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Asymmetric synthesis of substituted 1-aminocyclopropane-1-carboxylic acids *via* diketopiperazine methodology

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Diketopiperazinespirocyclopropane **12** is prepared in > 98% d.e. *via* the conjugate addition of a phosphorus ylide to (6*S*)-*N*,*N*′-bis(*p*-methoxybenzyl)-3-methylenepiperazine-2,5-dione **2**. Deprotection and hydrolysis of adduct **12** and subsequent peptide coupling demonstrate the applicability of this methodology to the asymmetric synthesis of 1-aminocyclopropane-1-carboxylic acids for incorporation into novel peptides. A model for the high level of diastereofacial selectivity observed in the cyclopropanation reaction is presented. A highly selective asymmetric approach (> 98% d.e.) to (*S*)-[2,2-$^{2}H_2$]-1-aminocyclopropane-1-carboxylic acid **29** is also reported *via* a deuterated sulfur ylide addition to acceptor **2**.

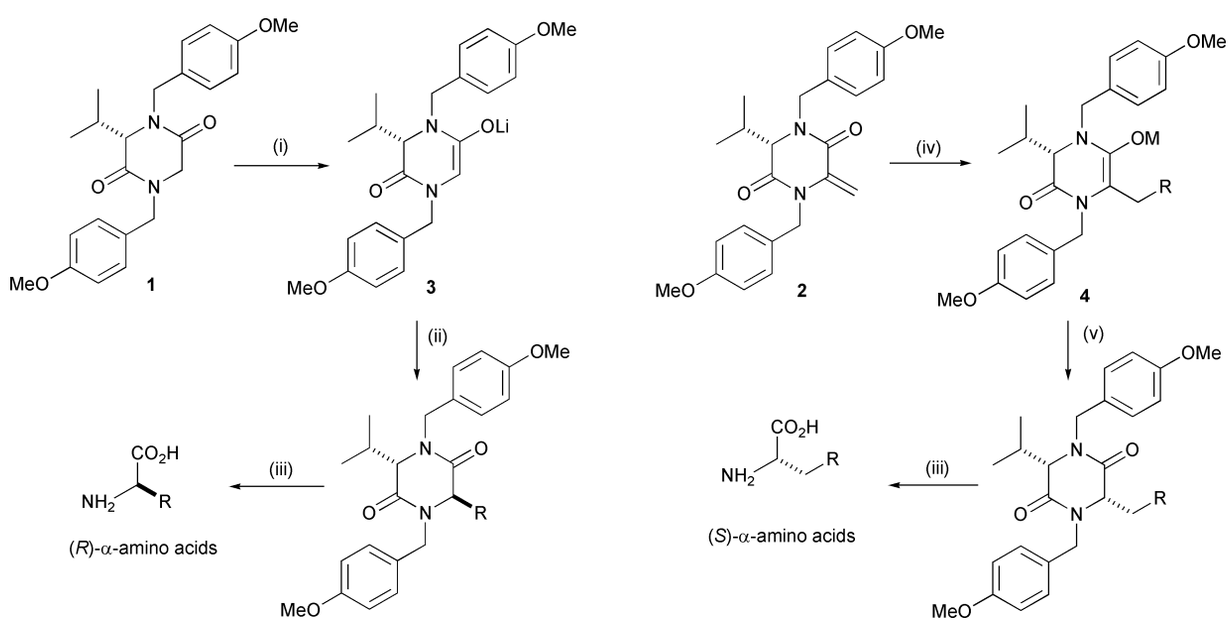
Introduction

The construction of peptides incorporating non-proteinogenic α-amino acids, which restrict the conformational flexibility of the peptide, is an active area of research. Three major classes of residue have been identified as allowing subtle perturbations of overall structure without wholly disrupting secondary structural features: α-methyl-α-amino acids, β-methyl-α-amino acids and 1-aminocyclopropane-1-carboxylic acids.[1,2] The aminocyclopropanecarboxylic acids are of particular interest due to their potent biological activity,[3] and the importance of the parent 1-aminocyclopropane-1-carboxylic acid in the biosynthesis of ethylene, a significant plant hormone.[4] The asymmetric synthesis of these residues has been approached in a number of ways,[5] including the alkylation of glycine enolate equivalents with 1,2-bis-electrophiles,[6] cyclisation of γ-functionalised α-amino acids, asymmetric ylide reactions,[7] and diazoalkyl cycloaddition chemistry,[8] in addition to a number of resolution approaches.[9] Previous work within this laboratory has delineated a diketopiperazine derived chiral relay auxiliary for the asymmetric synthesis of (*R*)-α-amino acids, *via* the alkylation of lithium enolate **3**, and the synthesis of (*S*)-α-amino acids *via* conjugate addition of organocuprates to the related dehydroalanine acceptor **2**, followed by diastereoselective protonation of the enolate **4** (Scheme 1).[10]

As part of the ongoing development of *N*-protected diketopiperazine auxiliary methodology for the asymmetric synthesis of quaternary α-amino acids, we report herein the cyclopropanation of acceptor **2** for the synthesis of dipeptides containing 1-aminocyclopropane-1-carboxylic acid residues.

Results and discussion

The synthesis of 1-aminocyclopropane-1-carboxylic acids has been achieved previously *via* the elaboration of dehydro-amino acid derived substrates, with the application of a sulfur or phosphorus ylide conjugate addition–elimination protocol an attractive method for the synthesis of cyclopropane rings from



Scheme 1 *Reagents and conditions*: (i) LHMDS, THF, −78 °C; (ii) alkyl halide, THF, −78 °C; (iii) CAN (6 equivalents), H_2O, CH_3CN; then 6 M HCl, 100 °C; (iv) 2 × RMgX or 2 × RLi, CuCN, $BF_3{\cdot}OEt_2$; THF, −78 °C; (v) NH_4Cl_{aq}.

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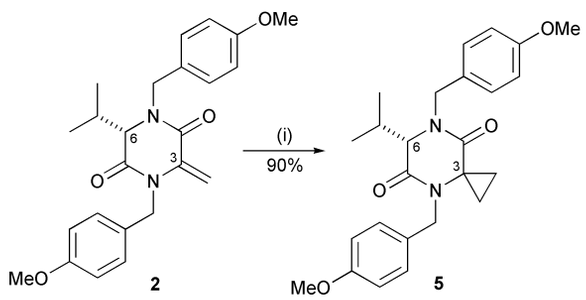
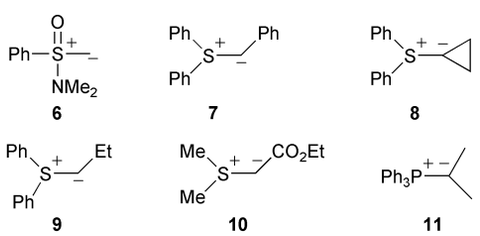
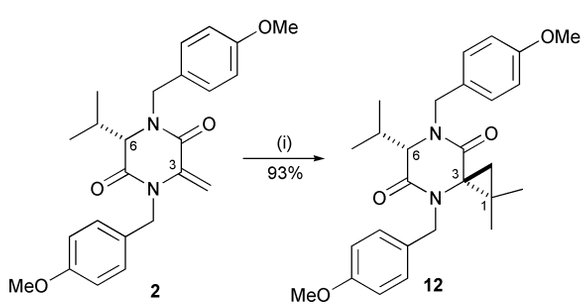
this class of substrate.[11] To evaluate the suitability of this methodology towards diketopiperazine auxiliary chemistry, initial model studies focused on the addition of a simple sulfur ylide, dimethylsulfoxonium methylide,[12] to the methylene acceptor **2**. Treatment of trimethylsulfoxonium iodide with butyllithium followed by the addition of acceptor **2** at room temperature provided (6*S*)-*N*,*N*′-bis(*p*-methoxybenzyl)piperazine-2,5-dione-3-spiro-1-cyclopropane **5** in excellent yield (90%) after chromatographic purification (Scheme 2).



Scheme 2 *Reagents and conditions*: (i) Me_2SOCH_2Li, THF, room temperature.

Having established the viability of this cyclopropanation protocol, studies focused on the extension of this methodology to the preparation of substituted cyclopropane rings. A number of substituted sulfur ylides **6**–**10**[13] were assayed for reaction with acceptor **2** but, in contrast to the trimethylsulfoxonium derived ylide, no addition products could be detected. However, treatment of **2** with the phosphonium derived ylide, isopropylidenetriphenylphosphorane **11**,[14] generated *in situ* from butyllithium and isopropyltriphenylphosphonium iodide, did afford (3*S*,6*S*)-*N*,*N*′-bis(*p*-methoxybenzyl)-6-isopropylpiperazine-2,5-dione-3-spiro-1,1-dimethylcyclopropane **12** in an excellent isolated yield (93%). Only a single diastereoisomer could be detected in the ^{1}H NMR spectrum of the crude reaction mixture (> 98% d.e.) demonstrating excellent diastereoselectivity for the overall cyclopropanation process (Scheme 3).





Scheme 3 *Reagents and conditions*: (i) $Me_2C(Li)PPh_3$, THF, room temperature.

The relative configuration of the C3 and C6 stereogenic centres within **12** was initially assigned from ^{1}H NMR NOESY experiments since a cross peak was observed between the isopropyl Me_2CH and one of the cyclopropane ring *gem*-dimethyl substituents, consistent with a *cis* relationship between these groups (Fig. 1). Further corroborating NOESY correlations were not available from NOESY data due to poor signal dispersion in the ^{1}H NMR spectrum, however the assigned configuration was unambiguously confirmed by single crystal X-ray crystallographic analysis, with the absolute (3*S*,6*S*)-configuration being derived from the known configuration of (*S*)-valine (Fig. 2).

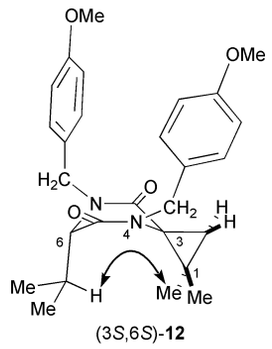


Fig. 1 Selected ^{1}H NOESY correlations for **12**.

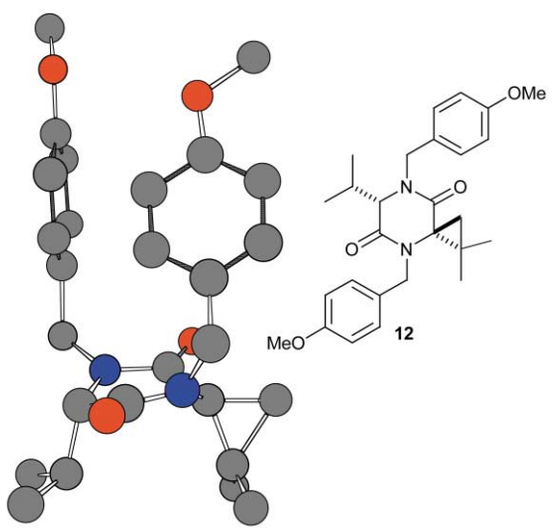
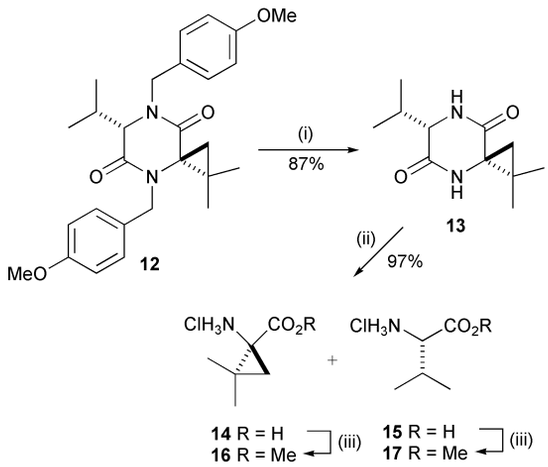


Fig. 2 Chem3D representation of X-ray crystal structure of **12**.[15]

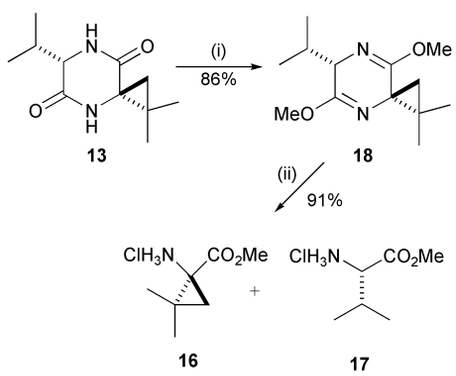
In order to demonstrate the effectiveness of this strategy for the synthesis and incorporation of 1-aminocyclopropane-1-carboxylic acids into linear peptides, the deprotection and hydrolysis of diketopiperazine **12**, and subsequent peptide coupling of the resultant hindered 1-aminocyclopropane-1-carboxylic acid was investigated. Treatment of **12** with refluxing trifluoroacetic acid provided **13** in 87% yield, with hydrolysis in 6 M HCl at 100 °C affording a mixture of α-amino acid hydrochlorides **14** and **15** which were converted to the corresponding methyl ester hydrochloride salts **16** and **17** in excellent yield (97%) (Scheme 4).

An alternative route for the preparation of methyl ester hydrochloride salts **16** and **17**, avoiding the harsh amide hydrolysis conditions, was also achieved through conversion of **13** to bis-lactim ether **18** (86% yield) by treatment with trimethyloxonium tetrafluoroborate in the ionic liquid, *N*-butyl-*N*′-methylimidazolium tetrafluoroborate ($BmimBF_4$).[16] Mild hydrolysis of bis-lactim ether **18** with 2 M HCl for two hours at room temperature afforded a mixture of methyl ester hydrochloride salts **16** and **17** in high yield (91%) (Scheme 5).

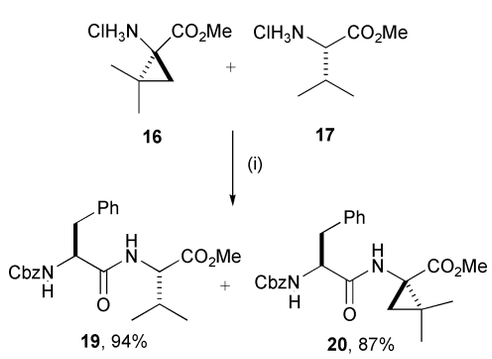
Coupling of the mixture of (*S*)-valine and dimethyl substituted α-amino acid methyl esters **16** and **17** with (*S*)-*N*-Cbz-phenylalanine afforded a separable mixture of dipeptides **19** and **20**, which were isolated in excellent yield (94% and 87% respectively) (Scheme 6). Both **19** and **20** were obtained as single diastereoisomers indicating that no epimerisation of the starting (*S*)-valine or the cyclopropane ring stereogenic centre had occurred during any of the synthetic manipulations.



Scheme 4 *Reagents and conditions*: (i) TFA, Δ; (ii) 6 M HCl, 100 °C; (iii) $SOCl_2$, MeOH, Δ.



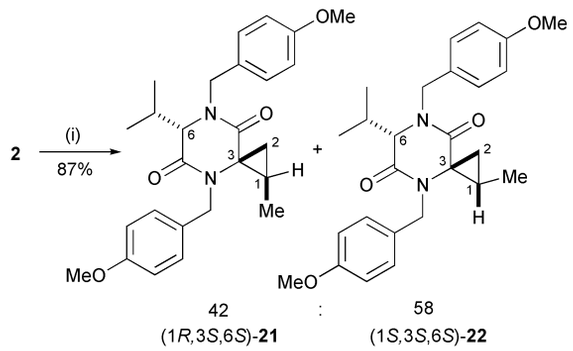
Scheme 5 *Reagents and conditions*: (i) Me_3OBF_4, $BmimBF_4$; (ii) 2 M HCl_{aq}, THF, room temperature.



Scheme 6 *Reagents and conditions*: (i) isobutyl chloroformate, NMM, (*S*)-*N*-Cbz-Phe, DMF, THF.

Having demonstrated that the cyclopropanation reaction utilising the symmetrical ylide **11** exhibits high levels of diastereofacial selectivity, the addition of a mono substituted phosphorane was investigated in order to examine the potential for the stereoselective formation of two new stereogenic centres in the preparation of C1 mono-substituted cyclopropane rings. In this study acceptor **2** was treated with ethylidenetriphenylphosphorane to afford a 42 : 58 mixture of diastereoisomers (1*R*,3*S*,6*S*)-**21** and (1*S*,3*S*,6*S*)-**22** in good combined yield (87%). Repeated column chromatography enabled the isolation of pure samples of diastereoisomers **21** and **22**, which facilitated their characterisation (Scheme 7).

The relative configurations of the C3 and C6 substituents of both 1-methyl substituted isomers **21** and **22** were apparent from ^{1}H NMR NOESY experiments. Both **21** and **22** showed diagnostic cross peaks between the isopropyl Me_2CH and both the C1-*Me* and the C1-*H*, indicating a *cis* relationship between these groups, with the (3*S*)-configuration derived from the known configuration of the starting (*S*)-valine. Furthermore,



Scheme 7 *Reagents and conditions*: (i) $CH_3CH(Li)PPh_3$, THF, room temperature.

the (1*S*)-configuration of major isomer **22** was determined *via* the identification of the (pro *S*)-C2-*H*, from a NOESY correlation with both N_4-*p*-methoxybenzyl protons. A strong correlation between C1-*H* and the (pro *S*)-C2-*H* then indicated that C1-*H* lies on the same face of the cyclopropane ring and allowed assignment of (*S*)-configuration at C1. Complementary ^{1}H NMR NOESY data for isomer **21** showed a correlation between the (pro *S*)-C2-*H* and a single N_4-*p*-methoxybenzyl-*H*, and a further correlation between the (pro *S*)-C2-*H* and the C1-*Me*, allowing the assignment of the (1*R*)-configuration at C1 and the (1*R*,3*S*,6*S*) absolute configuration of **21** (Fig. 3).

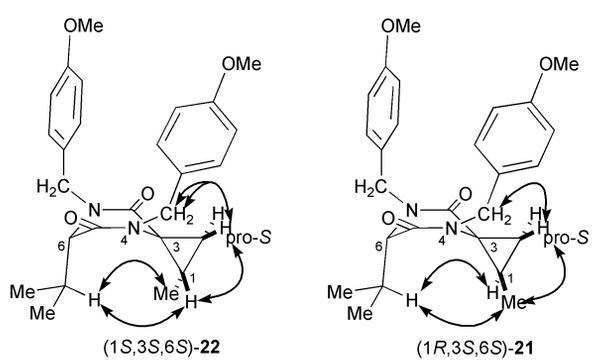
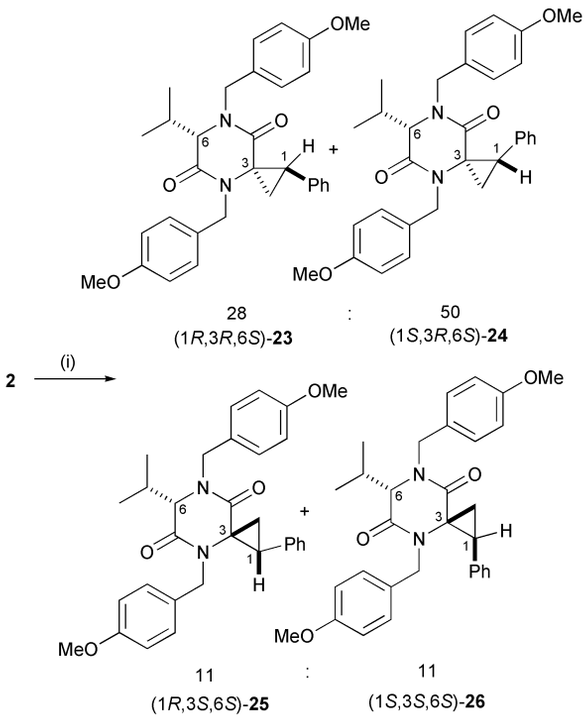


Fig. 3 Selected ^{1}H NOESY correlations for **21** and **22**.

While it is apparent that high levels of facial selectivity are maintained in the addition of this substituted phosphorus ylide, only very low levels of selectivity were afforded in the formation of the new C1 stereogenic centre in the substituted cyclopropane rings. In order to probe further the potential for stereocontrol at C1, an alternative route to C1 substituted 1-aminocyclopropane-1-carboxylic acids, employing the addition of a diazoalkane to acceptor **2**, was explored.[17] The treatment of acceptor **2** with phenyldiazomethane proceeded smoothly, and following pyrolysis of the intermediate pyrazines, provided a clean mixture containing only four diastereoisomeric products **23**, **24**, **25** and **26**, in the ratio of 28 : 50 : 11 : 11 respectively, as assessed by examination of the ^{1}H NMR spectrum of the crude reaction mixture. The major components (1*R*,3*R*,6*S*)-**23** and (1*S*,3*R*,6*S*)-**24**, and minor isomer (1*S*,3*S*,6*S*)-**26**, were isolated *via* column chromatography (16%, 35% and < 5% yields respectively) (Scheme 8).

The relative configurations at C1 and C3 within **23**, **24** and **26** were determined from ^{1}H NMR NOESY and NOE difference experiments which then allowed the absolute configurations of each to be derived from the unchanged configuration of the starting (*S*)-valine derived stereogenic centre. Both *trans*-(3*R*)-diastereoisomers **23** and **24** showed correlations between the Me_2CH and both C2-*H* indicating the C2 methylene group lies on the same side of the diketopiperazine ring as the C6 isopropyl group. Isomer **24** showed a NOESY correlation between both N_4-*p*-methoxybenzyl protons and the C1-*H* establishing



Scheme 8 *Reagents and conditions*: (i) $PhCHN_2$, PhMe, room temperature then 60 °C.

the (1*S*)-configuration at C1. The (1*R*)-C1 configuration of **23** was determined by the observation of a NOE difference correlation between the (pro *R*)-C2-*H* and one N_4-*p*-methoxybenzyl-*H*, allowing identification of the (pro *S*)-C2-*H*. A strong correlation between the (pro *S*)-C2-*H* and C1-*H* indicated these protons lie on the same face of the cyclopropane ring, which then allowed the configuration of (1*R*) to be assigned (Fig. 4).

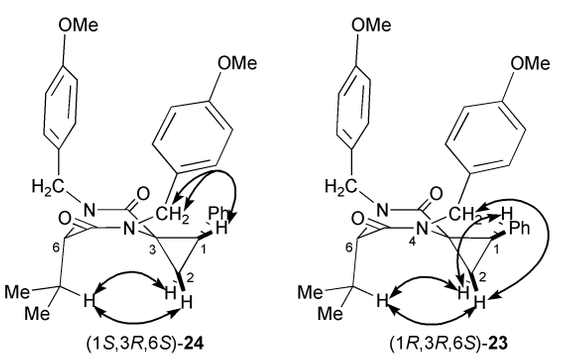


Fig. 4 Selected ^{1}H NOESY correlations for *trans*-3*R* isomers **23** and **24**.

The *cis*-(3*S*)-configuration of the minor isomer **26** was established by NOESY correlations between the isopropyl Me_2CH and C1-*H* while the (1*S*)-C1-configuration was apparent from correlations between (pro *S*)-C2-*H* and one N_4-*p*-methoxybenzyl-*H* and a strong correlation between C1-*H* and the (pro *R*)-C2-*H* (Fig. 5).

In support of these NOESY based configurational assignments, the relative configuration within (1*S*,3*R*,6*S*)-**24** was unambiguously confirmed by single crystal X-ray diffraction, with the absolute configuration derived from the known configuration of (*S*)-valine (Fig. 6).

The additions of alkyldiazomethanes to α,β-unsaturated acceptors are considered to proceed *via* a concerted cycloaddition process to give intermediate pyrazolines which then decompose to spiro-cyclopropanes. In similar systems the extrusion of nitrogen to give cyclopropanes generally occurs with retention of stereochemistry[18] and the configuration of the major addition products (1*R*,3*R*,6*S*)-**23** and (1*S*,3*R*,6*S*)-**24**

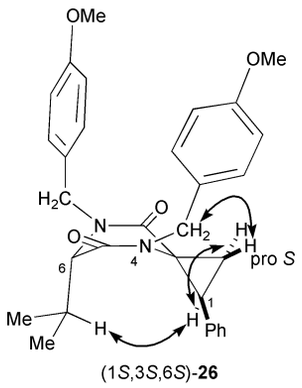


Fig. 5 Selected ^{1}H NOESY correlations for *cis*-3*S* isomer **26**.

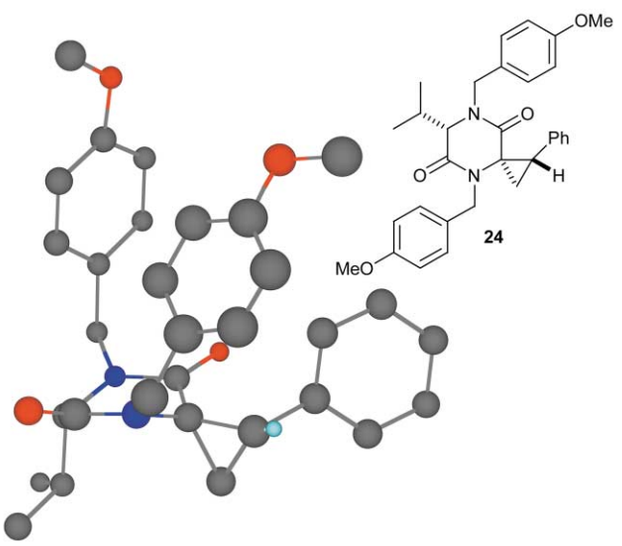
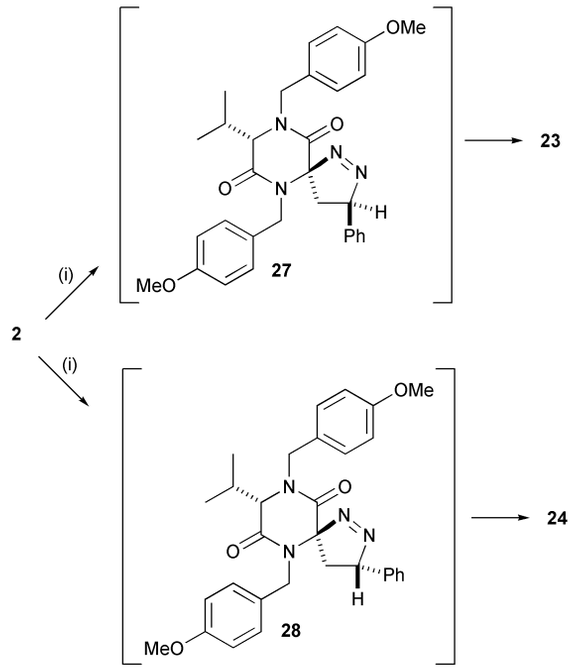


Fig. 6 Chem3D representation of X-ray crystal structure of **24**.

will reflect the configuration of the initially formed intermediate pyrazolines **27** and **28**, respectively. The 78 : 22 ratio of the (3*R*)-diastereoisomers **23** and **24** to (3*S*)-diastereoisomers **25** and **26** indicates a modest preference for initial cycloaddition of phenyldiazomethane on the *Re* face of acceptor **2**, *trans* to the C6 isopropyl group (Scheme 9). The low levels of facial selectivity observed in the attack of the methylene carbon in this reaction may be expected, given the remoteness of this centre from stereodirecting elements in the auxiliary.

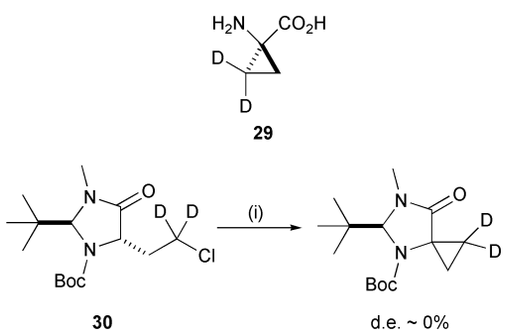
Synthesis of (*S*)-[2,2-$^2H_2$]-1-aminocyclopropane-1-carboxylic acid

Having established a protocol for the highly selective addition of symmetrical ylides to acceptor **2** this methodology was next applied to the asymmetric synthesis of a deuterium labelled 1-aminocyclopropane-1-carboxylic acid, which has been previously prepared as a probe into the biosynthesis of ethylene.[19] Arigoni and Hill *et al.* have reported the asymmetric synthesis of both (*R*)- and (*S*)- [2,2-$^2H_2$]-1-aminocyclopropane-1-carboxylic acid **29** utilising a Sharpless epoxidation in the synthesis of the (*R*)-enantiomer, and synthetic manipulation of resolved starting material to deliver the (*S*)-enantiomer.[4c] The asymmetric synthesis of **29** utilising a chiral auxiliary approach has been less successful and syntheses reported to date all exhibit poor to moderate diastereoselectivity in the cyclopropane ring forming step. This shortcoming is compounded by the difficulty in purifying the diastereoisomeric intermediates to homogeneity which precludes the enhancement of the enantiomeric excess of the final products. For example, Seebach *et al.* have prepared **29** *via* the alkylation of **30**. No diastereoselectivity was observed during the ring forming alkylation step, inconsistent with the generally high



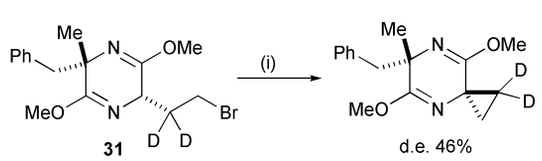
Scheme 9 *Reagents and conditions*: (i) $PhCHN_2$, $PhCH_3$, room temperature then 60 °C.

facial selectivities obtained for intermolecular alkylations, and the α-amino acid **29** obtained in this protocol was essentially racemic (Scheme 10).[20]



Scheme 10 *Reagents and conditions*: (i) LDA, DMPU.

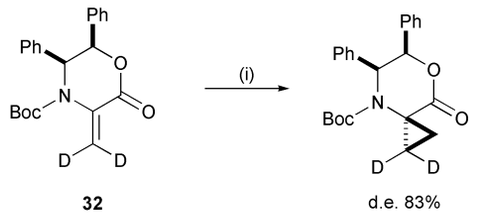
Low levels of diastereofacial selectivity have also been observed in the related cyclopropane forming step utilising bis-lactim auxiliary **31** which afforded labelled α-amino acid **29** in 46% e.e. upon hydrolysis (Scheme 11).[21]



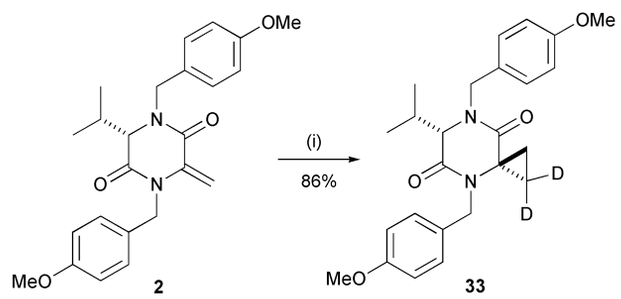
Scheme 11 *Reagents and conditions*: (i) BuLi, THF, −78 °C.

In perhaps the most successful approach to date, Williams *et al.* have prepared labelled cyclopropane α-amino acid **29** in 83% e.e., *via* sulfur ylide addition to dehydroalanine auxiliary **32** (Scheme 12).[11b]

The application of *N*-protected diketopiperazine conjugate addition methodology to the asymmetric synthesis of **29** was investigated *via* the cyclopropanation of **2** with deuterated dimethylsulfoxonium methylide.[22] Thus, reaction of acceptor **2** with the ylide derived from d_9-trimethyloxosulfonium iodide provided (3*S*,6*S*)-[2′,2′-$^2H_2$]-*N*,*N*′-bis(*p*-methoxybenzyl)-piperazine-2,5-dione-3-spiro-1′-cyclopropane **33** in high isolated yield (86%) and excellent d.e. (> 98%), as assessed by



Scheme 12 *Reagents and conditions*: (i) $PhS(O)(NEt_2)CH_2$, DMSO.



Scheme 13 *Reagents and conditions*: (i) $(CD_3)_2CD_2(Li)SO$, THF, room temperature.

examination of the ^{1}H NMR spectrum of the crude reaction mixture (Scheme 13).

The configuration within the deuterated analogue **33** was tentatively assigned from ^{1}H NMR NOESY data. NOESY studies on the related proteo spiro-cyclopropane **5** allowed the assignment of all four resonances corresponding to the cyclopropane ring protons from the correlations shown in Fig. 7.

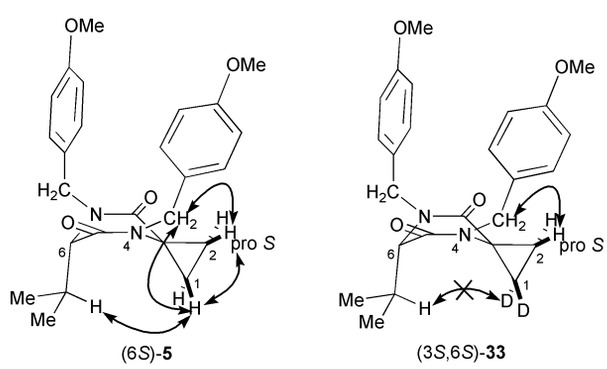
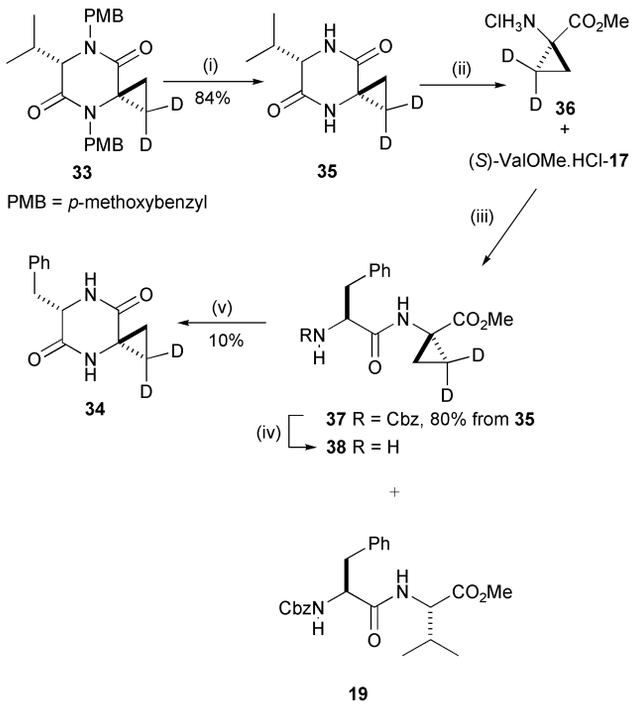


Fig. 7 Selected ^{1}H NMR NOESY correlations for **5** and **33**.

Examination of the ^{1}H NMR spectrum of deuterated analogue **33** revealed that deuterium was incorporated upon the carbon *cis* to the C6 isopropyl group since the resonances corresponding to these protons in the proteo analogue were absent. Furthermore, ^{1}H NMR NOESY experiments showed no correlations between the C6 isopropyl Me_2CH and the residual cyclopropyl methylene signals consistent with the C6 isopropyl group being *cis* to the deuterated methylene group. Finally the absolute configuration of the cyclopropyl α-amino acid fragment was unequivocally confirmed by chemical correlation with the known diketopiperazine **34**.[23] Removal of the nitrogen protecting groups from **33** with refluxing trifluoroacetic acid afforded **35** (84% yield), with acid hydrolysis (6 M HCl, 100 °C) and esterification giving a mixture of (*S*)-valine methyl ester hydrochloride **17** and [2,2-$^2H_2$]-1-aminocyclopropane-1-carboxylic acid methyl ester hydrochloride **36**. Subsequent coupling of this mixture with (*S*)-*N*-Cbz-phenylalanine and separation of the resultant dipeptides **37** and **19** by chromatography afforded **37** as a single diastereoisomer, in good yield (80% from **35**). Hydrogenolysis of the nitrogen protecting group afforded dipeptide **38**, with thermal cyclisation giving the known diketopiperazine **34**, albeit in poor isolated yield (10%) (Scheme 14).



Scheme 14 *Reagents and conditions*: (i) TFA, Δ; (ii) 6 M HCl, 100 °C; (iii) isobutyl chloroformate, NMM, DMF, THF; (*S*)-*N*-Cbz-Phe; chromatographic separation; (iv) H_2, Pd/C, MeOH; (v) $PhCH_3$, Δ.

Examination of the ^{1}H and ^{2}H NMR data for dipeptide **38** and diketopiperazine **34** revealed considerable solvent dependance of the chemical shift for the cyclopropane methylene protons and deuterons which initially hampered the direct comparison of the synthetic material and the literature data. For comparison purposes, non-deuterated analogue **39** was prepared from commercially available 1-aminocyclopropane-1-carboxylic acid methyl ester and Cbz-phenylalanine *via* coupling, deprotection and cyclisation. Table 1 shows selected cyclopropyl-methylene ^{1}H and ^{2}H NMR chemical shift data for dipeptide **38** in a variety of solvents. Table 2 shows selected cyclopropyl-methylene ^{1}H and ^{2}H NMR chemical shift data for diketopiperazines **34** and **39** in TFA, MeOH and AcOH along with literature values.

Comparison of the chemical shifts of both the ^{1}H and ^{2}H NMR spectra with those reported by Arigoni *et al.*[24] allowed correlation of the (3*S*,6*S*)-configuration of diketopiperazine **34**, establishing the configuration of the synthetic (*S*)-[2,2-$^2H_2$]-1-aminocyclopropane-1-carboxylic acid **29** and the (3*S*,6*S*)-configuration of **33** (Table 2). These data demonstrate that the cyclopropanation of **2** with the deuterated methylene sulfur ylide also proceeds with overall *Si* face selectivity, *cis* to the C6 isopropyl group, similar to that observed in the preparation of **12**.

Mechanism and stereoselectivity of cyclopropanation

The formation of the new quaternary stereogenic centre upon cyclopropanation of acceptor **2** *via* phosphorus or sulfur ylide chemistry proceeds with excellent diastereofacial selectivity. In this addition/elimination process the configuration of the new C3 stereogenic centre is independent of the initial conjugate addition step with the product configuration being controlled in the intramolecular enolate alkylation ring closure. The observed product configuration must arise from displacement of the leaving group by attack from the *Si* face (*cis* to the C-6 isopropyl group) of the enolate intermediate **40**. In terms of the initial conjugate addition step there are two indistinguishable modes for the formation of diketopiperazinespirocyclopropanes **12**, **21**, **22** and **33**. Firstly, initial addition may occur on the *Si* face of acceptor **2** placing the leaving group in the correct position to be displaced by attack from the *Si* face of the enolate intermediate **40**. Alternatively conjugate addition may occur on the *Re* face of acceptor **2** followed by a conformational change to place the leaving group on the *Si* face of the enolate, *cis* to the C3 isopropyl group, prior to elimination (Fig. 8).

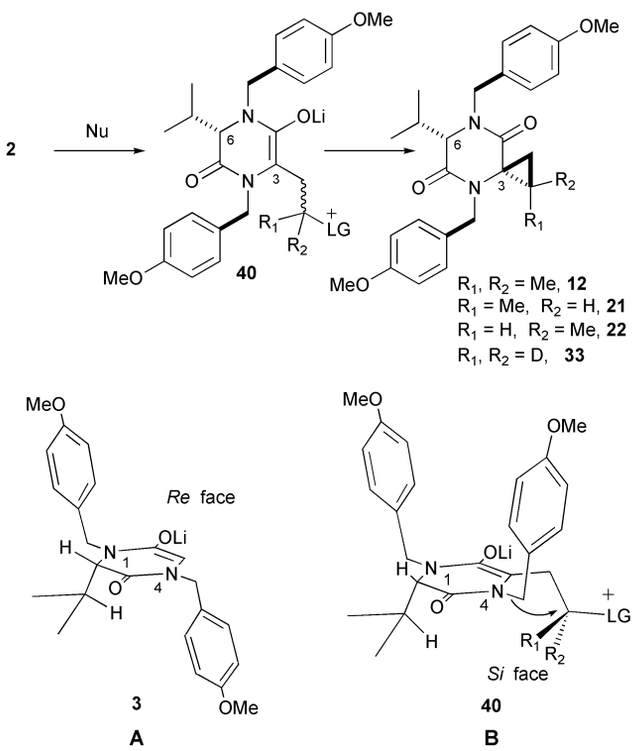
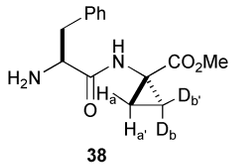


Fig. 8 Mechanism of cyclopropane ring formation *via Si* face ring closure.

The cyclopropane ring forming intramolecular alkylation occurs *cis* to the C6 isopropyl group, upon the *Si* face of the intermediate enolate, and is in complete contrast to the *trans* (*Re* face) selectivity observed in both the intermolecular alkylation of unsubstituted lithium enolate **3** with alkyl halides and the protonation of the substituted enolate **4**.[10] In the intermolecular alkylation of the parent enolate **3**, the *trans* selectivity is controlled by the conformationally labile *N*-protecting groups which serve to relay and enhance the stereodirecting effect of the (*S*)-valine derived isopropyl group *via* a conformation which places the N_4-*p*-methoxybenzyl group on the *Si* face of the enolate (Fig. 8 A). Related conformational preferences may also operate to control the conformation of intermediate enolate **40** and direct the intramolecular alkylation to the *Si* face. Molecular modelling suggests that the most stable conformation of the intermediate **40** is one in which both of the conformationally labile *N*-*p*-methoxybenzyl groups occupy a position on the *Re* face of the enolate with the pendant group of the C3 substituent *cis* to the isopropyl group (for example, intermediate enolate **40a** leading to **12**, Fig. 9).[25] In this arrangement the steric interactions between the (*S*)-valine derived isopropyl group and the adjacent N_4-*p*-methoxybenzyl group are minimised. In order to minimise steric interaction with the N_1-protecting group the proximal C3 substituent occupies a position on the *Si* face of the enolate and the N_4-protecting group then occupies the position away from the C3 substituent on the *Re* face of the auxiliary. Displacement of the leaving group from this conformation then affords spirocyclopropane adducts in high d.e. The alternative relay arrangement, similar to that postulated for parent auxiliary enolate **3**, would unfavourably place the C3 substituent on the same face as the N_1-*p*-methoxybenzyl group.

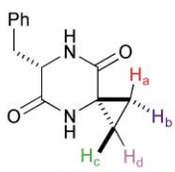
Table 1 Selected ^1H and ^2H NMR data for dipeptide **38**



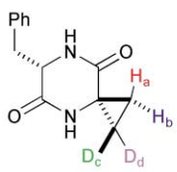
38

Compound	Solvent	H_a (δ)	$H_{a'}$ (δ)	D_b (δ)	$D_{b'}$(δ)
38	AcOH-d_4	0.95	1.43		
38	MeOH-d_4	0.91	1.43		
38	TFA-d_1	1.35	1.98		
	TFA			1.30 (^2H)	1.81 (^2H)

Table 2 Selected ^1H and ^2H NMR data for diketopiperazines **34** and **39**



39



34

Compound	Solvent	H_a (δ)	H_b (δ)	H_c (D_c)(δ)	H_d(D_d)(δ)
39	AcOH-d_4	0.92	1.45	0.34	0.73
34	AcOH-d_4	0.90	1.42		
34	AcOH			0.35 (^2H)	0.76 (^2H)
epi-**34**[a,b]	AcOH-d_4			0.34	0.71
epi-**34**[a,b]	AcOH	0.90 (^2H)	1.45 (^2H)		

Compound	Solvent	H_a (δ)	H_b (δ)	H_c (D_c)(δ)	H_d (D_d)(δ)
39	MeOH-d_4	0.83	1.29	0.21	0.56
34	MeOH-d_4	0.81	1.24		
34	MeOH			0.20 (^2H)	0.54 (^2H)

Compound	Solvent	H_a (δ)	H_b (δ)	H_c (D_c)(δ)	H_d (D_d)(δ)
39	TFA-d_1	1.25	1.83	0.72	1.11
39 [a]	TFA-d_1	1.26	1.82	0.74	1.12
34	TFA-d_1	1.27	1.88		
34	TFA			0.76 (^2H)	1.12 (^2H)
34 [a]	TFA-d_1	1.27	1.82		
34 [a,c]	TFA			0.74 (^2H)	1.04 (^2H)
epi-**34** [a,c]	TFA	1.27 (^2H)	1.83 (^2H)		

[a] Lit.[24] ; [b] Lit.[4(e)]; [c] Lit.[4(b)].

Due to the hindered nature of the enolate and the strain arising from the ring forming step, the displacement of the leaving group by the lithium enolate intermediate is expected be the slow step in the cyclopropanation process. It may then be assumed that displacement of the sulfur or phosphorus leaving group occurs from the thermodynamically most stable conformation of enolate **40**, which places the leaving group on the *Si* face, leading to the observed stereoselectivity. Equilibration to this stable conformer may occur either *via* conformational rearrangement of intermediate **40** or through reversible addition of the ylide to acceptor **2**.

The high levels of facial selectivity observed in the intramolecular cyclopropane ring forming step from enolates of type **40** may be interpreted as the result of a chiral relay network which operates in a similar manner to that which controls the facial selectivity in the intermolecular alkylations of enolate **3**. In the case of enolate **3** the system exhibits a double relay with the C6 isopropyl group directing the N_1-*p*-methoxybenzyl group *anti*, which in turn places the N_4-*p*-methoxybenzyl group on the alternate face of the auxiliary. The arrangement of stereocontrolling elements in enolate **40** may be interpreted as a triple relay in which the proximal C6 isopropyl and N_1-*p*-methoxybenzyl groups along with the pendant C3 substituent and the N_4-*p*-methoxybenzyl group each occupy positions on alternate faces of the auxiliary, resulting in the observed high levels of stereocontrol.

Conclusion

The conjugate addition of phosphorus and sulfur ylides to dehydroalanine acceptor **2** proceeds to give cyclopropane substituted diketopiperazines **12** and **33** in excellent yield and diastereoisomeric excess (> 98%). The subsequent incorporation of the cyclopropane α-amino acids derived from this method into simple dipeptides demonstrates the utility of this methodology for the synthesis and incorporation of these residues into peptide sequences.

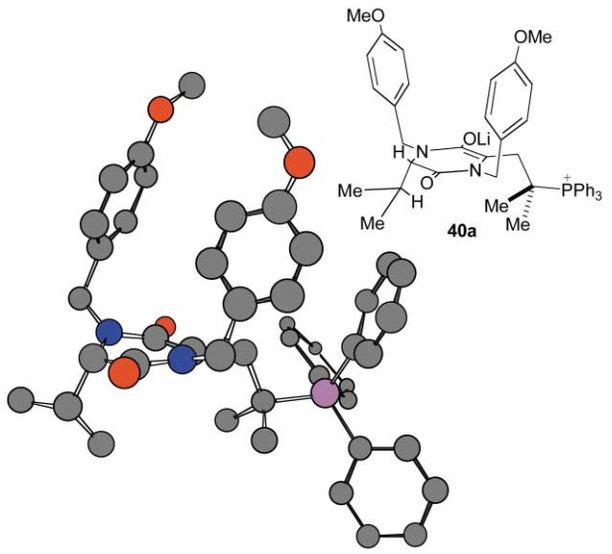


Fig. 9 Chem3D representation of a molecular model of lowest energy conformation of enolate **40a**.[25]

Experimental

General

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. Flash 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, ^{2}H: 76.7 MHz and ^{13}C: 125 MHz) spectrometer in the deuterated solvent stated. All chemical shifts (δ) are quoted in ppm and coupling constants (J) in Hz. Coupling constants are quoted twice, each being recorded as observed in the spectrum without averaging. Residual signals from the solvents were used as an internal reference. ^{13}C multiplicities were assigned using a DEPT sequence. Infrared spectra were recorded on a Perkin-Elmer 1750 IR Fourier Transform spectrophotometer using either thin films on NaCl plates (film) or KBr discs (KBr) as stated. Only the characteristic peaks are quoted in cm^{-1}. Optical rotations were recorded on a Perkin-Elmer 241 polarimeter with a path length of 1 dm. Concentrations are quoted in g/100 ml. Low resolution mass spectra were obtained upon a VG micromass ZAB IF, a VG MassLab 20-250, a VG Bio Q or an APCI Platform spectrometer with only molecular ions, fragments from molecular ions and major peaks being reported. High resolution mass spectroscopic data were obtained using Micromass AutoSpec or Micromass ToFSpec spectrometers. Elemental analyses were performed by the microanalysis service of the Inorganic Chemistry Laboratory, University of Oxford.

(*S*)-4,7-Bis(4-methoxybenzyl)-6-isopropyl-4,7-diazaspiro[2.5]octane-5,8-dione 5. To a suspension of trimethylsulfoxonium iodide (1.65 g, 7.5 mmol) in THF (50 ml) was added n-BuLi (4.6 ml, 1.6 M in hexane, 7.5 mmol) under nitrogen at room temperature. After 30 minutes a solution of **2** (1.22 g, 3.0 mmol) in THF (10 ml) was added over a period of 15 minutes and the resulting mixture was stirred for 30 min. The reaction was cooled (0 °C) and saturated ammonium chloride (50 ml) was added. The mixture was partitioned between water and ethyl acetate and the aqueous layer was extracted with ethyl acetate. The combined organic layers were dried ($MgSO_4$) and the solvent removed *in vacuo*. Chromatography (silica, petroleum ether–ethyl acetate 1 : 1) of the residue afforded **5** as a colourless oil (1.08 g, 84%). $[\alpha]_D^{24}$ −94.6 (*c* 1.00 in $CHCl_3$); ν_{max}/cm^{-1} (thin film): 2970–2836, 1661 (C=O), 1613 (C=O), 1585, 1513, 1450, 1412; δ_H (400 MHz, $CDCl_3$) 0.82 (1H, m, C1-(pro *S*)-*H*), 1.10 (3H, d, *J* 6.8, CH(C*H*$_3$)$_2$), 1.12 (1H, m, C1-(pro *R*)-*H*), 1.14 (3H, d, *J* 6.8, CH(C*H*$_3$)$_2$), 1.47 (1H, m, C2-(pro *S*)-*H*), 1.85 (1H, m, C2-(pro *R*)-*H*), 2.38 (1H, m, C*H*(CH$_3$)$_2$), 3.79–3.81 (7H, m, C6-*H* and 2 × O*Me*), 3.86 (1H, d, *J* 14.8, N7-C*H*$_2$), 4.18 (1H, d, *J* 15.6, N4-C*H*$_2$), 4.70 (1H, d, *J* 15.6, N4-C*H*$_2$), 5.39 (1H, d, *J* 14.8, N7-C*H*$_2$), 6.81 (2H, m, Ar*H*), 6.86 (2H, m, Ar*H*), 7.03 (2H, m, ArH), 7.14 (2H, m, Ar*H*); δ_C (100 MHz, $CDCl_3$) 11.3, 16.7, 19.2, 20.3, 31.4, 41.8, 44.9, 49.4, 55.2, 55.3, 66.3, 114.1, 114.2, 127.9, 128.1, 129.1, 129.3, 158.8, 159.1, 167.8, 168.5; HRMS for $C_{25}H_{31}N_2O_4$ (MH^+) requires 423.2284, found 423.2281.

(3*S*,6*S*)-4,7-Bis(4-methoxybenzyl)-1,1-dimethyl-6-isopropyl-4,7-diazaspiro[2.5]octane-5,8-dione 12. To a suspension of isopropyltriphenylphosphonium iodide (9.32 g, 21.6 mmol) in THF (65 ml) was added n-BuLi (13.5 ml, 1.6 M in hexane, 21.6 mmol) under nitrogen at room temperature. After 30 minutes a solution of **2** (4.40 g, 10.8 mmol), in THF (35 ml), was added *via* cannula over 15 minutes and the resulting mixture was stirred for a further 30 minutes. The reaction mixture was cooled in an ice bath and quenched with saturated ammonium chloride. The organic solvent was removed in vacuum and ethyl acetate was added. The mixture was washed with water and dried over $MgSO_4$ before removal of the solvent under reduced pressure. Flash column chromatography (silica, petroleum ether–ethyl acetate 4 : 6) of the residue afforded the desired compound **12** as a colourless solid (4.50 g, 93%). Mp 117 °C; $[\alpha]_D$ −222 (*c* 1.00 in $CHCl_3$); ν_{max}/cm^{-1} (KBr) 3056–2840, 1668, 1614, 1585, 1514, 1451, 1403; δ_H (400 MHz, $CDCl_3$) 1.07–1.17 (12H, m, CH(C*H*$_3$)$_2$, C(C*H*$_3$)$_2$), 1.15 (1H, d, *J* 6.7, CC*H*$_2$), 1.75 (1H, d, *J* 6.7, CC*H*$_2$), 2.01 (1H, m, C*H*(CH$_3$)$_2$), 3.56 (1H, d, *J* 11.2, C6-*H*), 3.58 (1H, d, *J* 15.2, N4-C*H*$_2$), 3.70 (1H, d, *J* 14.7, N7-C*H*$_2$), 3.78 (3H, s, OMe), 3.79 (3H, s, OMe), 5.29 (1H, d, *J* 15.2, N4-C*H*$_2$), 5.43 (1H, d, *J* 14.7, N7-C*H*$_2$), 6.73 (2H, m, Ar*H*), 6.79 (2H, m, Ar*H*), 6.93 (2H, m, Ar*H*), 7.02 (2H, m, Ar*H*); δ_C (100 MHz, $CDCl_3$) 19.7, 19.9, 20.3, 20.5, 22.2, 26.8, 31.4, 47.0, 49.6, 50.9, 55.1, 55.2, 68.4, 113.9, 114.1, 128.4, 128.6, 128.8, 129.3, 158.8, 159.1, 166.8, 170.4; *m*/*z*; HRMS for $C_{27}H_{35}N_2O_4$ (MH^+) requires 451.2584, found 451.2596.

X-ray crystal structure data for **12**:

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.[26] Crystal data for **12** [$C_{27}H_{20}N_2O_4$], colourless block, M = 436.47, monoclinic, space group P 1 21 1, a = 9.2515(1), b = 28.6084(4), c = 9.4481(1) Å, β = 99.9280(6)°, U = 2463.19(5) Å^3, Z = 4, μ = 0.080, crystal dimensions 0.2 × 0.2 × 0.2 mm. A total of 5686 unique reflections were measured for $5 < \theta < 27$ and 5605 reflections were used in the refinement. The final parameters were wR_2 = 0.1407 and R_1 = 0.0657 [$I > -3\sigma(I)$]. Crystallographic data (excluding structure factors) have been deposited with the Cambridge Crystallographic Data Centre.†

† CCDC 198088. See http://www.rsc.org/suppdata/ob/b3/b303348a/ for crystallographic data in .cif or other electronic format.

(3*S*,6*S*)-1,1-Dimethyl-6-isopropyl-4,7-diazaspiro[2.5]octane-5,8-dione 13. A solution of **12** (4.34 g, 9.64 mmol) in TFA (200 ml) was subject to reflux for 48 hours. The TFA was removed under reduced pressure and the dark green residue obtained was triturated with diethyl ether (3 × 50 ml). The resultant solid was suspended in dichloromethane and heated for 30 minutes before cooling to room temperature. The solid was isolated by filtration and recrystallised from acetone affording **13** as a colourless solid (1.78 g, 87%). Mp 253–257 °C; $[a]_D^{23}$ +8.4 (*c* 0.5 in EtOH); ν_{max}/cm^{-1} (KBr) 3204, 3093, 2967, 1689; δ_H (400 MHz, DMSO-d_6) 0.81 (1H, d, *J* 5.1, CH_2), 0.89 (3H, d, *J* 6.7, CH(CH_3)$_2$), 0.93 (3H, d, *J* 6.8, CH(CH_3)$_2$), 1.06 (6H, s, C(CH_3)$_2$), 1.27 (1H, d, *J* 5.1, CH_2), 1.79 (1H, m, C*H*(CH$_3$)$_2$), 3.28 (1H, m, 6-*H*), 8.31 (1H, s, N*H*), 8.36 (1H, d, *J* 4.3, N*H*); δ_C (100 MHz, DMSO-d_6) 18.4, 19.1, 19.2, 20.4, 22.0, 25.8, 32.4, 44.1, 61.9, 167.3, 169.7; HRMS for $C_{11}H_{19}N_2O_2$ (MH^+) requires 211.1450, found 211.1446.

(3*S*,6*S*)-5,8-Dimethoxy-1,1-dimethyl-6-isopropyl-4,7-diazaspiro[2.5]octa-4,7-diene 18. To a solution of **13** (294 mg, 1.40 mmol) in *N*-butyl-*N*′-methylimidazolium tetrafluoroborate (8 ml) was added trimethyloxonium tetrafluoroborate (827 mg, 5.59 mmol). The reaction mixture was stirred under vacuum for 4 days before the mixture was added to saturated $NaHCO_3$ (15 ml). The product was extracted with ethyl acetate and the combined organic phases dried over $MgSO_4$ before removal of solvent under reduced pressure to furnish bis-lactim ether **18** as a colourless oil that required no further purification. $[a]_D$ +15.7 (*c* 0.7 in $CHCl_3$); ν_{max}/cm^{-1} (thin film) 3004–2872, 1682, 1667, 1463, 1438; δ_H (400 MHz, $CDCl_3$) 0.86 (3H, d, *J* 6.8, CH(CH_3)$_2$), 0.93 (1H, d, *J* 4.6, CH_2), 1.09 (3H, d, *J* 6.8, CH(CH_3)$_2$), 1.15 (3H, s, C(CH_3)$_2$), 1.16 (3H, s, C(CH_3)$_2$), 1.59 (1H, d, *J* 4.6, CH_2), 1.94 (1H, m, C*H*(CH$_3$)$_2$), 3.65 (3H, s, OMe), 3.68 (3H, s, OMe), 4.09 (1H, d, *J* 5.0, C6-*H*); δ_C (100 MHz, $CDCl_3$) 17.9, 19.2, 20.6, 21.9, 27.7, 28.0, 32.7, 47.0, 52.4, 52.6, 63.1, 165.0, 165.4; HRMS for $C_{13}H_{23}N_2O_2$ (MH^+) requires 239.1760, found 239.1759.

(1*S*)-1-Amino-2,2-dimethylcyclopropanecarboxylic acid methyl ester 16 and (*S*)-valine methyl ester 17. Method A: a solution of **13** (43 mg, 0.20 mmol) in HCl (3 ml, 6 M) was subject to reflux for 24 hours. The aqueous phase was washed with diethyl ether and concentrated under vacuum to afford a mixture of the amino acids **14** and **15** that were dissolved in MeOH (5 ml) and cooled to 0 °C before thionyl chloride (0.15 ml) was added. The reaction mixture was subject to reflux overnight before concentration under vacuum afforded a 1 : 1 mixture of the methyl ester amino hydrochlorides **16** and **17** as a colourless solid (69 mg) that was used without further purification.

Method B: bis-lactim ether **18** (288 mg, 1.21 mmol) was dissolved in THF (2 ml) and HCl (3 ml, 2 M). The reaction mixture was stirred for 2.5 hours before dilution with DCM. The product was extracted with water and the combined aqueous phases concentrated under reduced pressure to furnish a 1 : 1 mixture of amino esters **16** and **17** as a colourless solid (379 mg) that was used without further purification.

δ_H (200 MHz, MeOH-d_4) 0.11 (1H, d, *J* 7.1, CH_2C(CH$_3$)$_2$), 1.10 (3H, d, *J* 2.4, CHCH(CH_3)$_2$), 1.14 (3H, d, *J* 2.4, CHCH-(CH_3)$_2$), 1.31 (3H, s, CH$_2$C(CH_3)$_2$), 1.46 (3H, s, CH$_2$C(CH_3)$_2$), 1.47 (1H, d, *J* 7.13, CH_2C(CH$_3$)$_2$), 2.29–2.47 (1H, m, CHC*H*-(CH$_3$)$_2$), 4.02 (1H, d, *J* 4.2, C*H*CH(CH$_3$)$_2$), 3.88 (3H, s, OMe), 3.89 (3H, s, OMe).

***N*-Cbz-(*S*)-phenylalanine-(*S*)-valine methyl ester 19 and *N*-Cbz-(*S*)-phenylalanine-(*S*)-2,2-dimethylcyclopropanecarboxylic acid methyl ester 20.** To a solution of (*S*)-*N*-CBz-phenylalanine (665 mg, 2.22 mmol) in DMF (20 ml) and THF (20 ml) at 0 °C, was added *N*-methylmorpholine (0.45 ml, 4.07 mmol) and isobutyl chloroformate (0.29 ml, 2.22 mmol). The reaction mixture was stirred for 15 minutes before a solution of the amino esters **16** and **17** (320 mg, 1.85 mmol) in DMF (20 ml) was added *via* cannula. Stirring was continued for a further 45 minutes before dilution with ethyl acetate. The organic phase was washed with water, saturated aqueous $NaHCO_3$, 10% aqueous citric acid, brine, dried over $MgSO_4$ and the solvent removed *in vacuo*. Purification by column chromatography (silica, diethyl ether–ethyl acetate 6 : 4) afforded **19** as a colourless solid (371 mg, 94%). δ_H (200 MHz, $CDCl_3$) 0.82 (3H, d, *J* 7.4, (CH_3)$_2$CH), 0.91 (3H, d, *J* 7.4, (CH_3)$_2$CH), 2.04–2.14 (1H, m, (CH$_3$)$_2$C*H*), 3.07–3.11 (2H, m, PhCH_2CH), 3.70 (3H, s, OMe), 4.42–4.49 (2H, m, ^{i}PrC*H* and PhCH$_2$C*H*), 5.1 (2H, s, PhCH_2O), 5.37 (1H, d, *J* 7.6, N*H*), 6.28 (1H, d, *J* 8.4, N*H*), 7.27–7.39 (10H, m, Ph).[27]

Further elution afforded **20** as a colourless solid (341 mg, 87%). Mp 140–141 °C; $[a]_D$ −118.0 (*c* 1.0 in $CHCl_3$); ν_{max}/cm^{-1} (KBr) 3316, 1681, 1670, 1666; δ_H (400 MHz, $CDCl_3$) 0.88 (1H, d, *J* 5.3, CCH_2), 1.06 (3H, s, C(Me)$_2$), 1.18 (3H, s, C(Me)$_2$), 1.70 (1H, d, *J* 5.3, CCH_2), 2.99 (1H, dd, *J* 14.0, 6.4, PhCH_2CH), 3.13 (1H, dd, *J* 14.0, 6.5, PhCH_2CH), 3.61 (3H, s, OMe), 4.51 (1H, br s, N*H*), 5.02 (2H, s, PhCH_2O), 5.63 (1H, d, *J* 8.3, PhCH$_2$-C*H*CO), 6.82 (1H, br s, CON*H*), 7.36–7.19 (10H, m, Ph); δ_C (100 MHz, $CDCl_3$) 19.5, 21.8, 27.8, 28.6, 37.8, 42.4, 52.1, 53.5, 55.8, 57.3, 66.9, 95.7, 126.9, 127.9, 128.1, 128.4, 128.5, 129.3, 129.4, 136.2, 136.6, 156.1, 171.2, 171.2; HRMS for $C_{24}H_{29}N_2O_5$ (MH^+) requires 425.2079, found 425.2076.

(1*R*,3*S*,6*S*)- and (1*S*,3*S*,6*S*)- 4,7-Bis(4-methoxybenzyl)-6-isopropyl-1-methyl-4,7-diazaspiro[2.5]octane-5,8-dione 21 and 22. To a suspension of ethyltriphenylphosphonium bromide (742 mg, 2.0 mmol) in THF (20 ml) was added a solution of n-BuLi (1.24 ml, 1.6 M in hexane, 2.0 mmol) under an atmosphere of nitrogen at room temperature. After 30 minutes a solution of **2** (408 mg, 1.0 mmol) in THF (5 ml) was added *via* cannula over a period of 15 minutes and the resulting mixture was stirred for a further 30 minutes. The reaction was cooled in an ice bath and quenched with saturated ammonium chloride. The organic layer was separated and the aqueous layer extracted with ethyl acetate. The combined organic layers were dried over $MgSO_4$, filtered and the solvent removed under reduced pressure. Flash column chromatography (silica, diethyl ether–hexane 4 : 6) afforded a mixture of **21** and **22** (380 mg, 87%). Further, exhaustive chromatography afforded pure samples for characterisation. First eluting isomer **21** Oil. $[a]_D$ −152.0 (*c* 0.5 in $CHCl_3$); ν_{max}/cm^{-1}(thin film) 3500–2950, 1667, 1613, 1585, 1513, 1455, 1404; δ_H (500 MHz, $CDCl_3$) 1.08 (1H, m, C2-(pro *S*)-*H*), 1.10 (3H, d, *J* 6.2, CH(CH_3)), 1.16 (3H, d, *J* 6.8, CH(CH_3)$_2$), 1.18 (3H, d, *J* 6.7, CH(CH_3)$_2$), 1.31 (1H, m, C*H*(CH$_3$)), 2.08 (1H, dd, *J* 9.8, 6.5, C2-(pro *R*)-*H*), 2.22 (1H, m, C*H*(CH$_3$)$_2$), 3.67 (1H, d, *J* 15.4, N4-CH_2), 3.68 (1H, d, *J* 10.4, C6-*H*), 3.80 (1H, d, *J* 14.7, N7-CH_2), 3.83 (3H s, OMe), 3.85 (3H, s, OMe), 5.36 (1H, d, *J* 15.4, N4-CH_2), 5.44 (1H, d, *J* 14.7, N7-CH_2), 6.80 (2H, m, Ar*H*), 6.87 (2H, m, Ar*H*), 6.99 (2H, m, Ar*H*), 7.10 (2H, m, Ar*H*); δ_C (100 MHz, $CDCl_3$) 12.3, 17.7, 19.6, 20.9, 22.8, 31.6, 45.1, 47.3, 50.7, 55.1, 55.2, 68.2, 114.0, 114.1, 128.4, 128.8, 129.2, 158.8, 159.1, 168.6, 170.2. HRMS for $C_{26}H_{33}N_2O_4$ (MH^+) requires 451.2440, found 451.2439.

Second eluting isomer **22** Oil. $[a]_D$ −80.5 (*c* 0.75 in $CHCl_3$); ν_{max}/cm^{-1} (thin film) 3500–2830, 1660, 1613, 1585, 1513, 1462, 1412; δ_H (400 MHz, $CDCl_3$) 1.09–1.10 (4H, m, CHCH_3 and CH_2CHCH$_3$), 1.14 (6H, m, CH(CH_3)$_2$), 1.51–1.60 (2H, m, CH_2CHCH$_3$ and CH$_2$C*H*CH$_3$), 2.31 (1H, m, C*H*(CH$_3$)$_2$), 3.63 (1H, d, *J* 10.0, C6-*H*), 3.79 (3H, s, OMe), 3.80 (3H, s, OMe), 3.80 (1H, d, *J* 14.8, NCH_2), 4.18 (1H, d, *J* 15.6, NCH_2), 4.68 (1H, d, *J* 15.6, NCH_2), 5.44 (1H, d, *J* 14.8, NCH_2), 6.79 (2H, m, Ar*H*), 6.84 (2H, m, Ar*H*), 6.99 (2H, m, Ar*H*), 7.12 (2H, m, Ar*H*); δ_H (400 MHz, C_6D_6) 0.8–0.92 (1H, m, C*H*(Me)CH$_2$), 1.01 (3H, d, *J* 6.8, CH(CH_3)$_2$), 1.13 (3H, d, *J* 7.1, CHCH_3), 1.22 (3H, d, *J* 6.7, CH(CH_3)$_2$), 1.41 (1H, dd, *J* 10, 6.4, C2-(pro *S*)-

H), 1.87 (1H, dd, *J* 8.1, 6.5, C2-(pro *R*)-*H*), 2.38–2.31 (1H, m, C*H*(CH_3)$_2$), 3.43 (3H, s, OMe), 3.47 (3H, s, OMe), 3.81 (1H, d, *J* 14.8, N7-CH_2), 3.81 (1H, d, *J* 9.9, C*H*CH(CH_3)$_2$), 4.18 (1H, br d, *J* 15.4, N4-CH_2), 4.60 (1H, br d, 15.6, N4-CH_2), 5.62 (1H, d, *J* 14.8, N7-CH_2), 6.73–6.89 (4H, m, Ar*H*), 7.07–7.11 (2H, m, Ar*H*), 7.18–7.26 (2H, m, Ar*H*); δ_C (100 MHz, $CDCl_3$) 12.3, 16.5, 19.8, 20.3, 23.2, 31.1, 45.2, 46.5, 50.6, 55.2, 55.3, 67.5, 114.0, 114.2, 127.9, 128.4, 129.2, 129.3, 158.7, 159.2, 166.0, 169.3. HRMS for $C_{26}H_{33}N_2O_4$ (MH^+) requires 451.2440, found 451.2440.

(1*R*,3*R*,6*S*)-, (1*S*,3*R*,6*S*)- and (1*S*,3*S*,6*S*)-4,7-Bis(4-methoxybenzyl)-6-isopropyl-1-phenyl-4,7-diazaspiro[2.5]octane-5,8-dione 23, 24 and 26. To a solution of tosylhydrazide (1.86 g, 10 mmol) in glacial acetic acid (5 ml) was added benzaldehyde (1.27 g, 12 mmol) and the mixture was refluxed until precipitation started. The mixture was cooled and the solid was isolated by filtration and washed sequentially with cold acetic acid, acetic acid–water (1 : 1), cold water and hexane to furnish the tosylhydrazone as a colourless solid (1.92 g, 70%). A solution of the tosylhydrazone (922 mg, 3.36 mmol) in toluene (40 ml) was added to a solution of benzyltriethylammonium chloride (192 mg, 0.84 mmol) in aqueous sodium hydroxide (40 ml, 14% w/v). The mixture was heated to 70 °C for 2 h before cooling to room temperature. The aqueous layer was separated, leaving the organic solution of phenyldiazomethane, which was used directly in the addition to acceptor **2**. To this freshly prepared solution of phenyldiazomethane in toluene was added **2** (227 mg, 0.56 mmol). The mixture was stirred at room temperature for 4 days, before heating to 60 °C for 24 hours. The reaction mixture was concentrated under reduced pressure and examination of the ^{1}H NMR spectrum of the crude reaction mixture indicated a 28 : 11 : 11 : 50 mixture of four diastereoisomers. Purification by flash column chromatography (silica, hexane–ethyl acetate 7 : 3) furnished, in order of elution, **23** (46 mg, 16%), a 1 : 1 mixture of **26** and **25** (10 mg, 3.5%) and **24** (99 mg, 35%). Exhaustive chromatography allowed for sufficient quantities of **26** to be isolated for characterisation.

(1*R*,3*R*,6*S*)-23. Colourless oil (46 mg, 16%). $[\alpha]_D$ +11.6 (*c* 0.83 in $CHCl_3$); ν_{max}/cm^{-1} (thin film): 3580–2837, 1661, 1613; δ_H (500 MHz, $CDCl_3$) 1.06 (3H, d, *J* 6.8, CH(CH_3)$_2$), 1.14 (3H, d, *J* 6.8, CH(CH_3)$_2$), 1.78 (1H, dd, *J* 8.6, 5.8, C2-(pro *S*)-*H*), 2.00 (1H, dd, *J* 10.2, 5.8, C2-(pro *R*)-*H*), 2.50 (1H, m, C*H*(CH_3)$_2$), 3.29 (1H, dd, *J* 10.2, 8.6, C*H*Ph), 3.77 (s, 3H, OMe), 3.81 (s, 3H, OMe), 3.82 (1H, d, *J* 6.5, C6-*H*), 3.88 (1H, d, *J* 15.8, N4-CH_2), 3.97 (1H, d, *J* 14.9, N7-CH_2), 4.06 (1H, d, *J* 15.8, N4-CH_2), 5.42 (1H, d, *J* 14.9, N7-CH_2), 6.70 (4H, m, Ar*H*), 6.86 (2H, m, Ar*H*), 7.11 (2H, m, Ar*H*), 7.14–7.18 (2H, m, Ar*H*), 7.24–7.27 (3H, m, Ar*H*); δ_C (175 MHz, $CDCl_3$) 18.1, 18.8, 20.4, 29.9, 30.7, 45.7, 47.3, 48.6, 55.1, 55.2, 65.2, 113.6, 114.3, 127.4, 127.9, 128.3, 128.6, 128.9, 129.0, 129.2, 134.4, 158.5, 159.1, 168.6, 169.3; HRMS for $C_{31}H_{35}N_2O_4$ (MH^+) requires 499. 2597, found 499.2604.

(1*S*,3*S*,6*S*)-26. Colourless oil (10 mg). $[\alpha]_D$ −112 (*c* 0.07 in $CHCl_3$); ν_{max}/cm^{-1} (KBr) 3433, 1654, 1639; δ_H (400 MHz, $CDCl_3$) 0.66 (3H, d, *J* 6.7, CH(CH_3)$_2$), 1.12 (3H, d, *J* 6.7, CH(CH_3)$_2$), 1.84 (2H, m, C2-(pro *S*)-H), 2.11–2.19 (2H, m, C*H*(CH_3)$_2$), 2.49–2.53 (2H, m, C*H*CH_2 and C2-(pro *R*)-H), 3.52 (1H, d, *J* 10.6, C6-*H*), 3.67 (1H, d, *J* 15.2, NCH_2), 3.77 (1H, d, *J* 14.7, NCH_2), 3.79 (3H, s, OMe), 3.80 (3H, s, OMe), 5.26 (1H, d, *J* 15.2, NCH_2), 5.42 (1H, d, *J* 14.7, NCH_2), 6.77 (2H, m, *ArH*), 6.78 (2H, m, *ArH*), 6.96 (2H, m, *ArH*), 7.00 (2H, m, *ArH*), 7.11 (2H, m, *ArH*), 7.25–7.28 (1H, m, Ar*H*), 7.31–7.35 (2H, m, Ar*H*); δ_H (400 MHz, C_6D_6) 0.80 (3H, d, *J* 6.7, CH(CH_3)$_2$), 0.94 (3H, d, *J* 6.7, CH(CH_3)$_2$), 1.63 (1H, apparent t, C2-(pro *S*)-H), 2.20–2.26 (2H, m, C*H*(CH_3)$_2$), 2.56 (1H, dd, *J* 10.2, 7.7, C*H*CH_2), 2.74 (1H, dd, *J* 10.2, 6.7, C2-(pro *R*)-H), 3.43 (3H, s, OMe), 3.44 (3H, s, OMe), 3.58 (1H, d, *J* 15.2, N4-CH_2), 3.68 (1H, d, *J* 14.9, N7-CH_2), 3.70 (1H, s, C*H*CH(CH_3)$_2$), 5,45 (1H, d, *J* 15.1, N4-CH_2), 5.63 (1H, d, *J* 14.8, N7-CH_2), 6.77 (4H, m, *ArH*), 6.89 (2H, m, *ArH*), 7.03 (2H, m, *ArH*), 7.11–7.22 (5H, m, *ArH*); δ_C (175 MHz, $CDCl_3$) 16.5, 19.2, 20.8, 31.8, 34.2, 47.6, 47.9, 50.8, 55.2, 68.9, 114.0, 114.1, 127.2, 128.0, 128.2, 128.6, 128.7, 128.8, 129.2, 134.5, 158.9, 159.1, 167.9, 170.2; HRMS for $C_{31}H_{35}N_2O_4$ (MH^+) requires 499.2597, found 499.2597.

(1*R*,3*S*,6*S*)-25. Contaminated with **26**, colourless oil (10 mg). Selected data: δ_H (500 MHz, $CDCl_3$) 0.57 (3H, d, *J* 6.7, CH-(CH_3)$_2$), 1.11 (3H, d, *J* 6.7, CH(CH_3)$_2$), 2.00 (1H, dd, *J* 10.2, 7.4, CH(CH_2)), 2.23–2.28 (2H, m, C*H*Ph or 1 × CH(CH_2) and C*H*(CH_3)$_2$), 2.45 (1H, dd, *J* 9.2, 7.4, CH(CH_2) or C*H*(CH_2)), 3.53 (1H, d, *J* 10.4, C6-*H*), 3.60 (1H, d, *J* 14.8, NCH_2), 3.79 (s, 3H, OMe), 3.81 (s, 3H, OMe), 4.26 (1H, d, *J* 15.6, NCH_2), 4.85 (1H, d, *J* 15.6, NCH_2), 5.17 (1H, d, *J* 14.8, NCH_2), 6.81 (2H, m, Ar*H*), 6.84 (2H, m, Ar*H*), 7.04 (2H, m, Ar*H*), 7.05 (2H, m, Ar*H*), 7.16–7.26 (3H, m, Ar*H*), 7.27–7.31 (2H, m, Ar*H*); δ_C (175 MHz, $CDCl_3$) 15.6, 19.6, 19.9, 31.5, 34.4, 45.0, 50.0, 50.8, 55.2, 67.8, 114.1, 114.2, 126.7, 128.0, 128.1, 128.3, 128.6, 129.0, 129.1, 134.4, 158.9, 159.1, 163.6, 169.7.

(1*S*,3*R*,6*S*)-24. Colourless plates (99 mg, 35%). Mp 128 °C; $[\alpha]_D$ −366.8 (*c* 1.00 in $CHCl_3$); ν_{max}/cm^{-1} (KBr) 3047–2833, 1663, 1612; δ_H (500 MHz, $CDCl_3$) 1.10 (3H, d, *J* 6.8, CH(CH_3)$_2$), 1.15 (3H, d, *J* 6.8, CH(CH_3)$_2$), 1.56 (1H, dd, *J* 10.4, 5.8, C2-(pro *S*)-H), 2.05 (1H, dd, *J* 8.8, 5.8, C2-(pro *R*)-H), 2.38 (1H, m, C*H*(CH_3)$_2$), 3.02 (1H, dd, *J* 10.4, 8.8, C*H*Ph), 3.72 (1H, d, *J* 15.0, N7-CH_2), 3.80 (1H, d, *J* 5.6, C6-*H*), 3.81 (s, 3H, OMe), 3.83 (s, 3H, OMe), 4.26 (1H, d, *J* 15.9, N4-CH_2), 5.03 (1H, d, *J* 15.9, N4-CH_2), 5.31 (1H, d, *J* 15.0, N7-CH_2), 6.79 (2H, m, Ar*H*), 6.86–6.91 (6H, m, Ar*H*), 7.11 (2H, m, Ar*H*), 7.19–7.25 (3H, m, Ar*H*); δ_C (175 MHz, $CDCl_3$) 18.4, 18.9, 20.4, 30.4, 30.9, 44.8, 45.7, 47.6, 55.2, 55.4, 64.4, 114.1, 114.4, 126.5, 127.8, 128.0, 128.2, 128.4, 129.1, 135.4, 159.0, 166.5, 168.7; HRMS for $C_{31}H_{35}N_2O_4$ (MH^+) requires 499.2597, found 499.2601.

X-ray crystal structure data for **24**:

Data were collected using an Enraf Nonius Kappa CCD diffractometer with graphite monochromated Mo-Kα radiation using standard procedures at 190 K. The structure was solved by direct methods (Sir92), all non-hydrogen atoms were refined with anisotropic thermal parameters. Hydrogen atoms were added at idealised positions. The structure was refined using CRySTALS.[26] Crystal data for **24** [$C_{31}H_{34}N_2O_4$], colourless plate, M = 498.62, monoclinic, space group P 1 21 1. a = 10.4793(2), b = 10.5310(3), c = 12.0380(4) Å, β = 96.237(1)°, U = 1320.62(6) Å^3, Z = 2, μ = 0.083, crystal dimensions 0.1 × 0.2 × 0.3 mm, A total of 3196 unique reflections were measured for 5 < θ < 27 and 2613 reflections were used in the refinement. The final parameters were wR_2 = 0.050 and R_1 = 0.051 [$I > 1\sigma(I)$]. Crystallographic data (excluding structure factors) have been deposited with the Cambridge Crystallographic Data Centre. ‡

(3*S*,6*S*)-4,7-Bis(4-methoxybenzyl)-[1,1-^{2}H]-6-isopropyl-4,7-diazaspiro[2.5]octane-5,8-dione 33. To a suspension of trimethylsulfoxonium-d_9 iodide (1.7 g, 7.5 mmol) in THF (100 ml) was added n-BuLi (9.0 ml, 1.6 M in hexane, 15.0 mmol) under nitrogen at room temperature. After 30 minutes the mixture was cooled in an ice bath and a solution of **2** (2.4 g, 6 mmol) in THF (20 ml) was added *via* cannula over a period of 15 minutes. The resulting mixture was warmed to room temperature and stirred overnight. The reaction was quenched with saturated ammonium chloride, the organic layer separated and the aqueous layer extracted with ethyl acetate. The combined

‡ CCDC 206108. See http://www.rsc.org/suppdata/ob/b3/b303348a/ for crystallographic data in .cif or other electronic format.

organic phases were dried over $MgSO_4$, filtered and the solvent was removed under vacuum. Flash column chromatography (silica, 1 : 1 petroleum ether–ethyl acetate) of the residue afforded **33** as a colourless oil (2.2 g, 86%). $[a]_D$ −99.3 (*c* 1.00 in $CHCl_3$); ν_{max}/cm^{-1} (thin film) 2963, 2935, 1661, 1613, 1585, 1513, 1455, 1415; δ_H (400 MHz, $CDCl_3$) 1.10 (3H, d, *J* 6.8, $CH(CH_3)_2$), 1.14 (3H, d, *J* 6.8, $CH(CH_3)_2$), 1.45 (1H, d, *J* 6.3, C2-(pro *S*)-*H*), 1.84 (1H, d, *J* 6.3, C2-(pro *R*)-*H*), 2.39 (1H, m, $CH(CH_3)_2$), 3.79–3.81 (7H, m, C6-*H* and 2 × O*Me*), 3.86 (1H, d, *J* 14.8, N7-CH_2), 4.18 (1H, d, *J* 15.6, N4-CH_2), 4.70 (1H, d, *J* 15.6, N4-CH_2), 5.39 (1H, d, *J* 14.8, N7-CH_2), 6.81 (2H, m, Ar*H*), 6.86 (2H, m, Ar*H*), 7.03 (2H, m, Ar*H*), 7.14 (2H, m, Ar*H*); δ_C (100 MHz, $CDCl_3$) 11.3, 16.7, 19.2, 20.3, 31.4, 41.8, 44.9, 49.4, 55.2, 55.3, 66.3, 95.7, 114.1, 114.2, 127.9, 128.1, 129.1, 129.3, 158.8, 159.1, 167.8, 168.5; HRMS for $C_{25}H_{28}D_2N_2O_4$ (M^+) requires 424.2329, found 424.2331.

(3*S*,6*S*)-[1,1-^{2}H]-6-Isopropyl-4,7-diazaspiro[2.5]octane-5,8-dione 35. A solution of **33** (2 g, 4.7 mmol) in TFA (100 ml) was refluxed for 48 hours before concentrating under reduced pressure. The dark green residue was triturated with diethyl ether (3 × 25 ml) before recrystallisation from acetone afforded **35** as a colourless solid (720 mg, 84%). Mp 239–241 °C; $[a]_D$ +16.8 (*c* 0.5 in MeOH); ν_{max}/cm^{-1} (KBr) 3300–2700, 3187, 3050, 2961, 2895, 1674, 1458; δ_H (500 MHz, DMSO-d_6) 0.90 (3H, d, *J* 6.8, $CH(CH_3)_2$), 0.95 (3H, d, *J* 7.0, $CH(CH_3)_2$), 0.99 (1H, d, *J* 4.4, $CH_2(CH_2)$), 1.27 (1H, d, *J* 4.4, $CH_2(CH_2)$), 2.13 (1H, m, $CH(CH_3)_2$), 3.66 (1H, d, *J* 3.4, C6-*H*), 8.18 (1H, s, N*H*), 8.25 (1H, s, N*H*); δ_C (125 MHz, DMSO-d_6) 13.2, 16.8, 17.3, 18.7, 32.8, 36.2, 60.9, 168.1, 168.6; HRMS for $C_9H_{12}D_2N_2O_2$ (M^+) requires 184.1186, found 184.1181.

(*S*)-1-Amino-[2,2-^{2}H]-cyclopropanecarboxylic acid methyl ester 36 and (*S*)-valine methyl ester 17. A suspension of **33** (552 mg, 3.0 mmol) in HCl (30 ml, 6 M) was refluxed 24 hours before cooling to room temperature and washing with diethyl ether. The aqueous phase was concentrated under vacuum to afford a mixture of amino acids that were dissolved in MeOH (75 ml) and cooled to 0 °C before thionyl chloride (2.25 ml) was added. The reaction mixture was subject to reflux overnight before concentration under vacuum afforded a 1 : 1 mixture of the amino ester hydrochlorides **17** and **36**, as colourless solids that were used without further purification (733 mg). δ_H (300 MHz, D_2O) 0.85 (3H, d, *J* 6.8, $CH(CH_3)_2$), 0.86 (3H, d, *J* 6.8, $CH(CH_3)_2$), 1.26 (1H, d, *J* 6.1, CH_2), 1.43 (1H, d, *J* 6.1, CH_2), 2.18 (1H, m, $CH(CH_3)_2$), 3.63 (3H, s, O*Me*), 3.68 (3H, s, O*Me*), 3.86 (1H, d, *J* 4.6, Val·HCl-C*H*).

***N*-Cbz-(*S*)-phenylalanine-(*S*)-[2,2-^{2}H]-cyclopropanecarboxylic acid methyl ester 37.** To a solution of *N*-CBz-(*S*)-phenylalanine (728 mg, 2.43 mmol) in DMF (22 ml) and THF (22 ml) at 0 °C, was added *N*-methylmorpholine (0.49 ml, 4.46 mmol) and isobutyl chloroformate (0.32 ml, 2.43 mmol). The reaction mixture was stirred for 15 minutes before a solution of the amino esters **17** and **36** (355 mg, 2.03 mmol) in DMF (30 ml) was added *via* cannula. Stirring was continued for a further 45 minutes before dilution with ethyl acetate. The organic phase was washed with water, saturated aqueous $NaHCO_3$, 10% aqueous citric acid, brine and dried over $MgSO_4$ and the solvent removed *in vacuo*. Purification of the residues by column chromatography (silica, diethyl ether–hexane 6 : 4) afforded **19** as a colourless solid (338 mg, 81%). Further elution furnished **37** as a colourless solid (376 mg, 93%). Mp 127–133 °C; $[a]_D$ +4.6 (*c* 0.5 in $CHCl_3$); ν_{max}/cm^{-1} (KBr) 3299, 1732, 1683, 1663; δ_H (400 MHz, $CDCl_3$) 0.86 (1H, d, *J* 4.6, $CC\!H_2$), 1.43 (1H, d, *J* 4.6, $CC\!H_2$), 3.04 (2H, m, $PhCH_2CH$), 3.62 (3H, s, O*Me*), 4.44 (1H, br s, N*H*), 5.07 (2H, m, $PhCH_2O$), 5.62 (1H, d, *J* 7.2, N*H*CBz), 7.40–7.19 (10H, m, Ph); δ_C (100 MHz, $CDCl_3$) 17.4, 33.1, 38.5, 52.5, 55.9, 67.0, 77.3, 127.0, 128.0, 128.2, 128.5, 128.6, 129.4, 136.1, 136.5, 156.0, 171.9, 172.4; HRMS for $C_{22}H_{22}D_2N_2O_5Na$ (MNa^+) requires 421.1702, found 421.1708.

(*S*)-Phenylalanine-(*S*)-[2,2-^{2}H]-cyclopropanecarboxylic acid methyl ester 38. To a solution of peptide **37** (220 mg, 0.51 mmol) in degassed MeOH (1 ml) was added Pd/C (40 mg, 20 w/w). The resultant mixture was stirred overnight under a hydrogen balloon (1 atm) before filtration through Celite®. The solvent was removed under vacuum and the crude reaction mixture was purified by flash column chromatography (silica, diethyl ether–methanol 8 : 2) furnishing **38** as a colourless oil (126 mg, 87%). ν_{max}/cm^{-1} (thin film) 2360, 2340, 1727, 1670; δ_H (400 MHz, AcOH-d_4) 0.95 (1H, d, *J* 4.9, $CC\!H_2$), 1.43 (1H, d, *J* 4.9, $CC\!H_2$), 3.21–3.34 (2H, m, $PhCH_2$), 3.69 (3H, s, O*Me*), 4.57 (1H, t, *J* 7.1, $PhCH_2CHNH_2$), 7.29–7.37 (5H, m, Ph); δ_H (200 MHz, MeOH-d_4) 0.91 (1H, d, *J* 4.6, $CC\!H_2$), 1.43 (1H, d, *J* 4.6, $CC\!H_2$), 2.95 (2H, dd, *J* 11.6, 7.0, $PhCH_2$), 3.69 (3H, s, O*Me*), 4.83 (1H, m, $PhCH_2CHNH_2$), 7.23–7.37 (5H, m, Ph); δ_H (500 MHz, TFA-d_1) 1.35 (1H, d, *J* 5.2, $CC\!H_2$), 1.98 (1H, d, *J* 5.2, $CC\!H_2$), 3.61–3.73 (2H, m, $PhCH_2$), 4.13 (3H, s, O*Me*), 4.91 (1H, t, *J* 7.5, $PhCH_2CH$); δ_D (76.7 MHz, TFA ref DCM-d_2) 1.30, 1.81; δ_C (100 MHz, MeOH-d_4) 16.7, 16.9, 33.5, 41.4, 52.0, 56.4, 126.8, 127.4, 128.5, 129.4, 130.6, 137.7, 173.3, 176.9; HRMS for $C_{14}H_{17}D_2N_2O_3$ (MH^+) requires 264.1441, found 264.1440.

(3*S*,6*S*)-[1,1-^{2}H]-6-Benzyl-4,7-diazaspiro[2.5]octane-5,8-dione 34. Dipeptide **38** (125 mg, 0.46 mmol) was subject to reflux overnight in toluene (75 ml). The solvent was then removed under reduced pressure and the crude residue was repeatedly triturated with diethyl ether before recrystallisation from acetone afforded **34** as a colourless solid (11 mg, 10%). Mp 277–280 °C; $[a]_D$ +13.2 (*c* 0.5 in MeOH); ν_{max}/cm^{-1} (KBr) 2360, 2340, 1727, 1670; δ_H (400 MHz, AcOH-d_4) 0.90 (1H, d, *J* 5.5, $CC\!H_2$), 1.42 (1H, d, *J* 5.5, $CC\!H_2$), 3.09 (1H, dd, *J* 13.9, 4.5, $PhCH_2$), 3.31 (1H, dd, *J* 13.9, 4.5, $PhCH_2$), 4.61 (1H, t, *J* 4.5, $PhCH_2CH$), 7.21–7.39 (5H, m, Ph); δ_H (400 MHz, MeOH-d_4) 0.81 (1H, d, *J* 5.0, $CC\!H_2$), 1.24 (1H, d, *J* 5.0, $CC\!H_2$), 3.01 (1H, dd, *J* 13.7, 4.7, $PhCH_2$), 3.27 (1H, dd, *J* 13.7, 4.1, $PhCH_2$), 4.35 (1H, t, *J* 4.5, $PhCH_2CH$), 7.19–7.37 (5H, m, Ph); δ_H (500 MHz, TFA-d_1) 1.27 (1H, d, *J* 5.4, $CC\!H_2$), 1.88 (1H, d, *J* 5.4, $CC\!H_2$), 3.57–3.74 (2H, m, $PhCH_2$), 4.91 (1H, t, *J* 7.4, $PhCH_2CH$), 7.40–7.56 (2H, m, Ph), 7.63–7.71 (3H, m, Ph); δ_D (76.7 MHz, AcOH ref DCM-d_2) 0.35, 0.76; δ_D (76.7 MHz, MeOH ref DCM-d_2) 0.20, 0.54; δ_D (76.7 MHz, TFA ref DCM-d_2) 0.76, 1.12; δ_C (125 MHz, AcOH-d_4) 16.9, 14.2, 37.6, 39.9, 57.0, 127.7, 128.8, 129.0, 129.8, 130.7, 135.1, 171.6, 173.4; HRMS for $C_{13}H_{12}D_2N_2O_2$ (MH^+) requires 233.1252, found 233.1252.

(*S*)-6-Benzyl-4,7-diazaspiro[2.5]octane-5,8-dione 39. To a solution of *N*-CBz-(*S*)-phenylalanine (849 mg, 2.84 mmol) in DMF (8 ml) and THF (8 ml) at 0 °C, was added *N*-methylmorpholine (0.31 ml, 2.84 mmol) and isobutyl chloroformate (0.37 ml, 2.84 mmol). The reaction mixture was stirred for 15 minutes before a solution of 1-amino-1-cyclopropanecarboxylic acid methyl ester (391 mg, 2.58 mmol) in DMF (8 ml) was added *via* cannula. Stirring was continued for a further 45 minutes before dilution with ethyl acetate. The organic phase was washed with water, saturated aqueous $NaHCO_3$, 10% aqueous citric acid, brine and dried over $MgSO_4$. After removal of solvent the residues were crystallised from ethyl acetate–hexane to afford *N*-Cbz-(*S*)-phenylalanine-(*S*)-cyclopropanecarboxylic acid methyl ester **41** (946 mg, 96%). $[a]_D^{23}$ +2.5 (*c* 1.0 in $CHCl_3$); $[a]_D^{24}$ −12.5 (*c* 0.2 in MeOH); (Lit.[28] $[a]_D^{20}$ −19.9 [*c* 0.2 in MeOH]), (Lit.[29] $[a]_D^{20}$ −5 [*c* 0.1 in CH_2Cl_2]); δ_H (400 MHz, AcOH-d_4) 0.90 (1H, d, *J* 5.5, $CC\!H_2$), 1.42 (1H, d, *J* 5.5, $CC\!H_2$), 3.09 (1H, dd, *J* 13.9, 4.5, $PhCH_2$), 3.31 (1H, dd, *J* 13.9, 4.5, $PhCH_2$), 4.61 (1H, t, *J* 4.5, $PhCH_2CH$), 7.21–7.39 (5H, m, Ph).

To a solution of peptide **41** (100 mg, 0.26 mmol) in degassed MeOH (5 ml) was added Pd/C (20 mg, 20 w/w). The resultant mixture was stirred overnight under a hydrogen balloon (1 atm) before filtration through Celite®. The solvent was removed

under vacuum and the residues were subject to reflux overnight in toluene (25 ml). The solvent was then removed under reduced pressure and the crude residue was repeatedly triturated with diethyl ether before recrystallisation from acetone afforded **39** as a colourless solid (24 mg, 40%). $[\alpha]_D^{23}$ +20.4 (*c* 0.25 in MeOH) (Lit.[28] $[\alpha]_D$ +35.7 [*c* 0.2 in MeOH]); Mp °C 262–265 °C; ν_{max}/cm^{-1} (KBr) 1731, 1670; δ_H (400 MHz, AcOH-d_4) 0.31–0.37 (1H, m, CCH_2), 0.69–0.75 (1H, m, CCH_2), 0.88–0.95 (1H, m, CCH_2), 1.41–1.52 (1H, m, CCH_2), 3.09 (1H, dd, *J* 13.8, 4.6, PhCH_2), 3.31 (1H, dd, *J* 13.9, 4.3, PhCH_2), 4.61 (1H, t, *J* 4.4, PhCH$_2$C*H*), 7.20–7.40 (5H, m, Ph); δ_H (400 MHz, MeOH-d_4) 0.18–0.24 (1H, m, CCH_2), 0.52–0.58 (1H, m, CCH_2), 0.81–0.86 (1H, m, CCH_2), 1.25–1.45 (1H, m, CCH_2), 3.01 (1H, dd, *J* 13.7, 4.6, PhCH_2), 3.27 (1H, dd, *J* 13.7, 4.0, PhCH_2), 4.35 (1H, t, *J* 4.5, PhCH$_2$C*H*), 7.21–7.63 (5H, m, Ph); δ_H (500 MHz, TFA-d_1) 0.71–0.77 (1H, m, CCH_2), 1.08–1.14 (1H, m, CCH_2), 1.24–1.30 (1H, m, CCH_2), 1.79–1.89 (1H, m, CCH_2), 3.38 (1H, dd, *J* 14.3, 4.2, PhCH_2), 3.52 (1H, dd, *J* 14.2, 4.5, PhCH_2), 4.95 (1H, t, *J* 4.4, PhCH$_2$C*H*), 7.21–7.38 (2H, m, Ph), 7.58–7.61 (3H, m, Ph); δ_C (100.6 MHz, DMSO-d_6) 13.7, 16.3, 36.7, 39.9, 57.2, 127.5, 128.9, 131.0, 136.8, 168.5, 168.8; HRMS for $C_{13}H_{15}N_2O_2$ (MH^+) requires 231.2705, found 231.2709.

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