Diastereoselective synthesis of quaternary α-amino acids from diketopiperazine templates†

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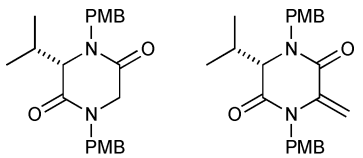
Sequential enolate alkylations of (*S*)-*N*(1)-methyl-5-methoxy-6-isopropyl-3,6-dihydropyrazin-2-one and (*S*)-*N*(1)-*p*-methoxybenzyl-5-methoxy-6-isopropyl-3,6-dihydropyrazin-2-one proceed with excellent levels of diastereoselectivity (>90% de) affording quaternary α-amino acids in high enantiomeric excess (>98% ee) after deprotection and hydrolysis.

Introduction

The asymmetric synthesis of non-proteinogenic quaternary (α,α-disubstituted) amino acids is of interest due to the biological activity of these small molecules and peptides containing such residues.[1] Furthermore these materials have application in protein engineering due to their ability to restrict the conformational flexibility of peptides and allow the subtle perturbations of overall structure without wholly disrupting secondary structural features.[2] The asymmetric synthesis of this class of α-amino acid has been reviewed[1] and recently a wide variety of approaches including phase transfer catalysis,[3] asymmetric catalytic allylation,[4] chiral auxiliary,[5] rearrangement,[6] and chiral memory[7] have been reported.[8] We have previously reported the asymmetric synthesis of both (*R*) and (*S*) tertiary α-amino acids from the alkylation of *N*,*N*′-bis-*p*-methoxybenzyl-3-isopropyl-diketopiperazine (DKP) templates **1**[9] and **2**[10] (Fig. 1) and wished to extend the alkylation chemistry of these templates to the asymmetric preparation of quaternary α-amino acids. We describe herein the results of these investigations, and the use of modified diketopiperazine derived templates for the efficient asymmetric synthesis of tertiary and quaternary α-amino acids.



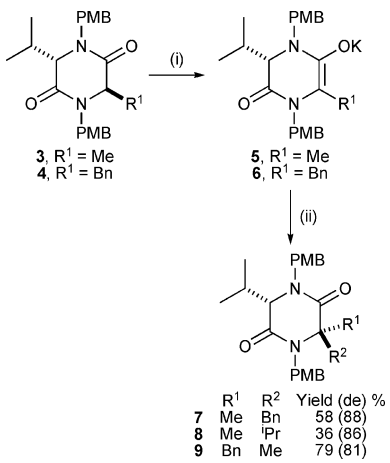
1 **2**

Fig. 1 DKPs **1** and **2**.

Results and discussion

Alkylation of *N*,*N*′-bis-*p*-methoxybenzyl-3-isopropyl-6-alkyl-piperazine-2,5-dione templates

In preliminary investigations alkylations of the lithium enolates of the known substituted 6-methyl-DKP **3** and 6-benzyl-DKP **4** with a range of alkyl halides were found to proceed with poor conversion and yield. The corresponding potassium enolates **5** and **6**, however, were found to be more reactive and afforded dialkylated products **7–9** in moderate yield and de. Notably the alkylation of **5** with sterically hindered isopropyl iodide gave **8** in only 36% isolated yield (Scheme 1).



Scheme 1 *Reagents and conditions*: (i) KHMDS (3 eq.), THF, −78 °C; (ii) R^2X.

These results are in marked contrast to the reactivity and high levels of diastereoselectivity observed upon mono-alkylation of the lithium enolate of DKP **1**. The poor reactivity and selectivity observed in the present case is presumably due to an increase in steric hindrance at the substituted carbon centre of the enolate undergoing alkylation. The presence of the *N*(1)-alkyl substituent close to the site of alkylation may also contribute to the steric crowding of these enolates and it was therefore proposed that

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mono-lactim ether substrates such as **18** and **19** (Fig. 2) may show greater reactivity in alkylation reactions, allowing the efficient alkylation of substituted enolates. In support of this hypothesis the dialkylations of Schöllkopf's bis-lactim ether auxiliary **10**[11] and *N*(1)-benzyl mono-lactim ether template **11**[12] (Fig. 2) have been reported to proceed efficiently, and with high levels of *trans* diastereofacial selectivity. We chose to investigate systematically the reactivity and selectivity of templates *N*(1)-methyl **18** and *N*(1)-*p*-methoxybenzyl **19** in order to appraise their general utility for the preparation of a range of quaternary α-amino acids.

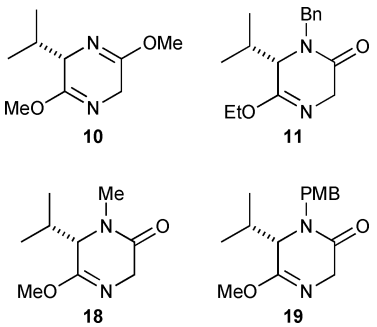
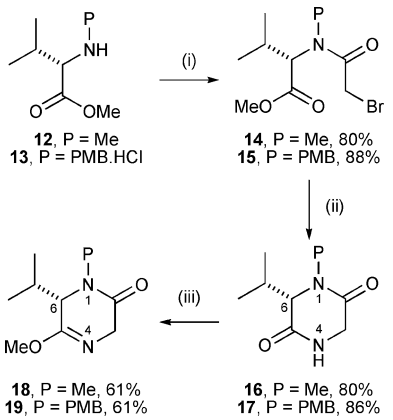


Fig. 2 Schöllkopf's bis-lactim ether auxiliary **10**, and mono-lactim ether templates **11**, **18** and **19**.

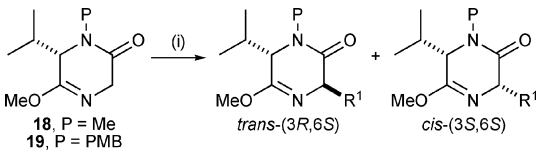
Mono-alkylation of *N*(1)-methyl and *N*(1)-*p*-methoxybenzyl mono-lactim ether templates

N(1)-Methyl and *N*(1)-*p*-methoxybenzyl mono-lactim ether templates **18** and **19** were prepared in 39 and 44% overall yield, respectively, from the appropriate (*S*)-*N*-alkyl-valine methyl ester hydrochlorides **12**[13] and **13**,[14] *via* *N*-acylation with bromoacetyl bromide, bromide displacement and concomitant cyclisation with ammonia, and subsequent *O*-methylation with trimethyloxonium tetrafluoroborate under vacuum in the ionic liquid solvent *N*-butyl-*N*′-methyl-imidazolium tetrafluoroborate ($BmimBF_4$)[15] (Scheme 2).



Scheme 2 *Reagents and conditions*: (i) $BrCH_2COBr$, Et_3N, DCM, −78 °C; (ii) NH_3, EtOH, rt, 48 h; (iii) Me_3OBF_4, $BmimBF_4$, vacuum, rt.

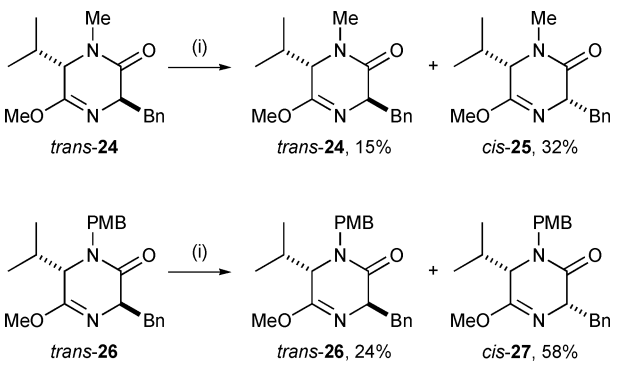
Efficient and exclusive C(3)-alkylation of mono-lactim ether templates **18** and **19** was achieved with 1.0 eq. of BuLi followed by addition of 1.1 eq. of three representative electrophiles *viz.* methyl iodide, benzyl bromide and isopropyl iodide. All alkylations afforded the corresponding *trans*-(3*R*,6*S*)-product as the major diastereoisomer, and the diastereoselectivity was independent of the choice of *N*-alkyl substituent: both the *N*(1)-methyl and *N*(1)-*p*-methoxybenzyl templates **18** and **19** delivered similar levels of diastereoselectivity. Good to excellent diastereoselectivities were observed in the alkylations with benzyl bromide (>98% de) and isopropyl iodide (88 and 95% de), whilst lower levels of selectivity were observed in the alkylations with methyl iodide (68 and 70% de) (Scheme 3).[16] In each case, the diastereoisomeric excess of the alkylation reaction was determined by analysis of the ^1H NMR spectrum of the crude reaction mixture. The lower selectivity observed for alkylation with methyl iodide was not the result of epimerisation of the alkylation products during the reaction since treatment of either *trans*-**22** (>98% de) or *cis*-**23** (>98% de) with 0.5 eq. of the lithium enolate of mono-lactim ether **19** returned diastereoisomerically pure starting material.



P	R^1	dr (*trans*:*cis*)[a]	*trans* yield (de)[b] %	*cis* yield (de)[b] %
Me	Me	84.5:14.5	**20**, 57 (>98)	**21**, 13 (>98)
PMB	Me	84:16	**22**, 62 (>98)	**23**, 4 (>98)
Me	Bn	>99:<1	**24**, 82 (>98)	**25**, 0
PMB	Bn	>99:<1	**26**, 94 (>98)	**27**, 0
Me	^{i}Pr	94:6	**28**, 84 (>98)	**29**, 3 (>98)
PMB	^{i}Pr	97.5:2.5	**30**, 62 (>98)	**31**, 2 (>98)

Scheme 3 *Reagents and conditions*: (i) BuLi (1.0 eq.), THF, −78 °C then R^1X (1.1 eq.) [[a] crude; [b] purified].

Due to the high levels of diastereoselectivity (>98% de) observed in the benzylation of mono-lactim ether templates **18** and **19** authentic samples of minor diastereoisomers *cis*-**25** and *cis*-**27** were prepared separately *via* epimerisation of *trans*-**24** and *trans*-**26** to enable unambiguous determination of the stereoselectivities in the benzylation reactions. Treatment of *trans*-**24** with BuLi followed by reprotonation with acetic acid, afforded a 25 : 75 mixture of *trans*-**24** : *cis*-**25** from which diastereoisomerically pure *trans*-**24** and *cis*-**25** were isolated in 15 and 32% yield respectively. Similar treatment of *trans*-**26** gave a 25 : 75 mixture of *trans*-**26** : *cis*-**27** from which *trans*-**26** and *cis*-**27** were isolated in 24 and 58% yield respectively (Scheme 4).



Scheme 4 *Reagents and conditions*: (i) BuLi, THF, −78 °C, then AcOH.

The relative *trans* configuration of the C(3) and C(6) ring substituents of the major *trans* diastereoisomeric alkylation products

20, **22** and **30**, and the relative *cis* configuration within minor diastereoisomer **25**, were assigned from ^{1}H NMR NOE difference experiments, with the relative configurations of the remaining diastereoisomers being assigned by analogy. The stereochemical outcome in these alkylation reactions is also in accord with previously reported alkylations of structurally related mono-lactim ether templates[12,17] (Fig. 3).

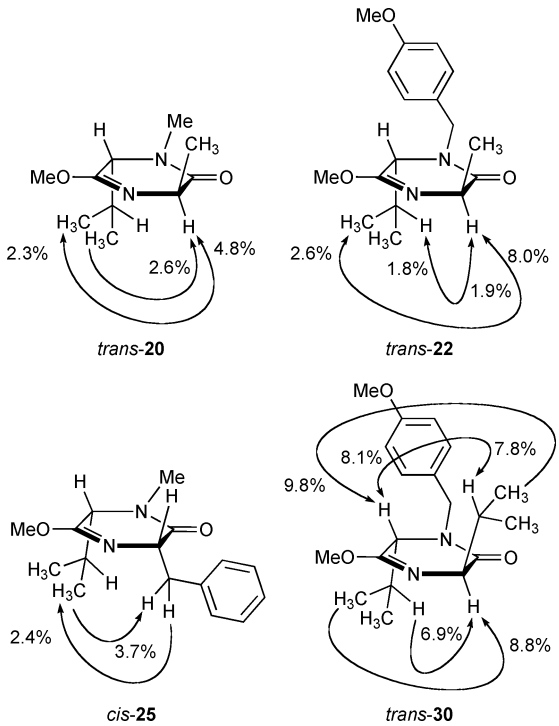
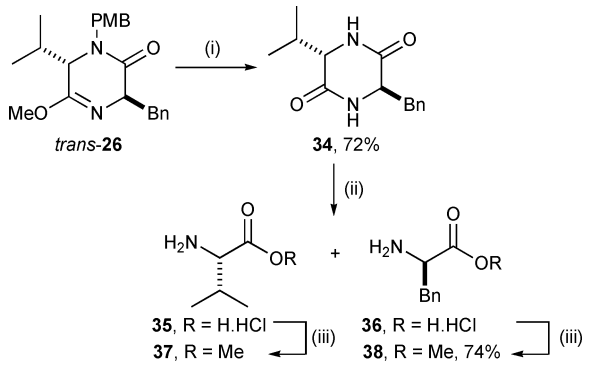


Fig. 3 Selected NOE enhancements for *trans*-**20**, *trans*-**22**, *cis*-**25** and *trans*-**30**.

The relative and absolute configuration of *trans*-**26** was established *via* deprotection and hydrolysis to afford (*R*)-phenylalanine methyl ester **38** which also demonstrated the viability of this template for the asymmetric synthesis of tertiary α-amino acids. *N*-Deprotection and lactim ether hydrolysis was achieved by treatment with refluxing TFA to give DKP **34** in 72% yield. Treatment of DKP **34** with refluxing 10 M HCl furnished a mixture of (*S*)-valine and (*R*)-phenylalanine hydrochloride salts **35** and **36** respectively, in 98% yield, which was converted to a mixture of the corresponding methyl ester hydrochloride salts **37** and **38**. Neutralisation, followed by removal of the (*S*)-valine methyl ester **37** under vacuum gave (*R*)-phenylalanine methyl ester **38** in 98% ee[18] and 61% overall yield from *trans*-**26** {$[\alpha]_D^{23}$ −32.2 (*c* 1.0 in EtOH) for **38**·HCl, lit.[19] $[\alpha]_D^{25}$ −37.0 (*c* 2.0, EtOH) for **38**·HCl} (Scheme 5).



Scheme 5 *Reagents and conditions*: (i) TFA, reflux; (ii) HCl (10 M aq.), reflux; (iii) $SOCl_2$, MeOH, reflux, then conc. NH_3, then distillation.

Regioselectivity of deprotonation and alkylation

Having examined the mono-alkylation chemistry of both *N*(1)-methyl and *N*(1)-*p*-methoxybenzyl mono-lactim ether templates **18** and **19**, studies were directed toward the alkylation of substituted templates. The effective dialkylation of these templates is reliant upon regioselective deprotonation of the substituted auxiliary at C(3), away from the C(6) stereodirecting isopropyl group. In *N*,*N*′-bis-*p*-methoxybenzyl protected DKP **1**, and Schöllkopf's bis-lactim ether auxiliary **10**, the regioselectivity of deprotonation is controlled by the isopropyl substituent which serves to direct deprotonation exclusively to the unsubstituted position due to steric and stereoelectronic factors arising from 1,2-torsional strain.[20] The related mono-lactim ether template **41**, meanwhile, undergoes deprotonation of the more acidic C(3) proton to give the corresponding *O*-stabilised enolate **42** (Fig. 4).[21]

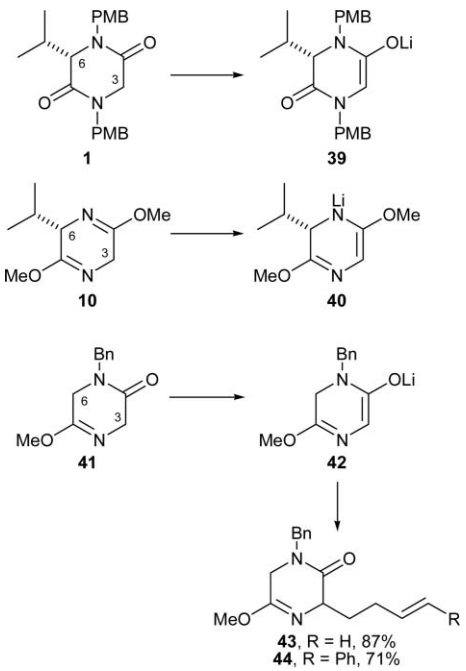
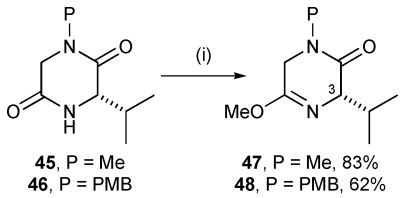


Fig. 4 Regioselective deprotonation of templates **1**, **10** and **41**.

In order to examine the potential limitations enforced by the competing contributions of a bulky substituent and lactim ether functionality to deprotonation regioselectivity, isopropyl lactim ethers **47** and **48** were prepared and alkylated. Templates **47** and **48** were prepared from the corresponding *N*(1)-alkyl DKPs **45**[22] and **46**,[23] by treatment with trimethyloxonium tetrafluoroborate in $BmimBF_4$.[15] The deprotonation of **47** and **48** with BuLi (1 eq.) and subsequent alkylation with either methyl iodide or benzyl bromide afforded **49–52**, products arising exclusively from alkylation at C(3) bearing the isopropyl substituent (Scheme 6).



	P	R	Yield %
49	Me	Me	72
50	Me	Bn	64
51	PMB	Me	81
52	PMB	Bn	64

Scheme 6 *Reagents and conditions*: (i) Me_3OBF_4, $BmimBF_4$, vacuum, rt; (ii) BuLi (1 eq.), THF, −78 °C, then RX.

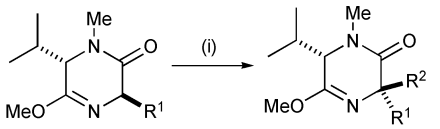
It is apparent that the regioselectivity of deprotonation of **45** and **46** is predominantly controlled by the significant difference in stability of the two alternative *O*- or *N*-stabilised anions. Furthermore the high yields of alkylated materials **49–52** obtained from this protocol indicate that even templates bearing very bulky substituents should be good substrates for the stereoselective generation of quaternary amino acids.

Alkylation of substituted templates

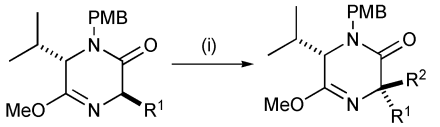
The stereoselective alkylation of the substituted templates **20**, **22**, **24**, **26**, **28** and **30** was then examined. In an initial study, deprotonation of *N*(1)-*p*-methoxybenzyl-3-methyl template *trans*-**22** with BuLi (1 eq.) followed by addition of benzyl bromide gave (3*R*,6*S*)-*N*(1)-*p*-methoxybenzyl-3-benzyl-3-methyl **59** in 98% de, which was isolated in 78% yield and as a single diastereoisomer (>98% de). The diastereoisomer (3*S*,6*S*)-*N*(1)-*p*-methoxybenzyl-3-benzyl-3-methyl **60** was prepared by deprotonation and methylation of *N*(1)-*p*-methoxybenzyl-3-benzyl template *trans*-**26**, to give **60** in 96% de, isolated in 68% yield as a single diastereoisomer (>98% de) (Scheme 7). The general utility of this procedure was further investigated by the alkylation of the range of substituted *N*-methyl and *N*-*p*-methoxybenzyl protected templates **20**, **22**, **24**, **26**, **28** and **30**, furnishing quaternary templates **53–64** with absolute regioselectivity and high *trans*-diastereoselectivity in all cases. Comparison of the reactions for the *N*-methyl and *N*-*p*-methoxybenzyl templates indicated that the nature of the *N*-protecting group has little effect on the reaction diastereoselectivity (Scheme 7).

The relative configuration of dialkylation products **53–64** was assigned by analogy to the diastereoselectivity observed in mono-alkylation reactions.[12] This assignment was further supported by NOE difference studies performed on **60** and **64**, where enhancements consistent with a *cis* relative configuration of the C(3)-R^1 and C(6)-isopropyl substituents were observed (Fig. 5).[24]

The methylation of *cis*-**27** under identical conditions to those employed for methylation of *trans*-**26** afforded the same disubstituted diastereoisomer **60**, resulting from alkylation *trans* to the C(6)-isopropyl group, in 98% de. This result demonstrates that, as expected, the alkylation is a stereoselective and not a stereospecific process, and that selectivity is independent of the relative stereochemistry of the starting material (Scheme 8).



Template	Product	R^1	R^2	de[a] %	Yield (de)[b] %
20	**53**	Me	Bn	98	81 (>98)
24	**54**	Bn	Me	93	50 (>98)
20	**55**	Me	^{i}Pr	>98	82 (>98)
28	**56**	^{i}Pr	Me	98	90 (>98)
24	**57**	Bn	^{i}Pr	>98	94 (>98)
28	**58**	^{i}Pr	Bn	>98	75 (>98)



Template	Product	R^1	R^2	de[a] %	Yield (de)[b] %
22	**59**	Me	Bn	98	78 (>98)
26	**60**	Bn	Me	96	68 (>98)
22	**61**	Me	^{i}Pr	85	72 (>98)
30	**62**	^{i}Pr	Me	98	93 (>98)
26	**63**	Bn	^{i}Pr	96	82 (>98)
30	**64**	^{i}Pr	Bn	>98	74 (>98)

Scheme 7 *Reagents and conditions*: (i) BuLi, THF, −78 °C, then R^2X [[a] crude; [b] purified].

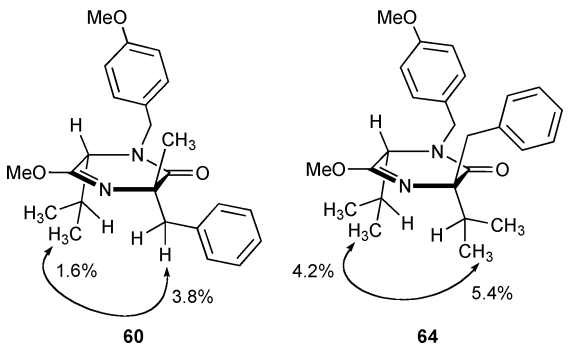
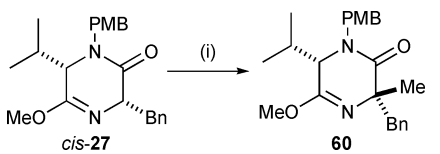
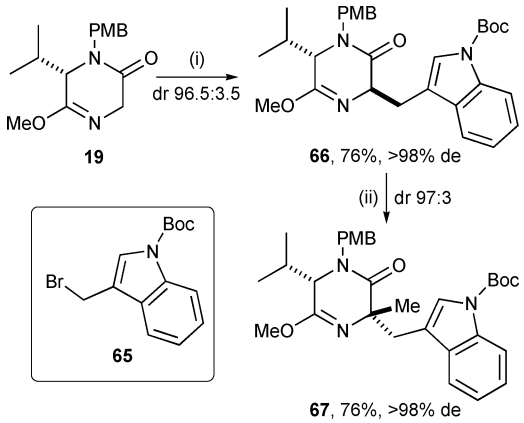


Fig. 5 Selected NOE enhancements for **60** and **64**.



Scheme 8 *Reagents and conditions*: (i) BuLi (1 eq.), THF, −78 °C, then MeI.

In order to probe further the utility of this alkylation protocol, alkylation with the functionalised *N*-Boc-3-bromomethylindole **65** was examined, as this may give access to the biologically important quaternary amino acid tryptophan hydrolase substrates.[25] *N*(1)-*p*-Methoxybenzyl template **19** was alkylated with bromide **65** under standard conditions, to give **66** in 93% de, which was isolated in 76% yield as a single diastereoisomer (Scheme 9).



Scheme 9 *Reagents and conditions*: (i) BuLi (1 eq.), THF, −78 °C, then **65**; (ii) BuLi (1 eq.), THF, −78 °C, then MeI.

The relative configuration within **66** was established by ^{1}H NMR NOESY spectroscopy (Fig. 6) and unambiguously confirmed by X-ray crystallographic analysis‡, with the absolute (3*R*,6*S*) configuration known from the (*S*)-valine derived stereocentre (Fig. 7). Subsequent deprotonation of **66** and methylation gave **67** in 94% de, isolated in 76% yield as a single diastereoisomer (Scheme 9). X-Ray crystallography unambiguously established the *trans*-configuration of the isopropyl and methyl substituents, with the absolute (3*S*,6*S*) configuration following from the (*S*)-valine derived stereocentre (Fig. 8).

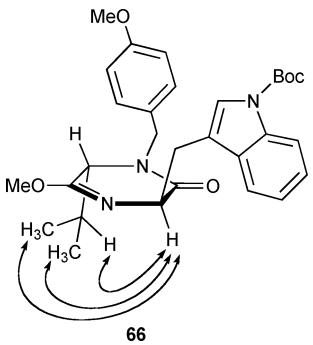


Fig. 6 Selected NOESY data for **66**.

Deprotection and hydrolysis of templates

The deprotection and hydrolysis of the disubstituted *N*-*p*-methoxybenzyl protected substrates to afford the desired quaternary α-amino acids was then investigated. Subjecting **59–64** to reflux in TFA for 4 days furnished diketopiperazines **68–73** in good yield (60–87%) as single diastereoisomers (Scheme 10).

The isomeric 3-benzyl-3-methyl quaternary substituted diketopiperazines **68** and **69** were then hydrolysed in concentrated HCl to give a mixture of the corresponding amino acid hydrochloride salts **35** and **74**, which were subsequently converted to mixtures of the corresponding methyl esters **37** and **75**, and the (*S*)-valine methyl ester **37** was removed *via* distillation under vacuum to

‡ CCDC reference numbers 292510 (**66**) and 292511 (**67**). For crystallographic data in CIF or other electronic format see DOI: 10.1039/b704475e

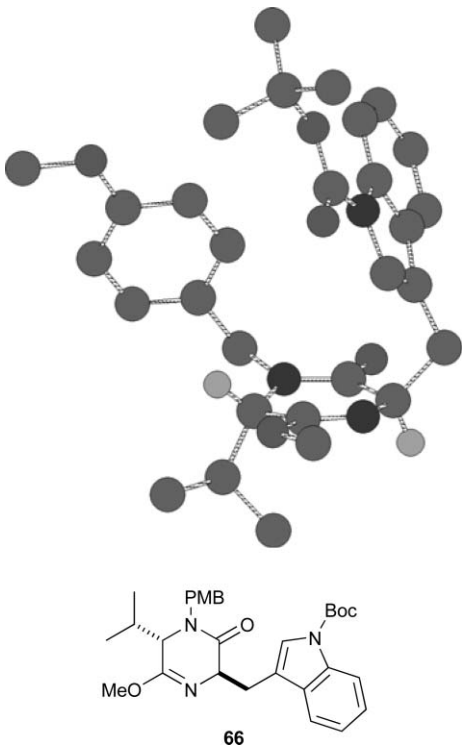


Fig. 7 Chem3D representation of the X-ray crystal structure of **66** (some H atoms removed for clarity).

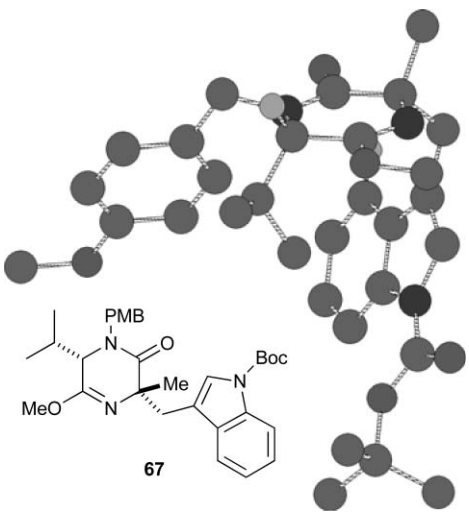
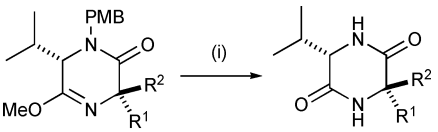


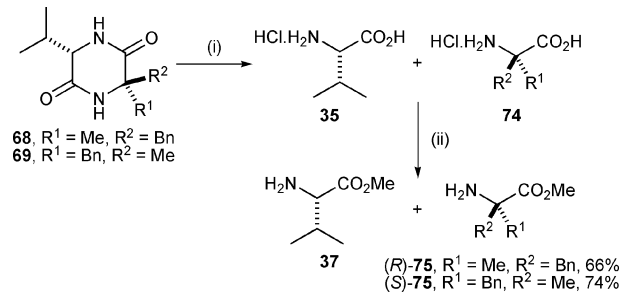
Fig. 8 Chem3D representation of the X-ray crystal structure of **67** (some H atoms removed for clarity).



Product	R^1	R^2	Product	Yield (de) %
59	Me	Bn	**68**	60 (>98)
60	Bn	Me	**69**	66 (>98)
61	Me	^{i}Pr	**70**	71 (>98)
62	^{i}Pr	Me	**71**	87 (>98)
63	Bn	^{i}Pr	**72**	66 (>98)
64	^{i}Pr	Bn	**73**	86 (>98)

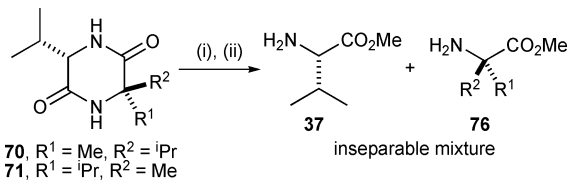
Scheme 10 *Reagents and conditions*: (i) TFA, reflux.

give the enantiomeric (*R*)- and (*S*)-2-methyl-phenylalanine methyl esters (*R*)-**75** and (*S*)-**75** in 66 and 72% overall yield from **68** and **69**, respectively, and in 99% ee[18] (Scheme 11).

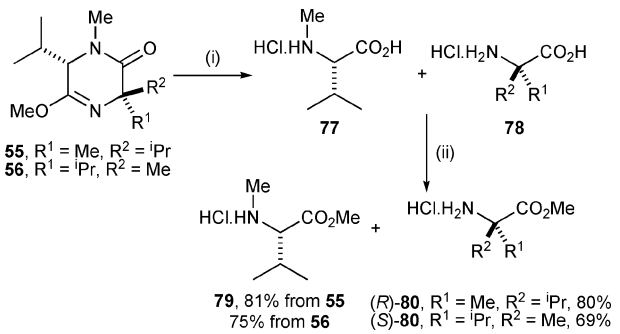


Scheme 11 *Reagents and conditions*: (i) conc. HCl, reflux; (ii) $SOCl_2$, MeOH, reflux, then conc. NH_3, then distillation.

Repetition of this protocol with the diastereoisomeric 3-isopropyl-3-methyl templates **70** and **71** furnished a mixture of (*S*)-valine methyl ester **37** and the corresponding homochiral quaternary α-amino ester **76**, which due to similarities in both volatility and polarity could not be separated by distillation or chromatography (Scheme 12). However, direct hydrolysis of the *N*-methyl templates **55** and **56** with hydrochloric acid gave a mixture of **77** and **78**; subsequent esterification followed by neutralisation afforded a mixture of *N*-methyl-valine methyl ester hydrochloride **79** and the corresponding homochiral quaternary α-methyl-α-isopropyl α-amino acid methyl ester **80**, which were then readily separated by chromatography as the free amino esters and re-acidified to afford (*R*)-**80** and (*S*)-**80** from **55** and **56** respectively, in 99% ee[18] (Scheme 13).

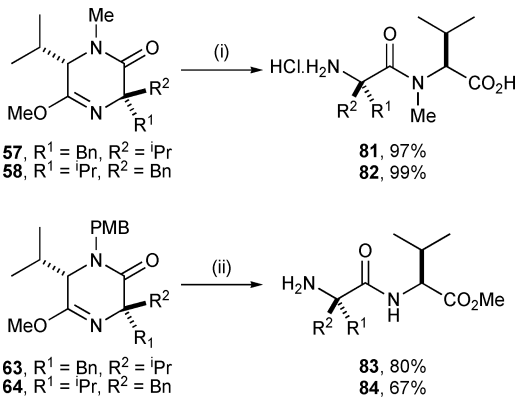


Scheme 12 *Reagents and conditions*: (i) conc. HCl, reflux; (ii) $SOCl_2$, MeOH, reflux, then conc. NH_3.



Scheme 13 *Reagents and conditions*: (i) conc. HCl, reflux; (ii) $SOCl_2$, MeOH, reflux, then conc. NH_3, then chromatography, then HCl.

Treatment of the sterically encumbered 3-isopropyl-3-benzyl substituted diketopiperazines **72** or **73** in refluxing concentrated HCl and under more forcing conditions (concentrated HI, 120 °C, or 5 M aq. KOH, 100 °C) did not effect the hydrolysis of the diketopiperazine. Given the recalcitrance of **72** or **73** to hydrolysis, an alternative deprotection strategy to afford dipeptides containing the α-isopropyl-α-benzyl disubstituted amino acids was examined. Hydrolysis of the lactim ether functionality of the *N*-methyl templates **57** and **58** was achieved by treatment with concentrated hydrochloric acid to afford *N*-methyl dipeptides **81** and **82** in good yields. Furthermore, lactim ether hydrolysis and *N*-deprotection of *N*-*p*-methoxybenzyl template **63** was achieved *via* treatment with ceric ammonium nitrate (CAN) in aqueous acetonitrile to afford dipeptide **83** in 80% yield,[26] while analogous treatment of the diastereoisomeric 3-isopropyl-3-benzyl template **64** afforded dipeptide **84** in 67% isolated yield (Scheme 14).



Scheme 14 *Reagents and conditions*: (i) HCl, reflux; (ii) CAN, H_2O–MeCN.

Conclusion

Mono lactim-ether templates **18** and **19** undergo highly stereoselective alkylations to generate tertiary and quaternary stereocentres, with a range of unbranched, branched and functionalised electrophiles, in high levels of diastereoisomeric purity. The deprotection and hydrolysis of these templates affords homochiral quaternary amino acids or (*S*)-valine-quaternary α-amino acid dipeptides.

Experimental

General experimental

All reactions involving organometallic or other moisture-sensitive reagents were carried out under a nitrogen or argon atmosphere using standard vacuum line techniques and glassware that was flame dried and cooled under nitrogen before use. Solvents were dried according to the procedure outlined by Grubbs and co-workers.[27] Water was purified by an Elix® UV-10 system. All other solvents were used as supplied (analytical or HPLC grade) without prior purification. Organic layers were dried over $MgSO_4$. Thin layer chromatography was performed on aluminium plates coated with 60 F_{254} silica. Plates were visualised using UV light (254 nm), iodine, 1% aq. $KMnO_4$, or 10% ethanolic phosphomolybdic acid. Flash column chromatography was performed on Kieselgel 60 silica.

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

General procedure 1 for mono-lactim ether formation

A mixture of DKP (1.0 eq.) and Me_3OBF_4 (2.0 eq.) was stirred in $BmimBF_4$ for 96 h under vacuum before quenching with sat aq. $NaHCO_3$ solution. The product was extracted with Et_2O, dried, concentrated *in vacuo* and purified by flash column chromatography.

General procedure 2 for mono-lactim ether alkylation

BuLi (solution in hexanes, 1.0 eq.) was added dropwise to a stirred solution of template (1.0 eq.) in THF at −78 °C. After 45 min, the electrophile (1.1 eq.) was added dropwise *via* syringe. The reaction solution was then allowed to warm slowly to rt. After 16 h, the reaction mixture was quenched with sat. aq. NH_4Cl solution and stirred for a further 10 min. The product was then extracted with EtOAc, washed with H_2O, dried, concentrated *in vacuo* and purified by flash column chromatography.

General procedure 3 for lactim-ether hydrolysis

The alkylated template was dissolved in TFA and subjected to reflux for 4 days. After this time the solvent was removed *in vacuo.* The remaining solid residue was triturated with Et_2O, filtered under suction and then dried under vacuum.

General procedure 4 for DKP hydrolysis

The DKP was dissolved in conc. aq. HCl and subjected to reflux for 3 days. Concentration of the reaction mixture *in vacuo* yielded a mixture of amino acid hydrochloride salts which were dried under vacuum.

General procedure 5 for formation of amino acid methyl esters

$SOCl_2$ (3.0 eq.) was added to a solution of amino acid hydrochloride salts (1.0 eq.) in MeOH at 0 °C, and subsequently set at reflux. After 16 h this solution was concentrated *in vacuo* to yield a mixture of amino acid methyl ester hydrochloride salts. This mixture was taken up into an aq. solution and conc. aq. NH_3 was added dropwise until pH 10 was reached when it was extracted with DCM. The combined organic extracts were dried and concentrated *in vacuo* to furnish a mixture of amino acid methyl esters. Valine methyl ester was distilled off under vacuum yielding the desired amino acid methyl ester.

(*S*)-*N*(1)-*p*-Methoxybenzyl-5-methoxy-6-isopropyl-3, 6-dihydropyrazin-2-one 19

Following *General procedure 1*, DKP **17** (6.20 g, 22.4 mmol) and Me_3OBF_4 (6.64 g, 44.9 mmol) in $BmimBF_4$ (30 mL) gave, after purification *via* flash column chromatography (eluent Et_2O), **19** as a pale brown crystalline solid (1.66 g, 61%); mp 94–96 °C (DCM–heptane); $[\alpha]_D^{23}$ +23.4 (*c* 1.0 in $CHCl_3$); ν_{max} (KBr) 1697, 1658; δ_H (400 MHz, $CDCl_3$) 0.92 (3H, d, *J* 6.4, C*H*$_3$CHCH$_3$), 1.02 (3H, d, *J* 7.0, CH$_3$CHC*H*$_3$), 2.16–2.24 (1H, m, CH$_3$C*H*CH$_3$), 3.67 (3H, s, C(5)O*Me*), 3.69 (1H, ddd, *J* 2.0, 1.1, 1.0, C(6)*H*), 3.82 (3H, s, ArO*Me*), 3.84 (1H, d, *J* 14.9, NC*H*HAr), 4.12 (1H, dd, *J* 19.6, 1.1, C(3)*H*H), 4.24 (1H, dd, *J* 19.6, 1.0, C(3)H*H*), 5.42 (1H, d, *J* 14.9, NCH*H*Ar), 6.83–6.89 (2H, m, *Ar*), 7.15–7.18 (2H, m, *Ar*); δ_C (100 MHz, $CDCl_3$) 17.4, 19.9, 31.8, 46.5, 50.9, 52.7, 55.2, 60.9, 114.2, 127.9, 129.6, 159.2, 161.0, 168.0; *m*/*z* (ESI$^+$) 313 ([M + Na]$^+$, 83%), 291 (100); HRMS (ESI$^+$) $C_{16}H_{23}N_2O_3$ ([M + H]$^+$) requires 291.1709; found 291.1707.

(3*R*,6*S*)-*N*(1)-*p*-Methoxybenzyl-3-benzyl-5-methoxy-6-isopropyl-3,6-dihydropyrazin-2-one *trans*-26

Following *General procedure 2*, BuLi (1.6 M in hexanes, 6.39 mL, 10.2 mmol), **19** (2.70 g, 9.29 mmol), and BnBr (1.22 mL, 10.2 mmol) in THF (120 mL) gave a >99 : <1 mixture of *trans*-**26** : *cis*-**27**. Purification *via* flash column chromatography (eluent 7 : 3 40–60 °C petrol : EtOAc) gave *trans*-**26** as a colourless oil (3.29 g, 94%, >98% de); $[\alpha]_D^{22}$ +3.1 (*c* 1.1 in $CHCl_3$); ν_{max} (film) 1648; δ_H (400 MHz, $CDCl_3$) 0.88 (3H, d, *J* 7.0, C*H*$_3$CHCH$_3$), 0.98 (3H, d, *J* 7.0, CH$_3$CHC*H*$_3$), 2.12–2.20 (1H, m, CH$_3$C*H*CH$_3$), 3.37–3.39 (2H, m, C(3)C*H*$_2$), 3.50 (1H, dd, *J* 5.0, 1.3, C(6)*H*), 3.68 (3H, s, C(5)O*Me*), 3.72 (1H, d, *J* 15.2, NC*H*HAr), 3.77 (3H, s, ArO*Me*), 4.40 (1H, td, *J* 4.6, 1.3, C(3)*H*), 5.44 (1H, d, *J* 15.2, NCH*H*Ar), 6.72–6.76 (4H, m, *Ar*), 7.26–7.28 (3H, m, *Ph*), 7.35–7.37 (2H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 17.3, 19.8, 31.3, 39.6, 46.1, 52.5, 55.2, 59.3, 60.9, 114.1, 126.1, 127.7, 129.1, 130.7, 127.3, 138.4, 158.9, 159.1, 160.3; *m*/*z* (ESI$^+$) 381 ([M + H]$^+$, 100%); HRMS (ESI$^+$) $C_{23}H_{29}N_2O_3$ ([M + H]$^+$) requires 381.2178; found 381.2180.

(3*S*,6*R*)-3-Isopropyl-6-benzyl-piperazine-2,5-dione 34

Following *General procedure 3*, **26** (1.45 g, 3.81 mmol) and TFA (50 mL) gave **34** (676 mg, 72%) as an off white solid; mp 256–257 °C; $[\alpha]_D^{23}$ −58.3 (*c* 1.0 in AcOH); ν_{max} (KBr) 3193, 1670; δ_H (400 MHz, DMSO-d_6) 0.75 (3H, d, *J* 6.8, C*H*$_3$CHCH$_3$), 0.82 (3H, d, *J* 7.1, CH$_3$CHC*H*$_3$), 1.99–2.08 (1H, m, CH$_3$C*H*CH$_3$), 2.87 (1H, dd, *J* 13.6, 4.9, C(6)C*H*HPh), 2.95 (1H, dd, *J* 2.5, 2.0, C(3)*H*), 3.15 (1H, dd, *J* 13.6, 3.8, C(6)CH*H*Ph), 4.17 (1H, ddd, *J* 4.9, 3.8, 2.0, C(6)*H*), 7.18–7.28 (5H, m, *Ph*), 7.96 (1H, app br s, N(4)*H*), 8.15 (1H, app br s, N(1)*H*); δ_C (100 MHz, DMSO-d_6) 17.4, 19.0, 32.4, 38.8, 56.0, 59.8, 127.5, 128.8, 131.0, 136.9, 167.9, 168.2;

m/z (ESI$^+$) 247 ([M + H]$^+$, 100%); HRMS (ESI$^+$) $C_{14}H_{19}N_2O_2$ ([M + H]$^+$) requires 247.1447; found 247.1437.

(*R*)-Phenylalanine methyl ester 38

Following *General procedure 4*, **34** (275 mg, 1.11 mmol) and conc. HCl (30 mL) gave a mixture of amino acid hydrochloride salts **35** and **36** (447 mg); δ_H (400 MHz, MeOD) 1.11 (6H, d, *J* 7.2, C*H*$_3$CHC*H*$_3$), 2.28–2.40 (1H, m, CH$_3$C*H*CH$_3$), 3.23 (1H, dd, *J* 14.5, 7.2, C*H*HPh), 3.33 (1H, dd, *J* 14.5, 5.8, CH*H*Ph), 3.89 (1H, d, *J* 4.1, ^{i}PrC*H*), 4.29 (1H, app t, *J* 6.5, C*H*CH$_2$Ph), 7.31–7.41 (5H, m, *Ph*). Subsequently, following *General procedure 5*, the mixture of amino acid salts **35** and **36**, $SOCl_2$ (0.28 mL, 2.26 mmol) and MeOH (40 mL) gave a mixture of methyl ester hydrochloride salts which was neutralised and distilled as outlined in *General procedure 5*, to give **38** as a colourless oil (142 mg, 74%); $[\alpha]_D^{23}$ −32.2 (*c* 1.0 in EtOH) for **38**·HCl, {lit.[19] $[\alpha]_D^{25}$ −37.0 (*c* 2.0 in EtOH) for **38**.HCl}; ν_{max} (film) 3378, 1738; δ_H (400 MHz, $CDCl_3$) 1.51 (2H, br s, N*H*$_2$), 2.84 (1H, dd, *J* 13.6, 7.9, C*H*HPh), 3.07 (1H, dd, *J* 13.6, 5.1, CH*H*Ph), 3.68 (3H, s, O*Me*), 3.71 (1H, m, C*H*), 7.15–7.31 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 41.1, 51.9, 55.8, 126.8, 128.5, 129.2, 137.2, 175.4; *m/z* (ESI$^+$) 180 ([M + H]$^+$, 100%); HRMS (ESI$^+$) $C_{10}H_{14}NO_2$ ([M + H]$^+$) requires 180.1025; found 180.1020.

(3*R*,6*S*)-*N*(1)-*p*-Methoxybenzyl-3-benzyl-3-methyl-5-methoxy-6-isopropyl-3,6-dihydropyrazin-2-one 59

Following *General procedure 2*, BuLi (2.5 M in hexanes, 0.21 mL, 0.53 mmol), **22** (162 mg, 0.53 mmol), THF (10 mL) and BnBr (70 μL, 0.59 mmol) gave a 99 : 1 mixture of **59** : **60**. Purification *via* flash column chromatography (eluent 3 : 1 hexane : Et_2O) gave **59** as a colourless oil (164 mg, 78%, >98% de); $C_{24}H_{30}N_2O_3$ requires C, 73.1; H, 7.7; N, 7.1%; found C, 72.9; H, 7.7; N, 7.1%; $[\alpha]_D^{22}$ −53.1 (*c* 1.3 in $CHCl_3$); ν_{max} (film) 1651; δ_H (400 MHz, $CDCl_3$) 0.81 (3H, d, *J* 6.8, C*H*$_3$CHCH$_3$), 0.89 (3H, d, *J* 6.8, CH$_3$CHC*H*$_3$), 1.63 (3H, s, C(3)*Me*), 1.98–2.09 (1H, m, CH$_3$C*H*CH$_3$), 2.90 (1H, d, *J* 12.7, C(3)C*H*HPh), 3.26 (1H, d, *J* 2.8, C(6)*H*), 3.42 (1H, d, *J* 12.7, C(3)CH*H*Ph), 3.63 (1H, d, *J* 15.0, NC*H*HAr), 3.70 (3H, s, C(5)O*Me*), 3.75 (3H, s, ArO*Me*), 5.38 (1H, d, *J* 15.0, NCH*H*Ar), 6.44–6.47 (2H, m, *Ar*), 6.64–6.67 (2H, m, *Ar*), 7.20–7.28 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 17.1, 20.1, 28.9, 29.4, 45.1, 48.7, 52.1, 55.1, 59.6, 62.4, 113.9, 126.2, 126.9, 127.8, 129.4, 130.8, 137.7, 156.5, 158.8, 171.0; *m/z* (ESI$^+$) 395 ([M + H]$^+$, 100%); HRMS (ESI$^+$) $C_{24}H_{31}N_2O_3$ ([M + H]$^+$) requires 395.2335; found 395.2328.

(3*S*,6*S*)-*N*(1)-*p*-Methoxybenzyl-3-benzyl-3-methyl-5-methoxy-6-isopropyl-3,6-dihydropyrazin-2-one 60

Following *General procedure 2*, BuLi (1.6 M in hexanes, 0.28 mL, 0.45 mmol), **26** (158 mg, 0.45 mmol), THF (10 mL) and MeI (28 μL, 0.45 mmol) gave a 2 : 98 mixture of **59** : **60**. Purification *via* flash column chromatography (eluent 3 : 1 hexane : Et_2O) gave **60** as a colourless oil (112 mg, 68%, >98% de); $[\alpha]_D^{23}$ −17.0 (*c* 0.95 in $CHCl_3$); ν_{max} (film) 1644; δ_H (400 MHz, $CDCl_3$) 0.26 (3H, d, *J* 6.8, C*H*$_3$CHCH$_3$), 0.89 (3H, d, *J* 6.8, CH$_3$CHC*H*$_3$), 1.43 (3H, s, C(3)*Me*), 1.85–1.95 (1H, m, CH$_3$C*H*CH$_3$), 3.02 (1H, d, *J* 12.9, C(3)C*H*HPh), 3.35 (1H, d, *J* 12.9, C(3)CH*H*Ph), 3.63 (3H, s, C(5)O*Me*), 3.64 (1H, d, *J* 3.2, C(6)*H*), 3.80 (3H, s, ArOC*H*$_3$), 3.83 (1H, d, *J* 14.0, NC*H*HAr), 5.41 (1H, d, *J* 14.0, NCH*H*Ar), 6.82–6.88 (2H, m, *Ar*), 7.08–7.16 (2H, m, *Ar*), 7.18–7.27 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 15.8, 20.4, 29.7, 30.8, 46.2, 46.4, 52.0, 55.2, 60.7, 61.9, 114.1, 126.4, 127.7, 129.4, 131.2, 128.3, 137.6, 155.9, 159.0, 172.1; *m/z* (ESI$^+$) 417 ([M + Na]$^+$, 100%), 395 (35); HRMS (ESI$^+$) $C_{24}H_{31}N_2O_3$ ([M + H]$^+$) requires 395.2335; found 395.2333.

(3*R*,6*S*)-3-Benzyl-3-methyl-6-isopropyl-piperazine-2,5-dione 68

Following *General procedure 3*, **59** (1.29 g, 3.26 mmol) and TFA (50 mL) gave **68** as an off white solid (509 mg, 60%); mp 280–282 °C; $[\alpha]_D^{23}$ −22.0 (*c* 0.9 in CH_3CO_2H); ν_{max} (KBr) 3193, 1670; δ_H (400 MHz, DMSO-d_6) 0.70 (3H, d, *J* 6.8, C*H*$_3$CHCH$_3$), 0.78 (3H, d, *J* 6.8, CH$_3$CHC*H*$_3$), 1.42 (3H, s, C(3)*Me*), 1.93–2.02 (1H, m, CH$_3$C*H*CH$_3$), 2.67 (1H, dd, *J* 2.5, 1.7, C(6)*H*), 2.67 (1H, d, *J* 12.9, C(3)C*H*HPh), 3.08 (1H, d, *J* 12.9, C(3)CH*H*Ph), 7.11–7.15 (2H, m, *Ph*), 7.22–7.26 (3H, m, *Ph*), 7.76 (1H, app br s, N(1)*H*), 8.24 (1H, app br s, N(4)*H*); δ_C (100 MHz, DMSO-d_6) 17.3, 18.9, 28.6, 31.8, 47.3, 59.6, 60.4, 127.6, 128.7, 131.1, 137.0, 167.1, 170.4; *m/z* (CI$^+$) 261 ([M + H]$^+$, 100%); HRMS (CI$^+$) $C_{15}H_{21}N_2O_2$ ([M + H]$^+$) requires 261.1603; found 261.1610.

(3*S*,6*S*)-3-Benzyl-3-methyl-6-isopropyl-piperazine-2,5-dione 69

Following *General procedure 3*, **60** (775 mg, 1.96 mmol) and TFA (40 mL) gave **69** as an off white solid (459 mg, 66%); mp 283–285 °C; $[\alpha]_D^{23}$ −11.7 (*c* 1.1 in AcOH); ν_{max} (KBr) 1656; δ_H (400 MHz, DMSO-d_6) 0.11 (3H, d, *J* 6.8, C*H*$_3$CHCH$_3$), 0.57 (3H, d, *J* 7.1, CH$_3$CHC*H*$_3$), 1.44 (3H, s, C(3)*Me*), 1.66–1.74 (1H, m, CH$_3$C*H*CH$_3$), 2.61 (1H, d, *J* 13.1, C(3)C*H*HPh), 3.19 (1H, d, *J* 13.1, C(3)CH*H*Ph), 3.59 (1H, dd, *J* 3.3, 1.8, C(6)*H*), 7.12–7.23 (5H, m, *Ph*), 7.72 (1H, app br s, N(1)*H*), 8.21 (1H, br, s, N(4)*H*); δ_C (100 MHz, DMSO-d_6) 16.6, 18.8, 30.4, 31.5, 45.3, 59.8, 60.6, 127.3, 128.6, 131.4, 137.5, 166.7, 170.0; *m/z* (CI$^+$) 261 ([M + H]$^+$, 100%); HRMS (CI$^+$) $C_{15}H_{21}N_2O_2$ ([M + H]$^+$) requires 261.1603; found 261.1607.

(*R*)-α-Methyl-phenylalanine methyl ester (*R*)-75

Following *General procedure 4*, **68** (297 mg, 1.14 mmol) and conc. HCl (35 mL) gave a mixture of amino acid hydrochloride salts **35** and (*R*)-**74** (360 mg); δ_H (400 MHz, MeOD) 1.12 (6H, d, *J* 6.8, C*H*$_3$CHC*H*$_3$), 1.66 (3H, s, C*Me*), 2.30–2.39 (1H, m, CH$_3$C*H*CH$_3$), 3.16 (1H, d, *J* 14.3, C*H*HPh), 3.33 (1H, d, *J* 14.3, CCH*H*Ph), 3.89 (1H, d, *J* 4.4, ^{i}PrC*H*), 7.29–7.41 (5H, m, *Ph*). Subsequently, following *General procedure 5*, the mixture of amino acid hydrochloride salts **35** and **74** (360 mg), $SOCl_2$ (0.21 mL, 2.75 mmol) and MeOH (40 mL) gave a mixture of amino acid methyl ester hydrochloride salts, which was neutralised and distilled to give (*R*)-**75** as a colourless oil (166 mg, 66%); $[\alpha]_D^{24}$ +11.9 (*c* 0.9 in $CHCl_3$); ν_{max} (film) 3368, 1734; δ_H (400 MHz, $CDCl_3$) 1.39 (3H, s, C*Me*), 2.82 (1H, d, *J* 13.1, C*H*HPh), 3.09 (1H, d, *J* 13.1, CH*H*Ph), 3.68 (3H, s, O*Me*), 4.81 (2H, br s, N*H*$_2$), 7.12–7.32 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 24.9, 46.2, 51.6, 58.8, 127.1, 128.4, 130.0, 136.6, 176.8; *m/z* (ESI$^+$) 194 ([M + H]$^+$, 100%); HRMS (ESI$^+$) $C_{11}H_{16}NO_2$ ([M + H]$^+$) requires 194.1181; found 194.1182.

(*S*)-α-Methyl-phenylalanine methyl ester (*S*)-75

Following *General procedure 4*, **69** (266 mg, 1.02 mmol) and conc. HCl (30 mL) gave a mixture of amino acid hydrochloride salts **35** and (*S*)-**74** (351 mg). Subsequently, following *General procedure 5*, the mixture of amino acid hydrochloride salts **35** and (*S*)-**74** (351 mg), $SOCl_2$ (0.04 mL, 0.73 mmol) and MeOH (10 mL) gave a mixture of methyl ester hydrochloride salts, which was neutralised and distilled to give (*S*)-**75** as a colourless oil (129 mg, 74%); $[\alpha]_D^{23}$ −14.1 (*c* 1.6 in $CHCl_3$).

Acknowledgements

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References and notes

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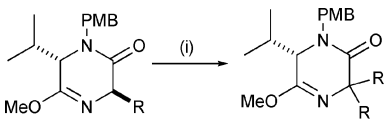

Reagents and conditions: (i) BuLi, THF, −78 °C then RX.

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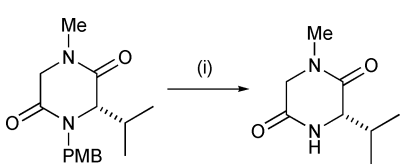

Reagents and conditions: (i) CAN, MeCN–H_2O (3 : 1), rt.

23 **46** was prepared according to the procedure of S. D. Bull, S. G. Davies,

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