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Tetrahedron: Asymmetry 15 (2004) 3989–4001
Tetrahedron: Asymmetry

2-Halo-diketopiperazines as chiral glycine cation equivalents

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Received 3 November 2004; accepted 11 November 2004

Abstract—A range of (2*S*,5*S*)-5-isopropyl-2-halo-*N*,*N*′-bis-(*p*-methoxybenzyl)-piperazine-3,6-diones **8** (Cl), **11**, **12** (F) and **13** (Br) have been prepared, either via electrophilic halogenation of the corresponding lithiated diketopiperazine, or via transhalogenation from fluoro-**11** and **12**. The product distribution and stereoselectivity of additions of allyltrimethylsilane, sodium thiophenolate and a range of organomagnesium reagents to chloro **8** are reported. In the reactions with Grignard reagents the observed stereo- and regioselectivities are dependent on the reagent employed, with *C*-3 carbonyl addition products predominating upon addition of allyl or methylmagnesium chloride and stereodivergent formal *C*-2 addition predominating with benzyl or isopropylmagnesium chloride. A model to account for the different reactivity and stereoselectivity in these reactions is proposed.

1. Introduction

The addition of Grignard reagents to imines is well documented in the literature,[1] with stereoselective versions of this protocol having found wide application in organic synthesis, including the asymmetric synthesis of α-amino acids.[2] While this methodology has been the subject of many investigations, the reaction of Grignard reagents with the corresponding cationic *N*-acyliminium or iminium species has received much less attention.[3]

We have recently reported two new diketopiperazine derived chiral auxiliaries **1** and **2** for the asymmetric synthesis of homochiral α-amino acids based upon the alkylation of chiral glycine anion equivalent **1**,[4] and conjugate addition followed by protonation of chiral dehydroalanine equivalent **2** (Fig. 1).[5]

As an extension of this methodology, we wished to investigate the utility of *N*,*N*′-bis-(*p*-methoxybenzyl)-protected diketopiperazines as asymmetric glycine cation equivalents. Although a number of cyclic auxiliary based asymmetric syntheses of α-amino acids using this strategy have been reported,[6] our initial investigations in this area showed that the addition of allyltrimethylsilane to *N*-acyliminium ion **5** (derived from either of the diastereoisomeric acetates **3** or **4**) gave an 80:20 mixture of allylation products **6** and **7** (Scheme 1).[7]

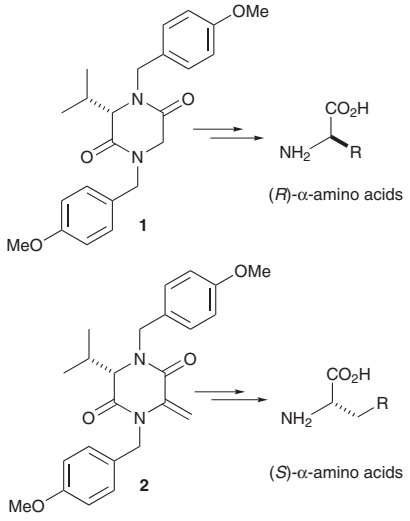

Figure 1.

While this approach demonstrated the viability of the diketopiperazine template to act as a glycine cation equivalent, it was envisaged that the addition of organomagnesium reagents to the chiral glycine cation **5** would offer greater scope for the asymmetric synthesis of α-amino acids, potentially allowing the stereoselective

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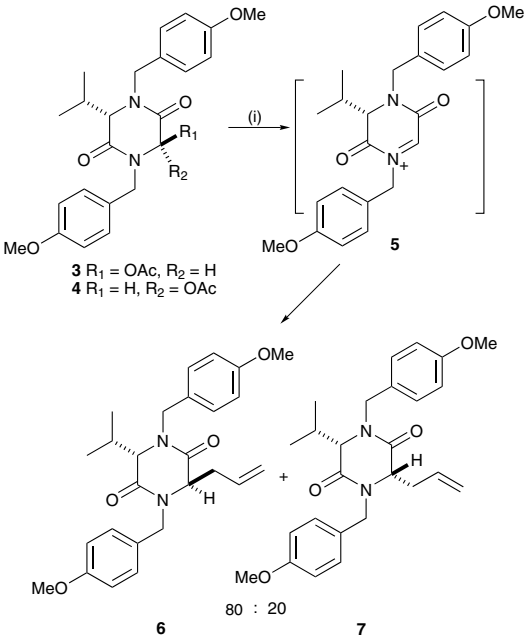
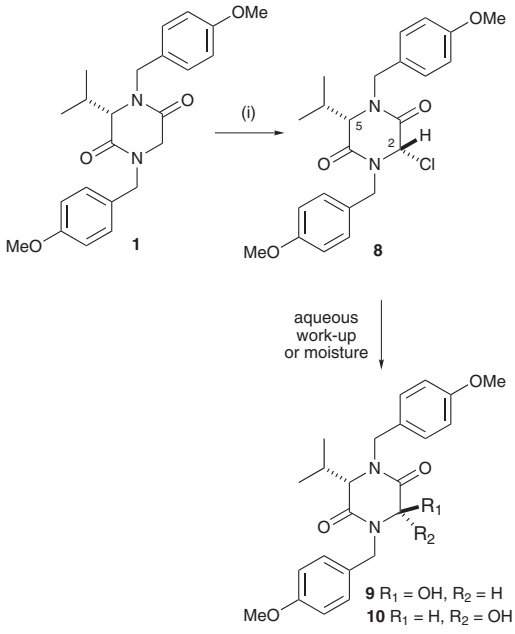
0957-4166/$ - see front matter © 2004 Published by Elsevier Ltd.
doi:10.1016/j.tetasy.2004.11.022



Scheme 1. Reagents and conditions: (i) allyltrimethylsilane, $BF_3{\cdot}OEt_2$, CH_2Cl_2, −78 °C.



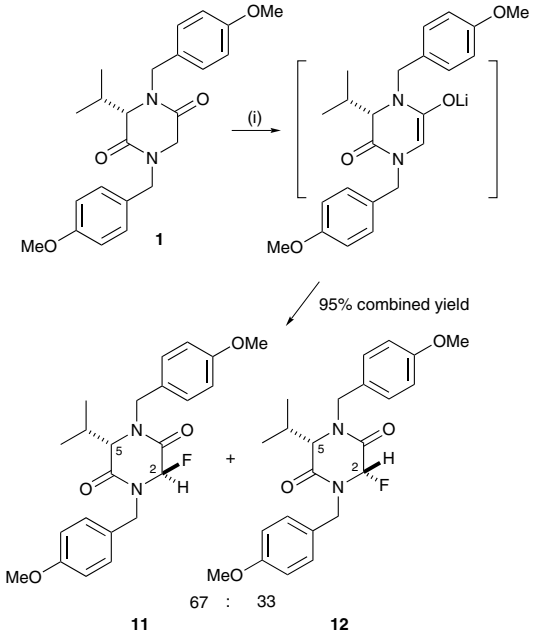
Scheme 2. Reagents and conditions: (i) LHMDS, THF, −78 °C, C_2Cl_6.

introduction of a wide variety of substituents. We report herein our studies directed towards the asymmetric synthesis of α-amino acids based upon addition of Grignard reagents to 2-halo-diketopiperazines as glycine cation equivalents.[8]

2. Results and discussion

2.1. Synthesis of 2-halo-diketopiperazines

Initial investigations focused on the preparation of 2-chloro-diketopiperazine **8** via an electrophilic chlorination protocol.[6a] Treatment of the lithium enolate of **1** with hexachloroethane at low temperature followed by the removal of solvent revealed a crude reaction mixture containing predominantly *cis*-(2*S*,5*S*)-chloro **8** (vide infra) (Scheme 2). However, 2-chloro-diketopiperazine **8** was readily hydrolysed to the known hydroxy diketopiperazines *trans*-**9** and *cis*-**10**[7] (in a 33:67 ratio, respectively) upon exposure to moisture, and chloro **8** obtained without aqueous workup was necessarily contaminated with inorganic salts and excess reagents. With the limitations of this protocol delineated, an alternative approach to the synthesis of **8** was pursued.

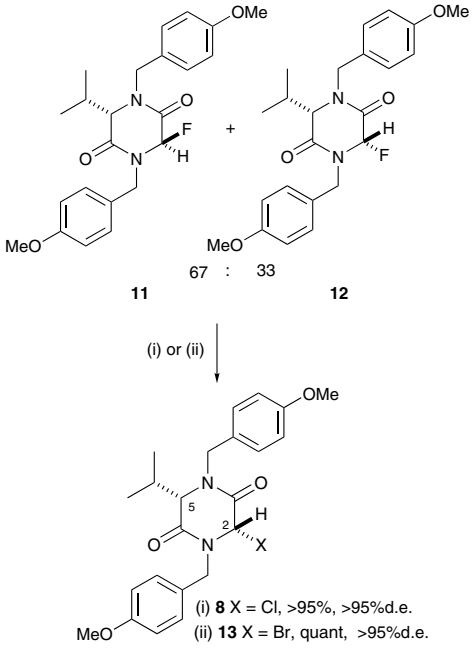


Scheme 3. Reagents and conditions: (i) LHMDS, THF, −78 °C, *N*-fluorobenzenesulfonimide.

The preparation of the potentially more stable fluoro substituted diketopiperazine was next investigated. Treatment of the lithium enolate of **1** with *N*-fluorodibenzenesulfonimide afforded a 67:33 mixture of epimeric fluorides *trans*-(2*R*,5*S*)-**11** and *cis*-(2*S*,5*S*)-**12**, respectively, in good purity and high combined yield (95%) (Scheme 3). This oily mixture was stable to aqueous workup, but unstable to chromatographic purification, with characterisation data and subsequent manipulations being performed upon the mixture of **11** and **12**. The observed 67:33 mixture of *trans*-fluoro-**11** and *cis*-fluoro-**12** is consistent with predominant *trans* selectivity observed in alkylation of the enolate of **1**,[4] while the poor diastereoselectivity of the reaction may reflect the high reactivity of the fluorinating agent.

Chloro substituted diketopiperazine *cis*-**8** was subsequently prepared from the 67:33 mixture of fluorides **11** and **12** by treatment with chlorotrimethylsilane (TMSCl) in dichloromethane to afford, upon removal of volatile residues, (2*S*,5*S*)-chloro **8** as a single diastereoisomer (>95% de) and in excellent yield (95%), free

of inorganic salts and excess reagents. Similar treatment of fluoride mixture **11** and **12** with bromotrimethylsilane (TMSBr) afforded (2*S*,5*S*)-bromo **13** as a single diastereoisomer (>95% de) in quantitative yield. As noted above *cis*-chloro **8**, and *cis*-bromo **13**, obtained from this route were moisture sensitive and unstable to chromatography, and so were characterised without further purification (Scheme 4).



Scheme 4. Reagents and conditions: (i) TMSCl, CH_2Cl_2, room temperature; (ii) TMSBr, CH_2Cl_2, room temperature.

The relative configuration within (2*S*,5*S*)-chloro **8** was assigned from ^{1}H NMR spectroscopic data. The diagnostic difference in chemical shift between the diastereotopic isopropyl methyl groups ($\Delta\delta_{Me}$ 0.09 ppm) indicated a *cis* relative configuration of the *C*-2 chloro and *C*-5 isopropyl groups. Similar ^{1}H NMR spectroscopic data for (2*S*,5*S*)-bromo **13** ($\Delta\delta_{Me}$ 0.09 ppm) also indicated a *cis* relative configuration for this compound.[9] Furthermore, ^{1}H NMR NOE. difference experiments for chloro **8** also revealed a small (1%) signal enhancement of 2-*H* upon irradiation of 5-*H*, suggesting that these hydrogen atoms lie on the same face of the diketopiperazine ring, consistent with the assigned *cis* configuration. The absolute (2*S*,5*S*)-configuration within chloro **8** and bromo **13** follows from the known *C*-5 stereogenic centre derived from (*S*)-valine (Fig. 2).

The novel trimethylsilylhalide mediated transformation of the mixture of epimeric fluorides **11** and **12** provides *cis*-chloro **8** or *cis*-bromo **13** in high de (>95%). The reaction presumably proceeds reversibly via *N*-acyliminium intermediate **5**, formed under Lewis acid catalysis by the trimethylsilylhalide.[10] Previous investigations concerning the alkylation of diketopiperazine template **1** and addition of allyltrimethylsilane to *N*-acyliminium species **5** under kinetic conditions have shown that the corresponding *trans*-substituted diketopiperazines are formed predominantly with diastereocontrol directed

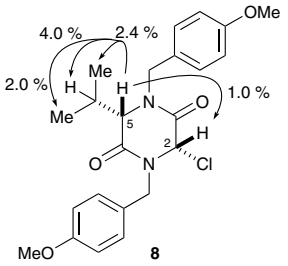
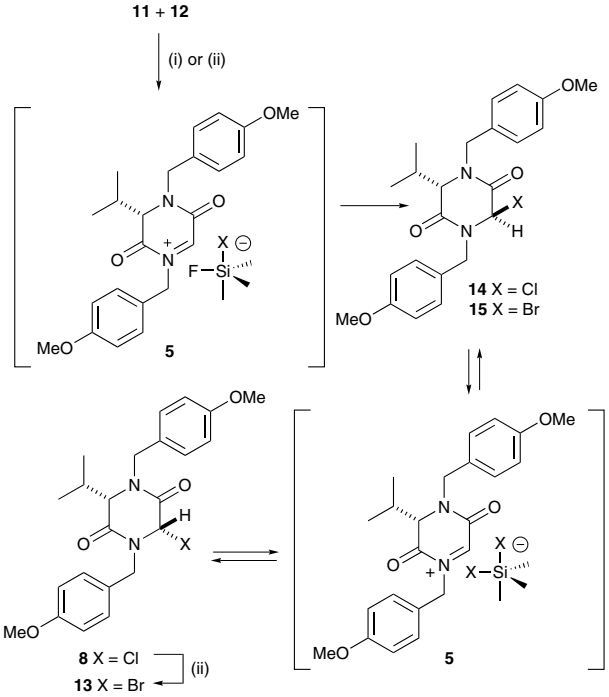


Figure 2. Selected NOE difference enhancement for **8**.

by the isopropyl group. However for *N*,*N*-dialkyl substituted diketopiperazines *cis* isomers have been shown to be thermodynamically more stable, presumably due to the introduction of 1,2 torsion strain caused by the interaction between the *N*-alkyl and ring substituents in the corresponding *trans* isomers.[8e,11]

Chloro **8** and bromo **13** are obtained as single, *cis* diastereoisomers and most probably derive from equilibration of the kinetic addition products under the reaction conditions. While initial delivery of halide onto the *Re*-face of *N*-acyliminium ion **5**, *anti* to the isopropyl group will preferentially afford the (2*R*)-halo compounds **14** or **15**, epimerisation of these products is expected to provide the thermodynamically more stable *cis*-(2*S*)-halo compounds **8** or **13**. This isomerisation may potentially occur via either a *N*-acyliminium intermediate or an enolisation pathway, although in support of a *N*-acyliminium mediated epimerisation, the treatment of chloro **8** with TMSBr gave bromo **13**, suggesting that the abstraction of chloride from **8** by TMSBr is a viable process (Scheme 5).

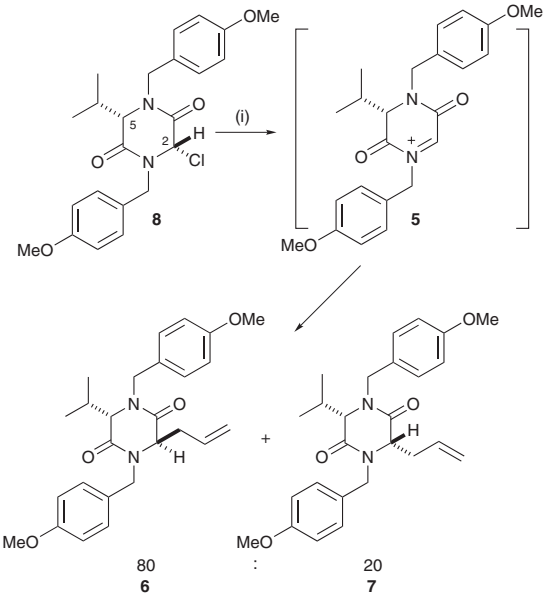


Scheme 5. Reagents and conditions: (i) Me_3SiCl, CH_2Cl_2, room temperature; (ii) Me_3SiBr, CH_2Cl_2, room temperature.

In the reaction of the lithium enolate of **1** with hexachloroethane the anomalous diastereoselectivity observed may also result from initial chlorination of the enolate on the *Re*-face of the auxiliary, to afford *trans*-(2*R*,5*S*)-chloro **14**, followed by equilibration to provide *cis*-(2*S*,5*S*)-epimer **8**.

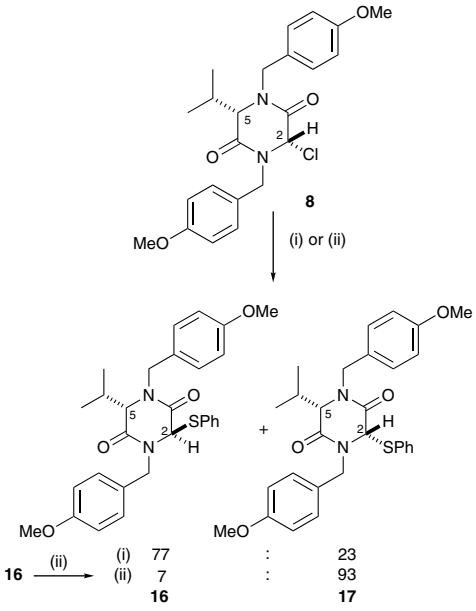
2.2. Substitution reactions

With the 2-fluoro-, 2-chloro- and 2-bromo-diketopiperazines in hand, their utility in synthetic transformations was assessed. Preliminary investigations into the use of 2-halo-diketopiperazines **8**, **11**, **12** and **13** for synthesis revealed that chloro **8** was the simplest, in practical terms, for evaluation as a glycine cation equivalent. The reaction of **8** with allyltrimethylsilane was initially examined and, while no reaction was observed in the absence of halophilic reagents, treatment of **8** with $SbCl_5$ and allyltrimethylsilane provided an 80:20 mixture of *trans*-allyl **6** and *cis*-allyl **7** (Scheme 6).[12] The observed 80:20 ratio of *trans*-allyl **6** and *cis*-allyl **7** is in accord with the 80:20 ratio of **6** and **7** observed in the related reaction of acetates **3** or **4** with allyltrimethylsilane in the presence of $BF_3{\cdot}OEt_2$, consistent with both reactions proceeding via the same *N*-acyliminium intermediate **5**.



Scheme 6. Reagents and conditions: (i) $CH_2{=}CH_2CH_2SiMe_3$, $SbCl_5$, CH_2Cl_2, room temperature.

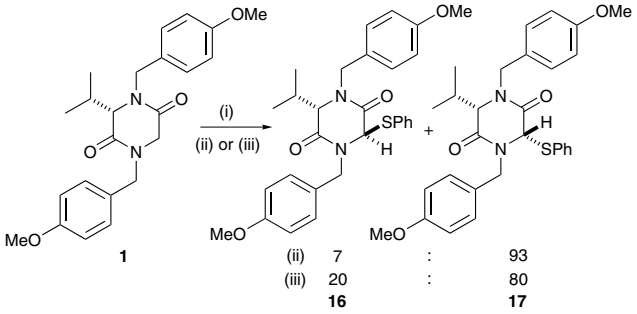
The addition of sodium thiophenolate to chloro **8** was next examined. Treatment of **8** with 0.9 equiv of sodium thiophenolate provided a 77:23 mixture of *trans*-(2*R*,5*S*)-sulfide **16** and *cis*-(2*S*,5*S*)-sulfide **17** from which *trans*-**16** was isolated by chromatography (48% yield), while treatment of chloro **8** with 2 equiv of sodium thiophenolate gave a 7:93 mixture of *trans*-**16** and *cis*-**17**, respectively (**17**, 86% de) (Scheme 7). Furthermore, treatment of *trans*-(2*R*,5*S*)-sulfide **16** (>98% de) with 2 equiv of sodium thiophenolate also afforded a 7:93 mixture of *trans*-**16** and *cis*-**17**, respectively, from which



Scheme 7. Reagents and conditions: (i) 0.9 equiv NaSPh, THF; (ii) 2 equiv NaSPh, THF.

cis-(2*S*,5*S*)-sulfide **17** was isolated in 83% yield after chromatography.

Attempts to prepare an authentic sample of *trans*-sulfide **16** via treatment of the lithium enolate of **1** with diphenyldisulfide, a protocol which has been shown to predominantly afford *trans* addition products in similar alkylation reactions,[4] afforded a 7:93 mixture of *trans*-(2*R*,5*S*)-sulfide **16** and *cis*-(2*S*,5*S*)-sulfide **17** (**17**, 86% de). Furthermore the reaction of the lithium enolate of **1** with *S*-phenyl benzenethiosulfonate gave a 20:80 mixture of *trans*-**16** and *cis*-**17** (**17**, 60% de) (Scheme 8).



Scheme 8. Reagents and conditions: (i) LHMDS, THF, −78 °C; (ii) PhS–SPh; (iii) PhS–SO_2Ph.

The relative configurations of (2*R*,5*S*)-**16** and (2*S*,5*S*)-**17** were readily discerned from the ^{1}H NMR spectroscopic data via analysis of the characteristic isopropylmethyl chemical shift differences {*trans*-(2*R*,5*S*)-**16**, $\Delta\delta_{Me} = 0.31$ ppm; *cis*-(2*S*,5*S*)-**17**, $\Delta\delta_{Me} = 0.07$ ppm}.[7] The relative configuration within *cis*-(2*S*,5*S*)-sulfide **17** was unambiguously confirmed by single crystal X-ray diffraction with the absolute configuration following from the known configuration of the (*S*)-valine derived stereogenic centre (Fig. 3).

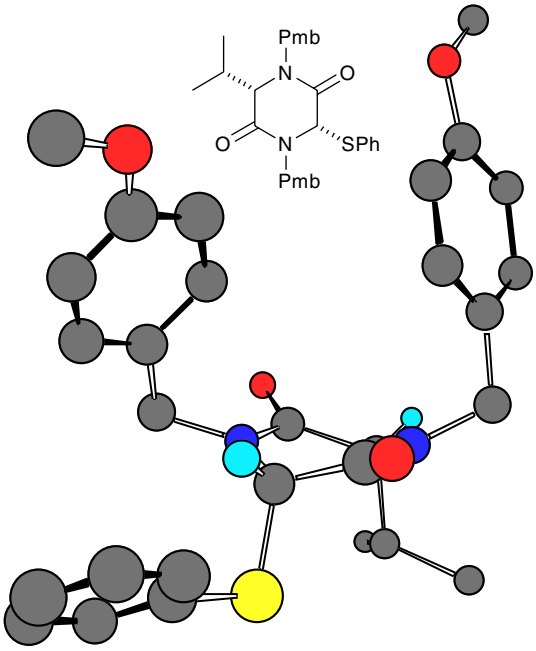
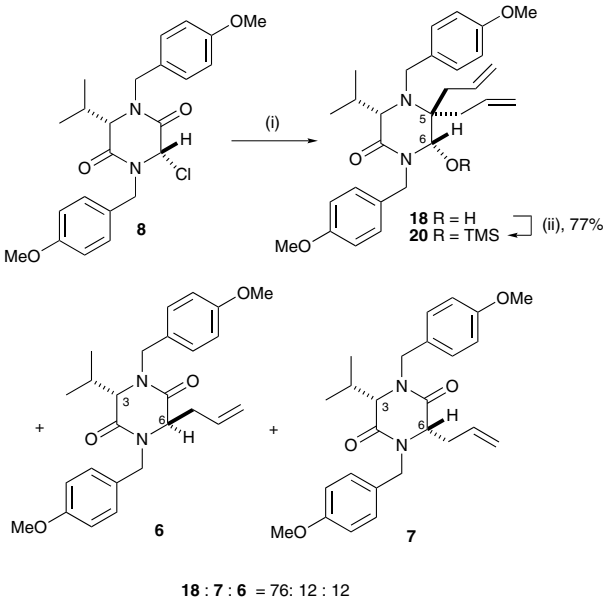


Figure 3. Chem 3D® representation of X-ray crystal structure of (2*S*,5*S*)-sulfide **17** (some H omitted for clarity).



Scheme 9. Reagents and conditions: (i) $CH_2{=}CH_2CH_2MgCl$, THF, −78 °C; (ii) trimethylsilylimidazole, DCM.

In the reaction of sodium thiophenolate with *cis*-chloro **8** the mixtures of epimeric sulfides **16** and **17** may plausibly be formed via several different pathways. S_N1 reaction of chloro **8** can afford a mixture of *trans*- and *cis*-sulfides **16** and **17**, in which the *trans*-sulfide **16** may be expected to predominate due to preferential attack upon the *Re*-face of the *N*-acyliminium ion intermediate. Alternatively, *trans*-sulfide **16** could arise from direct S_N2 displacement of chloride, with the *cis*-sulfide **17** deriving from *C*-2 epimerisation of the initially formed *trans*-**16**. Thus, in the reaction of chloro **8** with 0.9 equiv of sodium thiolate the product ratio (77:23, **16**:**17**) is suggestive of a S_N1 process via *N*-acyliminium ion **5**, given that the 77:23 ratio of diastereoisomers **16**:**17** is similar to the 80:20 ratio of diastereoisomers **6**:**7** derived from reaction of chloro **8** with allyltrimethylsilane. However these results are also consistent with, and indistinguishable from, an alternative mechanistic pathway involving direct S_N2 displacement of chloride to afford *trans*-**16**, accompanied by epimerisation to afford *cis*-**17**. While epimerisation in this system may occur via *N*-acyliminium intermediates, the reaction of **8** with excess sodium thiophenolate and the reaction of the lithium enolate of **1** with diphenyl disulfide, predominantly afford *cis*-sulfide **17** (7:93 ratio of **16**:**17**), suggesting a thiophenolate catalysed equilibration via an enolate to give the thermodynamically more stable *cis* isomer.[8e] The 20:80 ratio of **16** to **17** observed in the addition of enolate of **1** to *S*-phenyl benzenethiosulfonate may represent a partially equilibrated mixture due to the lower basicity of the lithium phenylsulfinate by-product.[13]

2.3. Reactions with Grignard reagents

Previous investigations using the acetate substituted chiral glycine cation equivalents **3** and **4** indicated that their synthetic utility was restricted to Lewis acid catalysed reaction with allyltrimethylsilane. In contrast 2-chlorodiketopiperazine **8** should have the potential to react with Grignard reagents, and as such the addition of a range of organomagnesium species to chloro **8** was next explored. The reaction of chloro **8** with allylmagnesium chloride gave a 76:12:12 mixture of novel diallyl addition product (3*S*,6*S*)-**18** and *C*-2 addition products (3*S*,6*R*)-**6** and (3*S*,6*S*)-**7**, respectively, from which the major reaction product **18** was isolated in 60% yield after chromatography (Scheme 9). The connectivity of the carbon framework within diallyl **18** was determined from ^1H and ^1H–^{13}C correlation NMR data. HMBC correlations indicated that both allyl groups were attached to the *C*-5 quaternary carbon centre, while ^1H–^1H coupling between *H*-6 and the adjacent hydroxyl proton established the presence of tertiary *C*-6, discounting plausible alternative structure **19**. The relative configuration of the isopropyl and *C*-6 hydroxyl groups within **18** was established from NOE data for trimethylsilyl ether derivative **20**, prepared from **18** by treatment with trimethylsilylimidazole. These studies showed a NOESY cross peak from the trimethylsilyl methyl groups to one isopropyl methyl signal, indicating a *cis* arrangement of the *C*-3 isopropyl substituent and the *C*-6 oxygen atom, with the absolute (3*S*,6*S*)-configuration following from the known (*S*)-valine derived stereogenic centre (Fig. 4).

Treatment of chloro **8** with methylmagnesium chloride afforded a 56:17:22:5 mixture of dimethyl (3*S*,6*S*)-**21** in >95% de, reduction product **1** (presumably arising from transmetallation) and the known *C*-2 addition products *cis*-(3*S*,6*S*)-**22** and *trans*-(3*S*,6*R*)-**23** (**22**, 63% de)[4] from which **21**, **1** and **22** were isolated in 44%, 7% and 14% yield, respectively after chromatography. The configuration of **21** was assigned by analogy to (3*S*,6*S*)-**18**, while the configuration of **22** has previously been established[4] (Scheme 10).

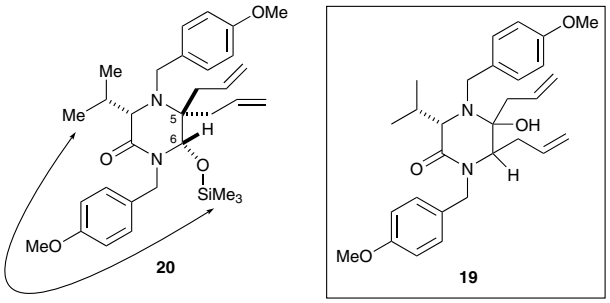
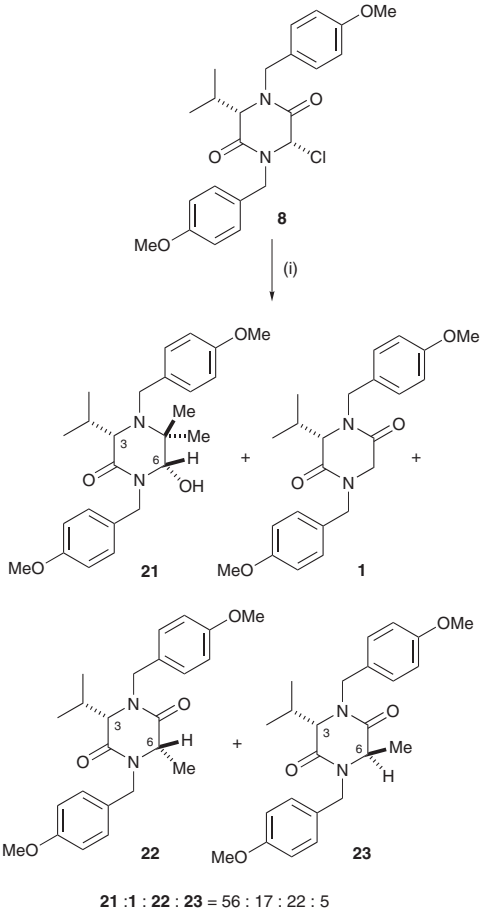
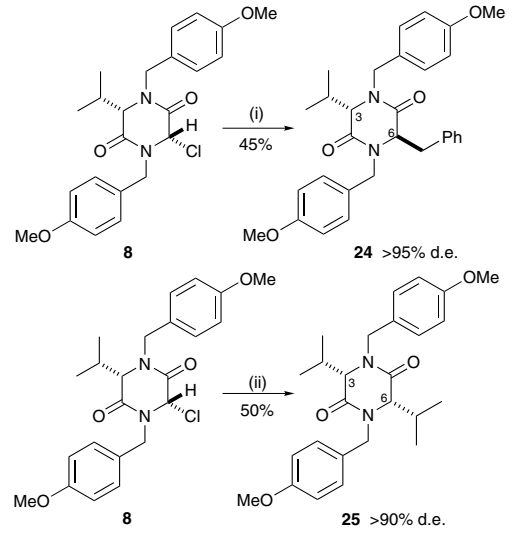


Figure 4. Selected NOESY correlations for **20**.



Scheme 10. Reagents and conditions: (i) MeMgCl, THF, −78 °C.

Treatment of chloro **8** with benzylmagnesium chloride provided *C*-2 addition product *trans*-(3*S*,6*R*)-benzyl **24** in >95% de as the major product, comprising 70% of the crude mixture, along with a number of unidentified minor products, from which **24** was isolated in 45% yield and >98% de after chromatography (Scheme 11). The relative configuration within (3*S*,6*R*)-benzyl **24** was established by comparison with an authentic sample, obtained from the alkylation of the lithium enolate of **1**, the configuration of which has been unequivocally established previously by X-ray crystal structure determination and deprotection and hydrolysis to the constituent α-amino acids, (*S*)-valine and (*R*)-phenylalanine.[14] In contrast, treatment of chloro **8** with isopropylmagnesium chloride gave *cis* configured (3*S*,6*S*)-diisopropyl **25** as the major product comprising 60% of the crude mixture, in >90% de, and afforded **25** in 50% yield and >98% de after chromatography (Scheme 11). ^{1}H NMR spectroscopic data for **25** were not consistent with the known achiral *trans*-diisopropyl isomer derived from the enolate alkylation protocol, and the ^{1}H NMR spectroscopic data and specific rotation $\{[\alpha]_D^{23} = -253.6$ (*c* 2.06, $CHCl_3)\}$ indicated a chiral *cis* configured diisopropyl substituted diketopiperazine. The relative configuration of (3*S*,6*S*)-diisopropyl **25** was unequivocally confirmed by X-ray crystallographic analysis, with the absolute configuration following from the known (*S*)-valine derived stereogenic centre (Fig. 5). This



Scheme 11. Reagents and conditions: (i) BnMgCl, THF, −78 °C; (ii) $(CH_3)_2CHMgCl$, THF, −78 °C.

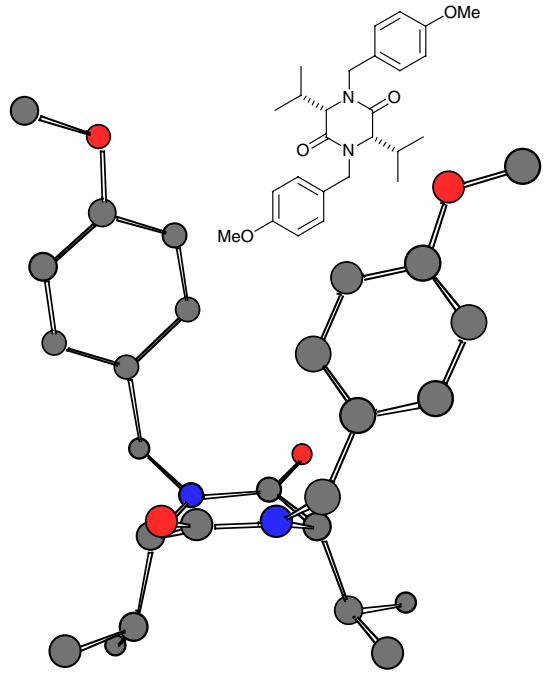


Figure 5. Chem3D™ representation of X-ray crystal structure of (3*S*,6*S*)-diisopropyl **25** (some H omitted for clarity).

assignment was also confirmed by the preparation of an authentic sample of **25** from (*S*,*S*)-*cyclo*-(val-val) $\{[\alpha]_D^{23} = -257.4$ (*c* 4.05, $CHCl_3)\}$. In this case the synthetic protocol represents a formal self-reproduction of chirality in which a second valine unit is generated under the control of the starting (*S*)-valine stereogenic centre.

2.4. Model for the regio- and stereoselectivity of Grignard additions to 8

The reaction of **8** with Grignard reagents affords products formally arising from addition of the alkyl magnesium halide to either the *C*-3 carbonyl group or *C*-2 of chloro **8**. The differences in the regioselectivity and stereoselectivity of Grignard additions must reflect reactivity and structural differences between the organomagnesium species in these reactions. In the addition of Grignard reagents to carbonyl compounds via a polar mechanism, the relative reactivity order is determined by a combination of steric bulk and carbanion stability and has been established as allyl > benzyl > methyl > isopropyl.[15] The different modes of reaction of these reagents with **8** may then be expected to reflect this reactivity order. For all Grignard reagents employed in reaction with **8**, the reaction reasonably proceeds by initial co-ordination of magnesium to the *C*-3 carbonyl oxygen followed by either: attack at the *C*-3 carbonyl and subsequent reaction (Fig. 6, path A), or formation of an *N*-acyliminium species (by Lewis acid catalysed extraction of chloride) and attack on this functionality (Fig. 6, path B).

In the reaction with allylmagnesium chloride, fast attack on the *C*-3 carbonyl group of **8** (Fig. 6, path A), *anti* to the *C*-5 isopropyl group is promoted by a kinetically favourable six membered cyclic transition state. Following this addition loss of chloride affords *N*-acyliminium intermediate **26**, which undergoes intramolecular cyclisation to afford epoxy species **27**. Subsequent reaction

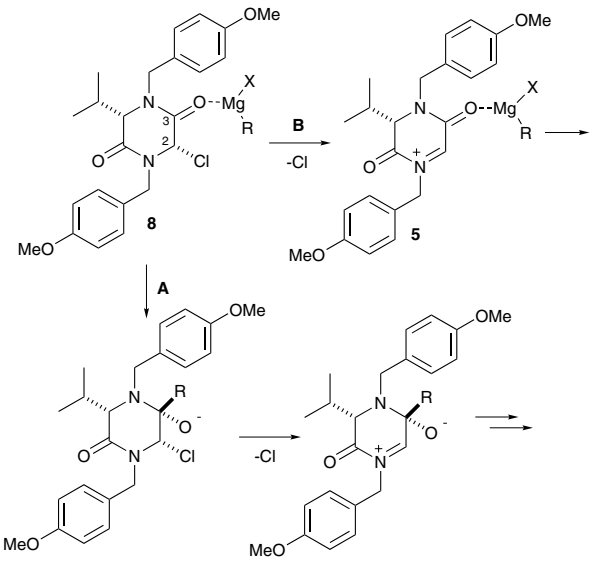


Figure 6. Potential reaction pathways in the reaction of **8** with Grignard reagents.

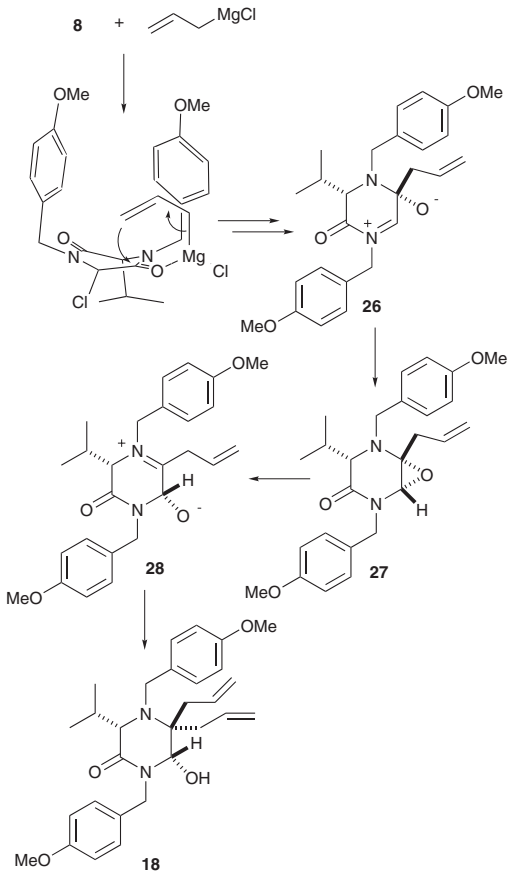


Figure 7. Possible mechanism for allylmagnesium chloride addition and hydroxyl migration to afford **18**.

with a further equivalent of Grignard reagent, via iminium ion **28**, gives diallyl **18** (Fig. 7). The diastereoisomeric minor addition products **6** and **7** presumably arise from competitive direct addition to *N*-acyliminium ion intermediate **5** (Fig. 6, path B).

The addition of methylmagnesium chloride to **8** affords a mixture of **21**, **22** and **23**. This mixture must arise from a competition between addition to the *C*-3 carbonyl group, followed by hydroxyl migration and further addition to afford **21**, and direct addition to the *N*-acyliminium carbon centre of **5** to give **22** and **23**. The observation of products from both these reaction modes reflects the lower reactivity of this reagent in carbonyl additions allowing competitive formation and reaction of the *N*-acyliminium intermediate **5**.

Given the high reactivity of benzylmagnesium chloride toward carbonyl addition, the reaction of benzylmagnesium chloride with **8** may reasonably be expected to proceed via addition to the *C*-3 carbonyl group. Furthermore the reaction of benzylic Grignard reagents with a number of simple aldehydes and ketones has been shown to afford predominantly products arising from *ortho* addition.[16] The observed *C*-2 addition product is consistent with stereoselective *ortho* addition at *C*-3, *anti* to the *C*-5 isopropyl group, followed by *N*-acyliminium ion formation, to give unstable intermediate **29**, which

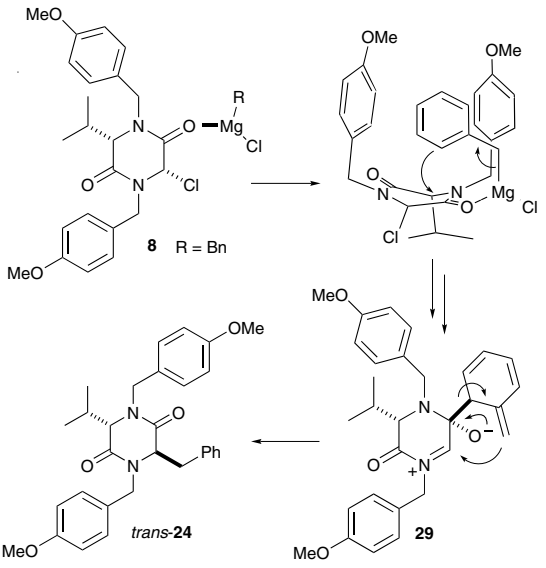


Figure 8. Possible mechanism of benzylmagnesium chloride addition to **8**.

subsequently undergoes preferential alkyl group migration to give *trans*-substituted diketopiperazine **24** (Fig. 8).

In the case of isopropyl magnesium chloride addition, the lower reactivity and steric bulk of the reagent is expected to retard the rate of attack onto the *C*-3 carbonyl group, resulting in the reaction of the *N*-acyliminium ion predominating (Fig. 6, path B). The observed *cis* stereoselectivity of this addition contrasts with the predominant *trans* addition of allytrimethylsilane to the similar *N*-acyliminium ion derived from acetates **3** or **4**.[7] However, the observed stereoselectivity of the isopropylmagnesium chloride addition may be rationalised by a mechanism involving initial co-ordination of the Grignard reagent to the *C*-3 carbonyl group followed by formation of the *N*-acyliminium species and attack by a second equivalent of isopropyl magnesium chloride. In this addition, the trajectory of approach to the *N*-acyliminium carbon centre will be hindered by the proximal isopropyl magnesium chloride co-ordinated on the *Re*-face of the auxiliary, thus directing attack onto the *Si*-face, affording *cis*-substituted-**25** (Fig. 9). Presumably a similar mode of reaction and stereocontrol operates to afford the *cis*-methyl addition product **22**.

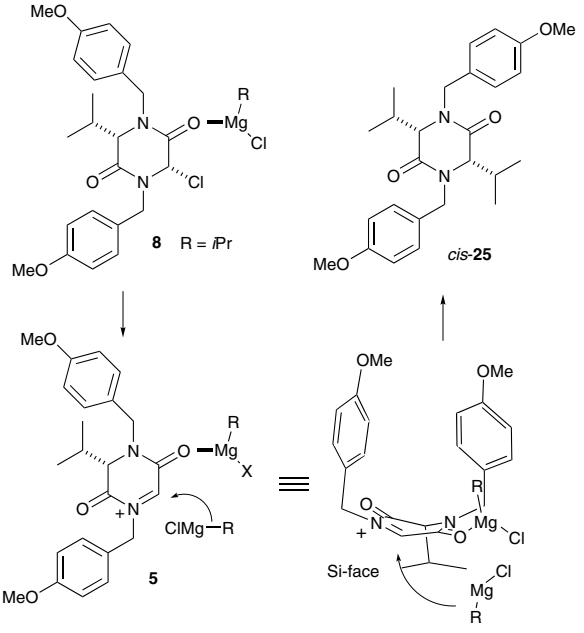


Figure 9. Possible mechanism of isopropylmagnesium chloride addition to **8**.

3. Conclusion

In conclusion, reactive 2-chloro and 2-bromo diketopiperazine derivatives **8** and **13** have prepared from fluorodiketopiperazines **11** and **12** via a novel silylhalide mediated transhalogenation reaction. The reactions of 2-chloro **8** with allyltrimethylsilane, sodium thiophenolate and Grignard reagents have been assessed. The regio- and stereoselectivity observed in the addition of Grignard reagents was found to be dependent on the nature of the organomagnesium reagent and affords, in high de, either rearranged *C*-3-carbonyl addition products (**18**, **21** and **24**) upon the addition of allyl-, methyl- or benzylmagnesium chloride, or *cis*-substituted diketopiperazine **25**, from direct addition to the *N*-acyliminium carbon centre, upon addition of isopropylmagnesium chloride.

4. Experimental

4.1. General experimental

All reactions involving organometallic or moisture sensitive reagents were performed under an atmosphere of nitrogen via standard vacuum line techniques. All glassware was flame dried and allowed to cool under vacuum. In all cases, the reaction diastereoselectivity was assessed by peak integration in the ^{1}H NMR spectrum of the crude reaction mixture. Tetrahydrofuran was distilled under an atmosphere of dry nitrogen from sodium benzophenone ketyl. All other solvents were used as supplied (Analytical or HPLC grade), without prior purification. Thin layer chromatography was performed on aluminium sheets coated with 60 F_{254} silica. Sheets were visualised using 10% phosphomolybdic acid in ethanol. Chromatography was performed on Kieselgel 60 silica. Nuclear magnetic resonance (NMR) spectra were recorded on a Bruker AC 200 (^{1}H: 200 MHz and ^{13}C: 50.3 MHz) or Bruker DPX 400 (^{1}H: 400 MHz and ^{13}C: 100.6 MHz) spectrometer in the deuterated solvent stated. All chemical shifts (δ) are quoted in ppm and coupling constants (J) in Hz. Coupling constants are quoted twice, each being recorded as observed in the spectrum without averaging. Residual signals from the solvents were used as an internal reference. ^{13}C multiplicities were assigned using a DEPT sequence. Infrared spectra were recorded on a Perkin–Elmer 1750 IR

Fourier Transform spectrophotometer using either thin films on NaCl plates (film) or KBr discs (KBr) as stated. Only the characteristic peaks are quoted in cm^{-1}. Optical rotations were recorded on a Perkin–Elmer 241 polarimeter with a path length of 1 dm. Concentrations are quoted in g/100 mL. Low resolution mass spectra were obtained upon a VG micromass ZAB IF, a VG MassLab 20-250, a VG Bio Q or an APCI Platform spectrometer with only molecular ions, fragments from molecular ions and major peaks being reported. High resolution mass spectroscopic data was obtained upon Micromass AutoSpec or Micromass ToFSpec spectrometer. Elemental analyses were performed by the microanalysis service of the Inorganic Chemistry Laboratory, University of Oxford.

4.2. (2*R*,5*S*)- and (2*S*,5*S*)-*N*,*N*′-Bis-(*p*-methoxybenzyl)-2-fluoro-5-isopropyl-piperazine-3,6-dione 11 and 12

To a solution of **1**[4b] (2.0 g, 5.05 mmol) in dry THF (30 mL) was added lithium hexamethyldisilazide (5.6 mL, 1 M THF solution, 5.6 mmol) at −78 °C after stirring for 1 h the mixture was treated with *N*-fluorobenzenesulfonimide (1.75 g, 5.6 mmol). The mixture stirred for 30 min then warmed to −30 °C and aqueous saturated NH_4Cl (10 mL) was added. Water (100 mL) was then added and the mixture was extracted with ether, the organic layer was dried ($MgSO_4$) and the solvent removed to afford a 67:33 mixture of *trans* and *cis*-fluorides **11** and **12** as an oil (2.05 g, 98%).

Data for mixture of **11** and **12***. υ_{max} (film)/cm^{-1} 2963, 2986, 2837, 1682, 1514; δ_H (500 MHz, $CDCl_3$) 0.70 (3H, d, *J* 6.9, C*H*$_3$*CHCH$_3$), 0.98 (3H, d, *J* 6.9, C*H*$_3$CHCH$_3$), 1.07 (3H, d, *J* 7.0, CH$_3$CHC*H*$_3$*), 1.14 (3H, d, *J* 7.0, CH$_3$CHC*H*$_3$), 2.28 (2H, m, CH$_3$C*H*CH$_3$), 3.72–3.80 (2H, m, 2 × 3-*H*), 3.80 (12H, s, 4 × O*Me*), 3.87 (1H, d, *J* 14.7, ArC*H*$_2$), 3.90 (1H, d, *J* 14.5, ArC*H*$_2$*), 4.02 (1H, d, *J* 14.1, ArCH$_2$*), 4.26 (1H, dd, *J* 14.6, 1.4 ($^4J_{HF}$), ArC*H*$_2$N-1), 4.96 (1H, d, *J* 14.8, ArC*H*$_2$), 5.27–5.41 (3H, m, ArC*H*$_2$*), 5.52 (1H, d, 58.7 ($^2J_{HF}$), 2-*H**), 5.60 (1H, d, 57.5 ($^2J_{HF}$), 2-*H*), 6.80–6.91 (8H, m, aromatic C*H*), 7.09–7.29 (8H, m, aromatic C*H*); δ_C (125 MHz, $CDCl_3$): 16.0*, 18.0, 19.3*, 20.1, 31.2*, 32.2, 45.2*, 46.4, 47.5 48.1, 55.2, 62.8, 64.6, 88.8 (d, $^1J_{CF}$ 197, *C*F), 91.9 (d, $^1J_{CF}$ 207, *C*F*), 113.6, 113.7, 114.2, 114.4, 114.9, 126.8, 129.6, 129.7, 130.0, 130.9, 159.5, 159.6, 160.0, 160.2, 164.4, 166.9.

4.3. (2*S*,5*S*)-*N*,*N*′-Bis-(*p*-methoxybenzyl)-2-chloro-5-isopropyl-piperazine-3,6-dione 8

Fluorides **11** and **12** (2:1 mixture, 1.0 g, 2.41 mmol) and chlorotrimethylsilane (2 mL) were stirred in dry dichloromethane (20 mL) for 2 h at room temperature. The solvent and excess chlorotrimethylsilane were then removed in vacuo to afford a crude foam of chloride **8** (1.02 g, 98%) which was >95% pure as assessed ^1H NMR. This moisture sensitive material was stable under nitrogen at −20 °C for a several weeks and was generally used immediately. $[\alpha]_D^{23} = -119.1$ (*c* 1.11, $CHCl_3$); υ_{max} (film)/cm^{-1} 2963, 1681, 1612, 1513, 1249; δ_H (500 MHz, $CDCl_3$): 1.15 (d, 1H, *J* 6.8, C*H*$_3$CHCH$_3$), 1.24 (d, 1H, 6.90, CH$_3$CHC*H*$_3$), 2.58 (m, 1H, CH$_3$C*H*CH$_3$), 3.75 (d, 1H, *J* 7.0, 5-*H*), 3.85 (s, 3H, O*Me*), 3.85 (s, 3H, O*Me*), 3.98 (d, 1H, *J* 14.6, ArC*H*$_2$), 4.01 (d, 1H, *J* 14.6, ArC*H*$_2$), 5.32 (d, 1H, *J* 14.6, ArC*H*$_2$), 5.40 (d, 1H, *J* 14.6, ArC*H*$_2$), 5.70 (s, C*H*Cl), 6.88–6.95 (m, 4H, aromatic *H*), 7.12–7.15 (m, 2H, aromatic *H*), 7.20–7.31 (m, 2H, aromatic *H*); irradiation at δ 3.75 gave NOE enhancements at δ 1.15 (2%), 1.24 (2.4%), 2.58 (4%), 3.98 (2%), 5.40 (1.2%), 5.70 (1%) and 7.12–7.15 (2.4%); δ_C (125 MHz, $CDCl_3$): 19.3, 20.6, 31.9, 46.3, 49.0, 55.2 × 2, 64.9, 68.2, 114.3, 114.4, 126.0, 126.8, 129.4, 130.2, 159.4, 159.7, 161.1, 166.8; *m*/*z* (CI) 448 (M+NH_4^+, 14%), 395 (76), 190 (100). Found: M^+-Cl, 395.1962. $C_{23}H_{27}N_2O_4^+$ requires 395.1971.

4.4. (2*S*,5*S*)-*N*,*N*′-Bis-(*p*-methoxybenzyl)-2-bromo-5-isopropyl-piperazine-3,6-dione 13

Fluorides **11** and **12** (2:1 mixture, 400 mg, 0.97 mmol) and bromotrimethylsilane (1.0 mL) were stirred in dry dichloromethane (5 mL) for 2 h at room temperature. The solvent and excess bromotrimethylsilane were then removed in vacuo to afford bromo **13** as a viscous oil (460 mg, 100%), which was >95% pure as assessed ^1H NMR. $[\alpha]_D^{23} = -92.0$ (*c* 2.10, $CHCl_3$); υ_{max} (film)/cm^{-1} 2964, 2837, 1651, 1514; δ_H (400 MHz, $CDCl_3$): 1.13 (d, 1H, *J* 6.8, C*H*$_3$CHCH$_3$), 1.21 (d, 1H, *J* 6.9, CH$_3$CHC*H*$_3$), 2.71 (m, 1H, CH$_3$C*H*CH$_3$), 3.71 (d, 1H, *J* 7.5, 3-*H*), 3.81 (s, 3H, O*Me*), 3.82 (s, 3H, O*Me*), 3.87 (d, 1H, *J* 14.5, ArC*H*$_2$), 3.93 (d, 1H, *J* 14.9, ArC*H*$_2$), 5.29 (d, 1H, *J* 14.5, ArC*H*$_2$), 5.37 (d, 1H, *J* 14.9, ArC*H*$_2$), 5.88 (s, C*H*Br), 6.81–6.90 (m, 4H, aromatic C*H*), 7.06–7.21 (m, 4H, aromatic C*H*); δ_C (100 MHz, $CDCl_3$): 19.6, 20.8, 31.2, 46.7, 49.4, 55.26, 55.30, 59.6, 65.1, 114.4, 114.5, 125.7, 126.9, 129.4, 130.2, 159.5, 159.8, 161.4, 167.1.

4.5. (3*S*,6*R*)- and (3*S*,6*S*)-*N*,*N*′-Bis-(*p*-methoxybenzyl)-6-allyl-3-isopropyl-piperazine-2,5-dione 6 and 7

To chloride **8** (50 mg, 0.12 mmol) in dichloromethane (5 mL) was added antimony pentachloride (0.13 mL, 1 M in dichloromethane, 0.13 mmol) then allyltrimethylsilane (50 μL, 0.44 mmol) and the mixture stirred 12 h at room temperature. The mixture was partitioned between water and dichloromethane, the organic phase dried ($MgSO_4$) and the solvent removed in vacuo to afford a crude gum. Examination of the ^1H NMR spectrum of the reaction mixture indicated an 80:20 mixture of **6** and **7**.

4.6. (2*R*,5*S*)-*N*,*N*′-Bis-(*p*-methoxybenzyl)-5-isopropyl-2-thiophenyl-piperazine-3,6-dione 16

Chloride **8** (200 mg, 0.46 mmol) in THF (2 mL) was added to sodium phenylthiolate {prepared from thiophenol (44 mg, 0.40 mmol) and sodium hydride (16 mg, 60% dispersion in oil, 0.4 mmol)} in THF (5 mL). This mixture was stirred (12 h, room temperature) then partitioned between ether and saturated aqueous copper sulfate solution, the organic phase dried

($MgSO_4$) and the solvent removed in vacuo. Chromatography (silica, 1:1 ether/hexane) gave **16** as a colourless wax (112 mg, 48%). $[\alpha]_D^{23} = -106.8$ (*c* 1.10, $CHCl_3$); υ_{max} (KBr disc) cm^{-1} 2961, 1650, 1613, 1513, 1248; δ_H (400 MHz, $CDCl_3$): 0.65 (3H, d, *J* 6.9, CH_3CHCH_3), 0.96 (3H, d, *J* 7.0, CH_3CHCH_3), 2.14 (1H, m, CH_3CHCH_3), 3.17 (1H, d, *J* 2.7, 5-*H*), 3.79 (3H, s, O*Me*), 3.81 (3H, s, O*Me*), 3.95 (1H, d, *J* 14.9, $ArCH_2$), 4.39 (1H, d, *J* 14.1, $ArCH_2$), 4.82 (1H, d, *J* 14.9, $ArCH_2$), 4.97 (1H, s, 2-*H*), 5.55 (1H, d, *J* 14.1, $ArCH_2$), 6.75 (4H, m, aromatic C*H*), 6.86 (2H, m, aromatic C*H*), 7.24–7.40 (4H, m, aromatic C*H*), 7.45 (3H, m, aromatic C*H*); δ_C (100 MHz, $CDCl_3$): 15.4, 19.6, 30.6, 45.7, 47.3, 55.26, 55.29, 62.6, 65.4, 114.0, 114.3, 126.6, 129.2, 129.3, 129.7, 129.9, 130.9, 136.1, 159.3, 159.5, 163.3, 164.6. *m/z* ($APCI^+$) 505 (MH^+, 4%), 395 ($MH^+ - SPh$, 32), 121 ($MeOC_6H_4CH_2^+$, 100). [HRMS (TOF FI) Found: M^+, 504.2091. $C_{29}H_{32}N_2O_4S$ requires 504.2083].

4.7. (2*S*,5*S*)-*N*,*N*′-Bis-(*p*-methoxybenzyl)-5-isopropyl-2-thiophenyl-piperazine-3,6-dione 17

trans-Sulfide **16** (35 mg, 0.07 mmol) in THF (1 mL) was added to sodium phenylthiolate {prepared from thiophenol (15.2 mg, 0.14 mmol) and sodium hydride (5.5 mg, 60% dispersion in oil, 0.14 mmol)} in THF (3 mL). This mixture was stirred (12 h, room temperature) then partitioned between ether and saturated aqueous copper sulfate solution, the organic phase dried ($MgSO_4$) and the solvent removed in vacuo. Chromatography (silica, 1:1 ether/hexane) afforded *cis*-sulfide **17** as a colourless solid (29 mg, 83%). Mp 101 °C; (found: C, 69.2; H, 6.4; N, 5.5. $C_{29}H_{32}N_2O_4S$ requires C, 69.0; H, 6.4; N, 5.6); $[\alpha]_D^{23} = -255.2$ (*c* 1.03, CH_2Cl_2); ν_{max} (KBr disc)/cm^{-1} 1668 (NC=O), 1612, 1514, 1245; δ_H (400 MHz; $CDCl_3$) 1.14 (3H, d, *J* 6.8, CH_3CHCH_3), 1.21 (3H, d, *J* 6.9, CH_3CHCH_3), 2.32 (1H, m, CH_3CHCH_3), 3.70 (1H, d, *J* 7.2, 5-*H*), 3.74 (3H, s, O*Me*), 3.79 (3H, s, O*Me*), 3.88 (1H, d, *J* 14.5, $ArCH_2$), 3.91 (1H, d, *J* 14.8, $ArCH_2$), 4.94 (1H, s, 2-*H*), 5.34 (1H, d, *J* 14.5, $ArCH_2$), 5.38 (1H, d, *J* 14.8, $ArCH_2$), 6.67 (2H, m, aromatic C*H*), 6.74 (2H, m, aromatic C*H*), 6.84 (2H, m, aromatic C*H*), 7.01 (2H, m, aromatic C*H*), 7.37 (3H, m, aromatic C*H*), 7.70 (2H, m, aromatic C*H*); δ_C (100 MHz, $CDCl_3$): 19.3, 20.5, 33.1, 45.6, 49.3, 55.2, 55.3, 65.3, 67.1, 113.8, 114.0, 114.1, 114.3, 126.7, 127.5, 128.4, 128.5, 129.2, 129.4, 129.9, 132.8, 134.8, 159.3, 164.7, 165.6. *m/z* ($APCI^+$) 505 (MH^+, 4%), 121 (100%). Found 505.2161; $C_{29}H_{33}N_2O_4S^+$ requires 505.2161.

4.7.1. X-ray crystal structure data for 17. Data were collected using a Nonius Kappa CCD diffractometer with graphite monochromated Mo-Kα radiation using standard procedures at 190 K. The structure was solved by direct methods (Sir92). All nonhydrogen atoms were refined with anisotropic thermal parameters. Hydrogen atoms were added at idealised positions. The structure was refined using CRYSTALS.[17]

Crystal data for **17** [$C_{29}H_{32}N_2O_4S$], colourless plate, $M = 504.64$, orthorhombic, space group $P2_12_12_1$, $a = 9.3120(2)$ Å, $b = 16.9551(3)$ Å, $c = 17.0130(3)$ Å, $U = 2686$ Å^3, $Z = 4$, $\mu = 0.157$, crystal dimensions $0.4 \times 0.6 \times 0.6$ mm, A total of 4315 unique reflections were measured for $1 < \theta < 27$ and 3816 reflections were used in the refinement. The final parameters were $wR_2 = 0.041$ and $R_1 = 0.032$ [$I > 3\sigma(I)$].

Crystallographic data (excluding structure factors) has been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 187478. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44 01223 336033 or deposit@ccdc.cam.ac.uk].

4.7.2. Alkylation of 1 with diphenyldisulfide. Lithium hexamethyldisilazide (1.10 mmol, 1.10 mL, 1 M in THF) was added to **1**[4b] (400 mg, 1.01 mmol) in THF (20 mL) at −78 °C, under a nitrogen atmosphere. After stirring for 1 h at −78 °C, diphenyl disulfide (240 mg, 1.1 mmol) in THF (2 mL) was added. The reaction mixture was stirred at −78 °C for 30 min and left to warm to room temperature overnight before addition of excess saturated aqueous ammonium chloride. The mixture was partitioned between saturated copper sulfate solution and ethyl acetate and the aqueous phase extracted with ethyl acetate. The combined organic layers were dried ($MgSO_4$), filtered and concentrated in vacuo to yield the crude product. Chromatography (silica 1:3 ether/hexane) yielded **17** as a colourless crystalline solid (246 mg, 49%) with spectroscopic properties identical to those described above.

4.7.3. Alkylation of 1 with *S*-phenyl benzenethiosulfonate. Lithium hexamethyldisilazide (0.60 mmol, 1.10 mL, 1 M in THF) was added to **1**[4b] (200 mg, 0.50 mmol) in THF (10 mL, degassed) at −78 °C, under a nitrogen atmosphere. After stirring for 1 h at −78 °C, *S*-phenyl benzenethiosulfonate (153 mg, 0.55 mmol) was added and the reaction mixture was stirred at −78 °C for 4 h then left to warm to room temperature overnight before addition of excess saturated ammonium chloride solution. The mixture was partitioned between saturated copper sulfate solution and ethyl acetate and the aqueous phase extracted with ethyl acetate. The combined organic layers were dried ($MgSO_4$), filtered and concentrated in vacuo to yield a crude gum (238 mg). Analysis of the ^{1}H NMR spectrum of the crude reaction mixture showed a 80:20 mixture of *cis*-**17** and *trans*-**16**, respectively.

4.8. General procedure for the treatment of chloride 8 with Grignard reagents

Alkylmagnesium chloride was added dropwise to freshly prepared **8** in anhydrous THF (10 mL) at −78 °C. This mixture was stirred (4 h, −78 °C), warmed to room temperature over 12 h then saturated NH_4Cl (2 mL) was added. The mixture was then partitioned between water and ether, the aqueous phase extracted with ether, the organic layer dried ($MgSO_4$) and the solvent removed in vacuo to afford the crude product. Products were isolated by chromatography.

4.9. (3*S*,6*S*)-*N*,*N*′-Bis-(*p*-methoxybenzyl)-5,5-diallyl-6-hydroxy-3-isopropyl-piperazine-2-one 18

Treatment of **8** (1.00 g, 2.32 mmol) with allylmagnesium chloride (2.50 mL, 2 M solution in THF, 5.0 mmol) according to the General procedure gave after chromatography (silica, 1:1 ether/hexane) **18** as a colourless oil as the first eluting compound (672 mg, 60%). $[\alpha]_D^{23} = -10.0$ (*c* 1.05, $CHCl_3$); υ_{max} (film)/cm^{-1} 3424, 2957, 2873, 1652 (NC=O), 1612, 1512, 1247; δ_H (500 MHz, $CDCl_3$): 0.95 (d, 1H, *J* 6.8, CH_3CHCH_3), 1.26 (d, 1H, *J* 7.1, CH_3CHCH_3), 1.82 (dd, 1H, *J* 14.6, 7.4, $CH_2CH{=}CH_2$), 2.01 (m, 1H, (CH_3CHCH_3), 2.20 (dd, 1H, *J* 7.2 and 14.4, $CH_2CH{=}CH_2$), 2.43 (m, 2H, $CH_2CH{=}CH_2$), 3.39 (d, 1H, *J* 17.4, $ArCH_2$), 3.48 (d, 1H, *J* 1.7, 3-*H*), 3.55 (d, 1H, *J* 11.6, O*H*), 3.85 (s, 3H, O*Me*), 3.85 (s, 3H, O*Me*), 4.17 (d, 1H, *J* 14.3, $ArCH_2$), 4.30 (d, 1H, *J* 11.6, C*H*OH), 4.40 (d, 1H, *J* 17.4, $ArCH_2$), 5.03 (d, 1H, *J* 14.3, $ArCH_2$), 5.08-5.12 (m, 4H, $CH_2CH{=}CH_2$), 5.68–5.74 (m, 1H, $CH_2CH{=}CH_2$), 5.74–5.87 (m, 1H, $CH_2CH{=}CH_2$), 6.87–6.93 (m, 4H, aromatic *H*), 7.23–7.32 (m, 2H, aromatic *H*), 7.36–7.39 (m, 2H, aromatic *H*); δ_C (125 MHz, $CDCl_3$): 16.7, 21.6, 30.9, 34.5, 38.7, 47.8, 53.6, 55.3 × 2, 62.8, 71.3, 81.3, 113.8, 113.9, 119.2, 119.8, 127.0, 129.1, 130.5, 132.3, 133.5, 134.5, 158.3, 159.0, 169.2; *m*/*z* (APCI$^+$) 479 (MH^+, 18%), 357(4), 341(5), 121(100); [HRMS (TOF, FI) found: M^+, 478.2826. $C_{29}H_{38}N_2O_4$ requires 478.2832].

4.10. (3*S*,6*S*)-*N*,*N*′-4-Bis-(*p*-methoxybenzyl)-6-trimethylsiloxy-5,5-diallyl-3-isopropyl-piperazine-2-one 20

Compound **18** (26 mg, 0.048 mmol) and trimethylsilylimidazole (0.5 mL) in dichloromethane (0.5 mL) were stirred for 12 h at room temperature then partitioned between water and ether, the organic layer dried ($MgSO_4$) and solvent removed in vacuo. Chromatography (silica, 1:9 ether–hexane) gave **20** as a colourless solid (23 mg, 77%). Mp 136 °C (ether/hexane). Found: C, 69.6; H, 8.2; N, 5.1. $C_{32}H_{46}N_2O_4Si$ requires C, 69.8; H, 8.4; N, 5.1; $[\alpha]_D^{23} = -36.4$ (*c* 1.03, $CHCl_3$); υ_{max} (KBr disc) cm^{-1} 2946, 1653 (NC=O), 1611, 1513, 1240; δ_H (400 MHz, $CDCl_3$): 0.31 (s, 9H, $Si(CH_3)_3$), 1.00 (d, 3H, *J* 6.7, CH_3CHCH_3), 1.14 (d, 3H, *J* 7.7, CH_3CHCH_3), 1.52 (dd, 1H, *J* 14.5, 7.0, $CH_2CH{=}CH_2$), 1.81 (m, 1H, CH_3CHCH_3), 2.15 (dd 1H, *J* 14.5, 8.0 $CH_2CH{=}CH_2$), 2.32 (d, 2H, *J* 7.1, $CH_2CH{=}CH_2$), 3.31 (d, 1H, *J* 18.2, $ArCH_2$), 3.45 (d, 1H, *J* 0.6 Hz, 3-*H*), 3.61 (d, 1H, *J* 14.3, $ArCH_2$), 3.80 (s, 3H, O*Me*), 3.81 (s, 3H, O*Me*), 4.45 (d, 1H, *J* 18.2, $ArCH_2$), 4.45 (s, 1H, 6-*H*), 4.92 (m, 4H, $CH_2CH{=}CH_2$), 5.43 (d, 1H, *J* 14.3, $ArCH_2$), 5.53–5.75 (m, 2H, $CH_2CH{=}CH_2$), 6.82–6.88 (m, 4H, aromatic C*H*), 7.34 (m, 2H, aromatic C*H*), 7.43 (m, 2H, aromatic *H*). NOESY cross peak observed between $\delta_H = 0.31$ and $\delta_H = 1.00$; δ_C (100 MHz, $CDCl_3$): 0.8, 16.8, 21.3, 31.5, 35.1, 37.4, 47.4, 53.1, 55.2 (× 2), 61.9, 71.2, 82.6, 113.2, 113.8, 118.7, 119.0, 127.1, 129.2, 130.4, 132.8, 134.0, 136.1, 157.9, 159.1, 170.6 ; *m*/*z* (TOF FI) 551 (M^+, 97%) 509 ($M^+ - CH_2{=}CHCH_2$, 100).

4.11. (3*S*,6*S*)-*N*,*N*′-Bis-(*p*-methoxybenzyl)-5,5-dimethyl-6-hydroxy-3-isopropyl-piperazine-2-one 21, (3*S*,6*S*)-*N*,*N*′-bis-(*p*-methoxybenzyl)-3-isopropyl-6-methyl-piperazine-2,5-dione 22 and (3*S*)-*N*,*N*′-bis-(*p*-methoxybenzyl)-3-isopropyl-piperazine-2,5-dione 1

Treatment of **8** (430 mg, 1.00 mmol) with methylmagnesium chloride (0.50 mL, 3 M in ether, 1.5 mmol) according to the General procedure gave oily crude mixture (400 mg). Chromatography (silica, 1:1 ether/hexane) afforded **21** as a clear oil (187 mg, 44%). $[\alpha]_D^{23} = -13.1$ (*c* 1.05, $CHCl_3$); υ_{max} (film)/cm^{-1} 3441(OH), 2959, 2934, 2872, 2834, 1651, 1511, 1245; δ_H (500 MHz, $CDCl_3$): 0.81 and 0.93 (s, 3H, Me_2C), 1.01 (d, 1H, *J* 6.9, CH_3CHCH_3), 1.24 (d, 1H, 7.1, CH_3CHCH_3), 2.02 (m, 1H, CH_3CHCH_3), 3.20 (d, 1H, *J* 1.7, 3-*H*), 3.40 (d, 1H, *J* 16.9, $ArCH_2$), 3.44 (d, 1H, *J* 11.9, CHO*H*), 3.79 (s, 3H, O*Me*), 3.80 (s, 3H, O*Me*), 3.93 (d, 1H, *J* 16.2, $ArCH_2$), 3.96 (d, 1H, *J* 14.2, $ArCH_2$), 4.05, (d, 1H, *J* 11.9, C*H*OH), 5.21 (d, *J* 14.3, $ArCH_2$), 6.82–6.91 (m, 4H, aromatic *H*), 7.20–7.23 (m, 2H, aromatic *H*), 7.28–7.31 (m, 2H, Ar*H*); δ_C (125 MHz, $CDCl_3$): 16.1, 17.4, 21.5, 26.1, 31.5, 47.0, 53.0, 55.1, 55.2, 58.3, 70.5, 84.0, 113.8, 113.81, 127.5, 129.1, 130.4, 134.1, 158.3, 159.0, 169.1; *m*/*z* (APCI) 427 (MH^+, 48%), 121 (100); [HRMS (CI) found: MH^+, 427.2597. $C_{25}H_{35}N_2O_4$ requires 427.2597].

Further elution gave *cis*-methyl **22** as a colourless oil (61 mg, 14%). $[\alpha]_D^{23} = -194$ (*c* 1.00, $CHCl_3$) [lit.[4b] −202 (*c* 0.89, $CHCl_3$)]; δ_H (400 MHz, $CDCl_3$): 1.04 (d, 1H, *J* 6.9, (CH_3CHCH_3), 1.17 (d, 1H, *J* 7.00, CH_3CHCH_3), 1.55 (d, *J* 7.1, $NCHCH_3$), 2.20 (m, 1H, CH_3CHCH_3), 3.74 (d, 1H, *J* 5.6, 3-*H*), 3.81 (s, 3H, O*Me*), 3.81 (s, 3H, O*Me*), 3.87 (d, 1H, *J* 14.8, $ArCH_2$), 3.99 (q, *J* 7.5, 6-*H*), 4.00 (d, 1H, *J* 14.9, $ArCH_2$), 5.11 (d, 1H, *J* 14.7, $ArCH_2$), 5.35 (d, 1H, *J* 14.8, $ArCH_2$), 6.83–6.86 (m, 4H, aromatic *H*), 7.08–7.16 (m, 4H, aromatic *H*); *m*/*z* (APCI) 411 (MH^+, 90%), 303 (10), 121 (100). Spectroscopic data was identical to authentic material.

Further elution gave **1** as a colourless solid (28 mg, 7%). δ_H (200 MHz, $CDCl_3$): 0.92 (3H, d, *J* 7.0, CH_3CHCH_3), 1.10 (3H, d, *J* 7.0, CH_3CHCH_3), 2.22 (1H, m, CH_3CHCH_3), 3.75 (1H, d, *J* 5.0, 3-*H*), 3.80 (1H, d, *J* 17.0, 6-*H*), 3.81 (3H, s, O*Me*), 3.81 (3H, s, O*Me*), 3.85 (1H, d, *J* 15.0, $ArCH_2$), 3.94 (1H, d, *J* 17.5, 6-*H*), 4.21 (1H, d, *J* 14.0, $ArCH_2$), 4.82 (1H, d, *J* 14.0, $ArCH_2$), 5.33 (1H, d, *J* 15.0, $ArCH_2$), 6.85–7.19 (8H, m, aromatic *H*). Spectroscopic data was identical to authentic material.

4.12. (3*S*,6*R*)-*N*,*N*′-Bis-(*p*-methoxybenzyl)-3-isopropyl-6-benzyl-piperazine-2,5-dione 24

Treatment of **8** (430 mg, 1.0 mmol) with benzylmagnesium chloride (1.20 mmol, 0.60 mL, 2 M solution in THF) according to the General procedure gave an oily crude mixture. Chromatography (silica, 1:1 ether/hexane) gave **24** as the first eluting compound (218 mg, 45%). Mp 168 °C; $[\alpha]_D^{23} = +54.6$ (*c* 1.09, $CHCl_3$) [lit.[4b] $[\alpha]_D^{23} = +58.6$ (*c* 0.99, $CHCl_3$)]; δ_H (400 MHz, $CDCl_3$) 0.74 (3H, d, *J* 7.0, CH_3CHCH_3), 0.99 (3H, d, *J* 7.0,

CH_3CHCH_3), 2.16 (1H, m, CH_3CHCH_3), 3.31 (1H, d, *J* 3.0, 3-*H*), 3.36 (1H, dd, *J* 14.5 and 4.0, $PhCH_2CH$), 3.40 (1H, dd, *J* 14.5 and 4.0, $PhCH_2CH$), 3.79 (1H, d, *J* 15.0, $MeOC_6H_4CH_2$), 3.79 (3H, s, O*Me*), 3.83 (3H, s, O*Me*), 3.98 (1H, d, *J* 15.0, $MeOC_6H_4CH_2$), 4.26 (1H, t, *J* 4.0, 6-*H*), 5.08 (1H, d, *J* 15.0, $MeOC_6H_4CH_2$), 5.66 (1H, d, *J* 15.0, $MeOC_6H_4CH_2$), 6.58–7.49 (13H, m, aromatic *H*); *m*/*z* ($APCI^+$) 487 (MH^+, 100%), 379 ($MH^+-MeOC_6H_4$, 8), 121(32). Spectroscopic data was identical to authentic material.

4.13. (3*S*,6*S*)-*N*,*N*′-Bis-(*p*-methoxybenzyl)-3,6-diisopropyl-piperazine-2,5-dione 25

Treatment of **8** (430 mg, 1.00 mmol) with isopropylmagnesium chloride (1.0 mL, 2.0 M solution in THF, 2.0 mmol) according to the General procedure gave a mixture containing **25** (60%) as assessed by analysis of the ^1H NMR spectrum of the crude reaction mixture. Chromatography (silica, 1:1 ether/hexane) gave **25** as a colourless solid (210 mg, 51%). Mp 110 °C (ether). Found: C, 71.0; H, 7.7; N, 6.3. $C_{26}H_{34}N_2O_4$ requires C, 71.2; H, 7.8; N, 6.4; $[\alpha]_D^{23} = -253.6$ (*c* 2.06, $CHCl_3$); υ_{max} (KBr disc)/cm^{-1} 2971, 2874, 1661 (C=O), 1613, 1513, 1245; δ_H (500 MHz, $CDCl_3$) 1.16 (d, 6H, *J* 6.6, CH_3CHCH_3), 1.17 (d, 6H, *J* 6.8, CH_3CHCH_3), 2.15 (m, 1H, CH_3CHCH_3), 3.55 (d, 2H, *J* 9.5, 3-*H*, 6-*H*), 3.69 (d, 2H, *J* 14.8, $ArCH_2$), 3.80 (s, 6H, 2 × OMe), 5.44 (d, 2H, *J* 14.8, $ArCH_2$), 6.79–6.82 (m, 4H, aromatic *H*), 6.99–7.02 (m, 4H, aromatic H); δ_C (125 MHz, $CDCl_3$): 20.7, 21.0, 34.1, 49.8, 55.2, 66.1, 114.2, 128.0, 129.2, 159.2, 167.4; *m*/*z* (APCI) 439 (MH^+, 100%), 121 (10). Ee was assessed as >98% by examination of the ^1H NMR spectrum of **25** with the chiral solvating reagent (*R*)-1,1,1-trifluoro-2-(9-anthryl)-ethanol and comparison to racemic sample.

4.13.1. X-ray crystal structure data for 25. Data were collected using a Nonius Kappa CCD diffractometer with graphite monochromated Mo-Kα radiation using standard procedures at 190 K. The structure was solved by direct methods (Sir92). All nonhydrogen atoms were refined with anisotropic thermal parameters. Hydrogen atoms were added at idealised positions. The structure was refined using CRYSTALS.[17]

Crystal data for **19** [$C_{14}H_{19}NO_2$], colourless plate, $M = 233.31$, orthorhombic, space group $Pcan$, $a = 12.0566(2)$ Å, $b = 14.1730(3)$ Å, $c = 14.7730(3)$ Å, $U = 2524.4$ Å^3, $Z = 8$, $\mu = 0.082$, crystal dimensions $0.4 \times 0.4 \times 0.8$ mm, a total of 2872 unique reflections were measured for $4.36 < \theta < 27.48$ and 2367 reflections were used in the refinement. The final parameters were $wR_2 = 0.0187$ and $R_1 = 0.0373$ [$I > 3\sigma(I)$].

Crystallographic data (excluding structure factors) has been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 238325. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44 01223 336033 or e-mail: deposit@ccdc.cam.ac.uk].

4.13.2. Preparation of 25 from (*S*,*S*)-*cyclo* (val-val). (*S*,*S*)-*cyclo* (Val-val)[18] (390 mg, 1.97 mmol) was added portion wise to NaH (156 mg, 60% suspension in oil, 3.96 mmol) in DMF (50 mL) at 0 °C followed by dropwise addition of *p*-methoxybenzyl chloride (0.53 mL, 3.96 mmol) and the mixture stirred for 2 h at 0 °C then warmed to room temperature and stirred for a further 12 h. Water was added and the mixture partitioned between ethyl acetate and water, aqueous layers were extracted with ethyl acetate and organic fractions dried ($MgSO_4$) and the solvent removed in vacuo. Chromatography (1:1 ether–pentane) then crystallisation from dichloromethane/hexane afforded **25** as colourless plates (398 mg, 46%). $[\alpha]_D^{23} = -257.4$ (*c* 4.05, $CHCl_3$). Spectroscopic data identical to that reported above.

Acknowledgements

The authors thank New College, Oxford for a Junior Research Fellowship (A.D.S.).

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