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Conjugate additions of organocuprates to a 3-methylene-6-isopropyldiketopiperazine acceptor for the asymmetric synthesis of homochiral α-amino acids

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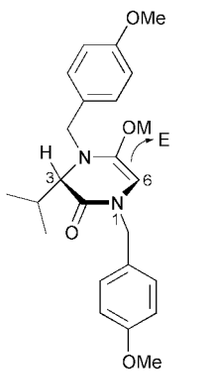
Addition of a range of organocuprates to (*S*)-*N*,*N*′-bis(*p*-methoxybenzyl)-3-methylene-6-isopropylpiperazine-2,5-dione **8** affords *cis*-3-isopropyl-6-alkyldiketopiperazines in excellent yield and >95% de. Subsequent deprotection and hydrolysis of these *cis*-3-isopropyl-6-alkyldiketopiperazines affords homochiral (*S*)-α-amino acids in excellent yield.

Introduction

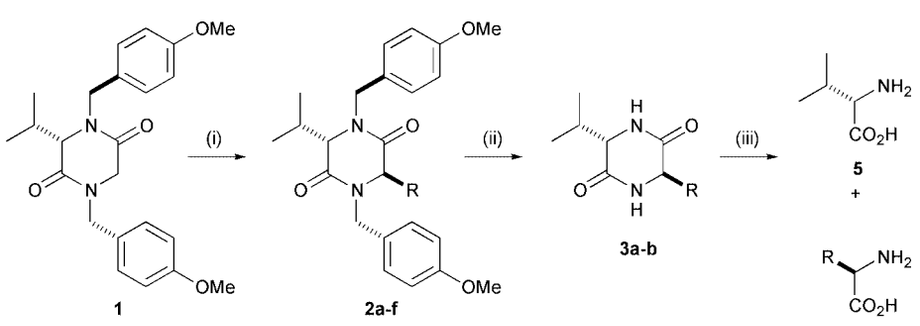
Homochiral α-amino acids are important synthetic targets for the development of new methodologies for asymmetric synthesis.[1] As a consequence, a large number of simple heterocyclic chiral auxiliaries have been developed, many of which are based on the diastereoselective alkylation of masked glycine enolate fragments.[2] In order to address many of the problems associated with the scale-up of this class of auxiliary, we have recently reported on (*S*)-*N*,*N*′-bis(*p*-methoxybenzyl)-3-isopropylpiperazine-2,5-dione **1** as a new chiral relay for the preparation of homochiral (*R*)-α-amino acids.[3] Alkylation of the enolate derived from **1** with a representative range of alkyl halides gave highly crystalline *trans*-alkylated products **2a**–**f** in >90% de, which, after simple recrystallisation of the crude reaction products, afforded pure homochiral *trans*-alkylated diastereoisomers **2a**–**f** in good yield (Scheme 1). The high diastereoselectivities observed have been interpreted to result from a chiral relay mechanism involving the conformational preference of the *N*-*p*-methoxybenzyl protecting groups (Fig. 1).[3a,4] Deprotection of the *trans*-alkylated auxiliaries **2a** or **2b** to their constituent α-amino acids was easily achieved *via* oxidative removal of the *p*-methoxybenzyl groups using ceric ammonium nitrate in CH_3CN–H_2O, to afford **3a** or **3b** in good yield. Subsequent acid catalysed hydrolysis of these *trans*-diketopiperazines gave a mixture of the (*R*)-amino acids **4a** or **4b** and (*S*)-valine **5** which were separated by ion exchange chromatography to afford homochiral (*R*)-phenylalanine **4a** and (*R*)-alanine **4b** respectively, in good yield (Scheme 1).[3a,b]



Electrophile attacks *anti* to both the C3 isopropyl and N1 protecting group.

Fig. 1

While this methodology is ideally suited to the preparation of homochiral α-amino acids of known absolute configuration, situations often arise where both enantiomers of a target α-amino acid are required.[5] Although both enantiomers of the target α-amino acid may be prepared separately *via* duplicate syntheses employing the same chiral auxiliary of opposite absolute configuration, this approach is tedious and inherently wasteful. An attractive alternative to this parallel synthesis approach would involve the preparation of both enantiomers of an α-amino acid from the same homochiral auxiliary *via* a



a) benzyl, **b**) methyl, **c**) allyl, **d**) propargyl, **e**) ethyl, **f**) isopropyl

Scheme 1 *Reagents and conditions*: (i) LiHMDS, THF, −78 °C; RX; (ii) CAN, H_2O–CH_3CN; (iii) 6 M HCl, Δ.

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stereodivergent approach. In this case the stereoselective synthesis of the *cis*-3-isopropyl-6-alkyl derivatives **6** from **1** would enable a complementary route to homochiral (*S*)-α-amino acids **7** to be achieved. For example, we have recently communicated that *cis*-alkyldiketopiperazine **6a** may be obtained from **1** *via* an approach involving regioselective deprotonation–reprotonation of *trans*-(3*S*,6*R*)-3-isopropyl-6-benzyldiketopiperazine derivative **2a**. Thus, treatment of **2a** with *n*-BuLi in THF at −78 °C resulted in regioselective deprotonation at C6, affording an enolate which was stereoselectively reprotonated at C6 from the *Re*-face to afford *cis*-(3*S*,6*S*)-3-isopropyl-6-benzyldiketopiperazine **6a** (92% de, 93% yield). Chromatographic purification of the reaction mixture afforded diastereoisomerically pure and homochiral **6a** with no evidence of any racemisation at the C3 stereogenic centre, enabling deprotection of **6a** to afford homochiral (*S*)-phenylalanine **7a** in excellent yield (Scheme 2).[6]

In order to widen the range of substrates to which this stereodivergent approach may be applied we now report herein that a wide range of *cis*-3-isopropyl-6-alkyldiketopiperazines **6** may be prepared in excellent de, *via* a versatile synthetic approach involving 1,4-conjugate addition of organocuprates to the 6-methylene acceptor **8**. Part of this work has been previously communicated.[7]

Results and discussion

Conjugate addition of organocuprates to (*S*)-3-methylene-6-isopropyldiketopiperazine acceptor 8

There have been many reports detailing the use of chiral auxiliaries to control the asymmetric 1,4-conjugate addition of nucleophiles to α,β-unsaturated acid fragments,[8] however the use of this of strategy for the asymmetric synthesis of homochiral α-amino acids is less well investigated. Strategies involving the conjugate addition of chiral nucleophiles to α,β-unsaturated acceptors, or the addition of nucleophiles to chiral α,β-unsaturated acceptors have been reported, however these methodologies suffer from practical problems that affect either the yield or ee of the target α-amino acid.[9] In order to address the synthetic problems associated with this conjugate addition methodology, we proposed that addition of organocuprates to (6*S*)-*N*,*N*′-bis(*p*-methoxybenzyl)-3-methylene-6-isopropylpiperazine-2,5-dione **8** (derived from methylenation of **1**), would afford an enolate fragment **9** which would be diastereoselectively reprotonated to afford *cis*-3-isopropyl-6-alkyldiketopiperazines **6** in excellent de. Subsequent deprotection and hydrolysis of *cis*-**6**, according to our previously published procedure, would afford the desired (*S*)-α-amino acids **7**. The dehydroalanine derived acceptor **8** was easily prepared in 92% yield *via* deprotonation of **1** with *n*-BuLi in THF at −78 °C, quenching the resulting enolate with paraformaldehyde, and heating the crude reaction mixture for 1 hour prior to workup. The stereochemical integrity of the C3 stereocentre of **8** was confirmed to be >95% ee by comparison of the 500 MHz ^{1}H NMR spectrum of homochiral **8** with that of an authentic sample of (±)-**8** (prepared *de novo* from racemic valine) in the presence of the chiral solvating agent 2,2,2-trifluoro-1-(9-anthryl)ethanol.

Table 1 Yields for organocuprate additions to methylene acceptor **8** to afford **6a–f**

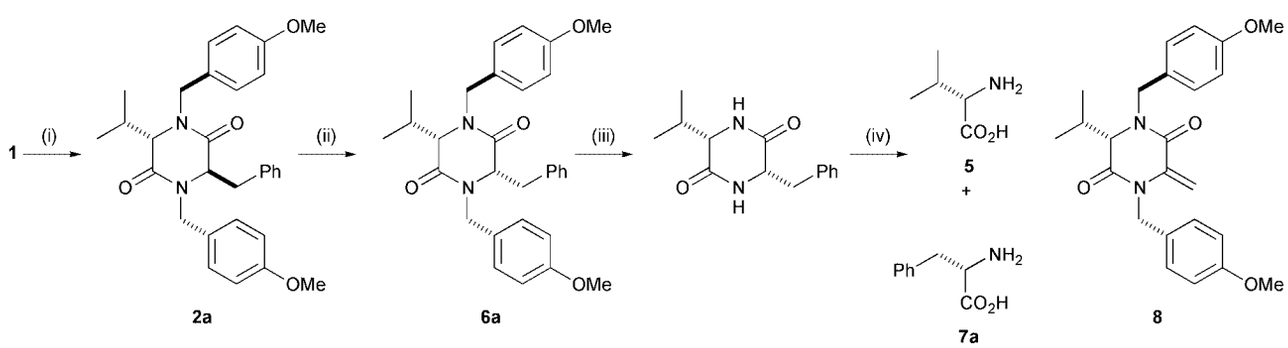
Product	R	Cuprate conditions	Isolated yield (%)
6a	Ph	2 PhLi–CuCN	88
6b	^{t}Bu	2 ^{t}BuMgCl–CuCN	90
6c	Me	2 MeLi–CuCN	91
6d	*n*-Bu	2 *n*-BuLi–CuCN	91
6e	Cy	2 CyMgBr–CuCN	92
6f	^{i}Pr	2 ^{i}PrMgBr–CuCN	88

Addition of $Ph_2CuCNLi_2$ to methylene acceptor **8**, in THF at −78 °C, followed by quenching of the resulting enolate **9a** with aqueous ammonium chloride, afforded a crude reaction mixture which contained the *cis*-(3*S*,6*S*)-3-isopropyl-6-benzyldiketopiperazine **6a** as the only identifiable product. The diastereoselectivity of this reaction was confirmed as >95% by examination of the ^{1}H NMR spectra of the crude reaction mixture which revealed the absence of any resonances corresponding to the known[3b] minor diastereoisomer *trans*-(3*S*,6*R*)-3-isopropyl-6-benzyldiketopiperazine **2a** (Scheme 3, Table 1). Purification of the crude reaction mixture *via* chromatography afforded the desired homochiral diastereoisomerically pure *cis*-(3*S*,6*S*)-3-isopropyl-6-benzyldiketopiperazine **6a** as a viscous oil in 88% yield. Following this general conjugate addition protocol five further *cis*-3-isopropyl-6-alkyldiketopiperazine derivatives **6b–f** were prepared *via* addition of the corresponding organocuprate to the methylene acceptor **8** in >95% de and in 88–92% isolated yield (Scheme 3, Table 1).

The excellent *cis* diastereoselectivity observed in these additions arises from highly selective *Re*-face protonation of enolate **9** resulting from the conjugate addition. We have proposed that the high degree of facial selectivity in alkylation of the unsubstituted parent auxiliary **1** is the result of a chiral relay involving the *p*-methoxybenzyl protecting groups operating within the system and the selectivity in the protonation of the metallated enolate **9a–f** presumably derives from similar factors (Fig. 2).[3,4] Notably the de obtained *via* reprotonation of the copper enolate **9a** with aqueous ammonium chloride is superior to that obtained *via* direct deprotonation of *trans*-**2a** and reprotonation of the lithium enolate (92% de) utilising the hindered proton source, 2,6-di-*tert*-butylphenol.[6] Indeed reprotonation of the lithium enolate derived from **2a** with ammonium chloride gives **6a** in 91% de while reprotonation of the copper enolates **9a–f** with the same proton source leads to uniformly high diastereoselectivities.

Deprotection and hydrolysis of *cis*-3-isopropyl-6-alkyldiketopiperazines 6a–f to afford homochiral α-amino acids 7a–f

Deprotection of homochiral *N*,*N*′-bis(*p*-methoxybenzyl)-3-isopropyl-6-alkyldiketopiperazines **6a–f** was achieved in good yield *via* a three step process. Oxidative removal of the



Scheme 2 *Reagents and conditions*: (i) LiHMDS; BnBr; (ii) *n*-BuLi, −78 °C; 2,6-di-*tert*-butylphenol; (iii) CAN, CH_3CN–H_2O; (iv) 6 M HCl, Δ.

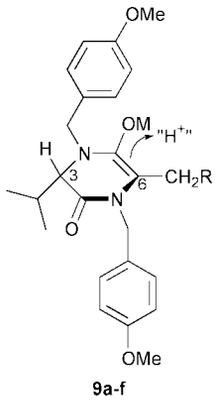


Fig. 2 Reprotonation of enolate **9a**–**f**.

p-methoxybenzyl groups with ceric ammonium nitrate in CH_3CN–H_2O (3 : 1) followed by chromatographic purification over alumina to remove cerium salts afforded homochiral *cis*-3-isopropyl-6-alkyldiketopiperazines **10a**–**f** in good yield. Hydrolysis of **10a**–**f**, by refluxing in 6 M HCl, afforded a mixture of (*S*)-valine **5** and the desired (*S*)-α-amino acids **7a**–**f**. Whilst these α-amino acids **7a**–**f** could be separated from the valine chiral auxiliary *via* ion exchange chemistry over Dowex 50-XH, this approach proved tedious especially when carried out on a large scale. As a result, an alternative separation approach was adopted whereby treatment of the mixture of α-amino acids **5** and **7a**–**f** with HCl–MeOH afforded a mixture of (*S*)-valine methyl ester **11** and (*S*)-α-aminoesters **12a**–**f**.[10] The free amino-esters (*S*)-**12a**,**b**,**d**,**e** were easily separated from **11** by fractional distillation under vacuum, whilst the more volatile esters (*S*)-**12c** and (*S*)-**12f** were separated from (*S*)-valine methyl ester **11** *via* silica chromatography. Subsequent hydrolysis of (*S*)-**12a**–**f** to their corresponding homochiral α-amino acids (*S*)-**7a**–**f** was achieved by treatment with refluxing 6 M HCl. The enantiomeric excess of each α-amino acid (*S*)-**7a**–**f** was confirmed to be >99% ee by comparison with authentic racemic samples using chiral HPLC analysis (Scheme 4, Table 2).

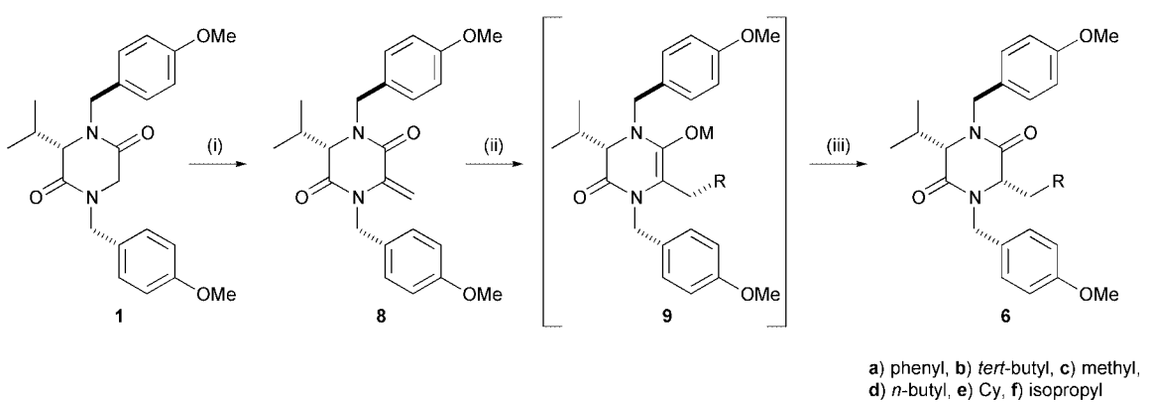
Conclusion

In conclusion, we have shown that conjugate addition of organocuprates to *N*,*N*′-bis(*p*-methoxybenzyl)-3-methylene-6-isopropyldiketopiperazine **8** provides simple access to *cis*-(3*S*,6*S*)-diketopiperazines **6** which may be deprotected to afford homochiral (*S*)-α-amino acids **7** in good yield. Importantly this methodology is more efficient than the previously described approach based on alkylation of the enolate of **1** and provides access to α-amino acids, such as **7b**, previously unavailable from our methodology.

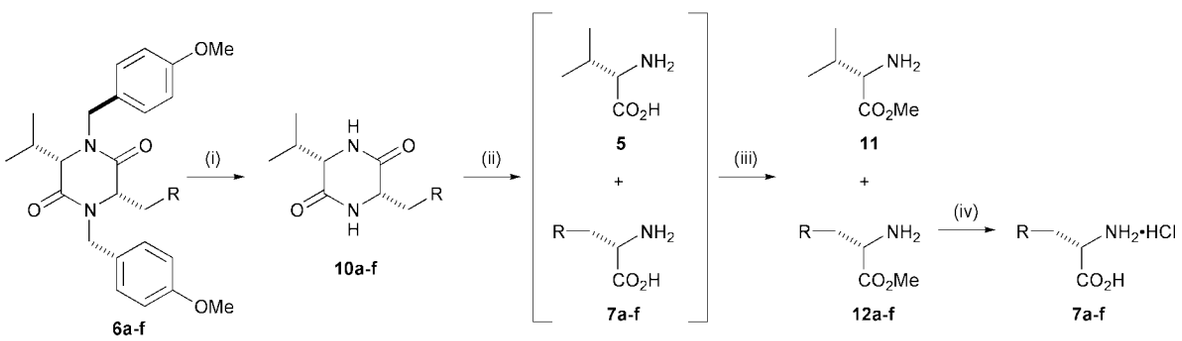
Experimental

General

Melting points (mp) were obtained using a Thermogalen™ III or Griffin Gallenkamp melting point apparatus and are uncorrected. Optical rotations were measured with a Perkin-Elmer 241 polarimeter with a thermally jacketed 10 cm cell at approximately 20 °C and are reported in units of 10^{-1} deg cm^2 g^{-1}. Concentrations (*c*) are given in g per 100 ml. Infrared (IR) spectra were recorded as KBr discs on a Perkin-Elmer 1750 Fourier Transform spectrometer. Absorptions are reported in wavenumbers (cm^{-1}). Proton magnetic resonance spectra (^{1}H NMR) were recorded at 200 MHz on a Varian Gemini 200 or a Bruker AC200 spectrometer, at 300 MHz on a Bruker WH300, at 400 MHz on a Bruker AC400 and at 500 MHz on a Bruker AM500 spectrometer and are referenced to the residual solvent peak. The following abbreviations were used: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet and br, broad. Coupling constants (*J*) were recorded in hertz to the nearest 0.05 Hz. Carbon magnetic resonance spectra (^{13}C NMR) were recorded at 50.3 MHz on a Varian Gemini 200 or Bruker AC200 spectrometer, at 100.6 MHz on a Bruker AC400 spectrometer and at 125.7 MHz on a Bruker AMX500 spectrometer using DEPT editing. Diastereomeric excesses were determined by peak integration of the ^{1}H NMR spectra of the crude reaction product. Low resolution mass spectra (*m*/*z*) were recorded on



Scheme 3 *Reagents and conditions*: (i) 1.1 equiv. *n*-BuLi, THF, −78 °C; 2 equiv. $(CH_2O)_n$; Δ; (ii) organocuprate, THF, −78°C; aq. NH_4Cl.



Scheme 4 *Reagents and conditions*: (i) CAN, CH_3CN–H_2O; (ii) 6 M HCl, Δ; (iii) a) HCl, MeOH; b) K_2CO_3 (aq); c) separate by distillation (R = Ph, *tert*-butyl, *n*-butyl, Cy) or *via* chromatography (R = Me, isopropyl); (iv) 6 M HCl, Δ.

Table 2 Isolated yields for deprotection of **6a**–**f** to **10a**–**f** and α-amino acids **7a**–**7f** (Scheme 4)

Adduct	R	Diketopiperazine	Yield (%)	(*S*)-α-Amino acid	Yield (%)	Ee (%)
6a	Ph	**10a**	88	**7a**	90	>99
6b	^{t}Bu	**10b**	92	**7b**	89	>99
6c	Me	**10c**	90	**7c**	88	>99
6d	*n*-Bu	**10d**	87	**7d**	95	>99
6e	Cy	**10e**	91	**7e**	92	>99
6f	^{i}Pr	**10f**	90	**7f**	91	>99

a VG Micromass ZAB 1F, a VG Masslab 20–250, a GCMS Trio 1, a VG BIO Q or a APCI Platform spectrometer, with only molecular ions (M^+), fragments from molecular ions and major peaks being reported. Microanalyses were performed by Mrs V. Lamburn or Mr R. Prior, Dyson Perrins Laboratory, University of Oxford. Column chromatography was performed on silica gel (Kieselgel 60). Anhydrous THF was obtained by distillation from sodium–benzophenone ketyl under nitrogen. Unless otherwise stated all reactions were performed and worked-up under a nitrogen atmosphere. (*S*)-Isopropylpiperazine-2,5-dione was prepared according to the literature procedure.[3b]

(3*S*)-*N*,*N*′-Bis(4-methoxybenzyl)-3-methylene-6-isopropylpiperazine-2,5-dione 8

To a stirred solution of **1** (5.0 g, 12.6 mmol) in anhydrous THF (20 ml) at −78 °C was added a solution of *n*-butyllithium in hexanes (8.25 ml, 1.53 M, 12.6 mmol) at −78 °C, over a period of two minutes. The resultant solution was allowed to stir at −78 °C for a further 15 minutes prior to the addition of solid paraformaldehyde (*ca*. 10 g) and subsequent removal of the cooling bath. The resultant suspension was then heated at 70 °C for one hour, cooled, water (3 ml) added and the mixture was partitioned between ether and water, extracted with ether and the organic phase dried ($MgSO_4$); the solvents were removed *in vacuo*. Filtration through a short stub of silica using ether as the eluent and removal of the solvents *in vacuo* afforded the *title compound* **8** as a thick, pale yellow coloured gum that was used without further purification (4.72 g, 91%). Mp 88–90 °C; $[a]_D^{23}$ −129.4 (*c* 2.30, $CHCl_3$); ν_{max} (KBr)/cm^{-1} 2993, 2962, 2930, 2835, 1677 (s, C=O), 1617 (s, C=O), 1514, 1253; δ_H (500 MHz, $CDCl_3$) 0.90 (3H, d, *J* 6.8, C*H*$_3$CHCH$_3$), 1.04 (3H, d, *J* 6.8, CH$_3$CHC*H*$_3$), 2.24 (1H, m, CH$_3$C*H*CH$_3$), 3.78 (3H, s, OC*H*$_3$), 3.80 (3H, s, OC*H*$_3$), 3.89 (1H, d, *J* 7.5, 3-*H*), 3.93 (1H, d, *J* 14.7, ArC*H*$_2$), 4.58 (1H, d, *J* 14.8, ArC*H*$_2$), 5.02 (1H, d, *J* 1.1, 6-C=C*H*$_A$H$_B$), 5.13 (1H, d, *J* 14.7, ArC*H*$_2$), 5.40 (1H, d, *J* 14.8, ArC*H*$_2$), 5.81 (1H, d, *J* 1.1, 6-C=CH$_A$*H*$_B$), 6.80–6.89 (4H, m, aromatic C*H*), 7.15–7.20 (4H, m, aromatic C*H*); δ_C (125 MHz, $CDCl_3$) 17.4, 19.4, 32.7, 46.9, 48.0, 55.2 (×2), 64.4, 104.3, 114.2, 114.3, 127.5, 128.5, 129.6, 137.4, 158.9, 159.3, 159.5 (C=O), 164.3 (C=O); *m*/*z* (CI) 409 (MH^+, 40%) (Found: MH^+, 409.2127. $C_{24}H_{29}N_2O_4^+$ requires 409.2127).

General procedure I: conjugate additions

To a flame dried Schlenk tube charged with anhydrous copper(I) cyanide (267 mg, 2.94 mmol) and anhydrous THF (20 ml) at −78 °C under a nitrogen atmosphere was added the alkyllithium or Grignard reagent (5.88 mmol). The suspension was allowed to stir at −78 °C for 5 min prior to the removal of the cooling bath. The mixture was allowed to slowly warm to *ca*. −20 °C by which time it had become homogeneous. This mixture was then recooled to −78 °C and BF_3·OEt_2 (0.24 ml, 2.45 mmol) added and the reaction stirred for 10 minutes at −78 °C. Then **8** (1.00 g, 2.45 mmol) was added, the reaction stirred for 2 h at −78 °C and then allowed to warm to room temperature over 4–5 h. The reaction mixture was quenched with saturated aqueous NH_4Cl (*ca*. 15 ml), extracted with ether (5 ml), then ethyl acetate (2 × 5 ml) and the combined organic phases were washed with water (5 ml), dried ($MgSO_4$), and the solvents removed *in vacuo*. ^{1}H NMR analysis of the crude reaction products confirmed the de to be >95% in all cases.

(3*S*,6*S*)-*N*,*N*′-Bis(4-methoxybenzyl)-3-isopropyl-6-benzylpiperazine-2,5-dione 6a. Treatment of **8** according to general procedure I using phenyllithium (3.27 ml, 1.8 M in cyclohexane–ether) gave a crude reaction mixture which was chromatographed on silica gel using ethyl acetate–hexane (1 : 5) to afford the *title compound* **6a** as a pale yellow oil (1.05 g, 88%). $[a]_D^{23}$ −234 (*c* 1.00, $CHCl_3$); ν_{max} (KBr)/cm^{-1} 2962, 1666 (s, C=O), 1612, 1513, 1456, 1248; δ_H (500 MHz, $CDCl_3$) 0.99 (3H, d, *J* 6.8, C*H*$_3$CHCH$_3$), 1.05 (3H, d, *J* 6.8, CH$_3$CHC*H*$_3$), 1.86 (1H, dsept, *J* 7.9, 6.8, CH$_3$C*H*CH$_3$), 2.99 (1H, d, *J* 14.7, MeOC$_6$H$_4$C*H*$_2$), 2.99 (1H, dd, *J* 14.0, 8.4, C$_6$H$_5$C*H*$_2$), 3.34 (1H, dd, *J* 14.0, 4.3, C$_6$H$_5$C*H*$_2$), 3.53 (1H, d, *J* 7.9, 3-*H*), 3.69 (3H, s, OC*H*$_3$), 3.71 (3H, s, OC*H*$_3$), 3.71 (1H, d, *J* 14.9, MeOC$_6$H$_4$C*H*$_2$), 4.06 (1H, dd, *J* 8.4, 4.3, 6-*H*), 5.09 (1H, d, *J* 14.7, MeOC$_6$H$_4$C*H*$_2$), 5.32 (1H, d, *J* 14.8, MeOC$_6$H$_4$C*H*$_2$), 6.61–6.70 (4H, m, aromatic C*H*), 6.70–6.75 (2H, m, aromatic C*H*), 6.93–6.97 (2H, m, aromatic C*H*), 7.15–7.18 (2H, m, aromatic C*H*), 7.20–7.30 (3H, m, aromatic C*H*); δ_C (75 MHz, $CDCl_3$) 19.8, 20.9, 33.7, 40.6, 47.0, 49.3, 55.3 (×2), 61.0, 65.3, 114.1, 114.3, 127.4, 127.78, 127.82, 129.0, 129.1, 129.4, 129.5, 129.7, 137.6, 159.2, 159.3, 166.2 (C=O), 167.2 (C=O); *m*/*z* (CI) 487 (MH^+, 100%) (Found: MH^+, 487.2603. $C_{30}H_{35}N_2O_4^+$ requires 487.2596).

(3*S*,6*S*)-*N*,*N*′-Bis(4-methoxybenzyl)-3-isopropyl-6-neopentylpiperazine-2,5-dione 6b. Treatment of **8** according to general procedure I using *tert*-butylmagnesiumchloride (2.94 ml, 2 M in ether) gave a crude reaction mixture from which the *title compound* **6b** was crystallised directly (ethyl acetate–hexane) (1.03 g, 90%). Mp 113–114 °C; $[a]_D^{23}$ −198.6 (*c* 1.00, $CHCl_3$); ν_{max} (KBr)/cm^{-1} 2962, 1657 (s, C=O), 1510, 1245; δ_H (500 MHz, $CDCl_3$) 1.02 (9H, s, C(CH$_3$)$_3$), 1.12 (3H, d, *J* 6.7, C*H*$_3$CHCH$_3$), 1.18 (3H, d, *J* 6.7, CH$_3$CHC*H*$_3$), 1.58 (1H, dd, *J* 14.4, 2.2, C*H*$_2$), 1.98 (1H, dd, *J* 14.4, 8.0, C*H*$_2$), 2.16 (1H, dsept, *J* 8.9, 6.7, CH$_3$C*H*CH$_3$), 3.59 (1H, d, *J* 8.9, 3-*H*), 3.66 (1H, d, *J* 15.0, ArC*H*$_2$), 3.73 (1H, d, *J* 14.8, ArC*H*$_2$), 3.80 (6H, s, 2 × OC*H*$_3$), 3.83 (1H, dd, *J* 8.0, 2.2, 6-*H*), 5.32 (1H, d, *J* 15.0, ArC*H*$_2$), 5.42 (1H, d, *J* 14.8, ArC*H*$_2$), 6.78–6.84 (4H, m, aromatic C*H*), 6.98–7.04 (2H, m, aromatic C*H*), 7.15–7.09 (2H, m, aromatic C*H*); δ_C (125 MHz, $CDCl_3$) 20.0, 20.6, 29.7 (×3), 30.9, 33.8, 45.9, 49.6, 50.0, 55.2 (×2), 56.0, 65.9, 114.4, 128.1, 128.3, 129.1, 129.3, 159.4, 159.5, 167.1 (C=O), 169.9 (C=O); *m*/*z* (CI) 467 (MH^+, 100%) (Found: MH^+, 467.2908. $C_{28}H_{39}N_2O_4^+$ requires 467.2909).

(3*S*,6*S*)-*N*,*N*′-Bis(4-methoxybenzyl)-3-isopropyl-6-ethylpiperazine-2,5-dione 6c. Treatment of **8** according to general procedure I using methyllithium·LiBr (4.2 ml, 1.4 M in ether) gave a crude reaction mixture which was chromatographed on silica gel using 1 : 5 ethyl acetate–hexane to afford the *title compound* **6c** as an oil (945 mg, 91%). $[a]_D^{23}$ −178.2 (*c* 1.00, $CHCl_3$); ν_{max} (KBr)/cm^{-1} 2965, 1660 (s, C=O), 1612, 1459, 1248; δ_H (500 MHz, $CDCl_3$) 1.10 (3H, d, *J* 6.9, C*H*$_3$CHCH$_3$), 1.14 (3H, t, *J* 7.6, CH$_2$C*H*$_3$), 1.18 (3H, d, *J* 6.9, CH$_3$CHC*H*$_3$), 1.92 (2H, m, C*H*$_2$CH$_3$), 2.18 (1H, dsept, *J* 7.2, 6.8, CH$_3$C*H*CH$_3$), 3.67 (1H, d, *J* 7.2, 3-*H*), 3.78 (1H, t, *J* 6.8, 6-*H*), 3.81 (6H, s, 2 × OC*H*$_3$), 3.83

(1H, d, *J* 14.8, $ArCH_2$), 3.90 (1H, d, *J* 14.7, $ArCH_2$), 5.19 (1H, d, *J* 14.7, $ArCH_2$), 5.37 (1H, d, *J* 14.8, $ArCH_2$), 6.80–6.86 (4H, m, aromatic CH), 7.06–7.15 (4H, m, aromatic CH); δ_C (75 MHz, $CDCl_3$) 12.0, 19.6, 20.7, 27.4, 33.2, 47.1, 48.8, 55.2 (×2), 60.6, 65.1, 114.2, 127.9, 128.0, 129.2, 129.4, 159.2, 165.9 (C=O), 167.2 (C=O); *m*/*z* (CI) 425 (MH^+, 100%) (Found: MH^+, 425.2441. $C_{25}H_{33}N_2O_4^+$ requires 425.2440).

(3*S*,6*S*)-*N*,*N*′-Bis(4-methoxybenzyl)-3-isopropyl-6-*n*-pentylpiperazine-2,5-dione 6d. Treatment of **8** according to general procedure I using butyllithium (3.68 ml, 1.6 M in hexanes) gave a crude reaction mixture from which the *title compound* **6d** was crystallised (ether–hexane) (1.04 g, 91%). Mp 70 °C; $[\alpha]_D^{21}$ −186.7 (*c* 1.00, $CHCl_3$); ν_{max} (KBr)/cm^{-1} 1652 (s, C=O), 1515, 1468, 1252; δ_H (500 MHz, $CDCl_3$) 0.89 (3H, t, *J* 7.0, CH_2CH_3), 1.08 (3H, d, *J* 6.9, CH_3CHCH_3), 1.16 (3H, d, *J* 6.9, CH_3CHCH_3), 1.21–1.36 (4H, m, $(-CH_2-)_2$), 1.43–1.54 (1H, m, CH_2), 1.56–1.65 (1H, m, CH_2), 1.74–1.92 (2H, m, CH_2), 2.16 (1H, dsept, *J* 7.3, 6.9, CH_3CHCH_3), 3.64 (1H, d, *J* 7.3, 3-*H*), 3.79 (1H, d, *J* 14.7, $ArCH_2$), 3.79 (6H, s, 2 × OCH_3), 3.80 (1H, dd, *J* 8.3, 7.0, 6-*H*), 3.87 (1H, d, *J* 14.7, $ArCH_2$), 5.17 (1H, d, *J* 14.7, $ArCH_2$), 5.37 (1H, d, *J* 14.7, $ArCH_2$), 6.80–6.84 (4H, m, aromatic CH), 7.04–7.11 (4H, m, aromatic CH); δ_C (75 MHz, $CDCl_3$) 14.0, 19.7, 20.7, 22.4, 27.1, 31.5, 33.3, 34.4, 47.1, 48.8, 55.3 (×2), 59.3, 65.1, 114.2, 127.9, 128.1, 129.2, 129.4, 159.2, 159.3, 165.9 (C=O), 167.5 (C=O); *m*/*z* (CI) 467 (MH^+, 100%) (Found: MH^+, 467.2906. $C_{28}H_{39}N_2O_4^+$ requires 467.2909).

(3*S*,6*S*)-*N*,*N*′-Bis(4-methoxybenzyl)-3-isopropyl-6-(cyclohexylmethyl)piperazine-2,5-dione 6e. Treatment of **8** according to general procedure I with cyclohexylmagnesium chloride (2.94 ml, 2 M in ether) gave a crude reaction mixture which was chromatographed on silica gel using 1 : 5 ethyl acetate–hexane to afford the *title compound* **6e** as a clear oil (1.11 g, 92%). $[\alpha]_D^{23}$ −159.4 (*c* 1.00, $CHCl_3$); ν_{max} (KBr)/cm^{-1} 2924, 2850, 1661 (s, C=O), 1513, 1248; δ_H (500 MHz, $CDCl_3$) 0.80–1.00 (2H, m, $(CH_2)_n$), 1.11 (3H, d, *J* 6.8, CH_3CHCH_3), 1.15–1.40 (6H, m, $(CH_2)_n$), 1.18 (3H, d, *J* 6.8, CH_3CHCH_3), 1.51–1.92 (5H, m, $(CH_2)_n$), 2.18 (1H, dsept, 7.6, 6.8, CH_3CHCH_3), 3.66 (1H, d, *J* 7.6, 3-*H*), 3.78 (1H, d, *J* 14.8, $ArCH_2$), 3.79 (1H, d, *J* 14.8, $ArCH_2$), 3.81 (6H, s, 2 × OCH_3), 3.91 (1H, dd, *J* 9.2, 3.8, 6-*H*), 5.22 (1H, d, 14.8, $ArCH_2$), 5.40 (1H, d, *J* 14.8, $ArCH_2$), 6.81–6.85 (4H, m, aromatic CH), 7.05–7.10 (4H, m, aromatic CH); δ_C (125 MHz, $CDCl_3$) 19.8, 20.6, 25.9, 26.0, 26.3, 32.5, 33.4, 33.8, 35.0, 42.4, 46.6, 48.9, 55.2 (×2), 56.4, 65.3, 114.1, 127.9, 128.0, 129.1, 129.2, 159.2, 166.1 (C=O), 167.8 (C=O); *m*/*z* (CI) 493 (MH^+, 100%) (Found: MH^+, 493.3065. $C_{30}H_{41}N_2O_4^+$ requires 493.3066).

(3*S*,6*S*)-*N*,*N*′-Bis(4-methoxybenzyl)-3-isopropyl-6-isobutylpiperazine-2,5-dione 6f. Treatment of **8** according to general procedure I with isopropylmagnesiumbromide (2.94 ml, 2 M in THF) gave a crude reaction mixture which was chromatographed on silica gel using 1 : 5 ethyl acetate–hexane to afford the *title compound* **6f** as a viscous oil (978 mg, 88%). $[\alpha]_D^{23}$ −208.3 (*c* 1.00, $CHCl_3$); ν_{max} (KBr)/cm^{-1} 1661 (s, C=O), 1513, 1247; δ_H (500 MHz, $CDCl_3$) 0.98 (3H, d, *J* 6.6, CH_3CHCH_3), 0.99 (3H, d, *J* 6.5, CH_3CHCH_3), 1.11 (3H, d, *J* 6.8, CH_3CHCH_3), 1.19 (3H, d, *J* 6.9, CH_3CHCH_3), 1.56 (1H, ddd, *J* 13.8, 9.1, 4.1, 6–CH–CH_2), 1.86 (1H, ddd, *J* 13.8, 9.2, 5.3, 6–CH–CH_2), 1.95–2.06 (1H, m, CH_3CHCH_3), 2.18 (1H, dsept, *J* 7.6, 6.9, CH_3CHCH_3), 3.66 (1H, d, *J* 7.6, 3-*H*), 3.79 (1H, d, *J* 14.8, $ArCH_2$), 3.80 (1H, d, *J* 14.8, $ArCH_2$), 3.82 (6H, s, 2 × OCH_3), 3.88 (1H, dd, *J* 9.2, 4.1, 6-*H*), 5.24 (1H, d, *J* 14.8, $ArCH_2$), 5.40 (1H, d, *J* 14.8, $ArCH_2$), 6.80–6.90 (4H, m, aromatic CH), 7.05–7.13 (4H, m, aromatic CH); δ_C (125 MHz, $CDCl_3$) 19.9, 20.8, 21.9, 23.2, 26.0, 33.4, 44.0, 46.7, 49.0, 55.3 (×2), 57.3, 65.3, 114.3, 128.0, 128.2, 129.2, 129.4, 159.3, 166.1, 167.8; *m*/*z* (CI) 453 (MH^+, 100%) (Found: MH^+, 453.2747. $C_{27}H_{37}N_2O_4^+$ requires 453.2753).

General procedure II: deprotection of 6a–f

To a solution of **6a–f** (~1.0 g) in water (6 ml) and acetonitrile (18 ml) was added ceric ammonium nitrate (6 equiv.) in one portion. The resultant suspension was stirred at room temperature for one hour, neutral alumina added (*ca*. 1 g), the solvent removed *in vacuo*, and the crude residue applied to a column of neutral alumina (gradient elution EtOAc⟶EtOAc–EtOH 4 : 1) to afford **10a–f**.

(3*S*,6*S*)-3-Isopropyl-6-benzylpiperazine-2,5-dione 10a. Deprotection of **6a** (910 mg, 1.87 mmol) by general procedure II using CAN (6.14 g, 11.2 mmol) gave the *title compound* **10a** as a colourless solid (405 mg, 88%). Mp 263–265 °C; $[\alpha]_D^{23}$ −65.9 (*c* 0.50, AcOH); ν_{max} (KBr)/cm^{-1} 3438, 3317, 3193, 3086, 3059, 2966, 2930, 2887, 1669 (s, C=O), 1453; δ_H (500 MHz, DMSO-d_6) 0.27 (3H, d, *J* 6.8, CH_3CHCH_3), 0.66 (3H, d, *J* 7.1, CH_3CHCH_3), 1.71 (1H, dsept, *J* 4.5, 6.8, CH_3CHCH_3), 2.88 (1H, dd, *J* 13.5, 5.0, $C_6H_5CH_AH_B$), 3.16 (1H, dd, *J* 13.5, 4.3, $C_6H_5CH_AH_B$), 3.52–3.56 (1H, m, 3-*H*), 4.20–4.23 (1H, m, 6-*H*), 7.16–7.21 (3H, m, aromatic CH), 7.23–7.28 (2H, m, aromatic CH), 7.92 (1H, br s, NH), 8.12 (1H, br s, NH); δ_C (50 MHz, DMSO-d_6) 16.1, 18.2, 31.0, 37.8, 55.0, 59.2, 126.5, 127.9, 130.3, 136.3, 166.4, 166.5; *m*/*z* (CI) 247 (MH^+, 100%) (Found: MH^+, 247.1440. $C_{14}H_{19}N_2O_2$ requires 247.1446).

(3*S*,6*S*)-3-Isopropyl-6-neopentylpiperazine-2,5-dione 10b. Deprotection of **6b** (1.00 g, 2.14 mmol) by general procedure II using CAN (7.06 g, 12.8 mmol) gave the *title compound* **10b** (445 mg, 92%). Mp 205 °C (sub.); $[\alpha]_D^{23}$ −53.0 (*c* 0.94, AcOH); ν_{max} (KBr)/cm^{-1} 3321, 3198, 3091, 3038, 2962, 2874, 1679 (s, C=O), 1457; δ_H (500 MHz, DMSO-d_6) 0.82 (3H, d, *J* 6.8, CH_3CHCH_3), 0.88 (9H, s, $C(CH_3)_3$), 0.92 (3H, d, *J* 7.0, CH_3CHCH_3), 1.37 (1H, dd, *J* 14.1, 7.5, CH_2), 1.84 (1H, dd, *J* 14.1, 3.4, CH_2), 2.00–2.02 (1H, m, CH_3CHCH_3), 3.50–3.75 (1H, m, 3-*H*), 3.64–3.78 (1H, m, 6-*H*), 7.92 (1H, br s, NH), 8.08 (1H, br s, NH); δ_C (50 MHz, DMSO-d_6) 17.7, 18.8, 29.4 (×3), 30.4, 31.2, 48.0, 52.0, 59.8, 167.8 (C=O), 169.8 (C=O); *m*/*z* (CI) 227 (MH^+, 100%) (Found: MH^+, 227.1751. $C_{12}H_{23}N_2O_2$ requires 227.1759).

(3*S*,6*S*)-3-Isopropyl-6-ethylpiperazine-2,5-dione 10c. Deprotection of **6c** (870 mg, 2.05 mmol) by general procedure II using CAN (6.75 g, 12.3 mmol) gave the *title compound* **10c** (339 mg, 90%). Mp 210 °C (sub.); $[\alpha]_D^{23}$ −41.5 (*c* 1.00, AcOH); ν_{max} (KBr)/cm^{-1} 3320, 3194, 3057, 2967, 2880, 1665 (s, C=O), 1451; δ_H (500 MHz, DMSO-d_6) 0.83 (3H, d, *J* 6.9, CH_3CHCH_3), 0.85 (3H, t, *J* 7.4, CH_2CH_3), 0.94 (3H, d, *J* 7.1, CH_3CHCH_3), 1.69 (2H, m, CH_2CH_3), 2.17 (1H, m, CH_3CHCH_3), 3.68 (1H, m, 3-*H*), 3.79 (1H, m, 6-*H*), 8.00 (1H, br s, NH), 8.12 (1H, br s, NH); δ_C (125 MHz, DMSO-d_6) 9.2, 17.0, 18.5, 26.2, 31.0, 54.8, 59.3, 167.0, 167.8; *m*/*z* (CI) 185 (MH^+, 100%) (Found: MH^+, 185.1289. $C_9H_{17}N_2O_2$ requires 185.1290).

(3*S*,6*S*)-3-Isopropyl-6-*n*-pentylpiperazine-2,5-dione 10d. Deprotection of **6d** (907 mg, 1.95 mmol) by general procedure II using CAN (6.40 g, 11.7 mmol) gave the *title compound* **10d** (383 mg, 87%). Mp 236 °C; $[\alpha]_D^{23}$ −36.2 (*c* 0.91, AcOH); ν_{max} (KBr)/cm^{-1} 3324, 3199, 3091, 3038, 2961, 2876, 1456; δ_H (500 MHz, DMSO-d_6) 0.82–0.89 (6H, m, CH_2CH_3 and CH_3CHCH_3), 0.95 (3H, d, *J* 7.1, CH_3CHCH_3), 1.15–1.45 (6H, m, 3 × CH_2), 1.55–1.80 (2H, m, CH_2), 2.10–2.25 (1H, m, CH_3CHCH_3), 3.67–3.70 (1H, m, 3-*H*), 3.80–3.82 (1H, m, 6-*H*), 8.00 (1H, s, NH), 8.13 (1H, s, NH); δ_C (75 MHz, DMSO-d_6) 14.0, 17.3, 18.8, 22.2, 24.2, 31.2, 31.4, 33.7, 54.1, 59.5, 167.1, 168.2; *m*/*z* (CI) 227 (MH^+, 100%) (Found: MH^+, 227.1757. $C_{12}H_{23}N_2O_2$ requires 227.1759).

(3*S*,6*S*)-3-Isopropyl-6-(cyclohexylmethyl)piperazine-2,5-dione 10e. Deprotection of **6e** (1.46 g, 2.97 mmol) by general procedure II using CAN (9.76 g, 17.8 mmol) gave the *title compound* **10e** (748 mg, 91%). Mp 227 °C (sub.); $[\alpha]_D^{23}$ −37.8 (*c* 1.10, AcOH); ν_{max} (KBr)/cm^{-1} 3193, 3056, 2963, 2925, 2853, 1665 (s, C=O), 1449; δ_H (500 MHz, DMSO-d_6) 0.80–1.0 (2H, m, CH_2), 1.11–1.30 (4H, m, 2 × CH_2), 1.45–1.81 (7H, m, 3 × CH_2 and CH_2CHCH_2), 0.89 (3H, d, *J* 6.8, CH_3CHCH_3), 0.99 (3H, d, *J* 7.0, CH_3CHCH_3), 2.10–2.20 (1H, m, CH_3CHCH_3), 3.64–3.68 (1H, m, 3-*H*), 3.82–3.86 (1H, m, 6-*H*), 8.06 (1H, br s, N*H*), 8.20 (1H, br s, N*H*); δ_C (125 MHz, DMSO-d_6) 17.3, 18.7, 25.5, 25.8, 26.0, 31.4, 32.0, 32.6, 33.4, 42.2, 51.7, 59.5, 166.8, 168.5; *m*/*z* (CI) 253 (MH^+, 100%) (Found: MH^+, 253.1915. $C_{14}H_{25}N_2O_2$ requires 253.1916).

(3*S*,6*S*)-3-Isopropyl-6-isobutylpiperazine-2,5-dione 10f. Deprotection of **6f** (817 mg, 1.81 mmol) by general procedure II using CAN (5.94 g, 10.8 mmol) gave the *title compound* **10f** (345 mg, 90%). Mp 212 °C (sub.); $[\alpha]_D^{23}$ −55.1 (*c* 0.90, AcOH); ν_{max} (KBr)/cm^{-1} 3276, 3196, 3058, 2962, 2874, 2875, 1666 (C=O), 1453; δ_H (500 MHz, DMSO-d_6) 0.85 (3H, d, *J* 6.9, CH_3CHCH_3), 0.87 (3H, d, *J* 6.8, CH_3CHCH_3), 0.89 (3H, d, *J* 7.0, CH_3CHCH_3), 1.00 (3H, d, *J* 6.9, CH_3CHCH_3), 1.45–1.52 (1H, m, CH_2), 1.68–1.73 (1H, m, CH_2), 1.80–1.85 (1H, m, CH_3CHCH_3), 2.10–2.15 (1H, m, CH_3CHCH_3), 3.65–3.70 (1H, m, 3-*H*), 3.76–3.80 (1H, m, 6-*H*), 8.20 (1H, br s, N*H*), 8.47 (1H, br s, N*H*); δ_C (125 MHz, DMSO-d_6) 17.3, 18.7, 21.7, 23.1, 23.5, 31.4, 43.9, 52.3, 59.5, 166.8, 168.4; *m*/*z* (CI) 213 (MH^+, 100%) (Found: MH^+, 213.1602. $C_{11}H_{21}N_2O_2$ requires 213.1602).

General procedure III: isolation of amino acid hydrochloride salts

A solution of **10a**–**f** (200–500 mg) was refluxed in 6 M HCl (60 ml) overnight and the solvent was removed *in vacuo*. The resultant mixture of amino acid hydrochloric acid salts was refluxed in methanolic HCl for 2 hours. The solvents were removed to afford a residue which was neutralised with $NaHCO_3$ (aq), extracted with CH_2Cl_2 (3 × 30 ml), dried ($MgSO_4$), and the solvents again removed *in vacuo* (**Warning**: amino acid methyl esters volatile) to give a mixture of (*S*)-valine methyl ester and the appropriate amino acid methyl ester **12a**–**f**. The (*S*)-α-amino esters **12a**, **12b**, **12d**, and **12e** were purified by fractional distillation/removal of the more volatile (*S*)-valine methyl ester under high vacuum at *ca*. 40 °C for 30 minutes. The volatile and (*S*)-α-amino acid methyl esters **12c** and **12f** were purified by chromatography on silica using ethyl acetate–hexanes (3 : 7) as eluent and the solvent carefully removed *in vacuo*. The resultant amino esters were then heated in 6 M HCl under reflux for 30 minutes, and the solvents evaporated *in vacuo* to yield the parent α-amino acids as their HCl salts.

The enantiomeric excess of the (*S*)-α-amino acids was determined by chiral HPLC analysis by either method A or method B.

Method A. Benzyl chloroformate (0.15 ml) and triethylamine (0.15 ml) were added to the amino acid hydrochloride (50 mg) in dioxane (1 ml) and the mixture was stirred at room temperature for 1 hour. This crude mixture was analysed by HPLC using a Cyclobond™ I 2000 RSP (β-cyclodextrin hydroxypropyl capped bonded stationary phase) column eluting with [6–15 : 94–85 CH_3CN–TEAA (1–1.5%)] with UV detection at 210 nm. The ee was determined by integration of signals and comparison of the retention times of the synthetic material and commercially available or similarly prepared racemic Cbz-α-amino acids.

Method B. The amino acid hydrochloride was analysed by HPLC using a Chirobiotic I column eluting with 33–50% water–ethanol with UV detection at 190 nm. The ee was determined by integration of signals and comparison of the retention times of synthetic and commercially available racemic amino acid hydrochlorides.

(*S*)-Phenylalanine hydrochloride 7a. Treatment of **10a** (200 mg) by general procedure III gave **7a** (147 mg, 90%). δ_H (200 MHz, D_2O) 3.15 (1H, dd, *J* 14.5, 7.7, CH_2), 3.28 (1H, dd, *J* 14.7, 5.9, CH_2), 4.29 (1H, dd, *J* 7.2, 5.9, NC*H*), 7.21–7.38 (5H, m, aromatic C*H*); ee > 99% method B; $[\alpha]_D^{23}$ −8.2 (*c* 1.00, H_2O).

(*S*)-2-Amino-4,4-dimethylpentanoic acid hydrochloride 7b. Treatment of **10b** (500 mg) by general procedure III gave **7b** (354 mg, 89%). δ_H (200 MHz, D_2O) 0.72 (9H, s, $C(CH_3)_3$), 1.40 (1H, dd, *J* 14.8, 7.4, CH_2), 1.68 (1H, br dd, *J* 14.9, 4.8, CH_2), 3.47–3.52 (1H, m, NC*H*); ee > 99% method A; $[\alpha]_D^{23}$ +4.7 (*c* 1.00, H_2O) [lit.[12] +4.2 (*c* 8.5 in H_2O)].

(*S*)-2-Aminobutyric acid hydrochloride 7c. Treatment of **10c** (200 mg) by general procedure III gave **7c** (132 mg, 88%). δ_H (200 MHz, D_2O) 0.86 (3H, t, *J* 7.5, CH_3), 1.75–1.93 (2H, m, CH_2), 3.86 (1H, t, *J* 6.3, NC*H*); ee > 99% method A; $[\alpha]_D^{23}$ +12.9 (*c* 1.00, H_2O) [lit.[11] +10.1 (*c* 1.11 in H_2O)].

(*S*)-2-Aminoheptanoic acid hydrochloride 7d. Treatment of **10d** (200 mg) by general procedure III gave **7d** (130 mg, 88%). δ_H (200 MHz, D_2O) 0.92–1.44 (15H, m, CH_3 and $(CH_2)_3$), 3.46–3.54 (1H, m, NC*H*); ee > 99% method B; $[\alpha]_D^{23}$ +4.9 (*c* 0.20, H_2O) [lit.[11] +4.4 (*c* 0.2 in H_2O)].

(*S*)-2-Amino-3-cyclohexylpropanoic acid hydrochloride 7e. Treatment of **10e** (200 mg) by general procedure III gave **7e** (151 mg, 92%). δ_H (200 MHz, D_2O) 0.66–0.86 (2H, m, CH_2), 0.90–1.17 (3H, m, CH_2), 1.20–1.23 (1H, m, CH_2), 1.37–1.59 (6H, m, CH_2), 1.63–1.66 (1H, m, CH_2), 3.84 (1H, dd, *J* 8.6, 5.4, NC*H*); ee > 99% method A; $[\alpha]_D^{23}$ +3.1 (*c* 1.00, H_2O) [lit.[12] +3.4 (*c* 0.5 in H_2O)].

(*S*)-Leucine hydrochloride 7f. Treatment of **10f** (200 mg) by general procedure III gave **7f** (157 mg, 91%). δ_H (200 MHz, D_2O) 0.89 (3H, d, *J* 7.0, CH_3CHCH_3), 0.93 (3H, d, *J* 7.0, CH_3CHCH_3), 1.54–1.75 (3H, m, CH_2CH), 3.86–3.89 (1H, m, NC*H*); ee > 99% method B; $[\alpha]_D^{23}$ +3.0 (*c* 1.00, H_2O) [lit.[12] +2.8 (*c* 0.6 in H_2O)].

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