A chiral relay auxiliary for the synthesis of homochiral α-amino acids

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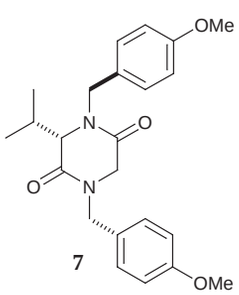
A new chiral auxiliary (3*S*)-*N*,*N*′-bis(*p*-methoxybenzyl)-3-isopropylpiperazine-2,5-dione 7 has been developed for the asymmetric synthesis of α-amino acids. The auxiliary 7 employs a novel chiral relay network based on non-stereogenic *N*-benzyl protecting groups which enhance the diastereoselectivity observed during alkylation of its C_6 enolate 25.

Introduction

The central rôle that homochiral α-amino acids play in nature enables this class of natural product to provide many challenging targets for the development of new methodology for asymmetric synthesis.[1] Proteinogenic α-amino acids are the building blocks of all peptides, proteins and peptidoglycans.[2] They may also act as neurotransmitters,[3] or as precursors for the biosynthesis of other important naturally occurring biomolecules.[4] Naturally occurring non-proteinogenic α-amino acids are normally isolated as secondary metabolites from microbial sources, where they act in selective defence mechanisms to confer evolutionary advantages to the host organism.[5] As a result of their pivotal rôle in microbial biochemistry, many of these non-proteinogenic α-amino acids exhibit a wide range of pharmaceutical and herbicidal activities.[5] While proteinogenic (*S*)-α-amino acids are commercially available as products of microbial fermentation,[6] many highly desirable non-proteinogenic α-amino acids can only be isolated in small quantities, and many are not commercially available. As a consequence of this shortage in supply, the majority of new asymmetric methodology for the synthesis of α-amino acids has been directed towards the preparation of natural products.[1] There is, however, an increasing interest and demand for novel unnatural α-amino acids for incorporation into novel peptide sequences, which have great potential in the development of new medicinal agents,[7] or as selective probes for investigating the conformational dynamics of protein folding.[8]

The structural diversity of the many naturally occurring and synthetic α-amino acids dictates that there is not one single asymmetric methodology which can be universally applied to the synthesis of every α-amino acid.[1] This structural diversity ensures that careful consideration is required to match closely the structure of the desired α-amino acid with the merits of the methodology employed for the synthesis. Generally, the methodology which has proven to be the most versatile and widely used is enolate alkylation, which relies on the use of simple heterocyclic chiral auxiliaries.[9] Such auxiliaries rely on covalently attached homochiral residues to control the diastereoselective alkylation of a masked glycine enolate fragment. Ideally, this protocol will afford a major, or unique diastereoisomer containing one or more new stereocentres. Subsequent cleavage and purification of the transformed glycine equivalent affords the desired homochiral α-amino acid and the chiral auxiliary, which may then be recycled as required. Notable examples of this class of auxiliary include Seebach's imidazolidinone **1**,[10] Oppolzer's chiral sultam **2**,[11] Williams' oxazinone **3**,[12] Myers' pseudoephedrine **4**,[13] Evans' oxazolidinone **5**,[14] and Schöllkopf's bis-lactim ether **6**[15] (Scheme 1).

Although the synthetic utility of auxiliaries **1**–**6** has been demonstrated on a small scale, these approaches are not generally amenable to large scale synthesis, and we now wish to report the development of a new chiral auxiliary, diketopiperazine (DKP) **7**, which addresses many of the problems associated with the scale up of this class of auxiliary. Part of this work has been previously communicated.[16]



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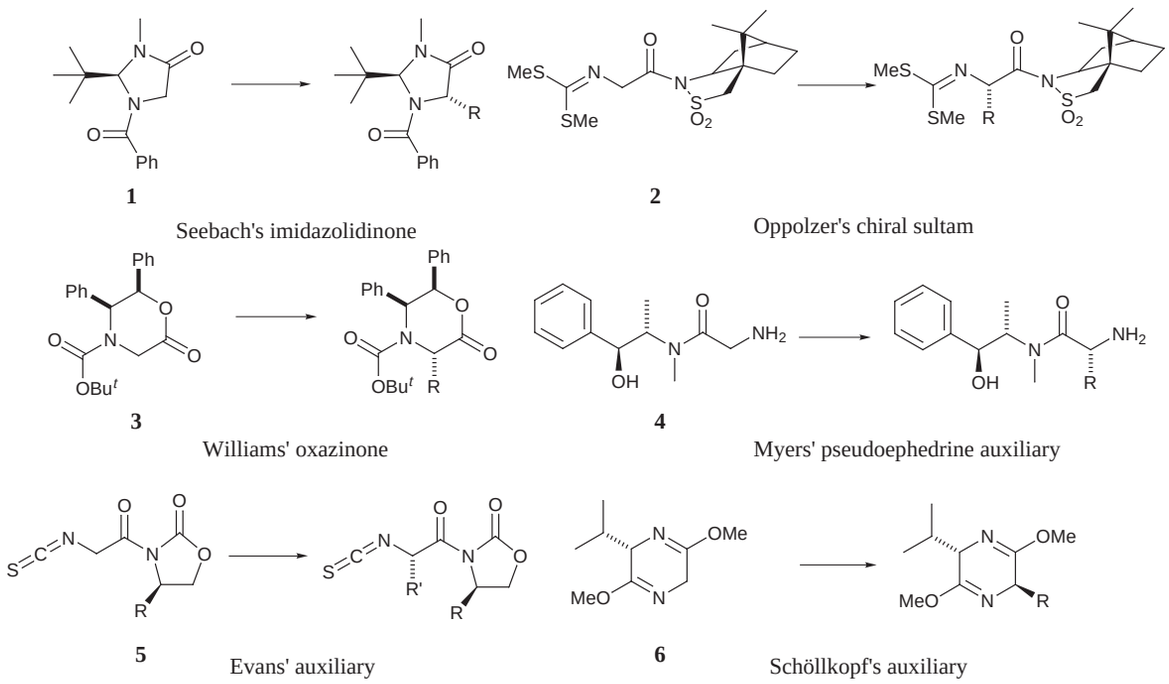
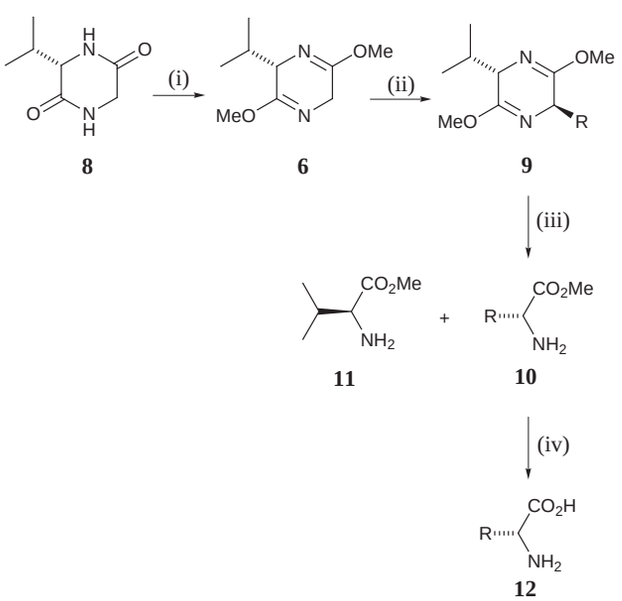
Diketopiperazine derived chiral auxiliaries

We envisaged that an auxiliary based on a suitably protected DKP ring system derived from glycine and a homochiral α-amino acid would be ideally suited to the asymmetric synthesis of homochiral α-amino acids. The stereochemical information of an existing homochiral α-amino acid would be used to control the creation of a new homochiral α-amino acid from glycine. This approach, based on alkylation of a DKP equivalent, has been applied previously, albeit indirectly, by Schöllkopf *et al*. who introduced chiral auxiliary **6** for the synthesis of homochiral α-amino acids in 1981.[15] Auxiliary **6** is prepared by *O*-methylation of DKP **8** with Me_3OBF_4,[17] followed by deprotonation with Bu^{n}Li and *trans*-alkylation with the appropriate electrophile to afford a major diastereoisomer **9**. This diastereoisomer is then purified, and cleaved to its parent α-amino acid methyl esters **10** and **11** by treatment with 0.1 M HCl. Subsequent separation of the mixture of α-amino acid methyl esters (as their free amines), *via* flash chromatography, or fractional distillation, affords the desired α-amino acid methyl ester **10** which can be hydrolysed to its parent α-amino acid **12** as required, by treatment with 6 M HCl (Scheme 2).[15]



Scheme 1 Commonly used auxiliaries based on a glycine anion equivalent



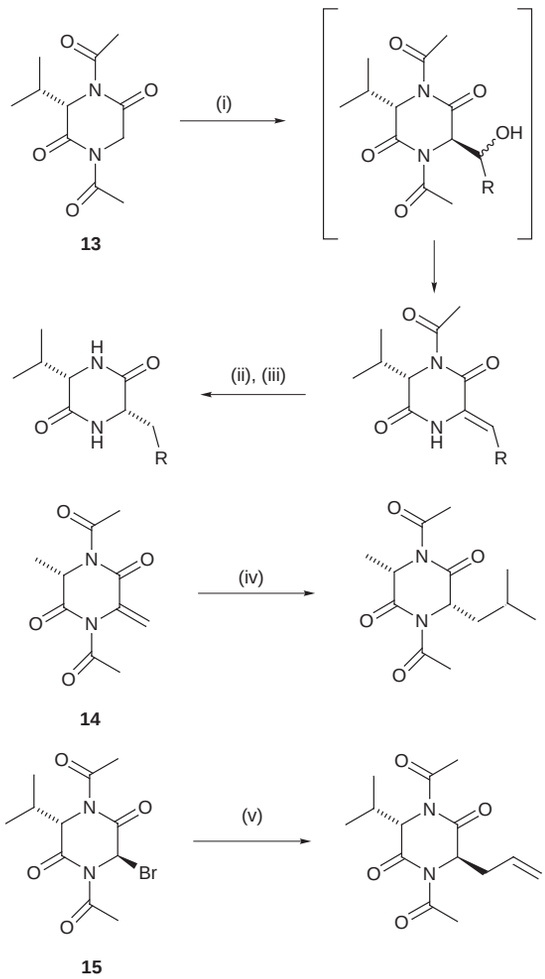
Scheme 2 *Reagents and conditions*: (i) $Me_3O^+BF_4^-$; (ii) Bu^{n}Li, THF, −78 °C; RX; (iii) 0.1 M HCl; basify and separate; (iv) 6 M HCl; propylene oxide

Although the range of homochiral α-amino acids that have been prepared using Schöllkopf's auxiliary **6** is highly impressive,[18] with over 400 syntheses having been reported to date,[19] there are practical problems associated with its use. It is a volatile oil which is difficult to prepare and purify, and its enolate often exhibits poor diastereoselectivities when alkylated with linear or β-branched electrophiles, resulting in poor yields of the desired α-amino acid — reaction of **6** with prop-2-ynyl bromide, for example, affords *trans*-alkylated products in only 52% de.[20] Purification of the major *trans*-diastereoisomers to homogeneity often leads to decreased yields since *trans*-alkylated dihydropyrazines **9** are oily in nature and susceptible to acid catalysed hydrolysis, a factor which restricts the range of synthetic transformations which can be carried out using these functionalised auxiliaries.

The physical properties of *N*,*N*′-diprotected diketopiperazines are in direct contrast to those of bis-lactim *O*-alkylated auxiliaries **6**, as they are generally robust, highly crystalline compounds. These properties are ideal for chiral auxiliaries. It is unsurprising, therefore, that a number of different DKP-based auxiliaries have been developed for the asymmetric synthesis of homochiral α-amino acids, with each auxiliary **13**–**16** employing a different synthetic strategy, ranging from hydrogenation[21] and free radical addition[22]/substitution[23] to enolate alkylation (Scheme 3).[24]

The diketopiperazine auxiliary **16** developed by Sandri *et al*.,[24] derived from two molecules of homochiral α-methylbenzylamine, attracted our attention since this type of auxiliary has the potential to afford two molecules of homochiral α-amino acids from two equivalents of glycine. However, the potential of auxiliary **16** was not realised as the initial alkylation of this auxiliary occurred with very poor diastereoselectivity for a range of electrophiles, affording a mixture of *cis*- and *trans*-diastereoisomers (**17** and **18**, 20% de, for Pr^{n}Br) (Scheme 4). Diastereoisomers **17** and **18** were separated by chromatography, and subsequently alkylated with different selectivities. DKP **17** gave *cis*-dialkylated material **19** as the only detectable product, whereas the corresponding diastereoisomer, DKP **18**, gave a mixture of *cis*-and *trans*-dialkylated isomers **20** and **21** (16% de).

The 1,4-inductive effect of the C_3 stereocentre of a DKP ring normally results in a net *trans*-directing effect. It is clear that the configurations and conformation of the α-methylbenzyl groups result in these two fragments directing the sense of alkylation in opposing fashions. A similar mis-matched effect is obviously operating for DKP **18**. However, we were intrigued by the observation that DKP **17** affords *cis*-dialkylated product DKP **19** as the only isolable product, because its stereochemistry is opposite to the *trans*-stereochemistry normally observed with auxiliaries based on glycine anion equivalents. Although Sandri *et al*. have proposed a transition state model to rationalise the selectivity for these auxiliaries, the conformational flexibility of the two competing *N*,*N*′-protecting groups complicates any analysis of the stereoselectivity observed for this class of DKP substrate. We wished to simplify these conformational and stereocontrolling factors, and proposed that high diastereoselection would also be observed for a DKP based auxiliary **7** which employed *non-stereogenic N*,*N*′-benzyl groups for protection.



Scheme 3 *Reagents and conditions*: (i) RCHO, KOBu^t; (ii) N_2H_4; (iii) H_2, Pd, MeOH; (iv) Pr^{i}HgCl, $NaBH_4$, H_2O; (v) allyltributyltin, AIBN

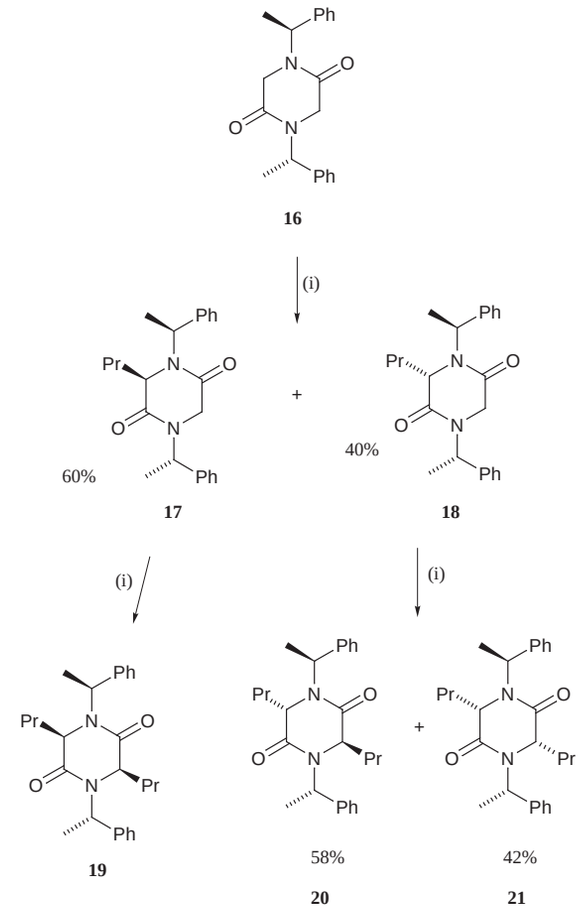
Results and discussion

Auxiliary design incorporating a chiral relay network to enhance stereoselectivity

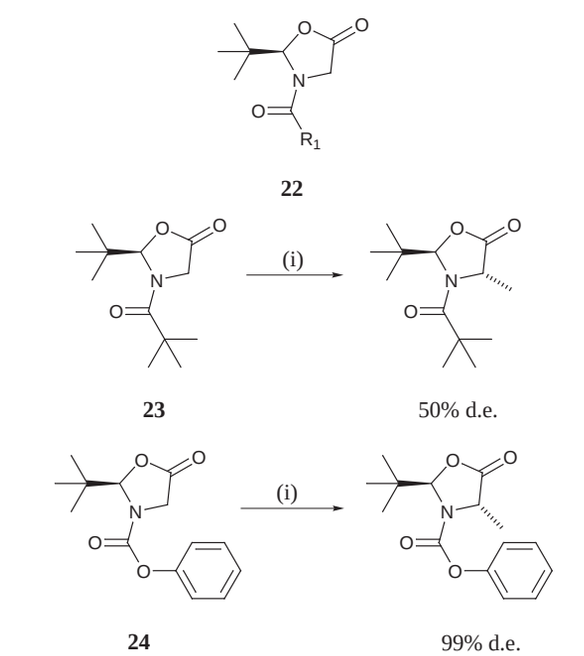
Close examination of the enolates of chiral auxiliaries **1**–**6** (Scheme 1) reveals that the diastereoselectivity observed during alkylation is controlled by a remote stereogenic centre under either 1,3 and/or 1,4 inductive control. Although protecting groups are generally considered to act as simple spectator groups, it has been noted by Seebach *et al*. that changing the nature of a protecting group in an auxiliary can significantly affect the degree of asymmetric induction obtained.[25] For example, the diastereoselectivity for the alkylation of parent oxazolidinone **22** is highly dependent on the nature of the *N*-acyl protecting group; the facial selectivity is improved from 50% de to >99% de by simply changing the *N*-acyl fragment from a pivaloyl group (**23**) to a phenyloxycarbonyl group (**24**).[25]

We wished to utilise the principle of protecting group participation to design a new auxiliary in which a non-stereogenic protecting group would serve to relay the chiral information of a remote stereogenic centre close to the point of enolate alkylation. Careful choice of protecting group functionality should result in a chiral relay system which would not only serve to transfer but also amplify the chiral information from the existing stereogenic centre. We envisaged that this type of chiral relay network could be achieved using a *N*,*N*′-bis-benzylated piperazine-2,5-dione ring system. Molecular modelling studies revealed that an enolate of type **25** can adopt a conformation to enable the stereochemical information of the C_3-carbon atom to be relayed through space *via* the non-stereogenic benzyl protecting groups (Fig. 1).[26]

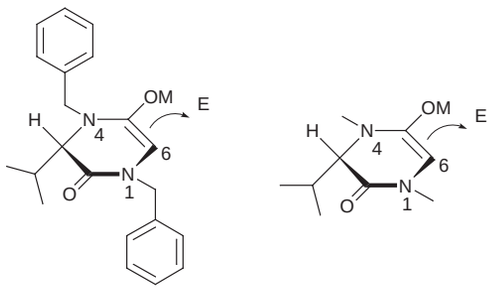
Modelling studies revealed that the ring system of enolate **25** would be essentially planar with its isopropyl group fixing the conformation of the proximal N_4 benzyl into an *anti* position. The N_4 benzyl group in turn directs the distal N_1 benzyl group *syn* to the isopropyl group. The N_1 benzyl group would effectively block the *Si* face of enolate **25** close to the point of alkylation at C_6, resulting in significantly higher alkylation diastereoselectivities than would be achieved for the enolate of an auxiliary such as *N*,*N*′-dimethylated DKP **26** which relies on 1,4-asymmetric induction alone (Fig. 1).



Scheme 4 *Reagents and conditions*: (i) LHMDS, THF, −78 °C, Pr^{n}Br



Scheme 5 *Reagents and conditions*: (i) LHMDS, THF, −78 °C; (ii) MeI



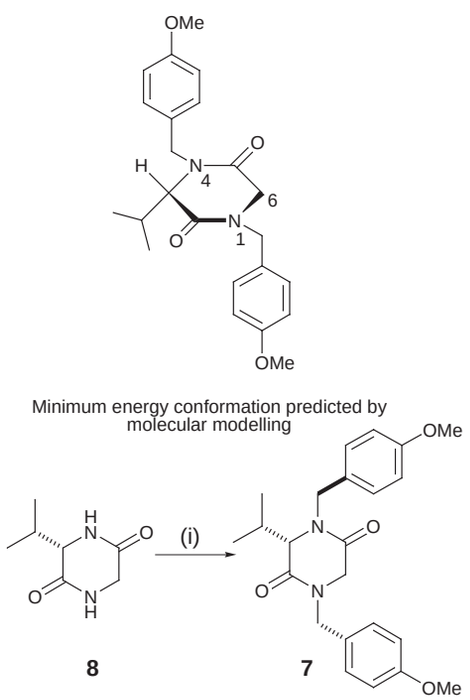
25 **26**

Electrophile attacks *anti* to both the C_3 isopropyl and N_1 protecting group.

Electrophile attack controlled by C_3 isopropyl alone

Fig. 1

In order to test whether this chiral relay design would be viable we prepared benzylated DKP **7** and examined its conformation for evidence of a chiral relay network. *p*-Methoxybenzyl groups were chosen as *N*,*N*′-protecting groups with the aim of creating a fully functioning chiral auxiliary due to their ease of removal by oxidative cleavage with ceric ammonium nitrate.[27] Highly crystalline (3*S*)-*N*,*N*′-bis(*p*-methoxybenzyl)-3-isopropylpiperazine-2,5-dione **7** was prepared in 85% yield by dropwise addition of *p*-methoxybenzyl chloride to *cyclo*-[L-Val-Gly] **8** and sodium hydride in DMF (Scheme 6).



8 **7**

Scheme 6 *Reagents and conditions*: (i) NaH, *p*-MeOBnCl, DMF. Minimum energy conformation predicted by molecular modelling

The enantiomeric purity of DKP **7** was established by direct comparison of the ^{1}H NMR spectrum of DKP (*S*)-**7** with that of authentic racemic material (*RS*)-**7** (prepared from racemic valine), in the presence of chiral solvating reagent (*S*)-(+)-2,2,2-trifluoro-1-(9-anthryl)ethanol.[28] Homochiral DKP **7** was carefully recrystallised from ethyl acetate and subjected to X-ray structural analysis in order to determine the confirmation of the auxiliary.† The X-ray crystal structure revealed, consistent with the molecular models, that both *N*-benzyl groups of the auxiliary were arranged in an antiperiplanar conformation, with the isopropyl and the N_1 benzyl protecting groups occupying a *syn* orientation on the *Si* face of the auxiliary (Fig. 2).

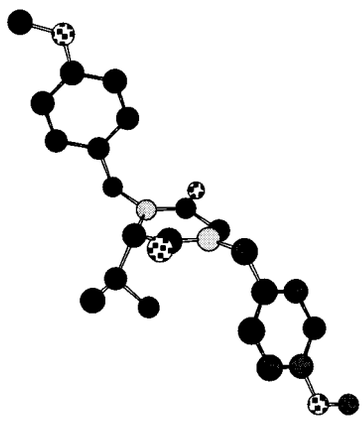


Fig. 2 X-Ray crystal structure of DKP **7**

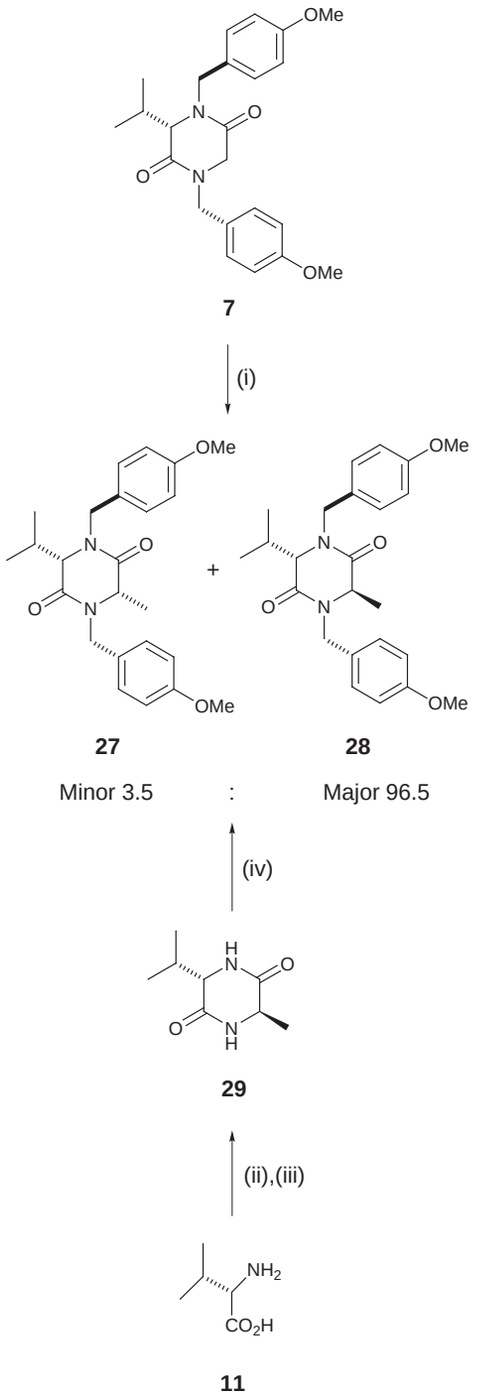
Having clearly demonstrated that the conformation adopted by this auxiliary had the potential to act as a chiral relay, initial enolate alkylation studies were carried out on auxiliary **7**. The use of methyl iodide as an electrophile provided a demanding test for our auxiliary design. DKP **7** was deprotonated with one equivalent of lithium hexamethyldisilazide in THF at −78 °C followed by addition of excess methyl iodide to afford a mixture of C_6-methylated diastereoisomers **27** and **28** in 93% de (Scheme 7). The diastereoisomers were separated by chromatography. The configuration of the major diastereoisomer could not be determined by simple spectroscopic analysis due to similarities in the ^{1}H NMR spectra of the major and minor diastereoisomers. In order to assign the relative configuration of the major diastereoisomer a direct comparison was made with an authentic sample of **28** prepared *de novo* by *N*-*p*-methoxybenzylation of DKP **29**, derived from L-valine **11** and D-alanine methyl ester **30**, revealing that the major diastereoisomer was a product of *trans*-alkylation (Scheme 7).

X-Ray crystallographic analysis revealed that DKP **28** exhibits a conformation similar to that observed for the parent auxiliary **7**. The benzyl substituents adopt orientations above and below the plane of the DKP ring to ensure that adjacent functional groups on the DKP ring have an antiperiplanar arrangement (Fig. 3).

Direct comparison of the alkylation diastereoselectivities observed for methylation of DKP **7** (93% de) with those obtained for methylation of Schöllkopf's auxiliary **6** (50% de) clearly demonstrated the superiority of our new DKP auxiliary **7** (Table 1). We now required evidence that the benzylic *N*,*N*′-protecting groups were responsible for the improved performance of auxiliary **7** since the improved methylation diastereoselectivity may simply have been due to differences in enolate reactivities. We therefore prepared DKP auxiliary **31**, bearing *N*-methyl protecting groups which do not have the capacity to enhance the diastereoselectivity of enolate alkylation *via* the proposed relay mechanism. (3*S*)-*N*,*N*′-Dimethyl-3-isopropylpiperazine-2,5-dione **31** was prepared by treatment of DKP **8** with NaH and methyl iodide in DMF and the near-planar conformation of the DKP ring confirmed by X-ray crystallographic analysis (Fig. 4). DKP 31 was methylated using LHMDS and methyl iodide (under identical conditions described for DKP **7**) to afford a mixture of *trans*-(3*S*,6*R*)-6-methyl-**32** and *cis*-(3*S*,6*S*)-6-methyl-**33** in 33% de (Scheme 8). The stereochemistry of the major diastereoisomer **32** was confirmed as *trans* by comparison of the proton NMR spectrum with that for an authentic sample prepared by *N*,*N*′-methylation of DKP **29**.

The results obtained for methylation of the enolates of DKPs

† Full crystallographic details, excluding structure factor tables, have been deposited at the Cambridge Crystallographic Data Centre (CCDC). For details of the deposition scheme, see 'Instructions for Authors', *J. Chem. Soc., Perkin Trans. 1*, available *via* the RSC Web page (http://www.rsc.org/authors). Any request to the CCDC for this material should quote the full literature citation and the reference number 207/227.



Scheme 7 *Reagents and conditions*: (i) LHMDS, THF, −78 °C; MeI; (ii) $COCl_2$; (iii) (*R*)-alanine methyl ester **30**, triethylamine; toluene, Δ; (iv) NaH, *p*-MeOBnCl, DMF

7 and **31** are consistent with the proposed chiral relay network operating to enhance diastereoselectivity. It is of interest that the diastereoselectivity observed for alkylation of the enolate derived from **31** is significantly poorer than that obtained for alkylation of the enolate of Schöllkopf's auxiliary **6** (50% de). This observation indicates that in the absence of any chiral relay effects, the diastereofacial selectivity observed for a basic DKP skeleton is less than that observed for the corresponding bis-lactim ether skeleton (possibly due to differences in enolate reactivity). Furthermore, the energy difference between the *Re* and *Si* faces of enolate **25** in the transition state is increased by at least 7.6 KJ mol^{-1} in the presence of the chiral relay mechanism.

Deprotection of *trans*-methylated auxiliary **28** to its parent α-amino acids was easily achieved, *via* oxidative removal of the *p*-methoxybenzyl groups using ceric ammonium nitrate

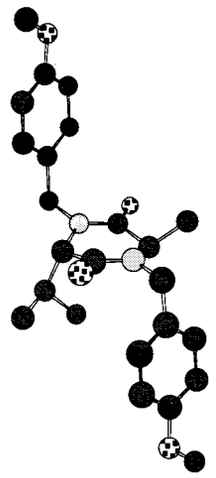


Fig. 3 X-Ray crystal structure of DKP **28**

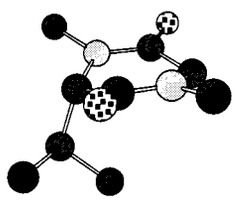
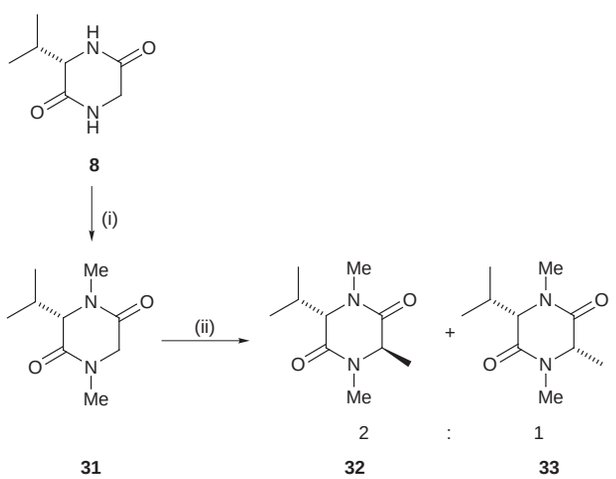
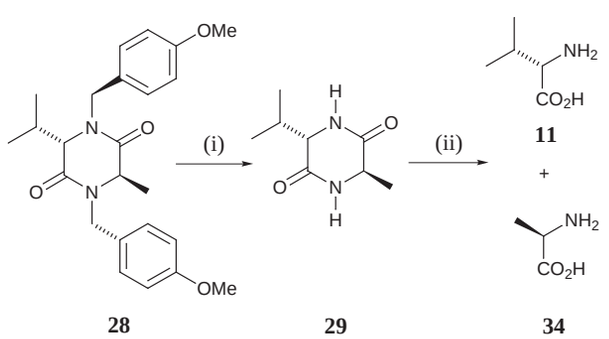


Fig. 4 X-Ray structure of DKP **31**



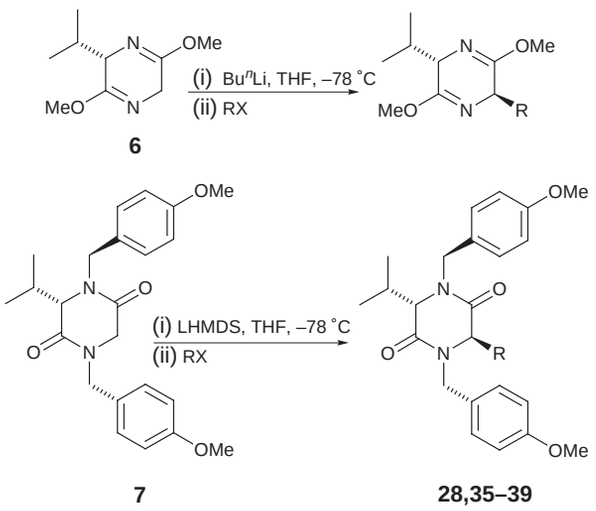
Scheme 8 *Reagents and conditions*: (i) NaH, MeI, THF; (ii) LHMDS, THF, −78 °C; 10 equiv. MeI



Scheme 9 *Reagents and conditions*: (i) CAN, CH_3CN–H_2O; (ii) 6 M HCl, Dowex 50-XH

in CH_3CN–H_2O,[27] to afford the DKP **29**. Acid catalysed hydrolysis of DKP **29** gave a mixture of (*S*)-valine **11** and (*R*)-alanine **34** which was separated by ion exchange chromatography[29] to afford homochiral (*R*)-alanine, **34** ($[a]_D^{23}$ −14.0, *c* 0.6 in 1 M HCl)[30] in 86% yield (Scheme 9).

Table 1 Comparison of diastereoselectivity and yield for alkylation of auxiliaries **6** and **7**



Electrophile RX	% de (from **6**)	% de (from **7**)	% Yield (from **6**)	% Yield (from **7**)
Methyl iodide	50	93 (**28**)	54	77 (**28**)
Benzyl bromide	91[10]	98 (**35**)	81[10]	88 (**35**)
Allyl bromide	76[31]	94 (**36**)	83[32]	71 (**36**)
Prop-2-ynyl bromide	52[20]	89 (**37**)	70[20]	73 (**37**)
Ethyl iodide	—[33]	90 (**38**)	—[33]	78 (**38**)
Isopropyl iodide	—[33]	96 (**39**)	—[33]	64 (**39**)

In order to determine the synthetic utility of our auxiliary we alkylated the enolate of DKP **7** with a representative range of alkyl halides under standard conditions to afford highly crystalline *trans*-alkylated products **35**–**39** in >90% de (Table 1). The diastereoselectivities observed for alkylation of the enolate of Schöllkopf's auxiliary **6** are also provided for comparison purposes. It can be clearly seen that the diastereoselectivities observed for alkylation of DKP **7** are superior in all cases. Simple recrystallisation, or column chromatography of the crude reaction product afforded the major *trans*-diastereoisomers pure in good yield, and the non-basic character of enolate **25** ensured that electrophiles which were prone to β-elimination (ethyl iodide or isopropyl iodide) gave *trans*-alkylated products **38**, **39** in excellent yield. All *cis*/*trans* diastereoselectivities could be easily determined by ^{1}H NMR spectroscopic analysis of the crude reaction products because the diastereotopic benzylic protons of the two protecting groups appear at distinctive chemical shifts depending on the stereochemistry of the DKP ring.

Conclusion

In conclusion, we have developed a new chiral auxiliary DKP **7** for the asymmetric synthesis of homochiral α-amino acids. This auxiliary incorporates a novel chiral relay network whereby the non-stereogenic benzyl protecting groups serve to relay the chiral information of the C_3 stereogenic centre close to the point of enolate alkylation. The conformation adopted by enolate **25** serves both to transfer and to amplify the chiral information of the existing stereogenic centre, thus affording improved diastereocontrol during enolate alkylation. We believe the principle of employing non-stereogenic protecting groups to enhance stereocontrol is a useful design feature for increasing the efficiency of chiral auxiliary technology, and we are currently investigating the use of chiral relay networks to enhance the diastereoselectivities of other auxiliaries.

Experimental

Melting points (mp) were obtained using a Thermogalen™ III or Griffin Gallenkamp melting point apparatus and are uncorrected. Optical rotations were measured with a Perkin-Elmer 241 polarimeter with a thermally jacketed 10 cm cell at approximately 20 °C. Concentrations (*c*) are given in g 100 ml^{-1}. Infrared (IR) spectra were recorded as KBr discs on a Perkin-Elmer 1750 Fourier Transform spectrometer. Absorptions are reported in wavenumbers (cm^{-1}). Proton magnetic resonance spectra (^{1}H NMR) were recorded at 200 MHz on a Varian Gemini 200 or a Bruker AC200 spectrometer, at 300 MHz on a Bruker WH300, at 400 MHz on a Bruker AC400 and at 500 MHz on a Bruker AM500 spectrometer and are referenced to the residual solvent peak. The following abbreviations were used: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet and br, broad. Coupling constants (*J*) were recorded in hertz to the nearest 0.5 Hz. Carbon magnetic resonance spectra (^{13}C NMR) were recorded at 50.3 MHz on a Varian Gemini 200 or Bruker AC200 spectrometer, at 100.6 MHz on a Bruker AC400 spectrometer and at 125.7 MHz on a Bruker AMX500 spectrometer using DEPT editing. Diastereomeric excesses were determined by peak integration of the crude reaction products' ^{1}H. Low resolution mass spectra (*m*/*z*) were recorded on a VG Micromass ZAB 1F, a VG Masslab 20-250, a GCMS Trio 1, a VG BIO Q or a APCI Platform spectrometer, with only molecular ions (M^+), fragments from molecular ions and major peaks being reported. Microanalyses were performed by Mrs V. Lamburn or Mr R. Prior, Dyson Perrins Laboratory, University of Oxford. Column chromatography was performed on silica gel (Kieselgel 60). Anhydrous THF was obtained by distillation from sodium/benzophenone ketyl under nitrogen. Petrol refers to light petroleum (bp 40–60 °C), redistilled before use. Unless otherwise stated all reactions were performed and worked-up under a nitrogen atmosphere. (*S*)-3-Isopropylpiperazine-2,5-dione was prepared according to the literature procedure.[17]

Preparation of (*S*)-*N*,*N*′-bis(*p*-methoxybenzyl)-3-isopropylpiperazine-2,5-dione 7

NaH (9.0 g, 0.22 mol) as a 60% dispersion in mineral oil, was washed with hexane (3 × 5 ml) and suspended in dimethylformamide (130 ml). The mixture was cooled to 0 °C and (*S*)-3-isopropylpiperazine-2,5-dione (16.0 g, 0.10 mol) added. *p*-Methoxybenzyl chloride (33.9 ml, 0.25 mol) was added dropwise over a period of 1 h. The reaction was stirred for a further 4 h before being quenched by cautious addition of water (5 ml) followed by excess saturated aqueous ammonium chloride. The mixture was extracted with ethyl acetate (3 × 200 ml), the combined organic layers were washed with water (100 ml), dried ($MgSO_4$) and concentrated *in vacuo*. Recrystallisation from ethyl acetate afforded the product as a colourless crystalline solid (31.6 g, 80%). Mp 134 °C (Found: C, 69.69; H, 7.16; N, 7.06. $C_{23}H_{28}N_2O_4$ requires C, 69.68; H, 7.12; N, 7.07%); $[\alpha]_D^{23}$ −53.7 (*c* 0.995 in $CHCl_3$); ν_{max}(KBr disc)/cm^{-1} 1666 (lactam C=O), 1609 (CH_3O), 1510 (aromatic C=C); δ_H(500 MHz; $CDCl_3$) 0.92 (3H, d, *J* 7.0, C*H*$_3$CHCH$_3$), 1.10 (3H, d, *J* 7.0, CH$_3$CHC*H*$_3$), 2.22 (1H, m, CH$_3$C*H*CH$_3$), 3.75 [1H, d, *J* 5.0, MeCH(C*H*)Me], 3.80 (1H, d, *J* 17.0, NC*H*$_2$CO), 3.81 (3H, s, C*H*$_3$O), 3.81 (3H, s, C*H*$_3$O), 3.85 (1H, d, *J* 15.0, MeOC$_6$H$_4$C*H*$_2$), 3.94 (1H, d, *J* 17.0, NC*H*$_2$CO), 4.21 (1H, d, *J* 14.0, MeOC$_6$H$_4$C*H*$_2$), 4.82 (1H, d, *J* 14.0, MeOC$_6$H$_4$C*H*$_2$), 5.33 (1H, d, *J* 15.0, MeOC$_6$H$_4$C*H*$_2$), 6.85–7.19 (8H, m, aromatic C*H*); δ_C(50 MHz; $CDCl_3$) 17.66 (*C*H$_3$CHCH$_3$), 19.74 (CH$_3$CH*C*H$_3$), 32.26 (CH$_3$*C*HCH$_3$, 47.47, 48.81 (MeOC$_6$H$_4$*C*H$_2$), 49.42 (*C*H$_2$CO), 55.23 (*C*H$_3$O), 64.45 [MeCH(*C*H)Me], 114.37, 127.76, 129.73, 130.09 (aromatic *C*H), 159.68 (CH$_3$O*C*), 164.94, 165.40 (*C*=O); *m*/*z* (APCI$^+$) 397.2 (MH$^+$, 17%), 289.1 (M^+ − MeOC$_6$H$_4$, 10%), 120.9 (MeOC$_6$H$_4$CH$_2^+$, 100%).

Alkylation of auxiliary using LHMDS—General procedure I
n-Butyllithium (1.44 ml, 2.78 mmol) was added dropwise to a stirred solution of hexamethyldisilazane (1.1 ml, 5.56 mmol) in THF (4 ml) −78 °C, under a nitrogen atmosphere. The solution was allowed to warm to 0 °C, before recooling to −78 °C, and transferred *via* cannula to a solution of (*S*)-**7** (1 g, 2.53 mmol) in THF (15 ml) at −78 °C. The resulting yellow solution was stirred for 1 h at −78 °C prior to the addition of the alkyl halide *via* syringe. The reaction was stirred at −78 °C for a further 3 h, before quenching with excess saturated aqueous ammonium chloride. The solution was allowed to warm to ambient temperature, the volatiles removed *in vacuo* and the residues partitioned between ethyl acetate (30 ml) and water (30 ml). The aqueous phase was extracted with ethyl acetate (3 × 20 ml) and the combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo* to yield the crude product.

(3*S*,6*R*)-*N*,*N*′-Bis(*p*-methoxybenzyl)-3-isopropyl-6-methylpiperazine-2,5-dione 28. Treatment of (*S*)-**7** with LHMDS and 10 equiv. MeI as for General Procedure I, followed by recrystallisation of the crude product from ethyl acetate afforded the *title compound* **28** as a colourless crystalline solid (1.99 g, 77%). Mp 115 °C (Found: C, 70.41; H, 7.27; N, 6.74. $C_{24}H_{30}N_2O_4$ requires C, 70.22; H, 7.37; N, 6.82%); $[\alpha]_D^{23}$ +22.5 (*c* 0.98 in $CHCl_3$); ν_{max}(KBr disc)/cm^{-1} 2965m (C–H), 1656s (lactam C=O), 1608m (aromatic C=C), 1510s (aromatic C=C); δ_H(500 MHz; $CDCl_3$) 0.92 (3H, d, *J* 7.0, CH_3CHCH$_3$), 1.12 (3H, d, *J* 7.0, CH$_3$CHCH_3), 1.60 (3H, d, *J* 7.0, CH_3CH), 2.29 (1H, m, CH$_3$C*H*CH$_3$), 3.78 [1H, d, *J* 4.5, MeCH(C*H*)Me], 3.80 (3H, s, CH_3O), 3.81 (3H, s, CH_3O), 3.85 (1H, d, *J* 15.0, MeOC$_6$H$_4$CH_2), 4.02 (1H, q, *J* 7.0, CH$_3$C*H*), 4.03 (1H, d, *J* 15.0, MeOC$_6$H$_4$CH_2), 5.33 (1H, d, *J* 15.0, MeOC$_6$H$_4$CH_2), 5.38 (1H, d, *J* 15.0, MeOC$_6$H$_4$CH_2), 6.84–7.27 (8H, m, aromatic C*H*); δ_C(50 MHz; $CDCl_3$) 17.54 (*C*H$_3$CHCH$_3$), 17.76 (*C*H$_3$CH), 19.81 (CH$_3$CH*C*H$_3$), 31.82 (CH$_3$*C*HCH$_3$), 45.25, 47.58 (MeOC$_6$H$_4$*C*H$_2$), 53.40 (CH$_3$*C*H), 55.25 (*C*H$_3$O), 63.89 [MeCH(*C*H)Me], 114.26, 114.44, 127.93, 128.38, 129.63 (aromatic *C*H), 135.26 (*ipso-C*), 159.39, 159.57 (CH$_3$O*C*), 166.30, 168.09 *C*=O); *m*/*z* (APCI$^+$) 411.2 (MH$^+$, 98%), 303.2 (MH$^+$ − MeOC$_6$H$_4$, 23%), 120.9 (MeOC$_6$H$_4$CH$_2^+$, 100%).

(3*S*,6*S*)-*N*,*N*′-Bis(*p*-methoxybenzyl)-3-isopropyl-6-methylpiperazine-2,5-dione 27. Isolated from the above reaction by flash column chromatography (SiO_2; 50 : 50 diethyl ether–petrol as a colourless oil. $[\alpha]_D^{23}$ −202.25 (*c* 0.89 in $CHCl_3$); ν_{max}(thin film)/cm^{-1} 2963m, 2996m (C–H), 1658s (lactam C=O), 1612s (aromatic C=O), 1513s (aromatic C=C); δ_H(500 MHz; $CDCl_3$) 1.04 (3H, d, *J* 7.0, CH_3CHCH$_3$), 1.17 (3H, d, *J* 7.0, CH$_3$-CHCH_3), 1.55 (3H, d, *J* 7.0, CH_3CH), 2.20 (1H, m, CH$_3$C*H*CH$_3$), 3.74 [1H, d, *J* 5.5, MeCH(C*H*)Me], 3.81 (3H, s, CH_3O), 3.81 (3H, s, CH_3O), 3.98 (1H, d, *J* 15.0, MeO-C$_6$H$_4$CH_2), 3.99 (1H, q, *J* 7.0, CH$_3$C*H*), 4.00 (1H, d, *J* 15.0, MeOC$_6$H$_4$CH_2), 5.11 (1H, d, *J* 14.5, MeOC$_6$H$_4$CH_2), 5.35 (1H, d, *J* 15.0, MeOC$_6$H$_4$CH_2), 6.83–7.16 (8H, m, aromatic C*H*); δ_C(50 MHz; $CDCl_3$) 18.61 (*C*H$_3$CHCH$_3$), 18.86 (*C*H$_3$CH), 20.33 (CH$_3$CH*C*H$_3$), 32.05 (CH$_3$*C*HCH$_3$), 46.31, 47.93 (MeO-C$_6$H$_4$*C*H$_2$), 54.77 (CH$_3$*C*H), 55.23 (*C*H$_3$O), 64.39 [MeCH-(*C*H)Me], 114.33, 114.40, 127.83, 128.23, 129.55, 129.72 (aromatic *C*H), 131.12 (*ipso-C*), 159.57 (CH$_3$O*C*), 165.21, 167.98 (*C*=O); *m*/*z* (APCI$^+$) 411.2 (MH$^+$, 100%), 120.8 (MeOC$_6$H$_4$CH$_2^+$, 21%).

(3*S*,6*R*)-*N*,*N*′-Bis(*p*-methoxybenzyl)-3-isopropyl-6-benzylpiperazine-2,5-dione 35. Treatment of (*S*)-**7** with LHMDS and 2 equiv. benzyl bromide as for General Procedure I, followed by recrystallisation of the crude product from ethyl acetate afforded the *title compound* **35** as a colourless crystalline solid (4.31 g, 88%). Mp 168 °C (Found: C, 74.06; H, 6.98; N, 5.78. $C_{30}H_{34}N_2O_4$ requires C, 74.05; H, 7.04; N, 5.76%); $[\alpha]_D^{23}$ +58.6 (*c* 0.99 in $CHCl_3$); ν_{max}(KBr disc)/cm^{-1} 2962m, 2934m (C–H), 1641s (lactam C=O), 1514s (aromatic C=C); δ_H(500 MHz; $CDCl_3$) 0.74 (3H, d, *J* 7.0, CH_3CHCH$_3$), 0.99 (3H, d, *J* 7.0, CH$_3$CHCH_3), 2.16 (1H, m, CH$_3$C*H*CH$_3$), 3.31 [1H, d, *J* 3.0, MeCH(C*H*)Me], 3.36 (1H, dd, *J* 14.5 and 4.0, PhCH_2CH), 3.40 (1H, dd, *J* 14.5 and 4.0, PhCH_2CH), 3.79 (1H, d, *J* 15.0, MeO-C$_6$H$_4$CH_2), 3.79 (3H, s, CH_3O), 3.83 (3H, s, CH_3O), 3.98 (1H, d, *J* 15.0, MeOC$_6$H$_4$CH_2), 4.26 (1H, t, *J* 4.0, PhCH$_2$C*H*), 5.08 (1H, d, *J* 15.0, MeOC$_6$H$_4$CH_2), 5.66 (1H, d, *J* 15.0, MeO-C$_6$H$_4$CH_2), 6.58–7.49 (13H, m, aromatic C*H*); δ_C(50 MHz; $CDCl_3$), 15.98 (*C*H$_3$CHCH$_3$), 19.59 (CH$_3$CH*C*H$_3$), 30.84 (CH$_3$*C*HCH$_3$), 35.58 (Ph*C*H$_2$), 45.50 (MeOC$_6$H$_4$*C*H$_2$), 46.35 (MeOC$_6$H$_4$*C*H$_2$, 55.23 (*C*H$_3$O), 58.95 (PhCH$_2$*C*H), 62.00 [MeCH(*C*H)Me], 114.15, 114.40, 126.71, 127.25, 127.42, 128.91, 129.91, 130.13, 130.56 (aromatic *C*H), 135.34 (*ipso-C*), 159.32, 159.72, (CH$_3$O*C*), 165.55, 166.04 (*C*=O); *m*/*z* (APCI$^+$) 487.2 (MH$^+$, 100%), 379.2 (MH$^+$ − MeOC$_6$H$_4$, 16%), 120.9 (MeOC$_6$H$_4$CH$_2^+$, 36%).

(3*S*,6*R*)-*N*,*N*′-Bis(*p*-methoxybenzyl)-3-isopropyl-6-allylpiperazine-2,5-dione 36. Treatment of (*S*)-**7** with LHMDS and 10 equiv. allyl bromide as for General Procedure I, followed by recrystallisation of the crude product from ethyl acetate afforded the *title compound* **36** as a colourless crystalline solid (1.57 g, 71%). Mp 127 °C (Found: C, 71.40; H, 7.27; N, 6.30. $C_{26}H_{32}N_2O_4$ requires C, 71.54 H, 7.39; N, 6.42%); $[\alpha]_D^{23}$ +25.8 (*c* 0.985 in $CHCl_3$); ν_{max}(KBr disc)/cm^{-1} 2937m, 2832m (C–H), 1640s (lactam C=O), 1613s (C=C), 1513s (aromatic C=C), 1253s; δ_H(500 MHz; $CDCl_3$) 0.84 (3H, d, *J* 7.0, CH_3CHCH$_3$), 1.10 (3H, d, *J* 7.0, CH$_3$CHCH_3), 2.31 (1H, m, CH$_3$C*H*CH$_3$), 2.78 (1H, dt, *J* 12.5 and 6.0, CH_2CH=CH$_2$), 2.97 (1H, ddt, *J* 15.0, 7.0 and 1.0, CH_2CH=CH$_2$), 3.78 [1H, d, *J* 4.0, MeCH-(C*H*)Me], 3.80 (1H, d, *J* 15.5, MeOC$_6$H$_4$CH_2) 3.81 (3H, s, CH_3O), 3.81 (3H, s, CH_3O), 3.81 (1H, d, *J* 14.5, MeO-C$_6$H$_4$CH_2), 3.99 (1H, dd, *J* 5.0 and 2.5, C*H*CH$_2$CHCH$_2$), 5.12 (1H, d, *J* 10.5, CHCH_2), 5.19 (1H, dd, *J* 17 and 1.5, CHCH_2), 5.41 (1H, d, *J* 14.5, MeOC$_6$H$_4$CH_2), 5.53 (1H, d, *J* 15.0, MeO-C$_6$H$_4$CH_2), 5.54 (1H, m, CH$_2$C*H*CH$_2$), 6.85 (2H, d, *J* 8.5, MeOCC*H* × 2), 6.87 (2H, d, *J* 8.5, MeOCC*H* × 2), 7.16 (2H, d, *J* 8.5, MeOCCHC*H*), 7.23 (2H, d, *J* 8.5, MeOCCHC*H*); δ_C(50 MHz; $CDCl_3$) 16.67 (*C*H$_3$CHCH$_3$), 19.64 (CH$_3$CH*C*H$_3$), 31.62 (CH$_3$*C*HCH$_3$), 34.48 (*C*H$_2$CHCH$_2$), 44.92, 46.77 (MeO-C$_6$H$_4$*C*H$_2$), 55.25 (*C*H$_3$O), 56.78 (*C*HCH$_2$CHCH$_2$), 62.80 [MeCH(*C*H)Me], 114.32, 120.22 (CH$_2$CH*C*H$_2$), 127.45, 127.61, 130.12, 130.24, 131.11 (aromatic *C*H), 159.59 (CH$_3$O*C*), 165.86, 166.49 (C=O); *m*/*z* (APCI$^+$) 437.1 (MH$^+$, 77%), 120.9 (MeO-C$_6$H$_4$CH$_2^+$, 100%).

(3*S*,6*R*)-*N*,*N*-Bis(*p*-methoxybenzyl)-3-isopropyl-6-prop-2-ynylpiperazine-2,5-dione 37. Treatment of (*S*)-**7** with LHMDS and 5 equiv. prop-2-ynyl bromide as for General Procedure I, followed by recrystallisation of the crude product from ethyl acetate afforded the *title compound* **37** as a colourless crystalline solid (796 mg, 73%). Mp 148 °C (Found: C, 72.01; H, 7.15; N, 6.50. $C_{26}H_{30}N_2O_4$ requires C, 71.87; H, 6.96; N, 6.45%); $[\alpha]_D^{23}$ +14.6 (*c* 0.975 in $CHCl_3$); ν_{max}(KBr disc)/cm^{-1} 3277s (acetylenic C–H), 2963s, 2935m, 2834m (C–H), 1640s (lactam C=O), 1611s (OCH$_3$), 1513s (aromatic C=C); δ_H(500 MHz; $CDCl_3$), 0.90 (3H, d, *J* 7.0, CH_3CHCH$_3$), 1.12 (3H, d, *J* 7.0, CH$_3$CHCH_3), 1.99 (1H, t, *J* 2.5, CH$_2$CC*H*); 2.33 (1H, m, CH$_3$C*H*CH$_3$), 2.88 (1H, ddd, *J* 17.5, 5.0 and 2.5, CH_2CCH), 3.16 (1H, dt, *J* 17.5 and 2.5, CH_2CCH), 3.78 [1H, d, *J* 4.0, MeCH(C*H*)Me], 3.79 (3H, s, CH_3O), 3.80 (3H, s, CH_3O), 3.80 (1H, d, *J* 14.5, MeOC$_6$H$_4$CH_2), 3.84 (1H, d, *J* 15.5, MeOC$_6$H$_4$CH_2), 3.95 (1H, dd, *J* 5.0 and 2.5, C*H*CH$_2$CCH), 5.54 (1H, d, *J* 15.0, MeOC$_6$H$_4$CH_2), 5.61 (1H, d, *J* 15.0, MeOC$_6$H$_4$CH_2), 6.82–7.22 (8H, m, aromatic *C*H); δ_C(50 MHz; $CDCl_3$) 16.89 (*C*H$_3$CHCH$_3$), 19.65 (CH$_3$CH*C*H$_3$), 22.02 (CH*C*H$_2$CCH), 31.52 (CH$_3$*C*HCH$_3$), 45.05, 46.76 (MeOC$_6$H$_4$*C*H$_2$), 55.26 (*C*H$_3$O × 2), 55.88 [MeCH(*C*H)Me], 62.68 (*C*HCH$_2$CCH), 72.62 (CHCH$_2$*C*CH), 78.08 (CH*C*H$_2$CCH), 114.23, 114.44, 127.18, 117.32, 128.91, 129.90, 129.99, 130.56 (aromatic *C*H), 135.36 (*ipso-C*), 159.64 (CH$_3$O*C* × 2), 165.79, 165.98 (*C*=O); *m*/*z* (APCI$^+$) 435.2 (MH$^+$, 57%), 120.9 (MeOC$_6$H$_4$CH$_2^+$, 100%).

(3*S*,6*R*)-*N*,*N*′-Bis(*p*-methoxybenzyl)-3-isopropyl-6-ethylpiperazine-2,5-dione 38. Treatment of (*S*)-**7** with LHMDS and

2 equiv. ethyl iodide as for General Procedure I, followed by recrystallisation of the crude product from ethyl acetate afforded the *title compound* **38** as a colourless crystalline solid (1.67 g, 78%). Mp 140 °C (Found: C, 70.62; H, 7.45; N, 6.45. $C_{25}H_{32}N_2O_4$ requires C, 70.73; H, 7.60; N, 6.60%); $[\alpha]_D^{23}$ +46.1 (*c* 0.995 in $CHCl_3$); ν_{max}(KBr disc)/cm^{-1} 2961w, 2935w (C–H), 1648s (lactam C=O), 1510s (aromatic C=C); δ_H(500 MHz; $CDCl_3$) 0.73 (3H, t, *J* 7.5, CH_3CH$_2$), 0.84 (3H, d, *J* 7.0, CH_3CHCH$_3$), 1.11 (3H, d, *J* 7.0, CH$_3$CHCH_3), 2.06 (1H, m, CH$_3$C*H*CH$_3$), 2.29 (2H, m, CH$_3$CH_2CH), 3.73 (1H, d, *J* 14.5, MeOC$_6$H$_4$CH_2), 3.81 (1H, d, *J* 14.5, MeOC$_6$H$_4$CH_2), 3.81 (3H, s, CH_3O), 3.81 (3H, s, CH_3O), 3.82 [1H, d, *J* 3.0, MeCH(C*H*)Me], 3.96 (1H, dd, *J* 2.5 and 2.0, CH$_3$CH$_2$C*H*), 5.43 (1H, d, *J* 14.5, MeOC$_6$H$_4$CH_2), 5.52 (1H, d, *J* 14.5, MeOC$_6$H$_4$CH_2), 6.85–7.24 (8H, m, aromatic C*H*); δ_C(50 MHz; $CDCl_3$) 6.68 (*C*H$_3$CH$_2$CH), 16.67 (*C*H$_3$CHCH$_3$), 19.62 (CH$_3$CH*C*H$_3$), 23.25 (CH$_3$*C*H$_2$CH), 31.80 (CH$_3$*C*HCH$_3$), 44.74, 46.81 (MeOC$_6$H$_4$*C*H$_2$), 55.24 (*C*H$_3$O × 2), 57.45 (CH$_3$CH$_2$*C*H), 62.83 [MeCH(*C*H)Me], 114.21, 114.40, 127.69, 127.84, 130.02, 130.27 (aromatic *C*H), 135.25 (*ipso-C*), 159.51, 159.60 (CH$_3$O*C*), 166.12, 166.92 (*C*=O); *m*/*z* (APCI$^+$) 425.3 (MH$^+$, 100%), 120.9 (MeOC$_6$H$_4$CH$_2^+$, 35%).

(3*S*,6*R*)-*N*,*N*-Bis(*p*-methoxybenzyl)-3,6-diisopropylpiperazine-2,5-dione 39. Treatment of (*S*)-**7** with LHMDS and 5 equiv. isopropyl iodide as for General Procedure I, followed by recrystallisation of the crude product from ethyl acetate afforded the *title compound* **39** as a white crystalline solid (143 mg, 64%). Mp 180 °C (Found: C, 70.9; H, 8.0; N, 6.2. $C_{26}H_{34}N_2O_4$ requires C, 71.2; H, 7.8; N, 6.4%); ν_{max}(KBr disc)/cm^{-1} 1640 (lactam C=O); δ_H(500 MHz; $CDCl_3$) 0.81 (6H, d, *J* 7.0, CH_3CHCH$_3$ × 2), 1.12 (6H, d, *J* 7.0, CH_3CHCH$_3$ × 2), 2.35 (2H, m, *J* 2.5 and 7.0, CH$_3$C*H*CH$_3$ × 2), 3.78 [2H, d, *J* 2.5, MeCH(C*H*)Me × 2], 3.80 (6H, s, CH_3O × 2), 3.90 (2H, d, *J* 14.5, MeOC$_6$H$_4$CH_2), 5.31 (2H, d, *J* 14.5, MeOC$_6$H$_4$CH_2), 6.86 (4H, d, *J* 8.5, MeOCC*H* × 4), 7.18 (4H, d, *J* 8.5, MeOCCHC*H* × 4); δ_C(50 MHz; $CDCl_3$) 15.6 (*C*H$_3$CHCH$_3$), 19.8 (CH$_3$CH*C*H$_3$), 30.6 (CH$_3$*C*HCH$_3$), 46.2 (MeOC$_6$H$_4$*C*H$_2$), 55.2 (*C*H$_3$O), 62.5 [MeCH(*C*H)Me], 114.3 [MeOCCH*C*H × 4], 130.3 (MeOC*C*H × 4), 159.5 (CH$_3$O*C*), 165.9 (*C*=O); *m*/*z* (CI) 439 (MH$^+$, 92%), 121 (MeOC$_6$H$_4$CH$_2^+$, 100%).

(3*S*,6*R*)-3-Isopropyl-6-methylpiperazine-2,5-dione 29

D-Alanine methyl ester hydrochloride (1.95 g, 13.99 mmol) was suspended in chloroform (20 ml) and triethylamine (3.89 ml, 27.97 mmol) added. The mixture was stirred at ambient temperature under a nitrogen atmosphere to dissolve the solid and then cooled to −78 °C. A solution of (*S*)-4-isopropyloxazolidine-2,5-dione (2.00 g, 14.00 mmol) in THF (15 ml) was added over a period of 10 min and further chloroform (10 ml) added. The reaction mixture was stirred for 4 h at −78 °C and then stored at −20 °C overnight. The triethylamine hydrochloride precipitate was removed by filtration through Celite and the filtrate concentrated *in vacuo* to yield a pale yellow oil which was dissolved in toluene (25 ml) and heated under reflux for 10 h. Filtration and removal of residual toluene by gentle heating *in vacuo*, and recrystallisation from ethanol and water afforded the product as a white crystalline solid (2.38 g, 100%). Subl. 210 °C (Found: C, 56.16; H, 8.52. $C_8H_{14}N_2O_2$ requires C, 56.45; H, 8.29%); $[\alpha]_D^{23}$ +31.0 (*c* 0.51 in H_2O) {lit. $[\alpha]_D^{23}$ + 26.7 (*c* 1.0 in CH_3CO_2H}[34]; ν_{max}(thin film)/cm^{-1} C–H), (lactam C=O), 1612s (CH$_3$O), 1513s (aromatic C=C); δ_H(200 MHz; DMSO) 0.82 (3H, d, *J* 7.0, CH_3CHCH$_3$), 0.90 (3H, d, *J* 7.0, CH$_3$CHCH_3), 1.22 (3H, d, *J* 7.0, CH_3CH), 2.09 (1H, m, CH$_3$C*H*CH$_3$), 3.51 [1H, d, *J* 3.5, MeCH(C*H*)Me], 3.90 (1H, q, *J* 7.0, CH$_3$C*H*).

(*S*)-*N*,*N*′-Dimethyl-3-isopropylpiperazine-2,5-dione 31

NaH (282 mg, 7.05 mmol) as a 60% dispersion in mineral oil, was washed with hexane (3 × 5 ml) and suspended in THF (30 ml). The mixture was cooled to 0 °C and (*S*)-3-isopropylpiperazine-2,5-dione (500 mg, 3.205 mmol) added. Methyl iodide (2.00 ml, 32.05 mmol) was added dropwise. The reaction was stirred for a further 16 h before being quenched by cautious addition of water (1 ml). The reaction mixture was concentrated *in vacuo* and the produce extracted into $CHCl_3$. The residual solid was dissolved in brine (15 ml) and extracted with $CHCl_3$ (3 × 15 ml), dried (Na_2SO_4) and concentrated *in vacuo*, to give the product as a colourless crystalline solid (372 mg, 63%). Mp 125 °C (lit. 118 °C)[35] (Found: C, 58.66; H, 8.96; N, 14.97. $C_9H_{16}N_2O_2$ requires C, 58.67; H, 8.75; N, 15.25%); $[\alpha]_D^{21}$ +90.4 (*c* 1.02 in $CHCl_3$); ν_{max}/cm^{-1} 2936s (C–H), 1656s (lactam C=O); δ_H(200 MHz; $CDCl_3$) 0.96 (3H, d *J* 7.0, CH_3CHCH$_3$), 1.08 (3H, d, *J* 7.0, CH$_3$CHCH_3), 2.25 (1H, dsept, *J* 7.0 and 4.5, CH$_3$C*H*CH$_3$), 2.96 (3H, s, CH_3N), 3.00 (3H, s, CH_3N), 3.72 [1H, d, *J* 4.0, MeCH(C*H*)Me], 3.80 (1H, d, *J* 17.5, CH_2NMe), 4.10 (1H, d, *J* 17.5); δ_C(50 MHz; $CDCl_3$) 17.95 (*C*H$_3$CHCH$_3$), 19.07 (CH$_3$CH*C*H), 32.64 (CH$_3$*C*HCH$_3$), 33.28, 34.04 (N*C*H$_3$), 51.91 (MeN*C*H$_2$), 68.40 (MeCH(*C*H),Me), 164.49, 165.58 (*C*=O); *m*/*z* (APCI$^+$) 185.1 (MH$^+$, 100%).

(3*S*,6*R*)-*N*,*N*′-Dimethyl-3-isopropyl-6-methylpiperazine-2,5-dione 32

NaH (129 mg, 3.23 mmol) as a 60% dispersion in mineral oil, was washed with hexane (3 × 5 ml) and suspended in THF (10 ml). The mixture was cooled to 0 °C and (3*S*,6*R*)-3-isopropyl-6-methylpiperazine-2,5-dione **29** (250 mg, 1.47 mmol) added. Methyl iodide (0.92 ml, 14.7 mmol) was added dropwise and the reaction was stirred for a further 16 h before being quenched by water (0.5 ml). The reaction mixture was concentrated *in vacuo*, the produce extracted into chloroform (20 ml), and dried (Na_2SO_4). Recrystallisation from ethyl acetate afforded the product as a white solid (230 mg, 79%). Mp 99 °C; $[\alpha]_D^{21}$ +47.9 (*c* 1.01 in $CHCl_3$); δ_H(200 MHz; $CDCl_3$) 0.88 (3H, d, *J* 7.0, CH_3CHCH$_3$), 1.07 (3H, d, *J* 7.0, CH$_3$CHCH_3), 1.55 (3H, d, *J* 6.5, CH_3CH), 2.32 (1H, m, CH$_3$C*H*CH$_3$), 2.98 (3H, s, CH_3N), 2.99 (3H, s, CH_3N), 3.93 [1H, d, *J* 3.5, MeCH(C*H*)Me], 4.21 (1H, q, *J* 6.5, CH$_3$C*H*); *m*/*z* (APCI$^+$ 199.1 (MH$^+$, 79%), 156.0 (M$^+$ − 3 × CH$_3$, 100%).

Deprotection of (3*S*,6*R*)-*N*,*N*′-bis(*p*-methoxybenzyl)-3-isopropyl-6-methylpiperazine-2,5-dione 28

Ceric ammonium nitrate (1.0 g) was added to a solution of **28** (410 mg) in CH$_3$CN–H$_2$O (1 : 1, 10 ml) and the reaction mixture stirred for 4 h. The solvent was removed *in vacuo* to afford the crude product (1.6 g). Column chromatography (Al_2O_3; ethyl acetate to methanol) afforded **29** {160 mg, $[\alpha]_D^{23}$ +30.0 (*c* 0.50 in H_2O)} in 94% yield. **29** (200 mg) was then refluxed in 6 M HCl (5 ml) for 24 h, the solvent removed *in vacuo*, and the solid residue dissolved in water (2 ml) and adsorbed onto ion exchange resin Amberlist H-15. The resin was washed with distilled water, then eluted with 5 M NH_4OH to recover (*R*)-alanine **34** $[\alpha]_D^{23}$ −14.0 (*c* 6.0, 1 M HCl), {Lit.[30] $[\alpha]_D^{23}$ −14.2 (*c* 6.0, 1 M HCl)} and (*S*)-valine **11** $[\alpha]_D^{23}$ +27.5, (*c* 8.0, 6 M HCl), [Lit.[30] $[\alpha]_D^{23}$ +27.5 (*c* 8.0, 6 M HCl)] in 86% yield.

X-Ray crystal structure determination

The selected crystals were mounted on nylon fibres using a drop of perfluoropolyether oil. they were then rapidly cooled in a flow of cold nitrogen using an Oxford Cryosystems CRYOSTREAM cooling system. The data were collected on an Enraf-Nonius DIP2020 image-plate diffractometer using graphite monochromated Mo-Kα radiation (λ = 0.7107 Å). The images were processed using the DENZO and SCALEPACK suite of programs.[36] Data were corrected for Lorentz and polarisation effects and a partial absorption correction applied by multi-frame scaling of the image-plate data using equivalent reflections. Crystal data, data collection and refinement parameters are given in Table 2.

Table 2 Crystal data, data collection and refinement parameters for **7**, **28** and **31**

Compound	**7**-DKP	**28** Me-DKP	**31**-N,N′-dimethyl DKP
Formula	$C_{23}H_{28}O_4N_2$	$C_{24}H_{30}O_4N_2$	$C_{18}H_{32}O_4N_4$
M_r	396.49	410.51	368.48
Crystal system	Orthorhombic	Monoclinic	Monoclinic
Space group	$P2_12_12_1$	$P2_1$	$P2_1$
a/Å	7.195(1)	7.632(1)	7.134(1)
b/Å	11.971(1)	18.366(2)	11.003(1)
c/Å	23.929(1)	7.666(1)	12.182(1)
β/°	90	96.117(5)	90.707(3)
V/Å^3	2061.04	1068.42	956.16
Z	4	2	2
D_x/g cm^{-3}	1.28	1.28	1.28
μ/mm^{-1}	0.08	0.08	0.09
T/K	100	150	150
Crystal shape	Block	Block	Block
Crystal size/mm	0.30 × 0.50 × 0.50	0.30 × 0.20 × 0.15	0.40 × 0.30 × 0.20
Colour	Colourless	Colourless	Colourless
Measured reflections	6825	7451	4233
Independent reflections	2197	2187	1964
Reflections with $I > 3\sigma(I)$	2104	1723	1931
Merging R	0.019	0.03	0.016
θ_{max}/°	26.37	26.00	26.61
h	−8→8	−9→8	−8→8
k	−14→14	−23→23	−13→13
l	−29→29	−9→9	−14→15

The structures were solved by direct methods, SIR92,[37] giving all non-hydrogen atom positions. The structures were refined using full-matrix least-squares procedures with anisotropic thermal parameters for all non-hydrogen atoms. The hydrogen atoms were placed in calculated positions during the final cycles of refinement. A three parameter Chebychev weighting scheme[38] and corrections for anomolous dispersion were applied to all data. All crystallographic calculations were carried out using CRYSTALS[39] on a PC/AT computer. Neutral atom scattering factors were taken from International Tables for X-ray Crystallography (1974, vol. IV, Table 2.2B).

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