On the origins of diastereoselectivity in the alkylation of diketopiperazine enolates

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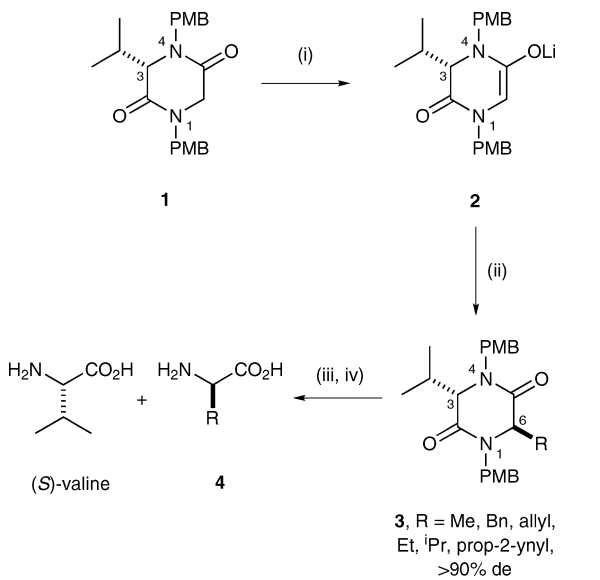
High levels of diastereoselectivity are observed for benzylation of the lithium enolates of (*S*)-*N*,*N*′-bis-*para*-methoxybenzyl-3-*iso*-propyl-piperazine-2,5-dione, (*S*)-*N*(1)-*para*-methoxybenzyl-*N*(4)-methyl-3-*iso*-propyl-piperazine-2,5-dione and (*S*)-*N*(1)-methyl-*N*(4)-*para*-methoxybenzyl-3-*iso*-propyl-piperazine-2,5-dione. These data suggest that the high diastereofacial selectivity observed for alkylation of these diketopiperazine templates is mainly a consequence of the relay of stereochemical information from C(3) to C(6) *via* the influence of 1,2-torsional strain introduced by the *N*-alkyl substituents, rather than through minimisation of steric interactions alone.

Introduction

The central role that homochiral α-amino acids play in Nature has ensured that a panoply of methods have been developed for their asymmetric synthesis.[1] Perhaps the most versatile and widely used strategy within this area is the stereoselective alkylation of protected glycine enolates derived from simple heterocycles that contain chiral auxiliary fragments.[2] This approach relies on the homochiral component to control facial selectivity during alkylation of the masked glycine enolate to afford a major diastereoisomeric product containing one or more new stereogenic centres in high de. Subsequent purification and cleavage of the stereoselectively-transformed glycine equivalent affords the desired homochiral α-amino acid. We have previously reported (*S*)-*N*,*N*′-bis-*para*-methoxybenzyl-3-*iso*-propyl-piperazine-2,5-dione (**1**) as a chiral auxiliary for the asymmetric synthesis of homochiral α-amino acids.[3] Deprotonation of **1** with LiHMDS generates lithium enolate **2**, which can be alkylated with a range of electrophiles to give *trans*-(3*S*,6*R*)-*N*,*N*′-bis-*para*-methoxybenzyl-3-*iso*-propyl-6-alkyl-piperazine-2,5-diones **3** in >90% de. Subsequent *N*-*para*-methoxybenzyl deprotection with ceric ammonium nitrate (CAN) and acid hydrolysis of the resultant diketopiperazine (DKP) gives a mixture of the constituent α-amino acids, which may be readily separated to afford (*R*)-α-amino acids **4** and (*S*)-valine (Scheme 1).

In our original study[3] we noted that the diastereoselectivity in alkylations of **1**, bearing conformationally labile *N*-*para*-methoxybenzyl (PMB) protecting groups, was enhanced in comparison to the corresponding alkylations of Schöllkopf's related bis-lactim ether auxiliary **7**.[4] For example, methylation of enolate **2** gave a 96.5 : 3.5 mixture of *trans*-**5** : *cis*-**6**, whilst methylation of enolate **8** gave a 75 : 25 mixture of *trans*-**9** : *cis*-**10** (Scheme 2).

Applying Ockham's razor[5] to these observations led to the proposal that the high diastereofacial selectivity observed for the *trans*-alkylation of lithium enolate **2** might be the result of a "steric chiral relay" operating to enhance the facial selectivity; a concept which has subsequently been validated in a number of chemical systems.[6,7] In the proposed steric chiral relay mechanism, the diketopiperazine enolate **2** occupies a preferred conformation in which minimisation of 1,2-steric interactions between the C(3)-*iso*-propyl group and the *N*(4)-*para*-methoxybenzyl group causes the latter to project over the Re face of **2**, thus causing the *N*(1)-*para*-methoxybenzyl group to preferentially occupy a position over the Si face of the auxiliary. The high levels of stereoselectivity in alkylation reactions of **2** then derive from an enhanced steric bias towards Re face alkylation due to the presence of the



Scheme 1 *Reagents and conditions:* (i) LiHMDS, THF, −78 °C; (ii) RX (10 equiv.), −78 °C to r.t.; (iii) CAN, MeCN–H_2O (v/v 3 : 1), r.t.; (iv) HCl (6 M, aq.), reflux, then Dowex 50-XH.

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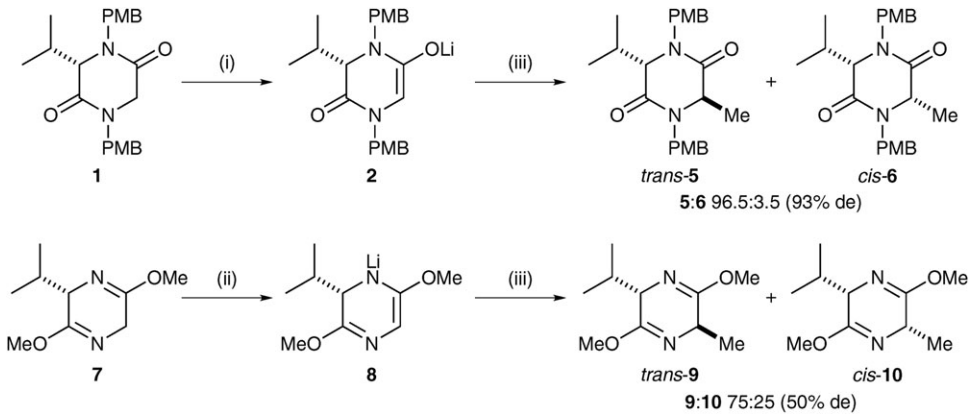


Scheme 2 *Reagents and conditions:* (i) LiHMDS, THF, −78 °C; (ii) BuLi, THF, −78 °C; (iii) MeI (10 equiv.), −78 °C to r.t.

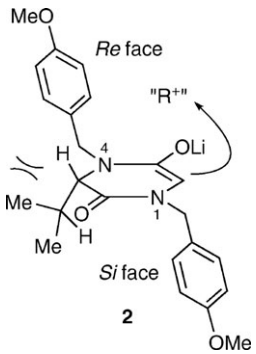


Fig. 1 Proposed steric chiral relay network in the alkylation of lithium enolate **2**.

N(1)-*para*-methoxybenzyl group on the Si face close to the site of alkylation at C(6) (Fig. 1).

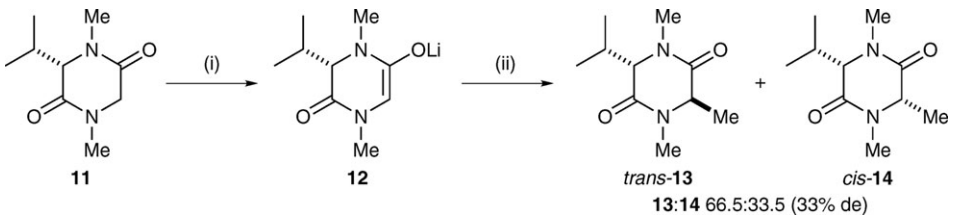
Whilst the steric chiral relay proposal relies on the conformational preference of the *N*-*para*-methoxybenzyl groups, one alternative rationale is that reactivity differences between the oxy-enolate **2** and the aza-enolate **8** may account for the observed differences in diastereoselectivity between the two templates. In preliminary studies,[3] this second possibility was investigated *via* the alkylation of *N*,*N*′-dimethyl substituted DKP **11**. The lithium enolate, **12**, of this template was expected to be electronically similar to the *N*,*N*′-bis-PMB enolate **2**; however, the *N*-methyl substituents are now incapable of substantially projecting onto either face of the auxiliary, precluding any steric chiral relay mechanism. Alkylation of *N*,*N*′-dimethyl enolate **12** with methyl iodide proceeded with lower levels of *trans*-diastereoselectivity to give *trans*-**13** in 33% de (Scheme 3), compared to the analogous alkylation of *N*,*N*′-bis-PMB enolate **2**, which gave *trans*-**5** in 93% de (Scheme 2), therefore supporting the assumption that the enolate reactivity, relative to Schöllkopf's auxiliary **7**, is not the primary source of the enhanced selectivity in alkylations of **1**.

In order to probe further the validity of the proposed steric chiral relay mechanism, we report herein the preparation and alkylation of a series of cyclic Val-Gly templates—(*S*)-*N*,*N*′-dimethyl-3-*iso*-propyl-piperazine-2,5-dione (**11**), (*S*)-*N*(1)-methyl-*N*(4)-*para*-methoxybenzyl-3-*iso*-propyl-piperazine-2,5-dione (**18**) and (*S*)-*N*(1)-*para*-methoxybenzyl-*N*(4)-methyl-3-*iso*-propyl-piperazine-2,5-dione (**22**)—in which either or both of the *N*-*para*-methoxybenzyl protecting groups within the DKP framework have been systematically replaced with an *N*-methyl substituent (Fig. 2). This strategy was proposed to allow any contribution to the selectivity provided by either the *N*(1)- or *N*(4)-*para*-methoxybenzyl groups to be delineated, and the results of these investigations are reported herein.

Results and discussion

Preparation of diketopiperazine templates

N,*N*′-bis-PMB-DKP **1** and *N*,*N*′-dimethyl-DKP **11** were prepared as previously described[3] by the bis-alkylation of (*S*)-cyclo-Val-Gly.[8] An alternative strategy based upon sequential incorporation of *N*-substituents prior to formation of the DKP heterocycle[9] was explored in the preparation of differentially *N*-substituted DKPs **18** and **22**. Accordingly, (*S*)-*N*-(*para*-methoxybenzyl)valine methyl ester hydrochloride (**15**), prepared by the reductive amination of *para*-anisaldehyde with (*S*)-valine methyl ester, was condensed with bromoacetyl



Scheme 3 *Reagents and conditions:* (i) LiHMDS, THF, −78 °C; (ii) MeI (10 equiv.).

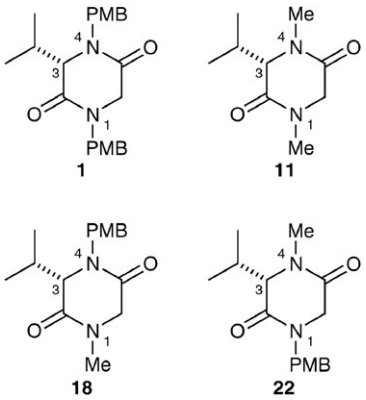


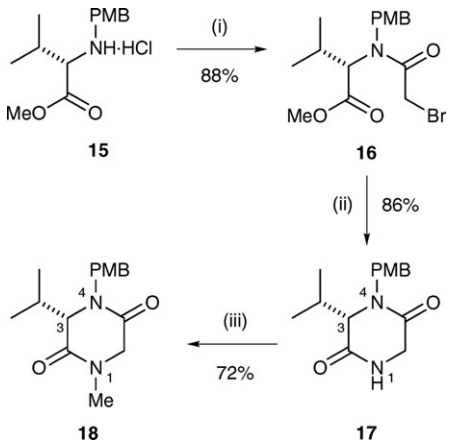
Fig. 2 DKPs **1**, **11**, **18** and **22**.

bromide to give α-bromoamide **16** in 88% yield. Bromide displacement with ammonia and concomitant cyclisation provided **17** in 86% yield. *N*(1)-Methylation of **17** with sodium hydride and methyl iodide then afforded *N*(1)-methyl-*N*(4)-PMB-DKP **18** in 72% yield (Scheme 4).

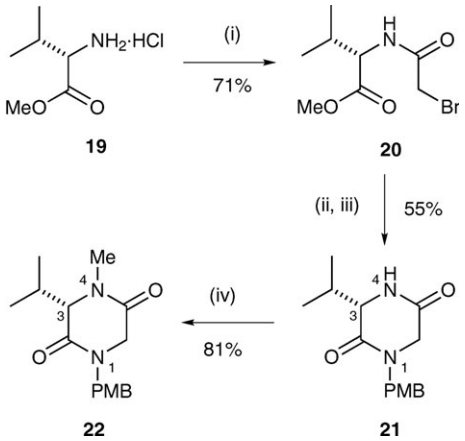
The *N*(1)-PMB-*N*(4)-methyl-DKP **22** was prepared in an analogous fashion. Condensation of (*S*)-valine methyl ester hydrochloride (**19**) and bromoacetyl bromide gave α-bromoamide **20** in 71% yield. The addition of α-bromoamide **20** to *para*-methoxybenzylamine and triethylamine in acetonitrile afforded a seemingly complex mixture, which, upon heating in *sec*-butanol, acetic acid and *N*-methyl morpholine (90 : 9 : 1), gave **21** in 55% yield after chromatographic purification. Subsequent *N*(4)-methylation with sodium hydride and methyl iodide gave **22** in 81% yield (Scheme 5).

Probing the steric chiral relay mechanism: alkylation of diketopiperazine templates

The reactivity and diastereoselectivity upon alkylation of the lithium enolates of these differentially *N*-substituted DKP templates was then examined using two representative electrophiles, *viz*. methyl iodide and benzyl bromide. The alkylation of *N*,*N*′-bis-PMB-DKP **1** has been optimised previously in our laboratory and involves reaction of the pre-formed lithium



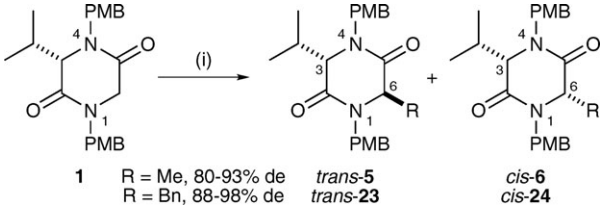
Scheme 4 *Reagents and conditions*: (i) $BrCH_2COBr$, Et_3N, DCM, −78 °C; (ii) NH_3, EtOH, r.t., 48 h; (iii) NaH, THF, r.t., 30 min, then MeI, 12 h.



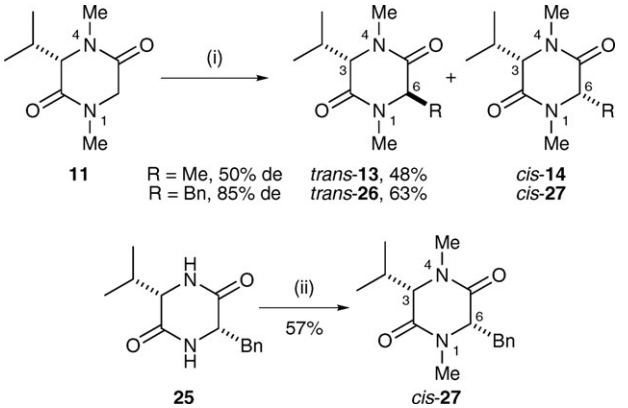
Scheme 5 *Reagents and conditions*: (i) $BrCH_2COBr$, Et_3N, DCM, −78 °C; (ii) *para*-methoxybenzylamine, CH_3CN, Δ; (iii) *N*-methyl morpholine, ^{s}BuOH, AcOH, reflux; (iv) NaH, THF, r.t., 30 min, then MeI, 12 h.

enolate **2** with the electrophile at −78 °C in THF, followed by slow warming to r.t. Although methylation and benzylation of **1** has been reported by us to afford the corresponding *trans*-alkylated diketopiperazines *trans*-**5** and *trans*-**23** with levels of diastereoselectivity as high as 93 and 98% de, respectively, several repetitions of these alkylations demonstrated that the diastereoselectivity for methylation varied between 80–93% de, and that for benzylation between 88–98% de, as determined by analysis of the ^{1}H NMR spectra of the crude reaction mixtures (Scheme 6). The relative and absolute configurations of the major diastereoisomeric alkylation products *trans*-**5** and *trans*-**23** have previously been established;[3] however, ^{1}H NMR spectroscopic data has also proven a powerful indicator of *C*(3)–*C*(6) relative stereochemistry within DKP systems.[10] Diagnostic chemical shift differences ($\Delta\delta_H$) between the two 3H doublets corresponding to the *iso*-propyl CH_3 groups were observed for the diastereoisomeric products *trans*-**5** and *cis*-**6**, and *trans*-**23** and *cis*-**24**: larger values of $\Delta\delta_H$ were observed for the *trans*-configured diastereoisomer than for the corresponding *cis*-isomer.[11]

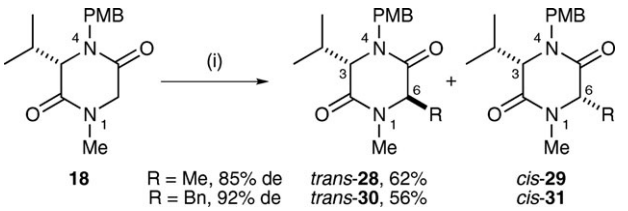
Attention turned next to the alkylation of *N*,*N*′-dimethyl-DKP **11**. Alkylation with methyl iodide proceeded to give *trans*-**13** in 50% de,[12] whilst benzylation performed under the same conditions afforded *trans*-**26** in 85% de. The major diastereoisomers, *trans*-**13** and *trans*-**26**, were isolated in >98% de after column chromatography in 48 and 63% yield, respectively. The relative configuration of the C(3)-*iso*-propyl and C(6)-benzyl group within minor diastereoisomer *cis*-**27** was unambiguously established by its independent synthesis from (*S*,*S*)-cyclo-Val-Phe **25**: *N*,*N*′-dimethylation of **25** with



Scheme 6 *Reagents and conditions*: (i) LiHMDS, THF, −78 °C then RX.



Scheme 7 *Reagents and conditions*: (i) LiHMDS, THF, −78 °C then RX; (ii) KO^{t}Bu, MeI, THF.

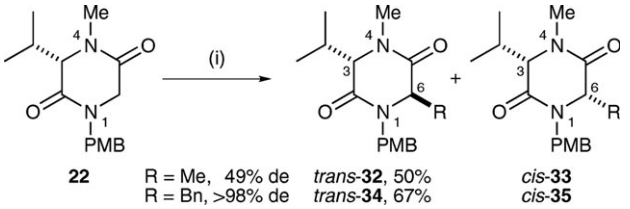


Scheme 8 *Reagents and conditions:* (i) LiHMDS, THF, −78 °C then RX.

potassium *tert*-butoxide and methyl iodide gave *cis*-**27** in 57% yield. ^{1}H NMR spectroscopic data for *trans*-**13** and *cis*-**14**, and *trans*-**26** and *cis*-**27** also followed the diagnostic trend in $\Delta\delta_H$ for the *iso*-propyl CH_3 groups (Scheme 7).[10,11]

Alkylations of the differentially *N*-substituted templates **18** and **22** were then studied in order to differentiate between any potential contributions to selectivity provided by the bulk of the substituent on either *N*(1) or *N*(4). Methylation of *N*(1)-methyl-*N*(4)-PMB-DKP **18** gave a 92.5 : 7.5 mixture of *trans*-**28** : *cis*-**29** (85% de) whilst benzylation gave a 96 : 4 mixture of *trans*-**30** : *cis*-**31** (92% de). Purification allowed isolation of *trans*-**28** in 62% yield and >98% de, and *trans*-**30** in 56% yield and >98% de (Scheme 8).

Analogous methylation conditions applied to *N*(1)-PMB-*N*(4)-methyl-DKP **22** gave a 74.5 : 25.5 mixture of *trans*-**32** : *cis*-**33** (49% de), with benzylation giving a >99 : <1 mixture of *trans*-**34** : *cis*-**35** (>98% de). Chromatographic purification allowed isolation of the major diastereoisomers *trans*-**32** in 50% yield and *trans*-**34** in 67% yield, in >98% de in both cases (Scheme 9).



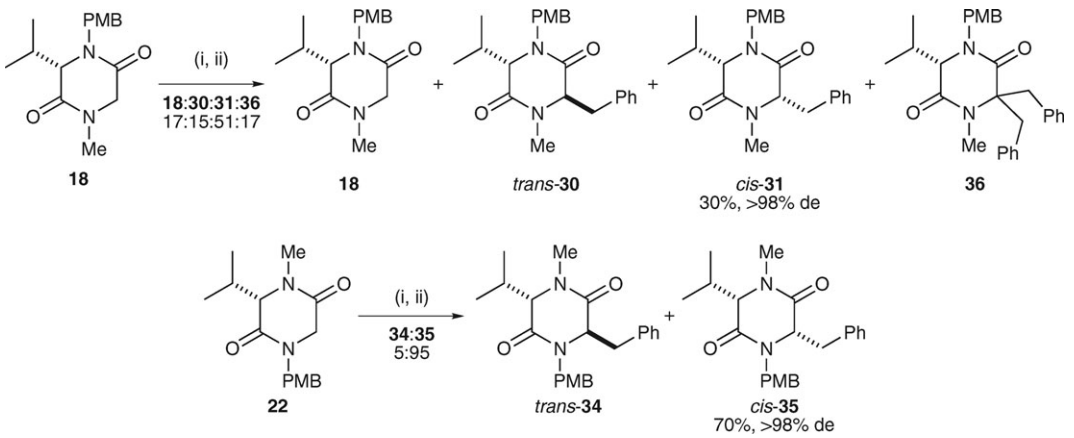
Scheme 9 *Reagents and conditions:* (i) LiHMDS, THF, −78 °C then RX.

Authentic samples of the minor diastereoisomers from the benzylation reactions were prepared in order to establish unambiguously the de in these alkylation reactions. This was achieved *via* alkylation of DKPs **18** and **22** in the presence of an excess of base and subsequent protonation under kinetic conditions. Treatment of DKP **18** with excess LiHMDS (3 equiv.) and benzyl bromide (1 equiv.) afforded a 17 : 15 : 51 : 17 mixture of DKP **18**, *trans*-**30**, *cis*-**31** and a fourth compound, assigned as dibenzylated **36**, from which *cis*-**31** was isolated as a single diastereoisomer in 30% yield. The *N*(1)-PMB-*N*(4)-methyl-DKP diastereoisomer *cis*-**35** was selectively prepared by the treatment of DKP **22** under identical conditions, which afforded *cis*-**35** in 90% de, and 70% isolated yield (>98% de) after chromatography (Scheme 10).

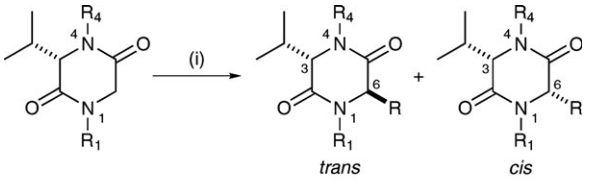
The relative configuration of the C(3)-*iso*-propyl and C(6)-alkyl groups within **28–35** were assigned from ^{1}H NMR spectroscopic data: the *trans* diastereoisomers **28**, **30**, **32** and **34** consistently showed $\Delta\delta_H$ values for the *iso*-propyl CH_3 groups that were larger than those for the corresponding *cis*-diastereoisomers **29**, **31**, **33** and **35**, respectively.[10,11]

Factors controlling regioselective deprotonation and diastereoselective alkylation of diketopiperazine templates

For a steric chiral relay to operate in these templates, the *N*(1) substituent is required to project onto the Si face of the enolate in order to provide a steric bias at the point of alkylation. In



Scheme 10 *Reagents and conditions:* (i) LiHMDS (3 equiv.), THF, −78 °C; (ii) BnBr (1 equiv.).



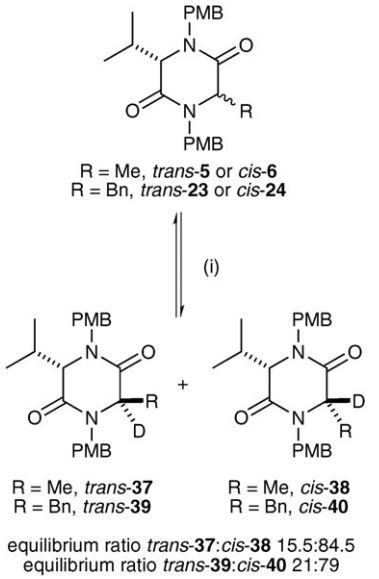
DKP Template	R_1	R_4	*trans* de (R = Me)	*trans* de (R = Bn)
1	PMB	PMB	80-93	88-98
11	Me	Me	50	85
18	Me	PMB	85	92
22	PMB	Me	49	>98

Scheme 11 *Reagents and conditions:* (i) LiHMDS, THF, −78 °C then RX, −78 °C to r.t.

the case of the *N*,*N*-dimethyl-DKP **11** and *N*(1)-methyl-*N*(4)-PMB-DKP **18**, however, the *N*(1)-methyl substituent cannot sterically block either face of the enolate. In this study, the observed diastereoselectivity for the benzylation of *N*(1)-methyl-DKPs **11** and **18** is comparable to that for the *N*(1)-PMB-DKPs **1** and **22**. While the methylation studies reveal more significant deviations in *trans*-selectivity, these data suggest that a steric chiral relay is not the primary means by which the stereochemical information at C(3) is relayed to the C(6) centre undergoing alkylation (Scheme 11).

It was postulated that the marked differences in selectivity upon methylation of these substrates (49–93% de) may be due to epimerisation of the initially formed *trans*-products upon exposure to basic species such as unreacted enolate or excess base under the reaction conditions. Given that *cis*-configured disubstituted DKPs are generally thermodynamically more stable than the corresponding *trans*-isomers,[13] any *in situ* epimerisation of the newly formed C(6) stereogenic centre will lead to an observed de lower than the intrinsic alkylation diastereoselectivity. In order to investigate this possibility, the susceptibility of 3,6-disubstituted DKPs to epimerisation upon exposure to base, and thus the relative thermodynamic stability of the alkylation products, was tested through equilibration of both the *trans*- and *cis*-diastereoisomers derived from alkylation of *N*,*N*′-bis-PMB-DKP **1**. Treatment of either of the 6-methyl-substituted diastereoisomers, *trans*-**5** (>98% de) or *cis*-**6** (>98% de), with KO^{t}Bu in CD_3OD gave a 15.5 : 84.5 mixture of *trans*-**37** : *cis*-**38** with >98% deuterium incorporation solely at C(6) (Scheme 12). Similar equilibration of either of the 6-benzyl-substituted diastereoisomers, *trans*-**23** (>98% de) or *cis*-**24** (>98% de), gave a 21 : 79 mixture of *trans*-**39** : *cis*-**40**, with >98% deuterium incorporation solely at C(6) (Scheme 12). These data confirm that the alkylation reaction is not under thermodynamic control, and furthermore indicate that product stability is not relevant when considering plausible alkylation transition states.

Both the regioselective C(6) deuteration observed upon epimerisation and the regioselective enolate formation at C(6) within the parent DKPs **1**, **11**, **18** and **22** are presumably directed by stereoelectronic factors,[14] which disfavour deprotonation adjacent to the bulky C(3)-*iso*-propyl group due to the introduction of 1,2-torsional strain between the C(3)-*iso*-propyl group and the *N*(4)-substituent. Deprotonation at C(6) proceeds preferentially through half-chair **A**, with the C(3)-*iso*-propyl group in a pseudo-axial position to minimise 1,2-



Scheme 12 *Reagents and conditions*: (i) KO^{t}Bu, CD_3OD.

torsional strain. The alternative half-chair conformation, **B**, for C(3)-deprotonation would be disfavoured due to unfavourable 1,2-torsional strain between the pseudo-equatorial C(3)-*iso*-propyl group and the *N*(4)-substituent (Fig. 3).

The deprotonation of 3,6-dialkylated DKPs is also expected to proceed *via* a half-chair conformation; deprotonation of the 3,6-*trans* products *via* half-chair transition state **C**, however, would result in both the C(3)-*iso*-propyl group and the C(6)-alkyl group being placed in pseudo-equatorial positions, which would be disfavoured due to severe 1,2-torsional strain (Fig. 4). The rate of epimerisation would therefore be affected by the steric bulk of both the C(6)-substituent, and the *N*(1)- and *N*(4)-alkyl substituents. Following this analysis, the *in situ* epimerisation of C(6)-methylated products bearing *N*-methyl substituents is expected to be more facile than for the *N*-*para*-methoxybenzyl substrates. In accordance with these assumptions, *N*,*N*′-dimethyl-6-methyl-DKP *trans*-**13** and *N*(1)-*para*-methoxybenzyl-*N*(4)-methyl-6-methyl-DKP *trans*-**32** are obtained in poor de (50 and 49% de, respectively).

Following this model, the preference for *trans*-diastereoselectivity upon alkylation of the DKP templates may also be due, in part, to relay of the stereochemical information through minimisation of 1,2-torsional strain in the transition state for alkylation at C(6). Molecular modelling studies of all four enolates derived from diketopiperazines **1**, **11**, **18** and **22**[15]

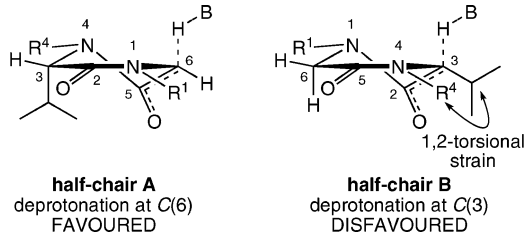


Fig. 3 Proposed transition state for regioselective C(6)-deprotonation of DKP templates **1**, **11**, **18** and **22**.

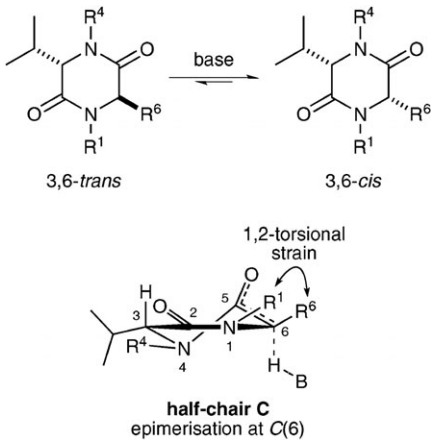


Fig. 4 Proposed transition state for deprotonation/epimerisation of 3,6-dialkylated DKPs.

suggest that these lithiated species preferentially adopt a conformation **D**, in which the diketopiperazine ring is close to planar with the C(3)-*iso*-propyl substituent occupying a pseudo-axial position (Fig. 5). This conformation serves to minimise 1,2-torsional strain between this group and the neighbouring *N*(4)-alkyl group, which is present in the alternative pseudo-equatorial conformer **E** (Fig. 5). In conformation **D**, the C(3)-*iso*-propyl group projects onto the Si face of the enolate, where it may hinder the approach trajectory of an electrophile; given the high levels of stereoselectivity observed in these alkylations, however, stereoelectronic factors must also contribute to the observed selectivity through preferential axial alkylation of the near planar enolate. In the alkylation transition state, the *N*(1)–*C*(2) amide bond will remain planar, while *N*(4) is expected to be sp^3-hybridised, precluding any

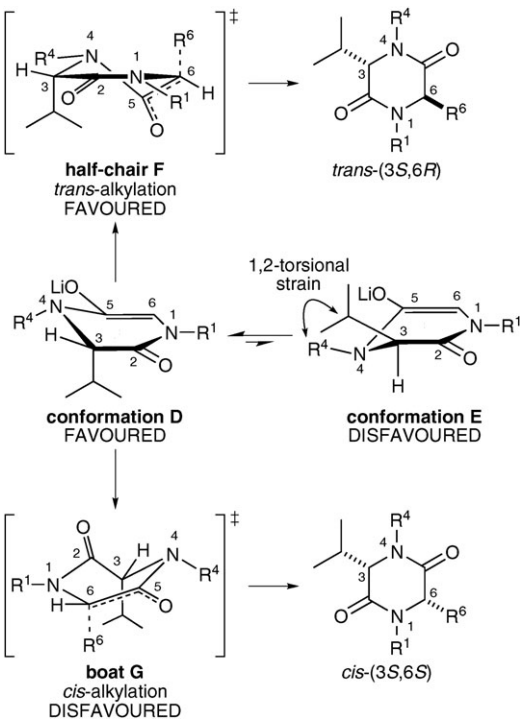


Fig. 5 Proposed transition states for enolate alkylations.

significant *N*(4)–*C*(5) double bond character.[16] Based on these assumptions, two alternative transition states may be considered: half-chair **F**, leading to *trans*-substituted products, and boat **G**, leading to *cis*-substituted products. The conformational preference of the enolate ring system in the transition state will closely resemble that of cyclohexene, of which the half-chair **F** is considerably energetically more favourable than boat **G**.[17] The high levels of facial selectivity observed upon enolate alkylation derive from this stereoelectronic preference, combined with the steric protection of the Si face afforded by the pseudo-axial C(3)-*iso*-propyl group (Fig. 5).

Conclusion

An examination of the diastereoselective alkylation of a series of (*S*)-cyclo-Val-Gly based DKPs, in which the steric requirements of both the *N*(1) and *N*(4)-substituents (PMB and methyl) are varied, indicates that excellent levels of diastereoselectivity can be achieved by the introduction of a *para*-methoxybenzyl protecting group at either or both of the nitrogen atoms. The observed high levels of selectivity are inconsistent with a purely steric chiral relay and indicate that the selectivity in these reactions may be controlled by relay of the stereochemical information from C(3) to C(6) *via* the minimisation of 1,2-torsional strain in the transition state for C(6)-alkylation.

Experimental

General

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.[18] 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 100 mL^{-1}. 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 made on either a Bruker MicroTOF (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.

Syntheses

(*S*)-*N*-(*para*-Methoxybenzyl)valine methyl ester hydrochloride (15). To a stirred solution of L-valine methyl ester hydrochloride (10 g, 0.06 mol) in THF (100 mL) at 0 °C was added *para*-anisaldehyde (8 mL, 0.07 mol), Et_3N (16.7 mL, 0.12 mol) and $MgSO_4$ (20 g), and the reaction mixture was allowed to warm to r.t. over 18 h. The $MgSO_4$ was then filtered off and washed with THF (60 mL), and the filtrate was concentrated *in vacuo*. The residue was dissolved in MeOH (100 mL), and the solution was de-gassed and placed under N_2. 10% Pd/C (1 g) was then added, and the reaction vessel was flushed with H_2 and stirred at r.t. for 18 h. The reaction mixture was then filtered through sand and Celite®, and the plug washed with MeOH and concentrated *in vacuo*. The residue was dissolved in Et_2O (100 mL) and HCl gas was bubbled through the solution for a few seconds. The resulting crystals were collected and washed with Et_2O (100 mL) to give **15** as a white powder (14.0 g, 82%); mp 152–154 °C; $[\alpha]_D^{25}$ +10.8 (*c* 1.0 in MeOH); ν_{max} (KBr) 3481, 1747, 1617, 1562, 1519; δ_H (400 MHz, CD_3OD) 1.01 (3H, d, J = 7.0 Hz, CH_3CHCH$_3$), 1.12 (3H, d, J = 7.0 Hz, CH$_3$CHCH_3), 2.35 (1H, septd, J = 7.0, 4.0 Hz, CH$_3$CHCH$_3$), 3.81 (3H, s, O*Me*), 3.84 (3H, s, O*Me*), 3.93 (1H, d, J = 4.0 Hz, CHCHN), 4.21 (2H, A_2 system, NCH_2Ar), 7.01 (2H, m, *Ar*), 7.43 (2H, m, *Ar*); δ_C (100 MHz, CD_3OD) 16.3, 18.7, 29.8, 50.1, 52.5, 54.9, 64.7, 114.5, 122.0, 132.2, 161.4, 168.4; *m*/*z* (ESI$^+$) 252 ([M + H]$^+$, 100%); HRMS (ESI$^+$) $C_{14}H_{22}NO_3$ ([M + H]$^+$) requires 252.1600, found 252.1591.

(*S*)-*N*-*para*-Methoxybenzyl-*N*-(2-bromoacetyl)valine methyl ester (16). A solution of **15** (20 g, 69.5 mmol) and Et_3N (21.3 mL, 153 mmol) in DCM (125 mL) were added dropwise over 1 h to a solution of bromoacetyl bromide (9.1 mL, 104 mmol) in DCM (375 mL) at −78 °C, before overnight warming to r.t. After 16 h, the crude reaction solution was washed with distilled water, dried and concentrated *in vacuo*. Purification by chromatography (silica, eluent hexane/Et_2O 3 : 1) gave **16** as an orange oil (20.0 g, 88%); $[\alpha]_D^{22}$ −40.9 (*c* 1.6 in $CHCl_3$); ν_{max} (film) 1741, 1659; δ_H (500 MHz, PhMe-d_8, 373 K) 0.86 (3H, d, J = 6.7 Hz, CH_3CHCH$_3$), 0.91 (3H, d, J = 6.7 Hz, CH$_3$CHCH_3), 2.27–2.37 (1H, m, CH$_3$CHCH$_3$), 3.26 (3H, s, CO$_2$*Me*), 3.46 (3H, s, ArO*Me*), 3.67 (2H, s, COCH_2Br), 4.47 (1H, d, J = 14.5 Hz, NCHHAr), 4.49 (1H, d, J = 12.4 Hz, ^{i}PrCHN), 4.54 (1H, d, J = 14.5 Hz, NCHHAr), 6.70–6.75 (2H, m, *Ar*), 6.99–7.10 (2H, m, *Ar*); δ_C (125 MHz, PhMe-d_8, 373 K) 19.0, 20.1, 28.8, 49.0, 51.0, 55.0, 64.8, 114.3, 127.0, 129.6, 159.9, 167.7, 170.3; *m*/*z* (ESI$^+$) 396 ([M + Na]$^+$, ^{81}Br, 100%), 394 (100), 374 (40), 372 (40); HRMS (ESI$^+$) $C_{16}H_{23}{}^{79}BrNO_4$ ([M + H]$^+$, ^{79}Br) requires 372.0810, found 372.0817.

(*S*)-*N*(1)-*para*-Methoxybenzyl-6-*iso*-propylpiperazine-2,5-dione (17). 16 (17.8 g, 47.8 mmol) was added to a saturated solution of ammonia in ethanol (400 mL) and stirred for 48 h before concentration *in vacuo*. The reaction mixture was then extracted with EtOAc and washed with two portions of distilled water before the organic layer was concentrated *in vacuo* to yield the crude solid. Purification by chromatography (silica, eluent EtOAc) gave **17** as a colourless crystalline solid (11.5 g, 86%); $C_{15}H_{20}N_2O_3$ requires C, 65.2; H, 7.3; N, 10.1%; found C, 65.3; H, 7.3; N, 10.1%; mp 119–120 °C (DCM–hexane); $[\alpha]_D^{22}$ −22.8 (*c* 1.6 in $CHCl_3$); ν_{max} (KBr) 3299, 1654, 1631; δ_H (400 MHz, $CDCl_3$) 1.03 (3H, d, J = 6.9 Hz, CH_3CHCH$_3$), 1.11 (3H, d, J = 7.0 Hz, CH$_3$CHCH_3), 2.21–2.29 (1H, m, CH$_3$CHCH$_3$), 3.65 (1H, d, J = 4.7 Hz, C(3)H), 3.79 (3H, s, O*Me*), 3.84 (1H, d, J = 14.8 Hz, NCHHAr), 3.94 (1H, dd, J = 16.8, 3.5 Hz, C(6)HH), 4.10 (1H, dd, J = 16.8, 3.5 Hz, C(6)HH), 5.37 (1H, d, J = 14.8 Hz, NCHHAr), 6.84–6.87 (2H, m, *Ar*), 7.15–7.18 (2H, m, *Ar*), 7.27 (1H, app s, NH); δ_C (100 MHz, $CDCl_3$) 17.7, 19.8, 31.9, 45.3, 47.7, 55.3, 64.2, 114.3, 127.5, 129.6, 159.4, 164.6, 168.1; *m*/*z* (APCI$^+$) 277 ([M + H]$^+$, 85%); HRMS (APCI$^+$) $C_{15}H_{21}N_2O_3$ ([M + H]$^+$) requires 277.1552, found 277.1550.

(*S*)-*N*(1)-Methyl-*N*(4)-*para*-methoxybenzyl-3-*iso*-propylpiperazine-2,5-dione (18). NaH (290 mg, 7.24 mmol, 60% dispersed in mineral oil) was added to a stirred solution of **17** (2.00 g, 7.24 mmol) in THF (200 mL). After 30 min, methyl iodide (0.50 mL, 7.9 mmol) was added. The reaction mixture was allowed to stir at ambient temperature for 16 h before sequential quenching with MeOH, distilled water and saturated $NaHCO_3$ solution. The product was extracted from this mixture with EtOAc. The organic layer was then washed with water (2 × 100 mL), dried and concentrated *in vacuo*. Purification *via* flash column chromatography (silica, eluent EtOAc) gave **18** as a colourless oil (1.62 g, 72%); $C_8H_{14}N_2O_2$ requires C, 66.2; H, 7.6; N, 9.7%; found C, 66.0; H, 7.8; N, 9.6%; $[\alpha]_D^{23}$ −46.0 (*c* 1.1 in $CHCl_3$); ν_{max} (film) 1668; δ_H (400 MHz, $CDCl_3$) 0.74 (3H, d, J = 7.1 Hz, CH_3CHCH$_3$), 0.88 (3H, d, J = 7.1 Hz, CH$_3$CHCH_3), 1.97–2.08 (1H, m, CH$_3$CHCH$_3$), 2.72 (3H, s, N*Me*), 3.51 (1H, d, J = 4.3 Hz, C(3)HCN), 3.54 (3H, s, O*Me*), 3.67 (1H, d, J = 17.6 Hz, C(6)HH), 3.68 (1H, d, J = 14.2 Hz, NCHHAr), 3.96 (1H, d, J = 17.6 Hz, C(6)HH), 5.12 (1H, d, J = 14.2 Hz, NCHHAr), 6.62–6.65 (2H, m, *Ar*), 6.96–6.98 (2H, m, *Ar*); δ_C (100 MHz, $CDCl_3$) 17.4, 19.7, 31.8, 33.0, 47.1, 51.8, 55.0, 64.1, 114.1, 127.6, 129.4, 159.1, 163.4, 164.9; *m*/*z* (ESI$^+$) 291 ([M + H]$^+$, 100%); HRMS (ESI$^+$) $C_{16}H_{23}N_2O_3$ ([M + H]$^+$) requires 291.1709, found 291.1708.

(*S*)-*N*-(2-Bromoacetyl)valine methyl ester (20). A solution of (*S*)-valine methyl ester hydrochloride (**19**) (5.00 g, 30.5 mmol) and Et_3N (11.1 mL, 83.9 mmol) in DCM (125 mL) were added dropwise over 1 h to a solution of bromoacetyl bromide (5.00 mL, 45.7 mmol) in DCM (100 mL) at −78 °C, before overnight warming to r.t. After 16 h, the crude reaction solution was washed with distilled water, dried, concentrated *in vacuo* and purified by chromatography (silica, eluent Et_2O), giving **20** as an orange oily solid (6.85 g, 71%); $[\alpha]_D^{22}$ +22.6 (*c* 1.1 in $CHCl_3$); ν_{max} (film) 3312, 1738, 1650; δ_H (400 MHz, $CDCl_3$) 0.93 (3H, d, J = 6.8 Hz, CH_3CHCH$_3$), 0.96 (3H, d, J = 6.8 Hz, CH$_3$CHCH_3), 2.18–2.26 (1H, m, CH$_3$CHCH$_3$), 3.78

(3H, s, CO_2Me), 3.93 (2H, s, CH_2Br), 4.53 (1H, dd, J = 9.0, 7.2 Hz, ^{i}PrC*H*NH), 7.00 (1H, br d, J = 7.2 Hz, N*H*); δ_C (100 MHz, $CDCl_3$) 17.7, 18.8, 28.6, 31.3, 52.4, 57.7, 165.8, 171.8; m/z (ESI$^+$) 254 ([M + H]$^+$, ^{81}Br, 100%), 252 (100); HRMS (ESI$^+$) $C_8H_{14}{}^{79}BrNO_3$ ([M + H]$^+$, ^{79}Br) requires 252.0235, found 252.0238.

(*S*)-*N*(1)-*para*-Methoxybenzyl-3-*iso*-propylpiperazine-2,5-dione (21). A solution of **20** (580 mg, 2.30 mmol) in MeCN (10 mL) was added dropwise over 1 h to a mixture of *para*-methoxybenzylamine (0.40 mL, 2.99 mmol) and Et_3N (0.28 mL, 2.30 mmol) in MeCN (20 mL), and the resultant solution was subjected to reflux overnight. The precipitate was then removed by filtration from the crude reaction mixture before the solvent was removed *in vacuo*. *N*-methyl morpholine (0.72 mL, 6.56 mmol), AcOH (3.25 mL, 56.8 mmol) and butan-2-ol (32.5 mL) were added to the crude reaction mixture, which was then subjected to reflux overnight at 100 °C. The solvent was then removed *in vacuo*. The product was extracted with EtOAc, washed with distilled water and concentrated *in vacuo*. Purification of the residue *via* flash column chromatography (silica, eluent EtOAc) gave **21** as a white solid (398 mg, 55%); mp 134–135 °C; $[\alpha]_D^{22}$ +8.0 (*c* 0.6 in $CHCl_3$); ν_{max} (KBr) 3254, 1653; δ_H (400 MHz, $CDCl_3$) 0.85 (3H, d, J = 6.9 Hz, CH_3CHCH_3), 1.01 (3H, d, J = 6.9 Hz, CH_3CHCH_3), 2.38–2.45 (1H, m, CH_3CHCH_3), 3.75 (1H, d, J = 17.9 Hz, C(6)*H*H), 3.78 (3H, s, O*Me*), 3.84 (1H, d, J = 17.9 Hz, C(6)H*H*), 3.89 (1H, d, J = 2.6 Hz, C(3)*H*), 4.34 (1H, d, J = 14.3 Hz, NC*H*HAr), 4.64 (1H, d, J = 14.3 Hz, NCH*H*Ar), 6.83–6.86 (2H, m, *Ar*), 7.17–7.21 (2H, m, *Ar*), 7.74 (1H, br s, N*H*); δ_C (100 MHz, $CDCl_3$) 16.1, 18.8, 33.2, 48.4, 49.0, 55.3, 60.7, 114.2, 127.3, 130.0, 159.4, 165.5, 166.6; m/z (CI$^+$) 277 ([M + H]$^+$, 100%); HRMS (CI$^+$) $C_{15}H_{21}N_2O_3$ ([M + H]$^+$) requires 277.1552, found 277.1554.

(*S*)-*N*(1)-*para*-Methoxybenzyl-*N*(4)-methyl-3-*iso*-propylpiperazine-2,5-dione (22). NaH (535 mg, 13.4 mmol, 60% dispersed in mineral oil) was added to a stirred solution of **21** (3.7 g, 13.4 mmol) in THF (250 mL). After 30 min, methyl iodide (0.94 mL, 15.7 mmol) was added. The reaction mixture was allowed to stir at ambient temperature for 12 h before quenching with distilled water. The product was extracted with EtOAc, dried over $MgSO_4$ and concentrated *in vacuo*. Purification of the residue *via* flash column chromatography (silica, eluent EtOAc) gave **22** as a white solid (3.15 g, 81%); mp 51–53 °C; $[\alpha]_D^{25}$ +64.9 (*c* 1.0 in $CHCl_3$); ν_{max} (KBr) 1652 (C=O); δ_H (400 MHz, $CDCl_3$) 0.95 (3H, d, J = 7.0 Hz, CH_3CHCH_3), 1.09 (3H, d, J = 7.0 Hz, CH_3CHCH_3), 2.24–2.28 (1H, m, CH_3CHCH_3), 2.99 (3H, s, N*Me*), 3.75 (1H, d, J = 17.4 Hz, C(6)*H*H), 3.77 (1H, d, J = 4.2 Hz, C(3)*H*), 3.80 (3H, s, O*Me*), 3.87 (1H, d, J = 17.4 Hz, C(6)H*H*), 4.31 (1H, d, J = 14.1 Hz, NC*H*HAr), 4.72 (1H, d, J = 14.1 Hz, NCH*H*Ar), 6.86 (2H, d, J = 8.4 Hz, *Ar*), 7.20 (2H, d, J = 8.4 Hz, *Ar*); δ_C (100 MHz, $CDCl_3$) 18.2, 19.3, 32.8, 34.1, 48.9, 49.2, 55.3, 68.5, 114.2, 127.4, 130.0, 159.4, 164.5, 165.1; m/z (ESI$^+$) 291 ([M + H]$^+$, 100%); HRMS (ESI$^+$) $C_{16}H_{23}N_2O_3$ ([M + H]$^+$) requires 291.1709, found 291.1699.

Alkylation of DKP templates

General procedure 1. LiHMDS (1.0 M in THF, 1.1 equiv.) was added to a solution of the DKP (1 equiv.) in de-gassed THF at −78 °C. After stirring for 1 h at −78 °C, the alkyl halide (1 equiv.) was added and the reaction mixture allowed to warm to r.t. over 12 h. The reaction mixture was quenched with sat. aq. NH_4Cl, extracted with EtOAc, dried and concentrated *in vacuo* to give the crude product.

General procedure 2: with excess base. LiHMDS (1.0 M in THF, 3 equiv.) was added to a solution of the DKP (1 equiv.) in de-gassed THF at −78 °C. After stirring for 1 h at −78 °C, the alkyl halide (1 equiv.) was added and stirring continued for a further 4 h at −78 °C. The reaction mixture was quenched with acetic acid at −78 °C, allowed to warm to r.t. and partitioned between H_2O and EtOAc. The organic layer was washed with sat. aq. $NaHCO_3$, dried and concentrated *in vacuo* to give the crude product.

(3*S*,6*R*)-*N*,*N*′-Dimethyl-3-*iso*-propyl-6-benzylpiperazine-2,5-dione (*trans*-26). 11 (100 mg, 0.54 mmol) in THF (20 mL), LiHMDS (1.0 M in THF, 0.60 mL, 0.60 mmol) and BnBr (71 μL, 0.60 mmol) were reacted according to *General procedure 1* to give a 92.5 : 7.5 mixture of *trans*-**26** : *cis*-**27**. Chromatography (silica, eluent 40–60° petrol/EtOAc 2 : 1) gave *trans*-**26** as a white solid (94 mg, 63%, >98% de); mp 81–83 °C; $[\alpha]_D^{26}$ −1.3 (*c* 0.9 in $CHCl_3$); ν_{max} (KBr) 1640; δ_H (400 MHz, $CDCl_3$) 0.78 (3H, d, J = 7.0 Hz, CH_3CHCH_3), 1.01 (3H, d, J = 7.0 Hz, CH_3CHCH_3), 2.13 (1H, m, CH_3CHCH_3), 2.69 (3H, s, N*Me*), 2.97 (1H, d, J = 2.5 Hz, C(3)*H*), 3.05 (3H, s, N*Me*), 3.16 (1H, dd, J = 14.0, 4.1 Hz, C*H*HPh), 3.32 (1H, dd, J = 14.0, 3.2 Hz, CH*H*Ph), 4.25 (1H, m, C(6)*H*), 7.01–7.03 (2H, m, *Ar*), 7.21–7.26 (3H, m, *Ar*); δ_C (100 MHz, $CDCl_3$) 16.5, 19.1, 31.7, 32.4, 33.2, 37.2, 62.3, 66.0, 127.3, 128.3, 129.6, 134, 165.2, 165.4; m/z (APCI$^+$) 275 ([M + H]$^+$, 100%).

(*S*,*S*)-*N*,*N*′-Dimethyl-3-*iso*-propyl-6-benzylpiperazine-2,5-dione (*cis*-27). KO^{t}Bu (143 mg, 1.30 mmol) was added to (*S*,*S*)-cyclo-Val-Phe **25** (150 mg, 0.61 mmol) and MeI (70 μL, 1.20 mmol) in THF (10 mL). After 45 min, MeOH (50 mL) and sat. aq. NH_4OH (0.5 mL) were added. The solvent was then removed *in vacuo*. Chromatography (silica, eluent EtOAc) gave *cis*-**27** as a colourless oil (95 mg, 57%. >98% de); $[\alpha]_D^{26}$ −59.5 (*c* 0.9 in $CHCl_3$); ν_{max} (film) 1651; δ_H (500 MHz, $CDCl_3$) 0.95 (3H, d, J = 6.9 Hz, CH_3CHCH_3), 1.02 (3H, d, J = 6.9 Hz, CH_3CHCH_3), 1.67 (1H, m, CH_3CHCH_3), 2.67 (3H, s, N*Me*), 3.02 (3H, s, N*Me*), 3.09 (1H, dd, J = 14.0, 7.8 Hz, C*H*HPh), 3.38 (1H, dd, J = 14.0, 4.4 Hz, CH*H*Ph), 3.55 (1H, d, J = 7.1 Hz, C(3)*H*), 4.13 (1H, dd, J = 7.8, 4.4 Hz, C(6)*H*), 7.23–7.33 (5H, m, *Ph*); δ_C (50 MHz, $CDCl_3$) 19.4, 20.4, 33.4, 33.8, 40.2, 65.1, 68.9, 127.4, 129.1, 129.6, 137.3, 166.1, 166.7; m/z (APCI$^+$) 275 ([M + H]$^+$, 100%).

(3*S*,6*R*)-*N*(1)-Methyl-*N*(4)-*para*-methoxybenzyl-3-*iso*-propyl-6-methylpiperazine-2,5-dione (*trans*-28). 18 (100 mg, 0.34 mmol) in THF (20 mL), LiHMDS (1.0 M in THF, 0.37 mL, 0.37 mmol) and MeI (24 μL, 0.37 mmol) were reacted according to *General procedure 1* to give a 92.5 : 7.5 mixture of *trans*-**28** : *cis*-**29**. Chromatography (silica, eluent 40–60° petrol/EtOAc 3 : 1) gave *trans*-**28** as a colourless oil (65 mg, 62%, >98% de); $[\alpha]_D^{25}$ −48.4

(c 1.0 in $CHCl_3$); ν_{max} (film) 1658; δ_H (400 MHz, $CDCl_3$) 0.91 (3H, d, J = 6.9 Hz, CH_3CHCH_3), 1.08 (3H, d, J = 6.9 Hz, CH_3CHCH_3), 1.61 (3H, d, J = 6.8 Hz, C(6)*Me*), 2.21–2.29 (1H, m, CH_3CHCH_3), 2.95 (3H, s, N*Me*), 3.72 (1H, d, J = 3.8 Hz, C(3)*H*), 3.78 (3H, s, O*Me*), 3.83 (1H, d, J = 14.9 Hz, NC*H*HAr), 4.05–4.11 (1H, q, J = 6.8 Hz, C(6)*H*), 5.37 (1H, d, J = 14.9 Hz, NCH*H*Ar), 6.83 (2H, d, J = 8.6 Hz, *Ar*), 7.12 (2H, d, J = 8.6 Hz, *Ar*); δ_C (100 MHz, $CDCl_3$) 17.2, 19.9, 18.4, 31.0, 32.0, 47.3, 55.3, 56.0, 63.7, 114.3, 127.7, 129.5, 159.3, 165.4, 167.2; m/z (ESI^+) 305 ($[M + H]^+$, 100%); HRMS (ESI^+) $C_{17}H_{25}N_2O_3$ ($[M + H]^+$) requires 305.1865, found 305.1877.

(3*S*,6*R*)-*N*(1)-Methyl-*N*(4)-*para*-methoxybenzyl-3-*iso*-propyl-6-benzylpiperazine-2,5-dione (*trans*-30). 18 (100 mg, 0.34 mmol) in THF (20 mL), LiHMDS (1.0 M in THF, 0.37 mL, 0.37 mmol) and BnBr (44 μL, 0.37 mmol) were reacted according to *General procedure 1* to give a 96 : 4 mixture of *trans*-**30** : *cis*-**31**. Chromatography (silica, eluent 40–60° petrol/EtOAc 1 : 1) gave *trans*-**30** as a colourless oil (74 mg, 56%, >98% de); $[\alpha]_D^{25}$ −76.1 (c 1.0 in $CHCl_3$); ν_{max} (film) 1654; δ_H (400 MHz, $CDCl_3$) 0.80 (3H, d, J = 7.2 Hz, CH_3CHCH_3), 0.97 (3H, d, J = 7.2 Hz, CH_3CHCH_3), 2.11–2.19 (1H, m, CH_3CHCH_3), 3.09 (3H, s, N*Me*), 3.27 (1H, dd, J = 14.4, 3.6 Hz, C*H*HPh), 3.29 (1H, d, J = 4.4 Hz, C(3)*H*), 3.46 (1H, dd, J = 14.4, 4.0 Hz, C*H*HPh), 3.74 (1H, d, J = 14.8 Hz, NC*H*HAr), 3.77 (3H, s, O*Me*), 4.35 (1H, m, C(6)*H*), 5.17 (1H, d, J = 14.8 Hz, NCH*H*Ar), 6.52 (2H, d, J = 8.6 Hz, *Ar*), 6.67 (2H, d, J = 8.6 Hz, *Ar*), 7.07–7.23 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 15.9, 19.6, 31.0, 32.3, 36.5, 46.1, 55.2, 61.9, 62.0, 114.0, 126.4, 127.0, 128.7, 129.4, 129.6, 129.9, 135.0, 159.0, 165.0, 165.2; m/z (ESI^+) 381 ($[M + H]^+$, 100%); HRMS (ESI^+) $C_{23}H_{29}N_2O_3$ ($[M + H]^+$) requires 381.2178, found 381.2177.

(*S*,*S*)-*N*(1)-Methyl-*N*(4)-*para*-methoxybenzyl-3-*iso*-propyl-6-benzylpiperazine-2,5-dione (*cis*-31). 18 (100 mg, 0.34 mmol) in THF (20 mL), LiHMDS (1.0 M in THF, 0.7 mL, 0.7 mmol) and BnBr (44 μL, 0.37 mmol) were reacted according to *General procedure 2* to give a 17 : 15 : 51 : 17 mixture of **18** : *trans*-**30** : *cis*-**31** : **36**. Chromatography (silica, eluent 40–60° petrol/EtOAc 2 : 1) gave *cis*-**31**as a colourless oil (40 mg, 30%, >98% de); $[\alpha]_D^{25}$ −95.2 (c 1.0 in $CHCl_3$); ν_{max} (film) 1658; δ_H (400 MHz, $CDCl_3$) 0.95 (3H, d, J = 6.8 Hz, CH_3CHCH_3), 1.10 (3H, d, J = 6.8 Hz, CH_3CHCH_3), 1.80–1.88 (1H, m, CH_3CHCH_3), 2.65 (3H, s, N*Me*), 3.12 (1H, dd, J = 3.1 Hz, 13.9, C*H*HPh), 3.44 (1H, J = 4.4 Hz, 13.9, CH*H*Ph), 3.63 (1H, d, J = 6.5 Hz, C(3)*H*), 3.79 (3H, s, O*Me*), 3.85 (1H, d, J = 14.7 Hz, NC*H*HAr), 4.19 (1H, m, C(6)*H*), 5.40 (1H, d, J = 14.7 Hz, NCH*H*Ar), 6.83 (2H, d, J = 8.4 Hz, *Ar*), 7.16 (2H, d, J = 8.4 Hz, *Ar*), 7.26–7.35 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 19.2, 20.8, 32.8, 33.8, 40.5, 48.6, 55.2, 64.6, 65.2, 114.3, 127.7, 127.2, 128.9, 129.4, 129.6, 137.1, 159.7, 165.6, 166.4; m/z (ESI^+) 381 ($[M + H]^+$, 100%); HRMS (ESI^+) $C_{23}H_{29}N_2O_3$ ($[M + H]^+$) requires 381.2178, found 381.2177.

(3*S*,6*R*)-*N*(1)-*para*-Methoxybenzyl-*N*(4)-methyl-3-*iso*-propyl-6-methylpiperazine-2,5-dione (*trans*-32). 22 (100 mg, 0.34 mmol) in THF (20 mL), LiHMDS (1.0 M in THF, 0.37 mL, 0.37 mmol) and MeI (24 μL, 0.37 mmol) were reacted according to *General procedure 1* to give a 74.5 : 25.5 mixture of *trans*-**32** : *cis*-**33**. Chromatography (silica, eluent 40–60° petrol/EtOAc 3 : 1) gave *trans*-**30** as a colourless oil (55 mg, 42%, >98% de); $[\alpha]_D^{25}$ +99.7 (c 1.0 in $CHCl_3$); ν_{max} (film) 1652; δ_H (400 MHz, $CDCl_3$) 0.92 (3H, d, J = 7.1 Hz, CH_3CHCH_3), 1.10 (3H, d, J = 7.1 Hz, CH_3CHCH_3), 1.55 (3H, d, J = 6.9 Hz, C(6)*Me*), 2.24–2.34 (1H, m, CH_3CHCH_3), 2.97 (3H, s, N*Me*), 3.79 (3H, s, O*Me*), 3.82 (1H, d, J = 4.3 Hz, C(3)*H*), 3.87–3.96 (1H, q, J = 6.9 Hz, C(6)*H*), 4.03 (1H, d, J = 14.9 Hz, NC*H*HAr), 5.33 (1H, d, J = 14.9 Hz, NCH*H*Ar), 6.85 (2H, d, J = 8.6, *Ar*), 7.19 (2H, d, J = 8.6, *Ar*); δ_C (100 MHz, $CDCl_3$) 17.9, 18.0, 19.3, 32.5, 34.5, 45.4, 53.4, 55.2, 67.9, 114.1, 128.1, 129.4, 159.1, 165.8, 167.6; m/z (ESI^+) 305 ($[M + H]^+$, 100%); HRMS (ESI^+) $C_{17}H_{25}N_2O_3$ ($[M + H]^+$) requires 305.1865, found 305.1861.

(3*S*,6*R*)-*N*(1)-*para*-Methoxybenzyl-*N*(4)-methyl-3-*iso*-propyl-6-benzylpiperazine-2,5-dione (*trans*-34). 22 (100 mg, 0.34 mmol) in THF (20 mL), LiHMDS (1.0 M in THF, 0.37 mL, 0.37 mmol) and BnBr (44 μL, 0.37 mmol) were reacted according to *General procedure 1* to give a >99 : <1 mixture of *trans*-**34** : *cis*-**35**. Chromatography (silica, eluent 40–60° petrol/EtOAc 1 : 1) gave *trans*-**34** as a white solid (70 mg, 67%, >98% de); mp 120–122 °C; $[\alpha]_D^{25}$ +52.2 (c 1.0 in $CHCl_3$); ν_{max} (KBr) 1646; δ_H (400 MHz, $CDCl_3$) 0.82 (3H, d, J = 7.1 Hz, CH_3CHCH_3), 1.07 (3H, d, J = 7.1 Hz, CH_3CHCH_3), 2.18–2.23 (1H, m, CH_3CHCH_3), 2.73 (3H, s, N*Me*), 2.94 (1H, d, J = 2.6 Hz, C(3)*H*), 3.29 (2H, s, CH_2Ph), 3.86 (3H, s, O*Me*), 3.97 (1H, d, J = 14.5 Hz, NC*H*HAr), 4.21 (1H, m, C(6)*H*), 5.64 (1H, d, J = 14.5 Hz, NCH*H*Ar), 6.88–7.34 (9H, m, *Ar*, *Ph*); δ_C (100 MHz, $CDCl_3$) 17.1, 19.6, 32.1, 33.5, 37.1, 46.2, 55.8, 58.8, 66.3, 114.7, 127.7, 127.8, 128.8, 129.0, 130.2, 130.6, 135.0, 159.9, 165.6, 166.2; m/z (ESI^+) 381 ($[M + H]^+$, 100%); HRMS (ESI^+) $C_{23}H_{29}N_2O_3$ ($[M + H]^+$) requires 381.2178, found 381.2174.

(*S*,*S*)-*N*(1)-*para*-Methoxybenzyl-*N*(4)-methyl-3-*iso*-propyl-6-benzylpiperazine-2,5-dione (*cis*-35). 22 (100 mg, 0.34 mmol) in THF (20 mL), LiHMDS (1.0 M in THF, 0.7 mL, 0.7 mmol) and BnBr (40 μL, 0.34 mmol) were reacted according to *General procedure 2* to give a 5 : 95 mixture of *trans*-**34** : *cis*-**35**. Chromatography (silica, eluent 40–60° petrol/EtOAc 2 : 1) gave *cis*-**35** as a colourless oil (95 mg, 70%, >98% de); $[\alpha]_D^{25}$ −109.5 (c 1.0 in $CHCl_3$); ν_{max} (film) 1656; δ_H (400 MHz, $CDCl_3$) 1.03 (3H, d, J = 6.8 Hz, CH_3CHCH_3), 1.06 (3H, d, J = 6.8 Hz, CH_3CHCH_3), 1.71–1.79 (1H, m, CH_3CHCH_3), 2.99 (3H, s, N*Me*), 3.07 (1H, dd, J = 7.7, 14.2 Hz, C*H*HPh), 3.31 (1H, d, J = 14.6 Hz, NC*H*HAr), 3.38 (1H, dd, J = 4.5, 14.2 Hz, CH*H*Ph), 3.61 (1H, d, J = 7.35 Hz, C(3)*H*), 3.76 (3H, s, O*Me*), 4.14 (1H, m, C(6)*H*), 5.22 (1H, d, J = 14.6 Hz, NCH*H*Ar), 6.76 (2H, d, J = 8.6 Hz, *Ar*), 6.92 (2H, d, J = 8.6 Hz, *Ar*), 7.22–7.36 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 19.8, 20.7, 32.6, 33.9, 40.2, 46.8, 55.2, 60.5, 69.1, 114.1, 127.6, 127.3, 128.9, 129.4, 129.9, 137.4, 159.3, 165.8, 166.6; m/z (ESI^+) 381 ($[M + H]^+$, 100%); HRMS (ESI^+) $C_{23}H_{29}N_2O_3$ ($[M + H]^+$) requires 381.2178, found 381.2182.

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