.2, 62.8, 113.9, 114.2, 127.3, 127.5, 129.6, 129.9, 159.1, 159.3, 165.7, 165.7, 174.1; *m*/*z* (CI^+) 483 ([M+H]$^+$, 40%), 378 (10), 121 (100); HRMS (CI^+) $C_{27}H_{35}N_2O_6^+$ ([M+H]$^+$) requires 483.2495, found 483.2496.

4.1.3.20. (3*R*,6*S*,2′*R*)-*N*,*N*′-Bis-(*p*-methoxybenzyl)-3-*iso*-propyl-6-(2′-*tert*-butylpropanoate)piperazine-2,5-dione 38. Compound **1** (200 mg, 0.5 mmol) in THF (10 mL), LiHMDS (1.0 M in THF, 0.55 mL, 0.55 mmol) and (*RS*)-**34** (1.04 g, 5.0 mmol) were reacted together according to Section 4.1.1 to give a crude oil. Chromatography (silica, ether/hexane 1:1) gave **38** as a colourless solid (220 mg, 83%); $C_{30}H_{40}N_2O_6$ requires C, 68.7; H, 7.7; N, 5.3%. Found C, 68.2; H, 7.6; N, 5.1%; $[\alpha]_D^{23}$ −10.3 (*c* 1.0 in $CHCl_3$); ν_{max} (KBr) 2965, 1716, 1648; δ_H (400 MHz, $CDCl_3$) 0.65 (3H, d, *J* 7.0, C*H*$_3$CHCH$_3$), 1.01 (3H, d, *J* 7.0, CH$_3$CHC*H*$_3$), 1.10 (3H, d, *J* 7.3, (^{t}BuO$_2$C)CHC*H*$_3$), 1.42 (9H, s, C(CH$_3$)$_3$), 2.24 (1H, m, CH$_3$C*H*CH$_3$), 3.41 (1H, dq, *J* 1.8, 7.3, (^{t}BuO$_2$C)C*H*CH$_3$), 3.69 (1H, d, *J* 14.8, NCH$_2$ArOMe), 3.72 (1H, d, *J* 3.3, 6-*H*), 3.77 (3H, s, OCH$_3$), 3.78 (3H, s, OCH$_3$), 3.92 (1H, d, *J* 14.8, NCH$_2$ArOMe), 4.61 (1H, d, *J* 1.2, 3-*H*), 5.18 (1H, d, *J* 14.8, NCH$_2$ArOMe), 5.28 (1H, d, *J* 14.8, NCH$_2$ArOMe), 6.81–6.86 (4H, m, Ar), 7.17–7.28 (4H, m, Ar); δ_C (100 MHz, $CDCl_3$) 12.3, 16.2, 19.8, 27.9, 31.3, 43.4, 46.2, 47.2, 55.2, 55.2, 60.5, 62.9, 81.6, 113.8, 114.1, 127.5, 128.3, 129.8, 130.0, 159.1, 159.2, 165.4, 166.0, 172.8; *m*/*z* (ESI^+) 547 ([M+Na]$^+$, 100%); HRMS (ESI^+) $C_{30}H_{40}N_2NaO_6^+$ ([M+Na]$^+$) requires 547.2784, found 547.2779.

4.1.3.21. (3*R*,6*S*,2′*R*)-*N*,*N*′-Bis-(*p*-methoxybenzyl)-3-*iso*-propyl-6-(2′-ethylbutanoate)piperazine-2,5-dione 39. Compound **1** (200 mg, 0.5 mmol) in THF (10 mL), LiHMDS (1.0 M in THF, 0.55 mL, 0.55 mmol) and (*RS*)-**35** (975 mg, 5.0 mmol) were reacted together according to Section 4.1.1 to give a crude oil. Chromatography (silica, ether/hexane 1:1) gave **39** as a colourless solid (212 mg, 82%); $[\alpha]_D^{23}$ −28.3 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 2960, 1731, 1657; δ_H (400 MHz, $CDCl_3$) 0.79 (3H, d, *J* 7.0, CH$_3$CHC*H*$_3$), 0.86 (3H, t, *J* 7.4, CHCH$_2$C*H*$_3$), 1.07 (3H, d, *J* 7.0, CH$_3$CHC*H*$_3$), 1.14 (3H, t, *J* 7.2, OCH$_2$C*H*$_3$), 1.49 (1H, m, CHC*H*$_2$CH$_3$), 1.90 (1H, m, CHC*H*$_2$CH$_3$), 2.30 (1H, m, CH$_3$C*H*CH$_3$), 3.12 (1H, m, (EtO$_2$C)C*H*CH$_2$CH$_3$), 3.73 (1H, d, *J* 3.0, 6-*H*), 3.77 (3H, s, OC*H*$_3$), 3.77 (3H, s, OC*H*$_3$), 3.80 (1H, d, *J* 14.4, NC*H*$_2$ArOMe), 3.92 (1H, d, *J* 14.9, NC*H*$_2$ArOMe), 3.96 (1H, m, OC*H*$_2$CH$_3$), 4.11 (1H, m, OC*H*$_2$CH$_3$), 4.34 (1H, d, *J* 2.1, 3-*H*), 5.28 (1H, d, *J* 14.4, NC*H*$_2$ArOMe), 5.31 (1H, d, *J* 14.9, NC*H*$_2$ArOMe), 6.82–6.85 (4H, m, Ar), 7.14–7.20 (4H, m, Ar); δ_C (100 MHz, $CDCl_3$) 12.7, 14.0, 16.2, 19.9, 21.3, 31.0, 46.0, 47.0, 49.1, 55.2, 58.9, 61.0, 62.8, 114.0, 127.4, 127.4, 129.7, 130.0, 159.2, 159.2, 165.4, 165.6, 172.9; *m*/*z* (ESI^+) 533 ([M+Na]$^+$, 100%); HRMS (ESI^+) $C_{29}H_{38}N_2NaO_6^+$ ([M+Na]$^+$) requires 533.2628, found 533.2622.

4.1.3.22. (3*S*,6*R*,2′*R*)-*N*,*N*′-Bis-(*p*-methoxybenzyl)-3-*iso*-propyl-6-(2′-ethylhexanoate)piperazine-2,5-dione 40. Compound **1** (200 mg, 0.5 mmol) in THF (10 mL), LiHMDS (0.55 mL, 1 M in THF, 0.55 mmol) and (*RS*)-**36** (1.11 g, 5.0 mmol) were reacted together according to Section 4.1.1 to give a crude oil. Chromatography (silica, ether/hexane 1:1) gave **40** as a colourless oil (233 mg, 86%); $[\alpha]_D^{23}$ −30.1 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 1731, 1658, 1513, 1248; δ_H (400 MHz, $CDCl_3$) 0.78 (3H, d, *J* 7.0, CH$_3$CHC*H*$_3$), 0.84 (3H, t, *J* 7.4, CH$_2$CH$_2$C*H*$_3$), 1.07 (3H, d, *J* 7.0, CH$_3$CHC*H*$_3$), 1.14 (3H, t, *J* 7.2, OCH$_2$C*H*$_3$), 1.10–1.42 (3H, m, CH$_2$C*H*$_2$CH$_3$ and C*H*$_2$CH$_2$CH$_3$), 1.82 (1H, m, C*H*$_2$CH$_2$CH$_3$), 2.30 (1H, m, CH$_3$C*H*CH$_3$), 3.21 (1H, m, (EtO$_2$C)C*H*(CH$_2$)$_2$CH$_3$), 3.74 (1H, d, *J* 3.2, 6-*H*), 3.77 (3H, s, OC*H*$_3$), 3.78 (3H, s, OC*H*$_3$), 3.79 (1H, d, *J* 14.6, NC*H*$_2$ArOMe), 3.91 (1H, d, *J* 14.6), 3.94 (1H, m, OC*H*$_2$CH$_3$), 4.13 (1H, m, OC*H*$_2$CH$_3$), 4.38 (1H, d, *J* 1.6, 3-*H*), 5.30 (1H, d, *J* 14.6, NC*H*$_2$ArOMe), 5.33 (1H, d, *J* 14.6, NC*H*$_2$ArOMe), 6.81–6.86 (4H, m, Ar), 7.13–7.21 (4H, m, Ar); δ_C (100 MHz, $CDCl_3$) 13.9, 14.0, 16.3, 19.9, 22.6, 27.5, 30.5, 31.1, 46.0, 47.1, 47.7, 55.2, 59.3, 61.0, 62.8, 114.0, 114.1, 127.4, 127.4, 129.7, 130.0, 159.2, 159.3, 165.5, 165.6, 173.2; *m*/*z* (CI^+) 539 ([M+H]$^+$, 20%) 121 (100); HRMS (CI^+) $C_{31}H_{43}N_2O_6^+$ ([M+H]$^+$) requires 538.3121, found 539.3114.

4.1.3.23. (3*R*,6*S*,1′*S*)-1,4-*N*,*N*′-Bis-(*p*-methoxybenzyl)-6-*iso*-propyl-3-(1-phenylethylethanoate)piperazine-2,5-dione 46. Compound **1** (200 mg, 0.5 mmol) in THF (10 mL), LiHMDS (1.0 M in THF, 0.62 mL, 0.6 mmol) and (*RS*)-**45** (0.14 mL, 1.1 mmol) were reacted together according to Section 4.1.1 to give a brown oil. Chromatography (silica, ether/hexane 1:9) gave **46** as a colourless crystalline solid (210 mg, 75%); $C_{33}H_{38}N_2O_6$ requires C, 70.9; H, 6.9; N, 5.0%. Found C, 70.6; H, 6.9; N, 5.0%; mp 115–118 °C (EtOAc/hexane); $[\alpha]_D^{23}$ +81.2 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 1744, 1645, 1513; δ_H (400 MHz, $CDCl_3$) 0.63 (3H, d, *J* 7.0, C*H*$_3$CHCH$_3$), 0.95 (3H, d, *J* 7.0, CH$_3$CHC*H*$_3$), 1.27

(3H, t, *J* 7.1, OCH_2CH_3), 2.09 (1H, m, $(CH_3)_2CH$), 3.10 (1H, d, *J* 2.8, $(CH_3)_2CHCH$), 3.78 (3H, s, OCH_3), 3.82 (3H, s, OCH_3), 3.96 (1H, d, *J* 14.9, NCH_2ArOMe), 4.10 (1H, d, *J* 14.9, NCH_2ArOMe), 4.19–4.34 (3H, m, OCH_2CH_3 and $NCHCH(Ph)CO_2Et$), 4.74 (1H, d, *J* 14.9, NCH_2ArOMe), 5.00 (1H, d, *J* 3.2, $CHCH(CO_2Et)Ph$), 5.48 (1H, d, *J* 14.9, NCH_2ArOMe), 6.76–6.93 (6H, m, Ar), 7.22–7.35 (7H, m, Ar); δ_C (100 MHz, $CDCl_3$) 14.1, 15.7, 19.8, 31.0, 46.1, 47.4, 51.3, 55.2, 55.3, 60.8, 61.3, 62.8, 114.0, 114.2, 126.9, 126.9, 128.1, 128.4, 129.8, 130.5, 130.7, 132.3, 159.1, 159.5, 164.7, 165.4, 169.9; *m/z* ($APCI^+$) 559 ($[M+H]^+$, 95%), 121 (100).

4.1.3.24. X-ray crystal structure determination for 46. Data were collected using an Enraf–Nonius Mach 3 diffractometer with graphite monochromated Cu radiation using standard procedures at 293 K. The structure was solved by direct methods (SIR97). All non-hydrogen atoms were refined with anisotropic thermal parameters. Hydrogen atoms were added at idealised positions. The structure was refined using CRYSTALS.[21]

Crystal data for **46** [$C_{33}H_{38}N_2O_6$]: M=558.67; monoclinic; space group $P1\,21\,1$; a=10.612(2) Å, b=12.349(2) Å, c=12.274(2) Å; β=107.82(2)°; V=1531.4 Å^3; Z=2; μ=0.674 mm^{-1}; colourless plate; crystal dimensions 0.06×0.06×0.6 mm^3. A total of 3271 unique reflections were measured for $22<\theta<42$ and 2710 reflections were used in the refinement. The final parameters were wR_2=0.096 and R_1=0.076 (all data).

Crystallographic data (excluding structure factors) have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC280789. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk].

4.1.3.25. (3*R*,6*S*,2′*R*)-3-*iso*-Propyl-6-(2′-ethylpropanoate)piperazine-2,5-dione 48. Compound **31** (400 mg, 0.81 mmol) was stirred in TFA (5 mL) at reflux for 48 h. The mixture was cooled and excess TFA removed in vacuo. Column chromatography (Al_2O_3; ether/hexane 1:1, followed by ethyl acetate/ethanol 3:1) afforded diketopiperazinedione **48** as a colourless solid (124 mg, 60%); mp 204 °C; $[\alpha]_D^{23}$ +88.5 (*c* 1.0 in $CHCl_3$); ν_{max} (KBr) 1741, 1673; δ_H (400 MHz, MeOH-d_4) 0.98 (3H, d, *J* 6.9, CH_3CHCH_3), 1.07 (3H, d, *J* 7.1, CH_3CHCH_3), 1.23 (3H, d, *J* 7.2, $(EtO_2C)CHCH_3$), 1.30 (3H, t, *J* 7.1, OCH_2CH_3), 2.32 (1H, m, CH_3CHCH_3), 3.23 (1H, dq, *J* 2.6, 7.2, $(EtO_2C)CHCH_3$), 3.87 (1H, dd, *J* 3.3, 0.8, 6-*H*), 4.21 (2H, m, OCH_2CH_3), 4.50 (1H, dd, *J* 2.6, 0.8, 3-*H*), 7.18–7.56 (2H, br s, N*H*); δ_C (100 MHz, MeOH-d_4) 11.9, 14.8, 17.4, 19.2, 34.7, 43.7, 57.2, 61.8, 169.5, 170.1, 175.4; *m/z* (CI^+) 257 ($[M+H]^+$, 40%), 211 (100); HRMS (CI^+) $C_{12}H_{21}N_2O_4^+$ ($[M+H]^+$) requires 257.1506, found 257.1501.

4.1.3.26. (3*R*,6*S*,2′*R*)-3-*iso*-Propyl-2,5-dimethoxy-(2′-ethylpropanoate)-3,6-(2*H*)pyrazine 49. Compound **48** (100 mg, 0.39 mmol) and Me_3OBF_4 (230 mg, 1.56 mmol) were stirred in 1-butyl-3-1*H*-methylimidazolium tetrafluoroborate (4 mL) under vacuum (2 mmHg) at rt for four days. The mixture was then poured into satd $NaHCO_3$ (100 mL) and extracted with ether, the organic phase dried and the solvent removed under vacuum to provide **49** as a clear oil (105 mg, 95%); $[\alpha]_D^{23}$ +27.3 (*c* 0.7 in $CHCl_3$); ν_{max} (film) 1738, 1696; δ_H (400 MHz, $CDCl_3$) 0.70 (3H, d, *J* 6.8, CH_3CHCH_3), 0.90 (3H, d, *J* 6.9, CH_3CHCH_3), 1.04 (3H, d, *J* 6.9, $(EtO_2C)CHCH_3$), 1.28 (3H, t, *J* 7.3, OCH_2CH_3), 2.25 (1H, m, CH_3CHCH_3), 3.05 (1H, dq, *J* 4.0, 6.9, $(EtO_2C)CHCH_3$), 3.63 (3H, s, OCH_3), 3.71 (3H, s, OCH_3), 3.97 (1H, t, *J* 3.4, 3.7 Hz, 6-*H*), 4.20 (2H, q, *J* 7.3, OCH_2CH_3), 4.57 (1H, t, *J* 4.0, 3.7, 3-*H*); δ_C (100 MHz, $CDCl_3$) 9.9, 14.2, 16.6, 19.0, 31.8, 42.2, 52.41, 52.46, 57.3, 60.4, 60.8, 161.9, 164.1, 173.9; *m/z* ($APCI^+$) 285 ($[M+H]^+$, 100%); HRMS (CI^+) $C_{14}H_{25}N_2O_4^+$ ($[M+H]^+$) requires 285.1814, found 285.1822.

4.1.3.27. (2*R*,3*R*)-3-Methyl-aspartic acid 4-ethyl-1-methyl diester 50. Bis-lactim ether **49** (200 mg, 0.70 mmol) was stirred in 0.5 M aq TFA (5 mL) and THF (10 mL) at rt for 24 h then the solvent removed and the resultant oil was loaded onto a short column of silica. Elution (ether/dimethylethylamine 20:1) gave a mixture of **50** and (*S*)-valine methyl ester, which were separated by removal of the (*S*)-valine methyl ester under vacuum (0.5 mmHg, ambient temperature) to give **50** as an oil (104 mg, 76%); $[\alpha]_D^{23}$ −8.6 (*c* 0.7 in $CHCl_3$); ν_{max} (film) 3391, 2980, 1732; δ_H (400 MHz, $CDCl_3$) 1.17 (3H, d, *J* 7.1, $(EtO_2C)CHCH_3$), 1.26 (3H, t, *J* 7.1, OCH_2CH_3), 2.15 (2H, br s, NH_2), 2.96 (1H, m, $(EtO_2C)CHCH_3$), 3.75 (3H, s, CO_2CH_3), 3.97 (1H, br s, $CHNH_2$), 4.17 (2H, q, *J* 7.1, OCH_2CH_3); δ_C (100 MHz, $CDCl_3$) 11.3, 14.1, 42.7, 52.2, 55.8, 60.9, 174.2; *m/z* ($APCI^+$) 190 ($[M+H]^+$, 100%), 116 (89); HRMS (CI^+) $C_8H_{16}NO_4^+$ ($[M+H]^+$) requires 190.1079, found 190.1082.

The diastereoisomeric excess (>95%) and enantiomeric excess (>98%) of **50** were determined from the ^{19}F NMR spectrum of the Mosher's amide derivative.

4.1.3.28. (3*R*,6*S*,2′*S*)-3-*iso*-Propyl-6-(2′-ethylpropanoate)piperazine-2,5-dione 51. Compound **32** (100 mg, 0.20 mmol) was stirred in TFA (2 mL) at reflux for 48 h. The mixture was cooled and excess TFA removed in vacuo. Column chromatography (Al_2O_3; ether/hexane 1:1, followed by ethyl acetate/ethanol 3:1) afforded diketopiperazinedione **51** as a colourless solid (23 mg, 60%); mp 214 °C; $[\alpha]_D^{23}$ −23.8 (*c* 1.0 in $CHCl_3$); ν_{max} (KBr) 1739, 1664; δ_H (400 MHz, $CDCl_3$) 0.93 (3H, d, *J* 7.0, CH_3CHCH_3), 1.05 (3H, d, *J* 7.0, CH_3CHCH_3), 1.24 (3H, t, *J* 7.2, OCH_2CH_3), 1.29 (3H, d, *J* 7.4, EtO_2CCHCH_3), 2.43 (1H, m, CH_3CHCH_3), 3.11 (1H, dq, *J* 3.4, 7.4, $(EtO_2C)CHCH_3$), 3.91 (1H, s, 6-*H*), 4.14 (2H, q, *J* 7.2, OCH_2CH_3), 4.24 (1H, d, *J* 3.4, 3-*H*), 7.26 (1H, br s, N*H*), 7.57 (1H, br s, N*H*); δ_C (100 MHz, $CDCl_3$) 12.2, 14.3, 16.0, 31.8, 42.2, 56.7, 60.1, 61.0, 62.1, 167.7, 168.7, 171.9; *m/z* (CI^+) 257 ($[M+H]^+$, 50%), 211 (100); HRMS (ESI^+) $C_{12}H_2N_2NaO_4^+$ ($[M+Na]^+$) requires 279.1321, found 279.1315.

4.1.3.29. (3*R*,6*S*,2′*R*)-3-*iso*-Propyl-2,5-dimethoxy-(2′-ethylpropanoate)-3,6-(2*H*)pyrazine 52. Compound **51** (100 mg, 0.39 mmol) and Me_3OBF_4 (440 mg, 2.97 mmol) were stirred in 1-butyl-3-1*H*-methylimidazolium tetrafluoroborate (2 mL) under vacuum (2 mmHg) at rt for four days. The mixture was then poured into satd $NaHCO_3$ (100 mL) and extracted with ether, the organic phase dried

and the solvent removed under vacuum to provide **52** as a clear oil (110 mg, 99%); $[\alpha]_D^{23}$ −15.0 (*c* 1.0 in $CHCl_3$); ν_{max} (KBr) 1732, 1698; δ_H (400 MHz, $CDCl_3$) 0.71 (3H, d, *J* 7.0, CH_3CHCH_3), 1.04 (3H, d, *J* 7.0, CH_3CHCH_3), 1.12 (3H, d, *J* 7.1, $(EtO_2C)CHCH_3$), 1.22 (3H, t, *J* 7.2, OCH_2CH_3), 2.26 (1H, m, CH_3CHCH_3), 2.99 (1H, dq, *J* 3.2, 6.8, $(EtO_2C)CHCH_3$), 3.67 (6H, s, $2\times OCH_3$), 3.96 (1H, t, *J* 3.8, 6-*H*), 4.12 (2H, m, OCH_2CH_3), 4.36 (1H, t, *J* 3.2, 3-*H*); δ_C (100 MHz, $CDCl_3$) 14.1, 16.7, 18.9, 20.8, 31.9, 43.4, 52.3, 52.4, 57.9, 60.2, 60.9, 162.0, 164.4, 173.3; *m*/*z* (APCI$^+$) 285 ([M+H]$^+$, 100%); HRMS (CI$^+$) $C_{14}H_{25}N_2O_4^+$ ([M+H]$^+$) requires 285.1814, found 285.1815.

4.1.3.30. (2*R*,3*S*)-3-methyl-aspartic acid 4-ethyl-1-methyl diester 53. Bis-lactim ether **52** (110 mg, 0.39 mmol) was stirred in 0.5 M aq TFA (5 mL) and THF (10 mL) at rt for 24 h then the solvent removed and the resultant oil was loaded onto a short column of silica. Elution (ether/dimethylethylamine 20:1) gave a mixture of **53** and (*S*)-valine methyl ester, which were separated by removal of the (*S*)-valine methyl ester under vacuum (0.5 mmHg, ambient temperature) to give **53** as an oil (55 mg, 73%); $[\alpha]_D^{23}$ −6.8 (*c* 1.2 in $CHCl_3$); ν_{max} (film) 3390, 2979, 1738; δ_H (400 MHz, $CDCl_3$) 1.23 (3H, d, *J* 7.2, $(EtO_2C)CHCH_3$), 1.24 (3H, t, *J* 7.2, OCH_2CH_3), 1.87 (2H, br s, NH_2), 2.95 (1H, dq, *J* 5.2, 7.2, $(EtO_2C)CHCH_3$), 3.60 (1H, d, *J* 5.2, $CHNH_2$), 3.73 (3H, s, OCH_3), 4.15 (2H, m, OCH_2CH_3); δ_C (125 MHz, $CDCl_3$) 13.9, 14.1, 43.5, 53.3, 57.0, 60.7, 173.6, 174.5; *m*/*z* (APCI$^+$) 190 ([M+H]$^+$, 95%) 144 (20), 116 (100); HRMS (CI$^+$) $C_8H_{16}NO_4^+$ ([M+H]$^+$) requires 190.1079, found 190.1081.

The diastereoisomeric excess (>95%) and enantiomeric excess (>98%) of **53** were determined from the ^{19}F NMR spectrum of the Mosher's amide derivative.

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