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Asymmetric conjugate reductions with samarium diiodide: asymmetric synthesis of (2*S*,3*R*)- and (2*S*,3*S*)-[2-^{2}H,3-^{2}H]-leucine-(*S*)-phenylalanine dipeptides and (2*S*,3*R*)-[2-^{2}H,3-^{2}H]-phenylalanine methyl ester

Stephen G. Davies,* Humberto Rodríguez-Solla, Juan A. Tamayo, Andrew R. Cowley, Carmen Concellón, A. Christopher Garner, Alastair L. Parkes and Andrew D. Smith

Department of Organic Chemistry, University of Oxford, Chemistry Research Laboratory, 12 Mansfield Road, Oxford, UK OX1 3TA. E-mail: steve.davies@chem.ox.ac.uk

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The highly diastereoselective samarium diiodide and D_2O-promoted conjugate reduction of homochiral (*E*)- and (*Z*)-benzylidene and isobutylidene diketopiperazines (*E*)-**5,7** and (*Z*)-**6,8** has been demonstrated. This methodology allows the asymmetric synthesis of methyl (2*S*,3*R*)-dideuteriophenylalanine **27** in ≥95% de and >98% ee, and (2*S*,3*R*)- or (2*S*,3*S*)-dideuterioleucine-(*S*)-phenylalanine dipeptides **37** and **38** in moderate de, 66% and 74% respectively. A mechanism is proposed to account for this process.

Introduction

The incorporation of isotopically labelled α-amino acid residues into proteins has become a vital tool in the determination of protein structure by NMR techniques. The indiscriminate incorporation of the NMR active isotopes ^{15}N and ^{13}C enables the effective employment of heteronuclear correlation experiments, while the incorporation of ^{2}H simplifies the assignment of the residual ^{1}H resonances facilitating structural determination through the interpretation of NOE data. Within this context, the incorporation of regio- and stereoselectively deuterated α-amino acids into polypeptides is a powerful tool in the structural determination of large biomolecules.[1] The asymmetric synthesis of residues which are stereoselectively deuterated at the α position has been reported,[2] along with the asymmetric synthesis of residues stereoselectively labelled in both the side chain and the α and β positions.[3] Side chain isotopically labelled α-amino acids have also found utility as valuable probes into biosynthetic pathways.[4]

Previous work from this laboratory has demonstrated the utility of diketopiperazine enolate **1**, prepared by conjugate addition to the methylene diketopiperazine **2** or deprotonation of a substituted diketopiperazine **3**, for the asymmetric synthesis of (*S*)-α-amino acids *via* stereoselective protonation[5] (Fig. 1).

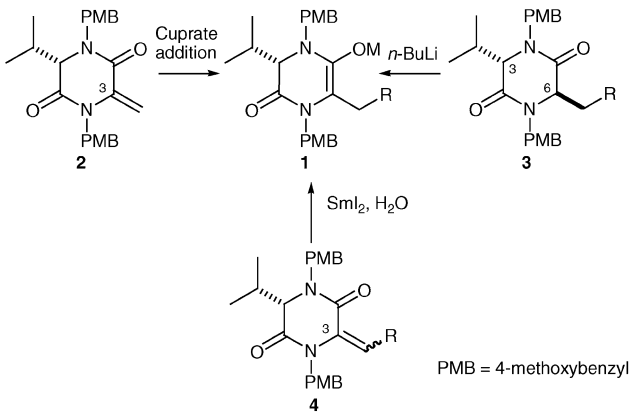

Fig. 1 Generation of substituted diketopiperazine enolates.

In seeking to develop reductive processes to extend this methodology we have noted that samarium diiodide[6] promotes the reduction of the C=C double bond of α,β-unsaturated esters and amides, and while additives such as *N*,*N*-dimethylacetamide[7] or HMPA[8] are typically required to facilitate this reaction, Concellón *et al.* have recently shown that conjugate reductions can be carried out using SmI_2 and either H_2O or D_2O.[9,10] Although the diastereoselective conjugate reduction of α,β-unsaturated carbonyl systems using this methodology has received only minimal attention, it was envisaged that the reductive deuteration of an alkylidene diketopiperazine template[11] has the potential to stereoselectively generate two new stereogenic centres and provide a route to α,β-dideuterated α-amino acids. We report herein full studies concerning the conjugate reduction of diketopiperazine enamide template **4** and studies into the mechanism and scope of the reaction. Part of this work has been previously communicated.[12]

Results and discussion

To examine the potential for diastereoselective reductive deuteration of diketopiperazine enamides, initial studies focused on the preparation of the diastereoisomeric 3-benzylidene and 3-isobutylidene substituted templates, (*E*)-**5**, (*Z*)-**6**, (*E*)-**7** and (*Z*)-**8**. It was envisaged that the (*E*)-diastereoisomers **5** and **7** could be prepared utilising Horner–Wadsworth–Emmons (HWE) methodology from a diketopiperazine phosphonate reagent.[13] (2*S*,5*S*)-Chloro **9**, prepared from **10** *via* an electrophilic fluorination and transhalogenation protocol,[14] was treated with triethylphosphite to give a 67 : 33 mixture of *cis*-(2*S*,5*S*)-phosphonate **11** and *trans*-(2*R*,5*S*)-phosphonate **12** in a 60% combined yield over three steps (Scheme 1). Chromatographic separation of this mixture afforded *cis*-(2*S*,5*S*)-**11** and a 20 : 80 mixture of *cis*-(2*S*,5*S*)-**11** and *trans*-(2*R*,5*S*)-**12**, respectively. On standing, *trans*-**12** partially epimerised to *cis*-**11**, and data for the minor isomer *trans*-**12** were obtained from the 20 : 80 mixture of **11** and **12**. The relative configuration within *cis*-(2*S*,5*S*)-**11** was evident from ^{1}H NMR spectroscopic data[15] and supported by ^{1}H NMR NOE difference experiments (Fig. 2).

The HWE reaction of phosphonate **11** with benzaldehyde and isobutyraldehyde proceeded with high levels of *E* stereoselectivity affording (*E*)-3-ylidenes **5** and **7** in >98% and 97% de and 63% and 67% yield respectively after chromatography (Scheme 2). The (*E*)-double bond geometry of **5** and **7** was established from ^{1}H NMR NOESY data with correlations between both the benzylic and the *ortho*-aromatic hydrogen resonances of the *N*-4-*p*-methoxybenzyl group upon irradiation of the double bond CH. The assigned double bond geometry of **7** was unequivocally confirmed by X-ray crystallographic analysis

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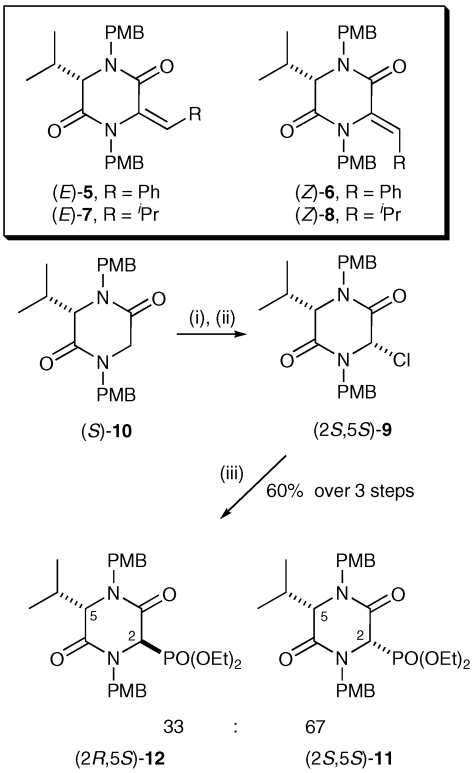


Scheme 1 *Reagents and conditions*: (i) LHMDS, THF, −78 °C, $(PhSO_2)_2NF$; (ii) TMSCl, CH_2Cl_2, room temperature; (iii) $P(OEt)_3$, room temperature, 3 d.

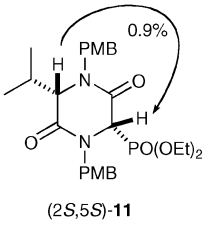
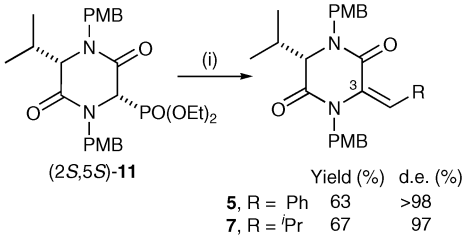
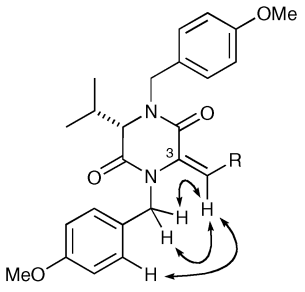


Fig. 2 Selected ^{1}H NMR NOE difference enhancement for **11**.



Scheme 2 *Reagents and conditions*: (i) NaH, PhCHO or ^{i}PrCHO, THF, 0 °C.

(Fig. 3). The diastereoselectivity in these thermodynamically controlled reactions presumably derives from the steric demand imposed by the *N*-4-*p*-methoxybenzyl *N* protecting group which disfavours the *Z* isomers.



Selected ^{1}H NMR NOESY correlations for **5** and **7**.

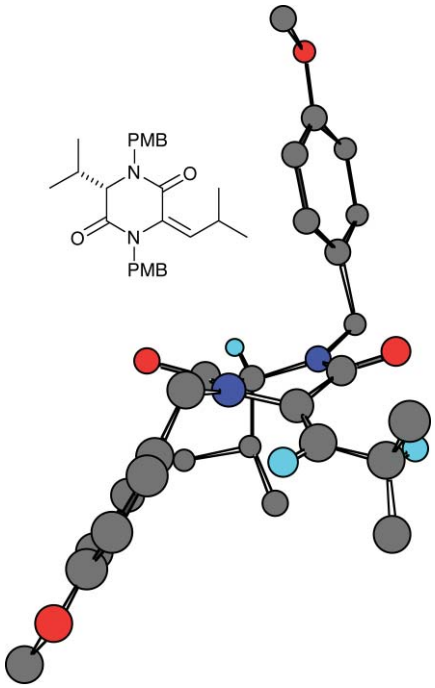
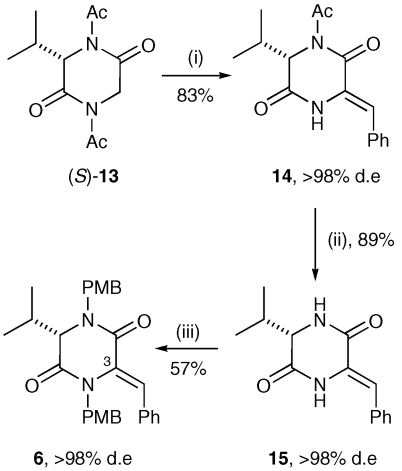


Fig. 3 Chem 3D® representation of the X-ray crystal structure of (3*E*,6*S*)-**7** (some H omitted for clarity).

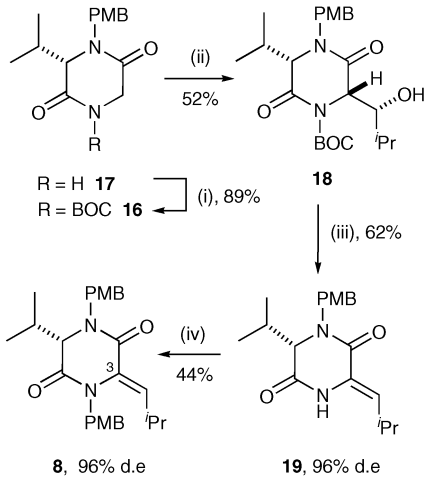
Attention then turned to the preparation of the corresponding *Z*-alkylidene templates **6** and **8**. Benzylidene **6** was prepared from *N*,*N*′-diacetyl-diketopiperazine **13** *via* a modified literature procedure.[16] The potassium *tert*-butoxide mediated aldol condensation of diacetyl **13** with benzaldehyde proceeded with concomitant *N*-4 deacylation and elimination to afford (3*Z*,6*S*)-3-isobutylidene **14** in >98% de, which was subsequently *N*-1 deacylated to afford **15** in >98% de and 74% yield over 2 steps. *N*-Alkylation at *N*-1 and *N*-4 with sodium hydride and *p*-methoxybenzyl chloride then gave (3*Z*,6*S*)-**6** in 57% yield (Scheme 3).



Scheme 3 *Reagents and conditions*: (i) ^{t}BuOK, PhCHO, THF; (ii) NaOH, MeOH; (iii) *p*-methoxybenzyl chloride, NaH, DMF.

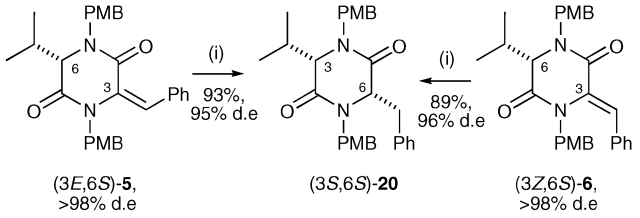
Unfortunately similar treatment of diacetyl **13** with potassium *tert*-butoxide and isobutyraldehyde gave complex mixtures of unidentified material and therefore the aldol condensation of a template bearing alternative *N*-protection was investigated. *N*-1-Boc-*N*-4-*p*-methoxybenzyl **16** was prepared from the *N*-4-*p*-methoxybenzyl **17**[17] by treatment with $(Boc)_2O$ and DMAP in 89% yield. Treatment of **16** with LHMDS and isobutyraldehyde at low temperature then afforded a mixture from which the major component, aldol adduct (3*S*,6*S*,1′*R*)-**18** was isolated in moderate yield (52%) as a single diastereoisomer. The

cis-(3*S*,6*S*) relative configuration of the diketopiperazine ring substituents within **18** was apparent from ^{1}H NMR spectroscopic data while the (1′*R*) configuration of **18** was tentatively assigned from the coupling constant between *H*-1′ and *H*-3.[18] Subsequent deprotonation of **18** with KHMDS effected elimination and deacylation, affording *Z*-isobutylidene **19** in 96% de and moderate isolated yield (62%) after chromatography. *N*-Alkylation of **19** with NaH and *p*-methoxybenzyl chloride then gave (3*Z*,6*S*)-isobutylidene **8** in 96% de and 44% yield after chromatography (Scheme 4).



Scheme 4 *Reagents and conditions*: (i) $(BOC)_2O$, $NaHCO_3$, EtOH; (ii) LHMDS, ^{i}PrCHO, THF; (iii) KHMDS, THF; (iv) PMBCl, NaH, DMF.

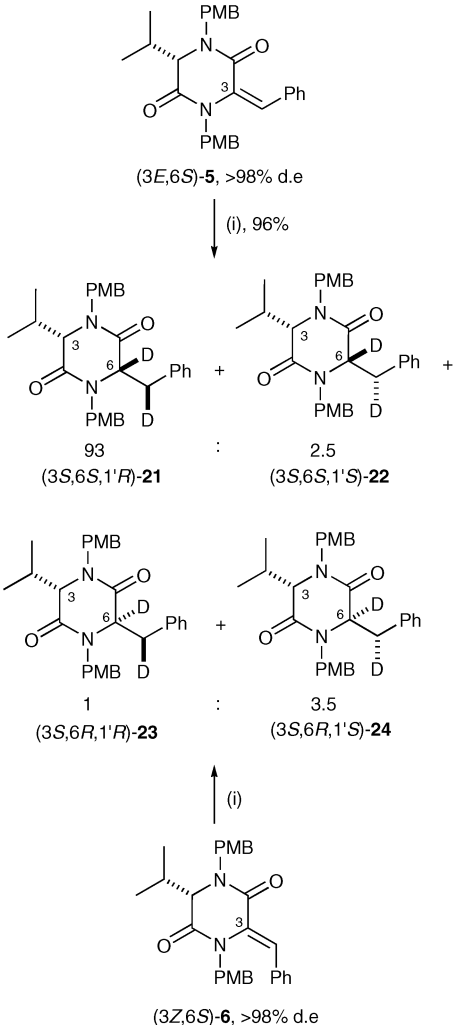
With representative alkylidene templates in hand, preliminary studies focused on the conjugate reduction of benzylidene templates **5** and **6** with SmI_2 and H_2O, a process leading to the generation of a *C*-3 stereogenic centre. Treatment of (3*E*,6*S*)-**5** with SmI_2 in THF and subsequent addition of deoxygenated H_2O led to clean reduction of the α,β-unsaturated enamide to afford the known *cis*-(3*S*,6*S*)-**20** in 95% de,[5c–e] and in 93% isolated yield. Similar reduction of the diastereoisomeric benzylidene (3*Z*,6*S*)-**6** also afforded *cis*-(3*S*,6*S*)-**20** in 96% de and 89% isolated yield (Scheme 5).



Scheme 5 *Reagents and conditions*: (i) SmI_2, THF, H_2O, room temperature.

The high levels of *cis*-selectivity afforded in both these reductions are similar to the selectivity observed in the protonation of substituted enolates derived from organocuprate additions to enamide **2** or deprotonation of substituted diketopiperazines **3**. This selectivity is consistent with the formation of a common samarium enolate intermediate which also undergoes stereoselective protonation *anti* to the isopropyl group. In accordance with this hypothesis, the geometry of the enamide has no effect on the diastereoselectivity in this reduction.

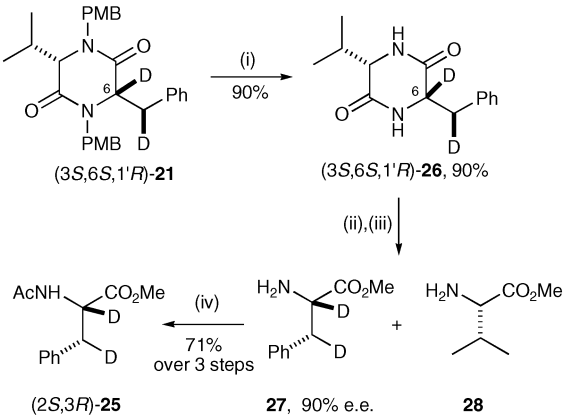
Having established that the auxiliary confers high levels of diastereofacial selectivity in the generation of a single stereogenic centre, studies turned to the dideuteration of these enamide templates, a process which has the potential to stereoselectively generate two new stereogenic centres at *C*-6 and *C*-1′. Treatment of either (3*E*,6*S*)-**5**, (3*Z*,6*S*)-**6**, or a 7 : 1 mixture of (3*E*,6*S*)-**5** : (3*Z*,6*S*)-**6** with a solution of SmI_2 in THF and D_2O gave *C*-1′,*C*-3-dideuterated-diketopiperazine (3*S*,6*S*,1′*R*)-**21** with >99% incorporation of two deuterium atoms (Scheme 6). Examination of the ^{1}H NMR spectrum of the crude reaction mixture indicated an approximate 92 : 8 ratio of (3*S*,6*S*,1′*R*)-**21** and combined (3*S*,6*S*,1′*S*)-**22**, (3*S*,6*R*,1′*R*)-**23** and (3*S*,6*R*,1′*S*)-**24** diastereoisomers, respectively and a 95.5 : 4.5 ratio of *cis*-(3*S*,6*S*) **21** + **22** to *trans*-(3*S*,6*R*) **23** + **24** diastereoisomers respectively. Chromatographic removal of the samarium residues afforded **21** (as a ~92 : 8 mixture of **21** and minor diastereoisomers **22**–**24**) in 96% yield. Careful chromatographic separation of the 95.5 : 4.5 *cis*-**21** + **22** : *trans*-**23** + **24** mixture derived from reduction of **5** afforded a 26 : 74 mixture of *trans*-(3*S*,6*R*,1′*R*)-**23** and *trans*-(3*S*,6*R*,1′*S*)-**24** in 2% yield, and a 97.5 : 2.5 mixture of *cis*-(3*S*,6*S*,1′*R*)-**21** and *cis*-(3*S*,6*S*,1′*S*)-**22** in 51% yield. The chromatographic separation of diastereoisomers differing in isotopic substitution at C1′ is not expected and these data indicate a 93 : 2.5 : 1 : 3.5 ratio of *cis*-**21**, *cis*-**22**, *trans*-**23** and *trans*-**24**, respectively in the original mixture.



Scheme 6 *Reagents and conditions*: (i) SmI_2, THF, D_2O, room temperature.

The (3*S*,6*S*,1′*R*)-configuration within dideuterio **21** was established by conversion to the known methyl (2*S*,3*R*)-*N*-acetyl-2-amino-2,3-dideuterio-3-phenylpropionate **25**.[19] *N*-Deprotection of diastereoisomeric reduction mixture **21**–**24** with ceric ammonium nitrate afforded (3*S*,6*S*,1′*R*)-dideuterio-diketopiperazine **26**, as a corresponding mixture of diastereoisomers, in 90% yield. Subsequent hydrolysis followed by esterification yielded a mixture of (2*S*,3*R*)-dideuterio-phenylalanine methyl ester **27** and (*S*)-valine methyl ester **28** as the hydrochloride salts which were separated by distillation of the free amino esters to afford (2*S*,3*R*)-dideuterio-phenylalanine methyl ester **27** in 93% de

and 90% ee.[20] *N*-Acetylation of **27** afforded, after chromatographic purification, *N*-acetyl (2*S*,3*R*)-**25** in 71% overall yield (Scheme 7).



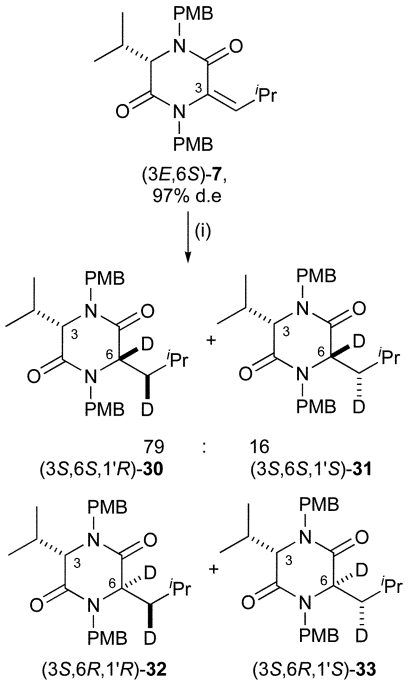
Scheme 7 *Reagents and conditions*: (i) ceric ammonium nitrate, H_2O, MeCN, rt; (ii) HCl conc., Δ; (iii) $SOCl_2$, MeOH, Δ, $NaHCO_3$, distillation; (iv) Ac_2O, NEt_3, DMAP, DCM, room temperature.

The relative configuration within **25** was identified unambiguously by comparison with an authentic 42 : 58 mixture of racemic dideuterio (2*SR*,3*RS*)-*rac*-**25** and dideuterio epimer (2*SR*,3*SR*)-**29**, derived from the D_2O promoted SmI_2 reduction of methyl (*Z*)-α-acetamido-cinnamate, and comparison with the ^1H NMR spectroscopic data of the literature.[19] The absolute configuration of (3*S*,6*S*,1′*R*)-diketopiperazine **21** and the (2*S*,3*R*)-phenylalanine derivatives **25** and **27** follows from the configuration of the (*S*)-valine derived stereogenic centre of the starting auxiliary and was confirmed by the sign of the specific rotation of the hydrochloride salt of methyl (2*S*,3*R*)-2-amino-2,3-dideuterio-3-phenylpropionate **27** $\{[\alpha]_D^{21}$ +29.9 (*c* 0.70 in EtOH), lit.[21] $[\alpha]_D$ +35.7 (*c* 1.06 in EtOH)$\}$. The observed ee and de for **25** are consistent with a 93 : 2.5 : 1 : 3.5 ratio of **21 : 22 : 23 : 24** in the original reduction mixture, within an experimental error of ±0.5%, and allow the assignment of the major *trans* diastereoisomer as (3*S*,6*R*,1′*S*)-**24**. While the deprotection and hydrolysis of the mixture of diastereoisomers allows confirmation of the observed reduction de, the deprotection and hydrolysis of a sample of purified *cis*-(3*S*,6*S*,1′*R*)-**21** + *cis*-(3*S*,6*S*,1′*S*)-**22** (97.5 : 2.5, **21 : 22**) provided homochiral (2*S*,3*R*)-dideuterio-phenylalanine methyl ester **27** in ≥95% de and >98% ee.[20]

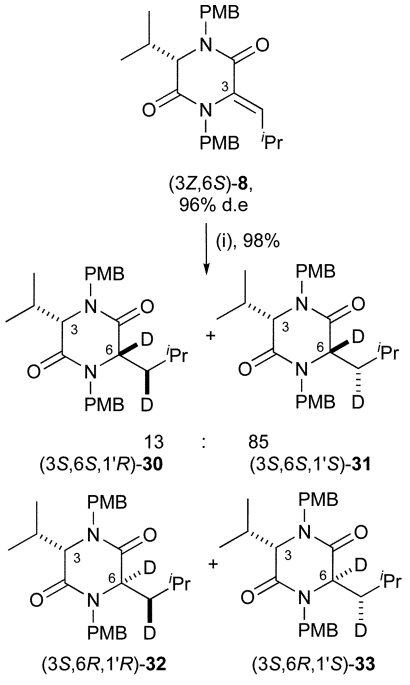
The conjugate reduction of the isobutylidene templates (*E*)-**7** and (*Z*)-**8** was next examined. Treatment of (*E*)-**7** with a solution of SmI_2 in THF and D_2O gave a 79 : 16 : 5 mixture of dideuterio *cis*-(3*S*,6*S*,1′*R*)-**30**, *cis*-(3*S*,6*S*,1′*R*)-**31** and combined *trans*-(3*S*,6*R*,1′*R*)-**32** + *trans*-(3*S*,6*R*,1′*S*)-**33**, respectively, with >98% deuterium incorporation, in 94% purified yield after chromatographic removal of the samarium residues (Scheme 8).

Similar conjugate reduction of (*Z*)-**8** with SmI_2 in THF and D_2O gave a 13 : 85 : 2 mixture of dideuterio *cis*-(3*S*,6*S*,1′*R*)-**30**, *cis*-(3*S*,6*S*,1′*S*)-**31** and combined *trans*-(3*S*,6*R*,1′*R*)-**32** + *trans*-(3*S*,6*R*,1′*S*)-**33**, respectively, with >98% deuterium incorporation, in 98% purified yield after chromatographic removal of the samarium residues (Scheme 9).

The relative configuration of the *C*-3 and *C*-6 diketopiperazine ring substituents within *cis*-(3*S*,6*S*,1′*R*)-**30** and *cis*-(3*S*,6*S*,1′*S*)-**31** was readily determined by comparison of the ^1H NMR spectra with the known protio *cis*-(3*S*,6*S*)-6-isobutyl-diketopiperazine **34**.[5c,e] *Trans* isomers (3*S*,6*R*,1′*RS*)-**32** and (3*S*,6*R*,1′*SR*)-**33** were identified by comparison with the ^1H NMR spectrum of protio **35**, prepared by the diastereoselective *trans* alkylation of parent auxiliary (*S*)-**10** with isobutyl bromide. The alkylation of the lithium enolate of (*S*)-**10** with this hindered electrophile proceeded slowly, giving a 50 : 50 mixture of (3*S*,6*R*)-**35** in 90% de and hydroxylated (3*S*,6*R*)-**36** at 66% conversion, from which **35** was isolated in 31% yield and >98% de after chromatography (Scheme 10). The by-product hydroxy-(3*S*,6*R*)-**36**[15] presumably derives from oxidation of the intermediate enolate by adventitious oxygen despite degassing of the solvent.

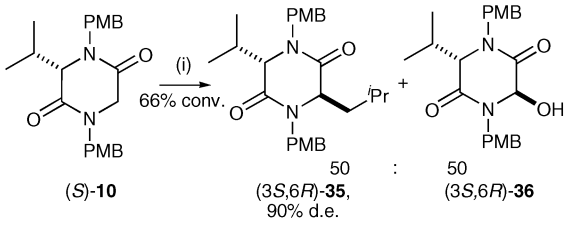


Scheme 8 *Reagents and conditions*: (i) SmI_2, THF, D_2O, room temperature.



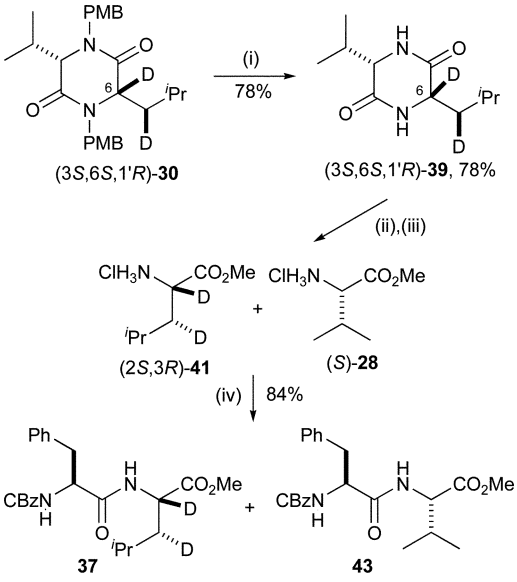
Scheme 9 *Reagents and conditions*: (i) SmI_2, THF, D_2O, room temperature.

The relative configuration of the *C*-1′ stereogenic centre within (3*S*,6*S*,1′*R*)-**30** and (3*S*,6*S*,1′*S*)-**31** was established by deprotection, hydrolysis and derivatisation of the dideuterioleucine residues with (*S*)-*N*-CBz-phenylalanine to afford methyl (*S*)-*N*-CBz-phenylalanyl-(2*S*,3*R*)-[2,3-$^2H_2$]-leucinate **37** and methyl (*S*)-*N*-CBz-phenylalanyl-(2*S*,3*S*)-[2,3-$^2H_2$]-leucinate **38**, respectively. *N*-Deprotection of (1′*R*)-**30** (83 : 17, **30 : 31**) or



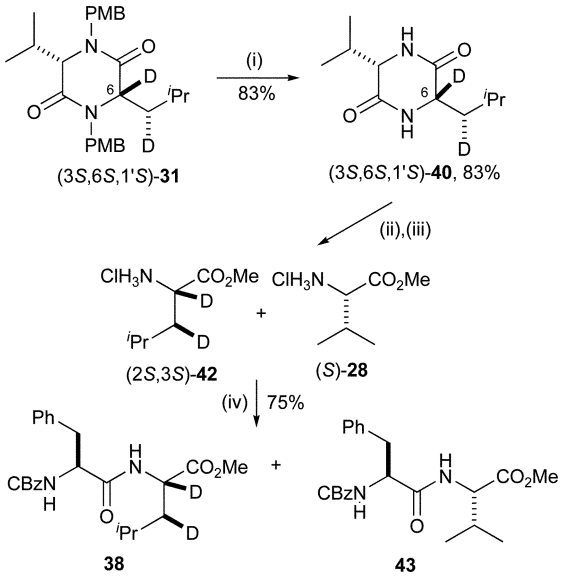
Scheme 10 *Reagents and conditions*: (i) LHMDS, $^{i}PrCH_2I$, THF, −78 °C.

(1′*S*)-**31** (13 : 87, **30 : 31**) with ceric ammonium nitrate afforded the corresponding (3*S*,6*S*,1′*R*)- or (3*S*,6*S*,1′*S*)-dideuterio-diketopiperazine **39** or **40** (as corresponding mixtures of diastereoisomers) with subsequent hydrolysis followed by esterification yielding a mixture of (2*S*,3*R*)- or (2*S*,3*S*)-dideuterio-leucine methyl ester **41** or **42** and (*S*)-valine methyl ester **28** as hydrochloride salts. The direct coupling of these mixtures with (*S*)-*N*-CBz-phenylalanine afforded a mixture of deuterio-dipeptide **37** or deuterio-dipeptide **38** and (*S*)-*N*-Cbz-Phe-(*S*)-Val·OMe **43**, which were separated by chromatography to afford dipeptides **37** and **38**, respectively (Scheme 11 and 12).

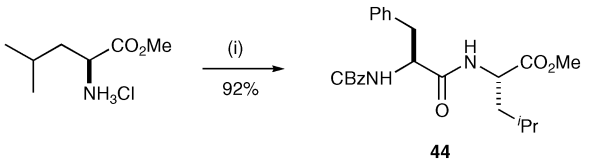


Scheme 11 *Reagents and conditions*: (i) ceric ammonium nitrate, H_2O, MeCN, room temperature; (ii) HCl conc., Δ; (iii) $SOCl_2$, MeOH, room temperature; (iv) NEt_3, HOBT, (*S*)-CBz-*N*-phenylalanine, EDC, $CHCl_3$, room temperature, chromatography.

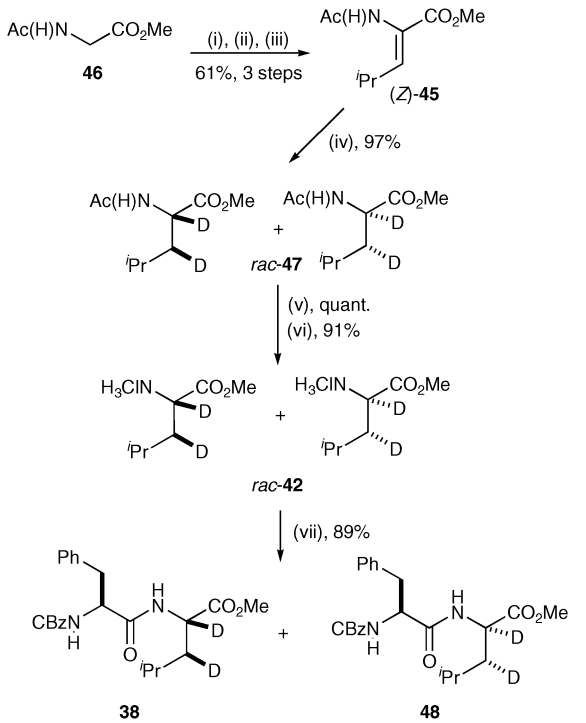
For comparison purposes, an authentic sample of the protio dipeptide **44** was prepared from the appropriate amino acid derivatives by standard coupling methods (Scheme 13), while dideuterio methyl (*S*)-*N*-CBz-phenylalanyl-(2*S*,3*S*)-[2,3-$^2H_2$]-leucinate **38** was prepared *via* a rhodium catalysed deuterogenation protocol. (*Z*)-*N*-Acetyl-dehydroleucine **45** (>98% de), prepared in 3 steps from *N*-acetyl glycine methyl ester **46** in 61% yield,[22] was stereospecifically *cis* deuterogenated with deuterium gas and Wilkinson's catalyst[23] to afford racemic (2*RS*,3*RS*)-[2,3-$^2H_2$]-*N*-acetyl-leucine **47** in >98% de and provided the hydrochloride salt of (2*RS*,3*RS*)-[2,3-$^2H_2$]-*N*-acetyl-leucine methyl ester **42** after protecting group manipulation. Coupling of this material with (*S*)-*N*-CBz-phenylalanine afforded a 50 : 50 mixture of (*S*)-*N*-CBz-phenylalanyl-(2*S*,3*S*)-[2,3-$^2H_2$]-leucinate **38** and (*S*)-*N*-CBz-phenylalanyl-(2*R*,3*R*)-[2,3-$^2H_2$]-leucinate **48**, which were separated by chromatography to afford **38** in 89% yield (Scheme 14).



Scheme 12 *Reagents and conditions*: (i) ceric ammonium nitrate, H_2O, MeCN, room temperature; (ii) HCl conc., Δ; (iii) $SOCl_2$, MeOH, room temperature; (iv) NEt_3, HOBT, (*S*)-CBz-*N*-phenylalanine, EDC, $CHCl_3$, room temperature, chromatography.



Scheme 13 *Reagents and conditions*: (i) NEt_3, HOBT, (*S*)-CBz-*N*-phenylalanine, EDC, $CHCl_3$, room temperature.



Scheme 14 *Reagents and conditions*: (i) NBS, AIBN, CCl_4; (ii) $P(OMe)_3$; (iii) tetramethylguanidine, $^{i}PrCHO$; (iv) $RhCl(PPh_3)_3$, 1 atm D_2; (v) HCl conc., Δ; (vi) MeOH, $SOCl_2$, room temperature; (vii) NEt_3, HOBT, (*S*)-CBz-*N*-phenylalanine, EDC, $CHCl_3$, room temperature, chromatography.

Mechanistic proposal for conjugate reductions

The reductions of benzylidenes (3*E*,6*S*)-**5** and (3*Z*,6*S*)-**6** and isobutylidenes (3*E*,6*S*)-**7** and (3*Z*,6*S*)-**8** all proceed to give *cis*-(3*S*)-diastereoisomeric products **21, 30** and **31** in high de. The overall reduction of these enamides may be rationalized by a mechanism which proceeds *via* two stepwise single electron

reductions of the α,β-unsaturated system. Assuming that protonation of the initially formed radical anion is relatively slow, successive reductions will generate a dianionic species,[24] potentially constituted with one or two bound samarium(III) moieties, represented by **49-I** or **49-II** respectively, from which sequential deuteration at *C*-1′ then *C*-6 will afford the dideuterated product. The high levels of stereoselectivity in the generation of the *C*-6 stereogenic centre observed in all these reductions then arise from a stereoselective deuteration of a samarium enolate intermediate **50** at *C*-6, *trans* to the isopropyl group, consistent with the previously observed *re* face selective protonation of the related lithium enolates (Fig. 4).

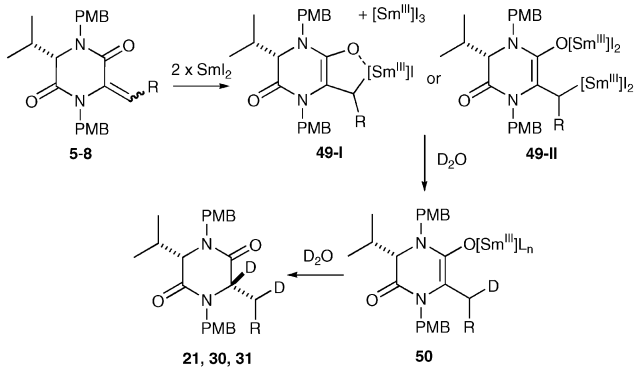


Fig. 4 Proposed mechanism for the stereoselective conjugate reduction with SmI_2.

The reduction of isobutylidene (3*E*,6*S*)-**7** and (3*Z*,6*S*)-**8** proceeds stereoselectively and stereospecifically to generate two new stereogenic centres at *C*-6 and *C*-1′, while reduction of either benzylidene (3*E*,6*S*)-**5** or (3*Z*,6*S*)-**6** stereoselectively, but not stereospecifically, generates the same product diastereoisomer. Mechanistically, the diastereoselective generation of the *C*-1′ stereogenic centre most probably derives from the stereospecific deuteration with retention of configuration[25] of a stereodefined *C*-1′ organosamarium intermediate.[26] For reduction of isobutylidenes (3*E*,6*S*)-**7** and (3*Z*,6*S*)-**8** the major product diastereoisomers **30** and **31** respectively, derive from *syn* dideuteration of the *re* face of the auxiliary, consistent with deuteration with retention of configuration of organosamarium intermediates **51** and **52** respectively. While the exact nature of these intermediates has not been established, the proposed *C*-1′ configurations of **51** and **52** are consistent with a formal addition of samarium to the *C*-1′ of ketyl precursors **53** and **54** respectively, *anti* to the *C*-6 isopropyl group. Following this mechanism the isobutylidene double bond geometry determines the *C*-1′ configuration with *E*-**7** affording predominantly (3*S*,6*S*,1′*R*)-**30** (83 : 17, 1′*R*-**30** : 1′*S*-**31**) while reduction of *Z*-**8**, *via* an analogous mechanism, will afford (3*S*,6*S*,1′*S*)-**31** (13 : 87, 1′*R*-**30** : 1′*S*-**31**) (Fig. 5).

Reduction of benzylidenes (3*E*,6*S*)-**5** or (3*Z*,6*S*)-**6** both furnish the same product diastereoisomer. One possible mechanism accounting for this reduction selectivity involves the interconversion of (3*E*,6*S*)-**5** and (3*Z*,6*S*)-**6** under the reaction conditions to the thermodynamically more stable benzylidene prior to reduction. To investigate this possibility, partial reductions of (3*E*,6*S*)-**5** and (3*Z*,6*S*)-**6** were carried out. Treatment of either (3*E*,6*S*)-**5** or (3*Z*,6*S*)-**6** with a solution of SmI_2 (1 eq) in THF and D_2O proceeded to ~50% conversion, giving only the expected diketopiperazine (3*S*,6*S*,1′*R*)-**21** and unchanged starting material, in each case. Furthermore, treatment of a 50 : 50 mixture of (3*E*,6*S*)-**5** : (3*Z*,6*S*)-**6** under identical conditions proceeded to 50% conversion, furnishing (3*S*,6*S*,1′*R*)-**21** and returning a 50 : 50 mixture of (3*E*,6*S*)-**5** : (3*Z*,6*S*)-**6**, indicating that the rates of reduction of the two diastereoisomeric diketopiperazines are identical.

The observed stereoselectivity in the reductions of the benzylidene geometric isomers (*E*)-**5** or (*Z*)-**6** may then be rationalized

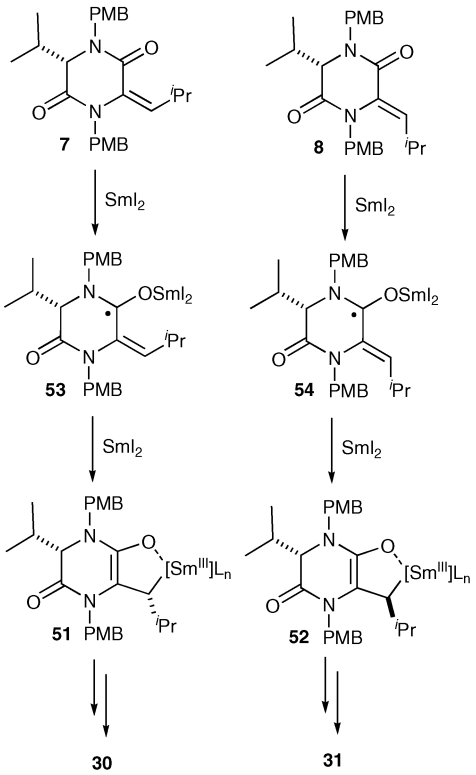


Fig. 5 Proposed mechanism for the stereospecific conjugate reduction of **6** and **8** with SmI_2.

by a two-step reduction process similar to that proposed for isobutylidenes **7** and **8**. In the benzylidene case, initial single electron reduction of either **5** or **6** by SmI_2 will generate an allylic ketyl radical intermediate (*E*)- or (*Z*)-**55**, which is sufficiently stabilised by the *C*-2′ phenyl group to allow isomerization of the double bond to the thermodynamically more stable (*E*)-**55**, prior to stereoselective formation of organosamarium **56** which is then deuterated with retention of configuration to eventually afford **21** (Fig. 6).

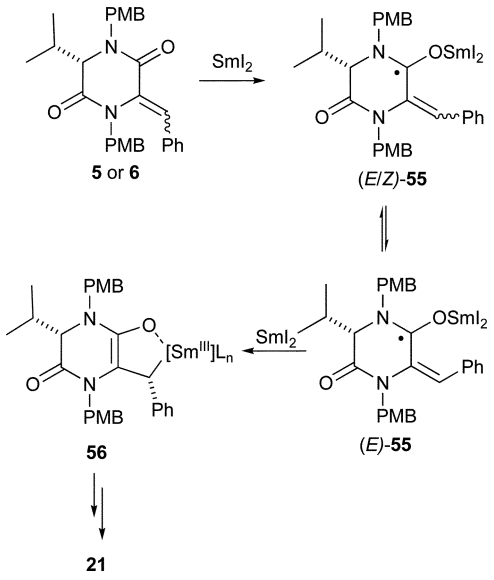


Fig. 6 Proposed mechanism for the stereoselective conjugate reduction of **5** and **6** with SmI_2.

Conclusion

In conclusion, conjugate reductions of 3-alkylidene substituted diketopiperazine templates have been carried out using samarium diiodide in THF and D_2O. Isobutylidene enamides (*E*)-**7**

and (*Z*)-**8** have been shown to be reduced stereoselectively and stereospecifically to provide diastereoisomeric dideuterated products (3*S*,6*S*,1′*R*)-**30** and (3*S*,6*S*,1′*S*)-**31** respectively, while benzylidene enamides (*E*)-**5** and (*Z*)-**6** are highly stereoselectively, but non-stereospecifically, dideuterated to afford the same product diastereoisomer (3*S*,6*S*,1′*R*)-**21**.

Experimental

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), Bruker DPX 400 (^{1}H: 400 MHz and ^{13}C: 100.6 MHz) or Bruker AMX 500 (^{1}H: 500 MHz and ^{13}C: 125.7 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^{-1}. 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 were obtained upon a Micromass AutoSpec or a Micromass ToFSpec spectrometer. Elemental analyses were performed by the microanalysis service of the Inorganic Chemistry Laboratory, University of Oxford.

General procedures

General procedure *1*. Horner–Wadsworth–Emmons synthesis of **5** and **7**.

Sodium hydride (2.20 mmol) was stirred in THF (10 ml) and the slurry was cooled to 0 °C. To this, **11** (0.94 mmol) and benzaldehyde or isobutyraldehyde (3.0 mmol) in THF (10 ml) were added at 0 °C *via* cannula over approximately 5 min. The reaction mixture was stirred at 0 °C for 2 h and then allowed to warm to room temperature over 15 min, after which time saturated $NH_4Cl_{(aq.)}$ (15 ml) was added and the mixture extracted with EtOAc (3 × 15 ml). The combined organics were dried ($MgSO_4$) and concentrated *in vacuo* to yield compounds **5** and **7** after chromatography (silica, petrol 40–60/ethyl acetate, 3 : 1).

General procedure *2*. Samarium reductions.

Under nitrogen, a solution of SmI_2[27] (10 mmol) in THF (100 mL) was added dropwise to a stirred solution of **5–8** (4.0 mmol) in THF (20 ml) at room temperature. The reaction mixture was stirred for 10 min and then deoxygenated H_2O or D_2O (10 ml) was added. After stirring for 1 hour the mixture was treated with 0.1 M aqueous HCl (50 ml). Standard workup afforded crude **20, 21, 30**, or **31** which was purified by chromatography (silica, petrol 40–60/ethyl acetate, 3 : 1).

General procedure *3*. CAN-mediated *N*-deprotection.

Compound **21, 30**, or **31** (1.0 mmol) was dissolved in a mixture of CH_3CN/H_2O, 3 : 2 (25 mL) and CAN (6.0 mmol) was added. The mixture was stirred for 1 h at room temperature. The organic solvent was evaporated, 20 ml of ether were added, the solid (**26, 39**, or **40**) was filtered and washed with ether.

General procedure *4*. Hydrolysis and amino acid esterification.

A solution of the diketopiperazine **26, 39** or **40** (4.0 mmol) in HCl conc. (25 mL) was subject to reflux for 36 h. Aqueous HCl was then evaporated *in vacuo* to afford a mixture of amino acid and (*S*)-valine hydrochlorides that were dissolved in MeOH (20 mL) and cooled to 0 °C before thionyl chloride (7.5 mmol) was added. The reaction mixture was stirred at room temperature for 12 h. Concentration under vacuum afforded a 1 : 1 mixture of the methyl ester amino hydrochloride **27, 41**, or **42** and methyl (*S*)-valinate hydrochloride **28** as a colourless solid.

General procedure *5*. Dipeptide synthesis.

Triethylamine (4.3 mmol), 1-hydroxybenzotriazole hydrate (1.05 mmol), (*S*)-*N*-Cbz-phenylalanine (0.86 mmol), and EDC (1.05 mmol) were added successively to a solution of the corresponding aminoester salt (0.86 mmol) in $CHCl_3$ (40 ml), at 0 °C, then allowed to warm to ambient temperature. After 16 hours, the reaction mixture was washed with 1 M HCl, aqueous $NaHCO_3$, and brine, dried and concentrated *in vacuo*. Purification by chromatography (silica, petrol 30–40/ether, 5 : 1) afforded **37, 38, 43, 44** or **48** as a colourless solid.

[(2*S*,5*S*)-*N*,*N*′-Bis-(4-methoxybenzyl)-5-isopropyl-3,6-dioxo-piperazin-2-yl]-phosphonic acid diethyl ester, 11 and [(2*R*,5*S*)-*N*,*N*′-bis-(4-methoxybenzyl)-5-isopropyl-3,6-dioxo-piperazin-2-yl]-phosphonic acid diethyl ester, 12. To a solution of **10**[5a,b] (1.55 g, 3.91 mmol) in THF (50 ml) at −78 °C was added LHMDS (4.3 ml, 1.0 M in THF, 4.3 mmol) and the mixture stirred for 1 h. *N*-Fluorobenzenesulfonamide (1.36 g, 4.31 mmol) was then added and the mixture stirred at −78 °C for 30 min, after which time it was allowed to warm to −30 °C when saturated aqueous NH_4Cl (10 mL) was added. The mixture was then partitioned between water (100 mL) and ether and the aqueous phase extracted with ether. The combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo* to yield a 1 : 1 mixture of *cis*- and *trans*-fluorides as a yellow oil (2.07 g). This crude mixture was then dissolved in dichloromethane (10 ml) and chlorotrimethylsilane (3.25 ml) was added. The mixture was stirred for 2 h at room temperature and then concentrated *in vacuo* to yield **9**[14] as an orange foam (2.1 g). This crude product was then dissolved in dry dichloromethane (15 ml), triethylphosphite (0.80 ml, 4.67 mmol) was added and the mixture stirred at room temperature for 3 days. Solvents were removed *in vacuo* to yield an orange oil (2.1 g). Chromatography (ether/petroleum ether 1 : 1, then ethyl acetate/petroleum ether 1 : 1) yielded a 6 : 1 mixture of **11** and **12** as an oil (1.24 g, 60%). Further chromatography yielded a pure sample of **11** and a sample comprising a 4 : 1 mixture of **12** and **11**, from which data for the former were obtained. **11**: $[\alpha]_D^{24}$ −237.1 (*c* 0.25, $CHCl_3$); ν_{max}/cm^{-1} ($CHCl_3$) 1666 (C=O); δ_H (400 MHz, $CDCl_3$) 1.12 (3H, d, *J* 6.7, $(CH_3)_2CH$), 1.17 (3H, d, *J* 6.7, $(CH_3)_2CH$), 1.37 (3H, d, *J* 7.1, CH_3CH_2), 1.40 (3H, d, *J* 7.2, CH_3CH_2), 2.59 (1H, dsept, *J* 9.8, 6.7, $(CH_3)_2CH$), 3.54 (1H, d, *J* 9.8, $(CH_3)_2CHCH$), 3.79 (1H, d, *J* 14.8, NCH_2Ar), 3.81 (3H, s, CH_3O), 3.81 (3H, s, CH_3O), 3.88 (1H, d, *J* 14.6, NCH_2Ar), 4.18–4.30 (4H, m, 2 × CH_2CH_3), 4.39 (1H, d, $^2J_{PH}$ 22.6, PC*H*N), 5.42 (1H, d, *J* 14.8, NCH_2Ar), 5.56 (1H, d, *J* 14.6, NCH_2Ar), 6.80–6.86 (4H, m, *Ar*), 6.99–7.10 (4H, m, *Ar*); δ_C (125 MHz, $CDCl_3$) 16.8 (d, $^3J_{PC}$ 6.3), 16.9 (d, $^3J_{PC}$ 6.3), 20.5, 21.5, 33.9, 48.0, 50.8, 55.7, 55.7, 58.9 (d, $^1J_{PC}$ 147.1), 63.8 (d, $^2J_{PC}$ 7.5), 64.2 (d, $^2J_{PC}$ 7.5), 66.7, 114.7, 114.8, 127.6, 128.2, 129.4, 130.2, 159.8, 160.0, 162.3,

166.4; *m/z* (ES$^+$) 533 (100%, MH$^+$), 555 (66%, MNa$^+$); (found: MH$^+$, 533.2415; $C_{27}H_{38}N_2O_7P^+$ requires 533.2417).

4 : 1 of mixture **12 : 11**: $[\alpha]_D^{24}$ −70.0 (*c* 0.32, $CHCl_3$); ν_{max}/cm^{-1} ($CHCl_3$) 1659 (C=O); δ_H (400 MHz, $CDCl_3$) 0.87 (3H, d, *J* 6.7, $(CH_3)_2CH$), 1.16 (3H, d, *J* 6.7, $(CH_3)_2CH$), 1.28 (3H, d, *J* 7.1, CH_3CH_2), 1.39 (3H, d, *J* 7.2, CH_3CH_2), 2.41 (1H, dsept, *J* 6.7, 2.5, $(CH_3)_2CH$), 3.81 (3H, s, CH_3O), 3.81 (3H, s, CH_3O), 3.83 (1H, dd, *J* 4.1, 2.5, $(CH_3)_2CHCH$), 3.93 (1H, d, *J* 15.2, NCH_2Ar), 4.11–4.28 (5H, m, 2 × CH_2CH_3 and NCH_2Ar), 4.31 (1H, d, $^2J_{PH}$ 14.9, PCHN), 5.48 (1H, d, *J* 14.6, NCH_2Ar), 5.49 (1H, d, *J* 15.2, NCH_2Ar), 6.84–6.89 (4H, m, *Ar*), 7.19–7.25 (4H, m, *Ar*); δ_C (125 MHz, $CDCl_3$) 15.3, 16.2 (d, $^3J_{PC}$ 5.0), 16.3 (d, $^3J_{PC}$ 5.0), 20.0, 29.4, 45.8, 47.1, 55.2, 55.2, 57.3 (d, $^1J_{PC}$ 139.5), 61.9, 63.5 (d, $^2J_{PC}$ 7.5), 63.6 (d, $^2J_{PC}$ 7.5), 114.2, 114.3, 126.9, 127.0, 129.5, 130.4, 159.1, 159.4, 161.8, 165.9; *m/z* (ES$^+$) 533 (100%, MH$^+$), 555 (77%, MNa$^+$); (found: MH$^+$, 533.2419; $C_{27}H_{38}N_2O_7P^+$ requires 533.2417).

(6*SE*,)-3-Benzylidene-6-isopropyl-1,4-bis-(4-methoxybenzyl)-piperazine-2,5-dione 5. 11 (500 mg, 0.94 mmol) was treated following general procedure *1* to afford a yellow oil. Chromatography afforded **5** as a colourless solid (285 mg, 63%). Mp 110–112 °C; $[\alpha]_D^{25}$ −186.1 (*c* 0.84, $CHCl_3$); ν_{max}/cm^{-1} (KBr) 1678 (C=O); δ_H (400 MHz, $CDCl_3$) 1.10 (3H, d, *J* 6.8, $(CH_3)_2CH$), 1.18 (3H, d, *J* 6.8, $(CH_3)_2CH$), 2.32 (1H, dsept, *J* 7.2, 6.8, $(CH_3)_2CH$), 3.76 (1H, d, *J* 7.2, $(CH_3)_2CHCH$), 3.80 (6H, s, 2 × CH_3O), 3.82 (1H, d, *J* 14.7, NCH_2Ar), 4.78 (1H, d, *J* 15.4, NCH_2Ar), 5.12 (1H, d, *J* 15.4, NCH_2Ar), 5.44 (1H, d, *J* 14.7, NCH_2Ar), 6.59 (1H, s, PhCHC), 6.82–6.89 (4H, m, *Ar*), 7.12–7.20 (4H, m, *Ar*), 7.25–7.36 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 19.1, 19.9, 33.2, 47.8, 48.9, 55.3, 55.3, 65.9, 114.2, 114.3, 123.7, 127.9, 128.0, 128.3, 128.6, 129.3, 129.6, 131.2, 134.2, 159.0, 159.3, 160.5, 166.0; *m/z* (ES$^+$) 485 (100%, MH$^+$), 507 (34%, MNa$^+$); (found: MH$^+$, 485.2437; $C_{30}H_{33}N_2O_4^+$ requires 485.2440).

(6*S*,3*E*)-3-Isobutylidene-6-isopropyl-1,4-bis-(4-methoxybenzyl)-piperazine-2,5-dione 7. 11 (500 mg, 0.94 mmol) was treated following general procedure *1* to afford a yellow oil. After chromatography, **7** was obtained as a colourless solid (285 mg, 67%). Mp 89–90 °C; $[\alpha]_D^{23}$ −238.1 (*c* 0.53, $CHCl_3$); ν_{max}/cm^{-1} (KBr) 1680, 1658 (C=O); δ_H (400 MHz, $CDCl_3$) 0.93 (3H, d, *J* 6.6, $(CH_3)_2CHCH$=C), 0.99 (3H, d, *J* 6.9, $(CH_3)_2CHCHN$), 1.01 (3H, d, *J* 6.6, $(CH_3)_2CHCH$=C), 1.09 (3H, d, *J* 6.9, $(CH_3)_2CHCHN$), 2.17 (1H, m, $(CH_3)_2CHCHN$), 3.57 (1H, m, $(CH_3)_2CHCH$=C), 3.69 (1H, d, *J* 6.8, $(CH_3)_2CHCH$), 3.80 (6H, s, 2 × CH_3O), 3.86 (1H, d, *J* 14.8, NCH_2Ar), 4.78 (1H, A*B*, NCH_2Ar), 4.85 (1H, *A*B, NCH_2Ar), 5.37 (1H, d, *J* 14.8, NCH_2Ar), 5.46 (1H, d, *J* 10.0, C=CHCH), 6.81–6.87 (4H, m, *Ar*), 7.08–7.14 (4H, m, *Ar*); δ_C (100 MHz, $CDCl_3$) 18.9, 19.8, 22.9, 23.0, 26.5, 32.9, 47.6, 48.6, 55.2, 55.3, 65.9, 114.0, 114.3, 128.1, 128.5, 128.9, 128.9, 129.3, 135.0, 158.9, 159.3, 161.2, 165.6; elem. anal. found C, 72.10, H, 7.61, N, 6.22; $C_{27}H_{34}N_2O_4$ requires C, 71.97, H, 7.61, N, 6.22%; *m/z* (ES$^+$) 451 (100%, MH$^+$); (found: MH$^+$, 451.2595; $C_{27}H_{35}N_2O_4^+$ requires 451.2597).

X-Ray crystal structure data for 7

Data were collected using an Enraf-Nonius Kappa CCD diffractometer with graphite monochromated Mo–Kα radiation using standard procedures at 150 K. The structure was solved by direct methods (Sir92). All non-hydrogen atoms were refined with anisotropic thermal parameters. Hydrogen atoms were added at idealised positions. The structure was refined using CRYSTALS.[28]

Crystal data for **7** [$C_{27}H_{34}N_2O_4$], colourless plate, $M = 450.58$, monoclinic, space group *P* 1 21 1, $a = 13.3830(4)$ Å, $b = 7.0716(2)$ Å, $c = 13.9236(5)$ Å, $U = 1230.8$ Å^3, $Z = 2$, $\mu = 0.081$, crystal dimensions 0.18 × 0.30 × 0.30 mm, a total of 2996 unique reflections were measured for $5 < \theta < 28$ and 2510 reflections were used in the refinement. The final parameters were $wR_2 = 0.0354$ and $R_1 = 0.0316$ [$I > 3\sigma(I)$].†

(6*S*,3*Z*)-3-Benzylidene-6-isopropyl-piperazine-2,5-dione 15. Potassium *tert*-butoxide (1.85 g, 16.5 mmol) was added to a stirred solution of diacetate **13**[29] (4.35 g, 18.1 mmol) and benzaldehyde (1.67 ml, 16.5 mmol) in THF (60 ml) at room temperature. After 30 min the mixture was partitioned between ethyl acetate and aqueous NH_4Cl, the aqueous layer extracted with ethyl acetate, the combined organic layers dried ($MgSO_4$) and the solvents removed *in vacuo* to provide **14** as a viscous oil. Chromatography (silica, hexane/ethyl acetate, 4 : 1) afforded **14** as a colourless solid (4.30 g, 83%). To a solution of **14** (4.30 g, 15 mmol) in methanol (20 ml) was added NaOH (600 mg, 15.0 mmol) and the mixture stirred for 30 min at room temperature. Methanol was then removed *in vacuo*, ether added and the colourless solid collected by filtration to afford **15** (3.26 g, 89%). $[\alpha]_D^{23}$ −1.0 (*c* 1.0, DMSO); ν_{max}/cm^{-1} (thin film) 3480, 3411, 1680, 1636 (C=O); δ_H (400 MHz, DMSO-d_6) 0.81 (3H, d, *J* 6.3, $(CH_3)_2CH$), 0.89 (3H, d, *J* 6.6, $(CH_3)_2CH$), 2.03–2.17 (1H, m, $(CH_3)_2CH$), 3.73 (1H, s, $(CH_3)_2CHCH$), 6.75 (1H, s, C=CHCH), 7.20–7.30 (1H, m, *Ph*), 7.30–7.40 (2H, m, *Ph*), 7.45–7.55 (2H, m, *Ph*), 8.49 (1H, br s, NH), 9.98 (1H, br s, NH); δ_C (100 MHz, DMSO-d_6) 17.8, 19.1, 34.3, 61.4, 114.5, 128.6, 129.4, 130.0, 134.5, 161.5, 167.4; *m/z* (CI$^+$) 245 (20%, MH$^+$), 106 (100); (found: MH$^+$, 245.1281; $C_{14}H_{17}N_2O_2^+$ requires 245.1290).

(6*S*,3*Z*)-*N*,*N*′-Bis-(4-methoxybenzyl)-3-benzylidene-6-isopropyl-piperazine-2,5-dione 6. NaH (687 mg, 17.2 mmol, 60% dispersion in mineral oil) was washed with hexane and suspended in dimethylformamide (30 ml). The mixture was cooled to 0 °C and **15** (1.87 g, 7.66 mmol) was added, followed by the dropwise addition of *p*-methoxybenzyl chloride (2.60 ml, 19.1 mmol) over a period of 30 min. The reaction mixture was stirred for a further 4 hours before the cautious addition of water (5 ml) followed by excess saturated ammonium chloride solution. The mixture was partitioned between ethyl acetate (50 ml) and water (50 ml), and the aqueous phase extracted with ethyl acetate (2 × 50 ml). The combined organic layers were washed with 0.1 M HCl (2 × 30 ml), dried and concentrated *in vacuo*. Chromatography (silica, petrol 40–60/ethyl acetate, 2 : 1) yielded **6** as a colourless oil (2.11 g, 57%). $[\alpha]_D^{23}$ −7.6 (*c* 1.0, $CHCl_3$); ν_{max}/cm^{-1} (thin film) 1685, 1615 (C=O); δ_H (400 MHz, $CDCl_3$) 1.10 (3H, d, *J* 6.9, $(CH_3)_2CH$), 1.12 (3H, d, *J* 7.0, $(CH_3)_2CH$), 2.17–2.26 (1H, m, $(CH_3)_2CH$), 3.61 (1H, d, *J* 7.9, $(CH_3)_2CHCH$), 3.78 (1H, d, *J* 14.9, NCH_2Ar), 3.76 (3H, s, CH_3O), 3.79 (3H, s, CH_3O), 3.94 (1H, d, *J* 14.5, NCH_2Ar), 5.17 (1H, d, *J* 14.5, NCH_2Ar), 5.45 (1H, d, *J* 14.9, NCH_2Ar), 6.70 (2H, m, *Ar*), 6.75 (2H, m, *Ar*), 6.81 (2H, m, *Ar*), 6.86 (2H, m, *Ar*), 7.01 (2H, d, *J* 8.6, *Ar*), 7.19 (1H, s, C=CHCH), 7.35–7.45 (5H, m, *Ph*); δ_C (62.5 MHz, $CDCl_3$) 19.4, 20.3, 33.2, 47.5, 49.4, 55.4 (x 2), 67.0, 113.9, 114.4, 122.7, 128.1, 128.9, 129.1, 129.5, 129.7, 129.9, 133.9, 159.2, 159.3, 163.4, 167.5; *m/z* (ES$^+$) 485 (100%, MH$^+$); (found: MH$^+$, 485.2434; $C_{30}H_{33}N_2O_4^+$ requires 485.2440).

(3*S*)-*N*-1-(*tert*-Butoxycarbonyl)-*N*-4-(4-methoxybenzyl)-3-isopropyl-piperazine-2,5-dione 16. To **17**[17] (2.00 g, 7.25 mmol) in EtOH (50 ml) was added *tert*-butoxycarbonyl anhydride (1.74 g, 7.97 mmol) followed by $NaHCO_3$ (2.40 g, 29 mmol). The mixture was sonicated for 12 h then the residue was filtered and the solvent removed *in vacuo* to afford a crude oil which was purified by chromatography (silica, EtOAc) to give **16** as a clear oil (2.43 g, 89%). $[\alpha]_D^{25}$ −71.2 (*c* 1.0, $CHCl_3$); ν_{max}/cm^{-1} (KBr) 1677, 1750 (2 × C=O); δ_H (400 MHz, $CDCl_3$) 1.05 (3H, d, *J* 6.8, $(CH_3)_2CHCH$), 1.11 (3H, d, *J* 6.8, $(CH_3)_2CHCH$), 1.24

† CCDC reference numbers 260374. See http://www.rsc.org/suppdata/ob/b5/b500566c/ for crystallographic data in .cif or other electronic format.

(9H, s, $(CH_3)_3CO$), 2.17–2.26 (1H, m, $(CH_3)_2CH$), 3.66 (1H, d, *J* 6.8, $(CH_3)_2CHCH$), 3.80 (3H, s, CH_3O), 3.83 (1H, d, *J* 14.9, NCH_2Ar), 4.21 (1H, d, *J* 17.7, $NCOCH_2$), 5.37 (1H, d, *J* 14.6, NCH_2Ar), 5.58 (1H, d, *J* 17.7, $NCOCH_2$), 6.86 (2H, d, *J* 8.7, *Ar*), 7.15 (2H, d, *J* 8.7, *Ar*); δ_C (100 MHz, $CDCl_3$) 18.6, 20.0, 27.9, 32.1, 48.3, 55.3, 66.4, 114.4, 127.1, 129.7, 150.3, 160.5, 164.2, 165.3; *m*/*z* (ES^+) 377 (100%, MH^+).

(6*S*,3*S*,1′*R*)-*N*-1-(4-Methoxybenzyl)-*N*-4-(*tert*-butoxycarbonyl)-3-(1-hydroxy-2-methylpropyl)-6-isopropyl-piperazine-2,5-dione 18. A solution of **16** (600 mg, 1.6 mmol) in degassed THF (30 ml) was cooled to −78 °C, and LHMDS (1.0 M in THF, 1.76 ml) was added. The mixture was stirred for 1 hour then isobutyraldehyde (0.16 ml, 1.76 mmol) was added and the mixture stirred for 30 min at −78 °C. Saturated aqueous NH_4Cl (30 ml) was added and the mixture was extracted with ethyl acetate (3 × 25 ml), dried ($MgSO_4$), and the solvent removed *in vacuo* to afford a mixture from which the major product was purified by chromatography (silica, petrol 30–40/ethyl acetate, 3 : 1) to yield **18** as a colourless solid (400 mg, 52%). Mp 156–158 °C; $[\alpha]_D^{25}$ −99.1 (*c* 1.0, $CHCl_3$); ν_{max}/cm^{-1} (KBr) 1681, 1748 (2 × C=O); δ_H (400 MHz, $CDCl_3$) 1.02 (3H, d, *J* 6.8, $(CH_3)_2CHCHOH$), 1.03 (3H, d, *J* 6.8, $(CH_3)_2CHCHOH$), 1.05 (3H, d, *J* 6.8, $(CH_3)_2CHCH$), 1.10 (3H, d, *J* 6.8, $(CH_3)_2CHCH$), 1.45 (9H, s, $(CH_3)_3CO$), 1.94–2.03 (1H, m, $(CH_3)_2CHCHOH$), 2.22–2.30 (1H, m, $(CH_3)_2CHCH$), 3.61 (1H, d, *J* 4.4, $(CH_3)_2CHCH$), 3.79 (3H, s, CH_3O), 3.80 (1H, d, *J* 15.2, NCH_2Ar), 4.22 (1H, d, *J* 2.4, $CHCH(OH)^iPr$), 5.24 (1H, dd, *J* 2.4, 8.4, $(CH_3)_2CHCHOH$), 5.53 (1H, d, *J* 14.8, NCH_2Ar), 5.91 (1H, s, OH), 6.85 (2H, d, *J* 8.4, *Ar*), 7.16 (2H, d, *J* 8.4, *Ar*); δ_C (100 MHz, $CDCl_3$) 17.5, 18.4, 18.6, 19.7, 21.8, 23.1, 27.7, 30.3, 31.6, 47.3, 54.7, 55.2, 63.4, 78.8, 82.4, 114.3, 127.3, 129.4, 152.8, 159.2, 165.1, 166.8; *m*/*z* (ES^+) 449.2 (100%, MH^+); (found: MH^+, 449.2645; $C_{24}H_{37}N_2O_6^+$ requires 449.2652).

(6*S*,3*Z*)-*N*-1-(4-Methoxybenzyl)-3-isobutylidene-6-isopropyl-piperazine-2,5-dione 19. A solution of **18** (565 mg, 1.3 mmol) in THF (30 ml) under N_2, was cooled to −78 °C, and stirred for 30 minutes then KHMDS (0.5 M in toluene, 2.86 ml, 1.43 mmol) was added. The mixture was stirred for 1 hour at −78 °C, and then allowed to warm to ambient temperature. After a further 2 hours, saturated aqueous NH_4Cl (30 ml) was added and the reaction mixture was extracted with ethyl acetate (3 × 25 ml), dried ($MgSO_4$), and the solvent removed *in vacuo*. Purification by chromatography (silica, petrol 30–40/EtOAc, 2 : 1) afforded **19** as a colourless oil (265 mg, 62%). $[\alpha]_D^{25}$ −116.6 (*c* 1.0, $CHCl_3$); ν_{max}/cm^{-1} (thin film) 1637, 1681 (2 × C=O); δ_H (400 MHz, $CDCl_3$) 0.94 (3H, d, *J* 7.1, $(CH_3)_2CHCHN$), 1.06 (3H, d, *J* 6.6, $(CH_3)_2CHCHN$), 1.08 (3H, d, *J* 6.5, $(CH_3)_2CHCH{=}C$), 1.09 (3H, d, *J* 6.5, $(CH_3)_2CHCH{=}C$), 2.20–2.28 (1H, m, $(CH_3)_2CHCHN$), 2.44–2.53 (1H, m, $(CH_3)_2CHCH{=}C$), 3.79 (1H, d, *J* 4.8, $(CH_3)_2CHCHN$), 3.80 (3H, s, CH_3O), 3.90 (1H, d, *J* 15.0, NCH_2Ar), 5.41 (1H, d, *J* 14.9, NCH_2Ar), 6.00 (1H, d, *J* 10.1, $CHCH{=}C$), 6.86 (2H, d, *J* 8.6, *Ar*), 7.19 (2H, d, *J* 8.6, *Ar*), 7.79 (1H, br, N*H*); δ_C (100 MHz, $CDCl_3$) 16.8, 19.4, 21.9, 22.0, 25.5, 32.6, 47.7, 55.3, 64.4, 114.0, 124.9, 126.2, 127.7, 129.7, 158.9, 162.2, 164.8; *m*/*z* (ES^+) 331.0 (100%, MH^+); (found: MH^+, 331.2019; $C_{19}H_{27}N_2O_3^+$ requires 331.2022).

(6*S*,3*Z*)-*N*,*N*′-Bis-(4-methoxybenzyl)-3-isobutylidene-6-isopropyl-piperazine-2,5-dione 8. NaH (75 mg, 1.83 mmol, 60% dispersion in mineral oil) was washed with hexane (3 × 5 ml) and suspended in dimethylformamide (30 ml). The mixture was cooled to 0 °C and **19** (550 mg, 1.66 mmol) was added, followed by the dropwise addition of *p*-methoxybenzyl chloride (0.25 ml, 1.83 mmol) over a period of 30 min. The reaction mixture was stirred for a further 6 hours before the cautious addition of water (5 ml) followed by excess saturated ammonium chloride solution. The mixture was partitioned between ethyl acetate (50 ml) and water (50 ml), and the aqueous phase extracted with ethyl acetate (2 × 50 ml). The combined organic layers were washed with 0.1 M HCl (2 × 30 ml), dried and concentrated *in vacuo*. Chromatography (silica, petrol 40–60/ethyl acetate, 2 : 1) yielded **8** as a colourless oil (330 mg, 44%). $[\alpha]_D^{23}$ −50.4 (*c* 1.0, $CHCl_3$); ν_{max}/cm^{-1} (thin film) 1684, 1663 (C=O); δ_H (400 MHz, $CDCl_3$) 0.99 (3H, d, *J* 6.8, $(CH_3)_2CHCHN$), 1.01 (3H, d, *J* 6.9, $(CH_3)_2CHCHN$), 1.06 (3H, d, *J* 6.8, $(CH_3)_2CHCH{=}C$), 1.14 (3H, d, *J* 6.8, $(CH_3)_2CHCH{=}C$), 2.05–2.14 (1H, m, $(CH_3)_2CHCHN$), 2.66–2.75 (1H, m, $(CH_3)_2CHCH{=}C$), 3.55 (1H, d, *J* 7.8, $(CH_3)_2CHCH$), 3.77 (1H, d, *J* 14.8, NCH_2Ar), 3.79 (3H, s, CH_3O), 3.80 (3H, s, CH_3O), 4.40 (1H, d, *J* 14.9, NCH_2Ar), 5.13 (1H, d, *J* 14.9, NCH_2Ar), 5.37 (1H, d, *J* 14.8, NCH_2Ar), 6.07 (1H, d, *J* 10.8, $C{=}CHCH$), 6.75 (2H, d, *J* 8.6, *Ar*), 6.80 (2H, d, *J* 8.6, *Ar*), 6.91 (2H, d, *J* 8.6, *Ar*), 7.06 (2H, d, *J* 8.6, *Ar*); δ_C (100 MHz, $CDCl_3$) 19.0, 20.1, 21.7, 22.2, 27.2, 32.5, 49.2, 49.9, 55.2, 55.3, 66.7, 113.9, 114.1, 128.0, 128.5, 128.6, 128.8, 129.0, 129.8, 130.0, 130.5, 133.6, 158.9, 159.1, 163.5, 166.9; *m*/*z* (ES^+) 451 (100%, MH^+); (found: MH^+, 451.2582; $C_{27}H_{35}N_2O_4^+$ requires 451.2597).

(3*S*,6*S*)-*N*,*N*′-Bis-(4-methoxybenzyl)-benzyl-6-isopropyl-piperazine-2,5-dione 20. (*E*)-Benzylidene **5** (755 mg, 1.55 mmol) was treated with SmI_2 and H_2O according to general procedure *2* to yield **20** (95% de) as a colourless oil (698 mg, 93%). Similar treatment of (*Z*)-benzylidene **6** (755 mg, 1.55 mmol) afforded **20** (96% de) as an oil (672 mg, 89%). Spectroscopic data was identical to the authentic sample.[5c–e,1]

(3*S*,6*S*,1′*R*)-*N*,*N*′-Bis-(4-methoxybenzyl)-3-deuterio-3-(deuteriophenylmethyl)-6-isopropyl-piperazine-2,5-dione 21. (*E*)-Benzylidene **5** (1.94 g, 4.00 mmol) was treated with SmI_2 and D_2O according to general procedure *2* to yield a 92 : 8 mixture of **21** and (**22** + **23** + **24**) as a colourless oil (1.87 g, 96%). Similar treatment of (*Z*)-benzylidene **6** or a 7 : 1 mixture of **5** and **6** afforded identical mixtures.

Data for **21**: $[\alpha]_D^{25}$ −267.5 (*c* 1.0, $CHCl_3$); ν_{max}/cm^{-1} (thin film) 1654 (C=O); δ_H (500 MHz, $CDCl_3$) 1.08 (3H, d, *J* 7.0, $(CH_3)_2CH$), 1.14 (3H, d, *J* 7.0, $(CH_3)_2CH$), 1.88–1.99 (1H, m, $(CH_3)_2CH$), 3.09 (1H, d, *J* 14.6, NCH_2Ar), 3.40 (1H, s, CHD), 3.63 (1H, d, *J* 7.9, $(CH_3)_2CHCH$), 3.77 (3H, s, CH_3O), 3.79 (3H, s, CH_3O), 3.80 (1H, d, *J* 14.9, NCH_2Ar), 5.18 (1H, d, *J* 14.9, NCH_2Ar), 5.41 (1H, d, *J* 14.9, NCH_2Ar), 6.74–6.84 (6H, m, *Ar*), 7.02–7.05 (2H, m, *Ar*), 7.25–7.37 (5H, m, *Ph*); δ_C (125 MHz, $CDCl_3$) 19.7, 20.8, 34.1, 40.0 (t, $^1J_{CD}$ 19.8), 47.4, 49.7, 55.7 (x 2), 60.5 (t, $^1J_{CD}$ 21.8), 65.8, 114.4, 114.7, 128.7, 128.2, 128.3, 129.1, 129.4, 129.6, 129.8, 129.9, 130.1, 130.7, 130.4, 130.8, 137.9, 159.7, 159.8, 166.7, 166.6; *m*/*z* (ES^+) 489 (100%, MH^+); (found: MH^+, 489.2723; $C_{30}H_{33}D_2N_2O_4^+$ requires 489.2722).

(3*S*,6*S*,1′*R*)-3-Deuterio-3-(deuteriophenylmethyl)-6-isopropyl-piperazine-2,5-dione 26. Compound **21** (488 mg, 1.0 mmol) was treated according to general procedure *3*. After washing the solid with ether, product **26** was obtained as a colourless solid (229 mg, 90%). Mp 178–180 °C; $[\alpha]_D^{25}$ −15.4 (*c* 0.50, DMSO); ν_{max}/cm^{-1} (KBr) 1667 (C=O); δ_H (400 MHz, DMSO-d_6) 0.24 (3H, d, *J* 6.8, $(CH_3)_2CH$), 0.63 (3H, d, *J* 6.8, $(CH_3)_2CH$), 1.65–1.73 (1H, m, $(CH_3)_2CH$), 2.84 (1H, s, CHD), 3.52 (1H, br s, $(CH_3)_2CHCH$), 7.13–7.25 (5H, m, *Ph*), 7.37 (1H, s, N*H*), 8.10 (1H, s, N*H*); δ_C (125 MHz, $CDCl_3$) 17.1, 19.1, 31.9, 38.3 (t, $^1J_{CD}$ 18.8), 55.5 (t, $^1J_{CD}$ 20.3), 60.1, 127.3, 128.8, 131.1, 137.1, 167.3, 167.5; *m*/*z* (ES^+) 249 (100%, MH^+); (found: MH^+, 249.1580; $C_{14}H_{17}D_2N_2O_2^+$ requires 249.1580).

(2*S*,3*R*)-2-Amino-2,3-dideuterio-3-phenylpropionic acid methyl ester 27 and (*S*)-valine methyl ester 28. **26** (800 mg, 3.22 mmol) was treated following general procedure *4* to afford a mixture of **27** and **28** as a colourless solid (700 mg). δ_H (400 MHz, $CDCl_3$) 1.07 (3H, d, *J* 7.1, $(CH_3)_2CH$), 1.09 (3H, d, *J* 7.1, $(CH_3)_2CH$), 2.26–2.35 (1H, m, $(CH_3)_2CH$), 3.21 (1H, s, CHD), 3.82 (3H, s, CH_3O), 3.86 (3H, s, CH_3O), 3.94 (1H, d, *J* 4.6, $(CH_3)_2CHCH$), 7.27–7.40 (5H, m, *Ph*). Methyl (*S*)-valinate hydrochloride was

then removed by washing the mixture with a saturated solution of $NaHCO_3$ and removal of the free (*S*)-valine methyl ester under vacuum afforded the free amino ester **27**. δ_H (400 MHz, $CDCl_3$) 3.04 (1H, s, C*H*D), 3.69 (3H, s, CH_3O), 7.09–7.36 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 40.6 (t, $^1J_{CD}$ 20), 51.9, 55.5 (t, $^1J_{CD}$ 21), 126.7, 128.6, 129.6, 137.1, 175.4. Specific rotation for the hydrochloride salt, **27**·HCl: $[a]_D^{21}$ +29.9 (*c* 0.70, EtOH), {lit.[21] +35.7 (*c* 1.06, EtOH)}.

Methyl (2*S*,3*R*)-[2,3-$^2H_2$]-*N*-acetyl-phenylalaninate 25. To a cooled solution of the free amino ester **27** (225 mg, 1.26 mmol), Et_3N (0.55 mL, 3.9 mmol) and DMAP (50 mg) in dry dichloromethane (30 mL), was added acetic anhydride (0.38 mL, 3.9 mmol) and the mixture was stirred at room temperature for 6 h. The reaction mixture was washed with 0.1 M aqueous HCl, saturated aqueous $NaHCO_3$ and brine. The organic phase was dried over $MgSO_4$ and the solvent removed *in vacuo*. Purification by chromatography (silica, petrol 40–60/ethyl acetate, 4 : 1) afforded **25** (197 mg, 71%). δ_H (400 MHz, DMSO) 1.81 (3H, s, CO*Me*), 2.97 (1H, s, C(3)H_S), 3.61 (3H, s, CO_2Me), 7.21–7.35 (5H, m, Ar*H*), 8.37 (1H, br s, N*H*).

Selected literature data[19] for methyl (*RS*)-*N*-acetyl-phenylalaninate (^{1}H 400 MHz, DMSO) 2.86 (1H, dd, *J* 13.7, 9.3, C(3)H_R), 3.00 (1H, dd, *J* 13.7, 5.4, C(3)H_S), 4.44 (1H, ddd, *J* 9.3, 7.3, 5.4, C(2)H); for methyl (2*S*,3*R*)-[3-^{2}H]-*N*-acetyl-phenylalaninate (^{1}H 800 MHz, DMSO) 2.98 (1H, d, *J* 5.5, C(3)H_S); methyl (2*S*,3*S*)-[2,3-$^2H_2$]-*N*-acetyl-phenylalaninate (^{1}H 400 MHz, DMSO) 2.84 (1H, s, C(3)H_R).

(3*R*,6*S*,1′*R*)-*N*,*N*′-Bis-(4-methoxybenzyl)-3-deuterio-3-(deuteriophenylmethyl)-6-isopropyl-piperazine-2,5-dione 30. Isobutylidene **7** (1.8 g, 4.0 mmol) was treated according to general procedure *5* to yield **30** [79 : 16 : 5 mixture of **30 : 31** : (**32** + **33**)] as a colourless oil (1.78 g, 98%). $[a]_D^{25}$ −219.6 (*c* 1.0, $CHCl_3$); ν_{max}/cm^{-1} (thin film) 1660 (C=O); δ_H (400 MHz, $CDCl_3$) 0.96 (3H, d, *J* 6.6, (CH_3)$_2$CHCD), 0.97 (3H, d, *J* 6.3, (CH_3)$_2$CHCD), 1.11 (3H, d, *J* 6.8, (CH_3)$_2$CHCH), 1.18 (3H, d, *J* 6.8, (CH_3)$_2$CHCH), 1.82 (1H, d, *J* 5.1, (CH$_3$)$_2$CHC*H*D), 1.95–2.01 (1H, m, (CH$_3$)$_2$C*H*CHD), 2.13–2.22 (1H, m, (CH$_3$)$_2$C*H*CHN), 3.65 (1H, d, *J* 7.6, (CH$_3$)$_2$CHC*H*N), 3.78 (1H, d, *J* 14.7, NCH_2Ar), 4.79 (1H, d, *J* 14.7, NCH_2Ar), 3.81 (6H, s, 2 × CH_3O), 5.23 (1H, d, *J* 14.7, NCH_2Ar), 5.40 (1H, d, *J* 14.7, NCH_2Ar), 6.83–6.87 (4H, m, *Ar*), 7.06–7.10 (4H, m, *Ar*); δ_C (100 MHz, $CDCl_3$) 19.8, 20.7, 21.8, 23.1, 25.8, 33.4, 43.4 (t, $^1J_{CD}$ 18.8), 46.6, 48.9, 55.3, 56.8 (t, $^1J_{CD}$ 20.2), 65.3, 114.2, 114.3, 126.9, 127.9, 128.1, 128.2, 128.3, 129.1, 129.3, 159.2, 159.3, 166.1, 167.7; *m*/*z* (ES$^+$) 455.1 (100%, MH$^+$); (found: MH$^+$, 455.2879; $C_{27}H_{35}D_2N_2O_4^+$ requires 455.2879).

(3*S*,6*S*,1′*S*)-*N*,*N*′-Bis-(4-methoxybenzyl)-[3-^{2}H,1′-^{2}H]-3-benzyl-6-isopropyl-piperazine-2,5-dione 31. Isobutylidene **8** (0.90 g, 2.0 mmol) was treated according to general procedure *2* to yield **31** [13 : 85 : 2 mixture of **30 : 31** : (**32** + **33**)] as a colourless oil (860 mg, 95%). $[a]_D^{25}$ −181.0 (*c* 1.0, $CHCl_3$); ν_{max}/cm^{-1} (thin film) 1643 (C=O); δ_H (400 MHz, $CDCl_3$) 0.95 (3H, d, *J* 6.6, (CH_3)$_2$CHCD), 0.96 (3H, d, *J* 6.6, (CH_3)$_2$CHCD), 1.10 (3H, d, *J* 6.8, (CH_3)$_2$CHCH), 1.16 (3H, d, *J* 6.8, (CH_3)$_2$CHCH), 1.52 (1H, d, *J* 9.1, (CH$_3$)$_2$CHC*H*D), 1.93–2.02 (1H, m, (CH$_3$)$_2$C*H*CHD), 2.11–2.20 (1H, m, (CH$_3$)$_2$C*H*CHN), 3.64 (1H, d, *J* 7.6, (CH$_3$)$_2$CHC*H*N), 3.76 (1H, d, *J* 14.9, NCH_2Ar), 3.78 (1H, d, *J* 14.7, NCH_2Ar), 3.79 (6H, s, 2 × CH_3O), 5.22 (1H, d, *J* 14.7, NCH_2Ar), 5.38 (1H, d, *J* 14.9, NCH_2Ar), 6.81–6.83 (4H, m, *Ar*), 7.05–7.09 (4H, m, *Ar*); δ_C (100 MHz, $CDCl_3$) 19.8, 20.7, 21.8, 23.1, 25.8, 33.4, 43.4 (t, $^1J_{CD}$ 18.3), 46.6, 48.9, 55.3, 56.8 (t, $^1J_{CD}$ 20.0), 65.3, 114.2, 114.3, 127.9, 128.1, 129.1, 129.3, 159.2, 159.3, 166.1, 167.7; *m*/*z* (ES$^+$) 455.1 (100%, MH$^+$); (found: MH$^+$, 455.2876; $C_{27}H_{35}D_2N_2O_4^+$ requires 455.2879).

(3*S*,6*R*)-*N*,*N*′-Bis(4-methoxybenzyl)-3-isopropyl-6-isobutyl-piperazine-2,5-dione 35. To a degassed solution of **10**[5a,b] (200 mg, 0.5 mmol) in dry THF (10 ml) was added lithium hexamethyldisilazide (0.55 ml, 1 M solution in THF, 0.55 mmol) at −78 °C; after stirring for 1 hour the mixture was treated with isobutyliodide (0.063 ml, 0.55 mmol). The mixture was stirred for 1 hour at −78 °C and then allowed to slowly warm to room temperature over 12 hours. Aqueous saturated NH_4Cl (10 ml) was added and the mixture was partitioned between ether and water, extracted with ether, the combined organic layers were dried ($MgSO_4$) and the solvent removed to afford a 34 : 33 : 33 mixture of **10, 35** and **36**. Chromatography (silica, 30–40 petrol/ether, 1 : 1) afforded **35** as a colourless oil (69 mg, 31%). $[a]_D^{20}$ +25.4 (*c* 0.50, $CHCl_3$); ν_{max}/cm^{-1} (KBr) 1650 (C=O); δ_H (400 MHz, $CDCl_3$) 0.77 (3H, d, *J* 7.1, (CH_3)$_2$CH), 0.82 (3H, d, *J* 6.6, (CH_3)$_2$CHCH$_2$), 0.92 (3H, d, *J* 6.8, (CH_3)$_2$CHCH$_2$), 1.11 (3H, d, *J* 6.8, (CH_3)$_2$CH), 1.62–1.75 (1H, m, (CH$_3$)$_2$C*H*CH$_2$), 1.89–1.95 (1H, m, (CH$_3$)$_2$CHCH_2), 2.00–2.05 (1H, m, (CH$_3$)$_2$CHCH_2), 2.28–2.39 (1H, m, (CH$_3$)$_2$C*H*), 3.75 (1H, d, *J* 14.6, ArCH_2), 3.80 (1H, d, *J* 7.6, (CH$_3$)$_2$C*H*N), 3.81 (3H, s, CH_3O), 3.82 (3H, s, CH_3O), 3.88 (1H, d, *J* 14.6, ArCH_2), 3.96–4.00 (1H, m, (CH$_3$)$_2$CHCH$_2$C*H*), 5.32 (1H, d, *J* 14.6, ArCH_2), 5.47 (1H, d, *J* 14.6, ArCH_2), 6.84–6.87 (4H, m, aromatic C*H*), 7.16–7.24 (4H, m, aromatic C*H*); δ_C (100 MHz, $CDCl_3$) 16.3, 19.9, 22.6, 23.5, 24.1, 31.4, 38.9, 45.4, 46.8, 55.2, 55.3, 56.4, 62.8, 114.0, 114.1, 127.2, 127.7, 130.0, 130.1, 159.2. 159.3, 165.3, 167.1; *m*/*z* (ES$^+$) 511.4 (100%, MNH$_4^+$ + MeCN); (found: MH$^+$, 453.2742; $C_{27}H_{37}N_2O_4^+$ requires 453.2753).

(3*S*,6*S*,1′*R*)-3-Deuterio-3-(1-deuterio-2-methylpropyl)-6-isopropylpiperazine-2,5-dione 39. **30** (908 mg, 2.0 mmol) was treated according to general procedure *3*. After washing the solid with ether, product **39** was obtained as a colourless solid (334 mg, 78%). Mp 151–153 °C; $[a]_D^{25}$ −28.5 (*c* 1.0, DMSO); ν_{max}/cm^{-1} (KBr) 1657, 1662 (2 × C=O); δ_H (400 MHz, DMSO-d_6) 0.84 (3H, d, *J* 6.8, (CH_3)$_2$CHCD), 0.85 (3H, d, *J* 6.3, (CH_3)$_2$CHCD), 0.87 (3H, d, *J* 6.6, (CH_3)$_2$CHCH), 0.94 (3H, d, *J* 7.1, (CH_3)$_2$CHCH), 1.58 (1H, d, *J* 8.8, (CH$_3$)$_2$CHC*H*D), 1.78–1.87 (1H, m, (CH$_3$)$_2$C*H*CHD), 2.04–2.16 (1H, m, (CH$_3$)$_2$C*H*CHN), 3.60–3.61 (1H, m, (CH$_3$)$_2$CHC*H*N), 8.04 (1H, br s, NH), 8.16 (1H, br s, NH); δ_C (100 MHz, $CDCl_3$) 18.2, 19.6, 22.6, 23.9, 24.3, 32.3, 44.3 (t, $^1J_{CD}$ 18.8), 52.9 (t, $^1J_{CD}$ 23.4), 60.4, 167.7, 169.3; *m*/*z* (ES$^+$) 215.1 (100%, MH$^+$); (found: MH$^+$, 215.1731; $C_{11}H_{19}D_2N_2O_2^+$ requires 215.1729).

(2*S*,3*R*)-2-Amino-2,3-dideuterio-4-methylpentanoic acid methyl ester 41 and (*S*)-valine methyl ester 28. **39** (450 mg, 2.10 mmol) was treated following general procedure *5* to afford a mixture of **41** and **28** as a colourless solid (400 mg) which was used without further purification. δ_H (400 MHz, CD_3OD) 1.01 (3H, d, *J* 6.5, (CH_3)$_2$CHCHD), 1.02 (3H, d, *J* 6.5, (CH_3)$_2$CHCHD), 1.07 (3H, d, *J* 7.1, (CH_3)$_2$CHCHN), 1.09 (3H, d, *J* 7.1, (CH_3)$_2$CHCHN), 1.75–1.85 (2H, m, (CH_3)$_2$CHCHD and *C*HD), 2.26–2.35 (1H, m, (CH$_3$)$_2$C*H*CHN), 3.86 (3H, s, OCH_3), 3.87 (3H, s, OCH_3), 3.95 (1H, d, *J* 4.4, (CH$_3$)$_2$CHC*H*).

***N*-Cbz-(*S*)-phenylalanine-(2*S*,3*R*)-2-amino-2,3-dideuterio-4-methyl-pentanoic acid methyl ester 37.** Amino-ester hydrochloride salts **28** and **41** (400 mg) were treated following general procedure *5*. Purification by chromatography afforded **37** as a colourless solid (350 mg, 84%). Mp 87 °C; $[a]_D^{25}$ −3.0 (*c* 1.0, $CHCl_3$); ν_{max}/cm^{-1} (KBr) 1667, 1692 & 1655 (3 × C=O); δ_H (500 MHz, $CDCl_3$) 0.89 (6H, t, *J* 6.1, (CH_3)$_2$CH), 1.48–1.56 (2H, m, (CH$_3$)$_2$C*H* and C*H*D), 3.05 (1H, dd, *J* 7.0, 13.9, CH_2Ph), 3.13 (1H, dd, *J* 6.3, 14.0, CHCH_2Ph), 3.70 (3H, s, OCH_3), 4.43–4.47 (1H, m, C*H*CH$_2$Ph), 5.10 (2H, s, OCH_2Ph), 5.31 (1H, br s, N*H*CH), 6.14 (1H, s, N*H*CD), 7.20–7.39 (10H, m, 2 × *Ph*); δ_C (125 MHz, $CDCl_3$) 21.8, 22.5, 24.5, 38.2, 40.9 (t, $^1J_{CD}$ 19.3), 50.4 (t, $^1J_{CD}$ 21.4), 52.1, 55.9, 67.0, 126.9, 127.9, 128.1, 128.4, 128.5, 129.3, 136.0, 136.1, 159.8, 170.4, 172.6; *m*/*z* (ES$^+$) 429 (100%, MH$^+$); (found: MH$^+$, 429.2359; $C_{24}H_{29}D_2N_2O_5^+$ requires 429.2359).

(3*S*,6*S*,1′*S*)-3-Deuterio-3-(1-deuterio-2-methylpropyl)-6-isopropylpiperazine-2,5-dione 40. **31** (908 mg, 2.0 mmol) was treated

according to general procedure *3*. After washing the solid with ether, product **40** was obtained as a colourless solid (355 mg, 83%). Mp 154–156 °C; $[\alpha]_D^{25}$ −31.0 (*c* 0.50, DMSO); ν_{max}/cm^{-1} (KBr) 1662 (2 × C=O); δ_H (400 MHz, DMSO-d_6) 0.84 (3H, d, *J* 6.8, $(CH_3)_2CHCD$), 0.86 (3H, d, *J* 6.6, $(CH_3)_2CHCD$), 0.87 (3H, d, *J* 6.8, $(CH_3)_2CHCH$), 0.94 (3H, d, *J* 7.1, $(CH_3)_2CHCH$), 1.41 (1H, d, *J* 5.3, $(CH_3)_2CHCHD$), 1.77–1.87 (1H, m, $(CH_3)_2CHCHD$), 2.06–2.14 (1H, m, $(CH_3)_2CHCHN$), 3.60–3.61 (1H, m, $(CH_3)_2CHCHN$), 8.05 (1H, br s, NH), 8.16 (1H, br s, NH); δ_C (100 MHz, $CDCl_3$) 18.2, 19.6, 22.6, 23.9, 24.3, 32.3, 44.3 (t, $^1J_{CD}$ 18.9), 52.9 (t, $^1J_{CD}$ 22.9), 60.4, 167.7, 169.3; *m/z* (ES^+) 215.1 (100%, MH^+); (found: MH^+, 215.1727; $C_{11}H_{19}D_2N_2O_2^+$ requires 215.1729).

(2*S*,3*S*)-2-Amino-2,3-dideuterio-4-methylpentanoic acid methyl ester 42 and (*S*)-valine methyl ester 28. **40** (350 mg, 1.65 mmol) was treated following general procedure *4* to afford a colourless solid (320 mg) which was used without further purification. δ_H (400 MHz, CD_3OD) 1.01 (3H, d, *J* 6.5, $(CH_3)_2CHCHD$), 1.02 (3H, d, *J* 6.5, $(CH_3)_2CHCHD$), 1.08 (3H, d, *J* 7.2, $(CH_3)_2CHCHN$), 1.09 (3H, d, *J* 7.2, $(CH_3)_2CHCHN$), 1.68 (1H, d, *J* 6.9, CHD), 1.75–1.85 (1H, m, $(CH_3)_2CHCHD$), 2.27–2.35 (1H, m, $(CH_3)_2CHCHN$), 3.86 (3H, s, OCH_3), 3.87 (3H, s, OCH_3), 3.95 (1H, d, *J* 4.4, $(CH_3)_2CHCH$).

***N*-Cbz-(*S*)-phenylalanine-(2*S*,3*S*)-2-amino-2,3-dideuterio-4-methyl-pentanoic acid methyl ester 38.** An amino-ester hydrochloride mixture of **28** and **42** (300 mg) was treated following general procedure *5* to afford **38** (280 mg, 75%) as a colourless solid. Mp 89 °C; $[\alpha]_D^{25}$ −2.0 (*c* 1.0, $CHCl_3$); ν_{max}/cm^{-1} (KBr) 1650, 1690, 1749 (3 × C=O); δ_H (400 MHz, $CDCl_3$) 0.89 (6H, t, *J* 6.1, $(CH_3)_2CH$), 1.43 (1H, d, *J* 7.5, CHD), 1.48–1.56 (1H, m, $(CH_3)_2CH$), 3.04–3.13 (2H, m, CH_2Ph), 3.13 (1H, dd, *J* 6.3, 14.0, $CHCH_2Ph$), 3.70 (3H, s, OCH_3), 4.45–4.50 (1H, m, $CHCH_2Ph$), 5.09 (2H, s, OCH_2Ph), 5.43 (1H, br s, $NHCH$), 6.36 (1H, s, $NHCD$), 7.18–7.38 (10H, m, 2 × *Ph*); δ_C (100 MHz, $CDCl_3$) 21.9, 22.6, 24.6, 32.4, 40.9 (t, $^1J_{CD}$ 19.6), 50.4 (t, $^1J_{CD}$ 22.0), 52.3, 56.0, 67.0, 127.0, 128.0, 128.2, 128.5, 128.6, 129.4, 136.1, 136.3, 155.9, 170.6, 172.8; *m/z* (ES^+) 429 (MH^+, 100%); (found: MH^+, 429.2355; $C_{24}H_{29}D_2N_2O_5^+$ requires 429.2359).

***N*-Cbz-(*S*)-phenylalanine-(2*S*)-2-amino-4-methylpentanoic acid methyl ester 44.** (*S*)-Leucine methylester hydrochloride (400 mg, 2.20 mmol) was treated following general procedure *5*. After work up and purification by chromatography, **44** was afforded as a colourless solid (863 mg, 92%). $[\alpha]_D^{20}$ −2.4 (*c* 0.50, $CHCl_3$); ν_{max}/cm^{-1} (KBr) 1667, 1692, 1749 (3 × C=O); δ_H (400 MHz, $CDCl_3$) 0.90 (6H, m, $(CH_3)_2CH$), 1.43–1.62 (3H, m, $(CH_3)_2CH$ and $(CH_3)_2CHCH_2$), 3.06 (1H, dd, *J* 6.8, 13.9, $CHCH_2Ph$), 3.12 (1H, dd, *J* 6.6, 13.9, $CHCH_2Ph$), 3.71 (3H, s, OCH_3), 4.44–4.60 (2H, m, $CHNH$ and $CHCH_2Ph$), 5.10 (2H, s, OCH_2Ph), 5.38 (1H, br s, $NHCH$), 6.27 (1H, s, $NHCD$), 7.19–7.39 (10H, m, 2 × *Ph*); δ_C (100 MHz, $CDCl_3$) 21.8, 22.6, 24.6, 32.3, 41.4, 50.7, 52.2, 56.0, 67.0, 127.0, 128.0, 128.2, 128.5, 128.6, 129.3, 136.1, 136.2, 156.0, 170.5, 172.7; *m/z* (ES^+) 485.4 (100%, MNH_4^+ + MeCN); (found: MH^+, 427.2236; $C_{24}H_{31}N_2O_5^+$ requires 427.2233).

(*Z*)-2-Acetylamino-4-methyl-pent-2-enoic acid methyl ester 45. To a suspension of *N*-acetylglycine (Aldrich®, 11.7 g, 100 mmol) in MeOH (60 ml), $SOCl_2$ was added (14.6 ml, 200 mmol) at 0 °C. The resulting clear solution was stirred at room temperature overnight. The reaction mixture was evaporated to give *N*-acetyl glycine methyl ester **46** as a colourless solid (11.79 g, 90%). δ_H (400 MHz, MeOD-d_4) 2.03 (3H, s, CH_3), 3.73 (3H, s, CH_3O), 3.95 (2H, s, CH_2).

A mixture of the glycine derivative **46** (3.99 g, 30.5 mmol) and *N*-bromosuccinimide (5.97 g, 33.5 mmol) in CCl_4 (250 mL) was heated at reflux for five hours under nitrogen, whilst being irradiated with a sunlamp. The mixture was then cooled to room temperature and filtered, and the filtrate was concentrated under reduced pressure, to afford the α-bromoglycine derivative (5.45 g, 85%) as a pale orange oil. δ_H (400 MHz, $CDCl_3$) 2.11 (3H, s, CH_3), 3.87 (3H, s, CH_3O), 6.48 (1H, d, *J* 10.3, CH), 7.10 (1H, br d, *J* 10.3, NH); δ_C (100 MHz, $CDCl_3$) 23.3, 48.8, 53.7, 167.3, 169.2. To a solution of α-bromo-*N*-acetylglycine methyl ester (1.45 g, 6.9 mmol) in ethyl acetate (38 ml) was added trimethyl phosphite (0.81 mL, 6.9 mmol). The resulting solution was stirred at room temperature overnight. The mixture was evaporated to afford methyl-2-(acetylamino)-2-(dimethylphosphoryl) acetate (1.31 g, 80%) as a yellow oil. ν_{max}/cm^{-1} (thin film) 1747, 1653 (2 × C=O); δ_H (400 MHz, $CDCl_3$) 2.09 (3H, s, CH_3), 3.80 (3H, s, CH_3O), 3.83 (3H, s, CH_3O), 3.85 (3H, s, CH_3O), 5.22 (1H, d *J* 8.87, PCH), 6.60 (1H, br s, NH); δ_C (100 MHz, $CDCl_3$) 22.7, 50.0 (d, $^1J_{PC}$ 148.9), 53.3, 54.2, 54.4, 167.0, 170.0; *m/z* (ES^+) 298 (100%, MNH_4^+ + MeCN); (found: MNa^+, 262.0463; $C_7H_{14}NONaP^+$ requires 262.0456).

Finally, to a solution of methyl-2-(acetylamino)-2-(dimethylphosphoryl) acetate (680 mg, 2.84 mmol) in tetrahydrofuran (10.5 ml) at −78 °C under nitrogen, was added 1,1,3,3-tetramethylguanidine (0.43 mL, 2.70 mmol). After stirring for fifteen minutes, isobutyraldehyde (0.3 ml, 2.58 mmol) was added in one portion. The mixture was stirred for 2 h at −78 °C, then 30 min at 25 °C. After diluting with ethyl acetate, the solution was washed with aqueous ammonium chloride. Then the aqueous layer was extracted with ethyl acetate and finally the solvent was evaporated *in vacuo* to recover a yellow oil. Chromatography (petrol 40–60/ethyl acetate, 1 : 1) afforded **45** as a pale yellow oil (473 mg, 90%). δ_H (400 MHz, $CDCl_3$) 1.05 (6H, d, *J* 6.48, $(CH_3)_2CH$), 2.12 (3H, s, CH_3), 2.45–2.68 (1H, m, $(CH_3)_2CH$), 3.77 (3H, s, CH_3O), 6.52 (1H, d, *J* 10.5, CH), 6.72 (1H, br s, NH); δ_C (100 MHz, $CDCl_3$) 21.5, 23.3, 28.1, 52.3, 122.9, 145.9, 165.4, 169.1; *m/z* (CI^+) 186 (100%, MH^+); (found: MH^+, 186.1129; $C_9H_{16}NO_3^+$ requires 186.1130).

(*RS*)-2-Acetylamino-2,3-dideuterio-4-methyl-pentanoic acid methyl ester 47. A solution of (*Z*)-2-acetylamino-4-methylpent-2-enoic acid methyl ester **45** (300 mg, 1.62 mmol) and Wilkinson's catalyst (75 mg) in deuterated methanol (12 ml) was degassed under nitrogen. The atmosphere inside the flask was replaced with deuterium gas and the mixture stirred for 2 days under 1 atmosphere of deuterium gas. The reaction mixture was then filtered through Celite® and the filter cake washed with diethyl ether. Solvents were removed *in vacuo* and *rac*-2-acetylamino-2,3-dideuterio-4-methylpentanoic acid methyl ester **47** was obtained as a pale yellow oil (294 mg, 97%). ν_{max}/cm^{-1} (thin film) 1747, 1656 (2 × C=O); δ_H (400 MHz, $CDCl_3$) 0.90 (3H, d, *J* 6.56, CH_3CH), 0.91 (3H, d, *J* 6.56, CH_3CH), 1.47 (1H, br d, *J* 5.30, CHD), 1.59–1.67 (1H, m, $(CH_3)_2CH$), 1.99 (3H, s, CH_3CO), 3.70 (3H, s, CH_3O), 6.14 (1H, br s, NH); δ_C (100 MHz, $CDCl_3$) 21.9, 22.7, 23.1, 24.7, 41.2 (t, $^1J_{CD}$ 19.2), 50.5 (t, $^1J_{CD}$ 23.2), 52.2, 169.9, 173.7; *m/z* (CI^+) 190.2 (100%, MH^+); (found: MH^+, 190.1410; $C_9H_{16}D_2NO_3^+$ requires 190.1412).

2-Amino-2,3-dideuterio-4-methyl-pentanoic acid methyl ester hydrochloride 42. *Rac*-2-acetylamino-2,3-dideuterio-4-methyl-pentanoic acid methyl ester **47** (100 mg, 0.53 mmol) was refluxed in HCl conc. for 12 h. After 12 h, aqueous HCl was evaporated at low pressure and *rac*-2-amino-2,3-dideuterio-4-methylpentanoic acid hydrochloride as a colourless solid was recovered. Yield: quant.; ν_{max}/cm^{-1} (KBr) 3428 (OH), 1610 (C=O); δ_H (400 MHz, D_2O) 0.84 (3H, d, *J* 6.06, CH_3CH), 0.86 (3H, d, *J* 6.06, CH_3CH), 1.59–1.68 (2H, m, $(CH_3)_2CH$ and CHD); δ_C (100 MHz, D_2O) 21.2, 21.9, 24.2, 28.5 (t, $^1J_{CD}$ 19.2), 38.8 (t, $^1J_{CD}$ 20.0), 173.4.

2-Amino-2,3-dideuterio-4-methylpentanoic acid hydrochloride (84.7 mg, 0.5 mmol) was stirred for 12 h in $SOCl_2$ (0.068 mL, 0.90 mmol) and MeOH (25 mL) then the solvent was evaporated at low pressure and **42** was recovered as a colourless solid (83.5 mg, 91%); δ_H (400 MHz, CD_3OD) 0.90–0.93 (6H, br m,

(CH_3)$_2$CH), 1.58–1.70 (2H, br m, (CH_3)$_2$C*H* and C*H*D), 3.77 (3H, s, CH_3O); δ_C (125 MHz, CD_3OD) 25.0, 25.2, 27.9, 42.8 (t, $^1J_{CD}$ 20.0), 54.9 (t, $^1J_{CD}$ 23.0), 56.9, 173.7.

***N*-Cbz-(*S*)-phenylalanine-(2*S*,3*S*)-2-amino-2,3-dideuterio-4-methyl-pentanoic acid methyl ester 38 and *N*-Cbz-(*S*)-phenylalanine-(2*R*,3*R*)-2-amino-2,3-dideuterio-4-methyl-pentanoic acid methyl ester 48.** Methyl aminoester hydrochloride salt (2*RS*,3*RS*)-**42** (400 mg, 2.18 mmol) was treated following general procedure *5* which after work up afforded a 1 : 1 mixture of **38** and **48** as a colourless solid (933 mg, 89%). Purification by chromatography (silica, petrol 30–40/ether, 5 : 1) afforded a sample of **48** (~10% contaminated with **38**) followed by **38**. Data for **48**: mp 90 °C; ν_{max}/cm^{-1} (KBr) 1736, 1675 (2 × C=O); δ_H (400 MHz, $CDCl_3$) 0.87–0.93 (6H, m, (CH_3)$_2$CH), 1.35–1.41 (2H, m, (CH_3)$_2$C*H* and C*H*D), 3.03–3.22 (2H, m, CH_2Ph), 3.72 (3H, s, CH_3O), 4.42–4.54 (1H, m, C*H*CH$_2$Ph), 5.12 (2H, s, OCH_2Ph), 5.39 (1H, br s, N*H*CH), 6.10 (1H, s, N*H*CD), 7.21–7.41 (10H, m, 2 × *Ph*); δ_C (100 MHz, $CDCl_3$) 21.8, 22.6, 24.5, 38.5, 40.7 (t, $^1J_{CD}$ 19.3), 50.2 (t, $^1J_{CD}$ 21.9), 52.1, 56.1, 67.0, 126.9, 127.9, 128.1, 128.4, 128.5, 129.3, 136.0, 136.1, 159.8, 170.4, 172.6; *m*/*z* (ES$^+$) 487 (100%, MNH_4^+ + MeCN); (found: MH$^+$, 429.2362; $C_{24}H_{29}D_2N_2O_5^+$ requires 429.2359).

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